Pharmaceutical Press

Martindale

THE COMPLETE DRUG REFERENCE

38TH EDITION

Martindale

The Complete Drug Reference

Thirty-eighth Edition

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Thirty-eighth Edition

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About the authors

Martindale is published by the Pharmaceutical Press, the publishing division of the Royal Pharmaceutical Society. Content is created and updated by the Martindale Editorial Team, a group of pharmacists and life science graduates with relevant expertise who are given formal training in literature evaluation and searching techniques, as well as on-the-job training in internal procedures. The Editorial Team is supported by a number of external contributors.

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Preface

Drug information is constantly developing as the use of existing drugs grows, new drugs emerge, new preparations are launched, and old preparations are abandoned, reformulated, or redefined. The needs of those practising pharmacy and medicine are also changing, and during its long history Martindale has evolved to meet those needs by becoming much more than a simple encyclopaedia of medicines. It aims to provide healthcare professionals with evaluated, unbiased information on drugs and medicines used throughout the world. Our content is also carefully structured to enable readers to find this information easily and quickly, whether it is to answer specific questions about drugs or to give a broad overview of pharmaceutical topics.

Our readers should note that Martindale is not a book of standards: the inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation and readers are reminded that knowledge and best practice in this field are constantly changing. While considerable efforts have been made to check the material in Martindale, neither the publisher nor the authors accept any responsibility for errors and omissions. The publisher and authors make no representation, expressed or implied, that doses are correct for particular purposes and readers should check up to date product information, codes of conduct, and safety regulations. The reader is also assumed to possess the necessary knowledge to interpret the information that Martindale provides. It is the responsibility of practitioners to determine dosages and treatments for individual patients, taking into account up to date therapeutic standards, and to take all appropriate safety precautions.

Further details on the basic editorial philosophy behind content creation, as well as guidance on how the data is set out, are provided in the guide to Martindale section on the next page.

Major changes for the 38TH Edition

There have been several changes to this new edition of Martindale, but the most striking is its new format. The cover design has been refreshed and, to overcome a common problem, the page layout has been totally re-designed with a new and larger font. This ensures that the page is easier to read as well as making it quicker to find the information the reader is looking for on the page. Alongside this, and in response to user feedback, the layout of the monographs has been restructured and readers will now find a monograph's uses at the start of a monograph; knowing how a drug acts and is used may help to contextualise any subsequent adverse effects and precautions related to that drug. In addition, a drug's nomenclature information is highlighted within its own shaded text box. To allow for these changes, the chemical structure graphics are no longer reproduced in the print editions of Martindale; however, they remain available on our digital platform, MedicinesComplete.

Alongside much of the revalidation work that is undertaken with every edition of Martindale, other changes for this edition include:

- over 200 new monographs including:
  - the sodium-glucose co-transporter 2 inhibitors, canagliflozin and dapagliflozin, have been added as a new drug group to the chapter on antidiabetic drugs
  - the antivirals, daclatasvir and sofosbuvir, for use in the management of hepatitis C
- restructuring of the section on diabetes mellitus management in the antidiabetic drugs chapter, to improve its readability
- updated reviews on the treatment of acute lymphoblastic leukaemia and non-small cell lung cancer, which prototype a new approach to our treatment reviews
- revised paracetamol nomograms for the treatment of paracetamol poisoning
- extensive revision of the porphyria abstracts
- expansion of the coverage of proprietary preparations to cover 43 countries and regions, including China

The Martindale editorial team have been assisted by many individuals in the production of this edition, and it is their valuable contribution that help to ensure Martindale's validity. Thanks are due to Lina Bladh, Alessandro Gabbi, Judy van Engeldorp Gastelaars, Špela Godec, Jan Horn, Montserrat Jané, Andrius Kairys, Maria Kouimtzi, Carla Oliveira, Kamila Ramešová, Elsa Simon, Gyöngyver Soós, Carina Tukukino, Robert Wasilewski, Larry Callahan, and Frank Switzer.

The team have also been able to call on the advice and expertise of other members of the Royal Pharmaceutical Society's Pharmaceutical Press division. In particular, the Editor would like to thank Rachel Ryan and the staff of the British National Formulary, Claire Preston and the staff of Stockley's Drug Interactions, and Sam Driver and the Science team. Thanks are also due to Tamsin Cousins and Linda Paulus, for their patience and guidance in handling the various aspects of producing a print publication, and to David Granger, Mesfin Mebrate, Karl Parsons, and Ian White, for their technical expertise in producing digital and print datasets. We are also grateful for the support of Karen Baxter, Frank Gibson, and Alina Lourie.

The Editor would also like to thank Sean Sweetman, Paul Blake, Gail Neathercoat, Anne Parsons, Susan Handy, Fauziah Hashmi, Joanna Humm, Kelli Kalb, Priya Patel, Gerda Viedge, Elizabeth King, and Christine Iskandar. Their input over the years and to this edition has been greatly valued and is not forgotten.

Our digital version of Martindale, which is updated quarterly, is available on MedicinesComplete (www.medicinescomplete.com). It maintains the familiar layout of the print publication but, as it is not limited in its size, extra content such as the archive chapter of deleted monographs and graphical representations of the chemical structures of many of the drugs are also available. For more information about the digital product, please visit our website.

We continue to value our readers' feedback and anyone wishing to contact us may do so at our email address: PhpEditorial@rpharms.com

London, February 2014

A guide to Martindale

Martindale contains information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, vitamins and nutritional agents, vaccines, radiopharmaceuticals, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides.

The information on over 6000 drugs and other substances is arranged into monographs that contain details on nomenclature, properties, and actions. These text sections summarise the relevant information, notably for licensed uses, followed, if appropriate, by referenced abstracts or reviews that expand upon the details given in the text or add additional information. Multicentre studies, meta-analyses, and systematic reviews play an important role in the study of drug treatment, and their findings and conclusions are considered in much of our content. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate. In compiling the text of a Martindale monograph, use is made of the drug's licensed product information as published in various countries and approved by the relevant regulatory authorities. Acknowledgement is also given to information referenced from a number of authoritative sources including the *British National Formulary*, the *British National Formulary for Children*, the *British Pharmacopoeia*, the *European Pharmacopoeia*, the *United States National Formulary*, and the *United States Pharmacopeia*.

In addition, disease treatment reviews offer overviews of nearly 700 diseases and the drugs used in their treatment, along with key references and guidelines. Cross-references are provided between these treatment reviews and relevant drug monographs.

Preparations summaries of more than 180,000 proprietary products from 43 countries or regions are included. Information is provided on proprietary name, manufacturer or distributor, country/region of origin, active ingredients, and a summary of the indications as given by the manufacturer. Page numbers link ingredients to an appropriate drug monograph where possible.

Philosophy and methodology

Martindale's uses are as varied as its users. However, the primary aims are:

- to summarise clinically useful information on all drugs and medicines around the world
- to provide accurate, unbiased, and reasonably comprehensive information in a concise format
- to provide a lead-in to the published evidence base from which we derive our information

To achieve the above aims, working practices have to be safe and efficient, while making optimum use of available information. This section describes some of these working practices.

Data collection

The team proactively monitor the published literature for potential content updates. This involves regularly searching selected major medical journals and websites of regulatory authorities such as EMA, FDA, Health Canada, and MHRA; other sources of high-quality systematic reviews and guidelines, including the Cochrane library and NICE, are also monitored, as are pharmacopoeial, governmental, and WHO publications, for information relating to drugs and drug therapy.

The list of sources used has been developed over many years by analysis of previous citations, and is reviewed and updated regularly.

Licensed product information for 43 countries and regions is evaluated, to maintain the widest possible coverage of drugs in use internationally. Preparation names, manufacturers, ingredients, and licensed uses are included in the internal Martindale database for review during the revision process.

Editorial processes

Write, review, and approve. To maintain the quality and currency of our content, it is constantly revised and updated. Our revision processes cover both scheduled revision of the content, and revision of particular points in reaction to new information as it arrives.

The revision procedure involves the editorial writer re-evaluating standing information, assessing newly-collected references for quality and relevance, and searching bibliographic databases and the Internet to identify further candidate information.

Once the material for new content has been re-evaluated and updated, it is rigorously reviewed by a second editorial writer to ensure not only that all changes are valid and appropriate, but also that important points have not been missed.

The material is then passed to the editor, who performs a final, high-level check and approval of the data. This process is designed to ensure consistency of approach and style, as well as offering an opportunity to pick up any errors that may have been missed. Changes and questions are fed back to the writer.

Keying, proof-reading, and dose-checking. Once approved by the editor, content changes can be made in the database, which has remained untouched until this stage as a security measure. These changes are then proofread for errors, corrected if necessary, and any corrections checked. Extensive electronic testing for spelling, style, and format is also carried out at all stages.

The amended content then undergoes an independent review of the dose information against its recorded sources. This review is performed by a writer not involved in the original content generation process, and is an additional safeguard against the inadvertent introduction of potentially dangerous dose errors.

Release. Once past all these stages, the data are cleared for release and can be published in the next update of the Martindale digital products; changes to the print version will appear in the next edition.

Additional checks for publication. Some additional checks are made before publishing a print edition of Martindale. A second independent dose review of all chapters is made by external experts.

How the information is arranged

Martindale is divided into 2 volumes:

Volume A covers:

- **Monographs on drugs and ancillary substances.** This section contains over 6000 monographs arranged in 49 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The disease treatment reviews, which provide descriptions of diseases together with reviews of the choice of treatments, are usually located in the chapter introduction. The chapter titled Miscellaneous Drugs and Other Substances contains monographs on drugs not easily classified, herbals, and drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

Volume B includes:

- **Preparations**. This section contains over 180,000 proprietary preparations from a range of countries and regions. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.
- **Directory of manufacturers**. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with contact details if available. Manufacturers' records are listed alphabetically. This directory contains over 20,000 entries.
- **Pharmaceutical terms in various languages**. This index lists nearly 5600 of the commoner pharmaceutical forms and routes in 13 major European languages. It is provided as an aid to the non-native speaker in interpreting packaging, product information, or prescriptions written in another language.
- **General index.** To make the fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index, prepared from over 175,000 entries, including entries for drugs

(approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page and in which volume the entry may be found. To improve clarity and the ease of location of index entries, long chemical names have been omitted from the index.

- **Cyrillic index**. Both non-proprietary and proprietary names may be found in Cyrillic alphabetical order in this section.

The monographs

Chapters within Martindale are composed of an introduction of varying length, and a set of monographs describing individual drugs. Each monograph begins with its title, synonyms in English and other languages, identificatory codes, and chemical and pharmaceutical information about the compound, including any pharmacopoeial standards. This is followed by one or more sections describing pharmacological and therapeutic information about the drug or substance. A typical monograph includes:

- Nomenclature
- Uses and Administration
- Adverse Effects
- Treatment of Adverse Effects
- Precautions
- Interactions
- Pharmacokinetics

Sections begin with unreferenced summary text, based on licensed product information and other high-quality validated sources. This may optionally be followed by abstracts or referenced text expanding on particular points, and providing a lead-in to the published literature from which we derive our information.

Lists of single and multi-ingredient proprietary and non-proprietary preparations are given at the end of each monograph.

Nomenclature

The nomenclature section of each monograph may include the following information:

Titles and synonyms. The title of each monograph is in English, with preference usually being given to International Nonproprietary Names (INN), British Approved Names (BAN), and United States Adopted Names (USAN). These 3 authorities are shown where appropriate. A European Directive (92/27/EEC) requires the use of Recommended International Nonproprietary Names (rINNs) in the labelling of medicinal products throughout member states of the European Union and where the BAN and INN differed in the past the BAN has been changed to accord with the rINN. The major exception to this convention is the retention of the names adrenaline and noradrenaline, these being the terms used as the titles of the monographs in the European Pharmacopoeia and therefore the official names in the member states. In some approved names it is general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists should be sought in alternative spellings if the expected spellings are not found. Inevitably there may be some inconsistencies of style with older approved names but wherever possible the names used for drugs or radicals in Martindale have been altered in accordance with the guidelines on the use of INNs for pharmaceutical substances. For a table of contracted names for ions and groups used in approved names and titles see p. xii.

This section also includes names given as synonyms such as commonly used abbreviated names; Latin versions of the titles in the European Pharmacopoeia; English, American, Spanish, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. BAN names for substance combinations and United States Pharmacy Equivalent Names (PEN) for dosage forms containing two or more active ingredients are given in the text of the relevant monographs; these names start with the prefix 'Co-'.

Official titles and synonyms used in the British, European, and US Pharmacopoeias are given in the section on pharmacopoeias where the relevant pharmacopoeial substance is described.

Street Names. Street terms and other slang names for drugs of abuse are included for guidance only and should be used with caution. Because of the very nature of their origin they cannot be relied upon for definitive identification of a substance. The use of such terms changes rapidly, and can vary between different geographical locations, and any given name may potentially be applied to more than one substance or even to a mixture of substances. Furthermore, established or well recognised generic drug names or herbal names have sometimes been misused as street terms for completely unrelated substances. In order to enable the reader to distinguish them from the better validated synonyms in the index, such names are included in italics and in quotation marks.

CAS Registry numbers. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parentheses.

ATC codes. Codes from the Anatomical Therapeutic Chemical (ATC) classification system (see http://www.whocc.no) have been provided, where available, for each monograph substance to help readers refer to other information systems. The codes assigned in the equivalent classification system for veterinary medicines (ATC Vet–see http://www.whocc.no/atcvet) and herbal medicines have been included where possible.

UNII codes. The unique ingredient identifiers, which are generated by the joint FDA/USP Substance Registration System have been provided, where available. Numbers for various forms of the monograph or related substances are listed with the variation in form given in parentheses.

Atomic and molecular weights. Atomic weights are based on the table of Atomic Weights as revised in 2011 by the Commission on Isotopic Abundances and Atomic Weights, International Union of Pure and Applied Chemistry (IUPAC) and based on the ^{12}C scale (see p. xiv). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. A description of the substance and a summary of the pharmaceutical information that appears in the British, European, or US Pharmacopoeias is also included. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include *British, British Veterinary, Chinese, European, French, German, International, Italian, Japanese, Polish, Spanish, Swiss, United States* (including the *National Formulary*), and *Vietnamese*. The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale (see p. ix), which also includes details of the edition and/or supplement(s) consulted.

Several countries are parties to the Convention on the Elaboration of a European Pharmacopoeia. This means that they must adopt the standards of the European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom, the Former Yugoslav Republic of Macedonia, and the European Union. Hence the European Pharmacopoeia is cited in the drug monograph lists of pharmacopoeias rather than these individual national pharmacopoeias.

Official preparations, mainly from the current British, European, and US Pharmacopoeias, are listed at the end of drug monographs.

Pharmaceutical information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph.

Percentage strengths. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

Solubility. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15 degrees and 25 degrees. The information

usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

- very soluble: 1 in less than 1
- freely soluble: 1 in 1 to 1 in 10
- soluble: 1 in 10 to 1 in 30
- sparingly soluble: 1 in 30 to 1 in 100
- slightly soluble: 1 in 100 to 1 in 1000
- very slightly soluble: 1 in 1000 to 1 in 10,000
- practically insoluble: 1 in more than 10,000

Storage. Substances and preparations should be stored under conditions that prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. The term 'a cool place' is generally used to describe a place in which the temperature is between 8 degrees and 15 degrees. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

Temperature. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Drugs in Sport

Wherever possible we have attempted to indicate those drugs and substances that may be subject to restriction in some or all sports, either in their own right, or because they are a derivative of a restricted substance or a member of a prohibited group. Proprietary preparations containing such compounds are also marked in the preparation section. The guide used for identifying restricted drugs is the Prohibited List issued by the World Anti-Doping Agency (WADA–see www.wada-ama.org). These regulations, which are issued annually, are subject to interpretation and therapeutic exemption, and may vary from sport to sport; particular sporting authorities may also issue additional restrictions, and competitors should always check with the appropriate body. The rules are constantly evolving and the absence of any indication of restriction in Martindale should not be taken as absolute confirmation that the substance may legitimately be taken by a competitor.

Pharmacological and therapeutic information

Information on uses and administration, adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, and pharmacokinetics of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains nearly 14,000 such abstracts or reviews based on information in an ever widening range of publications.

An increasing amount of information is published digitally and this material is available on the Internet as web pages. Because of the nature of the Internet, there is no way to guarantee that the material referred to by a URL will remain at that location, as many sites are subject to periodic reorganisation; additionally, the content of Internet documents may change without warning. The accession date given in the citation represents the last date on which the content of the document referred to was revalidated.

Much information has been found in sources such as WHO publications, government reports and legislation, and other official and standard publications. Licensed product information and manufacturers' literature have been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the fetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Some drugs given to the mother are distributed into breast milk and therefore may pose a risk to a breast-fed infant. Whenever possible, information has been included to help determine the safety of continuing to breast feed while the mother is receiving a particular drug. Safety during breast feeding should not be inferred from the absence of a statement for any drug.

Doses. Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities that are generally regarded as suitable for adults when given orally. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v and sodium chloride injection is 0.9% w/v.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

The Preparations

This part of Martindale contains brief details of proprietary preparations available in a number of countries or regions and includes those supplied on prescription as well as those sold directly to the public. They are provided to help the reader identify preparations and to suggest their uses. Inclusion is not an endorsement of the activity of any ingredient, nor of the preparation's indications.

For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, the United Arab Emirates, UK, USA, and Venezuela. Generally, each entry consists of the proprietary name, the manufacturer or distributor and country, the active ingredients and a summary of the indications as given by the manufacturer. Where possible, entries from different countries but with the same name and active ingredients have been amalgamated for clarity. Instances where a preparation name has been used for preparations with significantly different ingredients have been highlighted. Such names may be for actively marketed preparations or for preparations that have been withdrawn from the market.

An entry may cover a range of dosage forms and strengths. Dosage forms are only specified when different forms have the same proprietary name but different active ingredients. Furthermore, this section is not intended as a guide to prescribing; where a preparation is to be supplied the dose should be appropriate for that preparation and that particular patient, and authoritative local sources should be consulted.

With the exception of homoeopathic preparations the names of the ingredients have been translated into English. Almost all the ingredients listed are described in the monographs in Drugs and Ancillary Substances, and readers are directed to an appropriate monograph by the page numbers provided after the ingredient.

Preparations that have been withdrawn from the market in the last few years or are no longer being actively marketed may be identified by the symbol †. These preparations are retained in Martindale since they may still be in circulation or their names may still be referred to in the literature and in practice. Readers should be aware that since this section was prepared other preparations are likely to have been withdrawn or introduced; also ingredients may change, as may indications.

The manufacturer's full name and contact details can be found in the Directory of Manufacturers.

Each preparation title is listed in the General Index. Where thought helpful, preparation titles have been listed at the end of the relevant monograph. However, it should be noted that the absence of such a list at the end of a monograph is no indication as to the availability of a substance as many drugs are marketed as generic or unbranded preparations.

Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, in Volume B.

ACE—angiotensin-converting enzyme.
ADHD—attention deficit hyperactivity disorder.
agg.—aggregate (in botanical names), including 2 or more species which resemble each other closely.
AIDS—acquired immunodeficiency syndrome.
a.m.—*ante meridiem*, 'before noon'.
ARC—AIDS-related complex.
Arg.—Argentina.
ATC—Anatomical Therapeutic Chemical classification.
AUC—area under the concentration-time curve.
Austral.—Australia.
AV—atrioventricular.
BAN—British Approved Name.
BANM—British Approved Name Modified.
Belg.—Belgium.
BMA—British Medical Association.
BMI—body mass index.
BNF—British National Formulary.
BNFC—British National Formulary for Children.
b.p.—boiling point.
BP—British Pharmacopoeia. Unless otherwise specified, BP references are to the 2014 edition.
BP(Vet)—British Pharmacopoeia (Veterinary) 2014.
BPC—British Pharmaceutical Codex.
Br.—British.
Braz.—Brazil.
Bulg.—Bulgaria.
BUN—Blood-urea-nitrogen.
°C—degrees Celsius (centigrade). Unless otherwise indicated in the text, temperatures are expressed in this thermometric scale.
Canad.—Canada.
CAPD—continuous ambulatory peritoneal dialysis.
CAS—Chemical Abstracts Service.
CCPD—continuous cycle peritoneal dialysis.
CDC—Centers for Disease Control and Prevention (USA) (formerly Centers for Disease Control).
Chin. P.—Chinese Pharmacopoeia 2005.
CHM—Commission on Human Medicines (UK).
CI—Colour Index.
CMV—cytomegalovirus.
CNS—central nervous system.
cP—centipoise(s).
CPMP—Committee on Proprietary Medicinal Products of the European Union.
cs—Czech.
CSF—cerebrospinal fluid.
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines).
cSt—centistokes.
Cz.—Czech Republic.
D & C—designation applied in USA to dyes permitted for use in drugs and cosmetics.
de—German.
d.c.—direct current.
DEFRA—Department for Environment, Food, and Rural Affairs (UK).
Denm.—Denmark.
DHSS—the former Department of Health and Social Security (UK).
dL—decilitre(s).
DNA—deoxyribonucleic acid.
DoH—Department of Health (UK).
DTF—Drug Tariff Formulary.
ECG—electrocardiogram.
ECT—electroconvulsive therapy.
Ecuad.—Ecuador.
ed.—editor(s) *or* edited by *or* edition.
EEC—European Economic Community, now the European Union.
EEG—electro-encephalogram.
e.g.—*exempli gratia* 'for example'.
el—Greek.
EMA/EMEA—European Medicines Agency.
ENL—erythema nodosum leprosum.
es—Spanish.
ESRD—end-stage renal disease.
et al.—*et alii*, 'and others': for three or more co-authors or co-workers.
et seq.—and what follows.
EU—European Union.
Eur. P.—see Ph. Eur.
Ext. D & C—designation applied in USA to dyes permitted for use in external drug and cosmetic preparations.
°F—degrees Fahrenheit.
FAC—Food Additives and Contaminants Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FAO—Food and Agriculture Organization of the United Nations.
FAO/WHO—Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FDA—Food and Drug Administration of USA.
FdAC—Food Advisory Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FD & C—designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FEV_1—forced expiratory volume in 1 second.
Fin.—Finland.
FIP—Fédération Internationale Pharmaceutique.
f.p.—freezing point.
FPA—Family Planning Association (UK).
fr—French.
Fr.—France.
Fr. P.—French Pharmacopoeia 1982 (Pharmacopée Francaise, Xe Edition) and updates up to 2003.
g—gram(s).
Ger.—Germany.
Ger. P.— German Pharmacopoeia (Deutsches Arzneibuch, 2007).
GFR—glomerular filtration rate.
G6PD—glucose-6-phosphate dehydrogenase.
Gr.—Greece.
HAART—highly active antiretroviral therapy.

Hb— haemoglobin.
Hib—*Haemophilus influenzae* type b.
HIV—human immunodeficiency virus.
HLA—human lymphocyte antigens.
HLB—hydrophilic-lipophilic balance.
HRT—hormone replacement therapy.
HSE—Health and Safety Executive (UK).
hu—Hungarian.
Hung.—Hungary.
IARC—International Agency for Research on Cancer.
ibid.—*ibidem*, 'in the same place (journal or book)'.
idem—'the same': used for the same authors and titles.
i.e.—*id est*, 'that is'.
Ig—immunoglobulin.
Indon.—Indonesia.
INN—International Nonproprietary Name.
INNM—International Nonproprietary Name Modified.
Int. P.—International Pharmacopoeia 4th ed., 2006, and Supplement 1, 2008.
IPCS—International Programme on Chemical Safety.
IQ—intelligence quotient.
Irl.—Ireland.
ISH—International Society of Hypertension.
it—Italian.
It. P.—Italian Pharmacopoeia 11th ed., 2002 (Farmacopea Ufficiale della Repubblica Italiana, XI Edizione, 2002).
Ital.—Italy.
IUD—intra-uterine device.
IUPAC—International Union of Pure and Applied Chemistry.
IVF—*in-vitro* fertilisation.
J—joule(s).
Jpn—Japan.
Jpn P.—The Pharmacopoeia of Japan, 15th ed., 2006 and Supplement 1.
K—kelvin.
kcal—kilocalorie(s).
kg—kilogram(s).
kJ—kilojoule(s).
lb—pound(s) avoirdupois.
LD50—a dose lethal to 50% of the specified animals or micro-organisms.
Lf—limes flocculation.
lt—Lithuanian.
m—metre(s).
m^2—square metre(s).
m^3—cubic metre(s).
M—molar.
MAFF—the former Ministry of Agriculture, Fisheries and Food (UK), now Department of Environment, Food, and Rural Affairs (DEFRA).
MAOI—monoamine oxidase inhibitor.
max.—maximum.
MBC—minimum bactericidal concentration.
MCA—Medicines Control Agency, now MHRA (UK).
mEq—milliequivalent(s).
Mex.—Mexico.
mg—milligram(s).
MHRA—Medicines and Healthcare products Regulatory Agency (UK).
MIC—minimum inhibitory concentration.
min—minute.
min.—minimum.
MJ—megajoule(s).
mL—millilitre(s).
mm—millimetre(s).
mm^2—square millimetre(s).
mm^3—cubic millimetre(s).
mmHg—millimetre(s) of mercury.
mmol—millimole.
mol—mole.
mol. wt—molecular weight.
Mon.—Monaco.
mosmol—milliosmole.
m.p.—melting point.
MRC—Medical Research Council (UK).
MRSA—meticillin-resistant *Staphylococcus aureus*.
μg—microgram(s).
μm—micrometre(s).
N—normal.
n.b.—*nota bene*, note carefully.
Neth.—The Netherlands.
NICE—National Institute for Health and Clinical Excellence (formerly the National Institute for Clinical Excellence) (UK).
NIH—National Institutes of Health (USA).
nl—Dutch.
nm—nanometre(s).
NMDA—*N*-methyl-D-aspartate.
NNRTI—non-nucleoside reverse transcriptase inhibitor.
Norw.—Norway.
NRTI—nucleoside reverse transcriptase inhibitor.
NSAID—nonsteroidal anti-inflammatory drug.
NYHA—New York Heart Association.
NZ—New Zealand.
OP—over proof.
o/w—oil-in-water.
P—probability.
Pa—pascal(s).
Pak.—Pakistan.
pCO_2—plasma partial pressure (concentration) of carbon dioxide.
p_aCO_2—arterial plasma partial pressure (concentration) of carbon dioxide.
PEN—Pharmacy Equivalent Name, see page vi.
pg—picogram(s).
pH—the negative logarithm of the hydrogen ion concentration.
Ph. Eur.—European Pharmacopoeia, 8th ed., 2014.
Pharm. Soc. Lab. Rep.—Royal Pharmaceutical Society's Laboratory Report.
Philipp.—Philippines.
PHLS—Public Health Laboratory Service (UK).
pINN—Proposed International Nonproprietary Name.
pINNM—Proposed International Nonproprietary Name Modified.
pK_a—the negative logarithm of the dissociation constant.
pl—Polish.
p.m.—*post meridiem*, 'afternoon'.
pO_2—plasma partial pressure (concentration) of oxygen.
p_aO_2—arterial plasma partial pressure (concentration) of oxygen.
Pol.—Poland.
Pol. P.—Polish Pharmacopoeia 6th ed., 2002 (Farmakopea Polska VI, 2002) and Supplement 2005.
Port.—Portugal.
ppm—parts per million.
PSGB—The Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society.

pt—Portuguese.
PUVA—psoralen with UVA light irradiation.
PVC—polyvinyl chloride.
RCGP—Royal College of General Practitioners (UK).
RIMA—reversible inhibitor of monoamine oxidase type A.
rINN—Recommended International Nonproprietary Name.
rINNM—Recommended International Nonproprietary Name Modified.
RNA—ribonucleic acid.
RPSGB—The Royal Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society
RSV—respiratory syncytial virus.
Rus.—Russia.
S. Afr.—South Africa.
SGOT—serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase *now preferred*).
SGPT—serum glutamic pyruvic transaminase (serum alanine aminotransferase *now preferred*).
SI—Statutory Instrument *or* Système International d'Unités (International System of Units).
sic—written exactly as it appears in the original.
SLE—systemic lupus erythematosus.
sp.—species (plural spp.).
sp. gr.—specific gravity.
Span.—Spanish.
Span. P.—Spanish Pharmacopoeia 2nd ed., 2002 (Real Farmacopoea Española, Segunda Edición, 2002) and Supplement 2.1.
SSRI—selective serotonin reuptake inhibitor.
St—stokes.
subsp.—subspecies.
suppl—supplement(s).
sv—Swedish.
Swed.—Sweden.
Swiss P.—Swiss Pharmacopoeia 2006 (Pharmacopoea Helvetica, 10 Ausgabe, Deutsche Ausgabe).
Switz.—Switzerland.
Thai.—Thailand.
TNF—tumour necrosis factor.
THM—traditional herbal medicine.
THMP—traditional herbal medicinal product.
TPN—total parenteral nutrition.
Turk.—Turkey.
UAE—United Arab Emirates.
UK—United Kingdom.
Ukr.—Ukraine.
UNICEF—United Nations Children's Fund.
UP—under proof.
Urug.—Uruguay.
US and ***USA***—United States of America.
USAN—United States Adopted Name.
USNF—The United States 'National Formulary 31', 2013.
USP—The United States Pharmacopeia 36, 2013.
UV—ultraviolet.
var.—variety.
Venez.—Venezuela.
Viet.—Vietnamese.
Viet. P.—Vietnamese Pharmacopoeia 2002 (Pharmacopoeia Vietnamica, Editio III).
vol.—volume(s).
v/v—volume in volume.
v/w—volume in weight.
WHO—World Health Organization.
w/o—water-in-oil.
wt—weight.
wt per mL—weight per millilitre.
w/v—weight in volume.
w/w—weight in weight.

Contracted Names for Ions and Groups

Contracted Name	Chemical Name
acefurate	acetate (ester) and furan-2-carboxylate (ester)
aceglumate	*rac*-hydrogen *N*-acetylglutmate
aceponate	acetate (ester) and propionate (ester)
acetonide	isopropylidenedioxy or propane-2,2-diylbis(oxy)
aceturate	*N*-acetylglycinate
acibutate	acetate (ester) and 2-methylpropanoate (ester)
acistrate	acetate (ester) and stearate (salt)
acoxil	acetoxymethyl or (acetyloxy)methyl
alfoscerate	(2*R*)-2,3-dihydroxypropyl hydrogen phosphate
alideximer	poly([oxy(2-hydroxyethane-1,1-diyl)]{oxy[1-(hydroxymethyl)ethane-1,2-diyl]}) partly *O*-etherified with carboxymethyl groups with some carboxy groups amide linked to the tetrapeptide residue (glyglyglycyl-L-phenylalanylglycyl)
amsonate	4,4′-diaminostilbene-2,2′-disulfonate or 2,2′-ethene-1,2-diylbis(5-aminobenzene-1-sulfonate)
anisatil	2-(4-methoxyphenyl)-2-oxoethyl or *p*-methoxyphenacyl
arbamel	2-(dimethylamino)-2-oxoethyl or ester with *N,N*-dimethylglycolamide
argine	30^{B}α-L-argine-30^{B}β-L-argine
aritox	ricin A chain-MAB immunotoxine
aspart	28^{B}-L-aspartic acid-
axetil	(*RS*)-1-acetoxyethyl or *rac*-1-(acetyloxy)ethyl
beloxil	benzyloxy
benetonide	*N*-benzoyl-2-methyl-β-alanine (ester) and acetonide
besilate (besylate)	benzenesulfonate
betadex	β-cyclodextrin
bezomil	(benzoyloxy)methyl
buciclate	*trans*-4-butylcyclohexanecarboxylate
bunapsilate	3,7-di-*tert*-butylnaphthalene-1,5-disulfonate
buteprate	butyrate (ester) and propionate (ester)
camsilate (camsylate)	camphor-10-sulfonate or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate
caproate	hexanoate
carbesilate	4-sulfobenzoate
ciclotate (cyclotate)	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate
cilexetil	(*RS*)-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl or *rac*-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl
cipionate (cypionate)	cyclopentanepropionate or 3-cyclopentylpropanoate
cituxetan	*rac*-*N*-(4-{2-[bis(carboxymethyl)amino]-3-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)propyl}phenyl)thiocarbamoyl
clofibrol	2-(4-chlorophenoxy)-2-methylpropyl
closilate (closylate)	4-chlorobenzene-1-sulfonate
crobefate	*rac*-{3-[(3*E*)-4-methoxybenzylidene]-2-(4-methoxyphenyl)chroman-6-yl phosphate(2-)}
cromacate	2-[(6-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate
cromesilate	6,7-dihydroxycoumarin-4-methanesulfonate or (6,7-dihydroxy-2-oxo-2*H*-chromen-4-yl)methanesulfonate

Contracted Name	Chemical Name
crosfumaril	(2*E*)-but-2-enedioyl
cyclamate	cyclohexylsulfamate
daloxate	L-alaninate (ester) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
daropate (dapropate)	*N,N*-dimethyl-β-alaninate or 3-(dimethylamino)propanoate
deanil	2-(dimethylamino)ethyl
decil	decyl
defalan	des-1^{B}-L-phenylalanine-insulin
detemir	tetradecanoyl
dibudinate	2,6-di-*tert*-butylnaphthalene-1,5-disulfonate
dibunate	2,6-di-*tert*-butylnaphthalene-1-sulfonate
dicibate	dicyclohexylmethyl carbonate
diftitox	*N*-L-methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diphtheriae* strain C7) (388→2′)-protein
digolil	2-(2-hydroxyethoxy)ethyl
diolamine	2,2′-azanediyldiethanol or diethanolamine
docosil	docosyl
dofosfate	octadecyl hydrogen phosphate
ecamate	*N*-ethylcarbamate
edamine	ethane-1,2-diamine or ethylenediamine
edetate	ethylenediamine-*NNN′N′*-tetra-acetate
edisilate (edisylate)	ethane-1,2-disulfonate
embonate	4,4′-methylenebis(3-hydroxynaphthalene-2-carboxylate) or 4,4′-methylenebis(3-hydroxy-2-naphthoate) (=pamoate)
emtansine	4-({3-[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,-20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-2-oxoethyl]methylamino}-3-oxopropyl)sulfanyl]-2,5-dioxopyrrolidin-1-yl}methyl)cyclohexylcarbonyle
enantate (enanthate)	heptanoate
enbutate	acetate (ester) and butanoate (ester)
epolamine	1-pyrrolidineethanol or 2-(pyrrolidin-1-yl)ethanol
erbumine	*tert*-butylamine or 2-methylpropan-2-amine
esilate (esylate)	ethanesulfonate
estolate	propanoate (ester) and dodecyl sulfate (salt) or propionate dodecyl sulfate
etabonate	(ethoxycarbonyl)oxy (=ethyl carbonate)
etilsulfate	ethyl sulfate
farnesil	(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl
fendizoate	2-(6-hydroxybiphenyl-3-carbonyl)benzoate
fostedate	tetradecyl hydrogen phosphate
furetonide	1-benzofurane-2-carboxylate (ester) and propane-2,2-diylbis(oxy)
gamolenate	(6*Z*,9*Z*,12*Z*)-octadeca-6,9,12-trienoate
glargine	21^{A}-glycine-30^{B}α-L-arginine-30^{B}β-L-arginine
gluceptate	D-*glycero*-D-*gulo*-heptanoate or D-*glycero*-D-*gulo*-heptonate
glulisine	[3^{B}-L-lysine,29^{B}-L-glutamic acid]

Contracted Name	Chemical Name
glutamer	glutaraldehyde polymer
guacil	2-methoxyphenyl
hemisuccinate	hydrogen butanedioate
hexacetonide	3,3-dimethylbutanoate (ester) and propan-2,2-diylbis(oxy) or 3,3-dimethylbutyrate (ester) and acetonide
hibenzate (hybenzate)	2-(4-hydroxybenzoyl)benzoate
hyclate	monohydrochloride hemi-ethanolate hemihydrate
hydroxynaphtoate	3-hydroxynapthalene-2-carboxylate
isetionate (isethionate)	2-hydroxyethane-1-sulfonate
laurate	dodecanoate
lauril	dodecyl
laurilsulfate (lauryl sulphate)	dodecyl sulfate
lisetil	L-lysinate (ester) and diethyl (ester)
lisicol	{*N*-[(5*S*)-5-carboxy-5-(3α,7α,12α-trihydroxy-5β-cholan-24-amido)pentyl]carbamothioyl}amino
lispro	28^{B}-L-lysine-29^{B}-L-proline
mafenatox	enterotoxin A (227-alanine) (*Staphylococcus aureus*)
medoxomil	(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
megallate	3,4,5-trimethoxybenzoate
meglumine	*N*-methylglucamine
merpentan	4,5-bis(2-mercaptoacetamido) valeric acid or {*N*,*N*′-[1-(3-oxopropyl)ethane-1,2-diyl]bis(2-sulfanylacetamidato)}(4-)
mertansine	tetrakis{(4*RS*)-4[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-oxoethyl]methylamino}-3-oxopropyl)disulfanyl]pentanoyl}
mesilate (mesylate)	methanesulfonate
metembonate	4,4′-methylenebis(3-methoxynaphthalene-2-carboxylate)
methonitrate	*N*-methyl, nitrate (salt)
metilsulfate	methyl sulfate
metiodide	*N*-methyl, iodide (salt)
methylbromide	*N*-methyl, bromide (salt)
mofetil	2-(morpholino)ethyl or 2-(morpholin-4-yl)ethyl
napadisilate	naphthalene-1,5-disulfonate
napsilate (napsylate)	naphthalene-2-sulfonate
nicotinate	pyridine-3-carboxylate
octil	octyl
olamine	2-aminoethanol or ethanolamine
oleate	(9*Z*)-octadec-9-enoate
oxoglurate	hydrogen 2-oxopentanedioate
palmitate	hexadecanoate
pamoate	4,4′-methylenebis(3-hydroxy-2-naphthoate) (=embonate)
pegol	α-(2-carboxyethyl)-ω-methoxypoly(oxyethane-1,2-diyl)
pendetide	N^{6}-{*N*-[2-({2-[bis(carboxymethyl)amino]-ethyl}(carboxymethyl)amino)ethyl]-*N*-(carboxymethyl)glycyl}-N^{2}-(*N*-glycyl-L-tyrosyl)-L-lysine
pentexil	(*RS*)-1-[(2,2-dimethylpropanoyl)oxy]ethyl
phenpropionate	3-phenylpropionate
pivalate	2,2-dimethylpropanoate (ester) or trimethylacetate
pivoxetil	*rac*-1-[(2-methoxy-2-methylpropanoyl)oxy]ethyl or 1-(2-methoxy-2-methylpropionyloxy)ethyl
pivoxil	(2,2-dimethyl-1-oxopropoxy)methyl or [(2,2-dimethylpropanoyl)oxy]methyl or (pivaloyloxy)methyl
poliglumex	[poly(L-glutamic acid)$_{z}$—(L-glutamate-γ-ester)—poly(L-glutamic acid)$_{y}$]$_{n}$
probutate	17-(1-oxobutoxy) (ester) and 21-(1-oxopropoxy) (ester) or propionate (ester) and butyrate (ester)
proxetil	1-[(isopropoxycarbonyl)oxy]ethyl or *rac*-1-{[(propan-2-yloxy)carbonyl]oxy}ethyl
raffimer	(2*S*,4*R*,6*R*,8*S*,11*S*,13*S*)-2,4,8,13-tetrakis(hydroxymethyl)-4,6,11-tris(ylomethyl)-3,5,7,10,12-pentaoxatetradecane-1,14-diyl
salicylate	2-hydroxybenzoate
sesquioleate	(9*Z*)-octadec-9-enoate(1.5)
soproxil	{[(propan-2-yloxy)carbonyl]oxy}methyl
steaglate	2-(octadecanoyloxy)acetate (ester)
stearate	octadecanoate
stinoprate	*N*-acetylcysteinate (salt) and propanoate (ester)
succinil	3-carboxypropanoyl
sudotox	248-L-histidine-249-L-methionine-250-L-alanine-251-L-glutamic acid-248-613-endotoxin A (*Pseudomonas aeruginosa* reduced)
suleptanate	monosodium 8-[methyl(2-sulfoethyl)amino]-8-oxooctanoate or monosodium 7-[methyl(2-sulfonatomethyl)carbamoyl]heptanoyl
sulfoxylate	sulfinomethyl, monosodium salt
tafenatox	enterotoxin A (*Staphylococcus aureus*)
tartrate	(2*R*,3*R*)-2,3-dihydroxybutanedioate
tebutate	*tert*-butylacetate or 3,3-dimethylbutyrate
tenoate	thiophene-2-carboxylate
teoclate	8-chloro-1,3-dimethyl-2,6-dioxo-3,6-dihydro-1*H*-purin-7-(2*H*)-ide or 8-chlorotheophyllinate
teprosilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propane-1-sulfonate
tidoxil	*rac*-2-(decyloxy)-3-(dodecylsulfanyl)propyl
tiuxetan	*N*-(4-{(2*S*)-2-[bis(carboxymethyl)amino]-3-[(2*RS*)-{2-[bis(carboxymethyl)amino]propyl}(carboxymethyl)amino]propyl}phenyl)thiocarbamoyl
tocoferil	*rac*-(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]chroman-6-yl
tofesilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)ethane-1-sulfonate
tosilate (tosylate)	4-methylbenzene-1-sulfonate or toluene-4-sulfonate
triclofenate	2,4,5-trichlorophenolate
triflutate	trifluoroacetate
trioleate	(9*Z*)-octadec-9-enoate(3) or tris[(9*Z*)-octadec-9-enoate]
tristearate	octadecanoate(3) or tris(octadecanoate)
trolamine	2,2′,2″-nitrilotriethanol or triethanolamine
troxundate	[2-(2-ethoxyethoxy)ethoxy]acetate or 3,6,9-trioxaundecanoate
undecylate	undecanoate
undecylenate	undec-10-enoate
valerate	pentanoate
xinafoate	1-hydroxynaphthalene-2-carboxylate or 1-hydroxy-2-naphthoate

Atomic Weights of the Elements—$^{12}C=12$

Atomic Number	Name	Symbol	Atomic Weight
89	Actinium[1]	Ac	
13	Aluminium	Al	26.9815386
95	Americium[1]	Am	
51	Antimony	Sb	121.760
18	Argon	Ar	39.948
33	Arsenic	As	74.92160
85	Astatine[1]	At	
56	Barium	Ba	137.327
97	Berkelium[1]	Bk	
4	Beryllium	Be	9.012182
83	Bismuth[2]	Bi	208.98040
107	Bohrium[1]	Bh	
5	Boron[3]	B	10.81
35	Bromine[3]	Br	79.904
48	Cadmium	Cd	112.411
55	Caesium	Cs	132.9054519
20	Calcium	Ca	40.078
98	Californium[1]	Cf	
6	Carbon[3]	C	12.011
58	Cerium	Ce	140.116
17	Chlorine[3]	Cl	35.45
24	Chromium	Cr	51.9961
27	Cobalt	Co	58.933195
112	Copernicium[1]	Cn	
29	Copper	Cu	63.546
96	Curium[1]	Cm	
110	Darmstadtium[1]	Ds	
105	Dubnium[1]	Db	
66	Dysprosium	Dy	162.500
99	Einsteinium[1]	Es	
68	Erbium	Er	167.259
63	Europium	Eu	151.964
100	Fermium[1]	Fm	
114	Flerovium[1]	Fl	
9	Fluorine	F	18.9984032
87	Francium[1]	Fr	
64	Gadolinium	Gd	157.25
31	Gallium	Ga	69.723
32	Germanium	Ge	72.630
79	Gold	Au	196.966569
72	Hafnium	Hf	178.49
108	Hassium[1]	Hs	
2	Helium	He	4.002602
67	Holmium	Ho	164.93032
1	Hydrogen[3]	H	1.008
49	Indium	In	114.818
53	Iodine	I	126.90447
77	Iridium	Ir	192.217
26	Iron	Fe	55.845
36	Krypton	Kr	83.798
57	Lanthanum	La	138.90547
103	Lawrencium[1]	Lr	
82	Lead	Pb	207.2
3	Lithium[3]	Li	6.94
116	Livermorium[1]	Lv	
71	Lutetium	Lu	174.9668
12	Magnesium[3]	Mg	24.305
25	Manganese	Mn	54.938045
109	Meitnerium[1]	Mt	
101	Mendelevium[1]	Md	
80	Mercury	Hg	200.592
42	Molybdenum	Mo	95.96
60	Neodymium	Nd	144.242
10	Neon	Ne	20.1797
93	Neptunium[1]	Np	
28	Nickel	Ni	58.6934
41	Niobium	Nb	92.90638
7	Nitrogen[3]	N	14.007
102	Nobelium[1]	No	
76	Osmium	Os	190.23
8	Oxygen[3]	O	15.999
46	Palladium	Pd	106.42
15	Phosphorus	P	30.973762
78	Platinum	Pt	195.084
94	Plutonium[1]	Pu	
84	Polonium[1]	Po	
19	Potassium	K	39.0983
59	Praseodymium	Pr	140.90765
61	Promethium[1]	Pm	
91	Protactinium[2]	Pa	231.03588
88	Radium[1]	Ra	
86	Radon[1]	Rn	
75	Rhenium	Re	186.207
45	Rhodium	Rh	102.90550
111	Roentgenium[1]	Rg	
37	Rubidium	Rb	85.4678
44	Ruthenium	Ru	101.07
104	Rutherfordium[1]	Rf	
62	Samarium	Sm	150.36
21	Scandium	Sc	44.955912
106	Seaborgium[1]	Sg	
34	Selenium	Se	78.96
14	Silicon[3]	Si	28.085
47	Silver	Ag	107.8682
11	Sodium	Na	22.98976928
38	Strontium	Sr	87.62
16	Sulfur[3]	S	32.06
73	Tantalum	Ta	180.94788
43	Technetium[1]	Tc	
52	Tellurium	Te	127.60
65	Terbium	Tb	158.92535
81	Thallium[3]	Tl	204.38
90	Thorium[2]	Th	232.03806
69	Thulium	Tm	168.93421
50	Tin	Sn	118.710
22	Titanium	Ti	47.867
74	Tungsten	W	183.84
118	Ununoctium[1]	Uuo	
115	Ununpentium[1]	Uup	
117	Ununseptium[1]	Uus	
113	Ununtrium[1]	Uut	
92	Uranium[2]	U	238.02891
23	Vanadium	V	50.9415
54	Xenon	Xe	131.293
70	Ytterbium	Yb	173.054
39	Yttrium	Y	88.90585
30	Zinc	Zn	65.38
40	Zirconium	Zr	91.224

1. Elements with no stable isotopes. IUPAC states "There is no general agreement on which of the isotopes of radioactive elements is, or is likely to be judged, 'important'. Various criteria, such as 'longest half-life', 'production in quantity', and 'used commercially', have been applied in the past."

2. Radioactive elements with a characteristic terrestrial isotopic composition for which atomic weights are given.

3. Conventional atomic-weight value. These have been provided as representative values for elements that have a variation in atomic weight related to two or more stable isotopes in natural terrestrial occurrences.

IUPAC Commission on Isotopic Abundances and Atomic Weights. Atomic Weights of the Elements 2011. Available at http://www.chem.qmul.ac.uk/iupac/AtWt/

Analgesics Anti-inflammatory Drugs and Antipyretics

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The drugs described in this chapter are used mainly in the relief of pain, inflammation and, in some cases, fever. They can be grouped broadly into one of the categories briefly described below.

Drug Groups

Aspirin and other salicylates

Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties. Like other NSAIDs (see below) they are inhibitors of the enzyme cyclo-oxygenase; however, aspirin (though not the non-acetylated salicylates) irreversibly acetylates the enzyme whereas other NSAIDs compete with arachidonic acid for the active site. Salicylates are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Some salicylates are applied topically in rubefacient preparations for the relief of muscular and rheumatic pain. Aspirin also inhibits platelet aggregation and is used in cardiovascular disorders. Non-acetylated salicylates do not have antiplatelet activity.

For further discussion of the actions and uses of salicylates, see Aspirin, p. 22.2.

Described in this chapter are

Aloxiprin, p. 20.3
Aluminium Aspirin, p. 20.3
Ammonium Salicylate, p. 21.1
Amyl Salicylate, p. 21.2
Aspirin, p. 22.2
Bornyl Salicylate, p. 30.1
Carbasalate Calcium, p. 36.2
Choline Magnesium Trisalicylate, p. 39.2
Choline Salicylate, p. 39.2
Diethylamine Salicylate, p. 51.3
Diflunisal, p. 51.3
Ethenzamide, p. 56.2
Ethyl Salicylate, p. 56.3
Glycol Salicylate, p. 66.2
Imidazole Salicylate, p. 71.2
Lysine Aspirin, p. 84.3
Magnesium Salicylate, p. 85.2
Methyl Butetisalicylate, p. 91.3
Methyl Salicylate, p. 92.1
Morpholine Salicylate, p. 97.1
Salamidacetic Acid, p. 129.2
Salicylamide, p. 129.2
Salix, p. 129.2
Salol, p. 129.3
Salsalate, p. 130.1
Sodium Salicylate, p. 132.2
Thurfyl Salicylate, p. 137.1
Trolamine Salicylate, p. 141.2

Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory properties thought to be mediated, in some cases, by the inhibition of the release or activity of cytokines. They are used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis; some are also of benefit in ankylosing spondylitis and psoriatic arthritis. Many DMARDs also possess other therapeutic properties and are used in non-rheumatic conditions. The DMARD gold is referred to below; other DMARDs include sulfasalazine (p. 1893.1), penicillamine (p. 1567.1), the antimalarials chloroquine (p. 650.1) and hydroxychloroquine (p. 655.2), the monoclonal antibody rituximab (p. 852.1), and the immunosuppressants azathioprine (p. 1944.3), ciclosporin (p. 1949.2), cyclophosphamide (p. 771.1), and methotrexate (p. 822.2).

Described in this chapter are

Abatacept, p. 15.2
Actarit, p. 17.1
Adalimumab, p. 17.2
Anakinra, p. 21.2
Certolizumab, p. 39.1
Etanercept, p. 55.1
Golimumab, p. 66.3
Infliximab, p. 74.2
Leflunomide, p. 81.3
Tocilizumab, p. 77.3
Tofacitinib, p. 138.1

Gold compounds

Gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. The mechanism of action of gold compounds in rheumatic disorders is as yet unknown.

For further discussion of the actions and uses of gold compounds, see Sodium Aurothiomalate, p. 130.2.

Described in this chapter are

Auranofin, p. 27.3
Aurothioglucose, p. 28.2
Aurotioprol, p. 28.2
Gold Keratinate, p. 66.3
Sodium Aurothiomalate, p. 130.2
Sodium Aurotiosulfate, p. 132.1

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of structurally unrelated organic acids that have analgesic, anti-inflammatory, and antipyretic properties (see p. 102.3). NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and so directly inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p. 2598.1). There are 2 forms of cyclo-oxygenase (COX), COX-1, which is the constitutive form of the enzyme, and COX-2, which is the form induced in the presence of inflammation. Inhibition of COX-2 is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory, and antipyretic properties of NSAIDs whereas inhibition of COX-1 is thought to produce some of their toxic effects, particularly those on the gastrointestinal tract. Most NSAIDs available for clinical use inhibit both COX-1 and COX-2, although some selective COX-2 inhibitors such as celecoxib are also marketed.

NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Indometacin and some other NSAIDs are used to close patent ductus arteriosus in premature neonates. Some NSAIDs are applied topically for the relief of muscular and rheumatic pain, and some are used in ophthalmic preparations for ocular inflammatory disorders. Aspirin (see above) is considered to be an NSAID, although it also has other properties.

Described in this chapter are

Aceclofenac, p. 16.2
Acemetacin, p. 16.3
Alminoprofen, p. 20.2
Aminophenazone, p. 21.1
Ampiroxicam, p. 21.1
Amtolmetin Guacil, p. 21.1
Azapropazone, p. 28.3
Bendazac, p. 29.1
Benzydamine, p. 29.2
Beta-aminopropionitrile, p. 30.1
Bromfenac, p. 30.1
Bufexamac, p. 30.2
Bumadizone, p. 30.2
Carprofen, p. 36.3
Celecoxib, p. 36.3
Clofexamide, p. 40.1
Clofezone, p. 40.1
Clonixin, p. 40.1
Dexibuprofen, p. 43.1
Dexketoprofen, p. 79.1
Diclofenac, p. 48.3
Dipyrone, p. 53.3
Eltenac, p. 54.2
Epirizole, p. 54.3
Etodolac, p. 57.1
Etofenamate, p. 57.2
Etoricoxib, p. 57.3
Felbinac, p. 58.3
Fenbufen, p. 59.1
Fenoprofen, p. 59.2
Fentiazac, p. 64.2
Fepradinol, p. 64.2
Feprazone, p. 64.3
Firocoxib, p. 64.3
Floctafenine, p. 64.3
Flufenamic Acid, p. 65.1
Flunixin, p. 65.1
Flurbiprofen, p. 65.2
Glucametacin, p. 66.2
Ibuprofen, p. 68.2
Indometacin, p. 71.2
Isonixin, p. 78.3
Kebuzone, p. 78.3
Ketoprofen, p. 79.1
Ketorolac, p. 80.2
Licofelone, p. 83.2
Lornoxicam, p. 83.2
Loxoprofen, p. 83.3
Lumiracoxib, p. 84.1
Meclofenamic acid, p. 85.2
Mefenamic Acid, p. 85.3
Meloxicam, p. 86.3
Mofezolac, p. 92.2
Morniflumate, p. 92.2
Nabumetone, p. 97.1
Naproxen, p. 98.2
Nepafenac, p. 101.1
Niflumic Acid, p. 101.2
Nimesulide, p. 101.3
Oxaprozin, p. 112.3
Oxyphenbutazone, p. 114.3
Parecoxib, p. 119.3
Phenazone, p. 124.1
Phenylbutazone, p. 125.1
Piketoprofen, p. 125.3
Piroxicam, p. 125.3
Pranoprofen, p. 127.1
Proglumetacin, p. 127.1
Propyphenazone, p. 127.3
Proquazone, p. 128.1
Rofecoxib, p. 128.3
Sulindac, p. 134.2
Suprofen, p. 135.3
Suxibuzone, p. 136.1
Tenoxicam, p. 136.2
Tepoxalin, p. 137.1
Tetridamine, p. 137.1
Tiaprofenic Acid, p. 137.1
Tiaramide, p. 137.3
Tinoridine, p. 138.1
Tolfenamic Acid, p. 138.3
Tolmetin, p. 139.1
Valdecoxib, p. 141.3
Vedaprofen, p. 142.1
Zaltoprofen, p. 142.2

Opioid analgesics

Opioid analgesics include the opium alkaloids morphine and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist and antagonist activity at opioid receptors (see p. 108.1). The term opiate analgesics refers only to those opioids derived from opium, or their semisynthetic congeners. The term narcotic analgesics has legal connotations and is no longer used pharmacologically or clinically.

Most opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Opioids such as codeine are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. More potent opioids such as morphine are used in severe acute and chronic pain, including cancer pain. Some opioids such as codeine, morphine, and diamorphine are also used as antitussives, although the latter two are usually reserved for use in terminal lung disease. Some opioid analgesics such as fentanyl and its congeners are used mainly as adjuncts to anaesthesia; some of these may also be used in higher doses as the sole anaesthetic drug.

Some opioids are rarely if ever used as analgesics and are described elsewhere; they include the antitussives dextromethorphan (p. 1660.1) and pholcodine (p. 1675.1), and the antidiarrhoeals diphenoxylate (p. 1838.3) and loperamide (p. 1857.2).

Opioids can produce physical dependence and withdrawal symptoms if suddenly stopped. They are also subject to abuse.

Described in this chapter are

Alfentanil, p. 18.2
Anileridine, p. 22.2
Buprenorphine, p. 30.2
Butorphanol, p. 33.2
Carfentanil, p. 36.2
Codeine, p. 40.2
Dextromoramide, p. 43.2
Dextropropoxyphene, p. 43.2
Dezocine, p. 45.2
Diamorphine, p. 46.1
Dihydrocodeine, p. 52.2
Dipipanone, p. 53.2
Embutramide, p. 54.2
Ethoheptazine, p. 56.2
Ethylmorphine, p. 56.3
Etorphine, p. 58.3
Fentanyl, p. 60.1
Hydrochlorides of Mixed Opium Alkaloids, p. 112.2
Hydrocodone, p. 67.2
Hydromorphone, p. 67.3
Ketobemidone, p. 78.3
Levacetylmethadol, p. 83.1
Levomethadone, p. 83.1
Levorphanol, p. 83.2
Meptazinol, p. 87.3
Methadone, p. 88.3
Morphine, p. 92.3
Nalbuphine, p. 97.3
Nicomorphine, p. 101.1

Opium, p. 111.3
Oxycodone, p. 113.1
Oxymorphone, p. 114.2
Papaveretum, p. 112.2
Pentazocine, p. 120.3
Pethidine, p. 121.3
Piritramide, p. 125.3
Remifentanil, p. 128.1
Sufentanil, p. 132.3
Tapentadol, p. 136.1
Tilidine, p. 137.3
Tramadol, p. 139.2
Trimeperidine, p. 141.2

Paracetamol and other para-aminophenols

Paracetamol is the principal para-aminophenol derivative in use. Acetanilide and phenacetin have generally been replaced by safer analgesics. Propacetamol is hydrolysed to paracetamol in the plasma.

Paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity. The mechanism of analgesic action remains to be fully elucidated, but may be due to inhibition of prostaglandin synthesis both centrally and peripherally. Paracetamol is used for the relief of mild to moderate pain and minor febrile conditions.

Described in this chapter are

Acetanilide, p. 17.1
Paracetamol, p. 115.1
Phenacetin, p. 124.1
Propacetamol, p. 127.2

Analgesia and Pain

Pain is defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

Under normal circumstances pain is the result of stimulation of peripheral receptors that transmit impulses through pain pathways to the brain. Pain receptors or nociceptors are of two basic types:

- *mechanoheat receptors* have a high stimulation threshold and respond to intense or potentially damaging noxious stimuli. These receptors are associated with rapidly conducting, thinly myelinated A δ fibres, and their stimulation produces rapid sharp localised pain that serves to activate withdrawal reflexes
- *polymodal nociceptors* respond to mechanical, thermal, or chemical insults. These receptors are also activated by cellular components that are released after tissue damage. Their impulses are transmitted slowly along unmyelinated C type fibres and produce dull, aching, and poorly localised pain with a slower onset

Nerve fibres from nociceptors terminate in the dorsal root of the spinal cord before transmission by ascending pathways to the brain. There have been many theories on the processing of pain signals at the spinal level but the 'gate theory' proposed by Melzack and Wall is one of the best known. This theory postulates that the transmission of impulses to the brain is modulated by a gate mechanism in the substantia gelatinosa. Stimulation of small fibres opens the gate and facilitates transmission whereas stimulation of large fibres, which normally carry non-painful sensory input, can close the gate and inhibit transmission. Transmission also appears to be modulated by several other mechanisms which can influence the sensitivity of the gate.

Inflammatory mediators such as bradykinin, histamine, serotonin, and prostaglandins produced in response to tissue damage can produce peripheral sensitisation so that receptors respond to low intensity or innocuous stimuli; central sensitisation also occurs. Pain associated with tissue damage hence results in increased sensitivity of the sensory system so that the pain can occur in the absence of a clear stimulus. Pain that occurs due to a stimulus that does not usually provoke pain is termed *allodynia*; this applies to conditions such as sunburn, inflammation, and trauma that may result in sensitisation of the skin. *Hyperalgesia* is defined as an increased response to a stimulus that is usually painful. *Hyperaesthesia* is an increased sensitivity to stimulation, excluding the special senses and includes allodynia and hyperalgesia. *Hyperpathia* is characterised by an abnormally painful reaction to a stimulus, particularly a repetitive stimulus, and may occur with allodynia, hyperalgesia, or hyperaesthesia.

Pain is often classified as being acute or chronic in nature.

- **Acute pain** is associated with trauma or disease and usually has a well-defined location, character, and timing. It is accompanied by symptoms of autonomic hyperactivity such as tachycardia, hypertension, sweating, and mydriasis.
- **Chronic pain** is usually regarded as pain lasting more than a few months. It may not be clearly associated with trauma or disease or may persist after the initial injury has healed; its localisation, character, and timing are more vague than with acute pain. Furthermore, as the autonomic nervous system adapts, the signs of autonomic hyperactivity associated with acute pain disappear. Some forms of pain regarded as being chronic may consist of intermittent attacks of pain followed by relatively long pain-free periods. Patients with chronic pain have physical, psychological, social, and functional deterioration which contributes towards exacerbation of the pain.

Physiologically, pain may be divided into nociceptive pain and neuropathic pain.

- **Nociceptive pain** follows activation of nociceptors by noxious stimuli as described above but is not associated with injury to peripheral nerves or the CNS. It may be somatic or visceral, depending on which receptors or nerves are involved. *Somatic pain* is usually well localised and may be described as deeply located, sharp or dull, nagging, stabbing, throbbing, or pressure-like. *Visceral pain* is generally less localised and more diffuse than somatic pain and may be referred to remote areas of the body. Depending on the structure involved it is variously described as deeply located, aching, nagging, cramping, or pressing and may be accompanied by nausea and vomiting. Nociceptive pain usually responds to treatment with conventional analgesics.
- Pain resulting from damage or dysfunction of peripheral nerves/receptors or of the CNS is known as **neuropathic pain** (or neurogenic pain). The term covers *sympathetically maintained pain* including causalgia and reflex sympathetic dystrophy, and painful conditions such as postherpetic and trigeminal neuralgia, and diabetic neuropathy. Neuropathic pain associated with central nervous tissue, such as in central post-stroke pain (the thalamic syndrome) is referred to as *central pain*. The clinical signs of neuropathic pain can vary greatly. Some of the more common features include heightened pain sensitivity and sensations of superficial burning or stabbing (lancinating) pain. The pain may be associated with areas of sensory deficit or some form of autonomic instability. Neuropathic pain responds poorly to conventional analgesics and can be difficult to treat.

Early **treatment** of pain is important as unrelieved pain can have profound psychological effects on the patient, and acute pain that is poorly managed initially can degenerate into chronic pain, which may prove to be much more difficult to treat. It is important to assess and treat the mental and emotional aspects of the pain as well as its physical aspects. Although drug therapy is a mainstay of pain treatment (see Choice of Analgesic, below), physical methods such as physiotherapy (including massage and the application of heat and cold), surgery, and nervous system stimulation techniques such as acupuncture, spinal cord stimulation, and transcutaneous electrical nerve stimulation (TENS) are also used.

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Choice of analgesic

Paracetamol and **NSAIDs** are the first choice analgesics for treating mild to moderate pain and are also used in moderate to severe pain to potentiate the effects of opioids. They are suitable for use in acute or chronic pain. Effective relief of acute pain can be achieved with oral NSAIDs and with paracetamol (particularly in combination with an opioid—see below). Dependence and tolerance are not a problem with non-opioid analgesics but they have a rather flat dose-response curve: as the dose is increased, the increase in pain relief may be quite small. Aspirin and other non-selective NSAIDs inhibit blood platelet function, adversely affect the gastrointestinal tract, and can precipitate hypersensitivity reactions including asthma. The risk of severe upper gastrointestinal adverse effects may be less with selective inhibitors of cyclo-oxygenase-2 (COX-2) such as the coxibs, but their use has been greatly restricted by concerns about serious cardiovascular effects. Paracetamol does not have the haematological or gastrointestinal adverse effects of aspirin but large doses can produce severe or sometimes fatal hepatotoxicity. Giving paracetamol with an NSAID improves analgesia.

For the treatment of moderate or moderate to severe opioid-sensitive pain **codeine** is the traditional choice; alternatives include **dihydrocodeine** and **tramadol**. They are often given with non-opioid analgesics. Combinations of codeine with paracetamol at full doses produce a small but significant increase in analgesia compared with paracetamol alone and are one of the most effective options for acute pain, but the incidence of adverse effects increases with repeated use. Combinations of **dextropropoxyphene** with paracetamol or aspirin are no more effective in acute pain than the non-opioid alone; efficacy in chronic pain is unclear and adverse effects may become troublesome. The EMEA and the FDA have recommended that *all* dextropropoxyphene-containing preparations be no longer available in the EU and USA, respectively, because of the risk of toxicity in overdosage and of cardiotoxicity; such preparations remain on the market in other countries.

More potent opioids such as **morphine** are mainly used in the treatment of severe acute non-malignant pain and cancer pain (see p. 7.1). Their use in chronic non-malignant pain is somewhat controversial because of fears of psychological dependence and respiratory depression. However, in practice such problems rarely occur and those fears should not prevent patients being given effective analgesic therapy. Opioids may also be of value in neuropathic pain in some patients.

Morphine is the opioid of choice in severe pain. It is absorbed when given orally and has a short half-life so that the use of immediate-release oral preparations offers a flexible means of dosage titration in, for example, palliative care. Once initial pain relief has been achieved, use of a modified-release preparation every 12 or 24 hours is more convenient for maintenance of analgesia in severe chronic pain. It may also be given parenterally (e.g. for control of acute severe pain in emergency departments or in patient-controlled analgesia—see also p. 5.3), or rectally or transdermally, where there would be problems with the oral route.

Occasionally **other opioids** may be useful. Switching to an alternative opioid may be effective in patients who have inadequate pain control or intolerable adverse effects with morphine. Methadone (which also acts as an NMDA antagonist) or oxycodone have a longer duration of action than morphine, but it should be noted that methadone, which has a long half-life, should not be given more than twice daily when used long term because of the risk of progressive CNS depression and overdosage. A rapid onset of action is provided by alfentanil and fentanyl but use of pethidine is no longer recommended. Diamorphine or hydromorphone may be preferred to morphine when the parenteral route has to be used because they are more soluble and can be given in a smaller volume. Tramadol, which may impair respiratory and gastrointestinal function less than other opioids at equianalgesic doses, is also of benefit in neuropathic pain.

Adverse effects of opioids include sedation, nausea, vomiting, constipation, and, most seriously, respiratory depression. Tolerance generally develops to all of these effects except constipation, which may be prevented by regular use of laxatives.

Some other groups of drugs have significant roles in pain management either alone or as **analgesic adjuvants**.

Subantidepressant doses of tricyclic **antidepressants** (usually amitriptyline) are considered to be useful in refractory chronic pain, including neuropathic pain of the burning, dysaesthetic type such as postherpetic neuralgia and diabetic neuropathy; shooting pain has also been reported to respond. They may be used in addition to conventional analgesics, notably in the treatment of cancer pain of mixed aetiology. There is little evidence for benefit in acute pain although musculoskeletal pain has sometimes responded. Amitriptyline has also been found to be useful for tension-type headache and for the prophylaxis of migraine. The role of other antidepressants in the treatment of neuropathic pain is less clear although venlafaxine may be useful.

Antiepileptics (often carbamazepine and, more recently, gabapentin and pregabalin) have been found useful in the relief of neuropathic pain, especially when there is a stabbing (lancinating) element, as in trigeminal neuralgia; there have also been reports of efficacy in the treatment of diabetic neuropathy and for migraine prophylaxis.

Benzodiazepines and **other muscle relaxants** such as baclofen or dantrolene are useful for relieving painful muscle spasm in acute or chronic conditions.

Bone modulating drugs such as calcitonin and bisphosphonates may be useful in cancer pain arising from bone metastases (see p. 7.1) but have a slow onset of action and are second choice to NSAIDs. Bisphosphonates may cause an initial transient increase in bone pain.

Caffeine has been used with the aim of enhancing the effects of non-opioid and opioid analgesics but is of debatable benefit. There are similar doubts about whether caffeine enhances the effect of ergotamine in the treatment of migraine (see Pharmacokinetics, p. 675.3); it may also add to gastrointestinal adverse effects and in large doses can itself cause headache.

Corticosteroids have produced improvement, often substantial, in neuropathic pain. They can also relieve headache caused by raised intracranial pressure and refractory pain caused by bone metastases, and have the added benefits of increasing well-being and appetite.

Some **inhalational anaesthetics** are used in subanaesthetic doses as inhalation analgesics for acute pain. In particular, nitrous oxide is given with oxygen for pain relief in obstetrics and during dental and other procedures, and in emergency management. Isoflurane, enflurane, and in some countries methoxyflurane or trichloroethylene have been used similarly.

Miscellaneous drugs. After the discovery that epidural or intrathecal injection of opioids can produce effective analgesia many other drugs have been tried by these routes, either alone or with opioids or local anaesthetics, but their role, if any, in the management of pain is unclear. Some, such as clonidine and ketamine, also appear to have analgesic properties when given by other routes, and ketamine may be useful in reducing opioid requirements. Some antiarrhythmics (including systemic lidocaine) may be effective in chronic neuropathic pain, but must be used with extreme caution. The use of antipsychotics, such as the phenothiazines, as adjuvant analgesics is controversial; levomepromazine is sometimes used as an adjunct in palliative care.

See below for discussions of the use of patient-controlled analgesia (below), and rubefacients and topical analgesics (p. 6.3). Nerve blocks are discussed under Pain, on p. 1981.1.

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Choice of analgesics in children

Pain has often been undertreated in infants and children because of fears of respiratory depression, cardiovascular collapse, depressed levels of consciousness, and addiction with potent opioid analgesics. Assessment of pain is also a problem in children of all ages[1-3] and it is not that long since it was widely believed that neonates were incapable of feeling pain.

Non-opioid analgesics are used in ***infants and children***, either alone for minor pain or as an adjunct to opioid analgesics in severe pain,[4-6] (they can reduce opioid requirements,[1,7] perhaps by up to 40%[4]). Paracetamol is frequently used but it lacks any anti-inflammatory effect. NSAIDs such as ibuprofen are useful for minor pain,[4,6,8] especially when associated with inflammation or trauma. The use of aspirin is greatly restricted by its association with Reye's syndrome.

The **opioids** are still the mainstay of analgesia for moderate to severe pain in paediatric patients, and morphine is the standard against which the others are compared. It is given intravenously for rapid relief of severe pain (for example after burns, fractures or other injuries), and is titrated to achieve a suitable analgesic dose.[4-6,8,9] Where intravenous access is not readily achievable, oral morphine may be given but its onset is slower and less predictable; some favour intranasal diamorphine as an alternative to intravenous morphine.[6] Continuous intravenous morphine infusion with or without initial loading doses has become popular for postoperative pain relief,[7,9] but titration of the infusion rate is necessary to achieve a balance between analgesia and respiratory depression (particular care is needed in neonates, see below). Subcutaneous infusions of morphine have also been used,[4] mostly for the relief of terminal cancer pain in children. Intramuscular injections are painful[8-11] and therefore probably only suitable for short-term use. Fentanyl has also been widely used for short-term analgesia in surgical procedures,[7-9,11,12] and other opioids such as buprenorphine, hydromorphone, oxycodone, and tramadol have been given.[4] The use of codeine in children is restricted by its significantly increased risk of serious and life-threatening adverse effects in ultrarapid metabolisers.

Patient-controlled analgesia using morphine (see below) has been tried in children. Morphine has also been given to children by the epidural route;[9] experience with the intrathecal route is more limited. Other methods of opioid drug delivery of possible value in paediatric analgesia include transmucosal,[7,12] nasal,[6,8] and transdermal[7,10] dosage.

Cancer pain in children may be treated using the analgesic ladder scheme described under Cancer Pain (see p. 7.1).

Inhaled **nitrous oxide** and oxygen mixtures may be useful for preliminary pain relief and short, painful procedures.[6,8,9,11]

Local anaesthetics are especially suitable for the management of acute pain in day-care situations. Single injections given by the epidural route are often used to provide analgesia during and after surgery. Continuous epidural infusions of local anaesthetics have also been used. However, simpler techniques such as wound infiltration or peripheral nerve blocks can also provide effective analgesia for some procedures and are free of the problems of lower limb weakness or urinary retention associated with caudal blocks.[4,8,9,11] Application of eutectic creams (see Surface Anaesthesia, p. 1993.3) containing lidocaine with prilocaine to intact skin, to produce surface anaesthesia, may be sufficient for some minor painful procedures in children.[5,7-10,12]

Ketamine is used in outpatients for brief, painful procedures such as fracture reduction and to provide immobility for repair of facial lacerations in young children.[5,12,13] The emergence reactions that limit its use in adults are less common in children,[12] and can be ameliorated by benzodiazepines.[8,11]

Most ***neonates*** requiring analgesia and receiving respiratory support can be managed with an infusion of morphine but in neonates who are breathing spontaneously there is a substantial risk of respiratory depression. Morphine has been used in such neonates[9] but should be limited to those under intensive care, as for example after major surgery (see also Intensive Care, p. 1033.1). Fentanyl citrate[1] has also been used in neonates. **Sucrose** and other sweet tasting solutions have been shown to reduce physiologic and behavioural indicators of stress and pain in neonates undergoing painful procedures[10] although there had been some doubt expressed over whether this indicates effective analgesia.[14] The American Academy of Pediatrics has suggested that oral sucrose together with other non-pharmacological methods such as swaddling should be used for minor routine procedures; topical local anaesthetics may be used for more painful procedures such as venepuncture if time permits. Opioids should be the basis of postoperative analgesia after major surgery in the absence of regional anaesthesia; a rapidly acting opioid such as fentanyl is advocated, together with infiltration of the site with a local anaesthetic where time permits, for insertion of a chest drain.[15] Similar recommendations for painful procedures in neonates have been made by an international consensus group.[16]

The use of **analgesic adjuvants** (see Choice of Analgesic, p. 4.2) has also been advocated in some children.[17]

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Nerve blocks

For a discussion of the use of nerve blocks in the management of pain, see under Pain, p. 1981.1.

Patient-controlled analgesia

Patient-controlled analgesia (PCA) involves the use of automated delivery systems that enable patients to receive doses of an analgesic on demand. The technique is now widely favoured in the management of acute pain,[1-3] and appears to produce slightly better analgesia, and greater patient acceptance, than conventional analgesic methods.[4,5] It has been used successfully in children as young as 4 years, and in elderly patients.[6] Most experience relates to systems using intravenous opioids.

Initial analgesia must be established by giving the patient bolus doses of the analgesic, to achieve effective blood concentrations.[2,3] In the simplest type of PCA the patient is then able to self-administer a small fixed dose on demand; further doses are not permitted until a pre-programmed lockout interval has expired. The demand dose should be large enough to produce an appreciable analgesic effect, but not large enough to lead readily to toxic concentrations; the lockout period should also be long enough for the maximum analgesic effect to be felt before another dose is permitted, and should therefore relate to the speed of onset of action of the drug.[2] Some devices allow the dose to be given as a short infusion[2] to reduce adverse effects associated with high peak concentrations of opioids. In another commonly used method, sometimes described as patient-augmented analgesia, the patient is given a continuous background infusion which is supplemented by self-administered bolus doses.[2,3,6] However, with this method patients may receive more opioids without any improvement in analgesia;[6,7] There is also a greater risk of adverse effects, including respiratory depression.[2,3,7] It remains to be seen if there is any advantage with the more sophisticated devices that can be programmed to adjust the background infusion according to the frequency of the bolus demands.[6,7]

Most of the common opioids have been used successfully for PCA.[2] Morphine remains the gold standard, and fentanyl, hydromorphone, or tramadol are widely used alternatives.[2,3] Use of pethidine is no longer advised because of the risk of accumulation of its toxic metabolite, norpethidine.[2] Drugs with very short (remifentanil) or very long (methadone) half-lives may be less suitable for use.

Although generally perceived as safer than conventional opioid analgesia, occasional serious adverse effects and fatalities have resulted from errors in programming, or incorrect or inappropriate use (including operation by persons other than the patient). These risks can be minimised by safety features built into the PCA device itself, and by the development of standard protocols for the use of the technique.[2,3]

Most experience relates to the use of the intravenous route. However, epidural PCA is also used. It appears to be as effective, or more effective, than intravenous PCA,[2,3] although it may not be suitable in all cases, and carries additional risks to do with the placement of the epidural catheter.[3] Epidural PCA generally produces analgesia with a combination of a lipid-soluble opioid such as fentanyl or sufentanil plus a long-acting local anaesthetic such as bupivacaine or ropivacaine; the optimum combination has yet to be defined.[2,3] In addition, unlike intravenous PCA, the use of a background infusion is recommended.

Other routes have been investigated, including intranasal[7] and, in particular, transdermal[2,8] PCA. An iontophoretic patient-controlled delivery system for transdermal fentanyl that allowed PCA to be given in a non-invasive manner was available;[8,9] however, this was withdrawn from the market because of a defective delivery system.

Although it is not always considered in terms of PCA, inhaled nitrous oxide in oxygen also has a long history of effective use as a patient-controlled analgesic during childbirth; opioid PCA may not be suitable for such pain although local anaesthetics have been used with satisfactory results.[10]

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Postoperative analgesia

Pain relief after surgery has often been inadequate and it is now recognised that pain control should be adjusted for each patient and each situation.[1-3] Multimodal regimens, using several classes of analgesic, and ideally more than one route, are now generally favoured.[3-5] Pre-operative evaluation of the patient,[2,4] and frequent assessment of pain intensity after surgery (both to allow appropriate analgesia, and to detect possible complications)[3] are fundamental. Evidence-based procedure-specific guidelines have been issued.[6,7] Giving pain control on a preventative basis (pre-emptive analgesia) has been recommended, and may be more effective than conventional management, at least for some regimens, although results have varied.[8,9]

Patients undergoing minor surgery can be adequately managed with oral analgesics, such as paracetamol, NSAIDs, tramadol, and oxycodone. Those undergoing more extensive surgery usually require parenteral opioids or local analgesic techniques such as regional block, sometimes in combination.[3]

- **Opioid analgesics**, in particular morphine, are the mainstay of treatment for moderate to severe postoperative pain.[3] Opioid dose should be individually titrated; they may be given by several routes, but intravenous doses give more predictable results than intramuscular or subcutaneous doses and are widely favoured.[2,3,10] Intravenous *patient-controlled analgesia* (see p. 5.3) is now a standard method of management for postoperative pain.[3,4] Where it is unavailable, intramuscular or subcutaneous dosage every 2 hours as needed for 24 to 72 hours, followed by conversion to an oral analgesic regimen, may be an alternative.[3] Careful monitoring for potential adverse effects, in particular respiratory depression, is needed.[3]
  Opioids injected centrally via the epidural and intrathecal routes provide effective regional analgesia[2,4,10] (and may be more effective than intravenous opioids,[11] although whether this improves the ultimate outcome is unclear[3]). Morphine is the opioid most commonly given centrally, but others such as fentanyl, which is more lipid soluble, may be preferable in the case of epidural injection. The epidural and intrathecal routes have also been used for patient-controlled analgesia.
  Oral opioids may not be suitable in the immediate postoperative period, but oral regimens are generally preferred if the patient can swallow and gastrointestinal function has recovered.[1,3] Tramadol is useful in patients undergoing minor or intermediate surgery.[3]
  Management of postoperative pain in patients who have been receiving long-term opioids before surgery may be particularly difficult.[3,12] Baseline requirements should be calculated for each patient, but may go up or down after surgery; typically, at least 50% of the baseline dose will be needed postoperatively, with additional opioids titrated according to pain requirements. Such patients may thus require larger than normal doses of opioids to be given, and a balanced multimodal approach to analgesia is particularly important.[12]
- **NSAIDs** and **paracetamol** are useful analgesic adjuncts that can improve pain relief,[3] but are not suitable alone after major surgery.[2] After minor or intermediate surgery an oral regimen of paracetamol plus an NSAID such as naproxen may be adequate, with oxycodone or tramadol being given for breakthrough pain.[3] NSAIDs can be used effectively with other drugs, and use of an NSAID with an opioid after major surgery enables the dose of the opioid to be reduced without loss of analgesic effect.[1-5,10] However, the risk of gastric ulceration, impaired coagulation, and reduced renal function may limit the use of NSAIDs in some patients,[3,10] and the potential cardiovascular effects of the selective inhibitors of cyclooxygenase-2 (COX-2) have also been a cause of great concern.[3]
  Diclofenac, flurbiprofen, ketoprofen, ketorolac, lornoxicam, and naproxen are among the NSAIDs used for postoperative pain; the COX-2 inhibitors including parecoxib have also been used. Diclofenac, ketoprofen, ketorolac, and parecoxib may be given by injection, and a parenteral formulation of paracetamol is available in some countries.
- Infiltration of **local anaesthetics** at the site of operation is a simple method of preventing postoperative wound pain.[1,4] Central nerve blocks obtained with epidural or intrathecal local anaesthetics produce excellent analgesia,[1,2,4] although again, whether this improves outcome is unclear.[2,3] Insertion of a catheter during the operation allows subsequent infusion or bolus injection.[10] However, there may be complications related to both the procedure and the drugs used (see also Adverse Effects of Central Block, p. 1982.1). Local anaesthetics are rarely used alone, as a mixture of an opioid and a local anaesthetic produces effective analgesia using relatively smaller doses of each drug.[10] Such combinations are also used in patient-controlled epidural analgesia (see p. 5.3).
- There is growing interest in the use of **analgesic adjuvants**, including antiepileptics such as gabapentin or pregabalin,[13] or the NMDA antagonist ketamine,[14,15] to modulate opioid dosage and efficacy for postoperative pain. (For further discussion of analgesic adjuvants see Choice of Analgesic, p. 4.2.)

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Rubefacients and topical analgesia

Substances applied topically can relieve local pain through several different mechanisms.[1] Rubefacients or counter-irritants can relieve superficial or deep-seated local pain probably by producing counter stimulation, which according to the 'gate theory' of pain (see Analgesia and Pain, p. 4.1) helps to inhibit the transmission of pain signals. Their topical application produces hyperaemia or irritation of the skin and they are used alone or as an adjunct to massage in the management of a variety of painful musculoskeletal conditions.[2] Some are also traditionally used in preparations for the symptomatic relief of minor peripheral vascular disorders such as chilblains. Substances commonly used in **rubefacient** preparations include nicotinate and salicylate compounds, essential oils, capsicum, solutions of ammonia, camphor, and nonivamide. However, a systematic review[3] concluded that the evidence did not support the use of rubefacient preparations containing salicylate compounds for acute musculoskeletal pain, and suggested that their efficacy compared poorly with topical NSAIDs for chronic musculoskeletal pain; no evidence was found to support the use of rubefacient preparations containing other substances. **Capsaicin**, which is one of the active ingredients of capsicum, is used alone as a topical analgesic in a range of painful conditions, including neuropathic pain and rheumatic disorders; its benefits are modest though it may be useful in some patients.[4] It does not rely on vasodilatation in the skin and it is therefore not considered to be a traditional counter-irritant.

Some **NSAIDs** have been used topically in the treatment of soft-tissue injuries and inflammatory musculoskeletal conditions, although this route does not necessarily avoid the adverse effects of systemic treatment. There is evidence[5,6] to suggest that topical NSAIDs are more effective than placebo.

Other agents used as topical analgesics include compounds such as ethyl chloride and the halogenated hydrocarbon propellants; their evaporation produces an intense cold that numbs the tissues. Transdermal clonidine has been used in the treatment of chronic pain. Ketamine also appears to have some local analgesic effect when applied topically.[1]

Local anaesthetics are sometimes included in topical preparations used for the relief of painful skin and musculoskeletal disorders.

Application of heat to the skin can also help to relieve pain and melted hard paraffin has been used in wax baths as an adjunct to physiotherapy for painful joints and sprains. Warm kaolin poultices have also been used as a means of applying heat for pain relief.

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Specific pain states

Biliary and renal colic. Gallstones (see Ursodeoxycholic Acid, p. 2639.1) or other biliary disorders that result in obstruction of the bile ducts may produce **biliary colic**. Morphine may relieve the accompanying pain, but as it can also produce spasm of the sphincter of Oddi it can raise intrabiliary pressure and exacerbate the pain. It is therefore usually recommended that morphine and its derivatives should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Historically, pethidine has been regarded as a more suitable choice because it was thought to have less smooth muscle activity than morphine; however, this has been questioned. Prostaglandins have also been implicated in the aetiology of biliary colic and NSAIDs such as diclo-

fenac or ketorolac have been successfully used to relieve the pain.[1-3] Antimuscarinic antispasmodics have been tried for their action on biliary smooth muscle and the sphincter of Oddi.

Ureteral obstruction, such as in the formation and passage of renal calculi (see p. 2350.3), produces painful **renal** or **ureteral colic**.[4-6] The acute pain of renal or ureteral colic has been traditionally relieved using opioid analgesics such as pethidine that were thought to have a minimal effect on smooth muscle, although morphine has also been used.[4,6] However, opioids, and especially pethidine, are particularly associated with nausea and vomiting,[5,7] and NSAIDs are increasingly used in their place; they appear to be at least comparable with the opioids in terms of efficacy.[4-7] They can be given intramuscularly, intravenously, orally, and rectally, although the best route is unclear.[5,8] Diclofenac sodium given intramuscularly is recommended as first-line treatment by some authors.[6] Parenteral ketorolac also seems to be effective.[5] The use of intranasal desmopressin has also been studied.[4,5]

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Cancer pain. The pain cancer patients have may be acute, chronic, or intermittent. It may result from tumour involvement of the viscera and extension into soft tissues, tumour-induced nerve compression and injury, raised intracranial pressure, or bone metastases. Pain may also arise as a result of adverse effects of treatment, or from a concurrent disease, and may be exacerbated by emotional or mental changes. Many patients will have more than one type of pain. There may also be exacerbations due to movement (incident pain) or worsening of cancer: pain occurs in about a quarter of patients with newly diagnosed malignancies, but in up to three-quarters of those with advanced disease.

Pain relief involves the treatment of the cause of the pain as well as treatment of the pain itself, together with explanation, reassurance, and supportive care to improve any mental and social complicating factors. The mainstay of cancer pain management is drug treatment with non-opioid or opioid analgesics, or both together, plus adjuvant analgesics if necessary. A small proportion of patients (about 10 to 20%) may have pain that responds poorly or not at all to opioid analgesics given at tolerable doses, e.g. neuropathic pain resulting from nerve destruction or compression, incident bone pain, pancreatic pain, and muscle spasm.

In the management of cancer pain the aim is to achieve adequate continuous pain relief with the minimum of adverse effects and this calls for appropriate assessment of the intensity and quality of pain, and regular monitoring of the treatment. Guidelines for the relief of cancer pain, published by WHO in 1986[1] and revised in 1996,[2] are widely endorsed by specialists in pain relief and the care of the terminally ill[3-7] despite some questions about the robustness of supporting studies.[7] Subsequent guidelines issued by the Scottish Intercollegiate Guidelines Network[8] in 2008 and the British Pain Society[9] in 2010, and the annually updated guidelines of the US National Comprehensive Cancer Network (NCCN)[10] are also available. Specific guidelines for the relief of cancer pain in children have also been published.[11]

Treatment should be given regularly, orally if possible, and should follow the accepted three-step **'analgesic ladder'**.[1,2] This approach is often described as treatment 'by mouth, by the clock, and by the ladder'. Regular dosage rather than treatment as required aims to prevent pain re-emerging and to minimise the expectation of pain. The analgesic ladder consists of 3 stages, treatment beginning at step 1 and progressing to step 3 if pain is uncontrolled or increases. The stages are as follows:

1. a non-opioid analgesic such as aspirin, other NSAIDs, or paracetamol; an adjuvant (see below) may also be given if necessary to tackle specific pain or associated symptoms
2. an opioid analgesic such as codeine, dihydrocodeine, or tramadol plus a non-opioid analgesic; an adjuvant may also be given
3. a potent opioid analgesic such as oral morphine; a non-opioid analgesic may also be given, as may an adjuvant.

Combining analgesics with different pharmacological actions can produce additive or synergistic increases in analgesia but only one analgesic from each of the 3 groups (non-opioid, less potent opioid, potent opioid) should be used at the same time.

Evidence to support the **choice of analgesic** is often scanty. A systematic review[12] found some evidence of benefit from the use of NSAIDs to treat cancer pain, and supported their use in mild pain (WHO step 1), but there was little to support the choice of one NSAID over another, and little evidence for the addition of an opioid to an NSAID in moderate pain (WHO step 2).

In moderate to severe pain (WHO step 3), morphine is generally held to be the opioid of choice;[5] alternatives include fentanyl, hydrocodone, and oxycodone.[5,8,10] Mixed opioid agonist-antagonists may precipitate withdrawal symptoms in opioid-dependent patients; opioids with long half-lives (such as methadone or levorphanol) are also less suitable for treatment than pure opioid agonists with less prolonged actions.[10] In patients who do not achieve effective analgesia at an acceptable level of adverse effects with one opioid, **opioid rotation**, switching to an alternative opioid at an equivalent dose, may enable pain control.[8,10,13]

The optimal **route** for use is oral dosage. For best effect, both conventional (for dose titration) and modified-release (for maintenance) dosage forms are required. The European Association for Palliative Care (EAPC) suggests[5] that the simplest method of dose titration is with conventional morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue' dose may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take account of the amount needed for breakthrough pain. If pain returns consistently before the next dose is due the regular dose should be increased. Conventional formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain. For patients taking conventional morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep.

Similar recommendations are given by the NCCN.[10] They advise that the oral rescue dose for breakthrough pain should be calculated as 10 to 20% of the total 24-hour requirement; this may then be increased by 50 to 100% in patients who still have increased pain, with hourly reassessment of efficacy and adverse effects. If inadequate response is still seen after 2 or 3 cycles, a change of route (e.g. intravenous titration) may be considered.

If patients are unable to take morphine orally the EAPC considers the preferred alternative route to be subcutaneous,[5] and the NCCN suggests either continuous parenteral infusion, intravenous, or subcutaneous dosage.[10] There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful.[5] In the UK diamorphine hydrochloride is often preferred to morphine sulfate for parenteral use because it is more soluble and allows a smaller dose volume. Hydromorphone hydrochloride is an alternative to diamorphine.

Epidural or intrathecal opioids, either by injection or infusion, have been used when conventional routes have failed.[10,14] Some advocate the use of these routes because smaller doses may produce analgesia equivalent to that of larger doses given orally or parenterally, although there has been little conclusive evidence for a lower incidence of adverse effects or a better quality of analgesia.

The buccal, sublingual, and nebulised routes have been investigated, but these are not recommended for morphine because there is no current evidence of clinical advantage over conventional routes.[5] However, buprenorphine is given sublingually and may be a useful alternative in patients with dysphagia, although experience of long-term use in cancer pain is limited. Transdermal opioids are an alternative to oral morphine in patients whose pain and opioid requirements are stable.[5,8,10] Buprenorphine or fentanyl can be given via a transdermal system that provides continuous and controlled delivery for up to 72 hours. Calculating an appropriate conversion regimen for transfer of patients from oral or parenteral therapy to transdermal can be difficult,[15] but the NCCN suggests that the total daily requirement of oral morphine is equivalent to about 2000 times the hourly dose of transdermal fentanyl.[10] Oral transmucosal dosage forms[10,16] and an intranasal spray of fentanyl are also available for the management of breakthrough cancer pain.

Automated delivery systems for self-administration of parenteral analgesics (patient-controlled analgesia) have been used to administer opioid analgesics (see p. 5.3).

Adjuvant drugs that may be necessary at any stage include antidepressants, antiepileptics, and class I antiarrhythmics for neuropathic pain, corticosteroids for nerve compression and headache resulting from raised intracranial pressure, and muscle relaxants for muscle spasm. Radiotherapy and radioisotopes such as strontium-89 may be of use when the bone pain of metastases is unresponsive to analgesics.[17] Bone modulating drugs such as calcitonin and bisphosphonates may be of additional benefit but have a slow onset of action and bisphosphonates may cause an initial transient increase in pain. Corticosteroids have been used as an alternative to NSAIDs in refractory bone pain but long-term use should be avoided. Nerve blocks with local anaesthetics or neurolytic solutions may benefit a few patients, in particular those with sympathetically maintained pain or specific localised pain (see under Pain, p. 1981.1). Topical local anaesthetics or NSAIDs may also be of use in some patients.[10] Physiotherapy and relaxation techniques may be useful for painful muscle spasm. The addition of an NMDA antagonist such as dextromethorphan or ketamine to conventional analgesic regimens has been tried with some success in patients with refractory pain.[13] Adjuvant therapy should be fully explored before moving on to the next 'rung' of the treatment ladder or increasing the dosage of an opioid analgesic.[18] For further details of analgesic adjuvants, see Choice of Analgesic, p. 4.2. Nabiximols (a mixture of cannabis extracts containing dronabinol and cannabidiol) has been used as adjunctive analgesic treatment in adult patients with advanced cancer who have persistent moderate to severe background pain despite maximal opioid therapy.

Management of cancer pain also requires monitoring to prevent and reduce **adverse effects** of therapy, particularly of opioids. Appropriate bowel regimes to manage constipation should be started at the same time as opioid therapy, as should antiemetic therapy; sedation and nausea usually become less marked as treatment progresses,[5] and warrant reassessment if they persist for longer than a week.[10] Concerns about respiratory depression and dependence should not be allowed to interfere with appropriate treatment: patients whose pain ameliorates can generally reduce and stop opioid treatment without difficulty.[5]

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Central post-stroke pain. Central pain is a neuropathic pain arising from lesions of the CNS.[1-6] Pain following a cerebrovascular accident has been referred to as thalamic syndrome but is now commonly known as central post-stroke pain and may arise not only from classical stroke but also from surgery or trauma to the head. The pain,

which has been described as burning, stabbing, and aching, may be mild to intolerable and occurs spontaneously or in response to a mild stimulus.

As in other types of neuropathic pain, whether opioid analgesics can be of benefit is controversial: it has been suggested that the value of conventional opioids such as high-dose morphine is modest, but that NMDA receptor antagonists such as methadone may be of more benefit.[2] Ketamine, another NMDA antagonist, may also be of value. Conventional management of central post-stroke pain involves the use of antidepressants such as amitriptyline and antiepileptics including lamotrigine or gabapentin. Early peripheral sympathetic blockade may produce temporary relief in some cases. Mexiletine may be of use in patients with refractory pain; it has often been given with amitriptyline. Oral or intrathecal baclofen may be tried. Transcutaneous electrical nerve stimulation (TENS) may occasionally be of help but some advocate brain or spinal cord stimulation. Surgical treatment generally gives disappointing results.

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Complex regional pain syndrome. Complex regional pain syndrome (CRPS) is a regional, post-traumatic neuropathic pain that generally affects the limbs. CRPS has also been referred to as reflex sympathetic dystrophy, post-traumatic dystrophy, causalgia, Sudeck's atrophy, and shoulder-hand syndrome. Causalgia has also been used to describe the burning pain that follows a penetrating injury. Historically, it was considered that the pain was maintained by the sympathetic nervous system and the term 'reflex sympathetic dystrophy' was commonly used to describe the syndrome (although recent studies have shown that the sympathetic nervous system is not always involved). However, the terms given above are now considered to be inappropriate and CRPS is now broadly classified as:

- Type I: (previously reflex sympathetic dystrophy) which develops after tissue trauma, such as that accompanying myocardial infarction, stroke, burns, frostbite, fractures, and shoulder or limb injury, but where there is no identifiable nerve lesion
- Type II: (previously causalgia) which develops after trauma to a major peripheral nerve

Clinically the two subsets are identical and typical symptoms include pain, allodynia, and hyperalgesia; as the syndrome becomes chronic, trophic changes to the bone, muscles, and skin may occur. Sympathetic dysfunction may also be present. If the pain is relieved by a sympathetic block (see below), this pain is regarded as 'sympathetically-maintained', if not it is known as 'sympathetically-independent' pain.

The treatment of CRPS is difficult especially in chronic disorders and is usually aimed at pain control and restoring limb function. The cornerstone of treatment is physiotherapy, with pain relief provided in order to allow physical exercise. Patients with mild disease may not require pain management; those with moderate pain should be tried with a tricyclic antidepressant, an antiepileptic such as gabapentin, or a less potent opioid. Oral or intravenous bisphosphonates have also produced some promising results. A sympathetic nerve block with bretylium or perhaps a local anaesthetic may be useful in carefully selected patients with sympathetically-maintained pain; those who do not respond to a sympathetic nerve block may be given an epidural block. Other methods that have been tried in refractory pain include spinal cord stimulation and intrathecal baclofen or opioids. There are small studies or anecdotal reports of the use of a variety of other drugs and interventions.

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Diabetic neuropathy. Sensory polyneuropathy, a complication of diabetes mellitus, is the commonest of the neuropathies producing neuropathic pain. The pain mainly manifests as a burning sensation, sometimes accompanied by shooting, or aching pain. Painful neuropathy may benefit from optimal diabetic control (see p. 467.2). Non-opioid analgesics such as aspirin or other NSAIDs, or paracetamol may be tried, although neuropathic pain is often resistant to conventional analgesics, and the treatment of painful diabetic neuropathy is generally as for postherpetic neuralgia (see p. 10.3). Relief may be obtained using tricyclic antidepressants and the *BNF* considers amitriptyline and nortriptyline to be the drugs of choice. SSRIs have been tried but studies suggest that they are ineffective or less effective than tricyclic antidepressants. Duloxetine, a serotonin and noradrenaline reuptake inhibitor, is licensed for use in diabetic neuropathy. Antiepileptics such as carbamazepine, gabapentin, phenytoin, and pregabalin can be used to control any shooting or stabbing components of the pain; lamotrigine and topiramate are also under investigation. Antiarrhythmics such as lidocaine given intravenously or mexiletine given orally have been shown to be effective against some components of the pain, although it has been suggested that in the absence of strong efficacy data the latter should be confined to patients with extreme refractory pain and no cardiac risk. Topical application of capsaicin or lidocaine may have some effect; use of capsaicin may be limited by the burning sensation it can cause. Neuropathic pain may respond partially to some opioid analgesics, such as methadone, oxycodone, and tramadol, and they may be of use when other treatments are ineffective. Transcutaneous electrical nerve stimulation (TENS) may also be tried.

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Dysmenorrhoea. Dysmenorrhoea is painful menstruation. The primary form arises from uterine contractions produced by release of prostaglandins from the endometrium in the luteal phase of the menstrual cycle. For this reason, drugs that inhibit ovulation or prostaglandin production are often effective treatments.[1] NSAIDs inhibit cyclo-oxygenase (prostaglandin synthetase) and are usually the drugs of first choice.[1-6] They are taken at the onset of discomfort and continued for a few days while symptoms persist. Those most commonly used have included aspirin, diflunisal, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, naproxen, and piroxicam. Theoretically, mefenamic acid has the advantage of inhibiting both the synthesis and the peripheral action of prostaglandins, but clinical studies have not consistently shown fenamates to be more effective than other cyclo-oxygenase inhibitors. Paracetamol has also been given for pain relief. A systematic review[2] comparing several of these drugs concluded that ibuprofen appeared to have the best risk-benefit ratio in dysmenorrhoea and was the preferred analgesic; naproxen, mefenamic acid, and aspirin were also effective, but the limited data on paracetamol did not show such clear benefits. Another such review considered that there was insufficient evidence to determine which NSAID should be preferred.[3]

Patients who fail to respond to analgesics may benefit from the use of progestogens either alone for part of the cycle or more usually with oestrogens in the form of combined oral contraceptive preparations.[1,4-6] A systematic review[7] found limited evidence of pain improvement with the use of such preparations for primary dysmenorrhoea; however, the authors noted a paucity of studies, and that the included studies were of variable quality and had methodological flaws.

Antispasmodic drugs such as hyoscine butylbromide are included in some preparations promoted for the relief of spasm associated with dysmenorrhoea but the *BNF* considers that they do not generally provide significant relief. There is limited evidence[8] that vitamin B_1 may be effective and some consider[1] that it may be worth trying; evidence of benefit from other therapies such as magnesium or vitamin E is considered to be weaker.[1,8,9]

Secondary dysmenorrhoea is associated with various other disorders such as endometriosis, and treatment is mainly aimed at the underlying cause.

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Headache. Aspirin and other NSAIDs, or paracetamol are often tried first for the symptomatic treatment of various types of headache including migraine (p. 670.3) and tension-type headache (p. 671.3). NSAIDs may also be effective for the prophylaxis of migraine, although they are not considered first-line options.

Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine or tension-type headache, but are best avoided, especially in patients who have frequent attacks.

Labour pain. It is important to assess the adverse effects, on both the mother and the fetus, when selecting any method for the management of labour pain. Non-pharmacological methods of pain relief may include relaxation techniques, transcutaneous electrical nerve stimulation (TENS) (which is popular with patients, although there is no robust evidence of benefit[1]), and various other complementary therapies: of the latter, there is some evidence of benefit with the use of acupuncture and hypnosis.[2] Water immersion (use of a birthing pool) during the first stage of labour has been shown to reduce reported maternal pain.[3] Subcutaneous or intradermal injection of sterile water into the back has also been used for the relief of low back pain during labour.[4,5]

However, at some point during labour many women will request some sort of pharmacological analgesia.

The inhalational anaesthetic **nitrous oxide**, given with oxygen, is suitable for self-administration and is commonly used to relieve labour pain. It is relatively safe and can produce substantial analgesia in most patients.[6] Other inhalational analgesics such as isoflurane or sevoflurane are also sometimes used[7] (see Choice of Analgesic, p. 4.2).

Opioid analgesics have been given systemically in the management of labour pain for many years, although they do not appear to provide adequate analgesia in most patients at a tolerable dosage.[8,9] There is no clear evidence to favour one opioid over another.[10] Morphine is considered unsuitable,[7] and the widest experience has been with pethidine.[7,10] However, its efficacy has been queried,[7,10] and its use has declined in many countries.[7] Fentanyl and its derivatives sufentanil and alfentanil have been used, particularly when given as intravenous patient-controlled analgesia (PCA),[7] but it is not clear that they have any great

advantages, and as with other opioids they may cross the placenta and produce respiratory depression and other adverse effects in the newborn. The use of the very short-acting opioid remifentanil for PCA during labour has been investigated, with some benefit,[11] but although it is less likely to produce effects on neonatal respiration it is not clear that the degree of supervision required to guard against unacceptable respiratory depression in the mother can be widely achieved on busy labour wards.[7] Nalbuphine has been used in some countries because of its mixed agonist/antagonist action,[7] although there does not seem to be clear evidence that it conveys any substantial benefit.

Epidural analgesia with a *local anaesthetic* is now considered the gold standard for treatment and provides the most effective pain relief during labour.[9,12-14] Medical indications may include a history of malignant hyperthermia, certain cardiovascular or respiratory disorders, or pre-eclampsia, but the primary indication is the patient's desire for pain relief.[9,13] Bupivacaine is one of the local anaesthetics most often used in epidural analgesia; others include ropivacaine and lidocaine.[14]

Epidural block has few contra-indications and serious adverse events are rare. Nonetheless, it has been associated with an increased risk of prolonged second-stage labour, forceps delivery, and caesarean section[9,13,14] (although meta-analysis[8] and a systematic review[14] refute the latter), and it may not improve maternal experience of childbirth. Many centres stop epidural analgesia for the second stage of labour to reduce the incidence of forceps delivery but substantive evidence for this is lacking.[15] Central blocks may also produce adverse effects including shivering, post-puncture headache, and hypotension (for further details of the adverse effects of and precautions for epidural block, see p. 1982.1 and p. 1983.2, respectively). Occasionally epidural local anaesthetic does not produce adequate analgesia due to patchy or incomplete block.

Some of the adverse effects associated with epidural analgesia are associated with the motor block and profound analgesia resulting from traditional techniques using relatively high concentrations of local anaesthetic. There has therefore been an increasing trend to the use of lower-dose techniques. Although *opioid analgesics* are not particularly effective for labour analgesia when given systemically (see above), addition of a small amount of an opioid to epidural solutions enables effective analgesia to be achieved with lower concentrations of local anaesthetic, and with less motorblock;[9,12,16,17] however, the incidence of pruritus (a known effect of opioids) is greater than with a local anaesthetic alone.[18] There is no standard combination of local anaesthetic and opioid, although one large study used bupivacaine 0.1% with fentanyl 2 micrograms/mL.[16] Sufentanil is also widely used with either bupivacaine[18] or ropivacaine. The epidural use of other adjuvants such as clonidine and neostigmine is also being studied.[19] Low-dose techniques are the basis of so-called 'ambulatory' or 'walking' epidural management, although it is unclear to what extent this mobility improves outcomes or patient satisfaction.[20]

Once an initial block is established, additional analgesia can be provided through a catheter by intermittent 'top-up' doses or by a continuous epidural infusion; a combination of the two methods forms the basis of some types of patient-controlled epidural analgesia.

Another method of reducing the adverse effects of traditional epidural techniques is to combine a spinal block, which is quick acting but not long lasting enough to be used alone for analgesia in labour, with epidural delivery. Although studies have reported superior pain relief[17] with such **combined spinal-epidural analgesia**, a systematic review[18] considered that there was no overall benefit with the technique when compared with low-dose epidural techniques, although onset of analgesia was faster.

The use of **spinal blocks** in obstetrics has been more commonly associated with anaesthesia and management of postoperative pain in caesarean section.[12] Spinal blocks with local anaesthetics have a greater tendency to produce hypotension and headache than epidural blocks (for further details of the adverse effects of and precautions for spinal block, see p. 1982.1 and p. 1983.2, respectively).

Pudendal nerve blocks with lidocaine followed by a local anaesthetic given into the perineum provide pain relief during labour.[12] However, the technique of paracervical local anaesthetic block is now largely of historic interest in labour analgesia[21] because of reports of fetal arrhythmias, acidosis, and asphyxia and isolated reports of fetal death.

Local anaesthetics have been applied topically for **perineal pain** caused by tearing or episiotomy in women who have given birth. However, a systematic review[22] considered that the evidence of efficacy was not compelling.

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Low back pain. Low back pain (sometimes referred to as lumbago), is a common complaint but only a small percentage of patients suffer from a recognised organic disease, most frequently disc disease. In patients with a lumbar disc prolapse or herniation, the rupture of one of the fibrocartilagenous intervertebral discs can exert pressure on spinal nerve roots and produce a condition characterised by severe and often acute pain radiating from the back along the distribution of the nerves affected (radiculopathy). The sciatic nerve may be involved and patients have pain (sciatica), usually in one leg along the typical distribution of the nerve. Non-specific back pain (back pain of unknown origin) is usually self-limiting with a good prognosis, although recurrence is common.[1-3] Back pain is considered to be acute if it lasts for less than 6 weeks, subacute if it lasts for 6 to 12 weeks, or chronic if it persists for more than 12 weeks.[4]

Treatment for **acute back pain** should be given early to prevent the condition becoming chronic. For simple back pain (in the absence of nerve root symptoms or signs of serious spinal pathology) paracetamol should be tried first. NSAIDs are probably more effective,[2,5] but are associated with a higher frequency of adverse effects and should be reserved for those in whom paracetamol is ineffective.[2,4-8] If these treatments fail, muscle relaxants, including baclofen or tizanidine, may be added to therapy, although adverse effects may limit their usefulness;[1-6,9,10] benzodiazepines such as diazepam (which should only be given for a short period because of the risk of dependence)[2] are among the most effective muscle relaxants, but there is little comparative evidence, and some suggest that they act mainly as sedatives.[6] Opioids have moderate benefits in severe or disabling pain not relieved by paracetamol or NSAIDs,[2,5,6,8] but again should only be used in the short term.[3,8] There is strong evidence that remaining active speeds recovery and reduces the risk of chronicity, even if pain or discomfort is caused; bed rest delays recovery and is not recommended.[1,3,4,9,11,12] Other non-pharmacological approaches that have evidence of a benefit include topical heat wraps and spinal manipulation.[1,2,4,8,13,14] There is little or no clinical evidence that acupuncture, transcutaneous electrical nerve stimulation (TENS), massage, traction, specific back exercises, or lumbar support are beneficial.[1,2,4,11,14] However, in the UK, NICE[8] recommends offering acupuncture, manual therapy, or a structured exercise programme as part of the treatment regimen for persistent or recurrent non-specific acute or chronic lower back pain. Moreover, patient expectations of benefit from different therapies may influence outcomes, and this should be taken into consideration.[2]

Sciatica usually resolves with conservative management including analgesics and continued activity; however, if sciatic pain persists for longer than 6 to 8 weeks, surgery may be indicated.[15] Dissolution of the disc by injection of enzymes (chemonucleolysis) such as chymopapain or collagenase has been used as an effective alternative to surgery, but concerns about its safety have led to a decline in use, and discectomy is often preferred.[16]

Epidural injections of corticosteroids, using either the caudal or lumbar route, have been given to patients with sciatica; any relief is temporary only, the evidence of a benefit is conflicting, and their use is no longer recommended.[15,17] There is no evidence of benefit in patients with non-specific acute or chronic back pain;[1,4,8,18,19] however, it cannot be ruled out that some types of injection therapy may be effective in some subgroups of patients.[19]

About 2 to 7% of patients with acute lower back pain go on to develop **chronic** pain,[4] and in the majority of cases, the source of the pain cannot be identified. Chronic pain is not necessarily the same as prolonged acute back pain and treatment is difficult. Conservative treatment is as for acute pain (see above);[1,2,5,18,20] tricyclic antidepressants may also be tried[1-3,5,8,18,20] although a systematic review found the evidence of benefit to be lacking.[21] Topical application of capsaicin may be considered for short-term relief.[18] Surgery may be indicated for disc disease (see above) or spondylosis,[22] although it is not recommended for non-specific chronic back pain until conservative treatments have been tried for at least 2 years.[18] Epidural corticosteroids, intra-articular corticosteroid injections, local facet nerve blocks, trigger point injections, and spinal cord stimulation also lack evidence of efficacy.[18] Other methods that may be tried for intractable chronic back pain include multidisciplinary physical and psychological approaches;[1-3,8,14,18] evidence for TENS, massage, acupuncture, laser therapy, and traction is either equivocal or scant, however.[1,18,20,23,24]

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Myocardial infarction pain. The severe pain of acute myocardial infarction is located in the retrosternal area with radiation to the arms, neck, jaw, and epigastrium. Pain relief is of benefit not only in its own right but also because pain may cause adverse haemodynamic effects such as increases in blood pressure, heart rate, and stroke volume. Although early treatment of the myocardial infarction (p. 1257.1) may relieve pain dramatically, opioid analgesics are the first-line treatment for pain and should be given intravenously as soon as possible, that is before hospital admission, to patients with suspected infarction.[1-4] Opioids can also help to reduce anxiety. An inhaled mixture of nitrous oxide and oxygen has sometimes been used to provide pain relief before arrival in hospital; sublingual glyceryl trinitrate or an alternative fast-acting nitrate may also be given.

Diamorphine or morphine given by slow intravenous injection have generally been the opioids of choice, partly because of a better haemodynamic profile, but pethidine has also been used. An intravenous antiemetic such as metoclopramide or, if left ventricular function is not compromised, cyclizine, should also be given. The intramuscular route should only be used if venous access is unobtainable since it is relatively ineffective in shocked patients, complicates the enzymatic assessment of the infarction, and may result in large haematomas when patients are given thrombolytics. Alternative analgesics include nalbuphine or buprenorphine, although the latter may not produce pain relief as quickly as diamorphine. The cardiovascular effects of pentazocine make it unsuitable for use during or after myocardial infarction. Selective cyclooxygenase-2 (COX-2) inhibitors and non-selective NSAIDs (other than aspirin) should not be used in patients with acute myocardial infarction because of their known cardiovascular risks[5] (see Thrombotic Events under Adverse Effects of NSAIDs, p. 105.1).

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Neuropathic pain syndromes. The definition and characteristics of neuropathic pain are described under Analgesia and Pain, p. 4.1. Treatment can be difficult and is best undertaken in specialist pain clinics, since neuropathic pain often responds poorly to conventional analgesics.[1-8] The painful disorders characterised by neuropathic pain (either as the predominant form of pain or as one component of the overall pain) discussed in this section are:

- Central Post-stroke Pain (p. 7.3)
- Complex Regional Pain Syndromes (p. 8.1)
- Diabetic Neuropathy (p. 8.2)
- Phantom Limb Pain (below)
- Postherpetic Neuralgia (below)
- Trigeminal Neuralgia (p. 11.2)

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Orofacial pain. Orofacial pain may arise from many disorders so its effective management depends very much on the correct identification and treatment of any underlying cause, which may include:

- dental disease
- cluster headache (p. 670.1)
- migraine (p. 670.3)
- trigeminal neuralgia (see p. 11.2)
- sinusitis (p. 208.2)
- ear disease such as otitis media (p. 197.2)
- giant cell arteritis (p. 1604.2)
- aneurysms
- neoplasms

In the treatment of dental pain, analgesics are used judiciously as a temporary measure until the underlying cause has been effectively managed. Paracetamol or aspirin or other NSAIDs are adequate for most purposes. Opioid analgesics are relatively ineffective and are rarely needed.

Burning mouth syndrome (stomatodynia; glossodynia) is characterised by a burning sensation or other dysaesthesias of the oral mucosa in the absence of specific oral lesions. It is often accompanied by xerostomia and altered taste. Those treatments for which there is the best evidence of efficacy include topical therapy with clonazepam, systemic treatment with thioctic acid, SSRIs, or amisulpride, and cognitive therapy. Other treatments that may produce some benefit include capsaicin used topically or systemically, topical lidocaine, or systemic therapy with other antidepressants.

In addition, a large number of patients have a type of facial pain of unknown cause which is typically exacerbated by stress and can develop into a chronic debilitating disorder. Many patients with such idiopathic facial pain respond to non-opioid analgesics, explanation, and reassurance. Antidepressants such as the tricyclics are often of value. Antiepileptics, including carbamazepine and sodium valproate, and the oral lidocaine analogue mexiletine have been used as adjuncts to the tricyclics. Topical treatment with capsaicin has also been tried. Treatment needs to be continued for several months to avoid pain recurrence on withdrawal. Psychological treatments can also be helpful. Botulinum A toxin has been tried for the relief of facial pain associated with some disorders of the orofacial muscles.

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Pancreatic pain. Pain in pancreatitis (p. 2580.2) can be severe and may require opioid analgesics. Concerns over the long-term use of opioids in non-malignant pain should not prevent the patient being given effective analgesia which may be achieved by following the general principles recommended by the WHO for treatment of cancer pain (see p. 7.1); this involves giving non-opioid analgesics such as NSAIDs for mild attacks, with or without antispasmodics such as antimuscarinics, and progressing to 'weak' opioids such as codeine, and 'strong' opioids including morphine, according to the severity of pain.

There has been some controversy about the appropriate choice of opioid: traditionally, morphine and its derivatives have been avoided in favour of pethidine, in the belief that they are more likely to cause spasm of the sphincter of Oddi. However, the evidence supporting this has been questioned. Some suggest that κ-receptor agonists such as oxycodone may be of value. In addition, there is some evidence that pancreatic pain may have a neuropathic element, and the use of an antiepileptic such as gabapentin, or an SSRI such as paroxetine, may be considered for pain syndromes associated with chronic pancreatitis.

Analgesics are given before meals to help to alleviate the postprandial exacerbation of pain. They should be given on a regular basis and doses titrated for each patient. Pancreatic extracts may ease the pain but are otherwise reserved for those with symptomatic malabsorption. Coeliac plexus block has been used for the relief of severe intractable pain in some patients with chronic pancreatitis; it has also been used similarly in patients with cancer of the pancreas. However, the benefits of such a block are unclear.

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Phantom limb pain. Phantom limb pain is associated with an amputated limb and is more common when there has been severe pre-amputation pain. It is frequently a mixture of neuropathic and other types of pain. Management may be difficult[1-6] but in a survey of war veteran amputees, for those who took any form of treatment for phantom limb pain, conventional analgesics such as NSAIDs or paracetamol with or without opioid analgesics were reported as being satisfactory.[1] The use of the WHO analgesic ladder, as in cancer pain (see p. 7.1) may guide the choice of analgesic;[6] although the use of opioids has been questioned in what is essentially a neuropathic pain syndrome, many consider them of potential value in phantom limb pain.[5,6] Transcutaneous electrical nerve stimulation (TENS) was another method used by some and considered to be at least as effective as other therapies.[1] Tricyclic antidepressants and antiepileptics may be of help for the neuropathic components of the pain[2,4] and some relief may be obtained with sympathetic blocks. Intravenous ketamine may also be of use.[2-4] From a review[7] of studies investigating the effect of regional anaesthesia in preventing phantom limb pain in patients undergoing lower-limb amputation it appeared that epidural blockade started before and continuing for the duration of surgery or for several days after amputation conferred more protection from long-term pain than blockade begun late intra-operatively or postoperatively. However, a randomised, double-blind, controlled study[8] failed to show any benefit of pre-emptive analgesia using epidural blockade in such patients. A subsequent review[3] that included this study concluded that the pre-emptive use of epidural block was of limited success.

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Postherpetic neuralgia. About 10% of patients who have had acute herpes zoster still have neuropathic pain resulting from peripheral nerve injury one month or more after the rash has healed. The elderly are the most susceptible. The affected area (commonly head, neck, and limbs) is extremely sensitive to any stimuli; even the pressure of clothing can produce unbearable pain. Spontaneous remission occurs in many patients within a few months. However, in a small percentage of patients the pain can last for several years.

Attempts have been made to **prevent** the development of postherpetic neuralgia. An early meta-analysis[1] concluded that, if started within 72 hours of the onset of rash, aciclovir might reduce the incidence of residual pain at 6 months in some patients. A more recent systematic review[2] found that oral aciclovir or famciclovir did not have a significant effect on the incidence of postherpetic neuralgia 4 or 6 months after the onset of rash when compared with placebo. It is, however, generally agreed that antiviral treatment does reduce the duration of postherpetic neuralgia.[3-5] Epidural injection of methylprednisolone with bupivacaine has been shown to reduce short-term pain from herpes zoster, but was ineffective in preventing postherpetic neuralgia in the longer term,[6] and evidence of the preventive value of corticosteroids is generally lacking.[7]

Various **treatments** have been tried once neuralgia develops.[3-5,8-15] The value of conventional analgesics is limited because of the neuropathic character of the pain although opioid analgesics have been used in refractory

cases (see below). Low-dose tricyclics such as amitriptyline, or in particular nortriptyline, have been widely used for treatment, and appear to be of benefit in about half of all cases;[5] however, the antiepileptics gabapentin and pregabalin may now be preferred, and gabapentin is licensed for this indication in some countries. A comparative study has suggested that gabapentin is as effective as nortriptyline and better tolerated.[16] Topical lidocaine has also been licensed for treatment of postherpetic neuralgia, but the evidence for such use has been questioned.[17] However, it is likely to be better tolerated than the other main topical alternative, capsaicin.[5] Opioids, including methadone, morphine, and oxycodone, are usually reserved for patients who fail to respond to tricyclics or gabapentin.[10] Nerve blocks and surgical techniques may provide temporary pain relief, but results have generally been disappointing. Transcutaneous electrical nerve stimulation (TENS) has also been tried. Topical preparations of aspirin or indometacin, have shown some promise.

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Sickle-cell crisis. The management of pain of sickle-cell crisis that can occur in sickle-cell disease (p. 1123.2) is similar to that of other forms of acute pain. The pain of mild crises may be controlled using oral analgesics such as paracetamol, an NSAID, codeine, or dihydrocodeine. Partial agonist and antagonist opioids such as buprenorphine are not recommended to treat acute pain before transfer to hospital.[1] Crises severe enough to need hospital admission usually require the use of more potent parenteral opioid analgesics but NSAIDs may be useful as an adjunct for bone pain. In most centres, morphine is the opioid of choice for moderate to severe pain. Some patients appear to prefer pethidine but many clinicians[2-8] avoid its use if possible as control of pain may be inadequate and doses of pethidine needed to manage crises can lead to accumulation of its neuroexcitatory metabolite norpethidine and precipitate seizures (see also Effects on the Nervous System, p. 122.3). UK guidelines[8,9] recommend that pethidine should only be used in exceptional circumstances such as in patients hypersensitive to other opioids. Diamorphine, fentanyl, hydromorphone, and methadone have been used as alternatives to morphine. Nalbuphine may also be suitable.[10] As the dose of opioid required to control the pain can vary considerably, not only during each episode but also from one episode to another and between individual patients, patient-controlled analgesia (see p. 5.3) may be of help to manage the pain once initial pain relief has been obtained with loading doses of parenteral opioids;[4,11,12] opioids used have included morphine and fentanyl. The use of continuous epidural analgesia with local anaesthetics alone or with opioids has been tried. However, a randomised study[13] of morphine for the management of severe painful sickle-cell crises in children showed that oral modified-release morphine was a safe and effective alternative to continuous intravenous morphine. Inhalation of a mixture of nitrous oxide and oxygen may be a useful analgesic during transfer to hospital.[1,9]

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Trigeminal neuralgia. Trigeminal neuralgia (tic douloureux) is a neuropathic pain characterised by sudden, brief, sharp, agonising, episodic pain in the distribution of one or more branches of the fifth cranial nerve. There may be several episodes (lasting several seconds or minutes) a day over a number of weeks, followed by a pain-free interval that may last for weeks or years. Trigeminal neuralgia generally has a 'trigger zone' in which even a very light stimulus such as a draught of air produces pain. In some cases firm pressure applied around but not to the zone itself may help to relieve pain. Trigeminal neuralgia may be idiopathic or may be secondary to nerve compression (such as that caused by a tumour), facial injury, or multiple sclerosis.

The management of trigeminal neuralgia is distinct from other forms of neuropathic pain. Carbamazepine is the drug of choice and initially may produce satisfactory pain relief in 70% or more of patients, although increasingly large doses may be required.[1-8] If pain relief is inadequate phenytoin or baclofen may be added to carbamazepine therapy; these drugs may also be used alone in patients intolerant of carbamazepine.[4] Other antiepileptics such as gabapentin, lamotrigine, oxcarbazepine, valproate, and clonazepam have also been used in patients intolerant of, or resistant to, carbamazepine.[1-6,8] Evidence for the value of non-antiepileptic drugs in trigeminal neuralgia is mostly poor.[9]

In some patients drug therapy eventually fails to control the pain or produces unacceptable adverse effects and invasive procedures become necessary. These may include the selective destruction of pain bearing nerve fibres with radiofrequency thermocoagulation, instillation of glycerol (although the efficacy and safety of the procedure is debatable), gamma knife radiation, and microvascular decompression of the trigeminal nerve root.[2,3,6-8]

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Increased Body Temperature

The hypothalamus is the centre of the thermoregulatory system and is responsible for maintaining the body temperature at a set point (known as the set-point temperature) which is normally 37 degrees. Mechanisms that produce or conserve body heat include passive heat absorption from the environment, peripheral vasoconstriction, and thermogenic processes such as metabolic reactions and shivering. Heat loss is achieved mainly through sweating and peripheral vasodilatation. Various states may lead to an abnormal increase in body temperature.

Fever and hyperthermia

As mentioned above, body temperature is normally regulated by the hypothalamus. *Fever* (pyrexia) is a controlled increase in body temperature due to an elevated hypothalamic set-point temperature. Common reasons for this include infections, inflammatory disorders, neoplastic disease, and some drug treatment. *Hyperthermia* (hyperpyrexia) implies a disturbance of thermoregulatory control. It is caused by external factors such as injury to the hypothalamus, heat stroke following defective heat loss (as occurs in dehydration or excessive heat production following strenuous activities), excessive dosage of some drugs, or a reaction to certain drugs such as anaesthetics (malignant hyperthermia, p. 2024.1) or antipsychotics (neuroleptic malignant syndrome, p. 1050.2). Underlying thermoregulatory defects may be a particular problem in sedentary elderly subjects.

Whenever possible the underlying cause of **fever** should be identified and treated.[1] Body temperatures up to 41 degrees are relatively harmless[2] and it is not clear if there is any value in treating fever at lower temperatures,[1] but some groups may be more vulnerable, such as young children, pregnant women, or patients who are already dehydrated or malnourished or those with cardiac, respiratory, or neurological diseases.

Both physical means and antipyretics may be used to reduce body temperature in fever. Maintaining an adequate fluid intake is important. Fanning, removal of clothing, and tepid sponging are often used,[1-3] but they do not reduce the set-point of the hypothalamus, and lead to shivering (rigor) or other adverse effects as the body tries to meet the raised set-point, and their value is therefore questionable;[1,4,5] similarly, cold baths should not be used as they may actually increase body temperature by inducing vasoconstriction, and the risks of a cold-induced pressor response should be borne in mind. Antipyretics appear mostly to help return the set-point temperature to normal by inhibiting central synthesis and release of prostaglandin E_2, which mediates the effect of endogenous pyrogens in the hypothalamus.[6] This mechanism cannot lower the body temperature below normal, and antipyretics are ineffective against raised body temperature not associated with fever.

Choice of antipyretic in children has been widely debated. The drugs most commonly used are paracetamol and ibuprofen; salicylates (including aspirin) are generally contra-indicated because of the possible link between their use and the development of Reye's syndrome. A systematic review[7] found inconsistent evidence to support the use of paracetamol to reduce fever in children, since the number of reliable studies was too low to be sure that it was effective. Although studies have found that ibuprofen was superior to paracetamol in terms of both efficacy and duration of action, some of the doses of paracetamol were below those recommended in the UK and NICE did not consider that either drug had a significant advantage over the other.[1] Alternation of the two may be more effective than either alone[8,9] but again this is controversial.[1,4,5,9-12]

Antipyretics should not be given to all children with fever, but only to those in obvious discomfort or distress because of the fever or associated symptoms such as headache or myalgia.[1,4,5,13] It has been suggested that the use of antipyretics might prolong infection,[2] and that in severe infection the use of antipyretics might increase mortality:[14] WHO has[14] recommended that in developing countries antipyretics should not be given routinely to children with fever but should be reserved for those with severe discomfort or high fever. In the UK, the Joint Committee on Vaccination and Immunisation recommends antipyretic therapy to treat post-immunisation fever developing after some vaccines. However, if the fever persists after the second dose of antipyretic medical advice should be sought.

Antipyretics have also been given as *prophylaxis* against febrile convulsions, especially in those with a history of such seizures or in those with epilepsy. However, antipyretic therapy does not appear to prevent recurrence of febrile convulsions (p. 511.2).[1,15,16] There is also little to support the use of antipyretics for prophylaxis of post-immunisation fever. Furthermore, there is preliminary evidence that, although effective in preventing fever, prophylactic paracetamol can reduce antibody response to the vaccine.[17] Routine use may not be justified although some have suggested offering it to infants at higher risk of seizures receiving diphtheria-tetanus-pertussis or polio immunisation.[18]

Recommendations for management of fever in adults are similar to those for children,[2,6] although salicylates such as aspirin may also be used.

Hyperthermia may produce body temperatures greater than 41 degrees. These high temperatures are life-threatening and need to be lowered immediately. Antipyretics are ineffective since the high temperatures are a result of thermoregulatory failure. One of the most rapid and effective means of cooling is to immerse the patient in very

cold water but core temperature should be monitored to avoid inducing hypothermia.[19] Evaporative cooling methods may be more efficient.[20] Intravenous or intraperitoneal administration of cool fluids, gastric lavage or enemas with ice water have also been used.[19,21]

When hyperthermia is associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, as in the neuroleptic malignant syndrome and malignant hyperthermia, temperature reductions may be obtained using the muscle relaxant dantrolene. There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents. However, dantrolene is not an effective treatment for all types of hyperthermia and rigidity accompanying poisoning. Although dantrolene has been tried in patients with heat stroke, there is no evidence that it affects outcome.[22] In severe cases of hyperthermia when neuromuscular hyperactivity may also impair ventilation, a neuromuscular blocker has been used, although suxamethonium is best avoided as it can itself precipitate malignant hyperthermia.

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Musculoskeletal and Joint Disorders

The **rheumatic disorders** are painful disorders affecting mainly the joints and related structures of the musculoskeletal system, but there may also be widespread involvement of other systems. The term arthritis is used when the disease is largely confined to the joints. Some of the most common forms of arthritis are discussed in this section and these include rheumatoid arthritis (p. 13.2), osteoarthritis (below), juvenile idiopathic arthritis (below), and the spondyloarthropathies (p. 14.3) such as ankylosing spondylitis. Other conditions that are associated with arthritis and which are discussed elsewhere include gout (p. 600.1) and SLE (p. 1613.3).

The names **soft-tissue rheumatism** (see p. 14.2) and **non-articular rheumatism** have been used to describe some painful conditions associated with disease of the structures that surround a joint. For a discussion of the management of **low back pain**, see p. 9.2.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (juvenile chronic arthritis) is a term used to describe a clinically heterogeneous group of idiopathic arthritides occurring in children under 16 years of age; subtypes include systemic arthritis, oligoarthritis and extended oligoarthritis (particularly of leg joints), polyarthritis, either positive or negative for rheumatoid factor, and enthesitis-related arthritis (commonly affects the joints of the leg and spine).[1-3]

Treatment involves many of the same drugs used for rheumatoid arthritis in adults (see p. 13.2), although there may be limited evidence for their use in children.[1-11] Appropriate management will depend on the subtype of disease, but there is no definitive consensus on the drugs of choice.

- The **NSAIDs** have been a mainstay of treatment for many years, and continue to be important.[1,2] Most children begin therapy with an NSAID,[1] and they may be particularly useful in oligoarthritis.[2] Naproxen, ibuprofen, or indometacin are among the most often used.[1] Aspirin is now rarely prescribed,[9] although in many juvenile idiopathic arthritis remains one of its few licensed indications in children.
- Intra-articular injections of a **corticosteroid** (often triamcinolone hexacetonide) are rapidly effective, and well tolerated, and are often used in oligoarthritis with, or instead of, NSAIDs;[1-3,6,10] they may reduce the development of deformity secondary to contracture.[1] They also have a role in the management of disease flare in patients already taking second-line drugs, although it is unclear whether multiple intra-articular injections would be preferable to systemic corticosteroids in patients with polyarthritis.[6]
  Moderate or high-dose systemic corticosteroids are more generally reserved for patients with systemic arthritis whose disease is not controlled by NSAIDs. In other subtypes, the adverse effects of systemic therapy are likely to outweigh the benefits. A course of low-dose prednisone might be considered for reduction of pain and stiffness in patients with severe polyarthritis who are unresponsive to other drugs, or awaiting response to slow-acting second-line treatments.[1]
- The second-line treatment of choice in children with persistent active arthritis is **methotrexate**.[1-3,7,9,10] Like several other second-line drugs it is of less benefit in systemic arthritis than in polyarthritis or refractory oligoarthritis.[9] Improvement may take up to 12 weeks to be seen.[1]
- The so-called **biological therapies** have become increasingly important in managing more severe or refractory forms of juvenile idiopathic arthritis.[1-3,5,9,11] The TNF inhibitor etanercept, which is licensed for paediatric use in many countries, produces excellent responses in many patients with polyarthritis, particularly those who are rheumatoid-factor positive.[9] Like methotrexate, it may be less effective in those with systemic juvenile idiopathic arthritis.[2,11] Infliximab, although unlicensed, also seems to be of benefit,[1-3,9,11] and may be more effective than etanercept in the treatment of associated uveitis.[2] Other drugs that have been tried with some evidence of benefit include abatacept, adalimumab, tocilizumab, anakinra, and canakinumab;[1,2,9,11,12] there is some evidence that the interleukin-1 receptor antagonist, anakinra, may be more effective than the TNF inhibitors in treating patients with systemic arthritis.[2] Abatacept, adalimumab, canakinumab, and tocilizumab are now licensed in some countries for paediatric use in active disease.
- Many **other drugs** have been tried in juvenile idiopathic arthritis, often on the basis of efficacy in adults. Sulfasalazine may be of benefit in late-onset oligoarthritis[1] but adverse effects are often troublesome.[9,10] Concern about adverse effects may also have limited the use of cytotoxic and immunosuppressant drugs other than methotrexate, and there are few controlled studies,[9] although benefit has been reported with leflunomide in polyarticular disease.[1,9,10] Thalidomide has been suggested for treatment-resistant systemic arthritis.[1] In very severe unremitting disease, autologous bone marrow transplantation has been tried.[1,3,8-10]

Drug treatment aimed at the complications of disease, rather than the disease process itself, may be needed. There is some evidence that bisphosphonates may be useful in controlling low bone mineral density and fragility fractures associated with juvenile idiopathic arthritis.[1,13] Growth hormone has also been widely used to moderate the severe growth retardation that is often seen.[1] Topical treatment with glucocorticoids and mydriatics may be needed for eye disease.[1]

Physiotherapy and occupational therapy are also important components of disease management, and surgery may be needed in selected cases.[1]

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Osteoarthritis

Osteoarthritis is the clinical and pathological outcome of a range of disorders that cause structural and functional failure of synovial joints. It is characterised by involvement of the entire joint, with loss and erosion of articular cartilage, subchondral bone changes, meniscal degeneration, mild to moderate synovial inflammation, and outgrowth of bone and cartilage at the joint margins (osteophytes). These changes result in pain, stiffness (especially after inactivity) and reduced mobility, although patients with changes characteristic of osteoarthritis are often asymptomatic. Increased loading of the joint, and mechanical factors such as misalignment and muscle weakness, contribute to joint damage and loss of function. The joints most often affected are hands, hips, and knees.

Current treatment for osteoarthritis is not curative, and management is largely concerned with relief of pain and maintenance of joint function.[1-6]

Physical methods of treatment may be preferred initially, and include physiotherapy, heat and cold therapy, exercises, splinting, correction of misalignment, and weight reduction in the obese.[1-8] Acupuncture may also be tried, and appears to be of benefit in improving pain and functionality in knee osteoarthritis.[9] Transcutaneous electrical nerve stimulation (TENS) may also be of benefit; however, a systematic review[10] was found to be inconclusive due to the inclusion of small and poor studies.

For the management of pain, paracetamol is recommended as the drug of first choice.[1-6,8] Despite its benefits paracetamol has been shown to be less effective than an NSAID in patients with osteoarthritis,[11] and the latter may therefore be considered as an alternative first-line treatment.[2,4] However, the possibility of cardiovascular, gastrointestinal, or renal toxicity with NSAID treatment should be considered as its use is in a largely elderly group of patients; it is generally advised that a low-dose NSAID should only be added or substituted in patients with an inadequate response to paracetamol alone,[2,4-6] and the long-term use needed for osteoarthritis management may be problematic.[12]

In order to reduce the risk of gastrointestinal toxicity with NSAIDs, use of a gastroprotective drug such as a proton pump inhibitor or misoprostol has been recommended.[1-6,8] Cardiovascular safety is a particular concern with NSAIDs such as celecoxib that are selective inhibitors of cyclo-oxygenase-2 (COX-2); their use is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Effects on the Gastrointestinal Tract, p. 105.3). The use of topical NSAIDs has also been advocated,[4,6,8] although a meta-analysis[13] in 2004 found little evidence of long-term benefit.

In patients in whom paracetamol and/or NSAIDs are ineffective or not tolerated, addition of an opioid analgesic may be appropriate;[2,3,5,6,8,14] codeine or dihydrocodeine are often used as combinations with paracetamol, and there is evidence of benefit with tramadol, but more potent opioids such as hydrocodone, oxycodone, transdermal fentanyl, or morphine, may have a role in a selected subgroup of patients.[14]

The anthraquinone derivative diacerein has been widely used in some countries, and appears to produce a small but consistent benefit in the treatment of osteoarthritis.[15] Topical capsaicin also produces some relief of pain.[1,4-6,8] There are some interesting data[16] to suggest that doxycycline may have a favourable effect on the progression of osteoarthritis, which might open the way for the development of disease-modifying drugs. Experimental therapies include anakinra[17] and the combined cyclo-oxygenase/lipoxygenase inhibitor licofelone.[18]

Systemic corticosteroids have no place in the management of osteoarthritis. Intra-articular injection of a corticosteroid produces short-term relief of pain and inflammation,[2-4,6,8,19,20] and may be useful for acute exacerbations. Triamcinolone hexacetonide appears to be more effective than betamethasone.[20] There may also be some benefit from intra-articular injection of hyaluronic acid, to improve the viscosity and elasticity of the synovial

fluid;[21,22] improvement may be longer lasting than with intra-articular corticosteroids.[20]

Alternative and complementary therapies have been widely used in osteoarthritis.[2] Powdered rose hip has been reported to be of benefit,[23] as has a mixture of unsaponifiable fractions from avocado and soya oils (avocado-soybean unsaponifiables; ASU).[24] Particular attention has focused on the use of oral glucosamine and chondroitin. Results, however, have been ambiguous:[25-28] overall it is not clear to what extent these therapies have a benefit over placebo, but there is some evidence that combined treatment may be useful in the subset of patients with moderate to severe knee pain.[25] Evidence for chondroitin seems particularly weak.[28] An evidence-based report[29] by the Arthritis Research Campaign in the UK of 27 alternative and complementary medicines used for osteoarthritis, including ASU, capsaicin, chondroitin, glucosamine, and rose hip, found topical capsaicin to be the most effective and that ademetionine, the active derivative of methionine, may also be effective; evidence for the efficacy of glucosamine was inconclusive. However, a systematic review[30] of ademetionine therapy for osteoarthritis of the knee or hip was found to be inconclusive and routine use was not recommended.

Surgery, including joint replacement, is of great benefit to patients with severe osteoarthritis that cannot be effectively managed by physical or medical therapy.[2-6,8]

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Rheumatoid arthritis

Rheumatoid arthritis is a common chronic systemic inflammatory disease that results in progressive disability and increased mortality. Early disease is characterised mainly by inflammation of the synovium (the inner membrane of the capsule of synovial joints); as the disease progresses the patient suffers destruction of cartilage and bone. Extra-articular features commonly include general malaise, fatigue, weight loss, fever, and anaemia. More severe disease may be associated with vasculitis, pericarditis, pleurisy, pleural effusion, pulmonary interstitial fibrosis, peripheral neuropathies, subcutaneous and pulmonary nodules, scleritis, and Sjögren's syndrome. Palindromic rheumatism is characterised by repeated episodes of arthritis and periarthritis without fever; the joints appear normal between attacks.

The severity and course of rheumatoid arthritis varies greatly between patients. Some have brief attacks with little or no disease progression, but the majority will have slowly progressive joint destruction and deformity despite intermittent relapses and remissions; a few patients may have very severe and rapidly progressive disease. Because irreversible joint damage occurs early in the course of disease, rapid diagnosis and institution of treatment aimed at preventing progression is crucial.[1-4] Although there is no cure, remission or substantial slowing of the disease process is increasingly seen as an achievable goal in the majority of patients.[4-6]

The choice of **drugs for relief of pain** depends upon the severity of symptoms. NICE[7] recommends using analgesics such as paracetamol, codeine, or combination preparations in patients with inadequate pain control, to potentially reduce their need for long-term treatment with NSAIDs. Nevertheless, most patients prefer an NSAID; although these are thought to have an advantage because of their anti-inflammatory effects, the clinical evidence for this has been questioned.[8] There is little apparent difference between the various NSAIDs in terms of anti-inflammatory activity, but patient responses vary widely. When starting an NSAID the dose is gradually increased to the recommended maximum over 1 to 2 weeks; if the response is inadequate after a total of about 4 weeks, or if adverse effects are intolerable, other NSAIDs are tried. In the light of concerns about cardiovascular safety, treatment with selective inhibitors of cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors[9] (see Effects on the Gastrointestinal Tract, p. 105.3). Topical analgesics such as NSAIDs or capsaicin, or rubefacients may provide slight relief of pain but their role, if any, is unclear.

Once the diagnosis is confirmed and severity and progression of the disease have been assessed, introduction of a **disease-modifying antirheumatic drug** (DMARD) should take place as early as possible.[1-3,5] Although opinions vary, there is an increasing trend to aggressive management in early disease, with tight control of the disease process.[4-7,10]

Available DMARDs include antimalarials (hydroxychloroquine), sulfasalazine, gold compounds (auranofin, sodium aurothiomalate), penicillamine, conventional immunosuppressants (methotrexate, azathioprine, ciclosporin, cyclophosphamide, and leflunomide), and Janus tyrosine kinase inhibitors (tofacitinib). So-called biological therapies include the TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), co-stimulation blockers (abatacept), interleukin-1 receptor antagonists (anakinra), and B-cell-targeted monoclonal antibodies (rituximab). It is thought that most DMARDs inhibit the release or activity of cytokines involved in maintaining the inflammatory process, although other actions may also contribute. Since any therapeutic effect may not be apparent for 4 to 6 months, treatment should continue for at least 6 months before considered ineffective.

There is evidence of disease-modifying effect for methotrexate, sulfasalazine, leflunomide, and intramuscular gold, with less compelling data for hydroxychloroquine, penicillamine, oral gold, ciclosporin, and azathioprine.[10-16] Concerns about toxicity or efficacy mean that gold compounds and penicillamine seem now to be less widely used. There is good evidence of the efficacy of the TNF-α inhibitors,[5,6,10,16-20] and some in favour of anakinra,[17,19] but good evidence of an effect of other biological therapies on disease progression is currently scanty, although clinical benefit has been found with, for example, abatacept and rituximab.[6,17,19,21]

The choice of DMARD to begin treatment is based on the risk/benefit ratio, with the antimalarial hydroxychloroquine an option in mild disease, and sulfasalazine or methotrexate preferred in those with moderate to severe disease, or judged likely to progress.[10] Methotrexate has become the DMARD of first choice in the majority of patients.[1,2,4,10] Subcutaneous or intramuscular methotrexate may be an option in patients who cannot be satisfactorily managed with weekly oral dosage.[1,10] Addition of sulfasalazine, hydroxychloroquine, or both may be a suitable option in patients refractory to optimal methotrexate therapy,[1,10] and addition of corticosteroids or leflunomide are also options, although evidence for combining methotrexate with ciclosporin is not entirely convincing.[10] At what stage biological therapies are to be recommended remains a matter of debate. In the UK, official recommendations are still that TNF-α inhibitors should be reserved for patients who have failed treatment with two conventional (non-biological) DMARDs,[18,20,22] but others permit earlier introduction, for example after failure of the first conventional DMARD.[17,23,24] Other classes of biological therapy are likely to be reserved for patients in whom TNF-α inhibitors are ineffective or contra-indicated, as is currently the case with abatacept[4,24] and rituximab.[4,21,24,25] In the UK, rituximab is recommended in patients who have an inadequate response to TNF-α inhibitors; abatacept or an alternative TNF-α inhibitor may be tried in those who cannot be given, or have an inadequate response to, rituximab.[21]

There is also some evidence in favour of beginning therapy with a combination of DMARDs, and subsequently 'stepping down' once control is achieved.[1,5,6,10,26,27] Indeed, NICE[7] in the UK recommends using a combination of DMARDs (including methotrexate and at least one other conventional DMARD, plus short-term corticosteroids) as first-line treatment, ideally within 3 months of the onset of persistent symptoms. The large, multicentre BeSt study found that although initial combination therapy (methotrexate and infliximab, or methotrexate, sulfasalazine, and tapered high-dose prednisone) produced earlier clinical improvement and less progression of joint damage, the ultimate clinical improvement was similar in patients assigned to sequential monotherapy or 'step-up' therapy.[28] There is a concern that combination therapy may expose patients to an increased risk of toxicity,[26] although the BeSt study did not find this to be the case.[28] Combinations of TNF-α inhibitors with other biological therapies such as anakinra or abatacept are not advisable, because of an increased risk of serious infection.[6,17]

Since rheumatoid arthritis is a chronic disease, treatment may need to be very prolonged, but evidence of the long-term tolerability and efficacy of DMARDs is patchy. Studies have suggested that many DMARDs are stopped after a few years, usually because of a decline in efficacy rather than adverse events.[29]

Addition of **corticosteroids** to DMARD therapy may be useful in early disease to control synovitis, or as bridging therapy when starting or increasing DMARDs, since they produce rapid symptomatic control.[10] Although they produce bone loss, this may be outweighed (at least short-term) by their beneficial effects on the disease process: there is good evidence that adding a corticosteroid to treatment reduces the progression of joint erosion.[30] Short- and moderate-term intermittent use of relatively low doses has therefore been suggested (not exceeding the equivalent of 15 mg of prednisolone daily).[31,32] However, prolonged therapy is associated with significant adverse effects and long-term use is not usually considered justified,[10] except in a select group of patients with established disease where all other treatment options (including biological DMARDs) have been tried.[7] Intra-articular injection is recommended for acute flares, and may be particularly effective when combined with aggressive DMARD therapy.[10]

There is little good evidence to support most **other drugs** tried in rheumatoid arthritis. Meta-analysis[33] has confirmed that tetracyclines, and in particular minocycline, can produce some reduction in disease activity; effects on serological markers appear to be more marked than clinical improvements in tender and swollen joints. The effects may be greater in patients with early disease; minocycline has been recommended[24] for those with low disease activity. Much research has been conducted into immunomodulators and immunotherapy. Although alternative immunosuppressants such as mycophenolate mofetil and tacrolimus have been tried, most interest in recent years has surrounded new biological therapies. The interleukin-6 receptor antagonist tocilizumab is given with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in patients who have not responded to, or are intolerant of, conventional DMARDs or TNF-α inhibitors. It may also be given as monotherapy to patients who are unable to tolerate methotrexate or in whom methotrexate would otherwise be inappropriate. Matrix metalloproteinase inhibitors have proved disappointing, but modulators of B-cell function such as atacicept, belimumab, and epratuzumab are under investigation. In addition, denosumab is of interest for its potential to control joint destruction.[6] Other methods of treatment that are being or have been investigated include gene therapy and autologous bone marrow transplantation. A rheumatoid

arthritis vaccine is also in clinical trials. Induction of tolerance with collagen and other antigens given orally has also been tried, but results are reported to be variable.[34]

Many alternative and herbal therapies have been tried. Some studies suggest that addition of fish oils[35] and/or evening primrose oil to standard antirheumatic therapy might help to reduce pain and joint swelling. However, an evidence-based report[36] by the Arthritis Research Campaign in the UK of 21 alternative and complementary medicines used for rheumatoid arthritis, including collagen, evening primrose oil, fish oils, and green-lipped mussel, only found evidence of efficacy for fish oils.

There has been considerable interest in the possibility that statins such as atorvastatin may produce clinical improvements, albeit modest, in symptoms of rheumatoid arthritis,[37] as well as in any accompanying cardiovascular risk factors.

The importance of managing comorbidity in patients with rheumatoid arthritis has been emphasised;[1] in particular infection (especially pulmonary infection), cardiovascular disease, and osteoporosis require appropriate management and action to reduce risk factors.

The treatment of rheumatoid arthritis during **pregnancy** presents its own problems; some of the most effective DMARDs such as methotrexate and leflunomide have teratogenic properties, and for others, including the biological therapies, there is little evidence.[38,39] Hydroxychloroquine, and perhaps azathioprine and sulfasalazine, may be relatively safe to use, but it is important to weigh benefit against risk for each individual case.[38]

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Soft-tissue rheumatism

Soft-tissue rheumatism includes conditions such as:

- bursitis (e.g. housemaid's knee)
- fasciitis
- fibromyalgia (fibrositis, muscular rheumatism, myofascial pain)
- frozen shoulder
- humeral epicondylitis (e.g. tennis or golfer's elbow)
- sprains and strains
- tendinitis
- tenosynovitis
- Tietze's syndrome

Inflamed or displaced tissue may also impinge on nearby nerves and produce compression neuropathies such as carpal tunnel syndrome.

Some forms of soft-tissue rheumatism respond to selective rest of the affected region, massage, splinting, or application of heat, cold, or rubefacients.[1-3] Exercise is of value in neck pain,[3,4] fibromyalgia,[5-10] and frozen shoulder,[11] but its benefit in epicondylitis is unclear.[4]

For patients with epicondylitis oral or topical NSAIDs may offer short-term pain relief, but it is unclear if they are effective in producing longer term benefit.[3,4] They are of unknown benefit in frozen shoulder,[11] and are not thought to be helpful in fibromyalgia,[5,12,13] although some benefit has been reported with paracetamol and tramadol.[8,10,12-14]

Corticosteroid injections produce dose-dependent benefit for up to 9 months in shoulder pain such as that associated with rotator cuff tendinitis or frozen shoulder,[15] and oral corticosteroids may be of benefit for up to 6 weeks although it is not clear that benefit is subsequently maintained[16] (a study[17] in patients with epicondylitis suggested that benefits of corticosteroid injection in this group were paradoxically reversed after 6 weeks). Corticosteroid injections are often combined with a local anaesthetic; injection of a local anaesthetic alone has been shown to be of benefit in chronic neck pain.[4]

Botulinum toxin has been tried in epicondylitis[18] and myofascial pain.[19] There is evidence that nitric oxide plays a role in healing in patients with tendinitis, and topical application of a patch containing glyceryl trinitrate has proved of benefit in patients with epicondylitis or tendinitis.[20]

Fibromyalgia appears to be associated with abnormal pain responses, and some consider it a central pain syndrome rather than a rheumatic syndrome. There is strong evidence that low-dose tricyclic antidepressants are of benefit in many patients, as is the tricyclic compound cyclobenzaprine. Combination of amitriptyline with the SSRI fluoxetine also appears beneficial, although SSRIs alone have produced equivocal results; serotonin and noradrenaline reuptake inhibitors (SNRIs) such as duloxetine, milnacipran, or venlafaxine have also been reported to be of value. A meta-analysis[21] of antidepressants (the aforementioned drug groups and MAOIs) in the treatment of fibromyalgia found strong evidence for their efficacy in reducing pain, sleep disturbances, and depressed mood, and improving health-related quality of life; however, effect sizes were small. Nevertheless, the authors suggested using short-term amitriptyline (based on effect size) and duloxetine (based on number of patients studied) for the treatment of pain and sleep disturbances. The antiepileptics pregabalin and gabapentin have been shown to be of benefit in controlled studies.[5,6,8,10,12-14] Duloxetine, milnacipran, and pregabalin are now licensed in some countries for the treatment of fibromyalgia. Sodium oxybate has also been reported to show some benefit. Alternative and complementary therapies have been tried;[13] however, an evidence-based report[22] by the Arthritis Research Campaign in the UK of 4 such therapies, including ademetionine (the active derivative of methionine) and topical capsaicin, found no evidence of efficacy.

Surgery may be of benefit in some conditions such as epicondylitis and possibly shoulder pain.[3,4] Surgical decompression is also the definitive treatment for carpal tunnel syndrome,[23] although there is also evidence of benefit from splinting[2,24] and local corticosteroid injection[2,25] (although benefit may not be long term, and the procedure carries some risks[26]). A systematic review[27] concluded that surgical treatment was significantly better than splinting for symptomatic relief of carpal tunnel syndrome. However, further study is needed to determine if it is better than corticosteroid injection or for patients with mild symptoms. Oral corticosteroids and ultrasound have also shown benefit in patients with carpal tunnel syndrome.[24]

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Spondyloarthropathies

The spondyloarthropathies are a group of seronegative arthritides which include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disorders (enteropathic arthritis), and arthritis associated with infection as in reactive arthritis (aseptic arthritis).

Ankylosing spondylitis is characterised by arthritis of the spine and sacroiliac joints and sometimes there is also asymmetrical peripheral involvement. Axial spondyloarthritis is considered an early stage of ankylosing spondylitis. Males under 40 years of age are mainly affected. The aim of

management of the disease is to reduce pain and stiffness and to prevent spine and joint deformity, which is accomplished using a combination of active physical therapy and drug therapy. Exercises are used to strengthen muscles and to maintain a good posture and range of movement in joints. NSAIDs are used to relieve pain and inflammation, thus allowing the exercises to be performed; they do not influence the progression of the disease. Some patients may need to add other non-opioid analgesics such as paracetamol for additional pain control. Systemic corticosteroids are rarely indicated but intra-articular injections of corticosteroids may be beneficial when one or two peripheral joints are severely affected. The disease-modifying antirheumatic drug (DMARD) sulfasalazine is of benefit for peripheral arthritis, but not for spinal symptoms. The efficacy of most other DMARDs used in rheumatoid arthritis (see p. 13.2) remains to be shown. However, the TNF-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab improve spinal pain, function, and peripheral joint disease. They produce rapid benefit (usually within 12 weeks) although most patients relapse once they are withdrawn. Treatment with a TNF-α inhibitor should be considered in patients with active disease despite conventional treatments. There is some evidence that early intervention may produce better remission rates, but it is yet unknown if this results in longer-lasting remission on withdrawal. Evidence is mostly lacking for other biological therapies, but no marked benefit has been seen in conflicting studies with the interleukin-1 receptor antagonist anakinra.

Psoriatic arthritis (or psoriatic arthropathy) is an inflammatory seronegative arthritis occurring in patients with psoriasis. In some patients the spine may be involved when the condition may be indistinguishable from ankylosing spondylitis. Less frequently some patients have a form of symmetrical arthritis resembling rheumatoid arthritis. The psoriasis (p. 1688.1) and the arthritis usually require separate treatment. Treatment of the arthritis is initially as for ankylosing spondylitis with NSAIDs and physical therapy. If these methods fail treatment with a DMARD may be instituted, although chloroquine and hydroxychloroquine should be avoided since they may precipitate skin reactions (see Psoriatic Arthritis, p. 653.2). There is most evidence to support the use of sulfasalazine or methotrexate. Leflunomide may be effective but is likely to be restricted by its toxicity and prolonged half-life. Ciclosporin is also restricted by its toxicity. As in ankylosing spondylitis, however, significant benefit has now been found with the TNF-α inhibitors, and treatment with these is recommended in patients with active disease despite treatment with NSAIDs and/or conventional (non-biological) DMARDs. Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are available and treatment should be individualised; a monoclonal antibody such as adalimumab or infliximab may be advocated in patients who also have inflammatory bowel disease. There is some suggestion that alefacept may also be of benefit in psoriatic arthritis. Systemic corticosteroids have little or no place in the management of psoriatic arthritis.

Reactive arthritis (aseptic arthritis) is characterised by sterile synovitis following 1 to 4 weeks after an infection, most commonly of the gastrointestinal or genito-urinary tract. Extra-articular features involving the skin, eyes, or genito-urinary tract may or may not be present. Reactive arthritis is also a feature of Reiter's syndrome. Reactive arthritis is treated with physical therapy and NSAIDs and, if indicated, intra-articular injections of corticosteroids; the role of antibacterials is less certain (see Bone and Joint Infections, p. 177.1).

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Still's disease

Adult-onset Still's disease is a syndrome characterised by high fever, with body temperature classically spiking daily or twice daily, an evanescent pink maculopapular rash, and arthritis (usually oligoarthritis initially). It is most common in patients aged 16 to 35 years.

Treatment has traditionally relied on NSAIDs, corticosteroids, and immunosuppressants or other DMARDs similar to those used in rheumatoid arthritis (p. 13.2).[1-3] A trial of NSAIDs is worthwhile in patients with mild disease, but most patients cannot be managed with NSAIDs alone.[2,3] Corticosteroids may be needed for initial therapy if manifestations are severe, but will eventually be needed in about 80% of cases.[2] DMARDs (generally methotrexate) are introduced when corticosteroid therapy fails to control the disease or when their adverse effects become problematic. Most patients will respond to methotrexate although liver function must be closely monitored. The value of other DMARDs is uncertain. Intravenous immunoglobulin is also frequently tried, although supporting evidence is lacking.[2,3]

The TNF-α inhibitors have also been tried,[2,3] but results have been variable.[2] There is, however, some evidence that interleukin-1 and interleukin-6 play a role in pathogenesis of the condition, and there have been a few reports of dramatic improvement with anakinra (an interleukin-1 receptor antagonist) in resistant disease, while tocilizumab (an interleukin-6 receptor antagonist) has also been suggested as an investigational therapy.[2,3]

The name Still's disease has also been used rather inconsistently to describe some types of juvenile idiopathic arthritis (p. 12.1).

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Abatacept *(BAN, USAN, rINN)*

Abataceptum; BMS-188667; CTLA4-Ig; Абатацепт.

1-25-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human heavy chain fragment), bimolecular (146→146')-disulfide.

CAS — 332348-12-6.
ATC — L04AA24.
ATC Vet — QL04AA24.
UNII — 7D0YB67S97.

Uses and Administration

Abatacept, a fusion protein, is a co-stimulation blocker. It prevents the activation of T-cells; activated T-cells have been found in the synovium of patients with rheumatoid arthritis. Abatacept is described as a biological disease-modifying antirheumatic drug (DMARD).

Abatacept is used in the treatment of moderate to severe active rheumatoid arthritis (below). In the UK, it is licensed for use in patients who have had an inadequate response to at least one other DMARD, including methotrexate or a TNF inhibitor; in the USA, it is licensed for use in early disease. In the UK, abatacept is licensed for use with methotrexate; however, in the USA it may be given alone or with other DMARDs (but see Interactions, p. 16.1).

Abatacept is given by *intravenous infusion* over a period of 30 minutes in the following doses, based on body-weight:

- 500 mg for patients weighing less than 60 kg
- 750 mg for those weighing 60 to 100 kg
- 1 g for those over 100 kg

The dose is repeated at 2 and 4 weeks, then every 4 weeks thereafter. If a response to treatment is not seen within 6 months, the benefits of continuing abatacept may need to be considered.

Abatacept may also be self-administered by *subcutaneous injection*. After a single intravenous loading dose given according to body-weight (as above), the first subcutaneous dose of 125 mg should be injected within a day; thereafter, 125 mg is injected once weekly. Patients who are unable to receive an infusion can start weekly subcutaneous injections without an intravenous loading dose. Those who are transferring from intravenous therapy should inject the first subcutaneous dose instead of receiving the next scheduled intravenous dose.

For the use of abatacept in children, and recommended doses, see below.

Abatacept is also being studied for other auto-immune diseases such as inflammatory bowel disease, psoriatic arthritis, and SLE.

Administration in children. Abatacept is licensed in the treatment of moderate to severe, active juvenile idiopathic arthritis in children aged 6 years and above; it may be used alone or with methotrexate. The dose is calculated according to body-weight and is given as an *intravenous infusion* over 30 minutes; those weighing less than 75 kg should be given 10 mg/kg initially, while heavier children may receive the appropriate adult intravenous dose (see above). Doses should be repeated at 2 and 4 weeks, and then every 4 weeks thereafter.

Rheumatoid arthritis. References to the use of abatacept in rheumatoid arthritis[1-9] (p. 13.2) and juvenile idiopathic arthritis[10-12] (p. 12.1).

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Adverse Effects and Precautions

Reactions commonly occur within 1 hour of starting an infusion of abatacept. The most frequently reported infusion events are dizziness, headache, and hypertension; hypo-

tension and dyspnoea occur less commonly. Other acute events include nausea, flushing, pruritus, rash, and wheezing. Most events are usually mild to moderate although stopping treatment may be necessary in a few patients.

Other common adverse effects include headache, nasopharyngitis, nausea, dyspepsia, diarrhoea, dizziness, back pain, fatigue, cough, and abnormal liver function values. Antibodies to abatacept may develop and anaphylaxis or anaphylactic reactions have been reported rarely. Uncommon adverse reactions include paraesthesia, thrombocytopenia, and leucopenia.

Infections are frequent in patients treated with abatacept and most often affect the respiratory and urinary tracts. More serious infections such as pneumonia, sepsis, cellulitis, bronchitis, diverticulitis, and acute pyelonephritis have also been rarely associated with abatacept treatment; some of these infections have been fatal. Treatment should be stopped in patients who develop a serious infection. Since immunosuppressive therapy has been associated with progressive multifocal leukoencephalopathy (PML) treatment with abatacept should be discontinued if neurological symptoms suggestive of PML occur during use. Abatacept should not be given to patients with severe and uncontrolled infections such as sepsis and opportunistic infections. It should be used with caution in patients with a history of recurrent infections, with underlying conditions that may predispose to infections, or with chronic, latent, or localised infections. Patients should be screened for latent tuberculosis before starting treatment; those testing positive should be treated with standard chemoprophylaxis before beginning abatacept.

Some disease-modifying antirheumatic drugs have been associated with hepatitis B reactivation; licensed product information for abatacept recommends screening for viral hepatitis before starting treatment.

Adverse effects of abatacept are more frequent in patients with chronic obstructive pulmonary disease and may include a worsening of their respiratory symptoms.

Carcinogenicity. The role of abatacept in the onset of malignancies such as lymphoma in humans is not known.

In placebo-controlled studies the overall frequency of malignancies in patients treated with abatacept compared with those who received placebo was similar (1.4% and 1.1%, respectively). However, there were more cases of lung cancer and lymphomas in those given abatacept. In studies in *mice*, increases in lymphomas and mammary tumours have been noted, although these increases have not been seen in some studies with other mammals.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies abatacept as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Interactions

Live vaccines should not be given with abatacept, or within 3 months of stopping it, as its effect on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with abatacept may increase the risk of serious infections (see under Infliximab, p. 77.3); such combinations are not recommended. Many of the serious infections reported have occurred in patients also receiving immunosuppressive therapy (see also p. 15.3). Use with anakinra or rituximab is also not recommended because of insufficient evidence to assess safety.

Pharmacokinetics

Abatacept is reported to have linear pharmacokinetics at usual dosages. After repeated intravenous doses, its mean terminal half-life is about 13 days. The mean terminal half-life after subcutaneous administration is about 14 days; bioavailability relative to intravenous use is about 79%.

Studies in *animals* suggest that abatacept is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Orencia; ***Austral.***: Orencia; ***Austria***: Orencia; ***Belg.***: Orencia; ***Braz.***: Orencia; ***Canad.***: Orencia; ***Chile***: Orencia; ***Cz.***: Orencia; ***Denm.***: Orencia; ***Fr.***: Orencia; ***Ger.***: Orencia; ***Gr.***: Orencia; ***Hong Kong***: Orencia; ***Hung.***: Orencia; ***Irl.***: Orencia; ***Israel***: Orencia; ***Ital.***: Orencia; ***Jpn***: Orencia; ***Neth.***: Orencia; ***Norw.***: Orencia; ***NZ***: Orencia; ***Pol.***: Orencia; ***Port.***: Orencia; ***Singapore***: Orencia; ***Spain***: Orencia; ***Swed.***: Orencia; ***Switz.***: Orencia; ***Turk.***: Orencia; ***UK***: Orencia; ***USA***: Orencia.

Aceclofenac *(BAN, rINN)*

Acéclofénac; Aceclofenaco; Aceclofenacum; Aceklofenak; Aceklofenák; Aceklofenakas; Aseklofenaakki; Aseklofenak; Ацеклофенак.

[*o*-(2,6-Dichloroanilino)phenyl]acetate glycolic acid ester; 2-(2,6-Dichloroanalino)phenylacetoxyacetic acid.

$C_{16}H_{13}Cl_2NO_4$=354.2

CAS — 89796-99-6.

ATC — M01AB16; M02AA25.

ATC Vet — QM01AB16; QM02AA25.

UNII — RPK779R03H.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Aceclofenac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Protect from light.

Uses and Administration

Aceclofenac, a phenylacetic acid derivative, is an NSAID (see p. 102.3) related to diclofenac (p. 48.3). It is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, in usual oral doses of 100 mg twice daily. Reduced doses should be used in patients with hepatic impairment, see below.

The sodium salt andaceclofenac betadex (aceclofenac betacyclodextrin) have been used similarly.

Reviews.

1. Dooley M, *et al.* Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. *Drugs* 2001; **61:** 1351–78.
2. Reginster JY, *et al.* Comment positionner l'acéclofénac au sein de l'arsenal thérapeutique des pathologies ostéo-articulaires chroniques? *Rev Med Liege* 2001; **56:** 484–8.
3. Legrand E. Aceclofenac in the management of inflammatory pain. *Expert Opin Pharmacother* 2004; **5:** 1347–57.
4. Lee J, *et al.* Formulation of microemulsion systems for transdermal delivery of aceclofenac. *Arch Pharm Res* 2005; **28:** 1097–1102.

Administration in hepatic impairment. The initial oral dose of aceclofenac should be reduced to 100 mg daily in patients with hepatic impairment.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Hypersensitivity. Leucocytoclastic vasculitis, a type III hypersensitivity reaction, has been reported after therapy with aceclofenac.[1,2] Anaphylaxis has also occurred.[3]

1. Epelde F, Boada L. Leukocytoclastic vasculitis and hemoptysis after treatment with aceclofenac. *Ann Pharmacother* 1995; **29:** 1168.
2. Morros R, *et al.* Hypersensitivity vasculitis related to aceclofenac. *Br J Rheumatol* 1997; **36:** 503–4.
3. Rojas-Hijazo B, *et al.* Anaphylactic reaction after aceclofenac intake. *Allergy* 2006; **61:** 511.

Precautions

As for NSAIDs in general, p. 107.1.

Aceclofenac should be avoided in patients with moderate to severe renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aceclofenac as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Aceclofenac is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. Aceclofenac is more than 99% bound to plasma proteins. The plasma-elimination half-life is about 4 hours. About two-thirds of a dose is excreted in the urine, mainly as hydroxymetabolites. A small amount is converted to diclofenac.

It has been suggested[1] that low concentrations of diclofenac, a minor metabolite, may account for some of the actions of aceclofenac.

1. Hinz B, *et al.* Aceclofenac spares cyclooxygenase 1 as a result of limited but sustained biotransformation to diclofenac. *Clin Pharmacol Ther* 2003; **74:** 222–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Berlofen; Urodulox; ***Belg.***: Air-Tal; Biofenac; ***Braz.***: Cecofene; Proflam; ***China***: Ai Fen (爱芬)†; AiFen (爱芬); Bei Su Qing (贝速清); Fen Ke Jing (分可靖); Ji Li Da (济力达); Lai Yi Fen (莱亿芬); Meinuofen (美诺芬); Wei Pu Fen (维朴芬); Xi Li Te (喜力特); ***Fr.***: Cartrex; ***Ger.***: Beofenac; ***Gr.***: Aceclonac; Arlina; Biofenac; Fractopon; Iasan; Sovipan; ***Hung.***: Acecgen; Aflamin; Flemac; ***India***: Abate-SR; Abdal; AC; ACB; Accept; Aceact; Acebloc; Acec; Aceclo; Acefen; Aceforce; Acelofan; Acelom; Acemove-SR; Acemove; Acenac; Acenez; Acent; Acerap; Acetuff; Acewin-SR; Aci-SR; Acicloflex; Acifact; Acifon; Acilex; Aciz; Aclo; Aclocta; Aclofen; Aclonac-SR; Acota; Afesan; Alnase; Aloo-SR; Alto; Altraflam; Arflur-100; Arflur; Aroff BCD; Aroff; Arrestin; Asiclo; Asonac; Atofen; Avir; Axsol SR; Canefo; Carnil AC; Catrix; Ceco; Celfast SR; Clonac; Cynac; Diplofen; Dipt; Dolochek; Dolokind; Dolostat; Dolour; Dolowin; Eclonac; Ecnac-SR; Elfenac-SR; Elven; Erinac; Fastnac SR; Fepra; Fico; Flamace; Flamtop-SR; Flaxinac-SR; Fornac; Fortafen; Genac; Hifenac; Hinac; Icenac; Icobit; Inane; Kairnac; Kinectine; Labace; Labonac; Letgo; Locet; Mahanac; Megadox; Micronac; Movace; Movexx; Moviz; Movon; Nacku; Naid; NBace-P; Neflo; Niplonac; Novo; Novoflam; Nusaid; Otonac; Painout; Panace; Zerodol; ***Ital.***: Airtal; Gladio; Kafenac; ***Mex.***: Bristaflam; Dexenac; Mycinadol; ***Neth.***: Biofenac; ***Philipp.***: Clanza; ***Port.***: Airtal; Biofenac; ***Rus.***: Airtal (Аэртал); Asinac (Асинак); ***Spain***: Aclocen; Airtal Difucrem; Airtal; Aracenac; Falcol; Gerbin; ***Turk.***: Biofenac; ***UAE***: Aceclofar; ***UK***: Preservex; ***Ukr.***: Airtal (Аэртал); Zerodol (Зеродол); ***Venez.***: Bristaflam.

Multi-ingredient Preparations. ***India***: Abate-CZ; Abate; Abdal Plus; Abdal-SP; AC Para; AC Sera; AC-Plus; AC2; ACB Plus; ACB-S; Accept-P; Accept-SP; Accept; Accetiz-P; Ace-Proxyvon; Ace-Q-Para; Ace-X; Aceact-P; Acebloc-P; Acec Plus; Acec-P; Aceclo Plus; Aceclo-MR; Aceclo-Sera; Acecloren-P; Acecloren; Acedase-P; Acedase; Acefen-P; Acefen-SP; Aceflow-P; Aceforce-MR; Aceforce-P; Aceforce-SP; Acelofan Plus; Acelofan-SP; Acelom-P; Acelom-SP; Acemag-P; Acemiz-MR; Acemove Plus; Acemove-MR; Acemove-XT; Acemove; Acenac-P; Acenec; Acenez-P; Acent-MR; Acent-P; Acent-SD; Acent-TZ; Acent; Acepar-MR; Acepar; Acepara-S; Acepara; Acepil-P; Acerap-P; Aceroc-P; Acetal-SP; Acetech-P; Acetrop; Acetuff-MR; Acetuff-SP; Acewin; Aci-MR; Aciana-P; Acicloflex-MR; Acicloflex-SP; Acidol-P; Acifact-P; Acilex-P; Acimol-S; Aciz Plus; Aciz-SP; Aclocta-P; Aclodase; Aclofen Plus; Aclog-CX; Aclog-SD; Aclog; Aclomp-P; Aclomp-SP; Aclonac-P; Aclonac-SN; Acloson-P; Acloson-SP; Aclozox; Acota-3; Acota-MR; Adifax-P; Adifax-SP; Afen-P; Afesan-CZ; Afesan-P; Afesan-SP; Alco-P; Alco-PS; Aleron; Algin-P; Alnase-P; Alnase-SP; Aloo; Alora; Alostar-SP; Alto P; Alto-3D; Alto; Altraflam-P; Anbrol-A; Ankare; Anodyne-P; Anthro; Ara; Arflur-3D; Arflur-MR; Arflur-P; Arflur; Arifnac-P; Aroff Plus; Aroff-EZ; Arrestin-P; Arrestin-SP; Arthocerin-A; Ascapar-P; Asflam; Asimol-AC; Asonac Forte; Asonac Plus; Asonac-SR Plus; Asonac-SR; Atofen Plus; Away-P; Axsol-P; Canefo-Plus; Carnil ACP; Catrix-P; Ceco Plus; Ceco-SP; Cedia-AC; Ceklif Plus; Celfast Plus; Celfast; Clobee-SP; Clofen-SP; Clonac Plus; Clonac-SP; Clophen-P; Combihext; Combodol; Conac-P; Conac-PT; Curejoint-AC; Cyka Plus; Cynac-MR; Cynac-P; Cynac-S; Cynac-SP; Decomb; Dersy-AP; Dinal-AP; Diplofen 3D; Diplofen-MR; Diplofen-P; Diplofen; Dipt-P; Diptase; Dolochek-P; Dolokind Plus; Dolokind-AA; Dolokind-MR; Doloral P; Doloral; Doloroff-AP; Doloroff-ASP; Dolostat-MR; Dolostat-PC; Dolour-X; Dolowin Forte; Dolowin Plus; Dolowin-MR; Dolowin; Dublace-P; Dublace-SP; Dycerin-A; Eclo-P; Eclonac-P; Ecnac-P; Elaxic-P; Elfenac Plus; Elfenac-MR; Elven-P; Erinac-P; Esnil; Essmol-3 Plus; Essmol-AF; Extranac; Fan-P; Fastnac; Fenbest MR; Fenbest P; Fenbest Plus; Fepra-P; Fico-P; Fico-SP; Flago; Flamace-MR; Flamace-P; Flamace-S; Flamace-SP; Flamtop; Flaxinac-SP; Flaxinac; Flexibel-AD; Flexidol-P; Flexidol; Flozen-AA; Fornac-CZ; Fornac-P; Fornac-SP; Fortafen Plus; Fortafen; Gag-PR; Genac-SP; Gesnac-P; Gramol-P; Gramol-SP; GS-AP; Hifenac-D; Hifenac-MR; Hifenac-P; Icenac-P; Icobit-MR; Icobit-P; Icobit-Plus; Icobit-S; Inane-P; Indofenac-P; Inflahit-P; Inflahit-SP; Inflameri; Isiko-Plus; Jacpar; Kairnac-P; Kinectine P; Kinectine-MR†; Klonac-P; Klonac-XS; Kudzu; Labace-P; Lacfen-P; Leofenac-MR; Leofenac-SP; Litonac-MR; Litonac-P; Litonac-SP; Locet-P; Lofen; Mahadol; Mahanac Pro; Masai; Maxinac; Maxoflam-A; MDace-P; MDace-SP; Micronac Plus; Micronac-MR; Micronac; Molsee; Morcet Plus; Morcet-MR; Morcet; Movace Plus; Movelite Plus; Mover; Movexx Plus; Moviz XP; Moviz-3D; Movon-MR; Movon-P; Movon-PT; Mumo; Nacku-P; Naid-P; Neflo-P; Nimopace A; Niplonac-MR; Niplonac-P; Nismol-S; Nismol; Novo-Plus; Novodase; Novoflam-Plus; Novonac-P; Novozox; Nusaid-MR; Nusaid-P; Nusaid-SP; Onspot; Opinac; Optiflam-P; Otonac-P; Pacinac; Pacinac; Panace-P; Panace; Panama Plus; Panama-SP; Paratel-AC; Paratel-ACP; Parclo-AP; Zerodol-MR; Zerodol-P.

Acemetacin *(BAN, rINN)*

Acemetacina; Acémétacine; Acemetacinum; Asemetasin; Bay-f-4975; Indometasinin Glikolik Asit Esteri; TVX-1322; Ацеметацин.

O-[(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-yl)acetyl] glycolic acid.

$C_{21}H_{18}ClNO_6$=415.8

CAS — 53164-05-9.

ATC — M01AB11.

ATC Vet — QM01AB11.

UNII — 5V141XK28X.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Acemetacin). A yellow or greenish-yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in anhydrous alcohol; soluble in acetone. Protect from light.

Uses and Administration

Acemetacin, a glycolic acid ester of indometacin, is an NSAID (p. 102.3). Its pharmacological activity is due to both acemetacin and its major metabolite, indometacin (p. 71.2). Acemetacin is used in rheumatoid arthritis, osteoarthritis, and low back pain, and for postoperative pain and inflammation. Usual oral doses are 120 to 180 mg daily in divided doses. Acemetacin is eliminated by both hepatic and renal routes, although pharmacokinetics are not affected by moderate renal or hepatic impairment and appear to be unchanged in the elderly.

References.
1. Jones RW, *et al.* Comparative pharmacokinetics of acemetacin in young subjects and elderly patients. *Br J Clin Pharmacol* 1991; **31:** 543–5.
2. Hazleman B, Bernstein RM. Acemetacin in the long-term therapy of rheumatoid arthritis. *Curr Med Res Opin* 1993; **13:** 119–26.
3. Chou CT, Tsai YY. A double-blind, randomized, controlled parallel group study evaluating the efficacy and safety of acemetacin for the management of osteoarthritis. *Int J Clin Pharmacol Res* 2002; **22:** 1–6.
4. Leeb BF, *et al.* Behandlung der Gonarthrose: Wirksamkeit und Verträglichkeit von retardiertem Acemetacin im Vergleich zu Celecoxib. *Orthopade* 2004; **33:** 1032–41.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Acemetacin is well absorbed after oral dosage. Its major metabolite is indometacin (p. 71.2) which, after repeated doses, is present at higher concentrations than those of acemetacin. Acemetacin is bound to plasma proteins to a slightly lesser extent than indometacin. It is eliminated via both the liver and the kidneys.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Rheutrop; ***China***: Rantudil (优妥); Shun Song (顺松); ***Cz.***: Rantudil†; ***Ger.***: Acemetadoc†; Rantudil; ***Gr.***: Gamespir; Rantudal; ***Hung.***: Rantudil; ***Jpn***: Rantudil; ***Malaysia***: Acemet; ***Mex.***: Rantudil; ***Philipp.***: Rantudil†; ***Pol.***: Rantudil; ***Port.***: Rantudil; ***Switz.***: Tilur; ***Turk.***: Rantudil; ***UK***: Emflex; ***Venez.***: Pranex.

Multi-ingredient Preparations. ***Arg.***: Rucaten Forte; Rucaten Prednisolona; ***Thai.***: Aceo.

Acetanilide

Acetanilid; Acetanilida; Acétanilide; Antifebrin; Asetanilidi; Ацетанилид; Антифебрин.

N-Phenylacetamide.

C_8H_9NO=135.2

CAS — 103-84-4.

UNII — SP86R356CC.

Pharmacopoeias. In *Fr.*

Profile

Acetanilide, a para-aminophenol derivative related to paracetamol (p. 115.1), has analgesic and antipyretic properties. It was replaced by safer analgesics.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Fr.***: Neurocynesine†; ***Neth.***: Neurocynesine†.

Actarit *(rINN)*

Actaritum; MS-932; Актарит.

(*p*-Acetamidophenyl)acetic acid.

$C_{10}H_{11}NO_3$=193.2

CAS — 18699-02-0.

UNII — HW5B6351RZ.

Profile

Actarit is reported to be a disease-modifying antirheumatic drug. It has been given in the treatment of rheumatoid arthritis in a usual oral dose of 100 mg three times daily.

Adverse effects. A photosensitivity reaction developed in a 52-year-old woman one month after starting actarit and doxycycline.[1] Photopatch tests for both drugs were only positive for the patches containing actarit.

1. Kawada A, *et al.* Photosensitivity due to actarit. *Contact Dermatitis* 1997; **36:** 175–6.

Use. References.

1. Nakamura H, *et al.* Clinical effects of actarit in rheumatoid arthritis: improvement of early disease activity mediated by reduction of serum concentrations of nitric oxide. *Clin Exp Rheumatol* 2000; **18:** 445–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Ji Xin (安吉欣)†; Kai Mai Si (凯迈思); ***Jpn***: Mover; Orcl.

Adalimumab *(BAN, USAN, rINN)*

Adalimumabum; D2E7; LU-200134; Адалимумаб.

Immunoglobulin G1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7κ-chain, dimer.

CAS — 331731-18-1.

ATC — L04AB04.

ATC Vet — QL04AB04.

UNII — FYS6T7F842.

Uses and Administration

Adalimumab is a recombinant human monoclonal TNF antibody that binds specifically to TNF-α and blocks its interaction with endogenous cell-surface TNF receptors. It also modulates biological responses that are induced or regulated by TNF. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis (p. 18.1), axial spondyloarthritis, ankylosing spondylitis, and psoriatic arthritis (see Spondyloarthropathies, p. 18.1), plaque psoriasis (below), and Crohn's disease and ulcerative colitis (see Inflammatory Bowel Disease, below). Adalimumab is described as a biological disease-modifying antirheumatic drug (DMARD).

Adalimumab is used in the treatment of moderate to severe, active **rheumatoid arthritis** and active and progressive **psoriatic arthritis**. In the UK, it is licensed for use in patients who have had an inadequate response to standard DMARDs, although in severe progressive rheumatoid arthritis it may be used in patients not previously treated with methotrexate; in the USA, it is licensed for use in early disease. Adalimumab is also used in the treatment of active **ankylosing spondylitis**: UK licensed product information recommends that it should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used in early disease. In the UK, it is also used in the treatment of severe **axial spondyloarthritis** without radiographic evidence of ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of, NSAIDs. For all the above indications, it is given by subcutaneous injection in a dose of 40 mg every other week. In the treatment of rheumatoid arthritis, UK licensed product information recommends that adalimumab should be given with methotrexate, although monotherapy may be used where treatment with methotrexate would be inappropriate. When used as monotherapy in rheumatoid arthritis, some patients may benefit from increasing the dose to 40 mg every week. In the UK, NICE recommends that adalimumab be stopped if there is no adequate response after 6 months for the treatment of rheumatoid arthritis, and after 12 weeks for psoriatic arthritis or ankylosing spondylitis.

Adalimumab is used in the treatment of moderate to severe, active **Crohn's disease** and **ulcerative colitis** unresponsive to conventional treatment; it may also be used in patients with Crohn's disease who have relapsed while taking infliximab. For both these indications, patients may be given an initial dose of 160 mg subcutaneously on day 1 (given as four 40-mg injections in one day or two 40-mg injections daily for 2 consecutive days), followed by 80 mg two weeks later (day 15). After a further two weeks (day 29), a maintenance dose of 40 mg every other week may be started. There is a high risk of adverse effects associated with the above induction dose, consequently, in those with Crohn's disease who do not require a more rapid response to therapy, UK licensed product information advises that a lower dose of 80 mg may be given initially, followed by 40 mg 2 weeks later; thereafter, usual maintenance doses may be given. A clinical response is usually seen within 8 or 12 weeks of starting treatment for ulcerative colitis or Crohn's disease, respectively; for both indications, those patients who relapse while on adalimumab may benefit from increasing the maintenance dose to 40 mg every week.

In the treatment of moderate to severe chronic **plaque psoriasis** in patients unresponsive to, or intolerant of, conventional systemic therapy including phototherapy, the recommended initial dose of adalimumab is 80 mg subcutaneously; this may be followed by a maintenance dose of 40 mg subcutaneously on alternate weeks, starting 1 week after the initial dose. A clinical response is usually seen within 16 weeks of starting treatment.

For the uses of adalimumab in children, and recommended doses, see below.

Administration in children. Adalimumab is used in the treatment of active polyarticular **juvenile idiopathic arthritis** in children. In the UK, it is licensed for use in those aged 2 years and older who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs). The dose in children aged 2 to 12 years is calculated according to body-surface and is given subcutaneously: 24 mg/m^2 up to a maximum dose of 20 mg in those younger than 4 years of age and 40 mg in those aged 4 to 12 years may be given every other week. Older children may receive 40 mg every other week regardless of body-surface area. Licensed product information also recommends that it should be given with methotrexate, although monotherapy may be used where treatment with methotrexate is inappropriate. In the USA, adalimumab is licensed for use in children aged 4 to 17 years to reduce the signs and symptoms of moderately to severely active disease; the dose is calculated according to body-weight and is given subcutaneously: those weighing 15 kg to less than 30 kg should be given 20 mg every other week, while heavier children may receive 40 mg every other week.

In the UK, adalimumab is also licensed for the treatment of severe, active **Crohn's disease** in children aged 6 years and older who have had an inadequate response to conventional therapy, or who have contra-indications for or are intolerant of such treatments. The dose is given subcutaneously, according to body-weight: those weighing less than 40 kg should be given an initial dose of 80 mg on day 1, followed by 40 mg 2 weeks later (day 15). After a further 2 weeks (day 29), a maintenance dose of 20 mg every other week may be started. There is a high risk of adverse effects associated with the above induction dose, consequently, in those who do not require a more rapid response to therapy, licensed product information advises that a lower dose of 40 mg may be given initially, followed by 20 mg 2 weeks later; thereafter, usual maintenance doses may be given. Patients who have an insufficient response may benefit from increasing the maintenance dose to 20 mg every week. Heavier children may be given the usual adult dose (see above) for this indication.

Hidradenitis suppurativa. For mention of adalimumab having been used in the treatment of hidradenitis suppurativa, see under Infliximab, p. 75.1.

Inflammatory bowel disease. Adalimumab is used in the management of inflammatory bowel disease (p. 1811.3) such as Crohn's disease and ulcerative colitis.[1-9] It has also been tried in children.[10-12]

1. Plosker GL, Lyseng-Williamson KA. Adalimumab: in Crohn's disease. *BioDrugs* 2007; **21:** 125–32.
2. NICE. Infliximab (review) and adalimumab for the treatment of Crohn's disease (includes a review of NICE technology appraisal guidance 40): Technology Appraisal Guidance 187 (issued May 2010). Available at: http://www.nice.org.uk/nicemedia/live/12985/48552/48552.pdf (accessed 19/10/10)
3. Huang ML, *et al.* Efficacy and safety of adalimumab in Crohn's disease: meta-analysis of placebo-controlled trials. *J Dig Dis* 2011; **12:** 165–72.
4. Guidi L, *et al.* Update on the management of inflammatory bowel disease: specific role of adalimumab. *Clin Exp Gastroenterol* 2011; **4:** 163–72.
5. Wasan SK, Kane SV. Adalimumab for the treatment of inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2011; **5:** 679–84.
6. Reinisch W, *et al.* Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60:** 780–7.
7. Sandborn WJ, *et al.* Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142:** 257–65.e1–3.
8. Burness CB, Keating GM. Adalimumab: a review of its use in the treatment of patients with ulcerative colitis. *BioDrugs* 2013; **27:** 247–62.
9. Panaccione R, *et al.* Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther* 2013; **38:** 1236–47.
10. Viola F, *et al.* Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. *Am J Gastroenterol* 2009; **104:** 2566–71.
11. Russell RK, *et al.* A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33:** 946–53.
12. Hyams JS, *et al.* Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012; **143:** 365–74. e2.

Psoriasis. Adalimumab is used in the treatment of plaque psoriasis[1-7] (p. 1688.1).

1. NICE. Adalimumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 146 (issued June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA146Guidance.pdf (accessed 25/07/08)
2. Papoutsaki M, *et al.* Adalimumab for the treatment of severe psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2008; **8:** 363–70.
3. Traczewski P, Rudnicka L. Adalimumab in dermatology. *Br J Clin Pharmacol* 2008; **66:** 618–25.
4. Croom KF, McCormack PL. Adalimumab: in plaque psoriasis. *Am J Clin Dermatol* 2009; **10:** 43–50.
5. Iaconi A, *et al.* Psoriasis and its treatment with adalimumab. *Expert Opin Biol Ther* 2010; **10:** 133–52.
6. Leonardi C, *et al.* Efficacy, safety and medication cost implications of adalimumab 40 mg weekly dosing in patients with psoriasis with

suboptimal response to 40 mg every other week dosing: results from an open-label study. *Br J Dermatol* 2012; **167:** 658–67.
7. Saraceno R, *et al.* Adalimumab in the treatment of plaque-type psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2013; **13:** 1325–34.

Rheumatoid arthritis. Some references[1-9] to the use of adalimumab in rheumatoid arthritis (p. 13.2) and juvenile idiopathic arthritis (p. 12.1).

1. Navarro-Sarabia F, *et al.* Adalimumab for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 13/06/08).
2. Cvetković RS, Scott LJ. Adalimumab: a review of its use in adult patients with rheumatoid arthritis. *BioDrugs* 2006; **20:** 293–311.
3. Chen Y-F, *et al.* NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 31/10/08)
4. Mease PJ. Adalimumab in the treatment of arthritis. *Ther Clin Risk Manag* 2007; **3:** 133–48.
5. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36): Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 03/11/08)
6. Lovell DJ, *et al.* Pediatric Rheumatology Collaborative Study Group. Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008; **359:** 810–20.
7. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
8. Wiens A, *et al.* Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. *Pharmacotherapy* 2010; **30:** 339–53.
9. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Expert Opin Drug Safety* 2011; **10:** 655–73.

Spondyloarthropathies. References[1-13] to the use of adalimumab in ankylosing spondylitis, axial spondyloarthritis, and psoriatic arthritis (p. 14.3).

1. Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. *Drugs* 2006; **66:** 1487–96.
2. McLeod C, *et al.* NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation (issued August 2007). Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 31/10/08)
3. Mease PJ. Adalimumab in the treatment of arthritis. *Ther Clin Risk Manag* 2007; **3:** 133–48.
4. Papoutsaki M, *et al.* Adalimumab for the treatment of severe psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2008; **8:** 363–70.
5. NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis: Technology Appraisal Guidance 143 (issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf (accessed 31/10/08)
6. Mease PJ, *et al.* Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis* 2009; **68:** 702–9.
7. van der Heijde D, *et al.* ATLAS Study Group. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009; **68:** 922–9.
8. Poddubnyy DA, Rudwaleit M. Adalimumab for the treatment of psoriatic arthritis. *Expert Rev Clin Immunol* 2009; **5:** 671–81.
9. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)
10. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Expert Opin Drug Safety* 2011; **10:** 655–73.
11. Sieper J, *et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2012. Available at: doi:10.1136/annrheumdis-2012-201766
12. Burness CB, Deeks ED. Adalimumab: in non-radiographic axial spondyloarthritis. *Drugs* 2012; **72:** 2385–95.
13. Saraceno R, *et al.* Adalimumab in the treatment of plaque-type psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2013; **13:** 1325–34.

Uveitis. Adalimumab has been tried with some success in the treatment of idiopathic uveitis[1,2] (p. 1615.1). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with adalimumab may improve ocular symptoms in addition to its effect on the primary disorder.

1. Vazquez-Cobian LB, *et al.* Adalimumab therapy for childhood uveitis. *J Pediatr* 2006; **149:** 572–5.
2. Biester S, *et al.* Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007; **91:** 319–24.

Adverse Effects, Treatment, and Precautions

As for Infliximab, p. 75.3.

Injection site reactions including erythema, itching, pain, and swelling are the most common adverse reactions with adalimumab; however, most reactions are mild and do not result in drug withdrawal. Other common reactions include headache, rashes, back pain, hypertension, paraesthesias, increased alkaline phosphate levels, and cough.

Autoantibodies to adalimumab have been detected.

References.

1. Burmester GR, *et al.* Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2012. Available at: doi:10.1136/annrheumdis-2011-201244

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adalimumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Interactions

As for Infliximab, p. 77.3.

Methotrexate is reported to reduce the clearance of adalimumab by up to 44% but licensed product information for the latter states that dosage adjustment for either drug does not appear to be necessary.

Pharmacokinetics

Adalimumab is reported to have linear pharmacokinetics at usual dosages. After subcutaneous injection peak concentrations are reached in about 3 to 8 days and bioavailability is estimated to be 64%. The mean terminal half-life is about 2 weeks. Adalimumab crosses the placenta and is distributed into breast milk.

References.

1. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; **74** (suppl): 13–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Humira; ***Austral.***: Humira; ***Austria***: Humira; ***Belg.***: Humira; ***Braz.***: Humira; ***Canad.***: Humira; ***Chile***: Humira; ***China***: Humira (修美乐); ***Cz.***: Humira; ***Denm.***: Humira; ***Fin.***: Humira; ***Fr.***: Humira; ***Ger.***: Humira; ***Gr.***: Humira; Trudexa; ***Hong Kong***: Humira; ***Hung.***: Humira; ***Irl.***: Humira; ***Israel***: Humira; ***Ital.***: Humira; ***Jpn***: Humira; ***Malaysia***: Humira; ***Mex.***: Humira; ***Neth.***: Humira; ***Norw.***: Humira; ***NZ***: Humira; ***Pol.***: Humira; ***Port.***: Humira; ***Rus.***: Humira (Хумира); ***S.Afr.***: Humira; ***Singapore***: Humira; ***Spain***: Humira; ***Swed.***: Humira; ***Switz.***: Humira; ***Turk.***: Humira; ***UK***: Humira; ***Ukr.***: Humira (Хумира); ***USA***: Humira; ***Venez.***: Humira.

Alfentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

Alfentaniilihydrokloridi; Alfentanil, Chlorhydrate d'; Alfentanil Hidroklorür; Alfentanil-hidroklorid; Alfentanilhydrochlorid; Alfentanil-hydrochlorid; Alfentanilhydroklorid; Alfentanili Hydrochloridum; Alfentanilio hidrochloridas; Alfentanilo, hidrocloruro de; Hidrocloruro de alfentanilo; R-39209; Альфентанила Гидрохлорид.

N-{1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-(methoxymethyl)-4-piperidyl}propionanilide hydrochloride.

$C_{21}H_{32}N_6O_3$,HCl=453.0

CAS — 71195-58-9 (alfentanil); 69049-06-5 (anhydrous alfentanil hydrochloride); 70879-28-6 (alfentanil hydrochloride monohydrate).

ATC — N01AH02.

ATC Vet — QN01AH02.

UNII — 11S92G0TIW.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Alfentanil Hydrochloride). A white or almost white powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

USP 36: (Alfentanil Hydrochloride). A white to almost white powder. Soluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in acetone. Store in airtight containers.

Uses and Administration

Alfentanil is a short-acting opioid analgesic (p. 108.1) related to fentanyl (p. 60.2).

Alfentanil is used in surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. It is also used as an analgesic and respiratory depressant in the management of mechanically ventilated patients under intensive care.

Alfentanil is given intravenously as the hydrochloride although doses are expressed in terms of the base. Alfentanil hydrochloride 108.8 micrograms is equivalent to about 100 micrograms of alfentanil. A peak effect may be seen within 1.5 to 2 minutes of an injection and analgesia can be expected to last for up to 10 minutes; dose supplements are therefore required if it is to be used for more prolonged surgical procedures. It may be given by continuous intravenous infusion in ventilated patients.

The dosage of alfentanil used depends on whether the patient has spontaneous respiration or assisted ventilation and on the expected duration of anaesthesia. Doses are adjusted according to the needs of the patient. Children may require higher or more frequent doses than adults, whereas the elderly or debilitated patients may require lower or less frequent doses. Obese patients may require doses based on their ideal (lean) body-weight.

When used as an adjunct in the **maintenance of general anaesthesia** the initial licensed dose in the UK is as follows:

- in patients with *spontaneous respiration*, up to 500 micrograms may be given slowly over about 30 seconds with supplementary doses of 250 micrograms
- *ventilated* patients may be given 30 to 50 micrograms/kg with supplements of 15 micrograms/kg. When given by infusion to ventilated patients there is an initial loading dose of 50 to 100 micrograms/kg given as a bolus or by infusion over 10 minutes, followed by infusion at a rate of 0.5 to 1 microgram/kg per minute

Typical doses that have been used in the USA are as follows:

- for *short surgical procedures of less than 1 hour* in patients with spontaneous respiration or assisted ventilation, the dose is 8 to 20 micrograms/kg; this may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.5 to 1 microgram/kg per minute. Alternatively patients with assisted or controlled ventilation may be given an initial dose of 20 to 50 micrograms/kg, followed by supplementary doses of 5 to 15 micrograms/kg every 5 to 20 minutes
- in *general surgical procedures* in patients with assisted or controlled ventilation, an initial dose of 50 to 75 micrograms/kg may be followed by an infusion of 0.5 to 3 micrograms/kg per minute. If alfentanil has been given in anaesthetic doses (see below) for the induction of anaesthesia, infusion rates may need to be reduced by 30 to 50% during the first hour of maintenance

Maintenance infusions of alfentanil should be stopped 10 to 30 minutes before the anticipated end of surgery.

The dose for the **induction of anaesthesia** in patients with assisted ventilation undergoing procedures of at least 45 minutes is 130 to 245 micrograms/kg, followed by an inhalation anaesthetic or maintenance doses of alfentanil of 0.5 to 1.5 micrograms/kg per minute.

For details of doses in children, see below.

In the UK, *ventilated* patients in **intensive care** may be given alfentanil initially at an infusion rate of 2 mg/hour or a loading dose of 5 mg may be given in divided doses over 10 minutes or more slowly if hypotension or bradycardia occur. Thereafter a suitable rate of infusion should be determined for each patient (rates of 0.5 to 10 mg/hour have been used); patients should be carefully monitored and the duration of treatment should not generally exceed 4 days. During continuous infusion additional bolus injections of 0.5 to 1 mg may be given if required to provide analgesia for short painful procedures that may be carried out in intensive care.

Alfentanil is also used as an analgesic in patients with *spontaneous respiration* receiving monitored anaesthesia care; in the USA, an initial dose of 3 to 8 micrograms/kg may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.25 to 1 microgram/kg per minute.

Administration. Alfentanil is usually given by intravenous injection or infusion, but has also been given intramuscularly,[1,2] intrathecally,[3] or epidurally (see Pain, p. 19.1).

1. Arendt-Nielsen L, *et al.* Analgesic efficacy of i.m alfentanil. *Br J Anaesth* 1990; **65:** 164–8.
2. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; **71:** 507–11.
3. Hughes DA, Hill DA. Intrathecal alfentanil with and without bupivacaine for analgesia in labour. *Anaesthesia* 2000; **55:** 1116–21.

Administration in children. In the UK, the *BNFC* recommends the use of intravenous alfentanil in *ventilated* children as an analgesic and adjunct to general anaesthetics; the following doses, given according to age, are suggested:

for **short procedures** in patients with assisted ventilation by *injection* over 30 seconds

- neonates, 5 to 20 micrograms/kg initially, followed by supplementary doses of up to 10 micrograms/kg
- 1 month to 18 years, 10 to 20 micrograms/kg initially, followed by supplementary doses of up to 10 micrograms/kg

for **longer procedures** in patients with assisted ventilation by *infusion*

- neonates, 10 to 50 micrograms/kg over 10 minutes initially, followed by 0.5 to 1 microgram/kg per minute
- 1 month to 18 years, 50 to 100 micrograms/kg over 10 minutes initially, followed by 0.5 to 2 micrograms/kg

per minute (or 1 microgram/kg per minute when used with an intravenous anaesthetic)

Similar doses are licensed in the UK for use in children with spontaneous respiration or assisted ventilation although age ranges are not specified; equipment for assisted ventilation should be available for use, even for short procedures in those who are breathing spontaneously.

Anaesthesia. Alfentanil, like fentanyl (p. 61.2), appears to produce fewer circulatory changes than morphine and may be preferred for anaesthetic use, especially in cardiovascular surgery. It is generally considered to have a shorter duration of action than fentanyl. It has been used with propofol to facilitate intubation, and for total intravenous anaesthesia.

For a discussion of the drugs used to facilitate intubation and of opioids such as alfentanil used to control the pressor response and the rise of intra-ocular pressure associated with intubation, see Anaesthesia, p. 2028.1. For reference to a study indicating that pretreatment with alfentanil can reduce the pain associated with injection of propofol, see p. 1914.3.

CAESAREAN SECTION. UK licensed product information contra-indicates the use of alfentanil before clamping the cord during caesarean section because of the risk of respiratory depression in the neonate. A study of alfentanil 30 micrograms/kg in women undergoing caesarean section was abandoned after massive respiratory depression had occurred in 4 of 5 neonates.[1] Another study[2] in patients undergoing elective caesarean section found that although maternal haemodynamic responses to intubation were minimised when alfentanil 10 micrograms/kg was given intravenously immediately before induction, neonates in the alfentanil group had lower Apgar scores compared with those in the placebo group.

However, alfentanil has been used successfully to minimise haemodynamic responses to intubation and surgery in patients with severe cardiovascular disorders undergoing caesarean section.[3,4] A baby delivered after the successful use of alfentanil 35 micrograms/kg in a mother with severe aortic stenosis[3] was apnoeic and unresponsive with poor muscle tone; the baby responded rapidly to naloxone. Alfentanil 10 micrograms/kg immediately before induction attenuated the cardiovascular response to intubation in patients with severe pregnancy-induced hypertension[4] and was considered a suitable alternative to fentanyl 2.5 micrograms/kg; no effect on neonatal mortality could be attributed to anaesthetic technique. However, it has been suggested that the use of smaller doses of alfentanil of 7.5 micrograms/kg with magnesium sulfate 30 mg/kg may provide better cardiovascular control.[5]

1. Leuwer M, *et al.* Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during caesarean section. *Br J Anaesth* 1990; **64:** 398P–399P.
2. Gin T, *et al.* Alfentanil given immediately before the induction of anesthesia for elective cesarean delivery. *Anesth Analg* 2000; **90:** 1167–72.
3. Redfern N, *et al.* Alfentanil for caesarean section complicated by severe aortic stenosis: a case report. *Br J Anaesth* 1987; **59:** 1309–12.
4. Rout CC, Rocke DA. Effects of alfentanil and fentanyl on induction of anaesthesia in patients with severe pregnancy-induced hypertension. *Br J Anaesth* 1990; **65:** 468–74.
5. Ashton WB, *et al.* Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing caesarean section. *Br J Anaesth* 1991; **67:** 741–7.

PHAEOCHROMOCYTOMA. Alfentanil does not release histamine and was of value in the anaesthetic management of patients with phaeochromocytoma.[1] It has a very rapid onset of action, good vasodilating properties, and a relatively short elimination half-life. These patients are often very somnolent for the first 48 hours after surgery and postoperative opioid dosage requirements may be less than expected. Alfentanil infusion continued into the postoperative period allows careful titration of dosage.

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

Pain. *POSTOPERATIVE ANALGESIA.* Continuous on-demand epidural infusions of alfentanil 200 micrograms/hour or fentanyl 20 micrograms/hour provided comparable analgesia to morphine 200 micrograms/hour in the early postoperative period;[1] alfentanil (16 minutes) and fentanyl (13 minutes) had the advantage of more rapid onset of analgesia than morphine (44 minutes). However, some considered that there was no overall advantage of epidural over intravenous alfentanil either as patient-controlled analgesia[2] or by continuous infusion.[3]

1. Chrubasik J, *et al.* Relative analgesic potency of epidural fentanyl, alfentanil, and morphine in treatment of postoperative pain. *Anesthesiology* 1988; **68:** 929–33.
2. Chauvin M, *et al.* Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. *Anesth Analg* 1993; **76:** 1251–8.
3. van den Nieuwenhuyzen MCO, *et al.* Epidural vs intravenous infusion of alfentanil in the management of postoperative pain following laparotomies. *Acta Anaesthesiol Scand* 1996; **40:** 1112–18.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1, and for Fentanyl, p. 62.1.

Effects on the cardiovascular system. Sinus arrest had occurred[1] during intubation in 2 patients given alfentanil 30 micrograms/kg.

1. Maryniak JK, Bishop VA. Sinus arrest after alfentanil. *Br J Anaesth* 1987; **59:** 390–1.

Effects on mental function. Like fentanyl, alfentanil 7.5 or 15 micrograms/kg intravenously had no effect on memory in healthy subjects.[1] In another study impairment of memory for new facts did occur 2 hours after operation in patients anaesthetised with alfentanil 7.5 micrograms/kg, but not in those given fentanyl;[2] methohexital might have contributed to the impairment.

1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
2. Kennedy DJ, Ogg TW. Alfentanil and memory function: a comparison with fentanyl for day case termination of pregnancy. *Anaesthesia* 1985; **40:** 537–40.

Effects on the respiratory system. Alfentanil, like other opioid agonists, causes dose-related respiratory depression; it is significant with doses of more than 1 mg. Recovery has been reported to be faster after alfentanil than after fentanyl (see p. 62.2),[1,2] possibly reflecting the shorter elimination half-life of alfentanil. Even so, accumulation of alfentanil is possible with large doses over a prolonged period. Profound analgesia is accompanied by marked respiratory depression which may persist or recur postoperatively.

Sudden respiratory arrest usually within an hour after the end of alfentanil infusion has been reported in patients who initially appeared to have made a rapid recovery from anaesthesia;[3-5] all responded to treatment with naloxone. Close monitoring of respiration in the initial postoperative period was recommended and this was reinforced by the manufacturers;[6] factors such as hyperventilation and the use of opioid premedication might enhance or prolong the respiratory depressant effects of alfentanil.

1. Andrews CJH, *et al.* Ventilatory effects during and after continuous infusion of fentanyl or alfentanil. *Br J Anaesth* 1983; **55:** 211S–16S.
2. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
3. Sebel PS, *et al.* Respiratory depression after alfentanil infusion. *BMJ* 1984; **289:** 1581–2.
4. Krane BD, *et al.* Alfentanil and delayed respiratory depression: cases studies and review. *Anesth Analg* 1990; **70:** 557–61.
5. Sternlo JEG, Sandin RH. Recurrent respiratory depression after total intravenous anaesthesia with propofol and alfentanil. *Anaesthesia* 1998; **53:** 378–81.
6. Waldron HA, Cookson RF. Respiratory depression after alfentanil infusion. *BMJ* 1985; **290:** 319.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Children. Alfentanil given to preterm infants undergoing paralysis and mechanical ventilation for respiratory distress syndrome resulted in a rapid and significant fall in heart rate and blood pressure, emphasising that proper evaluation of the pharmacological and clinical effects was necessary.[1]

The half-life of alfentanil is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required.

1. Marlow N, *et al.* Hazards of analgesia for newborn infants. *Arch Dis Child* 1988; **63:** 1293.

The elderly. EEG changes suggested that elderly patients had increased brain sensitivity to alfentanil,[1] and that lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons. See also under Pharmacokinetics, p. 20.1.

1. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.

Handling. Avoid contact with the skin and the inhalation of particles of alfentanil hydrochloride.

Inflammatory bowel disease. Patients with Crohn's disease required higher doses of alfentanil than control patients[1] although there were no differences in alfentanil pharmacokinetics between the 2 groups of patients.

1. Gesink-van der Veer BJ, *et al.* Influence of Crohn's disease on the pharmacokinetics and pharmacodynamics of alfentanil. *Br J Anaesth* 1993; **71:** 827–34.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alfentanil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. UK licensed product information contra-indicates the use of alfentanil in labour, or before clamping of the cord during caesarean section, because placental transfer means there is a risk of neonatal respiratory depression.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Drugs that depress the heart or increase vagal tone, such as beta blockers and anaesthetic drugs, may predispose patients given alfentanil to develop bradycardia and hypotension. Use of alfentanil with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

The metabolism of alfentanil via the cytochrome P450 isoenzyme CYP3A4 may be reduced by potent inhibitors of this isoenzyme, resulting in a risk of prolonged or delayed respiratory depression. Reduced doses of alfentanil may be required if given with a CYP3A4 inhibitor such as cimetidine, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, or ritonavir.

Antibacterials. The elimination half-life of alfentanil was increased and clearance decreased when given after a 7-day course of oral *erythromycin* in healthy subjects.[1] Prolonged respiratory depression has also occurred in a 32-year-old man given alfentanil during anaesthesia after three 1-g doses of erythromycin in the 24 hours before surgery.[2] In another study of healthy subjects, the clearance (three-compartment model) of alfentanil was reduced by 70% in those given oral *troleandomycin*.[3]

Other hepatic enzyme inhibitors and drugs interfering with hepatic blood flow might also affect the clearance of alfentanil.

1. Bartkowski RR, *et al.* Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; **46:** 99–102.
2. Bartkowski RR, McDonnell TE. Prolonged alfentanil effect following erythromycin administration. *Anesthesiology* 1990; **73:** 566–8.
3. Kharasch ED, *et al.* The role of cytochrome P450 3A4 in alfentanil clearance: implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology* 1997; **87:** 36–50.

Antifungals. Azole antifungals such as *fluconazole*, *ketoconazole*, or *voriconazole* can inhibit the metabolism of alfentanil. In a study,[1] giving alfentanil 1 hour after intravenous or oral fluconazole decreased the clearance of alfentanil by 60 and 55%, respectively and increased the mean half-life of alfentanil from 1.5 hours to 2.7 and 2.5 hours, respectively. Similarly, another study[2] found that giving alfentanil 1 hour after oral voriconazole decreased the clearance of alfentanil by 85% and increased the mean half-life of alfentanil to 6.6 hours.

1. Palkama VJ, *et al.* The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. *Anesth Analg* 1998; **87:** 190–4.
2. Saari TI, *et al.* Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. *Clin Pharmacol Ther* 2006; **80:** 502–8.

Pharmacokinetics

After parenteral doses alfentanil hydrochloride has a rapid onset and short duration of action. Alfentanil is about 90% protein bound and has a small volume of distribution. Its terminal elimination half-life is about 1 to 2 hours. It is metabolised in the liver; oxidative *N*- and *O*-dealkylation by the cytochrome P450 isoenzyme CYP3A4 leads to inactive metabolites, which are excreted in the urine. Alfentanil crosses the blood-brain barrier and the placenta and has been detected in colostrum.

Alfentanil is less lipid-soluble than fentanyl, but more so than morphine. It is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. Decreased lipid solubility can be expected to limit penetration of the blood-brain barrier when compared with fentanyl, but the majority of unbound alfentanil is unionised and can rapidly gain access to the CNS. Alfentanil has a smaller volume of distribution than fentanyl and its elimination half-life is shorter. The manufacturers have given values for a three-compartment pharmacokinetic model with a distribution half-life of 0.4 to 3.1 minutes, a redistribution half-life of 4.6 to 21.6 minutes, and a terminal elimination half-life of 64.1 to 129.3 minutes after single bolus injections of 50 or 125 micrograms/kg. Accumulation is less likely than with fentanyl, but can occur after repeated or continuous dosage especially in patients with reduced clearance. The mean elimination half-life reported is usually about 90 minutes, but this is reduced in children (p. 20.1) and increased in the elderly and neonates (p. 20.1), in hepatic impairment (p. 20.2), in the obese (p. 20.2), and during cardiopulmonary bypass (p. 20.1).

Reviews.
1. Hull CJ. The pharmacokinetics of alfentanil in man. *Br J Anaesth* 1983; **55** (suppl 2): 157S–164S.
2. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; **8:** 422–46.
3. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11:** 18–35.
4. Bodenham A, Park GR. Alfentanil infusions in patients requiring intensive care. *Clin Pharmacokinet* 1988; **15:** 216–26.
5. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. *Clin Pharmacokinet* 1996; **31:** 275–92.

Administration. *CONTINUOUS INTRAVENOUS INFUSION.* Small studies of alfentanil by continuous intravenous infusion[1-3] have found pharmacokinetic parameters to be similar to those after a single bolus injection, but with some conflicting results. In 29 patients undergoing orthopaedic surgery an initial bolus intravenous injection of alfentanil 50 micrograms/kg was followed by intravenous infusion of 1 microgram/kg per minute, continued for 44 to 445 minutes; a second bolus injection of 50 micrograms/kg was given immediately before incision and an additional bolus injection of 1 mg given if necessary.[4] The time course of the plasma-alfentanil concentration fitted a two-compartmental model in 26 patients. Terminal half-lives varied widely from 56 to 226 minutes (mean 106 minutes), the highest values being mainly in patients over 60 years. There was no significant correlation between pharmacokinetic parameters and the duration of the infusion or the total dose. Plasma clearance and volumes of distribution did not correlate significantly with body-weight although steady-state volume of distribution was enlarged with increasing age. The mean estimated steady-state concentration was 293 nanograms/mL (range 147 to 636 nanograms/mL).
1. Fragen RJ, *et al.* Pharmacokinetics of the infusion of alfentanil in man. *Br J Anaesth* 1983; **55:** 1077–81.
2. Shafer A, *et al.* Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. *Anesth Analg* 1986; **65:** 1021–8.
3. Reitz JA, *et al.* The pharmacokinetics of alfentanil in gynecologic surgical patients. *J Clin Pharmacol* 1986; **26:** 60–4.
4. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; **62:** 610–15.

INTRAMUSCULAR. See The Elderly, below.

Burns. The volume of distribution and total clearance of alfentanil were reduced and its elimination half-life prolonged in patients with burns.[1] This was due, in part, to raised concentrations of α_1-acid glycoprotein leading to increased protein binding.
1. Macfie AG, *et al.* Disposition of alfentanil in burns patients. *Br J Anaesth* 1992; **69:** 447–50.

Cardiopulmonary bypass. The elimination half-life of alfentanil increased from 72 minutes before cardiopulmonary bypass to 195 minutes afterwards in 5 patients.[1] This was attributed to an increase in volume of distribution, based in part on a dilution-induced decrease in plasma protein binding. Others[2,3] found that on starting cardiopulmonary bypass total serum concentrations of alfentanil were halved, mainly because of dilution of α_1-acid glycoprotein and an increase in unbound alfentanil.
1. Hug CC, *et al.* Alfentanil pharmacokinetics in patients before and after cardiopulmonary bypass. *Anesth Analg* 1983; **62:** 266.
2. Kumar K, *et al.* The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. *Eur J Clin Pharmacol* 1988; **35:** 47–52.
3. Hynynen M, *et al.* Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *Br J Anaesth* 1994; **72:** 571–6.

Children. Alfentanil has been shown to have a shorter elimination half-life (about 40 minutes) and a smaller volume of distribution in children than in adults.[1] However, the half-life of alfentanil is prolonged in neonates. See also Hepatic Impairment, below.
1. Meistelman C, *et al.* A comparison of alfentanil pharmacokinetics in children and adults. *Anesthesiology* 1987; **66:** 13–16.

The elderly. Plasma clearance of alfentanil after a single intravenous dose of 50 micrograms/kg was reduced in patients more than 65 years old when compared with that in healthy young adults.[1] Mean elimination half-life was 137 minutes in the elderly and 83 minutes in the young adults. Volumes of distribution were similar and it was considered that reduced clearance might be due to decreased hepatic metabolism in the elderly. In a study in male patients the terminal elimination half-life of alfentanil increased with age, although clearance was not significantly affected.[2] In patients given alfentanil 1 microgram/kg per minute by continuous intravenous infusion during orthopaedic surgery,[3] terminal half-life increased linearly with age in those older than 40 years and steady-state volume of distribution was enlarged with increasing age; clearance did not correlate significantly with age and was thought to be more variable during a continuous infusion in long-term surgery than after a single bolus injection. Others have reported[4] that the effects of age on alfentanil pharmacokinetics are dependent on gender. In this study total plasma clearance decreased and terminal half-life increased with increasing age in women, but not in men. It has been suggested that this effect in women may be more dependent on menopausal status than on age.[5]

In a study[6] in elderly patients plasma concentrations of alfentanil were greater and the maximum concentration occurred earlier when alfentanil was injected into the deltoid muscle compared with injection into the gluteal muscle.
1. Helmers H, *et al.* Alfentanil kinetics in the elderly. *Clin Pharmacol Ther* 1984; **36:** 239–43.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.
3. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; **62:** 610–15.
4. Lemmens HJM, *et al.* Influence of age on the pharmacokinetics of alfentanil: gender dependence. *Clin Pharmacokinet* 1990; **19:** 416–22.
5. Rubio A, Cox C. Sex, age and alfentanil pharmacokinetics. *Clin Pharmacokinet* 1991; **21:** 81.
6. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; **71:** 507–11.

Hepatic impairment. Total plasma clearance and protein binding of alfentanil were decreased in patients with alcoholic cirrhosis when compared with control subjects. Elimination half-life was prolonged from 90 to 219 minutes in the cirrhotic patients following a single intravenous dose of 50 micrograms/kg and was attributed in part to alterations in binding sites of α_1-acid glycoprotein.[1] There might be different effects on alfentanil disposition in patients with non-alcoholic cirrhosis or other liver disorders.[2] The pharmacokinetics of alfentanil were apparently not affected in children with cholestatic hepatic disease whereas clearance was reduced postoperatively in 3 patients who had undergone liver transplantation.[3]
1. Ferrier C, *et al.* Alfentanil pharmacokinetics in patients with cirrhosis. *Anesthesiology* 1985; **62:** 480–4.
2. Bower S, *et al.* Effects of different hepatic pathologies on disposition of alfentanil in anaesthetized patients. *Br J Anaesth* 1992; **68:** 462–5.
3. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; **68:** 579–83.

Obesity. The pharmacokinetics of alfentanil are reportedly altered in obesity.[1] Elimination half-life was 172 minutes in 6 obese patients compared with 92 minutes in 7 who were not obese. Plasma clearance of alfentanil was also decreased, although others[2] found that obesity had no effect on clearance, but it did have a direct relationship with the volume of the central compartment.
1. Bentley JB, *et al.* Obesity and alfentanil pharmacokinetics. *Anesth Analg* 1983; **62:** 251.
2. Maitre PO, *et al.* Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; **66:** 3–12.

Renal impairment. The pharmacokinetics of alfentanil were not affected significantly in adults[1] or children[2] with chronic renal failure. In another study[3] increased volume of distribution of alfentanil at steady state was associated with decreased plasma protein binding in patients with chronic renal failure.
1. Van Peer A, *et al.* Alfentanil kinetics in renal insufficiency. *Eur J Clin Pharmacol* 1986; **30:** 245–7.
2. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; **68:** 579–83.
3. Chauvin M, *et al.* Pharmacokinetics of alfentanil in chronic renal failure. *Anesth Analg* 1987; **66:** 53–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Brevafen; ***Austral.***: Rapifen; ***Austria***: Rapifen; ***Belg.***: Rapifen; ***Braz.***: Alfast; Rapifen; ***Chile***: Rapifen; ***Cz.***: Rapifen; ***Denm.***: Rapifen; ***Fin.***: Rapifen; ***Fr.***: Rapifen; ***Ger.***: Rapifen; ***Gr.***: Rapifen; ***Hong Kong***: Rapifen; ***Hung.***: Rapifen†; ***Irl.***: Rapifen; ***Israel***: Rapifen†; ***Ital.***: Fentalim; ***Mex.***: Rapifen; ***Neth.***: Rapifen; ***Norw.***: Rapifen; ***NZ***: Rapifen; ***Port.***: Rapifen; ***S.Afr.***: Rapifen; ***Singapore***: Rapifen; ***Spain***: Fanaxal†; Limifen; ***Swed.***: Rapifen; ***Switz.***: Rapifen; ***Turk.***: Rapifen; ***UK***: Rapifen; ***USA***: Alfenta; ***Venez.***: Rapifen.

Pharmacopoeial Preparations
USP 36: Alfentanil Injection.

Alminoprofen *(rINN)*

Alminoprofène; Alminoprofeno; Alminoprofenum; Альминопрофен.
4-[(2-Methylallyl)amino]hydratropic acid.
$C_{13}H_{17}NO_2$=219.3
CAS — 39718-89-3.
ATC — M01AE16.
ATC Vet — QM01AE16.
UNII — 0255AHR9GJ.

Pharmacopoeias. In *Jpn.*

Profile

Alminoprofen, a propionic acid derivative related to ibuprofen (p. 68.2), is an NSAID (p. 102.3). It has been used in inflammatory and rheumatic disorders in oral doses of up to 900 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Minalfene.

Aloxiprin *(BAN, rINN)*

Acetilsalicilato de polioxoaluminio; Aloksipriini; Aloxiprina; Aloxiprine; Aloxiprinum; Алоксиприн.
CAS — 9014-67-9.
ATC — B01AC15; N02BA02.
ATC Vet — QB01AC15; QN02BA02.
UNII — 6QT214X4XU.

Pharmacopoeias. In *Br.*

BP 2014: (Aloxiprin). A polymeric condensation product of aluminium oxide and aspirin. A fine, white or slightly pink powder, odourless or almost odourless. It contains not less than 7.5% and not more than 8.5% of aluminium and not less than 79.0% and not more than 87.4% of total salicylates, calculated as aspirin, $C_9H_8O_4$, both calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in ether; slightly soluble in chloroform.

Profile

Aloxiprin, a polymeric condensation product of aluminium oxide and aspirin, has actions similar to those of aspirin (p. 22.2); aloxiprin 600 mg is equivalent to about 500 mg of aspirin. Aloxiprin has been used as an analgesic and anti-inflammatory in musculoskeletal and joint disorders. It has also been used in the treatment and prevention of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Superpyrin.

Multi-ingredient Preparations. ***UK***: Askit†.

Pharmacopoeial Preparations
BP 2014: Aloxiprin Tablets.

Aluminium Aspirin

Acetilsalicilato de aluminio; Aluminum Acetylsalicylate; Aluminum Aspirin; Aluminum Bis(acetylsalicylate); Aspirin Aluminium; Аспирин Алюминий; Алюминий Аспирина.
Bis(2-acetoxybenzoato-*O*')hydroxyaluminium.
$C_{18}H_{15}AlO_9$=402.3
CAS — 23413-80-1.
UNII — E33TS05V6B.

Pharmacopoeias. In *Jpn.*

Profile

Aluminium aspirin is a salicylic acid derivative (see Aspirin, p. 22.2) that has been given orally in the management of fever, pain, and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Remasal†.

Amfenac Sodium *(BANM, USAN, rINNM)*

AHR-5850; AHR-5850D; Amfénac Sodique; Amfenaco sódico; Natrii Amfenacum; Натрий Амфенак.
Sodium (2-amino-3-benzoylphenyl)acetate monohydrate.
$C_{15}H_{12}NNaO_3.H_2O$=295.3
CAS — 51579-82-9 (amfenac); 61618-27-7 (amfenac sodium).
UNII — PPF9V8J28Y.

Profile

Amfenac sodium, an arylacetic derivative, is an NSAID (p. 102.3). It has been given orally for the relief of pain and inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Fenazox.

Aminophenazone *(rINN)*

Amidazofen; Amidopyrine; Amidopyrine-Pyramidon; Aminofenatsoni; Aminofenazon; Aminofenazona; Aminophénazone; Aminophenazonum; Aminopyrine; Dimethylaminoantipyrine; Dimethylaminophenazone; Аминофеназон.
4-Dimethylamino-1,5-dimethyl-2-phenyl-4-pyrazolin-3-one.
$C_{13}H_{17}N_3O$=231.3
CAS — 58-15-1.
ATC — N02BB03.
ATC Vet — QN02BB03.
UNII — 01704YP3MO.

Pharmacopoeias. In *It.*

Profile

Aminophenazone, a pyrazolone derivative, is an NSAID (p. 102.3), but the risk of agranulocytosis is sufficiently great to render it unsuitable for systemic use. Onset of agranulocytosis may be sudden and unpredictable. Aminophenazone has been used as salts or complexes, including topically as the salicylate.

Precautions. *CARCINOGENICITY.* Aminophenazone may be regarded as a potential carcinogen because it has reacted readily with nitrous acid to form dimethylnitrosamine.[1] The reaction was catalysed by thiocyanate present in the saliva particularly in smokers.

1. Boyland E, Walker SA. Catalysis of the reaction of aminopyrine and nitrite by thiocyanate. *Arzneimittelforschung* 1974; **24:** 1181–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Germicid.

Multi-ingredient Preparations. ***Hung.***: Antineuralgica; Demalgon; Demalgonil†; Dolor†; Germicid-C; Kefalgin; Meristin; ***Ital.***: Virdex; ***Mex.***: Flumil.

Ammonium Salicylate

Salicilato de amonio; Аммоний Салицилат.
$C_7H_9NO_3$=155.2
CAS — 528-94-9.
UNII — 0T3Q181657.

Profile

Ammonium salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for the relief of pain in musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Radian-B.

Ampiroxicam *(BAN, rINN)*

Ampiroxicamum; CP-65703; Ампироксикам.
4-[1-(Ethoxycarbonyloxy)ethoxy]-2-methyl-*N*^{2}-pyridyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.
$C_{20}H_{21}N_3O_7S$=447.5
CAS — 99464-64-9.
UNII — 0PV32JZB1J.

Profile

Ampiroxicam is an NSAID (p. 102.3) that is reported to be metabolised to piroxicam (p. 125.3). It has been given orally for the relief of pain and inflammation particularly in musculoskeletal disorders such as rheumatoid arthritis and osteoarthritis.

Adverse effects. Photosensitivity reactions have occurred during ampiroxicam treatment.[1-3]

1. Kurumaji Y. Ampiroxicam-induced photosensitivity. *Contact Dermatitis* 1996; **34:** 298–9.
2. Toyohara A, *et al.* Ampiroxicam-induced photosensitivity. *Contact Dermatitis* 1996; **35:** 101–2.
3. Chishiki M, *et al.* Photosensitivity due to ampiroxicam. *Dermatology* 1997; **195:** 409–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Flucam.

Amtolmetin Guacil *(rINN)*

Amtolmetina guacilo; Amtolmétine Guacil; Amtolmetinum Guacilum; MED-15; ST-679; Амтолметин Гуацил.
N-[(1-Methyl-5-*p*-toluoylpyrrol-2-yl)acetyl]glycine *o*-methoxyphenyl ester.
$C_{24}H_{24}N_2O_5$=420.5
CAS — 87344-06-7.
UNII — 323A00CRO9.

Profile

Amtolmetin guacil is an NSAID (p. 102.3) that is an ester prodrug of tolmetin (p. 139.1). It is used in painful and inflammatory disorders in oral doses of 600 to 1200 mg daily.

References.

1. Biasi G, Marcolongo R. Efficacia e tollerabilità dell'amtolmetina guacil nel trattamento dell'artrosi in fase di riacutizzazione. *Minerva Med* 2001; **92:** 315–24.
2. Jajic Z, *et al.* Gastrointestinal safety of amtolmetin guacyl in comparison with celecoxib in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005; **23:** 809–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Artricol; Artromed; Eufans.

Amyl Salicylate

Isoamyl Salicylate; Isopentyl Salicylate; Salicilato de isoamilo; Salicilato de isopentilo; Амилсалицилат.
3-Methylbutyl 2-hydroxybenzoate.
$C_{12}H_{16}O_3$=208.3
CAS — 87-20-7.
UNII — M25E4ZMR0N.

Pharmacopoeias. In *Fr.*

Profile

Amyl salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for its analgesic and anti-inflammatory actions. It has also been used in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Atomo Desinflamante C; Atomo Desinflamante Familiar; Atomo Desinflamante; Rati Salil Crema; ***Fr.***: Baume Saint-Bernard.

Anakinra *(BAN, USAN, rINN)*

Anakinrum; rhIL-1ra; r-metHuIL-1ra; Анакинра.
N^2-L-Methionylinterleukin 1 receptor antagonist (human isoform x reduced).
CAS — 143090-92-0.
ATC — L04AC03.
ATC Vet — QL04AC03.
UNII — 9013DUQ28K.

Uses and Administration

Anakinra is a recombinant receptor antagonist of interleukin-1 (p. 2533.3), an inflammatory mediator found in the plasma and synovial fluid of patients with rheumatoid arthritis. Anakinra is described as a biological disease-modifying antirheumatic drug (DMARD).

Anakinra is used for the treatment of the signs and symptoms of moderate to severely active **rheumatoid arthritis** in patients who have had an inadequate response to methotrexate or another DMARD alone (but see below). In the UK, it is only licensed for use with methotrexate; however, in the USA, it may be given either alone or with another DMARD, although not one that inhibits TNF (see Interactions, p. 22.1). The usual dose is 100 mg once daily by subcutaneous injection. The dose should be given at about the same time each day.

Anakinra is also used in the management of **cryopyrin-associated periodic syndromes** (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID) [also known as chronic infantile neurological, cutaneous, articular syndrome (CINCA)], familial cold auto-inflammatory syndrome (FCAS), and Muckle-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders (below) in adults and children from 8 months of age who weigh at least 10 kg. The usual initial dose is 1 to 2 mg/kg daily by subcutaneous injection; patients with mild disease may be maintained on this dose. In those with severe disease, the dose may be increased if necessary, after 1 to 2 months in steps of 0.5 to 1 mg/kg; the usual maintenance dose is 3 to 4 mg/kg daily. A maximum dose of 8 mg/kg daily should not be exceeded. Once-daily injections are recommended; however, the dose may be divided to give twice daily. In severe CAPS, evaluation of clinical symptoms, inflammatory markers, and inflammation of the CNS including the inner ear and eyes are recommended after the first 3 months of therapy and every 6 months thereafter until patients are well controlled, at which point, CNS and ophthalmological monitoring may then be carried out annually.

For use of anakinra in patients with renal impairment, see below.

Anakinra has been tried in septic shock and graft-versus-host disease in transplant recipients, but results were disappointing.

Administration in children. Anakinra is licensed for use in children and adolescents for the treatment of cryopyrin-associated periodic syndromes (CAPS). For doses see Uses and Administration, above.

Administration in renal impairment. Caution may be advisable if anakinra is used in patients with renal impairment. A study[1] in patients with varying degrees of renal function indicated that no dosage adjustment was needed for anakinra in patients with mild or moderate renal impairment but dosage on alternate days appeared advisable in those with severe renal impairment. US licensed product information also recommends alternate-day dosing in patients with severe impairment or end-stage disease (creatinine clearance less than 30 mL/minute). However, in the UK, licensed product information contra-indicates use in those with this degree of impairment.

Dialysis does not affect anakinra concentrations to any significant degree.

1. Yang B-B, *et al.* Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* 2003; **74:** 85–94.

Cryopyrin-associated periodic syndromes. Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that inhibits the binding of the proinflammatory cytokines, IL-1α and IL-1β, to IL-1 receptors, thus ameliorating systemic and organ inflammation. It is used in the treatment of cryopyrin-associated periodic syndromes (CAPS), which are rare inherited auto-inflammatory disorders associated with excessive production of IL-1.[1-4]

1. Neven B, *et al.* Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum* 2010; **62:** 258–67.
2. Kuemmerle-Deschner JB, *et al.* Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome. *Arthritis Rheum* 2011; **63:** 840–9.
3. Rigante D, *et al.* Long-term response after 6-year treatment with anakinra and onset of focal bone erosion in neonatal-onset multisystem inflammatory disease (NOMID/CINCA). *Rheumatol Int* 2011; **31:** 1661–4.
4. Sibley CH, *et al.* Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes. *Arthritis Rheum* 2012; **64:** 2375–86.

Familial Mediterranean fever. For mention of anakinra having been tried in familial Mediterranean fever, see p. 605.1.

Rheumatoid arthritis. In the UK, anakinra is licensed for the treatment of rheumatoid arthritis[1-10] (p. 13.2) in patients with an inadequate response to methotrexate alone; however, NICE[11] does not recommend its use except in the context of a controlled, long-term clinical study.

1. Bresnihan B, *et al.* Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; **41:** 2196–2204.
2. Cohen S, *et al.* Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 614–24.
3. Nuki G, *et al.* Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 2838–46.
4. Fleischmann RM, *et al.* Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; **48:** 927–34.
5. Schiff MH. Durability and rapidity of response to anakinra in patients with rheumatoid arthritis. *Drugs* 2004; **64:** 2493–2501.
6. Waugh J, Perry CM. Anakinra: a review of its use in the management of rheumatoid arthritis. *BioDrugs* 2005; **19:** 189–202.
7. Reiff A. The use of anakinra in juvenile arthritis. *Curr Rheumatol Rep* 2005; **7:** 434–40.
8. den Broeder AA, *et al.* Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 2006; **65:** 760–2.
9. Burger D, *et al.* Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol* 2006; **20:** 879–96.
10. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 20/10/09).
11. National Collaborating Centre for Chronic Conditions/NICE. Rheumatoid arthritis: national clinical guideline for management and treatment in adults (issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG79FullGuideline.pdf (accessed 20/10/09)

Adverse Effects and Precautions

Mild to moderate injection site reactions with symptoms of erythema, bruising, swelling, and pain are common with anakinra particularly in the first month of treatment. Other common reactions include headache, nausea, diarrhoea, and abdominal pain. Antibodies to anakinra may develop. Allergic reactions such as rashes have been reported rarely; if a severe allergic reaction occurs, anakinra should be stopped and appropriate treatment given.

Serious infections have been reported with anakinra, particularly in patients with asthma. These infections are mainly bacterial, such as cellulitis, pneumonia, and bone and joint infections. More rarely, opportunistic infections involving fungal, mycobacterial, and viral pathogens have also been seen. Anakinra should be stopped in those who develop a serious infection. In addition, therapy should not be started in patients with active infections, including chronic or localised infections; caution is recommended in those with a history of recurrent infections or with underlying conditions that may predispose to infections.

A small decrease in absolute neutrophil count (ANC) is commonly seen with anakinra treatment; however, true neutropenia (ANC <1500 cells/mm^3) is rare. Licensed product information recommends that neutrophil counts should be taken before starting anakinra and periodically throughout treatment. UK licensed information recommends monthly monitoring during the first 6 months and then quarterly thereafter; US licensed information requires monthly monitoring for the first 3 months and then quarterly monitoring for a period of up to 1 year. Anakinra should not be started in patients with neutropenia. Small reductions in the total white blood cell and platelets counts and a small increase in eosinophils have also been noted. Anakinra is also associated with an increased incidence of lymphoma in patients with rheumatoid arthritis.

For caution in patients with renal impairment see under Uses and Administration, p. 21.3.

Effects on the cardiovascular system. A 29-year-old woman with refractory adult-onset Still's disease developed shortness of breath, which progressed to cardiorespiratory failure, 3 months after being started on anakinra;[1] although resuscitation was tried, the patient died. The authors considered that the role of anakinra in this event was unclear, particularly as the patient had shown some evidence of myocardial or pulmonary dysfunction before starting the drug.

1. Ruiz PJ, *et al.* Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra. *Ann Rheum Dis* 2007; **66:** 422–3.

Effects on the skin. Inflammatory lesions at injection sites were reported in 5 patients after anakinra use.[1] The lesions were erythematous, oedematous, painful, and itchy plaques, and were seen within 16 days of starting treatment. Treatment with anakinra was completely stopped in 1 patient and interrupted in 2 other patients; when reintroduced, one patient developed abdominal pain, dyspnoea, and facial and abdominal erythema with pruritus.

A patient with rheumatoid arthritis developed psoriasis 9 months after starting anakinra therapy;[2] the lesions improved significantly when the drug was stopped and with topical corticosteroids and vitamin D therapy.

1. Vila AT, *et al.* Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005; **153:** 417–23.
2. González-López MA, *et al.* New-onset psoriasis following treatment with the interleukin-1 receptor antagonist anakinra. *Br J Dermatol* 2008; **158:** 1146–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anakinra as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Interactions

Live vaccines should not be given with anakinra as its effect on vaccine efficacy or the risk of infection transmission is unknown.

The risk of serious infection and neutropenia is increased when anakinra and etanercept are used together (see under Infliximab, p. 77.3); a similar effect may occur with other TNF antagonists. The use of anakinra with etanercept or other TNF inhibitors is not recommended.

Pharmacokinetics

After subcutaneous doses, peak plasma concentrations of anakinra occur in 3 to 7 hours. Its terminal half-life is about 4 to 6 hours. Anakinra is excreted mainly in the urine.

References.

1. Urien S, *et al.* Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes. *BMC Pharmacol Toxicol* 2013; **14:** 40. Available at: http://www.biomedcentral.com/content/pdf/2050-6511-14-40.pdf (accessed 08/11/13)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Kineret; ***Austria***: Kineret; ***Canad.***: Kineret; ***Cz.***: Kineret; ***Denm.***: Kineret; ***Fin.***: Kineret; ***Fr.***: Kineret; ***Ger.***: Kineret; ***Gr.***: Kineret; ***Irl.***: Kineret; ***Israel***: Kineret; ***Ital.***: Kineret; ***Neth.***: Kineret; ***Norw.***: Kineret; ***Pol.***: Kineret; ***Port.***: Kineret; ***Spain***: Kineret; ***Swed.***: Kineret; ***UK***: Kineret; ***USA***: Kineret.

Anileridine *(BAN, rINN)*

Anileridiini; Anileridin; Anileridina; Aniléridine; Anileridinum; Анилеридин.

Ethyl 1-(4-aminophenethyl)-4-phenylpiperidine-4-carboxylate.

$C_{22}H_{28}N_2O_2$=352.5

CAS — 144-14-9.

ATC — N01AH05.

ATC Vet — QN01AH05.

UNII — 71Q1A3O279.

Pharmacopoeias. In *US.*

USP 36: (Anileridine). A white to yellowish-white, odourless or practically odourless, crystalline powder. When exposed to light and air it oxidises and darkens in colour. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80 degrees and the other at about 89 degrees. Very slightly soluble in water; soluble 1 in 2 of alcohol and 1 in 1 of chloroform; soluble in ether but solutions may be turbid. Store in airtight containers. Protect from light.

Anileridine Hydrochloride *(BANM, rINNM)*

Anileridina, hidrocloruro de; Aniléridine, Chlorhydrate d'; Anileridini Hydrochloridum; Hidrocloruro de anileridina; Анилеридина Гидрохлорид.

$C_{22}H_{28}N_2O_2$,2HCl=425.4

CAS — 126-12-5.

UNII — 915Q054DLC.

Pharmacopoeias. In *US.*

USP 36: (Anileridine Hydrochloride). A white or nearly white odourless crystalline powder. Soluble 1 in 5 of water and 1 in 80 of alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is 2.5 to 3.0. Store in airtight containers. Protect from light.

Anileridine Phosphate *(BANM, rINNM)*

Aniléridine, Phosphate d'; Anileridini Phosphas; Fosfato de anileridina; Анилеридина Фосфат.

$C_{22}H_{28}N_2O_2$,H_3PO_4=450.5

CAS — 4268-37-5.

UNII — 3584484N8V.

Profile

Anileridine, a phenylpiperidine derivative, is an opioid analgesic (p. 108.1) chemically related to pethidine (p. 121.3) and with similar actions. It has been used as the hydrochloride in the management of moderate to severe pain. Anileridine has also been given by injection as the phosphate.

Preparations

Pharmacopoeial Preparations

USP 36: Anileridine Hydrochloride Tablets; Anileridine Injection.

Aspirin *(BAN)*

Acetilsalicílico, ácido; Acetilsalicilo rūgštis; Acetilszalicilsav; Acetylsal. Acid; Acetylsalicylic Acid; Acetylsalicylsäure; Acetylsalicylsyra; Acide acétylsalicylique; Acidum Acetylsalicylicum; Asetilsalisilik Asit; Asetyylisalisyylihappo; Kwas acetylosalicylowy; Kyselina acetylsalicylová; Polopiryna; Salicylic Acid Acetate; Аспирин.

O-Acetylsalicylic acid; 2-Acetoxybenzoic acid.

$C_9H_8O_4$=180.2

CAS — 50-78-2.

ATC — A01AD05; B01AC06; N02BA01.

ATC Vet — QA01AD05; QB01AC06; QN02BA01.

UNII — R16CO5Y76E.

NOTE. The use of the name Aspirin is limited; in some countries it is a trade-mark.

Compounded preparations of aspirin may be represented by the following names:

- Co-codaprin (*BAN*)—aspirin 50 parts and codeine phosphate 1 part (w/w)
- Co-codaprin (*PEN*)—aspirin and codeine phosphate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Acetylsalicylic Acid; Aspirin BP 2014). White or almost white, crystalline powder or colourless crystals. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 36: (Aspirin). White crystals, commonly tubular or needle-like, or white crystalline powder; odourless or has a faint odour. Is stable in dry air; in moist air it gradually hydrolyses to salicylic and acetic acids. Soluble 1 in 300 of water, 1 in 5 of alcohol, 1 in 17 of chloroform, and 1 in 10 to 15 of ether; sparingly soluble in absolute ether. Store in airtight containers.

Uses and Administration

Aspirin is a salicylate NSAID and has many properties in common with non-aspirin NSAIDs (p. 102.3). Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties; they act as inhibitors of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p. 2598.1). Aspirin also inhibits platelet aggregation; non-acetylated salicylates do not.

Aspirin is used for the relief of mild to moderate pain such as headache, dysmenorrhoea, myalgias, and dental pain. It has also been used in the management of pain and inflammation in acute and chronic rheumatic disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis. In the treatment of minor febrile conditions, such as colds or influenza, aspirin can reduce temperature and relieve headache and joint and muscle pains.

Aspirin is also used for its antiplatelet activity in the initial treatment of cardiovascular disorders such as angina pectoris and myocardial infarction and for the prevention of cardiovascular events in patients at risk. Other such uses include the treatment and prevention of cerebrovascular disorders such as stroke. For further details see Antiplatelet Therapy, below.

Aspirin is usually taken orally. Gastric irritation may be reduced by taking doses after food. Various dosage forms are available including plain uncoated tablets, buffered tablets, dispersible tablets, enteric-coated tablets, and modified-release tablets. In some instances aspirin may be given rectally by suppository.

The usual oral dose of aspirin as an analgesic and antipyretic is 300 to 900 mg, repeated every 4 to 6 hours according to clinical needs, to a maximum of 4 g daily. The dose as suppositories is 450 to 900 mg every 4 hours to a maximum of 3.6 g daily.

Plasma-salicylate concentrations of 150 to 300 micrograms/mL are required for optimal anti-inflammatory activity (but see also Adverse Effects, p. 24.2). Doses need to be adjusted individually to achieve optimum concentrations. Generally doses of about 4 to 8 g daily in divided doses are used for acute rheumatic disorders such as rheumatoid arthritis or osteoarthritis. Doses of up to 5.4 g daily in divided doses may be sufficient in chronic conditions.

Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3), but include Kawasaki disease (see p. 23.3), and juvenile idiopathic arthritis and Still's disease (see Rheumatic Disorders, p. 24.1).

Sodium aspirin has also been used for the treatment of pain and fever.

Homoeopathy

Aspirin has been used in homoeopathic medicines under the following names: Acetylsalicylicum acidum; Acetylsalac.

Administration in children. Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3). For further information, including some doses, see Antiplatelet Therapy, Kawasaki Disease, and Rheumatic Disorders, below, p. 23.3, and p. 24.1, respectively.

Antiplatelet therapy. Aspirin is an inhibitor of the enzyme cyclo-oxygenase, the **action** being considered to be due to an irreversible acetylation process.

- In blood platelets such enzyme inhibition prevents the synthesis of thromboxane A_2, a compound which is a vasoconstrictor, causes platelet aggregation, and is thus potentially thrombotic.
- In blood vessel walls the enzyme inhibition prevents the synthesis of prostacyclin, which is a vasodilator, has

anti-aggregating properties, and is thus potentially anti-thrombotic.

Aspirin therefore appears to have opposing biological effects. The duration of these effects, however, may differ, with the *effects on the vascular tissue generally being shorter than the effects on the platelets* (although the *animal* species studied, the type of blood vessel used, and the prevailing experimental conditions may alter the results). The difference may be explained by the fact that vascular cells regain the ability to regenerate prostacyclin in a few hours but platelets are unable to re-synthesise cyclo-oxygenase, which results in no new thromboxane A_2 being produced for about 24 hours until more platelets are released by the bone marrow; as platelet activity in bone marrow may also be affected by aspirin it is generally considered that aspirin only needs to be given once daily for inhibition of platelet aggregation to occur. The inhibitory effect on thromboxane is rapid and unrelated to serum concentrations of aspirin, probably because of the inactivation of cyclo-oxygenase in platelets in the presystemic circulation. Since the effect is unrelated to systemic bioavailability, modified-release and dermal delivery preparations which do not achieve high systemic concentrations of aspirin are being developed to limit extraplatelet effects of aspirin. Inhibition is cumulative on repeated dosage, and it has been estimated that a daily dose of 20 to 50 mg will result in virtually complete suppression of platelet thromboxane synthesis within a few days. Large doses of 150 to 300 mg can produce maximum suppression almost instantaneously.

Uses. Aspirin's antiplatelet activity has led to its use for the treatment or prevention of a variety of disorders.[1-7]

- It is used as part of the initial **treatment** of unstable *angina* (p. 1254.3) and is given in the early treatment of *myocardial infarction* (p. 1257.1); it is also of benefit in the initial treatment of acute *ischaemic stroke* (p. 1269.2).
- Aspirin is used for its combination of anti-inflammatory, antipyretic, and antiplatelet activity in the treatment of *Kawasaki disease* (see below). It is also used to treat thrombotic symptoms associated with *antiphospholipid syndrome*, such as occurs in patients with SLE (p. 1613.3), and has been recommended for prophylactic use in pregnant patients with antiphospholipid antibodies who are at risk of fetal loss. The thrombolytic action of aspirin has also led to its use in *thrombotic thrombocytopenic purpura* (see Thrombotic Microangiopathies, p. 1159.1). Aspirin provides a modest reduction in risk of *pre-eclampsia* and its complications (see Hypertension, p. 1251.1) and is recommended in some women.
- It is of value for the **prevention** of cardiovascular events in patients at high risk, including those with stable or unstable angina, current or previous myocardial infarction, ischaemic stroke, or transient ischaemic attack[8,9] (see Cardiovascular Risk Reduction, p. 1246.1). It has also been used in the long-term management of atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1) for the prevention of stroke in patients with contra-indications to warfarin or if there are no other risk factors for stroke.
- The value of aspirin for **primary prevention** of cardiovascular events, particularly *myocardial infarction* and *stroke* depends upon the accurate estimation of overall cardiovascular risk but routine use is probably not justified in healthy individuals.[7-12] Published evidence of unequivocal benefit with low-dose aspirin in such patients is lacking; furthermore, there is an increased risk of gastrointestinal haemorrhage with long-term treatment.

  Although evidence suggests aspirin may provide some protection against *venous thromboembolism* (p. 1274.1) in hospitalised patients, anticoagulants are preferred since they are much more effective. However, it is recommended for use in preventing thrombotic complications associated with procedures such as angioplasty and coronary bypass grafting (see Reperfusion and Revascularisation Procedures, p. 1259.2). Aspirin has been given as an adjunct to patients with *peripheral arterial thromboembolism* (p. 1273.3) to prevent propagation of the clot and also to prevent postoperative complications. Antiplatelet therapy is recommended as part of aggressive cardiovascular risk reduction measures in patients with *peripheral arterial occlusive disease* (p. 1272.3), although a meta-analysis[13] of small and short-term studies did not find a statistically significant benefit (i.e. 12% relative risk reduction) of its use on cardiovascular events when compared with placebo or dipyridamole.

  The benefit of aspirin for the primary prevention of cardiovascular events in patients with *diabetes mellitus* and who have no other cardiovascular risk factors remains to be determined. Use may be recommended in those at increased risk (see Diabetes-associated Cardiovascular Disease, p. 465.3 for further details).

  The value of adding aspirin to anticoagulants for the prophylaxis of thromboembolism in patients with *prosthetic heart valves* (see Valvular Heart Disease, p. 1264.3) is also still to be firmly established. It is usually recommended as an adjunct in patients with other risk factors. Aspirin alone may be considered in patients with bioprosthetic valves who do not require anticoagulation.

Several pharmacological studies have attempted to find a **dose** of aspirin that would inhibit synthesis of platelet thromboxane A_2 while sparing the effect on prostacyclin production[14-16] but it has been pointed out[3] that in patients with vascular disease accompanying or caused by endothelial dysfunction, such as in atherosclerosis, a selective sparing of vascular prostacyclin production may not be obtained at any effective antiplatelet dose. However, the clinical relevance of inhibiting the synthesis of prostacyclin may have been exaggerated.[17] Experimental evidence indicates that aspirin is thrombogenic only at extremely high doses (200 mg/kg), far exceeding the minimum dose required to inhibit prostacyclin production. Also aspirin is clinically effective as an antithrombotic drug at doses that inhibit the synthesis of prostacyclin. Further support for the lack of importance of inhibition of prostacyclin synthesis comes from epidemiological studies in patients with arthritis given large doses of aspirin and patients with congenital cyclo-oxygenase deficiency; neither of these groups of patients have experienced an excess of thrombotic episodes.

In a meta-analysis conducted by the Antithrombotic Trialists' Collaboration[8] daily doses of 75 to 325 mg appeared to be equally effective for their antiplatelet effect; doses greater than 500 mg did not appear to be superior and caused more gastrointestinal adverse effects. Whether doses less than 75 mg offer the same efficacy with reduced gastrointestinal toxicity is unknown (see Effects on the Gastrointestinal Tract, p. 24.3). The meta-analysis concluded that for the long-term prevention of serious vascular events in high-risk patients, a daily dose of aspirin in the range of 75 to 150 mg should be effective; if an immediate effect is required as in the initial treatment of acute myocardial infarction, acute ischaemic stroke, or unstable angina, a loading dose of 150 to 300 mg may be given. Other analyses[18] have made similar dose recommendations. However, another review[19] has suggested that doses as low as 75 or 80 mg daily may be inadequate for the primary prevention of stroke and myocardial infarction; it was considered that the most appropriate dose of aspirin for primary prevention was 160 mg daily. Aspirin should be chewed or dispersed in water; chewing a tablet of aspirin ensures that some buccal absorption occurs.

The use of aspirin in **children** is limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3); however, it may be specifically indicated in those at risk of clot formation after cardiac surgery or for the prophylaxis of stroke in high-risk children. The *BNFC* has suggested oral doses of 1 to 5 mg/kg (up to a usual maximum of 75 mg) once daily in neonates and children up to 12 years of age; older children may be given 75 mg daily.

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19. Dalen JE. Aspirin to prevent heart attack and stroke: what's the right dose? *Am J Med* 2006; **119:** 198–202.

Behçet's syndrome. For reference to the use of aspirin in the management of vasculitic symptoms of Behçet's syndrome, see p. 1601.1.

Cataract. Evidence to support or disprove the hypothesis that aspirin has a protective effect against cataract formation is considered inconclusive. A study in the USA in over 22 000 males concluded that low-dose aspirin (325 mg on alternate days) for 5 years was unlikely to have a major effect on cataract formation but that a slightly decreased risk for cataract extraction could not be excluded.[1] In a later study[2] in the UK ophthalmic examination of over 1800 patients who were receiving 300 mg to 1.2 g of aspirin daily for transient ischaemic attacks failed to confirm any protective effect. Re-analysis[3] of the results of the original US study identified additional cases of cataract formation or extraction although these cases did not affect the overall conclusions of the original study. However, when the study patients were followed up over 15 years, observational data[4] suggested that the use of low-dose aspirin may, in fact, increase the risk of cataract development. It was considered that further studies were needed to establish the role of long-term aspirin in cataract prevention.

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Dysmenorrhoea. Drugs such as aspirin and other NSAIDs that inhibit prostaglandin production through inhibition of cyclo-oxygenase are effective drugs in the treatment of dysmenorrhoea (p. 8.2).

Fever. Methods for controlling fever (see p. 11.3) include the use of antipyretics and/or physical cooling methods (although the value of the latter is questionable). Paracetamol, salicylates such as aspirin, and some other NSAIDs are the main antipyretics used. However, salicylates are generally contra-indicated for the management of fever in children because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects, p. 25.3).

Headache. Aspirin is often used for the symptomatic treatment of various types of headache including migraine (see p. 670.3) and tension-type headache (see p. 671.3). Aspirin given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

References.

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Kawasaki disease. Aspirin has been given in regimens with normal immunoglobulins to children with Kawasaki disease (p. 2405.2) because of its anti-inflammatory, antipyretic, and antiplatelet activity.[1-4]

The usual practice is to use an anti-inflammatory regimen until the fever has settled and then convert to an antithrombotic regimen. The *BNFC* recommends an oral dose of aspirin 30 to 50 mg/kg daily in 4 divided doses in children aged 1 month and over (neonates may be given 32 mg/kg daily in 4 divided doses); this should be continued until the patient is afebrile or for the first 14 days after the onset of symptoms. Once fever and signs of inflammatory disease resolve, the aspirin dose is reduced to 2 to 5 mg/kg daily (neonates may be given 5 mg/kg daily) as a single dose for its antiplatelet effect. Aspirin may be stopped 6 to 8 weeks after the onset of illness but is usually continued for at least one year if coronary abnormalities are present and is continued indefinitely if coronary aneurysms persist. Similar regimens[3,4] are used in the USA although the initial dose of aspirin is more usually 80 to 100 mg/kg daily.

Despite this widespread use the optimum dose and duration of treatment have not been clearly established, and the value of aspirin in the initial management of Kawasaki disease has been questioned. In a meta-analysis[5] fever duration was significantly shorter in those on high-dose aspirin; however, other studies[6] have not shown such a benefit. Meta-analyses[5,7] have also shown that the incidence of coronary artery abnormalities is not significantly different for regimens using high (over 80 mg/kg daily) or low doses of aspirin. Furthermore, a retrospective study[8] suggested that aspirin use (irrespective of dose) in the acute phase of the disease may be unnecessary as its addition to immunoglobulin treatment had no effect on the rate of coronary artery abnormalities. A more recent review[9] found that evidence from comparative studies failed to show that aspirin reduced the rate of coronary artery abnormalities; a lack of good quality randomised controlled studies prevented any recommendations on the use of aspirin in the treatment of Kawasaki disease.

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Leg ulcers. A 4-month placebo-controlled study[1] in 20 patients suggested that aspirin 300 mg daily aided healing of chronic venous leg ulcers; the mechanism of action was unclear.[2] However, the validity of the findings has been challenged.[3] The management of leg ulcers is discussed on p. 1690.1.

1. Layton AM, *et al.* Randomised trial of oral aspirin for chronic venous leg ulcers. *Lancet* 1994; **344:** 164–5.
2. Ibbotson SH, *et al.* The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. *Br J Dermatol* 1995; **132:** 422–6.
3. Ruckley CV, Prescott RJ. Treatment of chronic leg ulcers. *Lancet* 1994; **344:** 1512–13.

Malignant neoplasms. For references to studies suggesting that regular use of aspirin and other NSAIDs may reduce the risk of developing malignant neoplasms of the gastrointestinal tract, see under NSAIDs, p. 104.1.

Myeloproliferative disorders. Aspirin in low doses may be used to provide symptomatic relief for erythromelalgia (burning pain and erythema of the hands and feet) in patients with polycythaemia vera (p. 695.2) and primary thrombocythaemia (p. 695.2).

Pain. Aspirin, along with other NSAIDs and paracetamol, may be used for treating mild or moderate pain (see Choice of Analgesic, p. 4.2) and is also used in moderate or severe pain to potentiate the effects of opioids. It is suitable for use in acute or chronic pain. Aspirin should not be used for pain relief in children because of its association with Reye's syndrome (see under Adverse Effects, p. 25.3).

Dependence and tolerance are not a problem with non-opioid analgesics such as aspirin, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

References.

1. Rees J, *et al.* Single dose oral aspirin for acute pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/11/06).
2. Hersch EV, *et al.* Over-the-counter analgesics and antipyretics: a critical assessment. *Clin Ther* 2000; **22:** 500–48.
3. Vergne P, *et al.* Aspirine, douleurs et inflammation. *Rev Med Interne* 2000; **21** (suppl 1): 89s–96s.

Rheumatic disorders. Aspirin was once widely used in the treatment of rheumatoid arthritis (p. 13.2) but has been superseded by better tolerated NSAIDs; however, juvenile idiopathic arthritis (p. 12.1) including Still's disease are among the limited number of indications for aspirin use in children. The *American Hospital Formulary Service*[1] suggests that children weighing 25 kg or less may be given an initial oral dose of 60 to 130 mg/kg daily in divided doses; heavier children should be started on 2.4 to 3.6 g daily. Alternatively, an initial oral dose of 1.5 g/m^2 daily may be given in divided doses. The usual maintenance dose is 80 to 100 mg/kg daily although up to 130 mg/kg daily may be required in some children; however, because of the risk of toxicity, it is recommended that children weighing over 25 kg should not receive doses of 100 mg/kg daily or above.

1. McEvoy GK (ed), AHFS Drug Information. online] Bethesda, MD: American Society of Health-System Pharmacists. Available at: http://www.medicinescomplete.com (accessed 13/01/10)

Adverse Effects and Treatment

Aspirin has many properties in common with the non-aspirin NSAIDs, the adverse effects of which are described on p. 104.3.

The most common adverse effects of therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, dyspepsia, and vomiting. Gastrointestinal symptoms may be minimised by giving aspirin with food. Irritation of the gastric mucosa with erosion, ulceration, haematemesis, and melaena may occur. Histamine H_2-antagonists, proton pump inhibitors, and prostaglandin analogues such as misoprostol may be used in the management of NSAID-induced ulceration (see Peptic Ulcer Disease, p. 1816.2), including that caused by aspirin. Slight blood loss, which is often asymptomatic, may occur in about 70% of patients; it is not usually of clinical significance but may, in a few patients, cause iron-deficiency anaemia during long-term therapy. Such occult blood loss is not affected by giving aspirin with food but may be reduced by use of enteric-coated or other modified-release tablets, H_2-antagonists, or high doses of antacids. Major upper gastrointestinal bleeding occurs rarely.

Some persons, especially those with asthma, chronic urticaria, or chronic rhinitis, exhibit notable hypersensitivity to aspirin (see also p. 25.2), which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis, and severe, even fatal, paroxysmal bronchospasm and dyspnoea. Persons sensitive to aspirin often have cross-sensitivity to other NSAIDs.

Aspirin increases bleeding time, decreases platelet adhesiveness, and, in large doses, can cause hypoprothrombinaemia. It may cause other blood disorders, including thrombocytopenia.

Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders. In children the use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children. For further details, see Reye's Syndrome, p. 25.3.

Aspirin given rectally may cause local irritation; anorectal stenosis has been reported.

Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. Tinnitus can occur at the plasma concentrations of 150 to 300 micrograms/mL required for optimal anti-inflammatory activity; more serious adverse effects occur at concentrations above 300 micrograms/mL. Symptoms of more severe intoxication or of acute poisoning following overdosage include hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis. Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur. In children drowsiness and metabolic acidosis commonly occur; hypoglycaemia may be severe.

In acute oral salicylate overdosage the UK National Poisons Information Service (NPIS) recommends that an oral dose of activated charcoal be given if the patient is suspected of ingesting more than 125 mg/kg of salicylate, or any amount of methyl salicylate, within 1 hour of presentation. Activated charcoal not only prevents the absorption of any salicylate remaining in the stomach but also aids the elimination of any that has been absorbed. Gastric lavage should be considered in patients who have ingested more than 500 mg/kg of salicylate within 1 hour of presentation.

Measurement of plasma-salicylate concentration should be carried out in patients who have ingested more than 125 mg/kg of aspirin, or any amount of methyl salicylate or salicylamide, although the severity of poisoning cannot be estimated from plasma concentrations alone. Absorption of aspirin can be delayed by reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. In consequence, plasma concentrations should be measured at least 2 hours (symptomatic patients) or 4 hours (asymptomatic patients) after ingestion and repeated 2 hours later. A second dose of activated charcoal may be given to those whose plasma-salicylate concentration continues to rise or those who have ingested enteric-coated preparations. If necessary, measurements should be repeated every 3 hours until the concentrations fall.

Fluid and electrolyte management is essential to correct acidosis, hyperpyrexia, hypokalaemia, and dehydration. Intravenous sodium bicarbonate is given to enhance urinary salicylate excretion if plasma-salicylate concentrations exceed 500 micrograms/mL (350 micrograms/mL in children). Haemodialysis or haemoperfusion are also effective methods of removing salicylate from the plasma. The *BNF* considers haemodialysis the method of choice in severe poisoning; it should be seriously considered when the plasma-salicylate concentration is more than 700 micrograms/mL or if there is severe metabolic acidosis. Vulnerable patients such as children (aged under 10 years) or the elderly (aged over 70 years) may require dialysis at an earlier stage.

References to salicylate toxicity and its management.

1. Notarianni L. A reassessment of the treatment of salicylate poisoning. *Drug Safety* 1992; **7:** 292–303.
2. Woods D, *et al.* Acute toxicity of drugs: salicylates. *Pharm J* 1993; **250:** 576–8.
3. Collee GG, Hanson GC. The management of acute poisoning. *Br J Anaesth* 1993; **70:** 562–73.
4. Watson JE, Tagupa ET. Suicide attempt by means of aspirin enema. *Ann Pharmacother* 1994; **28:** 467–9.
5. Dargan PI, *et al.* An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emerg Med J* 2002; **19:** 206–9.
6. Rivera W, *et al.* Delayed salicylate toxicity at 35 hours without early manifestations following a single salicylate ingestion. *Ann Pharmacother* 2004; **38:** 1186–8. Correction. *ibid.* 2006; **40:** 999.

Effects on the blood. Although it has beneficial effects on platelets, aspirin can cause adverse blood effects. An indication of this toxicity is given by an early reference[1] to reports submitted to the UK CSM. There were 787 reports of adverse reactions to aspirin reported to the CSM between June 1964 and January 1973. These included 95 reports of blood disorders (17 fatal) including thrombocytopenia (26; 2 fatal), aplastic anaemia (13; 7 fatal), and agranulocytosis or pancytopenia (10; 2 fatal). Aspirin has also been associated with haemolytic anaemia in patients with G6PD deficiency.[2]

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2:** 600–9.
2. Magee P, Beeley L. Drug-induced blood dyscrasias. *Pharm J* 1991; **246:** 396–7.

Effects on the cardiovascular system. Salicylate poisoning may result in cardiovascular collapse but details of such cases have not been widely reported. In 2 patients with salicylate intoxication asystole developed after intravenous diazepam.[1] It was suggested that diazepam-induced respiratory depression affected the acid–base balance so that the concentration of non-ionised membrane-penetrating fraction of salicylate was increased. Fatal aspirin intoxication in a 5-year-old child was marked by hypotension and rapidly progressive cardiac symptoms including ventricular tachycardia and AV block.[2] Extensive myocardial necrosis was found at autopsy.

For reference to the effects of aspirin on blood pressure compared with other NSAIDs, see p. 105.1.

1. Berk WA, Andersen JC. Salicylate-associated asystole: report of two cases. *Am J Med* 1989; **86:** 505–6.
2. Peña-Alonso YR, *et al.* Aspirin intoxication in a child associated with myocardial necrosis: is this a drug-related lesion? *Pediatr Dev Pathol* 2003; **6:** 342–7.

Effects on the gastrointestinal tract. Clinical and epidemiological evidence suggests that aspirin produces dose-related gastrointestinal toxicity[1,2] that is sometimes, but rarely, fatal.[2] Meta-analysis[3] suggests that the risk of gastrointestinal bleeding is not significantly lowered with the use of oral low-dose aspirin (less than 300 mg daily). A systematic review[4] of observational epidemiologic studies also concurred with this finding. Another systematic review[5] of randomised, controlled studies found that although low-dose aspirin (up to 325 mg daily) increased the risk of major bleeding including gastrointestinal bleeding by twofold when compared with placebo, the actual risk of bleeding was modest; for every 833 patients taking low-dose aspirin for cardiovascular prophylaxis only 1 additional major bleeding episode will occur annually. In a population-based study,[6] the annual excess risk of upper gastrointestinal complications was about an extra 5 cases per 1000 patients; however, the excess risk varied with underlying gastrointestinal risk factors such as old age and might exceed an extra 10 cases per 1000 patients in a higher-risk group comprising over 10% of aspirin users. It has been suggested that very small doses of aspirin can produce prophylactic benefits in cardiovascular disease without the risk of gastrointestinal toxicity,[7] although others have reported gastric injury even with doses of 10 mg daily.[8]

There appears to be no convincing evidence that the risk of major gastrointestinal bleeding associated with a 75-mg

dose is reduced by using enteric-coated or modified-release formulations rather than soluble aspirin,[3,4,9] although individual studies have reported a reduction in acute mucosal injury with enteric coating.[10]

All known NSAIDs have the potential for causing acute damage to the gastric mucosa (see p. 105.3), and comparative studies of acute gastric mucosal damage caused by such drugs consistently associate aspirin with the most severe lesions.[1] Gastric mucosal injury can occur even with cutaneous application.[11]

1. Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med* 1986; **104:** 390–8.
2. Roderick PJ, *et al*. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993; **35:** 219–26.
3. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000; **321:** 1183–7.
4. Garcia Rodríguez LA, *et al*. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001; **52:** 563–71.
5. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; **119:** 624–38.
6. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006; **4:** 22. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-22.pdf (accessed 11/12/06)
7. Lee M, *et al*. Dose effects of aspirin on gastric prostaglandins and stomach mucosal injury. *Ann Intern Med* 1994; **120:** 184–9.
8. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999; **117:** 17–25.
9. Anonymous. Which prophylactic aspirin? *Drug Ther Bull* 1997; **35:** 7–8.
10. Cole AT, *et al*. Protection of human gastric mucosa against aspirin—enteric coating or dose reduction? *Aliment Pharmacol Ther* 1999; **13:** 187–93.
11. Cryer B, *et al*. Effects of cutaneous aspirin on the human stomach and duodenum. *Proc Assoc Am Physicians* 1999; **111:** 448–56.

Effects on hearing. Studies have shown that tinnitus develops at serum-salicylate concentrations above 200 micrograms/mL.[1] However, there appears to be considerable intersubject variation in the response of the ear to salicylate;[2] tinnitus may occur at lower concentrations, whereas patients with pre-existing hearing loss may not have tinnitus despite serum-salicylate concentrations of 311 to 677 micrograms/mL.[1] A graded increase in intensity of ototoxicity with increasing salicylate dose and plasma concentration has been shown.[2] For example, at an average total plasma-salicylate concentration of 110 micrograms/mL, the hearing loss at any given frequency was about 12 decibels; such a deficit might be relevant to patients with pre-existing hearing impairment.[2]

1. Mongan E, *et al*. Tinnitus as an indication of therapeutic serum salicylate levels. *JAMA* 1973; **226:** 142–5.
2. Day RO, *et al*. Concentration-response relationships for salicylate-induced ototoxicity in normal volunteers. *Br J Clin Pharmacol* 1989; **28:** 695–702.

Effects on the kidneys. Although abuse of combined analgesic preparations containing aspirin has been implicated in the development of analgesic nephropathy, kidney damage associated with the therapeutic use of aspirin alone appears to be comparatively rare. Many studies have failed to find an increased risk of renal damage in patients taking aspirin.[1-9]

1. New Zealand Rheumatism Association Study. Aspirin and the kidney. *BMJ* 1974; **1:** 593–6.
2. Walker BR, *et al*. Aspirin and renal function. *N Engl J Med* 1977; **297:** 1405.
3. Akyol SM, *et al*. Renal function after prolonged consumption of aspirin. *BMJ* 1982; **284:** 631–2.
4. Bonney SL, *et al*. Renal safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1986; **40:** 373–7.
5. Sandler DP, *et al*. Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
6. Pommer W, *et al*. Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol* 1989; **9:** 403–12.
7. Dubach UC, *et al*. An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
8. Perneger TV, *et al*. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.
9. Rexrode K, *et al*. Analgesic use and renal function in men. *JAMA* 2001; **286:** 315–21.

Effects on the liver. Aspirin-induced hepatic injury is generally mild and manifests as a mild to moderate elevation in aminotransferase values; however, there is a risk of severe liver injury.[1] One review[2] reported an increase in aminotransferase values in 59 of 439 patients given aspirin; the increase was considered to be probably related to aspirin in 23. Hepatotoxicity appears to be correlated with serum-salicylate concentrations greater than 150 micrograms/mL and with active rheumatoid disease. Aspirin-induced liver injury is usually reversible on stopping the drug.[2]

See also under Reye's Syndrome, below.

1. Lewis JH. Hepatic toxicity of nonsteroidal anti-inflammatory drugs. *Clin Pharm* 1984; **3:** 128–38.
2. Freeland GR, *et al*. Hepatic safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1988; **43:** 473–9.

Effects on the mouth. Aspirin burn (ulceration of the mucosal layer of the lips) developed in a 26-year-old woman after taking an aspirin-containing powder for a migraine.[1] The woman had swallowed the powder undissolved rather than adding to water.

1. Dellinger TM, Livingston HM. Aspirin burn of the oral cavity. *Ann Pharmacother* 1998; **32:** 1107.

Hypersensitivity. The main clinical features of patients who have aspirin hypersensitivity include middle-age, female gender, diagnoses of asthma or rhinitis, a personal or family history of atopy, and a history of nasal polyps.[1,2] Aspirin sensitivity occurring with asthma and nasal polyps has been referred to in some reports as the 'aspirin triad'. Other sensitivities often found concomitantly include allergy to food dyes such as tartrazine and to drugs such as other NSAIDs.

The prevalence of aspirin-induced asthma can vary according to the method used to measure it. A systematic review[3] calculated the prevalence of aspirin-induced asthma to be 21% in the general adult asthma population and 5% in children when determined by oral provocation testing. However, when based on medical history alone it was only 2.7% in adults and 2% in children. In another study[4] using data from patient questionnaires the prevalence of aspirin-induced asthma was 10 to 11% in patients with asthma and 2.5% in non-asthmatics.

There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. In a systematic review[3] cross-sensitivity to other non-selective NSAIDs (ibuprofen, diclofenac, and naproxen) occurred in over 90% of those patients with aspirin-induced asthma. A review of the literature[5] found little evidence of cross-reactivity with selective cyclo-oxygenase-2 (COX-2) inhibitors and aspirin particularly in patients with aspirin-induced asthma; however, although there have been isolated reports of asthma in such patients after taking celecoxib or rofecoxib. About 4% of patients with aspirin-induced skin reactions may develop a cutaneous reaction when challenged with a COX-2 selective NSAID. Paracetamol is usually safe in patients sensitive to aspirin and cross-sensitivity to paracetamol has been calculated as about 7%.[3] Based on these figures, it is considered that less than 2% of asthmatic patients would be likely to react to both paracetamol and aspirin.

The response to individual NSAIDs is believed to be closely linked to the extent to which they inhibit prostaglandin synthesis.[6,7] There may be a dose threshold below which no detectable symptoms occur and patients who may be tolerant of regular low-dose aspirin can develop symptoms when they take larger doses.[7] Some[7] use a formal challenge with a 300-mg oral dose of aspirin to confirm a diagnosis of NSAID sensitivity but others[8] consider this to be a dangerous technique and use inhalation of lysine aspirin which they consider to be a safer and more predictable alternative. Intranasal challenge with lysine aspirin has also been used.[9,10]

1. Kwoh CK, Feinstein AR. Rates of sensitivity reactions to aspirin: problems in interpreting the data. *Clin Pharmacol Ther* 1986; **40:** 494–505.
2. Schiavino D, *et al*. The aspirin disease. *Thorax* 2000; **55** (suppl 2): S66–S69.
3. Jenkins C, *et al*. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; **328:** 434–7.
4. Vally H, *et al*. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002; **57:** 569–74.
5. Knowles SR, *et al*. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. *Ann Pharmacother* 2007; **41:** 1191–1200.
6. Power I. Aspirin-induced asthma. *Br J Anaesth* 1993; **71:** 619–21.
7. Frew A. Selected side-effects: 13. non-steroidal anti-inflammatory drugs and asthma. *Prescribers' J* 1994; **34:** 74–7.
8. Davies BH. NSAIDs and asthma. *Prescribers' J* 1994; **34:** 163–4.
9. Casadevall J *et al*. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. *Thorax* 2000; **55:** 921–4.
10. Alonso-Llamazares A, *et al*. Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). *Allergy* 2002; **57:** 632–5.

DESENSITISATION. Successful desensitisation has been achieved using oral aspirin challenge protocols.[1-6] Incremental doses of aspirin (traditionally starting at 30 mg) are given until an allergic response occurs; aspirin is readministered at the dose that caused the response and again incremental doses are given until finally a 650-mg dose is tolerated.[1,2] After desensitisation, an interruption of continuous aspirin dosage results in the reappearance of sensitivity. Desensitisation has been maintained indefinitely with as little as 81 mg daily of aspirin.[6]

1. Asad SI, *et al*. Effect of aspirin in "aspirin sensitive" patients. *BMJ* 1984; **288:** 745–8.
2. Stevenson DD. Desensitization of aspirin-sensitive asthmatics: a therapeutic alternative? *J Asthma* 1983; **20:** 31–8.
3. Gollapudi RR, *et al*. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004; **292:** 3017–23.
4. Cormican LJ, *et al*. Improvements in an oral aspirin challenge protocol for the diagnosis of aspirin hypersensitivity. *Clin Exp Allergy* 2005; **35:** 717–22.
5. Pfaar O, Klimek L. Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements. *Curr Opin Allergy Clin Immunol* 2006; **6:** 161–6.
6. Knowles SR, *et al*. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. *Ann Pharmacother* 2007; **41:** 1191–1200.

Hypoglycaemia. A review of the literature[1] on drug-induced hypoglycaemia highlighted the fact that overdosage with salicylates could produce hypoglycaemia in children. Although therapeutic doses of salicylates in adults can lower blood-glucose concentrations in diabetic and non-diabetic subjects alike, opinion on the clinical significance of this effect varies. Salicylates have been implicated in a few cases of hypoglycaemia in adults[1] and some[2] suggest that patients with renal impairment or those receiving large doses, such as in the treatment of rheumatoid arthritis, may be at risk. Hypoglycaemia has been reported in a patient with renal failure after excessive application of a topical preparation containing salicylic acid.[3]

1. Seltzer HS. Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 1989; **18:** 163–83.
2. Pandit MK, *et al*. Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
3. Raschke R, *et al*. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 1991; **151:** 591–3.

Reye's syndrome. Reye's syndrome is a disorder characterised by acute encephalopathy and fatty degeneration of the liver. It occurs almost exclusively in young children although cases have been seen[1] in patients over the age of 12. Many factors may be involved in its aetiology but it typically occurs after a viral infection such as chickenpox or influenza and may be precipitated by a chemical trigger. Several large studies, as well as individual case reports, have found a link between Reye's syndrome and the prior ingestion of aspirin;[2-7] the evidence for other salicylates could not be adequately evaluated.[4] More recently, *in-vitro* studies have shown biological plausibility for the role of aspirin in the development of Reye's syndrome.[6]

Although a causal relationship remains to be established, the use of aspirin and other acetylated salicylates as analgesics or antipyretics is generally considered contra-indicated in children under the age of 12 years and, in some countries, in teenagers. For example, the UK MHRA has recommended that all children aged under 16 years should not take aspirin.[8] (This advice superseded their earlier recommendations to avoid aspirin during fever or viral infection in children under 16 years of age; this advice was considered too complex for products on general sale and, given the wide availability of other analgesic preparations, there was no need to expose this age group to any risk.) Some countries also extend these recommendations to non-acetylated salicylates. In the UK, the MHRA[9] contra-indicates the use of topical oral pain relief preparations containing salicylates in children under 16 years of age due to the theoretical risk of Reye's syndrome (for details, see Choline Salicylate, p. 39.3).

One group of workers[10] who re-examined some of the original studies suggested that there might also be a link between Reye's syndrome and the use of antiemetics, phenothiazines, and some other antihistamines, but their conclusions have been criticised.[11] More recently, others[12] have suggested that Reye's syndrome was caused by a viral mutation or the result of misdiagnoses of metabolic disorders but again these conclusions have been questioned.[6,13]

1. Hall SM, Lynn R. Reye's syndrome. *N Engl J Med* 1999; **341:** 845–6.
2. Waldman RJ, *et al*. Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982; **247:** 3089–94.
3. Halpin TJ, *et al*. Reye's syndrome and medication use. *JAMA* 1982; **248:** 687–91.
4. Hurwitz ES, *et al*. Public health service study of Reye's syndrome and medications: report of the main study. *JAMA* 1987; **257:** 1905–11.
5. Hall SM, *et al*. Preadmission antipyretics in Reye's syndrome. *Arch Dis Child* 1988; **63:** 857–66.
6. Glasgow JFT. Reye's syndrome: the case for a causal link with aspirin. *Drug Safety* 2006; **29:** 1111–21.
7. Schrör K. Aspirin and Reye syndrome: a review of the evidence. *Pediatr Drugs* 2007; **9:** 195–204.
8. MHRA. Aspirin and Reye's syndrome: questions and answers (issued 4th April, 2003). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019512&RevisionSelectionMethod=LatestReleased (accessed 29/11/06)
9. MHRA. Press release: new advice on oral salicylate gels in under 16s (issued 23rd April, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON044014 (accessed 24/04/09)
10. Casteels-Van Daele M, Eggermont E. Reye's syndrome. *BMJ* 1994; **308:** 919–20.
11. Hall SM. Reye's syndrome. *BMJ* 1994; **309:** 411.
12. Orlowski JP, *et al*. Is aspirin a cause of Reye's syndrome? A case against. *Drug Safety* 2002; **25:** 225–31.
13. Waller P, Suvarna R. Is aspirin a cause of Reye's syndrome? *Drug Safety* 2004; **27:** 71–3.

Precautions

Aspirin has many properties in common with the non-aspirin NSAIDs, the precautions of which are described on p. 107.1.

Aspirin should be used cautiously, if at all, in patients prone to dyspepsia or known to have a lesion of the gastric mucosa. It should not be given to patients with haemophilia or other haemorrhagic disorders, nor to treat patients with gout (since low doses increase urate concentrations).

Aspirin should be used with caution in patients with asthma or allergic disorders. It should not be given to patients with a history of sensitivity reactions to aspirin or other NSAIDs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by such drugs (for further details of risk factors see Hypersensitivity under Adverse Effects, p. 25.2).

Caution is necessary when renal or hepatic function is impaired; aspirin should be avoided in severe renal or hepatic impairment. Aspirin should be used cautiously in dehydrated patients and in the presence of uncontrolled hypertension.

High doses may precipitate acute haemolytic anaemia in patients with G6PD deficiency. Aspirin may interfere with insulin and glucagon control in diabetics (see Hypoglycaemia under Adverse Effects, p. 25.3).

The use of aspirin in children is extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3, and Uses and Administration, p. 22.3).

Although low-dose aspirin might be used in some pregnant patients, analgesic doses of aspirin should not be used at term as they may be associated with delayed onset and prolongation of labour and with maternal and neonatal bleeding. High doses may cause closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension in the newborn (but see Pregnancy, below); kernicterus may occur in jaundiced neonates.

Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding.

Aspirin should be stopped several days before scheduled surgical procedures (see below).

Aspirin and other salicylates can interfere with thyroid function tests.

Breast feeding. The American Academy of Pediatrics[1] considers that salicylates should be given with caution to breast-feeding mothers, since aspirin has been associated with metabolic acidosis in the infant.[2] The *BNF* also recommends that aspirin should be avoided in breast-feeding mothers because of the possible risk of Reye's syndrome in nursing infants; they also advise that infants with neonatal vitamin K deficiency may be at risk of hypoprothrombinaemia after the regular use of high doses of aspirin in breast-feeding mothers. However, a prospective study[3] found no adverse effects in 15 breast-fed infants whose mothers were receiving aspirin.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 23/11/06)
2. Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)* 1981; **20:** 53–4.
3. Ito S, *et al.* Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; **168:** 1393–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aspirin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pregnancy. The potential adverse effects of aspirin when used during pregnancy have been reviewed.[1] Salicylates readily cross the placenta and have been shown to be teratogenic in *animals*. Although some studies and anecdotal reports have implicated aspirin in the formation of congenital abnormalities, most large studies[2-4] have failed to find any significant risk or evidence of teratogenicity. Analysis of data collected by the Slone Epidemiology Unit Birth Defects Study suggests that use of aspirin during the early months of pregnancy, when the fetal heart is developing, is not associated with an increased risk of cardiac defects.[5] The ability of aspirin, however, to alter platelet function may be a potential risk. There have been a few reports of haemorrhagic disorders in infants whose mothers had consumed aspirin during pregnancy[6] and of salicylate-associated haemorrhagic complications in mothers.[7] However, no clinically significant adverse effects on maternal or neonatal bleeding or on fetal ductus flow were reported in a meta-analysis[8] of 6 controlled studies which evaluated low-dose aspirin (less than 325 mg daily) in pregnancy-induced hypertension. Two more recent placebo-controlled studies[9,10] have also found no clinically significant adverse effects on neonatal bleeding with low-dose aspirin. It appeared that the degree of cyclo-oxygenase inhibition produced by aspirin was unlikely to be great enough to cause premature closure of the ductus arteriosus or to affect the pulmonary blood vessels.[1] However, in some studies in patients considered to have high-risk pregnancies the risk of abruptio placentae[11] or consequent perinatal death[12] was increased by maternal dosage with aspirin.

For reference to a possible association between aspirin and other NSAIDs and persistent pulmonary hypertension of the newborn, and a possible association between simple analgesics including aspirin and congenital cryptorchidism, see under NSAIDs, p. 107.2.

Although aspirin has the potential to inhibit uterine contractions of labour it was considered that intermittent or low-dose aspirin was unlikely to inhibit cyclo-oxygenase for long enough to prolong pregnancy or labour.[1]

See also Surgical Procedures, below.

1. de Swiet M, Fryers G. The use of aspirin in pregnancy. *J Obstet Gynaecol* 1990; **10:** 467–82.
2. Slone D, *et al.* Aspirin and congenital malformations. *Lancet* 1976; **1:** 1373–5.
3. Shapiro S, *et al.* Perinatal mortality and birth-weight in relation to aspirin taken during pregnancy. *Lancet* 1976; **i:** 1375–6.
4. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
5. Werler MM, *et al.* The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. *N Engl J Med* 1989; **321:** 1639–42.
6. Bleyer WA, Breckenridge RT. Studies on the detection of adverse drug reactions in the newborn II: the effects of prenatal aspirin on newborn hemostasis. *JAMA* 1970; **213:** 2049–53.
7. Collins E, Turner G. Maternal effects of regular salicylate ingestion in pregnancy. *Lancet* 1975; **ii:** 335–7.
8. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. *JAMA* 1991; **266:** 261–4.
9. Louden KA, *et al.* Neonatal platelet reactivity and serum thromboxane B_2 production in whole blood: the effect of maternal low dose aspirin. *Br J Obstet Gynaecol* 1994; **101:** 203–8.
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11. Sibai BM, *et al.* Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med* 1993; **329:** 1213–18.
12. Hamid R, *et al.* Low dose aspirin in women with raised maternal serum alpha-fetoprotein and abnormal Doppler waveform patterns from the uteroplacental circulation. *Br J Obstet Gynaecol* 1994; **101:** 481–4.

Resistance. Some patients given aspirin for the management of cardiovascular disease do not respond to treatment, a phenomenon that has been described as aspirin resistance. At present, aspirin resistance is poorly understood and further studies are needed to define it.

References

1. Sanderson S, *et al.* Narrative review: aspirin resistance and its clinical implications. *Ann Intern Med* 2005; **142:** 370–80.
2. Hankey GJ, EikelboomJW. Aspirin resistance. *Lancet* 2006; **367:** 606–17.
3. Michos ED, *et al.* Aspirin and clopidogrel resistance. *Mayo Clin Proc* 2006; **81:** 518–26.
4. Undas A, *et al.* Antithrombotic properties of aspirin and resistance to aspirin: beyond strictly antiplatelet actions. *Blood* 2007; **109:** 2285–92.
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8. Gasparyan AY, *et al.* The role of aspirin in cardiovascular prevention: implications of aspirin resistance. *J Am Coll Cardiol* 2008; **51:** 1829–43.

Surgical procedures. Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation. This effect is irreversible and new platelets must be released into the circulation before bleeding time can return to normal. Therefore aspirin therapy should be stopped several days before surgical procedures. In some clinical situations, aspirin may have been given shortly before a surgical procedure. When emergency coronary bypass surgery is required for myocardial infarction, most patients would have received aspirin as part of the initial treatment for infarction. Perioperative bleeding, transfusion requirements, and surgical re-exploration rates may be increased when aspirin is given.[1] However, some studies[2,3] have shown that the increase in bleeding is not significant; in addition, there have been reports that pre-operative aspirin may reduce the rate of perioperative myocardial infarction (with aprotinin),[4] improve oxygenation,[5] and even decrease mortality.[3,6] Desmopressin may reduce the risk of perioperative bleeding (see under Haemorrhagic Disorders, p. 2355.3).

Aspirin is sometimes given during the second and third trimester for the prevention of pregnancy-induced hypertensive disease (see under Hypertension, p. 1251.1). Studies indicate that when given in a dose of 325 mg daily or less, clinically significant effects on maternal or neonatal bleeding do not occur.[7] Some have suggested that aspirin therapy may increase the risk of formation of extradural haematoma thus making epidural anaesthesia inadvisable[8] but a subsequent study[9] found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia.

Patients on low-dose aspirin, in whom tourniquets are used for nerve blocks or other procedures, may be at increased risk of developing purpuric rash.[10]

It has been suggested that in patients undergoing dermatological,[11] or minor dental[12] surgery, aspirin need only be stopped before surgery in those patients with a prolonged bleeding time, whereas patients with a normal bleeding time could continue therapy.

1. Goldman S, *et al.* Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation* 1988; **77:** 1324–32.
2. Reich DL, *et al.* Aspirin does not increase homologous blood requirements in elective coronary bypass surgery. *Anesth Analg* 1994; **79:** 4–8.
3. Dacey LJ, *et al.* Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg* 2000; **70:** 1986–90.
4. Klein M, *et al.* Aprotinin counterbalances an increased risk of perioperative hemorrhage in CABG patients pre-treated with aspirin. *Eur J Cardiothorac Surg* 1998; **14:** 360–6.
5. Gerrah R, *et al.* Preoperative aspirin administration improves oxygenation in patients undergoing coronary artery bypass grafting. *Chest* 2005; **127:** 1622–6.
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8. Macdonald R. Aspirin and extradural blocks. *Br J Anaesth* 1991; **66:** 1–3.
9. Sibai BM, *et al.* Low-dose aspirin in nulliparous women: safety of continuous epidural block and correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; **172:** 1553–7.
10. Runcie CJ, *et al.* Aspirin and intravenous regional blocks. *Br J Hosp Med* 1990; **43:** 229–30.
11. Lawrence C, *et al.* Effect of aspirin and nonsteroidal antiinflammatory drug therapy on bleeding complications in dermatologic surgical patients. *J Am Acad Dermatol* 1994; **31:** 988–92.
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Interactions

Aspirin has many properties in common with the non-aspirin NSAIDs, the interactions of which are described on p. 107.3.

Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol. Use of gold compounds with aspirin may exacerbate aspirin-induced liver damage.

Use of aspirin with dipyridamole may result in an increase in plasma-salicylate concentrations. Drugs such as metoclopramide in patients with migraine headache result in earlier absorption of aspirin and higher peak plasma-salicylate concentrations. Metoprolol may also increase peak plasma-salicylate concentrations. Salicylate intoxication has occurred in patients on high-dose salicylate regimens and carbonic anhydrase inhibitors.

Plasma-salicylate concentrations may be reduced by corticosteroids. This interaction is likely to be important in patients receiving high-dose long-term salicylate treatment. Conversely, salicylate toxicity may occur if corticosteroids are withdrawn. Also the risk of gastrointestinal bleeding and ulceration associated with aspirin is increased when used with corticosteroids. Antacids may increase the excretion of aspirin in alkaline urine.

Aspirin may increase the activity of coumarin anticoagulants, sulfonylurea hypoglycaemic drugs, zafirlukast, methotrexate, phenytoin, and valproate. Aspirin diminishes the effects of uricosurics such as probenecid and sulfinpyrazone. The manufacturer of mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by aspirin or NSAIDs may alter the efficacy of mifepristone.

Use of aspirin with other NSAIDs should be avoided because of the increased risk of adverse effects; the cardioprotective effects of aspirin may be abolished by ibuprofen and possibly other NSAIDS. Aspirin may decrease the plasma concentration of some other NSAIDs, for example, fenbufen, indometacin, and piroxicam.

References.

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ACE inhibitors. For a discussion of aspirin and other NSAIDs reducing the activity of ACE inhibitors, see p. 1288.3.

Anagrelide. For the potential effect of aspirin in patients taking anagrelide, see p. 2443.1.

Antiepileptics. Aspirin may inhibit the metabolism of *valproate*; for further details, see Analgesics, p. 557.2.

Antifungals. Plasma-salicylate concentrations in an 8-year-old child receiving long-term aspirin therapy for rheumatic heart disease were markedly reduced when treatment with *griseofulvin* was started.[1] It was suggested that griseofulvin might interfere with absorption of aspirin.

1. Phillips KR, *et al.* Griseofulvin significantly decreases serum salicylate concentrations. *Pediatr Infect Dis J* 1993; **12:** 350–2.

Calcium-channel blockers. The antiplatelet effects of aspirin and calcium-channel blockers may be increased when they are used together; there have been isolated reports[1,2] of disturbed haemostasis including abnormal

bruising, prolonged bleeding times, and ecchymosis in patients taking aspirin and *verapamil* concurrently.

1. Ring ME, *et al*. Clinically significant antiplatelet effects of calcium-channel blockers. *J Clin Pharmacol* 1986; **26:** 719–20.
2. Verzino E, *et al*. Verapamil-aspirin interaction. *Ann Pharmacother* 1994; **28:** 536–7.

General anaesthetics. For the effect of aspirin on *thiopental* anaesthesia, see p. 1919.3.

NSAIDs. It has been suggested that *ibuprofen* and possibly other *NSAIDs* may reduce the cardioprotective effect of aspirin. A study[1] involving 7107 patients found that cardiovascular mortality was increased in patients taking low-dose aspirin for cardiovascular disease when also taking ibuprofen (adjusted hazard ratio 1.73 times that of patients not taking ibuprofen). Another study[2] found that although taking low-dose aspirin or NSAIDs alone decreased the incidence of myocardial infarction, there was a non-significant increase in the risk of myocardial infarction when both were taken. Another large study also found the risk to be increased in those taking regular rather than intermittent NSAID treatment with aspirin.[3] However, a study[4] involving 14 098 patients concluded that the risk of myocardial infarction was reduced in patients taking ibuprofen and aspirin when compared with those taking aspirin alone. Furthermore, a study[5] in 70 316 patients found that the risk of death in patients prescribed aspirin and ibuprofen was comparable to that of patients prescribed aspirin alone or with another NSAID.

The timing of doses may be important; a study[6] has shown that irreversible platelet aggregation occurred when a single daily dose of ibuprofen was given 2 hours after aspirin; however, when ibuprofen was given before aspirin as a single daily dose or given three times daily, platelet aggregation was reversible which may limit the cardioprotective effects of aspirin.

There are limitations to all these studies and further studies are needed before any recommendations can be made.[7-11]

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2. Kimmel SE, *et al*. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* 2004; **43:** 985–90.
3. Kurth T, *et al*. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003; **108:** 1191–5.
4. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. *Arch Intern Med* 2004; **164:** 852–6.
5. Curtis JP, *et al*. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ* 2003; **327:** 1322–3.
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9. Curtis JP, Krumholz HM. The case for an adverse interaction between aspirin and non-steroidal anti-inflammatory drugs: is it time to believe the hype? *J Am Coll Cardiol* 2004; **43:** 991–3.
10. Cheema AA. Should people on aspirin avoid ibuprofen? A review of the literature. *Cardiol Rev* 2004; **12:** 174–6.
11. Corman SL, *et al*. Impact of nonsteroidal antiinflammatory drugs on the cardioprotective effects of aspirin. *Ann Pharmacother* 2005; **39:** 1073–9.

Spironolactone. For the effect of aspirin in patients taking spironolactone, see p. 1502.2.

Pharmacokinetics

Aspirin and other salicylates are absorbed rapidly from the gastrointestinal tract when taken orally but absorption after rectal doses is less reliable. Aspirin and other salicylates can also be absorbed through the skin.

After oral doses, absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose aspirin is the main form of the drug in the plasma. Aspirin is 80 to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 mL/kg in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylate appears in breast milk and crosses the placenta.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. After a 325-mg aspirin dose, elimination is a first-order process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

Salicylate is removed by haemodialysis.

References.

1. Needs CJ, Brooks PM. Clinical pharmacokinetics of the salicylates. *Clin Pharmacokinet* 1985; **10:** 164–77.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aspirina; Aspirinetas; Bayaspirina; Cardioaspirina; Desenfriolito; Ecotrin; Geniol Prevencion; Geniol SC sin Cafeina; Lafeaspirina; Nuevapina; Vipirina Ginsex Corazon; ***Austral.***: Aspro Protect†; Aspro; Astrix; Cardiprin; Cartia; Disprin Direct; Disprin; Solprin; ***Austria***: Acekapton†; Aspirin Protect; Aspro; ASS; CorProtect; Herz ASS; Herzschutz ASS; Thrombo ASS; Thrombostad; Togal Mono†; ***Belg.***: Acenterine; Alka-Seltzer; Asaflow; Aspaxa; Aspirine; Cardioaspirine; Cardiphar; Dispril†; Sedergine; ***Braz.***: AAS; Aceticil; Analgesin; Antifebrin; Aspirina; Bufferin; Cardio AAS; Cimaas; Ecasil; Hipotermal†; Salicetil; Salicil; Salicin; Salipirin; Salisvit; Salitil; Sifaas; Somalgin; ***Canad.***: Apo-Asa; ASA; Asadol†; Asaphen; Asatab; Aspergum; Aspirin with Stomach Guard; Bufferin; Entrophen; Equate Daily Low-Dose; Life Brand Daily Low Dose ASA†; Lowprin; Novasen; PMS-ASA; Pro-AAS; Relief ASA; Rivasa; Tri-Buffered ASA†; ***Chile***: Aspirina; Cardioaspirina; Corvasol; Disgren; Ecotrin; Fluicor; Hassapirin; Thrombo AS; ***China***: An Ni Tuo (安尼妥); Bamyl (巴米尔); Bayaspirin Protect (拜阿司匹灵); Bo Ji (伯基); Jie Ning (介宁); Sai Ning (塞宁); Shi Tai Le (施泰乐); Si Er Li (司尔利); Xie Mei Da (协美达); Xin Dong (欣动); Yixinxue (益欣雪); ***Cz.***: Acylpyrin; Anopyrin; Axanum; Godasal; ***Denm.***: Carnyl†; Hjerdyl; Hjertealbyl; Hjertemagnyl; Hjertemin; Idotyl†; Magnyl; ***Fin.***: Aspirin Cardio; Aspirin Zipp; Disperin; Primaspan; Thrombo ASA; ***Fr.***: Aspirine pH8; Aspirine; Aspirisucre†; Aspro; ***Ger.***: Acesal; ASS; Axanum; Godamed; HerzASS; Miniasal†; Togal ASS; ***Gr.***: Alka-Seltzer N; Apyr; Ascriptin; Bufferin; Measurin; Neospir; Salospir; Upsalgin-N; ***Hong Kong***: Aspilets; Astrix†; Bokey; Cardiprin; Disprin; Ecotrin†; Glyprin; LAsprin†; Propirin; Uni-Acetil†; ***Hung.***: Aspirin Protect; Astrix; Colfarit†; Kalmopyrin; ***India***: Alpyrin; ASA; Ascad; Asicom; Aspent; Aspicot†; Aspin; Aspisol; Colsprin; Cotasprin; CV-Sprin; Delisprin; Disprin; E-Prin; Ecosprin; Gra; Insprin-ER; LDA; Linzi; Loprin; Manospirin; Mazoral; Nusprin; Od-Prin; Optaz; Otaspirin; ***Indon.***: Aptor; Ascardia; Aspilets; Aspitrom; Astika; Bodrexin; Cardio Aspirin; Contrexyn; Farmasal; Inzana†; Miniaspi; Minigrip; Naspro; Procardin†; Proxime; Restor; Rheumapill†; Thrombo Aspilets; ***Irl.***: Asacard; Aspro†; Caprin; Disprin Direct; Disprin Extra Strength; Disprin; Lowasa†; Nu-Seals; Nuasa; Nuprin; Resprin†; ***Israel***: Acetosal; Alka-Seltzer†; Aspirin Cardio; Buffered Pirin†; Cardiopirin; Cartia; Godamed; Micropirin; Tevapirin; ***Ital.***: Ascriptin; Aspiglicina; Aspirina 03; Aspirina; Aspirinetta; Aspro; Cardioaspirin; ***Malaysia***: Aceprin; Aspirin Cardio; Cardiprin; Casprin; Disprin; Glyprin; ***Mex.***: Acetil-A; Acetin†; Acitab; Antacsal; ASA; Ascriptin; Aspirina Protect; Disprina†; Doloquim; Ecotrin†; Midolen; Vastecel; ***Neth.***: Asacard; Aspirine Protect; Aspro; Axanum; Cardioral; Togal†; ***Norw.***: Acetyratio†; Albyl-E; Axanum; Globoid; Magnyl-E†; ***NZ***: Aspec; Aspro; Cartia; Disprin; Ecotrin†; Solprin; ***Philipp.***: Aceprin; Anthrom; Asaprim; Aspec; Aspen; Aspilets; Asthromed; Astrix; Bayprin; Cor-30; Cortal; Enteroprin; Tromcor; ***Pol.***: Acard; Acesan; Alka-Prim; Alka-Seltzer; ASA†; Asaltec; Aspimag; Aspirin Protect; Asprocard†; Asprocol; Bestpirin; Calcipiryna†; Cardiofil; Encopirin; Galocard†; Hascopiryn; Nipas; Polocard; Polopiryna S; Polopiryna; Proficar†; Salpirin; Upsarin; ***Port.***: AAS; Actipiril; Asacard; ASP; Aspirina; Cartia; DuoCover; DuoPlavin; Migraspirina; Toldex; Tromalyt; ***Rus.***: Acecardol (Ацекардол); Alka-Prim (Алька-Прим); Asa-Cardio (Аск-Кардио); Aspikor (Аспикор); Aspinat (Аспинат); Aspinat Cardio (Аспинат Кардио); Aspirin Cardio (Аспирин Кардио); CardiASK (КардиАСК); Cardiomagnyl (Кардиомагнил); Cardiopyrin (Кардиопирин); Nextrim Fast (Некстрим Фаст); Taspir (Таспир); Thrombo ASS (Тромбо АСС); Trombopol (Тромбопол); Upsarin (Упсарин); ***S.Afr.***: Coprin; Disprin; Ecotrin; Myoprin; ***Singapore***: Aspro†; Astrix†; Bokey; Cardiprin; Disprin; Dusil†; Glyprin; Platet†; ***Spain***: AAS; Adiro; Aspirina; Bioplak; Okal†; Okaldol; Rhonal†; Sedergine; Tromalyt; ***Swed.***: Albyl minor; Bamyl; Magnecyl; Trombyl; ***Switz.***: ASA; Asperivo; Aspirine Cardio; Aspro; ASS Cardio; Axanum; Cardiax-ASS; Thrombace Neo†; Tiatral 100 SR; Togal ASS; ***Thai.***: Actorin†; Anassa; Arpisine; ASA; Asatab; Ascot; Aspaco; Aspent; Aspilets; Aspipac; Aspirine; Asrina; B-Aspirin; Buntaopoad-Bura; Caparin; Cardiprin; Empirin; Entrarin; Pirin; Seferin; SP; V-AS†; ***Turk.***: Algo Bebe; Algo†; Asabrin; Asinpirine; Aspapirine; Aspimirin; Aspinal; Ataspin; Babyprin; Coraspin; Dispril; Ecopirin; Isaspin; Notras; Opon; Pharmaspirin; ***UAE***: Jusprin; ***UK***: Alka; Angettes†; Aspro; Caprin; Disprin Direct; Disprin; Enprin; Flamasacard; Micropirin; Nu-Seals; Pure Health; ***Ukr.***: Acecardin (Ацекардин); Acecor Cardio (Ацекор Кардио); Alka-Prim (Алька-Прим); Aspecard (Аспекард); Aspeter (Аспетер)†; Aspirin Cardio (Аспирин Кардио); Cardiomagnyl (Кардиомагнил); Combi-ASA (Комби-АСК); Ecorin (Экорин)†; Godasal (Годасал); Magnikor (Магникор); Polocard (Полокард); ***USA***: Adprin-B; Arthritis Pain Formula; Ascriptin; Aspergum†; AspirLow; Bayer Low Adult Strength; Bufferin; Buffex; Cama Arthritis Pain Reliever; Easprin; Ecotrin; Empirin; Extra Strength Bayer Plus; Genprin; Halfprin; Miniprin; Norwich Extra Strength; Norwich Regular Strength; Regular Strength Bayer; St. Joseph Adult Chewable; ZORprin; ***Venez.***: Asaprol; Ascriptin; Azacard; Cardipirina; Coraspirina.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Aspirin and Caffeine Tablets; Aspirin Tablets; Co-codaprin Tablets; Dispersible Aspirin Tablets; Dispersible Co-codaprin Tablets; Effervescent Soluble Aspirin Tablets; Gastro-resistant Aspirin Tablets;

USP 36: Acetaminophen and Aspirin Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Aspirin and Codeine Phosphate Tablets; Aspirin Capsules; Aspirin Delayed-release Capsules; Aspirin Delayed-release Tablets; Aspirin Effervescent Tablets for Oral Solution; Aspirin Extended-release Tablets; Aspirin Suppositories; Aspirin Tablets; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Buffered Aspirin Tablets; Butalbital and Aspirin Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol and Aspirin Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Orphenadrine Citrate, Aspirin, and Caffeine Tablets; Oxycodone and Aspirin Tablets; Pentazocine and Aspirin Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Aspirin Tablets.

Auranofin *(BAN, USAN, rINN)*

Auranofiini; Auranofina; Auranofine; Auranofinum; Oranofin; SKF-39162; SKF-D-39162; Ауранофин.

(1-Thio-β-D-glucopyranosato)(triethylphosphine)gold 2,3,4,6-tetra-acetate.

$C_{20}H_{34}AuO_9PS$=678.5

CAS — 34031-32-8.

ATC — M01CB03.

ATC Vet — QM01CB03.

UNII — 3H04W2810V.

Uses and Administration

Auranofin is a gold compound with a gold content of about 29%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It is given orally in active progressive rheumatoid arthritis (p. 28.1); such oral treatment is less toxic than intramuscular gold but is also much less effective. The usual initial dose of auranofin is 6 mg daily given in two divided doses at first, then, if tolerated, as a single dose. Treatment should be continued for at least 6 months to assess the response; the dose may be increased after 6 months, if the response is inadequate, to 3 mg three times daily. If the response is still inadequate after 3 months at this dosage, then treatment should be stopped.

Asthma. A systematic review[1] found that oral or parenteral gold compounds reduced corticosteroid requirements in the management of asthma (p. 1195.2); however, it was considered that the effect was probably of limited clinical significance and, given the adverse effects and monitoring requirements of gold compounds, their use in asthma could not be recommended.

1. Evans DJ, *et al*. Gold as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 11/01/11).

Lupus. Since the introduction of less toxic drugs gold compounds are now rarely used in the treatment of SLE, however, there have been anecdotal reports suggesting that auranofin may be of use in patients with discoid lupus erythematosus[1] or cutaneous lupus erythematosus[2] refractory to conventional treatment.

1. Dalziel K, *et al*. Treatment of chronic discoid lupus erythematosus with an oral gold compound (auranofin). *Br J Dermatol* 1986; **115:** 211–16.
2. Farrell AM, Bunker CB. Oral gold therapy in cutaneous lupus erythematosus (revisited). *Br J Dermatol* 1996; **135** (suppl 47): 41.

Pemphigus. A patient with long-standing pemphigus foliaceus being treated with prednisolone and hydroxychloroquine had healing of his lesions within 6 months of auranofin being substituted for the hydroxychloroquine.[1]

1. Bagheri MM, *et al*. Pemphigus foliaceus presenting as eruptive seborrheic keratosis and responding to oral gold treatment. *J Drugs Dermatol* 2002; **1:** 333–4.

Psoriasis. Although topical auranofin has been shown in a placebo-controlled study[1] to be effective in the treatment of plaque-type psoriasis (p. 1688.1) the high incidence of

adverse skin reactions, such as contact dermatitis, was thought to outweigh any benefit.

1. Helm KF, *et al.* Topical auranofin ointment for the treatment of plaque psoriasis. *J Am Acad Dermatol* 1995; **33:** 517–19.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p. 13.2). Oral gold is less toxic than intramuscular gold but is also much less effective. Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p. 14.3) and have been used in juvenile idiopathic arthritis (p. 12.1).

References.

1. Suarez-Almazor ME, *et al.* Auranofin versus placebo in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 11/01/11).

Adverse Effects and Treatment

The most common adverse effects of auranofin involve the gastrointestinal tract and include nausea, abdominal pain, and sometimes vomiting, but most often diarrhoea, which can affect up to 50% of patients and may be severe enough to cause patients to withdraw from treatment. Other adverse effects are similar to those of sodium aurothiomalate (p. 131.1), although they appear to be less troublesome since fewer patients stop treatment with auranofin than with injectable gold. As with other gold salts, treatment of adverse effects is generally symptomatic (see p. 131.3). Modifying the diet to increase bulk, use of a bulking agent such as bran, or a temporary reduction in auranofin dosage, may help the diarrhoea (but see Effects on the Gastrointestinal Tract, below).

Reviews.

1. Tozman ECS, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; **2:** 177–89.

Effects on the gastrointestinal tract. Diarrhoea and abdominal pain are common with auranofin. The mechanism of gastrointestinal toxicity has not been established but may be associated with a reversible defect in intestinal permeability.[1] Although some have suggested that diarrhoea may occur in up to 50% of patients taking auranofin, a study in 269 patients given the drug for rheumatoid arthritis found that only about 15% had loose and watery stools over a 6-month period.[2] Although bulking agents have been recommended in the management of auranofin-induced diarrhoea, no overall difference in incidence was seen between patients given prophylactic psyllium and those given placebo; however, patients given psyllium had slightly fewer days with loose and watery stools.

Gold-induced colitis has also been reported in patients taking auranofin.[3,4]

1. Behrens R, *et al.* Investigation of auranofin-induced diarrhoea. *Gut* 1986; **27:** 59–65.
2. van Beusekom HJ, *et al.* The moderate intestinal side effects of auranofin do not require prophylactic therapy with a bulkforming agent. Dutch Ridaura Study Group. *Clin Rheumatol* 1997; **16:** 471–6.
3. Michet CJ, *et al.* Auranofin-associated colitis and eosinophilia. *Mayo Clin Proc* 1987; **62:** 142–4.
4. Langer HE, *et al.* Gold colitis induced by auranofin treatment of rheumatoid arthritis: case report and review of the literature. *Ann Rheum Dis* 1987; **46:** 787–92.

Effects on the kidneys. In a retrospective review[1] of 1283 patients given auranofin for treatment of rheumatoid arthritis 41 (3.2%) were found to have developed proteinuria. In most cases proteinuria was treated by stopping auranofin therapy. Long-term follow-up of 36 patients indicated that proteinuria had resolved in 31 within 2 years and in 29 within 1 year. Seven of 8 patients later rechallenged with auranofin had no relapses. In a further review of 2 comparative double-blind studies using gold compounds in the treatment of rheumatoid arthritis, proteinuria was found to have developed in 27% (23 of 85) of patients treated with sodium aurothiomalate, in 17% (42 of 247) of those treated with auranofin, and in 17% (36 of 210) of those receiving placebo. All patients were receiving NSAIDs.

1. Katz WA, *et al.* Proteinuria in gold-treated rheumatoid arthritis. *Ann Intern Med* 1984; **101:** 176–9.

Precautions

As for Sodium Aurothiomalate, p. 131.3. Urine and blood tests should be carried out before starting auranofin and monthly thereafter; licensed product information advises that auranofin should be withdrawn if the platelet count falls below 100 000 cells/mm^3 or if signs and symptoms suggestive of thrombocytopenia, leucopenia, or aplastic anaemia occur. Licensed product information states that baseline renal and liver function levels should also be established before starting auranofin therapy. Auranofin should be used with caution in patients with inflammatory bowel disease.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies auranofin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/07/11)

Interactions

As for Sodium Aurothiomalate, p. 132.1.

Pharmacokinetics

Auranofin is incompletely absorbed from the gastrointestinal tract, only about 25% of the gold being absorbed. Gold from auranofin is bound to plasma proteins as well as to red blood cells. After 2 to 3 months of treatment the steady-state concentration of gold in the blood is reported to be about 700 nanograms/mL. The average terminal plasma half-life of gold at steady state is about 26 days while the biological half-life is 80 days. Tissue retention and total gold accumulation in the body are less than with intramuscular gold. Gold from auranofin penetrates into synovial fluid.

Most of a dose of auranofin appears in the faeces due to its poor absorption. About 60% of the absorbed gold from auranofin is excreted in the urine and the remainder in the faeces.

Reviews.

1. Blocka KLN, *et al.* Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; **11:** 133–43.
2. Benn HP, *et al.* Pharmacokinetics of auranofin: a single dose study in man. *J Rheumatol* 1990; **17:** 466–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ridaura; ***Austria***: Ridaura; ***Belg.***: Ridaura; ***Canad.***: Ridaura; ***China***: Ridaura (瑞得); ***Denm.***: Ridaura; ***Fin.***: Ridaura; ***Gr.***: Ridaura; ***Hong Kong***: Ridaura; ***India***: Goldar; ***Irl.***: Ridaura†; ***Israel***: Ridaura; ***Ital.***: Ridaura; ***Norw.***: Ridaura†; ***NZ***: Ridaura; ***Port.***: Ridaura; ***Rus.***: Auropan (Ауропан)†; ***S.Afr.***: Ridaura†; ***Spain***: Ridaura†; ***Swed.***: Ridaura; ***UK***: Ridaura†; ***USA***: Ridaura.

Aurothioglucose

1-Aurothio-D-glucopyranose; Aurotioglucosa; (D-Glucosylthio)gold; Gold Thioglucose; Ауротиоглюкоза.
(1-Thio-D-glucopyranosato)gold.
$C_6H_{11}AuO_5S$=392.2
CAS — 12192-57-3.
ATC — M01CB04.
ATC Vet — QM01CB04.
UNII — 2P2V9Q0E7B.

Pharmacopoeias. In *US*.

USP 36: (Aurothioglucose). A yellow odourless or practically odourless powder. An aqueous solution is unstable on long standing. It is stabilised by the addition of a small amount of sodium acetate. pH of a 1% solution in water is about 6.3. Freely soluble in water; practically insoluble in alcohol, in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Profile

Aurothioglucose is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It has been used intramuscularly in the treatment of active rheumatoid arthritis and juvenile idiopathic arthritis.

For comment on the relative efficacy and tolerability of aurothioglucose and aurothiomalate, see Rheumatic Disorders, under Sodium Aurothiomalate, p. 130.3.

Effects on the blood. Thrombocytopenia developed in 2 patients treated with intramuscular aurothioglucose.[1]

1. Levin M-D, *et al.* Two patients with acute thrombocytopenia following gold administration and five-year follow-up. *Neth J Med* 2003; **61:** 223–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Solganal†.

Pharmacopoeial Preparations

USP 36: Aurothioglucose Injectable Suspension.

Aurotioprol

Aurothiopropanol Sodium Sulfonate; Aurothiopropanolsulfonate de Sodium; Aurotiopropanol Sodium Sulfonate; Ауротиопрол.
Sodium 3-aurothio-2-hydroxypropane-1-sulphonate.
$C_3H_6AuNaO_4S_2$=390.2
CAS — 27279-43-2.
ATC — M01CB05.
ATC Vet — QM01CB05.
UNII — G7097J63E9.

Profile

Aurotioprol is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It is given by intramuscular injection for the treatment of rheumatoid arthritis (p. 13.2). The initial dose is 25 mg weekly, increased to 50 to 100 mg weekly, until a total dose of 1.2 to 1.5 g has been given. If improvement has occurred with no signs of toxicity, this may be followed by a dose of 50 to 100 mg intramuscularly every month.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Allochrysine.

Azapropazone *(BAN, rINN)*

AHR-3018; Apazone (USAN); Atsapropatsoni; Azapropazon; Azapropazona; Azapropazonum; Mi85; NSC-102824; Азапропазон.
5-Dimethylamino-9-methyl-2-propylpyrazolo[1,2-*a*][1,2,4]benzotriazine-1,3(2*H*)-dione.
$C_{16}H_{20}N_4O_2$=300.4
CAS — 13539-59-8.
ATC — M01AX04.
ATC Vet — QM01AX04.
UNII — K2VOT966ZI.

Pharmacopoeias. *Br.* includes the dihydrate.

BP 2014: (Azapropazone). The dihydrate is a white to pale yellow crystalline powder. Very slightly soluble in water and in chloroform; soluble in alcohol; dissolves in solutions of alkali hydroxides.

Profile

Azapropazone is an NSAID (see p. 102.3), structurally related to phenylbutazone (p. 125.1). It also has uricosuric properties. Because azapropazone appears to be associated with a higher incidence of adverse effects than with some other NSAIDs, its use was restricted to the treatment of rheumatoid arthritis, ankylosing spondylitis, and acute gout in patients for whom other NSAIDs have been ineffective.

Breast feeding. Small quantities of azapropazone are excreted into breast milk.[1] However, the American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of azapropazone by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Bald R, *et al.* Excretion of azapropazone in human breast milk. *Eur J Clin Pharmacol* 1990; **39:** 271–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)

Effects on the blood. Auto-immune haemolytic anaemia, occasionally fatal, often with pulmonary infiltration, allergic alveolitis, pulmonary fibrosis, or fibrosing alveolitis, has been reported in patients receiving azapropazone.[1-3]

1. Chan-Lam D, *et al.* Red cell antibodies and autoimmune haemolysis after treatment with azapropazone. *BMJ* 1986; **293:** 1474.
2. Albazzaz MK, *et al.* Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1986; **293:** 1537–8.
3. Montgomery RD, Babb RG. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.

Effects on the gastrointestinal tract. In a review[1] of the relative safety of 7 oral NSAIDs, the UK CSM commented that azapropazone was associated with the highest risk of gastrointestinal reactions in both epidemiological studies and an analysis of spontaneous reporting of adverse reactions. Although it appeared that some patients over 60 years of age had received doses exceeding those recommended for this age group, it was considered that even when this was taken into account a marked difference remained between gastrointestinal reactions for azapropazone compared with other NSAIDs.

The CSM recommended that azapropazone should be restricted to use in rheumatoid arthritis, ankylosing spondylitis, and acute gout and only when other NSAIDs have been ineffective. Its use in patients with a history of peptic ulceration was contra-indicated. It was also recommended that when used in patients over 60 years of age for rheumatoid arthritis or ankylosing spondylitis the dose should be reduced.

Azapropazone has been withdrawn in many countries including the UK.

1. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Effects on the skin. Of 917 reports of adverse reactions associated with azapropazone forwarded to the WHO Collaborating Centre for International Drug Monitoring[1] before September 1984, 190 (21%) were of photosensitivity. Of 154 reports of photosensitivity evaluated, a causal relationship to use of azapropazone was considered certain in 6, probable in 138, and possible in 10. In May 1994 the UK CSM stated[2] that since 1976 they had received 464 reports of photosensitivity reactions associated with azapropazone and commented that, when corrected for prescription volume, reporting of this reaction was 50 times greater than with other commonly prescribed NSAIDs. They recommended that patients should be advised to avoid direct exposure to sunlight or to use sunblock preparations.

1. Olsson S, *et al*. Photosensitivity during treatment with azapropazone. *BMJ* 1985; **291:** 939.
2. CSM/MCA. Photosensitivity associated with azapropazone (Rheumox). *Current Problems* 1994; **20:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Prolixan; ***S.Afr.***: Rheumox†; ***Turk.***: Prodisan.

Pharmacopoeial Preparations
BP 2014: Azapropazone Capsules; Azapropazone Tablets.

Bendazac *(BAN, USAN, rINN)*

AF-983; Bendazaco; Bendazacum; Bindazac; Бендазак.
(1-Benzyl-1*H*-indazol-3-yloxy)acetic acid.
$C_{16}H_{14}N_2O_3$=282.3
CAS — 20187-55-7.
ATC — M02AA11; S01BC07.
ATC Vet — QM02AA11; QS01BC07.
UNII — G4AG71204O.

Bendazac Lysine *(BANM, rINNM)*

AF-1934; Bendazac lisina; Bendazaco de lisina; Bendazacum Lysinum; Бендазак Лизин.
L-Lysine-(1-benzyl-1*H*-indazol-3-yloxy)acetic acid.
$C_{22}H_{28}N_4O_5$=428.5
CAS — 81919-14-4.
ATC — S01BC07.
ATC Vet — QS01BC07.
UNII — CL7T957EGC.

Pharmacopoeias. In *Chin.*

Profile

Bendazac is an NSAID (p. 102.3) structurally related to indometacin (p. 71.2). It has been used topically in preparations containing 1 or 3% for the treatment of various inflammatory skin disorders.

Bendazac lysine has been used in the management of cataract, eye drops containing 0.5% being instilled three times daily.

Hepatotoxicity has been reported.

References.

1. Balfour JA, Clissold SP. Bendazac lysine: a review of its pharmacological properties and therapeutic potential in the management of cataracts. *Drugs* 1990; **39:** 575–96.
2. Prieto de Paula JM, *et al*. Hepatotoxicidad por bendazaco: análisis de 16 casos. *Rev Clin Esp* 1995; **195:** 387–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Sha Pu Ai Si (莎普爱思); ***Gr.***: Bendalina; Versalba; Zebinor; ***Ital.***: Bendalina; Versus; ***Philipp.***: Bendalina; ***Port.***: Bendalina; ***Venez.***: Bendalina.

Benorilate *(BAN, rINN)*

Benorilaatti; Benorilat; Bénorilate; Benorilato; Benorilatum; Benorylate; FAW-76; Fenasprate; Win-11450; Бенорилат.
4-Acetamidophenyl *O*-acetylsalicylate.
$C_{17}H_{15}NO_5$=313.3
CAS — 5003-48-5.
ATC — N02BA10.
ATC Vet — QN02BA10.
UNII — W1QX9DV96G.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Benorilate). A white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in chloroform.

Profile

Benorilate is an aspirin-paracetamol ester with analgesic, anti-inflammatory, and antipyretic properties. After absorption, it is rapidly metabolised to salicylate and paracetamol. It has been used orally in the treatment of mild to moderate pain and fever. It has also been used in osteoarthritis, rheumatoid arthritis, and soft-tissue rheumatism.

When an overdose of benorilate is suspected, it has been suggested that plasma concentrations of both salicylate and paracetamol should be measured since a normal plasma-paracetamol concentration cannot necessarily be assumed from a normal plasma-salicylate measurement.

References.

1. Aylward M. Toxicity of benorylate. *BMJ* 1973; **2:** 118.
2. Symon DNK, *et al*. Fatal paracetamol poisoning from benorylate therapy in child with cystic fibrosis. *Lancet* 1982; **ii:** 1153–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Beilijin (贝利金); YiNuo (益诺).

Multi-ingredient Preparations. ***China***: Bei Shu (备疏).

Pharmacopoeial Preparations
BP 2014: Benorilate Oral Suspension; Benorilate Tablets.

Benzydamine Hydrochloride

(BANM, USAN, rINNM)

AF-864; Bencidamina, hidrocloruro de; Benzidamin Hidroklorür; Benzindamine Hydrochloride; Benzydamine, Chlorhydrate de; Benzydamini Hydrochloridum; Benzydaminy chlorowodorek; Hidrocloruro de bencidamina; Бензидамина Гидрохлорид.
3-(1-Benzyl-1*H*-indazol-3-yloxy)-*NN*-dimethylpropylamine hydrochloride.
$C_{19}H_{23}N_3O$,HCl=345.9
CAS — 642-72-8 (benzydamine); 132-69-4 (benzydamine hydrochloride).
ATC — A01AD02; G02CC03; M01AX07; M02AA05.
ATC Vet — QA01AD02; QG02CC03; QM01AX07; QM02AA05.
UNII — K2GI407R4Q.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Benzydamine Hydrochloride). A white crystalline powder. Very soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 5.5.

Uses and Administration

Benzydamine hydrochloride is an NSAID (p. 102.3). It is used topically on the skin in concentrations of 3 to 5% in painful musculoskeletal and soft-tissue disorders. Benzydamine hydrochloride is also used as a mouthwash or spray in concentrations of 0.15% for the relief of inflammatory conditions of the mouth and throat. It has been given orally or rectally for the relief of painful and inflammatory conditions, and as a topical solution for vaginal irrigation.

Benzydamine salicylate (benzasal) has been used topically on the skin as a 6% cream or spray.

Mouth disorders. Results of a randomised placebo-controlled study in patients undergoing radiotherapy for oropharyngeal cancer indicated that benzydamine as an oral rinse was effective in reducing the area and severity of mucositis.[1] Benzydamine is also used locally for the management of mouth ulcers (p. 1814.2) although an early study[2] found it no more useful than placebo.

1. Epstein JB, *et al*. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer* 2001; **92:** 875–85.
2. Matthews RW, *et al*. Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; **63:** 189–91.

Adverse Effects

After topical application to the skin local reactions such as erythema or rash may occur and photosensitivity has been reported. After use as mouth and throat preparations, numbness or stinging sensations of the oral mucosa have been reported; hypersensitivity reactions including urticaria, photosensitivity, and bronchospasm may also occur rarely.

Effects on the kidneys. A 57-year-old woman who had used 400 g of a topical cream containing benzydamine hydrochloride 3% over a period of 4 months was found to have raised plasma concentrations of creatinine and urea consistent with a substantial reduction in glomerular filtration rate.[1]

1. O'Callaghan CA, *et al*. Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.

Effects on the skin. Photoallergic contact dermatitis developed on the hands of a 65-year-old woman after the use of a genital wash containing benzydamine 0.1% for several years.[1] The lesions disappeared once the patient stopped using the solution.

1. Lasa Elgezua O, *et al*. Photoallergic hand eczema due to benzydamine. *Eur J Dermatol* 2004; **14:** 69–70.

Overdose. A 6-year old girl had hallucinations[1] after receiving 500 mg of benzydamine orally; it had been intended as a vaginal douche for pruritus vulvae; recovery was spontaneous.

1. Gómez-López L, *et al*. Acute overdose due to benzydamine. *Hum Exp Toxicol* 1999; **18:** 471–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actifedrin†; Bencifem; Ernex; Sandival Desleible; ***Austral.***: Difflam Anti-inflammatory Throat Spray; Difflam Solution; Difflam; ***Austria***: Tantum; ***Braz.***: Benflogin; Benzidrol; Benziflex; Benzitrat; Ciflogex; Flogo-Rosa; Flogolab; Flogomin; Flogoral; Fonergoral; Gargojuice; Neoflogin; ***Canad.***: Sun-Benz; Tantum; ***Cz.***: Rosalgin; Tantum; ***Denm.***: Andolex; Zyx; ***Fin.***: Zyx; ***Fr.***: Opalgyne; ***Ger.***: Tantum Rosa; Tantum Verde; ***Gr.***: Tantum; ***Hong Kong***: Dantum; Difflam Anti-inflammatory Lozenges; Difflam; Veraxt; ***Hung.***: Rosalgin; Tantum Lemon; Tantum Verde; ***Indon.***: Tanflex; Tantum; ***Irl.***: Difflam; Tantum Verde; ***Israel***: Easy Gel; Tantum Rosa; ***Ital.***: Afloben†; Ginesal; Saniflor Collutorio; Tantum; Verax; Xentafid; ***Malaysia***: Difflam Anti-inflammatory Lozenges; Difflam Forte Anti-Inflammatory Throat Spray; Difflam Solution†; ***Mex.***: Artroben; Beniflant; Cifhir; Lonol; Vantal; ***Neth.***: Tantum; ***NZ***: Difflam; ***Philipp.***: Difflam; ***Pol.***: Hascosept; Septolux; Tantum; ***Port.***: Flogoraft; Flogoral; Momen; Rosalgin; Tantum Rosa; Tantum Verde; Tantum Verde; Tantum; ***Rus.***: Tantum Rose (Тантум Роза); Tantum Verde (Тантум Верде); ***S.Afr.***: Andolex; Andosept; ***Singapore***: Difflam; ***Spain***: Fulgium; Rosalgin; Tantum Verde; Tantum; ***Swed.***: Andolex; Zyx; ***Switz.***: Bucco-Tantum; ***Thai.***: Difflam; ***Turk.***: Beniflex; Benzidan; Farengil; Tanflex; Tantum; Ternex; ***UK***: Difflam; ***Ukr.***: Tantum Rose (ТантумРоза); Tantum Verde (Тантум Верде); ***Venez.***: Azutan; Bevi Dam; Biozendi; Flodont; Tantum Verde; Tantum; Zydan.

Multi-ingredient Preparations. ***Arg.***: Buchex; Ernex Duo; Espectocural; ***Austral.***: Difflam Anti-inflammatory Lozenges with Cough Suppressant; Difflam Lozenges; Difflam Mouth Gel; Difflam-C; Logicin Rapid Relief; ***Braz.***: Angino-Rub; ***Hong Kong***: Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Mouth Gel; Difflam-C; Kloroben; Logicin Rapid Relief; ***Hung.***: Tantum Rosa†; ***Ital.***: Gola Action; Linea F; Tantum Orosan; ***Malaysia***: Difflam Anti-inflammatory Lozenges (with Antibacterial); Difflam Anti-Inflammatory Lozenges (with cough suppressant); Difflam Mouth Gel; Difflam-C; ***Mex.***: Lonol Sport; ***NZ***: Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Cough; Difflam Mouth Gel; Difflam-C; ***Philipp.***: Difflam Orange; ***Port.***: Benoral; Gartun; Tantum Verde; ***S.Afr.***: Andolex-C; Andolex-C; Andosept-Co; ***Singapore***: Difflam Anti-inflammatory Anti-Bacterial Lozenges; Difflam Anti-Inflammatory Throat Spray; Difflam Cough Lozenges; Difflam Mouth Gel; Difflam-C; Logicin Rapid Relief; ***Spain***: Eternol Antitusivo†; Mentamida†; Prosturol; Tantum†; Vinciseptil Otico; ***Turk.***: Cloder Plus; Farhex; Geral; Klodamin; Kloroben; Oroheks Plus; ***Venez.***: Amicets; Gencivol Compuesto; Solunovar Compuesto.

Pharmacopoeial Preparations
BP 2014: Benzydamine Cream; Benzydamine Mouthwash; Benzydamine Oromucosal Spray.

Benzyl Nicotinate

Bensylnikotinat; Bentsyylinikotinaatti; Benzil Nikotinat; Benzyli Nicotinas; Nicotinato de bencilo; Бензил Никотинат.
Benzyl pyridine-3-carboxylate.
$C_{13}H_{11}NO_2$=213.2
CAS — 94-44-0.
UNII — S497LCF9C9.

Pharmacopoeias. In *Ger.*

Profile

Benzyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Pernionin Thermo Teilbad; Pernionin Thermo Vollbad; Rubriment-BN†; Rubriment†.

Multi-ingredient Preparations. ***Arg.***: Oxa Sport; Pergalen; ***Austria***: Ambenat†; Derivon; Mobilisin plus; Rheumex†; Rilfit-Rheumasalbe; Rubriment; Thermo-Rheumon; Thrombophob; ***Braz.***: Trombofob; ***Fin.***: Trombosol; ***Fr.***: Lumbalgine; ***Ger.***: Camphopin†; Pelvichthol N†; Rubriment†; ***Gr.***: Air Salonpas; Bayolin; Ehrlich; Striafissan; Thermo-Roiplon; ***Hong Kong***: Salomethyl†; ***Hung.***: Air Salonpas; ***India***: Arjet; Beparine; Thrombophob; ***Indon.***: Stop X; Thrombophob; Zeropain; ***Ital.***: Salonpas; Sloan†; ***Mex.***: Bayro Termo; ***Pol.***: Lumbolin†; Thermo-Rheumon; ***Port.***: Balsamo Analgesico; Medalginan; ***Rus.***: Capsicam (Капсикам); Heparin Ointment (Гепариновая Мазь); ***Switz.***: Assan thermo; Dolo Demotherm†; Histalgane; Marament-N; Sportusal assan thermo; ***Turk.***: Thermo-Doline; Thermo-Rheumon; Thermoflex; Thermove; ***UK***: Salonair†; ***Ukr.***: Capsicam (Капсикам); Kamfart (Камфарт); ***Venez.***: Ehrlich Balsamo.

Beta-aminopropionitrile

β-Aminopropionitrile; Aminopropionitrile; β-Aminopropionitrilo; BAPN; Beta-aminopropionityrile; Бета-аминопропионитрил.

3-Aminopropionitrile.

$C_3H_6N_2$=70.10

CAS — 151-18-8 (beta-aminopropionitrile); 1119-28-4 (beta-aminopropionitrile fumarate).

ATC Vet — QM01AX91.

UNII — 38D5LJ4KH2.

Profile

Beta-aminopropionitrile, a lysyl oxidase inhibitor, is an anti-inflammatory used as the fumarate in veterinary medicine for the treatment of tendinitis.

Bornyl Salicylate

Borneol Salicylate; Salicilato de borniło; Борнилсалицилат.

2-Hydroxybenzoic acid 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester.

$C_{17}H_{22}O_3$=274.4

CAS — 560-88-3.

Profile

Bornyl salicylate is a salicylic acid derivative that has been used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for the relief of pain in musculoskeletal and joint disorders.

Bromfenac Sodium *(USAN, rINNM)*

AHR-10282; AHR-10282B; Bromfénac Sodique; Bromfenaco sódico; Natrii Bromfenacum; Натрий Бромфенак.

Sodium [2-amino-3-(*p*-bromobenzoyl)phenyl]acetate sesquihydrate.

$C_{15}H_{11}BrNNaO_3$,1½H_2O=383.2

CAS — 91714-94-2 (bromfenac); 91714-93-1 (bromfenac sodium); 120638-55-3 (bromfenac sodium).

ATC — S01BC11.

ATC Vet — QS01BC11.

UNII — 8ECV571Y37.

Profile

Bromfenac, a phenylacetic acid derivative related to diclofenac (p. 48.3), is an NSAID (p. 102.3) used for ocular pain and inflammation including postoperative inflammation in patients who have undergone cataract extraction. It is given as the sodium salt although the eye drop strength may be expressed in terms of the free acid; 1 mg of bromfenac sodium is equivalent to about 0.9 mg of bromfenac. Eye drops containing the equivalent of 0.09% bromfenac are instilled twice daily in inflammatory ocular conditions. When used postoperatively, drops containing the equivalent of 0.07% or 0.09% bromfenac are instilled once daily starting one day before, and continuing until 14 days after, surgery. Alternatively, twice daily administration of 0.09% bromfenac drops are started the day after surgery and continued for the next 14 days.

It was formerly given orally in the management of acute pain but was withdrawn from the market after reports of severe and sometimes fatal hepatic failure.

Effects on the eyes. Severe corneal melting (ulceration) was seen in 3 patients after topical use of bromfenac sodium.[1] All patients recovered after bromfenac was withdrawn. Similar effects have been reported with other ophthalmic NSAID preparations; for further details see under Adverse Effects of Diclofenac, p. 50.1.

1. Asai T, *et al.* Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea* 2006; **25:** 224–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Natax; ***Denm.***: Yellox; ***Fr.***: Yellox; ***Ger.***: Yellox; ***Irl.***: Yellox; ***Jpn***: Bronuck; ***Neth.***: Yellox; ***Norw.***: Yellox; ***Spain***: Yellox; ***Swed.***: Yellox; ***UK***: Yellox; ***USA***: Bromday; Prolensa; Xibrom†.

Bufexamac *(BAN, rINN)*

Bufeksamaakki; Bufeksamakas; Bufexamaco; Bufexamacum; Bufexamak; Bufexamák; Буфексамак.

2-(4-Butoxyphenyl)acetohydroxamic acid.

$C_{12}H_{17}NO_3$=223.3

CAS — 2438-72-4.

ATC — M01AB17; M02AA09.

ATC Vet — QM01AB17; QM02AA09.

UNII — 4T3C38J78L.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bufexamac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dimethylformamide; slightly soluble in ethyl acetate and in methyl alcohol. Protect from light.

Profile

Bufexamac is an NSAID (p. 102.3) that is applied topically in concentrations of 5% in various skin disorders. Stinging and burning may occur after application; hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Parfenac; ***China***: Kerun (可润); ***Fr.***: Parfenac†; ***Ger.***: Haemo-Exhirud Bufexamac†; Jomax†; Parfenac†; Windol†; ***Ital.***: Fansamac; ***Port.***: Parfenac†; ***Switz.***: Parfenac; ***Turk.***: Isoderm.

Multi-ingredient Preparations. ***Austral.***: Paraderm Plus†; Resolve; ***Cz.***: Mastu S†; ***Ger.***: Anaesthesin akut†; Faktu akut†; Hamoratiopharm N†; Hamoagil plus†; Hexamon Bufexamac†; Mastu akut†; ***Hong Kong***: Fungo Soothing Balm†; Mastu S†; ***Hung.***: Mastu S†; ***NZ***: Paraderm Plus†; ***Rus.***: Proctosan (Проктозан); ***Thai.***: Mastu S†; ***Ukr.***: Proctosan (Проктозан).

Bumadizone Calcium *(rINNM)*

Bumadizona cálcica; Bumadizone Calcique; Calcii Bumadizonum; Кальций Бумадизон.

Calcium 2-(1,2-diphenylhydrazinocarbonyl)hexanoate hemihydrate.

$(C_{19}H_{21}N_2O_3)_2Ca$,½H_2O=699.9

CAS — 3583-64-0 (bumadizone); 34461-73-9 (bumadizone calcium).

ATC — M01AB07.

ATC Vet — QM01AB07.

UNII — 7PSH384AJD (bumadizone calcium hemihydrate); 142R7TU2TN (anhydrous bumadizone calcium).

Profile

Bumadizone calcium is an NSAID (p. 102.3) that is metabolised to phenylbutazone (p. 125.1) and oxyphenbutazone (p. 114.3). Use has been limited by the risk of agranulocytosis and other haematological adverse effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Desflam.

Buprenorphine *(BAN, rINN)* ⊗

Buprenorfiini; Buprenorfin; Buprenorfina; Buprenorphin; Buprénorphine; Buprenorphinum; RX-6029-M; Бупренорфин.

(6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6-*O*-methyl-6,14-ethano-17-normorphine; (2*S*)-2-[(-)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]-3,3-dimethylbutan-2-ol.

$C_{29}H_{41}NO_4$=467.6

CAS — 52485-79-7.

ATC — N02AE01; N07BC01.

ATC Vet — QN02AE01; QN07BC01.

UNII — 40D3SCR4GZ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of buprenorphine:

TEM; Tems.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Buprenorphine). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in acetone; slightly soluble in cyclohexane; soluble in methyl alcohol. It dissolves in dilute solutions of acids. Protect from light.

Buprenorphine Hydrochloride

(BANM, USAN, rINNM) ⊗

Buprenorfiinihydrokloridi; Buprenorfina, hidrocloruro de; Buprenorfin-hidroklorid; Buprenorfin-hydrochlorid; Buprenorfinhydroklorid; Buprenorfino hidrochloridas; Buprénorphine, Chlorhydrate de; Buprenorphinhydrochlorid; Buprenorphini Hydrochloridum; CL-112302; Hidrocloruro de buprenorfina; NIH-8805; UM-952; Бупренорфина Гидрохлорид.

$C_{29}H_{41}NO_4$,HCl=504.1

CAS — 53152-21-9.

UNII — 56W8MW3EN1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Buprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in cyclohexane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Buprenorphine Hydrochloride). pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers. Protect from light.

Uses and Administration

Buprenorphine is an opioid analgesic (p. 108.1) classified as an opioid agonist and antagonist. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Buprenorphine is also used in the treatment of opioid dependence.

Buprenorphine has a relatively slow onset but prolonged duration of action. On intramuscular injection analgesia is apparent within 15 minutes and lasts up to 6 hours. A slower, more prolonged response is achieved after sublingual doses. The analgesic effects of buprenorphine after transdermal application may not be seen for at least 12 to 24 hours or up to 72 hours in the case of the once-weekly patch.

Buprenorphine is usually given by intramuscular or intravenous injection or sublingually as the hydrochloride or as transdermal patches as the base. For all routes doses are expressed in terms of the base. Buprenorphine hydrochloride 107.8 micrograms is equivalent to about 100 micrograms of buprenorphine.

Buprenorphine is given by all the above routes for opioid analgesia in moderate to severe **pain**.

- The dose by intramuscular or slow intravenous injection is 300 to 600 micrograms repeated every 6 to 8 hours as required
- By the sublingual route, doses of 200 to 400 micrograms may be repeated every 6 to 8 hours as required
- For opioid treatment of chronic pain in patients aged 18 years and over transdermal patches delivering varying amounts of buprenorphine are available. Doses should be individually titrated for each patient according to previous opioid usage. During transfer to treatment with buprenorphine patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-buprenorphine concentrations. Depending on dose required up to 2 patches may be applied, however, this should be done at the same time to avoid confusion. Buprenorphine patches are not appropriate for acute pain. In the UK and USA, transdermal buprenorphine patches are available as follows:

  Transtec (*Napp, UK*) delivering buprenorphine in a range of 35 to 70 micrograms/hour. Initial dosages should not exceed 35 micrograms/hour in *opioid-naive* patients. For *patients who have been receiving a strong opioid analgesic* the initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 35 micrograms/hour of buprenorphine is roughly equivalent to 30 to 60 mg daily of oral morphine sulfate. Patches should be replaced every 96 hours at the latest with the new patch being applied to a different site; use of the same area of the skin should be avoided for at least the next 2 applications.

  BuTrans (*Napp, UK*) and *Butrans* (*Purdue, USA*) delivering buprenorphine in a range of 5 to 20 micrograms/hour. UK licensed product information states that initial dosages should not exceed 5 micrograms/hour in *all* patients, whereas in the USA, this dose is licensed for the initial treatment of *opioid-naive* patients or those who have been receiving a strong opioid analgesic whose daily dose is *less than 30mg of oral morphine* or its equivalent. US licensed information recommends an

initial dose of 10 micrograms/hour for opioid-tolerant patients whose daily dose is *between 30 and 80 mg of oral morphine* or its equivalent. In those requiring *more than 80 mg daily of oral morphine* or its equivalent the use of patches providing 20 micrograms/hour of buprenorphine may not provide adequate analgesia; however, application of multiple patches to provide doses greater than 20 micrograms/hour is not licensed in the USA (see Adverse Effects and Treatment, below). Patches should be replaced every 7 days with the new patch being applied to a different site; use of the same area of the skin should be avoided for the next 3 to 4 weeks.

When used in balanced **anaesthesia** 300 micrograms may be given intramuscularly or 400 micrograms sublingually for premedication; 300 to 450 micrograms may be given intravenously as a perioperative analgesic supplement.

For the treatment of **opioid dependence** in patients aged 16 years and over, the initial dose is 0.8 to 4 mg sublingually once daily. The dose may be increased as necessary but maintenance doses should not exceed 32 mg daily. Once the patient has been stabilised, the dosage should be reduced gradually to a lower maintenance dose; treatment may eventually be stopped if appropriate. For addicts who have not undergone opioid withdrawal before starting buprenorphine, the first dose of buprenorphine should not be given until the first signs of craving appear or until at least 4 (USA) or 6 (UK) hours after the last opioid use. In those already receiving methadone replacement, the dose of methadone should be reduced to a maximum of 30 mg daily before starting buprenorphine therapy. As a deterrent to abuse, combined sublingual preparations of buprenorphine hydrochloride and naloxone hydrochloride are available in some countries for the treatment of opioid dependence. Naloxone may also increase the analgesic effect of buprenorphine, see Administration with Buprenorphine, under Naloxone, p. 1563.3.

For details of doses in **children**, see below.

Action. Buprenorphine is generally described as a mixed agonist-antagonist acting mainly as a partial agonist at μ opioid receptors, with some antagonist activity at κ receptors. It has also been shown to bind at μ, δ, and κ opioid binding sites and to have high affinity for the μ and δ receptors and lesser affinity for the κ receptor.[1] Buprenorphine, like fentanyl, has high lipid solubility, but has a lower intrinsic activity than fentanyl. Differences between buprenorphine and pure μ opioid agonists such as fentanyl, including relatively slow onset of action, prolonged duration of action, resistance to antagonism by naloxone, and lack of correlation between plasma concentrations and analgesic effects, have been explained by differences in the way buprenorphine binds to opioid receptors. In a study *in vitro* buprenorphine had slow rates of association and dissociation from the opioid receptor when compared with fentanyl.[2]

1. Bovill JG. Which potent opioid? Important criteria for selection. *Drugs* 1987; **33:** 520–30.
2. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine: the significance of receptor binding. *Br J Anaesth* 1985; **57:** 192–6.

Administration in children. Buprenorphine is used for the relief of moderate to severe **pain** in children. In the UK, those aged from 6 months to 12 years may be given 3 to 6 micrograms/kg by *intramuscular* or slow *intravenous* injection every 6 to 8 hours; up to 9 micrograms/kg may be given if required in refractory cases. In the USA, parenteral buprenorphine is licensed in children aged 2 years and over; usual doses of 2 to 6 micrograms/kg may be given intramuscularly or intravenously every 4 to 6 hours to those up to 12 years old.

The *sublingual* route is licensed in the UK in children aged from 6 to 12 years and the following doses are given every 6 to 8 hours according to body-weight:

- 16 to 25 kg: 100 micrograms
- 25 to 37.5 kg: 100 to 200 micrograms
- 37.5 to 50 kg: 200 to 300 micrograms

Older children requiring pain relief may be given the usual adult dose (see p. 30.3) for all the above routes.

Buprenorphine is also used in the treatment of **opioid dependence**; adolescents aged 16 years and over may be given the usual adult dose (see p. 30.3).

Opioid dependence. Buprenorphine is used in the treatment of opioid dependence (p. 109.2). Its agonist-antagonist properties may mean that it has a lower potential for dependence and a lower risk of respiratory depression in overdose than pure agonists such as methadone. Buprenorphine can be used as substitution therapy in patients with moderate opioid dependence for acute management of withdrawal and in maintenance treatment as an alternative to or with methadone. However, in patients dependent on high doses of opioids buprenorphine may precipitate withdrawal due to its partial antagonist properties; the daily opioid dose should be reduced gradually in such patients before beginning buprenorphine. Abuse of the preparation, as with other substitution therapies, may be a problem. A combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries as a deterrent to abuse.

References.

1. Kakko J, *et al.* 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 2003; **361:** 662–8.
2. Fudala PJ, *et al.* Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003; **349:** 949–58.
3. Montoya ID, *et al.* Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther* 2004; **75:** 34–48.
4. Fiellin DA, *et al.* Consensus statement on office-based treatment of opioid dependence using buprenorphine. *J Subst Abuse Treat* 2004; **27:** 153–9.
5. Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. *Am Fam Physician* 2006; **73:** 1573–8.
6. Sung S, Conry JM. Role of buprenorphine in the management of heroin addiction. *Ann Pharmacother* 2006; **40:** 501–5.
7. Robinson SE. Buprenorphine-containing treatments: place in the management of opioid addiction. *CNS Drugs* 2006; **20:** 697–712.
8. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)
9. Boothby LA, Doering PL. Buprenorphine for the treatment of opioid dependence. *Am J Health-Syst Pharm* 2007; **64:** 266–72.
10. Mattick RP, *et al.* Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 26/06/08).
11. Sullivan LE, Fiellin DA. Narrative review: buprenorphine for opioid-dependent patients in office practice. *Ann Intern Med* 2008; **148:** 662–70.
12. Schottenfeld RS, *et al.* Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **371:** 2192–2200.
13. Woody GE, *et al.* Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA* 2008; **300:** 2003–11. Correction. *ibid.* 2009; **301:** 830.
14. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs* 2009; **69:** 577–607.
15. Gowing L, *et al.* Buprenorphine for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 30/10/09).

Pain. *ACUTE PAIN.* The *BNF* considers that buprenorphine may antagonise the analgesic effect of other opioids and is generally not recommended for the management of *post-operative* pain. Nonetheless, it can be given intramuscularly, intravenously, or sublingually for this purpose, although the intravenous route may be preferred for acute pain relief. The epidural route[1] and continuous subcutaneous infusion[2] have also been used; an intranasal formulation of buprenorphine has been investigated for the management of postoperative pain.[1] Patient-controlled analgesia with intravenous[3] and intramuscular[4] buprenorphine is effective although its long half-life may limit such use.

Buprenorphine had no adverse cardiovascular effects when given intravenously after open-heart surgery,[5] suggesting that it was a suitable analgesic for patients with unstable circulation. Epidural analgesia with buprenorphine has also been used after cardiac surgery.[6] Buprenorphine was also considered suitable for the relief of pain in *myocardial infarction.*[7]

1. Miwa Y, *et al.* Epidural administered buprenorphine in the perioperative period. *Can J Anaesth* 1996; **43:** 907–13.
2. Kawamata T, *et al.* Pain management after lumbar spinal fusion surgery using continuous subcutaneous infusion of buprenorphine. *J Anesth* 2005; **19:** 199–203.
3. Dingus DJ, *et al.* Buprenorphine versus morphine for patient-controlled analgesia after cholecystectomy. *Surg Gynecol Obstet* 1993; **177:** 1–6.
4. Harmer M, *et al.* Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine, and meptazinol. *BMJ* 1983; **286:** 680–2.
5. Rosenfeldt FL, *et al.* Haemodynamic effects of buprenorphine after heart surgery. *BMJ* 1978; **2:** 1602–3.
6. Mehta Y, *et al.* Lumbar versus thoracic epidural buprenorphine for postoperative analgesia following coronary artery bypass graft surgery. *Acta Anaesthesiol Scand* 1999; **43:** 388–93.
7. Hayes MJ, *et al.* Randomised trial comparing buprenorphine and diamorphine for chest pain in suspected myocardial infarction. *BMJ* 1979; **2:** 300–2.

CHRONIC PAIN. Transdermal buprenorphine is used for chronic intractable cancer pain.[1-5] It has also been used successfully in chronic non-cancer pain including neuropathic pain;[1-3,5-7] however, licensed product information states that this route is not suitable for the treatment of acute pain.

1. Böhme K. Buprenorphine in a transdermal therapeutic system—a new option. *Clin Rheumatol* 2002; **21** (suppl 1): S13–S16.
2. Evans HC, Easthope SE. Transdermal buprenorphine. *Drugs* 2003; **63:** 1999–2010.
3. Sittl R. Transdermal buprenorphine in the treatment of chronic pain. *Expert Rev Neurother* 2005; **5:** 315–23.
4. Sittl R. Transdermal buprenorphine in cancer pain and palliative care. *Palliat Med* 2006; **20** (suppl 1): S25–S30.
5. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain* 2009; **13:** 219–30.
6. Bálint G. Buprenorphine treatment of patients with non-malignant musculoskeletal diseases. *Clin Rheumatol* 2002; **21** (suppl 1): S17–S18.
7. Hans G. Buprenorphine—a review of its role in neuropathic pain. *J Opioid Manag* 2007; **3:** 195–206.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Buprenorphine may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, p. 32.2). Abrupt withdrawal of buprenorphine is said to produce only a mild abstinence syndrome, which may be delayed in onset.

Buprenorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, above).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Acute hepatotoxicity, including elevated liver enzyme values, hepatitis with jaundice, hepatic failure, necrosis, and encephalopathy, and hepatorenal syndrome, has been reported in opioid-dependent addicts; these reactions have also occurred after the misuse of buprenorphine, particularly after high doses or intravenous use.

Local reactions such as rash, erythema, and itching have been reported with the transdermal patches. In isolated cases delayed local allergic reactions with marked signs of inflammation have occurred; the patches should be withdrawn in such cases. US licensed product information for *Butrans* (*Purdue, USA*) also warns that prolongation of the QT interval has occurred with transdermal buprenorphine when given at a dose of 40 micrograms/hour.

Treatment of adverse effects is similar to that for other opioid analgesics (p. 110.3). The effects of buprenorphine are only partially reversed by naloxone (see Effects on the Respiratory System, p. 32.1) but use of the latter is still recommended.

Incidence of adverse effects. Adverse effects reported[1] after *parenteral* buprenorphine in 8187 patients were nausea (8.8%), vomiting (7.4%), drowsiness (4.3%), sleeping (1.9%), dizziness (1.2%), sweating (0.98%), headache (0.55%), confusion (0.53%), lightheadedness (0.38%), blurred vision (0.28%), euphoria (0.27%), dry mouth (0.11%), depression (0.09%), and hallucinations (0.09%). Some studies[2,3] have reported nausea, vomiting, and dizziness to be more troublesome with buprenorphine than with morphine.

In a study[4] of *sublingual* buprenorphine, 50 of 141 cancer patients withdrew because of adverse effects, especially dizziness, nausea, vomiting, and drowsiness; constipation was not reported. A woman developed[5] a painless ulcer on the upper surface of her tongue after she had put sublingual buprenorphine tablets on rather than under her tongue.

Shock occurred[6] in 2 patients 2 hours after receiving *epidural* buprenorphine 300 micrograms; treatment with naloxone was unsuccessful but symptoms disappeared spontaneously after 2 to 3 hours.

In a multicentre study[7] of *transdermal* buprenorphine, 252 of 1223 patients with moderate to severe cancer pain or non-cancer pain withdrew due to adverse effects. The most commonly reported were nausea (11%), vomiting (9.2%), constipation (7.8%), dizziness (7.5%), drowsiness (4.0%), retching (3.7%), generalised pruritus (2.0%), and headache (1.6%); local adverse effects included pruritus (1.4%), dermatitis (1.3%), and erythema (1.3%). Another study[8] reported oedema, headache, nausea, palpitation, and difficulty concentrating as causes for therapy withdrawal in 4 out of 90 patients.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; **2:** 163–5.
2. Sear JW, *et al.* Buprenorphine for postoperative analgesia. *Br J Anaesth* 1979; **51:** 71.
3. Kjaer M, *et al.* A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. *Br J Clin Pharmacol* 1982; **13:** 487–92.
4. Robbie DS. A trial of sublingual buprenorphine in cancer pain. *Br J Clin Pharmacol* 1979; **7** (suppl 3): 315S–317S.
5. Lockhart SP, Baron JH. Tongue ulceration after lingual buprenorphine. *BMJ* 1984; **288:** 1346.
6. Christensen FR, Andersen LW. Adverse reaction to extradural buprenorphine. *Br J Anaesth* 1982; **54:** 476.
7. Muriel C, *et al.* Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther* 2005; **27:** 451–62.
8. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2004; **26:** 1808–20.

Effects on the heart. For a report of myocardial infarction associated with abuse of buprenorphine, see Abuse under Precautions, p. 32.2.

Effects on mental function. Psychotomimetic effects have been relatively uncommon with buprenorphine. Hallucinations were reported[1] in only 7 of 8147 patients (0.09%) given buprenorphine by injection. There have been reports of hallucinations after sublingual[2] or epidural[3] use.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; **2:** 163–5.
2. Paraskevaides EC. Near fatal auditory hallucinations after buprenorphine. *BMJ* 1988; **296:** 214.
3. MacEvilly M, O'Carroll C. Hallucinations after epidural buprenorphine. *BMJ* 1989; **298:** 928–9.

Effects on the respiratory system. There have been varying reports on the occurrence of respiratory depression with buprenorphine. It may be subject to a 'ceiling effect' in which respiratory depression does not increase further above doses of about 3 micrograms/kg.[1] However, high doses of 30 or 40 micrograms/kg given as sole intravenous analgesic in balanced anaesthesia have been associated with severe respiratory depression.[2]

Respiratory depression may be delayed in onset and more prolonged than with morphine and is only partially reversed by naloxone, possibly because buprenorphine is very firmly bound to opioid receptors. A study of sublingual buprenorphine for postoperative pain relief was abandoned when 3 of the first 16 patients showed signs of late-onset respiratory depression after the second dose of buprenorphine; the respiratory depression did not respond to naloxone.[3] Successful reversal has been shown in healthy subjects with buprenorphine-induced respiratory depression given large doses of naloxone 5 or 10 mg, but not with 1 mg; reversal was gradual in onset and decreased the duration of the normally prolonged respiratory depression.[4] Other studies found that lower doses of naloxone 2 to 4 mg given over 30 minutes,[5,6] or bolus doses of 2 to 3 mg followed by a continuous infusion of 4 mg/hour,[6] were effective in reversing buprenorphine-induced respiratory depression. The authors of both these studies suggested that a longer duration of naloxone infusion may be needed for reversal of respiratory depression caused by high doses of buprenorphine. The respiratory depressant and analgesic effects of buprenorphine were decreased by the *concomitant* use of naloxone.[7] It should be noted that a combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries for the treatment of opioid dependence.

1. Dahan A, *et al.* Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005; **94:** 825–34.
2. Schmidt JF, *et al.* Postoperative pain relief with naloxone: severe respiratory depression and pain after high dose buprenorphine. *Anaesthesia* 1985; **40:** 583–6.
3. Thörn S-E, *et al.* Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet* 1988; **i:** 179–80.
4. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther* 1989; **45:** 66–71.
5. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med* 2006; **20** (suppl 1): s3–s8.
6. van Dorp E, *et al.* Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* 2006; **105:** 51–7.
7. Lehmann KA, *et al.* Influence of naloxone on the postoperative analgesic and respiratory effects of buprenorphine. *Eur J Clin Pharmacol* 1988; **34:** 343–52.

Overdosage. A small case series reported[1] acute buprenorphine intoxication in 5 children, aged from 15 to 22 months, after accidental ingestion of sublingual tablets; of these, 4 had ingested a combined preparation containing naloxone (*Suboxone; Reckitt Benckiser, USA*). Symptoms included drowsiness and miosis; decreased respiratory rates were reported in 4. All 5 children required hospital admission; 4 were treated with naloxone and 1 needed mechanical ventilation. Accidental poisoning has also been reported[2] in a 9-month-old infant who ingested *Suboxone*; his symptoms were reversed by naloxone. A retrospective review[3] of buprenorphine overdoses in children under 6 years of age reported by US poison centres to a national surveillance system from November 2002 to December 2005 concluded that overdosage is generally well tolerated. Out of 86 reports, 54 children developed symptoms of toxicity. Such symptoms included: drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). There were no fatalities, and significant CNS and respiratory depression occurred in 7%. *Suboxone* preparations were the most commonly ingested products. The authors considered that any child who has ingested more than 2 mg and any aged under 2 years who has had more than a lick or taste should be referred to the emergency department.

During the years 1980 to 2002, buprenorphine was mentioned in 43 cases of adult fatalities in the UK.[4] Of these, 27 deaths were confirmed to have involved buprenorphine including 7 cases where it was taken alone. In those deaths where multiple drugs were involved sedatives or benzodiazepines were detected in 23 cases and other opioids were found in 17 cases; alcohol had also been taken in 10 cases. The authors also found an increase in buprenorphine-related fatalities since 1999 when the high-dose formulation became available.

1. Geib A-J, *et al.* Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics* 2006; **118:** 1746–51.
2. Cho CS, *et al.* Exploratory buprenorphine ingestion in an infant. *Ann Emerg Med* 2006; **48:** 109.
3. Hayes BD, *et al.* Toxicity of buprenorphine overdoses in children. Abstract: *Pediatrics* 2008; **121:** 807–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/4/e782 (accessed 22/07/08)
4. Schifano F, *et al.* Buprenorphine mortality, seizures and prescription data in the UK, 1980–2002. *Hum Psychopharmacol* 2005; **20:** 343–8.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Buprenorphine has opioid antagonist actions and may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

Respiratory depression, if it occurs, is relatively slow in onset and of prolonged duration; it may be only partially reversed by naloxone.

Licensed product information states that baseline liver function levels should be established before starting buprenorphine therapy, and periodic monitoring of liver function should be performed throughout therapy in patients being treated for opioid dependence. It should be used with caution in all patients with pre-existing hepatic impairment.

Absorption of buprenorphine from transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take up to 30 hours for plasma concentrations of buprenorphine to decrease by 50% after removal of a patch; patients who have had adverse effects should be monitored during this period. US licensed product information for *Butrans* (*Purdue, USA*) recommends that transdermal buprenorphine should be avoided in patients with a personal or family history of QT interval prolongation and used with caution in those with hypokalaemia or unstable cardiac disease such as atrial fibrillation, congestive heart failure, or myocardial ischaemia.

Abuse. A 22-year-old man had chest pains on each of two occasions after he had inhaled crushed buprenorphine tablets.[1] An ECG taken after the second episode suggested that the patient had suffered a myocardial infarction. Intravenous injection of crushed sublingual tablets was associated with rhabdomyolysis and sciatic neuropathy in 2 patients.[2] A case series[3] of 4 patients reported severe limb and digit complications, such as ischaemia and gangrene, from parenteral abuse of sublingual buprenorphine tablets; intra-arterial injection in 2 cases resulted in amputation of the affected digits or limb. The use of adulterants in illicit preparations may also cause adverse effects: 4 patients on substitution treatment developed candida endophthalmitis after intravenously injecting sublingual buprenorphine diluted with lemon juice.[4]

Hepatotoxicity has been seen in opioid-dependent addicts after buprenorphine abuse (see Adverse Effects and Treatment, p. 31.3).

1. Cracowski J-L, *et al.* Myocardial infarction associated with buprenorphine. *Ann Intern Med* 1999; **130:** 537.
2. Seet RCS, Lim ECH. Intravenous use of buprenorphine tablets associated with rhabdomyolysis and compressive sciatic neuropathy. *Ann Emerg Med* 2006; **47:** 396–7.
3. Loo HW, *et al.* Severe upper limb complications from parenteral abuse of Subutex. *Ann Acad Med Singapore* 2005; **34:** 575–8.
4. Cassoux N, *et al.* Presumed ocular candidiasis in drug misusers after intravenous use of oral high dose buprenorphine (Subutex). *Br J Ophthalmol* 2002; **86:** 940–1.

Breast feeding. From a study[1] of a breast-feeding mother who was receiving sublingual buprenorphine 4 mg daily, it was estimated that at the age of 4 weeks the total amount ingested by the infant during a 24-hour period was 3.28 micrograms for buprenorphine and 330 nanograms for norbuprenorphine. Another study[2] found that buprenorphine, also taken sublingually, was present in the breast milk of a breast-feeding mother with a maternal milk-to-plasma ratio of about one. The authors of both studies considered the amount absorbed through breast feeding to be low.

Some licensed product information state that buprenorphine, regardless of route, should not be given to mothers who are breast feeding. However, the *BNF* permits breast feeding and recommends that breast-fed infants should be monitored for opioid-induced adverse effects.

Studies in *rats* have shown that it may inhibit lactation.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Johnson RE, *et al.* Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend* 2001; **63:** 97–103.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies buprenorphine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. An infant born to a mother who was being treated with sublingual buprenorphine 4 mg daily for diamorphine addiction suffered a minor withdrawal syndrome 2 days after birth.[1] The infant rapidly recovered without any treatment. No further signs of withdrawal occurred when breast feeding was abruptly stopped at the age of 8 weeks. In another report[2] of 15 opioid-dependent mothers who had received buprenorphine maintenance sublingually during their pregnancies, withdrawal symptoms were either absent or mild in 12 of the neonates. The remaining 3 neonates required treatment with morphine. There appeared to be no correlation between the buprenorphine dose and the degree of withdrawal symptoms. A literature review[3] found that of about 309 infants born to opioid-dependent mothers maintained on buprenorphine (sublingual dose range: 0.4 to 24 mg daily), 193 developed neonatal abstinence syndrome; of these, 149 required treatment. More than 40% of treated cases were confounded by misuse of other drugs. Onset of symptoms occurred within the first 12 to 48 hours and peaked within about 72 to 96 hours; duration of symptoms was about 120 to 168 hours although in some infants, it was reported to last for 6 to 10 weeks.

The 67 pregnancies of 66 women using sublingual buprenorphine have been followed in a prospective study.[4] The incidences of premature birth, caesarean section, and low Apgar scores in buprenorphine-exposed neonates were no greater than those seen in the general population although the mean birth-weight of the exposed neonates was significantly lower. In the exposed group, 91% of neonates needed intensive care treatment: 76% had neonatal abstinence syndrome and 57% needed opioid replacement therapy. There were also 2 cases of sudden infant deaths in the exposed group, which was considered to be higher than that generally expected.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Fischer G, *et al.* Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction* 2000; **95:** 239–44.
3. Johnson RE, *et al.* Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend* 2003; **70** (suppl 2): S87–S101.
4. Kahila H, *et al.* A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. *Acta Obstet Gynecol Scand* 2007; **86:** 185–90.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Buprenorphine is metabolised by the cytochrome P450 isoenzyme CYP3A4; consequently, use with other drugs that induce or inhibit this isoenzyme may result in changes in plasma concentrations of buprenorphine and, possibly adverse effects. Some manufacturers state that dosage adjustment of buprenorphine may be necessary when used with such drugs. The UK licensed product information for one sublingual formulation (*Subutex; Schering-Plough*) recommends that the dose of buprenorphine should be halved when starting treatment with the potent CYP3A4 inhibitor, ketoconazole.

There have been reports of respiratory and cardiovascular collapse in patients given therapeutic doses of intravenous buprenorphine and diazepam.

Use with other potentially hepatotoxic drugs may increase the risk of liver damage.

Analgesics. There is a risk that, with opioid agonist-antagonists such as buprenorphine, their antagonistic effects might impair more effective analgesic therapy. This appeared to happen in 2 cancer patients both of whom were given sublingual buprenorphine that was later substituted by *morphine*.[1] Conventional doses of morphine were inadequate and in one patient raising the dose of morphine proved fatal.

1. Overweg-van Kints J, Stricker BHC. Falende pijnbestrijding tijdens sublinguaal gebruik van buprenorfine. *Ned Tijdschr Geneeskd* 1987; **131:** 1973–4.

Antivirals. Various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and most are also substrates for CYP3A4; thus, they have the potential to interact with buprenorphine. A pharmacokinetic study[1] found that usual doses of *nelfinavir*, *ritonavir*, and *lopinavir-ritonavir* given to HIV-negative patients taking buprenorphine with naloxone for opiate dependence did not produce any clinically significant interactions: ritonavir increased the area under the concentration-time curve (AUC) of buprenorphine by about 57%, although no adverse effects were seen. Another pharmacokinetic study[2] in a similar group of patients also found no clinically significant interactions between buprenorphine with naloxone and *delavirdine* or *efavirenz*: delavirdine increased the AUC of buprenorphine fourfold, and efavirenz decreased it by about 50%, but no adverse effects were seen. However, a small case series[3] of 3 opioid-dependent patients reported symptoms of buprenorphine toxicity, such as dizziness, daytime somnolence, and decreased mental functioning, with concomitant *atazanavir* and ritonavir therapy.

Buprenorphine does not appear to significantly affect the pharmacokinetics of antiretrovirals.[1,2]

1. McCance-Katz EF, *et al*. Interactions between buprenorphine and antiretrovirals: I—The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis* 2006; **43** (suppl 4): S224–S234.
2. McCance-Katz EF, *et al*. Interactions between buprenorphine and antiretrovirals: II—The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. *Clin Infect Dis* 2006; **43** (suppl 4): S235–S246.
3. Bruce RD, Altice FL. Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. *AIDS* 2006; **20:** 783–4.

Pharmacokinetics

After intramuscular injection, buprenorphine rapidly reaches peak plasma concentrations. Absorption also takes place through the buccal mucosa after sublingual doses and peak plasma concentrations occur after 90 minutes. Transdermal application results in absorption through the skin; the minimum effective concentration is reached in 12 to 24 hours and peak plasma concentrations occur after about 60 hours. However, there is a lack of correlation between plasma concentrations and analgesic activity. Buprenorphine is about 96% bound to plasma proteins.

Elimination of buprenorphine is bi- or triphasic; metabolism takes place in the liver by oxidation via the cytochrome P450 isoenzyme CYP3A4 to the pharmacologically active metabolite *N*-dealkylbuprenorphine (norbuprenorphine), and by conjugation to glucuronide metabolites. Buprenorphine is subject to considerable first-pass metabolism after oral doses. However, when given by the usual routes buprenorphine is excreted mainly unchanged in the faeces; there is some evidence for enterohepatic recirculation. Plasma elimination half-lives have ranged from 1.2 to 7.2 hours after intravenous injection; elimination half-lives after sublingual or transdermal use are longer and may range from 20 to 36 hours or more. Metabolites are excreted in the urine, but very little unchanged drug is excreted in this way. Buprenorphine crosses the placenta and small amounts are distributed into breast milk.

References.

1. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 2005; **44:** 661–80.

Administration. *BUCCAL ROUTE.* Absorption of sublingual buprenorphine is relatively slow. In a 10-hour study[1] plasma concentrations after 400 or 800 micrograms given sublingually peaked at about 200 minutes (range 90 to 360 minutes) and buprenorphine was still detected in plasma at the end of the study. Systemic availability was about 55% (range 16 to 94%) and absorption was more or less complete 5 hours after a dose. However, the authors of a subsequent study[2] considered that this was an overestimation, possibly due to methodological flaws. The later study results indicated that the bioavailability of sublingual buprenorphine is about 30% and that sublingual holding times between 3 and 5 minutes are bioequivalent. Another single-dose study[3] found that the bioavailability of sublingual buprenorphine was 50% less from a tablet than from a liquid formulation. Later studies[4,5] noted that the bioavailability of buprenorphine from a sublingual tablet relative to a sublingual liquid formulation was about 70% after daily dosing for 7 days. One of these studies[4] also found that the bioavailability of sublingual buprenorphine from a tablet formulation containing naloxone was higher than from a single-ingredient tablet formulation and similar to that seen with liquid formulations.

1. Bullingham RES, *et al*. Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br J Clin Pharmacol* 1982; **13:** 665–73.
2. Mendelson J, *et al*. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997; **37:** 31–7.
3. Nath RP, *et al*. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J Clin Pharmacol* 1999; **39:** 619–23.
4. Strain EC, *et al*. Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug Alcohol Depend* 2004; **74:** 37–43.
5. Compton P, *et al*. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. *Drug Alcohol Depend* 2006; **82:** 25–31.

Children. The terminal elimination half-life of buprenorphine was only about 1 hour in small children aged 4 to 7 years given 3 micrograms/kg intravenously as premedication, but could not be estimated reliably because of the rapid decline in plasma-buprenorphine concentrations.[1] Clearance values did, however, appear higher than in adults; steady-state volume of distribution was similar. Premature neonates (gestational age 27 to 32 weeks) given a similar dose followed by an infusion of 720 nanograms/kg per hour had a considerably lower clearance rate and had a mean elimination half-life of 20 hours.[2] Although this dosing regimen appeared to be safe, sedation was judged to be inadequate in 4 of the 12 neonates studied. It was suggested that as buprenorphine given by infusion might not produce consistent sedation and analgesia in premature neonates, it could not be recommended for use in neonatal care.

1. Olkkola KT, *et al*. Pharmacokinetics of intravenous buprenorphine in children. *Br J Clin Pharmacol* 1989; **28:** 202–4.
2. Barrett DA, *et al*. The pharmacokinetics and physiological effect of buprenorphine infusion in premature neonates. *Br J Clin Pharmacol* 1993; **36:** 215–19.

Renal impairment. Buprenorphine clearance appears to occur mainly by hepatic extraction and metabolism and would not be expected to be related to renal function, whereas metabolites are excreted in urine. In a study, buprenorphine kinetics were similar in anaesthetised healthy patients to those in patients with renal impairment, with a mean elimination half-life of 398 and 239 minutes, respectively.[1] Plasma concentrations of the metabolites norbuprenorphine and buprenorphine-3-glucuronide were increased about 4 times and 15 times, respectively in patients with renal impairment,[1] but significant pharmacological activity was unlikely since norbuprenorphine has little analgesic activity compared with the parent compound and buprenorphine-3-glucuronide has none.

1. Hand CW, *et al*. Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth* 1990; **64:** 276–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Restiva; ***Austral.***: Norspan; Suboxone; Subutex; Temgesic; ***Austria***: Suboxone; Subutex; Temgesic; Transtec; Triquisic; ***Belg.***: Suboxone; Subutex; Temgesic; Transtec; ***Braz.***: Temgesic; ***Canad.***: BuTrans; Suboxone; ***Chile***: Transtec; ***China***: Sha Fei (沙菲); Shumeifen (舒美奋); ***Cz.***: Norspan; Ravata; Suboxone; Subutex; Temgesic; Transtec; Trapamaphin; ***Denm.***: Buprenotex; Norspan; Norvipren; Suboxone; Subutex; Temgesic; Transtec; ***Fin.***: Norspan; Subutex†; Temgesic; ***Fr.***: Suboxone; Subutex; Temgesic; ***Ger.***: Cras; Norspan; Suboxone; Subutex; Temgesic; Transtec; ***Gr.***: Prenorvine; Suboxone; Subutex; ***Hong Kong***: Suboxone; Subutex†; Temgesic; ***Hung.***: Bupren†; Suboxone; Transtec; ***India***: Addnok; Bunogesic; Buprigesic; Buprinor; Norphin; Pentorel; Tidigesic; ***Indon.***: Suboxone; Subutex; ***Irl.***: BuTrans; Centradol†; Suboxone; Subutex; Temgesic; Transtec; ***Israel***: BuTrans; Nopan†; SBT; Subutex; ***Ital.***: Suboxone; Subutex; Temgesic; Transtec; ***Jpn***: Norspan; ***Malaysia***: Suboxone; ***Mex.***: Brospina; Temgesic; Transtec; ***Neth.***: BuTrans; Suboxone; Subutex†; Temgesic; Transtec; ***Norw.***: Norspan; Suboxone; Subutex; Temgesic; ***NZ***: Norspan; Suboxone; Temgesic; ***Philipp.***: Norspan; ***Pol.***: Bunondol; Suboxone; Transtec; ***Port.***: Buprex; Norspan†; Suboxone; Subutex; Transtec; Trapamafin; Triquisic; ***Rus.***: Bupranal (Бупранал); Nopan (Нопан); Transtec (Трансtек); ***S.Afr.***: Subutex; Temgesic; ***Singapore***: Temgesic; ***Spain***: Buprex; Suboxone; Transtec; ***Swed.***: Buprenotex; Norspan; Suboxone; Subutex; Temgesic; ***Switz.***: Subutex; Temgesic; Transtec; ***Thai.***: Buprine†; ***Turk.***: Suboxone; ***UK***: BuTrans; Hapoctasin; Suboxone; Subutex; Temgesic; Tephine; Transtec; ***USA***: Buprenex; Butrans; Suboxone; Subutex†.

Multi-ingredient Preparations. ***USA***: Zubsolv.

Pharmacopaeial Preparations

BP 2014: Buprenorphine Injection; Buprenorphine Sublingual Tablets; Buprenorphine Transdermal Patches.

Butorphanol Tartrate *(BANM, USAN, rINNM)*

Butorfanol, tartrato de; Butorfanolitartraatti; Butorfanoltartrat; Butorphanol, Tartrate de; Butorphanoli Tartras; *levo*-BC-2627 (butorphanol); Tartrato de butorfanol; Буторфанола Тартрат.

(-)-17-(Cyclobutylmethyl)morphinan-3,14-diol hydrogen tartrate.

$C_{21}H_{29}NO_2.C_4H_6O_6$=477.6

CAS — 42408-82-2 (butorphanol); 58786-99-5 (butorphanol tartrate).

ATC — N02AF01.

ATC Vet — QN02AF01.

UNII — 2L7172RUHN.

Pharmacopoeias. In *US*.

USP 36: (Butorphanol Tartrate). A white powder. Its solutions are slightly acidic. Sparingly soluble in water; insoluble in alcohol, in chloroform, in ether, in ethyl acetate, and in hexane; slightly soluble in methyl alcohol; soluble in dilute acids. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Butorphanol tartrate, a phenanthrene derivative, is an opioid analgesic (p. 108.1) with opioid agonist and antagonist properties; it is pharmacologically similar to pentazocine (p. 120.3). Butorphanol is used for the relief of moderate to severe pain, including the pain of labour, and as an adjunct to anaesthesia. Onset of analgesia occurs within 15 minutes of intramuscular injection or an intranasal dose and may last for 3 to 4 hours after parenteral doses or for 4 to 5 hours after intranasal doses.

For the relief of moderate to severe **pain**, butorphanol tartrate is given in doses of 1 to 4 mg (usually 2 mg) by intramuscular injection or in doses of 0.5 to 2 mg (usually 1 mg) by intravenous injection every 3 to 4 hours. It may also be given as a nasal spray, in usual doses of 1 mg (1 spray in 1 nostril), repeated after 60 to 90 minutes, if necessary. This sequence may be repeated after 3 to 4 hours as needed. An initial dose of 2 mg (1 spray in each nostril) may be given for severe pain, but should not be repeated until 3 to 4 hours later.

In *obstetric analgesia* 1 to 2 mg may be given by intramuscular or intravenous injection during early labour in women at term. This dose may be repeated after 4 hours if necessary but an alternative analgesic should be used if delivery is expected within 4 hours.

In **anaesthesia**, 2 mg may be given intramuscularly for premedication 60 to 90 minutes before surgery. For use in balanced anaesthesia, a usual dose is 2 mg given intravenously shortly before induction and/or 0.5 to 1 mg given intravenously in increments during anaesthesia. The total dose needed varies but most patients require 4 to 12.5 mg.

Dosage adjustment may be needed in the elderly. When given by injection the initial dose of butorphanol for pain should be half the usual initial adult dose. Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours. Similar recommendations have also been made for patients with hepatic or renal impairment, see below.

References.

1. Atkinson BD, *et al*. Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *Am J Obstet Gynecol* 1994; **171:** 993–8.
2. Gillis JC, *et al*. Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. *Drugs* 1995; **50:** 157–75.
3. Commiskey S, *et al*. Butorphanol: effects of a prototypical agonist-antagonist analgesic on κ-opioid receptors. *J Pharmacol Sci* 2005; **98:** 109–16.

Administration in hepatic or renal impairment. The dosage of butorphanol may need to be adjusted in patients with hepatic or renal impairment. When given by injection the initial dose for pain should be half the usual initial dose (see above). Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours.

Headache. Butorphanol has been advocated for use as a nasal spray in the treatment of migraine, but there have been problems with abuse and dependence (see p. 34.1) and its place in therapy, if any, still remains to be established. See also Antimigraine Drugs, under Interactions, p. 34.2.

References.

1. Freitag FG. The acute treatment of migraine with transnasal butorphanol (TNB). *Headache Q* 1993; **4** (suppl 3): 22–8.
2. Hoffert MJ, *et al*. Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; **35:** 65–9.
3. Melanson SW, *et al*. Transnasal butorphanol in the emergency department management of migraine headache. *Am J Emerg Med* 1997; **15:** 57–61.

Pruritus. Results from a small study[1] of 6 patients with severe opioid-induced pruritus unresponsive to diphenhydramine, and from a case series of 5 patients with intractable pruritus from other causes,[2] suggest that intranasal butorphanol may be an effective treatment. Doses have ranged from 1 mg every other day to 2 mg every 4 to 6 hours.

1. Dunteman E, *et al*. Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manage* 1996; **12:** 255–60.
2. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; **54:** 527–31.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Butorphanol may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, p. 34.1). Abruptly stopping chronic butorphanol has produced a less severe withdrawal syndrome than with morphine.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1, and for Pentazocine, p. 121.1.

Headache, and feelings of floating may also occur. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. In addition insomnia and nasal congestion may occur frequently when butorphanol is given intranasally.

Because butorphanol has opioid agonist and antagonist activity, naloxone is the recommended antagonist for the treatment of overdosage.

Effects on the respiratory system. Butorphanol 2 mg produces a similar degree of respiratory depression to morphine 10 mg, but a ceiling effect is apparent with higher doses of butorphanol.[1] It has been reported to be a less potent respiratory depressant than fentanyl,[2] but more potent than nalbuphine.[3]

1. Nagashima H, *et al.* Respiratory and circulatory effects of intravenous butorphanol and morphine. *Clin Pharmacol Ther* 1976; **19:** 738–45.
2. Dryden GE. Voluntary respiratory effects of butorphanol and fentanyl following barbiturate induction: a double-blind study. *J Clin Pharmacol* 1986; **26:** 203–7.
3. Zucker JR, *et al.* Respiratory effects of nalbuphine and butorphanol in anesthetized patients. *Anesth Analg* 1987; **66:** 879–81.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Although cardiovascular effects may be less than with pentazocine, butorphanol should generally be avoided after myocardial infarction.

Butorphanol may precipitate withdrawal symptoms if given to patients physically dependent on opioids. The dosage regimen of butorphanol may need to be adjusted in the elderly and in patients with hepatic or renal impairment.

Abuse. A WHO expert committee considered in 2006 that the likelihood of butorphanol abuse was low and was not great enough to warrant international control.[1] Abuse had been reported infrequently and only in a few countries. The committee also commented that, pharmacologically, intranasal preparations of butorphanol do not appear to differ in their abuse potential from parenteral preparations; however, other factors such as availability and usage patterns may affect the likelihood of abuse. Indeed, US licensed product information states that there have been more reports of abuse with intranasal preparations than with injectable ones.

Cases of butorphanol abuse have been published[2,3] including a report of fibrous myopathy associated with chronic intramuscular abuse.

1. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
2. Wagner JM, Cohen S. Fibrous myopathy from butorphanol injections. *J Rheumatol* 1991; **18:** 1934–5.
3. Loder E. Post-marketing experience with an opioid nasal spray for migraine: lessons for the future. *Cephalalgia* 2006; **26:** 89–97.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given butorphanol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In a study[2] of 12 women, butorphanol was detected in breast milk after both intramuscular and oral doses. However, the milk-to-plasma ratio after a 2-mg intramuscular dose (0.7) was significantly less than that after an 8-mg oral dose (1.9). Although the mothers were not breast feeding at the time of the study, the authors concluded that the potential for any adverse effects on nursing infants after maternal butorphanol use would be minimal.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Pittman KA, *et al.* Human perinatal distribution of butorphanol. *Am J Obstet Gynecol* 1980; **138:** 797–800.

Pregnancy. Two instances of sinusoidal fetal heart rate pattern were noted out of 188 consecutive cases of butorphanol use in active-phase labour.[1] Visual hallucinations and paranoid delusions developed in a woman on receiving a 1-mg intravenous injection of butorphanol early in labour; the psychosis had resolved 40 hours after the injection and was not noted on follow-up 2 weeks later.[2]

1. Welt SI. Sinusoidal fetal heart rate and butorphanol administration. *Am J Obstet Gynecol* 1985; **152:** 362–3.
2. Davis A, *et al.* Acute psychosis associated with butorphanol. *J Neuropsychiatr Clin Neurosci* 1998; **10:** 236–7.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Antimigraine drugs. No pharmacokinetic interactions were reported when butorphanol nasal spray and subcutaneous *sumatriptan* were used within a minute of each other in healthy subjects.[1] However, another study[2] in healthy subjects found that the AUC and peak plasma concentration of intranasal butorphanol were reduced by about 29% and 38%, respectively when given 1 minute after intranasal sumatriptan. No such effect was noted when administration was separated by 30 minutes. It was suggested that sumatriptan may reduce butorphanol absorption by inducing transient nasal vasoconstriction.

1. Srinivas NR, *et al.* Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* 1995; **35:** 432–7.
2. Vachharajani NN, *et al.* A pharmacokinetic interaction study between butorphanol and sumatriptan nasal sprays in healthy subjects: importance of the timing of butorphanol administration. *Cephalalgia* 2002; **22:** 282–7.

Pharmacokinetics

Butorphanol is absorbed from the gastrointestinal tract but it undergoes extensive first-pass metabolism. Peak plasma concentrations occur 0.5 to 1 hour after intramuscular and intranasal doses and 1 to 1.5 hours after oral doses. Butorphanol has a plasma elimination half-life of about 4.5 hours. About 80% is bound to plasma proteins.

Butorphanol is extensively metabolised in the liver through hydroxylation, *N*-dealkylation, and conjugation; only 5% being excreted unchanged. Excretion is mainly in the urine; about 15% of a parenteral dose is excreted in the bile. It crosses the placenta and is distributed into breast milk.

Administration. *INTRANASAL ROUTE.* References.

1. Davis GA, *et al.* Pharmacokinetics of butorphanol tartrate administered from single-dose intranasal sprayer. *Am J Health-Syst Pharm* 2004; **61:** 261–6.
2. Davis GA, *et al.* Bioavailability of intranasal butorphanol administered from a single-dose sprayer. *Am J Health-Syst Pharm* 2005; **62:** 48–53.
3. Wermeling DP, *et al.* Pharmacokinetics, bioequivalence, and spray weight reproducibility of intranasal butorphanol after administration with 2 different nasal spray pumps. *J Clin Pharmacol* 2005; **45:** 969–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China:*** Nuo Yang (诺扬); ***India:*** Butodol; Butrum; ***Mex.:*** Stadol; ***Philipp.:*** Stadol†; ***Rus.:*** Stadol (Стадол); ***USA:*** Stadol.

Pharmacopoeial Preparations

USP 36: Butorphanol Tartrate Injection; Butorphanol Tartrate Nasal Solution.

Canakinumab *(BAN, USAN, rINN)*

ACZ-885; Canakinumabum; Канакинумаб.

immunoglobulin G1, anti-[*Homo sapiens* interleukin 1, beta (IL1B)] human monoclonal ACZ885; gamma1 heavy chain (*Homo sapiens* VH-IGHG1*03) (221-214′)-disulfide with kappa light chain (*Homo sapiens* V-KAPPA-IGKC*01); (227-227″:230-230″)-bisdisulfide dimer.

CAS — 914613-48-2 (canakinumab); 402710-27-4 (light chain); 402710-25-2 (heavy chain).

ATC — L04AC08.

ATC Vet — QL04AC08.

UNII — 37CQ2C7X93.

Uses and Administration

Canakinumab is a recombinant human monoclonal interleukin-1β antibody used for the symptomatic treatment of frequent gouty arthritis attacks (defined as at least 3 attacks in the previous 12 months) when the use of NSAIDs and colchicine are contra-indicated, not tolerated, or produce an inadequate response, and repeated courses of corticosteroids are inappropriate. Canakinumab may be used for the treatment of juvenile idiopathic arthritis. It is also used in the management of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders.

For the treatment of gouty arthritis attacks, canakinumab should be used as on-demand therapy; hyperuricaemia should be managed with appropriate urate-lowering therapy (see Gout and Hyperuricaemia, p. 600.1). The recommended dose is 150 mg given by subcutaneous injection as a single dose as soon as possible after the onset of an attack. Patients who do not respond to initial treatment should not be re-treated with canakinumab. Those who respond may be given another dose at least 12 weeks after the initial dose.

For the treatment of CAPS, canakinumab is given by subcutaneous injection as a single dose; patients with a body-weight greater than 40 kg may be given an initial dose of 150 mg, followed by a usual maintenance dose of 150 mg every 8 weeks. A second dose of 150 mg may be given 7 days after the initial dose if the response has been unsatisfactory; if this produces a full response after 7 days, the dose should be maintained at 300 mg every 8 weeks. If the response has been unsatisfactory, a third dose of 300 mg may be given 7 days after the second dose and if this produces a full response after 7 days, the dose should be maintained at 600 mg every 8 weeks.

For details of use and dosage in children, including use in juvenile idiopathic arthritis, see Administration in Children, below.

References.

1. Lachmann HJ, *et al.* Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med* 2009; **360:** 2416–25.
2. Koné-Paut I, *et al.* Canakinumab in CAPS Study Group. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. *Arthritis Res Ther* 2011; **13:** R202.
3. Schlesinger N, *et al.* Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. *Ann Rheum Dis* 2012; **71:** 1839–48.
4. Ruperto N, *et al.* PRINTO. PRCSG. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; **367:** 2396–2406.

Administration in children. Canakinumab may be used in children for the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). It is given by subcutaneous injection as a single dose, according to age and body-weight. In the UK, the following regimen is used in children aged 2 years or older:

- ⩾2 years, weighing ⩾7.5 kg and <15 kg: 4 mg/kg initially, followed by a usual maintenance dose of 4 mg/kg every 8 weeks; a second dose of 4 mg/kg may be given 7 days after the initial dose if the response has been unsatisfactory, and if this produces a full response after 7 days, the dose should be maintained at 8 mg/kg every 8 weeks
- ⩾4 years, weighing ⩾15 kg and ⩽40 kg: 2 mg/kg initially, followed by a usual maintenance dose of 2 mg/kg every 8 weeks; a second dose of 2 mg/kg may be given 7 days after the initial dose if the response has been unsatisfactory, and if this produces a full response after 7 days, the dose should be maintained at 4 mg/kg every 8 weeks. If the response has been unsatisfactory, a third dose of 4 mg/kg may be given 7 days after the second dose and if this produces a full response after 7 days, the dose should be maintained at 8 mg/kg every 8 weeks
- ⩾4 years, weighing >40 kg: the usual adult dose (see Uses and Administration, above) may be given

Similar initial doses are used in the USA in children aged 4 years and over, and weighing at least 15 kg; a dose of 3 mg/kg has been suggested for those with an inadequate response.

Canakinumab is also licensed for the treatment of active systemic juvenile idiopathic arthritis (p. 12.1) in children aged 2 years or older. The recommended dose in those weighing 7.5 kg or more is 4 mg/kg (maximum of 300 mg) given as a single subcutaneous injection every 4 weeks.

Adverse Effects and Precautions

The adverse effects reported most commonly with canakinumab are headache, nasopharyngitis, nausea, diarrhoea, respiratory-tract infections including influenza, and vertigo. Injection site reactions have also occurred.

Canakinumab has been associated with an increased incidence of serious infections and it should therefore be given with caution to patients with active infections, a history of recurring infections, or underlying conditions that may predispose them to developing infections. Canakinumab treatment should not be started or continued in patients with severe infections that require treatment. Patients should be screened for active and latent tuberculosis infection before starting canakinumab treatment. Patients should be up to date with appropriate immunisation schedules, including pneumococcal vaccine and inactivated influenza, before starting treatment with canakinumab; live vaccines should not be given at the same time as canakinumab unless the benefits clearly outweigh the risks (see also Interactions, p. 35.1).

Treatment with canakinumab should not be started in patients with neutropenia, and it is recommended that neutrophil counts should be taken before starting treatment, 1 to 2 months later, and periodically thereafter.

Patients who have vertigo during treatment with canakinumab should avoid driving or operating machinery.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies canakinumab as possibly porphyrinogenic; it should be used only when no

safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

There are no formal interaction studies with canakinumab; however, it is recommended that live vaccines should not be given at the same time as canakinumab as its effect on vaccine efficacy or the risk of infection transmission is unknown. If use together is unavoidable, live vaccines should not be given until at least 3 months after the last, and before the next, dose of canakinumab.

The use of TNF inhibitors with canakinumab may increase the risk of serious infections and neutropenia; such combinations are not recommended. A similar effect may also occur when used with other interleukin-1 antagonists.

During inflammation the expression of cytochrome P450 isoenzymes is suppressed by cytokines such as interleukin-1β, and cytochrome P450 expression may therefore be normalised when treatment with a cytokine inhibitor such as canakinumab is started. This becomes clinically significant for cytochrome P450 isoenzyme substrates that have narrow therapeutic ratios where the dose has to be individually adjusted (e.g. warfarin). Therefore when starting or stopping therapy with canakinumab, patients being treated with such drugs should be monitored as doses of these drugs may need to be adjusted.

Pharmacokinetics

Peak serum concentrations occur about 7 days after a single subcutaneous injection of canakinumab; the mean terminal half-life is about 26 days. The absolute bioavailability was estimated to be 66%.

References.

1. Chakraborty A, *et al*. Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1β monoclonal antibody. *Clin Pharmacokinet* 2012; **51:** e1–e18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ilaris; ***Austria***: Ilaris; ***Braz.***: Ilaris; ***Canad.***: Ilaris; ***Cz.***: Ilaris; ***Denm.***: Ilaris; ***Fr.***: Ilaris; ***Ger.***: Ilaris; ***Gr.***: Ilaris; ***Irl.***: Ilaris; ***Israel***: Ilaris; ***Ital.***: Ilaris; ***Jpn***: Ilaris; ***Neth.***: Ilaris; ***Norw.***: Ilaris; ***NZ***: Ilaris; ***Pol.***: Ilaris; ***Port.***: Ilaris; ***Spain***: Ilaris; ***Swed.***: Ilaris; ***Switz.***: Ilaris; ***Turk.***: Ilaris; ***UK***: Ilaris; ***USA***: Ilaris.

Capsaicin

Capsaicina; Capsaicinum; Kapsaicin; Kapsaicyna; Kapsaisiini; Капсаицин.

(*E*)-8-Methyl-*N*-vanillylnon-6-enamide.

$C_{18}H_{27}NO_3$=305.4

CAS — 404-86-4.

ATC — M02AB01; N01BX04.

ATC Vet — QM02AB01; QN01BX04.

UNII — S07O44R1ZM.

NOTE. Do not confuse capsaicin with capsicin, which is capsicum oleoresin (see Capsicum, p. 2469.3).

Pharmacopoeias. In *US.*

USP 36: (Capsaicin). An off-white powder. M.p. 57 degrees to 66 degrees. Practically insoluble in cold water; soluble in alcohol, in chloroform, and in benzene; slightly soluble in carbon disulfide. Store in a cool place in airtight containers. Protect from light.

Uses and Administration

Capsaicin is the active principle of the dried ripe fruits of *Capsicum* spp. It is used as a topical analgesic (p. 6.3) in peripheral neuropathic pain including postherpetic neuralgia after the lesions have healed and diabetic neuropathy (see Neuropathic Pain, below), and in osteoarthritis and rheumatoid arthritis (see Rheumatic Disorders, below).

Capsaicin is usually applied sparingly 3 or 4 times daily (and not more often than every 4 hours) as a 0.025% or 0.075% *cream*; in the UK these creams are not licensed for use in children, but in the USA they may be used in children over 2 years of age. A more concentrated cream containing 0.25% capsaicin is available in some countries.

Capsaicin cream should be rubbed well into the skin until little or no residue is left on the surface. Therapeutic response may not be evident for 1 to 2 weeks for arthritic disorders, or 2 to 4 weeks for neuralgias (or even longer if the head or neck are involved). For the management of painful diabetic neuropathy, UK licensed product information recommends that capsaicin should only be used under specialist supervision and that treatment should be reviewed after the first 8 weeks and regularly re-evaluated thereafter.

Although not a counter-irritant itself, capsaicin has been included in rubefacient preparations for the relief of muscular and rheumatic pain.

A high-concentration *transdermal patch* containing capsaicin 8% (equivalent to 179 mg in total) is available for the treatment of peripheral neuropathic pain in non-diabetic patients, either as monotherapy or as an adjunct. The treatment area and surrounding 1 to 2 cm should be pretreated with a topical anaesthetic before applying the patch, for example, topical lidocaine 4% left for 60 minutes. Up to a maximum of 4 patches may be applied to the most painful areas of the skin and left in place for 30 minutes on the feet (e.g. in HIV-associated neuropathy) or for 60 minutes on other locations (e.g. in postherpetic neuralgia). Treatment may be repeated every 90 days if necessary.

A long-acting *topical solution* has been investigated for painful conditions such as postoperative, musculoskeletal, and trauma-induced neuropathic pain including interdigital neuroma.

Action. The action of capsaicin and related compounds (vanilloids) are complex and still being investigated. Capsaicin has been found to produce burning pain[1-3] by activating specific vanilloid receptors such as TRPV1 (transient receptor potential channel, vanilloid subfamily member 1) which are also stimulated by heat and acids. TRPV1 is expressed by nerves and other tissues such as the keratinocytes of the epidermis, bladder urothelium and smooth muscle, and liver.

The analgesic effect of capsaicin has been suggested to be due to both depletion of substance P from local sensory C-type nerve fibres[4-8] and to the desensitisation of vanilloid receptors.[1-3,9] Since the effect of capsaicin does not rely on vasodilatation in the skin it is therefore not considered to be a traditional counter-irritant.

1. Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; **51:** 159–211.
2. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1: an update. *Eur J Biochem* 2004; **271:** 1814–19.
3. Wang Y. The functional regulation of TRPV1 and its role in pain sensitization. *Neurochem Res* 2008; **33:** 2008–12.
4. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP Ann Pharmacother* 1991; **25:** 381–7.
5. Cordell GA, Araujo OE. Capsaicin: identification, nomenclature, and pharmacotherapy. *Ann Pharmacother* 1993; **27:** 330–6.
6. Winter J, *et al*. Capsaicin and pain mechanisms. *Br J Anaesth* 1995; **75:** 157–68.
7. Del Bianco E, *et al*. The effects of repeated dermal application of capsaicin to the human skin on pain and vasodilatation induced by intradermal injection of acid and hypertonic solutions. *Br J Clin Pharmacol* 1996; **41:** 1–6.
8. Fusco BM, Giacovazzo M. Peppers and pain: the promise of capsaicin. *Drugs* 1997; **53:** 909–14.
9. Tominaga M, Julius D. Capsaicin receptor in the pain pathway. *Jpn J Pharmacol* 2000; **83:** 20–4.

Administration in children. In the USA, capsaicin cream is licensed in children, for details see above.

Headache. Prevention of attacks of *cluster headache* (p. 670.1) by repeated application of capsaicin to the nasal mucosa has been reported.[1] The *Z*-isomer (zucapsaicin; civamide) has also been found to be modestly effective.[2]

Repeated nasal application of capsaicin has also been found to be effective in *chronic migraine*[3] (p. 670.3).

1. Fusco BM, *et al*. Preventative effect of repeated nasal applications of capsaicin in cluster headache. *Pain* 1994; **59:** 321–5.
2. Saper JR, *et al*. Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol* 2002; **59:** 990–4.
3. Fusco BM, *et al*. Repeated intranasal capsaicin applications to treat chronic migraine. *Br J Anaesth* 2003; **90:** 812.

Micturition disorders. Intravesical instillation of capsaicin or its analogue resiniferatoxin have been tried for painful bladder disorders and to treat bladder detrusor hyperreflexia.[1-9] Results have been variable, and they are considered to be of limited use.[10,11] Instillation into the ureter has also been tried in the management of the loin pain/haematuria syndrome[12] but pain relief appears to be at best short-term and its use is associated with significant adverse effects.[13]

1. Lazzeri M, *et al*. Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. *J Urol (Baltimore)* 1996; **156:** 947–52.
2. de Sèze M, *et al*. Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. *Neurourol Urodyn* 1998; **17:** 513–23.
3. Petersen T, *et al*. Intravesical capsaicin in patients with detrusor hyperreflexia: a placebo-controlled cross-over study. *Scand J Urol Nephrol* 1999; **33:** 104–10.
4. de Sèze M, *et al*. Intravesical instillation of capsaicin in urology: a review of the literature. *Eur Urol* 1999; **36:** 267–77.
5. de Sèze M, *et al*. Capsaïcine intravésicale et hyperréflexie du détrusor: expérience de 100 instillations sur une période de cinq ans. *Ann Readapt Med Phys* 2001; **44:** 514–24.
6. Szallasi A, Fowler CJ. After a decade of intravesical vanilloid therapy: still more questions than answers. *Lancet Neurol* 2002; **1:** 167–72.
7. El-Mahrouky AS, *et al*. The effect of intravesical capsaicin and resiniferatoxin in neurogenic bladder dysfunction. *Adv Exp Med Biol* 2003; **539:** 359–79.
8. de Sèze M, *et al*. Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. *J Urol (Baltimore)* 2004; **171:** 251–5.
9. Lazzeri M, *et al*. Intravesical vanilloids and neurogenic incontinence: ten years experience. *Urol Int* 2004; **72:** 145–9.
10. Andersson K-E, *et al*. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. *Curr Opin Urol* 2009; **19:** 380–94.
11. Yamaguchi O, *et al*. Neurogenic Bladder Society. Clinical guidelines for overactive bladder. *Int J Urol* 2009; **16:** 126–42.
12. Bultitude MI. Capsaicin in treatment of loin pain/haematuria syndrome. *Lancet* 1995; **345:** 921–2.
13. Uzoh CC, *et al*. The use of capsaicin in loin pain-haematuria syndrome. *BJU Int* 2009; **103:** 236–9.

Neuropathic pain. Capsaicin has been tried topically in various types of pain including neuropathic pain, which does not generally respond to conventional systemic analgesics. Topical capsaicin cream (in a usual strength of 0.075%) is used in the management of diabetic neuropathy (p. 8.2) and postherpetic neuralgia (p. 10.3). A high-concentration transdermal capsaicin patch 8% is also available for the treatment of peripheral neuropathic pain in non-diabetic patients. A systematic review[1] suggested that capsaicin, given as either a repeated dose of the cream or a single application of the patch, was of benefit in neuropathic pain, although limited data and inconsistent definition of outcomes meant that estimates of benefit and harm were not robust. Other types of pain syndrome for which capsaicin has been tried include reflex sympathetic dystrophy (see Complex Regional Pain Syndrome, p. 8.1), postmastectomy neuroma, amputation stump pain, chronic neck pain, and the pain of oral mucositis.[2]

See also Rheumatic Disorders, below, for use in musculoskeletal pain.

1. Derry S, *et al*. Topical capsaicin for chronic neuropathic pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 29/01/10).
2. Hautkappe M, *et al*. Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.

Pruritus. Substance P is a possible mediator of itch sensations and since capsaicin acts as a depletor of substance P it has been tried in the relief of pruritus (p. 1687.3) associated with various diseases and haemodialysis.[1-8] It has also been used to provide relief from pruritus induced by hetastarch[9] and for the itch and pain associated with PUVA therapy.[10,11] However, a systematic review[12] in 2010 considered that there was currently no convincing evidence that topical capsaicin was effective for the treatment of pruritus in any medical condition.

1. Breneman DL, *et al*. Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; **26:** 91–4.
2. Leibsohn E. Treatment of notalgia paresthetica with capsaicin. *Cutis* 1992; **49:** 335–6.
3. Hautmann G, *et al*. Aquagenic pruritus, PUVA and capsaicin treatments. *Br J Dermatol* 1994; **131:** 920–1.
4. Fölster-Holst R, Brasch J. Effect of topically applied capsaicin on pruritus in patients with atopic dermatitis. *J Dermatol Treat* 1996; **7:** 13–15.
5. Hautkappe M, *et al*. Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.
6. Ständer S, *et al*. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; **44:** 471–8.
7. Lysy J, *et al*. Topical capsaicin—a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut* 2003; **52:** 1323–6.
8. Makhlough A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. *Iran J Kidney Dis* 2010; **4:** 137–40.
9. Szeimies R-M, *et al*. Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994; **131:** 380–2.
10. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131:** 584–5.
11. Kirby B, Rogers S. Treatment of PUVA itch with capsaicin. *Br J Dermatol* 1997; **137:** 152.
12. Gooding SM, *et al*. Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol* 2010; **49:** 858–65.

Psoriasis. Since substance P has been implicated in the pathophysiology of several inflammatory dermatological processes, capsaicin, a substance P depletor, has been tried with some benefit in some skin disorders including psoriasis.[1-3]

The usual management of psoriasis is discussed on p. 1688.1.

1. Bernstein JE, *et al*. Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. *J Am Acad Dermatol* 1986; **15:** 504–7.
2. Ellis CN, *et al*. A double-blind evaluation of topical capsaicin in pruritic psoriasis. *J Am Acad Dermatol* 1993; **29:** 438–42.
3. Hautkappe M, *et al*. Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.

Rheumatic disorders. Topical capsaicin is used for the temporary relief of the pain of arthritis. From the results of a meta-analysis[1] of randomised, double-blind, placebo-controlled studies and later studies[2,3] it appears that capsaicin is effective in easing the pain of osteoarthritis (p. 12.3). Based on these results, the Arthritis Research Campaign in the UK[4] considered topical capsaicin to be safe and can be effective in reducing pain and tenderness in the affected joints. Published evidence[5] for efficacy in rheumatoid arthritis (p. 13.2) appears to be limited. A review of use in both neuropathic and musculoskeletal chronic pain concluded that its benefits were at best moderate, but noted that in a minority of patients unrespon-

sive to, or intolerant of, other treatments it might be useful.[6] Capsaicin may be a useful therapy for pain associated with primary fibromyalgia[4,7] (see Soft Tissue Rheumatism, p. 14.2), which responds poorly to conventional treatment.

1. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol* 1994; **46:** 517–22.
2. Altman RD, *et al*. Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 25–33.
3. McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *Eur J Pain* 2000; **4:** 355–60.
4. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 28/07/10)
5. Deal CL, *et al*. Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 1991; **13:** 383–95.
6. Mason L, *et al*. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328:** 991–4.
7. McCarty DJ, *et al*. Treatment of pain due to fibromyalgia with topical capsaicin: a pilot study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 41–7.

Adverse Effects

A warm, stinging, or burning sensation may occur at the site of application; this usually disappears after a few days of use but may persist for longer if applications are less frequent than recommended (see Uses and Administration, p. 35.1). This sensation may be particularly painful in patients receiving the high-concentration transdermal patches; in some cases, the treatment-related increase in pain has led to transient increases in blood pressure.

Coughing, sneezing, runny eyes, or other signs of irritation may occur if vapours or dried residue from topical preparations are inhaled. There have been a few reports of dyspnoea, wheezing, and exacerbation of asthma.

Precautions

Capsaicin should be handled with care. Particles should not be inhaled nor come into contact with any part of the body.

For topical application, contact with eyes and broken or irritated skin should be avoided. Thick applications of the *cream* should be avoided. The hands should be washed after application of the cream, unless the hands are the treated areas, in which case, they should be washed 30 minutes after application. If bandages are used to cover treated areas they should not be wound too tightly. Nitrile gloves should be worn when handling the high-concentration *transdermal patch* and when cleansing treatment areas; after careful removal of the patch, the cleansing gel supplied by the manufacturer should be applied liberally to the treatment area and left for at least 1 minute before wiping off and the area washed with soap and water. Heating pads should not be used with capsaicin, and patients should avoid taking a hot bath or shower immediately before or after application, as the burning sensation may be exacerbated.

Patients who develop increased pain with the high-concentration transdermal patch should be given supportive treatment such as local cooling or oral analgesics; however, those who are already taking high-dose opioid analgesics may not respond to oral opioids given for acute pain during and after the treatment procedure. Blood pressure should be monitored during the treatment procedure with transdermal patches.

Minor and temporary changes in sensory function such as heat detection have been reported with capsaicin; patients at risk from such effects should be cautious when using capsaicin.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies capsaicin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/07/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zostrix; ***Austria***: Hansaplast Warme-Creme; Qutenza; ***Belg.***: Hansamedic Warmtepleister; ***Braz.***: Moment; ***Canad.***: Rub A-535 Antiphlogistine Capsaicin; Zoderm; Zostrix; Zuacta; ***Chile***: Presyc; ***China***: Jin Lang (劲朗); Ou Tong (欧通); ***Cz.***: Qutenza; ***Denm.***: Qutenza; ***Fr.***: Qutenza; ***Ger.***: Qutenza; ***Gr.***: Arthralgon; Capser; Gelcen; Qutenza; Sensocaps; Zacin; ***India***: Capsain-P; ***Indon.***: Capzacin; ***Irl.***: Axsain; Qutenza; Zacin; ***Israel***: Zostrix; ***Ital.***: Cerotto Bertelli; Dolpyc; ***Malaysia***: Menzza NP; Menzza OA; ***Mex.***: Capsidol; ***Neth.***: Qutenza; ***Norw.***: Capsina; Qutenza; ***NZ***: Zostrix; ***Pol.***: Qutenza; ***Port.***: Hansaplast Emplastro Termico; Hansaterm; Qutenza; ***Singapore***: Menzza OA; Theragen; ***Spain***: Arafarmadol†; Capsicin; Capsicum Farmaya†; Capsidol; Gelcen†; Hansaterm; Picasum; Qutenza; Sensedol; ***Swed.***: Capsina; Qutenza; ***Switz.***: Isola Capsicum N; Qutenza; ***Thai.***: Capsika; ***UK***: Axsain; Qutenza; Zacin; ***USA***: Axsain; Capsin; Capzasin-HP; Capzasin-P; Doublecap†; No Pain-HP; Qutenza; R-Gel†; Rid-a-Pain HP; Theragen†; Zostrix.

Multi-ingredient Preparations. ***Arg.***: Atomo Desinflamante C; Rati Salil Crema; Rati Salil Flex; ***Canad.***: Menthacin; Rub A-535 Extra Strength Arthritis; Tiger Balm Patch Warm; ***Cz.***: Capsicolle; ***Fr.***: Capsaine; Capsic†; ***Gr.***: Ponostop; ***Hong Kong***: Salomethyl†; ***Hung.***: Inno Rheuma Forte; Nicoflex; Salonpas Liniment; ***India***: Accept; Acent; Alto; Arflur; Arthrill; Axane; Capsidol; Diclomax Power Gel; Diplofen; Diptase; Divexx; Dofec Plus; Dolowin; Mahadol; Myolaxin-D; Nam; Nelsid; Niclofen; Nimulid Nugel; Nise Gel; Onspot; Opinac; ***Indon.***: Flexozin; Nostren; ***Ital.***: Perfluxi Cremagel; Remystick; ***Pol.***: Capsigel N; Neo-Capsiderm; ***Rus.***: Nicoflex (Никофлекс); ***Switz.***: DUL-X warm; Isola Capsicum N Plus; ***UK***: NatraFlex; ***Ukr.***: Nizer (Найзер)†; ***USA***: Aspercreme Max; Bio-Therm Pain Relieving Lotion; Capzasin Quick Relief; Dendracin Neurodendtraxcin; Exoten-C; Gold Bond Foot Pain Relieving; Gold Bond Pain Relieving Foot Roll-On; Heet; Icy Hot PM; LidoPro; Medi-Derm; Medrox; Menthacin; New Terocin; Pain Doctor; Ultracin; Ziks; Zostrix Hot & Cold Therapy System.

Carbasalate Calcium *(BAN, rINN)*

Calcium Acetylsalicylate Carbamide; Calcium Carbaspirin; Carbasalat-Calcium; Carbasalate Calcique; Carbasalato cálcico; Carbasalatum Calcicum; Carbasalatum Calcium; Carbaspirin Calcium (USAN); Karbasalaattikalsium; Karbasalát vápenatá sůl; Karbasalatkalcium; Karbasalato kalcio druska; Karbaszalát-kálcium; Карбасалат Кальций.

Calcium bis[2-(acetoxy)benzoate]—urea.

$C_{19}H_{18}CaN_2O_9$=458.4

CAS — 5749-67-7.

ATC — 801AC08; N02BA15.

ATC Vet — QB01AC08; QN02BA15.

UNII — N667F17JP1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Carbasalate Calcium). A white or almost white, crystalline powder. It contains not less than 99.0% and not more than the equivalent of 101.0% of an equimolecular compound of calcium di[2-(acetyloxy)benzoate] and urea, calculated with reference to the anhydrous substance. Freely soluble in water and in dimethylformamide; practically insoluble in acetone and in anhydrous methyl alcohol. Store in airtight containers.

Uses and Administration

Carbasalate calcium is a 1:1 complex of calcium acetylsalicylate and urea. It is metabolised to aspirin after absorption and thus has the actions of aspirin (p. 22.3). Carbasalate calcium 100 mg is equivalent to about 78 mg of aspirin. Carbasalate calcium is given in oral doses equivalent to about 400 to 800 mg of aspirin every 4 to 8 hours up to a maximum of about 3 g daily for pain or fever. Carbasalate calcium has also been used in the management of thromboembolic disorders.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2.

Carbasalate calcium, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Effects on hearing. As of June 2006 the Netherlands Pharmacovigilance Centre[1] database contained 8 reports of tinnitus and 1 of ototoxicity associated with use of low oral doses of carbasalate calcium (38 or 100 mg usually once daily). The association between low-dose carbasalate calcium and tinnitus was considered to be disproportional.

1. Nederlands Bijwerkingen Centrum. Low dosage carbasalate calcium and tinnitus. Available at: http://www.lareb.nl/documents/kwb_2006_3_carbas.pdf (accessed 12/04/07)

Interactions

For interactions associated with aspirin, see p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Iromin; Vascal†; ***Irl.***: Ascal; ***Neth.***: Ascal; ***Port.***: Ascal; ***Switz.***: Alcacyl.

Multi-ingredient Preparations. ***Austria***: Irocopar c C†; Irocophan; Iromin Vitamin C; Iromin-Chinin-C†; ***Switz.***: Alca-C; ***Turk.***: Alca-C.

Carfentanil Citrate *(USAN, rINNM)* ⊗

Carfentanil, Citrate de; Carfentanili Citras; Carfentanilo, citrato de; Citrato de carfentanilo; R-33799; Карфентанила Цитрат.

Methyl 1-phenethyl-4-(*N*-phenylpropionamido)isonipecotate citrate.

$C_{24}H_{30}N_2O_3.C_6H_8O_7$=586.6

CAS — 59708-52-0 (carfentanil); 61380-27-6 (carfentanil citrate).

UNII — 7LG286J8GV.

Profile

Carfentanil citrate is an opioid analgesic related to fentanyl (p. 60.1). It is used in veterinary medicine.

Carprofen *(BAN, USAN, rINN)*

C-5720; Carprofène; Carprofeno; Carprofenum; Karprofeeni; Karprofen; Ro-20-5720/000; Карпрофен.

(±)-2-(6-Chlorocarbazol-2-yl)propionic acid.

$C_{15}H_{12}ClNO_2$=273.7

CAS — 53716-49-7.

ATC Vet — QM01AE91.

UNII — FFL0D546HO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Carprofen for Veterinary Use). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol; slightly soluble in isopropyl alcohol. It exhibits polymorphism. Protect from light.

USP 36: (Carprofen). A white crystalline powder. Practically insoluble in water; freely soluble in acetone, in ether, in ethyl acetate, and in solutions of sodium carbonate and of sodium hydroxide. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Carprofen, a propionic acid derivative, is an NSAID (p. 102.3) used in veterinary medicine.

Adverse effects. Pruritic, erythematous, eczematous eruptions have been seen in workers after occupational exposure to carprofen.[1,2] Patch testing showed a strong positive photoallergic reaction to carprofen.

1. Walker SL, *et al*. Occupational photoallergic contact dermatitis in a pharmaceutical worker manufacturing carprofen, a canine nonsteroidal anti-inflammatory drug. *Br J Dermatol* 2006; **154:** 569–70.
2. Kerr AC, *et al*. Occupational carprofen photoallergic contact dermatitis. *Br J Dermatol* 2008; **159:** 1303–8.

Preparations

Pharmacopoeial Preparations

USP 36: Carprofen Tablets.

Celecoxib *(BAN, USAN, rINN)*

Célécoxib; Celecoxibum; Celekoksyb; Celekoxib; SC-58635; Selekoksib; Selekoksibi; YM-177; Целекоксиб.

p-[5-*p*-Tolyl-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide.

$C_{17}H_{14}F_3N_3O_2S$=381.4

CAS — 169590-42-5.

ATC — L01XX33; M01AH01.

ATC Vet — QL01XX33; QM01AH01.

UNII — JCX84Q7J1L.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Celecoxib). A white or almost white, crystalline or amorphous powder. It shows polymorphism. Practically insoluble in water; freely soluble to soluble in dehydrated alcohol; soluble in dichloromethane.

USP 36: (Celecoxib). A white or almost white, crystalline or amorphous powder. Practically insoluble in water; soluble to freely soluble in alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light and moisture.

Uses and Administration

Celecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is licensed for the treatment of rheumatoid arthritis including juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis. In the USA, celecoxib is also licensed for use in the management of acute pain and dysmenorrhoea. Celecoxib has also been used as an adjunct to standard therapy to reduce the number of adenomatous colorectal polyps in patients with familial adenomatous polyposis (see p. 37.1).

For **osteoarthritis** the recommended oral dose is 200 mg daily given as a single dose or in 2 divided doses. If necessary a dose of 200 mg twice daily may be used. For **rheumatoid arthritis** the dose is 100 to 200 mg given twice daily. Celecoxib is also used for **ankylosing spondylitis** in an initial oral dose of 200 mg daily, as a single dose or in 2 divided doses. In the USA, the dose may be increased to 400 mg daily after 6 weeks, although if no

response is seen at this dose after a further 6 weeks, alternative treatments should be considered; a similar increase is also permitted in the UK. However, for all the above indications, UK licensed product information recommends that if ineffective, the higher dose should only be continued for 2 weeks before considering alternative treatments.

For doses in children with **juvenile idiopathic arthritis**, see below.

In the treatment of **pain** and **dysmenorrhoea**, an initial oral dose of 400 mg followed by an additional dose of 200 mg, if necessary, is recommended on the first day; thereafter the dose is 200 mg twice daily.

Reduced doses are recommended in patients with hepatic impairment (see below) and in those also taking fluconazole, a potent inhibitor of the cytochrome P450 isoenzyme CYP2C9 (see Interactions, p. 38.3). The dose of celecoxib should be reduced to half the lowest recommended dose in patients who are deficient in CYP2C9 and hence poor metabolisers of celecoxib.

Reviews.
1. Clemett D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; **59:** 957–80.
2. Frampton JE, Keating GM. Celecoxib: a review of its use in the management of arthritis and acute pain. *Drugs* 2007; **67:** 2433–72.

Administration in children. In the USA, celecoxib is licensed for the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral doses, based on body-weight, are:
- 10 to 25 kg: 50 mg twice daily
- over 25 kg: 100 mg twice daily

Licensed product information recommends that the contents of a celecoxib capsule may be sprinkled onto apple sauce if a patient has difficulty swallowing the capsules. The sprinkled capsule should be taken immediately; however, it remains stable at a temperature of between 2 degrees to 8 degrees for up to 6 hours.

Administration in hepatic impairment. Licensed product information recommends that doses of celecoxib should be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh category B); its use is contra-indicated in those with severe impairment (Child-Pugh category C or a score of 10 or more).

Familial adenomatous polyposis. Celecoxib has been used in the treatment of familial adenomatous polyposis, an inherited syndrome known to predispose sufferers to the development of colonic cancer. An early randomised study[1,2] found that treatment with celecoxib in an oral dose of 400 mg twice daily reduced the number of colonic polyps; the authors considered celecoxib to be a useful adjunct to the standard therapy of colectomy.

Marketing authorisations for the use of celecoxib as adjunctive treatment in familial adenomatous polyps were issued in the USA and the EU with the requirement that further data on safety and efficacy were provided; however, in 2011, the manufacturer, *Pfizer*, voluntarily withdrew this indication as it had been unable to fulfill this requirement due to slow enrolment into clinical studies.

1. Steinbach G, *et al*. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342:** 1946–52.
2. Phillips RKS, *et al*. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50:** 857–60.

Malignant neoplasms. Celecoxib is under investigation as adjuvant therapy in the treatment of cancer;[1-9] preliminary results have been variable. It has also been investigated for chemoprevention of malignancy[10-13] (see also Familial Adenomatous Polyposis, above), but a large study for the prevention of colon cancer was terminated early because of increased cardiovascular risk.[11,12]

1. Dang CT, *et al*. Phase II study of celecoxib and trastuzumab in metastatic breast cancer patients who have progressed after prior trastuzumab-based treatments. *Clin Cancer Res* 2004; **10:** 4062–7.
2. Reardon DA, *et al*. Phase II trial of irinotecan plus celecoxib in adults with recurrent malignant glioma. *Cancer* 2005; **103:** 329–38.
3. Nugent FW, *et al*. Docetaxel and cyclooxygenase-2 inhibition with celecoxib for advanced non-small cell lung cancer progressing after platinum-based chemotherapy: a multicenter phase II trial. *Lung Cancer* 2005; **48:** 267–73.
4. Gasparini G, *et al*. The combination of the selective cyclooxygenase-2 inhibitor celecoxib with weekly paclitaxel is a safe and active second-line therapy for non-small cell lung cancer: a phase II study with biological correlates. *Cancer J* 2005; **11:** 209–16.
5. Prince HM, *et al*. A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. *Clin Cancer Res* 2005; **11:** 5504–14.
6. Pan CX, *et al*. A phase II trial of irinotecan, 5-fluorouracil and leucovorin combined with celecoxib and glutamine as first-line therapy for advanced colorectal cancer. *Oncology* 2005; **69:** 63–70.
7. Csiki I, *et al*. Targeting cyclooxygenase-2 in recurrent non-small cell lung cancer: a phase II trial of celecoxib and docetaxel. *Clin Cancer Res* 2005; **11:** 6634–40.
8. Chow LWC, *et al*. Serum lipid profiles in patients receiving endocrine treatment for breast cancer—the results from the Celecoxib Anti-Aromatase Neoadjuvant (CAAN) Trial. *Biomed Pharmacother* 2005; **59** (suppl 2): S302–S305.
9. Ferrari V, *et al*. Gemcitabine plus celecoxib (GECO) in advanced pancreatic cancer: a phase II trial. *Cancer Chemother Pharmacol* 2006; **57:** 185–90.
10. Limburg PJ, *et al*. Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. *Gastroenterology* 2005; **129:** 863–73.
11. Solomon SD, *et al*. Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352:** 1071–80.
12. Bertagnolli MM, *et al*. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.
13. Arber N, *et al*. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.

Musculoskeletal and joint disorders. Celecoxib is used in the treatment of osteoarthritis (p. 12.3) and rheumatoid arthritis (p. 13.2) including juvenile idiopathic arthritis (p. 12.1). However, in the UK it is recommended that the use of celecoxib and other selective cyclo-oxygenase-2 (COX-2) inhibitors be limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Adverse Effects, below).

Celecoxib is also used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p. 14.3).

References.
1. Bensen WG, *et al*. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; **74:** 1095–1105.
2. Simon LS, *et al*. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–28.
3. Emery P, *et al*. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; **354:** 2106–11.
4. Dougados M, *et al*. Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* 200 1; **44:** 180–5.
5. Stengaard-Pedersen K, *et al*. Celecoxib 200 mg qd is efficacious in the management of osteoarthritis of the knee or hip regardless of the time of dosing. *Rheumatology (Oxford)* 2004; **43:** 592–5.
6. Schnitzer TJ, *et al*. VACT-1 and VACT-2 (Protocols 106 and 150) Study Groups. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee: a combined analysis of the VACT studies. *J Rheumatol* 2005; **32:** 1093–1105.
7. Singh G, *et al*. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am J Med* 2006; **119:** 255–66.
8. Barkhuizen A, *et al*. Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol* 2006; **33:** 1805–12.
9. Luyten FP, *et al*. A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip. *Ann Rheum Dis* 2007; **66:** 99–106.
10. Foeldvari I, *et al*. A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. *J Rheumatol* 2009; **36:** 174–82.

Palmar-plantar erythrodysesthesia syndrome. Celecoxib has been investigated in the treatment of capecitabine-induced hand-foot (palmar-plantar erythrodysesthesia) syndrome; for references, see under Adverse Effects and Precautions of Capecitabine, p. 758.3.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with celecoxib. Other hypersensitivity reactions, including anaphylaxis and angioedema, have also occurred. Celecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions have been seen in patients with a history of allergic reactions to sulfonamides and licensed product information contra-indicates the use of celecoxib in such patients (but see also Hypersensitivity, under Sulfamethoxazole, p. 367.3).

Celecoxib should not be used after coronary artery bypass surgery as there may be an increased risk of adverse effects such as myocardial infarction and stroke. It should be used with caution, if at all, in patients with a history of ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease; it should also be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. For further details, see Effects on the Cardiovascular System, below.

Therapy is contra-indicated in patients with moderate to severe heart failure (NYHA class II to IV), inflammatory bowel disease, and renal impairment associated with a creatinine clearance of less than 30 mL/minute. Celecoxib should also not be used in patients with severe hepatic impairment (Child-Pugh category C). Caution is recommended when using celecoxib in dehydrated patients; rehydration may be advisable before giving celecoxib.

Celecoxib treatment may need to be stopped if signs or symptoms of organ toxicity develop.

Poor metabolisers of celecoxib (see Pharmacokinetics, p. 38.3) may have an increased risk of adverse reactions.

Incidence of adverse effects. A prescription-event monitoring study[1] conducted after the introduction of celecoxib in England in May 2000 found that the most common adverse events reported were gastrointestinal effects including dyspepsia (4.7% of all events), abdominal pain (1.8%), nausea or vomiting (1.6%), and diarrhoea (1.4%). Rash (1.2%) was also common. Uncommon events included anaemia, cough, anxiety, hypertension, visual disturbances, and insomnia. Blood dyscrasias, gastrointestinal bleeds, myocardial infarction, heart failure, abnormal liver function tests, nephritis, confusion, hallucinations, serious skin disorders, anaphylaxis, and bronchospasm were rare.

1. Layton D, *et al*. Safety profile of celecoxib as used in general practice in England: results of a prescription-event monitoring study. *Eur J Clin Pharmacol* 2004; **60:** 489–501.

Breast feeding. No adverse effects were noted in 2 older infants (aged 17 and 22 months) whose mothers took celecoxib while breast feeding.[1] The authors of this report also measured celecoxib plasma concentrations in 2 other women; from these values, the average milk-to-plasma ratio was calculated to be 0.23 and infant exposure was estimated at about 0.3% of the weight-adjusted maternal dose. Similar values have also been estimated from a study of blood and milk concentrations of celecoxib in 6 women.[2] Nonetheless, UK licensed product information contra-indicates the use of celecoxib in breast-feeding women.

1. Hale TW, *et al*. Transfer of celecoxib into human milk. *J Hum Lact* 2004; **20:** 397–403.
2. Gardiner SJ, *et al*. Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol* 2006; **61:** 101–4.

Effects on the blood. Severe methaemoglobinaemia has been reported in an elderly patient after taking celecoxib for 1 month.[1]

1. Kaushik P, *et al*. Celecoxib-induced methemoglobinemia. *Ann Pharmacother* 2004; **38:** 1635–8.

Effects on the cardiovascular system. Prelicensing studies did not report any increased risk of serious cardiovascular effects in patients given celecoxib.[1,2] Nonetheless, by February 2001 the UK CSM had received a small number of reports[3] of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors. There were also 3 cases of *torsade de pointes* associated with celecoxib use.[4] Subsequently, in September 2004, the COX-2 inhibitor rofecoxib was generally withdrawn worldwide by the manufacturer after further reports of cardiovascular adverse effects (see p. 128.3) and this has prompted re-evaluation of the safety of other selective COX-2 inhibitors.

In December 2004 a large study of celecoxib for prevention of colon polyps (the APC study) was halted because of an increased risk of cardiovascular events (including death from cardiovascular causes, myocardial infarction, stroke, and heart failure) in patients receiving the drug compared with those receiving placebo.[5] The results of this long-term study suggested that there was a 2.8-fold increase in the risk of such events in patients taking either celecoxib 400 or 800 mg daily and that the increase was dose-related. The possibility of a dose-adverse effect relationship was supported by some at-the-time unpublished studies, the PreSAP and ADAPT studies, that showed no increase in the risk of cardiovascular effects with celecoxib 400 mg daily when compared with placebo.[6] These studies[7,8] have since been published and their finished reports were less reassuring than initially thought. The risk of serious cardiovascular events was found to be increased in the celecoxib group when compared with the placebo group although the difference was not significant. In addition, an update[9] of the original APC study confirmed that the risk of adverse cardiovascular events was significantly increased for both high-dose (800 mg daily) and low-dose (400 mg daily) celecoxib when compared with placebo treatment; however, high-dose treatment was associated with the greatest risk. Increases in blood pressure were also more likely with both celecoxib groups than with placebo. An analysis[10] using pooled data from 6 randomised placebo-controlled studies, including the APC, PreSap, and ADAPT studies, found the following relationship between dose and adverse cardiovascular effect, in descending order of risk: 400 mg twice daily (adjusted hazard ratio 3.1 times that of placebo), 200 mg twice daily (hazard ratio 1.8), and 400 mg once daily (hazard ratio 1.1). (The result for 400 mg once daily was not statistically significant.) There was also evidence to suggest that the adverse effect of dose is more pronounced in patients with higher baseline cardiovascular risk.

In 2005, based on the findings of studies available at the time, EU regulatory authorities[11-13] recommended that:
- selective COX-2 inhibitors should not be used in patients with established ischaemic heart disease or cerebrovascular disease; they are also contra-indicated in those with peripheral arterial disease

- patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes, and smoking should be carefully monitored if given selective COX-2 inhibitors
- all patients should be assessed individually on the risks and benefits of selective COX-2 inhibitor treatment, particularly cardiovascular and gastrointestinal risk factors, and alternative treatments considered

Similar advice has also been issued by the FDA;[14] however, the only absolute contra-indication is in the immediate postoperative period after coronary artery bypass surgery. (In the USA celecoxib is currently the only available selective COX-2 inhibitor.)

COX-2 inhibitors such as celecoxib do not possess the intrinsic antiplatelet activity associated with aspirin and possibly other non-selective NSAIDs and consequently do not provide protection against ischaemic cardiac events.[3,15]

1. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
2. White WB, *et al.* Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002; **89:** 425–30.
3. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
4. Pathak A, *et al.* Celecoxib-associated torsade de pointes. *Ann Pharmacother* 2002; **36:** 1290–1.
5. Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352:** 1071–80.
6. FDA. Celecoxib (marketed as Celebrex) (issued 7th April, 2005). Available at: http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf (accessed 01/11/07)
7. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.
8. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Available at: http://clinicaltrials.plosjournals.org/archive/1555-5887/1/7/pdf/10.1371_journal.pctr.0010033-L.pdf (accessed 01/11/07)
9. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.
10. Solomon SD, *et al.* Cross Trial Safety Assessment Group. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation* 2008; **117:** 2104–13.
11. MHRA. Updated advice on the safety of selective COX-2 inhibitors. Message from Professor G Duff, Chairman of CSM (issued 17th February, 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
12. EMEA. European Medicines Agency announces regulatory action on COX-2 inhibitors (issued 17th February, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/6275705en.pdf (accessed 29/08/08)
13. EMEA. European Medicines Agency concludes action on COX-2 inhibitors (issued 27th June, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/20776605en.pdf (accessed 01/11/07)
14. FDA. FDA issues public health advisory recommending limited use of cox-2 inhibitors: agency requires evaluation of prevention studies involving cox-2 selective agents. (issued 23rd December, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html (accessed 01/11/07)
15. Bing RJ, Lomnicka M. Why do cyclo-oxygenase-2 inhibitors cause cardiovascular events? *J Am Coll Cardiol* 2002; **39:** 521–2.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as celecoxib may cause less gastrotoxicity than the non-selective inhibition of the traditional NSAIDs.

Results from controlled studies suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a placebo-controlled study[1] the incidence of endoscopically determined gastroduodenal ulcers in patients taking celecoxib for rheumatoid arthritis (dose range 200 to 800 mg daily) was not significantly different to that seen with the placebo group. Another study[2] in patients taking celecoxib at supratherapeutic doses (800 mg daily) concluded that there was a lower combined incidence of symptomatic gastrointestinal ulcers and ulcer complications (bleeding, perforation, and obstruction) after 6 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or diclofenac 150 mg daily). However, the incidence of ulcer complications alone was not significantly different to that seen with other NSAIDs. A re-analysis of the study by the FDA, including both the 6-month and full-term data, also found that there was no significant reduction in the rate of ulcer complications with celecoxib compared with the non-selective NSAIDs although, in subjects not taking aspirin, there was a strong trend in favour of celecoxib compared with ibuprofen.[3] The risk of ulcer complications was also significantly increased in celecoxib users taking concomitant low-dose aspirin.[2] A later systematic review[4] of studies of patients receiving celecoxib or NSAIDs for at least 12 weeks claimed to show improved gastrointestinal safety and tolerability in those receiving celecoxib (including in patients also taking low-dose aspirin) but this has been criticised on grounds of data selection.[5,6]

It has been noted that the use of aspirin appears to nullify any potential protective effect of COX-2 selectivity by celecoxib.[7,8]

There have been individual case reports of gastrotoxicity with celecoxib.[9-11]

1. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–8.
2. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
3. FDA. Celebrex capsules (celecoxib) NDA 20-998/S009—Medical Officer Review. 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 01/11/07)
4. Deeks JJ, *et al.* Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002; **325:** 619–23.
5. Jüni P, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: problems compromise review's validity. *BMJ* 2003; **326:** 334.
6. Metcalfe S, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: celecoxib's relative gastrointestinal safety is overstated. *BMJ* 2003; **326:** 334–5.
7. Lichtenstein DR, Wolfe MM. COX-2-selective NSAIDs: new and improved? *JAMA* 2000; **284:** 1297–9.
8. Bates DE, Lemaire JB. Possible celecoxib-induced gastroduodenal ulceration. *Ann Pharmacother* 2001; **35:** 782–3.
9. Mohammed S, Croom DW. Gastropathy due to celecoxib, a cyclooxygenase-2 inhibitor. *N Engl J Med* 1999; **340:** 2005–6.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Celecoxib: early Australian reporting experience. *Aust Adverse Drug React Bull* 2000; **19:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0006.pdf (accessed 29/08/08)
11. Adverse Drug Reactions Advisory Committee (ADRAC). Serious gastrointestinal effects with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 01/11/07)

Effects on the kidneys. Increasing evidence suggests that selective cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib appear to have adverse effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Some references to the adverse renal effects of celecoxib.

1. Boyd IW, *et al.* COX-2 inhibitors and renal failure: the triple whammy revisited. *Med J Aust* 2000; **173:** 274.
2. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
3. Graham MG. Acute renal failure related to high-dose celecoxib. *Ann Intern Med* 2001; **135:** 69–70.
4. Alkhuja S, *et al.* Celecoxib-induced nonoliguric acute renal failure. *Ann Pharmacother* 2002; **36:** 52–4.
5. Ahmad SR, *et al.* Renal failure associated with the use of celecoxib and rofecoxib. *Drug Safety* 2002; **25:** 537–44.
6. Alper AB, *et al.* Nephrotic syndrome and interstitial nephritis associated with celecoxib. *Am J Kidney Dis* 2002; **40:** 1086–90.
7. Akhund L, *et al.* Celecoxib-related renal papillary necrosis. *Arch Intern Med* 2003; **163:** 114–15.
8. Markowitz GS, *et al.* Membranous glomerulopathy and acute interstitial nephritis following treatment with celecoxib. *Clin Nephrol* 2003; **59:** 137–42.
9. Brewster UC, Perazella MA. Acute tubulointerstitial nephritis associated with celecoxib. *Nephrol Dial Transplant* 2004; **19:** 1017–18.
10. Clifford TM, *et al.* Celecoxib-induced nephrotoxicity in a renal transplant recipient. *Pharmacotherapy* 2005; **25:** 773–7.
11. Tabibian JH, *et al.* Late-onset celecoxib-induced combined hepatonephrotoxicity. *Br J Clin Pharmacol* 2008; **66:** 150–1.

Effects on the liver. Cholestatic hepatitis developed in a 54-year-old woman taking celecoxib;[1] her liver function tests improved and her symptoms resolved after drug withdrawal. Despite the temporal relationship between celecoxib use and the onset of hepatotoxicity, the manufacturers stated that evidence available at that time did not support such a relationship.[2] However, other cases[3,4] have since been reported, including a case report[5] of late-onset hepatorenal toxicity where symptoms developed 10 months after starting therapy. Licensed product information now states that cases of severe hepatic reactions, including fulminant hepatitis (some fatal), liver necrosis, and hepatic failure (some fatal or requiring transplant), have been reported. Of the cases that reported time to onset, most of these reactions had developed within 1 month of starting celecoxib therapy. Patients with signs and/or symptoms suggesting hepatic dysfunction, or in whom an abnormal liver test has occurred, should be monitored closely; celecoxib therapy should be stopped if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur.

For a case of acute hepatitis with pancreatitis, see Pancreatitis, below.

1. O'Beirne JP, Cairns SR. Cholestatic hepatitis in association with celecoxib. *BMJ* 2001; **323:** 23.
2. Arellano FM, *et al.* Case of cholestatic hepatitis with celecoxib did not fulfil international criteria. *BMJ* 2002; **324:** 789–90.
3. Grieco A, *et al.* Acute cholestatic hepatitis associated with celecoxib. *Ann Pharmacother* 2002; **36:** 1887–9.
4. Chamouard P, *et al.* Prolonged cholestasis associated with short-term use of celecoxib. *Gastroenterol Clin Biol* 2005; **29:** 1286–8.
5. Tabibian JH, *et al.* Late-onset celecoxib-induced combined hepatonephrotoxicity. *Br J Clin Pharmacol* 2008; **66:** 150–1.

Effects on the lungs. Report of a case of pulmonary oedema and possible pneumonitis in a patient taking celecoxib.[1]

1. Olin JL, *et al.* Pulmonary edema and possible pneumonitis associated with celecoxib. *Ann Pharmacother* 2004; **38:** 1086.

Effects on the nervous system. Acute neuropsychiatric reactions such as confusion, somnolence, and insomnia, have occurred after celecoxib use.[1] There has also been a case report of aseptic meningitis.[2]

1. Adverse Drug Reations Advisory Committee (ADRAC). Acute neuropsychiatric events with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 01/11/07)
2. Papaioannides DH, *et al.* Aseptic meningitis possibly associated with celecoxib. *Ann Pharmacother* 2004; **38:** 172.

Hypersensitivity. A 52-year-old man developed allergic vasculitis after 8 days of treatment with celecoxib.[1] Despite intensive treatment the patient died from multiple organ failure and diffuse cutaneous necrolysis. The authors noted that potentially fatal skin reactions have occurred with other sulfa-containing drugs, although there is some evidence[2] suggesting that the potential for cross-reactivity in patients sensitive to sulfonamides is relatively low (see also p. 367.3) nonetheless, licensed product information contra-indicates the use of celecoxib in such patients.

1. Schneider F, *et al.* Fatal allergic vasculitis associated with celecoxib. *Lancet* 2002; **359:** 852–3.
2. Shapiro LE, *et al.* Safety of celecoxib in individuals allergic to sulfonamide: a pilot study. *Drug Safety* 2003; **26:** 187–95.

Pancreatitis. Acute hepatitis and pancreatitis developed in an elderly patient with a reported history of hypersensitivity to sulfonamides who was given celecoxib.[1] Symptoms resolved on stopping the drug. Pancreatitis has also been reported in a sulfonamide-tolerant patient.[2]

Celecoxib was one of the more commonly implicated drugs cited in case reports of drug-induced pancreatitis received by the Adverse Drug Reactions Advisory Committee in Australia.[3]

1. Carrillo-Jimenez R, Nurnberger M. Celecoxib-induced acute pancreatitis and hepatitis: a case report. *Arch Intern Med* 2000; **160:** 553–4.
2. Baciewicz AM, *et al.* Acute pancreatitis associated with celecoxib. *Ann Intern Med* 2000; **132:** 680.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 01/11/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies celecoxib as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

The metabolism of celecoxib is mediated mainly by the cytochrome P450 isoenzyme CYP2C9. Use with other drugs that inhibit or induce or are metabolised by this isoenzyme may result in changes in plasma concentration of celecoxib; fluconazole has increased plasma concentrations of celecoxib and UK licensed product information recommends that the dose of celecoxib should be halved when given with fluconazole.

Celecoxib is an inhibitor of the isoenzyme CYP2D6 and the potential therefore exists for an effect on drugs metabolised by this enzyme.

For interactions associated with NSAIDs in general, see p. 107.3.

Pharmacokinetics

Celecoxib is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 3 hours. Protein binding is about 97%. Celecoxib is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; the three identified metabolites are inactive as inhibitors of cyclo-oxygenase-1 (COX-1) or COX-2 enzymes. It is eliminated mainly as metabolites in the faeces and urine; less than 3% is recovered as unchanged drug. The effective terminal half-life is about 11 hours. Celecoxib is distributed into breast milk. The pharmacokinetics of celecoxib may vary in different ethnic groups; it has been stated that the area under the concentration-time curve is elevated in patients of Afro-Caribbean origin, although any clinical significance is unclear.

References.

1. Davies NM, *et al.* Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2000; **38:** 225–42.
2. Stempak D, *et al.* Single-dose and steady-state pharmacokinetics of celecoxib in children. *Clin Pharmacol Ther* 2002; **72:** 490–7. Correction. *ibid.* 2006; **80:** 667.

3. Kirchheiner J, *et al.* Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* 2003; **13:** 473–80.
4. Lundblad MS, *et al.* Accumulation of celecoxib with a 7-fold higher drug exposure in individuals homozygous for CYP2C9*3. *Clin Pharmacol Ther* 2006; **79:** 287–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Algybrex†; Celebrex; Coxtenk; Radicacine; ***Austral.***: Celebrex; ***Austria***: Celebrex; Onsenal†; ***Belg.***: Celebrex; Onsenal†; ***Braz.***: Celebra; ***Canad.***: Celebrex; ***Chile***: Celebra; ***China***: Celebrex (西乐葆); ***Cz.***: Celebrex; Onsenal†; ***Denm.***: Celebra; Celebrex; Onsenal†; ***Fin.***: Celebra; ***Fr.***: Celebrex; Onsenal†; ***Ger.***: Celebrex; Onsenal†; ***Gr.***: Aclarex; Celebrex; ***Hong Kong***: Celebrex; ***Hung.***: Celebrex; ***India***: CE; Celact; Celcib; Celcox; Celecap; Celedol; Celemax; Celetop; Celib†; Cobix; Colcibra; Coxib; Eloxib; Icel; Orthocel; Zycel; ***Indon.***: Celebrex; ***Irl.***: Celebrex; Onsenal†; ***Israel***: Celcox; Celebra; ***Ital.***: Artilog; Celebrex; ***Malaysia***: Celebrex; ***Mex.***: Celebrex; ***Neth.***: Celebrex; Onsenal†; ***Norw.***: Celebra; ***NZ***: Celebrex; ***Philipp.***: Aubrex; Celcoxx; Celebrex; Celexib; Coxbitor; Coxoral; Coxzan; Dolcelox; Euroflam; Flamar; Lexib; Lincox; ***Pol.***: Celebrex; ***Port.***: Celebrex; Onsenal†; Solexa; ***Rus.***: Celebrex (Целебрекс); ***S.Afr.***: Celebrex; ***Singapore***: Celebrex; ***Spain***: Artilog; Celebrex; Onsenal†; ***Swed.***: Celebra; Onsenal†; ***Switz.***: Celebrex; ***Thai.***: Celebrex; ***Turk.***: Celebrex; ***UK***: Celebrex; Onsenal†; ***Ukr.***: Celebrex (Целебрекс); Flogoxib (Флогоксиб); Ranselex (Ранселекс); Reumoxib (Ревмоксиб); ***USA***: Celebrex; ***Venez.***: Cexb.

Certolizumab Pegol *(BAN, USAN, rINN)*

CDP-870; Certolizumab Pégol; Certolizumabum Pegolum; PHA-738144; Цертолизумаб Пегол.
CAS — 428863-50-7.
ATC — L04AB05.
ATC Vet — QL04AB05.
UNII — UMD07X179E.

Uses and Administration

Certolizumab pegol is a pegylated TNF antibody fragment that binds specifically to TNFα and neutralises membrane-associated and soluble human TNFα in a dose-dependent manner. It also inhibits the production of lipopolysaccharide-induced TNFα and interleukin-1β (IL-1β). Elevated levels of TNF and IL-1 have been found in the affected tissues and fluids of patients with rheumatoid arthritis (p. 13.2), ankylosing spondylitis including axial spondyloarthritis, and psoriatic arthritis (see Spondyloarthropathies, p. 14.3), and Crohn's disease (see Inflammatory Bowel Disease, p. 1811.3). Certolizumab pegol is described as a biological disease-modifying antirheumatic drug (DMARD).

Certolizumab pegol is used in the treatment of moderate to severe, active **rheumatoid arthritis** and active **psoriatic arthritis**. In the treatment of rheumatoid arthritis, UK licensed product information recommends that certolizumab pegol should be given with methotrexate to patients who have had an inadequate response to DMARDs, although monotherapy may be used in those who have had an inadequate response to, or are intolerant of, methotrexate. Certolizumab pegol is also used in the treatment of active **ankylosing spondylitis**: UK licensed product information recommends that it should only be used in patients with severe disease who have had an inadequate response to, or are intolerant of, NSAIDs. In the UK, it is also licensed for the treatment of severe **axial spondyloarthritis** without radiographic evidence of ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of, NSAIDs. Certolizumab pegol is used in the treatment of moderate to severe, active **Crohn's disease** unresponsive to conventional treatment. For all the above indications, the initial dose is 400 mg given as two subcutaneous injections of 200 mg, repeated after 2 and 4 weeks. In the treatment of inflammatory joint disorders, this is followed by 200 mg every other week although maintenance with 400 mg every 4 weeks may be considered. Patients with Crohn's disease who have a clinical response may receive a maintenance dose of 400 mg every 4 weeks.

References.
1. Sandborn WJ, *et al.* PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357:** 228–38.
2. Schreiber S, *et al.* PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357:** 239–50. Correction. *ibid.*: 1357.
3. Keystone E, *et al.* Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008; **58:** 3319–29.
4. Fleischmann R, *et al.* Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis* 2009; **68:** 805–11.
5. Smolen J, *et al.* Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009; **68:** 797–804.
6. Shao LM, *et al.* Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. *Aliment Pharmacol Ther* 2009; **29:** 605–14.
7. Smith LS, *et al.* Certolizumab pegol: a TNF-α antagonist for the treatment of moderate-to-severe Crohn's disease. *Ann Pharmacother* 2010; **44:** 333–42.
8. Evans AT, Lee SD. A review and expert opinion of the use of certolizumab for Crohn's disease. *Expert Opin Biol Ther* 2012; **12:** 363–70.
9. Deeks ED. Certolizumab pegol: a review of its use in the management of rheumatoid arthritis. *Drugs* 2013; **73:** 75–97.
10. Keystone E, *et al.* Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. *Ann Rheum Dis* 2013. Available at: doi:10.1136/annrheumdis-2013-203695
11. Song IH, Rudwaleit M. Certolizumab pegol in axial spondyloarthritis. *Expert Rev Clin Immunol* 2013; **9:** 1161–72.
12. Mease PJ, *et al.* Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomisedplacebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; **73:** 48–55.
13. Landewé R, *et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014; **73:** 39–47.

Adverse Effects and Precautions

As for Infliximab, p. 75.3.

References.
1. Bykerk VP, *et al.* Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Ann Rheum Dis* 2013. Available at: doi:10.1136/annrheumdis-2013-203660

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies certolizumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Studies in *animals* have not shown harm to the fetus when certolizumab is given during pregnancy. There are few human data, although one case report in a woman with Crohn's disease who received 2 doses of certolizumab during pregnancy (one during the first, and one during the third trimester) reported normal growth and development of the child up to 1 month of age. Genital bleeding due to retention of part of the placenta occurred 9 weeks after the second dose of certolizumab.[1]

1. Oussalah A, *et al.* Certolizumab use in pregnancy. *Gut* 2009; **58:** 608.

Interactions

As for Infliximab, p. 77.3

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cimzia; ***Austria***: Cimzia; ***Belg.***: Cimzia; ***Canad.***: Cimzia; ***Cz.***: Cimzia; ***Denm.***: Cimzia; ***Fr.***: Cimzia; ***Ger.***: Cimzia; ***Gr.***: Cimzia; ***Irl.***: Cimzia; ***Jpn***: Cimzia; ***Neth.***: Cimzia; ***Norw.***: Cimzia; ***Pol.***: Cimzia; ***Port.***: Cimzia; ***Spain***: Cimzia; ***Swed.***: Cimzia; ***Switz.***: Cimzia; ***UK***: Cimzia; ***USA***: Cimzia.

Choline Magnesium Trisalicylate

Trisalicilato de colina y magnesio; Холин Магнезиум Трисалицилаты.
$C_{26}H_{29}O_{10}NMg$=539.8
CAS — 64425-90-7.
UNII — DJJ95FJP1H.

Profile

Choline magnesium trisalicylate is a combination of the salicylic acid derivatives choline salicylate (below) and magnesium salicylate (p. 85.2). It has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p. 22.3). After oral administration, choline magnesium trisalicylate dissociates and the salicylate moiety is rapidly absorbed. Each unit dose of 500 mg of salicylate is provided by about 293 mg of choline salicylate with 362 mg of magnesium salicylate (anhydrous). Choline magnesium trisalicylate has been used in osteoarthritis, rheumatoid arthritis, and other arthritides; it has also been used in the general management of other forms of pain and fever.

Choline Salicylate *(BAN, USAN, rINN)*

Choline, Salicylate de; Cholini Salicylas; Koliinisalisylaatti; Kolinsalicylat; Salicilato de colina; Холина Салицилат.
(2-Hydroxyethyl)trimethylammonium salicylate.
$C_{12}H_{19}NO_4$=241.3
CAS — 2016-36-6.
ATC — N02BA03.
ATC Vet — QN02BA03.
UNII — KD510K1IQW.

Pharmacopoeias.

Br. includes a solution.

BP 2014: (Choline Salicylate Solution). An aqueous solution containing 47.5 to 52.5% of choline salicylate. It is a clear colourless liquid. It may contain a suitable antimicrobial preservative.

Profile

Choline salicylate is a salicylic acid derivative (see Aspirin, p. 22.2) used in the treatment of pain and fever, and in the management of rheumatic disorders. In terms of salicylate content, choline salicylate 435 mg is equivalent to about 325 mg of aspirin. Choline salicylate is given orally in doses of 435 to 870 mg every four hours as necessary for pain and fever, and in doses of 4.8 to 7.2 g daily in divided doses for rheumatic disorders.

Choline salicylate is also used as a local analgesic. Solutions containing up to about 20% choline salicylate are used in ear disorders such as the relief of pain in otitis media and externa but are considered to be of doubtful value; they are also used to soften ear wax as an aid to removal (see p. 1839.3). An 8.7% gel is used for lesions of the mouth (p. 1814.2). Choline salicylate has also been applied topically in a rubefacient preparation for the relief of muscular and rheumatic pain.

Choline salicylate is also given in the form of choline magnesium trisalicylate (see above).

Adverse effects and precautions. A 21-month-old boy developed salicylate poisoning after his mother had rubbed the contents of 3 tubes of *Bonjela* teething ointment (containing a total of 2.61 g of choline salicylate) on his gums over 48 hours.[1]

In another case, an 8-year-old boy with G6PD deficiency developed an oral mucosal burn a few hours after application of about half a tube of *Teejel* oral gel.[2] He developed mouth ulcers and displayed signs of apathy, lethargy, and nasal congestion 3 days after exposure. His condition improved after a week. The authors felt that G6PD deficiency may have been a contributing factor in the occurrence of adverse effects.

In the UK, the MHRA contra-indicates the use of topical oral pain relief preparations containing salicylates in children under 16 years of age (for details, see Reye's Syndrome, below).

1. Paynter AS, Alexander FW. Salicylate intoxication caused by teething ointment. *Lancet* 1979; **ii:** 1132.
2. Sapir S, Bimstein E. Cholinsalicylate gel induced oral lesion: report of case. *J Clin Pediatr Dent* 2000; **24:** 103–6.

REYE'S SYNDROME. The link between aspirin use in children and the development of Reye's syndrome is well recognised although a causal relationship remains to be established and the evidence for other salicylates could not be adequately evaluated (see p. 25.3). However, a 20-month-old boy who had received a teething gel containing choline salicylate (applied in doses of 1.31 g daily, equivalent to acetylsalicylate 100 mg/kg daily, which exceeds the recommended dose) developed Reye's syndrome following a viral illness.[1] The authors noted that the MHRA in the UK were aware of two earlier reports suggesting an association between choline salicylate and Reye's syndrome. As of April 2009, the MHRA[2] had received 3 such reports in which all 3 children were hospitalised but Reye's syndrome was not confirmed in any of them; in addition, 4 reports of vomiting or diarrhoea after the use of choline salicylate oral gel had been received. Consequently, the MHRA contra-indicated the use of topical oral pain relief preparations containing salicylates in children under 16 years of age due to the theoretical risk of Reye's syndrome.

1. Oman TK, *et al.* Topical choline salicylates implicated in Reye's syndrome. *BMJ* 2008; **336:** 1376.
2. MHRA. Press release: new advice on oral salicylate gels in under 16s (issued 23rd April, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON044014 (accessed 24/04/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dercolina; ***Austral.***: Applicaine†; Herron Baby Teething Gel; Ora-Sed Jel; ***Austria***: Mundisal; ***Cz.***: Mundisal; ***Hong Kong***: Ora-Sed; ***India***: Gelora; Oraflora Gel; Zytee; ***Irl.***: Audax; ***Malaysia***: Ora-Sed; ***NZ***: Ora-Sed; ***Pol.***: Cholinex; Otinum; ***Port.***: Bucagel; ***Rus.***: Mundisal (Мундизал); Otinum (Отинум); ***Singapore***: Ora-Sed; ***Switz.***: Mundisal; ***Turk.***: Dencol; ***Ukr.***: Faringin (Фарингин); Otinum (Отинум).

Multi-ingredient Preparations. ***Arg.***: Pansoral; ***Austral.***: Bonjela; Sedagel; ***Belg.***: Givalex; Teejel; ***Fr.***: Givalex; Pansoral; ***Gr.***: Mundisal; ***Hong Kong***: Bonjela; Dermojela; Oris-gel†; ***Hung.***: Mundisal; ***India***: Bonzela; Clenora; Clenorush; Dentogel; Dentra; Dologel-CT; Dologel; Nitra-Dent; Ora-G; Ora-Sore; Orasia; Orawin; Orex-Lo; Orex; ***Irl.***: Bonjela; Teejel†; ***Israel***: Baby

Gum; Bonjela†; Teejel; ***Malaysia***: Bonjela; Orregel; ***NZ***: Bonjela; ***Pol.***: Sachol zel Stomatologiczny; ***Rus.***: Cholisal (Холисал); Dologel (Дологель); Pansoral (Пансорал); ***S.Afr.***: Bonjela; ***Singapore***: Bonjela; Soragel; ***Switz.***: Pansoral†; Tenderdol; ***Thai.***: Bonjela; ***UK***: Bonjela Cool Mint; Bonjela; Earex Plus†; ***Ukr.***: Angilex (Ангилекс); Cholisal (Холисал); Givalex (Гивалекс); Heppylor (Хепилор).

Pharmacopoeial Preparations
BP 2014: Choline Salicylate Ear Drops; Choline Salicylate Oromucosal Gel.

Clofexamide *(rINN)*

ANP-246; Clofexamida; Clofexamidum; Клофексамид.
2-(4-Chlorophenoxy)-*N*-(2-diethylaminoethyl)acetamide.
$C_{14}H_{21}ClN_2O_2$=284.8
CAS — 1223-36-5.
UNII — 071P4J77HF.

Profile

Clofexamide has been used topically as the hydrochloride in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clofezone *(rINN)*

ANP-3260; Clofezona; Clofézone; Clofezonum; Клофезон.
An equimolar combination of clofexamide and phenylbutazone.
$C_{14}H_{21}ClN_2O_2$,$C_{19}H_{20}N_2O_2$,$2H_2O$=629.2
CAS — 60104-29-2.
ATC — M01AA05; M02AA03.
ATC Vet — QM01AA05; QM02AA03.
UNII — TPT3MH65LD.

Profile

Clofezone, a combination molecule containing clofexamide (above) and phenylbutazone (p. 125.1), has been given orally and by rectal suppository and applied topically in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clonixin *(USAN, rINN)*

CBA-93626; Clonixine; Clonixino; Clonixinum; Sch-10304; Клониксин.
2-(3-Chloro-*o*-toluidino)nicotinic acid.
$C_{13}H_{11}ClN_2O_2$=262.7
CAS — 17737-65-4.
UNII — V7DXN0M42R.

Clonixin Lysine *(rINNM)*

Clonixin Lysinate; Clonixine Lysine; Clonixino lisina; Clonixinum Lysinum; L-104; Lysine Clonixinate; R-173; Клониксина Лизин.
$C_{13}H_{11}ClN_2O_2$, $C_6H_{14}N_2O_2$=408.9
CAS — 55837-30-4.
UNII — 06PW4M190R.

Profile

Clonixin is an NSAID (p. 102.3). It has been used as the lysine salt in oral doses of up to 250 mg four times daily for the relief of pain. Clonixin lysine has also been given by intramuscular or intravenous injection and as a rectal suppository.

References.
1. Eberhardt R, *et al.* Analgesic efficacy and tolerability of lysine-clonixinate versus ibuprofen in patients with gonarthrosis. *Curr Ther Res* 1995; **56**: 573–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clonixil; Diclen; Dolex; Dorixina; Lazalgena; ***Braz.***: Dolamin; ***Chile***: Adoplan; Blonax; Celex; Clonalgin; Colmax; Dentagesic; Diminon†; Lafigesic; Medigesic; Nefersil; Traumicid†; ***Mex.***: Disinal; Donodol; Dorixina; Firac; Lixitin; Lonixer; Prestodol; Sedepron; ***Port.***: Algimate; Clonix; ***Spain***: Dolalgial; ***Venez.***: Dorixina.

Multi-ingredient Preparations. ***Arg.***: Amplibenzatin Bronquial; Antispasmina Compuesto; Becebuen Compuesto; Dorixina B1 B6 B12; Dorixina Forte; Dorixina Relax; Espasmo Dolex; Migra Dorixina; Mikesan; Nova Paratropina Compositum; Propalgin; Sertal Compuesto; ***Braz.***: Dolamin Flex; ***Chile***: Clonalgin Compuesto; Ergonef; Migra-Nefersil; Nefersil B; Neurocam; ***Mex.***: Doltrix; Donodol Compuesto; Dorixina Relax; Espacil Compuesto; Firac Plus; Klonaza; Optium; Plidan Compuesto; Prestodol Compuesto; Prestoflam; Yuredol; ***Venez.***: Dologinex; Dorixina Flex; Migradorixina; Plidan Compuesto.

Codeine *(BAN)*

Codein; Codeína; Codéine; Codeinum; Codeinum Monohydricum; Kodeiini; Kodein; Kodein monohydrát; Kodeina; Kodeinas; Methylmorphine; Metilmorfina; Morphine Methyl Ether; Кодеин.
7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol monohydrate.
$C_{18}H_{21}NO_3,H_2O$=317.4
CAS — 76-57-3 (anhydrous codeine); 6059-47-8 (codeine monohydrate).
ATC — R05DA04.
ATC Vet — QR05DA04.
UNII — Q830PW7520.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of codeine:

AC/DC; Barr; Captain Cody; Cody; Coties; Cough Syrup; Down; Karo; Lean; Nods; School boy; Schoolboy; T3.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Codeine). White or almost white, crystalline powder or colourless crystals. Soluble in boiling water; freely soluble in alcohol. Protect from light.

USP 36: (Codeine). Colourless or white crystals or white crystalline powder. It effloresces slowly in dry air. Soluble 1 in 120 of water, 1 in 2 of alcohol, 1 in 0.5 of chloroform, and 1 in 50 of ether. Its saturated solution in water is alkaline to litmus. Store in airtight containers. Protect from light.

Codeine Hydrochloride *(BANM)*

Codeína, hidrocloruro de; Codéine (chlorhydrate de) dihydraté; Codeini Hydrochloridum Dihydricum; Kodeiinihydroklorididihydraatti; Kodein-hidroklorid-dihidrát; Kodeinhydrochlorid dihydrát; Kodeinhydrokloriddihydrat; Kodeino hidrochloridas dihidratas; Кодеина Гидрохлорид.
$C_{18}H_{21}NO_3,HCl,2H_2O$=371.9
CAS — 1422-07-7 (anhydrous codeine hydrochloride).
UNII — NTZ53GG7XN.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Codeine Hydrochloride Dihydrate; Codeine Hydrochloride BP 2014). Small colourless crystals or a white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. Protect from light.

Codeine Phosphate *(BANM)*

Codeína, fosfato de; Codéine, phosphate de; Codeine Phosphate Hemihydrate; Codeini Phosphas; Codeini Phosphas Hemihydricus; Codeinii Phosphas; Codeinphosphat-Hemihydrat; Kodeiinifosfaatti; Kodein-fosfát hemihydrát; Kodeinfosfathemi; Kodein-foszfát-hemihidrát; Kodeino fosfatas hemihidratas; Kodeiny fosforan; Kodeiny fosforan półwodny; Methylmorphine Phosphate; Кодеина Фосфат.
$C_{18}H_{21}NO_3,H_3PO_4,½H_2O$=406.4
CAS — 52-28-8 (anhydrous codeine phosphate); 41444-62-6 (codeine phosphate hemihydrate); 5913-76-8 (codeine phosphate sesquihydrate).
UNII — GSL05Y1MN6 (codeine phosphate hemihydrate); 2X585M1M3T (anhydrous codeine phosphate).

NOTE. Compounded preparations of codeine phosphate may be represented by the following names:
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—codeine phosphate and paracetamol
- Co-codaprin (*BAN*)—codeine phosphate 1 part and aspirin 50 parts (w/w)
- Co-codaprin (*PEN*)—codeine phosphate and aspirin.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Pharmacopoeias may specify the hemihydrate, sesquihydrate, or both, either under one monograph or as separate monographs.

Ph. Eur. 8: (Codeine Phosphate Hemihydrate; Codeine Phosphate BP 2014). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble or very slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

Ph. Eur. 8: (Codeine Phosphate Sesquihydrate; Codeini Phosphas Sesquihydricus). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Codeine Phosphate). The hemihydrate occurs as fine, white, needle-shaped crystals or white crystalline powder; odourless. Soluble 1 in 2.5 of water, 1 in 0.5 of water at 80 degrees, 1 in 325 of alcohol, and 1 in 125 of boiling alcohol. Its solutions are acid to litmus. Store in airtight containers at a temperature up to 40 degrees as permitted by the manufacturer. Protect from light.

Incompatibility. Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two drugs, even at a low moisture level.[1] *Animal* work suggested that the analgesic activity of codeine was not affected by acetylation.[2]

1. Galante RN, *et al.* Solid-state acetylation of codeine phosphate by aspirin. *J Pharm Sci* 1979; **68**: 1494–8.
2. Buckett WR, *et al.* The analgesic properties of some 14-substituted derivatives of codeine and codeinone. *J Pharm Pharmacol* 1964; **16**: 174–82.

Codeine Sulfate *(BANM)*

Codeína, sulfato de; Codeine Sulphate; Кодеина Сульфат.
$(C_{18}H_{21}NO_3)_2,H_2SO_4,3H_2O$=750.9
CAS — 1420-53-7 (anhydrous codeine sulfate); 6854-40-6 (codeine sulfate trihydrate).
UNII — 11QV9BS0CB.

Pharmacopoeias. In *US.*

USP 36: (Codeine Sulfate). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 30 of water, 1 in 6.5 of water at 80 degrees, and 1 in 1300 of alcohol; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Codeine sulfate solutions appear to be intrinsically more stable than codeine phosphate solutions.[1]

1. Powell MF. Enhanced stability of codeine sulfate: effect of pH, buffer, and temperature on the degradation of codeine in aqueous solution. *J Pharm Sci* 1986; **75**: 901–3.

Uses and Administration

Codeine, a phenanthrene derivative, is an opioid analgesic (p. 108.1) obtained from opium or made by methylating morphine. It is much less potent as an analgesic than morphine and has relatively mild sedative effects.

Codeine or its salts, especially the phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. The phosphate is also given by intramuscular injection, in doses similar to those used orally, for the relief of pain; the intravenous, subcutaneous, and rectal routes have also been used.

For the relief of **pain** codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive **cough** codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of **acute diarrhoea** in doses of 15 to 60 mg given 3 or 4 times daily.

For details of doses in children, see below.

Other codeine salts used include the hydrochloride, sulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Administration in children. In the UK, the use of codeine is restricted to the short-term treatment of acute, moderate *pain* in children over 12 years of age who do not respond to other analgesics such as paracetamol or ibuprofen (for further details, see Genetic Polymorphism, p. 41.3). The recommended oral dose is 30 to 60 mg (or 0.5 to 1 mg/kg) of codeine phosphate given every 6 hours when necessary, up to the usual adult maximum dose of 240 mg daily; the duration of treatment should not exceed 3 days. The *BNFC* suggests that this dose may also be given by intramuscular injection. Guidelines[1] for analgesia in children in Accident and Emergency departments in the UK recommend the use of oral codeine as an alternative, or in addition, to diclofenac, for moderate pain such as that associated with small burns or scalds, finger tip injuries, forearm, elbow, or ankle fracture, or appendicitis. Case reports of adverse reactions such as vasodilatation, severe hypotension, and apnoea in infants and children after intravenous doses of codeine have precluded its use by this route in children of all ages.[2]

Antimotility drugs such as codeine should not be used in infants and young children with acute *diarrhoea*.[3,4] Those aged over 12 years may be given the usual adult dose of codeine phosphate for this indication (see above).

The MHRA advises that over-the-counter *cough* and *cold* preparations containing codeine should not be used in those aged under 18 years (for details, see Cough, p. 41.1). However, codeine phosphate is licensed to allay

non-productive cough in children over 12 years of age; the usual adult dose for this indication (see p. 40.3) may be given.

1. The College of Emergency Medicine. Best practice guideline: management of pain in children (issued July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)
2. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; **79:** 787–95.
3. Anonymous. Drugs in the management of acute diarrhoea in infants and young children. *Bull WHO* 1989; **67:** 94–6.
4. Cimolai N, Carter JE. Antimotility agents for paediatric use. *Lancet* 1990; **336:** 874.

Administration in renal impairment. See under Precautions, p. 42.1.

Cough. A systematic review[1] of over-the-counter (OTC) preparations for acute cough (p. 1651.2) concluded that codeine appeared no more effective than placebo in reducing cough symptoms in adults or children, although the number of patients in the studies considered was small. More recently, in October 2010, the MHRA[2] advised that OTC cough and cold preparations containing codeine should not be used in those aged under 18 years. The review they had conducted also found a lack of robust evidence of its efficacy in the symptomatic treatment of cough in children of any age. Safety concerns over its central mode of action, significant variability in its metabolism to morphine, and possible abuse and dependence in adolescents were considered to outweigh the possible benefits of such use.

1. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 26/06/08).
2. MHRA. Oral liquid cough medicines containing codeine: should not be used in children and young people under 18 years (issued 11th October, 2010). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON096796 (accessed 25/01/11) See also: MHRA. Public Assessment Report. Oral liquid cough medicines containing codeine: should not be used in children and young people under 18 years (issued October 2010). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON096798&RevisionSelectionMethod=Latest (accessed 25/01/11)

Pain. Systematic reviews[1,2] comparing paracetamol-codeine combinations versus paracetamol alone concluded that in single-dose studies addition of codeine to paracetamol produced a comparatively small but statistically significant increase in analgesic effect; however, there was an increased incidence of adverse effects with the combination. Another systematic review[3] of analgesic use in moderate to severe postoperative pain found that single oral doses of codeine alone provided low levels of clinically useful pain relief when compared with placebo; better pain relief was noted with other commonly used analgesics such as NSAIDs and paracetamol, given alone and in combination preparations with codeine.

1. de Craen AJM, *et al.* Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996; **313:** 321–5.
2. Toms L, *et al.* Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 02/11/09).
3. Derry S, *et al.* Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 30/06/10).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Codeine is subject to abuse (see under Precautions, below), but produces less euphoria and sedation than morphine.

Neonatal abstinence syndrome. Some of the symptoms characteristic of the neonatal abstinence syndrome were seen in a neonate whose mother had taken about 90 mg of codeine daily during the last 2 months of pregnancy.[1]

1. Khan K, Chang J. Neonatal abstinence syndrome due to codeine. *Arch Dis Child* 1997; **76:** F59–F60.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

In therapeutic doses codeine is much less liable than morphine to produce adverse effects, although constipation may be troublesome with long-term use. After large doses of codeine, excitement and convulsions may occur.

Codeine, like morphine, has a dose-related histamine-releasing effect. Anaphylactic reactions after intravenous use have been reported rarely.

Effects on mental function. Central effects of codeine phosphate appeared to be limited, but dose-related, in subjects given 30, 60, or 90 mg; visuo-motor coordination was altered with doses of 60 and 90 mg and dynamic visual acuity with 90 mg.[1] Drowsiness reported by subjects given 90 mg of codeine phosphate could not be linked with impaired performance whereas nausea could.

1. Bradley CM, Nicholson AN. Effects of a μ-opioid receptor agonist (codeine phosphate) on visuo-motor coordination and dynamic visual acuity in man. *Br J Clin Pharmacol* 1986; **22:** 507–12.

Effects on the pancreas. A 26-year-old woman developed acute pancreatitis on 2 separate occasions a few hours after taking a single, 40-mg dose of codeine.[1] There was no history of alcohol consumption and her recovery was uneventful. Other cases have been reported.[2-5]

1. Hastier P, *et al.* Pancreatitis induced by codeine: a case report with positive rechallenge. *Gut* 1997; **41:** 705–6.
2. Locher C, *et al.* Pancréatite aiguë après la prise d'une association paracétamol-codéine. *Gastroenterol Clin Biol* 2003; **27:** 124–5.
3. Kohlen K, *et al.* Codein-induzierte Pankreatitis. *Dtsch Med Wochenschr* 2005; **130:** 878–9.
4. Moreno Escobosa MC, *et al.* Pancreatitis due to codeine. *Allergol Immunopathol (Madr)* 2005; **33:** 175–7.
5. Belhassen García M, *et al.* Pancreatitis secundaria a paracetamol-codeína. *An Med Interna* 2006; **23:** 400–401.

Effects on the skin. Pruritus and burning erythemato-vesicular plaques that developed in a patient in response to oral codeine were attributed to a fixed drug eruption.[1] A similar reaction occurred in another patient after taking various analgesics including a combined preparation of paracetamol and codeine;[2] patch testing showed a positive response for codeine only. Maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate;[3] fever, splenomegaly, and lymphadenopathy also occurred.

1. Gonzalo-Garijo MÁ, Revenga-Arranz F. Fixed drug eruption due to codeine. *Br J Dermatol* 1996; **135:** 498–9.
2. Gastaminza G, *et al.* Erythrodermia caused by allergy to codeine. *Contact Dermatitis* 2005; **52:** 227–8.
3. Enomoto M, *et al.* Codeine phosphate-induced hypersensitivity syndrome. *Ann Pharmacother* 2004; **38:** 799–802.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Acute codeine intoxication in 430 children, due to accidental ingestion of antitussive preparations, was reviewed.[1] The children were nearly all between 1 and 6 years old. Symptoms in decreasing order of frequency included somnolence, rash, miosis, vomiting, itching, ataxia, and swelling of the skin. Respiratory failure occurred in 8 children and 2 died; all 8 had taken 5 mg/kg or more. Infants are at special risk and there have been fatalities[2-4] and severe adverse effects[4-7] after inappropriate treatment in infants and young children given products containing codeine.

Opioid toxicity, in addition to severe salicylate toxicity, has occurred in adults after overdoses of aspirin and codeine tablets.[8]

1. von Mühlendahl KE, *et al.* Codeine intoxication in childhood. *Lancet* 1976; **ii:** 303–5.
2. Ivey HH, Kattwinkel J. Danger of Actifed-C. *Pediatrics* 1976; **57:** 164–5.
3. Magnani B, Evans R. Codeine intoxication in the neonate. Abstract: *Pediatrics* 1999; **104:** 1379. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/6/e75 (accessed 26/06/08)
4. Ferreirós N, *et al.* Fatal and severe codeine intoxication in 3-year-old twins—interpretation of drug and metabolite concentrations. *Int J Legal Med* 2009; **123:** 387–94.
5. Wilkes TCR, *et al.* Apnoea in a 3-month-old baby prescribed compound linctus containing codeine. *Lancet* 1981; **i:** 1166–7.
6. Lee AC, *et al.* A case of probable codeine poisoning in a young infant after the use of a proprietary cough and cold medicine. *Hong Kong Med J* 2004; **10:** 285–7.
7. Hermanns-Clausen M, *et al.* Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *Eur J Pediatr* 2009; **168:** 819–24.
8. Leslie PJ, *et al.* Opiate toxicity after self poisoning with aspirin and codeine. *BMJ* 1986; **292:** 96.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Abuse. Although the risk of dependence on codeine is low with normal use,[1] it is the subject of deliberate abuse. In France[2] and in the UK linctuses containing codeine have been particularly liable to abuse. Reports in the literature include the use in New Zealand of codeine-containing preparations to produce demethylated products known as "Homebake" containing variable amounts of morphine[3] and abuse of co-codaprin tablets for their codeine content.[4-6]

1. Rowden AM, Lopez JR. Codeine addiction. *DICP Ann Pharmacother* 1989; **23:** 475–7.
2. Armand C, *et al.* 10 ans de détournement d'usage du Néocodion entre 1992 et 2002: Neocodion misuse: evolution between 1992 and 2002. *Therapie* 2004; **59:** 547–53.
3. Shaw JP. Drug misuse in New Zealand. *Pharm J* 1987; **238:** 607.
4. Sakol MS, Stark CR. Codeine abuse. *Lancet* 1989; **ii:** 1282.
5. Paterson JR, *et al.* Codeine abuse from co-codaprin. *Lancet* 1990; **335:** 224.
6. Sakol MS, Stark CR. Codeine abuse from co-codaprin. *Lancet* 1990; **335:** 224.

Breast feeding. Breast-fed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite, morphine, if the mother is an ultrarapid metaboliser of codeine. In one report,[1] a 13-day-old infant died from opioid toxicity after being exposed to morphine in his mother's breast milk; the mother had been taking oral codeine 30 mg twice daily as part of a combination preparation with paracetamol for about 2 weeks. Assayed morphine concentrations in the breast milk were found to be 87 nanograms/mL; the usual range is 1.9 to 20.5 nanograms/mL after repeated doses of codeine 60 mg four times daily. Later investigations found that the mother's genotype for the cytochrome P450 isoenzyme CYP2D6 (the enzyme involved in the conversion of codeine to morphine) classified her as an ultrarapid metaboliser of codeine. Others[2] have subsequently reported severe neonatal toxicity in breast-fed infants whose mothers were CYP2D6 ultrarapid metabolisers. Furthermore, a quantitative mechanistic modeling study to simulate opiate uptake in nursing neonates[3] suggested that there would be little difference in the rate and extent of morphine formation from codeine in mothers with the extensive metaboliser genotype when compared with ultrarapid metabolisers. The model also suggested that low morphine clearance in either the mother or neonate was a significant factor for reaching potentially toxic morphine concentrations in a breast-fed neonate.

The FDA has advised[4] that nursing mothers taking codeine should be informed of the potential risk of morphine overdose and the need to monitor breast-fed infants for signs of toxicity such as increased sleepiness, difficulty feeding or breathing, or limpness. Nursing mothers, themselves, may also develop overdose symptoms including extreme sleepiness, confusion, shallow breathing, and severe constipation. Similar advice has also been issued by Health Canada.[5] In the UK, the MHRA has advised[6] against the use of codeine in nursing mothers. Nonetheless, codeine appears to have been used safely for many years in breast-feeding mothers and the last available guidance from the American Academy of Pediatrics[7] considered that it is usually compatible with breast feeding. Moreover, some of the findings of the original case report have been questioned; in particular, the amount of paracetamol found in the infant's blood at post-mortem was considered too high to be derived from breast milk.[8]

Oxycodone has been used as an alternative to codeine. However, in a retrospective cohort study the incidence of CNS depression was similar in the breast-fed infants of women given either oxycodone or codeine.[9]

1. Koren G, *et al.* Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; **368:** 704.
2. Madadi P, *et al.* Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* 2009; **85:** 31–5.
3. Willmann S, *et al.* Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol Ther* 2009; **86:** 634–43.
4. FDA. Information for healthcare professional: use of codeine products in nursing mothers (issued 17th August, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124889 (accessed 02/08/10)
5. Health Canada/Janssen-Ortho. Important safety information about use of ᴺTylenol* with codeine NO 2,3,4 and elixir in nursing mothers and ultra-rapid metabolizers of codeine (issued 6th October, 2008). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/tylenol_codeine_hpc-cps-eng.pdf (accessed 01/02/10)
6. MHRA/CHM. Codeine for analgesia: restricted use in children because of reports of morphine toxicity. *Drug Safety Update* 2013; **6** (12): A1. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296400 (accessed 13/12/13)
7. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
8. Bateman DN, *et al.* Codeine and breastfeeding. *Lancet* 2008; **372:** 625.
9. Lam J, *et al.* Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr* 2012; **160:** 33–7.

Children. See Overdosage, above, Genetic Polymorphism, below, and Administration in Children, p. 40.3.

Driving. Codeine phosphate 50 mg alone and with alcohol had a deleterious effect on driving skills in a simulated driving test.[1]

1. Linnoila M, Häkkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. *Clin Pharmacol Ther* 1974; **15:** 368–73.

Genetic polymorphism. Life-threatening toxicity in a patient given moderate doses of codeine was thought to be due to a genotype predisposing him to ultrarapid metabolism of the drug into morphine by the cytochrome P450 isoenzyme CYP2D6; this was in addition to drug-induced inhibition of the usual major metabolic pathway mediated by CYP3A4, and transient reduction in renal function.[1]

Genetic polymorphism was also considered to contribute to the death of a 2-year-old **child** given codeine after an adenotonsillectomy had been performed to resolve sleep apnoea and snoring problems.[2] Other contributory factors include evidence of bronchopneumonia at post-mortem. A third report[3] detailed two fatalities and a case of severe respiratory depression following the use of codeine in 3 young children, aged 3 to 5 years, for pain following

adenotonsillectomy. Two of the children had CYP2D6 polymorphisms for extensive or ultrarapid metabolism phenotypes (which can overlap), and this was suspected in the third child given the high morphine concentrations found relative to codeine.

The FDA subsequently issued advice[4] concerning the risks of life-threatening respiratory depression and death following the use of codeine in children for pain following adenotonsillectomy, and contra-indicated its use in this patient group. For the management of other types of pain in children, they advised that codeine should be prescribed for use only when required, at the lowest effective dose for the shortest period of time. Carers should also be advised of the clinical signs of serious adverse effects of codeine. Similar advice has been issued by the UK MHRA;[5] they further advised that codeine should only be used to relieve acute, moderate pain in children older than 12 years of age and only if the use of other analgesics such as paracetamol or ibuprofen is ineffective. They also recommended against the use of codeine in children whose breathing may be compromised, including those with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory-tract or lung infections, multiple trauma, or undergoing extensive surgical procedures. Health Canada has also restricted[6] the use of codeine to children who are 12 years of age or older.

The MHRA has recommended that codeine is contra-indicated in patients of **all ages** who are known CYP2D6 ultrarapid metabolisers.[5]

For the effect of this genotype in breast-feeding mothers, see Breast Feeding, p. 41.2.

1. Gasche Y, *et al.* Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004; **351:** 2827–31. Correction. *ibid.* 2005; **352:** 638.
2. Ciszkowski C, *et al.* Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med* 2009; **361:** 827–8.
3. Kelly LE, *et al.* More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 2012; **129:** e1343–e1347.
4. FDA. Drug Safety Communication: safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy (issued 20th February, 2013). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf (accessed 13/12/13)
5. MHRA/CHM. Codeine for analgesia: restricted use in children because of reports of morphine toxicity. *Drug Safety Update* 2013; **6** (12): A1. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296400 (accessed 13/12/13)
6. Health Canada. Health Canada's review recommends codeine only be used in patients aged 12 and over (issued 6th June, 2013). Available at: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php (accessed 13/12/13)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies codeine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. See Neonatal Abstinence Syndrome under Dependence and Withdrawal, p. 41.1.

Renal impairment. The renal clearance of codeine and its metabolites is significantly reduced in patients with end-stage renal disease on regular haemodialysis therapy. One such elderly patient developed tonic-clonic seizures 7 days after starting oral codeine phosphate 30 mg 4 times daily; no further seizures occurred after codeine was stopped and naloxone started.[1] The dosage of codeine should be reduced according to renal function in patients with renal impairment but no specific recommendations appear to be given in the literature.

1. Kuo S-C, *et al.* Probable codeine phosphate-induced seizures. *Ann Pharmacother* 2004; **38:** 1848–51.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Quinidine. For reference to a suggestion that quinidine can inhibit the analgesic effect of codeine, see Metabolism under Pharmacokinetics, below.

Pharmacokinetics

Codeine and its salts are absorbed from the gastrointestinal tract. Rectal absorption of codeine phosphate has been reported. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. Codeine is metabolised by *O*- and *N*-demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism (see also p. 41.3). Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

The plasma half-life has been reported to be between 3 and 4 hours after an oral or intramuscular dose.

Codeine crosses the placenta and is distributed into breast milk.

References.

1. Guay DR, *et al.* Pharmacokinetics of codeine after single- and multiple-oral-dose administration to normal volunteers. *J Clin Pharmacol* 1987; **27:** 983–7.
2. Persson K, *et al.* The postoperative pharmacokinetics of codeine. *Eur J Clin Pharmacol* 1992; **42:** 663–6.
3. Lafolie P, *et al.* Urine and plasma pharmacokinetics of codeine in healthy volunteers: implications for drugs-of-abuse testing. *J Anal Toxicol* 1996; **20:** 541–6.
4. Kim I, *et al.* Plasma and oral fluid pharmacokinetics and pharmacodynamics after oral codeine administration. *Clin Chem* 2002; **48:** 1486–96.

Administration. In a comparative study[1] codeine had an oral/intramuscular analgesic relative potency ratio of 6:10. This was high compared with that of morphine and was attributed to protection from rapid first-pass metabolism rather than more efficient absorption after oral doses. In a comparative study in children[2] the absorption rate of codeine from a suppository was found to be similar to that from an intramuscular injection; however, peak plasma concentrations were not as high when given rectally.

1. Beaver WT, *et al.* Analgesic studies of codeine and oxycodone in patients with cancer I: comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *J Pharmacol Exp Ther* 1978; **207:** 92–100.
2. McEwan A, *et al.* A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* 2000; **10:** 189–93.

Metabolism. The analgesic effect of codeine may be partly due to its metabolite morphine and it has been suggested that its efficacy may be impaired in patients who are poor metabolisers of codeine[1-4] or in those who are also receiving drugs, such as quinidine, that impair its metabolism.[1] However, patients unable to demethylate codeine to produce detectable plasma concentrations of morphine obtained a similar analgesic effect to patients with detectable plasma morphine concentrations.[5] A study[6] involving infants aged 6 to 10 months has indicated that children were capable of demethylating codeine to morphine at the age of 6 months although glucuronidation of the morphine appeared to be impaired when compared with older children.

For reports of severe toxicity thought to be due to altered metabolism of codeine see Genetic Polymorphism, p. 41.3.

1. Desmeules J, *et al.* Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991; **41:** 23–6.
2. Chen ZR, *et al.* Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol* 1991; **31:** 381–90.
3. Sindrup SH, *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1991; **49:** 686–93.
4. Williams DG, *et al.* Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; **89:** 839–45.
5. Quiding H, *et al.* Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. *Eur J Clin Pharmacol* 1993; **44:** 319–23.
6. Quiding H, *et al.* Infants and young children metabolise codeine to morphine: a study after single and repeated rectal administration. *Br J Clin Pharmacol* 1992; **33:** 45–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Actacode; ***Austria***: Codipertussin; Codipront Mono†; Tricodein†; ***Belg.***: Bromophar; Broncho-pectoralis Codeine; Bronchodine; Bronchosedal; Glottyl; Toux-San Codeine; ***Canad.***: Codeine Contin; Procet; ***China***: Nikekang (尼柯康); ***Fr.***: Antarene Codeine; Codedrill; Codenfan; Neo-Codion; Paderyl; ***Ger.***: Bronchicum Mono Codein; codi OPT; Codicaps mono; Codicaps Neo; Codicompren; Codipertussin; Makatussin Codein†; Optipect Kodein; Tussoret; ***Gr.***: Codipront N; ***Hong Kong***: Cough-C†; ***India***: Codifos; Codin; Codine; Lincotuss; Montokuf; ***Irl.***: Codant†; Codinex; ***Israel***: Codical; Rekod; ***Neth.***: Bronchicum Extra Sterk; Melrosum Extra Sterk; ***Philipp.***: Codipront N; ***Port.***: Toseina; ***Rus.***: Neo-Codion (Нео-Кодион)†; ***Singapore***: Colinctus; LTR Cough Linctus; LTR; SP-Codin; ***Spain***: Bisoltus; Codeisan; Fludan Codeina; Histaverin; Notusin; Perduretas Codeina; Toseina; ***Switz.***: Codicalm; Iropect pastilles pour les bronches; Makatussin; Pectocalmine Junior N; ***Thai.***: Para-Co; Zorituss; ***Turk.***: Nurofen Plus; ***UK***: Bepro; Galcodine; ***Venez.***: Codebromil; Codipront Mono.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Co-codamol Capsules; Co-codamol Tablets; Co-codaprin Tablets; Codeine Linctus; Codeine Phosphate Injection; Codeine Phosphate Oral Solution; Codeine Phosphate Tablets; Dispersible Co-codaprin Tablets; Effervescent Co-codamol Tablets; Paediatric Codeine Linctus; Paracetamol, Codeine Phosphate and Caffeine Capsules; Paracetamol, Codeine Phosphate and Caffeine Tablets;

USP 36: Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Aspirin and Codeine Phosphate Tablets; Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Codeine Phosphate Injection; Codeine Phosphate Oral Suspension; Codeine Phosphate Tablets; Codeine Sulfate Tablets; Guaifenesin and Codeine Phosphate Syrup; Terpin Hydrate and Codeine Elixir.

Croton Oil

Aceite de crotón; Aceite de croton; Oleum Crotonis; Oleum Tiglii; Кротоновое Масло.

CAS — 8001-28-3.

UNII — WK97EQG57S.

Pharmacopoeias. *Chin.* includes fruits of *Croton tiglium*.

Profile

Croton oil is an oil expressed from the seeds of *Croton tiglium* (Euphorbiaceae). Externally, it is a powerful counter-irritant and vesicant. Croton oil is also used with phenol in cosmetic chemical peeling of the skin.

Croton oil has such a violent purgative action that it should not be used as a laxative. Croton oil contains phorbol esters, which are carcinogenic.

Homoeopathy

Croton has been used in homoeopathic medicines under the following names: Croton tiglium; Crot. tig.

References.

1. Bensimon RH. Croton oil peels. *Aesthet Surg J* 2008; **28:** 33–45. Correction. *ibid.*; 221.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Canad.***: Homeo-Form CO†.

Devil's Claw Root

Djävulsklorot; Harpagofytový kořen; Harpagonjuuri; Harpagophyti Radix; Harpagophyton; Harpagophyton, racine d'; Harpagophytum; Inkaruočių šaknys; Ördögcsáklya gyökér; Raíz de harpagofito; Teufelskrallenwurzel; Гарпагофитум; Дьявольский Коготь.

CAS — 19210-12-9 (harpagoside).

ATC Herb — HM01AW5009 (Harpagophytum procumbens: root).

UNII — 1OYM338E89.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract.

Ph. Eur. 8: (Devil's Claw Root; Devil's Claw BP 2014). The cut and dried tuberous, secondary roots of *Harpagophytum procumbens* and/or *H. zeyheri*. Greyish-brown to dark brown with a bitter taste. Contains not less than 1.2% harpagoside ($C_{24}H_{30}O_{11}$ = 494.5), calculated with reference to the dried drug. Protect from light.

Profile

Devil's claw root is used in herbal remedies for musculoskeletal and joint disorders. Its activity is attributed in part to the plant's content of iridoid glycosides, notably harpagoside.

Reviews.

1. Brendler T, *et al.* Devil's Claw (*Harpagophytum procumbens* DC): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2006; **6:** 89–126.
2. Anonymous. *Harpagophytum procumbens* (devil's claw). *Altern Med Rev* 2008; **13:** 248–52.

Pain. Preparations containing devil's claw root have been tried with some success in the treatment of musculoskeletal disorders such as low back pain and osteoarthritis. There is some evidence of efficacy for daily oral doses standardised to 50 to 100 mg harpagoside but the quality of reporting in studies is generally poor and its place in therapy is not established.[1,2] An evidence-based report[3] by the Arthritis Research Campaign in the UK concluded that although devil's claw root may be effective for osteoarthritis, adverse effects remain a concern. Serious, but uncommon, adverse effects such as abnormal heart rhythm and bleeding have been reported.

1. Gagnier JJ, *et al.* Harpgophytum [sic] procumbens for osteoarthritis and low back pain: a systematic review. *BMC Complement Altern Med* 2004; **4:** 13.
2. Gagnier JJ, *et al.* Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).
3. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 28/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Arpadol; Garra do Diabo†; Tenitrat†; ***Denm.***: AEgte Venustorn; ***Fr.***: Artrophytum†; Elusanes Harpagesic†; Harpadol; ***Ger.***: Arthrotabs; Bomarthros†; Cefatec†; Dolo-Arthrosetten H; Doloteffin; flexi-loges; Harpagoforte; Jucurba; Pascoe-Agil; Rheuma-Sern; Rivoltan; Sogoon†; Teltonal†; Teufelskralle; ***Hung.***: Sanhelios Teufelskralle; ***Irl.***: Atrosan; ***Mon.***: Dolosoft; ***Neth.***: Harpadol; ***Pol.***: Reumaphyt; ***Spain***: Allynat; Harpagofito Orto†; HarpagoMed; Harpax†; Normoreum; ***Swed.***: Helaflex; ***Switz.***: HarpagoMed; Pascoe-Agil; Sanaflex; ***UK***: Atrosan; DiaBackpain; DiaHarp; Flexiherb; Harpadol; HarpagoCaps; JointEeze; Moveze; ***Ukr.***: Reumafit (Ревмафит).

Multi-ingredient Preparations. ***Austral.***: Arthri Plus†; Arthriforte†; Arthritic Pain Herbal Formula 1†; Boswellia Compound; Devils Claw Plus†; Extralife Arthri-Care†; ***Belg.***: Algi-Cool†; ***Canad.***: Restorativ Glucosamine Muscle and Joint; ***Cz.***: Antirevmaticky Caj†; ***Fr.***: Arkophytum†; Chondrosteo; Fleximax; Geldolor; OM3flex†; ***Ger.***: Dr Wiemanns Rheumatonikum†; ***Ital.***: Body Guard; Cartago; Flodolor; Lik-Gel†; Nevril; Pik Gel; Proctocella Complex; Reumafort; Reumilase Plus; Reumilase; Valedol; ***Mex.***: Rodan; ***Pol.***: Reumaherb; ***Switz.***: A Vogel Comprimes en cas de rhumatisme.

Homoeopathic Preparations. ***Austria***: Globuli gegen Gelenkschmerzen; ***Ger.***: Bomarthros Harpagophytum Complex; Pascoe-Agil HOM; Rheuma-Hevert.

Dexibuprofen *(BAN, USAN, rINN)*

Deksibuprofeeni; Dexibuprofène; Dexibuprofeno; Dexibuprofenum; *S*-(+)-Ibuprofen; Дексибупрофен.

CAS — 51146-56-6.
ATC — M01AE14.
ATC Vet — QM01AE14.
UNII — 671DKG7P5S.

Profile

Dexibuprofen is the *S*(+)-enantiomer of ibuprofen (p. 68.2) and is used similarly in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache, postoperative pain, dental pain, sprains, and soft-tissue rheumatism. It is also used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. It may be used as an antipyretic to reduce fever.

The usual oral dose is 600 to 900 mg daily in up to 3 divided doses, adjusted according to response, to a usual maximum of 1.2 g daily. Elderly patients should be started at the lower end of the dose range; dosage may then be increased according to tolerance. Dose reductions are also recommended in patients with hepatic or renal impairment, see below.

For doses in children, see below.

References.

1. Phleps W. Overview on clinical data of dexibuprofen. *Clin Rheumatol* 2001; **20** (suppl 1): S15–S21.
2. Mayrhofer F. Efficacy and long-term safety of dexibuprofen [S(+)-ibuprofen]: a short-term efficacy study in patients with osteoarthritis of the hip and a 1-year tolerability study in patients with rheumatic disorders. *Clin Rheumatol* 2001; **20** (suppl 1): S22–S29.
3. Hawel R, *et al.* Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip. *Int J Clin Pharmacol Ther* 2003; **41**: 153–64.
4. Moore RA, *et al.* Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 08/09/09).

Administration in children. Although dexibuprofen is not licensed for use in children under 18 years of age in the UK, some countries permit such use. For example, in Switzerland, dexibuprofen has been given to children aged 6 years and over; usual oral doses are 10 to 15 mg/kg daily in 2 to 4 divided doses. Licensed product information for one preparation recommends a maximum dose of 300 mg daily for those weighing less than 30 kg.

A multicentre randomised study[1] in children aged 6 months to 14 years found single doses of dexibuprofen 5 or 7 mg/kg to be as effective as ibuprofen 10 mg/kg in reducing fever.

1. Yoon JS, *et al.* The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection. *Br J Clin Pharmacol* 2008; **66**: 854–60.

Administration in hepatic and renal impairment. UK licensed product information specifies that the initial dose of dexibuprofen should be reduced in patients with mild to moderate hepatic or renal impairment; it should not be used in those with severe impairment.

Pharmacokinetics. For mention of the metabolism of *R*-(-)-ibuprofen to dexibuprofen, see p. 70.2.

Further references.

1. Eller N, *et al.* Pharmacokinetics of dexibuprofen administered as 200 mg and 400 mg film-coated tablets in healthy volunteers. *Int J Clin Pharmacol Ther* 1998; **36**: 414–17.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexibuprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefalex VL; ***Austria***: Eu-Med Neu; Seractil; ***Chile***: Dexelle; ***Cz.***: Seractil†; ***Denm.***: Seractiv; ***Ger.***: Deltaran; Dolomagon; ***Gr.***: Seractil; ***Hung.***: Seractil; ***India***: Brutek; Sibet; ***Ital.***: Seractil; ***Neth.***: Seractil; ***Norw.***: Seractiv; ***Pol.***: Dexprofen†; Seractil; ***Port.***: Seractil; ***Spain***: Atriscal; Seractil; ***Swed.***: Tradil; ***Switz.***: DexOptifen†; Seractil; ***Turk.***: Tradil; ***UK***: Seractil.

Multi-ingredient Preparations. ***India***: Brutek-P; Dexigesic-P.

Dextromoramide *(BAN, pINN)* ⊗

Dekstromoramidi; Dextrodiphenopyrine; Dextromoramid; Dextromoramida; Dextromoramidum; *d*-Moramid; Pyrrolamidol; Декстроморамид.

(+)-1-(3-Methyl-4-morpholino-2,2-diphenylbutyryl)pyrrolidine.

$C_{25}H_{32}N_2O_2$=392.5
CAS — 357-56-2.
ATC — N02AC01.
ATC Vet — QN02AC01.
UNII — 9S4S6CIY83.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dextromoramide:

Palf.

Dextromoramide Tartrate *(BANM, pINNM)* ⊗

Bitartrate de Dextromoramide; Dekstromoramiditartraatti; Dekstromoramido tartratas; Dextromoramida, tartrato de; Dextromoramide Acid Tartrate; Dextromoramide Hydrogen Tartrate; Dextromoramide, Tartrate de; Dextromoramidhydrogentartrat; Dextromoramidi tartras; Dextromoramidtartarát; Dextromoramidtartrat; Tartrato de dextromoramida; Декстроморамида Тартрат.

$C_{25}H_{32}N_2O_2,C_4H_6O_6$=542.6
CAS — 2922-44-3.
UNII — J778U505W5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dextromoramide Tartrate). A white or almost white, crystalline or amorphous powder. Soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 3.0 to 4.0.

Profile

Dextromoramide is an opioid analgesic (p. 108.1) structurally related to methadone (p. 88.3). It has been used in the treatment of severe pain although it was not recommended for use in obstetric analgesia because of an increased risk of neonatal depression. Dextromoramide is subject to abuse.

Dextromoramide has been given orally as the tartrate. It has also been given rectally as suppositories and by subcutaneous or intramuscular injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Palfium†; ***Neth.***: Palface†; Palfium.

Pharmacopoeial Preparations

BP 2014: Dextromoramide Tablets.

Dextropropoxyphene *(BAN, pINN)*

Dekstropropoksifeeni; Dextropropoxifen; Dextropropoxifeno; Dextropropoxyphène; Dextropropoxyphenum; Propoxyphene; Декстропропоксифен.

(+)-(1*S*,2*R*)-1-Benzyl-3-dimethylamino-2-methyl-1-phenylpropyl propionate.

$C_{22}H_{29}NO_2$=339.5
CAS — 469-62-5.
ATC — N02AC04.
ATC Vet — QN02AC04.
UNII — S2F83W92TK.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dextropropoxyphene:

Dummies.

Dextropropoxyphene Hydrochloride

(BANM, pINNM)

Dekstropropoksifeenihydrokloridi; Dekstropropoksifeno hidrochloridas; Dextropropoxifén-hidroklorid; Dextropropoxifenhydroklorid; Dextropropoxifeno, hidrocloruro de; Dextropropoxyfen-hydrochlorid; Dextropropoxyphène, Chlorhydrate de; Dextropropoxyphenhydrochlorid; Dextropropoxypheni Hydrochloridum; Hidrocloruro de dextropropoxifeno; Propoxyphene Hydrochloride (USAN); Декстропропоксифена Гидрохлорид.

$C_{22}H_{29}NO_2$,HCl=375.9
CAS — 1639-60-7.
UNII — CB2TL9PS0T.

NOTE. Compounded preparations of dextropropoxyphene hydrochloride may be represented by the following names:

- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dextropropoxyphene Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Propoxyphene Hydrochloride). A white odourless crystalline powder. Freely soluble in water; soluble in alcohol, in acetone, and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers.

Dextropropoxyphene Napsilate

(BANM, pINNM)

Dextropropoxifeno, napsilato de; Dextropropoxyphène, Napsilate de; Dextropropoxyphene Napsylate; Dextropropoxypheni Napsilas; Napsilato de dextropropoxifeno; Propoxyphene Napsylate (USAN); Декстропропоксифена Напсилат.

Dextropropoxyphene naphthalene-2-sulphonate monohydrate.

$C_{22}H_{29}NO_2,C_{10}H_8O_3S,H_2O$=565.7
CAS — 17140-78-2 (anhydrous dextropropoxyphene napsilate); 26570-10-5 (dextropropoxyphene napsilate monohydrate).
UNII — 3BM219L1OJ.

NOTE. Compounded preparations of dextropropoxyphene napsilate may be represented by the following names:

- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Dextropropoxyphene Napsilate). An odourless or almost odourless white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform.

USP 36: (Propoxyphene Napsylate). A white powder having essentially no odour. Very slightly soluble in water; soluble 1 in 15 of alcohol and 1 in 10 of chloroform; soluble in acetone and in methyl alcohol. Store in airtight containers.

Uses and Administration

Dextropropoxyphene is an opioid analgesic (p. 108.1) structurally related to methadone (p. 88.3). It has mild analgesic activity and is given orally as the hydrochloride or napsilate to alleviate mild to moderate pain. Unlike the laevo-isomer (levopropoxyphene), dextropropoxyphene has little antitussive activity.

Dextropropoxyphene is mainly used with other analgesics that have anti-inflammatory and antipyretic effects, such as aspirin or paracetamol. The usual licensed dose is 65 mg of the hydrochloride or 100 mg of the napsilate given every 4 hours up to a maximum total daily dose of 390 mg or 600 mg, respectively. In the UK similar doses were given three or four times daily.

The EMEA and the FDA have recommended that *all* dextropropoxyphene-containing preparations be no longer available in the EU and USA, respectively (see also Overdosage, p. 44.2) although such preparations remain on the market in other countries.

Pain. A detailed review[1] of the analgesic efficacy of dextropropoxyphene suggested that with respect to single oral doses, recommended doses of dextropropoxyphene were no more (and probably less) effective than usual doses of paracetamol, aspirin, or other NSAIDs. However, the comparative efficacy may vary substantially depending on the cause of the pain.

When it comes to comparative studies involving combinations of dextropropoxyphene with other analgesics, findings are even less clear-cut.[2] The efficacy of co-proxamol has long been a matter of controversy yet despite this a

survey[3] conducted in 30 UK teaching hospitals found that co-proxamol was the most widely used paracetamol-containing analgesic at the time. It was suggested that the popularity of co-proxamol was purely down to prescribing habits passed on to new medical staff, rather than hard evidence regarding efficacy. This view has been refuted by others[4] who say that a large number of studies have shown clear analgesic effects for dextropropoxyphene. However, any assumption that the combination was widely used because it was more effective than paracetamol alone was not supported by a systematic overview of single-dose studies.[5] This concluded that while co-proxamol was indeed an effective analgesic it was no better than paracetamol alone. Although the evidence from this and other systematic reviews indicate that co-proxamol should be replaced by paracetamol alone for acute pain, the position for chronic use is considered to be not so clear (but see below).[6]

Concerns about the safety and efficacy of dextropropoxyphene, in particular its safety in overdose, have led the EMEA and the FDA to recommend that *all* dextropropoxyphene-containing preparations be no longer available in the EU and USA, respectively, although such preparations remain on the market in other countries. For further details see Effects on the Cardiovascular System and Overdosage, below.

1. Beaver WT. Analgesic efficacy of dextropropoxyphene and dextropropoxyphene-containing combinations: a review. *Hum Toxicol* 1984; **3** (suppl): 191S–220S.
2. Moore RA, *et al*. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 26/06/08).
3. Haigh S. 12 Years on: co-proxamol revisited. *Lancet* 1996; **347:** 1840–1. Correction. *ibid*.; **348:** 346.
4. Sykes JV, *et al*. Coproxamol revisited. *Lancet* 1996; **348:** 408.
5. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997; **315:** 1565–71. Correction *ibid*. 1998; **316:** 116 and 656.
6. Anonymous. Co-proxamol or paracetamol for acute pain? *Drug Ther Bull* 1998; **36:** 80.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Dextropropoxyphene has been subject to abuse (see under Precautions, p. 45.1).

Reports of dextropropoxyphene dependence and its treatment.

1. Wall R, *et al*. Addiction to Distalgesic (dextropropoxyphene). *BMJ* 1980; **280:** 1213–14.
2. D'Abadie NB, Lenton JD. Propoxyphene dependence: problems in management. *South Med J* 1984; **77:** 299–301.

Adverse Effects

As for Opioid Analgesics in general, p. 110.1.

In the recommended dosage the adverse effects of dextropropoxyphene are less marked than those of morphine. Gastrointestinal effects, dizziness, and drowsiness are the most common. Liver impairment, manifest as abnormal liver function tests and, more rarely, as reversible jaundice, has been reported.

There have been a large number of fatalities from either accidental or intentional overdosage with dextropropoxyphene. Many reports emphasise the rapidity with which death ensues; death within an hour of overdosage is not uncommon, and it can occur within 15 minutes. Overdosage is often complicated by patients also taking other CNS depressants such as alcohol and using mixed preparations such as dextropropoxyphene with paracetamol or aspirin.

Symptoms of overdosage are similar to those of opioid poisoning in general, but in addition patients may have psychotic reactions. There may be cardiac conduction abnormalities and arrhythmias.

Dextropropoxyphene injections are painful and have a very destructive effect on soft tissues and veins when abused in this way.

Anorectal reactions have followed the prolonged use of suppositories containing dextropropoxyphene; the reactions appear to be dose dependent.

Effects on the blood. A 12-year history of haemolysis and subsequent significant haemolytic anaemia in an elderly woman[1] was associated with chronic, periodic, and occasionally excessive intake of co-proxamol.

1. Fulton JD, McGonigal G. Steroid responsive haemolytic anaemia due to dextropropoxyphene paracetamol combination. *J R Soc Med* 1989; **82:** 228.

Effects on the cardiovascular system. In November 2010, the FDA reported on its safety review of dextropropoxyphene.[1] A randomised, double-blind, placebo-controlled study in 18 healthy subjects receiving an oral daily dose of dextropropoxyphene [napsilate] titrated to 600 mg (the maximum licensed dose) or 900 mg for 11 days found significant prolongation of the QT interval in both cohorts; dose-dependent prolongation of the PR and QRS intervals was also noted. Indeed, the study was halted because of safety concerns. Consequently, based on this and other data available at that time, the FDA considered that the risks of dextropropoxyphene outweighed its benefits and requested its withdrawal from the US market (see also Overdosage, below).

1. FDA. FDA drug safety communication: FDA recommends against the continued use of propoxyphene (issued 19th November, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm234338.htm (accessed 23/11/10)

Effects on the ears. A report of complete nerve deafness associated with chronic abuse of co-proxamol was made to the UK CSM.[1] The CSM had received 2 other reports of permanent hearing loss attributed to co-proxamol abuse; transient hearing loss had also been reported in 2 patients taking usual doses; 7 further reports described tinnitus.

1. Ramsay BC. Complete nerve deafness after abuse of co-proxamol. *Lancet* 1991; **338:** 446–7.

Effects on the liver. There have been occasional reports of jaundice in patients taking dextropropoxyphene alone but many of the 49 suspected hepatic reactions with dextropropoxyphene reported to the UK CSM by 1985[1] had involved use with paracetamol; clinical features including malaise, jaundice, raised serum transaminases, and sometimes fever, were however generally characteristic of dextropropoxyphene alone. Relapsing jaundice mimicking biliary disease was attributable to the dextropropoxyphene component of co-proxamol in 3 patients,[2] whereas there was no abnormality of liver function in 11 patients on long-term co-proxamol analgesia.[3] Another report of 9 cases found that the hepatotoxicity of dextropropoxyphene mimicked symptoms of large bile duct obstruction, and suggested that such toxicity might be misdiagnosed.[4] A more recent review[5] also concluded that hepatotoxicity with dextropropoxyphene might mimic a biliary tract disease, sometimes with few or no symptoms.

1. CSM. Hepatotoxicity with dextropropoxyphene. *Current Problems 17* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024424&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. Bassendine MF, *et al*. Dextropropoxyphene induced hepatotoxicity mimicking biliary tract disease. *Gut* 1986; **27:** 444–9.
3. Hutchinson DR, *et al*. Liver function in patients on long-term paracetamol (co-proxamol) analgesia. *J Pharm Pharmacol* 1986; **38:** 242–3.
4. Rosenberg WMC, *et al*. Dextropropoxyphene induced hepatotoxicity: a report of nine cases. *J Hepatol* 1993; **19:** 470–4.
5. Bergeron L, *et al*. Dextropropoxyphène et atteintes hépatiques: à propos de 4 cas et revue de littèrature. *Therapie* 2002; **57:** 464–72.

Effects on the lungs. Hypersensitivity pneumonitis and skin rash have been reported in a patient taking co-proxamol.[1] No such reaction occurred when the patient was subsequently given paracetamol alone.

1. Matusiewicz SP, *et al*. Hypersensitivity pneumonitis associated with co-proxamol (paracetamol + dextropropoxyphene) therapy. *Postgrad Med J* 1999; **75:** 475–6.

Hypoglycaemia. Hypoglycaemia has occasionally been reported with the use of dextropropoxyphene.[1-6]

1. Wiederholt IC, *et al*. Recurrent episodes of hypoglycemia induced by propoxyphene. *Neurology* 1967; **17:** 703–4.
2. Almirall J, *et al*. Propoxyphene-induced hypoglycemia in a patient with chronic renal failure. *Nephron* 1989; **53:** 273–5.
3. Laurent M, *et al*. Hypoglycémie sous dextropropoxyphène chez des grands vieillards: 7 cas. *Presse Med* 1991; **20:** 1628.
4. Lowenstein W, *et al*. Hypoglycémie au dextropropoxyphène: une urgence chez le toxicomane. *Presse Med* 1993; **22:** 133.
5. Santos Gil I, *et al*. Hipoglucemia secundaria a ingestión de dextropropoxifeno en un paciente adicto a drogas. *Med Clin (Barc)* 1998; **110:** 475–6.
6. Shah P, *et al*. Propoxyphene-induced hypoglycemia in renal failure. *Endocr Pract* 2006; **12:** 170–3.

Overdosage. There have been several reviews or retrospective studies of acute self-poisoning with dextropropoxyphene.[1-4] At a symposium on the safety and efficacy of dextropropoxyphene[5] many of the participants dealt with the problems of dextropropoxyphene overdosage, often in conjunction with paracetamol and sometimes with alcohol. Profound and even fatal CNS depression can develop rapidly as a result of the dextropropoxyphene content and in many cases death has occurred within an hour;[6] it was suggested that as few as 15 to 20 tablets of co-proxamol may be fatal.[7,8] Analysis of suicides involving drugs in England and Wales between 1997 and 1999 revealed that the odds of dying after overdose with co-proxamol were 2.3 times that for tricyclic antidepressant overdose, and 28.1 times greater than for paracetamol.[9] Another analysis of suicides due to poisoning in 3 areas of the UK between 2000 and 2001 identified 123 cases of fatal overdose with co-proxamol;[10] those who also consumed alcohol had generally taken fewer co-proxamol tablets than those who had not, emphasising the increased toxicity of the combination.

An analysis of overdosage involving combination analgesic preparations prescribed in Scotland between 2000 and 2002 also found that overdoses with co-proxamol were 10 times more likely to be fatal when compared with co-dydramol or co-codamol.[11] In the USA[12] the incidence of dextropropoxyphene-associated deaths reached a peak in 1977 and then fell at a rate that was not matched by a decline in prescribing.

It is not clear whether the metabolite, nordextropropoxyphene, plays an important role in fatalities.[12] However, nordextropropoxyphene, like dextropropoxyphene, is considered to have local anaesthetic activity and the membrane stabilising activity of dextropropoxyphene has been implicated as a major factor responsible for its severe cardiac depressant effect.[13]

In January 2005, the UK CSM found the risk of toxicity of co-proxamol in overdose to be unacceptable;[14] consequently, co-proxamol has been gradually withdrawn from the UK market. Around that time, fixed-dose combinations of dextropropoxyphene and paracetamol were also withdrawn in several other countries including Sweden and Switzerland. Subsequently, in June 2009, the EMEA[15] recommended that *all* dextropropoxyphene-containing preparations, both single- and multi-constituent, be withdrawn throughout the EU; it was considered that the benefits of dextropropoxyphene did not outweigh its risks, particularly the risk of fatal overdose. In October 2009 a re-analysis requested by the product licence holders upheld the EMEA's original recommendation for non-parenteral preparations of dextropropoxyphene.[16] For parenteral preparations, it was considered that, although their safety in overdosage may be less of a concern given their supervised use in hospitals, data on efficacy were lacking. Consequently, the EMEA recommended that product licences for parenteral preparations be suspended until further data on their efficacy are provided. At that time, dextropropoxyphene-containing preparations remained available in the USA although steps such as improving prescriber awareness were taken to reduce the risk of overdose.[17] However, in November 2010, the FDA requested that all dextropropoxyphene-containing preparations be withdrawn from the US market after a safety review had shown evidence of significant cardiotoxicity (see Effects on the Cardiovascular System, above, for further details).

An analysis[18] of prescription data in England and Wales from 1998 to 2007 found that although the withdrawal of co-proxamol resulted in a significant increase of prescriptions for analgesics such as co-codamol, co-dydramol, codeine, and paracetamol, there was no statistical evidence for an increase in deaths by poisoning due to substitution with these analgesics or other drugs.

1. Young RJ. Dextropropoxyphene overdosage: pharmacological considerations and clinical management. *Drugs* 1983; **26:** 70–9.
2. Madsen PS, *et al*. Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand* 1984; **28:** 661–5.
3. Segest E. Poisoning with dextropropoxyphene in Denmark. *Hum Toxicol* 1987; **6:** 203–7.
4. Jonasson U, *et al*. Correlation between prescription of various dextropropoxyphene preparations and their involvement in fatal poisonings. *Forensic Sci Int* 1999; **103:** 125–32.
5. Bowen D, *et al*. (ed). Distalgesic; safety and efficacy. *Hum Toxicol* 1984; **3** (suppl): 1S–238S.
6. Proudfoot AT. Clinical features and management of Distalgesic overdose. *Hum Toxicol* 1984; **3** (suppl): 85S–94S.
7. Whittington RM. Dextropropoxyphene deaths: coroner's report. *Hum Toxicol* 1984; **3** (suppl): 175S–185S.
8. Young RJ, Lawson AAH. Distalgesic poisoning—cause for concern. *BMJ* 1980; **280:** 1045–7.
9. Hawton K, *et al*. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisonings. *BMJ* 2003; **326:** 1006–8.
10. Hawton K, *et al*. A multicentre study of coproxamol poisoning suicides based on coroners' records in England. *Br J Clin Pharmacol* 2005; **59:** 207–12.
11. Afshari R, *et al*. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. *Br J Clin Pharmacol* 2005; **60:** 444–7.
12. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; **3** (suppl): 115S–34S.
13. Henry JA, Cassidy SL. Membrane stabilising activity: a major cause of fatal poisoning. *Lancet* 1986; **i:** 1414–17.
14. MHRA. Withdrawal of co-proxamol products and interim updated prescribing information. Message from Professor G Duff, Chairman of CSM (issued 31st January, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf (accessed 28/08/08)
15. EMEA. Press release: European Medicines Agency recommends withdrawal of dextropropoxyphene-containing medicines (issued 25th June, 2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010365.pdf (accessed 02/08/10)
16. EMEA. Questions and answers on the withdrawal of the marketing authorisations for medicines containing dextropropoxyphene (issued 22nd October, 2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/dextropropoxyphene_31/WC500014076.pdf (accessed 02/08/10)
17. FDA. News release: FDA takes actions on Darvon, other pain medications containing propoxyphene (issued 7th July, 2009). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm170769.htm (accessed 01/02/10)
18. Hawton K, *et al*. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. Abridged version: *BMJ* 2009; **339:** 435–8. Full version: http://www.bmj.com/cgi/reprint/338/jun18_2/b2270 (accessed 02/11/09)

Treatment of Adverse Effects

As for Opioid Analgesics in general, p. 110.3.

Rapid treatment of overdosage with naloxone and assisted respiration is essential. Cardiac effects may not be reversed by naloxone. Although the benefit of gastric decontamination is uncertain, activated charcoal may be of value within 1 hour of ingesting a potentially toxic amount; dialysis is of little use.

Convulsions may require control with an anticonvulsant, bearing in mind that the CNS depressant effects of dextropropoxyphene can be exacerbated (see also Interactions, below). Stimulants should not be used because of the risk of inducing convulsions.

Patients taking overdoses of dextropropoxyphene with paracetamol will also require treatment for paracetamol poisoning (p. 116.2). Mixtures of dextropropoxyphene and aspirin may be involved; the treatment of aspirin poisoning is described on p. 24.2.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Abuse. There have been reports[1] of the abuse of dextropropoxyphene, and some[2] considered that the ready availability of dextropropoxyphene made it liable to abuse although it was a relatively weak opioid analgesic. However, others[3] thought there was no evidence that dextropropoxyphene was frequently associated with abuse, or concluded that, although there was abuse potential, it was of relatively low importance in terms of the community as a whole.[4]

A severe withdrawal syndrome has been reported[5] in an elderly patient who covertly consumed a daily dose of dextropropoxyphene of 1 to 3 g for at least 12 months. The patient was treated by a gradually decreasing dosage schedule of dextropropoxyphene over 9 weeks.

1. Tennant FS. Complications of propoxyphene abuse. *Arch Intern Med* 1973; **132:** 191–4.
2. Lader M. Abuse of weak opioid analgesics. *Hum Toxicol* 1984; **3** (suppl): 229S–36S.
3. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; **3** (suppl): 115S–34S.
4. Turner P. Final remarks. *Hum Toxicol* 1984; **3** (suppl): 237S–8S.
5. Hedenmalm K. A case of severe withdrawal syndrome due to dextropropoxyphene. *Ann Intern Med* 1995; **123:** 473.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving dextropropoxyphene, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dextropropoxyphene as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Plasma concentrations of dextropropoxyphene are increased by ritonavir, with a resultant risk of toxicity; they should not be given together.

CNS depressants, including alcohol, may contribute to the hazards of dextropropoxyphene, see also Overdosage, p. 44.2. The convulsant action of high doses of dextropropoxyphene may be enhanced by CNS stimulants.

Dextropropoxyphene interacts with several other drugs through inhibition of liver metabolism. Drugs reported to be affected include antidepressants (see p. 408.2), benzodiazepines (see p. 1068.1), beta blockers (see p. 1322.2), carbamazepine (see p. 516.2), phenobarbital (see p. 537.2), phenytoin (see p. 542.2), and warfarin (see p. 1530.2).

Antimuscarinics. A suggested interaction between *orphenadrine* and dextropropoxyphene has been questioned (see p. 911.1).

Pharmacokinetics

Dextropropoxyphene is readily absorbed from the gastrointestinal tract, the napsilate tending to be more slowly absorbed than the hydrochloride, but both are subject to considerable first-pass metabolism. Peak plasma concentrations occur about 2 to 2.5 hours after ingestion. It is rapidly distributed and concentrated in the liver, lungs, and brain. About 80% of dextropropoxyphene and its metabolites are reported to be bound to plasma proteins. Dextropropoxyphene crosses the placenta. It has been detected in breast milk.

Dextropropoxyphene is *N*-demethylated to nordextropropoxyphene (norpropoxyphene) in the liver. It is excreted in the urine mainly as metabolites. It is now recognised that dextropropoxyphene and nordextropropoxyphene have prolonged elimination half-lives; values of 6 to 12 hours and 30 to 36 hours, respectively, have been reported. Accumulation of dextropropoxyphene and its metabolites may occur with repeated doses and nordextropropoxyphene may contribute to the toxicity seen with overdosage.

Reviews.

1. Pearson RM. Pharmacokinetics of propoxyphene. *Hum Toxicol* 1984; **3** (suppl): 37S–40S.

The elderly. The elimination half-lives of dextropropoxyphene and its metabolite nordextropropoxyphene were prolonged in healthy elderly subjects when compared with young controls.[1] After multiple dosing median half-lives of dextropropoxyphene and nordextropropoxyphene were 36.8 and 41.8 hours, respectively in the elderly compared with 22.0 and 22.1 hours in the young subjects. In this study[1] there was a strong correlation between half-life of nordextropropoxyphene and estimated creatinine clearance.

1. Flanagan RJ, *et al.* Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989; **28:** 463–9.

Hepatic impairment. Plasma concentrations of dextropropoxyphene were higher in patients with cirrhosis given the drug than in healthy subjects whereas concentrations of nordextropropoxyphene were lower.[1]

1. Giacomini KM, *et al.* Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt. *Clin Pharmacol Ther* 1980; **28:** 417–24.

Renal impairment. Higher and more persistent plasma concentrations of dextropropoxyphene and nordextropropoxyphene in anephric patients when compared with healthy subjects[1] were attributed to decreased first-pass metabolism of dextropropoxyphene and decreased renal excretion of nordextropropoxyphene in the anephric patients.

1. Gibson TP, *et al.* Propoxyphene and norpropoxyphene plasma concentrations in the anephric patient. *Clin Pharmacol Ther* 1980; **27:** 665–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Doloxene; ***Belg.***: Depronal†; ***Canad.***: 642†; Darvon-N†; ***Denm.***: Abalgin; Doloxene†; ***Fin.***: Abalgin†; ***Gr.***: Romidon; Zideron; ***Hong Kong***: Dolpoxene†; Dopoxy†; ***India***: Parvodex; ***Mex.***: Darvon Simple†; Saludex; ***Neth.***: Depronal†; ***S.Afr.***: Doloxene; ***Singapore***: Dolpoxene; ***Spain***: Deprancol†; ***Swed.***: Dexofen†; Doloxene†; ***Thai.***: Pardex; ***USA***: Darvon-N†; Darvon†.

Multi-ingredient Preparations. ***Arg.***: Artifene; Calmopirin; Dexprofeno†; Dextro + Dipirona†; Dextrodip†; Dorixina Forte; Dorixina Forte; Gobbicalm; Gobbigesic†; Klosidol B1 B6 B12; Klosidol; Profium Plus; Supragesic D; Supragesic; Vicefeno; ***Austral.***: Capadex; Di-Gesic; Paradex; ***Austria***: APA†; ***Belg.***: Algophene†; ***Braz.***: Doloxene-A; ***China***: Da Ning (达宁); Tong Li Tuo (同立妥); ***Fr.***: Dextroref†; Di Dolko†; Di-Antalvic†; Dialgirex†; Dioalgo†; Propofan†; ***Hong Kong***: Cosalgesic†; Dolocin; Dolpocetmol; Medonol; Procetalette†; Procetamol†; Propoxymol†; Uni-Proxamol†; ***Hung.***: Novopyrin†; ***India***: Butaproxyvon; Centrivon; Colidex; Corbutyl; Cyclo-P; Darvocet; Dexovon; Hyvon-Spas; Ibruvon Forte; Ibu-Proxyvon; Lobain; Lupivon-D; Lupivon; Neurovon; Nimodex; Novodex; Orthodex Plus; Orthodex; Oxymark; Parvon Forte; Parvon Spas; Parvon-N; Parvon; Proxytab; Proxyvon; Spasmo-Proxyvon; Spasmocip Plus; Spasmocip; Sudhinol; Walagesic; Wygesic; ***Israel***: Algolysin†; Proxol; Rogaan†; ***Mex.***: Neo-Percodan; Qual; ***Norw.***: Aporex†; ***NZ***: Capadex†; Paradex†; ***Port.***: Algifene; ***S.Afr.***: Distalgesic; Doloxene Co; Doxyfene; Lentogesic; Synap; ***Singapore***: Dolpocetmol; ***Thai.***: Davol; ***USA***: Balacet†; Darvocet-N†; Darvocet†; PC-Cap†; Propacet†; Trycet†.

Pharmacopoeial Preparations

BP 2014: Co-proxamol Tablets; Dextropropoxyphene Capsules;
USP 36: Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Hydrochloride Capsules; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Acetaminophen Tablets; Propoxyphene Napsylate and Aspirin Tablets; Propoxyphene Napsylate Oral Suspension; Propoxyphene Napsylate Tablets.

Dezocine *(USAN, rINN)*

Dezocina; Dézocine; Dezocinum; Wy-16225; Дезоцин.
(-)-13β-Amino-5,6,7,8,9,10,11a,12-octahydro-5a-methyl-5,11-methanobenzocyclodecen-3-ol.
$C_{16}H_{23}NO$=245.4
CAS — 53648-55-8.
ATC — N02AX03.
ATC Vet — QN02AX03.
UNII — VHX8K5SV4X.

Profile

Dezocine is an opioid analgesic structurally related to pentazocine (p. 120.3), with opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jialuoning (加罗宁).

Diacerein *(rINN)*

Diacereína; Diacéréine; Diacereinum; Diacerhein; Diacetylrhein; 2,4-Dichlorobenzylique, Alcool; Rhein Diacetate; SF-277; Диацереин.
9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthroic acid diacetate.
$C_{19}H_{12}O_8$=368.3
CAS — 13739-02-1.
ATC — M01AX21.
ATC Vet — QM01AX21.
UNII — 4HU6J11EL5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Diacerein). A yellow, crystalline powder. Practically insoluble in water and in anhydrous alcohol; soluble in dimethylacetamide; slightly soluble in tetrahydrofuran. Store in airtight containers. Protect from light.

Profile

Diacerein is an anthraquinone derivative that is used in osteoarthritis (p. 12.3) in oral doses of 50 mg twice daily. Doses should be halved in patients with creatinine clearance less than 30 mL/minute. Diarrhoea is a common adverse effect with diacerein. Its active metabolite, rhein, a constituent of rhubarb (p. 1887.2), is reported to act as an interleukin-1 inhibitor.

Administration in renal impairment. See above and Pharmacokinetics, below.

Musculoskeletal and joint disorders. Diacerein is thought to act via inhibition of interleukin-1β,[1] which plays a role in inflammatory processes. Systematic reviews[2-4] on the use of diacerein in the treatment of osteoarthritis have indicated that diacerein produces a small, but consistent, improvement in pain. Further research is necessary to confirm its short- and long-term efficacy and safety but there is some evidence of residual benefit on stopping treatment,[3] which has been postulated to represent an improvement in the disease process. The increased risk of diarrhoea was a noted effect with diacerein.[4]

1. Van den Berg WB. Les mécanismes d'action de la diacerhéine, premier inhibiteur de l'interleukine 1 dans l'arthrose. *Presse Med* 2004; **33:** 10–12.
2. Fidelix TSA, *et al.* Diacerein for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 06/10/06).
3. Rintelen B, *et al.* A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med* 2006; **166:** 1899–1906.
4. Bartels EM, *et al.* Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2010; **18:** 289–96.

Pharmacokinetics. References.

1. Debord P, *et al.* Influence of renal function on the pharmacokinetics of diacerein after a single oral dose. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 13–19.
2. Nicolas P, *et al.* Clinical pharmacokinetics of diacerein. *Clin Pharmacokinet* 1998; **35:** 347–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Artrodar; Cominar; Nulartrin; ***Austria***: Artrolyt; Verboril; ***Braz.***: Artrodar; ***Chile***: Artrizona; ***China***: Artrodar (安必丁); ***Cz.***: Artrodar; ***Fr.***: Art; Zondar; ***Gr.***: Arthrofar; Arthrorein; Deserein; Diacer; Diaceril; Idealite; Inflabion; Myobloc; Ostirein; Pentacrin; Reumanisal; Verbodon; Verboril; ***Hong Kong***: Artrodar; ***India***: Acer; Alnamax; Altocerin; Ance; Arthocerin; Arthromuv; Artifit; Artrodar; Biojoint; Cartidin; Cartiel D; Cartifact; Cartiz; Cartrodar; Cedia; Cerdia; Cerin; Daicart; Dencerin; Diacer; Diacure; Dialeed; Diasim; Diasol; Dici; Dicimax; Diez; Diosteo; Diskare; Durajoint; Dycerin; Eljoint; Ferine; Flexibel-D; Glocerin; Gudcerin; Hilin; Icerin; Jaizzy; Joincerin; Lecerein; Lefax; Mycer; Nucerin; Orcerin; Ordi; Orthobact; Ortocer; Osticer; Ostogard; Ostokind; Ostorin; ***Indon.***: Artrodar; Bondi; ***Israel***: Art; Diatrim; ***Ital.***: Fisiodar; ***Malaysia***: Artrodar; ***Port.***: Artrolyt; Cartivix; ***Rus.***: Arthrocare (Артрокер); Artodarin (Артродарин); ***Spain***: Artrizan; Galaxdar;

Glizolan; ***Thai.***: Artrodar; ***Turk.***: Artrodar; Rexena; ***Venez.***: Artrodar.

Multi-ingredient Preparations. ***India***: Alnamax-G; Altocerin-GM; Artheal; Arthocerin-A; Arthocerin-G; Arthodia-G; Arthrovit Plus; Cartimost GM; Cartiz-GM; Cedia-AC; Compensate; Cosa-G; Curejoint-AC; Dicimax-G; Difirin Plus; Dims-GM; DN Plus; Durajoint-GM; Dycerin-A; Dycerin-GM; Flexibel-AD; Flextra-D; Icerin-GM; Jaizzy-GM; Lecerein-GM; Lecerein-P; Lefax-G; Mycer G; OA Plus; Ordi-G; Orthocerin-G; Ostakair-D; Ostawin; Osteojoin-D; Ostifin-G; Ostodia-G; Paclo-GMD; ***Mex.***: Dolocartigen.

Diamorphine Hydrochloride

(BANM) ⊗

Diacetilmorfina, hidrocloruro de; Diacetylmorphine Hydrochloride; Heroin Hydrochloride; Hidrocloruro de diamorfina; Hidrocloruro de heroína; Героин Гидрохлорид; Диаморфина Гидрохлорид.

4,5-Epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate.

$C_{21}H_{23}NO_5,HCl,H_2O$=423.9

CAS — 561-27-3 (diamorphine); 1502-95-0 (diamorphine hydrochloride).

ATC — N07BC06.

ATC Vet — QN07BC06.

UNII — 8H672SHT8E.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of diamorphine:

57 Chevy; A Sidani; AIP; Al Capone; Amelia; Antifreeze; Aries; Aunt Hazel; Auntie Hazel; Aunty Hazel; Bacalhau; Bad bundle; Bad seed; Ball; Ballot; Bart Simpson; Batman; Beast; Big Bad Boy; Big bag; Big doodig; Big H; Big Harry; Bin laden; Bindle; Birdie powder; Black; Black Dragon; Black eagle; Black Girl; Black pearl; Black stuff; Black tar; Black tootsie roll; Blanche; Blanco; Blast; Bleue; Block busters; Blow; Blows; Blue bag; Blue hero; Blue star; Bobby Brown; Bomb; Bomba; Bombe; Bombido; Bombita; Bombitas; Bombs away; Bone; Bonita; Boy; Bozo; Brad; Brain damage; Brea; Brick gum; Broja; Brother; Brown; Brown crystal; Brown rhine; Brown sugar; Brown tape; Bugger; Bull dog; Bundle; Burra; Butu; Caballo; Caca; Calbo; Capital H; Caps; Captain Jack; Carga; Carne; Cavalo; Chang; Chapopote; Charley; Chatarra; Cheese; Cheevah; Cheva; Cheval; Chi; Chiba; Chick; Chicken; Chicle; Chieva; China cat; China white; Chinche; Chinese H; Chinese red; Chinese Rocks; Chinoise; Chip; Chiva; Chocofan; Chocofan; Chueva; Chunks; Climax; Cocofan; Coffee; Cotics; Cotton Candy; Courage pills; Crank; Crap; Crop; Crown crap; Cura; Dead on arrival; Dead president; Deuce; Diesel; Diggidy; Dirt; DOA; Dog food; Dogee; Dogie; Doogie; Doojee; Dookey Rocks; Dooley; Doosey; Dope; Downtown; Dr. Feelgood; Dragon; Dreck; DT; Dugee; Dugie; Duji; Dujra; Dujre; Dust; Dyno; Dyno-pure; Eggs; Eight; Eighth; Elephant; Estuffa; Fachiva; Ferry dust; Fix; Flea powder; Foil; Foo foo stuff; Foolish powder; Furra; Galloping horse; Gallup; Gamot; Garbage; Gato; Gear; George; George smack; Ghost; Girl; Glacines; Glass; Goat; Gold; Golden Brown; Golden girl; Golpe; Goma; Good; Good H; Good Horse; Good and plenty; Goods; Goop; Grape Jolly Rancher; Gravy; Grey shields; H; H22; H-bomb; H Caps; Hache; Hair; Hairpiece; Hairy; Hammer; Hard candy; Hard stuff; Harriet Tubman; Harry; Harry Jones; Hayron; Hazel; Heaven; Heaven dust; Heavy stuff; Helen; Hell dust; Henry; Hera; Hero; Hero of the underworld; Heroa; Heroina; Heron; Herone; Hessle; Him; Holy terror; Hombre; Homebake; Homicide; Hong-yen; Hood; Hop; Horning; Horse; Horsebite; Hot dope; Hot heroin; HRN; Isda; Jack; Jee gee; Jerry Springer; Jesus; Jive; Jive doo jee; Joharito; Jojee; Jones; Joy; Joy dust; Joy flakes; Joy powder; Judas; Junco; Junk; Kabayo; Kaka Water; Karachi; Kermit the Frog; La Buena; La Chiva; Lady H; Layne; LBJ; Lemonade; Life saver; Little bomb; Man; Manteca; Matsakow; Mayo; Mexican Black Tar; Mexican brown; Mexican Dirt; Mexican horse; Mexican mud; Mister Brownstone; Mojo; Money talks; Monkey; Montego; Morse Code Features; Morotgara; Mortal combat; Mother pearl; Mr. Brownstone; Mud; Murotugora; Muzzle; Nanoo; Nice and easy; Nickel bag; Nickel deck; Nixon; Noddy Brown; Noise; Nose; Nose drops; Number 3; Number 4; Number 8; Nurse; Oddy Noddy; Of course my horse; Ogoy; Oil; Old garbage; Old navy; Old Steve; One way; Orange line; Outfit; Pack; Pakistanaise; Pako; Pangonadalot; Parachute; P-dope; Peg; Pepper; Perfect high; P-funk; Pluto; Po; Poeira; Poison; Polvo; Poppy; Poudre; Powder; Predator; Primo; Produto; Pulborn; Pure; Quill; Race horse Charlie; Racehorse Charlie; Ragweed; Rain; Rambo; Rane; Raw; Raw fusion; Raw hide; Raw Opportunities; Ready rock; Red chicken; Red devil; Red eagle; Red rock; Red rum; Reindeer dust; Rhine; Ring of Turd; Rob Flaherty; Rock; Rocks; Rush hour; Sack; Salt; Scag; Scat; Scate; Schmack; Schmeck; Schmeek; Scott; Scramble; Second to none; Shit; Shmeck; Shmeek; Shmek; Shoot; Silk; Skag; Skid; Skunk; Slack-dad-eat-your-heart-out; Slam; Sleeper; Sleepers; Slime; Slow; Sludge; Smack; Snotty; Snow; Spider; Spider blue; Stuff; Stunna; Sugar; Suicide; Sweet dreams; Sweet Jesus; Sweet stuff; Synthe; Tang; Tar; Taste; Tecata; Tecate; Thailandaise; Thanie; The beast; The fake throwdown; The Jack Bauer; The Loud-House Permadillo; The Nax; The witch; Thing; Thunder; Tiger; Tigre; Tigre Blanco; Tigre del Norte; Tits; TNT; T.N.T.; Tongs; Tootsie roll; Top drool; Train; Trash; Twin towers; Twists; Vidrio; Whack; Whicked; White; White Bitch; White boy; White dragon; White dynamite; White girl; White horse; White junk; White lady; White nurse; White Pony; White stuff; White Tiger; Wicked; Wings; Witch; Witch hazel; WTC; Zoquete.

Pharmacopoeias. In *Br.* and *Swiss*. *Swiss* also includes the anhydrous form.

BP 2014: (Diamorphine Hydrochloride). A white or almost white crystalline powder, odourless when freshly prepared but develops an odour characteristic of acetic acid on storage. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether. Protect from light.

Incompatibility. Diamorphine hydrochloride is incompatible with mineral acids and alkalis and with chlorocresol.[1]

The *BNF* notes that cyclizine may precipitate from mixtures with diamorphine hydrochloride at concentrations of cyclizine greater than 10 mg/mL, or in the presence of sodium chloride 0.9%, or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also liable to precipitate after 24 hours.

It also considers that mixtures of diamorphine and haloperidol are liable to precipitate after 24 hours if the haloperidol concentration is above 2 mg/mL. Under some conditions mixtures of metoclopramide and diamorphine may become discoloured and should be discarded.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; **158:** 260–2.

Stability. Diamorphine is relatively unstable in aqueous solution and is hydrolysed to 6-*O*-monoacetylmorphine and then morphine to a significant extent at room temperature; 3-*O*-monoacetylmorphine is only occasionally detected. The rate of decomposition is at a minimum at about pH 4.[1,2]

In a study of the stability of aqueous solutions of diamorphine in chloroform water it was concluded that such solutions should be used within 3 weeks of preparation when stored at room temperature.[3] Another study[4] noted that the degradation products of diamorphine were not devoid of analgesic activity. Using a more sensitive analytical method it was reported that although the pH range of maximum stability of diamorphine in aqueous solution was 3.8 to 4.4, the addition of buffers reduced stability.[5] Simple unbuffered chloroform water gave maximum stability, the shelf-life of such a solution being 4 weeks at room temperature.

The BP 2014 recommends that solutions for injection be prepared immediately before use by dissolving Diamorphine Hydrochloride for Injection in Water for Injections. This may pose a problem with solutions for subcutaneous infusion when concentrated solutions may remain in infusion pump reservoirs for some time.[6] Investigation of 9 concentrations of diamorphine stored at 4 different temperatures for 8 weeks[7] revealed instability under conditions of concentration, time, and temperature prevalent during subcutaneous infusion. Degradation of diamorphine occurred at all concentrations (0.98 to 250 mg/mL) at temperatures of 4 degrees and above; the effect of temperature was significant at 21 degrees and 37 degrees. The percentage fall in diamorphine concentration was directly related to initial concentration and was accompanied by a corresponding increase in 6-*O*-monoacetylmorphine and, to a lesser extent, morphine; other possible breakdown products such as 3-*O*-monoacetylmorphine were not present in detectable quantities. Diamorphine degradation was associated with a fall in pH and the development of a strong acetic acid-like odour. Precipitation and a white turbidity was seen in solutions of 15.6 mg/mL and above after incubation for 2 weeks at 21 degrees and 37 degrees. It has been noted that solutions for infusion are generally freshly prepared and used within 24 hours, but that signs of precipitation should be watched for, especially when using longer-term infusions and high concentrations of diamorphine.[7]

In another stability study[8] diamorphine hydrochloride in concentrations of both 1 and 20 mg/mL in sodium chloride 0.9% was stable for a minimum of 15 days at room temperature (23 degrees to 25 degrees) and 4 degrees when stored in a PVC container. In one type of disposable infusion device (Infusor) similar solutions were stable for 15 days even at 31 degrees. In another infusion device (Intermate 200) diamorphine was stable for a minimum of 15 days at both concentrations and all temperatures except for the 1 mg/mL solution kept at 31 degrees when stability was only maintained for a minimum of 2 days. When stored in glass syringes both strengths of diamorphine hydrochloride were stable for 15 days at 4 degrees and at room temperature the 1 mg/mL solution was stable for a minimum of 7 days and the 20 mg/mL solution was stable for a minimum of 12 days. There were no substantial changes in physical appearance or pH.

1. Davey EA, Murray JB. Hydrolysis of diamorphine in aqueous solutions. *Pharm J* 1969; **203:** 737.
2. Davey EA, Murray JB. Determination of diamorphine in the presence of its degradation products using gas liquid chromatography. *Pharm J* 1971; **207:** 167.
3. Cooper H, *et al*. Stability of diamorphine in chloroform water mixture. *Pharm J* 1981; **226:** 682–3.
4. Twycross RG. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 218.
5. Beaumont IM. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 41.
6. Jones VA, *et al*. Diamorphine stability in aqueous solution for subcutaneous infusion. *Br J Clin Pharmacol* 1987; **23:** 651P.
7. Omar OA, *et al*. Diamorphine stability in aqueous solution for subcutaneous infusion. *J Pharm Pharmacol* 1989; **41:** 275–7.
8. Kleinberg ML, *et al*. Stability of heroin hydrochloride in infusion devices and containers for intravenous administration. *Am J Hosp Pharm* 1990; **47:** 377–81.

Uses and Administration

Diamorphine hydrochloride is an acetylated morphine derivative and is a more potent opioid analgesic (p. 108.1) than morphine (p. 93.2). Diamorphine is used for the relief of severe pain especially in palliative care. It is also used similarly to morphine for the relief of dyspnoea due to pulmonary oedema resulting from left ventricular failure. Diamorphine has a powerful cough suppressant effect and has been given as Diamorphine Linctus (BPC 1973) to control cough associated with terminal lung cancer although morphine is now preferred.

In the treatment of **acute pain** usual doses of diamorphine hydrochloride by subcutaneous or intramuscular injection are 5 to 10 mg every 4 hours. Doses equivalent to one-quarter to one-half of the corresponding intramuscular dose may be given by slow intravenous injection.

For the pain of myocardial infarction doses of 5 mg are given by slow intravenous injection at a rate of 1 to 2 mg/minute with a further dose of 2.5 to 5 mg if required; doses may be reduced by one-half for elderly or frail patients. Doses of 2.5 to 5 mg may be given intravenously at the same rate for acute **pulmonary oedema**.

For **chronic pain** 5 to 10 mg may be given by subcutaneous or intramuscular injection every 4 hours; the dose may be increased according to needs. Similar doses may be given orally, although it is converted to morphine by first-pass metabolism (see Pharmacokinetics, p. 48.2). Diamorphine hydrochloride may also be given by continuous subcutaneous or intravenous infusion or intraspinally.

For details of doses in children, see below.

Action. Because of its abuse potential, supply of diamorphine is carefully controlled and in many countries it is not available for clinical use; morphine can provide equivalent analgesia by dose adjustment. There has been much debate regarding the relative merits of analgesia with diamorphine or morphine. Many now regard oral morphine to be the opioid analgesic of choice although diamorphine hydrochloride may be preferred for injection because it is more soluble in water thus allowing the use of smaller dose volumes. Diamorphine hydrochloride may also be preferred to morphine salts for intraspinal use because it is more lipid-soluble.

As a guide to relative potency:

- diamorphine hydrochloride 5 mg given intramuscularly is equivalent to about 10 mg given orally, which in turn is equivalent to about 15 mg of oral morphine sulfate
- when either drug is given by subcutaneous infusion, diamorphine hydrochloride 10 mg every 24 hours is equivalent to about 15 mg every 24 hours of morphine sulfate

Administration in children. In the treatment of acute or chronic pain in children, the *BNFC* suggests the following doses of diamorphine hydrochloride according to age or body-weight, and adjusted according to response:

by continuous intravenous infusion:

- neonates with spontaneous respiration may be given 2.5 to 7 micrograms/kg per hour
- ventilated neonates may be given 50 micrograms/kg initially by intravenous injection over 30 minutes followed by 15 micrograms/kg per hour by continuous intravenous infusion
- 1 month to 12 years: 12.5 to 25 micrograms/kg per hour

by intravenous injection:

- 1 to 3 months: 20 micrograms/kg every 6 hours
- 3 to 6 months: 25 to 50 micrograms/kg every 6 hours
- 6 to 12 months: 75 micrograms/kg every 4 hours

- 1 to 12 years: 75 to 100 micrograms/kg (maximum of 5 mg) every 4 hours

orally:

- 1 month to 12 years: 100 to 200 micrograms/kg (maximum of 10 mg) every 4 hours

In a study[1] of the effects of diamorphine in 34 premature infants (gestational age 26 to 40 weeks), a loading dose of 50 micrograms/kg given as an *intravenous* infusion over 30 minutes followed by a continuous infusion at a rate of 15 micrograms/kg per hour was considered to be safe and resulted in plasma concentrations of morphine comparable with those that usually produce adequate analgesia in children and adults; the duration of the infusion ranged from 14 to 149 hours. Small but significant reductions in heart rate and mean blood pressure were noted but these were not associated with any clinical deterioration. The fall in respiration rate reflected the desired intention to encourage synchronisation of the infants' breathing with the ventilator. The authors concluded that intravenous diamorphine could be given safely to neonates and would provide adequate analgesia. A later study[2] indicated that the use of a 200 micrograms/kg loading dose conferred no benefit over a 50 micrograms/kg dose and might produce undesirable physiological effects. In a comparative study[3] with morphine (200 micrograms/kg loading dose over 2 hours, followed by maintenance infusion of 25 micrograms/kg per hour) in ventilated preterm neonates requiring sedation, diamorphine (120 micrograms/kg over 2 hours and then 15 micrograms/kg per hour) was as effective as morphine in producing sedation and also had a faster onset of action. The small but significant drop in blood pressure noted during morphine infusions was not seen with diamorphine infusions.

The *subcutaneous* route appeared to be as effective and safe as the intravenous route for infusions in children for postoperative pain relief after elective abdominal surgery.[4] The dose of diamorphine used in both groups of children was 1 mg/kg given at a rate of 20 micrograms/kg per hour.

Intranasal diamorphine has been investigated in adults and children, and appears to be effective and well tolerated; because it does not require a needle it may offer particular advantages in children.[5] Guidelines[6] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intranasal diamorphine as an alternative to, or before treatment with, intravenous morphine for severe pain such as that associated with large burns, long bone fracture or dislocation, appendicitis, or sickle-cell crisis. In the UK, an intranasal spray containing the equivalent of 720 or 1600 micrograms of diamorphine per actuation is licensed for the treatment of acute severe nociceptive pain in children and adolescents aged 2 to 15 years in a hospital setting. The preparation and dose given are dependent on the child's body-weight; children weighing under 30 kg should receive the *nasal spray delivering 720 micrograms per actuation* in the following doses:

- 12 to < 18 kg: 2 sprays (1.44 mg)
- 18 to < 24 kg: 3 sprays (2.16 mg)
- 24 to < 30 kg: 4 sprays (2.88 mg)

Heavier children should receive the *nasal spray delivering 1600 micrograms per actuation* as follows:

- 30 to < 40 kg: 2 sprays (3.2 mg)
- 40 to 50 kg: 3 sprays (4.8 mg)

1. Elias-Jones AC, *et al*. Diamorphine infusion in the preterm neonate. *Arch Dis Child* 1991; **66:** 1155–7.
2. Barker DP, *et al*. Randomised, double blind trial of two loading dose regimens of diamorphine in ventilated newborn infants. *Arch Dis Child* 1995; **73:** F22–F26.
3. Wood CM, *et al*. Randomised double blind trial of morphine versus diamorphine for sedation of preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F34–F39.
4. Semple D, *et al*. Comparison of iv and sc diamorphine infusions for the treatment of acute pain in children. *Br J Anaesth* 1996; **76:** 310–12.
5. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42:** 501–13.
6. The College of Emergency Medicine. Best practice guideline: management of pain in children (July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)

Opioid dependence. The treatment of opioid dependence is discussed on p. 109.2. Many opiate misusers have expressed a preference for withdrawal using diamorphine rather than methadone. In a comparative study stabilisation was achieved using either diamorphine or methadone 1 mg/mL oral solutions;[1] patients could not identify which they had been given. Whenever signs of physical withdrawal were seen 10 mL of either solution was given and the total amount over the first 24 hours taken as the patient's daily requirement. The mean dose of diamorphine required for stabilisation was 55 mg compared with 36 mg for methadone. Some centres have given diamorphine in the form of reefers. Diamorphine has also been prescribed with methadone in the management of addicts.[2] A systematic review[3] that included this study failed to produce conclusive results about the efficacy of diamorphine (alone or with methadone) in maintenance treatment; however, since the studies were not directly comparable, continued evaluation in clinical studies is required. Oral tablets[4] and intravenous injection[5,6] of diamorphine have also been tried in severely dependent, treatment-resistant patients.

Breast feeding has been used to treat diamorphine dependence in the offspring of dependent mothers but this is no longer considered to be the best method and some authorities recommend that breast feeding should be stopped.

1. Ghodse AH, *et al*. Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. van den Brink W, *et al*. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Abridged version: *BMJ* 2003; **327:** 310–12. Correction. *ibid.*; 724. Full version: http://www.bmj.com/cgi/reprint/327/7410/310 (accessed 26/06/08)
3. Ferri M, *et al*. Heroin maintenance for chronic heroin dependents. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 26/06/08).
4. Frick U, *et al*. A prospective cohort study on orally administered heroin substitution for severely addicted opioid users. *Addiction* 2006; **101:** 1631–9.
5. March JC, *et al*. Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat* 2006; **31:** 203–11.
6. Oviedo-Joekes E, *et al*. Diacetylmorphine versus methadone for the treatment of opioid addiction. *N Engl J Med* 2009; **361:** 777–86.

Pain. *ACUTE PAIN.* Rapid pain relief may be obtained with the intravenous injection of diamorphine. Other routes include the intraspinal route for which diamorphine is well suited because of its lipid solubility and pharmacokinetics. Epidural doses of diamorphine have ranged from 0.5 to 10 mg.[1] Analgesia was significantly more prolonged and more intense after epidural rather than intramuscular injection of diamorphine 5 mg in women who had had caesarean section;[2] itching was reported by 50% of patients undergoing epidural analgesia. Epidural diamorphine alone[3] or with bupivacaine[4] has been used for analgesia during labour; addition of adrenaline appeared to improve the quality and duration of analgesia with diamorphine.[3] In another study addition of diamorphine to bupivacaine produced a high incidence of pruritus and drowsiness.[5] A study[6] of patient-controlled analgesia for postoperative pain found that although epidural diamorphine, used alone or with bupivacaine, reduced the analgesic dose requirement, there was little clinical advantage over the subcutaneous route.

Continuous epidural infusion of diamorphine 500 micrograms/hour in 0.125% bupivacaine provided postoperative analgesia superior to that with either drug alone in patients undergoing major abdominal gynaecological surgery.[7] A similar infusion produced analgesia superior to that with either epidural bolus injection or patient-controlled intravenous diamorphine in patients undergoing total abdominal hysterectomy.[8] However, more patients receiving the continuous epidural infusion were hypoxaemic than in the other 2 groups.

Diamorphine has also been given intrathecally for postoperative analgesia and should be effective at lower doses than with the epidural route because of greater CSF concentrations. Diamorphine 250 or 500 micrograms given intrathecally with bupivacaine spinal anaesthesia both provided greater postoperative analgesia than bupivacaine alone,[9] but the incidence of adverse effects, especially nausea, vomiting, and urinary retention, was still high with either dose and routine use of this technique was not recommended. Intrathecal diamorphine with bupivacaine has also been used for analgesia during labour[10,11] and caesarean section.[12-16] In a study[12] in patients undergoing caesarean section, intrathecal diamorphine 250 micrograms showed comparable postoperative analgesia with a 5-mg epidural dose and was associated with less postoperative nausea and vomiting. Other studies[13,15] found that intrathecal diamorphine reduced supplemental analgesic requirements during and after caesarean section when compared with intrathecal fentanyl. Intrathecal diamorphine 400 micrograms was considered by some[14] to be the lowest dose required to reduce intraoperative analgesic supplementation to below 5%; however, lower doses of 300 micrograms have been used in practice.[16]

Diamorphine has been extensively used by cardiologists in the UK for the management of pain in acute left ventricular failure, unstable angina, and myocardial infarction. It has been theorised that diamorphine may offer benefits over morphine because its stimulatory effects at opioid δ receptors on the myocardium may reduce the extent of myocardial damage.[17] Evidence to support this theory is, however, lacking.

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Macrae DJ, *et al*. Double-blind comparison of the efficacy of extradural diamorphine, extradural phenoperidine and im diamorphine following caesarean section. *Br J Anaesth* 1987; **59:** 354–9.
3. Keenan GMA, *et al*. Extradural diamorphine with adrenaline in labour: comparison with diamorphine and bupivacaine. *Br J Anaesth* 1991; **66:** 242–6.
4. McGrady EM, *et al*. Epidural diamorphine and bupivacaine in labour. *Anaesthesia* 1989; **44:** 400–3.
5. Bailey CR, *et al*. Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Gopinathan C, *et al*. A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. *Eur J Anaesthesiol* 2000; **17:** 189–96.
7. Lee A, *et al*. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60:** 845–50.
8. Madej TH, *et al*. Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. *Br J Anaesth* 1992; **69:** 554–7.
9. Reay BA, *et al*. Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery. *Br J Anaesth* 1989; **62:** 248–52.
10. Kestin IG, *et al*. Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
11. Vaughan DJA, *et al*. Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine. *Br J Anaesth* 2001; **86:** 567–9.
12. Hallworth SP, *et al*. Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82:** 228–32.
13. Cowan CM, *et al*. Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; **89:** 452–8.
14. Saravanan S, *et al*. Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section. *Br J Anaesth* 2003; **91:** 368–72.
15. Lane S, *et al*. A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60:** 453–7.
16. Wrench IJ, *et al*. Dose response to intrathecal diamorphine for elective caesarean section and compliance with a national audit standard. *Int J Obstet Anesth* 2007; **16:** 17–21.
17. Poullis M. Diamorphine and British cardiology: so we are right! *Heart* 1999; **82:** 645–6.

CHRONIC PAIN. Patients with chronic opioid-sensitive pain are often treated with diamorphine given by continuous subcutaneous infusion using a small battery-operated syringe driver. The following technique has been described.[1] Diamorphine hydrochloride 1 g could be dissolved in 1.6 mL of water to give a solution with a volume of 2.4 mL (415 mg/mL), but the maximum suggested concentration was 250 mg/mL. If the analgesic requirement was unknown the following protocol was recommended:

- Start injections every 4 hours of 2.5 or 5 mg diamorphine, or, if the patient has already been taking opioids, a dose that is equivalent to the last dose
- If this is unsatisfactory increase this dose in 50% increments until the patient reports even a little pain relief
- Calculate the 24-hour requirement by multiplying by six, and start the infusion at this level
- Increase the 24-hour dosage in the pump by 50% increments until the pain is controlled. Note that requirements may vary from less than 20 mg to more than 5 g per 24 hours

When starting an infusion it is important not to allow any breakthrough pain. This may be achieved either by starting the infusion more than 2 hours before the previous oral dose wears off or by giving a loading dose injection of the 4-hourly requirement.

Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous subcutaneous infusions.[2]

The intraspinal[3] and intraventricular[4] routes have also been used successfully in patients with intractable pain. Topical application of diamorphine has also been tried[5,6] for the control of pressure ulcer pain in a small number of palliative care patients.

1. Dover SB. Syringe driver in terminal care. *BMJ* 1987; **294:** 553–5.
2. Hoskin PJ, *et al*. Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
3. Baker L, *et al*. Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; **18:** 507–15.
4. Reeve WG, Todd JG. Intraventricular diamorphine via an Ommaya shunt for intractable cancer pain. *Br J Anaesth* 1990; **65:** 544–7.
5. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage* 2003; **25:** 547–54.
6. Abbas SQ. Diamorphine-Intrasite dressings for painful pressure ulcers. *J Pain Symptom Manage* 2004; **28:** 532–4.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Diamorphine is subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Diamorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, above).

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Pulmonary oedema after overdosage is a common cause of fatalities among diamorphine addicts. Nausea and hypotension are claimed to be less common than with morphine.

There are many reports of adverse effects associated with the abuse of diamorphine, usually obtained illicitly in an adulterated form.

Abuse. Most of the reports of adverse effects with diamorphine involve its abuse. In addition to the central effects, there are effects caused by the administration methods

and by the adulterants.[1,2] Thus in many instances it is difficult to identify the factor causing the toxicity. Most body systems are involved including the immune system,[3] kidneys,[4,5] liver,[6] respiratory system,[7-11] and the nervous system.[12-17]

Other aspects of the illicit use of diamorphine include fatal overdose[18] and smuggling by swallowing packages of drug[19,20] or other methods of internal bodily concealment.

1. Hendrickse RG, *et al.* Aflatoxins and heroin. *BMJ* 1989; **299:** 492–3.
2. CDC. Atypical reactions associated with heroin use: five states, January–April 2005. *MMWR* 2005; **54:** 793–6. Correction. *ibid.;* 852.
3. Husby G, *et al.* Smooth muscle antibody in heroin addicts. *Ann Intern Med* 1975; **83:** 801–5.
4. Cunningham EE, *et al.* Heroin-associated nephropathy. *JAMA* 1983; **250:** 2935–6.
5. do Sameiro Faria M, *et al.* Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant* 2003; **18:** 2308–13.
6. Weller IVD, *et al.* Clinical, biochemical, serological, histological and ultrastructural features of liver disease in drug abusers. *Gut* 1984; **25:** 417–23.
7. Anderson K. Bronchospasm and intravenous street heroin. *Lancet* 1986; **i:** 1208.
8. Cygan J, *et al.* Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. *Chest* 2000; **117:** 272–5.
9. Boto de los Bueis A, *et al.* Bronchial hyperreactivity in patients who inhale heroin mixed with cocaine vaporized on aluminium foil. *Chest* 2002; **121:** 1223–30.
10. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. *Chest* 2001; **120:** 1628–32.
11. Whale CI, *et al.* Inhaled heroin causing a life-threatening asthma exacerbation and marked peripheral eosinophilia. *Br J Hosp Med* 2007; **68:** 332–3.
12. Sempere AP, *et al.* Spongiform leucoencephalopathy after inhaling heroin. *Lancet* 1991; **338:** 320.
13. Roulet Perez E, *et al.* Toxic leucoencephalopathy after heroin ingestion in a 2½-year-old child. *Lancet* 1992; **340:** 729.
14. Zuckerman GB. Neurologic complications following intranasal administration of heroin in an adolescent. *Ann Pharmacother* 1996; **30:** 778–81.
15. Kriegstein AR, *et al.* Heroin inhalation and progressive spongiform leukoencephalopathy. *N Engl J Med* 1997; **336:** 589–90.
16. Long H, *et al.* A fatal case of spongiform leukoencephalopathy linked to "chasing the dragon". *J Toxicol Clin Toxicol* 2003; **41:** 887–91.
17. Dabby R, *et al.* Acute heroin-related neuropathy. *J Peripher Nerv Syst* 2006; **11:** 304–9.
18. Kintz P, *et al.* Toxicological data after heroin overdose. *Hum Toxicol* 1989; **8:** 487–9.
19. Stewart A, *et al.* Body packing—a case report and review of the literature. *Postgrad Med J* 1990; **66:** 659–61.
20. Traub SJ, *et al.* Pediatric "body packing". *Arch Pediatr Adolesc Med* 2003; **157:** 174–7.

Administration. Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous *subcutaneous* infusions.[1] Acute dysphoric reactions have been reported after the use of *epidural* diamorphine.[2]

1. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
2. Holder KJ, Morgan BM. Dysphoria after extradural diamorphine. *Br J Anaesth* 1994; **72:** 728.

Breast feeding. The American Academy of Pediatrics has stated[1] that, when used as a drug of abuse by breast-feeding mothers, diamorphine has caused adverse effects in the infant, notably tremors, restlessness, vomiting, and poor feeding. However, the *BNF* considers that diamorphine when given in therapeutic doses to a breast-feeding mother is unlikely to affect the breast-fed infant.

See also Opioid Dependence under Uses and Administration, p. 47.1.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Hypersensitivity. Anaphylaxis occurred in a patient given *intrathecal* diamorphine and bupivacaine for surgical anaesthesia;[1] the authors noted that the patient received patient-controlled analgesia with morphine shortly after the reaction without problem. Subsequent skin prick tests identified diamorphine as the likely causative agent.

1. Gooch I, Gwinnutt C. Anaphylaxis to intrathecal diamorphine. *Resuscitation* 2006; **70:** 470–3.

Phaeochromocytoma. Diamorphine can liberate endogenous histamine which may in turn stimulate release of catecholamines. Its use provoked hypertension and tachycardia in a patient with phaeochromocytoma.[1]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; **2:** 538.

Pregnancy and the neonate. Some references[1-7] to diamorphine dependence in pregnant women and the effects on the fetus and neonate.

1. Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *Am J Dis Child* 1978; **132:** 360–6.
2. Ostrea EM, Chavez CJ. Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. *J Pediatr* 1979; **94:** 292–5.
3. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; **102:** 686–91.
4. Klenka HM. Babies born in a district general hospital to mothers taking heroin. *BMJ* 1986; **293:** 745–6.
5. Gregg JEM, *et al.* Inhaling heroin during pregnancy: effects on the baby. *BMJ* 1988; **296:** 754.
6. Little BB, *et al.* Maternal and fetal effects of heroin addiction during pregnancy. *J Reprod Med* 1990; **35:** 159–62.
7. Mur Sierra A, *et al.* Asociación entre el consumo de heroína durante la gestación y anomalías estructurales de los cilios respiratorios en el período neonatal. *An Esp Pediatr* 2001; **55:** 335–8.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

Diamorphine hydrochloride is well absorbed from the gastrointestinal tract, although this may be erratic, and after subcutaneous or intramuscular injection. On injection it is rapidly hydrolysed to the active metabolite 6-*O*-monoacetylmorphine (6-acetylmorphine) in the blood and then to morphine (p. 95.3). Oral doses are subject to extensive first-pass metabolism to morphine; neither diamorphine nor 6-acetylmorphine has been detected in the blood after giving diamorphine by this route. Both diamorphine and 6-acetylmorphine readily cross the blood-brain barrier. Morphine glucuronides are the main excretion products in the urine. A small amount is excreted in the faeces.

References.

1. Boerner U, *et al.* The metabolism of morphine and heroin in man. *Drug Metab Rev* 1975; **4:** 39–73.
2. Inturrisi CE, *et al.* The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1984; **310:** 1213–17.
3. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
4. Barrett DA, *et al.* Morphine kinetics after diamorphine infusion in premature neonates. *Br J Clin Pharmacol* 1991; **32:** 31–7.
5. Girardin F, *et al.* Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts. *Clin Pharmacol Ther* 2003; **74:** 341–52.
6. Halbsguth U, *et al.* Oral diacetylmorphine (heroin) yields greater morphine bioavailability than oral morphine: bioavailability related to dosage and prior opioid exposure. *Br J Clin Pharmacol* 2008; **66:** 781–91.

Administration. *INHALATIONAL ROUTE.* A literature review[1] found that intranasal diamorphine had a similar pharmacokinetic profile to that of intramuscular diamorphine. It is rapidly absorbed, as a dry powder, via the nasal mucosa although this is not as complete as by intramuscular injection; intranasal absorption appeared to be dose dependent.

The pharmacokinetics of inhaled diamorphine fumes ("chasing the dragon") have been studied[2] in diamorphine addicts receiving substitution therapy with diamorphine and methadone. Absorption through the lungs occurred very rapidly and was virtually complete immediately after inhalation; bioavailability was estimated to be about 53%.

1. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42:** 501–13.
2. Rook EJ, *et al.* Population pharmacokinetics of heroin and its major metabolites. *Clin Pharmacokinet* 2006; **45:** 401–17.

INTRASPINAL ROUTE. Diamorphine is much more lipid-soluble and has a more rapid onset and shorter duration of action than morphine. Although deacetylation to morphine occurs rapidly in the blood it occurs only slowly in the CSF after intraspinal injection of diamorphine.[1] After intrathecal injection diamorphine was removed from the CSF much more rapidly than morphine.[2] Peak plasma concentrations of morphine after epidural diamorphine injection were significantly higher and were achieved significantly faster than after epidural injection of morphine.[3]

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35:** 40–5.
3. Watson J, *et al.* Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin. *Anesth Analg* 1984; **63:** 629–34.

Children. Loading doses of either 50 micrograms/kg or 200 micrograms/kg of diamorphine were given as an intravenous infusion over 30 minutes to 19 ventilated neonates followed by a continuous infusion of 15 micrograms/kg per hour, and the pharmacokinetics of the products of diamorphine metabolism (morphine, morphine-6-glucuronide, and morphine-3-glucuronide) studied.[1] Although the overall elimination of morphine was reduced compared with adults, the relative contributions of the various metabolic routes of morphine remained similar between neonates and adults. Data from this study did not indicate any advantage for the higher loading dose (see also under Uses and Administration, p. 46.3).

1. Barrett DA, *et al.* Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol* 1996; **41:** 531–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Diaphin; ***UK***: Ayendi.

Pharmacopoeial Preparations

BP 2014: Bupivacaine and Diamorphine Injection; Diamorphine Injection;

BPC 1973: Diamorphine Linctus.

Diclofenac *(BAN, rINN)*

Diclofénac; Diclofenaco; Diclofenacum; Diklofenaakki; Diklofenak; Диклофенак.

[2-(2,6-Dichloroanilino)phenyl]acetic acid.

$C_{14}H_{11}Cl_2NO_2$=296.1

CAS — 15307-86-5.

ATC — D11AX18; M01AB05; M02AA15; S01BC03.

ATC Vet — QD11AX18; QM01AB05; QM02AA15; QS01BC03.

UNII — 144O8QL0L1.

Diclofenac Diethylamine *(BANM)*

Diclofenac Diethylammonium; Diclofenaco dietilamina; Diklofenak Dietilamonyum; Диклофенак Диэтиламин.

$C_{18}H_{22}Cl_2N_2O_2$=369.3

CAS — 78213-16-8.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — 6TGQ35Z71K.

Pharmacopoeias. In *Br.*

BP 2014: (Diclofenac Diethylamine). A white to light beige, crystalline powder. Sparingly soluble in water and in acetone; freely soluble in alcohol and in methyl alcohol; practically insoluble in 1M sodium hydroxide. The pH of a 1% solution in alcohol (10%) is between 6.4 and 8.4. Store in airtight containers. Protect from light.

Diclofenac Epolamine

DHEP; Diclofenac Hydroxyethylpyrrolidine; Диклофенак Эполамин.

$C_{14}H_{11}Cl_2NO_2$, $C_6H_{13}NO$=411.3

CAS — 119623-66-4.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — X5F8EKL9ZG.

Diclofenac Potassium *(BANM, USAN, rINNM)*

CGP-45840B; Diclofenac-Kalium; Diclofénac Potassique; Diclofenaco potásico; Diclofenacum kalicum; Diklofenaakkikalium; Diklofenak draselná sůl; Diklofenak Potasyum; Diklofenakkalium; Diklofenák-kálium; Diklofenako kalio druska; Kalii Diclofenacum; Калия Диклофенак.

Potassium [*o*-(2,6-dichloroanilino)phenyl]acetate.

$C_{14}H_{10}Cl_2KNO_2$=334.2

CAS — 15307-81-0.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — L4D5UA6CB4.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Diclofenac Potassium). A white or slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Diclofenac Potassium). pH of a 1% solution in water is between 7.0 and 8.5. Store at a temperature of 20 degrees to 25 degrees. Protect from light.

Diclofenac Sodium *(BANM, USAN, rINNM)*

Diclofenac-Natrium; Diclofénac sodique; Diclofenaco sódico; Diclofenacum natricum; Diclophenac Sodium; Diklofenaakkinatrium; Diklofenak sodná sůl; Diklofenak Sodyum; Diklofenaknatrium; Diklofenák-nátrium; Diklofenako natrio druska; GP-45840; Natrii Diclofenacum; Натрий Диклофенак.

Sodium [2-(2,6-dichloroanilino)phenyl]acetate.

$C_{14}H_{10}Cl_2NNaO_2$=318.1

CAS — 15307-79-6.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — QTG126297Q.

NOTE. DICL is a code approved by the BP 2014 for use on single unit doses of eye drops containing diclofenac sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn, US,* and *Viet.*

Ph. Eur. 8: (Diclofenac Sodium). A white to slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Diclofenac Sodium). A white to off-white, hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store in airtight containers. Protect from light.

Uses and Administration

Diclofenac, a phenylacetic acid derivative, is an NSAID (p. 102.3). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions: musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendinitis; soft-tissue disorders such as sprains and strains; and other painful conditions such as renal colic, acute gout, dysmenorrhoea, migraine, and after some surgical procedures. It has also been used in some countries for the management of actinic keratoses and fever. Eye drops of diclofenac sodium are used for the prevention of intra-operative miosis during cataract extraction, for the treatment of inflammation after surgery or laser treatment of the eye, for pain in corneal epithelial defects after surgery or accidental trauma, and for the relief of ocular signs and symptoms of seasonal allergic conjunctivitis.

The usual **oral** or **rectal** dose of diclofenac sodium is 75 to 150 mg daily in divided doses. In the UK the maximum dose regardless of route or indication is 150 mg daily; however, in the USA a maximum oral dose of 200 mg daily is allowed in the treatment of rheumatoid arthritis. Modified-release preparations of diclofenac sodium are available for oral use. Diclofenac has also been given in equivalent oral doses as the free acid in dispersible preparations for short-term treatment up to 3 months long. Diclofenac is also given orally as the potassium salt. Doses of the potassium salt are similar to those for diclofenac sodium. Diclofenac potassium is also used in the treatment of migraine in an initial dose of 50 mg taken at the first signs of an attack; an additional dose of 50 mg may be taken after 2 hours if symptoms persist. If necessary further doses of 50 mg may be taken every 4 to 6 hours to a maximum daily dose of 200 mg.

Diclofenac sodium may also be given by deep intramuscular **injection** into the gluteal muscle in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. Diclofenac sodium may also be given as a continuous or intermittent intravenous infusion in glucose 5% or sodium chloride 0.9% (both previously buffered with sodium bicarbonate) or as a bolus intravenous injection. For the treatment of postoperative pain a dose of 75 mg may be given over 30 to 120 minutes or as a bolus injection. The dose may be repeated once after 4 to 6 hours if necessary. To prevent postoperative pain, an initial dose of 25 to 50 mg diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg/hour to a maximum of 150 mg daily. Alternatively, the initial dose may be given as a bolus injection over 5 to 60 seconds followed by additional injections up to the maximum daily dosage; this may be repeated after 4 to 6 hours if necessary although the *total* dose should not exceed the maximum daily dose of 150 mg. The maximum period recommended for parenteral use is 2 days. Diclofenac sodium is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary.

For dosage details in children, see below.

Diclofenac sodium is used as a 0.1% **ophthalmic solution** in various situations:

- for the prevention of intra-operative miosis during cataract surgery, it is instilled in the appropriate eye 4 times during the 2 hours before surgery
- for the treatment of postoperative inflammation after cataract surgery, it is instilled 4 times daily for up to 28 days starting 24 hours after surgery
- for the control of post-photorefractive keratectomy pain, it is instilled twice in the hour before surgery, then one drop twice at 5-minute intervals immediately after the procedure, and then every 2 to 5 hours while awake for up to 24 hours
- for pain control after accidental trauma, one drop is instilled 4 times daily for up to 2 days
- in the treatment of inflammation and discomfort after strabismus surgery, one drop is instilled 4 times daily for the first week; this is reduced to 3 times daily in the second week, twice daily in the third week, and as required for the fourth week
- for the control of inflammation after argon laser trabeculoplasty, one drop is instilled 4 times during the 2 hours before the procedure followed by one drop 4 times daily for up to 7 days after the procedure
- for the treatment of pain and discomfort after radial keratotomy, one drop is instilled before surgery followed by one drop immediately after surgery and then one drop 4 times daily for up to 2 days
- to relieve symptoms of seasonal allergic conjunctivitis, one drop is instilled 4 times daily as necessary

Diclofenac diethylamine is used **topically** as a gel containing the equivalent of 1% of diclofenac sodium for the local symptomatic relief of pain and inflammation; it is applied to the affected site 3 or 4 times daily; treatment should be reviewed after 14 days or after 28 days if used for osteoarthritis. A topical spray containing diclofenac sodium 4% is also available; 4 or 5 sprays (32 or 40 mg of diclofenac sodium) may be applied 3 times daily, up to a maximum of 15 sprays (120 mg of diclofenac sodium) daily; treatment should be reviewed after 7 or 8 days. A topical solution of diclofenac sodium 1.6% is available for the treatment of osteoarthritis in superficial joints such as the wrist or knee; it is applied in small aliquots to achieve a total of 20 or 40 drops, depending on the size of the joint, and repeated four times daily. Diclofenac is also used in the management of actinic keratoses; it is applied twice daily as diclofenac sodium gel 3% for 60 to 90 days but the optimum therapeutic effect may not be seen until 30 days after the end of treatment. Diclofenac epolamine is also used topically as a plaster containing the equivalent of 1% of diclofenac sodium for local symptomatic pain relief in ankle sprain and epicondylitis. In the treatment of ankle sprain, 1 plaster is applied once daily for a maximum of 3 days and for epicondylitis, 1 plaster is applied twice daily for a maximum of 14 days.

Diclofenac is available as a combination preparation with misoprostol (p. 2140.3) for patients at risk of NSAID-induced peptic ulceration.

Administration. *IN CHILDREN.* In children aged 1 to 12 years the licensed UK *oral* or *rectal* dose of diclofenac sodium for juvenile idiopathic arthritis is 1 to 3 mg/kg daily in divided doses. In children aged 6 to 12 years diclofenac sodium may also be given rectally for the treatment of acute postoperative pain, either alone or as an adjunct to opiate therapy; a usual dose is 1 to 2 mg/kg daily in divided doses for a maximum of 4 days. The *parenteral route* is not licensed for use in children although it has been used (see below).

The *BNFC* suggests slightly different doses of diclofenac sodium: in the management of rheumatic disease, including juvenile idiopathic arthritis, in children from 6 months to 18 years of age, it recommends an oral dose of 3 to 5 mg/kg daily, in 2 or 3 divided doses. For relief of mild to moderate pain and inflammation in, for example, soft-tissue disorders, the recommended oral or rectal dose in children from 6 months to 18 years of age is 0.3 to 1 mg/kg given three times daily; children 2 to 18 years of age may be given a similar dose once or twice daily *by intravenous infusion* or *deep intramuscular (gluteal) injection* for up to 2 days for postoperative pain. Rectal doses may also be given for postoperative pain to children from 6 months to 18 years of age, according to body-weight, for a maximum of 4 days: those weighing 8 to 12 kg may be given 12.5 mg twice daily and heavier children 1 mg/kg three times daily.

Regardless of route or indication, a maximum daily dose of 150 mg should not be exceeded.

Diclofenac potassium has also been used in children aged over 14 years for the treatment of rheumatic disease, musculoskeletal disorders, and postoperative pain; it is given in an *oral* dose of 75 to 100 mg daily in 2 or 3 divided doses.

TOPICAL References to the use of plasters providing sustained topical release of diclofenac epolamine,[1-6] and reviews of the use of a topical solution of diclofenac with dimethyl sulfoxide to treat osteoarthritis.[7,8] The latter was found to be effective and better tolerated than oral use.

1. Galeazzi M, Marcolongo R. A placebo-controlled study of the efficacy and tolerability of a nonsteroidal anti-inflammatory drug, DHEP plaster, in inflammatory peri-and extra-articular rheumatological diseases. *Drugs Exp Clin Res* 1993; **19:** 107–15.
2. Dreiser RL, Tisne-Camus M. DHEP plasters as a topical treatment of knee osteoarthritis—a double-blind placebo-controlled study. *Drugs Exp Clin Res* 1993; **19:** 117–23.
3. Affaitati G, *et al.* Effects of topical diclofenac (DHEP plaster) on skin, subcutis and muscle pain thresholds in subjects without spontaneous pain. *Drugs Exp Clin Res* 2001; **27:** 69–76.
4. Jenoure P-J. Évaluation d'un anti-inflammatoire non stéroïdien topique dans le traitement de la douleur et de l'inflammation: exemple de Flector Tissugel 1% dispositif local bioadhésif de diclofénac épolamine. *Presse Med* 2004; **33:** 10–13.
5. Brühlmann P, *et al.* Short-term treatment with topical diclofenac epolamine plaster in patients with symptomatic knee osteoarthritis: pooled analysis of two randomised clinical studies. *Curr Med Res Opin* 2006; **22:** 2429–38.
6. Alessandri F, *et al.* Topical diclofenac patch for postoperative wound pain in laparoscopic gynecologic surgery: a randomized study. *J Minim Invasive Gynecol* 2006; **13:** 195–200.
7. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2006; **33:** 567–73.
8. Moen MD. Topical diclofenac solution. *Drugs* 2009; **69:** 2621–32.

Actinic keratoses. Diclofenac sodium 3% in hyaluronic acid gel is used[1-3] in the treatment of actinic keratoses (see Basal Cell and Squamous Cell Carcinoma, p. 714.2), and a meta-analysis[4] found it to be of benefit, despite previous concerns that the preparation may not be significantly more effective than hyaluronic acid gel alone.[5] An open-label comparison involving 30 patients with multiple actinic keratoses suggested that 90 days of treatment with diclofenac sodium 3% gel (to lesions on one side of the face and scalp) was better tolerated, but slightly less effective, than 28 days of treatment with fluorouracil 5% cream (to lesions on the other side).[6]

1. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997; **133:** 1239–42.
2. Rivers JK, *et al.* Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146:** 94–100.
3. Ulrich C, *et al.* Treatment of multiple actinic keratoses with topical diclofenac 3% gel in organ transplant recipients: a series of six cases. *Br J Dermatol* 2007; **156** (suppl 3): 40–2.
4. Pirard D. *et al.* Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. *Arch Dermatol Res* 2005; **297:** 185–9.
5. McEwan LE, Smith JG. Topical diclofenac/hyaluronic acid gel in the treatment of solar keratoses. *Australas J Dermatol* 1997; **38:** 187–9.
6. Smith SR, *et al.* Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol* 2006; **5:** 156–9.

Pain. Reviews.

1. McCormack PL, Scott LJ. Diclofenac sodium injection (Dyloject): in postoperative pain. *Drugs* 2008; **68:** 123–30. Correction. *ibid.*; 801.
2. Derry P, *et al.* Single dose oral diclofenac for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 09/09/09).
3. Standing JF, *et al.* Diclofenac for acute pain in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/03/10).

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

There may be pain and, occasionally, tissue damage at the site of injection when diclofenac is given intramuscularly. Diclofenac suppositories can cause local irritation. Transient burning and stinging may occur with diclofenac ophthalmic solution; more serious corneal adverse effects have also occurred (see Effects on the Eyes, p. 50.1). Topical preparations of diclofenac, such as plasters and gel, may cause application site reactions.

Incidence of adverse effects. A review of worldwide clinical studies with diclofenac[1] has reported the incidence of drug-associated adverse effects to be about 12%; about 16% of patients who had adverse effects stopped treatment (a figure corresponding to about 2% of the entire patient sample). The most frequently reported adverse effects were gastrointestinal and were reported in 7.6% of patients. CNS-related adverse effects were reported in 0.7% of patients and allergy or local reactions in 0.4%. This and other reviews[2] have shown that adverse effects associated with diclofenac are usually mild and transient and appear to be unrelated to the dose given.

The incidence of adverse effects in children is similar to that in adults.[3]

1. Willkens RF. Worldwide clinical safety experience with diclofenac. *Semin Arthritis Rheum* 1985; **15** (suppl 1): 105–10.
2. Small RE. Diclofenac sodium. *Clin Pharm* 1989; **8:** 545–8.
3. Standing JF, *et al.* Prospective observational study of adverse drug reactions to diclofenac in children. *Br J Clin Pharmacol* 2009; **68:** 243–51.

Effects on the blood. Results of a large survey undertaken to assess the relation between agranulocytosis, aplastic anaemia, and drug exposure indicated that diclofenac was significantly associated with aplastic anaemia, providing an estimated tenfold increase in risk.[1] There are reports of other haematological abnormalities including haemolytic anaemia,[2,3] thrombocytopenia,[4,5] neutropenia,[5] and agranulocytosis[6] occurring in patients given diclofenac.

Localised spontaneous bleeding,[7] bruising,[8] inhibition of platelet aggregation,[7] and prolonged bleeding time[8] have been reported.

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. López A, *et al.* Autoimmune hemolytic anemia induced by diclofenac. *Ann Pharmacother* 1995; **29:** 787.
3. Ahrens N, *et al.* Misdiagnosis in patients with diclofenac-induced hemolysis: new cases and a concise review. *Am J Hematol* 2006; **81:** 128–31.
4. George S, Rahi AHS. Thrombocytopenia associated with diclofenac therapy. *Am J Health-Syst Pharm* 1995; **52:** 420–1.
5. Kim HL, Kovacs MJ. Diclofenac-associated thrombocytopenia and neutropenia. *Ann Pharmacother* 1995; **29:** 713–15.
6. Colomina P, Garcia S. Agranulocytosis caused by diclofenac. *DICP Ann Pharmacother* 1989; **23:** 507.
7. Price AJ, Obeid D. Spontaneous non-gastrointestinal bleeding associated with diclofenac. *Lancet* 1989; **ii:** 1520.
8. Khazan U, *et al.* Diclofenac sodium and bruising. *Ann Intern Med* 1990; **112:** 472–3.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including diclofenac, see p. 105.1.

Effects on electrolytes. A syndrome resembling the syndrome of inappropriate antidiuretic hormone secretion has been reported in elderly women given diclofenac.[1,2] Also the UK CSM had received a report of fatal hyponatraemia in another elderly woman.[2]

1. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
2. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.

Effects on the eyes. A patient who had been taking oral diclofenac for several years and had increasingly complained of dry, gritty eyes noticed that eye irritation disappeared within 3 days when diclofenac had to be stopped because of gastrointestinal effects.[1]

Ocular diclofenac and related drugs have been implicated in reports of corneal toxicity. Ulceration of the conjunctiva or cornea, corneal or scleral melts, and perforations have been reported in patients using diclofenac eye drops, particularly after cataract surgery.[2-5] Keratitis and perforations were also reported with ketorolac eye drops,[4] although less frequently. For mention of corneal melting with bromfenac, see p. 30.1.

1. Reid ALA, Henderson R. Diclofenac and dry, irritable eyes. *Med J Aust* 1994; **160:** 308.
2. Lin JC, *et al*. Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. *Arch Ophthalmol* 2000; **118:** 1129–32.
3. Congdon NG, *et al*. Corneal complications associated with topical ophthalmic use of nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg* 2001; **27:** 622–31.
4. Guidera AC, *et al*. Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. *Ophthalmology* 2001; **108:** 936–44.
5. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. *Trans Am Ophthalmol Soc* 2001; **99:** 205–10.

Effects on the gastrointestinal tract. The most frequent adverse effects reported in patients given diclofenac systemically are gastrointestinal in nature. Typical reactions include epigastric pain, nausea, vomiting, and diarrhoea. Rarely peptic ulcer and gastrointestinal bleeding have occurred. Diclofenac has also been implicated as the causative agent in colonic ulceration,[1] small bowel perforation,[2] and pseudomembranous colitis.[3] Diclofenac suppositories may cause local reactions such as itching, burning, or exacerbation of haemorrhoids.

1. Carson J, *et al*. Colonic ulceration and bleeding during diclofenac therapy. *N Engl J Med* 1990; **323:** 135.
2. Deakin M, *et al*. Small bowel perforation associated with an excessive dose of slow release diclofenac sodium. *BMJ* 1988; **297:** 488–9.
3. Gentric A, Pennec YL. Diclofenac-induced pseudomembranous colitis. *Lancet* 1992; **340:** 126–7.

Effects on the kidneys. Renal papillary necrosis[1] and nephrotic syndrome[2-4] have been reported in patients taking diclofenac. See also Effects on Electrolytes, p. 49.3.

1. Scott SJ, *et al*. Renal papillary necrosis associated with diclofenac sodium. *BMJ* 1986; **292:** 1050.
2. Beun GDM, *et al*. Isolated minimal change nephropathy associated with diclofenac. *BMJ* 1987; **295:** 182–3.
3. Yinnon AM, *et al*. Nephrotic syndrome associated with diclofenac sodium. *BMJ* 1987; **295:** 556.
4. Tattersall J, *et al*. Membranous nephropathy associated with diclofenac. *Postgrad Med J* 1992; **68:** 392–3.

Effects on the liver. Elevations of serum aminotransferase activity and clinical hepatitis,[1-8] including fatal fulminant hepatitis[2,5] have occurred in patients taking diclofenac. There has also been a case report of hepatorenal damage attributed to diclofenac.[9] Analysis[10] of 180 of the cases of diclofenac-associated hepatic injury received by the FDA between November 1988 and June 1991 suggested an increased risk of hepatotoxicity in female patients and those taking diclofenac for osteoarthritis. Hepatotoxicity had been detected within 6 months of starting diclofenac in 85% of the patients. The biochemical pattern of injury was hepatocellular or mixed hepatocellular in 66% of patients and cholestatic injury was found in 8% of patients. Signs of hypersensitivity were uncommon and it was considered that the mechanism of hepatic injury was likely to be a metabolic idiosyncratic reaction rather than due to intrinsic toxicity of diclofenac.

1. Dunk AA, *et al*. Diclofenac hepatitis. *BMJ* 1982; **284:** 1605–6.
2. Breen EG, *et al*. Fatal hepatitis associated with diclofenac. *Gut* 1986; **27:** 1390–3.
3. Schapira D, *et al*. Diclofenac-induced hepatotoxicity. *Postgrad Med J* 1986; **62:** 63–5.
4. Ryley NG, *et al*. Diclofenac associated hepatitis. *Gut* 1989; **30:** A708.
5. Helfgott SM, *et al*. Diclofenac-associated hepatotoxicity. *JAMA* 1990; **264:** 2660–2.
6. Purcell P, *et al*. Diclofenac hepatitis. *Gut* 1991; **32:** 1381–5.
7. Bhogaraju A, *et al*. Diclofenac-associated hepatitis. *South Med J* 1999; **92:** 711–13.
8. Greaves RRSH, *et al*. Inadvertent diclofenac rechallenge from generic and non-generic prescribing, leading to liver transplantation for fulminant liver failure. *Eur J Gastroenterol Hepatol* 2001; **13:** 71–3.
9. Diggory P, *et al*. Renal and hepatic impairment in association with diclofenac administration. *Postgrad Med J* 1989; **64:** 507–8.
10. Banks AT, *et al*. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22:** 820–7.

Effects on the skin. Self-limiting skin reactions such as rash or pruritus may occur in patients given diclofenac. More serious skin reactions attributed to diclofenac include bullous dermatitis[1] and erythema multiforme.[2,3] Local irritation and necrosis have occurred on intramuscular injection of diclofenac.[4-7]

1. Gabrielsen TØ, *et al*. Drug-induced bullous dermatosis with linear IgA deposits along the basement membrane. *Acta Derm Venereol (Stockh)* 1981; **61:** 439–41.
2. Morris BAP, Remtulla SS. Erythema multiforme major following use of diclofenac. *Can Med Assoc J* 1985; **133:** 665.
3. Young J. Erythema multiforme-like eruption as a result of 'Solaraze' treatment. *J Dermatol Treat* 2003; **14:** 189.
4. Stricker BHC, van Kasteren BJ. Diclofenac-inducedisolated myonecrosis and the Nicolau syndrome. *Ann Intern Med* 1992; **117:** 1058.
5. Pillans PI, O'Connor N. Tissue necrosis and necrotising fasciitis after intramuscular administration of diclofenac. *Ann Pharmacother* 1995; **29:** 264–6.
6. Ezzedine K, *et al*. Nicolau syndrome following diclofenac administration. *Br J Dermatol* 2004; **150:** 385–7.
7. Mutalik S, Belgaumkar V. Nicolau syndrome: a report of 2 cases. *J Drugs Dermatol* 2006; **5:** 377–8.

Hypersensitivity. Aspirin-sensitive asthmatic patients have developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) when challenged with diclofenac in doses of 10 to 25 mg[1] and the UK CSM has received a report of an aspirin-sensitive patient who died from acute asthma 4 hours after a single 25-mg dose of diclofenac.[2]

Anaphylactic shock has been reported.[3]

1. Szczeklik A, *et al*. Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2:** 231–2.
2. CSM/MCA. Avoid all NSAIDs in aspirin-sensitive patients. *Current Problems* 1993; **19:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
3. Dux S, *et al*. Anaphylactic shock induced by diclofenac. *BMJ* 1983; **286:** 1861.

Precautions

As for NSAIDs in general, p. 107.1.

Systemic diclofenac is contra-indicated in patients with moderate to severe heart failure (NYHA class II to IV), ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular events such as hypertension, hyperlipidaemia, diabetes mellitus, and smoking. Systemic diclofenac is also contra-indicated in patients with severe hepatic or renal impairment.

In addition, use of intravenous diclofenac is contra-indicated in patients with moderate or severe renal impairment, hypovolaemia, or dehydration; it should also not be given intravenously to patients with a history of haemorrhagic diathesis, cerebrovascular bleeding (including suspected), or asthma nor in patients undergoing surgery with a high risk of haemorrhage.

Ophthalmic preparations containing diclofenac should not be used by patients who wear soft contact lenses.

Breast feeding. Diclofenac is distributed into breast milk although the *BNF* considers the amount to be too small to be harmful to breast-fed infants.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diclofenac as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Veterinary use. Veterinary use of diclofenac in cattle in South Asia has been associated with severe decline in the numbers of vultures, to whom the residues are highly toxic if they consume the carcasses.[1,2] Meloxicam (p. 86.3) has been suggested as an alternative.

1. Shultz S, *et al*. Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. *Proc Biol Sci* 2004; **271** (suppl 6): S458–S460.
2. Sharp D. Meloxicam to prevent rabies? *Lancet* 2006; **367:** 887–8.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Diclofenac should not be given intravenously to patients already receiving other NSAIDs or anticoagulants including low-dose heparin.

Ciclosporin. Deterioration in renal function has been attributed to the use of diclofenac with ciclosporin.[1] Increased concentrations of diclofenac were also noted with ciclosporin;[2] licensed product information for ciclosporin recommends that the dosage of diclofenac should be reduced by about one-half when the two are given together.

1. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337:** 252.
2. Kovarik JM, *et al*. Cyclosporine and nonsteroidal antiinflammatory drugs: exploring potential drug interactions and their implications for the treatment of rheumatoid arthritis. *J Clin Pharmacol* 1997; **37:** 336–43.

Corticosteroids. Concomitant use of ophthalmic preparations containing diclofenac with those containing corticosteroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications.

Diuretics. Deterioration in renal function has been attributed to the use of diclofenac with *triamterene*.[1]

1. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; **293:** 698–9.

Gastrointestinal drugs. A decrease in the plasma concentration of diclofenac has been reported[1] when given after *sucralfate*.

1. Pedrazzoli J, *et al*. Short-term sucralfate administration alters potassium diclofenac absorption in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43:** 104–8.

Lipid regulating drugs. *Colestyramine* appears substantially to reduce the bioavailability of diclofenac when the two drugs are given together;[1] *colestipol* produces a similar but smaller effect.

1. al-Balla SR, *et al*. The effects of cholestyramine and colestipol on the absorption of diclofenac in man. *Int J Clin Pharmacol Ther* 1994; **32:** 441–5.

Misoprostol. The plasma concentration of diclofenac was reduced when it was given as a 100-mg dose daily in the form of a modified-release preparation to subjects receiving misoprostol 800 micrograms daily.[1] Use together was also associated with an increase in the incidence and severity of gastrointestinal effects. Studies by the manufacturer[2] had failed to find any significant pharmacokinetic interactions between diclofenac and misoprostol when given in a formulation containing diclofenac 50 mg and misoprostol 200 micrograms.

1. Dammann HG, *et al*. Differential effects of misoprostol and ranitidine on the pharmacokinetics of diclofenac and gastrointestinal symptoms. *Br J Clin Pharmacol* 1993; **36:** 345–9.
2. Karim A. Pharmacokinetics of diclofenac and misoprostol when administered alone or as a combination product. *Drugs* 1993; **45** (suppl 1): 7–14.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Diclofenac is rapidly absorbed when given as an oral solution, sugar-coated tablets, rectal suppository, or by intramuscular injection. It is absorbed more slowly when given as enteric-coated tablets, especially when this dosage form is given with food. Although diclofenac given orally is almost completely absorbed, it is subject to first-pass metabolism so that about 50% of the drug reaches the systemic circulation in the unchanged form. Diclofenac is also absorbed percutaneously. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid where concentrations may persist even when plasma concentrations fall; small amounts are distributed into breast milk. The terminal plasma half-life is about 1 to 2 hours. Diclofenac is metabolised to 4′-hydroxydiclofenac, 5-hydroxydiclofenac, 3′-hydroxydiclofenac, and 4′,5-dihydroxydiclofenac. It is then excreted in the form of glucuronide and sulfate conjugates, mainly in the urine (about 60%) but also in the bile (about 35%); less than 1% is excreted as unchanged diclofenac.

References.

1. Fowler PD, *et al*. Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur J Clin Pharmacol* 1983; **25:** 389–94.
2. Maggi CA, *et al*. Comparative bioavailability of diclofenac hydroxyethylpyrrolidine vs diclofenac sodium in man. *Eur J Clin Pharmacol* 1990; **38:** 207–8.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac: therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997; **33:** 184–213.
4. Brenner SS, *et al*. Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet* 2003; **42:** 283–92.
5. Hinz B, *et al*. Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* 2005; **59:** 80–4.
6. Standing JF, *et al*. Population pharmacokinetics of oral diclofenac for acute pain in children. *Br J Clin Pharmacol* 2008; **66:** 846–53.
7. Miyatake S, *et al*. Randomized clinical comparisons of diclofenac concentration in the soft tissues and blood plasma between topical and oral applications. *Br J Clin Pharmacol* 2009; **67:** 125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ainedif; Aldoron NF; Algicler; Algioxib; Anaflex; ATM 101; Atomo Desinflamante Geldic; Banoclus; Befol; Blokium Prost†; Blokium; Calmoflex; Curinflam VL; Curinflam; DFN; Diastone; Diclac; Diclofilab; Diclogesic; Diclograng; Diclolabsa; Diclolam; Diclomar; Diclonex; Dicloreumol; Difenac Forte; Difenac; Dilam†; Dioxaflex Protect; Dioxaflex; Disipan; Distec; Dolo Tomanil; Dolofenac; Doloneitor; Dolvan; Doxtran; Excelentia Analgesico; Faboflem†; Flexin; Flexiplen; Flogolisin; Fluxpiren; Gel Antiinflamatorio; Gentisalyl; Iglodine; Imanol; Ingeclof†; Kamox†; Kinalgin; Klonafenac; Levedad; Lorbifenac; Metaflex NF; Miocalm†; Nalgiflex; Natura Fenac; Norviken; Oxa; Oxaprost; Pronix; Quer-Out; Rati Salil D; Reumosan; Rodinac; Salicrem Forte; Silfox; Tomanil; Vesa-

lion; Viartril NF; Vimultisa; Virobron Gel; Virobron NF; Volforte; Voltaren Colirio; Voltaren Migra†; Voltaren; Xedenol; ***Austral.***: Arthrotec; Clonac†; Dencorub Anti-Inflammatory; Diclac†; Diclohexal†; Dinac†; Fenac; Imflac; Solaraze; Viclofen; Voltaren Ophtha; Voltaren; Voltfast; ***Austria***: Algefit; Arthrotec; Dedolor; Deflamat; DiclacHexal; Diclobene; Diclomelan; Diclostad; Diclosyl; Dolostrip; Dolpasse; Flector; Solaraze; Tratul; Voltadol; Voltaren; ***Belg.***: Arthrotec; Cataflam; Dicloabak; Diclofast†; Diclofemed†; Diclotop†; Docdiclofe†; Flector; Kinespir; Motifene; Polyflam; Voltapatch; Voltaren; ***Braz.***: Artren; Belfaren; Benevran; Biofenac; Cataflam; Cataflex; Cataflexym; Cinaflan; Cinatil; Clofenak; Clofenid; Deltaflogin; Deltaren; Diclac; Diclo P; Dicloflogil; Diclogenom; Diclonaco; Diclonax; Diclonil; Diclosodico†; Diclostir; Dicloton; Dioxaflex; Dnaren; Dorflan; Dorgen; Dryltac; Fenaflan; Fenaren; Fenburil†; Fisioren; Fladon†; Flamatrat P; Flanakin†; Flanaren; Flodin Duo; Flogan; Flogiren; Flotac; Infladex; Inflamax; Kindaren†; Maxilerg; Neocoflan; Neotaflan; Neotaren; Olfen†; Ortoflan†; Poltax; Probenxil; Prodofenaco†; Sodix; Still; Tekaflex; Vendrex; Volflanil; Voltaflan; Voltaflex; Voltaren Colirio; Voltaren; Voltrix; Zotac; ***Canad.***: Apo-Diclo; Arthrotec; Novo-Difenac†; Nu-Diclo; Pennsaid; Pro-Diclo; Voltaren Ophtha; Voltaren; ***Chile***: 3A Ofteno; Amofen; Artren; Autdol; Cataflam; Deflamat; Diclac; Diclotaren; Dicogel; Elitiran; Exflam†; Flamesan; Flector; Flotac; Klafenac; Lertus; Merpal; Oftic; Pirexyl; Piroflam; Pro Lertus; Sipirac; Turbogesic; Voltaren; ***China***: Aofen (澳芬); Apo-Diclo (奥贝); Arthrotec (奥斯克); Bi Si Fu (毕斯福); Chen Jing (辰景); De Fu Ka (得富卡); Di Fu Xin (迪扶欣); Di Pu (迪普); Diclac (迪克乐克); Difene (戴芬); Difnal (迪弗纳); Digen (迪根); Fei Ya Ning (菲亚宁); Fei Yan (非言)†; Fen Di Ning (芬迪宁); Fen Na Ke (芬那克); Fendi (芬迪); Gede (格得); Ji Song (吉松); Jiu Ning (久宁); Kaflan (扶他捷); Kang Tai (康泰); Lai Bi Xin (来比新); Li Shu (立舒); Lu Lin (路林); Luck (乐可); Luo Pu Jia (洛普佳); Novolten (诺福丁); Olfen (奥尔芬); Pu Ta Ning (普他宁); Rui Pei En (瑞培恩); Shi Xiang (仕象); Si Fu Xin (思孚欣); Tian Jun Li (天君利); Tian Xin Li Do (天新利博); Tong Du Ding (同杜叮); Voltaren (扶他林); Voren (非言); Xi Shu (昔舒); Xin Pu Fen (欣普芬); Yi Er Song (依尔松); Yi Ke (依柯); Yi Ke Lin (宜克林); Yi Lin (依林); Yingtaiqing (英太青); Zhi Qing (至清); ***Cz.***: Almiral; Apo-Diclo; Dicloabak; Diclofen†; Dicloreum; DIKY; Dolmina; Dorosan†; Flector; Monoflam; Myogit; Naklofen; Olfen; Rewodina†; Uniclophen; Uno; Veral; Voltaren; ***Denm.***: Alterflex; Arthrotec; Diclodan; Diclon; Diclopax; Dicuno; Difenet; Eeze; Fenacop†; Fenacta; Flector†; Instantin; Modifenac†; Solaraze; Voltaren; ***Fin.***: Arthrotec; Diclomex; Dicuno; Eeze; Flector†; Motifene; Solaraze; Voltaren; ***Fr.***: Artotec; Compralfene; Dicloced; Dispadol; Flector; Solaraze; Tendol; Tevalgiespray†; VoltarenActigo; Voltarendolo; Voltarene; Voltarenophta; Volterenplast; Xenid; ***Ger.***: Allvoran†; Arthotec; Diclabeta; Diclac†; Diclo-Divido†; Diclo-Puren†; Diclo-saar†; Diclo; Diclodoc†; Diclofenbeta; Difen; Dolgit-Diclo†; Effekton; Flector; Jutafenac†; Monoflam; Optalidon Zahnschmerz mit Diclofenac†; Rewodina†; Sandoz Schmerzgel†; Solaraze; Voltaren Ophtha; Voltaren; ***Gr.***: Actisuny; Anthraxiton; Arthrotec; Batafil; Cataflam; Clonac; Contralg; Counterflame; Declofon; Delimon; Denaclof; DicloDuo; Diclofast; Diclojet; Diclophlogont; Dicloplast; Dicloral; Difend; Dinaclon; Evinopon; Eyeclof; Fenoclof; Figrel; Flefarmin; Inflaforte; Javipren; Linobol; Miniflam; Optobet; Pengon; Pennsaid; Relipain; Rheumavek; Ruvominox; Sfinac; Topalgon; Urigon; Vilacril; Vilonit; Voltaren; Vurdon; ***Hong Kong***: Almiral; Apo-Diclo; Artharen†; Arthrotec; Aston†; Cataflam; Clofec; Clofenac; Curinflam; Diclo-Denk; Diclofen; Diclogesic†; Dicofen; Difenac; Difenol†; Doroxan; Erdon; Eurofenac; Fenac; Fenadium; Flector; Flogofenac†; Grofenac†; Inflanac; Lesflam; Olfen; Painoff†; Panaflex; Remafen; Remethan; Ren; Rhemofenax†; Ruvominox; Synfenac†; Taks†; Tapain; Uniren; Vartelon; Viclofenac†; Voltaren Ophtha; Voltaren; Volton†; Votalen†; Zolterol; ***Hung.***: Cataflam; Diclac; Diclomel; Flameril†; Flector; Fortedol; Voltaren Ophta; Voltaren; ***India***: Aclomax; Adgel; Adiflam; Agile-K; Agile; Alefen; Antiflam; Argesic; Ark; Armdic; Artilov; B-Nac; Beconac; Bestodek; Bidnac; Bionac; Bioran; Cadmax; Cannact; Capsigyl-D; Caredec; Clopar; Cofenac; Combinac; D-Nova; Dacron; Deeclo; Defcin; Delbitol; Delta-K; Demo; Dersy; Devona; Diclam; Diclasia; Diclo-DT; Diclo-K; Dicloact; Dicloat; Diclobit; Diclodol; Diclodyne; Diclofam; Diclofast; Diclofen; Dicloflam; Diclofloame; Diclolab; Dicloma; Diclomax; Diclomol; Diclomol; Diclomove; Diclonac; Diclonet; Diclonij; Diclonip; Diclonova; Dicloran; Diclostar; Diclotal; Diclovar; Diclowin; Diclozed; Dicnac; Dicnacx; Dico; Dicol; Dicoliv; Dicos; Dicron; Dicven; Difenac; Difenic; Difin; Difisal; Diklofen; Dikonb; Dikpa; Dikul; Dilofen; Dilona; Dion; Disoral; Divexx; Divon; DLF; Dofec; Doflex; Dolact; Dolocide K; Dolocide Plus; Dolzy; DS-15; Dynapar; E-Nac; E-Par; Emflam; Emflam; Esgipyrin DS; Exflam; Fenac; Fenbest; Fendase; Fengel; Fensaid; Fensaide; Fento; Fineact; Flamese; Flexigesic-K; Flexigesic; Gic; Haloran; I-Gesic; Imflamol; Inac; Indofen; Intragesic; Jonac; Justin; K-Fenac; Knac; Lafen; Leemax; Lipcy; Lofen; Lofy; Lysoflam; Mifenac; Mindol; Mishanac; Misonac; Mobiaid; Mobyle; Nac Gel; Nac; Naclo; Nal-M; Neodol; Nifdec; Noctel; Novofen; Novoflam; NSAID Eye; Nudiclo; Nufenac; Nupatch; Odonac; Onafen; Ontac; Oronac; Osteoflam; Oxalgin-D; Oxalgin-SR; Oxalgin; Oxynal; Painkair; Panama; Parafortan; Profenac; Reactine; Relaxyl; Relaxyl; Solunac†; Tromagesic; Tromax; Voveran; ***Indon.***: Abdiflam†; Aclonac; Alflam; Araclof; Atranac; Berifen†; Cataflam; Catanac; Deflamat; Dicloflam; Diclomec†; Diflam; Divoltar; Eflagen; Elithris; Exaflam; Fenaren†; Fenavel; Flamar; Flamenac†; Flamic; Inflam; Kadiflam; Kaditic; Kaflam; Kamaflam; Klotaren; Laflanac; Linac; Matsunaflam; Merflam; Nacoflar; Nadifen; Neurofenac; Nichoflam; Nilaren; Potazen†; Prostanac†; Provoltar; Reclofen; Renadinac; Renvol; Scanaflam; Scantaren; Tirmaclo; Troflam; Valto; Volmatik; Voltadex; Voltaren Ophtha; Voltaren; Voren; X-Flam; Xepathritis; Yariflam; Zegren; ***Irl.***: Arthrotec; Cataflam; Diclac; Diclo; Diclomax†; Diclomel†; Difene; Flector; Kyflam; Solaraze; Voltarol Ophtha; Voltarol; Voltfast; ***Israel***: Abitren; Arthrotec; Betaren; Cataflam; Demofenac; Diclofti; Dicloplast; Dicloreng el; Olfen; Physicare Gel; Swiss Relief; Voltaren Ophtha; Voltaren; ***Ital.***: Algosenac; Artrotec; Dealgic; Deflamat; Diclocular; Diclofan; Dicloftil; Dicloral; Dicloreum; Diclotears; Diep Grat; Dolaut; Doroxan; Dropflam; Fenadol; Fender; Flector; Flogofenac; Itami; Leviogel; Misofenac; Nadiclopht; Novapirina; Pennsaid; Solaraze; Topfans†; Traulen; Voltadol; Voltadvance; Voltaren; Voltfast; Zeroflog; ***Jpn***: Anavan; ***Malaysia***: Almiral; Analpan; Cataflam; Clofec; Clofenac†; Difnal; Doroxan; Fenac; Inflanac; Lesflam; Neo-Pyrazon†; Olfen; Panaflex Extra; Remafen†; Remethan; Rhemofenax; Uniren; Vokam; Voltaren; Voren; Zolterol; ***Mex.***: 3A Ofteno; Alsidexten†; Ariflam; Artrenac Pro; Artrenac; Artrene; Artrotec; Atalak; Calaffler; Catafast; Cataflam; Clo-Far; Clofenix; Clonodifen†; Coral; Deflox; Dicfafena; Diclac; Diclopisa; Dicloran; Diclosol; Dioxaflex; Diqfanol; Dirret; Docril; Dofen†; Doflatem; Dolaren; Dolflam; Dolofenac; Doltarac; Evadol; Fenagel; Fenalgin; Fervex; Flamydol; Flamygel; Flankol; Flogoken; Flotac; Fortical; Fustaren†; Galedol; Hipo Sport; Lertus; Lifenac; Liroken; Lodyfen; Lonatec; Lufac-Z; Mafena; Manacon; Merxil; Metracin†; Musol; Nediclon; Neo-Dolaren; Pharmaflam; Practiser; Precifenac; Selectofen; Solof; Still; Vicmafen†; Volfenac; Voltaren; ***Neth.***: Arthrotec; Cataflam; Dicloabak; Eminocs; Itami†; Misofenac†; Naclof; Normulen†; Otriflu; Voltaren Emulgel; Voltaren; ***Norw.***: Arthrotec; Cataflam; Modifenac; Otriflu†; Solaraze; Voltaren Ophtha; Voltaren; Voltarol; ***NZ***: Apo-Diclo; Cataflam; Diclax; Diclohexal†; Flameril; Voltaren Ophtha; Voltaren; Voltfast; ***Philipp.***: Acuflam; Canefol; Cataflam; Cataflin; Clofenix; Clofil; Clonaren†; Curafen; Dafenac; Diclogen; Difenamin; Difenax; Diflapane; Doloflam; Dycon; Dynapar; Eslofen†; Fenaspec; Fendil; Klaxon; Lobafen; Lofenax; Maxi; Medclof; Neo-Pyrazon; Nepenthe†; Parafortan; Rheuflam; Uniclonax†; Vifenac; Vodefen; Volfenn; Voltaren; Voren; Votan; Zobid; ***Pol.***: Apo-Diclo†; Arthrotec; Cataflam; Diclac; Dicloabak; Dicloberl; Diclobion†; DicloDuo; Dicloratio; Dicloreum; Dicloziaja; Difadol; Diklonat P; Dikloziaja†; Diky; Felogel; Glimbax; Majamil; Naclof; Naklofen; Olfen; Ratiogel†; Rewodina†; Veral; Voltaren; Voltenac; ***Port.***: Arthrotec; Cataflam; Clofen; Dagesil; Dicloabak; Diclodent; Diclofar; Dicloftal†; Diclospray; Diclotec†; Dofene; Dolacen; Dorcalor; Fenac; Fenil-V; Flameril; Flector; Frenalgil; Olfen; Otriflu; Painex; Pennsaid; Solaraze; Voltadol; Voltaren; ***Rus.***: Almiral (Алмирал)†; Apo-Diclo (Апо-дикло)†; Arthrotec (Артротек); Bioran (Биоран); Diclac (Диклак); Diclo-F (Дикло-ф); Diclobene (Диклобене); Dicloberl (Диклоберл)†; Diclogen (Диклоген); Diclonat (Диклонат); Dicloran (Диклоран); Diclovit (Дикловит); Etyfenac (Этифенак); Flameril (Фламерил); Naclof (Наклоф)†; Naklofen (Наклофен); Naklofen Duo (Наклофен Дуо); Neodol (Неодол); Ortofen (Ортофен); Ortofer (Ортофер); Ortoflex (Ортофлекс); Ortophen (Ортофен); Rapten Duo (Раптен дуо); Rapten Rapid (Раптен Рапид); Rheumavek (Ревмавек); Uniclophen (Униклофен); Voltaren (Вольтарен); ***S.Afr.***: Adco-Clofelam; Arcanafenac†; Arthrotec; Arthru-Derm; Catafast; Cataflam; Dicloflam; Diclohexal; Difen; Difenject; Dynak; Fenisun; Flexagen†; Fortfen; Infla-Ban†; K-Fenak; Panamor; Veltex; Voltaren Ophtha; Voltaren; ***Singapore***: Almiral; Analpan; Apo-Diclo; Cataflam; Clofec; Clofenac; Diclo-Denk; Diclo; Dicloran; Difenac; Difnal; Fenac; Fenadium; Flector; Inac; Inflanac; Lesflam; Neodol; Olfen; Panaflex Extra†; Panamax; Pritaren; Remafen; Remethan; Rhewlin; SP-Nadofen; Ultrafen; Uniren; Voltaren Ophtha; Voltaren; Voltfast; Voren; Zolterol; ***Spain***: Artrotec; Di Retard; Dicloabak; Dolo Nervobion†; Dolo-Voltaren; Dolotren; Luase†; Normulen†; Ratioparch†; Solaraze; Voltadol; Voltaren; Xibol; ***Swed.***: Arthrotec; Dicuno; Eeze; Eezeneo; Flector†; Solaraze; Voltaren Ophtha; Voltaren T; Voltaren; ***Switz.***: Arthrotec; Diclac; Dicloabak; Diclosifar†; Difen-Stulln; Ecofenac; Effigel; Fenisole†; Fenisun; Flam-X; Flector; Fortenac; Grofenac; Inflamac; Olfen; Primofenac; Relova; Solaraze; Tonopan; Vifenac; Voltaren Dolo; Voltaren Emulgel; Voltaren Ophta; Voltarene; Voltfast; ***Thai.***: Ammi-Votara; Amminac; Antenac; Arclonac; Cataflam; Catanac; Cencenac; Chinclona; Chinclonac; Clofec; Clofon; Covonac; D-Fiam; Demac; Diclo; Diclogel; Diclogesic; Diclolan; Diclomol†; Diclosian; Difaren; Difelene; Difen†; Difenac; Difengesic; Difeno; Difensic; Dinac; Dinefec; Dolonil; Dosanac; Fema; Fenac; Fenacaine; Fenacil; Fenagel; Flexy; Infenac; Inflamma; Inflanac; Klyzen; Lesflam; Lofenac; Manfenac; Masaren; Myfenax; Myonac; N-Zen; Naclof†; Ostaren; Pai-Noren; Painelief; Posnac†; Remethan; Rhumanol; Sefnac; Sinclonac; Subsyde; Taks†; Tarjen; Tarjena; Uniren; V-Therlen; Vasalen†; Veenac; Ventarone; Vesconac; Volfen†; Volfenac; Volnac; Volta; Voltanac; Voltaren; Voltex Kool; Volverac; Voren; Votamed; ***Turk.***: Actinoma; Arthrotec; Cataflam; Deflamat; Dicloflam; Diclomec; Dicol; Difenak; Diklo-S; Diklopain; Dikloron; Dikloron; Dikloteva; Dolorex; Flector; Inflased; Kalidren; Miyadren; Romatim; Volfenaks; Voltaflam; Voltaren Ophta; Voltaren; ***UAE***: Clofen; ***UK***: Arthrotec; Defanac; Defenac; Dexomon; Dicloflex; Diclomax; Diclovol; Diclozip; Dyloject; Econac; Fenactol; Flamatak; Flamrase; Misofen; Mobigel†; Motifene; Pennsaid; Rheumatac; Rhumalgan; Slofenac; Solaraze; Volraman; Volsaid; Voltarol Ophtha; Voltarol; ***Ukr.***: Catafast (Катафаст); Clodifen (Клодифен); Diclac (Диклак); Diclo-F (Дикло-Ф); Diclobene (Диклобене); Dicloberl (Диклоберл); Diclobru (Диклобрю); Diclocain (Диклокаин); Dicloperol (Диклоперол)†; Diftal (Дифталь); Megafen Plus (Мегафен Плюс)†; Naclof (Наклоф); Naklofen (Наклофен); Olfen (Олфен); Rapten (Раптен); Voltaren (Вольтарен); ***USA***: Arthrotec; Cambia; Cataflam; Flector; Pennsaid; Solaraze; Voltaren; Voltaren Zipsor; Zorvolex; ***Venez.***: 3 A Ofteno; Arthrotec; Artren; Campal; Cataflam; Clofen; Clofenac; Diagesic; Diclofen P; Diclosal; Difenac; Diklason; Diralon; Dival; Flogaren; Flotac; Klafenac; Viavox; Voltaren; Volten; Votaxil.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Diclofenac Gel; Gastro-resistant Diclofenac Tablets; Prolonged-release Diclofenac Capsules; Prolonged-release Diclofenac Tablets;

USP 36: Diclofenac Potassium Tablets; Diclofenac Sodium Delayed-release Tablets; Diclofenac Sodium Extended-Release Tablets.

Diethylamine Salicylate

Diaethylamini Salicylas; Dietylaminsalicylat; Dietyyliamiinisalisylaatti; Salicilato de dietilamina; Salisilat Dietilamin; Диэтиламин Салицилат; Салицилат Диэтиламина.

$C_{11}H_{17}NO_3$=211.3

CAS — 4419-92-5.

UNII — 5V7PT38BJU.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Diethylamine Salicylate). White or almost white, odourless or almost odourless crystals. Very soluble in water; freely soluble in alcohol and in chloroform. Protect from light. Avoid contact with iron or iron salts.

Profile

Diethylamine salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for rheumatic and muscular pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Algesal†; ***Canad.***: Chirogesic; Physiogesic; ***China***: Duo Rui (多瑞); ***Fin.***: Algesal†; ***Fr.***: Algesal; ***Gr.***: Algesal; ***Hung.***: Aciphen; ***India***: Multigesic; ***Neth.***: Algesal†; ***Norw.***: Algesal; ***Pol.***: Saldiam; ***Port.***: Algicum†; Algiderma†; Massagim; ***Swed.***: Algesal; ***Turk.***: Algesal; Reparil; ***UK***: Algesal; Lloyd's Cream; ***Venez.***: Alesal.

Multi-ingredient Preparations. ***Arg.***: Algesal; Cartiflex; Crema Antiinflamatoria; Rati Salil Flex; Salicrem; ***Austral.***: Rubesal; ***Austria***: Algesal; Derivon; Dolo-Menthoneurin; Latesyl; Reparil; Rheugesal†; Rilfit-Rheumasalbe; Traumasal; ***Belg.***: Reparil; ***Braz.***: Reparil; Reparil; ***Chile***: Repariven; ***China***: Ou Lai (欧莱); Reparil-Gel N (利百素凝胶); ***Cz.***: Algesal; Reparil-Gel N; ***Fr.***: Algesal Suractive; Reparil; Traumalgyl†; ***Ger.***: Algesal†; Reparil-Gel N; ***Gr.***: Algesal Suractive; Ponostop; ***Hong Kong***: Reparil; Rubesal†; ***Hung.***: Algesal; Reparil N; ***India***: Neurophen; ***Indon.***: Algesal Superactive; ***Ital.***: Edeven; Liotontrauma; Reparil CM; Sedalpan; Viamal Trauma; ***Malaysia***: Reparil-Gel N; ***Neth.***: Algesal Forte†; ***Philipp.***: Reparil N; ***Pol.***: Reparil N; ***Port.***: Algesal; Latesil; Medalginan; Venoparil; ***Rus.***: Reparil-Gel N (Репарил-Гель Н); ***S.Afr.***: Reparil; ***Singapore***: Reparil-Gel N; ***Spain***: Algesal; Contusin; Dolmitin†; Feparil; Radio Salil; ***Switz.***: Mavena Proctal-Gen†; Reparil N; ***Thai.***: Reparil; Veno-Gel†; ***Turk.***: Algesal Suractive; Prepagel; ***UAE***: Rubicalm; ***UK***: Fiery Jack; Transvasin Heat Spray; ***Ukr.***: Reparil-Gel N (Репарил-Гель Н); ***Venez.***: Lemazol.

Pharmacopoeial Preparations

BP 2014: Diethylamine Salicylate Cream.

Diflunisal *(BAN, USAN, rINN)*

Diflunisaali; Diflunisalis; Diflunisalum; Difluniszal; MK-647; Дифлунисал.

5-(2,4-Difluorophenyl)salicylic acid.

$C_{13}H_8F_2O_3$=250.2

CAS — 22494-42-4.

ATC — N02BA11.

ATC Vet — QN02BA11.

UNII — 7C546U4DEN.

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*

BP 2014: (Diflunisal). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol. Dissolves in dilute solutions of alkali hydroxides. It exhibits polymorphism. Protect from light.

USP 36: (Diflunisal). A white to off-white, practically odourless, powder. Insoluble in water and in hexane; freely soluble in alcohol and in methyl alcohol; soluble in acetone and in ethyl acetate; slightly soluble in carbon tetrachloride, in chloroform, and in dichloromethane.

Uses and Administration

Diflunisal is a salicylic acid derivative (see Aspirin, p. 22.3) but it is not hydrolysed to salicylate and its clinical effects resemble more closely those of propionic acid derivative NSAIDs such as ibuprofen (p. 68.3). Diflunisal is given in the

acute or long-term management of mild to moderate pain, and pain and inflammation associated with osteoarthritis and rheumatoid arthritis. The usual initial oral dose for pain relief is 1 g followed by a maintenance dose of 500 mg every 12 hours although some patients may require 500 mg every 8 hours. In others, a lower initial dose of 500 mg followed by 250 mg every 8 to 12 hours may be sufficient. The usual oral dose for arthritis is 500 mg to 1 g daily in 2 divided doses, adjusted according to response. Maintenance doses greater than 1.5 g daily are not recommended regardless of indication. Doses may need to be reduced in patients with renal impairment, see below.

Diflunisal arginine has been used similarly given orally or by intramuscular or intravenous injection.

Administration in renal impairment. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3. The commonest adverse effects occurring with diflunisal are gastrointestinal disturbances, headache, and rash. Peptic ulceration and gastrointestinal bleeding have been reported. Dizziness, drowsiness, insomnia, and tinnitus may also occur.

Effects on the blood. Haematological adverse effects associated with diflunisal appear to be infrequent. Thrombocytopenia associated with diflunisal-induced peripheral platelet destruction has been reported in a patient with rheumatoid arthritis.[1] Heinz-body haemolytic anaemia has also been reported, see Hypersensitivity, below.

1. Bobrove AM. Diflunisal-associated thrombocytopenia in a patient with rheumatoid arthritis. *Arthritis Rheum* 1988; **31:** 148–9.

Effects on the kidneys. Acute interstitial nephritis, presenting as acute oliguric renal failure, erythroderma, and eosinophilia has followed the use of diflunisal.[1]

1. Chan LK, *et al.* Acute interstitial nephritis and erythroderma associated with diflunisal. *BMJ* 1980; **280:** 84–5.

Effects on the lungs. For reference to pneumonitis associated with diflunisal therapy, see Hypersensitivity, below.

Effects on the skin. Reports of Stevens-Johnson syndrome associated with diflunisal.[1,2] See also Hypersensitivity, below.

1. Hunter JA, *et al.* Diflunisal and Stevens-Johnson syndrome. *BMJ* 1978; **2:** 1088.
2. Grom JA, *et al.* Diflunisal-induced erythema multiforme major. *Hosp Formul* 1986; **21:** 353–4.

Hypersensitivity. Three cases of hypersensitivity to diflunisal in which the main clinical features were fever, elevated liver enzyme values, erythroderma, and eosinophilia, have been reported.[1] Heinz-body haemolytic anaemia occurred in one of the patients. Other hypersensitivity reactions associated with diflunisal therapy have included pneumonitis[2] and fulminant necrotising fasciitis.[3]

1. Cook DJ, *et al.* Three cases of diflunisal hypersensitivity. *Can Med Assoc J* 1988; **138:** 1029–30.
2. Rich MW, Thomas RA. A case of eosinophilic pneumonia and vasculitis induced by diflunisal. *Chest* 1997; **111:** 1767–9.
3. Krige JEJ, *et al.* Necrotising fasciitis after diflunisal for minor injury. *Lancet* 1985; **ii:** 1432–3.

Overdosage. Diflunisal poisoning has sometimes been fatal.[1,2] A dose of 15 g has been reported to have caused death when no other drugs were involved but a dose of 7.5 g has also been fatal when taken with other drugs.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. Levine B, *et al.* Diflunisal related fatality: a case report. *Forensic Sci Int* 1987; **35:** 45–50.

Precautions

As for NSAIDs in general, p. 107.1. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe. Aspirin and other acetylated salicylates are not recommended for use in children unless specifically indicated, because of the risk of Reye's syndrome. Although this precaution has not been specifically extended to diflunisal it is not generally licensed for use in children.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diflunisal as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Aspirin may produce a small decrease in the plasma concentration of diflunisal. Diflunisal has been reported to increase the plasma concentrations of indometacin and paracetamol; diflunisal with indometacin has been associated with fatal gastrointestinal haemorrhage and therefore the combination should not be used. Regular use of antacids may reduce the absorption of diflunisal.

Benzodiazepines. For the effect of diflunisal on plasma concentrations of *oxazepam*, see p. 1068.1.

Probenecid. Average steady-state plasma concentrations of diflunisal were increased by 65% when it was given with probenecid.[1] This was due mainly to reduced formation of the phenolic and acyl glucuronides. However, plasma concentrations of these glucuronides and the sulfate conjugate were also increased even more because probenecid also reduced their renal clearance.

1. Macdonald JI, *et al.* Effect of probenecid on the formation and elimination kinetics of the sulphate and glucuronide conjugates of diflunisal. *Eur J Clin Pharmacol* 1995; **47:** 519–23.

Pharmacokinetics

Diflunisal is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 3 hours after ingestion of a single dose. It is more than 99% bound to plasma protein and has a plasma half-life of about 8 to 12 hours. Diflunisal exhibits non-linear pharmacokinetics so that doubling the dose more than doubles drug accumulation. Due to the long half-life and non-linear kinetics, several days are required to reach steady-state plasma concentrations after multiple dosing. The time to steady-state concentrations can be reduced by giving an initial loading dose. Concentrations of diflunisal in synovial fluid reach about 70% of those in plasma. Diflunisal is excreted in the urine mainly as glucuronide conjugates. Some biliary recycling may also occur. Diflunisal is distributed into breast milk with concentrations reported to be about 2 to 7% of those in plasma.

References.

1. Loewen GR, *et al.* Effect of dose on the glucuronidation and sulphation kinetics of diflunisal in man: single dose studies. *Br J Clin Pharmacol* 1988; **26:** 31–9.
2. Eriksson L-O, *et al.* Influence of renal failure, rheumatoid arthritis and old age on the pharmacokinetics of diflunisal. *Eur J Clin Pharmacol* 1989; **36:** 165–74.
3. Verbeeck RK, *et al.* The effect of multiple dosage on the kinetics of glucuronidation and sulphation of diflunisal in man. *Br J Clin Pharmacol* 1990; **29:** 381–9.
4. Macdonald JI, *et al.* Sex-difference and the effects of smoking and oral contraceptive steroids on the kinetics of diflunisal. *Eur J Clin Pharmacol* 1990; **38:** 175–9.
5. Nuernberg B, *et al.* Pharmacokinetics of diflunisal in patients. *Clin Pharmacokinet* 1991; **20:** 81–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Cleating (巨力新); Ning Hu Shu Xin (宁湖舒欣); ***Gr.***: Analeric; Di-Flu; ***Thai.***: Dolobid; ***Turk.***: Dolphin.

Pharmacopoeial Preparations
BP 2014: Diflunisal Tablets;
USP 36: Diflunisal Tablets.

Dihydrocodeine *(BAN, rINN)*

Dihidrocodeína; Dihydrocodéine; Dihydrocodeinum; Дигидрокодеин.

4,5-Epoxy-3-methoxy-17-methylmorphinan-6-ol.

$C_{18}H_{23}NO_3$=301.4

CAS — 125-28-0.

ATC — N02AA08.

ATC Vet — QN02AA08.

UNII — N9I9HDB855.

Dihydrocodeine Phosphate *(BANM, rINNM)*

Dihidrocodeína, fosfato de; Dihydrocodéine, Phosphate de; Dihydrocodeini Phosphas; Fosfato de dihidrocodeína; Hydrocodeine Phosphate; Дигидрокодеина Фосфат.

$C_{18}H_{23}NO_3,H_3PO_4$=399.4

CAS — 24204-13-5.

ATC — N02AA08.

ATC Vet — QN02AA08.

UNII — 5D9XI60ASE.

Pharmacopoeias. In *Jpn*.

Dihydrocodeine Tartrate *(BANM, rINNM)*

Dihidrocodeína, tartrato de; Dihidrokodein-hidrogén-tartrát; Dihidrokodeino-vandenilio tartratas; Dihydrocodeine Acid Tartrate; Dihydrocodeine Bitartrate; Dihydrocodeine Hydrogen Tartrate; Dihydrocodéine, hydrogénotartrate de; Dihydrocodéine, Tartrate de; Dihydrocodeini Bitartras; Dihydrocodeini Hydrogenotartras; Dihydrocodeini Tartras; Dihydrocodein[(R,R)-tartrat]; Dihydrokodeiinivetytartratti; Dihydrokodein-tartarát; Dihydrokodeinvätetartrat; Dihydrokodeiny wodorowinian; Drocode Bitartrate; Hydrocodeine Bitartrate; Tartrato de dihidrocodeína; Дигидрокодеина Тартрат.

$C_{18}H_{23}NO_3,C_4H_6O_6$=451.5

CAS — 5965-13-9.

UNII — 8LXS95BSA9.

NOTE. Compounded preparations of dihydrocodeine tartrate may be represented by the following names:

- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dihydrocodeine tartrate:

DFs; Diffs; Duncan Flockharts.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Dihydrocodeine Hydrogen Tartrate; Dihydrocodeine Tartrate BP 2014). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 3.2 to 4.2. Protect from light.

USP 36: (Dihydrocodeine Bitartrate). pH of a 10% solution in water is between 3.2 and 4.2. Store in airtight containers.

Uses and Administration

Dihydrocodeine is an opioid analgesic (p. 108.1). It is related to codeine (p. 40.3) and has similar analgesic activity. Dihydrocodeine is used for the relief of moderate to severe pain, often in combination preparations with paracetamol. It has also been used as a cough suppressant.

For **analgesia** the usual oral dose of dihydrocodeine tartrate is 30 mg after food every 4 to 6 hours; up to 240 mg daily may be given for severe pain. Modified-release preparations are available for twice daily dosage in patients with chronic severe pain.

Dihydrocodeine tartrate may also be given by deep subcutaneous or intramuscular injection in doses of up to 50 mg every 4 to 6 hours.

For details of doses in children, see below.

As a **cough suppressant** dihydrocodeine tartrate may be given in oral doses of 10 to 30 mg up to three times daily.

Dihydrocodeine phosphate has also been used. Other salts of dihydrocodeine used, mainly for their antitussive effects, include the hydrochloride, the polistirex, and the thiocyanate. Dihydrocodeine polistirex has also been used in modified-release preparations.

Administration in children. In the UK, dihydrocodeine tartrate may be given orally, or by deep subcutaneous or intramuscular injection, for analgesia in children aged from 4 to 12 years in usual doses of 0.5 to 1 mg/kg (to a maximum of 30 mg) every 4 to 6 hours; older children may be given the usual adult dose (see above). Although unlicensed in children aged under 4 years, the *BNFC* suggests giving those aged 1 to 4 years 500 micrograms/kg every 4 to 6 hours.

Dyspnoea. Dihydrocodeine has been reported[1] to have produced benefit in normocapnic patients severely disabled by breathlessness due to chronic airflow obstruction. A dose of 15 mg was taken 30 minutes before exercise up to three times daily.

1. Johnson MA, *et al.* Dihydrocodeine for breathlessness in 'pink puffers'. *BMJ* 1983; **286:** 675–7.

Pain. Dihydrocodeine is used in the management of moderate to severe pain. However, dose-related increase in postoperative pain has been seen[1] in patients given 25 or 50 mg dihydrocodeine tartrate intravenously after dental surgery, and it has been proposed that dihydrocodeine might act as an antagonist in situations where acute pain was accompanied by high opioid activity.[2] Systematic review of the use of single oral doses of dihydrocodeine has indicated that these are insufficient to provide adequate relief of postoperative pain, and that dihydrocodeine is less effective than ibuprofen.[3]

1. Seymour RA, *et al.* Dihydrocodeine-induced hyperalgesia in postoperative dental pain. *Lancet* 1982; **i:** 1425–6.
2. Henry JA. Dihydrocodeine increases dental pain. *Lancet* 1982; **ii:** 223.
3. Moore RA, *et al.* Single dose dihydrocodeine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 26/06/08).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Dihydrocodeine has been subject to abuse (see under Precautions, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1; adverse effects of dihydrocodeine are less pronounced than those of morphine.

Overdosage. A 29-year-old man who had taken 2.1 g of dihydrocodeine had biochemical evidence of acute renal and hepatic impairment when admitted 13 hours after the overdose.[1] Severe life-threatening respiratory depression subsequently developed 36 hours after the overdose and only responded to treatment with naloxone after large doses (a total of 46.6 mg of naloxone) over a long period (106 hours). Commenting on this report some questioned the evidence for hepatic impairment and considered that the raised liver enzyme values were of muscular origin as a result of rhabdomyolysis.[2-4] Rhabdomyolysis may also have contributed to renal failure.

An anaphylactoid reaction after an overdose with an unspecified number of dihydrocodeine tablets[5] appeared to respond to intravenous naloxone.

1. Redfern N. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 751–2.
2. Buckley BM, Vale JA. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
3. Blain PG, Lane RJM. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
4. Wen P. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1548.
5. Panos MZ, *et al.* Use of naloxone in opioid-induced anaphylactoid reaction. *Br J Anaesth* 1988; **61:** 371.

Pain. For reference to increased postoperative pain associated with the use of dihydrocodeine, see under Uses and Administration, p. 52.3.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Abuse. Dihydrocodeine has been reported to be widely abused by opiate addicts.[1-4]

1. Swadi H, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **300:** 1313.
2. Robertson JR, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
3. Strang J, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
4. Seymour A, *et al.* The role of dihydrocodeine in causing death among drug users in the west of Scotland. *Scott Med J* 2001; **46:** 143–6.

The elderly. Despite some renal impairment an elderly group of patients[1] appeared to handle dihydrocodeine similarly to healthy young subjects. There was marked variability in all measurements and on the basis of this study no clear conclusions on guidelines for dosage in elderly patients could be drawn. However, the recommendation that small doses be given initially with subsequent doses according to response was endorsed.

1. Davies KN, *et al.* The effect of ageing on the pharmacokinetics of dihydrocodeine. *Eur J Clin Pharmacol* 1989; **37:** 375–9.

Renal impairment. Caution is necessary when giving dihydrocodeine to patients with severe renal impairment. Severe narcosis occurred in a patient with anuria and on maintenance haemodialysis after she had received dihydrocodeine orally for 4 days.[1] She responded to treatment with naloxone.

See also under Pharmacokinetics, below.

1. Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *BMJ* 1983; **286:** 438–9.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Quinidine. Dihydrocodeine is metabolised via the cytochrome P450 isoenzyme CYP2D6 to active metabolites, which may perhaps play a role in its analgesic activity in extensive metabolisers; quinidine impairs this metabolism, but a study in 11 healthy subjects did not find any reduced analgesic activity when dihydrocodeine was given with quinidine, despite a three- to fourfold reduction in plasma concentrations of the metabolite dihydromorphine.[1]

1. Wilder-Smith CH, *et al.* The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Clin Pharmacol* 1998; **45:** 575–81.

Pharmacokinetics

Peak concentrations of dihydrocodeine occur about 1.2 to 1.8 hours after oral doses; oral bioavailability is only about 20%, probably because of substantial first-pass metabolism in the gut wall or liver. Dihydrocodeine is metabolised in the liver via the cytochrome P450 isoenzyme CYP2D6, to dihydromorphine, which has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be mainly due to the parent compound; some is also converted via CYP3A4 to nordihydrocodeine. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life is reported to range from about 3.5 to 5 hours.

References.

1. Rowell FJ, *et al.* Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *Eur J Clin Pharmacol* 1983; **25:** 419–24.
2. Fromm MF, *et al.* Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. *Clin Pharmacol Ther* 1995; **58:** 374–82.
3. Ammon S, *et al.* Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple dosing. *Br J Clin Pharmacol* 1999; **48:** 317–22.
4. Webb JA, *et al.* Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modelling analysis. *Br J Clin Pharmacol* 2001; **52:** 35–43.

Renal impairment. The pharmacokinetics of dihydrocodeine tartrate, given as a single oral 60-mg dose, were affected in 9 patients with chronic renal failure treated with haemodialysis when compared with 9 healthy subjects.[1] Time to peak plasma concentration in those with renal failure was 3 hours compared with 1 hour in healthy subjects; the area under the plasma concentration-time curve was greater in those with renal failure; and after 24 hours dihydrocodeine was still detectable in the plasma of all renal failure patients, but in only 3 of the healthy subjects.

1. Barnes JN, *et al.* Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. *BMJ* 1985; **290:** 740–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Paracodin†; Rikodeine; ***Austria***: Codidol; Dehace; Paracodin; Paracodin; ***Belg.***: Codicontin†; Paracodine; ***China***: Xi Gai Ke (西盖克); ***Cz.***: DHC Continus; ***Fr.***: Dicodin; ***Ger.***: DHC; Paracodin N; Paracodin; Tiamon Mono; ***Gr.***: Dolcontin; ***Hong Kong***: DF 118; ***Hung.***: DHC; Hydrocodin; ***Irl.***: DF 118; DHC Continus†; Paracodin; ***Ital.***: Paracodina; ***Malaysia***: DF 118; Dicogesic; Suncodin; ***NZ***: DHC Continus; ***Pol.***: DHC Continus; ***S.Afr.***: DF 118; Paracodin; ***Spain***: Paracodina; Tosidrin; ***Switz.***: Codicontin; Paracodin; ***UK***: DF 118; DHC Continus.

Multi-ingredient Preparations. ***Arg.***: Lentusin; ***Austral.***: Codox†; ***China***: Gugaike (路盖克); ***Hong Kong***: Codaewon; ***Irl.***: Paramol; ***Ital.***: Cardiazol-Paracodina; Paracodina; ***Jpn***: Colgen Kowa IB; Lightgen; ***Malaysia***: Dihydrocodeine P; ***Switz.***: Escotussin; Makatussin Comp; ***UK***: Dypracet; Paramol; Remedeine; ***USA***: Alahist DHC; Despec PDC; Despec-EXP†; DHC Plus; DiHydro-CP†; DiHydro-GP†; DiHydro-PE†; Donatuss DC; Duohist DH; EndaCof-DH†; J-COF DHC; J-Max DHC; Novahistine DH; Pancof PD†; Pancof-EXP†; Pancof†; Panlor†; Poly Hist DHC; Poly-Tussin DHC; Poly-Tussin EX; Synalgos-DC; Trezix.

Pharmacopoeial Preparations

BP 2014: Co-dydramol Tablets; Dihydrocodeine Injection; Dihydrocodeine Oral Solution; Dihydrocodeine Tablets.

Dipipanone Hydrochloride *(BANM, rINNM)*

Dipipanona, hidrocloruro de; Dipipanone, Chlorhydrate de; Dipipanoni Hydrochloridum; Hidrocloruro de dipipanona; Phenylpiperone Hydrochloride; Piperidyl Methadone Hydrochloride; Piperidylamidone Hydrochloride; Дипипанона Гидрохлорид.

(±)-4,4-Diphenyl-6-piperidinoheptan-3-one hydrochloride monohydrate.

$C_{24}H_{31}NO,HCl,H_2O$=404.0

CAS — 467-83-4 (dipipanone); 856-87-1 (dipipanone hydrochloride).

UNII — 8VY00AJ0RL.

Pharmacopoeias. In *Br.*

BP 2014: (Dipipanone Hydrochloride). An odourless or almost odourless, white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in acetone; practically insoluble in ether. A 2.5% solution in water has a pH of 4.0 to 6.0.

Profile

Dipipanone hydrochloride is an opioid analgesic (p. 108.1) structurally related to methadone (p. 88.3). Used alone it is reported to be less sedating than morphine. It is used in the treatment of moderate to severe pain.

Dipipanone hydrochloride is usually given in combination preparations with the antiemetic cyclizine hydrochloride to reduce the incidence of nausea and vomiting, but the use of such preparations is not recommended for the management of chronic pain, as the antiemetic is usually only required for the first few days of treatment. The usual oral dose of dipipanone hydrochloride is 10 mg, repeated every 6 hours. The dose may be increased if necessary in increments of 5 mg; it is seldom necessary to exceed a dose of 30 mg. After an oral dose the analgesic effect begins within an hour and lasts about 4 to 6 hours.

Preparations of dipipanone hydrochloride with cyclizine hydrochloride are subject to abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Wellconal; ***UK***: Diconal†.

Pharmacopoeial Preparations

BP 2014: Dipipanone and Cyclizine Tablets.

Dipyrone *(BAN, USAN)*

Aminopyrine-sulphonate Sodium; Analginum; Dipiron; Dipirona; Dipyron; Dipyroni; Dipyronum; Metamitsolinatrium; Metamizol; Metamizol-Natrium; Metamizol sódico; Metamizol sodná sůl monohydrát; Metamizol sodowy; Metamizol Sodyum; Métamizole sodique; Metamizole Sodium (pINN); Metamizolnatrium; Metamizol-nátrium; Metamizolo natrio druska; Metamizolum Natricum; Metamizolum Natricum Monohydricum; Methampyrone; Methylmelubrin; Natrium Novaminsulfonicum; Noramidazophenum; Novamidazofen; Novaminsulfone Sodium; NSC-73205; Sodium Noramidopyrine Methanesulphonate; Sulpyrine; Метамизол Натрий.

Sodium *N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-*N*-methylaminomethanesulphonate monohydrate.

$C_{13}H_{16}N_3NaO_4S,H_2O$=351.4

CAS — 68-89-3 (anhydrous dipyrone); 5907-38-0 (dipyrone monohydrate).

ATC — N02BB02.

ATC Vet — QN02BB02.

UNII — 6429L0L52Y (dipyrone); V5U62Z74ON (anhydrous dipyrone).

NOTE. Confusingly the term dipyrone sodium also appears to be used synonymously for dipyrone itself. Dipyrone is referred to in some countries by the colloquial name 'Mexican aspirin'. The names noraminophenazonum and novaminsulfon have apparently been applied to dipyrone, but it is not clear whether these are the sodium salt.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Metamizole Sodium Monohydrate; Dipyrone BP 2014). A white or almost white crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Uses and Administration

Dipyrone is the sodium sulfonate of aminophenazone (p. 21.1) and has similar properties. Because of the risk of serious adverse effects, in many countries its use is considered justified only in severe pain or fever where no alternative is available or suitable. Dipyrone has been given orally in doses of 0.5 to 4g daily in divided doses. It has also been given by intramuscular or intravenous injection and rectally as a suppository.

A magnesium congener of dipyrone, metamizole magnesium has been used similarly to dipyrone as has the calcium congener metamizole calcium.

Adverse Effects and Precautions

Use of dipyrone is associated with an increased risk of agranulocytosis and with shock.

References.

1. Levy M. Hypersensitivity to pyrazolones. *Thorax* 2000; **55** (suppl 2): S72–S74.

Effects on the blood. Data collected from 8 population groups in Europe and Israel by the International Agranulocytosis and Aplastic Anemia Study[1] revealed that there was a significant regional variability in the rate-ratio estimate for agranulocytosis and dipyrone (0.9 in Budapest to 33.3 in Barcelona). Although a large relative increase in risk between agranulocytosis and use of dipyrone was found, the incidence was less than some previous reports had suggested.

Blood dyscrasias such as agranulocytosis and granulocytopenia have continued to be reported where dipyrone remains available.[2-7]

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2002; **58:** 265–74.
3. Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. *J Int Med Res* 2002; **30:** 488–95.
4. Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004; **10:** PI93–PI95.

5. Ibanez L, *et al*. Agranulocytosis associated with dipyrone (metamizol). *Eur J Clin Pharmacol* 2005; **60:** 821–9.
6. Hamerschlak N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J* 2005; **123:** 247–9.
7. Garcia S, *et al*. Dipyrone-induced granulocytopenia: a case for awareness. *Pharmacotherapy* 2006; **26:** 440–2.

Effects on the skin. Dipyrone has been considered responsible for a case of drug-induced toxic epidermal necrolysis.[1]

1. Roujeau J-C, *et al*. Sjögren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985; **i:** 609–11.

Hypersensitivity. Cross-sensitivity between aspirin and dipyrone occurred in a patient.[1] Dipyrone produced an exacerbation of dyspnoea, cyanosis, and respiratory arrest.

1. Bartoli E, *et al*. Drug-induced asthma. *Lancet* 1976; **i:** 1357.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dipyrone (metamizole sodium) as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/11/11)

Pharmacokinetics

After oral doses dipyrone is rapidly hydrolysed in the gastrointestinal tract to the active metabolite 4-methylamino-antipyrine, which after absorption undergoes metabolism to 4-formyl-amino-antipyrine and other metabolites. Dipyrone is also rapidly undetectable in plasma after intravenous doses. None of the metabolites of dipyrone are extensively bound to plasma proteins. Most of a dose is excreted in the urine as metabolites. Dipyrone metabolites are also distributed into breast milk.

References.

1. Heinemeyer G, *et al*. The kinetics of metamizol and its metabolites in critical-care patients with acute renal dysfunction. *Eur J Clin Pharmacol* 1993; **45:** 445–50.
2. Levy M, *et al*. Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinet* 1995; **28:** 216–34.
3. Zylber-Katz E, *et al*. Dipyrone metabolism in liver disease. *Clin Pharmacol Ther* 1995; **58:** 198–209.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Analgina; Dioxadol; Dipigrand; Ditral; Fiebrol; Integrobe; Lisalgil; Novacler; Novalgina; Novemina; Taxenil; Unibios Simple; ***Austria***: Novalgin; ***Belg.***: Analgine; Novalgine; ***Braz.***: Algirona; Anador; Analgesil†; Apiron; Baralgin; Conmel; Difebril; Dipigina; Dipimax; Dipiron†; Dipix; Diprin; Dornal†; Dorona; Dorpinon†; Magnopyrol; Maxiliv; Mirador; Nofebrin; Novagreen; Novalgina; Pirogina; Prodopirona†; Santidor; Termonal; Termopirona; Termoprins†; ***Chile***: Baralgina M; Conmel; ***China***: Di Shuang (迪爽); ***Cz.***: Novalgin; ***Ger.***: Analgin; Berlosin; Nopain†; Novalgin; Novaminsulfon; ***Gr.***: Natralgin; Telalgin; ***Hung.***: Algopyrin; Algozone; Novalgin†; Panalgorin; ***India***: Analgin; Baralgan-M; Novalgin; ***Indon.***: Antalgin; Antrain; Cornalgin; Foragin; Lexagin; Licogin; Norages; Novalgin; Panstop; Pragesol; Pyronal; Ronalgin; Scanalgin; Unagen; ***Israel***: Optalgin; Phanalgin†; V-Dalgin; V-Talgin†; ***Ital.***: Novalgina; Piralgin; ***Mex.***: Alnex; Anaprol†; Anapyrol†; Avafontan; Conmel; Dalmasin; Dalsin; Defin; Dimetirol; Dipydol; Dofisan; Dolgan; Dolizol; Dolofur†; Domenal†; Exodalina; Fandall; Fardolpin; Farlin; Gelcom; Indigon; Infatem; Lozima; Mach-2; Macodin; Magnidol; Magnil; Magnol; Magnolonas; Magnopyrol; Magsons; Mayoprina; Medipirol†; Mermid†; Messelfenil; Metapirona; Midelin; Minoral; Mizoltec; Modimet†; Neo-Melubrina; Neomelin†; Neosedal; Paleodina†; Pifrol†; Pirandall; Pirasod; Pirinovag; Piromebrina; Precidona; Prodolina; Prolubrin; Pyranol; Pyron; Suprin; Termonil†; Utidol; Vegal†; ***Neth.***: Novalgin; ***Pol.***: Pyrahexal; Pyralgin; Pyralgina; Pyralginum†; ***Port.***: Dolocalma; Nolotil; ***Rus.***: Analgin (Анальгин); Baralgin M (Баралгин М); ***Spain***: Algi; Dolemicin; Lasain†; Metalgial; Neo Melubrina†; Nolotil; ***Switz.***: Minalgin; Novalgin; ***Thai.***: Centagin†; Deparon†; Genergin†; Invoigin†; Kno-Paine†; Mezabox†; Nivagin†; Novalgin†; Olan-Gin†; Pyronpac; V Day Pyrin; ***Turk.***: Adepiron; Andolor; Baralgin M; Devaljin; Feninox†; Geralgine-M; Kafalgin; Nogesic; Novakom-S; Novalgin; Novo-Plan; Novopyrine; Sebon; Sedalmine; Seskaljin; Veraljin; ***Urug.***: Dolanet; ***Venez.***: Bral; Conmel; Delsal; Dipamona; Dipidol; Novalcina; Promel.

Multi-ingredient Preparations. ***Arg.***: Antispasmina; Apasmo Compuesto; Apasmo; Artifene; Bellatotal; Buscapina Compositum; Calmopirin; Cifespasmo Compuesto; Colobolina D; Cronopen Balsamico; Dentolina Plus†; Dextro + Dipirona†; Dextrodip†; Dioxadol; Dorixina Forte; Espasmo Biotenk; Espasmo Dioxadol; Fadagrip; Flexicamin A; Gastrolina Compuesta; Gobbicalm; Hioscina Compuesta; Integrobe Plus; Klosidol B1 B6 B12; Klosidol; Lisalgil Compuesto; Luar-G Compositum; Migra Dioxadol; Migral Compositum; Migral; Multin; Novopasmil Compuesto; Paratropina Compuesta; Pasmodina Compuesta; Profium Plus; Rupe-N Compuesto; Solacil; Sumal; Supragesic D; Tetralgin Novo; Tetralgin; Vicefeno; ***Austria***: Buscopan Compositum; ***Belg.***: Buscopan Compositum; ***Braz.***: Algexin; Algice; Ana-Flex; Analgin C-R; Belspan; Besodin; Bicavine; Binospan; Bioflex; Buscopan Composto; Buscoveran Composto; Butilamin†; Cafilisador; Cefaldina†; Cefaliv; Dalgex†; Dexalgen; Disbuspan†; Doralgex; Doralgina; Dorciflex†; Dorflex; Dorgil; Doricin; Doridina; Dorilen; Doriless; Dorsedin; Dorspan Composto; Dorzone; Drenogrip; Enxak; Espasmocron†; Espasmodid Composto; Flexalgex; Flexdor; Gripsay; Hioariston; Hiospan Composto; Kindpasm†; Lisador; Lisantil; Migraliv; Migranette; Mionevrix; Miorrelax; Neocopan; Neosaldina; Neuralgina; Nevralgex; Nogripe; Novralflex; Par; Reflex; Relaflex; Rielex; Royflex; Sedador; Sedalene; Sedalex; Sedalgina; Sedalin†; Sedamed; Sedol; Spasmotropin; Tensaldin; Tetrapulmo†; Tropinal; Veratropran Composto†; ***Chile***: Bramedil Compuesto; Buscapina Compositum; Cefadol; Cefalmin; Cinabel; Crotalgina; Dolcopin; Dolnix; Dolonase; Esamigran; Fredol; Migragesic; Migranol; Migratam; Neo Butartrol; Nospasmin Compuesto; Piretanyl; Piretanyl; Precenid; Scopanil; Ultrimin; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; ***Cz.***: Algifen Neo; Algifen; Analgin; ***Fin.***: Litalgin; ***Gr.***: Dispalgine; ***Hung.***: Algopyrin Complex; Quarelin; ***India***: Ketonal-D; ***Indon.***: Analsik; Arsinal; Biomega†; Cetalgin-T; Cetalgin; Corsanural; Dactron†; Danalgin; Deparon†; Dolo Scanneuron; Dolo-Licobion; Dormi Comp; Foraneural; Goralgin; Hedix; Hexalgin; Ikaneuron Plus; Metaneuron; Neuralgin RX; Neurindo; Neuro Panstop; Neurobat A; Neurodial; Neurogen†; Neurosanbe Plus; Neurotropic Plus; Neuroval; Opineuron; Penagon; Potensik; Pritagesic; Procolic; Proneuron; Spaslic; Spasmal; Spasminal†; Stileran; Supranal; Tropineuron; Unthecol†; Viron; ***Mex.***: Algosfar; Alivin Plus; Anadil; Benfol†; Biomesina Compuesta; Bipasmin Compuesto; Buscapina Compositum; Busconet; Busepan; Busprina; Colepren; Dolo-Tiaminal; Espasmogress; Hiosultrina-F; Korifen†; Mebuxina; Neo-Brontyl†; Neo-Pasmonal; Pasmodil†; Pirobutil; Respicil; Retodol Compositum; Selpiran; Serralpina Compuesta; Singril; Viladol-Met†; ***Pol.***: Gardan P†; Scopolan Compositum; Spasmalgon; Tolargin†; ***Rus.***: Analgin-Chinin (Анальгин-Хинин); Andipal (Андипал); Antigrippin-ANVI (Антигриппин-АНВИ); Benalgin (Бенальгин); Bioralgin (Биоралгин); Bral (Брал); Bralangine (Браланжин); Maxigan (Максиган); Nebalgan (Небалган); Pentabufen (Пентабуфен); Pentalgin-N (Пенталгин-Н); Plenalgin (Пленалгин); Pyralgin (Пиралгин); Quintalgine (Квинталгин); Renalgan (Реналган); Revalgin (Ревалгин); Santoperalgin (Сантопералгин); Santotiralgin (Сантотиралгин); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); Tempalgin (Темпалгин); Tempanginol (Темпангинол); Tetralgin (Тетралгин); ***S.Afr.***: Buscopan Compositum; Scopex Co; ***Spain***: Buscapina Compositum; ***Thai.***: Butarion†; Nalgin-P; Novapam†; ***Turk.***: Buscopan Compositum†; Penikin†; Peraljin†; Skopolin†; ***Ukr.***: Baralginus (Баралгинус)†; Bellalgin (Беллалгин); Sedal-M (Седал-М); Spasgan (Спазган); Spasmadol (Спазмадол)†; Spasmalgon (Спазмалгон); Spasmil-M (Спазмил-М); Tempalgin (Темпалгин); Tempanal (Темпанал); Tetralgin (Тетралгин); ***Venez.***: Buscapina Compositum; Butilamina Compuesta; Flemibar; Praxona; Sistalcin Compositum.

Eltenac *(rINN)*

Elténac; Eltenaco; Eltenacum; Эльтенак.
4-(2,6-Dichloroanilino)-3-thiopheneacetic acid.
$C_{12}H_9Cl_2NO_2S$=302.2
CAS — 72895-88-6.
UNII — A153L3JA99.

Profile

Eltenac is an NSAID (p. 102.3) used in veterinary medicine.

Embutramide *(BAN, USAN, rINN)*

Embutramida; Embutramidum; Hoe-18-680; Эмбутрамид.
N-(β,β-Diethyl-*m*-methoxyphenethyl)-4-hydroxybutyramide.
$C_{17}H_{27}NO_3$=293.4
CAS — 15687-14-6.
UNII — 3P4TQG94T1.

Profile

Embutramide is an opioid analgesic used in veterinary medicine for euthanasia.

Enoxolone *(BAN, rINN)*

Ácido glicirrético; Ácido glicirretínico; Enoksolonas; Enoksoloni; Enoxolon; Enoxolona; Énoxolone; Enoxolonum; Glycyrrhetic Acid; Glycyrrhetinic Acid; Kwas glicyryzynowy; Эноксолон.
3β-Hydroxy-11-oxo-olean-12-en-30-oic acid.
$C_{30}H_{46}O_4$=470.7
CAS — 471-53-4.
ATC — D03AX10.
ATC Vet — QD03AX10.
UNII — P540XA09DR.

NOTE. Do not confuse with glycyrrhizic acid (p. 2520.2).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Enoxolone). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Enoxolone is a complex triterpene prepared from glycyrrhizic acid (p. 2520.2), a constituent of liquorice (p. 1856.2). Enoxolone is used locally in preparations for the treatment of non-infective inflammatory disorders of the skin, mouth, throat, and rectum. Enoxolone potassium (potassium glycyrrhetinate) has been used similarly.

Derivatives of enoxolone, including its aluminium salt (p. 1843.3) and carbenoxolone (p. 1828.3) have been used in the treatment of benign peptic ulcer disease and other gastrointestinal disorders.

Enoxolone is a potent inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase, which inactivates cortisol, and use with hydrocortisone has been shown in *animal* studies to potentiate the activity of hydrocortisone in skin.[1] Whether this also increased the systemic absorption and toxicity of hydrocortisone was unclear.[2] However, for reference to adverse effects attributed to systemic inhibition of cortisol when enoxolone (glycyrrhetinic acid) is produced during metabolism of ingested liquorice, see Mineralocorticoid Effects, p. 1856.3.

A cream containing enoxolone with hyaluronic acid, telmesteine, and a grape extract, has been investigated with apparent benefit in the management of mild to moderate eczema[3,4] and is available for such use in some countries. However, topical application of enoxolone has been associated with contact dermatitis.[5]

1. Teelucksingh S, *et al*. Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. *Lancet* 1990; **335:** 1060–3.
2. Greaves MW. Potentiation of hydrocortisone activity in skin by glycerrhetinic acid. *Lancet* 1990; **336:** 876.
3. Belloni G, *et al*. A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair) in the treatment of mild to moderate atopic dermatitis. *Eur J Dermatol* 2005; **15:** 31–6.
4. Abramovits W, Boguniewicz M. Adult Atopiclair Study Group. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. *J Drugs Dermatol* 2006; **5:** 236–44.
5. Tanaka S, *et al*. Allergic contact dermatitis from enoxolone. *Contact Dermatitis* 2001; **44:** 192.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Dermanox; ***Fr.***: Arthrodont; PO 12; ***Hung.***: Arthrodont; ***S.Afr.***: Arthrodont†; ***Singapore***: Arthrodont; ***USA***: PruClair.

Multi-ingredient Preparations. ***Arg.***: Anastim; Empecid Pie; ***Austral.***: Atopiclair†; ***Braz.***: Capilos; ***Chile***: Gelclair; Ruboril; Sebium AKN†; Suavigel; ***Fr.***: Dermeol; Erygine†; Hexalyse; Humex Gorge Irritee†; Hyseke Solaire; Hyseke; Kelual DS; Kelual DS; Night Peel†; Novophane DS; Novophane K; Phlebocreme; Phlebosup; Pyreflor†; Sebium AKN; Sedorrhoide; Vocadys; ***Ger.***: Gelclair; ***Hong Kong***: Alox†; Hexalyse; ***Indon.***: Aloclair; Atopiclair; Polik†; ***Israel***: Aphtagone†; Aptha-X†; Atopiclair; Xclair; ***Ital.***: Acnesan; Bactilene†; Biolastic T5; Biothymus DS; Blogofort†; Brunex; Flogofort Cremagel; Fluocaril; Lenipasta; Lenirose; Lisomucil Gola; Neo-Stomygen; Perfluxi Cremagel; Prurex; Resvelife Sole; Resvelife; Skab 2†; Vaginol; ***Mex.***: Angenovag; Periodentyl; ***Mon.***: Phytospray; ***Port.***: Despigmentante†; ***Rus.***: Hexalyse (Гексализ); ***Singapore***: Atopiclair; Vetic; ***Spain***: Angileptol; Anginovag; Roberfarin; ***UK***: Atopiclair; Gelclair; Xclair; ***Ukr.***: Anginovag (Ангиновaг); Anzibel (Анзибел); Hexalyse (Гексализ); ***USA***: Atopiclair; Gelclair; ***Venez.***: Sebium AKN; Sensibio DS.

Epirizole *(USAN, pINN)*

DA-398; Epirizol; Épirizole; Epirizolum; Mepirizole; Эпиризол.
4-Methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methylpyrimidine.
$C_{11}H_{14}N_4O_2$=234.3
CAS — 18694-40-1.
UNII — 3B46O2FH8I.

Pharmacopoeias. In *Jpn*.

Profile

Epirizole is an NSAID (p. 102.3) that has been given in a usual oral dose of 150 to 450 mg daily in divided doses; larger doses of up to 600 mg daily have been used in patients with rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Mebron; ***Venez.***: Dalex.

Eptazocine Hydrobromide *(rINNM)*

Eptazocine, Bromhydrate d'; Eptazocini Hydrobromidum; Hidrobromuro de eptazocina; ST-2121; Эптазоцина Гидробромид.

(-)-(1S,6S)-2,3,4,5,6,7-Hexahydro-1,4-dimethyl-1,6-methano-1*H*-4-benzazonin-10-ol hydrobromide.

$C_{15}H_{21}NO,HBr$=312.3

CAS — 72522-13-5 (eptazocine); 72150-17-5 (eptazocine hydrobromide).

UNII — 865626Y4ON.

Profile

Eptazocine hydrobromide is an opioid analgesic with mixed opioid agonist and antagonist actions. It has been given by subcutaneous or intramuscular injection for the relief of pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Sedapain.

Etanercept *(BAN, USAN, rINN)*

Étanercept; Etanerceptum; Etanersept; Etanersepti; rhu-TNFR:Fc; TNR-001; Этанерцепт.

A dimer of 1-235 tumour necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment).

CAS — 185243-69-0.

ATC — L04AB01.

ATC Vet — QL04AB01.

UNII — OP401G7OJC.

Uses and Administration

Etanercept is a recombinant version of soluble human TNF receptor that binds specifically to tumour necrosis factor (p. 878.2) and blocks its interaction with endogenous cell-surface TNF receptors. This interaction prevents the important effect of TNF in the inflammatory processes of rheumatoid arthritis; elevated TNF levels are also found in psoriatic plaques, in the synovium of patients with psoriatic arthritis, and in the serum and synovium of patients with ankylosing spondylitis. Etanercept is described as a biological disease-modifying antirheumatic drug (DMARD).

Etanercept is used in the treatment of moderately to severely active **rheumatoid arthritis** (below) and active and progressive **psoriatic arthritis** (see Spondyloarthropathies, below). In the UK, it is licensed for use in patients who have had an inadequate response to standard DMARDs although in severe rheumatoid arthritis it may be used in patients not previously treated with methotrexate. In the USA, it is licensed to treat early rheumatoid arthritis or psoriatic arthritis. Etanercept is also indicated in the treatment of severely active **ankylosing spondylitis** (see Spondyloarthropathies, below); in the UK, its use is again limited to those who have had an inadequate response to conventional therapy. For all the above indications, it is given as a subcutaneous injection in a dose of 25 mg twice weekly at intervals of 3 or 4 days; the equivalent weekly dose of 50 mg may also be given as a single 50-mg injection. In the UK, NICE recommends that etanercept be stopped if there is no adequate response after 6 months for the treatment of rheumatoid arthritis, and after 12 weeks for psoriatic arthritis or ankylosing spondylitis.

Etanercept is also used in the treatment of chronic, moderate to severe **plaque psoriasis** (below). In the UK, its use is usually limited to patients unresponsive to, or intolerant of, conventional systemic therapy including photochemotherapy. The recommended initial dose is 25 mg twice weekly. Alternatively, an initial dose of 50 mg twice weekly at intervals of 3 or 4 days may be given for 12 weeks; the dose should then be reduced to 25 mg twice weekly or 50 mg once weekly. Initial doses of 25 or 50 mg once weekly have also been shown to be effective. Treatment should continue until remission is achieved, for up to 24 weeks. Etanercept should be stopped after 12 weeks in patients who show no response.

For details of uses and dosage in children, see below.

Administration in children. Etanercept is used in the treatment of moderately to severely active polyarticular **juvenile idiopathic arthritis** in children aged 2 years and older. In the UK, it is licensed for the treatment of polyarthritis or extended oligoarthritis in those who have had an inadequate response to, or who are intolerant of, the disease-modifying antirheumatic drug (DMARD) methotrexate. Etanercept is given subcutaneously in a dose of 400 micrograms/kg (up to a maximum dose of 25 mg) twice weekly at intervals of 3 or 4 days; alternatively, 800 micrograms/kg (up to a maximum dose of 50 mg) may be given once weekly. In the USA, etanercept is licensed for use in children aged 2 years and older to reduce the signs and symptoms of moderately to severely active polyarticular disease. Similar doses are used although doses to be given as 2 separate injections may either be given on the same day or 3 to 4 days apart. In the UK, NICE recommends that treatment be stopped in children if there is no response after 6 months, or an initial response is not maintained.

In the UK, etanercept is also licensed for the treatment of enthesitis-related arthritis and **psoriatic arthritis** in those aged 12 years and older who have had an inadequate response to, or who are intolerant of, conventional therapy; doses are similar to those given for polyarticular juvenile idiopathic arthritis above.

Etanercept is also used in the treatment of chronic severe plaque **psoriasis** in children aged 6 years and older; its use is limited to those in whom other systemic treatments are not suitable. The UK licensed dose is 800 micrograms/kg (up to a maximum dose of 50 mg) subcutaneously once weekly for up to 24 weeks; treatment should be stopped after 12 weeks in those who show no response.

Asthma. TNF inhibitors such as etanercept have been investigated in the treatment of refractory asthma (p. 1195.2).[1-3] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[4]

1. Howarth PH, *et al*. Tumour necrosis factor (TNFα) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005; **60:** 1012–18.
2. Berry MA, *et al*. Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006; **354:** 697–708.
3. Morjaria JB, *et al*. The role of a soluble TNFα receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. *Thorax* 2008; **63:** 584–91.
4. Brightling C, *et al*. Targeting TNF-α : a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Dementia. A small pilot study[1] and individual case reports[2] have suggested that perispinal injection of etanercept, in doses of 25 to 50 mg weekly, may improve signs of dementia in patients with Alzheimer's disease. However, randomised controlled studies are required to confirm any benefit.

1. Tobinick E, *et al*. TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. *MedGenMed* 2006; **8:** 25. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1785182/?tool=pubmed (accessed 28/07/10)
2. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008; **5**: 2. Available at: http://www.jneuroinflammation.com/content/pdf/1742-2094-5-2.pdf (accessed 13/06/08)

Psoriasis. Etanercept is effective in patients with moderate to severe plaque psoriasis (p. 1688.1).[1-12] It has also been successfully tried in the treatment of erythrodermic psoriasis,[13] and of plaque psoriasis in children and adolescents.[14]

Efficacy may be dose-related; in one study,[1] 25% of patients in the low-dose (25 mg once weekly) group showed at least a 75% improvement compared with 44% in the medium-dose group (25 mg twice weekly) and 59% in the high-dose group (50 mg twice weekly) after 24 weeks of etanercept treatment. However, a later multicentre study[2] in patients with chronic plaque psoriasis found that the therapeutic effect of etanercept was maintained when the dose was reduced after 12 weeks from 50 mg twice weekly to 25 mg twice weekly. An open-label extension[8] of these 2 studies found that efficacy was also sustained when patients who had received etanercept 25 mg twice weekly for at least 24 weeks had their dose altered to 50 mg once weekly.

1. Leonardi CL, *et al*. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349:** 2014–22.
2. Papp KA, *et al*. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152:** 1304–12.
3. NICE. Etanercept and efalizumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 103 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA103guidance.pdf (accessed 13/06/08)
4. Boehncke W-H, *et al*. European Dermatology Expert Group. Recommendations for the use of etanercept in psoriasis: a European dermatology expert group consensus. *J Eur Acad Dermatol Venereol* 2006; **20:** 988–98.
5. Woolacott N, *et al*. NHS Health Technology Assessment Programme. Etanercept and efalizumab for the treatment of psoriasis: a systematic review (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1046.pdf (accessed 13/06/08)
6. Tyring S, *et al*. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143:** 719–26.
7. Romero-Maté A, *et al*. Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8:** 143–55.
8. Elewski B, *et al*. Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; **156:** 138–42.
9. Ahmad K, Rogers S. Two years of experience with etanercept in recalcitrant psoriasis. *Br J Dermatol* 2007; **156:** 1010–14.
10. van de Kerkhof PCM, *et al*. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *Br J Dermatol* 2008; **159:** 1177–85.
11. Ortonne J-P, *et al*. Patients with moderate-to-severe psoriasis recapture clinical response during re-treatment with etanercept. *Br J Dermatol* 2009; **161:** 1190–5.
12. Sterry W, *et al*. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Abridged version: *BMJ* 2010; **340:** 300. Full version: http://www.bmj.com/cgi/reprint/340/feb02_2/c147 (accessed 06/05/10)
13. Esposito M, *et al*. Treatment of erythrodermic psoriasis with etanercept. *Br J Dermatol* 2006; **155:** 156–9.
14. Paller AS, *et al*. Etanercept Pediatric Psoriasis Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008; **358:** 241–51.

Rheumatoid arthritis. Some references[1-22] to the use of etanercept in rheumatoid arthritis (p. 13.2) and juvenile idiopathic arthritis (p. 12.1).

1. NICE. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis: Technology Appraisal Guidance 35 (issued March 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf (accessed 13/06/08)
2. Klareskog L, *et al*. TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) Study Investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363:** 675–81.
3. Genovese MC, *et al*. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005; **32:** 1232–42.
4. Bathon JM, *et al*. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J Rheumatol* 2006; **33:** 234–43.
5. van Riel PLCM, *et al*. ADORE (Add Enbrel or Replace Methotrexate) Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. *Ann Rheum Dis* 2006; **65:** 1478–83.
6. Moreland LW, *et al*. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006; **33:** 854–61.
7. van der Heijde D, *et al*. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006; **54:** 1063–74.
8. Chen Y-F, *et al*. NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 13/06/08)
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Spondyloarthropathies. References[1-16] to the use of etanercept in the treatment of ankylosing spondylitis and psoriatic arthritis (p. 14.3).

1. Davis JC, *et al*. Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; **48:** 3230–6.
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3. Baraliakos X, *et al.* Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. *Arthritis Rheum* 2005; **53:** 856–63.
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10. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8:** 143–55.
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16. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)

Vasculitic syndromes. For a preliminary report on the use of etanercept in Takayasu's arteritis, see p. 1614.3.

Adverse Effects, Treatment, and Precautions

As for Infliximab, p. 75.3.

Mild to moderate injection site reactions with symptoms of erythema, itching, pain, or swelling are common with etanercept. Other common reactions include headache, dizziness, asthenia, nausea and vomiting, abdominal pain, dyspepsia, and allergic reactions. Antibodies to etanercept may develop.

Etanercept should be used with caution in patients with heart failure.

References.
1. Sánchez Carazo JL, *et al.* Safety of etanercept in psoriasis: a critical review. *Drug Safety* 2006; **29:** 675–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etanercept as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Wegener's granulomatosis. The addition of etanercept to standard therapy (including cyclophosphamide or methotrexate and corticosteroids) was not shown to be effective in patients with Wegener's granulomatosis and was associated with an increased incidence of various non-cutaneous malignancies.[1] Licensed product information recommends that etanercept should not be added to therapy in patients with Wegener's granulomatosis.

1. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; **352:** 351–61.

Interactions

As for Infliximab, p. 77.3. The use of etanercept with sulfasalazine has resulted in decreased white blood cell counts; however, the clinical significance of this is unknown. For an increased incidence of malignancy when etanercept was added to standard immunosuppressive therapy in patients with Wegener's granulomatosis, see above.

Pharmacokinetics

After a single subcutaneous dose of etanercept, UK licensed product information states that the mean half-life is about 70 hours, and the time to peak serum concentration 48 hours. In contrast, US information gives the half-life as 102 hours and the time to peak concentration as about 70 hours, although with a considerable range. Repeated dosing was noted to result in a two- to sevenfold increase in serum levels of etanercept in some patients.

References.
1. Korth-Bradley JM, *et al.* The pharmacokinetics of etanercept in healthy volunteers. *Ann Pharmacother* 2000; **34:** 161–4.
2. Zhou H. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. *J Clin Pharmacol* 2005; **45:** 490–7.
3. Yim D-S, *et al.* Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 246–56.
4. Don BR, *et al.* The pharmacokinetics of etanercept in patients with end-stage renal disease on haemodialysis. *J Pharm Pharmacol* 2005; **57:** 1407–13.
5. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; **74** (suppl): 13–18.
6. Sullivan JT, *et al.* Bioequivalence of liquid and reconstituted lyophilized etanercept subcutaneous injections. *J Clin Pharmacol* 2006; **46:** 654–61.
7. Nestorov I, *et al.* Pharmacokinetics of subcutaneously administered etanercept in subjects with psoriasis. *Br J Clin Pharmacol* 2006; **62:** 435–45.
8. Elewski B, *et al.* Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; **156:** 138–42.
9. Zhou SY, *et al.* Integrated population pharmacokinetics of etanercept in healthy subjects and in patients with rheumatoid arthritis and ankylosing spondylitis. *J Clin Pharmacol* 2011; **51:** 864–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Enbrel; ***Austral.***: Enbrel; ***Austria***: Enbrel; ***Belg.***: Enbrel; ***Braz.***: Enbrel; ***Canad.***: Enbrel; ***Chile***: Enbrel; ***China***: Enbrel (恩利); Yisaipu (益赛普); ***Cz.***: Enbrel; ***Denm.***: Enbrel; ***Fin.***: Enbrel; ***Fr.***: Enbrel; ***Ger.***: Enbrel; ***Gr.***: Enbrel; ***Hong Kong***: Enbrel; ***Hung.***: Enbrel; ***India***: Enbrel; Enbrol; ***Indon.***: Enbrel; ***Irl.***: Enbrel; ***Israel***: Enbrel; ***Ital.***: Enbrel; ***Malaysia***: Enbrel; ***Mex.***: Enbrel; ***Neth.***: Enbrel; ***Norw.***: Enbrel; ***NZ***: Enbrel; ***Philipp.***: Enbrel; ***Pol.***: Enbrel; ***Port.***: Enbrel; ***Rus.***: Enbrel (Энбрел); ***S.Afr.***: Enbrel; ***Singapore***: Enbrel; ***Spain***: Enbrel; ***Swed.***: Enbrel; ***Switz.***: Enbrel; ***Thai.***: Enbrel; ***Turk.***: Enbrel; ***UK***: Enbrel; ***USA***: Enbrel; ***Venez.***: Enbrel.

Ethenzamide *(BAN, rINN)*

Aethoxybenzamidum; Etentsamidi; Etenzamid; Etenzamida; Etenzamide; Éthenzamide; Ethenzamidum; Ethoxybenzamide; Ethylsalicylamide; HP-209; Этензамид.

2-Ethoxybenzamide.

$C_9H_{11}NO_2$=165.2

CAS — 938-73-8.

ATC — N02BA07.

ATC Vet — QN02BA07.

UNII — L929ZCK4BF.

Pharmacopoeias. In *Jpn*.

Profile

Ethenzamide is a salicylic acid derivative (see Aspirin, p. 22.2) given orally in painful and inflammatory conditions and to reduce fever.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Helopyrin; Seltoc†; ***Indon.***: Farapon; Neo Novapon Plus; ***Jpn***: Sin Colgen Kowa Kaze†; ***Pol.***: Erka; Etomar; Etopiryna; ***Port.***: Cephyl†; ***Rus.***: Nextrim Aktiv (Некстрим Актив).

Ethoheptazine Citrate *(BANM, rINNM)*

Citrato de etoheptacina; Éthoheptazine, Citrate d'; Ethoheptazini Citras; Etoheptacina, citrato de; Wy-401; Этогептазина Цитрат.

Ethyl 1-methyl-4-phenylperhydroazepine-4-carboxylate dihydrogen citrate.

$C_{16}H_{23}NO_2,C_6H_8O_7$=453.5

CAS — 77-15-6 (ethoheptazine); 6700-56-7 (ethoheptazine citrate); 2085-42-9 ((±)-ethoheptazine citrate).

UNII — LXK8EE245D.

Profile

Ethoheptazine citrate is an opioid analgesic (p. 108.1) structurally related to pethidine (p. 121.3). It has been used as an analgesic in the short-term treatment of mild to moderate pain, usually with other drugs such as aspirin and meprobamate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Equagesic; ***S.Afr.***: Equagesic†.

Ethyl Nicotinate

Nicotinato de etilo; Этилникотинат.

$C_8H_9NO_2$=151.2

CAS — 614-18-6.

UNII — NU3H353YH.

Profile

Ethyl nicotinate is used in concentrations of up to 2% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It has also been used as suppositories in anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Mucotherm.

Multi-ingredient Preparations. ***Belg.***: Transvane; ***Hung.***: Nicoflex; ***Irl.***: Transvasin†; ***Rus.***: Nicoflex (Никофлекс); ***Switz.***: Baume Esco Forte†; Knobel Huile N†; Ziegella†; ***UK***: Boots Pain Relief Heat Rub; Boots Pain Relief Heat Spray; Pain Relief Balm†; PR Heat Spray†; Transvasin Heat Rub.

Ethyl Salicylate

Salicilato de etilo; Этилсалицилат.

Ethyl 2-hydroxybenzoate.

$C_9H_{10}O_3$=166.2

CAS — 118-61-6.

UNII — 555U6TZ2MV.

Profile

Ethyl salicylate is a salicylic acid derivative that is used similarly to methyl salicylate (p. 92.1) in concentrations of up to 5% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Deep Heat; ***Belg.***: Rado-Salil; ***Chile***: Calorub Sport; ***Hung.***: Deep Heat Spray; ***Irl.***: Deep Heat; Ralgex; ***Israel***: Deep Heat Spray; ***Ital.***: Remystick; ***Pol.***: Deep Heat; ***S.Afr.***: Deep Heat Spray†; ***UK***: Deep Heat Spray; Dubam; Numark Muscle Spray†; ***Ukr.***: Deep Heat (Дип Хит).

Ethylmorphine Hydrochloride *(BANM)*

Aethylmorphinae Hydrochloridum; Aethylmorphini Hydrochloridum; Chlorhydrate de Codéthyline; Ethylmorfin-hydrochlorid dihydrát; Éthylmorphine, chlorhydrate d'; Ethylmorphinhydrochlorid; Ethylmorphini Hydrochloridum; Ethylmorphini Hydrochloridum Dihydricum; Ethylmorphinium Chloride; Etilmorfina, hidrocloruro de; Etilmorfin-hidroklorid; Etilmorfino hidrochloridas; Etylmorfinhydroklorid; Etylomorfiny chlorowodorek; Etyylimorfiinihydrokloridi; Этилморфина Гидрохлорид.

3-*O*-Ethylmorphine hydrochloride dihydrate; 7,8-Didehydro-4,5-epoxy-3-ethoxy-17-methylmorphinan-6-ol hydrochloride dihydrate.

$C_{19}H_{23}NO_3.HCl.2H_2O$=385.9

CAS — 76-58-4 (ethylmorphine); 125-30-4 (ethylmorphine hydrochloride).

ATC — R05DA01; S01XA06.

ATC Vet — QR05DA01; QS01XA06.

UNII — MFM5450P3T (ethylmorphine hydrochloride); 407X3NQV4N (ethylmorphine hydrochloride dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Ethylmorphine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. A 2% solution in water has a pH of 4.3 to 5.7. Protect from light.

Profile

Ethylmorphine hydrochloride is an opioid analgesic (p. 108.1) and has properties similar to those of codeine (p. 40.2). It is used mainly as a cough suppressant. It has also been used for its analgesic and antidiarrhoeal properties. It was formerly given in eye drops as a lymphagogue.

Ethylmorphine free base and the camphorate and camsilate have also been used.

References.
1. Aasmundstad TA, *et al.* Biotransformation and pharmacokinetics of ethylmorphine after a single oral dose. *Br J Clin Pharmacol* 1995; **39:** 611–20.
2. Jonasson B, *et al.* Fatal poisonings where ethylmorphine from antitussive medications contributed to death. *Int J Legal Med* 1999; **112:** 299–302.
3. Helland A. *et al.* Death of a 10-month-old boy after exposure to ethylmorphine. *J Forensic Sci* 2010; **55:** 551–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dionina; ***Belg.***: Codethyline; ***Cz.***: Diolan†; ***Fin.***: Cocillana; ***Fr.***: Clarix Toux Seche Codethyline; Pectosan Toux Seche†; Peter's Sirop; ***India***: Dionindon; ***UK***: Collins Elixir.

Multi-ingredient Preparations. ***Belg.***: Baume Pulmonaire; Longbalsem†; Saintbois; ***Chile***: Codelasa; ***Fin.***: Indalgin; ***Fr.***: Ephydion†; Tussipax; Tussipax; Vegetoserum†; Vegetoserum; ***Hong Kong***: Fritussin†; ***Hung.***: Dolor†; ***India***: Bell Diono Resolvent†; Bell Resolvent†; ***Norw.***: Cosylan; Solvipect comp; ***Spain***: Demusin†; ***Swed.***: Cocillana-Etyfin; Lepheton; ***Switz.***: PholTux; Sano Tuss; ***Turk.***: Fenokodin†; Neocodin; ***Venez.***: Novacodin.

Etodolac *(BAN, USAN, rINN)*

AY-24236; Etodolaakki; Étodolac; Etodolaco; Etodolacum; Etodolak; Etodolák; Etodolakas; Etodolic Acid; Этодолак.

1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

$C_{17}H_{21}NO_3$=287.4

CAS — 41340-25-4.

ATC — M01AB08.

ATC Vet — QM01AB08.

UNII — 2M36281008.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Etodolac). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone.

USP 36: (Etodolac). Store in airtight containers.

Uses and Administration

Etodolac, a pyrano-indoleacetic acid derivative, is an NSAID (p. 102.3) reported to be a preferential inhibitor of cyclo-oxygenase-2 (COX-2). It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, and osteoarthritis and for the treatment of acute pain.

For the treatment of rheumatoid arthritis and osteoarthritis, the recommended oral dose is initially 0.6 to 1 g daily in divided doses adjusted according to response to a usual dose of 300 to 600 mg daily. Modified-release preparations are available for once-daily use in these conditions. For doses in children, see below.

For the treatment of acute pain, the recommended dose is 200 to 400 mg every 6 to 8 hours to a maximum of 1 g daily.

Reviews.

1. Tirunagari SK, *et al.* Single dose oral etodolac for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 09/09/09).

Administration in children. In the USA modified-release preparations of etodolac may be given for the oral treatment of juvenile idiopathic arthritis in children aged 6 to 16 years. Doses are given once daily according to bodyweight as follows:

- 20 to 30 kg: 400 mg
- 31 to 45 kg: 600 mg
- 46 to 60 kg: 800 mg
- over 60 kg: 1 g

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

The presence of phenolic metabolites of etodolac in the urine may give rise to a false-positive reaction for bilirubin.

Effects on the blood. Agranulocytosis has been reported in a patient receiving etodolac.[1] Coombs-positive haemolytic anaemia due to sensitivity to etodolac metabolites has also been reported.[2]

1. Cramer RL, *et al.* Agranulocytosis associated with etodolac. *Ann Pharmacother* 1994; **28:** 458–60.
2. Cunha PD, *et al.* Immune hemolytic anemia caused by sensitivity to a metabolite of etodolac, a nonsteroidal anti-inflammatory drug. *Transfusion* 2000; **40:** 663–8.

Effects on the gastrointestinal tract. Etodolac is reported to be a preferential inhibitor of cyclo-oxygenase-2 (COX-2) and consequently it may produce less gastric toxicity than the non-selective NSAIDs such as naproxen.[1-3]

1. Taha AS, *et al.* Effect of repeated therapeutic doses of naproxen and etodolac on gastric and duodenal mucosal prostaglandins (PGs) in rheumatoid arthritis (RA). *Gut* 1989; **30:** A751.
2. Bianchi Porro G, *et al.* A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med* 1991; **229:** 5–8.
3. Weideman RA, *et al.* Risks of clinically significant upper gastrointestinal events with etodolac and naproxen: a historical cohort analysis. *Gastroenterology* 2004; **127:** 1322–8.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Etodolac is a chiral compound given as the racemate. Peak plasma concentrations of the active *S*-enantiomer and of the inactive *R*-enantiomer usually occur within about 2 hours of an oral dose but plasma concentrations of the *R*-enantiomer have been reported to greatly exceed those of the *S*-enantiomer. Both enantiomers are highly bound to plasma proteins. Both are also distributed to the synovial fluid, although the difference in their concentrations may not be as large as the difference in plasma concentrations. The plasma half-life of total etodolac has been reported to be about 7 hours; excretion is mainly in the urine as hydroxylated metabolites and glucuronide conjugates; some may be excreted in the bile.

References.

1. Brocks DR, *et al.* Stereoselective disposition of etodolac enantiomers in synovial fluid. *J Clin Pharmacol* 1991; **31:** 741–6.
2. Brocks DR, *et al.* The stereoselective pharmacokinetics of etodolac in young and elderly subjects, and after cholecystectomy. *J Clin Pharmacol* 1992; **32:** 982–9.
3. Brocks DR, Jamali F. Etodolac clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 259–74.
4. Boni J, *et al.* Pharmacokinetic and pharmacodynamic action of etodolac in patients after oral surgery. *J Clin Pharmacol* 1999; **39:** 729–37.
5. Boni JP, *et al.* Pharmacokinetics of etodolac in patients with stable juvenile rheumatoid arthritis. *Clin Ther* 1999; **21:** 1715–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Flancox; ***China***: Etolac (依特); Lodine (罗丁); Na Zhi (那止); Shu Ya Ke (舒雅柯); Yi Fen (依芬); ***Denm.***: Todolac; ***Fin.***: Lodine; ***Fr.***: Lodine; ***Gr.***: Ecridoxan; Etolac; Impovituss; Lonine; Lubetyl; Ofniskel; Silgonitran; ***Hong Kong***: Etonox†; Lodine†; ***India***: Etofact; Etolor; Etomax; Etova; ***Indon.***: Lonene†; ***Israel***: Etopan; ***Jpn***: Hypen; ***Philipp.***: Etoflam; ***Port.***: Acudor†; Articulan†; Dualgan; Exodolan; Sodolac; ***Switz.***: Lodine; ***Thai.***: Etonox; ***Turk.***: Dolarit; Edolar; Esodax; Etodin; Etol; Etopan; Etoteva; Etoxa; Lodine; Tadolak; Tilac; ***UK***: Eccoxolac; Etopan; Lodine; ***Ukr.***: Etol (Этол Форт).

Multi-ingredient Preparations. ***India***: Etolex-P; Etolor-P; Etomax-P; Etova-P.

Pharmacopoeial Preparations

BP 2014: Etodolac Capsules; Etodolac Tablets;

USP 36: Etodolac Capsules; Etodolac Extended-Release Tablets; Etodolac Tablets.

Etofenamate *(BAN, USAN, rINN)*

B-577; Bay-d-1107; Etofenamaatti; Etofenamat; Etofenamát; Etofenamatas; Étofénamate; Etofenamato; Etofenamatum; TV-485; TVX-485; WHR-5020; Этофенамат.

2-(2-Hydroxyethoxy)ethyl *N*-(αα α-trifluoro-*m*-tolyl)anthranilate.

$C_{18}H_{18}F_3NO_4$=369.3

CAS — 30544-47-9.

ATC — M02AA06.

ATC Vet — QM02AA06.

UNII — KZF0XM66JC.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Etofenamate). A yellowish viscous liquid. Practically insoluble in water; miscible with alcohol and with ethyl acetate.

Profile

Etofenamate is an NSAID (p. 102.3) that has been applied topically in a concentration of 5 or 10% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. It has also been given by deep intramuscular injection in single doses of 1 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flogol; ***Austria***: Rheumon; Traumon; ***Belg.***: Flexium; ***Braz.***: Aspisport; Bayro; ***Chile***: Bayagel†; Flogojet; Valorel; ***China***: Rheumon (优迈); ***Cz.***: Rheumon†; Traumon; ***Ger.***: Rheuma-Gel†; Rheumon; Traumon†; ***Gr.***: Celanat; Cimal; Etofenol; Etogel; Fenam; Ferepat; Herponil; Irifone; Kovotherm; Melferut; Pazergicel; Radermin; Reumina; Roiplon; Vellodrying; ***Hong Kong***: Flogoprofen; Rheuma-Denk†; ***Hung.***: Activon; Rheumon; ***Irl.***: Etoflam; ***Ital.***: Gemadol; ***Mex.***: Bayro; ***Pol.***: Rheumon; Traumon; ***Port.***: Fenogel†; Inalgex; Reumon; Traumon†; ***Spain***: Aspitopic; Flogoprofen; Zenavan; ***Switz.***: Rheumon; Traumalix; ***Turk.***: Doline; Flexo; Painex; Rheumon; ***Venez.***: Traflan.

Multi-ingredient Preparations. ***Arg.***: Bayagel; ***Austria***: Thermo-Rheumon; ***Gr.***: Thermo-Roiplon; ***Mex.***: Bayro Termo; ***Pol.***: Thermo-Rheumon; ***Turk.***: Thermo-Doline; Thermo-Rheumon; Thermoflex; Thermove; ***Venez.***: Reugel.

Etoricoxib *(BAN, USAN, rINN)*

Étoricoxib; Etoricoxibum; Etorikoksib; Etorikoksibi; Etorikoxib; L-791456; MK-0663; MK-663; Эторикоксиб.

5-Chloro-6′-methyl-3-[*p*-(methylsulfonyl)phenyl]-2,3′-bipyridine.

$C_{18}H_{15}ClN_2O_2S$=358.8

CAS — 202409-33-4.

ATC — M01AH05.

ATC Vet — QM01AH05.

UNII — WRX4NFY03R.

Uses and Administration

Etoricoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used in the symptomatic relief of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis.

In osteoarthritis, etoricoxib is given orally in a usual dose of 30 mg once daily, increased to 60 mg once daily if necessary. The recommended dose in rheumatoid arthritis and in ankylosing spondylitis is 90 mg once daily; higher doses of 120 mg once daily are used in gouty arthritis although such doses should only be used for the acute symptomatic period and for a maximum of 8 days. For dosage recommendations in patients with hepatic impairment, see below.

References.

1. Patrignani P, *et al.* Clinical pharmacology of etoricoxib: a novel selective COX2 inhibitor. *Expert Opin Pharmacother* 2003; **4:** 265–84.
2. Dallob A, *et al.* Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003 **43:** 573–85.
3. Martina SD, *et al.* Etoricoxib: a highly selective COX-2 inhibitor. *Ann Pharmacother* 2005; **39:** 854–62.

Administration in hepatic impairment. The maximum oral dose of etoricoxib in patients with mild hepatic impairment (Child-Pugh score of 5 to 6), regardless of indication, is 60 mg once daily; those with moderate impairment (Child-Pugh 7 to 9) should be given a maximum of 60 mg every other day or 30 mg once daily. Etoricoxib should not be given to patients with severe hepatic impairment (Child-Pugh 10 or more).

Musculoskeletal and joint disorders. The selective cyclo-oxygenase-2 (COX-2) inhibitor etoricoxib is used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p. 14.3), osteoarthritis (p. 12.3), and rheumatoid arthritis (p. 13.2); it is also used in gouty arthritis (p. 600.1). However, in the UK, it is recommended that the use of selective COX-2 inhibitors is limited to patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p. 105.3).

References.

1. Cochrane DJ, *et al.* Etoricoxib. *Drugs* 2002; **62:** 2637–51.
2. Schumacher HR, *et al.* Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ* 2002; **324:** 1488–92.
3. Gottesdiener K, *et al.* Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. *Rheumatology (Oxford)* 2002; **41:** 1052–61.
4. Wiesenhutter CW, *et al.* Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 470–9.
5. van der Heijde D, *et al.* Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; **52:** 1205–15.
6. Curtis SP, *et al.* Etoricoxib in the treatment of osteoarthritis over 52-weeks: a double-blind, active-comparator controlled trial [NCT00242489]. *BMC Musculoskelet Disord* 2005; **6:** 58. Available at: http://www.biomedcentral.com/content/pdf/1471-2474-6-58.pdf (accessed 01/11/07)
7. Bingham CO, *et al.* Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology (Oxford)* 2007; **46:** 496–507.
8. Croom KF, Siddiqui MAA. Etoricoxib: a review of its use in the symptomatic treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gouty arthritis. *Drugs* 2009; **69:** 1513–32.

Pain. A systematic review[1] found that a single 120-mg dose of etoricoxib, given orally, provided effective pain relief after surgery. When compared indirectly, etoricoxib was considered to be at least as effective as other commonly used analgesics.

1. Clarke R, *et al.* Single dose oral etoricoxib for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 09/09/09).

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving etoricoxib; it should be stopped at the first signs of hypersensitivity.

Etoricoxib should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Etoricoxib, particularly at high doses, may be associated with more frequent and severe hypertension compared with other NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors; blood pressure monitoring during etoricoxib treatment is recommended. Etoricoxib should not be used in patients with hypertension whose blood pressure is not controlled (see also Effects on the Cardiovascular System, below).

Etoricoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and renal impairment associated with a creatinine clearance of less than 30 mL/minute. It should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more). Therapy should be stopped if persistently abnormal liver enzyme values are seen. Caution is recommended when using etoricoxib in dehydrated patients; it may be advisable to rehydrate patients before giving etoricoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p. 128.3). The cardiovascular safety of etoricoxib has been assessed in the MEDAL programme,[1] which pooled data from 3 studies involving over 30 000 patients with either osteoarthritis or rheumatoid arthritis. Patients with osteoarthritis were given etoricoxib 60 or 90 mg daily; those with rheumatoid arthritis received 90 mg daily. In all studies, diclofenac 150 mg daily was given as the comparator; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After an average treatment duration of 18 months, the rates of thrombotic events such as myocardial infarction, stroke, and sudden or unexplained death with etoricoxib were similar to those for diclofenac. (It has been suggested that diclofenac itself may increase the risk of some thrombotic events; for further details, see p. 105.1.) The programme also found that the rate of some other non-thrombotic cardiovascular events was increased with etoricoxib: one of the 3 studies showed that there was a non-significant increase in the rate of heart failure with etoricoxib 90 mg daily compared with diclofenac; withdrawals due to oedema were also more frequent with high-dose etoricoxib than with diclofenac or etoricoxib 60 mg daily. In addition, the number of patients stopping treatment because of hypertension was higher with both doses of etoricoxib than with diclofenac. Similar results were seen in the other 2 studies.

In another study[2] that pooled pre-licensing data, the risk of thrombotic events with etoricoxib, given at a dose of at least 60 mg daily, was also found to be similar to that for placebo treatment, ibuprofen (2.4 g daily), diclofenac (150 mg daily), and naproxen (1 g daily), although there was a trend towards more events with etoricoxib than with naproxen. For details on the relative risk of thrombotic events associated with non-selective NSAIDs, see p. 105.1.

After a recommendation from the EMEA's Committee for Medicinal Products for Human Use (CHMP),[3] licensed product information for etoricoxib states that it must not be given to patients whose blood pressure is persistently above 140/90 mmHg and inadequately controlled; in addition, high blood pressure should be controlled before starting treatment and monitored for 2 weeks afterwards then regularly thereafter.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p. 37.3.

1. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368:** 1771–81.
2. Curtis SP, *et al.* Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective inhibitor etoricoxib. *Curr Med Res Opin* 2006; **22:** 2365–74.
3. EMEA. EMEA recommends strengthening warnings and contra-indications for etoricoxib-containing medicines used in the treatment of rheumatoid arthritis and ankylosing spondylitis (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/33363608en.pdf (accessed 16/07/08)

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as etoricoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information states that upper gastrointestinal perforation, ulceration, and bleeds, in some cases fatal, have occurred with etoricoxib treatment; consequently, it should be used with caution in patients with a history of, or at risk of developing, such events. In addition, etoricoxib should not be used in patients with active gastrointestinal ulceration or bleeding.

Results from controlled studies have suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a study[1] of the pooled data from 3 randomised clinical studies, etoricoxib (in doses of 60 or 90 mg daily) was associated with significantly less frequent upper gastrointestinal clinical events than diclofenac (150 mg daily). The result was attributed to the lower rate of uncomplicated ulcers with etoricoxib compared with diclofenac; there was no difference in the rate of complicated gastrointestinal events between the 2 drugs. The lower rate of uncomplicated events with etoricoxib compared with diclofenac was not affected by treatment with low-dose aspirin or proton pump inhibitors. An analysis[2] by the manufacturer, of pooled data from 10 randomised clinical studies, found that etoricoxib (in daily doses of 60, 90, or 120 mg) was associated with a lower combined risk of upper gastrointestinal perforations and bleeding, and symptomatic gastroduodenal ulcers when compared with non-selective NSAIDs (diclofenac 150 mg daily, ibuprofen 2.4 g daily, or naproxen 1 g daily) as a group. This reduced risk was seen even in patients with known risk factors for such complications such as the elderly and those with a history of gastrointestinal reactions.

1. Laine L, *et al.* Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007; **369:** 465–73.
2. Ramey DR, *et al.* The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: an updated combined analysis. *Curr Med Res Opin* 2005; **21:** 715–22.

Effects on the kidneys. Limited evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as etoricoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etoricoxib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

The metabolism of etoricoxib is mediated by the cytochrome P450 isoenzyme CYP3A4. Use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of etoricoxib. In addition, *in vitro* studies suggest that several other isoenzymes may also mediate the main metabolic pathway of etoricoxib. Rifampicin, a potent inducer of CYP isoenzymes, has produced decreased plasma concentrations of etoricoxib.

Etoricoxib is an inhibitor of human sulfotransferase activity and has been shown to increase the plasma concentration of ethinylestradiol. Interactions with other drugs, such as oral salbutamol and minoxidil, also metabolised by this enzyme may be a possibility and licensed product information advises care with such combinations.

For interactions associated with NSAIDs in general, see p. 107.3.

Pharmacokinetics

Etoricoxib is well absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur in about 1 hour in fasted adults; food delays absorption by about 2 hours, although it has no effect on the extent of absorption. Plasma protein binding is about 92%. At steady state the half-life of etoricoxib is about 22 hours. Etoricoxib is extensively metabolised with less than 2% of a dose recovered in the urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6′-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6′-carboxylic acid derivative, the major metabolite. Both are inactive or only weak cyclo-oxygenase-2 (COX-2) inhibitors. Excretion is mainly via the urine (70%) with only 20% of a dose appearing in the faeces. Studies in *animals* suggest that etoricoxib may cross the placenta and that some is distributed into breast milk.

References.
1. Agrawal NGB, *et al.* Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. *J Clin Pharmacol* 2003; **43:** 268–76.
2. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with hepatic impairment. *J Clin Pharmacol* 2003; **43:** 1136–48.
3. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with renal impairment. *J Clin Pharmacol* 2004; **44:** 48–58.
4. Takemoto JK, *et al.* Clinical pharmacokinetic and pharmacodynamic profile of etoricoxib. *Clin Pharmacokinet* 2008; **47:** 703–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arcoxia; ***Austral.***: Arcoxia; ***Austria***: Arcoxia; Auxib†; ***Belg.***: Arcoxia; Ranacox; ***Braz.***: Arcoxia; ***Chile***: Arcoxia; ***China***: Arcoxia (安康信); ***Cz.***: Arcoxia; ***Denm.***: Arcoxia; ***Fin.***: Arcoxia; Turox†; ***Fr.***: Arcoxia; ***Ger.***: Arcoxia; ***Gr.***: Arcoxia; Turox; ***Hong Kong***: Arcoxia; ***Hung.***: Arcoxia; ***India***: Alcoxib; Coxet; Coxifact; Doricox; E-Trom; Ebov; Eleton; Erofica; Eteron; Eticox; Etobus; Etocos; Etody; Etofan; Etolex; Etom; Etori; Etorica; Etosaid; Etoshine; Etosym; Etoxib; Etozox; Etrik; Etro; Etrobax; Ezact; Hicox; Hireto; Ifydrox; Intacoxia; Ixidol; Kingcox; Kretos; L-Kon; M-Kon; Nucoxia; O-Cox; ***Indon.***: Arcoxia; ***Irl.***: Acoxxel; Arcoxia; ***Israel***: Arcoxia; ***Ital.***: Algix; Arcoxia; Exinef; Tauxib; ***Malaysia***: Arcoxia; ***Mex.***: Arcoxia; ***Neth.***: Arcoxia; Auxib; ***Norw.***: Arcoxia; ***NZ***: Arcoxia; ***Philipp.***: Arcoxia; ***Port.***: Arcoxia; Exxiv; Turox; ***Rus.***: Arcoxia (Аркоксиа); ***S.Afr.***: Arcoxia; ***Singapore***: Arcoxia; ***Spain***: Acoxxel; Arcoxia; Exxiv; ***Swed.***: Arcoxia; Turox; ***Switz.***: Arcoxia; ***Thai.***: Arcoxia; ***UK***: Arcoxia; ***Ukr.***: Arcoxia (Аркоксия); ***Venez.***: Arcoxia.

Multi-ingredient Preparations. ***India***: Etro-P; Nucoxia-MR; Nucoxia-P; Nucoxia-SP.

Etorphine Hydrochloride *(BANM, rINNM)*

Etorfina, hidrocloruro de; Étorphine, Chlorhydrate d'; Etorphini Hydrochloridum; Hidrocloruro de etorfina; M-99; 19-Propylorvinol Hydrochloride; Эторфина Гидрохлорид.

(6*R*,7*R*,14*R*)-7,8-Dihydro-7-[(1*R*)-1-hydroxy-1-methylbutyl]-6-*O*-methyl-6,14α-ethenomorphine hydrochloride; (2*R*)-2-[(-)-(5*R*,6*R*,7*R*,14*R*)-4,5-Epoxy-3-hydroxy-6-methoxy-9a-methyl-6,14-ethenomorphinan-7-yl]pentan-2-ol hydrochloride.

$C_{25}H_{33}NO_4$,HCl=448.0

CAS — 14521-96-1 (etorphine); 13764-49-3 (etorphine hydrochloride).

UNII — 8CBE01N748.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Etorphine Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Etorphine hydrochloride is a highly potent opioid analgesic (p. 108.1) used for reversible neuroleptanalgesia (see Anaesthetic Techniques, p. 1899.3) in veterinary medicine. It is given with acepromazine maleate or levomepromazine (*Immobilon*) to restrain animals and before minor veterinary surgery. The duration of action of etorphine is up to about 45 to 90 minutes depending on the species but it may be longer in man, especially if the large animal preparation is involved.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1. Etorphine is not used therapeutically in humans.

Etorphine hydrochloride is highly potent and rapid acting; minute amounts can exert serious effects leading to coma. It may be absorbed through skin and mucous membranes. It is thus advisable to inject an antagonist *immediately* after contamination of skin or mucous membranes with preparations containing etorphine hydrochloride and to wash the affected areas copiously. Accidental injection or needle scratch injuries should also be treated immediately by injecting an antagonist. Naloxone is preferred as the antagonist in medical treatment. However, veterinary preparations of etorphine are supplied with a preparation (*Revivon*) containing diprenorphine hydrochloride (p. 1550.2) and this should be used for immediate first-aid antagonism if naloxone is not available.

Felbinac *(BAN, USAN, rINN)*

CL-83544; Felbinaakki; Felbinaco; Felbinacum; Felbinak; LJC-10141; Фелбинак.

Biphenyl-4-ylacetic acid.

$C_{14}H_{12}O_2$=212.2

CAS — 5728-52-9.

ATC — M02AA08.

ATC Vet — QM02AA08.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Felbinac). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

Uses and Administration

Felbinac, an active metabolite of fenbufen (below), is an NSAID (p. 102.3). It is used topically in the symptomatic treatment of musculoskeletal pain including that due to soft-tissue injuries. It is applied as a 3% gel or a 3.17% foam to unbroken skin over affected areas 2 to 4 times daily. The total daily dose of gel or foam should not exceed 25 g regardless of the size or number of affected areas. Therapy should be reviewed after 14 days.

Diisopropanolamine felbinac has been used similarly.

References.
1. Hosie GAC. The topical NSAID, felbinac, versus oral ibuprofen: a comparison of efficacy in the treatment of acute lower back injury. *Br J Clin Res* 1993; **4:** 5–17.

Adverse Effects and Precautions

Mild local reactions such as erythema, dermatitis, and pruritus have occurred in patients using felbinac topically. More serious adverse effects including bullous dermatoses such as epidermal necrolysis and erythema multiforme, photosensitivity, anaphylaxis, and bronchospasm or wheeziness have also been reported. Gastrointestinal disturbances may occur.

Felbinac preparations should be avoided in patients with a history of hypersensitivity reactions to aspirin or other NSAIDs.

Incidence of adverse effects. The UK CSM had received 49 reports of adverse reactions associated with felbinac by October 1989, about 11 months after it was released on the UK market.[1] Bronchospasm or wheeziness was reported in 8 patients using felbinac gel. Four of these patients had a history of asthma of whom 3 were reported to have had a similar reaction to aspirin or other NSAIDs. Other reported reactions included rashes (17 cases), local application site reactions (7 cases), and dyspepsia (6 cases).

1. CSM. Felbinac (Traxam) and bronchospasm. *Current Problems 27* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024444&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Flexfree; ***China***: Tong Er Qi (通尔其); ***Gr.***: Dolinac; ***Irl.***: Traxam; ***Ital.***: Dolinac; ***Jpn***: Napageln; Seltouch; ***UK***: Traxam.

Pharmacopoeial Preparations
BP 2014: Felbinac Cutaneous Foam; Felbinac Gel.

Fenbufen *(BAN, USAN, rINN)*

CL-82204; Fenbufeeni; Fenbufén; Fenbufenas; Fenbufène; Fenbufenum; Фенбуфен.

4-(Biphenyl-4-yl)-4-oxobutyric acid.

$C_{16}H_{14}O_3$=254.3

CAS — 36330-85-5.

ATC — M01AE05.

ATC Vet — QM01AE05.

UNII — 9815R1WR9B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Fenbufen). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in acetone, and in dichloromethane.

Uses and Administration

Fenbufen, a propionic acid derivative, is an NSAID (p. 102.3). It is given for the relief of pain and inflammation associated with musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in oral doses of 900 mg daily; the dose may be either 450 mg in the morning and evening or 300 mg in the morning with 600 mg in the evening.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3, although the commonest adverse effects of fenbufen are rashes, usually occurring within the first 2 weeks of therapy, and particularly in women and in patients with seronegative rheumatoid arthritis or psoriatic arthritis. Disorders such as epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome have also been reported. A small number of patients who develop rash may go on to develop a severe illness characterised by pulmonary eosinophilia or allergic alveolitis. Treatment with fenbufen should be stopped immediately if a rash appears.

Breast feeding. UK licensed product information advises that fenbufen should be avoided in breast-feeding mothers, because of the presence of its metabolites in breast milk.

Effects on the blood. Haemolytic anaemia[1] and aplastic anaemia[2] have been reported in patients receiving fenbufen.

1. Martland T, Stone WD. Haemolytic anaemia associated with fenbufen. *BMJ* 1988; **297:** 921.
2. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the lungs. In January 1989 the UK CSM reported that it had received 7 reports of a suspected association between rash and an allergic interstitial lung disorder in patients receiving fenbufen.[1] In 5 patients, the lung disorder was diagnosed as pulmonary eosinophilia; in the 2 other patients the pulmonary component of the reaction was described as allergic alveolitis. Several of these reactions have been reported in the literature.[2,3]

1. CSM. Fenbufen, rash and pulmonary eosinophilia. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
2. Swinburn CR. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.
3. Burton GH. Rash and pulmonary eosinophilia associated with fenbufen. *BMJ* 1990; **300:** 82–3.

Effects on the skin. In September 1988 the UK CSM reported[1] that it was still receiving large numbers of reports of adverse reactions to fenbufen when such reports were expected to have declined. Fenbufen was the most commonly reported suspect drug in 1986 and 1987. At the time of the report more than 6000 such reports had been received, 80% concerning mucocutaneous reactions and most involving a generalised florid erythematous rash, often with pruritus. There were 178 reports of erythema multiforme, 30 of Stevens-Johnson syndrome, and 2 fatalities.

1. CSM. Fenbufen and mucocutaneous reactions. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Hypersensitivity. See under Effects on the Lungs (above).

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Use of fenbufen with aspirin may result in decreased serum concentrations of fenbufen and its metabolites.

Pharmacokinetics

Fenbufen is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations occur in about 70 minutes. Fenbufen is over 99% bound to plasma proteins. It is metabolised in the liver to the active metabolites, biphenylacetic acid and 4-hydroxy-biphenylbutyric acid. Fenbufen and its metabolites are reported to have plasma half-lives of about 10 to 17 hours and are mainly eliminated as conjugates in the urine. Metabolites of fenbufen have been detected in breast milk in small amounts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Cybufen†; ***Irl.***: Lederfen†; ***Port.***: Basifen; ***Thai.***: Cepal; Cinopal; Forbufen; ***Turk.***: Cinopal†; ***UK***: Lederfen†.

Pharmacopoeial Preparations
BP 2014: Fenbufen Capsules; Fenbufen Tablets.

Fenoprofen Calcium *(BANM, USAN, rINNM)*

Calcii Fenoprofenum; Fénoprofène Calcique; Fenoprofeno cálcico; Lilly-53858 (fenoprofen); Lilly-61169 (fenoprofen sodium); Lilly-69323; Кальций Фенопрофен.

Calcium (±)-2-(3-phenoxyphenyl)propionate dihydrate.

$(C_{15}H_{13}O_3)_2Ca,2H_2O$=558.6

CAS — 31879-05-7 (fenoprofen); 34597-40-5 (anhydrous fenoprofen calcium); 53746-45-5 (fenoprofen calcium dihydrate).

ATC — M01AE04.

ATC Vet — QM01AE04.

UNII — 0X2CW1QABJ.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Fenoprofen Calcium). A white or almost white odourless or almost odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol.

USP 36: (Fenoprofen Calcium). A white crystalline powder. Slightly soluble in water, in methyl alcohol, and in n-hexanol; practically insoluble in chloroform. Store in airtight containers.

Uses and Administration

Fenoprofen, a propionic acid derivative, is an NSAID (p. 102.3) used in the management of mild to moderate pain and for the relief of pain and inflammation associated with disorders such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is given as the calcium salt although doses are expressed in terms of the base; fenoprofen calcium (dihydrate) 1.2 g is equivalent to about 1 g of fenoprofen. A usual oral dose is the equivalent of 300 to 600 mg of fenoprofen three or four times daily, adjusted thereafter according to response. In the USA, lower doses of 200 mg every 4 to 6 hours are recommended for mild to moderate pain. It has been recommended that the total daily dose should not exceed 3 g (UK) or 3.2 g (USA).

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Dysuria, cystitis, haematuria, interstitial nephritis, and acute renal insufficiency have been reported with fenoprofen. Nephrotic syndrome, which may be preceded by fever, rash, arthralgia, oliguria, azotaemia, and anuria, has also occurred. Upper respiratory-tract infection and nasopharyngitis have been reported. There have been reports of severe hepatic reactions, including jaundice and fatal hepatitis.

Breast feeding. Fenoprofen is distributed into breast milk although the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. In contrast, licensed product information does not recommend its use since safety has not been established.

Effects on the blood. Haematological adverse effects including agranulocytosis,[1] aplastic anaemia,[2] and thrombocytopenia[3,4] have been reported in patients taking fenoprofen; licensed product information also reports haemolytic anaemia.

1. Simon SD, Kosmin M. Fenoprofen and agranulocytosis. *N Engl J Med* 1978; **299:** 490.
2. Ashraf M, *et al*. Aplastic anaemia associated with fenoprofen. *BMJ* 1982; 284: 1301–2.
3. Simpson RE, *et al*. Acute thrombocytopenia associated with fenoprofen. *N Engl J Med* 1978; **298:** 629–30.
4. Katz ME, Wang P. Fenoprofen-associated thrombocytopenia. *Ann Intern Med* 1980; **92:** 262.

Effects on the liver. Cholestatic jaundice and hepatitis developed in a 68-year-old woman after receiving fenoprofen 600 mg four times daily for 7 weeks. Subsequent use of naproxen and indometacin did not result in hepatotoxicity.[1] However, there has been a report of cross-hepatotoxicity between fenoprofen and naproxen.[2]

1. Stennett DJ, *et al*. Fenoprofen-induced hepatotoxicity. *Am J Hosp Pharm* 1978; **35:** 901.
2. Andrejak M, *et al*. Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the skin. Toxic epidermal necrolysis was associated with fenoprofen in 2 patients.[1]

1. Stotts JS, *et al*. Fenoprofen-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1988; **18:** 755–7.

Overdosage. Coma, respiratory depression, hypotension, and metabolic acidosis occurred in a patient who had ingested between 24 and 36 g of fenoprofen.[1] The patient responded to gastric lavage and activated charcoal and intensive supportive care.

1. Kolodzik JM, *et al*. Nonsteroidal anti-inflammatory drugs and coma: a case report of fenoprofen overdose. *Ann Emerg Med* 1990; **19:** 378–81.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Aspirin is reported to reduce plasma concentrations of fenoprofen.

Antiepileptics. *Phenobarbital* might increase the rate of metabolism of fenoprofen.[1] US licensed product information suggests that dosage adjustment of fenoprofen may be required when given with phenobarbital.

1. Helleberg L, *et al*. A pharmacokinetic interaction in man between phenobarbitone and fenoprofen, a new anti-inflammatory agent. *Br J Clin Pharmacol* 1974; **1:** 371–4.

Pharmacokinetics

Fenoprofen is readily absorbed from the gastrointestinal tract; bioavailability is about 85% but food and milk may reduce the rate and extent of absorption. Peak plasma concentrations occur 1 to 2 hours after a dose. The plasma half-life is about 3 hours. Fenoprofen is 99% bound to plasma proteins. About 90% of a dose is excreted in the urine in 24 hours, chiefly as the glucuronide and the glucuronide of hydroxylated fenoprofen. Fenoprofen is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: FeiLin (飞林); ***Fr.***: Nalgesic; ***Gr.***: Expron; Nazipons; ***UK***: Fenopron; ***USA***: Nalfon.

Pharmacopoeial Preparations
BP 2014: Fenoprofen Tablets;
USP 36: Fenoprofen Calcium Capsules; Fenoprofen Calcium Tablets.

Fentanyl *(BAN, rINN)* ⊗

Fentanil; Fentanilis; Fentanilo; Fentanylum; Fentanyyli; Фентанил.

N-(1-Phenethyl-4-piperidyl) propionanilide.

$C_{22}H_{28}N_2O$=336.5

CAS — 437-38-7.

ATC — N01AH01; N02AB03.

ATC Vet — QN01AH01; QN02AB03.

UNII — UF599785JZ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of fentanyl:

Apache; China girl; China town; China white; Dance fever; Fentanest; Friend; Goodfellas; Great bear; He-man; Jackpot; King ivory; Murder 8; Poison; Tango & Cash; TNT; T.N.T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fentanyl). A white or almost white polymorphic powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Fentanyl). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Fentanyl Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de fentanilo; Fentanil-citrát; Fentanilio citratas; Fentanilo, citrato de; Fentanyl, citrate de; Fentanylcitrat; Fentanyl-citrát; Fentanyli Citras; Fentanylu cytrynian; Fentanyylisitraatti; McN-JR-4263-49; Phentanyl Citrate; R-4263; Фентанила Цитрат.

N-(1-Phenethyl-4-piperidyl)propionanilide dihydrogen citrate.

$C_{22}H_{28}N_2O,C_6H_8O_7$=528.6

CAS — 990-73-8.

UNII — MUN5LYG46H.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Fentanyl Citrate). White or almost white powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Fentanyl Citrate). A white crystalline powder or white glistening crystals. Sparingly soluble in water; slightly soluble in chloroform; soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Fentanyl Hydrochloride *(BANM, rINNM)* ⊗

Fentanyl, Chlorhydrate de; Fentanyli Hydrochloridum; Hidrocloruro de fentanilo; Фентанила Гидрохлорид.

$C_{22}H_{28}N_2O$,HCl=372.9

CAS — 1443-54-5.

UNII — 59H156XY46.

Incompatibility. Fentanyl citrate is incompatible with thiopental sodium and methohexital sodium.

A thick white precipitate formed in the intravenous tubing when fentanyl citrate with droperidol was given shortly after nafcillin sodium. There was no precipitate when fentanyl citrate alone was mixed with nafcillin sodium.[1]

Fentanyl citrate underwent rapid and extensive loss when admixed with fluorouracil in PVC containers.[2] The loss was due to sorption of fentanyl to the PVC as a result of the alkaline pH of the admixture, and presumably could occur from admixture of fentanyl citrate with any sufficiently alkaline drug.

See also Stability, below.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462, 464.
2. Xu QA, *et al.* Rapid loss of fentanyl citrate admixed with fluorouracil in polyvinyl chloride containers. *Ann Pharmacother* 1997; **31:** 297–302.

Stability. In a 48-hour study fentanyl citrate in glucose 5% or sodium chloride 0.9% was stable when stored at room temperature under usual light conditions in glass or PVC containers;[1] the concentration of fentanyl delivered by a patient-controlled system was relatively constant throughout a 30-hour study period. Fentanyl citrate injection diluted to 20 micrograms/mL with sodium chloride 0.9% was stable for 30 days at 3 degrees or 23 degrees in PVC reservoirs for portable infusion pumps.[2] In another study[3] fentanyl citrate diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.

An admixture of fentanyl citrate and bupivacaine in sodium chloride 0.9% appeared[4] compatible and stable when stored for up to 30 days at 3 degrees or 23 degrees in a portable infusion pump. In another study[5] the stability of solutions containing fentanyl, bupivacaine, and adrenaline, alone and in combination was studied over a period of 56 days when stored at various temperatures in the light or in the dark in PVC bags. Both fentanyl and bupivacaine were adsorbed from solution onto the PVC for the first 3 days but thereafter concentrations of these drugs remained relatively stable; freezing appeared to slow the concentration change for bupivacaine but not for fentanyl. Solutions containing adrenaline became more acidic during the study as the adrenaline progressively deteriorated but this was greatly reduced by freezing. Autoclaving produced a further reduction in the concentration of all drugs. There was no sign of precipitation from any of the solutions studied.

An admixture of fentanyl citrate, ketamine hydrochloride, and droperidol in sodium chloride 0.9% was stable[6] for at least 30 days when stored in glass bottles at 25 degrees; the minor decrease in the concentrations of all 3 drugs was attributed to either hydrolytic degradation or adsorption. This admixture also appeared compatible when stored in PVC bags at 4 degrees and 25 degrees; the small increase in drug concentrations over 30 days may be a result of water permeation and evaporation through the bags.

Fentanyl is potentially unstable in PVC containers when mixed with alkaline drugs (see Incompatibility, above).

1. Kowalski SR, Gourlay GK. Stability of fentanyl citrate in glass and plastic containers and in a patient-controlled delivery system. *Am J Hosp Pharm* 1990; **47:** 1584–7.
2. Allen LV, *et al.* Stability of fentanyl citrate in 0.9% sodium chloride solution in portable infusion pumps. *Am J Hosp Pharm* 1990; **47:** 1572–4.
3. Chapalain-Pargade S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; **32:** 90–7.
4. Tu Y-H, *et al.* Stability of fentanyl citrate and bupivacaine hydrochloride in portable pump reservoirs. *Am J Hosp Pharm* 1990; **47:** 2037–40.
5. Dawson PJ, *et al.* Stability of fentanyl, bupivacaine and adrenaline solutions for extradural infusion. *Br J Anaesth* 1992; **68:** 414–17.
6. Lee DKT, *et al.* Compatibility of fentanyl citrate, ketamine hydrochloride, and droperidol in 0.9% sodium chloride injection stored in polyvinyl chloride bags. *Am J Health-Syst Pharm* 2005; **62:** 1190–2.

Uses and Administration

Fentanyl, a phenylpiperidine derivative, is a potent opioid analgesic (p. 108.1) chemically related to pethidine (p. 121.3) and is mainly a μ-opioid agonist.

Fentanyl is used as an analgesic, as an adjunct to general anaesthetics, and as an anaesthetic for induction and maintenance. It is also used as a respiratory depressant in the management of mechanically ventilated patients under intensive care. When used with an antipsychotic such as droperidol it can induce a state of neuroleptanalgesia in which the patient is calm and indifferent to his surroundings and is able to cooperate with the surgeon.

Fentanyl is usually given parenterally, intranasally, or by the transmucosal route as the citrate, or in transdermal patches as the base. The hydrochloride was available as an iontophoretic transdermal delivery preparation but this was withdrawn from the market because of a defective delivery system. Fentanyl citrate 157 micrograms and fentanyl hydrochloride 111 micrograms are each equivalent to about 100 micrograms of fentanyl. Doses are expressed in terms of the base.

It is more lipid soluble than morphine and after an intravenous injection of 100 micrograms the effects of fentanyl begin almost immediately, although maximum analgesia and respiratory depression may not occur for several minutes; the duration of action of fentanyl depends on the dose and the intensity of the pain involved, and may vary from 10 minutes to several hours.

For **premedication** the equivalent of 50 to 100 micrograms of fentanyl may be given *intramuscularly* 30 to 60 minutes before the induction of anaesthesia.

As an **adjunct** to general anaesthesia, fentanyl is usually given by *intravenous* injection. Dosage recommendations show a wide range depending on the technique.

- *Patients with spontaneous respiration* may be given 50 to 200 micrograms as an initial dose with supplements of 50 micrograms. In the USA it is recommended that doses above 2 micrograms/kg be accompanied by assisted ventilation. Significant respiratory depression follows doses of more than 200 micrograms
- *Patients whose ventilation is assisted* may be given 300 micrograms to 3.5 mg (up to 50 micrograms/kg) as an initial dose, with supplements of 100 to 200 micrograms depending on the patient's response. High doses have been reported to moderate or attenuate the response to surgical stress (see Anaesthesia, p. 61.2)

Fentanyl may also be given by intravenous infusion. In ventilated patients a loading dose of about 1 microgram/kg per minute is given for the first 10 minutes followed by an infusion of about 100 nanograms/kg per minute; alternatively, the loading dose may be given as a bolus. The infusion rate should be titrated according to response and rates of up to 3 micrograms/kg per minute have been used in cardiac surgery. Infusions should be stopped about 40 minutes before the end of surgery unless artificial ventilation is to be continued postoperatively. In patients with spontaneous respiration, lower infusion rates of 50 to 80 nanograms/kg per minute are used.

Reduced doses are used in *the elderly* or debilitated patients.

Similar doses to those used for premedication may also be given by *intramuscular* injection **postoperatively**, and by *intramuscular* or *slow intravenous injection* as an adjunct to **regional anaesthesia**.

For the treatment of **intractable chronic pain** in adults when opioid analgesia is indicated *transdermal* patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour are available. In the **UK**, fentanyl patches may be used in strong opioid-naive patients; however, in the USA, use is restricted to patients who are already tolerant to opioid therapy of comparable potency.

- Doses should be individually titrated for each patient according to previous opioid usage. Initial dosages should not exceed 25 micrograms/hour in *opioid-naive* patients; in addition, it is recommended that these patients are initially titrated with low doses of short-acting opioids before transferring to fentanyl patches
- For *patients who have been receiving a strong opioid analgesic* the initial dose of the fentanyl patch should be based on the previous 24-hour opioid requirement. Use of a patch providing 25 micrograms of fentanyl per hour is equivalent to about 60 to 90 mg daily of oral morphine sulfate. During transfer to treatment with fentanyl patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-fentanyl concentrations
- More than one patch may be applied if doses greater than 100 micrograms/hour are required (applied at the same time to avoid confusion); additional or alternative analgesic therapy should be considered if doses greater than 300 micrograms/hour are required. Patches should be replaced every 72 hours; however, replacement after 48 hours is permitted in patients who have a marked decrease in analgesia before the 72-hour period ends. The new patch should be applied to a different site; use of the same area of the skin should be avoided for several days
- *Elderly* or debilitated patients should be observed carefully for signs of toxicity and the dose reduced if necessary

Fentanyl patches are not appropriate for acute or postoperative pain. The bioavailability of different brands of fentanyl transdermal patches may not be equivalent and patients should not switch brands without further advice.

A lozenge-on-a-stick dosage form of fentanyl citrate for *transmucosal* delivery is used as an analgesic in the management of **breakthrough cancer pain** in those already receiving and tolerant to opioid treatment. Lozenges containing the equivalent of 200 micrograms to up to 1.6 mg of fentanyl are available. An initial unit dose of 200 micrograms may be taken over 15 minutes for an episode of breakthrough pain and repeated once if necessary after a further 15 minutes. Doses are subsequently titrated according to response, up to a unit dose of 1.6 mg if necessary. Once the patient has been stabilised on an effective dose, no more than 4 unit doses should be taken daily.

Buccal and sublingual tablets containing fentanyl citrate for transmucosal delivery are also available and licensed for the same indication as the lozenge. Tablets containing the equivalent of 100 to 800 micrograms of fentanyl are available. An initial dose of 100 micrograms may be taken for an episode of breakthrough pain and repeated once if necessary after 30 minutes; thereafter, depending on the brand used, patients must wait at least 2 or 4 hours before treating another episode. A buccal film containing fentanyl citrate for transmucosal delivery is also available; the films contain the equivalent of 200 micrograms to 1.2 mg of fentanyl. An initial dose of 200 micrograms may be taken for an episode of breakthrough pain; thereafter, patients must wait at least 4 hours before treating another episode. Doses are subsequently titrated according to response. The dose of the maintenance opioid used for persistent pain should be re-evaluated if the patient has more than 4 episodes of breakthrough pain daily.

Caution must be exercised when switching between the different transmucosal preparations as the extent of absorption may be substantially different.

Intranasal preparations containing fentanyl citrate, equivalent to 50 to 400 micrograms of fentanyl per spray, are available for the same indication as the transmucosal

preparations. Depending on the brand used, an initial dose of 50 or 100 micrograms is sprayed into one nostril for an episode of breakthrough pain and repeated once if necessary after 10 minutes; thereafter, depending on the brand used, patients must wait at least 2 or 4 hours before treating another episode. Doses are subsequently titrated according to response; up to a maximum of 4 episodes may be treated daily. The dose of the maintenance opioid used for persistent pain should be re-evaluated if the patient has more than 4 episodes of breakthrough pain daily.

For details of doses in *children*, see below.

Administration. *INHALATION ROUTE.* In a study[1] inhaled fentanyl provided plasma concentrations similar to those after intravenous doses; use as patient-controlled analgesia was suggested. Inhaled formulations of fentanyl are under investigation for the treatment of breakthrough cancer pain and acute pain.

1. Mather LE, *et al.* Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. *Br J Clin Pharmacol* 1998; **46:** 37–43.

INTRANASAL ROUTE. Studies[1-3] have shown that intranasal fentanyl is as effective as the intravenous route for post-operative pain management and that it can be used in a patient-controlled analgesia system. Intranasal fentanyl has also been studied[4-6] for the management of acute pain in children.

An intranasal spray formulation of fentanyl is available for the treatment of breakthrough cancer pain.[7-9]

1. Striebel HW, *et al.* Intranasal fentanyl titration for postoperative pain management in an unselected population. *Anaesthesia* 1993; **48:** 753–7.
2. Striebel HW, *et al.* Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. *Anesth Analg* 1996; **83:** 548–51.
3. Toussaint S, *et al.* Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anesth* 2000; **47:** 299–302.
4. Manjushree R, *et al.* Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anesth* 2002; **49:** 190–3.
5. Borland ML, *et al.* Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* 2005; **31:** 831–7.
6. Borland M, *et al.* A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007; **49:** 335–40.
7. Kress HG, *et al.* Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clin Ther* 2009; **31:** 1177–91.
8. Portenoy RK, *et al.* A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. *Pain* 2010; **151:** 617–24.
9. Mystakidou K, *et al.* Fentanyl nasal spray for the treatment of cancer pain. *Expert Opin Pharmacother* 2011; **12:** 1653–9.

INTRASPINAL ROUTE. For a discussion on the intraspinal use of fentanyl, see Postoperative Pain, below.

TRANSDERMAL ROUTE. Transdermal fentanyl is used for chronic intractable cancer pain in adults and children.[1-7] It is also used in the treatment of chronic non-cancer pain;[4,5,8] however, such use is contra-indicated in the management of acute or postoperative pain because the problems of dose titration in the short term increase the possibility of development of significant respiratory depression[4] (see also Effects on the Respiratory System, p. 62.2 and Transdermal Route, under Precautions, p. 63.1).

Although the usual interval for transdermal patches of fentanyl is 72 hours studies have suggested that up to about 25% of cancer patients may require more frequent application with some patients requiring fresh patches every 48 hours.[9,10] Equally, in an attempt to supply lower doses than are allowed for by existing transdermal dosage forms, patches have sometimes been cut, folded, or partially masked with non-porous dressings; the manufacturers do not recommend such practices as they consider the dose supplied will be unreliable, and there is potential for overdosage.

An iontophoretic drug delivery preparation containing fentanyl hydrochloride was also available for the management of acute moderate to severe postoperative pain in a hospital setting (see Postoperative Pain, below for some references) but was withdrawn from the market because of a defective delivery system.

1. Jeal W, Benfield P. Transdermal fentanyl: a review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs* 1997; **53:** 109–38.
2. Muijsers RBR, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* 2001; **61:** 2289–2307.
3. Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol* 2001; **2:** 165–72.
4. Kornick CA, *et al.* Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Safety* 2003; **26:** 951–73.
5. Zernikow B, *et al.* Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *J Pain* 2007; **8:** 187–207.
6. Hoy SM, Keating GM. Fentanyl transdermal matrix patch (Duroteр MT patch; Durogesic DTrans; Durogesic SMAT): in adults with cancer-related pain. *Drugs* 2008; **68:** 1711–21.
7. Hair PI, *et al.* Transdermal matrix fentanyl membrane patch (Matrifen): in severe cancer-related chronic pain. *Drugs* 2008; **68:** 2001–9.
8. Allan L, *et al.* Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001; **322:** 1154–8.
9. Donner B, *et al.* Long-term treatment of cancer pain with transdermal fentanyl. *J Pain Symptom Manage* 1998; **15:** 168–75.
10. Radbruch L, *et al.* Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med* 2001; **15:** 309–21.

TRANSMUCOSAL ROUTE. Transmucosal fentanyl has been tried for sedation and analgesia before anaesthesia or painful procedures in adults[1] and children[2,3] and is used for breakthrough cancer pain in opioid-tolerant patients.[4-7] It has been noted[8] that this dosage method can cause all the adverse effects of parenteral opioids; nausea and vomiting are common and potentially lethal respiratory depression can occur (see also under Precautions, p. 63.1). Dosage guidelines have been suggested.[9]

1. Macaluso AD, *et al.* Oral transmucosal fentanyl citrate for premedication in adults. *Anesth Analg* 1996; **82:** 158–61.
2. Nelson PS, *et al.* Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam, and atropine for premedication in children. *Anesthesiology* 1989; **70:** 616–21.
3. Schechter NL, *et al.* The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics* 1995; **95:** 335–9.
4. Blick SKA, Wagstaff AJ. Fentanyl buccal tablet: in breakthrough pain in opioid-tolerant patients with cancer. *Drugs* 2006; **66:** 2387–93.
5. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 26/06/08).
6. Rauck R, *et al.* Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncol* 2010; **21:** 1308–14.
7. Chwieduk CM, McKeage K. Fentanyl sublingual: in breakthrough pain in opioid-tolerant adults with cancer. *Drugs* 2010; **70:** 2281–8.
8. Anonymous. Oral transmucosal fentanyl citrate. *Med Lett Drugs Ther* 1994; **36:** 24–5.
9. Aronoff GM, *et al.* Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. *Pain Med* 2005; **6:** 305–14.

Administration in children. Indications for fentanyl therapy in children are similar to those in adults (see Uses and Administration, p. 60.2).

Fentanyl is usually given by *intravenous* injection as an **adjunct** to general anaesthesia. In the UK recommended initial doses range from 1 to 3 micrograms/kg in children aged 2 to 12 years with *spontaneous respiration*; supplements of 1 to 1.25 micrograms/kg may be given. (The *BNFC* suggests initial doses of 1 to 3 micrograms/kg for those aged from 1 month to 12 years, with supplements of 1 microgram/kg.) When *ventilation* is *assisted*, the initial recommended dose is also 1 to 3 micrograms/kg, with supplements of 1 to 1.25 micrograms/kg. (The *BNFC* suggests an initial dose of 1 to 5 micrograms/kg for neonates and children up to 12 years of age, with supplements of 1 to 3 micrograms/kg.) In the USA, doses are similar to those licensed in the UK.

The *BNFC* suggests that fentanyl may be given by intravenous infusion to provide **analgesia and respiratory depression** in ventilated children under intensive care. A loading dose of 1 to 5 micrograms/kg is given by intravenous injection, followed by an infusion of 1.5 micrograms/kg per hour in neonates, or 1 to 6 micrograms/kg per hour in those aged 1 month to 18 years, adjusted according to response.

Transdermal patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour may be used for the treatment of **intractable chronic pain** in children aged 2 to 16 years who are already tolerant to opioid therapy of comparable potency. The initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 12 micrograms of fentanyl per hour is equivalent to about 30 to 44 mg daily of oral morphine sulfate. See Uses and Administration, p. 60.2 for further details. Patches should be applied to the upper backs of young children to minimise the potential for removal.

The *transmucosal* lozenge-on-a-stick formulation is licensed for use in adolescents aged 16 years and older for the management of **breakthrough pain** in those already receiving and tolerant to opioid treatment; the usual adult dose may be given (see p. 60.2).

Anaesthesia. Fentanyl and its congeners alfentanil, remifentanil, and sufentanil are shorter-acting than morphine and appear to produce fewer circulatory changes; they are preferred for use as supplements during anaesthesia with inhalational or intravenous drugs. Fentanyl is widely used as the analgesic component of balanced anaesthesia. It has been used to attenuate cardiovascular stress responses to intubation (see Anaesthesia, p. 2028.1), and may be used in higher doses in an attempt to reduce the cardiovascular, endocrine, and metabolic changes that may accompany surgery. When attenuation of surgical stress is especially important, for example in cardiac surgery, intravenous fentanyl 50 to 100 micrograms/kg with oxygen and a neuromuscular blocker, and sometimes up to 150 micrograms/kg, may be used for general anaesthesia. Total intravenous anaesthesia with fentanyl and propofol has been successful.[1]

Satisfactory anaesthesia has been reported[2] with high-dose fentanyl citrate (30 to 50 micrograms/kg) in *premature infants* when used as sole anaesthetic, with pancuronium, for ligation of patent ductus arteriosus; cardiovascular stability was maintained throughout the procedure. However, others[3] found significant hypotension in preterm infants given either fentanyl 20 micrograms/kg, isoflurane, halothane, or ketamine; systolic arterial pressure was best maintained with the ketamine technique. The surgical stress response in preterm babies was abolished by the addition of fentanyl 10 micrograms/kg intravenously to an anaesthetic regimen of nitrous oxide and tubocurarine.[4] Dose responses of fentanyl in *neonatal* anaesthesia have been discussed.[5]

For details of doses in neonates and children, see above.

Neuroleptanalgesia. An injection of short-acting fentanyl 50 micrograms/mL with the longer-acting antipsychotic droperidol 2.5 mg/mL has been used for neuroleptanalgesia, premedication, and as an adjunct to anaesthesia. However, the use of such a fixed-ratio combination cannot be recommended.

1. Jenstrup M, *et al.* Total iv anaesthesia with propofol-alfentanil or propofol-fentanyl. *Br J Anaesth* 1990; **64:** 717–22.
2. Robinson S, Gregory GA. Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. *Anesth Analg* 1981; **60:** 331–4.
3. Friesen RH, Henry DB. Cardiovascular changes in preterm neonates receiving isoflurane, halothane, fentanyl, and ketamine. *Anesthesiology* 1986; **64:** 238–42.
4. Anand KJS, *et al.* Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **i:** 243–8.
5. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology* 1987; **66:** 433–5.

PHAEOCHROMOCYTOMA. Unlike morphine and some other opioids, fentanyl and alfentanil do not release histamine and may be used safely in the anaesthetic management of patients with phaeochromocytoma.[1]

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

POSTOPERATIVE SHIVERING. As pethidine appears to be effective in the treatment of postoperative shivering, other opioids including fentanyl have also been tried. Not all opioids are necessarily effective but fentanyl has been reported to be so,[1] although information is scanty.[2]

1. Alfonsi P, *et al.* Fentanyl, as pethidine, inhibits post anaesthesia shivering. *Br J Anaesth* 1993; **70** (suppl 1): 38.
2. Kranke P, *et al.* Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; **94:** 453–60.

Intensive care. Despite the short duration of action of fentanyl after single doses, rapid redistribution in the body results in an elimination half-life longer than that of morphine. Consequently fentanyl is not a short-acting drug when used for analgesia in intensive care, and may offer little advantage over morphine.[1]

1. Aitkenhead AR. Analgesia and sedation in intensive care. *Br J Anaesth* 1989; **63:** 196–206.

Pain. *CANCER PAIN.* Transdermal fentanyl is used in the management of chronic intractable cancer pain; for references see Administration, Transdermal Route, above. For references to the use of intranasal and transmucosal fentanyl in the management of breakthrough cancer pain, see Administration, Intranasal Route and Transmucosal Route, above.

LABOUR PAIN. Fentanyl has been reported to be an effective intravenous analgesic during active labour. Epidural fentanyl is unreliable when used alone,[1,2] although it does enhance the epidural analgesia achieved with the local anaesthetic bupivacaine. The reduction in the minimum local analgesic concentration of epidural bupivacaine for labour pain increased with increasing dose of fentanyl added to bupivacaine.[3] However, the incidence of pruritus increased significantly with fentanyl in a dose of 4 micrograms/mL and therefore the optimum dose of fentanyl may be 3 micrograms/mL for bupivacaine-sparing epidural analgesia during labour. Respiratory depression has also been reported with the combination.[4]

1. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; **63:** 251–3.
2. Lindow SW, *et al.* A randomised double-blind comparison of epidural fentanyl versus fentanyl and bupivicaine [sic] for pain relief in the second stage of labour. *Br J Obstet Gynaecol* 2004; **111:** 1075–80.
3. Lyons G, *et al.* Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent. *Br J Anaesth* 1997; **78:** 493–7.
4. McClure JH, Jones G. Comparison of bupivacaine and bupivacaine with fentanyl in continuous extradural analgesia during labour. *Br J Anaesth* 1989; **63:** 637–40.

POSTOPERATIVE PAIN. Small intravenous bolus doses of an opioid analgesic may be injected immediately after surgery for postoperative analgesia and faster acting opioids such as fentanyl may be preferable to morphine.[1] Fentanyl has also been given by epidural injection in doses of 100 or 200 micrograms or by continuous epidural infusion in doses of 20 to 80 micrograms/hour; patient-controlled systems have been used.[2]

Epidural fentanyl or sufentanil provided effective postoperative analgesia after caesarean section with comparable adverse effect profiles.[3] The suggested optimal dose of fentanyl was 100 micrograms. For references comparing epidural fentanyl with alfentanil, see Postoperative Analgesia under Uses and Administration of Alfentanil, p. 19.1. In a review[4] of perioperative pain management epidural opioids were considered to provide effective

analgesia at lower doses than systemic opioids. Fentanyl may be given through a lumbar epidural catheter that is often inserted immediately postoperatively. After an initial loading dose of 1 to 1.5 micrograms/kg of fentanyl, infusion at the rate of 0.7 to 2 micrograms/kg per hour is begun and continued for about 48 hours on average. Some prefer to use intermittent injection. A small study[5] comparing 2 patient-controlled routes of administration found that cervical epidural fentanyl provided better postoperative pain relief at rest than intravenous fentanyl; however, there was no decrease in the total dose required and the authors considered that the benefits of epidural fentanyl did not outweigh its potential complications.

Combined opioid and local anaesthetic epidural infusions have also proved effective, for example fentanyl 1 microgram/mL with bupivacaine 0.1%; both could be infused at lower rates than either drug alone. Although a study[6] comparing bupivacaine-fentanyl combinations with each drug alone for epidural analgesia after caesarean section confirmed an additive analgesic effect for the combination, there was no demonstrable clinical benefit compared with fentanyl alone in this patient group who expect early mobilisation. However, the combination may be of greater benefit in patients for whom early ambulation is not routine.

Fentanyl has also been given by epidural injection to children for postoperative analgesia.[7]

Fentanyl has been tried by intrathecal injection for postoperative pain.[8]

As mentioned in Administration, Transdermal Route, p. 61.1, an iontophoretic transdermal system for postoperative pain was also available.[9-11]

1. Mitchell RWD, Smith G. The control of acute postoperative pain. *Br J Anaesth* 1989; **63:** 147–58.
2. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
3. Grass JA, *et al*. A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; **85:** 365–71.
4. Swarm RA, *et al*. Pain treatment in the perioperative period. *Curr Probl Surg* 2001; **38:** 835–920.
5. Roussier M, *et al*. Patient-controlled cervical epidural fentanyl compared with patient-controlled i.v. fentanyl for pain after pharyngolaryngeal surgery. *Br J Anaesth* 2006; **96:** 492–6.
6. Cooper DW, *et al*. Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after caesarean section. *Br J Anaesth* 1996; **76:** 611–15.
7. Lejus C, *et al*. Postoperative extradural analgesia in children: comparison of morphine with fentanyl. *Br J Anaesth* 1994; **72:** 156–9.
8. Sudarshan G, *et al*. Intrathecal fentanyl for post-thoracotomy pain. *Br J Anaesth* 1995; **75:** 19–22.
9. Chelly JE. An iontophoretic, fentanyl HCl patient-controlled transdermal system for acute postoperative pain management. *Expert Opin Pharmacother* 2005; **6:** 1205–14.
10. Koo PJ. Postoperative pain management with a patient-controlled transdermal delivery system for fentanyl. *Am J Health-Syst Pharm* 2005; **62:** 1171–6.
11. Mayes S, Ferrone M. Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. *Ann Pharmacother* 2006; **40:** 2178–86.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Fentanyl and illicitly manufactured analogues are subject to abuse (see under Precautions, below).

Plasma concentrations required to produce satisfactory sedation have been reported to increase steadily in neonates receiving continuous infusions, suggesting the development of *tolerance* to the sedating effects of fentanyl.[1]

Movement disorders, extreme irritability, and symptoms characteristic of *opioid abstinence syndrome* have been reported in children after withdrawal of prolonged fentanyl infusions.[2,3] Similarly, withdrawal symptoms and, in one case, myoclonus have occurred in adults when fentanyl transdermal patches have been stopped.[4,5] Acute opioid withdrawal syndrome has also been seen in cancer patients switched from modified-release oral morphine to transdermal fentanyl despite adequate analgesia being maintained.[6]

1. Arnold JH, *et al*. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991; **119:** 639–43.
2. Lane JC, *et al*. Movement disorder after withdrawal of fentanyl infusion. *J Pediatr* 1991; **119:** 649–51.
3. Dominguez KD, *et al*. Opioid withdrawal in critically ill neonates. *Ann Pharmacother* 2003 **37:** 473–7.
4. Han PKJ, *et al*. Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. *J Pain Symptom Manage* 2002; **23:** 66–72.
5. Ishihara C, *et al*. Withdrawal symptom after discontinuation of transdermal fentanyl at a daily dose of 0.6 mg. *Pharm World Sci* 2005; **27:** 13–15.
6. Anonymous. Opiate withdrawal with transdermal fentanyl. *Pharm J* 1995; **255:** 680.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Respiratory depression, which occurs especially with high doses of fentanyl, responds to naloxone (see also Effects on the Respiratory System, below). Atropine may be used to block the vagal effects of fentanyl such as bradycardia. Unlike morphine, fentanyl is reported not to cause significant histamine release. Transient hypotension may follow intravenous dosage. Muscle rigidity can occur and may require neuromuscular blockers.

Local reactions such as rash, erythema, and itching have been reported with transdermal use. Gum bleeding and irritation, and taste perversion have been reported with transmucosal use. Intranasal use may cause throat irritation, epistaxis, nasal ulcers, and rhinorrhoea.

Effects on the cardiovascular system. For a reference to the effects of fentanyl on histamine release compared with some other opioids, see under Pethidine, p. 122.3.

Effects on mental function. Fentanyl had some dose-related effects on mental function and motor activity in healthy subjects,[1] but immediate and delayed recall were not affected. See also under Alfentanil (p. 19.2).

Acute toxic delirium has been reported after treatment with transdermal fentanyl.[2]

1. Scamman FL, *et al*. Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
2. Kuzma PJ, *et al*. Acute toxic delirium: a uncommon reaction to transdermal fentanyl. *Anesthesiology* 1995; **83:** 869–71.

Effects on the nervous system. There have been reports of seizures with low and high doses of fentanyl or sufentanil.[1] There was, however, no EEG evidence of cortical seizure activity in a patient who had seizure-like muscle movements during a fentanyl infusion;[2] the muscle movements might have been due to myoclonus produced by depression of higher CNS inhibitory centres or to a pronounced form of opioid-induced muscle rigidity.

For a report of encephalopathy associated with prolonged use of fentanyl and midazolam in infants in intensive care, see Encephalopathy under Adverse Effects of Diazepam, p. 1066.2.

1. Zaccara G, *et al*. Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Scott JC, Sarnquist FH. Seizure-like movements during a fentanyl infusion with absence of seizure activity in a simultaneous EEG recording. *Anesthesiology* 1985; **62:** 812–14.

Effects on the respiratory system. Fentanyl, like other opioid agonists, causes dose-related respiratory depression; it is significant with *intravenous* fentanyl doses of more than 200 micrograms and may be more prolonged than analgesia. Anaesthesia with fentanyl may result in either prolonged or delayed respiratory depression postoperatively.[1] Consequently, patients should continue to be monitored postoperatively until spontaneous breathing has been re-established. Severe respiratory depression in a 14-month-old child after intravenous sedation with fentanyl and midazolam has also highlighted the necessity for careful monitoring when giving with other respiratory depressants.[2] If present at the end of operation respiratory depression may be reversed by an opioid antagonist such as naloxone; alternatively, a respiratory stimulant such as doxapram that does not reverse analgesia has been given.

Rigidity of the respiratory muscles (chest wall rigidity) may occur during fentanyl anaesthesia. The effects can be minimised by using a slow intravenous injection but a neuromuscular blocker may be required to allow artificial ventilation; rigidity has been reversed postoperatively by naloxone. Similar muscle rigidity induced by alfentanil could be attenuated by pretreatment with a benzodiazepine whereas small doses of neuromuscular blockers appeared to be ineffective.[3]

Coughing has been associated[4] with intravenous fentanyl; incidence was decreased with a longer injection time,[5] in light cigarette smokers,[5,6] and in older patients.[6] For the use of beclometasone and lidocaine to prevent cough associated with intravenous fentanyl in anaesthesia, see p. 1622.1 and p. 1980.3, respectively.

The risk of respiratory depression associated with *epidural* doses of fentanyl, a highly lipid-soluble opioid, has been considered relatively small and only slight ventilatory depression was noted[7] after a dose of 50 micrograms. However, profound delayed respiratory depression has been reported in 2 women 100 minutes[8] and 80 minutes,[9] respectively after fentanyl 100 micrograms had been given epidurally for caesarean section. No adverse effects on neonatal respiration or neurobehaviour were detected in a study[10] of neonates of mothers given epidural infusions of bupivacaine and fentanyl during labour. However, a later report[11] described 2 neonates who developed respiratory depression after their mothers were given epidural fentanyl during labour; the effect was reversed by intramuscular naloxone 400 micrograms. The authors noted that the doses of fentanyl used were higher than those in the previous study.

Respiratory depression is also a risk with *topically* applied fentanyl preparations. Severe hypoventilation with some fatalities has occurred in patients given fentanyl as a transdermal patch for minor painful conditions.[12] More recently, Health Canada had received 2 reports of fatal respiratory depression associated with the use of transdermal fentanyl patches in adolescents for relatively minor conditions (chronic headache and throat pain);[13] in both cases the respiratory depression developed within 24 hours of applying the first and only patch. See also Administration, Transdermal Route, under Precautions p. 63.1.

1. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; **1:** 41–56.
2. Yaster M, *et al*. Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86:** 463–7.
3. Sanford TJ, *et al*. Pretreatment with sedative-hypnotics, but not with nondepolarizing muscle relaxants, attenuates alfentanil-induced muscle rigidity. *J Clin Anesth* 1994; **6:** 473–80.
4. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg* 2001; **92:** 1442–3.
5. Lin J-A, *et al*. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. *Anesth Analg* 2005; **101:** 670–4.
6. Oshima T, *et al*. Identification of independent risk factors for fentanyl-induced cough. *Can J Anesth* 2006; **53:** 753–8.
7. Morisot P, *et al*. Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine and fentanyl. *Br J Anaesth* 1989; **63:** 97–102.
8. Brockway MS, *et al*. Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; **64:** 243–5.
9. Wang CY. Respiratory depression after extradural fentanyl. *Br J Anaesth* 1992; **69:** 544.
10. Porter J, *et al*. Effect of epidural fentanyl on neonatal respiration. *Anesthesiology* 1998; **89:** 79–85.
11. Kumar M, Paes B. Epidural opioid analgesia and neonatal respiratory depression. *J Perinatol* 2003; **23:** 425–7.
12. *FDC Reports Pink Sheet* 1994; January 24: 12.
13. Health Canada. Transdermal fentanyl (Duragesic): respiratory arrest in adolescents. *Can Adverse React News* 2004; **14** (4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 26/06/08)

Effects on the skin. A patient developed a macular rash covering the whole body, except for the face and scalp, while using transdermal fentanyl patches.[1]

1. Stoukides CA, Stegman M. Diffuse rash associated with transdermal fentanyl. *Clin Pharm* 1992; **11:** 222.

Effects on the urinary tract. Urinary retention developed in 2 premature infants after sedation with fentanyl infusion at a dose of 3 micrograms/kg per hour.[1] In both cases catheterisation relieved symptoms.

1. Das UG, Sasidharan P. Bladder retention of urine as a result of continuous intravenous infusion of fentanyl: 2 case reports. *Pediatrics* 2001; **108:** 1012–1015.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Caution is advised in patients with myasthenia gravis; the effects of muscular rigidity on respiration may be particularly pronounced in these patients.

US licensed product information contra-indicates the use of standard transdermal fentanyl patches in opioid-naive patients because of the risk of fatal respiratory depression (see Effects on the Respiratory System, above and Administration, Transdermal Route, p. 63.1). Similar contra-indications apply to transmucosal formulations of fentanyl (see also Administration, Transmucosal Route, p. 63.1). The use of fentanyl intranasal spray is contra-indicated in opioid-naive patients, and in those with previous facial radiotherapy or recurrent episodes of epistaxis.

Absorption of fentanyl from standard transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take 17 hours or longer for plasma concentrations of fentanyl to decrease by 50% after removal of a transdermal patch; patients who have had adverse effects should be monitored for up to 24 hours and those requiring replacement opioid therapy should initially receive low doses increased gradually thereafter. Similar advice has also been given for patients receiving fentanyl via an iontophoretic drug delivery system; the mean half-life of fentanyl in this system is 11 hours.

The bioavailability of different transmucosal fentanyl preparations is not equivalent and consequently they should not be substituted on a dose-per-dose basis.

Abuse. Several synthetic analogues of fentanyl, so-called 'designer drugs', have been manufactured illicitly for recreational use, particularly in the USA. They are highly potent, and respiratory depression and death may occur very rapidly.[1] The 'fentanyls' have been smoked or snorted as well as injected intravenously.

Fentanyl analogues identified by WHO[2,3] as being subject to street abuse or likely to be abused include: α-methylfentanyl (also known as 'China white' or 'synthetic heroin'), 3-methylfentanyl, acetyl-α-methylfentanyl, α-methylthiofentanyl, *p*-fluorofentanyl, β-hydroxyfentanyl, β-hydroxy-3-methylfentanyl, thiofentanyl, and 3-methylthiofentanyl.

Fentanyl itself is also subject to illicit use. It is chemically unrelated to morphine and does not react in screening tests for morphine-related opioids. It has therefore been recommended[4] that fentanyl should be tested for specifically in cases with suspected opioid misuse.

Used fentanyl transdermal systems may contain significant amounts of fentanyl and have been subject to abuse. In some cases the contents of the patches have been injected intravenously; such abuse has resulted in death.[5,6] Licensed product information advises that used patches should be folded firmly in half, adhesive side inwards to conceal the release membrane, and disposed of safely.

1. Buchanan JF, Brown CR. Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988.
3. WHO. WHO expert committee on drug dependence: twenty-sixth report. *WHO Tech Rep Ser 787* 1989.
4. Berens AIL, *et al.* Illicit fentanyl in Europe. *Lancet* 1996; **347:** 1334–5.
5. Reeves MD, Ginifer CJ. Fatal intravenous misuse of transdermal fentanyl. *Med J Aust* 2002; **177:** 552–3.
6. Tharp AM, *et al.* Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches. *Am J Forensic Med Pathol* 2004; **25:** 178–81.

Administration. *INTRAVENOUS ROUTE.* Fentanyl is much more lipid-soluble than morphine and after standard single intravenous doses has a rapid onset and short duration of action. However, fentanyl is rapidly redistributed in the body and its half-life (see under Pharmacokinetics, below) is longer than that of morphine. Hence, with high or repeated doses, fentanyl becomes a relatively long-acting drug; to avoid accumulation patients should be monitored and doses adjusted accordingly.

Repeated intra-operative doses of fentanyl should be given with care, since not only may the respiratory depression persist into the postoperative period but it may become apparent for the first time postoperatively when the patient is away from immediate nursing attention.

TRANSDERMAL ROUTE. Fatalities have been associated with the use of standard fentanyl transdermal patches (see Effects on the Respiratory System, p. 62.2). Incorrect or inappropriate use resulting in serious adverse effects and fatalities had prompted regulatory authorities to issue warnings and recommendations for changes to product labelling; in particular transdermal fentanyl patches are not appropriate for the treatment of acute or postoperative pain. Nonetheless, reports of fatalities and life-threatening adverse reactions have continued to be received[1-4] and, in December 2007, the FDA[1] reiterated that:

- fentanyl patches are indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients
- licensed product information must be consulted when determining the initial dose as overestimating when converting patients from another opioid analgesic can result in fatal overdose with the first dose
- use with any inhibitors of the cytochrome P450 isoenzyme CYP3A4 may result in an increase in plasma-fentanyl concentrations, which may cause potentially fatal respiratory depression; patients who are taking CYP3A4 inhibitors and using fentanyl patches for an extended period of time should be monitored and the dose of fentanyl adjusted if necessary

1. FDA. Information for healthcare professionals: fentanyl transdermal system (marketed as Duragesic and generics) (issued 21st December, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm084307 (accessed 02/08/10)
2. Health Canada. Fentanyl transdermal patch and fatal adverse reactions. *Can Adverse React News* 2008; **18** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v18n3-eng.pdf (accessed 23/07/08)
3. MHRA/CHM. Fentanyl patches: serious and fatal overdose from dosing errors, accidental exposure, and inappropriate use. *Drug Safety Update* 2008; **2** (2): 2–3. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON025631 (accessed 03/11/09)
4. Health Canada. Fentanyl transdermal patches and accidental child exposure. *Can Adverse React News* 2009; **19** (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v19n3-eng.pdf (accessed 03/11/09)

TRANSMUCOSAL ROUTE. The FDA[1] has received reports of serious adverse effects, including fatalities, in patients who have taken the fentanyl buccal tablets, *Fentora* (*Cephalon, USA*), resulting from inappropriate use in patients who were not opioid tolerant, misunderstanding of dosing instructions, or inappropriate substitution for other fentanyl-containing formulations. The FDA reiterated that *Fentora*:

- should only be used for breakthrough pain in opioid-tolerant cancer patients
- should not be used in those who only need an opioid on an intermittent, or as required, basis and who are not on around-the-clock opioids
- should not be used for the management of acute or postoperative pain including headaches, migraines, and pain due to injury
- should not be directly substituted for other fentanyl-containing formulations

Similar restrictions are also mentioned in the licensed product information for other transmucosal preparations of fentanyl.

1. FDA. Information for healthcare professionals: fentanyl buccal tablets (marketed as Fentora) (issued 26th September, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126082 (accessed 02/08/10)

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect in infants of breast-feeding mothers given fentanyl, and that therefore it may be considered to be usually compatible with breast feeding. However, licensed product information states that, since fentanyl is distributed into breast milk, it should be avoided in nursing mothers because of the possibility of sedation or respiratory depression in breast-fed infants. The *BNF* recommends that breast-fed infants should be monitored for opioid-induced adverse effects.

A study[2] using fentanyl 100 micrograms intravenously for induction of anaesthesia in 5 mothers concluded that the amount of fentanyl excreted into breast milk within 24 hours of induction was less than 0.1% of the maternal dose, and hence unlikely to affect a healthy full-term breast-feeding infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.

Children. The half-life of fentanyl is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required. See also under Pharmacokinetics, p. 64.1.

Exercise. Opioid toxicity requiring naloxone treatment occurred in a patient who wore a fentanyl patch while engaging in vigorous outdoor exercise.[1] Physicians should be aware that along with fever and external heat sources, physical activity may cause increased absorption of transdermal fentanyl.

1. Carter KA. Heat-associated increase in transdermal fentanyl absorption. *Am J Health-Syst Pharm* 2003; **60:** 191–2.

Handling. Avoid contact with skin and the inhalation of fentanyl citrate particles.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fentanyl as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2. Use of fentanyl with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

Fentanyl is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with potent inhibitors of this isoenzyme, such as ritonavir and other HIV-protease inhibitors, may increase fentanyl plasma concentrations.

Antidepressants. For reference to a possible case of serotonin syndrome associated with use of fentanyl and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1.

Antivirals. *Ritonavir*, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, might prolong fentanyl-induced respiratory depression. The plasma clearance of fentanyl was decreased, and the elimination half-life and area under the plasma concentration-time curve increased, when given with ritonavir in a study in healthy subjects.[1]

1. Olkkola KT, *et al.* Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* 1999; **91:** 681–5.

Benzodiazepines. For the effects of opioids such as fentanyl with benzodiazepines, see Analgesics under Interactions of Diazepam, p. 1068.1 and Effects on the Respiratory System, p. 62.2.

Propofol. For reference to the effect that fentanyl has on blood concentrations of propofol, see p. 1915.2.

Pharmacokinetics

After parenteral doses fentanyl citrate has a rapid onset and short duration of action. After transmucosal delivery, up to 50% of the dose is rapidly absorbed from the buccal mucosa; the remainder is swallowed and slowly absorbed from the gastrointestinal tract. Some first-pass metabolism occurs via this route. The absolute bioavailability of transmucosal delivery is about half that for intravenous fentanyl but varies between formulations. The absolute bioavailability of intranasal delivery is about 89% and fentanyl is absorbed very rapidly through the nasal mucosa. Absorption is slow after transdermal application. Fentanyl is metabolised in the liver by *N*-dealkylation and hydroxylation via the cytochrome P450 isoenzyme CYP3A4. Metabolites and some unchanged drug are excreted mainly in the urine. The short duration of action is probably due to rapid redistribution into the tissues rather than metabolism and excretion. The relatively longer elimination half-life reflects slower release from tissue depots. About 80% has been reported to be bound to plasma proteins. Fentanyl appears in the CSF. It crosses the placenta and has been detected in breast milk.

Marked differences in results of pharmacokinetic studies of fentanyl have been attributed[1] to differences in assay methods. The need for sensitive assay methods has been emphasised because the potency of fentanyl means that small doses are used. However, there are differences in pharmacokinetics between bolus doses and prolonged infusion with highly lipophilic drugs such as fentanyl.[2] Terminal half-lives ranging from 2 to 7 hours have been reported in healthy subjects and surgical patients. However, the duration of action of fentanyl after a single intravenous dose of up to 100 micrograms may be only 30 to 60 minutes as a result of rapid redistribution into the tissues. US licensed product information has given values for a three-compartment pharmacokinetic model with a distribution time of 1.7 minutes, a redistribution time of 13 minutes, and a terminal elimination half-life of 219 minutes. Giving repeated or large doses, or continuous infusions, may result in accumulation and a more prolonged action.

The clinical significance of secondary peak plasma-fentanyl concentrations and the possible role of enterosystemic recirculation[3] has been controversial, but some[4] considered that irregular decay curves were not unlikely for lipophilic compounds such as fentanyl, especially in patients undergoing operations and subject to large changes in blood flow. Unexpectedly high plasma-fentanyl concentrations in a patient following epidural use were thought to be a result of aortic clamping and might reflect the effect of changes in blood flow.[5]

The main metabolites of fentanyl, which are excreted in the urine, have been identified as 4-*N*-(*N*-propionylanilino) piperidine and 4-*N*-(*N*-hydroxypropionylanilino) piperidine; 1-(2-phenethyl)-4-*N*-(*N*-hydroxypropionylanilino) piperidine is a minor metabolite.[6] Fentanyl has no active or toxic metabolites.[4]

1. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; **8:** 422–46.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; **31:** 275–92.
3. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; **1:** 41–56.
4. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
5. Bullingham RES, *et al.* Unexpectedly high plasma fentanyl levels after epidural use. *Lancet* 1980; **i:** 1361–2.
6. Goromaru T, *et al.* Identification and quantitative determination of fentanyl metabolites in patients by gas chromatography-mass spectrometry. *Anesthesiology* 1984; **61:** 73–7.

Administration. Some references to the pharmacokinetics of fentanyl after constant rate intravenous infusion,[1] transdermal application,[2-5] use of the oral sublingual[6] and transmucosal[7-11] routes, intranasal dosage,[12,13] subcutaneous infusion,[14] and epidural use.[15-17]

1. Duthie DJR, *et al.* Pharmacokinetics of fentanyl during constant rate iv infusion for the relief of pain after surgery. *Br J Anaesth* 1986; **58:** 950–6.
2. Grond S, *et al.* Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. *Clin Pharmacokinet* 2000; **38:** 59–89.
3. Solassol I, *et al.* Inter- and intraindividual variabilities in pharmacokinetics of fentanyl after repeated 72-hour transdermal applications in cancer pain patients. *Ther Drug Monit* 2005; **27:** 491–8.
4. Marier J-F, *et al.* Pharmacokinetics, tolerability, and performance of a novel matrix transdermal delivery system of fentanyl relative to the commercially available reservoir formulation in healthy subjects. *J Clin Pharmacol* 2006; **46:** 642–53.
5. Marier J-F, *et al.* Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation. *Br J Clin Pharmacol* 2007; **63:** 121–4.
6. Lennernäs B, *et al.* Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol* 2005; **59:** 249–53.
7. Streisand JB, *et al.* Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology* 1991; **75:** 223–9.
8. Darwish M, *et al.* Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clin Pharmacokinet* 2005; **44:** 1279–86.
9. Darwish M, *et al.* Comparison of equivalent doses of fentanyl buccal tablets and arteriovenous differences in fentanyl pharmacokinetics. *Clin Pharmacokinet* 2006; **45:** 843–50.
10. Darwish M, *et al.* Single-dose and steady-state pharmacokinetics of fentanyl buccal tablet in healthy volunteers. *J Clin Pharmacol* 2007; **47:** 56–63.
11. Darwish M, *et al.* Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* 2007; **47:** 343–50.
12. Walter SH, *et al.* Pharmacokinetics of intranasal fentanyl. *Br J Anaesth* 1993; **70** (suppl 1): 108.
13. Foster D, *et al.* Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery. *Ann Pharmacother* 2008; **42:** 1380–7.
14. Miller RS, *et al.* Plasma concentrations of fentanyl with subcutaneous infusion in palliative care patients. *Br J Clin Pharmacol* 1995; **40:** 553–6.
15. Gourlay GK, *et al.* Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. *Pain* 1989; **38:** 253–9.

16. Bader AM, *et al*. Maternal and neonatal fentanyl and bupivacaine concentrations after epidural infusion during labor. *Anesth Analg* 1995; **81:** 829–32.
17. Moises EC, *et al*. Pharmacokinetics and transplacental distribution of fentanyl in epidural anesthesia for normal pregnant women. *Eur J Clin Pharmacol* 2005; **61:** 517–22.

Cardiopulmonary bypass. In general, studies[1,2] indicate that serum concentrations of fentanyl during cardiopulmonary bypass decrease initially and then remain stable. The fall in concentrations has been attributed to haemodilution although adsorption to the bypass apparatus has also been found.

1. Buylaert WA, *et al*. Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1989; **17:** 10–26.
2. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75:** 344–51.

Children. The disposition of intravenous fentanyl 10 to 50 micrograms/kg in 14 neonates undergoing various major surgical procedures was highly variable.[1] The mean elimination half-life of 317 minutes and other pharmacokinetic parameters including volume of distribution and total body clearance were greater than reported in adults, but both pharmacodynamic and pharmacokinetic mechanisms appeared responsible for the very prolonged respiratory depression that can occur in neonates after fentanyl anaesthesia. In 9 premature neonates given fentanyl 30 micrograms/kg intravenously for induction of anaesthesia[2] the elimination half-life ranged from 6 to 32 hours, but cautious interpretation was advised because of the method of calculation.

1. Koehntop DE, *et al*. Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986; **65:** 227–32.
2. Collins C, *et al*. Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. *Anesth Analg* 1985; **64:** 1078–80.

The elderly. In one study the elimination half-life of intravenous fentanyl increased from 265 minutes in patients with a mean age of 36 years to 945 minutes in those with a mean age of 67 years.[1] The authors of another study were critical of the relatively short sampling time used and in contrast found that major fentanyl pharmacokinetic parameters did not correlate with age.[2] However, elderly patients had increased brain sensitivity to intravenous fentanyl, as shown by EEG changes[2] and lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons.

1. Bentley JB, *et al*. Age and fentanyl pharmacokinetics. *Anesth Analg* 1982; **61:** 968–71.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.

Hepatic impairment. The pharmacokinetics of fentanyl were not affected significantly in surgical patients with cirrhosis of the liver.[1] A 1987 review[2] considered that fentanyl had not been associated with clinical problems when given to patients with liver dysfunction.

1. Haberer JP, *et al*. Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. *Br J Anaesth* 1982; **54:** 1267–70.
2. Moore RA, *et al*. Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Renal impairment. Clearance of fentanyl from plasma was reported to be enhanced in surgical patients with end-stage renal disease,[1] although clearance was reduced and elimination half-life increased in patients with renal failure undergoing transplantation,[2] possibly because of the influence of uraemia on metabolism in the liver. Nevertheless, a 1987 review[2] noted that fentanyl had no active or toxic metabolites and had not been associated with clinical problems when given to patients with renal dysfunction.

1. Corall IM, *et al*. Plasma concentrations of fentanyl in normal surgical patients and those with severe renal and hepatic disease. *Br J Anaesth* 1980; **52:** 101P.
2. Moore RA, *et al*. Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Durogesic; Fentax; Gray-F; Nafluvent; Sublimaze; Talnur; ***Austral.***: Actiq; Denpax; Durogesic; Sublimaze; ***Austria***: Actiq; Durogesic; Effentora; Fentamed; Fentaplast; Fentoron; Instanyl; Matrifen; ***Belg.***: Abstral; Durogesic; Instanyl; Matrifen; ***Braz.***: Biofent; Durogesic; Fentabbott; Fentanest; Fentatil; Unifental; ***Canad.***: Abstral; Duragesic; Onsolis†; ***Chile***: Durogesic; ***China***: Durogesic (多瑞吉); ***Cz.***: Adolor; Dolforin; Durogesic; Effentora; Fentagesic†; Fentahexal†; Fentalis; Instanyl; Lunaldin; Matrifen; PecFent; Tocril; Wintanyl†; ***Denm.***: Abstral; Actiq; Breakyl; Dermagesic†; Durogesic; Haldid; Instanyl; Lafene; Matrifen; ***Fin.***: Abstral; Actiq†; Breakyl; Durogesic; Matrifen; ***Fr.***: Abstral; Actiq; Durogesic; Effentora; Instanyl; Matrifen; PecFent; ***Ger.***: Abstral; Actiq; Durogesic; Effentora; Fentadolon; FentaMat†; Instanyl; Matrifen; PecFent; Ribofentanyl†; ***Gr.***: Abstral; Actiq; Demogyl; Dolfen; Durogesic; Fentadur; Instanyl; Matrifen; Meganyl; Myfene; ***Hong Kong***: Durogesic; ***Hung.***: Dolforin; Durogesic; Matrifen; Sedaton; ***India***: Durogesic; Fendrop; Fenilate; Fenstud; Fent; Trofentyl; ***Indon.***: Durogesic; ***Irl.***: Abstral; Actiq; Breakyl; Durogesic; Effentora; Fentadur; Fental; Fetanex; Instanyl; Matrifen; Mytanyl; PecFent; Sublimaze; ***Israel***: Abstral; Actiq; Durogesic†; Fenta; Tanyl; ***Ital.***: Actiq; Durogesic; Fentanest; Fenvel; Matrifen; Quatrofen; ***Jpn***: Durotep; E-fen; OneDuro; ***Malaysia***: Durogesic; Talgesil; ***Mex.***: Durogesic; Fenodid; Fentanest; Filtaten; ***Neth.***: Abstral; Actiq; Breakyl; Durogesic; Effentora; Fenylat; Instanyl; PecFent; ***Norw.***: Abstral; Actiq†; Buquel; Durogesic; Instanyl; Leptanal; Matrifen†; ***NZ***: Durogesic; Sublimaze; ***Philipp.***: Durogesic; Sublimax; Sublimaze; Trofentyl; ***Pol.***: Dolforin; Durogesic; Effentora; Fenta MX; Fentagesic; Fentahexal†; Instanyl; Lunaldin; Matrifen; PecFent; ***Port.***: Actiq; Ardicat; Durogesic; Effentora; Fentanest; Instanyl; Nilfene; PecFent; ***Rus.***: Durogesic (Дюрогезик); Fendivia (Фендивия); ***S.Afr.***: Durogesic; Sublimaze; Tanyl†; ***Singapore***: Durogesic; Fantamax; ***Spain***: Abstral; Actiq; Durogesic; Effentora; Fendivia; Fentanest; Instanyl; Matrifen; PecFent; Quidorfen†; ***Swed.***: Abstral; Actiq; Durogesic; Instanyl; Leptanal; Matrifen; ***Switz.***: Abstral; Actiq; Durogesic; Effentora; Matrifen; Sintenyl; ***Thai.***: Durogesic; ***Turk.***: Actiq; Durogesic; ***UK***: Abstral; Actiq; Breakyl; Durogesic; Effentora; Fentalis; Instanyl; Matrifen; Mezolar; Opiodur; Osmach; Osmanil; PecFent; Sublimaze; Tilofyl; ***Ukr.***: Matrifen (Матрифен)†; ***USA***: Abstral; Actiq; Duragesic; Fentora; Ionsys†; Lazanda; Onsolis†; Sublimaze; Subsys; ***Venez.***: Durogesic.

Multi-ingredient Preparations. ***Arg.***: Disifelit; ***Austral.***: Marcain with Fentanyl; Naropin with Fentanyl; ***Braz.***: Nilperidol; ***Gr.***: Thalamonal; ***NZ***: Bupafen; Marcain with Fentanyl; Naropin with Fentanyl; ***UK***: Bufyl.

Pharmacopoeial Preparations
BP 2014: Bupivacaine and Fentanyl Injection; Fentanyl Injection;
USP 36: Fentanyl Citrate Injection.

Fentiazac *(BAN, USAN, rINN)*

BR-700; Fentiazaco; Fentiazacum; Wy-21894; Фентиазак.
[4-(4-Chlorophenyl)-2-phenylthiazol-5-yl]acetic acid.
$C_{17}H_{12}ClNO_2S$=329.8
CAS — 18046-21-4.
ATC — M01AB10; M02AA14.
ATC Vet — QM01AB10; QM02AA14.
UNII — 0YHF6E6NLS.

Profile

Fentiazac is an NSAID (p. 102.3) that has been used for the relief of pain and inflammation associated with musculoskeletal, joint, peri-articular, and soft-tissue disorders. It has also been used in the treatment of fever. Fentiazac has been given orally; it has also been applied topically and has been given rectally as the calcium salt.

Fenyramidol Hydrochloride *(BANM, rINNM)*

Feniramidol, hidrocloruro de; Feniramidol Hidroklorür; Fényramidol, Chlorhydrate de; Fenyramidoli Hydrochloridum; Hidrocloruro de feniramidol; IN-511; MJ-505; NSC-17777; Phenyramidol Hydrochloride (USAN); Phenyramidol Hydrochloride; Фенирамидола Гидрохлорид.
1-Phenyl-2-(2-pyridylamino)ethanol hydrochloride; α-(2-Pyridylaminomethyl)benzyl alcohol hydrochloride.
$C_{13}H_{14}N_2O$,HCl=250.7
CAS — 553-69-5 (fenyramidol); 326-43-2 (fenyramidol hydrochloride).
ATC — M03BX03.
ATC Vet — QM03BX03.
UNII — M574V6XQH7.

Profile

Fenyramidol hydrochloride has analgesic and skeletal muscle relaxant properties and has been used in the treatment of muscular pain and stiffness.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Cabral; ***Turk.***: Cabral; Capral.

Fepradinol *(rINN)*

Fépradinol; Fepradinolum; Фепрадинол.
(±)-α-{[(2-Hydroxy-1,1-dimethylethyl)amino]methyl}benzyl alcohol.
$C_{12}H_{19}NO_2$=209.3
CAS — 63075-47-8.
UNII — 860MHI4WBA.

Profile

Fepradinol is an NSAID (p. 102.3) that has been used topically in a concentration of 6% for the relief of pain and inflammation. The hydrochloride has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Sinalgia; ***Spain***: Dalgen.

Feprazone *(BAN, rINN)*

DA-2370; Feprazona; Féprazone; Feprazonum; Phenylprenazone; Prenazone; Фепразон.
4-(3-Methylbut-2-enyl)-1,2-diphenylpyrazolidine-3,5-dione.
$C_{20}H_{20}N_2O_2$=320.4
CAS — 30748-29-9 (feprazone); 57148-60-4 (feprazone piperazine salt 1:1).
ATC — M01AX18; M02AA16.
ATC Vet — QM01AX18; QM02AA16.
UNII — 7BVX6J0CGR.

Profile

Feprazone, a phenylbutazone (p. 125.1) derivative, is an NSAID (p. 102.3). It has been given orally in the treatment of mild to moderate pain, fever, and inflammation associated with musculoskeletal and joint disorders. Feprazone has also been given rectally and used topically as a 5% cream.

Pinazone, the piperazine salt of feprazone, has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xitong (希同); ***Ital.***: Zepelin; ***Spain***: Brotazona†; ***Venez.***: Vapesin.

Firocoxib *(USAN, rINN)*

Firocoxibum; ML-1785713; Фирококсиб.
3-(Cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5*H*)-one.
$C_{17}H_{20}O_5S$=336.4
CAS — 189954-96-9.
ATC Vet — QM01AH90.
UNII — Y6V2W4S4WT.

Profile

Firocoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, is an NSAID (p. 102.3) used in veterinary medicine for the treatment of inflammation and pain associated with osteoarthritis in dogs.

Floctafenine *(BAN, USAN, rINN)*

Floctafenina; Floctafénine; Floctafeninum; R-4318; RU-15750; Флоктафенин.
2,3-Dihydroxypropyl *N*-(8-trifluoromethyl-4-quinolyl)anthranilate.
$C_{20}H_{17}F_3N_2O_4$=406.4
CAS — 23779-99-9.
ATC — N02BG04.
ATC Vet — QN02BG04.
UNII — O04HVX6A9Q.

Uses and Administration

Floctafenine, an anthranilic acid derivative, is an NSAID (p. 102.3) used in oral doses of up to 800 mg daily, in divided doses, for the short-term relief of pain.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Anaphylactic shock has been reported, and may be preceded by minor allergic manifestations; floctafenine should be stopped in any patient who develops signs suggestive of allergy (such as pruritus or urticaria). Reactions may also involve the liver.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Floctafenine is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 2 hours after ingestion. Its plasma half-life is about 8 hours. It is

metabolised in the liver to floctafenic acid. It is excreted mainly as glucuronide conjugates in the urine and bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Idarac; ***Thai.***: Idarac.

Flufenamic Acid *(BAN, USAN, rINN)*

Acide Flufénamique; Ácido flufenámico; Acidum Flufenamicum; CI-440; CN-27554; Flufenaamihappo; Flufenámico, ácido; Flufenamsyra; INF-1837; Kwas flufenamowy; NSC-82699; Флуфенамовая Кислота.

N-(αααα-Trifluoro-*m*-tolyl)anthranilic acid.

$C_{14}H_{10}F_3NO_2$=281.2

CAS — 530-78-9 (flufenamic acid); 61891-34-7 (flufenamate aluminium); 16449-54-0 (flufenamate aluminium).

ATC — M01AG03.

ATC Vet — QM01AG03.

UNII — 60GCX7Y6BH.

Uses and Administration

Flufenamic acid, an anthranilic acid derivative related to mefenamic acid (p. 86.1), is an NSAID (p. 102.3). Flufenamic acid is mainly used topically in a concentration of 3 or 3.5% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. Flufenamic acid and its aluminium salt have also been given orally.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving flufenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

An early study[2] found that only very small amounts of flufenamic acid were excreted into breast milk after oral doses.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)
2. Buchanan RA, *et al*. The breast milk excretion of flufenamic acid. *Curr Ther Res* 1969; **11**: 533–8.

Effects on the gastrointestinal tract. Acute proctocolitis has been associated with oral flufenamic acid.[1]

1. Ravi S, *et al*. Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62**: 773–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Mobilat Intens; ***Jpn***: Opyrin.

Multi-ingredient Preparations. ***Austria***: Mobilisin plus; Mobilisin; Rheugesal†; Traumasal; ***Belg.***: Mobilisin; ***Braz.***: Mobilisin Composto; ***Gr.***: Movilisin; ***India***: Movelisin; ***Ital.***: Mobilisin; ***Port.***: Latesil; Mobilisin; Mobilisin; ***Spain***: Movilisin†; ***Switz.***: Assan thermo; Assan; Mobilat Intense; Mobilisin†; Sportusal assan thermo.

Flunixin Meglumine *(BANM, USAN, rINNM)*

Fluniksiinimeglumiini; Flunixin megluminová sůl; Flunixine méglumine; Flunixini Megluminum; Flunixinmeglumin; Flunixino meglumina; Flunixinum Megluminicum; Meglumini Flunixinum; Sch-14714 (flunixin); Меглумина Флуниксин.

2-{[2-Methyl-3-(trifluoromethyl)phenyl]amino}-3-pyridinecarboxylic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1); 2-(α³,α³,α³-Trifluoro-2,3,-xylidino)nicotinic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1).

$C_{14}H_{11}F_3N_2O_2.C_7H_{17}NO_5$=491.5

CAS — 38677-85-9 (flunixin); 42461-84-7 (flunixin meglumine).

UNII — 8Y3JK0JW3U.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Flunixin Meglumine for Veterinary Use; Flunixin Meglumine BP(Vet) 2014). A white to almost white crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 7.0 to 9.0.

USP 36: (Flunixin Meglumine). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ethyl acetate. pH of a 5% solution in water is between 7.0 and 9.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Flunixin meglumine is an NSAID (p. 102.3) used in veterinary medicine for the relief of pain and inflammation in acute and chronic disorders and as adjunctive therapy in the treatment of endotoxic or septic shock and mastitis.

Flupirtine Maleate *(BANM, USAN, rINNM)*

D-9998; Flupirtina, maleato de; Flupirtine, Maléate de; Flupirtini Maleas; Maleato de flupirtina; W-2964M; Флупиртина Малеат.

Ethyl 2-amino-6-(4-fluorobenzylamino)-3-pyridylcarbamate maleate.

$C_{15}H_{17}FN_4O_2.C_4H_4O_4$=420.4

CAS — 56995-20-1 (flupirtine); 75507-68-5 (flupirtine maleate).

ATC — N02BG07.

ATC Vet — QN02BG07.

UNII — 0VCI53PK4A.

Profile

Flupirtine maleate is an analgesic that has been given for the relief of pain (see Choice of Analgesic, p. 4.2) in usual doses of 100 mg three or four times daily orally, or 150 mg three or four times daily as a rectal suppository; daily doses of up to 600 mg orally or 900 mg rectally have been used where necessary. Flupirtine has also been given by intramuscular injection as the gluconate in the management of acute pain. It is also being investigated for the treatment of fibromyalgia.

There has been some interest in the potential of flupirtine to treat prion diseases such as Creutzfeldt-Jakob disease (see below).

References.

1. Friedel HA, Fitton A. Flupirtine: a review of its pharmacological properties, and therapeutic efficacy in pain states. *Drugs* 1993; **45**: 548–69.
2. Klawe C, Maschke M. Flupirtine: pharmacology and clinical applications of a nonopioid analgesic and potentially neuroprotective compound. *Expert Opin Pharmacother* 2009; **10**: 1495–1500.
3. Devulder J. Flupirtine in pain management: pharmacological properties and clinical use. *CNS Drugs* 2010; **24**: 867–81.

Creutzfeldt-Jakob disease. A double-blind placebo-controlled study[1] from 2004 in 28 patients with Creutzfeldt-Jakob disease (CJD) found flupirtine to have beneficial effects on cognitive function.

1. Otto M, *et al*. Efficacy of flupirtine on cognitive function in patients with CJD: a double-blind study. *Neurology* 2004; **62**: 714–18.

Overdosage. A 17-year-old girl who had had symptoms of headache, blurred vision, shivering, drowsiness, disturbed speech, ataxia, and syncope was found to have bright green urine and high concentrations of flupirtine.[1] A strong green discoloration of the urine has also been reported in another patient who abused flupirtine.[2] A further patient who had taken an overdose of flupirtine was drowsy and on neurological examination had cortical hyperexcitability with intermittent myoclonus, tremor of the extremities, nystagmus, and a pronounced cerebellar syndrome.[3] Blood-flupirtine concentrations were 10.9 micrograms/mL nine hours after ingestion, compared with a therapeutic range of 0.5 to 1.5 micrograms/mL. Flupirtine was undetectable at 3 days post-ingestion. No specific treatment was given.

1. Hufschmidt A, *et al*. A girl with headache, confusion and green urine. *J Neurol* 2009; **256**: 1169–70.
2. Maier A, *et al*. Green urine following exposure to flupirtine. *Am J Kidney Dis* 2010; **56**: 1014–15.
3. Hoffmann O, *et al*. Paradoxical cerebral cortical hyperexcitability following flupirtine overdose. *J Toxicol Clin Toxicol* 2004; **42**: 913–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Katadolon; ***China***: Katadolon (科达得龙); ***Ger.***: Flupigil; Katadolon; Trancolong; Trancopal Dolo; ***Israel***: Katadolon; ***Ital.***: Efiret; ***Pol.***: Katadolon; ***Port.***: Metanor; Novocebrin†; ***Rus.***: Katadolon (Катадолон); ***Ukr.***: Katadolon (Катадолон).

Flurbiprofen *(BAN, USAN, rINN)*

BTS-18322; Flurbiprofeeni; Flurbiprofén; Flurbiprofenas; Flurbiprofène; Flurbiprofeno; Flurbiprofenum; U-27182; Флурбипрофен.

2-(2-Fluorobiphenyl-4-yl)propionic acid.

$C_{15}H_{13}FO_2$=244.3

CAS — 5104-49-4.

ATC — M01AE09; M02AA19; R02AX01; S01BC04.

ATC Vet — QM01AE09; QM02AA19; QR02AX01; QS01BC04.

UNII — 5GRO578KLP.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Flurbiprofen). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane; dissolves in aqueous solutions of alkali hydroxides and carbonates.

USP 36: (Flurbiprofen). A white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in ether, and in methyl alcohol; soluble in acetonitrile. Store in airtight containers.

Flurbiprofen Sodium *(BANM, rINNM)*

Flurbiprofène Sodique; Flurbiprofeno sódico; Natrii Flurbiprofenum; Натрий Флурбипрофен.

Sodium (±)-2-(2-fluoro-4-biphenylyl)propionate dihydrate.

$C_{15}H_{12}FNaO_2.2H_2O$=302.3

CAS — 56767-76-1.

ATC — R02AX01.

ATC Vet — QR02AX01.

UNII — Z5B97MU9K4.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Flurbiprofen Sodium). A white to creamy-white, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Uses and Administration

Flurbiprofen, a propionic acid derivative, is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft-tissue disorders such as sprains and strains, for postoperative pain, and in mild to moderate pain including dysmenorrhoea and migraine. Flurbiprofen is also used as lozenges in the symptomatic relief of sore throat. Flurbiprofen sodium is used in eye drops to inhibit intraoperative miosis and to control postoperative inflammation of the anterior segment of the eye.

For **pain and inflammation**, flurbiprofen is given in usual oral doses of 150 to 200 mg daily in divided doses, increased to 300 mg daily in acute or severe conditions if necessary. A modified-release preparation for once-daily use is also available. Patients with dysmenorrhoea may be given an initial dose of 100 mg followed by 50 to 100 mg every four to six hours to a maximum total daily dose of 300 mg. Flurbiprofen has also been given rectally as suppositories in doses similar to those given orally.

For the relief of **sore throat**, a lozenge containing 8.75 mg of flurbiprofen may be sucked or allowed to dissolve slowly in the mouth every 3 to 6 hours to a maximum daily dose of 5 lozenges. It is recommended that treatment should be limited to a maximum of 3 days.

To inhibit intra-operative miosis during **ocular surgery** one drop of flurbiprofen sodium 0.03% is instilled into the eye every 30 minutes beginning 2 hours before surgery and ending not less than 30 minutes before surgery. To control postoperative inflammation the same dosage regimen is used before ocular surgery followed 24 hours after surgery by the instillation of one drop 4 times daily for 1 to 3 weeks. Flurbiprofen sodium eye drops have also been used in the topical treatment of cystoid macular oedema.

Flurbiprofen axetil has been given in some countries by intravenous injection for severe pain.

The *R*-enantiomer, tarenflurbil, has been investigated in the management of Alzheimer's disease but the results of phase III studies have been disappointing.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Minor symptoms of ocular irritation including transient burning and stinging have been reported on instillation of flurbiprofen sodium eye drops; there may be increased bleeding from ocular surgery and wound healing may be delayed. Local irritation has also followed rectal use, and local effects including a sensation of warming or burning in the mouth may be seen after using flurbiprofen lozenges.

Incidence of adverse effects. Reports from the manufacturers on the range and incidence of the adverse effects of flurbiprofen.[1,2]

1. Sheldrake FE, *et al*. A long-term assessment of flurbiprofen. *Curr Med Res Opin* 1977; **5**: 106–16.
2. Brooks CD, *et al*. Clinical safety of flurbiprofen. *J Clin Pharmacol* 1990; **30**: 342–51.

Effects on the CNS. A severe symmetrical parkinsonian syndrome developed in a 52-year-old man who had taken flurbiprofen for 7 days.[1]

1. Enevoldson TP, *et al*. Acute parkinsonism associated with flurbibrofen [sic]. *BMJ* 1990; **300**: 540–1.

Effects on the kidneys. Renal papillary necrosis has been described in a patient who had used flurbiprofen for many years.[1] Acute flank pain and reversible renal dysfunction has been reported in 2 patients treated with flurbiprofen.[2,3] Membranous nephropathy also developed in a patient who took flurbiprofen daily for 12 to 18 months.[4]

1. Nafría EC, *et al.* Renal papillary necrosis induced by flurbiprofen. *DICP Am Pharmacother* 1991; **25:** 870–1.
2. Kaufhold J, *et al.* Flurbiprofen-associated tubulointerstitial nephritis. *Am J Nephrol* 1991; **11:** 144–6.
3. McIntire SC, *et al.* Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; **92:** 459–60.
4. MacKay K. Membranous nephropathy associated with the use of flurbiprofen. *Clin Nephrol* 1997; **47:** 279–80.

Effects on the liver. Cholestatic jaundice probably due to flurbiprofen has been reported.[1]

1. Kotowski KE, Grayson MF. Side effects of non-steroidal anti-inflammatory drugs. *BMJ* 1982; **285:** 377.

Effects on the skin. Cutaneous vasculitis apparently due to flurbiprofen occurred in a 59-year-old woman with long-standing rheumatoid arthritis.[1] Contact dermatitis has also been seen in a 22-year-old woman who applied a poultice containing flurbiprofen to her wrist.[2]

1. Wei N. Flurbiprofen and cutaneous vasculitis. *Ann Intern Med* 1990; **112:** 550–1.
2. Kawada A, *et al.* Contact dermatitis due to flurbiprofen. *Contact Dermatitis* 2000; **42:** 167–8.

Hypersensitivity. A diffuse, pruritic, maculopapular rash developed in a patient 48 hours after taking a second dose of flurbiprofen.[1] Two days later, the rash had become urticarial, and angioedema and hypotension were also noted. Patch testing with flurbiprofen powder was positive.

See also Effects on the Skin, above.

1. Romano A, Pietrantonio F. Delayed hypersensitivity to flurbiprofen. *J Intern Med* 1997; **241:** 81–3.

Precautions

As for NSAIDs in general, p. 107.1.

Breast feeding. Small amounts of flurbiprofen are distributed into breast milk; licensed product information advises to avoid in breast-feeding mothers.

Herpes simplex keratitis. Whether flurbiprofen can exacerbate infection when used to treat ocular herpes simplex is unclear from *animal* studies,[1,2] but licensed product information for flurbiprofen sodium eye drops recommends that they should not be used in patients with active epithelial herpes simplex keratitis. Patients with a history of herpes simplex keratitis should also be monitored closely when undergoing treatment with these eye drops.

1. Trousdale MD, *et al.* Effect of flurbiprofen on herpes simplex keratitis in rabbits. *Invest Ophthalmol Vis Sci* 1980; **19:** 267–70.
2. Hendricks RL, *et al.* The effect of flurbiprofen on herpes simplex virus type 1 stromal keratitis in mice. *Invest Ophthalmol Vis Sci* 1990; **31:** 1503–11.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations and for flurbiprofen sodium eye drops states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Flurbiprofen is readily absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur about 1 to 2 hours after ingestion. Absorption after rectal doses may be more rapid. It is about 99% bound to plasma proteins and has a plasma half-life of about 3 to 6 hours. It is metabolised mainly by hydroxylation (via the cytochrome P450 isoenzyme CYP2C9) and conjugation in the liver and excreted in urine. Flurbiprofen is distributed into breast milk.

Flurbiprofen is a chiral compound given as the racemate and the above pharmacokinetic characteristics refer to the racemic mixture. Allowance may have to be made for the different activities of the enantiomers.

References.

1. Aarons L, *et al.* Plasma and synovial fluid kinetics of flurbiprofen in rheumatoid arthritis. *Br J Clin Pharmacol* 1986; **21:** 155–63.
2. Smith IJ, *et al.* Flurbiprofen in post-partum women: plasma and breast milk disposition. *J Clin Pharmacol* 1989; **29:** 174–84.
3. Kean WF, *et al.* The pharmacokinetics of flurbiprofen in younger and elderly patients with rheumatoid arthritis. *J Clin Pharmacol* 1992; **32:** 41–8.
4. Davies NM. Clinical pharmacokinetics of flurbiprofen and its enantiomers. *Clin Pharmacokinet* 1995; **28:** 100–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clinadol; Flurbic; Luarprofeno; Tolerane; ***Austral.***: Ocufen; Strepfen; ***Austria***: Strepfen†; Strepsils; ***Belg.***: Froben; Strepfen; ***Braz.***: Ocufen; Strepsils; Targus; ***Canad.***: Ansaid; Novo-Flurprofen; Ocufen†; ***Chile***: Ansaid; Distex; Ocufen; ***China***: Kai Fen (凯纷); Ocufen (欧可芬); ***Cz.***: Strepfen; ***Denm.***: Flurofen†; Strefen; ***Fr.***: Cebutid; Ocufen; Strefen; ***Ger.***: Dobendan Direkt; Oculflur; ***Gr.***: Bedice; Bonatol-R; Demoval; Eyeflur; Fievrinol; Fladolef-B; Flodisona; Flurofen; Fluroptic; Inflaflur; Iovic; Kirik; Neliacan; Ocuflur; Pizar; Rograpon; Strepfen; ***Hung.***: Flugalin; Strepfen; ***India***: Arflur; Brufen Gel; Cadiflur; Eyefen; FBN; Fludrop; Flufen; Flur; Flurofen; Froben; Laboflur; Lorphen; Mep-Fovea; Ocuflur; Optifen; Optiflur; Oxiber; ***Irl.***: Froben; Strepsils Intensive; ***Ital.***: Benactiv; Flubifix; Froben; Ocufen; Tantum Activ Gola; Transact Lat; ***Jpn***: Ropion; ***Malaysia***: Acustop Cataplasma; ***Mex.***: Ansaid; Ocufen; ***Mon.***: Antadys; ***Neth.***: Froben†; Strepfen; Strepflam; ***NZ***: Ocufen; Strepfen; ***Pol.***: Flugalin; Strepsils Intensive; ***Port.***: Edolfene; Froben; Strepfen; Transact Lat; ***Rus.***: Raxtan (Ракстан); Strepfen (Стрепфен); ***S.Afr.***: Froben†; Ocufen†; Strepsils Intensive; TransAct; ***Singapore***: Acustop Cataplasma; Froben; Ocufen†; Strepfen; ***Spain***: Froben; Strefen; ***Switz.***: Froben; Strepfen; ***Thai.***: Flurozin†; ***Turk.***: Ansaid; Flurflex; Fortine; Frolix; Majezik; Maxaljin; Maximus; Ocufen; Zero-P; ***UK***: Froben; Ocufen; Strefen; ***Ukr.***: Strepsils Intensiv (Стрепсилс Интенсив); ***USA***: Ansaid†; Ocufen.

Multi-ingredient Preparations. ***India***: Binea; Flubichlor; Flubip; Flurbiren.

Pharmacopoeial Preparations
BP 2014: Flurbiprofen Eye Drops; Flurbiprofen Suppositories; Flurbiprofen Tablets;
USP 36: Flurbiprofen Sodium Ophthalmic Solution; Flurbiprofen Tablets.

Glucametacin *(rINN)*

Glucametacina; Glucamétacine; Glucametacinum; Глюкаметацин.
2-{2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetamido}-2-deoxy-D-glucose.
$C_{25}H_{27}ClN_2O_9$=518.9
CAS — 52443-21-7.
UNII — N1EXE5EHAN.

Profile

Glucametacin, a derivative of indometacin (p. 71.2), is an NSAID (p. 102.3) that has been given orally in musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Teoremin; ***Mex.***: Teoremac.

Multi-ingredient Preparations. ***Chile***: Fibrorelax.

Glycol Salicylate

Ethylene Glycol Monosalicylate; Glycoli Salicylas; Glykolisalisylaatti; Glykolsalicylat; Hidroksietilo salicilatas; Hidroxietilszalicilát; Hydroksietyylisalisylaatti; Hydroxietylsalicylat; Hydroxyaethyli Salicylas; Hydroxyéthyle, salicylate d'; Hydroxyethylis Salicylas; Hydroxyethyl-salicylát; Salicilato de glicol; Гликоль Салицилат.
2-Hydroxyethyl salicylate.
$C_9H_{10}O_4$=182.2
CAS — 87-28-5.
UNII — 3I1VBB7AXH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hydroxyethyl Salicylate). An oily, colourless or almost colourless liquid or colourless crystals. M.p. about 21 degrees. Sparingly soluble in water; freely soluble in alcohol; very soluble in acetone and in dichloromethane. Protect from light.

Profile

Glycol salicylate is a salicylic acid derivative used similarly to methyl salicylate (p. 92.1) in topical rubefacient preparations in usual concentrations of 5 to 15% for the relief of muscular and rheumatic pain. Dipropylene glycol salicylate has been used in similar preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Dolo-Arthrosenex M; Dolo-Arthrosenex N; Etrat Sportgel HES†; Salhumin Gel.

Multi-ingredient Preparations. ***Arg.***: Venostasin; ***Austral.***: Deep Heat; ***Austria***: Ambenat†; Etrat; Mobilisin; Moviflex; Rheumex†; Rubriment; ***Belg.***: Algipan; Emerxil; Mobilisin; Percutalgine; Rado-Salil; Stilene; ***Braz.***: Hematom; Mobilisin Composto; Salonpas; ***Canad.***: Salonpas; ***Chile***: Calorub Sport; Salonpas; ***Cz.***: Arnidol; ***Fr.***: Algipan†; Cortisal; Lumbalgine; Percutalgine; ***Ger.***: Rheuma Bad†; Sportino Akut†; ***Gr.***: Air Salonpas; Bayolin; Export Salonpas; Movilisin; ***Hong Kong***: Air Salonpas†; New Patecs A†; Panadal Pain Relief Patch†; Panadol Pain Relief; Salomethyl†; Salonpas Medicated Plaster†; Salonsip Hot Patch†; Salonsip Plaster†; ***Hung.***: Air Salonpas; Deep Heat Spray; Nicoflex; ***India***: Algipan; Arjet; Movelisin; ***Irl.***: Deep Heat; Ralgex Heat Spray; Ralgex; Ralgex; ***Israel***: Deep Heat Spray; ***Ital.***: Balsamo Sifcamina; Mobilisin; Salonpas; Sloan†; ***Malaysia***: Panaflex; Salonpas; ***Neth.***: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; ***Pol.***: Deep Heat; Lumbolin†; ***Port.***: DM Creme; DM Gel; ***Rus.***: Nicoflex (Никофлекс); ***S.Afr.***: Deep Heat Spray†; Infrarub†; ***Spain***: Movilisin†; ***Switz.***: Assan rem; Assan thermo; Assan; Dolo Demotherm†; Dolo-Arthrosenex; Histalgane mite; Histalgane; Midalgan Nouvelle Formule†; Mobilat Intense; Mobilisin†; Radalgin†; Sportusal assan thermo; Sportusal Spray sine heparino; Sportusal; Venucreme; Venugel; ***UK***: Cremalgin†; Deep Heat Spray; Dubam; Fiery Jack; Pain Relief Balm†; Ralgex Freeze Spray†; Ralgex Heat Spray (low-odour)†; Ralgex†; Salonair†; Salonpas; Transvasin Heat Spray; ***Ukr.***: Deep Heat (Дип Хит).

Gold Keratinate

Aurothiopolypeptide; Queratinato de oro.
CAS — 9078-78-8.

Profile

Gold keratinate is a gold compound with a gold content of about 13%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It has been given by intramuscular injection as the calcium salt for the treatment of rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aurochobet.

Golimumab *(BAN, USAN, rINN)*

CNTO-148; Golimumabum; Голимумаб.
Immunoglobulin G1, anti-(human tumor necrosis factor α) (human monoclonal CNTO 148 γ1-chain), disulfide with human monoclonal CNTO 148 κ-chain, dimer.
CAS — 476181-74-5.
ATC — L04AB06.
ATC Vet — QL04AB06.
UNII — 91X1KLU43E.

Uses and Administration

Golimumab is a human monoclonal antibody to TNF α, a pro-inflammatory mediator, and has actions similar to other TNF inhibitors (see Infliximab, p. 74.2); it is described as a biological disease-modifying antirheumatic drug (DMARD). It is used in the treatment of moderately to severely active rheumatoid arthritis (p. 13.2), active and progressive psoriatic arthritis, and severely active ankylosing spondylitis (see Spondyloarthropathies, p. 14.3). In the UK, golimumab is licensed for use in patients with rheumatoid or psoriatic arthritis who have had an inadequate response to standard DMARDs (including the non-biological DMARD methotrexate for rheumatoid arthritis) and in those with ankylosing spondylitis who have had an inadequate response to conventional therapy; in severe and progressive rheumatoid arthritis it may also be used in patients who have not been treated with methotrexate. Golimumab is also used in the treatment of moderate to severe active ulcerative colitis (see Inflammatory Bowel Disease, p. 1811.3) in patients who show an inadequate response to or fail to tolerate other treatments, or who are corticosteroid dependent.

For the treatment of rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, a dose of 50 mg is given by subcutaneous injection once a month. Alternatively, patients with rheumatoid arthritis may be treated with doses of 2 mg/kg given by intravenous infusion over 30 minutes; after an initial dose, the second dose is given 4 weeks later and maintenance doses are then given once every 8 weeks. Golimumab should be given with methotrexate in patients with rheumatoid arthritis; in those with psoriatic arthritis or ankylosing spondylitis it may be given alone or with other non-biological DMARDs. Regardless of indication, concurrent therapy with corticosteroids, non-biological DMARDs, and/or NSAIDs may be continued. UK licensed product information recommends that continuing therapy should be reconsidered if there is no adequate response within 12 to 14 weeks of starting subcutaneous treatment. Patients weighing more than

100 kg with an inadequate response during this period may benefit from a higher dose of 100 mg once a month; continuing therapy should be reconsidered if there is no adequate response within 12 to 14 weeks of receiving this dose.

In the treatment of ulcerative colitis an induction regimen consists of 200 mg given by subcutaneous injection followed 2 weeks later by a dose of 100 mg. Thereafter, a maintenance dose of 100 mg is given every 4 weeks.

Golimumab is also being studied for the treatment of chronic sarcoidosis and psoriasis.

References.

1. Kay J, *et al*. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; **58:** 964–75.
2. Inman RD, *et al*. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; **58:** 3402–12.
3. Keystone EC, *et al*. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD study. *Ann Rheum Dis* 2009; **68:** 789–96.
4. Kavanaugh A, *et al*. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; **60:** 976–86.
5. Smolen JS, *et al*. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; **374:** 210–21. Correction. *ibid.*; 1422.
6. NICE. Golimumab for the treatment of psoriatic arthritis: Technology Appraisal Guidance 220 (issued April 2011). Available at: http://www.nice.org.uk/nicemedia/live/13441/54169/54169.pdf (accessed 05/08/11)
7. NICE. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs: Technology Appraisal Guidance 225 (issued June 2011). Available at: http://www.nice.org.uk/nicemedia/live/13490/54929/54929.pdf (accessed 05/08/11)

Adverse Effects and Precautions

As for Infliximab, p. 75.3.

Most injection site reactions to golimumab are mild, with erythema being the most frequent manifestation.

Interactions

As for Infliximab, p. 77.3.

Mean steady-state trough concentrations of golimumab are reported to be up to about 52% higher when given with methotrexate but licensed product information for the former states that dosage adjustment for either drug does not appear to be necessary.

Pharmacokinetics

Golimumab shows linear pharmacokinetics. After subcutaneous injection peak concentrations occur in about 2 to 6 days and the absolute bioavailability is estimated to be about 53%. The mean terminal half-life is about 2 weeks.

References.

1. Zhou H, *et al*. Pharmacokinetics and safety of golimumab, a fully human anti-TNF-α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007; **47:** 383–96.
2. Xu Z, *et al*. Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-α human monoclonal antibody, in patients with psoriatic arthritis. *J Clin Pharmacol* 2009; **49:** 1056–70.
3. Xu Z, *et al*. Subcutaneous bioavailability of golimumab at 3 different injection sites in healthy subjects. *J Clin Pharmacol* 2010; **50:** 276–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Simponi; ***Austria***: Simponi; ***Belg.***: Simponi; ***Braz.***: Simponi; ***Canad.***: Simponi; ***Cz.***: Simponi; ***Denm.***: Simponi; ***Ger.***: Simponi; ***Gr.***: Simponi; ***Hong Kong***: Simponi; ***Hung.***: Simponi; ***Irl.***: Simponi; ***Israel***: Simponi; ***Jpn***: Simponi; ***Neth.***: Simponi; ***Norw.***: Simponi; ***NZ***: Simponi; ***Pol.***: Simponi; ***Port.***: Simponi; ***Spain***: Simponi; ***Swed.***: Simponi; ***Switz.***: Simponi; ***UK***: Simponi; ***USA***: Simponi.

Hexyl Nicotinate

Heksyylinikotinaatti; Hexylnicotinatum; Hexylnikotinat; Nicotinato de hexilo; Гексилникотинат.

n-Hexyl nicotinate.

$C_{12}H_{17}NO_2$=207.3

CAS — 23597-82-2.

UNII — BN07PB44IV.

Profile

Hexyl nicotinate is used in usual concentrations of up to 2% in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Transvane; ***Irl.***: Transvasin†; ***UK***: Boots Pain Relief Heat Rub; Transvasin Heat Rub.

Hydrocodone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidrocodona; Hidrocodona, hidrocloruro de; Hydrocodone, Chlorhydrate d'; Hydrocodoni Hydrochloridum; Гидрокодона Гидрохлорид.

$C_{18}H_{21}NO_3$,HCl,2½H_2O=380.9

CAS — 25968-91-6 (anhydrous hydrocodone hydrochloride).

ATC — R05DA03.

ATC Vet — QR05DA03.

UNII — QKZ0920OV3.

Hydrocodone Tartrate *(BANM, rINNM)*

Dihydrocodeinone Acid Tartrate; Hidrocodona, tartrato de; Hydrocodone Acid Tartrate; Hydrocodone Bitartrate (USAN); Hydrocodone, Tartrate d'; Hydrocodoni Bitartras; Hydrocodoni Tartras; Hydrocone Bitartrate; Tartrato de dihidrocodeinona; Tartrato de hidrocodona; Гидрокодона Тартрат.

6-Deoxy-3-*O*-methyl-6-oxomorphine hydrogen tartrate hemipentahydrate; (-)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-one hydrogen tartrate hemipentahydrate.

$C_{18}H_{21}NO_3$,$C_4H_6O_6$,2½H_2O=494.5

CAS — 125-29-1 (hydrocodone); 143-71-5 (anhydrous hydrocodone tartrate); 34195-34-1 (hydrocodone tartrate hemipentahydrate).

ATC — R05DA03.

ATC Vet — QR05DA03.

UNII — NO70W886KK.

NOTE. Compounded preparations of hydrocodone tartrate may be represented by the following names:

- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of hydrocodone tartrate:

Cough Syrup; Vikes.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Hydrocodone Hydrogen Tartrate 2.5-Hydrate). White or almost white, hygroscopic, crystalline powder. Freely soluble or soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 2% solution in water has a pH of 3.2 to 3.8. Store in airtight containers. Protect from light.

USP 36: (Hydrocodone Bitartrate). Fine, white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 2% solution in water is between 3.2 and 3.8. Store in airtight containers. Protect from light.

Profile

Hydrocodone, a phenanthrene derivative, is an opioid analgesic (p. 108.1) related to codeine (p. 40.2) and has similar actions, but is more potent on a weight-for-weight basis. Hydromorphone (below) is one of the metabolites of hydrocodone.

Hydrocodone is used mainly as the tartrate in combination preparations for the relief of irritant cough, though it has no particular advantage over codeine. Hydrocodone tannate has been used similarly. Hydrocodone tartrate is also used for the relief of moderate to moderately severe pain, usually with paracetamol. The usual oral dose of hydrocodone tartrate in such combination preparations is 5 to 10 mg every 4 to 6 hours.

For details of doses in children, see below.

Hydrocodone hydrochloride is given orally and also by injection. The polistirex derivative (a hydrocodone and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Hydrocodone has also been used in the treatment of dyspnoea.

Abuse. The abuse or overuse of preparations containing hydrocodone and paracetamol has been associated with *sensorineural hearing loss*.[1,2] Cochlear implants improved the hearing loss in some of the patients.

Intranasal abuse of preparations of hydrocodone and paracetamol has also been reported.[3,4]

1. Friedman RA, *et al*. Profound hearing loss associated with hydrocodone/acetaminophen abuse. *Am J Otol* 2000; **21:** 188–91.
2. Ho T, *et al*. Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; **10:** 467–72.
3. Jewers WM, *et al*. Palatal perforation associated with intranasal prescription narcotic abuse. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99:** 594–7.
4. Sloan PA, Klimkina O. Intranasal abuse of prescription hydrocodone/acetaminophen results in oronasal fistula: a case report. *J Opioid Manag* 2009; **5:** 383–5.

Administration in children. Hydrocodone tartrate may be given as part of a combination preparation for the relief of irritant cough in children aged from 6 to 12 years in usual oral doses of 2.5 mg every 4 to 6 hours. Older children may be given the usual adult dose (see above).

Pharmacokinetics. References.

1. Hutchinson MR, *et al*. CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol* 2004; **57:** 287–97.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Hycodan; ***Ger.***: Dicodid†; ***Switz.***: Hydrocodeinon†; ***USA***: Zohydro.

Multi-ingredient Preparations. ***Arg.***: Hidronovag Complex; ***Canad.***: Dalmacol; Dimetane Expectorant DC; Hycomine†; Novahistex DH; Novahistine DH; ratio-Calmydone; ratio-Coristex-DH; Tussionex; Vasofrinic DH; ***China***: Norco (耐而可); ***USA***: Alor†; Anaplex HD†; Anexsia; Atuss G†; Atuss HC†; Atuss HD†; Atuss HS†; Atuss HX†; Ceta Plus†; Co-Gesic; Co-Tuss V; Codal-DH†; Codiclear DH†; Codimal DH†; Cophene XP; Cordron-HC†; Cytuss HC†; Cytuss-HC NR†; Damason-P; De-Chlor HC†; De-Chlor MR†; De-Chlor NX†; Deconamine CX†; Dolacet; Donatussin DC; Drocon-CS; Duocet; Duratuss HD†; Dytan-HC; ED Tuss HC†; ED-TLC†; Endagen-HD; Endal-HD Plus†; Endal-HD; Entex HC†; Entuss Expectorant; Entuss Expectorant; Entuss-D Jr; Entuss-D; Entuss-D; Histex HC†; Histinex D†; Histinex HC; Histinex PV†; Histussin HC; Hy-KXP†; Hy-Phen†; Hycet; HycoClear Tuss; Hycodan†; Hycomine Compound; Hycotuss†; Hydex PD†; Hydro DP†; Hydro-GP; Hydro-Tussin HG†; Hydrocet†; Hydrocodone CP; Hydrocodone GF; Hydrocodone HD; Hydrogesic; Hydromet; Hydron CP†; Hydron EX†; Hydron KGS†; Hydron PSC†; Hydropane; Hyphed†; HyTan†; Ibudone; Iodal; Iotussin HC; J-Tan D HC†; Kwelcof†; Levall 5.0; Liquicet; Lorcet 10/650; Lorcet Plus; Lorcet-HD†; Lortab ASA†; Lortab; Lortuss HC†; Marcof†; Margesic H; Maxi-Tuss HCG†; Maxi-Tuss HCX†; Maxidone; Nalex DH; Nalex Expectorant; Narcof; Nariz HC; Neo HC; Norco; Notuss PD; Notuss-Forte; Novasus; Oncet; P-V-Tussin†; Pancof XP†; Pancof-HC†; Pancof-XL†; Para-Hist HD; Pneumotussin†; Poly-Tussin†; Pro-Red†; Relacon-HC†; Relasin-HCX; Reprexain; Rezira; S-T Forte 2; SRC Expectorant; Stagesic; Su-Tuss HD†; T-Gesic; Tusana-D†; Tusdec-HC†; Tusnel-HC†; Tussafed-HCG; Tussafin Expectorant; Tussanil DH; Tussend; TussiCaps; Tussigon; Tussionex Pennkinetic; Tusso-DF; Tusso-HC†; Tussplex; Tyrodone; Unituss HC; Vanex Expectorant; Vanex-HD; Vanex-HD; Vazotuss HC†; Vicodin Tuss; Vicodin; Vicoprofen; Vitussin†; Vituz; Xodol; Z-Cof HC; Zamicet; Zolvit; Zutripro; Zydone; Zymine HC†.

Pharmacopoeial Preparations

USP 36: Hydrocodone Bitartrate and Acetaminophen Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets; Hydrocodone Bitartrate Tablets.

Hydromorphone Hydrochloride

(BANM, rINNM) ⊗

Dihydromorphinone Hydrochloride; Hidrocloruro de dihidromorfinona; Hidrocloruro de hidromorfona; Hidromorfona, hidrocloruro de; Hidromorfono hidroclioridas; Hydromorfon-hydrochlorid; Hydromorfonhydroklorid; Hydromorfonihydrokloridi; Hydromorphone, Chlorhydrate d'; Hydromorphonhydrochlorid; Hydromorphoni Hydrochloridum; Гидроморфона Гидрохлорид.

6-Deoxy-7,8-dihydro-6-oxomorphine hydrochloride; (-)-(5*R*)-4,5-Epoxy-3-hydroxy-9a-methylmorphinan-6-one hydrochloride.

$C_{17}H_{19}NO_3$,HCl=321.8

CAS — 466-99-9 (hydromorphone); 71-68-1 (hydromorphone hydrochloride).

ATC — N02AA03.

ATC Vet — QN02AA03.

UNII — L960UP2KRW.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of hydromorphone:

Dillies; HillBilly Heroin; Hospital heroin.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Hydromorphone Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Hydromorphone Hydrochloride). A fine white, or practically white, odourless, crystalline powder. Soluble 1 in 3 of water; sparingly soluble in alcohol; practically insoluble in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with hydromorphone hydrochloride in 5% glucose injection.[1] Mixtures of hydromorphone hydrochloride and dexamethasone sodium phosphate showed concentration-dependent incompatibility.[2] White cloudiness, haziness, or precipitation developed 4 hours after mixing thiopental sodium and hydromorphone hydrochloride.[3]

Stability of mixtures of fluorouracil and hydromorphone hydrochloride in 0.9% sodium chloride or 5% glucose depended on the concentration of fluorouracil present.[4] Hydromorphone hydrochloride 500 micrograms/mL with fluorouracil 1 mg/mL was stable for at least 7 days at 32 degrees and for at least 35 days at 23 degrees, 4 degrees, or -20 degrees. When the concentration of fluorouracil was increased to 16 mg/mL, hydromorphone was noted to decompose incurring unacceptable losses after 3 days at 32 degrees or after 7 days at 23 degrees, but was stable for at least 35 days at 4 degrees or -20 degrees.

1. Nieves-Cordero AL, *et al*. Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
2. Walker SE, *et al*. Compatibility of dexamethasone sodium phosphate with hydromorphone hydrochloride or diphenhydramine hydrochloride. *Am J Hosp Pharm* 1991; **48:** 2161–6.
3. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
4. Xu QA, *et al*. Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.

Uses and Administration

Hydromorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p. 108.1). It is related to morphine (p. 93.2) but with a greater analgesic potency. Hydromorphone hydrochloride is used for the relief of moderate to severe pain; it has been used for the relief of non-productive cough.

In the treatment of pain, hydromorphone hydrochloride is a useful alternative to morphine for subcutaneous use since its greater solubility in water allows a smaller dose volume. After injection onset of action usually occurs within 15 minutes and analgesia is reported to last for more than 5 hours; after oral doses onset of analgesia is usually within 30 minutes. It is given by subcutaneous or intramuscular injection in initial doses of 1 to 2 mg every 4 to 6 hours as necessary. It may also be given by slow intravenous injection or by intravenous or subcutaneous infusion, with doses adjusted according to individual requirements. Higher parenteral doses may be given to opioid-tolerant patients using a highly concentrated solution containing 10 mg/mL that allows smaller dose volumes. In the UK, the initial oral dose is 1.3 mg every 4 hours; thereafter the dose may be increased as necessary. In the USA, initial oral doses of 2 mg may be given every 4 to 6 hours; doses may be increased to 4 mg or more for severe pain. Modified-release preparations are available for less frequent administration, but see Alcohol, under Interactions, below. By rectum, the usual dose is 3 mg every 6 to 8 hours.

References.

1. Bruera E, *et al*. A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. *J Clin Oncol* 1996; **14:** 1713–17.
2. Miller MG, *et al*. Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage* 1999; **18:** 9–16.
3. Quigley C. Hydromorphone for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 26/06/08).
4. Murray A, Hagen NA. Hydromorphone. *J Pain Symptom Manage* 2005; **29** (suppl): S57–S66.
5. Grosset AB, *et al*. Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage* 2005; **29:** 584–94.
6. Du Pen S, *et al*. Intrathecal hydromorphone for intractable nonmalignant pain: a retrospective study. *Pain Med* 2006; **7:** 10–15.
7. Chang AK, *et al*. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med* 2006; **48:** 164–72.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

UK licensed product information contra-indicates the use of hydromorphone hydrochloride in patients with hepatic impairment; however, product information in the USA permits its cautious use although doses may need to be reduced. It should also be used with caution and given in reduced doses to those with renal impairment.

Effects on the nervous system. Myoclonus has been reported[1] in a 55-year-old man given relatively low doses of intravenous hydromorphone with a total daily dose of 4 mg on day 1 and 6 mg on day 2; symptoms resolved when the drug was stopped on day 3. A chart review[2] for neuroexcitatory symptoms in 48 patients with terminal illnesses on hydromorphone found 13 cases of agitation, 9 of myoclonus, and 4 of seizures; maximal dose and treatment duration were noted to increase the risk of neurotoxicity.

1. Patel S, *et al*. A myoclonic reaction with low-dose hydromorphone. *Ann Pharmacother* 2006; **40:** 2068–70.
2. Thwaites D, *et al*. Hydromorphone neuroexcitation. *J Palliat Med* 2004; **7:** 545–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydromorphone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Alcohol. The FDA received data from pharmacokinetic studies in healthy subjects which showed that significantly higher peak plasma concentrations of hydromorphone were achieved, as a result of dose-dumping, when alcohol was ingested with once-daily hydromorphone modified-release capsules (*Palladone; Purdue Frederick, USA*); these increases were considered potentially lethal, even in opioid-tolerant patients.[1] Subsequently, this formulation was voluntarily withdrawn by the US manufacturer in July 2005.

1. FDA. Information for healthcare professionals: hydromorphone hydrochloride extended-release capsules (marketed as Palladone) (issued July 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288 (accessed 02/08/10)

Pharmacokinetics

Hydromorphone hydrochloride is rapidly but incompletely absorbed from the gastrointestinal tract after oral doses; peak plasma concentrations occur within 0.5 to 1 hour. Oral bioavailability is about 50% as it undergoes extensive first-pass metabolism. Hydromorphone is about 8 to 19% bound to plasma proteins. A plasma elimination half-life of about 2.5 hours has been reported after oral or intravenous doses. Hydromorphone appears to be widely distributed in the tissues; it crosses the placenta and is distributed into breast milk. It is extensively metabolised by glucuronidation in the liver and excreted in the urine mainly as conjugated hydromorphone, dihydroisomorphine, and dihydromorphine.

References.

1. Vallner JJ, *et al*. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *J Clin Pharmacol* 1981; **21:** 152–6.
2. Parab PV, *et al*. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos* 1988; **9:** 187–99.
3. Vashi V, *et al*. Clinical pharmacology and pharmacokinetics of once-daily hydromorphone hydrochloride extended-release capsules. *J Clin Pharmacol* 2005; **45:** 547–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dolonovag; ***Austral.***: Dilaudid; Jurnista; ***Austria***: Hydal; Jurnista; ***Belg.***: Palladone; ***Braz.***: Jurnista; ***Canad.***: Dilaudid; Hydromorph; Jurnista; ***Cz.***: Jurnista; Palladone; ***Denm.***: Jurnista; Palladon; ***Fin.***: Palladon; ***Fr.***: Sophidone; ***Ger.***: Jurnista; Palladon; ***Gr.***: Palladone; ***Hung.***: Jurnista; Palladone; ***Irl.***: Palladone; ***Israel***: Jurnista†; Palladone; ***Ital.***: Jurnista; ***Mex.***: Liberaxim; ***Neth.***: Palladon; ***Norw.***: Palladon; ***Philipp.***: Jurnista; ***Port.***: Jurnista; Palladone†; ***Singapore***: Jurnista; ***Spain***: Jurnista; Palladone; ***Swed.***: Palladon; ***Switz.***: Jurnista; Palladon; ***Turk.***: Jurnista; ***UK***: Palladone; ***USA***: Dilaudid; Exalgo.

Multi-ingredient Preparations. ***Swed.***: Palladon Comp†; ***USA***: Dilaudid Cough†.

Pharmacopoeial Preparations

USP 36: Hydromorphone Hydrochloride Injection; Hydromorphone Hydrochloride Oral Solution; Hydromorphone Hydrochloride Tablets.

Ibuprofen *(BAN, USAN, rINN)*

Ibuprofeeni; Ibuprofén; Ibuprofenas; Ibuprofène; Ibuprofeno; Ibuprofenum; RD-13621; U-18573; Ибупрофен.

2-(4-Isobutylphenyl)propionic acid.

$C_{13}H_{18}O_2$=206.3

CAS — 15687-27-1.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

UNII — WK2XYI10QM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ibuprofen). A white or almost white, crystalline powder or colourless crystals. M.p. 75 degrees to 78 degrees. Practically insoluble in water; freely soluble in acetone, in dichloromethane, and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides and carbonates.

USP 36: (Ibuprofen). A white to off-white crystalline powder having a slight characteristic odour. Practically insoluble in water; very soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ethyl acetate. Store in airtight containers.

Ibuprofen Lysine *(USAN)*

Ibuprofen Lysinate; Soluphene; Ибупрофен Лизин.

Lysine 2-(4-isobutylphenyl)propionate.

$C_{19}H_{32}N_2O_4$=352.5

CAS — 57469-77-9.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

UNII — N01ORX9D6S.

Stability. Solutions of ibuprofen lysine in Water for Injections stored at room temperature were found to be most stable when protected from light.[1]

1. Volonté MG, *et al*. Stability of ibuprofen in injection solutions. *Am J Health-Syst Pharm* 2005; **62:** 630–3.

Uses and Administration

Ibuprofen, a propionic acid derivative, is an NSAID (p. 102.3). Its anti-inflammatory properties may be weaker than those of some other NSAIDs.

Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, periarticular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

Ibuprofen is also used as an alternative to indometacin in the treatment of patent ductus arteriosus.

The usual **oral** dose for painful conditions is 1.2 to 1.8 g daily in divided doses although maintenance doses of 600 mg to 1.2 g daily may be effective in some patients. If necessary the dose may be increased; in the UK the maximum recommended dose is 2.4 g daily whereas in the USA it is 3.2 g daily. Modified-release preparations of ibuprofen are available for once- or twice-daily dosing, although actual dosages vary with different preparations. Patients with rheumatoid arthritis generally require higher doses of ibuprofen than those with osteoarthritis. The recommended dose for fever reduction is 200 to 400 mg every 4 to 6 hours to a maximum of 1.2 g daily. For oral doses in children, see Administration in Children, below.

Ibuprofen may be given **parenterally** by intravenous infusion for the management of mild to moderate pain and as an adjunct to opioid analgesics for moderate to severe pain, and for reduction of fever. For painful conditions, 400 to 800 mg may be given every 6 hours as necessary. For fever reduction, an initial dose of 400 mg may be followed by 400 mg every 4 to 6 hours or 100 to 200 mg every 4 hours as necessary. Regardless of indication, infusion time must be no less than 30 minutes and a dose of 3.2 g daily should not be exceeded. Ibuprofen is also given parenterally for the treatment of patent ductus arteriosus in preterm infants; for details of doses, see p. 69.1.

Ibuprofen is applied **topically** as a 5% cream, foam, gel, or spray solution; a 10% gel is also available. It is also used topically as a dressing containing 500 micrograms/cm^2 of ibuprofen for the management of ulcers and superficial wounds.

Ibuprofen is usually given as the base but **derivatives**, including various salts, esters, and other complexes, have also been used. These include lysine (see Patent Ductus Arteriosus, p. 69.1), potassium, and sodium salts, guaiacol and pyridoxine esters, and mabuprofen (ibuprofen aminoethanol), isobutanolammonium, and meglumine derivatives.

Ibuprofen is usually given as a racemic mixture but preparations containing only the *S*-(+)-isomer dexibuprofen (p. 43.1) are available in some countries.

Administration in children. In the UK, the following oral doses of ibuprofen, given according to age, are recommended by the *BNFC* for the treatment of **pain, inflammation of soft-tissue injuries,** or **fever** in children:

- 1 to 3 months: 5 mg/kg 3 or 4 times daily
- 3 to 6 months: 50 mg 3 times daily

- 6 to 12 months: 50 mg 3 or 4 times daily
- 1 to 4 years: 100 mg 3 times daily
- 4 to 7 years: 150 mg 3 times daily
- 7 to 10 years: 200 mg 3 times daily
- 10 to 12 years: 300 mg 3 times daily
- 12 to 18 years: initially 300 to 400 mg 3 or 4 times daily increased, if necessary, to a maximum of 2.4 g daily; maintenance doses of 200 to 400 mg 3 times daily may be adequate
- for more *severe* symptoms in children aged between 3 months and 12 years, a dose of 30 mg/kg (maximum 2.4 g) daily in 3 or 4 divided doses may be given

In the USA, suggested doses for children aged 6 months and over are: for fever, 5 to 10 mg/kg (depending on the severity of the fever) and for pain, 10 mg/kg; doses may be given every 6 to 8 hours up to a maximum daily dose of 40 mg/kg.

In the treatment of **rheumatic disease** including juvenile idiopathic arthritis, the *BNFC* recommends a dose of 10 mg/kg 3 or 4 times daily (maximum 2.4 g daily) in children aged 3 months and over; if necessary up to 60 mg/kg daily in 4 to 6 divided doses (maximum 2.4 g daily) may be given in systemic juvenile idiopathic arthritis. A usual daily dose in the USA for juvenile idiopathic arthritis is 30 to 40 mg/kg in divided doses.

Similar dosage regimens are also suggested by UK licensed product information for all the above indications; however, ibuprofen use is not generally recommended in children weighing less than 5 kg or under 3 months of age.

For **post-immunisation pyrexia**, a dose of 50 mg has been recommended; a second dose may be given after 6 hours. If the pyrexia persists after the second dose, medical advice should be sought. Infants aged 2 to 3 months may also be given a 50-mg dose of ibuprofen for post-immunisation pyrexia on the advice of a doctor.

Ibuprofen or its lysine salt are also used in the treatment of **patent ductus arteriosus** in preterm infants; dosage details for this indication are given below.

Cachexia. For reference to the use of ibuprofen with megestrol to treat cancer cachexia, see p. 2289.3.

Cystic fibrosis. In patients with cystic fibrosis (see p. 179.2), the inflammatory response to chronic pulmonary infection with *Pseudomonas* organisms contributes to lung destruction. NSAIDs have been studied in patients with cystic fibrosis as an alternative to corticosteroids to reduce pulmonary inflammation. Some reviews[1,2] found evidence in support of using high-dose NSAIDs, most notably ibuprofen, to slow the progression of lung damage in patients with cystic fibrosis. However, there are limited data about the long-term safety of high doses[1] and some consider that this may have limited such use of NSAIDs;[3] others remain to be convinced that a benefit has been shown.[4] Furthermore there were sufficient data to recommend that NSAIDs be temporarily stopped when intravenous aminoglycosides or other nephrotoxic drugs are used.[1]

1. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 07/11/07).
2. Konstan MW. Ibuprofen therapy for cystic fibrosis lung disease: revisited. *Curr Opin Pulm Med* 2008; **14:** 567–73.
3. Fennel PB, *et al*. Use of high-dose ibuprofen in a pediatric cystic fibrosis center. *J Cyst Fibros* 2007; **6:** 153–8.
4. Bush A, Davies J. Non! to non-steroidal anti-inflammatory therapy for inflammatory lung disease in cystic fibrosis (at least at the moment). *J Pediatr* 2007; **151:** 228–30.

Pain. Findings from a long-term study[1] in 585 patients (mean age of 64 years) with knee pain suggested that oral and topical ibuprofen had an equivalent analgesic effect although the former was associated with more minor adverse effects; there was no difference in the rate of major adverse effects.

Single dose, oral ibuprofen is an effective analgesic for the treatment of postoperative pain.[2]

1. Underwood M, *et al*. Topical or oral ibuprofen for chronic knee pain in older people: the TOIB study. *Health Technol Assess* 2008; **12:** 1–176.
2. Derry C, *et al*. Single dose oral ibuprofen for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 15/09/09).

Patent ductus arteriosus. Ibuprofen or its lysine salt may be given **parenterally** for the treatment of patent ductus arteriosus (p. 72.2) in preterm infants of less than 34 weeks' gestation; doses are expressed in terms of ibuprofen. Three intravenous doses (infused over 15 minutes) are given at 24-hour intervals; the initial dose is equivalent to 10 mg/kg of ibuprofen followed by two further doses of 5 mg/kg. If, 48 hours after this course of therapy the ductus remains open, a second course may be given, but if this produces no response surgery may be necessary. Ibuprofen injection, *when given as the base*, should be used undiluted, but if necessary it may be reconstituted with sodium chloride 0.9% or glucose 5% for injection. *When given as the lysine salt*, it should be diluted with sodium chloride 0.9% or glucose 5%.

For a suggestion that ibuprofen might be a better choice than indometacin for the treatment of patent ductus arteriosus, see p. 72.2.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3. Ibuprofen may be better tolerated than other NSAIDs.

Adverse effects that may be associated with the use of ibuprofen injection in premature **neonates** include intraventricular haemorrhage, periventricular leucomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, necrotising enterocolitis, intestinal perforation, oliguria, fluid retention, and haematuria; hypoxaemia and gastrointestinal haemorrhage have also been reported. In addition ibuprofen injection should not be given to neonates with life-threatening infection, with significant renal impairment, or with known or suspected necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should also not be given parenteral ibuprofen, and those given it should be monitored during treatment for signs of bleeding. Renal function should be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

Symptoms of nausea, vomiting, epigastric pain, and tinnitus have been reported after ibuprofen overdosage. More serious toxicity is uncommon, but giving activated charcoal followed by supportive measures is recommended if the quantity ingested within the previous hour exceeds 400 mg/kg.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ibuprofen, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount of ibuprofen distributed into breast milk to be too small to be harmful to a breast-fed infant. A study[2] estimated that a breast-fed infant would ingest about 0.0008% of the maternal dose. However, licensed product information for some preparations, including some topical preparations, recommends that breast feeding should be avoided during ibuprofen treatment.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)
2. Walter K, Dilger C. Ibuprofen in human milk. *Br J Clin Pharmacol* 1997; **44:** 211–12.

Children. An analysis[1] of the outcome of treatment of 83 915 children found that the risk of hospitalisation for gastrointestinal bleeding, renal failure, or anaphylaxis was no greater in children given ibuprofen than in those given paracetamol.

1. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. *JAMA* 1995; **273:** 929–33.

Effects on the blood. Blood disorders including agranulocytosis, aplastic anaemia,[1] pure white-cell aplasia,[2] and thrombocytopenia[3] have been reported in patients taking ibuprofen. Fatal haemolytic anaemia occurred in a man taking ibuprofen and oxazepam.[4]

1. Gryfe CI, Rubenzahl S. Agranulocytosis and aplastic anemia possibly due to ibuprofen. *Can Med Assoc J* 1976; **114:** 877.
2. Mamus SW, *et al*. Ibuprofen-associated pure white-cell aplasia. *N Engl J Med* 1986; **314:** 624–5.
3. Jain S. Ibuprofen-induced thrombocytopenia. *Br J Clin Pract* 1994; **48:** 51.
4. Guidry JB, *et al*. Fatal autoimmune hemolytic anemia associated with ibuprofen. *JAMA* 1979; **242:** 68–9.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including ibuprofen, see p. 105.1.

Effects on the CNS. Aseptic meningitis has occurred in patients taking NSAIDs. A review[1] of NSAID-related CNS adverse effects summarised 23 literature reports of NSAID-associated aseptic meningitis; 17 reports involved ibuprofen, 4 sulindac, 1 naproxen, and 1 tolmetin. Of the 23 reports, 11 were in patients with a diagnosis of SLE. Typically the reaction is seen in patients who have just restarted NSAID therapy after a gap in their treatment. Within a few hours of restarting the NSAID the patient develops fever, headache, and a stiff neck; abdominal pain may be present. The patient may become lethargic and eventually comatose. Symptoms resolve if the NSAID is stopped. It is believed to be a hypersensitivity reaction but there does not appear to be cross-reactivity between NSAIDs.

Similar conclusions have also been reported more recently.[2] After experience of 2 cases, a review of the literature identified 71 episodes of ibuprofen-induced aseptic meningitis in 36 patients; 22 patients had recurrent episodes after repeated ibuprofen use. An underlying autoimmune connective tissue disorder was noted in 22 patients of whom 14 had SLE, 6 had an undifferentiated or mixed disorder, 1 had rheumatoid arthritis, and 1 had Sjögren's syndrome. In most cases, symptoms developed within 24 hours of starting ibuprofen although 1 patient had been taking ibuprofen for 2 years before the onset of symptoms. Cross-reactivity was reported in only 1 patient who had also developed aseptic meningitis with both naproxen and rofecoxib.

1. Hoppmann RA, *et al*. Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151:** 1309–13.
2. Rodríguez SC, *et al*. Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature. *Medicine* 2006; **85:** 214–20.

Effects on electrolytes. Hyponatraemia has been described in patients taking ibuprofen;[1-3] other risk factors such as pre-existing renal impairment or use with desmopressin were generally present.

1. Blum M, Aviram A. Ibuprofen induced hyponatraemia. *Rheumatol Rehabil* 1980; **19:** 258–9.
2. Rault RM. Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs. *Am J Med Sci* 1993; **305:** 318–20.
3. García EBG, *et al*. Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease. *Haemophilia* 2003; **9:** 232–4.

Effects on the eyes. Reversible amblyopia has been reported in patients taking ibuprofen.[1,2] For reference to effects on the optic nerve associated with ibuprofen, see p. 105.3.

1. Collum LMT, Bowen DI. Ocular side-effects of ibuprofen. *Br J Ophthalmol* 1971; **55:** 472–7.
2. Palmer CAL. Toxic amblyopia from ibuprofen. *BMJ* 1972; **3:** 765.

Effects on the gastrointestinal tract. Ibuprofen may be associated with a lower risk of upper gastrointestinal effects than some other NSAIDs, but nonetheless it can cause dyspepsia, nausea and vomiting, gastrointestinal bleeding, and peptic ulcers and perforation. Colitis and its exacerbation have occurred.[1,2]

1. Ravi S, *et al*. Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.
2. Clements D, *et al*. Colitis associated with ibuprofen. *BMJ* 1990; **301:** 987.

Effects on the kidneys. Reports of adverse renal effects with ibuprofen include an increase in serum creatinine concentration,[1] acute renal failure,[2-6] and nephrotic syndrome.[7] Cystitis, haematuria, and interstitial nephritis may occur. Acute flank pain and reversible renal dysfunction has been reported in some patients treated with ibuprofen.[8,9] See also Effects on Electrolytes, above.

1. Whelton A, *et al*. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison. *Ann Intern Med* 1990; **112:** 568–76.
2. Brandstetter RD, Mar DD. Reversible oliguric renal failure associated with ibuprofen treatment. *BMJ* 1978; **2:** 1194–5.
3. Kimberly RP, *et al*. Apparent acute renal failure associated with therapeutic aspirin and ibuprofen administration. *Arthritis Rheum* 1979; **22:** 281–5.
4. Spierto RJ, *et al*. Acute renal failure associated with the use of over-the-counter ibuprofen. *Ann Pharmacother* 1992; **26:** 714.
5. Fernando AHN, *et al*. Renal failure after topical use of NSAIDs. *BMJ* 1994; **308:** 533.
6. Moghal NE, *et al*. Ibuprofen and acute renal failure in a toddler. *Arch Dis Child* 2004; **89:** 276–7.
7. Justiniani FR. Over-the-counter ibuprofen and nephrotic syndrome. *Ann Intern Med* 1986; **105:** 303.
8. McIntire SC, *et al*. Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; **92:** 459–60.
9. Wattad A, *et al*. A unique complication of nonsteroidal anti-inflammatory drug use. *Pediatrics* 1994; **93:** 693.

Effects on the liver. Raised liver transaminase values were noted in 3 patients with chronic hepatitis C infection after taking ibuprofen.[1] Values returned to normal on stopping the drug; the effect recurred in one patient who was re-exposed. Other hepatic adverse effects reported with ibuprofen include hepatitis[2] and liver failure.[3]

See also Effects on the Skin, below.

1. Riley TR, Smith JP. Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: a case series. *Am J Gastroenterol* 1998; **93:** 1563–5.
2. Borel I, *et al*. Hépatite aiguë sévère après prise d'ibuprofène. *Gastroenterol Clin Biol* 2001; **25:** 430–2.
3. Rodríguez-González FJ, *et al*. Orthotopic liver transplantation after subacute liver failure induced by therapeutic doses of ibuprofen. *Am J Gastroenterol* 2002; **97:** 2476–7.

Effects on the skin. Rashes may occur during hypersensitivity reactions although serious dermatological effects attributed to ibuprofen are rare. Reports of more serious effects have included Stevens-Johnson syndrome (often associated with hepatotoxicity),[1-4] photosensitivity,[5] and bullous leucocytoclastic vasculitis.[6]

1. Sternlieb P, Robinson RM. Stevens-Johnson syndrome plus toxic hepatitis due to ibuprofen. *N Y State J Med* 1978; **78:** 1239–43.
2. Srivastava M, *et al*. Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. *Gastroenterology* 1998; **115:** 743–6.

3. Taghian M, *et al*. Acute vanishing bile duct syndrome after ibuprofen therapy in a child. *J Pediatr* 2004; **145:** 273–6.
4. Health Canada. Ibuprofen: Stevens-Johnson syndrome. *Can Adverse React News* 2005; **15** (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3-eng.pdf (accessed 29/08/08)
5. Bergner T, Przybilla B. Photosensitization caused by ibuprofen. *J Am Acad Dermatol* 1992; **26:** 114–16.
6. Davidson KA, *et al*. Ibuprofen-induced bullous leukocytoclastic vasculitis. *Cutis* 2001; **67:** 303–7.

Hypersensitivity. A fatal asthma attack occurred in a 65-year-old woman, with adult-onset asthma, 30 minutes after ingestion of ibuprofen 800 mg.[1]

For other hypersensitivity reactions or possible reactions see also Effects on the CNS (p. 69.2) and Effects on the Skin, p. 69.3.

1. Ayres JG, *et al*. Asthma death due to ibuprofen. *Lancet* 1987; **i:** 1082.

Meningitis. For reports of aseptic meningitis after use of ibuprofen, see Effects on the CNS, p. 69.2.

Overdosage. There was a substantial increase in the number of cases of ibuprofen overdose reported to the National Poisons Information Service of the UK in the 2 years after its introduction as an 'over-the-counter' medication.[1] However, no concurrent increase in severity of poisoning was found and in only 1 of 203 cases was ibuprofen thought to have caused serious problems. It was concluded that ibuprofen appeared to be much less toxic in acute overdose than either aspirin or paracetamol. Current advice is that doses below 100 mg/kg are unlikely to cause toxicity in *children*, whereas clinical features will occur in children who have ingested more than 400 mg/kg. In *adults* the dose-response effect is less clear cut, but those who have ingested less than 100 mg/kg are unlikely to require treatment.

Nonetheless, reports illustrate the complexity of major overdosage with ibuprofen. A syndrome of coma, hyperkalaemia with cardiac arrhythmias, metabolic acidosis, pyrexia, and respiratory and renal failure was reported[2] in a 17-year-old man after major overdosage with ibuprofen and minor overdosage with doxepin. Hyperkalaemia was not evident until 14 hours after hospital admission and was thought to be due to a combination of potassium replacement for initial hypokalaemia, acidosis, muscle damage, and ibuprofen-induced renal failure. A 6-year-old child developed[3] shock, coma, and metabolic acidosis after ingestion of a dose of ibuprofen equivalent to 300 mg/kg. Treatment consisting of intubation, mechanical ventilation, fluid resuscitation, gastric lavage, and activated charcoal proved successful. In another report,[4] in which a 21-month-old child had ingested the equivalent of 500 mg/kg of ibuprofen, the presenting symptoms were acute renal failure with severe metabolic acidosis. The child developed tonic-clonic seizures 46 hours after ingestion, with significant hypocalcaemia and hypomagnesaemia, which may have been exacerbated by use of sodium polystyrene sulfonate and furosemide. The seizures, which could not be controlled with diazepam, phenytoin, and phenobarbital, ceased on correction of electrolyte balance.

1. Perry SJ, *et al*. Ibuprofen overdose: the first two years of over–the–counter sales. *Hum Toxicol* 1987; **6:** 173–8.
2. Menzies DG, *et al*. Fulminant hyperkalaemia and multiple complications following ibuprofen overdose. *Med Toxicol Adverse Drug Exp* 1989; **4:** 468–71.
3. Zuckerman GB, Uy CC. Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. *Ann Pharmacother* 1995; **29:** 869–71.
4. Al-Harbi NN, *et al*. Hypocalcemia and hypomagnesemia after ibuprofen overdose. *Ann Pharmacother* 1997; **31:** 432–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibuprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Antineoplastics. For the effect of ibuprofen on the metabolism of *pemetrexed*, see p. 845.3.

Aspirin. It has been suggested that ibuprofen may reduce the cardioprotective effect of aspirin but see NSAIDS, under Interactions of Aspirin, p. 27.1.

Lipid regulating drugs. For a report of rhabdomyolysis and renal failure attributed to an interaction between ibuprofen and *ciprofibrate*, see p. 1325.2.

Muscle relaxants. *Baclofen* toxicity may develop after starting ibuprofen; for further details, see p. 2017.1.

Pharmacokinetics

Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is also absorbed on rectal use. It is partially absorbed after topical application to the skin; some licensed product information state that percutaneous absorption from topical gel is about 5% of that from an oral dose form. Ibuprofen is 90 to 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in the urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. There appears to be little, if any, distribution into breast milk.

The above figures refer to racemic ibuprofen. However, ibuprofen's disposition is stereoselective and there is some metabolic conversion of the inactive *R*-(-)-enantiomer to the active *S*-(+)-enantiomer, dexibuprofen (p. 43.1).

References.

1. Davies NM. Clinical pharmacokinetics of ibuprofen: the first 30 years. *Clin Pharmacokinet* 1998; **34:** 101–54.
2. Sharma PK, *et al*. Pharmacokinetics of oral ibuprofen in premature infants. *J Clin Pharmacol* 2003; **43:** 968–73.
3. Gregoire N, *et al*. Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. *J Clin Pharmacol* 2004; **44:** 1114–24.
4. Han EE, *et al*. Pharmacokinetics of ibuprofen in children with cystic fibrosis. *Clin Pharmacokinet* 2004; **43:** 145–56.
5. Hao H, *et al*. Enantioselective pharmacokinetics of ibuprofen and involved mechanisms. *Drug Metab Rev* 2005; **37:** 215–34.
6. Kyllonen M, *et al*. Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. *Paediatr Anaesth* 2005; **15:** 566–73.
7. Kokki H, *et al*. Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. Abstract: *Pediatrics* 2007; **120:** 882. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/4/e1002 (accessed 15/09/09)
8. Gregoire N, *et al*. Population pharmacokinetic analysis of ibuprofen enantiomers in preterm newborn infants. *J Clin Pharmacol* 2008; **48:** 1460–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actron; Acuilfem; Afebril; Atomo Desinflamante Ibu; Butidiona; Causalon Ibu; Copiron; Dolorsyn; Druisel; Fabogesic; Febratic; Fontol; Ibu Evanol; Ibu-Novalgina; Ibu; Ibubenitol; Ibucalmin; Ibucler; Ibufabra; Ibufix; Ibufull; Ibulam; Ibulgia; Ibumar; Ibumultin; Ibup; Ibupirac; Ibupiretas; Ibuprofenix; Ibuprofex; Ibusi; Ibusol; Ibusumal†; Ibutenk; Ibuxfar; Ibuxim; Ibuzidine; Matrix; Novo Geniol; Oxibut; Pakurat; Ponstil Mujer; Ponstin; Ponstinetas; Salivia; Sindol; Teprix; Tonal; Vefren; ***Austral.***: ACT-3†; Actiprofen†; Advil; Brufen; Dimetapp Pain & Fever Relief; Nurofen Migraine; Nurofen Zavance; Nurofen; Proven; Rafen; Tri-Profen†; ***Austria***: Adolorin Ibuforte; Aktren; Brufen; Dismenol Neu; Dolgit; Dolofort; Duafen†; Duanibu; Ibumetin; Ibutop; Kratalgin; Momento†; Nureflex; Nurofen; Pedea; ratioDolor; ***Belg.***: Adulfen Lysine†; Advil Mono†; Brufen; Buprophar; Dolofin; Epsilon; Extrapan; Ibumed; Ibutop; Malafene; Nurofen; Optalidon Nieuwe Formule; Pedea; Perdofemina; Perdophen; Perviam†; Spidifen; ***Braz.***: Actiprofen; Advil; Algi-Reumatril; Algiflex; Alivium; Artril; Buprovil; Buscofem; Dalsy; Doraliv; Dorigren; Febsen; Ibuflex; Ibufran; Ibupril; Ibuprofan; Ibuvix; Lombalgina; Maxifen; Motrin; Novalfem; Parartrin; Spidufen; Uniprofen; Vantil; ***Canad.***: Advil; Caldolor; Europrofen; Infants Motrin; Motrin; Novo-Profen; Pamprin Ibuprofen; ***Chile***: Actron; Bediatil; Deucodol; Dolorub; Esanterm; Fortapal†; Ibu; Ibucon; Ibupirac; Ipson; Kin; Motrin; Niofen; Pediaprofen; Pironal; Pyriped; ***China***: Advil (雅维); An Rui Ke (安瑞克); Bang Qi (邦奇); Bei De Fen (倍得芬); Bei Fen (倍芬); Childrens Motrin (美林); Di Er Nuo (迪尔诺); Efficover (芬克); EtIbufen (布洛芬缓释); Fen Su (芬苏); Fenbid (芬必得); Fennikang (芬尼康); Fu Er Da (抚尔达); Fu Er Shuan (福尔栓); Huanshifen (缓士芬); Jie Le (捷乐); Jihao (吉浩); Jiubaofen (久保芬); Qin Fu (琴福); Qing Fen (清芬); Sai Ke (赛可); Spedifen (司百得); Tai Bao (泰宝); Tian Qian (恬倩); Tuen (托恩); Xin Di Fen (欣荻芬); Xin Wei (欣卫); Yi Fen Ning (怡芬宁); Zefen (泽芬); ***Cz.***: Advil; Baroc†; Brufen; Dolgit; Ibalgin; Ibuberl; Ibudolor; Ibumax; Iburion; Nurofen Advance†; Nurofen Stopgrip; Nurofen; Pabiprofen†; Panafen; Pedea; Solpaflex†; Tomaflex†; Urgo†; ***Denm.***: Brufen; Burana; Fenasol; Ibumax; Ibumetin; Ibumil; Ibustar; Ibutop; Ipren; Nurofen; Pedea; Xpri; ***Fin.***: Burana; Ibumax; Ibumetin; Ibusal; Ibutabs; Ibuxin; MIG; ***Fr.***: Advil; Advilcaps; AdvilEff; Adviltab; Anadvil†; Antarene Codeine; Antarene; Biatain-Ibu; Brufen; Dolgit; Doltaque†; Ergix Douleur et Fievre; Expanfen†; Gelufene; Hemagene Tailleur; Ibutop; Intralgis; Nureflex; Nurofen; Nurofenfem; Nurofenflash; Nurofenpro; Nurofentabs; Pedea; Solufen†; Spedifen; Spifen; Tiburon; Upfen; ***Ger.***: Advel†; Aktren; Analgin Akut; Anco†; Biatain-Ibu; Dismenol N; Dolgit; Dolo Sanol†; Dolo-Puren†; Dolobene Ibu; Dolodoc†; Dolormin; Esprenit; Eudorlin Extra; Eudorlin Migrane; Gyno-Neuralgin; Ib-u-ron; ibu-Attritin†; Ibu-Lysin; Ibu-ratiopharm; Ibu; Ibubeta; Ibudolor; Ibuflam†; Ibuhexal†; Ibutad†; Ibutop†; Imbun; Kontagripp†; Mensoton; Migranin Ibuprofen†; Neuralgin extra; Nurofen; Optalidon Ibu†; Opturem†; Pedea; Pfeil; Schmerz-Dolgit†; Spidifen; Tabalon†; Tispol Ibu-DD; Trauma-Dolgit; Tussamag Fieber- und Schmerztabletten†; Urem; ***Gr.***: Advil; Algofren; Brufen; Buscofem; Chrobifen; Drin; Fenbid; Focus; Forbiphen; Ibodezil; Ibugel†; Ibuspel; Londodact; Nurofen; Pedea; Pinafor; Rozovin; ***Hong Kong***: Bifen; Brufen; Brumed; Cortal Ibuprofen†; Ibufac; Ibupen†; Infacalm; Maprofen†; Neutropain; Nurofen; Perofen; Profen; Rafen†; Schufen; Spedifen; Synprofen†; Zofen; ***Hung.***: Advil; Algoflex; Dolgit; Ibumax; Ibutop; Melfen; Nurofen; Solpaflex†; Spedifen; ***India***: Alfam; Bren; Brufen; Cipgesic; Ibrumac; Ibu; Ibubid; Ibucon; Ibuf; Ibugesic; Ibugin; Ibupal; Ibuspan; Ibusynth; Inflapen; Mybu; Myofen; Norswel; Nuren; ***Indon.***: Anafen; Arfen; Arthrifen; Bufect; Dofen; Dolofen-F; Ethifen; Farsifen; Febryn†; Fenatic; Fenris; Iprox; Lexaprofen; Mofen; Nofena†; Ostarin; Prifen†; Profen; Proris; Prosic; Prosinal; Rhelafen; Ribunal; Shelrofen†; Spedifen; Yariven; ***Irl.***: Actiprofen; Advil; Brufen; Bufigen†; Buplex; Easofen; Fenopine; Ibugel; Ibuleve†; Melfen; Nurofen Advance; Nurofen; Pedea; Phorpain; Proflex†; Provin; ***Israel***: Adex; Advil; Artofen; Iboo; Ibufen; Ibuleve; Nurofen; Tiptipot Ibutaf; ***Ital.***: Algofen; Antalfebal; Antalfort; Antalgil; Antalisin; Arfen; Brufen; Buscofen; Calmine; Cibalgina Dol; Cibalgina Due Fast; Cibalginafor; Dolofast; Edenil; Gineflor; Ginenorm; Ibupas; Kendo; Moment; Momentact; Nureflex†; Nurofast†; Nurofen; Nuroflash; Nurosolv; Pedea; Sinifev; Spidifen; Stibupatch; Subitene; Vicks Febbre e Dolore; Visquo; ***Malaysia***: Bifen; Brufen; Ibufac; Nurofen; Perofen†; Spedifen; ***Mex.***: ABKI; Actron; Adivon†; Advil; Aflusil; Ainex†; Aldofen; Algidol; Bestafen; Carone; Citalgan; Dadicil; Days; Dibufen†; Dipofen; Diprodol; Dolprin; Dolprofen†; Dolval; Dolver; Eufenil; Febratic†; Fidoin-Q; Flexafen; Gelidol; Gobrosan; Ibuflam; Ibuflex; Ifentil; Inpained; Maxifen; Medifen; Motrin; Nafendol; Pro-XB; Proartinal†; Probuxil; Quadrax; Realdrax; Ribufen†; Tabalon; Zoafalet-H; ***Neth.***: Advil; Brufen; Burana; Femapirin†; Ibosure†; Nurofen; Pedea; Roco†; Sarixell; Spidifen; Zafen; ***Norw.***: Brufen; Burana; Ibumetin; Ibuprox; Ibux; Pedea; ***NZ***: ACT-3; Brufen; Fenpaed; Ibucare†; Nurofen Migraine; Nurofen Tension Headache; Nurofen; Panafen; ***Philipp.***: Advil; Brufen†; Dolafen; Dolan; Faspic; Genselax; Ibuped; Idyl; Medbufen; Medicol; Midol; Rheuxan; ***Pol.***: Aprofen; Bolinet†; Bufenik; Dolgit; Ibalgin; Ibufen; Ibum; Ibupar; Ibuprom; Iburion; Kidofen; MIG; Nurofen Migrenol†; Nurofen; Pedea; ***Port.***: Anadvil; Arfen; Baroc; Brufen; Calbrun†; Dolocyl; Dolomate; Faspic; Fenibu†; Fenpic; Frenidor; Kifen; Liderfen; Moment; Nolofene; Norvectan; Nurofen; Ozonol; Pedea; Perdofen; Seclodin†; Solufen; Solvium; Spidifen; Sporfen; Tricalma; Trifene; Zafen; Zip-A-Dol; ***Rus.***: Aldospray (Альдоспрей); Artro-Cam (АртроКам); Bonifen (Бонифен); Brufen (Бруфен); Burana (Бурана); Dolgit (Долгит); Faspic (Фаспик); Ibalgin (Ибалгин); Ibufen (Ибуфен); Ibuprom (Ибупром); Mig (Миг); Nurofen (Нурофен); Pedea (Педеа); Solpaflex (Солпафлекс); ***S.Afr.***: Adfen†; Advil; Betagesic; Betaprofen; Bren; Brufen; Dynofen; Iboflam; IBU; Ibugesic; Ibuleve; Ibumax; Ibumed; Ibunate; Inza; Lenafen; Norflam T; Nurofen; Pedea; Ranfen; ***Singapore***: Bifen; Brufen; Children's Advil; Ibufen; Ibuleve; Nurofen; Perofen; Sugafen; Zofen; ***Spain***: Advil†; Aldospray Analgesico; Algiasdin; Algidrin; Algifast; Alogesia; Apirofeno; Aragel; Articalm; Bexistar†; Brufen; Dadosel†; Dalsy; Dersindol; Diltix; Doctril; Dolencar; Dolorac; Doltra; Dorival†; Espididol; Espidifen; Factopan†; Femaprin†; Feminalin†; Fenomas†; Fenospin; Fiedosin†; Frenaterm in†; Gelobufen; Gelofeno; Gelopiril†; Ibufarmalid; Ibufen; Ibukey; Ibumac; Ibuprox†; Ibustick; Junifen; Levedol; Liderfeme; Narfen†; Neobrufen; Nodolfen; Normodol; Norvectan; Nurofen; Oberdol†; Optajun†; Paidofebril; Pedea; Pirexin; Ratiodol†; Saetil; Solvium; Termalfeno†; Todalgil; Unodol; ***Swed.***: Alindrin; Brufen; Burana; Ibumax; Ibumetin; Ibuzin; Ipren; Nurofen; Pedea; ***Switz.***: Alges-X; Algifor; Artofen†; Brufen; Contre-Douleurs IL; Dismenol; Dolgit; Dolo-Spedifen; Dolocyl; Ecoprofen†; Grefen; Ibu; Ibufen-L; Ibuscent†; Ibusifar; Iproben; Irfen; Nurofen; Optifen; Perskindol Ibuprofen acute; Saridon N; Spedifen; Treupel Dolo Ibuprofen; ***Thai.***: Ambufen; Anbifen†; Anufen; Aprofen; Borafen; Borakid†; Brufen†; Brufenin; Brugin; Bruprin; Brusil; Buflex; Bumed; Bunofen; Cefen; Cenbufen; Coprofen; Duran; Eufen; Fafen; Faspic†; G-Fen; Gesica; Gofen; Greatofen; Heidi; I Fen F; I-Profen; Ibrofen; Ibu†; Ibufac; Ibufex; Ibugan; Ibukids; Ibulan; Ibulium; Ibuman; Ibumax; Ibupac; Junimol; Mano-Bruzone; Nurofen; P-Fen†; Pippen; Probue†; Probufen; Profen; Profeno; Rabufen; Rheumanox; Rumasian†; Rumatifen†; S-Pro; Sanofen†; Schufen; Sinprofen; Skelan IB†; Spedifen; Suphen; Tofen; Trofen; Tyhofen; Umafen†; ***Turk.***: Advil; Algifen; Artril; Balafen; Bebol†; Berkofen; Biophen; Brufen; Dolgit; Dolven; Gerofen; Ibu-600; Ibufen; Kiddyfen; Nurofen Plus; Nurofen; Pedifen; Profen; Repozal; Rofen; Siyafen; Suprafen; Temsofen†; Ultrafen; Upren; ***UAE***: Profinal; ***UK***: Advil; Anadin Ibuprofen; Anadin Joint Pain; Anadin LiquiFast; Anadin Ultra; Arthrofen; Biatain-Ibu; Brufen; Calprofen; Cuprofen; Ebufac; Fenbid; Fenpaed; Feverfen; Galprofen; Hedex Ibuprofen; Ibrufhalal; Ibufem; Ibugel; Ibuleve; Ibumousse; Ibuspray; Ibutop Cuprofen; Ibutop Ralgex†; Librofem; Mandafen; Manorfen; Mentholatum Ibuprofen; Migrafen; Novaprin; Nurofen Migraine; Nurofen; Obifen; Orbifen; Pacifene; Pedea; Phor Pain; Proflex†; Radian-B Ibuprofen; Relcofen; Rimafen; ***Ukr.***: Bofen (Бофен); Caffetin Lady (Каффетин Леди); Dolgit (Долгит); Ibufen (Ибуфен); Ibuprom (Ибупром); Ibutard (Ибутард); Imet (Имет); Irfen (Ирфен); Nortafen (Нортафен)†; Nurofen (Нурофен); Pedea (Педеа); ***USA***: Advil Migraine; Advil; Anadar; Caldolor; Duexis; Ibu-Tab; Ibu-4, -6, -8; Ibu; Ibutab; Menadol; Midol Cramp & Body Aches; Motrin; NeoProfen; PediaCare Childrens Pain Reliever Fever Reducer IB; PediaCare Infants Pain Reliever Fever Reducer; Saleto-200; ***Venez.***: Advil; Brugesic; Buprodol; Dologesic; Femicaps; Femmex Plus; Ibucaps; Ibufen; Ibuprin; Ibutan; Lumbax; Max; Maydol; Mestral; Motrin; Pedibu.

Multi-ingredient Preparations. ***Arg.***: Aliviagrip; Buscapina Fem; Dexprofeno†; Espasmo Ibuprofeno; Espasmofin; Feminity; Gobbigesic†; Ibu Evanol Extra; Ibu Evanol Plus; Ibu-Buscapina; Ibu-Tetralgin; Ibudolofrix; Ibudristan; Ibufem; Ibunastizol; Ibupirac Fem; Ibupirac Flex; Ibupirac Migra; Ibuxim Fem; Labsyna Caf; Labsyna Fem; Mensalgin; Migral II; Roveril; Supragesic; Teprix Fem; Vefren Flex; ***Austral.***: Dimetapp Headcold & Flu;

Nurofen Cold & Flu; Nurofen Plus; Panafen Plus; Proven Plus; Rafen Plus; Sudafed PE Sinus + Anti-inflammatory Pain Relief; Sudafed Sinus & Anti-inflammatory Pain Relief†; ***Braz.***: Reuplex†; ***Canad.***: Advil Cold & Sinus Nighttime; Advil Cold & Sinus Plus; Advil Cold & Sinus; Advil Nighttime; Analgesic and Muscle Relaxant Caplets; Childrens Advil Cold; Cold + Sinus; Motrin Cold & Sinus; Robax Platinum; Sudafed Sinus Advance; Summit Ultra; Vicks DayQuil Sinus & Pain Relief; ***Chile***: Adona†; Artritapsin; Butartrol; Deucodol Plus; Dolnix; Dolo Winasorb; Dolo-Niofen; Dolo-Octirona; Dolonase; Ibu Kitadol; Ibupirac Compuesto; Ibupirac Flu; Ipson-D; Neo Butartrol; Niofen Cold HBP; Niofen Flu; Pironal Flu; Precenid; Predual; Termo-Niofen; ***China***: Ai Fei Le (爱菲乐); Bo Shu (伯舒); Brustan (保施泰); Chen Gong Zai Xin (臣功再欣); De Er (得尔); Fenshida (芬世达); Gan Ning (敢宁); Kang Tai Ke Qing (康泰克清); Ke Tai Shu (可泰舒); Keluoqu (克洛曲); Nuo He (诺合); Pu Feng Qing (扑风清); Pu Luo Bi Da (普洛必达); Shuang Ji (双佶); Si Wei Pu (思为普); Tuoan (托安); Ya Ke (雅克); Ya Zhou Kang (牙周康); Zaikang (再康); ***Cz.***: Advil Cold†; Ibu-Hepa; Modafen; ***Fin.***: Ardinex; Burana-C; ***Fr.***: Adviltab Rhume†; Cliptol; Nurofen Rhume; Rhinadvil; Rhinureflex; ***Gr.***: Nurofen Cold & Flu; Vicks†; ***Hong Kong***: Neuroquick†; ***Hung.***: Advil Cold†; Algoflex-M; Deep Relief; Nurofen Cold & Flu; Rhinathiol Cold; ***India***: Abufen-C; Acks†; Actimol-F; Adiflam Plus; Alcofen; Anaflam; Answell; Arcure; Armix; Arpa; Artiifen Plus; Artigesic; Bestofen; Bestoflame; Bren Plus; Brenfed; Brenlax; Briflam; Bruace; Brucet; Brufamol-M; Brufamol; Brufen-MR; Brupal; Brustin; Bufex Kid; Bufex Plus; Bufex-C; Buwin Plus; C-Gesic; Calpol Plus; Cipgesic Plus; Codistar Plus; Combiflam; Decofed-DS; Dolocrat; Dolomed-MR; Dolomed; Dolomed; DT-Ibuflam; Dualflam; Duoflam Plus; Duoflam; Efen; Emflam Plus; Fenceta; Fentrex; Fitflam; Flexon-MR; Flexon; Iben Forte; Iben Plus; Ibruvon Forte; Ibu-Proxyvon; Ibubid Plus; Ibucet; Ibuclin; Ibucon Plus; Ibudol-A Kid; Ibudol; Ibuflamar-P; Ibugesic Plus; Ibugesic-M; Ibumac Plus; Ibumet P; Ibumol; Ibun; Ibunij; Ibupar-M; Ibura; Iburic Plus; Ibuspan-P; Ibutop; Ibuwin; Icparil; Imol Plus; Imol; Ipecee; IPM; Lederflam Plus; Lobain; Lumbril-T; Lupiflam-C; Lupiflam; Magadol; Maxofen; New Artifen Plus; Nuren-Ace; Orthodex Plus; Orthodex; Ospidyne; Osyfen Plus; Oxymark; Paraflax; Parvon Forte; Reactine Forte; Robiflam; Somaflam; ***Indon.***: Aknil†; Arthrifen Plus; Axalan†; Bodrex Extra; Iremax; Limasip†; Neo Rheumacyl Neuro; Neo Rheumacyl; Neuralgin; Oskadon SP; Profenal; Shelrod-Plus†; ***Irl.***: Advil Cold & Flu; Nurofen Cold & Flu; Nurofen Plus; Vicks Action†; ***Israel***: Advil Cold & Sinus; Deep Relief†; Nurofen Cold & Flu; Nurofen Plus; ***Ital.***: Nurofen Influenza e Raffreddore; Vicks Flu-Action; ***Jpn***: Colgen Kowa IB; ***Mex.***: Actron Plus; Algitrin; Buscapina Fem; Carbager-Plus; Dualgos; Eufenil M28; Gelidol-X-Press; Sinutab Advance†; ***NZ***: Ibucode Plus; Maxigesic; Nurofen Cold & Flu†; Nurofen Plus; ***Philipp.***: Alaxan; Anoflam; Brustan†; Fladexon; Flexan; Flexigesic; I-Laxx; Muskelax; Proflex; Relievo; Restolax; Selxan; ***Pol.***: Acatar Zatoki; Ardinex†; Dip Rilif; Ibalgin Sport; Ibum Grip; Ibum; Ibuprom Zatoki; Metafen; Modafen; Nurofen Antigrip; Nurofen Plus; ***Rus.***: Brustan (Брустан); Deep Relief (Дип Рилиф); Ibuclin (Ибуклин); Novigan (Новиган); Nurofen Plus (Нурофен Плюс); Pentabufen (Пентабуфен); Theraflex Advance (Терафлекс Адванс); ***S.Afr.***: Advil CS†; Benylin For Colds; Dentopain Forte; Dentopain; Gen-Payne; Ibucod; Ibumol; Ibupain Forte; Ibupain; Lotem; Mybucod; Mybulen; Mypaid; Myprodol; Nurofen Cold & Flu; Nurofen Plus†; Panado Plus; Sinumax Cold & Flu; Sinutab 3-Way; ***Singapore***: Nurofen Cold & Flu; ***Spain***: Astefor; Hyltrin; Ibucod; Neobrufen con Codeina; Nidol; Salvarina; ***Swed.***: Ardinex; ***Switz.***: Ibufen-L; ***Thai.***: Alaxan PI†; Bruno; Brustan; Cetan†; Dologen; Lofen; Panofen; Parafen; Rumatifen-Plus†; Skelan†; ***Turk.***: Dolorin Cold; Iburamin Cold; Nurofen Cold & Flu; ***UAE***: Profinal Cold & Sinus; Profinal FM†; Profinal XP; ***UK***: Cuprofen Plus; Deep Relief; Lemsip Flu 12Hr; Lemsip Max All Day Cold & Flu; Lemsip Max All Day Flu Relief; Lemsip Max All Night Cold & Flu; Lemsip Max All Night Flu Relief; Lemsip Pharmacy Powercaps†; Non-Drowsy Sudafed Dual Relief Max; Nurofen All Night Cold & Flu; Nurofen All Night Flu Relief; Nurofen Cold & Flu Relief; Nurofen Cold & Flu; Nurofen Plus; Nurofen Sinus†; Nuromol; Orbifen Cold & Flu; Soleve; Solpadeine Migraine; Solpaflex; ***Ukr.***: Deep Relief (Дип Рилиф); Ibuprom Sinus (Ибупром Синус)†; Novigan (Новиган); Tamipul (Тамипул); Theraflex Advance (Терафлекс Адванс); ***USA***: Advil Allergy Sinus; Advil Cold & Sinus; Advil PM; Anadar Cold & Flu; Childrens Advil Cold; Childrens Ibuprofen Cold; Childrens Motrin Cold; Combunox†; Dimetapp Childrens Cold & Fever; Dimetapp Sinus; Dristan Sinus; Ibudone; Motrin IB Sinus; Reprexain; Sine-Aid IB; Vicoprofen; ***Venez.***: Brudol; Brugesic Plus; Brugesina; Colfene; Femmexultra; Ibucoden.

Pharmacopoeial Preparations

BP 2014: Ibuprofen Cream; Ibuprofen Gel; Ibuprofen Oral Suspension; Ibuprofen Tablets; Prolonged-release Ibuprofen Capsules; Prolonged-release Ibuprofen Tablets;

USP 36: Diphenhydramine Citrate and Ibuprofen Tablets; Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Ibuprofen Oral Suspension; Ibuprofen Tablets.

Iguratimod *(rINN)*

Iguratimodum; T-614; Иуратимод.

N-{7-[(Methylsulfonyl)amino]-4-oxo-6-phenoxy-4*H*-1-benzopyran-3-yl}formamide.

$C_{17}H_{14}N_2O_6S$=374.4

CAS — 123663-49-0.

UNII — 4IHY34Y2NV.

Profile

Iguratimod is a disease-modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis.

References.

1. Hara M, *et al.* Long-term safety study of iguratimod in patients with rheumatoid arthritis. *Mod Rheumatol* 2007; **17:** 10–16.
2. Hara M, *et al.* Efficacy and safety of iguratimod compared with placebo and salazosulfapyridine in active rheumatoid arthritis: a controlled, multicenter, double-blind, parallel-group study. *Mod Rheumatol* 2007; **17:** 1–9.
3. Mucke HA. Iguratimod: a new disease-modifying antirheumatic drug. *Drugs Today* 2012; **48:** 577–86.
4. Ishiguro N, *et al.* Iguratimod-Clinical Study Group. Concomitant iguratimod therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial. *Mod Rheumatol* 2012;.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Iremod (艾得辛); ***Jpn***: Careram; Kolbet.

Imidazole Salicylate *(rINN)*

Imidazole, Salicylate d'; Imidazoli Salicylas; Salicilato de imidazol; Имидазола Салицилат.

Imidazole compounded with salicylic acid.

$C_{10}H_{10}N_2O_3$=206.2

CAS — 36364-49-5.

ATC — N02BA16.

ATC Vet — QN02BA16.

UNII — 4JVD4X01MJ.

Profile

Imidazole salicylate is a salicylic acid derivative (see Aspirin, p. 22.2) that has been used in the treatment of fever and inflammatory respiratory-tract and otorhinolaryngeal disorders. Imidazole salicylate has been given in oral doses of up to 2.25 g daily in divided doses. It has also been given as a rectal suppository and has been applied topically as a 5% gel for the relief of muscular and rheumatic pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Chulai (楚来); ***Ital.***: Selezen.

Indometacin *(BAN, rINN)*

Indometacina; Indometacinas; Indométacine; Indometacinum; Indometacyna; Indometasiini; Indometasin; Indomethacin (USAN); Indomethacin; Индометацин.

[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid.

$C_{19}H_{16}ClNO_4$=357.8

CAS — 53-86-1.

ATC — C01EB03; M01AB01; M02AA23; S01BC01.

ATC Vet — QC01EB03; QM01AB01; QM02AA23; QS01BC01.

UNII — XXE1CET956.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Indometacin). A white or yellow, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Indomethacin). A pale yellow to yellow-tan, crystalline powder having not more than a slight odour. It exhibits polymorphism. Practically insoluble in water; soluble 1 in 50 of alcohol, 1 in 30 of chloroform, and 1 in 40 of ether. Protect from light.

Stability. Indometacin is unstable in alkaline solution.

Indometacin Sodium *(BANM, rINNM)*

Indometacina sódica; Indométacine Sodique; Indomethacin Sodium (USAN); Indomethacin Sodium Trihydrate; Natrii Indometacinum; Натрий Индометацин.

Sodium 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate, trihydrate.

$C_{19}H_{15}ClNNaO_4.3H_2O$=433.8

CAS — 74252-25-8.

UNII — 0IMX38M2GG.

Pharmacopoeias. In *US.*

USP 36: (Indomethacin Sodium). Protect from light.

Incompatibility. Indometacin sodium injection is reconstituted with preservative-free sodium chloride for injection 0.9% or preservative-free water for injection. Preparations containing glucose should not be used; reconstitution at a pH below 6 may cause precipitation of indometacin. Visual incompatibility has been reported between indometacin sodium injection and tolazoline hydrochloride,[1] 7.5 and 10% glucose injection, calcium gluconate, dobutamine, dopamine, cimetidine,[2] gentamicin sulfate, levofloxacin,[3] and tobramycin sulfate.[4] A pH below 6 may account for the visual incompatibility of indometacin sodium and several of these drugs.

1. Marquardt ED. Visual compatibility of tolazoline hydrochloride with various medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 1802–3.
2. Ishisaka DY, *et al.* Visual compatibility of indomethacin sodium trihydrate with drugs given to neonates by continuous infusion. *Am J Hosp Pharm* 1991; **48:** 2442–3.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–90.
4. Thompson DF, Heflin NR. Incompatibility of injectable indomethacin with gentamicin sulfate or tobramycin sulfate. *Am J Hosp Pharm* 1992; **49:** 836–8.

Stability. A reconstituted solution of indometacin sodium 500 micrograms/mL was stable for 14 days when stored at 2 degrees to 6 degrees in either the manufacturer's original glass vial or in a polypropylene syringe.[1]

1. Walker SE, *et al.* Stability of reconstituted indomethacin sodium trihydrate in original vials and polypropylene syringes. *Am J Health-Syst Pharm* 1998; **55:** 154–8.

Uses and Administration

Indometacin, an indole acetic acid derivative, is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and acute gout, and in peri-articular disorders such as bursitis and tendinitis. It may also be used in inflammation, pain, and oedema following orthopaedic procedures, in mild to moderate pain in conditions such as dysmenorrhoea, and it has been used in the management of postoperative pain as an adjunct to opioids, and in the treatment of fever. Indometacin is also used as the sodium salt to close patent ductus arteriosus in premature infants (see p. 72.2).

The usual initial oral dose in **chronic musculoskeletal and joint disorders** is 25 mg two or three times daily increased, if required, by 25 to 50 mg at weekly intervals to 150 to 200 mg daily. To alleviate night pain and morning stiffness, up to 100 mg of the total daily dose may be given orally, or rectally as a suppository, on retiring. Alternatively, the total daily dose may be given rectally as 100 mg in the morning and at night. The total daily combined oral and rectal dose should not exceed 200 mg. In acute gout the daily dose is 150 to 200 mg in divided doses until all symptoms and signs subside; in dysmenorrhoea up to 75 mg daily has been suggested. Modified-release preparations of indometacin are available for use once or twice daily. For doses in children, see below.

Indometacin is used as 0.1% eye drops to **prevent miosis during cataract surgery**; the usual dose is 2 drops, repeated after 2 hours, on the day before surgery, then 2 drops 3 hours before and 2 drops 1 hour before surgery. To prevent **cystoid macular oedema**, 1 drop may then be instilled postoperatively 4 times daily for 15 days, decreasing to 3 times daily thereafter; treatment should be continued until inflammatory signs have disappeared. A 0.5% eye drop is also available for the prevention of miosis and inflammation associated with cataract surgery. Indometacin eye drops are also used in **other inflammatory eye disorders**; the usual dose is 1 drop of the 0.1% strength 4 to 6 times daily until symptoms are resolved.

Meglumine indometacin and indometacin farnesil, a lipid soluble ester of indometacin ($C_{34}H_{40}ClNO_4$ = 562.1), have also been given for painful and inflammatory conditions. A complex of indometacin and L-arginine, known as indoarginine, has also been used.

Administration in children. Although indometacin is not licensed in the UK for the treatment of **rheumatic diseases** such as juvenile idiopathic arthritis in children, the *BNFC* suggests an oral dose of 0.5 to 1 mg/kg twice daily in those aged 1 month to 18 years; higher doses may be used under specialist supervision

Indometacin is also used in the treatment of **patent ductus arteriosus** in premature infants; see p. 72.2 for further details including doses.

Bartter's syndrome. The treatment of Bartter's syndrome can often be difficult (see p. 1779.3). Blocking the kinin-prostaglandin axis with a cyclo-oxygenase inhibitor such as indometacin improves hypokalaemia and other clinical features (including growth retardation) in children with the syndrome.[1-5]

1. Littlewood JM, *et al.* Treatment of childhood Bartter's syndrome with indomethacin. *Lancet* 1976; **ii:** 795.
2. Seidel C, *et al.* Pre-pubertal growth in the hyperprostaglandin E syndrome. *Pediatr Nephrol* 1995; **9:** 723–8.
3. Craig JC, Falk MC. Indomethacin for renal impairment in neonatal Bartter's syndrome. *Lancet* 1996; **347:** 550.

4. Mourani CC, *et al.* Bartter syndrome in a neonate: early treatment with indomethacin. *Pediatr Nephrol* 2000; **14:** 143–5.
5. Vaisbich MH, *et al.* Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 2004; **19:** 858–63.

Diabetes insipidus. Indometacin and other prostaglandin synthetase inhibitors have been reported to decrease urine volume in all types of nephrogenic diabetes insipidus (p. 2348.2).

References.

1. Rosen GH, *et al.* Indomethacin for nephrogenic diabetes insipidus in a four-week-old infant. *Clin Pharm* 1986; **5:** 254–6.
2. Libber S, *et al.* Treatment of nephrogenic diabetes insipidus with prostaglandin synthesis inhibitors. *J Pediatr* 1986; **108:** 305–11.
3. Allen HM, *et al.* Indomethacin in the treatment of lithium-induced nephrogenic diabetes insipidus. *Arch Intern Med* 1989; **149:** 1123–6.
4. Martinez EJ, *et al.* Lithium-induced nephrogenic diabetes insipidus treated with indomethacin. *South Med J* 1993; **86:** 971–3.
5. Hohler T, *et al.* Indomethacin treatment in amphotericin B induced nephrogenic diabetes insipidus. *Clin Investig* 1994; **72:** 769–71.
6. Lam SS, Kjellstrand C. Emergency treatment of lithium-induced diabetes insipidus with nonsteroidal anti-inflammatory drugs. *Ren Fail* 1997; **19:** 183–8.

Malignant neoplasms. In common with some other NSAIDs (see p. 104.1) it has been suggested that indometacin might possess some antineoplastic activity.[1] Some NSAIDs such as indometacin may also be of value for the differential diagnosis and the management of neoplastic fever, as they appear to be more effective in reducing this type of fever than against fever associated with infections.[2] Indometacin has also been tried for the treatment of fever and flu-like symptoms associated with interleukin-2 therapy although there has been concern over exacerbation of renal toxicity (see NSAIDs, under Interactions, p. 812.1).

1. Mertens WC, *et al.* Effect of indomethacin plus ranitidine in advanced melanoma patients on high-dose interleukin-2. *Lancet* 1992; **340:** 397–8.
2. Engervall P, *et al.* Antipyretic effect of indomethacin in malignant lymphoma. *Acta Med Scand* 1986; **219:** 501–5.

Neonatal intraventricular haemorrhage. Indometacin has been tried prophylactically to prevent the development of intraventricular haemorrhage in neonates at risk (see p. 1128.3). Several mechanisms have been proposed for its possible action including reduction of cerebral flow as a result of vasoconstriction, reduction of oxygen free-radical damage, and accelerated maturation of blood vessels around the ventricles. Early studies[1-3] of the use of indometacin for prevention of intraventricular haemorrhage produced conflicting results. A subsequent large multicentre study[4] (the Indomethacin Intraventricular Haemorrhage Prevention Trial, IIHP) suggested that indometacin could reduce the incidence and severity of intraventricular haemorrhage, especially for the more severe forms. Neonates with a birth-weight of 600 to 1250 g were given indometacin in a dose of 100 micrograms/kg intravenously at 6 to 12 hours after delivery and then every 24 hours for 2 additional doses. There was, however, concern[5] that an unusually large number of neonates with severe intraventricular haemorrhage in the control group might have biased the findings.

A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps. Follow-up at 3 years,[6] at 4½ years,[7] and at 8 years of age[8] in the infants included in the IIHP study reported no adverse effects on cognitive or motor development. However, another large multicentre study[9] (the Trial of Indomethacin Prophylaxis in Preterms, TIPP) in extremely-low-birth-weight infants (less than 1000 g) found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[10] also concluded that indometacin prophylaxis did not improve survival free of neurosensory disability although, again, the incidence of severe intraventricular haemorrhage was reduced.

Further analysis of the data from the IIHP study has suggested that indometacin might reduce intraventricular haemorrhage in boys but have little effect in girls;[11] verbal scores at ages 3 to 8 years were also higher in those boys treated with indometacin when compared with a control group of boys treated with saline; no differences in scores were noted in indometacin-treated girls and their control group. Re-analysis of data from the TIPP study[12] in extremely-low-birth-weight neonates suggested a weak gender difference in the effect of indometacin treatment when all primary outcomes such as death, cerebral palsy, cognitive delay, and severe intraventricular haemorrhage were considered; however, when outcomes were considered individually, there was a significant reduction in intraventricular haemorrhage in boys when compared with girls. The authors considered the results to be a consequence of an unfavourable effect of indometacin in girls rather than any positive effects in boys. Any true difference in effect between the sexes remains to be confirmed.

Indometacin does not appear to prevent the progression of existing haemorrhage.[13]

1. Ment LR, *et al.* Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. *J Pediatr* 1985; **107:** 937–43.
2. Rennie JM, *et al.* Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986; **61:** 233–8.
3. Bada HS, *et al.* Indomethacin reduces the risks of severe intraventricular hemorrhage. *J Pediatr* 1989; **115:** 631–7.
4. Ment LR, *et al.* Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994; **93:** 543–50.
5. Volpe JJ. Brain injury caused by intraventricular hemorrhage: is indomethacin the silver bullet for prevention? *Pediatrics* 1994; **93:** 673–7.
6. Ment LR, *et al.* Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the multicenter indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 1996; **98:** 714–18.
7. Ment LR, *et al.* Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000; **105:** 485–91.
8. Vohr BR, *et al.* School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Abstract: *Pediatrics* 2003; **111:** 874. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/4/e340 (accessed 07/11/07)
9. Schmidt B, *et al.* Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344:** 1966–72.
10. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F464–F466.
11. Ment LR, *et al.* Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004; **145:** 832–4.
12. Ohlsson A, *et al.* Male/female differences in indomethacin effects in preterm infants. *J Pediatr* 2005; **147:** 860–2.
13. Ment LR, *et al.* Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr* 1994; **124:** 951–5.

Patent ductus arteriosus. In the fetal circulation the ductus arteriosus connects the pulmonary artery and the descending aorta. After birth, various mechanisms, including a fall in prostaglandin concentration, trigger its closure but in some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. This condition may be found in infants with congenital heart defects but is more commonly seen in premature neonates, especially those with respiratory distress syndrome.

- Some infants may be asymptomatic or have only slight clinical symptoms and no immediate intervention is required. In many cases spontaneous closure will occur after several months, or else surgical ligation may be performed if clinical symptoms persist.
- In some infants a patent ductus arteriosus is necessary for maintaining some oxygenation of the blood, for example in pulmonary artery atresia or transposition of the great arteries. These infants require treatment with a prostaglandin such as *alprostadil* or *dinoprostone* to maintain patency of the ductus arteriosus until surgery can be performed to correct the malformation.
- Infants with haemodynamically significant ductus arteriosus, signs of heart failure, and who require ventilation should undergo treatment to close the patent ductus arteriosus.

Initial **management** involves fluid restriction, diuretics, correction of anaemia, and support of respiration. *Chlorothiazide* and *furosemide* are diuretics commonly used. There has been concern that furosemide might delay closure in infants with respiratory distress syndrome.[1,2] A systematic review[3] concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

If initial treatment fails to control symptoms after 24 to 48 hours then *indometacin* is generally given to promote closure of the ductus.[1,4-6] The benefits of treatment with indometacin as soon as symptoms become apparent, rather than delaying treatment until signs of congestive failure develop, have been debated.[7,8] Early treatment may significantly reduce the morbidities arising from a persistent patent ductus arteriosus.[7] However, delaying treatment until the end of the first week of life can allow for spontaneous closure and avoid the need of exposing infants to the toxic effects of indometacin.[8]

Indometacin probably leads to closure of the ductus through inhibition of prostaglandin synthesis. It is given as the sodium salt in three intravenous doses at 12- to 24-hour intervals; each dose should be infused over 20 to 30 minutes. Indometacin sodium injection is reconstituted with preservative-free sodium chloride 0.9% for injection or water for injection; glucose solutions should not be used (see Incompatibility, p. 71.2). The dose of indometacin sodium (expressed as indometacin) depends upon the age of the neonate and the following doses have been suggested based upon the age at the first dose:

- less than 48 hours old: 200 micrograms/kg initially followed by two further doses of 100 micrograms/kg each
- 2 to 7 days old: three doses of 200 micrograms/kg each
- over 7 days old: 200 micrograms/kg initially followed by two further doses of 250 micrograms/kg each

If, 48 hours after this course of therapy the ductus remains open or re-opens, a second course may be used, but if this produces no response (which may be the case in 25% of infants treated[4,9]) surgery may be necessary.

Indometacin has been given orally where the injection is unavailable, but absorption of oral indometacin is poor and incomplete in premature neonates.

A decreased need for surgical closure and reduced recurrences were seen in neonates in whom standard intravenous indometacin therapy was then followed by maintenance therapy (intravenous indometacin 200 micrograms/kg daily for an additional 5 days).[10] Prolonged therapy using high doses of up to 1 mg/kg as a single dose every 12 hours has also been used with some success in a few infants who have not responded to standard regimens.[11] Similar beneficial findings were reported[12] in infants given prolonged low-dose indometacin therapy (100 micrograms/kg daily for 6 days). An additional benefit was a lower incidence of adverse effects; fewer infants had a rise in serum creatinine or urea concentrations. However, a systematic review[13] has suggested that such regimens are no more effective than the shorter standard regimens, and found an increased rather than decreased incidence of adverse effects (including a trend towards increased risk of necrotising enterocolitis[1,6]). Prolonged treatment with indometacin could not be recommended.[13] Prophylactic treatment or treatment of asymptomatic ductus with indometacin has been tried in premature infants, and there is good evidence to suggest that this is effective in reducing the risk of symptomatic patent ductus arteriosus and intraventricular haemorrhage (see above) in such patients;[7,14,15] however, prophylactic treatment has not been shown to significantly reduce the risk of short-term pulmonary complications such as bronchopulmonary dysplasia. Systematic reviews[14,15] have also found no evidence of either benefit or harm in neurological development or other longer term outcomes.

Some other NSAIDs have also been tried in the treatment of patent ductus arteriosus. A recent systematic review[16] found that ibuprofen was as effective as indometacin, and also reduced the risk of necrotising enterocolitis and transient renal impairment. Given its lower risk of adverse effects, the authors suggested that ibuprofen is the drug of choice; however, data on longer term outcomes are needed before any recommendations regarding the use of indometacin or ibuprofen can be made. Ibuprofen is also effective when used prophylactically; however, there have been reports of pulmonary hypertension with such use and ibuprofen is not recommended.[17]

Oral therapy with ibuprofen has also been tried.[18,19]

1. Bhatt V, Nahata MC. Pharmacologic management of patent ductus arteriosus. *Clin Pharm* 1989; **8:** 17–33.
2. Anonymous. Delayed closure of the ductus. *Lancet* 1983; **ii:** 436.
3. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 07/11/07).
4. Silove ED. Pharmacological manipulation of the ductus arteriosus. *Arch Dis Child* 1986; **61:** 827–9.
5. Barst RJ, Gersony WM. The pharmacological treatment of patent ductus arteriosus: a review of the evidence. *Drugs* 1989; **38:** 249–66.
6. Archer N. Patent ductus arteriosus in the newborn. *Arch Dis Child* 1993; **69:** 529–32.
7. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr* 1996; **128:** 601–7.
8. Van Overmeire B, *et al.* Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 2001; **138:** 205–11.
9. Gersony WM, *et al.* Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983; **102:** 895–906.
10. Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. *J Pediatr* 1990; **117:** 771–6.
11. Sperandio M, *et al.* Effectiveness and side effects of an escalating, stepwise approach to indomethacin treatment for symptomatic patent ductus arteriosus in premature infants below 33 weeks of gestation. *Pediatrics* 2005; **116:** 1361–6.
12. Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. *Arch Dis Child* 1991; **66:** 55–8.
13. Herrera C, *et al.* Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 07/11/07).
14. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 07/11/07).
15. Cooke L, *et al.* Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 07/11/07).
16. Ohlsson A, *et al.* Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 16/08/10).
17. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 07/11/07).
18. Heyman E, *et al.* Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. Abstract: *Pediatrics* 2003; **112:** 1170. Full version: http://pediatrics.aappublications.org/cgi/reprint/112/5/e354.pdf (accessed 07/11/07)
19. Cherif A, *et al.* Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. Abstract: *Pediatrics* 2008; **122:** 1361–2. Full version: http://pediatrics.aappublications.org/cgi/reprint/122/6/e1256 (accessed 16/09/09)

Polyhydramnios. Indometacin may be of benefit in the management of polyhydramnios (an excessive accumulation of amniotic fluid).[1-3] Polyhydramnios is a feature of the neonatal variant of Bartter's syndrome (see also p. 71.3).

1. Cabrol D, *et al.* Treatment of symptomatic polyhydramnios with indomethacin. *Eur J Obstet Gynecol Reprod Biol* 1996; **66:** 11–15.
2. Abhyankar S, Salvi VS. Indomethacin therapy in hydramnios. *J Postgrad Med* 2000; **46:** 176–8.
3. Kriplani A, *et al.* Indomethacin therapy in the treatment of polyhydramnios due to placental chorioangioma. *J Obstet Gynaecol Res* 2001; **27:** 245–8.

Premature labour. The most common approach to postponing premature labour (p. 2131.1) with drugs has historically been with a selective beta$_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Comparative studies[1,2] have shown that indometacin and ritodrine are equally effective in inhibiting uterine contractions and delaying delivery in patients in preterm labour who have intact membranes and in whom the gestational age is less than or equal to 34 weeks. In one study[2] an initial oral loading dose of indometacin 50 mg was given, followed by 25 to 50 mg orally every 4 hours until contractions stopped and then by a maintenance dose of 25 mg every 4 to 6 hours. In the other comparative study[1] indometacin was given as a 100-mg rectal suppository followed by 25 mg orally every 4 hours for 48 hours; if regular uterine contractions persisted 1 to 2 hours after the initial suppository, an additional 100-mg suppository was given before beginning oral therapy. Terbutaline was given for maintenance therapy.

Unfortunately indometacin can constrict the ductus arteriosus,[3-5] which may lead to pulmonary hypertension,[2] and has also been associated with bronchopulmonary dysplasia,[6] reduced volume of amniotic fluid (oligohydramnios)[2,4] and possible renal damage (see Effects on the Kidneys, below) in the fetus. Another complication is that prenatal indometacin exposure may increase both the incidence and severity of patent ductus arteriosus in premature infants,[7,8] as shown by the increased need for post-natal indometacin therapy and surgical ligation in such infants. However, there is evidence to suggest that there is no significant increase in the risk of neonatal complications in infants exposed to indometacin tocolysis when compared with control groups of infants who received either no treatment or tocolysis with drugs other than indometacin.[9,10]

The evidence for any overall benefit of indometacin in delaying labour is equivocal,[11-13] and it is generally reserved as a second-line tocolytic or for use with an intravenous tocolytic when an additive effect is required.

1. Morales WJ, *et al.* Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor: a randomized study. *Obstet Gynecol* 1989; **74:** 567–72.
2. Besinger RE, *et al.* Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. *Am J Obstet Gynecol* 1991; **164:** 981–8.
3. Moise KJ, *et al.* Indomethacin in the treatment of premature labor: effects on the fetal ductus arteriosus. *N Engl J Med* 1988; **319:** 327–31.
4. Hallak M, *et al.* Indomethacin for preterm labor: fetal toxicity in a dizygotic twin gestation. *Obstet Gynecol* 1991; **78:** 911–13.
5. Vermillion ST, *et al.* The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. *Am J Obstet Gynecol* 1997; **177:** 256–61.
6. Eronen M, *et al.* Increased incidence of bronchopulmonary dysplasia after antenatal administration of indomethacin to prevent preterm labor. *J Pediatr* 1994; **124:** 782–8.
7. Norton ME, *et al.* Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med* 1993; **329:** 1602–7.
8. Hammerman C, *et al.* Indomethacin tocolysis increases post-natal patent ductus arteriosus severity. Abstract: *Pediatrics* 1998; **102:** 1202–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/102/5/e56 (accessed 07/11/07)
9. Vermillion ST, Newman RB. Recent indomethacin tocolysis is not associated with neonatal complications in preterm infants. *Am J Obstet Gynecol* 1999; **181:** 1083–6.
10. Loe SM, *et al.* Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. *Obstet Gynecol* 2005; **106:** 173–9.
11. Macones GA, Robinson CA. Is there justification for using indomethacin in preterm labor? An analysis of neonatal risks and benefits. *Am J Obstet Gynecol* 1997; **177:** 819–24.
12. Panter KR, *et al.* The effect of indomethacin tocolysis in preterm labour on perinatal outcome: a randomised placebo-controlled trial. *Br J Obstet Gynaecol* 1999; **106:** 467–73.
13. Macones GA, *et al.* The controversy surrounding indomethacin for tocolysis. *Am J Obstet Gynecol* 2001; **184:** 264–72.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Adverse effects are more frequent with indometacin than with many other NSAIDs, the most common being gastrointestinal disturbances, headache, vertigo, dizziness, and lightheadedness. Gastrointestinal perforation, ulceration, and bleeding may also occur; rarely, intestinal strictures have been reported. Other adverse effects include depression, drowsiness, tinnitus, confusion, insomnia, psychiatric disturbances, syncope, convulsions, coma, peripheral neuropathy, blurred vision, corneal deposits and other ocular effects, oedema and weight gain, hypertension, haematuria, rashes, pruritus, urticaria, stomatitis, alopecia, and hypersensitivity reactions. Leucopenia, purpura, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, epistaxis, hyperglycaemia, hypoaldosteronism and hyperkalaemia, and vaginal bleeding have been reported. There have also been reports of hepatitis, jaundice, and renal failure. Hypersensitivity reactions may also occur in aspirin-sensitive patients. Rectal irritation and bleeding have been reported occasionally in patients who have received indometacin suppositories.

Adverse effects associated with the use of indometacin injection in premature **neonates** may also include haemorrhagic, renal, gastrointestinal, metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection may also occur.

Effects on the blood. There were 1261 reports of adverse reactions to indometacin reported to the UK CSM between June 1964 and January 1973. These included 157 reports of blood disorders (25 fatal) including thrombocytopenia (35; 5 fatal), aplastic anaemia (17; no fatalities), and agranulocytosis or leucopenia (21; 3 fatal).[1] Subsequently, the First Report from the International Agranulocytosis and Aplastic Anemia Study confirmed a significant relationship between the use of indometacin and agranulocytosis and aplastic anaemia.[2] Neutropenia has also been noted in a premature infant with patent ductus arteriosus after use of indometacin.[3]

Although use of indometacin in 20 women being treated for premature labour did not affect maternal prothrombin or activated partial thromboplastin time, maternal bleeding time during therapy was increased.[4] However, no cases of neonatal intraventricular haemorrhage or maternal postpartum haemorrhage were seen.

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2:** 600–10.
2. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
3. Bengtsson B-OS, *et al.* Indomethacin-associated neutropenia with subsequent Gram-negative sepsis in a preterm infant: cause or coincidence? *J Perinatol* 2006; **26:** 381–3.
4. Lunt CC, *et al.* The effect of indomethacin tocolysis on maternal coagulation status. *Obstet Gynecol* 1994; **84:** 820–2.

Effects on cerebral blood flow. See Patent Ductus Arteriosus under Uses and Administration, p. 72.2.

Effects on the eyes. Severe and irreversible retinopathy, presumably due to long-term ingestion of high doses of indometacin occurred in a 33-year-old man.[1] A summary of previous literature reports of indometacin-induced ocular effects indicated that indometacin was retinotoxic, although to what degree was uncertain. For reference to effects on the optic nerve associated with indometacin, see p. 105.3.

1. Graham CM, Blach RK. Indomethacin retinopathy: case report and review. *Br J Ophthalmol* 1988; **72:** 434–8.

Effects on the gastrointestinal tract. Nausea, vomiting, dyspepsia, gastrointestinal lesions, and serious reactions including gastrointestinal bleeding, ulceration, and perforation have occurred in patients receiving indometacin. Although it is well established that NSAIDs can produce adverse effects on the upper gastrointestinal tract, indometacin and other NSAIDs can also affect the large intestines.[1] Giving indometacin to preterm neonates increases the risk of small bowel perforation and necrotising enterocolitis.[2-4] Risk seems to be increased in very-low-birthweight or extremely premature infants.

1. Oren R, Ligumsky M. Indomethacin-induced colonic ulceration and bleeding. *Ann Pharmacother* 1994; **28:** 883–5.
2. Grosfeld JL, *et al.* Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. *Ann Surg* 1996; **224:** 350–7.
3. Shorter NA, *et al.* Indomethacin-associated bowel perforations: a study of possible risk factors. *J Pediatr Surg* 1999; **34:** 442–4.
4. Fujii AM. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. *J Perinatol* 2002; **22:** 535–40.

Effects on the joints. For references to concern that NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis, see Effects on Bone, under NSAIDs, p. 104.3.

Effects on the kidneys. Acute renal failure,[1] nephrotic syndrome,[2] and renal papillary necrosis[3] have been reported in patients given indometacin. There have been suggestions that misoprostol might reduce the risk of indometacin-induced renal toxicity.[4,5]

Renal impairment has also occurred in **neonates** given indometacin intravenously for patent ductus arteriosus. Although rare, and usually reversible, the effect may be serious in neonates with pre-existing renal disorders.[6] Serious or fatal renal toxicity has been reported in neonates exposed to indometacin due to maternal ingestion.[7] The renal effects of prenatal indometacin may be prolonged.[8]

1. Chan X. Fatal renal failure due to indomethacin. *Lancet* 1987; **ii:** 340.
2. Boiskin I, *et al.* Indomethacin and the nephrotic syndrome. *Ann Intern Med* 1987; **106:** 776–7.
3. Mitchell H, *et al.* Indomethacin-induced renal papillary necrosis in juvenile chronic arthritis. *Lancet* 1982; **ii:** 558–9.
4. Weir MR, *et al.* Minimization of indomethacin-induced reduction in renal function by misoprostol. *J Clin Pharmacol* 1991; **31:** 729–35.
5. Wong F, *et al.* The effect of misoprostol on indomethacin-induced renal dysfunction in well-compensated cirrhosis. *J Hepatol* 1995; **23:** 1–7.
6. Cuzzolin L, *et al.* NSAID-induced nephrotoxicity from the fetus to the child. *Drug Safety* 2001; **24:** 9–18.
7. van der Heijden BJ, *et al.* Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. *Am J Obstet Gynecol* 1994; **171:** 617–23.
8. Butler-O'Hara M, D'Angio CT. Risk of persistent renal insufficiency in premature infants following the prenatal use of indomethacin for suppression of preterm labor. *J Perinatol* 2002; **22:** 541–6.

Effects on the liver. Cholestasis occurred in a 52-year-old woman several days after starting indometacin;[1] liver function values returned to normal once indometacin was stopped.

1. Cappell MS, *et al.* Indomethacin-associated cholestasis. *J Clin Gastroenterol* 1988; **10:** 445–7.

Hypersensitivity. Hypersensitivity reactions including acute asthma have been reported after use of indometacin suppositories,[1] eye drops,[2] or capsules[3] by patients who were aspirin-sensitive or had a history of asthma.

1. Timperman J. A fatal asthmatic attack following administration of an indomethacin suppository. *J Forensic Med* 1971; **18:** 30–2.
2. Sheehan GJ, *et al.* Acute asthma attack due to ophthalmic indomethacin. *Ann Intern Med* 1989; **111:** 337–8.
3. Johnson NM, *et al.* Indomethacin-induced asthma in aspirin-sensitive patients. *BMJ* 1977; **2:** 1291.

Precautions

As for NSAIDs in general, p. 107.1.

Indometacin should be used with caution in patients with epilepsy, parkinsonism, or psychiatric disorders. Dizziness may affect the performance of skilled tasks such as driving. Patients on long-term indometacin therapy should be examined regularly for adverse effects, and the *BNF* particularly recommends periodic blood and ophthalmic examinations. Rectal use should be avoided in patients with proctitis and haemorrhoids.

In addition indometacin should not be given to **neonates** with untreated infection, with significant renal impairment, or with necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should not be given indometacin and those receiving indometacin should be monitored during treatment for signs of bleeding. Electrolytes and renal function should also be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

False-negative results in the dexamethasone suppression test have been reported in patients taking indometacin.

Breast feeding. Convulsions in a one-week old breast-fed infant appeared to be associated with maternal ingestion of indometacin;[1] the child had normal motor and mental development at the age of 1 year and seizures had not recurred.

Indometacin has been detected in breast milk, but some workers[2,3] and the *BNF* consider that the amount is too small to be harmful to a breast-fed infant. The American Academy of Pediatrics[4] also states that indometacin is usually compatible with breast feeding despite acknowledging the above case report of convulsions. However, licensed product information recommends that indometacin should not be used in nursing mothers.

1. Eeg-Olofsson O, *et al.* Convulsions in a breast-fed infant after maternal indomethacin. *Lancet* 1978; **ii:** 215.
2. Beaulac-Baillargeon L, Allard G. Distribution of indomethacin in human milk and estimation of its milk to plasma ratio in vitro. *Br J Clin Pharmacol* 1993; **36:** 413–16.
3. Lebedevs TH, *et al.* Excretion of indomethacin in breast milk. *Br J Clin Pharmacol* 1991; **32:** 751–4.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

The elderly. After a study[1] of the pharmacokinetics of indometacin in the elderly it was suggested that the maintenance dose of indometacin in elderly patients should be reduced by 25%. The total clearance of indometacin in elderly subjects had been reduced when compared with that in young subjects; this was thought to be due to reduced hepatic metabolism in the elderly.

1. Oberbauer R, *et al.* Pharmacokinetics of indomethacin in the elderly. *Clin Pharmacokinet* 1993; **24:** 428–34.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies indometacin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Pregnancy. See Premature Labour under Uses and Administration, p. 73.1.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Anti-inflammatory doses of aspirin decrease indometacin blood concentrations by about 20%. Diflunisal decreases the renal clearance and increases plasma concentrations of indometacin. Use of diflunisal with indometacin has also resulted in fatal gastrointestinal haemorrhage, and the two should not be used together. Plasma concentrations of indometacin are likely to be increased in patients receiving probenecid.

Antibacterials. Indometacin has been reported to increase plasma concentrations of *aminoglycosides*.

Antipsychotics. Severe drowsiness and confusion have been reported in patients given *haloperidol* with indometacin.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; **i:** 830–1.

Bone modulating drugs. Indometacin has been reported to increase the bioavailability of *tiludronate*, see p. 1192.3.

Desmopressin. The effect of desmopressin may be enhanced by indometacin.

Digoxin. In addition to increasing digoxin serum concentrations (see p. 1358.1), combination of digoxin with indometacin has been reported to reduce the half-life of the latter in premature neonates (see Half-life under Pharmacokinetics, below).

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Indometacin is readily absorbed from the gastrointestinal tract in adults; peak plasma concentrations occur about 2 hours after a dose. Absorption may be slowed by food or by aluminium- or magnesium-containing antacids. In premature neonates, absorption of oral indometacin is poor and incomplete. The bioavailability of rectal suppositories in adults has been reported to be comparable with or slightly less than the bioavailability with oral dosage forms.

Indometacin is about 99% bound to plasma proteins. It is distributed into synovial fluid, the CNS, and placenta. Low concentrations have been distributed into breast milk. The terminal plasma half-life has been reported to range from 2.6 to 11.2 hours in adults. The terminal half-life in neonates has been reported to be between 12 and 28 hours (see also below). Indometacin is metabolised in the liver to its glucuronide conjugate and to desmethylindometacin, desbenzoylindometacin, desmethyl-desbenzoylindometacin, and to their glucuronides. Some indometacin undergoes *N*-deacylation. Indometacin and its conjugates undergo enterohepatic circulation. Excretion of indometacin and its metabolites is mainly in the urine with lesser amounts appearing in the faeces.

References.

1. Moise KJ, *et al.* Placental transfer of indomethacin in the human pregnancy. *Am J Obstet Gynecol* 1990; **162:** 549–54.
2. Mannila A, *et al.* Plasma and cerebrospinal fluid concentrations of indomethacin in children after intravenous administration. *J Clin Pharmacol* 2007; **47:** 94–100.

Half-life. The plasma half-life of indometacin in premature infants can be variable but appears to be inversely proportional to post-natal age and weight.[1,2] One population model suggests that for an infant of 1.17 kg, half-life would be 22.3 hours at a post-natal age of 8 days, but 16.1 hours at 25 days (and only 11.2 hours if also receiving digoxin).[2]

1. Wiest DB, *et al.* Population pharmacokinetics of intravenous indomethacin in neonates with symptomatic patent ductus arteriosus. *Clin Pharmacol Ther* 1991; **49:** 550–7.
2. Smyth JM, *et al.* Intravenous indometacin in preterm infants with symptomatic patent ductus arteriosus: a population pharmacokinetic study. *Br J Clin Pharmacol* 2004; **58:** 249–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agilex; IM 75; Indogesic; Indotex; Klonametacina; ***Austral.***: Arthrexin; Indocid PDA; Indocid; ***Austria***: Indobene; Indocid; Indocollyre; Indomelan; Luiflex; ***Belg.***: Dolcidium; Indocid; Indocollyre; Sportflex; ***Braz.***: Agilisin; Indocid; ***Canad.***: Indocid PDA†; Novo-Methacin; Nu-Indo; Pro-Indo; Rhodacine†; ***Chile***: Flexono; Moviflex†; ***China***: Bi Nuo (比诺); Di Ke Shi (狄克施); He Lin Kou Fu Ye (鹤临口服液); Indocontin (意施丁); Lu Qi (露奇); Meidaxin (美达新); Patecs (必艾得); ***Cz.***: Elmetacin; Indobene; Indocollyre; Vonum Cutan; ***Denm.***: Confortid; ***Fin.***: Indocid†; Indometin; ***Fr.***: Chrono-Indocid; Indocid; Indocollyre; ***Ger.***: Indo EDO; Indo Top; Indo-paed†; Indo; Indocolir; Indomet-ratiopharm; Mobilat Schmerzspray; Rheubalmin Indo; ***Gr.***: Afardin; Algibron; Bavilon; Begincalm; Bonatol; Cindol; Dolcispray; Dolopas; Fortathrin; Frangerton; Hastel; Indocid; Indocontin; Indomethol; Intobutaz; Intomin; Itapredin; Labestran; Nuricon; Reumacid; Reumadolor; Reumastop; Rheumafar; ***Hong Kong***: Arthrexin†; Indocap†; Indocid; Indocin PDA; Indocollyre; Indoxen; Methacin†; ***Hung.***: Elmetacin; Indobene; Indocollyre; ***India***: Artisid; Ducain; Idicin; Indocap; Indocid; Indoflam; Indoriv; Inmecin; Inocin; Microcid; ***Indon.***: Dialon; ***Irl.***: Flexin Continus†; Indocid PDA†; ***Israel***: Indocin; Indocollyre; Indomed; Indotard†; Indovis; ***Ital.***: Indocid; Indocollirio; Indom; Indoxen; Liometacen; Metacen; ***Jpn***: Catlep; Idomethine; Infree; Inteban; ***Malaysia***: Indo; Indomen; ***Mex.***: Antalgin; Artaxol; Biometacin; Draxil; Indaflex; Indocarsil†; Indocid; Indoman; Indotrin; Italon; Malival; Mefazil; Soltacina†; Stratasin; ***Neth.***: Indocid PDA†; Indocid†; Indocollyre; ***Norw.***: Confortid†; Indocid†; ***NZ***: Arthrexin; Indocid PDA; Rheumacin†; ***Philipp.***: Infree; Vi-Gel; ***Pol.***: Elmetacin; Indocollyre; Metindol; ***Port.***: Autritis; Dolovin†; Elmetacin; Indocid; Indocollyre; Reumacide; ***Rus.***: Indocollyre (Индоколлир); Indomin (Индомин)†; Indovis (Индовис); Metindol (Метиндол); ***S.Afr.***: Acuflex†; Adco-Indogel; Aflamin†; Amdocin; Arthrexin; Betacin; Elmetacin; Famethacin; Flamaret†; Flamecid; Indocid; Mediflex; Methocaps; Nisaid; Restameth-SR; ***Singapore***: HD-Methacin; Indo; Indocap; Indocid; Indocin; Indocollyre; Indomen; Methacid; ***Spain***: Aliviosin; Artrinovo; Flogoter; Inacid; Indolgina†; Indonilo; Reusin; ***Swed.***: Confortid; Indomee†; ***Switz.***: Bonidon†; Elmetacin; Indocid; Indophtal; ***Thai.***: Ammi-Indocin; Andocit; Docin; Elmego; Elmetacin; IDC; Incosit; Indo-Mathacin†; Indo-Trustman; Indo; Indocid†; Indocin; Indocollyre†; Indoman; Indomed; Indometh; Indometin; Indono; Inflamate†; Inthacine; Liometacen†; M-CIN; Metindo; S-Docid; Satogesic; Zonema; ***Turk.***: Endol; Endosetin; Indocid; Indocolir; Inomet; ***UAE***: Rothacin; ***UK***: Indocid PDA; Indocid; Indolar SR; Pardelprin; Rimacid†; Slo-Indo; ***Ukr.***: Indocollyre (Индоколлир); Metindol (Метиндол); ***USA***: Indocin; Indocin; ***Venez.***: Cevimin; Elmetacin; Indocid.

Multi-ingredient Preparations. ***Austria***: Vonum; ***China***: Ai Mei Xing (爱美幸); Compound Indometacin (复方吲哚美辛); Vantelinkowa (万特力); ***Fin.***: Indalgin; ***Fr.***: Indobiotic; ***Hong Kong***: Artrolin-F†; ***India***: Inmecin-P; ***Ital.***: Difmetre; ***Jpn***: Vantelin; ***Mex.***: Ardosons; Artridol; Artridol; Deximet; Indarzona; Malival Compuesto; Morlan; Reupat; ***Port.***: Indobiotic; ***Rus.***: Indovasin (Индовазин); ***Spain***: Artri†; Fiacin†; ***Thai.***: Dometa; Sancago; ***Turk.***: Indobiotic; ***Ukr.***: Indovenol (Индовенол).

Pharmacopoeial Preparations

BP 2014: Indometacin Capsules; Indometacin Suppositories;
USP 36: Indomethacin Capsules; Indomethacin Extended-release Capsules; Indomethacin for Injection; Indomethacin Oral Suspension; Indomethacin Suppositories; Indomethacin Topical Gel.

Infliximab *(BAN, rINN)*

cA2; CenTNF; Infliksimab; Infliksimabi; Infliximabum; Инфликсимаб.

Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light chain, dimer.

CAS — 170277-31-3.
ATC — L04AB02.
ATC Vet — QL04AB02.
UNII — B72HH48FLU.

Uses and Administration

Infliximab is a chimeric monoclonal antibody to TNF α, a pro-inflammatory mediator. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and Crohn's disease and ulcerative colitis. Elevated TNF levels are also found in psoriatic plaques. Infliximab is described as a biological disease-modifying antirheumatic drug (DMARD).

Infliximab is given by intravenous infusion over a usual period of not less than 2 hours; shorter infusion times have been used in some patients with rheumatoid arthritis (see below for further details).

Infliximab is used with methotrexate in the management of moderate to severe, active **rheumatoid arthritis** (p. 75.2). In the UK it is licensed for use in patients who have had an inadequate response to standard DMARDs although, in severe progressive cases, it may be used in patients not previously treated with methotrexate or other DMARDs; in the USA it may be used for treating early rheumatoid arthritis. Infliximab is given in a dose of 3 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. For the first 3 doses infliximab should be infused for at least 2 hours; however, UK licensed product information suggests that subsequent infusion times may be reduced to a minimum period of 1 hour in those who tolerate the initial infusions. A clinical response is usually achieved within 12 weeks of starting treatment. Patients with an inadequate response during this period or who later relapse may benefit by increasing the dose: in the UK, a maximum dose of 7.5 mg/kg every 8 weeks (with increases made in steps of 1.5 mg/kg) is recommended whereas, in the USA, a maximum dose of 10 mg/kg is allowed. Alternatively, a dose of 3 mg/kg may be given as often as every 4 weeks in such patients. Continuing therapy in those who show no response within the first 12 weeks of treatment or after dose adjustment should be carefully reconsidered: in the UK NICE recommends that infliximab be withdrawn if there is no adequate response within 6 months of starting treatment.

Infliximab is used in the treatment of severe, active **Crohn's disease** (see Inflammatory Bowel Disease, p. 75.1) unresponsive to conventional treatment; in the USA, it is also licensed for use in moderate disease. Patients may be given an initial single dose of 5 mg/kg. This may be followed by a maintenance regimen of additional infusions of 5 mg/kg at 2 and 6 weeks after the initial infusion and then every 8 weeks thereafter, or the drug may be readministered when signs and symptoms of the disease recur (but see below). UK licensed product information does not recommend further doses in patients who are unresponsive after the first 2 doses; in the USA, a patient is not considered to be unresponsive until 3 doses have been given. US product information also suggests that doses of up to 10 mg/kg may be used in patients who relapse after an initial response. A similar regimen is used in patients with fistulising Crohn's disease although therapy should not be considered ineffective until after the third dose of infliximab. Infliximab is also used in the treatment of moderate to severe, active **ulcerative colitis** (see Inflammatory Bowel Disease, p. 75.1) in patients unresponsive to conventional therapy; the recommended dose is 5 mg/kg given in a regimen similar to that used for Crohn's disease (see above). Therapy should not be considered ineffective until after the third dose of infliximab.

In the treatment of active **ankylosing spondylitis** (see Spondyloarthropathies, p. 75.2), UK licensed product information recommends that infliximab should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used in early treatment. The initial dose is 5 mg/kg, repeated at 2 and 6 weeks and then every 6 to 8 weeks thereafter; if there is no response after 2 doses no further treatment should be given.

Infliximab is also used in the treatment of active and progressive **psoriatic arthritis** (see Spondyloarthropathies, p. 75.2); in the UK, its use is limited to patients who have had an inadequate response to standard DMARDs but, as before, US licensed product information allows earlier use. In the USA, it may be given with or without methotrexate; however, UK product information only recommends use without methotrexate in those patients who are intolerant of, or have contra-indications to, such treatment. It is given in a single dose of 5 mg/kg, repeated at 2 and 6 weeks and then every 8 weeks thereafter. Guidance issued by NICE in the UK recommends that treatment with infliximab is stopped after 12 weeks in those who show an inadequate response.

Infliximab is used in the treatment of severe **plaque psoriasis** (p. 75.2) in patients unresponsive to, or intolerant of, conventional systemic therapy including photochemotherapy; in the UK, it is also licensed for use in moderate disease. Infliximab is given in a dose of 5 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. Treatment should be stopped after 14 weeks (4 doses) in patients who show no response.

If the signs and symptoms of rheumatoid arthritis or Crohn's disease recur infliximab may be readministered if within 16 weeks of the last infusion. **Readministration** after a drug-free interval of more than 16 weeks may be associated with an increased risk of delayed hypersensitivity (see Delayed Reactions, p. 76.3) and consequently is not recommended. Recommendations regarding the readministration of infliximab for other indications (other than those detailed above) have not been established. Limited data from readministration with a single dose of infliximab in psoriasis after an interval of 20 weeks suggest reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared with the initial regimen.

For details of infliximab use in children, see p. 75.1.

Administration in children. Infliximab is licensed for use in moderate to severe, active Crohn's disease and ulcerative colitis in children aged 6 years and over who have not responded to conventional therapy, or who have contra-indication for or are intolerant of such treatments; doses are the same as those used in adults (see p. 74.2). In the treatment of Crohn's disease, UK licensed product information suggests that the dosage interval may be adjusted to maintain any benefits; however, further treatment is unlikely to be of use in patients not responding within the first 10 weeks. In ulcerative colitis, further treatment is not recommended in those who do not respond within the first 8 weeks.

Although unlicensed for such use in the UK, infliximab has also been used in children with fistulising Crohn's disease; the *BNFC* recommends that those aged 6 to 18 years may be treated with the same dosage regimen that is used for this indication in adults (see p. 74.2).

Asthma. TNF inhibitors such as infliximab have been investigated in the treatment of refractory asthma (p. 1195.2).[1,2] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[2]

1. Erin EM, *et al*. The effects of a monoclonal antibody directed against tumor necrosis factor- α in asthma. *Am J Respir Crit Care Med* 2006; **174:** 753–62.
2. Brightling C, *et al*. Targeting TNF-alpha: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Hidradenitis suppurativa. TNF inhibitors such as infliximab and adalimumab have been used[1-3] with some success in the treatment of hidradenitis suppurativa, a chronic skin disease characterised by purulent inflammation of occluded hair follicles and sebaceous glands typically in intertriginous areas such as the axillae and groin.

1. Haslund P, *et al*. Treatment of hidradenitis suppurativa with tumour necrosis factor- α inhibitors. *Acta Derm Venereol* 2009; **89:** 595–600.
2. Kimball AB, *et al*. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157:** 846–55.
3. van Rappard DC, *et al*. The off-label treatment of severe hidradenitis suppurativa with TNF- α inhibitors: a systematic review. *J Dermatolog Treat* 2013; **24:** 392–404.

Inflammatory bowel disease. Infliximab is used in adults for the treatment of Crohn's disease[1-6] and ulcerative colitis[2,7-9] (p. 1811.3); it is also used in children.[10-13]

In the treatment of ulcerative colitis, guidance issued by NICE recommends against the use of infliximab in subacute manifestations of moderately to severely active disease (defined as that which would normally be managed in an outpatient setting, and does not require hospitalisation or the consideration of urgent surgical intervention).[14] In the treatment of acute exacerbations of severely active ulcerative colitis, NICE guidance recommends use of infliximab only in patients in whom ciclosporin is contra-indicated or clinically inappropriate; otherwise, it should only be used for such treatment in the context of clinical studies.[15]

1. Siddiqui MAA, Scott LJ. Infliximab: a review of its use in Crohn's disease and rheumatoid arthritis. *Drugs* 2005; **65:** 2179–2208. Correction. *ibid*. 2006; **66:** 1359.
2. Rutgeerts P, *et al*. Review article: infliximab therapy for inflammatory bowel disease—seven years on. *Aliment Pharmacol Ther* 2006; **23:** 451–63.
3. Osterman MT, Lichtenstein GR. Infliximab in fistulizing Crohn's disease. *Gastroenterol Clin North Am* 2006; **35:** 795–820.
4. Etchevers MJ, *et al*. Optimizing the use of tumour necrosis factor inhibitors in Crohn's disease: a practical approach. *Drugs* 2010; **70:** 109–20.
5. NICE. Infliximab (review) and adalimumab for the treatment of Crohn's disease (includes a review of NICE technology appraisal guidance 40): Technology Appraisal Guidance 187 (issued May 2010). Available at: http://www.nice.org.uk/nicemedia/live/12985/48552/48552.pdf (accessed 19/10/10)
6. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 04/05/12).
7. Lawson MM, *et al*. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
8. Aberra FN, Lichtenstein GR. Infliximab in ulcerative colitis. *Gastroenterol Clin North Am* 2006; **35:** 821–36.
9. Gisbert JP, *et al*. Systematic review: infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25:** 19–37.
10. de Ridder L, *et al*. Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45:** 3–14.
11. Veres G, *et al*. Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 2007; **67:** 1703–23.
12. Parashette KR, *et al*. Infliximab therapy in pediatric Crohn's disease: a review. *Clin Exp Gastroenterol* 2010; **3:** 57–63.
13. Hyams J, *et al*. T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2012; **10:** 391–9.
14. NICE. Infliximab for subacute manifestations of ulcerative colitis: Technology Appraisal Guidance 140 (issued April 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA140Guidance.pdf (accessed 28/07/08)
15. NICE. Infliximab for acute exacerbations of ulcerative colitis: Technology Appraisal Guidance 163 (issued December 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA163Guidance.pdf (accessed 27/10/09)

Leprosy. Infliximab has been used[1] in the treatment of recurrent type 2 (erythema nodosum leprosum) lepra reactions (p. 190.3). However, 2 cases of rapidly progressive leprosy developing in patients given infliximab for rheumatoid arthritis have also been described;[2] reversal (type 1) reactions occurred in both when infliximab was stopped.

1. Faber WR, *et al*. Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med* 2006; **355:** 739.
2. Scollard DM, *et al*. Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis* 2006; **43:** e19–e22.

Psoriasis. Infliximab is used in the treatment of moderate to severe plaque psoriasis (p. 1688.1).[1-8] However, TNF inhibitors have been associated with various adverse effects on the skin, see Effects on the Skin, p. 77.1.

1. Benoit S, *et al*. Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. *Br J Dermatol* 2004; **150:** 1009–12.
2. Gottlieb AB, *et al*. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51:** 534–42.
3. Reich K, *et al*. EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366:** 1367–74.
4. Reich K, *et al*. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154:** 1161–8.
5. Smith CH, *et al*. Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006; **155:** 160–9.
6. Menter A, *et al*. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2006; **56:** 31. e1–15.
7. Poulalhon N, *et al*. A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. *Br J Dermatol* 2007; **156:** 329–36.
8. NICE. Infliximab for the treatment of adults with psoriasis: Technology Appraisal Guidance 134 (issued January 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA134Guidance.pdf (accessed 22/08/08)

Rheumatoid arthritis. TNF inhibitors play an increasingly important role in the management of rheumatoid arthritis; they tend to be reserved for patients who are unresponsive to more conventional disease-modifying antirheumatic drugs (DMARDs), although some favour use earlier in management.

Some references[1-10] to the use of infliximab in rheumatoid arthritis (p. 13.2) and juvenile idiopathic arthritis (p. 12.1).

1. Maini R, *et al*. ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354:** 1932–9.
2. Lipsky PE, *et al*. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1594–1602.
3. Maini RN, *et al*. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004; **50:** 1051–65.
4. Quinn MA, *et al*. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 27–35.
5. Voulgari PV, *et al*. Infliximab therapy in established rheumatoid arthritis: an observational study. *Am J Med* 2005; **118:** 515–20.
6. Chen Y-F, *et al*. NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 31/10/08)
7. Ruperto N, *et al*. Paediatric Rheumatology International Trials Organisation. Pediatric Rheumatology Collaborative Study Group. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3096–3106.
8. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36): Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 03/11/08)
9. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
10. Wiens A, *et al*. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. *Pharmacotherapy* 2010; **30:** 339–53.

Sarcoidosis. For a mention of possible benefit from infliximab in sarcoidosis, see p. 1612.2. However, there have been individual case reports of TNF-inhibitor-induced sarcoidosis (see p. 77.3).

Spondyloarthropathies. References[1-9] to the use of infliximab in the treatment of ankylosing spondylitis and psoriatic arthritis (p. 14.3). Guidance issued by NICE in the UK does not recommend the use of infliximab for the treatment of ankylosing spondylitis; adalimumab or etanercept are preferred.[7]

1. Brandt J, *et al*. Infliximab in the treatment of active and severe ankylosing spondylitis. *Clin Exp Rheumatol* 2002; **20** (suppl 28): S106–S110.
2. Brandt J, *et al*. Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-alpha monoclonal antibody infliximab. *J Rheumatol* 2002; **29:** 118–22.
3. Collantes-Estévez E, *et al*. Infliximab in refractory spondyloarthropathies: a multicentre 38 week open study. *Ann Rheum Dis* 2003; **62:** 1239–40.
4. Robinson DM, Keating GM. Infliximab: in ankylosing spondylitis. *Drugs* 2005; **65:** 1283–91.
5. Rott S, *et al*. Successful treatment of severe psoriatic arthritis with infliximab in an 11-year-old child suffering from linear psoriasis along lines of Blaschko. *Br J Dermatol* 2007; **157:** 191–2.
6. McLeod C, *et al*. NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation (issued August 2007). Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 31/10/08)
7. NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis: Technology Appraisal Guidance 143 (issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf (accessed 31/10/08)
8. Baraliakos X, Braun J. Anti-TNF- α therapy with infliximab in spondyloarthritides. *Expert Rev Clin Immunol* 2010; **6:** 9–19.
9. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)

Uveitis. Infliximab has been tried[1-12] with some success in the treatment of uveitis (p. 1615.1) including that associated with Behçet's syndrome (p. 1601.1). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with infliximab may improve ocular symptoms in addition to its effect on the primary disorder.

1. Murphy CC, *et al*. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology* 2004; **111:** 352–6.
2. Bodaghi B, *et al*. Therapeutic use of infliximab in sight threatening uveitis: retrospective analysis of efficacy, safety, and limiting factors. *Ann Rheum Dis* 2005; **64:** 962–4.
3. Braun J, *et al*. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; **52:** 2447–51.
4. Richards JC, *et al*. Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Experiment Ophthalmol* 2005; **33:** 461–8.
5. Lindstedt EW, *et al*. Anti-TNF- α therapy for sight threatening uveitis. *Br J Ophthalmol* 2005; **89:** 533–6.
6. Saurenmann RK, *et al*. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006; **45:** 982–9.
7. Kahn P, *et al*. Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006; **113:** 860–4.
8. Guignard S, *et al*. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006; **65:** 1631–4.
9. Tynjälä P, *et al*. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007; **66:** 548–50.
10. Ardoin SP, *et al*. Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol* 2007; **144:** 844–9.
11. Pipitone N, *et al*. Infliximab for the treatment of Neuro-Behçet's disease: a case series and review of the literature. *Arthritis Rheum* 2008; **59:** 285–90.
12. Yamada Y, *et al*. Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. *Br J Ophthalmol* 2010; **94:** 284–8.

Vasculitic syndromes. For a preliminary report on the use of infliximab in Takayasu's arteritis, see p. 1614.3. Infliximab has also been investigated in the management of Kawasaki disease (p. 2405.2) in patients who are unresponsive to standard treatment.[1-4]

1. Burns JC, *et al*. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.
2. Saji T, Kemmotsu Y. Infliximab for Kawasaki syndrome. *J Pediatr* 2006; **149:** 426.
3. O'Connor MJ, Saulsbury FT. Incomplete and atypical Kawasaki disease in a young infant: severe, recalcitrant disease responsive to infliximab. *Clin Pediatr (Phila)* 2007; **46:** 345–8.
4. Burns JC, *et al*. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008; **153:** 833–8.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions during or within 1 to 2 hours of infusion are common with infliximab, and other TNF inhibitors, particularly with the first or second dose. Symptoms include fever, chills, pruritus, urticaria, dyspnoea, chest pain, and hypertension or hypotension. Mild reactions may respond to a reduced rate of infusion or a temporary interruption. If reactions are more severe, therapy should be stopped. Pretreatment with paracetamol, corticosteroids, and antihistamines may be considered. TNF inhibitors should only be given where facilities for resuscitation are available. Delayed reactions have occurred 3 to 12 days after infliximab treatment; symptoms include myalgia, arthralgia, fever, and rash. Similar delayed reactions may also be seen when infliximab has been restarted after an extended period without treatment (see p. 76.3).

Other, common, adverse effects include nausea and vomiting, abdominal pain, diarrhoea, fatigue, dizziness, headache, and back pain. Antibodies to infliximab (human antichimeric antibodies) may develop, and are associated with an increased incidence of hypersensitivity reactions. Antinuclear antibodies and anti-double-stranded-DNA antibodies have also developed with TNF inhibitor therapy. A lupus-like syndrome has occurred rarely; treatment should be stopped if it develops. Sarcoidosis or a sarcoid-like reaction has also been reported rarely.

Infections are common in patients treated with infliximab or other drugs that inhibit TNF, and most often affect the upper respiratory tract and the urinary tract. TNF inhibitors have also been associated rarely with the development of serious opportunistic infections, sepsis, pneumonia, and onset or reactivation of tuberculosis (see Infection, p. 77.2), particularly in patients with underlying conditions predisposing them to infections; in some cases death has resulted. TNF inhibitors should not be given to patients with severe infection, including active tuberculosis, abscesses, and opportunistic infections, and should be stopped if these develop. Patients should be evaluated for latent and active tuberculosis before beginning therapy; if evidence of latent tuberculosis is found, the risks and benefits of treatment should be considered carefully and chemoprophylaxis should be started before giving a TNF inhibitor. They should also be used with care in those with chronic infections, a history of recurrent infections, or with underlying conditions that may predispose to infections. Patients with fistulising Crohn's disease with suppurative fistulas should not be given infliximab until possible infection sources such as abscesses have been ruled out. Patients should be instructed to seek medical advice if symptoms suggestive of tuberculosis (such as persistent cough, weight loss, or low grade fever) occur. Patients should be monitored for signs of infection after stopping treatment: for those TNF inhibitors with long half-lives (such as adalimumab, certolizumab, golimumab, and infliximab) monitoring should continue for up to 6 months; because of its relatively shorter half-life, the elimination of etanercept may be quicker.

There have been rare reports of severe hepatic reactions such as acute liver failure, jaundice, hepatitis, and cholestasis with infliximab; some cases have been fatal or required transplantation. Patients with signs or symptoms of hepatotoxicity should be evaluated and infliximab should be stopped in those patients with jaundice or marked elevations in liver enzyme values. Infliximab and other TNF inhibitors have also been associated with the reactivation of hepatitis B in chronic carriers, which has resulted in fatalities in some cases. Patients at risk of hepatitis B infection should be screened before starting treatment; it is recommended that carriers treated with a TNF inhibitor are closely monitored during, and for several months after stopping, treatment.

Blood dyscrasias, including leucopenia, thrombocytopenia, pancytopenia, and aplastic anaemia, have been reported rarely with TNF inhibitors; in some cases the outcome was fatal. They should be used with caution in patients with a history of blood dyscrasias.

Rare, and sometimes fatal, cases of interstitial lung disease including pulmonary fibrosis and pneumonitis have been reported with TNF inhibitors.

Infliximab and other TNF inhibitors are also associated with an increased incidence of malignancies including lymphomas and leukaemias (see also Carcinogenicity, below), although occurrences are rare. Some groups of patients treated with TNF inhibitors may already have an increased background risk of developing malignancies, regardless of drug treatment. Care has been advocated in patients with a history of malignancy.

Anaphylactic reactions have been reported rarely with TNF inhibitors. Infliximab should be avoided in patients with a history of hypersensitivity to the drug or other murine proteins.

TNF inhibitors have been associated in rare cases with seizures and clinical or radiological worsening of demyelinating disorders such as multiple sclerosis or optic neuritis; care is required in prescribing it to patients with such disorders or symptoms suggestive of their onset.

Worsening and, in some cases, new-onset heart failure has been reported with TNF inhibitors (see Effects on the Heart, below). In the UK, infliximab is contra-indicated in patients with moderate to severe heart failure (NYHA class III or IV); however, US licensed product information advises that doses up to 5 mg/kg may be used in such patients. It should be used with caution in patients with mild heart failure (NYHA class I or II). All patients with heart failure should be closely monitored and infliximab stopped in those who develop new or worsening symptoms of heart failure. Similar recommendations are given for the TNF inhibitors adalimumab, certolizumab, etanercept, and golimumab although UK licensed information for etanercept only advises caution in patients with heart failure.

General references.

1. Hansen RA, *et al*. Serious adverse events with infliximab: analysis of spontaneously reported adverse events. *Clin Gastroenterol Hepatol* 2007; **5:** 729–35.
2. Lecluse LLA, *et al*. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol* 2008; **159:** 527–36.
3. Zabana Y, *et al*. Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice. *Aliment Pharmacol Ther* 2010; **31:** 553–60.
4. O'Donnell S, *et al*. Safety of infliximab in 10 years of clinical practice. *Eur J Gastroenterol Hepatol* 2011; **23:** 603–6.

Carcinogenicity. Malignancies, especially lymphomas, have been seen in patients treated with TNF inhibitors for rheumatoid arthritis and Crohn's disease;[1] however, the suggestion of a causal relationship is controversial. A meta-analysis[2] in 2006 identified 24 published reports of malignancies in 3493 study patients with rheumatoid arthritis who had received at least one dose of a TNF inhibitor (adalimumab or infliximab) along with 2 cases in 1512 control patients; further, unpublished, cases were also found using FDA data to give 29 malignancies in the treatment groups and 3 in the control groups. Based on these figures, there was a 3.3-fold increase in the risk of malignancy in patients receiving TNF inhibitors when compared with controls. These results have, however, been criticised[3] on several points including the difficulty in applying them to current practice because etanercept was not included in the analysis, and, in particular, the unexpectedly low rate of malignancies in the control groups. Other studies in patients with rheumatoid arthritis[4-6] and Crohn's disease[7] have generally concluded that the overall risk of malignancies is not significantly increased in patients taking TNF inhibitors when compared with patients who have not taken these drugs. Some studies[4,8] in patients with rheumatoid arthritis have, however, shown a possible increased risk of lymphoma with TNF inhibitor treatment, but caution in interpreting these results was recommended as they were based on a small number of cases; in addition, the background risk of lymphoma is increased in rheumatoid arthritis regardless of treatment.

Rare cases of hepatosplenic T-cell lymphoma have been seen in adolescents and young adults given infliximab for the treatment of Crohn's disease. In July 2006, the manufacturer was aware of 6 cases of this type of lymphoma in 5 adolescents aged 12 to 19 years and one 31-year-old adult;[9] 4 of the 6 cases occurred in males. The treatment duration ranged from 1 or 2 infusions to over 4 years of therapy; in all cases, patients were also taking or had taken azathioprine or 6-mercaptopurine. This type of lymphoma is aggressive and 5 of the above patients died. A causal relationship was not clearly established although it could neither be excluded. Further cases have since been reported.[10] Hepatosplenic T-cell lymphoma has also been associated with adalimumab. In July 2008, the manufacturer was aware of 3 cases;[11] of these, 2 had occurred in young men also taking azathioprine or 6-mercaptopurine for inflammatory bowel disease. (Details of the third case were not provided).

Concerns about the risk of cancer in children and adolescents receiving TNF inhibitors prompted the FDA[12] to review all cases of cancer in children taking adalimumab, etanercept, or infliximab. (Certolizumab and golimumab were not included in the review as neither were licensed for use in children and were minimally used during the review period.) In August 2009, their findings were reported. Forty eight cases of malignancies in children and adolescents were identified; of these, about half were lymphomas, including Hodgkin's and non-Hodgkin's lymphomas. Other reported malignancies included leukaemia, melanoma, and solid organ cancers; malignancies that are rare in children such as leiomyosarcoma, hepatic malignancies, and renal cell carcinoma were also reported. About 88% of the 48 patients were also taking other immunosuppressants such as azathioprine and methotrexate. There were 11 fatalities reported, comprising 9 cases of hepatosplenic T-cell lymphoma, 1 of T-cell lymphoma, and 1 of sepsis after achieving remission of the lymphoma. The FDA considered that there is an increased risk of malignancy with TNF inhibitors although they were unable to characterise the strength of this association due to factors such as the relatively rare occurrence of these cancers, the limited number of paediatric patients on TNF inhibitor therapy, and the possible role of concurrent immunosuppressants.

In a second analysis the FDA[12] reviewed 147 reports of leukaemia associated with TNF inhibitors in all patients, including adults. Of these, the most frequently reported were acute myeloid leukaemia (44 cases), chronic lymphocytic leukaemia (31 cases), and chronic myeloid leukaemia (23 cases). About 61% of the patients were also receiving other immunosuppressants. There were 30 fatalities reported; of these, 26 were due to leukaemia. The average time to onset of leukaemia was within the first 2 years of TNF inhibitor therapy. Based on the available data, the FDA concluded that there is a possible association between TNF inhibitor therapy and leukaemia.

1. Brown SL, *et al*. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002; **46:** 3151–8.
2. Bongartz T, *et al*. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295:** 2275–85. Correction. *ibid*.; 2482.
3. Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. *Arthritis Res Ther* 2006; **8:** 111.
4. Geborek P, *et al*. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; **64:** 699–703.
5. Setoguchi S, *et al*. Tumor necrosis factor α antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; **54:** 2757–64. Correction. *ibid*.; 3134.
6. Askling J, *et al*. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor α therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009; **60:** 3180–9.
7. Biancone L, *et al*. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 2006; **55:** 228–33.
8. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; **50:** 1740–51.
9. Schering, Canada. Health Canada endorsed important safety information on Remicade (infliximab) (issued 24th July, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/remicade_3_hpc-cps-eng.pdf (accessed 29/08/08)
10. Mackey AC, *et al*. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44:** 265–7.
11. Abbott, UK. Direct healthcare professional communication on reports of hepatosplenic T-cell lymphoma in patients treated with Humira (adalimumab) (issued 16th July, 2008). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON023075 (accessed 03/11/08)
12. FDA. Information for healthcare professionals: tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) (issued 4th August, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174474.htm (accessed 26/10/09)

Delayed reactions. Ten of 37 patients with Crohn's disease re-treated with infliximab after a 2- to 4-year period without treatment had delayed hypersensitivity reactions, of which 6 were considered serious. None of the patients had had infusion-related adverse effects with their original infliximab therapy. Adverse reactions developed in 9 of the 23 patients originally treated with a discontinued liquid formulation, and in 1 of the 14 patients who previously received the marketed formulation, leading to speculation that the formulation may have been a contributing factor.

Effects on blood lipids. A 35-year-old man with psoriatic arthritis and psoriasis developed markedly elevated triglyceride levels and a mildly increased total cholesterol level after a single infusion of infliximab;[1] previous tests had shown a mild hypertriglyceridaemia for which he had received no treatment. No further doses of infliximab were given and his triglyceride levels subsequently improved. Similarly, hypertriglyceridaemia and hypercholesterolaemia developed in a 39-year-old man with psoriatic arthritis and psoriasis after 8 weeks of treatment with adalimumab;[2] triglyceride levels were markedly elevated after 3 months of therapy although total cholesterol level remained unchanged. Levels improved 4 weeks after stopping the drug.

1. Antoniou C, *et al*. Elevated triglyceride and cholesterol levels after intravenous antitumour necrosis factor-α therapy in a patient with psoriatic arthritis and psoriasis vulgaris. *Br J Dermatol* 2007; **156:** 1090–1.
2. Stinco G, *et al*. Hypertriglyceridaemia during treatment with adalimumab in psoriatic arthritis. *Br J Dermatol* 2007; **157:** 1273–4.

Effects on the CNS. Aseptic meningitis developed in a patient after his fifth injection of infliximab for rheumatoid arthritis.[1] Similar symptoms also occurred after a sixth injection.

Two patients with inflammatory bowel disease developed acute motor neuropathy with multiple conduction blocks after infliximab treatment; both patients improved after infliximab was stopped.[2] Similar adverse effects were reported in 2 further patients:[3] one was taking etanercept for rheumatoid arthritis and the other infliximab for ankylosing spondylitis. Three cases of bilateral optic neuropathy associated with infliximab therapy have also been reported.[4] Other neuropathies have been associated with TNF inhibitor treatment, including Guillain-Barré syndrome.[5]

1. Marotte H, *et al*. Infliximab-induced aseptic meningitis. *Lancet* 2001; **358:** 1784.
2. Singer OC, *et al*. Acute neuropathy with multiple conduction blocks after TNFα monoclonal antibody therapy. *Neurology* 2004; **63:** 1754.
3. Richez C, *et al*. Neuropathy resembling CIDP in patients receiving tumor necrosis factor-α blockers. *Neurology* 2005; **64:** 1468–70.
4. ten Tusscher MPM, *et al*. Bilateral anterior toxic optic neuropathy and the use of infliximab. *BMJ* 2003; **326:** 579.
5. Stübgen J-P. Tumor necrosis factor-α antagonists and neuropathy. *Muscle Nerve* 2008; **37:** 281–92.

Effects on the heart. The FDA has reported[1] on 47 patients who developed heart failure during long-term therapy with TNF antibodies (etanercept and infliximab) for arthritic conditions or Crohn's disease. Of these, 38 developed new-onset heart failure, 19 having documented risk factors for heart failure, and 9 had exacerbation of existing heart failure. The median time to new-onset heart failure was 3.5 months. However, studies[2-4] investigating a possible association between TNF inhibitors and the development of heart failure have been equivocal and further investigation is warranted.

Preliminary investigations on the use of infliximab in the treatment of moderate to severe heart failure failed to show any clinical improvement in patients given infliximab 5 mg/kg or 10 mg/kg when compared with placebo;[5] in addition, those given the higher dose had an increased risk of death or hospitalisation due to worsening heart failure.

1. Kwon HJ, *et al*. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003; **138:** 807–11.
2. Jacobsson LTH, *et al*. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005; **32:** 1213–18.
3. Curtis JR, *et al*. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-α antagonists. *Rheumatology (Oxford)* 2007; **46:** 1688–93.
4. Listing J, *et al*. Does tumor necrosis factor α inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008; **58:** 667–77.
5. Chung ES, *et al*. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α , in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) trial. *Circulation* 2003; **107:** 3133–40.

Effects on the lungs. Infliximab treatment has been associated with a fatal exacerbation of previously asymptomatic fibrosing alveolitis in 3 patients with chronic rheumatoid arthritis;[1] all 3 patients were also taking azathioprine and prednisolone. There was no evidence of infection or other underlying causes for the decline in respiratory function.

1. Ostor AJK, *et al*. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 2004; **329:** 1266.

Effects on the skin. Patients with rheumatoid arthritis receiving TNF inhibitor therapy are more likely to develop adverse skin reactions than those who are not.[1] Of 289 patients taking TNF inhibitors (infliximab, etanercept, adalimumab, and lenercept), 72 (25%) reported 128 dermatological events including skin infections, eczema, drug-related eruptions, and malignancies such as actinic keratosis; of the 289 patients not taking TNF inhibitors, 37 (13%) reported dermatological events.

In another review,[2] cutaneous adverse effects were seen in 35 out of 150 patients receiving TNF inhibitors (adalimumab, etanercept, or infliximab) for rheumatic disorders; cases included dermatitis herpetiformis and leucocytoclastic vasculitis although eczematous and skin infections were more common or infectious. Perhaps unexpectedly, psoriasis-like lesions were seen in 8 patients, 6 of whom had no history of psoriasis; similar effects have also been noted in other patients with rheumatoid arthritis[3,4] or Crohn's disease[5,6] (see also below).

Rare cases of serious skin reactions have been associated with TNF inhibitor treatment.[7] Since approval in 1998, the FDA has received 15 cases of erythema multiforme, 5 cases of Stevens-Johnson syndrome, and 1 case of toxic epidermal necrolysis associated with infliximab; cases for etanercept, approved in the same year, included 13 reports of erythema multiforme, and 4 reports each of Stevens-Johnson syndrome and toxic epidermal necrolysis. For adalimumab, which was marketed late in 2002, there have been 4 cases of erythema multiforme and 2 of Stevens-Johnson syndrome.

In August 2009, the FDA[8] reported that it had reviewed 69 cases of new-onset psoriasis, including pustular (17 cases) and palmoplantar (15 cases) psoriasis, in all patients receiving TNF inhibitor therapy for auto-immune and rheumatic disorders other than psoriasis and psoriatic arthritis; of these, 2 cases were of children and 12 had resulted in hospitalisation. The time to onset of psoriasis ranged from weeks to years after starting TNF inhibitor therapy; symptoms improved in the majority of patients after stopping the drug. None of the cases had reported pre-existing psoriasis.

Cutaneous pseudolymphoma has been reported after 2 doses of adalimumab in a patient with psoriasis and recurred when infliximab treatment was introduced;[9] both eruptions resolved completely on withdrawal of the drug. Etanercept has also been associated with cutaneous pseudolymphoma[10] in a patient with rheumatoid arthritis. The eruption occurred after one year of treatment and resolved on withdrawal; subsequent treatment with adalimumab did not induce the skin reaction.

For reports of drug-induced lupus or lupus-like syndrome associated with TNF inhibitors, see Lupus, below.

1. Flendrie M, *et al*. Dermatological conditions during TNF-α -blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; **7:** R666–R676.
2. Lee H-H, *et al*. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-α antagonists. *Br J Dermatol* 2007; **156:** 486–91.
3. Dereure O, *et al*. Psoriatic lesions induced by antitumour necrosis factor-α treatment: two cases. *Br J Dermatol* 2004; **151:** 506–7.
4. Teraki Y, *et al*. A case of generalized psoriasiform and pustular eruption induced by infliximab: evidence for skin-homing Th17 in the pathogenesis. *Br J Dermatol* 2010; **163:** 1347–51.
5. Verea MM, *et al*. Psoriasiform eruption induced by infliximab. *Ann Pharmacother* 2004; **38:** 54–7.
6. Conklin LS, *et al*. Rash induced by anti-tumor necrosis factor agents in an adolescent with Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2010; **7:** 174–7.
7. FDA. Tumor necrosis factor alpha (TNF-α) antagonists. Infliximab (marketed as Remicade), etanercept (marketed as Enbrel), and adalimumab (marketed as Humira). Serious skin reactions. *FDA Drug Safety Newsletter* 2007; **1:** 18–20. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109169 (accessed 28/07/10)
8. FDA. Information for healthcare professionals: tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) (issued 4th August, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174474.htm (accessed 27/10/09)
9. Imafuku S, *et al*. Cutaneous pseudolymphoma induced by adalimumab and reproduced by infliximab in a patient with arthropathic psoriasis. *Br J Dermatol* 2012; **166:** 675–8.
10. Guis S, *et al*. Cutaneous pseudolymphoma associated with a TNF-alpha inhibitor treatment: etanercept. *Eur J Dermatol* 2008; **18:** 474–6.

Infection. TNF inhibitors (such as infliximab, adalimumab, certolizumab, etanercept, and golimumab) are known to suppress the immune system and infections are commonly reported with these drugs. However, serious, life-threatening, opportunistic infections involving multiple organ systems and sites have also been reported rarely in patients taking TNF inhibitors.[1-7] Of particular concern are bacterial infections such as legionellosis, leprosy (see also under Uses and Administration, p. 75.1), listeriosis, nocardiosis, tuberculosis, and nontuberculous mycobacteria, invasive fungal infections such as aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and pneumocystosis, viruses such as hepatitis B, and parasitic organisms. Infections frequently have been disseminated rather than localised.

The risk for developing an opportunistic infection is higher for patients who are 65 years of age and older and for those taking concomitant immunosuppressive agents. Delay in diagnosis and treatment of infections, especially fungal, has resulted in fatalities; patients should be closely monitored for signs and symptoms of systemic infection before, during, and after treatment with TNF inhibitors. Empirical antifungal therapy may be considered in those thought to be at risk of endemic fungal infections.[8,9]

There have been reports of onset or reactivation of tuberculosis in patients treated with infliximab and other TNF inhibitors, including cases of miliary tuberculosis and unusual extrapulmonary disease.[1,2,4,5] Guidelines have therefore been issued by the British Thoracic Society[10] to quantify the risks of reactivation of tuberculosis with TNF inhibitors and to advise on the treatment of such infection in patients being assessed for TNF inhibitor therapy. Other guidelines[11] have also been issued based on a review of the literature and current national recommendations.

1. CSM/MCA. Infliximab (Remicade) and tuberculosis. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
2. Schaible TF [Centocor, Inc. Important drug warning (issued 5th October, 2001). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm174242 (accessed 28/07/10)
3. Wallis RS, *et al*. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004; **38:** 1261–5. Correction. *ibid*.; **39:** 1254–5.
4. Health Canada. Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis. *Can Adverse React News* 2004; **14** (4): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 29/08/08)
5. Mohan AK, *et al*. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis* 2004; **39:** 295–9.
6. Tsiodras S, *et al*. Fungal infections complicating tumor necrosis factor α blockade therapy. *Mayo Clin Proc* 2008; **83:** 181–94.
7. FDA. Drug safety communication: drug labels for the tumor necrosis factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria (issued 7th September, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm270849.htm (accessed 11/10/11)
8. FDA. Information for healthcare professionals: Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab) (issued 4th September, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm (accessed 27/10/09)
9. Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-α inhibitor therapy. *Drugs* 2009; **69:** 1403–15.
10. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-α treatment. *Thorax* 2005; **60:** 800–5. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Anti%20TNF%20Treatment/Guidelines/antitnf_treatment.pdf (accessed 13/06/08)
11. Perlmutter A, *et al*. Tuberculosis and tumour necrosis factor-α inhibitor therapy: a report of three cases in patients with psoriasis—comprehensive screening and therapeutic guidelines for clinicians. *Br J Dermatol* 2009; **160:** 8–15.

Lupus. In June 2009, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] stated that 36 out of 87 reports of drug-induced lupus erythematosus or lupus-like syndrome received since 2003 were associated with TNF inhibitor therapy. Of these, 21 reports were associated with infliximab, 10 with adalimumab, and 5 with etanercept.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced lupus erythematosus: an emerging association with TNF inhibitors. *Aust Adverse Drug React Bull* 2009; **28:** 10–11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0906.pdf (accessed 27/10/09)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies infliximab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Sarcoidosis. Although infliximab has been tried in the treatment of sarcoidosis, the TNF inhibitors adalimumab, etanercept, and infliximab have been associated with reports of sarcoidosis in patients being treated for rheumatoid or psoriatic arthritis or plaque psoriasis.[1,2] Non-specific respiratory symptoms typically developed within about 2 years of starting treatment, and generally resolved within a year of stopping the drug.

1. Massara A, *et al*. Sarcoidosis appearing during anti-tumor necrosis factor α therapy: a new "class effect" paradoxical phenomenon. Two case reports and literature review. *Semin Arthritis Rheum* 2010; **39:** 313–19.
2. Pink AE, *et al*. The development of sarcoidosis on antitumour necrosis factor therapy: a paradox. *Br J Dermatol* 2010; **163:** 648–9.

Interactions

Live vaccines should not be given with infliximab or other drugs that inhibit TNF as the effect of such drugs on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with the interleukin-1 receptor antagonist anakinra may increase the risk of serious infections and neutropenia; such combinations are not recommended. A similar interaction has been seen with TNF inhibitors and the co-stimulation blocker abatacept.

Abatacept. Use of the TNF inhibitor etanercept with abatacept has resulted in an increase in the incidence of serious adverse effects including serious infections; in addition, there was no increase in clinical benefit.[1] Combinations of abatacept with TNF inhibitors are not recommended by UK licensed product information.

1. Weinblatt M, *et al*. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis* 2007; **66:** 228–34.

Anakinra. The incidence of serious infections, injection site reactions, and neutropenia is increased when anakinra is given with the TNF inhibitor etanercept.[1] In addition, the combination did not provide any further clinical benefit when compared with etanercept alone. Similar findings may be expected if anakinra is given with other TNF inhibitors.

1. Genovese MC, *et al*. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004; **50:** 1412–19.

Pharmacokinetics

Infliximab shows linear pharmacokinetics. It is distributed mainly in the vascular compartment and, after single doses, has a terminal elimination half-life of 8 to 9.5 days. After repeated doses, infliximab has been detected in serum for at least 8 weeks.

References.

1. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; **74** (suppl): 13–18.
2. Klotz U, *et al*. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; **46:** 645–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Remicade; ***Austral.***: Remicade; ***Austria***: Remicade; ***Belg.***: Remicade; ***Braz.***: Remicade; ***Canad.***: Remicade; ***Chile***: Remicade; ***China***: Remicade (类克); ***Cz.***: Remicade; ***Denm.***: Remicade; ***Fin.***: Remicade; ***Fr.***: Remicade; ***Ger.***: Remicade; ***Gr.***: Remicade; ***Hong Kong***: Remicade; ***Hung.***: Remicade; ***Indon.***: Remicade; ***Irl.***: Remicade; ***Israel***: Remicade; ***Ital.***: Remicade; ***Jpn***: Remicade; ***Malaysia***: Remicade; ***Mex.***: Remicade; ***Neth.***: Remicade; ***Norw.***: Remicade; ***NZ***: Remicade; ***Philipp.***: Remicade; ***Pol.***: Remicade; ***Port.***: Remicade; ***Rus.***: Remicade (Ремикейд); ***S.Afr.***: Revellex; ***Singapore***: Remicade; ***Spain***: Remicade; ***Swed.***: Remicade; ***Switz.***: Remicade; ***Thai.***: Remicade; ***Turk.***: Remicade; ***UK***: Remicade; ***Ukr.***: Remicade (Ремикейд); ***USA***: Remicade; ***Venez.***: Remicade.

Interleukin-6 Receptor Antagonists

Tocilizumab *(USAN, rINN)*

Atlizumab; MRA; R-1569; Tocilizumabum; Тоцилизумаб.

Immunoglobulin G1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer.

CAS — 375823-41-9.

ATC — L04AC07.

ATC Vet — QL04AC07.
UNII — I031V2H011.

Uses and Administration

Antagonists to the interleukin-6 receptor block the actions of interleukin-6 (p. 2534.1) and are under investigation for rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, Crohn's disease, and haemolytic anaemia.

Tocilizumab is a recombinant monoclonal antibody that targets the interleukin-6 receptor and is used for the treatment of rheumatoid arthritis (p. 13.2) and some forms of juvenile idiopathic arthritis (p. 12.1). It is also used for the treatment of Castleman's disease, a rare lymphoproliferative disorder.

Tocilizumab is given with methotrexate (p. 822.2) for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have not responded to, or are intolerant of, disease-modifying antirheumatic drugs including TNF antagonists. It may also be given as monotherapy in patients who are unable to tolerate methotrexate or in whom methotrexate would otherwise be inappropriate. Tocilizumab is given every 4 weeks by intravenous infusion over 1 hour in a dose of 8 mg/kg; the initial dose may be 4 or 8 mg/kg and the maximum dose per infusion is 800 mg. For doses in children with juvenile idiopathic arthritis see Administration in Children, below.

Neutrophil and platelet counts and liver enzyme values should be monitored during treatment, and in the event of altered or abnormal counts or levels, tocilizumab treatment may need to be suspended until there is improvement, or treatment stopped altogether.

References.

1. Nishimoto N, *et al*. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000; **95:** 56–61.
2. Ito H, *et al*. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; **126:** 989–96.
3. Nishimoto N. Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan. *Clin Rev Allergy Immunol* 2005; **28:** 221–30.
4. Maini RN, *et al*. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; **54:** 2817–29.
5. Paul-Pletzer K. Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs Today* 2006; **42:** 559–76.
6. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006; **2:** 619–26. Correction. *ibid*.; 691.
7. Kanda J, *et al*. Reversible cardiomyopathy associated with multicentric Castleman disease: successful treatment with tocilizumab, an anti-interleukin 6 receptor antibody. *Int J Hematol* 2007; **85:** 207–11.
8. Matsuyama M, *et al*. Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. *Intern Med* 2007; **46:** 771–4.
9. Smolen JS, *et al*. OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; **371:** 987–97.
10. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. *Am J Health-Syst Pharm* 2008; **65:** 1413–8.
11. Genovese MC, *et al*. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008; **58:** 2968–80.
12. Emery P, *et al*. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; **67:** 1516–23.
13. Oldfield V, *et al*. Tocilizumab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2009; **69:** 609–32.
14. Jones G, *et al*. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010; **69:** 88–96.
15. NICE. Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). Technology Appraisal Guidance 247 (issued February 2012). Available at: http://www.nice.org.uk/nicemedia/live/13669/58202/58202.pdf (accessed 02/08/13)
16. Gabay C, *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013; **381:** 1541–50.

Administration in children. Tocilizumab may be used alone or with methotrexate for the treatment of active systemic juvenile idiopathic arthritis or juvenile idiopathic polyarthritis, in children aged 2 years and over.[1-5] The recommended dose in systemic juvenile idiopathic arthritis is 12 mg/kg in children weighing less than 30 kg, or 8 mg/kg in those weighing 30 kg and over; doses should be given once every 2 weeks as an intravenous infusion over 1 hour. The recommended dose in juvenile idiopathic polyarthritis is 10 mg/kg in children weighing less than 30 kg, or 8 mg/kg in those weighing 30 kg and over; doses should be given once every 4 weeks as an intravenous infusion over 1 hour.

1. Yokota S, *et al*. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; **371:** 998–1006.
2. NICE. Tocilizumab for the treatment of systemic juvenile idiopathic arthritis: Technology Appraisal Guidance 238 (issued December 2011). Available at: http://www.nice.org.uk/nicemedia/live/13627/57489/57489.pdf (accessed 02/08/13)
3. Decelle K, Horton ER. Tocilizumab for the treatment of juvenile idiopathic arthritis. *Ann Pharmacother* 2012; **46:** 822–9.
4. De Benedetti F, *et al*. PRINTO. PRCSG. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; **367:** 2385–95.
5. Imagawa T, *et al*. Safety and efficacy of tocilizumab, an anti-IL-6-receptor monoclonal antibody, in patients with polyarticular-course juvenile idiopathic arthritis. *Mod Rheumatol* 2012; **22:** 109–15.

Adverse Effects and Precautions

The adverse effects reported most commonly with tocilizumab are headache, hypertension, nasopharyngitis, respiratory-tract infections, hypercholesterolaemia, and increased liver enzyme values. Conjunctivitis, dizziness, gastritis, mouth ulceration, pruritus, and rash have also been reported. Infusion reactions and hypersensitivity have also occurred and fatal anaphylaxis has been reported. If a hypersensitivity reaction is suspected, the infusion should be stopped immediately and appropriate treatment given. Tocilizumab treatment should be permanently discontinued in those patients.

Treatment with tocilizumab should not be started in patients with active infections. If a patient develops a serious infection during treatment, tocilizumab should be interrupted until the infection has been controlled. Tocilizumab should be used with caution in patients with a history of recurrent or chronic infections or with underlying disorders (e.g. diverticulitis, diabetes mellitus) that may increase the risk of developing infections. Patients should be screened for latent tuberculosis infection before starting tocilizumab treatment.

Complications of diverticulitis have occasionally been reported with tocilizumab, and it should therefore be used with caution in patients with a history of this condition or of gastrointestinal ulceration. Patients presenting with symptoms such as abdominal pain, haemorrhage, or unexplained change in bowel habits with fever that might indicate complicated diverticulitis should be evaluated promptly.

As raised liver enzyme values have been reported with tocilizumab, particularly when given with methotrexate, it should be used with caution in patients with hepatic impairment since its safety in such patients has not been adequately studied.

Decreases in neutrophil and platelet counts have occurred with tocilizumab given with methotrexate, and the risk of neutropenia may be increased in patients previously treated with a tumour necrosis factor antagonist. Tocilizumab should therefore be used with caution in patients with low neutrophil or platelet counts; it should not be started in treatment-naive patients if the absolute neutrophil count is below 2000 cells/microlitre.

Live or attenuated vaccines should not be given at the same time as tocilizumab because of lack of safety data. For similar reasons, tocilizumab is not recommended for use with other biological agents used in the treatment of rheumatoid arthritis.

Dizziness has been reported with tocilizumab; if affected, patients should avoid driving or operating machinery.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tocilizumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

During inflammation the expression of cytochrome P450 isoenzymes is suppressed by cytokines such as interleukin-6, and cytochrome P450 expression may therefore be normalised when treatment with a cytokine inhibitor such as tocilizumab is started. Also, since tocilizumab has a long elimination half-life, its effect on cytochrome P450 isoenzyme activity may last for several weeks after stopping treatment. Therefore when starting or stopping therapy with tocilizumab, patients being treated with drugs that are metabolised by cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4, (e.g. atorvastatin, calcium-channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses of these drugs may need to be adjusted.

References.

1. Kim S, *et al*. Interleukin-6 and cytochrome-P450, reason for concern? *Rheumatol Int* 2012; **32:** 2601–4.

Pharmacokinetics

Tocilizumab undergoes biphasic elimination from the circulation after intravenous dosing. Its clearance and half-life are concentration-dependent; at low serum concentrations, clearance is non-linear due to binding of tocilizumab to the interleukin-6 receptor, while at higher concentration the non-linear pathway is saturated and clearance is dominated by a linear clearance pathway mediated by the reticuloendothelial system. Furthermore, the non-linear pathway is not saturated continuously within a 4-week dosing interval, and half-life declines within the dosing period.

In adults with rheumatoid arthritis, tocilizumab has a half-life of up to 11 days at steady-state dosing of 4 mg/kg every 4 weeks, and up to 13 days with 8 mg/kg every 4 weeks. The half-life in patients with systemic juvenile idiopathic arthritis is up to 23 days, and up to 16 days for those with juvenile idiopathic polyarthritis.

References.

1. Frey N, *et al*. Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis. *J Clin Pharmacol* 2010; **50:** 754–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actemra; ***Austral.***: Actemra; ***Austria***: RoActemra; ***Belg.***: RoActemra; ***Braz.***: Actemra; ***Canad.***: Actemra; ***Chile***: Actemra; ***Cz.***: RoActemra; ***Denm.***: RoActemra; ***Fr.***: RoActemra; ***Ger.***: RoActemra; ***Gr.***: RoActemra; ***Hong Kong***: Actemra; ***Hung.***: RoActemra; ***Irl.***: RoActemra; ***Israel***: Actemra; ***Jpn***: Actemra; ***Mex.***: RoActemra; ***Neth.***: RoActemra; ***Norw.***: RoActemra; ***NZ***: Actemra; ***Philipp.***: Actemra; ***Pol.***: RoActemra; ***Port.***: RoActemra; ***Rus.***: Actemra (Актемра); ***Spain***: RoActemra; ***Swed.***: RoActemra; ***Switz.***: Actemra; ***Thai.***: Actemra; ***UK***: RoActemra; ***Ukr.***: Actemra (Актемра); ***USA***: Actemra.

Isonixin *(rINN)*

Isonixine; Isonixino; Isonixinum; Изониксин.
2-Hydroxy-*N*-(2,6-dimethylphenyl)nicotinamide.
$C_{14}H_{14}N_2O_2$=242.3
CAS — 57021-61-1.
UNII — BYX6E7M5QE.

Profile

Isonixin is an NSAID (p. 102.3) that has been used in the management of pain and inflammation associated with musculoskeletal and joint disorders. It has been used in doses of 400 mg two to four times daily orally or by rectal suppository. It has also been applied topically as a 2.5% cream.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Nixyn.

Multi-ingredient Preparations. ***Spain***: Nixyn.

Kebuzone *(rINN)*

Kebuzona; Kébuzone; Kebuzonum; Ketophenylbutazone; Кебузон.
4-(3-Oxobutyl)-1,2-diphenylpyrazolidine-3,5-dione.
$C_{19}H_{18}N_2O_3$=322.4
CAS — 853-34-9.
ATC — M01AA06.
ATC Vet — QM01AA06.
UNII — 4VD83UL6Y6.

Profile

Kebuzone, a phenylbutazone derivative, is an NSAID (p. 102.3). It has been given for musculoskeletal, joint, and soft-tissue disorders in oral doses of up to 1.5 g daily in divided doses. Kebuzone has also been given as the sodium salt by intramuscular injection in doses equivalent to 1 g of base once or twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Rheumesser.

Ketobemidone Hydrochloride *(BANM, rINNM)*

Cetobemidona, hidrocloruro de; Cétobémidone, Chlorhydrate de; Cetobemidone Hydrochloride; Cetobemidoni Hydrochloridum; Hidrocloruro de cetobemidona; Ketobemidonhydrochlorid; Ketobemidon-hydrochlorid; Ketobemidonhydroklorid; Ketobemidoni Hydrochloridum; Ketobemidonihydrokloridi; Ketobemidono hidrochloridas; Кетобемидона Гидрохлорид.
1-(4-*m*-Hydroxyphenyl-1-methyl-4-piperidyl)propan-1-one hydrochloride.

$C_{15}H_{21}NO_2$,HCl=283.8
CAS — 469-79-4 (ketobemidone); 5965-49-1 (ketobemidone hydrochloride).
ATC — N02AB01.
ATC Vet — QN02AB01.
UNII — U9U6LTV80K.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ketobemidone Hydrochloride). White or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 5.5.

Profile

Ketobemidone is an opioid analgesic (p. 108.1). It has been given as the hydrochloride orally, by injection, or rectally, sometimes with an antispasmodic.

References.

1. Al-Shurbaji A, Tokics L. The pharmacokinetics of ketobemidone in critically ill patients. *Br J Clin Pharmacol* 2002 **54:** 583–6.
2. Jylli L, *et al.* Comparison of the analgesic efficacy of ketobemidone and morphine for management of postoperative pain in children: a randomized, controlled study. *Acta Anaesthesiol Scand* 2004; **48:** 1256–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketobemidone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Norw.***: Ketorax; ***Swed.***: Ketogan Novum.

Multi-ingredient Preparations. ***Denm.***: Ketogan; ***Norw.***: Ketogan; ***Swed.***: Ketogan.

Ketoprofen *(BAN, USAN, rINN)*

Ketoprofeeni; Ketoprofén; Ketoprofenas; Kétoprofène; Ketoprofeno; Ketoprofenum; RP-19583; Кетопрофен.
(RS)-2-(3-Benzoylphenyl)propionic acid.
$C_{16}H_{14}O_3$=254.3
CAS — 22071-15-4 (ketoprofen); 57469-78-0 (ketoprofen lysine); 57495-14-4 (ketoprofen sodium).
ATC — M01AE03; M02AA10.
ATC Vet — QM01AE03; QM02AA10.
UNII — 90Y4QC304K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ketoprofen). A white or almost white, crystalline powder. M.p. 94 degrees to 97 degrees. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.

USP 36: (Ketoprofen). Store in airtight containers.

Dexketoprofen Trometamol *(BANM, rINNM)*

(*S*)-(+)-Dexketoprofen Trometamol; Dexkétoprofène Trométamol; Dexketoprofeno trometamol; Dexketoprofenum Trometamolum; Декскетопрофен Трометамол.
CAS — 22161-81-5 (dexketoprofen).
ATC — M01AE17.
ATC Vet — QM01AE17.
UNII — N674F7L21E.

Uses and Administration

Ketoprofen, a propionic acid derivative, is an NSAID (p. 102.3). Its anti-inflammatory properties may be weaker than those of some other NSAIDs. Ketoprofen is a racemic mixture; in *animal* studies the *S*-(+) enantiomer, dexketoprofen, has about twice the analgesic activity of ketoprofen by weight.

Ketoprofen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and in peri-articular disorders such as bursitis and tendinitis. It is also used in dysmenorrhoea, postoperative pain, in painful and inflammatory conditions such as acute gout or soft-tissue disorders, and to reduce fever. Dexketoprofen is used in the treatment of mild to moderate pain such as musculoskeletal pain, dysmenorrhoea, or dental pain.

In the treatment of rheumatic disorders a usual oral daily dose of ***ketoprofen*** is 100 to 200 mg in 2 to 4 divided doses; modified-release formulations taken once daily may also be used. Some licensed product information suggests initial oral doses of 75 mg three times daily or 50 mg four times daily increased as needed to a maximum of 300 mg daily in divided doses. Ketoprofen may also be given rectally as suppositories in a dose of 100 mg at night or 100 mg twice daily. It is recommended that the total daily combined oral and rectal dose should not exceed 200 mg. The usual oral dose for the treatment of other painful conditions including dysmenorrhoea is 25 to 50 mg every 6 to 8 hours. For details on the use of ketoprofen in patients with hepatic or renal impairment, see below.

Ketoprofen may be given by deep intramuscular injection into the gluteal muscle for acute exacerbations of musculoskeletal, joint, peri-articular, and soft-tissue disorders, and in the management of pain after orthopaedic surgery. Doses of 50 to 100 mg may be given every 4 hours, up to a maximum dose of 200 mg in 24 hours for up to 3 days. In some countries, ketoprofen has also been given intravenously in similar doses.

Ketoprofen may be applied as a 2.5% gel for local pain relief. Doses vary slightly between preparations: typically, they are applied 2 to 4 times daily for up to 10 days.

Dexketoprofen is given orally as the trometamol salt. Doses are expressed in terms of the base; dexketoprofen trometamol 36.9 mg is equivalent to about 25 mg of dexketoprofen. Usual doses are 12.5 mg every 4 to 6 hours or 25 mg every 8 hours; the total daily dose should not exceed 75 mg. Elderly patients should be started on a total daily dose not exceeding 50 mg. Dose reductions are also necessary in patients with hepatic or renal impairment, see below. It is usually recommended that NSAIDs are taken with or after food to reduce any adverse gastrointestinal effects; however, licensed product information for dexketoprofen states that absorption is delayed if the drug is taken with food and therefore recommends that in acute pain dexketoprofen should be given at least 30 minutes before food.

Ketoprofen has also been used as the hydrochloride, lysine, and sodium salts.

Reviews.

1. Mauleón D, *et al.* Preclinical and clinical development of dexketoprofen. *Drugs* 1996; **52:** 24–46.
2. Moore RA, Barden J. Systematic review of dexketoprofen in acute and chronic pain. *BMC Clin Pharmacol* 2008; **8:** 11. Available at: http://www.biomedcentral.com/content/pdf/1472-6904-8-11.pdf (accessed 17/09/09)

Administration in hepatic or renal impairment. No specific dosage recommendations for racemic *ketoprofen* in patients with hepatic or renal impairment are given by UK licensed product information, although the drug is contra-indicated in severe renal impairment and it is advised that the dose be kept as low as possible and renal function be monitored in more moderate renal impairment (but see also Renal Impairment, below). In the USA, however, it has been recommended that patients with hepatic impairment and a serum albumin concentration of less than 3.5 g/dL should be given a maximum initial daily dose of 100 mg orally. Patients with mild renal impairment should be given a maximum daily dose of 150 mg and those with more severe impairment (GFR less than 25 mL/minute per 1.73 m^2 or end-stage renal impairment) should not exceed a maximum daily dose of 100 mg.

UK licensed product information for *dexketoprofen* recommends a reduced initial daily dose of 50 mg orally in patients with mild to moderate hepatic or mild renal impairment. Dexketoprofen should not be used in patients with severe hepatic or moderate to severe renal impairment.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

When ketoprofen is given intramuscularly there may be pain at the injection site and occasionally tissue damage. Topical preparations containing ketoprofen may cause application site reactions. Ketoprofen suppositories may cause local irritation; rectal use should be avoided in patients with a history of proctitis or haemorrhoids. Ketoprofen should be used with caution in patients with renal or hepatic impairment; it should not be used in those with severe renal impairment.

Dexketoprofen should be avoided in patients with moderate to severe renal or severe hepatic impairment, and in those with severe heart failure.

Effects on the skin. Contact and photoallergic dermatitis have been seen after topical use of ketoprofen.[1,2] A retrospective study[3] found that of the 139 cases of contact reactions to topical NSAIDs reported to the Spanish Pharmacovigilance System between 1996 and 2001, 84 involved ketoprofen (16 allergy; 68 photoallergy). Totals for other NSAIDs included piroxicam (21), etofenamate (10), piketoprofen (5), salicylates (4), fepradinol (3), diclofenac (3), indometacin (2), phenylbutazone (2), benzydamine (2), aceclofenac (1), naproxen (1), and mabuprofen (1). Analysis indicated that the number of reports for topical ketoprofen was disproportionately high in relation to its usage.

1. Matthieu L, *et al.* Contact and photocontact allergy to ketoprofen: the Belgian experience. *Contact Dermatitis* 2004; **50:** 238–41.
2. Hindsén M, *et al.* Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; **54:** 150–7.
3. Diaz RL, *et al.* Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; **54:** 239–43.

Hypersensitivity. Life-threatening asthma, urticaria, and angioedema developed in 2 aspirin-sensitive patients after taking ketoprofen 50 mg orally.[1] Cardiac and respiratory arrest occurred in an asthmatic patient shortly after taking ketoprofen.[2] Life-threatening asthma has also occurred after topical application of ketoprofen.[3]

Delayed skin hypersensitivity was seen in a patient who used a topical gel containing ketoprofen.[4] The reaction recurred on rechallenge to ketoprofen gel but not to a similar gel containing diclofenac. The authors of the report noted that the UK CSM had received 15 reports of skin reactions to ketoprofen gel, including two each of dermatitis and urticaria.

See also Effects on the Skin, above.

1. Frith P, *et al.* Life-threatening asthma, urticaria, and angioœdema after ketoprofen. *Lancet* 1978; **ii:** 847–8.
2. Schreuder G. Ketoprofen: possible idiosyncratic acute bronchospasm. *Med J Aust* 1990; **152:** 332–3.
3. Kashiwabara K, Nakamura H. Analgesic-induced asthma caused by 2.0% ketoprofen adhesive agents, but not by 0.3% agents. *Intern Med* 2001; **40:** 124–6.
4. Oh VMS. Ketoprofen gel and delayed hypersensitivity dermatitis. *BMJ* 1994; **309:** 512.

Myasthenia gravis. A cholinergic crisis was precipitated by a single oral dose of ketoprofen 50 mg in a patient with well-controlled myasthenia gravis.[1] The patient had previously noted a similar but milder reaction with aspirin, but not with paracetamol.

1. McDowell IFW, McConnell JB. Cholinergic crisis in myasthenia gravis precipitated by ketoprofen. *BMJ* 1985; **291:** 1094.

Pancreatitis. Pancreatitis has been associated with ketoprofen use.[1,2]

1. Cobb TK, Pierce JR. Acute pancreatitis associated with ketoprofen. *South Med J* 1992; **85:** 430–1.
2. Mété D, *et al.* Pancréatite aiguë et kétoprofène. *Gastroenterol Clin Biol* 2001; **25:** 721–2.

Photosensitivity. Ketoprofen causes photosensitivity reactions[1,2] and cross-sensitivity to other drugs, notably the fibrates bezafibrate, ciprofibrate, and fenofibrate, has also been reported. The cross reactions were attributed to the benzoyl ketone structure that the drugs have in common.

See also Effects on the Skin (above).

1. Bagheri H, *et al.* Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data. *Drug Safety* 2000; **22:** 339–49.
2. Veyrac G, *et al.* Bilan de l'enquête nationale sur les effets indésirables cutanés du kétoprofène gel enregistrés entre le 01/09/1996 et le 31/08/2000. *Therapie* 2002; **57:** 55–64.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketoprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Renal impairment. The elimination half-life and unbound plasma concentrations of dexketoprofen are increased in patients with renal impairment given racemic ketoprofen;[1,2] this appears to be mainly attributable to impaired renal clearance of the acyl-glucuronide conjugates in a stereoselective fashion, with subsequent hydrolysis of the unstable conjugate back to the aglycone producing increased plasma-ketoprofen concentrations.[2,3] The authors of one study suggested[3] that dosage adjustments of racemic ketoprofen were indicated only for patients with moderately severe renal failure (creatinine clearance of less than 20 mL/minute).

For advice on the dose of dexketoprofen in patients with renal impairment see under Uses and Administration, above. See also Adverse Effects and Precautions, above.

1. Hayball PJ, *et al.* The influence of renal function on the enantioselective pharmacokinetics and pharmacodynamics of ketoprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1993; **36:** 185–93.
2. Grubb NG, *et al.* Stereoselective pharmacokinetics of ketoprofen and ketoprofen glucuronide in end-stage renal disease: evidence for a 'futile cycle' of elimination. *Br J Clin Pharmacol* 1999; **48:** 494–500.
3. Skeith KJ, *et al.* The influence of renal function on the pharmacokinetics of unchanged and acyl-glucuroconjugated ketoprofen enantiomers after 50 and 100 mg racemic ketoprofen. *Br J Clin Pharmacol* 1996; **42:** 163–9.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Probenecid delays the excretion of ketoprofen and decreases its extent of protein binding resulting in increased plasma-ketoprofen concentrations. Not unexpectedly, a similar interaction may be seen with dexketoprofen and probenecid.

Pharmacokinetics

Ketoprofen is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur about 0.5 to 2 hours after an oral dose. When ketoprofen is given with food, the

bioavailability is not altered but the rate of absorption is slowed. Ketoprofen is well absorbed from the intramuscular and rectal routes; only a small amount of percutaneous absorption occurs after topical application. Ketoprofen is 99% bound to plasma proteins and substantial concentrations of drug are found in the synovial fluid. The elimination half-life in plasma is about 1.5 to 4 hours. Ketoprofen is metabolised mainly by conjugation with glucuronic acid, and is excreted mainly in the urine.

Ketoprofen possesses a chiral centre. It is usually given as the racemate but its pharmacological actions appear to be due largely to the *S*-enantiomer, dexketoprofen. The pharmacokinetics of ketoprofen appear to show little stereoselectivity (but see under Renal Impairment, p. 79.3).

References.

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2. Flouvat B, *et al*. Pharmacokinetics of ketoprofen in man after repeated percutaneous administration. *Arzneimittelforschung* 1989; **39:** 812–15.
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4. Geisslinger G, *et al*. Pharmacokinetics of ketoprofen enantiomers after different doses of the racemate. *Br J Clin Pharmacol* 1995; **40:** 73–5.
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6. Kokki H, *et al*. Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000; **40:** 354–9.
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8. Kokki H, *et al*. Pharmacokinetics of intravenous and rectal ketoprofen in young children. *Clin Pharmacokinet* 2003; **42:** 373–9.
9. Valles J, *et al*. Clinical pharmacokinetics of parenteral dexketoprofen trometamol in healthy subjects. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl A): 7–12.
10. Valles J, *et al*. Single and repeated dose pharmacokinetics of dexketoprofen trometamol in young and elderly subjects. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl A): 13–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Enantyum; Helenil; Ketfren; Salicrem K; ***Austral.***: Orudis; Oruvail; ***Austria***: Enantyum; Fastum; Ketesse; Ketospray; Profenid; ***Belg.***: Bi-Rofenid; Enantyum; Fastum; Ketesse; Rofenid; ***Braz.***: Artrifenil; Artrinid; Artrosil; Bi-Profenid; Ceprofen; Cetofenid; Flamador; Profenid; ***Canad.***: Apo-Keto; Novo-Keto†; ***Chile***: Bonil; Cirus; Desketo; Dolo-Ketazon; Dolofar; Dolostat; Fastum†; Flogofin; Profenid; Relatene; Talflex; ***China***: Ao Ding Ni (奥丁尼); Arket (琪和); Fastum (法斯通); Fen Li (芬利); Ketotop (基多托); Kui La Lan (葵拉兰); Ricfen (锐迈); San Si Teng (散斯腾); Shu Li Ang (枢力昂); Wei Kang Li (维康利); Youbaifen (优百芬); ***Cz.***: Dexoket; Fastum; Keplat; Ketesse; Ketonal; Profenid; Prontoflex; Prontoket†; ***Denm.***: Enantyum†; Fastum; Ketesse; Ketospray; Orofen†; Orudis†; ***Fin.***: Enantyum†; Ketesse; Keto; Ketomex; Ketorin; Orudis; Zon†; ***Fr.***: Bi-Profenid; Ketesse; Ketum; Profemigr; Profenid; Topfena†; Toprec; ***Ger.***: Advel†; Alrheumun; Dolormin mit Ketoprofen†; Effekton mit Ketoprofen; Gabrilen; Phardol Schmerz; Spondylon†; Sympal; ***Gr.***: Drastirel; Farbovil; Ketodur; Menaril; Nosatel; Oruvail; Profinject; Solu-Ket; Totifen; Viaxal; Vofen; ***Hong Kong***: Apo-Keto-E†; Fastum; Mohrus; Orudis; Oruvail†; ***Hung.***: Algoflex; Fastum; Keplat; Ketodex; Ketospray; Profenid; Prontoket†; ***India***: Fastum; Infen; Ketofen; Ketopatch; Ostofen; ***Indon.***: Altofen; Fetik; Gatofen; Kaltrofen; Ketesse; Ketros; Lantiflam; Molaflam; Nasaflam; Nazovell; Noflam; Ovurila; Profecom; Profenid; Profika; Pronalges; Protofen; Remapro; Rematof†; Rhetoflam; Rofiden; Suprafenid; ***Irl.***: Fastum; Keral; Orugesic†; Oruvail; ***Israel***: Fastum†; Ketospray; Profenid; ***Ital.***: Alket; Ardbeg; Artrosilene; Desketo; Dolgosin; Enantyum; Euketos; Fastum; Flexen; Hiruflog; Ibifen; Isofenal; Keplat; Ketartrium†; Ketesse; Ketodol; Ketofarm; Ketoplus; Ketoselect; Ketum; Lasoartro; Lasonil Gel; Liotondol; Oki; Orudis; Steofen; ***Jpn***: Mohrus; ***Malaysia***: Apo-Keto; Fastum; KefenTech; Kenhancer; Kenofen; Ketofen; Orudis; ***Mex.***: Arket†; Arthril; Bi-Profenid; Bibix†; Efiken; K-Profen; Keral; Ketoflex; Oki 3A; Orudis; Painsik; Profenid; Stadium; ***Neth.***: Enantyum; Orudis; Oruvail; Oscorel; Rilies; Stadium; ***Norw.***: Orudis; Zon†; ***NZ***: Orudis†; Oruvail; ***Philipp.***: Fastum; Floramil; Keon; Ketofen†; Ketotop; Orudis; Udzapen†; ***Pol.***: Bi-Profenid; Dexak; Fastum; Febrofen; Ketonal; Ketoprom; Ketopronil; Ketores; Ketospray; Profenid; Refastin; Ultrafastin; ***Port.***: Enantyum; Fastum; Keplat; Ketesse; Profenid; ***Rus.***: Artrosilen (Артрозилен); Artrum (Артрум); Bystrumgel (Быструмгель); Dexalgin (Дексалгин); Fastum (Фастум); Febrofid (Феброфид); Flamax (Фламакс); Flexen (Флексен); Ketonal (Кетонал); Oki (Оки); ***S.Afr.***: Fastum; Ketoflam; Myproflam; Oruvail†; ***Singapore***: Apo-Keto; Fastum; KefenTech; Kenhancer; Ketesse; Oruvail; Pronalges; ***Spain***: Adolquir; Arcental; Enangel; Enantyum; Extraplus; Fastum; Ketesgel; Ketesse; Orudis; Quiralam; Quirgel; ***Swed.***: Enantyum; Ketesse; Ketoflex†; Orudis; Siduro; Zon†; ***Switz.***: Fastum; Ketesse; ***Thai.***: Fastum; Kaprofen†; Lolita; Oruvail; Profenid†; Rhumafen; Rofepain; Vestam; ***Turk.***: Arveles; Bi-Profenid; Fastjel; Ketesse; Keto; Ketofen†; Profenid; Proflam; ***UK***: Axorid; Keral; Ketocid; Ketovail; Larafen; Orudis; Oruvail; Powergel; Tiloket; ***Ukr.***: Dexalgin (Дексалгин); F-Gel (Ф-Гель); Fastum (Фастум); Ketonal (Кетонал); Ketum (Кетум)†; Ultrafastin (Ультрафастин); Valusal (Валусал); ***Venez.***: Dolomax; Kelfen; Keto; Ketoprof; Keydol; Lindilan; Orofeno; Peindol; Profenid.

Multi-ingredient Preparations. ***Gr.***: Profenil Complex; ***India***: Ketonal-D; Lupiflex; ***Mex.***: Bifebral; Dolo Bedoyecta; Reumophan Alka; Reumophan Vit.

Pharmacopoeial Preparations

BP 2014: Ketoprofen Capsules; Ketoprofen Gel;
USP 36: Ketoprofen Extended-Release Capsules.

Ketorolac Trometamol *(BANM, rINNM)*

Ketorolaakkitrometamoli; Ketorolac-Trometamol; Kétorolac Trométamol; Ketorolac Tromethamine (USAN); Ketorolaco trometamol; Ketorolacum Trometamoli; Ketorolacum trometamolum; Ketorolak Trometamol; Ketorolak z trometamolem; Ketorolak-trometamol; Ketorolaktrometamol; RS-37619-00-31-3; RS-37619 (Ketorolac); Кеторолак Трометамол.

(±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1 : 1).

$C_{19}H_{24}N_2O_6$=376.4

CAS — 74103-06-3 (ketorolac); 74103-07-4 (ketorolac trometamol).

ATC — M01AB15; S01BC05.

ATC Vet — QM01AB15; QS01BC05.

UNII — 4EVE5946BQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. & (Ketorolac Trometamol). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 5.7 to 6.7. Protect from light.

USP 36: (Ketorolac Tromethamine). A white to off-white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol, in dehydrated alcohol, and in tetrahydrofuran; practically insoluble in acetone, in acetonitrile, in butyl alcohol, in dichloromethane, in dioxan, in ethyl acetate, in hexane, and in toluene. pH of a 1% solution in water is between 5.7 and 6.7. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Ketorolac, a pyrrolizine carboxylic acid derivative structurally related to indometacin (p. 71.2), is an NSAID (p. 102.3). It is used mainly as an analgesic.

Ketorolac is used intramuscularly, intravenously, or orally as the trometamol salt in the short-term management of moderate to severe **postoperative pain**. However, it should be noted that because of concerns over the high incidence of reported adverse effects with ketorolac its dosage and maximum duration of use are restricted. The recommended maximum duration for parenteral therapy is 2 days in the UK; if required, patients should be transferred to oral therapy with another analgesic. In the USA it is recommended that the maximum combined duration of use of parenteral and oral ketorolac should not exceed 5 days.

- In the UK the recommended initial dose by the *parenteral* route is 10 mg of ketorolac trometamol followed by 10 to 30 mg every 4 to 6 hours as required, although ketorolac may be given as often as every 2 hours in the initial postoperative period if required. The total maximum daily dose is 90 mg (60 mg in the elderly, patients with mild renal impairment, and in those weighing less than 50 kg). Intravenous injections should be given over at least 15 seconds.
- Regimens in use in the USA include a single intramuscular dose of 60 mg or a single intravenous dose of 30 mg, or a multiple-dose regimen comprising 30 mg every 6 hours intramuscularly or intravenously, up to a maximum of 120 mg daily. These doses should be halved in the elderly (aged 65 years or older), the renally impaired, and those weighing less than 50 kg.
- In the USA ketorolac trometamol may also be given *orally* as continuation therapy from parenteral dosing. The recommended dose is 20 mg (10 mg in the elderly, the renally impaired, and those weighing under 50 kg), followed by 10 mg every 4 to 6 hours to a maximum of 40 mg daily.

For doses in children see Administration in Children, below.

In the USA, ketorolac trometamol is also approved for the short-term management of moderate to moderately severe **acute pain** as an *intranasal* spray. It is recommended that the maximum duration of use either alone or with other ketorolac preparations should not exceed 5 days; it should not be used at the same time as other ketorolac preparations. The recommended dose is 15.75 mg in each nostril every 6 to 8 hours to a total maximum daily dose of 126 mg. In patients aged 65 years or older, the renally impaired, and those weighing less than 50 kg, the recommended dose is 15.75 mg in one nostril every 6 to 8 hours to a total maximum daily dose of 63 mg.

Ketorolac trometamol is used as 0.5% eye drops to relieve **ocular itching** associated with seasonal allergic conjunctivitis. Ketorolac trometamol eye drops 0.5% have also been used for the topical treatment of **cystoid macular oedema** and for the prevention and reduction of **inflammation** associated with ocular surgery. In the USA, 0.4 or 0.45% eye drops are also available for postoperative ocular inflammation.

Reviews.

1. Gillis JC, Brogden RN. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; **53:** 139–88.
2. Di Massa A, *et al*. Ketorolac for paediatric postoperative pain: a review. *Minerva Anestesiol* 2000; **66:** 749–56.
3. Arora S, *et al*. Myth: parenteral ketorolac provides more effective analgesia than oral ibuprofen. *CJEM* 2007; **9:** 30–2.
4. Schechter BA. Ketorolac tromethamine 0.4% as a treatment for allergic conjuctivitis [sic]. *Expert Opin Drug Metab Toxicol* 2008; **4:** 507–11.
5. Sinha VR, *et al*. Ketorolac tromethamine formulations: an overview. *Expert Opin Drug Deliv* 2009; **6:** 961–75.

Administration in children. Ketorolac trometamol may be used for the short-term management of moderate to severe postoperative pain in children. In the USA, children aged between 2 to 16 years may be given a single intramuscular dose of 1 mg/kg of ketorolac trometamol up to a maximum of 30 mg or a single intravenous dose of 500 micrograms/kg up to a maximum of 15 mg. In the UK, parenteral ketorolac is only licensed for those aged 16 and over; doses are as for adults (see above). However, the *BNFC* suggests that children aged 6 months to 16 years may be given an initial intravenous injection of 0.5 to 1 mg/kg (maximum of 15 mg), followed by 0.5 mg/kg (maximum of 15 mg) every 6 hours as required, to a maximum daily dose of 60 mg.

Oral ketorolac is not licensed for use in children.

Administration in renal impairment. Ketorolac is contra-indicated in patients with moderate to severe renal impairment; for suggested doses in less advanced renal impairment, see Uses and Administration, above.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Concern over the high incidence of reported adverse effects with ketorolac trometamol has led to its withdrawal in some countries while in others its permitted dosage and maximum duration of treatment have been reduced.

Adverse effects reported include gastrointestinal disturbances including gastrointestinal bleeding (especially in the elderly), perforation, and peptic ulceration. Hypersensitivity reactions such as anaphylaxis, rash, bronchospasm, laryngeal oedema, and hypotension have also occurred. Other adverse effects reported include drowsiness, dizziness, headache, mental and sensory changes, psychotic reactions, sweating, dry mouth, thirst, fever, convulsions, myalgia, aseptic meningitis, hypertension, dyspnoea, pulmonary oedema, bradycardia, chest pain, palpitations, fluid retention, increases in blood urea and creatinine, acute renal failure, oedema, hyponatraemia, hyperkalaemia, urinary frequency or retention, nephrotic syndrome, flank pain with or without haematuria, purpura, thrombocytopenia, epistaxis, inhibition of platelet aggregation, increased bleeding time, postoperative wound haemorrhage, haematoma, flushing or pallor, and pancreatitis. Severe skin reactions including Stevens-Johnson syndrome and Lyell's syndrome have been reported. Liver function changes may occur; hepatitis and liver failure have been reported. There may be pain at the site of injection.

The most frequently reported adverse effects of ketorolac intranasal spray were mild and transient local reactions such as nasal discomfort or irritation.

Ketorolac eye drops may produce transient stinging and other minor symptoms of ocular irritation. As with some other NSAIDs used in the eye, ketorolac has been implicated in reports of corneal toxicity (see Effects on the Eyes, p. 50.1).

Incidence of adverse effects. Adverse effects reported with ketorolac are mainly those common to all NSAIDs with gastrointestinal reactions being the most frequent followed by haematological, renal, hypersensitivity, and then neurological reactions. From 1990 to 1993, 97 reactions with a fatal outcome were reported worldwide.[1] The causes of death were: gastrointestinal bleeding or perforation (47 cases); renal impairment or insufficiency (20 cases); anaphylaxis or asthma (7 cases); haemorrhagic reactions (4 cases); and unexplained or miscellaneous causes (19 cases). Concern over the safety of ketorolac has led to adverse reactions being monitored closely and to the implementation of restrictions on dose and duration of treatment (see Uses and Administration, above). A post-marketing surveillance study[2] examined the risks of parenteral ketorolac in 9 900 patients given 10 272 courses of

ketorolac. The results indicated a dose-response relationship with average daily ketorolac dose for both gastrointestinal bleeding and operative site bleeding, the expected major risks, and an association between gastrointestinal bleeding and therapy for over 5 days. The risk of serious gastrointestinal bleeding and operative site bleeding was higher for elderly patients [licensed product information recommends that the elderly should not receive daily parenteral doses greater than 60 mg]. Although the overall associations between ketorolac use and both gastrointestinal bleeding and operative site bleeding are small, the risk becomes clinically important as doses increase, in elderly patients, and, for gastrointestinal bleeding only, when used for longer than 5 days.

US product information has consequently emphasised that ketorolac is a potent NSAID and is indicated only for the short-term management of moderate to severe pain and not for minor or chronic painful conditions; its use carries many risks and related adverse effects can be serious especially when used inappropriately. After examining data from the above study the EU Committee for Proprietary Medicinal Products adopted the opinion that ketorolac had a narrow therapeutic margin but that it was indicated for the short-term management of moderate to severe acute postoperative pain.

Further references to ketorolac's adverse effects are given below.[3-12]

1. CSM/MCA. Ketorolac: new restrictions on dose and duration of treatment. *Current Problems* 1993; **19:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 07/11/07)
2. Strom BL, *et al*. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a postmarketing surveillance study. *JAMA* 1996; **275:** 376–82.
3. Rotenberg FA, Giannini VS. Hyperkalemia associated with ketorolac. *Ann Pharmacother* 1992; **26:** 778–9.
4. Boras-Uber LA, Brackett NC. Ketorolac-induced acute renal failure. *Am J Med* 1992; **92:** 450–2. Correction *ibid*.; **93:** 117.
5. Schoch PH, *et al*. Acute renal failure in an elderly woman following intramuscular ketorolac administration. *Ann Pharmacother* 1992; **26:** 1233–6.
6. Goetz CM, *et al*. Anaphylactoid reaction following ketorolac tromethamine administration. *Ann Pharmacother* 1992; **26:** 1237–8.
7. Randi ML, *et al*. Haemolytic uraemic syndrome during treatment with ketorolac trometamol. *BMJ* 1993; **306:** 186.
8. Fong J, Gora ML. Reversible renal insufficiency following ketorolac therapy. *Ann Pharmacother* 1993; **27:** 510–12.
9. Corelli RL, Gericke KR. Renal insufficiency associated with intramuscular administration of ketorolac tromethamine. *Ann Pharmacother* 1993; **27:** 1055–7.
10. Buck ML, Norwood VF. Ketorolac-induced acute renal failure in a previously healthy adolescent. *Pediatrics* 1996; **98:** 294–6.
11. Feldman HI, *et al*. Parenteral ketorolac: the risk for acute renal failure. *Ann Intern Med* 1997; **126:** 193–9.
12. Reinhart DJ, *et al*. Minimising the adverse effects of ketorolac. *Drug Safety* 2000; **22:** 487–97.

Precautions

As for NSAIDs in general, p. 107.1.

In light of the concern over its toxicity, licensed product information for ketorolac recommends that it should not be used during pregnancy or labour, nor given to mothers who are breast feeding (but see below).

Ketorolac is contra-indicated in patients with a history of hypersensitivity to aspirin or other NSAIDs, a history of asthma, nasal polyps, bronchospasm, or angioedema, a history of peptic ulceration or gastrointestinal bleeding, in patients with moderate or severe renal impairment, and in those with hypovolaemia or dehydration. Ketorolac should not be given to patients with coagulation or haemorrhagic disorders or those with confirmed or suspected cerebrovascular bleeding. It is contra-indicated as a prophylactic analgesic before surgery and for intraoperative use because of its inhibitory effects on platelets; it should also not be given postoperatively to those who have undergone procedures with a high risk of haemorrhage.

The total daily dose of ketorolac should be reduced in the elderly and in patients weighing less than 50 kg. It is recommended that patients with mild renal impairment should receive a reduced dose of ketorolac and undergo close monitoring of renal function. Ketorolac should be used with caution in heart failure, hepatic impairment, and conditions leading to reduction in blood volume or in renal blood flow. Ketorolac should be withdrawn if clinical symptoms of hepatotoxicity develop.

Drowsiness and dizziness may affect the performance of skilled tasks such as driving.

Breast feeding. The concentration of ketorolac distributed into breast milk is very low and a study[1] considered that the amount ingested by the infant would probably be too small to be harmful. The American Academy of Pediatrics[2] also states that there have been no reports of any clinical effect on the infant associated with the use of ketorolac by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. Similarly, the *BNF* considers the amount to be too small to be harmful to breast-fed infants and US licensed product information permits its use. However, UK product information recommends that ketorolac should be avoided in mothers who are breast feeding.

1. Wischnik A, *et al*. The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. *Eur J Clin Pharmacol* 1989; **36:** 521–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketorolac trometamol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Ketorolac should not be given to patients already receiving anticoagulants or to those who will require prophylactic anticoagulant therapy, including low-dose heparin. The risk of ketorolac-associated bleeding is also increased by other NSAIDs or aspirin and by pentoxifylline and use together should be avoided. Probenecid increases the half-life and plasma concentrations of ketorolac and the two drugs should not be given together.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Ketorolac trometamol is absorbed after intramuscular or oral doses. At physiological pH ketorolac trometamol dissociates to form an anionic ketorolac molecule which is less hydrophilic than the trometamol salt. Peak plasma concentrations of ketorolac occur within about 30 to 60 minutes; absorption after intramuscular injection may be slower than that after oral doses in some individuals. Ketorolac is over 99% bound to plasma proteins. It does not readily penetrate the blood-brain barrier. Ketorolac crosses the placenta and small amounts of drug are distributed into breast milk. The terminal plasma half-life is about 4 to 6 hours, but is about 6 to 7 hours in the elderly and 9 to 10 hours in patients with renal dysfunction. The major metabolic pathway is glucuronic acid conjugation; there is some *para*-hydroxylation. About 90% of a dose is excreted in urine as unchanged drug and conjugated and hydroxylated metabolites, the remainder is excreted in the faeces.

References.

1. Kauffman RE, *et al*. Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. *Clin Pharmacol Ther* 1999; **65:** 382–8.
2. Hamunen K, *et al*. Stereoselective pharmacokinetics of ketorolac in children, adolescents and adults. *Acta Anaesthesiol Scand* 1999; **43:** 1041–6.
3. Dsida RM, *et al*. Age-stratified pharmacokinetics of ketorolac tromethamine in pediatric surgical patients. *Anesth Analg* 2002; **94:** 266–70.
4. McAleer SD, *et al*. Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol* 2007; **47:** 13–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acular; Blocadol; Dolten; Kelac; Kemanat; Kerarer; Ketopharm; Klenac; Poenkerat; Sinalgico; Teledol; Tenkdol; Unicalm; ***Austral.***: Acular; Ketoral; Toradol; ***Austria***: Acular; ***Belg.***: Aculare; Taradyl; ***Braz.***: Acular; Cetrolac; Optilar; Toradol; Toragesic; ***Canad.***: Acular; Acuvail; Toradol; ***Chile***: Acular; Brodifac; Burten; Dilox; Dolgenal; Netaf; Poenkerat†; Syndol; ***China***: Acular (安贺拉); Ni Song (尼松); ***Denm.***: Acular; Toradol; ***Fin.***: Acular; Toradol; ***Fr.***: Acular; ***Ger.***: Acular; ***Gr.***: Acular; Errkes; Toradol; ***Hong Kong***: Acular; Keto; Toradol; ***India***: Acular; Alexis; Apsolox; Cadolac; Centagesic; Doloket; Ked; Kelac; Kenalfin; Ketanov; Ketin; Ketlac; Ketlur; Ketodrops; Ketofan; Ketolas; Ketonic; Ketorol; Ketroc; Ketrol; Ketzy; Key; Labolac; Nato; Nodine; Oculac; Torolac; ***Indon.***: Dolac; Farpain; K-Pain; Ketopain; Ketrobat; Lactor; Lantipain; Matolac; Remopain; Rolac; Scelto; Teranol; Toradol; Toramine; Torasic; Torpain; Trolac; Xevolac; ***Irl.***: Acular; ***Ital.***: Acular; Benketol; Girolac; Kevindol; Lixidol; Nasvical; Rolacsin; Tora-Dol; ***Malaysia***: Acular; Keto; Toradol; ***Mex.***: Acularen; Ainelac†; Aitornet; Alidol†; Apotoke; Brunacol; Celfax; Dobelor; Doket; Dolac; Dolcoplaz; Dolikan; Drometak; Efimerol; Estopein; Exorol; Finlac; Geldako; Gesilac†; Glicima; Godek; Italker†; Katamisine; Kendol; Kendolit; Koprak; Lacdol; Lacomin; Landaco; Lenaken; Lokefar; Lorotec; Mavidol; Onemer; Plusindol; Poenkerat; Ranketo†; Rapix; Rolesen; Rolodiquim; Rometran-K; Sebapain; Supradol; Toloran; Toral; Torkol; Trodorol; Tromedal; Ultilap; Voydol; Zafidol; ***Neth.***: Acular; ***Norw.***: Toradol; ***NZ***: Acular; ***Philipp.***: Acular; Eurolac; Inco; Ketanov; Ketero; Keto; Ketodol; Ketomed; Kortezor; Remopain; Teromac; Togesic; Toradol; Tral; ***Port.***: Acular; Elipa; Toradol; ***Rus.***: Adolor (Адолор); Dolac (Долак); Dolomine (Доломин); Ketalgin (Кеталгин); Ketanov (Кетанов); Ketofreel (Кетофрил); Ketolac (Кетолак); Ketorol (Кеторол); ***S.Afr.***: Acular; Bedoral; Tora-Dol; ***Singapore***: Acular; Keto; Toradol; ***Spain***: Acular; Algikey†; Droal†; Toradol; ***Swed.***: Toradol; ***Switz.***: Acular; Tora-Dol; ***Thai.***: Acular; Ketolac; ***Turk.***: Acular; ***UK***: Acular; Toradol; ***Ukr.***: Emodol (Эмодол)†; Ketanov (Кетанов); Ketolong (Кетолонг); Novalket (Новалькет); ***USA***: Acular; Acuvail; Sprix; ***Venez.***: Dolak; Kelac; Notolac; Ocudol; Poenkerat.

Multi-ingredient Preparations. ***India***: Doloket-O; Ketlur Plus; Keto-PC; Ketoflox; Milflox Plus; Omeflox-KT; ***Mex.***: Gammadol; Sinergix; Supradol-F; Voydol-C.

Pharmacopoeial Preparations

USP 36: Ketorolac Tromethamine Injection; Ketorolac Tromethamine Tablets.

Leflunomide *(BAN, USAN, rINN)*

HWA-486; Leflunomid; Leflunomida; Léflunomide; Leflunomidi; Leflunomidum; RS-34821; SU-101; Лефлуномид.

α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide.

$C_{12}H_9F_3N_2O_2$=270.2

CAS — 75706-12-6.

ATC — L04AA13.

ATC Vet — QL04AA13.

UNII — G162GK9U4W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Leflunomide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in methyl alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Leflunomide). White to almost white powder. Practically insoluble in water; freely soluble in acetone, in acetonitrile, in alcohol, in chloroform, in ethyl acetate, in isopropyl alcohol, and in methyl alcohol. Store at a temperature not exceeding 30 degrees.

Uses and Administration

Leflunomide has immunosuppressant and antiproliferative properties. It is used as a disease-modifying antirheumatic drug (DMARD) in the treatment of active rheumatoid arthritis (below). It is also used in the treatment of active psoriatic arthritis (see Spondyloarthropathies, p. 82.1) and has been investigated in the management of various solid neoplasms.

Because of the long half-life of the principal metabolite, a loading dose of leflunomide is required to reach steady-state concentrations relatively rapidly. Therapy should start with an oral loading dose of 100 mg once daily for 3 days. However, in practice, the loading dose may be omitted in those patients at an increased risk of adverse effects, particularly haematological or hepatic effects. The maintenance dose is 10 to 20 mg once daily for rheumatoid arthritis and 20 mg once daily for psoriatic arthritis. Dose adjustments may be necessary in patients who develop abnormal liver enzyme values, see below. The therapeutic effect usually starts after 4 to 6 weeks of therapy and further improvements may occur for up to 6 months.

Administration in hepatic impairment. Leflunomide is contra-indicated in patients with hepatic impairment. Patients who develop moderate elevations of liver enzyme values (defined as transaminase levels 2 to 3 times the normal upper limit) while receiving leflunomide treatment should have their dose reduced to 10 mg daily; if necessary, monitoring of liver enzyme values should also be performed at weekly intervals. If moderate elevations persist or if severe elevations occur, leflunomide should be stopped and washout procedures started (see p. 82.3).

Inflammatory bowel disease. Leflunomide has been tried, with some success, in the management of Crohn's disease[1] (p. 1811.3).

1. Prajapati DN, *et al*. Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. *J Clin Gastroenterol* 2003; **37:** 125–8.

Rheumatoid arthritis. References[1-8] to the use of leflunomide in rheumatoid arthritis (p. 13.2).

1. Strand V, *et al*. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999; **159:** 2542–50.
2. Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. *Drugs* 1999; **58:** 1137–64.
3. Emery P, *et al*. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39:** 655–65.
4. McCarey DW, *et al*. Leflunomide in treatment of rheumatoid arthritis. *Lancet* 2002; **359:** 1158.
5. Miceli-Richard C, Dougados M. Leflunomide for the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2003; **4:** 987–97.

6. Maddison P, *et al*. Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology (Oxford)* 2005; **44:** 280–6. Correction. *ibid.*; 569.
7. Silverman E, *et al*. Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2005; **52:** 554–62.
8. Silverman E, *et al*. Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2005; **352:** 1655–66.

Spondyloarthropathies. References[1-6] to the use of leflunomide in ankylosing spondylitis and psoriatic arthritis (p. 14.3).

1. Cuchacovich M, Soto L. Leflunomide decreases joint erosions and induces reparative changes in a patient with psoriatic arthritis. *Ann Rheum Dis* 2002; **61:** 942–3.
2. Kaltwasser JP, *et al*. Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; **50:** 1939–50.
3. Haibel H, *et al*. Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 124–6.
4. van Denderen JC, *et al*. Double blind, randomised, placebo controlled study of leflunomide in the treatment of active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 1761–4.
5. Schmitt J, Wozel G. Psoriasis-arthritis—Langzeit-therapie zweier Patienten mit Leflunomid. *J Dtsch Dermatol Ges* 2005; **2:** 763–6.
6. Nash P, *et al*. Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. *Dermatology* 2006; **212:** 238–49.

Adverse Effects, Treatment and Precautions

Common adverse effects seen with leflunomide are hypertension, gastrointestinal disturbances (particularly diarrhoea), weight loss, headache, dizziness, leucopenia, asthenia, paraesthesia, joint disorders and synovitis, upper respiratory-tract infections, alopecia, eczema, and dry skin. Hypersensitivity reactions may occur and a few cases of Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, or vasculitis have been reported. Hepatotoxicity has occurred. It is usually mild and reversible but rare cases of severe, sometimes fatal, liver disease, including acute hepatic necrosis, have been seen particularly in the first 6 months of therapy. Other adverse effects that have been reported include anxiety, peripheral neuropathy, hypokalaemia, and mild hyperlipidaemia. There have been rare reports of pancytopenia, agranulocytosis, and thrombocytopenia; these effects are more common when leflunomide is given with other myelosuppressive drugs (see Interactions, below). There have been occasional reports of pancreatitis, interstitial lung disease, and severe infections, including fatal sepsis. Renal failure has also been reported.

The active metabolite of leflunomide, A-771726, has a half-life of about 2 weeks. Consequently, the adverse effects of leflunomide may continue even after therapy has been stopped. When severe reactions occur, a drug washout procedure (see below) may be required.

Leflunomide should not be given to immunocompromised patients or to patients with severe infections, hepatic or moderate to severe renal impairment, severe hypoproteinaemia, or bone-marrow dysplasia. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided for the same reason. Blood pressure should be monitored regularly during therapy.

In the UK, licensed product information recommends that liver enzyme values should be checked before beginning therapy and at fortnightly intervals during the first 6 months of treatment; US product information recommends monthly monitoring for the first 6 months. Subsequent monitoring should be carried out at 6- to 8-week intervals. Dosage should be reduced if moderate elevations of liver enzyme values occur (see Administration in Hepatic Impairment, p. 81.3); for persistent or more severe elevations leflunomide should be stopped and washout procedures begun. Monitoring of liver enzymes should be continued after stopping therapy until they return to within the normal range. Blood counts should also be checked at the same time as liver enzyme values.

References.

1. Alcorn N, *et al*. Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. *Drug Safety* 2009; **32:** 1123–34.

Effects on the lungs. Up to December 2006, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) had received 142 reports of respiratory symptoms with leflunomide use since its introduction in 2000.[1] Of these, 22 reports mentioned at least one of the following serious reactions: pneumonitis (8), interstitial lung disease (9), lung infiltration (4), or pulmonary fibrosis (3); it was considered that all these were likely to represent interstitial lung disease. Four patients died, but relative causality was difficult to assign as methotrexate was also given in many cases, however, several patients had been on methotrexate long-term without any problems. It was recommended that the pulmonary status of patients should be considered before starting leflunomide and monitored during treatment; if symptoms such as cough or dyspnoea develop or worsen, leflunomide may need to be stopped. ADRAC subsequently reported[2] that in June 2009 the number of reports of respiratory symptoms with leflunomide had increased to 196. Of these, 153 reports mentioned use with methotrexate including 23 of the 39 reports of interstitial lung disease.

The risk of interstitial lung disease with leflunomide has also been assessed using data from a large cohort study.[3] This study found that, overall, there was a twofold increase in the risk of interstitial lung disease in patients treated with leflunomide compared with those who did not receive leflunomide. However, subgroup analysis showed that this increase was limited to those patients with a history of methotrexate use or interstitial lung disease; in those with no previous methotrexate use or no history of interstitial lung disease, there was no increased risk with leflunomide. See also under Interactions, below.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and interstitial lung disease. *Aust Adverse Drug React Bull* 2006; **25:** 22–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 13/06/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Is it leflunomide lung? *Aust Adverse Drug React Bull* 2009; **28:** 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0908.pdf (accessed 23/10/09)
3. Suissa S, *et al*. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006; **54:** 1435–9.

Effects on the nervous system. Peripheral neuropathy has been associated with leflunomide use.[1-5] Up to October 2006, the Australian Adverse Drug Reactions Advisory Committee had received 659 reports of adverse reactions associated with leflunomide, 30 of which mentioned neuropathy or peripheral neuropathy;[4] leflunomide was the sole suspected drug in 24 of these cases. Recovery was noted after drug withdrawal in 6 patients, of whom 3 underwent washout procedures; however, 15 patients had not recovered at the time of the reports and there was no information on the remaining cases. More recently, up to October 2009, Health Canada[5] had received 26 reports of peripheral neuropathy symptoms associated with leflunomide. Of these, 9 reports had specified peripheral neuropathy; the duration of leflunomide therapy ranged from 2 months to 2 years and the reaction abated after stopping leflunomide.

1. Bonnel RA, Graham DJ. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther* 2004; **75:** 580–5.
2. Martin K, *et al*. Neuropathy associated with leflunomide: a case series. *Ann Rheum Dis* 2005; **64:** 649–50.
3. Metzler C, *et al*. Peripheral neuropathy in patients with systemic rheumatic diseases treated with leflunomide. *Ann Rheum Dis* 2005; **64:** 1798–1800.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and peripheral neuropathy. *Aust Adverse Drug React Bull* 2006; **25:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 13/06/08)
5. Health Canada. Leflunomide and peripheral neuropathy. *Can Adverse React News* 2010; **20** (2): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n2-eng.pdf (accessed 07/05/10)

Effects on the skin. A 58-year-old woman developed lupus erythematosus 1 month after starting leflunomide 20 mg daily for treatment of Sjögren's syndrome.[1] The rash resolved within 4 weeks of stopping leflunomide but recurred on 2 separate occasions when she took the drug again.

1. Gensburger D, *et al*. Lupus erythematosus with leflunomide: induction or reactivation? *Ann Rheum Dis* 2005; **64:** 153–5.

Overdose. Unintentional overdoses with leflunomide have been reported in 2 patients. In one case, no adverse effects were seen in a 40-year-old woman who had mistakenly taken both a 100-mg and a 20-mg tablet daily for 28 days;[1] in another case, a 70-year-old man who took 100 mg weekly, in addition to 20 mg daily, for over 2 years was found to have interstitial nephritis which improved after leflunomide was stopped.[2] In both cases, the 100-mg dose was meant to be taken for 2 or 3 days only as a loading dose.

1. Kamali S, *et al*. An unusual overdose of leflunomide in a patient with rheumatoid arthritis. *Ann Pharmacother* 2004; **38:** 1320–1.
2. Haydar AA, *et al*. Chronic overdose of leflunomide inducing interstitial nephritis. *Nephrol Dial Transplant* 2004; **19:** 1334–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies leflunomide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Pregnancy. Leflunomide is contra-indicated during pregnancy as its active metabolite has been shown to be teratogenic in *animals*. Pregnancy should therefore be excluded before beginning therapy, and licensed product information states that reliable contraception should be used in women of child-bearing potential (UK product information also recommends reliable contraception in men treated with leflunomide). Women wishing to become pregnant should wait for 2 years after stopping therapy, or if this is infeasible, a washout procedure (see below) should be performed and a waiting period of 6 weeks be observed from the time plasma concentrations of the metabolite fall below 20 nanograms/mL before attempting conception. A washout procedure with a waiting period of at least 3 months is recommended in men who wish to father children. Women who become pregnant during therapy should also undergo a washout procedure.

Washout procedure. If serious adverse effects occur during leflunomide therapy, licensed product information recommends that a drug washout procedure is performed. This may also be considered if a patient becomes pregnant while taking leflunomide, or if it is necessary to swap to another disease-modifying antirheumatic drug such as methotrexate.

For the washout procedure, either 8 g of colestyramine is given orally 3 times daily or 50 g of activated charcoal is given orally or via a nasogastric tube 4 times daily. Therapy is normally continued for 11 days, but should be repeated until plasma concentrations of the primary metabolite A-771726 are below 20 nanograms/mL, verified by two separate tests at least 14 days apart.

Interactions

Increased adverse effects may occur if leflunomide is given with other hepatotoxic or myelosuppressive drugs; these effects may also be seen when leflunomide treatment is followed by such drugs without a drug washout procedure (above). The risks of combined use with other disease-modifying antirheumatic drugs, particularly in the long term, have not been studied and such use is not advised in the UK; however, US licensed product information recommends that if long-term combined use is necessary, liver enzyme values and blood counts should be monitored monthly, for the first 6 months, rather than every 6 to 8 weeks (see Adverse Effects, Treatment, and Precautions, above).

See above for precautions about use with live vaccines.

Anticoagulants. For reference to the effect of leflunomide on the activity of *warfarin*, see under Immunosuppressants, p. 1534.2.

Methotrexate. Leflunomide therapy has been rarely associated with pancytopenia. Of the 18 cases (median age 65.5 years) reported in one series, 14 patients were also receiving methotrexate therapy.[1] The pancytopenia was typically severe and required hospitalisation; 5 patients had died, 4 of whom were also taking methotrexate. Time to onset of pancytopenia ranged from 11 days to 4 years. The authors concluded that the risk of pancytopenia during leflunomide treatment appeared to increase when used with methotrexate, and emphasised the importance of ongoing monitoring of blood counts.

Leflunomide therapy with or without methotrexate has also been rarely associated with interstitial lung disease including interstitial pneumonitis (see above). Up to March 2006, the Centre for Adverse Reactions Monitoring in New Zealand[2] had received 7 reports of pneumonitis associated with leflunomide in patients who were also taking methotrexate. Of these, 4 had taken methotrexate (which is also associated with pneumonitis) for more than 1 year. Respiratory symptoms developed 12 to 36 weeks after starting leflunomide therapy; 5 patients recovered, 1 died, and another improved but had some persisting respiratory impairment.

For advice on a drug washout procedure, see above.

1. Chan J, *et al*. Leflunomide-associated pancytopenia with or without methotrexate. *Ann Pharmacother* 2004; **38:** 1206–11.
2. Savage R. Leflunomide and pneumonitis. *Prescriber Update* 2006; **27:** 7–9.

Pharmacokinetics

After oral doses leflunomide undergoes rapid first-pass metabolism in the liver and gut wall to teriflunomide (A-771726), which is responsible for the majority of the *in vivo* activity. The bioavailability of leflunomide after oral doses ranges from 82 to 95%. Peak plasma concentrations of the active metabolite may occur from 1 to 24 hours after a dose.

For details on the distribution and elimination of teriflunomide, see p. 2626.3.

References.

1. Rozman B. Clinical pharmacokinetics of leflunomide. *Clin Pharmacokinet* 2002; **41:** 421–30.
2. Shi J, *et al*. Population pharmacokinetics of the active metabolite of leflunomide in pediatric subjects with polyarticular course juvenile rheumatoid arthritis. *J Pharmacokinet Pharmacodyn* 2005; **32:** 419–39.
3. Chan V, *et al*. Population pharmacokinetics and association between A77 1726 plasma concentrations and disease activity measures following administration of leflunomide to people with rheumatoid arthritis. *Br J Clin Pharmacol* 2005; **60:** 257–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Afiancen; Arava; Filartros; Inmunoartro; Lefluar; ***Austral.***: Arabloc; Arava; ***Austria***: Arava; ***Belg.***: Arava; ***Braz.***: Arava; ***Canad.***: Arava; ***Chile***: Arava; Artrilab; Artrimod†; Leflucross; ***China***: Airuohua (爱若华); Aokelu (奥克鲁); Guanping (关平); Hepai (赫派); Tuo Shu (妥抒); Youtong (优通); ***Cz.***: Arava; Repso; ***Denm.***: Arava; ***Fin.***: Arava; ***Fr.***: Arava; ***Ger.***: Arava; ***Gr.***: Arava; ***Hong Kong***: Arava; ***Hung.***: Arava; ***India***: Arava; Cleft; Lefno; Lefra; Lefumide; Lisifen; Rumalef; ***Indon.***: Arava; ***Irl.***: Arava; Repso; ***Israel***: Arava; ***Ital.***: Arava; ***Malaysia***: Arava; ***Mex.***: Arava; ***Neth.***: Arava; Repso; ***Norw.***: Arava; ***NZ***: Arava; ***Philipp.***: Arava; ***Pol.***: Arava; ***Port.***: Arava; ***Rus.***: Arava (Арава); ***S.Afr.***: Arava; ***Singapore***: Arava; ***Spain***: Arava; ***Swed.***: Arava; ***Switz.***: Arava; ***Thai.***: Arava; ***Turk.***: Arava; ***UK***: Arava; ***Ukr.***: Arava (Арава); ***USA***: Arava; ***Venez.***: Arava.

Pharmacopoeial Preparations
USP 36: Leflunomide Tablets.

Levacetylmethadol *(rINN)*

l-α-Acetylmethadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); LAM; Levacetilmetadol; Levacetylmetadol; Lévacétylméthadol; Levacetylmethadolum; Levasetyylimetadoli; Levomethadyl Acetate (USAN); *l*-Methadyl Acetate; Левацетилметадол.
(-)-4-Dimethylamino-1-ethyl-2,2-diphenylpentyl acetate.
$C_{23}H_{31}NO_2$=353.5
CAS — 1477-40-3 (levomethadyl); 34433-66-4 (levacetylmethadol).
ATC — N07BC03.
ATC Vet — QN07BC03.
UNII — R3B637Y991.

Levacetylmethadol Hydrochloride *(rINNM)*

Hidrocloruro de levacetilmetadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); Levacetilmetadol, hidrocloruro de; Lévacétylméthadol, Chlorhydrate de; Levacetylmethadoli Hydrochloridum; Levomethadyl Acetate Hydrochloride (USAN); Levomethadyl Acetate Hydrochloride; MK-790; Левацетилметадола Гидрохлорид.
(-)-(3*S*,6*S*)-6-(Dimethylamino)-4,4-diphenyl-3-heptanol acetate hydrochloride.
$C_{23}H_{31}NO_2$,HCl=390.0
CAS — 43033-72-3.
ATC — N07BC03.
ATC Vet — QN07BC03.
UNII — B54CW5KG52.

Profile

Levacetylmethadol, a diphenylheptane derivative, is a long-acting opioid analgesic (p. 108.1); it is a derivative of methadone (p. 88.3). It was used as the hydrochloride in the management of opioid dependence. However, the proarrhythmic effects led to its withdrawal in the EU and the USA.

Levomethadone Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levometadona; Levometadona, hidrocloruro de; Levometadonhidroklorid; Levometadonhydroklorid; Levometadonihydrokloridi; Levometadono hidrochloridas; Lévométhadone, Chlorhydrate de; Levomethadon-hydrochlorid; Levomethadonhydrochlorid; Levomethadoni Hydrochloridum; (-)-Methadone Hydrochloride; Левометадона Гидрохлорид.
(-)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.
$C_{21}H_{27}NO$,HCl=345.9
CAS — 125-58-6 (levomethadone); 5967-73-7 (levomethadone hydrochloride).
UNII — V57LC776C0.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Levomethadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

Profile

Levomethadone is an opioid analgesic (p. 108.1). It is the active isomer of racemic methadone (p. 88.3) and is used similarly, as the hydrochloride, in the treatment of severe pain and in the management of opioid dependence.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: L-Polamidon.

Levorphanol Tartrate *(BANM, rINNM)*

Levorfanol, tartrato de; Levorphan Tartrate; Levorphanol Bitartrate; Lévorphanol, Tartrate de; Levorphanoli Tartras; Methorphinan Tartrate; Tartrato de levorfanol; Леворфанола Тартрат.
(-)-9a-Methylmorphinan-3-ol hydrogen tartrate dihydrate.
$C_{17}H_{23}NO,C_4H_6O_6.2H_2O$=443.5
CAS — 77-07-6 (levorphanol); 125-72-4 (anhydrous levorphanol tartrate); 5985-38-6 (levorphanol tartrate dihydrate).
UNII — 04WQU6T9QI.

Pharmacopoeias. In *US.*

USP 36: (Levorphanol Tartrate). A practically white, odourless, crystalline powder. Soluble 1 in 50 of water and 1 in 120 of alcohol; insoluble in chloroform and in ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Levorphanol tartrate, a phenanthrene derivative, is a potent opioid analgesic (p. 108.1) used in the management of moderate to severe pain. The analgesic effect usually begins about 10 to 60 minutes after oral doses and lasts up to about 8 hours. A usual initial oral dose of levorphanol tartrate is 2 mg repeated in 6 to 8 hours if necessary; the dose may be increased to 3 mg every 6 to 8 hours, adjusted according to response. The maximum initial daily dose in non-opioid tolerant patients should not exceed 12 mg. Elderly or debilitated patients may require lower doses; initial doses should be reduced by 50% or more.

Levorphanol tartrate has also been given by intramuscular, subcutaneous, or slow intravenous injection for pain relief and for premedication.

References.

1. Prommer E. Levorphanol: the forgotten opioid. *Support Care Cancer* 2007; **15:** 259–64.

Preparations

Pharmacopoeial Preparations
USP 36: Levorphanol Tartrate Injection; Levorphanol Tartrate Tablets.

Licofelone *(rINN)*

Licofelona; Licofélone; Licofelonum; ML-3000; Ликофельон.
[6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl]acetic acid.
$C_{23}H_{22}ClNO_2$=379.9
CAS — 156897-06-2.
UNII — P5T6BYS22Y.

Profile

Licofelone is an NSAID (p. 102.3) stated to be both a cyclooxygenase and lipoxygenase inhibitor. It has been investigated for the treatment of osteoarthritis.

References.

1. Kulkarni SK, Singh VP. Licofelone—a novel analgesic and anti-inflammatory agent. *Curr Top Med Chem* 2007; **7:** 251–63.
2. Fischer L, *et al*. The molecular mechanism of the inhibition by licofelone of the biosynthesis of 5-lipoxygenase products. *Br J Pharmacol* 2007; **152:** 471–80.
3. Raynauld JP, *et al*. Canadian Licofelone Study Group. Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. *Ann Rheum Dis* 2009; **68:** 938–47.

Lornoxicam *(BAN, USAN, rINN)*

Chlorotenoxicam; Chlortenoxicam; CTX; Lornoksikaami; Lornoksikam; Lornoxicamum; Lornoxicanum; Lornoxikam; Ro-13-9297; TS-110; Лорноксикам.
6-Chloro-4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-thieno[2,3-*e*][1,2]-thiazine-3-carboxamide 1,1-dioxide.
$C_{13}H_{10}ClN_3O_4S_2$=371.8
CAS — 70374-39-9.
ATC — M01AC05.
ATC Vet — QM01AC05.
UNII — ER09126G7A.

Profile

Lornoxicam, an oxicam derivative, is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis; it is also used in the treatment of other painful conditions including postoperative pain.

In the treatment of osteoarthritis and rheumatoid arthritis lornoxicam is given in an initial oral daily dose of 12 mg in two or three divided doses; if necessary the daily dose may be increased to a maximum of 16 mg.

Lornoxicam is given in oral doses of 8 to 16 mg daily for the treatment of pain; similar doses may be given by intravenous or intramuscular injection.

The hydrochloride salt has also been used.

References.

1. Balfour JA, *et al*. Lornoxicam: a review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996; **51:** 639–57.
2. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam: a short half-life oxicam. *Clin Pharmacokinet* 1998; **34:** 421–8.
3. Frizziero L, *et al*. Studio a lungo termine su efficacia e sicurezza terapeutica di lornoxicam nell'artrite reumatoide. *Minerva Med* 2002; **93:** 315–20.
4. Thienthong S, *et al*. Treatment of pain after spinal surgery in the recovery room by single dose lornoxicam: a randomized, double blind, placebo-controlled trial. *J Med Assoc Thai* 2004; **87:** 650–5.
5. Zhao H, *et al*. Application of lornoxicam to patient-controlled analgesia in patients undergoing abdominal surgeries. *Chin Med Sci J* 2005; **20:** 59–62.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lornoxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hypodol; Xefo; ***Austria***: Xefo; ***Braz.***: Xefo; ***China***: Da Lu (达路); Qinda (沁达); Xafon (可塞风); Zheng Ting (正庭); ***Cz.***: Xefo; ***Denm.***: Xefo; ***Ger.***: Telos†; ***Gr.***: Xefo; ***Hung.***: Xefo; ***India***: C-Cum; Camri; Flexilor; Lenor; Lofecam; Loni; Lormoto; Lornica; Lornistar; Lorniz; Lornofan; Lornoxi; Lorox; Lorsaid; Lorwalk; Loxcam; Mitilor; Movilor; Neucam; Nextcam; Noxi; ***Irl.***: Xefo; ***Israel***: Xefo; ***Ital.***: Noxon; Taigalor; ***Jpn***: Lorcam; ***Neth.***: Xefo†; ***Pol.***: Xefo; ***Port.***: Acabel; Bosporon; ***Rus.***: Xefocam (Ксефокам); ***S.Afr.***: Xefo; ***Spain***: Acabel; Bosporon; ***Swed.***: Xefo; ***Switz.***: Xefo; ***Turk.***: Xefo; ***Ukr.***: Xefocam (Ксефокам); ***Venez.***: Acabel.

Multi-ingredient Preparations. ***India***: Campar; Cincam-P; Lenor-P; Lezdes-P; Lolira-P; Loni-Plus; Lorbit-P; Lorchek-MR; Lorchek-P; Lorflam-P; Lormoto-P; Lornistar-P; Lornofan-P; Lornoxi-P; Lorsaid-P; Lorter-P; Lorthox-P; Lorup Plus; Lorwalk-P; Loxcam-P; Loxicam-P; Luloxy-P; Movilor-P; Neucam-P; Nextcam-P; Noxi-P; Orilox-P; Paratel-LC.

Loxoprofen Sodium *(rINNM)*

CS-600 (loxoprofen); Loxoprofène Sodique; Loxoprofeno sódico; Natrii Loxoprofenum; Натрий Локсопрофен.
Sodium (±)-*p*-[(2-oxocyclopentyl)methyl]hydratropate dihydrate.
$C_{15}H_{17}O_3Na,2H_2O$=304.3
CAS — 68767-14-6 (loxoprofen); 80382-23-6 (loxoprofen sodium); 226721-96-6 (loxoprofen sodium dihydrate).
UNII — NDC2M7399S (anhydrous loxoprofen sodium); Z2DR42L11Y (loxoprofen sodium dihydrate).

Pharmacopoeias. In *Jpn.*

Profile

Loxoprofen sodium is an NSAID (p. 102.3) used in painful and inflammatory conditions. It is given as the dihydrate although doses are expressed in terms of the anhydrous salt. Anhydrous loxoprofen sodium 10 mg is equivalent to about 11.3 mg of loxoprofen sodium dihydrate.

For the management of pain and inflammation associated with musculoskeletal and joint disorders, or operative procedures, a usual oral dose equivalent to 60 mg of the anhydrous form has been given three times daily. It has also been applied topically as a poultice containing the equivalent of 100 mg of the anhydrous form or as a 1% gel.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Oxeno; ***Braz.***: Loxonin; ***China***: An Pu Luo (安普洛); Bei Luo (倍珞); Loxonin (乐松); Luo Lie Tong (洛列通); Luo Na (洛那); Qing Fu (庆福); Ruo Mai (若迈); Sai Ke Tong (赛克同); San Yuan Shu Xing (三元舒星); Weikang DiKe (康威迪克); Zhen Tong Yan (真恫言); ***Jpn***: Lobu; Loxonin; ***Mex.***: Loxonin; ***Philipp.***: Loxonin†; ***Thai.***: Loxonin; ***Venez.***: Loxonin.

Lumiracoxib *(BAN, USAN, rINN)*

Cox-189; Lumiracoxibum; Лумиракоксиб.

2-{[(2-Chloro-6-fluorophenyl)amino]-5-methylphenyl}acetic acid.

$C_{15}H_{13}ClFNO_2$=293.7

CAS — 220991-20-8.

ATC — M01AH06.

ATC Vet — QM01AH06.

UNII — V91T9204HU.

Uses and Administration

Lumiracoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It has been withdrawn in many countries after reports of hepatotoxicity. Lumiracoxib has been used in the treatment of osteoarthritis of the knee and hip in an oral dose of 100 mg once daily. Higher doses of up to 400 mg daily have also been used but may be associated with an increased risk of hepatotoxicity (see Effects on the Liver, below).

References.

1. Lyseng-Williamson KA, Curran MP. Lumiracoxib. *Drugs* 2004; **64:** 2237–46.
2. Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second-generation cyclooxygenase 2 selective inhibitor. *Expert Opin Invest Drugs* 2005; **14:** 521–33.
3. Rordorf CM, *et al*. Clinical pharmacology of lumiracoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2005; **44:** 1247–66.
4. Schnitzer TJ, *et al*. Lumiracoxib in the treatment of osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: results of three dose-response studies. *Curr Med Res Opin* 2005; **21:** 151–61.
5. Berenbaum F, *et al*. Efficacy of lumiracoxib in osteoarthritis: a review of nine studies. *J Int Med Res* 2005; **33:** 21–41.
6. Sheldon E, *et al*. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005; **27:** 64–77.
7. Fleischmann R, *et al*. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. *Clin Rheumatol* 2006; **25:** 42–53.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving lumiracoxib; it should be stopped at the first signs of hypersensitivity.

Lumiracoxib use, particularly at high doses, may cause severe liver toxicity (see Effects on the Liver, below) and its use is contra-indicated in patients with hepatic disease. It should also not be used in those with a history of drug-induced increases in transaminase values greater than 3 times the upper limit of normal (ULN) or in those taking other drugs known to cause clinically significant hepatotoxicity. All patients should have baseline liver function tests before starting lumiracoxib treatment; those in whom transaminases are more than 1.5 times the ULN should not start treatment. Liver function tests should be repeated monthly and lumiracoxib should be stopped in those patients with an increase in transaminases greater than 3 times the ULN; in those with an increase greater than 2 times the ULN, liver function tests should be repeated in 7 days. Patients should be advised to report any symptoms suggestive of liver toxicity such as anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine, and jaundice.

Lumiracoxib should not be used in patients with ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus.

Lumiracoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and moderate to severe renal impairment associated with a creatinine clearance of less than 50 mL/minute. Caution is recommended when using lumiracoxib in dehydrated patients; it may be advisable to rehydrate patients before giving lumiracoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p. 128.3). The cardiovascular safety of lumiracoxib has been assessed in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[1] which involved over 18 000 patients with osteoarthritis. Lumiracoxib 400 mg daily (2 to 4 times the recommended dose) was compared against either naproxen 1 g daily, or ibuprofen 2.4 g daily; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After a planned treatment duration of 1 year, the incidence of myocardial infarction, stroke, or cardiovascular death with lumiracoxib was found to be similar to that for ibuprofen or naproxen. More events were noted in the lumiracoxib versus naproxen subgroup than in the lumiracoxib versus ibuprofen group; however, this difference was not statistically significant and the authors considered that the higher number of patients with a history of vascular risk in the lumiracoxib versus naproxen subgroup could explain this finding. In addition, it was noted that the incidence of heart failure was less frequent with lumiracoxib although, again, this was not significant; however, blood pressure changes from baseline were significantly less likely with lumiracoxib than with ibuprofen or naproxen.

More recently, a meta-analysis[2] by the manufacturer (which included the above study along with other published and unpublished clinical studies of lumiracoxib in the treatment of osteoarthritis and rheumatoid arthritis) has also found no evidence that the risk of thrombotic events with lumiracoxib is significantly increased when compared with placebo, with naproxen (1 g daily), or with the NSAIDs diclofenac (150 mg daily), ibuprofen (2.4 g daily), celecoxib (up to 400 mg daily), and rofecoxib (25 mg daily) as a group.

For further details on the relative risk of cardiovascular thrombotic events with NSAIDs, see p. 105.1.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p. 37.3.

1. Farkouh ME, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; **364:** 675–84.
2. Matchaba P, *et al*. Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials ⩾1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. *Clin Ther* 2005; **27:** 1196–1214.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as lumiracoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information has stated that upper gastrointestinal ulceration and bleeds, in some cases fatal, have occurred with lumiracoxib treatment; consequently it should be used with caution in patients at risk of such events.

Results from controlled studies confirm that NSAIDs selective for COX-2 are associated with a lower incidence of serious gastrointestinal effects. A study[1] in patients with osteoarthritis taking lumiracoxib at supratherapeutic doses (400 mg daily) concluded that there was a lower incidence of definite or probable upper gastrointestinal ulcer complications (bleeding, perforation, or obstruction) after 12 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or naproxen 1 g daily). The incidence of endoscopically-detected ulcers was also less with lumiracoxib than with non-selective NSAIDs. However, the use of low-dose aspirin appeared to nullify any protective gastrointestinal effect of lumiracoxib.

An analysis[2] of pooled data from 15 pre-licensing studies in patients with rheumatoid arthritis or osteoarthritis has also concluded that the risk of upper gastrointestinal ulcers and ulcer complications is less with lumiracoxib than with non-selective NSAIDs (diclofenac, naproxen, and ibuprofen).

1. Schnitzer TJ, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; **364:** 665–74.
2. Hawkey CJ, *et al*. Gastrointestinal tolerability of lumiracoxib in patients with osteoarthritis and rheumatoid arthritis. *Clin Gastroenterol Hepatol* 2006; **4:** 57–66.

Effects on the kidneys. Limited evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as lumiracoxib suggests that these NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Effects on the liver. In August 2007, the regulatory authority in Australia withdrew lumiracoxib from the market after reports of hepatotoxicity.[1,2] In the 6 months since marketing, there had been 8 reports of serious adverse liver reactions resulting in 2 deaths and 2 transplantations. There was some concern that pre-licensing clinical study data seemed to suggest that those patients who developed elevated liver function tests while on lumiracoxib would recover once the drug was stopped; however, in the 8 Australian cases, some patients did not improve because of the severity of the hepatic damage.

In response to the Australian data, the MHRA in the UK reported that it had received 16 reports of suspected adverse reactions to lumiracoxib;[3] of these, one was a case of hepatotoxicity in which the patient recovered after the drug was withdrawn. Worldwide, the MHRA was aware of 11 reports of serious hepatotoxicity including 9 cases of liver failure, 2 deaths, and 3 liver transplants suspected to be at least possibly related to lumiracoxib use. The dose used in most of the cases was higher than the maximum dose of 100 mg daily that is recommended in the UK and other European countries. (Higher maximum daily doses have been licensed in other countries; in Australia, the licensed maximum dose was 400 mg daily for some conditions.) At that time in the UK, new prescribing restrictions on the use of lumiracoxib in osteoarthritis were issued (see Adverse Effects and Precautions, above) while its safety continued to be reviewed by European regulatory authorities. After a review in October 2007, the MHRA reiterated its earlier prescribing restrictions for lumiracoxib and stated the issue of hepatotoxicity would continue to be monitored. They also advised that, worldwide up until then, there had been 19 cases of severe liver reactions, including 13 of liver failure, 2 deaths, and 3 liver transplants suspected to be possibly related to use of lumiracoxib.[4] At about the same time, lumiracoxib was withdrawn from the Canadian market after Health Canada noted 4 cases of severe hepatotoxicity, including 2 in Canada, associated with the 100-mg dose of lumiracoxib.[5] Subsequently, in November 2007, the MHRA suspended the product licence for lumiracoxib after a further review of worldwide safety data showed an increased number of serious liver reactions with the 100-mg dose which, in some cases, occurred with short-term use.[6] In addition, the EMEA[7] has recommended its withdrawal in the EU.

1. Australian Therapeutic Goods Administration. Urgent advice regarding management of patients taking lumiracoxib (Prexige) (issued 13th August, 2007). Available at: http://www.tga.gov.au/alerts/prexige.htm (accessed 08/11/07)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Withdrawal of lumiracoxib in Australia. *Aust Adverse Drug React Bull* 2008; **27:** 6–7. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0804.pdf (accessed 17/07/08)
3. MHRA. New (interim) restrictions on prescription of lumiracoxib, following concerns over liver safety (issued 24th August, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032098 (accessed 29/08/08)
4. MHRA. Lumiracoxib and liver adverse reactions (issued 16th October, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032831 (accessed 29/08/08)
5. Health Canada. Withdrawal of market authorisation for Prexige. (issued 4th October, 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_141_e.html (accessed 30/10/07)
6. MHRA. Lumiracoxib (Prexige): suspension of marketing authorisations (issued 19th November, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033073 (accessed 29/08/08)
7. EMEA. European Medicines Agency recommends withdrawal of the marketing authorisations for lumiracoxib-containing medicines (issued 13th December, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/PR_Lumiracoxib_57930107en.pdf (accessed 17/07/08)

Interactions

For interactions associated with NSAIDs in general, see p. 107.3. Lumiracoxib may cause liver toxicity and consequently it should not be used with other drugs known to cause clinically significant hepatotoxicity.

There is the possibility that lumiracoxib may decrease the clearance of drugs that are cytochrome P450 CYP2C9 substrates and caution is advised when it is given with CYP2C9 substrates that have a narrow therapeutic index such as phenytoin and warfarin.

Pharmacokinetics

Lumiracoxib is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations occur in about 2 hours. Protein binding is at least 98%. Lumiracoxib undergoes extensive hepatic metabolism; several enzymes appear to be involved including glucuronosyltransferase and cytochrome P450 isoenzymes. The main oxidative pathway is mediated by the CYP2C9 isoenzyme; however, this does not appear to be the major pathway. Three major metabolites have been identified: 4′-hydroxy-lumiracoxib, 5-carboxy-lumiracoxib, and 4′-hydroxy-5-carboxy-lumiracoxib. The 4′-hydroxy metabolite is active as a cyclo-oxygenase-2 (COX-2) inhibitor although it is less potent than lumiracoxib. The plasma half-life of lumiracoxib is about 4 hours. Slightly more of a dose is excreted in the urine (54%) than in the faeces (about 43%); only about 5% of a dose is excreted unchanged.

References.

1. Scott G, *et al*. Pharmacokinetics of lumiracoxib in plasma and synovial fluid. *Clin Pharmacokinet* 2004; **43:** 467–78.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prexige; ***Austria***: Prexige†; ***Braz.***: Prexige; ***Chile***: Prexige†; ***Gr.***: Frexocel; Prexige; ***Hung.***: Prexige†; ***Indon.***: Prexige†; ***NZ***: Prexige†; ***Swed.***: Prexige†; ***Turk.***: Prexige.

Lysine Aspirin

Acetilsalicilato de lisina; Aspirin DL-Lysine; Lysiiniasetyylisalisylaatti; Lysinacetylsalicylat; DL-Lysine Acetylsalicylate; Lysine Acetylsalicylate; Lysinum Acetylsalicylicum; Лизин-Аспирин.

$C_{15}H_{22}N_2O_6$=326.3
CAS — 62952-06-1.
UNII — 2JJ274J145.

Pharmacopoeias. In *Fr.*

Uses and Administration

Lysine aspirin has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p. 22.3). When given, lysine aspirin dissociates into lysine and aspirin; aspirin is then hydrolysed to salicylic acid. Lysine aspirin 900 mg is equivalent to about 500 mg of aspirin.

Lysine aspirin is used in the treatment of pain, fever, and rheumatic disorders. It is given in oral doses equivalent to 0.5 to 1 g of aspirin, repeated every 4 to 8 hours as needed up to a maximum of 3 g of aspirin daily (2 g daily in the elderly) for pain and fever. The dose for rheumatic disorders is equivalent to 3 to 6 g of aspirin daily in 3 or 4 divided doses. Lysine aspirin is also given intramuscularly or intravenously in similar doses; the maximum daily parenteral dose is equivalent to 4 g of aspirin for very severe pain and to 6 g of aspirin for rheumatic disorders.

Lysine aspirin is also used with metoclopramide in the treatment of migraine.

Lysine aspirin has also been used in the management of thromboembolic disorders.

Headache. Some references to the use of lysine aspirin, often with metoclopramide, in the treatment of migraine.

1. Tfelt-Hansen P, *et al.* The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346:** 923–6.
2. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. *Cephalalgia* 1999; **19:** 581–8.
3. Tfelt-Hansen P. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide (Migpriv) in the treatment of migraine attacks: comparison with placebo and oral sumatriptan. *Funct Neurol* 2000; **15** (suppl 3): 196–201.

Nasal polyps. Two long-term controlled studies[1] suggested that topical (endonasal) lysine aspirin may be effective in preventing the recurrence of nasal polyps after surgical removal (see p. 1608.2) in both aspirin-tolerant and aspirin-sensitive patients. This effect may be attributed to the non-specific anti-inflammatory properties of lysine aspirin. Although no adverse effects were reported in this study, hypersensitivity reactions have been seen after use of salicylates in the presence of nasal polyps (see Hypersensitivity under Adverse Effects of Aspirin, p. 25.2).

In another study[2] intranasal lysine aspirin did not show significant clinical benefit in preventing the recurrence of nasal polyps when compared with placebo. However, significant improvement at a microscopic level was noted.

1. Nucera E, *et al.* Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax* 2000; **55** (suppl 2): S75–78.
2. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. *Laryngoscope* 2005; **115:** 1385–90.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2. Anaphylactic shock has been reported in patients given lysine aspirin by injection.

Lysine aspirin, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Hypersensitivity. For a suggestion that inhaled or intranasal lysine aspirin might be more suitable than aspirin for the diagnosis of sensitivity to NSAIDs, see under Hypersensitivity on p. 25.2.

Interactions

For interactions associated with aspirin, see p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aspirina; Decitriol; Yectaspirin†; ***Belg.***: Aspegic; Cardegic; ***China***: Lai Bi Lin (来比林); ***Cz.***: Kardegic; ***Fr.***: Aspegic; Cardiosolupsan†; Kardegic; ***Gr.***: Aspicalm; Draspir; Egicalm Cardio†; Egicalm; Ogiflegon; ***Hung.***: Aspegic; Kardegic; ***Ital.***: Aspegic†; Cardirene; Flectadol; ***Mex.***: Coraspir; Kardegic; ***Neth.***: Aspegic; ***Pol.***: Laspal†; ***Port.***: Aspegic; Inesprin†; Intraspir†; Kardegic†; Lisaspin; ***Spain***: Inyesprin; ***Switz.***: Alcacyl instantanee; Aspegic; Kardegic; ***Turk.***: Aspegic; ***Ukr.***: Acelysin (Ацелизин).

Multi-ingredient Preparations. ***Belg.***: Migpriv; ***Chile***: Dolotol 12; ***Fin.***: Migpriv†; ***Fr.***: Aspegic Codeine†; Migpriv; ***Gr.***: Egityl; Premig; ***Hung.***: Migpriv; ***India***: Biospirin; ***Ital.***: Migpriv; Migraprim; ***Mex.***: Antigram; ***Neth.***: Migrafin; ***Pol.***: Migpriv; ***Swed.***: Migpriv†; ***Switz.***: Migpriv†; ***Turk.***: Migprin; ***UK***: Migramax.

Magnesium Salicylate

Salicilato magnésico; Магния Салицилат.
$C_{14}H_{10}MgO_6.4H_2O$=370.6
CAS — 18917-89-0 (anhydrous magnesium salicylate); 18917-95-8 (magnesium salicylate tetrahydrate).
UNII — 41728CY7UX (magnesium salicylate); JQ69D454N1 (anhydrous magnesium salicylate).

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Magnesium Salicylate). A white, odourless, efflorescent, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Magnesium salicylate has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p. 22.3). Anhydrous magnesium salicylate 1 g is equivalent to about 1.2 g of aspirin. It is used in the treatment of pain and fever and has been used in the management of inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and other arthritides. Usual oral doses of magnesium salicylate, expressed in terms of anhydrous magnesium salicylate, are about 300 to 600 mg every 4 hours for pain or fever.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2. Magnesium salicylate should also be used with caution in renal impairment because of the risk of hypermagnesaemia.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to magnesium salicylate.

Interactions

For interactions associated with salicylates, see Aspirin, p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Herbogesic†; ***USA***: Backache Maximum Strength Relief; Bayer Select Maximum Strength Backache; Doans; Magan; Mobidin; Momentum Muscular Backache Formula; MST.

Multi-ingredient Preparations. ***Cz.***: Cholagol; ***Hung.***: Cholagol; ***Rus.***: Cholagol (Холагол); ***Ukr.***: Cholagol (Холагол); ***USA***: Back Pain-Off; Cafgesic Forte†; Combiflex ES†; Durabac Forte; Extra Strength Doans PM; Painaid Back Relief; Painaid BRF Back Relief Formula; Tetra-Mag†.

Pharmacopoeial Preparations
USP 36: Magnesium Salicylate Tablets.

Meclofenamic Acid *(BAN, USAN, rINN)*

Acide Méclofénamique; Ácido meclofenámico; Acidum Meclofenamicum; CI-583; INF-4668; Meclofenámico, ácido; Меклофенамовая Кислота.
N-(2,6-Dichloro-*m*-tolyl)anthranilic acid.
$C_{14}H_{11}Cl_2NO_2$=296.1
CAS — 644-62-2.
ATC — M01AG04; M02AA18.
ATC Vet — QM01AG04; QM02AA18.
UNII — 48I5LU4ZWD.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Meclofenamic Acid). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in ether; soluble in dimethylformamide and in 1M sodium hydroxide.

Meclofenamate Sodium *(BANM, USAN, rINNM)*

Méclofénamate de Sodium; Meclofenamato sódico; Natrii Meclofenamas; Натрий Меклофенамат.
$C_{14}H_{10}Cl_2NNaO_2.H_2O$=336.1
CAS — 6385-02-0.
UNII — 94NJ818U2W.

Pharmacopoeias. In *US.*

USP 36: (Meclofenamate Sodium). A white to creamy white, odourless to almost odourless, crystalline powder. Freely soluble in water, the solution sometimes being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; the solution is clear above pH 15. Slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Meclofenamic acid, an anthranilic acid derivative similar to mefenamic acid (p. 86.1), is an NSAID (p. 102.3). It is given orally as the sodium salt in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, in mild to moderate pain, and in dysmenorrhoea and menorrhagia.

Doses of meclofenamate sodium are expressed in terms of the equivalent amount of meclofenamic acid. Meclofenamic acid 100 mg is equivalent to about 113.5 mg of meclofenamate sodium. In arthritic conditions it is given in doses equivalent to 200 to 400 mg daily; daily doses are usually given in 3 or 4 divided doses. For relief of mild to moderate pain doses are 50 to 100 mg every 4 to 6 hours; the daily dose should not exceed 400 mg. The dose in the treatment of dysmenorrhoea and menorrhagia is 100 mg three times daily for up to 6 days during menstruation.

Meclofenamic acid has been given as a rectal suppository and is also used in veterinary medicine.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Incidence of adverse effects. The commonest adverse effect in 2500 patients given meclofenamate sodium was gastrointestinal disturbance.[1] Diarrhoea occurred in 11.2% of patients in double-blind studies and 32.8% of patients in long-term studies (up to 3 years). Ulcers were detected in 22 patients during therapy and rashes occurred in 4% of patients. Transient increases in serum aminotransferases and BUN occurred in some patients.

1. Preston SN. Safety of sodium meclofenamate (Meclomen™). *Curr Ther Res* 1978; **23** (suppl 4S): S107–S112.

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with meclofenamate therapy.

1. Wishner AJ, Milburn PB. Meclofenamate sodium-induced agranulocytosis and suppression of erythropoiesis. *J Am Acad Dermatol* 1985; **13:** 1052–3.
2. Rodriguez J. Thrombocytopenia associated with meclofenamate. *Drug Intell Clin Pharm* 1981; **15:** 999.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Meclofenamate sodium is readily absorbed when given orally. Peak plasma concentrations occur about 0.5 to 2 hours after ingestion. Meclofenamate is over 99% bound to plasma proteins. The plasma elimination half-life of meclofenamate sodium is about 2 to 4 hours. It is metabolised by oxidation, hydroxylation, dehalogenation, and conjugation with glucuronic acid and excreted in urine mainly as glucuronide conjugates of the metabolites. About 20 to 30% is recovered in the faeces. One of the metabolites, a 3-hydroxymethyl compound, is reported to be active although to a lesser extent than the parent drug.

References.

1. Koup JR, *et al.* A single and multiple dose pharmacokinetic and metabolism study of meclofenamate sodium. *Biopharm Drug Dispos* 1990; **11:** 1–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Meclomen; ***Gr.***: Meclomen; ***Ital.***: Lenidolor; Movens.

Pharmacopoeial Preparations
USP 36: Meclofenamate Sodium Capsules.

Mefenamic Acid *(BAN, USAN, rINN)*

Acide Méfénamique; Ácido mefenámico; Acidum Mefenamicum; CI-473; CN-35355; INF-3355; Kwas mefenamowy; Kyselina mefenamová; Mefenaamihappo; Mefenámico, ácido; Mefenamik Asit; Mefenaminsäure; Mefenaminsav; Mefenamo rūgštis; Mefenamsyra; Мефенамовая Кислота.
N-(2,3-Xylyl)anthranilic acid.
$C_{15}H_{15}NO_2$=241.3
CAS — 61-68-7.
ATC — M01AG01.
ATC Vet — QM01AG01.
UNII — 367589PJ2C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Mefenamic Acid). A white to almost white, microcrystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; dissolves in dilute solutions of alkali hydroxides.

USP 36: (Mefenamic Acid). A white to off-white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in chloroform; soluble in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Uses and Administration

Mefenamic acid, an anthranilic acid derivative, is an NSAID (p. 102.3), although its anti-inflammatory properties are considered to be minor.

It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, and dysmenorrhoea, in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and in menorrhagia.

In the UK, the usual oral dose is 500 mg three times daily. US licensed product information recommends an initial dose of 500 mg followed by 250 mg every 6 hours as needed. In addition, in the USA, when mefenamic acid is used in the treatment of mild to moderate pain in adults and adolescents aged 14 years and over, it is also recommended that it should not be given for longer than 7 days at a time.

For doses of mefenamic acid in children, see below.

Mefenemate sodium has also been used.

Administration in children. In the UK, licensed product information states that mefenamic acid may be used in children for the treatment of Still's disease (see Juvenile Idiopathic Arthritis, p. 12.1) and fever, and for dysmenorrhoea in older children; a suggested oral dose in those over 6 months of age is 25 mg/kg daily in divided doses. Treatment in children should be given for no longer than 7 days unless they are receiving mefenamic acid for Still's disease. However, the *BNFC* only recommends mefenamic acid for acute pain, including dysmenorrhoea and menorrhagia, in those aged 12 years and over who may be given the usual adult dose (see above).

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Treatment should be stopped if diarrhoea and rashes occur. Other effects reported include drowsiness, and effects on the blood such as thrombocytopenia, occasionally haemolytic anaemia, and rarely aplastic anaemia. Convulsions may occur on overdosage.

Mefenamic acid is contra-indicated in patients with inflammatory bowel disease. Licensed product information recommends that blood counts and liver and renal function should be monitored during long-term therapy. Drowsiness may affect the performance of skilled tasks.

Mefenamic acid may give a false positive in some tests for the presence of bile in the urine.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given mefenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of mefenamic acid distributed into breast milk is too small to be harmful to a breast-fed infant. An early study[2] confirms that the distribution of mefenamic acid into breast milk is minimal. However, licensed product information contra-indicates the use of mefenamic acid in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Buchanan RA, *et al.* The breast milk excretion of mefenamic acid. *Curr Ther Res* 1968; **10:** 592–6.

Effects on the blood. References to haematological reactions in patients taking mefenamic acid including haemolytic anaemia,[1] leucopenia,[2] neutropenia,[3] and agranulocytosis.[4]

1. Scott GL, *et al.* Autoimmune haemolytic anaemia and mefenamic acid therapy. *BMJ* 1968; **3:** 534–5.
2. Burns A, Young RE. Mefenamic acid induced leucopenia in the elderly. *Lancet* 1984; **ii:** 46.
3. Handa SI, Freestone S. Mefenamic acid-induced neutropenia and renal failure in elderly females with hypothyroidism. *Postgrad Med J* 1990; **66:** 557–9.
4. Muroi K, *et al.* Treatment of drug-induced agranulocytosis with granulocyte-colony stimulating factor. *Lancet* 1989; **ii:** 55.

Effects on the gastrointestinal tract. Reversible steatorrhoea has occurred[1] with mefenamic acid; it may also provoke colitis in patients without a history of this condition.[2]

1. Marks JS, Gleeson MH. Steatorrhoea complicating therapy with mefenamic acid. *BMJ* 1975; **4:** 442.
2. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.

Effects on the kidneys. Nonoliguric renal failure has occurred in elderly patients who had had diarrhoea and vomiting while taking mefenamic acid and had continued to take the drug. It is normally recommended that mefenamic acid be stopped in the event of diarrhoea and it was suggested that in these patients the gastrointestinal toxicity had led to fluid and electrolyte depletion, thus predisposing these patients to mefenamic acid's nephrotoxicity.[1] There has been a subsequent report[2] of nonoliguric renal failure in elderly patients given mefenamic acid for musculoskeletal pain.

1. Taha A, *et al.* Non-oliguric renal failure during treatment with mefenamic acid in elderly patients: a continuing problem. *BMJ* 1985; **291:** 661–2.
2. Grant DJ, MacConnachie AM. Mefenamic acid is more dangerous than most. *BMJ* 1995; **311:** 392.

Effects on the skin. Bullous pemphigoid, together with haemolytic anaemia and diarrhoea,[1] and fixed drug eruptions[2-4] have been associated with the use of mefenamic acid. Additionally, Stevens-Johnson syndrome, together with cholestatic hepatitis and haemolytic anaemia, in one patient has been attributed to mefenamic acid.[5] It is generally recommended that mefenamic acid should be withdrawn if skin reactions develop.

1. Shepherd AN, *et al.* Mefenamic acid-induced bullous pemphigoid. *Postgrad Med J* 1986; **62:** 67–8.
2. Wilson CL, Otter A. Fixed drug eruption associated with mefenamic acid. *BMJ* 1986; **293:** 1243.
3. Long CC, *et al.* Fixed drug eruption to mefenamic acid: a report of three cases. *Br J Dermatol* 1992; **126:** 409–11.
4. Rallis E. Dalmatian dog'-like skin eruption (two cases of multifocal fixed drug eruption induced by mefenamic acid). *J Eur Acad Dermatol Venereol* 2005; **19:** 753–5.
5. Chan JCN, *et al.* A case of Stevens-Johnson syndrome, cholestatic hepatitis and haemolytic anaemia associated with use of mefenamic acid. *Drug Safety* 1991; **6:** 230–4.

Overdosage. Mefenamic acid overdose has been associated with CNS toxicity, especially with convulsions.[1] Coma[2,3] has also been reported.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. Gössinger H, *et al.* Coma in mefenamic acid poisoning. *Lancet* 1982; **ii:** 384.
3. Hendrickse MT. Mefenamic acid overdose mimicking brainstem stroke. *Lancet* 1988; **ii:** 1019.

Pancreatitis. A report of pancreatitis associated with mefenamic acid.[1]

1. van Walraven AA, *et al.* Pancreatitis caused by mefenamic acid. *Can Med Assoc J* 1982; **126:** 894.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Mefenamic acid is absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2 to 4 hours after ingestion. The plasma elimination half-life is reported to be about 2 to 4 hours. Mefenamic acid is more than 90% bound to plasma proteins. It is distributed into breast milk. Mefenamic acid is metabolised by the cytochrome P450 isoenzyme CYP2C9 to 3-hydroxymethyl mefenamic acid, which may then be oxidised to 3-carboxymefenamic acid. Over 50% of a dose may be recovered in the urine, as unchanged drug or, mainly, as conjugates of mefenamic acid and its metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ponstil; ***Austral.***: Mefic†; Ponstan; ***Austria***: Mefenabene; Parkemed; ***Braz.***: Ponsdril; Ponstan; Pontin; Pontrex; Standor; ***Canad.***: Ponstan; ***Chile***: Adesna; Algex; Algifemin; Flipal; Sicadol; T-Nol; Tanston; Templadol; Truasinol; ***Fin.***: Ponstan; ***Fr.***: Ponstyl; ***Gr.***: Acinic; Aidol; Algopress; Calmin; Demostan; Kpeitton; Padomil; Penta; Ponstan; Vidan; ***Hong Kong***: Gynogesic†; Hamitan†; Hostan†; Medicap; Mefa; Mefamic†; Mefen; Mefenac†; Mefencid†; Mefic; Metsyn†; Namic; Napan; Painnox†; Pekaso†; Pongesic; Ponsis†; Ponstan; Pontacid†; Sefmic; Uni-Fenamic†; ***Hung.***: Ponmel; ***India***: Dysmen 500; Mefac; Mefacid; Mefdol; Meflup; Mefsine; Meftal; Ponstan; ***Indon.***: Analspec; Asam; Asimat; Benostan; Cetalmic; Corstanal; Datan; Dogesic; Dolfenal†; Dolos; Dystan†; Femisic; Fensik; Gitaramin; Grafix; Lapistan; Licostan; Maxtan; Mectan†; Mefast; Mefinal; Mefinter; Mefix; Menin; Molasic; Nichostan; Opistan; Pehastan; Ponalar; Poncofen; Pondex; Ponsamic; Ponstan; Ponstelax; Solasic; Stanalin; Stanza†; Stelpon†; Teamic; Topgesic; Tropistan; ***Irl.***: Mefac; Ponalgic; Ponmel†; Ponstan; ***Ital.***: Lysalgo; ***Malaysia***: Beafemic; Mefic†; Namic; Napan; Ponstan; Pontacid; Pontalon; Sefmic; ***Mex.***: Artriden; Namifen; Ponstan; ***NZ***: Ponstan; ***Philipp.***: Acidan; Afligec; Algifort; Analcid; Analmin; Aprostal†; Arthran; Atmose; Belfedane; Calibral; Dolfenal; Dolmetine†; Dolsten; Escandar†; Eurostan; Finox; Fromefen; Gardan; Gisfen; Hispen; Inflasic; Isagesic; Istan; Kramon; Laffed; Marfen; Mecid A; Medianon; Mefan; Mefenax; Mefril†; Metaflam; MFE; Neostan; Penomor; Ponser; Ponstan; Pontaser; Ralgec; Remifein; Revalan; Selmac; Senflam†; Spegic; Stangesic; Suprazen; Totagesic; Tynostan; Vamgesic†; Vandifen†; Zanovic; ZapAn†; Zestan; ***Pol.***: Mefacit; ***Port.***: Ponstan; ***S.Afr.***: Fenamin; Ponac; Ponstan; Ponstel; ***Singapore***: Alfoxan; Beafemic; Fenagesic; Hostan; Medicap; Mefenix; Mefril; Napan; Pontacid; Pontalon; Pontyl; SP-Famic; Zeet; ***Spain***: Coslan; ***Switz.***: Mefenacid; Mefenamin; Mefenaminacid†; Mephadolor; Ponstan; Spiralgine; Sportusal†; ***Thai.***: Anagan; Anagic; Coly; Conamic; Dismen; Dolfen; Fastan; Femen; Femic; Fenamic; Fennic; Gandin; Gynogesic; Locpan; Manic; Manomic; Masafen†; Meditan; Mednil; Mefa; Mefamed; Mefamic; Mefen; Mefenac; Mefenan; Mefnasic; Menamic; Nalgesin; Namic; Nufemic; Pacamic; Painnox; Panamic†; Pefamic; Ponacap; Ponatap; Pondnadysmen; Pongesics; Ponnac; Ponnesia; Ponstan; Pontalon; Pronamic; Prostan; Pynamic; Sefmic†; TV Gin; Vestan; ***Turk.***: Ponstan; Roladol; Rolan; ***UK***: Ponstan; ***USA***: Ponstel; ***Venez.***: Ponstan.

Multi-ingredient Preparations. ***India***: Abdowin; Apodrot; Baralgan-DM; Bio-Stat-MF; Chromostat; Clip-MF; Coastat-Gyne; Coease-M; Coligon Plus; Colimef; Colispas; Cyclocos-TX; Cyclocos; Cyclomeff; Cyclopam Plus; Cyclosym-TX; Cyclosym; Dam-Spas; Decolic-V; Detrim; Divo-M; Dora-M; Dortsil-M; Dotarin-MF; Dotra-M; Dozee-M; Drat-MF; Drobel-MF; Drofem; Drofic; Drolid-M; Drosym-MF; Drotikind-M; Drotin-M; Drotmic; Drotwell-M; Dubatran-MF; Dutora-M; DVN Plus; Dymef; Dynamet; Dysmen Forte; Dysmen; Dysmeryl; Efespas; Eginor; Eklot-MF; Eldrot-Plus; Emverin-MF; Etosys-MF; Examic-MF; Fenamic; Fetran-MF; Fibran-M; Florasyl-MF; Fodro-M; Gefplus; Gefspass; Griprid; Gynae-Pil Forte; Hamodam-M; HMT; Inorine-M; Kolispas; Lenagesic; Maff-D; Mafia; Majispa; MD-MF; Mef-T; Mefac Spas; Mefacid Forte; Mefamic-D; Mefar-PD; Mefatin-Spas; Mefcil Spas; Mefdi; Mefdic; Mefdol Spas; Mefegesic; Meffnex; Mefitrax; Meflam; Meflaxin; Meflup Forte; Mefmin Spas; Mefnex; Mefnic Spas; Mefnic-D; Mefsaid-D; Mefsaid; Mefsym-Spas; Mefsyn-TX; Meftagesic; Meftagesic; Meftal Forte; Meftal-MR; Meftal-Spas; Meftal-TX; Meftrax; Mefze Spas; Mefzys; Menogia-MF; Menospan-MF; Menotran; Mepar; Mespas; Mouzex-MF; Neurospas-MF; No Blos For; Noblifen; Normospas; Novaspas; NTSpass; Pal-MF; Paraspas; Spasmonil Forte; Spasmonil Plus; Tranfib MF; Ze-Spas; ***Singapore***: Orcigesic; ***Thai.***: Anpuzz; Difemic; Mainnox; ***Ukr.***: No-Spasma (Но-Спазма)†.

Pharmacopoeial Preparations

BP 2014: Mefenamic Acid Capsules; Mefenamic Acid Tablets;
USP 36: Mefenamic Acid Capsules.

Meloxicam *(BAN, USAN, rINN)*

Meloksikaami; Meloksikam; Méloxicam; Meloxicamum; Meloxikam; UH-AC-62; UH-AC-62XX; Мелоксикам.

4-Hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

$C_{14}H_{13}N_3O_4S_2$=351.4

CAS — 71125-38-7.

ATC — M01AC06.

ATC Vet — QM01AC06.

UNII — VG2QF83CGL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Meloxicam). A pale yellow powder. It exhibits polymorphism. Practically insoluble in water; very slightly soluble in alcohol; soluble in dimethylformamide. Protect from light. A pale yellow powder. Practically insoluble in water; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone; soluble in dimethylformamide.

USP 36: (Meloxicam). A pale yellow powder. Practically insoluble in water; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone; soluble in dimethylformamide.

Uses and Administration

Meloxicam, an oxicam derivative, is an NSAID (p. 102.3). It is reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). Meloxicam is used in the management of rheumatoid arthritis, for the short-term symptomatic treatment of acute exacerbations of osteoarthritis, and for the symptomatic treatment of ankylosing spondylitis. It may also be used in the treatment of juvenile idiopathic arthritis.

In the treatment of rheumatoid arthritis and ankylosing spondylitis, meloxicam is given in a usual oral dose of 15 mg daily as a single dose. Those with an increased risk of adverse reactions should be started on 7.5 mg daily. A dose of 7.5 mg daily is recommended for long-term treatment in the elderly. In the treatment of acute exacerbations of osteoarthritis the usual oral daily dose of meloxicam is 7.5 mg, increased if necessary to a maximum of 15 mg daily given as a single dose.

For dosage details in children, see below.

Meloxicam may be given by rectal suppository in doses similar to those used orally.

For the dose of meloxicam in patients with renal impairment, see p. 87.1.

Administration in children. In the USA, meloxicam is used in the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral dose is 125 micrograms/kg once daily, up to a maximum of 7.5 mg daily. In the UK, licensed product information states that meloxicam should not be used in children aged under 16 years. However, the *BNFC* has suggested the following oral doses, according to body-weight, for the relief

of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in those aged 12 to 18 years who are intolerant of other NSAIDs:
- less than 50 kg: 7.5 mg once daily
- over 50 kg: 15 mg once daily

Administration in renal impairment. Meloxicam is normally contra-indicated in patients with severe renal impairment. However, in dialysed patients, meloxicam may be given in a dose of 7.5 mg daily orally or rectally as suppositories. No dose reduction is required in those with mild to moderate renal impairment (creatinine clearance of greater than 25 mL/min).

Musculoskeletal and joint disorders. Meloxicam is used in the treatment of osteoarthritis (p. 12.3), rheumatoid arthritis (p. 13.2) including juvenile idiopathic arthritis (p. 12.1), and ankylosing spondylitis (see Spondyloarthropathies, p. 14.3). However, in the UK, the use of meloxicam and other selective cyclo-oxygenase-2 (COX-2) inhibitors is limited to those patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p. 105.3).

References.
1. Lemmel EM, *et al.* Efficacy and safety of meloxicam in patients with rheumatoid arthritis. *J Rheumatol* 1997; **24:** 282–90.
2. Yocum D, *et al.* Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern Med* 2000; **160:** 2947–54.
3. Combe B, *et al.* Comparison of intramuscular and oral meloxicam in rheumatoid arthritis patients. *Inflamm Res* 2001; **50** (suppl 1): S10–S16.
4. Fleischmann R, *et al.* Meloxicam. *Expert Opin Pharmacother* 2002; **3:** 1501–12.

Veterinary use. For the suggestion that meloxicam should be used as an alternative to diclofenac in cattle in South Asia (to reduce toxicity to vultures who may consume their carcasses), see under Precautions of Diclofenac, p. 50.2

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Incidence of adverse effects. Between September 1996, when meloxicam was first marketed in the UK, and mid-June 1998 the UK CSM had received a total of 773 reports of 1339 suspected adverse reactions for meloxicam.[1] Of all the reactions 41% were gastrointestinal and of these 18% involved gastrointestinal perforation, ulceration and/or bleeding; the mean age of the patients involved was 64 years. Although most patients recovered after withdrawal of meloxicam and/or treatment, 5 died. A total of 193 reactions involved the skin, the most common being pruritus, rash, and urticaria. There were also reports of angioedema (25 reports), photosensitivity (12 reports), and bullous dermatoses, including erythema multiforme and Stevens-Johnson syndrome (5 reports). No patients died from skin reactions and most recovered after meloxicam was withdrawn. Other frequently reported reactions were neurological (mostly headache), cardiovascular (oedema and palpitations), dizziness, flushing, and fatigue. A prescription event monitoring study has also analysed events reported with meloxicam use.[2] In a cohort of 19 087 patients who had received meloxicam some time between December 1996 and March 1997, 203 patients had had 252 events considered to be suspected adverse reactions. The majority of reactions were not serious or were labelled adverse effects of meloxicam. Rare, serious suspected adverse reactions included 2 reports of thrombocytopenia and 1 each of interstitial nephritis and idiosyncratic liver abnormality. The most frequent gastrointestinal event was dyspepsia; other more serious gastrointestinal events occurring during meloxicam exposure included upper gastrointestinal bleeding (33 reports) and peptic ulcer (19 reports). However, it was considered that the incidence of gastrointestinal disturbance was low in the absence of gastrointestinal risk factors. Adverse drug reactions reported during the first year of marketing of meloxicam to the Swedish Medical Products Agency suggested a similar safety profile to other NSAIDs.[3] Of the 15 reports, 6 were for gastrointestinal disturbances and 5 involved skin reactions.

1. CSM/MCA. Meloxicam (Mobic): gastrointestinal and skin reactions. *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Martin RM, *et al.* The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study. *Br J Clin Pharmacol* 2000; **50:** 35–42.
3. Anonymous. Meloxicam safety similar to other NSAIDs. *WHO Drug Information* 1998; **12:** 147.

Effects on the gastrointestinal tract. It is generally accepted that inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of NSAIDs, and that selective inhibition of the other isoform, COX-2, by NSAIDs such as meloxicam may cause less gastrotoxicity than that seen with the non-selective inhibition of traditional NSAIDs. However, there has been little convincing evidence that the risk of severe gastrointestinal events is lower with meloxicam than with other NSAIDs at equi-effective doses.[1] Two large multicentre studies[2,3] have reported a lower incidence of gastrointestinal adverse effects with meloxicam than with non-selective cyclo-oxygenase inhibitors (diclofenac[2] or piroxicam[3]) but in one of these[2] the dose of meloxicam given also appeared to be less effective than the reference drug. A more recent systematic review[4] also found a lower risk of serious gastrointestinal toxicity with meloxicam 7.5 mg daily when compared with diclofenac (100 or 150 mg daily), naproxen (500 mg twice daily), or piroxicam (20 mg daily); however, when given at a dose of 15 mg daily, the risk of toxicity with meloxicam was significantly lower only when compared with piroxicam.

Individual case reports of gastrointestinal toxicity with meloxicam included one of ischaemic colitis associated with high-dose (15 mg daily) meloxicam treatment.[5]

1. Anonymous. Meloxicam—a safer NSAID? *Drug Ther Bull* 1998; **36:** 62–4.
2. Hawkey C, *et al.* Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol* 1998; **37:** 937–45.
3. Dequeker J, *et al.* Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of COX-inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998; **37:** 946–51.
4. Singh G, *et al.* Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. *Am J Med* 2004; **117:** 100–106.
5. Garcia B, *et al.* Ischaemic colitis in a patient taking meloxicam. *Lancet* 2001; **357:** 690.

Precautions

As for NSAIDs in general, p. 107.1.

Meloxicam should be avoided in severe hepatic impairment, in bleeding disorders, and in patients with renal failure unless receiving dialysis. Rectal use should be avoided in patients with a history of proctitis, haemorrhoids, or rectal bleeding.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies meloxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Renal impairment. The pharmacokinetics of meloxicam were not substantially altered in patients with a creatinine clearance (CC) of 41 to 60 mL/minute compared with those with normal renal function.[1] In those with a CC of 20 to 40 mL/minute, total plasma-meloxicam concentrations were lower but meloxicam free fractions were higher. Such free meloxicam concentrations were similar to the other groups. On the basis of these results, it was suggested that it was not necessary to reduce meloxicam doses in patients with a CC greater than 20 mL/minute.

1. Boulton-Jones JM, *et al.* Meloxicam pharmacokinetics in renal impairment. *Br J Clin Pharmacol* 1997; **43:** 35–40.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Colestyramine increases the clearance and decreases the half-life of meloxicam.

Pharmacokinetics

Meloxicam is well absorbed after oral or rectal doses and peak plasma concentrations occur within 6 hours. It is 99% bound to plasma proteins. Meloxicam has a plasma-elimination half-life of about 20 hours. It is extensively metabolised, mainly by oxidation to its major metabolite, 5′-carboxymeloxicam. *In vitro* studies suggest that the cytochrome P450 isoenzyme CYP2C9 plays an important role in the metabolism of meloxicam with CYP3A4 involved to a lesser degree. Meloxicam, in the form of metabolites, is excreted in similar amounts in the urine and in the faeces; less than 5% of a dose is excreted unchanged. The volume of distribution is increased in renal failure.

References.
1. Narjes H, *et al.* Pharmacokinetics and tolerability of meloxicam after i.m. administration. *Br J Clin Pharmacol* 1996; **41:** 135–9.
2. Türck D, *et al.* Clinical pharmacokinetics of meloxicam. *Arzneimittelforschung* 1997; **47:** 253–8.
3. Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam: a cyclooxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clin Pharmacokinet* 1999; **36:** 115–26.
4. Meineke I, Türck D. Population pharmacokinetic analysis of meloxicam in rheumatoid arthritis patients. *Br J Clin Pharmacol* 2003; **55:** 32–8.
5. Burgos-Vargas R, *et al.* Pharmacokinetics of meloxicam in patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2004; **44:** 866–72.

Renal impairment. For reference to the pharmacokinetics of meloxicam in renal impairment, see under Precautions, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bronax; Dominadol; Flexidol; Flexium; Loxitenk; Meloracˆ; Meloxid; Mextran; Miolox; Mobic; Telaroidˆ; Tenaron; ***Austral.***: Meloxibell; Mobic; Movalis; Moxicam; ***Austria***: Metosan; Movalis; ***Belg.***: Docmeloxiˆ; Mobic; ***Braz.***: Alivian; Bioflac; Dormelox; Flamatec; Inicox; Leutrol; Loxam; Loxiflan; Melocox; Melotec; Meloxigran; Meloxil; Menoxiton; Mevamox; Movacox; Movatec; Movoxicam; ***Canad.***: Mobicox; ***Chile***: Anposel; Ecax; Hyflex; Isox; Melic; Melodol; Mexan; Mexilal; Mibloc FT; Mioflam; Mobex; Sition; Tenaron; ***China***: An Li Qing (安立青); He Chang (和畅); Hong Qiang (宏强); Ji Kang Ning (吉康宁); Jie Zong (节宗); Keyi (可伊); Luo Guan Jian (络贯健); Luo Ke (洛珂); Mei Er Tong (美尔同); Mi Nuo Xi (米诺希); Mo Le Xin (莫乐新); Mobic (莫比可); Mokelin (莫刻林); Nai Bang (奈邦); PuLiLuo (普利洛); Qing Qing (清轻); Sai Ke Si (赛可斯); Sai Ou Si (塞欧斯); Si Lai Mei (斯莱美); Tong Ke (统克); Wu Yan (吾琰); You Ni (优尼); Ze Li (则立); ***Cz.***: Antrend; Artrilom; Duplicamˆ; Enaros; Galoxiwayˆ; Melobax; Melocox; Melovis; Meloxistad; Movalis; Movmaks; Noflamen; Oramellox; Recoxa; ***Denm.***: Celomix; Loxime; ***Fin.***: Latonidˆ; Mobic; ***Fr.***: Mobic; ***Ger.***: Melloxˆ; Mobec; ***Gr.***: Arsitec; Arthrox; Auroxicam; Brosiral; Doctinon; Examel; Farmelox; Flelox; Flumidon; Iamaxicam; Iaten; Iconal; Infomel; Loxitan; Mecalox; Medoxicam; Melcam; Melice; Melocalm; Melock; Melocox; Melodim; Meloprol; Melorem; Melorilif; Melotec; Melotop; Melox; Meloxeron; Meloxil; Meloxitor; Melus; Meomel; Movatec; Movaxin; Moxalid; Notpel; Parogal; Partial; Philipon-S; Rentilox; Reumotec; Reumotherm; Sanetron; Saniflam; Starmelox; Supercad; Transantor; Tropofin; Valoxin; Vexicam; Zametrixal; Zerelin; ***Hong Kong***: Arrox; Melcam; Melflam; Melox; Mobic; Partial; ***Hung.***: Borbin; Camelox; Melodyn; Melogen; Melox; Meloxan; Movalis; Moxicam; Noflamen; ***India***: Ecwin; M-Cam; Mel-OD; Melflam; Melogesic; Melone; Melosuganril; Mexam; Movac; Muvera; Muvik; ***Indon.***: Arimed; Artrilox; Cameloc; Flamoxi; Flasicox; Loxil; Loxinic; Mecox; Meflam; Meloxin; Mevilox; Mexpharm; Mobiflex; Movi-Cox; Movix; Moxam; Moxic; Nulox; Ostelox; Paxicam; Relox; Remacam; Rhemacox; Velcox; X-Cam; ***Irl.***: Areloger; Melcam; Mobic; Mobicam; Mobiglan; Movox; ***Ital.***: Gixal; Leutrol; Mobic; ***Jpn***: Mobic; ***Malaysia***: Arrox; Avegesic; Mel-OD; Melartin; Melocam; Melox; Mobic; Rafree; ***Mex.***: Aflamid; Anpre; Auricamˆ; Coxylan; Dolocam; Exel; Flexiver; Flexol; Lexpram; Loxamˆ; Loxibach; Loxibest; Mavicam; Maxoflam; Meflen; Melarthryl; Melican; Melosteral; Menflixil; Mobicox; Promotion; Reosan; Retoflam; ***Neth.***: Movalisˆ; Movicox; ***Norw.***: Mobicˆ; ***NZ***: Melorex; Mobic; ***Philipp.***: Bexxam; Caxlem; Cloxim; Meflam; Mel-OD; Melart; Melcom; Melocox; Meloflam; Melora; Meloxin; Mobic; Moxen; Neoxicam; Newsicam; Osteolax; Rafree; ***Pol.***: Aglan; Aspicam; Celomix; Lormed; Melobax; Meloksam; Melokssiaˆ; Melotev; Meloxic; MeloxiLek; Meloxistad; Mexan; Movalis; Movmax; Opokan; ***Port.***: Dortex; Lador; Marlex; Melpor; Movalis; ***Rus.***: Amelotex (Амелотекс); Artrozan (Артрозан); Lem (Лем); Mataren (Матарен); Melbek (Мелбек); Meloflam (Мелофлам); Melokan (Мелокан)ˆ; Melox (Мелокс); Mesipol (Месипол); Mirlox (Мирлокс); Mixol (Миксол); Movalis (Мовалис); Movasin (Мовасин); Movix (Мовикс); ***S.Afr.***: Arthrocox; Coxflam; Flamaryx; Flexocam; Loxiflam; M-Cam; Melflam; Mobic; ***Singapore***: Melox; Mobic; ***Spain***: Aliviodol; Movalis; Parocin; Uticoxˆ; ***Swed.***: Mobicˆ; ***Switz.***: Mobicox; ***Thai.***: Cambic; Mel-OD; Melcam; Melobic; Melox; Mobic; ***Turk.***: Exen; Meksun; Melcam; Melox; Melurjin; Meskun; Mobic; Mone; Romacox; Runomex; Zeloxim; ***UK***: Mobicˆ; ***Ukr.***: Melbek (Мелбек); Meloksam (Мелоксам)ˆ; Meloxic (Мелоксик)ˆ; Movalis (Мовалис); Reumoxicam (Ревмоксикам); ***USA***: Mobic; ***Venez.***: Biomelox; Melonax; Melovax; Mobic; Taucaron.

Multi-ingredient Preparations. ***Arg.***: Aldoron Flex; Aldoron M; Bronax Flex; Dolo Asotrex; Dolo Baliartrin; Flexidol Relax; Mextran Flex; Tenaron Flex; ***India***: Melodol; ***Mex.***: Dolocam Plus; Dolocartigen; Dorsal; Flexamolˆ; Nuro-B; Retoflam F; Tremecox.

Pharmacopoeial Preparations
BP 2014: Meloxicam Tablets;
USP 36: Meloxicam Oral Suspension; Meloxicam Tablets.

Meptazinol Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de meptazinol; IL-22811 (meptazinol); Meptazinol, Chlorhydrate de; Meptazinol, hidrocloruro de; Meptazinoli Hydrochloridum; Wy-22811 (meptazinol); Мептазинола Гидрохлорид.

3-(3-Ethyl-1-methylperhydroazepin-3-yl)phenol hydrochloride.

$C_{15}H_{23}NO,HCl$=269.8

CAS — 54340-58-8 (meptazinol); 59263-76-2 (meptazinol hydrochloride); 34154-59-1 (±-meptazinol hydrochloride).

ATC — N02AX05.

ATC Vet — QN02AX05.
UNII — T62FQ4ZCPA.

Pharmacopoeias. In *Br.*

BP 2014: (Meptazinol Hydrochloride). A white or almost white powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol; very slightly soluble in acetone; dissolves in dilute solutions of alkali hydroxides. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Meptazinol is a mixed opioid agonist and antagonist with partial opioid agonist activity at the μ_1 opioid receptor (see p. 108.1); it also has cholinergic activity. Meptazinol is used in the treatment of moderate to severe pain. It has a shorter duration of action than morphine.

Meptazinol hydrochloride is given orally or by intramuscular or intravenous injection; doses are expressed in terms of the base. Meptazinol hydrochloride 115.6 mg is equivalent to about 100 mg of meptazinol. For the short-term treatment of moderate pain meptazinol is given in an oral dose of 200 mg every 3 to 6 hours, as required. The intramuscular dose is 75 to 100 mg given every 2 to 4 hours, as required; for obstetric pain a dose of 2 mg/kg (100 to 150 mg) may be used. Meptazinol is also given by slow intravenous injection in doses of 50 to 100 mg every 2 to 4 hours, as required.

Administration. *EPIDURAL ROUTE.* Epidural meptazinol 90 mg for postoperative pain was reported to be superior to an intramuscular dose of 90 mg.[1] However, in another study[2] a 30-mg dose was ineffective and associated with an unacceptable incidence of adverse effects. A 60-mg dose was also found to be ineffective because of its short duration of action.[3]

UK licensed product information states that the injectable formulation is not suitable for epidural or intrathecal use.

1. Verborgh C, *et al.* Meptazinol for postoperative pain relief in man: comparison of extradural and im administration. *Br J Anaesth* 1987; **59:** 1134–9.
2. Francis RI, Lockhart AS. Epidural meptazinol. *Anaesthesia* 1986; **41:** 88–9.
3. Birks RJS, Marsh DRG. Epidural meptazinol. *Anaesthesia* 1986; **41:** 883.

Administration in hepatic impairment. See under Pharmacokinetics, below for a suggestion that doses may need to be reduced in patients with cirrhosis.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

In assessing the dependence potential of meptazinol, a WHO expert committee[1] noted in 1989 that abrupt discontinuation of chronic meptazinol use precipitated only slight withdrawal signs in *animals* and that meptazinol did not suppress opioid withdrawal signs and symptoms in humans dependent on morphine. Abuse had not been reported. They considered that the likelihood of abuse was moderate and that international control was not warranted at that time.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Gastrointestinal adverse effects are commonly reported with meptazinol and include abdominal pain, constipation, dyspepsia, diarrhoea, and nausea and vomiting. Meptazinol is claimed to have a low incidence of respiratory depression; nonetheless, UK licensed product information states that it should not be used in patients with acute respiratory depression. There have been occasional reports of psychiatric disorders such as hallucinations, confusion, and depression. As meptazinol has both antagonist and agonist properties its effects may be only partially reversed by naloxone, but use of the latter is still recommended in overdosage.

Meptazinol has the potential to precipitate withdrawal symptoms if given to patients who are physically dependent on opioids.

Abuse. See under Dependence and Withdrawal, above.

Effects on the respiratory system. Meptazinol is said to have a relatively low potential for respiratory depression and in healthy subjects was reported to produce substantially less respiratory depression than morphine or pentazocine at usual analgesic doses.[1] However, respiratory depression does occur in anaesthetised patients given meptazinol[2] and the effects on respiration may be similar to those of morphine[3,4] or pethidine.[5,6] Compensatory mechanisms may come into play after repeated doses of meptazinol but the intravenous use of meptazinol during anaesthesia should be viewed with as much caution as with any other opioid.[6]

Respiratory arrest occurred after an *overdose* of 50 meptazinol 200-mg tablets and a quarter of a bottle of whisky.[7] Full recovery eventually followed supportive measures although spontaneous respiration was not re-established by naloxone intravenously to a cumulative total dose of 10 mg.

1. Jordan C, *et al.* A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br J Anaesth* 1979; **51:** 497–502.
2. Hardy PAJ. Meptazinol and respiratory depression. *Lancet* 1983; **ii:** 576.
3. Frater RAS, *et al.* Analgesia-induced respiratory depression: comparison of meptazinol and morphine in the postoperative period. *Br J Anaesth* 1989; **63:** 260–5.
4. Verborgh C, Camu F. Post-surgical pain relief with zero-order intravenous infusions of meptazinol and morphine: a double-blind placebo-controlled evaluation of their effects on ventilation. *Eur J Clin Pharmacol* 1990; **38:** 437–42.
5. Wilkinson DJ, *et al.* Meptazinol—a cause of respiratory depression in general anaesthesia. *Br J Anaesth* 1985; **57:** 1077–84.
6. Lee A, Drummond GB. Ventilatory effects of meptazinol and pethidine in anaesthetised patients. *Br J Anaesth* 1987; **59:** 1127–33.
7. Davison AG, *et al.* Meptazinol overdose producing near fatal respiratory depression. *Hum Toxicol* 1987; **6:** 331.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Plasma concentrations of meptazinol may be increased by ritonavir and use together should be avoided (see also p. 111.2).

Pharmacokinetics

After oral doses of meptazinol peak plasma concentrations have occurred within 0.5 to 2 hours, but bioavailability is low since it undergoes extensive first-pass metabolism. Systemic availability is improved after rectal doses. Peak plasma concentrations have occurred 30 minutes after rectal or intramuscular use. Plasma protein binding has averaged only about 27%. Elimination half-lives of about 2 hours have been reported. Meptazinol is extensively metabolised in the liver and is excreted mainly in the urine as the glucuronide conjugate. Less than 10% of a dose has been recovered from the faeces. Meptazinol crosses the placenta.

References.

1. Franklin RA, *et al.* Studies on the metabolism of meptazinol, a new analgesic drug. *Br J Clin Pharmacol* 1976; **3:** 497–502.
2. Franklin RA, *et al.* Studies on the absorption and disposition of meptazinol following rectal administration. *Br J Clin Pharmacol* 1977; **4:** 163–7.
3. Davies G, *et al.* Pharmacokinetics of meptazinol in man following repeated intramuscular administration. *Eur J Clin Pharmacol* 1982; **23:** 535–8.
4. Norbury HM, *et al.* Pharmacokinetics of the new analgesic, meptazinol, after oral and intravenous administration to volunteers. *Eur J Clin Pharmacol* 1983; **25:** 77–80.
5. Murray GR, *et al.* The systemic availability of meptazinol in man after oral and rectal doses. *Eur J Clin Pharmacol* 1989; **36:** 279–82.

The elderly. A lower clearance and longer elimination half-life have been reported for meptazinol in elderly patients, but dosage reduction was not considered warranted on pharmacokinetic grounds. Mean half-lives in elderly and young subjects were 3.39 and 1.94 hours, respectively after single oral doses[1] and 2.93 and 2.06 hours, respectively after intravenous doses.[2]

1. Norbury HM, *et al.* Pharmacokinetics of meptazinol after single and multiple oral administration to elderly patients. *Eur J Clin Pharmacol* 1984; **27:** 223–6.
2. Murray GR, *et al.* Pharmacokinetics of meptazinol after parenteral administration in the elderly. *Eur J Clin Pharmacol* 1987; **31:** 733–6.

Hepatic impairment. Oral bioavailability of meptazinol appeared to be enhanced in patients with liver disease. After a single oral dose of meptazinol mean peak plasma concentrations were 184 nanograms/mL, 131 nanograms/mL, and 53 nanograms/mL in cirrhotic patients, patients with non-cirrhotic liver disease, and patients with normal liver function, respectively, although there was no evidence of accumulation after chronic dosing.[1] There were no significant differences in plasma clearance after an intravenous dose. Reduced oral doses of meptazinol might be advisable in cirrhotic patients.

1. Birnie GG, *et al.* Enhanced oral bioavailability of meptazinol in cirrhosis. *Gut* 1987; **28:** 248–54.

Pregnancy. In women given an intramuscular injection of 100 to 150 mg during labour, meptazinol was found to cross the placenta readily but was rapidly eliminated from the neonate.[1] This contrasted with pethidine which was known to be excreted very slowly from neonates. As in the adult, elimination of meptazinol by the neonate appeared to take place mainly by conjugation with glucuronic acid.[2] A half-life of 3.4 hours, similar to that in adults, has been reported in the neonate,[3] in contrast to 22.7 hours for pethidine in neonates.

Disposition of meptazinol appears not to be significantly affected by pregnancy. Mean half-lives of 1.36 and 1.68 hours were reported in pregnant and non-pregnant women, respectively,[4] compared with 2.06 hours in men.

1. Franklin RA, *et al.* Preliminary studies on the disposition of meptazinol in the neonate. *Br J Clin Pharmacol* 1981; **12:** 88–90.
2. Dowell PS, *et al.* Routes of meptazinol conjugation in the neonate. *Br J Clin Pharmacol* 1982; **14:** 748–9.
3. Jackson MBA, Robson PJ. Preliminary clinical and pharmacokinetic experiences in the newborn when meptazinol is compared with pethidine as an obstetric analgesic. *Postgrad Med J* 1983; **59** (suppl 1): 47–51.
4. Murray GR, *et al.* The disposition of meptazinol after single and multiple intravenous administration to pregnant and non-pregnant women. *Eur J Clin Pharmacol* 1989; **36:** 273–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Meptid; ***Gr.***: Nestan; ***Irl.***: Meptid; ***UK***: Meptid.

Pharmacopoeial Preparations

BP 2014: Meptazinol Injection; Meptazinol Tablets.

Methadone Hydrochloride

(BANM, pINNM) ⊗

Amidine Hydrochloride; Amidone Hydrochloride; Hidrocloruro de amidina; Hidrocloruro de metadona; Metadon Hidroklorür; Metadona, hidrocloruro de; Metadon-hidroklorid; Metadonhydroklorid; Metadonihydrokloridi; Metadono hidrochloridas; Metadonu chlorowodorek; Methadon hydrochlorid; Méthadone, chlorhydrate de; Methadonhydrochlorid; Methadoni Hydrochloridum; Phenadone; Метадона Гидрохлорид; (±)-Methadone Hydrochloride.

(±)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

$C_{21}H_{27}NO,HCl=345.9$

CAS — 76-99-3 (methadone); 297-88-1 (±methadone); 1095-90-5 (methadone hydrochloride); 125-56-4 (±methadone hydrochloride).

ATC — N07BC02.

ATC Vet — QN07BC02.

UNII — 229809935B.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methadone:

Amidone; Balloons; Breeze; Burdock; Buzz bomb; Dollies; Dolls; Done; Doses; Fizzies; Juice; Jungle juice; Junk; Meta; Mud; Phy; Phyamps; Tootsie roll.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Methadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Methadone Hydrochloride). Odourless colourless crystals or white crystalline powder. Soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerol. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. There appears to be adequate evidence that stable solutions containing methadone hydrochloride and hydroxybenzoate esters can be formulated but the risk of precipitation exists if syrup preserved with hydroxybenzoates is used to extemporaneously prepare a methadone mixture 1 mg/mL to the DTF formula.[1] An oral formulation of methadone hydrochloride 5 mg/mL containing methyl hydroxybenzoate 0.1% as preservative rather than chloroform has been reported stable for at least 4 months at room temperature.[2]

1. *PSGB Lab Report P180/1* 1980.
2. Ching MS, *et al.* Stability of methadone mixture with methyl hydroxybenzoate as a preservative. *Aust J Hosp Pharm* 1989; **19:** 159–61.

Uses and Administration

Methadone hydrochloride, a diphenylheptane derivative, is an opioid analgesic (p. 108.1) that is mainly a μ-opioid agonist. Single doses of methadone have a less marked sedative action than single doses of morphine. Methadone is a racemic mixture and levomethadone (p. 83.1) is the active isomer.

Methadone hydrochloride is used in the treatment of moderate to severe pain; it may be of use for those patients who have excitation or exacerbation of pain with morphine. Methadone is also used in the management of opioid dependence. It has a depressant action on the cough centre and has been used as a cough suppressant in terminal illness, although the *BNF* discourages this use because of the risks of accumulation.

For **pain relief** starting oral doses of methadone hydrochloride may range from 2.5 to 10 mg given every 6 to 8 hours or longer and thereafter adjusted as necessary. Methadone may also be given parenterally. In the UK, the

subcutaneous and intramuscular routes are licensed with the intramuscular route being recommended for prolonged use; US licensed product information states that the intravenous, intramuscular, and subcutaneous routes may be used although it gives doses for the intravenous route only. Initial dose ranges for parenteral routes are similar to those used orally; however, if transferring between oral and parenteral methadone, US product information states that the initial conversion dose should be based on the guide that 10 mg of oral methadone is equivalent to about 5 mg of parenteral methadone. The analgesic effect of methadone begins about 10 to 20 minutes after parenteral injection and about 30 to 60 minutes after oral doses, the effect of a single dose usually lasting about 4 hours. As accumulation occurs with repeated doses, the effects become more prolonged. Consequently, to avoid the risk of opioid overdose, it is recommended that in prolonged use methadone should not be given more than twice daily.

Methadone is used as part of the treatment of **opioid dependence**, although prolonged use of methadone itself may result in dependence. Initially, methadone hydrochloride is given in doses sufficient to suppress signs of opioid withdrawal but avoid toxicity; the *BNF* and US licensed product information recommended a starting dose of 10 to 40 mg daily. Subsequent dose adjustments should be made cautiously because of the risks of accumulation; the *BNF* suggests adjusting the dose in steps of up to 10 mg to a maximum weekly increase of 30 mg. Once the dose has been stabilised, patients may choose to receive prolonged therapy with a carefully selected methadone dose for each individual; most patients in such maintenance programmes are stabilised on once-daily doses of 60 to 120 mg. Alternatively, detoxification may be appropriate with the dose of methadone being gradually decreased until total withdrawal is achieved. Methadone is usually given orally for the treatment of dependence although parenteral routes may be used, particularly when oral therapy is not possible; the doses stated above may be given orally or parenterally. In the UK, oral treatment is commonly given as a mixture containing 1 mg/mL of methadone hydrochloride.

For details of doses in children, see below.

For the control of intractable **cough** associated with terminal lung cancer, methadone hydrochloride is usually given in the form of a linctus in a dose of 1 to 2 mg every 4 to 6 hours, but reduced to twice daily on prolonged use.

Administration. Although duration of action after single doses of methadone is similar to that of morphine, it increases considerably with multiple dosing of methadone because of the long elimination half-life (see under Pharmacokinetics, p. 91.1). The minimum effective dose of methadone can be difficult to titrate for the individual patient. A fixed 10-mg oral dose with a flexible patient-controlled dosage interval has been used in patients with chronic cancer pain.[1] Dosage not more frequently than every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient's requirements, was advised.

A suggested initial dose for patients who need to switch from oral morphine to methadone because of poor pain control is one tenth of the total daily dose of morphine, but not greater than 100 mg, given at intervals determined by the patient, typically every 8 hours.[2]

When switching from oral to parenteral use it was suggested[3] that the dose of methadone should be halved and adjusted thereafter as necessary.

Evidence of the prolonged effect of methadone was seen when a single intravenous bolus dose of 20 mg resulted in postoperative analgesia lasting about 25 hours.[4] An initial 2-hour loading intravenous infusion of methadone 100 to 200 micrograms/kg per hour to provide rapid analgesia followed by infusion at a lower maintenance rate of 10 to 20 micrograms/kg per hour for continuous pain relief has been used in burn patients.[5] Methadone has also been given by continuous subcutaneous infusion for severe cancer pain[6,7] although this route has been associated with local tissue irritation and induration. Epidural methadone has been used successfully in doses of up to 5 mg for analgesia with bupivacaine.[8,9] Intermittent and continuous epidural infusion of methadone has also been tried[10] in postoperative analgesia.

A small case series[11] found topical methadone powder to be effective for pain relief of open, exudative wounds.

1. Säwe J, *et al*. Patient-controlled dose regimen of methadone for chronic cancer pain. *BMJ* 1981; **282:** 771–3.
2. Morley JS, *et al*. Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342:** 1243.
3. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11:** 87–106.
4. Gourlay GK, *et al*. Methadone produces prolonged postoperative analgesia. *BMJ* 1982; **284:** 630–1.
5. Denson DD, *et al*. Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30:** 70–5.
6. Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. *J Pain Symptom Manage* 1999; **18:** 49–52.
7. Makin MK, Morley JS. Subcutaneous methadone in terminally-ill patients. *J Pain Symptom Manage* 2000; **19:** 237–8.
8. Drenger B, *et al*. Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy. *Br J Anaesth* 1989; **62:** 82–6.
9. Martin CS, *et al*. Extradural methadone and bupivacaine in labour. *Br J Anaesth* 1990; **65:** 330–2.
10. Prieto-Alvarez P, *et al*. Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations. *Can J Anaesth* 2002; **49:** 25–31.
11. Gallagher RE, *et al*. Analgesic effects of topical methadone: a report of four cases. *Clin J Pain* 2005; **21:** 190–2.

Administration in children. Methadone is not licensed for use in children. However, it has been tried[1] intravenously in children aged 3 to 7 years to prevent postoperative **pain**; a dose of 200 micrograms/kg was given perioperatively followed postoperatively by 50 micrograms/kg every 10 minutes until the patient was both comfortable and adequately alert. Methadone has also been tried[2] orally for the treatment of severe pain in hospitalised children; daily doses ranged from 200 to 600 micrograms/kg for up to 6 weeks.

Methadone is used for the management of **neonatal abstinence syndrome** (p. 110.1). The *BNFC* suggests an initial oral dose of 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; once stabilised, the total daily dose is given in 2 divided doses for maintenance. When withdrawing methadone, the dose should be reduced over 7 to 10 days.

1. Berde CB, *et al*. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr* 1991; **119:** 136–41.
2. Shir Y, *et al*. Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. *Clin J Pain* 1998; **14:** 350–3.

Cancer pain. Methadone is used as an alternative to morphine in the treatment of severe cancer pain (p. 7.1). A better understanding of its pharmacokinetics and of equianalgesic doses may address early concerns about the risk of cumulative toxicity associated with prolonged use. However, its long terminal half-life makes it less suitable for the treatment of breakthrough pain.

Methadone has been given by the oral, rectal, and parenteral routes.

References.
1. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000; **173:** 536–40.
2. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med* 2002; **5:** 127–38.
3. Bruera E, *et al*. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22:** 185–92.
4. Moryl N, *et al*. Methadone in the treatment of pain and terminal delirium [sic] in advanced cancer patients. *Palliat Support Care* 2005; **3:** 311–17.
5. Mannino R, *et al*. Methadone for cancer-related neuropathic pain: a review of the literature. *J Opioid Manag* 2006; **2:** 269–76.
6. Nicholson AB. Methadone for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 26/06/08).

Opioid dependence. The treatment of opioid dependence is discussed on p. 109.2. In the UK, oral liquid preparations of methadone hydrochloride 1 mg/mL are widely used for this purpose. It is important to note that these preparations are 2.5 times **stronger** than Methadone Linctus (BP 2014), and although some are licensed for analgesia in severe pain, many are licensed for the treatment of opioid dependence only. Methadone Oral Solution (1 mg/mL) (BP 2014) is available as a ready-to-use solution or may be prepared from Methadone Hydrochloride Oral Concentrate. However, most commercially available preparations in the UK still follow an earlier formula formerly listed in the Drug Tariff Formulary (DTF):

Methadone Mixture 1 mg/mL
methadone hydrochloride 10 mg
Green S and Tartrazine Solution (BP 1980) 0.02 mL
Compound Tartrazine Solution (BP 1980) 0.08 mL
syrup, unpreserved 5 mL
chloroform water, double-strength to 10 mL.

Some commercially available forms of DTF Methadone Mixture 1 mg/mL use a preservative system based on hydroxybenzoate esters rather than chloroform; however, syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing (see Incompatibility, p. 88.3).

References.
1. Ghodse AH, *et al*. Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. Wolff K, *et al*. Measuring compliance in methadone maintenance patients: use of a pharmacologic indicator to "estimate" methadone plasma levels. *Clin Pharmacol Ther* 1991; **50:** 199–207.
3. Wilson P, *et al*. Methadone maintenance in general practice: patients, workload, and outcomes. *BMJ* 1994; **309:** 641–4.
4. Farrell M, *et al*. Methadone maintenance treatment in opiate dependence: a review. *BMJ* 1994; **309:** 997–1001.
5. Henry JA. Methadone: where are we now? *Hosp Med* 1999; **60:** 161–4.
6. Faggiano F, *et al*. Methadone maintenance at different dosages for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 28/08/08).
7. Amato L, *et al*. Methadone at tapered doses for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).
8. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)
9. Mattick RP, *et al*. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 11/11/09).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Methadone withdrawal symptoms are similar to, but more prolonged than, those produced by morphine or diamorphine. They develop more slowly and do not usually appear until 3 to 4 days after the last dose.

Methadone is used for substitution therapy in the management of opioid dependence (see Uses and Administration, p. 88.3) including neonatal abstinence syndrome (see Administration in Children, above).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Methadone has a more prolonged effect than morphine and readily accumulates with repeated doses. It may have a relatively greater respiratory depressant effect than morphine and, although reported to be less sedating, repeated doses of methadone may result in marked sedation. QT prolongation and torsade de pointes have been reported rarely with methadone use, particularly at doses above 100 mg daily. After gross overdosage symptoms are similar to those of morphine poisoning. Pulmonary oedema after overdosage is a common cause of fatalities among addicts.

Methadone causes pain at injection sites; subcutaneous injection causes local tissue irritation and induration.

Effects on the cardiovascular system. Methadone prolongs the QT interval and has rarely been associated with torsade de pointes. In a retrospective case series,[1] 17 patients on high-dose methadone (mean daily dose of 397 mg) developed torsade de pointes; of these, 14 had potential risk factors for arrhythmia and 6 had had their dose increased within the last month. In another study[2] torsade de pointes developed in 5 patients taking methadone (mean daily dose 268 mg); however, they all had other contributing risk factors. Other studies[3,4] did not find instances of torsade de pointes and the increase in QT interval was considered clinically insignificant; in one study,[4] the mean daily dose of methadone was 110 mg and some patients also had risk factors for arrhythmia.

For a report of QT interval prolongation in an infant born to a mother on maintenance methadone therapy for opioid addiction, see Pregnancy, p. 90.2.

In a small case-controlled study of sudden cardiac deaths,[5] the prevalence of underlying cardiac disease or structural abnormalities was lower in the 22 cases with evidence of therapeutic methadone levels when compared with the 106 cases without evidence of methadone use. The authors considered that the low prevalence of cardiac risk factors in the methadone group suggested a role for methadone itself in the pathogenesis of sudden death in this group.

1. Krantz MJ, *et al*. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 2002; **137:** 501–4.
2. Sticherling C, *et al*. Methadone-induced torsade de pointes tachycardias. *Swiss Med Wkly* 2005; **135:** 282–5.
3. Martell BA, *et al*. The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003; **139:** 154–5.
4. Cruciani RA, *et al*. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage* 2005; **29:** 385–91.
5. Chugh SS, *et al*. A community-based evaluation of sudden death associated with therapeutic levels of methadone. *Am J Med* 2008; **121:** 66–71.

Effects on the endocrine system. Hypoadrenalism has been found in chronic methadone addicts. Findings consistent with deficient ACTH production and subsequent secondary hypoadrenalism have been reported[1] although there is also evidence[2] of methadone-induced primary adrenal cortical hypofunction.

Hyperprolactinaemia and galactorrhoea have also been reported.[3] See also Effects on Sexual Function, p. 90.1.

1. Dackis CA, *et al*. Methadone induced hypoadrenalism. *Lancet* 1982; **ii:** 1167.
2. Pullan PT, *et al*. Methadone-induced hypoadrenalism. *Lancet* 1983; **i:** 714.
3. Bennett J, Whale R. Galactorrhoea may be associated with methadone use. *BMJ* 2006; **332:** 1071.

Effects on the nervous system. Choreic movements occurred in a 25-year-old man on long-term methadone maintenance treatment of 45 to 60 mg daily for diamorphine addiction.[1] Similar adverse effects were seen in a 41-year-old woman taking 5 mg methadone four times daily for complex regional pain syndrome.[2] In both cases, symptoms resolved when methadone was stopped.

1. Wasserman S, Yahr MD. Choreic movements induced by the use of methadone. *Arch Neurol* 1980; **37:** 727–8.
2. Clark JD, Elliott J. A case of a methadone-induced movement disorder. *Clin J Pain* 2001; **17:** 375–7.

Effects on the respiratory system. Sleep apnoea has been reported[1,2] in patients on stable methadone maintenance treatment.

1. Teichtahl H, *et al.* Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction* 2001; **96:** 395–403.
2. Wang D, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; **128:** 1348–56.

Effects on sexual function. Sexual performance was impaired in 29 male diamorphine addicts receiving methadone maintenance therapy.[1] The function of secondary sex organs was markedly suppressed when compared with untreated diamorphine addicts or controls and serum-testosterone concentrations were 43% lower in those on methadone. However, in a more recent study[2] in 92 opioid addicts also receiving methadone maintenance, rates of sexual dysfunction (erectile, libido, and orgasm dysfunction) were found to be similar to that of the general population. Rates of dysfunction between patients just started on methadone and those on methadone for at least 60 days were not significantly different although new patients generally had lower rates. Mean plasma concentrations of testosterone and prolactin were within normal ranges and although 8 individuals had low testosterone concentrations, only 1 case of dysfunction was reported in this group.

1. Cicero TJ, *et al.* Function of the male sex organs in heroin and methadone users. *N Engl J Med* 1975; **292:** 882–7.
2. Brown R, *et al.* Methadone maintenance and male sexual dysfunction. *J Addict Dis* 2005; **24:** 91–106.

Overdosage. Most cases of methadone poisoning occur in persons not on maintenance,[1-4] particularly children or family members of maintenance patients.[2] Methadone is highly toxic to anyone who is not tolerant to opioids; 50 to 100 mg can be life-threatening in non-tolerant adults and 10 mg can be fatal in a young child.[2] Furthermore, life-threatening toxicity from oral doses as low as 5 mg has been reported in children.[1,4]

Various groups[5,6] have found that the risk of death from methadone toxicity is greatest during the first 2 weeks of maintenance therapy. This has been attributed to the difficulty in determining a safe and effective starting dose of methadone and unreliable accounts of a patient's recent drug use.

1. Aronow R, *et al.* Childhood poisoning: an unfortunate consequence of methadone availability. *JAMA* 1972; **219:** 321–4.
2. Harding-Pink D. Opioid toxicity: methadone: one person's maintenance dose is another's poison. *Lancet* 1993; **341:** 665–6.
3. Zador DA, Sunjic SD. Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug Alcohol Rev* 2002; **21:** 131–6.
4. Sachdeva DK, Stadnyk JM. Are one or two dangerous? Opioid exposure in toddlers. *J Emerg Med* 2005; **29:** 77–84.
5. Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Med J Aust* 1999; **170:** 104–9.
6. Buster MCA, *et al.* An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction* 2002; **97:** 993–1001.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Methadone should be given with caution to patients at risk of developing prolongation of the QT interval including those with cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with a family history of sudden death. It should also be used with caution in patients who are taking other potentially arrhythmogenic drugs, drugs likely to cause electrolyte imbalance, or drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 (see under Interactions, below). ECG monitoring is recommended before starting methadone treatment in these patients, with a further test at dose stabilisation. ECG monitoring is also recommended before and at 7 days after dose titration above 100 mg daily in patients without recognised risk factors.

Administration. Methadone has a long half-life and accumulation may occur with repeated doses, especially in elderly or debilitated patients. An 81-year-old woman given methadone 5 mg three times daily orally for 2 days became deeply unconscious but awoke immediately when given naloxone 400 micrograms intravenously.[1]

Sudden death in 10 diamorphine addicts occurred between 2 and 6 days after starting a methadone maintenance programme.[2] The mean prescribed dose of methadone at the time of death had been about 60 mg. There was evidence of chronic persistent hepatitis in all cases and liver disease could have reduced methadone clearance resulting in higher than expected blood concentrations. Liver function tests and urine testing for the presence of drugs before entry into methadone maintenance programmes, and lower starting doses, might decrease the likelihood of such deaths. Like dextropropoxyphene, methadone has membrane stabilising activity and can block nerve conduction, and it was suggested[3] that the sudden deaths were mainly due to accumulation of methadone over several days resulting in complications such as cardiac arrhythmias or cardiovascular collapse (see Effects on the Cardiovascular System, p. 89.3). See also Overdosage, above.

For the effects of hepatic and renal impairment on the disposition of methadone, see under Pharmacokinetics, p. 91.2.

1. Symonds P. Methadone and the elderly. *BMJ* 1977; **i:** 512.
2. Drummer OH, *et al.* Deaths of heroin addicts starting on a methadone maintenance programme. *Lancet* 1990; **335:** 108.
3. Wu C, Henry JA. Deaths of heroin addicts starting on methadone maintenance. *Lancet* 1990; **335:** 424.

Breast feeding. The American Academy of Pediatrics considers that the use of methadone in breast-feeding mothers is usually compatible with breast feeding.[1] The *BNF* also permits breast feeding by mothers on methadone maintenance although the dose should be as low as possible and the infant monitored to avoid sedation. Others have suggested that the amount of methadone in breast milk is unlikely to have any pharmacological effect on the infant.[2-8] However, there has been a report of the death of a 5-week-old breast-fed infant whose mother was on methadone maintenance.[9]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Blinick G, *et al.* Methadone assays in pregnant women and progeny. *Am J Obstet Gynecol* 1975; **121:** 617–21.
3. Wojnar-Horton RE, *et al.* Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. *Br J Clin Pharmacol* 1997; **44:** 543–7.
4. Geraghty B, *et al.* Methadone levels in breast milk. *J Hum Lact* 1997; **13:** 227–30.
5. McCarthy JJ, Posey BL. Methadone levels in human milk. *J Hum Lact* 2000; **16:** 115–20.
6. Begg EJ, *et al.* Distribution of R- and S-methadone into human milk during multiple, medium to high oral dosing. *Br J Clin Pharmacol* 2001; **52:** 681–5.
7. Jansson LM, *et al.* Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics* 2008; **121:** 106–14.
8. Jansson LM, *et al.* Methadone maintenance and long-term lactation. *Breastfeed Med* 2008; **3:** 34–7.
9. Smialek JE, *et al.* Methadone deaths in children. *JAMA* 1977; **238:** 2516–17.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methadone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. Methadone is not recommended for use in labour because its prolonged duration of action increases the risk of neonatal respiratory depression.

Neonatal abstinence syndrome and low birth-weight are immediate problems in infants born to women receiving methadone for the management of opioid addiction; increased still-birth rates have also been noted.[1-3] In the neonatal period moderate to severe opioid abstinence syndrome occurred in 75% of infants in a study,[2] as well as reduced head circumference and raised systolic blood pressure. At follow-up over 18 months these children had a higher incidence of otitis media, of reduced head circumference, and of abnormal eye findings when compared with drug-free controls. Neurobehavioural abnormalities and lower scores on mental and motor developmental indices were thought to be possible predictors of later learning and behavioural problems. In a later study,[4] the use of methadone alone during pregnancy as part of a maintenance program was claimed to increase the risk of prematurity twofold, of intra-uterine growth retardation fourfold, and of microcephaly threefold when compared with a normal population. In addition, in those mothers who continued to abuse other drugs, as well as receive methadone, the risks of these events were further increased. However, an earlier study[5] has reported that methadone or diamorphine had no specific effect on intra-uterine and postnatal growth.

The relationship between maternal methadone dose and the incidence and severity of neonatal abstinence syndrome is unclear. Although a retrospective study[6] found a correlation in some pregnancies, others[7,8] did not and there was no evidence of an increased incidence of neonatal withdrawal symptoms even with high maternal doses of 100 mg or more daily.[8]

A small retrospective study[9] comparing the use of methadone during pregnancy for the treatment of chronic pain with use in maintenance therapy for opioid addiction found a lower incidence of neonatal abstinence syndrome and better growth parameters in infants born to the former group of mothers; however, a higher rate of slight prematurity was also found in this group of infants. The authors suggested that lower maternal doses and shorter durations of treatment may account for the favourable findings, in addition to better maternal health, nutrition, and socio-economic status.

Clinically significant prolongation of the QT interval has been reported[10] in an infant born to a mother taking methadone 50 mg daily for maintenance therapy; the infant had mild withdrawal symptoms and follow-up at 2 months of age was normal.

1. Blinick G, *et al.* Methadone maintenance, pregnancy, and progeny. *JAMA* 1973; **225:** 477–9.
2. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. *J Pediatr* 1982; **101:** 192–6.
3. KalterH, Warkany J. Congenital malformations. *N Engl J Med* 1983; **308:** 491–7.
4. Arlettaz R, *et al.* Methadone maintenance program in pregnancy in a Swiss perinatal center (II): neonatal outcome and social resources. *Acta Obstet Gynecol Scand* 2005; **84:** 145–50.
5. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; **102:** 686–91.
6. Dashe JS *et al.* Relationship between maternal methadone dosage and neonatal withdrawal. *Obstet Gynecol* 2002; **100:** 1244–9.
7. Berghella V, *et al.* Maternal methadone dose and neonatal withdrawal. *Am J Obstet Gynecol* 2003; **189:** 312–17.
8. McCarthy JJ, *et al.* High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. *Am J Obstet Gynecol* 2005; **193:** 606–10.
9. Sharpe C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F33–F36.
10. Hussain T, Ewer AK. Maternal methadone may cause arrhythmias in neonates. *Acta Paediatr* 2007; **96:** 768–9.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Methadone is metabolised in the liver mainly via the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 are also thought to be involved. Consequently, use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of methadone and, possibly adverse effects. There is a risk of cardiac events in patients receiving methadone who are also taking drugs that affect cardiac conduction or electrolyte balance.

Drugs that *acidify* or *alkalinise* the urine may have an effect on methadone pharmacokinetics since body clearance is increased at acidic pH and decreased at alkaline pH.[1]

1. Nilsson M-I, *et al.* Effect of urinary pH on the disposition of methadone in man. *Eur J Clin Pharmacol* 1982; **22:** 337–42.

Antibacterials. Withdrawal symptoms have been reported in patients maintained on methadone when they were given the enzyme inducer *rifampicin*.[1-3] Conversely, the use of *ciprofloxacin*, which inhibits CYP1A2 and CYP3A4, has resulted in signs of methadone toxicity.[4]

1. Kreek MJ, *et al.* Rifampin-induced methadone withdrawal. *N Engl J Med* 1976; **294:** 1104–6.
2. Bending MR, Skacel PO. Rifampicin and methadone withdrawal. *Lancet* 1977; **i:** 1211.
3. Raistrick D, *et al.* Methadone maintenance and tuberculosis treatment. *BMJ* 1996; **313:** 925–6.
4. Herrlin K, *et al.* Methadone, ciprofloxacin, and adverse drug reactions. *Lancet* 2000; **356:** 2069–70.

Antidepressants. *SSRIs* such as fluoxetine[1] and fluvoxamine[1,2] may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity. *St John's wort* reduced the plasma-methadone concentration to dose ratios by 47% in 4 patients on methadone maintenance therapy for opioid addiction; 2 patients reported symptoms suggestive of a withdrawal syndrome.[3]

1. Eap CB, *et al.* Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. *J Clin Psychopharmacol* 1997; **17:** 113–17.
2. Bertschy G, *et al.* Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Ther Drug Monit* 1994; **16:** 42–5.
3. Eich-Höchli D, *et al.* Methadone maintenance treatment and St. John's Wort: a case report. *Pharmacopsychiatry* 2003; **36:** 35–7.

Antiepileptics. Opioid withdrawal symptoms have been reported in patients maintained on methadone when they were given *carbamazepine*,[1,2] *phenobarbital*,[3] or *phenytoin*.[4,5] Conversely, methadone-induced respiratory depression developed in a patient on carbamazepine, gabapentin, and methadone for neuropathic pain, after carbamazepine was stopped.[6]

1. Bell J, *et al.* The use of serum methadone levels in patients receiving methadone maintenance. *Clin Pharmacol Ther* 1988; **43:** 623–9.
2. Saxon AJ, *et al.* Valproic acid, unlike other anticonvulsants, has no effects on methadone metabolism: two cases. *J Clin Psychiatry* 1989; **50:** 228–9.
3. Liu S-J, Wang RIH. Case report of barbiturate-induced enhancement of methadone metabolism and withdrawal syndrome. *Am J Psychiatry* 1984; **141:** 1287–8.
4. Finelli PF. Phenytoin and methadone tolerance. *N Engl J Med* 1976; **294:** 227.
5. Tong TG, *et al.* Phenytoin-induced methadone withdrawal. *Ann Intern Med* 1981; **94:** 349–51.
6. Benítez-Rosario MA, *et al.* Methadone-induced respiratory depression after discontinuing carbamazepine administration. *J Pain Symptom Manage* 2006; **32:** 99–100.

Antifungals. Use of methadone with *fluconazole* has been reported[1] to increase serum concentrations of methadone although the authors considered that for patients being treated for opioid dependence the interaction was unlikely

to require adjustment of the methadone dose. However, respiratory depression has been reported[2] after intravenous doses of fluconazole were given to a 60-year-old man also taking oral methadone for pain relief in advanced gastric cancer. Although a randomised placebo-controlled study[3] found that giving *voriconazole* to patients on methadone maintenance therapy for opioid addiction was generally safe and well tolerated, the authors recommended monitoring and possible dose reduction of methadone when the 2 drugs are used together. Similar recommendations are also given in the licensed product information for voriconazole.

1. Cobb MN, *et al.* The effect of fluconazole on the clinical pharmacokinetics of methadone. *Clin Pharmacol Ther* 1998; **63:** 655–62.
2. Tarumi Y, *et al.* Methadone and fluconazole: respiratory depression by drug interaction. *J Pain Symptom Manage* 2002; **23:** 148–53.
3. Liu P, *et al.* Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. *Antimicrob Agents Chemother* 2007; **51:** 110–18.

Antivirals. The potential for interaction between antiretrovirals and methadone has been reviewed.[1] Available evidence for HIV-protease inhibitors suggests that *atazanavir*, *indinavir*, and, possibly, *saquinavir* alone have no effect on plasma concentrations of methadone; *amprenavir*, *nelfinavir*, *ritonavir*, and *ritonavir-boosted saquinavir* may reduce plasma-methadone concentrations but the effect is unlikely to be clinically significant. *Lopinavir-ritonavir* may also reduce methadone concentrations and, although most studies found the interaction to be insignificant, one study reported opioid withdrawal symptoms in some patients. Unpublished data [also referred to in the licensed product information] on *tipranavir* (boosted with ritonavir) in healthy, opioid-naive subjects suggest that it may decrease plasma-methadone; licensed product information for tipranavir recommends that patients are monitored for symptoms of opioid withdrawal.

The NNRTIs *nevirapine* and *efavirenz* have both been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when they were given to patients receiving methadone. Conversely, *delavirdine* may increase methadone concentrations although the effect is unlikely to be clinically significant. Methadone possibly increases plasma concentrations of the NRTI *zidovudine* (see p. 1026.2).

1. Bruce RD, *et al.* Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr* 2006; **41:** 563–72.

Gastrointestinal drugs. Histamine H_2-antagonists such as *cimetidine* (see p. 111.3) may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity.

Grapefruit juice. Grapefruit juice, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, has been shown to modestly increase the bioavailability of methadone;[1] although no symptoms of methadone toxicity were seen in the studied patients, the authors commented that such effects may occur in patients with reduced opioid tolerance, particularly when starting methadone treatment.

1. Benmebarek M, *et al.* Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. *Clin Pharmacol Ther* 2004; **76:** 55–63.

Pharmacokinetics

Methadone hydrochloride is readily absorbed from the gastrointestinal tract and after subcutaneous or intramuscular injections. It is widely distributed in the tissues, diffuses across the placenta, and is distributed into breast milk. It is extensively protein bound. Methadone is metabolised in the liver, mainly by *N*-demethylation and cyclisation, and the metabolites are excreted in the bile and urine. Metabolism is mainly catalysed by CYP3A4, although other cytochrome P450 isoenzymes also play a role (see Interactions, p. 90.3). It has a prolonged half-life and is subject to accumulation.

In reviews of the pharmacokinetics of methadone[1-5] particular reference has been made to its long elimination half-life, accumulation after repeated doses, and wide interindividual variations.

Methadone is rapidly absorbed after oral doses and has high oral bioavailability; peak plasma concentrations have been reported 1 to 5 hours after a single tablet. It undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with α_1-acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methylpyrrolidine, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine with unchanged methadone. Other metabolites, including methadol and normethadol, have also been described. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver, and released again mainly unchanged. Urinary excretion of methadone is pH-dependent, the lower the pH the greater the clearance.

In addition to marked interindividual variations there are differences in the pharmacokinetics of methadone after single or multiple doses. Elimination half-lives vary considerably (a range of 15 to 60 hours has been quoted) and may be much longer than the 18 hours reported following a single dose. Careful adjustment of dosage is necessary with repeated doses.

Most studies have been in addicts. Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. These variations in kinetics have also been seen in cancer patients.

1. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11:** 87–106.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
3. Eap CB, *et al.* Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002; **41:** 1153–93.
4. Ferrari A, *et al.* Methadone—metabolism, pharmacokinetics and interactions. *Pharmacol Res* 2004; **50:** 551–9.
5. Lugo RA, *et al.* Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* 2005; **19:** 13–24.

Administration. Methadone is considerably more lipid-soluble than morphine. A study of plasma concentrations and analgesia after intramuscular injection indicated that more rapid and greater relief of pain might be achieved if lipid-soluble opioid analgesics were injected into the deltoid rather than the gluteal muscle; there was no significant difference in absorption of morphine from the two sites.[1]

Other routes investigated in pharmacokinetic studies include continuous intravenous infusion[2] and continuous epidural infusion.[3] Rectal administration[4] has also been studied.

1. Grabinski PY, *et al.* Plasma levels and analgesia following deltoid and gluteal injections of methadone and morphine. *J Clin Pharmacol* 1983; **23:** 48–55.
2. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30:** 70–5.
3. Shir Y, *et al.* Plasma concentrations of methadone during postoperative patient-controlled extradural analgesia. *Br J Anaesth* 1990; **65:** 204–9.
4. Dale O, *et al.* Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 156–62.

Hepatic impairment. Overall hepatic dysfunction does not seem unduly to disrupt methadone metabolism[1] and it has been suggested[2] that maintenance dosage of methadone need not be changed in stable chronic liver disease, although abrupt changes in hepatic status might result in substantial alterations in methadone disposition requiring dosage adjustments.

In a study of patients on methadone maintenance therapy[2] apparent terminal half-life of methadone was prolonged from a mean of 18.8 hours in those with healthy livers to 35.5 hours in patients with severe chronic liver disease. However, plasma concentrations were not increased in such patients.

1. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
2. Novick DM, *et al.* Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther* 1981; **30:** 353–62.

Pregnancy. Plasma concentrations of methadone were reduced in methadone-maintained pregnant women, probably due to enhanced metabolism.[1,2] It was suggested that the dose of methadone might need to be increased in such patients.

1. Pond SM, *et al.* Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther* 1985; **233:** 1–6.
2. Wolff K, *et al.* Changes to methadone clearance during pregnancy. *Eur J Clin Pharmacol* 2005; **61:** 763–8.

Renal impairment. The urinary excretion of methadone was reduced in renal failure,[1] but plasma concentrations were within the usual range and faecal excretion accounted for the majority of the dose. Very little methadone was removed by peritoneal dialysis or haemodialysis.

1. Kreek MJ, *et al.* Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980; **5:** 197–205.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gobbidona; Metacalmans; ***Austral.***: Biodone; Physeptone; ***Austria***: Heptadon; ***Belg.***: Mephenon; ***Braz.***: Metadon; Mytedom; ***Canad.***: Metadol; ***Fin.***: Dolmed; Metadon; ***Ger.***: Eptadone; Methaddict†; ***Hung.***: Depridol; Metadon; ***Irl.***: Phymet DTF; Pinadone DTF; ***Israel***: Adolan; ***Ital.***: Eptadone; ***Jpn***: Methapain; ***Malaysia***: Aseptone; Bennaston; ***Mex.***: Rubidexol; ***Neth.***: Eptadone; Pinadone†; Symoron; ***NZ***: Biodone; Methatabs; Pallidone; ***S.Afr.***: Physeptone; ***Spain***: Eptadone; Metasedin; ***Switz.***: Ketalgine; ***UK***: Eptadone; Martindale Methadone Mixture DTF; Methadose; Physeptone; Synastone; ***USA***: Diskets; Dolophine; Methadose.

Pharmacopoeial Preparations

BP 2014: Methadone Injection; Methadone Linctus; Methadone Oral Solution (1 mg per mL); Methadone Tablets;

USP 36: Methadone Hydrochloride Injection; Methadone Hydrochloride Oral Concentrate; Methadone Hydrochloride Oral Solution; Methadone Hydrochloride Tablets for Oral Suspension; Methadone Hydrochloride Tablets.

Methyl Butetisalicylate

Butetisalicilato de metilo; Methyl Diethylacetylsalicylate.
Methyl *O*-(2-ethylbutyryl)salicylate.
$C_{14}H_{18}O_4$=250.3

Profile

Methyl butetisalicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p. 92.1) as a rubefacient for the relief of musculoskeletal, joint, and soft-tissue pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Dolodermn.

Methyl Gentisate

Gentisato de metilo; Метилгентисат.
2,5-Dihydroxybenzoic acid methyl ester.
$C_8H_8O_4$=168.1
CAS — 2150-46-1.

Profile

Methyl gentisate has been used topically for the relief of musculoskeletal and joint pain. It is also used as a skin lightening agent.

References.

1. Gallo R, Baldari M. Allergic contact dermatitis from methyl gentisate in a bleaching cream. *Contact Dermatitis* 2006; **54:** 220–1.
2. Serra-Baldrich E, *et al.* Allergic contact dermatitis to methyl gentisate. *Contact Dermatitis* 2009; **60:** 225–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Reumacort.

Methyl Nicotinate *(USAN)*

Méthyle, nicotinate de; Methyli Nicotinas; Methylis nicotinas; Methylnicotinat; Methyl-nikotinát; Metilo nikotinatas; Metyl-nikotinat; Metyylinikotinaatti; Nicotinato de metilo; Метилникотинат.
Methyl pyridine-3-carboxylate.
$C_7H_7NO_2$=137.1
CAS — 93-60-7.
UNII — 7B1AVU9DJN.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Methyl Nicotinate). A white or almost white powder. M.p. 40 degrees to 42 degrees. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Methyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Pickles Chilblain Cream.

Multi-ingredient Preparations. ***Arg.***: Medex Rub; ***Austral.***: Deep Heat; ***Austria***: Berggeist; ***Belg.***: Algipan; Emerxil; Percutalgine; ***Canad.***: Le Baume Ehrlich†; ***Chile***: Calorub Sport; Frixio†; Konirub†; Mentobalsam†; ***Fr.***: Algipan†; Capsic†; Decontractyl; Gel Rubefiant; Percutalgine; ***Ger.***: Kytta-Balsam f; Rheuma Bad†; ***Gr.***: Faragel-Forte; Heet; ***Hung.***: Deep Heat Spray; ***India***: Algipan; Diclowin; Flamar†; Heelcare; Medicreme; Neurophen; Relaxyl; ***Indon.***: Remakrim†; ***Irl.***: Deep Heat; Ralgex Heat Spray; Ralgex; Ralgex; ***Israel***: Deep Heat Spray; ***Ital.***: Balsamo Sifcamina; Relaxar; Sedalpan; ***Neth.***: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; ***Pol.***: Deep Heat; ***S. Afr.***: Deep Heat Spray†; Infrarub†; Sloan's Heat Rub; ***Spain***: Doctofril Antiinflamat†; Radio Salil; ***Switz.***: Kytta Baume†; Midalgan Nouvelle Formule†; Radalgin†; ***UK***: Cremalgin†; Deep Heat Spray; Dubam; Fiery Jack; Radian-B Red Oils; Ralgex Heat Spray (low-odour)†; Ralgex†; Red Oil; Transvasin Heat Spray; ***Ukr.***: Deep Heat (Дип Хит); ***USA***: Musterole.

Methyl Salicylate

Methyl Sal.; Méthyle, salicylate de; Methyli Salicylas; Methylis Salicylas; Methylsalicylat; Methyl-salicylát; Metilsalicilatas; Metilsalisilat; Metil-szalicilát; Metylsalicylat; Metylu salicylan; Metyylisalisylaatti; Salicilato de metilo; Метилсалицилат.

Methyl 2-hydroxybenzoate.

$C_8H_8O_3$=152.1

CAS — 119-36-8.

*ATC Herb — HM02AW5005 (*Gaultheria procumbens*: essential oil); HM02AW5001 (*Betula lenta*: essential oil).*

UNII — LAV5U5022Y.

NOTE. Methyl salicylate and methyl salicylate liniment have been known previously as oil of wintergreen, wintergreen, and wintergreen oil. Wintergreen oil has also been known as sweet birch oil.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF.*

Ph. Eur. 8: (Methyl Salicylate). A colourless or slightly yellow liquid. Very slightly soluble in water; miscible with alcohol, and with fatty and essential oils. Protect from light.

USNF 31: (Methyl Salicylate). It is produced synthetically or is obtained from the leaves of *Gaultheria procumbens* (Ericaceae) [wintergreen] or from the bark of *Betula lenta* (Betulaceae) [sweet or black birch]. The source of the methyl salicylate must be indicated on the label.

A colourless, yellowish, or reddish liquid having the characteristic odour of wintergreen. Slightly soluble in water; soluble in alcohol and in glacial acetic acid. Store in airtight containers.

Storage. Certain plastic containers, such as those made from polystyrene, are unsuitable for liniments or ointments containing methyl salicylate.

Uses and Administration

Methyl salicylate is a salicylic acid derivative that is irritant to the skin and is used topically in rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It is also used for minor peripheral vascular disorders such as chilblains and as an ingredient in inhalations for the symptomatic relief of upper respiratory-tract disorders.

Wintergreen oil is also used in aromatherapy.

Adverse Effects, Treatment, and Precautions

Salicylate intoxication can occur after ingestion or topical application of methyl salicylate (see Overdosage, below).

Overdosage. Ingestion of methyl salicylate poses the threat of severe, rapid-onset salicylate poisoning because of its liquid concentrated form and lipid solubility.[1] It is readily absorbed from the gastrointestinal tract and most is rapidly hydrolysed to free salicylate. The symptoms, which may appear within 2 hours of ingestion, are similar to those of salicylate poisoning in general (see Adverse Effects of Aspirin, p. 24.2), although methyl salicylate is expected to be more toxic because of its lipid solubility. There have been reports of fatalities after ingestion of as little as 4 mL in a child and 6 mL in an adult, although the adult lethal dose is estimated to be 30 mL.[1] Topical Chinese herbal medicinal preparations may contain methyl salicylate in variable amounts, and salicylate poisoning has been reported in a 40-year-old man after a total body application of such a preparation.[2] Salicylate poisoning has also been reported in a woman who had attempted suicide by ingesting Red Flower Oil, a topical Chinese herbal oil.[3] The authors also noted that some patients took small amounts of this preparation orally in an attempt to enhance its analgesic effects.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; **15:** 747–50.
2. Bell AJ, Duggin G. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. *Emerg Med (Fremantle)* 2002; **14:** 188–90.
3. Chan TH, *et al.* Severe salicylate poisoning associated with the intake of Chinese medicinal oil ('Red Flower Oil'). *Aust N Z J Med* 1995; **25:** 57.

Percutaneous absorption. Like other salicylates, methyl salicylate may be absorbed through intact skin.[1] Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin. The amount absorbed will also be increased by application to large areas of skin.

Results from a study in healthy subjects showed that a considerable amount of salicylic acid may be absorbed through the skin after topical application of products containing methyl salicylate.[2] Both the rate and extent of absorption increased after repeated application; the bioavailability of the ointment preparation used in the study increased from 15% after the second dose to 22% after the third to eighth dose. The authors recommend that topical analgesic preparations containing methyl salicylate or other salicylates should be used with caution in patients at increased risk of developing salicylate adverse effects (see Precautions of Aspirin, p. 25.3).

Results from another study[3] showing high tissue to plasma ratios after topical application of a methyl salicylate formulation suggest that direct penetration and not recirculation in the blood is responsible for the salicylate concentrations found. The results also showed that methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application.

However, for a study suggesting limited absorption from a patch preparation containing camphor, menthol, and methyl salicylate, see Menthol, p. 2554.1.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; **15:** 747–50.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topical applied salicylate derivatives. *Ann Pharmacother* 1996; **30:** 935–40.
3. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350:** 636.

Interactions

Absorption of methyl salicylate through the skin can occur after excessive topical application (see Percutaneous Absorption, above), and interactions would be expected to be as for other salicylates (see Interactions of Aspirin, p. 26.3).

Anticoagulants. Potentiation of *warfarin* anticoagulation has been reported[1-3] after topical application of methyl salicylate preparations.

1. Littleton F. Warfarin and topical salicylates. *JAMA* 1990; **263:** 2888.
2. Tam LS, *et al.* Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust N Z J Med* 1995; **25:** 258.
3. Joss JD, LeBlond RF. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. *Ann Pharmacother* 2000; **34:** 729–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rati Salil Gel; ***Canad.***: Deep Heating; ***Chile***: Mentholatum Calorub Parche; ***China***: Qing Feng (清风); ***Ger.***: Dolo Roll-On; ***India***: Capsigyl-D; Dolocide Plus; ***Mex.***: Balsamo Nordin; Friccion Don Juan†; Tolan†; ***S. Afr.***: Thermo-Rub; ***Thai.***: Filup; Mygesal; ***UK***: Numark Muscle Rub; ***USA***: Gordogesic.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Canad.***: Stress L72†; ***Fr.***: L 72.

Pharmacopoeial Preparations

BP 2014: Kaolin Poultice; Methyl Salicylate Liniment; Methyl Salicylate Ointment; Surgical Spirit.

Mofezolac *(rINN)*

Mofézolac; Mofezolaco; Mofezolacum; N-22; Мофезолак.

3,4-Bis(*p*-methoxyphenyl)-5-isoxazoleacetic acid.

$C_{19}H_{17}NO_5$=339.3

CAS — 78967-07-4.

UNII — RVJ0BV3H3Y.

Profile

Mofezolac is an NSAID (p. 102.3) given orally in the management of pain and musculoskeletal and joint disorders. A usual dose is 75 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Disopain.

Morniflumate *(USAN, rINN)*

Morniflumato; Morniflumatum; UP-164; Морнифлумат.

2-Morpholinoethyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.

$C_{19}H_{20}F_3N_3O_3$=395.4

CAS — 65847-85-0.

ATC — M01AX22.

ATC Vet — QM01AX22.

UNII — R133MWH7X1.

Profile

Morniflumate, the morpholinoethyl ester of niflumic acid (p. 101.2), is an NSAID (p. 102.3). It has been used in inflammatory conditions in doses of 700 mg given twice daily orally or rectally as suppositories.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Nifluril; ***Gr.***: Niflamol; ***Ital.***: Flomax; Flumarin; Morniflu; Niflam; ***Spain***: Niflactol.

Morphine *(BAN)* ⊗

Morfiini; Morfin; Morfina; Morphinum; Морфин.

7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol.

$C_{17}H_{19}NO_3$=285.3

CAS — 57-27-2 (anhydrous morphine); 6009-81-0 (morphine monohydrate).

ATC — N02AA01.

ATC Vet — QN02AA01.

UNII — 76I7G6D29C (morphine); 41TQ665R1X (morphine monohydrate).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of morphine:

Adolf; Block; China White; Cube; Dreamer; Drug store dope; Drugstore dope; Emsel; First line; German boy; God's drug; Goma; Hard stuff; Hospital Heroin; Hows; Hydrogen Bomb; M; Miss Emma; Mister blue; Mojo; Monf; Monkey; Morf; Morfa; Morfs; Morphia; Morphina; Morpho; Morphy; Mr. Blue; M.S.; MS; Mud; Murphy; Nasty; Nazi; Sweet Jesus; Sweet Morpheus; Tar; Unkie; White Stuff.

Morphine Hydrochloride *(BANM)* ⊗

Morfiinihydrokloridi; Morfin Hidroklorür; Morfina, hidrocloruro de; Morfin-hidroklorid; Morfin-hydrochlorid trihydrát; Morfinhydroklorid; Morfino hidrochloridas; Morfiny chlorowodorek; Morphine, chlorhydrate de; Morphinhydrochlorid; Morphini hydrochloridum; Morphini Hydrochloridum Trihydricum; Morphinii Chloridum; Morphinum Chloratum; Морфина Гидрохлорид.

$C_{17}H_{19}NO_3HCl,3H_2O$=375.8

CAS — 52-26-6 (anhydrous morphine hydrochloride); 6055-06-7 (morphine hydrochloride trihydrate).

UNII — J28GE0ROVX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.*

Ph. Eur. 8: (Morphine Hydrochloride). Colourless, silky needles, cubical masses or a white or almost white, crystalline powder. It is efflorescent in a dry atmosphere. Soluble in water; slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

Incompatibility. See under Morphine Sulfate, below.

Morphine Sulfate *(BANM)* ⊗

Morfiinisulfaatti; Morfin Sülfat; Morfina, sulfato de; Morfino sulfatas; Morfinsulfat; Morfin-sulfát pentahydrát; Morfinszulfát; Morfiny siarczan; Morphine, sulfate de; Morphine Sulphate; Morphini sulfas; Morphini Sulfas Pentahydricus; Morphinsulfat; Морфина Сульфат.

$(C_{17}H_{19}NO_3)_2H_2SO_4,5H_2O$=758.8

CAS — 64-31-3 (anhydrous morphine sulfate); 6211-15-0 (morphine sulfate pentahydrate).

UNII — X3P646A2J0.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Morphine Sulfate). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

USP 36: (Morphine Sulfate). White, feathery, silky crystals, cubical masses of crystals, or a white crystalline powder. Is odourless and when exposed to air it gradually loses water of hydration. It darkens on prolonged exposure to light. Soluble 1 in 16 of water and 1 in 1 of water at 80 degrees; soluble 1 in 570 of alcohol and 1 in 240 of alcohol at 60 degrees; insoluble in chloroform and in ether. Store in airtight containers at a temperature up to 40 degrees as permitted by the manufacturer. Protect from light.

Incompatibility. Incompatibility data for morphine have been extensively studied[1,2] and may depend on many factors such as the formulation used, and order and ratio of mixing; however, most studies are usually only short term and contain few details on mixing the same drugs in a variety of different situations.

Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities, sometimes attributed to particular formulations, have included:

- Aciclovir sodium—precipitate noted 2 hours after admixture with morphine sulfate solution[3]
- Chlorpromazine hydrochloride injection—precipitation was considered to be due to chlorocresol present in the morphine sulfate injection[4]
- Doxorubicin—addition of morphine sulfate 1 mg/mL to doxorubicin hydrochloride liposomal injection 400 micrograms/mL in dextrose 5% resulted in turbidity changes[5]

- Fluorouracil—immediate precipitate formed after admixture of fluorouracil 1 or 16 mg/mL with morphine sulfate 1 mg/mL in dextrose 5% or sodium chloride 0.9%[6]
- Furosemide—precipitate noted 1 hour after admixture with morphine sulfate solution[3]
- Haloperidol—immediate precipitation seen after admixture of haloperidol and morphine sulfate solution[7]
- Heparin sodium—incompatibility has been reported from straightforward additive studies.[1] Another study[8] indicated that morphine sulfate and heparin sodium were only incompatible at morphine sulfate concentrations greater than 5 mg/mL and that this incompatibility could be prevented by using 0.9% sodium chloride solution as the admixture diluent rather than water
- Pethidine hydrochloride—incompatibility has been noted after admixture with morphine sulfate[1,9]
- Prochlorperazine edisilate—immediate precipitation was attributed to phenol in the morphine sulfate injection formulation[10,11]
- Promethazine hydrochloride—cloudiness was reported to develop when 12.5 mg of promethazine hydrochloride was drawn into a syringe containing morphine sulfate 8 mg.[12] Others[9] have noted no incompatibility
- Ranitidine hydrochloride—crystal needles and/or sticky spots seen in admixtures of morphine hydrochloride and ranitidine hydrochloride in various ratios stored at different temperatures[13]
- Tetracyclines—colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with morphine sulfate in 5% glucose injection[14]

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
2. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187:** 17–51.
3. Pugh CB, *et al.* Visual compatibility of morphine sulphate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 123–5.
4. Crapper JB. Mixing chlorpromazine and morphine. *BMJ* 1975; **i:** 33.
5. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
6. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.
7. LeBelle MJ, *et al.* Compatibility of morphine and midazolam or haloperidol in parenteral admixtures. *Can J Hosp Pharm* 1995; **48:** 155–60.
8. Baker DE, *et al.* Compatibility of heparin sodium and morphine sulfate. *Am J Hosp Pharm* 1985; **42:** 1352–5.
9. Parker WA. Physical compatibilities of preanesthetic medications. *Can J Hosp Pharm* 1976; **29:** 91–2.
10. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; **42:** 2651.
11. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; **44:** 67.
12. Fleischer NM. Promethazine hydrochloride—morphine sulfate incompatibility. *Am J Hosp Pharm* 1973; **30:** 665.
13. Vermeire A, *et al.* A new method to obtain and present complete information on the compatibility: study of its validity for eight binary mixtures of morphine with drugs frequently used in palliative care. *Palliat Med* 2002; **16:** 417–24.
14. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.

Stability. *INTRAVENOUS PREPARATIONS.* Solutions of morphine sulfate for intravenous infusion appear to be relatively stable. In a study[1] solutions containing 40 micrograms/mL or 400 micrograms/mL retained more than 90% of their initial concentration of morphine sulfate when stored at 4 degrees or 23 degrees for 7 days, whether or not they were protected from light. Solutions prepared from commercially available injection or from powder, in 0.9% sodium chloride or 5% glucose, and stored in PVC bags or glass bottles did not differ in stability from one another. In a further study[2] 10 mg/mL or 5 mg/mL solutions of morphine sulfate in glucose or sodium chloride and stored in portable infusion pump cassettes retained more than 95% of their initial concentration when kept at 23 degrees for 30 days. A 0.9% solution of sodium chloride containing morphine sulfate 2 mg/mL was stable for 6 weeks when stored in polypropylene syringes at ambient temperatures in the light or dark but a similar solution that also contained 0.1% sodium metabisulfite lost 15% of its potency during the same period.[3] Stability of such a solution with or without sodium metabisulfite was considered to be unacceptable when stored in glass syringes in the dark.[4]

A later review[5] (which included some of the above studies) has concluded that the degradation of morphine solutions is not affected by oxygen, light, diluent type, salt form, or morphine concentration when stored under normal conditions; it was considered that morphine solutions could be stored for at least 3 months without stability problems.

1. Vecchio M, *et al.* The stability of morphine intravenous infusion solutions. *Can J Hosp Pharm* 1988; **41:** 5–9, 43.
2. Walker SE, *et al.* Hydromorphone and morphine stability in portable infusion pump cassettes and minibags. *Can J Hosp Pharm* 1988; **41:** 177–82.
3. Grassby PF. The stability of morphine sulphate in 0.9 per cent sodium chloride stored in plastic syringes. *Pharm J* 1991; **248:** HS24–HS25.
4. Grassby PF, Hutchings L. Factors affecting the physical and chemical stability of morphine sulphate solutions stored in syringes. *Int J Pharm Pract* 1993; **2:** 39–43.
5. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187:** 17–51.

ORAL PREPARATIONS. Studies[1,2] have shown that for optimum stability of morphine content, Kaolin and Morphine Mixture (BP) needed to be stored in well-filled glass containers.

1. Helliwell K, Game P. Stability of morphine in kaolin and morphine mixture BP. *Pharm J* 1981; **227:** 128–9.
2. Helliwell K, Jennings P. Kaolin and morphine mixture BP: effects of containers on the stability of morphine. *Pharm J* 1984; **232:** 682.

TOPICAL PREPARATIONS. When mixed with about 8 g of *Intrasite* gel (*Smith & Nephew Healthcare, UK*) morphine sulfate, in a concentration of 1.25 mg/mL, remained chemically stable over a 28-day period stored at 4 degrees or at room temperature, irrespective of light exposure.[1] However, unless prepared under sterile conditions, the mixture should be used within 7 days because of the risk of microbial contamination once the gel has been opened.

1. Zeppetella G, *et al.* Stability of morphine sulphate and diamorphine hydrochloride in Intrasite gel®. *Palliat Med* 2005; **19:** 131–6.

Morphine Tartrate *(BANM)* ⊗

Morfina, tartrato de; Морфина Тартрат.

$(C_{17}H_{19}NO_3)_2C_4H_6O_6.3H_2O$=774.8

CAS — 302-31-8 (anhydrous morphine tartrate); 6032-59-3 (morphine tartrate trihydrate).

UNII — U3NSU23LHD.

Incompatibility. See under Morphine Sulfate, p. 92.3.

Uses and Administration

Morphine, a phenanthrene derivative, is the main alkaloid of opium (p. 111.3). It is now commonly obtained from whole opium poppies (*Papaver somniferum*) which are harvested as poppy straw; a concentrate of poppy straw is known as CPS.

Morphine is an opioid analgesic (p. 108.1) with agonist activity mainly at μ opioid receptors and perhaps at κ and δ receptors. It acts mainly on the CNS and smooth muscle. Although morphine is mainly a CNS depressant it has some central stimulant actions which result in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

Morphine may produce both physical and psychological dependence (see p. 109.1) and should therefore be used with discrimination. Tolerance may also develop.

Morphine is used for the relief of moderate to severe pain, especially that associated with cancer, myocardial infarction, and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain and it is useful as a hypnotic where sleeplessness is due to pain. It is also used in the management of neonatal abstinence syndrome (see Administration in Children, p. 94.1).

Morphine reduces intestinal motility but its role, if any, in the symptomatic treatment of diarrhoea is very limited. It also relieves dyspnoea associated with various conditions, including that due to pulmonary oedema resulting from left ventricular failure. It is an effective cough suppressant, but codeine is usually preferred as there is less risk of dependence; morphine may however be necessary to control intractable cough associated with terminal lung cancer. Morphine has been used pre-operatively as an adjunct to anaesthesia for pain relief and to allay anxiety. It has also been used in high doses as a general anaesthetic in specialised procedures such as open-heart surgery.

Morphine is usually **administered** as the sulfate, although the hydrochloride and the tartrate are used in similar doses. Doses are expressed as the salts. Dosage routes include the oral, subcutaneous, intramuscular, intravenous, intraspinal, and rectal routes. Subcutaneous injections are considered unsuitable for oedematous patients. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

Doses should generally be reduced in the elderly or debilitated, or in patients with hepatic or renal impairment (see also under Precautions, p. 95.1 and p. 95.2).

For **pain**:

- *Oral* doses are usually equivalent to 5 to 20 mg every 4 hours and may be given as an aqueous solution of the hydrochloride or sulfate, as modified-release granules or tablets, or as immediate-release tablets. With modified-release preparations the 24-hour dose is usually given as a single dose or in 2 divided doses; in the USA, a modified-release preparation (*MS Contin, Purdue*) that allows dosing every 8 or 12 hours is also available. With all modified-release preparations, additional doses of a conventional formulation may be needed if breakthrough pain occurs. As with the other routes, high oral doses may be required for effective analgesia in palliative care.
- Morphine is sometimes given *rectally* generally as suppositories in doses of 10 to 30 mg every 4 hours. Oral modified-release preparations have also been used rectally although such use is unlicensed in the UK and is generally not recommended except, possibly, in some emergency situations.
- The usual dose by *subcutaneous* or *intramuscular* injection is 10 mg every 4 hours but may range from 5 to 20 mg.
- For premedication, the *BNF* recommends that up to 10 mg may be given by subcutaneous or intramuscular injection 60 to 90 minutes before surgery.
- Doses of up to 15 mg have been given by slow *intravenous* injection, sometimes as a loading dose for continuous or patient-controlled infusion. For continuous intravenous administration maintenance doses have generally ranged from 0.8 to 80 mg/hour, although some patients have required and been given much higher doses. Similar doses have been given by continuous subcutaneous infusion.
- For myocardial infarction, the *BNF* recommends that 5 to 10 mg may be given by intravenous injection at a rate of 1 to 2 mg/minute followed by a further 5 to 10 mg if necessary; half this dose should be used in elderly or debilitated patients.
- Intraspinal doses are in the region of 5 mg for an initial *epidural* injection; if pain relief is unsatisfactory after one hour, further doses of 1 to 2 mg may be given up to a total dose of 10 mg per 24 hours. The recommended initial dose for continuous epidural infusion in opioid-naive patients ranges from 3.5 to 7.5 mg daily; those who have some degree of opioid tolerance may be given 4.5 to 10 mg daily. However, dosage requirements may increase significantly during treatment and up to 20 to 30 mg daily may be required in some patients. A modified-release formulation of liposomal morphine sulfate for lumbar epidural use is also available for the treatment of pain after major surgery; doses range from 10 to 20 mg, depending on the type of surgery, and should be given before the operation, or after clamping of the umbilical cord if used during caesarean section. It is intended for single-use only and no other drugs should be administered into the epidural space for at least the next 48 hours.
- *Intrathecal* use of morphine and its salts has tended to be less common than epidural. A single dose of 0.2 to 1 mg given by intrathecal injection may provide satisfactory pain relief for up to 24 hours. The recommended initial dose for continuous intrathecal infusion in opioid-naive patients ranges from 0.2 to 1 mg daily; those who have some degree of opioid tolerance may be given 1 to 10 mg daily. However, dosage requirements may increase during treatment and up to 20 mg daily may be required in some patients.

For details of doses in children, see p. 94.1.

In **acute pulmonary oedema** 5 to 10 mg may be given by intravenous injection at a rate of 2 mg/minute; half this dose should be used in elderly or debilitated patients.

For the control of intractable **cough** associated with terminal lung cancer, morphine oral solution is given in an initial dose of 5 mg every 4 hours.

As a deterrent to abuse a combined oral preparation of morphine sulfate and naltrexone hydrochloride is available in some countries.

Administration. *CONTINUOUS INFUSION.* Both acute and chronic pain have been controlled satisfactorily by continuous intravenous or subcutaneous infusions of morphine sulfate[1-3] but diamorphine hydrochloride or hydromorphone hydrochloride may be preferred for subcutaneous infusion because their greater solubility in water allows a smaller dose volume. Continuous subcutaneous infusions may be preferred to continuous intravenous infusions.[4] Continuous subcutaneous infusion may be less effective than epidural morphine for relief of postoperative pain;[5] however, it was still considered to provide simple and relatively effective analgesia with a low rate of adverse effects.

See also Patient-controlled Analgesia, p. 94.1.

1. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; **39:** 768–71.
2. Goudie TA, *et al.* Continuous subcutaneous infusion of morphine for postoperative pain relief. *Anaesthesia* 1985; **40:** 1086–92.
3. Stuart GJ, *et al.* Continuous intravenous morphine infusions for terminal pain control: a retrospective review. *Drug Intell Clin Pharm* 1986; **20:** 968–72.
4. Drexel H. Long-term continuous subcutaneous and intravenous opioid infusions. *Lancet* 1991; **337:** 979.
5. Hindsholm KB, *et al.* Continuous subcutaneous infusion of morphine—an alternative to extradural morphine for postoperative pain relief. *Br J Anaesth* 1993; **71:** 580–2.

INTRA-ARTICULAR ROUTE. Intra-articular injection of morphine into the knee at the end of arthroscopy has been reported to provide some degree of postoperative pain relief;[1,2] such pain relief may be more pronounced than that produced

by the same dose given intravenously[1] or intramuscularly.[2] The effect appears to be due to the action of morphine on peripheral opioid receptors[2] although a systemic effect has not been completely excluded.[1]

There have been conflicting results on whether addition of morphine to intra-articular bupivacaine improves analgesia[3,4] and a systematic review[5] concluded that from the few well-controlled studies there was no evidence of an added analgesic effect of morphine compared with saline alone.

Doses of morphine reported to have been injected intra-articularly have ranged from 1 to 10 mg.

1. Gupta A, *et al.* A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* 2001; **93:** 761–70.
2. Raj N, *et al.* Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. *Eur J Anaesthesiol* 2004; **21:** 932–7.
3. Laurent SC, *et al.* Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. *Br J Anaesth* 1994; **72:** 170–3.
4. Heine MF, *et al.* Intra-articular morphine after arthroscopic knee operation. *Br J Anaesth* 1994; **73:** 413–15.
5. Rosseland LA. No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med* 2005; **30:** 83–98.

INTRANASAL ROUTE. An intranasal formulation of morphine has been investigated for the relief of acute pain.

INTRASPINAL ROUTE. Morphine is given epidurally and intrathecally to relieve both acute and chronic pain. However, reviews on the role of spinal opioids have generally concluded that they should be reserved for pain not controlled by more conventional routes.[1-3] When converting from conventional routes it has been suggested that 1% of the total daily dose could be tried as the daily intrathecal dose and 10% as the epidural dose.[3] Conversion from intrathecal to oral dosage has also been investigated.[4]

Intrathecal morphine may be delivered continuously via an implanted programmable infusion pump for the long-term management of chronic non-malignant and cancer pain.

See also Patient-controlled Analgesia, below.

1. Anonymous. Spinal opiates revisited. *Lancet* 1986; **i:** 655–6.
2. Gustafsson LL, Wiesenfeld-Hallin Z. Spinal opioid analgesia: a critical update. *Drugs* 1988; **35:** 597–603.
3. McQuay HJ. Opioids in chronic pain. *Br J Anaesth* 1989; **63:** 213–26.
4. Sylvester RK, *et al.* The conversion challenge: from intrathecal to oral morphine. *Am J Hosp Palliat Care* 2004; **21:** 143–7.

PATIENT-CONTROLLED ANALGESIA. Morphine is one of the most frequently used opioid analgesics for patient-controlled analgesia (see p. 5.3). Most experience has been with the intravenous route, but the intramuscular, subcutaneous, oral, pulmonary, and epidural[1] routes have also been used. Reasonable initial settings recommended for intravenous use have been a demand dose of 1 to 2 mg of morphine sulfate (or its equivalent) and a lockout interval of 5 to 10 minutes.[2]

1. Sjöström S, *et al.* Patient-controlled analgesia with extradural morphine or pethidine. *Br J Anaesth* 1988; **60:** 358–66.
2. Grass JA. Patient-controlled analgesia. *Anesth Analg* 2005; **101** (suppl): S44–S61.

PULMONARY ROUTE. For reference to the use of nebulised morphine see Dyspnoea, below.

TOPICAL ROUTE. Morphine has been applied topically for local analgesia in oral mucositis[1,2] and cutaneous ulceration[3-6] including epidermolysis bullosa.[7]

1. Cerchietti LC, *et al.* Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* 2000; **95:** 2230–6. Correction. *ibid.* 2003; **97:** 1137.
2. Cerchietti L. Morphine mouthwashes for painful mucositis. *Support Care Cancer* 2007; **15:** 115–16.
3. Twillman RK, *et al.* Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999; **17:** 288–92.
4. Krajnik M, *et al.* Potential uses of topical opioids in palliative care–report of 6 cases. *Pain* 1999; **80:** 121–5.
5. Zeppetella G, *et al.* Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003; **25:** 555–8.
6. Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. *J Pain Symptom Manage* 2005; **29:** 118–19.
7. Watterson G, *et al.* Peripheral opioids in inflammatory pain. *Arch Dis Child* 2004; **89:** 679–81.

Administration in children. Opioid analgesics are used in children in the management of moderate to severe **pain** (see p. 5.2); morphine is the most widely used opioid for severe pain in children and is the standard against which other opioids are compared. Morphine may be given to children requiring acute analgesia as a result of surgery or invasive procedures. It may also be given for chronic non-malignant pain and is the opioid of choice for the oral treatment of severe pain in palliative care. Its analgesic and sedative properties are useful in the management of children in intensive care (see p. 1033.1); morphine is considered to be a more rational choice than fentanyl in settings where long-term infusions are required. Respiratory depression with morphine treatment is a risk in all children; however, neonates (and particularly those who are breathing spontaneously) may have an enhanced susceptibility because of the pharmacokinetic differences of morphine in this age group (see p. 96.2).

The following initial doses are recommended by the *BNFC* according to age; doses should thereafter be adjusted according to response:

By subcutaneous injection:
- neonates: 100 micrograms/kg every 6 hours
- 1 to 6 months: 100 to 200 micrograms/kg every 6 hours
- 6 months to 2 years: 100 to 200 micrograms/kg every 4 hours
- 2 to 12 years: 200 micrograms/kg every 4 hours
- 12 to 18 years: 2.5 to 10 mg every 4 hours

By intravenous injection over at least 5 minutes:
- neonates: 50 micrograms/kg every 6 hours
- 1 to 6 months: 100 micrograms/kg every 6 hours
- 6 months to 12 years: 100 micrograms/kg every 4 hours
- 12 to 18 years: 5 mg every 4 hours

The following doses given by slow intravenous injection are suggested as loading doses for *continuous intravenous infusion*:
- neonates: 50 micrograms/kg
- 1 month to 12 years: 100 micrograms/kg
- 12 to 18 years: 5 mg

The loading dose may be followed by an infusion given as follows:
- neonates: 5 to 20 micrograms/kg per hour
- 1 to 6 months: 10 to 30 micrograms/kg per hour
- 6 months to 18 years: 20 to 30 micrograms/kg per hour

By mouth or rectum:
- 1 to 3 months: 50 to 100 micrograms/kg every 4 hours
- 3 to 6 months: 100 to 150 micrograms/kg every 4 hours
- 6 to 12 months: 200 micrograms/kg every 4 hours
- 1 to 12 years: 200 to 300 micrograms/kg every 4 hours
- 12 to 18 years: 5 to 10 mg every 4 hours

In *palliative care*, modified-release oral preparations may be used; they are given as a single daily dose or in 2 divided doses.

By continuous subcutaneous infusion:
- 1 to 3 months: 10 micrograms/kg per hour
- 3 months to 18 years: 20 micrograms/kg per hour

Intraspinal doses of morphine that have been tried[1] in children are as follows:
- caudal epidural block, 100 micrograms/kg
- thoracic or lumbar epidural block, 50 micrograms/kg
- intrathecal doses of 20 or 30 micrograms/kg have provided satisfactory postoperative pain relief, but respiratory depression occurred in 10 and 25%, respectively

Guidelines[2] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intravenous morphine as an alternative to, or after initial treatment with, intranasal diamorphine for *severe pain* such as that associated with large burns, long bone fracture or dislocation, appendicitis, or sickle-cell crisis, but it should be used with caution if there is risk of depression of airway, breathing, or circulation.

In the UK, morphine is also used in the management of **neonatal abstinence syndrome** (p. 110.1) under specialist supervision. The *BNFC* recommends an initial oral dose of 40 micrograms/kg (increase dose if necessary) every 4 hours until symptoms are controlled; the dosage frequency should be reduced gradually over 6 to 10 days until a dose of 40 micrograms/kg once daily is achieved after which the drug should be stopped.

1. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.
2. The College of Emergency Medicine. Best practice guideline: management of pain in children (issued July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)

Cancer pain. Morphine is the opioid of choice for moderate to severe cancer pain (p. 7.1); guidelines for its use issued by the European Association for Palliative Care[1] include:
- the optimal route for use is orally. For best effect, both immediate-release (for dose titration) and modified-release (for maintenance) dosage forms are required
- the simplest method of dose titration is with immediate-release morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue dose' may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take into account the amount needed for breakthrough pain
- if pain returns consistently before the next dose is due the regular dose should be increased. Immediate-release formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain
- if an immediate-release formulation of morphine is not available and treatment is started with modified-release morphine, changes to the regular dose should not be made more often than every 48 hours, which means that dose titration will be prolonged
- for patients taking immediate-release morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep
- if patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful
- when converting dosage, the relative potency of oral to subcutaneous morphine is between about 1:2 and 1:3, so 20 to 30 mg of oral morphine is equianalgesic to 10 mg by subcutaneous injection
- in patients who need continuous parenteral morphine the preferred route is by subcutaneous infusion. However, intravenous infusion may be preferred:
  in patients who already have an indwelling intravenous line
  in those with generalised oedema
  if erythema, soreness, or sterile abscess develop during subcutaneous dosage
  in patients with coagulation disorders
  where peripheral circulation is poor
- when converting dosage, the relative potency of oral to intravenous morphine is also between about 1:2 and 1:3
- the buccal, sublingual, and nebulised routes of administration are not recommended in the absence of evidence for clinical advantage over more usual routes
- a small proportion of patients develop intolerable adverse effects with oral morphine (with adjuvant non-opioid analgesics as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid, or a change in the route should be considered. Although switching between opioids complicates pain management, adequate pain relief for some may depend on the use of alternative drugs, the use of intraspinal routes, or non-drug methods of pain control

Similar recommendations are given in guidelines issued by the US National Comprehensive Cancer Network.[2]

1. Hanks GW, *et al.* Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; **84:** 587–93.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: adult cancer pain (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf (accessed 02/08/10)

Dyspnoea. In the treatment of dyspnoea (p. 108.3), doses of morphine tend to be smaller than those used for pain relief. Morphine hydrochloride or sulfate may be given as an oral solution in carefully titrated doses, starting at a dose of 5 mg every 4 hours; as little as 2.5 mg every 4 hours may be sufficient for opioid-naive patients.[1] In acute pulmonary oedema, 5 to 10 mg may be given by slow intravenous injection. In patients already receiving morphine for pain relief the following doses have been suggested:[2]
- mild dyspnoea: 25 to 50% of usual analgesic dose
- moderate dyspnoea: 50 to 100% of usual analgesic dose
- severe dyspnoea: 100% or more of usual analgesic dose

Patients have also obtained relief from subcutaneous injection.[3]

Although it has been reported that a low dose of nebulised morphine (mean dose 1.7 mg) improved exercise endurance in patients with dyspnoea due to advanced chronic lung disease,[4] several subsequent studies[5-7] have failed to obtain significant improvements with doses up to 40 mg. It is considered that current evidence does not support the use of nebulised morphine for breathlessness.[1,8-10] Furthermore, bronchospasm can be a problem, particularly at high doses, and there is no consensus on the optimal dose, schedule, or method of dose titration.

1. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.
2. Twycross R, Wilcock A. *Palliative Care Formulary*. 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 280.
3. Bruera E, *et al.* Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993; **119:** 906–7.
4. Young IH, *et al.* Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989; **44:** 387–90.
5. Beauford W, *et al.* Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patients. *Chest* 1993; **104:** 175–8.
6. Noseda A, *et al.* Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *Eur Respir J* 1997; **10:** 1079–83.
7. Jankelson D, *et al.* Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease. *Eur Respir J* 1997; **10:** 2270–4.
8. Polosa R, *et al.* Nebulised morphine for severe interstitial lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 26/06/08).
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than that associated with κ-receptor agonists. With morphine, withdrawal symptoms usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside.

Morphine is used for substitution therapy in the management of neonatal abstinence syndrome (see Administration in Children, p. 94.1).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

References.

1. Cherny N, *et al.* Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001; **19:** 2542–54.

Effects on the cardiovascular system. For a reference to the effects of morphine on histamine release compared with some other opioids, see under Pethidine, p. 122.3.

Effects on the muscles. Severe rectovaginal spasms that occurred in a patient given intrathecal morphine[1] were successfully controlled with midazolam.

1. Littrell RA, *et al.* Muscle spasms associated with intrathecal morphine therapy: treatment with midazolam. *Clin Pharm* 1992; **11:** 57–9.

Effects on the nervous system. Myoclonus, often associated with hyperalgesia, has been reported in patients with advanced malignant disease treated with morphine.[1-5] It appears to be uncommon with typical oral doses of morphine and is more often associated with high intravenous and spinal doses. Neuroexcitatory metabolites of morphine are often implicated in the development of myoclonus;[2,4,5] however, other possible mechanisms such as drug interactions cannot be ruled out.[4-6]

It has been reported that myoclonus induced by morphine can be successfully controlled using a benzodiazepine such as midazolam.[7] Indeed, some researchers[8] consider benzodiazepines to be the drugs of choice: clonazepam, diazepam, and lorazepam were most frequently used. Dantrolene[5,8] and gabapentin[9] have also been tried.

1. Potter JM, *et al.* Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs. *BMJ* 1989; **299:** 150–3.
2. Glare PA, *et al.* Normorphine, a neurotoxic metabolite? *Lancet* 1990; **335:** 725–6.
3. De Conno F, *et al.* Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. *Pain* 1992; **47:** 337–9.
4. Sjøgren P, *et al.* Hyperalgesia and myoclonus in terminal cancer patients treated with continuous intravenous morphine. *Pain* 1993; **55:** 93–7.
5. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain* 1998; **74:** 5–9.
6. Quinn N. Myoclonus associated with high doses of morphine. *BMJ* 1989; **299:** 683–4.
7. Holdsworth MT, *et al.* Continuous midazolam infusion for the management of morphine-induced myoclonus. *Ann Pharmacother* 1995; **29:** 25–9.
8. Ferris DJ. Controlling myoclonus after high-dosage morphine infusions. *Am J Health-Syst Pharm* 1999; **56:** 1009–10.
9. Mercadante S, *et al.* Gabapentin for opioid-related myoclonus in cancer patients. *Support Care Cancer* 2001; **9:** 205–6.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Biliary-tract disorders. See under Precautions of Opioid Analgesics, p. 111.1.

Breast feeding. Measurable blood concentrations of morphine have been detected in 2 breast-fed infants whose mothers received oral or intrathecal morphine during and after their pregnancies; however, no adverse effects were reported in either of these infants.[1,2] In a group of 7 women given patient-controlled analgesia with intravenous morphine after caesarean delivery, the concentrations of morphine and its metabolite morphine-6 glucuronide in the colostrum were found to be very small.[3] Although no infants were breast fed during the study, it was considered that the effects of maternal morphine on breast-fed infants would be negligible.[3] The American Academy of Pediatrics[4] also states that the use of morphine is usually compatible with breast feeding.

1. Robieux I, *et al.* Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Toxicol Clin Toxicol* 1990; **28:** 365–70.
2. Oberlander TF, *et al.* Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment. *J Hum Lact* 2000; **16:** 137–42.
3. Baka N-E, *et al.* Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg* 2002; **94:** 184–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Hepatic impairment. In view of its hepatic metabolism, caution is generally advised when giving morphine to patients with hepatic impairment (but see under Pharmacokinetics, p. 96.3). The *BNF* advises that use should be avoided or the dose reduced because of the risk of precipitating a coma. However, it has also been noted that many patients with hepatic impairment tolerate morphine well. Others have considered that severe hepatic impairment may affect morphine metabolism but less severe impairment does not.[1]

The mean elimination half-life of morphine in 12 patients with cirrhosis was almost twice that in 10 healthy subjects after administration of a modified-release oral morphine preparation (*MST-Continus; Napp, UK*) and peak serum concentrations were almost three times as high.[2] Patients with cirrhosis had a greater degree of sedation but none developed encephalopathy. It was recommended that the dose for modified-release preparations should be reduced and that it be given less often when patients have cirrhosis.

In a later study[3] 15 patients with liver cancer were given the same oral morphine preparation and compared with 10 healthy subjects from the previous study; the area under the serum concentration-time curve of morphine was increased three- to fourfold in those with cancer. The elimination half-life of morphine was also prolonged in patients with primary cancer when compared with healthy subjects and those with secondary metastatic disease. Adverse effects were more frequent in the primary cancer group and included 2 cases of respiratory depression; the authors commented that altered blood-brain transportation may have been partly responsible for such effects.

1. Twycross R, Wilcock A. *Palliative Care Formulary.* 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 274.
2. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis. *Br J Anaesth* 1997; **79:** 804–6.
3. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma. *Br J Anaesth* 2005; **94:** 95–9.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma. For further details, see p. 111.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies morphine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Renal impairment. Severe and prolonged respiratory depression has occurred in patients with renal impairment given morphine. Toxicity in 3 such patients was attributed to the accumulation of the active metabolite morphine-6-glucuronide.[1] Plasma concentrations of this metabolite were found[2] to be ten times higher than normal in a 7-year-old girl with haemolytic uraemic syndrome given morphine intravenously although the half-life of morphine was also prolonged. Plasma concentrations of morphine-6-glucuronide were also reported[3] to be persistently increased 19 days after stopping morphine by intravenous infusion in a 17-year-old girl with normal renal function. The authors of the report suggested that alterations in bowel flora after antibacterial therapy or inhibition of morphine-3-glucuronide glucuronidation by lorazepam might be responsible. It has also been reported[4] that accumulation of morphine can occur in renal failure, although to a lesser extent than accumulation of metabolites (see also under Pharmacokinetics, p. 96.3).

1. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; **292:** 1548–9.
2. Hasselström J, *et al.* Long lasting respiratory depression induced by morphine-6-glucuronide? *Br J Clin Pharmacol* 1989; **27:** 515–18.
3. Calleja MA, *et al.* Persistently increased morphine-6-glucuronide concentrations. *Br J Anaesth* 1990; **64:** 649.
4. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; **54:** 158–67.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

US licensed product information for some once-daily modified-release preparations of morphine sulfate states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of rapid release and absorption of a potentially fatal dose of morphine; *in-vitro* studies showed that alcohol accelerated the release of morphine.

For references to myoclonus associated with morphine and the concurrent use of other drugs, see Effects on the Nervous System under Adverse Effects, above.

Antibacterials. Potent enzyme inducer *rifampicin* can reduce the serum concentration of morphine and decrease its analgesic effect;[1] induction of the enzymes responsible for conversion of morphine to the active glucuronide metabolite did not seem to occur.

1. Fromm MF, *et al.* Loss of analgesic effect of morphine due to coadministration of rifampin. *Pain* 1997; **72:** 261–7.

Benzodiazepines. An additive sedative effect is to be expected between opioid analgesics and benzodiazepines and has been reported with morphine and *midazolam.*[1]

For reference to a suggestion that *lorazepam* may inhibit morphine-3-glucuronide glucuronidation, see Renal Impairment under Precautions, above.

1. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; **68:** 282–5.

Cisapride. Plasma concentrations of morphine have been increased by oral cisapride.[1]

1. Rowbotham DJ, *et al.* Effect of cisapride on morphine absorption after oral administration of sustained-release morphine. *Br J Anaesth* 1991; **67:** 421–5.

Histamine H_2-antagonists. See under Opioid Analgesics, p. 111.3.

Local anaesthetics. Prior use of epidural *chloroprocaine*, when compared with lidocaine, has been reported to reduce the duration[1] and efficacy[2] of epidural morphine analgesia. However, a later study[3] found no such effects; the authors suggested that findings from the previous 2 studies were due to breakthrough pain caused by the early resolution of chloroprocaine anaesthesia occurring before the maximum onset of morphine analgesia.

1. Eisenach JC, *et al.* Effect of prior anesthetic solution on epidural morphine analgesia. *Anesth Analg* 1991; **73:** 119–23.
2. Karambelkar DJ, Ramanathan S. 2-Chloroprocaine antagonism of epidural morphine analgesia. *Acta Anaesthesiol Scand* 1997; **41:** 774–8.
3. Hess PE, *et al.* Chloroprocaine may not affect epidural morphine for postcesarean delivery analgesia. *J Clin Anesth* 2006; **18:** 29–33.

Metoclopramide. The effects of metoclopramide on morphine have included an increased rate of onset and degree of sedation when oral metoclopramide was given with modified-release morphine[1] and antagonism of the effects of morphine on gastric emptying by intravenous metoclopramide.[2]

1. Manara AR, *et al.* The effect of metoclopramide on the absorption of oral controlled release morphine. *Br J Clin Pharmacol* 1988; **25:** 518–21.
2. McNeill MJ, *et al.* Effect of iv metoclopramide on gastric emptying after opioid premedication. *Br J Anaesth* 1990; **64:** 450–2.

Tricyclic antidepressants. Both *clomipramine* and *amitriptyline* significantly increased the plasma availability of morphine when given to cancer patients taking oral morphine solution.[1] It was noted however that the potentiation of the analgesic effects of morphine by these drugs might not be confined to increased bioavailability of morphine; the dose of tricyclic to use with morphine in the treatment of cancer pain should be decided by clinical evaluation rather than by pharmacokinetic data.

1. Ventafridda V, *et al.* Antidepressants increase bioavailability of morphine in cancer patients. *Lancet* 1987; **i:** 1204.

Pharmacokinetics

Morphine salts are well absorbed from the gastrointestinal tract but have poor oral bioavailability since they undergo extensive first-pass metabolism in the liver and gut. After subcutaneous or intramuscular injection morphine is readily absorbed into the blood. The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide. The latter is considered to contribute to the analgesic effect of morphine, especially with repeated oral doses. Morphine-3-glucuronide on the other hand can antagonise the analgesic action and might be responsible for the paradoxical pain seen in some patients given morphine. Other active metabolites include normorphine, codeine, and morphine ethereal sulfate. Enterohepatic circulation probably occurs. Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the CSF as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35% is protein bound. Mean plasma elimination half-lives of about 2 hours for morphine and 2.4 to 6.7 hours for morphine-3-glucuronide have been reported.

Up to 10% of a dose of morphine may eventually be excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90% of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

Much has been published on the metabolism and disposition of morphine and its relevance to the clinical use of morphine, in particular the analgesic effect of repeated oral doses and the relative potency of oral to parenteral

doses. There has been uncertainty as to the contributions in man of first-pass metabolism in the liver and gut,[1-4] the possible role of renal metabolism,[2,4-6] the analgesic activity and clinical importance of the metabolite morphine-6-glucuronide,[2,7-21] and enterohepatic circulation.[2,9] There has also been interest in the effects of the metabolite morphine-3-glucuronide.[19,22-24]

1. Hanks GW, Aherne GW. Morphine metabolism: does the renal hypothesis hold water? *Lancet* 1985; **i:** 221–2.
2. Hanks GW, *et al*. Explanation for potency of repeated oral doses of morphine? *Lancet* 1987; **ii:** 723–5.
3. Moore RA, *et al*. Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
4. Bodenham A, *et al*. Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 380–4.
5. McQuay H, Moore A. Metabolism of narcotics. *BMJ* 1984; **288:** 237.
6. Moore A, *et al*. Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984; **35:** 641–5.
7. McQuay HJ, *et al*. Potency of oral morphine. *Lancet* 1987; **ii:** 1458–9.
8. Hanks GW, *et al*. Enterohepatic circulation of morphine. *Lancet* 1988; **i:** 469.
9. Osborne R, *et al*. Analgesic activity of morphine-6-glucuronide. *Lancet* 1988; **i:** 828.
10. Hanks GW, Wand PJ. Enterohepatic circulation of opioid drugs: is it clinically relevant in the treatment of cancer patients? *Clin Pharmacokinet* 1989; **17:** 65–8.
11. Paul D, *et al*. Pharmacological characterization of morphine-6 β-glucuronide, a very potent morphine metabolite. *J Pharmacol Exp Ther* 1989; **251:** 477–83.
12. Hanna MH, *et al*. Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine. *Br J Anaesth* 1990; **64:** 547–50.
13. Osborne R, *et al*. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; **47:** 12–19.
14. McQuay HJ, *et al*. Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clin Pharmacol Ther* 1990; **48:** 236–44.
15. Hanna MH, *et al*. Disposition of morphine-6-glucuronide and morphine in healthy volunteers. *Br J Anaesth* 1991; **66:** 103–7.
16. Portenoy RK, *et al*. The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. *Clin Pharmacol Ther* 1992; **51:** 422–31.
17. Thompson PI, *et al*. Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol* 1995; **40:** 145–52.
18. Lötsch J, Geisslinger G. Morphine-6-glucuronide: an analgesic of the future? *Clin Pharmacokinet* 2001; **40:** 485–99.
19. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. *J Pain Palliat Care Pharmacother* 2003; **16** (4): 5–18.
20. Wittwer E, Kern SE. Role of morphine's metabolites in analgesia: concepts and controversies. *AAPS J* 2006; **8:** E348–E352.
21. van Dorp ELA, *et al*. Morphine-6-glucuronide: morphine's successor for postoperative pain relief? *Anesth Analg* 2006; **102:** 1789–97.
22. Smith MT, *et al*. Morphine-3-glucuronide—a potent antagonist of morphine analgesia. *Life Sci* 1990; **47:** 579–85.
23. Morley JS, *et al*. Paradoxical pain. *Lancet* 1992; **340:** 1045.
24. Morley JS, *et al*. Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342:** 1243.

Administration. There have been many studies on the pharmacokinetics of morphine given by various routes and methods. These include the buccal route (see below), modified-release oral preparations,[1,2] the rectal route,[3,4] the topical route,[5] the pulmonary route,[6,7] continuous subcutaneous compared with intravenous infusion,[8] and the intraspinal route.[9-13]

Slow dural transfer of morphine and its prolonged presence in the CSF appear to correlate with its slow onset and long duration of action by epidural and intrathecal injection.[14] Modified release epidural preparations have further extended the duration of morphine.[15] More lipid-soluble opioids, such as diamorphine and pethidine, enter and leave the CSF more rapidly than morphine.

The pharmacokinetics of morphine given by 5 different routes—intravenous bolus injection and oral, sublingual, buccal, and modified-release buccal tablets—were studied[16] with particular reference to morphine-6-glucuronide, the active metabolite. This metabolite occurred in large quantities after intravenous doses and plasma concentrations rapidly exceeded those of morphine. After oral doses morphine-6-glucuronide and morphine-3-glucuronide were present in quantities similar to those seen after intravenous morphine; morphine concentrations in plasma were very low and the mean morphine-6-glucuronide to morphine area under the concentration-time curve ratio was 9.7 to 1. There was delayed absorption with attenuation and delay of peak morphine and metabolite plasma concentrations after sublingual or buccal dosage.

Compared with oral doses, concentrations of morphine were higher and those of its glucuronides lower when morphine was given rectally,[17] suggesting avoidance of first-pass metabolism.

Morphine was not absorbed systemically when applied topically to ulcers although some absorption may occur when a large surface area is involved.[5]

1. Pinnock CA, *et al*. Absorption of controlled release morphine sulphate in the immediate postoperative period. *Br J Anaesth* 1986; **58:** 868–71.
2. Savarese JJ, *et al*. Steady-state pharmacokinetics of controlled release oral morphine sulphate in healthy subjects. *Clin Pharmacokinet* 1986; **11:** 505–10.
3. Moolenaar F, *et al*. Drastic improvement in the rectal absorption profile of morphine in man. *Eur J Clin Pharmacol* 1985; **29:** 119–21.
4. Cole L, *et al*. Further development of a morphine hydrogel suppository. *Br J Clin Pharmacol* 1990; **30:** 781–6.
5. Ribeiro MDC, *et al*. The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage* 2004; **27:** 434–9.
6. Masood AR, Thomas SHL. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *Br J Clin Pharmacol* 1996; **41:** 250–2.
7. Ward ME, *et al*. Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. *Clin Pharmacol Ther* 1997; **62:** 596–609.
8. Waldmann CS, *et al*. Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; **39:** 768–71.
9. Gustafsson LL, *et al*. Disposition of morphine in cerebrospinal fluid after epidural administration. *Lancet* 1982; **i:** 796.
10. Moore A, *et al*. Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35:** 40–5.
11. Max MB, *et al*. Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. *Clin Pharmacol Ther* 1985; **38:** 631–41.
12. Nordberg G, *et al*. Extradural morphine: influence of adrenaline admixture. *Br J Anaesth* 1986; **58:** 598–604.
13. Ionescu TI, *et al*. The pharmacokinetics of intradural morphine in major abdominal surgery. *Clin Pharmacokinet* 1988; **14:** 178–86.
14. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
15. Viscusi ER, *et al*. Pharmacokinetics of extended-release epidural morphine sulfate: pooled analysis of six clinical studies. *Am J Health-Syst Pharm* 2009; **66:** 1020–30.
16. Osborne R, *et al*. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; **47:** 12–19.
17. Babul N, Darke AC. Disposition of morphine and its glucuronide metabolites after oral and rectal administration: evidence of route specificity. *Clin Pharmacol Ther* 1993; **54:** 286–92.

BUCCAL ROUTE. Conflicting results from studies on buccal morphine may reflect differences in formulation[1] and hence absorption. Some[2] reported equivalent analgesia with buccal and intramuscular morphine although others[3] found marked interindividual variability with mean peak serum concentrations of morphine some eight times lower after a buccal tablet than after an intramuscular injection and occurring a mean of 4 hours later. Morphine sulfate in aqueous solution has been reported to be moderately well absorbed from the buccal mucosa.[4] Absolute bioavailability for morphine was estimated to be 23.8% after an oral solution, 22.4% after a modified-release oral tablet (*MST Continus; Napp, UK*), and 20.2% after a modified-release buccal tablet, with peak plasma-morphine concentrations at 45 minutes, 2.5 hours, and 6 hours, respectively; mean ratios of area under the plasma concentration-time curve for morphine-6-glucuronide to morphine in plasma were 11:1 after buccal and oral morphine compared with 2:1 for intravenous morphine.[5] There was considerable inter-subject variation in plasma concentrations of the morphine metabolites, morphine-3-glucuronide and morphine-6-glucuronide after buccal doses of morphine as a modified-release formulation,[6] and lack of pain relief was subsequently reported with this buccal formulation.[7] Poor absorption of morphine from modified-release buccal tablets when compared with intramuscular injection was also reported;[8] bitterness of the tablets, leading to their premature removal, and poor dissolution may have contributed.

1. Calvey TN, Williams NE. Pharmacokinetics of buccal morphine. *Br J Anaesth* 1990; **64:** 256.
2. Bell MDD, *et al*. Buccal morphine—a new route for analgesia? *Lancet* 1985; **i:** 71–3.
3. Fisher AP, *et al*. Serum morphine concentrations after buccal and intramuscular morphine administration. *Br J Clin Pharmacol* 1987; **24:** 685–7.
4. Al-Sayed-Omar O, *et al*. Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide. *J Pharm Pharmacol* 1987; **39:** 934–5.
5. Hoskin PJ, *et al*. The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* 1989; **27:** 499–505.
6. Manara AR, *et al*. Pharmacokinetics of morphine following administration by the buccal route. *Br J Anaesth* 1989; **62:** 498–502.
7. Manara AR, *et al*. Analgesic efficacy of perioperative buccal morphine. *Br J Anaesth* 1990; **64:** 551–5.
8. Simpson KH, *et al*. An investigation of premedication with morphine given by the buccal or intramuscular route. *Br J Clin Pharmacol* 1989; **27:** 377–80.

Children. The pharmacokinetics of morphine in *children* are generally considered similar to those in adults;[1-3] in both an elimination half-life of about 2 hours has been reported after intravenous administration of morphine. In *neonates*, however, clearance is generally reduced[4-7] and pharmacokinetics are more variable.[8-10] Studies[7,11] have found significantly higher plasma concentrations of morphine and a significantly lower morphine-6-glucuronide to morphine ratio in neonates when compared with older infants and children; however, the morphine-6-glucuronide to morphine-3-glucuronide ratio remains constant irrespective of age.[7] Elimination half-lives of 6.7 and 10 hours have been reported in term and preterm infants, respectively after a single intravenous dose of morphine, with nearly 80% of the dose remaining unbound.[8] The reduced clearance, which is dependent on gestational age and birth weight,[12,13] and higher morphine concentrations are probably due to reduced metabolism in neonates as well as immature renal function: the capacity to conjugate morphine by glucuronidation is reduced in preterm infants,[6,9,10] and some premature neonates may lack the capacity entirely.[9]

1. Stanski DR, *et al*. Kinetics of high-dose intravenous morphine in cardiac surgery patients. *Clin Pharmacol Ther* 1976; **19:** 752–6.
2. Dahlström B, *et al*. Morphine kinetics in children. *Clin Pharmacol Ther* 1979; **26:** 354–65.
3. Olkkola KT, *et al*. Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet* 1995; **5:** 385–404.
4. Koren G, *et al*. Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J Pediatr* 1985; **107:** 963–7.
5. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. *Anesthesiology* 1987; **66:** 136–9.
6. Choonara IA, *et al*. Morphine metabolism in children. *Br J Clin Pharmacol* 1989; **28:** 599–604.
7. Bouwmeester NJ, *et al*. Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth* 2003; **90:** 642–52.
8. Bhat R, *et al*. Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. *J Pediatr* 1990; **117:** 477–81.
9. Bhat R, *et al*. Morphine metabolism in acutely ill preterm newborn infants. *J Pediatr* 1992; **120:** 795–9.
10. Hartley R, *et al*. Pharmacokinetics of morphine infusion in premature neonates. *Arch Dis Child* 1993; **69:** 55–8.
11. Bouwmeester NJ, *et al*. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* 2003; **29:** 2009–15.
12. Scott CS, *et al*. Morphine pharmacokinetics and pain assessment in premature newborns. *J Pediatr* 1999; **135:** 423–9.
13. Saarenmaa E, *et al*. Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther* 2000; **68:** 160–6.

The elderly. The pharmacokinetics of morphine were compared[1] in 7 healthy elderly (60 to 69 years) and 13 healthy young (24 to 28 years) subjects, after a single intravenous injection of morphine sulfate 10 mg per 70 kg. Although the terminal rate of drug disappearance from plasma was faster in the elderly group, apparent volume of distribution at steady state was about half that of the young group and plasma clearance was reduced.

1. Owen JA, *et al*. Age-related morphine kinetics. *Clin Pharmacol Ther* 1983; **34:** 364–8.

Hepatic impairment. The liver is a major site of morphine metabolism and therefore hepatic impairment could be expected to affect elimination (see under Precautions, p. 95.1). There is some evidence that in cirrhosis glucuronidation might be relatively spared compared with other metabolic processes and that some extrahepatic metabolism may occur. Several studies have served to illustrate these points:

- Hepatic extraction of morphine was impaired in cirrhotic patients, but less than expected[1]
- Morphine metabolism was minimal during the anhepatic phase of liver transplantation, but increased markedly when the new liver was reperfused[2]
- Morphine metabolism was virtually complete after liver transplantation with only 4.5% unchanged morphine being excreted in the urine 24 hours after administration[3]
- Morphine elimination was reduced when hepatic blood flow was impaired[4]

1. Crotty B, *et al*. Hepatic extraction of morphine is impaired in cirrhosis. *Eur J Clin Pharmacol* 1989; **36:** 501–6.
2. Bodenham A, *et al*. Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 380–4.
3. Shelly MP, *et al*. Pharmacokinetics of morphine in patients following orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 375–9.
4. Manara AR, *et al*. Morphine elimination and liver blood flow: a study in patients undergoing distal splenorenal shunt. *Br J Hosp Med* 1989; **42:** 148 (abstract).

Renal impairment. Only a small amount of morphine is excreted unchanged in the urine. There are conflicting reports of morphine accumulation in patients with renal impairment; some for,[1,2] others against.[3-5] It does seem clear though that morphine metabolites accumulate in such patients[5-9] including those on peritoneal dialysis;[10] the half-life of the active metabolite morphine-6-glucuronide was reported to be prolonged and its clearance reduced when morphine-6-glucuronide was given to patients with renal impairment.[11] Opioid intoxication[12] and a prolonged opioid effect[13] in patients with renal failure has been associated with morphine-6-glucuronide (see also under Precautions, p. 95.2).

1. Ball M, *et al*. Renal failure and the use of morphine in intensive care. *Lancet* 1985; **i:** 784–6.
2. Osborne R, *et al*. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; **54:** 158–67.
3. Säwe J, *et al*. Kinetics of morphine in patients with renal failure. *Lancet* 1985; **ii:** 211.
4. Woolner DF, *et al*. Renal failure does not impair the metabolism of morphine. *Br J Clin Pharmacol* 1986; **22:** 55–9.
5. Chauvin M, *et al*. Morphine pharmacokinetics in renal failure. *Anesthesiology* 1987; **66:** 327–31.
6. Säwe J, Odar-Cederlöf I. Kinetics of morphine in patients with renal failure. *Eur J Clin Pharmacol* 1987; **32:** 377–82.
7. Wolff J, *et al*. Influence of renal function on the elimination of morphine and morphine glucuronides. *Eur J Clin Pharmacol* 1988; **34:** 353–7.
8. Sear JW, *et al*. Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *Br J Anaesth* 1989; **62:** 28–32.
9. Peterson GM, *et al*. Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal

function and route of administration. *Eur J Clin Pharmacol* 1990; **38:** 121–4.
10. Pauli-Magnus C, *et al*. Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 1999; **14:** 903–9.
11. Hanna MH, *et al*. Morphine-6-glucuronide disposition in renal impairment. *Br J Anaesth* 1993; **70:** 511–14.
12. Osborne RJ, *et al*. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; **292:** 1548–9.
13. Bodd E, *et al*. Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Hum Exp Toxicol* 1990; **9:** 317–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Algedol; Amidiaz; Analmorph; Duramorph; GNO; MST Continus; Neocalmans; ***Austral.***: Anamorph; DepoDur; Kapanol; Momex; MS Contin; MS Mono; Ordine; Sevredol; ***Austria***: Compensan; Kapanol; M-Dolor; Morapid; Mundidol; Oramorph; Substitol; Vendal; ***Belg.***: Docmorfine†; Kapanol†; MS Contin; MS Direct; Oramorph; Stellorphine; ***Braz.***: Dimorf; Dolo Moff; Morfenil; ***Canad.***: Doloral; Kadian; M-Eslon; MOS; MS Contin; MSIR; Statex; ***Chile***: M-Eslon; ***China***: Meifeikang (美菲康); MS Contin (美施康定); Shi Ni Kang (史尼康); ***Cz.***: Efemorf; M-Eslon†; MSI; MST Continus†; Sevredol; Slovalgin†; Vendal; ***Denm.***: Contalgin; Depolan; Doltard; Malfin; Oramorph; ***Fin.***: Depolan; Dolcontin; Oramorph; ***Fr.***: Actiskenan; Kapanol†; Moscontin; Oramorph; Sevredol; Skenan; ***Ger.***: Capros; Kapanol†; M-beta; M-long; M-Stada; Morixon†; Morph†; Morphanton†; MSI; MSR; MST; Oramorph; Painbreak; Sevredol; ***Gr.***: Mongol; Morficontin; MXL; Oramorph; ***Hong Kong***: M-Eslon†; MST Continus; ***Hung.***: M-Eslon; MST Continus; Sevredol; ***India***: Duramor; Morcontin; Morf; Morphitroy; ***Indon.***: MST Continus; ***Irl.***: Ethirfin†; MST Continus; MXL†; Oramorph; Sevredol; ***Israel***: MCR; MIR; MSP†; ***Ital.***: MS Contin; Oramorph; Ticinan†; Twice; ***Jpn***: MS Contin; ***Malaysia***: MST Continus; ***Mex.***: Analfin; Graten; ***Neth.***: Kapanol; MS Contin; Oramorph; Sevredol†; Skenan†; ***Norw.***: Dolcontin; Oramorph; ***NZ***: Kapanol†; LA Morph†; M-Eslon; RA Morph; Sevredol; ***Philipp.***: M-Dolor†; Morin; MST Continus; Relimal; ***Pol.***: Doltard; MST Continus; Oramorph; Sevredol; Vendal†; ***Port.***: Ethirfin†; Grumorph; MST; Oramorph; Sevredol; Skenan†; ***S.Afr.***: MST Continus; SRM-Rhotard; ***Singapore***: MST Continus; SRM-Rhotard; Statex; ***Spain***: Dolq; MST Continus; Oramorph; Sevredol; Skenan†; Zomorph; ***Swed.***: Depolan; Dolcontin; Oramorph; ***Switz.***: Kapanol; M-retard; MST Continus; Oramorph; Sevre-Long; Sevredol; ***Thai.***: Kapanol; MST Continus; ***Turk.***: M-Eslon; Vendal; ***UK***: DepoDur; Filnarine; Morphgesic; MST Continus; MXL; Oramorph; Rhotard; Sevredol; Zomorph; ***USA***: Astramorph; Avinza; DepoDur; Duramorph; Embeda; Infumorph; Kadian; MS Contin; MSIR; Oramorph; RMS; Roxanol; ***Venez.***: MS Contin.

Multi-ingredient Preparations. ***China***: Gan Han (甘含); ***Irl.***: Cyclimorph; ***Ital.***: Cardiostenol; ***S.Afr.***: Chloropect; Cyclimorph; Enterodyne†; Pectrolyte; ***Swed.***: Spasmofen; ***Switz.***: Spasmosol†; ***UK***: Collis Browne's; Collis Browne's; Cyclimorph; Diocalm Dual Action; Opazimes.

Pharmacopoeial Preparations

BP 2014: Chloroform and Morphine Tincture; Morphine and Atropine Injection; Morphine Sulphate Injection; Morphine Suppositories; Morphine Tablets; Prolonged-release Morphine Tablets;

USP 36: Morphine Sulfate Extended-Release Capsules; Morphine Sulfate Injection; Morphine Sulfate Suppositories.

Morpholine Salicylate

Morfoliinisalisylaatti; Morfolinsalicylat; Morpholini Salicylas; Salicilato de morfolinio; Морфолин Салицилат.

2-Hydroxybenzoic acid compounded with morpholine (1 : 1).

$C_{11}H_{15}NO_4$=225.2

CAS — 147-90-0.

ATC — N02BA08.

ATC Vet — QN02BA08.

Profile

Morpholine salicylate is a salicylic acid derivative (see Aspirin, p. 22.2) that has been used for musculoskeletal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Dolical†.

Nabumetone *(BAN, USAN, rINN)*

BRL-14777; Nabumeton; Nabumetona; Nabumetonas; Nabumétone; Nabumetoni; Nabumetonum; Набуметон.

4-(6-Methoxy-2-naphthyl)butan-2-one.

$C_{15}H_{16}O_2$=228.3

CAS — 42924-53-8.

ATC — M01AX01.

ATC Vet — QM01AX01.

UNII — LW0TIW155Z.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in acetone; slightly soluble in methyl alcohol. Protect from light.

USP 36: (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Nabumetone is a non-active prodrug whose major metabolite is an NSAID (p. 102.3) structurally similar to naproxen (p. 98.2). It is used for the relief of pain and inflammation associated with osteoarthritis and rheumatoid arthritis in a usual oral dose of 1 g taken as a single dose in the evening; if necessary 0.5 to 1 g may be given additionally in the morning. It has been recommended that a dose of 1 g daily should not be exceeded in elderly patients and that 500 mg daily may be satisfactory in some cases.

References.
1. Friedel HA, *et al*. Nabumetone: a reappraisal of its pharmacology and therapeutic use in rheumatic diseases. *Drugs* 1993; **45:** 131–56.
2. Proceedings of a symposium: continuing developments with nabumetone: an investigators' update. *Am J Med* 1993; 95 (suppl 2A): 1S–45S.
3. Dahl SL. Nabumetone: a "nonacidic" nonsteroidal antiinflammatory drug. *Ann Pharmacother* 1993; **27:** 456–63.
4. Hedner T, *et al*. Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. *Drugs* 2004; **64:** 2315–43.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3. Nabumetone is contra-indicated in patients with severe hepatic impairment.

Effects on the gastrointestinal tract. Like other NSAIDs nabumetone can produce adverse effects on the gastrointestinal tract, although some studies have produced favourable comparisons with ibuprofen[1] or naproxen.[2] A recent review[3] noted that limited comparative data suggest that nabumetone has a similar gastrointestinal adverse effect profile to that of selective cyclo-oxygenase-2 (COX-2) inhibitors. It has been suggested[4] that nabumetone may be a preferential inhibitor of COX-2 but the significance of this in determining its adverse effects is uncertain.

1. Roth SH, *et al*. A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Arch Intern Med* 1993; **153:** 2565–71.
2. Roth SH, *et al*. A longterm endoscopic evaluation of patients with arthritis treated with nabumetone vs naproxen. *J Rheumatol* 1994; **21:** 1118–23.
3. Bannwarth B. Safety of the nonselective NSAID nabumetone: focus on gastrointestinal tolerability. *Drug Safety* 2008; **31:** 485–503.
4. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Effects on the lungs. Pulmonary fibrosis developed in a 68-year-old woman taking nabumetone 1.5 g daily; symptoms appeared after 2 weeks of therapy and worsened during the next 6 weeks.[1] There was rapid resolution on stopping nabumetone and starting treatment with oral corticosteroids.

1. Morice A, *et al*. Pulmonary fibrosis associated with nabumetone. *Postgrad Med J* 1991; **67:** 1021–2.

Effects on the skin. Pseudoporphyria characterised by blistering on the neck and hands developed in a 36-year-old woman taking nabumetone and auranofin for rheumatoid arthritis.[1] Stopping auranofin had no effect on the blistering, which only resolved once nabumetone was withdrawn. The authors of the report stated that the UK CSM had received 3 additional reports of pseudoporphyria suspected to be caused by nabumetone.

1. Varma S, Lanigan SW. Pseudoporphyria caused by nabumetone. *Br J Dermatol* 1998; **138:** 549–50. Correction. *ibid.* **139:** 759. [dose]

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nabumetone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Nabumetone is well absorbed from the gastrointestinal tract. Plasma concentrations after oral doses are too small to be measured, as it undergoes rapid and extensive first-pass metabolism in the liver to the principal active compound 6-methoxy-2-naphthylacetic acid (6-MNA) and other inactive metabolites. 6-MNA is more than 99% bound to plasma proteins. It diffuses into synovial fluid, crosses the placenta, and is distributed into breast milk. There is considerable interindividual variation in the plasma elimination half-life of 6-MNA, especially in the elderly; some reported mean values at steady state include 22 to about 27 hours for young adults and about 25 and 34 hours in elderly patients. 6-MNA eventually undergoes further metabolism by *O*-methylation and conjugation. About 80% of a dose is excreted in the urine as inactive or conjugated metabolites and less than 1% as unchanged 6-MNA.

References.
1. Brier ME, *et al*. Population pharmacokinetics of the active metabolite of nabumetone in renal dysfunction. *Clin Pharmacol Ther* 1995; **57:** 622–7.
2. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Gambaran; ***China***: Angtaifen (昂泰芬); Ao Sai Jing (奥赛金); Hong Xu Lai (弘旭来); Kefenting; Li Dao (力道); Nai Pu Tong (萘普酮); Relafen (瑞力芬); Si Rui Ke (司瑞克); Tong Shu Tong (彤舒通); Yifangtong (易方彤); ***Cz.***: Relifex†; ***Denm.***: Relifex; ***Fin.***: Relifex; ***Fr.***: Nabucox; ***Ger.***: Relifex; ***Gr.***: Akratol; Ameinon; Anfer; Ethyfen; Flogmed; Mevedal; Nabuton; Naditone; Relifex; ***Hung.***: Relifex; ***India***: Nabuflam; Nilitis; ***Indon.***: Goflex; ***Irl.***: Relifex; Religer†; ***Israel***: Nabuco; Relifex†; ***Ital.***: Artaxan; Nabuser; Relifex; ***Jpn***: Relifen; ***Mex.***: Naflam; Relifex; ***Neth.***: Mebutan; ***Norw.***: Relifex; ***Philipp.***: Relifex; ***Pol.***: Coxalgan; Coxeton†; Nabuton; Relifex†; Rodanol S; ***Port.***: Balmox; Elitar; ***Rus.***: Rodanol (Роданол)†; ***S. Afr.***: Relifen†; Relisan†; Relitone†; ***Spain***: Listran†; Relif; ***Swed.***: Relifex; ***Switz.***: Balmox; ***Thai.***: Aflex; Bumetone; Ensaid†; Fafex; Nabone; Nabonet†; Naflex; Nametone; Relifex†; Rheumetone; ***Turk.***: Relifex; ***UK***: Relifex; ***Ukr.***: Synmeton (Синметон).

Pharmacopoeial Preparations

BP 2014: Nabumetone Oral Suspension; Nabumetone Tablets;

USP 36: Nabumetone Tablets.

Nalbuphine Hydrochloride

(BANM, USAN, rINNM)

EN-2234A; Hidrocloruro de nalbufina; Nalbufina, hidrocloruro de; Nalbufine Hydrochloride; Nalbuphine, Chlorhydrate de; Nalbuphini Hydrochloridum; Налбуфина Гидрохлорид.

17-Cyclobutylmethyl-7,8-dihydro-14-hydroxy-17-normorphine hydrochloride; (-)-(5*R*,6*S*,14*S*)-9a-Cyclobutylmethyl-4,5-epoxymorphinan-3,6,14-triol hydrochloride.

$C_{21}H_{27}NO_4$,HCl=393.9

CAS — 20594-83-6 (nalbuphine); 23277-43-2 (nalbuphine hydrochloride).

ATC — N02AF02.

ATC Vet — QN02AF02.

UNII — ZU4275277R.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nalbuphine hydrochloride:

Nubian.

Incompatibility. Incompatibility has been reported between injections of nalbuphine hydrochloride and nafcillin sodium,[1] diazepam,[2] pentobarbital sodium,[2] or thiethylperazine maleate.[2] US licensed product information states that nalbuphine is also physically incompatible with ketorolac.

1. Jeglum EL, *et al*. Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462–4.
2. Jump WG, *et al*. Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; **39:** 841–3.

Uses and Administration

Nalbuphine hydrochloride, a phenanthrene derivative, is an opioid analgesic (p. 108.1). It has mixed opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Nalbuphine hydrochloride is reported to act within 15 minutes of subcutaneous or intramuscular injection or within 2 to 3 minutes of intravenous injection and generally to produce analgesia for 3 to 6 hours. It is given subcutaneously, intramuscularly, or intravenously. Intravenous infusion as part of a patient-controlled analgesia system has also been used.

The usual dose of nalbuphine hydrochloride for **pain** relief is 10 to 20 mg every 3 to 6 hours as required.

As an adjunct in balanced **anaesthesia** a usual dose is 0.3 to 3 mg/kg given intravenously over 10 to 15 minutes at induction. Maintenance doses of 250 to 500 micrograms/kg may be given as intravenous boluses if required.

Action. Nalbuphine is generally described as a mixed agonist and antagonist acting mainly as an agonist at κ opioid receptors and as an antagonist or partial agonist at μ receptors. It has shown antagonist activity similar to that seen with naloxone in opioid-dependent subjects.[1] Nalbuphine is structurally related to naloxone and oxymorphone. Pharmacologically nalbuphine is qualitatively similar to pentazocine, but nalbuphine is a more potent antagonist at μ opioid receptors, is less likely to produce psychotomimetic effects such as hallucinations, and is reported to produce no significant cardiovascular effects in patients with ischaemic heart disease. It differs from pure μ agonists such as morphine in that its analgesic, sedative, and respiratory depressant actions are subject to a 'ceiling' effect and may not increase proportionately with dose.

1. Preston KL, *et al*. Antagonist effects of nalbuphine in opioid-dependent human volunteers. *J Pharmacol Exp Ther* 1989; **248:** 929–37.

Administration. References to alternative routes or dosage schedules.

1. Krenn H, *et al*. Nalbuphine by PCA-pump for analgesia following hysterectomy: bolus application versus continuous infusion with bolus application. *Eur J Pain* 2001; **5:** 219–26.
2. Woollard M, *et al*. Hitting them where it hurts? Low dose nalbuphine therapy. *Emerg Med J* 2002; **19:** 565–70.
3. Sung KC, *et al*. Transdermal delivery of nalbuphine and its prodrugs by electroporation. *Eur J Pharm Sci* 2003; **18:** 63–70.
4. Gear RW, *et al*. Dose ratio is important in maximizing naloxone enhancement of nalbuphine analgesia in humans. *Neurosci Lett* 2003; **351:** 5–8.
5. Liu KS, *et al*. Antinociceptive effect of a novel long-acting nalbuphine preparation. *Br J Anaesth* 2004; **92:** 712–15.
6. Woollard M, *et al*. Less IS less: a randomised controlled trial comparing cautious and rapid nalbuphine dosing regimens. *Emerg Med J* 2004; **21:** 362–4.
7. Gordon AT, *et al*. Open-label exploration of an intravenous nalbuphine and naloxone mixture as an analgesic agent following gynecologic surgery. *Pain Med* 2007; **8:** 525–30.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

A WHO expert committee considered in 1989 that the likelihood of nalbuphine abuse was low to moderate and was not great enough to warrant international control.[1] Abuse had been reported infrequently and the withdrawal syndrome produced when naloxone was given after continuous nalbuphine dosage was less severe than that in morphine dependence. Subsequently, there have been occasional reports of abuse[2,3] including misuse among athletes.[4,5]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)
2. Spadari M, *et al*. Pharmacodépendance à la nalbuphine (Nubain): à propos de 2 cas. *Therapie* 2002; **57:** 504–5.
3. Klinzig F, *et al*. Hair analysis by LC-MS as evidence of nalbuphine abuse by a nurse. *J Anal Toxicol* 2007; **31:** 62–5.
4. McBride AJ, *et al*. Three cases of nalbuphine hydrochloride dependence associated with anabolic steroid use. *Br J Sports Med* 1996; **30:** 69–70.
5. Wines JD, *et al*. Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict* 1999; **8:** 161–4.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Headache may occur. Nausea and vomiting occur less than with other opioids. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. As nalbuphine has both antagonist and agonist activity its effects may be only partially reversed by naloxone, but use of the latter is still recommended in nalbuphine overdose.

Effects on the respiratory system. Nalbuphine produces similar respiratory depression to morphine at equianalgesic doses, but there is a ceiling effect with nalbuphine and, unlike morphine, respiratory depression does not increase appreciably with higher doses.[1] In a cumulative-dose study[2] a plateau effect was seen with nalbuphine above a total dose of 30 mg per 70 kg intravenously. Similar ventilatory depression has been noted[3] with single intravenous doses of nalbuphine of 15, 30, or 60 mg per 70 kg; naloxone failed to reverse the depression at the highest dose.

1. Klepper ID, *et al*. Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth* 1986; **58:** 625–9.
2. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980; **27:** 478–85.
3. Pugh GC, *et al*. Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers. *Br J Anaesth* 1989; **62:** 601–9.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Nalbuphine may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

The dose of nalbuphine should be reduced in patients with hepatic or renal impairment.

Abuse. See under Dependence and Withdrawal, above.

Pregnancy. When nalbuphine is used for analgesia during labour there is more placental transfer and sedation in mothers and their infants than with pethidine.[1] There have also been reports of bradycardia and respiratory depression in neonates whose mothers received nalbuphine during labour.[2,3] It was considered that nalbuphine should be given with caution during labour, especially by the intravenous route. Some[2] have recommended subcutaneous dosage and advised that nalbuphine should not be given around the expected time of delivery.

Further references on the transplacental transfer of nalbuphine are given under Pharmacokinetics, below.

1. Wilson CM, *et al*. Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Guillonneau M, *et al*. Perinatal adverse effects of nalbuphine given during parturition. *Lancet* 1990; **335:** 1588.
3. Sgro C, *et al*. Perinatal adverse effects of nalbuphine given during labour. *Lancet* 1990; **336:** 1070.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

There appears to be considerable first-pass metabolism of nalbuphine after oral doses. On intramuscular injection nalbuphine has been reported to produce peak plasma concentrations after 30 minutes. It is metabolised in the liver and is excreted in the urine and faeces as unchanged drug and conjugates. Nalbuphine crosses the placenta and small amounts are distributed into breast milk.

References.

1. Sear JW, *et al*. Disposition of nalbuphine in patients undergoing general anaesthesia. *Br J Anaesth* 1987; **59:** 572–5.
2. Kay B, *et al*. Pharmacokinetics of oral nalbuphine in postoperative patients. *Br J Anaesth* 1987; **59:** 1327P.
3. Aitkenhead AR, *et al*. The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers. *Br J Clin Pharmacol* 1988; **25:** 264–8.
4. Jaillon P, *et al*. Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. *Clin Pharmacol Ther* 1989; **46:** 226–33.

Pregnancy. References.

1. Wilson CM, *et al*. Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Dadabhoy ZP, *et al*. Transplacental transfer of nalbuphine in patients undergoing cesarean section: a pilot study. *Acta Anaesthesiol Ital* 1988; **39:** 227–32.
3. Nicolle E, *et al*. Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. *Eur J Clin Pharmacol* 1996; **49:** 485–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gobbinal; Naltrox†; Nubaina; Onfor; ***Braz.***: Nalfina; Nubain; ***Canad.***: Nubain; ***Cz.***: Nubain†; ***Denm.***: Nalpain; ***Fin.***: Nalpain; ***Ger.***: Nalpain; ***Gr.***: Mexifen; Nubain; ***Hong Kong***: Intapan†; ***Hung.***: Bufimorf; Nubain†; ***Irl.***: Lapainol; ***Malaysia***: Intapan; ***Mex.***: Bufigen; Bufilem; Fabitec; Nalcryn; ***Philipp.***: Nubain; Nukaine; ***Port.***: Nalpain; ***Singapore***: Intapan; Nubain; ***Swed.***: Nalpain; ***Thai.***: Nubain; ***USA***: Nubain†; ***Venez.***: Bufidol.

Naproxen *(BAN, USAN, rINN)*

Naprokseeni; Naproksen; Naproksenas; Naproxén; Naproxène; Naproxeno; Naproxenum; RS-3540; Напроксен.

(+)-2-(6-Methoxy-2-naphthyl)propionic acid.

$C_{14}H_{14}O_3$=230.3

CAS — 22204-53-1.

ATC — G02CC02; M01AE02; M02AA12.

ATC Vet — QG02CC02; QM01AE02; QM02AA12.

UNII — 57Y76R9ATQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Naproxen). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Naproxen). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in dehydrated alcohol, and in chloroform; sparingly soluble in ether. Store in airtight containers.

Naproxen Sodium *(BANM, USAN, rINNM)*

Naproksen Sodyum; Naproxen-Natrium; Naproxène Sodique; Naproxeno sódico; Naproxenum natricum; Natrii Naproxenum; RS-3650; Натрий Напроксен.

$C_{14}H_{13}NaO_3$=252.2

CAS — 26159-34-2.

UNII — 9TN87S3A3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Naproxen Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; freely soluble or soluble in methyl alcohol. A 2% solution in water has a pH of 7.0 to 9.8. Store in airtight containers. Protect from light.

USP 36: (Naproxen Sodium). A white to creamy crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol; very slightly soluble in acetone; practically insoluble in chloroform and in toluene. Store in airtight containers.

Uses and Administration

Naproxen, a propionic acid derivative, is an NSAID (p. 102.3).

Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. Naproxen is usually given *orally* as the free acid or as the sodium salt. The doses in the licensed product information are expressed in terms of the free acid or the sodium salt as appropriate for an individual preparation; however, the doses given below are expressed in terms of the equivalent amount of free acid only. Each 550 mg of naproxen sodium is equivalent to about 500 mg of naproxen.

In the treatment of **rheumatic disorders**, the usual dose of naproxen or naproxen sodium is the equivalent of 500 mg to 1 g of naproxen daily either as a single dose or in 2 divided doses. US licensed product information states that patients who tolerate lower doses may have their dosage increased to 1.5 g daily for a period of up to 6 months, if required. For dosage in children, see below.

In **other painful conditions** such as dysmenorrhoea and acute musculoskeletal disorders the usual regimen is the equivalent of 500 mg of naproxen initially, followed by 250 mg every 6 to 8 hours, up to a maximum daily dose of 1.25 g on the first day and 1 g thereafter.

In **acute gout** an initial dose equivalent to 750 mg of naproxen followed by 250 mg every 8 hours is used.

For the treatment of **migraine**, the equivalent of 750 mg of naproxen can be given at the first symptom of an impending attack and, if necessary, this may be followed after at least half an hour by further doses of 250 to 500 mg throughout the day to a total maximum daily dose of 1250 mg. See Headache, below for a suggested dose for the prophylaxis of migraine.

Naproxen has been given *rectally* in similar doses to those used orally.

Naproxen has also been used as the piperazine, aminobutanol, choline, and lysine salts, and as naproxen cetrimonium. Naproxen has been given as part of a combination pack with misoprostol (p. 2140.3) or lansoprazole (p. 1854.3), or as a modified-release combination preparation with esomeprazole (p. 1844.1) for patients at risk of NSAID-induced peptic ulceration.

Reviews.

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40:** 91–137.
2. Curran MP, Wellington K. Delayed-release lansoprazole plus naproxen. *Drugs* 2004; **64:** 1915–19.
3. Derry C, *et al*. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2009 (accessed 18/09/09).

Administration in children. In the treatment of juvenile idiopathic arthritis, US licensed product information recommends an oral dose of about 10 mg/kg daily of naproxen in 2 divided doses for children aged 2 years and over; in the UK, this dose is licensed for those aged over 5 years. In addition, higher doses may also be used: the *BNFC* suggests a dose of up to 15 mg/kg daily (maximum of 1 g daily) in children aged 2 to 18 years.

For pain and inflammation in musculoskeletal disorders and dysmenorrhoea, the *BNFC* suggests that those aged 1 month to 18 years may be given an oral dose of 5 mg/kg twice daily (maximum of 1 g daily).

Headache. An NSAID such as naproxen is among the drugs tried first for the symptomatic treatment of various types of headache including migraine (p. 670.3) and tension-type headache (p. 671.3). An NSAID given at the onset of symptoms can successfully treat an acute attack of migraine.[1,2] Co-treatment with a triptan may provide additional benefit and a preparation containing both sumatriptan succinate and naproxen sodium (*Treximet; GlaxoSmithKline, USA*) is available.[3-6]

NSAIDs also appear to be effective for the prophylaxis of migraine, although propranolol is generally preferred. Studies have indicated that naproxen sodium 550 mg [equivalent to 500 mg of naproxen] given twice daily may be useful for reducing the number of attacks suffered.[7-9]

Naproxen can be used to manage the aggravation of symptoms associated with the withdrawal of analgesics in medication-overuse headache (p. 670.2). An oral dose of 250 mg three times daily or 500 mg twice daily should be

taken regularly; some suggest a single course of 3 to 4 weeks, others a 6-week course with the dose of naproxen being reduced gradually.[10]

1. Treves TA, *et al*. Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. *Headache* 1992; **32:** 280–2.
2. Suthisisang CC, *et al*. Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. *Headache* 2010; **50:** 808–18.
3. Winner P, *et al*. Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. *Mayo Clin Proc* 2007; **82:** 61–8.
4. Brandes JL, *et al*. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007; **297:** 1443–54.
5. Mathew NT, *et al*. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache* 2009; **49:** 971–82.
6. Khoury CK, Couch JR. Sumatriptan-naproxen fixed combination for acute treatment of migraine: a critical appraisal. *Drug Des Devel Ther* 2010; **4:** 9–17.
7. Sargent J, *et al*. A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 1985; **25:** 320–4.
8. Welch KMA, *et al*. Successful migraine prophylaxis with naproxen sodium. *Neurology* 1985; **35:** 1304–10.
9. Sances G, *et al*. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990; **30:** 705–9.
10. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January, 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 21/06/11)

Malignant neoplasms. Some NSAIDs such as naproxen may be of value both for the differential diagnosis and the management of neoplastic fever[1-4] as they appear to be more effective in reducing this type of fever than against fever associated with infections. However, the reliability of naproxen in the diagnosis of neoplastic fever has been questioned.[5] In a group of 72 patients, naproxen decreased body temperature in 55% of patients with neoplastic disorders and 38% of patients with other conditions. Thus, the sensitivity of the test was calculated as 55% and its specificity as 62%, which the authors considered to be too low to be reliable.

1. Chang JC, Gross HM. Neoplastic fever responds to the treatment of an adequate dose of naproxen. *J Clin Oncol* 1985; **3:** 552–8.
2. Azeemuddin SK, *et al*. The effect of naproxen on fever in children with malignancies. *Cancer* 1987; **59:** 1966–8.
3. Economos K, *et al*. The effect of naproxen on fever in patients with advanced gynecologic malignancies. *Gynecol Oncol* 1995; **56:** 250–4.
4. Cunha BA, *et al*. Fever of unknown origin (FUO) caused by multiple myeloma: the diagnostic value of the Naprosyn test. *Heart Lung* 2006; **35:** 358–62.
5. Vanderschueren S, *et al*. Lack of value of the naproxen test in the differential diagnosis of prolonged febrile illnesses. *Am J Med* 2003; **115:** 572–5.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Suppositories containing naproxen may cause rectal irritation and occasional bleeding.

Naproxen should be used with caution in renal impairment, and use is not recommended in patients whose creatinine clearance is less than 20 mL/min.

Reviews.

1. Bansal V, *et al*. A look at the safety profile of over-the-counter naproxen sodium: a meta-analysis. *J Clin Pharmacol* 2001; **41:** 127–38.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of naproxen by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of naproxen distributed into breast milk is too small to be harmful to a breast-fed infant; however, some licensed product information recommends that breast feeding should be avoided during naproxen therapy.

In a study[2] of a breast-fed infant only 0.26% of the mother's dose was recovered from the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Jamali F, Stevens DRS. Naproxen excretion in milk and its uptake by the infant. *Drug Intell Clin Pharm* 1983; **17:** 910–11.

Effects on the blood. Haematological adverse effects reported in patients given naproxen include haemolytic anaemia,[1,2] aplastic anaemia,[3] agranulocytosis,[4] and immune thrombocytopenia.[5]

1. Hughes JA, Sudell W. Hemolytic anemia associated with naproxen. *Arthritis Rheum* 1983; **26:** 1054.
2. Lo TCN, Martin MA. Autoimmune haemolytic anaemia associated with naproxen suppositories. *BMJ* 1986; **292:** 1430.
3. McNeil P, *et al*. Naproxen-associated aplastic anaemia. *Med J Aust* 1986; **145:** 53–4.
4. Nygard N, Starkebaum G. Naproxen and agranulocytosis. *JAMA* 1987; **257:** 1732.
5. Bougie D, Aster R. Immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen. *Blood* 2001; **97:** 3846–50.

Effects on the cardiovascular system. For a discussion of the possible cardiovascular effects of naproxen, see p. 105.1.

Effects on the CNS. Aseptic meningitis has been associated with naproxen therapy;[1,2] attacks may be recurrent and cross-sensitivity with other NSAIDs has occurred.[2]

There has been a report[3] of a patient with Parkinson's disease whose symptoms had previously been well controlled but who deteriorated when she was given naproxen. She improved on withdrawal of naproxen and the effect was confirmed by rechallenge. It was noted that the UK CSM had recorded a case of parkinsonism associated with a combined preparation of naproxen and misoprostol and 12 other reports of tremor or ataxia precipitated by naproxen.

1. Weksler BB, Lehany AM. Naproxen-induced recurrent aseptic meningitis. *DICP Ann Pharmacother* 1991; **25:** 1183–4.
2. Seaton RA, France AJ. Recurrent aseptic meningitis following non-steroidal anti-inflammatory drugs – a reminder. *Postgrad Med J* 1999; **75:** 771–2.
3. Shaunak S, *et al*. Exacerbation of idiopathic Parkinson's disease by naproxen. *BMJ* 1995; **311:** 422.

Effects on the eyes. Keratopathy, characterised by whorl-like corneal opacities, occurred in a woman taking naproxen; complete regression occurred after stopping the drug.[1] There has also been a report of exacerbation of glaucoma in a 65-year-old woman given naproxen.[2]

For reference to effects on the optic nerve associated with naproxen, see p. 105.3.

1. Szmyd L, Perry HD. Keratopathy associated with the use of naproxen. *Am J Ophthalmol* 1985; **99:** 598.
2. Fincham JE. Exacerbation of glaucoma in an elderly female taking naproxen sodium: a case report. *J Geriatr Drug Ther* 1989; **3:** 139–43.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are among the most frequently reported during short- and long-term treatment with naproxen. Acute proctocolitis associated with the use of naproxen has been reported.[1] Oesophageal ulceration reported in 7 patients[2] may have arisen due to incorrect consumption (such as taking the dosage without fluids or lying down after a dose) but other causes could not be dismissed.

1. Ravi S, *et al*. Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.
2. Kahn LH, *et al*. Over-the-counter naproxen sodium and esophageal injury. *Ann Intern Med* 1997; **126:** 1006.

Effects on the kidneys. Acute renal failure,[1] renal papillary necrosis,[2,3] interstitial nephritis,[4] and hyperkalaemia[1] have been reported in patients receiving naproxen. As with other NSAIDs, renal adverse effects occur more frequently in patients with certain risk factors such as volume depletion, diuretic therapy, heart failure, and pre-existing renal dysfunction.[1]

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40:** 91–137.
2. Caruana RJ, Semble EL. Renal papillary necrosis due to naproxen. *J Rheumatol* 1984; **11:** 90–1.
3. Kovacevic L, *et al*. Renal papillary necrosis induced by naproxen. *Pediatr Nephrol* 2003; **18:** 826–9.
4. Quigley MR, *et al*. Concurrent naproxen- and penicillamine-induced renal disease in rheumatoid arthritis. *Arthritis Rheum* 1982; **25:** 1016–19.

Effects on the liver. There have been a few reports[1,2] of moderate to severe jaundice attributed to naproxen including one in which the patient also had a similar reaction with fenoprofen.[2]

1. Victorino RMM, *et al*. Jaundice associated with naproxen. *Postgrad Med J* 1980; **56:** 368–70.
2. Andrejak M, *et al*. Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the lungs. See Hypersensitivity, below.

Effects on the salivary glands. For reference to salivary gland swelling associated with naproxen therapy, see Hypersensitivity, below.

Effects on the skin. Cutaneous reactions reported in patients receiving naproxen include erythema nodosum,[1] lichen planus,[2] toxic pustular skin eruption,[3] bullous dermatosis,[4] and fixed drug eruption.[5] Photodermatitis, characterised by vesicle formation or increased skin fragility on sun-exposed skin, has been reported in adults[6-8] and children.[9,10]

A relapse of subacute cutaneous lupus erythematosus was reported to be possibly associated with naproxen.[11]

For reference to facial scars of unknown origin developing in children receiving NSAIDs, and in particular naproxen, see under NSAIDs, p. 107.1.

1. Grattan CEH, Kennedy CTC. Naproxen induced erythema nodosum. *BMJ* 1984; **288:** 114.
2. Heymann WR, *et al*. Naproxen-induced lichen planus. *J Am Acad Dermatol* 1984; **10:** 299–301.
3. Page SR, Grattan CEH. Pustular reaction to naproxen with cholestatic jaundice. *BMJ* 1986; **293:** 510.
4. Bouldin MB, *et al*. Naproxen-associated linear IgA bullous dermatosis: case report and review. *Mayo Clin Proc* 2000; **75:** 967–70.
5. Leivo T, Heikkilä H. Naproxen-induced generalized bullous fixed drug eruption. *Br J Dermatol* 2004; **151:** 232.
6. Howard AM, *et al*. Pseudoporphyria due to naproxen. *Lancet* 1985; **i:** 819–20.
7. Rivers JK, Barnetson RS. Naproxen-induced bullous photodermatitis. *Med J Aust* 1989; **151:** 167–8.
8. Levy ML, *et al*. Naproxen-induced pseudoporphyria: a distinctive photodermatitis. *J Pediatr* 1990; **117:** 660–4.
9. Parodi A, *et al*. Possible naproxen-induced relapse of subacute cutaneous lupus erythematosus. *JAMA* 1992; **268:** 51–2.
10. Lang BA, Finlayson LA. Naproxen-induced pseudoporphyria in patients with juvenile rheumatoid arthritis. *J Pediatr* 1994; **124:** 639–42.
11. Cox NH, Wilkinson DS. Dermatitis artefacta as the presenting feature of auto-erythrocyte sensitization syndrome and naproxen-induced pseudoporphyria in a single patient. *Br J Dermatol* 1992; **126:** 86–9.

Hypersensitivity. In an early case-report in 11 aspirin-sensitive asthmatic patients, all developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) after taking naproxen in low doses of 80 mg or less.[1] More recently, angioedema occurred after a single dose of naproxen in a patient known to be aspirin-sensitive.[2] Hypersensitivity to individual NSAIDs is believed to be closely linked to the extent to which these drugs inhibit prostaglandin synthesis (see under Aspirin, p. 25.2). There may therefore be a dose threshold below which no detectable symptoms occur. Such an effect has been reported[3] in a patient previously stabilised on naproxen for about one year who had a hypersensitivity reaction after a dosage increase.

A hypersensitivity reaction characterised by pulmonary infiltrates with eosinophilia[4,5] has been reported in patients taking naproxen. There has also been a report of a generalised hypersensitivity reaction with acute eosinophilic colitis in a 57-year-old woman treated with naproxen for osteoarthritis.[6] Bilateral swelling of the major salivary glands, a generalised rash, and eosinophilia suggestive of a hypersensitivity response was reported in another patient after use of naproxen.[7] Leucocytoclastic vasculitis with peripheral neuropathy and nephritis has also been noted in a 62-year-old woman after naproxen treatment.[8]

1. Szczeklik A, *et al*. Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2:** 231–2.
2. Ghislain P-D, Ghislain E. Oedème de Quincke de la nuque induit par l'acide acétylsalicylique, avec réaction croisée pour le naproxène sodique. *Ann Med Interne (Paris)* 2000; **151:** 227–9.
3. Briscoe-Dwyer L, Etzel JV. Dyspnea and periorbital edema following an increase in naproxen dose. *Ann Pharmacother* 1994; **28:** 1110.
4. Nader DA, Schillaci RF. Pulmonary infiltrates with eosinophilia due to naproxen. *Chest* 1983; **83:** 280–2.
5. Buscaglia AJ, *et al*. Pulmonary infiltrates associated with naproxen. *JAMA* 1984; **251:** 65–6.
6. Bridges AJ, *et al*. Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. *Am J Med* 1990; **89:** 526–7.
7. Knulst AC, *et al*. Salivary gland swelling following naproxen therapy. *Br J Dermatol* 1995; **133:** 647–9.
8. Schapira D, *et al*. Naproxen-induced leukocytoclastic vasculitis. *Clin Rheumatol* 2000; **19:** 242–4.

Parkinsonism. For a report of a patient whose symptoms of Parkinson's disease were exacerbated by naproxen, see Effects on the CNS, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naproxen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

The excretion of naproxen is delayed by probenecid resulting in raised plasma concentrations of naproxen.

Antiepileptics. For the effect of naproxen on the protein binding of *valproic acid*, see p. 557.2.

Pharmacokinetics

Naproxen and naproxen sodium are readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after ingestion of naproxen sodium and about 2 to 4 hours after ingestion of naproxen. Food reduces the rate but not the extent of absorption. Naproxen and naproxen sodium are also well absorbed rectally. At therapeutic concentrations naproxen is more than 99% bound to plasma proteins. Plasma concentrations of naproxen increase proportionally with dose up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen diffuses into synovial fluid; it crosses the placenta and is distributed into breast milk in small amounts. Naproxen has a plasma elimination half-life of about 12 to 17 hours. About 95% of a dose is excreted in urine as naproxen and 6-*O*-desmethylnaproxen and their conjugates. Less than 5% of a dose appears in the faeces.

References.

1. Bruno R, *et al*. Naproxen kinetics in synovial fluid of patients with osteoarthritis. *Br J Clin Pharmacol* 1988; **26:** 41–4.

2. Bertin P, *et al*. Sodium naproxen: concentration and effect on inflammatory response mediators in human rheumatoid synovial fluid. *Eur J Clin Pharmacol* 1994; **46:** 3–7.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. *Clin Pharmacokinet* 1997; **32:** 268–93.
4. Bowalgaha K, *et al*. S-Naproxen and desmethylnaproxen glucuronidation by human liver microsomes and recombinant human UDP-glucuronosyltransferases (UGT): role of UGT2B7 in the elimination of naproxen. *Br J Clin Pharmacol* 2005; **60:** 423–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aleve; Alidase; Bumaflex N; Congex; Debril; Fabralgina; Fadalivio; Flaxvan; Keldor; Melgar; Monarit; Mox; Naprofidex; Naprogen; Naprontag; Naprux; Neuralprona†; Tundra; ***Austral.***: Anaprox; Chemists Own Period Pain; Crysanal; Femme Free; Inza; Naprogesic; Naprosyn; Proxen; Vimovo; ***Austria***: Aleve; Miranax; Naprobene; Proxen; ***Belg.***: Aleve; Apranax; Naproflam; Naprosyne; Vimovo; ***Braz.***: Flanax; Napronax; Naprosyn; Naprox; Naxotec; ***Canad.***: Aleve; Anaprox; Apo-Napro-Na; Maxidol; Naprelan; Naprosyn; Novo-Naprox†; Nu-Naprox; Vimovo; ***Chile***: Atac; Deucoval; Eurogesic; Flogotone; Naprogesic; Triox NF; ***China***: An Li; Ao Pu Li (澳普利); Bai Tong (柏通); Bei Li (倍利); Hui Ke (惠可); Jia Dan (佳丹); Jie Jie (杰捷); Jinkangpuli (金康普力); Na Pu Xing (那普星); Napton (那普洛); Qi Gu Ke (奇谷克); Shi Luo Te (适洛特); Tai Ze (泰泽); YuanQi (元奇); ***Cz.***: Aleve; Emoxen; Nalgesin; Vimovo; ***Denm.***: Bonyl; Vimovo; ***Fin.***: Alpoxen; Miranax; Naprometin; Napromex; Naxopren; Pronaxen; Vimovo; ***Fr.***: Alevetabs; Antalnox; Apranax; Naprosyne; ***Ger.***: Alacetan NNA†; Aleve; Dolormin mit Naproxen; Dysmenalgit; Mobilat Schmerztabletten mit Naproxen†; Proxen; ***Gr.***: Anaprox; Anexopen; Momendol; Naprosyn; Nopron; Nycopren; ***Hong Kong***: Inza; Naprorex; Naprosyn†; Napxen†; Noflam-N; Soden; ***Hung.***: Aleve; Apranax; Napmel; Naprosyn; ***India***: Antesvel; Artagen; Easy Dayz; Movibon; Napexar; Napris; Naprosyn; Napryn; Naxen; Xenobid; ***Indon.***: Naxen†; Synflex†; Xenifar; ***Irl.***: Gerinap; Naprosyn; Synflex†; Vimovo; ***Israel***: Naproxi; Narocin; Naxyn; Point; Vimovo; ***Ital.***: Akudol; Aleve; Dropsen; Floginax; Gynestrel; Laser; Momendol; Napreben; Naprius; Naprocet; Naprossene; Naprosyn; Neo Eblimon; Nitens; Prexan; Provindol; Proxagol; Synalgo†; Synflex; Uninapro; Vimovo; Xenar; ***Malaysia***: Apo-Napro-Na; Safrosyn S; Seladin; Sunprox; Synflex; ***Mex.***: Actiquim; Analgen; Anapsyl†; Arsenal; Arxen; Atiflan†; Bioxan; Bixen; Dafloxen; Deflamox; Diferbest; Dolxen; Donaprox; Edem; Fagofen†; Faraxen; Flanax; Flavoxen; Flaxendol; Flogen; Fuxen†; Inflanox; Iqfasol; Luzapren; Messelxen; Naflapen†; Napoxol; Naprodil†; Navixen†; Naxen†; Naxopaar; Neonaxil; Novaxen; Pactens; Praxedol; Profaxen; Pronat†; Pronaxil; Pronoxen; Propional; Proxalin; Sertrixen; Sodixen; Tandax; Tanizona†; Unirelaxed†; Vantin; Velsay; ***Neth.***: Aleve; Momendol; Naprelan†; Naprovite†; Vimovo; ***Norw.***: Ledox†; Napren; Naprosyn†; Vimovo; ***NZ***: Naprogesic; Naprosyn; Naxen; Noflam; Sonaflam; Synflex; Vimovo; ***Philipp.***: Alpron; Flacidon; Flanax; Naflax; Napoxen; Naprelan†; Naprosyn; Sanomed; Skelan Protect; Skelan; ***Pol.***: Aleve; Anapran; Apo-Napro; Boloxen†; DiFortan†; Natrax; Naxii; Tarproxen†; ***Port.***: Momendol; Naprocet; Naprosyn; Reuxen; ***Rus.***: Algezir (Алгезир); Nalgesin (Налгезин); ***S.Afr.***: Acusprain†; Aleve; Nafasol; Napflam; Naproscript; Synflex; Traumox†; ***Singapore***: Aleve; Apo-Napro-Na; Inza; Naprosyn; Nuprafen; Seladin; Soden; Soproxen; SP-Anflam; Sunprox; Synflex; Vimovo; ***Spain***: Aleve; Aliviomas†; Antalgin; Denaxpren†; Lundiran; Momen; Naprosyn; Tacron†; Vimovo; ***Swed.***: Alpoxen†; Eox†; Naprosyn; Pronaxen; Vimovo; ***Switz.***: Aleve; Apranax; Proxen; Vimovo; ***Thai.***: Annoxen; Buproxen; Naproflex; Naprosian; Naprosyn; Napsen†; Nasin; Naxene; Polyxen; Prodaril-N; Proxen; Serviproxan†; Sonap; Soproxen; Synflex; Synogin; U-Proxyn†; Vinsen; ***Turk.***: A-Nox; Aleve; Anaprotab; Apraljin†; Apranax; Aprodent; Aprol; Apromed; Aprowell; Armanaks; Atren; Bonmin; Exvile; Femidolor; Floneks; Inaprol; Kapnax; Karoksen; Mednap; Naponal; Napradol; Napren; Napro-Pac; Naprodev; Naprodex; Naprosyn; Naprotab; Opraks; Relokap; Romaksen; Rumazolidin†; Seroksen; Synax; Syndol†; ***UK***: Arthroxen; Feminax Ultra; Napratec; Naprosyn; Period Pain Relief; Syndol Period Pain Relief; Synflex†; Vimovo; ***Ukr.***: Cefecon N (Цефекон Н); Nalgesin (Налгезин); Promax (Промакс); ***USA***: Aleve; Anaprox; Naprelan; Naprosyn; Prevacid NapraPAC†; Vimovo.

Multi-ingredient Preparations. ***Arg.***: Naprontag Flex; Naprux Disten; Papasine; ***China***: Gao Di (高迪); Pu Sen Ou Ke (普森欧克); Xi Tai Meng (西泰孟); ***India***: Naprodom; Naxdom; Pacinac-NP; ***Ital.***: Momendol; ***Mex.***: Analgen Forte; Arsenal Compuesto; Arxen Compositum; Bifardol; Blocacid†; Brax; Bremol; Caridoxen; Caxidol; Contraxen; Dafloxen-F; Decosil; Deflamox Plus; Dolotandax; Drunen; Farxen; Febrax; Fiverdol; Flaxenol; Flucol†; Grifed; Kensedal; Movex; Naprodil Plus†; Naxodol†; Nedoxal; Neorpan Plus; Onexmol; Pensodil; Polet; Profenlax†; Proxalin Plus; Raxenol; Reucortil; Somalgesic; Taxenan†; Ulpafie-N; Velsay-S Compuesto; Viplus; Xenorac's; ***Rus.***: Cefecon N (Цефекон Н); Pentalgin (Пенталгин); Pentalgin-N (Пенталгин-Н); Pyralgin (Пиралгин); ***USA***: Treximet.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Naproxen Tablets; Naproxen Oral Suspension; Naproxen Suppositories; Naproxen Tablets;

USP 36: Naproxen Delayed-Release Tablets; Naproxen Oral Suspension; Naproxen Sodium Tablets; Naproxen Tablets.

Nefopam Hydrochloride

(BANM, USAN, rINNM)

Benzoxazocine; Fenazoxine; Hidrocloruro de nefopam; Néfopam, Chlorhydrate de; Nefopam, hidrocloruro de; Nefopami Hydrochloridum; R-738; Нефопама Гидрохлорид.

3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine hydrochloride.

$C_{17}H_{19}NO,HCl$=289.8

CAS — 13669-70-0 (nefopam); 23327-57-3 (nefopam hydrochloride).

ATC — N02BG06.

ATC Vet — QN02BG06.

UNII — 685J48E13W.

Pharmacopoeias. In *Chin.*

Uses and Administration

Nefopam hydrochloride is a non-opioid analgesic considered to act centrally, although its mechanism of action is unclear. It also has some antimuscarinic and sympathomimetic actions. Nefopam hydrochloride is used for the relief of moderate acute and chronic pain. The usual oral dose range is 30 to 90 mg three times daily; the recommended initial dose is 60 mg (or 30 mg in elderly patients) three times daily. Nefopam hydrochloride may also be given in doses of 20 mg by intramuscular injection, repeated every 6 hours if necessary; it has been recommended that the patient should always be lying down when receiving the injection and should remain so for 15 to 20 minutes afterwards. It has also been given by slow intravenous injection in doses of 20 mg every 4 hours up to a maximum of 120 mg daily.

Hiccup. In three case series[1-3] involving 12 patients in total, hiccups refractory to standard therapy stopped after treatment with intravenous nefopam. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

1. Bilotta F, Rosa G. Nefopam for severe hiccups. *N Engl J Med* 2000; **343:** 1973–4.
2. Bilotta F, *et al*. Nefopam for refractory postoperative hiccups. *Anesth Analg* 2001; **93:** 1358–60.
3. Pajot S, *et al*. Hiccup during weaning from mechanical ventilation: the use of nefopam. *Br J Anaesth* 2007; **99:** 748–9.

Pain. Systematic reviews considered that there was little or no evidence to justify the use of nefopam as an analgesic for the management of postoperative pain.[1,2]

1. Evans MS, *et al*. Nefopam for the prevention of postoperative pain: quantitative systematic review. *Br J Anaesth* 2008; **101:** 610–17.
2. Kakkar M, *et al*. Single dose oral nefopam for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 28/07/10).

Shivering. Nefopam is one of several drugs tried[1-3] in the prevention of postoperative shivering (p. 1900.2).

1. Bilotta F, *et al*. Nefopam and tramadol for the prevention of shivering during neuraxial anesthesia. *Reg Anesth Pain Med* 2002; **27:** 380–4.
2. Piper SN, *et al*. A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; **59:** 559–64.
3. Bilotta F, *et al*. Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. *Anaesthesia* 2005; **60:** 124–8.

Adverse Effects and Treatment

Adverse effects occurring with nefopam include gastrointestinal disturbances, such as nausea and vomiting, sweating, drowsiness, insomnia, urinary retention, dizziness, hypotension, tremor, paraesthesia, palpitations, lightheadedness, nervousness, confusion, blurred vision, headache, dry mouth, syncope, angioedema, allergic reactions, and tachycardia. Euphoria, hallucinations, and convulsions have occasionally been reported, as has temporary pink discoloration of the urine. Symptoms of overdosage have included CNS and cardiovascular toxicity.

Incidence of adverse effects. The French Pharmacovigilance System has reported[1] that, from January 1995 to December 2004, it had received 324 reports of adverse reactions associated with the use of nefopam. The most frequently reported reactions were sweating (15 cases), nausea (10 cases), tachycardia (8 cases), malaise (6 reports), and vomiting (5 cases). Unexpected reactions included hallucinations (11 cases), confusion (11 cases), cutaneous reactions such as erythema (7 cases), pruritus (4 cases), and urticaria (3 cases), and anaphylactic reactions including anaphylactic shock (4 cases) and angioedema (2 cases). The anaphylactic reactions were reported to have occurred shortly after nefopam was given during the postoperative period. There was a single case of fatal convulsion and no cases of overdosage had been reported (but see below).

1. Durrieu G, *et al*. French Network of Pharmacovigilance Centers. Overview of adverse reactions to nefopam: an analysis of the French Pharmacovigilance database. *Fundam Clin Pharmacol* 2007; **21:** 555–8.

Effects on the urinary tract. In January 1989, the UK CSM[1] reported that it had received 53 reports in which nefopam was associated with the development of urinary retention or symptoms of hesitancy, poor stream, or dribbling. In one case there was a history of prostatism.

1. CSM. Nefopam hydrochloride (Acupan). *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)

Overdosage. There have been reports of fatal overdoses with nefopam.[1-4] One report[1] also provided details of 9 other patients who recovered with routine supportive treatment.

1. Piercy DM, *et al*. Death due to overdose of nefopam. *BMJ* 1981; **283:** 1508–9.
2. Urwin SC, Smith HS. Fatal nefopam overdose. *Br J Anaesth* 1999; **83:** 501–2.
3. Tracqui A, *et al*. Fatal overdosage with nefopam (Acupan). *J Anal Toxicol* 2002; **26:** 239–43.
4. Kerr DE, Fletcher AK. Fatal nefopam overdose. *Emerg Med J* 2010; **27:** 407–8.

Precautions

Nefopam is contra-indicated in patients with a history of convulsive disorders. It should be used with caution in the elderly and in patients with glaucoma, urinary retention, or impaired hepatic or renal function.

Abuse. Abuse of parenteral nefopam has been reported in 3 patients with a history of chronic pain.[1] Psychostimulant-like symptoms such as agitation, impatience, and violence, were noted in 2 of the patients; antimuscarinic effects were also seen. All 3 patients were found to be psychologically dependent; in 2 who attempted to stop nefopam, withdrawal symptoms were noted.

1. Villier C, Mallaret MP. Nefopam abuse. *Ann Pharmacother* 2002; **36:** 1564–6.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving nefopam, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding.

Studies in 5 healthy nursing mothers given nefopam for post-episiotomy pain indicated that nefopam was present in human milk in an equivalent concentration to that in plasma.[2] It was calculated that on a body-weight basis a breast-fed infant would receive less than 3% of the maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/10/06)
2. Liu DTY, *et al*. Nefopam excretion in human milk. *Br J Clin Pharmacol* 1987; **23:** 99–101.

Renal impairment. Following a single dose of nefopam 20 mg, given as an intravenous infusion, the clearance of nefopam was found to be reduced in 12 patients with end-stage renal disease (ESRD) when compared with aged-matched healthy subjects;[1] peak plasma concentrations of nefopam were also significantly higher in those with ESRD. The authors recommended that a 50% dosage reduction should be considered in those with severe renal impairment.

1. Mimoz O, *et al*. Nefopam pharmacokinetics in patients with end-stage renal disease. *Anesth Analg* 2010; **111:** 1146–53.

Interactions

It has been recommended that nefopam should not be given to patients receiving MAOIs and should be used cautiously in those receiving tricyclic antidepressants. The adverse effects of nefopam may be additive to those of other drugs with antimuscarinic or sympathomimetic activity.

Pharmacokinetics

Nefopam is absorbed from the gastrointestinal tract. Peak plasma concentrations occur 1 to 3 hours after an oral dose and up to 1 hour after intramuscular injection. About 73% is bound to plasma proteins. Nefopam is distributed into breast milk. It has an elimination half-life of about 4 hours. It is extensively metabolised and excreted mainly in urine, in which less than 5% of a dose is excreted unchanged. About 8% of a dose is excreted via the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Acupan; ***China***: Fu Lu Ke (福卢可); Fu Lu Na (福卢纳); Hong Kang Wei Si (弘康威司); Shengfu (圣福); ***Fr.***: Acupan; ***Gr.***: Leoplexamin; Pallopikeron; ***Irl.***: Acupan; ***NZ***: Acupan; ***Rus.***: Oxadol (Оксадол); ***UK***: Acupan; ***Ukr.***: Acupan (Акупан).

Nepafenac *(BAN, USAN, rINN)*

AHR-9434; AL-6515; Népafénac; Nepafenaco; Nepafenacum; Непафенак.

2-(2-Amino-3-benzoylphenyl)acetamide.

$C_{15}H_{14}N_2O_2$=254.3

CAS — 78281-72-8.

ATC — S01BC10.

ATC Vet — QS01BC10.

UNII — 0J9L7J6V8C.

Profile

Nepafenac, an NSAID (p. 102.3), is a prodrug of amfenac (p. 20.3). It is used in the treatment of pain and inflammation following cataract surgery. An ophthalmic suspension containing nepafenac 0.1% is instilled 3 times daily starting on the day before surgery and continuing for 2 weeks after surgery, to a maximum of 3 weeks if necessary. An additional drop should be instilled 30 to 120 minutes before surgery.

References.

1. Colin J, Paquette B. Comparison of the analgesic efficacy and safety of nepafenac ophthalmic suspension compared with diclofenac ophthalmic solution for ocular pain and photophobia after excimer laser surgery: a phase II, randomized, double-masked trial. *Clin Ther* 2006; **28:** 527–36.
2. Lane SS. Nepafenac: a unique nonsteroidal prodrug. *Int Ophthalmol Clin* 2006; **46:** 13–20.
3. Lane SS, *et al.* Nepafenac ophthalmic suspension 0.1% for the prevention and treatment of ocular inflammation associated with cataract surgery. *J Cataract Refract Surg* 2007; **33:** 53–8. Correction. *ibid.*; 564.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nevanac; ***Braz.***: Nevanac; ***Canad.***: Nevanac; ***Chile***: Nevanac; ***Cz.***: Nevanac; ***Denm.***: Nevanac; ***Gr.***: Nevanac; ***India***: Nevanac; ***Irl.***: Nevanac; ***Israel***: Nevanac; ***Jpn***: Nevanac; ***Malaysia***: Nevanac; ***Mex.***: Nevanac; ***Neth.***: Nevanac; ***Norw.***: Nevanac; ***NZ***: Nevanac; ***Philipp.***: Nevanac; ***Pol.***: Nevanac; ***Port.***: Nevanac; ***Singapore***: Nevanac; ***Spain***: Nevanac; ***Swed.***: Nevanac; ***Switz.***: Nevanac; ***Thai.***: Nevanac; ***Turk.***: Nevanac; ***UK***: Nevanac; ***USA***: Ilevro; Nevanac.

Nicoboxil *(rINN)*

Butoxyethyl Nicotinate; Nicoboxilo; Nicoboxilum; Никобоксил.

2-Butoxyethyl nicotinate.

$C_{12}H_{17}NO_3$=223.3

CAS — 13912-80-6.

UNII — GSD5B9US0W.

Profile

Nicoboxil is a nicotinate used in topical preparations as a rubefacient. It is also included in some topical preparations used for the treatment of acne vulgaris.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Finalgon; ***Austria***: Finalgon; ***Ger.***: Finalgon; ***Gr.***: Finalgon; ***Ital.***: Anti-Acne; ***Port.***: Finalgon; ***Rus.***: Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Finalgon (Финалгон); ***UK***: Actinac†; ***Ukr.***: Finalgon (Финалгон).

Nicomorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nicomorfina; Nicomorfina, hidrocloruro de; Nicomorphine, Chlorhydrate de; Nicomorphini Hydrochloridum; Никоморфина Гидрохлорид.

3,6-Di-*O*-nicotinoylmorphine hydrochloride; (-)-(5*R*,6*S*)-4,5-Epoxy-9a-methylmorphin-7-en-3,6-diyl dinicotinate hydrochloride.

$C_{29}H_{25}N_3O_5$,HCl=532.0

CAS — 639-48-5 (nicomorphine); 12040-41-4 (nicomorphine hydrochloride); 35055-78-8 (nicomorphine xHCl).

ATC — N02AA04.

ATC Vet — QN02AA04.

Profile

Nicomorphine hydrochloride is an opioid analgesic (p. 108.1) used in the treatment of moderate to severe pain. It is given in oral doses of 5 to 10 mg daily or by intramuscular, slow intravenous, or subcutaneous injection in doses of 10 to 20 mg; higher doses have also been used. It may also be given rectally in usual doses of 10 to 20 mg daily.

References.

1. Koopman-Kimenai PM, *et al.* Pharmacokinetics of intravenously administered nicomorphine and its metabolites in man. *Eur J Anaesthesiol* 1993; **10:** 125–32.
2. Koopman-Kimenai PM, *et al.* Rectal administration of nicomorphine in patients improves biological availability of morphine and its glucuronide conjugates. *Pharm World Sci* 1994; **16:** 248–53.
3. Koopman-Kimenai PM, *et al.* The bioavailability of intramuscularly administered nicomorphine (Vilan) with its metabolites and their glucuronide conjugates in surgical patients. *Int J Clin Pharmacol Ther* 1995; **33:** 442–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Vilan; ***Denm.***: Vilan; ***Neth.***: MorZet; ***Switz.***: Vilan.

Niflumic Acid *(BAN, rINN)*

Acide Niflumique; Ácido niflúmico; Acidum niflumicum; Niflúmico, ácido; Nifluminsäure; UP-83; Нифлумовая Кислота.

2-(aaa-Trifluoro-*m*-toluidino)nicotinic acid.

$C_{13}H_9F_3N_2O_2$=282.2

CAS — 4394-00-7.

ATC — M01AX02; M02AA17.

ATC Vet — QM01AX02; QM02AA17.

UNII — 4U5MP5IUD8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Niflumic Acid). A pale yellow, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol; freely soluble in acetone.

Uses and Administration

Niflumic acid, a nicotinic acid derivative, is an NSAID (p. 102.3). It has been used in inflammatory and musculoskeletal and joint disorders in usual oral doses of about 250 mg three or four times daily; up to 1500 mg daily has been used in severe disorders. It has also been used topically as a 3% ointment or 2.5% gel. The morpholinoethyl ester, morniflumate (p. 92.2), has similar uses.

Niflumic acid glycinamide has been used topically in inflammatory mouth disorders.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Fluoride-associated osteosis has been reported with prolonged use. Niflumic acid should be stopped if hypersensitivity skin reactions appear.

Effects on the skin. From a case-control study[1] of children admitted to a hospital emergency department in Italy it was calculated that the odds-ratio of users of niflumic acid, or its derivative morniflumate, developing serious cutaneous reactions was 4.9. Given this figure and the fact that safer drugs were available the authors considered that there was no indication for which niflumic acid was required in children. However, a large cohort study[2] involving 193 727 children aged between 0 and 14 years found that niflumic acid was not associated with a higher risk of mucocutaneous reactions when compared with other NSAIDs or paracetamol. The authors of the later study suggested that the conclusions of the original study may have been confounded because there was no adjustment for age or indication.

1. Menniti-Ippolito F, *et al.* Niflumic acid and cutaneous reactions in children. *Arch Dis Child* 2001; **84:** 430–1.
2. Sturkenboom M, *et al.* Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics. Abstract: *Pediatrics* 2005; **116:** 212. Full version: http://pediatrics.aappublications.org/cgi/content/full/116/1/e26 (accessed 08/11/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flogovital; ***Belg.***: Niflugel; ***Cz.***: Niflugel†; Nifluril†; ***Fr.***: Niflugel; Nifluril; ***Gr.***: Chrispapon; Livornex; Myoskelet; Niflamol; Novopone; Radiogen; Sariu; ***Hung.***: Donalgin; ***Ital.***: Niflam; ***Port.***: Nifluril; ***Rus.***: Donalgin (Доналгин); ***Spain***: Niflactol.

Multi-ingredient Preparations. ***Arg.***: Flogodisten.

Nimesulide *(BAN, rINN)*

Nimesulid; Nimesulida; Nimesulidas; Nimésulide; Nimesulidi; Nimesulidinum; Nimesulidum; Nimeszulid; R-805; Нимесулид.

4′-Nitro-2′-phenoxymethanesulphonanilide.

$C_{13}H_{12}N_2O_5S$=308.3

CAS — 51803-78-2.

ATC — M01AX17; M02AA26.

ATC Vet — QM01AX17; QM02AA26.

UNII — V4TKW1454M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nimesulide). A yellowish crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; freely soluble in acetone.

Profile

Nimesulide is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used to treat acute pain and dysmenorrhoea in oral doses of up to 100 mg twice daily; use in the EU is limited to second-line treatment for a maximum of 15 days due to reports of hepatotoxicity (see Adverse Effects, below). It has also been given rectally in a dose of 200 mg twice daily. In the symptomatic treatment of sprains and tendinitis nimesulide has been applied topically as a 3% gel.

Nimesulide betadex (nimesulide betacyclodextrin complex) has been used similarly.

References.

1. Bennett A, *etal.* Nimesulide: a multifactorial therapeutic approach to the inflammatory process? A 7-year clinical experience. *Drugs* 1993; **46:** (suppl 1): 1–283.
2. Senna GE, *et al.* Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* 1996; **14:** 94–103.
3. Vizzardi M, *et al.* Nimesulide beta cyclodextrin (nimesulide-betadex) versus nimesulide in the treatment of pain after arthroscopic surgery. *Curr Ther Res* 1998; **59:** 162–71.
4. Bernareggi A. Clinical pharmacokinetics of nimesulide. *Clin Pharmacokinet* 1998; **35:** 247–74.
5. Shah AA, *et al.* Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. *Gut* 2001; **48:** 339–46.
6. Nüing RM, *et al.* Pathogenetic role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome: therapeutic use of the cyclooxygenase-2 inhibitor nimesulide. *Clin Pharmacol Ther* 2001; **70:** 384–90.

Adverse effects. Although *thrombocytopenia* is a common feature in patients infected with HIV, a group of workers considered that thrombocytopenia in one of their patients was related to the use of nimesulide.[1]

There have been reports[2-4] of *hepatotoxicity* after treatment with nimesulide. Data from spontaneous reports have also suggested that nimesulide may be associated with a higher risk of hepatotoxicity than other NSAIDs.[4] A cohort study[5] involving about 400 000 users of NSAIDs in one region of Italy between 1997 and 2001 found that those taking nimesulide were 1.3 times more likely to develop hepatotoxicity than users of other NSAIDs and 1.9 times more likely to suffer severe liver injury. Reports of serious hepatotoxicity had led to the suspension of marketing authorisations of nimesulide in Finland and Spain in 2002. This issue was also reviewed by the EMEA[6] and in 2004 they reported that the risk/benefit ratio for nimesulide remained favourable; however, they recommended that its indications be restricted to acute pain, dysmenorrhoea, and osteoarthritis for systemic formulations, and to the relief of sprains and tendinitis for topical formulations. It was also recommended that the oral dose be reduced to a maximum of 100 mg twice daily. Subsequently, in May 2007 the Irish regulatory authority withdrew systemic formulations of nimesulide from the Irish market after concerns about hepatotoxicity.[7] Since being licensed in 1995, nimesulide had generated 53 adverse reaction reports involving liver toxicity, including 9 cases of liver failure, 3 of which resulted in death and 6 in liver transplantation; there had also been 1 other liver-related fatality. The withdrawal prompted another review by the EMEA[8] which concluded that the risk/benefit ratio of systemic formulations of nimesulide was still favourable; however, since most hepatic reactions were noted after 2 weeks of treatment, it was recommended that treatment with nimesulide should be limited to 15 days. After a full assessment of the risks and benefits of nimesulide, in 2011, the EMEA[9] further restricted the indications of systemic formulations to second-line treatment of acute pain and dysmenorrhoea only; use in osteoarthritis was no longer recommended.

There have been reports[10,11] of *toxic pustuloderma* (acute generalised exanthematous pustulosis) with oral nimesulide. *Fixed drug eruptions* have also been seen.[12]

An infant developed hypotension and hypothermia after inadvertently taking an *overdose* of 8 times the recommended daily dose of nimesulide.[13] The patient recovered

after gastric lavage with activated charcoal and supportive therapy.

1. Pasticci MB, *et al.* Nimesulide, thrombocytopenic purpura, and human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1990; **112:** 233–4.
2. McCormick PA, *et al.* COX 2 inhibitor and fulminant hepatic failure. *Lancet* 1999; **353:** 40–1.
3. Sbeit W, *et al.* Nimesulide-induced acute hepatitis. *Ann Pharmacother* 2001; **35:** 1049–52.
4. Maciá MA, *et al.* Hepatotoxicity associated with nimesulide: data from the Spanish pharmacovigilance system. *Clin Pharmacol Ther* 2002; **72:** 596–7.
5. Traversa G, *et al.* Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *BMJ* 2003; **327:** 18–22.
6. EMEA. CPMP opinion following an article 31 referral: nimesulide containing medicinal products (issued 7th May, 2004). Available at: http://www.ema.europa.eu/pdfs/human/referral/nimesulide/172404en.pdf (accessed 08/04/10)
7. Irish Medicines Board. Immediate suspension of the marketing of medicines containing nimesulide (issued 15th May, 2007). Available at: http://www.imb.ie/EN/Safety-Quality/Advisory-Warning-Recall-Notices/Human-Medicines/Nimesulide-Suspension.aspx?page=1&noticetypeid=-1&year=2007 (accessed 08/11/07)
8. EMEA. Questions and answers on the CHMP recommendation on nimesulide-containing medicines (issued 21st September, 2007). Available at: http://www.emea.europa.eu/pdfs/human/opinion/43098807en.pdf (accessed 08/11/07)
9. EMEA. Questions and answers on the review of systemic medicines containing nimesulide (issued 20th January, 2012). Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Referrals_document/Nimesulide_31/WC500107957.pdf (accessed 23/08/12)
10. Lateo S, Boffa MJ. Localized toxic pustuloderma associated with nimesulide therapy confirmed by patch testing. *Br J Dermatol* 2002; **147:** 624–5.
11. Teixeira M, *et al.* Acute generalized exanthematous pustulosis induced by nimesulide. *Dermatol Online J* 2006; **12:** 20. Available at: http://dermatology.cdlib.org/126/case_presentations/agep/teixeira.html (accessed 08/11/07)
12. Malheiro D, *et al.* Nimesulide-induced fixed drug eruption. *Allergol Immunopathol (Madr)* 2005; **33:** 285–7.
13. Yapakci E, *et al.* Hypoglycaemia and hypothermia due to nimesulide overdose. *Arch Dis Child* 2001; **85:** 510.

Pregnancy. Irreversible *end-stage renal failure* has been reported in a neonate born to a mother given nimesulide as a tocolytic from the 26th to the 32nd week of pregnancy.[1] Others have reported neonatal renal failure associated with nimesulide.[2] *Premature closure of the ductus arteriosus* leading, in some cases, to *persistent pulmonary hypertension* has also been seen in 10 neonates whose mothers self-medicated with nimesulide during the third trimester of pregnancy.[3]

1. Peruzzi L, *et al.* Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type-2 selective inhibitor nimesulide as tocolytic. *Lancet* 1999; **354:** 1615. Correction. *ibid.* 2000; **355:** 238.
2. Balasubramaniam J. Nimesulide and neonatal renal failure. *Lancet* 1999; **355:** 575.
3. Paladini D, *et al.* Severe ductal constriction in the third-trimester fetus following maternal self-medication with nimesulide. *Ultrasound Obstet Gynecol* 2005; **25:** 357–61.

Premature labour. Nimesulide has been tried as an alternative to indometacin to delay labour in patients with a history of preterm delivery (p. 2131.1). Nimesulide was given from 16 to 34 weeks of gestation and a successful delivery started 6 days after withdrawal.[1] There appeared to be no adverse effect on fetal renal function or the ductus arteriosus. The authors suggested that fetal prostaglandin synthesis might be mainly mediated through cyclo-oxygenase-1 (COX-1) and that a relatively selective COX-2 inhibitor such as nimesulide might produce fewer adverse effects on the fetus than other non-selective NSAIDs. However, in a small study short-term effects on the fetus were similar for nimesulide, indometacin, and sulindac.[2]

Adverse effects have been reported in some neonates whose mothers received nimesulide during their pregnancies, see above.

1. Sawdy R, *et al.* Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. *Lancet* 1997; **350:** 265–6.
2. Sawdy RJ, *et al.* A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003; **188:** 1046–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aldoron; Flogovital NF; Virobron; ***Austria***: Aulin†; ***Belg.***: Mesulid; ***Braz.***: Arflex; Cimelide; Deflogen; Deltaflan; Fasulide; Inflalid; Maxsulid; Mesalgin; Neosulida; Nimalgex; Nimesilam; Nimesubal; Nimesulin; Nimesulix; Nimesulon; Nisalgen; Nisoflan; Nisufar; Nisuflex; Nisulid; Nizuil; Prexulid; Scaflam; Scalid; Sintalgin; Sulonil; ***Chile***: Ainex†; Doloc; Nimepast; Nimesyl; Nisulid; Nisural; ***China***: Anjielishu (安洁力舒); BangNi (邦尼); Fu Mei Shu (孚美舒); Hua Shuang Jie (化双节); Huang Xing Yun Shu (皇星云舒); Li Nuo Ke (利诺刻); Li Shu Tong (力舒同); Nuo Zheng (诺正); Pu Fei Te (普菲特); Pu Wei (普威); Rui Li (锐丽); Rui Pu Le (瑞普乐); Rui Zhi Li (瑞芝利); Rui Zhi Qing (瑞芝清); Sai Pu Da (赛扑达); Shan Yi Ting (山易亭); Si Rui (斯瑞); Surong (苏榕); Tengke (腾克); Xianleke (先乐克); Yi Mei Li (怡美力); Yi Ya Xuan (益雅轩); ***Cz.***: Aulin; Coxtral; Mesulid; Nimed; Nimesil; ***Fr.***: Nexen; ***Gr.***: Aflogen; Alencast; Algosulid; Algover; Amocetin; Aulin; Auromelid; Bioxidol; Chemisulide; Cliovyl; Discorid; Dolostop; Edrigyl; Elinap; Erlecit; Erreflog; Fladalgin; Flogostop; G-Revm; Kartal; Lalide; Lasazin; Lemesil†; Lizepat; Londopon; Lovirem; Melicate; Melimont; Mesilex; Mesulid; Mesupon; Min-A-Pon; Mosuolit; Multiformil; Myxina; Naofid; Neo-Lemesil; Niberan; Nimegel; Nimelide; Nimesul; Omnibus; Rhemid; Ristolzit; Ritamine; Rolaket; Scaflam; Specilid; Sudinet; Tranzicalm; Ventor; Volonten; ***Hong Kong***: Mesulid; Nidol; Nimm; ***Hung.***: Mesulid; Nidol; Nimelid; Xilox; ***India***: Actinim; Adenim; Aglonim; Anafebrin; Anim; Antipen; Arinox-MD; Arsulide; Arthorid; Asilid; Auronim; Avinim; Benice-DT; Benim; Bestonim; Beta Nicip; Bio-Nim; Blisulide; Boflam; Brinimo; C-Nim; Canmet; Caslide; Ceralide-MD; Colide; Cunim; Dardnil; Delnim MD; Denim MD; Denim; Dolide; Dolonim; E-Nim-MD; Elide; Elnim-MD; Emsulide; Fenim; Fonim MD; Genlide; Gesnim; Hilyte; Kind-MD; Ladex; Lupisulide; Mangolide; Maxiflam; Maxulide; Mesulid; Milenim; Monogesic; Movinim-MD; Myonal; N-Lid; N-Side; Nam; Namosid; Nap; Nayanim; Neem-MD; Neet; Nelsid; Nemeriv; Nemil; Nemon; Neulab; Neulide; New Nicip; Ni-MD; Nicip; Nikee; Nile; Nilide; Nilup; Nimace-MD; Nimact; Nimagyl; Nimaid; Nimat; Nimbid; Nimbu; Nimbus; Nimcet; Nimdal; Nimdard; Nimeb; Nimegesic; Nimel; Nimeril; Nimesel; Nimesis-MD; Nimfast; Nimi; Nimica; Nimind CT; Nimiz; Nimkair; Nimkul; Nimlak-MD; Nimley-MD; Nimlid-MD; Nimlodi; Nimobid; Nimodol; Nimofen; Nimogem; Nimoril; Nimotas-CD; Nimpain-MD; Nimpic; Nimpure-MD; Nimras-MD; Nimriz; Nimsaid; Nimsutech; Nimtop; Nimucare; Nimuda; Nimulex-FD; Nimulid; Nimupain; Nimupet; Nimustar; Nimusym; Nimusyp; Nimutab; Nimutal; Nimvar-MD; Nimven-MD; Nimvista; Nisba; Nise; Nisulid; Nizapas-MD; Nizer; NMD; Nobel; Nodard; Nom; Novigan-M; Novolid; Nugesic; Nuleb; Nulide; Numel; Onalide-MD; Onim-MD; Orthobid; Osonim; Panim; Pansulide RD; Willgo; ***Indon.***: Arnid†; Aulin†; Nicox†; Nimed; Nimost†; Sohoflam†; Ximede; ***Irl.***: Aulin; Mesulid†; ***Israel***: Mesulid; ***Ital.***: Actalide; Algimesil; Algolider; Antalor; Areuma; Aulin; Delfos; Dimesul; Domes; Efridol; Erreflog; Eudolene†; Fansulide; Flolid; Isodol; Ledoren; Mesulid; Nerelid; Nimedex; Nimenol†; Nimesulene; Nims; Oronime; Pantames; Remov; Solving; Sulidamor; Sulide; ***Malaysia***: Precoxi; ***Mex.***: Apolide; Cargespril; Defam; Degorflan; Dexlin; Eskaflam; Fenoxil; Flamide; Flamozin; Igrexa; Inim; Lesiden; Lusemin; Medani; Meliden; Mesulid; Minus; Nidolin; Nilden; Nilid; Nimepis; Nizurin; Quidofril; Redaflam; Severin; Sidel†; Sindel; Sulidek; Sulidol-GB; Sundir; Ul-Flam; ***Philipp.***: Aulin†; Flamesul†; Mesulid†; Nidolid; Sorini†; Sulidin; ***Pol.***: Aulin; Coxtral; Minesulin; Nimesil; ***Port.***: Aulin; Donulide; Gerilide; Jabasulide; Nilmide; Nimalge†; Nimartin†; Nimed; Nimesulene; Reumolide; Sulidor; Sulimed†; Vitolide†; ***Rus.***: Actasulid (Актасулид); Aponil (Апонил); Auronim (Ауроним); Coxtral (Коксрал); Flolid (Флолид); Nimesil (Нимесил); Nimica (Нимика); Nimulid (Нимулид); Nise (Найз); Prolid (Пролид); ***Switz.***: Aulin; Nisulid; ***Thai.***: Emdon; Nemil-Os†; Neptide; Nidol; Nilide; Nimill; Nimind†; Nimlide; Nimo†; Nimulid; Veedol; ***Turk.***: Coxulid; Mesulid†; Motival; Nimelid; Nimes; Romasulid; Sulidin; ***Ukr.***: Nimegesic (Нимегезик); Nimesil (Нимесил); Nise (Найз); Remesulid (Ремесулид)†; Remisid (Ремисид); ***Venez.***: Ainex; Aulin; Drexel; Nimecox; Nimelid; Reduben; Scaflan.

Multi-ingredient Preparations. ***Arg.***: Mio Aldoron; Mio-Virobron; ***India***: Adenim Plus; Adenim-MR; Adnim-P; Aldee-P; Alsolide Plus; Alsolide-MR; Amidase-N; Anafortan-N; Anim-P; Anm-P; Antipen-T; Arinox Plus; Arnim-P; Arsulide-D; Arsulide-P; Arsulide-S; Arthorid; Artifen; Asilid Relief; Avinim Plus; Avinim-MR; Axinim; Baselide; Benim-P; Bestogesic MR; Bestogesic; Bestonim P; Biozobid-N; C-Nim Plus; Cadiflam-NP; Cadpo-N; Canmet-MR; Canmet-P; Canmet-SN; Carnil MR; Carnil Plus; Caslide-P; Ceralide-P; Cipzen N; Citanz; Cofev; Comspa; Cranim-P; Cunim Plus; Cuzen-NM; Cyclozed-N; Cyclozobid; Dacnis N; Dardnil-P; Delnim-P; Delnim-SP; Denim P; Denim Plus; Densera-N; Diplonim-MR; Diplonim; Dizer-N; Dolamide; Dolide Plus; Doloflam Plus; Doloflam-MR; Dolospan; Drolid; DS-15 Plus; Dyspas; E-Nim Plus; Edase-N; Elnim-D; Emanzen-N; Emsulide-Fen; Emsulide-P; Etiza; Fedol; Fevni-P; Flamar-P; Flozen-NS; Flupara-N; Flupara-SN; Fonim-P; Fonim-S; Genlide Plus; Gesnim-MR; Gesnim-P; Gesnim-S; Gonim; GSNim-P; Hilyte-P; Hitz-NP; Imosan; Imsimol; Indlide; Ingesic-MR; Ingesic-P; Inslide; Itzgon; Jumo; Jumocip; Kaylid-P; Khalli; Kind Plus; Ladex-P; Lebec-NP; Leebec-NP; Litnim; Lupisulide MR; Lupisulide-D; Lupisulide-P; Maxiflam-SP; Maxonim-P; Meriflam; Mesu-P; Minipar-P; Minipar-SP; Minipar-TZ; Minsu-P; Molide; Molulid; Mortrin-T; Movinim-P; Movinim-S; N-Plus; N-S-Plus; Nam Cold-L; Nam Cold-SR; Nam Cold; Nam-P; Nam; Namplus; Namsafe; Nap Plus; Need; Neet Plus; Neet-S; Nefter; Nelsid Fort; Nelsid Plus; Nelsid-MR; Nelsid-S; Nelsid; Nemeriv-P; Nency-P; Neomol-MR; Neomol-XP; Neosulide Plus; Nepar; Neulab Active; Neulab D; Neulab-MR; Neurophen-Compound; Nevis-P; Niap; Nicet; Niciflex-T; Nicip Cold; Nicip D; Nicip MR; Nicip Plus; Nicip Supergel; Nicip T; Nicispas; Nidic; Nifen MR; Nifen Plus; Nifen; Nile Plus; Nile-CZ; Nile-P; Nile-S; Nile-SP; Nile-TZ; Nilup-P; Nim-MR; Nimace-P; Nimace-SP; Nimagyl-PC; Nimaid-P; Nimat-MR; Nimat-Plus; Nimbra Plus; Nimbus Plus; Nimcare-A; Nimcet Plus; Nimcin-P; Nimdard Plus; Nimdase-P; Nimdase; Nimdin; Nimeb-P; Nimegesic-P; Nimelide Fen; Nimeril-T; Nimesel-P; Nimesis-P; Nimeter-A; Nimetiz; Nimi-LB; Nimica Plus; Nimitiz; Nimiz-Plus; Nimkair-P; Nimkul DCM; Nimkul Para; Nimkul SP; Nimkul-CZ; Nimkul-MR; Nimlak-Plus; Nimley-P; Nimley-S; Nimli-P; Nimlid-P; Nimnil-P; Nimodex; Nimodia-P; Nimofen-P; Nimofen-T; Nimopace; Nimotas-P; Nimotiz MR; Nimoven; Nimpa; Nimpain P; Nimpain PS; Nimpain T; Nimpar; Nimpara; Nimpep; Nimpure-P; Nimpure-PS; Nimriz Plus; Nims-P; Nimsaid-P; Nimsaid-S; Nimsaid-T; Nimsol Plus; Nimspa; Nimspas; Nimtech; Nimtiz-MR; Nimucare-P; Nimucet-Fen; Nimucet-MR; Nimucet; Nimucold; Nimudin; Nimuflex-MR; Nimuflex-P; Nimulid MR; Nimulid Nugel; Nimulid SP; Nimumol-P; Nimupain Plus; Nimuris-Plus; Nimuspas; Nimustar-P; Nimustar-S; Nimusym-Plus; Nimutal-Plus; Nimvar Plus; Nimvar-MR; Nimven Plus; Nimven-S; Nimven-T; Nimvista Plus; Nimvista-D; Nimvista-MR; Nimvon-S; Nisba Plus; Nise Gel; Nise-MR; Niser; Niza-Spas; Nizapas-MR; Nizapas-P; Nizapas-SP; Nizi; Nobel Plus; Nobel Spas; Nobel-MR; Nodard Plus; Noflam P; Nom-P; Normal; Norpy; Novolid-MR; Novolid-S; Nozy Cold; NP.Com; NPM; Nugesia; Nupar; Onalide-MR; Opel Plus; Opel-MR; Orthobid Plus; Orthobid-MR; Orthodex-MR; Osnip; Osonim-P; Ospas; Oxin Plus; Oxyprem; Pacimol Plus; Panum-P; Panum-SP; Paralide; Paratel-NP; Parazolandin; ***Mex.***: Amoxiclide; Zitroflam; ***Ukr.***: Inflarax (Инфларакс); Nizer (Найзер)†.

Nonivamide *(rINN)*

Nonivamida; Nonivamidum; Noniwamid; Nonylvanillamide; PAVA; Pelargonyl Vanillylamide; Pseudocapsaicin; Нонивамид.

N-Vanillylnonamide; *N*-[(4-Hydroxy-3-methoxyphenyl) methyl]nonanamide.

$C_{17}H_{27}NO_3$=293.4

CAS — 2444-46-4.

UNII — S846B891OR.

NOTE. Use of the term 'synthetic capsaicin' to describe nonivamide has arisen from the use of nonivamide as an adulterant for capsaicin and capsicum oleoresin.

Profile

Nonivamide is a synthetic analogue of capsaicin (p. 35.1) that is used in topical preparations for the relief of muscular and rheumatic pain.

Nonivamide has also been used as a food flavour and in 'pepper sprays' for law enforcement and self defence.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: ABC Hydrogel-Warmepflaster†; ***Ger.***: Capsi-med; Gothaplast Capsicum-Warmepflaster.

Multi-ingredient Preparations. ***Austral.***: Finalgon; ***Austria***: Finalgon; Rubriment; ***Cz.***: Capsicolle; ***Ger.***: Finalgon; Rubriment†; ***Gr.***: Finalgon; ***Port.***: Finalgon; ***Rus.***: Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Capsicam (Капсикам); Finalgon (Финалгон); ***Switz.***: Histalgane; Radalgin†; ***Thai.***: Ammeltz; ***UK***: Pain Relief Balm†; ***Ukr.***: Capsicam (Капсикам); Finalgon (Финалгон).

Nonsteroidal Anti-inflammatory Drugs

AINE; AINS; Fármacos antiinflamatorios no esteroideos; NSAIDs; NSAİİ'ler; НСПВП; НПВП; НПВС; Нестероидные Противовоспалительные Препараты.

Uses and Administration

Given as single doses or in short-term intermittent therapy NSAIDs can relieve mild to moderate pain. However, it may take up to 3 weeks of use before their anti-inflammatory effects become evident. The combined analgesic and anti-inflammatory effects make them particularly useful for the symptomatic relief of painful and/or inflammatory conditions including rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and the spondyloarthropathies, and also in peri-articular disorders, and soft-tissue rheumatism. Some NSAIDs are used in the management of dental or postoperative pain. Some NSAIDs, but not aspirin or other salicylates, are also used to treat acute gouty arthritis.

Generally, it is considered that there are only small differences in anti-inflammatory activity between the various NSAIDs and choice is largely empirical. Responses of individual patients vary widely. Thus, if a patient fails to respond to one NSAID, another drug may be successful. However, it has been recommended that NSAIDs associated with a low risk of gastrointestinal toxicity should generally be preferred and the lowest effective dose used. Treatment with NSAIDs that are selective inhibitors of cyclo-oxygenase-2 (COX-2), such as celecoxib, is limited in the UK to those patients with a history of serious gastrointestinal problems or considered to be at high risk of developing such problems if given a non-selective NSAID (see Effects on the Gastrointestinal Tract, p. 105.3).

NSAIDs are usually given orally, with or after food, although some such as diclofenac, ketoprofen, ketorolac, parecoxib, piroxicam, and tenoxicam can be given intramuscularly; diclofenac, ketorolac, parecoxib, and tenoxicam can also be given intravenously. Some NSAIDs are applied topically or given rectally as suppositories.

Several NSAIDs are used in ophthalmic preparations for the inhibition of intra-operative miosis, control of postoperative ocular inflammation, and prevention of cystoid macular oedema.

Action. Cyclo-oxygenases play an important role in the biosynthesis of prostaglandins (p. 2598.1). Non-selective NSAIDs inhibit both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2); the idea that inhibition of COX-1 is associated with adverse gastrointestinal effects while inhibition of COX-2 is associated with anti-inflammatory activity,[1-6] led to the development[7] of preferential or selective inhibitors of COX-2. Meloxicam and nimesulide are preferential inhibitors of COX-2, (i.e. they have a higher selectivity for COX-2 than COX-1 but are not exclusive COX-2 inhibitors); etodolac and nabumetone are also claimed to have preference for COX-2 although there is less evidence for this. Drugs with a very high selectivity for COX-2 are also available; celecoxib and parecoxib are two examples. Although the selective inhibition of COX-2 may be associated with reduced gastrointestinal toxicity, adverse effects associated with such inhibition have been noted in other body systems, see Thrombotic Events under Effects on the Cardiovascular System p. 105.1, and Effects on the Kidneys, p. 106.2.

There is evidence that NSAIDs may also have a central mechanism of action that augments the peripheral mechanism.[6]

Many NSAIDs possess centres of chirality within their molecular structure, with different chiral forms (enantiomers) having different degrees of pharmacological activity.[8,9] For example, indometacin, its analogues, and some arylpropionic acids are chiral drugs with the *S*(+)-enantiomer in most cases showing the dominant pharmacological activity. However, the ratio of *S*/*R* activity varies between drugs and between *animal* species. NSAIDs are generally used clinically as the racemate with only a few currently being given as the *S*-enantiomer (for example, dexibuprofen and dexketoprofen). The chirality of a drug may have subtle effects on its toxicity and interactions, and it may be more desirable to use a drug as its active enantiomer.[9]

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Colic pain. Prostaglandins have been implicated in the aetiology of biliary colic (p. 6.3), and some NSAIDs such as diclofenac, indometacin, and ketoprofen have been used to relieve such pain.

Dementia. Although NSAIDs have been associated with memory impairment and attention deficits in the elderly (see Effects on the CNS, p. 105.2), some studies have shown that long-term use may reduce the rate of cognitive decline[1,2] or the risk of developing Alzheimer's disease[3-5] (see Dementia, p. 390.1). A systematic review[6] of observational studies, which included some of these studies, also suggested that the risk of developing dementia is lower in patients who are taking NSAIDs. However, a randomised study[7] found no benefit from treatment with naproxen or rofecoxib in patients with existing mild to moderate Alzheimer's disease. Another systematic review[8] has suggested that the beneficial effects of NSAIDs seen in some studies are likely to be due to biases such as recall introduced by the study's design; the benefit of NSAIDs in preventing dementia or cognitive impairment was 50% in studies with prevalent (pre-existing) dementia cases, which decreased to 20% in studies of incident dementia cases (those developing during the study period), and was absent in those which used cognitive decline as an endpoint. Furthermore, a more recent randomised primary prevention study[9] concluded that neither naproxen nor celecoxib had a protective effect and there was some evidence that naproxen had a detrimental effect when compared with placebo. A large population-based cohort study[10] of the elderly also did not find a reduction in the risk of dementia or Alzheimer's disease among NSAID users. Instead, previous sustained use of NSAIDs was found to be associated with an increased incidence of dementia and Alzheimer's disease; the authors suggested that NSAIDs might only delay the onset of dementia. Further studies are needed to determine the role of NSAIDs in dementia.[10]

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Diabetes insipidus. NSAIDs such as indometacin have been used in the treatment of diabetes insipidus; for some references, see p. 72.1.

Ectopic ossification. Ectopic ossification (heterotopic ossification) is a condition in which mature bone develops in non-skeletal tissues, commonly the connective tissue of muscles. It occurs after local trauma, for example after joint dislocation or surgery such as total hip replacement, and also after neurological damage such as severe head or spinal cord injuries.[1,2] Ectopic bone formation usually starts about 2 weeks after the injury, though symptoms, which include localised pain, fever, swelling, erythema, and restriction of movement, may not appear for 8 to 12 weeks.[1,3] Neurogenic ectopic ossification may develop even several years after spinal cord injury.[3] A congenital form of ectopic ossification, myositis ossificans progressiva (fibrodysplasia ossificans progressiva), also occurs but is rare. The principal complications of ectopic ossification are loss of joint mobility and function.[1,2]

Ectopic ossification should be distinguished from the calcification of soft tissue which may occur in connective tissue disorders or in parathyroid disorders as a result of high circulating concentrations of calcium and or phosphate; in these conditions calcification occurs without bone formation.

Surgical resection can improve joint motion[1,3] in patients with ectopic ossification, but may be associated with severe complications and poor outcome, and ossification may recur postoperatively.[3] Delaying surgery as long as possible until bone formation has decreased may lessen the likelihood of these complications,[1] although earlier surgery may prevent fibrous ankylosis and muscle contracture.[3] Although there is no consensus on treatment, early, regular and cautious physiotherapy is recommended to mobilise joints;[1-3] aggressive manipulation may cause further ossification.

Prophylactic measures include radiotherapy or drug therapy. While prophylaxis does not always prevent the development of ectopic ossification, it can decrease its occurrence and severity. Prophylactic measures should be begun as early as possible and with regard to orthopaedic surgery may be started before the operation. Prophylaxis is also required if mature ectopic bone is to be surgically excised in order to minimise the rate of recurrence. Low-dose radiotherapy is as effective as high-dose, and pre-operative irradiation is as effective as postoperative.[4] Studies suggest that NSAID prophylaxis is of similar efficacy to radiotherapy.[4] NSAIDs appear to significantly reduce the incidence of ectopic bone formation,[2-5] possibly by inhibiting inflammation and suppressing mesenchymal cell proliferation.[3] While controversy exists as to duration and doses, indometacin is considered the NSAID of choice by some; naproxen, tenoxicam, and diclofenac may also be of benefit.[4] Ibuprofen has been tried; however, a study[6] has found that, although it significantly reduced the rate of ectopic bone formation, there were no clinical benefits 6 to 12 months after surgery. Bisphosphonates that inhibit the mineralisation of the deposited bone, such as etidronate, have also been used but they do not prevent the formation of the osteoid matrix. Also when etidronate is stopped, some mineralisation can occur, resulting in delayed ectopic or rebound ossification, though it is usually less severe. Prolonged treatment may be needed.[2,3] A systematic review,[7] however, found insufficient evidence to recommend the use of etidronate for the treatment of acute ectopic ossification.

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Eye disorders. Miosis resistant to conventional mydriatics often develops during ocular surgery, possibly due to release of prostaglandins and other substances associated with trauma. NSAIDs, which are prostaglandin synthetase inhibitors, are therefore used prophylactically as eye drops before ocular surgery to ameliorate intra-operative miosis but there has been some doubt that the effect they produce is of clinical significance. Those commonly used include diclofenac, indometacin, and flurbiprofen. These drugs do not possess intrinsic mydriatic properties.

Some NSAIDs are used topically or systemically in inflammatory ocular disorders, including inflammation and cystoid macular oedema following ocular surgery (see below). Topical NSAIDs are also effective analgesics when used in the management of corneal abrasions. However, their role in the treatment of macular oedema associated with uveitis (p. 1615.1) is less clear. NSAIDs are also used in the treatment of scleritis (see p. 1612.3). Diclofenac and ketorolac have also both been used in the management of seasonal allergic conjunctivitis (see p. 611.1).

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POSTOPERATIVE INFLAMMATORY OCULAR DISORDERS. Corticosteroids are used topically for the control of **postoperative ocular inflammation** but caution is required as they can delay wound healing and mask postoperative infection. They should only be used for short periods as they can cause glaucoma in susceptible individuals. Topical NSAIDs have also been tried and appear to be as effective as corticosteroids in controlling signs of inflammation after ocular surgery,[1] but there has been some concern about reports of corneal toxicity (see p. 50.1).

Cystoid macular oedema may follow cataract or retinal detachment surgery due to a disturbance of the blood-retinal barrier. NSAIDs[1-6] such as diclofenac, flurbiprofen, indometacin, and ketorolac are used topically with or without corticosteroids to prevent or relieve cystoid macular oedema. NSAIDs including indometacin are also used systemically in its management. However, a systematic review[6] has found insufficient evidence for the efficacy of NSAIDs (topical and oral) in acute or chronic cystoid macular oedema after cataract surgery although topical ketorolac may have a positive effect in chronic disease.

1. Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. *Drugs* 2007; **67:** 1291–1308.
2. Jampol LM. Pharmacologic therapy of aphakic and pseudophakic cystoid macular edema. *Ophthalmology* 1985; **92:** 807–10.
3. Flach AJ, *et al*. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. *Am J Ophthalmol* 1987; **103:** 479–86.
4. Jampol LM, *et al*. Nonsteroidal anti-inflammatory drugs and cataract surgery. *Arch Ophthalmol* 1994; **112:** 891–4.
5. Italian Diclofenac Study Group. Efficacy of diclofenac eyedrops in preventing postoperative inflammation and long-term cystoid macular edema. *J Cataract Refract Surg* 1997; **23:** 1183–9.
6. Sivaprasad S, *et al*. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 25/09/09).

Fever. Paracetamol, salicylates, and some other NSAIDs are the main antipyretics used to control fever (p. 11.3). Paracetamol is usually the antipyretic of choice in infants and children but ibuprofen is an effective alternative; alternation of the two may be better than either alone, although this is controversial. Salicylates are generally contra-indicated in these patients because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects of Aspirin, p. 25.3).

Gout. NSAIDs are the drugs usually used first for the treatment of acute attacks of gout (p. 600.1). Since the drug treatment of chronic gout can lead to the mobilisation of urate crystals from established tophi to produce acute attacks, NSAIDs may also be used for the prophylaxis of acute gout during the first few months of urate-lowering therapy.

Headache. An NSAID is often tried first for the symptomatic treatment of various types of headache including migraine (p. 670.3) and tension-type headache (p. 671.3). NSAIDs may also be effective prophylactic drugs for migraine, although propranolol is generally preferred. Paroxysmal hemicrania, a rare variant of cluster headache (p. 670.1), responds to indometacin.

Kidney disorders. Although NSAIDs can produce adverse effects on the kidney (see p. 106.2) they may have a role in the management of some types of glomerular kidney disease (p. 1604.3). They may be of use for the control of proteinuria due to nephrotic syndrome except when there is overt renal failure.

Malignant neoplasms. An early study by the American Cancer Society[1] suggested that regular use of aspirin might reduce the risk of developing fatal cancer of the oesophagus, stomach, colon, or rectum. Death rates due to other gastrointestinal cancers did not appear to be affected. Some studies[2-12] appear to support this reduced risk of colorectal cancer (see Prophylaxis, under Malignant Neoplasms of the Gastrointestinal Tract, p. 707.2) in regular users of aspirin or other NSAIDs, particularly in high-risk patients, conclusions that were cautiously endorsed by a systematic review.[13] Furthermore, a pooled analysis[14] of data from 2 randomised studies concluded that taking 300 mg, or more, of aspirin daily for at least 5 years is effective in reducing the risk of colorectal cancer, with a latency of 10 years. However, other studies[15,16] have found no evidence of an association between the use of aspirin or NSAIDs and the incidence of colorectal cancer; the authors suggest that these results may be explained by the short treatment period and the low dose of aspirin used. More recent reviews[17,18] prepared for the US Preventive Services Task Force (USPSTF) indicated that aspirin and NSAIDs, including selective cyclo-oxygenase-2 (COX-2) inhibitors, reduce the incidence of colonic adenomas, and that aspirin and NSAIDs also reduce the incidence of colorectal cancer; however, the USPSTF issued a statement[19] that, because of the adverse cardiovascular and gastrointestinal effects associated with these agents, their use to prevent colorectal cancer could not be recommended in those at average risk of colorectal cancer.

The potential role that inhibition of COX-2 may play in the management of cancer has been discussed[20,21] and a study[22] has found that regular use of aspirin appears to reduce the risk of colorectal cancers that overexpress COX-2 but not those with weak or absent expression of COX-2.

A large case-control study,[23] using data held on the UK General Practice Research Database, has examined information on NSAID use and the development of common cancers. This study also found that the use of NSAIDs (including aspirin) may protect against cancer of the oesophagus, stomach, colon, and rectum. However, the study failed to show any decrease in risk of non-gastrointestinal cancers. Subsequently, 2 meta-analyses[24,25] have also suggested that aspirin and NSAID use reduce the risk of other gastrointestinal cancers such as oesophageal or stomach cancer. In addition, one analysis[24] considered the effect of NSAID and aspirin use on non-gastrointestinal cancers: aspirin use showed a chemoprotective effect in pancreatic cancer although this was not significant statistically; there was also a slight, but nonetheless significant, reduction in the risk of breast cancer associated with both aspirin and NSAID use. The results for other sites, namely ovary, lung, bladder, and prostate, suggested no effect or possibly a slight reduced risk. The authors considered that it was unclear if any potential benefit in non-gastrointestinal cancers may be offset by the known adverse effects associated with the long-term use of these drugs particularly in those cancers with a low incidence.

Treatment with sulindac (see Gastrointestinal Disorders, p. 134.2) has been found to reduce the number of polyps in patients with familial adenomatous polyposis, a condition which predisposes to development of colorectal cancer. Celecoxib has similar effects (see p. 37.1).

1. Thun MJ, *et al.* Aspirin use and the risk of fatal cancer. *Cancer Res* 1993; **53:** 1322–7.
2. Rosenberg L, *et al.* A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J Natl Cancer Inst* 1991; **83:** 355–8.
3. Logan RFA, *et al.* Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case-control study of subjects participating in the Nottingham faecal occult blood screening programme. *BMJ* 1993; **307:** 285–9.
4. Giovannucci E, *et al.* Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann Intern Med* 1994; **121:** 241–6.
5. Giovannucci E, *et al.* Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995; **333:** 609–14.
6. Sandler RS, *et al.* Aspirin and nonsteroidal anti-inflammatory agents and risk for colorectal adenomas. *Gastroenterology* 1998; **114:** 441–7.
7. Smalley W, *et al.* Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. *Arch Intern Med* 1999; **159:** 161–6.
8. Jolly K, *et al.* NSAIDs and gastrointestinal cancer prevention. *Drugs* 2002; **62:** 945–56.
9. Sandler RS, *et al.* A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003; **348:** 883–90.
10. Baron JA, *et al.* A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003; **348:** 891–9.
11. Chan AT, *et al.* Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005; **294:** 914–23.
12. Chan AT, *et al.* Aspirin dose and duration of use and risk of colorectal cancer in men. *Gastroenterology* 2008; **134:** 21–8.
13. Asano TK, McLeod RS. Non steroidal anti-inflammatory drugs (NSAID) and aspirin for preventing colorectal adenomas and carcinomas. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 08/11/07).
14. Flossmann E, Rothwell PM. British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007; **369:** 1603–13.
15. Stürmer T, *et al.* Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. *Ann Intern Med* 1998; **128:** 713–20.
16. Stürmer T, *et al.* Colorectal cancer after start of nonsteroidal anti-inflammatory drug use. *Am J Med* 2006; **119:** 494–502.
17. Rostom A, *et al.* U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U. S. Preventive Services Task Force. *Ann Intern Med* 2007; **146:** 376–89.
18. Dubé C, *et al.* U.S. Preventive Services Task Force. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007; **146:** 365–75.
19. U. S. Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007; **146:** 361–4.
20. Liao Z, *et al.* Cyclo-oxygenase-2 and its inhibition in cancer: is there a role? *Drugs* 2007; **67:** 821–45.
21. Markowitz SD. Aspirin and colon cancer—targeting prevention? *N Engl J Med* 2007; **356:** 2195–8.
22. Chan AT, *et al.* Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007; **356:** 2131–42.
23. Langman MJS, *et al.* Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ* 2000; **320:** 1642–6.
24. González-Pérez A, *et al.* Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer* 2003; **3:** 28. Available at: http://www.biomedcentral.com/1471-2407/3/28 (accessed 08/11/07)
25. Wang WH, *et al.* Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003; **95:** 1784–91.

Menstrual disorders. Menorrhagia (p. 2300.3) is thought to be associated with abnormalities of prostaglandin production. Treatment with NSAIDs such as ibuprofen, mefenamic acid, or naproxen during menstruation, can reduce uterine blood loss by an average of 30% in women with menorrhagia. There does not appear to be any evidence that one NSAID is more effective than another.

NSAIDs are usually the first choice for the pain of dysmenorrhoea (p. 8.2). Mefenamic acid may have a theoretical advantage over other NSAIDs in being able to inhibit both the synthesis and the peripheral action of prostaglandins, but clinical studies have not shown fenamates to be more effective, and systematic review has suggested that ibuprofen may have the best risk/benefit ratio.

Migraine. See Headache, above.

Orthostatic hypotension. Fludrocortisone is usually the first drug tried in the treatment of orthostatic hypotension (p. 1634.3) when nonpharmacological treatment has failed. NSAIDs such as flurbiprofen, ibuprofen, or indometacin may be used alone or added to treatment if the response is inadequate.

Pain. NSAIDs have a similar analgesic effect to aspirin and paracetamol in single doses but, in regular full dosage, they have both a lasting analgesic and an anti-inflammatory effect. They are used in the management of mild to moderate pain (see Choice of Analgesic, p. 4.2) and are of particular value in pain due to inflammation. NSAIDs may be of benefit for inflammatory pain in infants and children (p. 5.2), although paracetamol is generally the preferred non-opioid analgesic in this age group. NSAIDs may be used in the treatment of acute low back pain (p. 9.2) if paracetamol fails to provide adequate pain relief. NSAIDs may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p. 7.1) and are particularly effective in bone pain of malignant origin. NSAIDs may be used for postoperative analgesia (p. 6.1), and are of particular value after day-case surgery because of their lack of sedative effects. They are not usually considered to be strong enough as the sole analgesic after major surgery, but may be used with stronger analgesics and may allow dosage reduction of opioids. The pain of mild sickle-cell crises (p. 11.1) may be controlled by analgesics such as NSAIDs or less potent opioids, for example codeine or dihydrocodeine; NSAIDs may be used with more potent opioids such as morphine for severe crises.

Dependence and tolerance are not a problem with non-opioid analgesics such as NSAIDs, but there is a ceiling of efficacy, above which, increasing the dose has no further therapeutic effect.

Rheumatic disorders. NSAIDs provide symptomatic relief for rheumatic disorders such as rheumatoid arthritis (p. 13.2) and spondyloarthropathies (p. 14.3), but they do not alter the course of the disease and additional antirheumatic drugs may need to be given to prevent irreversible joint damage. NSAIDs may also be used as an alternative to paracetamol for osteoarthritis (p. 12.3). Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue rheumatism (p. 14.2); topical formulations of some NSAIDs are also used.

Scleroderma. NSAIDs should be used with caution in scleroderma (p. 1942.3) because of the risk of exacerbating renal and other problems.

Adverse Effects and Treatment

The commonest adverse effects of NSAIDs are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhoea; these are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase-1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs; the selective inhibition of COX-2 improves gastrointestinal tolerance.

CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Patients with connective-tissue disorders such as SLE may be particularly susceptible to aseptic meningitis. Some patients may have visual disturbances.

Haematological adverse effects of NSAIDs include anaemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs.

Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy.

Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other cardiovascular adverse effects of NSAIDs, including those selective for COX-2 inhibition, are discussed in detail on p. 105.1.

Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis or Crohn's disease has also been reported. Long-term use of some NSAIDs has been associated with reduced female fertility that was reversible on stopping treatment.

Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

Incidence of adverse effects. The relative toxicity of NSAIDs is a subject of debate.[1] Attempts have been made to rank these drugs according to their toxicity on various body systems.[2] The toxicity of selective cyclo-oxygenase-2 (COX-2) inhibitors has also been reviewed.[3] For further details see below under individual headings.

1. Skeith KJ, *et al.* Differences in NSAID tolerability profiles: fact or fiction? *Drug Safety* 1994; **10:** 183–95.
2. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
3. Chaiamnuay S, *et al.* Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health-Syst Pharm* 2006; **63:** 1837–51.

Effects on the blood. The UK CSM has provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them NSAIDs for which there were 133 reports of agranulocytosis (45 fatal) and 187 of neutropenia (15 fatal). The most frequently implicated NSAID was phenylbutazone with 74 reports of agranulocytosis (39 fatal) and 40 of neutropenia (4 fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)

Effects on bone. Prostaglandins have been shown to play an important role in the bone-healing process and, consequently, the decrease in prostaglandin levels produced by NSAID use may impair the healing process.[1] Under experimental conditions, many NSAIDs including the cyclo-oxy-

genase-2 (COX-2) inhibitors have been shown to reduce healing.[1] However, clinical evidence of such an effect is rare.[2] There is also concern that some NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis.[3,4]

1. Harder AT, An YH. The mechanisms of the inhibitory effects of nonsteroidal anti-inflammatory drugs on bone healing: a concise review. *J Clin Pharmacol* 2003; **43:** 807–15.
2. Glassman SD. *et al*. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 1998; **23:** 834–8.
3. Rashad S, *et al*. Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **ii:** 519–22.
4. Huskisson EC, *et al*. Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. *J Rheumatol* 1995; **22:** 1941–6.

Effects on the cardiovascular system. *BLOOD PRESSURE.* A meta-analysis[1] of 50 randomised studies of the effects of NSAIDs on blood pressure in a total of 771 patients found that NSAIDs had elevated mean supine blood pressure by 5 mmHg. Piroxicam, indometacin, and ibuprofen had produced the greatest increase but the effect was only found to be statistically significant for piroxicam. Aspirin, sulindac, and flurbiprofen produced the smallest elevation in blood pressure while the effect of tiaprofenic acid, diclofenac, and naproxen was intermediate. The increase was more marked in studies in which patients had received antihypertensive therapy than in those where such treatment had not been used. NSAIDs had antagonised all antihypertensive therapy but the effect had been greater against beta blockers and vasodilators than against diuretics. An earlier meta-analysis of intervention studies had produced similar results.[2] Of the 1324 patients who had received NSAIDs, increases in mean arterial pressure were greatest in hypertensive patients who had taken either indometacin, naproxen, or piroxicam, although results were only significant for indometacin and naproxen. Sulindac and aspirin had minimal effects on mean arterial pressure.

It has been suggested that the use of NSAIDs in the elderly may increase the risk of the need for antihypertensive therapy.[3] A study[3] of 9411 patients aged 65 years or older who had just started treatment with antihypertensives found that 41% had used NSAIDs in the previous year compared with 26% of 9629 control patients not being treated with antihypertensives.

1. Johnson AG, *et al*. Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994; **121:** 289–300.
2. Pope JE, *et al*. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; **153:** 477–84.
3. Gurwitz JH, *et al*. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 1994; **272:** 781–6.

HEART FAILURE. The recent use of NSAIDs has been associated with an increased risk of developing heart failure in elderly patients.[1] A case-control study[2] found that the use of an NSAID in the previous week doubled the odds of being admitted to hospital with heart failure; this risk was increased tenfold in those with a history of heart disease. The study also suggested an association between both high-dose and long drug plasma half-life and an increased risk of heart failure.

1. Bleumink GS, *et al*. Nonsteroidal anti-inflammatory drugs and heart failure. *Drugs* 2003; **63:** 525–34.
2. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognised public health problem. *Arch Intern Med* 2000; **160:** 777–84.

THROMBOTIC EVENTS. After the introduction of the selective cyclo-oxygenase-2 (COX-2) inhibitors, concerns arose that the risk of thrombotic events such as myocardial infarction and stroke might be increased in patients treated with these selective NSAIDs, and their safety was continuously reviewed by some regulatory bodies. Subsequently, clinical study data confirmed that there was a small increased risk of these events with the COX-2 inhibitors which prompted the general world-wide withdrawal of rofecoxib (see p. 128.3) and valdecoxib (see p. 141.3). For those selective NSAIDs that remained, prescribing restrictions were imposed (for further details, see under Celecoxib, p. 37.3).

Concerns have also been raised that the increased risk of thrombotic events seen with the selective COX-2 inhibitors may also apply to the non-selective NSAIDs. After a review of data available at the time, the FDA[1] reported in April 2005 that the use of non-selective NSAIDs may potentially increase cardiovascular risk. In August 2005, the UK CSM advised that any cardiovascular risk with the non-selective NSAIDs was likely to be small and associated with continuous long-term treatment and higher doses;[2] no changes to current prescribing practices were recommended. This advice was endorsed a few months later by the EMEA in Europe.[3] However, new information has since become available and, in October 2006, the EMEA updated its advice.[4] Based on data which included the MEDAL programme[5] and reviews of several important epidemiological studies[6-8] the following points were made:

- the results from the MEDAL programme suggest that *diclofenac* (150 mg daily) has a risk of thrombotic events similar to that of etoricoxib (60 mg or 90 mg daily); however, at the time, further issues needed to be considered before this could be considered conclusive (see also below)
- based on study and epidemiological evidence, diclofenac, particularly at a high dose (150 mg daily), may be associated with an increased risk of thrombotic events
- clinical study data suggest that high-dose *ibuprofen* (2.4 g daily) is associated with an increased risk of thrombotic events; however, overall, epidemiological studies do not support an increased risk with low-dose ibuprofen (1.2 g daily or less)
- *naproxen* (1 g daily) may be associated with a lower risk for thrombotic events than the COX-2 inhibitors, but a small risk cannot be excluded; overall, there is no evidence of a cardioprotective effect
- for all *other non-selective NSAIDs* there are insufficient data to assess the thrombotic risk and consequently an increased risk cannot be excluded; a small increase in absolute risk seems most likely when used in high doses and for long-term treatment

In February 2009, the UK CHM[9] reported that results from 2 more recent epidemiological studies[10,11] support the view that an increase in thrombotic risk is associated with *all NSAIDs* and is independent of a patient's baseline cardiovascular risk factors or duration of NSAID use; however, the absolute risk for healthy users is very low.

After a Europe-wide review, the European Pharmacovigilance Risk Assessment Committee (PRAC)[12] concluded in June 2013 that the thrombotic risk of systemic diclofenac, particularly at high doses (150 mg daily) and in long-term treatment, is similar to that of the selective COX-2 inhibitors. This review included a meta-analysis[13] of more than 600 randomised studies which found that of 1000 patients allocated a COX-2 inhibitor or diclofenac for a year, 3 more had major cardiovascular events (1 of which was fatal) when compared with placebo; this finding was independent of baseline characteristics, including cardiovascular risk factors.

The American Heart Association[14] has also issued a statement about the cardiovascular effects of NSAIDs.

It has been suggested that NSAIDs may reduce the cardioprotective effect of aspirin, but see under Interactions of Aspirin, p. 27.1.

1. FDA. FDA announces series of changes to the class of marketed non-steroidal anti-inflammatory drugs (NSAIDs) (issued 7th April, 2005). Available at: http://www.fda.gov/bbs/topics/news/2005/NEW01171.html (accessed 08/11/07)
2. CSM. Cardiovascular safety of NSAIDs: review of evidence. Message from Professor G Duff, Chairman of CSM (issued August 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con1004303&RevisionSelectionMethod=Latest (accessed 08/11/07)
3. EMEA. European Medicines Agency update on non-selective NSAIDs (issued 17th October, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/29896405en.pdf (accessed 29/08/08)
4. EMEA. Opinion of the Committee for Medicinal Products for Human Use pursuant to article 5(3) of regulation (EC) no 726/2004, for non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 18th October, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/nsaids.pdf (accessed 08/11/07)
5. Cannon CP, *et al*. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368:** 1771–81.
6. Kearney PM, *et al*. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; **332:** 1302–8.
7. Hernández-Díaz S, *et al*. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; **98:** 266–74.
8. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; **296:** 1633–44.
9. MHRA/CHM. Non-steroidal anti-inflammatory drugs: cardiovascular risk. *Drug Safety Update* 2009; **2** (7): 3–4. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON038625 (accessed 24/09/09)
10. García Rodríguez LA, *et al*. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol* 2008; **52:** 1628–36.
11. Fosbøl EL, *et al*. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther* 2009; **85:** 190–7.
12. EMEA. PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors (issued 14th June, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diclofenac-containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144452.pdf (accessed 07/01/14)
13. Bhala N, *et al*. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; **382:** 769–79.
14. Antman EM, *et al*. Use of nonsteroidal antiinflammatory drugs: an update for clinicians—a scientific statement from the American Heart Association. *Circulation* 2007; **115:** 1634–42.

Effects on the CNS. A literature review[1] revealed that headache, hearing loss, and tinnitus are the most frequent CNS adverse effects in patients taking NSAIDs. Aseptic meningitis had occurred rarely in patients using NSAIDs such as naproxen, sulindac, or tolmetin, but the most common reports were in patients with SLE who were receiving ibuprofen (see also p. 69.2).

Reports of psychosis appear to be rare[1,2] and have involved indometacin or sulindac, but in some reviewers' experience it was probably under-reported and was typically seen in elderly patients given indometacin.[1]

Adverse CNS effects have also been reported with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[2]

The role of NSAIDs in the development of cognitive decline in the elderly is unclear. They have been associated with memory impairment and attention deficits in elderly patients,[1,3] especially when given in high doses;[4] however, NSAIDs have been reported to reduce the rate of cognitive decline or the risk of developing Alzheimer's disease (see Dementia, under Uses and Administration, p. 103.1).

1. Hoppmann RA, *et al*. Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151:** 1309–13.
2. Onder G, *et al*. NSAID-related psychiatric adverse events: who is at risk? *Drugs* 2004; **64:** 2619–27.
3. Saag KG, *et al*. Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. *J Rheumatol* 1995; **22:** 2142–7.
4. Karplus TM, Saag KG. Nonsteroidal anti-inflammatory drugs and cognitive function—do they have a beneficial or deleterious effect? *Drug Safety* 1998; **19:** 427–33.

Effects on electrolytes. See Effects on the Kidneys, p. 106.2.

Effects on the eyes. Ocular effects such as blurred vision occur rarely in patients taking NSAIDs. Other more serious effects on the eyes associated with NSAIDs also appear to be rare. In the USA the National Registry of Drug-Induced Ocular Side Effects analysed 144 reports they received of possible adverse optic nerve reactions associated with the use of NSAIDs.[1] Of the 24 cases of papilloedema with or without pseudotumor cerebri more than half were associated with propionic acid derivatives, but it was considered that the data indicated that, on rare occasions, most NSAIDs could cause this effect; the number of reports for individual drugs was: 7 for ibuprofen, 5 each for indometacin and naproxen, 3 for meclofenamate, and 1 each for diflunisal, ketoprofen, sulindac, and tolmetin. Almost two-thirds of the 120 cases of optic or retrobulbar neuritis were also associated with propionic acid derivatives; the number of reports for individual drugs was: ibuprofen 43, naproxen 17, indometacin 9, benoxaprofen 8, phenylbutazone 8, piroxicam 8, zomepirac 7, sulindac 6, fenoprofen 5, oxyphenbutazone 3, meclofenamate 2, tolmetin 2, diflunisal 1, and ketoprofen 1.

Ocular adverse effects have also been reported with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[2]

There have been reports of severe corneal toxicity associated with the use of some topical NSAIDs, such as diclofenac and ketorolac, in the eye (see p. 50.1).

1. Fraunfelder FT, *et al*. Possible optic nerve side effects associated with nonsteroidal anti-inflammatory drugs. *J Toxicol Cutan Ocul Toxicol* 1994; **13:** 311–16.
2. Coulter DM, *et al*. Celecoxib, rofecoxib, and acute temporary visual impairment. *BMJ* 2003; **327:** 1214–15.

Effects on fertility. Reversible infertility has been reported in women on long-term NSAIDs.[1-3] Prostaglandins are considered to be involved in the processes of ovulation and it is thought that NSAIDs may compromise ovulation via inhibition of cyclo-oxygenase-2 (COX-2). Women trying to become pregnant may need to avoid treatment with NSAIDs.

1. Mendonça LLF, *et al*. Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. *Rheumatology (Oxford)* 2000; **39:** 880–2.
2. Norman RJ. Reproductive consequences of COX-2 inhibition. *Lancet* 2001; **358:** 1287–8.
3. Stone S, *et al*. Nonsteroidal anti-inflammatory drugs and reversible female infertility: is there a link? *Drug Safety* 2002; **25:** 545–51.

Effects on the gastrointestinal tract. NSAIDs can cause clinically important damage of the gastrointestinal tract, increasing the incidence of bleeding in the upper gastrointestinal tract and of perforation, although serious complications and death are relatively infrequent. They have also been associated with damage to the distal small intestine and colon.[1-3]

The complex **mechanisms** involved are not fully understood, although it is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in gastrointestinal toxicity and that the selective COX-2 inhibitors are less gastrotoxic than the traditional NSAIDs (see below).[4-8] The gastric mucosa is damaged both by local and systemic effects of NSAIDs.[5] The local effect is pH-dependent and varies between individual drugs. The systemic effect is pH-independent, can occur with any route of administration, and is less drug specific; it is this effect that is thought to involve COX-1 inhibition.

Risk factors continue to be studied and so far the most important patient-related factors for upper gastrointestinal toxicity are old age, a history of peptic ulcers or bleeding of the gastrointestinal tract, and concomitant use of corticosteroids.[9] It has also been suggested that risk is

increased in children.[10] *Helicobacter pylori* infection exacerbates the risk of ulceration, but patients remain at increased risk even if infection is eradicated.[11] Duration of therapy is not thought to influence the risk for serious events; a cohort study[12] found that the risk of gastrointestinal bleeding or perforation with NSAIDs was constant throughout treatment, and risk quickly declines after NSAID withdrawal.[13]

Several studies[14-17] have been conducted on the **relative toxicity** of oral NSAIDs on the upper gastrointestinal tract and various rankings of these drugs have been discussed.[18-22] The UK CSM[20] examined 10 epidemiological studies for 7 oral non-aspirin NSAIDs and also examined the spontaneous reports they had received of gastrointestinal effects associated with NSAIDs. The CSM concluded that:

- azapropazone was associated with the *highest* risk of gastrointestinal reactions
- ibuprofen carried the *lowest* risk (but this may be related to dose, see below)
- piroxicam, ketoprofen, indometacin, naproxen, and diclofenac had an *intermediate* risk; it was considered that the risk for piroxicam might be higher than for the other NSAIDs with intermediate toxicity

A later update[23] by the CSM confirmed these findings.

The relative gastrointestinal toxicity of NSAIDs has also been reviewed by the EMEA[22] using data from epidemiological studies and spontaneous adverse drug reaction reports. Available evidence suggested that piroxicam and ketoprofen, particularly in high doses, were associated with the greatest risk of gastrointestinal toxicity when compared with diclofenac, etodolac, ibuprofen, indometacin, meloxicam, nabumetone, naproxen, and nimesulide. No firm conclusions were made for the other NSAIDs although there was weak evidence to suggest that the risk of toxicity was slightly higher for indometacin and naproxen than for diclofenac and ibuprofen. As a result of this review the EMEA carried out a full benefit-risk assessment for piroxicam and subsequently placed restrictions on its systemic usage (see p. 126.1).

In a systematic review[24] of controlled epidemiological studies that found a relation between NSAID use and hospital admission for gastric haemorrhage or perforation, the low risk of serious gastric toxicity with ibuprofen appeared to be attributable mainly to the low doses used clinically; higher doses of ibuprofen were associated with a similar risk to indometacin and naproxen. For reference to an association between aspirin and the most severe gastric lesions compared with other NSAIDs, see p. 24.3.

Results from controlled studies have confirmed that the **selective COX-2 inhibitors** are associated with a lower incidence of serious gastrointestinal effects, such as bleeding, perforation, and obstruction, than the traditional NSAIDs[25] (see also Celecoxib, p. 38.1 for further details). However, since the risk of such effects is inherently low in those with no history of peptic ulcer disease, the general prescribing of selective COX-2 inhibitors to all patients requiring an NSAID is questioned, particularly in the light of concerns about their cardiovascular effects (see Thrombotic Events, p. 105.1). In the UK, the use of selective COX-2 inhibitors is limited to patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID. High-risk patients include the elderly, those already receiving gastrotoxic drugs, and those with existing gastrointestinal disorders.

There has been concern that **topical** use of NSAIDs may also be associated with gastrointestinal toxicity but a case-controlled study[26] concluded that this route was not associated with significant upper gastrointestinal bleeding or perforation.

Apart from the selection of an NSAID with a lower risk for gastrointestinal toxicity, other methods used for the **prevention** or **treatment** of NSAID-associated ulceration are discussed under the treatment of peptic ulcer disease on p. 1816.2.

1. Kwo PY, Tremaine WJ. Nonsteroidal anti-inflammatory drug-induced enteropathy: case discussion and review of the literature. *Mayo Clin Proc* 1995; **70:** 55–61.
2. Gleeson MH, *et al*. Non-steroidal anti-inflammatory drugs, salicylates, and colitis. *Lancet* 1996; **347:** 904–5.
3. Evans JMM, *et al*. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997; **40:** 619–22.
4. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 521–2.
5. Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996; **101** (suppl 1A): 25S–32S.
6. Soll A. Pathogenesis of nonsteroidal anti-inflammatory drug-related upper gastrointestinal toxicity. *Am J Med* 1998; **105** (suppl 5A): 10S–16S.
7. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353:** 307–14. Correction. *ibid.;* 1440. [dose]
8. Wolfe MM, *et al*. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; **340:** 1888–99.
9. Seager JM, Hawkey CJ. ABC of the upper gastrointestinal tract: indigestion and non-steroidal anti-inflammatory drugs. *BMJ* 2001; **323:** 1236–9.
10. Mulberg AE, *et al*. Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122:** 647–9.
11. Pounder RE. Helicobacter pylori and NSAIDs—the end of the debate? *Lancet* 2002; **358:** 3–4.
12. MacDonald TM, *et al*. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315:** 1333–7.
13. Mellemkjaer L, *et al*. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. *Br J Clin Pharmacol* 2002; **53:** 173–81.
14. Kaufman DW, *et al*. Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993; **53:** 485–94.
15. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 769–72.
16. Langman MJS, *et al*. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 1075–8.
17. Lewis SC, *et al*. Dose–response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; **54:** 320–6.
18. Bateman DN. NSAIDs: time to re-evaluate gut toxicity. *Lancet* 1994; **343:** 1051–2.
19. Smith CC, *et al*. NSAIDs and gut toxicity. *Lancet* 1994; **344:** 56–7.
20. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
21. Laporte J-R, *et al*. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug Safety* 2004; **27:** 411–20.
22. EMEA. Public CHMP assessment report of medicinal products containing non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 7th November, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf (accessed 08/11/07)
23. CSM/MCA. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and gastrointestinal (GI) safety. *Current Problems* 2002; **28:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
24. Henry D, *et al*. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312:** 1563–6.
25. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345:** 433–42.
26. Evans JMM, *et al*. Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995; **311:** 22–6.

Effects on the kidneys. NSAIDs can produce renal disorders on systemic or topical use,[1] some of which are due to their inhibition of prostaglandin synthesis.[2,3] In the presence of renal vasoconstriction the vasodilator action of prostaglandins increases renal blood flow and thereby helps to maintain renal function.[4,5] Patients whose renal function is being maintained by prostaglandins are therefore at risk from NSAIDs. Such patients include those with impaired circulation, the elderly, those on diuretics, and those with heart failure or renal vascular disease.[2,4] Other risk factors for renal impairment with NSAIDs include dehydration, cirrhosis, surgery, sepsis,[6] and a history of gout or hyperuricaemia.[6,7] The half-life of an NSAID may be a more important determinant of the risk of developing functional renal impairment than the ingested dose.[7] Evidence of renal toxicity due to cyclo-oxygenase-2 (COX-2) selective inhibitors is less extensive; however, such NSAIDS appear to have effects on renal function similar to those of the non-selective NSAIDs.[8,9] A large pharmacoepidemiological analysis[10] of elderly patients taking non-selective NSAIDs or selective COX-2 inhibitors found that about 1 in 200 patients aged over 65 years developed acute kidney injury within 45 days of starting therapy. Most NSAIDs were found to have a similar risk when compared with celecoxib; however, rofecoxib, ibuprofen, and indometacin (listed in increasing order of risk) all showed a higher risk.

ACE inhibitors and angiotensin receptor antagonists can also produce renal impairment and combined use with NSAIDs should be undertaken with great care.[11,12] The Australian Adverse Drug Reactions Advisory Committee[11] stated in August 2003 that over 50% of cases of renal failure reported to the committee were associated with use of NSAIDs, ACE inhibitors, or diuretics (alone or together); where all these were taken together the fatality rate for reported cases of renal failure was 10%.

Prostaglandin inhibition may also lead to salt and water retention particularly when there is pre-existing hypertension or sodium depletion.[4] NSAIDs, therefore, tend to counteract the action of diuretics and antihypertensives.[2,4] There have been isolated reports of severe hyponatraemia and other symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion in patients taking NSAIDs.[13,14]

Potassium homoeostasis is less dependent on prostaglandins and hyperkalaemia occurs infrequently with NSAIDs.[3] It is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics.[3] Indometacin appears to be the main NSAID implicated.

NSAIDs may cause acute interstitial nephritis, perhaps involving an allergic response,[2,3,15] and it may progress to interstitial fibrosis or papillary necrosis.[3,16]

Analgesic abuse or prolonged excessive use can produce nephropathy, a condition characterised by renal papillary necrosis and chronic interstitial nephritis, and, eventually, renal failure.[17] Phenacetin, a para-aminophenol derivative, has long been recognised as being one of the main drugs responsible for analgesic nephropathy,[18,19] but nephropathy has also been associated with the long-term use of NSAIDs and paracetamol without phenacetin.[20]

1. O'Callaghan CA, *et al*. Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.
2. Kendall MJ, Horton RC. Clinical pharmacology and therapeutics. *Postgrad Med J* 1990; **66:** 166–85.
3. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol* 1991; **31:** 588–98.
4. Harris K. The role of prostaglandins in the control of renal function. *Br J Anaesth* 1992; **69;** 233–5.
5. Kenny GNC. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; **44** (suppl 5): 31–7.
6. MacDonald TM. Selected side-effects: 14. non-steroidal anti-inflammatory drugs and renal damage. *Prescribers' J* 1994; **34:** 77–80.
7. Henry D, *et al*. Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects: results of a case-control study. *Br J Clin Pharmacol* 1997; **44:** 85–90.
8. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
9. Noroian G, Clive D. Cyclo-oxygenase-2 inhibitors and the kidney: a case for caution. *Drug Safety* 2002; **25:** 165–72.
10. Winkelmayer WC, *et al*. Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. *Am J Med* 2008; **121:** 1092–8.
11. Adverse Drug Reactions Advisory Committee (ADRAC). ACE inhibitor, diuretic and NSAID: a dangerous combination. *Aust Adverse Drug React Bull* 2003; **22:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 08/11/07)
12. Loboz KK, Shenfield GM. Drug combinations and impaired renal function—the 'triple whammy'. *Br J Clin Pharmacol* 2005; **59:** 239–43.
13. Petersson I, *et al*. Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
14. Cheung NT, *et al*. Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.
15. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism. *Br J Clin Pharmacol* 1999; **47:** 203–10.
16. Sandler DP, *et al*. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med* 1991; **115:** 165–72.
17. De Broe ME, Elseviers MM. Analgesic nephropathy. *N Engl J Med* 1998; **338:** 446–52.
18. Sandler DP, *et al*. Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
19. Dubach UC, *et al*. An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
20. Perneger TV, *et al*. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.

Effects on the liver. A retrospective study involving over 220 000 adults who were either using, or had used, NSAIDs identified a small excess risk of serious, acute non-infectious liver injury; in current users there was a twofold increase in risk and there was a predominance of the cholestatic type of liver injury among such patients. Nonetheless, admissions to hospital for liver injury had been rare.[1] In a review[2] of cohort and case-control studies describing an association between NSAIDs and liver disease, the strongest evidence emerged for sulindac. There were also a significant number of reports of hepatotoxicity on rechallenge with diclofenac. Evidence of hepatotoxicity for other NSAIDs was weak, although the risk appeared to be high when they were used with other hepatotoxic drugs. However, the overall incidence of liver disease with NSAIDs was very low.

A later review has also concluded that NSAID-induced hepatotoxicity is an uncommon event.[3] Nevertheless, an increased risk of hepatotoxicity has been associated with the selective cyclo-oxygenase-2 (COX-2) inhibitor lumiracoxib which led to its subsequent withdrawal in many countries (see p. 84.2). For similar reasons, nimesulide has been withdrawn in some countries and its use is limited in others (see p. 101.3).

1. García Rodríguez LA, *et al*. The role of non-steroidal anti-inflammatory drugs in acute liver injury. *BMJ* 1992; **305:** 865–8. Correction. *ibid.;* 920.
2. Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. *Drug Safety* 1996; **15:** 64–71.
3. O'Connor N, *et al*. Hepatocellular damage from non-steroidal anti-inflammatory drugs. *Q J Med* 2003; **96:** 787–91.

Effects on the lungs. Adverse pulmonary effects such as pneumonitis, alveolitis, pulmonary infiltrates, and pulmonary fibrosis, often suggestive of an allergic or immune reaction, have been reported with several NSAIDs. For references, see under individual monographs.

Effects on the pancreas. A review[1] of drug-induced pancreatitis considered that sulindac was amongst the drugs for which a definite association with pancreatitis had been established. There had been isolated reports of pancreatitis with ketoprofen, mefenamic acid, and piroxicam but any association was considered to be questionable. A more recent population-based, case-controlled study found a substantial variation in the risk of pancreatitis between individual NSAIDs.[2] The increase in risk was highest for diclofenac and ketoprofen (adjusted odds ratios of 5.0 and 4.8, respectively), with indometacin and ibuprofen showing smaller but nonetheless significant increases (odds ratios of 3.6 and 1.5, respectively). Of the other NSAIDs studied (celecoxib, etodolac, naproxen, and rofecoxib), all

showed a small but non-significant increase in risk of pancreatitis in current NSAID users.

For further references see under individual monographs.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.
2. Sørensen HT, *et al*. Newer cyclo-oxygenase-2 selective inhibitors, other non-steroidal anti-inflammatory drugs and the risk of acute pancreatitis. *Aliment Pharmacol Ther* 2006; **24:** 111–16.

Effects on the skin. The diverse cutaneous reactions to NSAIDs including those selective for cyclo-oxygenase-2 (COX-2) inhibition have been reviewed.[1-3]

Of 250 children attending a rheumatology clinic 34 (13.6%) were found to have 4 or more facial scars of unknown origin.[4] This number of scars was found in 22.2% of the 116 children who had received naproxen and in 9.2% of the 87 who had received other NSAIDs. Children affected were more likely to have light skin and blue or green eyes. It was unknown whether this was a form of phototoxic reaction but pseudoporphyria-like eruptions associated with NSAIDs, and naproxen in particular (see p. 99.2), have been reported.[5,6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see p. 126.2).

See also Hypersensitivity, below.

1. Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. *J Am Acad Dermatol* 1985; **12:** 866–76.
2. La Grenade L, *et al*. Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Safety* 2005; **28:** 917–24.
3. Layton D, *et al*. Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. *Drug Safety* 2006; **29:** 687–96.
4. Wallace CA, *et al*. Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs. *J Pediatr* 1994; **125:** 819–22.
5. Checketts SR, *et al*. Nonsteroidal anti-inflammatory-induced pseudoporphyria: is there an alternative drug? *Cutis* 1999; **63:** 223–5.
6. Al-Khenaizan S, *et al*. Pseudoporphyria induced by propionic acid derivatives. *J Cutan Med Surg* 1999; **3:** 162–6.

Hypersensitivity. NSAIDs have produced various hypersensitivity reactions in susceptible individuals; the most common include skin rashes, urticaria, rhinitis, angioedema, bronchoconstriction, and anaphylactic shock. Hypersensitivity to NSAIDs appears to occur more frequently in patients with asthma or allergic disorders but other risk factors have been identified (for further details, see under Aspirin, p. 25.2). The occurrence of aspirin sensitivity in patients with asthma and nasal polyps has been referred to as the 'aspirin triad'. There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. For references to hypersensitivity reactions associated with NSAIDs, see under individual monographs. See also Effects on the Skin (p. 79.2) for a report suggesting that ketoprofen is more allergenic than other topical NSAIDs.

The selective cyclo-oxygenase-2 (COX-2) inhibitors contain the sulfa moiety ($-SO_2NH_2$) and the licensed product information for some products states that their use is contra-indicated in patients with a sulfonamide (sulfa) allergy. For further information on cross-reactivity between sulfa-containing drugs see Hypersensitivity, under Sulfamethoxazole, p. 367.3.

Overdosage. In general, symptoms of NSAID poisoning are mild, and usually include nausea and vomiting, epigastric pain, tinnitus, headache, drowsiness, blurred vision, and dizziness. Gastrointestinal bleeding may also occur. There have been isolated case reports of more serious toxicity, including seizures, hypotension, apnoea, coma, and renal failure, although usually after ingestion of substantial quantities. Exacerbation of asthma may occur in asthmatics. Seizures are a particular problem with mefenamic acid overdosage.

Treatment of NSAID overdosage is entirely supportive. The benefit of gastric decontamination is uncertain although activated charcoal may be of benefit within 1 hour of ingestion of a potentially toxic amount. Multiple doses of activated charcoal may be useful in enhancing elimination of NSAIDs with long half-lives such as piroxicam and sulindac. Forced diuresis, haemodialysis, or haemoperfusion are unlikely to be of benefit for NSAID overdosage, although haemodialysis may be required if oliguric renal failure develops.

Precautions

All NSAIDs are contra-indicated in patients with active peptic ulceration or gastrointestinal bleeding; in addition, the non-selective NSAIDs should be used with caution, if at all, in patients with a history of such disorders. To reduce the risk of gastrointestinal effects, NSAIDs may be taken with or after food or milk. Histamine H_2-antagonists, proton pump inhibitors such as omeprazole, or misoprostol may be used for a similar purpose in high-risk patients taking non-selective NSAIDs (see Peptic Ulcer Disease, p. 1816.2). The use of proton pump inhibitors with selective inhibitors of cyclo-oxygenase-2 (COX-2) may be appropriate for those with a history of bleeding or with several risk factors for ulceration. However, food, milk, and such measures may reduce the rate and extent of drug absorption. The UK CSM recommends that NSAIDs associated with the lowest risk of gastrointestinal toxicity (see Effects on the Gastrointestinal Tract, under Adverse Effects, p. 105.3) should be tried first in the lowest recommended dose, and not more than one oral NSAID should be used at a time; selective COX-2 inhibitors should be reserved for patients at highest risk of ulcer, perforation, or bleeding, and after assessment of cardiovascular risk. NSAIDs should be used with caution in patients with Crohn's disease or ulcerative colitis as these conditions may be exacerbated.

All NSAIDs are contra-indicated in severe heart failure. Furthermore, diclofenac and selective COX-2 inhibitors should not be used in patients with moderate to severe heart failure, ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease; these NSAIDs should also be used with caution in patients with hypertension, left ventricular dysfunction, oedema, or a history of cardiac failure, and in those with other risk factors for developing cardiovascular events. Other, non-selective NSAIDs should be used with caution in uncontrolled hypertension, heart failure, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, and when used long term in patients with risk factors for cardiovascular events.

NSAIDs should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked (for the suggestion that they should not be used in children with varicella see below). They should also be used with caution in patients with asthma or allergic disorders. NSAIDs (including topical NSAIDs) are contra-indicated in patients with a history of hypersensitivity reactions to such drugs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

Other general precautions to be observed include use in patients with haemorrhagic disorders, connective-tissue disorders, or impaired renal or hepatic function. Patients undergoing therapy with some NSAIDs may need to be monitored for the development of blood, kidney, liver, or eye disorders. NSAIDs should be used with caution in the elderly and may need to be given in reduced doses.

Some NSAIDs can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Further details concerning the precautions of the individual NSAIDs may be found under their respective monographs.

Pregnancy. Most licensed product information recommends avoidance of NSAIDs during pregnancy, unless the proposed benefit outweighs the risks, but in many cases published data on use of the drugs in pregnancy are scanty or absent, making an informed decision difficult. Use of NSAIDs during pregnancy may delay the onset of labour and increase its duration.

Use of NSAIDs during the third trimester of pregnancy may result in the *premature closure of fetal ductus arteriosus*. A recent meta-analysis[1] suggested that the short-term use of NSAIDs was associated with a fifteenfold increase in the risk of premature closure when compared with either placebo or other non-NSAIDs. There were insufficient data to predict the outcome of long-term NSAID treatment in late pregnancy; however, it seemed likely that the risk of premature closure would be even greater with such treatment.

Results from a case-control interview study[2] suggested that prenatal ingestion of aspirin or other NSAIDs might be implicated in *persistent pulmonary hypertension* of the newborn. The authors suggested that these drugs may be responsible for gestational structural or functional alterations of the pulmonary vasculature. However, the primary cause might also have been the underlying disorder for which the NSAIDs or aspirin were ingested. They were unable to pinpoint in which trimester the drugs might have their proposed action. Another study[3] has found that persistent pulmonary hypertension of the newborn is significantly associated with *in-utero* NSAID exposure, particularly to aspirin, ibuprofen, and naproxen. Fetal exposure to an NSAID was confirmed by meconium analysis.

More recently, the findings of a prospective cohort study have suggested that intrauterine exposure to simple analgesics such as aspirin, ibuprofen, and paracetamol may be a risk factor for developing congenital *cryptorchidism*.[4] In 491 Danish mothers directly questioned about analgesic use during pregnancy, there was a non-significant increase in the prevalence of cryptorchidism in boys whose mothers had used simple analgesics during pregnancy; the increase was significant for those mothers reporting the use of more than one analgesic and for those who had taken analgesics for more than 2 weeks. Use during the second trimester also significantly increased the risk. Similar results were noted from a self-administered questionnaire in 834 Danish women; however, in a group of 1463 Finnish women given the same questionnaire, there was generally no association between analgesic use and cryptorchidism. The authors did note that analgesic use appeared to have been under-reported in the questionnaire data.

The risk of *miscarriage* may be increased with NSAID use;[5,6] however, this observation remains to be confirmed. One study[5] also found no association between NSAID use and congenital abnormalities, low birth weight, or preterm birth.

1. Koren G, *et al*. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006; **40:** 824–9.
2. Van Marter LJ, *et al*. Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. *Pediatrics* 1996; **97:** 658–63.
3. Alano MA, *et al*. Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* 2001; **107:** 519–23.
4. Kristensen DM, *et al*. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum Reprod* 2010. Available at: http://humrep.oxfordjournals.org/content/early/2010/11/08/humrep.deq323.full.pdf+html (accessed 16/11/10)
5. Nielsen GL, *et al*. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001; **322:** 266–70.
6. Li D-K, *et al*. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003; **327:** 368–71.

Renal impairment. The *BNF* recommends that NSAIDs in general should be avoided if possible, or given at the lowest effective dose for the shortest possible duration to patients with renal impairment and that renal function, and sodium and water retention, should be carefully monitored.

See also under individual monographs.

Thyroid function tests. References[1,2] to the interference with thyroid function tests by some NSAIDs.

1. Bishnoi A, *et al*. Effect of commonly prescribed nonsteroidal anti-inflammatory drugs on thyroid hormone measurements. *Am J Med* 1994; **96:** 235–8.
2. Samuels MH, *et al*. Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; **88:** 5710–16.

Varicella. The French regulatory authorities noted in July 2004 that after the report of 3 cases of septic shock, 1 fatal, in children treated with NSAIDs for fever and pain, pharmacovigilance studies had discovered several other cases of severe complications relating to infection of the skin lesions of chickenpox in NSAID-treated children.[1] Although these, and a few reports in the literature[2,3] could not establish a causal relation, it was considered prudent to avoid the use of NSAIDs in children with chickenpox, and licensed product information for the relevant drugs was to be modified appropriately.[1] More recently, a nested case-control study[4] of nearly 250000 patients with chickenpox or shingles in the UK General Practice Research Database found an increased risk of severe skin and soft tissue complications associated with the use of NSAIDs, mostly in children with chickenpox.

1. Agence Française de Sécurité Sanitaire des Produits de Santé. L'utilisation d'anti-inflammatoires nonstéroïdiens (AINS), dans le traitement de la fièvre et/ou de la douleur, n'est pas recommandée chez l'enfant atteint de varicelle (issued 15th July, 2004). Available at: http://www.agmed.sante.gouv.fr/htm/10/filltrpsc/lp040701.htm (accessed 08/11/07)
2. Zerr DM, *et al*. A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999; **103:** 783–90.
3. Lesko SM, *et al*. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. *Pediatrics* 2001; **107:** 1108–15.
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Interactions

Interactions involving NSAIDs include enhancement of the effects of oral anticoagulants (especially by azapropazone and phenylbutazone) and increased plasma concentrations of lithium, methotrexate, and cardiac glycosides. The risk of nephrotoxicity may be increased if given with ACE inhibitors, ciclosporin, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and some diuretics, including potassium-sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced. Convulsions may occur due to an interaction with quinolones. NSAIDs may increase the effects of phenytoin and sulfonylurea antidiabetics.

Use of more than one NSAID together (including aspirin) should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids, the SSRIs, the SNRI venlafaxine, the antiplatelets clopidogrel and ticlopidine, iloprost, erlotinib, sibutramine, or, possibly, alcohol, bisphosphonates, or

pentoxifylline. There may be an increased risk of haematotoxicity if zidovudine is used with NSAIDs. Ritonavir may increase the plasma concentrations of NSAIDs. Licensed product information for mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by NSAIDs or aspirin may alter the efficacy of mifepristone. There have been occasional reports of increased adverse effects when NSAIDs were given with misoprostol although such combinations have sometimes been used to *decrease* the gastrointestinal toxicity of NSAIDs.

Further details concerning the interactions of the individual NSAIDs may be found under their respective monographs.

References.
1. Brouwers JRBJ, de Smet PAGM. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1994; **27:** 462–85.

Antihypertensives. For reference to the relative effects of NSAIDs in antagonising different types of antihypertensive drugs, see Effects on the Cardiovascular System and Effects on the Kidneys under Adverse Effects, p. 105.1 and p. 106.2, respectively.

Aspirin. It has been suggested that NSAIDS such as ibuprofen may reduce the cardioprotective effect of aspirin but see under Interactions of Aspirin, p. 27.1.

Pharmacokinetics

Details of the pharmacokinetics of individual NSAIDs may be found under their respective monographs.

General reviews.
1. Woodhouse KW, Wynne H. The pharmacokinetics of non-steroidal anti-inflammatory drugs in the elderly. *Clin Pharmacokinet* 1987; **12:** 111–22.
2. Walson PD, Mortensen ME. Pharmacokinetics of common analgesics, anti-inflammatories and antipyretics in children. *Clin Pharmacokinet* 1989; **17** (suppl 1): 116–37.
3. Simkin PA, *et al*. Articular pharmacokinetics of protein-bound antirheumatic agents. *Clin Pharmacokinet* 1993; **25:** 342–50.
4. Lapicque F, *et al*. Protein binding and stereoselectivity of nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1993; **25:** 115–25.
5. Day RO, *et al*. Pharmacokinetics of nonsteroidal anti-inflammatory drugs in synovial fluid. *Clin Pharmacokinet* 1999; **36:** 191–210.

Opioid Analgesics

Analgésicos opioides ᴜ opiáceos; Analgésiques Opioïdes; Opioid-analgetika; Опиоидные Аналгетики.

Uses and Administration

Opioid analgesics possess some of the properties of naturally occurring or **endogenous opioid peptides**. Endogenous opioid peptides are widely distributed in the CNS and are also found in other parts of the body. They appear to function as neurotransmitters, modulators of neurotransmission, or neurohormones. Their presence in the hypothalamus suggests a role in the regulation of endocrine function. Opioids have been shown to stimulate the release of some pituitary hormones, including prolactin and growth hormone, and to inhibit the release of others, including corticotropin.

Endogenous peptides include the enkephalins, endorphins, and dynorphins; their polypeptide precursors may also be precursors for non-opioid peptides. Pro-enkephalin is the precursor of met- and leu-enkephalin; pro-opiomelanocortin is the precursor of beta-endorphin, beta-lipotrophin, melanocyte-stimulating hormone, and corticotropin; and prodynorphin is the precursor of dynorphins and neoendorphins.

Pharmacologically the opioid analgesics are broadly similar; qualitative and quantitative differences may be dependent on their interaction with **opioid receptors**. There are several types of opioid receptor and they are distributed in distinct patterns through the central and peripheral nervous systems. The three main types in the CNS were originally designated μ (mu), κ (kappa), and δ (delta) although they have been reclassified as OP_3, OP_2, and OP_1, respectively. Activities attributed to the stimulation of these receptors have been as follows:

- μ —analgesia (mainly at supraspinal sites), respiratory depression, miosis, reduced gastrointestinal motility, and euphoria; μ_1 (supraspinal analgesia) and μ_2 (respiratory depression and gastrointestinal activity) subtypes have been postulated
- κ —analgesia (mainly in the spinal cord); less intense miosis and respiratory depression, dysphoria and psychotomimetic effects
- δ —less certain in man, but probably analgesia; selective for enkephalins
- Other receptors include σ (sigma) and ε (epsilon) receptors. The psychotomimetic effects of agonist-antagonists such as pentazocine that are poorly antagonised by naloxone have been thought by some to be mediated by σ receptors

Opioids act at one or more of these receptors as full or partial agonists, or as antagonists. Morphine and similar opioid agonists (sometimes called μ agonists) are considered to act mainly at μ and perhaps at κ and δ receptors. Opioid agonist-antagonists such as pentazocine appear to act as κ agonists and μ antagonists whereas buprenorphine is a partial agonist at μ receptors with some antagonist activity at κ receptors. The opioid antagonist naloxone acts at μ, κ, and δ receptors.

In addition to differing affinities for particular receptors the degree of activation once bound also differs. The full agonist morphine produces maximum activation at the μ receptor and its effects increase with dose, whereas partial agonists and agonist-antagonists may show a 'ceiling effect' in that above a certain level their effects do not increase proportionately with dose.

Other differences between opioid analgesics may relate to their lipid solubility and pharmacokinetics; speed of onset and duration of action may influence the choice of analgesic.

Opioid analgesics have traditionally been classified as weak or strong opioids but use of such terms has the potential to mislead or lead to suboptimal care. An alternative classification is that used in the WHO three-step analgesic ladder (see Cancer Pain, p. 7.1). In this system opioids are divided into those that are used for **mild to moderate pain** and those that are used for **moderate to severe pain**. Examples of opioids in the first group include codeine, dextropropoxyphene, and dihydrocodeine; such opioids are distinguished by the existence of a ceiling effect and are often used with non-opioid analgesics. The principal opioid for the treatment of moderate to severe pain is morphine. Others include diamorphine, fentanyl, methadone, and pethidine.

In addition to the relief of pain, opioids are used in **anaesthesia** for premedication, induction, or maintenance; however, pre-operative use is generally limited to patients who require control of existing pain. In balanced anaesthesia they are used with an anaesthetic and a neuromuscular blocker. When used with an antipsychotic they can produce a state of mild sedation with analgesia called neuroleptanalgesia.

Some opioids are used for analgesia, sedation, and suppression of respiration in the management of mechanically ventilated patients under **intensive care** (p. 1033.1).

Opioids such as codeine, hydrocodone, and hydromorphone are used for the suppression of **cough**; for intractable cough in terminal illness morphine may be used.

Opioids may relieve some forms of **dyspnoea**; morphine and diamorphine are probably the most commonly used in the UK, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried.

Methadone and buprenorphine are used in the treatment of opioid **dependence** (see p. 109.2).

References.
1. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs* 1996; **51:** 713–37.
2. Upton RN, *et al*. Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin Pharmacokinet* 1997; **33:** 225–44.
3. Walsh D. Advances in opioid therapy and formulations. *Support Care Cancer* 2005; **13:** 138–44.
4. Hanks GW, Reid C. Contribution to variability in response to opioids. *Support Care Cancer* 2005; **13:** 145–52.
5. Smith HS. Opioid metabolism. *Mayo Clin Proc* 2009; **84:** 613–24.

Action. Some references[1-6] to opioid receptors.

1. Pleuvry BJ. Opioid receptors and their ligands: natural and unnatural. *Br J Anaesth* 1991; **66:** 370–80.
2. Pleuvry BJ. Opioid receptors and awareness of the Greek alphabet. *Br J Hosp Med* 1992; **48:** 678–81.
3. Atcheson R, Lambert DG. Update on opioid receptors. *Br J Anaesth* 1994; **73:** 132–4.
4. Dhawan BN, *et al*. International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol Rev* 1996; **48:** 567–86.
5. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain* 2002; **18** (4 suppl): S3–S13.
6. Gourlay GK. Advances in opioid pharmacology. *Support Care Cancer* 2005; **13:** 153–9.

Administration in children. See under Precautions, p. 111.1.

Administration in the elderly. See under Precautions, p. 111.1.

Anaesthesia. Opioid analgesics have been given intravenously as supplements during general anaesthesia with inhalational or intravenous drugs. They have also been widely used as premedication before surgery to reduce anxiety, for smooth induction of anaesthesia, to reduce overall anaesthetic requirements, and to provide postoperative pain relief. Such use of opioids is now rare and is restricted to patients already in pain or to those who will be in pain before induction of anaesthesia. Very high doses of morphine have been infused intravenously to produce anaesthesia for cardiac surgery, but shorter acting drugs such as fentanyl and related opioids are generally used now; some may prefer agonist-antagonist opioids. Sedation and respiratory depression may be prolonged necessitating assisted ventilation; reversal of these effects can be achieved by opioid antagonists such as naloxone. For a discussion of the various drugs used to achieve and maintain conditions suitable for surgery, including the use of opioids in the induction and maintenance of anaesthesia, see p. 1899.1. Opioid analgesics, most commonly fentanyl, have been used with an antipsychotic to induce a state known as neuroleptanalgesia in which the patient is calm and indifferent to the surroundings yet is responsive to commands. For a brief discussion of neuroleptanalgesia and similar anaesthetic techniques, see p. 1899.3.

POSTOPERATIVE SHIVERING. Pethidine appears to be effective in the treatment of postoperative shivering (p. 1900.2) but not all opioids are necessarily effective.

Cough. Opioids are used to suppress cough (p. 1651.2). Pholcodine (p. 1675.1) and dextromethorphan (p. 1660.1), which lack classical analgesic activity and have fewer adverse effects, are the most commonly used opioids. Of the analgesic opioids, codeine is the most widely used as a cough suppressant. However, these opioids are seldom sufficiently potent to be effective in severe cough. Morphine and diamorphine are used for the relief of intractable cough in terminal illness, although morphine is now preferred. Methadone has also been used but should be avoided as it has a long duration of action and tends to accumulate.

Cough suppressants containing pholcodine or similar opioids (such as codeine) are generally not recommended for use in children, and should be avoided in those under 6 years of age.

Diarrhoea. Oral rehydration therapy, which is the treatment of choice for acute diarrhoea (p. 1808.2), prevents dehydration, but it does not necessarily shorten the duration of the diarrhoea. Preparations containing codeine, morphine, or other opioids have therefore been used for their antimotility action as adjuncts in the management of acute diarrhoea. However, the WHO considers that such antidiarrhoeal drug therapy is of limited value, and should never be given to children. Furthermore opioids should not be used in conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in diarrhoeal conditions such as severe ulcerative colitis or antibiotic-associated colitis.

Dyspnoea. Dyspnoea (a subjective feeling of abnormally uncomfortable, difficult, or laboured breathing) is associated with diseases that interfere with oxygenation of the blood. The course of dyspnoea should be established since it is often best relieved by treatment of the underlying disorder (the treatment of dyspnoea associated with asthma and chronic obstructive pulmonary disease (COPD) is discussed on p. 1195.2 and p. 1199.1, respectively). Where this is impossible or ineffective, symptomatic management is required.

Oxygen may reduce dyspnoea in some patients even if dyspnoea is not related to hypoxia. A flow of air directed across the face by a fan can also be effective. Despite the hazards of using benzodiazepines in patients with any form of respiratory depression or pulmonary insufficiency (see under Precautions of Diazepam, p. 1068.1), drugs such as diazepam, lorazepam, or midazolam may be helpful in patients with advanced cancer who have rapid shallow respiration, especially when this is associated with anxiety.[1] Levomepromazine is occasionally used as an alternative.

Opioids may relieve some forms of dyspnoea,[2-4] such as those due to acute left ventricular failure, pulmonary oedema, and malignant chest disease. Guidelines[5,6] (some based on the findings of systematic reviews[7]) and expert consensus statements[8] issued for the management of dyspnoea in palliative care recommend that opioids should be considered in patients with severe and unrelieved dyspnoea. Doses tend to be lower and increments smaller than those used for pain relief.[2] The use of opioids is generally not advised, or only with extreme caution, in patients with obstructive airways disease whose dyspnoea may be relieved by other means. However, they may be useful in patients with advanced COPD whose dyspnoea is resistant to conventional management.[9] Morphine and diamorphine are commonly used opioids for dyspnoea, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried. It is unclear if all opioids are equally effective.[4]

Nebulised morphine, hydromorphone, or fentanyl have been tried for the management of dyspnoea, and there are anecdotal reports of benefit, especially in palliative care, but evidence from controlled studies to date does not support such use.[2,3,5,10-13] See also under Morphine, p. 94.3.

In patients with advanced cancer and intractable dyspnoea unresponsive to the above measures, chlorpromazine may be useful to relieve air hunger and sedate dying patients who have unrelieved distress;[1] midazolam may be used as an alternative. Promethazine has also been used.

High doses of a corticosteroid such as dexamethasone may help to relieve dyspnoea in patients with airways obstruction due to a tumour by reducing oedema around the tumour.

1. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.
2. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.
3. Jennings AL, *et al*. Opioids for the palliation of breathlessness in terminal illness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 26/06/08).
4. Kvale PA, *et al*. American College of Chest Physicians. Lung cancer: palliative care. *Chest* 2003; **123** (suppl): 284S–311S. Also available at: http://www.chestjournal.org/cgi/reprint/123/1_suppl/284S.pdf (accessed 26/06/08)
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7. Lorenz KA, *et al*. Evidence for improving palliative care at the end of life: a systematic review. *Ann InternMed* 2008; **148:** 147–59. Correction. *ibid*. 2009; **151:** 674.
8. Mahler DA, *et al*. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest* 2010; **137:** 674–91.
9. Rocker G, *et al*. Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. *Thorax* 2009; **64:** 910–15.
10. Chandler S. Nebulized opioids to treat dyspnea. *Am J Hosp Palliat Care* 1999; **16:** 418–22.
11. Foral PA, *et al*. Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
12. Brown SJ, *et al*. Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.
13. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Pain. Opioid analgesics are used for the relief of acute and chronic pain (see Choice of Analgesic, p. 4.2). Not every type of pain responds; neuropathic pain, for example, may not be alleviated by opioid therapy. For further discussion of specific pain states and the role of opioid analgesics in their treatment see p. 6.3 onwards.

There has also been interest in the local analgesic effects of opioids themselves.[1,2]

The use of opioid analgesics in opioid-dependent patients receiving maintenance treatment with an opioid is the subject of much debate; however, some consider such use to be appropriate in the management of acute pain in these patients and recommendations have been issued.[3]

1. Thompson DF, Pierce DR. Local analgesia with opioid drugs. *Ann Pharmacother* 1995; **29:** 189–90.
2. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; **332:** 1685–90.
3. Alford DP, *et al*. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006; **144:** 127–34.

HEADACHE. Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine (p. 670.3) or tension-type headache (p. 671.3), but are best avoided, especially in patients who have frequent attacks.

Restless legs syndrome. Some opioids may be beneficial in the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2), although evidence is scanty.

Sedation. In addition to their analgesic action opioids have been used for their sedative properties. Mention of this use of opioids can be found in the discussions of anaesthesia (p. 1899.1), endoscopy (p. 1032.3), and intensive care (p. 1033.1).

Tetanus. Opioid analgesics can be used to provide analgesia and additional sedation in patients undergoing treatment for tetanus (see p. 211.2 and p. 2029.2). Opioids such as fentanyl, morphine, and sufentanil have also been given to control the sympathetic overactivity in such patients.[1-3]

1. Rocke DA, *et al*. Morphine in tetanus—the management of sympathetic nervous system overactivity. *S Afr Med J* 1986; **70:** 666–8.
2. Moughabghab AV, *et al*. Management of autonomic dysfunction in severe tetanus: the use of fentanyl. *Can J Anaesth* 1995; **42:** 955.
3. Bhagwanjee S, *et al*. Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: experience with 11 patients. *Crit Care Med* 1999; **27:** 1721–5.

Dependence and Withdrawal

Repeated use of opioids is associated with the development of psychological and physical dependence. Although this is less of a problem with legitimate therapeutic use, dependence may develop rapidly when opioids are regularly abused for their euphoriant effects. Drug dependence of the opioid type is characterised by an overwhelming need to keep taking the drug (or one with similar properties), by a physical requirement for the drug in order to avoid withdrawal symptoms, and by a tendency to increase the dose owing to the development of tolerance.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms may also follow the use of an opioid antagonist such as naloxone or a mixed agonist and antagonist such as pentazocine in opioid-dependent persons. Neonatal abstinence syndrome may occur in the offspring of opioid-dependent mothers and these infants can suffer withdrawal symptoms at birth.

Opioid analgesics can be classified according to the receptors at which they act (see Uses and Administration, p. 108.1) and withdrawal syndromes are characteristic for a receptor type. Cross-tolerance and cross-dependence can be expected between opioids acting at the same receptors. Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than those associated with κ-receptor agonists. Onset and duration of withdrawal symptoms also vary according to the duration of action of the specific drug. With morphine and diamorphine *withdrawal symptoms* usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside; they develop more slowly with methadone. Withdrawal symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Some physiological values may not return to normal for several months after the acute withdrawal syndrome.

Withdrawal symptoms may be terminated by a suitable dose of the original or a related opioid. Tolerance diminishes rapidly after withdrawal so that a previously tolerated dose may prove fatal.

For a discussion of the treatment of opioid dependence and neonatal abstinence syndrome, see below and p. 110.1, respectively.

Review.

1. Van Ree JM, *et al*. Opioids, reward and addiction: an encounter of biology, psychology, and medicine. *Pharmacol Rev* 1999; **51:** 341–96.

Diagnosis. Naloxone (p. 1564.2) and other opioid antagonists have been used to diagnose opioid dependence.

Treatment of opioid dependence. The treatment of opioid dependence has been the subject of many reviews and discussions.[1-10]

Planned withdrawal (**detoxification**) may be effected slowly or rapidly. The usual method in many countries is to replace the drug of dependence with *methadone* (an opioid agonist) given as a liquid oral preparation, and then gradually withdraw the methadone if possible. Methadone is suitable for withdrawal therapy because it can be given orally and its long half-life allows once daily use. Oral *diamorphine* has been used similarly to methadone; reefers containing diamorphine have also been used in some centres. *Dihydrocodeine* tablets have been used successfully. The partial opioid agonist *buprenorphine*, given sublingually, is another alternative to methadone in the treatment of opioid dependence, and withdrawal symptoms may possibly resolve more quickly than with methadone.[11] However, it should only be given to patients with moderate dependence; those dependent on high doses of opioids may have withdrawal symptoms when given buprenorphine. The methadone derivative *levacetylmethadol* was a more recent introduction but its proarrhythmic effects have led to its use being suspended.

Iatrogenic opioid dependence may occur in patients receiving μ-agonists such as morphine, fentanyl, or pethidine for the management of acute pain or in an intensive care setting for more than 5 to 10 days. Methadone has been used successfully to manage opioid withdrawal in adult intensive care patients.[12] However, some[13] avoid using methadone to manage withdrawal in children because of the stigma of its associations with managing withdrawal in drug addicts. In physically dependent but non-addicted patients, gradual weaning using the same opioid that was used therapeutically is preferred where possible, although in some cases, it may be necessary to change to a different opioid because of ease of use, duration of action, and ability to taper the dose; virtually any opioid can be used.[13]

Other drugs used in the management of opioid withdrawal include $alpha_2$-adrenoceptor agonists such as *clonidine* and opioid antagonists such as *naltrexone* and *naloxone*. Clonidine may help to suppress symptoms of opioid withdrawal, such as anxiety, insomnia, and muscle aches. It appears to be more effective when used in the control of symptoms after abrupt withdrawal than when used during gradual withdrawal of methadone. Hypotension may limit its usefulness in some patients. The clonidine analogue *lofexidine* may produce similar results to those obtained with clonidine and appears to be less hypotensive.[14]

Naltrexone and naloxone block the euphoriant effects of opioids although their use as monotherapy in detoxification is limited by unacceptable opioid withdrawal effects. Naltrexone may be used with $alpha_2$-adrenoceptor agonists such as clonidine or lofexidine to ameliorate symptoms but there are insufficient data to determine whether such combinations reduce the duration of withdrawal treatment or increase the rate of transfer to maintenance therapy with an opioid antagonist.[15] Naloxone and naltrexone are also being used in the relatively new technique of rapid or ultra rapid opioid detoxification,[16-18] which is achieved while the patient is heavily sedated or under *general anaesthesia* and hence unaware of any unpleasant withdrawal symptoms. However, although detoxification may be achieved within 24 hours and has a high initial success rate, the technique itself is not without risks and it does not obviate the need for maintenance treatment (see below).

Concomitant counselling and other psychosocial services have been shown to be important in the outcome of withdrawal therapy.[19,20] Detoxification alone does not ensure long-term abstinence.

Several other drugs may be of use as **adjuncts** in the management of withdrawal symptoms. *Diphenoxylate* with atropine or *loperamide* may be used for the control of diarrhoea. *Promethazine* has been used for its antiemetic and sedative actions. Beta blockers such as *propranolol* may be of use for patients with pronounced somatic anxiety symptoms. *Benzodiazepines* or *clomethiazole* can be given to relieve anxiety and associated insomnia but only short courses should be used in order to minimise the risk of dependence and abuse.

Long-term **maintenance** treatment (stabilisation treatment) with an opioid may be tried, with psychosocial support, to enable the patient to acquire some form of social stability before, if possible, planned withdrawal. *Methadone* is most commonly used; the use of *diamorphine* although feasible[21,22] is controversial[23] and is advocated by only a few individual centres. *Buprenorphine* is another possibility.[24] The use of methadone for maintenance has been reviewed.[25-27] *Naltrexone* can be effective in maintaining abstinence in opioid addicts after detoxification, especially after rapid or ultra rapid detoxification. It is considered that naltrexone would probably be of most use in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1,28,29]

The problems associated with the management of the **pregnant** patient with opioid dependence have been discussed.[30] The aim should be to stabilise the patient first using *methadone* since acute withdrawal can result in fetal death. Drug withdrawal is best done slowly during the second trimester. It has been suggested that if patients present during the final trimester and cannot be detoxified, maintenance with *diamorphine* might be preferable to the use of methadone as it might produce less severe withdrawal symptoms in the neonate.[31] The management of neonatal abstinence syndrome is discussed on p. 110.1.

1. Herridge P, Gold MS. Pharmacological adjuncts in the treatment of opioid and cocaine addicts. *J Psychoactive Drugs* 1988; **20:** 233–42.
2. Guthrie SK. Pharmacologic interventions for the treatment of opioid dependence and withdrawal. *DICP Ann Pharmacother* 1990; **24:** 721–34.
3. Wodak A. Managing illicit drug use: a practical guide. *Drugs* 1994; **47:** 446–57.
4. Mattick RP, Hall W. Are detoxification programmes effective? *Lancet* 1996; **347:** 97–100.
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6. National Concensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addition. *JAMA* 1998; **280:** 1936–43.
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14. Gowing L, *et al*. $Alpha_2$-adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 02/08/10).
15. Gowing L, *et al*. Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 02/08/10).
16. Justins D. Rapid opioid detoxification under anaesthesia. *HospMed* 1998; **59:** 180.
17. Cook TM, Collins PD. Rapid opioid detoxification under anaesthesia. *Hosp Med* 1998; **59:** 245–7.

18. Gowing L, *et al*. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 02/08/10).
19. McLellan AT, *et al*. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993; **269:** 1953–9.
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22. Rehm J, *et al*. Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. *Lancet* 2001; **358:** 1417–20.
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30. Gerada C, *et al*. Management of the pregnant opiate user. *Br J Hosp Med* 1990; **43:** 138–41.
31. Thomas CS, Osborn M. Inhaling heroin during pregnancy. *BMJ* 1988; **296:** 1672.

NEONATAL ABSTINENCE SYNDROME. Infants born to opioid-dependent mothers may suffer withdrawal, with signs including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress, yawning, sneezing, mottling, and fever. Onset of symptoms is partly dependent on the drug and varies from shortly after birth to 2 weeks of age, although most symptoms appear within 72 hours. Some symptoms may persist for 3 months or more. It is important to remember that many infants may have also been exposed to other licit and illicit substances, including alcohol

The American Academy of Pediatrics (AAP)[1] recommended that treatment of the neonate with abstinence syndrome should be mainly supportive and considered that many infants with signs of drug withdrawal could be managed in this way. They advised adoption of abstinence scoring methods to judge the need for drug therapy, although such systems do not appear to have been validated. Drugs that have been used for opioid withdrawal include paregoric (a USP 36 preparation containing opium), diluted tincture of opium, morphine, methadone, diazepam, chlorpromazine, phenobarbital, and clonidine. Naloxone should not routinely be given to infants of opioid-dependent mothers because of the risk of seizures with abrupt opioid withdrawal. The AAP[1] made no definite recommendations but considered that, when appropriate, specific drug therapy should be used for treatment of withdrawal symptoms. Thus for opioid withdrawal, tincture of opium was the preferred drug. Others favour treatment with oral morphine solution.[2,3] The *BNFC* also notes that morphine is widely used and the dose can be easily adjusted; however, it is stated that methadone may provide smoother control of symptoms.

Practice varies widely and evidence for the efficacy of particular drugs in the management of neonatal abstinence syndrome is scanty and difficult to compare.[4,5] It has been suggested that diazepam may be less useful than phenobarbital or paregoric but the use of paregoric (which contains both camphor and alcohol) has been questioned. In the UK, chlorpromazine has also been widely used[6] although a systematic review[7] found insufficient evidence to support such use. The authors[7] also found that phenobarbital may reduce the severity of withdrawal symptoms in those receiving an opioid; there was insufficient evidence to support the use of clonidine.

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3. Jansson LM, *et al*. The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag* 2009; **5:** 47–55.
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7. Osborn DA, *et al*. Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).

Adverse Effects

In usual doses the commonest adverse effects of opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance to these (except constipation) generally develops with long-term use. Micturition may be difficult and there may be ureteric or biliary spasm; the latter may be associated with alterations in liver enzyme values. There is also an antidiuretic effect. Dry mouth, dizziness, sweating, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido or potency, hallucinations, and miosis also occur. These effects tend to occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain. Raised intracranial pressure occurs in some patients. Muscle rigidity has been reported after high doses. The euphoric activity of opioids has led to their abuse. For a discussion of opioid dependence, see p. 109.1.

Larger doses of opioids produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur, especially in infants and children. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure. Toxic doses of specific opioids vary considerably with the individual and regular users may tolerate large doses. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops. Pulmonary oedema after overdosage is a common cause of fatalities among opioid addicts.

Morphine and some other opioids have a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. Contact dermatitis has been reported and pain and irritation may occur on injection. Anaphylactic reactions after intravenous injection have been reported rarely.

The adverse effects associated with individual opioid analgesics may reflect to some extent their activity at specific opioid receptors (see Uses and Administration, p. 108.1) or may result from a direct toxic effect.[1,2] Some adverse effects of pure opioid agonists, such as the respiratory depressant effect of morphine, are dose related, whereas agonist-antagonists such as buprenorphine, butorphanol, and nalbuphine exhibit a 'ceiling effect' as the dose increases.

The type and extent of adverse effects seen in practice may depend on whether or not opioid-sensitive pain is present, whether the opioid analgesic is being given for the control of chronic severe pain or acute pain, and the route used. In a review[3] of the use of opioids in *chronic pain* it was noted that, despite worries to the contrary, respiratory depression and dependence liability are not generally a problem when appropriate doses are used to treat opioid-sensitive pain. In fact the presence of opioid-sensitive pain appears to protect against the respiratory depressant effect, although it may occur if the source of opioid-sensitive pain is removed (e.g. by surgery) without adequate reduction in opioid dosage. The adverse effects of opioid analgesics when used in advanced cancer have also been discussed.[4] Constipation was considered to be the most troublesome adverse effect; significant respiratory depression was rarely seen with recommended regimens, since pain antagonises the central depressant effects of morphine.

In the context of *acute postoperative pain* opioid-induced respiratory depression is of concern but short-term postoperative use is unlikely to cause dependence (although see Treatment of Opioid Dependence, p. 109.2 for references to iatrogenic physical dependence).[5] It was hoped that giving opioids by the *spinal route* would result in fewer adverse effects, especially respiratory depression. In postoperative pain relief with spinal opioids, the incidence of adverse effects is said to be low when patients are properly monitored.[6] However, some[7] have reported pruritus, nausea and vomiting, and urinary retention to be common and respiratory depression to occur; more seriously the appearance of respiratory depression could be considerably delayed. These effects were more common with morphine, but all opioid analgesics had the propensity to produce respiratory depression when given spinally.[7] Delayed respiratory depression has been attributed to the poor lipid solubility of morphine, but does occur after other opioids. Some have considered that despite earlier worries, potentially fatal late respiratory depression was as rare with the spinal route as postoperative respiratory depression with the conventional route.[8,9] Disputes regarding the frequency of respiratory depression associated with even conventional use of opioid analgesics might be due to the methods used for measuring respiratory effects.[10] The incidence of ventilatory depression has been reported to be higher after intrathecal than epidural use of morphine.[11]

1. Duthie DJR, Nimmo WS. Adverse effects o f opioid analgesic drugs. *Br J Anaesth* 1987; **59:** 61–77.
2. Schug SA, *et al*. Adverse effects of systemic opioid analgesics. *Drug Safety* 1992; **7:** 200–13.
3. McQuay HJ. Opioids in chronic pain. *Br J Anaesth* 1989; **63:** 213–26.
4. Twycross RG, Lack SA. *Oral morphine in advanced cancer*. 2nd ed. Beaconsfield: Beaconsfield Publishers, 1989.
5. Mitchell RWD, Smith G. The control of acute postoperative pain. *Br J Anaesth* 1989; **63:** 147–58.
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7. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
8. Anonymous. Spinal opiates revisited. *Lancet* 1986; **i:** 655–6.
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10. Wheatley RG, *et al*. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *Br J Anaesth* 1990; **64:** 267–75.
11. Gustafsson LL, *et al*. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; **54:** 479–85.

Effects on the cardiovascular system. For reference to histamine release and cardiovascular effects following the intravenous administration of some opioids see under Pethidine, p. 122.3.

Effects on the endocrine system. Endogenous opioid peptides may have a role in the regulation of endocrine function. Like endorphin and enkephalins, morphine has been found to stimulate prolactin release[1] and synthetic analogues of morphine are reported to have similar properties; long-term intrathecal opioids (morphine or hydromorphone) have been reported to produce hypogonadotrophic hypogonadism, adrenal insufficiency, and growth hormone deficiency, although tolerance to the effects on prolactin develops with long-term use.[2] Opioids such as morphine are also part of a large group of drugs implicated in causing hyperglycaemia.[3]

1. Hell K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; **3:** 463–98.
2. Abs R, *et al*. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000; **85:** 2215–22.
3. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; **40:** 203–19.

Treatment of Adverse Effects

Activated charcoal may be given orally in conscious patients if a substantial overdose has been ingested within 1 hour provided that the airway can be protected (see below); it should be considered in all patients if a substantial amount of a modified-release preparation has been ingested.

Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used for rapid reversal of the severe respiratory depression and coma produced by excessive doses of opioid analgesics (see p. 1563.1). Since naloxone has a shorter duration of action than many opioids patients who have already responded should be kept under close observation for signs of relapse and repeated injections given according to the respiratory rate and depth of coma. Alternatively, in situations where repeated administration is required, such as where a longer acting opioid is known or suspected to be the cause of symptoms, a continuous intravenous infusion of naloxone, adjusted according to response, may be used. All patients should be observed for at least 6 hours after the last dose of naloxone.

The use of opioid antagonists such as naloxone in persons physically dependent on opioids may induce withdrawal symptoms.

Activated charcoal. The National Poisons Information Service in the UK considers the benefit of gastric decontamination in the management of overdosage with opioid analgesics to be uncertain. However, it is suggested that oral activated charcoal may be considered if given within 1 hour of ingestion and the quantity of opioid analgesic is substantial or, for these specific drugs, exceeds the following amount:

- buprenorphine: 100 micrograms/kg (adults and children)
- codeine: 3 mg/kg (adults and children)
- dihydrocodeine: 3 mg/kg (adults and children)
- methadone: any amount in an opioid-naive patient or more than the prescribed daily dose if on methadone therapeutically
- tramadol: 500 mg (adult); 10 mg/kg (child)

See also under individual monographs.

Constipation. For reference to the use of opioid antagonists, particularly naloxone, to relieve opioid-induced constipation without compromising analgesic control in patients receiving long-term therapy with opioids, see Reversal of Opioid Effects under Uses and Administration of Naloxone, p. 1564.1.

References.

1. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* 2003; **63:** 649–71.

Precautions

Opioid analgesics are generally contra-indicated in acute respiratory depression and obstructive airways disease, although opioids such as morphine are used in some forms of dyspnoea (see p. 108.3). They are also contra-indicated or should be used with great caution in acute alcoholism, convulsive disorders, head injuries, and conditions in which intracranial pressure is raised. They should not be given to comatose patients. They have an inhibitory effect on

gastrointestinal motility and should be avoided in patients at risk of paralytic ileus.

Opioid analgesics should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma or decreased respiratory reserve, renal or hepatic impairment, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, or myasthenia gravis. Dosage should be reduced in elderly or debilitated patients.

Opioid analgesics should be given with great care to infants, especially neonates. Their use during labour may cause respiratory depression in the neonate. Babies born to opioid-dependent mothers may suffer withdrawal symptoms (see Neonatal Abstinence Syndrome, p. 110.1).

Therapy with opioid analgesics should be stopped gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see Dependence, p. 109.1). Opioid analgesics with some antagonist activity, such as buprenorphine, butorphanol, nalbuphine, or pentazocine, may precipitate withdrawal symptoms in physically dependent patients who have recently used pure agonists such as morphine.

Drowsiness may affect the ability to perform skilled tasks; those so affected should not drive or operate machinery.

Asthma. Opioids appear to be safe and may be used with caution in controlled asthma; however, they should be avoided during acute exacerbations.[1]

1. Barnes PJ, Chung KF. Difficult asthma. *BMJ* 1989; **299:** 1031–2.

Biliary-tract disorders. It is usually recommended that opioids such as morphine should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi[1] and may therefore be expected to exacerbate rather than relieve pain in patients with biliary colic (p. 6.3) or other biliary-tract disorders. Biliary-type pain after cholecystectomy has also been associated with codeine[2] and morphine.[3]

Morphine caused a more marked delay in gallbladder emptying than pethidine, pentazocine, or butorphanol in a study[4] in healthy subjects; this was considered confirmation that morphine should be avoided in biliary disorders. In another study[5] fentanyl and sufentanil did not constrict the common bile duct like morphine; they may be suitable for perioperative pain control in patients in whom spasm of the common bile duct is undesirable. The suggestion that pethidine should be preferred to morphine in patients with acute pancreatitis (p. 10.2), because of its lesser effect on the bile duct, has been questioned.[6]

1. Helm JF, *et al.* Effects of morphine on the human sphincter of Oddi. *Gut* 1988; **29:** 1402–7.
2. Druart-Blazy A, *et al.* The underestimated role of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy. *Gastroenterol Clin Biol* 2005; **29:** 1220–3.
3. Roberts-Thomson IC, *et al.* Sympathetic activation: a mechanism for morphine induced pain and rises in liver enzymes after cholecystectomy? *Gut* 1990; **31:** 217–21.
4. Hahn M, *et al.* The effect of four narcotics on cholecystokinin octapeptide stimulated gall bladder contraction. *Aliment Pharmacol Ther* 1988; **2:** 129–34.
5. Vieira ZEG, *et al.* Evaluation of fentanyl and sufentanil on the diameter of the common bile duct by ultrasonography in man: a double blind, placebo controlled study. *Int J Clin Pharmacol Ther* 1994; **32:** 274–7.
6. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; **96:** 1266–72.

Children. Children under 6 months of age may be more sensitive to opioids; neonates in particular may be more sensitive to respiratory depression with morphine than adults. Pharmacokinetic differences may contribute to this increased sensitivity. Nonetheless, neonates can be treated with opioids such as morphine (see p. 94.1) if receiving respiratory support.

Older infants and children can be treated effectively with morphine or other opioid analgesics and from the age of 5 or 6 months morphine metabolism follows the course seen in adults.

For a discussion of the choice of analgesic in children see p. 5.2. The use of opioids for sedation and analgesia in neonates in intensive care is mentioned on p. 1033.1.

References.

1. Choonara IA. Pain relief. *Arch Dis Child* 1989; **64:** 1101–2.
2. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.
3. Bhatt-Mehta V. Current guidelines for the treatment of acute pain in children. *Drugs* 1996; **51:** 760–76.
4. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; **79:** 787–95.

The elderly. Ageing can affect the pharmacokinetics and pharmacodynamics of opioids although the net effects of these changes on opioid analgesia in the elderly remain unclear.[1] Practical recommendations include careful review of indication for opioid use both initially and at regular intervals thereafter, starting opioids cautiously at lower doses and with longer dosing intervals, and regular consideration given to dose reduction and drug substitution or discontinuation. If possible, further drugs should not be prescribed to manage the adverse effects of opioids.

1. Wilder-Smith OHG. Opioid use in the elderly. *Eur J Pain* 2005; **9:** 137–40.

Hepatic impairment. The pharmacokinetics of opioids may be altered in patients with hepatic dysfunction. A review[1] of opioid use in this patient group considered that opioids such as morphine and hydromorphone that are metabolised by glucuronidation were relatively safe when compared with those metabolised by cytochrome P450 isoenzymes; the half-lives of glucuronidated opioids were found to be maintained until late disease whereas the prolonged half-lives seen with opioids metabolised by P450 isoenzymes were not accurately predicted by disease severity. It was also recommended that oral immediate-release or parenteral, short-acting opioids were preferable to long-acting preparations such as transdermal or modified-release formulations.

1. Davis M. Cholestasis and endogenous opioids: liver disease and exogenous opioid pharmacokinetics. *Clin Pharmacokinet* 2007; **46:** 825–50.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release. Both diamorphine[1] and pethidine[2] have been reported to cause hypertension when given to patients with phaeochromocytoma and histamine-releasing opioids should be avoided in such patients. Alfentanil, like fentanyl, does not release histamine and may be the opioid of choice in the anaesthetic management of patients with phaeochromocytoma.[3]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; **2:** 538.
2. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; **1:** 149–50.
3. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

Renal impairment. A literature review[1] concluded that codeine and morphine are best avoided in patients with renal failure and/or on dialysis; hydromorphone may be used with caution and monitoring, and use of fentanyl and methadone appeared to be safe. Similar recommendations have been made for patients with end-stage renal disease who are not undergoing dialysis.[2] See also under the individual monographs.

1. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004; **28:** 497–504.
2. Murtagh FE, *et al.* The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 2007; **21:** 5–16.

Interactions

As serious and sometimes fatal reactions have followed use of pethidine in patients receiving MAOIs (including moclobemide), pethidine and related drugs are contra-indicated in patients taking MAOIs or within 14 days of stopping such treatment; other opioid analgesics should be avoided or given with extreme caution (for further details, see p. 447.1). Life-threatening reactions have also been reported when selegiline, a selective inhibitor of monoamine oxidase type B, was given with pethidine. The depressant effects of opioid analgesics are enhanced by other CNS depressants such as alcohol, anaesthetics, anxiolytics, hypnotics, tricyclic antidepressants, and antipsychotics. Cyclizine may counteract the haemodynamic benefits of opioids. Cimetidine inhibits the metabolism of some opioids, especially pethidine.

The actions of opioids may in turn affect the activities of other drugs. For instance, their gastrointestinal effects may delay absorption as with mexiletine or may be counteractive as with cisapride, metoclopramide, or domperidone. Opioid premedicants such as papaveretum have been reported to reduce serum concentrations of ciprofloxacin.

Alcohol. Rapid release or dose-dumping of hydromorphone from a modified-release preparation (*Palladone; Purdue Frederick, USA*) has been associated with the ingestion of alcohol (for further details, see under Interactions of Hydromorphone, p. 68.2). Health Canada[1] has warned that this interaction may occur with all modified-release formulations of opioid analgesics. Licensed product information for some modified-release preparations of morphine sulfate also warns against such use (see Interactions of Morphine, p. 95.2).

1. Health Canada. Potentially fatal interaction between slow-release opioid painkillers and alcohol (issued 3rd August, 2005). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2005/2005_84-eng.php (accessed 26/06/08)

Antivirals. Interactions between opioid analgesics and *HIV-protease inhibitors* or *reverse transcriptase inhibitors* are complex, and the results of the limited number of studies and reports *in vivo* have not always borne out predictions about the nature of potential interactions.

- Substantial **decreases** in the area under the plasma concentration-time curve (AUC) and in the plasma concentration have been reported for pethidine when given with *ritonavir*; however, plasma concentrations of the toxic metabolite norpethidine are greatly **increased**, and licensed product information for ritonavir counsels against such combined use. Ritonavir is predicted to reduce plasma concentrations of morphine. Plasma concentrations of methadone may be reduced if given with HIV-protease inhibitors although the effect may not be clinically significant. The NNRTIs *nevirapine* and *efavirenz* have also been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when given to patients receiving methadone. (For further details on the interactions of methadone with antivirals, see p. 91.1.) In addition, efavirenz has been reported to decrease the AUC of buprenorphine (see p. 32.3).
- In contrast, an **increase** in AUC and in elimination half-life of fentanyl has been reported in subjects also receiving ritonavir (see p. 63.2). Licensed product information for ritonavir also considers that increased plasma concentrations of buprenorphine (p. 32.3), dextropropoxyphene, and tramadol, with an increased likelihood of opioid toxicity, may occur if these drugs are given during ritonavir treatment. Licensed information for meptazinol also states that increased plasma concentrations of meptazinol have been noted when given with ritonavir. The NNRTI *delavirdine* has been reported to increase the plasma concentrations of buprenorphine (see p. 32.3) and methadone (p. 91.1).

Histamine. For the effect of opioid analgesics on histamine given exogenously, see p. 2525.3.

Histamine H_2-antagonists. Histamine H_2-antagonists may enhance the effects of some opioid analgesics. *Cimetidine* was reported to alter the clearance and volume of distribution of pethidine[1] whereas *ranitidine* did not.[2] Morphine has been considered less likely to interact with cimetidine than pethidine because of differences in metabolism. In a study[3] cimetidine did not affect the disposition of morphine in healthy subjects. A later study[4] in patients undergoing major surgery suggested that pre- or postoperative intravenous cimetidine did not significantly affect outcomes such as morphine consumption and incidence of adverse effects when compared with placebo. Nevertheless, there have been isolated reports of possible interactions between morphine and H_2-antagonists; apnoea, confusion, and muscle twitching have been associated with cimetidine plus morphine,[5] and confusion associated with ranitidine plus morphine.[6] There has also been a report[7] of a patient receiving regular analgesia with oral methadone and subcutaneous morphine who became unresponsive 6 days after starting cimetidine for prophylaxis of peptic ulcer; treatment with naloxone was required.

1. Guay DRP, *et al.* Cimetidine alters pethidine disposition in man. *Br J Clin Pharmacol* 1984; **18:** 907–14.
2. Guay DRP, *et al.* Ranitidine does not alter pethidine disposition in man. *Br J Clin Pharmacol* 1985; **20:** 55–9.
3. Mojaverian P, *et al.* Cimetidine does not alter morphine disposition in man. *Br J Clin Pharmacol* 1982; **14:** 809–13.
4. Chia Y-Y, *et al.* Randomized, double-blind study comparing postoperative effects of treatment timing with histamine H_2-receptor antagonist cimetidine. *Acta Anaesthesiol Scand* 2005; **49:** 865–9.
5. Fine A, Churchill DN. Potentially lethal interaction of cimetidine and morphine. *Can Med Assoc J* 1981; **124:** 1434, 1436.
6. Martinez-Abad M, *et al.* Ranitidine-induced confusion with concomitant morphine. *Drug Intell Clin Pharm* 1988; **22:** 914–15.
7. Sorkin EM, Ogawa GS. Cimetidine potentiation of narcotic action. *Drug Intell Clin Pharm* 1983; **17:** 60–1.

Opium

Gum Opium; Nyers ópium; Opijus, žaliavinis; Opio; Opium brut; Opium crudum; Opium surové; Raakaoopiumi; Råopium; Raw Opium; Опиум.

ATC — A07DA02; N02AA02.

ATC Vet — QA07DA02; QN02AA02.

*ATC Herb — HN02AA5001 (*Papaver somniferum*: dry latex); HR05DA5001 (*Papaver somniferum*: dry latex); HN05CW5004 (*Papaver somniferum*: dry latex); HA03AD5001 (*Papaver somniferum*: dry latex); HA07DA5001 (*Papaver somniferum*: dry latex).*

UNII — 37M3MZ001L.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of opium:

Ahpenyen; Ah-pen-yen; Aunti; Aunti Emma; Big O; Black; Black pill; Black shit; Black stuff; Black tar opium; Block; Boulette; Chandoo; Chandu; China; Chinese molasses; Chinese tobacco; Chocolate; Cruz; Dopium; Dover's deck; Dover's powder; Dream gum; Dream gun; Dream stick; Dreams; Dutch courage; Easing powder; Fidonie; Fi-do-nie; Fun-foon-fong; Gee; God's medicine; Goma; Gondola; Gong; Goric; Great tobacco; Gum; Guma;

Hard stuff; Hocus; Hop; Hops; Incense; Indonesian bud; Joy plant; Mash allah; Material negro; Midnight oil; Mira; Mud; O; Oj; Op; O.P.; Ope; O-Rock DC; Pen yan; Pen yen; Pin gon; Pin yen; Pox; Skee; Tar; Tin; Toxy; Toye; Toys; When-shee; Ze; Zero.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Chin., *Eur.*, and *US* include a monograph for prepared or powdered opium. *Eur.* also contains monographs for standardised opium dry extract or standardised opium tincture. *Jpn* includes prepared opium and a diluted opium powder containing 1% of anhydrous morphine.

Ph. Eur. 8: (Opium, Raw; Opium BP 2014). The air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* L. It has a characteristic odour and a blackish-brown colour. It should contain not less than 10% of anhydrous morphine, not less than 2% of anhydrous codeine, and not more than 3% of anhydrous thebaine. Protect from light.

Ph. Eur. 8: (Opium, Prepared; Opii Pulvis Normatus). Raw opium powdered and dried at a temperature not exceeding 70 degrees. It is a yellowish-brown or dark brown powder and contains 9.8 to 10.2% of morphine and not less than 1.0% of codeine, calculated with reference to the dried drug. The content may be adjusted by adding a suitable excipient or raw opium powder.

USP 36: (Opium). The air-dried milky exudate obtained by incising the unripe capsules of *Papaver somniferum* (Papaveraceae). Externally it is pale olive-brown or olive-grey; internally it is reddish-brown. It has a very characteristic odour and a very bitter taste. It yields not less than 9.5% of anhydrous morphine.

USP 36: (Powdered Opium). Opium dried at a temperature not exceeding 70 degrees, and reduced to a very fine light brown or moderately yellowish-brown powder that yields not less than 10% and not more than 10.5% of anhydrous morphine. It may contain any of the permitted diluents with the exception of starch.

Profile

Opium is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* (Papaveraceae). It contains morphine, codeine, and thebaine and a variable mixture of other alkaloids including noscapine and papaverine. The exuded latex is dried and manipulated to form cakes of uniform composition, variously shaped according to the country of origin, and known in commerce as Turkish, Indian, or European opium.

Opium has the properties of opioid analgesics (p. 108.1). Its analgesic and sedative actions are due mainly to its content of morphine (p. 93.2). It acts less rapidly than morphine since opium appears to be more slowly absorbed; the relaxing action of the papaverine and noscapine on intestinal muscle makes it more constipating than morphine.

Opium is intended only as the starting material for the manufacture of galenical preparations and is not dispensed as such. It is used as Prepared Opium (Ph. Eur. 8), as Powdered Opium (USP 36), as Opium Tincture (BP 2014 or USP 36), or as Camphorated Opium Tincture (BP 2014) or Paregoric (USP 36) in various oral preparations. These have included Opiate Squill Linctus (BP 2014) (Gee's linctus) for cough.

Paregoric (USP 36) has been advocated in the USA for the treatment of neonatal abstinence syndrome.

Abuse. Reports of squill-associated cardiotoxicity resulting from the abuse of opiate squill linctus (Gee's linctus).[1,2]

1. Thurston D, Taylor K. Gee's linctus. *Pharm J* 1984; **233:** 63.
2. Smith W, *et al*. Wenckebach's phenomenon induced by cough linctus. *BMJ* 1986; **292:** 868.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Elixir Paregorico; ***Israel***: Opii Simplex.

Multi-ingredient Preparations. ***Braz.***: Camomila; ***Denm.***: Pectyl; ***Fin.***: Tannopon†; ***Fr.***: Colchimax; Lamaline; Paregorique†; ***Hong Kong***: Brown Mixture†; ***Israel***: Doveri†; ***S.Afr.***: Paragoriese-Eliksер†; Tandpyndruppels†; ***Spain***: Tanagel; ***Switz.***: Bromocod N†; Pectocalmine N; ***USA***: B & O Supprettes No. 15A; B & O Supprettes No. 16A; ***Venez.***: Atrobel.

Homoeopathic Preparations. ***Fr.***: Abbe Chaupitre no 19†; ***Switz.***: HerBalance.

Pharmacopoeial Preparations

BP 2014: Camphorated Opium Tincture; Concentrated Camphorated Opium Tincture; Opium Tincture;
Ph. Eur.: Opium Dry Extract, Standardised; Opium Tincture, Standardised;
USP 36: Opium Tincture; Paregoric.

Hydrochlorides of Mixed Opium Alkaloids

Alkaloidosum Opii Hydrochloridum; Extractum Concentratum Opii; Mezclas de hidrocloruros de alcaloides del opio; Omnoponum; Opialum; Opium Concentratum; Гидрохлориды Смешанных Алкалоидов Опия.

Pharmacopoeias. Preparations of the hydrochlorides of mixed opium alkaloids are included in *Jpn*.

Papaveretum *(BAN)*

Папаверетум.

A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride, and 20 parts of codeine hydrochloride..

CAS — 8002-76-4.
ATC — N02AA10.
ATC Vet — QN02AA10.

NOTE. Do not confuse papaveretum with papaverine (p. 2362.2).

Pharmacopoeias. In *Br.*

BP 2014: (Papaveretum). It contains 80.0 to 88.4% of anhydrous morphine hydrochloride, 8.3 to 9.2% of papaverine hydrochloride, and 6.6 to 7.4% of anhydrous codeine hydrochloride. A white or almost white crystalline powder. Soluble in water, sparingly soluble in alcohol. A 1.5% solution in water has a pH of 3.7 to 4.7. Protect from light.

Profile

The opium alkaloids are the prototypical opioid analgesics (p. 108.1). Mixtures of opium alkaloids such as papaveretum have the analgesic and sedative properties of morphine (p. 93.2) and are used in the treatment of moderate to severe pain including postoperative and severe chronic pain. They may also be used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum (BP 2014) 15.4 mg contains the equivalent of about 10 mg of the major component, anhydrous morphine.

- In the UK, papaveretum formerly contained the hydrochlorides of morphine, codeine, noscapine, and papaverine. However, because of concern over the potential genotoxicity of noscapine (see Pregnancy, p. 1671.1) UK preparations containing papaveretum were reformulated to exclude the noscapine component and the name papaveretum was redefined in the BP 1993 to reflect this change of formulation. It is possible that in other countries the term papaveretum is still being used to describe a mixture containing noscapine.

Doses. Papaveretum is generally given by subcutaneous or intramuscular injection in doses of 7.7 to 15.4 mg every 4 hours if necessary. The initial dose in the elderly or debilitated patients should not exceed 7.7 mg.

In the treatment of pain and as an adjunct in anaesthesia, papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose. For pre-operative medication papaveretum is given intramuscularly or subcutaneously sometimes with hyoscine hydrobromide.

For details of doses in children, see below.

Oral preparations containing papaveretum with aspirin have been given for the management of moderate to severe pain.

Papaveretum has been confused with papaverine (p. 2362.2) and in one such case[1] a patient became unconscious after self-injection of papaveretum in mistake for papaverine.

1. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.

Administration in children. Papaveretum may be given to children in the treatment of moderate to severe pain including postoperative and severe chronic pain. It is also used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum is generally given by subcutaneous or intramuscular injection every 4 hours if necessary, according to age as follows:

- neonates: 115 micrograms/kg
- 1 to 12 months: 154 micrograms/kg
- 1 to 6 years: 1.93 to 3.85 mg
- 6 to 12 years: 3.85 to 7.7 mg

Older children may be given the usual adult dose (see above).

In the treatment of pain and as an adjunct to anaesthesia papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Omnopon (Омнопон); ***S. Afr.***: Omnopon.

Multi-ingredient Preparations. ***UK***: Aspav†.

Pharmacopoeial Preparations

BP 2014: Papaveretum Injection.

Oxaprozin *(BAN, USAN, rINN)*

Oksaprotsiini; Oxaprozina; Oxaprozine; Oxaprozinum; Wy-21743; Оксапрозин.

3-(4,5-Diphenyloxazol-2-yl)propionic acid.

$C_{18}H_{15}NO_3$=293.3

CAS — 21256-18-8.
ATC — M01AE12.
ATC Vet — QM01AE12.
UNII — MHJ80W9LRB.

Pharmacopoeias. In *Chin.*, *Jpn.*, and *US*.

USP 36: (Oxaprozin). A white to yellowish-white, crystalline powder. Store in airtight containers at a temperature of 20 degrees to 25 degrees. Protect from light.

Oxaprozin Potassium *(BANM, rINNM)*

Kalii Oxaprozinum; Oxaprozina potásico; Oxaprozine Potassique; Калия Оксапрозин.

$C_{18}H_{14}NO_3K$=331.4

CAS — 174064-08-5.
ATC — M01AE12.
ATC Vet — QM01AE12.
UNII — ML56O2Z92I.

Uses and Administration

Oxaprozin, a propionic acid derivative, is an NSAID (p. 102.3). Oxaprozin may be given orally as the base or potassium salt although doses are expressed in terms of the base; oxaprozin potassium 678 mg is equivalent to about 600 mg of oxaprozin. For the treatment of osteoarthritis and rheumatoid arthritis, a usual dose equivalent to 1.2 g of oxaprozin may be given once daily, although in osteoarthritis, patients with low body-weight or mild disease should be given an initial dose equivalent to 600 mg once daily. The recommended maximum daily dose is 1.8 g or 26 mg/kg, whichever is the lower.

For doses in patients with renal impairment and in children, see below.

References.

1. Miller LG. Oxaprozin: a once-daily nonsteroidal anti-inflammatory drug. *Clin Pharm* 1992; **11:** 591–603.
2. Anonymous. Oxaprozin for arthritis. *Med Lett Drugs Ther* 1993; **35:** 15–16.
3. Dallegri F, *et al*. A review of the emerging profile of the anti-inflammatory drug oxaprozin. *Expert Opin Pharmacother* 2005; **6:** 777–85.

Administration in children. Oxaprozin is given orally in the treatment of juvenile idiopathic arthritis in children aged 6 years and over. Doses are expressed in terms of body-weight and may be given once daily as follows:

- 22 to 31 kg: 600 mg
- 32 to 54 kg: 900 mg
- 55 kg and over: 1200 mg

Administration in renal impairment. US licensed product information for oxaprozin recommends that the initial oral dose in patients with severe renal impairment or on dialysis is 600 mg once daily. The dose may be increased to 1.2 g once daily, if necessary.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Diagnosis and testing. False-positive results for testing of benzodiazepines in urine have been reported in patients taking oxaprozin.[1] The manufacturer[2] has commented that the interaction occurs with some immunoassay tests and that thin-layer chromatography can successfully discriminate between benzodiazepines and oxaprozin. False-positive results for a fluorescence polarisation immunoassay for phenytoin have also been reported in patients receiving oxaprozin.[3]

1. Pulini M. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; **273:** 1905.
2. Raphan H, Adams MH. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; **273:** 1905–6.
3. Patel T, *et al*. Assay interaction between oxaprozin and phenytoin. *Ann Pharmacother* 1997; **31:** 254.

Effects on the liver. Fatal fulminant hepatitis occurred[1] in a 56-year-old woman who had received 600 to 1200 mg of oxaprozin daily for about 6 weeks. In another patient

symptomatic hepatitis developing during oxaprozin use resolved on stopping the drug.[2]

1. Purdum PP, *et al.* Oxaprozin-induced fulminant hepatitis. *Ann Pharmacother* 1994; **28:** 1159–61.
2. Kethu SR, *et al.* Oxaprozin-induced symptomatic hepatotoxicity. *Ann Pharmacother* 1999; **33:** 942–4.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Oxaprozin is slowly but extensively absorbed from the gastrointestinal tract; it is 99% bound to plasma proteins, mainly albumin. Peak plasma concentrations occur after about 2 to 3 hours. At steady state, the biological half-life is about 44 hours. Oxaprozin is metabolised mainly in the liver by microsomal oxidation and conjugation with glucuronic acid to form inactive metabolites which are excreted in the urine (65%) and faeces (35%).

References.

1. Karim A. Inverse nonlinear pharmacokinetics of total and protein unbound drug (oxaprozin): clinical and pharmacokinetic implications. *J Clin Pharmacol* 1996; **36:** 985–97.
2. Karim A, *et al.* Oxaprozin and piroxicam, nonsteroidal antiinflammatory drugs with long half-lives: effect of protein-binding differences on steady-state pharmacokinetics. *J Clin Pharmacol* 1997; **37:** 267–78.
3. Davies NM. Clinical pharmacokinetics of oxaprozin. *Clin Pharmacokinet* 1998; **35:** 425–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Duraprox; ***Canad.***: Daypro; ***Chile***: Duraprox†; Walix; ***China***: Ao Ke Qing (奥克清); Ao Pu Xin (澳谱欣); Lu Ming Ao Xin (鲁明奥欣); Nuo Bi Song (诺碧松); Nuo De Lun (诺德伦); Nuosong (诺松); ***Cz.***: Dayrun†; ***Gr.***: Duraprox; Misaf; Nisaid; Oxapron; Trimelot; ***Ital.***: Walix; ***Jpn***: Alvo; ***S.Afr.***: Deflam†; ***Turk.***: Duraprox; ***USA***: Daypro.

Pharmacopoeial Preparations
USP 36: Oxaprozin Tablets.

Oxycodone *(BAN, USAN, rINN)* ⊗

Dihydrone; 14-Hydroxydihydrocodeinone; NSC-19043; Oksikodoni; Oxicodona; Oxikodon; Oxycodonum; Оксикодон. 6-Deoxy-7,8-dihydro-14-hydroxy-3-*O*-methyl-6-oxomorphine; (-)-(5*R*,6*S*,14*S*)-4,5-Epoxy-14-hydroxy-3-methoxy-9a-methylmorphinan-6-one.

$C_{18}H_{21}NO_4$=315.4

CAS — *76-42-6.*
ATC — *N02AA05.*
ATC Vet — *QN02AA05.*
UNII — *CD35PMG570.*

NOTE. Compounded preparations of oxycodone may be represented by the following names:

- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of oxycodone:

40; 40-bar; 80; Blue; Cotton; Hillbilly heroin; Kicker; OC; Os; Ox; Oxy; Oxy Cotton; Oxycotton; Percs; Perks; Pills; Pink spoons; Rushbo.

Oxycodone Hydrochloride

(BANM, USAN, rINNM) ⊗

7,8-Dihydro-14-hydroxycodeinone hydrochloride; Dihydrone Hydrochloride; Hidrocloruro de oxicodona; Oksikodonihydrokloridi; Oksikodono hidrochloridas; Oxicodona, hidrocloruro de; Oxikodonhydroklorid; Oxycodone, Chlorhydrate d'; Oxycodonhydrochlorid; Oxycodoni hydrochloridum; Oxycone Hydrochloride; Oxykodon-hydrochlorid; Thecodine; Оксикодона Гидрохлорид.

$C_{18}H_{21}NO_4$.HCl=351.8

CAS — *124-90-3.*
ATC — *N02AA05.*
ATC Vet — *QN02AA05.*
UNII — *C1ENJ2TE6C.*

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Jpn* includes the trihydrate.

Ph. Eur. 8: (Oxycodone Hydrochloride). A white or almost white, hygroscopic, powder. Freely soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.

USP 36: (Oxycodone Hydrochloride). A white to off-white, odourless, hygroscopic crystals or powder. Soluble in water; slightly soluble in alcohol. Store in airtight containers.

Oxycodone Terephthalate ⊗

Oxicodona, tereftalato de; Оксикодона Терефталат.

4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one 1,4-benzenedicarboxylate (2:1) salt.

$(C_{18}H_{21}NO_4)_2.C_8H_6O_4$=796.9

CAS — *64336-55-6.*
UNII — *M04XWV43UF.*

Pharmacopoeias. In *US.*

USP 36: (Oxycodone Terephthalate). Store in airtight containers.

Uses and Administration

Oxycodone, a phenanthrene derivative, is an opioid analgesic (p. 108.1). Oxycodone hydrochloride is given orally or by subcutaneous or intravenous injection for the relief of moderate to severe pain.

A usual oral starting dose for opioid-naive patients in severe pain is 5 mg every 4 to 6 hours increased thereafter as necessary according to response. For patients who have been receiving a strong opioid analgesic the initial dose of oxycodone should be based on the daily opioid requirement; UK licensed product information suggests that 10 mg of oral oxycodone is equivalent to about 20 mg of oral morphine. Most patients do not require more than 400 mg daily. Preparations containing oxycodone hydrochloride and aspirin, ibuprofen, or paracetamol are also used. Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours. To counteract opioid-induced constipation a combined modified-release oral preparation of oxycodone hydrochloride and naloxone hydrochloride is available in some countries.

For details of doses in children, see below.

For opioid-naive patients, intravenous doses of oxycodone hydrochloride range from 1 to 10 mg initially, given over 1 to 2 minutes, and repeated not more often than every 4 hours; a dose of 2 mg/hour is the recommended starting dose as an intravenous infusion. The intravenous route may also be used for patient-controlled analgesia. When given subcutaneously to opioid-naive patients, the starting dose is 5 mg every 4 hours; subcutaneous infusions should be started at 7.5 mg daily. When transferring between oral and parenteral oxycodone, UK licensed product information advises that, as a guide, 2 mg of oral oxycodone is equivalent to about 1 mg of parenteral oxycodone.

Oxycodone has been given rectally as suppositories containing 30 mg of oxycodone (as the pectinate) or 10 or 20 mg of oxycodone hydrochloride; the dose may be repeated every 6 to 8 hours.

For doses in patients with hepatic or renal impairment, see below.

Oxycodone terephthalate is also used orally.

Administration in children. Although oxycodone hydrochloride is not licensed in the UK for use in children under 18 years old, the *BNFC* suggests that it may be given for the treatment of moderate to severe pain in palliative care. Those aged from 1 month to 12 years may be given initial oral doses of 200 micrograms/kg (up to 5 mg) every 4 to 6 hours increased thereafter as necessary according to response; older children may be given the usual adult dose (see above). Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours to those aged 8 years and older.

Administration in hepatic or renal impairment. The plasma concentrations of oxycodone may be increased in patients with hepatic or renal impairment and consequently dosage adjustment may be necessary in such patients. In the UK, licensed product information recommends that the oral starting dose for adult patients with mild hepatic impairment or mild to moderate renal impairment should be 2.5 mg given every 6 hours; it contra-indicates the use of oxycodone in those with moderate to severe hepatic impairment or severe renal impairment. US product information permits the cautious use of oxycodone in adult patients with severe hepatic or severe renal impairment.

Pain. References.

1. Curtis GB, *et al.* Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. *Eur J Clin Pharmacol* 1999; **55:** 425–9.
2. Gimbel JS, *et al.* Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003; **60:** 927–34.
3. Oldfield V, Perry CM. Oxycodone/ibuprofen combination tablet: a review of its use in the management of acute pain. *Drugs* 2005; **65:** 2337–54.
4. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005; **29** (suppl): S47–S56.
5. Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother* 2006; **20:** 33–9.
6. Reid CM, *et al.* Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 837–43. Correction. *ibid.*; 2387.
7. Portenoy RK, *et al.* Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain* 2007; **23:** 287–99.
8. Pan H, *et al.* Efficacy and tolerability of oxycodone hydrochloride controlled-release tablets in moderate to severe cancer pain. *Clin Drug Invest* 2007; **27:** 259–67.
9. Gaskell H, *et al.* Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 18/11/09).

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Oxycodone has been subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Takotsubo-like cardiomyopathy developed in a 61-year-old woman when her dose of oxycodone was inadvertently and greatly reduced 7 days after surgery for degenerative osteoarthritis.[1] The patient had a chronic history of opioid dependence and had been treated with oxycodone (80 mg daily) and hydromorphone (4 mg every 3 hours as needed) for several months before surgery; postoperatively, her dose of oxycodone had been increased to 120 mg daily with additional doses for breakthrough pain.

1. Rivera JM, *et al.* "Broken heart syndrome" after separation (from OxyContin). *Mayo Clin Proc* 2006; **81:** 825–8.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

UK licensed product information contra-indicates the use of oxycodone in patients with moderate to severe hepatic impairment or severe renal impairment; however, product information in the USA permits its cautious use in patients with severe hepatic or severe renal impairment although doses may need to be reduced.

Abuse. Oxycodone hydrochloride modified-release tablets have been subject to abuse.[1-3] The crushed tablets have been inhaled or injected by addicts and in some cases this has resulted in fatalities.

1. Wolf BC, *et al.* One hundred seventy two deaths involving the use of oxycodone in Palm Beach County. *J Forensic Sci* 2005; **50:** 192–5.
2. Cicero TJ, *et al.* Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002-2004. *J Pain* 2005; **6:** 662–72.
3. Adlaf EM, *et al.* Use of OxyContin by adolescent students. *Can Med Assoc J* 2006; **174:** 1303.

Breast feeding. For a report on the effects of oxycodone in breast feeding, see Breast Feeding under Codeine, p. 41.2.

Effects on the respiratory system. References[1,2] to respiratory depression occurring in children given oxycodone.

1. Olkkola KT, *et al.* Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; **38:** 71–6.
2. Kalso E. Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1995; **39:** 214.

Hepatic impairment. The clearance and elimination of oxycodone were prolonged in 6 women with end-stage liver cirrhosis awaiting liver transplantations.[1] Significant ventilatory depression also occurred. Pharmacokinetic values after successful transplantation were similar to those previously reported for healthy adults. It was recommended that, when giving oxycodone to patients with end-stage liver disease, the dosing frequency should be reduced and the dose lowered.

1. Tallgren M, *et al.* Pharmacokinetics and ventilatory effects of oxycodone before and after liver transplantation. *Clin Pharmacol Ther* 1997; **61:** 655–61.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxycodone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Antibacterials. Negative urine oxycodone screening tests have been reported[1] in a patient taking oral oxycodone 60 mg daily with the potent enzyme inducer *rifampicin*, amongst other drugs. The presence of oxycodone metabolites in the urine led the authors to conclude that rifampicin increased the metabolism of oxycodone, necessitating an increase in the dose of the latter. A later pharmacokinetic study[2] found that rifampicin decreased the AUC of intravenous and oral oxycodone by 53% and 86%, respectively, and decreased the oral bioavailability of oxycodone from 69% to 21%.

Conversely, the enzyme inhibitor *telithromycin* was found[3] to increase the AUC of oral oxycodone by 80% and decrease its clearance by 43%; it was suggested that the dose

of oxycodone be reduced by 25 to 50% when used with telithromycin.

1. Lee H-K, *et al.* Negative urine opioid screening caused by rifampin-mediated induction of oxycodone hepatic metabolism. *Clin Chim Acta* 2006; **367:** 196–200.
2. Nieminen TH, *et al.* Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. *Anesthesiology* 2009; **110:** 1371–8.
3. Grönlund J, *et al.* Effect of telithromycin on the pharmacokinetics and pharmacodynamics of oral oxycodone. *J Clin Pharmacol* 2010; **50:** 101–8.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of oxycodone and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1.

Antifungals. In a study,[1] the mean AUC, peak plasma concentration, and elimination half-life of oral oxycodone were increased 3.6-, 1.7-, and 2-fold, respectively, by the enzyme inhibitor *voriconazole*; lower doses of oxycodone may be needed when used together.

1. Hagelberg NM, *et al.* Voriconazole drastically increases exposure to oral oxycodone. *Eur J Clin Pharmacol* 2009; **65:** 263–71.

Pharmacokinetics

Oxycodone is absorbed from the gastrointestinal tract; oral bioavailability is about 60 to 87% due to lower pre-systemic and/or first-pass metabolism compared with other opioids. About 45% is bound to plasma proteins. It is metabolised to noroxycodone, via cytochrome P450 isoenzymes of the CYP3A family, and, to a lesser extent, to oxymorphone (below) via CYP2D6. Both metabolites undergo glucuronidation and are excreted with unchanged drug in urine. The elimination half-life of oxycodone is reported to be 2 to 4 hours. Oxycodone crosses the placenta and is distributed into breast milk.

References.

1. Pöyhiä R, *et al.* The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 1991; **32:** 516–18.
2. Leow KP, *et al.* Single-dose and steady-state pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. *Clin Pharmacol Ther* 1992; **52:** 487–95.
3. Mandema JW, *et al.* Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol* 1996; **42:** 747–56.
4. Kaiko RF, *et al.* Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Ther* 1996; **59:** 52–61.
5. Gammaitoni AR, Davis MW. Comparison of the pharmacokinetics of oxycodone administered in three Percocet® formulations. *J Clin Pharmacol* 2002; **42:** 192–7.
6. Lalovic B, *et al.* Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* 2006; **79:** 461–79.
7. Liukas A, *et al.* Plasma concentrations of oral oxycodone are greatly increased in the elderly. *Clin Pharmacol Ther* 2008; **84:** 462–7.

Children. The pharmacokinetics of oxycodone in children have been studied[1-4] and are generally considered similar to those in adults.[2,4] However, pharmacokinetics may be more variable in infants aged from 0 to 6 months, particularly those aged 2 months and under.[5]

1. Olkkola KT, *et al.* Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; **38:** 71–6.
2. Kokki H, *et al.* Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. *Clin Pharmacokinet* 2004; **43:** 613–22.
3. El-Tahtawy A, *et al.* Population pharmacokinetics of oxycodone in children 6 months to 7 years old. *J Clin Pharmacol* 2006; **46:** 433–42.
4. Kokki H, *et al.* Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. *Clin Pharmacokinet* 2006; **45:** 745–54.
5. Pokela ML, *et al.* Marked variation in oxycodone pharmacokinetics in infants. *Paediatr Anaesth* 2005; **15:** 560–565.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Oxicalmans; Oxinovag; Oxycontin; ***Austral.***: Endone; Oxycontin; Oxynorm; Proladone; Targin; ***Austria***: Oxycontin; Oxynorm; Targin; ***Belg.***: Oxycontin; Oxynorm; Targinact; ***Braz.***: Oxycontin; ***Canad.***: Oxy IR; Oxycontin†; Oxyneo; Supeudol; Targin; ***Chile***: Oxycontin; ***China***: Oxycontin (奥施康定); ***Cz.***: Dolocodon; Oxycontin; Targin; ***Denm.***: Oxycontin; Oxynorm; Targin; ***Fin.***: Oxanest; Oxycontin; Oxynorm; Targiniq; ***Fr.***: Oxycontin; Oxynorm; Oxynormoro; Targinact; ***Ger.***: Oxygesic; Targin; ***Hung.***: Oxycontin; ***Irl.***: Dancex; Oxycontin; Oxydon; Oxynorm; Targin; ***Israel***: Oxycod; Oxycontin; Targin; ***Ital.***: Oxycontin; Targin; ***Jpn***: Oxifast; Oxycontin; ***Malaysia***: Oxycontin; ***Neth.***: Oxycontin; Oxynorm; Targinact; ***Norw.***: Oxycontin; Oxynorm; Targiniq; ***NZ***: Oxycontin; Oxynorm; Targin; ***Philipp.***: Oxycontin; Oxynorm; ***Pol.***: Oxycontin; Oxynorm; ***Port.***: Oxycontin†; Oxynormoro; ***Singapore***: Oxycontin; Oxynorm; Targin; ***Spain***: Oxycontin; Oxynorm; Targin; ***Swed.***: Oxycontin; Oxynorm; Targiniq; ***Switz.***: Oxycontin; Oxynorm; Targin; ***UK***: Dolocodon; Longtec; Lynlor; Oxycontin; Oxynorm; Shortec; Targinact; ***USA***: ETH-Oxydose†; Oxecta; Oxycontin; Oxyfast; OxyIR; Roxicodone; ***Venez.***: Oxycontin.

Multi-ingredient Preparations. ***Arg.***: Oxinovag Complex; ***Canad.***: Endocet; Percocet; Percodan†; ratio-Oxycocet; ratio-Oxycodan; Rivacocet; ***China***: Tailening (泰勒宁); ***Israel***: Percocet; Percodan†; ***Ital.***: Depalgos; ***Mex.***: Plexicodim; ***USA***: Combunox†; Endocet; Magnacet; Narvox; Percocet; Percodan; Perloxx; Pimalev; Primlev; Roxicet; Roxilox; Tylox; Xolox.

Pharmacopoeial Preparations

BP 2014: Oxycodone Capsules; Oxycodone Injection; Oxycodone Oral Solution; Prolonged-release Oxycodone Tablets;
USP 36: Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Oxycodone and Aspirin Tablets; Oxycodone Hydrochloride Extended-Release Tablets; Oxycodone Hydrochloride Oral Solution; Oxycodone Hydrochloride Tablets.

Oxymorphone Hydrochloride

(BANM, rINNM) ⊗

7,8-Dihydro-14-hydroxymorphinone hydrochloride; Hidrocloruro de oximorfona; Oximorfona, hidrocloruro de; Oximorphone Hydrochloride; Oxymorphone, Chlorhydrate d'; Oxymorphoni Hydrochloridum; Оксиморфона Гидрохлорид.

6-Deoxy-7,8-dihydro-14-hydroxy-6-oxomorphine hydrochloride; (-)-(5*R*,6*S*,14*S*)-4,5-Epoxy-3,14-dihydroxy-9a-methylmorphinan-6-one hydrochloride.

$C_{17}H_{19}NO_4$,HCl=337.8

CAS — 76-41-5 (oxymorphone); 357-07-3 (oxymorphone hydrochloride).

UNII — 5Y2EI94NBC.

Pharmacopoeias. In *US.*

USP 36: (Oxymorphone Hydrochloride). A white or slightly off-white odourless powder, darkening on exposure to light. Its aqueous solutions are slightly acidic. Soluble 1 in 4 of water, 1 in 100 of alcohol, and 1 in 25 of methyl alcohol; very slightly soluble in chloroform and in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Oxymorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p. 108.1) with actions and uses similar to those of morphine (p. 92.3), apart from a lack of cough suppressant activity. Oxymorphone is given orally, parenterally, or rectally for the relief of moderate to severe pain, including pain in obstetrics, and is reported to provide analgesia for 3 to 6 hours. It may also be used parenterally for premedication, as an adjunct to anaesthesia, and to relieve dyspnoea due to pulmonary oedema resulting from left ventricular failure.

A usual *oral* starting dose for opioid-naive patients is 10 to 20 mg of oxymorphone hydrochloride every 4 to 6 hours adjusted thereafter as necessary; some patients may be started on lower doses of 5 mg. For patients who have been receiving a strong opioid analgesic the initial dose of oxymorphone should be based on the daily opioid requirement; licensed product information suggests that 10 mg of oral oxymorphone is equivalent to about 30 mg of oral morphine and recommends giving half the calculated equivalent dose of oxymorphone initially. Oxymorphone hydrochloride may also be given orally as a modified-release preparation every 12 hours. Oral preparations of oxymorphone should be taken on an empty stomach.

Oxymorphone hydrochloride is given by *intramuscular* or *subcutaneous injection* in initial doses of 1 to 1.5 mg, repeated every 4 to 6 hours as necessary; 500 micrograms may be given by intravenous injection. The usual dose for analgesia during labour is 0.5 to 1 mg intramuscularly. When transferring between oral and parenteral oxymorphone, licensed product information advises that, as a guide, 10 mg of oral oxymorphone is equivalent to about 1 mg of parenteral oxymorphone.

Oxymorphone hydrochloride is also given *rectally* as a suppository in a dose of 5 mg every 4 to 6 hours.

References.

1. Prommer E. Oxymorphone: a review. *Support Care Cancer* 2006; **14:** 109–15.
2. Chamberlin KW, *et al.* Oral oxymorphone for pain management. *Ann Pharmacother* 2007; **41:** 1144–52.
3. Mayyas F, *et al.* A systematic review of oxymorphone in the management of chronic pain. *J Pain Symptom Manage* 2010; **39:** 296–308.

Administration in hepatic impairment. Advice on the use of oxymorphone in patients with hepatic impairment is conflicting. Licensed product information for one range of preparations (*Opana* and *Opana ER tablets; Endo, USA*) recommends caution in patients with mild hepatic impairment; these patients should be started on the lowest oral dose and titrated slowly thereafter. In addition, it is stated that oxymorphone is contra-indicated in those with moderate or severe impairment. However, licensed information for another oxymorphone preparation (*Numorphan injection and suppositories; Endo, USA*) only recommends caution in hepatic disease although lower doses (unspecified) are advised in those patients with severe impairment.

Administration in renal impairment. In patients with moderate to severe renal impairment, the bioavailability of oxymorphone was found to increase by over 50%; consequently, it is recommended that oxymorphone is given with caution and in reduced doses (unspecified) to those with a creatinine clearance of less than 50 mL/minute.

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

For details on the use of oxymorphone in patients with hepatic or renal impairment, see above.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Licensed product information for a modified-release preparation of oxymorphone hydrochloride (*Opana ER; Endo, USA*) states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of increased plasma concentrations and a potentially fatal overdose of oxymorphone.

Pharmacokinetics

Oxymorphone hydrochloride is absorbed from the gastrointestinal tract after oral doses, but bioavailability is only about 10% because of first-pass metabolism. Absorption is increased after a high-fat meal. About 10% is bound to plasma proteins. Oxymorphone is extensively metabolised in the liver by glucuronidation and less than 1% of a dose appears in the urine and faeces as unchanged drug. With regard to its major metabolites between 33 and 38% of a dose is excreted in the urine as oxymorphone-3-glucuronide and less than 1% as 6-OH-oxymorphone. Oxymorphone crosses the placenta.

References.

1. Adams MP, Ahdieh H. Pharmacokinetics and dose-proportionality of oxymorphone extended release and its metabolites: results of a randomized crossover study. *Pharmacotherapy* 2004; **24:** 468–76.
2. Adams MP, Ahdieh H. Single- and multiple-dose pharmacokinetic and dose-proportionality study of oxymorphone immediate-release tablets. *Drugs R D* 2005; **6:** 91–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Numorphan; Opana.

Pharmacopoeial Preparations

USP 36: Oxymorphone Hydrochloride Injection; Oxymorphone Hydrochloride Suppositories.

Oxyphenbutazone *(BAN, rINN)*

G-27202; Hydroxyphenylbutazone; Oksifenbutatsoni; Oxifenbutazon; Oxifenbutazona; Oxyphenbutazonum; Оксифенбутазон.

4-Butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione monohydrate.

$C_{19}H_{20}N_2O_3.H_2O$=342.4

CAS — 129-20-4 (anhydrous oxyphenbutazone); 7081-38-1 (oxyphenbutazone monohydrate).

ATC — M01AA03; M02AA04; S01BC02.

ATC Vet — QM01AA03; QM02AA04; QS01BC02.

UNII — H806S4B3NS (oxyphenbutazone); A7D84513GV (anhydrous oxyphenbutazone).

Profile

Oxyphenbutazone, a metabolite of phenylbutazone (p. 125.1), is an NSAID (p. 102.3). It has been applied topically to the eye as an anti-inflammatory ointment in conditions such as episcleritis. Oxyphenbutazone was used systemically in disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis but such use is no longer considered justified because of the risk of severe haematological adverse effects (see also Effects on the Blood, under Phenylbutazone, p. 125.2).

The piperazine salt has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Oxy-Triactin; Sioril.

Multi-ingredient Preparations. ***Braz.***: Algiflamanil†; Febupen; Flamanan; ***Mex.***: Dartrizon.

Paracetamol (BAN, rINN)

Acetaminofeno; Acetaminophen; *N*-Acetyl-*p*-aminophenol; Asetaminofen; Paracétamol; Paracetamolis; Paracetamolo; Paracetamolum; Parasetamol; Parasetamoli; Парацетамол.

4'-Hydroxyacetanilide; *N*-(4-Hydroxyphenyl)acetamide.

$C_8H_9NO_2$=151.2

CAS — 103-90-2.

ATC — N02BE01.

ATC Vet — QN02BE01.

UNII — 362O9ITL9D.

NOTE. Compounded preparations of paracetamol may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—paracetamol and codeine phosphate
- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w)
- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol
- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol, respectively
- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol
- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w)
- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Paracetamol). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 36: (Acetaminophen). A white odourless crystalline powder. Soluble 1 in 20 of boiling water, 1 in 10 of alcohol, and 1 in 15 of 1*N* sodium hydroxide. Store in airtight containers. Protect from light. Protect from moisture and heat.

Uses and Administration

Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain (below) and for fever (p. 11.3). It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contra-indicated. Such patients include asthmatics, those with a history of peptic ulcer, and children.

The usual **oral** dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. Paracetamol may also be given as suppositories in a **rectal** dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Paracetamol is given by **intravenous** infusion over 15 minutes; dosage may be calculated according to bodyweight as follows:

- over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily
- from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 3 g) daily

A maximum intravenous dose of 3 g daily should also not be exceeded in patients with chronic alcoholism, chronic malnutrition, or dehydration, regardless of their bodyweight.

For doses in children, or in hepatic or renal impairment, see below.

References.

1. Prescott LF. *Paracetamol (acetaminophen): a critical bibliographic review.* London: Taylor & Francis, 1996.
2. Bannwarth B, Péhourcq F. Bases pharmacologiques de l'emploi du paracétamol: aspects pharmacocinétiques et pharmacodynamiques. *Drugs* 2003; **63** (suppl 2): 5–13.
3. Prescott LF. Nouvelles perspectives avec le paracétamol. *Drugs* 2003; **63** (suppl 2): 51–6.
4. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). *Drugs* 2009; **69:** 101–13.

Administration in children. In the UK, the licensed **oral** doses of paracetamol for pain and fever in children, given according to age, every 4 to 6 hours if necessary up to a maximum of 4 doses in 24 hours, are:

- 3 to 6 months: 60 mg
- 6 months to 2 years: 120 mg
- 2 to 4 years: 180 mg
- 4 to 6 years: 240 mg
- 6 to 8 years: 240 or 250 mg
- 8 to 10 years: 360 or 375 mg
- 10 to 12 years: 480 or 500 mg
- 12 to 16 years: 480 or 750 mg

In younger children the *BNFC* suggests the following doses:

- neonates 28 to 32 weeks postmenstrual age (gestational age at birth plus chronological age): 20 mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hours if necessary up to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 20 mg/kg as a single dose then 10 to 15 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours if necessary

The *BNFC* also suggests higher oral doses for use in children with ***severe*** postoperative pain:

- 1 month to 12 years: 20 to 30 mg/kg as a single dose followed by 15 to 20 mg/kg every 4 to 6 hours if necessary up to a maximum of 90 mg/kg daily. Usual adult maximum single and daily doses (see above) should not be exceeded

UK licensed **rectal** doses, which may be given to children every 4 to 6 hours if necessary, up to 4 times daily are:

- 3 months to 1 year: 60 to 125 mg
- 1 to 5 years: 125 to 250 mg
- 5 to 12 years: 250 to 500 mg

The *BNFC* suggests the following rectal doses in younger children:

- neonates 28 to 32 weeks postmenstrual age: 20 mg/kg as a single dose then 15 mg/kg every 12 hours if necessary to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 30 mg/kg as a single dose then 20 mg/kg every 8 hours if necessary to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours if necessary

The *BNFC* also suggests higher rectal doses for use in children with ***severe*** postoperative pain:

- 1 to 3 months: 30 mg/kg as a single dose followed by 15 to 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily
- older children: 30 to 40 mg/kg as a single dose followed by 15 to 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily. Usual adult maximum single and daily doses (see above) should not be exceeded

Doses by **intravenous** infusion in children, given, according to body-weight, over 15 minutes, are:

- full-term neonates and other children below 10 kg: single doses of 7.5 mg/kg every 4 or more hours, to a maximum of 30 mg/kg daily. The *BNFC* suggests a dose of 10 mg/kg every 4 to 6 hours to a maximum of 30 mg/kg daily; intravenous paracetamol has not been studied in premature neonates but the *BNFC* suggests for premature neonates over 32 weeks postmenstrual age, a dose of 7.5 mg/kg every 8 hours to a maximum of 25 mg/kg daily
- between 10 and 33 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 2 g) daily
- from 33 to 50 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 3 g) daily
- over 50 kg: usual adult doses (see above)

The intravenous solution may be diluted to a minimum strength of one-tenth of its original concentration in sodium chloride 0.9% or glucose 5%; the diluted solution should be used within 1 hour of preparation.

For ***post-immunisation pyrexia***, an oral or rectal dose of 60 mg has been recommended for children 2 to 3 months of age. If necessary a second dose may be given after 4 to 6 hours; if the pyrexia persists after that dose, medical advice should be sought.

It has been suggested[1] that the recommended doses of paracetamol for children may result in subtherapeutic blood concentrations, and that an initial loading dose should be given, followed by regular doses up to the recommended maximum daily dose. However, the appropriate maximum daily dose remains controversial, and there is obvious concern given the risks of overdosage. Indeed, there have been concerns about the potential for hepatotoxicity with therapeutic doses of paracetamol in children (defined as an oral or intravenous dose of ≤75 mg/kg daily, maximum of 4 g daily, or a rectal dose of ≤100 mg/kg daily, maximum of 5 g daily). Nevertheless, a systematic review[2] of controlled studies and case reports suggested that the risk of developing symptomatic hepatotoxicity with such use is less than 0.01%.

1. Zacharias M, Watts D. Pain relief in children. *BMJ* 1998; **316:** 1552.
2. Lavonas EJ, *et al.* Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics* 2010; **126:** e1430–e1444.

Administration in hepatic impairment. There is evidence to suggest that paracetamol can be safely used in patients with hepatic impairment (see under Precautions, p. 118.2); however, reduced doses may be warranted to avoid accidental overdosages. The *BNF* recommends avoiding large doses in patients with hepatic impairment; others have suggested that doses of 2 to 3 g daily should not be exceeded in patients with cirrhosis requiring long-term use although a daily dose of 3 to 4 g may be safe for short-term or one-off use.[1] UK licensed product information recommends that the maximum dose of intravenous paracetamol should not exceed 3 g daily in patients with hepatic impairment or chronic alcoholism; it also states that those with severe impairment should not be given paracetamol by this route.

1. Chandok N, Watt KDS. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 2010; **85:** 451–8.

Administration in renal impairment. In renally impaired patients with a creatinine clearance of 30 mL/minute or less it is recommended that the interval between each intravenous paracetamol dose is increased to 6 hours.

Headache. Non-opioid analgesics such as paracetamol, aspirin, and other NSAIDs are often tried first for the symptomatic treatment of various types of headache including migraine (see p. 670.3) and tension-type headache (see p. 671.3). These drugs given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

References.

1. Derry S, *et al.* Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Available in The Cochrane Database of Systematic Reviews; Issue 11. Chichester: John Wiley; 2010 (accessed 03/12/10).

Pain. Paracetamol is used in the management of mild to moderate pain (see Choice of Analgesic, p. 4.2). It is of similar potency to aspirin, but with weak anti-inflammatory activity. Paracetamol may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p. 7.1). Paracetamol is the preferred choice for pain in children (p. 5.2) because of the association of aspirin with Reye's syndrome in this age group (see p. 25.3). In the treatment of rheumatic disorders, a weak anti-inflammatory effect limits the role of paracetamol. However, it may be of benefit for simple pain control in rheumatoid arthritis (p. 13.2) and ankylosing spondylitis (see under Spondyloarthropathies, p. 14.3), although these patients usually require the additional anti-inflammatory effects provided by NSAIDs. Synovial inflammation is usually only a minor component of osteoarthritis (p. 12.3), and paracetamol is generally recommended as first choice of treatment before NSAIDs are tried. Paracetamol is useful for the relief of acute low back pain (p. 9.2).

Dependence and tolerance are not a problem with non-opioid analgesics such as paracetamol, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

Adverse Effects and Treatment

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Rashes and other hypersensitivity reactions occur occasionally.

Injection site reactions such as pain and a burning sensation are common after parenteral use; hypotension and tachycardia have been reported rarely. Application site reactions have also been noted after rectal use.

Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential and is discussed under Overdosage, p. 116.2.

References.

1. Graham GG, *et al.* Tolerability of paracetamol. *Drug Safety* 2005; **28:** 227–40.

Carcinogenicity. A prospective cohort study[1] involving over 64 000 men and women between 50 and 76 years of age found that use of paracetamol for more than 4 days a week for longer than 4 years was associated with a two-fold increase in the risk of haematological malignancies. The authors considered that other prospective studies were required before any recommendations about paracetamol use could be made.

1. Walter RB, *et al.* Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective vitamins and lifestyle (VITAL) study. *J Clin Oncol* 2011; **29:** 2424–31.

Effects on the cardiovascular system. Large cohort studies[1,2] have shown an association between the use of non-opioid analgesics, including paracetamol, and a significantly increased risk of hypertension in women; similar studies[3,4] in men have been equivocal but suggest a more moderate increase in risk. However, it has also been suggested[5] that the hypertension may have been caused by

pain itself or more likely to be detected in patients taking more paracetamol due to a higher frequency of visits to their doctor.

1. Dedier J, *et al.* Nonnarcotic analgesic use and the risk of hypertension in US women. *Hypertension* 2002; **40:** 604–8.
2. Forman JP, *et al.* Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension* 2005; **46:** 500–507.
3. Kurth T, *et al.* Analgesic use and risk of subsequent hypertension in apparently healthy men. *Arch Intern Med* 2005; **165:** 1903–9.
4. Forman JP, *et al.* Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007; **167:** 394–9.
5. Montgomery B. Does paracetamol cause hypertension? *BMJ* 2008; **336:** 1190–1.

Effects on the ears. A questionnaire study in nearly 27 000 male health professionals originally aged 40 years and over has examined the association between hearing loss and the regular use of aspirin, NSAIDs, and paracetamol.[1] During 369 079 person-years of follow-up, 3488 cases of hearing loss were reported; regular analgesic use (defined as 2 or more times a week) was found to be independently associated with an increased risk of hearing loss for all 3 types of analgesics. The hazard ratio of hearing loss for regular users of paracetamol was 1.22 when compared with those who used analgesics less frequently; the risk also increased with longer duration of use. Concomitant use of more than one type of analgesic also had an additive risk effect.

For reference to reports of hearing loss associated with the abuse or overuse of preparations containing paracetamol, see under Dextropropoxyphene, p. 44.2, and Hydrocodone, p. 67.2.

1. Curhan SG, *et al.* Analgesic use and the risk of hearing loss in men. *Am J Med* 2010; **123:** 231–7.

Effects on the kidneys. For reference to evidence that abuse or prolonged excessive use of analgesics, including paracetamol, can produce nephropathy, see under NSAIDs, p. 106.2.

See also under Overdosage, below.

Effects on metabolism. Use of paracetamol, alone or with other drugs (see under Flucloxacillin, p. 302.1), has been associated with accumulation of pyroglutamic acid, resulting in pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.[1-4]

1. Humphreys BD, *et al.* Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital. *Am J Kidney Dis* 2005; **46:** 143–6.
2. Fenves AZ, *et al.* Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. *Clin J Am Soc Nephrol* 2006; **1:** 441–7.
3. Alados Arboledas FJ, *et al.* Acidosis piroglutámica asociada a paracetamol. *An Pediatr (Barc)* 2007; **67:** 582–4.
4. Verma R, *et al.* 5-Oxoprolinuria as a cause of high anion gap metabolic acidosis. *Br J Clin Pharmacol* 2012; **73:** 489–91.

Effects on the respiratory tract. The results of a case-control study[1] have suggested that the frequent (daily or weekly) use of paracetamol may be associated with asthma. However, the UK CSM has commented that the results of this study do not alter any advice regarding the use of paracetamol and that it remains a safe and effective pain killer for many patients including asthmatics.

Subsequently, others have found an increase in the prevalence of asthma[2,3] and COPD[2] with frequent (daily or weekly) use of paracetamol. A link between paracetamol use in pregnancy and asthma in children has also been suggested (see Pregnancy under Precautions, p. 118.2). However, one review[4] stated that there have been very few actual reports of paracetamol causing asthma; furthermore, bronchospasm is not a recognised feature of paracetamol overdosage. This review concluded that a strong link between paracetamol use and asthma was unlikely.

More recently, analysis of questionnaire data[5] for 205 487 children aged 6 to 7 years from 31 countries suggested that the use of paracetamol in the first year of life and later childhood was associated with an increased risk of asthma and also symptoms of rhinoconjunctivitis and eczema. In another questionnaire study[6] by the same group involving 322 959 adolescents aged 13 to 14 years from 50 countries, the recent use of paracetamol was also found to increase the risk of asthma, rhinoconjunctivitis, and eczema. However, after considering the first study, the UK CHM[7] expressed concerns over data interpretation and concluded that it did not provide strong evidence that paracetamol use in infancy can cause asthma; the CHM reiterated that paracetamol remains a safe and appropriate analgesic for children. Furthermore, a small cohort study[8] has also found that, although the use of paracetamol in the first 2 years of life increased the crude risk of asthma in children aged 6 to 7 years, this increase was not noted after adjustment for early respiratory-tract infections or when paracetamol use was limited to non-respiratory-tract infections.

1. Shaheen SO, *et al.* Frequent paracetamol use and asthma in adults. *Thorax* 2000; **55:** 266–70.
2. McKeever TM, *et al.* The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005; **171:** 966–71.
3. Eneli I, *et al.* Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; **127:** 604–12.
4. Nuttall SL, *et al.* Does paracetamol cause asthma? *J Clin Pharm Ther* 2003; **28:** 251–7.
5. Beasley R, *et al.* ISAAC Phase Three Study Group. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008; **372:** 1039–48.
6. Beasley RW, *et al.* ISAAC Phase Three Study Group. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. *Am J Respir Crit Care Med* 2011; **183:** 171–8.
7. MHRA/CHM. Paracetamol use in infancy: no strong evidence for asthma link. *Drug Safety Update* 2008; **2**(4): 9. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON030923 (accessed 13/10/09)
8. Lowe AJ, *et al.* Paracetamol use in early life and asthma: prospective birth cohort study. Abridged version: *BMJ* 2010; **341:** 713. Full version: http://www.bmj.com/content/341/bmj.c4616.full.pdf (accessed 06/05/11)

Hypersensitivity. Reactions characterised by urticaria, dyspnoea, and hypotension have occurred after use of paracetamol in adults[1-4] and children.[5,6] Angioedema has also been reported.[7] Fixed drug eruptions, confirmed by rechallenge, have been described,[8-11] and toxic epidermal necrolysis has occurred.[12]

1. Stricker BHC, *et al.* Acute hypersensitivity reactions to paracetamol. *BMJ* 1985; **291:** 938–9.
2. Van Diem L, Grilliat JP. Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* 1990; **38:** 389–90.
3. Kumar RK, Byard I. Paracetamol as a cause of anaphylaxis. *Hosp Med* 1999; **60:** 66–7.
4. Bachmeyer C, *et al.* Acetaminophen (paracetamol)-induced anaphylactic shock. *South Med J* 2002; **95:** 759–60.
5. Ellis M, *et al.* Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry. *J Pediatr* 1989; **114:** 654–6.
6. Bousetta K, *et al.* Hypersensitivity reactions to paracetamol in children: a study of 25 cases. *Allergy* 2005; **60:** 1174–7.
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8. Thomas RHM, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986; **115:** 357–9.
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10. Harris A, Burge SM. Vasculitis in a fixed drug eruption due to paracetamol. *Br J Dermatol* 1995; **133:** 790–1.
11. Hern S, *et al.* Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern. *Br J Dermatol* 1998; **139:** 1129–31.
12. Halevi A, *et al.* Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; **34:** 32–4.

Overdosage. Acute ***oral*** overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Toxic doses of paracetamol may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Paracetamol-induced hepatotoxicity is a major cause of acute liver failure in western countries. Hepatotoxicity may occur after ingestion of more than 150 mg/kg, or rarely, as little as 75 mg/kg, of paracetamol within a 24-hour period. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.[1,2]

Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at high risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia, AIDS, or cystic fibrosis. Those who have not eaten for a few days or those with a low body-weight[3] are also predisposed to hepatotoxicity. These factors have previously been used for risk stratification in paracetamol overdosage; however, not all have been well characterised or applied consistently. Hence, the UK CHM has advised that individual risk factors should no longer be used for assessing the risk of toxicity.

Early **signs** of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured regularly. However, as both paracetamol[4] and acetylcysteine[5] can independently affect prothrombin time in the absence of hepatic injury, the use of prothrombin time as a marker for hepatotoxicity has been questioned and it has been recommended that treatment decisions are based on the entire liver biochemistry.[6]

Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

The **mechanism** of toxicity in overdosage with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)[2] in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamol overdosage, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamol overdosage. Acetylcysteine may also be involved in the repair of damaged tissue.

Treatment of oral paracetamol overdosage. The management of paracetamol overdosage as practised in the UK and USA has been the subject of many reviews.[6-15] Guidance is also available in the UK from the *National Poisons Information Service (NPIS)*. Separate consensus guidelines have been issued by clinical toxicologists in Australia and New Zealand.[16]

Prompt treatment is essential, even when there are no obvious symptoms, and patients should be admitted to hospital for full supportive measures to be instituted.

- Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given orally the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.
- There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.
- The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used, see Figure 1 (p. 117) and Figure 2 (p. 117). Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is on or above the reference (treatment) line.
- Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatotoxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.[17-19] Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdosage with modified-release preparations have been made.[20-22]
- Plasma-paracetamol concentrations and the Rumack-Matthew nomogram are also of little value in patients who have taken repeated supratherapeutic doses or multiple overdoses of paracetamol over a short period of time: such patients should be considered at serious risk and given antidote treatment.
- If there is any doubt about timing or the need to treat, or where the overdose is staggered, then a patient **should** be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma-paracetamol concentrations.[23]
- Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is on or above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.

Choice of antidote. Acetylcysteine (p. 1652.2) is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.[6,24] Intravenous use has been associated with anaphylactic reactions but is the preferred route in some countries including Australia, New Zealand, and the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is also licensed, and is clearly effective. The use of methionine (p. 1558.2) orally has the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and has been used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting. However, it has been largely superseded by acetylcysteine.

Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.

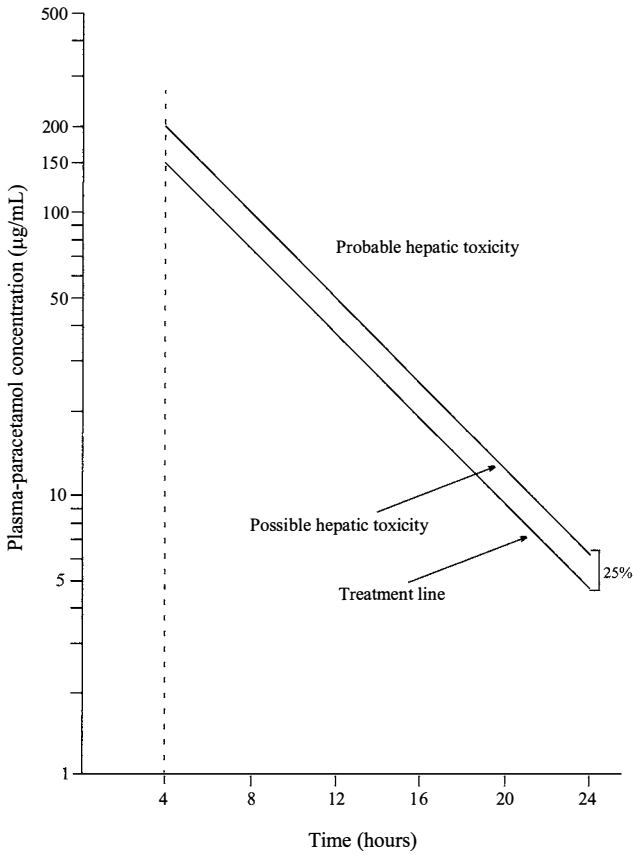

Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55:** 871–6.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. The solid line 25% below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose. Patients whose plasma-paracetamol concentrations are on or above this line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

Figure 2. A linear plot of plasma-paracetamol concentration against hours after ingestion.

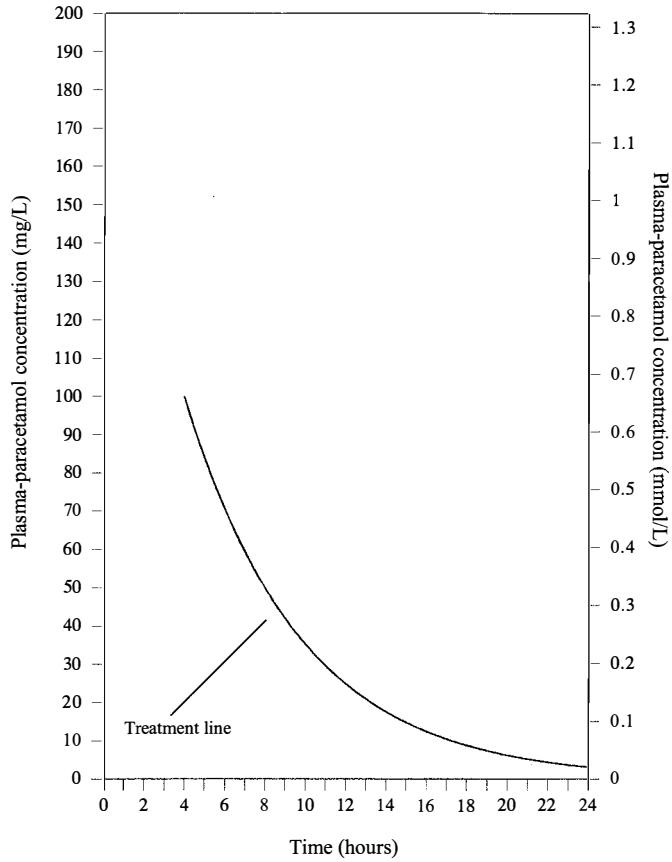

Courtesy of MHRA.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. Patients whose plasma-paracetamol concentrations are on or above the treatment line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

Acetylcysteine is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,[25] and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.[26,27] Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.[28]

- An initial dose of 150 mg/kg (maximum of 16.5 g) of acetylcysteine in 200 mL of glucose 5% is given intravenously over 60 minutes. This is followed by an intravenous infusion of 50 mg/kg (maximum of 5.5 g) in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg (maximum of 11 g) in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children or those with a body-weight of less than 40 kg. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate.
- In the USA, acetylcysteine is also licensed for oral use as an alternative to parenteral treatment. It is given as an initial dose of 140 mg/kg as a 5% solution followed by 70 mg/kg every 4 hours for an additional 17 doses. Similar doses have been recommended by the *NPIS* in the UK when venous access is not practicable. Some[29] have suggested increasing the loading dose of oral acetylcysteine when it is given after activated charcoal, whereas others[30] have found that the efficacy of acetylcysteine is not reduced by use of activated charcoal beforehand and consider a larger acetylcysteine dose unnecessary.
- *Pretreatment.* The *NPIS* recommends pretreating patients with antihistamines (histamine H_1- and H_2-antagonists) if they have previously had an anaphylactoid reaction to acetylcysteine: intravenous chlorphenamine 10 mg and intravenous ranitidine 50 mg diluted to 20 mL may be given over at least 2 minutes. Pretreatment with nebulised salbutamol can be used in those with a history of acetylcysteine-associated bronchospasm. A slower initial infusion rate may be warranted in patients who have previously had a severe reaction to acetylcysteine.

Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamol overdosage. However, it is not as effective if treatment is delayed[31-33] and hepatic damage is more frequent and severe if treatment with methionine is started more than 10 hours after ingestion; it may also precipitate hepatic encephalopathy.

- The usual oral dose of methionine in adults and children aged 6 years or older is 2.5 g every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol and provided the patient is not vomiting. Children aged under 6 years should be given 1 g every 4 hours for 4 doses.

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. Preparations containing both methionine and paracetamol (co-methiamol) have been formulated for use in situations where overdosage may occur.

Histamine H_2-antagonists. It has been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Although there have been several anecdotal reports claiming benefit for cimetidine in patients with paracetamol poisoning, there is no current evidence to support these claims.[6,10,12,34]

Liver transplantation may be considered as a last recourse in some patients.

After maternal **overdosage during pregnancy** fetal metabolism of paracetamol that crosses the placenta can produce sufficient hepatotoxic metabolites to cause fetal hepatotoxicity. Limited data from case reports and a case series suggest that early treatment with oral or intravenous acetylcysteine can be safe and effective in such cases;[35] the *UK National Teratology Information Service* recommends the use of acetylcysteine if clinically indicated. Pre-pregnancy body-weight should be used to calculate the toxic paracetamol dose and actual pregnant body-weight to calculate the antidote dose.

Dosage errors with ***intravenous*** paracetamol have been reported, particularly in young children; rarely, such errors have resulted in substantial overdoses and liver damage.[36,37] The standard nomogram may not be appropriate in determining treatment from plasma-paracetamol concentrations after overdosage by intravenous infusion, as it is based on data from acute paracetamol ingestion rather than intravenous administration. Plasma-paracetamol concen-

trations more than 4 hours after intravenous injection are usually lower than those predicted for the same oral dose at the same time-point after ingestion. Furthermore, patients receiving intravenous paracetamol are likely to have an increased risk of hepatotoxicity due to poor nutrition from acute fasting. The *NPIS* recommends antidote treatment with intravenous acetylcysteine (see above for doses) when 60 mg/kg or more of paracetamol in total has been given intravenously to adults and children within 24 hours. If there is uncertainty about the actual dose of paracetamol given, the standard nomogram may be used to determine the risk of liver damage. Antidote treatment (see above) is required if plasma-paracetamol concentrations, measured at least 4 hours after administration, are up to 50% below the reference line (for example—treat if the concentration is above 50 mg/L at 4 hours) (see Figure 1 and Figure 2, p. 117).

1. Miles FK, *et al*. Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999; **171:** 472–5.
2. American Academy of Pediatrics Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics* 2001; **108:** 1020–4.
3. Claridge LC, *et al*. Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults. *BMJ* 2010; **341:** 1269–70.
4. Whyte IM, *et al*. Acetaminophen causes an increased International Normalized Ratio by reducing functional factor VII. *Ther Drug Monit* 2000; **22:** 742–8.
5. Schmidt LE, *et al*. Effect of acetylcysteine on prothrombin index in paracetamol poisoning without hepatocellular injury. *Lancet* 2002; **360:** 1151–2.
6. Brok J *et al*. Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/10/06).
7. Whitcomb DC, *et al*. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* 1994; **272:** 1845–50.
8. Makin AJ, *et al*. Management of severe cases of paracetamol overdosage. *Br J Hosp Med* 1994; **52:** 210–13.
9. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; **346:** 547–52.
10. Prescott LF. Paracetamol overdose. In: *Paracetamol (acetaminophen): a critical bibliographic review*. London: Taylor & Francis, 1996: 401–73.
11. Routledge P, *et al*. Paracetamol (acetaminophen) poisoning. *BMJ* 1998; **317:** 1609–10.
12. Zed PJ, Krenzelok EP. Treatment of acetaminophen overdose. *Am J Health-Syst Pharm* 1999; **56:** 1081–91.
13. Kozer E, Koren G. Management of paracetamol overdose: current controversies. *Drug Safety* 2001; **24:** 503–12.
14. Dart RC, *et al*. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2006; **44:** 1–18.
15. Ferner RE, *et al*. Management of paracetamol poisoning. *BMJ* 2011; **342:** d2218.
16. Daly FFS, *et al*. Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration: a consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. *Med J Aust* 2008; **188:** 296–301. Also available at: http://www.mja.com.au/public/issues/188_05_030308/dal10916_fm.html (accessed 13/08/08)
17. Graudins A, *et al*. Overdose of extended-release acetaminophen. *N Engl J Med* 1995; **333:** 196.
18. Vassallo S, *et al*. Use of the Rumack-Matthew nomogram in cases of extended-release acetaminophen toxicity. *Ann Intern Med* 1996; **125:** 940.
19. Dart RC, *et al*. The safety profile of sustained release paracetamol during therapeutic use and following overdose. *Drug Safety* 2005; **28:** 1045–56.
20. Temple AR, Mrazik TJ. More on extended-release acetaminophen. *N Engl J Med* 1995; **333:** 1508.
21. Graudins A, *et al*. More on extended-release acetaminophen. *N Engl J Med* 1995; **333:** 1508–9.
22. Cetaruk EW, *et al*. Extended-release acetaminophen overdose. *JAMA* 1996; **275:** 686.
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24. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; **63:** 1821–7.
25. Parker D, *et al*. Safety of late acetylcysteine treatment in paracetamol poisoning. *Hum Exp Toxicol* 1990; **9:** 25–7.
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30. Spiller HA, *et al*. A prospective evaluation of the effect of activated charcoal before oral N-acetylcysteine in acetaminophen overdose. *Ann Emerg Med* 1994; **23:** 519–23.
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32. Vale JA, *et al*. Treatment of acetaminophen poisoning: the use of oral methionine. *Arch Intern Med* 1981; **141:** 394–6.
33. Tee LGB, *et al*. N-Acetylcysteine for paracetamol overdose. *Lancet* 1986; **i:** 331–2.
34. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; **55:** 1516–19.
35. Wilkes JM, *et al*. Acetaminophen overdose in pregnancy. *South Med J* 2005; **98:** 1118–22.
36. Beringer RM, *et al*. Intravenous paracetamol overdose: two case reports and a change to national treatment guidelines. *Arch Dis Child* 2011; **96:** 307–8.
37. Dart RC, Rumack BH. Intravenous acetaminophen in the United States: iatrogenic dosing errors. *Pediatrics* 2012; **129:** 349–53.

Pancreatitis. Drug-induced pancreatitis associated with paracetamol was reported[1] to be a rare reaction only occurring in patients taking more than recommended doses. In a retrospective study of data from 814 patients who had taken paracetamol overdoses, hyperamylasaemia was detected in 246, and was more common and more severe in patients transferred to a specialist unit because of more severe poisoning.[2] However, acute pancreatitis was diagnosed only in 33 cases.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.
2. Schmidt LE, Dalhoff K. Hyperamylasaemia and acute pancreatitis in paracetamol poisoning. *Aliment Pharmacol Ther* 2004; **20:** 173–9.

Precautions

Paracetamol should be given with care to patients with impaired kidney or liver function; the *BNF* recommends that large doses should be avoided in patients with hepatic impairment. It should also be given with care to patients with alcohol dependence, chronic malnutrition, or dehydration.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving paracetamol, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of paracetamol distributed into breast milk is too small to be harmful to a breast-fed infant.

Pharmacokinetic studies in 12 nursing mothers given a single dose of paracetamol showed that peak paracetamol concentrations in breast milk of 10 to 15 micrograms/mL were achieved in 1 to 2 hours. Plasma concentrations were determined in 2 mothers; a breast milk to plasma ratio of about 1 was reported.[2] Similar findings have been reported from other studies.[3,4]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/10/06)
2. Berlin CM, *et al*. Disposition of acetaminophen in milk, saliva, and plasma of lactating women. *Pediatr Pharmacol* 1980; **1:** 135–41.
3. Hurden EL, *et al*. Excretion of paracetamol in human breast milk. *Arch Dis Child* 1980; **55:** 969–72.
4. Bitzén P-O, *et al*. Excretion of paracetamol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 123–5.

Hepatic impairment. Reviews[1,2] have concluded that there is evidence that paracetamol could be and had been used safely in patients with liver disease. Studies had also shown that although the half-life of paracetamol was prolonged in such patients, glutathione concentrations in those taking recommended doses were not depleted to the critical levels that would enable accumulation of paracetamol's hepatotoxic metabolite.

1. Benson GD, *et al*. The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther* 2005; **12:** 133–41.
2. Chandok N, Watt KDS. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 2010; **85:** 451–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paracetamol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The *UK National Teratology Information Service* recommends that paracetamol may be used in pregnancy if appropriate. As a whole, *animal* and epidemiological studies show that the therapeutic use of paracetamol during pregnancy does not increase the risk of an adverse outcome.[1]

A large prospective study has reported that the frequent use of paracetamol (defined as most days or daily use) in late pregnancy (20 to 32 weeks of gestation) may be associated with an increased risk of persistent wheezing in the infant[2] which may persist into childhood;[3] use during early pregnancy was not associated with an increased risk. Several reviews and meta-analyses have considered the link between childhood asthma and wheezing and prenatal paracetamol exposure;[4-6] however, while some consider that there may be a link, others consider that the data were conflicting and evidence for a causal association is inconclusive (see also Effects on the Respiratory Tract, p. 116.1). Furthermore, the authors of the original study[2] emphasised that the number of pregnant women taking frequent doses was very small and they recommended that *infrequent* paracetamol should remain the analgesic of choice in pregnancy.

For reference to a possible association between simple analgesics including paracetamol and congenital cryptorchidism, see under NSAIDs, p. 107.2.

1. Scialli AR, *et al*. A review of the literature on the effects of acetaminophen on pregnancy outcome. *Reprod Toxicol* 2010; **30:** 495–507.
2. Shaheen SO, *et al*. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; **57:** 958–63.
3. Shaheen SO, *et al*. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; **35:** 18–25.
4. Scialli AR, *et al*. Childhood asthma and use during pregnancy of acetaminophen: a critical review. *Reprod Toxicol* 2010; **30:** 508–19.
5. Etminan M, *et al*. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* 2009; **136:** 1316–23.
6. Eyers S, *et al*. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011; **41:** 482–9.

Renal impairment. Caution is recommended when giving paracetamol to patients with renal impairment. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis.[1-3] It has been suggested that paracetamol itself may be regenerated from these metabolites.[1,2] There are conflicting data on whether the conjugates of paracetamol accumulate in patients with renal impairment receiving multiple doses.[2,3]

1. Prescott LF, *et al*. Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. *Eur J Clin Pharmacol* 1989; **36:** 291–7.
2. Martin U, *et al*. The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure. *Eur J Clin Pharmacol* 1991; **41:** 43–6.
3. Martin U, *et al*. The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis. *Eur J Clin Pharmacol* 1993; **45:** 141–5.

Interactions

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Reviews.

1. Toes MJ, *et al*. Drug interactions with paracetamol. *Am J Ther* 2005; **12:** 56–66.

Antibacterials. The plasma-paracetamol concentrations considered an indication for antidote treatment (see Overdosage, p. 116.2) should be halved in patients receiving enzyme-inducing drugs such as *rifampicin*. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving *isoniazid*, alone[1-3] or with other drugs for tuberculosis.[4]

For the effects of paracetamol on *chloramphenicol*, see p. 260.3.

For reports of metabolic effects when paracetamol is given with *flucloxacillin*, see under Adverse Effects and Precautions of Flucloxacillin, p. 302.1.

1. Murphy R, *et al*. Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann Intern Med* 1990; **113:** 799–800.
2. Moulding TS, *et al*. Acetaminophen, isoniazid, and hepatic toxicity. *Ann Intern Med* 1991; **114:** 431.
3. Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. *Am J Gastroenterol* 1993; **88:** 590–2.
4. Nolan CM, *et al*. Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. *Chest* 1994; **105:** 408–11.

Anticoagulants. For the effects of paracetamol on oral anticoagulants, see under Warfarin, p. 1530.2.

Antiepileptics. The plasma-paracetamol concentrations considered an indication for antidote treatment (see Overdosage, p. 116.2) should be halved in patients receiving enzyme-inducing drugs such as *carbamazepine*, *phenobarbital*, *phenytoin*, or *primidone*.

For the effects of paracetamol on *lamotrigine*, see p. 530.1.

Antivirals. For reports of adverse effects on the liver associated with use of paracetamol with antiviral drugs, see under Interferon Alfa, p. 997.2 and Zidovudine, p. 1026.2.

Probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.[1] Although urinary excretion of the sulfate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

1. Kamali F. The effect of probenecid on paracetamol metabolism and pharmacokinetics. *Eur J Clin Pharmacol* 1993; **45:** 551–3.

Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged

paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

References.

1. van der Marel CD, *et al*. Paracetamol and metabolite pharmacokinetics in infants. *Eur J Clin Pharmacol* 2003; **59:** 243–51.
2. Gregoire N, *et al*. Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. *Clin Pharmacol Ther* 2007; **81:** 401–5.
3. Kumpulainen E, *et al*. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics* 2007; **119:** 766–71.
4. Palmer GM, *et al*. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008; **101:** 523–30.
5. Liukas A, *et al*. Pharmacokinetics of intravenous paracetamol in elderly patients. *Clin Pharmacokinet* 2011; **50:** 121–9.
6. Allegaert K, *et al*. The pharmacokinetics of intravenous paracetamol in neonates: size matters most. *Arch Dis Child* 2011; **96:** 575–80.
7. Zuppa AF, *et al*. Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever. *J Pediatr Pharmacol Ther* 2011; **16:** 246–61.
8. Kulo A, *et al*. Pharmacokinetics of paracetamol and its metabolites in women at delivery and postpartum. *Br J Clin Pharmacol* 2012. Available at: doi:10.1111/j.1365-2125.2012.04402.x

Absorption. The absorption of paracetamol was slow and incomplete in vegetarian subjects compared with non-vegetarian subjects.[1]

1. Prescott LF, *et al*. Impaired absorption of paracetamol in vegetarians. *Br J Clin Pharmacol* 1993; **36:** 237–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acetolit; Alikal Dolor; Apracur Antifebril†; Apracur Te Antifebril; Bio Grip-T; Causalon; Dirox; Doxidol†; Fiebrolex†; Fiebrolito†; Flash; Inmunogrip T Caliente; Itedal; Mejoral; Nodipir; Novo Asat; Para Z Mol; Parageniol; Paratral; Parclen; Plovacal; Qura Plus; Tafirol T; Tafirol; Termofren; Tetradox; Vick Vitapyrena; Viclor; ***Austral.***: Chemists Own Pain & Fever; Childrens Panadol; Dymadon; Febridol; Lemsip; Panadol; Panamax; Parahexal†; Paralgin; Perfalgan; ***Austria***: Ben-u-ron; Duaneo; Grippostad; Mexalen; Momentum; Parakapton†; Paraspeed†; Perfalgan; Trimedil; ***Belg.***: Algostase Mono; Croix Blanche Mono†; Curpol†; Dafalgan; Docpara†; Dolol-Instant; Dolprone; Lemsip; Panadol; PeTam; Perdolan; Perfusalgan; Sanicopyrine; ***Braz.***: Acetamil; Acetofen; Anador PRT; Analgisen; Anatyl; Cefabrina; Cimegripe Bebe; Cimegripe-77c; Cyfenol; Din; Dorfen; Dorfenol; Dorico; Dorsanol; Emsgrip; Fervex; Gripotermon†; Paracen; Paracetrex; Paraflan; Paralgen; Paramol; Piramin†; Pratium; Pyrimel†; Sonridor; Termol; Tilekin†; Trifen; Trimedal D&F; Tyflen; Tylalgin; Tylecetamol; Tylenol; Tylephen; Tylidol; Tyneo; Unigrip; Zuplyn; ***Canad.***: Abenol; Acet; Apap; Arthritis Pain; Artritol; Atasol; Benylin DM-D-E-A Cold and Sinus; Childrens Feverhalt; Cold and Flu-in-One; Double Strength Children's Tempra; Fortolin; Infant Tempra; Infants Tylenol; Novo-Gesic; Painaid Free; Panadol; Pediaphen; Pediatrix; Procet; Rapid Action; Relief; Taminol; Tantaphen†; Tempra; Tylenol Arthritis Pain; Tylenol Muscle Aches & Body Pain; Tylenol; Vicks Custom Care Body Aches; ***Chile***: Acamol; Algiafin; Cotibin Analgesico Antipiretico; Cotibin Compuesto; Dolo-Esan; Geniol; Gesidol; Kitadol; Panadol; Panagesic; Parox Meltab; Rapidol; Sinflu; Supracalm; Tapsin Infantil; Tapsin Puro sin Cafeina†; Tapsin Puro; Tapsin SC; Winasorb; Xumadol; Zolben; ***China***: Ai Er Xing (爱尔星); Ai Sen (爱森); AnYi (安怡); Bei Le Xin (倍乐信); Ben-u-ron (悦诺清); Bufferin (百服宁); Childrens Bufferin (儿童百服咛); Childrens Tylenol (泰诺林); Er He Yi (尔合依); Er Re An (而热安); Fan Nuo (凡诺); Fortolin (保达琳); Infant's Tylenol (泰诺林口服); Kang Yu Deng Tong (康裕登通); Pa La Xin (帕拉辛); Panadol (必理通); Pu Le Er (普乐尔); Shi Ning (施宁); Snaplets-FR (斯耐普); Su Ting (素廷); Tylenol (泰诺林); Xing Le Ning (兴乐宁); Yi Di Qing (一滴清); Yi Li Miao (宜利妙); Yi Shang (易尚); ***Cz.***: Ben-u-ron; Calpol†; Daleron; Effect Comfort†; Efferalgan; Medipyrin; Mexalen; Panadol; Paralen; Paramax Rapid; Parameqal; Perfalgan; ***Denm.***: Arax; Pamol; Panam†; Panodil; Paratabs†; Perfalgan; Pinex; ***Fin.***: Pamol F; Pamol; Panadol; Para-Hot; Para-Suppo; Para-Tabs; Paraceon; Paramax; Perfalgan; ***Fr.***: Algodol; Claradol; Dafalgan; Dafalganhop; Doliprane; Dolipranelib; Dolipraneoro; Dolko; Dolotect†; Efferalgan; Efferalganodis; Expandox†; Geluprane; Panadol; Paralyoc; Perfalgan; Sedarene†; ***Ger.***: Ben-u-ron; Captin; Contac Erkaltungs-Trunk†; Enelfa†; Grippex; Grippostad Heissgetrank; Paedialgon†; Parapaed†; Perfalgan; Sinpro N†; Vivimed N; ***Gr.***: Algocit; Anadin; Apotel; Biocetamol; Calmodor; Cetinject; Dalminette; Depon Maximum; Depon Odis; Depon; Dolal; Efferalgan; Genspir; Lonarid Aplo; Neo-Kalmol; Panadol; Par; Paramin; Perfalgan; protAlgon; Tempra; Tunelzin; Tylenol; Zenol; ***Hong Kong***: Acetamol†; Ben-u-ron; BF-Paradac†; Biogesic; Childrens Fortolin†; Christamol; Cortal for Children; Dhamol; Europain; Panadol; Paracet†; Paracetal†; Paragram†; Parcemol†; Parmol; Pharmadol†; Progesic; Serimol; Setamol; Tiffy†; Uni-Febrin; Uni-Pamol†; ***Hung.***: Ben-u-ron; Efferalgan; Febrilin; Grippostad; Mexalen; Panadol; Paramax Rapid; Perfalgan; Rubophen; ***India***: A-125; Acicloflex; Alcocin; Algina; Alice; Anamol; Anthol; Asimol; Babygesic; Bactpar; Bambiti Kid; Bepamol; Calpol; Cemol; Cetanil; Cetofeb; Cofamol; Copanat; Crocin; Cropara; Disprin Paracetamol†; Doliprane; Dolko; Dolo; Dolodart; Dolopar; Essmol; Eupyric; Ezeepara; F-Nil; Fastpara; Febrex; Febridol; Febrinil; Fenace; Fenil; Fep; Fepamol; Fepanil; Fevastin; Flupara; Genmole; Hidol; Histacold; Hitem-MD; Hitz; Ibumax; Ifimol; Infadil; Jagcin†; Junimol; Kelvin; Lanol; Lit-King; Lotemp; Low-Deg; Lupipara; Malidens; Medomol; Metacin; Metalgin; Mino; Mol; Mortrin; Narmo; NBace-P; Neomol; Nofiva; Orimol; Oyup; P-125; P-37; Pacimol; Pamol; Panact; Parabig; Paracetanal; Paracin; Paracip; Parafizz; Parafort; Parage; Paraglow; Paral; Paralife; Parameter; Parasym; Paratel; Parazine; PF Drops; Pyrexon; Pyrigesic; Ultragin; ***Indon.***: Afebrin†; Alphamol; Biogesic; Bodrex Forte†; Bodrexin Demam; Calapol†; Contratemp; Cupanol; Dapyrin†; Dumin; Erphamol; Farmadol; Fevrin; Grafadon†; Gunaceta†; Ikacetamol; Itamol; Kamolas; Lanamol; Maganol; Moretic; Naprex; Nasamol; Nufadol; Ottopan; Pamol; Panadol Extra; Panadol; Paracetol†; Praxion; Progesic; Propyretic; Pyrex; Pyrexin; Pyridol; Sanmol; Sumagesic†; Tempra; Termorex†; Turpan; Xepamol; ***Irl.***: Anadin Paracetamol†; Calpol; Disprol†; Dolflash; Hedex; Lemsip Children's Cold Relief†; Medinol; Panadol; Panagram Max; Paralief; Paralink; Parapaed; Paratabs; Perfalgan; Rimadol†; Tipol; ***Israel***: Abrol; Abrolet; Acamol; Acamoli; Aldolor†; Avcamol; Avcamoli; Dexamol Kid; Dexamol; Maccabimol; Novimol; Panadol; Paracet; Paramol; Perfalgan; Rokamol; Sensamol; Supramol; Vimoli†; ***Ital.***: Acetamol; Adolef; Babyrinolo Feb Dol; Efferalgan; Liatamolo; Minofen; Normaflu; Panadol; Perfalgan; Piros; Sanipirina; Tachipirina; Termol; ***Malaysia***: Arfen; Avadol; Biogesic†; Dhamol; Hoemal; Panadol; Parafizz; Partamol; Poro; Rapidol; Remedol; Tempol; Uphamol; ***Mex.***: Abatem; Ac-Fast†; Acetafen; Acetif; Alpirex; Amolgen; Analphen; Andox†; Antidol; Biofer; Calinofen†; Coriver; Datril; Dismifen; Dolgan Flash†; Doluvital; Dolviran; Facetol; Farpik; Ferridal†; Filanc; Frilen; Icetazol; Infalgina†; Magnidol-Plus; Mejoral Acti-Rapido; Mejoral; Mejoralito; Minofen; Neodol; Nordinet Infantil; Notem; Panofen; Pharmacen; Piralgina 650†; Piralgina; Piralyn; Piremol; Precifen; Prosedal; Quitadol; Resfin†; Sedalito; Sinedol†; Soltadol; Sons Piral; Tafirol; Temperal; Tempire†; Tempofin†; Tempra; Temprin; Temzzard; Tylenol; Tylex; Ulpafie; Winasorb†; ***Neth.***: Daro; Democyl; Hedex; Momentum†; Panadol; Perfalgan†; Sinaspril-Paracetamol; Tylenol; Vicks Paracetamol; ***Norw.***: Pamol; Panodil; Paracet; Perfalgan; Pinex; ***NZ***: Lemsip Cold & Flu Original, Cold & Flu Max; Pacimol†; Pamol; Panadol; Paracare; Parapaed; Perfalgan; ***Philipp.***: Acet; Acetadol; Aeknil; Alvedon; Anaseran; Baropyrine; Biogesic; Biopain; Bioretic; Calpol; Clocephen; Cloxina; Corgic; Crocin†; Detramol; Dolexpel; Dolonil; Febrinil; Gendol†; Geran; Gifaril P; Kiddilets; Lexalgin; Medgenol; Myremol; Napalgin; Napran; Naprex; Nektol†; Neo-Kiddielets†; Nordex; Opigesic; Para-4-Kids; Para-IV; Paracef; Parvid; Poro; PRC; Rapidol; Rexidol; Riber; Rongesic; Saridon; Selegesic; Sinomol; Tempain; Tempcaire; Tempra; Teramol; Tylenol; Ultragesic; Zestagesic; Zydinol†; ***Pol.***: Acenol; Apap; Calpol; Codipar; Efferalgan; Gemipar; Grippostad; Novo-Gesic†; Panadol; Perfalgan; Tazamol†; ***Port.***: Anti-Gripe Asclepius; Atralidon; Beluron†; Ben-u-ron; Bisolgrip†; Cetol; Cofedron; Dafalgan; Efferalgan; Febridol; Gelocatil; Huber†; Katagrip†; Kelin†; Lisopan; Molpireos; Neogrip; Olpira†; Panadol; Panasorbe; Pantadolor; Paracetol; Paramolan; Parsel; Perfalgan; Singrips; Supofen; Takipirina; Tylenol; Xumadol; ***Rus.***: Арар (Апап); Calpol (Калпол); Cefecon D (Цефекон Д); Daleron (Далерон); Dolomol (Доломол)†; Efferalgan (Эффералган); Flutabs (Флютабс); Panadol (Панадол); Perfalgan (Перфалган); Strimol (Стримол); ***S.Afr.***: Actamol; Anadin-3†; Antalgic; Brunamol; Calpol; Dolorol; Dynadol; Empaped; Entalgic; Fevamol; Feverpain; Gencetamol; Go-Pain P; Medpramol†; Micro-Gesic; Napamol; Pacimol†; Painamol; Painblok; Painogesic; Panado; Paracet; Paradco†; Paramed; Parapane; Perfalgan; Prolief; Pyradol†; Pyralen; Tylenol; Varipan; Winpain; ***Singapore***: Acet; Alcetamol; Biogesic; Calpol; Cetamol; Childrens Panadol; Dhamol; Dolo; Double Parrot Brand; Familin; Fepril; Hoemal; Kame; Lemsip Cold & Flu Head Cold; Mei-Mei Children's Fever; Napa; Pacemol; Panadol; Panamol; Paramol-F; Paratab; Parcemol; Parmol; Paximol; Poro; Progesic; Rapidol; Remedol; Senkon Junior Fever; Setamol; Sunny Fever; Tylenol; Uphamol; ***Spain***: Acecat; Acertol†; Alador; Antidol; Apiredol; Apiretal; Cupanol; Dafalgan†; Dolgesic†; Dolocatil; Dolostop; Duorol†; Efetamol; Efferalgan; Febrectal; Frenagial†; Gelocatil; Nupeldol; Octomol†; Panadol; Parafludeten; Perfalgan; Resolvebohm; Sinmol†; Takipirina; Talgo; Termalgin; Termocatil†; Tylenol†; Unebril; Xumadol; ***Swed.***: Alvedon; Pamol; Panodil; Paracut; Perfalgan; Pinex; Reliv; ***Switz.***: Acetalgin; Arthrolur; Becetamol; Ben-u-ron; Contre-Douleurs P; Dafalgan; Dololur; Dolprone†; Influbene N; Kafa†; Panadol Extend; Panadol; Para-schmerz†; Perfalgan; Treupel Dolo Paracetamol; Treuphadol†; Tylenol; Zolben; ***Thai.***: A-Mol; Aceta-P; Aceta; Acetasil; Algogen; Ampol; Angela; Antispa Plus; Aoricet; Aspamol; Asumol; Bakamol; Biogesic†; Calpol; Cemol; Cetamol; Cetapol; Cetta; Codamol; Cotemp; Daga†; Denamol; Depyret; Diamol; Faron; Fenn†; Foramol; Icolid Plus; KB Gin; Kit; Lotemp; M-Aceta; Mymol; Mypara; Nasa; New-um; Newtol; Pamol; Panadol; Para-G†; Para; Paracap; Paracet; Paragin; Paraman; Paramed; Paramol TP; Paramol; Paranal-L†; Paranal†; Parano; Paranol; Parapro; Parat; Paratol†; Parcet†; Pardon; Partamol; Pat; Patum; Pemol; Poro; Pyracon; Pyrimed; Ramol; Saebegin; Salenol†; Sara; Sinogesic; Somagin†; St Luke's Fever; Temnol; Tempra; Thoho; TM Gin†; Totamol; Tumdi†; Tylenol Arthritis Pain; Tylenol; Tymol; Typanol; Umeda Para-J; Unicap†; Unimol; Uracet†; Vemol; Vetamol; Vikool; Xebramol; ***Turk.***: A-Per; Asomal; Babinoks; Berko-Setamol; Calpol; Derman; Durapan; Efferalgan; Efpa; Ekosetol; Geralgine-P; Gripin; Kataprin; Medaset; Minafen; Minoset; Noral†; Panadol; Para-Nox; Paracet; Paradine; Parasedol; Parcetol; Parol; Paroma; Pedipar; Perfalgan; Pharmadol; Pirofen; Polmofen; Sedalon; Seskamol; Setamol; Sifenol; Tamol; Tempo; Termacet; Termalgine; Tylol; Vermidon; Volpan; Zaldaks; ***UAE***: Adol; ***UK***: Abdine Cold Relief; Alvedon; Anadin Paracetamol; Boots Pain Relief Suspension 6 Years Plus; Calpol; Disprol; Fennings Childrens Cooling Powders; Galpamol; Hedex; Infadrops; Mandanol; Medinol; Miradol†; Obimol; Paldesic; Panadol; Panaleve; Paracets; Paraclear; Parapaed; Perfalgan; Salzone; ***Ukr.***: Cefecon D (Цефекон Д); Daleron Cold 3 (Далерон Колд 3); Efferalgan (Эффералган); Glycodin (Глікодин)†; Infulgan (Инфулган); Militan For Children (Мілистан Дитячий); Panadol (Панадол); Rapidol (Рапидол); ***USA***: Acephen; Aceta; Apacet; Apap; Aphen; Apra†; Arthritis Pain Formula Aspirin Free; Aspirin Free Anacin; Aspirin Free Pain Relief; BetaTemp; Bromo Seltzer†; Childrens Mapap; Comtrex Maximum Strength Sore Throat; Dolono; Feverall; Genapap; Genebs†; Halenol; Infantaire; Liquiprin; Mapap; Maranox; Nortemp; Ofirmev; Oraphen-PD; Panadol; Panitone; Pharbetol; Redutemp; Ridenol; Silapap; Tempra; Triaminic Infant's Fever Reducer/ Pain Reliever; Tylenol Sore Throat Daytime; Tylenol; UN-Aspirin; Uni-Ace; ***Venez.***: Acetafen; Acetalis; Aceval; Agurin; Alivax; Amifen; Ananty; Apiret; Apyrene; Atamel; Brexin; Paracor; Tachipirin; Tempra; Tylenol; Tylex; Vestax.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Co-codamol Capsules; Co-codamol Tablets; Co-dydramol Tablets; Co-proxamol Tablets; Dispersible Paracetamol Tablets; Effervescent Co-codamol Tablets; Effervescent Paracetamol Tablets; Paediatric Paracetamol Oral Solution; Paediatric Paracetamol Oral Suspension; Paracetamol and Caffeine Tablets; Paracetamol Capsules; Paracetamol Oral Suspension; Paracetamol Suppositories; Paracetamol Tablets; Paracetamol, Codeine Phosphate and Caffeine Capsules; Paracetamol, Codeine Phosphate and Caffeine Tablets; Soluble Paracetamol and Caffeine Tablets; Soluble Paracetamol Tablets;

USP 36: Acetaminophen and Aspirin Tablets; Acetaminophen and Caffeine Tablets; Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen and Tramadol Hydrochloride Tablets; Acetaminophen Capsules; Acetaminophen Extended-Release Tablets; Acetaminophen for Effervescent Oral Solution; Acetaminophen Oral Solution; Acetaminophen Oral Suspension; Acetaminophen Suppositories; Acetaminophen Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Hydrocodone Bitartrate and Acetaminophen Tablets; Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules; Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Napsylate and Acetaminophen Tablets; Tramadol Hydrochloride and Acetaminophen Oral Suspension.

Parecoxib Sodium *(BANM, USAN, rINNM)*

Natrii Parecoxibum; Parecoxib sódico; Parécoxib Sodique; SC-69124A; Натрий Парекоксиб.

N-{[*p*-(5-Methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl}propionamide sodium.

$C_{19}H_{17}N_2NaO_4S$=392.4

CAS — 198470-84-7 (parecoxib); 197502-82-2 (parecoxib sodium).

ATC — M01AH04.

ATC Vet — QM01AH04.

UNII — EB87433V6F.

Incompatibility. Parecoxib sodium should not be mixed with products other than those recommended in licensed product information (see Uses and Administration, below). In particular, the use of glucose 5% in lactated Ringer's solution will cause parecoxib to precipitate. Parecoxib should also not be given in the same syringe as opioids. The use of sterile water for injection is not recommended as the resulting solution is not isotonic.

Uses and Administration

Parecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is a prodrug of valdecoxib (p. 141.3) and is used for the short-term treatment of postoperative pain in patients aged 18 years and over. Parecoxib is given as the sodium salt although doses are expressed as the base; 42.4 mg of parecoxib sodium is equivalent to about 40 mg of parecoxib. The recommended dose is 40 mg given by intravenous or slow intramuscular injection; this may be followed by 20 or 40 mg every 6 to 12 hours as required. The maximum daily dose is 80 mg. Elderly patients weighing less than 50 kg should begin treatment with half the usual dose, repeated to

a maximum of 40 mg daily. Doses may need to be reduced in hepatic impairment, see below.

Parecoxib should be reconstituted with either sodium chloride 0.9%, glucose 5%, or sodium chloride 0.45% with glucose 5%; no other solvents are recommended in licensed product information. In addition the reconstituted solution may only be injected into intravenous lines delivering sodium chloride 0.9%, glucose 5%, sodium chloride 0.45% with glucose 5%, or lactated Ringer's solution. (See p. 119.3 for details on incompatibilities.)

References.

1. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; **61:** 1133–41.
2. Amabile CM, Spencer AP. Parecoxib for parenteral analgesia in postsurgical patients. *Ann Pharmacother* 2004; **38:** 882–6.
3. Mehlisch DR, *et al.* The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. *J Am Dent Assoc* 2004; **135:** 1578–90.
4. Malan TP, *et al.* The cyclooxygenase-2-specific inhibitor parecoxib sodium is as effective as 12 mg of morphine administered intramuscularly for treating pain after gynecologic laparotomy surgery. *Anesth Analg* 2005; **100:** 454–60.
5. Beaussier M, *et al.* A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* 2005; **100:** 1309–15.
6. Sindhvananda W, *et al.* Parecoxib versus tramadol for post-appendectomy pain. *J Med Assoc Thai* 2005; **88:** 1557–62.
7. Gajraj NM. COX-2 inhibitors celecoxib and parecoxib: valuable options for postoperative pain management. *Curr Top Med Chem* 2007; **7:** 235–49.
8. Lloyd R, *et al.* Intravenous or intramuscular parecoxib for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 21/09/09).

Administration in hepatic impairment. Licensed product information in the UK states that no dosage adjustment is generally necessary for parecoxib in patients with *mild* hepatic impairment (Child-Pugh score 5 or 6) and for those with *moderate* impairment (Child-Pugh score 7 to 9) parecoxib should be given at half the usual dose (see p. 119.3), repeated to a maximum dose of 40 mg daily. Use in patients with *severe* impairment (Child-Pugh score 10 and over) is not recommended as there is no clinical experience in such patients.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Hypersensitivity reactions, including anaphylaxis and angioedema and serious skin reactions, have been reported with valdecoxib and may therefore occur with parecoxib, a prodrug of valdecoxib (see also Effects on the Skin, p. 141.3). Parecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions occurred in patients with a history of allergic reactions to sulfonamides and the use of parecoxib is contra-indicated in such patients. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 367.3.)

Parecoxib should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more), inflammatory bowel disease, and moderate to severe heart failure (NYHA class II to IV). It should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should also not be used after coronary artery bypass graft surgery as there may be an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, stroke, renal impairment, deep surgical infections, and sternal wound complications. This may apply especially to obese patients or those with a history of cerebrovascular disease. Parecoxib should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Caution is also recommended when using parecoxib in dehydrated patients; rehydration may be advisable before giving parecoxib. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) or those who may be predisposed to fluid retention should be started at the lowest recommended dose and renal function closely monitored.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the general worldwide withdrawal of rofecoxib (see p. 128.3). The short-term use of parecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those given intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p. 37.3.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352:** 1081–91.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as parecoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information reports that upper gastrointestinal perforation, ulceration, and bleeds have occurred with parecoxib treatment and therefore it should be used with caution in patients with a history of such events.

Effects on the kidneys. Increasing evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as parecoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Up to June 2004, the Australian Adverse Drug Reactions Advisory Committee had received 20 reports of adverse reactions associated with parecoxib.[1] Of these, 13 mentioned renal impairment with raised creatinine levels and/or oliguria; acute renal failure was reported in 4 of the 13 cases and multiple doses of parecoxib had been given in 6 cases. (In Australia, parecoxib was approved for single-dose use only because of safety concerns about multiple doses.)

1. Adverse Drug Reactions Advisory Committee (ADRAC). Parecoxib—one shot only. *Aust Adverse Drug React Bull* 2004; **23:** 10–11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0406.pdf (accessed 08/11/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies parecoxib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Parecoxib is rapidly hydrolysed to its active metabolite, valdecoxib; the metabolism of valdecoxib is mainly mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Consequently, caution is recommended when using parecoxib with inhibitors of such isoenzymes. Licensed product information advises that the dose of parecoxib should be reduced if given with fluconazole, a CYP2C9 inhibitor; however, dose adjustment of parecoxib is not generally necessary when giving with ketoconazole, a CYP3A4 inhibitor, despite increased plasma concentrations of valdecoxib. The effects of enzyme inducers such as carbamazepine, dexamethasone, phenytoin, and rifampicin have not been studied; theoretically, the metabolism of valdecoxib may be increased by these drugs.

Valdecoxib has been noted to increase the plasma levels of dextromethorphan, a CYP2D6 substrate, and therefore caution is recommended when giving parecoxib with drugs that are metabolised via CYP2D6 and that have a narrow therapeutic index. Such drugs include flecainide, metoprolol, and propafenone. Valdecoxib may also affect the plasma levels of drugs that are metabolised via CYP2C19: an increase in the plasma levels of omeprazole was seen in patients using valdecoxib.

Pharmacokinetics

On intravenous or intramuscular injection, parecoxib is rapidly hydrolysed in the liver to its active metabolite, valdecoxib, and propionic acid; the plasma half-life of parecoxib is about 22 minutes. Plasma protein binding is about 98%. Valdecoxib is also extensively metabolised in the liver; pathways involved include those via the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and glucuronidation. Another active metabolite has been identified but it is not considered to contribute a significant clinical effect. Excretion is mainly via the urine with about 70% of a dose appearing as inactive metabolites. Less than 5% of a dose appears as unchanged valdecoxib in the urine. No unchanged parecoxib is found in the urine with only trace amounts in the faeces. The elimination half-life of valdecoxib is about 8 hours.

References.

1. Karim A, *et al.* A pharmacokinetic study of intramuscular (IM) parecoxib sodium in normal subjects. *J Clin Pharmacol* 2001; **41:** 1111–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dynastat; ***Austria***: Dynastat; ***Belg.***: Dynastat; ***Braz.***: Bextra IM/IV; ***Chile***: Pro-Bextra; ***China***: Dynastat (特耐); ***Cz.***: Dynastat; ***Denm.***: Dynastat; ***Fin.***: Dynastat; ***Fr.***: Dynastat; ***Ger.***: Dynastat; ***Gr.***: Dynastat; ***Hong Kong***: Dynastat; ***Hung.***: Dynastat; ***India***: Bioval-P; Coxegesic; Valcox; Valdixx; Valdone-P; Valus-P; Vorth-P; ***Indon.***: Dynastat; ***Irl.***: Dynastat; ***Ital.***: Dynastat; ***Malaysia***: Dynastat; ***Mex.***: Dynastat; ***Neth.***: Dynastat; ***Norw.***: Dynastat; ***NZ***: Dynastat; ***Philipp.***: Dynastat; ***Pol.***: Dynastat; ***Port.***: Dynastat; ***Rus.***: Dynastat (Династат); ***S.Afr.***: Rayzon; ***Spain***: Dynastat; ***Swed.***: Dynastat; ***Thai.***: Dynastat; ***UK***: Dynastat; ***Ukr.***: Dynastat (Династат).

Pentazocine *(BAN, USAN, rINN)* ⊗

NIH-7958; NSC-107430; Pentatsosiini; Pentazocin; Pentazocina; Pentazocinas; Pentazocinum; Win-20228; Пентазоцин.

(2*R**,6*R**,11*R**)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol.

$C_{19}H_{27}NO$=285.4

CAS — 359-83-1.

ATC — N02AD01.

ATC Vet — QN02AD01.

UNII — RP4A60D26L.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Pentazocine). A white or almost white powder. It shows polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Pentazocine). A white or very pale, tan-coloured powder. Practically insoluble in water; soluble 1 in 11 of alcohol, 1 in 2 of chloroform, and 1 in 42 of ether; soluble in acetone; sparingly soluble in ethyl acetate and in benzene. Store in airtight containers. Protect from light.

Pentazocine Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de pentazocina; Pentatsosiinihydrokloridi; Pentazocina, hidrocloruro de; Pentazocine, Chlorhydrate de; Pentazocin-hidroklorid; Pentazocinhydrochlorid; Pentazocin-hydrochlorid; Pentazocinhydroklorid; Pentazocini hydrochloridum; Pentazocino hidrochloridas; Пентазоцина Гидрохлорид.

$C_{19}H_{27}NO,HCl$=321.9

CAS — 2276-52-0; 64024-15-3.

UNII — A36BXO4PPX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pentazocine Hydrochloride). A white or almost white powder. It shows polymorphism. Sparingly soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Pentazocine Hydrochloride). A white crystalline powder. It exhibits polymorphism, one form melting at about 254 degrees and the other at about 218 degrees. Soluble 1 in 30 of water, 1 in 20 of alcohol, and 1 in 4 of chloroform; very slightly soluble in acetone and in ether; practically insoluble in benzene. Store in airtight containers. Protect from light.

Pentazocine Lactate *(BANM, USAN, rINNM)* ⊗

Lactato de pentazocina; Pentatsosiinilaktaatti; Pentazocina, lactato de; Pentazocine, Lactate de; Pentazocini lactas; Pentazocinlactat; Pentazocinlaktat; Pentazocin-laktát; Pentazocino laktatas; Пентазоцина Лактат.

$C_{19}H_{27}NO,C_3H_6O_3$=375.5

CAS — 17146-95-1.

UNII — 1P2XIB510O.

Pharmacopoeias. In *Eur.* (see p. vii). *US* includes only Pentazocine Lactate Injection.

Ph. Eur. 8: (Pentazocine Lactate). A white or almost white powder. Sparingly soluble in water; slightly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5. Protect from light.

BP 2014: (Pentazocine Lactate). A white to pale cream powder. Sparingly soluble in water, in alcohol, and in chloroform; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5.

Incompatibility. Commercial injections of pentazocine lactate are reported to be incompatible with soluble barbiturates and other alkaline substances including sodium bicarbonate. Diazepam and chlordiazepoxide have also been reported to be incompatible, as have glycopyrronium bromide[1] and nafcillin sodium.[2]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; **36:** 508–10.
2. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462, 464.

Uses and Administration

Pentazocine, a benzomorphan derivative, is an opioid analgesic (p. 108.1) that has mixed opioid agonist and antagonist actions. Agonist activity is thought to be mainly at κ opioid receptors (with possibly some σ receptor activity); it acts as a weak antagonist or partial agonist at μ

receptors. Pentazocine is used for the relief of moderate to severe pain including the pain of labour. Combined preparations with paracetamol or aspirin may also be used in the treatment of moderate pain. It may also be used for pre-operative sedation and as an adjunct to anaesthesia. Its analgesic effect declines more rapidly than that of morphine.

Pentazocine is given orally as the hydrochloride; doses may be expressed as either the base or the salt. Pentazocine is also given parenterally as the lactate; doses are expressed in terms of the base. Pentazocine 100 mg is equivalent to about 112.8 mg of pentazocine hydrochloride or 131.6 mg of pentazocine lactate.

A usual oral dose is the equivalent of 50 to 100 mg of pentazocine or pentazocine hydrochloride every 3 to 4 hours after food, to a maximum of 600 mg daily.

The usual initial dose by subcutaneous, intramuscular, or intravenous injection is the equivalent of pentazocine 30 mg as a single dose. Thereafter, the dose may be adjusted according to response; licensed product information recommends that single doses should not usually exceed 30 mg (500 micrograms/kg) intravenously, or 60 mg (1 mg/kg) intramuscularly or subcutaneously. Doses may be repeated every 3 to 4 hours; it should not be necessary to exceed 360 mg daily. Also if frequent injections are needed, the intramuscular route should be used rather than the subcutaneous route, and the injection sites should be varied. In obstetric analgesia 30 mg may be given as a single dose by intramuscular injection during labour; alternatively, 20 mg may be given by intravenous injection as soon as contractions occur at regular intervals and repeated 2 or 3 times at intervals of 2 to 3 hours if necessary.

For details of doses in children, see below.

Pentazocine lactate has also been given rectally as suppositories.

As a deterrent to abuse a combined oral preparation of pentazocine hydrochloride and naloxone hydrochloride is available in some countries.

Administration in children. In the UK, pentazocine is licensed for the relief of moderate to severe pain in children and doses may be repeated every 3 to 4 hours if necessary. Those aged 6 to 12 years may be given a usual oral dose of 25 mg. Children aged 1 to 12 years may be given doses of up to 1 mg/kg by intravenous injection.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Pentazocine is subject to abuse.

Pentazocine does produce physical dependence, but withdrawal symptoms are substantially less severe than with morphine. It does not typically produce drug-seeking behaviour of the same degree or intensity as morphine or other prototypic μ agonists, nor does it substitute for morphine in dependent subjects.[1] Pentazocine injection has been abused,[2] but street abuse, especially in the USA, has more often involved the intravenous use of crushed tablets of pentazocine and tripelennamine ('T's and Blues').[3-5] A decreased incidence of pentazocine abuse in the USA appeared to coincide with the introduction of oral tablets incorporating naloxone,[1] the rationale being that naloxone antagonises the effect of pentazocine if illicitly injected, but has no effect when taken orally. Some continued to abuse the new pentazocine/naloxone formulation;[6] intravenous abuse in one woman, who was unaware of the reformulation, resulted in opioid withdrawal symptoms and severe hypertension.[7] A 1989 report from the WHO committee[1] rated the likelihood of abuse of pentazocine as moderate, based on its pharmacological profile, dependence potential, and actual abuse. The committee considered that it should continue to be scheduled as a psychotropic substance rather than a narcotic drug.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 27/06/08)
2. Hunter R, Ingram IM. Intravenous pentazocine abuse by a nurse. *Lancet* 1983; **ii:** 227.
3. Poklis A, Whyatt PL. Current trends in the abuse of pentazocine and tripelennamine: the metropolitan St. Louis experience. *J Forensic Sci* 1980; **25:** 72–8.
4. Senay EC. Clinical experience with T's and B's. *Drug Alcohol Depend* 1985; **14:** 305–11.
5. Jackson C, *et al.* Fatal intracranial hemorrhage associated with phenylpropanolamine, pentazocine, and tripelennamine overdose. *J Emerg Med* 1985; **3:** 127–32.
6. Reed DA, Schnoll SH. Abuse of pentazocine-naloxone combination. *JAMA* 1986; **256:** 2562–4.
7. Reinhart S, Barrett SM. An acute hypertensive response after intravenous use of a new pentazocine formulation. *Ann Emerg Med* 1985; **14:** 591–3.

Adverse Effects

As for Opioid Analgesics in general, p. 110.1.

Pentazocine may cause hallucinations and other psychotomimetic effects such as nightmares and thought disturbances. High doses may result in hypertension and tachycardia; increased aortic and pulmonary artery pressure with an increase in cardiac work has followed intravenous use in patients with myocardial infarction. Like morphine it causes respiratory depression, but pentazocine is said to have a 'ceiling' effect and the depth of respiratory depression does not increase proportionately with higher doses.

Rare adverse effects with pentazocine have included agranulocytosis and serious skin reactions such as erythema multiforme and toxic epidermal necrolysis.

Pentazocine injections may be painful. Local tissue damage may occur at injection sites particularly after subcutaneous injection or multiple doses; there have been reports of muscle fibrosis associated with intramuscular injections.

Effects on the blood. There have been reports of agranulocytosis associated with pentazocine.[1-3]

1. Marks A, Abramson N. Pentazocine and agranulocytosis. *Ann Intern Med* 1980; **92:** 433.
2. Haibach H, *et al.* Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1984; **130:** 1165–6.
3. Sheehan M, *et al.* Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1985; **132:** 1401.

Effects on the CNS. Oculogyric crisis has been associated with the use of pentazocine.[1]

1. Burstein AH, Fullerton T. Oculogyric crisis possibly related to pentazocine. *Ann Pharmacother* 1993; **27:** 874–6.

Effects on the skin. Toxic epidermal necrolysis in a 62-year-old man was attributed to pentazocine;[1] he had taken 50 to 75 mg every 4 hours for 8 days. His severe uraemia was attributed to fluid loss through the skin.

1. Hunter JAA, Davison AM. Toxic epidermal necrolysis associated with pentazocine therapy and severe reversible renal failure. *Br J Dermatol* 1973; **88:** 287–90.

Treatment of Adverse Effects

As for Opioid Analgesics in general, p. 110.3.

As pentazocine has both opioid agonist and antagonist activity its effects may not be completely reversed by naloxone, but use of the latter is still recommended in pentazocine overdosage.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Pentazocine has weak opioid antagonist actions and may precipitate withdrawal symptoms if given to patients who are physically dependent on opioids. It should generally be avoided after myocardial infarction and in patients with heart failure or arterial or pulmonary hypertension.

When frequent injections are needed, pentazocine should be given intramuscularly rather than subcutaneously and the injection sites should be varied.

Abuse. See under Dependence and Withdrawal, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, has not classified pentazocine for porphyrinogenicity;[1] however licensed product information advises caution in the use of pentazocine in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/11/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Tobacco smoking. Smokers metabolised about 40% more pentazocine than non-smokers, although there was large inter-subject variation;[1] tobacco smoking might induce liver enzymes responsible for drug oxidation.

1. Vaughan DP, *et al.* The influence of smoking on the inter-subject variation in pentazocine elimination. *Br J Clin Pharmacol* 1976; **3:** 279–83.

Pharmacokinetics

Pentazocine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur in 1 to 3 hours after an oral dose; the half-life is reported to be about 2 to 3 hours. After intramuscular injection, peak plasma concentrations occur in 15 minutes to 1 hour and the half-life is about 2 to 5 hours. About 50 to 75% has been reported to be bound to plasma proteins. Pentazocine undergoes extensive first-pass metabolism in the liver; oral bioavailability is low with only about half of a dose reaching the systemic circulation. Metabolites and a small amount of unchanged drug are excreted in the urine. It crosses the placenta and is distributed into breast milk.

Hepatic impairment. Clearance of pentazocine was significantly reduced and terminal half-life and oral bioavailability increased in cirrhotic patients when compared with healthy subjects.[1]

1. Neal EA, *et al.* Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. *Gastroenterology* 1979; **77:** 96–102.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Fortal; ***Canad.***: Talwin; ***Cz.***: Fortral; ***Gr.***: Fortal; ***India***: Fortstar; Fortwin; Pentawin; ***Ital.***: Talwin; ***Jpn***: Peltazon; Pentagin; Sosegon; ***Neth.***: Fortral; ***S.Afr.***: Ospronim†; Sosenol; ***Singapore***: Talwin†; ***Spain***: Sosegon; ***Thai.***: Pangon; Sosegon; Tazcine; ***UK***: Fortral; ***USA***: Talwin NX†; Talwin.

Multi-ingredient Preparations. ***India***: Expergesic; Foracet; Fortagesic; ***USA***: Emergent-Ez; Talacen†.

Pharmacopoeial Preparations

BP 2014: Pentazocine Capsules; Pentazocine Injection; Pentazocine Suppositories; Pentazocine Tablets;

USP 36: Pentazocine and Aspirin Tablets; Pentazocine and Naloxone Tablets; Pentazocine Injection.

Pethidine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de petidina; Meperidine Hydrochloride; Péthidine, Chlorhydrate de; Pethidinhydrochlorid; Pethidinhydrochlorid; Pethidini Hydrochloridum; Petidiinihydrokloridi; Petidin Hidroklorür; Petidina, hidrocloruro de; Petidinhidroklorid; Petidinhydroklorid; Petidino hidrochloridas; Petydyny chlorowodorek; Петидина Гидрохлорид.

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

$C_{15}H_{21}NO_2$,HCl=283.8

CAS — 57-42-1 (pethidine); 50-13-5 (pethidine hydrochloride).

ATC — N02AB02.

ATC Vet — QN02AB02.

UNII — N8E7F7Q170.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of pethidine:

Bam; Peth.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Pethidine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Meperidine Hydrochloride). A fine white odourless crystalline powder. Very soluble in water; soluble in alcohol; sparingly soluble in ether. pH of a 5% solution in water is about 5. Protect from light.

Incompatibility. Solutions of pethidine hydrochloride are acidic. They are incompatible with barbiturate salts and loss of clarity was also seen in an early additive study[1] with other drugs including aminophylline, heparin sodium, meticillin sodium, morphine sulfate, nitrofurantoin sodium, phenytoin sodium, sodium iodide, sulfadiazine sodium, and sulfafurazole diolamine. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with pethidine hydrochloride in 5% glucose injection.[2] In the same study an immediate precipitate occurred on admixture with cefoperazone sodium or mezlocillin sodium; with nafcillin sodium an immediate cloudy appearance cleared on agitation. Incompatibility has also been seen between pethidine hydrochloride and aciclovir sodium, imipenem, furosemide,[3] liposomal doxorubicin hydrochloride,[4] and idarubicin.[5] Solutions of cefazolin sodium[6] and pethidine hydrochloride mixed in 5% glucose injection turned light yellow after storage for 5 days at 25 degrees; the admixture was stable for at least 20 days at 4 degrees.

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
2. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
3. Pugh CB, *et al.* Visual compatibility of morphine sulfate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 123–5.
4. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
5. Turowski RC, Durthaler JM. Visual compatibility of idarubicin hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 2181–4.
6. Lee DKT, *et al.* Stability of cefazolin sodium and meperidine hydrochloride. *Am J Health-Syst Pharm* 1996; **53:** 1608–10.

Stability. Pethidine hydrochloride injection 100 mg/mL was stable[1] for at least 24 hours at room temperature when diluted to a concentration of 300 mg/litre in glucose

5% and 4% and in sodium chloride injection (0.9%) and sodium chloride injection (0.9%) diluted 1 in 5.

Accelerated stability studies using elevated temperatures and humidities to simulate tropical conditions classified pethidine hydrochloride as a 'less stable drug substance'.[2] It was suggested that during quality assurance of preparations containing pethidine hydrochloride particular attention should be paid to their stability.

1. Rudd L, Simpson P. Pethidine stability in intravenous solutions. *Med J Aust* 1978; **2:** 34.
2. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 26/06/08)

Uses and Administration

Pethidine, a phenylpiperidine derivative, is a synthetic opioid analgesic (p. 108.1) that acts mainly as a μ-opioid agonist. Pethidine is used for the relief of most types of moderate to severe acute pain including the pain of labour. It is more lipid soluble than morphine and has a less potent and shorter lasting analgesic effect; analgesia usually lasts for 2 to 4 hours. Its short duration of action and accumulation of its potentially neurotoxic metabolite norpethidine on repeated dosage make it unsuitable for the management of chronic pain. Pethidine has a weaker action on smooth muscle than morphine and its lower potential to increase biliary pressure may make it a more suitable opioid analgesic for pain associated with biliary colic and pancreatitis (but see Biliary-tract Disorders, p. 111.1). It is also used for premedication and as an adjunct to anaesthesia. It has been given with phenothiazines such as promethazine to achieve basal narcosis. Pethidine has little effect on cough or on diarrhoea.

For the relief of **pain**, pethidine hydrochloride is given in oral doses of 50 to 150 mg every 4 hours if necessary. It may also be given by intramuscular or subcutaneous injection in doses of 25 to 100 mg and by slow intravenous injection in doses of 25 to 50 mg repeated after 4 hours. For *postoperative* pain, the *BNF* suggests that the subcutaneous or intramuscular doses may be given every 2 to 3 hours if necessary.

In *obstetric analgesia* 50 to 100 mg may be given by intramuscular or subcutaneous injection as soon as contractions occur at regular intervals. This dose may be repeated after 1 to 3 hours if necessary up to a maximum of 400 mg in 24 hours.

For **premedication** 25 to 100 mg may be given intramuscularly about 1 hour before surgery. It may also be given subcutaneously in similar doses. As an **adjunct to anaesthesia** 10 to 25 mg may be given by slow intravenous injection.

For details of doses in children, see below.

Administration. In addition to the conventional routes pethidine has been given epidurally,[1-4] intraperitoneally,[5,6] and intrathecally.[7-9] It has also been given by various routes as a patient-controlled system.[10-13] However, some consider that the use of pethidine should be avoided for patient-controlled analgesia because of the increased risk of norpethidine-induced seizures[14] (see also Incidence of Adverse Effects and Effects on the Nervous System, below).

1. Perriss BW. Epidural pethidine in labour: a study of dose requirements. *Anaesthesia* 1980; **35:** 380–2.
2. Husemeyer RP, *et al.* A study of pethidine kinetics and analgesia in women in labour following intravenous, intramuscular and epidural administration. *Br J Clin Pharmacol* 1982; **13:** 171–6.
3. Perriss BW, *et al.* Analgesia following extradural and im pethidine in post-caesarean section patients. *Br J Anaesth* 1990; **64:** 355–7.
4. Blythe JG, *et al.* Continuous postoperative epidural analgesia for gynecologic oncology patients. *Gynecol Oncol* 1990; **37:** 307–10.
5. Colbert ST, *et al.* An assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. *Anesth Analg* 2000; **91:** 667–70.
6. O'Hanlon DM, *et al.* Intraperitoneal pethidine versus intramuscular pethidine for the relief of pain after laparoscopic cholecystectomy: randomized trial. *World J Surg* 2002; **26:** 1432–6.
7. Acalovschi I, *et al.* Saddle block with pethidine for perineal operations. *Br J Anaesth* 1986; **58:** 1012–16.
8. Yu SC, *et al.* Addition of meperidine to bupivacaine for spinal anaesthesia for caesarean section. *Br J Anaesth* 2002; **88:** 379–83.
9. Vranken JH, *et al.* Plasma concentrations of meperidine and normeperidine following continuous intrathecal meperidine in patients with neuropathic cancer pain. *Acta Anaesthesiol Scand* 2005; **49:** 665–70.
10. Striebel HW, *et al.* Patient-controlled intranasal analgesia (PCINA) for the management of postoperative pain: a pilot study. *J Clin Anesth* 1996; **8:** 4–8.
11. Kee N, *et al.* Comparison of patient-controlled epidural analgesia with patient-controlled intravenous analgesia using pethidine or fentanyl. *Anaesth Intensive Care* 1997; **25:** 126–32.
12. Sharma SK, *et al.* Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87:** 487–94.
13. Chen PP, *et al.* Patient-controlled pethidine after major upper abdominal surgery: comparison of the epidural and intravenous routes. *Anaesthesia* 2001; **56:** 1106–12.
14. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27:** 29–32.

Administration in children. Pethidine is licensed for the relief of moderate to severe acute pain and for premedication in children. However, the *BNFC* does not recommend its use in this patient set.

For the relief of **pain**, pethidine hydrochloride may be given orally or by intramuscular injection in doses of 0.5 to 2 mg/kg, repeated after 4 hours if necessary. For *postoperative* pain, the *BNF* suggests that this dose may be given intramuscularly every 2 to 3 hours if necessary.

For **premedication**, the *BNF* suggests giving 0.5 to 2 mg/kg intramuscularly about 1 hour before surgery.

See also Lytic Cocktails, below.

Eclampsia and pre-eclampsia. See Lytic Cocktails under Sedation, below.

Pain. Pethidine produces prompt but short-lasting analgesia, and may be preferred to morphine when rapid control of acute pain is required. It has been widely used in obstetrics to control the pain of labour (although the *BNF* notes that morphine or other opioids are often preferred for obstetric pain), and for postoperative pain relief after caesarean section or other surgical procedures.

In a study of patients with intractable pain the minimum effective analgesic blood concentration ranged from 100 to 820 nanograms/mL (median 250 nanograms/mL) in 15 of 16; the remaining patient failed to obtain analgesia with pethidine. Additional measures were considered necessary[1] if the minimum effective concentration exceeded 400 nanograms/mL.

Pethidine has traditionally been given by intermittent intramuscular injection in the treatment of acute pain, but inconsistent pain relief can be expected because of fluctuating blood-pethidine concentrations;[2] continuous intravenous infusion might be more effective for acute pain. For reference to use by other routes see Administration, above.

1. Mather LE, Glynn CJ. The minimum effective analgesic blood concentration of pethidine in patients with intractable pain. *Br J Clin Pharmacol* 1982; **14:** 385–90.
2. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; **7:** 421–33.

SICKLE-CELL CRISIS. Concern has been expressed over the continued use of pethidine for analgesia in painful crises in sickle-cell disease. Control of pain may be inadequate and doses commonly used to manage crises may lead to accumulation of norpethidine, the neuroexcitatory metabolite of pethidine, and precipitate seizures.[1,2] See also Effects on the Nervous System, below.

1. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478–9.
2. Harrison JFM, *et al.* Pethidine in sickle cell crisis. *BMJ* 1992; **305:** 182.

Sedation. Some references[1-3] to the use of pethidine for endoscopy.

1. Bahal-O'Mara N, *et al.* Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. *Eur J Clin Pharmacol* 1994; **47:** 319–23.
2. Diab FH, *et al.* Efficacy and safety of combined meperidine and midazolam for EGD sedation compared with midazolam alone. *Am J Gastroenterol* 1996; **91:** 1120–5.
3. Laluna L, *et al.* The comparison of midazolam and topical lidocaine spray versus the combination of midazolam, meperidine, and topical lidocaine spray to sedate patients for upper endoscopy. *Gastrointest Endosc* 2001; **53:** 289–93.

LYTIC COCKTAILS. Lytic cocktails consisting of chlorpromazine, pethidine, and/or promethazine have been given intravenously in some countries for the management of pre-eclampsia and imminent eclampsia. However, the use of phenothiazines is generally not recommended late in pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p. 1251.1); the management of eclampsia, which is the convulsive phase, is discussed on p. 511.1.

Lytic cocktails have also been used for sedation and analgesia in children, by intramuscular or occasionally intravenous injection. However, there is a high rate of therapeutic failure as well as serious adverse effects with such combinations, and the American Academy of Pediatrics[1] had recommended that alternative sedatives and analgesics should be considered. Lytic cocktails are not the most appropriate means of sedation for short procedures since patients must be monitored for about 1 hour before the procedure while the drugs take effect, and for even longer during the recovery period.[2]

1. American Academy of Pediatrics Committee on Drugs. Reappraisal of Lytic cocktail/Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. *Pediatrics* 1995; **95:** 598–602.
2. Barst SM, *et al.* A comparison of propofol and Demerol-Phenergan-Thorazine for brief, minor, painful procedures in a pediatric hematology-oncology clinic. *Int J Pediatr Hematol/Oncol* 1995; **1:** 587–91.

Shivering. For reference to the use of pethidine in the management of shivering associated with anaesthesia, see under Adverse Effects of General Anaesthetics, p. 1900.2. Pethidine has also been used to treat amphotericin B-induced shaking chills.[1]

1. Burks LC, *et al.* Meperidine for the treatment of shaking chills and fever. *Arch Intern Med* 1980; **140:** 483–4.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Doses of pethidine as large as 3 or 4 g daily have been taken by addicts. As tolerance to the CNS stimulant and antimuscarinic effects is not complete with these very large doses, muscle twitching, tremor, mental confusion, dilated pupils, and sometimes convulsions may be present.

Withdrawal symptoms appear more rapidly than with morphine and are of shorter duration.

For the abuse of pethidine analogues, see under Precautions, p. 123.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

The effects on smooth muscle may be relatively less intense than with morphine and constipation occurs less frequently. Local reactions often follow injection of pethidine; general hypersensitivity reactions including anaphylaxis have been reported rarely. Pethidine given intravenously may increase the heart rate. After overdosage, symptoms are generally similar to those of morphine poisoning. However, stimulation of the CNS and convulsions may also occur, especially in tolerant individuals or after toxic oral doses; these have been attributed mainly to the metabolite norpethidine.

Incidence of adverse effects. The incidence of adverse effects in hospitalised patients receiving pethidine was monitored by the Boston Collaborative Drug Surveillance Program.[1] Adverse reactions to oral pethidine were reported in 16 of 366 patients and mainly involved the gastrointestinal tract. After pethidine by injection 102 of 3268 patients had adverse effects, the CNS being involved in 38.

More recently, 20 adverse reactions were identified in a chart review of 141 patients given pethidine and considered to be at high risk of developing toxicity;[2] high-risk patients were defined as those with renal impairment (creatinine clearance 50 mL/minute or less), those receiving patient-controlled analgesia (PCA) with pethidine, and those given intravenous pethidine in doses of over 200 mg daily for several days. The most common adverse reactions were confusion and anxiety; other reported adverse effects included nervousness, seizures, and hallucinations. Patients who developed adverse reactions were significantly older, more likely to be taking a benzodiazepine, and had longer hospital stays than those without adverse effects. Out of the 20 reports, 16 adverse effects were noted in the 123 patients who received pethidine via a PCA pump; cumulative doses for patients using PCA were found to be a significant risk factor in the development of adverse effects.

1. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. *J Clin Pharmacol* 1978; **18:** 180–9.
2. Seifert CF, Kennedy S. Meperidine is alive and well in the new millennium: evaluation of meperidine usage patterns and frequency of adverse drug reactions. *Pharmacotherapy* 2004; **24:** 776–83.

Effects on the cardiovascular system. Histamine release was more frequent after pethidine than after morphine, fentanyl, or sufentanil given intravenously for the induction of anaesthesia.[1] Increased plasma-histamine concentrations occurred in 5 of 16 patients given pethidine in a mean dose of 4.3 mg/kg and were generally accompanied by hypotension, tachycardia, erythema, and increased plasma-adrenaline concentrations. Only 1 of 10 given morphine and none of those receiving fentanyl or sufentanil showed evidence of histamine release. All of the histamine releasers were young women.

1. Flacke JW, *et al.* Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg* 1987; **66:** 723–30.

Effects on the nervous system. CNS excitatory effects of pethidine such as tremors, muscle twitches, and convulsions have been associated with toxic doses and have been attributed to the metabolite norpethidine. Accumulation of norpethidine may occur if large doses of pethidine are repeated at short intervals (including for patient-controlled analgesia) and is especially likely when renal function is impaired.[1-13]

1. Kaiko RF, *et al.* Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983; **13:** 180–5.
2. Lieberman AN, Goldstein M. Reversible parkinsonism related to meperidine. *N Engl J Med* 1985; **312:** 509.
3. Mauro VF, *et al.* Meperidine-induced seizure in a patient without renal dysfunction or sickle cell anemia. *Clin Pharm* 1986; **5:** 837–9.
4. Morisy L, Platt D. Hazards of high-dose meperidine. *JAMA* 1986; **255:** 467–8.
5. Armstrong PJ, Bersten A. Normeperidine toxicity. *Anesth Analg* 1986; **65:** 536–8.
6. Eisendrath SJ, *et al.* Meperidine-induced delirium. *Am J Psychiatry* 1987; **144:** 1062–5.
7. Kyff JV, Rice TL. Meperidine-associated seizures in a child. *Clin Pharm* 1990; **9:** 337–8.
8. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478–9.
9. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27:** 29–32.

10. Stone PA, *et al.* Norpethidine toxicity and patient controlled analgesia. *Br J Anaesth* 1993; **71:** 738–40.
11. Marinella MA. Meperidine-induced generalized seizures with normal renal function. *South Med J* 1997; **90:** 556–8.
12. McHugh GJ. Norpethidine accumulation and generalized seizure during pethidine patient-controlled analgesia. *Anaesth Intensive Care* 1999; **27:** 289–91.
13. Hubbard GP, Wolfe KR. Meperidine misuse in a patient with sphincter of Oddi dysfunction. *Ann Pharmacother* 2003; **37:** 534–7.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Pethidine should also be given cautiously to patients with a history of convulsive disorders or supraventricular tachycardias.

Abuse. A synthetic analogue of pethidine, MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), manufactured illicitly for recreational use, achieved notoriety when it was accidentally contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) leading to an epidemic of parkinsonism among intravenous drug abusers.[1] WHO has also identified another analogue, PEPAP (1-phenylethyl-4-phenyl-4-acetoxypiperidine) as being liable to abuse.[2]

1. Buchanan JF, Brown CR. Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988. Also available at: http://libdoc.who.int/trs/WHO_TRS_761.pdf (accessed 26/06/08)

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were given pethidine, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

The elderly. Pethidine had a slower elimination rate in elderly compared with young patients and a reduction in total daily dose might be necessary in elderly patients receiving repeated doses of pethidine.[1] Another study concluded that age-related changes in disposition were not sufficient to warrant modification of pethidine dosage regimens.[2]

1. Holmberg L, *et al.* Comparative disposition of pethidine and norpethidine in old and young patients. *Eur J Clin Pharmacol* 1982; **22:** 175–9.
2. Herman RJ, *et al.* Effects of age on meperidine disposition. *Clin Pharmacol Ther* 1985; **37:** 19–24.

Phaeochromocytoma. Pethidine provoked episodes of hypertension in a patient with phaeochromocytoma; the effect was suppressed by labetalol.[1] Like other histamine-releasing opioids, pethidine should be used with caution in such patients.

1. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; **1:** 149–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pethidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy and the neonate. Pethidine has been widely used for analgesia during labour. It rapidly crosses the placenta and like other opioid analgesics may cause respiratory depression in the neonate, although perhaps less so than morphine. Respiratory depression varies according to the timing and size of the maternal dose.

Fetal depression was not apparent when delivery occurred within 1 hour of giving pethidine, but was present in 6 of 24 infants delivered 1 to 3 hours after injection and in all of 5 infants delivered 3 to 6 hours after injection.[1] However, higher blood concentrations of pethidine were seen in infants delivered within 1 hour of an intramuscular dose of pethidine compared with those delivered 1 to 4 hours after injection. The role of pethidine metabolites was uncertain. It has also been reported[2] that depressed neonatal responses persisted for the first 2 days of life; depression was dose-related being greatest with the highest dose of pethidine (75 to 150 mg within 4 hours of delivery). Neonates appear able to metabolise pethidine, although probably more slowly than adults.[3] The amounts of pethidine and norpethidine excreted by the neonate increased significantly with the maternal dose-delivery interval for intervals of up to 5 hours and most of the placentally transferred pethidine should be excreted by the third day. Elimination of pethidine took up to 6 days in the neonates in another study.[4]

Further references on the transplacental transfer of pethidine can be found in Pregnancy under Pharmacokinetics, below.

Neither psychological nor physical effects were found in 5-year-olds born to mothers who had received pethidine during labour.[5] Neonatal behaviour does not appear to have been affected significantly by pethidine, although it has been acknowledged that the relationship between maternal analgesia in labour and subsequent infant behaviour is by no means simple.[6] The results of early studies that suggested an excess of cases of cancer in children whose mothers received pethidine during labour have been refuted by a later and larger study.[7]

1. Morrison JC, *et al.* Metabolites of meperidine related to fetal depression. *Am J Obstet Gynecol* 1973; **115:** 1132–7.
2. Hodgkinson R, *et al.* Double-blind comparison of the neurobehaviour of neonates following the administration of different doses of meperidine to the mother. *Can Anaesth Soc J* 1978; **25:** 405–11.
3. Hogg MIJ, *et al.* Urinary excretion and metabolism of pethidine and norpethidine in the newborn. *Br J Anaesth* 1977; **49:** 891–9.
4. Cooper LV, *et al.* Elimination of pethidine and bupivacaine in the newborn. *Arch Dis Child* 1977; **52:** 638–41.
5. Buck C. Drugs in pregnancy. *Can Med Assoc J* 1975; **112:** 1285.
6. Anonymous. To measure life. *Lancet* 1981; **ii:** 291–2.
7. Golding J, *et al.* Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.

Renal impairment. Caution is necessary when pethidine is given to patients with renal impairment; UK licensed product information recommends that it should be avoided in those with severe impairment, whereas US product information suggests to use reduced doses. Evidence of CNS excitation, including seizures and twitches, in 2 patients with renal insufficiency given multiple doses of pethidine was attributed to accumulation of the metabolite norpethidine; both patients had high norpethidine to pethidine plasma concentration ratios.[1]

See also under Pharmacokinetics, p. 124.1.

1. Szeto HH, *et al.* Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Ann Intern Med* 1977; **86:** 738–41.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Very severe reactions, including coma, severe respiratory depression, cyanosis, and hypotension have occurred in patients receiving MAOIs (including moclobemide and selegiline) and given pethidine. There are also reports of hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Pethidine should not be given to patients receiving MAOIs or within 14 days of their discontinuation. Use of pethidine with phenothiazines has produced severe hypotensive episodes and may prolong the respiratory depression due to pethidine.

Plasma concentrations of norpethidine are increased by ritonavir, with a resultant risk of toxicity; use together should be avoided (see also p. 111.2).

Antibacterials. See MAOIs below for interactions between pethidine and *isoniazid* and *linezolid*.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of pethidine and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1. See also MAOIs, below.

Antiepileptics. Opioid analgesics and barbiturates can be expected to have additive CNS depressant effects. Prolonged sedation with pethidine in the presence of *phenobarbital* has also been attributed to induction of *N*-demethylation of pethidine, resulting in the enhanced formation of the potentially neurotoxic metabolite norpethidine.[1,2] The hepatic metabolism of pethidine appears to be enhanced by *phenytoin*; use together resulted in reduced half-life and bioavailability in healthy subjects; blood concentrations of norpethidine were increased.[3]

1. Stambaugh JE, *et al.* A potentially toxic drug interaction between pethidine (meperidine) and phenobarbitone. *Lancet* 1977; **i:** 398–9.
2. Stambaugh JE, *et al.* The effect of phenobarbital on the metabolism of meperidine in normal volunteers. *J Clin Pharmacol* 1978; **18:** 482–90.
3. Pond SM, Kretschzmar KM. Effect of phenytoin on meperidine clearance and normeperidine formation. *Clin Pharmacol Ther* 1981; **30:** 680–6.

Histamine H_2-antagonists. See under Opioid Analgesics, p. 111.3.

MAOIs. Some of the most serious interactions involving pethidine have been with non-selective MAOIs and have been manifest as enhanced depressant effects or hyperexcitability (see Interactions, above). However, a life-threatening interaction has also been reported between pethidine and *selegiline*, a selective monoamine oxidase type B inhibitor.[1] Also, symptoms suggestive of a mild serotonin syndrome developed in a 73-year-old woman taking *moclobemide* (a reversible inhibitor of monoamine oxidase type A), nortriptyline, and lithium after she was given pethidine intravenously.[2]

Use of the antibacterial *isoniazid* with pethidine led to a drop in blood pressure and lethargy in a 54-year-old man.[3] Serotonin syndrome developed in a 27-year-old man after the use of pethidine with *linezolid*;[4] symptoms resolved when pethidine was stopped. The authors of both studies attributed the interaction to the inhibitory action of isoniazid and linezolid on monoamine oxidase.

1. Zornberg GL, *et al.* Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337:** 246. Correction. *ibid.;* 440.
2. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.
3. Gannon R, *et al.* Isoniazid, meperidine, and hypotension. *Ann Intern Med* 1983; **99:** 415. Correction. *ibid.;* 740.
4. Das PK, *et al.* Serotonin syndrome after concomitant treatment with linezolid and meperidine. *Clin Infect Dis* 2008; **46:** 264–5.

Phenothiazines. *Prochlorperazine* prolonged the respiratory depressant effect of pethidine in healthy subjects.[1] Enhanced CNS depression and hypotension were reported when healthy subjects were given *chlorpromazine* in addition to pethidine; there was evidence of increased *N*-demethylation of pethidine.[2]

1. Steen SN, Yates M. Effects of benzquinamide and prochlorperazine, separately and combined with meperidine, on the human respiratory center. *Clin Pharmacol Ther* 1972; **13:** 153.
2. Stambaugh JE, Wainer IW. Drug interaction: meperidine and chlorpromazine, a toxic combination. *J Clin Pharmacol* 1981; **21:** 140–6.

Pharmacokinetics

Pethidine hydrochloride is absorbed from the gastrointestinal tract, but only about 50% of the drug reaches the systemic circulation because of first-pass metabolism. Absorption after intramuscular injection is variable. Peak plasma concentrations have been reported 1 to 2 hours after oral doses. It is about 60 to 80% bound to plasma proteins.

Pethidine is metabolised in the liver by hydrolysis to pethidinic acid (meperidinic acid) or demethylation to norpethidine (normeperidine) and hydrolysis to norpethidinic acid (normeperidinic acid), followed by partial conjugation with glucuronic acid. Norpethidine is pharmacologically active and its accumulation may result in toxicity. Pethidine is reported to have a plasma elimination half-life of about 3 to 6 hours in healthy subjects; the metabolite norpethidine is eliminated more slowly, with a half-life reported to be up to about 20 hours. Both pethidine and norpethidine appear in the CSF. At the usual values of urinary pH or if the urine is alkaline, only a small amount of pethidine is excreted unchanged; urinary excretion of pethidine and norpethidine is enhanced by acidification of the urine. Pethidine crosses the placenta and is distributed into breast milk.

Reviews.

1. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; **7:** 421–33.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Administration. The elimination half-life of pethidine was prolonged and plasma clearance decreased when given perioperatively compared with postoperatively.[1]

During labour the pharmacokinetics of pethidine may depend on how it is given. In a comparison of intramuscular injection at different sites, absorption of pethidine from the gluteus muscle was impaired and the deltoid muscle was preferred.[2]

No statistically significant differences were found in pharmacokinetic parameters for deltoid and gluteal intramuscular injections in elderly postoperative patients.[3] However, substantial interpatient variability was noted for both sites, and the authors suggested that more rapid and predictable routes such as intravenous injection may be more appropriate for postoperative use in the elderly.

1. Tamsen A, *et al.* Patient-controlled analgesic therapy, part 1: pharmacokinetics of pethidine in the per- and postoperative periods. *Clin Pharmacokinet* 1982; **7:** 149–63.
2. Lazebnik N, *et al.* Intravenous, deltoid, or gluteus administration of meperidine during labor? *Am J Obstet Gynecol* 1989; **160:** 1184–9.
3. Erstad BL, *et al.* Site-specific pharmacokinetics and pharmacodynamics of intramuscular meperidine in elderly postoperative patients. *Ann Pharmacother* 1997; **31:** 23–8.

Hepatic impairment. The terminal half-life of pethidine was prolonged to about 7 hours in cirrhotic patients compared with 3 hours in healthy subjects, which was attributed to impairment of the drug-metabolising activity of the liver.[1] Another study concluded that although impaired hepatic metabolism might confer relative protection from norpethidine toxicity in patients with cirrhosis, there might be an increased risk of cumulative toxicity because of slow elimination of the metabolite.[2]

1. Klotz U, *et al.* The effect of cirrhosis on the disposition and elimination of meperidine in man. *Clin Pharmacol Ther* 1974; **16:** 667–75.
2. Pond SM, *et al.* Presystemic metabolism of meperidine to normeperidine in normal and cirrhotic subjects. *Clin Pharmacol Ther* 1981; **30:** 183–8.

Pregnancy. Some references[1-3] to the pharmacokinetics of pethidine during labour.

1. Tomson G, *et al.* Maternal kinetics and transplacental passage of pethidine during labour. *Br J Clin Pharmacol* 1982; **13:** 653–9.
2. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: I mother. *Am J Obstet Gynecol* 1985; **151:** 406–9.

3. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: II fetus and neonate. *Am J Obstet Gynecol* 1985; **151:** 410–15.

Renal impairment. Plasma protein binding of pethidine was reported to be decreased in renal disease and ranged from 58.2% in healthy subjects to 31.8% in anuric patients.[1] The same workers also reported prolonged elimination of pethidine in patients with renal dysfunction.[2]

See also under Precautions, p. 123.2.

1. Chan K, *et al.* Plasma protein binding of pethidine in patients with renal disease. *J Pharm Pharmacol* 1983; **35:** 94P.
2. Chan K, *et al.* Pharmacokinetics of low-dose intravenous pethidine in patients with renal dysfunction. *J Clin Pharmacol* 1987; **27:** 516–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cluyer; Meperol; ***Austria***: Alodan; ***Belg.***: Dolantine; ***Braz.***: Dolantina; Dolosal; Dornot; Petinan; ***Canad.***: Demerol; ***Cz.***: Dolsin; ***Ger.***: Dolantin†; Dolcontral; ***Hung.***: Dolargan; ***Israel***: Dolestine; ***Philipp.***: Deme; Demerol; ***Pol.***: Dolargan; Dolcontral; ***Spain***: Dolantina; ***Turk.***: Aldolan; ***USA***: Demerol.

Multi-ingredient Preparations. ***UK***: Pamergan P100; ***USA***: Meprozine†.

Pharmacopoeial Preparations
BP 2014: Pethidine Injection; Pethidine Tablets;
USP 36: Meperidine Hydrochloride Injection; Meperidine Hydrochloride Syrup; Meperidine Hydrochloride Tablets.

Phenacetin *(rINN)*

Aceto-*p*-phenetidide; Acetophenetidin; Acetylphenetidin; Fenacetin; Fenacetina; Fenacetine; Fenacetyna; Fenasetiini; Fenasetin; Paracetophenetidin; Phénacétine; Phenacetinum; Фенацетин.

p-Acetophenetidide; 4′-Ethoxyacetanilide; *N*-(4-Ethoxyphenyl)acetamide.

$C_{10}H_{13}NO_2$=179.2
CAS — 62-44-2.
ATC — N02BE03.
ATC Vet — QN02BE03.
UNII — ER0CTH01H9.

Uses and Administration

Phenacetin, a para-aminophenol derivative, has analgesic and antipyretic properties. It was usually given with aspirin, caffeine, or codeine but is now little used because of adverse haematological effects and nephrotoxicity.

Adverse Effects and Precautions

Phenacetin may cause methaemoglobinaemia, sulfhaemoglobinaemia, and haemolytic anaemia.

Prolonged use of large doses of analgesic mixtures containing phenacetin has been associated with the development of renal papillary necrosis (see Effects on the Kidneys, p. 106.2) and transitional-cell carcinoma of the renal pelvis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Antineuralgica; Dolor†.

Phenazone *(BAN, rINN)*

Analgésine; Antipyrin; Antipyrine; Azophenum; Fenatsoni; Fenazon; Fenazona; Fenazonas; Phenazon; Phénazone; Phenazonum; Phenyldimethylpyrazolone; Феназон.

1,5-Dimethyl-2-phenyl-4-pyrazolin-3-one.

$C_{11}H_{12}N_2O$=188.2
CAS — 60-80-0.
ATC — N02BB01; S02DA03.
ATC Vet — QN02BB01; QS02DA03.
UNII — T3CHA1B51H.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Phenazone). White or almost white crystalline powder or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Antipyrine). Colourless crystals or white crystalline powder. Is odourless. Very soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether. Solutions are neutral to litmus. Store in airtight containers.

Phenazone and Caffeine Citrate

Antipyrino-Coffeinum Citricum; Fenazona y citrato de cafeína; Migrenin; Феназон и Кофеина Цитрат.

UNII — 3Z4LOI7NPG.

Description. Phenazone and caffeine citrate is a powder usually containing phenazone 90%, caffeine 9%, and citric acid monohydrate 1%.

Pharmacopoeias. In *Jpn.*

Phenazone Salicylate

Antipyrin Salicylate; Fenatsonisalisylaatti; Fenazona salicilato; Fenazonsalicylat; Phenazoni Salicylas; Salipyrin; Феназона Салицилат.

$C_{11}H_{12}N_2O,C_7H_6O_3$=326.4
CAS — 520-07-0.
ATC — N02BB01; S02DA03.
ATC Vet — QS02DA03.
UNII — F558OJK9JG.

Pharmacopoeias. In *Fr.*

Uses and Administration

Phenazone is an NSAID (p. 102.3) and has been given orally; phenazone and caffeine citrate and phenazone salicylate have similarly been given orally as analgesics.

Solutions containing about 5% of phenazone have been used topically as ear drops in disorders such as acute otitis media (but see below).

Phenazone is used as a test for the activity of drug-metabolising enzymes in the liver.

Diagnosis and testing. A review[1] of normal plasma-phenazone pharmacokinetics, urinary metabolite disposition, and total body clearances of phenazone in the presence of cirrhosis, fatty liver, hepatitis, and cholestatis.

1. St Peter JV, Awni WM. Quantifying hepatic function in the presence of liver disease with phenazone (antipyrine) and its metabolites. *Clin Pharmacokinet* 1991; **20:** 50–65.

Otitis media. There appears to be no justification[1] for the inclusion of phenazone in topical preparations used in treating acute otitis media (p. 197.2). It is presumably included in such preparations because it is believed to have a local anti-inflammatory and, therefore, analgesic action. It would, however, seem unlikely that phenazone would have any action on the skin of the intact tympanic membrane and, therefore, on the pain which is due mainly to the stretching and distention of the membrane.

1. Carlin WV. Is there any justification for using phenazone in a local application prescribed for the treatment of acute otitis media? *BMJ* 1987; **294:** 1333.

Adverse Effects, Treatment, and Precautions

Phenazone is liable to give rise to skin eruptions and in susceptible individuals even small doses may have this effect. Hypersensitivity reactions and nephrotoxicity have been reported. Large oral doses may cause nausea, drowsiness, methaemoglobinaemia, coma, and convulsions. Although the benefit of gastric decontamination is uncertain, activated charcoal may be given to adults or children who have ingested more than 20 mg/kg within 1 hour of presentation. Thereafter, symptomatic and supportive therapy should be given as appropriate.

Effects on the blood. Phenazone can cause haemolytic anaemia in certain individuals with a deficiency of G6PD.[1] Episodes of agranulocytosis were reported[2] in 6 women using a cream containing phenazone; all recovered on withdrawal.

1. Prankerd TAJ. Hemolytic effects of drugs and chemical agents. *Clin Pharmacol Ther* 1963; **4:** 334–50.
2. Delannoy A, Schmit J-C. Agranulocytosis after cutaneous contact with phenazone. *Eur J Haematol* 1993; **50:** 124.

Effects on the kidneys. Phenazone is considered nephrotoxic but only limited clinical information on phenazone is available because it has been mainly used with phenacetin.[1]

1. Prescott LF. Analgesic nephropathy: a reassessment of the role of phenacetin and other analgesics. *Drugs* 1982; **23:** 75–149.

Effects on the skin. In a summary[1] of 77 cases of fixed drug eruption phenazone derivatives were considered to be the causative agent in 9 of the 14 cases that were severe generalised reactions.

1. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.

Hypersensitivity. Immediate allergic reactions to phenazone have been reported.[1,2] In one patient leucopenia was detected 8 weeks later.[1]

1. Kadar D, Kalow W. Acute and latent leukopenic reaction to antipyrine. *Clin Pharmacol Ther* 1980; **28:** 820–22.
2. McCrea JB, *et al.* Allergic reaction to antipyrine, a marker of hepatic enzyme activity. *DICP Ann Pharmacother* 1989; **23:** 38–40.

Interactions

Phenazone affects the metabolism of some other drugs and its own metabolism is affected by other drugs that increase or reduce the activity of liver enzymes.

Pharmacokinetics

Phenazone is absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 2 hours of ingestion. It is distributed throughout the body fluids and concentrations in the saliva and breast milk reach about the same levels as those in plasma. Less than 10% is bound to plasma proteins and it has an elimination half-life of about 12 hours. Phenazone is metabolised in the liver to 3 major metabolites 3-hydroxymethylphenazone, 4-hydroxyphenazone, and norphenazone. Phenazone, 3-hydroxymethylphenazone, and glucuronidated metabolites are all excreted in the urine. A small portion may be eliminated via the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Erasol†; ***Ger.***: Eu-Med; Migrane-Kranit; Migranin Phenazon†; ***Hong Kong***: Tropex; ***Irl.***: Tropex; ***Pol.***: Antotalgin; ***S.Afr.***: Adco-Otophen; Aurone; ***Venez.***: Otamina.

Multi-ingredient Preparations. ***Arg.***: Aqua Lent Colirio; Bideon Free; Bideon; Cerosporin; Clarisoft; Coliria; Cristalomicina; Irix Clasico; Kalopsis; Otalex G; Otocalmia Biotic; Otocerol; Otocuril; Otonorthia; Prednifarma; Sincerum; Usualix; Vislus; ***Austral.***: Auralgan; Ear Clear For Ear Ache Relief; ***Austria***: Coffo Selt; Otalgan; ***Belg.***: Hemorhinol†; ***Canad.***: Auralgan; Formule L2; ***Cz.***: Otipax; ***Denm.***: Koffisal; ***Fr.***: Brulex; HEC; Otipax; ***Ger.***: Otalgan; ***Gr.***: Otil; ***Hong Kong***: Neo-Active Antirheumatic†; ***Hung.***: Otipax; ***India***: Tytin; ***Israel***: Anaesthetic Ear Drops; Otidin; ***Ital.***: Otalgan; Otomidone; Otopax; ***Norw.***: Antineuralgica†; Fanalgin; ***NZ***: Auralgan; ***Philipp.***: Auralgan; ***Rus.***: Folicap (Фоликап); Otipax (Отипакс); Otirelax (Отирелакс); ***S.Afr.***: Adco-Otised; Auralyt†; Aurasept; Aurone Forte†; Covancaine; Ilvico†; Oto-Phen Forte†; Universal Earache Drops†; ***Singapore***: Tropex; ***Spain***: Epistaxol; Otosedol†; Quimpedor; Tabletas Quimpe†; ***Swed.***: Koffazon; ***Switz.***: Otalgan; Otipax; Otosan; Otothricinol; ***Thai.***: Auralgan; ***Ukr.***: Otipax (Отипакс); Otisol (Отизол); ***USA***: AABP; Allergen; Auralgan; Aurax; Auroguard Otic; Cy-Gesic; Ear-Gesic; Neotic†; Otic Edge†; Otozin; Treagan; ***Venez.***: Otan; Otirilin.

Pharmacopoeial Preparations
USP 36: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution.

Phenazopyridine Hydrochloride

(BANM, USAN, rINNM)

Fenazopiridin Hidroklorür; Chloridrato de Fenazopiridina; Fenazopiridina, hidrocloruro de; Fenazopirydyny chlorowodorek; Hidrocloruro de fenazopiridina; NC-150; NSC-1879; Phénazopyridine, Chlorhydrate de; Phenazopyridini Hydrochloridum; W-1655; Феназопиридина Гидрохлорид.

3-Phenylazopyridine-2,6-diyldiamine hydrochloride.

$C_{11}H_{11}N_5$,HCl=249.7
CAS — 94-78-0 (phenazopyridine); 136-40-3 (phenazopyridine hydrochloride).
ATC — G04BX06.
ATC Vet — QG04BX06.
UNII — 0EWG66BW17.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Phenazopyridine Hydrochloride). A light or dark red to dark violet crystalline powder. Is odourless or with a slight odour. Soluble 1 in 300 of cold water, 1 in 20 of boiling water, 1 in 59 of alcohol, 1 in 331 of chloroform, and 1 in 100 of glycerol; very slightly soluble in ether. Store in airtight containers.

Removal of stains. Phenazopyridine stains may be removed from fabric by soaking in a 0.25% solution of sodium dithionite.

Uses and Administration

Phenazopyridine is an azo dye that exerts an analgesic effect on the mucosa of the urinary tract and is used to provide symptomatic relief of pain and irritability in conditions such as cystitis (p. 2347.3), prostatitis (p. 2350.2), and urethritis (p. 214.3). Phenazopyridine hydrochloride has been given in usual oral doses of about 200 mg three times daily after food. If given with an antibacterial for the treatment of urinary-tract infections (see below), treatment should usually not exceed 2 days, although lower doses have been given as part of a combined preparation for at least a week.

Urinary-tract infections. There is no well-substantiated role for phenazopyridine in the treatment of urinary-tract

infections (p. 215.1) and its adverse effects are potentially serious.[1]

1. Zelenitsky SA, Zhanel GG. Phenazopyridine in urinary tract infections. *Ann Pharmacother* 1996; **30:** 866–8.

Adverse Effects

Phenazopyridine hydrochloride has caused gastrointestinal adverse effects, headache, and rashes. Hepatotoxicity, haemolytic anaemia, methaemoglobinaemia, and acute renal failure have also been reported, generally associated with overdosage or with therapeutic doses in patients with renal impairment. Crystal deposits of phenazopyridine have formed in the urinary tract.

Abnormal coloration of body tissues or fluids may occur. Urine is tinged either orange or red and underclothes are apt to be stained.

Effects on the CNS. Aseptic meningitis, with distinct episodes of fever and confusion, was associated with the use of phenazopyridine.[1]

1. Herlihy TE. Phenazopyridine and aseptic meningitis. *Ann Intern Med* 1987; **106:** 172–3.

Overdosage. A 2-year-old child developed cyanosis and methaemoglobinaemia after ingesting at most three 200-mg tablets of phenazopyridine hydrochloride;[1] she recovered after treatment with methylthioninium chloride. Acute renal failure has been reported in a 17-year-old HIV-positive girl, with no history of kidney disease, who took 1.2 g of phenazopyridine in a suicide attempt.[2]

1. Gold NA, Bithoney WG. Methemoglobinemia due to ingestion of at most three pills of pyridium in a 2-year-old: case report and review. *J Emerg Med* 2003; **25:** 143–8.
2. Onder AM, *et al.* Acute renal failure due to phenazopyridine (Pyridium) overdose: case report and review of the literature. *Pediatr Nephrol* 2006; **21:** 1760–4.

Precautions

Phenazopyridine hydrochloride is contra-indicated in patients with renal impairment or severe hepatitis and should be used with caution in those with G6PD deficiency. Treatment should be stopped if the skin or sclerae become discoloured; this may indicate accumulation as a result of impaired renal excretion. Phenazopyridine may interfere with urinalysis based on colour reactions or spectrometry.

Staining of contact lenses may occur.

Pharmacokinetics

Phenazopyridine hydrochloride is absorbed from the gastrointestinal tract. It is excreted mainly in the urine; up to 65% may be excreted as unchanged phenazopyridine and 18% as paracetamol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cistalgina; ***Belg.***: Uropyrine; ***Braz.***: Pyridium; Pyrisept; Urologin; Urovit; ***Canad.***: Phenazo; Pyridium; ***Chile***: Nazamit†; Nordox; ***China***: Karidine (科力定); Yi Du (怡度); ***Hong Kong***: CP-Pyridine; Phenadine; Phenazo; Pyridin†; Pyridium; ***India***: Pyridium; ***Indon.***: Pyridium†; Urogetix; ***Israel***: Sedural; ***Mex.***: Alvena; Azofur†; Bioferina; Pirimir; Urezol; ***Philipp.***: Azomir†; ***Pol.***: Nefrecil†; ***S.Afr.***: Pyridium†; ***Singapore***: Urogesic; ***Thai.***: Ammilazo†; Anazo; Phendiridine; Sumedium; Uzone-T; ***USA***: Azo-Standard; Baridium; Prodium; Pyridium; Re-Azo; Urogesic.

Multi-ingredient Preparations. ***Arg.***: Bacti-Uril; Medaflox Dol; Nor 2; Priper Plus; Urotem Dol; ***Braz.***: Minazol; Uroctrim; Uropac; Uropielon; ***Chile***: Uro-Micinovo; ***Hong Kong***: Urobilin†; ***India***: Nephrogesic; ***Mex.***: Azo-Uronalin; Azo-Wintomylon; Azogen; Azuron; Mictasol; Nalixone; Naxilan-Plus; Norflen; Pirifur; Urovec†; Vodelan; ***Spain***: Micturol Sedante; ***Thai.***: Pyrizole; ***Turk.***: Azo Gantrisin; Azosilin; Uriseptin; ***USA***: Phenazo-Forte Plus; Phenazopyridine Plus; Pyrelle HB†; Pyridium Plus; Trellium Plus†; Urelief Plus; Urobiotic-250; ***Venez.***: Azo-Mandelamine; Bacteval.

Pharmacopoeial Preparations

USP 36: Phenazopyridine Hydrochloride Tablets.

Phenylbutazone *(BAN, rINN)*

Butadione; Fenilbutazon; Fenilbutazona; Fenilbutazonas; Fenylbutazon; Fenylobutazon; Fenyylibutatsoni; Phenylbutazon; Phénylbutazone; Phenylbutazonum; Фенилбутазон.

4-Butyl-1,2-diphenylpyrazolidine-3,5-dione.

$C_{19}H_{20}N_2O_2$=308.4

CAS — 50-33-9 (phenylbutazone); 129-18-0 (phenylbutazone sodium); 4985-25-5 (phenylbutazone piperazine).

ATC — M01AA01; M02AA01.

ATC Vet — QM01AA01; QM02AA01.

UNII — GN5P7K3T8S.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Phenylbutazone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; it dissolves in alkaline solutions. Protect from light.

USP 36: (Phenylbutazone). A white to off-white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone and in ether. Store in airtight containers.

Profile

Phenylbutazone, a pyrazolone derivative, is an NSAID (p. 102.3). However, because of its toxicity and in particular its adverse haematological reactions (see Effects on the Blood, below), it is not used as a general analgesic or antipyretic. Although phenylbutazone is effective in almost all musculoskeletal and joint disorders including ankylosing spondylitis, acute gout, osteoarthritis, and rheumatoid arthritis, it should only be used in acute conditions where less toxic drugs have failed. In the UK its use has been restricted to the hospital treatment of ankylosing spondylitis unresponsive to other drugs. Initial oral doses of up to 600 mg daily in divided doses have been used in the treatment of rheumatic disorders. After 1 to 3 days, the dose should be reduced to the minimum effective amount, usually 100 to 300 mg daily; treatment should be given for the shortest period possible, up to a usual maximum of 1 week. If treatment is expected to continue for more than 1 week, blood cell counts should be performed before and regularly during therapy; monitoring of hepatic and renal function is also recommended. Reduced doses are recommended in elderly patients.

In some countries phenylbutazone has also been given as a rectal suppository and applied topically for musculoskeletal pain and in soft-tissue injury. It has also been given intramuscularly as the sodium salt. Other salts of phenylbutazone that have been used in musculoskeletal, joint, and soft-tissue disorders include the calcium, megallate, and piperazine salts.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given phenylbutazone, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, UK licensed product information states that phenylbutazone should be avoided during breast feeding as small amounts are distributed into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Both phenylbutazone[1-3] and oxyphenbutazone[2,3] are well known for their adverse effects on the blood and especially for fatal agranulocytosis and aplastic anaemia. Leucopenia, pancytopenia, haemolytic anaemia, and thrombocytopenia may also occur. The UK CSM[4] noted that between July 1963 and January 1993 it had received 74 reports of agranulocytosis (39 fatal) associated with phenylbutazone and 40 reports of neutropenia (4 fatal). Up-to-date figures were not provided on oxyphenbutazone, but it is considered to be more toxic to the bone marrow than phenylbutazone.[2]

1. Böttiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *BMJ* 1973; **3:** 339–43.
2. Anonymous. Phenylbutazone and oxyphenbutazone: time to call a halt. *Drug Ther Bull* 1984; **22:** 5–6.
3. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
4. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Butazolidina; Butazona; Neo Butazol; ***Fr.***: Butazolidine†; ***Ger.***: Ambene; exrheudon OPT; ***Indon.***: Akrofen; Berlison; Irgapan; ***Ital.***: Kadol; ***Mex.***: Astrofen†; Bloken; Bresal; Butalen; Butazolidina; Meprosona-F; ***Neth.***: Butazolidin; ***Pol.***: Butapirazol; ***Rus.***: Butadion (Бутадион); ***S.Afr.***: Inflazone; ***Spain***: Butazolidina; ***Switz.***: Butadion†; ***Thai.***: Butarzol; Butazone; KB Tazone; Leophen; Neo-Pyrazol†; Pantazone; Phenazone; Pyrazolone; Rhumacap; Rhumatab; Sugrarine; ***Ukr.***: Butadion (Бутадион); ***Venez.***: Ticinil Calcio.

Multi-ingredient Preparations. ***Braz.***: Mioflex; ***Chile***: Balsamo Analgesico con Fenilbutazona; Esanfrix; ***Fr.***: Dextrarine Phenylbutazone; ***Hung.***: Rheosolon; ***India***: Aristopyrin; ***Indon.***: Butamidon; Cetapyrin†; Enkapyrin; New Skelan; ***Mex.***: Butayonacol; Butisel; Dexadutil; Dibutasona; ***Rus.***: Ambene (Амбене); ***Spain***: Artrodesmol Extra; Doctofril Antiinflamat†; ***Switz.***: Butaparin†; ***Thai.***: Alaxan†; Asialax†; Butarion†; Myophen†.

Picolamine Salicylate *(rINNM)*

Picolamine, Salicylate de; Picolamini Salicylas; 3-Pyridylmethylamine Salicylate; Salicilato de picolamina; Пиколамина Салицилат.

3-(Aminomethyl)pyridine Salicylate.

CAS — 3731-52-0 (picolamine).

Profile

Picolamine salicylate is a salicylic acid derivative that has been used topically in rubefacient preparations in the treatment of musculoskeletal, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Algiospray.

Piketoprofen *(rINN)*

Pikétoprofène; Piketoprofeno; Piketoprofenum; Пикетопрофен.

m-Benzoyl-*N*-(4-methyl-2-pyridyl)hydratropamide.

$C_{22}H_{20}N_2O_2$=344.4

CAS — 60576-13-8.

UNII — 362QBC4NL0.

Profile

Piketoprofen is an NSAID (p. 102.3) that has been used topically as the hydrochloride in concentrations of about 2% in musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Picalm; Zemalex; ***Spain***: Calmatel; Triparsean†.

Piritramide *(BAN, rINN)*

Pirinitramide; Piritramid; Piritramida; Piritramidi; Piritramidum; R-3365; Пиритрамид.

1-(3-Cyano-3,3-diphenylpropyl)-4-piperidinopiperidine-4-carboxamide.

$C_{27}H_{34}N_4O$=430.6

CAS — 302-41-0.

ATC — N02AC03.

ATC Vet — QN02AC03.

UNII — 4RP92LYZ2F.

Profile

Piritramide is an opioid analgesic (p. 108.1).

It is used for the management of severe pain including postoperative pain, for premedication, and to provide analgesia during anaesthesia. It is given by intramuscular, subcutaneous, or slow intravenous injection as the tartrate in doses equivalent of up to about 30 mg of the base.

Reviews.

1. Kumar N, Rowbotham DJ. Piritramide. *Br J Anaesth* 1999; **82:** 3–5.
2. Bouillon T, *et al.* The pharmacokinetics of piritramide after prolonged administration to intensive care patients. *Eur J Anaesthesiol* 2004; **21:** 673–8.
3. Müller C, *et al.* Pharmacokinetics of piritramide in newborns, infants and young children in intensive care units. *Eur J Pediatr* 2006; **165:** 229–39.
4. Huenseler C, *et al.* Prospective evaluation of the pharmacodynamics of piritramide in neonates and infants. *Eur J Pediatr* 2008; **167:** 867–72.
5. Remane D, *et al.* Stability of piritramide in patient-controlled analgesia (PCA) solutions. *Pharmazie* 2009; **64:** 380–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dipidolor; ***Belg.***: Dipidolor; ***Cz.***: Dipidolor; ***Ger.***: Dipidolor; ***Neth.***: Dipidolor.

Piroxicam *(BAN, USAN, rINN)*

CP-16171; Piroksikaami; Piroksikam; Piroksikamas; Piroxicamum; Piroxikam; Piroxikám; Пироксикам.

4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

$C_{15}H_{13}N_3O_4S$=331.3

CAS — 36322-90-4.

ATC — M01AC01; M02AA07; S01BC06.

ATC Vet — QM01AC01; QM02AA07; QS01BC06.

UNII — 13T4O6VMAM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Piroxicam). A white or slightly yellow, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in dichloromethane. Protect from light.

USP 36: (Piroxicam). An off-white to light tan or light yellow, odourless powder. It forms a monohydrate that is yellow. Very slightly soluble in water, in dilute acids, and in most organic solvents; slightly soluble in alcohol and in aqueous alkaline solutions. Store in airtight containers. Protect from light.

Piroxicam Betadex *(USAN, rINNM)*

CHF-1194; Piroxicam Beta Cyclodextrin; Piroxicam Beta Cyclodextrin Complex; Piroxicam Bétadex; Piroxicamum Betadexum; Пироксикам Бетадекс.

$(C_{15}H_{13}N_3O_4S)_2,(C_{42}H_{70}O_{35})_3$=6337.6

CAS — 96684-40-1.

Uses and Administration

Piroxicam, an oxicam derivative, and piroxicam betadex are NSAIDs (p. 102.3). Piroxicam betadex may have a more rapid onset of therapeutic effect due to its enhanced solubility (see Pharmacokinetics below). Both have been used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis including juvenile idiopathic arthritis, in soft-tissue disorders, in acute gout, and in postoperative pain but systemic usage in the EU is now restricted (see below) to chronic painful and inflammatory conditions.

In rheumatic disorders the usual maximum recommended oral dose of *piroxicam* is 20 mg daily as a single dose; divided doses may be used if necessary. Piroxicam has been given in similar doses as a rectal suppository or on a short-term basis by intramuscular injection.

For dosage in children, see below.

Piroxicam is also used in the local treatment of a variety of painful or inflammatory conditions as a topical gel in a concentration of 0.5% applied three or four times daily; treatment should be reviewed after 4 weeks. A 1% gel is also available. Piroxicam has been used in some countries as a 0.5 or 1% cream and as eye drops in a concentration of 0.5%.

Doses of piroxicam betadex are expressed in terms of the equivalent amount of piroxicam. Piroxicam betadex 191.3 mg is equivalent to about 20 mg of piroxicam. In rheumatic disorders *piroxicam betadex* is given in an oral dose equivalent to 20 mg of piroxicam daily as a single dose. This dose may be reduced to 10 mg daily in elderly patients.

Other salts or compounds that have also been used include piroxicam cinnamate (cinnoxicam), piroxicam choline, and piroxicam pivalate.

After a review[1] of the benefit-risk balance for piroxicam the EMEA placed restrictions on its systemic use and stated that:

- *its use in acute painful and inflammatory conditions should be abandoned*
- *its use should be limited only to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis*
- *it should not be used as a first-line treatment*
- *the dose should be limited to 20 mg daily*
- *treatment should be reviewed within 14 days of starting*
- *it should only be started by doctors experienced in treating chronic painful and inflammatory conditions*
- *use with a gastroprotective drug should be considered*
- *it should not be given to patients at risk of gastrointestinal disorders associated with bleeding or to those who have had skin reactions to other drugs*
- *it should not be used with another NSAID or an anticoagulant*

1. EMEA. Questions and answers on the review of piroxicam (issued 21st June, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/piroxicam_26457807en.pdf (accessed 08/11/07)

Administration in children. Piroxicam has been used in children with juvenile idiopathic arthritis. The following doses, given according to body-weight, are recommended in the *BNFC* for children aged 6 years and over:

- less than 15 kg: 5 mg once daily
- 16 to 25 kg: 10 mg once daily
- 26 to 45 kg: 15 mg once daily
- 46 kg or over: 20 mg once daily

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Local irritation and occasionally bleeding may occur with piroxicam suppositories and there may be pain and occasionally tissue damage at the injection site on intramuscular use. Application site reactions have also occurred with topical preparations of piroxicam.

Piroxicam is considered to be associated with an intermediate risk of gastrointestinal effects although there is some suggestion that the risk may be higher than for other intermediate-risk NSAIDs (p. 105.3).

A report[1] of the adverse reactions associated with piroxicam in South Africa during 1981 to 1986 included two reactions, paraesthesia and hair loss, not previously recorded in the literature.

1. Gerber D. Adverse reactions of piroxicam. *Drug Intell Clin Pharm* 1987; **21:** 707–10.

Effects on the blood. Decreases in haemoglobin and haematocrit not associated with obvious gastrointestinal bleeding, have occurred in patients taking piroxicam. Thrombocytopenia, thrombocytopenic purpura,[1] and aplastic anaemia[2] have been described in patients on piroxicam.

1. Bjørnstad H, Vik Ø. Thrombocytopenic purpura associated with piroxicam. *Br J Clin Pract* 1986; **40:** 42.
2. Lee SH, *et al*. Aplastic anaemia associated with piroxicam. *Lancet* 1982; **i:** 1186.

Effects on electrolytes. Reversible hyperkalaemic hyperchloraemic acidosis has been reported[1,2] in patients receiving piroxicam. Severe hyponatraemia and symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion have also been associated with piroxicam.[3]

See also Effects on the Kidneys, below.

1. Grossman LA, Moss S. Piroxicam and hyperkalemic acidosis. *Ann Intern Med* 1983; **99:** 282.
2. Miller KP, *et al*. Severe hyperkalemia during piroxicam therapy. *Arch Intern Med* 1984; **144:** 2414–15.
3. Petersson I, *et al*. Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.

Effects on the kidneys. Acute nephropathy with characteristic features of Henoch-Schönlein purpura,[1] acute renal failure,[2] uraemia with hyperkalaemia, and acute interstitial nephritis[3] have been associated with systemic use of piroxicam. Nephrotic syndrome and interstitial nephritis have followed topical use of piroxicam gel.[4]

1. Goebel KM, Mueller-Brodmann W. Reversible overt nephropathy with Henoch-Schönlein purpura due to piroxicam. *BMJ* 1982; **284:** 311–12.
2. Frais MA, *et al*. Piroxicam-induced renal failure and hyperkalemia. *Ann Intern Med* 1983; **99:** 129–30.
3. Mitnick PD, Klein WJ. Piroxicam-induced renal disease. *Arch Intern Med* 1984; **144:** 63–4.
4. O'Callaghan CA, *et al*. Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.

Effects on the liver. Necrosis of the liver, sometimes fatal, has been associated with piroxicam.[1,2]

1. Lee SM, *et al*. Subacute hepatic necrosis induced by piroxicam. *BMJ* 1986; **293:** 540–1.
2. Paterson D, *et al*. Piroxicam induced submassive necrosis of the liver. *Gut* 1992; **33;** 1436–8.

Effects on the skin. As with other NSAIDs, rash has occurred in patients taking piroxicam. Phototoxic reactions have been described.[1] Serious skin reactions attributed to piroxicam therapy include toxic epidermal necrolysis,[2] pemphigus vulgaris,[3] erythema multiforme,[4] and Stevens-Johnson syndrome.[5] Fixed drug eruptions have also been reported.[6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see Uses and Administration, above).

1. Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal antiinflammatory agents. *N Engl J Med* 1983; **309:** 186–7.
2. Chosidow O, *et al*. Intestinal involvement in drug-induced toxic epidermal necrolysis. *Lancet* 1991; **337:** 928.
3. Martin RL, *et al*. Fatal pemphigus vulgaris in a patient taking piroxicam. *N Engl J Med* 1983; **309:** 795–6.
4. Prieto A, *et al*. Piroxicam-induced erythema multiforme. *Contact Dermatitis* 2004; **50:** 263.
5. Katoh N, *et al*. Piroxicam induced Stevens-Johnson syndrome. *J Dermatol* 1995; **22:** 677–80.
6. Cuerda Galindo E, *et al*. Fixed drug eruption from piroxicam. *J Eur Acad Dermatol Venereol* 2004; **18:** 586–7.

Overdosage. Details of 16 patients who were considered to have taken an overdosage of piroxicam alone were reported[1] to the National Poisons Information Service of the UK. Thirteen patients (including 5 children) had no symptoms after doses estimated to be up to 300 to 400 mg; 2 patients complained of dizziness and blurred vision after 200 to 300 mg; the last patient, who claimed to have taken 600 mg presented in coma, regained consciousness within one hour, and had recovered fully within 24 hours. Severe multisystem toxicity has been reported in a 2-year-old child after ingestion of 100 mg of piroxicam.[2]

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. MacDougall LG, *et al*. Piroxicam poisoning in a 2-year-old child: a case report. *S Afr Med J* 1984; **66:** 31–3.

Pancreatitis. Pancreatitis has been associated with piroxicam use.[1,2]

1. Haye OL. Piroxicam and pancreatitis. *Ann Intern Med* 1986; **104:** 895.
2. Heluwaert F, *et al*. Pancréatite aiguë au piroxicam. *Gastroenterol Clin Biol* 2006; **30:** 635–6.

Precautions

As for NSAIDs in general, p. 107.1.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given piroxicam, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount excreted into breast milk to be too small to be harmful to a breast-fed infant.

Piroxicam appears in breast milk in concentrations of about 1% of those in the maternal plasma.[2] Similar data are also included in the licensed product information although it does not recommend piroxicam use during breast feeding as clinical safety has not been established.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Østensen M. Piroxicam in human breast milk. *Eur J Clin Pharmacol* 1983; **25:** 829–30.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piroxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Use of aspirin with piroxicam results in decreased plasma concentrations of piroxicam to about 80% of normal. The UK licensed product information for ritonavir suggests that use of piroxicam with ritonavir may result in increased plasma concentrations of piroxicam and an increased risk of toxicity; it recommends that use together should be avoided.

Pharmacokinetics

Piroxicam is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 3 to 5 hours after an oral dose. It is more rapidly absorbed after intramuscular use and is also absorbed to some degree after topical application. Piroxicam is 99% bound to plasma proteins. It has been detected in breast milk. Piroxicam has a long plasma elimination half-life of about 50 hours and steady-state concentrations are not reached for 7 to 12 days. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid and excreted mainly in the urine with smaller amounts in the faeces. Enterohepatic recycling occurs. Less than 5% of the dose is excreted unchanged in the urine and faeces.

Piroxicam betadex dissociates in the gastrointestinal tract to its components piroxicam and betadex (p. 2180.3). Piroxicam absorption from piroxicam betadex is more rapid than that of unmodified piroxicam; peak plasma concentrations of piroxicam occur 30 to 60 minutes after an oral dose. Betadex is not absorbed but is metabolised in the colon to various sugars.

References.

1. Richardson CJ, *et al*. Piroxicam and 5′-hydroxypiroxicam kinetics following multiple dose administration of piroxicam. *Eur J Clin Pharmacol* 1987; **32:** 89–91.
2. Mäkelä A-L, *et al*. Steady state pharmacokinetics of piroxicam in children with rheumatic diseases. *Eur J Clin Pharmacol* 1991; **41:** 79–81 (higher clearance and shorter half-life in children).
3. Rudy AC, *et al*. The pharmacokinetics of piroxicam in elderly persons with and without renal impairment. *Br J Clin Pharmacol* 1994; **37:** 1–5.
4. Deroubaix X, *et al*. Oral bioavailability of CHF1194, an inclusion complex of piroxicam and β-cyclodextrin, in healthy subjects under single dose and steady-state conditions. *Eur J Clin Pharmacol* 1995; **47:** 531–6.
5. Karim A, *et al*. Oxaprozin and piroxicam, nonsteroidal antiinflammatory drugs with long half-lives: effect of protein-binding differences on steady-state pharmacokinetics. *J Clin Pharmacol* 1997; **37:** 267–78.
6. Wang D, *et al*. Comparative population pharmacokinetic-pharmacodynamic analysis for piroxicam-β-cyclodextrin and piroxicam. *J Clin Pharmacol* 2000; **40:** 1257–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Benisan; Brionot; Fabopxicam†; Flogosine; Homocalmefyba; Maxtol; Micar; Nac; Nalgesic; Osteocalmine; Piroalgin; Samaruc; Solocalm; Tirovel; Trixicam; ***Austral.***: Feldene; Mobilis; Pirohexal-D†; ***Austria***: Brexin; Felden; Pirocam; Pirorheum†; Piroxistad; ***Belg.***: Brexine; Docpiroxi†; Feldene; Piromed; Piroxitop†; Polydene; Solicam; ***Braz.***: Anartrit; Anflene; Brexin; Ciclador; Feldanax; Feldene; Flamostat; Flogene; Floxicam; Inflamene; Inflanan; Inflax; Piroflan; Pirogreen; Piroxene; Piroxifar†; Piroxil; Piroxin; Piroxinid; Prodoxidil†; ***Canad.***: Novo-Pirocam; Nu-Pirox; ***Chile***: Fabudol; Feldene; Foldox†; Pemar; Pricam; ***China***: An Er Ke (安尔克); Cycladol (喜来通); Ji Ke (基克); JiWei (吉维); Liang Ke (亮克); Luo Lin (络林); Reliagic (洛尔定); Trast; ***Cz.***: Flamexin; Hotemin; ***Denm.***: Felden; Feldene†; Pirom; ***Fin.***: Brexidol†; Felden;

Piroxin; ***Fr.***: Brexin; Cycladol; Feldene; Geldene; Inflaced†; Proxalyoc; Zofora; ***Ger.***: Brexidol†; Flexase†; Pirobeta; Piroflam; Pirox; ***Gr.***: Bleduran; Brexin; Calmopyrol; Conzila; Feldene; Fidinor; Flodeneu; Grecotens; Inflamase-N; Neo Axedil; Nilvo; Oximezin; Painrelipt-D; Pedifan; Proponol; Pyrcost; Reumaplus; Ruvamed; Sinartrol; Valopon; Zerospasm; Zitumex; ***Hong Kong***: CP-Pirox; Feldene; Mobilis†; Piram-D†; Piroxica†; Sefdene; Synoxicam†; Vidapirocam†; ***Hung.***: Brexin; Feldene; Flamexin; Hotemin; Pirorheum†; ***India***: Amida; Brexic; Camrox; Camsun; Cycladol; Dolocare; Dolocip; Dolodil; Dolokam; Dololup; Dolonex; Dolopir; Doloswift; Dupox; Estcom; Felcam; Feldex; Flexar; Kemonex; Lincitrax; Medicam; Meloxi; Micropec; Mobicam; Mobidin; Movon; Noxicam-MD; Pam; Panorox; Pirox; Suganril; ***Indon.***: Faxiden†; Felcam; Feldene; Infeld; Kifadene; Lanareuma; Licofel; Maxicam†; Pirocam; Pirodene†; Pirofel; Rexicam; Rexil; Rosic†; Roxidene; Scandene; Sofden†; Tropidene; Xicalom; ***Irl.***: Feldene; Pericam†; ***Israel***: Brexin; Exipan; Feldene; ***Ital.***: Antiflog; Artroxicam; Brexidol; Brexin; Brexivel; Bruxicam†; Cicladol; Clevian; Dexicam†; Euroxi; Feldene; Flodol; Ipsoflog; Kinski; Lampoflex; Lenotac; Pirobec; Piroftal; Reumagil; Roxene†; Roxenil†; Roxiden; Sinartrol; Zelis†; ***Jpn***: Baxo; ***Malaysia***: Brexin; Feldene; Rhumagel; Uphaxicam; ***Mex.***: Androxicam†; Arlexicam; Artyflam; Asabon†; Axtrim; Bapixied; Bioximil; Brexicam; Brexodin; Brucam; Campirex; Citoken T; Dixonal; Dolzycam; Edecam†; Facicam; Feldene; Glandicin; Laspiro; Osteral; Oxi-Reul; Oxicanol†; Pirodax†; Pirox; Piroxan†; R-Tyflam†; Reucam; Reutricam; Ripox; Serpicam; Tripirol; Vatrem; ***Neth.***: Brexine†; ***Norw.***: Brexidol; ***NZ***: Candyl; Piram-D†; Pirohexal-D†; ***Philipp.***: Feldene; Flamastat; Flaxine; Macroxam; Neperlan†; Palpasin; Parixam†; Pirostad†; Pixacor; Proximax; Raxicam; ***Pol.***: Feldene; Flamexin; Hotemin†; ***Port.***: Brexin; Feldene; Flexar; Flogocan†; Remisil; Reumoxican; Roxazin; ***Rus.***: Erazon (Эразон); Finalgel (Финалгель); ***S.Afr.***: Brexecam; Pixicam; Pyrocaps; Rheugesic; Roxifen; Xycam; ***Singapore***: Feldene; Rhumagel; Rosiden; Roxifen; Sefdene; Vitaxicam†; ***Spain***: Brexinil†; Cycladol†; Feldegel; Feldene; Improntal; Salvacam; Sasulen; Vitaxicam†; ***Swed.***: Brexidol; ***Switz.***: Felden; Pirocam†; Pirosol; ***Thai.***: Ammidene; Brexin; Butacinon; Cyclodex; Dexalin; Fasden; Felcam; Feldene; Felgesic; Felicam; Felnox; Felpac; Felrox; Felxicam; Flamic; Heropedd; Ifemed; Kobixam; Manoxicam; Maswin; Moxicam†; Neogel†; Neotica; Nutarzol; PC-20†; Pherazone; Pi-rock; Pidoxam; Piram; Pirax; Piraxil; Pircam; Pirox-Man; Pirox; Piroxal; Piroxam; Piroxcin; Piroxen†; Piroxidon; Piroxone; Piroxsil; Polyxicam; Posedene†; Rocki; Roxicam; Roxifen; Roxium; Roxycam; Roxycan; Rumadene; Rumaxicam; Setarox; Sotilen; Spamic; Verox; Xicam; ***Turk.***: Cycladol; Felden; Inflamex†; Oksikam; ***UK***: Brexidol; Feldene; ***Ukr.***: Finalgel (Финалгель); ***USA***: Feldene; ***Venez.***: Feldene; Feldenedi; Flamalit; Maxipiro; Pixorid.

Multi-ingredient Preparations. ***Arg.***: Buta Rut B12; Flexicamin A; Flexicamin B12; Flexicamin B12; Flexicamin; Flogiatrin B12; Flogiatrin B12; Flogiatrin; Peganix; Rumisedan Fuerte; Rumisedan; Solocalm Plus; Solocalm Plus; Solocalm-B; Solocalm-Flex; ***Braz.***: Rheumafim; ***India***: Capsidol; ***Indon.***: Counterpain-PXM; ***Thai.***: Counterpain Plus.

Pharmacopoeial Preparations
BP 2014: Piroxicam Capsules; Piroxicam Gel;
USP 36: Piroxicam Capsules; Piroxicam Cream.

Pranoprofen *(rINN)*

Pranoprofène; Pranoprofeno; Pranoprofenum; Пранопрофен.
α-Methyl-5*H*-[1]-benzopyrano[2,3-*b*]pyridine-7-acetic acid.
$C_{15}H_{13}NO_3$=255.3
CAS — 52549-17-4.
ATC — S01BC09.
ATC Vet — QS01BC09.
UNII — 2R7O1ET613.

Pharmacopoeias. In *Jpn*.

Profile

Pranoprofen, a propionic acid derivative, is an NSAID (p. 102.3). It is used as eye drops in a concentration of 0.1% for ocular inflammation. Pranoprofen has also been given orally for the treatment of pain, inflammation, and fever.

References.

1. Notivol R, *et al.* Treatment of chronic nonbacterial conjunctivitis with a cyclo-oxygenase inhibitor or a corticosteroid. *Am J Ophthalmol* 1994; **117**: 651–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Pranox; ***Braz.***: Difen; ***China***: Pranopulin (普南扑灵); ***Gr.***: Pranofen; ***Ital.***: Oftalar; Pranoflog; ***Jpn***: Niflan; ***Mex.***: Niflan; ***Port.***: Oftalar†; ***Spain***: Oftalar†; ***Turk.***: Oftalar.

Proglumetacin Maleate *(BANM, rINNM)*

CR-604; Maleato de proglumetacina; Proglumetacina, maleato de; Proglumétacine, Maléate de; Proglumetacinum Maleas; Protacine Maleate; Проглуметацина Малеат.

3-{4-[2-(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-ylacetoxy)ethyl]piperazin-1-yl}propyl 4-benzamido-*N*,*N*-dipropylglutaramate dimaleate.
$C_{46}H_{58}ClN_5O_8$,$2C_4H_4O_4$=1076.6
CAS — 57132-53-3 (proglumetacin); 59209-40-4 (proglumetacin maleate).
ATC — M01AB14.
ATC Vet — QM01AB14.
UNII — F2PUN24B8C.

Profile

Proglumetacin maleate, an indoleacetic acid derivative related to indometacin (p. 71.2), is an NSAID (p. 102.3). It has been used in musculoskeletal and joint disorders in oral doses of up to 600 mg daily, in divided doses. Proglumetacin maleate has also been given as rectal suppositories and topically as a 5% cream.

References.

1. Appelboom T, Franchimont P. Proglumetacin versus indometacin in rheumatoid arthritis: a double-blind multicenter study. *Adv Therapy* 1994; **11**: 228–34.
2. Martens M. Double-blind randomized comparison of proglumetacin and naproxen sodium in the treatment of patients with ankle sprains. *Curr Ther Res* 1995; **56**: 639–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bruxel; ***Belg.***: Tolindol; ***Ger.***: Protaxon; ***Hong Kong***: Afloxan; ***Ital.***: Proxil; ***Jpn***: Miridacin; ***Philipp.***: Afloxan; ***Port.***: Protaxil; ***Thai.***: Afloxan.

Propacetamol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propacetamol; Propacétamol, Chlorhydrate de; Propacetamol, hidrocloruro de; Propacetamol-hidroklorid; Propacetamolhydrochlorid; Propacetamol-hydrochlorid; Propacetamolhydroklorid; Propacetamoli Hydrochloridum; Propacetamolio hidrochloridas; Propasetamolihydrokloridi; Пропацетамола Гидрохлорид.
The hydrochloride of *N*,*N*-diethylglycine ester with paracetamol; 4-Acetamidophenyl diethylaminoacetate hydrochloride.
$C_{14}H_{20}N_2O_3$,HCl=300.8
CAS — 66532-85-2 (propacetamol).
ATC — N02BE05.
ATC Vet — QN02BE05.
UNII — SH41QYH8E5.

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Propacetamol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. Protect from moisture.

Profile

Propacetamol hydrochloride, a para-aminophenol derivative, is hydrolysed to paracetamol (p. 115.1) in the plasma; 1 g of propacetamol hydrochloride is hydrolysed to release about 500 mg of paracetamol. It has been given intramuscularly or intravenously for the treatment of pain and fever.

References.

1. Allegaert K, *et al.* Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F25–F28.
2. Walson PD, *et al.* Antipyretic efficacy and tolerability of a single intravenous dose of the acetaminophen prodrug propacetamol in children: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; **28**: 762–9.
3. Prins SA, *et al.* Pharmacokinetics and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery. *Paediatr Anaesth* 2008; **18**: 582–92.
4. McNicol ED, *et al.* Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. *Br J Anaesth* 2011; **106**: 764–75.

Adverse effects. Occupational contact dermatitis has been reported in healthcare professionals after preparing injections of propacetamol.[1-3]

Propacetamol is the hydrochloride of *N*,*N*-diethylglycine ester with paracetamol and the results of a study[4] have suggested that allergic reactions to propacetamol are related to sensitisation to the activated ester rather than to paracetamol itself.

A significant decrease in blood pressure was noted in 14 critically-ill patients following an intravenous infusion of propacetamol for the treatment of fever.[5] Interventions to control blood pressure were necessary.

1. Barbaud A, *et al.* Occupational allergy to propacetamol. *Lancet* 1995; **346**: 902.
2. Szczurko C, *et al.* Occupational contact dermatitis from propacetamol. *Contact Dermatitis* 1996; **35**: 299–301.
3. Gielen K, *et al.* Occupational allergic contact dermatitis from drugs in healthcare workers. *Contact Dermatitis* 2001; **45**: 273–9.
4. Berl V, *et al.* Mechanism of allergic contact dermatitis from propacetamol: sensitization to activated *N*,*N*-diethylglycine. *Contact Dermatitis* 1998; **38**: 185–8.
5. Hersch M, *et al.* Effect of intravenous propacetamol on blood pressure in febrile critically ill patients. *Pharmacotherapy* 2008; **28**: 1205–10.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propacetamol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Pro-Dafalgan†; ***Mex.***: Tempra.

Propyl Nicotinate

Nicotinato de propilo; Пропилникотинат.
$C_9H_{11}NO_2$=165.2
CAS — 7681-15-4.
UNII — 80CZF4GX8N.

Profile

Propyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Elacur.

Propyphenazone *(BAN, rINN)*

Isopropylantipyrine; Isopropylantipyrinum; Isopropylphenazone; Propifenazon; Propifenazona; Propifenazonas; Propyfenatsoni; Propyfenazon; Propyphenazon; Propyphénazone; Propyphenazonum; Пропифеназон.
4-Isopropyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.
$C_{14}H_{18}N_2O$=230.3
CAS — 479-92-5.
ATC — N02BB04.
ATC Vet — QN02BB04.
UNII — OED8FV75PY.

Pharmacopoeias. In *Eur*. (see p. vii) and *Jpn*.

Ph. Eur. 8: (Propyphenazone). A white or slightly yellowish crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Propyphenazone, a pyrazolone derivative related to phenazone (p. 124.1), has analgesic and antipyretic properties. It has been given orally and as a rectal suppository in the treatment of pain and fever. The usual oral dose is 0.5 to 1 g up to four times daily. There have been some reports of severe hypersensitivity reactions in patients receiving propyphenazone.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Demex.

Multi-ingredient Preparations. ***Arg.***: Algio-Bladuril; Espasmo Cibalena; Saridon; ***Austria***: Adolorin; Avamigran; Gewadal; Melabon; Migradon; Montamed; Nervan; Rapidol; Saridon; Spasmoplus; Tonopan; Vivimed; ***Braz.***: Saridon; Tonopan; ***Chile***: Abalgin; Droxel†; Espasmo Cibalgina Compuesta†; Espasmo Cibalgina; Gripasan Compuesto DN; Gripasan Compuesto; SAE; ***China***: Saridon (散利痛); ***Cz.***: Saridon; Valetol; ***Denm.***: Kodamid; ***Ger.***: Optalidon N†; Saridon†; ***Hong Kong***: Saridon†; ***Hung.***: Saridon; Trinell Pro; ***India***: Aristopyrin; Ciplador; Dart; Jiffy; ***Indon.***: Bodrex Migra; Butamidon; Cetapyrin†; Enkapyrin; Migran†; Oskadon Migra; Paramex†; Saridon; ***Ital.***: Cistalgan; Influvit; Neo-Optalidon; Odontalgico Dr. Knapp; Optalidon; Saridon; Sedol†; Spasmoplus; Uniplus; Veramon; ***Mex.***: Espasmo Cibalgina; Tonopan; ***Neth.***: Daro Hoofdpijnpoeders; Kruidvat PPC; Kruidvat; Para-don; Propyfenazon comp; Sanalgin; Saridon; ***Pol.***: Analget†; Cefalgin; Gardan P†; Krople Zoladkowe†; Krople Zoladkowe; Pabialgin P†; Saridon; ***Port.***: Optalidon; Saridon N; ***Rus.***: Algofetin (Альгофетин); Caffetin (Каффетин); Coffedon (Коффедон)†; Flucomp (Флюкомп); Gewadal (Гевадал)†; Kofan (Кофан); Pentalgin Plus (Пенталгин Плюс); Saridon (Саридон); ***S.Afr.***: Ilvico†; ***Spain***: Abdominol†; Calmoplex†; Dolodens†; Melabon†; Meloka†; Optalidon; Quimpedor; Saridon; Sulmetin Papaver†; Tabletas Quimpe†; Tonopan; ***Turk.***: Aljil; Bioptan†; Minoset Plus; Optalidon; Panalgine; ***Ukr.***: Caffetin (Каффетин); Kofan (Кофан); Nomigren (Номигрен); Novalgin (Новалгин); Pentased (Пентасед); Trinell (Тринелл)†.

Proquazone (BAN, USAN, rINN)

43-715; Procuazona; Prokuazon; Prokvatsoni; Prokvazon; Proquazonum; RU-43-715-n; Прокваzон.
1-Isopropyl-7-methyl-4-phenylquinazolin-2(1*H*)-one.
$C_{18}H_{18}N_2O$=278.4
CAS — 22760-18-5.
ATC — M01AX13.
ATC Vet — QM01AX13.
UNII — 42VPJ2980S.

Profile

Proquazone is an NSAID (p. 102.3) that has been used orally and rectally in musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Biarison.

Remifentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

GI-87084B; Hidrocloruro de remifentanilo; Rémifentanil, Chlorhydrate de; Remifentanili Hydrochloridum; Remifentanilo, hidrocloruro de; Ремифентанила Гидрохлорид.
4-Carboxyl-4-(*N*-phenylpropionamido)-1-piperidine propionic acid dimethyl ester monohydrate.
$C_{20}H_{28}N_2O_5$,HCl=412.9
CAS — 132539-07-2.
ATC — N01AH06.
ATC Vet — QN01AH06.
UNII — 5V444H5WIC.

Incompatibility. Remifentanil hydrochloride should not be mixed in the same intravenous solution as blood products. UK licensed product information states that it should not be mixed with lactated Ringer's injection with or without 5% glucose; however, in the USA the product literature states that remifentanil hydrochloride is stable for 4 hours at room temperature after reconstitution and dilution to 20 to 250 micrograms/mL with lactated Ringer's injection and for 24 hours if lactated Ringer's with 5% glucose is used. Incompatibilities have been reported between chlorpromazine hydrochloride 2 mg/mL and remifentanil 25 micrograms/mL (as the hydrochloride) in 5% glucose and cefoperazone sodium 40 mg/mL or amphotericin B 600 micrograms/mL and remifentanil 250 micrograms/mL (as the hydrochloride) in 5% glucose.[1]

1. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Uses and Administration

Remifentanil, an anilidopiperidine derivative, is an opioid analgesic (p. 108.1) related to fentanyl (p. 60.2). It is a short-acting μ-receptor opioid agonist used for analgesia during induction and/or maintenance of general anaesthesia. It is also used to provide analgesia into the immediate postoperative period, and may be used as the analgesic component of local or regional anaesthesia with or without benzodiazepine sedation. Remifentanil is also used to provide analgesia and sedation in mechanically ventilated patients under intensive care. It has also been tried in labour pain.

Remifentanil is given intravenously as the hydrochloride, usually by infusion. Its onset of action is within 1 minute and the duration of action is 5 to 10 minutes. Doses are expressed in terms of the base; remifentanil hydrochloride 1.1 mg is equivalent to about 1 mg of remifentanil. Initial doses for anaesthesia in elderly patients should be half the recommended adult doses and then titrated to individual requirements. Obese patients may require doses based on their ideal (lean) body-weight. For details of doses in children, see below.

When used to provide **analgesia** during *induction* of anaesthesia an intravenous infusion is given in doses of 0.5 to 1 micrograms/kg per minute. An additional initial intravenous bolus of 1 microgram/kg may be given over 30 to 60 seconds particularly if the patient is to be intubated less than 8 minutes after the start of the infusion.

For provision of analgesia during *maintenance* of anaesthesia in ventilated patients, usual infusion doses range from 50 nanograms/kg to 2 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response. Supplemental intravenous boluses of 500 nanograms/kg to 1 microgram/kg may be given every 2 to 5 minutes in response to light anaesthesia or intense surgical stress. The infusion dosage in spontaneous respiration is initially 40 nanograms/kg per minute adjusted according to response within a usual range of 25 to 100 nanograms/kg per minute. Bolus doses are not recommended during spontaneous ventilation.

For continuation of analgesia into the immediate *postoperative* period typical doses by intravenous infusion have ranged from 100 to 200 nanograms/kg per minute; supplemental intravenous bolus doses are not recommended during the postoperative period.

To provide **analgesia and sedation** in ventilated patients under intensive care, remifentanil is given as an intravenous infusion at an initial rate of 100 to 150 nanograms/kg per minute. Doses should then be titrated to provide adequate analgesia and sedation; a period of 5 minutes should be allowed between dose adjustments. Additional sedative drugs should be given to those patients inadequately sedated with remifentanil infusions of 200 nanograms/kg per minute. An increase in the rate of remifentanil infusion may be necessary if additional analgesia is required to cover stimulating or painful procedures such as wound dressing. Doses of up to 750 nanograms/kg per minute have been given to some patients. Bolus doses of remifentanil are not recommended in intensive care.

Remifentanil is also used as an analgesic in patients receiving monitored anaesthesia care. In the USA, it may be given intravenously in a single dose of 1 microgram/kg 90 seconds before the local anaesthetic; alternatively, a dose of 100 nanograms/kg per minute may be given as an intravenous infusion, starting 5 minutes before the local anaesthetic, which should be reduced to 50 nanograms/kg per minute after the local anaesthetic. Subsequent adjustments of 25 nanograms/kg per minute at 5-minute intervals may be made to maintain a balanced analgesia.

Remifentanil has a very rapid offset of action and no residual opioid action remains 5 to 10 minutes after stopping an infusion. When appropriate, alternative analgesics should be given before stopping remifentanil, in sufficient time to provide continuous and more prolonged pain relief.

References and reviews.

1. Davis PJ, Cladis FP. The use of ultra-short-acting opioids in paediatric anaesthesia: the role of remifentanil. *Clin Pharmacokinet* 2005; **44:** 787–96.
2. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005; **65:** 1793–1823. Correction. *ibid.*; 2286.
3. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. *Drugs* 2006; **66:** 365–85.
4. Welzing L, Roth B. Experience with remifentanil in neonates and infants. *Drugs* 2006; **66:** 1339–50.
5. Komatsu R, *et al.* Remifentanil for general anaesthesia: a systematic review. *Anaesthesia* 2007; **62:** 1266–80.
6. Hill D. Remifentanil in obstetrics. *Curr Opin Anaesthesiol* 2008; **21:** 270–4.
7. Wilhelm W, Kreuer S. The place for short-acting opioids: special emphasis on remifentanil. *Crit Care* 2008; **12** (suppl 3): S5. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2391266/pdf/cc6152.pdf (accessed 25/01/10)
8. Marsh DF, Hodkinson B. Remifentanil in paediatric anaesthetic practice. *Anaesthesia* 2009; **64:** 301–8.
9. Hinova A, Fernando R. Systemic remifentanil for labor analgesia. *Anesth Analg* 2009; **109:** 1925–9.

Administration in children. Remifentanil hydrochloride, given by continuous intravenous infusion, is used for analgesia during maintenance of general anaesthesia in children. Usual infusion doses (expressed as the base) for those aged from 1 to 12 years range from 50 nanograms/kg to 1.3 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response; supplemental intravenous boluses of 1 microgram/kg may be given over at least 30 seconds. US licensed product information also states that neonates and children aged up to 2 months may be given infusion doses of 400 nanograms/kg to 1 microgram/kg per minute with supplemental boluses of 1 microgram/kg. Similar doses are suggested in the *BNFC* for use in neonates although in the UK remifentanil is not licensed for use in children under 1 year of age.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1 and for Fentanyl, p. 62.1.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Administration. Remifentanil hydrochloride injections containing glycine should not be given by the epidural or intrathecal routes.

Hepatic impairment. Although the pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment, such patients may be more sensitive to the respiratory depressant effects and should be monitored with doses titrated to individual requirements.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies remifentanil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Renal impairment. The pharmacokinetics of remifentanil are not changed in patients with severe renal impairment (a creatinine clearance of less than 10 mL/minute) and licensed product information states that the carboxylic acid metabolite is unlikely to accumulate to clinically active concentrations in such patients after remifentanil infusions given for up to 3 days. Dosage adjustment is considered to be unnecessary. This is supported by pharmacokinetic studies[1,2] in intensive care patients with renal impairment given remifentanil infusions at a rate of 100 to 150 nanograms/kg per minute for up to 3 days.

1. Breen D, *et al.* Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. *Crit Care* 2004; **8:** R21–R30.
2. Pitsiu M, *et al.* Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. *Br J Anaesth* 2004; **92:** 493–503.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

After parenteral doses remifentanil hydrochloride has a rapid onset and short duration of action. Its effective biological half-life is about 3 to 10 minutes and is independent of dose. Remifentanil is about 70% bound to plasma proteins, mainly to α_1-acid glycoprotein. It is hydrolysed by non-specific esterases in blood and tissues to an essentially inactive carboxylic acid metabolite. About 95% of a dose of remifentanil is excreted in the urine as the metabolite. Studies in *animals* suggest that remifentanil may cross the placenta and is distributed into breast milk.

Licensed product information for remifentanil gives values for a three-compartment pharmacokinetic model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes.

References.

1. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal. *Clin Pharmacokinet* 1995; **29:** 80–94.
2. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. *Curr Opin Anaesthesiol* 2000; **13:** 449–55.
3. Ross AK, *et al.* Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg* 2001; **93:** 1393–1401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Remicit; Remiflo; Ultiva; ***Austral.***: Ultiva; ***Austria***: Ultiva; ***Belg.***: Ultiva; ***Braz.***: Ultiva; ***Canad.***: Ultiva; ***Chile***: Ultiva; ***China***: Rui Jie (瑞捷); ***Cz.***: Ultiva; ***Denm.***: Ultiva; ***Fin.***: Ultiva; ***Fr.***: Ultiva; ***Ger.***: Ultiva; ***Gr.***: Ultiva; ***Hong Kong***: Ultiva; ***Irl.***: Ultiva; ***Israel***: Ultiva; ***Ital.***: Ultiva; ***Mex.***: Ultiva; ***Neth.***: Ultiva; ***Norw.***: Ultiva; ***NZ***: Ultiva; ***Pol.***: Ultiva; ***Port.***: Ultiva; ***Rus.***: Ultiva (Утива); ***S.Afr.***: Ultiva; ***Singapore***: Ultiva; ***Spain***: Ultiva; ***Swed.***: Ultiva; ***Switz.***: Ultiva; ***Turk.***: Ultiva; ***UK***: Ultiva; ***USA***: Ultiva; ***Venez.***: Ultiva.

Rofecoxib (BAN, USAN, rINN)

MK-0966; MK-966; Rofécoxib; Rofecoxibum; Rofekoksibi; Rofekoxib; Рофекоксиб.
4-[*p*-(Methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone.
$C_{17}H_{14}O_4S$=314.4
CAS — 162011-90-7.
ATC — M01AH02.
ATC Vet — QM01AH02.
UNII — 0QTW8Z7MCR.

Profile

Rofecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis, and in the management of acute pain, dysmenorrhoea, and migraine but was generally withdrawn worldwide after reports of cardiovascular adverse effects (see below).

Rofecoxib has been applied topically in some countries.

Effects on the cardiovascular system. As of February 2001, the UK CSM had received a small number of reports of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[1] At that time it noted that COX-2 inhibitors such as rofecoxib did

not possess the intrinsic antiplatelet activity associated with aspirin, and consequently did not provide protection against ischaemic cardiac events. Data from a large, randomised study also showed the incidence of myocardial infarction to be greater in patients taking rofecoxib than in those taking naproxen.[2] Postmarketing surveillance of rofecoxib continued to provide further case reports of adverse cardiovascular effects. In addition, results of the then unpublished APPROVe study of rofecoxib for prevention of adenomatous polyposis indicated that the risk of myocardial infarction and stroke was markedly increased in patients receiving the drug compared with those on placebo; however, this difference was only apparent after 18 months of treatment. As a result, the study was stopped early and, in September 2004, the manufacturer generally withdrew rofecoxib worldwide. The cardiovascular findings from the APPROVe study were published in 2005;[3] the results showed a twofold increase in the risk of adverse cardiovascular events in patients receiving rofecoxib 25 mg daily when compared with those on placebo. More recently, data for patients in the APPROVe study have been re-analysed to include extended follow-up findings.[4] Overall, this analysis confirmed the increased risk of cardiovascular events such as myocardial infarction and stroke in patients taking rofecoxib when compared with those given placebo; there was also a non-significant increase in the risk of such events in the year after rofecoxib was stopped. Small patient numbers made it difficult to given any more precise details about when the increased risk began or ended; however, the data suggested an early increase in risk that persists for about 1 year after 3 years of treatment. Similar data, suggesting a 1.5-fold increase in risk of thrombotic events with rofecoxib, were reported from a study of adjuvant use for colorectal cancer.[5] A cumulative meta-analysis also indicated an increased risk of myocardial infarction in patients receiving rofecoxib.[6]

Subsequent investigation by US and European regulatory authorities has confirmed that other COX-2 inhibitors are also associated with some increased cardiovascular risk (see under Celecoxib, p. 37.3), as are some non-selective NSAIDs (see Thrombotic Events, p. 105.1).

A review[7] of prospective studies evaluating the effect of selective COX-2 inhibitors on blood pressure was unable to determine if there was any association between the use of these drugs and blood pressure elevations. Of the studies considered, a randomised study in elderly, hypertensive patients with osteoarthritis has suggested that the risk of developing *increased systolic blood pressure* is greater in those patients receiving rofecoxib than in those receiving celecoxib.[8] However, the manufacturers of rofecoxib have pointed out that the study used doses of rofecoxib greater than those recommended for elderly or hypertensive patients.

1. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Bombardier C, *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1520–8.
3. Bresalier RS, *et al*. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352:** 1092–1102. Correction. *ibid.* 2006; **355:** 221.
4. Baron JA, *et al*. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. *Lancet* 2008; **372:** 1756–64. Correction. *ibid.*; 1732.
5. Kerr DJ, *et al*. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* 2007; **357:** 360–9.
6. Jüni P, *et al*. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; **364:** 2021–9.
7. Johnson DL, *et al*. Effect of cyclooxygenase-2 inhibitors on blood pressure. *Ann Pharmacother* 2003; **37:** 442–6.
8. Whelton A, *et al*. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001; **8:** 85–95.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rofecoxib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Peroxx; ***India***: Doliib; Rofib†; Rofiz†; ***Turk.***: Ecrox; Raxtane; Reox; Rofemax; Romaryd; Vioref; ***Ukr.***: Denebol (Денебол); Rofica (Рофіка)†.

Multi-ingredient Preparations. ***Ukr.***: Denebol Gel (Денебол Гель).

Salamidacetic Acid

Carbamoylphenoxyacetic acid; Salamidacético, ácido; Salicylamide *O*-acetic acid; Натрия Салициламидацетат (sodium salamidacetate).
(2-Carbamoylphenoxy)acetic acid.
$C_9H_9NO_4$=195.2
CAS — 25395-22-6 (salamidacetic acid); 3785-32-8 (sodium salamidacetate).

Profile

Salamidacetic acid is a salicylic acid derivative (see Aspirin, p. 22.2) that has also been used as the sodium and diethylamine salts for the treatment of musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Akistin.

Multi-ingredient Preparations. ***Austria***: Rheumesser; ***Rus.***: Ambene (Амбене).

Salicylamide *(BAN, rINN)*

Salicilamida; Salicylamid; Salicylamidum; Salisyyliamidi; Салициламид.
2-Hydroxybenzamide.
$C_7H_7NO_2$=137.1
CAS — 65-45-2.
ATC — N02BA05.
ATC Vet — QN02BA05.
UNII — EM8BM710ZC.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Salicylamide). A white practically odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol and in propylene glycol; freely soluble in ether and in solutions of alkalis.

Profile

Salicylamide is a salicylic acid derivative (see Aspirin, p. 22.2) but is not hydrolysed to salicylate; it is almost completely metabolised to inactive metabolites during absorption and on first pass through the liver. It is given in usual oral doses of 325 to 650 mg, or more, three or four times daily for pain and fever; lower doses are used in combination preparations with other analgesics. Salicylamide has also been applied topically in various preparations in concentrations of up to 8.5% for the relief of muscular and rheumatic pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Waldheim Rheuma-Creme†; ***Ukr.***: Cefecon N (Цефекон Н).

Multi-ingredient Preparations. ***Arg.***: Funciogrip†; Venter; ***Austria***: Rubriment; ***Belg.***: Percutalgine; ***Braz.***: Coristina R; Gripinew; Respraxt; Vita Grip†; ***China***: Feidile (菲迪乐); Neosed (尔可适); ***Denm.***: Kodamid; Koffisal; ***Fr.***: Percutalgine; ***Gr.***: Myalgesic; ***Hong Kong***: Antamin†; Anticol†; Co-Fluenza†; DF Multi-Symptom†; Flu-Zep†; Flucap†; Neozep; Qualizep; ***Indon.***: Cold Cap; Corexin†; Neozep; ***Mex.***: Artrilan†; Butayonacol; ***NZ***: Calm-U; ***Pol.***: Reumosol; Scorbolamid; ***Rus.***: Cefecon N (Цефекон Н); ***S.Afr.***: Colcaps†; Flutex Cold and Flu†; Histamed Compound; Ilvico†; Specific Nerve Pain Remedy†; ***Singapore***: Con-Z-Lin; Consu; Fongtit; Semor Pain & Fever Relief; ***Spain***: Pridiot; Rinomicine Activada†; Rinomicine; Rinomicine; Yendol; ***Switz.***: Osa Gel de dentition; ***Thai.***: Apracur; Fecol; Painol; ***UAE***: Flukit; ***Ukr.***: Percutalgine (Перкуталжин)†; ***USA***: Anabar†; Be-Flex Plus†; By-Ache†; Combiflex†; Duraxin†; Levacet; Lobac†; Medi-First Extra Strength Pain Relief; Painaid; Saleto; ***Venez.***: Praxona.

Salix

Corteza de sauce; Écorce de Saule; Fűzfakéreg; Gluosnių žievė; Kora wierzby; Pajunkuori; Sälgbark; Salicis Cortex; Saule, Écorce de; Vrbová kůra; Weidenbaumrinde; Weidenrinde; White Willow Bark; Willow Bark; Ива.
UNII — S883J9JDYX.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Willow Bark). The whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of the genus *Salix*, including *Salix purpurea*, *S. daphnoides*, and *S. fragilis*. It contains not less than 1.5% of total salicylic derivatives, expressed as salicin ($C_{13}H_{18}O_7$ = 286.3), calculated with reference to the dried drug. Protect from light.

Profile

Salix contains variable amounts of tannin and also of salicin, which has antipyretic and analgesic actions similar to those of aspirin (p. 22.2). Salix has been used in a variety of herbal remedies for painful and inflammatory conditions and for fever. It was once used as a bitter.

Adverse effects. An *anaphylactic reaction* developed in a 25-year-old woman with asthma and a known allergy to aspirin, within 75 minutes of ingesting a dietary supplement containing willow bark extract.[1] The link between salicylate and willow bark allergy was also reported in a carpenter who developed a widespread *rash*, similar to that he had with aspirin, when working with willow wood.[2]

1. Boullata JI, *et al*. Anaphylactic reaction to a dietary supplement containing willow bark. *Ann Pharmacother* 2003; **37:** 832–5.
2. Jennings A. Link between salicylate and willow bark. *Pharm J* 2006; **276:** 417.

Pain. Preparations containing willow bark extract have been tried with some success in the treatment of musculoskeletal disorders such as low back pain[1-3] and osteoarthritis.[4] A report[5] by the Arthritis Research Campaign in the UK concluded that, based on limited evidence, willow bark may have a moderate effect in treating pain due to osteoarthritis and rheumatoid arthritis; however, it was not as effective as NSAIDs for pain relief in osteoarthritis. It appeared to be relatively safe when taken in the recommended doses.

1. Chrubasik S, *et al*. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000; **109:** 9–14.
2. Chrubasik S, *et al*. Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low back pain. *Rheumatology (Oxford)* 2001; **40:** 1388–93.
3. Gagnier JJ, *et al*. Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).
4. Biegert C, *et al*. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* 2004; **31:** 2121–30.
5. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_1101201015433l.pdf (accessed 28/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Zortrix; ***Ger.***: Assalix; Optovit actiflex; Proaktiv; ***Pol.***: Salicortex; ***Switz.***: Assalix; ***Ukr.***: Assalix (Ассаликс).

Multi-ingredient Preparations. ***Austral.***: Accelerex; Arthri Plus†; Cold & Flu Day/Night; Extralife Migrai-Care†; Extralife PMS-Care†; Full Motion; Nyal Cold + Flu Fighter Day + Night; Nyal Cold + Flu Fighter; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Nyal Sinus Relief Day + Night; Nyal Sinus Relief; ***Austria***: Digestodoron; ***Braz.***: Calman; Calmiplan; Floriny; Pasalix; Pasic; ***Canad.***: Rheuma Heilkrauter Tee†; ***Cz.***: Antirevmaticky Caj†; Calmonal†; Valofyt Neo†; ***Fr.***: Arkophytum†; Arthritisane†; Arthroflorine†; Dolores; Fibromyalgine Fort; Gripponyl†; Phytheol Force†; Santane A_4†; Silibiol; ***Ger.***: Digestodoron; Dr Wiemanns Rheumatonikum†; ***Gr.***: Passiflorine; ***Hung.***: Uroherb; ***Indon.***: Ositin; ***Ital.***: Biothymus DS; Biothymus DS; Body Guard; Donalg; Influ-Zinc; Influpiol C; Linfolipase; Nevril; Reumafort; ***Mex.***: Ifupasil; ***Pol.***: Enterosol; Infektoten†; Pyrosal; Reumacor; Reumosol; Rutinosal C; Termasil; ***S.Afr.***: Digestodoron†; ***Singapore***: Mincifit Body Shaper; ***Spain***: Passiflorine; ***Switz.***: Tisane antirhumatismale; ***UK***: Bio-Strath Willow Formula; Gerard House Reumalex; Herbal Pain Relief; St Johnswort Compound; ***Ukr.***: Insti (Інсті); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Osteoartisi Max (Остеоартизи Макс); ***Venez.***: Passiflorum.

Homoeopathic Preparations. ***Canad.***: Homeodel 15†; ***Ger.***: Chelidonium comp; ***UK***: Digestodoron.

Salol

Benzofenolsalicylaat; Benzophénol Salicylate; Fenylsalicylat; Fenylu salicylan; Fenyylisalisylaatti; Phenyli Salicylas; Phenylis Salicylas; Salicilato de fenilo; Салол.
Phenyl salicylate.
$C_{13}H_{10}O_3$=214.2
CAS — 118-55-8.
ATC — G04BX12.
ATC Vet — QG04BX12.
UNII — 28A37T47QO.

Pharmacopoeias. In *Pol.*

Profile

Salol is a salicylic acid derivative (see Aspirin, p. 22.2). It was formerly used as an intestinal antiseptic, but effective doses were toxic owing to the liberation of phenol. It is used in

oral preparations containing methenamine for the treatment of lower urinary-tract infections.

Salol has been used topically as a sunscreen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aussie Tan Sunstick†; ***Turk.***: Sanodolin.

Multi-ingredient Preparations. ***Austria***: Carl Baders Divinal; ***Belg.***: Borostyrol; ***Canad.***: Watkins Settelz†; ***Fr.***: Borostyrol; Dermophil Indien; Nisacalm†; ***Pol.***: Salotannal†; Urosal; ***Rus.***: Besalol (Бесалол); Parodontocide (Пародонтоцид); ***Switz.***: Dermophil Indien; Penta†; ***Thai.***: Mist Salol Menthol; ***Turk.***: Sandolin†; ***USA***: Atrosept; Darpaz†; Hyophen; MHP-A; MSP-Blu; Phosphasal; Prosed/DS; UAA; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Ustell; Uticap; Utira; Utrona-C.

Salsalate *(BAN, USAN, rINN)*

NSC-49171; Salicyl Salicylate; Salicylosalicylic Acid; Salicylsalicylic Acid; Salsalato; Salsalatum; Salysal; Sasapyrine; Сальсалат.

O-(2-Hydroxybenzoyl)salicylic acid.

$C_{14}H_{10}O_5$=258.2

CAS — 552-94-3.

ATC — N02BA06.

ATC Vet — QN02BA06.

UNII — V9MO595C9I.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Salsalate). Store in airtight containers.

Uses and Administration

Salsalate is a salicylic acid derivative that has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p. 22.3). It is used for pain and fever and also in inflammatory disorders such as osteoarthritis and rheumatoid arthritis. The usual initial oral dose for inflammatory disorders is 3 g daily, given in 2 or 3 divided doses with food; the usual maintenance dose is 2 to 4 g daily, adjusted according to response.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to salsalate.

Effects on the gastrointestinal tract. Salsalate is associated with less faecal blood loss than aspirin and has been reported to cause fewer gastric lesions than piroxicam.[1] However, small-bowel ulcerations were reported in a patient when salsalate was added to a regimen of ranitidine and metoclopramide which had been prescribed for duodenal ulcer.[2]

1. Porro GB, *et al.* Salsalate in the treatment of rheumatoid arthritis: a double-blind clinical and gastroscopic trial versus piroxicam: II—endoscopic evaluation. *J Int Med Res* 1989; **17:** 320–3.
2. Souza Lima MA. Ulcers of the small bowel associated with stomach-bypassing salicylates. *Arch Intern Med* 1985; **145:** 1139.

Effects on the kidneys. A case of minimal-change nephrotic syndrome associated with salsalate use.[1]

1. Vallès M, Tovar JL. Salsalate and minimal-change nephrotic syndrome. *Ann Intern Med* 1987; **107:** 116.

Effects on the mouth. Ulcerated lesions on the tongue of a 77-year-old man were caused by taking salsalate tablets incorrectly.[1] The patient had placed the tablets under his tongue rather than swallowing them whole, resulting in prolonged, direct contact with the tongue.

1. Ruscin JM, Astroth JD. Lingual lesions secondary to prolonged contact with salsalate tablets. *Ann Pharmacother* 1998; **32:** 1248.

Interactions

For interactions associated with salicylates, see Aspirin, p. 26.3.

Pharmacokinetics

Salsalate is insoluble in acidic gastric fluids but is soluble in the small intestine. One molecule of salsalate is hydrolysed to 2 molecules of salicylic acid; hydrolysis occurs both in the small intestine and after absorption of the parent compound. Additional details on the pharmacokinetics of salicylic acid are provided in aspirin (see p. 27.1). Not all of the absorbed salsalate is hydrolysed and about 13% of salsalate is excreted as glucuronide conjugates in the urine; thus, the amount of salicylic acid available from salsalate is less than that from aspirin when the two drugs are given in equimolar equivalents of salicylic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Amigesic; Argesic-SA; Artha-G; Disalcid; Marthritic; Salflex; Salsitab.

Pharmacopoeial Preparations

USP 36: Salsalate Capsules; Salsalate Tablets.

Sarracenia Purpurea

Pitcher Plant; Саррацения Пурпурная.

UNII — FOP08H143P.

Profile

The roots and leaves of *Sarracenia purpurea* (Sarraceniaceae) have been used in the form of an aqueous distillate, given by local injection, for neuromuscular or neuralgic pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Sarapin; ***USA***: Sarapin.

Sodium Aurothiomalate *(rINN)*

Aurothiomalate de Sodium; Aurotiomalato de sodio; Gold Sodium Thiomalate; Natrii aurothiomalas; Natriumaurothiomalat; Natrium-aurothiomalát; Natriumaurotiomalaatti; Natriumaurotiomalat; Sodium, aurothiomalate de; Sodium Aurothiosuccinate; Sodu aurotiojabłczan; Sodyum Orotiyomalat; Натрия Ауротиомалат.

CAS — 12244-57-4 (anhydrous xNa); 39377-38-3 (disodium monohydrate).

ATC — M01CB01.

ATC Vet — QM01CB01.

UNII — E4768ZY6GM.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Sodium Aurothiomalate). A mixture of monosodium and disodium salts of (2*RS*)-2-(aurosulphanyl)butanedioic acid. It contains 44.5 to 46.0% of gold and 10.8 to 11.8% of sodium, calculated with reference to the dried substance. A fine, pale yellow, hygroscopic powder. Very soluble in water; practically insoluble in alcohol and in dichloromethane. A 10% solution in water has a pH of 6.0 to 7.0. Store in airtight containers.

USP 36: (Gold Sodium Thiomalate). A mixture of the monosodium and disodium salts of gold thiomalic acid [(aurothio)succinic acid] ($C_4H_4AuNaO_4S$ = 368.1 and $C_4H_3AuNa_2O_4S$ = 390.1) that has a gold content of 44.8 to 49.6%, and 49.0 to 52.5% calculated on the dried alcohol-free and glycerol-free material. pH of a 10% solution in water is between 5.8 and 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Sodium aurothiomalate and other gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. (See Rheumatic Disorders, below). They are generally used as disease-modifying antirheumatic drugs (DMARDs) in patients whose symptoms are unresponsive to or inadequately controlled by NSAIDs alone.

Sodium aurothiomalate therapy should only be undertaken where facilities are available to carry out the tests specified under Precautions, p. 131.3.

Sodium aurothiomalate is given by deep intramuscular injection; the area should be gently massaged and, due to the possibility of vasomotor reactions, the patient should remain recumbent for 10 minutes and kept under close observation for 30 minutes after each injection.

The following dosage regimen is recommended in UK licensed product information; US licensed information also suggests a similar regimen. A dose of 10 mg is given in the first week to test the patient's tolerance. If satisfactory, this may be followed by doses of 50 mg at weekly intervals until signs of remission occur; the dosage interval is then increased to 2 weeks until full remission occurs and then increased gradually to every 4 to 6 weeks. Treatment may be continued for up to 5 years after remission.

Improvement may not be seen until a total dose of 300 to 500 mg has been given. If no major improvement has occurred after a total of 1 g has been given (excluding the test dose), therapy should be stopped; alternatively in the absence of toxicity, 100 mg may be given weekly for a further 6 weeks; should there be no response at this dose other forms of therapy should be tried. In patients who relapse while receiving maintenance therapy, the interval between doses should be reduced to one week and should not be increased again until control has been obtained; however, if no response is obtained within 2 months, alternative treatment should be used. It is important to avoid complete relapse since a second course of gold therapy is not usually effective.

For doses in juvenile idiopathic arthritis, see Administration in Children, below.

NSAIDs may be continued when sodium aurothiomalate therapy is begun.

Other gold compounds that have been used include auranofin (p. 27.3), aurothioglucose (p. 28.2), aurotioprol (p. 28.2), gold keratinate (p. 66.3), and sodium aurotiosulfate (p. 132.1).

Reviews.

1. Kean WF, Kean IRL. Clinical pharmacology of gold. *Inflammopharmacology* 2008; **16:** 112–25.

Administration in children. For children with progressive juvenile idiopathic arthritis, the suggested initial weekly dose of sodium aurothiomalate is 1 mg/kg by deep intramuscular injection to a maximum of 50 mg weekly (one-tenth to one-fifth of the calculated initial weekly dose may be given for 2 to 3 weeks to test the patient's tolerance). Weekly doses should continue until signs of remission occur, at which point the dosage interval may be increased to fortnightly. With full remission, the dosage interval may again be increased gradually to every 4 weeks. If no improvement has occurred after 20 weeks, the dose could be raised slightly or another antirheumatic drug tried.

In the UK, gold compounds are no longer used to treat juvenile idiopathic arthritis, see Rheumatic Disorders, below.

Asthma. For comment on the use of parenteral gold compounds in the treatment of asthma, see under Auranofin, p. 27.3.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p. 1687.1). Intramuscular gold therapy has been used concomitantly to permit a reduction in corticosteroid dosage; evidence for the corticosteroid-sparing effect is limited[1-3] and such use has waned with the advent of other adjunctive therapy, although it may still be of value in patients unresponsive to other treatment[3] or for those who cannot tolerate corticosteroids or in whom they are contra-indicated.[1] However, it should be noted that there have been isolated reports of pemphigus associated with the use of gold therapy itself.[4]

1. Bystryn J-C, Steinman NM. The adjuvant therapy of pemphigus: an update. *Arch Dermatol* 1996; **132:** 203–12.
2. Pandya AG, Dyke C. Treatment of pemphigus with gold. *Arch Dermatol* 1998; **134:** 1104–7.
3. Iranzo P, *et al.* Gold: an old drug still working in refractory pemphigus. *J Eur Acad Dermatol Venereol* 2007; **21:** 902–7.
4. Lo Schiavo A, *et al.* Pemphigus and chrysotherapy: all that glitters is not gold! *Int J Dermatol* 2008; **47:** 645–7.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p. 13.2). Although toxicity has now reduced its popularity, intramuscular gold has long been used for the treatment of rheumatoid arthritis[1-4] and was often the standard against which the efficacy of other treatments was measured. Oral gold is less toxic but is also much less effective. It is unclear if there are differences between available intramuscular forms, but a study[5] in 120 patients converted from aurothioglucose to aurothiomalate found that 29 withdrew from the latter drug within 12 months, mostly because of lack of efficacy or the development of adverse effects not seen with the previous drug.

Gold compounds have also been used in the treatment of juvenile idiopathic arthritis (p. 12.1); however, the *BNFC* states that gold is no longer used for this indication. (For suggested doses in juvenile idiopathic arthritis, see Administration in Children, above.)

Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p. 14.3).

1. Epstein WV, *et al.* Effect of parenterally administered gold therapy on the course of adult rheumatoid arthritis. *Ann Intern Med* 1991; **114:** 437–44.
2. Anonymous. Gold therapy in rheumatoid arthritis. *Lancet* 1991; **338:** 19–20.
3. Klinkhoff AV, Teufel A. How low can you go? Use of very low dosage of gold in patients with mucocutaneous reactions. *J Rheumatol* 1995; **22:** 1657–9.
4. Clark P, *et al.* Injectable gold for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1997 (accessed 13/11/06).
5. van Roon, EN, *et al.* Parenteral gold preparations: efficacy and safety of therapy after switching from aurothioglucose to aurothiomalate. *J Rheumatol* 2005; **32:** 1026–30.

Adverse Effects

Reports show a wide range for the incidence of adverse effects of sodium aurothiomalate. With careful treatment about one-third of patients will have adverse effects; in about 5% of patients these will be severe and sometimes fatal.

The most common effects involve the skin and mucous membranes with pruritus (an early sign of intolerance) and stomatitis (often with a metallic taste) being the most prominent. Rashes with pruritus often occur after 2 to 6 months of intramuscular treatment and may require stopping therapy. Other reactions affecting the skin and mucous membranes include erythema, maculopapular eruptions, erythema multiforme, urticaria, eczema, seborrhoeic dermatitis, lichenoid eruptions, alopecia, exfoliative dermatitis, glossitis, pharyngitis, vaginitis, photosensitivity reactions, and irreversible pigmentation (chrysiasis).

Toxic effects on the blood include eosinophilia, thrombocytopenia, leucopenia, agranulocytosis, and aplastic anaemia.

Effects on the kidneys include mild transient proteinuria which may lead to heavy proteinuria, haematuria, and nephrosis.

Other effects reported include pulmonary fibrosis, dyspnoea, toxic hepatitis, cholestatic jaundice, peripheral neuritis, encephalitis, psychoses, fever, and gastrointestinal disorders including enterocolitis. Gold deposits may occur in the eyes. Vasomotor or nitritoid reactions, with weakness, flushing, palpitations, and syncope, may occur after injection of sodium aurothiomalate. Local irritation may also follow injection.

Sometimes there is an initial exacerbation of the arthritic condition.

Some adverse effects of gold have an immunogenic component.

Reviews.

1. Tozman ECS, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; **2:** 177–89.
2. van Roon EN, *et al.* Parenteral gold preparations. Efficacy and safety of therapy after switching from aurothioglucose to aurothiomalate. *J Rheumatol* 2005; **32:** 1026–30.

Effects on the blood. Blood disorders such as eosinophilia, leucopenia, granulocytopenia, and thrombocytopenia have occurred in patients receiving gold therapy. Eosinophilia has been reported to be the most frequent haematological abnormality.[1] It has been estimated that thrombocytopenia develops in 1 to 3% of patients receiving gold salts.[2]

Fatal consumption coagulopathy occurred in 4 children after the second injection of sodium aurothioglucose or sodium aurothiomalate.[3]

1. Foster RT. Eosinophilia—a marker of gold toxicity. *Can J Hosp Pharm* 1985; **85:** 150–1.
2. Coblyn JS, *et al.* Gold-induced thrombocytopenia: a clinical and immunogenetic study of twenty-three patients. *Ann Intern Med* 1981; **95:** 178–81.
3. Jacobs JC, *et al.* Consumption coagulopathy after gold therapy for JRA. *J Pediatr* 1984; **105:** 674–5.

Effects on the cardiovascular system. Vasomotor or nitritoid reactions associated with gold compounds are usually transient and self-limiting and although they may be mild there have been isolated reports of associated complications such as myocardial infarction, stroke, transient ischaemic attack, and transient monocular visual loss.[1] Most reactions have been associated with sodium aurothiomalate (a reported incidence of 4.7%) but they have also occurred with auranofin and sodium aurothioglucose. Tachyphylaxis usually occurs to the reactions and most patients are able to continue treatment but paradoxically in some the severity increases with repeated doses; 2.8% of patients receiving sodium aurothiomalate may require a change of treatment due to recurrent reactions. It is important to distinguish such reactions from true anaphylactic reactions to gold.[1] Patients taking ACE inhibitors may be at increased risk of nitritoid reactions.[2,3] Transfer of the patient to sodium aurothioglucose or reduction of the dose by 50%, injection in the recumbent position, and observation for 20 minutes have been recommended for the next few injections after a reaction.[2]

1. Ho M, Pullar T. Vasomotor reactions with gold. *Br J Rheumatol* 1997; **36:** 154–6.
2. Arthur AB, *et al.* Nitritoid reactions: case reports, review, and recommendations for management. *J Rheumatol* 2001; **28:** 2209–12.
3. Nixon J, Pande I. Gold, nitritoid reactions and angiotensin-converting enzyme inhibitors. *Rheumatology (Oxford)* 2006; **45:** 118–19.

Effects on the gastrointestinal tract. Enterocolitis due to sodium aurothiomalate has been reported[1] and 27 other cases associated with gold therapy reviewed. For colitis associated with oral gold, see also under Auranofin, p. 28.1.

1. Jackson CW, *et al.* Gold induced enterocolitis. *Gut* 1986; **27:** 452–56.

Effects on the immune system. Details of a patient who developed an immune deficiency syndrome that was attributed to gold therapy with sodium aurothiomalate.[1]

1. Haskard DO, Macfarlane D. Adult acquired combined immune deficiency in a patient with rheumatoid arthritis on gold. *J R Soc Med* 1988; **81:** 548–9.

Effects on the kidneys. Proteinuria developed in 21 patients while receiving a standard regimen of sodium aurothiomalate.[1] The severity of the proteinuria varied greatly and in 11 it increased for 4 months after treatment was stopped. Eight patients were considered to have developed the nephrotic syndrome. The median duration of proteinuria was 11 months, resolving in all 21 patients when treatment was stopped; at 24 months 3 patients still had proteinuria and it was not until 39 months that all were free of the condition. Renal biopsy indicated several types of kidney damage.

See under Auranofin (p. 28.1) for a comparative incidence of proteinuria in patients receiving sodium aurothiomalate or auranofin.

1. Hall CL, *et al.* The natural course of gold nephropathy: long term study of 21 patients. *BMJ* 1987; **295:** 745–8.

Effects on the lungs. 'Gold lung' is the term used to describe symptoms of dyspnoea on exertion, weakness, dry cough, and malaise that are seen rarely in patients on gold treatment.[1] Such symptoms usually develop some weeks or months after starting gold treatment and are associated with cumulative doses of several hundred milligrams although, very rarely, they have been seen with cumulative doses of less than 100 mg.[2] Pulmonary insufficiency may eventually develop and there have been occasional fatalities.[3] The pulmonary lesions usually subside on stopping of gold therapy, although persistent symptoms have been reported.

Nonbacterial thrombotic endocarditis associated with gold-induced pulmonary disease has also been reported.[4] This was considered to be a manifestation of gold-induced immune complex deposition.

1. Sinha A, *et al.* Gold-induced pneumonitis: computed tomography findings in a patient with rheumatoid arthritis. *Rheumatology (Oxford)* 2001; **40:** 712–14.
2. Hafejee A, Burke MJ. Acute pneumonitis starting 2 hours after intramuscular gold administration in a patient with rheumatoid arthritis. *Ann Rheum Dis* 2004; **63:** 1525–6.
3. Soler MJ, *et al.* Fatal, gold-induced pneumonitis. *Rheumatol Int* 2003; **23:** 207–10.
4. Kollef MH, *et al.* Nonbacterial thrombotic endocarditis associated with gold induced pulmonary disease. *Ann Intern Med* 1988; **108:** 903–4.

Effects on the nails. A 34-year-old woman with severe rheumatoid arthritis receiving intramuscular gold developed yellow thickened toenails and fingernails after 2 years of treatment.[1] Although there was some improvement in nail growth on stopping treatment, some light yellow discoloration in all 20 nails persisted.

1. Roest MAB, Ratnavel R. Yellow nails associated with gold therapy for rheumatoid arthritis. *Br J Dermatol* 2001; **145:** 855–6.

Effects on the nervous system. Neurological complications with gold salts are infrequent but may include peripheral neuropathy, Guillain-Barré syndrome, myokymia (repeated involuntary contractions of muscle fibre), and encephalopathy. Some reports[1-6] are given below.

1. Dick DJ, Raman D. The Guillain-Barre syndrome following gold therapy. *Scand J Rheumatol* 1982; **11:** 119–20.
2. Schlumpf U, *et al.* Neurologic complications induced by gold treatment. *Arthritis Rheum* 1983; **26:** 825–31.
3. Cerinic MM, *et al.* Gold polyneuropathy in juvenile rheumatoid arthritis. *BMJ* 1985; **290:** 1042.
4. Cohen M, *et al.* Acute disseminated encephalomyelitis as a complication of treatment with gold. *BMJ* 1985; **290:** 1179–80.
5. Dubowitz MN, *et al.* Gold-induced neuroencephalopathy responding to dimercaprol. *Lancet* 1991; **337:** 850–1.
6. Garrido JA, *et al.* Mioquimias inducidas por sales de oro. *Neurologia* 1995; **10:** 235–7.

Effects on the skin. Chrysiasis is a distinctive pigmentation that develops in light-exposed skin of patients receiving parenteral gold salts. In a study[1] of 31 patients with chrysiasis who were receiving intramuscular sodium aurothiomalate for rheumatoid arthritis, it was noted that visible changes developed above a threshold equivalent to 20 mg/kg gold content. The severity of the pigmentation depended upon cumulative dose. Focal aggregates of gold are deposited in the reticular and papillary dermis with no obvious increase in melanin. The pigmentation is permanent but benign, although the cosmetic effects may cause some patients distress. Prevention of chrysiasis is difficult but avoidance of exposure to sunlight may be helpful.

For reference to pemphigus associated with gold therapy, see Pemphigus under Uses, p. 130.3.

1. Smith RW, *et al.* Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; **133:** 671–8.

Hypersensitivity. Many adverse effects associated with gold treatment have an immunological basis. Patients with contact allergy to gold may show a flare-up, associated with cytokine release, when given sodium aurothiomalate intramuscularly.[1] Small amounts of nickel have been detected in sodium aurothiomalate injection[2] and in sodium aurothioglucose injection[3] and it has been suggested that gold therapy may also exacerbate or induce hypersensitivity to nickel.[2-4] In some patients contact allergy to gold has been correlated to the presence of dental gold alloys.[5]

Anaphylaxis may occur occasionally[6] but vasomotor or nitritoid reactions (see Effects on the Cardiovascular System, above) may produce similar symptoms.

1. Möller H, *et al.* The flare-up reactions after systemic provocation in contact allergy to nickel and gold. *Contact Dermatitis* 1999; **40:** 200–4.
2. Choy EHS, *et al.* Nickel contamination of gold salts: link with gold-induced skin rash. *Br J Rheumatol* 1997; **36:** 1054–8.
3. Wijnands MJH, *et al.* Chrysotherapy provoking exacerbation of contact hypersensitivity to nickel. *Lancet* 1990; **335:** 867–8.
4. Fulton RA, *et al.* Another hazard of gold therapy? *Ann Rheum Dis* 1982; **41:** 100–1.
5. Ahlgren C, *et al.* Contact allergy to gold is correlated to dental gold. *Acta Derm Venereol* 2002; **82:** 41–4.
6. Neustadt DH. Another anaphylactic reaction after gold (aurothiomalate) injection. *J Rheumatol* 1995; **22:** 190.

Overdosage. A patient who received a total dose of 600 mg of aurotioprol intramuscularly, of which 400 mg was given in less than a week, developed cholestatic hepatotoxicity with cholangitis.[1] This evolved into ductopenia resulting in cholestasis still present 15 months later.

1. Basset C, *et al.* Prolonged cholestasis and ductopenia following gold salt therapy. *Liver Int* 2003; **23:** 89–93.

Pancreatitis. It was suggested that pancreatitis reported in a woman receiving gold injections and in a woman on oral gold therapy may have been due to a hypersensitivity reaction.[1]

1. Eisemann AD, *et al.* Pancreatitis and gold treatment of rheumatoid arthritis. *Ann Intern Med* 1989; **111:** 860–1.

Treatment of Adverse Effects

The treatment of the adverse effects of gold is usually symptomatic and most effects resolve when gold therapy is stopped. In severe cases a chelator such as dimercaprol (p. 1549.3) may be used.

Precautions

Gold therapy is contra-indicated in exfoliative dermatitis, SLE, necrotising enterocolitis, and pulmonary fibrosis. It should be used with caution in the elderly and in renal or hepatic impairment; use is contra-indicated if renal or hepatic disorders are severe. Patients with a history of haematological disorders or who have previously shown toxicity to heavy metals should not be given gold salts, nor should any severely debilitated patient.

It is recommended that diabetes mellitus and heart failure should be adequately controlled in any patient before gold is given. Patients with a history of urticaria, eczema, or colitis should be treated with caution. Patients with a poor sulfoxidation status may be more susceptible to adverse effects of sodium aurothiomalate.

Use of gold compounds with other therapy capable of inducing blood disorders should be undertaken with caution, if at all.

Because of the risk of vasomotor reactions, patients should remain recumbent for about 10 minutes after each injection.

Urine should be tested for albumin before each injection and a full blood count carried out. Patients receiving gold compounds either orally or parenterally should be warned to report the appearance of sore throat or tongue, metallic taste, pruritus, rash, buccal ulceration, easy bruising, purpura, epistaxis, bleeding gums, unexplained bleeding, menorrhagia, pyrexia, indigestion, diarrhoea, or unexplained malaise. The development of breathlessness or cough should also be reported. Effects such as eosinophilia, proteinuria, pruritus, and rash arising during gold treatment should be allowed to resolve before therapy is continued.

Licensed product information recommends that annual chest X-rays should be carried out.

Breast feeding. The last available guidance from the American Academy of Pediatrics considered that gold compounds are usually compatible with breast feeding.[1]

Gold has been detected in breast milk[2-4] and found bound to the red blood cells of breast-fed babies.[2,3] In a report[4] of a breast-fed infant it was calculated that the weight-adjusted dose of gold received by the infant exceeded that received by the mother although the infant showed no ill-effects during 100 days of breast feeding and developed normally thereafter. Nonetheless, because of the relatively high exposure it was recommended that breast-fed infants should be closely monitored.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 13/11/06)

2. Blau SP. Metabolism of gold during lactation. *Arthritis Rheum* 1973; **16:** 777–8.
3. Needs CJ, Brooks PM. Antirheumatic medication during lactation. *Br J Rheumatol* 1985; **24:** 291–7.
4. Bennett PN, *et al*. Use of sodium aurothiomalate during lactation. *Br J Clin Pharmacol* 1990; **29:** 777–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium aurothiomalate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/07/11)

Pregnancy. Based on evidence from *animal* studies and a report[1] of malformation in a child born to a woman treated with sodium aurothiomalate it has been suggested that gold might possibly have teratogenic effects. Indeed, licensed product information advises that sodium aurothiomalate should be avoided during pregnancy. However, others[2] consider that gold may be a suitable treatment option in women planning a pregnancy. Over a 14-year period, 20 pregnancies in 14 women taking gold were followed in an arthritis centre; 5 miscarriages and 16 healthy babies including one set of twins were noted. The majority of women stopped their gold treatment on discovering they were pregnant although 4 continued their treatment throughout. The authors of this report also pointed out that published literature supported the use of gold in pregnant women.

1. Rogers JG, *et al*. Possible teratogenic effects of gold. *Aust Paediatr J* 1980; **16:** 194–5.
2. Almarzouqi M, *et al*. Gold therapy in women planning pregnancy: outcomes in one center. *J Rheumatol* 2007; **34:** 1827–31.

Interactions

There is an increased risk of toxicity when gold compounds are given with other nephrotoxic, hepatotoxic, or myelosuppressive drugs. Use of gold compounds with penicillamine may increase the risk of haematologic or renal adverse reactions.

ACE inhibitors. For a possible increased risk of nitritoid reactions when gold compounds are given to patients taking ACE inhibitors, see Effects on the Cardiovascular System, p. 131.1.

Penicillamine. For a discussion on the effects of previous therapy with gold salts affecting penicillamine toxicity, see p. 1570.2.

Pharmacokinetics

Sodium aurothiomalate is absorbed readily after intramuscular injection and 85 to 95% becomes bound to plasma proteins. With doses of 50 mg weekly a steady-state serum concentration of gold of about 3 to 5 micrograms/mL occurs in 5 to 8 weeks. It is widely distributed to body tissues and fluids, including synovial fluid, and accumulates in the body.

The serum half-life of gold is about 5 to 6 days but this increases after successive doses and after a course of treatment, gold may be found in the urine for up to 1 year or more owing to its presence in deep body compartments. Sodium aurothiomalate is mainly excreted in the urine, with smaller amounts in the faeces.

Gold has been detected in the fetus when sodium aurothiomalate was given to the mother. Gold is distributed into breast milk.

Reviews.

1. Blocka KLN, *et al*. Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; **11:** 133–43.
2. Tett SE. Clinical pharmacokinetics of slow-acting antirheumatic drugs. *Clin Pharmacokinet* 1993; **25:** 392–407.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Myocrisin; ***Canad.***: Myochrysine; ***Cz.***: Tauredon; ***Denm.***: Myocrisin†; ***Fin.***: Myocrisin; ***Ger.***: Tauredon; ***Gr.***: Miocrin; Tauredon; ***India***: Aurocris; ***Irl.***: Myocrisin†; ***Neth.***: Tauredon; ***NZ***: Myocrisin; ***Port.***: Tauredon; ***Singapore***: Miocrin; ***Spain***: Miocrin†; ***Swed.***: Myocrisin; ***Switz.***: Tauredon; ***Thai.***: Myocrisin; ***UK***: Myocrisin; ***Ukr.***: Tauredon (Тауредон)†; ***USA***: Aurolate†; Myochrysine†.

Pharmacopoeial Preparations
BP 2014: Sodium Aurothiomalate Injection;
USP 36: Gold Sodium Thiomalate Injection.

Sodium Aurotiosulfate *(rINN)*

Aurotiosulfate de Sodium; Aurotiosulfato de sodio; Gold Sodium Thiosulphate; Natrii Aurotiosulfas; Natrii Aurotiosulphas; Natriumaurotiosulfaatti; Natriumaurotiosulfat; Sodium Aurothiosulphate; Sodium Dithiosulfatoaurate; Натрия Ауротиосульфат.

$Na_3Au(S_2O_3)_2.2H_2O$=526.2

CAS — 10233-88-2 (anhydrous sodium aurotiosulfate); 10210-36-3 (sodium aurotiosulfate dihydrate).
ATC — M01CB02.
ATC Vet — QM01CB02.
UNII — CKS1YQ9W1J (sodium aurotiosulfate dihydrate); 6GKU52ZCI0 (anhydrous sodium aurotiosulfate).

Profile

Sodium aurotiosulfate has a gold content of about 37%. It has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It is given by intramuscular injection for the treatment of rheumatoid arthritis (p. 13.2) in a usual dose of 56.1 mg every 5 to 7 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crytion; ***Chile***: Crytioro†; ***Ital.***: Fosfocrisolo.

Sodium Gentisate *(rINN)*

Gentisate de Sodium; Gentisato de sodio; Gentisato Sodico; Natrii Gentisas; Натрия Гентизат.

Sodium 2,5-dihydroxybenzoate dihydrate.

$C_7H_5NaO_4.2H_2O$=212.1

CAS — 490-79-9 (gentisic acid); 4955-90-2 (anhydrous sodium gentisate).
UNII — DX2PUD5H82 (anhydrous sodium gentisate); Y75S7S5FI3 (sodium gentisate hydrate).

Pharmacopoeias. In *Fr.*

Profile

Sodium gentisate has been used as an analgesic in the treatment of musculoskeletal and joint disorders. It is also used as a preservative.

Sodium Salicylate

Natrii salicylas; Natrio salicilatas; Natriumsalicylat; Natriumsalisylaatti; Nátrium-szalicilát; Salicilato sódico; Salicylan sodný; Sodium, salicylate de; Sodu salicylan; Sodyum Salisilat; Салицилат Натрия.

Sodium 2-hydroxybenzoate.

$C_7H_5NaO_3$=160.1

CAS — 54-21-7.
ATC — N02BA04.
ATC Vet — QN02BA04.
UNII — WIQ1H85SYP.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Salicylate). Colourless small crystals or shiny flakes, or white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Sodium Salicylate). Amorphous or microcrystalline powder or scales. It is colourless or has not more than a faint pink tinge. It is odourless or has a faint characteristic odour. A freshly made 10% solution in water is neutral or acid to litmus. Freely (and slowly) soluble in water and in glycerol; very soluble in boiling water and in boiling alcohol; slowly soluble in alcohol. Protect from light.

Uses and Administration

Sodium salicylate is a salicylic acid derivative that has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p. 22.3). Sodium salicylate 1 g is equivalent to about 1.1 g of aspirin. It is used in the treatment of pain, fever, and in rheumatic disorders such as osteoarthritis and rheumatoid arthritis. The usual oral dose of sodium salicylate for pain or fever is 325 to 650 mg every four hours as required. The oral dose for rheumatic disorders is 3.6 to 5.4 g daily in divided doses. Sodium salicylate has also been used in the symptomatic treatment of rheumatic fever but its high sodium content may cause problems in patients with cardiac complications.

Sodium salicylate has also been given by intravenous infusion and topically.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2.

Although sodium salicylate has been used in the treatment of rheumatic fever, its high sodium content may cause problems in patients with cardiac complications.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to sodium salicylate.

Effects on the eyes. Retinal haemorrhages were reported in a 60-year-old woman taking oral sodium salicylate 6 g daily for 2 months and in a 10-year-old girl taking oral sodium salicylate 4 g daily for 40 days.[1] In both cases the haemorrhages gradually resolved after the treatment was stopped.

1. Mortada A, Abboud I. Retinal haemorrhages after prolonged use of salicylates. *Br J Ophthalmol* 1973; **57:** 199–200.

Interactions

For interactions associated with salicylates, see Aspirin, p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Dodds†; Saliject; ***Turk.***: Enter-Sal; ***UK***: Jackson's Pain & Fever; ***USA***: Avosil.

Multi-ingredient Preparations. ***Braz.***: A Saude da Mulher; A Saude da Mulher; ***Canad.***: Formule L2; Plax†; ***Chile***: Eucerin Shampoo Anticaspa†; Eucerin Shampoo para el Tratamiento de la Caspa; Pectokast; ***Fr.***: Brulex; ***Hong Kong***: Gly Thymol; Glycerine Thymol Co†; ***Irl.***: TCP; ***Mon.***: Glyco-Thymoline; ***S.Afr.***: Colphen†; Doans Backache Pills†; Ilvico†; TCP†; ***UK***: Antiseptic Mouthwash; Doans Backache Pills; TCP; TCP; ***USA***: Cystex; Scot-Tussin Original 5-Action; Tussirex.

Homoeopathic Preparations. ***Canad.***: Urarthone†; ***Fr.***: Euphorbium Complexe No 88; Urarthone.

Pharmacopoeial Preparations
USP 36: Sodium Salicylate Tablets.

Sufentanil *(BAN, rINN)* ⊗

R-30730; Sufentaniili; Sufentanilis; Sufentanilo; Sufentanilum; Szufentanil; Суфентанил.

N-{4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide.

$C_{22}H_{30}N_2O_2S$=386.6

CAS — 56030-54-7.
ATC — N01AH03.
ATC Vet — QN01AH03.
UNII — AFE2YW0IIZ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sufentanil). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Sufentanil Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de sufentanilo; R-33800; Sufentaniilisitraatti; Sufentanil citrát; Sufentanil, Citrate de; Sufentanil Sitrat; Sufentanilcitrat; Sufentanili citras; Sufentanilio citratas; Sufentanilo, citrato de; Szufentanil-citrát; Суфентанила Цитрат.

N-{4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide citrate.

$C_{22}H_{30}N_2O_2S.C_6H_8O_7$=578.7

CAS — 60561-17-3.
ATC — N01AH03.
ATC Vet — QN01AH03.
UNII — S9ZFX8403R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sufentanil Citrate). A white or almost white powder. Soluble in water and in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Sufentanil Citrate). A white powder. Soluble in water; sparingly soluble in alcohol, in acetone, and in chloroform; freely soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Sufentanil (as the citrate) diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.[1]

1. Chapalain-Pargarde S, *et al*. Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; **32:** 90–7.

Uses and Administration

Sufentanil, a phenylpiperidine derivative, is an opioid analgesic (p. 108.1) related to fentanyl (p. 60.2). It is highly lipid-soluble and more potent than fentanyl. Sufentanil is used as an analgesic adjunct in anaesthesia and as a primary anaesthetic in procedures requiring assisted ventilation. It has a rapid onset and recovery is considered to be more

rapid than with fentanyl. It is also used as an analgesic in the management of postoperative pain and labour pain.

Sufentanil is given as the citrate either intravenously by slow injection or as an infusion, or epidurally. Doses are expressed as the base; sufentanil citrate 15 micrograms is equivalent to about 10 micrograms of sufentanil. Lower initial doses are advised in the elderly and debilitated patients. For obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of their lean body-weight. For details of doses in children, see below.

In all patients supplementary maintenance doses should be based on individual response and length of procedure. Doses of up to the equivalent of 8 micrograms/kg of sufentanil produce profound analgesia. Higher doses produce a deep level of anaesthesia but are associated with prolonged respiratory depression and assisted ventilation may be required in the postoperative period.

When used as an analgesic **adjunct to anaesthesia** with nitrous oxide and oxygen for surgical procedures lasting up to 8 hours, the total *intravenous* dosage should not exceed 1 microgram/kg per hour. It is usual to give about 75% of the dose before intubation followed as necessary during surgery by additional injections of 10 to 50 micrograms or by a suitable continuous or intermittent infusion given so that the total hourly dose is not exceeded. Thus, for an operation lasting 1 to 2 hours the total dose would be 1 to 2 micrograms/kg with 0.75 to 1.5 micrograms/kg being given before intubation.

When used as a **primary anaesthetic** in major surgery *intravenous* doses of 8 to 30 micrograms/kg are given with 100% oxygen; doses of 25 to 30 micrograms/kg block sympathetic response including catecholamine release and are indicated in procedures such as cardiovascular surgery or neurosurgery. Anaesthesia may be maintained by additional injections of 0.5 to 10 micrograms/kg or by a suitable continuous or intermittent infusion given so that the total dosage for the procedure does not exceed 30 micrograms/kg.

In postoperative **pain**, sufentanil is given *epidurally* in an initial dose of 30 to 60 micrograms, which should provide analgesia for 4 to 6 hours. Additional boluses of up to 25 micrograms may be given at intervals of not less than 1 hour if necessary.

Sufentanil is also given *epidurally* for the relief of pain during labour and delivery. Recommended doses are 10 to 15 micrograms given with 10 mL of bupivacaine 0.125% (or its equivalent) with or without adrenaline; the dose may be repeated twice at not less than one-hour intervals until delivery. The total dose of sufentanil should not exceed 30 micrograms.

Reviews.

1. Monk JP, *et al*. Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.
2. Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil, and alfentanil. *Clin Pharm* 1991; **10:** 581–93.
3. Savoia G, *et al*. Sufentanil: an overview of its use for acute pain management. *Minerva Anestesiol* 2001; **67** (suppl 1): 206–16.

Administration. Sufentanil is usually given intravenously, but the epidural route is also used (see below). Intranasal (see Anaesthesia, Pain, and Sedation, all below), intrathecal (see below), and sublingual use (see Pain, below) have also been tried.

EPIDURAL. In a laboratory assessment of epidural sufentanil in healthy subjects,[1] a dose of 50 micrograms produced analgesia for 2 to 3 hours; analgesia was intensified and prolonged, and respiratory and other adverse effects, especially drowsiness, were reduced by the addition of adrenaline. Epidural sufentanil or fentanyl provided effective postoperative analgesia following caesarean section with comparable adverse effect profiles.[2] Sufentanil doses of 20 and 30 micrograms showed equivalent efficacy and provided greater analgesia for a longer duration than a dose of 10 micrograms. Addition of sufentanil to local anaesthetics such as bupivacaine during labour has considerably reduced the local anaesthetic requirements[3] and improved the quality of epidural analgesia.[4] Combination of sufentanil with a local anaesthetic (ropivacaine or bupivacaine) has been used for patient-controlled epidural analgesia (PCEA),[5-9] although an early study suggested that PCEA with sufentanil alone had little advantage over patient-controlled analgesia with intravenous morphine.[10]

Effective analgesia has been achieved in children with epidural sufentanil.[11]

1. Klepper ID, *et al*. Analgesic and respiratory effects of extradural sufentanil in volunteers and the influence of adrenaline as an adjuvant. *Br J Anaesth* 1987; **59:** 1147–56.
2. Grass JA, *et al*. A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; **85:** 365–71.
3. Buyse I, *et al*. Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour. *Int J Obstet Anesth* 2007; **16:** 22–8.
4. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; **63:** 251–3.
5. Gogarten W, *et al*. A multicentre trial comparing different concentrations of ropivacaine plus sufentanil with bupivacaine plus sufentanil for patient-controlled epidural analgesia in labour. *Eur J Anaesthesiol* 2004; **21:** 38–45.
6. Boselli E, *et al*. Background infusion is not beneficial during labor patient-controlled analgesia with 0.1% ropivacaine plus 0.5 microg/ml sufentanil. *Anesthesiology* 2004; **100:** 968–72.
7. Bremerich DH, *et al*. Comparison of continuous background infusion plus demand dose and demand-only parturient-controlled epidural analgesia (PCEA) using ropivacaine combined with sufentanil for labor and delivery. *Int J Obstet Anesth* 2005; **14:** 114–20.
8. Missant C, *et al*. Patient-controlled epidural analgesia following combined spinal-epidural analgesia in labour: the effects of adding a continuous epidural infusion. *Anaesth Intensive Care* 2005; **33:** 452–6.
9. Schenk MR, *et al*. Postoperative analgesia after major spine surgery: patient-controlled epidural analgesia versus patient-controlled intravenous analgesia. *Anesth Analg* 2006; **103:** 1311–17.
10. Grass JA, *et al*. Patient-controlled analgesia after cesarean delivery: epidural sufentanil versus intravenous morphine. *Reg Anesth* 1994; **19:** 90–7.
11. Benlabed M, *et al*. Analgesia and ventilatory response to CO_2 following epidural sufentanil in children. *Anesthesiology* 1987; **67:** 948–51.

INTRATHECAL. Sufentanil, alone or in combination, has been given intrathecally for labour pain: a combination of sufentanil, bupivacaine, and adrenaline given intrathecally provided excellent analgesia during labour and had a more rapid onset, a longer duration of action, and reduced local anaesthetic requirements compared with epidural administration.[1] Intrathecal sufentanil and bupivacaine provided shorter duration of analgesia when given during the advanced stages of labour compared with early labour.[2] There has been some concern about the effect of intrathecal use on fetal heart rate. An early study[3] found no significant difference in the heart rate when intrathecal sufentanil was compared with epidural bupivacaine; however, a more recent study[4] reported that high-dose intrathecal sufentanil (7.5 micrograms) when given on its own increased the risk of fetal heart rate abnormalities when compared with low-dose intrathecal sufentanil (1.5 micrograms) given with bupivacaine and adrenaline. Nonetheless, there was no evidence of a difference in adverse neonatal outcomes between the groups.

A small study in patients undergoing hip replacement found that intrathecal sufentanil 7.5 micrograms produced better and longer lasting analgesia than the same dose given intravenously.[5]

Intrathecal sufentanil has also been tried in the treatment of chronic pain.[6]

1. Kartawiadi SL, *et al*. Spinal analgesia during labor with low-dose bupivacaine, sufentanil, and epinephrine: a comparison with epidural analgesia. *Reg Anesth* 1996; **21:** 191–6.
2. Viscomi CM, *et al*. Duration of intrathecal labor analgesia: early versus advanced labor. *Anesth Analg* 1997; **84:** 1108–12.
3. Nielsen PE, *et al*. Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. *Anesth Analg* 1996; **83:** 742–6.
4. Van de Velde M, *et al*. Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. *Anesth Analg* 2004; **98:** 1153–9.
5. Fournier R, *et al*. Intrathecal sufentanil is more potent than intravenous for postoperative analgesia after total-hip replacement. *Reg Anesth Pain Med* 2005; **30:** 249–54.
6. Waara-Wolleat KL, *et al*. A review of intrathecal fentanyl and sufentanil for the treatment of chronic pain. *Pain Med* 2006; **7:** 251–9.

Administration in children. Although experience of paediatric use is limited, sufentanil citrate is licensed for the induction and maintenance of anaesthesia in children under 12 years of age undergoing cardiovascular surgery. Intravenous doses of 10 to 25 micrograms/kg are given with 100% oxygen with maintenance doses of up to 25 to 50 micrograms.

Anaesthesia. Sufentanil, like fentanyl (p. 61.2), appears to produce fewer circulatory changes than morphine, which may offer some advantages in cardiovascular surgery.

Premedication with sufentanil given intranasally has been tried in children[1-3] and in adults.[4]

Sufentanil is one of the opioids that have been used with a neuroleptic to produce *neuroleptanalgesia*.

1. Henderson JM, *et al*. Pre-induction of sufentanil. *Anesthesiology* 1988; **68:** 671–5.
2. Zedie N, *et al*. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther* 1996; **59:** 341–8.
3. Bayrak F, *et al*. A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients. *J Opioid Manag* 2007; **3:** 74–8.
4. Helmers JHJH, *et al*. Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth* 1989; **36:** 494–7.

Pain. For the epidural or intrathecal use of sufentanil in the management of pain, see above. Intranasal sufentanil has been tried for breakthrough cancer pain[1] and postoperative analgesia.[2] It has also been tried sublingually in the management of breakthrough cancer pain.[3]

1. Jackson K, *et al*. Pilot dose finding study of intranasal sufentanil for breakthrough and incident cancer-associated pain. *J Pain Symptom Manage* 2002; **23:** 450–2.
2. Mathieu N, *et al*. Intranasal sufentanil is effective for postoperative analgesia in adults. *Can J Anesth* 2006; **53:** 60–6.
3. Gardner-Nix J. Oral transmucosal fentanyl and sufentanil for incident pain. *J Pain Symptom Manage* 2001; **22:** 627–30.

Sedation. Some references[1-3] to the use of sufentanil for sedation. See also Anaesthesia, above.

1. Bates BA, *et al*. A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; **24:** 646–51.
2. Lefrant JY, *et al*. Sufentanil short duration infusion for postoperative sedation in critically ill patients. *Br J Anaesth* 1995; **74** (suppl 1): 114.
3. Kinirons BP, *et al*. Sedation with sufentanil and midazolam decreases pain in patients undergoing upper limb surgery under multiple nerve block. *Anesth Analg* 2000; **90:** 1118–21.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1 and Fentanyl, p. 62.1.

Breast feeding. Concentrations of sufentanil were similar in colostrum and serum in 7 women given sufentanil by continuous epidural infusion during the first postoperative day after caesarean section. In the light of its poor oral availability such an amount was not considered to be a hazard to the breast-fed infant, and a maternal dose of 5 micrograms/hour epidurally was considered to be safe for such infants.[1]

1. Ausseur A, *et al*. Continuous epidural infusion of sufentanil after caesarean section: concentration in breast milk. *Br J Anaesth* 1994; **72** (suppl 1): 106.

Effects on the cardiovascular system. For a reference to the effects of sufentanil on histamine release compared with some other opioids, see under Pethidine, p. 122.3.

Effects on the nervous system. Tonic-clonic movements or seizures have been seen in a few patients receiving sufentanil.[1] There was no evidence of cortical seizure activity in a patient whose EEG was recorded,[2] suggesting that the myoclonus was not a convulsion or seizure.

1. Zaccara G, *et al*. Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Bowdle TA. Myoclonus following sufentanil without EEG seizure activity. *Anesthesiology* 1987; **67:** 593–5.

Effects on the respiratory system. Sufentanil, like other opioid agonists, causes dose-related respiratory depression. There have been reports of significant respiratory depression associated with chest wall rigidity in the early postoperative period after anaesthesia with intravenous sufentanil.[1,2] Respiratory depression has also been reported after intrathecal sufentanil for postoperative analgesia[3] and labour pain.[4] A retrospective chart review[3] of a 6-year period, during which 4870 patients received intrathecal sufentanil for the management of labour pain, found that the case above was the only one of respiratory arrest reported in the group.

1. Goldberg M, *et al*. Postoperative rigidity following sufentanil administration. *Anesthesiology* 1985; **63:** 199–201.
2. Chang J, Fish KJ. Acute respiratory arrest and rigidity after anesthesia with sufentanil: a case report. *Anesthesiology* 1985; **63:** 710–11.
3. Fournier R, *et al*. Respiratory depression after 5 microgramsrams of intrathecal sufentanil. *Anesth Analg* 1998; **87:** 1377–8.
4. Ferouz F, *et al*. Risk of respiratory arrest after intrathecal sufentanil. *Anesth Analg* 1997; **85:** 1088–90.

The elderly. The pharmacokinetics of sufentanil in elderly patients have been variable in different studies, but a review[1] considered that there had been no evidence overall for differences between the elderly and younger adults. Nevertheless, as with fentanyl, reduced initial doses have been advised in the elderly.

1. Monk JP, *et al*. Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.

Handling. Avoid contact with skin and the inhalation of particles of sufentanil citrate.

Obesity. The elimination half-life and volume of distribution of sufentanil were increased in obese subjects.[1,2] Licensed product information recommends that for obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of their lean body-weight.

1. Schwartz AE, *et al*. Pharmacokinetics of sufentanil in the obese. *Anesthesiology* 1986; **65** (suppl 3A): A562.
2. Schwartz AE, *et al*. Pharmacokinetics of sufentanil in obese patients. *Anesth Analg* 1991; **73:** 790–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sufentanil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Benzodiazepines. For the effects of using opioids such as sufentanil with benzodiazepines, see Analgesics under Interactions of Diazepam, p. 1068.1.

Pharmacokinetics

After parenteral doses sufentanil citrate has a rapid onset and short duration of action. The terminal elimination half-life of sufentanil is about 2.5 hours. It is extensively bound to plasma proteins (about 90%). It is metabolised in the liver and small intestine by *N*-dealkylation and *O*-demethylation and the inactive metabolites are excreted in the urine and faeces. About 80% of a dose is excreted within 24 hours and 2% is eliminated as unchanged drug. Sufentanil crosses the placenta and is distributed into breast milk.

The pharmacokinetics of sufentanil have been reviewed.[1,2] Sufentanil is very lipid-soluble. Like alfentanil it is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. The elimination half-life lies between that of alfentanil and fentanyl. The manufacturers of sufentanil have given values for a three-compartment pharmacokinetic model with a distribution half-life of 1.4 minutes, a redistribution half-life of 17.1 minutes, and an elimination half-life of 164 minutes. Accumulation may be relatively limited when compared with fentanyl. In practice the pharmacokinetics of sufentanil may vary according to the age and condition of the patient and the procedures undertaken. For example, the elimination half-life of sufentanil has been reported to be longer in patients undergoing cardiac surgery (595 minutes),[3] in hyperventilated patients (232 minutes),[4] in those undergoing abdominal aortic surgery (more than 12 hours),[5] and in ventilated intensive care patients under sedation (25.5 hours).[6]

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; **31:** 275–92.
3. Howie MB, *et al.* Serum concentrations of sufentanil and fentanyl in the post-operative course in cardiac surgery patients. *Anesthesiology* 1984; **61:** A131.
4. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. *Br J Anaesth* 1989; **63:** 385–8.
5. Hudson RJ, *et al.* Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology* 1989; **70:** 426–31.
6. Ethuin F, *et al.* Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients. *Intensive Care Med* 2003; **29:** 1916–20.

Administration. References to the pharmacokinetics of sufentanil given epidurally,[1,2] intrathecally,[1] or transdermally.[3]

1. Ionescu TI, *et al.* Pharmacokinetic study of extradural and intrathecal sufentanil anaesthesia for major surgery. *Br J Anaesth* 1991; **66:** 458–64.
2. Hansdottir V, *et al.* The cerebrospinal fluid and plasma pharmacokinetics of sufentanil after thoracic or lumbar epidural administration. *Anesth Analg* 1995; **80:** 724–9.
3. Sebel PS, *et al.* Transdermal absorption of fentanyl and sufentanil in man. *Eur J Clin Pharmacol* 1987; **32:** 529–31.

Children. Neonates (up to 1 month old) had a significantly lower plasma clearance rate and greater elimination half-life than infants (1 month to 2 years), children, and adolescents.[1] Others[2] have found that infants and small children (1 month to 3 years) with cardiac disease had higher clearance rates and shorter elimination half-lives than reported for adults. Older children (aged 2 to 8 years) with no history of cardiac, renal, or hepatic disease have also been noted to have shorter elimination half-lives and higher clearance rates than adults.[3]

1. Greeley WJ, *et al.* Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg* 1987; **66:** 1067–72.
2. Davis PJ, *et al.* Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. *Anesth Analg* 1987; **66:** 203–8.
3. Guay J, *et al.* Pharmacokinetics of sufentanil in normal children. *Can J Anaesth* 1992; **39:** 14–20.

Hepatic impairment. Because of the efficient hepatic extraction and clearance of sufentanil[1] liver dysfunction might be expected to affect its pharmacokinetics. However, elimination kinetics and plasma protein binding were found to be similar in cirrhotic and non-cirrhotic patients after a single dose of sufentanil.[2]

1. Schedewie H, *et al.* Sufentanil and fentanyl hepatic extraction rate and clearance in obese patients undergoing gastroplasty. *Clin Pharmacol Ther* 1988; **43:** 132.
2. Chauvin M, *et al.* Sufentanil pharmacokinetics in patients with cirrhosis. *Anesth Analg* 1989; **68:** 1–4.

Renal impairment. The pharmacokinetics of sufentanil were reported[1] to be unaffected in patients with chronic renal failure, although elevated plasma concentrations of sufentanil have been noted[2] in one such patient.

1. Sear JW. Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model. *Br J Anaesth* 1989; **63:** 60–7.
2. Wiggum DC, *et al.* Postoperative respiratory depression and elevated sufentanil levels in a patient with chronic renal failure. *Anesthesiology* 1985; **63:** 708–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sufenta; ***Austria***: Sufenta; ***Belg.***: Sufenta; ***Braz.***: Biosufenil; Fastfen; Sufenta; ***Chile***: Sufenta; ***China***: Su Fen Ni (舒芬尼); ***Cz.***: Sufenta; ***Denm.***: Sufenta; ***Fin.***: Sufenta; ***Fr.***: Sufenta; ***Ger.***: Sufenta; ***Gr.***: Fentamorf; ***Indon.***: Sufenta; ***Ital.***: Disufen; Fentatienil; ***Neth.***: Sufenta; ***Norw.***: Sufenta; ***Port.***: Sufenta; ***S.Afr.***: Sufenta; ***Swed.***: Sufenta; ***Switz.***: Sufenta; ***Turk.***: Sufenta; ***USA***: Sufenta.

Pharmacopoeial Preparations
USP 36: Sufentanil Citrate Injection.

Sulindac *(BAN, USAN, rINN)*

MK-231; Sulindaakki; Sulindaco; Sulindacum; Sulindak; Szulindak; Сулиндак.

(*Z*)-[5-Fluoro-2-methyl-1-(4-methylsulphinylbenzylidene) inden-3-yl]acetic acid.

$C_{20}H_{17}FO_3S$=356.4

CAS — 38194-50-2.

ATC — M01AB02.

ATC Vet — QM01AB02.

UNII — 184SNS8VUH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Sulindac). A yellow, polymorphic, crystalline powder. Very slightly soluble in water and in ether; sparingly soluble in alcohol; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Sulindac). A yellow, odourless or practically odourless, crystalline powder. Practically insoluble in water and in hexane; slightly soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; very slightly soluble in ethyl acetate and in isopropyl alcohol.

Uses and Administration

Sulindac is an NSAID (p. 102.3) structurally related to indometacin (p. 71.3); its activity appears to be due to its sulfide metabolite. Sulindac is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and also in the short-term management of acute gout and peri-articular conditions such as bursitis and tendinitis. It has also been used to reduce fever.

A usual initial oral dose of sulindac is 150 or 200 mg twice daily, reduced according to response; the maximum recommended daily dose is 400 mg. Licensed product information recommends that the treatment of peri-articular disorders should be limited to 7 to 14 days; for acute gout, 7 days of therapy is usually adequate.

Sulindac sodium has been given by rectal suppository.

Administration in hepatic or renal impairment. The dose of sulindac may need to be reduced in patients with hepatic or renal impairment but see Adverse Effects and Precautions, below.

Gastrointestinal disorders. In placebo-controlled studies[1,2] sulindac 150 to 200 mg twice daily for 6 to 9 months has reduced the number and size of polyps in patients with familial adenomatous polyposis but the effect may be incomplete and in a study[2] only polyps less than 2 mm in size regressed. In addition, the size and number of polyps have been reported[1] to increase on stopping treatment. The benefit of long-term therapy has therefore been studied. Reduced efficacy has been seen[3] with long-term use but others[4] have reported management of recurrences by adjustment of maintenance dosage; there seemed to be individual variations in sensitivity to sulindac with respect to prevention of polyp recurrence although an average maintenance dose of 200 mg daily appeared to be needed.[4]

There is evidence[5] that sulindac alters the ratio of apoptosis of surface cells relative to those lying deeper in the crypt of rectal mucosa, thus altering epithelial homoeostasis. Whether sulindac prevents malignant degeneration is unknown but there have been reports[6-8] of patients who developed rectal cancer during or after long-term therapy for adenomatous polyposis. A more recent, placebo-controlled study[9] has also reported that sulindac did not reduce the development of adenomas in patients with familial adenomatous polyposis. Some[1,9] consider that sulindac is unlikely to replace surgery as primary therapy for familial adenomatous polyposis.

A sulfone metabolite of sulindac, exisulind (p. 793.1) has also been investigated for the treatment of familial adenomatous polyposis.

Sulindac has also been reported to have produced beneficial effects in a patient with duodenal polyps associated with Gardner's syndrome[10] but a placebo-controlled study has suggested that it may not be effective against sporadic type colonic polyps.[11]

For a discussion of evidence suggesting that regular use of NSAIDs may protect against various types of malignant neoplasms of the gastrointestinal tract, see Malignant Neoplasms in NSAIDs, p. 104.1.

1. Giardiello FM, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; **328:** 1313–16.
2. Debinski HS, *et al.* Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet* 1995; **345:** 855–6.
3. Tonelli F, Valanzano R. Sulindac in familial adenomatous polyposis. *Lancet* 1993; **342:** 1120.
4. Labayle D, *et al.* Sulindac in familial adenomatous polyposis. *Lancet* 1994; **343:** 417–18.
5. Keller JJ, *et al.* Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac. *Gut* 1999; **45:** 822–8.
6. Thorson AG, *et al.* Rectal cancer in FAP patient after sulindac. *Lancet* 1994; **343:** 180.
7. Matsuhashi N, *et al.* Rectal cancer after sulindac therapy for a sporadic adenomatous colonic polyp. *Am J Gastroenterol* 1998; **93:** 2261–6.
8. Cruz-Correa M, *et al.* Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology* 2002; **122:** 641–5.
9. Giardiello FM, *et al.* Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002; **346:** 1054–9.
10. Parker AL, *et al.* Disappearance of duodenal polyps in Gardner's syndrome with sulindac therapy. *Am J Gastroenterol* 1993; **88:** 93–4.
11. Ladenheim J, *et al.* Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995; **108:** 1083–7.

Premature labour. The most common approach to postponing premature labour (p. 2131.1) with drugs has historically been with a selective beta$_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Sulindac has also been tried[1,2] as an alternative to indometacin as it appears to have little placental transfer and may therefore have fewer fetal adverse effects.[1] However, the authors of a subsequent study suggested that sulindac had many of the same adverse fetal effects as indometacin and its use could only be described as investigational.[3] A study[4] using relatively low doses of sulindac (100 mg twice daily) did not note any significant fetal or maternal adverse effects but also found the drug to be ineffective in extending gestation or improving outcome.

1. Carlan SJ, *et al.* Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labor. *Obstet Gynecol* 1992; **79:** 223–8.
2. Carlan SJ, *et al.* Outpatient oral sulindac to prevent recurrence of preterm labor. *Obstet Gynecol* 1995; **85:** 769–74.
3. Kramer WB, *et al.* A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. *Am J Obstet Gynecol* 1999; **180:** 396–401.
4. Humphrey RG, *et al.* Sulindac to prevent recurrent preterm labor: a randomized controlled trial. *Obstet Gynecol* 2001; **98:** 555–62.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3. Urine discoloration has occasionally been reported with sulindac.

Sulindac metabolites have been reported as major or minor components in renal stones. It should therefore be used with caution in patients with a history of renal stones and such patients should be kept well hydrated while receiving sulindac.

UK licensed product information recommends that patients with hepatic impairment should not be given sulindac; in the USA, however, licensed information states that patients with poor hepatic function may be given a reduced dose of sulindac with close monitoring. The dose of sulindac may also need to be reduced in those with renal impairment. Licensed information recommends that sulindac is not used in patients with advanced renal disease, but this appears to be based on a lack of data in such patients.

Effects on the blood. Agranulocytosis,[1] thrombocytopenia,[2] haemolytic anaemia,[3] and aplastic anaemia[4] have been reported in patients taking sulindac.

1. Romeril KR, *et al.* Sulindac induced agranulocytosis and bone marrow culture. *Lancet* 1981; **ii:** 523.
2. Karachalios GN, Parigorakis JG. Thrombocytopenia and sulindac. *Ann Intern Med* 1986; **104:** 128.
3. Johnson FP, *et al.* Immune hemolytic anemia associated with sulindac. *Arch Intern Med* 1985; **145:** 1515–16.
4. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the CNS. Acute deterioration of parkinsonism occurred in a patient after starting sulindac.[1]

See also Hypersensitivity, p. 135.1.

1. Sandyk R, Gillman MA. Acute exacerbation of Parkinson's disease with sulindac. *Ann Neurol* 1985; **17:** 104–5.

Effects on the endocrine system. A case of reversible gynaecomastia associated with sulindac therapy has been reported.[1] There has also been a report[2] of reversible hypothyroidism in an elderly patient taking sulindac.

1. Kapoor A. Reversible gynecomastia associated with sulindac therapy. *JAMA* 1983; **250:** 2284–5.

2. Iyer RP, Duckett GK. Reversible secondary hypothyroidism induced by sulindac. *BMJ* 1985; **290:** 1788.

Effects on the gallbladder. A "sludge" composed of crystalline metabolites of sulindac has been found in the common bile duct during surgery for biliary obstruction in patients who had been taking sulindac.[1]

1. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the kidneys. Sulindac-induced renal impairment, interstitial nephritis, and nephrotic syndrome have been reported.[1] It has been suggested that sulindac, as a prodrug, may not inhibit renal prostaglandin synthesis in therapeutic doses. However, this potentially important therapeutic advantage has not been uniformly seen in short-term studies in patients with renal dysfunction.[2-4]

There have been reports of renal stones consisting of between 10 and 90% of sulindac metabolites developing in patients given sulindac.[5]

1. Whelton A, *et al.* Sulindac and renal impairment. *JAMA* 1983; **249:** 2892.
2. Klassen DK, *et al.* Sulindac kinetics and effects on renal function and prostaglandin excretion in renal insufficiency. *J Clin Pharmacol* 1989; **29:** 1037–42.
3. Eriksson L-O, *et al.* Effects of sulindac and naproxen on prostaglandin excretion in patients with impaired renal function and rheumatoid arthritis. *Am J Med* 1990; **89:** 313–21.
4. Whelton A, *et al.* Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. *Ann Intern Med* 1990; **112:** 568–76.
5. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the liver. Hepatotoxicity reported in patients receiving sulindac includes hepatocellular injury and cholestatic jaundice.[1,2] Symptoms of hypersensitivity including rash, fever, or eosinophilia have been reported in 35 to 55% of patients with sulindac-induced liver damage;[2] in these patients the liver damage occurred usually within 4 to 8 weeks of beginning sulindac therapy. For reference to a report citing the strongest evidence for an association of sulindac with liver disease compared with other NSAIDs, see under NSAIDs, p. 106.3.

See also Effects on the Skin, below.

1. Gallanosa AG, Spyker DA. Sulindac hepatotoxicity: a case report and review. *Clin Toxicol* 1985; **23:** 205–38.
2. Tarazi EM, *et al.* Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. *Gastroenterology* 1993; **104:** 569–74.

Effects on the lungs. For reference to pneumonitis associated with sulindac therapy, see Hypersensitivity, below.

Effects on the skin. Toxic epidermal necrolysis has occurred in patients taking sulindac.[1] In a patient toxic hepatitis and the Stevens-Johnson/toxic epidermal necrolysis syndrome resulted in death.[2]

An unusual pernio-like reaction affecting the toes, which was also confirmed by rechallenge, has been reported.[3]

Sulindac has also been reported to cause photosensitivity reactions.[4]

1. Small RE, Garnett WR. Sulindac-induced toxic epidermal necrolysis. *Clin Pharm* 1988; **7:** 766–71.
2. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. *J Rheumatol* 1983; **10:** 512–13.
3. Reinertsen JL. Unusual pernio-like reaction to sulindac. *Arthritis Rheum* 1981; **24:** 1215.
4. Anonymous. Drugs that cause photosensitivity. *Med Lett Drugs Ther* 1986; **28:** 51–2.

Hypersensitivity. Hypersensitivity reactions to sulindac include pneumonitis,[1,2] generalised lymphadenopathy,[3] aseptic meningitis,[4] and anaphylactoid reaction.[5]

See also Effects on the Liver and Effects on the Skin, above.

1. Smith FE, Lindberg PJ. Life-threatening hypersensitivity to sulindac. *JAMA* 1980; **244:** 269–70.
2. Fein M. Sulindac and pneumonitis. *Ann Intern Med* 1981; **95:** 245.
3. Sprung DJ. Sulindac causing a hypersensitivity reaction with peripheral and mediastinal lymphadenopathy. *Ann Intern Med* 1982; **97:** 564.
4. Fordham von Reyn C. Recurrent aseptic meningitis due to sulindac. *Ann Intern Med* 1983; **99:** 343–4.
5. Hyson CP, Kazakoff MA. A severe multisystem reaction to sulindac. *Arch Intern Med* 1991; **151:** 387–8.

Pancreatitis. Reports[1-4] of pancreatitis associated with sulindac therapy.

1. Goldstein J, *et al.* Sulindac associated with pancreatitis. *Ann Intern Med* 1980; **93:** 151.
2. Siefkin AD. Sulindac and pancreatitis. *Ann Intern Med* 1980; **93:** 932–3.
3. Lilly EL. Pancreatitis after administration of sulindac. *JAMA* 1981; **246:** 2680.
4. Memon AN. Pancreatitis and sulindac. *Ann Intern Med* 1982; **97:** 139.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulindac as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Dimethyl sulfoxide reduces plasma concentrations of the active metabolite of sulindac and use of the two drugs together has also resulted in peripheral neuropathy. Diflunisal and aspirin are reported to reduce the plasma concentration of the active metabolite of sulindac. Unlike other NSAIDs, sulindac is reported not to reduce the antihypertensive effects of drugs such as thiazide diuretics, but nevertheless licensed product information recommends that blood pressure be closely monitored in patients taking antihypertensives with sulindac.

Pharmacokinetics

Sulindac is absorbed from the gastrointestinal tract. It is metabolised by reversible reduction to the sulfide metabolite, which appears to be the active form, and by irreversible oxidation to the sulfone metabolite. Peak plasma concentrations of the sulfide metabolite occur in about 2 hours. The mean elimination half-life of sulindac is about 7.8 hours and of the sulfide metabolite about 16.4 hours. Sulindac and its metabolites are over 90% bound to plasma proteins. About 50% is excreted in the urine mainly as the sulfone metabolite and its glucuronide conjugate, with smaller amounts of sulindac and its glucuronide conjugate; about 25% appears in the faeces, primarily as sulfone and sulfide metabolites. Sulindac and its metabolites are also excreted in bile and undergo extensive enterohepatic circulation.

References.

1. Davies NM, Watson MS. Clinical pharmacokinetics of sulindac: a dynamic old drug. *Clin Pharmacokinet* 1997; **32:** 437–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aclin; ***Belg.***: Clinoril†; ***Canad.***: Apo-Sulin; Novo-Sundac†; ***China***: Clinoril (奇诺力); Zulida (枢力达); ***Fr.***: Arthrocine; ***Gr.***: Norilafin; Sulen; Udolac; Zirofalen; ***Hong Kong***: Aclin; Clinoril†; ***Irl.***: Clinoril†; ***Ital.***: Clinoril; ***Mex.***: Atriser; Bio-Dac; Clinoril; Clison; Copal†; Kenalin; Renidac; Sulifur†; Vindacin; Zulsol†; ***NZ***: Clinoril; Daclin; ***Singapore***: Apo-Sulin; ***Spain***: Sulindal†; ***Swed.***: Clinoril†; ***Thai.***: Cenlidac; Clinoril; ***UK***: Clinoril†; ***USA***: Clinoril.

Pharmacopoeial Preparations
BP 2014: Sulindac Tablets;
USP 36: Sulindac Tablets.

Superoxide Dismutase

NK-341 (recombinant human superoxide dismutase); SOD; Superóxido dismutasa; Супероксиддисмутаза.

Description. Superoxide dismutase represents a group of water-soluble protein congeners widely distributed in nature which catalyse the conversion of superoxide radicals to peroxide. Several different forms exist, which vary in their metal content; forms containing copper or copper and zinc are common.

Orgotein *(BAN, USAN, rINN)*

Bovine Superoxide Dismutase; Orgoteiini; Orgoteína; Orgotéine; Orgoteinum; Ormetein; Оротеин.
CAS — 9016-01-7.
ATC — M01AX14.
ATC Vet — QM01AX14.
UNII — PKE82W49V1.

Description. Orgotein is a superoxide dismutase produced from beef liver as Cu-Zn mixed chelate. Mol. wt about 33 000 with a compact conformation maintained by about 4 gram-atoms of chelated divalent metal.

Pegorgotein *(USAN, rINN)*

Pegorgoteína; Pégorgotéine; Pegorgoteinum; PEG-SOD; Win-22118; Пегоротеин.
CAS — 155773-57-2.

Description. Pegorgotein is a superoxide dismutase conjugated with polyethylene glycol to prolong its duration of action.

Sudismase *(rINN)*

Sudismasa; Sudismasum; Судизмаза.
CAS — 110294-55-8.

Description. Sudismase is a human *N*-acetylsuperoxide dismutase produced by recombinant DNA technology and containing a copper and zinc prosthetic group.

Uses and Administration

Superoxide dismutases have anti-inflammatory properties. Orgotein, a bovine derived superoxide dismutase, has been given by local injection, into the joints for degenerative joint disorders, but hypersensitivity reactions have limited its use. It has also been tried for the amelioration of adverse effects from radiotherapy. Forms of human superoxide dismutase derived by recombinant DNA technology have been developed.

Superoxide dismutases have also been investigated for their free-radical scavenging properties in a variety of conditions; however, their value has been limited.

Bronchopulmonary dysplasia. Use of sudismase in premature infants treated for respiratory distress syndrome did not prevent development of bronchopulmonary dysplasia (p. 1602.1) in the first month.[1] However, treated infants subsequently showed a lower incidence of severe respiratory disease and hospitalisations in the first year, suggesting a reduction in chronic lung injury. The antioxidant was given intratracheally in a dose of 5 mg/kg every 48 hours as long as intubation and ventilation were necessary. A systematic review[2] was unable to reach a firm conclusion about the efficacy of superoxide dismutases in preventing chronic lung disease.

1. Davis JM, *et al.* Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 2003; **111:** 469–76.
2. Suresh GK, *et al.* Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/05/05).

Adverse Effects

Anaphylaxis and other hypersensitivity reactions, sometimes fatal, have been reported with orgotein. Local reactions and pain may occur at the site of injection of orgotein.

Pharmacokinetics

References.

1. Rosenfeld WN, *et al.* Safety and pharmacokinetics of recombinant human superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1996; **97:** 811–17.
2. Davis JM, *et al.* Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1997; **100:** 24–30.
3. Schwedhelm E, *et al.* Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. *Clin Pharmacokinet* 2003; **42:** 437–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sodermix; ***Rus.***: Rexod (Рексод).

Multi-ingredient Preparations. ***Fr.***: GliSODine Antioxidant; GliSODine Defenses; GliSODine Solaire; Proselem; Ultraselem; ***Indon.***: Glisodin; nutrivision; ***Ital.***: Legalon Plus; ***Mex.***: Avitil; Sodimel; ***Singapore***: Nutrivision†.

Suprofen *(BAN, USAN, rINN)*

R-25061; Suprofeeni; Suprofène; Suprofeno; Suprofenum; Sutoprofen; Супрофен.
2-[4-(2-Thenoyl)phenyl]propionic acid.
$C_{14}H_{12}O_3S$=260.3
CAS — 40828-46-4.
ATC — M01AE07.
ATC Vet — QM01AE07.
UNII — 988GU2F9PE.

Pharmacopoeias. In *US.*

USP 36: (Suprofen). A white to off-white powder, odourless or having a slight odour. Sparingly soluble in water.

Profile

Suprofen is an NSAID (p. 102.3). Suprofen has been used as 1% eye drops to inhibit the miosis that may occur during ocular surgery.

It was formerly given orally in mild to moderate pain and in osteoarthritis and rheumatoid arthritis but, after reports of adverse renal reactions, marketing of the oral dose form was suspended worldwide.

Preparations

Pharmacopoeial Preparations
USP 36: Suprofen Ophthalmic Solution.

Suxibuzone *(BAN, rINN)*

Suksibutsoni; Suksibuzonas; Suxibuzon; Suxibuzona; Suxibuzonum; Szuxibuzon; Суксибузон.
4-Butyl-4-hydroxymethyl-1,2-diphenylpyrazolidine-3,5-dione hydrogen succinate (ester).
$C_{24}H_{26}N_2O_6$=438.5

CAS — 27470-51-5.
ATC — M02AA22.
ATC Vet — QM01AA90; QM02AA22.
UNII — 86TDZ5WP2B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Suxibuzone). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone; practically insoluble in cyclohexane.

Profile

Suxibuzone, a derivative of phenylbutazone (p. 125.1), is an NSAID (p. 102.3) that has been applied topically at a concentration of about 7% in musculoskeletal and joint disorders. Concern over safety and toxicity after oral use has led to its withdrawal from the market in many countries.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Danilon†.

Tapentadol *(USAN, rINN)*

BN-200; CG-5503; Tapentadolum; Тапентадол.
3-[(1*R*,2*R*)-3-(Dimethylamino)-1-ethyl-2-methylpropyl] phenol.
$C_{14}H_{23}NO$=221.3
CAS — 175591-23-8.
ATC — N02AX06.
ATC Vet — QN02AX06.
UNII — H8A007M585.

Tapentadol Hydrochloride *(rINNM)*

Hidrocloruro de tapentadol; Tapentadol, Chlorhydrate de; Tapentadoli Hydrochloridum; Тапентадола Гидрохлорид.
$C_{14}H_{23}NO,HCl$=257.8
CAS — 175591-09-0.
ATC — N02AX06.
ATC Vet — QN02AX06.
UNII — 71204KII53.

Uses and Administration

Tapentadol is an opioid analgesic (p. 108.1) that is primarily a μ-opioid agonist and also a noradrenaline reuptake inhibitor. It is used in the treatment of moderate to severe acute pain and is given orally as the hydrochloride but doses are expressed in terms of the base; 58.2 mg of tapentadol hydrochloride is equivalent to about 50 mg of tapentadol. Doses of 50, 75, or 100 mg are given every 4 to 6 hours depending on the intensity of pain. On the first day, a second dose may be given 1 hour after the initial dose if pain relief is inadequate; subsequent doses should be given every 4 to 6 hours, adjusted according to response, to a maximum total dose of 700 mg on the first day and of 600 mg daily on subsequent days.

For doses in patients with hepatic impairment, see below.

References.

1. Hale M, *et al.* Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin* 2009; **25:** 1095–1104.
2. Hartrick C, *et al.* Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther* 2009; **31:** 260–71.
3. Daniels S, *et al.* A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin* 2009; **25:** 1551–61.
4. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. *Clin Ther* 2009; **31:** 2804–18.

Administration in hepatic impairment. Tapentadol hydrochloride should be given with caution to patients with moderate hepatic impairment; treatment should be started with oral doses equivalent to 50 mg of tapentadol given at intervals of no less than every 8 hours (maximum of 3 doses in 24 hours). Thereafter, maintenance of analgesia may be achieved by adjusting the dosing interval according to tolerability.

Use in patients with severe impairment has not been studied.

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tapentadol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

Tapentadol is subject to extensive first-pass metabolism with a mean absolute bioavailability of about 32%. It is widely distributed throughout the body and plasma protein binding is about 20%. Tapentadol is extensively metabolised, mainly by glucuronidation. It is also metabolised, to a lesser extent, via the cytochrome P450 isoenzymes CYP2C9, CYP2C19, and CYP2D6, before further conjugation. None of the metabolites have analgesic activity. After oral dosing, about 70% of the dose is excreted in the urine in the conjugated form and 3% as unchanged drug. The terminal half-life is about 4 hours after oral dosing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Nucynta; ***Cz.***: Palexia; Yantil; ***Denm.***: Palexia; ***Ger.***: Palexia; ***Irl.***: Palexia; Yantil; ***Neth.***: Palexia; Yantil; ***Norw.***: Palexia; ***Spain***: Palexia; ***Swed.***: Palexia; ***Switz.***: Palexia; ***UK***: Palexia; ***USA***: Nucynta.

Tenoxicam *(BAN, USAN, rINN)*

Ro-12-0068; Ro-12-0068/000; Tenoksikaami; Tenoksikam; Tenoksikamas; Ténoxicam; Tenoxicamum; Tenoxikam; Tenoxikám; Теноксикам.
4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide.
$C_{13}H_{11}N_3O_4S_2$=337.4
CAS — 59804-37-4.
ATC — M01AC02.
ATC Vet — QM01AC02.
UNII — Z1R9N0A399.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tenoxicam). A yellow, polymorphic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in dichloromethane; it dissolves in solutions of acids and alkalis. Protect from light.

Stability. An admixture of tenoxicam 0.02% and ceftazidime 0.5% (as the sodium salt) in glucose injection 5% appeared stable when stored for up to 120 hours at 25 degrees in glass bottles;[1] when stored in PVC bags, the admixture was stable for up to 72 hours at 25 degrees and for up to 144 hours at 4 degrees.

1. Wang D-P, *et al.* Compatibility and stability of ceftazidime sodium and tenoxicam in 5% dextrose injection. *Am J Health-Syst Pharm* 2004; **61:** 1924–7.

Uses and Administration

Tenoxicam, a piroxicam (p. 125.3) analogue, is an NSAID (p. 102.3). It is used in the symptomatic management of musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and also in the short-term management of soft-tissue injury. Tenoxicam is given as a single oral daily dose usually of 20 mg. In acute musculoskeletal disorders treatment for up to 7 days is usually sufficient but in severe cases it may be given for up to a maximum of 14 days. Doses similar to those given orally have been given by intramuscular or intravenous injection for initial treatment for 1 or 2 days. Tenoxicam has also been given by rectal suppository.

References.
1. Todd PA, Clissold SP. Tenoxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991; **41:** 625–46.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Incidence of adverse effects. Adverse effects associated with tenoxicam have been reviewed.[1] The majority of adverse effects relate to the gastrointestinal tract (11.4%), nervous system (2.8%), or skin (2.5%).

Gastrointestinal disturbances including nausea and vomiting (14.7%) and dyspepsia (2.3%), surgical site bleeding (4.3%), wound infection (2.7%), dizziness (5.7%), and headache (10.7%) were the most common adverse effects reported in a placebo-controlled study involving 1001 patients after the perioperative use of oral and intravenous tenoxicam.[2] It was noted, however, that the incidence of dizziness, nausea and vomiting, and headache was greater in the placebo group and that the difference in the incidence of dyspepsia between the 2 groups was not significant.

1. Todd PA, Clissold SP. Tenoxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991; **41:** 625–46.
2. Merry AF, *et al.* Clinical tolerability of perioperative tenoxicam in 1001 patients—a prospective, controlled, double-blind, multi-centre study. *Pain* 2004; **111:** 313–22.

Effects on the kidneys. A review[1] of the effects of tenoxicam on renal function concluded that tenoxicam could be given at normal recommended doses to elderly patients or those with mild to moderate renal impairment who were not at high risk of renal failure or receiving potentially nephrotoxic therapy. Data from the manufacturer's database[1] on 67 063 patients, including 17 005 over 65 years of age, who had received tenoxicam indicated that there had been 45 adverse events relating to urinary system function, described as severe in 7. The prevalence of adverse events was similar in elderly and non-elderly patients, the most common effects being dysuria and renal pain.

1. Heintz RCA. Tenoxicam and renal function. *Drug Safety* 1995; **12:** 110–19.

Effects on the liver. A report[1] of acute hepatitis associated with the use of tenoxicam.

1. Sungur C, *et al.* Acute hepatitis caused by tenoxicam. *Ann Pharmacother* 1994; **28:** 1309.

Effects on the skin. A report of 3 cases of toxic epidermal necrolysis (Lyell's syndrome) associated with tenoxicam.[1]

For the general incidence of dermatological effects see above.

1. Chosidow O, *et al.* Toxidermies sévères au ténoxicam (Tilcotil). *Ann Dermatol Venereol* 1991; **118:** 903–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tenoxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tenoxicam is well absorbed after oral doses; peak plasma concentrations occur within about 2 hours in fasting subjects; this may be delayed to about 6 hours when tenoxicam is given with food but the extent of absorption is unaffected. It is also rapidly absorbed after intramuscular injection. Tenoxicam is about 99% protein bound and penetrates synovial fluid. The plasma elimination half-life ranges from 42 to 81 hours; with daily dosage, steady-state concentrations occur within 10 to 15 days. Tenoxicam is completely metabolised to inactive metabolites, which are excreted mainly in the urine; there is some biliary excretion of glucuronide conjugates of the metabolites.

References.
1. Nilsen OG. Clinical pharmacokinetics of tenoxicam. *Clin Pharmacokinet* 1994; **26:** 16–43.
2. Guentert TW, *et al.* Relative bioavailability of oral dosage forms of tenoxicam. *Arzneimittelforschung* 1994; **44:** 1051–4.
3. Nilsen OG, *et al.* Single- and multiple-dose pharmacokinetics, kidney tolerability and plasma protein binding of tenoxicam in renally impaired patients and healthy volunteers. *Pharmacol Toxicol* 2001; **89:** 265–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Tilcotil; ***Braz.***: Inflagel; Prodoxican†; Teflan; Tenotec; Tilatil; Tilonax; Tiloxican; Titenil; ***Chile***: Bioflam; Mitrotil; Recaflex†; Tilcotil; ***Denm.***: Tilcitin; Tilcotil; ***Fin.***: Tilcotil†; ***Fr.***: Tilcotil; ***Gr.***: Admiral; Algin-Vek; Amcinafal; Ampirovix; Artroxicam; Aspagin; Biodruff; Docticam; Dranat; Hobaticam; Indo-bros; Istotosal; Liaderyl; Neo-adlibamin; Neo-antiperstam; Neo-endusix; Octiveran; Oxytel; Palitenox; Ponsolit; Portonal; Redac; Soral; Tenox; Tentepanil; Tilcitin; Toscacalm; Velasor; Voir; Zibelant; ***Hong Kong***: Tenox†; Tilcotil†; ***Hung.***: Tilcotil; ***India***: Novotil; Tobitil; ***Indon.***: Artricom; Meditil†; Notritis; Oxaflam; Pilopil; Thenil; Tilarco; Tilcotil; Tilflam; Xotilon; ***Ital.***: Bart; Dolmen; Rexalgan†; Tilcotil; ***Jpn***: Tilcotil†; ***Malaysia***: Analcam; Seftil; Tilcotil; ***Mex.***: Tilcotil†; ***NZ***: Tilcotil; ***Philipp.***: Rheuflex; Tilcotil†; ***Port.***: Doxican; Tenalgin; Tilcotil; ***Rus.***: Teksamen (Тексамен); ***S.Afr.***: Tilcotil†; ***Singapore***: Analcam; Nadament†; ***Spain***: Reutenox; ***Swed.***: Alganex; ***Switz.***: Tilcotil; ***Thai.***: Memzotil; Seftil; Sinoral†; Teconam; Tenax; Tenocam; Tenogesic; Tenox; Tenoxil; Tenoxman; Tenxil†; Tilcotil†; Tilnoxcam; Tonox; ***Turk.***: Artroksin; Ilkoten; Nobateks; Oksamen; Tenoksan; Tenoktil; Tenox; Tilcotil; Tilko; VienOks; Zikaral; ***UAE***: Tenoflam; ***UK***: Mobiflex; ***Ukr.***: Texamen (Тексамен); ***Venez.***: Rodix; Tenoxin.

Pharmacopoeial Preparations
BP 2014: Tenoxicam Injection; Tenoxicam Tablets.

Tepoxalin *(USAN, rINN)*

ORF-20485; RWJ-20485; Tepoksaliini; Tepoxalina; Tépoxaline; Tepoxalinum; Тепоксалин.
5-(*p*-Chlorophenyl)-1-(*p*-methoxyphenyl)-*N*-methylpyrazole-3-propionohydroxamic acid.
$C_{20}H_{20}ClN_3O_3$=385.8
CAS — 103475-41-8.
ATC Vet — QM01AE92.
UNII — TZ4OX61974.

Profile

Tepoxalin, a propionic acid derivative, is an NSAID (p. 102.3) used in veterinary medicine for the treatment of inflammation and pain in dogs.

Tetridamine *(rINN)*

POLI-67; Tetridamina; Tétridamine; Tetridaminum; Tetrydamine (USAN); Tetrydamine; Тетридамин.
4,5,6,7-Tetrahydro-2-methyl-3-(methylamino)-2*H*-indazole.
$C_9H_{15}N_3$=165.2
CAS — 17289-49-5.
UNII — NQ7W02PF6S.

Profile

Tetridamine is an NSAID (p. 102.3) that has been used as the maleate as a douche in the treatment of vaginitis.

Between January 1991 and December 2003 the Spanish Poison Control Center had received 77 reports where vaginal preparations containing tetridamine had been ingested alone, mainly due to erroneous misuse.[1] Of these, 60 patients were asymptomatic and in the remainder the most frequent symptoms were vomiting (5), epigastric pain (4), heartburn or oesophageal irritation (4), dizziness (4), and nausea (3). The clinical severity was mainly benign but 1 patient became comatose after taking 4g in a suicide attempt. No deaths occurred.

1. Ballesteros S, *et al.* Oral tetridamine exposures. *Clin Toxicol* 2009; **47:** 150–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Deb†; ***Spain***: Fomene†.

Thurfyl Salicylate

Salicilato de turfilo.
Tetrahydrofurfuryl salicylate.
$C_{12}H_{14}O_4$=222.2
CAS — 2217-35-8.

Profile

Thurfyl salicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p. 92.1) in topical rubefacient preparations at concentrations of up to 14% for musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Biosal Arthritis†; ***Belg.***: Transvane; ***Irl.***: Transvasin†; ***UK***: Boots Pain Relief Heat Rub; Transvasin Heat Rub.

Tiaprofenic Acid *(BAN, rINN)*

Acide Tiaprofénique; Ácido tiaprofénico; Acidum Tiaprofenicum; FC-3001; Kyselina tiaprofenová; RU-15060; Tiaprofeenihappo; Tiaprofénico, ácido; Tiaprofenik Asit; Tiaprofeno rūgštis; Tiaprofensäure; Tiaprofensyra; Тиапрофеновая Кислота.
2-(5-Benzoyl-2-thienyl)propionic acid.
$C_{14}H_{12}O_3S$=260.3
CAS — 33005-95-7.
ATC — M01AE11.
ATC Vet — QM01AE11.
UNII — 1LS1T6R34C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tiaprofenic Acid). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. Protect from light.

Uses and Administration

Tiaprofenic acid, a propionic acid derivative, is an NSAID (p. 102.3). It is used for the relief of pain and inflammation in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in periarticular disorders such as fibrositis and capsulitis, and in soft-tissue disorders such as sprains and strains. The usual oral dose is 600 mg daily given in 2 or 3 divided doses; in patients with cardiac, hepatic, or renal impairment, licensed product information suggests that the dose is reduced to 200 mg twice daily. A modified-release preparation may be available for once-daily use. Tiaprofenic acid has also been given rectally. It has been given intramuscularly as the trometamol salt in acute conditions.

References.
1. Plosker GL, Wagstaff AJ. Tiaprofenic acid: a reappraisal of its pharmacological properties and use in the management of rheumatic diseases. *Drugs* 1995; **50:** 1050–75.

Administration in hepatic or renal impairment. Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment; for dosage details in those with more moderate impairment, see Uses and Administration, above.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Tiaprofenic acid may cause cystitis, bladder irritation, and other urinary-tract symptoms (see below). It should not be given to patients with active urinary-tract disorders or prostatic disease or a history of recurrent urinary-tract disorders. It should be stopped immediately if urinary-tract symptoms occur and urinalysis and urine culture performed.

Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment.

Breast feeding. Although tiaprofenic acid is distributed into breast milk, the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. Licensed product information also states that exposure to tiaprofenic acid via breast milk is unlikely to be of pharmacological significance; however, it is recommended that either treatment or breast feeding is stopped as necessary.

Effects on the urinary tract. Cystitis and bladder irritation have been associated with the use of tiaprofenic acid.[1-6] In August 1994 the UK CSM stated[4] that since the introduction of tiaprofenic acid in the UK in 1982 they had received 69 reports of cystitis and 32 other reports of urinary-tract symptoms associated with tiaprofenic acid including frequency, dysuria, and haematuria whereas only 8 cases of cystitis had been reported for all other NSAIDs combined. Analysis of spontaneous reports received by WHO[7] confirmed that cystitis was more commonly associated with tiaprofenic acid than with other NSAIDs. The Australian Adverse Drug Reactions Advisory Committee had received similar reports.[3] Since the 1994 warning, the CSM[8] had received reports of a further 74 cases of cystitis, but the majority of these had occurred before the warning was issued. The duration of treatment in patients affected had varied considerably. Most patients recovered when tiaprofenic acid was withdrawn.

The CSM recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and that it should be stopped in patients who develop urinary-tract symptoms. Patients should be advised that if they develop symptoms such as urinary frequency, nocturia, urgency, or pain on urination, or have blood in their urine they should stop taking tiaprofenic acid and consult their doctor. Older patients may be at increased risk.[9]

1. Ahmed M, Davison OW. Severe cystitis associated with tiaprofenic acid. *BMJ* 1991; **303:** 1376.
2. O'Neill GFA. Tiaprofenic acid as a cause of non-bacterial cystitis. *Med J Aust* 1994; **160:** 123–5.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Update on tiaprofenic acid and urinary symptoms. *Aust Adverse Drug React Bull* 1994; **13:** 6.
4. CSM/MCA. Severe cystitis with tiaprofenic acid (Surgam). *Current Problems* 1994; **20:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
5. Harrison WJ, *et al.* Adverse reactions to tiaprofenic acid mimicking interstitial cystitis. *BMJ* 1994; **309:** 574.
6. Mayall FG, *et al.* Cystitis and ureteric obstruction in patients taking tiaprofenic acid. *BMJ* 1994: **309:** 599.
7. The ADR Signals Analysis Project (ASAP) Team. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacol Toxicol* 1997; **80:** 211–17.
8. Crawford MLA, *et al.* Severe cystitis associated with tiaprofenic acid. *Br J Urol* 1997; **79:** 578–84.
9. Buchbinder R, *et al.* Clinical features of tiaprofenic acid (surgam) associated cystitis and a study of risk factors for its development. *J Clin Epidemiol* 2000; **53:** 1013–19.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tiaprofenic acid is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1.5 hours after oral doses. It has a short elimination half-life of about 2 hours and is highly bound to plasma proteins (about 98%). Excretion of tiaprofenic acid and its metabolites is mainly in the urine in the form of acyl glucuronides; some is excreted in the bile. Tiaprofenic acid crosses the placenta and is distributed into breast milk.

References.
1. Davies NM. Clinical pharmacokinetics of tiaprofenic acid and its enantiomers. *Clin Pharmacokinet* 1996; **31:** 331–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Surgam; ***Cz.***: Surgam; Thialgin†; ***Denm.***: Surgamyl; ***Fin.***: Surgamyl†; ***Fr.***: Flanid; Surgam; ***Ger.***: Surgam; ***Gr.***: Surgam; ***Hung.***: Surgam; ***Irl.***: Surgam†; ***Ital.***: Surgamyl; ***Mex.***: Surgam; ***Neth.***: Surgam; ***NZ***: Surgam; ***Pol.***: Surgam; ***Port.***: Surgam; ***S.Afr.***: Surgam†; ***Thai.***: Fengam†; Surgam; ***Turk.***: Surgam; ***UK***: Surgam; ***Venez.***: Torpas.

Tiaramide Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de tiaramida; NTA-194; Tiaperamide Hydrochloride; Tiaramida, hidrocloruro de; Tiaramide, Chlorhydrate de; Tiaramidi Hydrochloridum; Тиарамида Гидрохлорид.
5-Chloro-3-[2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl] benzothiazolin-2-one hydrochloride.
$C_{15}H_{18}ClN_3O_3S,HCl$=392.3
CAS — 32527-55-2 (tiaramide); 35941-71-0 (tiaramide hydrochloride).
UNII — ITY1616X9T.

Pharmacopoeias. In *Jpn.*

Profile

Tiaramide hydrochloride is an NSAID (p. 102.3) that is given orally for the relief of pain and inflammation. A dose equivalent to 100 mg of the base may be given three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Solantal.

Tilidine Hydrochloride *(USAN, pINNM)*

Gö 1261-C; Hidrocloruro de tilidina; Tilidate Hydrochloride (BANM); Tilidiinihydrokloridihemihydraatti; Tilidina, hidrocloruro de; Tilidine, Chlorhydrate de; Tilidine (chlorhydrate de) hémihydraté; Tilidin-hydrochlorid hemihydrát; Tilidinhydroklorid hemihydrat; Tilidini Hydrochloridum; Tilidini Hydrochloridum Hemihydricum; Tilidino hidrochloridas hemihidratas; W-5759A; Тилидина Гидрохлорид.
(±)-Ethyl *trans*-2-dimethylamino-1-phenylcyclohex-3-ene-1-carboxylate hydrochloride hemihydrate.
$C_{17}H_{23}NO_2,HCl,½H_2O$=318.8
CAS — 20380-58-9 (tilidine); 27107-79-5 (anhydrous tilidine hydrochloride); 24357-97-9 (anhydrous +-trans-tilidine hydrochloride).
ATC — N02AX01.
ATC Vet — QN02AX01.
UNII — 4YI72J28N9.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tilidine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. A suitable antoxidant may be added. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Uses and Administration

Tilidine hydrochloride is an opioid analgesic (p. 108.1). It is used in the control of moderate to severe pain.

Tilidine hydrochloride may be given in usual oral doses of up to 50 mg four times daily. It has been given as a suppository, or by intravenous, intramuscular, or subcutaneous injection. Tilidine has also been given as the phosphate in modified release tablets. As a deterrent to abuse combined oral preparations of tilidine hydrochloride with naloxone hydrochloride are available in some countries.

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Overdosage. Cyanosis, respiratory depression, and seizures developed in a 28-year-old woman after an overdose of a combination preparation of tilidine and naloxone.[1] The authors commented that the amount of naloxone included in the preparation, in order to prevent abuse, was insufficient to prevent respiratory depression after severe overdose.

1. Regenthal R, *et al.* Poisoning with tilidine and naloxone: toxicokinetic and clinical observations. *Hum Exp Toxicol* 1998; **17:** 593–7.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

Tilidine is absorbed from the gastrointestinal tract. It is metabolised and excreted in the urine mainly as metabolites nortilidine (nortilidate) and bisnortilidine (bisnortilidate). Nortilidine is responsible for the analgesic activity of tilidine.

References.
1. Vollmer K-O, *et al.* Pharmacokinetics of tilidine and metabolites in man. *Arzneimittelforschung* 1989; **39:** 1283–8.
2. Seiler K-U, *et al.* Pharmacokinetics of tilidine in terminal renal failure. *J Clin Pharmacol* 2001; **41:** 79–84.
3. Hajda JP, *et al.* Sequential first-pass metabolism of nortilidine: the active metabolite of the synthetic opioid drug tilidine. *J Clin Pharmacol* 2002; **42:** 1257–61.
4. Brennscheidt U, *et al.* Pharmacokinetics of tilidine and naloxone in patients with severe hepatic impairment. *Arzneimittelforschung* 2007; **57:** 106–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Tinalox; Valtran; ***Ger.***: Andolor†; Celldolor†; Nalidin†; Tili Comp†; Tili-Puren†; Tilicomp; Tilidin comp†; Tilidin N†; Tilidin plus; Tilidin-saar†; Tilidin; Tilnalox†; Valoron N; ***S.Afr.***: Valoron; ***Switz.***: Valoron.

Tinoridine Hydrochloride *(rINNM)*

Hidrocloruro de tinoridina; Tienoridine Hydrochloride; Tinoridina, hidrocloruro de; Tinoridine, Chlorhydrate de; Tinoridini Hydrochloridum; Y-3642 (tinoridine); Тиноридина Гидрохлорид.

Ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate hydrochloride.

$C_{17}H_{20}N_2O_2S$,HCl=352.9

CAS — 24237-54-5 (tinoridine); 25913-34-2 (tinoridine hydrochloride).

UNII — 05IIB89IVA.

Profile

Tinoridine hydrochloride is an NSAID that has been used for pain and inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Nonflamin.

Tofacitinib *(USAN, pINN)*

CP-690550; Tasocitinib; Tofacitinibum; Тофацитиниб.

3-{(3*R*,4*R*)-4-Methyl-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxo-propanenitrile.

$C_{16}H_{20}N_6O$=312.4

CAS — 477600-75-2.

ATC — L04AA29.

ATC Vet — QL04AA29.

UNII — 87LA6FU830.

Tofacitinib Citrate *(USAN, pINNM)*

Citrato de tofacitinib; CP-690550-10; Tasocitinib Citrate; Tofacitinib, Citrate de; Tofacitinibi Citras; Тофацитиниба Цитрат.

$C_{16}H_{20}N_6O$,$C_6H_8O_7$=504.5

CAS — 540737-29-9.

ATC — L04AA29.

ATC Vet — QL04AA29.

UNII — O1FF4DIV0D.

Uses and Administration

Tofacitinib is an orally active Janus tyrosine kinase (JAK) inhibitor that is selective for JAK1 and JAK3. It is used as a disease-modifying antirheumatic drug (DMARD) in the treatment of moderately to severely active rheumatoid arthritis (p. 13.2) in patients who have had an inadequate response to, or intolerance of, methotrexate. It may be used as monotherapy, or in combination with methotrexate or another non-biological DMARD.

Tofacitinib is given as the citrate although doses are expressed in terms of the base; tofacitinib citrate 8 mg is equivalent to about 5 mg of tofacitinib. The usual oral dose is the equivalent of 5 mg of tofacitinib twice daily.

If a potent cytochrome P450 isoenzyme CYP3A4 inhibitor, or a combination of moderate CYP3A4 and potent CYP2C19 inhibitors, must also be used, the dose should be reduced to 5 mg once daily.

The dose of tofacitinib should also be reduced in patients with hepatic or renal impairment (see below).

Regular monitoring of haematological parameters is recommended; tofacitinib therapy should be interrupted or withdrawn if blood counts fall below acceptable levels (see Monitoring, under Adverse Effects and Precautions, below).

Tofacitinib is also being investigated for the treatment of various other auto-immune or immune-mediated disorders including ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, and ulcerative colitis, and for the prevention of graft rejection.

References.
1. Anonymous. Tofacitinib. *Drugs R D* 2010; **10:** 271–84. Correction. *ibid.* 2012; **12:** 41–3. [dose]
2. Fleischmann R, *et al.* ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012; **367:** 495–507.
3. van Vollenhoven RF, *et al.* ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012; **367:** 508–19.
4. Sandborn WJ, *et al.* Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012; **367:** 616–24.
5. Papp KA, *et al.* Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol* 2012; **167:** 668–77.
6. Burmester GR, *et al.* ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013; **381:** 451–60.

Administration in hepatic and renal impairment. The oral dose of tofacitinib should be reduced to 5 mg once daily in patients with moderate hepatic, or moderate or severe renal, impairment; it should not be used in those with severe hepatic impairment due to a lack of data.

Adverse Effects and Precautions

The most commonly reported adverse effects with tofacitinib are upper respiratory-tract infections, headache, diarrhoea, and nasopharyngitis. Serious and sometimes fatal infections caused by bacterial, mycobacterial, invasive fungal, or viral pathogens, such as pneumonia, cellulitis, herpes zoster, and urinary-tract infections may occur. Opportunistic infections such as tuberculosis, cryptococcus, oesophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, CMV, and BK virus have also been reported. Disseminated disease may develop, particularly in patients also taking other immunomodulators such as methotrexate or corticosteroids. Tofacitinib should not be given to patients with active, including localised, infections; it should be used with caution in those with chronic or recurrent infection, exposure to tuberculosis, a history of serious or opportunistic infection, or underlying conditions that may predispose to infection, or who have resided or travelled in areas of endemic tuberculosis or mycoses. Patients should be evaluated for latent or active tuberculosis before starting therapy; if evidence of latent tuberculosis is found, standard chemoprophylaxis should be started before giving tofacitinib. Patients should be monitored for signs and symptoms of any infection during and after treatment with tofacitinib; treatment should be interrupted until the infection is controlled. Reactivation of viral infections, such as herpes zoster, has also been reported.

Tofacitinib has been associated with an increased incidence of malignancies, including lymphomas; care is advocated in patients with a history of malignancy. Post-transplant lymphoproliferative disorder associated with the Epstein-Barr virus has been reported in renal transplant patients also taking immunosuppressants.

Gastrointestinal perforation has been reported and tofacitinib should be used with caution in patients with an increased risk, such as those with a history of diverticulitis.

Blood disorders such as lymphocytosis followed by lymphocytopenia, neutropenia, and anaemia have been reported (see also Monitoring, below); impaired hepatic and renal function, and increases in serum cholesterol levels have also been noted.

Monitoring. Blood counts should be performed before the start of, and during, tofacitinib therapy.

Tofacitinib therapy should *not be started* in patients with any of the following baseline counts:
- haemoglobin < 90 g/litre
- lymphocyte < 500 cells/mm³
- neutrophil (ANC) < 1000 cells/mm³

Therapy should be *interrupted* (and restarted when values normalise) in patients who develop:
- haemoglobin < 80 g/litre or > 20 g/litre decrease
- persistent ANC of 500 to 1000 cells/mm³

Therapy should be *withdrawn* in patients who develop:
- lymphocyte < 500 cells/mm³
- ANC < 500 cells/mm³

Interactions

Live vaccines should not be given with tofacitinib as its effect on vaccine efficacy or the risk of infection transmission is unknown. Tofacitinib should not be given with biological disease-modifying antirheumatic drugs (DMARDs) or other potent immunosuppressants.

The use of tofacitinib with a potent cytochrome P450 isoenzyme CYP3A4 inhibitor, or with a combination of moderate CYP3A4 and potent CYP2C19 inhibitors, may increase exposure to tofacitinib; the dosage of tofacitinib should be reduced (see Uses and Administration, above). Conversely, use with a potent CYP3A4 inducer may decrease exposure to tofacitinib.

Pharmacokinetics

After oral doses of tofacitinib, peak plasma concentrations occur within 0.5 to 1 hour, with an absolute bioavailability of 74%. Protein binding is about 40%, mainly to albumin, and is distributed equally between red blood cells and plasma. The elimination half-life is about 3 hours and 70% of tofacitinib is eliminated via hepatic metabolism and 30% via renal excretion. Tofacitinib is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2C19.

Studies in *animals* suggest that tofacitinib is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Xeljanz; ***USA***: Xeljanz.

Tolfenamic Acid *(BAN, rINN)*

Acide Tolfénamique; Ácido tolfenámico; Acidum Tolfenamicum; Kyselina tolfenamová; Tolfenaamihappo; Tolfenámico, ácido; Tolfenaminsäure; Tolfenaminsav; Tolfenamo rūgštis; Tolfenamsyra; Толфенамовая Кислота.

N-(3-Chloro-*o*-tolyl)anthranilic acid.

$C_{14}H_{12}ClNO_2$=261.7

CAS — 13710-19-5.

ATC — M01AG02.

ATC Vet — QM01AG02.

UNII — 3G943U18KM.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tolfenamic Acid). A white or slightly yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; soluble in dimethylformamide. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

Uses and Administration

Tolfenamic acid, an anthranilic acid derivative related to mefenamic acid (p. 86.1), is an NSAID (p. 102.3). In the treatment of acute attacks of migraine tolfenamic acid is given in a usual oral dose of 200 mg when the first symptoms appear; if a satisfactory response is not obtained this dose may be repeated once after 1 to 2 hours. Tolfenamic acid has also been given for the relief of mild to moderate pain in disorders such as dysmenorrhoea, rheumatoid arthritis, or osteoarthritis in doses of 100 to 200 mg three times daily.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Dysuria, most commonly in males and probably due to local irritation of the urethra by a metabolite, has been reported. Tremor, euphoria, and fatigue have also occurred. Tolfenamic acid is contra-indicated in patients with significant hepatic or renal impairment.

Breast feeding. Although tolfenamic acid is distributed into breast milk, the amount is considered by the *BNF* and licensed product information to be too small to be harmful to a breast-fed infant.

Effects on the lungs. Pulmonary infiltration has been associated with tolfenamic acid treatment in 6 patients.[1]

1. Strömberg C, *et al.* Pulmonary infiltrations induced by tolfenamic acid. *Lancet* 1987; **ii:** 685.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies tolfenamic acid as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tolfenamic acid is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 60 to 90 minutes after an oral dose. Tolfenamic acid is about 99% bound to plasma proteins. The plasma half-life is about 2 hours. Tolfenamic acid is metabolised in the liver; the metabolites and unchanged drug are conjugated with glucuronic acid. About 90% of an ingested dose is excreted in the urine and the remainder in the faeces. Tolfenamic acid is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flocur; ***China***: Te Fen Ta (特芬它); ***Cz.***: Migea†; ***Denm.***: Migea; ***Fin.***: Clotam; ***Gr.***: Clotam; Gantil; Migea; Polmonin; Primactam; Purfalox; Tolfamic; Turbaund; ***Norw.***: Migea; ***Pol.***: Migea; ***UK***: Clotam.

Tolmetin Sodium *(BANM, USAN, rINNM)*

McN-2559-21-98; McN-2559 (tolmetin); Natrii Tolmetinum; Tolmetina sódica; Tolmétine Sodique; Натрий Тольметин.

Sodium (1-methyl-5-*p*-toluoylpyrrol-2-yl)acetate dihydrate.

$C_{15}H_{14}NNaO_3.2H_2O$=315.3

CAS — 26171-23-3 (tolmetin); 35711-34-3 (anhydrous tolmetin sodium); 64490-92-2 (tolmetin sodium dihydrate).

ATC — M01AB03; M02AA21.

ATC Vet — QM01AB03; QM02AA21.

UNII — 02N1TZF99F.

Pharmacopoeias. In *US*.

USP 36: (Tolmetin Sodium). A light yellow to light orange crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; very slightly soluble in chloroform.

Uses and Administration

Tolmetin sodium is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, including juvenile idiopathic arthritis. It is given orally as the sodium salt although doses are expressed in terms of the base; tolmetin sodium dihydrate 122.5 mg is equivalent to about 100 mg of tolmetin.

For the treatment of rheumatoid arthritis and osteoarthritis, the usual initial oral dose is the equivalent of 400 mg of tolmetin three times daily. Doses should be adjusted after 1 to 2 weeks according to response; maintenance doses of 600 mg to a maximum of 1800 mg daily in divided doses have been used.

For dosage details in children, see below.

Tolmetin as the free acid has been applied as a topical gel.

Administration in children. For the treatment of juvenile idiopathic arthritis in children aged 2 years and over, tolmetin sodium is given in initial oral doses equivalent to 20 mg/kg of tolmetin daily in three or four divided doses; maintenance doses of 15 mg/kg to a maximum of 30 mg/kg daily have been used.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given tolmetin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, licensed product information recommends that tolmetin should be avoided in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with tolmetin.

1. Sakai J, Joseph MW. Tolmetin and agranulocytosis. *N Engl J Med* 1978; **298:** 1203.
2. Lockhart JM. Tolmetin-induced thrombocytopenia. *Arthritis Rheum* 1982; **25:** 1144–5.

Effects on the CNS. See Hypersensitivity, below.

Effects on the gastrointestinal tract. Erosive oesophagitis has been reported[1] in an 11-year-old child after ingestion of a dose of tolmetin while lying down and without drinking any water.

1. Palop V, *et al.* Tolmetin-induced esophageal ulceration. *Ann Pharmacother* 1997; **31:** 929.

Effects on the kidneys. Interstitial nephritis[1] and nephrotic syndrome[2,3] have been reported in patients given tolmetin.

1. Katz SM, *et al.* Tolmetin: association with reversible renal failure and acute interstitial nephritis. *JAMA* 1981; **246:** 243–5.
2. Chatterjee GP. Nephrotic syndrome induced by tolmetin. *JAMA* 1981; **246:** 1589.
3. Tietjen DP. Recurrence and specificity of nephrotic syndrome due to tolmetin. *Am J Med* 1989; **87:** 354–5.

Hypersensitivity. Anaphylactic shock,[1] urticaria and angioedema,[2] and aseptic meningitis[3] are among the hypersensitivity reactions reported in patients taking tolmetin.

1. Rossi AC, Knapp DE. Tolmetin-induced anaphylactoid reactions. *N Engl J Med* 1982; **307:** 499–500.
2. Ponte CD, Wisman R. Tolmetin-induced urticaria/angioedema. *Drug Intell Clin Pharm* 1985; **19:** 479–80.
3. Ruppert GB, Barth WF. Tolmetin-induced aseptic meningitis. *JAMA* 1981; **245:** 67–8.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tolmetin is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 30 to 60 minutes after ingestion. It is extensively bound to plasma proteins (over 99%) and has a biphasic plasma half-life of about 1 to 2 hours and 5 hours, respectively. Tolmetin penetrates synovial fluid and very small amounts are distributed into breast milk. It is excreted in the urine as an inactive dicarboxylic acid metabolite and its glucuronide and as tolmetin glucuronide with small amounts of unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Tolectin; ***Mex.***: Tolectin; ***S. Afr.***: Tolectin†; ***Spain***: Artrocaptin†; ***Turk.***: Tolectin; ***USA***: Tolectin.

Pharmacopoeial Preparations
USP 36: Tolmetin Sodium Capsules; Tolmetin Sodium Tablets.

Tramadol Hydrochloride

(BANM, USAN, rINNM)

CG-315; CG-315E; Hidrocloruro de tramadol; Tramadol, Chlorhydrate de; Tramadol, hidrocloruro de; Tramadol Hidroklorür; Tramadol-hidroklorid; Tramadol-hydrochlorid; Tramadolhydrochlorid; Tramadolhydroklorid; Tramadoli Hydrochloridum; Tramadolihydrokloridi; Tramadolio hidrochloridas; U-26225A; Трамадола Гидрохлорид.

(±)-*trans*-2-Dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

$C_{16}H_{25}NO_2$,HCl=299.8

CAS — 27203-92-5 (tramadol); 22204-88-2 (tramadol hydrochloride); 36282-47-0 (tramadol hydrochloride).

ATC — N02AX02.

ATC Vet — QN02AX02.

UNII — 9N7R477WCK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Tramadol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in acetone. Protect from light.

USP 36: (Tramadol Hydrochloride). A white, crystalline powder. Freely soluble in water and methyl alcohol; very slightly soluble in acetone. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Some manufacturers state that tramadol hydrochloride injection 50 mg/mL is incompatible with injections of diazepam, diclofenac sodium, flunitrazepam, glyceryl trinitrate, indometacin, midazolam, piroxicam, and phenylbutazone if mixed in the same syringe. A study[1] also found tramadol hydrochloride injection (diluted to 400 micrograms/mL) to be incompatible with aciclovir and clindamycin when mixed together.

1. Abanmy NO, *et al.* Compatibility of tramadol hydrochloride injection with selected drugs and solutions. *Am J Health-Syst Pharm* 2005; **62:** 1299–1302.

Stability. Oral suspensions of tramadol hydrochloride 5 mg/mL, prepared by mixing crushed tablets with a strawberry syrup and *Ora-Plus* (1:1) or with *Ora-Sweet* and *Ora-Plus* (1:1) were found to be stable for at least 90 days when stored either in the refrigerator or at room temperature.[1] Oral suspensions containing tramadol hydrochloride 7.5 mg/mL and paracetamol 65 mg/mL, prepared by mixing the crushed tablets of a combination preparation with the above vehicles, were also found to be stable for at least 90 days when stored under similar conditions.[2]

1. Wagner DS, *et al.* Stability of oral liquid preparations of tramadol in strawberry syrup and a sugar-free vehicle. *Am J Health-Syst Pharm* 2003; **60:** 1268–70.
2. Johnson CE, *et al.* Stability of tramadol hydrochloride–acetaminophen (Ultracet) in strawberry syrup and in a sugar-free vehicle. *Am J Health-Syst Pharm* 2004; **61:** 54–7.

Uses and Administration

Tramadol hydrochloride is an opioid analgesic (p. 108.1). It also has noradrenergic and serotonergic properties that may contribute to its analgesic activity. Tramadol is used for moderate to severe pain.

Tramadol hydrochloride is given orally, intravenously, or rectally as a suppository. The intramuscular route has also been used. It may also be given by infusion or as part of a patient-controlled analgesia system.

Usual *oral* doses are 50 to 100 mg every 4 to 6 hours. Tramadol hydrochloride may also be given orally as a modified-release preparation once or twice daily. The total oral daily dosage should not exceed 400 mg. Usual doses may be used in elderly patients although in those aged over 75 years the elimination half-life is increased and a reduced dose may be required; the licensed product information for one US preparation (*Ultram, PriCara*) recommends a maximum dose of 300 mg daily in such patients while an increase in the dosage interval is often suggested in UK product information. Preparations containing tramadol hydrochloride with other analgesics such as paracetamol are also used.

When used *parenterally*, a dose of 50 to 100 mg may be given every 4 to 6 hours by intramuscular or intravenous injection over 2 to 3 minutes, or by intravenous infusion. For the treatment of postoperative pain, the initial dose is 100 mg followed by 50 mg every 10 to 20 minutes if necessary to a total maximum (including the initial dose) of 250 mg in the first hour. Thereafter, doses are 50 to 100 mg every 4 to 6 hours up to a total daily dose of 600 mg.

Usual *rectal* doses by suppository are 100 mg up to 4 times daily.

For details of doses in children and in patients with hepatic or renal impairment, see below and p. 140.1, respectively.

References.

1. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; **60:** 139–76.
2. McClellan K, Scott LJ. Tramadol/paracetamol. *Drugs* 2003; **63:** 1079–86. Correction. *ibid.*; 1636.
3. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; **43:** 879–923.
4. Leppert W, Luczak J. The role of tramadol in cancer pain treatment—a review. *Support Care Cancer* 2005; **13:** 5–17.
5. Close BR. Tramadol: does it have a role in emergency medicine? *Emerg Med Australas* 2005; **17:** 73–83.
6. Cepeda MS, *et al.* Tramadol for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
7. Duehmke RM, *et al.* Tramadol for neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
8. Keating GM. Tramadol sustained-release capsules. *Drugs* 2006; **66:** 223–30.
9. Hair PI, *et al.* Tramadol extended-release tablets. *Drugs* 2006; **66:** 2017–27.
10. Freeman R, *et al.* Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin* 2007; **23:** 147–61.

Administration in children. In the UK, tramadol hydrochloride is licensed for the management of moderate to severe pain in children 12 years of age and older; usual adult doses may be given (see above). However, in some other European countries it is licensed in younger children although the age range permitted can vary: for example, in *France*, a usual dose in those aged 3 years and over is 1 to 2 mg/kg orally, which may be repeated 3 or 4 times daily, whereas in *Germany*, similar doses are permitted in children as young as 1 year old. Tramadol has also been given parenterally to children in doses similar to those used orally.

Some references[1-4] on the use of tramadol in children.

1. Finkel JC, *et al.* An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablets for the treatment of postsurgical pain in children. *Anesth Analg* 2002; **94:** 1469–73.
2. Demiraran Y, *et al.* A comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children. *Br J Anaesth* 2005; **95:** 510–13.
3. Bozkurt P. Use of tramadol in children. *Paediatr Anaesth* 2005; **15:** 1041–7.
4. Chu Y-C, *et al.* Intraoperative administration of tramadol for postoperative nurse-controlled analgesia resulted in earlier awakening

and less sedation than morphine in children after cardiac surgery. *Anesth Analg* 2006; **102:** 1668–73.

Administration in hepatic or renal impairment. A dosage interval of 12 hours is recommended for tramadol usage in severe hepatic impairment; US licensed product information suggests that patients with cirrhosis should be given oral doses of 50 mg every 12 hours. The dosage interval should also be increased to 12 hours in patients with a creatinine clearance (CC) of less than 30 mL/minute; in the USA licensed product information suggests that the maximum oral dose should not exceed 200 mg daily in these patients. Tramadol should not be given to patients with more severe renal impairment (CC less than 10 mL/minute).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Tramadol may have lower potential for producing dependence than morphine.

A WHO expert committee[1] considered in 2003 that the available information on tramadol was not sufficient to warrant international control. Studies in *animals* indicated that tramadol produced little tolerance, had mild withdrawal symptoms, and a lower abuse potential than codeine and pentazocine. Subsequently, when reviewed in 2006, the committee[2] considered that, despite an increase in its use, tramadol continued to show a low level of abuse and concluded that there was not sufficient evidence to justify a further review.

Nevertheless, there have been reports[3-8] of dependence and abuse, particularly in opioid-dependent persons, and of withdrawal symptoms. In October 1996, the UK CSM[9] commented that since June 1994 they had received reports of drug dependence in 5 patients and withdrawal symptoms associated with tramadol in 28 patients, which corresponded to a reporting rate of about 1 in 6000. Doses in excess of the recommended maximum of 400 mg daily had been taken by 5 of the patients. The duration of treatment before onset of these effects ranged from 10 to 409 days (average 3 months). Withdrawal symptoms reported were typically those of opioid withdrawal in general. A more recent report from the Swedish Medical Products Agency[10] stated that between 1996 to 2005 they had received 71 reports of withdrawal symptoms associated with tramadol; treatment duration ranged from 1 week to over 3 years at daily doses of between 50 mg to 2 g.

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Also available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 26/06/08)
2. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
3. Rodriguez Villamañan JC, *et al*. Withdrawal syndrome after long-term treatment with tramadol. *Br J Gen Pract* 2000; **50:** 406.
4. Yates WR, *et al*. Tramadol dependence with no history of substance abuse. *Am J Psychiatry* 2001; **158:** 964.
5. Brinker A, *et al*. Abuse, dependence, or withdrawal associated with tramadol. *Am J Psychiatry* 2002; **159:** 881.
6. Skipper GE, *et al*. Tramadol abuse and dependence among physicians. *JAMA* 2004; **292:** 1818–19.
7. Soyka M, *et al*. Tramadol use and dependence in chronic noncancer pain patients. *Pharmacopsychiatry* 2004; **37:** 191–2.
8. Ripamonti C, *et al*. Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry* 2004; **161:** 2326–7.
9. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; **22:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
10. Läkemedelsverket (Medical Products Agency—Sweden). Utsättningsreaktioner av tramadol—ett större problem än förväntat? (issued 14th November, 2006). Available at: http://www.lakemedelsverket.se/Allanyheter/NYHETER-2006/Utsattningsreaktioner-av-tramadol-ett-storre-problem-an-forvantat-/ (accessed 02/08/10)

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Tramadol may produce fewer typical opioid adverse effects such as respiratory depression and constipation. In addition to hypotension, hypertension has occasionally occurred.

Deaths associated with tramadol use have been reported in patients with a history of emotional disturbances, suicidal ideation or attempted suicide, or misuse of CNS depressants such as alcohol and anxiolytics.

Effects on the CNS. The UK CSM[1] commented in February 1995 that since June 1994 they had received reports of 15 patients who had had *confusion* and/or *hallucinations* while taking tramadol. The majority of the reactions developed 1 to 7 days after starting treatment and in most patients resolved rapidly on withdrawal. It was noted that psychiatric reactions comprised about 10% of all reactions reported with tramadol.

In a later comment[2] in October 1996, the CSM noted that 27 reports of *convulsions* and one of worsening epilepsy had been received, which corresponded to a reporting rate of about 1 in 7000. Of the 5 patients receiving intravenous tramadol, 2 had been given doses equivalent to 1.45 and 4 g daily, well in excess of those recommended (see also Overdosage, below). Of the patients receiving oral tramadol, the majority were taking other drugs known to cause convulsions, including tricyclic antidepressants and SSRIs. A similar pattern has been reported in the USA[3] and Australia.[4-6]

A debilitating CNS-mediated reaction to an initial dose of tramadol has been described in a patient.[7] Symptoms, which lasted about 4 hours, included ataxia, dilatation of the pupils, numbness in all limbs, tremulousness, and dysphoria. Although the exact mechanism of the reaction was unknown, it was suggested that since the patient was an extensive metaboliser with very high activity of the cytochrome P450 isoenzyme CYP2D6, high concentrations of the active *O*-desmethyl metabolite were the cause. The patient recovered with no sequelae. It is possible that this represents a case of the *serotonin syndrome*, since tramadol is known to be associated with this condition, particularly at high doses or when given with other drugs that raise serotonin concentrations.[4]

1. CSM/MCA. Tramadol (Zydol)—psychiatric reactions. *Current Problems* 1995; **21:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; **22:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
3. Kahn LH, *et al*. Seizures reported with tramadol. *JAMA* 1997; **278:** 1661.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Tramadol—four years experience. *Aust Adverse Drug React Bull* 2003; **22:** 1–2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 26/06/08)
5. Labate A, *et al*. Tramadol and new-onset seizures. *Med J Aust* 2005; **182:** 42–3.
6. Boyd IW. Tramadol and seizures. *Med J Aust* 2005; **182:** 595–6.
7. Gleason PP, *et al*. Debilitating reaction following the initial dose of tramadol. *Ann Pharmacother* 1997; **31:** 1150–2.

Effects on the respiratory system. Respiratory depression has been reported after tramadol infusion anaesthesia,[1] although in a postoperative study[2] tramadol had no significant respiratory depressant effect when equianalgesic doses of morphine, pentazocine, pethidine, piritramide, and tramadol were compared.

1. Paravicini D, *et al*. Tramadol-infusionsanaesthesie mit Substitution von Enfluran und differenten Lachgaskonzentrationen. *Anaesthesist* 1985; **34:** 20–7.
2. Fechner R, *et al*. Clinical investigations on the effect of morphine, pentazocine, pethidine, piritramide and tramadol on respiration. *Anasth Intensivmed* 1985; **26:** 126–32.

Overdosage. In a multicentre case series,[1] 126 cases of tramadol toxicity were reported between October 1995 and August 1996; of these, 87 involved exposure to tramadol alone. Common symptoms included lethargy, nausea, tachycardia, and agitation; seizures were also noted. Respiratory depression was seen in only 2 patients. The inhibitory effects of tramadol on monoamine reuptake, rather than its opioid effects, was considered to result in much of its toxicity. A similar pattern of toxicity has also been seen in a more recent report.[2] In 190 tramadol-only exposures reported between January 1999 and July 2001, the main symptoms of overdosage were CNS depression, nausea and vomiting, tachycardia, and seizures. Again, the incidence of respiratory depression was rare, with only 1 case reported.

1. Spiller HA, *et al*. Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol* 1997; **35:** 361–4.
2. Marquardt KA, *et al*. Tramadol exposures reported to statewide poison control system. *Ann Pharmacother* 2005; **39:** 1039–44.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Tramadol should not be given to patients who are suicidal or prone to addiction. It should be used with caution in those who use alcohol in excess, or suffer from emotional disturbance or depression. Tramadol should be used with care in patients with a history of epilepsy or those susceptible to seizures. See also Effects on the CNS under Adverse Effects, above.

Tramadol should also be used with caution in patients with renal or hepatic impairment and should be avoided if renal impairment is severe. Removal by haemodialysis is reported to be minimal at 7%.

Abuse. See under Dependence and Withdrawal, above.

Anaesthesia. Licensed product information warns against using tramadol during very light planes of general anaesthesia because of possible intra-operative awareness, although it may be used intra-operatively provided anaesthesia is maintained with a potent volatile or intravenous anaesthetic. Intra-operative awareness was reported in 65% of a group of 20 patients when used to provide analgesia during light general anaesthesia with nitrous oxide and intermittent enflurane.[1] However, in a study[2] of 51 patients given tramadol during stable light continuous isoflurane-nitrous oxide anaesthesia there was no clinically significant lightening of anaesthesia and others have commented that during extensive use of tramadol intraoperatively over several years, there had not been any incidence of recall in any patient treated at their clinic.[3]

1. Lehmann KA, *et al*. Zur Bedeutung von Tramadol als intraoperativem Analgetikum: eine randomisierte Doppelblindstudie im Vergleich zu Placebo. *Der Anaesthetist* 1985; **34:** 11–19.
2. Coetzee JF, *et al*. Effect of tramadol on depth of anaesthesia. *Br J Anaesth* 1996; **76:** 415–18.
3. Budd K. Tramadol. *Br J Anaesth* 1995; **75:** 500.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tramadol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Carbamazepine is reported to diminish the analgesic activity of tramadol by reducing serum concentrations.

The risk of seizures is increased if tramadol is used with other drugs that have the potential to lower the seizure threshold. See also Effects on the CNS, above.

Tramadol inhibits reuptake of noradrenaline and serotonin and enhances serotonin release and there is the possibility that it may interact with other drugs that enhance monoaminergic neurotransmission including lithium, tricyclic antidepressants, triptans, and SSRIs, thereby increasing the risk of serotonin syndrome; it should not be given to patients receiving MAOIs or within 14 days of their discontinuation.

Metabolism of tramadol is mediated by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Use with specific inhibitors of these enzymes may increase concentrations of tramadol and lower concentrations of its active metabolite. The clinical consequences of this effect are unclear although the risk of seizures or serotonin syndrome may be increased.

Anticoagulants. For reports of the effect of tramadol on oral anticoagulants, see Analgesics under Interactions of Warfarin, p. 1530.2.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of tramadol and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1.

5-HT$_3$-receptor antagonists. The pre-operative use of *ondansetron* has been noted to reduce the postoperative analgesic efficacy of tramadol.[1,2] In one study,[1] the cumulative dose of tramadol was up to 35% greater in those patients who also received ondansetron compared with those who received no antiemetic. In addition there was no difference in the incidence of postoperative nausea and vomiting between the two groups.

1. De Witte JL, *et al*. The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* 2001; **92:** 1319–21.
2. Arcioni R, *et al*. Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT$_3$ spinal receptor involvement in acute pain in humans. *Anesth Analg* 2002; **94:** 1553–7.

Pharmacokinetics

Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use and 100% after intramuscular injection. Plasma protein binding is about 20%. Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite *O*-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine as metabolites. Tramadol is widely distributed, crosses the placenta, and appears in small amounts in breast milk. The elimination half-life is about 6 hours.

References.

1. Karhu D, *et al*. Comparative pharmacokinetics of a once-daily tramadol extended-release tablet and an immediate-release reference product following single-dose and multiple-dose administration. *J Clin Pharmacol* 2010; **50:** 544–53.

Children. References.

1. Murthy BVS, *et al*. Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. *Br J Anaesth* 2000; **84:** 346–9.
2. Payne KA, *et al*. Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 years—a pilot study. *Anesth Prog* 2003; **49:** 109–12.
3. Zwaveling J, *et al*. Pharmacokinetics of rectal tramadol in postoperative paediatric patients. *Br J Anaesth* 2004; **93:** 224–7.
4. Garrido MJ, *et al*. Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res* 2006; **23:** 2014–23.
5. Saudan S, Habre W. Particularités pharmacologiques du tramadol chez l'enfant. *Ann Fr Anesth Reanim* 2007; **26:** 560–3.

The elderly. Pharmacokinetic parameters in elderly patients were found to be similar to those in younger patients.[1]

1. Likar R, *et al.* Pharmacokinetic and pharmacodynamic properties of tramadol IR and SR in elderly patients: a prospective, age-group—controlled study. *Clin Ther* 2006; **28:** 2022–39.

Metabolism. Production of the active metabolite *O*-desmethyltramadol is dependent on the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism.[1,2] For a reference to a debilitating CNS-mediated reaction in a patient who was an extensive metaboliser with high CYP2D6 activity, see Effects on the CNS, p. 140.1.

1. Poulsen L, *et al.* The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; **60:** 636–44.
2. Pedersen RS, *et al.* Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol* 2006; **62:** 513–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ana-Q; Calmador; Cloq; Nobligan; Trama-Klosidol; Tramal; Tramanovag; ***Austral.***: Durotram; Tradonal; Tramahexal; Tramal; Tramedo; Zydol; ***Austria***: Adamon; Contramal; Cromatodol; Noax Uno; Nobligan; Tradolan; Tramabene; Tramadolor; Tramal; Tramastad; Tramundal; ***Belg.***: Contramal; Doctramadol†; Dolzam; Tradonal; Tramium; ***Braz.***: Anangor; Dorless; Rapitram; Sensitram; Sylador; Timasen; Trabilin†; Tramaden; Tramadon; Tramal; Tramaliv; Zamadol; ***Canad.***: Durela; Ralivia; Tridural; Ultram; Zytram; ***Chile***: Manol; Minidol; Naxodol; Timarol; Tramal; Zaledor; Zodol; ***China***: An Tian (安田); Bei Pin (倍平); Bing Ning (冰宁); Da Ma Err (达吗尔); Feng Tong Ding (丰同叮); Hua Jie Wei (华捷威); Hua Qu (华曲); Jun Qing (君庆); Le Shi Pu Kang (乐施普康); Nao Tai (瑙泰); Qi Zhi (奇止); Qimaite (奇迈特); Qu Feng (曲芬); Qu Ming (区明); Qu Teng (曲腾); Qu Tong Kang (曲同康); Qutong (曲通); Rui Li Ping (瑞立平); Tai Mei Ding (泰美定); Ti Ma Er (替马尔); Tong Ting (通亭); Tramadolor (泰德洛); Tramal (舒敏); Tramcontin (奇曼丁); Xi Li Xi Meng (西利西蒙); Xiang Yang (祥阳); Yi Bang (宜邦); Yi Nuo Xing (依诺兴); Yin Jia (银加); Yu Tong (愈通); ***Cz.***: Mabron; Noax; Protradon; Tradef; Tralgit; Tramabene; Tramagit†; Tramal; Tramundin; ***Denm.***: Dolol; Gemadol; Mandolgin; Metracop†; Nobligan; Tadol; Tradolan; Tramium; ***Fin.***: Tradolan; Tramadin; Tramagetic†; Tramal; Trambo; Tramium; ***Fr.***: Biodalgic; Contramal; Monoalgic; Monocrixo; Monotramal; Orozamudol; Takadol; Topalgic; Trasedal†; Zamudol; Zumalgic; ***Ger.***: Amadol†; Jutadol†; T-long†; Trama†; Tramabeta; Tramadoc†; Tramadolor†; Tramagit; Tramal; Tramundin; Travex One; ***Gr.***: Oxxalgan; Tradol; Tramal; ***Hong Kong***: Mabron†; Sefmal; Tramal†; Tramo; ***Hung.***: Adamon; Contramal; Ralgen; Tramadolor; Tramalgic; ***India***: Acema; Adamon; Admadol; Amtadol; Anatram; Arrestadol; Atdol; Avdol; Bestodol; Bolodol; Bramadol; Cadol; Cemadol; CG-Mac; Contramal; Cormadol; Cradol; Damol; Decotram; Didol; Dol; Doleira; Dolodol; Dolomed-T; Dolotram; Dolriz; Dols; Dolstar; Doltel; Domadol; E-Dol; Eltram; Formador; FS; Gemodol; Haledol; Idol; Ivydol; Kamadol; Kevtram; Lagesic; Leedol; Madol; Medol; Meridol; Midol; Neutram; Nictram; Nobligan; Novadol; Opi-OT; Opiate; Orchidol; Ospidol; Painadol; Painex; Tramacip; Tramazac; TRD-Contin; Urgendol; ***Indon.***: Andalpha†; Bellatram†; Camigesik; Centrasic; Contram; Corsadol; Dolana; Dolgesik; Dolocap; Dolsic; Forgesic; Kamadol; Katrasic; Nonalges; Nufapotram; Orasic; Pinorec; Radol; Seminac; Simatral; Tlusic; Tradosik; Tradyl; Tragesik; Tramal; Trasik; Traumasik†; Trunal; Tugesal; Zephanal; Zumatram; ***Irl.***: Biodol; By-Madol; Tradol; Tramake; Tramapine; Tramex†; Troxidol; Xymel; Zamadol†; Zydol; ***Israel***: Trabar†; Trama; Tramadex; Tramal; ***Ital.***: Adamon; Contramal; Fortradol; Prontalgin; Tradonal; Traflash; Tralodie; Tramalin; Tramamed; Unitrama; Unitramarim; ***Jpn***: Tramal; ***Malaysia***: Acugesic; Analab; Domadol; Mabron; Pengesic; Sefmal; Trabilin; Tracidol; Tramada; Tramox; Tramundin; ***Mex.***: Durodor†; Nobligan; Prontofort; Tradol; Tralic; Tramed; Trexol; Veldrol; ***Neth.***: Doltard†; Theradol; Tradonal; Tramagetic; Tramajuna; Tramal; Tramazela†; Tramelene†; ***Norw.***: Nobligan; Tramagetic; ***NZ***: Durotram; Tramal; Tramedo†; Zytram; ***Philipp.***: Amaryll; Clomadol; Dolmal; Dolotral; Dolpaz; Doltrahex; Gesidol; Mardol; Microdol; Milador; MNS; Mosepan; Pengesic; Peptrad; Plazadol; Radol; Siverol; TDL; Tolma†; Tracaine; Tradomal; Tradonal; Tramadin; Tramal; Tramid; Tramkor; Tramundin; Unitral; Vistra; Vitral; ***Pol.***: Adamon; Noax Uno; Oratram; Poltram; Tramahexal; Tramal; Tramcod†; Tramundin; Travictol; ***Port.***: Dolpar†; Gelotralib; Nobligan; Paxilfar; Tramal; Tramy†; Travex; Tridural; Zydol; Zytram†; ***Rus.***: Mabron (Маброн); Plazadol (Плазадол); Sintradon (Синтрадон)†; Tradol (Традол); Tramaklosidol (Трамаклосидол); Tramal (Трамал); Tramolin (Трамолин); ***S.Afr.***: Dolotram; Domadol; Nobligan; Tramahexal; Tramal; Tramaspen; Tramazac; Tramgesic; ***Singapore***: Acugesic; Mabron; Pengesic; Sefmal; Tradol; Tramal; Tramium†; ***Spain***: Adolonta; Cepariding; Dolodol; Dolpar; Gelotradol; Nobligan†; Tioner; Tradonal; Zytram; ***Swed.***: Gemadol; Nobligan; Tiparol; Tradolan; Zamadol†; ***Switz.***: Dolotramine†; Ecodolor†; Trabar; Tradonal; Tramactil Uno; Tramal; Tramundin; ***Thai.***: Amanda; Ammitram†; Anadol; Analab; Mabron; Madol; Madola; Matradol; Millidol; Modsenal; Pacmadol; Paindol; Pharmadol; Ramadol; Rofy†; Sefmal; Tamolan; Tracine; Tradolgesic; Tradonal†; Tramada; Tramadil; Tramadon; Tramal; Tramamed; Tramax; Tramazac; Tramoda; Trasic; Traumed; Trosic; Vesnon; Volcidol; ***Turk.***: Contramal; Tramadolor; Ultramex; ***UK***: Dromadol†; Larapam; Mabron; Marol; Maxitram; Nobligan; Oldaram; Tilodol; Tradorec; Tramake; Tramquel; Tramulief; Zamadol; Zeridame; Zydol; ***Ukr.***: Tramalgin (Трамалгин)†; ***USA***: ConZip; Rybix; Ryzolt†; Ultram; ***Venez.***: Tramal.

Multi-ingredient Preparations. ***Arg.***: Calmador Plus; Cloq Plus; Trama-Klosidol Plus†; Tramacet; Tramal Plus; ***Austria***: Zaldiar; ***Belg.***: Pontalsic; Zaldiar; ***Braz.***: Paratram; Ultracet; ***Canad.***: Tramacet; ***Chile***: Analgex Sap; Cronus; Doloten; Minidol Plus; Naxodol Plus; Pramol†; Timarol-Par; Zafin; Zaldiar; Zaledor-P; ***China***: Keluoqu (克洛曲); Ultracet (及通安); ***Cz.***: Doreta; Partramec; Traparac; Zaldiar; ***Fr.***: Ixprim; Zaldiar; ***Ger.***: Dolevar†; Zaldiar; ***Gr.***: Zaldiar; ***Hong Kong***: Ultracet; ***Hung.***: Zaldiar; ***India***: Acema-P; Actidol-DP; Acuvin; Anatram-P; Anbrol; Arrestadol-P; Atdol Plus; Avdol-P; Bramadol-P; Cadol-P; Conac-PT; Cradol-P; Decotram-PD; Didol-D; Didol-P; Dolfen-P; Dolocet; Dols Plus; Dolwin-T; Domadol Plus; E-Dol Plus; Esgipyrin-T; Fentra; Freze; FS Plus; FS-D; Ibudol; Indolpara; Ingesic Forte; Kamadol-P; Kdol-P; Kevtram-DP; Kevtram-P; Leedol-P; Madol-P; Maxoflam-T; Meridol-D; Meridol; Miradol; Mortrin Compound; Movon-PT; Muzox; Neutram-P; Nictram Plus; Novadol-P; Novodol; Omodol; Opi-OT; Opiate-P; Opiate-PD; Oshdol; Osteodol; Otram; Painadol-P; Paratel-T; Tolydol; Tramacip Plus; Ultrazac; ***Indon.***: Patral; Ultracet; Zaldiar; ***Irl.***: Ixprim; ***Israel***: Zaldiar; ***Ital.***: Kolibri; Patrol; ***Jpn***: Tramcet; ***Malaysia***: Ultracet; ***Mex.***: Gammadol; Sinergix; Tramacet; Tremepen; Voydol-C; Zaldiar; ***Neth.***: Tilalgin†; Tramacet; Zaldiar; ***Philipp.***: Algesia; Cetodol; Cetra; Dolcet; ***Pol.***: Acutral; Doreta; Padolten; Poltram Combo; Zaldiar; ***Port.***: Tilalgin; Zaldiar; ***Rus.***: Forsodol (Форсодол); Zaldiar (Залдиар); ***S.Afr.***: Tramacet; ***Singapore***: Ultracet; ***Spain***: Pazital; Pontalsic; Zaldiar; ***Switz.***: Zaldiar; ***Thai.***: Ultracet; ***Turk.***: Zaldiar; ***UK***: Tramacet; ***Ukr.***: Zaldiar (Залдіар); ***USA***: Ultracet; ***Venez.***: Ultracet; Zaldiar.

Pharmacopoeial Preparations
BP 2014: Prolonged-release Tramadol Capsules; Prolonged-release Tramadol Tablets; Tramadol Capsules;
USP 36: Acetaminophen and Tramadol Hydrochloride Tablets; Tramadol Hydrochloride and Acetaminophen Oral Suspension; Tramadol Hydrochloride Extended-release Tablets; Tramadol Hydrochloride Oral Suspension; Tramadol Hydrochloride Tablets.

Trimeperidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimeperidina; Promedol (trimeperidine); Promedolum (trimeperidine); Trimeperidina, hidrocloruro de; Trimépéridine, Chlorhydrate de; Trimeperidini Hydrochloridum; Тримеперидина Гидрохлорид.
1,2,5-Trimethyl-4-phenyl-4-piperidyl propionate hydrochloride.
$C_{17}H_{25}NO_2$,HCl=311.8
CAS — 64-39-1 (trimeperidine); 125-80-4 (trimeperidine hydrochloride).

Profile

Trimeperidine hydrochloride is an opioid analgesic (p. 108.1) with actions and uses similar to those of pethidine (p. 121.3).

Trolamine Salicylate *(pINNM)*

Salicilato de trietanolamina; Salicilato de trolamina; Trietanolamina, salicilato de; Triethanolamine Salicylate; Trolamine, Salicylate de; Trolamini Salicylas; Троламина Салицилат.
$C_{13}H_{21}NO_6$=287.3
CAS — 2174-16-5.
UNII — H8O4040BHD.

Pharmacopoeias. In *US.*

USP 36: (Trolamine Salicylate). A compounded mixture of trolamine and salicylic acid in propylene glycol. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers in a cool place.

Profile

Trolamine salicylate is a salicylic acid derivative used similarly to methyl salicylate (p. 92.1) in topical rubefacient preparations in a concentration of 10 to 20% for the relief of muscular and rheumatic pain. It has also been used as a sunscreen.

Percutaneous absorption. In contrast to methyl salicylate, which undergoes considerable absorption and produces high subcutaneous and dermal concentrations of salicylic acid after application to intact skin, concentrations of salicylic acid after topical application of trolamine salicylate were substantially lower in tissue[1] and undetectable in serum.[2]

1. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350:** 636.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topically applied salicylate derivatives. *Ann Pharmacother* 1996; **30:** 935–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dencorub Arthritis; Goanna Arthritis Cream; Metsal AR Analgesic; ***Canad.***: Actiflex†; Analgesic Cream; Aspercreme; Bengay Muscle Pain No Odor; Myoflex; Rub A-535 Antiphlogistine No Odour; ***Mex.***: Myoflex†; ***Singapore***: Metsal AR Analgesic; ***Spain***: Bexidermil; ***USA***: Analgesia Creme; Analgesic Creme; Aspercreme; Coppertone Tan Magnifier; Flex-Power Performance Sports; Mobisyl; Myoflex; Sportscreme; Tropical Blend Tan Magnifier.

Multi-ingredient Preparations. ***Austral.***: Metsal Analgesic; ***Canad.***: Rub A-535 Extra Strength Arthritis.

Ufenamate *(rINN)*

Butyl Flufenamate; Ufénamate; Ufenamato; Ufenamatum; Уфенамат.
Butyl *N*-(α,α,α-trifluoro-*m*-tolyl)anthranilate.
$C_{18}H_{18}F_3NO_2$=337.3
CAS — 67330-25-0.
UNII — 8Z7O7C1SLZ.

Profile

Ufenamate is an NSAID (p. 102.3) that has been used topically in inflammatory skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Combec; Fenazol.

Valdecoxib *(BAN, USAN, rINN)*

SC-65872; Valdécoxib; Valdecoxibum; Valdekoksib; Вальдекоксиб.
p-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide.
$C_{16}H_{14}N_2O_3S$=314.4
CAS — 181695-72-7.
ATC — M01AH03.
ATC Vet — QM01AH03.
UNII — 2919279Q3W.

Profile

Valdecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally in the treatment of osteoarthritis and rheumatoid arthritis, and for the pain of dysmenorrhoea. The risk of serious skin reactions with valdecoxib (see below), in addition to its cardiovascular adverse effects (see below), prompted its general withdrawal worldwide in April 2005.

Effects on the cardiovascular system. The short-term use of parecoxib and valdecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those who had received intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days. Those patients who received oral valdecoxib only for 7 days postoperatively had a non-significant increase in risk for adverse cardiovascular effects.

The adverse cardiovascular effects associated with valdecoxib treatment were one of the reasons the drug was generally withdrawn in April 2005.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352:** 1081–91.

Effects on the skin. Toxic epidermal necrolysis developed in a patient who took valdecoxib for 8 days, despite stopping the drug at the first signs of a rash and starting treatment with oral prednisolone;[1] the patient had a history of hypersensitivity to sulfonamides. Health Canada[2] noted in January 2004 that it had received 5 reports of serious cutaneous adverse reactions associated with valdecoxib over less than 1 year from marketing of the drug in December 2002. However, none of these were erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis although such reactions had been reported to other regulatory authorities. In December 2004, the EMEA[3] stated that it had received reports of all 3 reactions, as well as exfoliative dermatitis; most of them had occurred within the first 2 weeks of starting treatment and the incidence rate appeared greater for valdecoxib than other selective cyclo-oxygenase-2 (COX-2) inhibitors. The EMEA also noted that use of parecoxib (a prodrug of valdecoxib, see p. 119.3) had been associated with serious skin reactions.

The increased risk of serious skin reactions with valdecoxib treatment was one of the reasons the drug was generally withdrawn in April 2005.

1. Glasser DL, Burroughs SH. Valdecoxib-induced toxic epidermal necrolysis in a patient allergic to sulfa drugs. *Pharmacotherapy* 2003; **23:** 551–3.
2. Health Canada. Valdecoxib (Bextra): severe cutaneous reactions. *Can Adverse React News* 2004; **14** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1-eng.pdf (accessed 29/08/08)
3. EMEA. EMEA public statement on valdecoxib (Bextra/Valdyn) and parecoxib sodium (Dynastat/Rayzon): cardiovascular risks in coronary artery bypass graft (CABG) surgery and serious adverse skin reactions (issued 15th December, 2004). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/20480204en.pdf (accessed 29/08/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Bioval; Creval; Leap; Mobyle-V; Nizox; Osra; Oval; Valdiff; Valdixx; Valdone; Valus.

Multi-ingredient Preparations. ***India***: Nizox-MR; Vectra-P.

Vedaprofen *(BAN, USAN, rINN)*

CERM-10202; PM-150; Vedaprofeeni; Védaprofène; Vedaprofeno; Vedaprofenum; Ведапрофен.

(±)-4-Cyclohexyl-α-methyl-1-naphthaleneacetic acid.

$C_{19}H_{22}O_2$=282.4

CAS — 71109-09-6.

ATC Vet — QM01AE90.

UNII — OKX88EO7OI.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Vedaprofen for Veterinary Use; Vedaprofen BP (Vet) 2014). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in acetone; it dissolves in dilute solutions of alkali hydroxides.

Profile

Vedaprofen, a propionic acid derivative, is an NSAID (p. 102.3) used in veterinary medicine for the treatment of inflammation and pain.

Viminol Hydroxybenzoate *(rINNM)*

Diviminol Hydroxybenzoate; Hidroxibenzoato de viminol; Viminol, hidroxibenzoato de; Viminol, Hydroxybenzoate de; Viminoli Hydroxybenzoas; Z-424 (viminol); Виминола Гидроксибензоат.

1-[1-(2-Chlorobenzyl)pyrrol-2-yl]-2-(di-*sec*-butyl)aminoethanol 4-hydroxybenzoate.

$C_{21}H_{31}ClN_2O.C_7H_6O_3$=501.1

CAS — 21363-18-8 (viminol); 21466-60-4 (viminol hydroxybenzoate); 23784-10-3 (viminol hydroxybenzoate).

ATC — N02BG05.

ATC Vet — QN02BG05.

Profile

Viminol hydroxybenzoate has analgesic and antipyretic properties. The equivalent of 400 mg daily of viminol has been given orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Dividol; ***Ital.***: Dividol.

Zaltoprofen *(rINN)*

CN-100; Zaltoprofène; Zaltoprofeno; Zaltoprofenum; ZC-102; Зальтопрофен.

(±)-10,11-Dihydro-α-methyl-10-oxodibenzo[*b*,*f*]thiepin-2-acetic acid.

$C_{17}H_{14}O_3S$=298.4

CAS — 89482-00-8.

UNII — H8635NG3PY.

NOTE. The names Borbit, Peleton, Peon, Salafapinon, Soleng, Soluirubin, and Zatferon have been used as trade marks for zaltoprofen.

Pharmacopoeias. In *Jpn*.

Profile

Zaltoprofen is an NSAID (p. 102.3) that has been given in an oral dose of 80 mg three times daily for pain and musculoskeletal and joint disorders.

References.

1. Ishizaki T, *et al.* Pharmacokinetic profile of a new nonsteroidal anti-inflammatory agent, CN-100, in humans. *Drug Invest* 1991; **3:** 1–7.
2. Hatori M, Kokubun S. The long-term efficacy and tolerability of the new anti-inflammatory agent zaltoprofen in rheumatoid arthritis. *Curr Med Res Opin* 1998; **14:** 79–87.
3. Hase K, *et al.* The effect of zaltoprofen on physiotherapy for limited shoulder movement in breast cancer patients: a single-blinded before-after trial. *Arch Phys Med Rehabil* 2006; **87:** 1618–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Soleton.

Ziconotide *(USAN, rINN)*

CI-1009; SNX-111; ω-Conotoxin M VIIA; Ziconotida; Ziconotidum; Зиконотид.

L-Cysteinyl-L-lysylglycyl-L-lysylglycl-L-alanyl-L-lysyl-L-cysteinyl-L-seryl-L-arginyl-L-leucyl-L-methionyl-L-tyrosyl-L-α-aspartyl-L-cysteinyl-L-cysteinyl-L-threonylglycyl-L-seryl-L-cysteinyl-L-arginyl-L-serylglycyl-L-lysyl-L-cysteinamide cyclic(1→16),(8→20),(15→25)-tris(disulfide).

$C_{102}H_{172}N_{36}O_{32}S_7$=2639.1

CAS — 107452-89-1.

ATC — N02BG08.

ATC Vet — QN02BG08.

UNII — 7I64C51O16.

Ziconotide Acetate *(rINNM)*

Acetato de ziconotida; Ziconotide, Acétate de; Ziconotidi Acetas; Зиконотида Ацетат.

$C_{102}H_{172}N_{36}O_{32}S_7$, $C_2H_4O_2$=2699.2

ATC — N02BG08.

ATC Vet — QN02BG08.

UNII — T2I226K69M.

Uses and Administration

Ziconotide is a synthetic form of a peptide derived from the venom of the cone shell *Conus magus* (a sea snail). It is reported to be an N-type (neurone-specific) calcium-channel blocker. Ziconotide is given as a continuous intrathecal infusion in the management of severe chronic pain in patients who are intolerant of or refractory to more conventional treatments (see Choice of Analgesic, p. 4.2).

Ziconotide is given intrathecally as the acetate; doses may be expressed in terms of the base or the acetate. In the EU, the initial licensed dose (expressed in terms of the base) is 2.4 micrograms daily adjusted according to response, in increments of up to 2.4 micrograms, to a maximum daily dose of 21.6 micrograms. It is recommended that the interval between dose increases is at least 2 days. In the USA, the initial licensed dose (expressed in terms of the acetate) should be no more than 2.4 micrograms daily, adjusted according to response. Dose increases of up to 2.4 micrograms two or three times a week are permitted, over a period of at least 3 weeks, up to a maximum daily dose of 19.2 micrograms.

References.

1. Wermeling D, *et al.* Pharmacokinetics and pharmacodynamics of intrathecal ziconotide in chronic pain patients. *J Clin Pharmacol* 2003; **43:** 624–36.
2. Staats PS, *et al.* Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA* 2004; **291:** 63–70.
3. Rauck RL, *et al.* A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage* 2006; **31:** 393–406.
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9. Kapural L, *et al.* Intrathecal ziconotide for complex regional pain syndrome: seven case reports. *Pain Pract* 2009; **9:** 296–303.
10. Rauck RL, *et al.* Intrathecal ziconotide for neuropathic pain: a review. *Pain Pract* 2009; **9:** 327–37.
11. Kress HG, *et al.* Intrathecal therapy: what has changed with the introduction of ziconotide. *Pain Pract* 2009; **9:** 338–47.
12. Schmidtko A, *et al.* Ziconotide for treatment of severe chronic pain. *Lancet* 2010; **375:** 1569–77.

Adverse Effects and Precautions

The most common adverse effects reported with ziconotide have included dizziness, nausea and vomiting, nystagmus, abnormal gait, blurred vision, headache, elevated creatine kinase levels, and asthenia. Cognitive impairment, particularly confusion and impaired memory, is also very common, and typically develops after several weeks of treatment. Severe CNS symptoms such as hallucinations, paranoid reactions, speech disorders, aphasia, and decreased alertness may occur but convulsions, stroke, delirium, encephalopathy, and coma have been reported less commonly. Creatine kinase may be elevated, and monitoring of blood concentrations is recommended, but clinical myopathy or rhabdomyolysis is uncommon. Ziconotide may cause or exacerbate depression. Patients with a history of psychosis should not be treated with ziconotide.

References.

1. Penn RD, Paice JA. Adverse effects associated with the intrathecal administration of ziconotide. *Pain* 2000; **85:** 291–6.

Effects on mental state. Suicidal ideation has been reported in 2 patients receiving intrathecal ziconotide for the severe chronic pain.[1] One patient committed suicide; the other, who had a history of depression, showed a moderate improvement in her depressive symptoms after stopping ziconotide.

1. Maier C, *et al.* Increased risk of suicide under intrathecal ziconotide treatment? — A warning. *Pain* 2011; **152:** 235–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Prialt; ***Cz.***: Prialt; ***Denm.***: Prialt; ***Fr.***: Prialt; ***Ger.***: Prialt; ***Gr.***: Prialt; ***Hung.***: Prialt; ***Irl.***: Prialt; ***Ital.***: Prialt; ***Neth.***: Prialt; ***Norw.***: Prialt†; ***Pol.***: Prialt; ***Port.***: Prialt; ***Spain***: Prialt; ***Swed.***: Prialt; ***Switz.***: Prialt; ***UK***: Prialt; ***USA***: Prialt.

Anthelmintics

Ancylostomiasis, p. 145
Angiostrongyliasis, p. 145
Ascariasis, p. 145
Capillariasis, p. 145
Clonorchiasis, p. 145
Cutaneous larva migrans, p. 145
Cysticercosis, p. 146
Diphyllobothriasis, p. 146
Dracunculiasis, p. 146
Echinococcosis, p. 146
Enterobiasis, p. 146
Fascioliasis, p. 147
Fasciolopsiasis, p. 147
Gnathostomiasis, p. 147
Heterophyiasis, p. 147
Hookworm infections, p. 147
Hymenolepiasis, p. 147
Intestinal fluke infections, p. 147
Liver fluke infections, p. 147
Loiasis, p. 147
Lung fluke infections, p. 147
Lymphatic filariasis, p. 148
Mansonella infections, p. 148
Metagonimiasis, p. 148
Nanophyetiasis, p. 148
Necatoriasis, p. 148
Onchocerciasis, p. 148
Opisthorchiasis, p. 149
Paragonimiasis, p. 149
Schistosomiasis, p. 149
Strongyloidiasis, p. 149
Syngamosis, p. 149
Taeniasis, p. 149
Toxocariasis, p. 149
Trichinosis, p. 150
Trichostrongyliasis, p. 150
Trichuriasis, p. 150

This chapter describes the important helminth or worm infections that occur in man (see Table 1, p. 144) and the anthelmintics used to treat them.

Choice of Anthelmintic

Helminth infections are among the most common infections in man, affecting a large proportion of the world's population, mainly in tropical regions. In developing countries they pose a large threat to public health, and contribute to the prevalence of malnutrition, anaemia, eosinophilia, and pneumonia. Helminth infections causing severe morbidity include lymphatic filariasis (a cause of elephantiasis), onchocerciasis (river blindness), and schistosomiasis (bilharziasis). These infections can affect the majority of populations in endemic areas with major economic and social consequences. WHO is making strenuous efforts to control a number of these infections in endemic areas. Control of these infections in both individuals and populations depends not only on the use of chemotherapeutic agents but also on preventing transmission by advice on food preparation and hygiene, the provision of adequate sanitation and sewage treatment (especially where sewage is used as fertiliser), the provision of safe potable water supplies, and effective vector control.

The worms that cause infection in man generally fall either into the phylum Nematoda, which includes the nematodes or roundworms, or into the phylum Platyhelminthes, which includes the cestodes or tapeworms and the trematodes or flukes.

The **nematodes** (or roundworms) are a large group of worms, some of which are capable of producing infections in man. In many cases man is the primary (definitive) host but human infections caused by parasites for which animals are the primary hosts also occur. Nematodes do not generally multiply in man; strongyloidiasis is an exception as re-infection can occur without environmental re-exposure. Nematode infections are most common in warm, moist climates, but some species of nematode can tolerate cool or arid conditions and infective forms can persist in the environment for long periods. An understanding of the life cycle of the infective species is necessary for diagnostic tests to be made at appropriate times, usually to coincide with the infective stage of the cycle, and for the choice of appropriate control measures.

The nematode infections can be divided into filarial infections, intestinal infections, and tissue infections.

Filarial nematodes are endemic in large areas of the tropics and produce considerable morbidity. The adult worms may live for several years, releasing large numbers of motile embryos known as microfilariae into the blood or skin, depending on the species. Transmission is usually by biting insects, which form the intermediate host. In some endemic areas multiple infections with filarial nematodes are common.

Filarial nematode infections include:
- loiasis, p. 147.3
- lymphatic filariasis, p. 148.1
- mansonella infections, p. 148.2
- onchocerciasis, p. 148.3.

Intestinal nematode infections (roundworms) are very common especially in developing countries in the tropics and subtropics. Children are particularly at risk and these infections contribute to morbidity through malnutrition, vitamin deficiencies, diarrhoea, anaemia, and pneumonia. Poor sanitation and sewage disposal perpetuate infections with soil-borne nematodes. Often several different worm infections are endemic in the same region, resulting in mixed infections. When this occurs, broad-spectrum anthelmintics may be used to reduce the overall infection burden in the population (see under Ascariasis, p. 145.2).

Intestinal nematode infections include:
- angiostrongyliasis, p. 145.2
- ascariasis, p. 145.2
- capillariasis, p. 145.3
- enterobiasis, p. 146.3
- hookworm infections, p. 147.1
- strongyloidiasis, p. 149.2
- trichostrongyliasis, p. 150.1
- trichuriasis, p. 150.1.

The *tissue nematodes* represent a miscellaneous group causing a variety of pathological conditions in man. In cutaneous larva migrans and toxocariasis, the nematodes have a primary animal host and the human disease is caused by infection with infective larvae which do not subsequently mature in man. Trichinosis and gnathostomiasis affect some carnivorous animals and man is an incidental host. Syngamosis is mainly an infection of domestic fowl and wild birds although infection in man has been reported rarely. In dracunculiasis, man is the primary (definitive) host. Although these diseases are not generally fatal they cause a considerable degree of morbidity and treatment is complicated by the lack of effective, non-toxic systemic anthelmintics.

Tissue nematode infections include:
- angiostrongyliasis, p. 145.2
- cutaneous larva migrans, p. 145.3
- dracunculiasis, p. 146.2
- gnathostomiasis, p. 147.1
- syngamosis, p. 149.3
- toxocariasis, p. 149.3
- trichinosis, p. 150.1.

The **cestodes** (flatworms, segmented worms, or tapeworms) cause infection in man in most parts of the world. Man may be the primary host, harbouring the adult worm in the intestine, or an intermediate host carrying the larval form. With the exception of *Hymenolepis nana* the adult worms do not usually multiply within the same host. However, larval forms may be produced and, as with infection or ingestion of these forms, systemic infection may develop.

Cestode infections include:
- cysticercosis, p. 146.1
- diphyllobothriasis, p. 146.2
- echinococcosis, p. 146.3
- hymenolepiasis, p. 147.2
- taeniasis, p. 149.3.

Trematode (or fluke) infections are caused by parasitic worms of the class Trematoda. There are 4 categories of fluke which are pathogenic in man; the blood flukes *Schistosoma* spp., the intestinal flukes *Fasciolopsis, Heterophyes, Metagonimus,* and *Nanophyetus* spp., the liver flukes *Clonorchis, Fasciola,* and *Opisthorchis* spp., and the lung flukes *Paragonimus* spp. Symptoms are usually only seen in heavy infections and commonly include fever, pain, and eosinophilia.

Trematode infections include:
- intestinal fluke infections, p. 147.2
- liver fluke infections, p. 147.3
- lung fluke infections, p. 147.3
- schistosomiasis, p. 149.1.

Ancylostomiasis

For infections caused by *Ancylostoma duodenale* see under Hookworm Infections, p. 147.1. Larvae of *Ancylostoma* spp. (usually *A. braziliense* and *A. caninum*) are also a cause of cutaneous larva migrans (see p. 145.3).

Angiostrongyliasis

Angiostrongyliasis[1,2] is due to accidental infection with species of the animal nematode *Angiostrongylus*. Infection may cause eosinophilic meningitis or abdominal angiostrongyliasis depending on the infecting species:
- **eosinophilic meningitis** is due to infection with *A. cantonensis*, the rat lungworm. Humans are infected by eating raw or undercooked snails or slugs, crustaceans, or contaminated vegetables. Although cases have been reported worldwide, most cases have been reported from endemic areas such as south Asia, Australia, and the Pacific and Caribbean Islands. Clinical symptoms are caused by the presence of larvae in the brain and by local host reactions. The disease is generally self-limiting but a minority of patients may develop severe encephalitis, coma, and death. Eye involvement is very rare and causes permanent visual impairment and a wide range of ocular inflammations (such as retinitis or optic neuritis).
- **abdominal angiostrongyliasis** is caused by infection with *A. costaricensis*. Cases have been reported from Central and South America and it most commonly occurs in young children after ingestion of vegetables contaminated by infected slugs. Abdominal angiostrongyliasis mimics appendicitis, with eosinophilia.

No drug treatment has been proven to be effective for the treatment of angiostrongyliasis. However, most patients infected with either species have a self-limiting course and recover completely.[3] Treatment of *A. cantonensis* infection is controversial, but symptomatic treatment with analgesics and removal of CSF to relieve pressure in the brain is usually recommended.[1-4] Treatment with corticosteroids for 2 weeks has been reported to be beneficial[5] and is considered reasonable,[1,5] although some studies have not reported benefit.[3] Anthelmintics are usually not recommended because of their potential to exacerbate neurological symptoms by release of antigens after the death of the parasite,[2] however, an anthelmintic (preferably albendazole or alternatively mebendazole), with or without a corticosteroid, may reduce the duration of headaches in patients with meningitis.[1-4,6] Praziquantel with a corticosteroid has also been tried.[4] Surgical removal or laser therapy has been tried in patients with ocular angiostrongyliasis but did not improve the patients visual acuity;[2] corticosteroids may be given in those patients who have eosinophilic meningitis with ocular angiostrongyliasis or other ocular inflammations.[2]

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Sawanyawisuth K, Sawanyawisuth K. Treatment of angiostrongyliasis. *Trans R Soc Trop Med Hyg* 2008; **102:** 990–6.
3. Ramirez-Avila L, *et al.* Eosinophilic meningitis due to Angiostrongylus and Gnathostoma species. *Clin Infect Dis* 2009; **48:** 322–7.
4. Wang QP, *et al.* Human angiostrongyliasis. *Lancet Infect Dis* 2008; **8:** 621–30.
5. Chotmongkol V, *et al.* Corticosteroid treatment of eosinophilic meningitis. *Clin Infect Dis* 2000; **31:** 660–2.
6. Chotmongkol V, *et al.* Treatment of eosinophilic meningitis with a combination of prednisolone and mebendazole. *Am J Trop Med Hyg* 2006; **74:** 1122–4.

Ascariasis

Ascariasis is an infection caused by *Ascari's lumbricoides*, the common or giant roundworm. It is commonly found in the tropics and especially in rural areas. On ingestion of mature eggs the larvae hatch and penetrate the intestinal wall. They migrate in the bloodstream via the liver to the lungs where they enter the alveoli. The larvae then move up the bronchial tree and are swallowed. The mature adult develops in the intestines, and it has been estimated that gravid females are produced about 2 months after infection. Eggs are excreted in the faeces and can remain viable in

Table 1. Helminths: classification and diseases.

Group	Helminth	Common Name	Clinical infection
Nematodes (filarial)	*Brugia malayi*		lymphatic filariasis (Malayan, brugian)
	Brugia timori		lymphatic filariasis (Timorian, brugian)
	Loa loa	eye-worm	loiasis
	Mansonella spp.		Mansonella infections
	Onchocerca volvulus		onchocerciasis (river blindness)
	Wuchereria bancrofti		lymphatic filariasis (bancroftian)
Nematodes (intestinal)	*Ancylostoma duodenale*	Old World hookworm	ancylostomiasis
	Angiostrongylus costaricensis		angiostrongyliasis
	*Ascaris lumbricoides**	common roundworm, giant roundworm	ascariasis
	Capillaria philippinensis		capillariasis
	*Enterobius vermicularis**	threadworm, pinworm	enterobiasis
	Necator americanus	New World hookworm	necatoriasis
	Strongyloides stercoralis	sometimes called threadworm in USA	strongyloidiasis
	Trichostrongylus spp.		trichostrongyliasis
	*Trichuris trichiura**	whipworm	trichuriasis
Nematodes (tissue)	*Ancylostoma* spp. (usually *A. braziliense* and *A. canium*)	dog/cat hookworm	cutaneous larva migrans (creeping eruption)
	Angiostrongylus cantonensis		angiostrongyliasis
	Dracunculus medinensis	guinea-worm	dracunculiasis (dracontiasis)
	Gnathostoma spinigerum		gnathostomiasis
	Syngamus spp.	gapeworm	syngamosis
	Toxocara spp.*		toxocariasis (visceral larva migrans, ocular larva migrans)
	*Trichinella spiralis**		trichinosis (trichinellosis)
Cestodes (tapeworms)	*Diphyllobothrium latum*	broad fish tapeworm	diphyllobothriasis
	Echinococcus spp.		echinococcosis (hydatid disease)
	Hymenolepis nana	dwarf tapeworm	hymenolepiasis
	*Taenia saginata**	beef tapeworm	taeniasis
	*Taenia solium**	pork tapeworm	cysticercosis (larval form), taeniasis (adult worm)
Trematodes (flukes)	*Clonorchis sinensis*	Chinese liver fluke	clonorchiasis
	Fasciola hepatica	liver fluke	fascioliasis
	Fasciolopsis buski	intestinal fluke	fasciolopsiasis
	Heterophyes heterophyes	intestinal fluke	heterophyiasis
	Metagonimus yokogawi	intestinal fluke	metagonimiasis
	Nanophyetus salmincola	intestinal fluke	nanophyetiasis
	Opisthorchis spp.	liver fluke	opisthorchiasis
	Paragonimus spp.	oriental lung fluke	paragonimiasis
	Schistosoma spp.	blood fluke	schistosomiasis (bilharziasis)

NOTE: Infections due to worms marked with an asterisk may occur in temperate climates. Infections due to other worms are generally limited to tropical or localised areas, but may occur in travellers who have visited those areas.

moist soil for several years. The life span of the adult worm is 1 to 2 years.

Ascariasis may be asymptomatic or intestinal infection may produce anorexia, abdominal pain, and diarrhoea; nutritional deficiency may result. The pulmonary stage may result in pneumonitis and bronchospasm, often accompanied by eosinophilia. Heavy infections can cause intestinal or biliary obstruction. Migration of the worm from the small intestine can rarely cause serious ectopic infection of the genito-urinary tract, lungs, liver, or heart.

Treatment is with a benzimidazole carbamate derivative such as albendazole or mebendazole[1-3] with both drugs being equally highly effective. Pyrantel embonate[3] and levamisole are alternatives, while the potential of nitazoxanide for the treatment of ascariasis is being investigated.[1] Ivermectin has also been used.[2] Such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Drugs such as tiabendazole with little or no activity against *Ascaris* should be avoided for the initial treatment of mixed infections since they may stimulate the worm to migrate to a different body site.

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease.[1] WHO recommends[4] the use of albendazole or mebendazole or alternatively levamisole or pyrantel targeted at preschool and school-age children, women of child-bearing age (including pregnant women in the second and third trimesters and lactating women), and adults engaged in high-risk occupations for soil-transmitted helminthiasis, such as tea-pickers and miners. Children less than 1 year of age and women in the first trimester of pregnancy are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence and intensity of infection among school-age children.

1. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; **367:** 1521–32.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.
4. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 27/08/09)

Capillariasis

Capillariasis is caused by infection with *Capillaria philippinensis*, a nematode endemic in the Philippines and southern Thailand. Infection in man is through eating raw or undercooked freshwater fish containing infective larvae. The larvae mature in the intestines and the adults produce both eggs and infective larvae so that auto-infection occurs and heavy infections can result. Symptoms are mostly gastrointestinal, with abdominal pain, vomiting, and severe prolonged diarrhoea leading to cachexia and muscle wasting. The infection has a mortality rate of between 20 and 30% if untreated. Prolonged treatment with mebendazole for 20 days[1] for new cases and 30 days for relapsed cases or, alternatively, albendazole for 10 days,[1] is necessary. Single oral doses of mebendazole are given 4 times a year as part of mass treatment control programmes.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Clonorchiasis

See under Liver Fluke Infections, p. 147.3.

Cutaneous larva migrans

Cutaneous larva migrans (creeping eruption)[1-4] occurs when man becomes accidentally infected with the larvae of animal hookworms, usually *Ancylostoma braziliense* or *A. caninum*, hookworms of cats and dogs. Other hookworms may also be involved or may cause other infections (see Hookworm Infections, p. 147.1).

Infection with *Gnathostoma spinigerum* or *Strongyloides stercoralis* can also cause cutaneous larva migrans (see Gnathostomiasis p. 147.1 and Strongyloidiasis, p. 149.2). Ocular and visceral larva migrans are features of toxocariasis (see p. 149.3) and gnathostomiasis.

The larvae penetrate the skin and then migrate causing characteristic trails in the skin sometimes with bullous lesions or folliculitis. This migration can persist for several months and can be a source of intense pruritus. Animal hookworm larvae cannot generally penetrate deeper tissues in humans, although there are rare reports of larvae migrating to the lungs causing eosinophilia and pulmonary symptoms. Secondary bacterial infections occur in about 8% of those infected.

Cutaneous larva migrans is a self-limiting condition and without any treatment, most cases will resolve within 2 to 8 weeks.[1,2] However, treatment with anthelmintics may shorten the disease course, ease pruritus and lead to resolution of skin tracks within 1 week. The drug of choice is ivermectin and cure rates after a single oral dose range from 77 to 100%.[4] If the initial treatment fails or the patient relapses, 1 or 2 repeat doses may be given.[2,4] Repeat treatments may also be required in hookworm folliculitis.[4] Oral albendazole daily for 3 to 5 days is an alternative;[1,4] treatment for 5 to 7 days showed cure rates of 92 to 100%.[4] Tiabendazole, given orally for 2 to 4 days, was formerly widely used; however, since both ivermectin and albendazole have better efficacy and less adverse events than tiabendazole, its use is not now recommended.[4] Albendazole (10%)[2] or tiabendazole (10 to 15%)[1,4] can also be applied topically 2 to 3 times a day for 5 to 10 days, but may be of limited value for multiple lesions and hookworm folliculitis.[1,4] Freezing with liquid nitrogen or carbon dioxide is not effective because the larva is usually located a few centimetres beyond the visible end of the trail.[1,2,4]

1. Caumes E. Treatment of cutaneous larva migrans. *Clin Infect Dis* 2000; **30:** 811–14.
2. Hochedez P, Caumes E. Hookworm-related cutaneous larva migrans. *J Travel Med* 2007; **14:** 326–33.
3. Bowman DD, *et al.* Hookworms of dogs and cats as agents of cutaneous larva migrans. *Trends Parasitol* 2010; **26:** 162–7.
4. Heukelbach J, Feldmeier H. Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. *Lancet Infect Dis* 2008; **8:** 302–9.

Cysticercosis

Infection with the pork tapeworm, *Taenia solium* may result in taeniasis (intestinal infection with adult tapeworms—see p. 149.3) or cysticercosis (tissue infection with larval forms). Cysticercosis may develop after ingestion of *T. solium* eggs in food or water contaminated with infected human faecal material, or as a result of auto-infection in intestinal carriers of adult tapeworms. Ingested eggs release larvae that may penetrate the intestinal wall to be carried via the bloodstream to skeletal muscles, heart, eyes, brain, and spinal cord where they form encapsulated cysts (cysticerci). Human cysticercosis is associated with poverty and endemic in areas where hygiene is poor and sanitation inadequate.

Infection is typically subclinical, but symptoms may develop when the encysted larvae die and elicit an inflammatory reaction. Clinical features depend on the number, size, location, and stage of development of the cysticerci, as well as on the host's immune response. Cysts in the CNS (**neurocysticercosis**) may result in seizures and headaches, and are a common cause of epilepsy in endemic areas. Other symptoms include confusion, attention deficit, and ataxia. Hydrocephalus and intracranial hypertension may result from obstruction of CSF flow. Cysts in the spinal cord, eyes, or heart may also cause serious morbidity.

The need for and approach to **treatment** of neurocysticercosis differs depending on factors such as the location, stage of evolution, and number of cysts, as well as the degree of inflammation and severity of symptoms.[1,2] Seizures are managed with antiepileptics; these can usually be stopped once patients have been seizure-free for more than 2 years.[3]

The use of anthelmintics in the treatment of neurocysticercosis remains controversial.[3-6] Live cysticerci usually do not provoke seizures whereas dead or dying

parasites can elicit an inflammatory response, seizures, and transient neurological effects, hence treatment does not necessarily reduce seizure frequency. Patients with viable or degenerating parenchymal cysts and those with extraparenchymal cysts (such as subarachnoid cysts, including giant cysts and racemose forms) may, however, benefit from anthelmintics.[3,5,7] Anthelmintics are of little or no benefit in patients with inactive, calcified lesions, and are contra-indicated in patients with cysticercotic encephalitis as they may exacerbate intracranial hypertension.[3,4] A double-blind, placebo-controlled study in patients with seizures due to viable parenchymal cysts confirmed that albendazole therapy (with dexamethasone) was safe and decreased the burden of parasites and the number of generalised seizures.[8] Albendazole is now considered to be the drug of choice,[2,9,10] but praziquantel may also be used.[2,3,7,10] High doses of the chosen anthelmintic should be given for a minimum of 8 days, but those with extraparenchymal cysts may need longer and multiple treatment courses.[1,10]

Adjunctive corticosteroids are recommended for parenchymal infections[6] if there are many cysts, or if neurological symptoms or intracranial hypertension develop after starting treatment. Patients with subarachnoid cysticercosis should also be given adjunctive corticosteroids,[4] and some favour use in almost all patients.[2] However, use of corticosteroids with praziquantel may be complicated by a pharmacokinetic interaction— see Corticosteroids, under Interactions of Praziquantel p. 166.3 for further details. If hydrocephalus is present, surgical removal of cysts or ventricular shunting may be indicated.[2,3] Detailed consensus guidelines for the treatment of neurocysticercosis have been developed.[4]

Prevention of infection with *T. solium* is possible by avoiding ingestion of undercooked pork and food and water contaminated with human faeces. Ideally, prevention measures should include adequate sanitation, sewage treatment, and abattoir inspection. Those already infected with *T.solium* and their close contacts should be treated with anthelmintics in order to interrupt or reduce the cycle of direct person-to-person transmission. Universal or selected treatment of human taeniasis with praziquantel has significantly reduced the prevalence in areas where *T. solium* infection is endemic.[5,11]

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10. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
11. WHO. *Control of neurocysticercosis*. Geneva: WHO, 2003. Also available at: http://apps.who.int/gb/archive/pdf_files/WHA56/ea5610.pdf (accessed 29/07/10)

Diphyllobothriasis

Diphyllobothriasis[1,2] is an intestinal infection with the fish tapeworm *Diphyllobothrium latum* and other *Diphyllobothrium* spp. and is acquired in man through ingestion of raw, infected, freshwater fish. The infection is rarely symptomatic. However, because the adult worm competes for vitamin B_{12}, some patients may develop megaloblastic anaemia with its associated neurological symptoms. Concentrations of other vitamins may also be reduced. Occasionally, infection may cause acute abdominal pain and intestinal obstruction; rarely migration of proglottids (segments) can cause cholangitis or cholecystitis.

Treatment is with a single dose of praziquantel; niclosamide is an alternative.[3] Vitamin supplements should also be given to correct any deficiencies.

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Dracunculiasis

Dracunculiasis (dracontiasis, guinea-worm infection)[1-4] is caused by infection with the nematode *Dracunculus medinensis*. It has been endemic in parts of Africa and Asia, but attempts are being made to eradicate it and during 2010 only 1797 cases were reported, the majority from the Sudan and the remainder from Ethiopia, Mali, Chad, Ghana, and Niger. The disease is transmitted through drinking water containing water fleas (*Cyclops species*) that have ingested *Dracunculus* larvae. The larvae penetrate the intestinal mucosa and develop into adult worms in connective tissue. The adult female slowly migrates to the subcutaneous tissues causing intense pain, sometimes with non-specific symptoms such as fever and rash, and about 10 to 14 months later emerges through the skin, usually at the feet, producing oedema, a blister and eventually an ulcer; secondary bacterial infection is a common complication. Pain and symptoms decrease once the blister has ruptured. When the affected body part comes into contact with water the female worms release their larvae and set in motion a new life cycle.

The most effective method of controlling dracunculiasis is by provision of safe drinking water. The WHO eradication campaign is based on health education, and the provision of safe water by measures including water treatment with pesticides such as temefos and encouraging the use of domestic filters.

There is no effective direct drug therapy against any stage in man. The traditional treatment is removal of the adult worm by gentle traction sometimes over several weeks. Metronidazole or tiabendazole may provide symptomatic benefit in the management of dracunculiasis although they have no direct anthelmintic effect. They are thought to act by weakening the anchorage of the worms within the subcutaneous tissues, thus allowing them to be removed more quickly. However, treatment with mebendazole has been linked with aberrant migration of worms, which resulted in infections in places other than the lower limbs.

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Echinococcosis

Echinococcosis, or hydatid disease, in man is infection with the larval stage of the cestode *Echinococcus granulosus* or *E. multilocularis*. These two species cause distinct forms of the disease known as cystic echinococcosis and alveolar echinococcosis respectively. Various animals are involved in the transmission of the disease, man becoming infected through ingestion of eggs from contaminated faeces. The eggs hatch in the intestine and the embryos penetrate the intestinal wall and invade body organs, usually the liver. The embryo develops into a cyst which slowly increases in size and may remain intact for many years. Symptomatic infection usually only occurs when the cyst is large enough to cause obstruction or to compress adjacent structures, or if rupture occurs. Where possible, surgical removal of the intact cyst is the first line of treatment.

In **cystic echinococcosis**, drugs may be given locally or systemically before surgery to kill infective larvae within the cyst and reduce the risk of further infection. They are also given postoperatively if a cyst ruptures during surgery. Local injection of a larvicidal agent such as alcohol, cetrimide, or hypertonic saline has been used. Chemotherapy is also used as an adjunct or when surgery is not possible. The preferred drug for associated systemic treatment is albendazole. Mebendazole may be used, although due to poorer absorption from the gastrointestinal tract it is not as effective as albendazole and very high doses must be taken for several months. Praziquantel has also been reported to be effective, and may be combined with albendazole. Albendazole may be a suitable alternative to surgery as initial treatment in uncomplicated cases; use with cimetidine (to inhibit its metabolism) may increase its efficacy. Nitazoxanide has also been tried in disseminated disease.

A further option when surgery is not possible is the PAIR (puncture/aspiration/injection/re-aspiration) procedure which consists of ultrasound-guided cyst puncture followed by aspiration of the cyst fluid, local injection of alcohol or hypertonic saline into the cyst, and re-aspiration of the cyst contents. Concomitant chemotherapy is recommended.

E. multilocularis infection (**alveolar echinococcosis**) is more invasive and is characterised by a tumour-like infiltrative growth; it usually requires both surgery and long-term treatment with a benzimidazole, such as albendazole, although some lesions are inoperable when diagnosed, and patients have improved on albendazole alone. Prolonged treatment has proved larvicidal in some patients.

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11. Kern P. Clinical features and treatment of alveolar echinococcosis. *Curr Opin Infect Dis* 2010; **23:** 505–12.
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13. Pérez-Molina JA, *et al*. Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review. *Am J Trop Med Hyg* 2011; **84:** 351–6.

Enterobiasis

Enterobiasis is an infection with *Enterobius vermicularis* (pinworm or threadworm), an intestinal nematode that occurs throughout the world. Infections are particularly common in school-aged children, in families or primary caregivers of infected children, and in institutionalised groups. It is an infection of the large intestine and transmission follows ingestion or inhalation of mature eggs. The larvae mature in the gut in about 2 months. Mature females do not release eggs into the gut contents but migrate to the anus at night and lay eggs on the perianal and perineal skin. Eggs become infective within 6 hours and may remain so for 20 days. Diagnosis is based on detecting eggs around the anus. The most common symptom is perianal itching but many infections are asymptomatic. Rarely, migration of the worm may lead to ectopic disease such as appendicitis or salpingitis. The adult worm has a life span of about 6 weeks and, if re-infection can be prevented, the infection is self-limiting.

Treatment is with a single dose of a benzimidazole carbamate derivative, such as albendazole or mebendazole, or with pyrantel embonate.[1] A second single dose is given 2 weeks later to eliminate possible re-infection. These drugs are also generally effective if the patient is suffering from a mixed intestinal nematode infection. Other anthelmintics used in enterobiasis include ivermectin, piperazine or pyrvinium embonate. While additional hygiene measures can reduce the rate of re-infection, treatment of the whole family with an anthelmintic at the same time as treating the index case is also recommended. In institutions, day care centers, and schools mass drug treatment during an outbreak can be successful. However, re-infection is still common and more than one course may be required.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Fascioliasis

See under Liver Fluke Infections, p. 147.3.

Fasciolopsiasis

See under Intestinal Fluke Infections, p. 147.2.

Gnathostomiasis

Gnathostomiasis[1-4] is a parasite infection with, in most cases, the larval form of the nematode *Gnathostoma spinigerum*, although other *Gnathostoma* spp. have been identified. It is endemic in parts of Southeast Asia (particularly Thailand and Japan), Central and South America, the Middle East, and Australia, but case reports are emerging from around the world. *G. spinigerum* inhabits the stomach of cats and dogs. Eggs shed in their faeces are ingested by freshwater crustaceans and hatch into larvae which are ingested by fish or other animals; humans usually acquire the infection by eating the raw or undercooked flesh of these secondary hosts or rarely through direct larval penetration.

Once ingested the larvae penetrate the gut wall (usually triggering generalised eosinophilia) and aggressively migrate through various tissues. Migration through the subcutaneous tissues to the skin causes intermittent, painful, migratory swellings (similar to cutaneous larva migrans, see p. 144.3). The visceral form involves migration into deeper tissues and internal organs to involve the lungs, eyes, ears, gastrointestinal and genito-urinary systems; rarely there is involvement of the CNS. Symptoms may recur for 10 to 12 years.

The preferred treatment of gnathostomiasis is surgical removal of the gnathostome but this is only possible when it is superficial and accessible. Albendazole or, alternatively, ivermectin, may be used;[1,2,4] multiple courses may be needed for some patients.[2] Albendazole appears to stimulate the larva to migrate outwards and may make it more

accessible to excision.[2] Treatment of neurological infection is mainly supportive; there is a risk that severe host reaction to the dying larvae may result from active treatment.[3]

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Heterophyiasis

See under Intestinal Fluke Infections, p. 147.2.

Hookworm infections

Infections with the hookworms *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis) are a major cause of iron-deficiency anaemia in large areas of the tropics and sub-tropics, especially in rural communities. Eggs deposited in warm moist soil hatch into larvae which develop further into the infective form. Infection is normally by penetration through the skin although it may be by ingestion. The larvae migrate to the lungs and are subsequently swallowed and mature to the adult form in the small intestine. Eggs appear in the faeces about 6 to 8 weeks after infection and the adult worm may live for several years. *A. duodenale* larvae are capable of remaining dormant in the tissues, only maturing to the adult when climatic conditions are favourable. Symptoms correspond to the stage of infection. Visitors to endemic areas may develop intense pruritus, erythema, and papulovesicular eruption at the site of infection, known as ground itch. Migration through the lungs during the first infection may cause pneumonitis and bronchospasm with accompanying eosinophilia. The main symptoms of intestinal infection are iron-deficiency anaemia and severe hypoalbuminaemia. In addition, abdominal pain, diarrhoea, and weight loss may occur.

Treatment is usually with a benzimidazole carbamate derivative such as mebendazole or albendazole,[1-3] and such broad-spectrum therapy can also be useful if the patient has a mixed intestinal nematode infection. Albendazole may be more effective than mebendazole.[4] Other anthelmintics used in hookworm infections include levamisole or pyrantel embonate,[2-4] but these may be less effective against *N. americanus* than against *A. duodenale*. Iron-deficiency anaemia caused by hookworm infections responds rapidly to oral iron therapy; folic acid supplements may be necessary in some patients.

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of infection.[2,5] WHO recommends[6] the use of albendazole or mebendazole or alternatively levamisole or pyrantel targeted at preschool and school-age children, women of child-bearing age (including pregnant women in the second and third trimesters and lactating women), and adults engaged in high-risk occupations for soil-transmitted helminthiasis, such as tea-pickers and miners. Children less than 1 year of age and women in the first trimester of pregnancy are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence and intensity of infection among school-age children.

1. Hotez PJ, *et al.* Hookworm infection. *N Engl J Med* 2004; **351:** 799–807.
2. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; **367:** 1521–32.
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6. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 27/08/09)

Hymenolepiasis

Hymenolepiasis is an infection of the intestine with *Hymenolepis nana*, or dwarf tapeworm. Infection is acquired through ingestion of eggs in contaminated food or water or on hands and can be passed directly from person to person. It is more common in children. Clinical symptoms occur in heavy infections and include diarrhoea and abdominal pain. Treatment is with a single dose of praziquantel.[1-3] Nitazoxanide[1,3] and niclosamide[2,3] may be used as alternatives.

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2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 27/08/09)
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Intestinal fluke infections

More than 65 species of flukes are known to infect the human gastrointestinal tract; the most well known intestinal fluke infections are **fasciolopsiasis** (caused by *Fasciolopsis buski*), **heterophyiasis**, (*Heterophyes heterophyes* and some other *Heterophyes* spp.), **metagonimiasis** (*Metagonimus yokogawai*), and **nanophyetiasis** (*Nanophyetus salmincola*). Fasciolopsiasis, heterophyiasis, and metagonimiasis are endemic in the Far East and Southeast Asia, and heterophyiasis is also common in the Middle East. Nanophyetiasis has occurred increasingly in the Pacific Northwest of the USA. Fasciolopsiasis is caused by the ingestion of infected aquatic plants, while undercooked or raw infected fish are the sources of *H. heterophyes*, *M. yokogawai*, and *N. salmincola* infections.

Fasciolopsiasis is usually asymptomatic, but heavy infections can cause diarrhoea, abdominal pain, and, rarely, intestinal obstruction and an allergic oedematous reaction. Metagonimiasis is also generally asymptomatic but may cause mild diarrhoea, while pain and mucous diarrhoea are common in heterophyiasis. Similar gastrointestinal symptoms plus eosinophilia occur in nanophyetiasis. Eggs of *M. yokogawai* and *H. heterophyes* may rarely penetrate the bowel wall and enter the bloodstream to be deposited in various organs, leading to serious complications such as heart failure or fatal embolism in the heart or brain.

Treatment of choice for intestinal fluke infections is with praziquantel;[1,2] triclabendazole is also effective. Niclosamide is effective against fasciolopsiasis and heterophyiasis infections.

1. WHO. Control of foodborne trematode infections. *WHO Tech Rep Ser 849* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_849_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_849_(part2).pdf (accessed 16/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Liver fluke infections

Fasciola hepatica, *F. gigantica*, *Opisthorchis viverrini*, *O. felineus*, and *Clonorchis sinensis* are liver flukes transmitted by the ingestion of infected aquatic plants, grasses or water (*F. hepatica* and *F. gigantica*), or raw or undercooked fish (*Opisthorchis* spp., *C. sinensis*). **Fascioliasis** is mainly a disease of sheep and cattle and human infections may occur wherever these animals are raised, whereas **clonorchiasis** and **opisthorchiasis** are seen mainly in Southeast Asia and eastern Europe.

Fascioliasis in the acute phase is usually characterised by fever, gastrointestinal symptoms, pain due to liver enlargement, and marked eosinophilia, but these symptoms decline as the worms enter their final habitat in the bile ducts. Acute symptoms occur rarely with clonorchiasis and opisthorchiasis and infections tend to be asymptomatic for many years. Adult flukes live in the bile ducts and symptoms of biliary-tract obstruction appear after repeated or heavy infections with liver flukes. Cholangiocarcinoma (bile-duct cancer) is now generally accepted to be associated with liver fluke infection although its exact pathogenesis is unclear.

Praziquantel is used for the treatment of most liver fluke infections,[1,2] (except *Fasciola* infections) and triclabendazole is considered the treatment of choice for liver fluke infections caused by *Fasciola*.[2] Bithionol is more effective than praziquantel in fascioliasis and is an alternative to triclabendazole; dehydroemetine has also been used, and nitazoxanide[2] may be effective.

Praziquantel remains the treatment of choice for clonorchiasis and opisthorchiasis.[1,2] Albendazole is a suggested alternative for clonorchiasis.[2]

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2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Loiasis

Loiasis is an infection with the filarial nematode *Loa loa* (sometimes also known as the African eye worm) which occurs in areas of Central and West Africa. It is transmitted by the biting tabanid fly *Chrysops*. The infective larvae mature to adult worms which migrate through subcutaneous tissues and occasionally the subconjunctiva. Symptoms include pruritus, swelling, and pain, with occasional subcutaneous swellings, often on the arms or legs, that are characteristic of the disease. Passage of a worm through the subconjunctiva produces intense conjunctivitis. Eosinophilia may be severe, especially in visitors from non-endemic areas. Other complications include renal disease, endomyocardial fibrosis, encephalopathy, and peripheral neuropathy.

Diethylcarbamazine is used for treatment;[1,2] it is effective against the microfilariae, larval forms, and a proportion of adult worms. In some cases, treatment has been associated with acute encephalitis, particularly in patients with heavy microfilaraemia. It has been assumed that this is related to blockage of capillaries in the brain and meninges and for this reason small doses of diethylcarbamazine are given initially, with a corticosteroid and antihistamine, gradually increasing to full therapeutic doses over several days. However this does not eliminate the risk of encephalitis entirely and the role of the microfilariae in this syndrome has been questioned. Albendazole may be useful where diethylcarbamazine is ineffective or cannot be used, but repeated courses may be needed.[1] Mebendazole has also been used.[2] Some consider that ivermectin could be used[1,2] but, as with diethylcarbamazine, there is concern over its potential neurotoxic effects in patients with heavy microfilaraemia; this is also a potential problem where ivermectin is distributed for mass treatment of onchocerciasis (p. 148.3) in areas co-endemic for both diseases.

Diethylcarbamazine is also used for prophylaxis[1,2] but it has been suggested that it should be reserved for subjects at high risk of exposure. Vector control is regarded as impractical and methods aimed at reducing contact with the vector such as window screens and protective clothing are recommended.

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2. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg* 2008; **102:** 983–9.

Lung fluke infections

The lung fluke infection **paragonimiasis** is caused by *Paragonimus* spp., commonly *P. westermani*, and occurs in Asia, Africa, and Central or South America. The disease is transmitted by the ingestion of raw infected freshwater crabs or crayfish, or from drinking infected water.

The flukes mature in the lungs where they cause local necrosis, haemorrhage, inflammation, and fibrosis. Symptoms of paragonimiasis include fever, pain, and chest complaints, but most light to moderate infections are asymptomatic. The worms may also develop at other sites, particularly the brain where they can cause epilepsy, symptoms of cerebral tumours, or cerebral embolism, which may be fatal.

Treatment is with praziquantel or bithionol[1] (though the latter is less often used because of more frequent adverse effects). Triclabendazole is considered effective and well tolerated.[1,2] Corticosteroids should be given with praziquantel for cerebral paragonimiasis.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 27/08/09)

Lymphatic filariasis

Lymphatic filariasis[1] is a parasitic disease caused by filarial nematodes. The three species of filariae that cause lymphatic filariasis are *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, and *B. timori* (brugian filariasis, also known as Malayan and Timorian filariasis respectively). Adult worms produce larvae (microfilariae) which enter the peripheral bloodstream and through mosquito vectors infective larvae may be transmitted from person to person. The larvae migrate from the skin to the lymphatic system where they mature into adult worms that may live for several years. Development of lymphatic filariasis requires multiple bites from infected mosquitoes over a prolonged period of time (months to years); consequently, people living in endemic areas are at greatest risk of developing the disease.

Filarial infection is usually contracted in childhood and most infections are initially asymptomatic, although nearly all those infected will have some degree of subclinical lymphatic and kidney damage. Infection may remain occult or species- and body-site-dependent symptoms may follow.

- Acute inflammatory reactions to immature and dead or dying adult worms in the lymphatic system are referred to as *adenolymphangitis*, and are characterised by episodic attacks of fever, malaise, and inflammation of the inguinal lymph nodes, testis, and spermatic cord, and focal lymphoedema. These acute episodes usually resolve spontaneously after about a week, but can recur several times a year.
- *Chronic filariasis* may develop 10 to 15 years after initial symptoms and results from recurrent inflammation with subsequent damage to the lymphatic system, leading to impaired lymph drainage and lymphoedema. Manifestations include mild to massive enlargement of the legs, arms, breasts, or genitals (testicular hydrocele or swelling of the vulva), chyluria, and elephantiasis (grossly swollen limbs with thickened, hard, rough, and fissured

skin). Lymphangitis may result from secondary bacterial infections.

- *Occult filariasis* refers to filarial infection in which microfilariae are not detected in the peripheral blood but may be found in other body fluids and tissues. It is rare and is thought to result from a hypersensitivity reaction to filarial antigens. Clinical manifestations include tropical pulmonary eosinophilia, glomerulopathies, endomyocardial fibrosis, filarial arthritis, and filarial granulomas in the breast.

There is no entirely satisfactory **treatment** for individuals with lymphatic filariasis. Current treatments are effective against microfilariae, and thus prevent disease transmission, but have little or no effect on the adult worms and do not halt the progression of symptoms once the disease has developed.

Diethylcarbamazine removes circulating microfilariae and is partially effective against the adult worm and is considered the treatment of choice.[2] Treatment may trigger acute lymphangitis, and diethylcarbamazine should not be given during an acute episode as it may cause further worm death and thus exacerbate the inflammatory response.

Ivermectin is only active against microfilariae and is mainly used in areas also endemic for onchocerciasis or loiasis.

Albendazole plus either of these two drugs is considered to increase their efficacy and such combinations are recommended for mass treatment programmes.[3] However, systematic reviews of randomised studies[4,5] found insufficient evidence to either confirm or reject the observation that albendazole with diethylcarbamazine or ivermectin is more effective than either drug given alone.

Secondary infections with bacteria and fungi occur in poorly vascularised tissues and therefore rigorous hygiene, skin care, physiotherapy, and other measures to promote lymph flow in the affected areas are recommended; in some cases antimicrobials are needed. Large hydroceles and scrotal elephantiasis are generally not reversible with drug therapy and usually require surgical intervention after a treatment course with diethylcarbamazine.

Tropical pulmonary eosinophilia responds to a 3-week course of diethylcarbamazine but patients may relapse and require re-treatment. Filarial arthritis responds rapidly to treatment with diethylcarbamazine.

Filaria have been shown to contain *Wolbachia* **endobacteria** which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of filariasis. In patients infected with *W. bancrofti* oral doxycycline for 4, 6, or, 8 weeks has resulted in a reduction in adult worms and prolonged reduction in microfilaraemia,[1,6] while a 3-week course of oral doxycycline followed by a single dose of ivermectin plus albendazole 4 months after the start of treatment, was found to be more effective in inducing long-term clearance of microfilariae than standard treatment with ivermectin plus albendazole, but was insufficient to kill adult worms.[7] In patients infected with *B. malayi* a 6-week course of oral doxycycline, either alone or followed by a single dose of diethylcarbamazine plus albendazole 4 months later, significantly reduced *Wolbachia* levels and led to a decrease in microfilaraemia that was sustained for at least 1 year after treatment.[8] Doxycycline may also prevent or ameliorate serious adverse effects to standard antifilarial treatment.[7,8]

In communities where lymphatic filariasis is endemic **mass treatment** of the entire community is the basis of the Global Programme to Eliminate Lymphatic Filariasis.[3] The primary goal is to eliminate microfilariae from the blood of infected individuals thereby interrupting transmission. The programme recommends a single dose of 2 drugs (albendazole plus either diethylcarbamazine or ivermectin) given once-yearly for 4 to 6 years.[3,4] Albendazole plus ivermectin is used in areas where onchocerciasis or loiasis are also endemic. Pregnant women, lactating women in the first week after birth, children under 90 cm in height (or weighing less than about 15 kg), and the severely ill are excluded from mass treatment programmes in areas where ivermectin and albendazole are used. In areas where diethylcarbamazine and albendazole are used, pregnant women, children under 2 years of age, and the severely ill are excluded.[9] An alternative approach is the use of diethylcarbamazine-medicated salt for 6 to 12 months throughout the community at risk.

Ongoing **vector control** should be carried out before or during peak transmission season, in order to consolidate the effects of mass chemotherapy. People living in or visiting endemic areas are advised to sleep under a mosquito net and use mosquito repellent on exposed skin between dusk and dawn.

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Mansonella infections

Infections with the filarial nematodes *Mansonella perstans*, *M. ozzardi*, and *M. streptocerca* are generally asymptomatic but symptoms including malaise, fever, joint pain, and meningeal symptoms have been described. Infection is transmitted by biting midges and flies.

Treatment varies according to the infecting species. A single oral dose of ivermectin has been suggested for *M. ozzardi* infections; diethylcarbamazine is ineffective.[1] *M. streptocerca* infections may be treated with diethylcarbamazine or ivermectin; diethylcarbamazine is active against the adult worms and microfilariae, while ivermectin is only effective against microfilariae.[1] Although diethylcarbamazine is generally recommended as a first-line drug for the treatment of *M. perstans* infection, this infection is generally considered to be relatively refractory to treatment with conventional antifilarial drugs and multiple treatments are needed to eliminate the infection.[2] Ivermectin and mebendazole have also been found to be ineffective for *M. perstans*.[1] A combination of mebendazole plus diethylcarbamazine was reported to be more effective than each drug given alone.[2] Tiabendazole has been tried but was found to be less effective than either mebendazole or diethylcarbamazine.[2]

Filaria have been shown to contain *Wolbachia* **endobacteria**, which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of filariasis. In patients infected with *M. perstans*, daily oral doxycycline for 6 weeks resulted in significant reductions in microfilaraemia at 12 months and continued suppression 36 months after treatment.[3]

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Metagonimiasis

See under Intestinal Fluke Infections, p. 146.2.

Nanophyetiasis

See under Intestinal Fluke Infections, p. 146.2.

Necatoriasis

For infections caused by *Necator americanus* see under Hookworm Infections, p. 146.1.

Onchocerciasis

Onchocerciasis (river blindness) is a parasitic disease caused by infection with the filarial nematode *Onchocerca volvulus*.[1,2] It is endemic in large areas of West and Central Africa, areas of Latin America, and Yemen. It is particularly prevalent near fast flowing rivers, the breeding ground of the blackfly which is the vector of the parasite. After infection, the larvae mature into adult worms in fibrous nodules, usually in the subcutaneous tissue. The adult female worms release large numbers of microfilariae which migrate from the nodules into other tissues, most notably the skin and the eyes. Death of microfilariae in the eyes causes severe inflammation and scarring that may lead to lesions in the eyes and impaired vision. There is some evidence that antigens released from symbiotic *Wolbachia* bacteria within the microfilariae also play a role.[3-5] Repeated infection over several years may result in irreversible blindness. In the skin the dying microfilariae trigger a subcutaneous inflammatory response that causes intense itching. Over time the skin becomes swollen and thickened (lizard skin) and may lose some of its elasticity and pigment (leopard skin).

Onchocerciasis is controlled either by treating the infected patient, thereby reducing the transmission of the infection from the human host to the vector, or by interrupting the transmission from vector to human. The drug of choice for the **treatment** of onchocerciasis is ivermectin.[4-7] A single oral dose of ivermectin rapidly eliminates microfilariae from the skin and more gradually eliminates them from the cornea and anterior chamber of the eye.[6] It has little effect on the adult worms although it suppresses release of microfilariae for several cycles. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Control of the disease in endemic areas relies upon the use of ivermectin every 12 months in Africa (and every 6 months in Central and South America) and this may be combined with vector control (see below). Because the adult worms live for about 15 years, treatment will need to be continued for many years. Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in *community-wide mass treatment programmes* in all countries in which onchocerciasis is endemic, where it is given to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg (equivalent to about 90 cm in height), and those unable to walk or otherwise seriously ill.[8,9] For further details, see under Ivermectin, p. 157.1. Increasing the frequency of the standard doses of ivermectin to every 3 months appears to increase efficacy compared with annual treatments.[10] Evidence from Ghana suggests that ivermectin-resistant populations of parasites are emerging and that its ability to suppress skin microfilariae repopulation is reduced over time in some communities.[11]

In areas where onchocerciasis and loiasis are co-endemic, care should be taken because ivermectin may cause serious adverse effects, including encephalopathy, in some patients with high *Loa loa* microfilaraemias (see Incidence of Adverse Effects, under Ivermectin, p. 158.1). The Mectizan Expert Committee and the Technical Consultative Committee[12] have implemented recommendations for ivermectin mass treatment programmes of onchocerciasis in areas co-endemic for loiasis.

Before the introduction of ivermectin in 1988, diethylcarbamazine was the usual treatment for onchocerciasis, but it is no longer recommended by WHO.[6] The major limitations to its use are the severe allergic reaction (the Mazzotti reaction) associated with its microfilaricidal action, aggravation of existing ocular lesions or precipitation of new ones, and the need to give repeated courses of treatment for continued suppression of the disease.[6] Suramin has also been used in the treatment of onchocerciasis and is effective against adult worms.[6] However, its use is restricted because of its toxicity.[1] Moxidectin is an anthelmintic used in veterinary medicine and is currently being evaluated for human use.[2,13] Amocarzine has also been evaluated in onchocerciasis.[6]

Recently it has been shown that adult worms contain *Wolbachia* **endobacteria**, which are essential for adult worm fertility and viability. This symbiotic dependency on *Wolbachia* has provided a new approach in the treatment of onchocerciasis. Treatment with oral doxycycline daily for 6 weeks has been shown to sterilise adult worms for the 4-month study period.[14] When given with a single dose of ivermectin, embryogenesis is interrupted for at least 18 months.[15] The long doxycycline treatment regimen is not suitable for mass treatment programmes, but it may be used with ivermectin for treatment of patients who permanently leave an endemic area.

In non-endemic areas ivermectin may be given every 3 to 6 months depending on the recurrence of symptoms or presence of microfilariae.

Vector control with larvicides, continued for the life span of an adult worm, is used to interrupt the transmission of infection and was the main strategy for onchocerciasis control before the introduction of ivermectin. However, despite initial success fly re-invasion became a problem, as the flight range of the vector was longer than expected.[16]

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Available at: http://www.mectizan.org/sites/default/files/EnglishMECTCCLoaRecs-June04_1.pdf (accessed 29/07/10)
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Opisthorchiasis

See under Liver Fluke Infections, p. 146.2.

Paragonimiasis

See under Lung Fluke Infections, p. 146.3.

Schistosomiasis

Schistosomiasis (bilharziasis) is a parasitic infection caused by *Schistosoma* spp., largely *S. mansoni*, *S. japonicum*, and *S. haematobium*, and to a lesser extent *S. intercalatum* and *S. mekongi*. The disease is seen mainly in Africa, Asia, South America, and the Caribbean, where it is a hazard to individuals exposed to fresh water containing the intermediate host, infected freshwater snails.

Free-swimming cercariae are released from the snail and penetrate human skin causing a pruritic papular rash in sensitised individuals (swimmer's itch). Parasites mature in the lungs and liver within about 6 weeks, then migrate to the blood vessels, the bladder, or intestines. Mature female worms produce eggs which are excreted in urine or stools, or become lodged in tissues, and immunological reaction to these eggs results in disease. The acute reaction to egg deposition has been termed Katayama fever, a self-limiting but sometimes fatal illness resembling serum sickness and most frequently seen in *S. japonicum* infection. The chronic phase of infection is often asymptomatic for many years, but usually results in granuloma formation and fibrosis in tissues where eggs are deposited, such as the liver, lungs, intestines, or urinary tract, the site depending on the infecting species.

Praziquantel is used for the **treatment** of chronic schistosomiasis[1-5] and is effective against all species of schistosomes. Metrifonate and oxamniquine have been used as alternatives against *S. haematobium*[1,2] and *S. mansoni*[1,3,4] respectively. The artemisinins have been found to be effective against immature schistosomes in laboratory studies[2] and artemisinin derivatives used alone or with praziquantel are under investigation for *S. mansoni*,[6,7] *S. haematobium*,[8] and *S. japonica*[9] infections. However, results from these studies are variable and a systematic review[2] on the use of drugs to treat *S. haematobium* found that evidence of benefit with artemisinins was inconclusive. Mefloquine plus artesunate, given orally once daily for 3 days, was found to be effective against *S. haematobium* infection in children; high cure rates and egg reduction rates were also seen in those coinfected with *S. mansoni*.[10]

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease. WHO recommends[11] the use of praziquantel targeted at school-age children, adults considered to be at risk (including pregnant and lactating women or those engaged in high-risk occupations involving contact with infested water), and entire communities living in endemic areas. Children less than 4 years of age or 94 cm in height are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence of infection or of visible haematuria (for *S. haematobium* only) among school-age children.

Niclosamide is used as a molluscicide for the treatment of water in schistosomiasis control programmes. Copper sulfate or sodium pentachlorophenate have also been used but to a lesser extent.

Schistosomiasis vaccines are in development.

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11. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers*. Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 09/09/09)

Strongyloidiasis

Strongyloidiasis[1,2] is an infection of the small intestine caused by *Strongyloides stercoralis*, known as threadworm in the USA. It generally occurs in the tropics and subtropics and can also occur in some areas of South and East Europe, Japan, and the USA. Infective larvae penetrate the skin, migrate to the lungs, move up the bronchial tree to be swallowed, and finally penetrate the mucosa of the small intestine where they mature. Eggs are deposited about 28 days after initial infection. These hatch before leaving the gastrointestinal tract, and can cause autoinfection, particularly in immunocompromised patients. Larvae reaching the soil can either mature into free-living adults or remain in an infective larval stage.

Infection may be asymptomatic, but commonly patients have symptoms relating to the stages of infection. Penetration of larvae through the skin causes intense pruritus and an erythematous rash. The rash may follow the course of migration and is one of the causes of cutaneous larva migrans (p. 144.3). An inflammatory response to migration through the lungs may be seen and may include pneumonitis and bronchospasm. In heavy infections, which are most common in immunocompromised patients as a result of autoinfection, massive pulmonary invasion can occur resulting in fatal alveolar haemorrhage. Abdominal symptoms include colicky pain, diarrhoea, and vomiting, leading to nutritional deficiencies and weight loss. Eosinophilia may also be present. Disseminated disease may occur in immunocompromised patients (including transplant patients[3]) and produce severe pulmonary and abdominal symptoms, shock, encephalopathy, meningitis, and Gram-negative septicaemia. Since strongyloidiasis is commonly fatal in these patients, vulnerable patients from endemic areas should be screened regularly and treated promptly at the first sign of infection.

Ivermectin is considered to be the treatment of choice.[1,2,4] Tiabendazole was widely used, and still is in some countries, but albendazole is more effective and better tolerated. Mebendazole has also been suggested but it must be given for longer periods than albendazole since it has only a limited effect on migrating larvae. These broad-spectrum anthelmintics (except tiabendazole) are also useful if the patient is suffering from a mixed intestinal nematode infection.

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4. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Syngamosis

Syngamosis, or gapeworm infection, is caused by *Syngamus* and *Mammomonogamus* spp. and is mainly an infection of domestic fowl and wild birds and mammals, although infection in man has been reported very rarely.[1-6] Man may become infected by eating foods contaminated with infective larvae which penetrate the intestinal wall and migrate to the lungs, where they mature into adult worms. The major symptom is cough, due to irritation of the bronchi and increased mucus production. The infection may be confused with asthma. Tiabendazole and mebendazole have been used successfully to treat the infection in man.

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Taeniasis

Taeniasis is an infection of the intestine with beef tapeworm, *Taenia saginata*, or pork tapeworm, *T. solium*, acquired through ingestion of contaminated raw or undercooked meat. The larval form of *T. solium* can cause the systemic infection cysticercosis (see p. 144.3).

Infection with the adult worm usually produces symptoms only when the worm reaches a size that can cause obstruction or related problems. Segments of the worm containing eggs may be excreted in the faeces so maintaining the cycle of reproduction. Treatment is with a single dose of praziquantel,[1] which has the advantage of also being active, in higher doses, against the larval form of *T. solium*. Niclosamide is also effective[1] but is only active against adult worms.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Toxocariasis

Toxocariasis[1] is infection with the larval form of *Toxocara canis* or, less commonly, *T. cati*. The adult worms live in the intestines of dogs and cats respectively, and man becomes infected when eggs excreted in animal faeces are ingested. Once ingested the eggs hatch and the larvae migrate from the intestine to other organs, most commonly the liver, lung, and eye. Most infections are asymptomatic but two clinical syndromes, ocular larva migrans and visceral larva migrans, can occur, usually in children.

Ocular larva migrans occurs when larvae invade the eye causing a granuloma which may impair vision and can cause blindness. There is no specific treatment.[2] Anthelmintics such as albendazole or tiabendazole, corticosteroids, ocular surgery, and laser photocoagulation have been used but assessment of their efficacy is difficult because of the variable natural course of the disease.

The clinical symptoms of visceral larva migrans depend upon the organs involved but commonly include cough, wheezing, fever, and hepatomegaly. Encephalitis and seizures may occur and there is usually eosinophilia. Acute infection normally resolves without treatment.[3] However, severe or prolonged infections may be treated with albendazole;[4] diethylcarbamazine,[5] mebendazole, or tiabendazole have also been used.[1,4]

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Trichinosis

Trichinosis[1] (trichinellosis or trichiniasis) is an infection caused by nematodes of the genus *Trichinella*, most commonly *Trichinella spiralis*. Man becomes infected through ingestion of raw or undercooked meat, usually pork, containing infective larvae. The larvae mature into adult worms in the small intestine and the mature females deposit larvae that migrate in the blood to skeletal muscle and sometimes to the myocardium. Symptoms usually occur only in heavy infections. Invasion of the intestines by the maturing adult worms can cause diarrhoea, abdominal pain, and vomiting followed about a week later by hypersensitivity reactions to the migrating larvae. These may include eosinophilia, fever, muscle pain, periorbital oedema and, more rarely, encephalitis, myocarditis, or pneumonia which may be fatal.

Treatment with anthelmintic drugs should be started as early as possible to kill the adult worms in the small intestine and thereby prevent the further release of larvae and subsequent muscular invasion.[1] Once the larvae have become established in skeletal muscle treatment may not completely eliminate the infection and associated symptoms. Albendazole or alternatively mebendazole are considered to be the anthelmintics of choice;[1,2] tiabendazole has also been used.[3] Pyrantel embonate may be given to pregnant women and children, although it is only effective against worms in the gut.[1] A corticosteroid should be given for severe hypersensitivity reactions.[1,2,4] If treatment is not started within the first few days of infection, repeated courses of treatment may be required.[1]

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2. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
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4. Shimoni Z, *et al*. The use of prednisone in the treatment of trichinellosis. *Isr Med Assoc J* 2007; **9:** 537–9.

Trichostrongyliasis

Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp. including *T. colubriformis*. *Trichostrongylus* spp. are normally parasites of herbivores, but infections in man have been found. They have a similar life cycle to *Ancylostoma duodenale* (see Hookworm Infections, p. 146.1). Pyrantel embonate, albendazole, or mebendazole are recommended for the treatment of trichostrongyliasis.[1] Successful treatment with ivermectin has occurred in areas where widespread use of

benzimidazole carbamate derivatives in grazing animals has led to resistance to these drugs.[2]

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Trichuriasis

Trichuriasis is an infection of the large intestine with *Trichuris trichiura*, sometimes known as whipworm. Distribution is worldwide, but most infections occur in the tropics and subtropics. Eggs are excreted in the faeces and can remain viable in the soil for extended periods. Under optimum conditions the eggs become infective in about 2 to 4 weeks. After ingestion, larvae are released from the eggs and develop within the wall of the small intestine for about 3 to 10 days, before migrating to the lumen of the large intestine where they remain attached to the mucosal lining. Eggs are detectable in the faeces about 1 to 3 months after infection. Trichuriasis is often asymptomatic, but heavy infection can result in anaemia, diarrhoea, and rectal prolapse.

Treatment is with a benzimidazole carbamate derivative such as albendazole or mebendazole[1-3] and such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Ivermectin[2] and nitazoxanide[4] are alternatives and addition of ivermectin to treatment with either albendazole or mebendazole has been shown to improve cure and egg reduction rates.[5] However, a systematic review[3] considered the treatment of trichuriasis to be unsatisfactory with current drugs.

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease. WHO recommends[6] the use of albendazole or mebendazole or alternatively levamisole or pyrantel targeted at preschool and school-age children, women of child-bearing age (including pregnant women in the second and third trimesters and lactating women), and adults engaged in high-risk occupations for soil-transmitted helminthiasis, such as tea-pickers and miners. Children less than 1 year of age and women in the first trimester of pregnancy are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence and intensity of infection among school-age children.

1. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; **367:** 1521–32.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.
4. Juan JO, *et al.* Comparative clinical studies of nitazoxanide, albendazole and praziquantel in the treatment of ascariasis, trichuriasis and hymenolepiasis in children from Peru. *Trans R Soc Trop Med Hyg* 2002; **96:** 193–6.
5. Knopp S, *et al.* Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis* 2010; **51:** 1420–8.
6. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 09/09/09)

Abamectin *(USAN, rINN)*

Abaimectin; Abamectina; Abamectine; Abamectinum; Abamektyna; MK-0936; Абамектин.

A mixture of abamectin component B_{1a} and abamectin component B_{1b}.

CAS — 65195-55-3 (component B_{1a}); 65195-56-4 (component B_{1b}).

ATC Vet — QP54AA02.

UNII — 5U8924T11H (abamectin); K54ZMM929K (abamectin component B_{1a}); W8DT67027W (abamectin component B_{1b}).

Profile

Abamectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

References.

1. Soyuncu S, *et al.* Abamectin intoxication with coma and hypotension. *Clin Toxicol* 2007; **45:** 299–300.

Albendazole *(BAN, USAN, rINN)*

Albendatsoli; Albendazol; Albendazolas; Albendazolo; Albendazolum; SKF-62979; Альбендазол; Албендазол.

Methyl 5-propylthio-1*H*-benzimidazol-2-ylcarbamate.

$C_{12}H_{15}N_3O_2S$=265.3

CAS — 54965-21-8.

ATC — P02CA03.

ATC Vet — QP52AC11.

UNII — F4216019LN.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8 (Albendazole). A white to faintly yellowish powder. Practically insoluble in water and in alcohol; very slightly soluble in dichloromethane; freely soluble in anhydrous formic acid. Protect from light.

USP 36: (Albendazole). A white to faintly yellowish powder. Practically insoluble in water and in alcohol; very slightly soluble in ether and in dichloromethane; freely soluble in anhydrous formic acid. Store in airtight containers.

Uses and Administration

Albendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 160.1) and with similar activity. It is used in relatively high doses in the treatment of the cestode infections cysticercosis and echinococcosis (hydatid disease). In some countries albendazole is used in the treatment of single and mixed intestinal nematode infections including ascariasis, enterobiasis, hookworm, strongyloidiasis, and trichuriasis. It may also be used in the treatment of angiostrongyliasis, capillariasis, gnathostomiasis, and trichostrongyliasis. Albendazole may be effective in the treatment of the tissue nematode infections cutaneous larva migrans, toxocariasis, and trichinosis and has been tried in loiasis, and, with other anthelmintics, in mass treatment programmes in areas where lymphatic filariasis is endemic. It may be given as an alternative to praziquantel in the treatment of liver fluke infections caused by *Clonorchis sinensis*. For discussions of these infections and their treatment, see under Choice of Anthelmintic (p. 143.1), and under the individual headings below.

In the treatment of **echinococcosis**, albendazole is given orally with meals in a dose of 400 mg twice daily for 28 days for patients weighing over 60 kg. A dose of 15 mg/kg daily in two divided doses (to a maximum total daily dose of 800 mg) is used for patients weighing less than 60 kg. For cystic echinococcosis, the 28-day course is repeated after 14 days without treatment to a total of 3 treatment cycles. For alveolar echinococcosis, cycles of 28 days of treatment followed by 14 days without treatment may need to continue for months or years.

In the treatment of **neurocysticercosis**, US licensed product information recommends doses of albendazole for parenchymal cysts similar to the doses used in echinococcosis (see above); the recommended duration of treatment is 8 to 30 days. Expert opinion also favours similar doses of 15 mg/kg daily but with a duration of treatment of only 8 days for parenchymal disease and about 1 month for extraparenchymal disease, such as subarachnoid, ventricular, and spinal cord cysticercosis. For further information on dosage regimens, see Cysticercosis, p. 151.1.

Albendazole is given orally, usually as a single dose, in the treatment of single or mixed **intestinal nematode infections**. The usual dose for those with ascariasis, enterobiasis, hookworm infections, or trichuriasis is 400 mg as a single dose; a 3-day course of treatment is needed for heavier infections with trichuriasis. In enterobiasis, the dose may be repeated in 2 to 4 weeks. For *mass treatment* control programmes against ascariasis, hookworm infections, and trichuriasis, a dose of 400 mg is given as a single dose once or twice a year depending on the prevalence and intensity of infection among school-age children. In strongyloidiasis, 400 mg is given once or twice daily for 3 consecutive days; this may be repeated after 3 weeks if necessary.

In the treatment of **clonorchiasis**, albendazole is given orally with meals in a dose of 10 mg/kg daily for 7 days.

Albendazole has also been used to treat **giardiasis** (p. 923.2); suggested oral doses are 400 mg daily for 5 days.

For details of doses in children, see p. 150.3.

Administration in children. Albendazole may be given orally to children for the treatment of single or mixed intestinal nematode infections and for cestode infections such as neurocysticercosis and echinococcosis.

For nematode infections the following doses are recommended:

- for **ascariasis, enterobiasis, hookworm infections, and trichostrongyliasis** children from 12 months to 2 years of age may be given 200 mg as a single dose and those more than 2 years of age may be given 400 mg as a single dose. For enterobiasis infections the dose should be repeated after 14 to 28 days
- for **capillariasis** children from 2 years of age may be given a dose of 400 mg daily for 10 days
- for **strongyloidiasis** children from 2 years of age may be given a dose of 400 mg once or twice daily for 3 days; the dose may be repeated after 3 weeks if necessary
- for **trichuriasis** children from 12 months to 2 years of age may be given 200 mg as a single dose for moderate infections; for more severe infections an initial dose of 200 mg is given followed by 100 mg twice daily for 3 days. Those more than 2 years of age may be given 400 mg as a single dose for moderate infections; for more severe infections the usual dose is 400 mg daily for 3 days

For *mass treatment* control programmes against ascariasis, hookworm infections, and trichuriasis, children from 12 to 23 months of age may be given a single dose of 200 mg, while those 2 years of age or older may be given a single dose of 400 mg. Doses are given once or twice a year depending on the prevalence and intensity of infection among school-age children.

For cestode infections the following doses are recommended:

- for **echinococcosis** children from 2 years of age may be given a dose of 7.5 mg/kg twice daily (to a maximum daily dose of 800 mg) for 28 days; the 28-day course is repeated after 14 days without treatment to a total of 2 to 3 treatment cycles
- for **neurocysticercosis** children may be given a dose of 15 mg/kg daily in 2 divided doses (to a maximum daily dose of 800 mg) for 8 to 30 days; treatment may be repeated if necessary

Ascariasis. Albendazole is used as an alternative to mebendazole in the treatment of ascariasis (p. 143.3). Both drugs are equally highly effective with a cure rate greater than 98% reported for albendazole in one study.[1]

1. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88:** 585–9.

Capillariasis. Albendazole in an oral dose of 400 mg daily for 10 days has been suggested[1] as an alternative to mebendazole for the treatment of capillariasis (p. 144.2).

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Cutaneous larva migrans. Albendazole has been reported[1-4] to be effective in the treatment of cutaneous larva migrans (p. 144.3) and is an alternative to tiabendazole or ivermectin. Albendazole, generally in an oral dose of 400 mg daily for three to five days,[1,2,5] has alleviated the discomfort of cutaneous larva migrans; treatment for seven days may be more effective and has not been associated with an increased incidence of adverse effects.[4] A single dose of 400 mg has also been effective.[3] An ointment containing albendazole 10%, applied 3 times daily for 10 days, was reported to be effective in treating cutaneous larva migrans in 2 young children.[6]

1. Jones SK, *et al.* Oral albendazole for the treatment of cutaneous larva migrans. *Br J Dermatol* 1990; **122:** 99–101.
2. Sanguigni S, *et al.* Albendazole in the therapy of cutaneous larva migrans. *Trans R Soc Trop Med Hyg* 1990; **84:** 831.
3. Oriheula AR, Torres JR. Single dose of albendazole in the treatment of cutaneous larva migrans. *Arch Dermatol* 1990; **126:** 398–9.
4. Veraldi S, Rizzitelli G. Effectiveness of a new therapeutic regimen with albendazole in cutaneous larva migrans. *Eur J Dermatol* 1999; **9:** 352–3.
5. Heukelbach J, Feldmeier H. Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. *Lancet Infect Dis* 2008; **8:** 302–9.
6. Caumes E. Efficacy of albendazole ointment on cutaneous larva migrans in 2 young children. *Clin Infect Dis* 2004; **38:** 1647–8.

Cysticercosis. The use of anthelmintics in the treatment of neurocysticercosis (see Cysticercosis, p. 144.3) remains controversial, but if indicated oral albendazole is considered to be the drug of choice.[1-3] The dose of albendazole originally used was the same as that used in echinococcosis, typically about 15 mg/kg daily orally for 1 month. There is now some evidence that shorter courses of treatment may be appropriate in some forms of neurocysticercosis. A study[4] confirmed that a 10-day course of albendazole 400 mg twice daily, with dexamethasone, was safe and decreased the burden of parasites and the number of generalised seizures in patients with viable parenchymal cysts. Albendazole has also been reported to be effective for extraparenchymal infection, such as subarachnoid, ventricular,[2,5,6] and spinal cord cysticercosis,[2] but the longer treatment period of 1 month with a dose of 15 mg/kg daily is usually used; multiple courses may be needed.[7] Alternatively, a higher dose of albendazole for a shorter time may be considered. A study[5] of 36 patients with subarachnoid and intraventricular cysticercosis found that 30 mg/kg daily for 8 days was safe and more effective than 15 mg/kg daily for 8 days, both regimens being given with corticosteroids. For patients with solitary cysticercus granuloma a dose of 15 mg/kg daily, in 2 to 3 divided doses (with or without corticosteroids), for 1 to 2 weeks has been recommended.[8]

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; **34:** 503–15.
2. Takayanagui OM. Therapy for neurocysticercosis. *Expert Rev Neurother* 2004; **4:** 129–39.
3. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel. *Ann Intern Med* 2006; **145:** 43–51.
4. Garcia HH, *et al.* A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 2004; **350:** 249–58.

5. Góngora-Rivera F, *et al.* Albendazole trial at 15 or 30 mg/kg/day for subarachnoid and intraventricular cysticercosis. *Neurology* 2006; **66:** 436–8.
6. Proaño JV, *et al.* Medical treatment for neurocysticercosis characterized by giant subarachnoid cysts. *N Engl J Med* 2001; **345:** 879–85.
7. Nash TE, *et al.* Treatment of neurocysticercosis: current status and future research needs. *Neurology* 2006; **67:** 1120–7.
8. Singh G, *et al.* A diagnostic and therapeutic scheme for a solitary cysticercus granuloma. *Neurology* 2010; **75:** 2236–45.

Echinococcosis. Albendazole is used in the treatment of echinococcosis (p. 145.2) as an adjunct to, or instead of, surgery. It is generally preferred to mebendazole.

References.

1. Teggi A, *et al.* Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37:** 1679–84.
2. Gil-Grande LA, *et al.* Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. *Lancet* 1993; **342:** 1269–72.
3. Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; **88:** 49–52.
4. Wen H, *et al.* Albendazole chemotherapy for human cystic and alveolar echinococcosis in north-western China. *Trans R Soc Trop Med Hyg* 1994; **88:** 340–3.
5. Liu Y, *et al.* Continuous long-term albendazole therapy in intraabdominal cystic echinococcosis. *Chin Med J (Engl)* 2000; **113:** 827–32.
6. Keshmiri M, *et al.* Albendazole versus placebo in treatment of echinococcosis. *Trans R Soc Trop Med Hyg* 2001; **95:** 190–4.
7. Falagas ME, Bliziotis IA. Albendazole for the treatment of human echinococcosis: a review of comparative clinical trials. *Am J Med Sci* 2007; **334:** 171–9.

Giardiasis. Albendazole has been tried in the treatment of giardiasis (p. 923.2) with variable results; however, a meta-analysis[1] of 8 studies suggested that an oral dose of 400 mg once daily for 5 days was as effective as, and better tolerated than, standard treatment with metronidazole.

1. Solaymani-Mohammadi S, *et al.* A meta-analysis of the effectiveness of albendazole compared with metronidazole as treatments for infections with *Giardia duodenalis*. *PLoS Negl Trop Dis* 2010; **4:** e682.

Gnathostomiasis. Albendazole has been reported to be effective in the treatment of gnathostomiasis (p. 145.3). Oral doses of 400 mg once or twice daily have been given for 2 or 3 weeks.[1-4]

1. Kraivichian P, *et al.* Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg* 1992; **86:** 418–21.
2. Suntharasamai P, *et al.* Albendazole stimulates outward migration of Gnathostoma spinigerum to the dermis in man. *Southeast Asian J Trop Med Public Health* 1992; **23:** 716–22.
3. Nontasut P, *et al.* Comparison of ivermectin and albendazole treatment for gnathostomiasis. *Southeast Asian J Trop Med Public Health* 2000; **31:** 374–7.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Hookworm infections. Hookworm infections (p. 146.1) are commonly treated with benzimidazole carbamates such as albendazole. In 77 patients with light necatoriasis (*Necator americanus* infection) albendazole, in a single 400-mg dose, produced an 84% cure rate and an 82% reduction in egg count in those patients not cured.[1] In another study,[2] although the cure rate was only 56.8% after a single 400-mg dose of albendazole this was superior to treatment with mebendazole which had a cure rate of 22.4%. A further study[3] comparing albendazole with mebendazole and pyrantel in the treatment of necatoriasis also found albendazole to be the most effective.

Albendazole is given in mass treatment programmes to reduce the overall burden of infection.[1,4]

1. Nahmias J, *et al.* Evaluation of albendazole, pyrantel, bephenium, pyrantel-praziquantel and pyrantel-bephenium for single-dose mass treatment of necatoriasis. *Ann Trop Med Parasitol* 1989; **83:** 625–9.
2. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88:** 585–9.
3. Sacko M, *et al.* Comparison of the efficacy of mebendazole, albendazole and pyrantel in treatment of human hookworm infections in the southern region of Mali, West Africa. *Trans R Soc Trop Med Hyg* 1999; **93:** 195–203.
4. Idris MA, *et al.* Effective control of hookworm infection in school children from Dhofar, Sultanate of Oman: a four-year experience with albendazole mass chemotherapy. *Acta Trop* 2001; **80:** 139–43.

Loiasis. Albendazole has been given[1-3] to reduce microfilariasis in patients infected with *Loa loa* (see Loiasis, p. 146.2). It may be a useful alternative drug in those patients with a heavy or dense microfilarial load who are at risk for serious adverse effects from diethylcarbamazine[4] or where diethylcarbamazine is ineffective or cannot be used.[5] An [oral] dose of 200 mg twice daily for 3 weeks is usually given.[4]; repeat courses may be necessary.[5]

1. Klion AD, *et al.* Albendazole in human loiasis: results of a double-blind, placebo-controlled trial. *J Infect Dis* 1993; **168:** 202–6.
2. Klion AD, *et al.* Albendazole therapy for loiasis refractory to diethylcarbamazine treatment. *Clin Infect Dis* 1999; **29:** 680–2.
3. Tabi TE, *et al.* Human loiasis in a Cameroonian village: a double-blind, placebo-controlled, crossover clinical trial of a three-day albendazole regimen. *Am J Trop Med Hyg* 2004; **71:** 211–15.
4. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg* 2008; **102:** 983–9.
5. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Lymphatic filariasis. Although the evidence for such use is relatively weak,[1,2] albendazole is used in the management of lymphatic filariasis (p. 146.3). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) with appropriate drugs can reduce the intensity of transmission and the incidence of disease. The Global Programme to eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single oral dose of albendazole 400 mg with either a single oral dose of ivermectin 150 to 200 micrograms/kg (if there is co-endemic loiasis or onchocerciasis) or with a single oral dose of diethylcarbamazine 6 mg/kg (if there is no co-endemic loiasis or onchocerciasis); these doses are given once each year for at least 5 years. Higher doses of albendazole and ivermectin (800 mg and 400 micrograms/kg respectively) given twice a year for 2 years, to 25 residents of an area of high *Wuchereria bancrofti* endemicity in Mali, were found to be more effective in reducing microfilarial levels than the standard annual dose regimen recommended by WHO. Higher-dose and/or more frequent treatment regimens could therefore potentially reduce the time necessary to interrupt transmission.[3]

1. Addiss D, *et al.* International Filariasis Review Group. Albendazole for lymphatic filariasis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 16/10/09).
2. Horton J. The development of albendazole for lymphatic filariasis. *Ann Trop Med Parasitol* 2009; **103** (suppl 1): S33–S40.
3. Dembele B, *et al.* Use of high-dose, twice-yearly albendazole and ivermectin to suppress *Wuchereria bancrofti* microfilarial levels. *Clin Infect Dis* 2010; **51:** 1229–35.

Microsporidiosis. Albendazole has been tried[1-6] in the treatment of the protozoal infection microsporidiosis (p. 925.3) in patients with AIDS. Albendazole has also been used empirically in the treatment of HIV-associated infections and complications (p. 960.3).

1. Blanshard C, *et al.* Treatment of intestinal microsporidiosis with albendazole in patients with AIDS. *AIDS* 1992; **6:** 311–13.
2. Dieterich DT, *et al.* Treatment with albendazole for intestinal disease due to Enterocytozoon bieneusi in patients with AIDS. *J Infect Dis* 1994; **169:** 178–82.
3. Franzen C, *et al.* Intestinal microsporidiosis with Septata intestinalis in a patient with AIDS—response to albendazole. *J Infect* 1995; **31:** 237–9.
4. Dore GJ, *et al.* Disseminated microsporidiosis due to Septata intestinalis in nine patients infected with the human immunodeficiency virus: response to therapy with albendazole. *Clin Infect Dis* 1995; **21:** 70–6.
5. Molina J-M, *et al.* Albendazole for treatment and prophylaxis of microsporidiosis due Encephalitozoon intestinalis in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis* 1998; **177:** 1373–7.
6. Tremoulet AH, *et al.* Albendazole therapy for Microsporidium diarrhea in immunocompetent Costa Rican children. *Pediatr Infect Dis J* 2004; **23:** 915–18.

Strongyloidiasis. Albendazole is generally preferred to tiabendazole or mebendazole in the treatment of strongyloidiasis (p. 148.2) although ivermectin is now generally considered to be the drug of choice. Both drugs have been used together in disseminated disease.

References.

1. Rossignol JF, Maisonneuve H. Albendazole: placebo-controlled study in 870 patients with intestinal helminthiasis. *Trans R Soc Trop Med Hyg* 1983; **77:** 707–11.
2. Chanthavanich P, *et al.* Repeated doses of albendazole against strongyloidiasis in Thai children. *Southeast Asian J Trop Med Public Health* 1989; **20:** 221–6.
3. Mojon M, Nielsen PB. Treatment of Strongyloides stercoralis with albendazole: a cure rate of 86 per cent. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 1987; **263:** 619–24.
4. Archibald LK, *et al.* Albendazole is effective treatment for chronic strongyloidiasis. *Q J Med* 1993; **86:** 191–5.
5. Pornsuriyasak P, *et al.* Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2004; **35:** 531–4.
6. Singthong S, *et al.* Randomized comparative trial of two high-dose albendazole regimens for uncomplicated human strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2006; **37** (suppl 3): 32–4.

Toxocariasis. Albendazole is one of the drugs that might be used for the treatment of toxocariasis (p. 148.3) but published controlled studies are mostly lacking. In a small study[1] it produced improvement similar to that achieved with tiabendazole but with fewer problems. An oral dose of 400 mg twice daily for 5 days has been recommended,[2,3] although the optimum duration of therapy is unknown and some would treat for 20 days.[3] In those with severe symptoms or eye involvement treatment may need to be extended; adjunctive corticosteroid treatment may also be necessary.[3]

1. Stürchler D, *et al.* Thiabendazole vs albendazole in treatment of toxocariasis: a clinical trial. *Ann Trop Med Parasitol* 1989; **83:** 473–8.
2. Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003; **16:** 265–72.
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Trichinosis. Albendazole may be effective in the treatment of trichinosis (p. 148.3). A retrospective study in 44 patients with trichinosis comparing albendazole treatment with tiabendazole found that, while the two drugs were of comparable efficacy, albendazole was the better tolerated.[1] An oral dose of 400 mg twice daily for 8 to 14 days has been recommended.[2] Albendazole has been used to treat a patient infected with *Trichinella pseudospiralis*, an organism related to *T. spiralis*, the usual cause of trichinosis.[3]

1. Cabié A, *et al.* Albendazole versus thiabendazole as therapy for trichinosis: a retrospective study. *Clin Infect Dis* 1996; **22:** 1033–5.
2. Gottstein B, *et al.* Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev* 2009; **22:** 127–45.
3. Andrews JRH, *et al.* Trichinella pseudospiralis in humans: description of a case and its treatment. *Trans R Soc Trop Med Hyg* 1994; **88:** 200–3.

Trichostrongyliasis. Albendazole in a single oral dose of 400 mg has been suggested[1] as an alternative to pyrantel embonate or mebendazole in the treatment of trichostrongyliasis (p. 148.3).

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Trichuriasis. Oral albendazole is used in the treatment of trichuriasis (p. 149.1). It is normally given in a single dose and is often used in mixed intestinal nematode infections.[1] However, it has been reported[1-3] that in children with mixed intestinal worm infections single doses of albendazole are ineffective in eliminating *Trichuris trichiura* and multiple doses are required to produce worthwhile reductions in egg production. Treatment for 3 days has been used for heavier infections[4] (but for a suggestion that such regimens may be associated with impaired growth in less heavily infected children, see Effects on Growth under Adverse Effects, p. 152.1). Combined use of albendazole with ivermectin may prove useful.[5] A systematic review[6] however considered that all current regimens for the treatment of trichuriasis were unsatisfactory.

1. Hall A, Anwar KS. Albendazole and infections with Trichuris trichiura and Giardia intestinalis. *Southeast Asian J Trop Med Public Health* 1991; **22:** 84–7.
2. Hall A, Nahar Q. Albendazole and infections with Ascaris lumbricoides and Trichuris trichiura in children in Bangladesh. *Trans R Soc Trop Med Hyg* 1994; **88:** 110–12.
3. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88:** 585–9.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
5. Ismail MM, Jayakody RL. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of Trichuris trichiura infections in Sri Lanka. *Ann Trop Med Parasitol* 1999; **93:** 501–4.
6. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.

Adverse Effects and Precautions

As for Mebendazole, p. 160.3.

Adverse effects are usually mild and resolve without treatment. However, in patients being treated for echinococcosis (hydatid disease), albendazole has caused mild to moderate increases of liver enzyme values in about 16% of patients; hepatitis and acute liver failure have also been reported. Leucopenia has occurred in less than 1% of patients; while agranulocytosis, aplastic anaemia, neutropenia, or thrombocytopenia are rare, deaths due to granulocytopenia and pancytopenia have been reported. Patients with liver disease, including hepatic echinococcosis, appear to be at increased risk of bone marrow suppression and in these patients blood cell counts and liver function should be closely monitored.

Patients being treated for neurocysticercosis should be given corticosteroids to prevent cerebral hypertensive episodes during the first week of therapy. Anticonvulsant therapy also may be necessary. Albendazole may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are given, and an ophthalmic examination should be performed before treatment to exclude intra-ocular cysts.

Incidence of adverse effects. Although *high-dose* therapy with albendazole for the treatment of cystic echinococcosis (hydatid disease) was generally well-tolerated, the following adverse reactions were reported in the first phase of WHO-coordinated studies[1] involving 30 patients: raised serum-transaminase levels (2 patients), reduced leucocyte counts (1 patient), gastrointestinal symptoms (1 patient), allergic conditions (1 patient), and loss of hair (1 patient). Treatment was stopped in a further patient with alveolar echinococcosis because of depressed bone-marrow activity. In the second phase of these studies,[2] of 109 patients given albendazole for cystic echinococcosis, 20 had adverse effects; similar findings were reported with mebendazole. The range of effects with albendazole was: elevation of transaminases (5 patients), abdominal pain and other gastrointestinal symptoms (7 patients), severe headache (4 patients), loss of hair (2 patients), leucopenia (2 patients), fever and fatigue (1 patient), thrombocytopenia (1 patient), and urticaria and itching (1 patient). Albendazole had to be withdrawn in 5 patients because of adverse effects, although in 3 the withdrawal was only temporary.

1. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64:** 383–8.

2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67:** 503–8.

Breast feeding. The results of a study[1] in 33 women given a single oral 400-mg dose of albendazole suggested that albendazole and its active metabolite attained low concentrations in breast milk. The authors considered that albendazole was unlikely to be harmful to breast-fed infants.

1. Abdel-tawab AM, *et al.* Albendazole and its metabolites in the breast milk of lactating women following a single oral dose of albendazole. *Br J Clin Pharmacol* 2009; **68:** 737–42.

Effects on growth. A multiple-dose regimen of albendazole in children with asymptomatic trichuriasis has been reported to be associated with impaired growth in those with low levels of infection.[1] However it was considered that this should not prevent the use of single doses in mass treatment programmes.[2]

1. Forrester JE, *et al.* Randomised trial of albendazole and pyrantel in symptomless trichuriasis in children. *Lancet* 1998; **352:** 1103–8.
2. Winstanley P. Albendazole for mass treatment of asymptomatic trichuris infections. *Lancet* 1998; **352:** 1080–1.

Effects on the liver. In a series of 40 patients given albendazole for echinococcosis, 7 developed abnormalities in liver function tests during therapy.[1] Six had a hepatocellular type of abnormality attributable to albendazole; the seventh had cholestatic jaundice which was probably not due to albendazole. See also Incidence of Adverse Effects, p. 150.3 for reports of raised serum-transaminase levels.

Albendazole should only be used in the treatment of echinococcosis if there is constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.[2]

1. Morris DL, Smith PG. Albendazole in hydatid disease—hepatocellular toxicity. *Trans R Soc Trop Med Hyg* 1987; **81:** 343–4.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67:** 503–8.

Pregnancy. Albendazole is teratogenic in some *animals* and there are no adequate and well controlled studies in human pregnancy. Albendazole is therefore usually contra-indicated during pregnancy and US licensed product information cautions against becoming pregnant while taking albendazole or within one month of completing treatment.

For reference to a study of women given albendazole with ivermectin during the second trimester of pregnancy, see p. 158.2.

Interactions

Anthelmintics. The plasma concentration of albendazole sulfoxide has been increased by *praziquantel*,[1] although the practical consequences of this were considered uncertain. A later study[2] in healthy subjects indicated that plasma concentrations of (+) and (-) enantiomers of albendazole sulfoxide were increased by about 260 and 360% respectively, albendazole sulfone by some 190%, and (-)-(*R*)-praziquantel by about 65%, when albendazole and praziquantel were given together. Although this raised the possibility of increased efficacy from the combination, the magnitude of the changes suggested that increased adverse effects might be a problem, and dose adjustment might be needed.[2]

1. Homeida M, *et al.* Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* 1994; **88:** 551–9.
2. Lima RM, *et al.* Albendazole-praziquantel interaction in healthy volunteers: kinetic disposition, metabolism and enantioselectivity. *Br J Clin Pharmacol* 2011; **71:** 528–35.

Antiepileptics. *Phenytoin, carbamazepine,* and *phenobarbital* appear to induce the oxidative metabolism of albendazole via the cytochrome P450 isoenzyme CYP3A by roughly the same extent, resulting in significantly reduced concentrations of albendazole sulfoxide. This interaction is likely to be clinically significant when albendazole is used to treat systemic worm infections, and increased doses of albendazole would be needed.[1] The interaction is probably not clinically significant when albendazole is used for intestinal worm infections.

1. Lanchote VL, *et al.* Pharmacokinetic interaction between albendazole sulfoxide enantiomers and antiepileptic drugs in patients with neurocysticercosis. *Ther Drug Monit* 2002; **24:** 338–45.

Corticosteroids. Plasma concentrations of the active metabolite of albendazole (albendazole sulfoxide) were reported to be raised by about 50% in a study in 8 patients receiving *dexamethasone*.[1]

1. Jung H, *et al.* Dexamethasone increases plasma levels of albendazole. *J Neurol* 1990; **237:** 279–80.

Gastrointestinal drugs. Concentrations of albendazole sulfoxide have been found to be raised in bile and hydatid cyst fluid when albendazole was given with *cimetidine*, which may increase efficacy in the treatment of echinococcosis.[1]

1. Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; **88:** 49–52.

Pharmacokinetics

Absorption of albendazole from the gastrointestinal tract is poor but may be enhanced by a fatty meal. Albendazole rapidly undergoes extensive first-pass metabolism. Its principal metabolite albendazole sulfoxide has anthelmintic activity and a plasma half-life of about 8.5 hours. Albendazole sulfoxide is widely distributed throughout the body including into the bile and the CSF. It is about 70% bound to plasma protein. Albendazole sulfoxide is eliminated in the bile; only a small amount appears to be excreted in the urine.

References.

1. Marriner SE, *et al.* Pharmacokinetics of albendazole in man. *Eur J Clin Pharmacol* 1986; **30:** 705–8.
2. Morris DL, *et al.* Penetration of albendazole sulphoxide into hydatid cysts. *Gut* 1987; **28:** 75–80.
3. Steiger U, *et al.* Albendazole treatment of echinococcosis in humans: effects on microsomal metabolism and drug tolerance. *Clin Pharmacol Ther* 1990; **47:** 347–53.
4. Jung H, *et al.* Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J Clin Pharmacol* 1992; **32:** 28–31.
5. Jung H, *et al.* Clinical pharmacokinetics of albendazole in children with neurocysticercosis. *Am J Ther* 1997; **4:** 23–6.
6. Dayan AD. Albendazole, mebendazole and praziquantel: review of non-clinical toxicity and pharmacokinetics. *Acta Trop* 2003; **86:** 141–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vastus; Vermizole; ***Austral.***: Eskazole; Zentel; ***Austria***: Eskazole; ***Braz.***: Alba-3; Albel; Albendrox; Albendy; Albentel; Albenzonil; Albezin; Alin; Benzol; Imavermil†; Mebenix; Monozol; Neo Bendazol; Parasin; Parazol; Vermiclase; Vermital; Zentel; Zolben; ***Chile***: Ceprazol†; Vermoil; Zentel; ***China***: Abentel (阿丙条); Zentel (肠虫清); ***Cz.***: Zentel†; ***Fr.***: Eskazole; Zentel; ***Ger.***: Eskazole; ***Gr.***: Albendol; Eskazole; Zentel; ***India***: ABD; Abide; ABZ; Abzole; AH-1; Al; Albacos; Albamaa; Albasym; Albazole; Albekon; Albendol; Albent; Albenzole; Albesan; Albest; Albestar; Albex; Albezole; Albol; Albosym; Alboven; Albrodo; Alenda; Alio; Alminth; Altec; Alworm; Alzad; Alzol; Anthel; Antiworm; Ariban; Asibend; Atbend; Aviband; Avizole; Band; Bandy; Banthel; Bendex; Bendol; Benrod; Benzys; Biwom; C-Band; C-Bend; C-Trop; Cidazole; Combantrin-A; Conthel; Cuwarm; Dazo; Dispel; E-Bend; Ebex; Ejectil; Elbend; Eleben; Elminex; Emanthal†; Enbenol; Foben; Gekare; Getrid; Janbol; Kiraza; Lupibend; Milibend; Morband; N-Bend; NBWorm; Nemaban; Nemofex; Nemozole; Noworm; Nubend; Oben; Odal; Olban; Olworm; Omnitel; Zentel; ***Israel***: Eskazole; ***Ital.***: Zentel; ***Malaysia***: Albendol†; Almex; Champs D-Worms; Mesin-C; Thelban; Vemizol; Zendal; Zenmex; Zentel; Zoben; ***Mex.***: Albensil†; Aldamin; Alfazol; Bendapar†; Bradelmin; Dazocan; Dazolin; Dezabil; Digezanol; Entoplus†; Eskazole; Euralben; Gascop; Helmisons†; Ilides; Kolexan; Loveral†; Lumbrifar; Lurdex; Olbendital†; Rivazol; Serbendazol; Synparyn; Tenibex†; Veranzol†; Vermin Plus; Vermisen; Zelfin; Zenaxin; Zentel; ***Neth.***: Eskazole; ***Philipp.***: Adazol; Alzel; Benzol; Zentel; ***Pol.***: Zentel; ***Port.***: Zentel; ***Rus.***: Nemozole (Немозол); Sanoxal (Саноксал); ***S.Afr.***: Bendex; Wormadole; Zentel; ***Singapore***: Albendol; Alzental; Zentel; ***Spain***: Eskazole; ***Switz.***: Zentel; ***Thai.***: Abentel†; Albatel; Alben-Hero; Alben-VC; Alben; Albenda; Albenz; Albezol; Alda; Aldazole; Alfuca; Alzol; Antheda†; Benyad; CB-400; Falben; Fatel; Gendazel; Labenda; Leo-400†; Manozide; Mesin; Mycotel†; Prodazole; San-San; Vermixide; Vetoben; Zeben; Zela; Zentel; Zenzera; ***Turk.***: Andazol; ***UAE***: Albenda; ***Ukr.***: Aldazole (Альдазол); Vormil (Вормил); Zentel (Зентел); ***USA***: Albenza; ***Venez.***: Albezol; Albicar; Bevindazol; Helal; Sostril; Taron; Vendazol; Zentel.

Multi-ingredient Preparations. ***India***: Ablaze-IM; ABZ Plus; Albacos-IR; Albosym-IR; Alvect; Anthel-UP; Ariban Plus; Ascapil A; Bandy Plus; Benrod-I; Benzole; D-Worm; Ectin-A; Elect-A; Elminova; Eradix; Eris Plus; Getrid-I; Hymin Plus; Hymin; Imectin Forte; Ivecop-AB; Ivercid-A; Iverzole; Ivoral; Kaybend; Kidi; Macbi Plus; Networm; ***Mex.***: C Cobistal; Farmiver; Oxal; ***Thai.***: Albemed.

Pharmacopoeial Preparations
USP 36: Albendazole Tablets.

Trivalent Antimony Compounds

Compuestos de antimonio trivalente; Трехвалентные Соединения Сурьмы.

Antimony Potassium Tartrate

Antim. Pot. Tart.; Antimónico potásico, tartrato; Antimonium Tartaricum; Antymonu potasu winian; Brechweinstein; Kalii Stibyli Tartras; Potassium Antimonyltartrate; Stibii et Kalii Tartras; Tartar Emetic; Tartarus Stibiatus; Антимонил-тартрат Калия.

Dipotassium bis[μ-[2,3-dihydroxybutanedioato(4-)-O^1,O^2:O^3,O^4]]-diantimonate(2-) trihydrate; Dipotassium bis[μ-tartrato (4-)]diantimonate(2-) trihydrate.

$C_8H_4K_2O_{12}Sb_2.3H_2O$=667.9

CAS — 11071-15-1 (anhydrous antimony potassium tartrate); 28300-74-5 (antimony potassium tartrate trihydrate).

UNII — DL6OZ476V3.

Pharmacopoeias. In *US*.

USP 36: (Antimony Potassium Tartrate). Odourless, colourless, transparent crystals or white powder. The crystals effloresce on exposure to air and do not readily rehydrate even on exposure to high humidity. Soluble 1 in 12 of water, 1 in 3 of boiling water, and 1 in 15 of glycerol; insoluble in alcohol. Its solutions are acid to litmus.

Antimony Sodium Tartrate

Antim. Sod. Tart.; Antimónico sódico, tartrato; Sodium Antimonyltartrate; Stibium Natrium Tartaricum; Антимонил-тартрат Натрия.

Disodium bis[μ-[2,3-dihydroxybutanedioato(4-)-O^1,O^2:O^3,O^4]] diantimonate(2-); Disodium bis[μ-[L-(+)-tartrato(4-)]]diantimonate(2-).

$C_8H_4Na_2O_{12}Sb_2$=581.6

CAS — 34521-09-0.

UNII — 3KUI0LP48L.

Pharmacopoeias. In *Int.* (as $C_4H_4NaO_7Sb$ = 308.8) and *US*.

USP 36: (Antimony Sodium Tartrate). Odourless, colourless, transparent crystals or white powder. The crystals effloresce on exposure to air. Freely soluble in water; insoluble in alcohol.

Sodium Stibocaptate *(BAN, rINN)*

Antimony Sodium Dimercaptosuccinate; Estibocaptato de sodio; Natrii Stibocaptas; Ro-4-1544/6; Sb-58; Stibocaptate; Stibocaptate de Sodium; TWSb/6; Натрия Стибокаптат.

Antimony sodium *meso*-2,3-dimercaptosuccinate. The formula varies from $C_{12}H_{11}NaO_{12}S_6Sb_2$ = 806.1 to $C_{12}H_6Na_6O_{12}S_6Sb_2$ = 916.0.

CAS — 3064-61-7 ($C_{12}H_6Na_6O_{12}S_6Sb_2$).

UNII — VFV49ULL8Q.

Stibophen

Estibofeno; Fouadin; Stibophenum; Стибофен.

Bis[4,5-dihydroxybenzene-1,3-disulphonato(4-)-O^4,O^5]antimonate(5-) pentasodium heptahydrate.

$C_{12}H_4Na_5O_{16}S_4Sb.7H_2O$=895.2

CAS — 15489-16-4 (stibophen heptahydrate).

ATC — P02BX03.

Uses and Administration

Trivalent antimony compounds were used in the treatment of the protozoal infection leishmaniasis until the advent of the less toxic pentavalent compounds. They continued to be used in the treatment of schistosomiasis, but have now been superseded by less toxic and more easily given drugs such as praziquantel.

Antimony sodium tartrate was formerly used as an emetic. The sodium tartrate and potassium tartrate have also been used as expectorants.

Adverse Effects and Treatment

Trivalent antimony compounds are more toxic than pentavalent antimonials such as sodium stibogluconate, possibly because they are excreted much more slowly. The most serious adverse effects are on the heart and liver. There are invariably ECG changes during treatment, but hypotension, bradycardia, and cardiac arrhythmias are more serious. Sudden death or cardiovascular collapse may occur at any time. Elevated liver enzyme values are common; liver damage with hepatic failure and death is more likely in patients with pre-existing hepatic disease.

Adverse effects immediately after intravenous use of trivalent antimonials, in particular the tartrates, have included coughing, chest pain, pain in the arms, vomiting, abdominal pain, fainting, and collapse, especially after rapid injection. Extravasation during injection is extremely painful because of tissue damage. An anaphylactoid reaction characterised by an urticarial rash, husky voice, and collapse has been reported after the sixth or seventh intravenous injection of a course of treatment.

Many less immediate adverse effects have occurred including gastrointestinal disturbances, muscular and joint pains, arthritis, pneumonia, dyspnoea, headache, dizziness, weakness, pruritus, rashes, facial oedema, fever, haemolytic anaemia, and kidney damage.

Large oral doses of antimony compounds have an emetic action. Continuous treatment with small doses of antimony

may give rise to symptoms of subacute poisoning similar to those of chronic arsenical poisoning.

Treatment of severe poisoning with antimony compounds is similar to that for arsenic poisoning (p. 2449.1); dimercaprol may be of benefit.

References.
1. Stemmer KL. Pharmacology and toxicology of heavy metals: antimony. *Pharmacol Ther* 1976; **1:** 157–60.

Precautions

Trivalent antimony therapy has generally been superseded by less toxic treatment. It is contra-indicated in the presence of lung, heart, liver, or kidney disease. Intravenous injections should be given very slowly and stopped if coughing, vomiting, or substernal pain occurs; extravasation should be avoided.

Some antimony compounds such as the tartrates cause severe pain and tissue necrosis and should not be given by intramuscular or subcutaneous injection.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of antimony by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Glucose-6-phosphate dehydrogenase deficiency. In the event of trivalent antimony compounds being used, patients with G6PD deficiency should be excluded. WHO lists stibophen[1] among the anthelmintics to be avoided in patients with this deficiency.

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67:** 601–11.

Pharmacokinetics

Antimony compounds are poorly absorbed from the gastrointestinal tract. They are slowly excreted, mainly in the urine, after parenteral doses. Antimony accumulates in the body during treatment and persists for several months afterwards. Trivalent antimony has a greater affinity for cell proteins than for plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Port.***: Stodal; ***Thai.***: Brown Mixture; Mist Tussis.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Childrens Cough Relief; Respatona Chesty Cough & Nasal Congestion; ***Austria***: Bronchalis-Heel; Pneumodoron Nr 2; Tartephedreel; Tonsan chronisch; ***Canad.***: Acne; Brocosin; Bronkeel†; Calnor†; Cou Complex†; Cough Syrup with Honey†; Hylands Cough; Hylands Formula CS; Stodal; ***Cz.***: Bronchalis-Heel; ***Fr.***: Boripharm No 12†; Cetraria Complexe No 61; Homeogene 14†; Homeogrippe†; Ipeca Compose; Pulmo-Drainol†; Stodal; Stodal; ***Ger.***: Bomarthros Harpagophytum Complex; Bronchiselect; Cefasulfon N†; Eupatorium N Oligoplex; Pneumodoron 2; Rheuma-Hevert; Rheuma-Hevert; Roth's RKT Tropfen; Rufebran broncho†; Vomistop; ***Hung.***: Bronchalis-Heel; Stodal; ***Neth.***: Bronchalis; Stodal; ***Rus.***: Атма (Atma); Stodal (Стодаль); ***S.Afr.***: Pneumodoron 2†; ***Switz.***: Bronchalis-Heel; Stodal; ***Ukr.***: Атма (Атма); Stodal (Стодаль).

Betanaphthol

2-Naftol; β-Naftol; 2-Naftoli; 2-Naftolo; Naphthol; Бетанафтол.
Naphth-2-ol.
$C_{10}H_8O$=144.2
CAS — 135-19-3.
UNII — P2Z71CIK5H.

Pharmacopoeias. In *Pol.* and *Swiss.*

Profile

Betanaphthol was formerly used as an anthelmintic in hookworm and tapeworm infections, but it has been superseded by less toxic and more efficient drugs.

Betanaphthol has a potent parasiticidal effect and has been used topically in the treatment of scabies, ringworm, and other skin diseases.

Betanaphthyl benzoate has been used in preparations for the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Hekabetol.

Bithionol *(BAN, rINN)*

Bithionololum; Bithionolum; Bitionol; Bitionolol; Bitionololi; Битионол.
2,2′-Thiobis(4,6-dichlorophenol).
$C_{12}H_6Cl_4O_2S$=356.0
CAS — 97-18-7.
ATC — D10AB01; P02BX01.
ATC Vet — QD10AB01; QP52AG07.
UNII — AMT77LS62O.

Pharmacopoeias. *Fr.* includes bithionol oxide for veterinary use.

Uses and Administration

Bithionol is a chlorinated bis-phenol with bactericidal and anthelmintic properties. It is active against most trematodes (flukes). Bithionol is used in preference to praziquantel in fascioliasis as an alternative to triclabendazole (see Liver Fluke Infections, p. 146.2). It is also used in paragonimiasis (see Lung Fluke Infections, p. 146.3) as an alternative to praziquantel. It may be given in an oral dose of 30 to 50 mg/kg on alternate days for 10 to 15 doses. Shorter regimens have been used.

Bithionol was formerly used topically as a bactericide but this use has declined because of photosensitivity reactions.

Adverse Effects

Adverse effects in patients taking oral bithionol include anorexia, nausea, vomiting, abdominal discomfort, diarrhoea, salivation, dizziness, headache, and rashes.

Photosensitivity reactions have occurred in persons using soap containing bithionol. Cross-sensitisation with other halogenated disinfectants has also occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Fonergine.

Bromofenofos *(rINN)*

Bromfenofos; Bromofenofós; Bromofénofos; Bromofenofosum; Bromophenophos; Bromphenphos; Бромофенофос.
3,3′,5,5′-Tetrabromo-2,2′-biphenyldiolmono(dihydrogen phosphate).
$C_{12}H_7Br_4O_5P$=581.8
CAS — 21466-07-9.
ATC Vet — QP52AB02.
UNII — XTH861Q3CR.

Profile

Bromofenofos is a bisphenol derivative used as an anthelmintic in veterinary medicine for the treatment of fluke infections.

Cambendazole *(BAN, USAN, rINN)*

Cambendazol; Cambendazolum; MK-905; Камбендазол.
Isopropyl 2-(thiazol-4-yl)-1*H*-benzimidazol-5-ylcarbamate.
$C_{14}H_{14}N_4O_2S$=302.4
CAS — 26097-80-3.
ATC Vet — QP52AC08.
UNII — 079X63S3DU.

Profile

Cambendazole is a benzimidazole carbamate anthelmintic structurally related to tiabendazole (p. 168.1). It is used in the treatment of strongyloidiasis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Cambem.

Multi-ingredient Preparations. ***Braz.***: Exelmin.

Chenopodium Oil

Aceite de quenopodio; Aetheroleum Chenopodii; Esencia de Quenopodio Vermifuga; Oil of American Wormseed; Wurmsamenöl; Маревое Масло; Амброзиевое Масло.
CAS — 8006-99-3.
UNII — 3009681U6R.

Profile

Chenopodium oil is distilled with steam from the fresh flowering and fruiting plants, excluding roots, of *Chenopodium ambrosioides* var. *anthelminticum*.It contains ascaridole and was formerly used as an anthelmintic for the expulsion of roundworms (*Ascaris*) and hookworms. It is toxic and has caused many fatalities.

Handling. Chenopodium oil may explode when heated.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Fr.***: Cina Complexe No 55†.

Clorsulon *(BAN, USAN, rINN)*

Clorsulón; Clorsulone; Clorsulonum; MK-401; Клорсулон.
4-Amino-6-(trichlorovinyl)benzene-1,3-disulphonamide.
$C_8H_8Cl_3N_3O_4S_2$=380.6
CAS — 60200-06-8.
UNII — EG1ZDO6LRD.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Clorsulon). A white to off-white powder. Slightly soluble in water; freely soluble in acetonitrile and in methyl alcohol; very slightly soluble in dichloromethane.

Profile

Clorsulon is a sulfonamide anthelmintic used in veterinary medicine for the treatment of liver fluke infections.

Closantel *(BAN, USAN, rINN)*

Closantelum; R-31520; Клозантел.
5′-Chloro-4′-(4-chloro-α-cyanobenzyl)-3,5-di-iodosalicyl-*o*-toluidide.
$C_{22}H_{14}Cl_2I_2N_2O_2$=663.1
CAS — 57808-65-8.
ATC Vet — QP52AG09.
UNII — EUL532EI54.

Closantel Sodium *(BANM, rINNM)*

Closantel sódico; Closantel Sodique; Closantelum natricum; Klosanteelinatrium; Klosantel sodná sůl; Klosantelnatrium; Natrii Closantelum; R-34828; Натрий Клозантел.
$C_{22}H_{14}Cl_2I_2N_2O_2Na$=686.1
UNII — 0ZBS9YC04P (anhydrous closantel sodium); 181924B87F (closantel sodium dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) as the dihydrate for veterinary use.

Ph. Eur. 8: (Closantel Sodium Dihydrate for Veterinary Use; Closantel Sodium Dihydrate BP(Vet) 2014). A yellow, slightly hygroscopic, powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Closantel is an anthelmintic used in veterinary medicine for the treatment of fluke and nematode infections.

Effects on the eyes. Loss of eyesight was reported in 11 women who received closantel (Flukiver) in mistake for a gynaecological product.[1] Sight was restored after closantel was stopped but incapacitating eye pain remained.

1. t Hoen E, *et al.* Harmful human use of donated veterinary drug. *Lancet* 1993; **342:** 308–9.

Diamfenetide *(BAN, rINN)*

Diamfenetida; Diamfénétide; Diamfenetidum; Diamphenethide; Диамфенетид.
β,β′-Oxybis(aceto-*p*-phenetidide).
$C_{20}H_{24}N_2O_5$=372.4
CAS — 36141-82-9.
UNII — U4TFJ7GB6T.

Profile

Diamfenetide is an anthelmintic that has been used in veterinary medicine for the control of fascioliasis in sheep.

Dichlorophen *(BAN, rINN)*

Dichlorofeen; Dichlorophène; Dichlorophenum; Diclorofeno; Di-phenthane-70; G-4; Дихлорофен.
2,2′-Methylenebis(4-chlorophenol).
$C_{13}H_{10}Cl_2O_2$=269.1
CAS — 97-23-4.
ATC — P02DX02.

ATC Vet — QP52AG01.
UNII — T1J0JOU64O.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Dichlorophen). A white or slightly cream-coloured powder with a not more than slightly phenolic odour. Practically insoluble in water; freely soluble in alcohol; very soluble in ether.

Profile

Dichlorophen is an anthelmintic that was used in the treatment of infection by tapeworms but has been superseded by praziquantel or niclosamide.

Dichlorophen also has antifungal and antibacterial activity and has been used topically in the treatment of fungal infections and as a germicide in soaps and cosmetics.

Hypersensitivity. Dichlorophen is used for its antibacterial and antifungal properties in various manufactured products and there is a report[1] of a patient whose eczema of the hands and face and vesicular-bullous lesions of the feet were associated with the presence of dichlorophen in the leather of her shoes. It was of note that the appearance of the reaction to dichlorophen in patch testing was delayed for 10 days.

1. Barbuzza O, *et al.* Late patch test reaction to dichlorophene. *J Investig Allergol Clin Immunol* 2008; **18:** 317–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK:* Mycota.

Pharmacopoeial Preparations
BP 2014: Dichlorophen Tablets.

Diethylcarbamazine Citrate

(BANM, rINNM)

Citrato de dietilcarbamazina; Diethylcarbam. Cit.; Diethylcarbamazindihydrogencitrat; Diethylcarbamazine Acid Citrate; Diéthylcarbamazine, citrate de; Diethylcarbamazini Citras; Diethylkarbamazin-citrát; Dietilcarbamazina, citrato de; Dietilkarbamazin-citrát; Dietilkarbamazino citratas; Dietylkarbamazincitrat; Dietyylikarbamatsiinisitraatti; Ditrazini Citras; RP-3799; Диэтилкарбамазина Цитрат.

NN-Diethyl-4-methylpiperazine-1-carboxamide dihydrogen citrate.

$C_{10}H_{21}N_3O,C_6H_8O_7$=391.4

CAS — 90-89-1 (diethylcarbamazine); 1642-54-2 (diethylcarbamazine citrate).
ATC — P02CB02.
UNII — OS1Z389K8S.

Pharmacopoeias. In *Chin.*, *Eur.* (sep. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Diethylcarbamazine Citrate). A white or almost white, crystalline, slightly hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in acetone. Store in airtight containers.

USP 36: (Diethylcarbamazine Citrate). A white, crystalline, slightly hygroscopic powder, odourless or has a slight odour. Very soluble in water; sparingly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether. Store in airtight containers.

Uses and Administration

Diethylcarbamazine is an anthelmintic used in the treatment of lymphatic filariasis due to *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, or *B. timori* (both known as brugian filariasis and as Malayan and Timorian filariasis respectively). It is also used in the treatment of loiasis due to *Loa loa* and toxocariasis (visceral larva migrans). Diethylcarbamazine is active against both the microfilariae and adult worms of *W. bancrofti*, *B. malayi*, and *Loa loa*, but only against the microfilariae of *Onchocerca volvulus*. It was used in onchocerciasis due to *O. volvulus* before ivermectin became available. It has been tried in *Mansonella* infections and may be most effective against *M. streptocerca*. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Diethylcarbamazine is usually given orally as the citrate.

In the treatment of **lymphatic filariasis** caused by *W. bancrofti* a total cumulative dose of 72 mg/kg is usually recommended; half this dose is usually effective in *B. malayi* and *B. timori* infections. To reduce the incidence and severity of hypersensitivity reactions due to the destruction of microfilariae an initial dose of 1 mg/kg is given and then gradually increased over 2 to 3 days to 6 mg/kg daily (preferably in divided doses) for 12 days. However, adverse effects of diethylcarbamazine may be reduced, without loss of efficacy, by giving a single dose of 6 mg/kg at weekly or monthly intervals. In areas where lymphatic filariasis is endemic, *mass treatment* campaigns can reduce the intensity of transmission and incidence of disease. Diethylcarbamazine may also be used in the form of medicated salt to control lymphatic filariasis. For further details, see p. 154.3.

In the treatment of **loiasis** diethylcarbamazine citrate 6 to 9 mg/kg daily in 3 divided doses for 21 days has been given. In heavy infections rapid killing of microfilariae can cause severe adverse effects including encephalitis and treatment should start with very small doses, increasing gradually over 3 days. A corticosteroid has been given concurrently. In the prophylaxis of loiasis, a dose of 300 mg weekly is recommended by WHO.

In the treatment of **toxocariasis** diethylcarbamazine citrate 6 mg/kg daily in 2 divided doses for 21 days may be given. Diethylcarbamazine is considered by some to be the treatment of choice while others do not recommend its use due to high rates of allergic reactions induced by dying larvae. To reduce the intensity of these reactions WHO suggests starting treatment at a dose of 1 mg/kg twice daily and increasing gradually to 3 mg/kg twice daily.

For details of doses in children, see p. 154.3.

Administration. Diethylcarbamazine was first used as the chloride, but was subsequently produced as the dihydrogen citrate which contains only half its weight as base. In reporting doses it was therefore important to indicate whether they referred to a specific salt or to the base; unless otherwise stated, it could generally be assumed that the dose referred to the citrate.[1]

1. WHO. Lymphatic filariasis: fourth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 702* 1984. Available at: http://libdoc.who.int/trs/WHO_TRS_702.pdf (accessed 16/07/08)

Administration in children. Diethylcarbamazine citrate may be given orally to children for the treatment of lymphatic filariasis, loiasis and toxocariasis (visceral larva migrans).

For the treatment of **lymphatic filariasis** US experts[1] consider that children may be given the same dose as for adults (see above), while WHO recommends that children under 10 years of age be given half the usual adult dose.[2]

For the treatment of **loiasis** US experts consider that children may be given a dose of 9 mg/kg daily in 3 divided doses for 21 days; treatment should start with very small doses, increasing gradually over 3 days.[1] No dose recommendation is given by WHO.[2]

For the treatment of **toxocariasis** WHO considers that children may be given the same dose as for adults (see above).[2]

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter,2013.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 19/11/09)

Loiasis. Diethylcarbamazine is the main drug used in the management of loiasis (p. 146.2).

References.
1. Nutman TB, *et al.* Loa loa infection in temporary residents of endemic regions: recognition of a hyperresponsive syndrome with characteristic clinical manifestations. *J Infect Dis* 1986; **154:** 10–18.
2. Nutman TB, *et al.* Diethylcarbamazine prophylaxis for human loiasis: results of a double-blind study. *N Engl J Med* 1988; **319:** 752–6.
3. Nutman TB, Ottesen EA. Diethylcarbamazine and human loiasis. *N Engl J Med* 1989; **320:** 320.
4. Klion AD, *et al.* Effectiveness of diethylcarbamazine in treating loiasis acquired by expatriate visitors to endemic regions: long-term follow-up. *J Infect Dis* 1994; **169:** 604–10.

Lymphatic filariasis. Diethylcarbamazine is used in the management of lymphatic filariasis (p. 146.3). In endemic areas *mass treatment* of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is no co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO with other international agencies, advocates a single oral dose of diethylcarbamazine citrate 6 mg/kg with a single oral dose of albendazole 400 mg, given once each year for at least 5 years. If diethylcarbamazine-medicated salt is to be employed then intake of salt needs to be on a daily basis for 6 to 12 months.

Mansonella infections. Diethylcarbamazine given orally at a dose of 6 mg/kg daily in 3 divided doses for 12 days,[1] is one of the drugs that has been suggested for the treatment of infections with *Mansonella streptocerca* (p. 147.2).

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter,2013.

Adverse Effects

Mild to moderate adverse effects are common but the incidence of serious adverse effects is very low. Adverse effects may be more severe and common in those with a high parasite burden. Commonly reported adverse effects include fever, dizziness, drowsiness, headache, malaise, microscopic haematuria, myalgia, nausea, and vomiting.

Hypersensitivity reactions arise from the death of the microfilariae. These can be serious, especially in onchocerciasis where there may also be sight-threatening ocular toxicity; fatalities have been reported. Encephalitis may be exacerbated in patients with loiasis and fatalities have occurred; those with very high microfilaria counts are at increased risk.

Reactions occurring during diethylcarbamazine treatment of **lymphatic filariasis** are basically of 2 types: pharmacological dose-dependent responses and a response of the infected host to the destruction and death of parasites.[1]

- Reactions of the first type include weakness, dizziness, lethargy, anorexia, and nausea. They begin within 1 to 2 hours of taking diethylcarbamazine, and persist for a few hours.
- Reactions of the second type are less likely to occur and are less severe in bancroftian than in brugian filariasis. They may be systemic or local, both with or without fever.

  Systemic reactions may occur a few hours after the first oral dose of diethylcarbamazine and generally do not last for more than 3 days. They include headache, aches in other parts of the body, joint pain, dizziness, anorexia, malaise, transient haematuria, allergic reactions, vomiting, and sometimes attacks of bronchial asthma in asthmatic patients. Fever and systemic reactions are positively associated with microfilaraemia. Systemic reactions are reduced if diethylcarbamazine is given in spaced doses or in repeated small doses. They eventually cease spontaneously and interruption of treatment is rarely necessary; symptomatic treatment with antipyretics or analgesics may be helpful.

  Local reactions tend to occur later in the course of treatment and last longer; they also disappear spontaneously and interruption of treatment is not necessary. Local reactions include lymphadenitis, abscess, ulceration, and transient lymphoedema; funiculitis and epididymitis may also occur in bancroftian filariasis.

It has been suggested that the release of interleukin-6 may be implicated in diethylcarbamazine's adverse effects in patients with lymphatic filariasis.[2]

In most patients with **onchocerciasis**, the microfilaricidal activity of diethylcarbamazine leads to a series of events with dermal, ocular, and systemic components, known as the *Mazzotti reaction*, within minutes to hours after its use.[3]

- Clinical manifestations can be severe, dangerous, and debilitating. Systemic reactions include increased itching, rash, headache, aching muscles, joint pain, painful swollen and tender lymph nodes, fever, tachycardia and hypotension, and vertigo. Most patients have eye discomfort in the first few hours after diethylcarbamazine treatment. Punctate keratitis can develop as can optic neuritis and visual field loss.

WHO no longer recommends the use of diethylcarbamazine in onchocerciasis as safer alternatives exist.

1. WHO. Lymphatic filariasis: the disease and its control: fifth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 821* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_821.pdf (accessed 19/11/09)
2. Yazdanbakhsh M, *et al.* Serum interleukin-6 levels and adverse reactions to diethylcarbamazine in lymphatic filariasis. *J Infect Dis* 1992; **166:** 453–4.
3. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987. Also available at: http://libdoc.who.int/trs/WHO_TRS_752_(part1).pdf (accessed 19/11/09)

Precautions

Treatment with diethylcarbamazine should be closely supervised since hypersensitivity reactions are common and may be severe, especially in patients with onchocerciasis or loiasis. Diets that promote the alkalinisation of the urine may increase the elimination half-life of diethylcarbamazine (see also Pharmacokinetics, p. 155.1); dose reductions may be needed. Patients with onchocerciasis should be monitored for eye changes. (The use of diethylcarbamazine to treat onchocerciasis is no longer recommended.) In patients with heavy *Loa loa* infection there is a small risk of encephalopathy and diethylcarbamazine should be stopped at the first sign of cerebral involvement.

Infants, pregnant women, the elderly, and the debilitated, especially those with cardiac or renal disease, are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Pregnancy. Pregnant women are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Animal studies[1] suggest that the uterine hypermotility induced by diethylcarbamazine is mediated via prostaglan-

din synthesis; this might explain the mechanism of the abortifacient action previously reported.[2]

1. Joseph CA, Dixon PAF. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol* 1984; **36:** 281–2.
2. Subbu VSV, Biswas AR. Ecbolic effect of diethyl carbamazine. *Indian J Med Res* 1971; **59:** 646–7.

Renal impairment. For a study on the effects of renal impairment on the pharmacokinetics of diethylcarbamazine, see under Pharmacokinetics, p. 155.2.

Pharmacokinetics

Diethylcarbamazine is readily absorbed from the gastrointestinal tract and also through the skin and conjunctiva. It is not significantly bound to plasma protein. It is widely distributed in tissues and is mainly excreted in the urine unchanged and as the *N*-oxide metabolite. Urinary excretion and hence plasma half-life is dependent on urinary pH, with a shorter half-life in acidic urine. About 5% of a dose is eliminated in the faeces.

Disposition. A pharmacokinetic study in 6 patients with onchocerciasis[1] indicated that diethylcarbamazine is absorbed quickly and almost completely from the gastrointestinal tract, and is eliminated largely as unchanged drug in urine, with relatively small amounts being excreted as the *N*-oxide metabolite. After a single radioactively labelled oral dose of diethylcarbamazine citrate 500 micrograms/kg given as an aqueous solution, peak plasma concentrations of 100 to 150 nanograms/mL were achieved in 1 to 2 hours, followed by a sharp decline, then a marked secondary rise 3 to 6 hours after dosing, followed by a steady decline. The half-life ranged from 9 to 13 hours. Urinary excretion of diethylcarbamazine and diethylcarbamazine *N*-oxide was complete within 96 hours; between 4 and 5% of the dose was recovered in the faeces. Disposition was similar in 5 healthy subjects given a single 50-mg tablet of diethylcarbamazine citrate. Peak plasma concentrations were initially 80 to 200 nanograms/mL, with a secondary rise 3 to 9 hours after dosing, the terminal half-life ranged from 5 to 13 hours, and urinary excretion of unchanged diethylcarbamazine and the *N*-oxide was complete within 48 hours.

When an alkaline urinary pH was maintained, the elimination half-life of diethylcarbamazine and the area under the plasma concentration versus time curve were significantly increased compared with when an acidic urinary pH was maintained.[2]

1. Edwards G, *et al.* Diethylcarbamazine disposition in patients with onchocerciasis. *Clin Pharmacol Ther* 1981; **30:** 551–7.
2. Edwards G, *et al.* The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol* 1981; **12:** 807–12.

Renal impairment. Results in patients with chronic renal impairment and in healthy subjects, given a single 50-mg oral dose of diethylcarbamazine citrate, indicated that the plasma half-life of diethylcarbamazine is prolonged and its 24-hour urinary excretion considerably reduced in those with moderate and severe degrees of renal impairment.[1] Mean plasma half-lives in 7 patients with severe renal impairment (creatinine clearance less than 25 mL/minute), in 5 patients with moderate renal impairment (creatinine clearance between 25 and 60 mL/minute), and in 4 healthy subjects, were 15.1, 7.7, and 2.7 hours, respectively. The patient with the longest plasma half-life of 32 hours did not have the poorest renal function, but it was considered likely that the abnormally slow elimination of diethylcarbamazine was due to the high urinary pH (7) resulting from sodium bicarbonate therapy. A further patient with a half-life longer than expected also had a less acidic urine.

1. Adjepon-Yamoah KK, *et al.* The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol* 1982; **13:** 829–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Notezine; ***Gr.***: Notezine; ***India***: Banocide; Decet; Dicarb; Hetrazan; ***Thai.***: Diethizine.

Multi-ingredient Preparations. ***India***: Carbamyl; Carcet; Decet-BD; Decet-OD; Dicarb Inga; Esnopil; Flary-Forte; Unicarbazan.

Pharmacopoeial Preparations
BP 2014: Diethylcarbamazine Tablets;
USP 36: Diethylcarbamazine Citrate Tablets.

Disophenol

Disofenol.
2,6-Diiodo-4-nitrophenol.
$C_6H_3I_2NO_3$=390.9
CAS — 305-85-1.
UNII — 3955ZJ6SYN.

Profile

Disophenol is an anthelmintic used in veterinary medicine for the treatment of hookworm and gapeworm infections.

Doramectin *(BAN, USAN, rINN)*

Doramectina; Doramectine; Doramectinum; Doramektiini; Doramektin; UK-67994; Дорамектин.
CAS — 117704-25-3.
ATC Vet — QP54AA03.
UNII — KGD7A54H5P.

Profile

Doramectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Embelia

Vidang; Виданга.
CAS — 550-24-3 (embelic acid).
*UNII — YA87U85J0D (*Embelia ribes*); X1Q40X9I5L (*Embelia ribes *fruit).*

Profile

Embelia consists of the dried fruits of *Embelia ribes* and *E. robusta* (= *E. tsjeriamcottam*) (Myrsinaceae), containing about 2.5% of embelic acid (embelin). It has been used in India and other Asian countries for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Herbadict; ***India***: Happy'tizer†; ***Ukr.***: Trypsidan (Трипсидан)†.

Eprinomectin *(USAN, rINN)*

Eprinomectina; Éprinomectine; Eprinomectinum; Eprinomektiini; Eprinomektin; MK-397; Эприномектин.
A mixture of eprinomectin component B_{1a} and eprinomectin component B_{1b}.
CAS — 159628-36-1 (eprinomectin); 123997-26-2 (eprinomectin); 133305-88-1 (component B_{1a}); 133305-89-2 (component B_{1b}).
ATC Vet — QP54AA04.
UNII — 75KP30FD8O (eprinomectin); 00OY54D31C (eprinomectin component B_{1a}); 31OML2QZ0Q (eprinomectin component B_{1b}).

Pharmacopoeias. In *US*.

USP 36: (Eprinomectin). Eprinomectin is a mixture of component B_{1a}($C_{50}H_{75}NO_{14}$ = 914.1) and component B_{1b} ($C_{49}H_{73}NO_{14}$ = 900.1). It contains not less than 90% of component B_{1a} and not less than 95% of components B_{1a} and B_{1b}, calculated on the anhydrous, solvent-free, and antoxidant-free basis. Antoxidants may be added. A white to off-white powder. Insoluble in cold water. Store in airtight containers at 2 degrees to 8 degrees.

Profile

Eprinomectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Epsiprantel *(BAN, rINN)*

BRL-38705; Epsipranteeli; Epsiprantelum; Эпсипрантел.
2-Cyclohexylcarbonyl-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepin-4-one.
$C_{20}H_{26}N_2O_2$=326.4
CAS — 98123-83-2.
ATC Vet — QP52AA04.
UNII — 0C1SPQ0FSR.

Profile

Epsiprantel is an anthelmintic closely related to praziquantel. It is used in veterinary medicine.

Febantel *(BAN, USAN, rINN)*

Bay-Vh-5757; Bay-h-5757; Febanteeli; Fébantel; Febantelum; Фебантел.
2′-[2,3-Bis(methoxycarbonyl)guanidino]-5′-phenylthio-2-methoxyacetanilide; Dimethyl {2-[2-(2-methoxyacetamido)-4-(phenylthio)phenyl]imidocarbonyl}dicarbamate.
$C_{20}H_{22}N_4O_6S$=446.5
CAS — 58306-30-2.
ATC Vet — QP52AC05.
UNII — S75C401OS1.

NOTE. The name Avicas has been used as a trade mark for febantel.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Febantel for Veterinary Use; Febantel BP(Vet) 2014). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in acetone.

Profile

Febantel is a prodrug that is converted to fenbendazole (see p. 156.1). It is an anthelmintic used in veterinary medicine for the treatment of nematode infections of the gastrointestinal tract and lungs and in tapeworm infections.

Fenbendazole *(BAN, USAN, rINN)*

Fenbendatsoli; Fenbendazol; Fenbendazolum; Hoe-881V; Фенбендазол.
Methyl 5-phenylthio-1*H*-benzimidazol-2-ylcarbamate.
$C_{15}H_{13}N_3O_2S$=299.3
CAS — 43210-67-9.
ATC — P02CA06.
ATC Vet — QP52AC13.
UNII — 621BVT9M36.

NOTE. The names Beaphar, Fenzol, Granofen, Norworm and Panacur have been used as trade marks for fenbendazole.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Fenbendazole for Veterinary Use; Fenbendazole BP(Vet) 2014). A white or almost white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Protect from light.

USP 36: (Fenbendazole). A white to off-white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Fenbendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 160.1). It is used in veterinary medicine for the treatment of nematode infections of the gastrointestinal tract and lungs and in tapeworm infections.

Flubendazole *(BAN, USAN, rINN)*

Flubendatsoli; Flubendazol; Flubendazolas; Flubendazolum; Fluoromebendazole; R-17889; Флубендазол.
Methyl 5-(4-fluorobenzoyl)-1*H*-benzimidazol-2-ylcarbamate.
$C_{16}H_{12}FN_3O_3$=313.3
CAS — 31430-15-6.
ATC — P02CA05.
ATC Vet — QP52AC12.
UNII — R8M46911LR.

NOTE. The names Flubenol, Flubenvet, and Solubenol have been used as trade marks for flubendazole.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flubendazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Flubendazole, a benzimidazole carbamate anthelmintic, is an analogue of mebendazole (p. 160.1) and has similar actions and uses.

For the treatment of enterobiasis in adults and children, flubendazole 100 mg is given as a single oral dose, repeated after 2 to 3 weeks. For ascariasis, hookworm infections, and trichuriasis 100 mg is given twice daily for 3 days. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1.

It is also used in veterinary medicine for the treatment of nematode and tapeworm infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flumoxal; ***Fr.***: Fluvermal; ***Port.***: Fluvermal; Teniverme; ***Spain***: Flicum†; ***Venez.***: Fluvermox.

Haloxon *(BAN, rINN)*

Haloxón; Haloxone; Haloxonum; Галоксон.

Bis(2-chloroethyl) 3-chloro-4-methylcoumarin-7-yl phosphate.

$C_{14}H_{14}Cl_3O_6P$=415.6

CAS — 321-55-1.

ATC Vet — QP52AB04.

UNII — T8KXA37068.

Profile

Haloxon is an organophosphorus compound (see Organophosphorus Insecticides, p. 2158.3) used as an anthelmintic in veterinary medicine.

Hygromycin B

Higromicina B; Hygromycine B; Гигромицин Б.

O-6-Amino-6-deoxy-L-glycero-D-galacto-heptopyranosylidene-(1→2-3)-*O*-β-D-talopyranosyl-(1→5)-2-deoxy-N^3-methyl-D-streptamine.

$C_{20}H_{37}N_3O_{13}$=527.5

CAS — 31282-04-9.

UNII — 3XQ2233B0B.

Profile

Hygromycin B is used as a feed additive in veterinary practice; use over several weeks is moderately effective in controlling gastrointestinal roundworms in pigs and poultry.

Ivermectin *(BAN, USAN, rINN)*

Ivermectina; Ivermectine; Ivermectinum; Ivermektiini; Ivermektin; Ivermektinas; Ивермектин.

CAS — 70288-86-7 (ivermectin); 71827-03-7 (component B_{1a}); 70209-81-3 (component B_{1b}).

ATC — P02CF01.

ATC Vet — QP54AA01; QS02QA03.

UNII — 8883YP2R6D (ivermectin); 91Y2202OUW (ivermectin component H_2B_{1a}); 0W28CYI3TU (ivermectin component H_2B_{1b}).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ivermectin). A mixture of ivermectin component H_2B_{1a} (5-*O*-demethyl-22,23-dihydroavermectin A_{1a}; $C_{48}H_{74}O_{14}$ = 875.1) and ivermectin component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}; $C_{47}H_{72}O_{14}$ = 861.1).

A white or yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

USP 36: (Ivermectin). A mixture of component H_2B_{1a} (5-*O*-demethyl-22,23-dihydro-avermectin A_{1a}; $C_{48}H_{74}O_{14}$ = 875.1) and component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-avermectin A_{1a}; $C_{47}H_{72}O_{14}$ = 861.1). It may contain small amounts of suitable antoxidant and chelating agents.

A white to yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in petroleum spirit; soluble in acetone and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Where the use of an antoxidant is allowed, store at 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Ivermectin is a semisynthetic derivative of one of the avermectins, a group of macrocyclic lactones produced by *Streptomyces avermitilis*.

It has a microfilaricidal action in onchocerciasis and reduces the microfilarial load without the toxicity seen with diethylcarbamazine. Ivermectin also has a microfilaricidal action in lymphatic filariasis and is used in endemic areas as part of a mass treatment regimen. Ivermectin is active in some other worm infections. It is used in the treatment of strongyloidiasis and has been tried in some *Mansonella* infections. For details of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below. It is used topically in the treatment of head pediculosis (see also p. 157.2).

In the treatment of **onchocerciasis**, a single oral dose of ivermectin, based roughly on 150 micrograms/kg may be given to patients weighing more than 15 kg; re-treatment is usually required, and is given after an interval of at least 3 months. For mass treatment in infected areas (see p. 157.1) the dose is given annually or every 6 months. No food should be taken for 2 hours before or after the dose. Similar or slightly higher doses, plus a dose of albendazole, are advocated by WHO in the mass treatment of **lymphatic filariasis** (see p. 157.1 for details).

For the treatment of **strongyloidiasis**, ivermectin 200 micrograms/kg as a single oral dose, or daily on two consecutive days, is given to patients weighing more than 15 kg.

Ivermectin is used in the treatment of **head pediculosis** as a single topical application of a 0.5% lotion in adults and children from 6 months of age. It should be applied to dry hair, left on for 10 minutes and then washed out.

Reviews.

1. Ottesen EA, Campbell WC. Ivermectin in human medicine. *J Antimicrob Chemother* 1994; **34:** 195–203.
2. Ōmura S. Ivermectin: 25 years and still going strong. *Int J Antimicrob Agents* 2008; **31:** 91–8.

Administration in children. Ivermectin may be given orally to children weighing more than 15 kg and over 5 years of age, for the management of onchocerciasis and lymphatic filariasis and also for the treatment of strongyloidiasis. Doses used are the same by weight as those used for adults (see above).

Cutaneous larva migrans. There are some reports[1-5] of ivermectin being effective in the treatment of cutaneous larva migrans (p. 144.3). An oral dose of 200 micrograms/kg daily for 1 to 2 days has been recommended.[6]

1. Caumes E, *et al.* Efficacy of ivermectin in the therapy of cutaneous larva migrans. *Arch Dermatol* 1992; **128:** 994–5.
2. Caumes E, *et al.* A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg* 1993; **49:** 641–4.
3. Bouchaud O, *et al.* Cutaneous larva migrans in travelers: a prospective study, with assessment of therapy with ivermectin. *Clin Infect Dis* 2000; **31:** 493–8. Correction. *ibid.* 2001; **32:** 523.
4. delMar Sáez-De-Ocariz M, *et al.* Treatment of 18 children with scabies or cutaneous larva migrans using ivermectin. *Clin Exp Dermatol* 2002; **27:** 264–7.
5. Senba Y, *et al.* Case of creeping disease treated with ivermectin. *J Dermatol* 2009; **36:** 86–9.
6. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Intestinal nematode infections. Ivermectin activity has been seen in man against *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Trichuris trichiura*;[1] although some have failed to detect activity against *Trichuris*,[2] ivermectin given with albendazole in doses similar to those recommended for mass treatment in the management of lymphatic filariasis (see p. 157.1), has been studied for the treatment of trichuriasis (p. 149.1) and may prove useful in areas where soil-transmitted worm infections and lymphatic filariasis are public health problems.[3] A randomised, controlled study in 548 school children in Zanzibar[4] found that single oral doses of ivermectin (200 micrograms/kg) plus either albendazole (400 mg) or mebendazole (500 mg) improved cure and egg reduction rates against *T. trichiura*. The highest cure and egg reduction rates were achieved with ivermectin plus mebendazole (55 and 97% respectively), while lower rates were seen with ivermectin plus albendazole (38% cure rate and 91% egg reduction rate). Roundworm expulsion has also been reported as a 'side-effect' of ivermectin when used in community-based treatment of onchocerciasis.[5] In a controlled study,[6] single oral doses of ivermectin 150 or 200 micrograms/kg produced cure rates of 94% in strongyloidiasis (see p. 157.3) and above 67% in ascariasis, trichuriasis, and enterobiasis. Although some activity has been seen against *Necator americanus*,[1] cure rates for hookworm were considered unsatisfactory.[6]

1. Freedman DO, *et al.* The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 1989; **159:** 1151–3.
2. Whitworth JAG, *et al.* A field study of the effect of ivermectin on intestinal helminths in man. *Trans R Soc Trop Med Hyg* 1991; **85:** 232–4.
3. Belizario VY, *et al.* A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against Ascaris and Trichuris spp. *Bull WHO* 2003; **81:** 35–42.
4. Knopp S, *et al.* Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis* 2010; **51:** 1420–8.
5. Whitworth JAG, *et al.* Community-based treatment with ivermectin. *Lancet* 1988; **ii:** 97–8.
6. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; **40:** 304–9.

Loiasis. There is evidence of reduced microfilaraemia after ivermectin treatment[1-5] in patients with loiasis (p. 146.2), but concern exists over its potential for neurotoxicity in patients with a high microfilarial burden.[6,7] There is some evidence[8] that a genetic predisposition to altered distribution of ivermectin may be a co-factor for the development of serious adverse events in patients with high numbers of microfilaria. Low-dose regimens (about 25 micrograms/kg) have been investigated[9] but did not seem to offer much advantage in reducing neurotoxicity.

1. Martin-Prevel Y, *et al.* Reduction of microfilaraemia with single high-dose of ivermectin in loiasis. *Lancet* 1993; 342: 442.
2. Ranque S, *et al.* Decreased prevalence and intensity of Loa loa infection in a community treated with ivermectin every three months for two years. *Trans R Soc Trop Med Hyg* 1996; **90:** 429–30.
3. Duong TH, *et al.* Reduced Loa loa microfilaria count ten to twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; **91:** 592–3.
4. Gardon J, *et al.* Marked decrease in Loa loa microfilaraemia six and twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; **91:** 593–4.
5. Chippaux J-P, *et al.* Impact of repeated large scale ivermectin treatments on the transmission of Loa loa. *Trans R Soc Trop Med Hyg* 1998; **92:** 454–8.
6. Anonymous. Encephalitis following treatment of loiasis. *WHO Drug Inf* 1991; **5:** 113–14.
7. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; **350:** 18–22.
8. Bourguinat C, *et al.* Analysis of the mdr-1 gene in patients co-infected with *Onchocerca volvulus* and *Loa loa* who experienced a post-ivermectin serious adverse event. *Am J Trop Med Hyg* 2010; **83:** 28–32.
9. Kamgno J, *et al.* Randomized, controlled, double-blind trial with ivermectin on Loa loa microfilaraemia: efficacy of a low dose (~25 μ g/kg) versus current standard dose (150 μ g/kg). *Trans R Soc Trop Med Hyg* 2007; **101:** 777–85.

Lymphatic filariasis. Ivermectin is used in the management of lymphatic filariasis (p. 146.3). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single oral dose of ivermectin 150 to 200 micrograms/kg with a single oral dose of albendazole 400 mg given once each year for at least 5 years.

Higher doses of albendazole and ivermectin (800 mg and 400 micrograms/kg respectively) given twice a year for 2 years, to 25 residents of an area of high *Wuchereria bancrofti* endemicity in Mali, were found to be more effective in reducing microfilarial levels than the standard annual dose regimen recommended by WHO. Higher-dose and/or more frequent treatment regimens could therefore potentially reduce the time necessary to interrupt transmission.[1]

1. Dembele B, *et al.* Use of high-dose, twice-yearly albendazole and ivermectin to suppress *Wuchereria bancrofti* microfilarial levels. *Clin Infect Dis* 2010; **51:** 1229–35.

Malaria. It has been suggested that ivermectin, given as part of mass treatment programs for filarial infections, may also kill malarial mosquitos when they bite treated patients, resulting in a reduction in malaria transmission.[1,2]

1. Kobylinski KC, *et al.* Ivermectin mass drug administration to humans disrupts malaria parasite transmission in Senegalese villages. *Am J Trop Med Hyg* 2011; **85:** 3–5.
2. Tanne JH. Antiparasite drug ivermectin cuts mosquito numbers by 80%. *BMJ* 2011; **343:** d4355.

Mansonella infections. The response of *Mansonella* infections (p. 147.2) to ivermectin depends on the species. It may be effective against *Mansonella ozzardi*, but studies in *M. perstans* infection have not shown ivermectin to produce a substantial reduction in microfilaraemia,[1,2] even used with albendazole.[3,4] A good response to a single oral dose of 150 micrograms/kg of ivermectin has been reported in infections with *M. streptocerca*.[5,6]

1. Van den Enden E, *et al.* Treatment failure of a single high dose of ivermectin for Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 1993; **87:** 90.
2. Schulz-Key H, *et al.* Efficacy of ivermectin in the treatment of concomitant Mansonella perstans infections in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 1993; **87:** 227–9.
3. Asio SM, *et al.* Mansonella perstans: safety and efficacy of ivermectin alone, albendazole alone and the two drugs in combination. *Ann Trop Med Parasitol* 2009; **103:** 31–7.
4. Asio SM, *et al.* A randomised, double-blind field trial of ivermectin alone and in combination with albendazole for the treatment of Mansonella perstans infections in Uganda. *Trans R Soc Trop Med Hyg* 2009; **103:** 274–9.
5. Fischer P, *et al.* Treatment of human Mansonella streptocerca infection with ivermectin. *Trop Med Int Health* 1997; **2:** 191–9.
6. Fischer P, *et al.* Long-term suppression of Mansonella streptocerca microfilariae after treatment with ivermectin. *J Infect Dis* 1999; **180:** 1403–5.

Onchocerciasis. Ivermectin has a microfilaricidal action against *Onchocerca volvulus* and is the main drug used in the control of onchocerciasis (p. 147.2). A single oral dose rapidly eliminates microfilariae from the skin, with maximum effect after 1 to 2 months,[1] and gradually eliminates them from the cornea and anterior chamber of the eye.[2] Ivermectin has little effect on the adult worms but does suppress the release of microfilariae from the adult worm for several cycles which accounts for its prolonged activity. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Its action against *O. volvulus* has been attributed to a GABA-agonist effect. Studies have also

indicated that ivermectin inhibits the transmission of microfilariae by reducing their uptake from man by the insect vector.[3-6]

Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in community-wide mass treatment programmes in all countries in which onchocerciasis is endemic, where it is given at a standard oral dose of 150 micrograms/kg once or twice a year to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg, and those unable to walk or otherwise seriously ill.[7] The adult worms live for about 15 years, therefore treatment will need to be continued for many years. Several studies have confirmed the long-term safety and efficacy of such programmes.[8-12] Studies have reported that increasing the frequency of the standard doses of ivermectin to every 3 or 6 months appears to increase efficacy compared with annual treatments[13,14] and that 3-monthly regimens may also reduce risk of adverse effects.[14,15] No additional benefit was noted by increasing the dose of ivermectin to 400 or 800 micrograms/kg given either 3-monthly or annually.

In non-endemic areas, repeated doses may be necessary to reduce recurrence; a study in the UK found that patients given three doses at monthly intervals had fewer relapses at 6 months than patients who received a single dose, but relapses were nevertheless seen in 50% of patients at 12 months.[16]

The ocular microfilarial load can be safely reduced by ivermectin[2,17] and early lesions of the anterior segment of the eye have improved.[17] A reduction in the incidence[18] and progression[19] of optic nerve damage has also been reported, but the effect on posterior segment disease is less certain.[20] A systematic review of 5 placebo-controlled studies, with data from 3810 individuals, found no statistically significant difference between ivermectin and placebo groups for preventing visual acuity loss.[21] Improvements in skin lesions have been reported.[22]

1. Basáñez MG, *et al.* Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8:** 310–22.
2. Newland HS, *et al.* Effect of single-dose ivermectin therapy on human Onchocerca volvulus infection with onchocercal ocular involvement. *Br J Ophthalmol* 1988; **72:** 561–9.
3. Taylor HR, *et al.* Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science* 1990; **250:** 116–18.
4. Trpis M, *et al.* Effect of mass treatment of a human population with ivermectin on transmission of Onchocerca volvulus by Simulium yahense in Liberia, West Africa. *Am J Trop Med Hyg* 1990; **42:** 148–56.
5. Chavasse DC, *et al.* Low level ivermectin coverage and the transmission of onchocerciasis. *Trans R Soc Trop Med Hyg* 1995; **89:** 534–7.
6. Boussinesq M, *et al.* Onchocerca volvulus: striking decrease in transmission in the Vina valley (Cameroon) after eight annual large scale ivermectin treatments. *Trans R Soc Trop Med Hyg* 1997; **91:** 82–6.
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8. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; **67:** 707–19.
9. Pacqué M, *et al.* Safety of and compliance with community-based ivermectin therapy. *Lancet* 1990; **335:** 1377–80.
10. Pacqué M, *et al.* Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. *J Infect Dis* 1991; **163:** 381–5.
11. Steel C, *et al.* Immunologic responses to repeated ivermectin treatment in patients with onchocerciasis. *J Infect Dis* 1991; **164:** 581–7.
12. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: clinical and parasitological responses to four doses given at six-monthly interval. *Trans R Soc Trop Med Hyg* 1992; **86:** 277–80.
13. Greene BM, *et al.* A comparison of 6-, 12-, and 24-monthly dosing with ivermectin for treatment of onchocerciasis. *J Infect Dis* 1991; **163:** 376–80.
14. Gardon J, *et al.* Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* 2002; **360:** 203–10.
15. Kamgno J, *et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; **98:** 496–504.
16. Churchill DR, *et al.* A trial of a three-dose regimen of ivermectin for the treatment of patients with onchocerciasis in the UK. *Trans R Soc Trop Med Hyg* 1994; **88:** 242.
17. Dadzie KY, *et al.* Changes in ocular onchocerciasis after two rounds of community-based ivermectin treatment in a holo-endemic onchocerciasis focus. *Trans R Soc Trop Med Hyg* 1991; **85:** 267–71.
18. Abiose A, *et al.* Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet* 1993; **341:** 130–4.
19. Cousens SN, *et al.* Impact of annual dosing with ivermectin on progression of onchocercal visual field loss. *Bull WHO* 1997; **75:** 229–36.
20. Whitworth JAG, *et al.* Effects of repeated doses of ivermectin on ocular onchocerciasis: community-based trial in Sierra Lione. *Lancet* 1991; **338:** 1100–1103.
21. Ejere H, *et al.* Ivermectin for onchocercal eye disease (river blindness). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 29/07/07).
22. Pacqué M, *et al.* Improvements in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 1991; **90:** 590–4.

Scabies and pediculosis. Scabies (p. 2148.1) is usually treated with a topically applied acaricide. However, a single oral dose of ivermectin has been reported to be effective.[1-3] In a study of 11 patients with uncomplicated scabies, a single oral dose of ivermectin 200 micrograms/kg was effective in curing infection after 4 weeks. In a group of 11 patients, also infected with HIV, scabies was cured in 8 after 2 weeks.[1] Two of the remaining 3 patients received a second dose of ivermectin which cured the scabies infection by the fourth week. Ivermectin does not sterilise the scabies eggs and in order to kill newly hatched mites a second dose of ivermectin is recommended, given at least 7 days after the first dose.[4] A single oral dose of ivermectin 150 micrograms/kg was partially effective in an outbreak of scabies in 1153 Tanzanian patients.[5] A systematic review[3] on the treatment of scabies found that oral ivermectin was less effective than topical permethrin, but appeared to be as effective as topical benzyl benzoate and more effective than topical lindane. However, a randomised, open-label study[6] found that one or two applications of 12.5% benzyl benzoate, each left on for 24 hours, were more effective than a single oral dose of ivermectin of 150 to 200 micrograms/kg; bacterial superinfection also occurred more often in those given ivermectin than in those treated with benzyl benzoate.

Crusted (Norwegian) scabies has also been reported to be effectively treated by a single oral dose of 12 mg of ivermectin in addition to topical application of 3% salicylic acid ointment in 2 patients; the treatment was effective in under one week.[2] A single oral dose of ivermectin 200 micrograms/kg was effective for crusted scabies in a 2-year-old infant who had contracted the disease following long-term corticosteroid use.[7] Ivermectin has also been successfully used in a small number of patients with treatment-resistant scabies.[8]

Ivermectin has also been investigated[9] as a possible treatment for pediculosis (p. 2147.3) although, again, topically applied insecticides are the usual method of control. A study *in vitro* and in *animals* showed that ivermectin killed nymphs and females of the human body louse (*Pediculus humanus humanus*). Ivermectin was known to be effective against other louse species that infect a range of *animals*.[10] Ivermectin has also been shown to be effective against head lice: two oral doses of 400 micrograms/kg at an interval of 7 days were more effective than applications of malathion 0.5% in a controlled double-blind study in patients with refractory infestations.[11] A 0.5% topical lotion has been licensed in the USA for the treatment of head pediculosis (see Uses and Administration, p. 155.1).

1. Meinking TL, *et al.* The treatment of scabies with ivermectin. *N Engl J Med* 1995; **333:** 26–30.
2. Aubin F, Humbert P. Ivermectin for crusted (Norwegian) scabies. *N Engl J Med* 1995; **332:** 612.
3. Strong M, Johnstone PW. Interventions for treating scabies. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 21/08/09).
4. Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. *N Engl J Med* 2010; **362:** 717–25.
5. Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol* 2000; **143:** 520–3.
6. Ly F, *et al.* Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. *Bull WHO* 2009; **87:** 424–30.
7. Marlière V, *et al.* Crusted (Norwegian) scabies induced by use of topical corticosteroids and treated successfully with ivermectin. *J Pediatr* 1999; **135:** 122–4.
8. Cook AM, Romanelli F. Ivermectin for the treatment of resistant scabies. *Ann Pharmacother* 2003; **37:** 279–81.
9. Foucault C, *et al.* Oral ivermectin in the treatment of body lice. *J Infect Dis* 2006; **193:** 474–6.
10. Mumcuoglu KY, *et al.* Systemic activity of ivermectin on the human body louse (Anoplura: Pediculidae). *J Med Entomol* 1990; **27:** 72–5.
11. Chosidow O, *et al.* Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010; **362:** 896–905. Correction. *ibid.*; 1647.

Strongyloidiasis. Ivermectin is effective in the treatment of strongyloidiasis (p. 148.2) and is considered by some authorities to be the drug of choice. Subcutaneous use has been investigated in patients with severe, disseminated disease.

References.
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2. Wijesundera M de S, Sanmuganathan PS. Ivermectin therapy in chronic strongyloidiasis. *Trans R Soc Trop Med Hyg* 1992; **86:** 291.
3. Lyagoubi M, *et al.* Chronic persistent strongyloidiasis cured by ivermectin. *Trans R Soc Trop Med Hyg* 1992; **86:** 541.
4. Datry A, *et al.* Treatment of Strongyloides stercoralis infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg* 1994; **88:** 344–5.
5. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; **169:** 1076–9.
6. Marti H, *et al.* A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg* 1996; **55:** 477–81.
7. Igual-Adell R, *et al.* Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother* 2004; **5:** 2615–9.
8. Marty FM, *et al.* Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. *Clin Infect Dis* 2005; **41:** e5–e8.
9. Pacanowski J, *et al.* Subcutaneous ivermectin as a safe salvage therapy in Strongyloides stercoralis hyperinfection syndrome: a case report. *Am J Trop Med Hyg* 2005; **73:** 122–4.
10. Salluh JI, *et al.* Successful use of parenteral ivermectin in an immunosuppressed patient with disseminated strongyloidiasis and septic shock. *Intensive Care Med* 2005; **31:** 1292.
11. Hauber HP, *et al.* Fatal outcome of a hyperinfection syndrome despite successful eradication of Strongyloides with subcutaneous ivermectin. *Infection* 2005; **33:** 383–6.
12. Turner SA, *et al.* Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. *Am J Trop Med Hyg* 2005; **73:** 911–4.
13. Leung V, *et al.* Case report: failure of subcutaneous ivermectin in treating Strongyloides hyperinfection. *Am J Trop Med Hyg* 2008; **79:** 853–5.
14. Lichtenberger P, *et al.* Hyperinfection strongyloidiasis in a liver transplant recipient treated with parenteral ivermectin. *Transpl Infect Dis* 2009; **11:** 137–42.

Trichostrongyliasis. For mention of the use of ivermectin in *Trichostrongylus* infections, see p. 148.3.

Adverse Effects and Precautions

The adverse effects reported with ivermectin in patients with filariasis are generally consistent with a mild Mazzotti reaction arising from its effect on microfilariae. They include fever, pruritus, rashes, arthralgia, myalgia, asthenia, orthostatic hypotension, tachycardia, oedema, lymphadenopathy, gastrointestinal symptoms, sore throat, cough, and headache. The effects tend to be transient and if treatment is required they respond to analgesics and antihistamines.

Ivermectin may cause mild ocular irritation. Somnolence, transient eosinophilia, and raised liver enzyme values have also been reported.

Ivermectin is not recommended during pregnancy. Mass treatment is generally withheld from pregnant women (see Pregnancy, p. 158.2), children under 15 kg, and the seriously ill.

Incidence of adverse effects. Some studies have shown quite a high incidence of adverse effects with ivermectin and have associated the effects with the severity of infection.[1-3] However, in none of these studies were the reactions considered to be life-threatening and only symptomatic treatment was required. The severity, incidence, and duration of adverse reactions was reported to be reduced after repeated annual doses.[4]

When larger groups of patients were considered in the Onchocerciasis Control Programme (OCP) in West Africa, a much lower incidence of adverse reactions was seen in patients given ivermectin for the first time[5] and when treatment was repeated a year later that incidence was reduced even further. The results from several studies in this programme[6] showed 93 severe reactions in 50 929 patients (1.83%), most of the reactions being orthostatic hypotension or dizziness (53). In a 3-year randomised, double-blind, controlled study of ivermectin for onchocerciasis control in 572 patients,[7] 3-monthly treatment with the standard dose of 150 micrograms/kg was associated with a reduced risk of adverse reactions, especially oedema, pruritus, and back pain, when compared with the same dose given annually. Higher doses of 400 then 800 micrograms/kg, given either 3-monthly or annually, were associated with subjective ocular problems.

Another study[8] found 22 severe reactions in 17 877 patients treated for onchocerciasis in an area also endemic for *Loa loa* infection, and showed a relationship to heavy *L. loa* microfilaraemia. The Mectizan Expert Committee and the Technical Consultative Committee have reported the incidence of encephalopathy after ivermectin treatment of onchocerciasis in *Loa loa* endemic areas to be less than 1 case in 10 000 treatments[9] and have implemented recommendations for ivermectin mass treatment programmes of onchocerciasis in areas co-endemic for loiasis to reduce the risk of serious adverse events, especially in areas where the population is ivermectin naive.

Some supervision is considered necessary after doses of ivermectin;[2,6] the OCP recommendation[6] is for resident nurses to monitor patients for a period of 36 hours after treatment, whatever the level of endemicity. However, the incidence of adverse reactions reported after repeated doses appears to be lower than after the first dose and the need for supervision on re-treatment has been questioned.[10]

Neurotoxicity seen in some breeds of *dogs* has not been seen in *cattle* or *horses*[11] and nor was it reported in man in the above studies. Another potential concern was the prolongation of prothrombin times seen in 28 patients given ivermectin,[12] but others have not confirmed this effect[13] or seen any bleeding disorders.[14]

There has been some concern over the use of ivermectin to treat scabies in elderly patients after a report suggesting a possible link to an increased incidence of death among a cohort of 47 patients.[15] It has, however, been argued that no such association has been seen in other populations of elderly patients and that the statistical methods used by the original authors were deficient.[16-18] There was no evidence of an increase in death rate associated with ivermectin in a community-based study in Papua New Guinea of diethylcarbamazine with or without ivermectin for lymphatic filariasis.[19]

1. Kumaraswami V, *et al.* Ivermectin for the treatment of Wuchereria bancrofti filariasis: efficacy and adverse reactions. *JAMA* 1988; **259:** 3150–3.
2. Rothova A, *et al.* Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989; **i:** 1439–41.
3. Zea-Flores R, *et al.* Adverse reactions after community treatment of onchocerciasis with ivermectin in Guatemala. *Trans R Soc Trop Med Hyg* 1992; **86:** 663–6.

4. Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis: results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 1993; **87:** 313–17.
5. De Sole G, *et al.* Lack of adverse reactions in ivermectin treatment of onchocerciasis. *Lancet* 1990; **335:** 1106–7.
6. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; **67:** 707–19.
7. Kamgno J, *et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; **98:** 496–504.
8. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; **350:** 18–22.
9. The Mectizan Expert Committee and The Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and loiasis. 2004. Available at: http://www.mectizan.org/sites/default/files/EnglishMECTCCLoaRecs-June04_1.pdf (accessed 29/07/10)
10. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: adverse reactions after the first five treatment rounds. *Trans R Soc Trop Med Hyg* 1991; **85:** 501–5.
11. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987. Available at: http://libdoc.who.int/trs/WHO_TRS_752_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_752_(part2).pdf (accessed 16/07/08)
12. Homeida MMA, *et al.* Prolongation of prothrombin time with ivermectin. *Lancet* 1988; **i:** 1346–7.
13. Richards FO, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i;** 1139–40.
14. Pacque MC, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i:** 1140.
15. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; **349:** 1144–5.
16. Diazgranados JA, Costa JL. Deaths after ivermectin treatment. *Lancet* 1997; **349:** 1698.
17. Reintjes R, Hoek C. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350:** 215.
18. Coyne PE, Addiss DG. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350:** 215–16.
19. Alexander NDE, *et al.* Absence of ivermectin-associated excess deaths. *Trans R Soc Trop Med Hyg* 1998; **92:** 342.

Breast feeding. Mean ivermectin concentrations in the breast milk of 4 healthy women who had been given a standard dose of ivermectin were 14.13 nanograms/mL.[1] It was considered that in view of this low concentration the precaution of excluding breast-feeding mothers from ivermectin mass treatment programmes should be reconsidered. Some authorities have recommended that ivermectin should not be given to mothers who are breast feeding until the infant is at least one week old. The American Academy of Pediatrics states that, since no adverse effects have been seen in breast-fed infants whose mothers were receiving ivermectin, it may be considered to be usually compatible with breast feeding.[2]

1. Ogbuokiri JE, *et al.* Ivermectin levels in human breast milk. *Eur J Clin Pharmacol* 1994; **46:** 89–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Encephalopathy. For information on encephalopathy after ivermectin treatment of onchocerciasis in *Loa loa* endemic areas, see Incidence of Adverse Effects, p. 156.3.

Pregnancy. Ivermectin is teratogenic in *animals* and there are no adequate and well controlled studies in human pregnancy. Ivermectin treatment is therefore usually contra-indicated during pregnancy and pregnant women should be excluded from mass treatment schedules with ivermectin. However, women not yet diagnosed as pregnant or unwilling to admit their pregnancy have been treated. An assessment[1] of 203 pregnancy outcomes in women who had taken ivermectin during pregnancy, mostly during the first 12 weeks, found that the rates of major congenital malformation, miscarriage, and still-birth associated with ivermectin were similar to those in untreated mothers. In another study, 110 women also inadvertently given ivermectin during pregnancy had a similar lack of adverse effect on pregnancy outcome;[2] it was considered that avoiding the use of ivermectin in women once they were known to be pregnant should be adequate precaution. An open-label study[3] in women in the second trimester of pregnancy who were given ivermectin alone or with albendazole did not note any significant effect on birth weight, prematurity, congenital abnormality, or neonatal mortality.

1. Pacqué M, *et al.* Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* 1990; **336:** 1486–9.
2. Chippaux J-P, *et al.* Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg* 1993; **87:** 318.
3. Ndyomugyenyi R, *et al.* Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmittedhelminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. *Am J Trop Med Hyg* 2008; **79:** 856–63.

Pharmacokinetics

Ivermectin is absorbed after oral doses and peak plasma concentrations occur after about 4 hours. Ivermectin is reported to be about 93% bound to plasma proteins and has a plasma elimination half-life of about 12 hours. It undergoes metabolism in the liver, mainly via the cytochrome P450 isoenzyme CYP3A4. It is excreted largely as metabolites over a period of about 2 weeks, chiefly in the faeces, with less than 1% appearing in the urine and less than 2% in breast milk (see also Breast Feeding, above).

References.
1. González Canga A, *et al.* The pharmacokinetics and interactions of ivermectin in humans—a mini-review. *AAPS J* 2008; **10:** 42–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermoper IV; Dermopero; Detebencil; Ivertal; Securo; ***Austral.***: Stromectol; ***Braz.***: Ivermec; Leverctin; Plurimec; Revectina; Vermectil; ***Chile***: Kaonol; Mediderm†; ***Fr.***: Mectizan†; Stromectol; ***Gr.***: Stromectol; ***India***: Ectin; Ectover; Elect; Ifact; Imectin; Ivecop; Iver-Sol; Ivercid; Iversan; Iverstar; Ivor; Ivori; Macbi; Mectin; ***Jpn***: Stromectol; ***Mex.***: Ivexterm; ***Neth.***: Stromectol; ***NZ***: Stromectol; ***Singapore***: Stromectol; ***Thai.***: Vermectin; ***USA***: Mectizan; Sklice; Stromectol.

Multi-ingredient Preparations. ***India***: Ablaze-IM; ABZ Plus; Albacos-IR; Albosym-IR; Alvect; Anthel-UP; Ariban Plus; Ascapil A; Bandy Plus; Benrod-I; Benzole; Ectin-A; Elect-A; Eris Plus; Getrid-I; Hymin Plus; Imectin Forte; Ivecop-AB; Ivercid-A; Iverzole; Ivoral; Kidi; Macbi Plus; Networm.

Pharmacopoeial Preparations

USP 36: Ivermectin and Pyrantel Pamoate Tablets; Ivermectin Tablets.

Levamisole *(BAN, rINN)*

Levamisol; Lévamisole; Levamisoli; Levamisolo; Levamisolum; Levamizol; Левамизол.

(*S*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*][1,3]thiazole.

$C_{11}H_{12}N_2S$=204.3

CAS — 14769-73-4.

ATC — P02CE01.

ATC Vet — QP52AE01.

UNII — 2880D3468G.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Levamisole for Veterinary Use; Levamisole BP (Vet) 2014). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Levamisole Hydrochloride *(BANM, USAN, rINNM)*

Cloridrato de Levamizol; Hidrocloruro de levamisol; ICI-59623; Levamisol, hidrocloruro de; Lévamisole, Chlorhydrate de; Levamisol-hydrochlorid; Levamisolhydrochlorid; Levamisolhydroklorid; Levamisoli Hydrochloridum; Levamisolihydrokloridi; Levamizol-hidroklorid; Levamizolio hidrochloridas; Lewamizolu chlorowodorek; NSC-177023; R-12564; RP-20605; *l*-Tetramisole Hydrochloride; Левамизола Гидрохлорид.

$C_{11}H_{12}N_2S,HCl$=240.7

CAS — 16595-80-5.

ATC — P02CE01.

UNII — DL9055K809.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Levamisole Hydrochloride). A white to almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane. A 5% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 36: (Levamisole Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 4.5. Protect from light.

Uses and Administration

Levamisole hydrochloride is the active laevo-isomer of tetramisole hydrochloride. It is used as an anthelmintic and has been used as an adjuvant in malignant disease. It has also been tried in several conditions where its stimulant effect on the depressed immune response might be useful.

Levamisole is active against intestinal nematodes and appears to act by paralysing susceptible worms which are subsequently eliminated from the intestines. In particular, levamisole is effective in the treatment of ascariasis (p. 143.3). It is also used in hookworm infections (p. 146.1).

Doses of levamisole hydrochloride are expressed in terms of the equivalent amount of levamisole. Levamisole hydrochloride 1.18 g is equivalent to about 1 g of levamisole. The usual dose for adults and children in **ascariasis** is 2.5 mg/kg of levamisole orally as a single dose. For **hookworm** infection (ancylostomiasis) or for **mixed ascariasis-hookworm** infections, both adults and children may be given 2.5 mg/kg as a single dose, repeated after 7 days in cases of severe hookworm infection.

Levamisole influences host defences by modulating cell-mediated immune responses; it restores depressed T-cell functions and has been described as an immunostimulant, although stimulation above normal levels does not seem to occur. It has been tried in many disorders, including bacterial and viral infections and rheumatic disorders, although in these conditions results have not been encouraging.

Levamisole has also been used as an adjunct in patients with malignant disease, although it is not clear that any response is due to its action on the immune system. Adjuvant treatment with levamisole and fluorouracil has been given to reduce recurrence after resection of adenocarcinoma of the colon with regional lymph node involvement (but see Malignant Neoplasms, p. 159.1).

Reviews.
1. Amery WKP, Bruynseels JPJM. Levamisole, the story and the lessons. *Int J Immunopharmacol* 1992; **14:** 481–6.
2. Scheinfeld N, *et al.* Levamisole in dermatology: a review. *Am J Clin Dermatol* 2004; **5:** 97–104.

Administration in children. Levamisole may be given orally to children for the treatment of ascariasis, hookworm infections, and mixed ascariasis and hookworm infections. Doses used are the same by weight as those used for adults (see above).

Hepatitis B. The CDC recommends that all dialysis patients be vaccinated against hepatitis B virus (HBV) because their potential exposure to blood, frequent transfusions, and sharing of dialysis equipment increases their risk of blood-borne viruses such as hepatitis B. However, the immune response to hepatitis B vaccination is impaired among those with chronic kidney disease. Levamisole is an immune modulator and meta-analyses[1,2] have shown that it has significant benefit as an adjuvant to HBV vaccination for upregulation of defective immune function in patients with chronic renal insufficiency.

1. Alavian SM, Tabatabaei SV. Effects of oral levamisole as an adjuvant to hepatitis B vaccine in adults with end-stage renal disease: a meta-analysis of controlled clinical trials. *Clin Ther* 2010; **32:** 1–10.
2. Fabrizi F, *et al.* Meta-analysis: levamisole improves the immune response to hepatitis B vaccine in dialysis patients. *Aliment Pharmacol Ther* 2010; **32:** 756–62.

Malignant neoplasms. Levamisole has been tried in the adjuvant treatment of various malignant neoplasms[1,2] with conflicting results. Based on the results of early adjuvant studies,[3-5] levamisole was formerly used with fluorouracil in patients with colorectal cancer, particularly in the USA. However, adjuvant levamisole alone was no more effective than placebo in 1 study,[6] and more recent studies have indicated that levamisole is no more effective than placebo when added to fluorouracil,[7] or to fluorouracil plus folinic acid.[8] For current management of colorectal cancer see p. 706.3.

1. Spreafico F. Use of levamisole in cancer patients. *Drugs* 1980; **20:** 105–16.
2. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; **5:** 1–9.
3. Laurie JA, *et al.* Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil: the North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol* 1989; **7:** 1447–56.
4. Moertel CG, *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322:** 352–8.
5. Moertel CG, *et al.* Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Ann Intern Med* 1995; **122:** 321–6.
6. Chlebowski RT, *et al.* Long-term survival following levamisole or placebo adjuvant treatment of colorectal cancer: a Western Cancer Study Group trial. *Oncology* 1988; **45:** 141–3.
7. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355:** 1588–96.
8. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; **17:** 3553–9.

Mouth ulceration. Levamisole might be beneficial in severe mouth ulceration (p. 1814.2) but is limited by its adverse effects. A review[1] of its use in recurrent aphthous stomatitis indicated that beneficial results have been reported with levamisole in open studies, but results of double-blind studies have been conflicting. Nevertheless, there have been patients with severe recurrent aphthous stomatitis refractory to all other modes of treatment who have responded to levamisole. Dosage has been with 150 mg daily in divided doses given for 3 days at the first sign of ulceration, followed by 11 days without treatment, repeated as necessary. A small controlled study[2] indicated that it was ineffective in the prevention of recurrent aphthous stomatitis.

1. Miller MF. Use of levamisole in recurrent aphthous stomatitis. *Drugs* 1980; **20:** 131–6.

2. Weckx LLM, *et al*. Levamisol não previne lesões de estomatite aftosa recorrente: um ensaio clínico randomizado, duplo-cego e controlado por placebo. *Rev Assoc Med Bras* 2009; **55:** 132–8.

Renal disorders. In a randomised double-blind study, children with frequently relapsing corticosteroid-sensitive and corticosteroid-dependent nephrotic syndrome were given placebo or levamisole 2.5 mg/kg on alternate days and corticosteroid therapy was gradually withdrawn.[1] Of 31 children being treated with levamisole, 14 were still in remission 112 days after the start of the study compared with 4 of 30 receiving placebo. An evaluation of 3 randomised, controlled studies,[2] including this study, found that levamisole reduces the risk of relapse during treatment but no conclusion could be reached on its corticosteroid-sparing effect. There have been similar reports of adjunctive use in children with nephrotic syndrome,[3-7] but its place in therapy remains unknown. For a discussion of the treatment of glomerular kidney disorders, including the nephrotic syndrome, see p. 1604.3.

1. British Association for Paediatric Nephrology. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. *Lancet* 1991; **337:** 1555–7.
2. Davin JC, Merkus MP. Levamisole in steroid-sensitive nephrotic syndrome of childhood: the lost paradise? *Pediatr Nephrol* 2005; **20:** 10–4.
3. Donia AF, *et al*. Levamisole: adjunctive therapy in steroid dependent minimal change nephrotic children. *Pediatr Nephrol* 2002; **17:** 355–8.
4. Fu LS, *et al*. Levamisole in steroid-sensitive nephrotic syndrome children with frequent relapses and/or steroid dependency: comparison of daily and every-other-day usage. *Nephron Clin Pract* 2004; **97:** c137–c141.
5. Sümegi V, *et al*. Long-term effects of levamisole treatment in childhood nephrotic syndrome. *Pediatr Nephrol* 2004; **19:** 1354–60.
6. Al-Saran K, *et al*. Experience with levamisole in frequently relapsing, steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2006; **21:** 201–5.
7. Boyer O, *et al*. Short- and long-term efficacy of levamisole as adjunctive therapy in childhood nephrotic syndrome. *Pediatr Nephrol* 2008; **23:** 575–80.

Vitiligo. In a study[1] involving 36 patients with limited slow-spreading vitiligo, response to levamisole treatment occurred in 34 within 2 to 4 months. Patients received 150 mg of oral levamisole daily on 2 consecutive days each week. Patients who were additionally treated with topical fluocinolone or clobetasol had higher rates of repigmentation. A later controlled study[2] involving 43 patients reported less benefit.

The usual treatment of vitiligo is discussed under Pigmentation Disorders, p. 1687.2.

1. Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. *Int J Dermatol* 1994; **33:** 584–7.
2. Agarwal S, *et al*. A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. *Br J Dermatol* 2005; **153:** 163–6.

Adverse Effects

When levamisole is used as an immunostimulant and given for longer periods, adverse effects are more frequent and diverse and, in common with other immunomodulators, may sometimes result from exacerbation of the primary underlying disease. Adverse effects associated especially with the more prolonged use of levamisole have included: hypersensitivity reactions such as fever, a flu-like syndrome, arthralgia, muscle pain, rashes, and cutaneous vasculitis; CNS effects including headache, insomnia, dizziness, and convulsions; haematological abnormalities such as agranulocytosis, leucopenia, and thrombocytopenia; and gastrointestinal disturbances, including an abnormal taste in the mouth. In many countries levamisole has been withdrawn from the market and is rarely used as an immunomodulator because of its severe adverse effects such as agranulocytosis and vasculitis. Levamisole has been added to cocaine as an adulterant and there are reports of these adverse effects among cocaine users (see under Abuse, p. 159.3).

Levamisole is, however, still available in some countries for the treatment of worm infections. When given in single doses for the treatment of ascariasis or other worm infections, levamisole is generally well tolerated and adverse effects are usually limited to nausea, vomiting, diarrhoea, abdominal pain, dizziness, and headache.

Incidence of adverse effects. In a review[1] (by the manufacturers) of 46 controlled studies in which 2635 cancer patients received adjuvant levamisole treatment, most patients received levamisole on 3 consecutive days every 2 weeks (1102 patients) or on 2 consecutive days every week (1156 patients), usually in a daily dose of 150 mg. Levamisole caused several adverse effects, such as rash, nausea, vomiting, and a metallic or bitter taste in the mouth, which although troublesome were relatively trivial and often regressed during therapy or disappeared on cessation of therapy. A total of 38 patients developed agranulocytosis and of these 36 had received weekly treatment. Several contracted possible life-threatening infections and 2 died of septic shock.

1. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; **5:** 1–9.

Effects on the endocrine system. Rechallenge confirmed that levamisole was responsible for inappropriate antidiuretic hormone syndrome in a patient receiving levamisole with fluorouracil.[1]

1. Tweedy CR, *et al*. Levamisole-induced syndrome of inappropriate antidiuretic hormone. *N Engl J Med* 1992; **326:** 1164.

Effects on the liver. Elevated aspartate aminotransferase concentrations in 2 of 11 patients given levamisole for recurrent pyoderma suggested liver toxicity, a very rarely occurring adverse effect.[1] In a later report, liver enzyme concentrations were raised in a 14-year-old boy treated with levamisole for minimal change nephrotic syndrome.[2]

1. Papageorgiou P, *et al*. Levamisole in chronic pyoderma. *J Clin Lab Immunol* 1982; **8:** 121–7.
2. Bulugahapitiya DTD. Liver toxicity in a nephrotic patient treated with levamisole. *Arch Dis Child* 1997; **76:** 289.

Effects on the nervous system. Reports[1,2] of inflammatory leukoencephalopathy were associated with the use of fluorouracil and levamisole in 4 patients being treated for adenocarcinoma of the colon. Active demyelination was found in 2 patients.[1] Clinical improvement occurred when chemotherapy was stopped; 3 patients were treated with corticosteroids.[1] A similar syndrome has been reported in a patient with a history of hepatitis C given levamisole alone.[3]

1. Hook CC, *et al*. Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. *Ann Neurol* 1992; **31:** 262–7.
2. Kimmel DW, Schutt AJ. Multifocal leukoencephalopathy: occurrence during 5-fluorouracil and levamisole therapy and resolution after discontinuation of chemotherapy. *Mayo Clin Proc* 1993; **68:** 363–5.
3. Lucia P, *et al*. Multifocal leucoencephalopathy induced by levamisole. *Lancet* 1996; **348:** 1450.

Precautions

The use of levamisole should be avoided in patients with pre-existing blood disorders. Patients given levamisole with fluorouracil should undergo appropriate monitoring of haematological and hepatic function.

Abuse. Cases of severe neutropenia and agranulocytosis associated with abuse of cocaine tainted with levamisole have been reported.[1,2] Necrotising vasculitides,[3] including retiform purpura[4] have been associated with abuse of such mixtures.[3] Fatalities have been reported.[5]

The purpose of adulterating cocaine with levamisole is unclear, but it is thought that it might be linked to a report of metabolism of levamisole to aminorex in racehorses. Aminorex and related compounds (specifically its analogue 4-methylaminorex) have high abuse potential because of their amfetamine-like pharmacological activity. Similar metabolism has since been reported in humans.[6]

1. Knowles L, *et al*. Levamisole tainted cocaine causing severe neutropenia in Alberta and British Columbia. *Harm Reduct J* 2009; **6:** 30.
2. CDC. Agranulocytosis associated with cocaine use — four states, March 2008–November 2009. *MMWR* 2009; **58:** 1381–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5849.pdf (accessed 18/05/10)
3. Bradford M, *et al*. Bilateral necrosis of earlobes and cheeks: another complication of cocaine contaminated with levamisole. *Ann Intern Med* 2010; **152:** 758–9.
4. Geller L, *et al*. Retiform purpura: a new stigmata of illicit drug use? *Dermatol Online J* 2011; **17:** 7.
5. Duflou JA, *et al*. Levamisole as an adulterant in a cocaine overdose fatality. *Med J Aust* 2010; **192:** 724.
6. Bertol E, *et al*. Determination of aminorex in human urine samples by GC-MS after use of levamisole. *J Pharm Biomed Anal* 2011; **55:** 1186–9.

Rheumatoid arthritis. The presence of HLA B27 in seropositive rheumatoid arthritis is an important predisposing factor to the development of agranulocytosis with levamisole; it is recommended that the use of levamisole in this group should be avoided.[1]

1. Mielants H, Veys EM. A study of the hematological side effects of levamisole in rheumatoid arthritis with recommendations. *J Rheumatol* 1978; **5** (suppl 4): 77–83.

Sjögren's syndrome. A study was stopped after adverse effects appeared in 9 of 10 patients with rheumatoid arthritis and Sjögren's syndrome while receiving levamisole.[1] Levamisole should be given with caution, if at all, to patients with Sjögren's syndrome.

1. Balint G, *et al*. Sjögren's syndrome: a contraindication to levamisole treatment? *BMJ* 1977; **2:** 1386–7.

Interactions

Alcohol. US licensed product information states that levamisole can produce a disulfiram-like reaction with *alcohol*.

Anticoagulants. For an increase in the activity of *warfarin* when given with levamisole and fluorouracil, see Interactions, Levamisole, under Warfarin, p. 1534.2.

Antiepileptics. For increased *phenytoin* concentrations when given with levamisole and fluorouracil, see Interactions, Antineoplastics, under Phenytoin, p. 544.1.

Pharmacokinetics

Levamisole is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1.5 to 2 hours. It is extensively metabolised in the liver. The plasma half-life for levamisole is 3 to 4 hours and for the metabolites is 16 hours. It is excreted mainly in the urine as metabolites and a small proportion in the faeces. About 70% of a dose is excreted in the urine over 3 days, with about 5% as unchanged levamisole.

References.

1. Luyckx M, *et al*. Pharmacokinetics of levamisole in healthy subjects and cancer patients. *Eur J Drug Metab Pharmacokinet* 1982; **7:** 247–54.
2. Kouassi E, *et al*. Novel assay and pharmacokinetics of levamisole and p-hydroxylevamisole in human plasma and urine. *Biopharm Drug Dispos* 1986; **7:** 71–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Levam; Meglum; ***Braz.***: Ascaridil; ***Gr.***: Ergamisol†; ***Hong Kong***: Decaris; ***Hung.***: Decaris; ***India***: Dewormis; Dicaris; L-Vin; Levomol; Vermisol; Vizole†; ***Indon.***: Askamex†; ***Israel***: Ergamisol†; ***Mex.***: Decaris; ***Rus.***: Decaris (Декарис); ***S.Afr.***: Ergamisol†; ***Turk.***: Helmazol; Paraks; Sitraks; ***Ukr.***: Decaris (Декарис).

Multi-ingredient Preparations. ***China***: Hai Mi Ke (海密克); ***India***: Eradix; Exit.

Pharmacopoeial Preparations
USP 36: Levamisole Hydrochloride Tablets.

Male Fern

Almindelig Mangeløv; Aspidium; Echter Wurmfarn; Erdei Pajzsika; Falguera Mascle; Farnwurzel; Felce Maschio; Feto Macho; Filix Mas; Fougère Mâle; Helecho Macho; Kaprad' Samec; Kelminis Papartis; Kivikkoalvejuuri; Maarja-sõnajalg; Mannetjesvaren; Nerecznica Samcza; Ormetelg; Rhizoma Filicis Maris; Stóriburkni; Träjon; Щитовник Мужской.

CAS — 114-42-1 (flavaspidic acid).
ATC Herb — HP02DW5002 (Dryopteris filix-mas: *rhizome*).
UNII — 584YXJ3H6L (Dryopteris filix-mas); *V4770BG68I* (Dryopteris filix-mas *leaf*); *C0ZK0RRF5X* (Dryopteris filix-mas *root*).

Pharmacopoeias. In *Chin.*

Profile

Male fern consists of the rhizome, frond-bases, and apical bud of *Dryopteris filix-mas* agg. (Polypodiaceae), collected late in the autumn, divested of the roots and dead portions and carefully dried, retaining the internal green colour. It contains not less than 1.5% of filicin. During storage the green colour of the interior gradually disappears, often after a lapse of 6 months, and such material is unfit for medicinal use.

Filicin is the mixture of ether-soluble substances obtained from male fern. Its activity is chiefly due to flavaspidic acid, a phloroglucinol derivative.

Male fern has anthelmintic properties and was formerly used as male fern extract (aspidium oleoresin) for the expulsion of tapeworms. However, male fern is highly toxic and has been superseded by other drugs.

Adverse effects include headache, nausea and vomiting, severe abdominal cramp, diarrhoea, dyspnoea, albuminuria, hyperbilirubinaemia, dizziness, tremors, convulsions, visual disturbances including blindness (possibly permanent), stimulation of uterine muscle, coma, respiratory failure, bradycardia, and cardiac failure. Fatalities have occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Digestodoron; ***Ger.***: Digestodoron; ***S.Afr.***: Digestodoron†.

Homoeopathic Preparations. ***Fr.***: Digestodoron; ***Ger.***: Agaricus comp Phosphorus; Chelidonium comp; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; ***UK***: Digestodoron.

Mebendazole *(BAN, USAN, rINN)*

Mebendatsoli; Mebendazol; Mebendazolas; Mébendazole; Mebendazolum; R-17635; Мебендазол.

Methyl 5-benzoyl-1*H*-benzimidazol-2-ylcarbamate.

$C_{16}H_{13}N_3O_3$=295.3

CAS — 31431-39-7.
ATC — P02CA01.
ATC Vet — QP52AC09.
UNII — 81G6I5V05I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Mebendazole). A white or almost white powder. It shows polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Mebendazole). A white to slightly yellow, almost odourless, powder. Practically insoluble in water, in alcohol, in chloroform, in ether, and in dilute mineral acids; freely soluble in formic acid.

Uses and Administration

Mebendazole, a benzimidazole carbamate derivative, is an anthelmintic with activity against most nematodes and some other worms; activity against some larval stages and ova has also been shown. It inhibits or destroys cytoplasmic microtubules in the worm's intestinal or absorptive cells. Inhibition of glucose uptake and depletion of glycogen stores follow as do other inhibitory effects leading to death of the worm within several days.

Mebendazole, being poorly absorbed from the gastrointestinal tract, is used mainly in the treatment of the intestinal nematode infections ascariasis (roundworm infection), enterobiasis (pinworm or threadworm infections), hookworm (ancylostomiasis and necatoriasis), and **trichuriasis** (whipworm infection); it is useful in mixed infections. During treatment with mebendazole, migration of worms with expulsion through the mouth and nose has occurred in some patients heavily infected with *Ascaris*. Mebendazole is also used in the treatment of capillariasis and trichostrongyliasis and has been used in strongyloidiasis. Other nematode infections which may respond to mebendazole are infection with the filarial nematode *Mansonella perstans*, and the tissue infections toxocariasis and trichinosis. Mebendazole has also been tried in high doses in the treatment of echinococcosis (hydatid disease). For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Mebendazole is given orally. The usual dose for adults and children aged over 2 years with **enterobiasis** is 100 mg as a single dose, repeated if necessary after 2 to 3 weeks; for **ascariasis**, **hookworm infections**, and trichuriasis the usual dose in adults and children over 1 year is 100 mg twice daily for 3 days, although a single dose of 500 mg may be effective and this dose is also used in *mass treatment* programmes for hookworm infections and trichuriasis. For mass treatment control programmes against ascariasis, hookworm infections, and trichuriasis a dose of 500 mg is given as a single dose once or twice a year depending on the prevalence and intensity of infection among school-age children. For the treatment of **capillariasis** in adults and children over 2 years of age, mebendazole is given in a dose of 200 mg twice daily for 20 days; for *mass treatment* control programmes a dose of 500 mg is given as a single dose 4 times a year.

Administration in children. Mebendazole may be given orally to children for the treatment of intestinal nematode infections, including ascariasis, capillariasis, enterobiasis, hookworm infections, trichostrongyliasis, and trichuriasis. Doses used are the same as those used for adults (see above).

Although licensed product information indicates that mebendazole should not be given to children under 2 years of age, there have been no reports of toxicity or adverse effects when used in this group of children.[1] After a review of human and animal toxicological data, WHO concluded that there were no reasons to exclude children as young as 12 months from treatment with benzimidazoles, such as mebendazole and albendazole, and they recommend that children from one year of age should be included in systematic de-worming programmes;[2] doses given are the same as those used for adults.[3]

1. Montresor A, *et al.* Is the exclusion of children under 24 months from anthelmintic treatment justifiable? *Trans R Soc Trop Med Hyg* 2002; **96:** 197–9.
2. Anonymous. Benzimidazoles: use in children. *WHO Drug Inf* 2003; **17:** 29–30.
3. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 27/08/09)

Angiostrongyliasis. Mebendazole was formerly used for the treatment of angiostrongyliasis (p. 143.3) but current opinion is that there is no convincing evidence to support its use.

Echinococcosis. Mebendazole has been used[1-9] in echinococcosis (p. 145.2), but albendazole is generally preferred. The usual oral dose of mebendazole in cystic echinococcosis is 40 to 50 mg/kg daily for at least 3 to 6 months.[8] A similar dose is used as an adjuvant to surgery. For alveolar echinococcosis, the dose is adjusted after 4 weeks to produce a plasma concentration of at least 250 nanomoles/litre (74 nanograms/mL), although adults should not be given more than 6 g daily. Treatment is continued for at least 2 years after radical surgery, or indefinitely in inoperable cases.

1. Ammann RW, *et al.* Recurrence rate after discontinuation of long-term mebendazole therapy in alveolar echinococcosis (preliminary results). *Am J Trop Med Hyg* 1990; **43:** 506–15.
2. Messaritakis J, *et al.* High mebendazole doses in pulmonary and hepatic hydatid disease. *Arch Dis Child* 1991; **66:** 532–3.
3. Teggi A, *et al.* Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37:** 1679–84.
4. Göçmen A, *et al.* Treatment of hydatid disease in childhood with mebendazole. *Eur Respir J* 1993; **6:** 253–7.
5. Ammann RW, *et al.* Effect of chemotherapy on the larval mass and the long-term course of alveolar echinococcosis. *Hepatology* 1994; **19:** 735–42.
6. Erdinçler P, *et al.* The role of mebendazole in the surgical treatment of central nervous system hydatid disease. *Br J Neurosurg* 1997; **11:** 116–20.
7. Vutova K, *et al.* Effect of mebendazole on human cystic echinococcosis: the role of dosage and treatment duration. *Ann Trop Med Parasitol* 1999; **93:** 357–65.
8. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull WHO* 1996; **74:** 231–42.
9. Smego RA, *et al.* Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. *Clin Infect Dis* 2003; **37:** 1073–83.

Giardiasis. For mention of the use of mebendazole for the treatment of giardiasis, see p. 923.2.

Loiasis. In those patients with a heavy or dense microfilarial load who are at risk for serious adverse effects from diethylcarbamazine, alternative drugs such as mebendazole have been given. An [oral] dose of 300 mg daily for several weeks was effective in slowly decreasing the microfilarial load.[1]

1. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg* 2008; **102:** 983–9.

Mansonella infections. Mebendazole, given orally at a dose of 100 mg twice daily for 30 days, is one of the drugs that has been suggested for the treatment of infections with *Mansonella perstans* (p. 147.2). Some patients have responded to mebendazole with levamisole,[1,2] diethylcarbamazine,[3] or to mebendazole alone.[3,4]

1. Maertens K, Wery M. Effect of mebendazole and levamisole on Onchocerca volvulus and Dipetalonema perstans. *Trans R Soc Trop Med Hyg* 1975; **69:** 359–60.
2. Bernberg HC, *et al.* The combined treatment with levamisole and mebendazole for a perstans-like filarial infection in Rhodesia. *Trans R Soc Trop Med Hyg* 1979; **73:** 233–4.
3. Bregani ER, *et al.* Comparison of different anthelmintic drug regimens against Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 2006; **100:** 458–63.
4. Wahlgren M, Frolov I. Treatment of Dipetalonema perstans infections with mebendazole. *Trans R Soc Trop Med Hyg* 1983; **77:** 422–3.

Strongyloidiasis. Mebendazole has been used for the treatment of strongyloidiasis (p. 148.2), but needs to be given for longer periods than albendazole to control autoinfection, so that, of the two, albendazole is preferred.[1-3]

1. Wilson KH, Kauffman CA. Persistent Strongyloides stercoralis in a blind loop of the bowel: successful treatment with mebendazole. *Arch Intern Med* 1983; **143:** 357–8.
2. Mravak S, *et al.* Treatment of strongyloidiasis with mebendazole. *Acta Trop (Basel)* 1983; **40:** 93–4.
3. Pelletier LL, Baker CB. Treatment failures following mebendazole therapy for chronic strongyloidiasis. *J Infect Dis* 1987; **156:** 532–3.

Syngamosis. Mebendazole has been used successfully[1] to treat syngamosis (p. 148.2).

1. Timmons RF, *et al.* Infection of the respiratory tract with Mammomanogamus (Syngamus) laryngeus: a new case in Largo, Florida, and a summary of previously reported cases. *Am Rev Respir Dis* 1983; **128:** 566–9.

Toxocariasis. Mebendazole has been used in the treatment of toxocariasis (p. 148.3). In comparative studies, mebendazole has been reported to produce similar improvements to those obtained with tiabendazole[1] and with diethylcarbamazine,[2] in each case with a lower incidence of adverse effects. An oral dose of 100 to 200 mg twice daily for 5 days has been recommended, however, the optimum duration of therapy is unknown and some would treat for 20 days.[3]

1. Magnaval JF, Charlet JP. Efficacité comparée du thiabendazole et du mébendazole dans le traitement de la toxocarose. *Therapie* 1987; **42:** 541–4.
2. Magnaval J-F. Comparative efficacy of diethylcarbamazine and mebendazole for the treatment of human toxocariasis. *Parasitology* 1995; **110:** 529–33.
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Trichinosis. Mebendazole is used for the treatment of trichinosis (p. 148.3) in some countries. An oral dose of 200 to 400 mg three times a day for 3 days followed by 400 to 500 mg three times a day for 10 days has been recommended.[1]

1. Gottstein B, *et al.* Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev* 2009; **22:** 127–45.

Adverse Effects

Since mebendazole is poorly absorbed from the gastrointestinal tract at the usual therapeutic doses, adverse effects have generally been restricted to gastrointestinal disturbances, such as transient abdominal pain and diarrhoea, and have tended to occur in patients being treated for heavy intestinal infection. Headache and dizziness have been reported. Adverse effects have been reported more frequently with the high doses tried in echinococcosis and have included allergic reactions, raised liver enzyme values, alopecia, and bone marrow depression.

Incidence of adverse effects. In the first phase[1] of WHO-coordinated multicentre studies on the treatment of echinococcosis (hydatid disease) involving *Echinococcus granulosus* or *E. multilocularis*, the most frequent adverse effects in the 139 patients given *high-dose* mebendazole, generally for 3 months, were reduced leucocyte count (25 patients), gastrointestinal symptoms (22 patients), and raised serum-transaminase values (22 patients). Other adverse effects were allergic conditions such as fever and skin reactions (4 patients), CNS symptoms including headache (6 patients), and loss of hair (7 patients). Seven patients stopped treatment because of adverse effects.

The second phase of studies[2] compared albendazole with mebendazole in more prolonged high-dosage schedules for cystic *E. granulosus* infection. Adverse effects were similar to those reported with the first phase. However, in the first phase the allergic consequences of the 14 ruptured lung cysts and the 4 ruptured liver cysts that occurred with mebendazole were not reported. In the second phase, 2 patients suffered anaphylactic shock as a result of rupture of a lung cyst and a cyst in the abdominal cavity. These 2 patients were withdrawn from mebendazole treatment, as were another 4 patients as a consequence of their adverse reactions, although in 3 the withdrawal was only temporary.

Although albendazole is preferred to mebendazole in the treatment of echinococcosis, if either drug is used there should be constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.[2]

1. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64:** 383–8.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67:** 503–8.

Overdosage. Respiratory arrest and tachyarrhythmia associated with continuous convulsions were reported[1] in an 8-week-old infant after accidental poisoning with mebendazole. Treatment by exchange transfusion and anticonvulsants was successful.

1. el Kalla S, Menon NS. Mebendazole poisoning in infancy. *Ann Trop Paediatr* 1990; **10:** 313–14.

Precautions

Patients given high doses of mebendazole, such as those with echinococcosis, should be supervised closely with blood counts and liver function being monitored; such high-dose therapy may be inappropriate in those with hepatic impairment (see under Incidence of Adverse Effects, above).

Monitoring drug concentrations. In a retrospective analysis of patients given high doses of mebendazole for echinococcosis,[1] no relationship was found between dose and plasma concentration of mebendazole and considerable intra- and interindividual variation in plasma concentrations was seen, emphasising the need for repeated monitoring. Several patients appeared to have what were considered to be subtherapeutic plasma concentrations.

1. Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; **31:** 443–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mebendazole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Mebendazole is teratogenic in *rats* and there are no adequate and well controlled studies in human pregnancy. Mebendazole is therefore usually contra-indicated during pregnancy. However, US licensed product information notes that in a survey of a limited number of pregnant women who had inadvertently taken mebendazole during the first trimester, the incidence of malformation and spontaneous abortion was no greater than that seen in the general population. The UK *National Teratology Information Service* (UKTIS) also considers that

the available data on the use of mebendazole in pregnancy does not show a significantly increased risk of congenital malformations; the rate of abnormalities present in the collected data was higher than expected, however, no specific pattern of defects was seen. UKTIS suggests that mebendazole may be given after the first trimester of pregnancy for the treatment of pinworms if hygiene measures are ineffective; it may be also be given for the treatment of hookworm where the benefit of treatment, even during the first trimester, could outweigh any risks.[1] This latter recommendation is supported by a randomised, double-blind, study undertaken in Peru (in a highly hookworm-endemic area),[2] among 1042 women in their second trimester of pregnancy, which compared mebendazole (500 mg given as a single oral dose) plus iron supplementation with placebo plus iron supplementation. There were no statistically significant differences in the numbers of congenital malformations, spontaneous abortions, still-births, or premature deliveries seen between the groups. However, the frequency of very low birth-weight infants decreased in those given mebendazole.

1. National Teratology Information Service. Use of mebendazole in pregnancy (issued July 2011). Available at: http:// www.toxbase.org/upload/Pregnancy%20pdfs/Mebendazole%202011.pdf (accessed 20/08/13)
2. Larocque R, *et al.* A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Trop Med Int Health* 2006; **11:** 1485–95.

Interactions

Antiepileptics. *Phenytoin* or *carbamazepine* have been reported to lower plasma-mebendazole concentrations in patients receiving high doses for echinococcosis, presumably as a result of enzyme induction; *valproate* had no such effect.[1]

1. Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; **31:** 443–8.

Histamine H_2-antagonists. Plasma concentrations of mebendazole have been raised when the enzyme inhibitor *cimetidine* was also given, and this has resulted in the resolution of previously unresponsive hepatic hydatid cysts.[1]

1. Bekhti A, Pirotte J. Cimetidine increases serum mebendazole concentrations: implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol* 1987; **24:** 390–2.

Pharmacokinetics

Mebendazole is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. Bioavailability after usual oral doses is therefore low but may be increased by taking mebendazole with a fatty meal. Peak plasma concentrations generally occur after 1.5 to 7.25 hours and show wide interpatient variation. The drug crosses the blood-brain barrier. Mebendazole, the conjugated forms of mebendazole, and its metabolites are excreted in the urine and bile. The apparent elimination half-life after an oral dose is 3 to 6 hours.

Mebendazole is highly protein bound (about 90 to 95%).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dazomet; Helmint; Mebutar; Nemasole; Tesical; Tru M; ***Austral.***: Chemists Own De Worm; Combantrin-1 with Mebendazole; Vermox; ***Austria***: Pantelmin; ***Belg.***: Docmebenda†; Vermox; ***Braz.***: Belmirax; Ductelmin; Geophagol; Kindelmin†; Mebental; Medazol; Menbel; Moben†; Multizol; Necamin; Neo Mebend; Novelmin; Panfugan; Pantelmin; Pluriverm†; Probendazol†; Sirben; Vermiben; Vermoplex; Vermoral; Verzol; ***Canad.***: Vermox; ***Chile***: Diacor; ***China***: Vermox (安乐士); ***Cz.***: Vermox; ***Denm.***: Vermox; ***Ger.***: Surfont; Vermox; ***Gr.***: Cecurin; Septinalis; Vermox; ***Hong Kong***: Mebenzole†; Vermox; ***Hung.***: Vermox; ***India***: Eben; Elmin; Helmintol; Idibend; Kit Kat; Lupimeb; Mebazole; Mebex; Mendazole; Neomex; Wormin; ***Indon.***: Gavox†; Vermox; ***Irl.***: Vermox; ***Israel***: Vermox; ***Ital.***: Vermox; ***Malaysia***: Quemox; Thelmox; Vermox; ***Mex.***: Amatol; Bensolmin; Bestelar; Daben; Diazolen; Edivertin; Exbenzol; Exteny; Fanciadazol; Hedazol; L-Ombrix; Lumbicid; Meb-Overoid; Mebelmin†; Mebendicin; Mebensole; Mebentiasis; Mebentral; Nemapres; Panvermin†; Profenzol; Revapol†; Vermicol; Vermidil†; Vermin-Dazol; Vermox; Vertizole; ***Neth.***: Anti-Worm†; Kruidvat Anti-worm; Madicure; Trekpleister Anti-Worm; Vermox; ***Norw.***: Vermox; ***NZ***: Combantrin-1; Vermox; ***Philipp.***: Antiox; Helmacon; Wormex; ***Pol.***: Vermox; ***Port.***: Pantelmin; Toloxim; ***Rus.***: Vermox (Вермокс); Wormin (Вормин); ***S.Afr.***: Adco-Wormex; Cipex; D-Worm; Rioworm; Rolab-Anthex†; Vermox; Wormgo; Wormstop; ***Spain***: Lomper; Sufil; ***Swed.***: Vermox; ***Switz.***: Vermox; ***Thai.***: Alworm; Anti-Worm; Benda; Bendazole; Benfu†; Big-Ben; Drivermide; Fuben; Fugacar; Hero-Benson; KB Bendazole; Masaworm-1; Meba; Meben; Mebenda-P; Medazole; Quemox; Rid-O-Worm; Vagaka; Warca; Wormob†; ***Turk.***: Vermazol; Versid; ***UAE***: Mebzol; ***UK***: Boots Threadworm Tablets 2 Years Plus; Ovex; Pripsen†; Vermox; ***USA***: Vermox; ***Venez.***: Bendacor; Bendamen; Eprofil; Vermalon.

Multi-ingredient Preparations. ***Arg.***: Aduar; Helmint Compuesto; Mebutar Compuesto; Tru Compuesto; ***Braz.***: Exelmin; Forverm†; Helmiben; Neovermin; Profium†; ***China***: Hai Mi Ke (海密克); ***India***: Exit; Mebex Plus; ***Mex.***: Amoebriz; Bensolmin Complex; Mebeciclol; Vermox-Plus; ***Ukr.***: Vermox (Вермокс).

Pharmacopoeial Preparations
USP 36: Mebendazole Tablets.

Melarsomine *(rINN)*

Melaminylthioarsenite; Melarsomina; Mélarsomine; Melarsominum; RM-110; Меларсомин.

Bis(2-aminoethyl) *p*-[(4,6-diamino-*s*-triazin-2-yl)amino]dithiobenzenearsonite.

$C_{13}H_{21}AsN_8S_2$=428.4

CAS — 128470-15-5 (melarsomine); 89141-50-4 (melarsomine dihydrochloride).

ATC Vet — QP51AD06.

UNII — 374GJ0S41A.

NOTE. The names Cymelarsan and Immiticide have been used as trade marks for melarsomine dihydrochloride.

Profile

Melarsomine is a trivalent arsenical derivative used in veterinary medicine for the control of canine heartworm (dirofilariasis).

Metrifonate *(BAN, rINN)*

Bayer-L-1359; DETF; Metrifonaat; Metrifonaatti; Metrifonat; Metrifonát; Metrifonatas; Métrifonate; Metrifonato; Metrifonatum; Metriphonate; Trichlorfon (USAN); Trichlorphon; Метрифонат.

Dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate.

$C_4H_8Cl_3O_4P$=257.4

CAS — 52-68-6.

ATC — P02BB01.

ATC Vet — QP52AB01; QP53AF02.

UNII — DBF2DG4G2K.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Metrifonate). A white or almost white, crystalline powder. M.p. is between 76 degrees and 81 degrees. Freely soluble in water, in alcohol, and in acetone; very soluble in dichloromethane. Protect from light.

USP 36: (Metrifonate). A white crystalline powder. M.p. about 78 degrees with decomposition. Freely soluble in water, in alcohol, in acetone, in chloroform, in ether, and in benzene; very soluble in dichloromethane; very slightly soluble in hexane and in pentane. Decomposed by alkali. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Metrifonate is an organophosphorus compound and is converted in the body to the active metabolite dichlorvos (p. 2152.3), an anticholinesterase.

Metrifonate has anthelmintic activity against *Schistosoma haematobium* and has been given orally as an alternative to praziquantel in the treatment of schistosomiasis due to *S. haematobium.* It has usually been given in three doses of 7.5 to 10 mg/kg at intervals of 2 weeks.

Metrifonate has also been used as an insecticide and is used in veterinary medicine as an ectoparasiticide and for the treatment of gastrointestinal roundworms.

Alzheimer's disease. Metrifonate, like some other cholinesterase inhibitors, has been tried in the treatment of Alzheimer's disease (see Dementia, p. 390.1). Clinical studies produced modest benefits but research was stopped after reports of muscle weakness, sometimes requiring respiratory support.[1]

1. López-Arrieta JM, Schneider L. Metrifonate for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/07/10).

Schistosomiasis. While praziquantel is now the main treatment for schistosomiasis (p. 148.1), metrifonate has been given as an alternative for infection due to *Schistosoma haematobium.* Cure rates with standard doses in schistosomiasis control programmes ranged from 40 to more than 80%, with a reduction of more than 80% in egg counts among those not cured. Although praziquantel and metrifonate appeared to be of similar efficacy a systematic review failed to find studies comparing the two drugs when used in standard doses.[1] However, metrifonate's dosage schedule of 3 doses at intervals of 2 weeks has caused problems of patient compliance;[2] giving 5 mg/kg three times in one day has produced similar results to a standard dosage schedule.[3]

1. Danso-Appiah A, *et al.* Drugs for treating urinary schistosomiasis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 29/07/10).
2. Aden Abdi Y, Gustafsson LL.. Poor patient compliance reduces the efficacy of metrifonate treatment of *Schistosoma haematobium* in Somalia. *Eur J Clin Pharmacol* 1989; **36:** 161–4.
3. Aden Abdi Y, Gustafsson LL. Field trial of the efficacy of a simplified and standard metrifonate treatments of *Schistosoma haematobium. Eur J Clin Pharmacol* 1989; **37:** 371–4.

Adverse Effects, Treatment, and Precautions

Metrifonate is generally well tolerated, but may cause nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, and weakness.

It is an organophosphorus compound and because of its anticholinesterase properties depresses plasma-cholinesterase concentrations. For a description of the toxic effects of organophosphorus compounds and the treatment of acute poisoning, see Organophosphorus Insecticides, p. 2158.3. Atropine has been used to relieve cholinergic adverse effects without affecting metrifonate's activity against *Schistosoma haematobium.*

Anticholinesterase effects. Metrifonate depresses cholinesterase activity and there has been the occasional report of severe cholinergic adverse effects.[1] However, it does not usually give rise to troublesome effects at doses normally used, even though there may temporarily be almost complete inhibition of plasma cholinesterase and considerable inhibition of erythrocyte cholinesterase[2] (but see also under Alzheimer's Disease, above).

The environmental aspects of metrifonate usage have been considered by WHO.[3]

1. Jamnadas VP, Thomas JEP. Metriphonate and organophosphate poisoning. *Cent Afr J Med* 1979; **25:** 130.
2. Pleština R, *et al.* Effect of metrifonate on blood cholinesterases in children during the treatment of schistosomiasis. *Bull WHO* 1972; **46:** 747–59.
3. WHO. Trichlorfon. *Environmental Health Criteria 132.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc132.htm (accessed 16/07/08)

Handling. Bulk metrifonate is very toxic when inhaled, swallowed, or spilled on the skin. It can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Pregnancy. WHO reported[1] that metrifonate had not shown embryotoxicity or teratogenicity, but did not recommend the use of metrifonate in pregnant patients unless immediate intervention was essential. There has been a report of an infant born with massive hydrocephalus and a large meningomyelocele whose mother had been treated twice with metrifonate during the second month of pregnancy.[2] A possible link between congenital abnormalities and the use of metrifonate to eradicate fish parasites has also been postulated.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Monson MH, Alexander K. Metrifonate in pregnancy. *Trans R Soc Trop Med Hyg* 1984; **78:** 565.
3. Czeizel AE, *et al.* Environmental trichlorfon and cluster of congenital abnormalities. *Lancet* 1993; **341:** 539–42.

Interactions

Patients treated with metrifonate should not be given depolarising neuromuscular blockers such as suxamethonium for at least 48 hours. The use of metrifonate should be avoided in those recently exposed to insecticides or other agricultural chemicals with anticholinesterase activity.

Pharmacokinetics

Metrifonate is absorbed after oral doses and some is converted to dichlorvos which is considered to be the active moiety. Plasma concentrations of dichlorvos are about 1% of those of metrifonate and peak concentrations of both substances occur within 2 hours. Excretion is via the kidney, mainly as glucuronides.

References.

1. Nordgren I, *et al.* Plasma levels of metrifonate and dichlorvos during treatment of schistosomiasis with Bilarcil. *Am J Trop Med Hyg* 1980; **29:** 426–30.
2. Nordgren I, *et al.* Levels of metrifonate and dichlorvos in plasma and erythrocytes during treatment of schistosomiasis with Bilarcil. *Acta Pharmacol Toxicol (Copenh)* 1981; **49** (suppl V): 79–86.
3. Pettigrew LC, *et al.* Pharmacokinetics, pharmacodynamics, and safety of metrifonate in patients with Alzheimer's disease. *J Clin Pharmacol* 1998; **38:** 236–45.

Milbemycin Oxime

CGA-179246; Milbemicina oxima; Milbemycinoxim; Мильбемицин Оксим.

A mixture of milbemycin A_4 5-oxime and milbemycin A_3 5-oxime.
CAS — 129496-10-2.
ATC Vet — QP54AB01.
UNII — 0502PUN0GT (milbemycin oxime); 053YPP119C (milbemycin A_3 5-oxime); 6ZWJ394628 (milbemycin A_4 5-oxime).

Profile

Milbemycin oxime is an anthelmintic used in veterinary medicine.

Morantel *(BAN, pINN)*

Moranteli; Morantelum; Морантел.
(*E*)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)vinyl]pyrimidine.
$C_{12}H_{16}N_2S$=220.3
CAS — 20574-50-9.
ATC Vet — QP52AF01.
UNII — 7NJ031HAX5.

Morantel Citrate *(BANM, pINNM)*

Citrato de morantel; Morantel, Citrate de; Morantel, citrato de; Moranteli Citras; Морантела Цитрат.
$C_{12}H_{16}N_2S,C_6H_8O_7,H_2O$=430.5
CAS — 69525-81-1.
ATC Vet — QP52AF01.

NOTE. The name Exhelm has been used as a trade mark for morantel citrate.

Morantel Tartrate *(BANM, USAN, pINNM)*

CP-12009-18; Moranteelivetytartraatti; Morantel, hydrogénotartrate de; Morantel, Tartrate de; Morantel, tartrato de; Morantel-hidrogén-tartarát; Morantel-hydrogen-tartarát; Moranteli hydrogenotartras; Moranteli Tartras; Morantelvätetartrat; Tartrato de morantel; UK-2964-18; Морантела Тартрат.
$C_{12}H_{16}N_2S,C_4H_6O_6$=370.4
CAS — 26155-31-7.
ATC Vet — QP52AF01.
UNII — 5WF7E9QC3F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Morantel Hydrogen Tartrate for Veterinary Use; Morantel Tartrate BP(Vet) 2014). A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. A 1% solution in water has a pH of 3.3 to 3.9. Protect from light.

USP 36: (Morantel Tartrate). A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. pH of a 1% solution in water is between 2.8 and 3.9. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Morantel is an analogue of pyrantel. The citrate and the tartrate are used as anthelmintics in veterinary medicine for the treatment of gastrointestinal roundworms.

Moxidectin *(BAN, USAN, rINN)*

CL-301423; Moksidektiini; Moxidectina; Moxidectine; Moxidectinum; Moxidektin; Моксидектин.
(6*R*,15*S*)-5-*O*-Demethyl-28-deoxy-25-[(*E*)-1,3-dimethylbut-1-enyl]-6,28-epoxy-23-oxomilbemycin B (*E*)-23-*O*-methyloxime.
$C_{37}H_{53}NO_8$=639.8
CAS — 113507-06-5.
ATC Vet — QP54AB02.
UNII — NGU5H31YO9.

NOTE. The names Cydectin, Equest, and Zermex have been used as trade marks for moxidectin.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use.

Ph. Eur. 8: (Moxidectin for Veterinary Use). A white or pale yellow, amorphous powder. Practically insoluble in water; very soluble in alcohol; slightly soluble in hexane.

USP 36: (Moxidectin). A white to pale yellow powder. Practically insoluble in water; very soluble in alcohol; slightly soluble in hexane. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Moxidectin is an anthelmintic used in veterinary medicine. It is also used as a systemic veterinary ectoparasiticide and for the treatment of intestinal roundworms and lungworms. It is under investigation for the treatment of human onchocerciasis.

References.
1. Cotreau MM, *et al.* The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol* 2003; **43:** 1108–15.
2. Korth-Bradley JM, *et al.* Excretion of moxidectin into breast milk and pharmacokinetics in healthy lactating women. *Antimicrob Agents Chemother* 2011; **55:** 5200–4.

Naftalofos *(BAN, USAN, rINN)*

Bay-9002; E-9002; ENT-25567; Naftalofós; Naftalofosum; Naphthalophos; Phthalophos; S-940; Нафталофос.
Diethyl naphthalimido-oxyphosphonate.
$C_{16}H_{16}NO_6P$=349.3
CAS — 1491-41-4.
ATC Vet — QP52AB06.
UNII — H5IT2P8H5I.

Profile

Naftalofos is an organophosphorus compound (see Organophosphorus Insecticides, p. 2158.3) used as an anthelmintic in veterinary medicine.

Netobimin *(BAN, USAN, rINN)*

Netobimina; Nétobimine; Netobiminum; Sch-32481; Нетобимин.
2-{3-Methoxycarbonyl-2-[2-nitro-5-(propylthio)phenyl]guanidino}ethánesulphonic acid.
$C_{14}H_{20}N_4O_7S_2$=420.5
CAS — 88255-01-0.
ATC Vet — QP52AC06.
UNII — U30C54N3MU.

Profile

Netobimin is a prodrug that is converted to albendazole (p. 149.1). It is used in veterinary medicine for the treatment of nematode, tapeworm, and fluke infections.

Niclosamide *(BAN, USAN, rINN)*

Anhydrous Niclosamide; Bay-2353; Niclosamid; Niclosamida; Niclosamida Anidra; Niclosamide anhydre; Niclosamidum; Niclosamidum anhydricum; Niklosamid; Niklosamid, vattenfri; Niklosamidi; Niklosamidi, vedetön; Niklozamid; Niklozamid bezwodny; Niklozamidas, bevandenis; Niklozamit; Phenasale; Vízmentes niklozamid; Никлозамид.
2′,5-Dichloro-4′-nitrosalicylanilide; 5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.
$C_{13}H_8Cl_2N_2O_4$=327.1
CAS — 50-65-7.
ATC — P02DA01.
ATC Vet — QP52AG03.
UNII — 8KK8CQ2K8G.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Int. permits the anhydrous substance or the monohydrate under the title Niclosamide.

Ph. Eur. 8: (Niclosamide, Anhydrous). Yellowish-white to yellowish, fine crystals. Practically insoluble in water; slightly soluble in dehydrated alcohol; sparingly soluble in acetone. Store in airtight containers. Protect from light.

Niclosamide Monohydrate *(BANM, rINNM)*

Niclosamid-Monohydrat; Niclosamida Mono-hidratada; Niclosamida monohidrato; Niclosamide Monohydraté; Niclosamidum monohydricum; Niklosamid monohydrát; Niklosamidimonohydraatti; Niklosamidmonohydrat; Niklozamidas monohidratas; Niklozamid-monohidrát; Никлозамид Моногидрат.
$C_{13}H_8Cl_2N_2O_4,H_2O$=345.1
ATC — P02DA01.
UNII — 20Z25R1145.

Pharmacopoeias. In *Eur.* (see p. vii).

Int. permits the monohydrate or the anhydrous substance under the title Niclosamide.

Ph. Eur. 8: (Niclosamide Monohydrate). Yellowish, fine crystals. Practically insoluble in water; slightly soluble in dehydrated alcohol; sparingly soluble in acetone. Protect from light.

Uses and Administration

Niclosamide is an anthelmintic that is active against most tapeworms, including the beef tapeworm (*Taenia saginata*), the pork tapeworm (*T. solium*), the fish tapeworm (*Diphyllobothrium latum*) and the dog tapeworm (*Dipylidium caninum*); it has also been given for infections with the dwarf tapeworm, *Hymenolepis nana.* For discussions of the treatment of tapeworm infections, see Diphyllobothriasis, p. 145.1, Hymenolepiasis, p. 146.1, and Taeniasis, p. 148.2. The activity of niclosamide against these worms appears to be due to inhibition of mitochondrial oxidative phosphorylation; anaerobic ATP production is also affected.

Niclosamide is given as tablets, which must be chewed thoroughly before swallowing and washed down with water.

For infections with pork tapeworm a single 2-g dose is given after a light breakfast. Niclosamide is not active against the larval form (cysticerci) and, although the risk of inducing cysticercosis appears to be theoretical, a laxative is given about 2 hours after the dose to expel the killed worms and minimise the possibility of the migration of ova of *T. solium* into the stomach; an antiemetic may also be given before treatment.

For infections with beef or fish tapeworms the 2-g dose of niclosamide may be divided, with 1 g taken after breakfast and 1 g an hour later.

In dwarf-tapeworm infections an initial dose of 2 g has been given on the first day followed by 1 g daily for 6 days.

Unless expulsion of the worm is aided by a laxative, portions are voided in a partially digested form after treatment with niclosamide; the scolex is rarely identifiable.

For details of doses in children, see p. 163.1.

In schistosomiasis (p. 148.1), niclosamide is used as a molluscicide in water-treatment control programmes.

Administration in children. Niclosamide may be given orally to children for the treatment of most tapeworm infections. Children 2 to 6 years of age are given half the usual adult dose; those under 2 years of age are given one-quarter the usual adult dose. Children over 6 years of age are given the usual adult dose (see above).

Malignant neoplasms. Studies in *animals* and *in vitro* have suggested[1,2] that niclosamide may have therapeutic potential as an antineoplastic.

1. Jin Y, *et al.* Antineoplastic mechanisms of niclosamide in acute myelogenous leukemia stem cells: inactivation of the NF-κB pathway and generation of reactive oxygen species. *Cancer Res* 2010; **70:** 2516–27.
2. Sack U, *et al.* Novel effect of antihelminthic niclosamide on S100A4-mediated metastatic progression in colon cancer. *J Natl Cancer Inst* 2011; **103:** 1018–36.

Vector control. Reference[1] to the use of niclosamide ethanolamine (sometimes referred to as clonitralide) as a molluscicide in the management of schistosomiasis.

1. Yang G-J, *et al.* Molluscicidal efficacies of different formulations of niclosamide: result of meta-analysis of Chinese literature. *Parasit Vectors* 2010; **3:** 84.

Adverse Effects and Precautions

Gastrointestinal disturbances may occur occasionally with niclosamide. Lightheadedness and pruritus have been reported less frequently.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies niclosamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Niclosamide is not significantly absorbed from the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Yomesan; ***Braz.***: Atenase; ***Fin.***: Kontal; ***Fr.***: Tredemine; ***Ger.***: Yomesan; ***Gr.***: Tredemine; Yomesan†; ***Hong Kong***: Leo-99†; ***India***: Niclosan; ***Israel***: Yomesan†; ***Ital.***: Yomesan; ***Mex.***: Overoid†; ***Neth.***: Yomesan; ***S. Afr.***: Yomesan; ***Swed.***: Yomesan; ***Thai.***: CB-99; Leo-99†; Manoverm; Shors Mesan†; Sinchoni; Sinper-Tabs; Telmitin; Topida; Unicide†; Utosamide; Yomesan; ***Turk.***: Yomesan; ***UK***: Yomesan.

Multi-ingredient Preparations. ***Thai.***: Anson; Heroanson; Taeniacide; Zenda.

Pharmacopoeial Preparations
BP 2014: Niclosamide Tablets.

The symbol † denotes a preparation no longer actively marketed

Nitroscanate *(BAN, USAN, rINN)*

CGA-23654; Nitroscanato; Nitroscanatum; Nitroskanaatti; Nitroskanat; Нитросканат.
4-(4-Nitrophenoxy)phenyl isothiocyanate.
$C_{13}H_8N_2O_3S$=272.3
CAS — 19881-18-6.
ATC Vet — QP52AX01.
UNII — P4IE5B6D6U.

NOTE. The name Troscan has been used as a trade mark for nitroscanate.

Profile

Nitroscanate is an isothiocyanate anthelmintic used in veterinary medicine for the treatment of gastrointestinal roundworm and tapeworm infections.

Nitroxinil *(BAN, rINN)*

Nitroxinilo; Nitroxinilum; Nitroxynil; Нитроксинил.
4-Hydroxy-3-iodo-5-nitrobenzonitrile.
$C_7H_3IN_2O_3$=290.0
CAS — 1689-89-0 (nitroxinil); 27917-82-4 (nitroxinil eglumine).
ATC Vet — QP52AG08.
UNII — 9L0EXQ7125.

NOTE. The name Trodax has been used as a trade mark for nitroxinil.

Pharmacopoeias. In *BP(Vet)*. Also in *Fr.* for veterinary use only.

BP(Vet) 2014: (Nitroxinil). A yellow to yellowish brown powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in ether; it dissolves in solutions of alkali hydroxides. Protect from light.

Profile

Nitroxinil is an anthelmintic used in veterinary medicine for the treatment of fascioliasis and some gastrointestinal roundworms in cattle and sheep.

Oxamniquine *(BAN, USAN, rINN)*

Oksamnichina; Oxamniquina; Oxamniquinum; UK-4271; Оксамнихин.
1,2,3,4-Tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolylmethanol.
$C_{14}H_{21}N_3O_3$=279.3
CAS — 21738-42-1.
ATC — P02BA02.
ATC Vet — QP52AA02.
UNII — 0O977R722D.

Pharmacopoeias. In *Fr.* and *Int.*

Uses and Administration

Oxamniquine is an anthelmintic used in the treatment of schistosomiasis caused by *Schistosoma mansoni*, but not by other *Schistosoma* spp. It causes worms to shift from the mesenteric veins to the liver where the male worms are retained; the female worms return to the mesentery, but can no longer release eggs. Resistance may occur.

Oxamniquine is given orally, preferably after food. Dosage depends on the geographical origin of the infection and total doses range from 15 mg/kg as a single dose to 60 mg/kg given over 2 to 3 days. A single dose of 15 mg/kg is recommended in West Africa, South America, and the Caribbean Islands; in East and Central Africa and the Arabian peninsula this dose should be increased to 30 mg/kg in 2 divided doses. A total dose of 60 mg/kg given over 2 to 3 days is recommended for Egypt and southern Africa but some experts recommend a total dose of 40 to 60 mg/kg given over 2 to 3 days for all African countries. A single dose should not exceed 20 mg/kg.

Schistosomiasis. Oxamniquine is an alternative to praziquantel for the treatment of schistosomiasis (p. 148.1) due to *Schistosoma mansoni*, although resistance has occurred, particularly in South America,[1] and it is somewhat less effective than praziquantel.[2] After the appropriate therapeutic dose of oxamniquine, cure rates of at least 60%, and often more than 90%, can be expected. Egg excretion in those not cured will be reduced by over 80%, and usually by over 90%, one year after treatment.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Ferrari ML, *et al.* Efficacy of oxamniquine and praziquantel in the treatment of Schistosoma mansoni infection: a controlled trial. *Bull WHO* 2003; **81:** 190–6.
3. WHO. The control of schistosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 728* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_728.pdf (accessed 16/07/08)

Adverse Effects

Oxamniquine causes severe pain at the injection site when given intramuscularly and is no longer given by this route.

It is generally well tolerated after oral doses, although dizziness with or without drowsiness occurs in at least a third of patients, beginning up to 3 hours after a dose and usually lasting for up to 6 hours. Headache and gastrointestinal effects such as nausea, vomiting, and diarrhoea are also common.

Hypersensitivity reactions including urticaria, pruritic skin rashes, and fever may occur. Liver enzyme values have been raised transiently in some patients. Epileptiform convulsions have been reported, especially in patients with a history of convulsive disorders. Hallucinations and excitement have occurred rarely.

A reddish discoloration of urine, probably due to a metabolite of oxamniquine, has been reported.

Effects on body temperature. A review[1] in 1987 noted that although a modest post-treatment rise in temperature had been reported occasionally, fever was not a common adverse effect of oxamniquine, except in Egypt where it appeared to be characteristic. The cause was unknown. Increased immune complexes and excretion of antigens occurred in only half the cases, there was no evidence that Egyptian patients metabolised the drug differently to produce a pyrogenic metabolite, and the effect had not been seen in other areas where a similar high-dose regimen was used.[1]

1. Foster R. A review of clinical experience with oxamniquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 55–9.

Effects on the nervous system. In 37 patients with *Schistosoma mansoni* infection treated successfully with oxamniquine,[1] dizziness and drowsiness were most common, but the most significant adverse effect was the development of EEG abnormalities in 6 of 34 patients whose pretreatment EEG was normal. Of the 3 patients with pre-existing EEG abnormalities, 1 suffered a tonic-clonic seizure during therapy as previously reported,[2] 1 did not suffer seizures, and the third received phenytoin prophylaxis during oxamniquine therapy. It was considered prudent to give antiepileptics before starting oxamniquine in patients with a history of seizure disorder. After completion of this study, a patient with no history of seizures suffered a tonic-clonic seizure 2 hours after each of the second and third doses of oxamniquine.

The main neuropsychiatric adverse effects seen in 180 Brazilian patients with *Schistosoma mansoni* infection treated with single oral doses of oxamniquine were: drowsiness (50.6%), dizziness (41.1%), headache (16.1%), temporary amnesia (2.2%), behavioural disturbances (1.7%), chills (1.1%), and seizures (1.1%).[3] An EEG was performed before and after treatment in 20 patients; there were alterations in 3 but they were not associated with neuropsychiatric changes.

1. Krajden S, *et al.* Safety and toxicity of oxamniquine in the treatment of Schistosoma mansoni infections, with particular reference to electroencephalographic abnormalities. *Am J Trop Med Hyg* 1983; **32:** 1344–6.
2. Keystone JS. Seizures and electroencephalograph changes associated with oxamniquine therapy. *Am J Trop Med Hyg* 1978; **27:** 360–2.
3. de Carvalho SA, *et al.* Neurotoxicidade do oxamniquine no tratamento da infeção humana pelo Schistosoma mansoni. *Rev Inst Med Trop Sao Paulo* 1985; **27:** 132–42.

Precautions

Oxamniquine should be used with caution in patients with epilepsy or a history of convulsive disorders. Patients should be warned that oxamniquine can cause dizziness or drowsiness and if affected they should not drive or operate machinery.

Pharmacokinetics

Oxamniquine is readily absorbed after oral doses and peak plasma concentrations occur after 1 to 3 hours. The plasma half-life is 1 to 2.5 hours.

It is extensively metabolised to inactive metabolites, mainly the 6-carboxy derivative, which are excreted in the urine. About 70% of a dose of oxamniquine is excreted as the 6-carboxy metabolite within 12 hours of a dose; traces of the 2-carboxy metabolite have also been detected in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Mansil.

Oxantel Embonate *(BANM, rINNM)*

CP-14445-16; Embonato de oxantel; Oxantel, Embonate d'; Oxantel, embonato de; Oxantel Pamoate (USAN); Oxanteli Embonas; Оксантела Эмбонат.
(*E*)-3-[2-(1,4,5,6-Tetrahydro-1-methylpyrimidin-2-yl)vinyl]phenol 4,4′-methylenebis(3-hydroxy-2-naphthoate).
$C_{13}H_{16}N_2O$,$C_{23}H_{16}O_6$=604.7
CAS — 36531-26-7 (oxantel); 68813-55-8 (oxantel embonate); 42408-84-4 (oxantel embonate).
ATC — P02CC02.
UNII — UPY1D732T0.

Profile

Oxantel is an analogue of pyrantel that has been used as the embonate in the treatment of trichuriasis. It is used with pyrantel embonate for various intestinal nematode infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Quantrel†; ***Philipp.***: Quantrel; ***Venez.***: Dualid; Quantrel.

Oxfendazole *(BAN, USAN, rINN)*

Oksfendatsoli; Oxfendazol; Oxfendazolum; RS-8858; Оксфендазол.
Methyl 5-phenylsulphinyl-1*H*-benzimidazol-2-ylcarbamate.
$C_{15}H_{13}N_3O_3S$=315.3
CAS — 53716-50-0.
ATC Vet — QP52AC02.
UNII — OMP2H17F9E.

NOTE. The names Bovex, Endoworm, and Parafend have been used as trade marks for oxfendazole.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Oxfendazole for Veterinary Use; Oxfendazole BP(Vet) 2014). A white or almost white powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Oxfendazole). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Oxfendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 158.3). It is used in veterinary medicine for the treatment of nematode and tapeworm infections.

Oxibendazole *(BAN, USAN, rINN)*

Oxibendazol; Oxibendazolum; SKF-30310; Оксибендазол.
Methyl 5-propoxy-1*H*-benzimidazol-2-ylcarbamate.
$C_{12}H_{15}N_3O_3$=249.3
CAS — 20559-55-1.
ATC Vet — QP52AC07.
UNII — 022N12KJ0X.

NOTE. The name Anthelcide has been used as a trade mark for oxibendazole.

Profile

Oxibendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 158.3). It is used in veterinary medicine for the treatment of nematode infections.

Oxyclozanide *(BAN, rINN)*

ICI-46683; Oxiclozanida; Oxyclozanidum; Оксиклозанид.
3,3′,5,5′,6-Pentachloro-2′-hydroxysalicylanilide.
$C_{13}H_6Cl_5NO_3$=401.4
CAS — 2277-92-1.
ATC Vet — QP52AG06.
UNII — 1QS9G4876X.

NOTE. The name Zanil has been used as a trade mark for oxyclozanide.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Oxyclozanide). A pale cream or cream-coloured powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone; slightly soluble in chloroform.

Profile

Oxyclozanide is an anthelmintic used in veterinary medicine for the control of fascioliasis in cattle and sheep.

Piperazine

Piperatsiini; Piperazin; Piperazina; Piperazinas; Pipérazine; Piperazinum; Piperazyna; Пиперазин.

$C_4H_{10}N_2$=86.14

CAS — 110-85-0.

ATC — P02CB01.

ATC Vet — QP52AH01.

UNII — 1RTM4PAL0V.

Pharmacopoeias. In *US.*

USP 36: (Piperazine). White to off-white lumps or flakes having an ammoniacal odour. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Piperazine Adipate

Piperatsiiniadipaatti; Piperaz. Adip.; Piperazina, adipato de; Piperazinadipat; Piperazin-adipát; Pipérazine, adipate de; Piperazini adipas; Piperazino adipatas; Piperazinum Adipicum; Пиперазина Адипат.

$C_4H_{10}N_2.C_6H_{10}O_4$=232.3

CAS — 142-88-1.

ATC — P02CB01.

UNII — V7P5P122LB.

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn,* and *Viet.*

In *US* for veterinary use only.

Ph. Eur. 8: (Piperazine Adipate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol.

USP 36: (Piperazine Adipate). A white crystalline powder. Soluble in water; practically insoluble in alcohol.

Piperazine Citrate

Hydrous Tripiperazine Dicitrate; Piperatsiinisitraatti; Piperazina, citrato de; Piperazincitrat; Piperazin-citrát; Piperazin-citrát hydrát; Pipérazine, citrate de; Piperazini Citras; Piperazini Citras Hydricus; Piperazino citratas; Пиперазина Цитрат.

$(C_4H_{10}N_2)_3.2C_6H_8O_7.xH_2O$=642.7 (anhydrous substance)

CAS — 144-29-6 (anhydrous piperazine citrate); 41372-10-5 (piperazine citrate hydrate).

ATC — P02CB01.

UNII — 63KP7FXF2I.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US,* and *Viet.*

Ph. Eur. 8: (Piperazine Citrate). A white or almost white granular powder. It contains a variable amount of water. Freely soluble in water; practically insoluble in alcohol.

USP 36: (Piperazine Citrate). A white, crystalline powder having not more than a slight odour. Soluble in water; insoluble in alcohol and in ether. pH of a 10% solution in water is about 5.

Stability. A decrease in the content of piperazine [as citrate] in syrups on storage was attributed to interaction with fructose and glucose formed by hydrolysis of sucrose.[1] A syrup prepared with sorbitol lost no potency when stored at 25 degrees for 14 months.

1. Nielsen A, Reimer P. The stability of piperazine in syrup. *Arch Pharm Chemi (Sci)* 1975; **3:** 73–8.

Piperazine Dihydrochloride

Пиперазина Дигидрохлорид.

$C_4H_{10}N_2.2HCl.xH_2O$=159.1 (anhydrous substance)

CAS — 142-64-3.

ATC — P02CB01.

UNII — 17VU4Z4W8B.

Pharmacopoeias.

In *US* for veterinary use only.

USP 36: (Piperazine Dihydrochloride). A white crystalline powder. Soluble in water. A 5% solution in water has a pH of 3.0 to 3.4.

Piperazine Hydrate

Piperatsiinihydraatti; Piperazin Heksahidrat; Piperazin hexahydrát; Piperazin-Hexahydrat; Piperazina hexahidrato; Piperazinas hidratas; Piperazine Hexahydrate; Pipérazine, hydrate de; Piperazin-hidrát; Piperazinhydrat; Piperazini Hydras; Piperazinium Hexahydricum; Piperazinum Hydricum; Piperazyna uwodniona; Пиперазина Гидрат.

Piperazine hexahydrate.

$C_4H_{10}N_2.6H_2O$=194.2

CAS — 142-63-2.

ATC — P02CB01.

UNII — P3M07B8U64.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Piperazine Hydrate). Colourless deliquescent crystals. M.p. about 43 degrees. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 10.5 to 12.0. Store in airtight containers. Protect from light.

Piperazine Phosphate

Piperazina, fosfato de; Piperazini Phosphas; Пиперазина Фосфат.

$C_4H_{10}N_2.H_3PO_4.H_2O$=202.1

CAS — 14538-56-8 (anhydrous piperazine phosphate); 18534-18-4 (piperazine phosphate monohydrate).

ATC — P02CB01.

UNII — 8TIF7T48FP.

Pharmacopoeias. In *Br., Chin., Jpn,* and *Viet.*

In *US* for veterinary use only.

BP 2014: (Piperazine Phosphate). A white odourless or almost odourless crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.5.

USP 36: (Piperazine Phosphate). A white crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.5. Store in airtight containers.

Uses and Administration

Piperazine is an anthelmintic effective against the intestinal nematodes *Ascaris lumbricoides* (roundworm) and *Enterobius vermicularis* (pinworm, threadworm), although other anthelmintics are usually preferred (see the discussions on the treatment of ascariasis and enterobiasis on p. 143.3 and p. 145.3). In roundworms piperazine produces a neuromuscular block leading to a flaccid muscle paralysis in susceptible worms, which are then easily dislodged by the movement of the gut and expelled in the faeces.

Piperazine is usually given as the citrate or phosphate, but the adipate may also be used. The dihydrochloride is used in veterinary practice. The dosage of the salts of piperazine is usually expressed in terms of piperazine hydrate; 100 mg of piperazine hydrate is equivalent to about 44.4 mg of piperazine, 120 mg of piperazine adipate, 125 mg of piperazine citrate (110 mg of anhydrous piperazine citrate), and to 104 mg of piperazine phosphate.

For the treatment of **ascariasis**, a single dose, repeated once after 14 days, has been used. In adults and children over 12 years of age, a dose equivalent to 4.5 g of piperazine hydrate is given orally.

For **enterobiasis**, piperazine has been given for 7 days. A second course after a 7-day interval may be required. Adults and children over 12 years of age are given the equivalent of 2.25 g of the hydrate once daily.

For details of doses in children, see p. 164.3.

Piperazine is also used as a preparation with senna in a single dose of 4 g of the phosphate for adults and children over 6 years of age, repeated after 14 days for enterobiasis, or repeated monthly if necessary for up to 3 months to treat and prevent ascariasis.

Administration in children. Piperazine may be given orally to children for the treatment of intestinal nematode infections, such as ascariasis (roundworm) and enterobiasis (pinworm and threadworm), although other anthelmintics are usually preferred.

For the treatment of **ascariasis**, a single dose equivalent to the following amount of piperazine hydrate is given, repeated once after 14 days:

- 9 to 12 years of age: 3.75 g
- 6 to 8 years of age: 3 g
- 4 to 5 years of age: 2.25 g
- 1 to 3 years of age: 1.5 g
- under 1 year of age (on medical advice only): 120 mg/kg has been suggested

For **enterobiasis**, piperazine has been given for 7 days in doses equivalent to the following amount of piperazine hydrate:

- 7 to 12 years of age: 1.5 g daily
- 4 to 6 years of age: 1.125 g daily
- 1 to 3 years of age: 750 mg daily
- under 1 year of age (on medical advice only): 45 to 75 mg/kg daily has been suggested

A second course of treatment after a 7-day interval may be required.

Adverse Effects

Serious adverse effects are rare with piperazine and generally indicate overdosage or impaired excretion. Nausea, vomiting, diarrhoea, abdominal pain, headache, rashes, and urticaria occasionally occur. Severe neurotoxicity and EEG abnormalities have been reported with symptoms including somnolence, dizziness, nystagmus, muscular incoordination ('worm wobble') and weakness, ataxia, paraesthesia, myoclonic contractions, choreiform movements, tremor, convulsions, and loss of reflexes.

Transient visual disturbances such as blurred vision have occurred occasionally and there were reports of cataract formation after treatment with piperazine although they do not appear to have been substantiated.

Hypersensitivity reactions such as bronchospasm, Stevens-Johnson syndrome, and angioedema have occurred in some individuals.

Piperazine has been taken off the market in some European countries because of general concern about its safety.[1] A study carried out in Sweden on 2 healthy subjects had indicated that mononitrosation of piperazine can occur in the stomach to produce the potential carcinogen *N*-mononitrosopiperazine; the more potent *N,N*-dinitrosopiperazine was not found.[2] However, the disease risk to man from such *N*-nitroso compounds has been questioned[3] and certainly reports of tumours associated with the use of piperazine have not been traced. Also, in the UK the CSM concluded that the incidence of serious adverse effects associated with piperazine was low and that, with appropriate pack warnings, piperazine products could remain as medicines available to the public through pharmacies.[1]

1. Anonymous. Data sheet changes for piperazine in pregnancy. *Pharm J* 1988; **240:** 367.
2. Bellander BTD, *et al.* Nitrosation of piperazine in the stomach. *Lancet* 1981; **ii:** 372.
3. Tannenbaum SR. N-nitroso compounds: a perspective on human exposure. *Lancet* 1983; **i:** 629–32.

Abuse. Derivatives of piperazine have been developed and abused as 'designer drugs'—see Benzylpiperazine (p. 2318.1).

Effects on the blood. A 4-year-old African boy with G6PD deficiency developed haemolytic anaemia; no cause for the haemolysis was found except that 2 days previously he had taken *Pripsen* (piperazine and senna).[1] Severe thrombocytopenia with epistaxis and haemoptysis, which developed in a 61-year-old man after piperazine self-medication, was probably the result of sensitisation to piperazine 15 years earlier.[2]

1. Buchanan N, *et al.* G-6-PD deficiency and piperazine. *BMJ* 1971; **2:** 110.
2. Cork MJ, *et al.* Pruritus ani, piperazine, and thrombocytopenia. *BMJ* 1990; **301:** 1398.

Effects on the liver. A reaction resembling viral hepatitis occurred on 2 occasions in a 25-year-old woman after use of piperazine; it appeared to be a hypersensitivity reaction.[1]

1. Hamlyn AN, *et al.* Piperazine hepatitis. *Gastroenterology* 1976; **70:** 1144–7.

Hypersensitivity. A patient had a serum-sickness-like illness associated with piperazine,[1] which was followed by a delayed hypersensitivity vasculitis. Occupational asthma related to exposure to piperazine citrate has also been reported.[2]

See also Effects on the Blood, above, and Effects on the Liver, above.

1. Balzan M, Cacciottolo JM. Hypersensitivity vasculitis associated with piperazine therapy. *Br J Dermatol* 1994; **131:** 133–4.
2. Quirce S, *et al.* Occupational asthma due to piperazine citrate. *J Investig Allergol Clin Immunol* 2006; **16:** 138–9.

Precautions

Piperazine is contra-indicated in patients with epilepsy or severe renal impairment and should be given with care to patients with neurological disturbances or mild to moderate renal impairment. It should also be avoided or given with extreme caution in patients with hepatic impairment.

Breast feeding. The UK licensed product information for *Pripsen* (piperazine and senna) states that piperazine is distributed into breast milk. Mothers should be advised to take a dose after breast feeding then not to breast feed for 8 hours during which period milk should be expressed and discarded at the regular feeding times.

Pregnancy. It has been reported that piperazine is teratogenic in *rabbits* and that there have been isolated reports of fetal malformations after clinical use, though no causal relationship has been established. Two infants with malformations have been described briefly:[1] one had bilateral hare lip, cleft palate, and anophthalmia; the other had an abnormality of one foot. Both mothers had taken *Pripsen* (piperazine and senna). UK licensed product information for *Pripsen* advises against use in pregnancy, especially during the first trimester, unless immediate treatment with piperazine is essential. However, the UK *National Teratology Information Service* notes that limited available data on the use of piperazine (with or without senna) in pregnancy does not show an increased risk of malformations or other adverse pregnancy outcomes and recom-

mends that treatment should not be withheld if clinically indicated.[2]

1. Leach FN. Management of threadworm infestation during pregnancy. *Arch Dis Child* 1990; **65:** 399–400.
2. National Teratology Information Service. Use of piperazine in pregnancy (issued July 2011). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Piperazine%202011.pdf (accessed 11/08/11)

Interactions

The anthelmintic effects of piperazine and pyrantel may be antagonised when the two compounds are used together. The possibility that piperazine may enhance the adverse effects of phenothiazines such as chlorpromazine is discussed on p. 1053.2.

Pharmacokinetics

Piperazine is readily absorbed from the gastrointestinal tract and is excreted in the urine within 24 hours, partly as metabolites. The rate at which different individuals excrete piperazine has been reported to vary widely. It is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Formule C34; ***Fr.***: Vermifuge; ***Gr.***: Oxyuran; ***India***: Avizine; ***Indon.***: Combicitrine; Piperacyl; ***Ital.***: Citropiperazina; ***Mex.***: Lu-Peracina; Overpon; Piperazil; Pipergress; Pirzinol; Verfid†; Vermin; ***Port.***: Pipermel; Pipertox; ***S.Afr.***: Padax; Pipralen†; Piprine; SB Tox Worm†; ***Singapore***: Mei-Mei Worm; ***Spain***: Mimedran†; Vermi; ***Thai.***: Bompar; Sinpermine; Vermex†; ***Turk.***: Asepar†; Askaripar; Helmicide; Helmipar; Oksiaskaril; Siropar; ***Venez.***: Ciperina; Piperato; Piperazil; Piperdin; Piperzan; Verpirol.

Multi-ingredient Preparations. ***Port.***: Biureol†; ***UK***: Pripsen†.

Pharmacopoeial Preparations

BP 2014: Chewable Piperazine Phosphate Tablets; Piperazine Citrate Elixir; Piperazine Phosphate Tablets;
USP 36: Piperazine Citrate Syrup; Piperazine Citrate Tablets.

Pomegranate Bark

Casca da Romeira; Corteccia del Melograno; Corteza de Granado; Ecorce de Grenadier; Granado; Granati Cortex; Granatrinde; Pomegranate; Pomegranate Root Bark; Кора Гранатового Дерева.

UNII — O2ZTS50U5E (Punica granatum); D9B634V4GP (Punica granatum flower); 56687D1Z4D (Punica granatum fruit); RS999V57DU (Punica granatum fruit rind); 995671U9KB (Punica granatum juice); O9486I5JXI (Punica granatum leaf); CLV24I3T1D (Punica granatum root bark); 7294Z34NS7 (Punica granatum seed).

Profile

Pomegranate bark, the dried bark of the stem and root of *Punica granatum* (Punicaceae) containing about 0.4 to 0.9% of alkaloids, has been used for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hexaporine.

Multi-ingredient Preparations. ***Chile***: Cellenergy; ***Fr.***: Acyprost; ***Ital.***: Pausanil; Rubis; ***Switz.***: Padma Digestin; ***USA***: Immunicare.

Homoeopathic Preparations. ***Fr.***: Poconeol no 34.

Praziquantel *(BAN, USAN, rINN)*

EMBAY-8440; Pratsikvanteli; Prazicuantel; Prazikvantel; Prazikvantelis; Praziquantelum; Prazykwantel; Празиквантел.

2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydropyrazino[2,1-*a*]isoquinolin-4-one.

$C_{19}H_{24}N_2O_2$=312.4

CAS — 55268-74-1.

ATC — P02BA01.

ATC Vet — QP52AA01.

UNII — 6490C9U457.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Praziquantel). White or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Praziquantel). A white or practically white crystalline powder; odourless or with a faint characteristic odour. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Protect from light.

Uses and Administration

Praziquantel is an anthelmintic with a broad spectrum of activity against trematodes (flukes) including all species of *Schistosoma* pathogenic to man, and against cestodes (tapeworms). It is used in the treatment of cysticercosis, diphyllobothriasis, hymenolepiasis, schistosomiasis, taeniasis, and intestinal, liver, and lung fluke infections. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Praziquantel is given orally with food.

In the treatment of **schistosomiasis** in adults and children over 4 years it is given on one day as three doses of 20 mg/kg at intervals of 4 to 6 hours or it is given as a single dose of 40 to 60 mg/kg (but see p. 166.1).

Doses in adults and children over 4 years in liver and lung **fluke infections** are 25 mg/kg three times daily for two days or a single dose of 40 mg/kg. Similar doses may be used in intestinal fluke infections (see p. 165.3).

Praziquantel may be given as an oral single dose in the treatment of **tapeworm infections** in adults and children over 4 years of age. For the treatment of *Taenia saginata* and *T. solium* infections the recommended dose is 5 to 10 mg/kg, for *Hymenolepis nana* infections the dose is 15 to 25 mg/kg, and for *Diphyllobothrium latum* infections doses of 5 to 25 mg/kg have been suggested.

Praziquantel is used in adults and children over 4 years in the treatment of **neurocysticercosis** in a dose of 50 mg/kg daily in 3 divided doses for 14 days. An alternative regimen of 3 doses of 25 mg/kg every 2 hours has been proposed.

Reviews.

1. Pearson RD, Guerrant RL. Praziquantel: a major advance in anthelmintic therapy. *Ann Intern Med* 1983; **99:** 195–8. Correction. *ibid.*; 574.
2. King CH, Mahmoud AAF. Drugs five years later: praziquantel. *Ann Intern Med* 1989; **110:** 290–6.
3. Cioli D, Pica-Mattocia L. Praziquantel. *Parasitol Res* 2003; **90** (suppl 1): S3–S9.
4. Ali BH. A short review of some pharmacological, therapeutic and toxicological properties of praziquantel in man and animals. *Pak J Pharm Sci* 2006; **19:** 170–5.

Administration in children. Praziquantel may be given orally to children over 4 years of age for the treatment of trematode infections (including schistosomiasis) and cestode infections such as cysticercosis, diphyllobothriasis, hymenolepiasis, and taeniasis. Doses used are the same by weight as those used for adults (see above).

Although pre-school children are habitually excluded from schistosomiasis control programs, a study[1] involving 104 Zimbabwean children aged 1 to 5 years found that treatment of *Schistosoma haematobium* infection with a standard dose of praziquantel (40 mg/kg) was as safe and effective in this younger age group as in older children.

1. Mutapi F, *et al. Schistosoma haematobium* treatment in 1-5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PLoS Negl Trop Dis* 2011; **5:** e1143.

Cysticercosis. Praziquantel is used in the treatment of neurocysticercosis (p. 144.3) although albendazole is also considered to be the drug of choice.

References.

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; **34:** 503–15.
2. Del Brutto OH, *et al.* Single-day praziquantel versus 1-week albendazole for neurocysticercosis. *Neurology* 1999; **52:** 1079–81.
3. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel. *Ann Intern Med* 2006; **145:** 43–51.

Echinococcosis. Praziquantel may be used as an adjunct to surgery in echinococcosis (p. 145.2). Praziquantel has been reported to possess a scolicidal effect *in vitro* and *in vivo* against *Echinococcus granulosus*, although it does not penetrate well into mature cysts.[1] There has been a report of the successful treatment of disseminated peritoneal hydatid disease with praziquantel and surgery.[2] In this case praziquantel was effective against the small cysts; 2 large cysts were removed surgically, one before praziquantel was started. However, activity in 9 other patients given praziquantel was disappointing.[3] A combination of praziquantel with albendazole may be more effective,[1,4] although better evidence is needed for firm recommendations.[1]

1. Bygott JM, Chiodini PL. Praziquantel: neglected drug? Ineffective treatment? Or therapeutic choice in cystic hydatid disease? *Acta Trop* 2009; **111:** 95–101.
2. Henriksen T-H, *et al.* Treatment of disseminated peritoneal hydatid disease with praziquantel. *Lancet* 1989; **i:** 272.
3. Piens MA, *et al.* Praziquantel dans l'hydatidose humaine: évaluation par traitement médical pré-opératoire. *Bull Soc Pathol Exot Filiales* 1989; **82:** 503–12.
4. Ayles HM, *et al.* A combined medical and surgical approach to hydatid disease: 12 years' experience at the Hospital for Tropical Diseases, London. *Ann R Coll Surg Engl* 2002; **84:** 100–105.

Intestinal fluke infections. Praziquantel, given orally, is used in the treatment of intestinal fluke infections (p. 146.2). In the treatment of fasciolopsiasis, heterophyiasis, and metagonimiasis, the usual recommended dose is 25 mg/kg three times daily for one day.[1] However, a single dose of 25 mg/kg has also been recommended.[2] Single doses of 15 mg/kg, 25 mg/kg, or 40 mg/kg all yielded a cure rate of 100% in a study in 72 primary-school children in Thailand who were harbouring *Fasciolopsis buski*, suggesting that a single dose of 15 mg/kg at bedtime might be tried.[3] In another study, 9 patients infected with the trematode *Nanophyetus salmincola* were treated with praziquantel 20 mg/kg three times daily for one day and were negative for eggs in their stools 2 to 12 weeks later,[4] and this has become the usual recommended dose.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 25/11/09)
3. Harinasuta T, *et al.* Efficacy of praziquantel on fasciolopsiasis. *Arzneimittelforschung* 1984; **34:** 1214–15.
4. Fritsche TR, *et al.* Praziquantel for treatment of human Nanophyetus salmincola (Troglotrema salmincola) infection. *J Infect Dis* 1989; **160:** 896–9.

Liver fluke infections. Praziquantel given orally is the treatment of choice for clonorchiasis and opisthorchiasis; it has also been used in the treatment of fascioliasis (p. 146.2) although in this latter infection triclabendazole, or alternatively bithionol or nitazoxanide, are preferred.

Various studies have shown praziquantel to be effective in clonorchiasis[1-4] and opisthorchiasis,[5,6] although one study in opisthorchiasis[7] showed that re-infection was common despite praziquantel therapy, particularly in those with heavy initial infection. A study in Thailand[8] confirmed that mass treatment for opisthorchiasis with a single dose of praziquantel was beneficial, although it was suggested that ideally treatment should be given twice a year.

While praziquantel is not the drug of choice for fascioliasis, there has been a report[9] of successful treatment of a patient with severe infection. Subsequent studies[10-12] have, however, shown praziquantel to be of little benefit.

1. Soh C-J. Clonorchis sinensis: experimental and clinical studies with praziquantel in Korea. *Arzneimittelforschung* 1984; **34:** 1156–9.
2. Chen C-Y, Hsieh W-C. Clonorchis sinensis: epidemiology in Taiwan and clinical experience with praziquantel. *Arzneimittelforschung* 1984; **34:** 1160–2.
3. Kuang Q-H, *et al.* Clonorchiasis: treatment with praziquantel in 50 cases. *Arzneimittelforschung* 1984; **34:** 1162–3.
4. Lee S-H. Large scale treatment of clonorchis sinensis infections with praziquantel under field conditions. *Arzneimittelforschung* 1984; **34:** 1227–8.
5. Bunnag D, *et al.* Opisthorchis viverrini: clinical experience with praziquantel in hospital for tropical diseases. *Arzneimittelforschung* 1984; **34:** 1173–4.
6. Ambroise-Thomas P, *et al.* Therapeutic results in opisthorchiasis with praziquantel in a reinfection-free environment in France. *Arzneimittelforschung* 1984; **34:** 1177–9.
7. Upatham ES, *et al.* Rate of re-infection by Opisthorchis viverrini in an endemic northeast Thai community after chemotherapy. *Int J Parasitol* 1988; **18:** 643–9.
8. Pungpak S, *et al.* Opisthorchis viverrini infection in Thailand: studies on the morbidity of the infection and resolution following praziquantel treatment. *Am J Trop Med Hyg* 1997; **56:** 311–14.
9. Schiappacasse RH, *et al.* Successful treatment of severe infection with Fasciola hepatica with praziquantel. *J Infect Dis* 1985; **152:** 1339–40.
10. Farag HF, *et al.* A short note on praziquantel in human fascioliasis. *J Trop Med Hyg* 1986; **89:** 79–80.
11. Farid Z, *et al.* Unsuccessful use of praziquantel to treat acute fascioliasis in children. *J Infect Dis* 1986; **154:** 920–1.
12. Farid Z, *et al.* Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; **82:** 299.

Lung fluke infections. Praziquantel, given orally, is used in the treatment of the lung fluke infection paragonimiasis (p. 146.3).

References.

1. Vanijanonta S, *et al.* Paragonimus heterotremus and other Paragonimus spp. in Thailand: pathogenesis clinic and treatment. *Arzneimittelforschung* 1984; **34:** 1186–8.
2. Pachucki CT, *et al.* American paragonimiasis treated with praziquantel. *N Engl J Med* 1984; **311:** 582–3.
3. De NV, *et al.* Epidemiology, symptoms and treatment of paragonimiasis in Sin Ho district, Lai Chau province, Vietnam. *Southeast Asian J Trop Med Public Health* 2000; **31** (suppl 1): 26–30.

Schistosomiasis. Praziquantel is the main drug[1-4] used in the treatment of schistosomiasis (p. 148.1). It is effective against all species of schistosomes,[1] although the possibility of resistance remains a concern.[5-7] Oral doses are either 20 mg/kg given three times in one day or a single dose of 40 to 60 mg/kg. WHO considers[1] that in the field such a single-dose treatment will produce a cure rate of 60 to 90% with a reduction in egg count in those not cured of 90 to 95%. Good as such results are, a single dose or one day's sole treatment should not be considered to be all that is required to achieve a permanent cure or prevent re-infection, and any treatment plan should be reassessed after 6 or 12 months.[8,9] Such an approach with annual screening and targeted chemotherapy can provide, at least in some endemic areas, successful protection for children against intense infection and consequent hepatic disease.[9]

Several studies indicate that doses lower than those recommended above might be effective and in some control programmes 20 mg/kg might be enough for *S. haematobium*[10-12] or 30 mg/kg for *S. mansoni*.[10] The extent to which low doses contribute to resistance, as has been suggested with oxamniquine,[13] is unclear, but refractory infections

have been reported. A 4-day treatment course was needed to produce a complete cure in a patient who relapsed twice following standard one-day treatment regimens.[14] Hepatic impairment, specifically hepatic fibrosis, is a feature of some schistosomal infections and patients with such liver involvement have benefited from treatment with praziquantel.[9,15]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Also available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 25/11/09)
2. Doenhoff MJ, Pica-Mattocia L. Praziquantel for the treatment of schistosomiasis: its use for control in areas with endemic disease and prospects for drug resistance. *Expert Rev Anti Infect Ther* 2006; **4:** 199–210.
3. Doenhoff MJ, *et al*. Praziquantel: its use in control of schistosomiasis in sub-Saharan Africa and current research needs. *Parasitology* 2009; **136:** 1825–35.
4. Dömling A, Khoury K. Praziquantel and schistosomiasis. *ChemMedChem* 2010; **5:** 1420–34.
5. Doenhoff MJ, *et al*. Resistance of Schistosoma mansoni to praziquantel: is there a problem? *Trans R Soc Trop Med Hyg* 2002; **96:** 465–9.
6. Doenhoff MJ, *et al*. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. *Curr Opin Infect Dis* 2008; **21:** 659–67.
7. Seto EY, *et al*. Human schistosomiasis resistance to praziquantel in china: should we be worried? *Am J Trop Med Hyg* 2011; **85:** 74–82.
8. Anonymous. The chemotherapy of schistosomiasis control. *Bull WHO* 1986; **64:** 23–5.
9. Anonymous. Mass treatment of schistosomiasis with praziquantel. *WHO Drug Inf* 1988; **2:** 184–5.
10. Taylor P, *et al*. Efficacy of low doses of praziquantel for Schistosoma mansoni and S. haematobium. *J Trop Med Hyg* 1988; **91:** 13–17.
11. King CH, *et al*. Dose-finding study for praziquantel therapy of Schistosoma haematobium in Coast Province, Kenya. *Am J Trop Med Hyg* 1989; **40:** 507–13.
12. Hatz C, *et al*. Ultrasound scanning for detecting morbidity due to Schistosoma haematobium and its resolution following treatment with different doses of praziquantel. *Trans R Soc Trop Med Hyg* 1990; **84:** 84–8.
13. Coles GC, *et al*. Tolerance of Kenyan Schistosoma mansoni to oxamniquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 782–5.
14. Murray-Smith SQ, *et al*. A case of refractory schistosomiasis. *Med J Aust* 1996; **165:** 458.
15. Zwingenberger K, *et al*. Praziquantel in the treatment of hepatosplenic schistosomiasis: biochemical disease markers indicate deceleration of fibrogenesis and diminution of portal flow obstruction. *Trans R Soc Trop Med Hyg* 1990; **84:** 252–6.

Taeniasis. Praziquantel is used in the treatment of taeniasis (p. 148.2). It has been studied in the mass control of taeniasis when a single dose of 5 mg/kg was used.[1]

Praziquantel is also effective against the larval form of *Taenia solium* and is used to treat neurocysticercosis (see p. 164.2).

1. Cruz M, *et al*. Operational studies on the control of Taenia solium taeniasis/cysticercosis in Ecuador. *Bull WHO* 1989; **67:** 401–7.

Adverse Effects

Adverse effects with praziquantel may be common but are usually mild and transient. Headache, diarrhoea, dizziness, drowsiness, malaise, abdominal discomfort, nausea, and vomiting have been reported most frequently. Hypersensitivity reactions such as fever, urticaria, pruritic rashes, and eosinophilia can occur; they may be due to death of the infecting parasites. Raised liver enzyme values have been reported rarely.

Most patients with neurocysticercosis who are given praziquantel suffer CNS effects, including headache, hyperthermia, seizures, and intracranial hypertension, which are thought to result from an inflammatory response to dead and dying parasites in the CNS. Use with corticosteroids is advised in such patients.

Effects on the gastrointestinal tract. Colicky abdominal pain and bloody diarrhoea occurred in a small community in Zaire shortly after treatment for *Schistosoma mansoni* infection with single oral doses of praziquantel 40 mg/kg.[1] A similar syndrome has been reported in some patients with *Schistosoma japonicum* infection given praziquantel.[2] The abdominal pain occurring in these patients was very different from the mild abdominal discomfort much more commonly reported with praziquantel therapy.

1. Polderman AM, *et al*. Side effects of praziquantel in the treatment of Schistosoma mansoni in Maniema, Zaire. *Trans R Soc Trop Med Hyg* 1984; **78:** 752–4.
2. Watt G, *et al*. Bloody diarrhoea after praziquantel therapy. *Trans R Soc Trop Med Hyg* 1986; **80:** 345–6.

Effects on the nervous system. Adverse nervous system effects are common in patients with neurocysticercosis given praziquantel. Neurological symptoms have also been reported[1] with the much lower doses of praziquantel used in the treatment of taeniasis in a patient with undiagnosed neurocysticercosis.

1. Flisser A, *et al*. Neurological symptoms in occult neurocysticercosis after single taenicidal dose of praziquantel. *Lancet* 1993; **342:** 748.

Hypersensitivity. A 35-year-old man developed sudden onset of pruritic urticaria over his entire body with dyspnoea, chest tightness, palpitation, dizziness, and vomiting 30 minutes after taking an oral dose of praziquantel for clonorchiasis. The patient had taken a dose of praziquantel 8 years ago, with no adverse effects, and was on no other drugs at the time of this episode. His symptoms resolved after gastric lavage, oxygen, and treatment with adrenaline, corticosteroids, and an antihistamine.[1]

1. Shen C, *et al*. A case of anaphylactic reaction to praziquantel treatment. *Am J Trop Med Hyg* 2007; **76:** 603–5.

Precautions

Praziquantel should not be used in patients with ocular or spinal cysticercosis because of the risk of severe, irreversible eye damage or paralysis resulting from destruction of the parasite.

Patients should be warned that praziquantel may cause dizziness or drowsiness and if affected they should not drive or operate machinery during or for 24 hours after treatment.

Breast feeding. Praziquantel is distributed into breast milk at a concentration of about a quarter that of the maternal serum; US licensed product information advises that mothers should not breast feed during treatment or for 72 hours thereafter. For further information on WHO opinion on the use of praziquantel in breast feeding, see p. 166.2.

Pregnancy. In a review of 637 women given praziquantel in a mass distribution programme, 88 had had a single oral dose during pregnancy, including 37 in their first trimester. All pregnancies ended in full-term babies and there was no evidence of clinical abnormality. No difference was found in the rates of preterm delivery or abortion compared with a control group.[1] WHO opinion is that praziquantel may be considered the safest of all anthelmintic drugs and that the risks to pregnant women or unborn or nursing children from use of praziquantel are very small.[2] Praziquantel is the drug of choice in schistosomiasis and delaying treatment may in fact result in more serious outcomes. It therefore suggests that pregnant and lactating women may be given the drug and should be included in national de-worming programmes.[2]

1. Adam I, *et al*. Is praziquantel therapy safe during pregnancy? *Trans R Soc Trop Med Hyg* 2004; **98:** 540–3.
2. Anonymous. Use of praziquantel in pregnant and lactating women. *WHO Drug Inf* 2003; **17:** 29.

Interactions

Praziquantel is metabolised via various cytochrome P450 isoenzymes including CYP3A4 and therefore has the potential to interact with drugs that are inhibitors or inducers of such enzymes. Enzyme-inducing drugs such as carbamazepine, dexamethasone, phenobarbital, and phenytoin may decrease plasma concentrations of praziquantel. Conversely, enzyme inhibitors such as cimetidine, erythromycin, itraconazole, and ketoconazole may increase plasma concentrations of praziquantel.

Concomitant use of rifampicin and praziquantel should be avoided as rifampicin is a strong inducer of cytochrome P450 isoenzymes and may cause subtherapeutic concentrations of praziquantel. If treatment with praziquantel is essential, rifampicin should be stopped 4 weeks before starting praziquantel; treatment with rifampicin can be restarted one day after finishing praziquantel therapy.

Anthelmintics. For reference to an interaction between of *albendazole* and praziquantel, see p. 151.1.

Antibacterials. A study[1] in healthy subjects found that oral *rifampicin* decreased plasma concentrations after single and multiple doses of oral praziquantel to subtherapeutic levels.

1. Riddtitid W, *et al*. Rifampin markedly decreases plasma concentrations of praziquantel in healthy volunteers. *Clin Pharmacol Ther* 2002; **72:** 505–13.

Antiepileptics. *Carbamazepine* and *phenytoin* have been reported to reduce the bioavailability of praziquantel.[1]

1. Quinn DI, Day RO. Drug interactions of clinical importance: an updated guide. *Drug Safety* 1995; **12:** 393–452.

Antifungals. A crossover study in 10 healthy subjects[1] suggested that the CYP3A4 and PgP inhibitor *ketoconazole* almost doubled exposure to, and mean peak plasma concentration of, praziquantel when both drugs were given together. It was suggested that standard doses of praziquantel should be halved when both drugs were given.

1. Riddtitid W, *et al*. Pharmacokinetic interaction between ketoconazole and praziquantel in healthy volunteers. *J Clin Pharm Ther* 2007; **32:** 585–93.

Antimalarials. *Chloroquine* has been reported to reduce the bioavailability of praziquantel.[1]

1. Masimirembwa CM, *et al*. The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. *Biopharm Drug Dispos* 1994; **15:** 33–43.

Corticosteroids. Corticosteroids may be used to reduce the inflammatory reactions that often occur within 2 to 3 days of starting cysticidal therapy. However, use is complicated by the fact that dexamethasone roughly halves the plasma concentration of praziquantel. It has therefore been suggested that when praziquantel is given in the 2-week treatment regimen, corticosteroids should not be given prophylactically but only if an inflammatory reaction develops. Dexamethasone is then given daily for 2 or 3 days and most of the treatment period will be free of pharmacokinetic interaction. When the short course praziquantel regimen is used (3 doses given 2 hours apart), the corticosteroid may be given prophylactically. The first dose of dexamethasone is given 4 hours after the last dose of praziquantel (when the concentration of praziquantel is starting to decrease and the pharmacological action is assumed to have been accomplished) and then daily for 2 to 3 days. No pharmacokinetic interaction would be expected at this point.[1]

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; **34:** 503–15.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase praziquantel bioavailability.[1,2]

1. Metwally A, *et al*. Effect of cimetidine, bicarbonate and glucose on the bioavailability of different formulations of praziquantel. *Arzneimittelforschung* 1995; **45:** 516–18.
2. Jung H, *et al*. Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. *Antimicrob Agents Chemother* 1997; **41:** 1256–9.

Pharmacokinetics

Praziquantel is rapidly absorbed after oral doses; more than 80% of a dose is reported to be absorbed. Peak plasma concentrations occur 1 to 4 hours after a dose, but there is a pronounced first-pass effect and praziquantel undergoes rapid and extensive metabolism in the liver, mainly via the cytochrome P450 isoenzymes CYP2B1 and CYP3A4, being hydroxylated to metabolites that are thought to be inactive. It is distributed into the CSF. The plasma elimination half-life of praziquantel is about 1 to 1.5 hours and that of the metabolites about 4 hours.

It is excreted in the urine, mainly as metabolites, about 80% of the dose being eliminated within 4 days and more than 90% of this in the first 24 hours.

Praziquantel is distributed into breast milk.

References.

1. Leopold G, *et al*. Clinical pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes: an example of a complex study covering both tolerance and pharmacokinetics. *Eur J Clin Pharmacol* 1978; **14:** 281–91.
2. Bühring KU, *et al*. Metabolism of praziquantel in man. *Eur J Drug Metab Pharmacokinet* 1978; **3:** 179–90.
3. Patzschke K, *et al*. Serum concentrations and renal excretion in humans after oral administration of praziquantel—results of three determination methods. *Eur J Drug Metab Pharmacokinet* 1979; **3:** 149–56.
4. Mandour M El M, *et al*. Pharmacokinetics of praziquantel in healthy volunteers and patients with schistosomiasis. *Trans R Soc Trop Med Hyg* 1990; **84** 389–93.
5. Godawska-Matysik A, Kieć-Kononowicz K. Biotransformation of praziquantel by human cytochrome p450 3A4 (CYP 3A4). *Acta Pol Pharm* 2006; **63:** 381–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prazitral; ***Austral.***: Biltricide; ***Braz.***: Cestox; Cisticid; ***Canad.***: Biltricide; ***Chile***: Cesol; Cisticid; ***Fr.***: Biltricide; ***Ger.***: Biltricide; Cesol; Cysticide; ***Gr.***: Biltricide; ***Hong Kong***: Biltricide; ***India***: Cest; Cysticide; Distocide; ***Israel***: Biltricide†; ***Mex.***: Cesol; Cisticid; Tecprazin; Teniken; Zifartel†; ***Neth.***: Biltricide; ***Rus.***: Azinox (Азинокс); Biltricid (Бильтрицид); ***S.Afr.***: Biltricide†; Cysticide; ***Singapore***: Distocide; ***Thai.***: Mycotricide†; Opticide; Praquantel; Prasikon; Prazite; V Day Prazide; Wormicide; Zentozide; ***Ukr.***: Biltricid (Бильтрицид); ***USA***: Biltricide; ***Venez.***: Cestox.

Pharmacopoeial Preparations
USP 36: Praziquantel Tablets.

Pyrantel Embonate *(BANM, rINNM)*

CP-10423-16; Embonato de pirantel; Pamoato de pirantel; Pirantel, embonato de; Pirantel Pamoat; Pirantel Pamoate; Pirantelio embonatas; Pyranteeliembonaatti; Pyrantel, embonate de; Pyrantel Pamoate (USAN); Pyrantelembonat; Pyrantel-embonát; Pyranteli Embonas; Pyrantelu embonian; Пирантела Эмбонат.

1,4,5,6-Tetrahydro-1-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine 4,4′-methylenebis(3-hydroxy-2-naphthoate).

$C_{11}H_{14}N_2S,C_{23}H_{16}O_6$=594.7

CAS — 15686-83-6 (pyrantel); 22204-24-6 (pyrantel embonate); 33401-94-4 (pyrantel tartrate).

ATC — P02CC01.

UNII — 81BK194Z5M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Pyrantel Embonate). A pale yellow or yellow powder. Practically insoluble in water and in methyl alcohol; soluble in dimethyl sulfoxide. Protect from light.

USP 36: (Pyrantel Pamoate). A yellow to tan solid. Practically insoluble in water and in methyl alcohol; soluble

in dimethyl sulfoxide; slightly soluble in dimethylformamide. Protect from light.

Uses and Administration

Pyrantel embonate is an anthelmintic effective against intestinal nematodes including roundworms (*Ascaris lumbricoides*), threadworms or pinworms (*Enterobius vermicularis*), and *Trichostrongylus* spp., the tissue nematode *Trichinella spiralis*, and hookworms, although it is possibly less effective against *Necator americanus* hookworms than against *Ancylostoma duodenale*. Pyrantel embonate is one of the anthelmintics that may be used in the treatment of infections with these worms, as discussed under Choice of Anthelmintic, p. 143.1. It appears to act by paralysing susceptible worms which are then dislodged by peristaltic activity.

Pyrantel is given orally as the embonate, but doses are described in terms of the base. Pyrantel embonate 2.9 g is equivalent to about 1 g of pyrantel.

Single or mixed **infections due to susceptible worms** may be treated with the equivalent of pyrantel 10 mg/kg as a single oral dose. **Ascariasis** occurring alone may only require 5 mg/kg; a single dose of 2.5 mg/kg given three or four times a year has been used in mass treatment programmes. In **necatoriasis**, 10 mg/kg daily for 3 or 4 days or 20 mg/kg daily for 2 days may be necessary. The response in **enterobiasis** may be improved by repeating the 10 mg/kg dose after 2 to 4 weeks. In **trichinosis**, a dose of 10 mg/kg daily for 5 days has been used.

Pyrantel tartrate has been used as a veterinary anthelmintic.

Administration in children. Doses of pyrantel embonate for the treatment of susceptible single or mixed worm infections in children are the same by weight as those for adults, see Uses and Administration, above.

Adverse Effects and Precautions

The adverse effects of pyrantel embonate are generally mild and transient. The most frequent are gastrointestinal effects such as nausea and vomiting, anorexia, abdominal pain, and diarrhoea. Other adverse effects reported include headache, dizziness, drowsiness, insomnia, rashes, and raised liver enzyme values.

Pyrantel embonate should be used with caution in patients with hepatic impairment.

Interactions

The anthelmintic effects of both pyrantel and piperazine may be antagonised when the two drugs are used together.

Pharmacokinetics

Due to its low water solubility only a small proportion of a dose of pyrantel embonate is absorbed from the gastrointestinal tract, thereby ensuring high concentrations of the drug in the intestinal lumen. The absorbed portion of the drug is partially metabolised by the liver. Up to about 7% is excreted as unchanged drug and metabolites in the urine but over half of the dose is excreted unchanged in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Anthel; Combantrin; Early Bird†; ***Austria***: Combantrin; ***Braz.***: Ascarical; ***Canad.***: Combantrin; Jaa Pyral; ***Chile***: Combantrin†; ***Fr.***: Combantrin; Helmintox; ***Ger.***: Helmex; ***Gr.***: Combantrin; ***Hong Kong***: Combantrin†; Pyrantin†; ***India***: Expent; Nemocid; Pa-Pa; ***Indon.***: Combantrin†; Konvermex†; Medicomtrin†; Piraska†; Proworm†; Upixon; ***Ital.***: Combantrin; ***Mex.***: Combantrin; Pirantrim; ***NZ***: Combantrin; ***Phil.ipp.***: Combantrin; Gelminthic; ***Port.***: Combantrin; ***Rus.***: Helmintox (Гельминтокс); Nemocid (Немоцид); ***S.Afr.***: Combantrin†; ***Singapore***: Bearantel; ***Spain***: Lombriareu†; Trilombrin; ***Switz.***: Cobantril; ***Thai.***: Bantel; Pyrapam; Pyteldon; ***Turk.***: Kontil; Pirantrin; ***Ukr.***: Helmintox (Гельминтокс); ***USA***: Pin-Rid; Pin-X; Reese's Pinworm; ***Venez.***: Combantrin; Tamoa.

Multi-ingredient Preparations. ***India***: Mebex Plus; ***Indon.***: Quantrel†; ***Phil.ipp.***: Quantrel; ***Venez.***: Dualid; Quantrel.

Pharmacopoeial Preparations

USP 36: Ivermectin and Pyrantel Pamoate Tablets; Pyrantel Pamoate Oral Suspension.

Pyrvinium Embonate *(rINNM)*

Embonato de pirvinio; Pirvinio, embonato de; Pirvinyum Pamoat; Pyrvinii Embonas; Pyrvinium, Embonate de; Pyrvinium Pamoate (BAN); Pyrvinium Pamoate; Viprynium Embonate; Viprynium Pamoate; Пирвиния Эмбонат.

Bis{6-dimethylamino-2-[2-(2,5-dimethyl-1-phenylpyrrol-3-yl)vinyl]-1-methylquinolinium} 4,4′-methylenebis(3-hydroxy-2-naphthoate).

$C_{52}H_{56}N_6C_{23}H_{14}O_6$=1151.4

CAS — 3546-41-6.

ATC — P02CX01.

UNII — 310X6S84LW.

Pharmacopoeias. In *US.*

USP 36: (Pyrvinium Pamoate). A bright orange or orange-red to practically black crystalline powder. Practically insoluble in water and in ether; slightly soluble in chloroform and in methoxyethanol; freely soluble in glacial acetic acid; very slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Pyrvinium embonate is an effective anthelmintic in the treatment of enterobiasis (p. 145.3), but has generally been superseded by other drugs.

Pyrvinium is given as the embonate but doses are described in terms of the base. Pyrvinium embonate 7.5 mg is equivalent to about 5 mg of pyrvinium.

It has been given orally in a single dose equivalent to pyrvinium 5 mg/kg, repeated after 2 to 3 weeks.

Adverse Effects

Pyrvinium occasionally causes nausea, vomiting, abdominal pain, and diarrhoea. Hypersensitivity reactions and photosensitivity have been reported. Headache may occur.

Pyrvinium stains the stools bright red and may stain clothing if vomiting occurs.

Pharmacokinetics

Pyrvinium embonate is not significantly absorbed from the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tru; ***Braz.***: Pyr-Pam; Pyverm; ***Denm.***: Vanquin; ***Fin.***: Pyrvin; ***Fr.***: Povanyl; ***Ger.***: Molevac; Pyrcon; ***Norw.***: Vanquin; ***Swed.***: Vanquin; ***Turk.***: Pirok.

Pharmacopoeial Preparations

USP 36: Pyrvinium Pamoate Oral Suspension; Pyrvinium Pamoate Tablets.

Rafoxanide *(BAN, USAN, rINN)*

MK-990; Rafoxanid; Rafoxanida; Rafoxanidum; Рафоксанид.

3′-Chloro-4′-(4-chlorophenoxy)-3,5-di-iodosalicylanilide.

$C_{19}H_{11}Cl_2I_2NO_3$=626.0

CAS — 22662-39-1.

ATC Vet — QP52AG05.

UNII — 22F4FLA7DH.

Profile

Rafoxanide is an anthelmintic used in veterinary medicine for the treatment of fascioliasis in cattle and sheep.

Santonin

Santoniini; Santonina; Santoninum; Сантонин.

(3*S*,3a*S*,5a*S*,9b*S*)-3a,5,5a,9b-Tetrahydro-3,5a,9-trimethylnaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione.

$C_{15}H_{18}O_3$=246.3

CAS — 481-06-1.

UNII — 1VL8J38ERO.

Pharmacopoeias. In *Jpn.*

Profile

Santonin is a crystalline lactone obtained from the dried unexpanded flowerheads of *Artemisia cina* (santonica, wormwood) and other species of *Artemisia* (Compositae). It was formerly used as an anthelmintic in the treatment of roundworm (*Ascaris*) infection, but has been superseded by other less toxic anthelmintics.

It is used as a flavour in food.

Selamectin *(BAN, USAN, rINN)*

Selamectina; Sélamectine; Selamectinum; Selamektiini; Selamektin; UK-124114; Селамектин.

(2a*E*,4*E*,5′*S*,6*S*,6′*S*,7*S*,8*E*,11*R*,13*R*,15*S*,17a*R*,20a*R*,20b*S*)-6′-Cyclohexyl-7-[(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-3′,4′,5′,6,6′,7,10,11,14,15,20a,20b-dodecahydro-20b-hydroxy-5′,6,8,19-tetramethylspiro(11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*p*,*q*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran)-17,20(17a*H*)-dione 20-oxime.

$C_{43}H_{63}NO_{11}$=770.0

CAS — 165108-07-6.

ATC Vet — QP54AA05.

UNII — A2669OWX9N.

NOTE. The name Stronghold has been used as a trade mark for selamectin.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Selamectin for Veterinary Use). A semisynthetic product derived from a fermentation product. A white or almost white, hygroscopic powder. Practically insoluble in water; soluble in acetone and in dichloromethane; freely soluble in isopropyl alcohol; sparingly soluble in methyl alcohol. Store in airtight containers.

Profile

Selamectin is an avermectin anthelmintic used in veterinary medicine as an ectoparasiticide and for the prophylaxis of gastrointestinal roundworms and heartworms.

Tetramisole Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tetramisol; ICI-50627; McN-JR-8299-11; R-8299; Tetramisol, hidrocloruro de; Tétramisole, Chlorhydrate de; Tetramisoli Hydrochloridum; Тетрамизола Гидрохлорид.

(±)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride.

$C_{11}H_{12}N_2S$,HCl=240.7

CAS — 5036-02-2 (tetramisole); 5086-74-8 (tetramisole hydrochloride).

UNII — 0NDK265MCV.

Pharmacopoeias. In *Fr.* for veterinary use only.

Profile

Tetramisole hydrochloride is an anthelmintic used in veterinary medicine for the control of nematode infections. It is a racemic mixture and the laevo-isomer, levamisole hydrochloride (p. 157.2), accounts for most of its activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Jetomisol-P.

Thiacetarsamide *(rINNM)*

Arsenamide; Thiacétarsamide; Thiacetarsamidum; Thioarsenite; Tiacetarsamida; Тиацетарсамид.

p-[Bis(carboxymethylmercapto)arsino]benzamide; 4-Carbamylphenyl bis[carboxymethylthio]arsenite.

$C_{11}H_{12}AsNO_3S_2$=377.3

CAS — 531-72-6.

ATC Vet — QP52AX08.

UNII — VMF4ELY9TZ.

Profile

Thiacetarsamide is an arsenical derivative used in veterinary medicine for canine heartworm.

Thiophanate *(BAN)*

Tiofanato; Тиофанат.

4,4′-*o*-Phenylenebis(ethyl 3-thioallophanate).

$C_{14}H_{18}N_4O_4S_2$=370.4

CAS — 23564-06-9.

ATC Vet — QP52AC04.

UNII — 5Q0Y96D5I8.

Profile

Thiophanate is a prodrug that is converted to the benzimidazole anthelmintic lobendazole. It has been used in veterinary medicine for the control of nematode infections.

Tiabendazole *(BAN, rINN)*

E233; MK-360; Thiabendazole (USAN); Thiabendazool; Tiabendatsoli; Tiabendazol; Tiabendazolas; Tiabendazolum; Тиабендазол.

2-(Thiazol-4-yl)-1*H*-benzimidazole.

$C_{10}H_7N_3S$=201.2

CAS — 148-79-8.
ATC — D01AC06; P02CA02.
ATC Vet — QD01AC06; QP52AC10.
UNII — N1Q45E87DT.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Tiabendazole). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; it dissolves in dilute mineral acids. Protect from light.

USP 36: (Thiabendazole). A white to practically white, odourless or practically odourless, powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; very slightly soluble in chloroform and in ether.

Uses and Administration

Tiabendazole, a benzimidazole derivative, is an anthelmintic with activity against most nematode worms; activity against some larval stages and ova has also been shown. It is no longer marketed in many countries due to its toxicity and the availability of safer and more effective alternative drugs. The mode of action is not certain, but tiabendazole may inhibit the fumarate-reductase system of worms thereby interfering with their source of energy. Tiabendazole also has antifungal activity and is used commercially as a fungicide.

Tiabendazole has been used in the treatment of cutaneous larva migrans, dracunculiasis (guinea worm infection), strongyloidiasis, trichinosis, and toxocariasis. Tiabendazole is also active against some intestinal nematodes, but should not be used as primary therapy; the treatment of mixed infections including ascariasis is not recommended since tiabendazole may cause the worms to migrate to other body organs causing serious complications. For discussions of the treatment of the above infections see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Tiabendazole is given orally, after meals, usually in a dose of 25 mg/kg twice daily for 2 or more days, the duration depending on the type of infection; the daily dose should not exceed 3 g. For those unable to tolerate 2 doses daily, 25 mg/kg may be given after the largest meal on day 1 and repeated 24 hours later after a similar meal on day 2. For mass treatment, a single dose of 50 mg/kg after the evening meal is suggested although the incidence of adverse effects may be higher than with 2 doses of 25 mg/kg.

In **cutaneous larva migrans**, 25 mg/kg may be given twice daily for 2 days, repeated after 2 days if necessary; topical treatment with a 10 to 15% suspension intended for oral use has also been advocated as an alternative or adjunct to oral treatment.

In **dracunculiasis**, 25 to 50 mg/kg may be given twice daily for one day; in massive infection a further 50 mg/kg may be given after 5 to 8 days.

In **strongyloidiasis**, 25 mg/kg may be given twice daily for 2 or 3 days or 50 mg/kg as a single dose; when the infection is disseminated treatment for at least 5 days may be necessary.

In **trichinosis**, 25 mg/kg may be given twice daily for 2 to 4 successive days.

In **toxocariasis**, 25 mg/kg may be given twice daily for 5 to 7 days.

Tiabendazole also has some antifungal activity. It is used as a fungicidal preservative for certain foods.

Dracunculiasis. Tiabendazole[1,2] has been used for symptomatic treatment of dracunculiasis (p. 145.1), although it has no direct anthelmintic effect. It is used to facilitate removal of the worm from subcutaneous tissues.

1. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57:** 683–9.
2. Kale OO, *et al.* Controlled comparative trial of thiabendazole and metronidazole in the treatment of dracontiasis. *Ann Trop Med Parasitol* 1983; **77:** 151–7.

Strongyloidiasis. Tiabendazole has been used in the treatment of strongyloidiasis (p. 148.2), but albendazole or ivermectin are generally preferred.

References.

1. Grove DI. Treatment of strongyloidiasis with thiabendazole: an analysis of toxicity and effectiveness. *Trans R Soc Trop Med Hyg* 1982; **76:** 114–18.
2. Barnish G, Barker J. An intervention study using thiabendazole suspension against strongyloides fuelleborni-like infections in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1987; **81:** 60–3.
3. Boken DJ, *et al.* Treatment of Strongyloides stercoralis hyperinfection syndrome with thiabendazole administered per rectum. *Clin Infect Dis* 1993; **16:** 123–6.
4. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; **169:** 1076–9.
5. Pitisuttithum P, *et al.* A randomized comparative study of albendazole and thiabendazole in chronic strongyloidiasis. *Southeast Asian J Trop Med Public Health* 1995; **26:** 735–8.
6. Schaffel R, *et al.* Thiabendazole for the treatment of strongyloidiasis in patients with hematologic malignancies. *Clin Infect Dis* 2000; **31:** 821–2.

Syngamosis. Tiabendazole has been used successfully[1,2] to treat syngamosis (p. 148.2) when it has occurred in man.

1. Grell GAC, *et al.* Syngamus in a West Indian. *BMJ* 1978; **2:** 1464.
2. Leers W-D, *et al.* Syngamosis, an unusual case of asthma: the first reported case in Canada. *Can Med Assoc J* 1985; **132:** 269–70.

Adverse Effects

Dizziness and gastrointestinal disturbances, especially anorexia, nausea and vomiting, diarrhoea, and abdominal pain are common during treatment with tiabendazole. Other adverse effects occurring occasionally include pruritus, rashes, headache, fatigue, drowsiness, drying of mucous membranes, hyperglycaemia, disturbance of vision including colour vision, leucopenia, tinnitus, effects on the liver including cholestasis and parenchymal damage (in some cases severe and irreversible), enuresis, crystalluria, and bradycardia and hypotension. There have also been reports of erythema multiforme, fatal Stevens-Johnson syndrome, toxic epidermal necrolysis, convulsions, and effects on mental state.

Fever, chills, angioedema, and lymphadenopathy have been reported, but may represent allergic response to dead parasites rather than to tiabendazole.

The urine of some patients taking tiabendazole may have a characteristic odour similar to that after eating asparagus; it is attributed to the presence of a tiabendazole metabolite.

Effects on the salivary glands. Dry mouth with swollen parotid and salivary glands suggestive of the sicca complex preceded the development of cholestatic jaundice in a 17-year-old boy given tiabendazole.[1]

1. Davidson RN, *et al.* Intrahepatic cholestasis after thiabendazole. *Trans R Soc Trop Med Hyg* 1988; **82:** 620.

Hypersensitivity. Severe erythema multiforme developed in a patient 16 days after a course of tiabendazole.[1] Many of the lesions encircled pre-existing melanocytic naevi.

1. Humphreys F, Cox NH. Thiabendazole-induced erythema multiforme with lesions around melanocytic naevi. *Br J Dermatol* 1988; **118:** 855–6.

Precautions

Tiabendazole should be used with caution in patients with hepatic or renal impairment. Tiabendazole causes drowsiness in some patients and those affected should not drive or operate machinery.

Tiabendazole should not be used in mixed worm infections involving *Ascaris lumbricoides* as it can cause the latter to migrate; live worms have emerged through the mouth or nose.

Pregnancy. Tiabendazole is teratogenic in *mice* although there are no adequate and well controlled studies in human pregnancy.

Renal impairment. Tiabendazole and its 5-hydroxy metabolite did not accumulate in an anephric patient on haemodialysis and haemoperfusion who was treated for severe strongyloidiasis.[1] However, the potentially toxic conjugated glucuronide and sulfate metabolites did accumulate. The clearance of all 3 metabolites was poor by haemodialysis; haemoperfusion was much more efficient, although for rapid removal the haemoperfusion columns should be changed every hour.

1. Bauer L, *et al.* The pharmacokinetics of thiabendazole and its metabolites in an anephric patient undergoing hemodialysis and hemoperfusion. *J Clin Pharmacol* 1982; **22:** 276–80.

Interactions

Xanthines. For the effect of tiabendazole on serum concentrations of *theophylline*, see p. 1236.3.

Pharmacokinetics

Tiabendazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1 to 2 hours. It is metabolised to 5-hydroxythiabendazole and excreted mainly in the urine as glucuronide or sulfate conjugates; about 90% is recovered in the urine within 48 hours of ingestion, but only 5% in the faeces. Absorption may occur from preparations applied to the skin or eyes.

References.

1. Tocco DJ, *et al.* Absorption, metabolism, and excretion of thiabendazole in man and laboratory animals. *Toxicol Appl Pharmacol* 1966; **9:** 31–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Foldan; ***Austral.***: Mintezol†; ***Braz.***: Benstatin; Foldan; Micosbel; Thiaben; Thiabose†; Thianax; Tiabiose; Tiadol; Tiaplex; ***Chile***: Soldrin; ***Gr.***: Mintezol; ***Mex.***: Eprofil†; ***USA***: Mintezol†.

Multi-ingredient Preparations. ***Braz.***: Derms; Folderm Pomada†; Forverm†; Helmiben; Micoplex; Neovermin; Profium†; Thiabena.

Pharmacopoeial Preparations
BP 2014: Tiabendazole Tablets;
USP 36: Thiabendazole Oral Suspension; Thiabendazole Tablets.

Triclabendazole *(BAN, rINN)*

Triclabendazol; Triclabendazolum; Triklabendazol; Триклабендазол.

5-Chloro-6-(2,3-dichlorophenoxy)-2-(methylthio)benzimidazole.

$C_{14}H_9Cl_3N_2OS$=359.6

CAS — 68786-66-3.
ATC — P02BX04.
ATC Vet — QP52AC01.
UNII — 4784C8E03O.

Profile

Triclabendazole is a benzimidazole anthelmintic used for the treatment of the fluke infections, fascioliasis (p. 169.1) and paragonimiasis (p. 169.1). Adverse effects of triclabendazole are usually mild and often include abdominal and epigastric pain, headache, and sweating. Other adverse effects are nausea, vomiting, dizziness, cough, fever, urticaria, and pruritus; rash and leucopenia are uncommon.

For the treatment of **fascioliasis** adults and children may be given a single oral dose of 10 mg/kg after food; if there has been previous treatment failure this may be followed by a second dose of 10 mg/kg after 12 to 24 hours. Children less than 4 years of age and pregnant or lactating women should be excluded from large-scale interventions, but may be given treatment in a clinical setting where they can be monitored. For the treatment of **paragonimiasis** WHO recommends that adults and children over 4 years of age be given a total daily oral dose of 20 mg/kg after food, in two divided doses.

Liver fluke infections. Although praziquantel is used to treat most food-borne trematode infections, it has little or no efficacy in fascioliasis (p. 146.2) and triclabendazole is considered to be the drug of choice.[1,2] Several studies[3-8] have shown the efficacy of triclabendazole in fascioliasis.

1. Keiser J, *et al.* Triclabendazole for the treatment of fascioliasis and paragonimiasis. *Expert Opin Invest Drugs* 2005; **14:** 1513–26.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Apt W, *et al.* Treatment of human chronic fascioliasis with triclabendazole: drug efficacy and serologic response. *Am J Trop Med Hyg* 1995; **52:** 532–5.
4. El-Karaksy H, *et al.* Human fascioliasis in Egyptian children: successful treatment with triclabendazole. *J Trop Pediatr* 1999; **45:** 135–8.
5. Millán JC, *et al.* The efficacy and tolerability of triclabendazole in Cuban patients with latent and chronic Fasciola hepatica infection. *Am J Trop Med Hyg* 2000; **63:** 264–9.
6. Graham CS, *et al.* Imported Fasciola hepatica infection in the United States and treatment with triclabendazole. *Clin Infect Dis* 2001; **33:** 1–5.
7. Talaie H, *et al.* Randomized trial of a single, double and triple dose of 10 mg/kg of a human formulation of triclabendazole in patients with fascioliasis. *Clin Exp Pharmacol Physiol* 2004; **31:** 777–82.
8. Marcos LA, *et al.* Natural history, clinicoradiologic correlates, and response to triclabendazole in acute massive fascioliasis. *Am J Trop Med Hyg* 2008; **78:** 222–7.

Lung fluke infections. Although praziquantel is usually given as the drug of choice in the treatment of paragonimiasis (p. 146.3), triclabendazole is recommended as an alternative.[1] Encouraging results were reported from a pilot study of triclabendazole.[2] In an open comparative study[3] in 62 patients, a more rapid parasitological response was obtained with triclabendazole in oral doses of 5 mg/kg once daily for 3 days, 10 mg/kg twice on one day, or 10 mg/kg as a single dose, than with praziquantel. Clinical symptoms resolved at a comparable rate in all groups. A later study compared the two one-day regimens in 154 patients.[4] After 3 months, the cure rates (assessed by clearance of eggs from sputum) were 84.4% in those given a single dose of 10 mg/kg, and 90.9% in those given two such doses on the same day. In those who were still infected at 3 months, a second two-dose course resulted in complete parasitological clearance at 1 year.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Ripert C, *et al.* Therapeutic effect of triclabendazole in patients with paragonimiasis in Cameroon: a pilot study. *Trans R Soc Trop Med Hyg* 1992; **86:** 417.
3. Calvopiña M, *et al.* Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg* 1998; **92:** 566–9.
4. Calvopiña M, *et al.* Comparison of two single-day regimens of triclabendazole for the treatment of human pulmonary paragonimiasis. *Trans R Soc Trop Med Hyg* 2003; **97:** 451–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Egaten; ***Gr.***: Egaten.

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This chapter includes antimicrobial drugs whose main use is the treatment and prophylaxis of bacterial infections. In practice the term 'antibiotics' is often, and in some instances erroneously, used to encompass all of these drugs. In *Martindale* the term antibacterial is preferred for the drugs in this chapter. The groups into which these drugs may be categorised are described p. 170.1. Antibacterials described elsewhere in *Martindale* include metronidazole (p. 938.1), nitazoxanide (p. 944.2), and tinidazole (p. 951.3), which, as well as being antiprotozoals, are used in the treatment of anaerobic bacterial infections.

Immunological approaches to the treatment and prophylaxis of bacterial infections are discussed under Vaccines Immunoglobulins and Antisera, p. 2373.1.

In addition, disinfectants and preservatives (p. 1731.1) are used to kill or inhibit the growth of micro-organisms.

Drug Groups

Although antibacterials are very diverse compounds they are often classified and discussed in groups. They may be classified according to their mode of action or spectrum of antimicrobial activity, but generally those with similar chemical structures are grouped together.

Aminoglycosides

The aminoglycosides are a closely related group of bactericidal antibacterials derived from bacteria of the order Actinomycetales or, more specifically, the genus *Streptomyces* (framycetin, kanamycin, neomycin, paromomycin, streptomycin, and tobramycin) and the genus *Micromonospora* (gentamicin and sisomicin). They are polycationic compounds that contain an aminocyclitol, usually 2-deoxystreptamine, or streptidine in streptomycin and related compounds, with cyclic amino-sugars attached by glycosidic linkages. Therefore, they have also been termed aminoglycosidic aminocyclitols. The sulfate salts are generally used.

The aminoglycosides have broadly similar toxicological features. Ototoxicity is a major limitation to their use; streptomycin and gentamicin are generally considered to be more toxic to the vestibular branch of the eighth cranial nerve and neomycin and kanamycin to be more toxic to the auditory branch. Other adverse effects common to the group include nephrotoxicity, neuromuscular blockade, and allergy, including cross-reactivity.

The pharmacokinetics of the aminoglycosides are very similar. Little is absorbed from the gastrointestinal tract but they are generally well distributed in the body after parenteral dosage although penetration into the CSF is poor. They are excreted unchanged in the urine by glomerular filtration.

The aminoglycosides have a similar antimicrobial spectrum and appear to act by interfering with bacterial protein synthesis, possibly by binding irreversibly to the 30S and to some extent the 50S portions of the bacterial ribosome. The manner in which they bring about cell death is not fully understood. They are most active against Gram-negative rods. *Staphylococcus aureus* is susceptible to the aminoglycosides but otherwise most Gram-positive bacteria, and also anaerobic bacteria, are naturally resistant. Aminoglycosides show enhanced activity with penicillins against some enterococci and streptococci. Bacterial resistance to streptomycin may occur by mutation, whereas with the other aminoglycosides it is usually associated with the plasmid-mediated production of inactivating enzymes which are capable of phosphorylation, acetylation, or adenylation. The aminoglycosides have a postantibiotic effect, that is antibacterial activity persisting after concentrations have dropped below minimum inhibitory concentrations.

Streptomycin was the first aminoglycoside to become available commercially and was isolated from a strain of *Streptomyces griseus* in 1944. Its use is now restricted mainly to the treatment of tuberculosis when it is always given with other antituberculous drugs because of the rapid development of resistance. *Dihydrostreptomycin,* a reduction product of streptomycin, is only rarely used because of its toxicity. The *neomycin* complex of antibacterials were the next to be isolated; neomycin itself is mainly a mixture of the B and C isomers; neomycin B is considered to be identical with *framycetin.* Because of their toxicity they are not given systemically. The related compound *paromomycin* (p. 945.3) also has antiprotozoal and anthelmintic properties and may be used in the treatment of intestinal amoebiasis, cestode infections, cryptosporidiosis, and leishmaniasis. *Kanamycin* is less toxic than neomycin and can be used systemically. Although it has been used in penicillin-resistant gonorrhoea, it is not active against *Pseudomonas aeruginosa* and has generally been replaced by gentamicin and other newer aminoglycosides.

Gentamicin was isolated from *Micromonospora purpurea* in 1963 and, being active against *Ps. aeruginosa* and *Serratia marcescens,* is widely used in the treatment of life-threatening infections. *Tobramycin* is one of several components of the nebramycin complex of aminoglycosides produced by *Streptomyces tenebrarius.* It has an antimicrobial spectrum very similar to that of gentamicin and is reported to be more active against *Ps. aeruginosa. Amikacin,* a

semisynthetic derivative of kanamycin, has a side-chain rendering it less susceptible to inactivating enzymes. It has a spectrum of activity like that of gentamicin but Gram-negative bacteria resistant to gentamicin, tobramycin, and kanamycin are often sensitive. *Sisomicin* is closely related structurally to gentamicin. *Netilmicin*, the *N*-ethyl derivative of sisomicin, may be active against some gentamicin-resistant strains of bacteria although not to the same extent as amikacin. Other aminoglycosides include *apramycin, arbekacin, astromicin, bekanamycin, dibekacin, etimicin, isepamicin*, and *micronomicin*.

Aminoglycosides should in general only be used for the treatment of serious infections because of their potential toxicity and antimicrobial spectrum. Doses must be carefully regulated to maintain plasma concentrations within the therapeutic range but avoid accumulation, especially in patients with renal impairment. Neomycin and framycetin, which are considered too toxic to be given parenterally, have been given orally to suppress the intestinal flora. The topical use of neomycin and gentamicin has been associated with allergic reactions and the emergence of resistant bacteria. Gentamicin or tobramycin are the drugs of choice in the treatment of life-threatening infections due to aminoglycoside-sensitive organisms and are often used with other antibacterials. With the continuing emergence of resistant strains, amikacin and netilmicin should be reserved for severe infections resistant to gentamicin and the other aminoglycosides.

Described in this chapter are

Amikacin, p. 216.1
Apramycin, p. 222.2
Arbekacin, p. 222.2
Astromicin, p. 222.3
Bekanamycin, p. 229.1
Dibekacin, p. 288.1
Dihydrostreptomycin, p. 288.3
Etimicin, p. 300.2
Framycetin, p. 303.2
Gentamicin, p. 306.2
Isepamicin, p. 313.1
Kanamycin, p. 316.3
Micronomicin, p. 326.2
Neomycin, p. 331.3
Netilmicin, p. 333.1
Sisomicin, p. 359.2
Streptomycin, p. 361.1
Tobramycin, p. 382.1

Antimycobacterials

The antimycobacterials are a miscellaneous group of antibacterials whose spectrum of activity includes *Mycobacterium* spp. and which are used in the treatment of tuberculosis, leprosy, and other mycobacterial infections. They include the rifamycins, also known as ansamycins or rifomycins, a group of antibacterials isolated from a strain of *Amycolatopsis mediterranei* (*Nocardia mediterranei*; *Streptomyces mediterranei*). The main antibacterial in this group, *rifampicin*, is a mainstay of regimens for the treatment of tuberculosis and leprosy, and is increasingly being used for other infections. The related drug *rifabutin* is also used in mycobacterial disease, especially nontuberculous mycobacterial infections due to *Mycobacterium avium* complex (MAC). Other rifamycins described in this chapter include *rifapentine, rifaximin* which is poorly absorbed and is mainly used for a local effect on the gastrointestinal tract, and *rifamycin sodium*, a rifamycin rarely used as it has been superseded by more effective drugs.

Another antimycobacterial widely used for tuberculosis is *isoniazid*, a derivative of isonicotinic acid; it is invariably used with other drugs to avoid or delay emergence of resistance. *Pyrazinamide*, a nicotinamide derivative, is also an important component of regimens for tuberculosis, while *ethambutol* and the aminoglycoside *streptomycin* are added when resistance to first-line drugs is likely. The thiosemicarbazone derivative *thioacetazone* is now less widely used in tuberculosis because of its toxicity and because more effective drugs are available, but is sometimes used in developing countries. Other drugs that have been used to treat tuberculosis including *aminosalicylic acid* and its salts, *bedaquiline fumarate, capreomycin, cycloserine, ethionamide, protionamide*, and *kanamycin* are regarded as secondary drugs and are reserved for patients in whom resistance or toxicity to first-line drugs is a problem. Delamanid is an imidazole derivative under investigation for multidrug-resistant tuberculosis.

The sulfones have been used since the 1940s in the treatment of leprosy, but the only one widely used now is *dapsone*, an important component of multidrug regimens. Its action is thought to involve inhibition of folate metabolism, similarly to the sulfonamides, and dapsone is also used for the prophylaxis of malaria and for prophylaxis and treatment of pneumocystis pneumonia. Also important in the treatment of leprosy is the phenazine dye *clofazimine*. Additionally, it has a role in the treatment of type 2 lepra reactions and has been used in other mycobacterial infections. The thioamides *ethionamide* and *protionamide* have been used in the treatment of leprosy and tuberculosis, but have generally been replaced by less toxic drugs, for example *clarithromycin, ofloxacin, minocycline*, or *pefloxacin*, in alternative antileprotic regimens.

Described in this chapter are

Aminosalicylic Acid, p. 217.2
Bedaquiline, p. 228.3
Capreomycin, p. 233.2
Clofazimine, p. 275.3
Cycloserine, p. 282.2
Dapsone, p. 283.2
Delamanid, p. 287.2
Ethambutol, p. 298.1
Ethionamide, p. 299.3
Ftivazide, p. 303.3
Isoniazid, p. 313.2
Morinamide, p. 328.3
Protionamide, p. 347.1
Pyrazinamide, p. 347.2
Rifabutin, p. 350.3
Rifampicin, p. 352.3
Rifamycin, p. 356.3
Rifapentine, p. 357.1
Rifaximin, p. 357.2
Thioacetazone, p. 379.2

Cephalosporins and related beta lactams

The cephalosporins or cephem antibacterials are semisynthetic antibacterials derived from cephalosporin C, a natural antibacterial produced by the mould *Cephalosporium acremonium*. The active nucleus, 7-aminocephalosporanic acid, is very closely related to the penicillin nucleus, 6-aminopenicillanic acid, and consists of a beta-lactam ring fused with a 6-membered dihydrothiazine ring and having an acetoxymethyl group at position 3. Cephalosporin C has a side-chain at position 7 derived from D-α-aminoadipic acid. Chemical modification of positions 3 and 7 has resulted in a series of drugs with different characteristics. Substitution at the 7-amino group tends to affect antibacterial action whereas at position 3 it may have more of an effect on pharmacokinetic properties.

The cephalosporins are bactericidal and, like the penicillins, they act by inhibiting synthesis of the bacterial cell wall. The most widely used system of classification of cephalosporins is by generations and is based on the general features of their antibacterial activity, but may depend to some extent on when they were introduced. Succeeding generations generally have increasing activity against Gram-negative bacteria. *Cefalotin* was one of the first cephalosporins to become available and is representative of the **first-generation** cephalosporins. It has good activity against a wide spectrum of Gram-positive bacteria including penicillinase-producing, but not meticillin-resistant, staphylococci; enterococci are, however, resistant. Its activity against Gram-negative bacteria is modest. Cefalotin is not absorbed from the gastrointestinal tract and must be given parenterally although intramuscular dosage is painful. Cefalotin has generally been replaced by *cefazolin* or *cefradine*. *Cefaloridine* is now rarely used because of its nephrotoxicity. Cefradine is absorbed from the gastrointestinal tract and can be given both orally and by injection. *Cefadroxil, cefatrizine*, and *cefalexin* are all given orally. All of these drugs have a very similar spectrum of antimicrobial activity to cefalotin. *Cefaclor* is also given orally. It has similar activity to cefalotin against Gram-positive cocci, but because of its greater activity against Gram-negative bacteria, particularly *Haemophilus influenzae*, it is often classified as a second-generation drug. *Cefprozil* is an oral cephalosporin with a longer half-life than cefaclor.

Cefamandole was the first available **second-generation** cephalosporin. It has similar or slightly less activity than cefalotin against Gram-positive bacteria, but greater stability to hydrolysis by beta lactamases produced by Gram-negative bacteria and enhanced activity against many of the Enterobacteriaceae and *Haemophilus influenzae*. It is given parenterally. *Cefuroxime* has a similar spectrum of activity to cefamandole although it is even more resistant to hydrolysis by beta lactamases. It is given parenterally but, *cefuroxime axetil*, the acetoxyethyl ester of cefuroxime, is given orally. Other drugs classified as second-generation cephalosporins and given parenterally include *cefonicid, ceforanide*, and *cefotiam*; these all have spectra of activity similar to cefamandole. Cephamycins (see below) are also classified with second-generation cephalosporins.

The **third-generation** cephalosporins, sometimes referred to as **extended-spectrum** cephalosporins, are even more stable to hydrolysis by beta lactamases than cefamandole and cefuroxime. Compared with the earlier generations of cephalosporins they have a wider spectrum and greater potency of activity against Gram-negative organisms, including most clinically important Enterobacteriaceae. Their activity against Gram-positive organisms is said to be less than that of the first-generation drugs, but they are very active against streptococci. *Cefotaxime* was the first of this group to become available and it has relatively modest activity against *Pseudomonas aeruginosa*. *Cefmenoxime, cefodizime, ceftizoxime*, and *ceftriaxone* are all very similar to cefotaxime in their antimicrobial activity. These drugs are all given parenterally and differ mainly in their pharmacokinetic characteristics. *Cefixime* is a third-generation cephalosporin given orally; others include *cefdinir, cefetamet pivoxil, cefpodoxime proxetil*, and *ceftibuten*. *Ceftazidime* is typical of a group of parenteral third-generation cephalosporins with enhanced activity against *Ps. aeruginosa*. *Cefoperazone* is similar in its activity to ceftazidime. *Cefpiramide* is structurally related to cefoperazone and has comparable activity. Although *cefsulodin* is classified as a third-generation cephalosporin its activity against Gram-negative bacteria is confined to *Ps. aeruginosa*. *Latamoxef* is an **oxacephalosporin** which differs from the true cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by an oxygen atom. It differs from cefotaxime mainly in its enhanced activity against *Bacteroides fragilis*.

The newer cephalosporins *cefepime* and *cefpirome* are generally considered to be **fourth-generation** because of their broad spectrum of activity. *Ceftobiprole* and *ceftaroline* are active against meticillin-resistant staphylococci, and are therefore sometimes termed **fifth-generation** cephalosporins.

The semisynthetic **cephamycins** are chemical modifications of cephamycin C, a beta-lactam antibacterial produced naturally by *Streptomyces* spp. They differ from the cephalosporins by the addition of a 7-α-methoxy group to the 7-aminocephalosporanic acid nucleus. Steric hindrance by this methoxy group is considered to be responsible for their greater stability to beta lactamases. For practical purposes they are generally classified with the second-generation cephalosporins, but are more active against anaerobic bacteria, especially *Bacteroides fragilis*. *Cefoxitin* was one of the first cephamycins available; *cefmetazole* and *cefotetan* have been introduced more recently. Another is *cefminox*. All these cephamycins must be given parenterally.

Imipenem was the first of the **carbapenem** group of antibacterials to become available; it is the *N*-formimidoyl derivative of thienamycin which is produced by *Streptomyces cattleya*. It is bactericidal, and, similarly to the cephalosporins, acts by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of antimicrobial activity including Gram-positive and Gram-negative aerobic and anaerobic organisms; it has good activity against both *Ps. aeruginosa* and *B. fragilis*. Imipenem is given parenterally with cilastatin, a dehydropeptidase I inhibitor that inhibits the renal metabolism of imipenem. Similarly, the carbapenem panipenem is given with the renal protectant betamipron. Two other carbapenems, *ertapenem* and *meropenem*, are relatively stable to renal dehydropeptidase and can be used without such an inhibitor. Ertapenem has a narrower spectrum of activity than other carbapenems, including no activity against *Ps. aeruginosa*. *Doripenem* is a carbapenem claimed to have particular activity against *Ps. aeruginosa*.

The **monobactams** were first identified as monocyclic beta lactams isolated from bacteria; they are now produced synthetically. *Aztreonam* was the first commercially available monobactam. It is bactericidal with a similar action on bacterial cell-wall synthesis to the cephalosporins. Its antimicrobial activity, however, differs from imipenem and the newer cephalosporins in that it is restricted to Gram-negative aerobic organisms. It has good activity against *Ps. aeruginosa*. Aztreonam is given parenterally. Other monobactams include *carumonam*.

Carbacephems are structurally related to the cephalosporins, but the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by a methylene group. *Loracarbef* is an oral carbacephem.

Described in this chapter are

Aztreonam, p. 226.1
Betamipron, p. 233.1
Biapenem, p. 233.1
Carumonam, p. 234.2
Cefaclor, p. 234.3
Cefadroxil, p. 235.2
Cefalexin, p. 236.1
Cefalonium, p. 236.3
Cefaloridine, p. 237.1
Cefalotin, p. 237.1
Cefamandole, p. 238.2
Cefapirin, p. 239.1
Cefatrizine, p. 239.2
Cefazolin, p. 239.2
Cefbuperazone, p. 240.2
Cefcapene, p. 240.3
Cefdinir, p. 240.3
Cefditoren, p. 241.1
Cefepime, p. 241.2
Cefetamet, p. 242.2
Cefixime, p. 242.3
Cefmenoxime, p. 243.2
Cefmetazole, p. 243.3
Cefminox, p. 244.1
Cefodizime, p. 244.2
Cefonicid, p. 244.3
Cefoperazone, p. 245.1
Ceforanide, p. 245.3
Cefoselis, p. 246.1
Cefotaxime, p. 246.1
Cefotetan, p. 247.3
Cefotiam, p. 248.1
Cefovecin, p. 248.2
Cefoxitin, p. 248.2
Cefozopran, p. 249.1
Cefpiramide, p. 249.2
Cefpirome, p. 249.2
Cefpodoxime, p. 250.1
Cefprozil, p. 250.2
Cefquinome, p. 251.1
Cefradine, p. 251.1
Cefsulodin, p. 251.3
Ceftaroline, p. 252.1
Ceftazidime, p. 252.2
Cefteram, p. 254.1
Ceftezole, p. 254.2
Ceftibuten, p. 254.2
Ceftiofur, p. 254.3
Ceftizoxime, p. 255.1
Ceftobiprole, p. 255.2
Ceftriaxone, p. 255.3
Cefuroxime, p. 257.2
Cilastatin, p. 262.3
Doripenem, p. 289.2
Ertapenem, p. 292.3
Faropenem, p. 300.2
Flomoxef, p. 301.1
Imipenem, p. 311.2
Latamoxef, p. 317.2
Loracarbef, p. 321.3
Meropenem, p. 323.3
Panipenem, p. 339.3

Chloramphenicols

Chloramphenicol is an antibacterial which was first isolated from cultures of *Streptomyces venezuelae* in 1947 but is now produced synthetically. It has a relatively simple structure and is a derivative of dichloroacetic acid with a nitrobenzene moiety. Chloramphenicol was the first broad-spectrum antibacterial to be discovered; it acts by interfering with bacterial protein synthesis and is mainly bacteriostatic. Its range of activity is similar to that of tetracycline and includes Gram-positive and Gram-negative bacteria, Rickettsia spp., and Chlamydiaceae. The sensitivities of *Salmonella typhi*, *Haemophilus influenzae*, and *Bacteroides*

fragilis to chloramphenicol have dictated the principal indications for its use.

Shortly after its introduction chloramphenicol was found to have a serious and sometimes fatal depressant effect on the bone marrow. The 'grey syndrome', another potentially fatal adverse effect, was reported later in neonates. As a result of this toxicity the systemic use of chloramphenicol has been restricted in many countries; it should only be given when there is no suitable alternative and never for minor infections.

Chloramphenicol is active when given orally and, unlike most other antibacterials, it diffuses into the CSF even when the meninges are not inflamed. The majority of a dose is inactivated in the liver, only a small proportion appearing unchanged in the urine.

Chloramphenicol is widely used for typhoid fever, although resistance is a problem in some countries. For *Haemophilus influenzae* infections, especially meningitis, the emergence of ampicillin-resistant strains led to a reappraisal of the use of chloramphenicol, and suggestions that ampicillin and chloramphenicol should both be given empirically to patients with meningitis until the sensitivity of the infecting organisms was known, but the newer third-generation cephalosporins are increasingly preferred because of resistance. For proven *H. influenzae* meningitis, chloramphenicol is used as an alternative to the third-generation cephalosporins, which are now regarded as treatment of choice. Chloramphenicol is also effective against many anaerobic bacteria and may be valuable in such conditions as cerebral abscess where anaerobes such as *Bacteroides fragilis* are often involved, although metronidazole may be preferred.

Chloramphenicol sodium succinate is used parenterally and the palmitate is given orally. Ophthalmic and other topical preparations of chloramphenicol are used widely in some countries.

Thiamphenicol is a semisynthetic derivative of chloramphenicol in which the nitro group on the benzene ring has been replaced by a methylsulfonyl group, resulting, in general, in a loss of activity *in vitro*. It has been claimed that thiamphenicol is less toxic than chloramphenicol and there have been fewer reports of aplastic anaemia but reversible bone-marrow depression may occur more frequently. It is also less likely to cause the 'grey syndrome'. Unlike chloramphenicol, thiamphenicol is not metabolised in the liver to any extent and is excreted largely unchanged in the urine. It has been used similarly to chloramphenicol in some countries.

Azidamfenicol is another analogue of chloramphenicol that has been used topically in the treatment of eye infections.

Described in this chapter are

- Azidamfenicol, p. 223.1
- Chloramphenicol, p. 259.1
- Florfenicol, p. 301.1
- Thiamphenicol, p. 378.3

Glycopeptides

Vancomycin has a glycopeptide structure; it acts by interfering with bacterial cell wall synthesis and is very active against Gram-positive cocci. Intravenous vancomycin is reserved for the treatment of severe staphylococcal infections and for the treatment and prophylaxis of endocarditis when other antibacterials cannot be used, either because of patient sensitivity or bacterial resistance. It is the treatment of choice for infections caused by meticillin-resistant staphylococci. Vancomycin hydrochloride is poorly absorbed when taken orally; it is used in the treatment of pseudomembranous colitis. *Teicoplanin* is a glycopeptide with similar properties to vancomycin, but a longer duration of action. It can be given intramuscularly as well as intravenously. *Telavancin* also has similar properties to vancomycin and is given intravenously for complicated skin and skin structure infections and nosocomial pneumonia (including ventilator associated pneumonia) known or suspected to be caused by MRSA. *Ramoplanin* is under investigation, especially for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for the prevention of infection due to vancomycin-resistant enterococci. Also under investigation are *dalbavancin* and *oritavancin*.

Described in this chapter are

- Avoparcin, p. 223.1
- Dalbavancin, p. 283.2
- Norvancomycin, p. 336.2
- Oritavancin, p. 338.1
- Ramoplanin, p. 350.1
- Teicoplanin, p. 371.3
- Telavancin, p. 373.1
- Vancomycin, p. 386.2

Lincosamides

Lincomycin is an antibacterial produced by a strain of *Streptomyces lincolnensis* and was first described in 1962; *clindamycin* is the 7-chloro-7-deoxy derivative of lincomycin.

Although not related structurally to erythromycin and the other macrolide antibacterials, the lincosamides have similar antimicrobial activity and act at the same site on the bacterial ribosome to suppress protein synthesis.

The lincosamides are bacteriostatic or bactericidal, depending on the concentration, and are active mainly against Gram-positive bacteria, and against *Bacteroides* spp. They also appear to have some antiprotozoal activity. Clindamycin and lincomycin have qualitatively similar activity but clindamycin is more active than lincomycin *in vitro*. Cross-resistance occurs between the lincosamides, macrolides, and streptogramins.

The lincosamides have been used, like erythromycin, as an alternative to penicillin, but reports of severe and sometimes fatal pseudomembranous colitis with lincomycin and clindamycin have led to the recommendation that they should only be used when there is no suitable alternative.

Both lincomycin and clindamycin can be given orally and parenterally, but clindamycin is much better absorbed from the gastrointestinal tract and less affected by the presence of food in the stomach. They both penetrate well into bone and have been used successfully in osteomyelitis. They have also been used topically in the treatment of acne vulgaris.

The main indication for the use of lincosamides is now in the treatment of severe anaerobic infections, although metronidazole (p. 938.2) or some beta lactams may be a more suitable choice in such infections. Clindamycin also has a role in the prophylaxis of endocarditis in penicillin-allergic patients and has been used, usually with other antiprotozoals, in babesiosis, chloroquine-resistant malaria, toxoplasmosis, and pneumocystis pneumonia.

Described in this chapter are

- Clindamycin, p. 271.3
- Lincomycin, p. 319.1
- Pirlimycin, p. 343.3

Macrolides

The macrolides are a large group of antibacterials mainly derived from *Streptomyces* spp. and having a common macrocyclic lactone ring to which one or more sugars are attached. They are all weak bases and only slightly soluble in water. Their properties are very similar and in general they have low toxicity and a similar spectrum of antimicrobial activity with cross-resistance between individual members of the group. The macrolides are bacteriostatic or bactericidal, depending on the concentration and the type of micro-organism, and are thought to interfere with bacterial protein synthesis. Their antimicrobial spectrum is similar to that of benzylpenicillin but they are also active against such organisms as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and some rickettsias, chlamydias, and chlamydophilas. Macrolides and related drugs have a postantibiotic effect: that is, antibacterial activity persists after concentrations have dropped below the minimum inhibitory concentration.

Erythromycin was discovered in 1952 and is the macrolide used most widely. It is destroyed by gastric acid and must therefore be given as enteric-coated formulations or as one of its more stable salts or esters such as the stearate or ethyl succinate. Hepatotoxicity has been reported after the use of erythromycin, most commonly as the estolate. Erythromycin lactobionate or gluceptate may be given intravenously. Cardiac arrhythmias have been reported occasionally after intravenous use. Erythromycin is used as an alternative to penicillin in many infections, especially in patients who are allergic to penicillin. It has similar uses to tetracycline in the treatment of infections due to *Mycoplasma pneumoniae* and *Chlamydia trachomatis*, and in acne vulgaris. It is also used in the treatment of infections caused by *Legionella pneumophila*.

More recently developed macrolides include *azithromycin*, *clarithromycin*, *dirithromycin*, and *roxithromycin*. These drugs all appear to have similar properties to erythromycin although they may differ in their pharmacokinetics. Clarithromycin and, to a lesser extent, azithromycin are more active than erythromycin against opportunistic mycobacteria such as *Mycobacterium avium* complex. Clarithromycin is also used in the treatment of leprosy and in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease. Both azithromycin and clarithromycin have activity against protozoa including *Toxoplasma gondii*.

Flurithromycin is another newer macrolide in use.

Other macrolides include *spiramycin*, which has been used extensively in Europe and has also been used in the treatment and prophylaxis of toxoplasmosis. It may be useful in the treatment of cryptosporidiosis.

Oleandomycin has been used orally and parenterally as the phosphate. Its ester, *troleandomycin*, is better absorbed from the gastrointestinal tract but, like erythromycin estolate, has proved hepatotoxic and more effective antibacterials are generally preferred. *Josamycin*, *kitasamycin*, *midecamycin*, and *rokitamycin* have been used in Europe and/or Japan. *Meleumycin* has been used in China.

Tilmicosin, *tulathromycin*, and *tylosin* are used in veterinary practice.

The **streptogramin** group of antibacterials are also derived from *Streptomyces* spp. and include *pristinamycin* and *virginiamycin*. They consist of two components that act synergistically and are therefore also known as synergistins. One of the components is structurally related to the macrolides, and they have a similar spectrum of antimicrobial activity to erythromycin. Semisynthetic derivatives such as *quinupristin/dalfopristin* may be useful in the treatment of infections with multidrug-resistant organisms including meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.

Cross-resistance often occurs between the macrolides, lincosamides, and streptogramins. The **ketolide** antibacterials *telithromycin* and *cethromycin* are semisynthetic derivatives of erythromycin A that have been developed to overcome macrolide resistance in respiratory-tract pathogens.

Described in this chapter are

- Azithromycin, p. 223.2
- Cethromycin, p. 259.1
- Clarithromycin, p. 268.2
- Dirithromycin, p. 289.1
- Erythromycin, p. 293.2
- Flurithromycin, p. 302.2
- Josamycin, p. 316.2
- Kitasamycin, p. 317.2
- Meleumycin, p. 323.2
- Midecamycin, p. 326.3
- Oleandomycin, p. 337.3
- Pristinamycin, p. 346.1
- Quinupristin/Dalfopristin, p. 349.1
- Rokitamycin, p. 358.1
- Roxithromycin, p. 358.2
- Spiramycin, p. 360.3
- Telithromycin, p. 373.3
- Tilmicosin, p. 382.1
- Troleandomycin, p. 385.2
- Tulathromycin, p. 385.2
- Tylosin, p. 385.3
- Virginiamycin, p. 389.3

Penicillins

Penicillin was the first antibacterial to be used therapeutically and was originally obtained, as a mixture of penicillins known as F, G, X, and K, from the mould *Penicillium notatum*. Better yields were achieved using *P. chrysogenum* and benzylpenicillin (penicillin G) was selectively produced by adding the precursor phenylacetic acid to the fermentation medium. The term 'penicillin' is now used generically for the entire group of natural and semisynthetic penicillins. Penicillins are still widely used; they are generally well tolerated, apart from hypersensitivity reactions, and are usually bactericidal by virtue of their inhibitory action on the synthesis of the bacterial cell wall.

Penicillins all have the same ring structure and are monobasic acids that readily form salts and esters; 6-aminopenicillanic acid, the penicillin nucleus, consists of a fused thiazolidine ring and a beta-lactam ring with an amino group at the 6-position.

The earlier or so-called 'natural' penicillins were produced by adding different side-chain precursors to fermentations of the *Penicillium* mould; *benzylpenicillin*, with a phenylacetamido side-chain at the 6-position, and *phenoxymethylpenicillin* (penicillin V), with a phenoxyacetamido side-chain, were 2 of the first and are still widely used. Benzylpenicillin can be considered the parent compound of the penicillins and is active mainly against Gram-positive bacteria and *Neisseria* spp. It is inactivated by penicillinase-producing bacteria and because of its instability in gastric acid it is usually injected. Long-acting preparations include *procaine benzylpenicillin* and *benzathine benzylpenicillin*, which slowly release benzylpenicillin after injection. Phenoxymethylpenicillin is acid-stable and is therefore given orally but it is also inactivated by penicillinase. It is generally used for relatively mild infections.

When no side-chain precursor is added to the fermentation medium, 6-aminopenicillanic acid itself is obtained. A range of penicillins has been synthesised from 6-aminopenicillanic acid by substitution at the 6-amino position in an effort to improve on the instability of benzylpenicillin to gastric acid and penicillinases, to widen its antimicrobial spectrum, and to reduce its rapid rate of renal excretion. Phenoxypenicillins with an α-phenoxypropionamido (*pheneticillin*) or α-phenoxybutyramido (*propicillin*) side-chain are more stable to acid than benzylpenicillin but offer no advantage over phenoxymethylpenicillin.

Meticillin has a 2,6-dimethoxybenzamido group at the 6-position and was the first penicillin found to be resistant to destruction by staphylococcal penicillinase. However, it is not acid-resistant and has to be injected. The isoxazolyl penicillins, *cloxacillin*, *dicloxacillin*, *flucloxacillin*, and *oxacillin*, are resistant to penicillinase and gastric acid. They have very similar chemical structures and differ mainly in their absorption characteristics. *Nafcillin* is a similar penicillinase-resistant antibacterial but is irregularly absorbed when taken orally.

Ampicillin has a D(-)-α-aminophenylacetamido side-chain and a broader spectrum of activity than benzylpenicillin; although generally less active against Gram-positive bacteria, some Gram-negative organisms including *Escherichia coli*, *Haemophilus influenzae*, and *Salmonella* spp. are sensitive although resistance is being reported increasingly. *Pseudomonas* spp. are not sensitive. Ampicillin is acid-stable and can be given orally but is destroyed by penicillinase. Prodrugs such as *bacampicillin* and *pivampicillin* are also said to be better absorbed and are hydrolysed to ampicillin *in vivo*. *Amoxicillin*, with a D(-)-α-aminohydroxyphenylacetamido side-chain, only differs from ampicillin by the addition

of a hydroxyl group, but is better absorbed from the gastrointestinal tract.

Carbenicillin, with an α-carboxyphenylacetamido side-chain, has marked activity against *Pseudomonas aeruginosa* and some *Proteus* spp. but otherwise is generally less active than ampicillin. It has to be given by injection and large doses are required. *Carindacillin* is the indanyl ester of carbenicillin and is hydrolysed to carbenicillin *in vivo* when taken orally. *Sulbenicillin* has an α-phenylsulfoacetamido side-chain and *ticarcillin* an α-carboxythienylacetamido side-chain and both have similar activity to carbenicillin; ticarcillin is more active against *Ps. aeruginosa*. The ureidopenicillins *azlocillin* and *mezlocillin*, and the closely related drug *piperacillin* are more active than carbenicillin against *Ps. aeruginosa* and have a wider range of activity against Gram-negative bacteria.

Temocillin, a 6-α-methoxy derivative of ticarcillin, is resistant to many beta lactamases and is active against most Gram-negative aerobic bacteria, but not *Ps. aeruginosa*.

Mecillinam is a penicillanic acid derivative with a substituted amidino group in the 6-position. Unlike the 6-aminopenicillanic acid derivatives it is active mainly against Gram-negative bacteria, although *Ps. aeruginosa*, and *Bacteroides* spp. are considered resistant. Mecillinam itself is not active orally; it is given as *pivmecillinam*, which is hydrolysed to mecillinam on absorption.

The beta-lactamase inhibitors *clavulanic acid*, *sulbactam*, and *tazobactam* are used to extend the antimicrobial range of certain beta-lactam antibacterials.

Described in this chapter are

Amoxicillin, p. 218.2
Ampicillin, p. 220.2
Aspoxicillin, p. 222.3
Azidocillin, p. 223.1
Azlocillin, p. 225.2
Bacampicillin, p. 227.2
Benethamine Penicillin, p. 229.1
Benzathine Benzylpenicillin, p. 229.2
Benzathine Phenoxymethylpenicillin, p. 230.1
Benzylpenicillin, p. 230.1
Carbenicillin, p. 234.1
Carindacillin, p. 234.2
Ciclacillin, p. 262.3
Clavulanic Acid, p. 270.3
Clemizole Penicillin, p. 271.2
Clometocillin, p. 276.3
Cloxacillin, p. 276.3
Dicloxacillin, p. 288.1
Flucloxacillin, p. 301.1
Lenampicillin, p. 317.3
Mecillinam, p. 323.1
Meticillin, p. 325.3
Mezlocillin, p. 326.1
Nafcillin, p. 330.2
Oxacillin, p. 338.2
Penethamate, p. 340.2
Pheneticillin, p. 340.2
Phenoxymethylpenicillin, p. 340.3
Piperacillin, p. 342.1
Pivampicillin, p. 343.3
Pivmecillinam, p. 344.1
Pivsulbactam, p. 362.1
Procaine Benzylpenicillin, p. 346.2
Propicillin, p. 346.3
Sulbactam, p. 362.1
Sulbenicillin, p. 362.3
Sultamicillin, p. 371.1
Tazobactam, p. 371.3
Temocillin, p. 374.3
Ticarcillin, p. 380.2

Quinolones

The quinolonecarboxylic acids, carboxyquinolones, or 4-quinolones are a group of synthetic antibacterials structurally related to nalidixic acid. The term 4-quinolone has been used as a generic name for the common 4-oxo-1,4-dihydroquinoline skeleton. Under this system nalidixic acid, a naphthyridene derivative, is an 8-aza-4-quinolone, cinoxacin, a cinnoline derivative, is a 2-aza-4-quinolone, and pipemidic and piromidic acids, pyrido-pyrimidine derivatives, are 6,8-diaza-4-quinolones.

Nalidixic acid is active against Gram-negative bacteria but has little activity against *Pseudomonas* and Gram-positive organisms. Because bactericidal concentrations can only be achieved in urine its use has generally been limited to the treatment of urinary-tract infections.

Modification of the structure of nalidixic acid has produced related antibacterials such as *oxolinic acid*, *cinoxacin*, and *rosoxacin*. Although some of these have a greater activity *in vitro* against Gram-negative organisms and activity against some Gram-positive organisms, none has been considered to represent a significant clinical advance over nalidixic acid; rosoxacin is only used in the treatment of gonorrhoea. Addition of a piperazinyl radical at position 7, as in *pipemidic acid*, appears to confer some activity against *Pseudomonas*. *Flumequine* was the first fluorinated 4-quinolone to be synthesised, but has no piperazinyl group. Addition of the 7-piperazinyl group and a fluorine atom at position 6 has produced a group of fluorinated piperazinyl quinolones or **fluoroquinolones** with a broader spectrum of activity than nalidixic acid and pharmacokinetic properties more suitable for the treatment of systemic infections. They include *ciprofloxacin*, *enoxacin*, *fleroxacin*, *gatifloxacin*, *gemifloxacin*, *levofloxacin*, *lomefloxacin*, *moxifloxacin*, *nadifloxacin*, *norfloxacin*, *ofloxacin*, *pazufloxacin*, *pefloxacin*, *rufloxacin*, and *sparfloxacin*. *Besifloxacin* is used topically. Several fluoroquinolones have been withdrawn because of toxicity including: *alatrofloxacin*, *clinafloxacin*, *grepafloxacin*, *temafloxacin*, and *trovafloxacin*. *Danofloxacin*, *enrofloxacin*, *ibafloxacin*, *marbofloxacin*, *orbifloxacin*, and *sarafloxacin* are used in veterinary practice. Development of *difloxacin* for human use was suspended because of the high incidence of adverse effects, but it is used in veterinary practice.

The fluoroquinolones are very active against aerobic Gram-negative bacilli and cocci including the Enterobacteriaceae, *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria gonorrhoeae* and are also active against *Pseudomonas aeruginosa*. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae*, although some fluoroquinolones now developed have increased activity against these organisms. They also have activity against mycobacteria, mycoplasmas, and rickettsias. Some, for example ofloxacin, have useful activity against *Chlamydia trachomatis*. Activity against anaerobic bacteria is generally poor. There is concern that the emergence of resistant strains of organisms may limit the usefulness of fluoroquinolones.

One disadvantage of the quinolone antibacterials is that they are generally not recommended for use in children, adolescents, and pregnant or breast-feeding women because of their propensity to cause joint erosions in immature *animals*.

Described in this chapter are

Balofloxacin, p. 228.3
Besifloxacin, p. 232.3
Cinoxacin, p. 263.1
Ciprofloxacin, p. 263.1
Danofloxacin, p. 283.2
Difloxacin, p. 288.3
Enoxacin, p. 292.2
Enrofloxacin, p. 292.3
Fleroxacin, p. 300.3
Flumequine, p. 302.2
Garenoxacin, p. 305.2
Gatifloxacin, p. 305.2
Gemifloxacin, p. 306.1
Ibafloxacin, p. 311.2
Levofloxacin, p. 317.3
Lomefloxacin, p. 321.2
Marbofloxacin, p. 323.1
Moxifloxacin, p. 328.3
Nadifloxacin, p. 330.1
Nalidixic Acid, p. 330.3
Norfloxacin, p. 335.3
Ofloxacin, p. 336.3
Orbifloxacin, p. 338.1
Oxolinic Acid, p. 338.3
Pazufloxacin, p. 340.1
Pefloxacin, p. 340.1
Pipemidic Acid, p. 341.3
Piromidic Acid, p. 343.3
Prulifloxacin, p. 347.1
Rosoxacin, p. 358.1
Rufloxacin, p. 359.1
Sarafloxacin, p. 359.2
Sparfloxacin, p. 359.3
Tosufloxacin, p. 383.2

Sulfonamides and diaminopyrimidines

The sulfonamides are analogues of *p*-aminobenzoic acid. The first sulfonamide of clinical importance was *Prontosil*, an azo dye that is metabolised *in vivo* to *sulfanilamide*. It was synthesised in Germany in 1932. Many sulfonamides have since been synthesised; they differ only slightly in their antimicrobial activity, but vary in their pharmacokinetic properties. The sulfonamides have been classified according to their rate of excretion as short-, medium- or intermediate-, long-, and ultra-long-acting. The **short-acting** sulfonamides are excreted in the urine in high concentrations and have therefore been of particular use in the treatment of urinary-tract infections. The solubility in urine of earlier short-acting sulfonamides, such as *sulfapyridine*, and their acetyl metabolites is low and hence crystalluria has been reported frequently. Of the short-acting sulfonamides most commonly used, *sulfadiazine* also has low solubility in urine whereas *sulfadimidine* and *sulfafurazole* and their acetyl conjugates are very soluble. Three short-acting sulfonamides (triple sulfonamides) have been given together to reduce the risk of crystalluria, as the constituent sulfonamides can co-exist in solution in urine without affecting each other's solubility. Preparations of mixed sulfonamides have, however, generally been replaced by the more soluble sulfonamides. The **medium-acting** sulfonamides such as *sulfamethoxazole*, the **long-acting** sulfonamides such as *sulfadimethoxine*, *sulfamethoxypyridazine*, and *sulfametoxydiazine*, and the **ultra-long-acting** sulfonamides such as *sulfadoxine* and *sulfametopyrazine* do not attain such high concentrations in the urine and rarely cause crystalluria. Sulfonamides that are slowly excreted from the body do appear, however, to have been more commonly implicated in the development of reactions such as the Stevens-Johnson syndrome.

The sulfonamides are usually bacteriostatic, and interfere with folic acid synthesis of susceptible organisms; their broad spectrum of antimicrobial activity has, however, been limited by the development of resistance. The clinical use of sulfonamides has therefore been greatly reduced; in general they are indicated only in the treatment of urinary-tract infections and a few other disorders such as nocardiosis. Sulfonamides such as *sulfaguanidine*, *succinylsulfathiazole*, *phthalylsulfacetamide*, and *phthalylsulfathiazole* are poorly absorbed from the gastrointestinal tract and have been used for the treatment of gastrointestinal infections although they are now rarely indicated. *Sulfadiazine silver*, *sulfathiazole silver*, and *mafenide* are applied topically for their antibacterial action in patients with burns. *Sulfasalazine* (p. 1893.1), a conjugate of 5-aminosalicylic acid (mesalazine) and sulfapyridine, is used in the treatment of inflammatory bowel diseases and in rheumatoid arthritis.

Trimethoprim is a diaminopyrimidine that also inhibits folic acid synthesis but at a different stage in the metabolic pathway to that inhibited by the sulfonamides. It has a similar spectrum of antimicrobial activity to sulfonamides and often shows synergy *in vitro* with these drugs. Trimethoprim was initially available only in combination with sulfonamides, most commonly with sulfamethoxazole as co-trimoxazole. It is now used alone particularly in the treatment of infections of the urinary and respiratory tracts. Analogues of trimethoprim include *baquiloprim*, *brodimoprim*, *iclaprim*, *ormetoprim*, and *tetroxoprim*.

Co-trimoxazole generally replaced use of sulfonamides alone in the treatment of systemic infections, although its use has also been restricted in some countries and trimethoprim may be preferred. Co-trimoxazole is however indicated for pneumocystis pneumonia and nocardiosis and may be useful in protozoal infections such as toxoplasmosis. Other sulfonamides which have been combined with trimethoprim include sulfadiazine (as *co-trimazine*), sulfamethoxypyridazine, sulfametopyrazine, sulfametrole, and sulfamoxole (see *co-trifamole*). Sulfadiazine has been used with tetroxoprim (see *co-tetroxazine*).

Sulfonamides have also been used with pyrimethamine (p. 662.3) in the treatment or prophylaxis of some protozoal infections. Common combinations are sulfadoxine and pyrimethamine for malaria, and sulfadiazine and pyrimethamine for the treatment of toxoplasmosis.

Described in this chapter are

Baquiloprim, p. 228.3
Brodimoprim, p. 233.1
Co-tetroxazine, p. 279.3
Co-trifamole, p. 279.3
Co-trimoxazole, p. 279.3
Formosulfathiazole, p. 302.2
Iclaprim, p. 311.2
Mafenide, p. 322.2
Ormetoprim, p. 338.2
Phthalylsulfacetamide, p. 341.2
Phthalylsulfathiazole, p. 341.3
Succinylsulfathiazole, p. 362.1
Sulfabenzamide, p. 362.3
Sulfacarbamide, p. 363.1
Sulfacetamide, p. 363.1
Sulfachlorpyridazine, p. 363.2
Sulfachrysoidine, p. 363.3
Sulfaclozine, p. 363.3
Sulfadiazine, p. 363.3
Sulfadiazine Silver, p. 364.3
Sulfadicramide, p. 365.1
Sulfadimethoxine, p. 365.2
Sulfadimidine, p. 365.2
Sulfadoxine, p. 365.3
Sulfafurazole, p. 366.1
Sulfaguanidine, p. 366.3
Sulfamerazine, p. 366.3
Sulfamethizole, p. 367.1
Sulfamethoxazole, p. 367.2
Sulfamethoxypyridazine, p. 369.2
Sulfamethylthiazole, p. 369.3
Sulfametopyrazine, p. 369.3
Sulfametrole, p. 370.1
Sulfamonomethoxine, p. 370.1
Sulfamoxole, p. 370.1
Sulfanilamide, p. 370.1
Sulfapyridine, p. 370.2
Sulfaquinoxaline, p. 370.2
Sulfathiazole, p. 370.3
Sulfathiazole Silver, p. 370.3
Sulfatroxazole, p. 371.1
Sulfisomidine, p. 371.1
Tetroxoprim, p. 378.3
Trimethoprim, p. 383.2

Tetracyclines

The tetracyclines are a group of antibacterials, originally derived from certain *Streptomyces* spp., having the same tetracyclic nucleus, naphthacene, and similar properties. Unlike the penicillins and aminoglycosides they are usually bacteriostatic at the concentrations achieved in the body but act similarly to the aminoglycosides by interfering with protein synthesis in susceptible organisms.

Tetracyclines all have a broad spectrum of activity which includes Gram-positive and Gram-negative bacteria, chlamydias and chlamydophilas, rickettsias, mycoplasmas, spirochaetes, some mycobacteria, and some protozoa, but the emergence of resistant strains and the development of other antimicrobials has often reduced their value. Adverse effects have also restricted their usefulness. Gastrointestinal disturbances are common and other important toxic effects include deposition in bones and teeth, precluding their use in pregnancy and young children; anti-anabolic effects, especially in patients with renal impairment; fatty changes in the liver; and photosensitivity, especially with demeclocycline. Allergic reactions are relatively uncommon. Because of these adverse effects tetracyclines should be avoided in pregnant women, children, and, apart from doxycycline and minocycline, patients with renal impairment.

The first tetracycline to be introduced was *chlortetracycline* in 1948 and, like chloramphenicol which was discovered at about the same time, it was found to have a broad spectrum of activity and to be active orally unlike benzylpenicillin or streptomycin, the only other antibacterials then in use. The discovery of chlortetracycline was followed closely by that of *oxytetracycline* and then *tetracycline*, a reduction product of chlortetracycline which may be produced semisynthetically. All three have very similar properties, although chlortetracycline is less well absorbed and oxytetracycline may cause less staining of teeth. *Demeclocycline*, demethylated chlortetracycline, has a longer half-life than tetracycline but is more often associated with phototoxic reactions. It has been used with some success in patients with the syndrome of inappropriate secretion of antidiuretic hormone.

These four tetracyclines are all natural products that have been isolated from *Streptomyces* spp. The more recent tetracyclines, such as methacycline, doxycycline, minocycline, lymecycline, meclocycline, and rolitetracycline are semisynthetic derivatives. *Methacycline*, like demeclocycline, has a longer half-life than tetracycline and has been given twice daily. *Doxycycline* and *minocycline* are both more active

in vitro than tetracycline against many species. More importantly, minocycline is active against some tetracycline-resistant bacteria, including strains of staphylococci. Both are well absorbed and, unlike the other tetracyclines, absorption is not significantly affected by the presence of food. They can be given in lower doses than the older members of the group and, having long half-lives, doxycycline is usually given once daily and minocycline twice daily. Also, they do not accumulate significantly in patients with renal impairment and can, with care, be given to such patients; however, usual doses of minocycline can lead to higher serum concentrations resulting in possible liver toxicity. Both doxycycline and minocycline are more lipid-soluble than the other tetracyclines and they penetrate well into tissues. The use of minocycline may, however, be limited by its vestibular adverse effects.

Tetracyclines are not generally the antibacterials of choice in Gram-positive or Gram-negative infections because of the emergence of resistant organisms and the discovery of drugs with narrower antimicrobial spectra. However, they have a place in the treatment of chlamydial infections, rickettsial infections such as typhus and the spotted fevers, mycoplasmal infections such as atypical pneumonia, pelvic inflammatory disease, Lyme disease, brucellosis, tularaemia, plague, cholera, periodontal disease, and acne. The tetracyclines have also been useful in the treatment of penicillin-allergic patients suffering from sexually transmitted diseases, actinomycosis, bronchitis, and leptospirosis. Minocycline may sometimes be used in multidrug regimens for leprosy. Doxycycline may be used for the treatment and prophylaxis of malaria; it is also used in the management of anthrax.

Described in this chapter are

- Chlortetracycline, p. 262.2
- Demeclocycline, p. 287.2
- Doxycycline, p. 290.1
- Lymecycline, p. 322.1
- Meclocycline, p. 323.2
- Methacycline, p. 324.3
- Minocycline, p. 326.3
- Oxytetracycline, p. 339.1
- Rolitetracycline, p. 358.1
- Tetracycline, p. 375.1

Miscellaneous Antibacterials

Spectinomycin is an aminocyclitol antibacterial with some similarities to streptomycin although it is not an aminoglycoside. Spectinomycin is active against many bacteria but its clinical use is restricted to the treatment of chancroid and gonorrhoea. Trospectomycin, a water-soluble derivative, has been investigated.

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens* with activity against most strains of staphylococci and streptococci and also some Gram-negative bacteria. It is applied topically.

Fosfomycin is a derivative of phosphonic acid; it is active against Gram-positive and Gram-negative bacteria and is given orally or parenterally.

The fusidane antibacterial *fusidic acid* is derived from *Fusidium coccineum* and has a narrow spectrum of antibacterial activity, but it is very active against *Staphylococcus aureus* and has been used both topically and systemically in the treatment of staphylococcal infections. Resistance develops readily and it is often used with other antibacterials.

The polymyxins are basic antibacterials produced by the growth of different strains of *Bacillus polymyxa* (*B. aerosporus*). *Polymyxin B* and *colistin* have been used clinically, but their systemic use has been more or less abandoned because of their toxicity, notably to the kidneys and nervous system. They are not absorbed when taken orally and have therefore been given in gastrointestinal infections for their bactericidal activity against Gram-negative bacteria. They continue to be widely used as components of topical preparations.

Bacitracin, gramicidin, gramicidin S, and *tyrothricin* are polypeptide antibacterials also produced by certain strains of *Bacillus* spp. but they are active against Gram-positive bacteria. Like the polymyxins, they are toxic when used systemically and are therefore mainly used topically.

The halogenated hydroxyquinoline *clioquinol* has antibacterial, antifungal, and antiprotozoal activity. It was formerly used in gastrointestinal infections including amoebiasis but is of little value and can produce severe neurotoxicity. It is now mainly used locally for superficial infections of the skin and external ear. *Chlorquinaldol* and *halquinol* are used similarly.

Urinary antimicrobials such as *nitrofurantoin,* and also *methenamine* which has generally been given as the hippurate or mandelate, may be used in the treatment and prophylaxis of infections of the lower urinary tract. They are concentrated in the urine, but do not usually achieve antimicrobial concentrations in the blood.

The oxazolidinone *linezolid* has activity against Gram-positive organisms including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is used in infections of the skin and respiratory tract due to these organisms.

The glycylcycline *tigecycline* has activity against Gram-positive bacteria, including meticillin-resistant *Staph. aureus*, and also against some Gram-negative and some anaerobic bacteria. It is used in the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia.

The pleuromutilin antibacterial *retapamulin* is derived from the fungus *Clitopilus passeckerianus*; it has activity against *Staphylococcus aureus* and *Streptococcus pyogenes*. It is applied topically.

Described in this chapter are

- Acediasulfone, p. 216.1
- Arsanilic Acid, p. 222.2
- Avilamycin, p. 222.3
- Bacitracin, p. 227.3
- Bambermycin, p. 228.3
- Carbadox, p. 233.3
- Chlorquinaldol, p. 262.1
- Clioquinol, p. 275.1
- Clofoctol, p. 276.3
- Colistin, p. 277.3
- Daptomycin, p. 286.2
- Fosfomycin, p. 302.3
- Furaltadone, p. 303.3
- Furazidin, p. 303.3
- Fusafungine, p. 304.1
- Fusidic Acid, p. 304.1
- Gramicidin, p. 310.3
- Gramicidin S, p. 311.1
- Halquinol, p. 311.1
- Linezolid, p. 319.3
- Magainins, p. 322.3
- Mandelic Acid, p. 322.3
- Methenamine, p. 324.3
- Mupirocin, p. 329.2
- Nifuroxazide, p. 333.3
- Nifurpirinol, p. 333.3
- Nifurtoinol, p. 333.3
- Nifurzide, p. 334.1
- Nisin, p. 334.1
- Nitrofurantoin, p. 334.1
- Nitrofurazone, p. 335.1
- Nitroxoline, p. 335.2
- Novobiocin, p. 336.2
- Polymyxin B, p. 344.3
- Retapamulin, p. 350.1
- Spectinomycin, p. 360.1
- Taurolidine, p. 371.2
- Terizidone, p. 375.1
- Thenoic Acid, p. 378.3
- Thiostrepton, p. 380.1
- Tiamulin, p. 380.1
- Tigecycline, p. 381.2
- Tyrothricin, p. 386.1
- Valnemulin, p. 386.1
- Xibornol, p. 389.3

Choice of Antibacterial

Ideally, antibacterial treatment of infections should be chosen after the infecting organisms have been identified and the results of sensitivity tests are known. In practice, empirical treatment is often necessary initially, bearing in mind local patterns of infection and resistance. Other factors such as site of infection and tissue penetration are also important in deciding which antibacterial to give.

The prophylactic use of antibacterials is restricted mainly to patients undergoing some types of surgery. Other groups requiring infection prophylaxis include patients at special risk of developing endocarditis and those who have had rheumatic fever, who are splenectomised, or who are immunocompromised.

Abscess, abdominal

See under Abscess, Liver, p. 174.3, and under Peritonitis, p. 199.2.

Abscess, brain

Brain abscesses can result from otitis media, sinusitis, trauma, or dental sepsis, or they may be metastatic secondary to, for example, lung abscesses. Opportunistic infections in immunocompromised patients may present as brain abscesses.

Treatment of brain abscesses entails removal of pus or excision and use of high doses of antibacterials. Ideally the choice of antibacterial depends on the infecting organisms and penetration by the antibacterial into brain tissue and abscess pus. Until organisms can be cultured empirical treatment should be given.

There is very little good quality published information on the treatment of brain abscess. For many years, combined treatment with benzylpenicillin and chloramphenicol was the mainstay of empirical therapy, but a report by the British Society for Antimicrobial Chemotherapy,[1] based on published information and the authors' expertise, recommended the following regimens for first-line empirical treatment, according to the site of the abscess and origin of the infection:

- for frontal lobe abscesses originating from infection of the paranasal sinuses or teeth, a combination of metronidazole with one of cefuroxime, cefotaxime, or ceftriaxone
- for temporal lobe or cerebellar abscesses originating from infection of the middle ear or sphenoidal sinuses, ampicillin and metronidazole with either ceftazidime or gentamicin
- for abscesses associated with penetrating trauma, flucloxacillin, cefuroxime, cefotaxime, or ceftriaxone
- for metastatic abscesses, usually in the area supplied by the middle cerebral artery, one of cefuroxime, cefotaxime, or ceftriaxone, with or without metronidazole, or, if associated with endocarditis or cyanotic congenital heart disease, benzylpenicillin

Similar suggestions have been made by a more recent review,[2] which also suggested the use of oxacillin with metronidazole and a third-generation cephalosporin for empirical management of abscesses associated with penetrating trauma, and vancomycin plus a third-generation cephalosporin for abscess occurring postoperatively. Another review[3] suggested the latter combination for abscesses both after neurosurgery and trauma.

1. Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. The rational use of antibiotics in the treatment of brain abscess. *Br J Neurosurg* 2000; **14:** 525–30.
2. Lu C-H, *et al*. Strategies for the management of bacterial brain abscess. *J Clin Neurosci* 2006; **13:** 979–85.
3. Hakan T. Management of bacterial brain abscesses. *Neurosurg Focus* 2008; **24:** E4. Available at: http://thejns.org/doi/pdf/10.3171/FOC/2008/24/6/E4 (accessed 31/03/10)

Abscess, liver

Bacteria commonly responsible for pyogenic liver abscesses include Enterobacteriaceae, especially *Escherichia coli* and in some countries[1] *Klebsiella pneumoniae*; anaerobes, especially *Bacteroides fragilis*; and *Streptococcus milleri* (these can be microaerophilic). As elsewhere in the abdomen (see under Peritonitis, p. 199.2), infections are often mixed. Treatment involves percutaneous aspiration and drainage of pus and the use of high doses of antibacterials.[2,3] Broad-spectrum empirical therapy should be started immediately; more specific therapy may be possible when the results of cultures following diagnostic percutaneous aspiration of the abscess are known. Gentamicin with clindamycin has been commonly used[4,5] but other antibacterial combinations, involving cefoxitin, chloramphenicol, carboxypenicillins, third-generation cephalosporins, and metronidazole, might be appropriate.[5] A regimen of ampicillin, gentamicin, and metronidazole has become standard in some centres, but may be hazardous in patients with *Klebsiella*-related liver abscess, in whom a combination of an aminoglycoside with either an extended-spectrum beta-lactam such as piperacillin or a second- or third-generation cephalosporin, may be preferred.[1] Antibacterial therapy has been successful without surgical intervention, but may not be consistently so,[6] although this might be due to inadequate treatment against enteric anaerobes, especially *B. fragilis*.[5]

For the treatment of amoebic liver abscess, see under Amoebiasis in Antiprotozoals, p. 921.1.

1. Lederman ER, Crum NF. Pyogenic liver abscess with a focus on Klebsiella pneumoniae as a primary pathogen: an emerging disease with unique clinical characteristics. *Am J Gastroenterol* 2005; **100:** 322–31.
2. Barakate MS, *et al*. Pyogenic liver abscess: a review of 10 years' experience in management. *Aust N Z J Surg* 1999; **69:** 205–9.
3. Alvarez Pérez JA, *et al*. Clinical course, treatment, and multivariate analysis of risk factors for pyogenic liver abscess. *Am J Surg* 2001; **181:** 177–86.
4. Herbert DA, *et al*. Pyogenic liver abscesses: successful non-surgical therapy. *Lancet* 1982; **i:** 134–6.
5. Herbert DA, *et al*. Medical management of pyogenic liver abscesses. *Lancet* 1985; **i:** 1384.
6. McCorkell SJ, Niles NL. Pyogenic liver abscesses: another look at medical management. *Lancet* 1985; **i:** 803–6.

Abscess, lung

Lung abscesses are often secondary to aspiration pneumonia and are discussed under Pneumonia, p. 202.1. The organisms involved are commonly anaerobic bacteria.

Actinomycosis

Actinomycosis is a rare, chronic, slow-growing, often polymicrobial infection caused mainly by Gram-positive anaerobic or microaerophilic bacteria of the genus *Actinomyces* (usually *A. israelii*) and sometimes by others such as *Propionibacterium* or *Bifidobacterium*. Such organisms are part of the normal flora of the oral cavity, gastrointestinal tract, female genital tract, or skin. They are of low pathogenicity and require a break in the mucosal barrier to cause infection; foreign bodies also appear to facilitate infection. Actinomycosis occurs worldwide and at any age but it is most commonly seen in men and those in the middle decades of life. Any site in the body can be involved; the most common are oral-cervicofacial and are usually associated with dental procedures or poor oral hygiene. Less commonly, thoracic, abdominal, or pelvic regions are involved (the latter usually associated with the use of intra-uterine contraceptive devices). Rarely, CNS, cutaneous, or disseminated infection may occur.

The infection is characterised by single or multiple indurations that spread regardless of tissue planes. Local swelling, inflammation, abscesses, woody fibrous tissue, and draining sinuses that exude characteristic yellow aggregates (sulfur granules) may develop. Diagnosis is difficult; the lesions may be mistaken for neoplasms.

Actinomycosis responds slowly to antibacterials, and long-term treatment is required to prevent recurrence.[1-3] The treatment of choice is high-dose intravenous benzylpenicillin for 2 to 6 weeks and then an oral penicillin (e.g. phenoxymethylpenicillin or amoxicillin) for 6 to 12 months,[1,2] although complicated cases may require up to 18 months of therapy.[2] Some patients may be successfully treated with less prolonged regimens of penicillin, especially if the disease burden is light;[1] uncomplicated oral-cervicofacial disease is particularly responsive to shorter treatment courses. Short-course regimes are generally not

advised for patients with large lesions and/or abdominal disease unless surgical debridement is performed.

Alternatives to penicillins include the tetracyclines, erythromycin, chloramphenicol, and clindamycin.[2,3] In one patient, actinomycosis resistant to conventional therapy responded to a prolonged course of ciprofloxacin;[4] in another, actinomycosis was eliminated with a 4-month course of levofloxacin.[5] There are also reports of success with imipenem, first generation cephalosporins, ceftriaxone, and piperacillin/tazobactam.[1,2,6] Actinomycosis is not susceptible to metronidazole, aminoglycosides, co-trimoxazole, penicillinase-resistant penicillins, or cefalexin.[2]

Most patients can be managed with medical therapy alone; however, drainage or aspiration of abscesses or excision of fistulas may be appropriate, and occasionally extensive surgery is indicated, especially if medical therapy fails or a critical location is involved.[2,3]

1. Sudhakar SS, Ross JJ. Short-term treatment of actinomycosis: two cases and a review. *Clin Infect Dis* 2004; **38:** 444–7.
2. Brook I. Actinomycosis: diagnosis and management. *South Med J* 2008; **101:** 1019–23.
3. Chaudhry SI, Greenspan JS. Actinomycosis in HIV infection: a review of a rare complication. *Int J STD AIDS* 2000; **11:** 349–55.
4. Macfarlane DJ, *et al*. Treatment of recalcitrant actinomycosis with ciprofloxacin. *J Infect* 1993; **27:** 177–80.
5. Ferreira D de FG, *et al*. Treatment of pulmonary actinomycosis with levofloxacin. *J Bras Pneumol* 2008; **34:** 245–8.
6. Yi F, *et al*. Actinomycotic infection of the abdominal wall mimicking a malignant neoplasm. *Surg Infect (Larchmt)* 2008; **9:** 85–9.

Anaerobic bacterial infections

Anaerobic bacteria (or anaerobes) are part of the normal microbial flora of the skin, mouth, gastrointestinal tract, and vagina. If their commensal relationship is disrupted by surgery, trauma, immunosuppression, poor blood supply, or tissue necrosis, some anaerobes can cause potentially serious infections. They often cause infections in the pleural spaces and lungs, upper respiratory tract, gastrointestinal tract, CNS, skin, and vagina; haematogenous spread can occur. Common anaerobic pathogens include *Bacteroides*, *Prevotella* (formerly non-fragilis *Bacteroides*), *Fusobacterium*, *Porphyromanas*, *Clostridium*, *Peptostreptococcus*, and *Actinomyces* spp. Apart from single species infections such as tetanus, gas gangrene, pseudomembranous colitis, and actinomycosis, most anaerobic infections are of mixed aetiology. Abscesses are often a feature. Infections include: brain abscess; acute necrotising gingivitis and other periodontal infections; chronic otitis media and chronic sinusitis; aspiration pneumonia and lung abscess; peritonitis and intra-abdominal abscess; bacterial vaginosis and pelvic inflammatory disease; cellulitis, ulcers, bites, and other wound infections.[1]

Management of anaerobic infections usually includes surgical procedures and antibacterial therapy. Sensitivity testing *in vitro* is often impractical and if done results may not be available for several days. Initial antibacterial treatment is therefore usually empirical,[1-5] should cover aerobes and anaerobes, and take into account local resistance rates and the site of infection. Antibacterials are usually given parenterally, in high doses, and for a prolonged duration (weeks to months).[3,5]

The antibacterials of choice are metronidazole, carbapenems, combinations of a beta lactam with a beta-lactamase inhibitor, and chloramphenicol as they have the highest activity (more than 95%) against obligate anaerobes. Tigecycline is also highly active and considered a promising new agent for anaerobic/mixed infections with multidrug-resistant bacteria. Cefoxitin and clindamycin are often effective, except for infections caused by *Bacteroides*. Penicillin alone is no longer recommended for mixed infection because of increasing resistance in Gram-negative anaerobes, but may still be used for gas gangrene and actinomycosis. Other antibacterials with low to moderate resistance rates include moxifloxacin and garenoxacin. Other drugs with potential for therapy may include oral nitazoxanide, ramoplanin, rifaximin, intravenous dalbavancin, and for topical use, retapamulin.[5]

Surveys of susceptibility patterns in clinical isolates of anaerobic bacteria have shown increasing resistance of the *B. fragilis* group (including *B. distasonis*, *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*) to clindamycin, continuing penicillin resistance in non-fragilis *Bacteroides* spp. (now reclassified as *Prevotella* spp. and including the type species *P. melaninogenica*), and rare beta-lactamase-mediated resistance of *Fusobacterium* to penicillin.[5] A clinical isolate of *B. fragilis*, simultaneously resistant to metronidazole, amoxicillin with clavulanic acid, and imipenem, was reported in the UK;[6] treatment with clindamycin was successful on this occasion. Resistance of some *Clostridium* spp. to penicillin and clindamycin had declined, but no changes were noted for *Cl. perfringens*. The emergence of multidrug-resistant anaerobes has been noted.[5]

1. Styrt B, Gorbach SL. Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections (first of two parts). *N Engl J Med* 1989; **321:** 240–6.
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6. Turner P, *et al*. Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of Bacteroides fragilis. *Lancet* 1995; **345:** 1275–7.

Anthrax

Anthrax is caused by *Bacillus anthracis*, a spore-forming Gram-positive aerobe found in the soil. It most commonly infects herbivorous mammals. Humans can become infected by contact with infected animals or infected or contaminated animal products, or by inhalation of anthrax spores. There have also been some reports of anthrax being acquired through injecting or inhaling heroin contaminated with anthrax spores. Person-to-person transmission is highly unlikely, although secondary cases of cutaneous anthrax have occasionally been reported; airborne transmission from person-to-person does not occur. Although rare in western countries anthrax remains a problem in many areas, including Africa, Asia, some southern European countries, the Americas, and parts of Australia. It has also been used as a weapon for biological warfare.

In humans anthrax presents most often in the cutaneous form which is usually curable with antibacterial treatment. In other types the prognosis is poor without prompt treatment; a 33% case fatality rate has been reported for injection anthrax in the UK.

- In *cutaneous* anthrax a painless, pruritic papule, which enlarges to an ulcer may develop within hours, or up to 12 days, after contact. Later (2 to 6 days) a vesicle with a black eschar develops.
- The incubation period for *inhalation* anthrax is usually about 10 days. An initial non-specific flu-like illness may last from a few hours to days and is followed in some patients by a short period of recovery while others progress directly to respiratory failure.
- *Gastrointestinal* anthrax has an incubation period of up to 1 week (usually 2 to 5 days), with fever, abdominal pain, nausea, vomiting, gastric ulcers, haematemesis, and diarrhoea (usually bloody) progressing to hypotension, shock, and death in as little as 2 to 5 days after initial symptoms.
- *Injection* anthrax has an incubation period of 1 to 2 days or longer. Patients may show signs of severe sepsis, with or without evidence of soft tissue infection (such as necrotising fasciitis and cellulitis). Meningitis (especially haemorrhagic meningitis) and gastrointestinal symptoms may also occur.

The **treatment** of naturally occurring anthrax has traditionally been with benzylpenicillin with ciprofloxacin or doxycycline (or other tetracycline) as alternatives. Other drugs with *in vitro* activity are aminoglycosides, amoxicillin, chloramphenicol, clindamycin, imipenem, linezolid, the macrolides, meropenem, rifampicin, and vancomycin.[1-4]

There are currently no clinical study data on the optimal treatment for anthrax. For the treatment of naturally occurring anthrax in developing countries WHO considers that *B. anthracis* is probably still susceptible to benzylpenicillin and recommends it as the drug of choice.[5] In developed countries treatment recommendations and guidelines[1,2,4,6] are based largely on the experience gained during the 1979 incident in Sverdlovsk (accidental release of biological warfare agents), the 2001 attack in the USA (deliberate release), isolated case reports of naturally occurring disease, and *in vitro* data.

- TREATMENT IN DEVELOPING COUNTRIES.
  For mild uncomplicated cases of naturally occurring *cutaneous* anthrax, WHO recommends intramuscular procaine benzylpenicillin for 3 to 7 days; oral alternatives are phenoxymethylpenicillin or amoxicillin.[5] For patients with severe or potentially life-threatening anthrax with signs of systemic involvement treatment should start with intravenous benzylpenicillin and then be switched to intramuscular procaine benzylpenicillin after clinical improvement. Treatment is usually given for 10 to 14 days. The addition of a second drug is often recommended; benzylpenicillin may be given with clindamycin or clarithromycin in treating *inhalational* anthrax or with an aminoglycoside (such as streptomycin) in *gastrointestinal* anthrax. For anthrax *meningoencephalitis* benzylpenicillin (or a fluoroquinolone) should be given with an antibacterial that penetrates well to the CNS.[5] Those with penicillin allergy may be treated with ciprofloxacin or doxycycline; a fluoroquinolone plus rifampicin and vancomycin should be given if such patients have anthrax meningoencephalitis.[5]
- TREATMENT IN DEVELOPED COUNTRIES.
  Because of the risks of engineered drug-resistant strains of *B. anthracis*, inducible beta-lactamases, and *in vitro* resistance to ofloxacin, guidelines[1,2,4] for the treatment of anthrax (occurring after deliberate release) recommend the use of 2 or more antibacterials which should be started as soon as possible. Corticosteroids may be given as adjunctive therapy.
  For *cutaneous* anthrax, oral ciprofloxacin or oral doxycycline is generally recommended. A change to amoxicillin, particularly in pregnant women and children, may be considered if the organism is found to be susceptible or first-line drugs cannot be taken. Treatment for 7 to 10 days is usually recommended for cutaneous anthrax, but in the event of a deliberate release or if concurrent inhalation is suspected then treatment should be continued for 60 days. If there are signs of systemic involvement, extensive oedema, or lesions on the head or neck, intravenous, and a multidrug approach is recommended.[1,4]
  For the treatment of *inhalation* and *gastrointestinal* anthrax ciprofloxacin or doxycycline plus one or two additional antibacterials with *in vitro* activity are recommended until antimicrobial susceptibility is known. Treatment should be given for 60 days and should initially be given intravenously and then switched to oral therapy when clinically appropriate.[1,4] Raxibacumab is a monoclonal antibody that can be used with antibacterials in the treatment of inhalation anthrax. It neutralises the anthrax toxin that is mainly responsible for the high mortality rate.[7]

Anthrax can be **prevented** by controlling and eliminating infected animals and vaccinating livestock. Anthrax vaccines may be used for active immunisation in humans and are recommended for persons working with potentially infected animals or animal products (including laboratory workers).[8]

Postexposure prophylaxis should be used after inhalation exposure to anthrax spores. UK guidelines[4] suggest oral ciprofloxacin for 60 days, or initial treatment with oral ciprofloxacin for 5 days followed by oral doxycycline for 55 days; amoxicillin may be considered if the organism is found to be susceptible. The vaccine may also be given depending on individual risk from exposure. If the vaccine is used, antibacterial prophylaxis may be reduced to 4 weeks.[4] However, US guidelines[8] recommend both antibacterials and vaccination for all previously unvaccinated persons, consisting of a 60-day course of oral ciprofloxacin or doxycycline (or amoxicillin for pregnant women depending on susceptibility) and 3 doses of vaccine. Antibacterial prophylaxis should continue until 14 days after the third vaccine dose, and may need to be given for more than 60 days if vaccination has been delayed. A shorter 30-day course of antibacterial prophylaxis is recommended for partially or fully vaccinated workers if respiratory protection has been disrupted during occupational exposure.[8] Antibacterial prophylaxis alone may be considered for 7 to 14 days after naturally occurring gastrointestinal exposure, but initial observation only is recommended following cutaneous exposure.[8] Raxibacumab is also licensed for prevention of inhalation anthrax when alternatives cannot be used.

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Antibiotic-associated colitis

See under Gastro-enteritis p. 185.1.

Arthritis, bacterial

See under Bone and Joint Infections, p. 177.1.

Bacillary angiomatosis

See under Cat Scratch Disease, p. 178.3.

Bacterial vaginosis

Bacterial vaginosis (anaerobic vaginosis; non-specific vaginitis) results from a reduction of the normal vaginal bacteria (*Lactobacillus* spp.) and an overgrowth of anaerobic bacteria (including *Gardnerella vaginalis*, *Mycoplasma hominis*, or *Mobiluncus* or *Prevotella* spp.). It is a common and often distressing condition that is not thought to be sexually transmitted but is generally associated with sexual activity. Infections may be asymptomatic or result in a fishy-smelling vaginal discharge.

Various antibacterial regimens for the **treatment** of bacterial vaginosis are recommended in guidelines issued in the UK,[1] and in the USA[2] and also by WHO[3] but relapse is common after any regimen.

- **WHO:**
  - oral metronidazole 400 or 500 mg twice daily for 7 days

  alternatives are:
  - a single oral dose of metronidazole 2 g
  - intravaginal metronidazole 5 g of a 0.75% gel twice daily for 5 days
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin 5 g of a 2% cream at bedtime for 7 days
- **UK:**
  - oral metronidazole 400 mg twice daily for 5 to 7 days, *or*
  - a single oral 2-g dose of metronidazole, *or*
  - intravaginal metronidazole 0.75% gel once daily for 5 days, *or*
  - intravaginal clindamycin as a 2% cream once daily for 7 days

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days
  - a single oral dose of tinidazole 2 g
- **USA:**
  - oral metronidazole 500 mg twice daily for 7 days, *or*
  - intravaginal metronidazole 5 g of a 0.75% gel once daily for 5 days, *or*
  - intravaginal clindamycin 5 g of a 2% cream at bedtime for 7 days

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin 100 mg at bedtime for 3 days
  - oral tinidazole 1 g daily for 5 days *or* 2 g daily for 2 days

A systematic review[4] of 24 clinical studies to assess the effects of antibacterials on bacterial vaginosis in non-pregnant women found clindamycin preparations (creams, ovules, and tablets), oral metronidazole, and oral or intravaginal tablets of lactobacillus probiotics to be effective. For further information on the use of probiotics in the treatment of bacterial vaginosis see Urological Infections, on p. 2597.2.

An association has been reported between bacterial vaginosis and adverse ***pregnancy*** outcomes, including miscarriage and premature births of low-weight infants, and some have advised treatment early in the second trimester of pregnancy.[5,6] A systematic review[7] of clinical studies has concluded that there is little evidence that screening and treatment of all pregnant women for bacterial vaginosis would prevent premature birth and its consequences, but there is some suggestion that treatment before 20 weeks of gestation may reduce the risk of preterm birth. Symptomatic pregnant women should be treated and the following regimens have been recommended:

- **WHO:**
  - oral metronidazole 200 or 250 mg three times daily for 7 days, after the first trimester, *or*
  - a single oral dose of metronidazole 2 g, if treatment is needed in the first trimester

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days *or*
  - intravaginal metronidazole 5 g of a 0.75% gel twice daily for 7 days
- **USA:**
  - oral metronidazole 500 mg twice daily *or* 250 mg three times daily for 7 days *or*
  - oral clindamycin 300 mg twice daily for 7 days

Treatment of male sex partners does not prevent the recurrence of bacterial vaginosis.[1-3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[2]

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Biliary-tract infections

Although the biliary-tract is normally free of bacteria, infections may follow partial or complete blockage of part of the biliary tree; the part blocked determines the clinical condition.

Acute cholecystitis results from blockage of the cystic duct, mostly caused by gallstones (acalculous cholecystitis refers to cholecystitis without gallstones). Bile stasis occurs after the blockage and leads to inflammation of the gallbladder and possibly secondary bacterial infection, which is mostly polymicrobial. Inadequate drainage increases the pressure within the bile duct, resulting in reflux of bacteria into the blood and lymph (bacteraemia). Complications can include gangrene, hepatic or intraperitoneal abscesses, peritonitis, and septicaemia. *Cholangitis* is caused by infection in an obstructed biliary system, usually the common bile duct. Suppurative cholangitis is associated with a higher mortality rate.

The organisms most commonly involved in both these conditions are *Escherichia coli* and *Klebsiella* spp.; *Enterococci* are less common. Anaerobes, mostly *Clostridium* and *Bacteroides* spp., are cultured in about 15% of cases, usually as part of a mixed infection and are more common in those with bile duct-to-bowel anastomosis or fistulas, the elderly, or seriously ill patients.[1-4]

In most cases of obstruction, definitive treatment depends on restoring drainage of bile by surgical or medical treatment of gallstones (p. 2639.1). Antibacterial therapy for cholecystitis and cholangitis is similar and aims to control bacteraemia; treatment may be complicated by the fact that biliary obstruction prevents adequate concentrations of many antibacterials being achieved in the bile. Choice of an antibacterial is determined by the severity of the disease, the suspected pathogen, antibacterial activity, and local antibacterial resistance patterns.[3-5]

Patients with mild illness may be treated with oral antibacterials; fluoroquinolones (levofloxacin and ciprofloxacin), first-generation cephalosporins (cefotiam, cefcapene, and cefazolin), or a broad-spectrum penicillin plus a beta-lactamase inhibitor (such as ampicillin with sulbactam) are options.[5] Broad-spectrum intravenous antibacterials that achieve high concentrations in both bile and blood are preferred for initial treatment in those with moderate to severe illness.[3-5] Antibacterials used for moderate illness and often, in combination, for severe infections, include the cephalosporins, fluoroquinolones, and ureidopenicillin (preferably mezlocillin and piperacillin).[1,3,4] Second-generation cephalosporins may be given for moderate infections, while third- and fourth-generation cephalosporins and aztreonam are given for more severe illness.[5] Metronidazole should be added if anaerobic infection is considered likely.[1,3,5] In penicillin-resistant cases (particularly for infections with *E. coli* or *Klebsiella* spp.) piperacillin with tazobactam may be considered. If patients have recently undergone nonsurgical biliary tract procedures or received a broad-spectrum antibacterial, it may be useful to add an aminoglycoside to cover *Pseudomonas* or *Enterobacter* spp.[1,3] In those with more severe illness, antibacterials with pseudomonal and enterococcal activity (such as imipenem, meropenem, or piperacillin with tazobactam)[4,5] and fluoroquinolones may be considered.[5] Antibacterial treatment is usually given for 5 to 14 days.[1,3,4]

Antibacterial prophylaxis is common in biliary surgery (see Surgical Infection, p. 211.1) to prevent acute cholangitis and wound infections. A single dose of an intravenous cephalosporin (cefazolin, cefoxitin, cefuroxime, or cefotaxime), piperacillin, or ciprofloxacin is often used for this purpose.[1,3]

Maintenance antibacterial therapy to reduce the number of episodes may have a role in those with recurrent cholangitis. Oral co-trimoxazole is the drug of choice, although there are also a few reports of oral ciprofloxacin being used;[1,3] a further alternative is amoxicillin (or ampicillin) plus a beta-lactamase inhibitor (clavulanic acid, sulbactam, or tazobactam).[1] An attempt is usually made after 3 to 4 months to stop this treatment.[1,3]

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Bites and stings

Dog, cat, or human bites are the most commonly encountered bite wounds. The resulting injury depends on the animal species and dentition, the ferocity of the attack, and the anatomical location of the bite. Dog bites most often cause crush injuries, lacerations, and abrasions, whereas the sharp pointed teeth of cats usually cause puncture wounds and lacerations. A major concern in all bite wounds is the risk of infection; it can be caused by nearly any group of pathogens (bacteria, viruses, rickettsia, spirochetes, or fungi). Patients presenting more than 8 hours after a bite injury often have infected wounds, with cat bites developing infection more rapidly than dog bites. Human bites have a higher complication and infection rate than animal bites.

Animal bite wound infections contain a mix of aerobes and anaerobes from both the skin of the patient and the mouth of the animal, although certain organisms are associated with particular animal species. Cat bites are most often associated with *Pasteurella multocida*; other organisms include *Porphyromonas* and *Moraxella* spp. *Bartonella henselae* can be transmitted via a scratch or bite of an infected cat or cat flea. See also under Cat Scratch Disease (p. 178.3). A common canine organism is *P. canis*. Other common organisms associated with cat and dog bites are *Streptococcus, Staphylococcus, Fusobacterium,* and *Bacteroides* spp.[1,2] A more unusual organism is *Capnocytophaga canimorsus* (formerly called dysgonic fermenter type 2 or DF-2) which has mostly been associated with dog bites.[3-5] It is an opportunistic pathogen especially hazardous to chronic alcohol users and immunocompromised patients, including splenectomised patients.[1,2] Infection with *C. canimorsus* after dog bites has led to fatal septicaemia, disseminated intravascular coagulation, meningitis, or endocarditis.[3]

Infected human bites are usually polymicrobial, however *Eikenella corrodens* has caused septic arthritis after a penetrating injury of the hand, and this may be complicated by infective endocarditis. Hepatitis B and C can be transmitted by human bites and HIV transmission has occasionally been reported.[2]

Management of cat and dog bites should include treatment of the wound to reduce the risk of acute infection. Prompt and thorough irrigation of the wound with tap water or normal saline aims to dislodge foreign matter and bacteria inoculated into the wound, and reduce the transmission of rabies virus. Established infection usually requires hospital admission for surgical debridement and drainage. A systematic review[6] concluded that there was insufficient evidence that prophylactic antibacterials given for dog bites were effective. There was evidence that antibacterials given after bites to the hand reduced infection and weak evidence to suggest that prophylactic antibacterials after human bites reduced infection. Prophylactic antibacterials are therefore not recommended for superficial and easily cleansed bite wounds;[1,5] prophylaxis should be reserved for the bites most likely to become infected (such as cat and human bites), where adequate debridement cannot be achieved, and in immunocompromised patients at high risk of infection.[5] If given, antibacterial prophylaxis should be given for 3 to 5 days;[2,5] it is initially empirical and should be directed toward the organisms that usually colonise the oral cavity of the animal until cultures results can direct treatment.[1]

Pasteurella spp. cause rapidly progressive skin and soft tissue infection and are generally resistant to dicloxacillin, flucloxacillin, first-generation cephalosporins, clindamycin, and erythromycin.[1,2] Benzylpenicillin is not effective against *S. aureus*, anaerobes, or *Eikenella*. Oral amoxicillin with clavulanic acid has excellent activity against *Pasteurella* spp., *Capnocytophaga* spp., anaerobes, and susceptible *S. aureus*, and is the drug of choice for prophylaxis.[1,2,5] Tetracycline or doxycycline with or without metronidazole is an alternative in penicillin-allergic patients.[1,2,5,7] Other alternatives include metronidazole with co-trimoxazole or a fluoroquinolone,[2] clindamycin with a fluoroquinolone, or clindamycin with co-trimoxazole (in children).[1] Parenteral ceftriaxone can be used in pregnancy;[1,5] cefuroxime and cefpodoxime are oral alternatives.[1] In areas where community-acquired MRSA incidence is high the choice of antibacterial may need to be modified. Doxycycline and co-trimoxazole are effective oral alternatives for coverage of MRSA; clindamycin may be a further alternative.[1] Antibacterials should be given parenterally when rapidly spreading cellulitis or signs of sepsis develop, or involvement of bone or joint is likely. Antibacterials for more severe established infections (as inpatient treatment) include combinations of a beta lactam and a beta-lactamase inhibitor (such as ampicillin with sulbactam, piperacillin with tazobactam, or ticarcillin with clavulanic acid). A carbapenem (such as ertapenem, meropenem, doripenem, or imipenem), ceftriaxone, aztreonam, or a fluoroquinolone with metronidazole are alternatives.[1] For very severe infections, empirical imipenem plus clindamycin has been given.[5] Treatment is usually given for 10 to 14 days for established cellulitis, 3 weeks for tenosynovitis, and 6 weeks for osteomyelitis.[5]

If necessary, prophylaxis or treatment for rabies (p. 2413.2) should be instituted. A combined tetanus and diphtheria vaccine (see p. 2383.1) should be given to patients whose primary tetanus immunisation is incomplete or unknown, or boosters are not up-to-date. For human

bites hepatitis B prophylaxis should be considered if the patient is not immune (see Hepatitis B Vaccine, p. 2389.3) and although there is limited evidence to support HIV postexposure prophylaxis it should be considered in high risk human bite injuries (see HIV Infection Prophylaxis, p. 961.1).[2]

Among the more unusual infections acquired from animals is seal finger, caused by an as yet unidentified organism and treated with tetracycline.[8] The Gram-negative bacilli *Spirillum minus* (or *minor*) and *Streptobacillus moniliformis* are both causes of rat-bite fever. In each case the treatment of choice is benzylpenicillin;[7] a tetracycline or streptomycin are alternatives.

Envenomation after bites and stings by snakes, scorpions, spiders, and some marine animals is usually treated symptomatically and with specific antivenoms and antisera (see Jellyfish Stings, p. 2397.1, Scorpion Stings, p. 2418.1, Snake Bites, p. 2419.2, Spider Bites, p. 2420.1, and Stone Fish Venom Antisera, p. 2420.2).

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Bone and joint infections

Infectious arthritis (septic or pyogenic arthritis) is an infection of the joints characterised by pain, fever, inflammation, and swelling. Bacteria are the most common cause of infectious arthritis, although fungi and viruses can also infect joints. In acute **bacterial arthritis**, joints are commonly infected from a contiguous source via the blood or from direct inoculation during a surgical procedure, injection, bite, or trauma. Infecting organisms include staphylococci, streptococci, enterococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, and anaerobes, although the commonest is probably *Staphylococcus aureus*. In prosthetic joint infections coagulase-negative staphylococci are often implicated. *Haemophilus influenzae* is a common cause in young children, as is *Neisseria gonorrhoeae* in sexually active young adults. In addition to gonococcal arthritis, other specific types of bacterial arthritis include Lyme disease and meningococcal, salmonellal, and tuberculous arthritis (see under the appropriate disease for further details).

In **reactive arthritis** (aseptic arthritis) joint inflammation follows infection elsewhere in the body. It is generally secondary to sexually transmitted, especially chlamydial, infections, or to enteric infections with organisms such as *Salmonella, Shigella, Yersinia, Campylobacter*, and *Clostridium difficile*. The term Reiter's syndrome is usually reserved for reactive arthritis associated with extra-articular features such as urethritis and conjunctivitis.

Acute **osteomyelitis**, an infection of bone, is also characterised by pain, fever, and inflammation. Chronic infection can develop, with long periods of latency and recurrent relapse, and is associated with necrosis of the bone. Osteomyelitis is most often caused by spread from a contiguous source of infection such as a penetrating wound, soft tissue infection, or surgery, but can also be disseminated by the blood or secondary to vascular insufficiency such as diabetic foot infection. With the exception of *N. gonorrhoeae*, infecting organisms are similar to those in bacterial arthritis.

A systematic review and meta-analysis[1] of antibacterial **treatment** of bone and joint infections concluded that there was little high-quality evidence to support use of any one drug. In practice, treatment is usually started intravenously; if high bone concentrations can be achieved with an appropriate oral antibacterial, patients may be switched to oral therapy.

Treatment for *bacterial arthritis* is usually started intravenously, although it need not be given parenterally for the whole course.[2,3] Synovial penetration for most antibacterials is generally good, although peak concentrations tend to be lower and slower to achieve than those in plasma. Typically, the recommended duration of treatment is several weeks.[2,4,5] A shorter treatment course of about 10 days, with a higher dose of antibacterial, has been evaluated in children with bacterial arthritis.[6]

- Empirical treatment regimens for bacterial arthritis (as for osteomyelitis) usually include antibacterials with activity against staphylococci and streptococci. These include flucloxacillin, nafcillin, oxacillin, or cephalosporins.[4,5,7,8] Clindamycin is an alternative in patients who are penicillin-allergic.[4,5] Benzylpenicillin and ceftriaxone are also active against streptococci.[7] Alternatively, gentamicin can be added to an antistaphylococcal drug.[4,5] Vancomycin[4,5] or teicoplanin[5] are used if meticillin-resistant *Staph. aureus* is suspected; a second- or third-generation cephalosporin,[4] rifampicin, fusidic acid, or doxycycline[5] have also been added. In patients unable to take vancomycin, linezolid has been used as an alternative.[7] Coagulase-negative staphylococci are treated similarly.[7]
- Empirical antibacterial treatment for infections caused by Gram-negative bacteria include a third-generation cephalosporin or ciprofloxacin.[7] Ceftriaxone may be used for empirical treatment of bacterial arthritis where infection is thought to be caused by *N. gonorrhoeae*[4,7] or *N. meningitidis*.[4] Young children should be given a cephalosporin such as cefotaxime because of the likelihood of *H. influenzae* infection.[5]
- Infections caused by anaerobes can be treated with clindamycin; ampicillin-sulbactam or metronidazole are alternatives.[8]

In the treatment of *osteomyelitis* similar drugs are typically chosen to those listed above for treatment of bacterial arthritis. However, because penetration of antibacterials into bone may be variable and slow, particularly where there is necrosis or poor vascularisation, treatment, at least in adults, has often been more prolonged.[2,7,8] Treatment is generally given by the intravenous route but with some drugs, such as the quinolones or clindamycin, an early switch to oral therapy is possible.[7,8] Debridement of necrotic bone is important in the management of chronic osteomyelitis.[7,8] Children with osteomyelitis may respond more rapidly to treatment because of the greater vascularity of developing bone; shorter courses, and initial oral[2] or an early switch from intravenous to oral treatment[9] may be possible.

Antibacterials which have a good activity against surface-adhering and biofilm-producing bacteria are required for *prosthetic joint infection*; rifampicin is commonly used with a fluoroquinolone.[10] In one study[11] use of rifampicin with ciprofloxacin improved control of staphylococcal infections related to joint prostheses or fracture fixation devices in comparison with ciprofloxacin alone. Rifampicin has also been used with a penicillinase-resistant penicillin, vancomycin, or teicoplanin[10] for initial intravenous treatment of prosthetic joint infections; fusidic acid,[8,10] co-trimoxazole, or minocycline[10] have been added to rifampicin for continued oral treatment. As in osteomyelitis prolonged intravenous therapy may be needed;[2,8] debridement and removal of the prosthesis is important.[2,7] For reference to infection prophylaxis in orthopaedic patients, see under Surgical Infection, p. 211.1.

In *reactive arthritis* the role of antibacterials is less certain.[12] Results in arthritis associated with chlamydial infections have been more promising than in that triggered by enteric infections.[13] Long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[14] For reference to the symptomatic treatment of reactive arthritis, see Spondyloarthropathies p. 14.3.

For mention of the use of tetracyclines, usually minocycline, in the treatment of *rheumatoid arthritis*, see under Musculoskeletal and Joint Disorders, p. 376.2.

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Botulism

For a discussion of botulism and its management, see p. 2380.2.

Bronchitis

Bronchitis may be defined as inflammation of the bronchi and is associated with excessive sputum production and cough. It may be either acute or chronic and may be as a result of infection or may be triggered by irritants such as tobacco smoke, pollution, chemicals, or dust.

Acute bronchitis is a common, self-limiting, respiratory infection that manifests mainly as a cough with or without sputum production and lasts for up to 3 weeks; if the cough persists for more than 3 weeks other diagnoses should be considered. Respiratory viruses, such as those that cause colds and influenza, are the most usual cause of acute bronchitis; less than 10% of cases have a bacterial cause. Bacteria associated with acute bronchitis include *Mycoplasma pneumoniae, Bordetella pertussis*, and *Chlamydophila pneumoniae*. *Acute bronchiolitis* affects the small bronchi and bronchioles and in infants is usually caused by RSV (see Respiratory Syncytial Virus Infection, p. 963.3).

Chronic bronchitis is defined as cough and sputum production occurring on most days and lasting longer than 3 months in each of 2 consecutive years; other causes of cough should also have been excluded. Chronic bronchitis is often a feature of chronic obstructive airways disease (COPD—p. 1199.1). Patients with chronic bronchitis or COPD may suffer acute infective exacerbations characterised by increased dyspnoea, sputum production, and sputum purulence. These may be viral in origin, but bacteria are often present in purulent sputum, the commonest being *Streptococcus pneumoniae, Moraxella catarrhalis*, and *Haemophilus influenzae*.

Treatment. ACUTE BRONCHITIS.

Antibacterials are not recommended in most cases of acute bronchitis.[1,2] A systematic review[3] and meta-analysis[4] of clinical studies in patients with acute bronchitis suggested that although they may reduce the duration of symptoms, the benefit is modest. Similar findings were reported when amoxicillin was given for the treatment of bronchitis in a community with a high prevalence of HIV-infected patients.[5] However, patients with acute bronchitis suspected or confirmed to be caused by pertussis infection should be treated with a macrolide or co-trimoxazole.[2] For further information on the treatment of pertussis, see p. 200.3.

Beta agonist bronchodilators are sometimes used to relieve the cough even in people who do not have asthma. A systematic review[6] on the use of oral or inhaled beta agonists concluded that they should not be used for the treatment of uncomplicated acute bronchitis. However, in patients with airflow obstruction and wheezing at the onset of the illness some benefit was seen, but the evidence is not well supported. The American College of Chest Physicians (ACCP) suggests that in selected adult patients with wheezing and a cough, treatment with a beta agonist bronchodilator may be useful.[2] Inhaled antimuscarinic bronchodilators have not been studied for acute bronchitis and are therefore not recommended.[2] Antitussives containing codeine or dextromethorphan are occasionally useful and can be given for short-term symptomatic relief of coughing; however, expectorants and mucolytics are not recommended.[2]

ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB).

Treatment of AECB includes bronchodilators, systemic corticosteroids, antibacterials, and oxygen as necessary. Treatment with antibacterials is discussed below, while treatment with other drugs is discussed under COPD (see p. 1199.1). The value of antibacterial treatment in AECB has been controversial and early studies were difficult to assess.[7-9] After a comparison of a broad-spectrum antibacterial (amoxicillin, co-trimoxazole, or doxycycline) with placebo,[10] it was considered that antibacterials were justified in patients with AECB characterised by increased dyspnoea, sputum production, and sputum purulence, a conclusion supported by a later systematic review.[11] An earlier meta-analysis of randomised studies also indicated a small improvement due to therapy in patients with AECB.[12] Amoxicillin, ampicillin, tetracyclines (such as doxycycline), broad-spectrum macrolides, second- or third-generation cephalosporins, or co-trimoxazole have traditionally been used for treatment of AECB,[13,14] but recent reports from the USA and Canada show reduced efficacy to penicillin, macrolides, and co-trimoxazole; however, antibacterial activity for the newer fluoroquinolones and combinations of a beta lactam and a beta-lactamase inhibitor have remained high.[13] Furthermore, a meta-analysis[14] to evaluate the comparative efficacy and safety of first-line antibacterials (considered to be amoxicillin, ampicillin, pivampicillin, co-trimoxazole, and doxycycline) and second-line antibacterials (considered to be amoxicillin with clavulanic acid, macrolides, second- or third-

generation cephalosporins, and fluoroquinolones) for the treatment of patients with AECB, reported that second-line antibacterials were more effective, but not less safe, compared with the first-line antibacterials.

Guidelines for the management of AECB were developed by the Canadian Chronic Bronchitis Working Group,[9] and the topic is also covered by general guidelines for the management of COPD available in many countries (see p. 1199.1), and internationally through the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[15] These guidelines stratify patients according to risk to identify those needing antibacterial therapy or more aggressive treatment. Generally, treatment is determined according to the infecting pathogen, patterns of local bacterial resistance, and severity of symptoms. The oral route is preferred and treatment is usually given for 3 to 10 days.[15,16] Broadly, no antibacterial treatment is needed for mild exacerbations. If treatment is needed then ampicillin, amoxicillin, doxycycline, or co-trimoxazole may be considered. Alternatives include combinations of a beta lactam and a beta-lactamase inhibitor such as amoxicillin with clavulanic acid, a second- or third-generation cephalosporin, a second-generation macrolide, or a ketolide such as telithromycin. Patients needing hospitalisation with moderate to very severe COPD, but without risk of *Pseudomonas aeruginosa* should be treated with a fluoroquinolone or amoxicillin with clavulanic acid. Those at risk of *P. aeruginosa* should be treated with a fluoroquinolone.

Long-term prophylaxis in patients with frequent exacerbations of bronchitis is controversial. A systematic review[17] of the value of antibacterial prophylaxis in chronic bronchitis concluded that it did have a small but significant effect in reducing the number of days of illness, but that it had no place in routine therapy because of concerns over adverse effects and the development of resistance. Guidelines for COPD management do not advocate prophylactic use of antibacterials.

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Brucellosis

Brucellosis (also known as undulant or Mediterranean fever) is caused by *Brucella* spp., aerobic Gram-negative bacteria found mainly in livestock and domestic animals. Humans can become infected by direct contact with infected animals or animal material (such as the placenta), indirectly by consuming infected and unpasteurised milk products, or by inhalation of contaminated dust or droplets. Rarely, human infection has been reported from exposure to some live veterinary vaccines.[1,2] The principal *Brucella* spp. affecting humans are *B. melitensis*, from sheep, goats, camels, and sometimes cattle; *B. abortus*, from cattle, buffalo, camels, and yaks; *B. suis*, from pigs; and rarely *B. canis*, from dogs. Although rare or controlled in countries such as the UK brucellosis remains a problem in many areas, including eastern Europe, the Mediterranean region, South and Central America, Mexico, the Caribbean, the Indian subcontinent, parts of Africa and Asia, and the Middle East.

Symptoms usually develop 2 to 8 weeks after infection and resemble a flu-like illness with anorexia, fever, headache, lethargy, malaise, depression, myalgia and back pain, sweating, and weakness. Laboratory findings include anaemia, leucopenia, lymphocytosis, pancytopenia, and thrombocytopenia. Brucellosis may be acute, relapsing, or chronic (disease duration of more than 1 year) and can affect any part of the body, including joints (peripheral arthritis, sacroiliitis, and spondylitis), heart (endocarditis), liver (hepatitis), the CNS (meningitis, encephalitis, meningoencephalitis, meningovascular disease, brain abscesses, and demyelinating syndrome), and the reproductive system (epididymo-orchitis). Relapses occur in about 10% of patients, usually in the first year after infection, and typically cause milder symptoms.[3]

Treatment of brucellosis shortens the duration of illness, and reduces complications and the risk of relapse. Tetracyclines, although highly active against *Brucella* spp., are associated with high relapse rates when given as monotherapy and therefore combination therapy is now used. Common regimens are:

- doxycycline and rifampicin both orally for at least 6 weeks[4,5]
- doxycycline orally for 6 weeks with a parenteral aminoglycoside (streptomycin,[6,7] gentamicin,[5,8,9] or netilmicin[10]) for the first 1 to 2 weeks

Fewer relapses have been reported with doxycycline and streptomycin than with doxycycline and rifampicin, perhaps due to rifampicin reducing plasma concentrations of doxycycline.[11] Higher relapse rates have been reported with netilmicin than with gentamicin.[10] Studies[12,13] have shown that treatment with a fluoroquinolone plus either doxycycline or rifampicin is effective although fluoroquinolone monotherapy is not. A review of the literature on fluoroquinolone-based combination treatment did not support their use as first-line treatment,[13] but they can be considered as part of an alternative regimen for patients who have relapse or toxicity problems with the usual first-line antibacterials. Co-trimoxazole when used is usually given in triple-drug regimens.[3]

A systematic review and meta-analysis[14] of 30 randomised controlled studies on the treatment of brucellosis found that a triple drug regimen of doxycycline, gentamicin, and rifampicin was better than doxycycline plus an aminoglycoside. It also found that 6 weeks of treatment was associated with a lower rate of relapse than treatment regimens of 30 days or less.

Tetracyclines should be avoided in young *children* (usually specified as below 8 years of age in the US and below 12 years in the UK). The preferred regimens for these children appear to be co-trimoxazole with rifampicin both orally for at least 6 weeks or co-trimoxazole orally with parenteral gentamicin for the first 2 weeks.[5,6] Alternative regimens include rifampicin orally for at least 6 weeks with either gentamicin or netilmicin for the first 5 days.[6]

For the treatment of brucellosis during *pregnancy*, WHO recommends rifampicin monotherapy for 6 weeks as the drug of choice and that co-trimoxazole or tetracycline should only be given if rifampicin is unavailable; streptomycin is contra-indicated.[4] Co-trimoxazole with rifampicin for 4 weeks has also been tried.[6]

No one antibacterial combination has been found to be superior for the treatment of *spondylitis* although a 3-month course of doxycycline with ciprofloxacin has been proposed based on an evaluation of the literature.[15] In the treatment of *neurobrucellosis*, the length of therapy appears to be of critical importance; relapses may occur after treatment lasting only 2 to 3 weeks and it is recommended that doxycycline be given with 2 or more other drugs (rifampicin, an aminoglycoside, co-trimoxazole, or ceftriaxone) for several months depending on the response. Corticosteroids are often given but their efficacy is unproven. A similar treatment regimen is used in the management of paediatric neurobrucellosis and a 3-drug regimen (doxycycline, rifampicin, and an aminoglycoside) given for 3 months has been shown to be effective. In young children doxycycline should be replaced with co-trimoxazole.[16] Treatment of *endocarditis* in adults generally requires long-term triple or quadruple drug regimens (a tetracycline, an aminoglycoside, rifampicin, and/or co-trimoxazole) usually with surgical valve replacement.[17,18] Treatment should be continued for 3 months or longer and some recommend the addition of ceftriaxone and/or a fluoroquinolone to reduce the need for surgery. Cardiac complications in children are generally less severe than in adults and treatment with tetracycline for 3 weeks with streptomycin for 2 weeks has been found to be effective.[18]

Brucellosis can be **prevented** by controlling and eliminating infected animals, pasteurising milk products, and vaccinating cattle and other livestock. There is no human vaccine currently available for brucellosis, although many have been tested and some have been available periodically in various countries.[3]

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Campylobacter enteritis

See under Gastro-enteritis p. 186.1.

Cat scratch disease

Cat scratch disease usually occurs in humans after a cat scratch or bite. The condition is characterised by regional lymphadenopathy and is often self-limiting, but may be disseminated in immunocompromised patients. Disseminated disease typically involves the nervous system (including the retina), visceral organs, or bone.

In the 1980s a Gram-negative bacillus presumed to be responsible for cat scratch disease was isolated and subsequently named *Afipia felis*. However, it has since become apparent that *Bartonella henselae* (formerly *Rochalimaea henselae*) is the main cause of cat scratch disease.[1-3] There has been no specific antibacterial therapy and treatment with antibacterials is generally not recommended in patients with mild to moderate infection.[1,2] There are, however, reports of successful treatment with gentamicin, co-trimoxazole, and ciprofloxacin.[2] Azithromycin has also been found to be of benefit in adults[4] and a 5-day oral regimen is considered the treatment of choice in both adults and children with extensive lymphadenopathy. Oral doxycycline with oral rifampicin may be given as an alternative for these patients and this combination, given for 4 to 6 weeks, is the recommended treatment for complicated cat scratch disease.[1]

Bacillary angiomatosis, in which both *B. henselae* and *B. quintana* (the causative organism of trench fever) have been implicated, and **bacillary peliosis hepatis** (caused by *B. henselae*) occur mainly in immunocompromised patients, especially in those with HIV. Bacillary angiomatosis is generally characterised by cutaneous or subcutaneous vascular lesions. Symptoms of bacillary peliosis, where lesions affect the liver, are non-specific, with or without cutaneous involvement.[1,3] Disseminated disease in immunocompromised patients has responded to treatment with doxycycline, erythromycin or azithromycin.[2] Oral erythromycin for 3 months is the drug of choice for bacillary angiomatosis; it should be given intravenously in severe disease. Oral or intravenous doxycycline may be given as an alternative. Immunocompromised patients with acute, life-threatening infection should be treated with rifampicin plus erythromycin or rifampicin plus doxycycline; the latter choice is preferred in CNS disease.[1,3] Care is required in patients with AIDS since the lesions of bacillary angiomatosis closely resemble those of Kaposi's sarcoma, and if the diagnosis is missed, life-saving antibacterial therapy may not be given.[5]

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Cellulitis

See under Skin Infections, p. 209.1.

Cervicitis

Gonorrhoea in women occurs mainly as cervicitis, but mucopurulent cervicitis is frequently caused by sexually transmitted *Chlamydia trachomatis*. The two infections often occur together and should be treated concurrently. Guidelines for treatment are given under Gonorrhoea, p. 206.2, and Chlamydial Infections, p. 179.1.

Chancroid

See under Sexually Transmitted Diseases, p. 206.2

Chlamydial infections

The chlamydia organism belongs to the family Chlamydiaceae. Species that are pathogenic in man are *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Chlamydia trachomatis*; they are generally sensitive to tetracyclines or erythromycin.

C. pneumoniae (formerly classified as a TWAR strain of *C. psittaci*) is a respiratory pathogen. It was first described as a cause of community-acquired pneumonia (see Pneumonia, p. 202.1), but has since been associated with other clinical presentations including pharyngitis (see p. 200.3) and has been implicated in the pathogenesis of ischaemic heart disease (see Atherosclerosis, p. 1250.2).

C. psittaci is transmitted to man from birds and causes psittacosis, which also affects the lungs (see Psittacosis, p. 204.1).

C. trachomatis causes a wide range of diseases. Many are sexually transmitted and the spectrum is similar to that with *Neisseria gonorrhoeae* (see Gonorrhoea, p. 206.2); infections with the two organisms often occur together. In women *C. trachomatis* may cause endometritis, pelvic inflammatory disease, ectopic pregnancy, and infertility. In the USA[1,2] routine screening for *C. trachomatis* infection is recommended in all sexually active women aged 25 years or younger, whether or not they are pregnant, and in women aged over 25 years if they are considered to be at increased risk of infection.

Guidelines produced by WHO,[3] by expert groups in the UK,[4,5] and by the CDC in the USA[2] for the **treatment** of uncomplicated anogenital infection with *C. trachomatis* are as follows:

- **WHO:**
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  alternatives, given for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily
- **UK:**
  - first-line therapy is the same as WHO

  alternatives are:
  - oral erythromycin 500 mg twice daily for 10 to 14 days
  - oral ofloxacin 200 mg twice daily *or* 400 mg once daily for 7 days
- **USA:**
  - first-line therapy is the same as WHO

  alternatives, given for 7 days, are:
  - oral erythromycin 500 mg four times daily
  - oral erythromycin ethylsuccinate 800 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral levofloxacin 500 mg once daily

Pregnant women infected with *C. trachomatis* may be at risk of premature rupture of membranes and preterm labour (see Premature Labour, p. 203.3). They may also infect their offspring to cause ophthalmia neonatorum (see Neonatal Conjunctivitis, p. 195.2) or pneumonia (p. 202.1). Infected pregnant women should be treated and the following regimens have been recommended:

- **WHO:** treatment for 7 days with:
  - oral erythromycin 500 mg four times daily *or*
  - oral amoxicillin 500 mg three times daily
- **UK:**
  - as for WHO, *or*
  - oral erythromycin 500 mg twice daily for 14 days, *or*
  - a single oral dose of azithromycin 1 g
- **USA:**
  - a single oral dose of azithromycin 1 g *or*
  - oral amoxicillin 500 mg three times daily for 7 days

  alternatives are:
  - erythromycin-containing regimens

Sexual partners of those infected with *C. trachomatis* should be tested and treated.[2-4]

For further reference to sexually transmitted *C. trachomatis* infections, see under Epididymitis (p. 183.2), Pelvic Inflammatory Disease (p. 198.3), and Urethritis (p. 214.3)

Specific serotypes of *C. trachomatis* are responsible for another sexually transmitted disease, lymphogranuloma venereum (p. 207.2).

Reactive arthritis (see Bone and Joint Infections, p. 175.1) may be secondary to chlamydial infections.

Other *C. trachomatis* infections that are not sexually transmitted include trachoma and inclusion conjunctivitis in adults (see Trachoma, p. 212.1).

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Cholera and other vibrio infections

See under Gastro-enteritis p. 186.2.

Cystic fibrosis

Cystic fibrosis is a genetic disorder associated with the production of abnormally viscous mucus. The underlying defect is mutation in the gene that codes for cystic fibrosis transmembrane conductance regulator (CFTR), a protein that functions as a chloride channel. Mutations result in defective ion transport with reduced chloride ion secretion and accelerated sodium ion absorption, and related changes in the composition and properties of mucin secreted. Now that patients with cystic fibrosis usually survive into adulthood, it is increasingly seen to be a multisystem disease. However, the main clinical manifestations are still pulmonary disease, with recurrent bacterial infections and the production of copious viscous sputum, and malabsorption due to pancreatic insufficiency. Other complications include male infertility and hepatobiliary disease. There is increased salt loss in sweat.

Pulmonary disease is the main cause of mortality. Cystic fibrosis is an underlying cause of bronchiectasis (chronic dilatation of the bronchi) as a result of excessive secretion of mucus and recurrent infections. Cough and excessive production of sputum are characteristic of cystic fibrosis and the lungs are generally colonised with bacterial pathogens, especially mucoid strains of *Pseudomonas aeruginosa*. Pseudomonal pulmonary infection is the main cause of morbidity and mortality in cystic fibrosis. Monitoring of bacterial pathogens in the sputum, including their sensitivity, is necessary for rational treatment. Apart from *Ps. aeruginosa*, *Staphylococcus aureus* is often present and may be the main pathogen in infants. *Burkholderia cepacia* complex (*Pseudomonas cepacia*) has been recognised as a cause of serious lung infection in cystic fibrosis and is readily transmitted by social contact. In a proportion who acquire it, *B. cepacia* has been associated with rapid deterioration and death. Other bacteria isolated include *Haemophilus influenzae* and atypical *Mycobacteria* spp.

Various diagnostic methods are available[1-3] and clinical diagnosis of cystic fibrosis may be confirmed by establishing that chloride concentrations in sweat are raised. This may be done by using the pilocarpine sweat test (see Pilocarpine, p. 2011.1). Identification of gene mutation is possible and may be used for further confirmation of the diagnosis and identification of carrier status. In some areas neonatal screening programs to measure immunoreactive trypsinogen concentrations (a marker associated with pancreatic injury) have been instituted, to allow for early intervention.[2,3]

The reduced morbidity and improved survival in patients with cystic fibrosis are largely due to the management of pulmonary disease with antibacterials and physiotherapy and to nutritional management. Several reviews have discussed both established and experimental therapy.[1-5] Despite the successes, the evidence base for some procedures is scanty,[2] and there may be variations in management between centres. However, the cornerstones of current management are:[1-3]

- mechanical airway clearance, with the use of adjuncts such as dornase alfa and hypertonic saline
- prevention or eradication of pulmonary infections in early disease
- suppression of bacterial load through antibacterial treatment of chronic infection in more advanced disease
- use of ibuprofen or azithromycin to control lung inflammation
- aggressive antibacterial treatment of pulmonary exacerbations
- nutritional support to ensure an adequate intake of calories and salt, with supplementation of pancreatic enzymes and the fat-soluble vitamins A, D, E, and K
- maintaining regular physical activity

Guidelines for the management of infants with cystic fibrosis have been developed by the Cystic Fibrosis Foundation in the USA.[6]

Airway clearance by manual chest percussion and mechanical techniques including chest-wall or airway oscillation helps to loosen secretions and aid their removal.[7] Dornase alfa[8] is given by aerosol inhalation and reduces the viscosity of the sputum by breaking down the large quantities of DNA released by degenerating inflammatory cells. The use of dornase alfa has been associated with some improvement in lung function and it might be a useful adjunct to bronchial drainage, although it is unclear whether it prevents the development of progressive lung damage. However, a randomised, multicentre, placebo-controlled study in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a 96-week period.[9] US guidelines therefore also recommend the long-term use of dornase alfa to improve lung function and reduce exacerbations.[10] Nebulised or oral mucolytics, such as acetylcysteine, carbocysteine, ambroxol, glutathione, and mesna are generally not considered to be effective in cystic fibrosis.[11] Inhalation of hypertonic saline has, however, been shown to be of benefit[12] (see p. 1798.1) and has become part of management in many centres.[1-3] Inhaled mannitol may be added to standard therapy to improve mucus clearance.[13] The time required for such therapies and their associated monitoring may prove challenging to patients and their families.[1]

In young patients with early disease, **prevention or eradication of infection** for as long as possible is a reasonable aim, in order to maintain good lung function.[2] Staphylococcal infections commonly develop during the first decade of life, and while some clinicians start antistaphylococcal antibacterials on diagnosis of cystic fibrosis, others wait until the first clinical infection occurs. Once started, antistaphylococcal therapy is continued indefinitely in some centres, while others only treat when symptomatic exacerbations or positive sputum cultures occur. Systematic reviews confirmed that antistaphylococcal treatment is effective and also concluded that prophylaxis is likely to be beneficial in young children with cystic fibrosis.[14,15] In the UK, flucloxacillin or co-amoxiclav are commonly given.[2] It is unclear whether intermittent or continuous therapy produces the best clinical outcome. Other potential disadvantages to prophylaxis are the possible early acquisition of *Ps. aeruginosa* infection[16] (this seems to be a risk mainly if broad spectrum cephalosporins are given) and an increased incidence of drug-resistant staphylococci with continuous therapy.[17] In view of this risk of earlier or more frequent *Ps. aeruginosa* infection, guidelines developed in the USA, by the Cystic Fibrosis Foundation, do not support the prophylactic use of oral antistaphylococcal antibacterials.[10]

Management of **chronic infection** is aimed at control of bacterial load,[2] (since permanent eradication is impossible), improving lung function, and reducing exacerbations.[10] Selection of an antibacterial must be individualised, and will depend on the infecting organisms,[2] and local prescribing policies and availability. Long-term intermittent treatment with inhaled antibacterials, particularly tobramycin, is favoured;[1-3,10] other nebulised antibacterials that may be of benefit include aztreonam and colistin.[1,18] A systematic review confirmed that inhaled antipseudomonal antibacterials improved lung function and reduced the frequency of exacerbations.[19] Although there is some evidence of an increase in resistance with such treatment,[19] it is claimed to be less frequent than feared.[1] However, US guidelines concluded that there was insufficient evidence to recommend for or against the long-term use of nebulised antibacterials other than tobramycin, including colistin, gentamicin, or ceftazidime.[10] Oral antipseudomonal therapy has not been conclusively shown to be of benefit in chronic infection,[20] and is generally avoided because of fears of resistance.[1]

The macrolide azithromycin is, however, used orally in chronic infection, but may be acting as an immunomodulator to **reduce inflammation** rather than specifically as an antibacterial.[1-3,10,21] A systematic review[22] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear. A small anti-inflammatory benefit has also been reported from treatment with high-dose oral ibuprofen,[23] and this is used in some centres, particularly in the USA to slow the loss of lung function.[2,10] However, there are some concerns about the potential for adverse effects; it has been recommended that if used, such therapy be stopped in patients who require intravenous aminoglycosides, and should be avoided in those with gastrointestinal risk factors.[23] Systematic reviews[24,25] and the US guide-

lines[10] concluded there was insufficient evidence to support a role for either inhaled or oral corticosteroid therapy, except in the management of patients who develop allergic bronchopulmonary aspergillosis.[2] However, a retrospective analysis of observational data collected for 2978 children, 6 to 17 years of age, who were given inhaled corticosteroid therapy reported a slower decline in lung function as determined by the FEV_1.[26]

Aggressive **management of exacerbations** with appropriate antibacterials is crucial.[1,2,27,28] Treatment should be based on recent culture results, but there appears to be no additional value in combination antibacterial sensitivity testing.[29] In patients with *Ps. aeruginosa* infection a combination of intravenous antibacterials, typically an aminoglycoside such as tobramycin and a beta-lactam with antipseudomonal activity such as ceftazidime, is favoured.[3,27,28,30,31] Once-daily dosing with the aminoglycoside is as effective as giving it in divided doses, and may be associated with less nephrotoxicity in children.[32] High doses are necessary because of the poor penetration of these antipseudomonal antibacterials into the site of infection and their increased renal clearance in patients with cystic fibrosis.[33,34] Treatment is generally given for 2 to 3 weeks although there is no good evidence to support a particular length of therapy.[31,35] Intermittent elective intravenous therapy has become more practical with the development of regimens that enable patients to be treated at home.[30,36] US guidelines[31] recommend that airway clearance should be increased as part of the treatment of an acute exacerbation and chronic maintenance therapies be continued; there is no clear evidence for or against continued use of inhaled antibacterials in patients given the same antibacterial intravenously.

Infection with *B. cepacia* complex is difficult to treat because most antipseudomonal antibacterials are ineffective. Co-trimoxazole has been suggested[37] and can be given orally;[28] meropenem and ceftazidime have some *in-vitro* activity, and temocillin has been tried.[28] Other problems may include meticillin-resistant *Staph. aureus* infections; intravenous teicoplanin has been used, as have oral doxycycline or linezolid where sensitivity patterns permit.[28] The possibility of fungal or viral infections should also be considered.[28]

Nutritional management of cystic fibrosis should ensure adequate calorie intake from a balanced diet in order to counteract malabsorption due to pancreatic insufficiency and the increased metabolic requirements of patients with cystic fibrosis.[38,39] Supplements of the fat-soluble vitamins A, D, and E, and sometimes vitamin K, may be necessary. Investigation of bone mineral density[40] and direct assessment of vitamin status[41] suggest that current supplements may be inadequate. Pancreatic enzymes, as pancreatin or pancrelipase, are taken before or with each meal or snack.[42]

Many **other interventions** have been tried.[43,44]

Bronchodilators including both beta agonists and antimuscarinics may be useful in selected patients although there are few meaningful results from clinical studies.[45] A therapeutic trial is often justified in individual patients since it is difficult to predict which patients will respond.[43] While use by nebuliser is regarded as most effective, inhalers may be more practical where compatibility with other nebulised drugs could be a problem.[44] $Alpha_1$-proteinase inhibitor, the main inhibitor of neutrophil elastase in the lung has also been investigated[46] as has pentoxifylline,[47] a drug with anticytokine activity. Although cysteinyl leukotrienes have been found in increased concentrations in airway secretions of patients with cystic fibrosis and thought to contribute to lung disease, there is insufficient evidence to recommend the routine use of leukotriene inhibitors and antagonists (such as montelukast) to improve lung function and reduce exacerbations.[10]

Treatment aimed at modifying the pulmonary disease process rather than treating the disease symptoms has also included ion transport therapy. This involves the use of drugs that either inhibit sodium ion absorption across airway epithelia (for example the sodium channel blocker amiloride) or induce chloride ion secretion. However, nebulised amiloride was not found to be a useful adjunct in patients on optimal treatment.[48] The use of oral ivacaftor, a CFTR potentiator that increases chloride ion transport, has been shown to improve lung function in patients with a G551D mutation in the CFTR gene.[49]

In patients with severe lung disease, oxygen therapy may give some relief of symptoms but its effect on mortality and morbidity is uncertain.[50] At present the only available treatment for patients with end stage pulmonary disease is lung transplantation. Although individuals with cystic fibrosis do as well as those referred for transplantation with other lung diseases, the 5-year survival rate after the procedure is reported to be only 50%.[1]

Somatic **gene therapy** represents the nearest approach to a cure for cystic fibrosis.[51] It aims to introduce the normal CFTR gene sequence into cells of affected tissue. Most effort has been directed at gene delivery to the lungs using adenovirus vectors or liposomes, but results have been variable.[52-55] Difficulties encountered include inefficient gene transfer, immunity to viral vectors, and a systemic inflammatory reaction provoked by plasmid DNA. For a discussion of the general principles of gene therapy, see p. 2511.2.

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Diarrhoea, infective

See Gastro-enteritis, p. 184.2.

Diphtheria

Diphtheria is an acute infection with the Gram-positive aerobe *Corynebacterium diphtheriae*, some strains of which produce an exotoxin. It occurs worldwide and is endemic to many countries. The efficacy of immunisation (see Diphtheria Vaccines, p. 2382.3) has rendered the disease rare in most developed countries, but infection is still common in parts of the world with low rates of immunisation. Although the risk to travellers is said to be low, diphtheria should be considered in patients returning from endemic areas with a sore throat; most cases occur in those who are unvaccinated or inadequately immunised.

Diphtheria has an incubation period of about 1 to 5 days;[1-3] onset of symptoms is gradual. These range from a moderately sore throat, low-grade fever, and swollen glands, to more serious manifestations caused by the exotoxin from toxigenic strains. The exotoxin causes local destruction of mucous membranes and epithelium, leading to the formation of a characteristic adherent pseudomembrane that coats the tonsillopharyngeal region and may obstruct the upper airways. Swelling of the neck occurs in severe cases. Toxin can be absorbed systemically, resulting in damage to cardiac, renal, hepatic, and neural tissue.[2,3] Respiratory diphtheria has a mortality rate of 5 to 10% even when treated. Cutaneous diphtheria, characterised by chronically infected skin lesions, is usually caused by non-toxigenic strains and has fewer complications.

Diphtheria is highly contagious and patients should be isolated.[1] Treatment of respiratory infection is mainly with antitoxin (see p. 2382.2).[1,4] Parenteral benzylpenicillin or erythromycin are also given to eliminate *C. diphtheriae*, thereby terminating toxin production and preventing the spread of infection to contacts.[1,4] Penicillin or erythromycin may be given orally once the patient is able to swallow comfortably. Antibacterials should be given for a total of 14 days; those who continue to harbour the bacteria should be treated for a further 10 days. Infection with diphtheria does not always confer immunity, therefore those recovering from the disease should also receive active immunisation.[3] Cutaneous infection is treated similarly, although antitoxin is of benefit only if very large ulcers are present. Close contacts of primary cases of diphtheria, and those in the community identified as asymptomatic carriers, may be given a 7-day prophylactic course of erythromycin orally or a single intramuscular dose of benzylpenicillin,[1] in addition to boosters or primary immunisation with diphtheria vaccine. Cultures should be taken 24 and 48 hours after stopping therapy to confirm eradication.[1] Epidemics are most effectively controlled by mass immunisation of the entire population.[2,3]

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Ear infections

See Otitis Externa, p. 197.1, and Otitis Media, p. 197.2.

Ehrlichiosis

Ehrlichioses are a group of diseases produced by infection with rickettsia-like bacteria of the family Anaplasmataceae, a family that contains the genera *Anaplasma, Ehrlichia, Neorickettsia,* and *Wolbachia.* At one time such organisms were considered to be only animal pathogens but it is now recognised that humans may also become infected.[1-8] One of the earliest human forms of ehrlichiosis identified was Sennetsu fever, a disease found in Japan and Malaysia, and which is caused by *N. sennetsu* (*E. sennetsu*). Subsequently *Anaplasma phagocytophilum* (*E. phagocytophila*), *E. chaffeensis, E. ewingii,* and possibly *E. canis* have emerged as tick-borne human pathogens.

E. chaffeensis mainly infects mononuclear cells and in humans the resulting disease is commonly called human monocytic (or monocytotropic) ehrlichiosis (HME) whereas *A. phagocytophilum* mainly infects granulocytes and in humans produces human granulocytic (or granulocytotropic) ehrlichiosis (HGE), now also known as human granulocytic anaplasmosis (HGA). *E. ewingii* and *E. canis* mainly infect granulocytes and mononuclear cells respectively.

Some patients with HGA may also be co-infected with *Borrelia burgdorferi,* the cause of Lyme disease, and/or *Babesia microti,* the cause of babesiosis, as they are all transmitted by tick bites from the same *Ixodes* spp. For details on the treatment of patients with HGA co-infected with Lyme disease, see p. 192.1.

Human ehrlichiosis is characterised by fever, headache, myalgia, and malaise. Laboratory findings include leucopenia, thrombocytopenia, and elevated liver enzymes.[1,2] Symptoms more commonly seen in patients with HME are gastrointestinal disturbances, cough, confusion, and skin rash. HME is a relatively severe infection and patients may require hospitalisation for complications such as acute respiratory distress, coagulopathy, hepatitis, hepatic failure, meningoencephalitis, acute renal failure, and shock. Fulminant infections may give rise to other opportunistic infections, particularly in immunocompromised patients. Fatalities have been reported in 2 to 3% of patients with HME. Clinical symptoms of infections with *E. ewingii* or *A. phagocytophilum* are generally similar to those of *E. chaffeensis*[3,4] although usually less severe. Cough, confusion, and skin rash have not been seen with infections caused by *E. ewingii* and most cases have been diagnosed in immunocompromised patients; no deaths have been reported. HGA is generally a mild, self-limiting disease, but may be severe in about 5 to 7% of patients and reported fatalities are less than 1%. Most severe cases have been diagnosed in immunocompromised patients. Skin rash, gastrointestinal and respiratory disturbances, and CNS involvement are less frequent with HGA.[1]

Prompt **treatment** is recommended[9] due to the potential for serious complications. Treatment for all infections is with a tetracycline, preferably doxycycline, given for 7 to 10 days or for at least 3 days after the patient has become afebrile. Chloramphenicol has been used as an alternative for HME, although its efficacy is controversial and it should not be considered as a first-line treatment.[1,5] It is also not effective against *A. phagocytophilum in vitro.* Despite the known adverse effects of doxycycline in children, the American Academy of Pediatrics[10] and the Infectious Diseases Society of America (IDSA)[11] state that a shortened course may be given to those who are less than 8 years of age who are severely ill and not co-infected with Lyme disease; the dose is 4 mg/kg daily in two divided doses (to a maximum of 100 mg/dose) and should be given for at least 3 days after the patient has become afebrile. Successful treatment of HGA with rifampicin has been reported in pregnancy (gestational age of 10 to 36 weeks)[12] and in 2 children with non-life-threatening infection.[13] The IDSA[11] recommends that patients with mild disease who cannot be given a tetracycline may be given rifampicin 300 mg twice daily for 7 to 10 days; children may be given 10 mg/kg twice daily. Antibacterial susceptibility testing has suggested that rifamycins and fluoroquinolones are promising alternatives in the treatment of HGA.[14]

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Endocarditis

Infective endocarditis[1-3] is an infection of the endocardium after invasion of the bloodstream by bacteria or fungi, and particularly affects the heart valves. Infection has traditionally been classified as acute or subacute; however, changes in the clinical spectrum of infection have meant that some now prefer to classify it into the categories:[1,4]

- native-valve endocarditis (often associated with congenital or chronic rheumatic heart disease, and classically due to streptococci although cases due to staphylococcal infection are increasingly frequent)
- prosthetic valve endocarditis (which may occur early, within 60 days of surgery, which is often due to staphylococci, or late, in which case it is often due to streptococci or more exotic organisms such as the HACEK group)
- endocarditis in intravenous drug users (usually associated with infection by skin pathogens, especially *Staphylococcus aureus*)
- nosocomial endocarditis (related to catheter implantation or other invasive medical or surgical procedures; it is usually due to staphylococci or enterococci and has a high mortality rate). An increasing incidence is also seen in patients undergoing haemodialysis

Treatment of infective endocarditis is essential, as infection can result in heart failure, embolisation and infarction of major organs, and death. Diagnosis is often difficult as many of the symptoms (which include fever, malaise, headache, petechiae, and splinter haemorrhages under the nails) are non-specific. A set of diagnostic criteria known as the Duke criteria have been developed, and some modifications subsequently proposed.[4,5] The Duke criteria identify endocarditis mainly on the basis of microbiological data (blood culture of the infecting organism) and anatomical lesions of the valves (identified by echocardiography or the development of new valvular regurgitation); minor criteria such as development of fever, or presence of predisposing conditions such as heart defects or intravenous drug use, are also considered.[4,5]

Virtually any organism can cause endocarditis but streptococci, enterococci, and staphylococci continue to be major culprits.

- Among the commonest causes are the alpha-haemolytic *streptococci* originating mainly from the mouth and throat; they have been called viridans streptococci or even '*Streptococcus viridans*' (although this is not a true species) and include *Str. mitis, Str. mutans, Str. oralis, Str. salivarius,* and *Str. sanguis.* Other streptococci originate in the gut and include *Str. bovis.*
- Also increasingly common is endocarditis due to *staphylococci* such as *Staphylococcus aureus,* a common cause in intravenous drug abusers, but endocarditis may also be caused by coagulase-negative *staphylococci,* particularly *Staph. lugdunensis.* Prosthetic valve infection is often caused by *Staph. epidermidis* or other staphylococci.
- *Enterococci* (faecal streptococci) originate in the gut and include *Enterococcus faecalis* and, to a lesser extent, *E. faecium.* Endocarditis due to any of these bacteria is commonly subacute or insidious.

Less common causes of endocarditis include:[3,4,6]

- Gram-negative bacteria such as the Enterobacteriaceae and
- *Pseudomonas* spp.
- the HACEK group of slow-growing organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*)
- the rickettsia *Coxiella burnetii* (the cause of Q fever, p. 204.1)
- *Bartonella* spp. (also formerly classified as rickettsia)
- fungi such as *Candida* and *Aspergillus* (see p. 565.3).

Guidelines for the treatment and prophylaxis of endocarditis have been issued by bodies in many countries. Although some common principles can be identified, recommendations must be localised because of differences in patterns of infection and drug resistance, variations in the availability of antibacterials and local policies for their use, and differences in medical practice. Countries also vary in the degree to which such guidelines are accepted in practice.

Endocarditis treatment.

Treatment of endocarditis relies on prompt identification of the infecting organisms and their sensitivity to antibacterials. Three sets of blood cultures, each from a separate venepuncture, should be taken before antimicrobial treatment is started; MICs for the causative organism should be measured. As already mentioned, guidelines vary,[7-10] but in general:

- a microbicidal antibacterial, or combination of antibacterials, should be used for treatment; many regimens are based on a beta-lactam or glycopeptide plus an aminoglycoside
- treatment should be given at high doses, and by the intravenous route
- except in the most sensitive infections, treatment should be given for at least 4 weeks (or at least 6 weeks if the patient has prosthetic valves or other prosthetic material implanted in the heart)
- ideally, it is preferable to wait for the results of blood culture before starting therapy; however, empirical treatment is given to patients presenting with acute or severe disease
- associated complications such as heart failure should be managed appropriately; management may include referral for early surgical intervention

If *empirical treatment* is to be given until the laboratory results are known, then it is most likely to be with gentamicin plus benzylpenicillin, ampicillin, or amoxicillin.[8] An isoxazolyl penicillin (cloxacillin, dicloxacillin, flucloxacillin, or oxacillin) may be added,[7] or used instead in more severe or acute presentations;[8] ampicillin with sulbactam or amoxicillin with clavulanic acid have also been recommended.[9] Vancomycin with[9] or without ciprofloxacin[7,8] is likely to be the antibacterial of choice in penicillin-allergic patients requiring empirical treatment. Vancomycin may be used empirically with an aminoglycoside and rifampicin in patients with prosthetic valves[8,9] or where penicillin resistance is suspected.[8]

Once the causative organism and its antibacterial susceptibility have been identified, appropriate *pathogen-directed* therapy may be begun.

- **Streptococcal endocarditis**. Streptococci vary in their susceptibility to penicillin, and guidelines generally divide regimens according to whether the organism is of low, intermediate, or high penicillin resistance, although at what MIC these categories are defined varies between guidelines.

  For uncomplicated cases of infection with the most *penicillin sensitive streptococci,* benzylpenicillin may be used, with or without gentamicin[7-10] or netilmicin.[9] Typically, if used alone in native-valve infection it would be given for 4 weeks, whereas the combination regimen is given only for 2 weeks.[7-10] Indicative doses would be 1.2 to 2.4 g of benzylpenicillin every 4 or 6 hours, and gentamicin 1 mg/kg every 8 hours or as a single daily dose of 3 mg/kg. Ceftriaxone[8-10] or vancomycin[7-10] may be considered as an alternative, although these are more often given to treat less sensitive strains, or in patients unable to tolerate penicillin.

  For *streptococci less sensitive to penicillin* benzylpenicillin may be given as above but for 4 to 6 weeks,[7-9] usually with gentamicin for at least the first 2 weeks. Alternatively, 4 weeks of treatment with ceftriaxone or vancomycin may be considered.[8-10] Typical doses are 2 g daily of ceftriaxone as a single injection, or 30 mg/kg of vancomycin daily (up to a usual maximum of 2 g daily), in 2 divided doses.

  For *penicillin resistant streptococci* treatment is similar to that for enterococcal endocarditis.[7-9] A combination of vancomycin and gentamicin may be given for 4 to 6 weeks. Streptomycin is a possible alternative to gentamicin for *gentamicin resistant* isolates.[8]

  For *streptococci in penicillin-allergic patients,* vancomycin for 4 to 6 weeks may be given;[9,10] UK guidelines advise 4 weeks of treatment combined with gentamicin for the first 2 weeks.[8] Teicoplanin, typically in doses of 6 to 10 mg/kg daily (higher loading doses should be given initially to establish a suitable trough concentration) is a possible alternative to vancomycin.[8]

  For patients with *prosthetic valve endocarditis,* a regimen similar to that for less sensitive streptococci (above) has been suggested, given for at least 6 weeks.[8-10]
- **Staphylococcal endocarditis**. The treatment of staphylococcal endocarditis is based on the use of an isoxazolyl penicillin or a glycopeptide. In contrast to streptococcal or enterococcal endocarditis, the benefits of adding an aminoglycoside are uncertain, and guidelines differ in whether they recommend this. Combination therapy is recommended where prosthetic valves or other intracardiac prostheses are present.

  For *meticillin sensitive staphylococci,* typically an isoxazolyl penicillin (such as flucloxacillin) is given in a dose of

2 g every 4 to 6 hours for at least 4 weeks.[7-10] Some guidelines continue to recommend addition of gentamicin for the first 3 to 5 days of therapy.[9,10] Patients with right-sided endocarditis due to intravenous drug abuse may respond to shorter courses of 2 weeks of combination therapy with an isoxazolyl penicillin plus gentamicin.[8,10]

For *staphylococci resistant to meticillin/oxacillin*, vancomycin may be given alone for 6 weeks,[7,10] or with rifampicin or perhaps gentamicin or sodium fusidate (depending on sensitivity) for at least 4 weeks.[8,9] Such combinations may also be appropriate in patients with *penicillin allergy*. Teicoplanin should not be used as the reported incidence of treatment failure is unacceptably high.[8]

For *staphylococcal endocarditis in the presence of intracardiac prostheses* either an isoxazolyl penicillin or vancomycin may be used with rifampicin or gentamicin or both; an indicative regimen might be intravenous doses of 2 g of the penicillin every 4 to 6 hours, or 1 g of vancomycin every 12 hours, plus rifampicin 300 mg orally every 8 hours, both given for at least 6 weeks, plus gentamicin 1 mg/kg intravenously every 8 hours (or as a single daily dose of 3 mg/kg) for the first 2 weeks.[8-10] Gentamicin may be given for the entire period of treatment if the infection is due to more recalcitrant strains of meticillin-resistant *Staph. aureus* or coagulase-negative staphylococci.[8]

- **Enterococcal endocarditis**. Treatment of enterococcal endocarditis is based on combinations of an aminoglycoside with another antibacterial, usually a beta lactam or a glycopeptide, depending on the sensitivity of the isolated organism.

  For *gentamicin sensitive, penicillin sensitive enterococci*: intravenous bolus injections of ampicillin or amoxicillin 2 g (or benzylpenicillin 2.4 g) every 4 hours and gentamicin 1 mg/kg every 8 or 12 hours (or as a single daily dose of 3 mg/kg), both given for at least 4 weeks.[7,8,10]

  If the patient is *allergic to penicillin*, or the isolate is *penicillin resistant but gentamicin sensitive*, then a combination of vancomycin or teicoplanin with gentamicin may be given for at least 4 weeks.[7-10]

  For *enterococci with high level gentamicin resistance*, a penicillin as above may be used with streptomycin 7.5 mg/kg twice daily (intramuscularly or intravenously) for at least 4 weeks.[8,10] If there is also *penicillin resistance*, or the patient is *penicillin allergic*, streptomycin as above may be given with vancomycin or teicoplanin.[8] If streptomycin cannot be used then more prolonged treatment courses should be given for at least 8 weeks.[8,9] Endocarditis due to *multiply resistant enterococci* not susceptible to penicillin, gentamicin, or vancomycin, is still infrequent and there seem to be no established regimens; options may include the use of linezolid, daptomycin, tigecycline, or quinupristin/dalfopristin where available.[7-10] A combination of ampicillin with ceftriaxone[9,10] or imipenem,[10] given for at least 8 weeks, has been suggested for multiply resistant *E. faecalis* infection.
- **HACEK endocarditis**. The HACEK organisms are slow and difficult to culture and treatment must often, therefore, be empirical. Traditionally, treatment for this group of organisms was based on ampicillin and gentamicin. However, because of the emergence of beta-lactamase producing strains, empirical treatment is now based on beta-lactamase-stable cephalosporins.

  Preferred treatment for native-valve endocarditis due to HACEK organisms is therefore with intramuscular or intravenous ceftriaxone (usually in a dose of 2 g once daily) for 4 weeks,[7-10] although cefotaxime[7] or other third-generation cephalosporin[9,10] may be used instead. UK guidelines recommend addition of gentamicin for the first 2 weeks of therapy.[8] Alternatively, if the isolate is penicillin sensitive, ampicillin plus 2 to 4 weeks of gentamicin,[8,9] or ampicillin-sulbactam[10] have been suggested. Some guidelines consider that a fluoroquinolone such as ciprofloxacin for 4 weeks, orally or intravenously, may also be effective.[9,10]
- **Endocarditis due to other organisms**. Treatment of endocarditis due to other organisms depends greatly on the organism and its susceptibility; early surgery is often required. For endocarditis due to *Pseudomonas* spp. a combination of an antipseudomonal beta lactam with tobramycin has been suggested.[9] Endocarditis associated with the intracellular pathogen *Coxiella burnetii* requires very prolonged oral therapy (see Q-fever, p. 204.1) with doxycycline,[8,9] in combination with hydroxychloroquine[9] or a fluoroquinolone (such as ciprofloxacin or ofloxacin).[8,9] Regimens suggested for *Bartonella* endocarditis have included a penicillin (or ampicillin with sulbactam) or ceftriaxone in combination with gentamicin or netilmicin, or doxycycline plus gentamicin.[8-10] For other potential causes of culture-negative endocarditis, empirical treatment with a penicillin or vancomycin plus gentamicin, sometimes in combination with a third antibacterial such as rifampicin or ciprofloxacin, has been suggested.[10]

Endocarditis prophylaxis.

Because of the potentially severe consequences of endocarditis, antibacterial prophylaxis was widely practised in patients considered to be at increased risk when they were exposed to procedures likely to produce bacteraemia. Much of the evidence to support the practice was circumstantial and the benefits and risks were therefore hard to calculate. Revision of this practice in recent years has resulted in a major shift of emphasis away from giving antibacterial prophylaxis to all at-risk patients, to recommending prophylaxis for high-risk patients only. Guidelines[9,11-15] have been periodically issued to guide the selection of patients considered to be at high risk for endocarditis, the high-risk procedures requiring prophylaxis, and the antibacterial to be used; recommendations may vary considerably between countries.

Patients generally considered to be at risk of developing endocarditis include those with:

- acquired valvular heart disease, including valve disease in patients who have received a cardiac transplant
- some types of congenital heart disease
- hypertrophic cardiomyopathy
- prosthetic valves or pulmonary shunts
- a history of endocarditis

Procedures that were thought likely to produce bacteraemia and therefore to require prophylactic treatment included any dental intervention likely to cause bleeding, other oral or upper-respiratory tract operations such as tonsillectomy, certain gastrointestinal procedures such as sclerotherapy for oesophageal varices or biliary-tract surgery, and some urinary-tract surgery. Whether prophylaxis is truly needed before dental procedures is a subject of controversy. A systematic review[16] concluded there was no evidence that antibacterial prophylaxis was effective or ineffective against bacterial endocarditis in people at risk undergoing an invasive dental procedure. US guidelines[12,14] recommend antibacterial prophylaxis only for dental procedures that involve manipulation of gingival tissues or periapical region of teeth, or perforation of oral mucosa in patients considered to be at the highest risk of developing adverse outcomes from endocarditis (such as those with a history of infective endocarditis, cardiac valve replacement surgery, or some patients with congenital heart disease). US guidelines also recommend antibacterial prophylaxis for high-risk patients for procedures on infected skin, skin structures, or musculoskeletal tissue, but do not recommend standard prophylaxis for respiratory, genito-urinary or gastrointestinal tract procedures.[14] Similar recommendations were made in the UK by the British Society for Antimicrobial Chemotherapy (BSAC) in 2006[11] for high-risk patients undergoing invasive dental procedures, but the BSAC was more cautious in modifying the guidance for respiratory, gastrointestinal, and genito-urinary procedures. Subsequent guidelines issued by NICE[13] and adopted by the *BNF* essentially abolished the requirement for standard antibacterial prophylaxis in any procedure. In 2009 the Task Force on Infective Endocarditis of the European Society of Cardiology[9] also reduced the number of indications for prophylaxis. Their guideline for antibacterial prophylaxis before dental procedures is similar to that for the US and UK (BSAC) and standard prophylaxis is also not generally recommended for respiratory, genito-urinary, or gastrointestinal tract procedures. Most guidelines still recommend appropriate antibacterial prophylaxis for high-risk patients undergoing invasive respiratory, gastrointestinal, or genito-urinary procedures to treat an established infection or where pre-existing infection is suspected.[9,12-14]

Antibacterial prophylaxis is aimed mainly at viridans streptococci and HACEK organisms before dental, oral, respiratory, and oesophageal procedures, and at enterococci, *Strep. bovis*, and the Enterobacteriaceae before gastrointestinal and genito-urinary procedures. Drugs should be given in a regimen that assures adequate blood concentrations throughout the procedure. They are generally given as a single dose before the procedure; the oral route is used if possible.

- A penicillin such as amoxicillin is the basis for prophylactic therapy, typically in a single dose of 2 to 3 g orally or 1 to 2 g intravenously or intramuscularly.[9,11,14,15] For *dental* procedures it may be replaced, in patients allergic to penicillin or who have received more than a single dose in the previous month, by clindamycin 600 mg orally or 300 to 600 mg intravenously, or by azithromycin or clarithromycin 500 mg orally. Doses should be given 30 to 60 minutes before the procedure.[9,11,14]
- For *gastrointestinal* or *genito-urinary* procedures the penicillin is usually combined with a single dose of gentamicin 1.5 or 2 mg/kg intravenously or intramuscularly before the procedure; a second dose of amoxicillin (typically half the initial dose) may be given after 6 hours. In patients allergic to penicillin, or who have received more than a single dose of penicillin in the previous month, amoxicillin may be substituted with an infusion of 1 g of vancomycin over 1 to 2 hours before the procedure,[15] or injection of 400 mg of teicoplanin immediately beforehand.[7,9,11]
- For *nasal packing and intubation* flucloxacillin 1 g intravenously is given; in penicillin allergic patients clindamycin 600 mg intravenously may be used.[11]
- For *infected skin, skin structure, or musculoskeletal tissue* procedures a penicillin such as amoxicillin is usually given in a single oral or intravenous dose of 2 g, or a cephalosporin such as cefalexin is given in a single oral dose of 2 g. Vancomycin or clindamycin may be given to patients allergic to penicillin or who are known or suspected of having an infection caused by a meticillin-resistant strain of staphylococcus.[12,14]

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Endometritis

Endometritis (or endomyometritis) is an infection of the endometrium and can be divided into obstetric and non-obstetric, acute and chronic endometritis. It is thought to result from an ascending infection from the lower genital tract. Spread occurs from there to the tubes and ovaries. In non-obstetric patients it may be a part of pelvic inflammatory disease (p. 198.3) or due to invasive gynaecologic procedures, while in obstetric patients it may be a postoperative complication of caesarean section. Symptoms include uterine tenderness, abdominal or pelvic pain, dyspareunia, dysuria, fever, malaise, and abnormal vaginal bleeding or discharge (including foul-smelling lochia in obstetric patients).

Endometritis is a polymicrobial disease usually involving 2 to 3 organisms some of which are found in the normal vaginal flora. Common causative organisms include Gram-positive cocci (such as *Staphylococcus* spp. and *Streptococcus* spp.), Gram-negative bacteria (such as *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Gardnerella vaginalis, Neisseria* spp.), anaerobes (such as *Bacteroides* spp. *Peptostreptococcus* spp.), and other organisms such as *Mycoplasma* spp., *Ureaplasma* spp., and *Mycobacterium tuberculosis*.

Women undergoing caesarean section are reported to have a 5 to 20-fold greater chance of infection than women who give birth vaginally and the incidence of endometritis for caesarean deliveries ranges from 20 to 85%. Antibacterial **prophylaxis** may be given at caesarean section to prevent postpartum endometritis as well as wound and urinary-tract infections. A systematic literature review[1] has shown prophylaxis to be beneficial after both elective and non-elective caesarean section; endometritis was reduced by two-thirds to three-quarters irrespective of whether the antibacterials were given before or after clamping of the umbilical cord. Traditionally prophylactic antibacterials for caesarean delivery have been given at cord clamping, but a meta-analysis provided evidence that prophylaxis given before skin incision significantly decreased the incidence of postpartum endometritis and other infectious morbidities, without affecting neonatal outcomes.[2]

Many different drug regimens have been reported to be effective in reducing postoperative infection but it is not clear if there is a drug of choice. Furthermore, differences in how prophylactic antibacterials have been given have been noted. A systematic review[3] to evaluate prophylactic antibacterial regimens used for caesarean section found that ampicillin and first-generation cephalosporins were appropriate. Extended-spectrum penicillins, second- or third-generation cephalosporins, and combination regimens were not more effective; there was also no evidence to suggest that a multiple-dose regimen was more effective than a single-dose regimen. Clindamycin was considererred to be an appropriate alternative for penicillin-allergic women.

Patients with endometritis should be **treated** with broad-spectrum antibacterials. For postpartum endometritis (also known as puerperal fever), intravenous gentamicin and clindamycin are appropriate.[4] A second- or third-generation cephalosporin plus metronidazole; or amoxicillin (or ampicillin) with gentamicin and metronidazole are alternatives; co-formulated ampicillin with sulbactam can be used as monotherapy. Doxycycline should be used if *Chlamydia* is suspected to be the causative organism. In most cases improvement is usually seen within 48 to 72 hours. Parenteral therapy is continued until the patient has been afebrile for longer than 24 hours; oral therapy is not necessary after successful intravenous therapy.[4]

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Enterococcal infections

Although enterococci are part of the normal intestinal flora they may also be responsible for serious infections. The genus *Enterococcus* includes at least 12 species with *Enterococcus faecalis* (formerly *Streptococcus faecalis*) and *E. faecium* being responsible for the majority of human infections. Infections commonly caused by enterococci include urinary-tract infections, endocarditis, bacteraemia, catheter-related infections, surgical wound infections, and intra-abdominal and pelvic infections; less commonly enterococci may infect the bone, joints, and the meninges.

Despite not being particularly pathogenic in humans, infections due to enterococci are of increasing concern because of drug resistance[1-7] The most significant types of resistance in the enterococci are:

- high-level resistance to the aminoglycosides
- ampicillin resistance caused by beta-lactamase production
- glycopeptide resistance including vancomycin resistance
- multidrug resistance to ampicillin, aminoglycosides (high-level resistance), and glycopeptides

Enterococci have both intrinsic resistance and the ability to acquire new mechanisms of resistance to antibacterials; although some species (such as *E. faecium*) are more intrinsically resistant than others.[3,6] Enterococci are intrinsically resistant to beta lactams (particularly cephalosporins and penicillinase-resistant penicillins), low concentrations of aminoglycosides, clindamycin, co-trimoxazole, and fluoroquinolones.[1,3] They also have acquired resistance to high concentrations of beta lactams and aminoglycosides, the glycopeptides (vancomycin and teicoplanin), chloramphenicol, erythromycin, fluoroquinolones, fusidic acid, nitrofurantoin, rifampicin, and tetracyclines.[3] At least 6 types of acquired vancomycin resistance have been described[6] (see also p. 389.1); those causing concern are VanA enterococci as they show high-level resistance to vancomycin and cross-resistance to teicoplanin and VanB organisms, which are resistant to a range of vancomycin concentrations but retain susceptibility to teicoplanin.[3,5,6] The epidemiology of vancomycin-resistant enterococci (VRE)[3-5] and resultant antibacterial prescribing practices differ between North America and Europe;[3] the USA has much higher rates of VRE than anywhere in Europe.[3,5-7]

Unusual patterns of susceptibility and drug and multidrug resistance make treatment of an infection difficult. Antibacterials must be chosen according to local patterns of resistance and antibacterial sensitivity tests.[2,3] In general, uncomplicated enterococcal infections, such as urinary-tract infections, tend to be treated with ampicillin, benzylpenicillin, or vancomycin.[1,5] For more serious enterococcal infections, including bacteraemia, meningitis, and endocarditis, an aminoglycoside (such as gentamicin or streptomycin) is added unless there is high-level resistance.[5] For penicillin-allergic patients or in treatment of ampicillin-resistant strains of bacteria vancomycin is given with an aminoglycoside.[1,3,5,6]

Benzylpenicillin and ampicillin are an option for patients infected with VRE isolates that still retain susceptibility.[2] However, most are resistant to benzylpenicillin and ampicillin and the choice of antibacterial is therefore limited to those introduced more recently into clinical practice such as quinupristin/dalfopristin or linezolid. Both these drugs have activity against vancomycin-resistant *E. faecium* infections and linezolid also has activity against non-*E. faecium* species, but most *E. faecalis* and non-*E. faecium* isolates are intrinsically resistant to quinupristin/dalfopristin.[1-3,6] Acquired resistance has been reported to quinupristin/dalfopristin[1] and linezolid-resistant enterococci have emerged[2,8,9] and spread nosocomially.[2] Daptomycin and tigecycline have *in-vitro* activity against VRE but clinical data on the treatment of VRE infections are lacking;[2] resistance to daptomycin has been reported.[10-12] The second generation glycopeptides, oritavancin and telavancin, are also often bactericidal against enterococci and although resistance to these newer drugs is rare, it has been documented.[6] Many VRE isolates are susceptible to nitrofurantoin, which has been used to treat lower urinary-tract infection but is not suitable for treating other VRE infections.[1,2] Dalbavancin is active against glycopeptide-resistant enterococci with the VanB phenotype, but has little activity against the more common VanA phenotype.[2] Chloramphenicol may be effective against VRE (see Enterococcal Infections, p. 260.1). Ramoplanin, ketolides,[3] and the mannopeptimycins (a new class of glycopeptides)[2] are being studied as further treatment options. In general, there are no effective antibacterials available to eradicate VRE in those colonised with the organism.[1,2]

A few cases of horizontal transfer of the vanA gene from vancomycin-resistant *E. faecalis* to MRSA, creating MRSA with high-level resistance to vancomycin, have been documented in hospitalised patients mainly in the USA,[4,7] The lack of effective antibacterials has placed emphasis on measures to prevent the spread of vancomycin-resistant enterococci;[13] without extensive control measures, large-scale emergence of vancomycin-resistant *S. aureus* (VRSA) may occur.[4]

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Epididymitis

Epididymitis is often associated with urethritis, and in young men (less than 35 years) occurs most commonly as a complication of sexually transmitted infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, but may occur in homosexual males as a result of infection with enteric organisms, particularly *Escherichia coli*.

In men over 35 years and in children, epididymitis is not usually sexually transmitted but generally results from bacteriuria secondary to urinary-tract infection with *Pseudomonas aeruginosa* and other Gram-negative bacilli, urinary-tract instrumentation or surgery, systemic disease, or immunosuppression.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of epididymitis are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- **WHO:**
  for chlamydial epididymitis:
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single dose of oral azithromycin 1 g

  alternatives, given for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily

  Unless it can be excluded, patients should also be treated concurrently for gonorrhoea (p. 206.2).
- **UK:**
  for disease most probably due to any sexually-transmitted pathogen:
  - a single intramuscular dose of ceftriaxone 500 mg, *plus* oral doxycycline 100 mg twice daily for 10 to 14 days

  for probable chlamydial infections or infections with other non-gonococcal organisms:
  - oral doxycycline 100 mg twice daily for 10 to 14 days, *or*
  - oral ofloxacin 200 mg twice daily for 14 days

  for infections most probably due to enteric organisms:
  - oral ofloxacin 200 mg twice daily for 14 days, *or*
  - oral ciprofloxacin 500 mg twice daily for 10 days

  in patients allergic to cephalosporins and/or tetracyclines infections from all causes may be treated with:
  - oral ofloxacin 200 mg twice daily for 14 days
- **USA:** empirical treatment recommended:
  recommended initial treatment:
  - a single intramuscular dose of ceftriaxone 250 mg *plus* oral doxycycline 100 mg twice daily for 10 days

  additional therapy if likely cause of infection is possibly an enteric organism:
  - oral ofloxacin 300 mg twice daily for 10 days, *or*
  - oral levofloxacin 500 mg once daily for 10 days

Sexual contacts should also be treated if epididymitis is caused by a sexually transmitted pathogen.[2,3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[3]

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Epiglottitis

Epiglottitis (or supraglottitis) is an inflammation of the epiglottis and adjacent structures that may occur at any age. It is a potentially life-threatening condition in which previously healthy persons may develop sudden upper airway obstruction within hours. Symptoms include severe sore throat, fever, dysphagia, drooling, distress, and inspiratory stridor. It is often due to bacteraemic infection with *Haemophilus influenzae* type b (see p. 188.2); other bacteria implicated include *H. parainfluenzae, Streptococcus pneumoniae, Pasteurella multocida, Staphylococcus aureus,* beta-haemolytic streptococci, *Branhamella catarrhalis,* and *Klebsiella pneumoniae.* Epiglottitis may also be caused by viruses, fungi, and mechanical injury. Traditionally epiglottitis has occurred mainly in young children, and although the incidence has decreased in this age group since the introduction of a vaccine,[1] cases due to *H. influenzae* still occur in young unvaccinated children, particularly in resource-poor countries. Acute epiglottitis is being increasingly seen in adults.[1-4]

Treatment and prophylaxis is similar to that for Haemophilus influenzae meningitis (see under Meningitis, p. 193.1). Immediate management includes the maintenance of an adequate airway and the intravenous use of antibacterials active against *H. influenzae* type b and other likely causative organisms. Chloramphenicol has been the drug of choice, but second- or third-generation cephalosporins such as cefuroxime, cefotaxime, and ceftriaxone with or without metronidazole are increasingly used.[1,2,4-7] Other intravenous antibacterials that have been used include amoxicillin with clavulanic acid, ampicillin with sulbactam, aminoglycosides, and erythromycin;[2,4,6] oral amoxicillin with clavulanic acid has been given as maintenance therapy.[4] Corticosteroids have been given to reduce mucosal oedema, although there are no data to prove any benefit.[6,7] Prophylaxis with rifampicin may be given to index cases and contacts (see Meningitis Prophylaxis under Rifampicin, p. 353.2).

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Escherichia coli enteritis

See p. 186.3.

Eye infections

Conjunctivitis is a common superficial eye disorder and may be caused by infection with bacteria, viruses, or, less often, fungi. Acute bacterial conjunctivitis is often caused by staphylococci or streptococci in adults, and *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) in children. Other causes of bacterial conjunctivitis include gonococci (see Gonorrhoea, p. 206.2) and *Chlamydia trachomatis* (see Trachoma, p. 212.1). Neonatal chlamydial and gonococcal conjunctivitis are discussed under Neonatal Conjunctivitis, p. 195.2. Uncomplicated bacterial conjunctivitis may be self-limiting but empirical treatment with topical antibacterials is often given. In the UK, topical chloramphenicol remains the treatment of choice despite concerns over the potential risk of aplastic anaemia (see Ocular Use under Precautions of Chloramphenicol, p. 260.3). Alternatives include gentamicin, tobramycin, erythromycin (especially when infection with Gram-positive organisms is suspected), fluoroquinolones including ciprofloxacin and ofloxacin, framycetin, fusidic acid (especially for staphylococcal infections), and polymyxin B in combination with bacitracin, trimethoprim, or neomycin.

Blepharitis is an infection of the lid margins. It usually presents as a chronic condition and may require prolonged treatment, typically involving local hygiene to remove encrustations and topical application of a broad-spectrum antibacterial ointment.

Keratitis may be caused by infection of the cornea by bacteria, fungi, viruses, or protozoa, usually after trauma to the surface of the eye, including that due to contact lens wear (see Contact Lens Care, p. 1731.2). Common bacterial pathogens include staphylococci, streptococci, *Pseudomonas* spp., and Enterobacteriaceae. Bacterial keratitis is potentially sight-threatening and requires prompt aggressive treatment with broad-spectrum antibacterials. It is customary to obtain material for sensitivity testing, but increasingly, empirical treatment is then begun without delay. Frequent or continuous topical application of drops or the use of local drug delivery devices have been used to ensure prolonged elevated drug concentrations. Subconjunctival or systemic therapy may occasionally be necessary. Topical treatment with cefazolin and either gentamicin or tobramycin has traditionally been used when *Pseudomonas* is not suspected. More recently, fluoroquinolones or ceftazidime have been used, and semisynthetic penicillins or vancomycin are other alternatives. For the treatment of Acanthamoeba keratitis, see p. 921.2.

Endophthalmitis is a devastating ocular disease resulting from infection of the ocular cavity, usually after penetrating trauma or surgery. Depending on the route of infection, causative organisms often include staphylococci, streptococci, *H. influenzae*, *Bacillus cereus*, and *Propionibacterium acnes*. Fungal infections occur less commonly. Bacterial endophthalmitis requires immediate aggressive treatment with antibacterials, usually given intravitreally. The value of concurrent parenteral antibacterials is unclear. The choice of antibacterial for intravitreal use depends on the most likely pathogen. Third-generation cephalosporins or vancomycin are used, but aminoglycosides may produce retinal toxicity. Clindamycin may be effective if *B. cereus* is suspected. Adjunctive treatment includes vitrectomy, surgical removal of infected lens structures, and corticosteroids to control inflammatory and immune responses.

For a discussion of fungal infections of the eye, see p. 565.3; for cytomegalovirus retinitis and ocular herpes simplex infections, see under Cytomegalovirus Infections, p. 956.2, and Herpes Simplex Infections, p. 957.2, respectively.

Some general references are given below.

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Gas gangrene

Gas gangrene (or clostridial myonecrosis) is a life-threatening bacterial infection caused by exotoxin-producing *Clostridium* spp., which invade muscle tissue and cause tissue necrosis, gas production, and systemic toxicity. They are anaerobic, Gram-positive bacteria normally found in soil and the gastrointestinal tract of humans and animals. Infection usually results from deep trauma or surgery, and more than 80% of cases are caused by *C. perfringens*. Spontaneous or nontraumatic gas gangrene is rare and is almost exclusively caused by *C. septicum*. The typical incubation period is usually less than 24 hours but may range from 6 hours to 6 weeks. However, once symptoms start clinical deterioration occurs within hours and is characterised by rapidly increasing pain, fever, and muscle swelling. Systemic toxicity may cause altered mental status, and the progression to septicaemia, shock, and death can be rapid. *C. perfringens* alpha toxin has a negative inotropic effect on cardiac myocytes causing severe, refractory hypotension, while the release of theta toxin leads to shock through peripheral vasodilatation; renal shutdown due to myonecrosis may occur. Mortality from traumatic gas gangrene is about 25% and for spontaneous gas gangrene ranges from 67 to 100%.

Mortality can be improved by rapid diagnosis and early treatment, which involves aggressive surgical exploration and debridement, and intravenous antibacterial therapy. Amputation may be needed in 15 to 20% of patients. Benzylpenicillin is the drug of choice; adding clindamycin is considered beneficial. However, it may be difficult to distinguish gas gangrene from other soft tissue infections and so empirical antibacterial treatment usually covers Gram-positive, Gram-negative, and anaerobic bacteria. Regimens that have been used include:

- a penicillin plus gentamicin and metronidazole
- a second-generation cephalosporin (such as cefuroxime) plus metronidazole
- clindamycin plus a fluoroquinolone in penicillin-allergic patients
- vancomycin or linezolid should be considered in those at risk for MRSA

Other antibacterials used have included combinations of a beta lactam and beta-lactamase inhibitor (such as ticarcillin with clavulanate, ampicillin with sulbactam, or piperacillin with tazobactam), third-generation cephalosporin, chloramphenicol, and tetracycline. Hyperbaric oxygen is used as an adjunct to surgical debridement although its efficacy has not been established. Gas-gangrene antitoxins are now rarely used.

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Gastro-enteritis

Diarrhoea is a symptom of simple gastro-enteritis and of most intestinal infections. It is a major problem in developing countries, but is common worldwide. Although viruses are often responsible, the severest forms of infectious diarrhoea are generally those due to bacteria. Common bacterial pathogens include *Campylobacter jejuni*, *Escherichia coli*, *Salmonella enteritidis*, *Shigella* spp., *Vibrio cholerae*, and *Yersinia enterocolitica*. Intestinal protozoa also cause diarrhoea and are important in AIDS-associated diarrhoea. For discussions of viral and protozoal gastro-enteritis and their treatment, see p. 953.3 and p. 923.2, respectively. Many of these organisms are easily transmitted through food or water, or from person to person, and some may be particularly severe in immunocompromised persons or those with structural abnormalities of the gastrointestinal tract.

Treatment of acute diarrhoea of any aetiology includes fluid replacement, antidiarrhoeal drugs, probiotics, vitamin and mineral supplementation, and antibacterials. Treatment with antibacterials is discussed below, while the classification of diarrhoea and other treatments are discussed under Diarrhoea (see p. 1808.2). WHO[1] recommends that diarrhoea be managed with oral rehydration therapy and continued feeding and that antibacterials should not be routinely given as it is often difficult to distinguish whether the diarrhoea is caused by an organism responsive to antibacterials. Furthermore drug sensitivity of the causative organism is not always known and use of antibacterials could promote the development of resistant bacteria.[1] However, diagnostic capacities are more widely available in the developed world and some clinicians consider such an approach to be unnecessarily conservative in adults with severe acute diarrhoea in developed countries[2] in whom empirical treatment with fluoroquinolones can relieve symptoms and shorten the illness without significant adverse effects. In the USA, empirical therapy is considered for any patients with moderate to severe, febrile, community-acquired diarrhoea, especially if invasive disease is suspected; stool samples should be obtained for identification of the causative organism.[3,4] Empirical therapy may also be given to those with severe nosocomial diarrhoea while waiting for results of assay for *C. difficile* toxin (see also Antibiotic-associated Colitis, p. 185.1), and for moderate to severe travellers' diarrhoea (below).[4]

In **infants and children** oral rehydration therapy is universally recognised as appropriate initial treatment of acute diarrhoea,[5] but it has been underutilised in both developed and developing countries.[6] and a preference for the use of intravenous rehydration therapy with Ringer's lactate solution or normal saline was noted in the USA.[7] Nutritional support and management of secondary complications, including systemic infections, is also particularly important in this age group. Antibacterials have little place in management in most cases[1,5] WHO[1] has stipulated that antibacterials should only be used in children with bloody diarrhoea that is probably caused by *Shigella* (see p. 188.1), suspected cholera with severe dehydration (see p. 186.2), or diarrhoea associated with serious non-intestinal infections (such as pneumonia or urinary-tract infection).[1] Treatment of protozoal infections such as giardiasis and amoebiasis is rarely indicated.[1]

Persistent or prolonged diarrhoea may not have an infective cause and antibacterial treatment should not be started unless a pathogen can be identified. **Tropical sprue** is a syndrome characterised by acute or chronic diarrhoea, weight loss, and malabsorption of nutrients. It occurs in residents of or visitors to the tropical and subtropical regions. The exact pathogenetic sequence is unknown but it is thought that bacterial overgrowth, disturbed gut motility, and hormonal and histopathologic abnormalities contribute to its development in susceptible persons.[8] Treatment with tetracycline and folate is effective in some patients, although relapses after treatment are common.[8]

HIV-associated diarrhoea. Diarrhoea is common in HIV infection and AIDS (p. 959.2) and causative organisms may be bacterial, protozoal, or viral. The most common bacterial cause is the *Mycobacterium avium* complex (see Nontuberculous Mycobacterial Infections, p. 196.1); others include *Campylobacter*, *Salmonella*, and *Shigella* spp. Supportive care and appropriate conventional antibacterial therapy may be adequate, as described under the specific infections, below.

'Food poisoning' is the term used when a preformed toxin in food is ingested, resulting in an intoxication rather than an enteric infection. It is generally a self-limiting form of gastro-enteritis and most people recover from a case of food poisoning within 1 to 2 days,[9] although serious outbreaks of foodborne illness have been associated with bacteria such as *Salmonella enteritidis*. *Staphylococcus aureus* can produce a heat-stable toxin that causes vomiting within 2 to 7 hours of eating improperly cooked or stored food containing it, while *Clostridium perfringens* toxin causes watery diarrhoea without vomiting within 8 to 14 hours after eating contaminated meat, vegetables, or poultry. *Bacillus cereus* may cause vomiting or diarrhoea, depending on the toxin produced, after eating contaminated fried rice, vegetable sprouts, or other food items.[9]

Travellers' diarrhoea.[10-14] is acquired by ingesting contaminated water or foodstuffs. Although it occurs worldwide, the highest rates (20 to 60%) are in travellers from developed, high-income countries visiting developing, low-income regions.[13,14] Travellers diarrhoea is most commonly caused by bacterial enteric pathogens, of which the commonest bacterial pathogen is enterotoxigenic *E. coli*, although enteroadherent *E. coli* is also sometimes involved. Other bacteria include *Campylobacter jejuni*, and *Salmonella* and *Shigella* spp., *Vibrio cholerae*, and non-cholera vibrios such as *V. parahaemolyticus* are rare in travellers. Viruses and the protozoa *Giardia intestinalis*, *Entamoeba histolytica*, and *Cryptosporidium* may also be responsible. Recommendations for the management of travellers' diarrhoea are published by national and international bodies including WHO,[15] the DOH in the UK,[16] and the CDC in the USA.[17] Clinical features depend on the pathogen responsible and treatment varies according to severity and duration of diarrhoea. Onset of diarrhoea is generally delayed with *Giardia* and *Entamoeba* because of the incubation period.

Diarrhoea is often mild and self-limiting and increased fluid intake (in adults) or oral rehydration therapy (for infants, young children, the elderly, or those with cholera-like diarrhoea) is usually all that will be required. Symptomatic treatment with antimotility drugs such as loperamide may be of benefit in mild to moderate diarrhoea. However, antimotility drugs may worsen diarrhoeal illness caused by invasive bacterial pathogens and should be used with caution in those with high fevers, chills, or bloody diarrhoea.[10] Bismuth salicylate may be used to reduce the frequency of diarrhoea. Information on the value of probiotics in the treatment of travellers' diarrhoea is insufficient.[13]

Studies have shown that antibacterials are effective and a single dose (or for up to 3 days of treatment) of an appropriate antibacterial will improve symptoms within 20 to 36 hours and shorten the duration of diarrhoea by 1 to 2 days.[13] Fluoroquinolones are effective in most areas of the world, except where potentially resistant *Campylobacter* is common (as in South and South East Asia). Azithromycin may be given as an alternative in these areas; it can also be used in the treatment of pregnant women and young children with travellers' diarrhoea. Co-trimoxazole was the drug of choice for many years but widespread bacterial resistance has now limited its usefulness.[10,12] It may still be used in those who fail to respond to a fluoroquinolone and antiprotozoal drugs (such as metronidazole) in areas where cyclosporiasis is suspected.[10] Rifaximin has been found to be effective treatment of mainly *E coli* associated travellers diarrhoea in Mexico and Jamaica, but is less effective and not recommended against invasive agents, such as *Campylobacter* and *Shigella*.[13,18] A systematic review and meta-analysis[19] found that combination treatment with an antibacterial and loperamide, given early in the course of the illness was superior to treatment with either agent alone; combination therapy could be considered for people who need prompt resolution of symptoms.[13] When the infecting bacteria are known, specific therapy may be necessary, as described for *Campylobacter* spp. (p. 186.1), cholera and other vibrio infections (p. 186.2), *Escherichia coli* (p. 186.3), *Salmonella* spp. (p. 187.2), *Shigella* spp. (p. 188.1), and *Yersinia* infections (p. 188.2).

The risk of developing travellers' diarrhoea can be reduced by avoiding possibly contaminated foods as embodied in the advice to ***'cook it, boil it, peel it, or forget it'***. Prophylactic drug regimens have been suggested, including various antibacterials, in addition to bismuth salicylate and probiotics. However, routine antimicrobial prophylaxis is not generally recommended because of the danger of drug reactions, superinfections, and increasing bacterial resistance;[10,11,13] it should be reserved for those at special risk.[10,11,20] Many authorities prefer early treatment, including self-medication (with an antibacterial), with clear instructions on when medical help should be sought. If prophylaxis is given it should be started at the start of the at-risk period, and continued for 2 days after the risk stops; prophylaxis should be limited to 3 weeks.[10] A fluoroquinolone is the drug of choice when travelling to most areas of the world; azithromycin can be considered an alternative and rifaximin may be considered for regions where *E coli* predominates, such as Latin America and Africa. Sulfonamides, co-trimoxazole, and tetracyclines should not be used because of widespread resistance.[10,13]

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Antibiotic-associated colitis. *Clostridium difficile* is an anaerobic Gram-positive organism; 2 toxins (A and B) formed by the organism are responsible for an infectious colitis that affects about 20% of hospitalised patients taking antibacterials. Synonymous terms used to refer to the spectrum of disease due to *C. difficile* are:

- antibiotic-associated colitis (AAC)
- *C. difficile*-associated diarrhoea (CDAD)
- *C. difficile* colitis, and
- pseudomembranous colitis (which specifically describes the formation of a membranous exudate in the colon and occurs in about 50% of cases of AAC)

The term antibiotic-associated diarrhoea is usually used for milder disease that is not caused by *C. difficile* or its toxins.

Exposure to antibacterials is the most significant risk factor for development of disease. Antibacterial use alters the normal bowel flora, predisposing to the overgrowth of *C. difficile* and the production of its toxins. The incidence of AAC varies considerably but is increasing worldwide due to broad-spectrum antibacterial use.[1,2] AAC has been associated with the use of most antibacterials, but particularly with clindamycin, lincomycin, ampicillin, amoxicillin, and cephalosporins (especially second and third generation); and, less frequently, with fluoroquinolones, tetracycline, carbapenems, trimethoprim, the macrolides (erythromycin, clarithromycin, azithromycin), and other penicillins. Antibacterials occasionally reported to cause the disease include aminoglycosides, co-trimoxazole, and chloramphenicol. The perception that fluoroquinolones are low risk for AAC has been challenged[3] and studies[4-6] have shown a significant association between ciprofloxacin usage and AAC, with the risk increasing with longer courses of therapy.[6] It has also been suggested that the newer fluoroquinolones (such as moxifloxacin and gatifloxacin) may have different effects on intestinal flora and therefore be more likely to cause AAC; preliminary data from 3 studies appear to support this hypothesis.[2] Antibacterials usually used to treat AAC such as vancomycin and metronidazole have also been shown to cause disease. The role of acid suppression in AAC is unclear.[7]

Symptoms usually develop 5 to 10 days after starting antibacterial therapy, but may develop after a single day of use or can occur up to 10 weeks after stopping treatment. Colonisation generally occurs after ingestion of the acid-resistant spores that are common contaminants from patients who harbour *C. difficile*. Hospitalised patients and residents of long-term care facilities are at higher risk of colonisation with *C. difficile* although colonisation can occur in the outpatient setting. The clinical presentation of AAC can range from mild self-limited diarrhoea to severe colitis with pseudomembrane formation complicated by development of toxic megacolon or colonic perforation. The usual presentation is cramping and abdominal pain with profuse, mucoid, greenish, malodorous watery stools.

Diarrhoea resolved within 48 to 72 hours in 20 to 25% of patients after stopping the offending drug,[1] and giving fluid and electrolyte replacement. If it is not possible to stop antibacterial treatment, a drug less likely to promote AAC may be given.[1,3] In the past early specific antibacterial **therapy** was only given to patients with severe illness characterised by high fever, marked abdominal pain, and marked leucocytosis and to elderly, toxic, or debilitated patients, or those unresponsive to supportive therapy.[8] However, with the increased incidence of fulminant AAC and the rapid clinical deterioration of some patients, delaying specific AAC antibacterial therapy is no longer advised.[1,3] Antibacterials are probably unnecessary in mild disease[9] and chemoprophylaxis for asymptomatic carriers is not recommended.[3,7] Antidiarrhoeal and antimotility drugs should be avoided since they may aggravate the condition and may occasionally increase the possibility of toxic megacolon.[1] A literature review,[10] however, concluded that antimotility drugs, used with an active antibacterial, may provide safe and effective symptomatic relief and assist in reducing the passage of infectious stools in the hospital environment.

The choice of initial antibacterial therapy depends on the severity of disease and different regimens are used to treat first or second episodes of AAC, recurrent episodes, and very severe or fulminant disease.[1] Vancomycin or metronidazole are widely used when antibacterial treatment is necessary.[1,3,7,8] Metronidazole can be given orally or intravenously as appropriate. Vancomycin is given orally or via a retention enema; it should not be given intravenously since it does not give rise to adequate concentrations of the drug in the bowel lumen.[1] Metronidazole tends to be the drug of first choice and vancomycin is reserved for those who do not respond to, or who cannot tolerate, metronidazole, for those who are severely immunocompromised, and for those with severe illness.[1,7,8] This view is also endorsed by expert bodies in the USA whose aim is to provide guidelines for preventing the spread of vancomycin resistance.[11] Oral fidaxomicin has also been shown to be effective and is a potential treatment alternative.[12,13] The severity of the diarrhoea often decreases within 48 to 72 hours, but may not stop for a week or more. Treatment is usually continued for 10 to 14 days.[1] Other drugs that have been investigated in the treatment of AAC include teicoplanin,[14-16] fusidic acid,[16,17] and bacitracin,[18] although experience with their use remains limited. A systematic review[9] found that metronidazole, bacitracin, rifaximin, nitazoxanide, or fusidic acid seemed to be as effective as vancomycin in terms of symptomatic cure, and teicoplanin might be slightly more effective. Bacitracin and fusidic acid seemed to be less effective than vancomycin in terms of bacteriological cure and resolution.[9] Ramoplanin has also been investigated.[1,3]

The anion-exchange resins colestyramine and colestipol hydrochloride have been shown to bind the *Cl. difficile* toxin *in vitro*, and colestyramine has been used to treat pseudomembranous colitis[19] and recurrent AAC.[1] The use of vancomycin together with colestyramine has been suggested,[20] but the value of the combination is uncertain. Colestyramine binds to vancomycin, resulting in a reduction of biologic activity in stool and in general, the use of colestyramine and colestipol is not recommended.[1,21] An experimental toxin-binding polymer, tolevamer (or GT 160-2461) has also been investigated.[1,3]

It is thought that patients who develop recurrent AAC are unable to mount a protective immune response to *C. difficile* and its toxins;[3,7,21] normal immunoglobulin products that contain IgG have been shown to neutralise the toxins A and B,[3] and may benefit patients with severe and/or relapsing AAC when no other therapeutic options are available.[1,21] Oral immunoglobulin A, used with vancomycin, was effective in controlling severe diarrhoea in a child who had not responded to other therapies.[22] Normal immunoglobulin given intravenously was also effective when added to vancomycin and metronidazole therapy in 2 elderly patients unresponsive to antibacterials alone.[23] Vaccines against *C. difficile* have also been investigated.[1] A single infusion of 2 monoclonal antibodies against *C. difficile* toxins A and B was reported to significantly reduce the recurrence of infection when given with either metronidazole or vancomycin therapy.[24]

Treatment and prevention strategies aimed at colonising the gut with non-pathogenic organisms have included use of lactic-acid-producing organisms (probiotics) such as *Lactobacillus*,[8,25] and the yeasts *Saccharomyces boulardii*,[8] and *S. cerevisiae*.[26] A systematic review[27] of studies that used probiotics as adjunctive therapy to antibacterials (vancomycin or metronidazole) for treatment of an initial episode of *C. difficile* colitis or recurrent infection in adults found there was insufficient evidence to recommend adjunctive probiotics. However, another systematic review[28] on the use of probiotics in children reported that they may be effective for preventing AAC. Data on regimens containing *Lactobacillus* organisms or *S. boulardii* for the treatment of recurrent AAC are poor and conflicting.[1,3] Some experts, however, consider probiotics to be a safe and reasonable option for prevention of initial infections and possibly for treatment of recurrent infections.[7]

For patients with severe or fulminantinfection who have a functioning gastrointestinal tract, oral vancomycin is the preferred therapy.[1] However, treatment of patients with a compromised gastrointestinal tract is difficult because reliable concentrations of orally administered drug at the site of infection cannot be assured.[1] Vancomycin given via a nasogastric tube or by retention enema plus intravenous metronidazole have been tried.[1,3,7] Intravenous tigecycline has been successfully used in 4 patients with severe refractory AAC.[29]

About 15 to 30% of patients develop a second episode of AAC after successful treatment of the first episode; treatment with the same drug used to treat the first episode is recommended.[1,3,7,21] Higher **recurrence** rates of up to 65% occur in patients who have had 2 or more previous episodes.[3,7] Vancomycin is usually preferred for the treatment of recurrent infection[1,3,7,21] because long or repeated courses of metronidazole have the potential to cause peripheral neuropathy.[1,7,21] Management strategies used have included tapered or pulsed dosed vancomycin followed by course of rifaximin,[1,7,21] nitazoxanide,[7] or rifampicin.[21] If episodes of recurrent AAC continue, other treatment options such as alternative antibacterials (nitazoxanide or rifaximin), probiotics, immunological therapy, faecal reconstitution (stool transplantation), and toxin-binding products may be tried.[7,21]

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Campylobacter enteritis. *Campylobacter* spp.[1-4] are the most common cause of bacterial gastroenteritis in both developed and developing countries. In developing countries, disease occurs mainly in young children, while in developed countries the highest rates are seen among children less than 5 years of age and young adults, particularly men from 20 to 29 years of age. It is also a common cause of diarrhoea in travellers to developing countries. Although about 16 species of *Campylobacter* have been identified, more than 90% of cases are caused by *C. jejuni* and most of the other infections are caused by *C. coli*.[5,6] Campylobacter enteritis is a zoonosis and the main route of transmission is thought to be foodborne, via undercooked meats and meat products. Other routes of transmission include raw or contaminated milk, contaminated water, contact with pets and farm animals, and from doorstep deliveries of foil-topped bottled milk that have been pecked by birds.

Symptoms usually occur 2 to 5 days after exposure, but can range from 1 to 11 days. Some patients may be asymptomatic while others may have diarrhoea (sometimes bloody), abdominal pain, fever, headache, nausea, and vomiting. Illness usually lasts for 2 to 6 days but may last up to several weeks. Significant post-infection complications may include irritable bowel syndrome (15%), reactive arthritis (1%), Guillain-Barré syndrome (0.1%), and toxic megacolon. Fatalities due to dehydration are rare and usually occur in the very young or elderly patients, or in those already suffering from another serious disease such as AIDS.

Infection is usually self-limiting and in most cases fluid and electrolyte replacement is generally sufficient (see Diarrhoea, p. 1808.2).[1,2] Antibacterials are generally not required but can be considered for patients with severe or prolonged symptoms or who are immunocompromised.[2,3] Those that have been used include erythromycin, azithromycin, tetracycline, and ciprofloxacin. However, due to widespread use of these antibacterials in veterinary practice and as additives to animal feeds (particularly poultry), selection for resistant *Campylobacter* spp. has occurred[4,6] and increasing numbers of ciprofloxacin-resistant cases are being reported worldwide.[2,6-8] Resistance rates in the USA and Canada are reported to be about 19 to 47%, while 17 to 99% of *Campylobacter* isolates in Europe are resistant to fluoroquinolones.[8] This has prompted the withdrawal of fluoroquinolones from use in commercial poultry farming in the USA.[9] Rates of macrolide resistance have stayed stable and low in many countries, but an increase has been reported in human strains in some countries,[5,6] particularly in the developing countries.[5] The prevalence of erythromycin resistance in *C. jejuni* has remained low (below 12% of isolates) but a higher frequency of resistance (up to 70%) is reported in *C. coli*. Globally, multiple antibacterial resistance (resistance to three or more different classes of antibacterial) is emerging in *Campylobacter* clinical isolates.[6]

Erythromycin is considered to be the drug of choice for treatment of *Campylobacter* infections; the newer macrolides, azithromycin and clarithromycin are alternatives.[2,10] *Campylobacter* species also are generally susceptible to aminoglycosides, chloramphenicol, clindamycin, nitrofurans, and imipenem,[2,6] but high rates of resistance make tetracycline, amoxicillin, ampicillin, metronidazole, or cephalosporins a poor choice.[2]

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Cholera and other vibrio infections. Cholera[1] results from infection with the enterotoxin-producing Gram-negative bacillus *Vibrio cholerae*, which causes acute secretory diarrhoea. Outbreaks are associated with two serogroups of *V. cholerae*, O1 and O139. Serogroup O1 can then be divided into two biotypes (classical and El Tor) and each of these has three serotypes (Inaba, Ogawa, and Hikojima). Other strains of *V. cholerae* can cause mild diarrhoea but such infections do not develop into epidemics. Cholera is considered to be endemic in many countries and the pathogen causing it cannot currently be eliminated from the environment.

Transmission occurs mainly through ingestion of contaminated water and food, but may also be spread through direct faecal-oral contamination. Severe disease is characterised by a sudden onset of acute watery diarrhoea that can lead to death within hours in previously healthy adults, due to severe dehydration. If untreated, as many as 50% of patients may die, but with proper treatment, the fatality rate is about 1%. Individuals with lower immunity, such as malnourished children or people infected with HIV, are at increased risk of death. The incubation period is usually 24 to 72 hours, but can range from 2 hours to 5 days. This short incubation period enhances the potentially explosive pattern of outbreaks, as the number of cases can rise very quickly. About 75% of people will not develop any symptoms. However, the pathogens stay in the faeces for 7 to 14 days and are shed back into the environment, potentially infecting others. Among people developing symptoms, 80% of episodes are of mild to moderate severity and the remaining cases may develop severe watery diarrhoea with signs of dehydration.

A guideline for the prevention and control of cholera outbreaks has been developed by WHO.[2] Individuals can reduce the risk of contracting cholera by good personal hygiene, avoiding possibly contaminated foodstuffs, and by boiling or otherwise disinfecting drinking water. Methods of preventing or containing cholera epidemics include ensuring a safe water supply, providing good sanitation, and promoting safe handling and preparation of foods. Routine treatment of a community with mass chemoprophylaxis, parenteral vaccination, and travel and trade restrictions are not effective. Oral cholera vaccines containing either live attenuated or inactivated strains are available in some countries. Mass vaccination campaigns using the oral killed whole-cell *V. cholerae* O1 with purified recombinant B-subunit of cholera toxoid (WC/rBS) vaccine have been conducted in emergency settings to protect at-risk populations from potential cholera outbreaks.[3] Use of oral cholera vaccines in such settings should not replace control measures such as improved water supplies, adequate sanitation, and health education.[2,3] Vaccination is not recommended once a cholera outbreak has started, because of its 2-dose regimen and the time required to reach protective efficacy.[2] Oral cholera vaccines are suitable for use by travellers. For further information on Cholera Vaccines see, p. 2381.1.

Most cases of vibrio gastro-enteritis are mild to moderate and generally require no therapy other than fluid and electrolyte replacement with an appropriate oral rehydration solution (see Diarrhoea, p. 1808.2). Patients with severe gastro-enteritis, dehydration, and shock should receive vigorous fluid replacement, preferably with intravenous isotonic solutions such as Ringer's lactate.[1,2,4] Supplementary zinc has been shown to be effective in reducing duration of diarrhoea and successive diarrhoeal episodes in children up to 5 years of age.[2,5,6] Antibacterials can be given in severe cholera to decrease the duration and volume of diarrhoea, reduce the volume of rehydration fluids needed, and shorten the duration of vibrio excretion.[1] WHO recommends a single dose of doxycycline (300 mg) for adults or a 3-day (12-dose) course of tetracycline or a 3-day (6-dose) course of co-trimoxazole for adults and children; furazolidone or erythromycin are considered suitable alternatives.[4] Recommendations from the USA for adults specify a tetracycline as the first choice with co-trimoxazole, azithromycin, or a fluoroquinolone such as ciprofloxacin as alternatives.[7] In the UK, tetracyclines or ciprofloxacin are usually used. One study has suggested that single-dose ciprofloxacin might be preferred to doxycycline, particularly in areas of tetracycline resistance,[8] and in Bangladesh, ampicillin has been found to be as effective as either erythromycin or tetracycline[9] and may be a useful alternative in children. Studies[10-12] in Bangladesh and India found single-dose azithromycin to be effective in children and adults. In children a single dose of ciprofloxacin was also reported to be effective in terms of clinical cure, but was less effective than a 3-day (12-dose) course of erythromycin in eradicating *V. cholerae* from stool.[13]

Widespread antibacterial resistance in *V. cholerae* was very uncommon before 1977, but reports of resistance to some antibacterials (including tetracycline, ampicillin, kanamycin, streptomycin, sulphonamides, trimethoprim, and gentamicin) have appeared from several cholera-endemic countries.[1] Fluoroquinolone-resistant strains have also been reported from India[1] and a multidrug resistant strain of *V. cholerae* O1 (resistant to co-trimoxazole, tetracycline, furazolidone, and erythromycin) has been reported from Bangladesh.[14] *V. cholerae* O139 strains are also resistant to co-trimoxazole, chloramphenicol, and low levels of streptomycin.[1] *V. cholerae* O1 and O139 show spatial and temporal fluctuations, with periods of resistance fluctuating with periods of sensitivity.[1]

Marine or halophilic *Vibrio* spp. known to cause gastroenteritis include *V. parahaemolyticus* which is responsible for food poisoning from raw or undercooked seafood, especially in Japan.[15,16] Another halophilic sp., *V. vulnificus*, is increasingly associated with wound infection and septicaemia.[15] On the basis of *in-vitro* sensitivity testing[17] and anecdotal clinical experience, empirical therapy with aminoglycosides, ceftazidime, imipenem, or ciprofloxacin should all be effective.[18]

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Escherichia coli enteritis. *Escherichia coli* is a normal intestinal commensal and member of the anaerobic Gram-negative family of bacteria the Enterobacteriaceae. However, some strains have acquired genes that enable them

to cause intestinal infection. When ingested, the following strains can cause diarrhoea:

- enteropathogenic *E. coli* (EPEC): may cause hospital nursery outbreak but is most often found in developing countries and mainly causes watery diarrhoea in infants and children
- enteroinvasive *E. coli* (EIEC): produces an invasive type of diarrhoea resembling that of *Shigella* dysentery
- enterotoxigenic *E. coli* (ETEC): is an important cause of travellers' diarrhoea and diarrhoea in infants and children (see Gastro-enteritis, p. 182.2). It is widespread in areas with poor sanitation and is a common contaminant of food and water sources. The incubation period is 1 to 3 days; the infection is usually self-limiting and lasts for less than 5 days
- enterohaemorrhagic *E. coli* (EHEC); also known as Shiga-toxin producing *E. coli* or STEC: is associated with haemorrhagic colitis, haemolytic-uraemic syndrome, and thrombotic thrombocytopenic purpura. Most outbreaks have been linked to 0157:H7 strains; the incubation period is 1 to 5 days and the illness usually lasts for 4 to 10 days. Children and the elderly are at greater risk of severe disease,[1] but the illness is usually self-limiting.[2] Cases have generally been linked with the consumption of foods derived from cattle, especially undercooked beef and unpasteurised milk, although there have been outbreaks associated with the consumption of fresh vegetables and unpasteurised juices, probably as a result of faecal contamination. Person-to-person spread is also common, and direct spread from infected animals may occur. *E. coli* O157 has also been reported as a cause of epidemic haemorrhagic colitis in Africa, where it may be difficult to distinguish from shigellosis[3,4]
- enteroadherent *E. coli* (EAEC): is a cause of chronic diarrhoea in young children

As with any form of diarrhoea (p. 1808.2), fluid and electrolyte replacement is key to treatment. The use of antibacterials is controversial. Those with mild symptoms or who are improving do not need antibacterial treatment. Treatment is advised for those with prolonged symptoms, those who relapse, or those considered to be high-risk; antibacterials may also be used for outbreaks of EPEC diarrhoea in nurseries.[5] Severe EIEC infection with evidence of systemic involvement can be treated with antibacterials recommended for shigellosis (see p. 188.1).[5,6] Treatment of EHEC is generally supportive, including correcting and maintaining the fluid and electrolyte balance.[2] There is uncertainty as to whether antibacterials influence the course of enterohaemorrhagic *E. coli* infection and the development of haemolytic-uraemic syndrome[7] or thrombotic thrombocytopenic purpura;[1,2,8] the non-antibacterial treatment of these two latter complications is discussed in Plasma, under Thrombotic Microangiopathies, p. 1159.1. In the absence of conclusive evidence, most experts do not recommend the use of empirical antibacterial treatment.[5,6] Oral preparations of Vero cytotoxin-binding resins are under investigation.

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Necrotising enterocolitis. Necrotising enterocolitis is characterised by diffuse or focal necrosis of the ileum or colon (or both) and is one of the most common gastrointestinal emergencies in newborn infants. It mainly affects those born before 36 weeks' gestational age, with the majority of cases occurring in very low birth-weight infants (less than 1500 g). Although the pathogenesis of necrotising enterocolitis is poorly understood, there is evidence to suggest that multiple, interacting mechanisms are involved, including immaturity of the gastrointestinal tract, intestinal ischaemia, reperfusion injury with activation of proinflammatory cellular cascades, enteral feeding, and the presence of pathogenic bacterial flora in the intestine. Bacteria implicated in the disease include *Pseudomonas, Escherichia coli, Klebsiella, Salmonella* spp., and *Clostridium* spp.

Onset of illness is usually 3 to 10 days (but may range from 1 to 90 days) after birth. Necrotising enterocolitis may present as a benign illness with mild inflammation of the intestinal wall and mainly gastrointestinal symptoms, or as a catastrophic illness characterised by full-thickness intestinal necrosis with perforation, respiratory and cardiovascular collapse, metabolic acidosis, disseminated intravascular coagulopathy, grossly bloody stools, multi-system organ failure, and in some cases death. Early signs are non-specific and sepsis rather than necrotising enterocolitis may initially be suspected.

The severity of the disease is usually staged according to modified Bell's criteria and recommendations for **management** of necrotising enterocolitis are based on these criteria.[1-3] Depending on the stage of disease, necrotising enterocolitis can be treated medically and/or surgically.[1] When necrotising enterocolitis is suspected treatment involves stopping oral feeds (bowel rest), starting total parenteral nutrition, and giving parenteral antibacterials to limit bacterial invasion and translocation.[3] Antibacterials should cover aerobic and anaerobic enteric bacteria. Ampicillin (or similar penicillin derivatives) or vancomycin may be used for Gram-positive aerobic cover and an aminoglycoside (such as gentamicin) or a third-generation cephalosporin (such as cefotaxime) may be used against Gram-negative aerobes. Metronidazole or clindamycin are given for anaerobic cover.[3] If the diagnosis of necrotising enterocolitis (Bells stage II or above) is confirmed then antibacterials are continued for 7 to 14 days.[2,3]

A systematic review has concluded that *prophylactic* oral antibacterials might well reduce the incidence of necrotising enterocolitis in low birth-weight or preterm infants in a high-risk environment,[4] but there are concerns about adverse outcomes, and prophylactic use (particularly of vancomycin) is not generally recommended because of the risk of inducing resistance. It has been suggested[5] that oral immunoglobulins may prevent necrotising enterocolitis in low-birth-weight infants; however, a systematic review[6] concluded that the available evidence did not support this claim. There is, however, good evidence that supplementation with enteral probiotics reduces the risk of severe necrotising enterocolitis and death in premature infants born weighing less than 1500 g,[7,8] but there were insufficient data to determine their value in infants weighing less than 1000 g at birth.[7] Supplementation with arginine has also been investigated,[9] but there is insufficient evidence to determine its value.

Necrotising enteritis in older children and adults, known as **pigbel**, has been attributed to toxins produced by *Clostridium perfringens*. Both sporadic and epidemic forms are mainly seen in the highlands of Papua New Guinea, but sporadic cases have been reported elsewhere. Treatment is supportive with surgical intervention where necessary. A vaccine is available for prophylaxis.

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Salmonella enteritis. *Salmonella* spp. are Gram-negative bacteria belonging to the Enterobacteriaceae family. They can be divided into:

- those causing enteric fever, namely *S. typhi* and *S. paratyphi*, where infection is systemic although affecting the gastrointestinal tract (see under Typhoid and Paratyphoid Fever, p. 214.1)
- non-typhoid *Salmonella* (NTS), including *S. enteritidis* and *S. typhimurium*, which cause acute gastro-enteritis invasive infections with bacteraemia, and localised infections, which are discussed here

NTS infection is usually transmitted through ingestion of contaminated food of animal origin, especially, beef, poultry and eggs, and dairy products. Animal-to-human transmissions can occur particularly after handling amphibians and reptiles, and outbreaks of hospital-acquired NTS have also been reported. NTS occurs worldwide; in developed countries it is usually a mild, self-limiting diarrhoeal disease that resolves in a few days without active treatment. In less developed areas NTS may cause serious invasive disease. Epidemiological data from some countries in sub-Saharan Africa indicate that it is one of the most common causes of bacteraemia in adults and children. Invasive disease is more common and symptoms most severe in the elderly, infants, people with chronic conditions such as diabetes, or those who are immunocompromised.

Gastroenteritis caused by *Salmonella* spp. is often clinically similar to that caused by other bacterial pathogens. Many patients are asymptomatic or have a mild disease. Symptoms usually begin 24 to 48 hours (range 8 to 72 hours) after infection, with fever, headache, abdominal cramps, and diarrhoea. These symptoms and possibly also nausea, loss of appetite, and vomiting, usually last for 3 to 7 days. Less than 5% of cases are complicated by *Salmonella* bacteraemia; complications of this can include endocarditis, meningitis, mycotic aneurysms, septic arthritis, and osteomyelitis.

Uncomplicated NTS enteritis is usually **managed** by fluid and electrolyte replacement (see Diarrhoea, p. 1808.2).[1,2] Antidiarrhoeal drugs are generally not recommended as they may prolong bacterial excretion.[1,2] Antibacterials have a limited role and are not usually recommended for uncomplicated cases.[1] A meta-analysis[3] of antimicrobial therapy for *Salmonella* enteritis found that antibacterial therapy produced no clinical benefit in uncomplicated disease and that it may prolong *Salmonella* detection in stools. Antibacterials may be given to those patients with severe gastroenteritis, those who are at a high risk for invasive disease, or those with proven bacteraemia.[1,2]

Drug resistance has limited the usefulness of traditional first-line empirical antibacterial agents such as benzylpenicillin, ampicillin, co-trimoxazole, chloramphenicol, tetracyclines, sulphonamides, streptomycin, and gentamicin.[2,4-6] Multiresistant R-type strains of *S. typhimurium*, including DT 104, have further limited the treatment options.[7-11] Empirical treatment with oral ciprofloxacin, oral azithromycin, or intravenous ceftriaxone is recommended although there is also increasing resistance to these antibacterials (especially ciprofloxacin).[1,4] Nalidixic acid resistance has been reported and has been shown to predict lack of response to fluoroquinolones.[2] Resistance to cephalosporins has also been recognised.[4,11-13] For patients with a recent travel history, azithromycin may therefore be the preferred first line option.[1] Carbapenems such as imipenem, meropenem, and ertapenem may be useful for multidrug resistant infections.[4]

Treatment is usually given for 3 to 7 days[1,2,4] and is often extended to 14 days in immunocompromised patients.[2] In HIV-infected adults, the CDC recommends ciprofloxacin for 7 to 14 days in those with a CD4+ T lymphocyte count of 200 cells/microlitre or more with mild gastroenteritis (with or without bacteraemia); 2 to 6 weeks treatment is recommended for those with a CD4+ T lymphocyte count of less than 200 cells/microlitre.[14] Relapses in infection have been well-documented in HIV-infected patients and recurrent *Salmonella* might require chronic suppressive therapy.[14]

Empirical treatment for patients with bacteraemia should be with both a fluoroquinolone and a third-generation cephalosporin to account for multidrug resistant organisms.[2] Monotherapy should be given once sensitivities are known;[2] third-generation cephalosporins may be used and ceftriaxone is considered appropriate for treatment of meningitis.[5,6] Bacteraemia usually needs a 7- to 14-day course of antibacterial treatment[2,6] and longer courses may be needed in those with immunosuppression.[6] Those with meningitis may need 4 weeks of treatment[6] and 6 weeks of treatment has been suggested for those with endovascular infections.[2]

Chronic carriage can be treated with amoxicillin (1 g three times daily for 3 months), co-trimoxazole (960 mg twice daily for 3 months), or ciprofloxacin (750 mg twice daily for 1 month).[2]

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Shigellosis. Shigellosis (bacillary dysentery) is an enteric infection caused by *Shigella dysenteriae*, *S. flexneri*, *S. boydii*, or *S. sonnei* (also called groups A, B, C, and D respectively), Gram-negative bacteria belonging to the Enterobacteriaceae family. It is endemic in most of the developing world and is the most important cause of bloody diarrhoea worldwide, resulting in at least 80 million cases and an estimated 700 000 deaths each year, mainly among children under 5 years of age.[1] *S. sonnei* and *S. boydii* usually cause relatively mild disease, whereas a specific serotype of *S. dysenteriae*, Sd1 or Shiga bacillus, is the organism responsible for shigella epidemics and causes the most severe, prolonged, and potentially fatal disease. The distribution of different species varies geographically.

Shigella are spread through the fecal-oral route, and disease is commonest where there is overcrowding and poor hygiene and sanitation. Onset typically occurs 12 to 96 hours after exposure, and the illness may range from mild, self-limiting, watery diarrhoea to severe colitis and dysentery with blood and mucous in the stools. Severity depends both on the infecting organism and patient-specific factors including age and degree of malnutrition.

As with any form of diarrhoea (p. 1808.2), rehydration is the key to treatment.[2] Although most milder infections, particularly those due to *S. sonnei*, will resolve without treatment within 4 to 7 days, all cases of bloody diarrhoea should be treated promptly with an antibacterial that is effective against *Shigella*. The aim of antibacterial therapy is to speed recovery, reduce the seriousness of the disease, and decrease the length of time that patients are infective. The choice of antibacterial has changed over time as resistance to various antibacterials developed; different patterns of resistance have been reported around the world. As widespread resistance has developed to traditional first-line drugs including ampicillin, co-trimoxazole, and nalidixic acid, WHO[1] considers ciprofloxacin to be the drug of choice for empirical treatment in patients of all age groups; in adolescents and children, for whom quinolones are not routinely recommended (see Precautions, under Ciprofloxacin, p. 266.1), the benefit is thought to outweigh the risk. Fluoroquinolone resistance has been reported in some parts of the world (particularly the Indian subcontinent),[2-5] and where local strains of *Shigella* are known to be resistant, second-line antibacterials recommended by WHO include oral pivmecillinam, and parenteral ceftriaxone. Azithromycin is also recommended for second-line use in adults by WHO, and as an alternative for children by the American Academy of Pediatrics,[6] although there have been concerns regarding rapid development of resistance; *Shigella* spp. resistant to azithromycin have already been reported in Europe[7] and resistance to azithromycin and ceftriaxone in the Indian subcontinent.[8] A systematic review[9] of 16 studies (1748 subjects) to evaluate the safety and efficacy of antibacterials in the treatment of *Shigella* dysentery found limited evidence that most of the commonly used antibacterials (ampicillin, co-trimoxazole, nalidixic acid, fluoroquinolones, pivmecillinam, ceftriaxone, and azithromycin) reduced diarrhoea and the duration of fever compared with no antibacterial treatment, but insufficient evidence to recommend any specific antibacterial. To accommodate temporal and geographical shifts and antibacterial resistance in *Shigella* strains around the world, it recommended that empirical therapy should be guided by local or regional antibacterial sensitivity patterns.[9] Effective antibacterial treatment should lead to symptomatic improvement within the first 48 hours; where this does not occur, the possibility of antibacterial resistance should be considered.[1]

Vitamin A may be a useful adjunct to treatment, especially in children in developing countries who are at risk for malnutrition (see Diarrhoea, under Vitamin A, p. 2100.1).[6] Supplemental zinc, which may reduce the incidence and severity of diarrhoea both in the acute period and in the next 2 to 3 months, is also recommended for children up to 5 years of age (see Diarrhoea, under Zinc Sulfate, p. 2127.2).[1]

Oral shigella vaccines are being studied for prophylaxis.

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Yersinia enteritis. *Yersinia enterocolitica* is a Gram-negative bacterium of the Enterobacteriaceae family and the species most commonly responsible for yersiniosis. *Y. enterocolitica* has been isolated in patients worldwide, but the infection appears to occur mainly in cooler climates and in some of these countries it rivals *Salmonella* and *Campylobacter* and exceeds *Shigella* as a cause of acute bacterial gastro-enteritis. Pigs are a major reservoir for *Y. enterocolitica* strains that infect humans and infection is usually transmitted by eating contaminated food, especially raw or undercooked pork products, or drinking contaminated unpasteurised milk or untreated water; transmission through blood transfusion is rare.

Infection with *Y. enterocolitica* occurs most often in young children. Symptoms usually develop 3 to 7 days after exposure and vary depending on the age of the person infected. Common symptoms in children include diarrhoea (which is often bloody), fever and abdominal pain, which last for up to three weeks or longer. Older children and adults can present with right-sided abdominal pain and fever that may be confused with appendicitis. In some patients, complications such as reactive polyarthropathy, erythema nodosum, and life-threatening bacteraemia may develop. Increased susceptibility to *Yersinia* infection has occurred in patients with iron overload treated with desferrioxamine (see p. 1547.2).

As with any form of diarrhoea (p. 1808.2), rehydration is the key to **treatment** and most forms of mild uncomplicated enteritis do not require antibacterials. However, systemic infection and bacteraemia require antibacterial treatment.[1] Reports of antibacterial susceptibility from different parts of the world indicate that *Y. enterocolitica* is susceptible to many antimicrobial agents.[1] Drugs with good intracellular activity such as trimethoprim, co-trimoxazole, tetracycline, chloramphenicol, or fluoroquinolones may be preferred.[2] Doxycycline or co-trimoxazole have been recommended[3] for complicated gastrointestinal and focal extra-intestinal infections or doxycycline and an aminoglycoside empirically in bacteraemia. Co-trimoxazole as first choice or alternatively a fluoroquinolone, an aminoglycoside, or cefotaxime have also been recommended.[4] A study[1] undertaken in a paediatric hospital in the USA to determine the antibacterial susceptibility pattern of *Y. enterocolitica* reported that susceptibility patterns of the organism had not changed over the 12-year study period. The most active agents *in vitro* were cefotaxime, ceftriaxone, cefepime, co-trimoxazole, gentamicin, tobramycin, imipenem, and ciprofloxacin; all were also considered to be clinically appropriate. Systemic cefotaxime and ceftriaxone were effective for treating bacteraemia. The majority of isolates were resistant to ampicillin and first-generation cephalosporins. Similar susceptibility patterns were reported in a study conducted in China.[5] A patient with chronic *Yersinia* infection who responded well to tetracycline or co-trimoxazole, but relapsed on withdrawal, was treated successfully with ciprofloxacin.[6]

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Gonorrhoea

See under Sexually Transmitted Diseases, p. 206.2.

Granuloma inguinale

See under Sexually Transmitted Diseases, p. 207.1.

Haemophilus influenzae infections

Haemophilus influenzae is a Gram-negative bacterium that colonises the upper respiratory tract in the majority of healthy people. Most are carriers of non-encapsulated (or nontypeable) strains, but a small proportion carry *H. influenzae* type b (Hib), the most virulent of the 6 encapsulated strains. Transmission is by close contact with an infected person or by inhalation of respiratory tract droplets. In most developed countries there has been a decrease in the rate of nasopharyngeal colonisation by Hib and in the incidence of Hib infection since the introduction and widespread use of Hib conjugate vaccine. However, Hib infection still occurs in unimmunised children or those who have not completed the childhood immunisation schedule; Hib infections are uncommon in children more than 6 years old. Hib strains cause systemic disease, the most serious being meningitis which mainly affects children less than 2 years old. Other invasive conditions include bacteraemia, cellulitis, epiglottitis, septic arthritis, and pneumonia and empyema. In developing countries pneumonia is responsible for more deaths than meningitis. Non-encapsulated strains invade the mucosal surface causing infections such as otitis media, sinusitis, and conjunctivitis and infect patients with chronic bronchitis. These strains are a common cause of community-acquired pneumonia in adults, especially those with chronic obstructive airways disease or AIDS.

Choice of treatment. For further details of these infections and their management, see under the specific disease side-headings. Ampicillin and chloramphenicol have been the antibacterials of choice against *H. influenzae*, but increasing resistance, especially to ampicillin, should be borne in mind; there have been several reports of multiresistant strains.[1-4] Parenteral cephalosporins such as ceftriaxone or cefotaxime have been found to be effective[5] and are currently preferred for serious *H. influenzae* type b infections.[6] There have been treatment failures in *H. influenzae* meningitis with cefuroxime and there is argument over its efficacy.[5] Meropenem is a further alternative.[6]

For upper respiratory infections and bronchitis caused by nontypable strains oral antibacterials may be used. About 20 to 35% of these strains are resistant to ampicillin and some experts suggest co-trimoxazole (or trimethoprim in the UK) as the preferred antibacterial; ampicillin, amoxicillin (with or without clavulanic acid), oral second- or third-generation cephalosporins, a tetracycline, a fluoroquinolone, or the macrolides azithromycin or clarithromycin are suggested alternatives.[6]

Prophylaxis. Immunisation is the most effective way of preventing Hib in infants and children and vaccination is included in the infant immunisation schedules in some developing and most developed countries including the UK and USA. However, there are no vaccines available for the prevention of disease caused by nontypable *H. influenzae*. For further information on haemophilus influenzae vaccines see p. 2387.2.

Young children who develop invasive Hib disease have a low but significant risk of a second episode of Hib infection and are also more likely to become asymptomatic carriers and transmit the organism to others. Household contacts of index cases, especially young children and those with underlying medical problems such as immunosuppression and asplenia, are also at increased risk of developing invasive Hib disease. Recommendations for the prevention of secondary Hib disease have been made[7,8] and usually include chemoprophylaxis with rifampicin (or alternatively ceftriaxone) for the index case and for close contacts of the index case. For further information on chemoprophylaxis see Meningitis Prophylaxis, under Uses and Administration of Rifampicin, p. 353.2.

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Helicobacter pylori infections

Antibacterial therapy is used to eradicate *Helicobacter pylori* infection in peptic ulcer disease (p. 1816.2) and MALT lymphoma of the stomach (p. 698.1). The role of *H. pylori* and the value of its eradication in dyspepsia (p. 1809.3) and gastro-oesophageal reflux disease (p. 1810.2) is less clear.

Infections in immunocompromised patients

Patients with a defective immune system are at increased risk of infection. Primary immune deficiency is rare, whereas secondary deficiency is more common: immunosuppressive therapy, cancer and its treatment, HIV infection, or splenectomy may cause neutropenia and

impaired humoral and cellular immunity in varying degrees. The risk and severity of infections depends upon the duration of compromised immunity, the degree to which immune function is compromised, whether cellular or humoral functions are affected, and upon breaches in physical barriers, for example due to severe mucositis or prolonged vascular access. Thus patients with profound neutropenia or a history of splenectomy are prone to rapidly progressive and potentially life-threatening infections; those with neutropenia induced by cytotoxic chemotherapy or by preparation for transplantation are particularly vulnerable to acute infections whereas those in whom immunosuppression results from viral infections or congenital defects are at lower risk of acute infections.[1] Patients in whom neutropenia persists for more than 10 days are not only at risk of opportunistic bacterial infections but also susceptible to viral, fungal, and parasitic infections.

Infectious diseases are a major cause of morbidity and mortality in patients with AIDS (see HIV-associated Infections and Complications, p. 960.3). Some are due to common pathogens, but others are opportunistic and are caused by normally avirulent commensals. Children with HIV infection appear to be at special risk of serious bacterial infections with common encapsulated bacteria. For further reference to some bacterial infections associated with AIDS, see Gastro-enteritis (p. 182.2), Nontuberculous Mycobacterial Infections (p. 196.1), and Tuberculosis (p. 212.2). Detailed guidelines for the prevention and treatment of opportunistic infections (including some bacterial infections) among HIV-infected adults, adolescents, and children have been developed in the USA.[2,3] Fungal, protozoal, and viral infections which can affect immunocompromised patients are discussed in the relevant chapters under Infections in Immunocompromised Patients, p. 566.2, p. 923.3, and p. 962.2, respectively.

Reports from Europe and the USA show that over the past few decades there has been a shift in the occurrence of bacteraemia in febrile neutropenic patients from Gram-negative organisms to Gram-positive organisms.[4] Factor influencing this change include changes in clinical practice such as the use of central venous catheters, changes in antibacterial use, and antibacterial resistance; when antibacterial prophylaxis is given, local resistance patterns have been shown to affect the aetiology of infections.[4]

TREATMENT. Onset of fever in neutropenic patients is indicative of potentially serious infection that may progress to septicaemia and death. The severity of infections depends on many factors (see above) and it is therefore difficult to produce a standard drug regimen; in addition, the choice of empirical therapy must be adapted according to prevailing local antibacterial susceptibility patterns. Guidelines have been produced in many countries, of which those issued by the Infectious Diseases Society of America[5] for both the initial and subsequent management of febrile neutropenic patients are fairly typical:

- empirical antibacterial therapy should be given promptly to all neutropenic patients at the onset of fever; afebrile neutropenic patients who show signs and symptoms compatible with infections should also receive empirical antibacterial treatment
- consideration should be given to whether the patient requires vancomycin therapy. If so, treatment should begin with vancomycin plus cefepime, ceftazidime, or a carbapenem, with or without an aminoglycoside.
- if vancomycin is not indicated, intravenous monotherapy should be given with
  - either a cephalosporin (cefepime, although concerns have been raised about its safety,[6] or ceftazidime) or a carbapenem (imipenem-cilastatin or meropenem) for uncomplicated cases
  - in more complicated cases, or where resistance is a problem, combined treatment should be given with an aminoglycoside and one of cefepime, ceftazidime, a carbapenem, or an antipseudomonal penicillin such as ticarcillin with clavulanic acid or piperacillin with tazobactam.
- low-risk patients may be treated empirically either orally with ciprofloxacin and amoxicillin with clavulanic acid, or intravenously as for uncomplicated cases above. Initial treatment with oral antibacterials alone is, however, not recommended for children[5]

The initial regimen usually needs to be given for 3 to 5 days in order to determine its efficacy. In *patients in whom fever resolves* and in whom a causative organism is identified, antibacterial treatment should be modified for the specific organisms and broad-spectrum antibacterials continued for at least 7 days or until culture results are negative and the patient has clinically recovered.[5] In afebrile patients in whom no causative organism is found but who were considered at high risk at the onset of treatment, the same antibacterials should be continued intravenously; those considered at low risk initially may be switched to oral therapy with ciprofloxacin plus either amoxicillin-clavulanic acid (adults) or cefixime (children).[5]

Patients in whom fever persists throughout the first 3 to 5 days but for whom no aetiology is determined may have a non-bacterial infection, a bacterial infection that is refractory to treatment, the emergence of a second infection, or drug fever.[5] Such patients should be reassessed and then one of three options followed. If the patient's condition is clinically stable, the same antibacterial treatment may be continued; if there is still no change in the patient's condition, consideration should be given to stopping vancomycin if it has been given. Alternatively, if there is evidence of progressive disease or drug toxicity, the antibacterials given may be changed; if vancomycin has not been given, it may be added to the regimen. The third option is to add an antifungal drug (amphotericin B) with or without a change to the antibacterial regimen if the patient is febrile through days 5 to 7 and resolution of neutropenia is not imminent.[5]

The optimum *duration of therapy* is governed by the clinical situation. The most important determinant of successfully stopping antibacterials is the neutrophil count:[5]

- if no infection is identified after day 3, the neutrophil count exceeds 500 cells/mm^3 for 2 consecutive days, and the patient has been afebrile for at least 48 hours, then antibacterial treatment may be stopped
- if neutropenia persists in the absence of fever, it is reasonable to stop antibacterial treatment after 5 to 7 days in patients who were initially considered at low risk and who are clinically well, though such patients should be closely monitored and intravenous antibacterials reinstigated immediately on recurrence of fever or evidence of infection.[5] In afebrile patients with profound neutropenia (less than 100 cells/mm^3), or in those with mucositis or other risk factors, continuous antibacterial treatment should be considered throughout the entire neutropenic period
- in patients with persistent fever and prolonged neutropenia in whom haematological recovery cannot be anticipated, consideration may be given to stopping antibacterials after 2 weeks if no infection has been identified and careful observation is possible.[5]
- clinically well patients with persistent fever may have their antibacterials stopped after 4 to 5 days if the neutrophil count remains at least 500 cells/mm^3 throughout this period and there is no sign of infection and no response to therapy; such patients should be closely monitored for subsequent infections which are usually easily treatable, and empirical amphotericin B should be considered despite cessation of antibacterials if fever persists for 5 to 7 days after the start of initial therapy[5]
- patients who remain febrile after recovery from neutropenia and despite broad-spectrum antibacterials should be reassessed for undiagnosed infection which may be fungal, mycobacterial, or viral

The routine use of colony-stimulating factors as an adjunct to antibacterial treatment is not generally recommended[5] but may be indicated in febrile neutropenic patients at high risk of serious infections or infection-related complications; examples include some patients with malignant neoplasms[7,8] and those with persistent severe neutropenia and infections that are not responsive to antibacterials alone.[5] A systematic review[9] of the use of colony-stimulating factors in patients with febrile neutropenia due to cancer chemotherapy concluded that their use did not affect overall mortality but did reduce time spent in hospital and the neutrophil recovery time.

PROPHYLAXIS. Most infections in immunocompromised patients are caused by organisms from their own alimentary tract and in cancer patients, for example, may follow chemotherapy-induced mucosal damage to the tract. Several prophylactic strategies have been used to try to reduce the risk of infection during severe neutropenia, such as isolation of the patient, granulocyte transfusion, active or passive immunisation, acceleration of granulocyte recovery, and antibacterial prophylaxis. Possible antibacterial prophylactic regimens have included selective decontamination of the alimentary tract using oral nonabsorbable antibacterials (see also under Intensive Care, p. 189.3) or treatment with absorbable antibacterials (most commonly a fluoroquinolone or co-trimoxazole). A systematic review of 101 randomised, controlled, studies in 12 599 afebrile neutropenic patients (mostly with leukaemia) found that antibacterial prophylaxis significantly decreased the risk of death from all causes by 34% when compared with no intervention; the most significant reduction in mortality was associated with the use of fluoroquinolones.[10]

Although antibacterial prophylaxis is also effective in afebrile patients likely to be neutropenic, the efficacy of empirical treatment means that prophylaxis is less widely used[11] and the Infectious Diseases Society of America[5] discourages routine use; reasons include toxicity of the antibacterial, potential fungal overgrowth, and problems of bacterial resistance.

Immunocompromised patients may benefit from appropriate immunisation against common infections, although precautions relating to the use of live vaccines in such patients should be observed (p. 2375.2).

The duration and severity of neutropenia can be reduced by the use granulocyte or granulocyte-macrophage colony-stimulating factors, and this may be a useful adjunct in infection control in selected patients.[7] Bone marrow protective agents such as amifostine are also being studied.

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Intensive care

Like immunocompromised patients (p. 186.3), those in intensive care units (ICUs) are often very susceptible to endogenous infections, especially respiratory and urinary-tract infections, arising from gastrointestinal colonisation by aerobic Gram-negative bacilli acquired in hospital. The incidence of pneumonia in ICU patients ranges from 7 to more than 40%,[1] and mortality from ventilator-associated pneumonia may exceed 30 to 50%.[2,3] For further information on ventilator-associated pneumonia see under Pneumonia, p. 202.1.

Selective decontamination regimens aim to reduce this risk by eliminating potentially pathogenic organisms from the throat and intestines while preserving the indigenous, mostly anaerobic, flora.[4]

- selective decontamination of the digestive tract (SDD), uses non-absorbable antibacterials given orally and through a nasogastric tube; in some studies systemic antibacterials (usually cephalosporins) were added in the first 4 days of the ICU stay to prevent early infections
- selective oropharyngeal decontamination, (SOD) uses topical oral application of antibacterials or antiseptics, such as chlorhexidine gluconate or povidone-iodine

In an initial report[5] in 1984 SDD reduced the incidence of nosocomial infection from 81 to 16% in a group of multiple trauma patients. Since then further studies have been done to evaluate the efficacy of SDD in ICU patients. While results showed that SDD reduced infection-related morbidity, its effect on mortality was not clear. Furthermore other outcomes, such as beneficial effects on duration of ventilation, ICU or hospital stay, and cost-efficacy were also uncertain.[6] Selection of antibacterial resistance is considered a serious adverse effect[6] and the preventive effects of SDD have been considerably lower in ICUs with high endemic levels of antibacterial drug resistance.[7] SOD may therefore be an attractive option because the antiseptics and antibacterials used have a low potential for induction and selection of antibacterial resistance.[8] A systematic review and meta-analysis[3] of 11 randomised controlled studies (up until May 2006) suggested that in mechanically ventilated patients, antiseptic SOD prophylaxis reduced the incidence of ventilator-associated pneumonia; but no firm conclusions could be made on the effect of antibacterial SOD. Neither of the two oral decontamination regimens appeared to affect mortality, duration of mechanical ventilation, or stay in the ICU. A later meta-analysis[1] of 36 randomised controlled studies (published up until March 2009 and involving 6914 patients) assessed the effect of prophylactic antibacterial regimens for the

prevention of respiratory-tract infections and overall mortality in adults receiving intensive care. It found that a combination of topical and systemic prophylactic antibacterials reduced respiratory-tract infections and overall mortality; treatment based on topical prophylaxis alone reduced respiratory infections but not mortality. A large, multicentre study[9] conducted in 13 ICUs using cluster randomisation showed that the use of either SOD or SDD was associated with improved mortality in critically ill adults.

The risk of antibacterial resistance was evaluated in only one study[1,10] This prospective, randomised, controlled study of 934 patients admitted to a surgical and medical ICU compared a SDD regimen with a control group receiving standard treatment.[10] Colonisation with Gram-negative bacteria resistant to ceftazidime, ciprofloxacin, imipenem, colistin, or tobramycin occurred in 16% of SDD patients and in 26% of those in the control group. No patient in either group was colonised with MRSA, while 1% of all patients were colonised with vancomycin-resistant enterococcus.

Although SDD reduces hospital-acquired pneumonia, US guidelines discourage routine antibacterial prophylaxis,[7,11] especially in hospital settings where there are high levels of antibacterial resistance,[7] and particularly in relation to prevention of nosocomial pneumonia.[11] CDC guidelines do, however, recommend topical oral chlorhexidine gluconate 0.12% during the perioperative period only for adults undergoing cardiac surgery.[7]

Another potential source of infection in intensive care is from the use of **intravascular catheters**. Catheter-related bloodstream infections occur in 3 to 10% of patients with inserted catheters[12,13] and are a leading cause of nosocomial bloodstream infection in ICUs.[13] Most serious catheter-related infections are associated with central venous catheters.[14] Conditions that compromise host defences (including severe burns and malnutrition), severe sepsis, or severe and sustained multiple organ dysfunctions are associated with a higher risk of catheter-related bloodstream infections.[15] Colonisation of the catheter tip due to migration of skin organisms from the insertion site into the cutaneous catheter tract is the most common route of infection for short-term central venous catheters.[13,15] For long-term catheters (those staying in place more than 15 days), colonisation is mainly due to manipulation of the venous line with migration of organisms along the internal lumen of the catheter.[13, 15] The ability of organisms to adhere to host proteins such as fibronectin that commonly build up on catheter tips, makes colonisation easier.[13,15] The organisms implicated most often are coagulase-negative staphylococci;[13,14] other organisms commonly involved include *Staphylococcus aureus*, *Candida* spp., *Enterococci*, and Gram-negative bacilli.[13]

Guidelines for the **prevention** of infection associated with both peripheral intravascular and central venous catheterisation have been developed.[14,16-18] Prevention and control of infection involves several interventions, which should be used in combination.[13-15,19] Intervention measures include:

- barrier precautions at the time of catheter insertion
- disinfection of the skin at the insertion site with chlorhexidine or alternatively povidone-iodine
- the use of catheters impregnated with antibacterial (usually rifampicin or minocycline) or antiseptic agents (commonly chlorhexidine or silver sulfadiazine)
- use of good aseptic technique and hand hygiene (see p. 1733.1) when accessing or maintaining the catheter system

Antibacterial prophylaxis has not been shown to reduce the rate of infection when given during catheter insertion,[13,15] but when antibacterials were given with a central venous catheter in place, risks for catheter colonisation and bloodstream infections were significantly reduced.[13] However, the use of prophylactic antibacterials is discouraged because of concern over the emergence of resistant organisms.[18,19] Antibacterial ointments (such as bacitracin, mupirocin, neomycin, and polymyxin B) or antiseptic ointments applied to catheter-insertion sites increase the rate of catheter colonisation by fungi, promote the emergence of antibacterial-resistant bacteria, and have not been shown to decrease the rate of infections.[13] Studies suggest that anticoagulants such as heparin and low-molecular-weight heparins are able to decrease fibrin sheath and thrombus formation around the catheter and in so doing reduce catheter-related infections.[15,20] Routine replacement of short-term catheters as a means to reduce infection rates is not recommended.[13,18]

Guidelines for the diagnosis and **management** of intravascular catheter-related infections have been developed by experts in the USA.[21] Antibacterials for catheter-related infections are often given empirically and the choice of drug should take into account local antibacterial susceptibility data and the severity of disease, and should usually cover coagulase-negative staphylococci. Empirical therapy with vancomycin is generally recommended where there is a high prevalence of MRSA. Daptomycin may be given as an alternative if isolates have vancomycin MIC values greater than 2 micrograms/mL. Linezolid is not recommended for empirical therapy.[21] For empirical treatment of infection thought to be caused by Gram-negative bacilli, a fourth-generation cephalosporin, carbapenem, or combinations of a beta lactam and beta-lactamase inhibitor, with or without an aminoglycoside is recommended; combination antibacterial treatment should be given when multidrug-resistant Gram-negative bacilli (such as *Pseudomonas aeruginosa*) are suspected in neutropenic or severely ill patients with sepsis, or in those known to be colonised with such pathogens.[21]

Antibacterial treatment can be stopped after 10 to 14 days if a response is seen within 2 to 3 days. A longer treatment duration of 4 to 6 weeks is recommended for patients with persistent fungaemia or bacteraemia after catheter removal, for patients who are found to have infective endocarditis or suppurative thrombophlebitis, and for paediatric patients with osteomyelitis; 6 to 8 weeks of treatment are recommended for adults with osteomyelitis.[21]

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Legionnaires' disease

Legionella pneumophila is an aerobic, Gram-negative bacterium that was first identified in 1977 as the result of an outbreak of severe pneumonia at a convention of the American Legion. Legionnaires' disease is the pneumonic form of the infection and is a relatively common cause of community acquired pneumonia (see p. 202.1); non-pneumonic infection (called Pontiac fever) is a milder, usually self-limiting, flu-like illness. Legionellosis has been suggested as a broad term to cover pneumonic and non-pneumonic clinical syndromes caused by any *Legionella* spp., which may include *L. bozemanii*, *L. micdadei* (Pittsburgh pneumonia agent), and *L. wadsworthii*. These bacteria are found worldwide in the environment and particularly in warm water and warm damp places. Infection is usually transmitted by aerosolisation or aspiration. Serious outbreaks have been associated with infected air-conditioning systems or water supplies. Older adults, smokers, and immunocompromised people are particularly susceptible to Legionnaires' disease. Symptoms usually begin 2 to 14 days after being exposed to the bacteria and are similar to other forms of pneumonia. The severity of disease ranges from a mild cough to a rapidly progressive pneumonia with respiratory failure, shock, and multi-organ failure.

The mortality rate from Legionnaires' disease is dependent on the severity of the disease, the appropriateness of initial antibacterial treatment, the setting where infection was acquired, and host factors. In untreated immunocompromised patients the mortality rate may be 40 to 80%; if treated appropriately this decreases to 5 to 30%. For immunocompetent patients the mortality rate is about 10 to 15%. The usual **treatment** for mild to moderate *Legionella* infections is with an oral macrolide, with erythromycin now increasingly replaced by azithromycin;[1,2] clarithromycin, roxithromycin, or telithromycin may be further acceptable alternative macrolides.[1,2] Oral fluoroquinolones (such as ciprofloxacin, levofloxacin, or moxifloxacin) are also increasingly recommended as alternatives to the macrolides.[1-3] Doxycycline or co-trimoxazole are further alternatives.[1,2,4] For severe infections or in immunocompromised patients parenteral therapy (if available) with azithromycin, clarithromycin, or a fluoroquinolone is recommended.[1,2] Combination intravenous treatment with erythromycin and rifampicin has also been used for severe infections.[2] Rifampicin has also been given with fluoroquinolones or doxycycline, especially in severe or deteriorating illness or in immunocompromised patients, although this may be of little further benefit.[2] Generally about 7 to 10 days of treatment should be given to those with mild to moderate infections, while those with more severe infections, multisystem disease, or who are immunocompromised should be treated for up to 21 days.[1,2] However, patients treated with oral azithromycin may only need 3 to 5 days treatment due to its long half-life and tissue retention.[1,2]

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Leprosy

Leprosy (Hansen's disease) is a chronic disease caused by the bacillus, *Mycobacterium leprae*; it has a prolonged incubation period (years) and slow onset of symptoms. Disease results from bacillary infiltration of the peripheral nervous system, skin, eyes, respiratory mucosa, bones, and testes. It is not highly infectious and transmission requires both prolonged close contact with an infected patient and an inherent immunological susceptibility to the disease in the exposed person. Clinical leprosy may be regarded as a consequence of deficient cell-mediated immunity in susceptible individuals; most individuals are naturally immune, and symptoms are suppressed. The clinical manifestations depend on the bacillary load and the host's immune response to the mycobacterium. Patients with leprosy may be classified as having:

- **Multibacillary** (or lepromatous) leprosy, which occurs when cellular immunity is largely deficient, and includes the sub-groups lepromatous (LL), borderline lepromatous (BL), and midborderline leprosy (BB), as well as any other types giving a positive skin smear for acid-fast bacilli. Generally the lepromin test (p. 2543.3) is negative.
- **Paucibacillary** (or tuberculoid) leprosy, which results when cellular immunity is only partially deficient, and includes the sub-groups borderline tuberculoid (BT), tuberculoid (TT), and indeterminate leprosy (I) when the skin smear is negative. Generally the lepromin test is positive.

For the purpose of treatment, WHO classifies patients with more than 5 skin lesions as having multibacillary leprosy, and those with 1 to 5 skin lesions as having paucibacillary leprosy. The use of this clinical classification avoids the necessity to provide facilities for bacteriological examination of skin smears.

Changes in the hosts immune response to the mycobacteria may result in **lepra reactions** and unless treated these may lead to severe nerve and tissue damage.[1] Most reactions belong to one of two main types:

- **Type 1** lepra reactions, or reversal reactions, are caused by spontaneous increases in T-cell reactivity to mycobacterial antigens (type IV hypersensitivity) and occur in patients with borderline forms of leprosy. These reactions are characterised by erythema and oedema of the skin and tenderness of peripheral nerves. Prompt treatment with corticosteroids is necessary to prevent permanent nerve damage.[2-5] Treatment is usually continued for 3 to 6 months. Adding azathioprine may

permit the use of lower cumulative doses of corticosteroid.[6] Methotrexate was found to be effective in treating a patient intolerant to corticosteroids,[7] while ciclosporin is considered to be effective for chronic neuritis.[2,8] Prophylactic use of low-dose corticosteroids during the first 4 months of standard multidrug treatment for leprosy has also been investigated, and found to decrease the number of reactional episodes by 75%; but the protective effect was lost by the end of 12 months.[9]

- **Type 2** lepra reactions, also known as erythema nodosum leprosum (ENL), represent a systemic inflammatory response (type III hypersensitivity) to dead bacteria and are accompanied by high levels of circulating tumour necrosis factor alpha (TNF α). This reaction occurs only in patients with borderline lepromatous or lepromatous leprosy. Mild type 2 reactions may be treated with anti-inflammatories but moderate or severe reactions should be treated with corticosteroids or thalidomide (in males and post menopausal women).[2-4] The incidence and severity of ENL has decreased since the inclusion of clofazimine in multidrug regimens, probably owing to the drug's anti-inflammatory action.[2] Clofazimine does not act as rapidly as either corticosteroids or thalidomide, nor is it as effective.[2] However, clofazimine may be used with a corticosteroid in patients with severe ENL who are not responding adequately to treatment with corticosteroids alone or when the risk of toxicity with corticosteroids is high; it may be given alone when corticosteroids are contra-indicated.[10] Other TNF α inhibiting drugs that have been tried include pentoxifylline[5,11] and infliximab.[12] Chloroquine has also been used with limited effect.[1] Antileprotic drug therapy is generally continued during lepra reactions.

Although measures to manage the consequences of nerve damage and lepra reactions are an important part of the management of leprosy, curative antibacterial therapy is the mainstay of **treatment**. Dapsone monotherapy, long the basis of this, has been replaced since the 1980s with multidrug oral regimens designed to overcome the development of resistance. Dapsone, rifampicin, and clofazimine form the elements of the standard combinations.[5,13] Newer alternatives include clarithromycin, minocycline, and fluoroquinolones such as ofloxacin, moxifloxacin, and pefloxacin. These may be used as second-line therapy for patients unable to tolerate dapsone or clofazimine. Ethionamide or protionamide have been used in light-skinned patients to avoid clofazimine's tendency to pigment the skin, but are no longer recommended because of their risk of hepatotoxicity.

The most widely used multidrug regimens are those recommended by WHO[10] and in these the choice of drugs and length of treatment are based on the clinical classification outlined above.

- MULTIBACILLARY LEPROSY

  The standard regimen recommended by WHO for multibacillary leprosy is rifampicin 600 mg and clofazimine 300 mg both given once a month, with clofazimine 50 mg and dapsone 100 mg both daily. Treatment is continued for 12 months.[4,10]

  A 2-year treatment duration was chosen originally because it is highly effective in the majority of cases and avoids the need to assess response with skin smears. However, such a long treatment duration is an obstacle to implementing treatment programmes in areas where healthcare is inaccessible or the infrastructure is poor. Ongoing clinical studies and experience with patients defaulting from treatment have encouraged WHO to now recommend that treatment for 12 months is adequate.[4] Early hopes that reducing duration of treatment to as little as one month would be possible have not been supported by a study using daily rifampicin and ofloxacin.[14]

  In patients for whom rifampicin is unsuitable because of resistance or intolerance, WHO recommends[10] daily treatment with clofazimine 50 mg, ofloxacin 400 mg, and minocycline 100 mg for the first 6 months; treatment is then continued for at least a further 18 months with clofazimine plus either minocycline or ofloxacin.

  If the toxic effects of dapsone are severe, it should be stopped and treatment continued with rifampicin and clofazimine in the standard dosage for 12 months.[10]

  Rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg (ROM) given once a month for 24 months was found to be as effective as the WHO standard regimen given for 24 months[15] and has been suggested as an alternative regimen, particularly for those who cannot take clofazimine.[3,10]

- PAUCIBACILLARY LEPROSY

  The WHO recommended regimen[4,10] for paucibacillary leprosy is rifampicin 600 mg monthly and dapsone 100 mg daily. Treatment is continued for 6 months. If there are severe toxic effects with dapsone it should be substituted with clofazimine 300 mg monthly and 50 mg daily for 6 months.[10]

  On the basis of a clinical study[16] showing that a single dose each of rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg given together is only slightly less effective than standard multidrug treatment, WHO has suggested that this is a suitable alternative for patients with single-lesion paucibacillary leprosy.[3] However, reservations have been expressed about the study, including concerns regarding the short follow-up[17] and poor microbiological rationale.[18]

- RELAPSE

  Relapse after a recommended course of multidrug therapy for multibacillary or paucibacillary leprosy can occur and WHO recommends re-treatment with the initial regimen.[3,4] Although the relapse rate after standard multidrug therapy for multibacillary leprosy is generally low,[3,19] there is insufficient information on the long-term efficacy of shorter treatment courses.[14]

- PREGNANCY

  Standard multidrug therapy is safe during pregnancy.[4,5] Leprosy patients who are pregnant or breast feeding may experience clinical deterioration and, in general, antileprotic therapy is continued in such patients.

- PROPHYLAXIS

  Leprosy is spread from person to person through respiratory droplets, so household contacts may become infected. A systematic review and meta-analysis[20] has concluded that prophylaxis, usually with dapsone, in some household contacts may prevent disease in this high-risk group. A large randomised placebo-controlled study[21] found that a single dose of rifampicin given to contacts of new patients with leprosy significantly reduced the incidence of developing leprosy in the first 2 years but no difference was noted beyond 2 years. WHO[3] suggests that contacts of newly diagnosed cases should be examined for evidence of leprosy and then advised how to watch for early signs of the disease; prophylaxis with rifampicin or other antileprotics is not recommended in leprosy control programmes. BCG vaccine appears to be protective. Vaccines specifically against leprosy are under investigation.

- ELIMINATION

  The multidrug therapy regimens recommended by WHO have been widely implemented in recent years raising the possibility of eliminating leprosy as a public health problem: that is, reducing the prevalence to less than 1 case per 10 000 population in endemic areas. Considerable progress towards this target has been made, and it was announced in 2001 that the global level of leprosy had decreased by over 90%. Full control of leprosy, however, has still not been attained in several countries and continued efforts are necessary. WHO has since developed a global strategy for the further reduction of the leprosy burden and sustained leprosy control.[22]

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Leptospirosis

Leptospirosis is a zoonotic infection caused by serovars of spirochaetes from the genus *Leptospira*, such as *Leptospira interrogans*. These are carried by wild, domestic, and farm animals, and can be spread to humans by contact with urine, blood, or tissue of infected animals or a contaminated environment. Leptospirosis is more common in tropical and subtropical areas, where the climate and greater contact with infected environments increase the likelihood of infection. Occupational groups most at risk include farmers and agricultural workers, although there have been outbreaks among participants in water-sports. The organisms enter the body through broken skin or intact mucous membranes, can infect any internal organ, and cause damage to the walls of small blood vessels. Many infected people remain asymptomatic and most patients with symptoms have a relatively mild course of infection with an acute flu-like illness characterised by fever, myalgia, headache, and conjunctival suffusion. A small proportion, however, develop severe leptospirosis (Weil's disease), with haemorrhagic complications, jaundice, and renal impairment.

The routine use of antibacterials to **treat** leptospirosis is controversial as most cases are self-limiting,[1] and there is insufficient evidence to provide clear guidelines for treatment. However, treatment is usually recommended as soon as the diagnosis of leptospirosis is suspected,[1,2] and preferably within 5 days of the onset of symptoms.[2] Intravenous benzylpenicillin is recommended for severe leptospirosis.[2] Intravenous ceftriaxone,[3] cefotaxime, or doxycycline[4] are alternatives. Aminoglycosides such as streptomycin are used in some countries.[5] Oral antibacterials such as amoxicillin, ampicillin, doxycycline, or erythromycin may be used in milder infections.[2] Jarisch-Herxheimer reactions may occur after penicillin treatment (see Adverse Effects, under Benzylpenicillin p. 231.2).[1] Preliminary data have suggested that azithromycin may be effective in mild to moderate leptospirosis; fluoroquinolones and carbapenems have also shown activity *in vitro*.[5]

The incidence of leptospirosis in US soldiers in Panama was reduced when they were given **prophylaxis** with weekly oral doxycycline throughout the period of exposure.[6] Prophylaxis has been suggested for travellers at increased risk of infection, beginning 1 to 2 days before and continuing throughout the period of exposure.[7] Leptospirosis vaccines are available in some countries (see p. 2397.3).

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Listeriosis

Listeriosis is an infection caused by *Listeria monocytogenes*, an anaerobic, food-borne, Gram-positive bacterium that occurs ubiquitously and is found in soil, water, and vegetation. It is able to grow in a wide range of temperatures, including those found under refrigeration.

Although exposure to *L. monocytogenes* is inevitable, infection is relatively rare in humans.[1-3] When it occurs, it follows ingestion of food contaminated with a high concentration of the bacteria; foods at high risk of contamination include processed and unprocessed dairy products (especially those made with unpasteurised milk), cold meats, pâté, raw vegetables, and salads. The incubation period may range from 1 or 2 days up to 3 months. Those who are immunocompetent may have a self-limiting gastroenteritis after consumption,[1,2] and a mild cutaneous infection has occurred in those who have directly handled infected products or animals.[1,2] Occasionally invasive disease (listeriosis) occurs, especially in the immunocom-

promised, the young and elderly, and in pregnant women and their fetuses and neonates. Listerial meningitis and bacteraemia are the most common presentations; the latter may lead to endocarditis.[1,3] *L. monocytogenes* may also cause meningoencephalitis, focal CNS infection, and infection of visceral organs, the eye, bones, and joints, and pleural, peritoneal, and pericardial spaces.[1,2] Listeriosis is fatal in up to a third of cases.[1,2,4]

Listerial infection is especially dangerous to the fetus and neonate. Pregnant women are prone to developing listerial bacteraemia (although CNS involvement is rare). The bacteria cross the placenta and infect the fetus; fetal distress, spontaneous abortion, still-birth, or premature delivery may then occur. Maternal deaths are rare but the fetal mortality rate is up to 50%. Infection may also occur during delivery, and perinatal sepsis or meningitis are common. Late-onset illness may develop up to a month after delivery.[1,2]

The treatment of choice is intravenous ampicillin at high doses,[1-4] although penicillin is also active. An aminoglycoside, usually gentamicin, is often added for synergy.[1-5] Those with a penicillin allergy may be given co-trimoxazole,[1,3-5] vancomycin,[1,3] teicoplanin,[1] or erythromycin.[5] Reports of the successful use of other antibacterials include listerial meningitis treated with levofloxacin and meropenem;[6] endocarditis in a patient intolerant of standard therapy treated with oral linezolid;[3] listerial meningitis and brain abscesses refractory to standard therapy treated with intravenous linezolid and meropenem;[4] and rhombencephalitis successfully treated with linezolid.[7] Rifampicin has also been used but resistance has been reported with monotherapy.[5] Cephalosporins,[1,5] fosfomycin,[5] and nalidixic acid[5] are ineffective. Some fluoroquinolones (such as ciprofloxacin) show decreased susceptibility, however, the newer fluoroquinolones such as levofloxacin and moxifloxacin have strong bactericidal activity against *L. monocytogenes*.[5] Therapy should continue for 2 weeks in those with bacteraemia, 3 weeks in meningitis, 4 to 6 weeks in endocarditis, and 6 to 8 weeks in brain abscess or encephalitis.

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Lyme disease

Lyme disease is a seasonal infectious disease caused by the spirochaete *Borrelia burgdorferi* and transmitted mainly by *Ixodes* ticks. *I. scapularis*, one of the species of ticks that may cause Lyme disease, may also be infected with, and transmit, *Anaplasma phagocytophilum* and/or *Babesia microti* and therefore the bite from this tick may lead to Lyme disease, human granulocytic anaplasmosis (see Ehrlichiosis, p. 179.1), or babesiosis (p. 922.2) as a single infection or as a co-infection.[1] Lyme disease was first recognised in the 1970s in Lyme, Connecticut, but when the spirochaete responsible was later identified, it was found to occur worldwide with regional variations. Lyme disease is a multisystem disease characterised by inflammatory reactions that mainly affects the skin, nervous system, heart, and joints, and can be divided into 3 stages. In the early stage a characteristic skin lesion (erythema migrans) occurs at the site of the tick bite and may be accompanied by flu-like or meningitis-like symptoms. This may be followed weeks or months later by signs of disseminated infection, including neurological and cardiac abnormalities, and even years later by chronic arthritis and the late skin manifestation acrodermatitis chronica atrophicans, both signs of persistent infection.

Appropriate **treatment** should prove curative, especially in the early stages. Recommendations for treatment[1-4] give oral tetracyclines (doxycycline or tetracycline) and the beta-lactam antibacterials (amoxicillin, phenoxymethylpenicillin, or cefuroxime) as the antibacterials of choice for *early* Lyme disease in the absence of neurological symptoms or advanced AV block. Treatment is usually for 14 days (range 10 to 21 days for doxycycline and 14 to 21 days for amoxicillin or cefuroxime). The macrolides (azithromycin, clarithromycin, erythromycin, and roxithromycin) are less effective and should only be used in patients allergic to, or who cannot be given, first-line drugs.[2,3] Young children (usually specified as below 8 years of age in the US and below 12 years in the UK) may be given amoxicillin or cefuroxime.[1,3] Pregnant women should avoid tetracyclines but may be given any of the other oral regimens.[1,3]

Adults and children presenting with *neurological symptoms*, either early or late, should be treated with intravenous ceftriaxone, cefotaxime, or benzylpenicillin for 14 to 28 days. Patients allergic to cephalosporins or penicillins may be given oral doxycycline 200 to 400 mg daily in 2 divided doses.[1,3] Early Lyme disease with *cardiac* complications may be treated with either an oral or intravenous antibacterial for 14 to 21 days. Lyme *arthritis* can generally be effectively treated with one of the oral regimens given for 28 days. Patients with ongoing or recurrent joint pain after the initial treatment course may be re-treated with either another 4-week course of oral antibacterials or with intravenous ceftriaxone for 2 to 4 weeks. *Acrodermatitis chronica atrophicans* may be treated with an oral antibacterial for 21 days.[3]

A small percentage of patients continue to have non-specific symptoms after appropriate treatment of Lyme disease; there is some controversy over whether prolonged treatment is effective in these patients and studies have suggested otherwise.[5-8] The use of antibacterials in patients with chronic (more than 6 months) subjective symptoms after recommended treatment is hotly debated[9,10] but the Infectious Diseases Society of America (IDSA) does not support such therapy.[3]

Adults and older children *co-infected* with *A. phagocytophilum* should be treated with doxycycline for 10 days. In the US, recommended treatment for severely ill children less than 8 years of age is doxycycline for 4 to 5 days followed by amoxicillin or cefuroxime to complete a 14-day course. Patients with mild illness and who cannot be given a tetracycline may be given rifampicin 300 mg twice daily for 7 to 10 days plus amoxicillin or cefuroxime.[3]

Preventive measures against Lyme disease include the use of tick repellents, physical protection,[3,11,12] and prompt removal of attached ticks.[3] Most guidelines[3,11] do not support the use of empirical antibacterial therapy or serologic testing after tick bites as generally the risk of infection is low,[13] particularly if the tick is removed promptly. The risk of infection may, however, be greater if the tick has fed to repletion.[14] A study[15] has shown that empirical treatment with a single dose of doxycycline given within 72 hours of a tick bite may be warranted in endemic areas where the probability of infection is high. Although routine antibacterial prophylaxis is not recommended by the IDSA,[3] they recommend that a single dose of doxycycline may be given provided that the tick has been attached for 36 hours or more, prophylaxis can be started within 72 hours of the time of tick removal, and the tick species can be identified as *I. scapularis*. Lyme disease vaccines are available in some countries.

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Lymphogranuloma venereum

See under Sexually Transmitted Diseases, p. 207.2.

Melioidosis

Melioidosis (or Whitmore's disease)[1-3] is caused by the Gram-negative aerobic bacterium *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), and *naturally occurring infection* is common in tropical and sub-tropical regions where it is found in soil, mud, and water; it is endemic in south-east Asia and northern Australia.[1] Its true incidence and distribution may, however, be much wider than originally thought. *B. pseudomallei* has some features that makes it a candidate for *deliberate release* as a bioweapon.

Naturally acquired infection usually occurs by inoculation, or sometimes by inhalation or aspiration. Most cases occur in people with some underlying medical condition such as diabetes, chronic kidney or liver disease, or those who are immunocompromised (but HIV infection does not appear to be a major risk factor); person-to-person spread is extremely rare. The incubation period ranges from 1 to 21 days and is thought to depend on the size and route of the inoculum; latent intervals as long as 62 years have been reported. The expected incubation period after deliberate release of aerosol-based biological weapons is 10 to 14 days. Diagnosis is difficult because of the broad range of clinical manifestations. Melioidosis ranges from localised infection to acute pneumonia and fulminant septic infection; any organ or part of the body can become chronically infected. However, most cases present as a febrile illness with severe pneumonia and sepsis. Patients may become overwhelmed by the infection and die from septic shock within 48 hours of developing symptoms. Untreated, the mortality rate for melioidosis with septicaemia approaches 100%, but with optimal treatment this can be reduced: in Thailand melioidosis is associated with a case fatality rate of about 50%,[1,2] while in Australia, the rate is about 20%.[2] The prognosis of melioidosis is much better in children than in adults, and relapse is rare.[1]

Melioidosis is difficult to treat, and response to **treatment** is often slow despite high-dose parenteral antibacterials being given. *B. pseudomallei* is also intrinsically resistant to many antibacterials including some third-generation cephalosporins, penicillins, rifamycins, and aminoglycosides; it shows relative resistance to fluoroquinolones and macrolides.[2] Treatment was based on anecdotal regimens until, in a study from Thailand,[4] intravenous ceftazidime halved the mortality of severe melioidosis when compared with conventional parenteral treatment with high doses of chloramphenicol intravenously, doxycycline, and co-trimoxazole. As a result ceftazidime came to be considered the treatment of choice for the intensive phase of treatment.[1,2,5] Alternatives include the carbapenems such as imipenem and meropenem.[1,2,5] Cefoperazone with sulbactam and amoxicillin with clavulanic acid have also proved effective and the latter may be given as empirical treatment for septicaemia in areas where melioidosis is endemical.[1,2] Resistance to ceftazidime and amoxicillin-clavulanic acid has been reported,[6] emphasising the importance of careful monitoring for the emergence of resistance during treatment. Ceftazidime plus co-trimoxazole, both given intravenously, has been advocated by some for severe melioidosis, especially in patients with septicaemia.[7] High dose parenteral antibacterial treatment should be given for at least 10 to 14 days for systemic infections followed by eradication-phase (or maintenance treatment) with oral antibacterials. Prolonged intensive-phase parenteral therapy is generally used for deep-seated infections such as osteomyelitis, multiple undrained abscesses, or CNS infection. Granulocyte colony-stimulating factor (G-CSF) has been added to intensive phase therapy (usually meropenem) to decrease early mortality in patients presenting with severe sepsis.[2,3] Introduction of G-CSF therapy at one hospital in Australia was reported to decrease the mortality rate from 95 to 10%.[8] However, a study in Thailand, reported no significant effect on mortality when G-CSF was given to patients with severe sepsis.[9]

Oral treatment should only be started when there is clear evidence of clinical improvement.[1] In Thailand, a conventional treatment regimen of chloramphenicol given for the first 8 weeks of oral treatment, with doxycycline and co-trimoxazole given for 20 weeks, has been associated with relapse rates of about 10%;[1,2] this rate increased to nearly 30% if antibacterial treatment was taken for 8 weeks or less.[1] Lower relapse rates have been reported in Australia where co-trimoxazole monotherapy is given for 3 to 6 months.[2] A regimen of co-trimoxazole with doxycycline was found to be equivalent to the conventional regimen, as defined by culture-confirmed recurrence,[10] and treatment for at least 12 to 20 weeks is recommended by some experts.[3] In children and pregnant women high doses of amoxicillin with clavulanic acid may be given.[1,2,11] Some patients with mild infections, including skin and soft-tissue lesions and parotid abscesses, have been successfully treated with the oral regimens alone.[12]

Although there is no evidence of the protective efficacy of postexposure antibacterial **prophylaxis** in preventing melioidosis, on the basis of *animal* experiments doxycycline or co-trimoxazole may be given orally for 7 days to those known to have been exposed to heavy contamination.[13]

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Meningitis

Meningitis[1-4] refers to infection of the subarachnoid space and meninges, which may be caused by viruses, bacteria, protozoa, or fungi. The symptoms and signs of meningitis result from the host inflammatory response to infection. Whereas viruses cause the majority of generally mild cases of infectious meningitis, bacterial meningitis is usually a more serious condition. Meningitis may occasionally be a manifestation of non-infectious (auto-immune or neoplastic) disease. This section discusses bacterial meningitis and its management. For reference to fungal meningitis, see p. 566.3.

The bacteria most often found in adult or childhood meningitis (from 3 months of age) are *Neisseria meningitidis* (meningococci) and *Streptococcus pneumoniae* (pneumococci). *N. meningitidis* A, C, and W135 are the main subtypes involved in epidemics in the African meningitis belt, whereas B and C subtypes are responsible for outbreaks in Europe and North America. *Haemophilus influenzae* meningitis was a common cause of meningitis in infants and young children before the availability of *H. influenzae* type b vaccine, and this pathogen is still found in non-vaccinated young children, particularly in resource-poor countries. In neonates, infants, pregnant women, immunocompromised patients, and the elderly, *Listeria monocytogenes* and Gram-negative bacilli may also be encountered, and *Str. agalactiae* may cause meningitis in neonates and infants. Meningitis after head trauma, neurosurgery, or in the presence of CSF shunts is not infrequently caused by staphylococci (both *Staphylococcus aureus* and coagulase-negative staphylococci) or Gram-negative bacilli.

The bacteria are transmitted from person to person through droplets of respiratory or throat secretions. Infection is spread by prolonged close contact (such as kissing, sneezing and coughing, living in close quarters or dormitories, and sharing eating or drinking utensils). The average incubation period is 4 days, ranging between 2 and 10 days. The clinical presentation of acute bacterial meningitis is largely dependent on the patient's age. The classic manifestations of meningitis in older children and adults, including fever, headache, neck stiffness, photophobia, confusion, and vomiting, are rarely present in infants. In general, the younger the patient, the more subtle and atypical are the signs and symptoms. Fatality rates can be as low as 2% in infants and children, and as high as 20 to 30% in neonates and adults depending on the causative bacteria and patient's age. Brain damage, transient or permanent deafness, or learning disability may occur in up to one-third of survivors. A less common but more severe (often fatal) form of meningococcal disease is meningococcal septicaemia which is characterised by a widespread haemorrhagic rash, acute adrenal insufficiency, and rapid circulatory collapse. (For further information see Meningococcal Infections, p. 194.1.)

Choice of treatment. Bacterial meningitis is a medical emergency and almost universally requires hospitalisation. Death may occur in a matter of hours if left untreated. If a patient with suspected bacterial meningitis cannot be transferred to hospital urgently, UK guidelines[5] advise that treatment with parenteral benzylpenicillin should be started before transfer. Alternative antibacterials include a third generation cephalosporin or chloramphenicol.[6] Patients with suspected or confirmed bacterial meningitis should have blood and/or CSF samples taken for culture and receive *empirical* therapy until the causative organism has been identified and susceptibility patterns have become available.[7-9] Empiric antibacterials are given intravenously in relatively high doses, and treatment should be targeted at specific organisms as soon as the results of blood and/or CSF cultures are known. The choice of empirical therapy depends on the bacterial pathogens (and their antibacterial susceptibility patterns) that are most likely to have caused meningitis and varies with age and the presence of predisposing factors such as trauma or neurosurgery. Guidelines have been published for the UK[7,8,10,11] and the USA,[9] and country specific guidelines should be consulted where available.

- In most countries, a third generation cephalosporin (high-dose ceftriaxone or cefotaxime) is recommended as empirical treatment for bacterial meningitis in adults and children. These drugs are active against *N. meningitidis*, most *Str. pneumoniae* strains, and *H. influenzae*, and penetrate CSF well.
- Where ceftriaxone or cefotaxime are not available or are unaffordable, a combination of ampicillin and chloramphenicol or chloramphenicol alone may be used as an alternative.[12] For those patients allergic to both penicillins and cephalosporins, a combination of vancomycin and chloramphenicol may be given.[7]
- In patients over 55 years ampicillin should be added to cover *Listeria*.[8]
- Empirical treatment in neonates may also include ampicillin to cover *Listeria*, and an aminoglycoside to cover Gram-negative organisms.[9,13]
- In the USA and other areas where penicillin and cephalosporin-resistant pneumococci or meticillin-resistant staphylococci are encountered, vancomycin (with or without rifampicin) should be given with a third-generation cephalosporin to children or adults with bacterial meningitis.[4,7-10]
- Vancomycin together with ceftazidime (or/cefepime or meropenem) should be given to patients with meningitis complicating neurosurgery, head trauma, or CSF shunts. Because of concern of suboptimal CSF penetration, vancomycin should not be used alone in patients with meningitis due to resistant pneumococci or staphylococci, especially when dexamethasone is given as well.

The duration of antibacterial treatment depends on the organism isolated. For *Str. pneumoniae* 10 to 14 days of treatment is recommended and for *H. influenzae* 7 to 14 days. For *N. meningitidis* 7 days, treatment is sufficient. In *L. monocytogenes* and group B streptococcal meningitis, antibacterials should be given for a minimum of 14 to 21 days while Gram-negative bacilli should be treated for a minimum of 3 weeks.[9,14] For discussion on a shorter duration of treatment see Meningitis, under Uses and Administration of Ceftriaxone, p. 256.1.

Chloramphenicol is effective for the treatment of epidemic meningococcal meningitis and ceftriaxone or chloramphenicol are the drugs of choice for patients over 2 years of age in areas with limited health facilities.[1,15] An intramuscular dose of ceftriaxone (100 mg/kg to a maximum of 4 g) was found to be as effective as an intramuscular dose of oily chloramphenicol (100 mg/kg to a maximum of 3 g) for the treatment of meningococcal meningitis during epidemics in resource-poor settings.[16] For children under 3 months, intravenous ampicillin plus cefotaxime or gentamicin are recommended to cover probable bacteria for this age group, while for children aged between 3 months and 5 years, intravenous ceftriaxone is recommended. Those older than 5 years of age may be given intravenous ceftriaxone or ampicillin.[15]

Prophylaxis. Immunisation is the most effective way of preventing bacterial meningitis in children and since the introduction of effective conjugate vaccines against the common meningeal pathogens the epidemiology of bacterial meningitis has changed. In the developed world where these vaccines are routinely given as part of childhood immunisation programmes bacterial meningitis has become a disease of adults rather than of infants and children.[3] Vaccination is recommended for travellers to areas affected by meningococcal outbreaks and is compulsory for pilgrims going to Saudi Arabia. Several vaccines are available to prevent bacterial meningitis. Unconjugated polysaccharide vaccines against *N. meningitidis* subtypes A, C, Y, and/ or W135, in various combinations, have been available for many years and are recommended for children older than 2 years who are at high risk of infection, such as those with asplenia and with terminal complement deficiencies, and students living in dormitories. A newer conjugated tetravalent ACWY meningococcal vaccine protects against A, C, W135 and Y meningococcal subtypes and is now a visa requirement for pilgrims to Saudi Arabia. A monovalent conjugate vaccine against *N. meningitidis* subtype C has recently been licensed in developed countries for use in children and adolescents. This conjugate vaccine produces better protection than unconjugated polysaccharide vaccine, in children under 2 years of age.[1,5] It has been more difficult to develop vaccines against the group B subtype, however, several avenues of research have resulted in the production of an effective vaccine against this subtype. For further information on meningococcal vaccines see, p. 2401.3. The newer conjugate *Haemophilus* vaccines (see p. 2387.2) are similarly more immunogenic than the polysaccharide vaccine, and universal immunisation of infants with these conjugate vaccines has been associated with more than 99% reduction in invasive *H. influenzae* type b diseases in developed countries.[2] In 2000, a conjugate vaccine, directed against the seven most prevalent invasive pneumococcal strains in the USA, was approved for routine childhood immunisation and since 2009 a 13-valent conjugate vaccine has been available in several countries. Three doses of the 7-valent vaccine, given at 2, 4, and 6 months of age, were associated with a reduction of more than 90% in invasive pneumococcal infections, including sepsis and meningitis.[2] For further information on pneumococcal vaccines see, p. 2410.1.

- Close contacts of patients infected with meningococcus A, Y, or W135 should be offered tetravalent meningococcal vaccine; children < 1 year of age should receive 2 doses 1 month apart.[5]
- Those exposed to serogroup C infection who are unimmunised or incompletely immunised should be vaccinated with a meningococcal C vaccine. Those who completed a course more than one year before should be offered a booster.[5]
- All unimmunised index cases under the age of 25 years should also be offered a meningococcal C vaccine. Cases of confirmed serogroup C disease who have previously been immunised with meningococcal C or tetravalent vaccines should be offered a meningococcal C vaccine before discharge from hospital.[5]

Antibacterial treatment does not eliminate nasopharyngeal carriage of *N. meningitidis* and **chemoprophylaxis** should be given to close contacts of the index case (irrespective of vaccination status) to reduce the risk of invasive disease.[5] A systematic review[17] found that ceftriaxone, ciprofloxacin, and rifampicin were all effective at eradicating carriage for up to 2 weeks although resistance to rifampicin may occur after prophylactic treatment; penicillin was less effective.

- A single oral dose of ciprofloxacin or, alternatively, oral rifampicin twice daily for 2 days should be given to close contacts as soon as possible (preferably within 24 hours) after diagnosis of the index case. For pregnant women, a single oral dose of either ciprofloxacin or azithromycin, or a single parenteral dose of ceftriaxone can be used.[5]
- If further cases occur within a group of close contacts within 4 weeks of receiving prophylaxis, then repeat prophylaxis should be with an alternative recommended antibacterial.[5]
- Index cases (except those whose disease was treated with ceftriaxone) should be given antibacterial prophylaxis before discharge from hospital.[5] Chemoprophylaxis is also recommended for healthcare workers whose mouth or nose is directly exposed to large particle droplets or secretions from the respiratory tract of a probable or confirmed index case of meningococcal disease during acute illness and until 24 hours of systemic antibacterial treatment has been completed.[5]

Similarly, treatment of *H. influenzae* meningitis does not eliminate nasopharyngeal carriage of the organism and rifampicin should be given to index cases for 4 days before discharge from hospital. Anyone who has been in direct or prolonged close contact with the infected persons should also be given rifampicin for 4 days. Unvaccinated children should be immunised.

Chemoprophylaxis is not normally indicated for close contacts of pneumococcal and other types of bacterial meningitis.[7,14]

The WHO recommendation for outbreak control is mass vaccination of persons residing in districts in the epidemic phase as well as surrounding districts in an alert phase. It is estimated that a mass immunisation campaign, promptly implemented, can avoid 70% of cases.[1]

Adjunctive treatment. Mortality and morbidity, including deafness in children, remain high in meningitis despite effective antibacterial therapy. Endotoxins and other microbial products, released from bacteria after antibacterial treatment, are able to elicit a severe inflammatory response, suggesting that anti-inflammatory drugs may be of benefit. A systematic review[18] of adjunctive corticosteroid therapy concluded that corticosteroids reduce mortality, neurological sequelae, and especially the risk of severe hearing loss in both children and adults. This systematic review concludes that corticosteroids should be given before, or with the first dose of antibacterial in adults; the same recommendations apply to children living in high-income countries. However, results from a study in sub-Saharan Africa[19] did not support the routine use of adjunctive corticosteroids in the treatment of adults with bacterial meningitis in resource-poor countries where *Strep. pneumoniae* is the main pathogen and where a large number of patients are also likely to have advanced HIV disease. Another study[20] of dexamethasone in Vietnamese patients over 14 years of age with suspected bacterial meningitis reported that dexamethasone did not improve survival in all patients; significant benefit was only seen in patients with proven bacterial meningitis, including those given prior

treatment with antibacterials. This finding was thought to be due to patients with tuberculosis meningitis in the treatment group. The results of a later systematic review and meta-analysis,[21] which included these 2 studies, suggested that in patient populations similar to those seen in high-income countries and in populations with a low prevalence of HIV, adjunctive treatment with corticosteroids improved survival and neurologic recovery in adults and adolescents. For information on the use of corticosteroids in tuberculous meningitis see Tuberculosis, under Uses of Corticosteroids, p. 1614.3.

Careful management of fluid and electrolyte balance may be important in the treatment of meningitis and fluid restriction to prevent cerebral oedema has been widely advocated and used in children.[22,23] This practice was based on reports of hyponatraemia which were attributed to inappropriately increased concentrations of antidiuretic hormone. However, subsequent studies have suggested that the raised concentration of antidiuretic hormone may be an appropriate host response to hypovolaemia, and that more liberal use of parenteral fluids may be beneficial.[2] A systematic review[22] concluded that there is some evidence to support the use of intravenous fluids, in preference to restricted fluid intake, particularly in the first 48 hours in settings with high mortality rates. However, where children present early and mortality rates are lower, there is probably little benefit and insufficient evidence to guide practice; it has been suggested that fluids should not be restricted in children.[14] The British Infection Society working party[7,8] recommends that adult patients with meningitis should not be fluid restricted in an attempt to reduce cerebral oedema.

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Meningococcal infections

Meningococcal disease[1-3] refers to systemic infection with *Neisseria meningitidis* and may present clinically either as meningitis or septicaemia, or both. Less common forms of metastatic meningococcal infection include polyarthritis, pericarditis, pneumonitis, and genito-urinary-tract infections. *N. meningitidis* is a Gram-negative bacterium, occurring worldwide, and is classified into several serotypes. Serotypes A, C, and W135 are responsible for epidemic meningitis in sub-Saharan Africa, while serotypes B and C are the cause of outbreaks in Europe and North America. The number of cases of meningococcal disease due to serotype C has decreased significantly after the introduction of vaccination in developed countries.

Infections are more common in young children under 5 years of age and in adolescents. *N. meningitidis* only infects humans and about 10 to 25% of the population may be carriers of the organism. The bacteria are carried in the pharynx and may sometimes penetrate the mucosa and spread through the bloodstream causing systemic disease that may rapidly progress to shock and death. Patients with meningococcal disease and asymptomatic nasopharyngeal carriers may spread meningococcal infection via respiratory droplets or throat secretions. Close and prolonged contact such as kissing, sneezing and coughing, living in close quarters, and sharing eating or drinking utensils are established risk factors.[1,2,4] Symptoms and signs during the early stage of meningococcal disease are non-specific and include fever, vomiting, malaise, and lethargy. Most patients with meningococcal septicaemia develop a vasculitic rash (petechiae or purpura) which is often scant or absent in patients with meningitis. Purpuric rash, drowsiness or impaired consciousness, and shock are late presentations and associated with high mortality rates, which may be up to 50% in severe forms. Meningococcal meningitis usually presents with headache, neck stiffness, photophobia, and drowsiness. Mortality from meningococcal meningitis is less than in septicaemia and may be below 5% with prompt treatment.[1,2,5]

Guidelines for prevention and control of meningococcal disease have been developed for the UK[6-8] and the USA.[9,10]

Choice of treatment. Mortality is reduced by early recognition of the disease and prompt treatment with antibacterials. In the UK, rapid admission to hospital is considered the highest priority in suspected meningococcal disease; benzylpenicillin should be given parenterally, preferably intravenously, as soon as possible (either before or after transfer).[1,5-8] Alternative antibacterials include a third-generation cephalosporin or chloramphenicol.[5] Both initial empirical and later treatment may be with benzylpenicillin, ampicillin, chloramphenicol, or third-generation cephalosporins such as cefotaxime or ceftriaxone.[4,5,7,11,12] However, there are concerns about calcium chelation when ceftriaxone is given with parenteral calcium-containing products and therefore some experts advise cefotaxime as the drug of choice.[7,13] In infants less than 3 months of age ampicillin (or amoxicillin) should be added to provide cover against listerial infection.[7] Oily chloramphenicol or ceftriaxone are used during epidemics in Africa and in areas with limited health facilities.[4] Uncomplicated meningococcal disease usually requires 7 days of antibacterial treatment. For further details of the treatment of meningococcal meningitis, including the treatment of close contacts, see Meningitis, p. 191.1. Immunisation is the most effective way of preventing meningococcal meningitis and several vaccines are available (see Meningococcal Vaccines, p. 2401.3).

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Mouth infections

Infections of the mouth include those of dental origin such as dental caries, abscesses, gingivitis, and periodontal infections, and those without a dental origin. Infections arising in the nasal cavity, middle ear, oropharynx, and paranasal sinuses can also affect the oral cavity. Emphasis has shifted from treatment to prevention of oral diseases.[1] This discussion deals mainly with infections of dental origin.

The organisms most often found in oral infections are viridans streptococci, a variety of anaerobes, and facultative streptococci.

Dental caries[2] is a chronic disease caused by the erosion of tooth enamel due to acid produced by bacteria (usually *Streptococcus mutans*) in plaque. This process is affected by salivary flow and composition, exposure to fluoride, dietary sugar content, and preventative measures such as tooth brushing and flossing. Fluoride in various forms is used in dental caries prophylaxis, where it may promote remineralisation or reduce acid production by plaque bacteria.[1,2] For further information on the use of fluoride for dental caries prophylaxis see under Uses and Administration of Sodium Fluoride, p. 2089.2. Sugar-free chewing gum can also help prevent caries by stimulating the production of saliva.[3,4] For further references see Dental Caries under Xylitol, p. 2220.3. Dental caries vaccines have been investigated.

The term **periodontal disease**[5] refers to conditions affecting the supporting structures around the teeth (periodontium), including the gingiva, peridontal ligament, cementum, and alveolar bone. Pathogenic bacteria in the plaque, genetic factors, tobacco and alcohol use, diabetes, immunosuppression, and the use of some drugs can contribute to such disease. **Gingivitis** (or gum disease) is an inflammation of the gums surrounding the teeth in response to bacterial biofilm or plaque that accumulates between the gingiva and the teeth; irritation from plaque causes pockets to develop where the gingiva separates from the tooth. Gingivitis may or may not develop into periodontitis, but periodontitis is always preceded by gingivitis. **Periodontitis** is an infection of the periodontium causing inflammation of the periodontal ligament, gingiva, cementum, and alveolar bone. With ongoing inflammation the periodontal connective tissue breaks down and destruction of the local alveolar bone occurs. Periodontal infections are usually mixed infections[6,7] and are associated with an increase in the number of Gram-negative and anaerobic bacteria.[5,6]

Most gingivitis and periodontitis can be prevented and treated by adequate oral hygiene and plaque removal using mechanical means such as toothbrushing. Mechanical removal of calculus is necessary where the build up is significant. Antiseptics may also help to reduce plaque accumulation and several, but most notably chlorhexidine, have been used.[6,8] Oral antibacterials may be used as an adjunct to scaling, root planing, or drainage in patients with refractory disease, who are immunocompromised, or have signs of systemic illness.[5,7] Antibacterials commonly used include tetracyclines, metronidazole, amoxicillin (with or without clavulanic acid), ciprofloxacin, and clindamycin.[6] Combination therapy with metronidazole and either amoxicillin or ciprofloxacin, or amoxicillin with clavulanic acid followed by doxycycline has also been used.[6] Dentoalveolar abscesses originating from the periodontal tissue (usually caused by anaerobic bacteria) may be treated with metronidazole; clindamycin is an alternative.[7] Those originating from periapical tissues (usually caused by mixed infections) can be treated with amoxicillin, metronidazole, or clindamycin.[7] Antibacterial treatment may be stopped once the systemic signs of the infection have resolved (usually after 2 to 3 days of treatment).[7] In the UK, the *BNF* advises against the routine use of clindamycin in oral infections, but notes that it can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or metronidazole.

Prevotella intermedia, fusiform bacteria, and spirochaetes have also been linked with **acute necrotising ulcerative gingivitis** (ANUG; also called Vincent's infection or trench mouth). ANUG may result in accelerated destruction of affected tissues, as well as local or systemic spread of infection. Treatment involves debridement and an oral penicillin with metronidazole; clindamycin monotherapy is an alternative. Antibacterials and antiseptics delivered locally to the periodontal pocket may be of value.[6]

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Mycetoma

Mycetoma[1,2] is a localised infection found worldwide, but most commonly in the tropics and subtropics. Infection mainly results from trauma to the skin, and may spread locally through the lymphatic system to surrounding tissues, progressively destroying connective tissue (fascia) and bone. It is characterised by painless soft-tissue swelling, draining sinus tracts, and discharge of grains composed of large aggregates of filaments (fungal or actinomycete). The foot is most often affected (70 to 80% of cases), less often hand (12%), legs, and knee joints. The term Madura foot is used for mycetoma affecting the foot. Mycetomas may be caused by various organisms; those caused by fungi such as *Madurella mycetomatis* are called eumycetomas and are discussed on p. 567.1. Those caused by the filamentous bacteria, actinomycetes, are called **actinomycetomas**: *Nocardia brasiliensis* is the commonest actinomycete responsible; others include *Actinomadura madurae, A. pelletieri*, and *Streptomyces somaliensis*. For details of systemic infections caused by *Nocardia* spp., see under Nocardiosis, p. 195.3.

Combined drug treatment is preferred for actinomycetomas so as to avoid resistance and eradicate residual infection; cures are usually achieved after treatment for 4 to 24 months.[1,2] The most common regimen is streptomycin and dapsone; co-trimoxazole may replace dapsone in patients who have not responded to initial treatment after a few months and in those who cannot tolerate dapsone. Successful treatment has been reported with amikacin, either as monotherapy or with co-trimoxazole.[1] Rifampicin, sulfonamides, or pyrimethamine with sulfadoxine, have been tried in resistant infections and are considered suitable for second-line therapy;[1] amoxicillin with clavulanic acid has also been used successfully.[3] A two-step regimen[4] has also been used: intensive therapy with benzylpenicillin, gentamicin, and co-trimoxazole for 5 to 7 weeks is followed by maintenance therapy with amoxicillin and co-trimoxazole for 2 to 5 months after clinical remission. More recently, a modified two-step regimen[5] has been tried, omitting benzylpenicillin and giving gentamicin and co-trimoxazole for 4 weeks followed by maintenance therapy with doxycycline and co-trimoxazole for 5 to 6 months after remission.

Surgery is indicated for patients with infections resistant to drug therapy, deep or extensive infections, or infections with bone involvement that will not respond to long-term conventional therapy; amputation may be required in some cases.[1,2]

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Necrotising enterocolitis

See p. 185.1.

Necrotising fasciitis

Necrotising fasciitis[1-5] is an uncommon but severe soft-tissue infection resulting in necrosis of the subcutaneous tissue and adjacent fascia, together with severe systemic illness, and is associated with high morbidity and mortality rates. Type I infections are caused by a mixture of aerobic and anaerobic organisms, whereas type II are monomicrobial infections due to group A streptococci or staphylococci and may be associated with a toxic shock syndrome (p. 211.3). Some definitions recognise type III infections due to *Vibrio vulnificus*, mainly occurring in patients with liver disease and often rapidly progressive and fatal. Necrotising fasciitis can affect any part of the body but is most common on the extremities, the perineum, and the trunk. (The term Fournier's gangrene has been used to describe rapidly progressive necrotising fasciitis of the perineum and genitals.) Necrotising fasciitis usually follows trauma, and most patients have pre-existing conditions that predispose to infection, such as diabetes mellitus, chronic renal failure, peripheral vascular disease, or parenteral drug abuse.

Complete debridement of the infected tissue is considered essential for treatment; repeated debridements are necessary until infection is controlled. Intravenous antibacterial therapy is given as an adjunct and should be continued until no further debridements are needed.[1-5] Antibacterial treatment regimens should cover Gram-positive, Gram-negative, and anaerobic organisms. The possibility of infection with group A *Streptococcus* or *Clostridium* species should also be considered. Possible treatment regimens for *mixed infections* include monotherapy with ertapenem, imipenem, meropenem, piperacillin-tazobactam, or tigecycline.[4] Multidrug regimens for mixed infections include:

- benzylpenicillin and clindamycin plus a fluoroquinolone or an aminoglycoside[4]
- benzylpenicillin and gentamicin plus metronidazole or clindamycin[1]
- ampicillin-sulbactam and clindamycin plus ciprofloxacin[2]
- patients known to be hypersensitive to penicillins may be given clindamycin or metronidazole with an aminoglycoside or fluoroquinolone[2]

If group A *Streptococcus* or *Clostridium* is the likely cause, a combination of clindamycin and benzylpenicillin should be used.[2]

Until *meticillin-resistant staphylococcal infection* has been ruled out, treatment regimens should also include vancomycin, daptomycin, linezolid, or quinupristin/dalfopristin.[4,5]

Hyperbaric oxygen therapy has also been beneficial although prospective controlled studies are lacking.[1,3-6] Intravenous normal immunoglobulins have also been tried in patients with staphylococcal or streptococcal necrotising fasciitis but further study is considered warranted.[2-5]

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Neonatal conjunctivitis

Conjunctivitis of the newborn, also known as ophthalmia neonatorum, is defined as any conjunctivitis with discharge occurring during the first 28 days of life.[1] That due to *Neisseria gonorrhoeae* is the most serious; it usually appears by the third day after birth and can rapidly result in blindness; systemic infections, especially severe septicaemia, may occur. *Chlamydia trachomatis* is another major cause of neonatal conjunctivitis (inclusion conjunctivitis); it characteristically occurs 5 to 14 days after birth and is less threatening to sight than gonococcal infection, but may also infect the nasopharynx and can cause pneumonia. Chlamydial conjunctivitis is more common than gonococcal conjunctivitis in developed countries. Both organisms are sexually transmitted and the infants of mothers with such genital-tract infections are infected during their passage through the birth canal. Other less serious bacterial causes of neonatal conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus* spp., and *Pseudomonas* spp.; they are often hospital-acquired.[1]

The management of gonococcal and chlamydial neonatal conjunctivitis varies from country to country depending on the prevalence of gonorrhoea and *C. trachomatis* infection and on bacterial resistance.

- PROPHYLAXIS

  The ideal method of prophylaxis is to treat the infected mother during pregnancy, but this is not always possible. Where the risk of *gonococcal infection* is high, ocular prophylaxis at birth is particularly important because of the rapid onset of conjunctivitis and its potential seriousness and is preferable to early diagnosis and treatment of the neonate.[2] Cleansing of the neonate's eyes immediately after birth followed by the topical application of either tetracycline 1% eye ointment,[3] erythromycin 0.5% eye ointment,[4] or silver nitrate 1% eye drops is advised[3] and is sometimes required by law.[4] Silver nitrate[1] is active against all strains of *N. gonorrhoeae* regardless of their susceptibility to antibacterials; it is inexpensive and widely available, but may cause chemical conjunctivitis and has been ineffective in preventing chlamydial conjunctivitis (see below). Tetracycline has been reported to be as effective as silver nitrate in protecting against gonococcal conjunctivitis caused by multiresistant strains[5] and WHO now lists both drugs as the drugs of choice.[3]

  The value of prophylaxis against *chlamydial neonatal conjunctivitis* is less certain. Tetracycline ointment has been reported to be less effective in preventing chlamydial infection than gonococcal infection[5] and erythromycin ointment has also been unreliable.[6] Silver nitrate is generally considered ineffective,[1] despite an unexpected reduction in the incidence of chlamydial conjunctivitis in one study.[5] The CDC[4] does not recommend prophylactic antibacterial treatment for infants born to mothers with untreated chlamydial infection. Screening and treatment of pregnant women for *C. trachomatis* infection may be a more effective method of control than ocular prophylaxis.[5,7] This approach also tackles the more serious problem of pneumonia.[8]

  Neonatal conjunctivitis continues to cause blindness, especially in developing countries. Povidone-iodine is less expensive and perhaps more readily available in such countries than silver nitrate or erythromycin. In a study in Kenya involving more than 3000 infants[9] a 2.5% ophthalmic solution of povidone-iodine appeared to be a more effective prophylactic than either a 1% ophthalmic solution of silver nitrate or erythromycin 0.5% eye ointment. In particular, there were fewer cases of chlamydial conjunctivitis with povidone-iodine.

- TREATMENT

  All cases of neonatal conjunctivitis should be treated for both *N. gonorrhoeae* and *C. trachomatis* because of the possibility of mixed infection.[3] *Gonococcal neonatal conjunctivitis* must be treated systemically. WHO[3] recommends ceftriaxone 50 mg/kg by intramuscular injection as a single dose (to a maximum of 125 mg) or, if ceftriaxone is not available, spectinomycin 25 mg/kg (to a maximum of 75 mg) or kanamycin 25 mg/kg (to a maximum of 75 mg) by intramuscular injection as a single dose.

  In the USA, CDC[4] recommends a single intravenous or intramuscular injection of ceftriaxone 25 to 50 mg/kg (up to 125 mg) when there is no evidence of disseminated infection.

  See also under Gonorrhoea (p. 206.2) for the treatment of infants exposed to gonorrhoea at birth or with established gonococcal infection at any site.

  For *nongonococcal neonatal conjunctivitis* WHO[3] and CDC[4] recommend erythromycin 50 mg/kg daily in 4 divided doses orally for 14 days; WHO[3] recommend co-trimoxazole 240 mg twice daily for 14 days as an alternative. There is no indication that topical therapy is of additional benefit.[3,4]

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Nocardiosis

Nocardia spp. are Gram-positive aerobic branching bacteria that cause systemic or localised infection. The principal pathogenic species in man is *N. asteroides*; others include *N. brasiliensis, N. pseudobrasiliensis*, and *N. caviae*. Localised chronic infection or actinomycetoma is described under Mycetoma (above). Systemic nocardiosis is mainly a lung infection and often involves abscess formation; it occurs especially in immunocompromised patients and may be disseminated with abscesses in the brain and subcutaneous tissues.

The treatment of choice has been a sulfonamide such as sulfadiazine or co-trimoxazole,[1-5] although a study *in vitro* indicated that the fixed ratio of trimethoprim:sulfamethoxazole in co-trimoxazole might contain too little trimethoprim for optimal activity.[6] Sulfafurazole[7] has been used successfully. There have been reports of the effective treatment of nocardiosis with amikacin,[8,9] linezolid,[10,11] minocycline,[12,13] or ciprofloxacin with doxycycline.[14] Imipenem may also be used,[15] and is most active when combined with amikacin; the combination is considered by some to be the best choice for initial therapy when parenteral antibacterials are required.[16,17] Other suggested alternatives include meropenem,[15,16] cefuroxime,[16] cefotaxime,[16] and ceftriaxone;[15,16] due to their relatively low toxicity and excellent CSF penetration, these antibacterials may be particularly useful in cerebral nocardiosis.[16]

Treatment of nocardiosis needs to be prolonged and may continue for at least 6 to 12 months, depending on the site of infection and the immune status of the patient.[5,16]

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Nontuberculous mycobacterial infections

Environmental mycobacteria are widespread, and many species other than those responsible for leprosy (p. 188.3) and tuberculosis (p. 212.2) are facultative parasites capable of producing disease in man. These organisms, which have been referred to as atypical, nontuberculous (NTM), tuberculoid, opportunistic, or MOTT (mycobacteria other than tuberculous), are rarely, if ever, transmitted from person to person but are acquired from the environment. Symptomatic infections are usually associated with focal or generalised defects in the host's immune system. The diseases produced include localised skin and soft tissue lesions, pulmonary infections, lymphadenitis, and disseminated infections.

Cutaneous disease may follow traumatic inoculation with *Mycobacterium marinum* ('swimming pool' or 'fish-tank' granuloma), *M. ulcerans* (Buruli ulcer), *M. chelonae* (*M. chelonei*), *M. abscessus* (formerly *M. chelonae* subspecies), or *M. fortuitum*. Ulcerated lesions due to *M. haemophilum* have been described mainly in immunocompromised patients.

Pulmonary disease may be clinically indistinguishable from pulmonary tuberculosis, and has most frequently been attributed to the *M. avium* complex (MAC), which includes *M. avium* and *M. avium-intracellulare*, or to *M. kansasii*, and to a lesser extent *M. xenopi*; less common causes include *M. abscessus*, *M. asiaticum*, *M. celatum*, *M. chelonae*, *M. fortuitum*, *M. malmoense*, *M. scrofulaceum*, *M. simiae*, and *M. szulgai*.

Lymphadenitis, which is usually self-limiting and occurs particularly in children under 5 years of age, may be caused by many species but the great majority of cases are due to *M. avium* complex, *M. genavense*, *M. malmoense*, and *M. scrofulaceum* (sometimes collectively known as the MAIS complex).

Dissemination of opportunistic mycobacterial infections may occur rapidly in immunocompromised patients. The majority of cases have been attributed to the *M. avium* complex; other species implicated include *M. abscessus*, *M. celatum*, *M. chelonae*, *M. genavense*, *M. haemophilum*, *M. kansasii*, *M. malmoense*, *M. scrofulaceum*, and *M. simiae*.

The treatment depends on the site and nature of the infection and whether immunodeficiency is present. Both HIV-negative and HIV-positive patients may be affected and the possibility of drug interactions should be borne in mind in patients receiving antiretroviral therapy.

- MYCOBACTERIUM AVIUM COMPLEX (MAC).

  US guidelines[1,2] produced by the CDC, National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America recommend that the **treatment** of **HIV-positive patients** with MAC should consist of at least 2 antimycobacterial drugs. Clarithromycin is the preferred first drug (with azithromycin as an alternative) and is given with ethambutol. Use of a third, and possibly, fourth, drug should be considered in patients with advanced immunosuppression (CD4+ T lymphocyte count less than 50 cells/microlitre), high mycobacterial loads, or if the patient is not taking effective HAART. Rifabutin is often used as the third drug, while a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) or aminoglycoside (amikacin or streptomycin) can be considered when a fourth drug is needed or rifabutin cannot be used. In ***disseminated*** disease, patients who are not taking HAART should generally delay starting antiretroviral treatment until after at least 2 weeks of treatment for MAC has been completed, in order to reduce the risk of significant drug interactions or complications due to immune reconstitution syndrome. Those already on HAART should continue this treatment if possible.

  Earlier UK guidelines from the British Thoracic Society (1999, not subsequently updated)[3] for treatment of HIV-positive patients with MAC broadly concur with the US recommendations. Rifampicin or rifabutin, ethambutol, and clarithromycin or azithromycin were recommended. A fluoroquinolone such as ciprofloxacin, or even amikacin, might be added for patients who were intolerant of first-line drugs or who failed to respond. UK guidelines recommended lifelong treatment; the US considers that treatment may be stopped in selected patients (see Chemoprophylaxis, below). In ***disseminated*** disease, the same treatment should be given and continued indefinitely.

  A prospective, randomised study[4] undertaken to compare 3 regimens (clarithromycin and ethambutol, clarithromycin and rifabutin, and all 3 drugs) for the treatment of disseminated MAC in patients with AIDS found that all regimens appeared to provide effective treatment and the differences were not statistically significant. However, patients taking the 3-drug regimen had greater overall clinical efficacy, a lower relapse rate, and a lower risk of death.

  The 1999 British Thoracic Society guidelines[3] state that treatment for **HIV-negative patients** with MAC pulmonary disease should consist of rifampicin and ethambutol for 24 months, with or without isoniazid. In extrapulmonary disease affecting lymph nodes, surgical excision of the nodes should be undertaken; chemotherapy with rifampicin, ethambutol, and clarithromycin for up to 2 years should be considered if disease recurred or where excision was incomplete or impossible. In sites other than lymph nodes, chemotherapy should be given for 18 to 24 months. US guidelines[5] from the American Thoracic Society and the Infectious Diseases Society of America suggest that for mild nodular or bronchiectatic pulmonary disease, an intermittent regimen of clarithromycin (or azithromycin), rifampicin, and ethambutol three times weekly is usually sufficient; therapy should be continued until sputum cultures have been negative for 12 months. For severe pulmonary disease or in previously treated patients, a daily regimen should be used; addition of intermittent amikacin or streptomycin for the first few months of therapy can also be considered.

  Prophylactic treatment is used to reduce the incidence of disseminated MAC disease in patients with HIV infection. There appears to be a tendency to delay starting prophylaxis until later in the disease process; US guidelines[2,5] recommend starting prophylaxis in adults and adolescents at a CD4+ T lymphocyte count of less than 50 cells/microlitre with either azithromycin or clarithromycin. If these drugs cannot be tolerated then rifabutin may be given as an alternative. Combination therapy with one of the macrolides and rifabutin is not recommended. US guidelines state that prophylaxis need not be lifelong in patients responding to HAART; specifically, primary prophylaxis may be stopped in adults and adolescents whose CD4+ T lymphocyte count has increased to more than 100 cells/microlitre for 3 months or more, but should be restarted if the CD4+ count falls to below 50 to 100 cells/microlitre again. Observational data from a large cohort of patients in the USA found no evidence of increased risk of MAC in patients who had stopped primary prophylaxis in accordance with these guidelines.[6]

  US guidelines[2,5] also state that it may be possible to stop secondary prophylaxis (chronic maintenance therapy) in HIV-infected adults and adolescents who have completed at least 12 months of treatment for MAC, who remain asymptomatic with respect to MAC, and who have a sustained response to HAART (CD4+ T lymphocyte count greater than 100 cells/microlitre for more than 6 months). Secondary prophylaxis should be restarted if CD4+ T lymphocyte count falls below 100 cells/microlitre. In children, CD4+ T lymphocyte count thresholds for starting, stopping, or resuming prophylaxis vary depending on the age of the child.[1]

  In the UK, however, the earlier British Thoracic Society guidelines noted there was no general agreement about when prophylaxis should be used. If prophylaxis were to be given to patients with a CD4+ T lymphocyte count below 50 cells/microlitre the first drug of choice would be azithromycin; clarithromycin was an alternative and azithromycin with rifabutin would be a third choice.[3] These guidelines, partly based on studies which predate the wide use of HAART, recommended that prophylaxis be continued indefinitely.[3]

- MYCOBACTERIUM KANSASII INFECTION.

  UK guidelines stated that infections with *M. kansasii* might be treated with rifampicin (or rifabutin) and ethambutol.[3] Pulmonary disease in HIV-negative patients was usually treated for 9 months whereas HIV-positive patients should receive therapy for 2 years or until the sputum has been negative for 12 months. For disseminated infection in HIV-positive patients, clarithromycin should be added and possibly also isoniazid. The place of macrolides and fluoroquinolones in pulmonary or disseminated *M. kansasii* infection remained to be established. In extrapulmonary disease in HIV-negative patients, chemotherapy with rifampicin and ethambutol might be used before excision of an infected lymph node. In other extrapulmonary disease the guidelines stated that the data were insufficient to make recommendations, but considered that rifampicin and ethambutol for 9 months appeared sensible, with the addition of protionamide and streptomycin and/or a macrolide if the condition is not responding.[3] US guidelines[5] suggest the use of rifampicin, ethambutol, and isoniazid for *M. kansasii* pulmonary infection; treatment should be continued until sputum cultures have been negative for 12 months. For disseminated disease in immunocompromised patients, indefinite treatment may be required until sufficient recovery of immune status occurs.

- OTHER OPPORTUNISTIC MYCOBACTERIA.

  In *M. malmoense* and *M. xenopi* **pulmonary** disease, UK guidelines have recommended that rifampicin and ethambutol should be given for 2 years in HIV-negative patients. Extrapulmonary *M. malmoense* infections should be treated in the same manner as extrapulmonary MAC or *M. kansasii* infections. *M. malmoense* infection rarely occurs in AIDS patients, but if necessary, treatment with rifampicin, ethambutol, and clarithromycin, and possibly isoniazid should be used. For *M. xenopi* in HIV-positive patients the guidelines stated that there was no evidence on which to base recommendations; treatment as for pulmonary or disseminated MAC infection was suggested.[3]

  For pulmonary disease due to rapidly growing bacteria (*M. abscessus*, *M. chelonae*, *M. fortuitum*, and *M. gordonae*) and other species (*M. genavense*, *M. haemophilum*, *M. simiae*, *M. szulgai*, and *M. ulcerans*) surgery should be used if possible. Drug therapy should probably include rifampicin, ethambutol, and clarithromycin. Amikacin, cefoxitin, imipenem, quinolones, and sulfonamides might have a place in treatment. For extrapulmonary disease due to these organisms, there had been several anecdotal reports outlining treatment but there was no evidence from controlled clinical studies.[3] Successful treatment of *M. simiae* infection in patients with AIDS was reported with clarithromycin, ethambutol, and ciprofloxacin.[7] Surgical treatment and intensive antibacterial regimens have been used for *M. scrofulaceum* infections.[8] Symptomatic improvement was achieved in an AIDS patient with *M. celatum* infection with a regimen of isoniazid, rifampicin, and ethambutol.[9]

  For **cutaneous** infections due to *M. marinum* (swimming-pool granuloma or fish-tank granuloma) many antibacterial regimens have been used,[10] including rifampicin with ethambutol[11] or isoniazid, rifabutin with ciprofloxacin,[12] minocycline with co-trimoxazole,[13] clarithromycin with rifabutin[14] or ciprofloxacin[12] or ethambutol.[12] Monotherapy with clarithromycin, minocycline, doxycycline, or co-trimoxazole have each been tried, mainly in small series of patients. US guidelines[5] suggest that for treatment of *M. marinum* infection, the use of 2 active antimycobacterials until 1 to 2 months after symptoms of infection have resolved may be a reasonable approach.

  Buruli ulcer, due to *M. ulcerans*, is difficult to treat and usually requires surgery; responses to antimycobacterial monotherapies have been generally disappointing. However, recent evidence suggests that combination antibacterial therapy may reduce the healing time and recurrence rates of ulcers, and minimise or avoid the need for surgery.[15] Treatment of nodules and plaques of early Buruli ulcers with rifampicin and streptomycin for up to 12 weeks, showed inhibition of growth 4 weeks after starting treatment.[16] Furthermore, no lesions enlarged during the treatment period. WHO therefore recommends the use of rifampicin and streptomycin or amikacin for 8 weeks.[17] Consensus recommendations issued by practitioners in Victoria, Australia[18] consider surgery to be the best treatment for Buruli ulcer, with antibacterial therapy being indicated for more extensive disease. Use of antibacterials may also possibly allow more conservative resection and reduce the risk of relapse. The recommended oral regimens were: at least 3 months of rifampicin given with clarithromycin, ciprofloxacin, or moxifloxacin. For more severe or extensive

disease patients may also require intravenous amikacin for 4 to 8 weeks in addition to oral therapy. Reports of other therapies include a beneficial response with topical nitrogen oxides in a small pilot study of 37 patients with Buruli ulcer,[19] and healing after local application of phenytoin.[20]

Cutaneous disease due to *M. haemophilum* infection has been treated with an initial treatment course of rifabutin, ciprofloxacin, and clarithromycin, followed by clarithromycin for 2 years.[21] *M. chelonae* was successfully treated with clarithromycin and linezolid for one month, followed by a further 5 months of treatment with clarithromycin.[22]

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Obstetric disorders

See under: Endometritis (the prophylaxis and treatment of postpartum endometritis), p. 180.3; Premature Labour, p. 203.3; and Urinary-Tract Infections in Pregnancy, p. 215.3. See also Neonatal Conjunctivitis, p. 193.2, and Perinatal Streptococcal Infections, p. 199.2.

Osteomyelitis

See under Bone and Joint Infections, p. 175.1.

Otitis externa

Otitis externa is a general term used to describe inflammation of the skin of the external auditory canal that may be due to infection with bacteria, viruses, or fungi or secondary to skin disorders such as eczema. Otitis externa is associated with high humidity, warmer temperatures, swimming, local trauma, or obstruction of the ear canal. Subtypes include acute localised otitis externa, acute diffuse otitis externa (swimmer's ear), chronic otitis externa, and necrotising (malignant) otitis externa. Acute diffuse disease is characterised by erythema, itching, pain, purulent discharge, oedema, fullness, and deafness. If left untreated or if treated inadequately it may progress to chronic otitis externa. Chronic otitis externa may also result from allergic contact dermatitis or other underlying skin conditions, such as eczema. Malignant otitis externa is rare and occurs mainly in immunocompromised persons and in diabetics and can be life-threatening if temporal bone infections occur.

The **treatment** of both acute and chronic otitis externa includes thorough cleansing and the use of appropriate acidifying and/or antibacterial ear drops, with or without a corticosteroid, even though some have doubted the value of topical antibacterials. A systematic review[1] that examined the effects of ear cleaning, topical treatments (generally acetic acid, antibacterials, corticosteroids, or combinations of these), and oral antibacterials on the resolution of acute uncomplicated otitis externa found that topical therapy was effective, but there was little evidence that one treatment was better than another in short-term management. Ear drops containing aminoglycosides, such as gentamicin, neomycin, or framycetin, or polymyxins should not be used when the ear drum is perforated because of the risk of ototoxicity.

The management of the various subtypes of otitis externa has been described.[2-5]

Acute localised otitis externa is an infection of the hair follicle (furunculosis), commonly due to *Staphylococcus aureus*. It may cause severe pain, which may be treated with an analgesic such as paracetamol or ibuprofen. If the furuncle is not pointing (ready to rupture spontaneously), local heat application and systemic treatment with a penicillinase-resistant penicillin such as flucloxacillin or a first-generation cephalosporin such as cefalexin may be used.[2] Others have suggested application of topical antibacterials using wicks which are left in the ear canal for 3 to 5 days.[4] Pointed furuncles require incision and drainage followed by a course of topical and/or oral antibacterials.[2,4]

In *acute diffuse otitis externa*, *Staphylococcus aureus*, *S. epidermidis*, and *Pseudomonas* spp. are often present. Treatment includes thorough cleansing of the ear canal and instillation of ear drops including acidifying agents (2% acetic acid) and antibacterials such as aminoglycosides, fluoroquinolones (ciprofloxacin and ofloxacin), chloramphenicol, or polymyxin B, with or without corticosteroids such as dexamethasone.[2,4] Antifungals may sometimes be required. A wick may be used if instillation proves difficult.[2] Systemic antibacterials may be necessary in severe cases of otitis externa.[2,4]

Chronic otitis externa is treated similarly, although the topical antibacterials and corticosteroids used should not be the same as those used previously for the treatment of acute disease.[2]

Necrotising (malignant) otitis externa, due to fulminating infection, especially with *Pseudomonas*, is uncommon but can occur in susceptible patients. Topical antibacterials are not effective and systemic treatment with antipseudomonal drugs such as gentamicin, ceftazidime, a carbapenem, or a fluoroquinolone is needed for about 4 to 8 weeks.[2,4] However, resistance to ciprofloxacin has been reported.[6] Combination treatment with an aminoglycoside and another antipseudomonal drug or a penicillin (such as azlocillin, piperacillin, or ticarcillin) may also be used.[2,4]

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Otitis media

Otitis media is a general term used to describe inflammation of the middle ear that usually results from dysfunction of the Eustachian tube after a viral infection of the nasopharynx. It is one of the most frequent childhood illnesses seen in general practice. Subtypes of otitis media may be classified as follows:

- *acute otitis media (AOM)* is seen especially in young children and is often due to bacterial and/or viral infection and is sometimes associated with upper respiratory-tract infection. It is characterised by rapid onset, ear discomfort, and pain. Common bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (*Branhamella catarrhalis*)
- *recurrent acute otitis media* refers to frequent episodes of AOM (3 or more episodes within 6 months or 4 episodes within 12 months) and may be due to relapse or re-infection
- *otitis media with effusion (OME) or serous otitis media*, commonly known as 'glue ear', is defined as the accumulation of fluid in the middle ear without local or systemic illness. It may be associated with recurrent upper respiratory-tract infection and is characterised by deafness although some episodes may be asymptomatic
- *chronic suppurative otitis media (CSOM)* is often preceded by one or more episodes of AOM and is associated with perforation of the ear drum, and continued infection and inflammation in the middle ear causing persistent or recurrent discharge and deafness. The condition has been divided into inactive or active. Inactive disease (tubotympanic disease) is typically characterised by perforation of the ear drum, deafness, and a profuse mucoid discharge associated with upper respiratory-tract infection. In active disease (attico-antral disease) there may be cholesteatoma with bone involvement. The commonest infecting organisms are *Pseudomonas aeruginosa* and anaerobes. Other common infecting aerobic organisms are diphtheroids, *Staphylococcus aureus*, and *Klebsiella*.[1]

TREATMENT

Treatment of *acute otitis media* aims to relieve symptoms, avoid complications, and prevent relapse, recurrence, and progression to the chronic state. Sometimes an analgesic such as paracetamol may be all that is required as long as frequent inspection is possible. However, it is common practice to prescribe a systemic antibacterial as well as an analgesic,[2] although the need for routine antibacterial treatment is questionable.[3-5] Systemic antibacterial treatment aims to speed resolution and prevent complications. However, meta-analyses and reviews have shown only modest benefits from routine use of antibacterials[6-8] and experience from studies where antibacterials were not given routinely for AOM has suggested that there is no consequent increase in complications.[4,8,9] Another meta-analysis[10] to estimate the natural history of AOM found that about 60% of children not initially treated with an antibacterial showed symptomatic improvement within 24 hours, and that symptoms resolved within 3 days in about 80% of these children. Suppurative complications occurred in about 0.12% of children not immediately treated with antibacterials and in 0.24% of those given immediate treatment. A systematic review[9] reported that clinical signs and symptoms resolved within 4 to 7 days in 78% of children not initially treated with an antibacterial. However, some clinicians have argued that although the benefit is modest, it is significant and therefore the routine use of antibacterials is clinically justifiable.[6] A later systematic review[11] concluded that antibacterials do provide a small benefit in very young children and a further meta-analysis[12] reported that most benefit was seen in children under 2 years of age with bilateral AOM, and in children with both AOM and discharge. Another suggested approach has been to delay the start of antibacterials for 72 hours and to then only give them if the patient remains unwell.[8,13,14] No one antibacterial has been found to be superior to another in the treatment of AOM.[9] Adjunctive treatment with topical and systemic decongestants and antihistamines has not been found to be beneficial[15] and there is insufficient information to conclude whether there is any benefit from the use of topical analgesics (including corticosteroids, local anaesthetics, and NSAIDs).[16]

The American Academy of Pediatrics has produced guidelines[17] for the diagnosis and management of uncomplicated AOM in children from 2 months to 12 years of age. They suggest that in a select group of children an observation period may be recommended depending on the patient's age, the diagnostic certainty, and the severity of illness. These children should be given symptomatic treatment and observed for 48 to 72 hours; if the illness worsens during the observation period or there is no improvement then systemic antibacterials should be considered. Pain management is important, and appropriate analgesics should be offered. If antibacterial treatment is given high-dose amoxicillin (80 to 90 mg/kg daily) is recommended for most children. In children with severe illness or those not responding to amoxicillin and thought to be infected with *H. influenzae* or *M. catarrhalis* high-dose amoxicillin with clavulanic acid should be given. Alternatives in penicillin-allergic children include cephalosporins, azithromycin, or clarithromycin. Similar recommendations have been made for the treatment of AOM in the UK.[18]

Duration of therapy for AOM has varied from 5 to 10 or more days. A systematic review[19] of published clinical studies suggests that a 5-day treatment course may be given to children with uncomplicated AOM. The American Academy of Pediatrics recommends treatment with antibacterials for 10 days in younger children (up to 6 years of age) and for children with severe disease; those aged 6 years or older with mild to moderate disease may be given treatment for 5 to 7 days.[17]

Penicillin-resistant strains of *Str. pneumoniae* have been reported in children with otitis media and are reported to be increasingly prevalent.[20] About one-quarter of *Str.*

pneumoniae isolates, one third of *H. influenzae* isolates, and nearly all *M. catarrhalis* isolates are resistant to penicillin and amoxicillin.[2] However, resistance rates vary between countries[21] and many penicillin-resistant strains remain sensitive *in vivo* to high-dose amoxicillin.[20,22,23]

Optimal treatment of *otitis media with effusion* is controversial and the majority of cases will resolve spontaneously within 3 months. Guidelines have been developed in the USA[24] for the diagnosis and management of uncomplicated disease in children from 2 months to 12 years of age. They suggest careful assessment and observation for at least 3 months before considering surgery. Those at increased risk of developmental difficulties such as children with cleft palate or Down's syndrome should be referred to a specialist. Similar recommendations have been made for the treatment of OME in the UK.[25] Antihistamines, decongestants, and mucolytics are ineffective.[24-26] Oral or topical intranasal corticosteroids alone or with an antibacterial have only short-term benefit[27] and their use is not recommended as routine treatment.[24,25] A meta-analysis[28] on the use of antibacterials for the treatment of OME failed to find any benefit and their use cannot be justified.[24,25]

Treatment of *chronic suppurative otitis media* aims to stop the discharge, eradicate the infection, heal the ear drum, and to prevent serious complications. Treatment options for uncomplicated cases include aural toilet (thorough cleansing and mopping of the ear), systemic antibacterials, and topical treatments with either an antiseptic or antibacterial, sometimes also with a corticosteroid. Surgery may be needed if complications develop.[1,29] There is controversy over the use of ear drops containing aminoglycosides or polymyxins in the presence of a perforated ear drum, as they are potentially ototoxic. However, it is considered that deafness is more likely to result from untreated disease than from a short course of these ear drops. A systematic review[29] found that treatment with topical fluoroquinolone ear drops was more effective at drying the ear than no drug treatment or topical antiseptics; effects of topical non-fluoroquinolone antibacterials when compared with no drug treatment or topical antiseptics were less clear. Another systematic review[30] found that ear drops containing fluoroquinolones were also more effective than systemic antibacterials at drying the ear. Effects of topical non-fluoroquinolone antibacterials or antiseptics were less clear and no additional benefit was noted by adding a systemic antibacterial to topical antibacterial treatment.

PREVENTION

Long-term antibacterial prophylaxis has been tried in children at high risk including those with *recurrent acute otitis media*,[31,32] but the evidence for its benefit is inconsistent. A meta-analysis[33] on the use of antibacterials to prevent recurrent AOM concluded that they appeared to have limited benefit and that 9 children would need to be treated to show an improved outcome in one. A later meta-analysis[34] concluded that antibacterials reduced the probability of disease recurring during the treatment period, but that the long-term benefits of treatment were unclear and that 5 children would need to be treated to show an improved outcome in one.

The use of xylitol, which inhibits the growth of *Str. pneumoniae*, as chewing gum[35,36] or as syrup for very young children[36,37] has been reported to reduce the incidence of AOM. Randomised studies[35,36] with xylitol chewing gum reported a 40% reduction in the incidence of AOM in children with recurrent AOM. However, xylitol was found to be ineffective when it was used only during an acute respiratory-tract infection[38] and the need for use 5 times daily may make this treatment impractical.[35,36]

Vaccination against AOM with pneumococcal vaccines has also been tried but unconjugated multivalent polysaccharide vaccines do not prevent AOM in children under 2 years of age[23,39] and their benefit in older children is minimal.[39] A meta-analysis[39] found that starting immunisation with the 7-valent pneumococcal conjugate vaccine during infancy has marginal beneficial effects in terms of reducing the incidence of recurrent AOM. Giving 7-valent pneumococcal conjugate vaccine, followed by 23-valent pneumococcal polysaccharide vaccine, to older children with recurrent infections appears to have no benefit in preventing further episodes.

Vaccination may also have a role in reducing the incidence and in preventing the development of antibacterial resistance[23] but use of conjugated pneumococcal vaccines was found to cause a shift in the pathogens responsible for AOM from vaccine-type pneumococci to nonvaccine-type strains and to *H. influenzae*.[23]

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Pancreatitis

The overall management of pancreatitis is discussed on p. 2580.2. **Pancreatic necrosis** is the most serious local complication of acute pancreatitis. When necrosis is sterile, mortality is low and *treatment* is conservative.[1] Morbidity and mortality increase if the initially sterile pancreatic necrosis becomes infected by bacteria from the gut.[1,2] When infection is proven and cultures reveal the presence of Gram-negative bacteria, choices for antibacterial treatment include a carbapenem, a fluoroquinolone plus metronidazole, or a third generation cephalosporin plus metronidazole; vancomycin is a reasonable choice for Gram-positive bacteria.[3]

There has been considerable interest in the early *prevention* of infected necrosis with antibacterials; cephalosporins, carbapenems, and fluoroquinolones have been studied as they are considered to have the best penetration into the pancreas.[4] There is, however, uncertainty about their value in acute necrotising pancreatitis due to concerns about promoting antibacterial resistance and opportunistic fungal infections,[5] and conflicting results from studies. A systematic review[6] of 5 studies in patients with proven pancreatic necrosis found that, despite variations in drugs used (cefuroxime, imipenem, or metronidazole with ciprofloxacin or ofloxacin) and in the quality and methodology of studies conducted, intravenous antibacterial prophylaxis appeared to reduce the risk of death in patients with pancreatic necrosis, but with only a trend towards a reduced rate of infected pancreatic necrosis. A subsequent meta-analysis[4] of 7 studies, including the 5 studies in the previous systematic review, found no reduction in the risk of infected pancreatic necrosis or death, and suggested that routine prophylactic antibacterials may not be useful. Guidelines therefore vary in their recommendations. Those developed in the USA[3] do not recommend antibacterial prophylaxis in patients with necrotising pancreatitis; however, if signs of sepsis are present, antibacterials may be given while the source of infection is investigated. Treatment should be stopped if no source of infection is found. UK guidelines[2] do not make a recommendation as there is no consensus on the issue, but state that if antibacterial prophylaxis is used, it should be given for a maximum of 14 days.

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Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is a broad term for infectious disorders of the upper genital tract in women and may include endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. It is generally due to ascending infection through the cervix and uterus to the fallopian tubes, resulting in salpingitis, and from there may extend to the ovaries and peritoneum. Long-term complications include infertility and ectopic pregnancy. The use of intrauterine contraceptive devices might increase the likelihood of PID although the risk may have been overstated;[1] it appears to be greatest during the first 20 days after insertion of the device.[2]

The majority of these infections are probably sexually transmitted and at one time were mainly due to *Neisseria gonorrhoeae*, but *Chlamydia trachomatis* is increasingly responsible and may be the commonest cause of PID in some areas. Other organisms that have been isolated include *Mycoplasma hominis*; *Ureaplasma urealyticum*; anaerobes such as *Bacteroides*, *Peptococcus*, and *Peptostreptococcus* spp.; Gram-negative enteric aerobes such as *Escherichia coli*; and Gram-positive aerobes such as group B streptococci. Some of these organisms occur in the abnormal vaginal flora associated with bacterial vaginosis (p. 174.1). Thus, the aetiology of PID appears to be polymicrobial; some think that primary infection with *N. gonorrhoeae* or *C. trachomatis*, or both, allows opportunistic infection with aerobic and anaerobic bacteria.[1]

Treatment regimens are of necessity broad spectrum and empirical and should include antibacterials active against the major pathogens. Many consider that treatment should be started in hospital so that drugs can be given parenterally. Guidelines produced by WHO,[3] by an expert group in the UK,[4] and by the CDC in the USA[5] are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- **WHO:**
  - *inpatients*:
    - intramuscular ceftriaxone 250 mg daily, *plus* oral or intravenous doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times daily), *plus*

oral or intravenous metronidazole 400 to 500 mg twice daily or chloramphenicol 500 mg four times daily
- intravenous clindamycin 900 mg every 8 hours, *plus* intravenous gentamicin 1.5 mg/kg every 8 hours
- oral ciprofloxacin 500 mg twice daily or intramuscular spectinomycin 1 g four times daily, *plus* oral or intravenous doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times daily), *plus* oral or intravenous metronidazole 400 to 500 mg twice daily or chloramphenicol 500 mg four times daily

Therapy should be continued for at least 48 hours after clinical improvement, and *then* followed by doxycycline or tetracycline orally for 14 days.

- *outpatients*:
  - a single-dose treatment for uncomplicated gonorrhoea such as a single intramuscular dose of ceftriaxone 125 mg is recommended (see Gonorrhoea, p. 206.2) *plus* oral metronidazole 400 to 500 mg twice daily *and* oral doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times daily) for 14 days.

- **UK:**
  - *inpatients*:

    with the regimens below intravenous therapy is continued until 24 hours after clinical improvement, and the oral regimen is *then* substituted until therapy has been given for at least 14 days.
    - intravenous ceftriaxone 2 g daily *plus* intravenous (or oral if tolerated) doxycycline 100 mg twice daily, until clinical improvement, *then* oral doxycycline 100 mg twice daily, *plus* oral metronidazole 400 mg twice daily
    - intravenous clindamycin 900 mg three times daily *plus* intravenous gentamicin (2 mg/kg as a loading dose, *then* 1.5 mg/kg three times daily *or* a single daily dose of 7 mg/kg) until clinical improvement, *then* either oral clindamycin 450 mg four times daily or oral doxycycline 100 mg twice daily *plus* oral metronidazole 400 mg twice daily

    alternative regimens, given for a total of 14 days, are:
    - intravenous ofloxacin 400 mg twice daily *plus* intravenous metronidazole 500 mg three times daily
    - intravenous ciprofloxacin 200 mg twice daily *plus* intravenous metronidazole 500 mg three times daily, *plus* intravenous or oral doxycycline 100 mg twice daily

    Metronidazole may be stopped in women with mild or moderate disease who tolerate it poorly, but the improved coverage of anaerobic infection that it provides is more important in women with severe disease.
  - *outpatients*:
    - a single intramuscular dose of ceftriaxone 500 mg, *then* oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days, *or*
    - oral ofloxacin 400 mg plus oral metronidazole 400 mg both twice daily for 14 days

    alternative regimens are:
    - a single intramuscular dose of ceftriaxone 500 mg, *then* azithromycin 1 g each week for 2 weeks, *or*
    - oral moxifloxacin 400 mg once daily for 14 days

- **USA:**
  - *parenteral* treatment:
    - (regimen A): intravenous cefoxitin 2 g every 6 hours or cefotetan 2 g every 12 hours *plus* oral or intravenous doxycycline 100 mg every 12 hours
    - (regimen B): intravenous clindamycin 900 mg every 8 hours *plus* parenteral gentamicin 2 mg/kg as a loading dose *then* 1.5 mg/kg every 8 hours; alternatively, a single daily dose regimen of 3 to 5 mg/kg daily can be used for maintenance

    In each case parenteral treatment is continued for 24 hours after substantial clinical improvement has occurred and *then* followed by oral therapy to complete a total of 14 days of treatment.
    - in regimen A, continuation is usually with oral doxycycline 100 mg twice daily; in patients with tubo-ovarian abscesses oral clindamycin *or* oral metronidazole should be added to doxycycline
    - in regimen B, continuation may be with oral clindamycin 450 mg four times daily *or* doxycycline; oral clindamycin is preferred in patients with tubo-ovarian abscesses

    Another parenteral regimen which has been tried is:
    - intravenous ampicillin/sulbactam 3 g every 6 hours *plus* oral or intravenous doxycycline 100 mg every 12 hours.
  - *oral* treatment:
    - a single intramuscular dose of cefoxitin 2 g *plus* oral probenecid 1 g, *or* a single intramuscular dose of ceftriaxone 250 mg (*or* an equivalent third-generation cephalosporin), *plus* oral doxycycline 100 mg twice daily, with or without oral metronidazole 500 mg twice daily, for 14 days

Pregnant women who have suspected PID disease should be hospitalised and treated with a parenteral regimen.[5]

Sexual partners of patients with PID should be tested and treated.[5]

Women co-infected with HIV appear to be more likely to develop tubo-ovarian abscesses but respond similarly to treatment compared with women who are HIV-negative.[5]

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Peptic ulcer disease

The Gram-negative bacterium *Helicobacter pylori* is involved in the aetiology of gastritis and peptic ulceration, and treatment regimens to eradicate the organism are recommended in peptic ulcer disease (p. 1816.2).

Perinatal streptococcal infections

Group B streptococci are a major cause of perinatal infections, often leading to neonatal pneumonia or septicaemia, sometimes with meningitis, although the incidence varies in different parts of the world. Maternal colonisation with group B streptococci in the genito-urinary or gastrointestinal tracts is the main risk factor for disease and neonatal infections are acquired vertically through maternal genital carriage during pregnancy. Infection in newborns occurring within the first week of life is termed early-onset disease, while late-onset infections occur in infants more than 1 week of age.

It has been suggested that *prevention* of group B streptococcal infection in infants may be achieved by giving appropriate antibacterials to the mother during labour,[1] but a systematic review found a lack of high-quality clinical evidence to support this practice.[2] Ideally maternal carriers of group B streptococci would be identified during pregnancy, but this may not be practical. Factors that increase the risk of acquiring neonatal infection include premature labour, prolonged rupture of membranes, maternal fever, a previous child with neonatal group B streptococcal infection, and multiple pregnancy and they will influence the decision of whether or not to give intrapartum antibacterial prophylaxis to the mother. A penicillin is the preferred drug.

Guidelines to prevent early-onset disease from the USA[1] recommend prophylaxis based on universal prenatal screening. Where required, they recommend benzylpenicillin or, alternatively, ampicillin, given intravenously during labour. In women allergic to penicillin but who are not considered to be at high risk of anaphylaxis, intravenous cefazolin is recommended as an alternative; those considered to be at high risk of anaphylaxis should be given clindamycin intravenously or, where there is resistance to clindamycin or susceptibility is unknown, intravenous vancomycin. Erythromycin is no longer recommended as an alternative for prophylaxis for penicillin-allergic women at high risk for anaphylaxis.

In other parts of the world, including Europe, the incidence of neonatal streptococcal infections is much lower and the US model for prophylaxis may not be appropriate.[3]

Another strategy suggested for areas with a high incidence of neonatal group B streptococcal disease (above 1.5 per 1000 live births) is to give a single intramuscular dose of penicillin to all neonates at birth.[4] However, despite positive results in some uncontrolled, retrospective, and non-randomised studies, a systematic review[5] found that routine use of intramuscular penicillin in neonates did not reduce the incidence of early-onset group B streptococcal disease, or mortality.

As mentioned under Premature Labour, p. 203.3, the elimination of bacteria such as group B streptococci in pregnant women might also reduce the risk of premature labour.

Streptococcus group B vaccines are under investigation for use in pregnant women to prevent neonatal infection.

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Peritonitis

Infective peritonitis, a type of intra-abdominal infection, is an inflammation of the peritoneum resulting from contamination of the peritoneal cavity with bacteria or fungi (for information on fungal peritonitis, see under Choice of Antifungal, p. 567.1). It may be primary or secondary or may be a complication of peritoneal dialysis (PD). Peritonitis may be complicated by intraperitoneal abscesses, and abscesses of the intra-abdominal viscera such as those of the liver (see under Abscess, Liver, p. 172.3), pancreas, and spleen.

Primary peritonitis. In primary or spontaneous bacterial peritonitis there is no specific focus of infection and it occurs most often as a complication of ascites, particularly in advanced liver disease. Infecting bacteria include *Escherichia coli*, other Enterobacteriaceae, and streptococci or enterococci; anaerobic bacteria are very rarely encountered. Infection is most often due to a single organism.

Because ascitic fluid cultures are often negative in primary peritonitis, initial antibacterial **treatment** is generally empirical and targeted towards the most likely pathogens. Historically, multidrug regimens such as ampicillin plus an aminoglycoside have been used, and more recently, other alternatives have included broad-spectrum penicillins, carbapenems, fluoroquinolones, and combinations of penicillins with beta-lactamase inhibitors.[1-4] Third-generation cephalosporins such as cefotaxime are considered by some to be the treatment of choice.[1,2,5] Current evidence, however, does not appear to show a significant advantage for the cephalosporins over other antibacterials in terms of resolution of infection or patient survival.[4]

Intravenous antibacterials are generally preferred, however, oral antibacterials such as amoxicillin-clavulanic acid, cefixime, and some fluoroquinolones[4] have been tried and may be as effective in patients with uncomplicated infection. The optimal duration of therapy is unclear. Intervals of 10 to 14 days have been used, but, in one study,[6] a 5-day regimen was noted to be as effective as a 10-day course. In most studies, however, length of treatment has been dictated by the resolution of signs and symptoms of disease, rather than completion of a predetermined course of therapy.[4]

Given the very high rate of recurrence in patients surviving an initial episode of primary peritonitis, long-term secondary **prophylaxis** has been advocated. In some studies, daily oral doses of norfloxacin have been associated with lower rates of subsequent peritonitis; in one, the probability of recurrent infection at 1 year was reduced from 68 to 20%.[7] Ciprofloxacin[8] and co-trimoxazole[9] are also reportedly effective.

In addition, long-term prophylaxis against first episodes of infection has also been suggested for some high-risk patient groups. Patients at highest risk appear to be those with low serum sodium or ascitic fluid protein concentration, as well as those with acute gastrointestinal bleeding, or very advanced liver disease.[4,10] A meta-analysis[8] examining efficacy of antibacterial prophylaxis in cirrhotic patients with advanced liver dysfunction or low ascitic fluid protein concentrations reported a 28% relative risk reduction for first-time incidence of primary peritonitis, but a trend towards survival benefit failed to reach statistical significance. It has been suggested that short courses of antibacterials may be of benefit in cirrhotic patients with ascites *without gastrointestinal bleeding*, but the body of evidence in support of this practice has been criticised.[11] Use of primary prophylaxis in such patients remains an area of controversy and is currently not routinely recommended.[2,3,10] In contrast, short courses of antibacterials have been associated with significantly reduced rates of subsequent infection, including peritonitis, and reductions in overall mortality, in cirrhotic patients *with acute gastrointestinal bleeds*;[12,13] as a result, routine antibacterial treatment for a minimum of 7 days has been recommended for all cirrhotic patients presenting with acute upper gastrointestinal haemorrhage.[2] Although most studies have involved the use of a fluoroquinolone, other drugs including third-generation cephalosporins, carbapenems, and amoxicillin-clavulanic acid have also been tried.[13]

Secondary peritonitis. Secondary peritonitis is associated with perforation of the gastrointestinal tract, conditions such as appendicitis and diverticulitis, and contamination at surgery. Infections are generally mixed and originate from the gastrointestinal tract. Bacteria responsible include *E. coli* and other Enterobacteriaceae, anaerobes (especially *Bacteroides fragilis*), enterococci, and sometimes *Pseudomonas aeruginosa*. Timely control of the source of infection, where possible, is critical for successful **treatment**, but antibacterial therapy is an important adjunct. Broad-spectrum antibacterial therapy is usually given, at least until the infecting organisms are known, and should generally include, at minimum, antibacterials effective against enteric Gram-negative aerobic and facultative bacilli, and enteric Gram-positive streptococci. Coverage for obligate anaerobic bacilli should also be included for infections derived from distal small-bowel, appendix, and colon, as well as for more proximal perforations in the presence of obstruction or paralytic ileus.[14] In addition, choice of regimen should take into account patient-specific risk factors for more resistant

infection. For patients with a history of antibacterial exposure or prolonged hospitalisation, a regimen with antipseudomonal activity should be considered.[15] Similarly, coverage for MRSA should be added for healthcare-associated infections in patients known to be colonised with MRSA, or who are at risk due to previous treatment failure and significant antibacterial exposure.[14] Coverage for enterococci has also been advocated in severely ill patients with a history of prolonged cephalosporin use or recurrent intra-abdominal infection, active immunosuppression, and in those with prosthetic heart valves.[16] Empirical antifungal treatment might also be considered in cases of gastrointestinal perforation, anastomotic leak, or severe necrotising pancreatitis.[15] For healthcare-associated infections, institution-specific resistance patterns are also an important consideration in the choice of therapy.

No empirical antibacterial regimen has been shown to be consistently superior or better tolerated than comparators,[17] and various single- and multidrug regimens have been suggested by the Infectious Diseases Society of America (IDSA) depending on infection severity and whether it is considered community-acquired or healthcare-associated.[14]

For *mild-to-moderate community-acquired infection,* the IDSA recommends the following regimens:

- monotherapy with ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline
- combination therapy with metronidazole and either cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin

For *high-severity community-acquired infection* a regimen with an expanded spectrum of activity against Gram-negative bacteria is suggested by the IDSA,[14] and suitable regimens include:

- monotherapy with meropenem, imipenem-cilastatin, doripenem, or piperacillin-tazobactam
- combination therapy with metronidazole and either ciprofloxacin, levofloxacin, ceftazidime, or cefepime (however, see below regarding *E.coli* resistance to quinolones)
- combination therapy with metronidazole, aztreonam, and another antibacterial effective against Gram-positive cocci

For *healthcare-associated infection,* empirical antibacterial regimens should be informed by hospital-specific microbiological and resistance data and may require drugs active against a wide spectrum of Gram-negative organisms. Multidrug regimens are suggested, and the IDSA recommends using metronidazole combined with either meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ceftazidime, or cefepime; use of colistin or an aminoglycoside may be required.[14]

Because *B. fragilis* has shown substantial acquired resistance to clindamycin, cefotetan, cefoxitin, and the fluoroquinolones, these drugs should not be used alone as initial therapy.[14] Given the high rate of fluoroquinolone-resistant *E. coli* in some communities, fluoroquinolones should not be used empirically unless hospital microbiological surveys indicate >90% susceptibility to fluoroquinolones.[14]

For patients with only mild or moderate community-acquired infection, drugs with the broadest spectrum of Gram-negative and Gram-positive coverage (such as ertapenem and tigecycline) have no advantage and may contribute to the emergence of more resistant organisms. Similarly, aminoglycosides are not routinely recommended due to their potential toxicity, although empirical use may be warranted in patients with healthcare-associated infection or intolerance to beta-lactam or fluoroquinolone-based regimens.[14]

The intravenous route is generally preferred, and therapy should be tailored to culture and susceptibility reports when available. Treatment is generally continued until clinical signs of infection and gastrointestinal function have returned to normal; where source control has been adequate, about 5 to 7 days has been suggested.[15]

For reference to the **prevention** of postoperative infection, see under Surgical Infection, p. 211.1.

PD peritonitis. Peritonitis is the main complication of peritoneal dialysis (PD). Like primary, and, unlike secondary peritonitis, above, a single infecting organism is often responsible. The most common infections have usually been due to Gram-positive organisms, especially staphylococci, but infections with Gram-negative bacteria (typically Enterobacteriaceae) are becoming more common, and fungi are an increasingly important cause of peritonitis in PD.[1] The origin of infection is often contamination of the dialysis catheter or the exit site.

The International Society for Peritoneal Dialysis recommends[18] that the choice of antibacterial for empirical **treatment** be based on the history of sensitivities of organisms causing peritonitis in the particular hospital or centre involved, and be active against both Gram-positive and Gram-negative organisms. In many cases, first-generation cephalosporins such as cefazolin or cefalotin provide adequate Gram-positive coverage, but in centres with high rates of meticillin-resistant infection empirical vancomycin may be needed. Drugs for Gram-negative coverage should possess activity against *Ps. aeruginosa* and may include the aminoglycosides, ceftazidime, cefepime, a carbapenem, or aztreonam. Fluoroquinolones are only appropriate for Gram-negative coverage if local susceptibility is shown.

Intraperitoneal dosage, by mixing the antibacterials with the dialysate, has been shown to be more effective than intravenous use. For many antibacterials, once-daily intermittent dosing regimens (in a single dialysate exchange) are appropriate and as effective as continuous regimens.[19] Intermittent doses of vancomycin are generally given once every 5 to 7 days.[18] Once the infecting organism is identified, an appropriate narrow-spectrum antibacterial can be substituted. Treatment is generally continued for 14 days in patients who have a clinical response. Treatment should be extended to 21 days in patients with severe infections (such as *Staph. aureus,* Gram-negative, or enterococcal peritonitis).

Exit-site infections can be treated with an oral penicillinase-resistant penicillin, a first-generation cephalosporin such as cefalexin, or co-trimoxazole for Gram-positive infections. Vancomycin should be avoided for routine use but may be needed if there is meticillin resistance. Rifampicin may be added in severe *Staph. aureus* infections. An oral fluoroquinolone such as ciprofloxacin may be used for Gram-negative infections.[18] Intraperitoneal ceftazidime may be added in cases of pseudomonal infection where resolution of infection is slow or where there is recurrence.

Long-term antibacterial **prophylaxis** is not generally effective, but intermittent use has been advocated in situations associated with higher risk of infection. Perioperative intravenous antibacterial prophylaxis during PD catheter insertion is recommended,[18] and has been shown to significantly reduce the risk of peritonitis in the first month after surgery.[20] *Staph. aureus* nasal carriage is associated with increased risk of exit-site infections and intranasal or exit-site mupirocin (cream, as ointment may damage the catheter) or exit-site gentamicin cream have been used to reduce them.[18] The results of a systematic review suggest that treating carriers with intranasal mupirocin significantly decreases overall rates of exit-site infections, although there does not appear to be an associated reduction in risk of peritonitis.[20] Dramatic reductions in peritonitis rates have been achieved with programmes based on stringent aseptic wound care and on minimising contact of the PD system with domestic water.[21]

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Pertussis

Pertussis or whooping cough[1] is caused by infection with the respiratory pathogen *Bordetella pertussis,* a Gram-negative aerobic bacterium. The related species *B. parapertussis* causes a similar but generally milder illness. Pertussis is very infectious and occurs most frequently in children, but may be more common in adults than once thought. The incidence of pertussis has been greatly reduced by the active immunisation of infants (see under Pertussis Vaccines, p. 2408.3) and effective prevention by the adequate uptake of vaccine remains the ultimate objective.

Erythromycin has been the antibacterial of choice, but the newer macrolides, clarithromycin and azithromycin, have similar efficacy and are also recommended for the **treatment** of pertussis.[1-3] Once infection has occurred antibacterial therapy is thought to render the patient non-infectious by eliminating nasopharyngeal carriage of *B. pertussis.* Such treatment is unlikely to affect the clinical course of pertussis because diagnosis is difficult until the paroxysmal stage, by which time the bacteria have already damaged the respiratory tract and released their toxins. Effective regimens include:[2,3]

- oral azithromycin 500 mg daily on the first day of treatment then 250 mg daily for 4 days; infants and children may be given oral azithromycin 10 mg/kg daily for 3 to 5 days, or 10 mg/kg daily on the first day of treatment then 5 mg/kg daily for 4 days
- oral clarithromycin 500 mg twice daily for 7 days; infants and children may be given oral clarithromycin 7.5 mg/kg twice daily for 7 days
- oral erythromycin 500 mg four times daily for 14 days; infants and children may be given oral erythromycin 40 to 50 mg/kg daily in 3 to 4 divided doses for 7 to 14 days, or 60 mg/kg daily in 3 divided doses for 14 days

Oral co-trimoxazole for 7 to 14 days may be given as an alternative treatment for patients unable to tolerate macrolides. Oxytetracycline or chloramphenicol are not recommended because of their potential adverse effects.

Macrolide antibacterials, given in the same doses as for treatment and within 3 weeks of onset of cough in the index patients, may also be given **prophylactically** to close contacts.[2] However, protection is limited and a systematic review[3] concluded there was insufficient evidence to determine the benefit of prophylactic treatment of healthy pertussis contacts.

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Pharyngitis

Pharyngitis and tonsillitis are upper respiratory-tract infections with similar causes and occur especially in children. Acute pharyngitis is an inflammatory syndrome of the oropharynx that may include the tonsils whereas tonsillitis is, strictly speaking, a more localised infection. The commonest causes are viral and a sore throat is often a symptom of the common cold as well as influenza and infectious mononucleosis. For further details of these viral infections, see under Choice of Antiviral, p. 953.1.

The most important bacterial cause of acute pharyngitis and tonsillitis is the group A beta-haemolytic ***streptococcus***, *Streptococcus pyogenes*. An erythrogenic toxin-producing strain causes pharyngitis and tonsillitis in scarlet fever.

In view of the prevalence of a viral cause, opinions have differed over whether and when to treat pharyngitis with antimicrobial drugs. Some have advocated waiting until a definite diagnosis of *Str. pyogenes* infection is made, but others treat immediately if streptococcal pharyngitis is suspected because of the risk of longer term complications such as rheumatic fever and the need to eradicate *Str. pyogenes* from the throat.[1-3] The incidence of rheumatic fever has been low for many years in developed countries, but there was evidence of a resurgence in parts of the USA in the mid-1980s. Thus, in addition to shortening the illness and interrupting transmission, the antibacterial treatment of streptococcal pharyngitis also serves as primary prevention of rheumatic fever (see below). However, in countries in which the incidence of rheumatic fever remains low the routine use of antibacterials for the management of sore throats is discouraged.[4,5]

Penicillin is the standard **treatment** for streptococcal pharyngitis or tonsillitis,[6-8] generally as phenoxymethylpenicillin orally for 10 days or a single intramuscular injection of benzathine benzylpenicillin. Both options are advocated by WHO[7] and the American Heart Association[8] for the primary prevention of rheumatic fever (see under Rheumatic Fever, p. 204.3), the latter particularly where compliance with a 10-day course of oral penicillin is unlikely. Oral amoxicillin is also effective[7,9] and a further treatment option for confirmed streptococcal pharyngitis;[8] however, some suggest that empirical use of aminopenicillins (including amoxicillin and ampicillin) should probably be avoided because of the risk of maculopapular rash if the patient proves to have infectious mononucleosis.[10] Erythromycin or another macrolide may be given to penicillin-allergic patients, except where there is evidence of significant resistance,[7,8] as in some parts of Europe,[7] the USA,[11] Japan,[12] and Finland;[13] it may also be a better choice than penicillin if there is a likelihood of infection with *Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*), but should be avoided if there is risk of infection with *Fusobacterium necrophorum* (see below). Clindamycin may also be used.[8] Oral cephalosporins are another alternative, and a meta-analysis[14] has shown that the likelihood of treatment failure with oral cephalosporins may be about half that with penicillin; first-generation cephalosporins appear no less effective than later generations,[14] and are generally preferred due to their narrower antibacterial spectrum.[8,14]

Despite the general efficacy of penicillin a trend of increasing numbers of relapses and recurrent infections has been noted.[15] Some treatment failures have been attributed to poor patient compliance with a 10-day course of penicillin and attempts to overcome this have included giving fewer daily doses or shortening the length of treatment. Meta-analysis of studies supports the use of twice-daily dosing of phenoxymethylpenicillin which appears to be as effective as doses three or four times daily,[16] but a single daily dose is less effective. Courses of phenoxymethylpenicillin shorter than 10 days have not proved effective.[17,18] There is some evidence that shorter courses may be possible with other antibacterials.[19] Courses of 5 days or less of erythromycin,[20] amoxicillin with clavulanic acid,[21] azithromycin,[22,23] clarithromycin,[24] josamycin,[25] telithromycin,[26] or cephalosporins[27] have been given as alternatives to a 10-day course of phenoxymethylpenicillin. However, definitive studies have not been done, and the broader spectrum and higher cost of these regimens are drawbacks.[6]

Penicillin resistance in *Str. pyogenes* remains rare. In addition to poor compliance, treatment failures with penicillin, leading to recurrent infection, might be explained by the presence of beta-lactamase-producing oropharyngeal bacteria that are able to protect *Str. pyogenes* against penicillin,[28] although this theory was not supported by a study in 462 children.[29] Antibacterials less susceptible to beta lactamase have been effective, sometimes more so than phenoxymethylpenicillin. They include the oral cephalosporins cefaclor,[30] cefuroxime axetil,[31] cefixime,[32] cefprozil,[33] and cefadroxil[34] and the combined preparation amoxicillin with clavulanic acid[35,36] (however, see above regarding the risk of rash with aminopenicillins). Clindamycin has eradicated *Str. pyogenes* and beta-lactamase-producing bacteria in children aged 12 years and under with recurrent tonsillitis, but might be less effective in older patients.[37] It was also effective where penicillin and erythromycin had failed in an outbreak of streptococcal pharyngitis.[38]

Pharyngeal carriage of *Str. pyogenes* is common, especially in primary-school children and thus its presence does not necessarily reflect acute infection. **Eradication** is generally unnecessary[7,8] but may be beneficial in selected cases and has been achieved by a single intramuscular injection of benzathine benzylpenicillin together with a 4-day course of oral rifampicin;[39] a 10-day course of oral clindamycin has also been effective.[40] In order to ensure that outbreaks of *Str. pyogenes* are prevented in closely confined populations, some have recommended prophylactic antibacterials for *all* members of these populations, without exception.[41]

Other bacterial causes of pharyngitis include *Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*), *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Corynebacterium diphtheriae* (see under Diphtheria, p. 178.3), *Fusobacterium necrophorum*, *Neisseria gonorrhoeae* (see under Gonorrhoea, p. 206.2), groups C and G beta-haemolytic streptococci, and anaerobic bacteria.

A. haemolyticum is thought to be an important cause of pharyngitis in adolescents and young adults; there is often an accompanying scarlatiniform rash. It has been reported to respond to a single injection of benzathine benzylpenicillin or a 10-day course of oral erythromycin, but not to phenoxymethylpenicillin.[6]

F. necrophorum is also common in adolescents and young adults, and is thought to cause about 10% of acute pharyngitis within this age group.[42] Of particular concern is its association with Lemierre syndrome, a life-threatening condition characterised by bacteraemia, metastatic infections, and suppurative thrombophlebitis of the internal jugular vein. Although susceptible to penicillins and cephalosporins, *F. necrophorum* does not respond to treatment with macrolides; it has therefore been suggested that empirical use of macrolides be avoided in adolescents and young adults with acute pharyngitis.[42]

For pharyngitis associated with *C. pneumoniae* infection, tetracycline or erythromycin are effective antibacterials.[43]

Systemic corticosteroids have been tried for the symptomatic relief of acute pharyngitis and in a meta-analysis,[44] patients with severe or exudative sore throat who took corticosteroids in addition to antibacterials were 3 times more likely to have complete resolution of pain at 24 hours than those who did not. However, it remains unclear whether corticosteroids offer additional benefits over simple analgesics, or if they are safe for use in pharyngitis not requiring antibacterial therapy.

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Pinta

See Syphilis, p. 207.2.

Plague

Plague[1,2] is caused by the Gram-negative bacillus *Yersinia pestis* (*Yersinia pseudotuberculosis* subsp. *pestis*) and is usually transmitted to man via rodents and their infected fleas. It has occurred as worldwide pandemics, for example, the Black Death in Europe in the Middle Ages. In the 1980s the largest numbers of cases reported were in Tanzania, Vietnam, Brazil, Peru and more recently in Madagascar. Plague may take several forms of which bubonic plague is the most common; others include pneumonic, septicaemic, and meningitic plague. Streptomycin, tetracycline, and chloramphenicol have traditionally been used in the treatment of plague[3] with streptomycin being the treatment of choice, although the possibility of a Jarisch-Herxheimer reaction resulting from the bactericidal effect of streptomycin must be borne in mind; it is also contra-indicated in pregnancy. Success has also been reported with aminoglycosides such as gentamicin and kanamycin. Although there is no clinical experience with fluoroquinolones, *in-vitro* susceptibilities and *animal* studies suggest that they would be effective.[3]

In the UK, the recommended treatment for adults is gentamicin (first choice in pregnancy); ciprofloxacin or doxycycline may be used if aminoglycosides are unsuitable and may also be used for first-line therapy in children, but doxycycline is only suitable for children over 8 years of age. If plague meningitis is suspected chloramphenicol should be used as it crosses the blood-brain barrier.[3] Similar information is provided by WHO,[4] with sulfonamides being mentioned as alternatives. European guidelines[5] consider either streptomycin or gentamicin to be appropriate for first-line treatment of plague in both adults and children, and suggest that ofloxacin and levofloxacin may be appropriate alternatives to ciprofloxacin for second-line treatment in adults.

In UK guidelines[3] ciprofloxacin is considered to be the drug of choice for prophylaxis in adults and children considered to be at risk after close contact with cases of pneumonic disease or after a deliberate release of *Y. pestis*; doxycycline may be used as an alternative in those over 12 years of age. European guidelines[5] offer similar advice, but consider levofloxacin and ofloxacin as possible options for prophylaxis in adults. Other suggested antibacterials include co-trimoxazole,[3,5] chloramphenicol,[3,5] and sulfadiazine.[5]

Commenting on the plague epidemic that occurred in India in 1994, workers from the US CDC[6] considered that prophylaxis should be given to those who have had face-to-face contact or who have occupied a closed space with someone who has pneumonic plague. For prophylaxis, tetracycline could be given to adults and older children or sulfonamides to children of 8 years or less; chloramphenicol was also effective.[6]

Infection with a strain of *Y. pestis* resistant to all the drugs usually effective against plague identified in a patient from Madagascar[7] responded to treatment with co-trimoxazole and streptomycin.

A vaccine is available for active immunisation.

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Pneumonia

Pneumonia[1] is a respiratory disease characterised by inflammation of the lung parenchyma with congestion. It is mostly due to bacterial or viral infection, but may be caused by fungi in immunocompromised patients or by the aspiration of chemical irritants. Pneumonia is a common illness occurring in all age groups and throughout the world; it is a major cause of death among the elderly and those who are chronically and/or terminally ill. Symptoms and signs of pneumonia include chills, cough, dyspnoea, fever, headache, myalgia, pleuritic chest pain, and sputum production. Treatment of pneumonia relies on prompt use of antibacterials and identification of the infecting organisms and their sensitivity to antibacterials. Cases of pneumonia are usually classified as community-acquired or hospital-acquired (nosocomial) pneumonia. Cases of community-acquired pneumonia can also be further sub-divided into those who can be treated in an ambulatory (outpatient) setting and those that need hospitalisation. Patients who need hospitalisation are generally infected with unusual pathogens and/or have more severe disease. Pneumonia occurring in long-term-care facilities can be treated as either community-acquired or hospital-acquired pneumonia. Cases of hospital-acquired pneumonia are generally classified according to the time of onset after hospital admission. These categories also provide a rough guide as to the likely pathogen and severity of the disease.

Other types of pneumonia include aspiration pneumonia and the various forms of interstitial pneumonia or pneumonitis (see also Aspiration Syndromes, p. 1807.2, and Interstitial Lung Disease, p. 1607.1). Interstitial pneumonitis is a common complication in cancer patients and has also been associated with certain drugs, for example amiodarone, bleomycin, and nitrofurantoin.

Community-acquired pneumonia. In community-acquired pneumonia (CAP)[2-7] the commonest pathogen in previously healthy subjects is *Streptococcus pneumoniae* (pneumococcus). Other common pathogens include *Haemophilus influenzae* and atypical pathogens such as *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Mycoplasma pneumoniae*, and *Legionella pneumophila* (see Legionnaires' Disease, p. 188.2).[2,5] Less common causes include *Staphylococcus aureus*, which usually occurs as a secondary bacterial infection after influenza and is associated with high mortality; *Moraxella catarrhalis* (*Branhamella catarrhalis*) occurs especially in patients with chronic lung disease; Gram-negative enteric bacilli; *Pseudomonas aeruginosa*; *Chlamydophila psittaci* (*Chlamydia psittaci*) (see Psittacosis, p. 204.1); and *Coxiella burnetii* (see Q Fever, p. 204.1). Gram-negative bacilli rarely cause pneumonia in the community, especially in previously healthy patients, although the frequency of such infections is increasing.[8] Anaerobic bacteria are associated with aspiration pneumonia. Viruses are the commonest pathogens in young children.

Pneumococcal pneumonia usually develops over several days and in elderly patients onset may be insidious. *Str. pneumoniae* has usually been considered to be sensitive to penicillins (benzylpenicillin, amoxicillin, or ampicillin), cephalosporins, erythromycin, or co-trimoxazole, but there is increasing prevalence of global resistance although there are marked geographical differences.[9,10] However, in clinical practice pneumococcal pneumonia frequently responds to high doses of penicillins or cephalosporins and the routine use of penicillin for CAP may still be reasonable in many countries.

The treatment of CAP is complicated by the increasing spectrum of causative organisms and prevalence of antibacterial resistance. Furthermore, since the causative pathogen is often unknown, initial antibacterial therapy is usually empirical. Guidelines for the treatment of pneumonia have been issued by bodies in many countries.[8,11-18] Although common principles can be identified, recommendations must be localised because of differences in patterns of infection and drug resistance, variations in the availability of antibacterials and local policies for their use, and differences in medical practice. Countries also vary in the degree to which such guidelines are accepted in practice. These guidelines generally give advice for differences associated with age, the severity of the infection, and the presence or absence of underlying or co-existent disorders.

In the UK, guidelines for the management of CAP have been produced by the British Thoracic Society (BTS).[8] For initial ***empirical treatment in the community*** oral amoxicillin is usually preferred. Alternatives in penicillin-allergic patients include doxycycline and the macrolides clarithromycin and erythromycin; clarithromycin is generally preferred to erythromycin due to better tolerance and more convenient dosing. The approach to treatment is similar for patients ***hospitalised with low-severity CAP***, many of whom are admitted to hospital for non-clinical reasons such as old age, family preference, inadequate home care, or adverse social circumstances; when oral therapy cannot be used in these patients, intravenous amoxicillin, benzylpenicillin, or clarithromycin are suitable alternatives.

In those patients ***hospitalised with moderately-severe CAP*** there is an increased likelihood of infection with atypical pathogens, or with *Legionella* spp.; consequently, combined empirical treatment orally with amoxicillin plus either erythromycin or clarithromycin is preferred.[8] When oral therapy is inappropriate, intravenous ampicillin or benzylpenicillin is given, with intravenous clarithromycin. For those intolerant of beta lactams and macrolides, oral doxycycline, levofloxacin, or moxifloxacin can be considered; intravenous alternatives include either monotherapy with levofloxacin, or the combination of a second- or third-generation cephalosporin (such as cefuroxime, cefotaxime, or ceftriaxone) with clarithromycin.[8]

Patients ***hospitalised with severe CAP*** should receive parenteral empirical treatment regardless of their ability to take oral medication. Since CAP caused by *Legionella* spp. is more likely to result in severe disease, the initial empirical regimen should include appropriate therapy. Current recommendations[8] are for combined intravenous treatment with a broad-spectrum beta-lactamase-stable antibacterial such as amoxicillin with clavulanic acid or a second- or third-generation cephalosporin such as cefuroxime, cefotaxime, or ceftriaxone, together with a macrolide (preferably clarithromycin). For life-threatening infection where *Legionella* is suspected, the further addition of levofloxacin should be considered. As an alternative to the above regimens, benzylpenicillin with either levofloxacin or ciprofloxacin can also be used.[8]

The following treatments are recommended in the UK,[8] along with local microbiological advice, for the minority of patients with CAP in whom the ***causative organism*** has been identified, usually in hospital:

- *Str. pneumoniae*: preferred treatment, oral amoxicillin or intravenous benzylpenicillin; alternatives, oral clarithromycin, or intravenous cefuroxime, cefotaxime, or ceftriaxone
- *M. pneumoniae* or *C. pneumoniae*: preferred treatment, oral or intravenous clarithromycin; alternatives, oral doxycycline or an oral or intravenous fluoroquinolone
- *C. psittaci* or *C. burnetii*: preferred treatment, oral doxycycline; alternatives, oral or intravenous clarithromycin
- *Legionella* spp.: preferred treatment, an oral or intravenous fluoroquinolone; alternatives, oral or intravenous clarithromycin (or azithromycin, if necessary)
- *H. influenzae* (non-beta-lactamase-producing): preferred treatment, oral or intravenous amoxicillin; alternatives, intravenous cefuroxime, cefotaxime, or ceftriaxone, or an oral or intravenous fluoroquinolone
- *H. influenzae* (beta-lactamase-producing): preferred treatment, oral or intravenous amoxicillin with clavulanic acid; alternatives, intravenous cefuroxime, cefotaxime, or ceftriaxone, or an oral or intravenous fluoroquinolone
- Gram-negative enteric bacilli: preferred treatment, intravenous cefuroxime, cefotaxime, or ceftriaxone; alternatives, intravenous fluoroquinolone, imipenem, or meropenem
- *Ps. aeruginosa*: preferred treatment, intravenous ceftazidime plus either gentamicin or tobramycin; alternatives, intravenous ciprofloxacin or piperacillin plus either gentamicin or tobramycin
- *Staph. aureus* (non-meticillin-resistant): preferred treatment, intravenous flucloxacillin with or without oral or intravenous rifampicin; alternatives, intravenous vancomycin, linezolid, or teicoplanin with or without oral or intravenous rifampicin
- *Staph. aureus* (meticillin-resistant): preferred treatment, intravenous vancomycin, linezolid, or teicoplanin with or without oral or intravenous rifampicin

In the USA, guidelines for the management of CAP in adults have been jointly produced by the Infectious Diseases Society of America (IDSA) and by the American Thoracic Society (ATS).[12] For previously healthy ***outpatients*** with no risk factors for drug-resistant *Str. pneumoniae* (DRSP) infection they recommend a macrolide (such as erythromycin, azithromycin, or clarithromycin); doxycycline may be given as an alternative. In those with co-existing cardiopulmonary disease and/or other complicating factors (such as renal disease, diabetes mellitus, alcoholism, malignancies, or asplenia), taking immunosuppressive drugs, those who have received antibacterial therapy within the previous 3 months, or those with other risks for DRSP infection a 'respiratory fluoroquinolone' (gemifloxacin, levofloxacin, or moxifloxacin) is recommended. Alternatively a beta-lactam (high-dose amoxicillin with or without clavulanic acid, or ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide (or doxycycline) may be given.

In ***hospitalised*** patients who are not in intensive care the preferred treatment is a beta lactam (cefotaxime, ceftriaxone, ampicillin, or ertapenem) plus a macrolide (or doxycycline). In penicillin-allergic patients a respiratory fluoroquinolone is recommended. In hospitalised patients who are in intensive care the preferred treatment is a beta lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. In penicillin-allergic patients a respiratory fluoroquinolone and aztreonam are recommended. For *Pseudomonas* infection, an antipneumococcal, antipseudomonal beta lactam (such as piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin are recommended. Alternative regimens include an antipneumococcal, antipseudomonal beta lactam plus an aminoglycoside and azithromycin, or an antipneumococcal, antipseudomonal beta lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone. In penicillin-allergic patients aztreonam should be used in place of the beta lactam. For community-acquired meticillin-resistant *Staph. aureus* (MRSA) infection, vancomycin or linezolid should be added.

In **children** pneumonia is caused by a wider spectrum of organisms than in adults. Viruses, especially RSV, are very common pathogens in infants and children up to 4 years of age and, as in adults, pneumococci are very common bacterial pathogens. Guidelines for the management of CAP in children have been produced by the BTS.[11] Amoxicillin is considered the antibacterial of first choice for empirical oral therapy in children under 5 years of age because it is effective against the majority of causative organisms. Alternatives are amoxicillin with clavulanic acid, cefaclor, erythromycin, clarithromycin, or azithromycin. Macrolides should be given as first-line empirical therapy in children over 5 years since *M. pneumoniae* pneumonia is more prevalent in older children. Macrolides should also be used in children of any age if either *M. pneumoniae* or *C. pneumoniae* are suspected. Amoxicillin should be used as first-line treatment at any age if *Str. pneumoniae* is thought to be the likely pathogen. If *Staph. aureus* is suspected then a macrolide or a combination of flucloxacillin with amoxicillin is appropriate. Intravenous therapy should be given in severe infection or when the child is unable to absorb oral antibacterials, for example due to vomiting; appropriate intravenous drugs for severe pneumonia include amoxicillin with clavulanic acid, cefuroxime, or cefotaxime. If the causative organism is known to be *Str. pneumoniae* a penicillin may be used alone. *Chlamydia trachomatis* is another common cause in infants up to 3 months of age for which erythromycin may be used or, alternatively, sulfafurazole.

Pneumonia in neonates is usually due to organisms acquired from the mother's genital tract, especially group B streptococci, *Escherichia coli*, and *Klebsiella pneumoniae*; initial treatment with gentamicin and benzylpenicillin or ampicillin has been suggested. For prophylaxis against group B streptococci in neonates, see under Perinatal Streptococcal Infections, p. 197.2.

Similar guidelines for the empirical management of CAP in children have been developed in South Africa.[15] Additional recommendations have been made to take into account the high prevalence of HIV infection. The drug of choice is amoxicillin; although standard doses of amoxicillin will treat most cases of pneumococcal pneumonia the use of high-dose amoxicillin (30 mg/kg given 3 times daily) is recommended in order to overcome and limit the emergence of resistant pneumococci, and to successfully treat those few children with high-level pneumococcal resistance the following additional factors should be considered:

- children younger than 2 months have more Gram-negative infections and therefore need an intravenous aminoglycoside or an intravenous cephalosporin, while children older than 5 years have more infections caused by *M. pneumoniae* and *C. pneumoniae* and need a macrolide (erythromycin, clarithromycin, or azithromycin)
- HIV-infected children requiring hospitalisation and those with a high risk of being HIV-infected or who have symptomatic HIV disease or who are severely malnourished should be given an aminoglycoside plus their empirical antibacterial regimen; alternatively they may be given a regimen that provides effective treatment against Gram-negative bacteria
- if pneumocystis pneumonia is suspected, co-trimoxazole should be added. All hospitalised HIV-exposed children less than 6 months of age should be treated empirically with co-trimoxazole, unless HIV infection status is

negative and the child is not being breast-fed. Empirical treatment with co-trimoxazole plus amoxicillin and an aminoglycoside should also be given to older HIV-infected children with features of AIDS who are not on co-trimoxazole prophylaxis
- when *Staph. aureus* is suspected, cloxacillin is the drug of choice. In HIV-infected children, about 60% of community-acquired *Staph. aureus* may be resistant to cloxacillin and vancomycin should be given

For the **prevention** of CAP, pneumococcal (p. 2410.1) and influenza (p. 2393.3) vaccines are generally recommended for active immunisation of individuals considered to be at high risk of pneumonia-related complications.[8,12] However, a meta-analysis[19] of pneumococcal vaccination in adults (with unconjugated vaccine) has suggested that the practice may not effectively prevent pneumonia, even in high-risk populations. The role of influenza vaccination in reducing the risk of CAP in elderly, immunocompetent patients has also been questioned.[20]

Hospital-acquired and healthcare-associated pneumonia. Pneumonia occurring at least 48 hours after hospital admission that was not incubating at initial presentation is termed nosocomial or hospital-acquired pneumonia (HAP). Ventilator-associated pneumonia (VAP) is a specific subtype of HAP defined as pneumonia occurring at least 48 hours after endotracheal intubation and/or mechanical ventilation, usually resulting from aspiration of pathogenic material that colonises the oropharynx. While early-onset HAP (occurring within the first 4 days of hospital admission) is usually caused by typical community organisms, late-onset infection can be caused by a wide spectrum of possible pathogens, many of which may be resistant to multiple antibacterials; these can include opportunistic Gram-negative bacilli such as *Ps. aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia, Burkholderia cepacia*, and the Enterobacteriaceae, as well as *Staph. aureus*. More recently, an increased incidence of these potentially drug-resistant bacteria among patients with early-onset pneumonia, thought to be a consequence of previous hospital stays or antibacterial use, has led to the concept of healthcare-associated pneumonia (HCAP). This is pneumonia occurring in any patient who has been hospitalised for at least 2 days in the previous 3 months, lives in a long-term care or nursing facility, has received intravenous antibacterials, chemotherapy, or wound care in the previous month, or attends a hospital or haemodialysis clinic.[21,22] The spectrum of bacteria causing HCAP is similar to late-onset HAP, and patients are considered to be at high risk of multidrug-resistant infection. Other risk factors for multidrug-resistant pneumonia include immunosuppressive disease or therapy, and high frequency of antibacterial resistance within the community or specific hospital unit.

Broad spectrum antibacterial therapy is essential for treatment of HAP and HCAP, and most initial therapy is empirical. As in the treatment of CAP, selection of antibacterials must be localised. For initial empirical treatment of early-onset HAP or VAP in patients with no known risk factors for multidrug-resistant pathogens, and any disease severity, ATS recommends[21] the following drugs: ceftriaxone; levofloxacin, moxifloxacin, or ciprofloxacin; ampicillin/sulbactam; or ertapenem. Where there is late-onset infection or risk factors for multidrug resistance (including possible HCAP) the following are recommended: an antipseudomonal cephalosporin (cefepime or ceftazidime) or an antipseudomonal carbapenem (imipenem or meropenem) or piperacillin-tazobactam together with an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin); if MRSA is likely then linezolid or vancomycin should also be used. Intravenous therapy should be given to all patients initially, and changed to the oral or enteral route as soon as possible. Efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to as little as 7 days provided *Ps. aeruginosa* is absent and that the patient shows a good clinical response. Guidelines for the management of HAP, VAP, and HCAP have also been issued in the UK,[22] and emphasise the need to choose initial antibacterial therapy based on patient-specific factors (such as previous antibacterial use, length of hospital stay, and comorbidities) as well as local microbiology and resistance patterns. For intensive care patients requiring mechanical ventilation for 48 hours or more, selective decontamination of the digestive tract (see under Intensive Care, p. 187.3) is recommended to reduce the risk of VAP.

Immunocompromised patients. Immunosuppressed patients are at increased risk of pneumonia. In addition to the bacteria mentioned above they are susceptible to opportunistic infections with *Mycobacterium tuberculosis* (see Tuberculosis, p. 212.2); viruses such as CMV and fungi, in particular *Pneumocystis jirovecii* (see p. 567.2), are also causes of pneumonia in these patients.

Aspiration pneumonia. Aspiration of organisms present in the upper respiratory tract into the lungs, often as a result of loss of consciousness or difficulty in swallowing, can cause aspiration pneumonia.[23] When community acquired the organisms responsible are mainly anaerobes, but in hospital-acquired aspiration pneumonia Gram-negative bacilli and *Staph. aureus* are also found. Confusion has arisen over the term 'aspiration pneumonia' because it has also been applied more generally to aspiration, for example, of gastric acid (Mendelson's syndrome), resulting in chemical pneumonitis and not associated with bacterial infection. *Lung abscess* generally characterises late-stage aspiration pneumonia involving anaerobic bacteria. The aetiology is rarely established, but specific anaerobic bacteria involved include *Peptostreptococcus, Prevotella melaninogenica* (*Bacteroides melaninogenicus*), and *Fusobacterium nucleatum.* Nearly all patients with anaerobic pulmonary infections are treated empirically. Some[23] workers have expressed the view that penicillin and clindamycin are inadequate and that antibacterials with activity against Gram-negative organisms, such as third-generation cephalosporins, fluoroquinolones, and piperacillin are usually required even in community-acquired aspiration pneumonia. Most patients with lung abscess receive parenteral therapy until they become afebrile and show clinical improvement; oral therapy may then continue for weeks or months if necessary.

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Pregnancy and the neonate

For infections associated specifically with pregnancy, see Endometritis (p. 180.3), Perinatal Streptococcal Infections (p. 197.2), and Premature Labour (p. 203.3).

Premature labour

Preterm birth, with or without rupture of membranes, causes significant perinatal morbidity and mortality. There is evidence that infection appears to have an important role in the cause or as a consequence of ruptured membranes[1,2] and as many as 50% of spontaneous preterm births are due to infection, with *Mycoplasma* spp. being the most commonly isolated organisms from the amniotic cavity.[3] Other bacteria that have been implicated include group B streptococci, *Chlamydia trachomatis*, and those associated with bacterial vaginosis. The role of antibacterial treatment has been evaluated. However, it is possible that maternal antibacterial treatment may suppress the stimulation of labour without effectively treating fetal infection[2] and concerns have been expressed that delaying delivery in the presence of a subclinical infection may not produce the best outcome for the neonate.[4]

A meta-analysis[5] and a systematic review[1] of studies of the routine use of antibacterials as adjuncts in the management of premature labour in women with *intact membranes* have failed to show an overall improvement in neonatal morbidity; indeed, an increase in neonatal mortality was actually noted.[5] Furthermore, a long-term follow-up study[6] indicated an increased rate of functional impairment among 7-year-olds whose mothers had received erythromycin for spontaneous preterm labour; an increased incidence of cerebral palsy was also noted among children exposed to either erythromycin or amoxicillin with clavulanic acid.

In women with preterm premature *rupture of membranes*, meta-analyses[7,8] and a systematic review[2] have shown that antibacterials could delay delivery, and reduce both maternal morbidity (chorioamnionitis and postpartum infections) and some aspects of neonatal morbidity (sepsis, pneumonia, and intraventricular haemorrhage). No effects on neonatal mortality or gestational age-related morbidity were noted,[2,8] and a long-term follow-up study found no evidence of negative health effects on the child.[9] However, an increased incidence of neonatal necrotising enterocolitis has been found after maternal use of amoxicillin with clavulanic acid specifically and it is considered best avoided in women at risk of premature delivery; erythromycin may be the antibacterial of choice.[2] A systematic review and meta-analysis[3] evaluated the effect of antibacterials on the rate of preterm births when given in the second trimester of pregnancy to women at risk of preterm births. Giving macrolides or clindamycin was associated with a lower rate of preterm delivery, whereas giving metronidazole alone in the second trimester was associated with a greater risk of preterm delivery in a high-risk population.

Clinical infections of the genito-urinary tract during pregnancy are a cause of significant morbidity in the neonate and antimicrobial treatment is necessary (see Bacterial Vaginosis, p. 174.1, Chlamydial Infections, p. 177.1, and Perinatal Streptococcal Infections, p. 197.2).

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Proctitis

Proctitis is inflammation of the rectum that may be caused by sexually transmitted pathogens, most commonly *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, or herpes simplex virus.

For empirical **treatment** of sexually transmitted proctitis the CDC[1] in the USA recommends a single intramuscular dose of ceftriaxone 125 mg, plus oral doxycycline 100 mg twice daily for 7 days.

The specific treatment of rectal infections caused by *C. trachomatis* and *N. gonorrhoeae* is discussed under Chlamydial Infections (p. 177.1) and Gonorrhoea (p. 206.2) respec-

tively. Patients with herpes proctitis should be treated in the same way as those with genital herpes (p. 957.2).

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Prostatitis

See under Urinary-tract Infections, p. 215.1.

Psittacosis

The causative organism of psittacosis[1,2] (ornithosis) is *Chlamydophila psittaci* (*Chlamydia psittaci*). It is usually transmitted to humans by direct or indirect contact with infected birds and the primary site of infection is the lung.[1] The clinical presentation of psittacosis can vary widely from a mild 'flu-like' illness to a fulminating toxic state with multiple organ involvement.[1] Most patients will have a cough, although this is not always prominent.[1] However, severe headache similar to that of meningitis is a characteristic symptom.[2] Tetracyclines are the treatment of choice[1,3] and early therapy may be life-saving; a 21-day course has been suggested since relapses have occurred after shorter periods,[1] although 14-day courses are also widely recommended.[2] An alternative is chloramphenicol.[3] Erythromycin or a similar macrolide have also been used successfully.[4,5]

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Q fever

Q fever[1,2] (or query fever) is a rickettsial infection (p. 205.2) caused by *Coxiella burnetii*. It is a zoonosis occurring worldwide and is transmitted to humans from domestic animals such as cattle and sheep, mainly by inhalation of infected dust. Q fever is asymptomatic in about 50 to 60% of infected persons. Symptomatic acute infection generally presents as a febrile flu-like illness and many patients may also have hepatitis or pneumonia that can progress to acute respiratory distress syndrome. Endocarditis is the most frequent form of chronic infection and the most serious form of Q fever; infection may be difficult to eradicate and prolonged treatment is generally needed. There is also evidence of long-term sequelae including lethargy and fatigue in patients who have not had cardiac involvement.

Subclinical **acute infections** should be treated if recognised and if possible treatment should be started within 3 days of the onset of symptoms. A tetracycline such as doxycycline for 14 days is the treatment of choice for acute Q fever. The role of macrolides in acute infection is unclear and clinical data on the use of fluoroquinolones are limited.[1,2] Co-trimoxazole is recommended for children younger than 8 years of age.[1] **Q fever endocarditis** is more difficult to treat and surgery may be required in addition to antibacterial treatment.[2] Monotherapy with tetracycline decreases symptoms but fails to eradicate *C. burnetii* and combination antibacterial therapy has been evaluated. Long-term treatment with doxycycline plus rifampicin or with ciprofloxacin alone[3] has been successful in individual patients with endocarditis, whereas pefloxacin alone[4] was not. A retrospective comparison of doxycycline alone or with rifampicin, fluoroquinolones (ofloxacin or pefloxacin), or co-trimoxazole, recommended treatment for at least 3 years with doxycycline plus a fluoroquinolone;[5] doxycycline plus rifampicin also appeared effective, but in most cases rifampicin had been stopped after a few months because of interactions with anticoagulants often prescribed at the same time. Patients given doxycycline plus hydroxychloroquine needed a shorter treatment course and had fewer relapses than those treated with doxycycline plus ofloxacin; mortality rate for both groups was 5%.[6] Successful treatment with doxycycline and chloroquine for 2 years has been reported in a patient with a biological prosthetic aortic valve and aortic homograft.[7] The combination of doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily, both given orally for at least 18 months, is considered to be the treatment of choice for Q fever endocarditis.[1,2] An alternative regimen for patients unable to tolerate hydroxychloroquine is doxycycline plus a fluoroquinolone for at least 3 to 4 years.[2]

Q fever during **pregnancy** may result in obstetric complications, such as spontaneous abortion, intra-uterine growth retardation, intra-uterine fetal death, and premature delivery.[8] Treatment with co-trimoxazole for at least 5 weeks during pregnancy was reported to protect against maternal chronic Q fever, placental infection, and obstetric complications (in particular intra-uterine fetal death).[8]

A vaccine is available in some countries for **prophylaxis** in occupational groups who regularly handle potentially infected animal tissues.

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Relapsing fever

Relapsing fever is caused by spirochaetes of the *Borrelia* genus that are transmitted to humans by body lice or *Ornithodoros* ticks. *B. recurrentis* causes louse-borne relapsing fever (LBRF). Global distribution and incidence of LBRF have reduced substantially due to improvements in sanitation and hygiene; however, it is endemic in some areas such as northeastern Africa, and can occur elsewhere in populations affected by war or natural disasters. Many species of *Borrelia* may cause tick-borne relapsing fever (TBRF), which has a global distribution, but is highly endemic in sub-Saharan Africa.

Clinical manifestations of LBRF and TBRF are similar. The onset is typically sudden, with high fever (sometimes with delirium), headache, chills, sweating, myalgia, arthralgia, and gastrointestinal disturbances. Complications include epistaxis, and gastrointestinal and CNS haemorrhage. Without treatment, symptoms intensify, resulting in a crisis. This comprises two phases: a chill phase characterised by rigors, increasing temperature, and hypermetabolism, and a flush phase of decreasing temperature, diaphoresis, and hypotension, which may be fatal. Death due to TBRF is rare. However, untreated LBRF has a high fatality rate, especially in malnourished populations.

The treatment of choice for relapsing fever is a tetracycline such as doxycycline; benzylpenicillin or erythromycin are alternatives; treatment is given orally where possible[1,2] Therapy with single oral doses of tetracycline, erythromycin, or chloramphenicol has been effective for LBRF, whereas treatment for 7 to 10 days is usually given for tick-borne disease,[2] because of the higher rate of treatment failure and relapses in these patients. Antibacterial treatment often causes a Jarisch-Herxheimer reaction within 4 hours of the first dose, and associated with a release of cytokines, the symptoms of which resemble the crisis phase of untreated patients;[2] this reaction tends to be more severe in LBRF. Attempts to prevent this reaction include use of paracetamol, NSAIDS, and corticosteroids, to little effect.[2] Antibodies against tumour necrosis factor α have also been tried.[3]

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Respiratory-tract infections

Principal community-acquired bacterial pathogens in the respiratory tract are *Streptococcus pneumoniae* and *Haemophilus influenzae*, although *Moraxella catarrhalis* (*Branhamella catarrhalis*) is increasingly important in some areas. Other respiratory pathogens include *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Legionella pneumophila*, and *Mycoplasma pneumoniae*. *Streptococcus pyogenes* is the predominant cause of pharyngitis. *Staphylococcus aureus* and aerobic Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Klebsiella* spp. may be responsible for hospital-acquired (nosocomial) infections.

Non-specific, community-acquired respiratory-tract infections are very common and usually viral in origin. Because these infections are generally self-limiting, US[1] and UK[2] guidelines suggest that antibacterials should not be routinely given, although they may be appropriate for some patients based on severity of illness or risk factors for serious complications.[2,3]

For details on infections of the upper respiratory tract, see under Epiglottitis (p. 181.3), Pharyngitis (p. 198.3), and Sinusitis (p. 208.2); see also Otitis Media (p. 195.2). For infections of the lower respiratory tract, see under Bronchitis (p. 175.3), Cystic Fibrosis (p. 177.2), and Pneumonia (p. 200.1); those with a specific cause include Legionnaires' Disease (p. 188.2), Nocardiosis (p. 193.3), Pertussis (p. 198.3), and Tuberculosis (p. 212.2). For discussion on the eradication of nasal staphylococci carriage, see Staphylococcal Infections, p. 210.2.

For details on the symptomatic management of respiratory-tract infection, see under Cough (p. 1651.2) and Fever and Hyperthermia (p. 11.3).

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Rheumatic fever

Acute rheumatic fever[1] occurs especially in children aged 6 to 15 years as a consequence of upper respiratory-tract infections, such as pharyngitis or tonsillitis, with rheumatogenic strains of the group A beta-haemolytic streptococcus, *Streptococcus pyogenes*. The pathogenesis of rheumatic fever is unknown, but an immune mechanism may be involved. There may be a latent period of 1 to 5 weeks after the initial infection, before clinical manifestations of rheumatic fever appear. The major ones are arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Those affecting the heart are the most serious and are a major cause of cardiovascular death in children and young adults in developing countries. Rheumatic fever has been associated with poverty and overcrowding and has declined dramatically in developed countries, but is still a major problem in the developing world. However, in the 1980s there was evidence of a resurgence in the USA with outbreaks of rheumatic fever reported in middle-class children[2] and military recruits.[3] Increased pathogenicity of *Str. pyogenes* serotypes might have contributed to this resurgence.[4] A high incidence is also seen among indigenous populations in Australia and New Zealand.[5]

Guidelines for the management and prevention of rheumatic fever have been published by sources including the American Heart Association,[6] WHO,[7] and expert groups from Australia and New Zealand[8] as well as India.[9] Rheumatic fever can usually be prevented by *primary prophylaxis*, that is, by the prompt treatment of streptococcal upper respiratory-tract infection with eradication of group A streptococci (GAS) from the throat. Penicillin is the drug of choice, either as a single intramuscular injection of benzathine benzylpenicillin or as an oral course of phenoxymethylpenicillin (or alternatively, amoxicillin) for 10 days.[6,7] An injection containing benzathine benzylpenicillin and procaine benzylpenicillin, which is less painful than benzathine benzylpenicillin alone, is a suitable alternative for use in children.[6] For patients who are intolerant of penicillin, a narrow-spectrum oral cephalosporin such as cefadroxil or cefalexin may be considered in those who do not have type I penicillin hypersensitivity. Further treatment options include oral clindamycin, and the macrolides erythromycin, clarithromycin, and azithromycin; however, because macrolide-resistant GAS are common in some areas of the world, there may be a higher risk of treatment failure when these drugs are used.[6] For further details on the treatment of streptococcal sore throat, see under Pharyngitis, p. 198.3. Failure to eradicate GAS is more common after oral antibacterials and in the USA many of these patients are asymptomatic, chronic streptococcal carriers;[6] re-treatment of these patients is usually unnecessary,[6,7] and should only be considered in those with a personal or family history of rheumatic fever.[6] Symptomatic individuals can be re-treated either with the same, or an alternative antibacterial regimen; where initial treatment with penicillin has failed, a narrow-spectrum cephalosporin, clindamycin, amoxicillin with clavulanic acid, or penicillin with rifampicin are all reasonable alternatives.[6] Broad-based primary prophylaxis in communities rather than individuals has been tried[10,11] but a study in military recruits showed that *Str. pyogenes* infection could not be prevented in closely confined communities unless all individuals in the population received prophylaxis.[11]

If acute rheumatic fever occurs, a full therapeutic course of penicillin should be given initially, as for primary prevention, to eradicate GAS.[6,8] Treatment then comprises bed rest and anti-inflammatory drugs, usually corticosteroids or salicylates, in an attempt to prevent valvular scarring. However, it is unclear whether anti-inflammatory treatment has any influence on such long-term sequelae.[12] Carbamazepine or valproate may be given for severe and distressing chorea.[8] *Secondary prevention* is then continued with prolonged antibacterial prophylaxis because of the high risk of recurrent attacks of rheumatic fever after subsequent streptococcal upper respiratory-tract infections.

Again, penicillin is the preferred antibacterial, the usual recommendation being an intramuscular injection of benzathine benzylpenicillin every 4 weeks, although injections every 3 weeks may be warranted where the risk of recurrence is high.[6-8] This advice has been influenced by reports of high recurrence rates with the monthly regimen in such situations.[13] A 12-year study in Taiwan[14] confirmed that prophylaxis with benzathine benzylpenicillin injections every 3 weeks is more effective than injections every 4 weeks and it was recommended that the 3-week regimen should be used in adults and children with a recent episode of rheumatic fever, especially in developing countries where exposure to streptococci is still intense. In addition, pharmacokinetic studies have indicated relatively low serum concentrations of penicillin in the fourth week after an intramuscular injection of benzathine benzylpenicillin,[15,16] despite the successful use of monthly injections in most patients. However, Australian and New Zealand guidelines consider the 4-week regimen suitable in most patients.[8] Alternatively, oral prophylaxis with phenoxymethylpenicillin or sulfadiazine may be given, although, over the long time scale involved, compliance is likely to be a problem;[5,7,8] a macrolide is suggested for the rare patient who is allergic to penicillin and sulfonamides.[6] Sulfonamides should *not* be used for primary prevention because they do not eradicate the streptococci.[6,7] The duration of secondary prophylaxis depends on the individual patient, but in those who have not had rheumatic carditis it should generally continue for a minimum of 5 years after the last attack of rheumatic fever, or until early adulthood (18 to 21 years of age), whichever is longer.[6,7] Those who have had rheumatic carditis but without residual valvular disease should perhaps receive prophylaxis at least until the age of 21[6] or 25 years,[7] or for 10 years after the last attack,[6] whichever is longer. For those with carditis and persistent valvular disease, prophylaxis should continue at least until the age of 40 years, or sometimes for life.[6,7] Fears of serious allergic reactions associated with long-term benzathine benzylpenicillin prophylaxis appear to be unfounded.[17]

Household contacts of rheumatic fever patients who themselves have positive streptococcal cultures should be treated.[6]

Some patients with rheumatic valvular heart disease as a result of rheumatic fever are at risk of developing infective endocarditis and those at highest risk may need additional appropriate short-term antibacterial prophylaxis when undergoing dental and some surgical procedures (see Endocarditis, p. 179.2).

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Rickettsial infections

Bacteria of the Rickettsiaceae family that infect man include *Rickettsia* spp. (see under Spotted Fevers, p. 210.1 and Typhus, p. 214.3) and *Coxiella burnetii* (see under Q fever, p. 202.1). *Ehrlichia* spp. (see under Ehrlichiosis, p. 179.1) and *Bartonella quintana* (*Rochalimaea quintana*) (see under Trench Fever, p. 212.2) are no longer classified as a rickettsia. The treatment of choice for rickettsial infections is doxycycline; chloramphenicol or a fluoroquinolone are alternatives.[1]

1. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 74.

Salmonella enteritis

See p. 185.2.

Salpingitis

See under Pelvic Inflammatory Disease, p. 196.3.

Septicaemia

Traditionally, transient bacteraemia (the presence of bacteria in the blood) has been regarded as a fairly common condition which does not usually cause complications, whereas uncontrolled bacteraemia leads to septicaemia with serious symptoms such as fever and shock. This distinction has not always been adhered to in published sources and the terms have sometimes been used interchangeably. Added to this, the identification of the cascade of inflammatory mediators involved and the realisation that what had been called 'sepsis' could arise in the absence of infection have prompted reassessment of the terminology used both in the UK and in the USA.[1] In the UK, some authorities[2] considered that the term 'septicaemia' should no longer be used since it does not distinguish between mild and severe disease. The term 'sepsis syndrome' was preferred for patients with a generalised systemic response together with evidence of organ dysfunction and 'septic shock' to describe patients who also have hypotension not due to hypovolaemia or cardiac causes. The American College of Chest Physicians and Society of Critical Care Medicine proposed the following series of definitions to cover the spectrum of syndromes resulting from this inflammatory response:[1,3]

- **systemic inflammatory response syndrome** (SIRS), the systemic inflammatory response to infection or various other severe clinical insults including pancreatitis, ischaemia, trauma, and haemorrhagic shock
- **sepsis**, the SIRS caused specifically by infection
- **severe sepsis**, sepsis associated with organ dysfunction, perfusion abnormalities (such as lactic acidosis, oliguria, or an acute alteration in mental status), or hypotension
- **septic shock**, sepsis with hypotension, despite adequate fluid resuscitation, together with perfusion abnormalities
- **multiple organ dysfunction syndrome** (MODS), the presence of altered organ function in an acutely ill patient such that homoeostasis cannot be maintained without intervention; it may be a cause as well as a consequence of SIRS.

Septicaemia can be caused by many bacteria.[4] **Community-acquired** primary septicaemia is often associated with a specific infectious disease, such as meningococcal septicaemia with meningococcal meningitis (p. 191.1) or streptococcal septicaemia with pneumonia (p. 200.1). *Streptococcus pneumoniae* and *Haemophilus influenzae* are common causes of primary septicaemia in children (although this pattern is changing in countries where immunisation against *H. influenzae* type b is routine); Gram-negative rods and group B streptococci are commonest in neonates. **Hospital-acquired** septicaemia is often iatrogenic and may occur as a complication of surgery or indwelling catheters[5] or may be associated with neutropenia in immunocompromised patients (see under Infections in Immunocompromised Patients, p. 186.3). Hospital-acquired septicaemia is often associated with acute respiratory distress syndrome (p. 1599.3).

Whatever the cause, septicaemia requires prompt empirical treatment.[6-8] Choice of antibacterial depends on the probable source of infection. For example, urinary-tract infection is likely to be associated with Gram-negative septicaemia due to *Escherichia coli*; abdominal sepsis with Gram-negative septicaemia due to mixed infection with *E. coli*, enterococci, and anaerobic bacteria; and skin sepsis, bacterial arthritis, acute osteomyelitis, and cardiovascular shunts with Gram-positive septicaemia due to staphylococci. The antibacterials used should also reflect current patterns of bacterial resistance in the community or hospital. International guidelines[9] have recommended starting intravenous antibacterial therapy as early as possible, and within the first hour of recognition of septic shock; the initial choice of therapy should be broad enough to cover all likely pathogens, and it should be reassessed daily to optimise activity and prevent the development of resistance. De-escalation of combination therapy to the most appropriate single therapy should be carried out as soon as susceptibility of the infection is known. The typical duration of therapy will be 7 to 10 days. *Empirical treatment* has often begun with a penicillin and an aminoglycoside, metronidazole being added if anaerobic infection is suspected. In the UK, the *BNF* recommends that initial empirical treatment for community-acquired septicaemia is with either a broad-spectrum antipseudomonal penicillin (such as piperacillin with tazobactam or ticarcillin with clavulanic acid) or a broad-spectrum cephalosporin (such as cefuroxime); if other resistant micro-organisms are suspected, a more broad-spectrum beta-lactam antibacterial such as meropenem should be used. For hospital-acquired septicaemia a broad-spectrum antipseudomonal beta-lactam antibacterial (such as ceftazidime, piperacillin with tazobactam, ticarcillin with clavulanic acid, imipenem, or meropenem) is recommended. In both cases, metronidazole should be added if anaerobic organisms are suspected, and vancomycin or teicoplanin if meticillin-resistant staphylococci are suspected. US guidelines[10] recommend a third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime), or piperacillin with tazobactam, or imipenem, or meropenem, in each case with vancomycin and sometimes also an aminoglycoside (gentamicin, tobramycin, or amikacin) for the initial treatment of life-threatening sepsis in adults. When there is some information on which to base choice of treatment, but before the infecting organisms are definitely known, the following treatment is suggested:

- suspected bacterial endocarditis—ceftriaxone with vancomycin, possibly with gentamicin as well
- suspected meticillin-resistant staphylococci—vancomycin, alone or with gentamicin and/or rifampicin

Once the infecting organisms have been identified, choice of treatment will again depend on their sensitivity and current patterns of resistance in the community or hospital. For comments on the consequences of emerging multidrug-resistant strains of enterococci and staphylococci, see Enterococcal Infections, p. 181.1, and Staphylococcal Infections, p. 210.2.

In addition to antimicrobial therapy, patients with sepsis or septic shock require rigorous supportive measures (p. 1279.3). Specific supportive treatment aimed at inhibiting endogenous mediators released in response to sepsis has been tried with little clinical success, and includes adjunctive therapy with endotoxin antibodies, anticytokines such as anakinra and tumour necrosis factor antibodies, soluble tumour necrosis factor receptor, bactericidal permeability increasing protein, nitric oxide synthase inhibitors, guanylate cyclase inhibitors such as methylthioninium chloride, and platelet-activating factor antagonists.[11-13] A systematic review[14] of the use of intravenous polyclonal immunoglobulin concluded that it had a promising role as adjuvant therapy in sepsis and septic shock. Specific monoclonal immunoglobulins were not effective.[14] Reduced mortality was reported[15] after the treatment of patients with severe sepsis with recombinant activated protein C [drotrecogin alfa (activated)] which has antithrombotic, anti-inflammatory, and pro-fibrinolytic properties. However, a systematic review[16] of this and subsequent studies found no mortality benefit, and a higher risk of bleeding. Drotrecogin alfa (activated) was withdrawn from the market in October 2011. Although deficiency of adrenal corticosteroid production has been described in severe sepsis, high-dose corticosteroid treatment was found to be of no benefit, but improved outcomes have been reported with the use of lower doses of corticosteroids.[6] International guidelines developed by the Surviving Sepsis Campaign[9] consider that low-dose intravenous hydrocortisone may be given to adults with septic shock who remain hypotensive despite adequate fluid resuscitation and vasopressor therapy; the addition of oral fludrocortisone is optional but dexamethasone is not recommended. The addition of daily oral fludrocortisone is suggested if an alternative corticosteroid is used that lacks significant mineralocorticoid activity.[9] However, since these guidelines were published a multicentre, randomised, double-blind, placebo-controlled study[17] of 499 patients with septic shock reported that low-dose hydrocortisone did not significantly affect survival rate at 28 days or the rate of reversal of shock either overall or in patients who did not have a response to corticotropin, but a decrease in time to reversal was noted in those patients in whom shock was reversed. Studies with other physiological anticoagulants such as antithrombin III[18] and tissue factor pathway inhibitor (tifacogin)[19] have not been successful.

Neonatal septicaemia may be divided into **early-onset**, which is acquired from the mother's genital tract and manifests itself during the first few days after birth, and **late-onset** which may be nosocomially acquired. Bacteria commonly causing early-onset sepsis include enterococci, *E. coli*, *H. influenzae*, *Listeria monocytogenes*, and streptococci. Some of these organisms may also produce meningitis in the neonate (p. 191.1). Empirical treatment for both early- and

late-onset sepsis is based on similar principles to those in other patients, giving consideration to local patterns of infection and resistance and to the suitability of individual antibacterials for this age group. However, early-onset sepsis is usually best controlled by prenatal treatment of the mother or by perinatal prophylaxis. Prophylaxis for group B streptococcal infections is discussed under Perinatal Streptococcal Infections, p. 197.2. While vancomycin has been shown to prevent infections with coagulase-negative staphylococci and to reduce the incidence of neonatal sepsis, widespread prophylactic use of this drug is not recommended.[20] Intravenous normal immunoglobulin (see Neonatal Infection, p. 2406.2) and filgrastim (see Neutropenia, p. 1152.3) have been tried for the prevention of septicaemia in preterm neonates with variable results.

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Sexually transmitted diseases

The sexually transmitted diseases, formerly termed venereal diseases, are defined as a group of communicable diseases that are transferred mainly by sexual contact. Many pathogens are known to be transmitted sexually including:

- bacteria:
  - *Chlamydia trachomatis* (see Lymphogranuloma Venereum, p. 207.2 and Chlamydial Infections, p. 177.1)
  - *Haemophilus ducreyi* (see Chancroid, p. 206.2)
  - *Klebsiella granulomatis* (see Granuloma Inguinale, p. 207.1)
  - *Neisseria gonorrhoeae* (see Gonorrhoea, p. 206.2)
  - *Treponema pallidum* (see Syphilis, p. 207.2)
  - *Ureaplasma urealyticum*
- protozoa:
  - *Trichomonas vaginalis* (see Trichomoniasis, p. 927.1).
- viruses:
  - human immunodeficiency virus (see HIV Infection and AIDS, p. 959.2)
  - hepatitis viruses (see Hepatitis, p. 954.1)
  - herpesviruses (see Herpesvirus Infections, p. 956.1)

Clinical syndromes associated with sexually transmitted diseases, and which are discussed in this section, include urethritis (p. 214.3) and epididymitis (p. 181.2) in men; cervicitis (p. 177.1), pelvic inflammatory disease (p. 196.3), and bacterial vaginosis (p. 174.1) in women; and proctitis (p. 201.3). Perinatal transmission of sexually transmitted pathogens from the mother can result in neonatal conjunctivitis (p. 193.2) or pneumonia (p. 200.1).

General guidelines for the management of sexually transmitted diseases have been published[1-3] although recommendations may need to be localised because of differences in patterns of infection and drug resistance. Early detection and treatment are required to prevent long-term complications, including infertility, still-births and neonatal infections, genital cancers, and an increased risk of acquiring and transmitting HIV.

The suggestion that spermicidal contraceptives may provide some protection against sexually transmitted diseases is discussed under Nonoxinols, p. 2199.1.

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). United Kingdom national guideline on the management of sexually transmitted infections and related conditions in children and young people (2009). Available at: http://www.bashh.org/documents/2275 (accessed 05/03/10)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60:** 18. [dose]

Chancroid. Chancroid is a sexually transmitted disease caused by the Gram-negative bacterium *Haemophilus ducreyi*. It occurs worldwide, but is endemic in parts of Africa and South East Asia, where it is a frequent cause of painful genital ulcers and a risk factor in the transmission of HIV.

Specific **treatment** guidelines have been provided by WHO,[1] by expert groups in the UK,[2] and by the CDC in the USA.[3] Treatment failure may be more common in patients also infected with HIV[1] (see below), but in other patients single-dose treatment regimens might be preferable if compliance is a problem. Guideline regimens are as follows:

- **WHO:**
  - oral ciprofloxacin 500 mg twice daily for 3 days, *or*
  - oral erythromycin 500 mg four times daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  an alternative regimen is:
  - a single intramuscular injection of ceftriaxone 250 mg
- **UK:**
  - a single oral dose of azithromycin 1 g, *or*
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - oral ciprofloxacin 500 mg twice daily for 3 days *or* as a single oral dose, *or*
  - oral erythromycin 500 mg four times daily for 7 days

  further alternatives are:
  - single oral doses of other fluoroquinolones such as fleroxacin 400 mg *or* norfloxacin 800 mg
  - a single intramuscular injection of spectinomycin 2 g
- **USA:**
  - a single oral dose of azithromycin 1 g, *or*
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - oral ciprofloxacin 500 mg twice daily for 3 days, *or*
  - oral erythromycin 500 mg three times daily for 7 days

Sexual partners of patients with chancroid should also be tested and treated.[2,3]

Patients co-infected with HIV have ulcers that heal more slowly and may need to be treated for longer to prevent treatment failure;[3] treatment failure is common with single-dose regimens.[1]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2007 National guideline for the management of chancroid. Available at: http://www.bashh.org/documents/85/85.pdf (accessed 05/03/10)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60:** 18. [dose]

Gonorrhoea. Gonorrhoea is a sexually transmitted disease caused by infection of mucosa with *Neisseria gonorrhoeae* (gonococcus), a Gram-negative bacterium. It occurs mainly in the lower genital tract as urethritis (p. 214.3) in men and cervicitis (p. 177.1) in women, but also as pharyngitis, proctitis (p. 201.3), or conjunctivitis. Infection may sometimes ascend to the upper genital tract to cause complications such as pelvic inflammatory disease (p. 196.3) in women and epididymitis (p. 181.2) in men. In the USA[1] routine screening is recommended for all sexually active women with an increased risk of infection. Disseminated gonococcal infection resulting from gonococcal bacteraemia is rare and may lead to septic arthritis, an arthritis-dermatitis syndrome (not to be confused with Reiter's disease which has been associated with non-gonococcal or non-specific urethritis), and more rarely to conditions such as endocarditis or meningitis. Gonorrhoea in pregnant women may cause neonatal gonococcal conjunctivitis (ophthalmia neonatorum).

Antibacterial drug resistance is a problem in the management of gonococcal infection. Penicillins were once the treatment of choice for *N. gonorrhoeae* but are no longer recommended. High-level plasmid-mediated and chromosomally mediated resistances have also been reported with tetracycline, and chromosomally mediated resistance to other antibacterials may occur. Gonococcal resistance is now monitored in England and Wales via the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP)[2] and in the USA by the Gonococcal Isolate Surveillance Project (GISP).[3] Worldwide resistance to fluoroquinolones has resulted in revision of treatment guidelines; in the UK fluoroquinolones are no longer recommended as first-line drugs and should only be used if the infection is known or anticipated to be sensitive, while in the USA they are no longer recommended for any gonococcal infections. Reports are also emerging of decreasing gonococcal susceptibility to extended-spectrum cephalosporins and verified treatment failures to oral cefixime have been reported.[4]

Infection with *Chlamydia trachomatis* (see under Chlamydial Infections, p. 177.1) often occurs along with gonorrhoea and should be tested for or treated presumptively usually with either oral azithromycin or doxycycline. WHO[5] generally recommends that unless infection with *C. trachomatis* has been excluded by a laboratory test, all patients with anogenital or pharyngeal gonorrhoea should be given concurrent anti-chlamydia treatment. UK[6] and US[1] guidelines recommend routine treatment, irrespective of the results of chlamydia testing, in order to delay the onset of widespread cephalosporin resistance.

Guidelines produced by WHO,[5] by an expert group in the UK,[6] and by the CDC in the USA[1,7] for the **treatment** of gonorrhoea are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- UNCOMPLICATED ANOGENITAL GONOCOCCAL INFECTIONS IN ADULTS.
  - **WHO:**
    - a single oral dose of ciprofloxacin 500 mg, *or*
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **UK:**

    All the treatment options given below should be given with a single oral 1-g dose of azithromycin.
    - a single intramuscular dose of ceftriaxone 500 mg

    alternative regimens are:
    - a single intramuscular dose of spectinomycin 2 g
    - a single oral dose of cefixime 400 mg
    - a single intramuscular dose of cefotaxime 500 mg
    - a single intramuscular dose of cefoxitin 2 g plus oral probenecid 1 g
    - a single oral dose of ciprofloxacin 500 mg
    - a single oral dose of ofloxacin 400 mg
    - a single oral dose of cefpodoxime 400 mg
    - a single oral dose of azithromycin to a total of 2 g
  - **USA:**
    - a single intramuscular dose of ceftriaxone 250 mg *plus* either a single oral 1-g dose of azithromycin *or* oral doxycycline 100 mg twice daily for 7 days

    alternative regimens are:
    - a single oral dose of cefixime 400 mg, if ceftriaxone is not available, *plus* either a single oral 1-g dose of azithromycin *or* oral doxycycline 100 mg twice daily for 7 days
    - in patients with severe cephalosporin allergy, a single oral dose of azithromycin 2 g
- PHARYNGEAL INFECTIONS.
  - **UK:**
    - a single intramuscular dose of ceftriaxone 500 mg *plus* a single oral 1-g dose of azithromycin, *or*
    - a single oral dose of ciprofloxacin 500 mg, *or*
    - a single oral dose of ofloxacin 400 mg
  - **USA:**
    - a single intramuscular dose of ceftriaxone 250 mg *plus* either a single oral 1-g dose of azithromycin *or* oral doxycycline 100 mg twice daily for 7 days
- GONOCOCCAL INFECTIONS IN PREGNANT WOMEN.
  - **WHO:**
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **UK:**

    Both regimens below should be given with a single oral 1-g dose of azithromycin.
    - a single intramuscular dose of ceftriaxone 500 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **USA:**
    - an intramuscular cephalosporin *plus* either a single oral 1-g dose of azithromycin *or* oral amoxicillin 500 mg three times daily for 7 days
    - azithromycin 2 g orally can be considered for women who are intolerant of cephalosporins
- GONOCOCCAL EYE INFECTIONS IN ADULTS.
  - **WHO:** frequent irrigation of the infected eye with saline together with:
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g, *or*
    - a single oral dose of ciprofloxacin 500 mg

    a further alternative is:
    - a single intramuscular dose of kanamycin 2 g
  - **UK:** irrigation of the infected eye with saline together with:
    - intramuscular ceftriaxone 500 mg daily for 3 days, *or*
    - intramuscular spectinomycin 2 g daily for 3 days, *or*
    - a single oral dose of azithromycin 2 g, *plus* oral doxycycline 100 mg twice daily for 7 days, *plus* oral ciprofloxacin 250 mg daily for 3 days
  - **USA:** irrigation of the infected eye with saline together with:
    - a single intramuscular dose of ceftriaxone 1 g
- DISSEMINATED GONOCOCCAL INFECTIONS IN ADULTS.
  - **WHO:**
    - parenteral ceftriaxone 1 g once daily for 7 days, *or*
    - intramuscular spectinomycin 2 g twice daily for 7 days

Another third-generation cephalosporin may be substituted if neither of these drugs is available. Treatment for endocarditis should continue for 28 days.

- **UK:**
  - parenteral ceftriaxone 1 g daily, *or*
  - intravenous cefotaxime 1 g 8 hourly, *or*
  - intravenous ciprofloxacin 500 mg 12 hourly, *or*
  - intramuscular spectinomycin 2 g 12 hourly

  Treatment should continue for 7 days but once improvement has been established for 24 to 48 hours, oral therapy with cefixime 400 mg twice daily *or* ciprofloxacin 500 mg twice daily *or* ofloxacin 400 mg twice daily, may be substituted for the remaining period.
- **USA:**
  - parenteral ceftriaxone 1 g every 24 hours

  alternatives are:
  - intravenous ceftizoxime 1 g every 8 hours
  - intravenous cefotaxime 1 g every 8 hours

  Once improvement has been established for 24 to 48 hours, oral therapy with cefixime 400 mg twice daily may be substituted until at least a 1-week treatment period is complete.

  For gonococcal meningitis and endocarditis, intravenous ceftriaxone 1 to 2 g every 12 hours is recommended; treatment for meningitis should continue for 10 to 14 days and for endocarditis for at least 4 weeks.

- GONOCOCCAL INFECTIONS IN NEONATES AND CHILDREN.

Neonates born to mothers with gonorrhoea are at high risk of infection and require *prophylaxis*:

- **WHO:**
  - a single intramuscular injection of ceftriaxone 50 mg/kg (maximum 125 mg)

  alternatives are:
  - a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg)
  - a single intramuscular dose of kanamycin 25 mg/kg (maximum 75 mg)
- **USA:**
  - a single parenteral dose of ceftriaxone 25 to 50 mg/kg (maximum 125 mg)

For those neonates with *disseminated gonococcal infection* (sepsis, arthritis, meningitis) or gonococcal scalp abscesses, US recommendations are:

- parenteral ceftriaxone 25 to 50 mg/kg once daily for 7 days, *or*
- parenteral cefotaxime 25 mg/kg every 12 hours for 7 days

Treatment should be extended to 10 to 14 days if meningitis is present.

Treatment for *children* with uncomplicated gonococcal infections, most commonly due to sexual abuse in pre-adolescents, is as for adults in those weighing more than 45 kg. For those weighing 45 kg or less a single intramuscular dose of ceftriaxone 125 mg is recommended. For disseminated infection in all children an intramuscular or intravenous dose of ceftriaxone 50 mg/kg once daily for 7 days, up to a maximum dose of 1 g in those weighing 45 kg or less is recommended.

The prevention and treatment of neonatal gonococcal conjunctivitis is discussed under Neonatal Conjunctivitis, p. 193.2.

Sexual partners of patients with gonococcal infection should be tested and treated.[1]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[1]

1. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60:** 18. [dose]
2. Health Protection Agency. GRASP 2010 report: The Gonococcal Resistance to Antimicrobials Surveillance Programme. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1316016752917 (accessed 18/07/12)
3. CDC. Gonococcal Isolate Surveillance Project (GISP). Available at: http://www.cdc.gov/std/gisp (accessed 18/07/12)
4. WHO. Emergence of multi-drug resistant *Neisseria gonorrhoeae*—threat of global rise in untreatable sexually transmitted infections. Geneva: WHO, 2011. Available at: http://whqlibdoc.who.int/hq/2011/WHO_RHR_11.14_eng.pdf (accessed 26/07/12)
5. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 20/06/07)
6. Clinical Effectiveness Group (British Association for Sexual Health and HIV). UK national guideline for the management of gonorrhoea in adults 2011. Available at: http://www.bashh.org/documents/3611 (accessed 18/07/12)
7. CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR* 2012; **61:** 590–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm (accessed 13/08/12)

Granuloma inguinale. Granuloma inguinale or donovanosis is caused by the Gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*) and occurs most commonly in the tropics and subtropics, especially Papua New Guinea and India. It is characterised by genital ulcers and is generally considered to be a sexually transmitted disease.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of granuloma inguinale are as follows:

- **WHO:**
  - oral azithromycin 1 g on the first day then 500 mg once daily, *or*
  - oral doxycycline 100 mg twice daily

  alternatives include:
  - oral erythromycin 500 mg four times daily
  - oral tetracycline 500 mg four times daily
  - oral co-trimoxazole 960 mg twice daily

  Treatment is continued until all lesions have completely resolved. The addition of parenteral gentamicin should be considered for HIV-infected patients. Streptomycin is no longer recommended because of its toxicity and the need to reserve it for tuberculosis.
- **UK:**
  - oral azithromycin 1 g once weekly or 500 mg daily, *or*
  - parenteral ceftriaxone 1 g once daily, *or*
  - oral co-trimoxazole 960 mg twice daily, *or*
  - oral doxycycline 100 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily, *or*
  - oral norfloxacin 400 mg twice daily

  Duration of treatment should be until lesions have healed; the addition of parenteral gentamicin 1 mg/kg every 8 hours should be considered if lesions do not respond during the first few days of treatment.
- **USA:**
  - oral doxycycline 100 mg twice daily for a minimum of 3 weeks and until all lesions have completely healed

  alternatives are:
  - oral ciprofloxacin 750 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily, *or*
  - oral azithromycin 1 g once weekly, *or*
  - oral co-trimoxazole 960 mg twice daily

  In each case treatment is for at least 3 weeks, and until all lesions have completely healed. The addition of an aminoglycoside may be considered if lesions do not respond during the first few days of treatment, in pregnant women, and in those co-infected with HIV.

Sexual partners of patients with granuloma inguinale should be tested and treated.[2,3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). United Kingdom national guideline for the management of donovanosis (granuloma inguinale) 2011. Available at: http://www.bashh.org/documents/3194 (accessed 24/07/12)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60:** 18. [dose]

Lymphogranuloma venereum. Lymphogranuloma venereum or chlamydial lymphogranuloma is an invasive, systemic infection caused by certain serotypes of *Chlamydia trachomatis* and is endemic in tropical and subtropical areas, but may also occur in the developed world. It is a sexually transmitted disease and in the early phase may cause genital ulceration although the commonest clinical manifestation is unilateral inguinal and/or femoral lymphadenopathy. Multisystem involvement occurs, and late complications, including those related to fibrosis and abnormal lymphatic drainage, may require surgery.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of lymphogranuloma venereum are as follows:

- **WHO:** treatment for 2 weeks with:
  - oral doxycycline 100 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily

  an alternative is:
  - oral tetracycline 500 mg four times daily
- **UK** and **USA:** treatment for 3 weeks with:
  - oral doxycycline 100 mg twice daily, *or*
  - oral tetracycline 2 g daily, *or*
  - oral minocycline 300 mg as a loading dose *then* 200 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily

  Sexual partners of patients with lymphogranuloma venereum should be treated with:
  - a single oral dose of azithromycin 1 g *or*
  - oral doxycycline 100 mg twice daily for 7 days

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative, although longer therapy may be required.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2006 National guideline for the management of lymphogranuloma venereum (LGV). Available at: http://www.bashh.org/documents/92/92.pdf (accessed 18/08/08)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60:** 18. [dose]

Syphilis. Syphilis is a sexually transmitted disease caused by the spirochaete *Treponema pallidum* and occurs worldwide. Non-venereal treponematoses include endemic syphilis or bejel, also caused by *T. pallidum*; pinta, caused by *T. carateum*; and yaws, caused by *T. pertenue*.

Syphilis may be **classified** as acquired or congenital and in each case has early and late stages. Syphilis may be described as latent, when serological tests are positive but the patient is asymptomatic.

- In acquired sexually transmitted disease the *early* stage includes primary and secondary syphilis and early latent infection; early latent infection is defined in the UK[1] and by WHO[2] as of not more than 2 years in duration or of less than 1 year in duration by the CDC in the USA.[3]
- *Late* stage disease includes late latent infection and all late clinical stages. The late clinical stages fall broadly into three types: *neurosyphilis* manifesting as neurological symptoms, commonly including dorsal column loss (tabes dorsalis), dementia, or meningovascular involvement; *cardiovascular* syphilis, characterised by aortitis which may manifest as aortic regurgitation, aortic aneurysm, or angina; and *gummata*, inflammatory fibrous nodules or plaques which may be locally destructive and which commonly affect the bone and skin but may occur in any organ. Some term all these late clinical stages tertiary syphilis whereas others use tertiary for benign gummatous syphilis and quaternary for the more serious complications of cardiovascular syphilis and neurosyphilis. The term neurosyphilis has generally been applied to late-stage symptomatic neurological disease, although it is recognised that CNS invasion by *T. pallidum* is common in early syphilis and that CNS involvement may occur at any stage.
- *Congenital syphilis* may result from transplacental infection at any stage of pregnancy and any stage of maternal syphilis.

The incidence of syphilis fell dramatically after the introduction of penicillin and *T. pallidum* remains sensitive to it. There has, however, been a resurgence of syphilis, linked in part with HIV infection. In HIV-infected patients syphilis appears more virulent and neurosyphilis occurs more quickly. Like other diseases causing genital ulcers, syphilis is a risk factor for HIV infection.

The **treatment** of choice for both early and late syphilis is still penicillin and long-acting injections are generally used. Treatment for late syphilis is less well-established than that for early disease and is usually given for longer. A Jarisch-Herxheimer reaction may occur after the first dose of antibacterial, especially in patients with early syphilis, and corticosteroid cover may be beneficial, especially in patients with cardiovascular or neurological involvement.

Guidelines produced by WHO,[2] by an expert group in the UK,[1] and by the CDC in the USA[3] for the treatment of acquired and congenital syphilis are as follows:

- EARLY SYPHILIS
  - **WHO**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) usually given as 2 injections at separate sites in a single session, *or*
    - intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily for 10 days

    alternatives for non-pregnant penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days, *or*
    - oral tetracycline 500 mg four times daily for 14 days

    Pregnant women allergic to penicillin may be given:
    - oral erythromycin 500 mg four times daily for 14 days (but see Syphilis in Pregnancy, below)
  - **UK**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) as a single dose, *or*
    - intramuscular procaine benzylpenicillin 600 mg (600 000 units) daily for 10 days

    An additional alternative if parenteral therapy is refused is:
    - oral amoxicillin 500 mg *plus* oral probenecid 500 mg, both four times daily for 14 days

    alternatives for penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days
    - oral erythromycin 500 mg four times daily for 14 days
    - oral azithromycin 2 g as a single dose
    - oral azithromycin 500 mg daily for 10 days
    - intramuscular ceftriaxone 500 mg daily for 10 days (in the absence of anaphylaxis to penicillin)
  - **USA**:
    - a single intramuscular dose of benzathine benzylpenicillin 1.8 g (2.4 million units)

    alternatives for penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days
    - oral tetracycline 500 mg four times daily for 14 days

    Preliminary data suggest that azithromycin 2 g orally as a single dose may also be effective, *or* parenteral ceftriaxone 1 g daily for 10 to 14 days may also be considered.
- LATE SYPHILIS
  - **WHO**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) once weekly for 3 consecutive weeks, *or*
    - intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily for 20 consecutive days

alternatives for non-pregnant penicillin-allergic patients are:
- oral doxycycline 100 mg twice daily for 30 days, *or*
- oral tetracycline 500 mg four times daily for 30 days

Pregnant women allergic to penicillin may be given:
- oral erythromycin 500 mg four times daily for 30 days

For those with *neurosyphilis*:
- intravenous benzylpenicillin 1.2 to 2.4 g (2 to 4 million-units) every 4 hours for 14 days, *or*
- if outpatient compliance can be ensured, intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily *plus* oral probenecid 500 mg four times daily each for 10 to 14 days

alternatives for non-pregnant penicillin-allergic patients are:
- oral doxycycline 200 mg twice daily for 30 days
- oral tetracycline 500 mg four times daily for 30 days

- **UK**:
  - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) weekly for 3 doses, *or*
  - intramuscular procaine benzylpenicillin 600 mg (600 000 units) daily for 17 days

  alternatives for patients allergic to penicillin and those declining parenteral therapy are:
  - oral doxycycline 100 mg twice daily for 28 days, *or*
  - if penicillin can be tolerated, oral amoxicillin 2 g three times daily *plus* oral probenecid 500 mg four times daily, both for 28 days

  For those with *neurosyphilis* recommendations are:
  - intramuscular procaine benzylpenicillin 1.8 to 2.4 g (1.8 to 2.4 million units) once daily *plus* oral probenecid 500 mg four times daily for 17 days, *or*
  - intravenous benzylpenicillin 1.8 to 2.4 g (3 to 4 million-units) every 4 hours for 17 days

  alternatives are:
  - oral doxycycline 200 mg twice daily for 28 days
  - oral amoxicillin 2 g three times daily *plus* oral probenecid 500 mg four times daily, both for 28 days
  - intramuscular or intravenous ceftriaxone 2 g daily for 10 to 14 days (in the absence of anaphylaxis to penicillin)
- **USA**:
  - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) weekly for 3 consecutive weeks

  alternatives in penicillin-allergic patients are:
  - oral doxycycline 100 mg twice daily for 28 days, *or*
  - oral tetracycline 500 mg four times daily for 28 days

  For those with *neurosyphilis*:
  - intravenous benzylpenicillin 1.8 to 2.4 g (3 to 4 million-units) every 4 hours for 10 to 14 days (or the total daily dose may be given by continuous infusion), *or*
  - if outpatient compliance can be ensured, then intramuscular procaine benzylpenicillin 2.4 g (2.4 millionunits) daily *plus* oral probenecid 500 mg four times daily, both for 10 to 14 days

  Since the duration of treatment for neurosyphilis is shorter than that for late syphilis in the absence of neurosyphilis, some clinicians give intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) once weekly for up to 3 weeks after completion of neurosyphilis treatment to provide a comparable total duration of treatment.

- SYPHILIS IN PREGNANCY

  All guidelines recommend penicillin as under early and late syphilis, together with close surveillance. In the USA, CDC[3] notes that some recommend a second dose of benzathine benzylpenicillin a week after the initial dose for patients with early syphilis. In the UK[1] it is recommended that when the first dose is given in the third trimester a second dose should be given one week later. According to CDC,[3] pregnant patients who are allergic to penicillin should be given penicillin, after desensitisation if necessary, since the alternatives, tetracyclines, are contra-indicated during pregnancy and the macrolides (azithromycin and erythromycin) cannot be relied upon to cure an infected fetus. WHO,[2] on the other hand, advises against desensitisation in a primary care setting and suggest that erythromycin, although inferior, should be given in these circumstances; consideration should probably be given to use of a third-generation cephalosporin in the absence of anaphylaxis. After treatment, the mother should be re-treated if there is serological evidence of re-infection or relapse, and the infant treated.[2] UK guidelines[1] list alternative antibacterials that may be given as: amoxicillin, ceftriaxone, erythromycin or azithromycin. they also state that desensitisation should be considered in those allergic to penicillin.

- CONGENITAL SYPHILIS
  - **WHO**:

    for early congenital syphilis, infants up to 2 years of age and having abnormal CSF may be given:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) twice daily for the first 7 days of life and then three times daily for a total of 10 days, *or*
    - intramuscular procaine benzylpenicillin 50 mg/kg (50 000 units/kg) once daily for 10 days

    For infants with normal CSF (although some treat all infants as if the CSF were abnormal):
    - a single intramuscular dose of benzathine benzylpenicillin 37.5 mg/kg (50 000 units/kg)

    Children older than 2 years may be given:
    - parenteral benzylpenicillin 30 mg/kg (50 000 units/kg) every 4 to 6 hours for 10 to 14 days

    For penicillin-allergic infants aged over 1 month:
    - oral erythromycin 7.5 to 12.5 mg/kg four times daily for 30 days
  - **UK**: recommended doses are as for infants up to 2 years with abnormal CSF in WHO guidelines, above.
  - **USA**:

    Neonates (up to 4 weeks of age) and having proven or probable disease:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) twice daily for the first 7 days of life and then three times daily for a total of 10 days, *or*
    - intramuscular procaine benzylpenicillin 50 mg/kg (50 000 units/kg) once daily for 10 days

    Neonates who have a normal physical examination and a nontreponemal serum titre the same as or less than 4 times the maternal titre may be given, depending on how successfully the mother was treated during pregnancy:
    - one of the above treatment regimens *or*
    - a single intramuscular dose of benzathine benzylpenicillin 37.5 mg/kg (50 000 units/kg)

    Infants and children may be given:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) every 4 to 6 hours for 10 days.

    Those who are allergic to penicillin should be desensitised if necessary.

Sexual partners of patients with syphilis in any stage should be examined, tested, and treated.[2,3]

Guidelines[1-3] advise that all cases of syphilis in HIV-infected patients be treated as for the appropriate stage of infection as in HIV-negative patients; in the UK, some experts recommend treatment as for neurosyphilis but the UK guidelines note that evidence for this policy is lacking.

1. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2008 UK national guidelines on the management of syphilis. http://www.bashh.org/documents/1771 (accessed 18/08/08)
2. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60:** 18. [dose]

Shigellosis

See p. 186.1.

Sickle-cell disease

For prophylaxis against pneumococcal infection in sickle-cell disease, see under Spleen Disorders, p. 209.3.

Sinusitis

Sinusitis or inflammation of the paranasal sinuses can be caused by viral, bacterial, or fungal infection or may be secondary to other disorders such as allergy. Sinusitis rarely occurs without rhinitis (rhinosinusitis).

Acute sinusitis often results from viral upper respiratory-tract infections. About 2% of cases are complicated by bacterial infection;[1] the most frequent bacterial pathogens are *Streptococcus pneumoniae* and unencapsulated *Haemophilus influenzae*, with *Moraxella catarrhalis* (*Branhamella catarrhalis*) increasingly important in children. Other bacterial causes, especially in adults, include mixed anaerobic bacteria (usually associated with dental disease and more frequent in chronic sinusitis), *Staphylococcus aureus, Streptococcus pyogenes,* and Gram-negative bacteria including Enterobacteriaceae and *Pseudomonas aeruginosa* (in nosocomial sinusitis). About 5% of primary sinusitis in young adults has been associated with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*).

Acute sinusitis usually resolves spontaneously, and symptomatic relief with simple analgesics is considered the mainstay of **treatment**.[1] Although antibacterials are widely prescribed for acute sinusitis, their use is controversial given the self-limiting nature of the condition and the relatively small proportion of cases where bacterial infection is confirmed. A systematic review of 57 studies concluded that any treatment effect of antibacterial therapy was small.[2] In the UK, guidance issued by NICE[3] suggests that antibacterial prescribing should be avoided or delayed, unless the patient is systemically very unwell or has signs or symptoms of, or is at high risk of developing, serious complications. US guidelines[4] suggest that appropriate criteria for use of antibacterials include symptoms of sinusitis for 10 to 14 days or severe symptoms (including fever with purulent nasal discharge, facial pain or tenderness, and periorbital swelling). However, a meta-analysis concluded that for immunocompetent adults with acute sinusitis, antibacterials could not be justified, even in patients who reported symptoms for longer than 7 or 10 days, and that the only reason for antibacterial treatment was the presence of signs suggestive of serious complications.[5] Guidelines from the American Academy of Pediatrics for the management of sinusitis in children[6] recommend that antibacterials be given to children clinically diagnosed with persistent or severe acute bacterial sinusitis in order to achieve a more rapid clinical cure.

If antibacterials are considered necessary, treatment should be given for an adequate length of time, usually 10 to 14 days;[4,6,7] however, in a meta-analysis[8] of 12 studies, no significant difference in efficacy was found between short-course (defined in various studies as 3 to 7 days) and long-course (6 to 10 days) treatment in patients with acute, uncomplicated, bacterial sinusitis. When antibacterial therapy is used, choosing the drug with the narrowest spectrum against the most probable pathogens is prudent to minimise the risk of resistance.[9] US guidelines[4] recommend amoxicillin as first-choice therapy in adults and children; co-trimoxazole can be used as an alternative in adults. Increased resistance has been noted among causative organisms, however, and local resistance patterns should be considered. For patients who do not respond to amoxicillin, high-dose amoxicillin plus clavulanic acid (90 mg/kg based on the amoxicillin component, to a maximum of 4 g daily) is recommended. For those intolerant of amoxicillin, alternatives include oral cephalosporins (such as cefpodoxime, cefdinir, and cefuroxime), macrolides, or fluoroquinolones. If associated with dental disease, coverage for anaerobes and Gram-negative bacteria is indicated.[9] Tetracycline or erythromycin are the most effective antibacterials against *Chlamydophila pneumoniae*.[10]

Intranasal corticosteroids reduce inflammation in the nasal mucosa. A systematic review[11] supported the use of intranasal corticosteroids for acute, uncomplicated sinusitis confirmed by radiology or nasal endoscopy, either as monotherapy or adjuncts to antibacterial treatment; although the authors noted that data were limited and the observed effects were modest.

Failure to treat acute sinusitis that does not resolve spontaneously can result in ***chronic sinusitis*** or rarely in complications such as orbital cellulitis, intraorbital abscesses (which may lead to blindness), cavernous sinus thrombosis, osteomyelitis of the frontal bone, extradural and subdural empyema, brain abscess, or meningitis.[1]

Management of chronic sinusitis is based on reducing obstruction of the sinus cavity using antihistamines, decongestants, anti-inflammatory drugs (including corticosteroids), and saline washes as appropriate.[1,7] A systematic review[12] concluded that intranasal saline irrigations, either as monotherapy or as adjuvant treatment, are beneficial for symptomatic management of chronic sinusitis, although they appear to be less effective than intranasal corticosteroids. The usefulness of antibacterials is more contentious,[13] although some clinicians advocate prolonged courses as part of initial treatment.[7] As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases including chronic sinusitis but large placebo-controlled studies are needed. Surgical intervention may be necessary for selected patients if medical treatment fails.

Exacerbations of chronic sinusitis are treated as for acute infection.

1. Ah-See KW, Evans AS. Sinusitis and its management. *BMJ* 2007; **334:** 358–61.
2. Ahovuo-Saloranta A, *et al.* Antibiotics for acute maxillary sinusitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 19/08/08).
3. NICE. Respiratory tract infections—antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care (issued July 2008). Available at: http://www.nice.org.uk/nicemedia/live/12015/41323/41323.pdf (accessed 26/04/10)
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Skin infections

Bacterial infections of the skin and soft tissue (skin structures) may result from invasion of skin structures by endogenous skin flora or by exogenous pathogenic organisms. They may involve any or all layers of the skin, fascia, and muscle, and can spread giving rise to complications such as endocarditis, Gram-negative sepsis, or streptococcal glomerulonephritis.

Clinical assessment of the infection is important for management and several classification schemes have been developed. Primary bacterial skin infections usually involve areas of previously healthy skin and are typically caused by a single organism. Secondary infections occur in areas of previously damaged skin and are frequently polymicrobial. Skin infections have also been classified as uncomplicated or complicated (when they involve deeper skin structures, need surgical treatment, or occur in immunocompromised patients). Another classification system divides skin and soft tissue infections into 4 classes based on the severity of local and systemic signs and symptoms of infection, and the presence and stability of any comorbidities.[1]

- Class 1 patients: are afebrile and otherwise healthy and usually can be managed with topical or oral antibacterials on an outpatient basis
- Class 2 patients: are febrile and have an ill appearance, but have no unstable comorbidities. Oral antibacterials may be helpful in some of these patients but most will need parenteral antibacterial treatment
- Class 3 patients: have a toxic appearance, at least one unstable comorbidity, or a limb-threatening infection and need treatment with parenteral antibacterials
- Class 4 patients: have sepsis syndrome or serious life-threatening infections, such as necrotising fasciitis (see p. 193.1) and always need treatment with parenteral antibacterials; some patients will also need surgical treatment

Treatment of skin infections is based on knowledge of the likely infecting organisms and patterns of resistance.[1,2] The majority of skin and soft tissue infections are caused by aerobic Gram-positive cocci, such as *Staphylococcus aureus* and streptococci. Increasing drug resistance of Gram-positive organisms and the rising incidence of nosocomial and more recently community-acquired MRSA is causing concern and complicating treatment options. Treatment alternatives for infections with these organisms are discussed under Staphylococcal Infections, p. 210.2. Guidelines and recommendations for the management and diagnosis of skin and soft-tissue infections have been developed in the USA.[1,3]

Impetigo is a superficial skin infection that consists of discrete purulent lesions usually on exposed areas of the body, most frequently the face and extremities and occurs most commonly in children aged 2 to 5 years. It is caused by β-haemolytic streptococci and/or *Staph. aureus*, and is highly contagious. The infection may be nonbullous or bullous in appearance; bullous impetigo is caused by *Staph. aureus*. Staphylococcal scalded skin syndrome is a severe manifestation of bullous impetigo caused by infection with strains of *Staph. aureus* producing exfoliative exotoxins. The term toxic epidermal necrolysis is used to cover both this syndrome and a morphologically identical syndrome of more varied aetiology. A syndrome resembling scarlet fever may also occur.

For patients with a limited number of lesions, topical therapy with mupirocin may be considered;[3,4] other topical antibacterials, such as bacitracin and neomycin are considerably less effective.[3] Topical retapamulin is licensed for the treatment of impetigo[5] due to either *Staph. aureus* or *Streptococcus pyogenes*.

Patients with many lesions or those who do not respond to topical drugs should be given oral antibacterials. Penicillinase-resistant penicillins (dicloxacillin, flucloxacillin, or cloxacillin) or a first-generation cephalosporin (cefalexin) are preferred;[3,4] alternatives include macrolides, clindamycin, and amoxicillin with clavulanic acid.[1,3] Intravenous benzylpenicillin, intramuscular benzathine benzylpenicillin, or oral phenoxymethylpenicillin may be given for infections likely to be caused only by streptococci.[1,6]

Cutaneous abscesses are collections of pus within the dermis and deeper skin tissues and are typically polymicrobial (containing normal skin bacteria and organisms from adjacent mucous membranes). *Staph. aureus* is found as a single pathogen in about 25% of cases. Treatment includes incision and drainage, and systemic antibacterials are rarely necessary but may be needed for those with multiple lesions, cutaneous gangrene, severely impaired host defences, extensive surrounding cellulitis, or severe systemic symptoms of infection.[3]

Folliculitis is an inflammation of the hair follicle which may result in superficial infection with pus only present in the epidermis. **Furuncles** (abscess or boil) are infections of the hair follicle in which suppuration extends through the dermis into the subcutaneous tissue, forming a small abscess.[3] A **carbuncle** forms when the infection extends to involve several adjacent follicles, producing a coalescent inflammatory mass with pus draining from multiple follicular orifices.[3] These skin infections are usually caused by *Staph. aureus*. Folliculitis and small furuncles may respond to the application of moist heat to promote localisation and drainage of pus. Topical antibacterials such as mupirocin, clindamycin, erythromycin, or benzoyl peroxide may also be used for management of folliculitis. Larger furuncles and all carbuncles require incision and drainage.[3] Patients who are febrile or also have extensive cellulitis may be treated with systemic antibacterials as for impetigo.[3,4] In patients at risk of recurrent furunculosis topical or systemic antibacterial therapy has been tried for eradicating nasal or extra-nasal *Staph. aureus* carriage (see under Staphylococcal Infections, p. 210.2).

Erysipelas (also known as St. Anthony's fire) is an infection of the more superficial layers of the skin and cutaneous lymphatics characterised by abrupt onset of fiery-red swelling of the face or extremities; it is mostly caused by β-haemolytic streptococci (usually group A). The treatment of choice is a penicillin, e.g. intravenous benzylpenicillin, intramuscular procaine benzylpenicillin, or oral phenoxymethylpenicillin depending on the severity of the infection.[3,6] Clindamycin or erythromycin are alternatives for those allergic to penicillin.[6] If *Staph. aureus* is suspected a penicillinase-resistant penicillin or a first-generation cephalosporin should be chosen.[3]

Cellulitis is an acute infection, initially affecting the epidermis and dermis, but may spread within the superficial fascia. It may also spread through the lymphatic tissue and to the bloodstream. Cellulitis is most commonly caused by beta-haemolytic streptococci and *Staph. aureus* although many other bacteria may cause infection. Parenteral drug abusers are most often infected with *Staph. aureus*, while mixed aerobic and anaerobic infections generally occur in diabetic patients. Mild infections caused by unidentified Gram-positive organisms or staphylococci may be treated with oral penicillinase-resistant penicillins or first-generation cephalosporins, while intravenous nafcillin, oxacillin, or cefazolin are given for moderate to severe infections.[3,4] Clindamycin and vancomycin are alternatives in those with life-threatening penicillin allergy.[3] Documented mild streptococcal infections are treated with oral phenoxymethylpenicillin or amoxicillin or intramuscular procaine benzylpenicillin; intravenous benzylpenicillin is given to those with moderate to severe infections. Infections due to Gram-negative bacilli may be treated with an oral second-generation cephalosporin (cefaclor or cefuroxime), an intravenous first- or second-generation cephalosporin, or an aminoglycoside depending on the severity of the infection. Those with polymicrobial infections (without anaerobes) may be treated with an aminoglycoside plus either intravenous benzylpenicillin (if streptococci are cultured) or a penicillinase-resistant penicillin (if staphylococci are cultured). Ceftazidime and the fluoroquinolones are effective against both Gram-positive and Gram-negative bacteria.[6] Patients with mild, polymicrobial infections (with anaerobes) may be treated with oral amoxicillin plus clavulanic acid or a fluoroquinolone (ciprofloxacin or levofloxacin) plus either oral clindamycin or oral metronidazole. Moderate to severe infections may be treated intravenously with an aminoglycoside plus clindamycin or metronidazole, or monotherapy with a second- or third-generation cephalosporin (cefoxitin or ceftizoxime), a carbapenem (imipenem, meropenem, or ertapenem), a beta lactam with a beta-lactamase inhibitor (piperacillin with tazobactam), or tigecycline.[6] Antibacterial treatment is usually continued for 10 to 14 days or until inflammation resolves,[4] but uncomplicated cellulitis may be treated for 5 days.[3,7]

Antibacterial resistance among *Staph. aureus* (meticillin resistance) and *Str. pyogenes* (erythromycin resistance) is problematic because both of these organisms commonly cause a variety of skin and soft-tissue infections.[3] Generally meticillin-sensitive *Staph. aureus* (MSSA) infections may be treated with oral antibacterials such as cloxacillin, flucloxacillin, dicloxacillin, or cefalexin; for penicillin-allergic patients clindamycin or a macrolide (erythromycin, clarithromycin, or azithromycin) may be given.[4] If parenteral antibacterial treatment is needed a penicillinase-resistant penicillin (nafcillin or oxacillin) or a cephalosporin (cefazolin, cefuroxime, or ceftriaxone) may be given; clindamycin may be used in penicillin-allergic patients. MRSA infections may be treated with oral antibacterials such as co-trimoxazole, doxycycline, minocycline, clindamycin, or linezolid.[4,5] Oral rifampicin with either doxycycline or co-trimoxazole has also been used.[5] The fluoroquinolones (levofloxacin and moxifloxacin) have been used in patients who could not tolerate any of the other drug choices,[4] but some advise against their use as resistance to them develops rapidly in *Staph. aureus*.[5] Parenteral vancomycin is the drug of choice for moderate to severe infections; appropriate parenteral alternatives may include clindamycin, daptomycin, tigecycline, linezolid, and quinupristin/dalfopristin depending on whether the infection is hospital- or community-acquired.[4,5]

For details on other skin and soft tissue infections, see under Acne (p. 1682.2), Bites and Stings (p. 174.2), Rosacea (p. 1688.3) and Surgical Infections (p. 211.1); systemic infections with cutaneous involvement include Anthrax (p. 173.2), Diphtheria (p. 178.3), and Mycetoma (p. 193.1).

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Spleen disorders

Patients with asplenia (due to splenectomy or congenital defect) or functional hyposplenism (associated with, for example, coeliac disease, haematopoietic stem cell transplantation, or haemoglobinopathies such as thalassaemia major or sickle-cell disease) have impaired immunity and, like other immunocompromised patients (p. 186.3), are at increased risk of infection.[1] Children are at special risk. Frequently, infection is caused by encapsulated bacteria such as *Haemophilus influenzae*, *Neisseria meningitidis*, and most commonly, *Streptococcus pneumoniae*,[1-4] which may cause severe overwhelming infection that is rapid in onset and sometimes fatal. *Salmonella* spp. are also important pathogens in children with sickle-cell disease.[4] More unusual organisms include *Capnocytophaga canimorsus* (formerly called DF-2), which may cause opportunistic infections in splenectomised patients after animal bites,[2] *Bordetella holmesii*, and tick-borne *Ehrlichia* spp.[3] There may also be an increased risk of falciparum malaria and babesiosis.[2,4]

Infections in asplenic or hyposplenic individuals are largely preventable, the general approach being through vaccination and the use of antibacterial prophylaxis. Practice guidelines based on published evidence and expert opinion have been published in countries including Australia and New Zealand[3] and the UK.[2,5]

Immunoprophylaxis. Immunisation with polyvalent pneumococcal vaccine is recommended for all asplenic patients and those with functional hyposplenism. *Haemophilus influenzae* (Hib) vaccine is recommended for all patients who have not previously received this vaccine, and influenza vaccination should be given annually.[3,5] Meningococcal vaccine is also recommended; however, the group C conjugate vaccine routinely used in some countries (including the UK) does not protect against *N. meningitidis* serotypes A, W135, or Y; therefore, patients travelling abroad to areas where these serotypes are endemic should receive additional vaccination with an appropriate polyvalent meningococcal vaccine.[1,5]

Antibacterial prophylaxis. Prophylaxis with a suitable antibacterial should be offered to asplenic and hyposplenic patients, and although opinion varies on the optimal duration, UK guidelines[2,5] consider that prophylaxis should be lifelong; it is considered particularly important in patients with underlying immunodeficiency, in children up to the age of 16 years, and for the first 2 years after splenectomy.[2] Phenoxymethylpenicillin is usually given, but amoxicillin (with or without clavulanic acid)[2,3] may also be used, particularly in adults, as amoxicillin is better absorbed after oral doses and has a broader spectrum of activity. Erythromycin is a suitable alternative in those unable to tolerate penicillins;[2,5] roxithromycin, moxifloxacin, cefuroxime, and co-trimoxazole have also been suggested[3] although specific choices should also be informed by local resistance patterns. On a practical level, compliance with lifelong prophylaxis is difficult, and guidelines from Australia and New Zealand[3] have therefore suggested that, in the absence of impaired patient immunity, the need for ongoing prophylaxis can be reconsidered after 2 years of use. There is also evidence to suggest that, in children who have received pneumococcal immunisation, there is no benefit in continuing penicillin prophylaxis beyond the age of 5 years,[6] although indefinite prophylaxis has been recommended for those who have had a previous

pneumococcal septic event.[7] Fears that prolonged prophylaxis could encourage the emergence of resistant pneumococci have not been substantiated,[8] although the prevalence of beta-lactam-resistant pneumococci continues to increase. Patients who are not otherwise taking antibacterial prophylaxis should be advised to do so during periods of travel abroad, with resistance patterns in travel destinations being used to guide the specific choice of antibacterial,[2] Malaria prophylaxis is also necessary if travel to endemic areas cannot be avoided.[2,3]

Antibacterial prophylaxis reduces, but does not completely eliminate the risk of infection, and progression to overwhelming sepsis can be rapid. Patients should therefore be advised to keep a supply of a suitable antibacterial for immediate use should symptoms of infection occur, and be instructed to seek medical advice urgently.[3,5] Suggested drugs are generally similar to those used for prophylaxis.

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Spotted fevers

Rickettsial infections of the spotted fever group are transmitted to man mostly by ticks and have also been called tick typhus. They include Rocky Mountain spotted fever, due to *Rickettsia rickettsii* and occurring especially in the USA but also in Canada, Mexico, and Central and South America; boutonneuse or Mediterranean spotted fever, due to *R. conorii* and occurring in Mediterranean countries including the Middle East, Africa, and India; African tick-bite fever, due to *R. africae* and occurring in sub-Saharan Africa and the Caribbean islands; Queensland tick typhus or Australian spotted fever, due to *R. australis* and occurring in Australia; north Asian or Siberian tick typhus, due to *R. sibirica* and occurring in Siberia and Mongolia; and oriental spotted fever, due to *R. japonica* and occurring in Japan and Korea. Rickettsialpox, due to *R. akari* is transmitted from mice by mites and occurs in the USA, Russia, and Africa. Flea-borne spotted fever is due to *R. felis*. It is transmitted by cat fleas and probably occurs worldwide.

Infection occurs after exposure to tick-infested environments or animals. The rickettsiae concentrate in the walls of small to medium blood vessels causing vasculitis. Generally, symptoms begin 4 to 10 days after a tick bite and may vary depending on the rickettsial species. Fever and headache are characteristic. As the infection progresses, an eschar at the tick bite site and/or a rash may develop. Myalgia, malaise, nausea and vomiting, and lymphadenopathy can also occur. Sequelae may include thrombocytopenia, encephalopathy, respiratory and renal failure, and myocarditis. Rocky Mountain spotted fever is the most severe of these fevers, but others are also potentially life-threatening.

The treatment of choice for all tick-borne rickettsioses is oral or intravenous doxycycline in both adults and children.[1] Tetracyclines are generally contra-indicated in young children; however, the risk of tooth staining with a single short course of doxycycline is considered negligible.[1-3] Susceptibility to rifampicin varies by species.[3]

- Chloramphenicol is a less effective alternative for *Rocky Mountain spotted fever*, used when doxycycline is not available or contra-indicated.[1-3] A fluoroquinolone has also been suggested,[4] although experience is limited.[1]
- Alternatives to doxycycline in patients with *Mediterranean spotted fever* include chloramphenicol[3] (although relapses have been reported after treatment[5]) and ciprofloxacin.[1] Macrolides such as azithromycin and clarithromycin are alternatives in children;[1,3,6] josamycin is also useful for pregnant women.[1] Short 2-day courses of ciprofloxacin or doxycycline were also curative for Mediterranean spotted fever in adults whose disease was not severe, although there was a more rapid response to doxycycline.[7]
- Infection with *R. australis* has been treated successfully with ciprofloxacin.[8]
- *Rickettsialpox* can be mistaken for chickenpox. It will respond to tetracycline although patients have generally recovered without treatment.[9]

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Staphylococcal infections

Staphylococci are Gram-positive bacteria pathogenic to man. Species may be differentiated by various methods, including the coagulase test. Those species of clinical importance are *Staphylococcus aureus*, which is usually coagulase-positive, and *Staph. epidermidis* and *Staph. saprophyticus*, which are coagulase-negative.

Staph. aureus colonises the skin and mucous membranes naturally and many people, including neonates, may be staphylococcal carriers from time to time. Localised *Staph. aureus* infections may follow surgery or trauma and commonly result in abscess formation. Staphylococcal skin infections include impetigo, carbunculosis, and furunculosis. Conditions associated with staphylococcal extracellular toxin production include staphylococcal scalded skin syndrome, toxic shock syndrome, and staphylococcal food poisoning. Staphylococcal septicaemia is usually a consequence of local infection and may sometimes be associated with intravascular or intraperitoneal catheters or with intravenous drug abuse. Septicaemia often results in staphylococcal endocarditis. Other possible complications of septicaemia are pneumonia and bone and joint infections, although in these cases aspiration or local trauma, respectively, may be the cause.

Staph. epidermidis is also a natural inhabitant of skin and mucous membranes and an important nosocomial pathogen. Many infections are hospital-acquired and are often associated with indwelling catheters. There has been an increased incidence of bacteraemia due to *Staph. epidermidis* in neonatal units.

Staph. saprophyticus is a common cause of urinary-tract infections in young women.

Staphylococci were sensitive to benzylpenicillin when it was first introduced, but the majority of strains are now resistant as a result of penicillinase production. Meticillin and other penicillinase-resistant penicillins such as flucloxacillin were developed because of their activity against these resistant staphylococci. However, meticillin-resistant staphylococci soon emerged. Both coagulase-negative staphylococci and *Staph. aureus* resistant to meticillin are generally resistant to all beta lactams and often have multiple resistance to other antibacterials (see Meticillin, Antimicrobial Action, p. 325.3). More studies have been published on MRSA than meticillin-resistant coagulase-negative staphylococci, but both types are a serious problem in hospitals around the world. Resistant strains may be endemic to a single hospital or may be epidemic causing outbreaks of infection at more than one hospital. Colonisation of hospital staff and patients with meticillin-resistant staphylococci is an important factor in the spread of these infections. Current trends are towards healthcare at home rather than in hospital and there are reports suggesting that MRSA is becoming more prevalent in the community.[1-4] Community-associated (community-acquired or community-onset; CA-MRSA) MRSA has clinical, epidemiologic, and bacteriologic characteristics distinct from hospital-associated (hospital-acquired) infections (HA-MRSA).[5] CA-MRSA refers to an MRSA infection with onset in the community in a person with no established risk factors for HA-MRSA, such as recent hospitalisation, surgery, residence in a long-term care facility, dialysis, or the presence of invasive medical devices.[3,5] The spectrum of disease caused by CA-MRSA appears to be similar to that of other *Staph. aureus* infections, although some manifestations such as skin and soft tissue infections are more common.[4,5]

Guidelines for the control of MRSA are available in many countries.[6] In the UK, revised guidelines[7] for the control of HA-MRSA were produced by a joint working party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association in 2006. They advise prompt isolation of infected or colonised patients, screening of patients and staff in contact with such patients, the use of protective clothing, handwashing with an antiseptic detergent, and the use by all patients of an antiseptic detergent for washing and bathing.

Although ciprofloxacin may be used to treat infection, the emergence of widespread resistance in meticillin-sensitive and meticillin-resistant *Staph. aureus* limits its usefulness (see p. 267.2). Combination therapy may be helpful. Rifampicin is highly active against MRSA, but it must always be used with another drug to prevent the emergence of resistance. Combinations of rifampicin with gentamicin, vancomycin, co-trimoxazole, fusidic acid, quinolones, or novobiocin have been tried.

Guidelines for the management of CA-MRSA have been developed in the USA[5] and in the UK.[8] Skin and soft tissue infections associated with CA-MRSA can usually be treated with incision and drainage, with or without topical antibacterials; in some cases systemic antibacterials may be needed.[3] CA-MRSA infections appear to be resistant to fewer antibacterials than HA-MRSA infections; CA-MRSA isolates are generally resistant to beta lactam penicillins and cephalosporins and macrolides (erythromycin, clarithromycin, and azithromycin). Resistance to fluoroquinolones and tetracyclines occurs, and may be increasing.[3,5] Most CA-MRSA isolates are susceptible to co-trimoxazole, gentamicin, tetracycline, and clindamycin[3,5] For more serious infections vancomycin is the drug of choice.[2,4]

For eradication of nasal carriage UK guidelines for the control of MRSA in healthcare facilities recommend mupirocin nasal ointment. Eradication at other colonised sites is more difficult: antiseptic detergents may be used for skin and hair washing.[7] A systematic review[9] has concluded that there is insufficient evidence to support the use of topical or systemic antimicrobial therapy for eradicating nasal or extra-nasal MRSA in colonised patients. A later systematic review[10] to determine the efficacy of topical or oral antibacterials, or both, for eradicating MRSA carriage found that short-term nasal application of mupirocin was the most effective treatment, with an estimated success rate of 90% 1 week after treatment and about 60% after a longer follow-up period. Drug resistance during treatment was reported in 1% and 9% of patients receiving mupirocin and oral antibacterials, respectively. Another systematic review[11] found that in those who are nasal carriers of *Staph. aureus*, use of mupirocin ointment significantly reduced the level of *Staph. aureus* infections. A randomised, double-blind, placebo-controlled study[12] concluded that rapid identification of *Staph. aureus* nasal carriers followed by treatment of nasal and extranasal sites with mupirocin nasal ointment and chlorhexidine soap respectively, significantly reduced the risk of HA-MRSA infection, especially among surgical patients. Although there is no data to support the use of mupirocin with or without chlorhexidine body washes to eliminate colonisation in people with CA-MRSA,[2,4,5] decolonisation treatment may be used in those with recurrent infections, or in high-risk patients.[2,5]

Isolated reports from around the world of MRSA with intermediate resistance or reduced susceptibility to vancomycin initially emerged in the late 1990s,[13-15] and in response the CDC produced interim[16] and later[17] guidelines for preventing the spread of vancomycin-intermediate *Staph. aureus* (VISA) and vancomycin-resistant *Staph. aureus* (VRSA). Newer antibacterials such as daptomycin, linezolid, quinupristin/dalfopristin, or tigecycline may be effective and may assume increasing importance.[4,18] Other antibacterials, either recently approved for use or in development, that may be effective alternatives to vancomycin are the glycopeptides (dalbavancin, oritavancin, or telavancin), ceftobiprole, and iclaprim.[18]

Staphylococcal vaccines have been used for the prophylaxis and treatment of staphylococcal infections.

For the management of staphylococcal infections in general, see under the specific disease headings.

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Surgical infection

Infection is an important cause of postoperative surgical morbidity and mortality and *antimicrobial prophylaxis* is one of several strategies used to reduce the risk of infection. The value of infection prophylaxis is well established in certain types of surgery, especially abdominal surgery and where prostheses are implanted, although recommendations as to the choice of antibacterial and the route, timing, and duration of treatment may vary. Surgical wounds are classified as following clean, clean-contaminated (potentially contaminated), contaminated, and dirty operations. Clean operations exclude those involving the gastrointestinal, genital, urinary, or respiratory tracts. Clean-contaminated operations include those where the gastrointestinal, genital, urinary, or respiratory tracts are opened, but without unusual contamination. Contaminated operations include those where there is acute inflammation or spillage from a hollow viscus. Dirty operations include those where there is pus, gangrene, or perforated viscera. In addition, surgery to repair compound fractures and lacerations due to animal or human bites is considered dirty.

ANTIMICROBIAL PROPHYLAXIS. Strictly speaking the term 'prophylaxis' should be confined to elective procedures with no evidence of sepsis at the time of operation. If possible any pre-existing infections should be treated before admission for surgery. For prophylaxis it is customary to give antibacterials systemically as a single pre-operative dose whereas more prolonged use is necessary when they are given therapeutically. Antimicrobial prophylaxis is used in clean-contaminated operations and in clean operations that involve the insertion of prosthetic materials or when an infection, however unlikely, would be catastrophic. The use of antibacterials for the management of contaminated or dirty surgery is considered to be therapeutic rather than prophylactic and should continue for several days postoperatively.

Guidelines for the management of surgical infections have been developed in the USA[1,2] and in the UK.[3,4] Additional guidelines for the diagnosis and management of complicated intra-abdominal infections have been produced in the USA by the Surgical Infection Society and the Infectious Disease Society of America.[5]

Contaminating organisms. The choice of prophylactic antibacterial will be influenced by the likely contaminants for a particular surgical procedure. The most frequently isolated pathogens include *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and *Escherichia coli*. Infections with antimicrobial-resistant pathogens including *Candida albicans* and MRSA are increasing. The most common source of infection is the endogenous flora of the patient's skin, mucous membranes, or viscera. Thus, aerobic Gram-positive organisms (for example staphylococci) are common infecting organisms when the source is the skin and mucous membranes, while infections with enterococci, Gram-negative aerobes (for example *E. coli*), and anaerobic bacteria (for example *Bacteroides fragilis*) can arise from the gastrointestinal tract.

Route of administration. Systemic dosage, usually by the intravenous route, is generally preferred. The chosen antibacterial is usually given as a single dose intravenously just before operation at the induction of anaesthesia. The pharmacokinetic properties should be such that adequate serum concentrations are maintained throughout the surgical procedure. Additional doses may be necessary when surgery is prolonged, when there is massive blood loss, or when an antibacterial with a short half-life is used. More controversial routes have included topical or intra-incisional use and peritoneal lavage. Giving non-absorbable antibacterials orally to suppress the intestinal flora was traditional before large bowel surgery, and neomycin with erythromycin is still given for this purpose in the USA. For reference to selective digestive tract decontamination (SDD), see under Intensive Care, p. 187.3. Other dosage forms include bone cement and chains of beads for implantation, both containing gentamicin and used prophylactically in orthopaedic surgery, and topical and sometimes subconjunctival antibacterials for ophthalmic surgery.

Certain categories of patient continue to be at long-term risk of infection after surgery and include splenectomised patients who have impaired immunity and are at risk of pneumococcal and other infections (see under Spleen Disorders, p. 207.3). Opinion has changed as to whether patients at special risk of endocarditis require prophylaxis before dental and surgical procedures (see Endocarditis, p. 179.2).

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Syphilis

See under Sexually Transmitted Diseases, p. 205.2.

Tetanus

Tetanus (or lockjaw)[1-3] is caused by the neurotoxin, tetanospasmin, produced by *Clostridium tetani*, a Gram-positive anaerobic spore-forming bacillus present in soil and faeces. The spores are resistant to heat, desiccation, and disinfectants and can survive for many years. Tetanus can be prevented by active immunisation with tetanus vaccine or passive immunisation with tetanus immunoglobulin. Nowadays it occurs mostly in those who are unimmunised or partially immunised; it may also occur in those who have been fully immunised but have not received further booster doses. Tetanus generally follows trauma, particularly deep penetrating injuries; patients with burns, surgical wounds, body piercings, or a history of injected drug abuse are at increased risk of developing tetanus. Infection may also develop postpartum in the uterus (maternal tetanus) and in the newborn (tetanus neonatorum). The mortality rate in mild to moderate tetanus is about 6% and increases to about 60% in severe disease; it may be 80 to 90% in newborns even if treated.

The goal of treatment is to relieve muscle spasm, prevent respiratory and metabolic complications, neutralise unbound or circulating toxin, and eliminate the source of toxin. Treatment includes the use of tetanus immunoglobulin to neutralise any circulating toxin (p. 2420.3) and the use of antibacterials to stop the production and release of toxins. Benzylpenicillin has traditionally been used, given intravenously or intramuscularly for 7 to 10 days, but many consider metronidazole to be the drug of choice;[1,2] given rectally it causes fewer spasms than when given parenterally.[1] Erythromycin, a tetracycline such as doxycycline, clindamycin, vancomycin, or chloramphenicol are second-line alternatives.[1,2]

Wounds should be cleaned and debrided. Drugs used to treat muscle spasm, rigidity, and seizures include sedative-hypnotic agents, general anaesthetics, centrally acting muscle relaxants, and neuromuscular blocking agents. For further information on the treatment of rigidity and spasms, see p. 2029.2.

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Tonsillitis

See Pharyngitis, p. 198.3.

Toxic shock syndrome

Toxic shock syndrome (TSS) is an acute, toxin-mediated, systemic illness often leading to multi-organ failure;[1] it may be characterised by shock, fever, rash, and gastrointestinal or CNS disturbances,[2] although bacteraemia is not always present.[1] TSS has most commonly been associated with *Staphylococcus aureus* and its bacterial exotoxin, toxic shock syndrome toxin-1 (TSST-1), or with group A streptococci (which produce streptococcal pyrogenic exotoxins A, B, and C).[2] More recently however, other bacteria including *Clostridium* spp.,[3] *Pseudomonas* spp., and *Klebsiella* spp. have also been implicated, and TSS is now considered to be a global immune response that may be caused by several different triggers.[2] In the early 1980s, TSS was reported mainly in menstruating women using high-absorbency tampons, but it is now appreciated that other foci of infection such as surgical wounds, burns, abscesses, and sinuses are often responsible.[4,5] Non-menstrual cases now occur more frequently than menstrual,[2] and mortality may be higher.[6]

As with any case of septic shock, the first consideration in the management of patients with acute TSS is **resuscitation and stabilisation**. For the general principles used in the treatment of shock, see p. 1279.3. A thorough investigation to find the infective focus, followed by effective **source control** is also necessary, and may include local measures such as removal of tampons or packing, wound debridement, or drainage of abscesses.

Appropriate, immediate antibacterial therapy is essential to **eliminate toxin-producing bacteria**. Where the infecting organism is unknown, initial regimens must cover both *Staph. aureus* and *S. pyogenes*; generally a beta lactam plus a lincosamide is considered appropriate. Where the causative organism has been identified, the following pathogen-specific regimens have been suggested:[1]

- Group A streptococcus: benzylpenicillin plus clindamycin
  beta-lactam intolerant patients: either a macrolide or fluoroquinolone plus clindamycin
- Macrolide-lincosamide-streptogramin-B-resistant (MLS_B phenotype) group A streptococcus: benzylpenicillin, plus either vancomycin or teicoplanin
  beta lactam intolerant patients: vancomycin or teicoplanin
- Meticillin-sensitive *Staph. aureus*: either cloxacillin, nafcillin, or cefazolin, plus clindamycin
  beta-lactam intolerant patients: clarithromycin plus clindamycin
- MRSA: clindamycin or linezolid plus vancomycin or teicoplanin
- Glycopeptide-resistant or intermediate *Staph. aureus* linezolid plus clindamycin (if sensitive)

Newer antibacterials such as linezolid, daptomycin, and tigecycline, that are effective against Gram-positive organisms, may be considered for third-line use.[1]

Continuing antibacterial treatment for 10 days during the convalescent phase to reduce the risk of recurrence has been recommended.[4] The use of prophylactic antibacterial therapy has been suggested in burns patients,[7] but this is controversial.

Provision of passive immunity through the use of fresh frozen plasma or intravenous normal immunoglobulins is considered by some to be one of the most important measures to stop the inflammatory escalation associated with TSS and prevent further tissue damage.[2] In a comparative observational study, improved 30-day survival was noted among patients with streptococcal TSS who were given intravenous immunoglobulins.[8] It has been suggested that such therapy be considered in cases where there has been no clinical response within the first 6 hours of aggressive supportive therapy.[1]

Toxic shock syndromes may be associated with necrotising fasciitis (see p. 193.1).

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Trachoma

Trachoma[1,2] results from chronic eye infection with certain *Chlamydia trachomatis* serotypes and is an important cause of preventable blindness. It is endemic mainly in Africa and the Middle East, and also in parts of Asia, Latin America, and the western Pacific. The reservoir is chronic eye infection and transmission occurs easily via contaminated fingers, personal effects, and flies that come in contact with the eyes or nose. Infection tends to cluster in families and communities, particularly where water shortage, poor sanitary conditions, and overcrowding occur. Although trachoma is not a sexually transmitted disease, inclusion conjunctivitis in infants (see under Neonatal Conjunctivitis, p. 193.2) and in adults is associated with sexually transmitted genital *C. trachomatis* infection and can progress to trachoma when there is persistent or recurrent eye infection.

First infection generally occurs early in life, leading to a usually self-limiting conjunctivitis. Re-infection is common, and over many years leads to conjunctival scarring, causing the eyelashes to turn inwards and scratch the cornea (trichiasis); eventually irreversible corneal damage and visual loss may occur.

Blindness can be prevented by several interventions, and an Alliance for the Global Elimination of Trachoma (GET 2020) was launched under WHO leadership in 1998 with the goal of eliminating blinding trachoma by 2020. Interventions are also promoted by the International Trachoma Initiative and follow the WHO recommended SAFE strategy: lid surgery for trichiasis, antibacterials to treat infection and suppress transmission, facial cleanliness, and environmental improvements.[3,4] In endemic areas, community-wide antibacterial treatment is recommended where the prevalence of active trachoma in children aged 1 to 9 years is 10% or higher;[3,4] where prevalence is between 5 and 10%, targeted treatment may be considered.[3]

Active treatment. Oral azithromycin regimens (usually a single oral dose or 3 oral doses at weekly intervals) have been shown to be at least as effective as topical tetracycline in resolving active infection.[5,6] Azithromycin 1.5% eye drops used twice daily for 2 or 3 days have been shown to be as effective as treatment with oral azithromycin.[7]

Mass treatment of communities with oral azithromycin once weekly for 3 weeks resulted in a lower incidence of trachoma at one-year follow-up than topical tetracycline given daily for 6 weeks.[8,9] This may be in part due to the fact that topical tetracycline does not treat extra-ocular reservoirs of infection, and its long treatment schedule has led to poor compliance. WHO therefore recommends the use of azithromycin, given as a single annual oral dose of 20 mg/kg (to a maximum of 1 g) for a minimum of 3 years. After that, the prevalence of active disease in the community should be re-assessed to determine whether treatment may be stopped. For those who cannot take azithromycin (including infants less than 6 months old) or where it is unavailable, tetracycline 1% eye ointment can be used twice daily for 6 weeks.[1-4] Pregnancy and breast feeding are not considered to be contra-indications to the use of oral azithromycin.[4] Azithromycin 1.5% eye drops have also been used successfully[10,11] and may present a possible alternative to the standard WHO-recommended treatments.

It is uncertain how often, and for how long mass treatment needs to be given in endemic communities to achieve disease control.[1] Although several studies have reported significant reductions in the prevalence of disease and infection after mass treatment with a single oral dose of azithromycin,[12,13] recurrence of infection within 12 to 24 months has been reported.[14,15] Infection may have been eliminated in a Tanzanian community 3 years after the completion of 2 rounds of mass azithromycin treatment, given at 24-month intervals;[16] the authors concluded that one or two rounds of high-coverage mass treatment might be sufficient to eliminate infection in communities with moderate disease burden. A comparative study[17] of annual versus twice-yearly mass treatment with oral azithromycin in pre-school children living in communities with a high prevalence of infection found that, after 24 months, twice-yearly treatment was significantly more effective in reducing ocular chlamydial infection prevalence than annual treatment. However, a subsequent comparative study[18] found that after 42 months, the prevalence of infection in children aged 0 to 9 years was similar for both annual and twice-yearly treatment groups. The mean elimination of infection in those treated twice yearly was, however, 7.5 months earlier than those treated annually.[18]

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Trench fever

Trench fever is a louse-borne Gram-negative bacterial infection so named because of its prevalence among soldiers in the First World War. It is caused by *Bartonella quintana* (formerly *Rochalimaea quintana*) which was previously classified as a rickettsia. *B. quintana* and *B. henselae* have also been implicated in bacillary angiomatosis, especially in immunocompromised patients, and *B. henselae* is considered to be a cause of cat scratch disease (p. 176.3). Contemporary *B. quintana* infections (also known as urban trench fever) have a global distribution and are mainly associated with poverty, alcoholism, homelessness or displacement, and body-lice infestation.

The disease varies from asymptomatic to severe. Clinical manifestations include fever, headache, weight loss, and leg pain. Many patients have been found to have chronic bacteraemia, and some patients have been diagnosed with *Bartonella* endocarditis.

Mild or uncomplicated infection can be treated with a 4- to 6-week course of an oral tetracycline such as doxycycline, oral erythromycin, or oral azithromycin.[1] Patients with chronic bacteraemia should receive oral doxycycline for 4 weeks plus intravenous gentamicin for 2 weeks,[2,3] mainly to prevent the development of endocarditis. The recommended treatment for documented *Bartonella* endocarditis is oral doxycycline for 6 weeks plus intravenous gentamicin for 2 weeks.[2,3] If gentamicin cannot be used, rifampicin is an alternative. For suspected *Bartonella* endocarditis, intravenous gentamicin is given for 2 weeks with intramuscular or intravenous ceftriaxone for 6 weeks; this regimen may be given with or without a 6-week course of oral doxycycline.[2]

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Tuberculosis

Tuberculosis[1] refers to disease caused mainly by *Mycobacterium tuberculosis* and occasionally by *M. bovis* or *M. africanum*. Infection results from inhalation of infected droplet nuclei. Primary infection is usually asymptomatic and in more than 95% of immunocompetent individuals is controlled by acquired (cell mediated) immunity. The immune response, however, is unable to eradicate the tubercle bacilli, and these bacilli may give rise to progressive primary infection (if disease occurs within 2 years of initial infection) or post-primary (reactivated) tuberculosis (if disease occurs years to decades after initial infection). Young children and immunocompromised patients are at increased risk of developing active disease. The most common manifestation of tuberculosis is pulmonary disease, although almost any organ may be affected. Patients usually present with cough, fever, night sweats, and weight loss.

During recent years the incidence of tuberculosis in many countries has increased along with the increasing prevalence of HIV infection. Supervised rifampicin-based (short-course) therapy, using fixed-dose combination tablets, is recommended by WHO to improve cure rates and reduce the emergence of drug-resistant tuberculosis.[2] WHO applies the term **DOTS** (Directly Observed Therapy – Short Course) to its tuberculosis control strategy, which includes standards for diagnosis, supervised therapy, ensuring secure drug supplies, and regular evaluation of the tuberculosis control programme. The feasibility of implantable dosage forms has also been investigated.

First-line treatment. Multidrug treatment for 6 to 8 months is required to cure tuberculosis, reduce the risk of relapse, and prevent the emergence of drug-resistant disease. Treatment regimens recommend an initial intensive phase of 2 to 3 months that is aimed at achieving rapid sputum conversion followed by a continuation phase of 4 to 6 months to eliminate residual bacilli and prevent relapse. The choice of regimen depends on local patterns of drug resistance and the availability of drugs, and are embodied in national and regional treatment protocols in many countries including those in Europe,[3] the UK,[4,5] and USA.[6] WHO recommended treatment regimens[7] are based on disease severity and history of previous tuberculosis treatment:

- **new cases** of pulmonary or extrapulmonary tuberculosis are generally treated with an initial phase consisting of rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) for 2 months, followed by a continuation phase with rifampicin and isoniazid for 4 months, such a regimen being described as: 2HRZE/4HR. Although a regimen using ethambutol in the continuous phase instead of rifampicin (2HRZE/6HE) has been used to reduce costs, it is no longer recommended by WHO due to an increased risk of relapse and death. All first-line drugs can be given intermittently if doses are directly observed (3 times each week), however, WHO advises that daily use is considered optimal. For tuberculous meningitis WHO recommends that ethambutol be replaced with streptomycin for the initial phase (although ethambutol is considered suitable by other authorities[5,6,8]); an extended continuation phase of up to 10 months with rifampicin and isoniazid is often recommended. Cure rates of greater than 90% are typically achieved in patients infected with drug-susceptible organisms who adhere to therapy.
- patients **previously treated** for tuberculosis are at higher risk for drug-resistant infection, and wherever possible, treatment should be guided by drug susceptibility testing (DST). Where DST is not available or is delayed, an initial empirical regimen should be chosen based on the perceived risk of multidrug-resistant infection, which is based on both patient-specific factors and the degree of resistance seen in the community. Those considered to be at low or medium risk may be empirically re-treated with first-line drugs; the initial treatment phase includes rifampicin, isoniazid, pyrazinamide, and ethambutol given for 3 months with streptomycin being added for the first 2 months, while the continuation phase includes 3 drugs (rifampicin, isoniazid, and ethambutol) and is extended to 5 months (2HRZES/1HRZE/5HRE). For those considered to be at high risk for multidrug-resistant infection, a regimen incorporating the use of second-line drugs is recommended (see below).

First-line drugs such as isoniazid, rifampicin, and particularly pyrazinamide may cause severe and possibly fatal drug-induced hepatitis. Further details covering hepatotoxicity and special precautions for use in patients with liver disorders are given in the respective drug monographs—see Isoniazid, p. 315.1; Rifampicin, p. 354.3; and Pyrazinamide, p. 348.2. UK[4] and US[6] guidelines recommend stopping all potentially hepatotoxic drugs if serum transaminases rise to more than 5 times the upper limit of normal or 3 times in the presence of symptoms of hepatitis or elevated bilirubin. Cautious sequential re-introduction of the same drugs (with or without pyrazinamide) after resolution of the biochemical abnormalities is often possible.[4,6,7] Patients in whom therapy is interrupted may be given streptomycin, ethambutol, and a fluoroquinolone until hepatotoxicity has resolved.[7]

Management of drug-resistant disease. The incidence of drug resistance amongst *M. tuberculosis* strains has increased over recent years typically in countries with poor tuberculosis control programmes.[9,10] Isoniazid and streptomycin resistance are the most prevalent. **Multidrug-resistant tuberculosis** (MDR-TB), caused by strains resistant to both isoniazid and rifampicin, requires a combination of first- and second-line drugs for at least 18 to 24 months (see below).[4,6,7,9] Drug-resistant tuberculosis is a reflection of poor tuberculosis management, control, and unreliable drug supply; it is difficult to treat, and not infrequently fatal, particularly in HIV-infected patients. Whereas the WHO DOTS programme may limit the development of MDR-TB, different strategies are required in areas where multidrug resistance is already established. These have been formulated by WHO in the **DOTS-plus** strategy for countries with well functioning tuberculosis control programmes.[11]

Patients with suspected or confirmed MDR-TB should receive a DOTS-plus regimen, which includes second-line

antituberculous drugs. These drugs are generally less effective and more toxic than standard therapy and need to be taken daily. They include injectable drugs such as the aminoglycosides (amikacin and kanamycin) and the polypeptide capreomycin, as well as further oral drugs such as the fluoroquinolones (levofloxacin, moxifloxacin, and ofloxacin), the diarylquinolines (bedaquiline fumarate), and bacteriostatic agents (aminosalicylic acid, cycloserine, ethionamide, protionamide, and terizidone). WHO advises that regimens should consist of at least 4 drugs with certain or almost certain efficacy, based on factors such as previous antituberculosis therapy, DST (where available), and country-specific drug-resistance patterns. Specific drugs should be chosen in hierarchical order based on potency and likely effectiveness; any suitable first-line oral drugs should be considered first, then addition of an injectable drug, a fluoroquinolone, and if necessary, 1 or more oral bacteriostatic drugs. Drugs that have potential for cross-resistance should not be used together.[7,9] Cross-resistance between rifampicin and rifabutin is common and rifabutin is therefore not recommended as a second-line drug. Cross-resistance between amikacin and kanamycin is also common, while cross-resistance is variable between the fluoroquinolones. Cross-resistance is complete between ethionamide and protionamide, and between cycloserine and terizidone.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis that is resistant to isoniazid and rifampicin and also resistant to fluoroquinolones and at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin).[12,13] XDR-TB can develop when the second-line drugs are misused or mismanaged and by early 2006 cases were being reported from every region in the world.[14] A report from the KwaZulu-Natal province of South Africa highlighted the risk for rapid death in HIV-infected persons with XDR-TB.[15] In this local case series, all but one of 53 patients died, and where the date of death could be confirmed the median survival was 16 days from the time of diagnosis. There are very limited clinical data available to guide treatment of XDR-TB, and management should always involve expert consultation. Although WHO[9] guidance for choice of treatment follows similar principles to those for MDR-TB, it may be impossible to construct an adequate regimen from among the usual first- and second-line drugs. Additional drugs such as clofazimine, linezolid, amoxicillin with clavulanic acid, thioacetazone, imipenem with cilastatin, or clarithromycin may have some activity against tuberculosis and should be considered in these cases, although their benefit remains unclear.

Children and infants can be treated with generally similar regimens to adults but with appropriate dose adjustments for age or body-weight.[4,6,16] While ethambutol is not usually given to young children because of the perceived difficulty in detecting ocular toxicity (see p. 299.1), a literature review[17] on its use in children found almost no ocular toxicity at daily doses of 15 to 30 mg/kg and it was considered safe in children of all ages.

Pregnancy, breast feeding, and the neonate. Tuberculosis, and especially drug-resistant tuberculosis, during pregnancy poses a serious risk to the mother, fetus, and neonate if not detected early and treated properly.[18] WHO recommends that pregnant women with tuberculosis are treated similarly to non-pregnant patients.[7] Fluoroquinolones, aminoglycosides, ethionamide, and protionamide are best avoided. Liver enzymes and symptoms of drug-induced hepatitis should be monitored.[4,6,18] Most antituberculous drugs may be used during breast feeding, but drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. WHO recommends that once active neonatal tuberculosis is ruled out, neonates of mothers with tuberculosis should receive preventative treatment with isoniazid for 6 months;[7,16] alternatively, isoniazid may be given for 3 months after which time the need for further treatment can be evaluated.[16] BCG vaccination is recommended when isoniazid is stopped.[7,16]

Co-infection with HIV increases the risk of patients developing both pulmonary and extrapulmonary tuberculosis, and mortality is higher than in HIV-negative patients in the absence of antiretroviral therapy. HIV patients (including children) with active pulmonary tuberculosis respond to short-course chemotherapy similarly to HIV-negative tuberculosis patients, and most can be treated with the standard 6-month regimen.[4,19-22] For most extrapulmonary infections, 6 to 9 months of therapy is recommended; 9 to 12 months is suggested for infections involving the bones and joints or CNS.[21] Although some experts endorse the use of either daily or intermittent dosing schedules in HIV-infected patients,[20,21] WHO[7] advises against intermittent dosing due to higher risk of treatment failure and relapse; dosing three times a week may be acceptable during the continuous phase of treatment if doses are directly observed. Treatment failures in HIV-infected patients have also been associated with reduced drug concentrations due to malabsorption of antimycobacterials.[23]

In HIV-infected patients with tuberculosis, adjunctive preventative therapy with co-trimoxazole has been associated with substantially lower mortality; WHO therefore recommends that co-trimoxazole be started as soon as possible after a diagnosis of tuberculosis, and continued for the duration of treatment.[7] Thioacetazone should not be used in HIV-positive patients because of the potential for severe skin toxicity.

In antiretroviral-naive patients, the issue of when to start antiretroviral treatment is controversial.[7,20-22] Although WHO has advised that antiretroviral treatment should be started a soon as possible after, and within the first 8 weeks of starting, tuberculosis treatment,[7] concerns include overlapping drug toxicity, drug interactions, pill burden, and risk for immune reconstitution syndrome; some clinicians may instead choose to base the decision on when to start antiretrovirals on the immune status of the patient.[20,21] In an open-label, randomised, controlled study[24] of 642 HIV-infected patients with CD4+ T lymphocyte counts < 500 cells/mm^3, starting antiretroviral therapy during tuberculosis treatment (during, or up to 4 weeks after completion of the intensive phase) led to significantly improved survival. The use of rifamycin-based regimens to treat tuberculosis is recommended as response rates are better compared with non-rifamycin-based regimens. However, drug interactions between rifamycins and antiretrovirals complicate the co-administration of HIV and tuberculosis treatment,[21,22,25] and certain combinations may require dose adjustment or be contra-indicated (for details of the interactions of rifampicin and antiretrovirals, see p. 355.2, and for those with rifabutin, see p. 352.1). It is important to note that guideline recommendations are based on pharmacokinetic studies, often performed in healthy subjects, rather than on studies of treatment outcome in patients. Paradoxical worsening of tuberculosis symptoms is common in HIV-infected patients who start antiretroviral therapy[26] and incidences of up to 35% have been noted.[25]

Adjunctive therapy. The inflammatory response to tuberculosis can cause considerable tissue damage and adjunctive corticosteroid therapy may be used to counter this. Corticosteroids are of little benefit in uncomplicated pulmonary tuberculosis. However, a systematic review[27] found that in tuberculous meningitis, adjunctive corticosteroids reduced the risk of death and disabling residual neurological deficit in HIV-negative patients. Systematic reviews of tuberculous pleurisy[28] and pericarditis,[29] have concluded that there is insufficient evidence to support the use of corticosteroids in these conditions. Nevertheless, WHO[19] suggests that corticosteroids may be useful adjuvants to antituberculous therapy for the management of tuberculous meningitis, pericarditis, pleural effusion, laryngitis, tuberculosis of the renal tract, adrenocortical insufficiency due to adrenal gland tuberculosis, and massive lymph node enlargement in both HIV-positive and -negative patients. Corticosteroids may also be useful for hypersensitivity reactions to antituberculous drugs. For further details on the possible role of corticosteroids as an adjunct to antituberculous therapy, see p. 1614.3.

Studies have suggested that injection of suspensions of killed *Mycobacterium vaccae* improved immune responsiveness in patients with pulmonary tuberculosis, although a systematic review[30] concluded that *M. vaccae* immunotherapy was of no benefit.

Prevention. Studies have found that *BCG vaccine* offers protection against serious forms of tuberculosis in children, such as miliary and meningeal tuberculosis, but has variable efficacy against pulmonary tuberculosis in adults. In high prevalence areas, vaccination is recommended for children at birth, except for children with HIV infection. For further information on BCG vaccine, see p. 2378.1.

Tuberculosis skin testing may identify persons with *latent M. tuberculosis* infection. Treatment of tuberculosis skin test-positive persons (also referred to as preventative therapy or chemoprophylaxis) reduces the risk of developing (reactivation) tuberculosis. Treatment is beneficial in HIV-infected patients, contacts of active cases, persons who have recently become tuberculosis skin test positive, and persons at high risk of disease. Chemoprophylaxis is not recommended routinely in developing countries where the priority is to detect and treat patients with active tuberculosis.[19,31] Latent tuberculosis has been treated with isoniazid or rifampicin given alone, or with rifampicin given with either isoniazid or pyrazinamide. Daily isoniazid for 6 to 12 months reduces the risk of active tuberculosis by 60 to 90%[1,32] and in HIV-infected, tuberculosis skin test-positive persons isoniazid for 6 months has also been shown to provide short-term protection against tuberculosis.[33] However, the combination of rifampicin and pyrazinamide has resulted in severe and fatal liver damage in HIV-negative persons and is no longer recommended for tuberculosis prophylaxis.[32,34,35] The American Thoracic Society and the CDC,[32,34] and NICE[5] have issued detailed recommendations for treatment of latent tuberculosis infection. Briefly, UK recommendations for HIV-negative adults and children over 2 years old are for either isoniazid alone for 6 months or isoniazid with rifampicin for 3 months; isoniazid alone for 6 months should be given to all HIV-positive patients. In the USA either isoniazid alone for 9 months (or 6 months in HIV-negative patients) or rifampicin alone for 4 months is recommended.

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Tularaemia

Tularaemia[1-4] is caused by the Gram-negative bacillus *Francisella tularensis*, an organism that mainly affects rodents and rabbits but may be transmitted to man, usually by handling infected animals or carcasses, or by the bites of insect vectors, or by ingestion of contaminated food or water. Tularaemia may also be caused by inhalation of airborne bacteria; there has been some concern about the potential use of airborne tularaemia as a biological weapon.

Symptoms usually appear 2 to 6 days after exposure, but can take up to 3 weeks. They depend on the route of exposure and may take several forms, the most common of which is the ulceroglandular. This is characterised by rash, ulceration at the site of inoculation, sudden onset of fever, chills, headache, muscle and joint pains, and lymphadenopathy. A glandular form without skin ulcers and a typhoidal (septicaemic) form are also seen, as are oculoglandular, oropharyngeal, and pneumonic forms. Possible complications of infection include endocarditis, hepatitis, meningitis, pericarditis, peritonitis, pneumonia, osteomyelitis, and sepsis and septic shock.

Parenteral streptomycin or gentamicin are considered the antibacterials of choice; treatment is usually given for about 10 days.[1-4] Tobramycin is not recommended. A tetracycline (such as doxycycline) or chloramphenicol have been given as alternatives but clinical relapses are more frequent than with the recommended aminoglycosides;[1-3] chloramphenicol is generally not recommended except in the treatment of tularaemia meningitis.[3] Fluoroquinolones have shown promise in treating tularaemia and ciprofloxacin, usually given orally for 10 days, is another suitable alternative,[1-4] especially for those patients who are allergic or intolerant of other treatments.

Oral doxycycline or oral ciprofloxacin given for 14 days are recommended for postexposure prophylaxis.[1]

A tularaemia vaccine is available in some countries for active immunisation against the disease.

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Typhoid and paratyphoid fever

Typhoid and paratyphoid fever are systemic infections caused respectively by *Salmonella typhi* and *S. paratyphi* A, B, or C, Gram-negative bacteria belonging to the Enterobacteriaceae family. They are sometimes termed collectively 'enteric fever' but, although initial infection is intestinal, dissemination in the blood leads to more widespread systemic effects. Typhoid and paratyphoid are endemic in many developing countries in Asia (particularly the southern regions), Africa, the Caribbean, and Central and South America, where they are associated with poor water supply and sanitary conditions. Most cases occurring in developed countries are contracted abroad. Infection is usually transmitted by ingestion of food or water contaminated with the faeces of infected individuals and the incubation period is generally 7 to 14 days. As well as non-specific symptoms such as fever and disturbances of bowel function, characteristic rose-coloured skin lesions may appear on the chest, abdomen, and back, and neuropsychiatric symptoms may occur. Severe typhoid reportedly develops in up to 10 to 15% of patients[1,2] and may be associated with serious complications including gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy.[1-3]

Treatment of typhoid fever has traditionally been with chloramphenicol or alternatively amoxicillin, ampicillin, or co-trimoxazole.[1] However, there has been a spread of *S. typhi* strains simultaneously resistant to all of these drugs (termed MDR strains)[4,5] in virtually all typhoid-endemic areas.[2] With widespread use of the fluoroquinolones to treat typhoid, resistance to these drugs is an increasing problem as well, particularly in Asia. Resistance may be total or partial; in the latter case, nalidixic acid-resistant (NAR) isolates typically appear sensitive to fluoroquinolones, however therapeutic use often results in clinical failure. As a result, some experts recommend nalidixic-acid resistance testing as a means of predicting reduced fluoroquinolone susceptibility.[2] Interestingly, there is some evidence that as fluoroquinolone resistance spreads, sensitivity to some of the older drugs used to treat the disease, such as chloramphenicol, may be returning.[6,7]

Treatment recommendations[2,5,8] emphasise the use of a fluoroquinolone such as ciprofloxacin or ofloxacin for initial treatment of both fully-sensitive, and MDR typhoid. Chloramphenicol, amoxicillin, and co-trimoxazole are now considered second-line drugs against fully susceptible strains, although there appears to be little sound evidence that fluoroquinolones are more effective against such isolates.[8,9]

Azithromycin, or third generation cephalosporins such as cefixime, cefotaxime, and ceftriaxone, are possible alternatives for both MDR and fluoroquinolone-resistant infections.[10] A systematic review found that azithromycin was associated with reduced clinical failure and shorter hospitalisation times than the fluoroquinolones, and reduced rate of relapse compared with ceftriaxone.[11] For infections caused by NAR isolates, the fluoroquinolones are still second-line alternatives, but higher doses and longer courses of treatment are advocated. Combination regimens have been investigated,[8] but a study in patients infected with strains showing both multidrug resistance and reduced susceptibility to fluoroquinolones found that azithromycin alone was preferable to azithromycin plus ofloxacin.[12]

Most treatment options used for uncomplicated typhoid are also considered suitable for severe cases, but again higher doses and longer treatment are recommended, and initial parenteral therapy is advised until at least 5 days after fever subsides.[2]

Although fluoroquinolones are not generally indicated in children because of potential toxicity, WHO considers that their benefits in typhoid fever outweigh any putative risk.[5] Azithromycin may also be given.[5] In pregnancy a beta-lactam such as ampicillin or one of the cephalosporins may be preferable,[5] although there are reports of the successful use of fluoroquinolones. WHO also suggests that although there is no evidence to suggest harm, azithromycin should not be used in pregnant or nursing women if alternatives are available.[5]

Patients who develop mental changes should be evaluated for meningitis; if typhoid meningitis is suspected, high-dose intravenous dexamethasone should be given in addition to antibacterial treatment.[5]

On recovery, typhoid patients may continue to excrete *S. typhi* in the faeces or urine for several weeks. Unlike these convalescent carriers, some 1 to 5% of patients become chronic carriers[5] who may excrete *S. typhi* for years without any symptoms. Eradication is difficult and prolonged treatment is necessary, but regimens using ciprofloxacin or norfloxacin for 4 weeks, or co-trimoxazole or a combination of probenecid with either amoxicillin or ampicillin for 6 to 12 weeks have all reportedly been effective.[1-3,5]

Typhoid vaccines are used for the **prevention** of typhoid fever, for details see p. 2422.2. No vaccine provides complete protection, however, and strict attention to personal, food, and water hygiene is important in preventing infection.[3]

Paratyphoid fever is less common and generally milder than typhoid fever. Treatment is similar; no licensed vaccines are currently available for prevention.

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Typhus

Rickettsial infections or fevers of the typhus group are transmitted to man by various insect vectors. Louse-borne or epidemic typhus, due to *Rickettsia prowazekii*, and flea-borne or murine typhus, due to the closely related *R. typhi* (*R. mooseri*), have occurred worldwide. Scrub typhus is due to *Orientia tsutsugamushi* (*R. tsutsugamushi*), transmitted by mites, and occurs mainly in Asia, Australia, and the Pacific Islands.

A tetracycline, often doxycycline, or chloramphenicol is the treatment of choice for these infections although strains of *O. tsutsugamushi* resistant to doxycycline and chloramphenicol have been reported in Thailand.[1,2] Ciprofloxacin may be an effective alternative,[3] and rifampicin has been shown to be more effective against scrub typhus than doxycycline.[4] Azithromycin[5,6] and telithromycin[7] have also been reported to be effective. Prophylaxis for scrub typhus with doxycycline has shown promise when started before exposure to infection.[8]

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Urethritis

Urethritis or urethral inflammation can result from infectious or noninfectious conditions. Infectious urethritis is a sexually transmitted disease seen most frequently in men. The most common causes are *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (termed nongonococcal urethritis or non-specific urethritis). Other organisms implicated have included *Mycoplasma genitalium* and *Ureaplasma urealyticum*. Gonococcal and chlamydial infections frequently occur together and if a specific clinical diagnosis cannot be made treatment for both infections should be given together otherwise postgonococcal urethritis due to *C. trachomatis* may follow the cure of gonorrhoea. For the treatment of gonococcal urethritis see Gonorrhoea (p. 204.2). For general management of chlamydial infections see p. 177.1.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of urethritis are as follows:

- **WHO:** for chlamydial urethritis:
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  alternative regimens for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily

  Unless it can be excluded, patients should also be treated concurrently for gonorrhoea (p. 204.2)
- **UK:** for nongonococcal urethritis:
  - a single oral dose of azithromycin 1 g, *or*
  - oral doxycycline 100 mg twice daily for 7 days

  alternative regimens are:
  - oral erythromycin 500 mg twice daily for 14 days
  - oral ofloxacin 400 mg daily in one single or two divided doses for 7 days

  Persistent or recurrent nongonococcal urethritis should be treated with:
  - oral azithromycin 500 mg to start then 250 mg daily for 4 days *plus* oral metronidazole 400 mg twice daily for 5 days, *or*
  - oral erythromycin 500 mg four times daily for 21 days *plus* oral metronidazole 400 mg twice daily for 5 days

  An alternative, second-line regimen is:
  - oral moxifloxacin 400 mg once daily for 10 days *plus* oral metronidazole 400 mg twice daily for 5 days
- **USA:** for nongonococcal urethritis:
  - as for the UK

  alternative regimens for 7 days, are:
  - oral erythromycin 500 mg four times daily
  - oral erythromycin ethylsuccinate 800 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral levofloxacin 500 mg once daily

  Persistent or recurrent nongonococcal urethritis should be treated with:
  - a single oral dose of either metronidazole 2 g or tinidazole 2 g *plus* oral azithromycin 1 g (if it was not used in the initial treatment regimen)

Sexual partners of patients with urethritis should be tested and treated.[2,3]

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Urinary-tract infections

Infections of the urinary tract are especially common in women. They are frequently due to enteric bacteria, in particular *Escherichia coli*, although a common cause in young women is *Staphylococcus saprophyticus*, a coagulase-negative staphylococcus. Other urinary pathogens include *Staph. epidermidis*, enterococci, and *Pseudomonas* spp. An arbitrary definition of urinary-tract infection has been significant bacteriuria with 10^5 or more colony forming units/mL of a midstream urine specimen; some also consider lower counts to be indicative of infection. Most urinary-tract infections are isolated uncomplicated infections of the lower urinary tract. Recurrent infections may be due to relapse, or more often, re-infection, and are more serious. Patients with complicated urinary-tract infections associated with urinary-tract abnormalities or diseases such as diabetes mellitus may be at risk of kidney damage.

Infections of the lower urinary tract in *women* generally present as cystitis (inflammation of the bladder) and symptoms include dysuria, frequency, and urgency with pyuria and significant bacteriuria; the urethral syndrome is similar, but there is no significant bacteriuria. In the upper urinary tract, acute pyelonephritis may occur as a complication of cystitis or, more rarely, may result from septicaemia. Asymptomatic bacteriuria may progress to acute pyelonephritis in *pregnant women* and should therefore be treated.

Urinary-tract infections in *men* are less common and are often associated with abnormalities of the genito-urinary tract such as prostatic hyperplasia. Acute bacterial prostatitis is usually caused by organisms similar to those responsible for cystitis in women. Chronic bacterial prostatitis is difficult to treat; the antibacterials used must be able to penetrate into the prostatic fluid. For other genito-urinary infections in men, see under Epididymitis, p. 181.2, and under Urethritis, p. 212.3.

In preschool *children*, especially girls, asymptomatic bacteriuria with vesicoureteric reflux can result in renal scarring and should be treated; the use of prophylactic antibacterials is complex and controversial. Long-term follow-up of girls who have had asymptomatic bacteriuria suggests that new kidney damage does not occur after 4 years of age, but highlights the importance of diagnosis and treatment in younger children.

The significance of asymptomatic bacteriuria in *old age* is disputed, but most consider treatment to be unnecessary.

Infections associated with *indwelling bladder catheters* occur in both men and women and probably account for the majority of hospital-acquired urinary-tract infections.

Treatment. Antibacterials used to treat urinary-tract infections need to be excreted in adequate concentrations in the urine. For *acute uncomplicated infections* oral amoxicillin, ampicillin, co-trimoxazole, nalidixic acid, nitrofurantoin, or trimethoprim (preferred to co-trimoxazole in the UK) have been given, although the choice will depend on local patterns of bacterial resistance; *E. coli* resistant to ampicillin and amoxicillin is widespread. Alternatives when resistance is prevalent include amoxicillin with clavulanic acid, oral cephalosporins, fluoroquinolones, or fosfomycin. In pregnant women, nitrofurantoin or a beta-lactam antibacterial can be used. Standard treatment schedules have been for 5 to 7 days; 3-day or single-dose regimens can also be effective and may be preferred in women. Single-dose treatment may be associated with reduced efficacy compared with 3-day regimens. Urinary alkalinising agents such as potassium citrate and sodium citrate have been given orally to relieve the pain of cystitis caused by lower urinary-tract infections. Recurrent infections may require long-term low-dose antibacterial prophylaxis.

Acute pyelonephritis may require broad-spectrum parenteral treatment initially with, for example, aztreonam, ceftazidime, cefuroxime, ciprofloxacin, or gentamicin.

Chronic bacterial prostatitis may require treatment for several weeks with trimethoprim, erythromycin, or a fluoroquinolone.

Catheter-related bladder infections may sometimes respond to localised treatment with bladder washouts containing chlorhexidine.

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Whipple's disease

Whipple's disease[1-3] (also known as intestinal lipodystrophy) is a rare, chronic, multisystem condition associated with infection with the Gram-positive bacillus *Tropheryma whipplei* (formerly *T. whippelii*). It most often affects the gastrointestinal system but other organs that may also be infected include the CNS, heart, joints, and eyes.

Whipple's disease mainly affects middle-aged white men and clinical signs and symptoms vary depending on the organ system affected. Symptoms include diarrhoea, steatorrhoea, abdominal pain, loss of appetite, weight loss, malabsorption, fever, and weakness. Arthritis, arthralgia, and myalgia often occur several years before gastrointestinal symptoms develop. About 10 to 40% of patients may also have neurological symptoms such as confusion, dementia, headache, memory impairment, or decreased level of consciousness.

Undiagnosed and untreated disease is progressive and fatal. However, appropriate long-term treatment with antibacterials results in rapid symptomatic improvement and lasting remission. Tetracycline was once considered the treatment of choice but relapse rates, especially CNS relapse, were high (up to 35%) and antibacterials that cross the blood-brain barrier are now generally recommended.[1-3] Induction treatment consists of a 2-week course of an

intravenous third-generation cephalosporin such as ceftriaxone, or a penicillin (either as intravenous benzylpenicillin or intramuscular procaine benzylpenicillin) with or without intramuscular streptomycin.[1-3] Intravenous meropenem has also been used successfully.[4] Patients allergic to ceftriaxone or penicillins may be treated with oral co-trimoxazole plus intramuscular streptomycin for 2 weeks.[3] The induction course is followed by long-term maintenance treatment with oral co-trimoxazole for 1 to 2 years.[1-3] An alternative oral maintenance regimen for those allergic to sulphonamides is doxycycline and hydroxychloroquine for more than 1 year.[3] Other alternative oral antibacterials that have been used for maintenance treatment are minocycline, tetracycline, phenoxymethylpenicillin,[1] or chloramphenicol. An exclusively oral treatment regimen of doxycycline and hydroxychloroquine for more than 1 year has been tried in some patients without CNS involvement; it has been suggested that in those with CNS involvement high dose sulfamethoxazole (which may be given as co-trimoxazole) or sulfadiazine should be added to the treatment regimen.[2,3]

Patients who relapse as a result of inadequate treatment may be re-treated with intravenous ceftriaxone or intravenous benzylpenicillin for 4 weeks, followed by an oral maintenance regimen for more than 1 year.[3] A patient with chronic Whipple's disease involving the CNS and refractory to antibacterial therapy was successfully treated with an induction course of ceftriaxone and chloramphenicol followed by long-term maintenance treatment with co-trimoxazole supplemented with interferon gamma.[5] Adjunctive treatment with interferon gamma has been suggested for patients who relapse despite appropriate treatment and who do not have inflammatory focal cerebral lesions.[3] Corticosteroids may be given to patients with cerebral lesions and to those with continued high fever after starting antibacterial treatment.[3]

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Yaws

See Syphilis, p. 205.2.

Yersinia enteritis

See p. 186.2.

Acediasulfone Sodium *(rINN)*

Acediasulfona sódica; Acédiasulfone Sodique; Acediasulfonnatrium; Acediasulfonum Natricum; Asediasulfoninatrium; Sodium Diaphenylsulphonacetate; Ацедиасульфон Натрий.

N-p-Sulphanilylphenylglycine sodium.

$C_{14}H_{13}N_2NaO_4S$=328.3

CAS — 127-60-6.

UNII — M45G7BJL52.

Profile

Acediasulfone sodium is reported to have antibacterial properties and is an ingredient of preparations used topically in the treatment of local infections of the ear.

Amikacin *(BAN, rINN)*

Amicacina; Amikacina; Amikacinas; Amikacine; Amikacinum; Amikacyna; Amikasiini; Амикацин.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-*N*[1]-[(2*S*)-4-amino-2-hydroxybutyryl]-2-deoxystreptamine.

$C_{22}H_{43}N_5O_{13}$=585.6

CAS — 37517-28-5.

ATC — D06AX12; J01GB06; S01AA21.

ATC Vet — QD06AX12; QJ01GB06; QS01AA21.

UNII — 84319SGC3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Amikacin). An antimicrobial substance obtained from kanamycin A. A white or almost white powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 9.5 to 11.5.

USP36: (Amikacin). A white crystalline powder. Sparingly soluble in water. pH of a 1% solution in water is between 9.5 and 11.5. Store in airtight containers.

Amikacin Sulfate *(BANM, USAN, rINNM)*

Amikacin Sulphate; Amikacina, sulfato de; Amikacin-disulfát; Amikacine, Sulfate d'; Amikacini Disulfas; Amikacini Sulfas; Amikacino sulfatas; Amikacinsulfat; Amikacin-szulfát; Amikacyny siarczan; Amikasiinisulfaatti; Amikasin Sülfat; BB-KB; Sulfato de amikacina; Амикацина Сульфат.

$C_{22}H_{43}N_5O_{13}.2H_2SO_4$=781.8

CAS — 39831-55-5.

ATC — D06AX12; J01GB06; S01AA21.

ATC Vet — QD06AX12; QJ01GB06; QS01AA21.

UNII — N6M33094FD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Amikacin Sulfate). A white or almost white powder. It loses not more than 13.0% of its weight on drying. Freely soluble in water; practically insoluble in alcohol and in acetone. The pH of a 1% solution in water is between 2.0 and 4.0. Store in airtight containers.

USP 36: (Amikacin Sulfate). Amikacin sulfate having a molar ratio of amikacin to H_2SO_4 of 1:2 contains the equivalent of not less than 674 micrograms and not more than 786 micrograms of amikacin per mg, calculated on the dried basis. Amikacin sulfate having a molar ratio of amikacin to H_2SO_4 of 1:1.8 contains the equivalent of not less than 691 micrograms and not more than 806 micrograms of amikacin per mg, calculated on the dried basis.

A white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 2.0 and 4.0 (1:2 salt) and 6.0 to 7.3 (1:1.8 salt). Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including amikacin, with beta lactams, see under Gentamicin Sulfate, p. 306.3. Amikacin is also reported to be incompatible with various other drugs. However, reports are contradictory in many cases, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Solutions may darken from colourless to pale yellow but this does not indicate a loss of potency.

Uses and Administration

Amikacin is a semisynthetic aminoglycoside antibacterial derived from kanamycin and is used similarly to gentamicin (p. 306.3) in the treatment of severe Gram-negative and other infections. It is given as the sulfate, and is generally reserved for the treatment of severe infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. Amikacin has also been given with antimycobacterials in the treatment of nontuberculous mycobacterial infections (p. 194.1) and multidrug-resistant tuberculosis (p. 210.2). As with gentamicin, amikacin may be used with penicillins and with cephalosporins; the injections should be given at separate sites.

Doses of amikacin sulfate are expressed in terms of amikacin base; 1.3 g of amikacin sulfate is equivalent to about 1 g of amikacin. Adults may be given 15 mg/kg daily in equally divided doses every 8 or 12 hours by intramuscular injection. In life-threatening infections, the dose may be increased up to a maximum of 500 mg every 8 hours. A dose of 7.5 mg/kg daily in two divided doses (equivalent to 250 mg twice daily) may be given for the treatment of uncomplicated urinary-tract infections. The same doses may be given by slow intravenous injection over 2 to 3 minutes, or by intravenous infusion.

For details of doses in children, see p. 216.3.

Treatment should preferably not continue for longer than 7 to 10 days, and the total dose given to adults should not exceed 15 g. Peak plasma concentrations greater than 30 to 35 micrograms/mL or trough plasma concentrations greater than 5 to 10 micrograms/mL should be avoided. Dosage should be adjusted in all patients according to plasma-amikacin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p. 307.2. See also Administration, p. 216.2. As with some other aminoglycosides, once-daily and extended-interval dose regimens have been used successfully with amikacin without increasing toxicity, but local guidelines should be consulted (see also Once-daily and Extended-interval Dose Regimens, p. 307.2).

A 0.25% solution has been instilled into body cavities in adults.

An inhaled liposomal formulation of amikacin is under investigation for the management of chronic lung infections such as nontuberculous mycobacteria and those caused by *Pseudomonas*.

Administration. It has been suggested that in patients with severe sepsis or septic shock, in whom the volume of distribution may be markedly increased, an initial intravenous loading dose of amikacin 25 mg/kg total body weight should be given, since standard doses of 15 mg/kg may not achieve therapeutic peak concentrations; however, evidence from a prospective open study in ICU patients[1] suggested that even with the higher dose, serum concentrations of amikacin were too low in about one-third of the patients. Subsequent doses should be determined on the basis of therapeutic drug monitoring.

1. Taccone FS, *et al*. Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. *Crit Care* 2010; **14:** R53.

Administration in children. Amikacin is licensed for use in neonates, infants, and children and may be given by intramuscular or intravenous injection or by intravenous infusion. For *severe infections caused by susceptible* bacteria in children beyond the newborn period, the American Academy of Pediatrics (AAP)[1] suggests an intravenous or intramuscular dose of amikacin of 15 to 22.5 mg/kg daily, in 3 divided doses.

For the treatment of *serious Gram-negative infections resistant to gentamicin* in infants and children the *BNFC* suggests:

- a **multiple daily dose regimen** of amikacin by slow intravenous injection over at least 3 to 5 minutes
  - in those 1 month to 12 years of age: 7.5 mg/kg every 12 hours
  - children 12 years of age and older: 7.5 mg/kg every 12 hours; in severe infections the dose may be increased to 7.5 mg/kg every 8 hours to a maximum dose of 500 mg every 8 hours for up to 10 days, *or*
- a **once-daily dose regimen** (other than for endocarditis or meningitis) given by intravenous injection or infusion of 15 mg/kg adjusted according to serum-amikacin concentration in those from 1 month of age

In the management of pseudomonal lung infection in *cystic fibrosis* the *BNFC* suggests a multiple daily dose regimen of amikacin given by slow intravenous injection or infusion, of 10 mg/kg every 8 hours (to a maximum dose of 500 mg every 8 hours) in those from 1 month of age.

For *neonatal sepsis* the *BNFC* suggests:

- an **extended-interval dose regimen** of 15 mg/kg every 24 hours by slow intravenous injection or intravenous infusion, *or*
- a **multiple daily dose regimen** of 10 mg/kg as a loading dose, followed by 7.5 mg/kg every 12 hours by intramuscular or slow intravenous injection or by infusion

An alternative regimen based on the age and birth-weight of the neonate is suggested by the AAP;[1] doses may be given by intramuscular or intravenous injection:

- for neonates aged ⩽7 days and weighing ⩽2 kg: 15 mg/kg every 48 hours
- for neonates aged ⩽7 days and weighing >2 kg: 15 mg/kg every 24 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 15 mg/kg every 24 to 48 hours; a dosing interval of 48 hours may be used until 2 weeks of life in extremely low birth-weight neonates (those weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 15 mg/kg every 12 to 24 hours

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 308.2. Peak plasma concentrations of amikacin greater than 30 to 35 micrograms/mL or trough concentrations greater than 5 to 10 micrograms/mL should be avoided. Comparisons with equipotent doses found that amikacin affects auditory (cochlear) function to about the same extent as gentamicin.

Effects on the eyes. A report of retinal damage after intravitreal injection of amikacin.[1]

1. Jackson TL, Williamson TH. Amikacin retinal toxicity. *Br J Ophthalmol* 1999; **83:** 1199–1200.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amikacin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Gentamicin Sulfate, p. 309.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 309.2. Amikacin is active against a similar range of organisms although it is also reported to have some activity against *Nocardia asteroides*, *Mycobacterium tuberculosis*, and some atypical mycobacterial

strains. Amikacin is not degraded by many of the common enzymes often responsible for acquired aminoglycoside resistance. In consequence, cross-resistance with gentamicin and other aminoglycosides is infrequent and amikacin may be effective against strains resistant to other aminoglycosides. However, resistant strains of Gram-negative bacteria and staphylococci have been reported, and it is generally reserved for infections resistant to other aminoglycosides, although reports differ as to the extent and speed of the development of amikacin resistance where it has been widely used.

References.
1. Ho YH, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p. 309.3.

On intramuscular injection, peak plasma-amikacin concentrations of about 20 micrograms/mL occur 1 hour after a 500-mg dose, reducing to about 2 micrograms/mL 10 hours after injection. A plasma concentration of 38 micrograms/mL has been reported after the intravenous infusion of 500 mg over 30 minutes, reducing to 18 micrograms/mL 1 hour later. Amikacin has been detected in body tissues and fluids after injection; it crosses the placenta but does not readily penetrate into the CSF, although substantial penetration of the blood-brain barrier has been reported in children with meningitis.

A plasma half-life of about 2 to 3 hours has been reported in patients with normal renal function. Most of a dose is excreted by glomerular filtration in the urine within 24 hours.

References.
1. Vanhaeverbeek M, *et al.* Pharmacokinetics of once-daily amikacin in elderly patients. *J Antimicrob Chemother* 1993; **31:** 185–7.
2. Gaillard J-L, *et al.* Cerebrospinal fluid penetration of amikacin in children with community-acquired bacterial meningitis. *Antimicrob Agents Chemother* 1995; **39:** 253–5.
3. Bressolle F, *et al.* Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother* 1996; **40:** 1682–9.
4. Canis F, *et al.* Pharmacokinetics and bronchial diffusion of single daily dose amikacin in cystic fibrosis patients. *J Antimicrob Chemother* 1997; **39:** 431–3.
5. Tod M, *et al.* Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. *Antimicrob Agents Chemother* 1998; **42:** 849–56.
6. Tréluyer JM, *et al.* Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother* 2002; **46:** 1381–7.
7. Okusanya OO, *et al.* Pharmacokinetic and pharmacodynamic evaluation of liposomal amikacin for inhalation in cystic fibrosis patients with chronic pseudomonal infection. *Antimicrob Agents Chemother* 2009; **53:** 3847–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biklin†; Greini; Riklinak; ***Austral.***: Amikin†; ***Austria***: Biklin; ***Belg.***: Amukin; ***Braz.***: Amicilon; Klebicil; Novamin; ***China***: Mi Li Xian (米丽先); Mi Ying Jie (米英杰); ***Cz.***: Amikin; ***Fin.***: Biklin; ***Fr.***: Amiklin†; ***Ger.***: Biklin†; ***Gr.***: Amicagel; Amicasil; Amikan; Biorisan; Briklin; Brucelin; Cinegel; Consumonit; Durocin; Farcyclin; Flexelite; Fromentyl; Kancin-Gap; Lanomycin; Lifermycin; Likacin; Medilen; Micalpha; Orlobin; Remikin; Rovericlin; Selaxa; Uzix; Xylanal; ***Hong Kong***: Amikin; ***Hung.***: Amikin†; Likacin; ***India***: Acil; Afcin; Alkanit; Alnamik; Amcin; Amexel; Amiact; Amibiotic; Amic; Amicaba; Amicin; Amicip; Amicom; Amijet; Amikable; Amikas; Amikater; Amikavel; Amikcin; Amikef; Amikin; Amilab; Amimac; Amimax; Aminocin; Amiron; Amistar; Amister; Amisulf; Amitax; Amivir; Amiz; Amiza; AMK; Amoka; Amricin; Amtop; Amzo; Anamika; Antinag; Arimic; Atmika; Avikacin; Avmik; Axcin; Bekacin; Blocin; Cadicin; Cinamica; Cinas; Coskacin; Curesin; D-Cin; Elcin; Elmik; Emcin; Emica; Emka; Endocin; Erkacin; Erocin; Erymik; Estacin; Eumik; Fokin; Fymika; Gabacin; Gekacin; Gemka; Glomika; Glykacin; Hosik; Icin; Ideg; Ikacin; Ikka; Inkacin; Ivimicin; Jyomik; Kacina; Kam; Kamsa; Kasino; Kawacin; Lemicin; Lexcin; Litomik; Lupamik; M-Cinn; Malaracin; MBKacin; Medcin; Megamica; Mepcin; Mica; Micare; Micin; Mikabit; Mikacin; Mikafine; Mikaject; Mikaphar; Mikastar; Mikatax; Miker; Mikif; Mikka; Mini; Mishacin; MKCN; Narish; NBCin; Nicin; Niksin; Nimicin; Nimika; Niskacin; Nosomik; Orkacin; Osin; ***Indon.***: Alostil; Amikin†; Glybotic; Mikasin; ***Irl.***: Amikin; ***Ital.***: Amicasil; Amik†; Amikan; BB-K8†; Chemacin; Dramigel; Likacin; Lukadin; Mediamik; Migracin; Mikan; Mikavir†; Nekacin; ***Malaysia***: Apalin; ***Mex.***: Agnicin; Akacin; Amicina; Amikafur; Amikalem†; Amikasons; Amikavi; Amikayect; Amikin; Amiyec; AMK; Beramikin; Biclin; Biokacin; Gamikal; Kafran†; Kana; Karmikin; Libamic; Lisobac; Mikazul†; Oprad; Plokim†; Sermicina; Tetralin; Yectamid†; ***NZ***: Amikin†; ***Philipp.***: Amikacide; Amikin†; Amitax; Cidacid; Cinmik; Kamin; Kormakin; Mikasul; Nica; Panmikin; ***Pol.***: Amikin; Biodacyna; ***Port.***: Amic; Biclin†; Kamina; ***Rus.***: Amikozit (Амикозит)†; Chemacin (Хемацин); Selemycin (Селемицин); ***S.Afr.***: Amikin; Kacinth-A†; ***Spain***: Biclin†; ***Swed.***: Biklin; ***Switz.***: Amikin; ***Thai.***: Akacin; Akicin; Amikin†; Anbikin†; Siamik; Tipkin; Tybikin; ***Turk.***: Amijeksin; Amiketem†; Amiklin; Amikozit; Mikasin†; ***UAE***: Mikacin; ***UK***: Amikin; ***Ukr.***: Amicil (Амицил); ***USA***: Amikin†; ***Venez.***: Amikavax; Behkacin; Biklin; Likacin.

Multi-ingredient Preparations. ***India***: Mikapime; Nicpime-AM; ***Ukr.***: Inflarax (Инфларакс).

Pharmacopoeial Preparations
BP 2014: Amikacin Injection;
USP 36: Amikacin Sulfate Injection.

Aminosalicylic Acid

Acidum Aminosalicylicum; Aminosalicílico, ácido; 4-Aminosalicylic Acid; Aminosalicylsyra; Aminosalisyylihappo; Aminosalylum; Para-aminosalicylic Acid; PAS; Pasalicylum; Аминосалициловая Кислота.

4-Amino-2-hydroxybenzoic acid.

$C_7H_7NO_3$=153.1

CAS — 65-49-6.

ATC — J04AA01.

ATC Vet — QJ04AA01.

UNII — 5B2658E0N2.

NOTE. Distinguish from 5-aminosalicylic acid (Mesalazine, p. 1862.2).

Pharmacopoeias. In *US*.

USP 36: (Aminosalicylic Acid). A white or practically white, bulky powder that darkens on exposure to light and air; it is odourless or has a slight acetous odour. Slightly soluble in water and in ether; soluble in alcohol; practically insoluble in benzene. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a saturated solution in water is between 3.0 to 3.7. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Calcium Aminosalicylate

Aminosalicilato cálcico; Aminosalicylate calcium; Aminosalylcalcium; Aminosalylkalcium; Aminosalyylikalsium; Calcii Aminosalicylas; Calcii Para-aminosalicylas; Calcium Para-aminosalicylate; Calcium PAS; Kalciumaminosalicylat; Kalsiumaminosalisylaatti; Аминосалицилат Кальция.

Calcium 4-amino-2-hydroxybenzoate trihydrate.

$(C_7H_6NO_3)_2Ca,3H_2O$=398.4

CAS — 133-15-3 (anhydrous calcium aminosalicylate).

ATC — J04AA03.

ATC Vet — QJ04AA03.

UNII — 9VF16M7FWU.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Sodium Aminosalicylate

Aminosalicilato sódico; Aminosalicylan sodný dihydrát; Aminosalicylate Sodium; Aminosalylnatrium; Monosodium 4-Aminosalicylate Dihydrate; Natrii Aminosalicylas; Natrii Aminosalicylas Dihydricus; Natrii Para-aminosalicylas; Natrii Paraaminosalicylas; Natrio aminosalicilatas dihidratas; Natriumaminosalicylat; Natriumaminosalicylatdihydrat; Natriumaminosalisylaatti; Natriumaminosalisylaattidihydraatti; Pasalicylum Solubile; Sodium (aminosalicylate de) dihydraté; Sodium Para-aminosalicylate; Sodium PAS; Sodu aminosalicylan; Аминосалицилат Натрия.

Sodium 4-amino-2-hydroxybenzoate dihydrate.

$C_7H_6NNaO_3,2H_2O$=211.1

CAS — 133-10-8 (anhydrous sodium aminosalicylate); 6018-19-5 (sodium aminosalicylate dihydrate).

ATC — J04AA02.

ATC Vet — QJ04AA02.

UNII — S38B9W6AXW.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Sodium Aminosalicylate Dihydrate). A slightly hygroscopic, white or almost white, crystalline powder, or white or almost white crystals. Freely soluble in water; sparingly soluble in alcohol, practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.

USP 36: (Aminosalicylate Sodium). A white to cream-coloured, practically odourless crystalline powder. Soluble 1 in 2 of water; sparingly soluble in alcohol; very slightly soluble in chloroform and in ether. Its solutions decompose slowly and darken in colour. Prepare solutions within 24 hours of use. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a 2% solution in water is between 6.5 and 8.5. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Stability. Aqueous solutions of aminosalicylates are unstable and should be freshly prepared.

Solutions of sodium aminosalicylate in sorbitol or syrup degraded more quickly to *m*-aminophenol than those in glycerol or propylene glycol.[1] Colour developed in all solutions but was not found to be an accurate indicator of decomposition of sodium aminosalicylate as it reflected only oxidation of *m*-aminophenol.

1. Blake MI, *et al.* Effect of vehicle on the stability of sodium aminosalicylate in liquid dosage forms. *Am J Hosp Pharm* 1973; **30:** 441–3.

Uses and Administration

Aminosalicylic acid and its salts are second-line antimycobacterials given orally in the treatment of multidrug-resistant **tuberculosis** (p. 210.2). They should always be given with other antituberculous drugs.

Aminosalicylic acid may be given as the acid or as the sodium salt. Sodium aminosalicylate 1.38 g is equivalent to about 1 g of aminosalicylic acid. However, a usual daily oral dose of 8 to 12 g in 2 or 3 divided doses has been recommended both for products containing the acid and those containing the sodium salt.

For details of doses in children, see p. 217.3.

Like 5-aminosalicylic acid (see Mesalazine, p. 1862.2), sodium aminosalicylate is also used in the treatment of **ulcerative colitis** (see Inflammatory Bowel Disease, p. 217.3). It is given rectally in a usual dose of 2 g once daily.

Attempts have been made in formulation to overcome the bulk and exceedingly unpleasant taste of the aminosalicylates. The salts appear to be better tolerated than the free acid and solutions in iced water prepared immediately before use may be less unpleasant to take.

References.
1. Anonymous. Para-aminosalicylic acid. *Tuberculosis (Edinb)* 2008; **88:** 137–8.

Administration. A small study suggested that giving aminosalicylic acid in a dose of 4 g twice daily produced adequate serum concentrations (well in excess of 1 microgram/mL, a typical MIC against *Mycobacterium tuberculosis*) for up to 12 hours after each dose.[1] The drug was taken with an acidic beverage such as fruit juice to prevent early release in the stomach. A single 4-g dose was not sufficient to maintain serum concentrations for the full 24-hour dosage interval. The authors had subsequently changed their practice to use a twice-daily regimen for aminosalicylic acid in patients with multidrug-resistant tuberculosis.

1. Peloquin CA, *et al.* Once-daily and twice-daily dosing of p-aminosalicylic acid granules. *Am J Respir Crit Care Med* 1999; **159:** 932–4.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] and WHO[2] suggest an oral dose of para-aminosalicylic acid 200 to 300 mg/kg daily, given in 2 to 4 divided doses, to a maximum dose of 10 g daily.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008.* Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 08/06/10)

Administration in renal impairment. It has been recommended that aminosalicylic acid should be avoided in patients with renal impairment.[1] An increase in plasma clearance of aminosalicylic acid (attributed to increased hepatic metabolism) has been noted in patients with renal impairment, hence attempting to give aminosalicylate in reduced doses to such patients may lead to subtherapeutic serum concentrations.[2]

1. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (first of three parts). *N Engl J Med* 1977; **296:** 663–70.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.

Inflammatory bowel disease. Derivatives of 5-aminosalicylic acid and corticosteroids are the mainstays of the treatment of inflammatory bowel disease (p. 1811.3). However, aminosalicylic acid (4-aminosalicylic acid) has also been investigated, and beneficial results have been reported with both enemas[1-4] and oral dose forms[5] in ulcerative colitis. Three patients who developed acute pancreatitis while taking mesalazine (5-aminosalicylic acid) for inflammatory bowel disease, later tolerated treatment with 4-aminosalicylic acid enemas.[6]

1. Campieri M, *et al.* 4-Aminosalicylic acid (4-ASA) and 5-aminosalicylic acid (5-ASA) in topical treatment of ulcerative colitis patients. *Gastroenterology* 1984; **86:** 1039.
2. Ginsberg AL, *et al.* Treatment of left-sided ulcerative colitis with 4-aminosalicylic acid enemas: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 195–9.
3. Sharma MP, Duphare HV. 4-Aminosalicylic acid enemas for ulcerative colitis. *Lancet* 1989; **i:** 450.
4. O'Donnell LJD, *et al.* Double blind, controlled trial of 4-aminosalicylic acid and prednisolone enemas in distal ulcerative colitis. *Gut* 1992; **33:** 947–9.
5. Beeken W, *et al.* Controlled trial of 4-ASA in ulcerative colitis. *Dig Dis Sci* 1997; **42:** 354–8.
6. Daniel F, *et al.* Tolerance of 4-aminosalicylic acid enemas in patients with inflammatory bowel disease and 5-aminosalicylic-induced acute pancreatitis. *Inflamm Bowel Dis* 2004; **10:** 258–60.

Manganese toxicity. Intravenous aminosalicylic acid, given as the sodium salt in a course of 6 g daily for 4 days a week, for fifteen courses, produced significant benefit in a patient with parkinsonism induced by chronic occupational manganese exposure.[1] The patient remained well on prolonged follow-up. Other cases of benefit had been reported in the Chinese literature.

1. Jiang Y-M, *et al.* Effective treatment of manganese-induced occupational Parkinsonism with p-aminosalicylic acid: a case of 17-year follow-up study. *J Occup Environ Med* 2006; **48:** 644–9.

Adverse Effects and Treatment

Aminosalicylic acid and its salts may cause the adverse effects of salicylates (see Aspirin, p. 24.2).

Gastrointestinal effects are common and include nausea, vomiting, and diarrhoea; they may be reduced by giving doses with food or with an antacid but occasionally may be severe enough that therapy has to be stopped. Alteration of gastrointestinal function may lead to malabsorption of vitamin B_{12}, folate, and lipids.

Hypersensitivity reactions have been reported in 5 to 10% of adults, usually during the first few weeks of treatment, and include fever, and rashes; arthralgia, lymphadenopathy, and hepatosplenomegaly are less common and a syndrome resembling infectious mononucleosis occurs rarely. Other adverse effects which have been attributed to a hypersensitivity reaction to aminosalicylate include jaundice and encephalitis. Blood disorders reported include haemolytic anaemia in patients with G6PD deficiency, agranulocytosis, eosinophilia, leucopenia, and thrombocytopenia. Psychosis may occasionally occur. Prolonged treatment may induce goitre and hypothyroidism. Crystalluria may occur.

Effects on the liver. Drug-induced hepatitis occurred in 0.32% of 7492 patients receiving antituberculous drugs; aminosalicylic acid was the most common cause.[1]

1. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. *Q J Med* 1975; **44:** 1–16.

Precautions

Aminosalicylic acid and its salts should be used with great care in patients with hepatic or renal impairment and in patients with gastric ulcer. They should be given with caution to patients with G6PD deficiency. The sodium salt should be used with caution in patients with heart failure.

Aminosalicylates interfere with tests for glycosuria using copper reagents and for urobilinogen using Ehrlich's reagent.

Breast feeding. Small amounts of aminosalicylic acid are present in breast milk. A maximum concentration of 1.1 microgram/mL has been reported in the breast milk of a woman 3 hours after a 4-g dose of aminosalicylic acid.[1]

1. Holdiness MR. Antituberculosis drugs and breast feeding. *Arch Intern Med* 1984; **144:** 1888.

Pregnancy. The use of aminosalicylic acid or its salts is not recommended in pregnant patients due to gastrointestinal intolerance.[1] In addition it has been noted that a study published in 1964 suggested first-trimester exposure might be associated with congenital defects, although other studies had not found similar effects.[2]

1. Snider D. Pregnancy and tuberculosis. *Chest* 1984; **86:** 10S–13S.
2. *et al. Drugs in pregnancy and lactation,* 8th ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2008.

Interactions

The adverse effects of aminosalicylates and salicylates may be additive. Probenecid may also increase toxicity by delaying renal excretion and enhancing plasma concentrations of aminosalicylate. The activity of aminosalicylic acid may be antagonised by ester-type local anaesthetics such as procaine.

Antimicrobial Action

Aminosalicylic acid is bacteriostatic and is active against *M. tuberculosis*. Other mycobacteria are usually resistant. It has a relatively weak action compared with other antituberculous drugs. Resistance develops quickly if aminosalicylic acid is used alone.

References.

1. Rengarajan J, *et al.* The folate pathway is a target for resistance to the drug para-aminosalicylic acid (PAS) in mycobacteria. *Mol Microbiol* 2004; **53:** 275–82.

Pharmacokinetics

When given orally, aminosalicylic acid and its salts are readily absorbed, and peak plasma concentrations occur after about 1 to 4 hours.

Aminosalicylate diffuses widely through body tissues and fluids, although diffusion into the CSF occurs only if the meninges are inflamed. About 15% of the sodium salt, and 50 to 70% of the acid, is bound to plasma proteins.

Aminosalicylate is metabolised in the intestine and liver mainly by acetylation. Urinary excretion is rapid, and 80% or more of a dose is excreted within 24 hours; 50% or more of the dose is excreted as the acetylated metabolite. The half-life of aminosalicylic acid is about 1 hour.

Aminosalicylate is distributed into breast milk (see under Precautions, above, for more details).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Aflogol; ***Fr.***: Paser; Quadrasa; ***Ger.***: Pas-Fatol N; ***Gr.***: Paser; ***India***: Monopas; ***Ital.***: Salf-Pas; ***Port.***: Paramino-Corazida; ***Rus.***: Aquapask (Аквапаск); Mac-Pas (Мак-Пас); Monopas (Монопас); Pas-Fatol N (Пас-Фатол Н); Pasconat (Пасконат); Paser (Пазер); Pask (ПАСК); Pask-Akri (Паск-Акри); ***Thai.***: PAS Sodium; ***Turk.***: PAS; ***Ukr.***: Pasconat (Пасконат); ***USA***: Paser.

Multi-ingredient Preparations. ***India***: Inapas; Mycospas; ***Rus.***: Isopask (Изопаск); Mac-Pas Plus (Мак-Пас Плюс).

Pharmacopoeial Preparations
USP 36: Aminosalicylate Sodium Tablets; Aminosalicylic Acid Tablets.

Amoxicillin *(BAN, rINN)*

Amoksisilin; Amoksisilliini; Amoxicilina; Amoxicilline; Amoxicillinum; Amoxycillin; Амоксициллин.

(6*R*)-6-[α-D-(4-Hydroxyphenyl)glycylamino]penicillanic acid.

$C_{16}H_{19}N_3O_5S$=365.4

CAS — 26787-78-0.

ATC — J01CA04.

ATC Vet — QG51AX01; QJ01CA04.

UNII — 9EM05410Q9.

Amoxicillin Sodium *(BANM, USAN, rINNM)*

Amoksicilino natrio druska; Amoksisilin Sodyum; Amoksisilliininatrium; Amoksycylina sodowa; Amoxicilin sodná sůl; Amoxicilina sódica; Amoxicillin-Natrium; Amoxicilline Sodique; Amoxicillinnatrium; Amoxicillin-nátrium; Amoxicillinum natricum; Amoxycillin Sodium; BRL-2333AB-B; Natrii Amoxicillinum; Натрий Амоксициллин.

$C_{16}H_{18}N_3NaO_5S$=387.4

CAS — 34642-77-8.

ATC — J01CA04.

ATC Vet — QJ01CA04.

UNII — 544Y3D6MYH.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Amoxicillin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

Amoxicillin Trihydrate *(BANM, rINNM)*

Amoksicilinas trihidratas; Amoksisilin Trihidrat; Amoksisilliinitrihydraatti; Amoksycylina trójwodna; Amoxicilin trihydrát; Amoxicilina trihidrato; Amoxicillin (USAN); Amoxicillin-Trihydrat; Amoxicilline Trihydratée; Amoxicillin-trihidrát; Amoxicillintrihydrat; Amoxicillinum Trihydricum; Amoxycillin Trihydrate; BRL-2333; Амоксициллин Тригидрат.

$C_{16}H_{19}N_3O_5S,3H_2O$=419.4

CAS — 61336-70-7.

ATC — J01CA04.

ATC Vet — QJ01CA04.

UNII — 804826J2HU.

NOTE. Compounded preparations of amoxicillin may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Amoxicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in fatty oils. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 0.2% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Amoxicillin). A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 0.2% solution in water is between 3.5 and 6.0. Store in airtight containers.

Uses and Administration

Amoxicillin is the 4-hydroxy analogue of ampicillin (p. 220.3) and is used similarly in susceptible infections. These include actinomycosis, anthrax, biliary-tract infections, bronchitis, endocarditis (particularly for prophylaxis), gastro-enteritis (including salmonella enteritis, but not shigellosis), gonorrhoea, Lyme disease, mouth infections, otitis media, pneumonia, spleen disorders (pneumococcal infection prophylaxis), typhoid and paratyphoid fever, and urinary-tract infections. The beta-lactamase inhibitor clavulanic acid (p. 270.3) widens amoxicillin's antimicrobial spectrum and a combined preparation (co-amoxiclav) can be used when resistance to amoxicillin is prevalent, for example in respiratory-tract infections due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), in the empirical treatment of animal bites, or in melioidosis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Amoxicillin is also given as part of treatment regimens to eradicate *Helicobacter pylori* infection in patients with peptic ulcer disease (p. 1816.2).

Amoxicillin is given orally as the trihydrate and by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of amoxicillin; 1.06 g of amoxicillin sodium and 1.15 g of amoxicillin trihydrate are each equivalent to about 1 g of amoxicillin.

The usual *oral* dose is 250 to 500 mg every 8 hours, or 500 to 875 mg every 12 hours. Higher oral doses of amoxicillin, either as a single dose or in short courses, are used in some conditions. For example, a dose of 3 g repeated once after 8 hours may be used for dental abscesses. A 3-g dose may be given for uncomplicated acute urinary-tract infections, and repeated once after 10 to 12 hours.

A high-dose regimen of 3 g twice daily may be used in patients with severe or recurrent infections of the respiratory tract. Amoxicillin has also been given as a single dose of 3 g, with probenecid 1 g, in the treatment of uncomplicated gonorrhoea in areas where gonococci remain sensitive.

For the prophylaxis of endocarditis in patients at risk, amoxicillin 2 or 3 g may be given about 1 hour before dental procedures. However, in the UK, NICE suggests that such prophylaxis is unnecessary (see p. 179.2).

For the eradication of *H. pylori*, amoxicillin is given with either metronidazole or clarithromycin and a proton pump inhibitor; usual doses of amoxicillin are 0.75 or 1 g twice daily or 500 mg three times daily.

An extended-release formulation containing 775 mg of amoxicillin as the trihydrate is available in the USA for the treatment of tonsillitis and pharyngitis due to *Streptococcus pyogenes* in patients aged 12 years or older. It is given orally in a dose of 775 mg daily for 10 days.

Amoxicillin is given by *intramuscular* or slow *intravenous* injection in doses of 500 mg every 8 hours. In severe infections, 1 g of amoxicillin may be given every 6 hours by slow intravenous injection over 3 to 4 minutes or by infusion over 30 to 60 minutes.

For details of doses in children, see p. 218.3.

Doses may need to be reduced in moderate to severe renal impairment (see p. 219.1).

Amoxicillin with clavulanic acid. Amoxicillin combined with clavulanic acid (co-amoxiclav) is given orally in a ratio of amoxicillin (as the trihydrate) 2, 4, 7, or 14 parts to 1 part of clavulanic acid (as the potassium salt), or intravenously in a ratio of 5 parts of amoxicillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses of the combination, calculated on amoxicillin content, are similar to those for amoxicillin used alone.

References.

1. Speller DCE, *et al.* , eds. Clavulanate/β-lactam antibiotics: further experience. *J Antimicrob Chemother* 1989; **24** (suppl B): 1–226.
2. Todd PA, Benfield P. Amoxicillin/clavulanic acid: an update of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1990; **39:** 264–307.
3. Malik ZA, Litman N. Ampicillin and amoxicillin. *Pediatr Rev* 2006; **27:** 434–6.
4. Geddes AM, *et al.* Introduction: historical perspective and development of amoxicillin/clavulanate. *Int J Antimicrob Agents* 2007; **30** (suppl 2): S109–S112.
5. Ball P. The clinical development and launch of amoxicillin/clavulanate for the treatment of a range of community-acquired infections. *Int J Antimicrob Agents* 2007; **30** (suppl 2): S113–S117.
6. Thanaviratananich S, *et al.* Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 06/08/09).
7. Salvo F, *et al.* Amoxicillin and amoxicillin plus clavulanate: a safety review. *Expert Opin Drug Safety* 2009; **8:** 111–8.

Administration in children. Amoxicillin may be given to neonates and children for the treatment of infections caused by susceptible organisms. It may be given orally, by intramuscular injection, by slow intravenous injection over 3 to 4 minutes, or by intermittent intravenous infusion over 30 to 60 minutes.

For the treatment of susceptible infections including urinary-tract infections, sinusitis, uncomplicated community-acquired pneumonia, oral infections, Lyme disease, and salmonellosis, the *BNFC* suggests the following *oral* doses for neonates and children; these may be doubled in severe or serious infections:

- 7 to 28 days of age: 30 mg/kg (to a maximum of 62.5 mg) 3 times daily
- 1 month to 1 year of age: 62.5 mg 3 times daily
- 1 to 5 years of age: 125 mg 3 times daily
- from 5 years of age: 250 mg 3 times daily The *BNFC* also recommends the following *intravenous* dose ranges for neonates and children which may be doubled in severe or serious infections:
- neonates: 30 mg/kg, given every 12 hours for neonates less than 7 days of age and every 8 hours for those 7 to 28 days of age
- from 1 month of age: 20 to 30 mg/kg (to a maximum of 500 mg) every 8 hours; the maximum recommended dose in severe infections is 4 g daily

In the USA, the following licensed *oral* doses are recommended for amoxicillin depending on infection severity:

- neonates and infants less than 12 weeks of age: a maximum of 30 mg/kg daily in divided doses every 12 hours
- children from 3 months of age weighing less than 40 kg: 25 to 45 mg/kg daily in divided doses every 12 hours, or 20 to 40 mg/kg in divided doses every 8 hours
- children from 3 months weighing 40 kg or more: as for adults (see Uses and Administration, p. 216.3)

Alternatively, for children from 1 month of age the American Academy of Pediatrics (AAP)[1] recommends *oral* doses of 25 to 50 mg/kg daily in 3 divided doses for most infections.

For **otitis media**, the *BNFC* recommends that children from 1 month of age may be given *oral* amoxicillin 40 mg/kg (to a maximum of 1.5 g) daily in 3 divided doses; alternatively the AAP recommends 90 mg/kg daily in 2 divided doses. Where compliance may be a challenge, UK licensed product information suggests an alternative course of 750 mg twice daily for 2 days for children from 3 to 10 years of age.

In patients with **cystic fibrosis** for the treatment of asymptomatic *Haemophilus influenzae* carriage or mild exacerbations, the *BNFC* recommends that the following oral doses may be given 3 times daily:

- children 1 month to 1 year of age: 125 mg
- children 1 to 7 years of age: 250 mg
- children from 7 years of age: 500 mg

For the treatment of **listerial meningitis, group B streptococcal infection, or enterococcal endocarditis**, the *BNFC* recommends the following intravenous doses:

- neonates: 50 mg/kg given every 12 hours for those less than 7 days of age and every 8 hours for those 7 to 28 days of age; doses may be doubled in meningitis
- children from 1 month of age: 50 mg/kg every 4 to 6 hours (to a maximum dose of 2 g every 4 hours)

For **prophylaxis of endocarditis** in children at risk, US experts[2] suggest a single *oral* dose of 50 mg/kg 30 to 60 minutes before high risk procedures.

For doses in children with renal impairment see p. 219.1.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Wilson W, *et al*. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116:** 1736–54. Correction. *ibid.*; e376–7. Also available at: http://circ.ahajournals.org/cgi/reprint/116/15/1736 (accessed 13/08/09)

Administration in renal impairment. Oral doses of amoxicillin should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: maximum 500 mg every 12 hours
- CC less than 10 mL/minute: maximum 500 mg every 24 hours
- haemodialysis patients: 250 to 500 mg every 24 hours and an additional dose both during and after the dialysis session.

In children weighing less than 40 kg and up to 10 years of age with renal impairment, UK licensed product information recommends dosage as follows:

- CC 10 to 30 mL/minute: 15 mg/kg (maximum 500 mg) every 12 hours
- CC less than 10 mL/minute: 15 mg/kg (maximum 500 mg) once daily

Dose reduction should also be considered when giving amoxicillin by parenteral routes.

Adverse Effects and Precautions

As for Ampicillin, p. 221.2.

The incidence of diarrhoea is less with amoxicillin than ampicillin.

Hepatitis and cholestatic jaundice have been reported with amoxicillin plus clavulanic acid (see p. 219.2); the clavulanic acid component has been implicated. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis have also been attributed occasionally to the use of amoxicillin with clavulanic acid.

Use of amoxicillin with clavulanic acid during pregnancy for premature rupture of the fetal membrane has been associated with an increased risk of neonatal necrotising enterocolitis. For further information, see under Premature Labour, p. 201.3.

Breast feeding. Although amoxicillin is excreted in breast milk in small amounts,[1] the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Kafetzis DA, *et al*. Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/04)

Effects on the liver. Hepatitis and cholestatic jaundice associated with the combination amoxicillin with clavulanic acid (co-amoxiclav) have been reported[1-4] and by 1993 the UK CSM had received 138 reports of hepatobiliary disorders, 3 of which were fatal.[5] It warned that, although usually reversible, the reaction often occurred after stopping therapy with a delay of up to 6 weeks. It appeared that the clavulanic acid was probably responsible. Retrospective analysis of cases reported in Australia[6] and a cohort study in the UK[7] found increasing age and prolonged treatment to be major risk factors for jaundice after co-amoxiclav; male sex is also a risk factor. By 1997 the CSM considered that cholestatic jaundice occurred with a frequency of about 1 in 6000 adult patients and that the risk of acute liver injury was about 6 times greater with co-amoxiclav than with amoxicillin alone. Therefore it recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant strains, and that treatment should not usually exceed 14 days.[8] Use is also considered contra-indicated in patients with a history of jaundice or hepatic dysfunction associated with co-amoxiclav or other penicillins.

1. Stricker BHC, *et al*. Cholestatic hepatitis due to antibacterial combination of amoxicillin and clavulanic acid (Augmentin). *Dig Dis Sci* 1989; **34:** 1576–80.
2. Wong FS, *et al*. Augmentin-induced jaundice. *Med J Aust* 1991; **154:** 698–701.
3. Larrey D, *et al*. Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases. *Gut* 1992; **33:** 368–71.
4. Hebbard GS, *et al*. Augmentin-induced jaundice with a fatal outcome. *Med J Aust* 1992; **156:** 285–6.
5. CSM/MCA. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 28/07/08)
6. Thomson JA, *et al*. Risk factors for the development of amoxycillin-clavulanic acid associated jaundice. *Med J Aust* 1995; **162:** 638–40.
7. Rodríguez LAG, *et al*. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med* 1996; **156:** 1327–32.
8. CSM/MCA. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023206&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Effects on the teeth. Tooth discoloration associated with the use of amoxicillin with clavulanic acid has been reported in 3 children.[1]

1. Garcia-López M, *et al*. Amoxycillin-clavulanic acid-related tooth discoloration in children. *Pediatrics* 2001; **108:** 819–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amoxicillin and co-amoxiclav as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of amoxicillin sodium contains about 2.6 mmol of sodium.

Interactions

As for Ampicillin, p. 221.2.

Antimicrobial Action

As for Ampicillin, p. 221.3.

Amoxicillin has been reported to be more active *in vitro* than ampicillin against *Enterococcus faecalis*, *Helicobacter pylori*, and *Salmonella* spp., but less active against *Shigella* spp.

Amoxicillin is inactivated by beta lactamases and complete cross-resistance has been reported between amoxicillin and ampicillin. The spectrum of activity of amoxicillin may be extended by use with a beta-lactamase inhibitor such as clavulanic acid (p. 270.3). As well as reversing resistance to amoxicillin in beta-lactamase-producing strains of species otherwise sensitive, clavulanic acid has also been reported to enhance the activity of amoxicillin against several species not generally considered sensitive. These have included *Bacteroides*, *Legionella*, and *Nocardia* spp., *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*). However, *Ps. aeruginosa*, *Serratia marcescens*, and many other Gram-negative bacteria remain resistant. Transferable resistance has been reported in *H. pylori*.

Pharmacokinetics

Amoxicillin is resistant to inactivation by gastric acid. It is more rapidly and more completely absorbed than ampicillin when given orally. Peak plasma-amoxicillin concentrations of about 5 micrograms/mL have been seen 1 to 2 hours after a dose of 250 mg, with detectable amounts present for up to 8 hours. Doubling the dose can double the concentration. The presence of food in the stomach does not appear to reduce the total amount absorbed.

Concentrations of amoxicillin after intramuscular injection are similar to those achieved with oral doses.

About 20% is bound to plasma proteins and plasma half-lives of 1 to 1.5 hours have been reported. The half-life may be prolonged in neonates, the elderly, and patients with renal impairment; in severe renal impairment the half-life may be 7 to 20 hours. Amoxicillin is widely distributed at varying concentrations in body tissues and fluids. It crosses the placenta; small amounts are distributed into breast milk. Little amoxicillin passes into the CSF unless the meninges are inflamed.

Amoxicillin is metabolised to a limited extent to penicilloic acid which is excreted in the urine. About 60% of an oral dose of amoxicillin is excreted unchanged in the urine in 6 hours by glomerular filtration and tubular secretion. Urinary concentrations above 300 micrograms/mL have been reported after a dose of 250 mg. Probenecid reduces renal excretion. Amoxicillin is removed by haemodialysis. High concentrations have been reported in bile; some may be excreted in the faeces.

Amoxicillin with clavulanic acid. The pharmacokinetics of amoxicillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

References.

1. Sánchez Navarro A. New formulations of amoxicillin/clavulanic acid: a pharmacokinetic and pharmacodynamic review. *Clin Pharmacokinet* 2005; **44:** 1097–115.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abiotyl; Abramox†; Almorsan; Amixen Duo; Amixen; Amox-G; Amoxi Duo; Amoxi; Amoxibiot†; Amoxicina; Amoxicler; Amoxidal Duo; Amoxidal; Amoxigrand; Amoxipenil; Amoxipoten†; Amoxitenk; Amoxol Duo; Amoxol; Antiamox†; Biotamoxal†; Bioxilina Duo; Bioxilina; Clofamox; Darzitil; Dunox; Fabamox; Flemoxon; Fullcilina†; Grinsil Duo; Grinsil; Mixcilin†; Moxitral; Nobactam; Optamox; Oximar†; Plamox†; Telmox; Trifamox Duo; Trifamox; ***Austral.***: Alphamox; Amohexal†; Amoxil; Bgramin; Cilamox; Fisamox; Ibiamox; Maxamox; Moxacin†; Moxiclav; Ranmoxy; ***Austria***: Amoxihexal; Amoxilan; Amoxistad; Clamoxyl; Ospamox; ***Belg.***: Amoxypen; Bactimed; Clamoxyl; Docamoxici†; Flemoxin; Moxitop†; ***Braz.***: Amoflux†; Amox; Amoxadene; Amoxi-Ped; Amoxibron†; Amoxidil; Amoxifar†; Amoxil; Amoximed; Amoxina; Amoxitan; Ductocilina; Farmoxil†; Hiconcil; Hincomox; Licilon; Moxiplus; Neo Moxicilin†; Neo Moxilin; Novocilin; Ocylin; Pharmox; Polimoxil; Probenil†; Prodoxil†; Sinot; Trimox; Ultramox; Uni Amox; Velamox; ***Canad.***: Amox; Apo-Amoxi; Novamoxin; Nu-Amoxi; Pro Amox; ***Chile***: Abiolex; Amobiotic; Amoval Duo; Amoval; Amoxipenil; Moxilanic; Optamox; ***China***: A Lin Xin (阿林新); Akelin (阿克林); Amoling (阿莫灵)†; Amoxian (阿莫仙)†; Amoxilin (阿莫西林); Amoxy (阿莫仙); Hypher (海夫安); Qingdi (青帝); Ri Ao (日奥); Xindabeining (新达贝宁); Yabao Like (亚宝力可); Yi Sa Lin (益萨林); Zai Lin (再林); ***Cz.***: Amoclen†; Amoxihexal; Duomox; Ospamox; ***Denm.***: Flemoxin; Imacillin; Imadrax; ***Fin.***: Amorion; Amoxin; ***Fr.***: Amodex; Bactox; Bristamox†; Clamoxyl; Hiconcil†; ***Ger.***: Amagesan†; Amoxi-Diolan†; Amoxi-Hefa†; Amoxi-saar; Amoxi-Tablinen†; Amoxi-Wolff†; Amoxi†; Amoxibeta; Amoxidoc†; Amoxihexal†; Amoxypen†; Baktocillin; Flui-Amoxicillin†; InfectoMox; Jutamox†; ***Gr.***: Amospes; Amoxil; Amoximycin; Aproxal; Bimoxal; Chromoxyl; Daminopen; Dipenocin; Drinus; Flemoxin; Geymocillina; Izoltil; Lamberin; Matasedrin; Ospamox; Paradroxil; Prevasal; Princimox; Selevistine; Stevencillin; Surmagal; Triodanin; Wesfem; ***Hong Kong***: Amon†; Amox†; Amoxapen; Amoxon†; Amoxy†; Aroxin; Edamox; Hamoxillin†; Hiconcil†; Moxcillin†; Moxcin†; Moxen†; Moxilen; Moxipen†; Moxlin; Ospamox; Promox;

Ranoxyl†; Reichamox†; Setmoxil†; Unimox; ***Hung.***: Clonamox; Duomox; Ospamox; ***India***: Actimox; Allmox; Amosym; Amox; Amoxil; Amoxinga; Amoxipen; Amoxivan; Amoxybid; Amoxyn; Amoxypen; Amyn; Antimox; Apimox; Aristomox; Atmox; Axcel; Axl; Betacillin; Betmox; Big Mox; Biomoxil; Bitamox; Blismox; Blumox; Brimox; Cidomex; Cipmox; Clearmox; Damoxy; Delamin; Dicimox; Dormox; Dynamox; E-Amox; Edomox; Erox P; Erox; Euphomox; Finemox; Flemoxin; Fydomox; Genmox; Glamoxin; Glymox; Gutenmox; Hipen; Hycimox; Idimox; Imox; Inmox; Jetmox; Kemox; Labmox; Lakmox; Lamoxy; Lexmox; Linmox; Lomox; Loxyn; Lupimox; Magcil; Max; Maxmox; Mokcan; Monamox; Mopen; Mormox; Mox; Moxi; Moxibact; Moxidat Kid; Moxiday; Moxileb; Moxilup; Moximet; Moximon; Moxind; Moxinova; Moxinta; Moxipal; Moxipil; Moxiplus; Moxitrac; Moxspen; Moxtid; Moxybiotic; Moxycarb; Moxydil; Moxylong; Moxystat; Natamox; Nepomox; Novamox; O-Moxy; Octamox; Olymox; Onamox; Optimox; Osomox; Ronemox; Symoxyl; ***Indon.***: Abdimox†; Aclam; Amobiotic; Amosine; Amoxil; Amoxillin; Amoxsan; Arcamox; Bellacid; Bintamox†; Bioxyllin†; Bufamoxy; Corsamox; Danoxilin; Dexymox; Erphamoxy; Ethimox; Farmoxyl; Ikamoxyl; Intermoxil; Kalmoxillin; Kimoxil; Lactamox; Lapimox; Leomoxyl; Medimox†; Medocyl†; Mestamox; Mexylin; Mokbios; Moxlin†; Moxtid†; Novax; Nufamox; Opimox; Ospamox; Pehamoxil; Penmox; Primoxil†; Pritamox; Rindomox; Robamox; Scannoxyl; Silamox†; Solpenox; Supramox; Topcillin; Vibramox; Wiamox; Widecillin; Xiltrop; ***Irl.***: Amoxil; Clonamox; Geramox; Oramox; Pinamox; Rimoxallin†; ***Israel***: Amoxi; Moxypen; Moxyvit; ***Ital.***: Alfamox; Amoflux; Amosol; Amox; Amoxillin†; Amoxina; Bradimox†; Hydramox; Mopen; Moxiren†; Neotetranase; Oralmox; Pamocil; Posmox; Sievert; Sintopen; Velamox; Zimox; ***Jpn***: Pasetocin; ***Malaysia***: Beamoxy; Betamox; Moxilen; Ospamox; ***Mex.***: Acimox; Acroxil; Ameclina†; Amicil; Amobay; Amoxifur; Amoxil; Amoxinovag†; Amoxisol; Amoxivet; Ampliron; Amsaxilina; Armoxin; Betabiot; Bimoxan†; Biotaxil; Biovicam; Brenoxil; Dimopen; Doxamil; Examolin; Flemoxon; Gimalxina; Grunicina†; Hidramox; Limoxin; Lorexil M; Lumox; Micro Mox; Micromox; Mocimed; Moxiclina; Moxlin; Penamox; Penticlox; Polymox; Prodomix; Servamox-F; Servamox; Solciclina; Vandix†; Xalyn-Or; ***Neth.***: Amoxi†; Flemoxin; ***Norw.***: Amoxillin; Imacillin; ***NZ***: Alpha-Amoxi; Alphamox; Amoxi; Amoxil; Apo-Amoxi; Flemoxin; Ibiamox; Ospamox; ***Philipp.***: Agpen; Amelox; Amoxico; Amoxil; Amusa†; AMX; Ardent; Axmel; Bactigent; Benemox; Bradoxil; Cartrimox; Cilamox; Cilfam; Clearamox; Cycamil; Daisamox; Eleomox; Eppitrexil; Essenmox†; Gexcil; Globamox; Globapen; Harbimox; Himox; Koact; Kramollex; Lewixin; Littmox; Maelenoxyl; Maroxil; Medimoxil; Medvox; Megamox; Moks; Montramox†; Moxillin; Moxiped†; Neomox; Novamox; Pediamox; Pediaxil; Penbiosyn; Pharmamox; Promox; Roddexil; Sterimox; Sumoxil; Syncloxil; Taimox; Telsimox; Teramoxyl; Termox; Trexil; Valmox†; Valzimox; Vastamox; Vaxman†; Vhellox; Westfimox; Xazexy†; Xybatron; Yugoxil; Zedroxyn; Zerrsox; Zymoxyl; ***Pol.***: Amotaks; Apo-Amoxi†; Duomox; Hiconcil; Novamox; Ospamox; ***Port.***: Amoxil; Amplamox; Cipamox; Clamoxyl; Flemoxin; Moxadent; Oraminax; Ospamox; ***Rus.***: Amosin (Амосин); Flemoxin (Флемоксин); Gramox (Грамокс); Hiconcil (Хиконцил); Ospamox (Оспамокс); Ranoxyl (Раноксил); ***S.Afr.***: A-Lennon†; Acucil†; Allmox; Amocas; Amocillin; Amoxicap; Amoxil; Amoxyfizz†; Betamox; C-Mox†; Ipcamox; Maxcil†; Moxan; Moxymax; Moxypen; Mymox; Promoxil; Ranmoxy; Saltermox; Spectramox; Xeracil†; Yomax; Zaloxy; Zoxil; ***Singapore***: Amoxa; Amoxapen; Amoxicap; Amoxigran; Amoxil; Apo-Amoxi; Aroxin; Betamox; Moxilen; Moxipen; Ospamox; Pulmoxy; Strimox; Synamox; Unimox; ***Spain***: Amitron; Amoxaren†; Amoxi Gobens; Apamox; Borbalan†; Britamox; Brondix†; Clamoxyl; Co Amoxin†; Dobriciclin†; Flubiotic†; Hosboral; ***Swed.***: Amimox; Imacillin; ***Switz.***: Amoxi-Mepha; Azilline; Clamoxyl; Spectroxyl†; Supramox†; ***Thai.***: Acticillin; Amacin; Amox; Amoxa†; Amoxcillin; Amoxi; Amoxidon; Amoxil; Amoxin; Amoxlin; Amoxy; Amoxylin†; Amoxypac; Asiamox; Augxil-G; Bomox; Camox; Clanoxy; Coamox; Dymoxin; Ibiamox; Kamoxin†; Manmox; Meixil; Milamox; Mox; Moxapen†; Moxcil; Moxcillin; Moxcin; Moxilcap; Moxilin; Moximed; Moxitab†; Moxno†; Moxodyl; Moxxo†; Moxycillin; Moxyno; Moxypac; Pondnoxcill; Promoxy; Pulmoxyl†; Pyramox; Rancil; Ranoxyl; Rapiclav; Samox; Samoxil†; Samoxin; Sanomox; Servamox; Sia-Mox; Sumoxcin; TO Cillin; TV Mox; U-Amox; Unimox; ***Turk.***: Alfoxil; Amoksilav; Amoksilin; Amoksina; Amosin; Atoksilin; Bioksil; Demoksil; Largopen; Moksilin; Neoamox; Remoxil; Topramoxin; Trimosin; Xibac; ***UAE***: Julphamox; ***UK***: Amix†; Amoram; Amoxident; Amoxil; Galenamox; Rimoxallin; ***Ukr.***: Amoxil (Амоксил-КМП); Flemoxin (Флемоксин); Gramox (Грамокс); Hiconcil (Хиконцил); Ospamox (Оспамокс); ***USA***: Amoxil; DisperMox; Moxatag; Trimox; ***Venez.***: Amitrexyl; Amofar; Amoxal; Amoxiduo; Amoxiga; Amoxilan; Amoxival; Amylin; Ospamox; Sentapen; Strimox; Sumopen; Trimoxal.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Amoxicillin Capsules; Amoxicillin Injection; Amoxicillin Oral Suspension; Co-amoxiclav Injection; Co-amoxiclav Oral Suspension; Co-amoxiclav Tablets; Dispersible Co-amoxiclav Tablets;

USP 36: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Amoxicillin and Clavulanic Acid Extended-Release Tablets; Amoxicillin Capsules; Amoxicillin for Oral Suspension; Amoxicillin Tablets for Oral Suspension; Amoxicillin Tablets.

Ampicillin *(BAN, USAN, rINN)*

Aminobenzylpenicillin; Ampicilin; Ampicilina; Ampicilinas, bevandenis; Ampicillin, vattenfritt; Ampicilline; Ampicilline anhydre; Ampicillinum; Ampicillinum Anhydricum; Ampicylina bezwodna; Ampisilin; Ampisilliini; Ampisilliini, vedetön; Anhydrous Ampicillin; AY-6108; BRL-1341; NSC-528986; P-50; Vízmentes ampicillin; Wasserfreies Ampicillin; Ампициллин.

(6*R*)-6-(α-D-Phenylglycylamino)penicillanic acid.

$C_{16}H_{19}N_3O_4S$=349.4

CAS — 69-53-4.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QJ51CA01; QS01AA19.

UNII — 7C782967RD.

NOTE. Compounded preparations of ampicillin may be represented by the following names:

- Co-fluampicil (*BAN*)—flucloxacillin 1 part and ampicillin 1 part (w/w).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.*

Int. and *US* permit anhydrous or the trihydrate.

Ph. Eur. 8: (Ampicillin, Anhydrous; Ampicillin BP 2014). A white or almost white, crystalline powder. It exhibits polymorphism. Sparingly soluble in water; practically insoluble in alcohol, in acetone, and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides. A 0.25% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30 degrees in airtight containers.

USP 36: (Ampicillin). It is anhydrous or contains three molecules of water of hydration. A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Ampicillin Sodium *(BANM, USAN, rINNM)*

Aminobenzylpenicillin Sodium; Ampicilin sodná sůl; Ampicilina sódica; Ampicilino natrio druska; Ampicillin-Natrium; Ampicilline Sodique; Ampicillinnatrium; Ampicillinnátrium; Ampicillinum Natricum; Ampicylina sodowa; Ampisilliininatrium; Natrii Ampicillinum; Sodyum Ampisilin; Натрий Ампициллин.

$C_{16}H_{18}N_3NaO_4S$=371.4

CAS — 69-52-3.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QS01AA19.

UNII — JFN36L5S8K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Ampicillin Sodium). A white or almost white hygroscopic powder. Freely soluble in water; sparingly soluble in acetone; practically insoluble in liquid paraffin and in fatty oils. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

USP 36: (Ampicillin Sodium). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Very soluble in water and in isotonic sodium chloride and glucose solutions. pH of a solution in water containing the equivalent of ampicillin 1% is between 8.0 and 10.0. Store in airtight containers.

Incompatibility. The incompatibility of ampicillin sodium and aminoglycosides is well established. Incompatibilities have also been reported with many other drugs, including other antibacterials, and appear to be more pronounced at higher concentrations and in solutions also containing glucose.

Stability. The stability of solutions of ampicillin sodium is dependent on many factors including concentration, pH, temperature, and the nature of the vehicle. Stability decreases in the presence of glucose, fructose, invert sugar, dextrans, hetastarch, sodium bicarbonate, and lactate. It is recommended that reconstituted solutions of ampicillin sodium for injection should be given within 24 hours of preparation, and should be stored at 2 degrees to 8 degrees but should not be frozen. Solutions for infusion are stable for varying periods and details are given in licensed product information.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2**(Mar): 22–39.

Ampicillin Trihydrate *(BANM, rINNM)*

Ampicilin trihydrát; Ampicilina trihidrato; Ampicilinas trihidratas; Ampicillin; Ampicillin-Trihydrat; Ampicilline Trihydratée; Ampicillin-trihidrát; Ampicillintrihydrat; Ampicillinum Trihydricum; Ampicylina trójwodna; Ampisilliinitrihydraatti; Ампициллин Тригидрат.

$C_{16}H_{19}N_3O_4S,3H_2O$=403.4

CAS — 7177-48-2.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QS01AA19.

UNII — HXQ6A1N7R6.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.* In *Chin.* under the title Ampicillin. *Int.* and *US* permit anhydrous or the trihydrate under the title Ampicillin.

Ph. Eur. 8: (Ampicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in alcohol and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides. A 0.25% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Ampicillin). It is anhydrous or contains three molecules of water of hydration. A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Uses and Administration

Ampicillin is used in the treatment of a variety of infections due to susceptible organisms (see Antimicrobial Action, p. 221.3). They include biliary-tract infections, bronchitis, endocarditis, gastro-enteritis (including salmonella enteritis and shigellosis), gonorrhoea, listeriosis, meningitis, perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), peritonitis, pneumonia, septicaemia, typhoid and paratyphoid fever, and urinary-tract infections. Resistance to ampicillin is increasingly a problem in some infections, for example, gonorrhoea, pneumococcal infections, respiratory-tract infections due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Salmonella* infections, shigellosis, and infections due to *Escherichia coli*. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

If beta-lactamase-producing organisms are present, ampicillin can be given with a beta-lactamase inhibitor such as sulbactam (see below) or a penicillinase-resistant drug such as cloxacillin, dicloxacillin, or flucloxacillin (known as co-fluampicil). It may also be used with an aminoglycoside to increase the spectrum of organisms covered; it is advisable to give the injections separately.

The dosage of ampicillin will depend on the severity of the disease, the age of the patient, and renal function. Ampicillin is usually given orally as the trihydrate and by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ampicillin; 1.06 g of ampicillin sodium and 1.15 g of ampicillin trihydrate are each equivalent to about 1 g of ampicillin.

The usual oral dose is 0.25 to 1 g every 6 hours taken at least 30 minutes before or 2 hours after food. For urinary-tract infections, ampicillin 500 mg is given orally every 8 hours. The usual dose by injection is 500 mg every 4 to 6 hours intramuscularly or by slow intravenous injection over 3 to 5 minutes or by infusion, although for severe infections higher doses are often used.

For typhoid and paratyphoid fever where *Salmonella typhi* strains remain sensitive to ampicillin, an oral dose of 1 to 2 g may be given every 6 hours for 2 weeks for acute infections, and for 4 to 12 weeks in carriers.

Ampicillin 2 g given with probenecid 1 g, as a single oral dose, has been used in the treatment of uncomplicated gonorrhoea in areas where gonococci remain sensitive; repeated doses are recommended in females.

In meningitis, higher parenteral doses may be used; 12 g daily given intravenously in divided doses every 4 or 6 hours has been suggested for listerial meningitis.

For intrapartum prophylaxis against group B streptococcal infection in the neonate, a maternal dose of 2 g by intravenous injection initially then 1 g every 4 hours until delivery has been suggested.

For details of doses in children, see p. 221.1.

Ampicillin has been given by other routes, usually as a supplement to systemic therapy. Intraperitoneal or intrapleural injections have been given in a dose of 500 mg daily dissolved in 5 to 10 mL of water. For intra-articular injection, ampicillin 500 mg daily has been given dissolved in up to 5 mL of water or a solution of procaine hydrochloride 0.5%.

Ampicillin benzathine has also been given by intramuscular injection.

Ampicillin with sulbactam. The sodium salts of ampicillin and sulbactam (p. 362.1) may be given intramuscularly or intravenously in the treatment of infections due to beta-lactamase-producing organisms. Doses are expressed in terms of the equivalent amounts of ampicillin and sulbactam; available injections contain ampicillin and sulbactam in the ratio 2:1, respectively. The usual dose is

ampicillin 1 g with sulbactam 500 mg every 6 hours; doses may be doubled in severe infections.

For oral use sultamicillin (p. 371.1), a mutual prodrug of ampicillin and sulbactam, may be given.

References.
1. Malik ZA, Litman N. Ampicillin and amoxicillin. *Pediatr Rev* 2006; **27:** 434–6.
2. Rafailidis PI, *et al*. Ampicillin/sulbactam: current status in severe bacterial infections. *Drugs* 2007; **67:** 1829–49.
3. Lode HM. Rational antibiotic therapy and the position of ampicillin/sulbactam. *Int J Antimicrob Agents* 2008; **32:** 10–28.

Administration in children. Ampicillin may be given to neonates and children for the treatment of infections caused by susceptible bacteria and may be given orally, by intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent intravenous infusion over 30 minutes.

For the treatment of susceptible infections including urinary-tract infections, otitis media, sinusitis, uncomplicated community-acquired pneumonia, and salmonellosis, the *BNFC* suggests the following *oral* doses for neonates and children; these may be doubled in severe or serious infections:

- neonates: 30 mg/kg (to a maximum of 62.5 mg) given 3 times daily for neonates 7 to 21 days old and 4 times daily for those 21 to 28 days old
- 1 month to 1 year of age: 62.5 mg 4 times daily
- 1 to 5 years of age: 125 mg 4 times daily
- from 5 to 12 years of age: 250 mg 4 times daily
- from 12 years of age: 250 to 500 mg 4 times daily

The *BNFC* also recommends the following *intravenous* dose ranges in neonates and children which may be doubled in severe or serious infections:

- neonates: 30 mg/kg, given every 12 hours for neonates less than 7 days old, every 8 hours for those 7 to 21 days old, and every 6 hours for those 21 to 28 days old
- children from 1 month of age: 25 mg/kg (to a maximum of 500 mg) every 6 hours

For listerial meningitis, group B streptococcal infection, and enterococcal endocarditis, the *BNFC* suggests the following *intravenous* doses;

- neonates: 50 mg/kg, given every 12 hours for neonates less than 7 days old, every 8 hours for those 7 to 21 days old, and every 6 hours for those 21 to 28 days old; the dose is doubled for the treatment of meningitis
- from 1 month of age: 50 mg/kg every 4 to 6 hours (to a maximum of 2 g every 4 hours) is recommended

In the USA, the American Academy of Paediatrics[1] suggests the following doses given *intramuscularly* or *intravenously*, although higher doses may be needed for the treatment of meningitis in neonates:

- for neonates aged ⩽7 days and weighing ⩽2 kg: 50 mg/kg every 12 hours; for the treatment of presumed early-onset group B streptococcal septicaemia, 100 mg/kg every 12 hours is also suggested
- for neonates aged ⩽7 days and weighing >2 kg: 50 mg/kg every 8 hours; for the treatment of presumed early-onset group B streptococcal septicaemia, 100 mg/kg every 12 hours is also suggested
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 50 mg/kg every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birthweight neonates (those weighing < 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 50 mg/kg every 6 hours
- for group B streptococcal meningitis in all the above weight groups: 75 mg/kg every 6 hours
- children 1 month and older: 100 to 150 mg/kg daily in 4 divided doses (to a maximum of 4 g daily). For severe infections, a total daily dose of 200 to 400 mg/kg (to a maximum of 12 g) is recommended

Alternatively, for mild to moderate infections in children from 1 month of age, a daily dose of 50 to 100 mg/kg *orally*, in 4 divided doses (to a maximum of 4 g daily), may also be used.

Ampicillin is also used in some countries in children to eradicate chronic carriage of *Salmonella typhi* and *S. paratyphi*, which can cause typhoid and paratyphoid fever respectively; an *intramuscular* dose of 10 mg/kg (to a maximum of 250 mg) every 6 hours for 4 to 6 weeks has been recommended.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. UK licensed product information advises that the dose of ampicillin should be reduced, or the dose interval increased, in severe renal impairment (creatinine clearance less than 10 mL/minute). Patients undergoing dialysis should receive an additional dose after the session.

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy recommends that patients undergoing continuous renal replacement therapy (CRRT) receive a loading dose of 2 g, followed by maintenance doses of 1 to 2 g at intervals depending on the type of CRRT:

- continuous venovenous haemofiltration (CVVH): every 8 to 12 hours
- continuous venovenous haemodialysis (CVVHD): every 8 hours
- continuous venovenous haemodiafiltration (CVVHDF): every 6 to 8 hours

For critically ill patients undergoing intermittent haemodialysis, the authors suggest a dosing regimen of 1 to 2 g every 12 to 24 hours.[1]

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects

As for Benzylpenicillin, p. 231.2.

Skin rashes are among the most common adverse effects and are generally either urticarial or maculopapular; the urticarial reactions are typical of penicillin hypersensitivity, while the erythematous maculopapular eruptions are characteristic of ampicillin and amoxicillin and often appear more than 7 days after starting treatment. Such rashes may be due to hypersensitivity to the beta-lactam moiety or to the amino group in the side-chain, or to a toxic reaction. The occurrence of a maculopapular rash during ampicillin use does not necessarily preclude the subsequent use of other penicillins. However, since it may be difficult in practice to distinguish between hypersensitive and toxic responses, skin testing for hypersensitivity may be advisable before another penicillin is used in patients who have had ampicillin rashes. Most patients with infectious mononucleosis develop a maculopapular rash when treated with ampicillin, and patients with other lymphoid disorders such as lymphatic leukaemia, and possibly those with HIV infection, also appear to be at higher risk. More serious skin reactions may occur and erythema multiforme associated with ampicillin has occasionally been reported.

Gastrointestinal adverse effects, particularly diarrhoea and nausea and vomiting, occur quite often, usually after oral use. Pseudomembranous colitis has also been reported.

Effects on the liver. Ampicillin has been associated with hepatic injury. Self-limiting cholestasis was reported in a 23-year-old man who received oral ampicillin;[1] recurrence followed each of 2 subsequent exposures to the drug. A case of chronic cholestasis associated with ampicillin use has also been reported.[2]

Severe and prolonged cholestasis has also been reported after treatment with ampicillin plus sulbactam; gradual resolution of the condition occurred over 7 months.[3]

1. Köklü S, *et al*. Recurrent cholestasis due to ampicillin. *Ann Pharmacother* 2003; **37:** 395–7.
2. Cavanzo FJ, *et al*. Chronic cholestasis, paucity of bile ducts, red cell aplasia, and the Stevens-Johnson syndrome: an ampicillin-associated case. *Gastroenterology* 1990; **99:** 854–6.
3. Köklü S, *et al*. Probable sulbactam/ampicillin-associated prolonged cholestasis. *Ann Pharmacother* 2004; **38:** 2055–8.

Precautions

As for Benzylpenicillin, p. 231.3.

Ampicillin should be stopped if a skin rash occurs. It should preferably not be given to patients with infectious mononucleosis since they are especially susceptible to ampicillin-induced skin rashes; patients with lymphatic leukaemia or possibly HIV infection may also be at increased risk of developing skin rashes.

Myasthenia gravis. The symptoms of a woman with myasthenia gravis were exacerbated when she was given ampicillin.[1]

1. Argov Z, *et al*. Ampicillin may aggravate clinical and experimental myasthenia gravis. *Arch Neurol* 1986; **43:** 255–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ampicillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of ampicillin sodium contains about 2.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 232.1.

Antigout drugs. An increased frequency of skin rashes has been reported in patients receiving ampicillin or amoxicillin, with *allopurinol*, compared with those receiving the antibacterial alone,[1] but this could not be confirmed in a subsequent study.[2]

1. Jick H, Porter JB. Potentiation of ampicillin skin reactions by allopurinol or hyperuricemia. *J Clin Pharmacol* 1981; **21:** 456–8.
2. Hoigné R, *et al*. Occurrence of exanthems in relation to aminopenicillin preparations and allopurinol. *N Engl J Med* 1987; **316:** 1217.

Antimalarials. The absorption of ampicillin has been reduced in healthy subjects taking *chloroquine*.[1]

1. Ali HM. Reduced ampicillin bioavailability following oral coadministration with chloroquine. *J Antimicrob Chemother* 1985; **15:** 781–4.

Antimicrobial Action

Ampicillin is a beta-lactam antibacterial. It is bactericidal and has a similar mode of action to that of benzylpenicillin (p. 232.1), but as an aminopenicillin with an amino group side-chain attached to the basic penicillin structure, ampicillin is better able to penetrate the outer membrane of some Gram-negative bacteria and has a broader spectrum of activity.

- Ampicillin resembles benzylpenicillin in its action against Gram-positive organisms, including *Streptococcus pneumoniae* and other streptococci, but, with the possible exception of activity against *Enterococcus faecalis*, it is slightly less potent than benzylpenicillin.
  Listeria monocytogenes is highly sensitive.
- The Gram-negative cocci *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *N. meningitidis* are sensitive.
- Ampicillin is more active than benzylpenicillin against some Gram-negative bacilli, including *Haemophilus influenzae* and Enterobacteriaceae such as *Escherichia coli*, *Proteus mirabilis*, *Salmonella* and *Shigella* spp. It is inactive against *Pseudomonas aeruginosa*.
- Ampicillin also has activity similar to benzylpenicillin against other organisms including many anaerobes and *Actinomyces* spp.

Activity with other antimicrobials. There is synergy against some beta-lactamase-producing organisms between ampicillin and beta-lactamase inhibitors such as clavulanic acid or sulbactam, and also penicillinase-stable drugs such as cloxacillin or flucloxacillin. Synergy has also been shown between ampicillin and aminoglycosides against a range of organisms, including enterococci. Variable effects ranging from synergy to antagonism have been reported between ampicillin and other beta lactams, bacteriostatic drugs such as chloramphenicol, and rifampicin.

Resistance. Like benzylpenicillin, ampicillin is inactivated by beta lactamases, although other mechanisms may be responsible for resistance in some species. There are geographical variations in the incidence of resistance, but most staphylococci and many strains of *E. coli*, *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, and *Salmonella* and *Shigella* spp. are resistant.

Pharmacokinetics

Ampicillin is relatively resistant to inactivation by gastric acid and is moderately well absorbed from the gastrointestinal tract after oral doses. Food can interfere with the absorption of ampicillin so doses should preferably be taken at least 30 minutes before meals. Peak concentrations in plasma occur in about 1 to 2 hours and after a 500-mg oral dose are reported to range from 3 to 6 micrograms/mL.

Peak plasma concentrations of ampicillin after a 500-mg intramuscular dose given as the sodium salt occur within about 1 hour and are reported to range from 7 to 14 micrograms/mL.

Ampicillin is widely distributed and therapeutic concentrations can be achieved in ascitic, pleural, and joint fluids. It crosses the placenta and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. About 20% is bound to plasma proteins and the plasma half-life is about 1 to 1.5 hours, but this may be increased in neonates, the elderly, and patients with renal impairment; in severe renal impairment half-lives of 7 to 20 hours have been reported.

Ampicillin is metabolised to some extent to penicilloic acid which is excreted in the urine.

Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion; it is reduced by probenecid. About 20 to 40% of an oral dose may be excreted unchanged in the urine in 6 hours; urinary concentrations have ranged from 0.25 to 1 mg/mL after a dose of 500 mg. After parenteral use about 60 to 80% is excreted in the urine within 6 hours. Ampicillin is removed by haemodialysis. High concentrations are reached in bile; it undergoes enterohepatic recycling and some is excreted in the faeces.

Ampicillin with sulbactam. The pharmacokinetics of ampicillin and sulbactam are broadly similar and neither appears to affect the other to any great extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alpovex; Ampi-Bis; Ampicler†; Ampigen; Ampigrand†; Ampinox; Ampitenk; Ampixen†; Atecilina; Bactilina; Fabopcilina†; Galciclina; Histopen†; Trifacilina; Trimicro†; Welticilina†; ***Austral.***: Alphacin†; Ampicyn; Austrapen; Ibimicyn; ***Austria***: Standacillin; ***Belg.***: Pentrexyl; ***Braz.***: Ampi†; Ampiciflan; Ampicil†; Ampicilab; Ampicilase; Ampicilil; Ampicilon; Ampigran; Ampilozin; Amplacilina; Amplacin; Amplibac†; Binotal; Cilinon; Cilipen†; Emicilin; Expectocilin; Gonol; Gramcilina†; Parenzyme Ampicilina; ***Canad.***: Apo-Ampi; Nu-Ampi; ***China***: Ai Luo Di (艾罗迪); An Tai Lin (安泰林); Anbixian (安必仙); Bixianshu (必仙素); En Pu Luo (恩普洛); Lingxu (灵旭); Yixide (伊西德); ***Denm.***: Pentrexyl; ***Fin.***: A-Pen; ***Ger.***: Binotal†; ***Gr.***: Abetathen; Adelcopen; Allomycin; Ampicipen; Competor; Comrarilin; Copercilex; Extrapen; Frateline; Fraxicilline; Isticilline; Pentrexyl; Picilin; Spiracillin; Stopan; Toscapen; Xanline; ***Hong Kong***: Ampisul†; Amprexyl; Apo-Ampi†; Pamecil; Penodil†; Pentrexyl†; Uni-Ampicin†; ***Hung.***: Semicillin; Standacillin; ***India***: Albercilin; Alfacillin; Ampijet; Ampilin; Ampipen; Ampisyn; Ampy; Aristocillin; Bacipen; Biocilin; Broacil; Broadicilin; Campicillin; Cincillin; Dabcilin; Dynacil; Eskaycillin; Ingacillin; JP-Cilin; Maxamp; Megasyn; Monocilin; Natcocillin; Neocillin; Nepocil; Osocillin; Roscillin; Synthocilin; ***Indon.***: Ambiopi; Amcillin†; Ampi; Arcocillin†; Binotal; Biopensyn†; Cetacillin†; Corsacillin; Kalpicilin; Opicillin; Parpicillin†; Penbiotic†; Penbritin†; Phapin; Polypen; Primacillin†; Sanpicillin; Standacillin; Ultrapen†; Viccillin; Xepacillin; ***Irl.***: Clonamp; Novapen†; Penbritin†; Rimacillin†; ***Israel***: Penibrin; ***Ital.***: Ampilux; Ampiplus Simplex†; Amplital; Amplizer†; Pentrexyl; ***Malaysia***: Ampilin; Pamecil; Standacillin; ***Mex.***: Acilmed; Alphapen; Alvedrin†; Am-An; Ambidrin†; Ambiosol; Ampex; Ampi-Quim; Ampi-Tecno; Ampigrin†; Ampimex; Amprexyn†; Amsapen; Anglopen†; Azpencil†; Bestcilina-A; Binotal; Bremecina†; Brupen; Deamcilina†; Dibacilina; Diferin; Expicin; Flamicina; Gramipen-F; Iqfacilina; Lampicin†; Luzampil; Marovilina; Meprizina†; Mexapin†; Mibiot; Omnipen; Pebiot; Penbritin; Pentiver; Pentrexyl; Procilina; Prodifer†; Promecilina; Sinaplin; Tronex; Yapamicin†; Zumorin; ***Norw.***: Pentrexyl; ***Philipp.***: Aldribid; Ampicin; Ampiclin; Ampico; Ampinex; Ampisan; Ampitrex; Ampizef; Bactimed†; Cilisod; Clovillin; Dincil; Dinpen; Eurocin; Excillin; Famacin; Gramcil; Mapciril; Microcilin; Obocil; Panacta; Penbritin; Pentrexyl†; Picaplin; Polypen; Rotocin; Shinapen; Sodampen; Trumepen; Vatacil; ***Port.***: Amplifar†; Estreptobroncol†; Hiperbiotico Retard; Hiperbiotico; ***Rus.***: Standacillin (Стандациллин); Zetsyl (Зетсил); ***S.Afr.***: Acupillin†; Ampimax†; Ampipen; Ampisalt†; Be-Ampicil; M-P-Cil; Penbritin†; Penrite†; Petercillin†; Ranamp; Spectracil†; ***Singapore***: Ampicap; Ampilin; Dhacillin; Pamecil†; Standacillin; ***Spain***: Britapen; Gobemicina; ***Swed.***: Doktacillin; ***Thai.***: Amicilin; Amilin†; Ampac; Ampi Frx; Ampi-Oral; Ampi; Ampicin; Ampicyn†; Ampihof; Ampilin; Ampillin; Ampimycin; Ampipac; Ampra; Amprexyl; Eracillin†; Medicillin; Penbritin†; Pencotrex†; Pentrexyl†; Siampicil†; Sumapen†; Utocillin; Vacillin†; Viccillin†; ***Turk.***: Alfasilin; Ampisid; Ampisina; Neosilin; Penbisin†; Seskasilin; Silina; ***UAE***: Julphapen; ***UK***: Magnapen†; Magnapen; Magnapen; Penbritin; Rimacillin; ***USA***: Principen; ***Venez.***: Alampen; Ampenina; Ampilan; Arcocilin.

Multi-ingredient Preparations. ***Arg.***: Aminoxidin Sulbactam; Ampi-Bis Plus; Ampigen SB; Amplibenzatin Bronquial; Cronopen Balsamico; Meticil; Prixin; Unasyna†; ***Austria***: Unasyn; ***Braz.***: Ambezetal; Amplotal†; Benzotal; Combactan; Durapen†; Optacilin; Unasyn; Uropielon; ***Chile***: Auropennz; Unasyn; ***China***: Fumaixin (孚麦欣); Jielite (洁利特); Kaifa (凯法); Pu Shu (普舒); Shu An Xin (舒氨新); Shuanxilin (舒氨西林); Shudi (舒敌); Shutabituo (舒他必妥); Stanyn (施坦宁); Unasyn (优立新); Xin An Lin (欣安林); Zhuo Tong (卓彤); ***Cz.***: Bitamon; Unasyn; ***Fr.***: Unacim; ***Ger.***: Ampicillin comp†; Unacid; ***Gr.***: Begalin-P; Demotine; ***Hong Kong***: Cloxamp†; Cloxampi†; Cloxampilin†; Co-Amclox†; Lampicin†; Pamedox†; Roscilox†; Unasyn; ***Hung.***: Unasyn; ***India***: ADC; Adilox; AK-60; Alcilox; Amci-Clox; Amclominus; Amclox; Amiclox Plus; Amisul; Amklok; Ampicloxa; Ampilong; Ampilox-LB; Ampilox; Ampitum; Amplus; Amplus; Ampoxin-LB; Ampoxin; Ampy C; Ampy S; Ampylox; Ampysul; Amsat; Baciclox; Bactimox Plus; Bactimox; Baxin-D-LB; Baxin-D; Baxin-LB; Baxin; Betamp; Biclopen; Bilactam; Broadiclox-LB; Broadiclox; Campicillin Plus; Campilox-LB; Campilox; Cilclox; Cinclox-S; Clacin; Clax; Climpen; Clomentin; Clompic; Clotrop; Cloxapene; Cloxcin; Combiclox-LB; Combilox; Combipen; D-Clox; Dabcilox; DC-Ped; DC; Duoclox; Elclox Plus; Elclox; Emulox; Eradiclox; Euphoclox; G-Clox; Hclox; Intaclox-D; Kloxamp; Magnacillin; Mediclox Plus; Megaclox LB; Megaclox; Megapen; Napi-D; Nepoclox; Omnipen; Osocillin-S; Sulbacin; ***Israel***: Unasyn; ***Ital.***: Amplium; Bethacil; Loricin; Unasyn; ***Jpn***: Unasyn-S; ***Malaysia***: Easyn; Shinasyn; Sulbacin; Sulbamp; Unasyn; ***Mex.***: Ampiclox-D†; Anglotex†; Bisolvon A; Brucilina; Brupen Compuesto; Diamprex†; Doxapen†; Mucolin; Panac K†; Panac; Penbritin Ex; Pentibrom; Pentidix; Pentrexyl Expec; Unasyna; ***Philipp.***: Ambacitam; Ampimax; Ampisul; Dinocin; Silgram; Subacillin; Sulbacin; Sultacillin; Unasan; Unasyn; ***Pol.***: Unasyn; ***Rus.***: Libakcil (Либакцил); Oxamp (Оксамп); Oxampicine (Оксампицин); Oxamsar (Оксамсар); Sulbacin (Сульбацин); Sultasin (Сультасин); Unasyn (Уназин)†; ***S.Afr.***: Ampiclox†; Ampoxin; Apen; Cloxam; Megamox; ***Singapore***: Unasyn; ***Spain***: Ampilevel†; Gobemicina Retard†; Retarpen; ***Thai.***: Ampcoxin; Ampiclox†; Sulam; Sulbaccin; Sulbacilline; Unasyn; Viccillin-S†; ***Turk.***: Alfasid; Azosilin; Combicid; Devasid; Duobak; Duobaktam; Duocid; Nobecid; Probicid; Sulbaksit; Sulcid; Sultasid; Sultibac; ***UK***: Magnapen†; Magnapen; Magnapen; ***Ukr.***: Ampisid (Амписид); Ampisulbin (Амписульбин); Unasyn (Уназин)†; ***USA***: Unasyn; ***Venez.***: Ampibactan; Fipexiam; Sinif; Unasyn.

Pharmacopoeial Preparations

BP 2014: Ampicillin Capsules; Ampicillin Injection; Ampicillin Oral Suspension; Co-fluampicil Capsules; Co-fluampicil Oral Suspension;

USP 36: Ampicillin and Probenecid for Oral Suspension; Ampicillin and Sulbactam for Injection; Ampicillin Capsules; Ampicillin for Injectable Suspension; Ampicillin for Injection; Ampicillin for Oral Suspension; Ampicillin Tablets.

Apramycin *(BAN, USAN, rINN)*

47657; Apramicina; Apramycine; Apramycinum; EL-857; EL-857/820; Nebramycin Factor 2; Апрамицин.

4-*O*-[(2*R*,3*R*,4a*S*,6*R*,7*S*,8*R*,8a*R*)-3-Amino-6-(4-amino-4-deoxy-α-D-glucopyranosyloxy)-8-hydroxy-7-methylaminoperhydropyrano[3,2-*b*]pyran-2-yl]-2-deoxystreptamine.

$C_{21}H_{41}N_5O_{11}$=539.6

CAS — 37321-09-8.

ATC Vet — QA07AA92; QJ01GB90; QJ51GB90.

UNII — 388K3TR36Z.

Apramycin Sulfate *(BANM, rINNM)*

Apramicina, sulfato de; Apramycin Sulphate; Apramycine, Sulfate d'; Apramycini Sulfas; Apramycinsulfat; Apramysiinisulfaatti; Sulfato de apramicina; Апрамицина Сульфат.

$C_{21}H_{41}N_5O_{11}$,2½H_2SO_4=784.8

CAS — 41194-16-5.

UNII — 8UYL6NAZ3Q.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Apramycin Sulfate). The sulfate of an antibiotic produced by certain strains of *Streptomyces tenebrarius* or by other means. The potency is not less than 430 units per mg, calculated with reference to the anhydrous substance. A light brown hygroscopic powder or granular material. Freely soluble in water; practically insoluble in alcohol, in acetone, in ether, and in methyl alcohol.

Profile

Apramycin is an aminoglycoside antibacterial used as the sulfate in veterinary practice for the treatment of susceptible infections.

Arbekacin Sulfate *(rINNM)*

ABK (arbekacin); AHB-DBK (arbekacin); Arbekacin Sulphate; Arbekacina, sulfato de; Arbékacine, Sulfate d'; Arbekacini Sulfas; HABA-Dibekacin (arbekacin); Sulfato de arbekacina; Арбекацина Сульфат.

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl-(1→6)]-*N*′-[(2*S*)-4-amino-2-hydroxybutyryl]-2-deoxy-L-streptamine sulphate.

$C_{22}H_{44}N_6O_{10}$.xH_2SO_4

CAS — 51025-85-5 (arbekacin).

ATC — J01GB12.

ATC Vet — QJ01GB12.

UNII — G7395HZ992.

Pharmacopoeias. In *Jpn*.

Profile

Arbekacin is an aminoglycoside antibacterial derived from dibekacin and has general properties similar to those of gentamicin (p. 306.2). It has been used as the sulfate in the treatment of serious infections due to meticillin-resistant *Staphylococcus aureus*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Habekacin.

Arsanilic Acid *(BAN, rINN)*

Acide Arsanilique; Ácido arsanílico; Acidum Arsanilicum; Aminarsonic Acid; Arsanílico, ácido; AS-101; Арсаниловая Кислота.

p-Aminobenzenearsonic acid; 4-Aminophenylarsonic acid.

$C_6H_8AsNO_3$=217.1

CAS — 98-50-0.

UNII — UDX9AKS7GM.

NOTE. The code AS-101 has also been used for an immunomodulator investigated as an antineoplastic and antiviral.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Arsanilic Acid). A white to off-white crystalline powder. Soluble in hot water, in amyl alcohol, and in solutions of alkali carbonates; slightly soluble in cold water, in alcohol, and in acetic acid; insoluble in acetone, in chloroform, in ether, in benzene, and in dilute mineral acids; sparingly soluble in concentrated mineral acids.

Sodium Arsanilate *(BANM, rINNM)*

Arsanilate de Sodium; Arsanilato sódico; Natrii Arsanilas; Sodium Aminarsonate; Sodium Anilarsonate; Натрий Арсанилат.

Sodium 4-aminophenylarsonate.

$C_6H_7AsNNaO_3$=239.0

CAS — 127-85-5.

UNII — UC2409302Q.

Pharmacopoeias. *Fr.* includes the anhydrous substance and the trihydrate.

Profile

Arsanilic acid and sodium arsanilate are used in veterinary medicine for the prophylaxis and treatment of enteric infections in pigs and also as growth-promoting agents.

Aspoxicillin *(rINN)*

Aspoxicilina; Aspoxicilline; Aspoxicillinum; TA-058; Аспоксициллин.

(2*S*,5*R*,6*R*)-6-{(2*R*)-2-[(2*R*)-2-Amino-3-(methylcarbamoyl)propionamido]-2-(*p*-hydroxyphenyl)acetamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid.

$C_{21}H_{27}N_5O_7S$=493.5

CAS — 63358-49-6.

UNII — 0745KNO26J.

Pharmacopoeias. *Jpn* includes the trihydrate.

Profile

Aspoxicillin is a ureidopenicillin that has been given intravenously in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Doyle.

Astromicin Sulfate *(USAN, pINNM)*

Abbott-44747; Astromicin Sulphate; Astromicina, sulfato de; Astromicine, Sulfate d'; Astromicini Sulfas; Fortimicin A Sulphate; KW-1070; Sulfato de astromicina; Астромицина Сульфат.

4-Amino-1-(2-amino-*N*-methylacetamido)-1,4-dideoxy-3-*O*-(2,6-diamino-2,3,4,6,7-pentadeoxy-β-L-*lyxo*-heptopyranosyl)-6-*O*-methyl-L-*chiro*-inositol sulphate.

$C_{17}H_{35}N_5O_6$,2H_2SO_4=601.6

CAS — 55779-06-1 (astromicin); 72275-67-3 (astromicin sulfate); 66768-12-5 (xH_2SO_4).

UNII — POY3S0T3BD.

Pharmacopoeias. In *Jpn*.

Profile

Astromicin is an aminoglycoside antibacterial produced by *Micromonospora* spp. and with actions and uses similar to those of gentamicin (p. 306.2). Astromicin sulfate has been given by intramuscular injection or intravenous infusion. Dosage should be adjusted based on serum-astromicin concentration monitoring.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Fortimicin†.

Avilamycin *(BAN, USAN, rINN)*

Avilamicina; Avilamycine; Avilamycinum; LY-048740 (avilamycin or avilamycin A); Авиламицин.

$C_{61}H_{88}Cl_2O_{32}$ (avilamycin A)=1404.2

CAS — 11051-71-1 (avilamycin); 69787-79-7 (avilamycin A); 69787-80-0 (avilamycin C).

UNII — 720WDX56D3.

Profile

Avilamycin is an antibacterial that has been used in veterinary medicine as a growth promotor.

Avoparcin (BAN, USAN, rINN)

Avoparcina; Avoparcine; Avoparcinum; Compound 254; Авопарцин.

CAS — 37332-99-3.

Profile

Avoparcin is a glycopeptide antibacterial usually produced by *Amycolatopsis coloradensis* (*Streptomyces candidus*). It has been incorporated into animal feedstuffs to promote growth.

Cross-resistance. There is evidence of cross-resistance between avoparcin and vancomycin.[1] Suggestions that vancomycin-resistant organisms could enter the human population from the food chain as a result of the use of avoparcin as a growth promotor in animals[2,3] were disputed by the manufacturers of avoparcin,[4,5] but such use has now been banned in many countries. After a ban in the EU on the use of avoparcin as a growth promotor in animals there has been some evidence[6,7] of a decrease in the prevalence of vancomycin-resistant enterococci in animal and human flora, but other studies in various countries[8-10] have indicated considerable persistence of such organisms.

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10. Lim SK, *et al.* Persistence of vanA-type Enterococcus faecium in Korean livestock after ban on avoparcin. *Microb Drug Resist* 2006; **12:** 136–9.

Azidamfenicol (BAN, rINN)

Azidamfénicol; Azidamfenicolum; Azidamphenicol; Azidanfenicol; Azidoamphenicol; Bayer-52910; Азидамфеникол.

2-Azido-*N*-[(α*R*,β*R*)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide.

$C_{11}H_{13}N_5O_5$=295.3

CAS — 13838-08-9.

ATC — S01AA25.

ATC Vet — QS01AA25.

UNII — 40257685LM.

Profile

Azidamfenicol is an antibacterial that is related structurally to chloramphenicol (p. 259.1). It has been used as 1% eye drops in the treatment of bacterial eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Thilocof.

Azidocillin Sodium (BANM, rINNM)

Azidobenzylpenicillin Sodium; Azidocilina sódica; Azidocilline Sodique; Natrii Azidocillinum; Натрий Азидоциллин.

Sodium (6*R*)-6-(D-2-azido-2-phenylacetamido)penicillanate.

$C_{16}H_{16}N_5NaO_4S$=397.4

CAS — 17243-38-8 (azidocillin); 35334-12-4 (azidocillin sodium).

ATC — J01CE04.

ATC Vet — QJ01CE04.

UNII — 0XPT6W6670.

Profile

Azidocillin is a semisynthetic penicillin with actions and uses similar to those of phenoxymethylpenicillin (p. 340.3). It has been given orally as the sodium salt in the treatment of susceptible infections. The potassium salt has also been used.

Azithromycin (BAN, USAN, rINN)

Atsitromysiini; Azithromycine; Azithromycinum; Azitromicina; Azitromicinas; Azitromisin; Azitromycin; Azytromycyna; CP-62993; XZ-450; Азитромицин.

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-(2,6-Dideoxy-3-C-3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)-1-oxa-6-azacyclopentadecan-15-one dihydrate; 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dihydrate.

$C_{38}H_{72}N_2O_{12}$,$2H_2O$=785.0

CAS — 83905-01-5 (anhydrous azithromycin); 121470-24-4 (azithromycin monohydrate); 117772-70-0 (azithromycin dihydrate).

ATC — J01FA10; S01AA26.

ATC Vet — QJ01FA10; QS01AA26.

UNII — F94OW58Y8V (azithromycin); J2KLZ20U1M (anhydrous azithromycin); JTE4MNN1MD (azithromycin monohydrate); 5FD1131I7S (azithromycin dihydrate).

Pharmacopoeias. In *Chin.* and *Jpn.*

Eur. (see p. vii) and *US* include the monohydrate and the dihydrate.

Ph. Eur. 8: (Azithromycin). A white or almost white powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. A 0.2% solution in a mixture of methyl alcohol and water (1:1) has a pH of 9.0 to 11.0. Store in airtight containers.

USP 36: (Azithromycin). A white or almost white powder. Practically insoluble in water; freely soluble in anhydrous alcohol and in dichloromethane. It is anhydrous or contains one or two molecules of water of hydration. pH of a 0.2% solution in a mixture of methyl alcohol and water (1:1) is between 9.0 and 11.0. Store in airtight containers.

Uses and Administration

Azithromycin is a nitrogen-containing macrolide (azalide) with actions and uses similar to those of erythromycin (p. 294.1). It is given in the treatment of respiratory-tract infections (including otitis media), in skin and soft-tissue infections, and in uncomplicated genital infections. Azithromycin may also be used for the prophylaxis, and as a component of regimens in the treatment, of *Mycobacterium avium* complex (MAC) infections. It is used in some countries for the prophylaxis of endocarditis in at-risk patients unable to take penicillin. It is also used in the management of trachoma and typhoid.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Azithromycin has been tried in protozoal infections such as babesiosis (p. 223.3), cryptosporidiosis (p. 923.1), and toxoplasmosis (p. 926.1).

It is given orally or by intravenous infusion usually as the dihydrate; doses are expressed in terms of the anhydrous substance. Azithromycin dihydrate 524 mg is equivalent to about 500 mg of anhydrous azithromycin. The capsule formulation should be given at least 1 hour before, or 2 hours after, meals.

The usual oral dose of azithromycin is 500 mg as a single dose daily for 3 days. Alternatively, an initial dose of 500 mg may be followed by 250 mg daily for a further 4 days.

For uncomplicated genital infections caused by *Chlamydia trachomatis* and for chancroid, 1 g of azithromycin is given as a single dose. For uncomplicated gonococcal infections a single oral 1-g dose of azithromycin with a single dose of a cephalosporin such as ceftriaxone is generally recommended. For the treatment of granuloma inguinale, an initial dose of 1 g followed by 500 mg daily may be given, or 1 g may be given once a week for at least 3 weeks, until all lesions have completely healed.

In the USA, a modified-release preparation given as an oral suspension is available. The product delivers a single 2-g dose and should also be taken on an empty stomach. It is licensed for the treatment of acute bacterial sinusitis or community-acquired pneumonia in adults.

For prophylaxis of disseminated MAC infections, azithromycin 1.2 g may be given once weekly. For treatment or secondary prophylaxis, 500 to 600 mg (depending on the formulation used) should be given once daily, with other antimycobacterials.

For mild or moderate typhoid caused by multidrug-resistant strains, 500 mg once daily may be given for 7 days.

For details of doses in children, see p. 223.3.

Azithromycin dihydrate may also be given initially by intravenous infusion to adults in doses equivalent to 500 mg of azithromycin as a single daily dose in the treatment of community-acquired pneumonia and pelvic inflammatory disease; treatment should be changed to the oral route after at least 2 days in pneumonia and after 1 or 2 days in pelvic inflammatory disease. It may be given either in a solution containing 1 mg/mL over 3 hours or in a solution containing 2 mg/mL over 1 hour.

Azithromycin is also available as 1% (as the base) or 1.5% (as the dihydrate) eye drops for the topical treatment of conjunctivitis caused by susceptible strains of bacteria; the 1.5% solution may also be used for the treatment of trachomatous conjunctivitis (see p. 224.1).

Reviews.

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7. Blumer JL. Evolution of a new drug formulation: the rationale for high-dose, short-course therapy with azithromycin. *Int J Antimicrob Agents* 2005; **26** (suppl 3): S143–S147.
8. Swainston Harrison T, Keam SJ. Azithromycin extended release: a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. *Drugs* 2007; **67:** 773–92.
9. Panpanich R, *et al.* Azithromycin for acute lower respiratory tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 18/06/08).
10. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 26/08/09).
11. Zuckerman JM, *et al.* Macrolides, ketolides, and glycylcyclines: azithromycin, clarithromycin, telithromycin, tigecycline. *Infect Dis Clin North Am* 2009; **23:** 997–1026.

Administration in children. Azithromycin is licensed for use in infants and children for the treatment of infections caused by susceptible organisms. The usual oral dose in those over 6 months of age is 10 mg/kg once daily for 3 days, or an initial dose of 10 mg/kg may be followed by 5 mg/kg daily for a further 4 days; those who weigh over 45 kg may be given the usual adult dose (see Uses and Administration, above). A single dose of 30 mg/kg may also be given for acute otitis media. For pharyngitis or tonsillitis in children aged over 2 years, 12 mg/kg once daily for 5 days may be given. In the USA, a modified-release preparation is available as an oral suspension; and may be used in a single dose of 60 mg/kg (maximum 2 g) for the treatment of community-acquired pneumonia among children 6 months of age and older.

In the UK, the *BNFC* suggests that azithromycin may be used in penicillin allergic children for the prevention of secondary cases of group A streptococcal infection; those 6 months and older may be given an oral dose of 12 mg/kg (to a maximum of 500 mg) once daily for 5 days.

For chronic *Pseudomonas aeruginosa* infection in cystic fibrosis, the *BNFC* suggests that azithromycin may be given orally, 3 times a week, to children from 6 years of age. Those weighing 25 to 40 kg may be given 250 mg, while those weighing more than 40 kg may be given a dose of 500 mg.

The *BNFC* also suggests giving azithromycin 10 mg/kg (to a maximum of 500 mg) once daily for 7 days in the treatment of mild to moderate typhoid caused by multidrug-resistant strains in those aged 6 months and over.

US guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children suggest that for prophylaxis of disseminated *Mycobacterium avium* complex infections, azithromycin 20 mg/kg (to a maximum of 1.2 g) once weekly or 5 mg/kg (to a maximum of 250 mg) once daily may be given.[1] For treatment, 10 to 12 mg/kg (to a maximum of 500 mg) once daily should be given with other antimycobacterials.[1]

1. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 09/12/13)

Babesiosis. In a prospective, randomised study[1] involving 58 patients with babesiosis (p. 922.2), azithromycin with atovaquone was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Azithromycin 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, with atovaquone 750 mg twice daily, both orally for 7 to 10 days, has been recommended by some experts[2] in the USA for the treatment of babesiosis. Immunocompromised patients should be given higher doses of azithromycin (600 to 1000 mg daily). Children may be given azithromycin 10 mg/kg (maximum 500 mg) on day 1 followed by 5 mg/kg (maximum 250 mg) once daily thereafter, with atovaquone 20 mg/kg (maximum 750 mg) twice daily, both orally for 7 to 10 days.[2,3] Azithromycin with quinine

was reported to be effective in 2 patients who had not responded to quinine plus clindamycin.[4,5]

1. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; **343:** 1454–8.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 12/08/08)
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
4. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; **91:** 214–15.
5. Shih C-M, Wang C-C. Ability of azithromycin in combination with quinine for the elimination of babesial infection in humans. *Am J Trop Med Hyg* 1998; **59:** 509–12.

Cholera. Azithromycin has been tried[1-3] in the treatment of cholera (p. 184.2). A single dose of 10 or 20 mg/kg was found to be effective in children[1,2] and 1 g in adults.[3]

1. Khan WA, *et al.* Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial. *Lancet* 2002; **360:** 1722–7.
2. Bhattacharya MK, *et al.* Azithromycin in the treatment of cholera in children. *Acta Paediatr* 2003; **92:** 676–8.
3. Saha D, *et al.* Single-dose azithromycin for the treatment of cholera in adults. *N Engl J Med* 2006; **354:** 2452–62.

Eye infections. Azithromycin 1 or 1.5% ophthalmic solution is effective[1-3] in the treatment of bacterial conjunctivitis, blepharitis, and dry eye, including contact lens-related dry eye. The 1.5% ophthalmic solution may also be used for the treatment of trachoma[3] including mass treatment programmes.[4] For further information on the management of trachoma, see p. 210.1.

1. Utine CA. Update and critical appraisal of the use of topical azithromycin ophthalmic 1% (AzaSite) solution in the treatment of ocular infections. *Clin Ophthalmol* 2011; **5:** 801–9.
2. Nichols JJ, *et al.* Safety and efficacy of topical azithromycin ophthalmic solution 1.0% in the treatment of contact lens-related dry eye. *Eye Contact Lens* 2012; **38:** 73–9.
3. Garnock-Jones KP. Azithromycin 1.5% ophthalmic solution: in purulent bacterial or trachomatous conjunctivitis. *Drugs* 2012; **72:** 361–73.
4. Amza A, *et al.* Elimination of active trachoma after two topical mass treatments with azithromycin 1.5% eye drops. *PLoS Negl Trop Dis* 2010; **4:** e895.

Hyperplasia. For reference to the use of azithromycin to control ciclosporin-induced gingival hyperplasia, see p. 1954.3.

Ischaemic heart disease. Macrolide antibacterials, including azithromycin,[1-4] clarithromycin,[5-9] and roxithromycin,[10-14] have been investigated in the prevention of ischaemic heart disease, based on a suggested link between atherosclerosis and infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) (see p. 177.1). Although preliminary results from some pilot studies were promising, longer-term studies in large numbers of patients were disappointing and none of the three macrolides decreased ischaemic events or provided clinical benefit; indeed, in one study[9] an unexpected increase in cardiovascular mortality was seen in those taking clarithromycin.

1. Anderson JL, *et al.* Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for Chlamydia pneumoniae infection: the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. *Circulation* 1999; **99:** 1540–7.
2. Cercek B, *et al.* Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet* 2003; **361:** 809–13.
3. O'Connor CM, *et al.* Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. *JAMA* 2003; **290:** 1459–66.
4. Grayston JT, *et al.* Azithromycin for the secondary prevention of coronary events. *N Engl J Med* 2005; **352:** 1637–45.
5. Sinisalo J, *et al.* Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-Q-wave coronary syndrome. *Circulation* 2002; **105:** 1555–60.
6. Berg HF, *et al.* Effect of clarithromycin on inflammatory markers in patients with atherosclerosis. *Clin Diagn Lab Immunol* 2003; **10:** 525–8.
7. Berg HF, *et al.* Treatment with clarithromycin prior to coronary artery bypass graft surgery does not prevent subsequent cardiac events. *Clin Infect Dis* 2005; **40:** 358–65.
8. Berg HF, *et al.* Effect of clarithromycin treatment on Chlamydia pneumoniae in vascular tissue of patients with coronary artery disease: a randomized, double-blind, placebo-controlled trial. *J Clin Microbiol* 2005; **43:** 1325–9.
9. Jespersen CM, *et al.* Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ* 2006; **332:** 22–7. Correction. *ibid.*; 151.
10. Gurfinkel E, *et al.* Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes: the final report of the ROXIS Study. *Eur Heart J* 1999; **20:** 121–7.
11. Wiesli P, *et al.* Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in Chlamydia pneumoniae seropositive men: a randomized, double-blind, placebo-controlled trial. *Circulation* 2002; **105:** 2646–52.
12. Zahn R, *et al.* Antibiotic therapy after acute myocardial infarction: a prospective randomized study. *Circulation* 2003; **107:** 1253–9.
13. Sander D, *et al.* Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of Chlamydia pneumoniae seropositivity. *Circulation* 2004; **109:** 1010–15.
14. Kaehler J, *et al.* A randomized trial in patients undergoing percutaneous coronary angioplasty: roxithromycin does not reduce clinical restenosis but angioplasty increases antibody concentrations against Chlamydia pneumoniae. *Am Heart J* 2005; **150:** 987–93.

Malaria. Azithromycin has been studied[1-7] in the management of malaria. Studies[1,4] have shown that an initial loading dose of 750 mg of azithromycin on the first day followed by 250 mg daily thereafter for 20 weeks was effective in the prophylaxis of *Plasmodium vivax* malaria; the drug was well tolerated and the most frequently reported adverse effects were heartburn, paraesthesia, and itching.[3] A study[5] of the treatment of *P. vivax* malaria found that azithromycin 1 g daily for 3 days produced an 88% clinical response rate by day 7, but had a slower onset of action than chloroquine 600 mg daily for 2 days then 300 mg on day 3, which produced a response of 99%.

Azithromycin in various doses (typically 500 mg one to three times daily) with other antimalarials, such as artesunate 200 mg daily[2,7] or quinine 10 mg/kg 3 times daily,[6,7] given for 3 days was found to be effective in the treatment of uncomplicated multidrug-resistant *P. falciparum* malaria in Southeast Asia. However, a later study among Tanzanian children[8] did not support the use of azithromycin with artesunate to treat malaria or acute febrile illness in children in areas of Africa with high levels of antimalarial drug resistance. A systematic review[9] of studies over a period of 14 years suggested that azithromycin was a weak antimalarial. Furthermore, there was no evidence that azithromycin-containing regimens were better than or equivalent to other antimalarials or to current first-line antimalarial combinations for the treatment of *P. falciparum* or *P. vivax*.

Further studies are warranted, especially in children and pregnant women.

1. Taylor WR, *et al.* Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. *Clin Infect Dis* 1999; **28:** 74–81.
2. Krudsood S, *et al.* A randomized clinical trial of combinations of artesunate and azithromycin for treatment of uncomplicated Plasmodium falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2000; **31:** 801–7.
3. Taylor WR, *et al.* Tolerability of azithromycin as malaria prophylaxis in adults in Northeast Papua, Indonesia. *Antimicrob Agents Chemother* 2003; **47:** 2199–2203.
4. Heppner DG, *et al.* Randomized, controlled, double-blind trial of daily oral azithromycin in adults for the prophylaxis of Plasmodium vivax malaria in Western Thailand. *Am J Trop Med Hyg* 2005; **73:** 842–9.
5. Dunne MW, *et al.* A double-blind, randomized study of azithromycin compared to chloroquine for the treatment of Plasmodium vivax malaria in India. *Am J Trop Med Hyg* 2005; **73:** 1108–11.
6. Miller RS, *et al.* Effective treatment of uncomplicated Plasmodium falciparum malaria with azithromycin-quinine combinations: a randomized, dose-ranging study. *Am J Trop Med Hyg* 2006; **74:** 401–6.
7. Noedl H, *et al.* Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated Plasmodium falciparum malaria in adults: a randomized, phase 2 clinical trial in Thailand. *Clin Infect Dis* 2006; **43:** 1264–71.
8. Sykes A, *et al.* Azithromycin plus artesunate versus artemether-lumefantrine for treatment of uncomplicated malaria in Tanzanian children: a randomized, controlled trial. *Clin Infect Dis* 2009; **49:** 1195–1201.
9. van Eijk AM, Terlouw DJ. Azithromycin for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 26/06/12).

Respiratory disorders. For reference to the use of azithromycin in the management of respiratory disorders, see under Erythromycin, p. 294.3.

Adverse Effects and Precautions

As for Erythromycin, p. 295.1.

Gastrointestinal disturbances are the most frequent adverse effect of azithromycin but are usually mild and less frequent than with erythromycin. Headache, somnolence, and taste disturbances may occur. Severe hypersensitivity reactions occur rarely but may be prolonged. Thrombocytopenia and mild transient neutropenia have been rarely reported in patients receiving azithromycin. Pain and inflammation may occur at the site of intravenous infusions particularly at high concentrations. Azithromycin may aggravate muscle weakness in patients with myasthenia gravis and new onset of myasthenic syndromes has been reported.

Licensed product information states that azithromycin should be used with caution in patients with hepatic or renal impairment. It should not be given to those with severe hepatic impairment as safety has not been established. Although plasma concentrations may be increased in renal impairment dosage adjustment is not usually required.

Incidence of adverse effects. In 39 patients given azithromycin daily long-term for mycobacterial infections,[1] gastrointestinal disorders occurred in 32 (82%), hearing impairment in 10 (26%), tinnitus in 18 (46%), and poor balance or dizziness in 11 (28%). In general, adverse effects were associated with higher serum-azithromycin concentrations.

1. Brown BA, *et al.* Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997; **24:** 958–64.

Effects on the ears. Reversible sensorineural hearing loss was reported in 3 patients given oral azithromycin 500 mg daily with clofazimine and ethambutol for the treatment of disseminated *Mycobacterium avium* complex infection.[1] Irreversible hearing loss has also been reported after low-dose exposure to oral azithromycin.[2,3] A patient who had had 8 days of treatment with intravenous azithromycin 500 mg daily for pneumonia reported complete deafness, which had resolved 20 days after stopping the drug.[4]

See also Incidence of Adverse Effects, above.

1. Wallace MR, *et al.* Ototoxicity with azithromycin. *Lancet* 1994; **343:** 241.
2. Ress BD, Gross EM. Irreversible sensorineural hearing loss as a result of azithromycin ototoxicity: a case report. *Ann Otol Rhinol Laryngol* 2000; **109:** 435–7.
3. Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. *J Otolaryngol* 2007; **36:** 257–63.
4. Bizjak ED, *et al.* Intravenous azithromycin-induced ototoxicity. *Pharmacotherapy* 1999; **19:** 245–8.

Effects on fluid and electrolyte homoeostasis. The syndrome of inappropriate antidiuretic hormone secretion was associated with azithromycin treatment in a patient.[1,2]

1. Cadle RM, *et al.* Symptomatic syndrome of inappropriate antidiuretic hormone secretion associated with azithromycin. *Ann Pharmacother* 1997; **31:** 1308–10.
2. Kintzel PE. Correction: symptomatic syndrome of inappropriate antidiuretic hormone secretion associated with azithromycin. *Ann Pharmacother* 1998; **32:** 388.

Effects on the kidneys. Acute interstitial nephritis leading to irreversible renal failure has been reported[1] in a patient who received azithromycin for 9 days. A later report[2] described a patient who developed recurrent acute interstitial nephritis after courses of azithromycin. Repeated exposure resulted in persistent renal damage; leucocytosis and eosinophilia were still present 1 year later.

1. Mansoor GA, *et al.* Azithromycin-induced acute interstitial nephritis. *Ann Intern Med* 1993; **119:** 636–7.
2. Soni N, *et al.* Recurrent acute interstitial nephritis induced by azithromycin. *Pediatr Infect Dis J* 2004; **23:** 965–6.

Effects on the liver. A case[1] of probable azithromycin-induced hepatotoxicity occurred in an elderly patient, with no history of liver disease, after receiving four days of high-dose oral azithromycin for the treatment of suspected bronchitis.

1. Lockwood AM, *et al.* Azithromycin-induced liver injury. *Am J Health-Syst Pharm* 2010; **67:** 810–14.

Hypersensitivity. A syndrome characterised by eosinophilia, arthralgia, fever, and rash was associated with azithromycin or roxithromycin treatment in a patient on separate occasions.[1] The authors believed the condition represented the Churg-Strauss syndrome, although this was disputed by others[2] and attributed to the eosinophilia-myalgia syndrome.

A fatal case of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome and hypersensitivity myocarditis associated with azithromycin use has been reported.[3] There has also been a report[4] of vanishing bile duct syndrome associated with the use of azithromycin and developing a month after initial presentation of Stevens-Johnson syndrome; the patient eventually required liver transplantation.

1. Hübner C, *et al.* Macrolide-induced Churg-Strauss syndrome in a patient with atopy. *Lancet* 1997; **350:** 563.
2. Kränke B, Aberer W. Macrolide-induced Churg-Strauss syndrome in patient with atopy. *Lancet* 1997; **350:** 1551–2.
3. Pursnani A, *et al.* Hypersensitivity myocarditis associated with azithromycin exposure. *Ann Intern Med* 2009; **150:** 225–6.
4. Danica J, *et al.* Vanishing bile duct syndrome associated with azithromycin in a 62-year-old man. *Basic Clin Pharmacol Toxicol* 2010; **106:** 62–5.

Overdosage. Bradycardia with complete heart block was reported[1] in a 9-month-old infant who had been inadvertently given about 50 mg/kg of azithromycin intravenously.

1. Tilelli JA, *et al.* Life-threatening bradyarrhythmia after massive azithromycin overdose. *Pharmacotherapy* 2006; **26:** 147–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azithromycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 296.2.

Giving azithromycin with antacids containing aluminium or magnesium salts can reduce the rate, but not the extent, of its absorption; azithromycin should be given at least 1 hour before or 2 hours after the antacid.

Antiretrovirals. Azithromycin serum concentrations are markedly increased when it is given with *nelfinavir*,[1] but

the clinical significance of this is uncertain. US licensed product information for azithromycin states that dosage adjustment is not required although the patient should be closely monitored for adverse effects.

1. Amsden GW, *et al.* A study of the pharmacokinetics of azithromycin and nelfinavir when coadministered in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1522–7.

Antimicrobial Action

As for Erythromycin, p. 297.1. Azithromycin is less active than erythromycin against streptococci and staphylococci, but has greater activity than erythromycin *in vitro* against some Gram-negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*), as well as having activity against some of the Enterobacteriaceae such as *Escherichia coli* and *Salmonella* and *Shigella* spp. Azithromycin is also more active than erythromycin against *Chlamydia trachomatis* and *Ureaplasma urealyticum*, and some opportunistic mycobacteria, including *Mycobacterium avium* complex. It has activity against the protozoa *Toxoplasma gondii* and *Plasmodium falciparum*.

Resistance. The pattern of resistance to azithromycin is similar to that seen with clarithromycin (p. 270.1).

Pharmacokinetics

Azithromycin given orally is rapidly absorbed and about 40% bioavailable. Absorption from capsules, but not tablets or suspension, is reduced by food. Peak plasma concentrations occur 2 to 3 hours after an oral dose and 1 to 2 hours after intravenous dosage. However, azithromycin is extensively distributed into the tissues, and tissue concentrations subsequently remain much higher than those in the blood; in contrast to most other antibacterials, plasma concentrations are therefore of little value as a guide to efficacy. High concentrations are taken up into white blood cells. There is little diffusion into the CSF when the meninges are not inflamed. Data from *animal* studies indicate that azithromycin crosses the placenta. Small amounts of azithromycin are demethylated in the liver, and it is excreted in bile mainly as unchanged drug and some inactive metabolites have also been detected. About 6% of an oral dose (representing about 20% of the amount in the systemic circulation) is excreted in the urine. The terminal elimination half-life is about 68 hours.

Reviews and references.

1. Lalak NJ, Morris DL. Azithromycin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 370–4.
2. Luke DR, *et al.* Safety, toleration, and pharmacokinetics of intravenous azithromycin. *Antimicrob Agents Chemother* 1996; **40:** 2577–81.
3. Rapp RP. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. *Ann Pharmacother* 1998; **32:** 785–93.
4. Chandra R, *et al.* Clinical pharmacokinetics and gastrointestinal tolerability of a novel extended-release microsphere formulation of azithromycin. *Clin Pharmacokinet* 2007; **46:** 247–59.
5. Salman S, *et al.* Pharmacokinetic properties of azithromycin in pregnancy. *Antimicrob Agents Chemother* 2010; **54:** 360–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arzomicin; Azibiotic; Aztral; Azitrogal; Azitrolabsa; Azitrolan; Azitrona; Azitrox; Cetaxim; Clearsing; Cronopen; Doyle; Fabodrox; Fabramicina; Macromax; Misultina; Naxocina; Neblic; Nifostin; Novozitron; Orobiotic; Sitrox; Talcilina; Tanezox; Triamid; Tritab; Tromiatlas; Vectocilina; Visag; Zitromax; ***Austral.***: Azith; Zedd; Zithromax; Zitrocin; ***Austria***: Azyter; Zithromax; ***Belg.***: Zitromax; ***Braz.***: Astro; Atromicin; Azalide†; Azatill†; Azi; Azimed; Azimix; Azinostil; Azitrin; Azitrogran; Azitrolab; Azitromicil; Azitron; Azitrophar; Azitrosol; Azitroxil†; Clindal; Ems-Max†; Mac Azi; Mazitrom; Novatrex; Selimax Pulso; Selimax; Tromix; Tromizir; Trozyman†; Zidimax; Zimicina; Zitril; Zitromax; Zitromil; Zitroneo; ***Canad.***: Z-Pak; Zithromax; Zmax; ***Chile***: Abacten; Atizor; Azimit; Azitrom; Ricilina; Trex; Zithromax; ***China***: A Sai Qi (阿赛奇); Ai Mi Qi (爱米琦); Ao Li Ping (澳立平); Ba Qi (八奇); Bin Qi (宾奇); BinQi (滨齐); Chen Yu (辰羽); Feng Da Qi (锋达齐); Fu Qi-Hua Yuan (弗奇); Fuqixing (芙琦星); Jun Jie (君洁); Jun Wei Qing (君维清); Kai Qi (开奇); Kang Qi (康奇); Ke Lin Da (克琳达); Ke Yan Li (克严力); Kuai Di (快迪); Kuai Yu (快宇); Li Ke Si (利可思); Li Li Kai (利力凯); Li Li Xing (利力欣); Lin Bi (林比); Lipuqi (利普奇); Lipuxin (利普欣); Lizhu Qile (丽珠奇乐); Lu Jia Kang (露家康); Luo Bei Er (洛贝尔); Luo Qi (洛奇); Luoxin Shoukang (罗欣首抗); Ming Qi Xin (明齐欣); Pai Fen (派芬); Pai Fu (派扶); Paiqi (派奇); Pu He (普贺); Pu Le Qi (浦乐齐); Pu Yang (普阳); Qi Gu Mei (奇谷美); Qi Mai Xing (齐迈星); Qi Xian (其仙); QiLi (奇力); Qiyue (琦玥); Rui Qi (瑞奇); Rui Qi Lin (瑞琦霖); Sai Jin Sha (赛金沙); Sai Le Xin (赛乐欣); Sai Qi (赛奇); Sheng Nuo Ling (圣诺灵); Shepherd (欣匹特); Shu Luo Kang (抒罗康); Su Shuang (苏爽); Sumamed (舒美特); Tailite (泰力特); Te Li Xin (特立欣); Tong Tai Qi Li (通泰奇力); TuoQi (托琪); Wei Zong (维宗); Weihong (维宏); Xi Le Xin (西乐欣); Xi Mei (悉美); Xin Da Kang (信达康); Xin Pu Rui (欣普瑞); Ya Rui (雅瑞); Yan Sha (岩沙); Yi Nuo Da (依诺达); Yi Ou Qing (亦欧青); Yi Xin (益欣); Yin Pei Kang (因培康); Yong Qi (永齐); You Ni Ke (尤尼克); Zaiqi (再奇); Ze Qi (泽奇); Zithromax (希舒美); ***Cz.***: Azibiot; Azitrox; Sumamed; Zetamac; Zitrocin; ***Denm.***: Azyter; Zitromax; ***Fin.***: Azyter; Zithromax; ***Fr.***: Azadose; Azyter; Ordipha; Zithromax; ***Ger.***: Azithro†; Azithrobeta; Azyter; Ultreon; Zithromax; ***Gr.***: Azibactron; Azifarm; Azirox; Azirutec; Azithral; Azithrin; Azitrolid; Azivirus; Azytan†; Bezanin; Binozyt; Disithrom; Figothrom; Flumax; Goldamycin; Gramokil; Novozithron; Razimax; Thoraxx; Throzimax; Zinfect; Zithro-Due; Zithrobest; Zithromax; Zithroned; Zithropan; Zithroplus; Zithrotel; Zithroxyn; Zitrax; Zyramycin; ***Hong Kong***: Azee; Azicine; Clindal AZ; Zithromax; Zmax; Zotax; ***Hung.***: Azi; Azibiot; Azicid†; Sumamed; Zitrocin; Zmax; ***India***: A-OD; Acex; Actimycin; Alicin; Apocin; Arcin; Arizith; Arz; Atm; Avzeth; Az-1; Azard; Azauk; Azbir; Azee; Azegud; Azeloc; Azforin; Azi-Big; Azibact; Azibest; Azicip; Azicos; Azicure; Azid; Azidraw; Azifast; Azifem; Azifine; Azigram; Azikab; Azikare; Azikil; Azileb; Azilide; Azilife; Azilin; Azilup; Azim; Azimac; Azimax; Azin; Azina; Azinex; Azinix; Azinova; Azintra; Aziom; Azipar; Azipokyn; Azipos; Aziral; Azirid; Aziriv; Azirock; Azis; Azisafe; Azisara; Azizet; Azisia; Azison; Azistar; Azisym; Azitas; Aziter; Azith; Azithom; Azithral; Azithro; Azitone; Azitoz; Azitrac; Azitrin; Azitrop; Azitsa; Azitus; Azivar; Aziwin; Aziwok; Azix; Azla; Azmag; Azmic; Azobac; Azolid; Azolife; Azom; Azomax; Azone; Azopet; Azostar; Azras; Azrea; Azro; Aztin; Aztus; Azvig; Azy; Azylin; Azysafe; Azystate; Azyxin; Azza; Bezit; Bio-AZ; Cazita; Cumycin; Dazy; Elgram; Elzee; Ertycin; Eszit; Ezith; Flaag; Forit; Fydozith; G-Thro; Gitro; Hizy; I-Thro; Infurox; Itha; Jocin; Kanny; L-Thro; Laz; Lazith; Lethro; LG-Thral; Loromycin; Macrosafe; Macrotar; Maxazi; Myza; Nizithro; Nodycin; Zithrocin; Zycin; ***Indon.***: Aztrin; Binozyt; Maxmor; Mezatrin; Trozin; Zarom; Zibramax; Zicho; Zifin; Zistic; Zithromax; Zycin; ***Irl.***: Azromax; Azyter; Zithromax; ***Israel***: Azenil; Zeto; Zithromax; Zmax; ***Ital.***: Azitrocin; Batif; Ribotrex; Trozocina; Zindel; Zitrobiotic; Zitromax; ***Jpn***: Zithromac; ***Malaysia***: Binozyt; Zithromax; Zmax; ***Mex.***: Amsati†; Atoxitom; Azibiot; Azidral; Aziphar; Aziteva†; Azitrocin; Azitrohexal†; Azo-Max; Charyn; Craztronin; Koptin; Macrozit; Marzivag; Medatz; Sicalan; Texis; Tromicina; Truxa; Zertalin; Zithran†; Zitroken; ***Neth.***: Azacleus†; Azyter; Nucaza†; Zithromax; ***Norw.***: Azitromax; Azyter; ***NZ***: Zithromax; ***Philipp.***: Azi; Azomycin; Azyth; Geozit; Macromax; Macrozyth; Trozin; Zenith; Zithromax; Zmax; ***Pol.***: Azibiot; Azimycin; AziTeva; Azitrin; Azitro-Mepha; AzitroLEK; Azitrox; Azycyna; Azyter; Canbiox; Macromax; Nobaxin; Oranex; Sumamed; Zetamax; ***Port.***: 3Z; Azimax†; Azimed; Aziton†; Azitrix; Azixratio†; Azyter; Biozitra†; Gigatrom†; Lazitrom†; Neofarmiz; Unizitro; Zithromax; Zitrina; Zitrozina; ***Rus.***: Azicid (Азицид); Azimycin (Азимицин); Azithrox (Азитрокс); Azithrus (Азитрус); Azitral (Азитрал); Aziwok (Азивок); Hemomycin (Хемомицин); Sumaklid (Сумаклид); Sumamecin (Сумамецин); Sumamed (Сумамед); Sumamox (Сумамокс); Sumazid (Сумазид); Tremak (Тремак); Zetamax (Зетамакс); ZI-Factor (ЗИ-фактор); Zithrocin (Зитроцин); Zitrolid (Зитролид); ***S.Afr.***: Azimax; Binozyt; Clamelle; Ultreon; Zeemide; Zithrogen; Zithromax; ***Singapore***: AZmycin; Binozyt; Zithromax; Zmax; ***Spain***: Altezym†; Aratro; Azydrop; Goxil†; Toraseptol†; Vinzam; Zentavion†; Zitromax; ***Swed.***: Azitromax; Azyter; ***Switz.***: Azitro; Zithromax; ***Thai.***: Azith; Azithrin; Azithro; Azycin; Azyter; Binozyt; Floctil; Onzet; Zithromax; Zmax; ***Turk.***: Azacid†; Azax; Azeltin; Azitro; Azitrotek; Azomax; Azro; Tremac; Zitromax; Zitrotek; ***UAE***: Azomycin; ***UK***: Azyter; Clamelle; Zedbac; Zithromax; ***Ukr.***: Azax (Азакс); Azicin (Азицин); Azimed (Азимед); Azinort (Азинорт); Azithro (Азитро); Azithro (Азитрогексал); Azitrox (Азитрокс); Aziwok (Азивок); Azo (Азо); Azro (Азро); Hemomicin (Хемомицин); Ormax (Ормакс); Sumamed (Сумамед); Zetamaks (Зетамакс); Zetamax (Зетамакс); Zithrocin (Зитроцин); Zithrolex (Зитролекс); Zomax (Зомакс); ***USA***: AzaSite; Zithromax; Zmax; ***Venez.***: Amizin; Amovin; Aruzilina; Arzomidol; Atromizin; Azigram; Azimakrol; Azitrom; Azitromin; Binozyt; Saver; Zitromax; Zival.

Multi-ingredient Preparations. ***India***: AF-Kit; Azintra-3; Azintra-AX; Azithral Jun; Azithral XP; Azro AM; Azyxin Plus; Corzi; Eradikit; Eve Kit; Fas-3 Kit; FC-Kit; Fiscon Tab; Flunec Combikit; Fulkit; Fygek-AS; Gyn-3; Gynotrim Kit; Hif-AS; Kit-3D; Laz-AX; Myconor-4; Nuforce-3 Kit; Od-Kit; Orflaz Kit; Saf Kit; ***Mex.***: Zitroflam; ***Rus.***: Safocid (Сафоцид); ***Ukr.***: Ginekit (Гинекит).

Pharmacopoeial Preparations
USP 36: Azithromycin Capsules; Azithromycin for Injection; Azithromycin Tablets.

Azlocillin *(BAN, USAN, rINN)*

Atslosilliini; Azlocilina; Azlocilline; Azlocillinum; Азлоциллин.

6-[*N*-(2-Oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

$C_{20}H_{23}N_5O_6S$=461.5

CAS — 37091-66-0.

ATC — J01CA09.

ATC Vet — QJ01CA09.

UNII — HUM6H389W0.

Azlocillin Sodium *(BANM, rINNM)*

Azlocilina sódica; Azlocilline Sodique; Azlocillinum Natricum; Azlocylina sodowa; Bay-e-6905; Natrii Azlocillinum; Натрий Азлоциллин.

Sodium (6*R*)-6-[D-2-(2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate.

$C_{20}H_{22}N_5NaO_6S$=483.5

CAS — 37091-65-9.

ATC — J01CA09.

ATC Vet — QJ01CA09.

UNII — DWV1EFW947.

Pharmacopoeias. In *Pol.*

Incompatibility. Azlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Uses and Administration

Azlocillin is a ureidopenicillin and, like piperacillin (p. 342.1), has been used mainly for the treatment of infections caused by *Pseudomonas aeruginosa*. It has been used particularly for septicaemia, and infections of the respiratory and urinary tracts, and also for peritonitis; for details of these infections, see under Choice of Antibacterial, p. 172.2.

Azlocillin has generally been used with an aminoglycoside; however, they should be given separately as they have been shown to be incompatible (see Incompatibility, above).

Azlocillin has been given intravenously as the sodium salt. Doses are expressed in terms of the equivalent amount of azlocillin; 1.05 g of azlocillin sodium is equivalent to about 1 g of azlocillin. A 10% solution in a suitable diluent may be given by slow injection for doses of 2 g or less; higher doses should be infused over 20 to 30 minutes.

A typical dose is 5 g every 8 hours for life-threatening infections, or 2 g every 8 hours for less severe infections and urinary-tract infections.

For details of doses in children, see p. 225.3.

Dosage of azlocillin may need to be adjusted in patients with hepatic or renal impairment (see p. 225.3).

Administration in children. Azlocillin has been used in neonates and children for the treatment of infections caused by susceptible organisms, given intravenously in the following doses:

- premature infants: 50 mg/kg twice daily
- neonates less than 7 days old: 100 mg/kg twice daily
- infants between 7 days and 1 year of age: 100 mg/kg 3 times daily
- children up to 14 years of age: 75 mg/kg 3 times daily

Administration in hepatic or renal impairment. The interval between doses of intravenous azlocillin may need to be increased to every 12 hours in moderate to severe renal impairment (creatinine clearance less than 30 mL/minute); additional dosage reductions may be needed in patients with both severe renal and hepatic impairment.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 234.1.

Prolongation of bleeding time has been less frequent and less severe with azlocillin than with carbenicillin.

Hypouricaemia. Reports of transient asymptomatic decreases in serum-uric acid concentrations during treatment with azlocillin.[1,2]

1. Faris HM, Potts DW. Azlocillin and serum uric acid. *Ann InternMed* 1983; **98:** 414.
2. Ernst JA, Sy ER. Effect of azlocillin on uric acid levels in serum. *Antimicrob Agents Chemother* 1983; **24:** 609–10.

Sodium content. Each g of azlocillin sodium contains about 2.1 mmol of sodium. As azlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p. 232.1.

Antibacterials. For the effect of azlocillin on the clearance of *cefotaxime*, and a report of neurotoxicity, see p. 246.3. For reference to azlocillin affecting the disposition of *ciprofloxacin*, see p. 267.1.

Neuromuscular blockers. Azlocillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p. 2032.1).

Antimicrobial Action

Azlocillin has an antimicrobial action similar to that of piperacillin (p. 343.1). Its activity *in vitro* against Enterobacteriaceae is generally less than that of mezlocillin or piperacillin, but it has comparable activity to piperacillin against *Pseudomonas aeruginosa*.

Pharmacokinetics

Azlocillin is not absorbed from the gastrointestinal tract to any significant extent. It has nonlinear dose-dependent pharmacokinetics. Doubling an intravenous dose results in more than double the plasma concentration. Between 20 and 46% of azlocillin in the circulation is bound to plasma proteins. The plasma half-life is usually about 1 hour, but is longer in neonates; in patients with renal impairment half-lives of 2 to 6 hours have been reported.

Azlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Azlocillin is metabolised to a limited extent. About 50 to 70% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours of a dose, resulting in high urinary concentrations. Azlocillin is partly excreted in the bile where it is also found in high concentrations.

Plasma concentrations are enhanced if probenecid is given.

Azlocillin is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Alocin (阿乐欣); ***Gr.***: Abrodil.

Aztreonam *(BAN, USAN, rINN)*

Atstreonaami; Azthreonam; Aztréonam; Aztreonamum; SQ-26776; Азтреонам.

(*Z*)-2-{2-Aminothiazol-4-yl-[(2*S*,3*S*)-2-methyl-4-oxo-1-sulphoazetidin-3-ylcarbamoyl]methyleneamino-oxy}-2-methylpropionic acid.

$C_{13}H_{17}N_5O_8S_2$=435.4

CAS — 78110-38-0.

ATC — J01DF01.

ATC Vet — QJ01DF01.

UNII — G2B4VE5GH8.

Pharmacopoeias. In *Jpn* and *US*, which allows the anhydrous or hydrated forms.

USP 36: (Aztreonam). A white, odourless crystalline powder. Very slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ethyl acetate, and in toluene; soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers.

Aztreonam Lysine *(BANM, USAN, rINNM)*

Aztreonam lisina; Aztréonam Lysine; Aztreonamum Lysinum; Corus-1020; Азтреонамк Лизин.

(*Z*)-2-{2-Aminothiazol-4-yl-[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfoazetidin-3-ylcarbamoyl]methyleneamino-oxy}-2-methylpropionic acid L-lysine.

$C_{13}H_{17}N_5O_8S_2.C_6H_{14}N_2O_2$=581.6

CAS — 827611-49-4.

ATC — J01DF01.

ATC Vet — QJ01DF01.

UNII — XNM7LT65NP.

Incompatibility and stability. Aztreonam has been reported to be incompatible with cefradine, metronidazole, nafcillin, and vancomycin.

References.

1. Bell RG, *et al.* Stability of intravenous admixtures of aztreonam and cefoxitin, gentamicin, metronidazole, or tobramycin. *Am J Hosp Pharm* 1986; **43:** 1444–53.
2. Riley CM, Lipford LC. Interaction of aztreonam with nafcillin in intravenous admixtures. *Am J Hosp Pharm* 1986; **43:** 2221–4.
3. Belliveau PP, *et al.* Stability of aztreonam and ampicillin sodium-sulbactam sodium in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1994; **51:** 901–4.
4. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 1086–90.
5. Trissel LA, *et al.* Compatibility and stability of aztreonam and vancomycin hydrochloride. *Am J Health-Syst Pharm* 1995; **52:** 2560–4.

Uses and Administration

Aztreonam is a monobactam or monocyclic beta-lactam antibacterial used for the treatment of infections caused by susceptible Gram-negative aerobic organisms. These have included bone and joint infections, gonorrhoea, intra-abdominal and pelvic infections, lower respiratory-tract infections (including pseudomonal infections in patients with cystic fibrosis), meningitis, septicaemia, skin and soft-tissue infections, and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2. To broaden the spectrum of activity for empirical treatment of infections, aztreonam should be used with other antibacterials. Use with an aminoglycoside may be of benefit in serious *Pseudomonas aeruginosa* infections.

Aztreonam is usually given *parenterally* by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion over 20 to 60 minutes. Single doses over 1 g should be given by the intravenous route. It is given in doses ranging from 1 to 8 g daily (usually 3 to 4 g daily), in divided doses every 6 to 12 hours, according to the severity of the infection. For infections due to *Ps. aeruginosa*, 2 g every 6 or 8 hours may be given for initial treatment.

A single intramuscular dose of 1 g has been recommended for the treatment of gonorrhoea or cystitis.

The dose of aztreonam may need to be reduced in renal impairment, see p. 226.3.

For details of doses in children, see p. 226.2.

Aztreonam lysine may be given by *inhalation* for the suppression of chronic respiratory-tract infections due to *Ps. aeruginosa* in patients with cystic fibrosis. The usual dose, expressed in terms of aztreonam, is 75 mg given 3 times within a 24 hour period for 28 days; doses should be taken at least 4 hours apart. Patients should use a bronchodilator before each dose; short-acting bronchodilators should be given 15 minutes to 4 hours before inhaled aztreonam, whereas long-acting bronchodilators may be given 30 minutes to 12 hours before. If patients require a mucolytic this should also be given before aztreonam (but after the bronchodilator). If additional courses of aztreonam are required, a minimum of 28 days between courses is recommended.

General references.

1. Brogden RN, Heel RC. Aztreonam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1986; **31:** 96–130.
2. Neu HC. ed. Aztreonam's role in the treatment of Gram-negative infections. *Am J Med* 1990; **88** (suppl 3C): 1S–43S.
3. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.

Administration. References to the use of aztreonam (as aztreonam lysine) by inhalation in the treatment of airway infections in patients with cystic fibrosis.[1-8]

1. Gibson RL, *et al.* Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2006; **41:** 656–65.
2. Retsch-Bogart GZ, *et al.* A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol* 2008; **43:** 47–58.
3. McCoy KS, *et al.* Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med* 2008; **178:** 921–8.
4. Retsch-Bogart GZ, *et al.* Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest* 2009; **135:** 1223–32.
5. Elborn JS, Henig NR. Optimal airway antimicrobial therapy for cystic fibrosis: the role of inhaled aztreonam lysine. *Expert Opin Pharmacother* 2010; **11:** 1373–85.
6. O'Sullivan BP, *et al.* Inhaled aztreonam. *Nat Rev Drug Discov* 2010; **9:** 357–8.
7. Plosker GL. Aztreonam lysine for inhalation solution: in cystic fibrosis. *Drugs* 2010; **70:** 1843–55.
8. Zeitler K, *et al.* Aztreonam lysine for inhalation: new formulation of an old antibiotic. *Am J Health-Syst Pharm* 2012; **69:** 107–15.

Administration in children. Aztreonam may be given to neonates and children for the treatment of infections caused by susceptible Gram-negative aerobic organisms including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*. It is usually given *parenterally* by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion over 20 to 60 minutes. Single doses over 1 g should be given by the intravenous route.

UK licensed product information recommends that aztreonam be given in the following doses:

- infants older than one week and children less than 2 years of age: 30 mg/kg every 6 or 8 hours
- children 2 to 12 years: 30 mg/kg every 6 or 8 hours which may be increased to 50 mg/kg every 6 or 8 hours in severe infection (to a maximum total daily dose of 8 g)

Although not licensed in the UK for neonates less than one week old, the *BNFC* suggests a dose of 30 mg/kg given intravenously every 12 hours.

In the USA, the American Academy of Pediatrics[1] suggests the following doses for aztreonam:

- neonates aged 7 days or less with a birth-weight of 2 kg or less: 30 mg/kg every 12 hours
- neonates aged 7 days or less with a birth-weight more than 2 kg: 30 mg/kg every 8 hours
- neonates aged 8 to 28 days with a birth-weight of 2 kg or less: 30 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- neonates aged 8 to 28 days with a birth-weight of more than 2 kg: 30 mg/kg every 6 hours
- children 1 month and older; 90 mg/kg in 3 divided doses (to a maximum daily dose of 3 g) for mild to moderate infections, or 90 to 120 mg/kg in 3 or 4 divided doses (to a maximum daily dose of 8 g) in severe infections

Aztreonam lysine may be given by *inhalation* for the suppression of chronic respiratory-tract infections due to *Ps. aeruginosa* in children aged 6 years and older with cystic fibrosis; doses are as for adults (see above).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of aztreonam should be reduced in moderate to severe renal impairment. Patients with renal impairment may be given a usual initial dose followed by a maintenance dose adjusted according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: half the initial dose
- CC less than 10 mL/minute: one-quarter of the initial dose
- haemodialysis patients: a supplementary dose of one-eighth of the initial dose should be given after each dialysis session

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy recommends that patients undergoing continuous renal replacement therapy (CRRT) receive a loading dose of 2 g, with the following maintenance doses, depending on the type of CRRT:

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours

For critically ill patients undergoing intermittent haemodialysis, the authors suggest a dosing regimen of 500 mg every 12 hours.[1]

Inhaled aztreonam lysine should be used with caution in patients whose serum creatinine is more then 2 times the upper limit of normal.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects

The adverse effects of aztreonam are similar to those of other beta lactams (see Benzylpenicillin, p. 231.2, and Cefalotin, p. 237.2). Hypersensitivity reactions, including rashes, urticaria, angioedema, exfoliative dermatitis, eosinophilia, bronchospasm, and rarely anaphylaxis and toxic epidermal necrolysis, may occur in patients receiving aztreonam, although it has been reported to be only weakly immunogenic. Gastrointestinal effects include diarrhoea, nausea, vomiting, mouth ulcer, and an abnormal taste.

Phlebitis or thrombophlebitis has been reported after the intravenous use of aztreonam, and pain or swelling after intramuscular injection.

Use of aztreonam may result in the overgrowth of non-susceptible organisms, including Gram-positive cocci. Pseudomembranous colitis or gastrointestinal bleeding may develop.

Other adverse effects that have been reported with aztreonam include jaundice and hepatitis, increases in liver enzymes, and prolongation of prothrombin and partial thromboplastin times.

Cough, wheezing, nasal congestion, fever, and occasional reports of bronchospasm have been associated with inhalation of aztreonam lysine.

Effects on the skin. References.

1. McDonald BJ, *et al.* Toxic epidermal necrolysis possibly linked to aztreonam in bone marrow transplant patients. *Ann Pharmacother* 1992; **26:** 34–5.
2. Gonzalo-Garijo MA, de Argila D. Erythroderma due to aztreonam and clindamycin. *J Investig Allergol Clin Immunol* 2006; **16:** 210–1.

Precautions

Aztreonam should not be given to patients who are hypersensitive to it and should be used with caution in those known to be hypersensitive to other beta lactams, although the incidence of cross-sensitivity appears to be low (but see p. 227.1).

Aztreonam should be used with caution in patients with renal or hepatic impairment.

Breast feeding. In a study in 12 healthy women given aztreonam, peak concentrations in breast milk were found to be less than 1% of those in serum and this was considered suggestive of a low risk of adverse effects in breast-fed infants.[1] The last available guidance from the American Academy of Pediatrics stated that no adverse effects had been seen in breast-fed infants whose mothers received aztreonam and considered it to be usually compatible with breast feeding,[2] although UK licensed product information recommends that mothers should refrain from breast feeding while receiving aztreonam.

1. Fleiss PM, *et al.* Aztreonam in human serum and breast milk. *Br J Clin Pharmacol* 1985; **19:** 509–11.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May

2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Aztreonam is said to show little cross-reactivity with most other beta lactams,[1,2] but there have been isolated reports of immediate hypersensitivity to aztreonam in patients with a history of hypersensitivity to penicillin.[3,4]

Ceftazidime (p. 252.2) and aztreonam share a common side-chain, and there are some data to suggest that cross-reactivity between the two may exist. Therefore, extra caution is required if aztreonam is to be used in ceftazidime-allergic patients.[2]

1. Patriarca G, *et al.* Tolerability of aztreonam in patients with IgE-mediated hypersensitivity to beta-lactams. *Int J Immunopathol Pharmacol* 2008; **21:** 375–9.
2. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother* 2009; **43:** 304–15.
3. Alvarez JS, *et al.* Immediate hypersensitivity to aztreonam. *Lancet* 1990; **335:** 1094.
4. Hantson P, *et al.* Immediate hypersensitivity to aztreonam and imipenem. *BMJ* 1991; **302:** 294–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aztreonam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Caution is recommended in patients receiving aztreonam and oral anticoagulants because of the possibility of increased prothrombin time.

Antimicrobial Action

Aztreonam is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall; it has a high affinity for the penicillin-binding protein 3 (PBP-3) of Gram-negative bacteria. The activity of aztreonam is restricted to Gram-negative aerobic organisms, with poor or no activity against Gram-positive aerobes or anaerobic organisms. It has good activity against *Haemophilus influenzae* and *Neisseria* spp., including beta-lactamase-producing strains. Aztreonam is also active against most Enterobacteriaceae (including *Escherichia coli, Citrobacter, Enterobacter, Klebsiella, Proteus, Providencia, Salmonella, Serratia, Shigella, Yersinia* spp., and *Morganella morganii*) providing that they do not produce extended-spectrum beta-lactamases (ESBLs) or KPC-type beta-lactamases, or hyperproduce AmpC beta-lactamases. Although *Pseudomonas aeruginosa* has historically been considered aztreonam-susceptible, antipseudomonal beta-lactam antibacterials such as ceftazidime are more active and about one-third of contemporary *Ps. aeruginosa* strains are resistant to aztreonam.

Synergy has been reported *in vitro* between aztreonam and aminoglycosides against *Ps. aeruginosa* and some Enterobacteriaceae.

Resistance. Aztreonam is stable to hydrolysis by many narrow-spectrum beta-lactamases but many current beta-lactamases, in particular the ESBLs and carbapenemases (but not metallo-β-lactamases), are associated with resistance to aztreonam. Hyperproduction of AmpC beta-lactamase (typically in *Enterobacter cloacae, Serratia marcescens, Citrobacter freundii*, and other related bacteria) also leads to aztreonam resistance.

Pharmacokinetics

Aztreonam is poorly absorbed from the gastrointestinal tract and is therefore given parenterally. Peak serum concentrations of about 90 and 200 micrograms/mL occur after single, 30-minute intravenous infusions of 1 and 2 g, respectively; when these doses are given by intravenous injection over 3 minutes, slightly higher peak serum concentrations (125 and 242 micrograms/mL) occur. Absorption after intramuscular injection is good, and serum concentrations at 1 hour are comparable for identical single intramuscular and intravenous doses. Aztreonam has a plasma half-life of about 1.7 hours. The half-life may be prolonged in neonates, in the elderly, in patients with renal impairment, and to some extent in those with hepatic impairment. Aztreonam is about 56% bound to plasma proteins. It is widely distributed in body tissues and fluids, including bile. Diffusion into the CSF is poor unless the meninges are inflamed. It crosses the placenta and enters the fetal circulation; small amounts are distributed into breast milk.

Aztreonam is not extensively metabolised. The principal metabolite, SQ-26992, is inactive and is formed by opening of the beta-lactam ring; it has a much longer half-life than the parent compound. Aztreonam is excreted mainly in the urine, by renal tubular secretion and glomerular filtration; about 60 to 70% of a dose appears within 8 hours as unchanged drug with only small quantities of metabolites. Only small amounts of unchanged drug and metabolites are excreted in the faeces.

Aztreonam is removed by haemodialysis and to a lesser extent by peritoneal dialysis.

Small but variable amounts are absorbed after inhalation of nebulised aztreonam lysine; about 10% of the dose is reported to be excreted in urine, largely as unchanged drug.

Reviews.

1. Mattie H. Clinical pharmacokinetics of aztreonam: an update. *Clin Pharmacokinet* 1994; **26:** 99–106.
2. Vinks AA, *et al.* Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using Monte Carlo simulation. *Antimicrob Agents Chemother* 2007; **51:** 3049–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Azactam; ***Austria***: Azactam; Cayston; ***Belg.***: Azactam; ***Braz.***: Azactam; Azanem; Uni Aztrenam; ***Canad.***: Cayston; ***Chile***: Azactam†; ***China***: Azactam (君刻单); ***Cz.***: Azactam†; Cayston; ***Denm.***: Azactam; Cayston; ***Fin.***: Azactam; ***Fr.***: Azactam; Cayston; ***Ger.***: Azactam†; Cayston; ***Gr.***: Azactam; Azenam; Aztreotic; Cayston; ***India***: Azactam; Azenam; Azom; Azotum; Aztreo; Trezam; ***Indon.***: Vebac; ***Irl.***: Azactam; Cayston; ***Ital.***: Azactam†; Primbactam; ***Jpn***: Azactam; ***Mex.***: Monobac; ***Neth.***: Cayston; ***Norw.***: Azactam; ***NZ***: Azactam; ***Philipp.***: Azactam†; Aztram; ***Pol.***: Azactam†; Cayston; ***Port.***: Azactam; Cayston; ***Rus.***: Aznam (Азнам); Aztreobol (Азтреабол); ***S.Afr.***: Azactam; ***Singapore***: Azactam; ***Spain***: Azactam; Cayston; ***Swed.***: Azactam; ***Switz.***: Azactam; ***UK***: Azactam; Cayston; ***USA***: Azactam; Cayston; ***Venez.***: Azactam.

Pharmacopoeial Preparations
USP 36: Aztreonam for Injection; Aztreonam Injection.

Bacampicillin Hydrochloride

(BANM, USAN, rINNM)

Ampicillin Ethoxycarbonyloxyethyl Hydrochloride; Bacampicilina, hidrocloruro de; Bacampicilline, chlorhydrate de; Bacampicillinhydrochlorid; Bacampicillini Hydrochloridum; Bakampicilin-hydrochlorid; Bakampicilino hidrochloridas; Bakampicillin-hidroklorid; Bakampicillinhydroklorid; Bakampisilin Hidroklorür; Bakampisilliinihydrokloridi; Carampicillin; EPC-272; Hidrocloruro de bacampicilina; Бакампициллина Гидрохлорид.

1-(Ethoxycarbonyloxy)ethyl (6*R*)-6-(α-D-phenylglycylamino) penicillanate hydrochloride.

$C_{21}H_{27}N_3O_7S,HCl$=502.0

CAS — 50972-17-3 (bacampicillin); 37661-08-8 (bacampicillin hydrochloride).

ATC — J01CA06.

ATC Vet — QJ01CA06.

UNII — PM034U953T.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bacampicillin Hydrochloride). A white or almost white hygroscopic powder or granules. Soluble in water and in dichloromethane; freely soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.5. Store in airtight containers.

Uses and Administration

Bacampicillin has actions and uses similar to those of ampicillin (p. 218.3) to which it is rapidly hydrolysed in the body. It is given orally as the hydrochloride for the treatment of infections caused by susceptible bacteria in doses of 0.8 to 2.4 g daily, in 2 divided doses. For details of doses in children, see p. 227.2.

In uncomplicated gonorrhoea a single dose of bacampicillin hydrochloride 1.6 g with probenecid 1 g may be given in areas where gonococci remain sensitive.

Administration in children. In children, bacampicillin has been used orally for the treatment of susceptible bacterial infections, similarly to ampicillin. In children over 5 years of age, doses of 25 to 50 mg/kg daily, in 2 divided doses, have been used.

Adverse Effects and Precautions

As for Ampicillin, p. 219.2. Diarrhoea has been reported to occur less frequently with bacampicillin.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bacampicillin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Benzylpenicillin, p. 232.1.

Antimicrobial Action

Bacampicillin has the antimicrobial action of ampicillin *in vivo* (p. 219.3). It possesses no intrinsic activity and needs to be hydrolysed to ampicillin.

Pharmacokinetics

Bacampicillin is more rapidly and completely absorbed from the gastrointestinal tract than ampicillin, to which it is hydrolysed in the intestinal wall and plasma. Peak plasma-ampicillin concentrations occur about 30 to 60 minutes after oral doses, and are about 2 to 3 times those after an equivalent dose of ampicillin. The absorption of bacampicillin from tablets does not appear to be affected by the presence of food in the stomach. About 75% of a dose is excreted in the urine as ampicillin within 8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Albaxin; ***India***: Penglobe; ***Ital.***: Bacacil; Bacagen; Bacasint; Bacillin; Winnipeg; ***Malaysia***: Bacamcillin; ***Philipp.***: Penglobe†; ***Thai.***: Penglobe; ***Turk.***: Bakamsilin; Penbak.

Pharmacopoeial Preparations
USP 36: Bacampicillin Hydrochloride Tablets.

Bacitracin *(BAN, rINN)*

Bacitracina; Bacitracinas; Bacitracine; Bacitracinum; Bacytracyna; Basitrasiini; Basitrasin; Бацитрацин.

CAS — 1405-87-4.

ATC — D06AX05; J01XX10; R02AB04.

ATC Vet — QA07AA93; QD06AX05; QJ01XX10; QR02AB04.

UNII — 58H6RWO52I (bacitracin); DDA3RRX0P7 (bacitracin A); 3968434C0D (bacitracin B1); AM2V8LQG5X (bacitracin B2); 1RE2J07DT4 (bacitracin B3).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Bacitracin). Mixture of antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* or *B. subtilis*. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or almost white hygroscopic powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 6.0 to 7.0. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

USP 36: (Bacitracin). A mixture of polypeptides produced by the growth of an organism of the *licheniformis* group of *Bacillus subtilis* (Bacillaceae). The main components are bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It is a white to pale buff, hygroscopic powder, odourless or having a slight odour. Freely soluble in water; soluble in alcohol, in glacial acetic acid, and in methyl alcohol, the solution in the organic solvents usually showing some insoluble residue; insoluble in acetone, in chloroform, and in ether. Its solutions deteriorate rapidly at room temperature. It is precipitated from its solutions and is inactivated by salts of many of the heavy metals. pH of a solution in water containing 10 000 units/mL is between 5.5 and 7.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Bacitracin Zinc *(BANM, rINNM)*

Bacitracin zinečnatý komplex; Bacitracin-Zink; Bacitracina zinc; Bacitracin-cink; Bacitracine Zincique; Bacitracine-zinc; Bacitracino cinko kompleksas; Bacitracins Zinc Complex; Bacitracinum Zincicum; Bacitracinum zincum; Bacytracyna cynkowa; Sinkkibasitrasiini; Zinc Bacitracin; Zinci Bacitracinum; Zinkbacitracin; Цинка Бацитрацин.

CAS — 1405-89-6.

ATC — D06AX05; J01XX10; R02AB04.

ATC Vet — QA07AA93; QD06AX05; QJ01XX10; QR02AB04.

UNII — 89Y4M234ES.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Bacitracin Zinc). The zinc complex of bacitracin. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or light-yellowish-grey hygroscopic powder. Slightly soluble in water and in alcohol. The filtrate of a saturated solution has a pH of 6.0 to 7.5. Store in airtight containers.

USP 36: (Bacitracin Zinc). The zinc complex of bacitracin, which consists of a mixture of antimicrobial polypeptides, the main components being bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It contains not less than

4% and not more than 6% of zinc, calculated with reference to the dried substance. A white or pale tan, hygroscopic powder, odourless or having a slight odour. Sparingly soluble in water. pH of a saturated solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Incompatibility. Bacitracin was slowly inactivated in bases containing stearyl alcohol, cholesterol, polyoxyethylene derivatives, and sodium laurilsulfate, and was rapidly inactivated in bases containing water, macrogols, propylene glycol, glycerol, cetylpyridinium chloride, benzalkonium chloride, ichthammol, phenol, and tannic acid.[1]

1. Plaxco JM, Husa WJ. The effect of various substances on the antibacterial activity of bacitracin in ointments. *J Am Pharm Assoc (Sci)* 1956; **45:** 141–5.

Stability. Bacitracin zinc was more stable than bacitracin and could be stored for 18 months at temperatures up to 40 degrees without appreciable loss of activity. Lozenges of bacitracin zinc and ointments and tablets containing bacitracin zinc with neomycin were more stable than the corresponding bacitracin preparations. Bacitracin zinc was less bitter than bacitracin and the taste was more readily disguised.[1]

1. Gross HM, *et al.* Zinc bacitracin in pharmaceutical preparations. *Drug Cosmet Ind* 1954; **75:** 612–13.

Units

The second International Standard Preparation (1964) of bacitracin zinc contains 74 units/mg.

Uses and Administration

Bacitracin and bacitracin zinc are applied **topically** (as a cream, ointment, dusting powder, or ophthalmic ointment), often with other antibacterials such as neomycin and polymyxin B, and sometimes with corticosteroids, in the treatment of local infections due to susceptible organisms. Typical concentrations of bacitracin or bacitracin zinc in such products are 400 to 500 units/g. Absorption from open wounds and from the bladder or peritoneal cavity may lead to adverse effects, although the dose-limiting toxicity of combined preparations is considered to be due to neomycin.

Parenteral use of bacitracin is usually avoided because of nephrotoxicity but it may be given intramuscularly for the treatment of infants with staphylococcal pneumonia and empyema due to susceptible organisms. For details of doses in children, see p. 228.1.

Bacitracin has been given **orally** in the treatment of antibiotic-associated colitis due to *Clostridium difficile*.

Administration in children. In the USA, bacitracin may be given intramuscularly for the treatment of infants with staphylococcal pneumonia and empyema due to susceptible organisms. Infants weighing less than 2.5 kg may be given a dose of 900 units/kg daily in 2 or 3 divided doses; those weighing more than 2.5 kg may be given 1000 units/kg daily in 2 or 3 divided doses.

Adverse Effects and Precautions

Systemic bacitracin may produce severe nephrotoxicity, resulting in renal failure due to tubular and glomerular necrosis. Renal function should be determined before, and daily during, therapy. Fluid intake and urinary output should be maintained to avoid kidney toxicity. If renal toxicity occurs, bacitracin should be stopped. Use with other nephrotoxic drugs should be avoided (see Interactions, p. 228.1).

Nausea and vomiting may occur, as well as pain at the site of injection. Hypersensitivity reactions, including rashes and anaphylaxis, have occurred with systemic, and more rarely with topical, use.

Hypersensitivity. References[1-6] to hypersensitivity reactions to bacitracin, including anaphylaxis.

1. Sood A, Taylor JS. Bacitracin: allergen of the year. *Am J Contact Dermat* 2003; **14:** 3–4.
2. Jacob SE, James WD. From road rash to top allergen in a flash: bacitracin. *Dermatol Surg* 2004; **30:** 521–4.
3. Freiler JF, *et al.* Intraoperative anaphylaxis to bacitracin during pacemaker change and laser lead extraction. *Ann Allergy Asthma Immunol* 2005; **95:** 389–93.
4. Greenberg K, *et al.* Anaphylaxis to topical bacitracin ointment. *Am J Emerg Med* 2007; **25:** 95–6.
5. Greenberg SB, *et al.* Successful resuscitation of a patient who developed cardiac arrest from pulsed saline bacitracin lavage during thoracic laminectomy and fusion. *J Clin Anesth* 2008; **20:** 294–6.
6. Cronin H, Mowad C. Anaphylactic reaction to bacitracin ointment. *Cutis* 2009; **83:** 127–9.

Interactions

Additive nephrotoxicity would be anticipated if bacitracin were given systemically with other nephrotoxic drugs, particularly colistin, kanamycin, neomycin, polymyxin B, and streptomycin; such use should be avoided. Bacitracin is reported to enhance the neuromuscular blocking action of certain drugs, such as neuromuscular blockers and anaesthetics, if given during surgery or postoperatively.

Antimicrobial Action

Bacitracin interferes with bacterial cell wall synthesis by blocking the function of the lipid carrier molecule that transfers cell wall subunits across the cell membrane. It is active against many Gram-positive bacteria including staphylococci, streptococci (particularly group A streptococci), corynebacteria, and clostridia. It is also active against *Actinomyces*, *Treponema pallidum*, and some Gram-negative species such as *Neisseria* and *Haemophilus influenzae*, although most Gram-negative organisms are resistant.

Acquired bacterial resistance to bacitracin rarely occurs, but resistant strains of staphylococci have been detected.

Pharmacokinetics

Bacitracin is not appreciably absorbed from the gastrointestinal tract or from intact or denuded skin, wounds, or mucous membranes; however, systemic absorption has been reported after peritoneal lavage. It is rapidly absorbed when given by intramuscular injection. Bacitracin readily diffuses into pleural and ascitic fluids but little passes into the CSF. About 10 to 40% of a single injected dose is excreted slowly by glomerular filtration and appears in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Baciject; Bacitin; ***USA***: Baci-IM; ***Venez.***: Baciderm.

Multi-ingredient Preparations. ***Arg.***: Biotaer an Caramelos; Biotaer Nebulizable; Butimerin; Carnot Colutorio; Cicatrex Biotic; ***Austral.***: Cicatrin†; Nemdyn; Neosporin†; ***Austria***: Baneocin; Eucillin; Nebacetin; ***Belg.***: Neobacitracine; Neobacitracine; ***Braz.***: Anaseptil; Bacidermina; Bacigen; Bacina; Bactoderm; Cicatrene; Cutiderm†; Dermase; Epicitrin; Ferid; Kindcetin†; Nebacetin; Nebaciderme; Nebacimed; Neobacipan; Neocetrin; Neotop†; Neotricin; Polysporin†; Teutomicin; ***Canad.***: Antibiotic Ointment; Antibiotique Onguent†; Bacimyxin; Band-Aid Antibiotic Adhesive Bandages plus Antibiotic; Bioderm; Cicatrin†; Complete Antibiotic Ointment; Cortimyxin; Cortisporin; Diosporin; Neosporin; Optimyxin; Ozonol Antibiotic Plus; Polyderm; Polysporin Complete; Polysporin Triple Antibiotic; Polysporin; Polytopic; Triple Antibiotic Ointment; ***Chile***: Anbiotop; Bacitopic Compuesto†; Banedif Oftalmico con Prednisolona†; Banedif Oftalmico†; Banedif ZN; Banedif†; Dermabiotico; Monticina; Nasomin; Oftabiotico; Pensulan; Rinobanedif; Unguento Dermico Antibiotico†; ***Cz.***: Framykoin; Ophthalmo-Framykoin Compositum; Ophthalmo-Framykoin; Pamycon; ***Fin.***: Bacibact; ***Fr.***: Bacicoline; ***Ger.***: Nebacetin†; Neobac†; Polyspectran HC; Polyspectran; ***Gr.***: Apobacyn; Lysopaine; Nebacetin; Sopain-Plus; Vioplex-T; ***Hong Kong***: Bacimyxin†; Polycin†; Polyspectran†; ***Hung.***: Baneocin; Bivacyn†; ***India***: Derbec-N; Nebasulf; Neosporin-H; Neosporin; Neotop; ***Indon.***: Liposin; N B; Nebacetin; Netracin†; Scanderma Plus; Tigalin; Tracetin; ***Irl.***: Cicatrin†; Polyfax; ***Israel***: Bamyxin; ***Ital.***: Bimixin; Cicatrene; Cicatrene; Enterostop; Orobicin; ***Malaysia***: Bacitracin-N; Baneocin; ***Mex.***: Nebacetina; Neosporin; Polixin; Soxaron; Tribiot; ***Neth.***: Bacicoline-B; ***Norw.***: Bacimycin; ***Philipp.***: BNP Ointment; Terramycin Plus; Trimycin-H; Trimycin; ***Pol.***: Baneocin; Bivacyn†; Maxibiotic; Multibiotic; Neotopic†; Scaldex; Tribiotic; ***Port.***: Baciderma; Bacitracina Zimaia; Cicatrin; Dimicina; Distop†; Polisulfade; ***Rus.***: Baneocin (Банеоцин); ***S.Afr.***: Cicatrin†; Polysporin†; ***Singapore***: Baneocin; Batramycin; Fast Powder†; Polybamycin; ***Spain***: Bacisporin†; Banedif†; Dermisone Tri Antibiotic; Dermo Hubber; Edifaringen†; Lizipaina; Neo Bacitrin†; Phonal; Pomada Antibiotica; Rinobanedif; Tulgrasum Antibiotico; ***Switz.***: Baneopol†; Batramycin†; Cicatrex; Lysopaine†; Neotracin; ***Thai.***: Bacal; Banocin; Banocin; Basina; Citacin; Genquin; Izac; Lobacin; Medcin†; My-B; Mybacin Dermic; Mybacin; Novacin; Thrody; ***Turk.***: Thiocilline; ***UK***: Polyfax; ***Ukr.***: Baneocin (Банеоцин); ***USA***: Ak-Poly-Bac; Ak-Spore†; Bacitraycin Plus; Cortimycin; Neocin; Neosporin + Pain Relief; Neotricin HC†; Ocu-Spor-B; Ocutricin; Polycin-B; Polymycin; Polysporin; Polytracin; ProCoMycin; Tri-Biozene; ***Venez.***: Dermabiotic.

Pharmacopoeial Preparations

BP 2014: Polymyxin and Bacitracin Eye Ointment; Polymyxin and Bacitracin Ointment;

USP 36: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin for Injection; Bacitracin Ointment; Bacitracin Ophthalmic Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin Sulfate and Bacitracin Ointment; Neomycin Sulfate and Bacitracin Zinc Ointment; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder.

Balofloxacin *(rINN)*

Balofloxacine; Balofloxacino; Balofloxacinum; Q-35; Балофлоксацин.

(±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-(methylamino)piperidino]-4-oxo-3-quinolinecarboxylic acid.

$C_{20}H_{24}FN_3O_4$=389.4

CAS — 127294-70-6.

UNII — Q022B63JPM.

Profile

Balofloxacin is a fluoroquinolone antibacterial used in the treatment of urinary-tract infections.

Reviews.

1. Alksne L. Balofloxacin Choongwae. *Curr Opin Investig Drugs* 2003; **4:** 224–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Heng Jie (恒捷); Tiantong (天统); ***Kor.***: Q-Roxin.

Bambermycin *(BAN, pINN)*

Bambermicina; Bambermycine; Bambermycins (USAN); Bambermycinum; Flavophospholipol; Бамбермицин.

$C_{69}H_{108}N_5O_{34}P$ = 1582.6 (moenomycin A)

CAS — 11015-37-5 (bambermycin); 76095-39-1 (moenomycin A).

UNII — PP922A42V2.

Profile

Bambermycin is an antibacterial complex containing mainly moenomycin A and moenomycin C and which may be obtained from cultures of *Streptomyces bambergiensis* or by other means. It is used as a growth promotor in veterinary practice.

Baquiloprim *(BAN, rINN)*

1380U; Bakiloprimi; Bakiloprim; Baquiloprima; Baquiloprime; Baquiloprimum; Бахилоприм.

5-(8-Dimethylamino-7-methyl-5-quinolylmethyl)pyrimidin-2,4-diyldiamine.

$C_{17}H_{20}N_6$=308.4

CAS — 102280-35-3.

UNII — 3DE766VIG6.

Profile

Baquiloprim is a diaminopyrimidine antibacterial used similarly to trimethoprim (p. 383.2) as a sulfonamide potentiator, in veterinary medicine. Preparations usually contain 1 part of baquiloprim to 5 parts of sulfonamide.

Bedaquiline *(USAN, rINN)*

Bedaquilina; Bédaquiline; Bedaquilinum; R-207910; TMC-207; Бедаквилин; Бедахилин.

(1*R*, 2*S*)-1-(6-Bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol.

$C_{32}H_{31}BrN_2O_2$=555.5

CAS — 843663-66-1.

UNII — 78846I289Y.

Bedaquiline Fumarate *(USAN, rINNM)*

Bédaquiline, Fumarate de; Bedaquilini Fumaras; Fumarato de bedaquilina; R-403323; Бедаквилин Фумарат; Бедахилин Фумарат.

$C_{32}H_{31}BrN_2O_2.C_4H_4O_4$=671.6

CAS — 845533-86-0.

UNII — P04QX2C1A5.

Profile

Bedaquiline is a diarylquinoline antimycobacterial that is used as part of combination therapy, with at least 3 other antituberculous drugs, in the treatment of multidrug-

resistant pulmonary tuberculosis (p. 210.2) when an effective treatment regimen cannot otherwise be provided.

It is given as the fumarate although doses are expressed in terms of the base; 120.89 mg of bedaquiline fumarate is equivalent to about 100 mg of bedaquiline. It is given orally with food for a total treatment course of 24 weeks according to the following regimen:

- weeks 1 and 2: 400 mg once daily
- weeks 3 to 24: 200 mg 3 times a week (with at least 48 hours between doses)

Bedaquiline has a terminal half-life of about 4 to 5 months which results in extended periods of exposure to low levels of bedaquiline. Consequently, to avoid acquired resistance developing, treatment with bedaquiline should be stopped 4 to 5 months before the other antituberculous drugs are scheduled to be stopped. It is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with other drugs that induce or suppress this isoenzyme should be avoided. The concurrent use of drugs known to cause QT prolongation could increase the risk of cardiotoxicity in patients taking bedaquiline.

References.
1. Chahine EB, *et al.* Bedaquiline: a novel diarylquinoline for multidrug-resistant tuberculosis. *Ann Pharmacother* 2013. Available at: doi:10.1177/1060028013504087.
2. Chan B, *et al.* A review of tuberculosis: focus on bedaquiline. *Am J Health-Syst Pharm* 2013; **70:** 1984–94.
3. CDC. Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR* 2013; **62** (RR-9): 1–12. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6209.pdf (accessed 02/12/13) Correction. *ibid.*; 906.
4. WHO. *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance.* Geneva: WHO, 2013. Available at: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf (accessed 02/12/13)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Sirturo.

Bekanamycin Sulfate *(rINNM)*

Aminodeoxykanamycin Sulphate; Bekanamicina, sulfato de; Bekanamycin Sulphate; Békanamycine, Sulfate de; Bekanamycini Sulfas; Kanamycin B Sulphate; KDM; NK-1006; Sulfato de bekanamicina; Беканамицина Сульфат.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine sulphate.

$C_{18}H_{37}N_5O_{10}.2½H_2SO_4$=728.7

CAS — 4696-76-8 (bekanamycin); 70550-99-1 (bekanamycin sulfate).

UNII — KB71EA86HM.

Pharmacopoeias. In *Jpn*.

Profile

Bekanamycin is an aminoglycoside antibacterial and is a congener of kanamycin. It has properties similar to those of gentamicin (p. 306.2). It is given topically as the sulfate for the treatment of eye infections. It has also been given intramuscularly and orally. It is reported to be more toxic than kanamycin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Visucloben Antibiotico; Visumetazone Antibiotico.

Benethamine Penicillin *(BAN, rINN)*

Bénéthamine Pénicilline; Benethaminum Penicillinum; Penicilina-benetamina; Бенетамин Пенициллин.

Benzyl(phenethyl)ammonium (6*R*)-6-(2-phenylacetamido) penicillanate.

$C_{15}H_{17}N,C_{16}H_{18}N_2O_4S$=545.7

CAS — 751-84-8.

ATC Vet — QJ01CE91.

UNII — O3S7RWT8R5.

Profile

Benethamine penicillin is a poorly soluble derivative of benzylpenicillin (p. 230.1) with similar actions and uses, although it is not recommended for chronic, severe, or deep-seated infections. After deep intramuscular injection it forms a depot from which it is slowly absorbed and hydrolysed to benzylpenicillin. Benethamine penicillin is usually given with benzylpenicillin sodium and also sometimes procaine benzylpenicillin to produce both an immediate and a prolonged effect; overall, the effect lasts for 2 to 3 days.

Benzathine Benzylpenicillin

(BAN, rINN)

Bensylpenicillinbensatin; Bensylpenicillinbenzatin; Bentsyylipenisilliinibentsatiini; Benzathin-benzylpenicilin; Benzathine benzylpénicilline; Benzathine Penicillin; Benzathini Benzylpenicillinum; Benzatin Penisilin; Benzatina bencilpenicilina; Benzethacil; Benzilpenicilinas benzatinas; Benzilpenicillina Benzatinica; Benzilpenicillin-benzantin; Benzylopenicylina benzatynowa; Benzylpenicillinum Benzanthinum; Benzylpenicillinum Benzathinum; Penicillin G Benzathine; Penisilin G Benzatin; Penzaethinum G; Бензатина Бензилпенициллин.

NN'-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenylacetamido)penicillanate].

$C_{16}H_{20}N_2(C_{16}H_{18}N_2O_4S)_2$=909.1

CAS — 1538-09-6 (anhydrous benzathine benzylpenicillin); 5928-83-6 (benzathine benzylpenicillin monohydrate); 41372-02-5 (benzathine benzylpenicillin tetrahydrate).

ATC — J01CE08.

ATC Vet — QJ01CE08.

UNII — RIT82F58GK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Int.*

Jpn and *US* include the tetrahydrate.

Ph. Eur. 8: (Benzylpenicillin, Benzathine). It contains a variable quantity of water. A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide and in formamide. Store in airtight containers.

USP 36: (Penicillin G Benzathine). The tetrahydrate is a white, odourless, crystalline powder. Soluble 1 in 5000 of water and 1 in 65 of alcohol. pH in a solution prepared by dissolving 50 mg in 50 mL of dehydrated alcohol, and adding 50 mL of water is between 4.0 and 6.5. Store in airtight containers.

Uses and Administration

Benzathine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p. 232.1), to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations of benzylpenicillin produced, its use should be restricted to micro-organisms that are highly susceptible to benzylpenicillin. In acute infections, and when bacteraemia is present, the initial treatment should be with benzylpenicillin by injection.

Infections treated with benzathine benzylpenicillin include diphtheria (asymptomatic carriers), pharyngitis (*Streptococcus pyogenes; Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*)), and syphilis (including non-venereal treponematoses). It is also used for primary and secondary prophylaxis of rheumatic fever. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Benzathine benzylpenicillin is given by deep intramuscular injection, sometimes with procaine benzylpenicillin and benzylpenicillin itself. It has been given orally for mild infections, although phenoxymethylpenicillin is usually preferred. Benzathine benzylpenicillin 900 mg is equivalent to about 720 mg of benzylpenicillin (1.2 million units).

For early syphilis, a single dose of benzathine benzylpenicillin 1.8 g by deep intramuscular injection is given, usually as 2 injections at separate sites. In late syphilis, 1.8 g is given at weekly intervals for 3 consecutive weeks. Benzathine benzylpenicillin is not usually recommended for the treatment of neurosyphilis because of reports of inadequate penetration into the CSF.

For the treatment of other treponemal infections, such as yaws, pinta, and endemic syphilis (bejel), a single intramuscular dose of benzathine benzylpenicillin 900 mg is given.

For streptococcal pharyngitis and the primary prevention of rheumatic fever, the adult dose is a single intramuscular injection of 900 mg. To prevent recurrences of acute rheumatic fever, 900 mg is given intramuscularly every 3 or 4 weeks.

For details of doses in children see p. 229.2.

Administration in children. Benzathine benzylpenicillin may be given by deep intramuscular injection to infants and children for the treatment of susceptible bacterial infections, including congenital syphilis and streptococcal pharyngitis, and for the prevention of rheumatic fever.

In the USA, the following doses have been recommended for treatment of **streptococcal pharyngitis** and **primary prevention of rheumatic fever** by the American Academy of Pediatrics (AAP):[1]

- newborns and infants: 37.5 mg/kg (50 000 units/kg) as a single dose
- children weighing less than 27 kg: 225 to 450 mg (300 000 to 600 000 units) as a single dose
- children weighing 27 kg or more: 675 mg (900 000 units) as a single dose

The American Heart Association (AHA)[2] suggests doses of:

- infants and children weighing 27 kg or less: 450 mg (600 000 units) as a single dose
- children weighing more than 27 kg: 900 mg (1 200 000 units) as a single dose

Alternatively, WHO recommend:

- children weighing less than 30 kg: 450 to 675 mg as a single dose
- children weighing 30 kg or more: 900 mg as a single dose

To **prevent recurrence of acute rheumatic fever**, the AAP and AHA recommend the following doses given once every 4 weeks or once every 3 weeks in high-risk areas:

- children weighing less than 27 kg: 450 mg (600 000 units)
- children weighing more than 27 kg: 900 mg (1 200 000 units)

Similar dose recommendations are made by WHO.

For treatment of **yaws, pinta, and bejel (endemic syphilis)** in children, 450 mg as a single dose is recommended by WHO.

For doses used to treat **congenital syphilis** in infants, see p. 205.2.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Gerber MA, *et al.* Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009; **119:** 1541–51. Also available at: http://circ.ahajournals.org/cgi/reprint/119/11/1541 (accessed 13/08/09)

Adverse Effects and Precautions

As for Benzylpenicillin, p. 231.2.

Non-allergic (embolic-toxic) reactions similar to those associated with procaine benzylpenicillin, p. 346.3, have been reported rarely with benzathine benzylpenicillin.

Benzathine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Interactions

As for Benzylpenicillin, p. 232.1.

Pharmacokinetics

When benzathine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in about 24 hours and are lower than those after an equivalent dose of benzylpenicillin potassium or sodium. However, depending on the dose, benzylpenicillin is usually detectable in plasma for up to 4 weeks (but see p. 229.3).

Distribution into the CSF is reported to be poor.

Due to the slow absorption from the site of injection, benzylpenicillin has been detected in the urine for up to 12 weeks after a single dose.

Benzathine benzylpenicillin is relatively stable in the presence of gastric juice, but absorption from the gastrointestinal tract is variable. Plasma concentrations of benzylpenicillin after an oral dose are lower than those from the same dose of a soluble penicillin; peak concentrations are also produced less rapidly, but may persist for longer.

Plasma concentrations. Benzathine benzylpenicillin has been given every 4 weeks for secondary prophylaxis against rheumatic fever, although some advocate giving it every 3 weeks to ensure adequate plasma concentrations of benzylpenicillin. Typical concentrations achieved after a single intramuscular injection of benzathine benzylpenicillin 900 mg have been cited as about 100, 20, and 2 nanograms/mL on days 1, 14, and 32 respectively. In one study[1] adequate concentrations (defined as 20 nanograms or more per mL) were seen in more than 80% of serum samples at 3 weeks, but in only 36% at 4 weeks. In a further study,[2] in which single doses of 900 mg, 1.35 g and 1.8 g were compared, it appeared that doses higher than the 900-mg dose of benzathine benzylpenicillin usually recommended might prolong the duration of protective plasma concentrations of benzylpenicillin (defined as above 25 nanograms/mL) and improve the efficacy of dosing every 4 weeks for prophylaxis against rheumatic fever.

1. Kaplan EL, *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1 200 000 units. *J Pediatr* 1989; **115:** 146–50.
2. Currie BJ, *et al.* Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. *Antimicrob Agents Chemother* 1994; **38:** 1203–4.

Pregnancy. The pharmacokinetics of benzathine benzylpenicillin appear to be altered in late pregnancy. Of 10 healthy pregnant women given benzathine benzylpenicillin 1.8 g intramuscularly before caesarean section, only 4 achieved adequate serum concentrations of benzylpenicillin (for syphilis, at least 18 nanograms/mL) for 7 days.[1]

1. Nathan L, *et al.* Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993; **82**: 338–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Benzetacil; Galtamicina; Pen di Ben; Retarpen; ***Austral.***: Bicillin L-A; ***Austria***: Retarpen; ***Belg.***: Penadur; ***Braz.***: Bactopen; Benzatron; Benzetacil; Bepeben; Longacilin; Pencil B†; ***Canad.***: Bicillin L-A; ***Cz.***: Pendepon Compositum; Retarpen†; ***Fr.***: Extencilline; ***Ger.***: Pendysin; ***Gr.***: Penadur; ***Hong Kong***: Pan-Benzathine G; ***India***: Longacillin; Pencom; Penidure; ***Israel***: Durabiotic; ***Ital.***: Diaminocillina†; ***Malaysia***: Retarpen; ***Mex.***: Benacilina†; Bencelin; Benzafur†; Benzanil Simple†; Benzetacil; Ipenxin; Lentopenil; Unicil 6:3:3; Unicil L-A; ***Neth.***: Penidural; ***NZ***: Bicillin L-A; ***Philipp.***: Penadur†; Zalpen; ***Pol.***: Debecylina; ***Port.***: Lentocilin S; ***Rus.***: Benzycillin 1 (Бензициллин 1); Bicillin-1 (Бициллин-1); Extencilline (Экстенциллин); Retarpen (Ретарпен); ***S.Afr.***: Bicillin L-A†; Penilente LA; ***Singapore***: Retarpen; ***Spain***: Benzetacil; Cepacilina†; ***Turk.***: Benzapen 6.3.3; Benzapen; Deposilin 6.3.3; Deposilin; Penadur 6.3.3; Penadur; Pentin; ***Ukr.***: Retarpen (Ретарпен); ***USA***: Bicillin L-A; Permapen; ***Venez.***: Benzetacil L-A.

Multi-ingredient Preparations. ***Austria***: Retarpen compositum; ***Ger.***: Retacillin compositum; Tardocillin; ***Mex.***: Bencelin Combinado; Benzanil Compuesto†; Benzetacil Combinado; Pecivax; Pendiben Compuesto†; ***Port.***: Lentocilin; ***Rus.***: Benzycillin 3 (Бензициллин 3); Benzycillin 5 (Бензициллин 5); Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.***: Ultracillin†; ***Spain***: Benzetacil Compuesta; Cepacilina 633†; Penilevel Retard; ***Ukr.***: Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***USA***: Bicillin C-R; ***Venez.***: Benzetacil 3-3; Benzetacil 6-3-3.

Pharmacopoeial Preparations

USP 36: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Benzathine Injectable Suspension; Penicillin G Benzathine Oral Suspension; Penicillin G Benzathine Tablets.

Benzathine Phenoxymethylpenicillin

Benzatin Fenoksimetil Penisilin; Benzatina fenoximetilpenicilina; Penicillin V Benzathine (USAN); Phenoxymethylpenicillini Dibenzylaethylendiaminum; Бензатинфеноксиметилпенициллин.

N,N'-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenoxyacetamido)penicillanate].

$(C_{16}H_{18}N_2O_5S)_2,C_{16}H_{20}N_2$=941.1

CAS — 5928-84-7 (anhydrous benzathine phenoxymethylpenicillin); 63690-57-3 (benzathine phenoxymethylpenicillin tetrahydrate).

ATC — J01CE10.

ATC Vet — QJ01CE10.

UNII — 3T4EMH59ZU.

Pharmacopoeias. In *US*.

USP 36: (Penicillin V Benzathine). A practically white powder having a characteristic odour. Soluble 1 in 3200 of water, 1 in 330 of alcohol, 1 in 37 of acetone, 1 in 42 of chloroform, and 1 in 910 of ether. pH of a 3% suspension in water is between 4.0 and 6.5. Store in airtight containers.

Profile

Benzathine phenoxymethylpenicillin has actions and uses similar to those of phenoxymethylpenicillin (p. 340.3) and is given orally in the treatment of susceptible mild to moderate infections. Doses are expressed in terms of phenoxymethylpenicillin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Abbocillin-V; Cilicaine V; ***Austria***: Ospen; ***Canad.***: Pen-Vee†; ***Cz.***: Ospen; ***Fr.***: Oracilline; ***Ger.***: InfectoBicillin; ***Gr.***: Ospen; ***Hung.***: Ospen; ***Pol.***: Ospen; ***Rus.***: Ospen (Оспен); ***Spain***: Benoral; ***Switz.***: Ospen; ***Turk.***: Pen-Os; ***Ukr.***: Ospen (Оспен)†; ***Venez.***: Ospen.

Pharmacopoeial Preparations

USP 36: Penicillin V Benzathine Oral Suspension.

Benzylpenicillin *(BAN, rINN)*

Bencilpenicilina; Bensylpenicillin; Bentsyylipenisilliinikalium; Benzilpenicilino kalio druska; Benzilpenicillin-kálium; Benzylopenicylina potasowa; Benzylpenicilin draselná sůl; Benzylpenicillin-Kalium; Benzylpénicilline potassique; Benzylpenicillinum Kalicum; Kalii Benzylpenicillinum; Penicilina G potásica; Penicillin G Potassium; Penisilin G Potasyum; Калия бензилпенициллин.

$C_{16}H_{17}KN_2O_4S$=372.5

CAS — 113-98-4.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

UNII — VL775ZTH4C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Benzylpenicillin Potassium). The potassium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 36: (Penicillin G Potassium). Colourless or white crystals, or white crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Very soluble in water, in sodium chloride 0.9%, and in glucose solutions; sparingly soluble in alcohol. Its solutions retain substantially full potency for several days at temperatures below 15 degrees, but are rapidly inactivated by acids, by alkali hydroxides, by glycerol, and by oxidising agents. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility and stability. See Benzylpenicillin Sodium, p. 230.2.

Benzylpenicillin Sodium *(BANM, rINNM)*

Bencilpenicilina sódica; Bensylpenicillinnatrium; Bentsyylipenisilliininatrium; Benzilpenicilino natrio druska; Benzilpenicillin-nátrium; Benzylopenicylina sodowa; Benzylpenicilin sodná sůl; Benzylpenicillin-Natrium; Benzylpénicilline Sodique; Benzylpenicillinum Natricum; Natrii Benzylpenicillinum; Penicilina G sódica; Penicillin G Sodium; Sodyum Penisilin G; Натрий бензилпенициллин.

$C_{16}H_{17}N_2NaO_4S$=356.4

CAS — 69-57-8.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

UNII — YS5LY7JF4N.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Benzylpenicillin Sodium). The sodium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 36: (Penicillin G Sodium). Colourless or white crystals, or white to slightly yellow crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15 degrees. Its solutions are rapidly inactivated by acids, by alkali hydroxides, by oxidising agents, and by penicillinase. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility. Benzylpenicillin has been reported to be incompatible with metal ions and some rubber products. Its stability may be affected by ionic and nonionic surfactants, oxidising and reducing agents, alcohols, glycerol, glycols, macrogols and other hydroxy compounds, some paraffins and bases, some preservatives such as chlorocresol or thiomersal, carbohydrate solutions in an alkaline pH, fat emulsions, blood and blood products, and viscosity modifiers. Benzylpenicillin is incompatible with many acidic and basic drugs (see Stability, p. 230.3) and several other antimicrobials, including amphotericin B, some cephalosporins, and vancomycin. Benzylpenicillin and aminoglycosides are mutually incompatible and injections should be given at separate sites.

Stability. Benzylpenicillin is hydrolysed in aqueous solutions by degradation of the beta-lactam ring and hydrolysis is accelerated by increased temperature or alkaline conditions; inactivation also occurs under acid conditions. Degradation products include penillic, penicillenic, and penicilloic acids which lower the pH and cause a progressive increase in the rate of deterioration; *N*-formylpenicillamine and very small amounts of penicillamine have also been detected. Degradation is minimal at about pH 6.8 and deterioration of benzylpenicillin in solution may be retarded by using a citrate buffer. Dilute solutions are more stable than concentrated ones.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2** (Mar): 22–39.
2. Bird AE, *et al.* N-Formylpenicillamine and penicillamine as degradation products of penicillins in solution. *J Pharm Pharmacol* 1986; **38**: 913–17.

Units

The second International Standard Preparation (1952) of benzylpenicillin sodium contained 1670 units of penicillin per mg but was withdrawn in 1968 since penicillin can now be characterised completely by chemical tests. Despite this, doses of benzylpenicillin are still expressed in units in some countries.

Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

Uses and Administration

Benzylpenicillin is used in the treatment of infections due to susceptible organisms (see Antimicrobial Action, p. 232.1). They include abscess, actinomycosis, anthrax, bites and stings, diphtheria, endocarditis, gas gangrene, leptospirosis, Lyme disease, meningitis, meningococcal infections, necrotising enterocolitis, necrotising fasciitis, neonatal conjunctivitis (if gonococci are sensitive), perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), pharyngitis (or tonsillitis), pneumonia, skin infections, syphilis (neurosyphilis and congenital syphilis), tetanus, toxic shock syndrome, and Whipple's disease. It is also used for surgical infection prophylaxis in first trimester abortion in women at high risk of pelvic infection. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Benzylpenicillin is usually given intramuscularly or intravenously. Where a prolonged effect is needed benzathine benzylpenicillin (p. 227.2) or procaine benzylpenicillin (p. 346.2) are preferred; they are given intramuscularly. Benzylpenicillin is sometimes given orally for infections of moderate severity, but one of the acid-resistant penicillins such as phenoxymethylpenicillin (p. 340.3) is preferable.

Benzylpenicillin is available as the potassium or sodium salt. The dose of benzylpenicillin should be sufficient to achieve an optimum bactericidal concentration in the blood as rapidly as possible; concentrations may be increased by giving it with probenecid (p. 608.1). In some countries, doses are still expressed in units. Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

For some infections, doses of 0.6 to 4.8 g of benzylpenicillin daily in 4 to 6 divided doses by intramuscular or slow intravenous injection or intravenous infusion may be adequate, but higher doses given intravenously, often by infusion, are more usual for severe infections. For example, in endocarditis, benzylpenicillin 7.2 g daily (1.2 g every 4 hours) intravenously, usually with an aminoglycoside, is recommended; doses of up to 18 g daily are not unusual for less sensitive streptococci and enterococci. In meningococcal and pneumococcal meningitis, benzylpenicillin 14.4 g daily (2.4 g every 4 hours) intravenously is recommended; up to 18 g daily has been recommended for meningococcal meningitis. High doses should be given slowly to avoid irritation of the CNS and electrolyte imbalance, and a rate of not more than 300 mg/minute is recommended for intravenous doses above 1.2 g. High doses may need to be reduced in patients with renal impairment (see p. 231.1).

In patients with suspected meningococcal infection, benzylpenicillin 1.2 g by intravenous or intramuscular injection should be given before transfer to hospital.

A dose for intrapartum prophylaxis against group B streptococcal infection is benzylpenicillin 3 g intravenously initially, then 1.5 g every 4 hours until delivery.

For details of doses in children, see p. 231.1.

Other routes. Benzylpenicillin eye drops and eye ointment are used in the treatment of susceptible eye infections. For subconjunctival injection, 300 or 600 mg of benzylpenicillin has been dissolved in 0.5 to 1.0 mL of water, or another suitable solvent such as lidocaine 2% with or without adrenaline 1 in 200 000 or similar.

Benzylpenicillin has also been given orally on an empty stomach in adult doses of 125 to 312 mg every 4 to 6 hours.

Intrathecal injections are no longer recommended.

Administration in children. Benzylpenicillin may be given to neonates and children for the treatment of infections caused by susceptible organisms by intramuscular injection, or by slow intravenous injection or infusion; the intravenous route is recommended for neonates and infants and in the treatment of endocarditis or meningitis. In the UK, the *BNFC* recommends the following doses:

For **mild to moderate susceptible infections**, including throat infections, otitis media, pneumonia, cellulitis, and neonatal sepsis:

- neonates under 7 days of age: 25 mg/kg every 8 to 12 hours
- neonates 7 to 28 days of age: 25 mg/kg every 8 hours; dose doubled for severe infection
- children from 1 month of age: 25 mg/kg every 6 hours; increased to 50 mg/kg every 4 to 6 hours (maximum 2.4 g every 4 hours) for severe infection

For **endocarditis**:

- children from 1 month of age: 25 mg/kg every 4 hours; dose may be doubled (maximum 2.4 g every 4 hours) if necessary

For **meningitis and meningococcal disease**:

- neonates: 50 mg/kg every 12 hours for those less than 7 days of age and every 8 hours for those 7 to 28 days of age
- children from 1 month of age: 50 mg/kg every 4 to 6 hours (maximum 2.4 g every 4 hours)

Where meningitis, and especially meningococcal disease are suspected, a single injection of benzylpenicillin is advised urgently before transfer to hospital in the following doses:

- infants under one year of age: 300 mg
- children 1 to 9 years of age: 600 mg
- children from 10 years of age: 1.2 g

In the USA, the American Academy of Pediatrics[1] suggests the following doses given intramuscularly or intravenously, although higher doses may be needed for the treatment of meningitis in neonates:

- for neonates aged 7 days or less (irrespective of body weight): 15 to 30 mg/kg (25 000 to 50 000 units/kg) every 12 hours
- for neonates aged 8 to 28 days (irrespective of body weight): 15 to 30 mg/kg (25 000 to 50 000 units/kg) every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- children 1 month and older: in mild to moderate infections 60 to 90 mg/kg (100 000 to 150 000 units/kg) daily in 4 divided doses, to a maximum of 4.8 g (8 million units) daily; in severe infection, doses of 120 to 180 mg/kg daily (200 000 to 300 000 units/kg) in 6 divided doses, to a maximum of 14.4 g (24 million units) daily may be used

Dosing recommendations in some neonatal populations have been suggested based on pharmacokinetic models. A study in 20 preterm neonates (less than 32 weeks gestational age)[2] confirmed that a regimen of 30 mg/kg (50 000 units/kg) every 12 hours is adequate for empirical treatment of common infections on the third day of life; but for infections due to highly susceptible organisms, a 24-hour dosing interval is likely sufficient. A study in very low birth-weight neonates (less than 1.2 kg) with gestational age less than 28 weeks[3] suggested that, for that population, 15 mg/kg (25 000 units/kg) every 12 hours was sufficient to achieve effective drug concentrations in the serum and CSF for the treatment of group B streptococcal infections.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Muller AE, *et al*. Pharmacokinetics of penicillin G in infants with a gestational age of less than 32 weeks. *Antimicrob Agents Chemother* 2007; **51:** 3720–5.
3. Metsvaht T, *et al*. Pharmacokinetics of penicillin G in very-low-birth-weight neonates. *Antimicrob Agents Chemother* 2007; **51:** 1995–2000.

Administration in renal impairment. Doses of parenteral benzylpenicillin should be reduced in patients with renal impairment, particularly when high-dose regimens are being used. For doses of 0.6 to 1.2 g, UK licensed product information suggests dosing intervals no more frequent than every 8 hours. For high-dose regimens used in the treatment of serious infections, it recommends the following doses based on creatinine clearance (CC):

- CC 60 mL/minute: 1.2 g every 4 hours
- CC 40 mL/minute: 900 mg every 4 hours
- CC 20 mL/minute: 600 mg every 4 hours
- CC 10 mL/minute: 600 mg every 6 hours
- anuric: 300 mg every 6 hours or 600 mg every 8 hours

Where advanced liver disease is associated with severe renal failure, the recommended dose is 300 mg every 8 hours. Haemodialysis patients should be given an additional 300 mg every 6 hours during the dialysis run.

Alternatively, some US experts recommend the following:

- CC 10 to 50 mL/minute: 75% of the total recommended dose
- CC less than 10 mL/minute: 20 to 50% of the total recommended dose (where haemodialysis is required, doses should be timed to be given after the dialysis run)

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy has suggested that those on intermittent haemodialysis may be given the usual recommended dose (see Uses and Administration, p. 228.3) for one dose, after which 25 to 50% of the usual dose should be given every 4 to 6 hours, or 50 to 100% of the dose may be given every 8 to 12 hours. For those on continuous renal replacement therapy (CRRT) a loading dose of 4 million-units (2.4 g) is recommended, with the following maintenance doses, depending on the type of CRRT, given every 4 to 6 hours:

- continuous venovenous haemofiltration (CVVH): 2 million units (1.2 g)
- continuous venovenous haemodialysis (CVVHD): 2 to 3 million units (1.2 to 1.8 g)
- continuous venovenous haemodiafiltration (CVVHDF): 2 to 4 million units (1.2 to 2.4 g)

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects

The most common adverse effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes; anaphylaxis occasionally occurs and has sometimes been fatal.

Gastrointestinal effects such as diarrhoea and nausea are the most common adverse effects after oral use of benzylpenicillin; a sore mouth or tongue or a black hairy tongue have occasionally been reported. Pseudomembranous colitis has been associated with the use of most antibacterials; ampicillin or amoxicillin are the most frequently implicated penicillins (see Antibiotic-associated Colitis, p. 183.1).

Other adverse effects have generally been associated with large intravenous doses of benzylpenicillin; patients with renal impairment are also at increased risk. These adverse effects include haemolytic anaemia and neutropenia, both of which might have some immunological basis; prolongation of bleeding time and defective platelet function; convulsions and other signs of CNS toxicity (encephalopathy has followed intrathecal dosage and can be fatal); and electrolyte disturbances because of the large amounts of potassium or sodium given when benzylpenicillin potassium or sodium, respectively, are used.

Hepatitis and cholestatic jaundice have been reported rarely with many penicillins, notably penicillinase-resistant penicillins such as flucloxacillin and oxacillin, and also combinations of amoxicillin or ticarcillin with clavulanic acid.

Nephropathy and interstitial nephritis, which may have some immunological basis, have been especially associated with meticillin, but may be produced by other penicillins.

Some patients with syphilis and other spirochaete infections may have a Jarisch-Herxheimer reaction shortly after starting treatment with penicillin, which is probably due to the release of endotoxins from the killed treponemes and should not be mistaken for a hypersensitivity reaction. Symptoms include fever, chills, headache, and reactions at the site of the lesions. The reaction can be dangerous in cardiovascular syphilis, or where there is a serious risk of increased local damage, such as with optic atrophy.

Hypersensitivity. The overall incidence of allergic reactions to penicillin has been reported to vary from about 1 to 10% although some patients may have been incorrectly labelled 'allergic to penicillin'. Anaphylactic reactions occur in about 0.05% of patients, usually after parenteral use, but they have also been reported after taking oral penicillin.

Hypersensitivity to penicillin gives rise to immediate reactions including anaphylaxis, angioedema, urticaria, and some maculopapular rashes. Late reactions may include serum sickness-like reactions and haemolytic anaemia. Reactions are considered to be due mainly to breakdown products produced *in vitro* before use or to metabolites of penicillin, and possibly penicillin itself. These act as haptens which, when combined with proteins and other macromolecules, produce potential antigens. As the hypersensitivity is related to the basic penicillin structure, patients who are genuinely allergic to benzylpenicillin must be assumed to be allergic to all penicillins; sensitised patients may also react to the cephalosporins and other beta-lactam antibacterials.

Tests for hypersensitivity may be used to determine those patients most likely to develop serious allergic reactions to penicillins. Skin tests are used to evaluate the current risk of immediate or accelerated IgE-mediated reactions, the most serious being anaphylaxis. Both the major and minor determinants of penicillin hypersensitivity should be used; the major determinant is available as penicilloyl-polylysine (p. 2585.3) and a minor-determinant mixture consisting of benzylpenicillin and its derivatives, including penicilloic acid and benzylpenicilloylamine, can be used, although if this is not available a solution of benzylpenicillin may be substituted. Adrenaline should be available in case an anaphylactic reaction develops. The results of skin tests are unreliable if a significant time has elapsed before beginning therapy. Several *in-vitro* tests including the radioallergosorbent test (RAST) have been developed.

Desensitisation may be attempted in patients allergic to penicillin when treatment with penicillin is considered essential. It involves very small doses of penicillin given at relatively short intervals of 15 minutes or more, and gradually increased to therapeutic concentrations. However, desensitisation may be hazardous and should only be carried out if the patient can be monitored continuously and adrenaline and resuscitation equipment are immediately available. Desensitisation should be regarded as temporary, and allergic reactions may recur during the next exposure to penicillin.

Neutropenia. Neutropenia has been widely reported in patients given high doses of beta lactams and an incidence of 5 to more than 15% has been reported in patients treated for 10 days or more. Warning signs include fever, rash, and eosinophilia. Monitoring of the leucocyte count is recommended during long-term treatment with high doses. Some have proposed a direct toxic effect whereas others have postulated an immune mechanism.

Electrolyte disturbances. Many penicillins have been associated with electrolyte disturbances, particularly of sodium and potassium. Benzylpenicillin potassium in high doses may lead to hyperkalaemia, particularly in those with renal impairment. While hypernatraemia can result from the high sodium loads associated with the sodium salts of benzylpenicillin, carbenicillin, flucloxacillin, and ticarcillin; hypokalaemia may also result from sodium-induced solute diuresis. In addition, many semisynthetic penicillins (including carbenicillin, cloxacillin, mezlocillin, nafcillin, piperacillin, and ticarcillin) can act as non-absorbable anions in the distal tubule, resulting in urinary potassium loss and hypokalaemia. This effect may be mediated by volume depletion, and has been seen mainly in severely ill patients.

Effects on the blood. References to neutropenia associated with penicillins.

1. Anonymous. Antibiotic-induced neutropenia. *Lancet* 1985; **ii:** 814.
2. Neftel KA, *et al*. Inhibition of granulopoiesis in vivo and in vitro by β-lactam antibiotics. *J Infect Dis* 1985; **152:** 90–8.
3. Olaison L, Alestig K. A prospective study of neutropenia induced by high doses of β-lactam antibiotics. *J Antimicrob Chemother* 1990; **25:** 449–53.
4. Peralta FG, *et al*. Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis* 2003; **37:** 1568–72.
5. Scheetz MH, *et al*. Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; **30:** 295–306.

Effects on the nervous system. References to CNS effects associated with penicillins.

1. Schliamser SE, *et al*. Neurotoxicity of β-lactam antibiotics: predisposing factors and pathogenesis. *J Antimicrob Chemother* 1991; **27:** 405–25.

Hypersensitivity. References to hypersensitivity reactions associated with penicillins.

1. Sullivan TJ, *et al*. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981; **68:** 171–80.
2. Beeley L. Allergy to penicillin. *BMJ* 1984; **288:** 511–12.
3. Holgate ST. Penicillin allergy: how to diagnose and when to treat. *BMJ* 1988; **296:** 1213–14.
4. Anonymous. Penicillin allergy in childhood. *Lancet* 1989; **i:** 420.
5. Surtees SJ, *et al*. Allergy to penicillin: fable or fact? *BMJ* 1991; **302:** 1051–2. Correspondence. *ibid.*: 1462–3.
6. Anonymous. Penicillin allergy. *Drug Ther Bull* 1996; **34:** 87–8.
7. Salkind AR, *et al*. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285:** 2498–2505.
8. Park MA, Li JT. Diagnosis and management of penicillin allergy. *Mayo Clin Proc* 2005; **80:** 405–10.
9. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. *Am J Med* 2008; **121:** 572–6.

Precautions

Patients known to be hypersensitive to penicillins should be given an antibacterial of another class; sensitised patients may also react to the cephalosporins and other beta lactams (but see also Hypersensitivity, under Cefalotin, p. 237.3). Desensitisation may be attempted if treatment with a penicillin is considered essential (see Adverse Effects, above). Penicillins should be given with caution to patients with a history of allergy, especially to drugs.

Care is necessary if very high doses of penicillins are given, especially if renal function is poor, because of the risk

of neurotoxicity. The intrathecal route should be avoided. Renal, hepatic, and haematological status should be monitored during prolonged and high-dose therapy. Because of the Jarisch-Herxheimer reaction, care is also necessary when treating patients with spirochaete infections, particularly syphilis.

Skin contact with penicillins should be avoided since sensitisation may occur.

Penicillin therapy changes the normal bacterial flora and can lead to superinfection with penicillin-resistant organisms including *Clostridium difficile* or *Candida*, particularly with prolonged use.

Penicillins may interfere with some diagnostic tests such as those for urinary glucose using copper sulfate, direct antiglobulin (Coombs') tests, and some tests for urinary or serum proteins. Penicillins may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies benzylpenicillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Potassium and sodium content. Each g of benzylpenicillin potassium contains about 2.7 mmol of potassium and each g of benzylpenicillin sodium contains about 2.8 mmol of sodium. Care is necessary if large doses of the potassium or sodium salts are given to patients with renal impairment or heart failure. High doses of benzylpenicillin potassium should also be used with caution in patients receiving potassium-containing drugs or potassium-sparing diuretics.

Interactions

Probenecid prolongs the half-life of benzylpenicillin by competing with it for renal tubular secretion and may be used therapeutically for this purpose. Clinically significant reductions in renal clearance have also been noted for amoxicillin, nafcillin, and ticarcillin. Benzylpenicillin may also interact with bacteriostatic antibacterials such as chloramphenicol and tetracyclines (see Antimicrobial Action, p. 232.1), and may be incompatible *in vitro* with other drugs, including some other antibacterials (see p. 228.2).

The possibility of a prolonged bleeding time after oral treatment with a broad-spectrum drug like ampicillin should be borne in mind in patients receiving anticoagulants. For further details, and for the effect of other penicillins on the activity of warfarin, see p. 1531.1.

Hormonal contraceptives. For the effect of penicillins on oral contraceptives, see p. 2243.1.

Methotrexate. For the effect of penicillins on methotrexate, see p. 827.3.

Antimicrobial Action

Benzylpenicillin is a beta-lactam antibacterial and has a bactericidal action against Gram-positive bacteria, Gram-negative cocci, some other Gram-negative bacteria, spirochaetes, and actinomycetes.

It exerts its killing action on growing and dividing bacteria by inhibiting bacterial cell-wall synthesis, although the mechanisms involved are still not precisely understood. Bacterial cell walls are held rigid and protected against osmotic rupture by peptidoglycan. Benzylpenicillin inhibits the final cross-linking stage of peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins on the inner surface of the bacterial cell membrane. However, it is now realised that other earlier stages in cell-wall synthesis can also be inhibited. Other mechanisms involved include bacterial lysis by the inactivation of endogenous inhibitors of bacterial autolysins.

Its action is inhibited by penicillinase and other beta-lactamases that are produced during the growth of certain micro-organisms.

Many Gram-negative organisms are intrinsically resistant by virtue of the inability of benzylpenicillin to penetrate their outer membranes. Intrinsic resistance can also be due to structural differences in the target penicillin-binding proteins. See under Resistance, below, for reference to acquired resistance.

The following pathogenic organisms are usually sensitive to benzylpenicillin:

- Gram-positive aerobes and anaerobes including *Bacillus anthracis, Clostridium perfringens, Cl. tetani, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Listeria monocytogenes, Peptostreptococcus* spp., non-beta-lactamase-producing staphylococci, and streptococci including *Streptococcus agalactiae* (group B), *Str. pneumoniae* (pneumococci), *Str. pyogenes* (group A), and some viridans streptococci; enterococci are relatively insensitive.
- Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *Neisseria gonorrhoeae* (gonococci), although beta-lactamase-producing strains are common.
- Gram-negative bacilli including *Pasteurella multocida, Streptobacillus moniliformis*, and *Spirillum minus* (or *minor*); most Gram-negative bacilli, including *Pseudomonas* spp. and Enterobacteriaceae, are insensitive although some strains of *Proteus mirabilis* and *Escherichia coli* may be inhibited by high concentrations of benzylpenicillin.
- Gram-negative anaerobes including *Prevotella* (non-fragilis *Bacteroides*) and *Fusobacterium* spp.
- Other organisms including *Actinomyces* and the spirochaetes, *Borrelia, Leptospira*, and *Treponema* spp.
- Mycobacteria, fungi, mycoplasmas, and rickettsias are not sensitive.

Activity with other antimicrobials. Benzylpenicillin may exhibit synergy with other antimicrobials, particularly the aminoglycosides, and such combinations have been used against enterococci and other relatively insensitive bacteria. Its activity may be enhanced by clavulanic acid and other beta-lactamase inhibitors, and both enhancement and antagonism have been shown for beta-lactam combinations. Antagonism has been reported to occur with some bacteriostatic drugs, such as chloramphenicol or tetracyclines, that interfere with active bacterial growth necessary for benzylpenicillin to achieve its effect.

Resistance. Susceptible Gram-positive bacteria acquire resistance to beta lactams mainly through the induction of beta-lactamases, including penicillinases. These enzymes are liberated extracellularly and hydrolyse the beta-lactam ring. This resistance is usually plasmid-mediated and can be transferred from one bacterium to another. Gram-negative bacteria produce beta-lactamases within their cell membranes which may be chromosomally or plasmid-mediated; all Gram-negative species probably contain small amounts of beta-lactamases. Resistance in Gram-negative species may also be due to changes in their outer membrane resulting in the failure of beta lactams to reach their target penicillin-binding proteins. Changes in the binding characteristics of penicillin-binding proteins may also result in resistance in Gram-positive and Gram-negative bacteria.

Most strains of *Staphylococcus aureus* are now resistant to benzylpenicillin. *Streptococcus pneumoniae* with reduced susceptibility or complete resistance to benzylpenicillin have increasingly been reported. Strains of *Neisseria meningitidis* with reduced sensitivity to benzylpenicillin have been identified. Penicillinase-producing *Neisseria gonorrhoeae* are widespread; reduced sensitivity of gonococci to benzylpenicillin may also result from alterations in penicillin-binding proteins. Most strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are now resistant.

Some organisms, usually Gram-positive cocci such as staphylococci or streptococci, may develop tolerance and are inhibited but not killed by benzylpenicillin; in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration.

Pharmacokinetics

Benzylpenicillin rapidly appears in the blood after intramuscular injection of water-soluble salts, and maximum concentrations are usually reached in 15 to 30 minutes; peak plasma concentrations of about 12 micrograms/mL have been reported after single doses of 600 mg.

When given orally, benzylpenicillin is inactivated fairly rapidly by gastric acid and only up to about 30% is absorbed, mainly from the duodenum; maximum plasma-penicillin concentrations usually occur in about 1 hour. In order to attain plasma-penicillin concentrations after oral use similar to those after intramuscular injection, up to 5 times as much benzylpenicillin may be necessary. Absorption varies greatly in different individuals and is better in patients with reduced gastric acid production, including neonates and the elderly. Food decreases the absorption of benzylpenicillin and oral doses are best given at least half an hour before or 2 to 3 hours after a meal.

Benzylpenicillin is widely distributed. It appears in pleural, pericardial, peritoneal, and synovial fluids, but in the absence of inflammation diffuses only to a small extent into abscess cavities, avascular areas, the eye, the middle ear, and the CSF. Inflamed tissue is, however, more readily penetrated and, for example, in meningitis higher concentrations of benzylpenicillin occur in the CSF. Active transport out of the CSF is reduced by probenecid. In patients with uraemia, other organic acids may accumulate in the CSF and compete with benzylpenicillin for active transport; toxic concentrations of benzylpenicillin sufficient to cause convulsions can result.

Benzylpenicillin diffuses across the placenta into the fetal circulation, and small amounts appear in breast milk.

The plasma half-life is about 30 minutes, although it may be longer in neonates and the elderly because of reduced renal function. In renal impairment the half-life may be increased to about 10 hours. About 60% is reported to be bound to plasma protein.

Benzylpenicillin is metabolised to a limited extent and the penicilloic acid derivative has been recovered in the urine. Benzylpenicillin is rapidly excreted in the urine, principally by tubular secretion, and about 20% of an oral dose appears unchanged in the urine; about 60 to 90% of a dose of aqueous benzylpenicillin given intramuscularly appears in the urine, mainly within the first hour. Significant concentrations occur in bile, but in patients with normal renal function only small amounts are excreted via the bile. Benzylpenicillin is removed by haemodialysis.

Renal tubular secretion is inhibited by probenecid (p. 607.3), which is sometimes given to increase plasma-penicillin concentrations and prolong half-life.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Penilfedrin P†; ***Austral.***: Benpen; ***Braz.***: Aricilina; Benzecilin; Cristalpen; Pencil P†; ***Canad.***: Crystapen; ***Fin.***: Geepenil; ***Ger.***: Infectocillin; ***India***: Pencip; Pentids; ***Irl.***: Crystapen; ***Mex.***: Declin; Farmabep; Pendiben L-A†; Pengesod†; Penisol†; Procasol; Prosodina; Sodipen; Unicil 3/1; Unicil 6:3:3; Unicil Mega; ***NZ***: Benpen; ***Philipp.***: Bentapen; Crystacin; Harbipen; Pencarv; ***S.Afr.***: Benzatec†; Bio-Pen; ***Spain***: Penibiot; Penilevel; Sodiopen; ***Thai.***: Pen-G; ***Turk.***: Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Kristapen; Kristasil; Penadur 6.3.3; Pencrist†; Penkain-K†; Pensilina†; Procillin†; ***UK***: Crystapen; ***USA***: Pfizerpen.

Multi-ingredient Preparations. ***Austria***: Retarpen compositum; ***Braz.***: Benapen; Benzapen G; Despacilina; Pencil 400†; Penkaron; Wycillin; ***Chile***: Prevepen Forte; ***Ger.***: Retacillin compositum; ***Hong Kong***: Pan-Fort Procaine†; Penicillin G Procaine Fortified†; ***Hung.***: Promptcillin Forte; ***India***: Bistrepen; Fortified PP; Fortified Procaine Peni; FPP; ***Malaysia***: Procaine Penicillin; ***Mex.***: Aguipental; Anapenil; Bencelin Combinado; Benzanil Compuesto†; Benzetacil Combinado; Hidrocilina; Lugaxil; Megapenil Forte†; Pecivax; Pendiben Compuesto†; Penicil; Penipot; Penisodina; Penprocilina†; Procilin†; Robencaxil; Suipen; ***Port.***: Atralcilina†; Lentocilin; ***Rus.***: Benzycillin 3 (Бензициллин 3); Bicillin-3 (Бициллин-3); ***S.Afr.***: Ultracillin†; ***Spain***: Benzetacil Compuesta; Cepacilina 633†; Penilevel Retard; ***Turk.***: Pencain K; Pronapen; ***Ukr.***: Bicillin-3 (Бициллин-3); ***Venez.***: Benzetacil 3-3; Benzetacil 6-3-3; Pronapen.

Pharmacopoeial Preparations

BP 2014: Benzylpenicillin Injection;

USP 36: Penicillin G Potassium Capsules; Penicillin G Potassium for Injection; Penicillin G Potassium for Oral Solution; Penicillin G Potassium Injection; Penicillin G Potassium Tablets; Penicillin G Sodium for Injection.

Besifloxacin *(rINN)*

Béfloxacine; Besifloxacino; Besifloxacinum; Безифлоксацин.

7-[(3*R*)-3-Aminoazepan-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

$C_{19}H_{21}ClFN_3O_3$=393.8

CAS — 141388-76-3.

ATC — S01AE08.

ATC Vet — QS01AE08.

UNII — BFE2NBZ7NX.

Besifloxacin Hydrochloride *(USAN, rINNM)*

Bésifloxacine, Chlorhydrate de; Besifloxacini Hydrochloridum; BOL-303224-A; Hidrocloruro de besifloxacino; SS-734; Безифлоксацин Гидрохлорид.

(+)-7-[(3*R*)-3-Aminohexahydro-1*H*-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

$C_{19}H_{21}ClFN_3O_3$,HCl=430.3

CAS — 405165-61-9.

ATC — S01AE08.

ATC Vet — QS01AE08.

UNII — 7506A6J57T.

Profile

Besifloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin. It is used topically as the hydrochloride in eye drops containing the equivalent of 0.6% besifloxacin for the treatment of conjunctivitis caused by susceptible bacteria.

References.

1. Tepedino ME, *et al.* Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. *Curr Med Res Opin* 2009; **25:** 1159–69.
2. Karpecki P, *et al.* Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: a multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. *Clin Ther* 2009; **31:** 514–26.

3. McDonald MB, *et al.* Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. *Ophthalmology* 2009; **116:** 1615–1623.e1.
4. Haas W, *et al.* Besifloxacin, a novel fluoroquinolone, has broad-spectrum in vitro activity against aerobic and anaerobic bacteria. *Antimicrob Agents Chemother* 2009; **53:** 3552–60.
5. Carter NJ, Scott LJ. Besifloxacin ophthalmic suspension 0.6%. *Drugs* 2010; **70:** 83–97.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Besivance; ***Singapore***: Besivance; ***USA***: Besivance.

Betamipron *(rINN)*

N-Benzoyl-β-alanine; Bétamipron; Betamipronum; CS-443; Бетамипрон.
3-Benzamidopropionic acid.
$C_{10}H_{11}NO_3$=193.2
CAS — 3440-28-6.
UNII — 3W0M245736.

Profile

Betamipron is a renal protectant used with the carbapenem antibacterial panipenem to reduce its adverse renal effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***China***: Carbenin (克倍宁); ***Jpn***: Carbenin.

Biapenem *(USAN, rINN)*

Biapénem; Biapenemum; CL-186815; L-627; LJC-10627; Биапенем.
6-{[(4*R*,5*S*,6*S*)-2-Carboxy-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]thio}-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]-s-triazol-4-ium hydroxide, inner salt.
$C_{15}H_{18}N_4O_4S$=350.4
CAS — 120410-24-4.
ATC — J01DH05.
ATC Vet — QJ01DH05.
UNII — YR5U3L9ZH1.

Profile

Biapenem is a carbapenem beta-lactam antibacterial similar to imipenem (p. 311.2), although it is reported to be more stable to renal dehydropeptidase I than imipenem. It has been given in usual doses of 300 mg twice daily by intravenous infusion over 30 to 60 minutes.

Reviews.
1. Perry CM, Ibbotson T. Biapenem. *Drugs* 2002; **62:** 2221–34.
2. Ikawa K, *et al.* Population pharmacokinetics and pharmacodynamics of biapenem in paediatric patients. *J Clin Pharm Ther* 2008; **33:** 203–10.
3. Ikawa K, *et al.* Pharmacokinetic-pharmacodynamic target attainment analysis of biapenem in adult patients: a dosing strategy. *Chemotherapy* 2008; **54:** 386–94.
4. Isobe Y, *et al.* Clinical and microbiological effects of biapenem in febrile neutropenic patients with hematologic malignancies. *Scand J Infect Dis* 2009; **41:** 237–9.
5. Nakagawa Y, *et al.* Clinical efficacy and safety of biapenem for febrile neutropenia in patients with underlying hematopoietic diseases: a multi-institutional study. *J Infect Chemother* 2011; **17:** 58–67. Correction. *ibid.*; 68–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Hua Jin (华劲); Newanti (安信); Nuo Jia Nan (诺加南); Tiance (天册); ***Jpn***: Omegacin.

Brodimoprim *(rINN)*

Brodimoprima; Brodimoprime; Brodimoprimum; Ro-10-5970; Бродимоприм.
2,4-Diamino-5-(4-bromo-3,5-dimethoxybenzyl)pyrimidine.
$C_{13}H_{15}BrN_4O_2$=339.2
CAS — 56518-41-3.
ATC — J01EA02.
ATC Vet — QJ01EA02.
UNII — V1YC7T6LLI.

Profile

Brodimoprim is a diaminopyrimidine antibacterial closely related structurally to trimethoprim (p. 383.2) and has been used in the treatment of infections of the respiratory tract and ear.

References.
1. Braunsteiner AR, Finsinger F. Brodimoprim: therapeutic efficacy and safety in the treatment of bacterial infections. *J Chemother* 1993; **5:** 507–11.

Capreomycin Sulfate

(BANM, USAN, rINNM)

34977; Capreomicina, sulfato de; Capreomycin Sulphate; Capréomycine, Sulfate de; Capreomycini Sulfas; Capromycin Sulphate; Sulfato de capreomicina; Капреомицина Сульфат.
CAS — 11003-38-6 (capreomycin); 1405-37-4 (capreomycin sulfate).
ATC — J04AB30.
ATC Vet — QJ04AB30.
UNII — 9H8D3J7V21.

Description. Capreomycin I consists of capreomycin IA ($C_{25}H_{44}N_{14}O_8$ = 668.7) and capreomycin IB ($C_{25}H_{44}N_{14}O_7$ = 652.7), which predominates. Capreomycin II, which makes up about 10% of the mixture, consists of capreomycin IIA and capreomycin IIB.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Capreomycin Sulfate). The disulfate of capreomycin, a polypeptide mixture produced by the growth of *Streptomyces capreolus*. It contains not less than 90% of capreomycin I. A white to practically white amorphous powder. Freely soluble in water; practically insoluble in most organic solvents. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers.

Uses and Administration

Capreomycin is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p. 210.2) as part of a multidrug regimen when resistance to primary drugs has developed.

Capreomycin is given as the sulfate by deep intramuscular injection or by intravenous infusion. The usual dose is the equivalent of 1 g of capreomycin base (maximum 20 mg/kg) given daily for 2 to 4 months, then 2 or 3 times weekly for the remainder of therapy.

For details of doses in children, the elderly, and those with renal impairment, see p. 233.2.

References.
1. Anonymous. Capreomycin. *Tuberculosis (Edinb)* 2008; **88:** 89–91.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an intramuscular dose of capreomycin 15 to 30 mg/kg daily, to a maximum dose of 1 g daily.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in the elderly. While licensed product information recommends that elderly patients (without renal impairment) may be given the same parenteral capreomycin dose as other adults, US tuberculosis treatment guidelines[1] advise that for those older than 59 years of age, the dose should be reduced to 10 mg/kg (maximum 750 mg) daily.

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 30/11/10) Correction. *ibid.* 2005: **53:** 1203. [dose]

Administration in renal impairment. As with aminoglycosides, the parenteral dose of capreomycin in patients with renal impairment must be reduced based on creatinine clearance (CC); licensed product information recommends adjusted doses to maintain a desired mean steady-state serum-capreomycin concentration of 10 micrograms/mL.

Alternatively, for patients with a CC < 30 mL/minute or those receiving haemodialysis, US[1] and WHO[2] tuberculosis treatment guidelines recommend a capreomycin dose of 12 to 15 mg/kg 2 or 3 times weekly (for those requiring haemodialysis, doses should be timed for after the dialysis run).

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 30/11/10) Correction. *ibid.* 2005: **53:** 1203. [dose]
2. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008*. Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 05/01/11)

Adverse Effects and Treatment

The effects of capreomycin on the kidney and eighth cranial nerve are similar to those of aminoglycosides such as gentamicin (p. 308.2). Nitrogen retention, renal tubular dysfunction, and progressive renal damage may occur. Hypokalaemia and other electrolyte abnormalities have been reported. Vertigo, tinnitus, and hearing loss may also occur and are sometimes irreversible. Abnormalities in liver function have been reported when capreomycin has been used with other antituberculous drugs. Hypersensitivity reactions including urticaria, maculopapular rashes, and sometimes fever have been reported. Leucocytosis and leucopenia have also occurred. Thrombocytopenia has been reported rarely. Eosinophilia is common with capreomycin. Capreomycin also has a neuromuscular blocking action. There may be pain, induration, and excessive bleeding at the site of intramuscular injection; sterile abscesses may also form.

Teratogenicity has been seen after high doses in *rodents.*

Treatment of overdose is generally supportive. Patients with normal renal function should be hydrated to maintain adequate urine output. Capreomycin may be removed by haemodialysis in patients with significant renal impairment.

Effects on the eyes. Report of a patient who developed optic neuritis 3 months after starting antimycobacterial therapy containing capreomycin.[1] His vision returned to normal within 10 weeks of withdrawal of capreomycin.

1. Magazine R, *et al.* Capreomycin-induced optic neuritis in a case of multidrug resistant pulmonary tuberculosis. *Indian J Pharmacol* 2010; **42:** 247–8.

Impurities. The manufacturer of a highly-purified capreomycin product (*Capacin; Cheiljedang, Kor.*) has claimed that such purification reduces the toxicity and alters the pharmacokinetics in *animal* studies, suggesting that some of the toxicity of capreomycin is due to such impurities.[1]

1. Lee SH, *et al.* The impurities of capreomycin make a difference in the safety and pharmacokineticprofiles. *Int J Antimicrob Agents* 2003; **22:** 81–3.

Precautions

Capreomycin should be given with care and in reduced dosage to patients with renal impairment. Care is also essential in patients with signs of eighth cranial nerve damage. It is advisable to monitor renal and auditory function and serum-potassium concentrations in patients before and during therapy. Periodic assessment of hepatic function is also recommended.

Interactions

Care should be taken when capreomycin is used with other drugs that have neuromuscular blocking activity. It should not be given with other drugs that are ototoxic or nephrotoxic.

Antimicrobial Action

Capreomycin has activity against various mycobacteria. Resistance develops readily if capreomycin is used alone. It shows cross-resistance with kanamycin and neomycin.

References.
1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.
2. Maus CE, *et al.* Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2005; **49:** 3192–7.

Pharmacokinetics

Capreomycin is poorly absorbed from the gastrointestinal tract. An intramuscular dose of 1 g has been reported to give a peak serum concentration of about 30 micrograms/mL after 1 or 2 hours. About 50% of a dose is excreted unchanged in the urine by glomerular filtration within 12 hours. Capreomycin is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Capastat†; ***China***: Hai Pu Mei Xin (海普美欣); ***Gr.***: Capastat; ***Rus.***: Capastat (Капастат); Capremabol (Капремабол); Capreostat (Капреостат); Capricyn (Каприцин); Kapocin (Капоцин); Lykocin (Лайкоцин); ***Spain***: Capastat; ***UK***: Capastat; ***USA***: Capastat.

Pharmacopoeial Preparations
USP 36: Capreomycin for Injection.

Carbadox *(BAN, USAN, pINN)*

Carbadoxum; GS-6244; Карбадокс.
Methyl 3-quinoxalin-2-ylmethylenecarbazate 1,4-dioxide.
$C_{11}H_{10}N_4O_4$=262.2
CAS — 6804-07-5.
UNII — M2X04R2E2Y.

Profile

Carbadox is an antibacterial that has been used in veterinary practice for treating swine dysentery and enteritis and for promoting growth. However, its use has been prohibited in

the EU and some other countries after reports of carcinogenicity.

Carbenicillin Sodium *(BANM, rINNM)*

BRL-2064; Carbenicilina sódica; Carbenicillin Disodium (USAN); Carbénicilline Sodique; Carbenicillinum natricum; α-Carboxybenzylpenicillin Sodium; CP-15-639-2; GS-3159 (carbenicillin potassium); Karbenicillin-nátrium; Karbenicylina sodowa; Natrii Carbenicillinum; NSC-111071; Натрий Карбенициллин.

The disodium salt of (6*R*)-6-(2-carboxy-2-phenylacetamido) penicillanic acid .

$C_{17}H_{16}N_2Na_2O_6S$=422.4

CAS — 4697-36-3 (carbenicillin); 4800-94-6 (carbenicillin disodium); 17230-86-3 (carbenicillin potassium).

ATC — J01CA03.

ATC Vet — QJ01CA03.

UNII — 9TS4B3H261.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Carbenicillin Disodium). A white to off-white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of carbenicillin 1% is between 6.5 and 8.0. Store in airtight containers.

Incompatibility. Carbenicillin sodium has been reported to be incompatible with aminoglycosides, tetracyclines, and many other drugs including other antimicrobials and these drugs should therefore be given separately.

Uses and Administration

Carbenicillin is a carboxypenicillin that has been given by injection as the disodium salt, often with gentamicin, in the treatment of infections due to *Pseudomonas aeruginosa*; however, other antipseudomonal penicillins such as ticarcillin (p. 380.2) or piperacillin (p. 342.1) are now preferred. It has also been given to treat serious infections due to non-penicillinase-producing strains of *Proteus* spp.

Esters of carbenicillin, such as carindacillin (p. 234.2), have been given orally in the treatment of urinary-tract infections.

Adverse Effects

As for Benzylpenicillin, p. 229.2.

Hypersensitivity reactions have been reported to be less frequent and less severe with carbenicillin than with benzylpenicillin.

Pain at the injection site and phlebitis may occur. Electrolyte disturbances, particularly hypokalaemia or hypernatraemia, may follow large doses of carbenicillin sodium.

A dose-dependent coagulation defect has been reported, especially in patients with renal impairment. Carbenicillin appears to interfere with platelet function thereby prolonging bleeding time; purpura and haemorrhage from mucous membranes and elsewhere may result.

Precautions

As for Benzylpenicillin, p. 229.3.

Sodium content. Each g of carbenicillin sodium contains about 4.7 mmol of sodium. Carbenicillin sodium should therefore be given with caution to patients on a restricted sodium diet.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

Carbenicillin has a bactericidal mode of action similar to that of benzylpenicillin, but with an extended spectrum of activity against Gram-negative bacteria.

- It has activity against *Pseudomonas aeruginosa*, although high concentrations are generally necessary. Activity against *Ps. aeruginosa* and some other organisms can be enhanced by gentamicin and other aminoglycosides.
- *Proteus*, including indole-positive spp. such as *Pr. vulgaris* are also sensitive.
- Against other Gram-negative bacteria activity is similar to ampicillin. Sensitive organisms include some Enterobacteriaceae, for example *Escherichia coli* and *Enterobacter* spp.; *Haemophilus influenzae*; and *Neisseria* spp. *Klebsiella* spp. are usually not susceptible.
- It has less activity against Gram-positive bacteria than benzylpenicillin.
- Anaerobic organisms are generally susceptible but high concentrations are required for *Bacteroides fragilis.*

Resistance. Carbenicillin is inactivated by penicillinases and some other beta-lactamases, although it is more stable to the chromosomally mediated beta-lactamases produced by some Gram-negative organisms, including *Ps. aeruginosa* and some *Proteus* spp. Resistance to carbenicillin may develop in *Ps. aeruginosa* during treatment with carbenicillin or other beta lactams. This resistance may be intrinsic where there are changes in cell wall permeability or penicillin-binding proteins, or it may be due to plasmid-mediated beta-lactamase production that may be transferred to and from certain strains of Enterobacteriaceae.

There may be cross-resistance between carbenicillin and other antipseudomonal penicillins.

Outbreaks of pseudomonal resistance to carbenicillin have been associated with extensive use in, for example, hospital burns units.

Pharmacokinetics

Carbenicillin is not absorbed from the gastrointestinal tract and has therefore been given either intramuscularly or intravenously.

The half-life of carbenicillin is reported to be about 1 to 1.5 hours; it is increased in patients with renal impairment, especially if there is also hepatic impairment, and also in neonates. Half-lives of 10 to 18 hours have been reported in renal impairment. Clearance is enhanced in patients with cystic fibrosis. Carbenicillin is about 50% bound to plasma proteins. Distribution of carbenicillin in the body is similar to that of other penicillins. Small amounts have been detected in breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Relatively high concentrations have been reported in bile, but carbenicillin is excreted principally by renal tubular secretion and glomerular filtration.

Probenecid increases and prolongs plasma concentrations of carbenicillin.

Carbenicillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Preparations

Pharmacopoeial Preparations

USP 36: Carbenicillin for Injection.

Carindacillin Sodium *(BANM, pINNM)*

Carbenicillin Indanyl Sodium (USAN); Carindacilina sódica; Carindacilline Sodique; CP-15464-2; Natrii Carindacillinum; Натрий Кариндациллин.

Sodium (6*R*)-6-[2-(indan-5-yloxycarbonyl)-2-phenylacetamido]penicillanate.

$C_{26}H_{25}N_2NaO_6S$=516.5

CAS — 35531-88-5 (carindacillin); 26605-69-6 (carindacillin sodium).

ATC — J01CA05.

ATC Vet — QJ01CA05.

UNII — 4OUL81K2RT.

Pharmacopoeias. In *US.*

USP 36: (Carbenicillin Indanyl Sodium). A white to off-white powder. Soluble in water and in alcohol. pH of a 10% solution in water is between 5.0 and 8.0. Store in airtight containers.

Profile

Carindacillin is the indanyl ester of carbenicillin (above) to which it is hydrolysed after absorption from the gastrointestinal tract. Its use has been restricted to the treatment of urinary-tract infections due to *Pseudomonas* spp. and other sensitive bacteria including *Proteus* spp.

Carindacillin may be given orally as the sodium salt; 535 mg of carindacillin sodium is equivalent to about 382 mg of carbenicillin. Usual doses, expressed in terms of carbenicillin, have been 382 to 764 mg four times daily.

Sodium content. Each g of carindacillin sodium contains about 1.9 mmol of sodium.

Preparations

Pharmacopoeial Preparations

USP 36: Carbenicillin Indanyl Sodium Tablets.

Carumonam Sodium *(BANM, USAN, rINNM)*

AMA-1080 (carumonam); Carumonam sódico; Carumonam Sodique; CRMN; Natrii Carumonamum; Ro-17-2301 (carumonam); Ro-17-2301/006 (carumonam sodium); Натрий Карумонам.

(*Z*)-(2-Aminothiazol-4-yl){[(2*S*,3*S*)-2-carbamoyloxymethyl-4-oxo-1-sulphoazetidin-3-yl]carbamoyl}methyleneamino-oxyacetic acid, disodium salt.

$C_{12}H_{12}N_6Na_2O_{10}S_2$=510.4

CAS — 87638-04-8 (carumonam); 86832-68-0 (carumonam sodium).

UNII — B4J4M4939D.

Pharmacopoeias. In *Jpn.*

Profile

Carumonam is a monobactam antibacterial with a spectrum of antimicrobial action *in vitro* similar to that of aztreonam (p. 225.1). It is given by intramuscular or intravenous injection as the sodium salt and doses are expressed in terms of carumonam; 1.09 g of carumonam sodium is equivalent to about 1 g of carumonam. The usual dose is 1 to 2 g daily in two divided doses.

Sodium content. Each g of carumonam sodium contains about 3.92 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Amasulin.

Cefaclor *(BAN, USAN, pINN)*

Céfaclor; Cefaclor-Monohydrat; Cefaclorum; Cefaclorum Monohydricum; Cefaklor; Cefaklór; Cefaklor monohydrát; Cefakloras; Compound 99638; Kefakloori; Sefaklor; Цефаклор.

(7*R*)-3-Chloro-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

$C_{15}H_{14}ClN_3O_4S,H_2O$=385.8

CAS — 53994-73-3 (anhydrous cefaclor); 70356-03-5 (cefaclor monohydrate).

ATC — J01DC04.

ATC Vet — QJ01DC04.

UNII — 69K7K19H4L (cefaclor); 3Z6FS3IK0K (anhydrous cefaclor).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 8: (Cefaclor). A white or slightly yellow powder. Slightly soluble in water; practically insoluble in dichloromethane and in methyl alcohol. A 2.5% suspension in water has a pH of 3.0 to 4.5.

USP 36: (Cefaclor). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in chloroform, in methyl alcohol, and in benzene. pH of a 2.5% suspension in water is between 3.0 and 4.5. Store in airtight containers.

Uses and Administration

Cefaclor is a cephalosporin antibacterial given orally in the treatment of susceptible Gram-positive and Gram-negative bacterial infections including upper and lower respiratory-tract infections, skin infections, and urinary-tract infections. Some classify cefaclor as a second-generation cephalosporin and its greater activity against *Haemophilus influenzae* makes it more suitable than cefalexin for the treatment of infections such as otitis media. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefaclor is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefaclor; 1.05 g of cefaclor monohydrate is equivalent to about 1 g of anhydrous cefaclor. The usual adult dose is 250 to 500 mg every 8 hours; up to 4 g daily has been given.

For details of doses in children, see p. 234.3.

Modified-release formulations of cefaclor are available in some countries.

Administration in children. Cefaclor may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including *Haemophilus influenzae*. For mild to moderate infections in children over 1 month of age, the American Academy of Pediatrics[1] suggests a dose of 20 to 40 mg/kg daily in 2 or 3 divided doses, to a maximum total daily dose of 750 mg to 1.5 g. The following alternative dose regimen is also recommended by the *BNFC*; doses may be doubled if necessary.

- children 1 month to 1 year of age: 62.5 mg 3 times daily
- children 1 to 5 years of age: 125 mg 3 times daily
- children over 5 years of age: 250 mg 3 times daily

For asymptomatic carriage of *H. influenzae* or mild exacerbations in cystic fibrosis the *BNFC* recommends the following oral doses:

- children 1 month to 1 year of age: 125 mg every 8 hours

- those aged 1 to 7 years: 250 mg 3 times daily
- those more than 7 years of age: 500 mg 3 times daily

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Precautions

As for Cefalexin, p. 236.2.

Hypersensitivity. Serum-sickness-like reactions may be more common with cefaclor than several other oral antibacterials[1] especially in young children,[2,3] and typically after several courses of cefaclor;[2] features include skin reactions and arthralgia. A relatively high incidence of anaphylactic reactions has been reported from Japan.[4]

There has been a report of myocarditis that developed as a hypersensitivity reaction to cefaclor in a 12-year-old child.[5]

1. McCue JD. Delayed detection of serum sickness caused by oral antimicrobials. *Adv Therapy* 1990; **7**: 22–7.
2. Vial T, *et al.* Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992; **26:** 910–14.
3. King BA, Geelhoed GC. Adverse skin and joint reactions associated with oral antibiotics in children: the role of cefaclor in serum sickness-like reactions. *J Paediatr Child Health* 2003; **39:** 677–81.
4. Hama R, Mori K. High incidence of anaphylactic reactions to cefaclor. *Lancet* 1988; **i**: 1331.
5. Beghetti M, *et al.* Hypersensitivity myocarditis caused by an allergic reaction to cefaclor. *J Pediatr* 1998; **132:** 172–3.

Interactions

As for Cefalexin, p. 236.2.

Anticoagulants. UK licensed product information recommends that monitoring of prothrombin time should be considered in patients receiving cefaclor and *warfarin* after rare reports of increased prothrombin times. It is not known whether this interaction is related to the vitamin K-related hypoprothrombinaemia seen with some cephalosporins (see Adverse Effects of Cefamandole, p. 238.3), but cefaclor does not contain the side-chain usually implicated in this reaction.

Antimicrobial Action

Cefaclor is bactericidal and has antimicrobial activity similar to that of cefalexin (p. 236.2) but is reported to be more active against Gram-negative bacteria including *Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae,* and *Proteus mirabilis,* and especially against *Haemophilus influenzae.* It is active against some beta-lactamase-producing strains of *H. influenzae.* It may be less resistant to staphylococcal penicillinase than cefalexin or cefradine and a marked inoculum effect has been reported *in vitro.*

Pharmacokinetics

Cefaclor is well absorbed from the gastrointestinal tract. Oral doses of 250 mg, 500 mg, and 1 g produce peak plasma concentrations of about 7, 13, and 23 micrograms/mL respectively after 0.5 to 1 hour. The presence of food may delay the absorption of cefaclor, but the total amount absorbed is unchanged. A plasma half-life of 0.5 to 1 hour has been reported; it may be slightly prolonged in patients with renal impairment. About 25% is bound to plasma proteins.

Cefaclor appears to be widely distributed in the body; it crosses the placenta and low concentrations have been detected in breast milk. It is rapidly excreted by the kidneys; up to 85% of a dose appears unchanged in the urine within 8 hours, the greater part within 2 hours. High concentrations of cefaclor occur in the urine within 8 hours of a dose; peak concentrations of 600, 900, and 1900 micrograms/mL have been reported after doses of 0.25, 0.5, and 1 g respectively. Probenecid delays excretion. Some cefaclor is removed by haemodialysis.

References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
2. Sourgens H, *et al.* Pharmacokinetic profile of cefaclor. *Int J Clin Pharmacol Ther* 1997; **35:** 374–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aclor; Ceclor; Cefkor†; Karlor; Keflor; Ozcef; ***Austria***: Cec; Ceclor; Cefastad; Cefax†; ***Belg.***: Doccefaclo†; ***Braz.***: Ceclor; Cefacloren; Clorcin-Ped; ***Canad.***: Ceclor; ***China***: Beinuoke (贝诺克); Ceclor (希刻劳); Di Suo (迪素); Heng Di Ke (恒迪克); Hengyun (恒运); Keflor (可福乐); Long Wei Xin (龙威欣); Ou Jia (欧佳); Shen Luo (申洛); Sheng Han (胜寒); Shi Hua Luo (施华洛); Shuai Xian (帅先); Su Ke Le (苏刻乐); Wan Min Xin (万敏新); Xi Nuo (希诺); Xi You Luo (希优洛); Xifulai (喜福来); Xin Ke Nuo (欣可诺); Xincatlor (新达罗); You Ke Nuo (优克诺); Zaike (再克); ***Cz.***: Ceclor†; Serviclor; Vercef; ***Fin.***: Kefolor; ***Fr.***: Alfatil; Haxifal; ***Ger.***: Cec†; Ceclorbeta†; Cef-Diolan†; InfectoCef; Panoral; ***Gr.***: Afecton; Camirox; Ceclor; Cefacloril; Fredyren; Hetaclox; Katinol; Makovan; Medelox; Panclor; Phacotrex; Streptocol-R; Ufoxillin; ***Hong Kong***: Ceclor; Clortrin†; Medoclor; Phaclor†; Qualiceclor; Qualiphor; Soficlor; Synfaclor†; Vercef; Vickclor; ***Hung.***: Ceclor; Cecloretta; Vercef†; ***India***: Acticlor; Articlor; Cecel; Ceflorr; Cloriv; Distaclor; Eclor; Halclor; Halocef; Keflor; Nayaclor; ***Indon.***: Capabiotic†; Ceclor†; Cloracef; Especlor†; Forifek; Medikoncef†; Soclor; ***Irl.***: Cefager†; Distaclor; Keftid; Pinaclor; ***Israel***: Cefalor; ***Ital.***: Altaclor; Bacticef; Bactigram; Cefulton; Clorad†; Clorazer†; Geniclor; Kliacef; Lafarclor; Macovan; Necloral; Oralcef; Panacef; Performer; Selviclor; Takecef; Tibifor; Valeclor; ***Malaysia***: Distaclor; Efaclor; Sifaclor; Soficlor; Vercef; ***Mex.***: Arcefal; Cec; Ceclor; Cefalan; Ceflacid†; Fasiclor; Fermed; Ranclor; Serviclor; Tecnoclor; Teraclox; ***Neth.***: Ceclor; ***NZ***: Clorotir†; ***Philipp.***: Aczebri†; Brelox†; Ceclobid; Ceclor; Cefmed; CFC; Clorcef; Clorotir†; Ephron; Lorcef; Remedlor; Solril; Surecef; Vefarol; Versef†; Verzat; Xelent; Xeztron†; Yucro; Zeclor; Zynolex; Zyrcef; ***Pol.***: Ceclor; Cek†; Panclor†; Serviclor†; Vercef; ***Port.***: Ceclor; ***Rus.***: Ceclor (Цеклор); Vercef (Верцеф)†; ***S.Afr.***: Cec†; Vercef; ***Singapore***: Cleancef; Distaclor†; Soficlor; Vercef; ***Spain***: Ceclor; ***Switz.***: Ceclor; ***Thai.***: Cefclor; Celco†; Clorotir; Distaclor; Sifaclor; Tefaclor; Vercef; ***Turk.***: Cec; Ceclor; Cekloteva; Kefsid; Losefar; Sanocef; ***UAE***: Recocef; ***UK***: Bacticlor; Distaclor; Keftid; ***USA***: Ceclor; Raniclor†; ***Venez.***: Ceclor.

Multi-ingredient Preparations. ***China***: An Bu (安卜); Bi Li (毕利); Pu Kuai (浦快); Xi Meng (熙蒙); Zheng Da Su Ke (正大素克); ***Mex.***: Ceclordox.

Pharmacopoeial Preparations

BP 2014: Cefaclor Capsules; Cefaclor Oral Suspension; Prolonged-release Cefaclor Tablets;

USP 36: Cefaclor Capsules; Cefaclor Chewable Tablets; Cefaclor Extended-Release Tablets; Cefaclor for Oral Suspension.

Cefadroxil *(BAN, USAN, pINN)*

BL-S578; Cefadroksilis monohidratas; Cefadroksyl jednowodny; Céfadroxil; Cefadroxil monohydrát; Cefadroxil-Monohydrat; Cefadroxil monohydraté; Cefadroxilmonohydrat; Cefadroxilo; Cefadroxilum; Cefadroxilum Monohydricum; Cephadroxil; Kefadroksiili; Kefadroksiilimonohydraatti; MJF-11567-3; Sefadroksil; Цефадроксил.

(7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-methyl-3-cephem-4-carboxylic acid monohydrate.

$C_{16}H_{17}N_3O_5S,H_2O$=381.4

CAS — 50370-12-2 (anhydrous cefadroxil); 119922-85-9 (cefadroxil hemihydrate); 66592-87-8 (cefadroxil monohydrate).

ATC — J01DB05.

ATC Vet — QJ01DB05.

UNII — Q525PA8JJB (anhydrous cefadroxil); 280111G160 (cefadroxil monohydrate); J9CMF6461M (cefadroxil hemihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US. Jpm* includes the anhydrous substance.

Ph. Eur. 8: (Cefadroxil Monohydrate). A white or almost white powder. Slightly soluble in water; very slightly soluble in alcohol. A 5% suspension in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Cefadroxil). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 5% suspension in water is between 4.0 and 6.0. Store in airtight containers.

Uses and Administration

Cefadroxil is a first-generation cephalosporin antibacterial that is the para-hydroxy derivative of cefalexin (p. 236.1), and is used similarly in the treatment of mild to moderate susceptible Gram-positive and Gram-negative bacterial infections. It is given orally, and doses are expressed in terms of the anhydrous substance; 1.04 g of cefadroxil monohydrate is equivalent to about 1 g of anhydrous cefadroxil. The usual dose is 1 to 2 g daily as a single dose or in two divided doses.

The dose of cefadroxil may need to be reduced in renal impairment, see p. 235.2. See also p. 235.2 for details of doses in children.

Cefadroxil has also been used as the lysine derivative.

Administration in children. Cefadroxil may be given orally to children for the treatment of mild to moderate infections caused by susceptible Gram-positive and Gram-negative bacteria. The American Academy of Pediatrics[1] suggests that children aged 1 month and older may be given a usual daily dose of 30 mg/kg in 2 divided doses. Other authorities, including the UK licensed product holder, suggest doses up to 50 mg/kg daily may be given. The usual adult dose of 1 to 2 g daily should not be exceeded.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Following an initial loading dose of 1 g, oral doses of cefadroxil should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 26 to 50 mL/minute per 1.73 m^2: 500 mg to 1 g every 12 hours
- CC 11 to 25 mL/minute per 1.73 m^2: 500 mg to 1 g every 24 hours
- CC 10 mL/minute per 1.73 m^2 or less: 500 mg to 1 g every 36 hours
- haemodialysis patients: an additional 500 mg to 1 g should be given at the end of each dialysis run

Adverse Effects and Precautions

As for Cefalexin, p. 236.2.

Breast feeding. Although higher concentrations of cefadroxil were reported in breast milk compared with cefalexin, cefalotin, cefapirin, and cefotaxime,[1] no detectable cefadroxil would be expected in breast-fed infants and no adverse effects have been seen in infants whose mothers were receiving cefadroxil. Accordingly, the American Academy of Pediatrics considers[2] that cefadroxil is usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefadroxil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Cefalexin, p. 236.2.

Antimicrobial Action

As for Cefalexin, p. 236.2.

Pharmacokinetics

Cefadroxil is almost completely absorbed from the gastrointestinal tract. After oral doses of 500 mg and 1 g, peak plasma concentrations of about 16 and 30 micrograms/mL respectively occur after 1.5 to 2 hours. Although peak concentrations are similar to those of cefalexin, plasma concentrations are more sustained. Dosage with food does not appear to affect the absorption of cefadroxil. About 20% of cefadroxil is reported to be bound to plasma proteins. The plasma half-life of cefadroxil is about 1.5 hours and is prolonged in patients with renal impairment.

Cefadroxil is widely distributed to body tissues and fluids. It crosses the placenta and appears in breast milk.

More than 90% of a dose of cefadroxil may be excreted unchanged in the urine within 24 hours by glomerular filtration and tubular secretion; peak urinary concentrations of 1.8 mg/mL have been reported after a dose of 500 mg. Cefadroxil is removed by haemodialysis.

References.

1. Tanrisever B, Santella PJ. Cefadroxil: a review of its antibacterial, pharmacokinetic and therapeutic properties in comparison with cephalexin and cephradine. *Drugs* 1986; **32** (suppl 3): 1–16.
2. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
3. Garrigues TM, *et al.* Dose-dependent absorption and elimination of cefadroxil in man. *Eur J Clin Pharmacol* 1991; **41**: 179–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefacar; Cefacilina; Cefadrox; Cefamar; Cefasin†; Cefatenk; Droxil†; Kandicin; Klondroxil; Versatic; ***Austria***: Duracef; ***Belg.***: Duracef; ***Braz.***: Cedroxil; Cefadroxon; Cefamox; Cefanaxil; Celocortin†; Neo Cefadril; ***Canad.***: Duricef†; ***Chile***: Adroxef; Cefamox; Sedafex†; Sefadex; ***China***: Lai Si (来斯); Li Xin Qi (力欣奇); Ouyi (欧意); Sai Feng (赛锋); Sai Fu Xi (赛复喜); Xianfengjiu (仙逢久); Yangyi (洋意); Yi Da (毅达); ***Cz.***: Biodroxil; Duracef; ***Fin.***: Duracef†; ***Fr.***: Oracefal; ***Ger.***: Gruncef; ***Gr.***: Biodroxil; Bitroxetan; Cefalom; Cyclomycine-K; Kleotrat; Med-Loral; Moxacef; Nefalox; Ultracef; ***Hong Kong***: Amben; Duracef†; Qualidrox; ***Hung.***: Duracef†; ***India***: Actidrox; Acudrox; Adriz; Apdil; Bicef; Bid; Biodrox; Bless; Bludrox; Brotzu; C-Drox; Caredrox; Cedil; Cedrox; Cedroxin; Cefadrox; Cefadur; Cefastar; Cefataur; Cefdox; Cefmac; Cefoxid; Cefoxid; Cefoxil; Ceftic; Cefwin; Cetron; Cexil; Codroxil; Cosdrox; Cudrox; Dax; Droma; Droxbit; Droxibid; Droxycad; Droxyceph; Droxyl; Edoxil; Eliminate; Enacxil; Eudrox; Gigacef; Hindrox; Kefloxin; Kefzen; Kidrox; Lactocef; LB-Drox DPS; Lydroxil; Mapradrox; Modcef; Monodrox; Mydrox; Neodrox; Odoxil; Omidrox; Pendrox; Vepan; Vistadrox; ***Indon.***: Alxil; Ancefa; Bidicef†; Biodroxil; Cefat; Dexacef; Doxef; Drovax; Droxal; Droxefa; Duricef†; Erphadrox; Ethicef; Grafacef; Kelfex; Lapicef; Libroceff†; Longcef; Lostacef; Opicef; Osadrox; Pyricef; Q Cef; Qidrox; Renasistin; Roksicap; Sedro-

fen; Staforin; Tisacef; Vocefa; Vroxil; Widrox; Yaricef; ***Irl.***: Ultracef†; ***Israel***: Biodroxil; ***Ital.***: Cefadril; Oradroxil; ***Malaysia***: Androxyl; Cefadur; Kefloxin; Sofidrox; ***Mex.***: Cefamox; Cepotec; Duracef; Inedit; Kefloxin; Teroxina; ***Philipp.***: Drolex; Droxil; Drozid; Lexipad; Wincocef; ***Pol.***: Biodroxil; Duracef; Tadroxil; ***Port.***: Cefacile†; Ceforal; ***S.Afr.***: Cipadur; Dacef; Duracef†; ***Singapore***: Androxyl; Dexacef; Sofidrox; ***Spain***: Duracef; ***Swed.***: Cefamox; ***Turk.***: Cefradur; Duricef; ***UK***: Baxan†; ***Ukr.***: Cedrohexal (Цедроксгексал)†; Cefangin (Цефангин); ***Venez.***: Bidroxyl; Cedroxim; Cefaval; Cefonax; Drocef; Droxifan; Grunicef; Sanodril.

Multi-ingredient Preparations. ***Arg.***: Cefacilina Bronquial; ***India***: Bidroxil; Biopro; Caredroxyl-LB; CDCV; Cedbrox; Cefastar; Dax-LA; Drofa; Droxflora; Droxyl Clav; Drozil LB; Kefdil-AX; Lactodrox-DT; LB-Drox; ***Mex.***: Duracef Expec; Fasinat.

Pharmacopoeial Preparations
BP 2014: Cefadroxil Capsules; Cefadroxil Oral Suspension;
USP 36: Cefadroxil Capsules; Cefadroxil for Oral Suspension; Cefadroxil Tablets.

Cefalexin *(BAN, pINN)*

66873; Cefaleksinas monohidratas; Cefaleksyna; Cefalexin monohydrát; Cefalexina; Céfalexine; Céfalexine monohydratée; Cefalexinmonohydrat; Cefalexinum; Cefalexinum Monohydricum; Cephalexin (USAN); Cephalexin; Kefaleksiini; Kefaleksiinimonohydraatti; Sefaleksin; Цефалексин.

(7*R*)-3-Methyl-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

$C_{16}H_{17}N_3O_4S,H_2O$=365.4

CAS — 15686-71-2 (anhydrous cefalexin); 23325-78-2 (cefalexin monohydrate).

ATC — J01DB01.

ATC Vet — QJ01DB01; QJ51DA01.

UNII — OBN7UD542Y (cefalexin); 5SFF1W6677 (anhydrous cefalexin).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cefalexin Monohydrate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 36: (Cephalexin). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 5% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Cefalexin Hydrochloride *(BANM, pINNM)*

Cefalexina, hidrocloruro de; Céfalexine, Chlorhydrate de; Cefalexini Hydrochloridum; Cephalexin Hydrochloride (USAN); Hidrocloruro de cefalexina; LY-061188; Цефалексина Гидрохлорид.

$C_{16}H_{17}N_3O_4S,HCl,H_2O$=401.9

CAS — 105879-42-3.

ATC — J01DB01.

ATC Vet — QJ01DB01.

UNII — 6VJE5G3D98.

Pharmacopoeias. In *US.*

USP 36: (Cephalexin Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 100 in water, in acetone, in acetonitrile, in alcohol, in dimethylformamide, and in methyl alcohol; practically insoluble in chloroform, in ether, in ethyl acetate, and in isopropyl alcohol. pH of a 1% solution in water is between 1.5 and 3.0. Store in airtight containers.

Uses and Administration

Cefalexin is a first-generation oral cephalosporin antibacterial for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria including infections of the respiratory and genito-urinary tracts, bones, and skin. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefalexin is usually given as the monohydrate although the hydrochloride is sometimes used. Doses are expressed in terms of the equivalent amount of anhydrous cefalexin; 1.05 g of cefalexin monohydrate and 1.16 g of cefalexin hydrochloride are each equivalent to about 1 g of anhydrous cefalexin.

It is given in doses ranging from 1 to 4 g daily in divided doses; 250 to 500 mg every 6 to 8 hours is typical. For skin and soft tissue infections, streptococcal pharyngitis, and uncomplicated urinary-tract infections a dose of 250 mg every 6 hours or 500 mg every 12 hours may be given. If daily doses greater than 4 g are needed, parenteral cephalosporins should be considered.

For the prophylaxis of recurrent urinary-tract infection, cefalexin may be given in a dose of 125 mg at night.

For details of doses in children, see p. 236.2.

The dose of cefalexin may need to be reduced in renal impairment, see p. 236.2.

Cefalexin sodium or cefalexin lysine have been used parenterally.

Administration in children. Cefalexin may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. The usual recommended dose is 25 to 50 mg/kg daily in 2 or 3 divided doses. In severe infections the dose may be doubled and for otitis media a dose of 75 to 100 mg/kg daily in 4 divided doses is recommended.

Alternative doses recommended by the *BNFC* are:

- children over 1 month of age: 12.5 mg/kg twice daily; dose should be doubled in severe infection (to a maximum dose of 1 g 4 times daily) *or*
- children 1 month to 1 year of age: 125 mg twice daily
- children 1 to 5 years of age: 125 mg 3 times daily
- children more than 5 years of age: 250 mg 3 times daily

Although not licensed in the UK for neonates, the *BNFC* suggests a dose of 25 mg/kg (to a maximum of 125 mg) may be given twice daily for neonates less than 7 days old, 3 times daily for those aged 7 to 21 days, and 4 times daily for those aged 21 to 28 days.

For the prophylaxis of recurrent urinary-tract infection the *BNFC* recommends that children over 1 month of age be given 12.5 mg/kg orally at night (to a maximum dose of 125 mg).

Administration in renal impairment. Oral doses of cefalexin may need to be reduced in patients with renal impairment. The *BNF* recommends the following maximum daily doses according to creatinine clearance (CC):

- CC 40 to 50 mL/minute per 1.73 m^2: maximum 3 g daily
- CC 10 to 40 mL/minute per 1.73 m^2: maximum 1.5 g daily
- CC less than 10 mL/minute per 1.73 m^2: maximum 750 mg daily

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 237.2.

The most common adverse effects of cefalexin and other oral cephalosporins are generally gastrointestinal disturbances and hypersensitivity reactions. Pseudomembranous colitis has been reported.

References.

1. Dave J, *et al.* Cephalexin induced toxic epidermal necrolysis. *J Antimicrob Chemother* 1991; **28**: 477–8.
2. Baran R, Perrin C. Fixed-drug eruption presenting as an acute paronychia. *Br J Dermatol* 1991; **125**: 592–5.
3. Clark RF. Crystalluria following cephalexin overdose. *Pediatrics* 1992; **89**: 672–4.
4. Murray KM, Camp MS. Cephalexin-induced Stevens-Johnson syndrome. *Ann Pharmacother* 1992; **26**: 1230–3.
5. Czechowicz RT, *et al.* Bullous pemphigoid induced by cephalexin. *Australas J Dermatol* 2001; **42**: 132–5.
6. Longstreth KL, *et al.* Cephalexin-induced acute tubular necrosis. *Pharmacotherapy* 2004; **24**: 808–11.
7. Skoog SM, *et al.* Cephalexin-induced cholestatic hepatitis. *J Clin Gastroenterol* 2004; **38**: 833.
8. Chan AL, *et al.* Fatal anaphylactic reaction to intravenous cephalexin. *Clin Drug Invest* 2005; **25**: 675–8.
9. Penttilä J, *et al.* Delirium in an adolescent patient during treatment with cephalexin. *J Adolesc Health* 2006; **39**: 782–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefalexin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

The renal excretion of cefalexin, and many other cephalosporins, is delayed by probenecid.

Hormonal contraceptives. There have been isolated reports of cefalexin decreasing the efficacy of oestrogen-containing oral contraceptives.[1] However, evidence does not generally support an interaction between broad-spectrum antibacterials and hormonal contraceptives (see p. 2243.1).

1. Friedman M, *et al.* Cephalexin and Microgynon-30 do not go well together. *J Obstet Gynaecol* 1982; **2**: 195–6.

Antimicrobial Action

As for Cefalotin Sodium, p. 238.1, although cefalexin is generally less potent. Some strains of Gram-negative bacteria may be inhibited only by the high concentrations achievable in the urinary tract. *Haemophilus influenzae* is moderately resistant to cefalexin.

Pharmacokinetics

Cefalexin is almost completely absorbed from the gastrointestinal tract and a peak plasma concentration of about 18 micrograms/mL occurs 1 hour after a 500-mg oral dose. If cefalexin is taken with food, absorption may be delayed, but the total amount absorbed is not appreciably altered. Up to 15% of a dose is bound to plasma proteins. The plasma half-life is about 1 hour; it increases with reduced renal function.

Cefalexin is widely distributed in the body but does not enter the CSF in significant quantities. It crosses the placenta and small quantities are found in breast milk. Cefalexin is not metabolised. About 80% or more of a dose is excreted unchanged in the urine in the first 6 hours by glomerular filtration and tubular secretion; urinary concentrations greater than 1 mg/mL have been achieved after a dose of 500 mg. Probenecid delays urinary excretion. Therapeutically effective concentrations may be found in the bile and some may be excreted by this route.

Cefalexin is removed by haemodialysis and peritoneal dialysis.

References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Beliam; Butefina†; Cefagrand; Cefapoten†; Cefarinol†; Cefasporina; Cefosporen; Ceporexin Duo; Ceporexin; Fabotop; Keforal; Lafexina; Lars; Lexin; Lorbicefax; Novalexin†; Ospexin; Perınvastat; Sanibiotic; Septilisin Duo; Septilisin; Trexina; Triblix; Velexina; ***Austral.***: Cephatrust; Cilex; Ialex; Ibilex; Keflex; Rancef; Sporahexal†; ***Austria***: Cephalobene; Keflex; Ospexin; Sanaxin; ***Belg.***: Keforal; ***Braz.***: Cefaben; Cefacimed; Cefagel; Cefagran; Cefalexol; Cefanal; Cefanid; Cefaxon; Cefexina; Celen†; Celexin†; Keflaxina; Keflex; Keforal†; Lexin; Neo Ceflex; Neoceflex; Primacef; Profalexina†; Valflex; ***Canad.***: Apo-Cephalex; Keflex; Novo-Lexin; Nu-Cephalex; ***China***: Bei Dun (贝盾); Fulin (福林); Meifeng (美丰); Shen Jia (申嘉); Sporidex (斯宝力克); ***Cz.***: Cefaclen†; Ospexin†; Sporidex†; ***Denm.***: Keflex; ***Fin.***: Kefalex; Kefexin; ***Fr.***: Cefacet; Ceporexine†; Keforal; ***Ger.***: Cephalex†; ***Gr.***: Kefalospes; Kefaxin; Keflex; Keflogen; Kekrinal; Medalexine; Neptolin; Nylichlor; Sinthecillin; Tricylamil; Zabytrex; ***Hong Kong***: Apo-Cephalex†; Cefacapxin†; Cefacin; Cephalexyl†; Cephin†; Felexin; Medolexin; Ora-C†; Ospexin; Sofilex; Solulexin†; Syntolexin†; ***Hung.***: Pyassan; ***India***: Alcephin; Alexin; Allsafe; Anphexin; Axin-LA; Bactocep; Betaspore; Biolex; Blucef; C-Lex; Cefacin; Cefact; Cefacure; Cefalex; Cefalin; Cefamax; Cefax; Cefbact; Cefcidal; Cefel; Ceff; Cefmix; Ceftop RM; Celexin; Cephadex; Cephal; Cephalex; Cephalkem; Cephalpet; Cephamax; Cepharil; Cephaxin; Cephaxtar; Cexin; Ciphlenat; Citaceph; Cucef; Culexin; DT LX-Kid; E Cef-OD; Emceph; Equitrol; Faxe; Fex; Gencef; Gexin; Halexin; Hycef; Keflex; Lecef; Lexa; Lexillin; Lexipil; LX; Mepycep; Mexef; Monacef; Neocef; Niphex; Nufex; Oralex; Oriphex; Phexin; Rofex; Sepexin; Sporidex; ***Indon.***: Cefabiotic; Madlexin; Ospexin; Pralexin†; Sofaxin; Tepaxin; Theralexin†; ***Irl.***: Keflex; ***Israel***: Ceforal; Cefovit; ***Ital.***: Ceporex; Keforal; Lafarin†; ***Jpn***: Larixin; ***Malaysia***: Celexin†; Cephanmycin; Felexin; Medolexin; Ospexin; Sofilex; Solulexin; Sporidex; Uphalexin; ***Mex.***: Acacin†; Ancetev†; Arlexen; Capxin; Cefalver; Ceporex; Facelit†; Fleximin†; Flextinol; Keflex; Nafacil; Naxifelar; Nixelaf-C; Optocef; Paferxin; Quimosporina; Servicef; Sporicef; ***Neth.***: Keforal; ***Norw.***: Keflex; ***Philipp.***: Airex; Bacilexin; Bandax; Benlexin; Bloflex; Canelin; Cefalin; Cendalex; Ceporex; CFA; Civalex; Clephin†; Difalex; Edexin; Eliphorin; Exel; Fablex; Falex; Falteria; Forexine; Halcepin†; Infexin; Ivynall; Keflex†; Lewimycin; Lexum; Lonarel†; Lyceplix; Madexin; Medilexin; Medoxine; Mefolex; Mexin; Montraflex†; Nefadon; Neolecsin; Nerfalex; Oneflex; Pediaflex; Respinal; Selzef; Servispor†; Sorlex; Sporidex†; Xeface; Xinflex; Zepharyl; Zeporin; Zepotex; Zexanta†; Zinace; Zucoflaxin†; ***Pol.***: Keflex; ***S.Afr.***: Belex; Keflex; Lenocef†; Ranceph; ***Singapore***: Apo-Cephalex; Celexin; Cephalen†; Cephanmycin; Ceporex; Felexin; Ospexin; Sofilex; Solulexin; Sporidex; Uphalexin; ***Spain***: Cefalexgobens†; Kefloridina; Lexincef†; Sulquipen†; Torlasporin†; ***Swed.***: Keflex; ***Thai.***: Cefexin†; Cefute; Celex; Celexin†; Cephalexyl; Cephin; Farmalex; Felexin; Ibilex; Keflex; Mycef; Neolexin†; Pondnacef†; Sefasin†; Sialexin; Sporicef; Sporidex†; Sporidin; Suphalex; Teplexin; Toflex; Ulflex; Vataceph†; Zeplex; ***Turk.***: Maksipor; Sef; ***UAE***: Cefrin; ***UK***: Ceporex; Keflex; ***Ukr.***: Lexin (Лексин); Ospexin (Оспексин)†; ***USA***: Cefanex; Keflex; ***Venez.***: Bidocef; Keforal; Stricef.

Multi-ingredient Preparations. ***China***: Pixian (彼先); Xindabao (新达宝); ***India***: Alcephin-LA; Caceff; Carbicef; Cecarb; Cefalong-DS; Cefel-B; Ceff-LA; Cep-Bro; Cephadex LB; ***Mex.***: Arlexen B; Cefabroxil; Cepobrom; Mucocef; Rombox.

Pharmacopoeial Preparations
BP 2014: Cefalexin Capsules; Cefalexin Oral Suspension; Cefalexin Tablets;
USP 36: Cephalexin Capsules; Cephalexin for Oral Suspension; Cephalexin Tablets for Oral Suspension; Cephalexin Tablets.

Cefalonium *(BAN, pINN)*

41071; Carbamoylcefaloridine; Cefalonio; Céfalonium; Cephalonium; Цефалоний.

(7*R*)-3-(4-Carbamoyl-1-pyridiniomethyl)-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.

$C_{20}H_{18}N_4O_5S_2$=458.5

CAS — 5575-21-3.

ATC Vet — QJ51DA90.
UNII — K2P920217W.

Pharmacopoeias. *BP(Vet)* includes the dihydrate.

BP(Vet) 2014: (Cefalonium). The dihydrate is a white or almost white crystalline powder. Very slightly soluble in water and in methyl alcohol; insoluble in alcohol, in dichloromethane, and in ether; soluble in dimethyl sulfoxide. It dissolves in dilute acids and in alkaline solutions. Store at temperature not exceeding 30 degrees. Protect from light.

Profile

Cefalonium is a cephalosporin antibacterial used in veterinary practice.

Cefaloridine *(BAN, pINN)*

40602; Cefaloridin; Cefaloridina; Céfaloridine; Cefaloridinum; Cephaloridine (USAN); Kefaloridiini; Цефалоридин.
(7*R*)-3-(1-Pyridiniomethyl)-7-[(2-thienyl)acetamido]-3-cephem-4-carboxylate.
$C_{19}H_{17}N_3O_4S_2$=415.5
CAS — 50-59-9.
ATC — J01DB02.
ATC Vet — QJ01DB02.
UNII — LVZ1VC61HB.

Profile

Cefaloridine was one of the first cephalosporin antibacterials to be available clinically. It has properties similar to those of cefalotin (p. 237.1), but is more nephrotoxic. It has been given by injection but is seldom used now.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Ceporan.

Cefalotin Sodium *(BANM, pINNM)*

38253; Cefalotin-Natrium; Cefalotin sodná sůl; Cefalotina sódica; Céfalotine sodique; Cefalotinnatrium; Cefalotinnátrium; Cefalotino natrio druska; Cefalotinum natricum; Cefalotyna sodowa; Cephalothin Sodium (USAN); Kefalotiininatrium; Natrii Cefalotinum; Sodium Cephalothin; Натрий Цефалотин.
Sodium (7*R*)-7-[2-(2-thienyl)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.
$C_{16}H_{15}N_2NaO_6S_2$=418.4
CAS — 153-61-7 (cefalotin); 58-71-9 (cefalotin sodium).
ATC — J01DB03.
ATC Vet — QJ01DB03.
UNII — C22G6EYP8B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefalotin Sodium). A white or almost white powder. Freely soluble in water; slightly soluble in dehydrated alcohol. A 10% solution in water has a pH of 4.5 to 7.0. Protect from light.

USP 36: (Cephalothin Sodium). A white to off-white, practically odourless, crystalline powder. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; insoluble in most organic solvents. pH of a 25% solution in water is between 4.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefalotin sodium has been reported to be incompatible with aminoglycosides and with many other drugs. Precipitation may occur in solutions with a pH of less than 5.

Uses and Administration

Cefalotin is a first-generation parenteral cephalosporin antibacterial that has been used in the treatment of infections due to susceptible bacteria, and for surgical infection prophylaxis, but has generally been replaced by newer cephalosporins. It has higher activity against Gram-positive than Gram-negative bacteria.

Cefalotin is given as the sodium salt by slow intravenous injection over 3 to 5 minutes or by intermittent or continuous infusion. It may be given intramuscularly but this route is painful. Doses are expressed in terms of the equivalent amount of cefalotin; 1.06 g of cefalotin sodium is equivalent to about 1 g of cefalotin. The usual dose is 0.5 to 1 g of cefalotin every 4 to 6 hours; up to 12 g daily has been given in severe infections.

For surgical infection prophylaxis, a dose of 2 g is given intravenously 30 to 60 minutes before the operation, followed by 2 g during surgery; 2 g is given every 6 hours postoperatively for 24 hours. For patients undergoing heart valve replacement or arthroplasty, cefalotin should be continued for up to 72 hours.

The dose of cefalotin may need to be reduced in renal impairment, see p. 237.2.

For details of doses in children, see p. 237.2.

Cefalotin sodium may be added to dialysis solutions or saline and given intraperitoneally.

Administration in children. Cefalotin may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given parenterally by deep intramuscular injection, by slow intravenous injection, or by intermittent or continuous intravenous infusion. The usual recommended dose is 80 to 160 mg/kg daily in divided doses.

For surgical infection prophylaxis, children may be given 20 to 30 mg/kg in the same dosing schedule as for adults (see Uses and Administration, above).

Administration in renal impairment. Reduced doses are recommended if cefalotin is given to patients with renal impairment. After an intravenous loading dose of 1 to 2 g patients may be given the following maximum doses according to their creatinine clearance (CC):

- CC 50 to 80 mL/minute: 2 g every 6 hours
- CC 25 to 50 mL/minute: 1.5 g every 6 hours
- CC 10 to 25 mL/minute: 1 g every 6 hours
- CC 2 to 10 mL/minute: 500 mg every 6 hours
- CC less than 2 mL/minute: 500 mg every 8 hours

Adverse Effects

The adverse effects associated with cefalotin and other cephalosporins are broadly similar to those described for penicillins (see Benzylpenicillin, p. 229.2). The most common are hypersensitivity reactions, including skin rashes, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis.

There may be a positive response to the Coombs' test although haemolytic anaemia rarely occurs. Neutropenia and thrombocytopenia have occasionally been reported. Agranulocytosis has been associated rarely with some cephalosporins. Bleeding complications related to hypoprothrombinaemia and/or platelet dysfunction have occurred especially with cephalosporins and cephamycins having an *N-methylthiotetrazole* side-chain, including

- cefamandole
- cefbuperazone
- cefmenoxime
- cefmetazole
- cefonicid
- cefoperazone
- ceforanide
- cefotetan
- cefpiramide
- latamoxef.

The presence of a *methylthiadiazolethiol* side-chain, as in cefazolin, or an *N-methylthiotriazine* ring, as in ceftriaxone, has also been associated with such bleeding disorders. Hypoprothrombinaemia which is usually reversible with vitamin K, was once thought to be due to an alteration in intestinal flora but interference with prothrombin synthesis now seems more likely.

Nephrotoxicity has been reported with cefalotin although it is less toxic than cefaloridine. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment, or when used with nephrotoxic drugs such as aminoglycosides. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

Transient increases in liver enzyme values have been reported. Hepatitis and cholestatic jaundice have occurred rarely with some cephalosporins.

Convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment.

Gastrointestinal adverse effects such as nausea, vomiting, and diarrhoea have been reported rarely. Prolonged use may result in overgrowth of non-susceptible organisms and, as with other broad-spectrum antibacterials, pseudomembranous colitis may develop (see also p. 237.2).

There may be pain at the injection site after intramuscular use, and thrombophlebitis has occurred on intravenous infusion of cephalosporins. Cefalotin appears to be more likely to cause such local reactions than other cephalosporins.

Antibiotic-associated colitis. Pseudomembranous colitis has occurred with many antibacterials, including broad-spectrum cephalosporins.[1-3] In 1991 the UK CSM warned[4] of the dangers of pseudomembranous colitis with the newer, as well as the older, oral cephalosporins. In addition to 33 reports of pseudomembranous colitis associated with cefalexin, cefradine, cefadroxil, and cefaclor, 6 of which proved fatal, they had received 12 reports of probable or confirmed cases with cefuroxime axetil and 15 with cefixime, one of them fatal. In clinical studies of cefuroxime axetil and cefixime, diarrhoea and pseudomembranous colitis appeared to be dose-related and therefore the CSM recommended that higher doses should be reserved for severe infections. In any event they advised that treatment should be stopped if symptoms suggestive of pseudomembranous colitis arose.

For further discussion of the management of this condition, see p. 183.1.

1. de Lalla F, *et al.* Third generation cephalosporins as a risk factor for Clostridium difficile-associated disease: a four-year survey in a general hospital. *J Antimicrob Chemother* 1989; **23:** 623–31.
2. Golledge CL, *et al.* Extended spectrum cephalosporins and Clostridium difficile. *J Antimicrob Chemother* 1989; **23:** 929–31.
3. Freiman JP, *et al.* Pseudomembranous colitis associated with single-dose cephalosporin prophylaxis. *JAMA* 1989; **262:** 902.
4. CSM. Pseudomembranous (antibiotic-associated) colitis and diarrhoea with cephalosporins. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the blood. References.

1. Lipsky JJ. Antibiotic-associated hypoprothrombinaemia. *J Antimicrob Chemother* 1988; **21:** 281–300.
2. Shearer MJ, *et al.* Mechanism of cephalosporin-induced hypoprothrombinemia: relation to cephalosporin side chain, vitamin K metabolism, and vitamin K status. *J Clin Pharmacol* 1988; **28:** 88–95.
3. Welage LS, *et al.* Comparative evaluation of the pharmacokinetics of N-methylthiotetrazole following administration of cefoperazone, cefotetan, and cefmetazole. *Antimicrob Agents Chemother* 1990; **34:** 2369–74.

Effects on the kidneys. References.

1. Zhanel GG. Cephalosporin-induced nephrotoxicity: does it exist? *DICP Ann Pharmacother* 1990; **24:** 262–5.
2. Tune BM. Nephrotoxicity of beta-lactam antibiotics: mechanisms and strategies for prevention. *Pediatr Nephrol* 1997; **11:** 768–72.

Hypersensitivity. Hypersensitivity reactions, up to and including rare reports of anaphylaxis, are recognised adverse effects of cephalosporins. However, there is some debate about the risks of cross-sensitivity between cephalosporins and penicillins, and between cephalosporins of different classes.[1,2]

A study in patients with documented penicillin allergy found that 14 of 128 had positive skin-test results to one or more of cefalotin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, or cefotaxime.[1] Of 101 patients with negative skin-test results to the latter 4 drugs, all tolerated subsequent test doses of cefuroxime axetil and ceftriaxone. However, the 11% cross-reactivity rate was considered to support the avoidance of cephalosporins in patients with positive results to penicillin skin tests.

In contrast, a review[2] questioned the evidence that cross-sensitivity rates between penicillins and cephalosporins are as high as the often-cited rates of 8 to 18%. It considered that the immune response to cephalosporins is highly dependent on their side-chain structure, which more closely resembles penicillins in some than in others. It was suggested that

- if a patient had a history consistent with a severe, IgE-mediated reaction to a penicillin then cephalosporins such as cefalotin and cefoxitin, with a similar 7-position side-chain on the beta-lactam ring, should be used with caution
- if the reaction followed use of ampicillin or amoxicillin the cephalosporins with a similar side-chain (cefalexin, cefradine, cefatrizine, cefadroxil, cefaclor, and cefprozil) should be used with caution
- patients who have had a non-IgE-mediated reaction to a penicillin, cephalosporins may be used (in uncertain cases, elective penicillin skin testing is advisable)

The incidence of cross-reactivity in penicillin-allergic patients appears to vary with the generation of the cephalosporin, being highest with the first-generation drugs (considered to be about 0.4%) and virtually absent for drugs such as cefuroxime, cefpodoxime, and cefdinir. Patients who have had a type-I reaction to a specific cephalosporin should probably never be given that drug again, but the risk of cross-sensitivity to another cephalosporin appears to be low if the side-chains of the drugs are not similar.

For mention of possible cross-reactivity between ceftazidime and aztreonam, see under Aztreonam, p. 225.1.

1. Romano A, *et al.* Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004; **141:** 16–22.
2. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics* 2005; **115:** 1048–57.

Precautions

Licensed product information states that cefalotin should not be given to patients who are hypersensitive to it or to other cephalosporins (but see also above). Immunological studies have suggested that up to 20% of penicillin-sensitive patients may also be allergic to cephalosporins although clinical studies indicate a lower frequency and the true

incidence is uncertain; great care should be taken if cefalotin is to be given to such patients. Care is also necessary in patients with a history of allergy.

Cefalotin should be given with caution to patients with renal impairment; dosage reduction may be necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy. Cefalotin and some other cephalosporins and cephamycins (ceforanide, cefotetan, cefoxitin, and cefpirome) may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function. Positive results to the direct Coombs' test have been found during treatment with cefalotin and these can interfere with blood cross-matching. The urine of patients being treated with cefalotin may give false-positive reactions for glucose using copper-reduction reactions.

Sodium content. Each g of cefalotin sodium contains about 2.39 mmol of sodium.

Interactions

The use of nephrotoxic drugs such as the aminoglycosides gentamicin and tobramycin may increase the risk of kidney damage with cefalotin. There is also some evidence for enhanced nephrotoxicity with the loop diuretic furosemide, but this is less certain than for furosemide with cefaloridine. As with penicillins, the renal excretion of cefalotin and many other cephalosporins is inhibited by probenecid. There may be antagonism between cefalotin and bacteriostatic antibacterials.

Antimicrobial Action

Cefalotin is a beta-lactam antibacterial. It is bactericidal and acts similarly to benzylpenicillin (p. 230.1) by inhibiting synthesis of the bacterial cell wall. It is most active against Gram-positive cocci, and has moderate activity against some Gram-negative bacilli.

- Sensitive Gram-positive cocci include both penicillinase- and non-penicillinase-producing staphylococci, although meticillin-resistant staphylococci are resistant; most streptococci are also sensitive, but not penicillin-resistant *Streptococcus pneumoniae;* enterococci are usually resistant.
  Some Gram-positive anaerobes are also susceptible. Cefalotin is usually inactive against *Listeria monocytogenes.*
- Among Gram-negative bacteria cefalotin has activity against some Enterobacteriaceae including strains of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella,* and *Shigella* spp., but not against *Enterobacter,* indole-positive *Proteus,* or *Serratia* spp.
  It is also active against *Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria* spp., though *Haemophilus influenzae* is moderately resistant.
  Bacteroides fragilis and *Pseudomonas aeruginosa* are not sensitive. Mycobacteria, mycoplasma, and fungi are resistant.

Resistance of bacteria to cefalotin may be due to several mechanisms: the drug may be prevented from reaching its site of action, for example in some Gram-negative organisms the cell wall may be a potential barrier; the target penicillin-binding proteins may be altered so that cefalotin cannot bind with these proteins; or, most importantly, the organism may produce beta-lactamases (cephalosporinases). Cefalotin is relatively resistant to hydrolysis by staphylococcal beta-lactamase, but is inactivated by a variety of beta-lactamases produced by Gram-negative organisms; resistance of Gram-negative organisms often depends on more than one factor. Resistance can be chromosomally or plasmid-mediated and may sometimes be inducible by cephalosporins.

Certain strains of bacteria may be inhibited but not killed by cephalosporins or penicillins and in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration; this is known as tolerance.

As well as with other cephalosporins, some cross-resistance may occur between cefalotin and the penicillinase-resistant penicillins.

Pharmacokinetics

Cefalotin is poorly absorbed from the gastrointestinal tract. After intramuscular injection peak plasma concentrations of about 10 and 20 micrograms/mL occur within 30 minutes of doses of 500 mg and 1 g, respectively. A concentration of 30 micrograms/mL has been reported 15 minutes after the intravenous injection of a 1-g dose; a range of 14 to 20 micrograms/mL has been achieved by the continuous intravenous infusion of 500 mg/hour.

Cefalotin is widely distributed in body tissues and fluids except the brain and CSF where the concentrations achieved are low and unpredictable. It crosses the placenta and low concentrations have been detected in breast milk. The plasma half-life varies from about 30 to 50 minutes, but may be longer in patients with renal impairment, especially that of the metabolite. About 70% of cefalotin is bound to plasma proteins.

About 20 to 30% of cefalotin is rapidly deacetylated in the liver and about 60 to 70% of a dose is excreted in the urine by the renal tubules within 6 hours as cefalotin and the less active metabolite, desacetylcefalotin. High urine concentrations of 800 micrograms/mL and 2.5 mg/mL have been seen after intramuscular doses of 500 mg and 1 g, respectively. Probenecid blocks the renal excretion of cefalotin. A very small amount is excreted in bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arecamin; Cefade; Dasuglor; Keflin; ***Austral.***: Keflin Neutral; ***Braz.***: Cefalin; Cefalotil; Cefariston; Kefalomax; Keflin; ***Canad.***: Ceporacin; ***China***: Fengsaixing (锋赛星); ***Gr.***: Practogen; ***Indon.***: Cephation†; Exion; Moraxine†; ***Mex.***: Cefelen†; Ceftina†; Falot; Famto; Keflin; Kefolit; Liroken I; Loriken; Lotin†; Tecphatil; ***Neth.***: Keflin; ***Norw.***: Keflin; ***Philipp.***: Fezef†; ***Singapore***: Cefadin; ***Thai.***: Cefadin; ***Venez.***: Ceflen.

Pharmacopoeial Preparations
USP 36: Cephalothin for Injection; Cephalothin Injection.

Cefamandole *(BAN, USAN, rINN)*

83405; Cefamandol; Céfamandole; Cefamandolum; Cephamandole; Compound 83405; Kefamandoli; Цефамандол.

(7*R*)-7-D-Mandelamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid;{6*R*-[6α,7β(*R**)]}-7-[(hydroxyphenylacetyl)amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{18}H_{18}N_6O_5S_2$=462.5
CAS — 34444-01-4.
ATC — J01DC03.
ATC Vet — QJ01DC03.
UNII — 5CKP8C2LLI.

Cefamandole Nafate *(BAN, USAN, rINNM)*

106223; Cefamandol, nafato de; Cefamandole Formate Sodium; Céfamandole, Nafate de; Cefamandole Nafate Sodium; Cefamandoli nafas; Cefamandoli Nafatum; Cefamandolio nafatas; Cefamandolnafat; Cefamandol-nafát; Cefamandolu nafan; Cefmandoli Nafas; Cephamandole Nafate; Kefamandolinafaatti; Nafato de cefamandol; Цефамандола Нафат.

Sodium (7*R*)-7-[(2*R*)-2-formyloxy-2-phenylacetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

$C_{19}H_{17}N_6NaO_6S_2$=512.5
CAS — 42540-40-9.
ATC — J01DC03.
ATC Vet — QJ01DC03.
UNII — 8HDO7941DO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cefamandole Nafate). A white, or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH, measured after 30 minutes, of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Cefamandole Nafate). A white, odourless, crystalline solid. Soluble in water and in methyl alcohol; practically insoluble in chloroform, in cyclohexane, in ether, and in benzene. pH of a 10% solution in water is between 3.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefamandole nafate has been reported to be incompatible with aminoglycosides and with metronidazole. Formulations of cefamandole nafate available for injection contain sodium carbonate and are incompatible with solutions containing calcium or magnesium salts. When reconstituted with water the sodium carbonate rapidly hydrolyses about 30% of the ester to cefamandole sodium; during storage of the reconstituted solution at room temperature carbon dioxide is produced.

References.
1. Frable RA, *et al.* Stability of cefamandole nafate injection with parenteral solutions and additives. *Am J Hosp Pharm* 1982; **39:** 622–7. Correction. *ibid.*; 1479.

Cefamandole Sodium *(BANM, rINNM)*

Cefamandol sódico; Céfamandole Sodique; Cephamandole Sodium; Natrii Cefamandolum; Натрий Цефамандол.

$C_{18}H_{17}N_6NaO_5S_2$=484.5
CAS — 30034-03-8.
ATC — J01DC03.
ATC Vet — QJ01DC03.
UNII — IY6234ODVR.

Uses and Administration

Cefamandole is a second-generation cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria (including infections of the respiratory and genito-urinary tracts, bones and joints, and of the skin and skin structure) and for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefamandole is given principally as cefamandole nafate (the sodium salt of cefamandole formyl ester). Doses are expressed in terms of the equivalent amount of cefamandole; 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate are each equivalent to about 1 g of cefamandole. It is given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous infusion in doses of 0.5 to 2 g every 4 to 8 hours depending on the severity of the infection. If cefamandole is used with an aminoglycoside, the drugs should be given separately.

For surgical infection prophylaxis, a dose of 1 or 2 g intravenously or intramuscularly 30 to 60 minutes before surgical incision, followed by 1 or 2 g every 6 hours for 24 to 48 hours, is recommended. For patients undergoing procedures involving implantation of prosthetic devices, cefamandole should be continued for up to 72 hours.

The dose of cefamandole may need to be reduced in patients with renal impairment, see p. 238.3.

For details of doses in children, see p. 238.3.

Administration in children. Cefamandole may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical infection prophylaxis. It is given parenterally by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous infusion.

For treatment, children over 1 month of age may be given 50 to 100 mg/kg daily in divided doses every 4 to 8 hours; 150 mg/kg daily may be given in severe infections, but this dose should not exceed the maximum adult dose (see Uses and Administration, above).

For surgical infection prophylaxis, children over 3 months of age may be given cefamandole in a similar schedule to adults (see above); 50 to 100 mg/kg is given daily in equally divided doses.

Administration in renal impairment. Parenteral doses of cefamandole should be reduced for patients with renal impairment. After an initial dose of 1 to 2 g the following maintenance doses have been recommended based on creatinine clearance (CC):

- CC 50 to 80 mL/minute per 1.73 m^2: 0.75 to 2 g every 6 hours
- CC 25 to 50 mL/minute per 1.73 m^2: 0.75 to 2 g every 8 hours
- CC 10 to 25 mL/minute per 1.73 m^2: 0.5 to 1.25 g every 8 hours
- CC 2 to 10 mL/minute per 1.73 m^2: 0.5 to 1 g every 12 hours
- CC less than 2 mL/minute per 1.73 m^2: 250 to 750 mg every 12 hours

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

As mentioned under Cefalotin, cephalosporins with an *N*-methylthiotetrazole side-chain such as cefamandole (and possibly those with methylthiadiazolethiol or *N*-methylthiotriazine side-chains as well) may produce bleeding disorders associated with hypoprothrombinaemia and/or platelet disorders.

Sodium content. 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate each contain about 2.2 mmol of sodium.

Interactions

A disulfiram-like interaction with alcohol may occur and has been attributed to the *N*-methylthiotetrazole side-chain of cefamandole; patients should avoid alcohol during, and for at least several days after, cefamandole treatment. Interactions are also possible with preparations containing significant amounts of alcohol.

Cefamandole, and other cephalosporins with an *N*-methylthiotetrazole side-chain, may enhance the hypoprothrombinaemic response to anticoagulants as discussed under Warfarin (p. 1531.1).

Probenecid reduces the renal clearance of cefamandole and many other cephalosporins.

References.
1. Portier H, *et al.* Interaction between cephalosporins and alcohol. *Lancet* 1980; **ii:** 263.
2. Drummer S, *et al.* Antabuse-like effect of β -lactam antibiotics. *N Engl J Med* 1980; **303:** 1417–18.

Antimicrobial Action

Cefamandole is bactericidal and acts similarly to cefalotin, but has a broader spectrum of activity. It generally has similar or less activity against Gram-positive staphylococci and streptococci, but is resistant to some beta-lactamases produced by Gram-negative bacteria. It is more active than cefalotin against many of the Enterobacteriaceae including some strains of *Enterobacter, Escherichia coli, Klebsiella, Salmonella,* and some *Proteus* spp. However, resistance to cefamandole and other beta lactams has emerged in some species, notably *Enterobacter,* during treatment with cefamandole. Cefamandole is very active *in vitro* against *Haemophilus influenzae* although an inoculum effect has been reported for beta-lactamase-producing strains. Like cefalotin, most strains of *Bacteroides fragilis* are resistant to cefamandole, as are *Pseudomonas* spp.

References.
1. Sabath LD. Reappraisal of the antistaphylococcal activities of first-generation (narrow-spectrum) and second-generation (expanded-spectrum) cephalosporins. *Antimicrob Agents Chemother* 1989; **33:** 407–11.

Pharmacokinetics

Cefamandole is poorly absorbed from the gastrointestinal tract. It is given intramuscularly or intravenously, usually as the nafate which is rapidly hydrolysed to release cefamandole *in vivo.* Peak plasma concentrations for cefamandole of about 13 and 25 micrograms/mL have occurred 0.5 to 2 hours after intramuscular doses of 500 mg and 1 g respectively; concentrations are very low after 6 hours. About 70% is bound to plasma proteins. The plasma half-life varies from about 0.5 to 1.2 hours depending on the route of injection; it is prolonged in patients with renal impairment.

Cefamandole is widely distributed in body tissues and fluids including bone, joint fluid, and pleural fluid; it diffuses into the CSF when the meninges are inflamed, but concentrations are unpredictable. Cefamandole has also been detected in breast milk. It is rapidly excreted unchanged by glomerular filtration and renal tubular secretion; about 80% of a dose is excreted within 6 hours and high urinary concentrations are achieved. Probenecid competes for renal tubular secretion with cefamandole resulting in higher and prolonged plasma concentrations of cefamandole. Therapeutic concentrations of cefamandole are achieved in bile.

Cefamandole is removed by haemodialysis to some extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mandol†; ***Austria***: Mandokef; ***Belg.***: Mandol†; ***China***: Mengdexin (孟得新); ***Gr.***: Acemycin; Cefadin; Kefabiotic; Mandocef†; Mandokef; ***Hung.***: Cefam†; ***Indon.***: Dardokef†; Dofacef; ***Ital.***: Cefam; Cemado†; Mancef; ***Neth.***: Mandol; ***NZ***: Mandol; ***Pol.***: Tarcefandol; ***Rus.***: Cefamabol (Цефамабол); Cefat (Цефат); Mandol (Мандол); ***S. Afr.***: Mandokef†; ***Switz.***: Mandokef; ***Thai.***: Cefadol†; Cefmandol.

Pharmacopoeial Preparations
USP 36: Cefamandole Nafate for Injection.

Cefapirin Sodium *(BANM, plNNM)*

BL-P-1322; Cefapirin-Natrium; Cefapirin sodná sůl; Cefapirina sódica; Céfapirine Sodique; Cefapirinnatrium; Cefapirin-nátrium; Cefapirino natrio druska; Cefapirinum Natricum; Cephapirin Sodium (USAN); Kefapiriininatrium; Natrii Cefapirinum; Натрий Цефапирин.

Sodium (7*R*)-7-[2-(4-pyridylthio)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(4-pyridylthio)acetamido]-3-cephem-4-carboxylate.

$C_{17}H_{16}N_3NaO_6S_2$=445.4

CAS — 21593-23-7 (cefapirin); 24356-60-3 (cefapirin sodium).

ATC — J01DB08.

ATC Vet — QJ01DB08.

UNII — 431LFF7171.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

US also includes Cephapirin Benzathine for veterinary use.

Ph. Eur. 8: (Cefapirin Sodium). A white or pale yellow powder. Soluble in water; practically insoluble in dichloromethane. A 1% solution in water has a pH of 6.5 to 8.5. Protect from light.

USP 36: (Cephapirin Sodium). A white to off-white crystalline powder, odourless or having a slight odour. Very soluble in water; insoluble in most organic solvents. pH of a solution in water containing the equivalent of cefapirin 1% is between 6.5 and 8.5. Store in airtight containers.

Profile

Cefapirin is a first-generation cephalosporin antibacterial with actions and uses very similar to those of cefalotin (p. 235.1). Doses have been expressed as either the sodium salt or as the base. 1.05 g of cefapirin sodium is equivalent to about 1 g of cefapirin. Usual doses of 0.5 to 1 g have been given every 4 to 6 hours by intramuscular injection or intravenously. In severe infections up to 12 g daily has been used.

Administration in renal impairment. Reduced parenteral doses of cefapirin sodium may be necessary in patients with renal impairment. One regimen, based on creatinine clearance (CC), that has been suggested is:

- CC 5 to 20 mL/minute: 1 g every 12 hours
- CC less than 5 mL/minute: 1 g every 24 hours

Patients undergoing haemodialysis may receive 7.5 to 15 mg/kg after each dialysis.

Sodium content. Each g of cefapirin sodium contains about 2.2 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cefaloject†; ***Gr.***: Cefatrex.

Pharmacopoeial Preparations
USP 36: Cephapirin for Injection.

Cefatrizine *(BAN, USAN, plNN)*

BL-S640; Cefatrizina; Céfatrizine; Cefatrizinum; S-640P; SKF-60771; Цефатризин.

(7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{18}H_{18}N_6O_5S_2$=462.5

CAS — 51627-14-6.

ATC — J01DB07.

ATC Vet — QJ01DB07.

UNII — 8P4W949T8K.

Cefatrizine Propylene Glycol *(BANM, plNNM)*

Cefatrizin-Propylenglycol; Cefatrizina propilenglicol; Cefatrizinas propilenglikolis; Céfatrizine Propylèneglycol; Cefatrizin-propilénglikol; Cefatrizin-propylenglykol; Cefatrizinpropylen-glykol; Cefatrizinum propylen glycolum; Cefatrizinum Propylenglycolum; Kefatritsiinipropyleeniglykoli; Цефатризин Пропиленгликол.

(7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylate propylene glycol.

$C_{13}H_{18}N_6O_5S_2 \cdot (C_3H_8O_2)_n$

CAS — 64217-62-5.

ATC — J01DB07.

ATC Vet — QJ01DB07.

UNII — 3731IA5GI9.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Cefatrizine Propylene Glycol). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane.

Profile

Cefatrizine is a first-generation cephalosporin antibacterial with actions and uses similar to those of cefalexin (p. 234.1), although it might be more active *in vitro.* It is given orally as the base or, more often, as a compound with propylene glycol, in usual doses equivalent to 500 mg twice daily of cefatrizine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cefaperos†; ***Gr.***: Anfagladin; Axelorax; Banadroxin; Ceftazin; Cetrizin; Clomin; Fica-F; Gertemycin; Izerin; Kentacef; Klevasin; Liamycin; Liferost; Lingopen; Mekan; Nibocin; Northiron; Phacobiotic; Relyovix; Specicef-N; Tedosin; Trixilan; Vagotrosin; Zirenol; ***Ital.***: Faretrizin†; Ketrizin†; Trizina†; ***Port.***: Macropen; Supracefa†.

Cefazolin *(BAN, plNN)*

Cefazolina; Céfazoline; Cefazolinum; Cephazolin; Kefatsoliini; Sefazolin; Цефазолин.

3-[(5-Methyl-1,3,4-thiadiazol-2-yl)thiomethyl]-7-(tetrazol-1-ylacetamido)-3-cephem-4-carboxylic acid.

$C_{14}H_{14}N_8O_4S_3$=454.5

CAS — 25953-19-9.

ATC — J01DB04.

ATC Vet — QJ01DB04; QJ51DA04.

UNII — IHS69L0Y4T.

Pharmacopoeias. In *US.*

USP 36: (Cefazolin). A white to slightly off-white, odourless crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in acetone; practically insoluble in chloroform, in dichloromethane, in ether, and in benzene; soluble in dimethylformamide and in pyridine; very slightly soluble in ethyl acetate, in isopropyl alcohol, and in methyl isobutyl ketone. Store in airtight containers.

Cefazolin Sodium *(BANM, USAN, plNNM)*

46083; Cefazolin-Natrium; Cefazolin sodná sůl; Cefazolina sódica; Céfazoline sodique; Cefazolinnatrium; Cefazolin-nátrium; Cefazolino natrio druska; Cefazolinum natricum; Cephazolin Sodium; Kefatsoliininatrium; Natrii Cefazolinum; Sefazolin Sodyum; SKF-41558; Натрий Цефазолин.

$C_{14}H_{13}N_8NaO_4S_3$=476.5

CAS — 27164-46-1.

ATC — J01DB04.

ATC Vet — QJ01DB04.

UNII — P380M0454Z.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Jpn also includes the pentahydrate.

Ph. Eur. 8: (Cefazolin Sodium). A white or almost white, very hygroscopic powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Cefazolin Sodium). A white to off-white, practically odourless, crystalline powder, or a white to off-white solid. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of cefazolin 10% is between 4.0 and 6.0. Store in airtight containers.

Incompatibility and stability. Cefazolin sodium has been reported to be incompatible with aminoglycosides and many other drugs. When the pH of a solution exceeds 8.5 there may be hydrolysis and when it is below 4.5 insoluble cefazolin may be precipitated.

References.
1. Nahata MC, Ahalt PA. Stability of cefazolin sodium in peritoneal dialysis solutions. *Am J Hosp Pharm* 1991; **48:** 291–2.
2. Wu C-C, *et al.* Stability of cefazolin in heparinized and nonheparinized peritoneal dialysis solutions. *Am J Health-Syst Pharm* 2002; **59:** 1537–8.
3. Lin Y-F, *et al.* Stability of cefazolin sodium in icodextrin-containing peritoneal dialysis solution. *Am J Health-Syst Pharm* 2002; **59:** 2362, 2364.

Uses and Administration

Cefazolin is a first-generation cephalosporin antibacterial used to treat infections due to susceptible Gram-positive and Gram-negative bacteria (including infections of the biliary, respiratory, and genito-urinary tracts, bones and joints, and of the skin and skin structure) and for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefazolin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion. Doses are expressed in terms of the equivalent amount of cefazolin; 1.05 g of cefazolin sodium is equivalent to about 1 g of cefazolin. The usual dose is the equivalent of 0.25 to 1 g of cefazolin every 6, 8, or 12 hours. In severe, life-threatening infections 1 to 1.5 g every 6 hours may be given; up to 12 g daily has been used.

For the prophylaxis of infection during surgery, a 1-g dose is given half to one hour before the operation, followed by 0.5 to 1 g during surgery for lengthy procedures. A dose of 0.5 to 1 g is given every 6 to 8 hours postoperatively for 24 hours, or up to 5 days in certain cases.

The dose of cefazolin may need to be modified in patients with renal impairment, see p. 240.1. See also p. 240.1 for details of doses in children, including dose modification for those with renal impairment.

Other routes used for cefazolin sodium include intraperitoneal use in peritoneal dialysis solutions, and intra-ocular injection.

In some countries a modified-release intramuscular formulation of cefazolin sodium with the less soluble dibenzylamine salt of cefazolin, in the ratio of 1:4, has been used.

Administration in children. Cefazolin may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given parenterally by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion. Children over 1 month of age may be given 25 to 50 mg/kg daily in 3 or 4 divided doses, increased in severe infections to a maximum of 100 mg/kg daily.

The dose of cefazolin should be modified in children with renal impairment. After a loading dose the following doses based on creatinine clearance (CC) have been suggested:

- CC 40 to 70 mL/minute: 60% of the normal daily dose in 2 divided doses
- CC 20 to 40 mL/minute: 25% of the normal daily dose in 2 divided doses
- CC 5 to 20 mL/minute: 10% of the normal daily dose every 24 hours

In the USA, the American Academy of Pediatrics[1] suggests that the following doses of cefazolin may be given to neonates:

- for neonates aged ⩽7 days (irrespective of weight): 25 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 25 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing >2 kg: 25 mg/kg every 8 hours

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral dosage of cefazolin should be reduced in patients with renal impairment and various modifications have been recommended. After a loading dose the licensed product information suggests the following doses based on creatinine clearance (CC):

- CC 55 mL or more per minute: usual doses
- CC 35 to 54 mL/minute: usual doses but at intervals of at least 8 hours
- CC 11 to 34 mL/minute: half the usual dose every 12 hours
- CC 10 mL or less per minute: half the usual dose every 18 to 24 hours

One report[1] indicated that, for patients on long-term haemodialysis, an intravenous dose of 20 mg/kg given 3 times weekly after dialysis maintained therapeutic cefazolin concentrations. Other authors[2] have suggested that critically ill patients receiving intermittent haemodialysis may be given doses of 500 mg to 1 g every 24 hours (after dialysis on dialysis days), or 1 to 2 g intravenously every 48 to 72 hours (after dialysis).

For critically ill patients undergoing continuous renal replacement therapy, an intravenous loading dose of 2 g has been recommended; maintenance doses are as follows:[2]

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours

1. Ahern JW, *et al.* Cefazolin dosing protocol for patients receiving long-term hemodialysis. *Am J Health-Syst Pharm* 2003; **60:** 178–81.
2. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2. Stevens-Johnson syndrome has occurred.

Like cephalosporins with an *N*-methylthiotetrazole side-chain, cefazolin has been associated with hypoprothrombinaemia.

Breast feeding. In a study[1] of 20 women receiving cefazolin, the amount of cefazolin in breast milk was found to be extremely small (equivalent to less than 0.075% of the dose). No adverse effects have been seen in breast-fed infants whose mothers were receiving cefazolin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Yoshioka H, *et al.* Transfer of cefazolin into human milk. *J Pediatr* 1979; **94:** 151–2.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the nervous system. References.

1. Manzella JP, *et al.* CNS toxicity associated with intraventricular injection of cefazolin: report of three cases. *J Neurosurg* 1988; **68:** 970–1.
2. Martin ES, *et al.* Seizures after intraventricular cefazolin administration. *Clin Pharm* 1992; **11:** 104–5.
3. Arkaravichien W, *et al.* Cefazolin induced seizures in hemodialysis patients. *J Med Assoc Thai* 2006; **89:** 1981–3.

Sodium content. Each g of cefazolin sodium contains about 2.1 mmol of sodium.

Interactions

Cefazolin contains a methylthiadiazolethiol side-chain; like cephalosporins containing the related *N*-methylthiotetrazole side-chain (see Cefamandole, p. 236.3), it may have the potential to cause a disulfiram-like reaction with alcohol, and enhance the effects of warfarin.

The renal excretion of cefazolin and many other cephalosporins is delayed by probenecid.

Antimicrobial Action

As for Cefalotin Sodium, p. 236.1, although cefazolin is more sensitive to staphylococcal beta-lactamase.

Pharmacokinetics

Cefazolin is poorly absorbed from the gastrointestinal tract and is given by the intramuscular or intravenous routes. After a 500-mg dose given intramuscularly, peak plasma concentrations of 30 micrograms or more per mL occur after 1 hour. About 85% of cefazolin is bound to plasma proteins. The plasma half-life of cefazolin is about 1.8 hours, and is increased in patients with renal impairment. Cefazolin diffuses into bone and into ascitic, pleural, and synovial fluid but not appreciably into the CSF. It crosses the placenta; only low concentrations are detected in breast milk.

Cefazolin is excreted unchanged in the urine, mainly by glomerular filtration with some renal tubular secretion, at least 80% of a dose given intramuscularly being excreted within 24 hours. Peak urine concentrations of more than 2 and 4 mg/mL have been reported after intramuscular doses of 0.5 and 1 g respectively. Probenecid delays excretion. Cefazolin is removed to some extent by haemodialysis.

High biliary concentrations have been reported, although the amount excreted by this route is small.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefalomicina; Cefamezin; ***Austral.***: Kefzol; ***Austria***: Kefzol; ***Belg.***: Kefzol; ***Braz.***: Ceftrat; Duocef†; Fazolon; Kefazol; ***China***: Saifuning (赛福宁); Xintailin (新泰林); ***Cz.***: Vulmizolin; ***Ger.***: Basocef; ***Gr.***: Biozolin; Kefarin; Kefzol; Tranclocin; Vifazolin; ***India***: Azolin; Cefadin; Cezolin; Ciprid; Orizolin; Ozolin; Reflin; ***Indon.***: Biozolin†; Cefazol; Evalin; ***Israel***: Cefamezin†; Kefazin; Pan-Cefazolin; ***Ital.***: Acef; Cefamezin; Cefazil; Cromezin; Nefazol; Recef; ***Jpn***: Cefamezin; Otsuka Cez†; ***Neth.***: Kefzol; Servazolin†; ***NZ***: Zepilen; ***Phil'ipp.***: Biocef; Cefazole; Cefazovit; Cifoxim; Cizo; Cloviz; Fazol; Fazonil; Fonvicol; Hazolin; Ilozef; Leklin; Lozan; Lupex†; Maxcep†; Novazef; Oryant; Plezolin; Samarial; Stancef; Suporin; Tefazol; Zalulin; Zofadep; Zolival; ***Pol.***: Biofazolin; Tarfazolin; ***Port.***: Cefamezin†; Kurgan†; ***Rus.***: Cefamezin (Цефамезин); Cezolin (Цезолин); Ifizol (Ифизол)†; Intrazoline (Интразолин); Kefzol (Кефзол); Lyzolin (Лизолин); Nacef (Нацеф); Orizolin (Оризолин); Orpin (Орпин); Reflin (Рефлин)†; Totacef (Тотацеф); Zolfin (Золфин); Zolin (Золин); ***S.Afr.***: Cefacidal†; Izacef†; Kefzol; Ranzol; ***Singapore***: Cefarizon; Cezolin; ***Spain***: Areuzolin†; Intrazolina; Kurgan; Tasep; Tecfazolina; Zolival; ***Switz.***: Kefzol; ***Thai.***: Cefalin†; Cefamezin; Cefazillin; Cefazol; Cefzolin; Fazolin; Zefa; Zolicef†; Zolimed†; ***Turk.***: Cefamezin; Cefozin; Cezol; Equizolin; Iespor; Maksiporin; Rebasin; Sefamax; Sefazol; ***Venez.***: Cefacidal; Cefarizon; Cellozina.

Pharmacopoeial Preparations

BP 2014: Cefazolin Injection;
USP 36: Cefazolin for Injection; Cefazolin Injection; Cefazolin Ophthalmic Solution.

Cefbuperazone *(USAN, rINN)*

BMY-25182; Cefbuperazona; Cefbupérazone; Cefbuperazonum; T-1982; Цефбуперазон.
7-[(2*R*,3*S*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-3-hydroxybutyramido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid..
$C_{22}H_{29}N_9O_9S_2$=627.6
CAS — 76610-84-9.
UNII — T0785J3X40.

Cefbuperazone Sodium *(rINNM)*

Cefbuperazona de sodio; Cefbupérazone Sodique; Natrii Cefbuperazonum; Натрий Цефбуперазон.
$C_{22}H_{28}N_9NaO_9S_2$=649.6
UNII — 1VX59V96BS.

Pharmacopoeias. In *Jpn.*

Profile

Cefbuperazone is a cephamycin antibacterial similar to cefoxitin (p. 248.2) but with an *N*-methylthiotetrazole side-chain like cefamandole (p. 236.2). It is given by injection as the sodium salt. Its spectrum of activity includes Enterobacteriaceae, but more especially anaerobic bacteria such as *Bacteroides fragilis.* Cefbuperazone does not appear to be active against cefoxitin-resistant strains of *B. fragilis.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tomiporan.

Cefcapene Pivoxil Hydrochloride *(rINNM)*

Cefcapène Pivoxil, Chlorhydrate de; Cefcapeni Pivoxili Hydrochloridum; Cefcapeno pivoxilo, hidrocloruro de; Hidrocloruro de cefcapeno pivoxilo; S-1006 (cefcapene); S-1108; Цефкапена Пивоксила Гидрохлорид.
Pivaloyloxymethyl (+)-(6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-pentenamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate monohydrochloride monohydrate.
$C_{23}H_{29}N_5O_8S_2$,HCl,H_2O=622.1
CAS — 135889-00-8 (cefcapene); 105889-45-0 (cefcapene pivoxil); 147816-23-7 (anhydrous cefcapene pivoxil hydrochloride); 147816-24-8 (cefcapene pivoxil hydrochloride).
ATC — J01DD17.
ATC Vet — QJ01DD17.
UNII — 5J77167P9E.

Pharmacopoeias. In *Jpn.*

Profile

Cefcapene is an oral cephalosporin antibacterial given orally as the pivaloyloxymethyl ester, cefcapene pivoxil hydrochloride.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Flomox.

Cefdinir *(BAN, USAN, rINN)*

Cefdinirum; CI-983; FK-482; Kefdiniiri; Цефдинир.
(-)-(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-oxime; 7-{(2-Amino-1,3-thiazol-4-yl)-2-[(*Z*)-hydroxyimino]acetamido}-3-vinylcephem-4-carboxylic acid.
$C_{14}H_{13}N_5O_5S_2$=395.4
CAS — 91832-40-5.
ATC — J01DD15.
ATC Vet — QJ01DD15.
UNII — CI0FAQ63WC.

Pharmacopoeias. In *Chin., Jpn,* and *US.*

USP 36: (Cefdinir). A white to light yellow crystalline powder. Practically insoluble in water, in alcohol, and in ether; sparingly soluble in 0.1M phosphate buffer (pH 7) solution. Store in airtight containers. Protect from light.

Uses and Administration

Cefdinir is a third-generation oral cephalosporin antibacterial used to treat infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the respiratory tract and of the skin and skin structures. For details of infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefdinir is given orally in a usual dose of 600 mg daily as a single dose or in two divided doses. Twice daily dosing should be used for pneumonia and skin infections.

The dose of cefdinir may need to be reduced in patients with renal impairment, see p. 241.1. See also p. 240.3 for details of doses in children.

Reviews.

1. Guay DRP. Cefdinir: an expanded-spectrum oral cephalosporin. *Ann Pharmacother* 2000; **34:** 1469–77.
2. Guay DR, *et al.* Cefdinir: an advanced-generation, broad-spectrum oral cephalosporin. *Clin Ther* 2002; **24:** 473–89.
3. Perry CM, Scott LJ. Cefdinir: a review of its use in the management of mild-to-moderate bacterial infections. *Drugs* 2004; **64:** 1433–64.
4. Sader HS, Jones RN. Cefdinir: an oral cephalosporin for the treatment of respiratory tract infections and skin and skin structure infections. *Expert Rev Anti Infect Ther* 2007; **5:** 29–43. Correction. *ibid.;* 754. [dose error]

Administration in children. Cefdinir may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children from 6 months of age may be given 14 mg/kg daily as a single dose or in two divided doses (to a maximum daily dose of 600 mg).

For details of doses in children with renal impairment see p. 241.1.

Administration in renal impairment. Oral doses of cefdinir should be reduced to 300 mg once daily in patients with renal impairment whose creatinine clearance is less than 30 mL/minute.

The dose of oral cefdinir should be reduced in *children* with renal impairment (creatinine clearance less than 30 mL/minute) to 7 mg/kg given once daily, up to a maximum dose of 300 mg.

Cefdinir is removed by haemodialysis; therefore patients on chronic haemodialysis should initially be given a dose of 300 mg (or 7 mg/kg) every alternate day. A dose of 300 mg (or 7 mg/kg) should be given at the conclusion of each haemodialysis session. Subsequent doses are then given every alternate day.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2. There have been reports of reddish stools in patients given cefdinir with iron supplements (see also Interactions, p. 241.1).

Interactions

Absorption of cefdinir is decreased by antacids or iron supplements and doses should be separated by an interval of at least 2 hours. Probenecid reduces the renal excretion of cefdinir.

Iron. A report[1] of red stools in an infant given cefdinir while being fed with an infant formula containing supplemental iron. It was considered important to be aware of the interaction because of the risk that it might be mistaken for a sign of gastrointestinal bleeding.

1. Lancaster J, *et al*. Nonbloody, red stools from coadministration of cefdinir and iron-supplemented infant formulas. *Pharmacotherapy* 2008; **28:** 678–81.

Antimicrobial Action

As for Cefixime, p. 243.1. However, cefdinir is reported to be much more active *in vitro* than cefixime against *Staphylococcus aureus*, but not meticillin-resistant strains, and it is less active against some Enterobacteriaceae.

Pharmacokinetics

Cefdinir is absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after an oral dose. Oral bioavailability has been estimated to range from 16 to 25%. It is widely distributed into tissues and is 60 to 70% bound to plasma proteins. Cefdinir is not appreciably metabolised and is excreted in the urine with an elimination half-life of 1.7 hours.

Cefdinir is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Cefzon (全泽复); Xi Fu Ni (希福尼); ***India***: Adcef; Adinir; Aldinir; Cednir; Cefcas; Cefdiel; Idinir; Kefdure; Kefnir; Maxicef-O; Oceph; Sefdin; ***Indon.***: Omnicef; ***Jpn***: Cefzon; ***Malaysia***: Cefdiel; ***Mex.***: Omnicef; ***Philipp.***: Cefnaxl; Nirocef; Omicef; Onicef; ***Thai.***: Omnicef; Samnir; ***Turk.***: Ceftinex; Cempes; ***USA***: Omnicef.

Multi-ingredient Preparations. ***India***: Cefrine.

Pharmacopoeial Preparations
USP 36: Cefdinir Capsules.

Cefditoren Pivoxil *(rINNM)*

Cefditorène, Pivoxil de; Cefditoreni Pivoxil; Cefditoreno pivoxilo; ME-1206 (cefditoren); ME-1207; Цефдиторена Пивоксил.

Pivaloyloxymethyl (+)-(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-3-[(*Z*)-2-(4-methyl-5-thiazolyl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 7²-(*Z*)-(*O*-methyloxime).

$C_{25}H_{28}N_6O_7S_3$=620.7

CAS — 104145-95-1 (cefditoren); 117467-28-4 (cefditoren pivoxil).

ATC — J01DD16.

ATC Vet — QJ01DD16.

UNII — 78THA212DH.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Cefditoren is a third-generation oral cephalosporin antibacterial used to treat infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the respiratory tract and of the skin and skin structures. For details of infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefditoren is given orally as the pivaloyloxymethyl ester, cefditoren pivoxil, but doses are expressed in terms of cefditoren; 245 mg of cefditoren pivoxil is equivalent to about 200 mg of cefditoren. A usual dose is 200 to 400 mg given twice daily.

For details of reduced doses to be used in patients with moderate to severe renal impairment, see p. 241.2.

Reviews.

1. Wellington K, Curran MP. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. *Drugs* 2004; **64:** 2597–2618.
2. Hernández-Martin J, *et al*. Cefditoren pivoxilo: una nueva cefalosporina oral para infecciones de vias respiratorias y de piel y tejidos blandos. *Rev Esp Quimioter* 2006; **19:** 231–46.
3. Biedenbach DJ, Jones RN. Update of cefditoren activity tested against community-acquired pathogens associated with infections of the respiratory tract and skin and skin structures, including recent pharmacodynamic considerations. *Diagn Microbiol Infect Dis* 2009; **64:** 202–12.

Administration in renal impairment. Oral doses of cefditoren pivoxil should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 30 to 49 mL/minute: the dose should not exceed 200 mg twice daily
- CC less than 30 mL/minute: the dose should be 200 mg once daily.

Adverse Effects and Precautions

As for Cefalotin, p. 235.2.

The most frequently reported adverse effects of cefditoren are gastrointestinal disturbances, especially diarrhoea.

For reference to carnitine deficiency with some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Interactions

Absorption of cefditoren after oral doses is decreased by antacids or histamine H_2-receptor antagonists. Probenecid reduces the renal excretion of cefditoren.

Antimicrobial Action

As for Cefixime, p. 243.1. Cefditoren also has activity against *Staphylococcus aureus*.

Pharmacokinetics

Cefditoren pivoxil is absorbed from the gastrointestinal tract and is hydrolysed to cefditoren by esterases to release active cefditoren in the bloodstream. Peak plasma concentrations average 1.8 micrograms/mL in fasting subjects 1.5 to 3 hours after a 200-mg dose. Bioavailability is about 14% in fasting subjects and is increased when cefditoren pivoxil is given with a high-fat meal. Plasma protein binding is reported to be 88%. The plasma half-life is about 1.6 hours and is prolonged in patients with renal impairment.

Cefditoren is not appreciably metabolised and is excreted mainly in the urine by glomerular filtration and tubular secretion. It is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Meiact (美爱克); ***Gr.***: Spectracef; ***India***: Cefdicare; Cefditran; Ceftorin; ***Indon.***: Meiact; ***Ital.***: Giasion; ***Jpn***: Meiact; ***Mex.***: Spectracef; ***Port.***: Meiact; Spectracef; ***Spain***: Meiact; Spectracef; Telo; ***Thai.***: Meiact; ***Turk.***: Meiact; Spektracef; ***USA***: Spectracef.

Cefepime Hydrochloride

(BANM, USAN, rINNM)

BMY-28142 (cefepime); Cefepima, hidrocloruro de; Céfépime, Chlorhydrate de; Céfépime, dichlorhydrate de; Cefepime Dihydrochloride; Cefepimi dihydrochloridum; Cefepimi Hydrochloridum; Hidrocloruro de cefepima; Sefepim Hidroklorür; Цефепима Гидрохлорид.

{6*R*-[6α,7β(*Z*)]}-1-[(7-{[(2-Amino-4-thiazolyl)-(methoxyimino)acetyl]amino}-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-methylpyrrolidinium chloride monohydrochloride monohydrate; 7-[(2-Amino-1,3-thiazol-4-yl)-2-[(*Z*)-methoxyimino]acetamido}-3-(1-methylpyrrolidiniomethyl)-3-cephem-4-carboxylate hydrochloride.

$C_{19}H_{25}ClN_6O_5S_2.HCl.H_2O$=571.5

CAS — 88040-23-7 (cefepime); 123171-59-5 (cefepime hydrochloride monohydrate).

ATC — J01DE01.

ATC Vet — QJ01DE01.

UNII — I8X1O0607P (cefepime hydrochloride monohydrate); 2A1O4F5N0C (anhydrous cefepime hydrochloride).

Pharmacopoeias. In *Eur*. (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefepime Dihydrochloride Monohydrate). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Cefepime Hydrochloride). A white to off-white, nonhygroscopic, crystalline powder. Freely soluble in water. Store in airtight containers. Protect from light.

Incompatibility and stability. References.

1. Stewart JT, *et al*. Stability of cefepime hydrochloride injection in polypropylene syringes at -20 degreesC, 4 degreesC, and 22-24 degreesC. *Am J Health-Syst Pharm* 1999; **56:** 457–9.
2. Stewart JT, *et al*. Stability of cefepime hydrochloride in polypropylene syringes. *Am J Health-Syst Pharm* 1999; **56:** 1134.
3. Williamson JC, *et al*. Stability of cefepime in peritoneal dialysis solution. *Ann Pharmacother* 1999; **33:** 906–9.
4. Baririan N, *et al*. Stability and compatibility study of cefepime in comparison with ceftazidime for potential administration by continuous infusion under conditions pertinent to ambulatory treatment of cystic fibrosis patients and to administration in intensive care units. *J Antimicrob Chemother* 2003; **51:** 651–8.
5. Trissel LA, Xu QA. Stability of cefepime hydrochloride in AutoDose infusion system bags. *Ann Pharmacother* 2003; **37:** 804–7.

Uses and Administration

Cefepime is a fourth-generation parenteral cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria, including those of the abdomen, urinary tract, respiratory tract, and skin and skin structures. It is effective against *Pseudomonas aeruginosa* and may be given empirically for febrile neutropenia. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefepime is given as the hydrochloride by deep intramuscular injection, or intravenously by infusion over at least 30 minutes. Doses are expressed in terms of the equivalent amount of cefepime; 1.19 g of cefepime hydrochloride is equivalent to about 1 g of cefepime. The usual dose is 1 to 2 g daily in 2 divided doses for mild to moderate infections, increased to 4 g daily in 2 divided doses in severe infections, although up to 6 g daily in 3 divided doses has been given for febrile neutropenia.

The dose of cefepime may need to be reduced in patients with renal impairment, see p. 241.3. See also p. 241.3 for details of doses in children, including dose recommendations for those with renal impairment.

Reviews.

1. Various. Cefepime: a β-lactamase-stable extended-spectrum cephalosporin. *J Antimicrob Chemother* 1993; **32** (suppl B): 1–214.
2. Barradell LB, Bryson HM. Cefepime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **47:** 471–505.
3. Okamoto MP, *et al*. Cefepime: a new fourth-generation cephalosporin. *Am J Hosp Pharm* 1994; **51:** 463–77.
4. Wynd MA, Paladino JA. Cefepime: a fourth-generation parenteral cephalosporin. *Ann Pharmacother* 1996; **30:** 1414–24.
5. Wong-Beringer A. Treating serious infections: focus on cefepime. *Pharmacotherapy* 2004; **24:** 216S–23S.
6. Roberts JA, *et al*. Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; **29:** 117–28.

Administration in children. Cefepime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Cefepime is given by deep intramuscular injection, or intravenously by infusion over at least 30 minutes. In the USA, the American Academy of Pediatrics (AAP)[1] suggests a dose of 30 mg/kg every 12 hours may be given to neonates; the dose may be increased to 50 mg/kg for *Pseudomonas* infections. For those beyond the neonatal period, the AAP suggests a dose of 100 mg/kg daily in 2 divided doses for the treatment of mild to moderate infections; up to 150 mg/kg daily, in 2 or 3 divided doses, may be given for the treatment of severe infections. US licensed product information suggests similar doses for children aged 2 months and over. The total dose should not exceed the recommended adult dosage (see above).

US licensed product information recommends that for children with renal impairment these doses of cefepime should be reduced by similar proportions to reductions in adults (see p. 241.3).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral dosage of cefepime should be modified in renal impairment. After a normal first dose the maintenance dosage should be adjusted according to the patient's creatinine clearance (CC) and the severity of the infection:

- CC 30 to 60 mL/minute: 0.5 to 2 g every 24 hours (2 g every 12 hours for febrile neutropenia)
- CC 11 to 29 mL/minute: 0.5 to 1 g every 24 hours (2 g every 24 hours for febrile neutropenia)
- CC 10 mL/minute or less: 250 to 500 mg every 24 hours (1 g every 24 hours for febrile neutropenia)

Patients undergoing haemodialysis should be given a dose of 1 g on the first day of treatment, followed by 500 mg daily; the dose should be given after haemodialysis on those days. A dose of 1 g daily should be used for febrile neutropenia. Patients undergoing continuous ambulatory peritoneal

dialysis should receive normal recommended doses at intervals of 48 hours. A dose of 2 g every 48 hours is used for febrile neutropenia.

For critically ill patients undergoing continuous renal replacement therapy, a loading dose of 2 g and the following maintenance doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours
- continuous venovenous haemodialysis (CVVHD) and haemodiafiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The safety of cefepime has been reviewed.[1-3] A meta-analysis[2] of studies involving cefepime suggested that there might be an increased risk of all-cause mortality compared with other beta-lactams. The FDA subsequently announced that it would review safety data to further evaluate the risk of death associated with cefepime use.[4] In June 2009, after this analysis, the FDA issued a statement that no statistically significant increase in mortality for cefepime-treated patients compared to comparator-treated patients was noted and that cefepime remains an appropriate therapy for its approved indications.[5]

1. Neu HC. Safety of cefepime: a new extended-spectrum parenteral cephalosporin. *Am J Med* 1996; **100** (suppl 6A): 68S–75S.
2. Yahav D, *et al.* Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; **7:** 338–48.
3. Drago L, De Vecchi E. The safety of cefepime in the treatment of infection. *Expert Opin Drug Safety* 2008; **7:** 377–87.
4. FDA. Early communication about an ongoing safety review: cefepime (marketed as Maxipime) (issued 14th November 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070496.htm (accessed 20/07/10)
5. FDA. Information for healthcare professionals: cefepime (marketed as Maxipime): (issued 17th June 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm167254.htm (accessed 19/06/09)

Effects on the nervous system. References to neurotoxicity,[1-10] sometimes manifesting as nonconvulsive status epilepticus, associated with use of cefepime (particularly but not exclusively in patients with impaired renal function).

1. Chow KM, *et al.* Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; **23:** 369–73.
2. Ferrara N, *et al.* Neurotoxicity induced by cefepime in a very old hemodialysis patient. *Clin Nephrol* 2003; **59:** 388–90.
3. Dakdouki GK, Al-Awar GN. Cefepime-induced encephalopathy. *Int J Infect Dis* 2004; **8:** 59–61.
4. Alpay H, *et al.* Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. *Pediatr Nephrol* 2004; **19:** 445–7.
5. Abanades S, *et al.* Reversible coma secondary to cefepime neurotoxicity. *Ann Pharmacother* 2004; **38:** 606–8.
6. Capparelli FJ, *et al.* Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology* 2005; **65:** 1840.
7. Maganti R, *et al.* Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav* 2006; **8:** 312–4.
8. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy* 2006; **26:** 1169–74.
9. Sonck J, *et al.* The neurotoxicity and safety of treatment with cefepime in patients with renal failure. *Nephrol Dial Transplant* 2008; **23:** 966–70.
10. Garces EO, *et al.* Renal failure is a risk factor for cefepime-induced encephalopathy. *J Nephrol* 2008; **21:** 526–34.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefepime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Antimicrobial Action

Cefepime is a fourth-generation cephalosporin and is active against many Gram-positive and Gram-negative aerobic organisms. Against Gram-positive cocci, its activity is similar to that of cefotaxime (p. 246.3) and includes staphylococci (but not meticillin-resistant *Staphylococcus aureus*) and streptococci. Against Enterobacteriaceae, it has a broader spectrum of activity than other cephalosporins, including activity against organisms producing chromosomally mediated beta-lactamases such as *Enterobacter* spp. and *Proteus vulgaris*. Against *Pseudomonas aeruginosa*, it has similar or slightly less activity than ceftazidime (p. 253.3), although it may be active against some strains resistant to ceftazidime.

Pharmacokinetics

Cefepime is given by injection as the hydrochloride. It is rapidly and almost completely absorbed on intramuscular injection and mean peak plasma concentrations of about 14 and 30 micrograms/mL occur about 1.5 hours after doses of 500 mg and 1 g respectively. Within 30 minutes of similar intravenous doses, peak plasma concentrations are 40 and 80 micrograms/mL respectively. The plasma half-life of cefepime is about 2 hours and is prolonged in patients with renal impairment. About 20% of cefepime is bound to plasma proteins.

Cefepime is widely distributed in body tissues and fluids. High concentrations occur in bile. Low concentrations have been detected in breast milk.

Cefepime is eliminated principally by the kidneys and about 85% of a dose is recovered unchanged in the urine. Cefepime is substantially removed by haemodialysis.

References.
1. Okamoto MP, *et al.* Cefepime clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 88–102.
2. Rybak M. The pharmacokinetic profile of a new generation of parenteral cephalosporin. *Am J Med* 1996; **100** (suppl 6A): 39S–44S.
3. Reed MD, *et al.* Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. *Antimicrob Agents Chemother* 1997; **41:** 1783–7.
4. Allaouchiche B, *et al.* Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 1997; **41:** 2424–7.
5. Blumer JL, *et al.* Review of the pharmacokinetics of cefepime in children. *Pediatr Infect Dis J* 2001; **20:** 337–42.
6. Capparelli E, *et al.* Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother* 2005; **49:** 2760–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefimen-K; Maxcef; Rivepime; ***Austral.***: Maxipime; ***Austria***: Maxipime; ***Belg.***: Maxipime; ***Braz.***: Clocef; Maxcef; Nepecef; Unifepim; ***Canad.***: Maxipime; ***Chile***: Maxipime; Pozineg; ***China***: Bo Shuai (博帅); Bo Zhi (博治); Da Li Neng (达力能); Heng Su (恒苏); Ka Luo Xin (卡洛欣); Kai Xin (凯欣); Laibixin (来比信); Li Si Ping (立斯平); Ling Di (灵迪); Luo Xin Wei (罗欣威); Maxipime (马斯平); Pai Nai Xin (派奈欣); Shi Rui Ping (士瑞平); Xian Ke Nuo (先可诺); XinLiWei (信力威); Ying Lan (英兰); ***Cz.***: Maxipime; ***Fin.***: Maxipime†; ***Fr.***: Axepim; ***Ger.***: Maxipime; ***Gr.***: Anticepim; Gencef; Maxinject; Maxipime; Verapime; Zefipime; ***Hong Kong***: Maxipime; ***Hung.***: Maxipime; ***India***: Adpime; Biopime; C-Pime; Cadpime; Calpime; Ceficad; Cefpime; Cefudix; Cepime; Chase; Effimax; Forpar; Inpime; Insipim; Ipacare; Ivipime; Kampi; Kefage; Kingcef; KPM; Leepime; Mapime; Maxicef; Maxipime; Megapime; Micropime; Neutrapime; Nitipime; Novapime; Orpime; ***Indon.***: Actacef; Biocepime; Caprifim; Ceforim; Emax; Exepime; Interpim; Macef; Maxicef; Maxilan; Maximer; Maxipime†; Procepim; Rapime; Rimax; Sandocef; Sopime; Vipime; ***Ital.***: Cepim; Cepimex; Maxipime; ***Malaysia***: Maxipime; Megapime; ***Mex.***: Imation; Maxef; Maxipime; ***NZ***: Maxipime; ***Philipp.***: Axera; Cepimax; Dimipra; Hapimax; Medipime; Pimcep; Pozineg; Sanpime; Vipefime; Zepim; Zepime; ***Pol.***: Maxipime; ***Port.***: Maxipime; ***Rus.***: Cepim (Цепим); Efepim (Эфипим); Maxipime (Максипим); Maxycef (Максицеф); Movizar (МОВИЗАР); ***S.Afr.***: Maxipime; ***Singapore***: Maxipime; ***Spain***: Maxipime; ***Swed.***: Maxipime†; ***Thai.***: Cefamax; Maxipime; Megapime; Orpime†; Pime; Sefpime; ***Turk.***: Ekipim; Maxipime; Unisef; ***UAE***: Qpime; ***Ukr.***: Cebopime (Цебопим); Efipime (Эфипим); Maxinort (Максинорт); Megapim (Мегапим); Pikcef (Пикцеф); Quadrocef (Квадроцеф); Quartacef (Квартацеф)†; ***USA***: Maxipime; ***Venez.***: Maxipime.

Multi-ingredient Preparations. ***India***: C-Pime-T; Magnova; Mikapime; Nicpime-AM.

Pharmacopoeial Preparations
USP 36: Cefepime for Injection.

Cefetamet (USAN, rINN)

Céfétamet; Cefetametum; LY-097964; Ro-15-8074; Цефетамет.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid.

$C_{14}H_{15}N_5O_5S_2$=397.4

CAS — 65052-63-3 (cefetamet).

ATC — J01DD10.

ATC Vet — QJ01DD10.

UNII — 4R5TV783X3.

Cefetamet Pivoxil Hydrochloride (rINNM)

Céfétamet Pivoxil, Chlorhydrate de; Cefetamet pivoxilo, hidrocloruro de; Cefetameti Pivoxili Hydrochloridum; Cefetametpivoxilhydroklorid; Cefetametum Pivoxili Hydrochloridum; Hidrocloruro de cefetamet pivoxilo; Kefetameettipivoksiilihydrokloridi; Ro-15-8075 (cefetamet pivoxil); Цефетамета Пивоксила Гидрохлорид.

Cefetamet pivaloyloxymethyl hydrochloride.

$C_{20}H_{25}N_5O_7S_2$,HCl=548.0

CAS — 65243-33-6 (cefetamet pivoxil); 111696-23-2 (cefetamet pivoxil hydrochloride).

ATC — J01DD10.

ATC Vet — QJ01DD10.

UNII — 2YE9732GFU.

Profile

Cefetamet is a third-generation cephalosporin antibacterial similar to cefixime (p. 242.3). It has been given orally as the hydrochloride of the pivaloyloxymethyl ester, cefetamet pivoxil hydrochloride, which is hydrolysed to cefetamet *in vivo*. The usual dose is 500 mg twice daily.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Reviews.
1. Bryson HM, Brogden RN. Cefetamet pivoxil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1993; **45:** 589–621.
2. Blouin RA, Stoeckel K. Cefetamet pivoxil clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 172–88.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Su Mei (安素美); Ansaitamei (安塞他美); Hua Xian Mei (华仙美); Kang Di Xin (康迪欣); Kang Mai Xin (康迈欣); Li Xin Mei (力欣美); Sai Fu Mei (赛福美); Tepuxin (特普欣); Wei Rui (威锐); Zhen Liang (珍良); ***Gr.***: Globocef; ***India***: Altamet; Cepime-O.

Cefixime (BAN, USAN, rINN)

Cefiksimas; Cefixim; Cefixim trihydrát; Cefixima; Céfixime; Cefiximum; Cefiximum Trihydricum; CL-284635; FK-027; FR-17027; Kefiksiimi; Sefiksim; Цефиксим.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-(carboxymethoxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylic acid trihydrate.

$C_{16}H_{15}N_5O_7S_2$,$3H_2O$=507.5

CAS — 79350-37-1.

ATC — J01DD08.

ATC Vet — QJ01DD08.

UNII — 97I1C92E55.

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 8: (Cefixime). A white or almost white, slightly hygroscopic, powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in ethyl acetate; freely soluble in methyl alcohol. A 5% suspension in water has a pH of 2.6 to 4.1. Store in airtight containers. Protect from light.

USP 36: (Cefixime). A white to light yellow crystalline powder. Practically insoluble in water, in ether, in ethyl acetate, and in hexane; slightly soluble in alcohol, in acetone, and in glycerol; soluble in methyl alcohol and in propylene glycol; very slightly soluble in 70% sorbitol and in octanol. pH of a solution in water containing the equivalent of cefixime 0.07% is between 2.6 and 4.1. Store in airtight containers.

Uses and Administration

Cefixime is generally classified as a third-generation cephalosporin antibacterial and is given orally to treat infections due to susceptible Gram-positive and Gram-negative bacteria, including gonorrhoea and infections of the respiratory and urinary tracts. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefixime is available as the trihydrate and doses are expressed in terms of anhydrous cefixime; 1.12 g of cefixime trihydrate is equivalent to about 1 g of anhydrous cefixime. It is given orally in doses of 200 to 400 mg daily as a single dose or in two divided doses; the higher dose is recommended in the USA. A single 400-mg dose is given for uncomplicated gonorrhoea.

The dose of cefixime may need to be reduced in patients with renal impairment, see p. 242.3. See also p. 242.3 for doses in children.

General references.
1. Leggett NJ, *et al.* Cefixime. *DICP Ann Pharmacother* 1990; **24:** 489–95.
2. AdamD, Wallace RJ, eds. Symposiumon cefixime. *Drugs* 1991; **42** (suppl 4): 1–32.
3. Markham A, Brogden RN. Cefixime: a review of its therapeutic efficacy in lower respiratory tract infections. *Drugs* 1995; **49:** 1007–22.
4. Hamilton-Miller JM. Overview of cefixime use in community-acquired infections. *Clin Microbiol Infect* 2000; **6** (suppl 3): 79–81.
5. Verhoef J, Gillissen A. Resistant Haemophilus influenzae in community-acquired respiratory tract infections: a role for cefixime. *Int J Antimicrob Agents* 2003; **21:** 501–9.

Administration in children. Cefixime may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children over 6 months and under 50 kg may be given 8 mg/kg daily as a single dose or in two divided doses.

Administration in renal impairment. Oral doses of cefixime should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC). UK licensed product information recommends that a dose of 200 mg daily should not be exceeded in patients

with a CC less than 20 mL/minute, as well as those on continuous ambulatory peritoneal dialysis or haemodialysis. In the USA licensed product information recommends doses adjusted as follows:

- CC 60 mL/minute or more: the usual dose of 400 mg daily
- CC 21 to 59 mL/minute or those on haemodialysis: 300 mg daily
- CC less than 20 mL/minute or those on continuous ambulatory peritoneal dialysis: 200 mg daily

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The most frequently reported adverse effects of cefixime are gastrointestinal disturbances, especially diarrhoea. Cefixime should be stopped if diarrhoea is severe.

Although cefixime does not have the *N*-methylthiotetrazole side-chain usually associated with hypoprothrombinaemia increases in prothrombin times have occurred in a few patients.

Antibiotic-associated colitis. For reports of diarrhoea and pseudomembranous colitis associated with cefixime, see Cefalotin, p. 235.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefixime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Care should be exercised in patients receiving anticoagulants and cefixime due to the possibility that cefixime may increase prothrombin times (see above).

Antimicrobial Action

Cefixime is bactericidal and is stable to hydrolysis by many beta-lactamases. It has a mode of action and spectrum of activity similar to those of the third-generation cephalosporin cefotaxime (p. 246.3), but some Enterobacteriaceae are less susceptible to cefixime. *Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria gonorrhoeae* are sensitive, including penicillinase-producing strains. Of the Gram-positive bacteria, streptococci are sensitive to cefixime but most strains of staphylococci, enterococci, and *Listeria* spp. are not.

Enterobacter spp., *Pseudomonas aeruginosa,* and *Bacteroides* spp. are resistant to cefixime.

Pharmacokinetics

Only 40 to 50% of an oral dose of cefixime is absorbed from the gastrointestinal tract, whether taken before or after meals, although the rate of absorption may be decreased in the presence of food. Cefixime is better absorbed from oral suspension than from tablets. Absorption is fairly slow; peak plasma concentrations of 2 to 3 micrograms/mL and 3.7 to 4.6 micrograms/mL have been reported between 2 and 6 hours after single doses of 200 and 400 mg, respectively. The plasma half-life is usually about 3 to 4 hours and may be prolonged when there is renal impairment. About 65% of cefixime is bound to plasma proteins.

Information on the distribution of cefixime in body tissues and fluids is limited. It crosses the placenta. Relatively high concentrations may occur in bile and urine. About 20% of an oral dose (or 50% of an absorbed dose) is excreted unchanged in the urine within 24 hours. Up to 60% may be eliminated by nonrenal mechanisms; there is no evidence of metabolism but some is probably excreted into the faeces from bile. It is not substantially removed by dialysis.

References.

1. Brittain DC, *et al.* The pharmacokinetic and bactericidal characteristics of oral cefixime. *Clin Pharmacol Ther* 1985; **38:** 590–4.
2. Guay DRP, *et al.* Pharmacokinetics of cefixime (CL-284,635; FK027) in healthy subjects and patients with renal insufficiency. *Antimicrob Agents Chemother* 1986; **30:** 485–90.
3. Faulkner RD, *et al.* Pharmacokinetics of cefixime in the young and elderly. *J Antimicrob Chemother* 1988; **21:** 787–94.
4. Stone JW, *et al.* Cefixime, in-vitro activity, pharmacokinetics and tissue penetration. *J Antimicrob Chemother* 1989; **23:** 221–8.
5. Westphal JF, *et al.* Biliary excretion of cefixime: assessment in patients provided with T-tube drainage. *Antimicrob Agents Chemother* 1993; **37:** 1488–91.
6. Somekh E, *et al.* Penetration and bactericidal activity of cefixime in synovial fluid. *Antimicrob Agents Chemother* 1996; **40:** 1198–1200.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Novacef; Vixcef; ***Austria***: Aerocef; Tricef; ***Braz.***: Neo Cefix; ***Canad.***: Suprax; ***Chile***: Tricef; Urotricef; ***China***: An Di Ke Tuo (安的克妥); An Di Ke Wei (安的克威); Ao De Ning (奥德宁); Cefspan (世福素); Dalifen (达力芬); Fu Xin Kang (扶欣抗); Han Guang Tuo (汉光妥); Hui Xin Sha (汇新沙); Ji Luo (基洛); Jin Chen (今辰); Jiu Bang (久邦); Jun Te (君特); Kang Pai (康哌); Ke Ao Sha (克沃莎); Ke Lin Dun (克林盾); Kui Ke (魁克); Li Jian Ke (立健克); Luo Wei Ke (洛伟克); Ou Jian (欧健); Qi An (琪安); Qin Ke Ao (勤克沃); Qing Ke Yi (青可奕); She Er (舍尔); Shi Rui Ke (士瑞克); Si Li Jie (司力捷); Suprax (速普乐); Te Pu Ning (特普宁); Xin Fu Su (新福素); Xindaxin (新达欣); Yan Ling (严灵); Yan Yi (严逸); Yu Shu (誉舒); Zai Wo (再握); ***Cz.***: Suprax; ***Fr.***: Oroken; ***Ger.***: Cephoral; InfectoOpticef; Suprax†; Uro-Cephoral; ***Gr.***: Ceftoral; Covocef-N; ***Hung.***: Suprax; ***India***: AB-CEF; Aelxim; Afixim; Almocef; Arcef; Aricef; Aroxim; Asicef; Astute; Atocef; Avcif; Axim; Axiom-OR; Belfix; Bestocef; Biotax-O; Bixigard; Brufix; C-Fix; C-FX; C-Tax-O; Cadifix; Canbicef; Candycef; Carcef; Casxim; Cebay; Cefaden-O; Cefcem; Cefcon; Cefesym; Cefexy; Cefi; Cefia; Cefiact; Ceficacy; Ceficin; Cefigard; Cefigo; Cefigram; Cefikab; Cefime; Cefimed; Cefimo; Cefinar; Cefind; Cefine; Cefio; Cefisym; Cefit; Cefiwel; Cefix; Cefiza; Ceflim; Cefnij; Cefo; Cefocef-LB; Cefox; Cefrub; Cefspan; Ceftas; Ceftiwin; Cefupop; Cefvel; Cefxi-O; Celitol; Cemax-O; Cemaxin; Ceme; Cevicim; Cexim; Cexime; Cifgen; Cifilac; Cifivar; Cifzone; Cinxim; Civic; Claferon-O; Clomid; Cocef; Daczim; Dotcef; E-Fix; Eden; Efoxim; Elce; Elcef; Elfi; Emtax; Esfix; Eurox; Evacef O; Excef; Extacef-P; Extacef; Femcef; Fevorit; Fexim; Fexitage; Fimi; Fixcef; Fixi; Fixsana; Fixsav; Fixtrim; Fixx; Focime-L; Formic-O; Gramocef-O; Halixim; Hifen-DS; Hifen; Hofim; I-M-Safe; Incef; Indcef; Jancef; Jidox; Kapdox CL; Kefix; Kxime; L-Cef; Labocef; Laximo; Laycef; LBCef; Letix; Lexime; Logcef; Magnexim; Mahacef; Medicip; Micfox; Milixim; Mintocef; Mytax-O; Nayafix; NBCef; Nitaxim-O; Nizocef; Novacef; Novafex; Nuclear; Nufix; O-Powercef; Oflomix; Omnapil; Omnatax-O; Orcef; Orfix; Oritaxim-O; Pancef-O; Si-Fixim; Xim; Ziprax; ***Indon.***: Anfix; Cefacef; Cefarox; Cefika; Cefila; Cefspan; Ceptik; Comsporin; Ethifix; Fixacep; Fixam; Fixef; Fixiphar; Lanfix; Maxpro; Nucef; Opixime; Profim; Pyxime; Simcef; Sofix; Spancef†; Spaxim; Sporetik; Starcef; Taxime; Tocef; Trixim; Urticef; Yafix; ***Irl.***: Suprax; ***Israel***: Supran†; ***Ital.***: Cefixoral; Stadium; Supracef; Suprax; Unixime; ***Jpn***: Cefspan; ***Malaysia***: Cefix; Cefixycin; Ixime; Minixime; ***Mex.***: Denvar; ***Philipp.***: Actimax; Aeruxim; Axetef; C-Tax P; Cefixmycin; Cifacure; Ezcef; Fix-A; Fixcef; Fixxx; Refixime; Savecef†; Septipan; Synmex; Taxocef; Tergecef; Ultraxime; Zefral; ***Pol.***: Suprax; ***Port.***: Bonocef†; Cefimix; Cefiton; Cefizel; Neocef; Tricef; ***Rus.***: Ceforal (Цефорал); Ixime (Иксим); Pancef (Панцеф); Suprax (Супракс); ***S.Afr.***: Fixime†; ***Spain***: Denvar; Necopen†; ***Switz.***: Cephoral; ***Thai.***: Cefspan; Sixime; ***Turk.***: Cephix; Fixef; Sancefix; Suprax; Zimaks; ***UK***: Suprax; ***Ukr.***: Cefix (Цефикс); Ceforal (Цефорал); Ixime (Иксим); Maxibat (Максибат)†; ***USA***: Suprax; ***Venez.***: Longacef.

Multi-ingredient Preparations. ***India***: Aelxim-CL; Afixim Clav; Alfi-CV; Astute-CV; Belfix-CV; Bestocef-LB; Bilactam-XL; Bilactam; Bixigard-C; C-Fix-XT; C-Tax-O XL; Canbicef; Casclav; Casxim-DT; Cebay; Ceemi; Cefcal; Cefexy-CV; Cefglobe; Cefi XL; Cefic; Cefiped; Cefirap; Cefit-OZ; Cefit-XL; Cefix LB; Cefix-CV; Cefla; Cefline; Cefnet; Cefo-L; Cefo-LX; Cefocef-DXL; Cefocef-XL; Cefoclav; Cefodin; Cefolac; Cefson; Ceftas AL; Ceftas-LB; Ceftobac; Cefupop-CV; Cefupop-XL; Ceme-CV; Cepoxit; Cexime-CL; Cifilac-CV; Cifivar-LB; Cifzone; Ciloxin; Clavtax-O; Clomid-CL; Clomid-LB; Cocef-LB; Comtrix-O; CX-Zim; Daczim-CL; E-Fix LB; Ecocef; Efelac; Elcef-LB; Elfi-XL; Emtax-CL; Extacef-LB; Extacef-P; Fevorit-LB; Fimi-CV; Fixcef-CL; Fixital; Fixsana-LB; Fixx Clav; Fixx LB; Formic-XL; Fydocef; Gefix; Glocef-CL; Glocef; Gramocef-CV; Hifen-CV; Hifen-LXX; HiFi-L; Hofim-C; Incef-CL; Incef-CV; Incef-LB; Jexime-LB; Jidox-C; L-Cef; Labocef-CV; Lafix; Laximo-XL; LBCef; Letix-C; Lexime-CV; Logcef-CV; Magnexim LB; Mahacef-CV; Mahacef-OZ; Mahacef-XL; Mahacef; MDCef-CV; MDCef; Mefi; Milixim-CV; Milixim-LX; Mucomelt Forte; Nufex Beta; Omnapil-CV; Omnatax-CV; Ornicef; Pancef-O LB.

Pharmacopoeial Preparations
USP 36: Cefixime for Oral Suspension; Cefixime Tablets.

Cefmenoxime Hydrochloride *(USAN, rINNM)*

Abbott-50192; Cefmenoxima, hidrocloruro de; Cefménoxime, Chlorhydrate de; Cefmenoxime Hemihydrochloride; Cefmenoximi Hydrochloridum; Hidrocloruro de cefmenoxima; SCE-1365 (cefmenoxime); Цефменоксима Гидрохлорид.

(*Z*)-(7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid hydrochloride.

$(C_{16}H_{17}N_9O_5S_2)_2.HCl$=1059.6

CAS — 65085-01-0 (cefmenoxime); 75738-58-8 (cefmenoxime hydrochloride).

ATC — J01DD05.

ATC Vet — QJ01DD05.

UNII — NON736D32W.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cefmenoxime Hydrochloride). White to light orange-yellow crystals or crystalline powder. Very slightly soluble in water; practically insoluble in dehydrated alcohol and in ether; freely soluble in formamide; slightly soluble in methyl alcohol. Store in airtight containers.

Profile

Cefmenoxime is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefotaxime (p. 246.1). It has been given as the hydrochloride by intramuscular injection, or intravenously by injection or infusion in the treatment of susceptible infections.

Like cefamandole (p. 236.2), cefmenoxime has an *N*-methylthiotetrazole side-chain and coagulopathy and a disulfiram-like interaction with alcohol have been reported rarely.

Cefmenoxime hydrochloride is also given as eye drops for the treatment of eye infections.

Reviews.

1. Campoli-Richards DM, Todd PA. Cefmenoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1987; **34:** 188–221.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: En Nuo Ni (恩诺尼); Lei Te Mai Xing (雷特迈星); ***Gr.***: Tacef; ***Jpn***: Bestcall; Bestron.

Pharmacopoeial Preparations
USP 36: Cefmenoxime for Injection.

Cefmetazole *(USAN, rINN)*

Cefmetazol; Cefmétazole; Cefmetazolum; U-72791; Цефметазол.

(6*R*,7*S*)-7-{2-[(Cyanomethyl)thio]acetamido}-7-methoxy-3-{[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{15}H_{17}N_7O_5S_3$=471.5

CAS — 56796-20-4.

ATC — J01DC09.

ATC Vet — QJ01DC09.

UNII — 3J962UJT8H.

Pharmacopoeias. In *US*.

USP 36: (Cefmetazole). Store in airtight containers.

Cefmetazole Sodium *(USAN, rINNM)*

Cefmetazol sódico; Cefmétazole Sodique; Cefmetazolnatrium; Cefmetazolum Natricum; CS-1170; Kefmetatsolinatrium; Natrii Cefmetazolum; SKF-83088; U-72791A; Натрий Цефметазол.

$C_{15}H_{16}N_7NaO_5S_3$=493.5

CAS — 56796-39-5.

ATC — J01DC09.

ATC Vet — QJ01DC09.

UNII — 37Y9VR4W7A.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cefmetazole Sodium). A white solid. Very soluble in water and in methyl alcohol; soluble in acetone; practically insoluble in chloroform. pH of a 10% solution in water is between 4.2 and 6.2. Store in airtight containers.

Uses and Administration

Cefmetazole is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p. 248.2) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. It may also be used in the treatment of gonorrhoea. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefmetazole is given intravenously as the sodium salt by infusion over 10 to 60 minutes or by slow injection over 3 to 5 minutes. Cefmetazole sodium is also used intramuscularly in some countries. Doses are expressed in terms of the equivalent amount of cefmetazole; 1.05 g of cefmetazole sodium is equivalent to about 1 g of cefmetazole.

The usual dose is 0.5 to 1 g intramuscularly or intravenously every 12 hours. For severe infections the dose may be increased to 3 to 4 g daily, given in divided doses every 6, 8, or 12 hours.

For details of reduced dosage of cefmetazole in patients with renal impairment, see p. 243.3.

References.

1. Finch R, *et al.* eds. Cefmetazole: a clinical appraisal. *J Antimicrob Chemother* 1989; **23** (suppl D): 1–142.

Administration in renal impairment. Parenteral doses of cefmetazole should be reduced in patients with renal impairment. It has been suggested that the interval between doses should be 12, 16, or 24 hours in patients with mild, moderate, or severe renal impairment, respectively; patients with virtually no renal function might be given cefmetazole every 48 hours, after haemodialysis.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefmetazole contains an *N*-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Effects on the blood. References.

1. Breen GA, St Peter WL. Hypoprothrombinemia associated with cefmetazole. *Ann Pharmacother* 1997; **31:** 180–4.

Sodium content. Each g of cefmetazole sodium contains about 2 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Antimicrobial Action

Cefmetazole is a cephamycin antibacterial with a similar spectrum of antibacterial activity to that of cefoxitin (p. 249.1), including the anaerobe *Bacteroides fragilis*.

References.

1. Cornick NA, *et al*. Activity of cefmetazole against anaerobic bacteria. *Antimicrob Agents Chemother* 1987; **31:** 2010–12.

Pharmacokinetics

After cefmetazole sodium 2 g intravenously every 6 hours, peak and trough plasma concentrations of 138 and 6 micrograms/mL have been achieved. Cefmetazole is 65 to 85% bound to plasma proteins, depending on the plasma concentration. A plasma half-life of about 1.1 to 1.5 hours has been reported; it is prolonged in patients with renal impairment. Small amounts have been detected in breast milk. Relatively high concentrations have been achieved in bile.

The majority of a dose is excreted unchanged in the urine resulting in high concentrations; up to 85% of a dose has been recovered within 12 hours. Cefmetazole is partly excreted by renal tubular secretion and probenecid prolongs elimination.

Cefmetazole is removed to some extent by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi Li Shu (毕立枢); Cefmetazon (先锋美他醇); Mei Zhi Quan (美之全); Xi Chang (悉畅); ***Indon.***: Qizol; ***Ital.***: Metafar; Metax; ***Jpn***: Cefmetazon.

Pharmacopoeial Preparations

USP 36: Cefmetazole for Injection; Cefmetazole Injection.

Cefminox Sodium *(pINNM)*

Cefminox sódico; Cefminox Sodique; MT-141; Natrii Cefminoxum; Натрий Цефминокс.

Sodium 7-[2-[(*S*)-2-amino-2-carboxyethyl]thioacetamido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

$C_{16}H_{20}N_7NaO_7S_3$=541.5

CAS — 75481-73-1 (cefminox).

UNII — YNM4DBJ3N8.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Profile

Cefminox sodium is a cephamycin antibacterial with properties similar to those of cefoxitin (p. 248.2) but with an *N*-methylthiotetrazole side-chain like cefamandole (p. 236.2). It is used in the treatment of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. It is given intravenously as the sodium salt but doses are expressed in terms of cefminox; 1.04 g of cefminox sodium is equivalent to about 1 g of cefminox. A usual dose is 2 to 4 g daily given in divided doses.

References.

1. Watanabe S, Omoto S. Pharmacology of cefminox, a new bactericidal cephamycin. *Drugs Exp Clin Res* 1990; **16:** 461–7.
2. Soriano F, *et al*. Comparative susceptibility of cefminox and cefoxitin to β-lactamases of Bacteroides spp. *J Antimicrob Chemother* 1991; **28:** 55–60.
3. Aguilar L, *et al*. Cefminox: correlation between in-vitro susceptibility and pharmacokinetics and serum bactericidal activity in healthy volunteers. *J Antimicrob Chemother* 1994; **33:** 91–101.
4. Mayama T, *et al*. Postmarketing surveillance on side-effects of cefminox sodium (Meicelin). *Int J Clin Pharmacol Ther* 1995; **33:** 149–55.
5. Hoellman DB, *et al*. In vitro activities of cefminox against anaerobic bacteria compared with those of nine other compounds. *Antimicrob Agents Chemother* 1998; **42:** 495–501.
6. Torres AJ, *et al*. Cefminox versus metronidazole plus gentamicin in intra-abdominal infections: a prospective randomized controlled clinical trial. *Infection* 2000; **28:** 318–22.

Sodium content. Each g of cefminox sodium contains about 1.84 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Dalibang (达力邦); Han Guang Nuo (汉光诺); Meicelin (美士灵); Melnox; Qipu (奇仆); Xian Feng Mei Nuo (先锋美诺); ***Jpn***: Meicelin; ***Port.***: Tencef; ***Spain***: Tencef; ***Thai.***: Meicelin.

Cefodizime Sodium *(BANM, rINNM)*

Cefodizima sódica; Céfodizime Sodique; HR-221; Natrii Cefodizimum; S-771221B; Sefodizim Disodyum; THR-221; TRH-221; Натрий Цефодизим.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-carboxymethyl-4-methylthiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid, disodium salt.

$C_{20}H_{18}N_6Na_2O_7S_4$=628.6

CAS — 69739-16-8 (cefodizime); 86329-79-5 (cefodizime sodium).

ATC — J01DD09.

ATC Vet — QJ01DD09.

UNII — HC1T51593A.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Cefodizime is a third-generation cephalosporin antibacterial with uses similar to those of cefotaxime (p. 246.1).

Cefodizime is given as the disodium salt by intramuscular injection or intravenously by injection or infusion in the treatment of susceptible infections. Doses are expressed in terms of the equivalent amount of cefodizime; 1.08 g of cefodizime sodium is equivalent to about 1 g of cefodizime. Adults are usually given 1 g every 12 or 24 hours for lower respiratory-tract infections and 1 or 2 g every 24 hours for upper and lower urinary-tract infections. Total daily doses of up to 6 g may be given for severe infection. In women with uncomplicated lower urinary-tract infections a single dose of 1 to 2 g may be sufficient. For gonorrhoea a single dose of 250 to 500 mg may be given. Doses may need to be reduced in patients with renal impairment (see p. 244.2).

References.

1. Finch RG, *et al*., eds. Cefodizime: a third generation cephalosporin with immunomodulating properties. *J Antimicrob Chemother* 1990; **26** (suppl C): 1–134.
2. Barradell LB, Brogden RN. Cefodizime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1992; **44:** 800–834.
3. Thalhammer F, *et al*. Single-dose cefodizime as infection prophylaxis in abdominal surgery: a prospective multicenter study. *Infection* 1998; **26:** 136–8.
4. Matsumoto T, *et al*. Single dose of cefodizime completely eradicated multidrug-resistant strain of Neisseria gonorrhoeae in urethritis and uterine cervicitis. *J Infect Chemother* 2006; **12:** 97–9.
5. Matsumoto T, *et al*. Multiple doses of cefodizime are necessary for the treatment of Neisseria gonorrhoeae pharyngeal infection. *J Infect Chemother* 2006; **12:** 145–7.

Administration in renal impairment. Although the first dose is the same as for those with normal renal function (see above), subsequent parenteral doses of cefodizime should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: 1 to 2 g daily
- CC less than 10 mL/minute: 0.5 to 1 g daily

In patients undergoing dialysis, 0.5 to 1 g daily is given after dialysis.

Adverse Effects and Precautions

As for Cefotaxime, p. 246.3.

Sodium content. Each g of cefodizime sodium contains about 3.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefodizime.

Antimicrobial Action

Cefodizime has similar antimicrobial activity to that of cefotaxime (p. 246.3) although cefodizime has no active metabolite. It has variable activity against *Citrobacter* spp., and *Pseudomonas aeruginosa* and *Bacteroides fragilis* are generally resistant.

Pharmacokinetics

Cefodizime is given by injection as the sodium salt. Intramuscular injection of 1 g cefodizime produces peak plasma concentrations of about 60 to 75 micrograms/mL at about 1 to 1.5 hours. Immediately after intravenous doses of 1 or 2 g cefodizime mean peak plasma concentrations of 215 and 394 micrograms/mL, respectively, have been achieved. Cefodizime is about 80% bound to plasma proteins and is widely distributed into body tissues and fluids. It crosses the placenta and small amounts have been detected in breast milk. Plasma elimination is reported to be triphasic with a terminal elimination half-life of about 4 hours. The half-life is prolonged by renal impairment.

The majority of a dose is excreted unchanged in the urine; up to 80% of a dose has been recovered within 24 hours. Cefodizime is mainly excreted by glomerular filtration with some tubular secretion. Probenecid delays excretion. Cefodizime is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Timecef†; ***China***: Gao De (高德); Jin Shan Qin (金汕秦); Kanglineng (康丽能); Li Mian (力勉); Modivid (莫敌); Newdizime; Zandixin (赞地新); ***Ital.***: Diezime; Modivid; Timecef; ***Jpn***: Kenicef; ***NZ***: Timecef†; ***Port.***: Modivid; ***Turk.***: Modivid.

Cefonicid Sodium *(BANM, USAN, rINNM)*

Cefonicid sódico; Cefonicide sodique; Céfonicide Sodique; Cefonicidum natricum; Natrii Cefonicidum; SKF-D-75073-Z (cefonicid monosodium); SKF-D-75073-Z_2; Натрий Цефоницид.

7-[(*R*)-Mandelamido]-3-(1-sulphomethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, disodium salt.

$C_{18}H_{16}N_6Na_2O_8S_3$=586.5

CAS — 61270-58-4 (cefonicid); 61270-78-8 (cefonicid disodium); 71420-79-6 (cefonicid monosodium).

ATC — J01DC06.

ATC Vet — QJ01DC06.

UNII — F74MFL78A1 (cefonicid sodium); QD9G66C5UF (cefonicid monosodium).

Pharmacopoeias. In *US*.

USP 36: (Cefonicid Sodium). A white to off-white solid. Freely soluble in water, in sodium chloride 0.9%, and in glucose 5%; very slightly soluble in dehydrated alcohol; soluble in methyl alcohol. pH of a 5% solution in water is between 3.5 and 6.5. Store in airtight containers.

Uses and Administration

Cefonicid is a second-generation cephalosporin antibacterial used similarly to cefamandole (p. 236.3) in the treatment of susceptible infections and for surgical infection prophylaxis.

It is given as the sodium salt by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion. Doses are expressed in terms of the equivalent amount of cefonicid; 1.08 g of cefonicid sodium is equivalent to about 1 g of cefonicid. The usual dose is cefonicid 1 g once daily. For uncomplicated urinary-tract infections, a dose of 500 mg once daily is recommended; up to 2 g once daily has been given in severe infections. More than 1 g should not be injected intramuscularly into a single site.

For surgical infection prophylaxis, a single dose of 1 g given 1 hour before surgical incision is usually sufficient, but may be given daily for a further 2 days in prosthetic arthroplasty or open-heart surgery.

References.

1. Saltiel E, Brogden RN. Cefonicid: a review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1986; **32:** 222–59.

Administration in renal impairment. For patients with renal impairment a loading dose equivalent to cefonicid 7.5 mg/kg is recommended, followed by reduced maintenance doses according to the creatinine clearance and the severity of the infection. A dose supplement is not required after dialysis.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefonicid contains a substituted *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia.

Effects on the blood. References.

1. Riancho JA, *et al*. Life-threatening bleeding in a patient treated with cefonicid. *Ann Intern Med* 1995; **123:** 472–3.

Effects on the liver. References.

1. Famularo G, *et al*. Eosinophilic hepatitis associated with cefonicid therapy. *Ann Pharmacother* 2001; **35:** 1669–71.

Sodium content. Each g of cefonicid sodium contains about 3.4 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Antimicrobial Action

Cefonicid sodium has an antimicrobial action and pattern of resistance similar to those of cefamandole (p. 237.1), although it is generally less active against Gram-positive cocci.

Pharmacokinetics

Cefonicid is given parenterally as the sodium salt. Peak plasma concentrations ranging from 67 to 126 micrograms/mL have been achieved 1 to 2 hours after a 1-g intramuscular dose. Cefonicid is more than 90% bound to plasma proteins. It has a plasma half-life of about 4.5 hours, which is prolonged in patients with renal impairment.

Therapeutic concentrations of cefonicid have been reported in many body tissues and fluids.

Up to 99% of a dose of cefonicid is excreted unchanged in the urine within 24 hours. Probenecid reduces excretion of cefonicid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xirui (西锐); ***Israel***: Monocef; ***Ital.***: Bioticic†; Cefodie; Cefoplus; Chefir; Daycef; Emidoxin; Fonicid; Krucef†; Lisa; Maxid†; Modiem; Monobiotic; Necid; Nokid; Praticef†; Raikocef; Sintocef; Sofarcid; Valecid†; ***Port.***: Monocid; ***Spain***: Monocid.

Pharmacopoeial Preparations
USP 36: Cefonicid for Injection.

Cefoperazone Sodium

(BANM, USAN, rINNM)

Cefoperazon-Natrium; Cefoperazon sodná sůl; Cefoperazon sodowy; Cefoperazona sódica; Céfopérazone Sodique; Cefoperazonnatrium; Cefoperazon-nátrium; Cefoperazono natrio druska; Cefoperazonum Natricum; CP-52640-2; CP-52640-3 (cefoperazone dihydrate); CP-52640 (anhydrous cefoperazone); Kefoperatsoninatrium; Natrii Cefoperazonum; Sefoperazon Sodyum; T-1551 (cefoperazone or cefoperazone sodium); Натрий Цефоперазон.

Sodium (7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-2-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate.

$C_{25}H_{26}N_9NaO_8S_2$=667.6

CAS — 62893-19-0 (cefoperazone); 62893-20-3 (cefoperazone sodium).

ATC — J01DD12.

ATC Vet — QJ01DD12.

UNII — 5FQG9774WD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefoperazone Sodium). A white or slightly yellow, hygroscopic, powder. If crystalline it exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 25% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Cefoperazone Sodium). A white to pale buff crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol; insoluble in acetone, in ether, and in ethyl acetate. pH of a 25% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. As with most beta lactams, admixture of cefoperazone sodium with aminoglycosides is not recommended because of the potential for inactivation of either drug.

There have been reports of incompatibility with other drugs including diltiazem,[1] doxorubicin,[2] pentamidine,[3] perphenazine,[4] pethidine,[5] promethazine,[6] and remifentanil.[7]

1. Gayed AA, *et al*. Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52:** 516–20.
2. Trissel LA, *et al*. Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
3. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.
4. Gasca M, *et al*. Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.
5. Nieves-Cordero AL, *et al*. Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
6. Scott SM. Incompatibility of cefoperazone and promethazine. *Am J Hosp Pharm* 1990; **47:** 519.
7. Trissel LA, *et al*. Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Uses and Administration

Cefoperazone is a third-generation cephalosporin antibacterial used similarly to ceftazidime (p. 253.1) in the treatment of susceptible infections, especially those due to *Pseudomonas* spp. It is not recommended for the treatment of meningitis because of poor penetration into the CSF.

Cefoperazone is given as the sodium salt by deep intramuscular injection or intravenously by intermittent or continuous infusion. Doses are expressed in terms of the equivalent amount of cefoperazone; 1.03 g of cefoperazone sodium is equivalent to about 1 g of cefoperazone. The usual dose is 2 to 4 g daily in 2 divided doses. In severe infections, up to 12 g daily in 2 to 4 divided doses may be given.

For details of dosage in patients with hepatic and renal impairment, see p. 245.2.

If cefoperazone is used with an aminoglycoside, the drugs should be given separately.

Cefoperazone has also been given with the beta-lactamase inhibitor sulbactam.

Administration in hepatic and renal impairment. In general, the parenteral dose of cefoperazone should not exceed 4 g daily in patients with liver disease or biliary obstruction or 1 to 2 g daily in those with both hepatic and renal impairment; if higher doses are used plasma concentrations of cefoperazone should be monitored.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Like cefotaxime (p. 246.3), cefoperazone has the potential for promoting colonisation and superinfection with resistant organisms. Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of cefoperazone; diarrhoea may occur more often.

Cefoperazone contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia. Hypoprothrombinaemia has been reported in patients treated with cefoperazone and has rarely been associated with bleeding episodes. Prothrombin time should be monitored in patients at risk of hypoprothrombinaemia and vitamin K used if necessary.

Sodium content. Each g of cefoperazone sodium contains about 1.5 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Unlike many other cephalosporins, the renal clearance of cefoperazone is not affected by probenecid.

Antimicrobial Action

Cefoperazone has antimicrobial activity similar to that of ceftazidime (p. 253.3), although it is slightly less active against some Enterobacteriaceae. It has good activity against *Pseudomonas aeruginosa*, but is less active than ceftazidime.

Cefoperazone is more susceptible than cefotaxime to hydrolysis by certain beta-lactamases.

Activity, particularly against Enterobacteriaceae and *Bacteroides* spp. has been enhanced in the presence of the beta-lactamase inhibitor sulbactam; resistant *Ps. aeruginosa* are not sensitive to the combination.

References.

1. Fass RJ, *et al*. In vitro activities of cefoperazone and sulbactam singly and in combination against cefoperazone-resistant members of the family Enterobacteriaceae and nonfermenters. *Antimicrob Agents Chemother* 1990; **34:** 2256–9.
2. Clark RB, *et al*. Multicentre study on antibiotic susceptibilities of anaerobic bacteria to cefoperazone-sulbactam and other antimicrobial agents. *J Antimicrob Chemother* 1992; **29:** 57–67.

Pharmacokinetics

Cefoperazone is given parenterally as the sodium salt. With intramuscular doses equivalent to cefoperazone 1 or 2 g, peak plasma concentrations of 65 and 97 micrograms/mL have been reported after 1 to 2 hours. The plasma half-life of cefoperazone is about 2 hours, but may be prolonged in neonates and in patients with hepatic or biliary-tract disease. Cefoperazone is 82 to 93% bound to plasma proteins, depending on the concentration.

Cefoperazone is widely distributed in body tissues and fluids, although penetration into the CSF is generally poor. It crosses the placenta, and low concentrations have been detected in breast milk.

Cefoperazone is excreted mainly in the bile where it rapidly achieves high concentrations. Urinary excretion is primarily by glomerular filtration. Up to 30% of a dose is excreted unchanged in the urine within 12 to 24 hours; this proportion may be increased in patients with hepatic or biliary disease. Cefoperazone A, a degradation product less active than cefoperazone, has been found only rarely *in vivo*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Cefobid; ***Braz.***: Neoperazona; ***Chile***: Cefobid†; ***China***: Cefobid (先锋必); Da Nuo Xin (达诺欣 ???); Lijunpaitong (利君派同); Medocef (麦道必); Saifubi (赛福必); Shilexin (施乐欣); Xianbi (仙毕); Xianbixian (先必先); Xiankang (先抗); Yi Mei Xin (依美欣); ***Cz.***: Cefobid; ***Hong Kong***: Cefobid; ***Hung.***: Cefobid; ***India***: Cefaking; Cefina; Cefomycin; Cefpar; Ceprazo; Cizon; CT Spar; Dalcefa; Frone; Kephazon; Luckcare; Magnamycin; Megacef; Myticef; Negaplus; NKZone; Novacip; Nuperazone; Over; ***Indon.***: Bifotik; Biorazon; Cefobid; Cefoject; Cefophar; Cepraz; Ceropid; Cerozon; Ferzobat; Logafox; Stabixin; Yazon; ***Ital.***: Bioperazone; Dardum; Farecef†; ***Jpn***: Cefobid; Cefoperazin; ***Malaysia***: Bicafar; Cefobid; Medocef; Shinfomycin†; ***Mex.***: Cefobid; ***Philipp.***: Bactizon; ***Pol.***: Biocefazon†; Cefobid; Dardum; ***Rus.***: Cefobid (Цефобид); Cefoperabol (Цефоперабол); Cefoperus (Цефоперус); Cefpar (Цефпар); Dardum (Дардум); Medocef (Медоцеф); Movoperiz (Мовопериз); Operaz (Операз); ***Singapore***: Cefobid; Cefozone; Dardum; ***Thai.***: Cefobid; Cefozone; Medocef†; ***Turk.***: Cefobid; ***Ukr.***: Cefobid (Цефобид); Cefobocid (Цефобоцид); Cerason (Церазон)†; Gepacef (Гепацеф).

Multi-ingredient Preparations. ***Chile***: Sulperazon; ***China***: Dalipaitan (达力哌坦); Dexiao (得消); Fanlin (凡林); Fengpaixin (锋派新); Kai Si (凯斯); Kaisheng (凯生); Kang Li Shu (康力舒); Lijunpaishu (利君派舒); Linglanxin (铃兰欣); Ruipuxin (瑞普欣); Sulperazon (舒普深); Xian Bi Ta (仙必他); Xian Qiang (先强); Xianjie (先捷); Xianpu (先普); Xianshu (先舒); Xinkuaixin (新快欣); Xinruipuxin (新瑞普欣); Zetong (泽同); ***Cz.***: Sulperazon; ***Hong Kong***: Sulperazon; ***India***: Apozone-S; Arifzon-SB; Atozon-S; Bacticid-CS; Bactonis; Bactorus; Bahutcef-SL; Burnex; C-Bact; C-Bactum; C-Lactum; Cadcef-S; Cafazone-S; Cebac; Cebanex; Cebect; Cefac; Cefactam; Cefasul; Cefbect; Cefdinex-SB; Cefglobe-S; Cefina-SB; Cefmate; Cefobac; Cefobel-S; Cefobeta; Cefoden-SB; Cefogard-S; Cefom-S; Cefonet-S; Cefonex; Ceforex; Cefosal; Cefosul; Cefosun S; Cefozed-S; Cefpar SB; Cefrobactum; Cefrosan; Ceftocin; Ceftop; Cefum; Cefurax-D; Cefzon SB; Ceprazo-S; Ceprozone-S; Cerazone-S; Cesal; Cezon-S; Cis-SL; Cizon-SB; CT Spar SM; Cucef-S; Curemax; Dalcefa-SB; Decef; Duozone; Fofone-S; Fro-Cef; Frone-SL; Fuzosul; Fytobact; Hosizone; Imex; Inbac Kit; Indobact; Iszu; Kaircef-S; Kefbactam; Kefchek; Kefsurge; Kephazon-S; Krasule; L-Cef; Lactagard; Magnazone; Magnex; Magtam; Mecef-S; Medinex; Monoact; Nebect; Nefsul; Neftum-SB; Nosobac; Novacip-S; Nubact; Nuperazone Plus; Ocefa-SB; Odospi-S; Ofirex; Oramax; Orozone-SB; Osul-S; Over-SB; Parabact; Sulbacef; Zosul; ***Indon.***: Bactazon; Ferotam; Fosular; Soperam; Stabactam; Sulbacef; Sulperazon; Zotam; ***Malaysia***: Sulperazon; ***Philipp.***: Sulperazone; ***Pol.***: Sulperazon; ***Rus.***: Bacperazone (Бакперазон); Cebanex (Цебанекс); Cephpar (Цефпар); Sulcef (Сульцеф); Sulcefazon (Сульцефазон); Sulmover (Сульмовер); Sulperacef (Сульперацеф); Sulperason (Сульперазон); Sulzoncef (Сульзонцеф); ***Thai.***: Bacticep; Cebactam; Cefpar; Cefper; Prazone-S; Sulcef; Sulperazon; Sulpermed; Zonbactam; ***Turk.***: Primasef†; Sefbaktam; Sulperazon; ***Ukr.***: Cebanex (Цебанекс); Cefoperazone Plus (Цефоперазон плюс); Cefosulbin (Цефосульбин); Cesulpin (Цесульпин); Gepacef Combi (Гепацеф Комби); Prazone-S (Празон-С); Sulperasone (Сульперазон); ***Venez.***: Sulperazon.

Pharmacopoeial Preparations
USP 36: Cefoperazone for Injection; Cefoperazone Injection.

Ceforanide *(BAN, USAN, rINN)*

BL-S786; Ceforanida; Céforanide; Ceforanidum; Цефоранид.

7-[2-(α-Amino-*o*-tolyl)acetamido]-3-(1-carboxymethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{20}H_{21}N_7O_6S_2$=519.6

CAS — 60925-61-3.

ATC — J01DC11.

ATC Vet — QJ01DC11.

UNII — 8M1YF8951V.

Pharmacopoeias. In *US*.

USP 36: (Ceforanide). A white to off-white powder. Practically insoluble in water, in chloroform, in ether, and in methyl alcohol; very soluble in 1N sodium hydroxide. pH of a 5% suspension in water is between 2.5 and 4.5. Store in airtight containers.

Profile

Ceforanide is a second-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p. 236.2), although it is reported to be less active *in vitro* against some bacteria, including staphylococci and *Haemophilus influenzae*. It is used in the treatment of susceptible infections and for surgical infection prophylaxis.

It is given as the lysine salt ($C_{26}H_{35}N_9O_8S_2$=665.7) but doses are expressed in terms of the equivalent amount of ceforanide; 1.28 g of ceforanide lysine is equivalent to about 1 g of ceforanide. It is given by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion, in a usual dose of 1 to 2 g every 12 hours. For surgical infection prophylaxis, a dose of 1 to 2 g

intravenously 1 hour before surgical incision is used. For doses in children, see p. 246.1.

Ceforanide contains a substituted *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia and alcohol intolerance. Probenecid does not affect the renal excretion of ceforanide.

References.

1. Campoli-Richards DM, *et al.* Ceforanide: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1987; **34:** 411–37.

Administration in children. Children have been given ceforanide lysine by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion in doses equivalent to ceforanide 20 mg/kg daily, in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Radacef.

Pharmacopoeial Preparations

USP 36: Ceforanide for Injection.

Cefoselis Sulfate *(rINNM)*

Céfosélis, Sulfate de; Cefoselís, sulfato de; Cefoselis Sulphate; Cefoselisi Sulfas; FK-037; Sulfato de cefoselís; Цефозелиса Сульфат.

(-)-5-Amino-2-{{(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl} methyl}-1-(2-hydroxyethyl)pyrazolium hydroxide, inner salt, 7^2-(*Z*)-(*O*-methyloxime) sulfate.

$C_{19}H_{22}N_8O_6S_2$, H_2SO_4=620.6

CAS — 122841-10-5 (cefoselis); 122841-12-7 (cefoselis sulfate).

Profile

Cefoselis sulfate is a cephalosporin antibacterial that has been used in the treatment of susceptible bacterial infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Feng Di (丰迪).

Cefotaxime Sodium *(BANM, USAN, rINNM)*

Cefotaksimo natrio druska; Cefotaksym sodowy; Cefotaxim-Natrium; Cefotaxim sodná sůl; Cefotaxima sódica; Céfotaxime sodique; Cefotaximnatrium; Cefotaxim-nátrium; Cefotaximum Natricum; CTX; HR-756; Kefotaksiiminatrium; Natrii Cefotaximum; RU-24756; Sefotaksim Sodyum; Натрий Цефотаксим.

Sodium (7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino) acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate.

$C_{16}H_{16}N_5NaO_7S_2$=477.4

CAS — 63527-52-6 (cefotaxime); 64485-93-4 (cefotaxime sodium).

ATC — J01DD01.

ATC Vet — QJ01DD01.

UNII — 258J72S7TZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefotaxime Sodium). A white or slightly yellow, hygroscopic, powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH of between 4.5 and 6.5. Store in airtight containers. Protect from light.

USP 36: (Cefotaxime Sodium). An off-white to pale yellow crystalline powder. Freely soluble in water; practically insoluble in organic solvents. pH of a 10% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. Cefotaxime sodium has been reported to be incompatible with alkaline solutions such as sodium bicarbonate. Licensed product information recommends that it should be given separately from aminoglycosides.

Uses and Administration

Cefotaxime is a third-generation parenteral cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structure, genito-urinary tract (including gonorrhoea) and respiratory tract, in gynaecological infections, and in early Lyme disease. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefotaxime is given as the sodium salt by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion over 20 to 60 minutes. Doses are expressed in terms of the equivalent amount of cefotaxime; 1.05 g of cefotaxime sodium is equivalent to about 1 g of cefotaxime. For mild to moderate infections cefotaxime is usually given in doses of 1 g 12-hourly and increased to 1 to 2 g every 8 hours for moderate to severe infections. For septicaemia up to 6 to 8 g daily may be given in 3 to 4 divided doses, while in the most severe infections up to 12 g may be given daily by the intravenous route in up to 6 divided doses. Pseudomonal infections usually require more than 6 g daily, but a cephalosporin with greater antipseudomonal activity, such as ceftazidime, is preferable.

In the treatment of gonorrhoea, a single dose of 0.5 or 1 g of cefotaxime is given.

For surgical infection prophylaxis, 1 g is given 30 to 90 minutes before surgery. At caesarean section, 1 g is given intravenously to the mother as soon as the umbilical cord is clamped and two further doses intramuscularly or intravenously 6 and 12 hours later.

The dose of cefotaxime may need to be reduced in patients with renal impairment, see p. 246.2.

For details of doses in children, see p. 246.2.

Cefotaxime may be used with an aminoglycoside as synergy may occur against some Gram-negative organisms, but the drugs should be given separately. It has sometimes been used with another beta lactam to broaden the spectrum of activity. Cefotaxime has also been used with metronidazole in the treatment of mixed aerobic-anaerobic infections.

General references to third-generation cephalosporins.

1. Neu HC, *et al.* , eds. Third-generation cephalosporins: a decade of progress in the treatment of severe infections. *Am J Med* 1990; **88** (suppl 4A): 1S–45S.

General references to cefotaxime.

1. Todd PA, Brogden RN. Cefotaxime: an update of its pharmacology and therapeutic use. *Drugs* 1990; **40:** 608–51.
2. Gentry LO. Cefotaxime and prophylaxis: new approaches with a proven agent. *Am J Med* 1990; **88** (suppl 4A): 32S–37S.
3. Davies A, Speller DCE, eds. Cefotaxime—recent clinical investigations. *J Antimicrob Chemother* 1990; **26** (suppl A): 1–83.
4. Brogden RN, Spencer CM. Cefotaxime: a reappraisal of its antibacterial activity and pharmacokinetic properties, and a review of its therapeutic efficacy when administered twice daily for the treatment of mild to moderate infections. *Drugs* 1997; **53:** 483–510.

Administration in children. Cefotaxime may be given to neonates and children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical prophylaxis. It is given by intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion over 20 to 60 minutes.

In the UK, the *BNFC* recommends the following doses for cefotaxime; the dose may be doubled for neonates with severe infection or meningitis:

- neonates under 7 days of age: 25 mg/kg every 12 hours
- neonates 7 to 21 days of age: 25 mg/kg every 8 hours
- neonates 21 to 28 days of age: 25 mg/kg every 6 to 8 hours
- children 1 month of age and older: 50 mg/kg every 8 to 12 hours; the frequency should be increased to every 6 hours in very severe infections and meningitis (to a maximum dose of 12 g daily)

In the USA, the American Academy of Pediatrics[1] suggests the following doses for cefotaxime:

- for neonates aged ⩽ 7 days (irrespective of body weight): 50 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ⩽ 2 kg: 50 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing > 2 kg: 50 mg/kg every 8 hours
- children 1 month and older: 50 to 180 mg/kg daily in 3 or 4 divided doses (to a maximum daily dose of 3 to 6 g) for mild to moderate infections, or 200 to 225 mg/kg daily in 4 or 6 divided doses (to a maximum daily dose of 8 to 12 g) in severe infections; up to 300 mg/kg daily in divided doses may be given for meningitis

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of cefotaxime should be reduced in severe renal impairment; after an initial loading dose of 1 g, halving the dose while maintaining the usual frequency of dosing has been suggested.

For critically ill patients undergoing renal replacement therapy, the following cefotaxime doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 8 to 12 hours
- continuous venovenous haemodialysis (CVVHD): 1 to 2 g every 8 hours
- continuous venovenous haemodiafiltration (CVVHDF): 1 to 2 g every 6 to 8 hours
- intermittent haemodialysis: 1 to 2 g every 24 hours (after the dialysis run)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2. Arrhythmias have been associated with rapid bolus dosage through a central venous catheter in a few cases.

The broad-spectrum third-generation cephalosporins have the potential for promoting colonisation and superinfection with resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter* spp., *Candida*, and enterococci, at various sites in the body, although the incidence has generally been low with cefotaxime. Changes in bowel flora are a predisposing factor and have been more marked with cefoperazone and ceftriaxone, possibly because of their greater biliary excretion. Pseudomembranous colitis, associated with *Clostridium difficile* infection, may occasionally be seen with any of the third-generation cephalosporins.

Reviews on adverse effects associated with third-generation cephalosporins.

1. Neu HC. Third generation cephalosporins: safety profiles after 10 years of clinical use. *J Clin Pharmacol* 1990; **30:** 396–403.
2. Fekety FR. Safety of parenteral third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 38S–44S.

Antibiotic-associated colitis. It has been suggested[1] that cefotaxime is associated with an increased risk of *Clostridium difficile* diarrhoea in elderly patients; however, the manufacturer[2] has disputed this, arguing that cefotaxime compares favourably with alternative third-generation cephalosporins.

1. Impallomeni M, *et al.* Increased risk of diarrhoea caused by Clostridium difficile in elderly patients receiving cefotaxime. *BMJ* 1995; **311:** 1345–6.
2. Rothschild E, *et al.* Risk of diarrhoea due to Clostridium difficile during cefotaxime treatment. *BMJ* 1996; **312:** 778.

Breast feeding. Although cefotaxime is excreted in breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants whose mothers were receiving cefotaxime, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefotaxime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of cefotaxime sodium contains about 2.09 mmol of sodium.

Interactions

As for many cephalosporins, probenecid reduces the renal clearance of cefotaxime, resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite.

Antibacterials. The total body clearance of cefotaxime has been reduced in patients with normal and reduced renal function by the ureidopenicillins *azlocillin*[1] or *mezlocillin*.[2] Doses of cefotaxime may need to be reduced if either of these penicillins is being given. Encephalopathy with focal motor status and generalised convulsions have been reported in a patient with renal failure given cefotaxime and high doses of azlocillin.[3]

1. Kampf D, *et al.* Kinetic interactions between azlocillin, cefotaxime, and cefotaxime metabolites in normal and impaired renal function. *Clin Pharmacol Ther* 1984; **35:** 214–20.
2. Rodondi LC, *et al.* Influence of coadministration on the pharmacokinetics of mezlocillin and cefotaxime in healthy volunteers and in patients with renal failure. *Clin Pharmacol Ther* 1989; **45:** 527–34.
3. Wroe SJ, *et al.* Focal motor status epilepticus following treatment with azlocillin and cefotaxime. *Med Toxicol* 1987; **2:** 233–4.

Antimicrobial Action

Cefotaxime is a third-generation cephalosporin. It has a bactericidal action similar to cefamandole, but a broader spectrum of activity. It is highly stable to hydrolysis by most beta-lactamases and has greater activity than first- or second-generation cephalosporins against Gram-negative bacteria. Although cefotaxime is generally considered to

have slightly less activity than first-generation cephalosporins against Gram-positive bacteria, many streptococci are very sensitive.

Desacetylcefotaxime is an active metabolite of cefotaxime and there may be additive or synergistic effects against some species.

Spectrum of activity.

- Among Gram-negative bacteria, cefotaxime is active *in vitro* against many Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., both indole-positive and indole-negative *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp.

  Other susceptible Gram-negative bacteria, including penicillin-resistant strains, are *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *N. meningitidis*. *Brucella melitensis* is also reported to be moderately sensitive. Some strains of *Pseudomonas* spp. are moderately susceptible to cefotaxime, but most are resistant.

  Desacetylcefotaxime is active against many of these Gram-negative bacteria, but not against *Pseudomonas* spp.
- Among Gram-positive bacteria, cefotaxime is active against staphylococci and streptococci. *Staphylococcus aureus*, including penicillinase-producing strains but not meticillin-resistant *Staph. aureus*, is sensitive. *Staph. epidermidis* is also sensitive but penicillinase-producing strains are resistant. *Streptococcus agalactiae* (group B streptococci), *Str. pneumoniae*, and *Str. pyogenes* (group A streptococci) are all very sensitive although truly penicillin-resistant pneumococci are apparently not sensitive.

  Enterococci and *Listeria monocytogenes* are resistant.
- Cefotaxime is active against some anaerobic bacteria. *Bacteroides fragilis* may be moderately sensitive, but many strains are resistant; synergy has been shown with desacetylcefotaxime *in vitro*. *Clostridium perfringens* is sensitive, but most *Cl. difficile* are resistant.
- Other organisms sensitive to cefotaxime include the spirochaete *Borrelia burgdorferi* and *Haemophilus ducreyi*.

Activity with other antimicrobials. In addition to possible synergy or additive effects with desacetylcefotaxime, the activity of cefotaxime may be enhanced by aminoglycosides such as gentamicin; synergy has been shown *in vitro* against Gram-negative bacteria including *Pseudomonas aeruginosa*. There have also been reports of enhanced activity *in vitro* with other antibacterials including fosfomycin and ciprofloxacin and variable results with penicillins.

Resistance may develop during treatment with cefotaxime due to derepression of chromosomally mediated beta-lactamases, and has been reported particularly in *Enterobacter* spp., with multiresistant strains emerging during treatment. This type of resistance has also developed in other bacteria including *Citrobacter*, *Serratia*, and *Pseudomonas* spp. Another mechanism of cefotaxime resistance is the development of plasma-mediated, extended-spectrum beta-lactamases, and this has occurred in *Klebsiella* spp. and also other Enterobacteriaceae. Resistance in *Str. pneumoniae* is due to the production of altered penicillin-binding proteins.

References to the antimicrobial activity of cefotaxime and other third-generation cephalosporins, including the problem of bacterial resistance.

1. Neu HC. Pathophysiologic basis for the use of third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 3S–11S.
2. Chow JW, *et al*. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; **115:** 585–90.
3. Sanders CC. New β-lactams: new problems for the internist. *Ann Intern Med* 1991; **115:** 650–1.
4. Thomson KS, *et al*. High-level resistance to cefotaxime and ceftazidime in Klebsiella pneumoniae isolates from Cleveland, Ohio. *Antimicrob Agents Chemother* 1991; **35:** 1001–3.
5. Piddock LJV, *et al*. Prevalence and mechanism of resistance to 'third-generation' cephalosporins in clinically relevant isolates of Enterobacteriaceae from 43 hospitals in the UK, 1990-1991. *J Antimicrob Chemother* 1997; **39:** 177–87.
6. Gums JG, *et al*. Differences between ceftriaxone and cefotaxime: microbiological inconsistencies. *Ann Pharmacother* 2008; **42:** 71–9.

Pharmacokinetics

Cefotaxime is given by injection as the sodium salt. It is rapidly absorbed after intramuscular injection and mean peak plasma concentrations of about 12 and 20 micrograms/mL have occurred 30 minutes after doses of 500 mg and 1 g of cefotaxime, respectively. Immediately after intravenous injection of 0.5, 1, or 2 g of cefotaxime, mean peak plasma concentrations of 38, 102, and 215 micrograms/mL, respectively, have occurred with concentrations ranging from about 1 to 3 micrograms/mL after 4 hours. The plasma half-life of cefotaxime is about 1 hour and that of the active metabolite desacetylcefotaxime about 1.5 hours; half-lives are increased in neonates and in patients with severe renal impairment, especially those of the metabolite, and a reduction in dosage may be necessary. The effects of liver disease on clearance of cefotaxime and its metabolite have been variable, but in general dosage adjustment has not been considered necessary. About 40% of cefotaxime is reported to be bound to plasma proteins.

Cefotaxime and desacetylcefotaxime are widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF particularly when the meninges are inflamed. Cefotaxime crosses the placenta and low concentrations have been detected in breast milk.

After partial metabolism in the liver to desacetylcefotaxime and inactive metabolites, elimination is mainly by the kidneys and about 40 to 60% of a dose has been recovered unchanged in the urine within 24 hours; a further 20% is excreted as the desacetyl metabolite. Relatively high concentrations of cefotaxime and desacetylcefotaxime occur in bile and about 20% of a dose has been recovered in the faeces.

Probenecid competes for renal tubular secretion with cefotaxime resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite. Cefotaxime and its metabolites are removed by haemodialysis.

When microbiological assays have been used, reported pharmacokinetic values may relate to cefotaxime plus its active metabolite, desacetylcefotaxime.

Hepatic impairment. References.

1. Höffken G, *et al*. Pharmacokinetics of cefotaxime and desacetylcefotaxime in cirrhosis of the liver. *Chemotherapy* 1984; **30:** 7–17.
2. Graninger W, *et al*. Cefotaxime and desacetyl-cefotaxime blood levels in hepatic dysfunction. *J Antimicrob Chemother* 1984; **14** (suppl B): 143–6.
3. Hary L, *et al*. The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; **36:** 613–16.
4. Ko RJ, *et al*. Pharmacokinetics of cefotaxime and desacetylcefotaxime in patients with liver disease. *Antimicrob Agents Chemother* 1991; **35:** 1376–80.

Renal impairment. References.

1. Matzke GR, *et al*. Cefotaxime and desacetyl cefotaxime kinetics in renal impairment. *Clin Pharmacol Ther* 1985; **38:** 31–6.
2. Paap CM, *et al*. Pharmacokinetics of cefotaxime and its active metabolite in children with renal dysfunction. *Antimicrob Agents Chemother* 1991; **35:** 1879–83.
3. Paap CM, *et al*. Cefotaxime and metabolite disposition in two pediatric continuous ambulatory peritoneal dialysis patients. *Ann Pharmacother* 1992; **26:** 341–3.
4. Paap CM, Nahata MC. The relation between type of renal disease and renal drug clearance in children. *Eur J Clin Pharmacol* 1993; **44:** 195–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefacolin; Terasep; ***Austria***: Claforan; ***Belg.***: Claforan; ***Braz.***: Ceforan; Claforan; Clafordil; Fotax; Kefaxim†; Kefozil; Taxima†; ***Canad.***: Claforan; ***Chile***: Grifotaxima; ***China***: Claforan (凯福隆); Dalilong (达力隆); Haifuxun (海复迅); Kaidilong (凯帝龙); Raxim (诺西福); Saifulong (赛福隆); Taxim (泰可欣); Xiankai (先凯); ***Cz.***: Ceftax; Sefotak; Taxcef†; ***Denm.***: Claforan†; ***Fin.***: Claforan†; ***Fr.***: Claforan; ***Ger.***: Claforan; ***Gr.***: Ceramil; Ciltiren; Claforan; Doctistatin; Flemycin; Gloryfen; Golafen; Letynol; Mastovet; Molelant; Naspor; Phacocef; Solubilax; Spirosine; Stoparen; ***Hong Kong***: Claforan; Valoran; ***Hung.***: Cefalekol; Claforan; Tirotax; ***India***: Amtaxime; Avicef; Axiom; Bestax; Biotax; C-Tax; Cefaden; Cefantral; Cefatox; Ceflin; Cefokil; Cefotim; Ceftex; Claforan; Desatax; Efotax; Evacef; Faxim; Flamotax; Haltax; Ivitax; Lyforan; Mutax; Nepotax; Nitaxim; Novatax; Nutaxin; Ominax; Omnatax; Omnicef; Oritaxime; Osotax; Zetaxim†; ***Indon.***: Baxima; Biocef; Cefarin; Cefor; Cefovell; Cefoxal†; Clacef; Clafexim; Claforan; Clatax; Combicef; Efotax; Ethiclaf; Fobet; Foxim; Glocef; Goforan; Kalfoxim; Lancef; Lapixime; Procefa; Rycef; Siclaxim; Soclaf; Starclaf; Taxecap; Taxef; Taxegram; Taximax; Tirdicef; ***Irl.***: Claforan; ***Israel***: Claforan; Kefotam; ***Ital.***: Aximad; Batixim; Cefomit; Delius; Lirgosin; Refotax; Salocef; Spectrocef; Taxime; Zariviz; Zimanel; ***Malaysia***: Claforan; Claraxim; Rekaxime; ***Mex.***: Baxytax†; Benaxima; Biosint; Cefotex; Cefradil; Ceftomax†; Claforan; Defradil†; Fot-Amsa; Fotexina; Sefoxiram; Sepsilem†; Taporin; Tebruxim; Tecnoxima; Tirotax; Viken†; Xendin; ***Neth.***: Claforan; Tirotax; ***NZ***: Claforan†; ***Philipp.***: Axitof; Cefotax; Cefox; Ceptax; Cetaxima; Cladex; Clafetam; Clafojen; Claforan; Clafoxim; Clavocef†; Clinbaxef; Fotexin; Foximet; Haxim; Lac-xim; Losforexan; Ofetaxim; Pantaxin; Sefotak; Tafoxam†; Taxim; Zalor; Zefocent; ***Pol.***: Biotaksym; Rantaksym; Tarcefoksym; Tirotax†; ***Port.***: Antadar; Ralopar; Resibelacta; Totam†; ***Rus.***: Cefabol (Цефабол); Cefantral (Цефантрал); Cefosin (Цефосин); Cefotex (Кефотекс); Cetax (Цетакс); Clafobrin (Клафобрин); Claforan (Клафоран); Intrataxime (Интратаксим); Lyforan (Лифоран); Oritax (Оритакс); Oritaxim (Оритаксим); Talcef (Талцеф); Tarcefoksym (Тарцефоксим); Tax-O-Bid (Такс-О-Бид); Tirotax (Тиротакс); ***S.Afr.***: Claforan†; Clatax; Kefotax; Klafotaxim; Oritaxim†; Reftax†; ***Singapore***: Clacef†; Claforan; ***Spain***: Claforan; ***Swed.***: Claforan; ***Switz.***: Claforan†; ***Thai.***: Cefomic; Ceforan; Cefotax†; Cefox; Ceftaxan†; Claforan; Claraxim; Fontax†; Fotax; Motaxim†; Necaxime; ***Turk.***: Betaksim; Claforan; Deforan†; Equitax; Sefagen; Sefoksim; Sefotak; Sefoxim; Taksidem; Taxocef; ***UAE***: Primocef; ***UK***: Claforan; ***Ukr.***: Sefotak (Сефотак)†; Tax-O-Bid (Такс-О-Бид); ***USA***: Claforan; ***Venez.***: Cefam; Cefatox; Claforan; Novatax; Tirotax.

Multi-ingredient Preparations. ***China***: Xinzhijun (新治君); ***India***: Augtax; Avicef-S; Cefalin-S; Cefantral-S; Cefup; Duotax; Effimax Plus; Evacef-S; Ivimax; Labicef-S; Magnatax; Maxitax; Montero; Mutax Plus; Nutaxin-S; Oritaximax; Osotax-S; Sultax; ***Ukr.***: Taxtam (Таксtам).

Pharmacopoeial Preparations

BP 2014: Cefotaxime Injection;

USP 36: Cefotaxime for Injection; Cefotaxime Injection.

Cefotetan *(BAN, USAN, rINN)*

Cefotetán; Céfotétan; Cefotetanum; ICI-156834 (cefotetan or cefotetan disodium); YM-09330 (cefotetan or cefotetan disodium); Цефотетан.

(7*S*)-7-[(4-Carbamoylcarboxymethylene-1,3-dithietan-2-yl) carboxamido]-7-methoxy-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid.

$C_{17}H_{17}N_7O_8S_4$=575.6

CAS — 69712-56-7.

ATC — J01DC05.

ATC Vet — QJ01DC05.

UNII — 48SPP0PA9Q.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cefotetan). Store in airtight containers.

Cefotetan Disodium *(BANM, USAN, rINNM)*

Cefotetán disódico; Céfotétan Disodique; Cefotetan Sodium; Cefotetanum Dinatricum; ICI-156834 (cefotetan or cefotetan disodium); YM-09330 (cefotetan or cefotetan disodium); Динатрий Цефотетан.

(7*S*)-7-[(4-Carbamoylcarboxymethylene-1,3-dithietan-2-yl) carboxamido]-7-methoxy-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid, disodium salt.

$C_{17}H_{15}N_7Na_2O_8S_4$=619.6

CAS — 74356-00-6.

ATC — J01DC05.

ATC Vet — QJ01DC05.

UNII — 0GXP746VXB.

Pharmacopoeias. In *US*.

USP 36: (Cefotetan Disodium). pH of a 10% solution in water is between 4.0 and 6.5. Store in airtight containers.

Incompatibility and stability. There may be incompatibility with aminoglycosides. Precipitation has been reported with promethazine hydrochloride.

References.

1. Das Gupta V, *et al*. Chemical stability of cefotetan disodium in 5% dextrose and 0.9% sodium chloride injections. *J Clin Pharm Ther* 1990; **15:** 109–14.
2. Erickson SH, Ulici D. Incompatibility of cefotetan disodium and promethazine hydrochloride. *Am J Health-Syst Pharm* 1995; **52:** 1347.

Uses and Administration

Cefotetan is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p. 248.2) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections.

It is given as the disodium salt by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion. Doses are expressed in terms of the equivalent amount of cefotetan; 1.08 g of cefotetan disodium is equivalent to about 1 g of cefotetan. The usual dose is 1 or 2 g every 12 hours. For the treatment of life-threatening infections, 3 g every 12 hours may be given intravenously. Doses of cefotetan should be reduced in patients with moderate to severe renal impairment (see p. 247.3).

For infection prophylaxis during surgical procedures, an intravenous dose of 1 or 2 g is given 30 to 60 minutes before surgery or, in caesarean section, as soon as the umbilical cord is clamped.

Administration in renal impairment. Parenteral doses of cefotetan should be reduced in patients with moderate to severe renal impairment. US licensed product information gives the following dosing guidelines based on creatinine clearance (CC):

- CC 10 to 30 mL/minute: the usual dose every 24 hours or one-half the usual dose every 12 hours
- CC less than 10 mL/minute: the usual dose every 48 hours or one-quarter the usual dose every 12 hours

In patients undergoing haemodialysis, one-quarter the usual dose may be given every 24 hours on days between dialysis and one-half the usual dose on the day of dialysis.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefotetan contains an *N*-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Cefotetan, especially at high doses, may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely elevated values; this should be borne in mind when measuring renal function.

Effects on the blood. Reviews[1,2] and a case report[3] of haemolytic anaemia associated with cefotetan.

1. Moes GS, MacPherson BR. Cefotetan-induced hemolytic anemia: a case report and review of the literature. *Arch Pathol Lab Med* 2000; **124:** 1344–6.
2. Viraraghavan R, *et al*. Cefotetan-induced haemolytic anaemia: a review of 85 cases. *Adverse Drug React Toxicol Rev* 2002; **21:** 101–7.
3. Robinson HE, *et al*. Cefotetan-induced life-threatening haemolysis. *Med J Aust* 2006; **184:** 251.

Sodium content. Each g of cefotetan disodium contains about 3.2 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Antimicrobial Action

Cefotetan is a cephamycin antibacterial with a mode of action and spectrum of activity similar to those of cefoxitin (p. 249.1). It is generally much more active *in vitro* than cefoxitin against the Gram-negative Enterobacteriaceae, but has similar activity against *Bacteroides fragilis* and may be less active against some other *Bacteroides* spp.

Pharmacokinetics

On intramuscular injection of cefotetan, peak plasma concentrations of about 70 micrograms/mL at 1 hour and 90 micrograms/mL at 3 hours have occurred after doses of 1 and 2 g, respectively. The plasma half-life of cefotetan is usually in the range of 3.0 to 4.6 hours and is prolonged in patients with renal impairment. About 88% of cefotetan may be bound to plasma proteins, depending on the plasma concentration.

Cefotetan is widely distributed in body tissues and fluids. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations occur in bile.

Cefotetan is excreted in the urine, primarily by glomerular filtration, as unchanged drug; 50 to 80% of a dose has been recovered in the urine in 24 hours and high concentrations are achieved. Small amounts of the tautomeric form of cefotetan have been detected in both plasma and urine.

Biliary excretion of cefotetan probably accounts for nonrenal clearance.

Some cefotetan is removed by dialysis.

References.

1. Martin C, *et al*. Clinical pharmacokinetics of cefotetan. *Clin Pharmacokinet* 1994; **26:** 248–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Cefotan†.

Pharmacopoeial Preparations
USP 36: Cefotetan for Injection; Cefotetan Injection.

Cefotiam Hydrochloride *(BANM, USAN, rINNM)*

Abbott-48999; Céfotiam, Chlorhydrate de; Cefotiam, hidrocloruro de; Cefotiami Hydrochloridum; CGP-14221E (cefotiam or cefotiam hydrochloride); Hidrocloruro de cefotiam; SCE-963; Цефотиама Гидрохлорид.

7-[2-(2-Amino-1,3-thiazol-4-yl)acetamido]-3-[1-(2-dimethylaminoethyl)-1*H*-tetrazol-5-ylthiomethyl]-3-cephem-4-carboxylic acid dihydrochloride.

$C_{18}H_{23}N_9O_4S_3,2HCl$=598.5

CAS — 61622-34-2 (cefotiam); 66309-69-1 (cefotiam hydrochloride).

ATC — J01DC07.

ATC Vet — QJ01DC07.

UNII — H7V12WDZ93.

Pharmacopoeias. In *Jpn* and *US*. *Jpn* also includes cefotiam hexetil hydrochloride.

USP 36: (Cefotiam Hydrochloride). Store in airtight containers.

Profile

Cefotiam is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p. 236.2). It is given intravenously or intramuscularly as the hydrochloride but doses are expressed in terms of the base; 1.14 g of cefotiam hydrochloride is equivalent to about 1 g of cefotiam. The usual dose is the equivalent of up to 6 g of cefotiam daily in divided doses, according to the severity of the infection.

Cefotiam hexetil hydrochloride, a prodrug of cefotiam, is given orally in doses equivalent to 200 to 400 mg of cefotiam twice daily.

References.

1. Brogard JM, *et al*. Clinical pharmacokinetics of cefotiam. *Clin Pharmacokinet* 1989; **17:** 163–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Spizef†; ***China***: Fengtixin (锋替新); Fontien (复仙安); Haitishu (海替舒); Sa Lan Xin (萨兰欣); ***Fr.***: Taketiam; Texodil; ***Ger.***: Spizef†; ***Gr.***: Takedrol; ***Indon.***: Aspil; Cefradol; Ceradolan; Ethidol; Fodiclo; Fotaram; ***Jpn***: Pansporin; ***Philipp.***: Ceradolan; Ceratim; Fotaram; Harolan; ***Singapore***: Ceradolan†; ***Thai.***: Ceradolan†.

Pharmacopoeial Preparations
USP 36: Cefotiam for Injection.

Cefovecin Sodium *(USAN, rINNM)*

Cefovecina sódica; Céfovécine Sodique; Natrii Cefovecinum; UK-287074-02; Натрий Цефовецин.

Sodium (6*R*,7*R*)-7-{[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino}-8-oxo-3-{(2*S*)-tetrahydrofuran-2-yl}-5-thia-1-azabicyclo[4.4.0]oct-2-ene-2-carboxylate.

$C_{17}H_{18}N_5NaO_6S_2$=475.5

CAS — 234096-34-5 (cefovecin); 141195-77-9 (cefovecin sodium).

UNII — DL8Q24959P.

Profile

Cefovecin sodium is a third-generation cephalosporin antibacterial used in veterinary medicine.

Cefoxitin Sodium *(BANM, USAN, rINNM)*

Cefoksitino natrio druska; Cefoksytyna sodowa; Cefoxitin-Natrium; Cefoxitin sodná sůl; Cefoxitina sódica; Céfoxitine sodique; Cefoxitinnatrium; Cefoxitin-nátrium; Cefoxitinum natricum; Kefoksitiininatrium; L-620388; MK-306; Natrii Cefoxitinum; Натрий Цефокситин.

Sodium 3-carbamoyloxymethyl-7-methoxy-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.

$C_{16}H_{16}N_3NaO_7S_2$=449.4

CAS — 35607-66-0 (cefoxitin); 33564-30-6 (cefoxitin sodium).

ATC — J01DC01.

ATC Vet — QJ01DC01.

UNII — Q68050H03T.

Pharmacopoeias. In *Eur*. (see p. vii) and *US*.

Ph. Eur. 8: (Cefoxitin Sodium). A white or almost white, very hygroscopic, powder. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH between 4.2 and 7.0. Store in airtight containers.

USP 36: (Cefoxitin Sodium). White to off-white, somewhat hygroscopic, granules or powder, having a slight characteristic odour. Very soluble in water; slightly soluble in acetone; insoluble in chloroform and in ether; sparingly soluble in dimethylformamide; soluble in methyl alcohol. pH of a 10% solution in water is between 4.2 and 7.0. Store in airtight containers at a temperature not exceeding 8 degrees.

Uses and Administration

Cefoxitin is a parenteral cephamycin antibacterial that differs structurally from the cephalosporins by the addition of a 7-α-methoxy group to the 7-β-aminocephalosporanic acid nucleus.

It is generally classified with the second-generation cephalosporins and can be used similarly to cefamandole (p. 236.3) for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, skin and skin structure, genito-urinary and respiratory tracts, and gynaecological infections including pelvic inflammatory disease. However, because of its activity against *Bacteroides fragilis* and other anaerobic bacteria, it is used principally in the treatment and prophylaxis of anaerobic and mixed bacterial infections. For details of infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Administration and dosage. Cefoxitin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion.

Doses are expressed in terms of the equivalent amount of cefoxitin; 1.05 g of cefoxitin sodium is equivalent to about 1 g of cefoxitin. For mild, uncomplicated infections cefoxitin is usually given in doses of 1 g every 6 to 8 hours and increased to 2 g every 6 to 8 hours for moderate to severe infections. For more severe infections up to 12 g may be given daily in 4 to 6 divided doses.

For the treatment of uncomplicated urinary-tract infections, cefoxitin 1 g twice daily has been given intramuscularly. For the treatment of uncomplicated gonorrhoea, a single dose of 2 g intramuscularly has been given with probenecid 1 g orally.

For surgical infection prophylaxis, the usual dose is cefoxitin 2 g intramuscularly or intravenously 30 to 60 minutes before the procedure and then every 6 hours, not usually for more than 24 hours.

At caesarean section a single 2-g dose may be given intravenously to the mother as soon as the umbilical cord is clamped. If necessary, a 3-dose regimen, with further 2-g doses 4 and 8 hours after the initial dose, may be used.

The dose of cefoxitin may need to be reduced in patients with renal impairment, see p. 248.3.

For details of doses in children, including those with renal impairment, see p. 248.3.

Reviews.

1. DiPiro JT, May JR. Use of cephalosporins with enhanced antianaerobic activity for treatment and prevention of anaerobic and mixed infections. *Clin Pharm* 1988; **7:** 285–302.
2. Goodwin CS. Cefoxitin 20 years on: is it still useful? *Rev Med Microbiol* 1995; **6:** 146–53.

Administration in children. Cefoxitin may be given to neonates and children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical infection prophylaxis. It is given intravenously by slow injection over 3 to 5 minutes or by intermittent or continuous infusion; it may also be given by intramuscular injection in children 3 months of age and older.

For treatment, neonates may be given 20 to 40 mg/kg, every 12 hours for premature infants (weighing more than 1.5 kg) and neonates up to 1 week old and every 8 hours for those aged 1 to 4 weeks. Infants and children may be given 20 to 40 mg/kg every 6 to 8 hours; in severe infections, up to 200 mg/kg daily may be given, to a maximum of 12 g daily.

Infants and children undergoing surgical procedures can be given doses of 30 to 40 mg/kg, at the same time intervals as adults (see Uses and Administration, above.); neonates may be given 30 to 40 mg/kg, but at intervals of 8 to 12 hours.

In children with renal impairment the dose of cefoxitin should be proportionally reduced, and the frequency of dosage modified, in accordance with the recommendation for adults, see p. 248.3.

Administration in renal impairment. In renal impairment, parenteral doses of cefoxitin should be reduced according to creatinine clearance (CC). After an initial loading dose of 1 to 2 g, maintenance doses are:

- CC 30 to 50 mL/minute: 1 to 2 g every 8 to 12 hours
- CC 10 to 29 mL/minute: 1 to 2 g every 12 to 24 hours
- CC 5 to 9 mL/minute: 0.5 to 1 g every 12 to 24 hours
- CC below 5 mL/minute: 0.5 to 1 g every 24 to 48 hours

In patients undergoing haemodialysis, the loading dose should be repeated after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefoxitin may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely high values; this should be borne in mind when measuring renal function.

Breast feeding. Cefoxitin is distributed into breast milk but is detectable only in low concentrations. In a study[1] in which cefoxitin was given prophylactically in doses of 2 to 4 g to 18 women undergoing caesarean section, only one sample of breast milk contained measurable concentrations of cefoxitin, 19 hours after the last dose. No adverse effects have been seen in breast-fed infants whose mothers were receiving cefoxitin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Roex AJM, *et al*. Secretion of cefoxitin in breast milk following short-term prophylactic administration in caesarean section. *Eur J Obstet Gynecol Reprod Biol* 1987; **25:** 299–302.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the gastrointestinal tract. Marked changes in anaerobic, facultative, and aerobic faecal flora have been noted with cefoxitin.[1]

1. Mulligan ME, *et al*. Alterations in human fecal flora, including ingrowth of Clostridium difficile, related to cefoxitin therapy. *Antimicrob Agents Chemother* 1984; **26:** 343–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefoxitin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/10/11)

Sodium content. Each g of cefoxitin sodium contains about 2.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefoxitin.

Antimicrobial Action

Cefoxitin is a cephamycin antibacterial which, like the other beta lactams, is bactericidal and is considered to act through the inhibition of bacterial cell wall synthesis.

It has a similar spectrum of activity to cefamandole (p. 237.1) but is more active against anaerobic bacteria, especially *Bacteroides fragilis*.

Cefoxitin can induce the production of beta-lactamases by some bacteria, and use of cefoxitin with other beta lactams have been shown to be antagonistic *in vitro*.

Cefoxitin itself is considered to be resistant to many beta-lactamases, including those produced by *Bacteroides* spp. However, acquired resistance to cefoxitin has been reported in *B. fragilis* (see Anaerobic Bacterial Infections, p. 173.1) and has been attributed to beta-lactamase as well as to alterations in penicillin-binding proteins or to outer membrane proteins; there may be cross-resistance to other antibacterials.

References.

1. Cuchural GJ, *et al.* Transfer of β-lactamase-associated cefoxitin resistance in Bacteroides fragilis. *Antimicrob Agents Chemother* 1986; **29:** 918–20.
2. Piddock LJV, Wise R. Cefoxitin resistance in Bacteroides species: evidence indicating two mechanisms causing decreased susceptibility. *J Antimicrob Chemother* 1987; **19:** 161–70.
3. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; **23:** 660–2.
4. Wexler HM, Halebian S. Alterations to the penicillin-binding proteins in the Bacteroides fragilis group: a mechanism for non-β-lactamase mediated cefoxitin resistance. *J Antimicrob Chemother* 1990; **26:** 7–20.
5. Cherubin CE, Appleman MD. Susceptibility of cefoxitin-resistant isolates of bacteroides to other agents including β-lactamase inhibitor/β-lactam combinations. *J Antimicrob Chemother* 1993; **32:** 168–70.

Pharmacokinetics

Cefoxitin is not absorbed from the gastrointestinal tract; it is given parenterally as the sodium salt. After 1 g by intramuscular injection a peak plasma concentration of up to 30 micrograms/mL at 20 to 30 minutes has been reported whereas concentrations of 125, 72, and 25 micrograms/mL have been achieved after intravenous doses of 1 g over 3, 30, and 120 minutes respectively. Cefoxitin is about 70% bound to plasma proteins. It has a plasma half-life of 45 to 60 minutes which is prolonged in renal impairment. Cefoxitin is widely distributed in the body but there is normally little penetration into the CSF, even when the meninges are inflamed. It crosses the placenta and has been detected in breast milk. Relatively high concentrations occur in bile.

The majority of a dose is excreted unchanged by the kidneys, up to about 2% being metabolised to descarbamylcefoxitin which is virtually inactive. Cefoxitin is excreted in the urine by glomerular filtration and tubular secretion and about 85% of a dose is recovered within 6 hours; probenecid slows this excretion. After an intramuscular dose of 1 g, peak concentrations in the urine are usually greater than 3 mg/mL.

Cefoxitin is removed to some extent by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mefoxin†; ***Austria***: Mefoxitin†; ***Braz.***: Cefoxan†; Cefoxin†; Cefton; Gamacef; Kefox; Mefoxin; ***China***: Daliding (达力叮); ***Fr.***: Mefoxin; ***Gr.***: Destrepen; Mefoxil; Metaptyl; ***Hong Kong***: Mefoxin†; ***Ital.***: Cefociclin; Mefoxin; ***NZ***: Mefoxin; ***Philipp.***: Cefoxivit; Dintaxin; Foxitin; Haxotin; Monowel; Pacetin; Panafox; Zepax; Zepotin; ***Port.***: Atralxitina; ***Rus.***: Anaerocef (Анаэроцеф); ***S.Afr.***: Mefoxin; ***Thai.***: Cefoxin; Cefxitin; Maxotin†; Zefin†; ***Turk.***: Mefoxim; ***USA***: Mefoxin.

Pharmacopoeial Preparations
BP 2014: Cefoxitin Injection;
USP 36: Cefoxitin for Injection; Cefoxitin Injection.

Cefozopran Hydrochloride *(rINNM)*

Céfozopran, Chlorhydrate de; Cefozoprán, hidrocloruro de; Cefozoprani Hydrochloridum; Hidrocloruro de cefozoprán; SCE-2787; Цефозопрана Гидрохлорид.

(-)-1-{[(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl}-1*H*-imidazo[1,2-*b*]pyridazin-4-ium hydroxide inner salt, 7²-(*Z*)-(*O*-methyloxime), hydrochloride.

$C_{19}H_{17}N_9O_5S_2$,HCl=552.0

CAS — 113359-04-9 (cefozopran); 113981-44-5 (cefozopran hydrochloride).
ATC — J01DE03.
ATC Vet — QJ01DE03.
UNII — 060I5C0GRC.

Pharmacopoeias. In *Jpn*.

Profile

Cefozopran is a cephalosporin antibacterial used parenterally as the hydrochloride.

References.

1. Iwahi T, *et al.* In vitro and in vivo activities of SCE-2787, a new parenteral cephalosporin with a broad antibacterial spectrum. *Antimicrob Agents Chemother* 1992; **36:** 1358–66.
2. Paulfeuerborn W, *et al.* Comparative pharmacokinetics and serum bactericidal activities of SCE-2787 and ceftazidime. *Antimicrob Agents Chemother* 1993; **37:** 1835–41.
3. Fujii R, *et al.* Pharmacokinetics and clinical effects of cefozopran in pediatric patients. *Jpn J Antibiot* 1996; **49:** 17–33.
4. Toyokawa M, *et al.* In vitro combined effects of cefozopran/teicoplanin and cefozopran/vancomycin on methicillin-resistant Staphylococcus aureus. *J Chemother* 2003; **15:** 31–6.
5. Nomura K, *et al.* Optimized dosage and frequency of cefozopran for patients with febrile neutropenia based on population pharmacokinetic and pharmacodynamic analysis. *J Antimicrob Chemother* 2008; **61:** 892–900.
6. Sato T, *et al.* A prospective, randomized study comparing cefozopran with piperacillin-tazobactam plus ceftazidime as empirical therapy for febrile neutropenia in children with hematological disorders. *Pediatr Blood Cancer* 2008; **51:** 774–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Firstcin.

Cefpiramide *(USAN, rINN)*

Cefpiramida; Cefpiramidum; SM-1652; Wy-44635; Цефпирамид.

(7*R*)-7-[(*R*)-2-(4-Hydroxy-6-methylnicotinamido)-2-(4-hydroxyphenyl)acetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{25}H_{24}N_8O_7S_2$=612.6

CAS — 70797-11-4.
ATC — J01DD11.
ATC Vet — QJ01DD11.
UNII — P936YA152N.

Pharmacopoeias. In *US*.

USP 36: (Cefpiramide). Store in airtight containers. pH of a 0.5% suspension in water is between 3.0 and 5.0.

Cefpiramide Sodium *(USAN, rINNM)*

Cefpiramida sódica; Cefpiramide Sodique; Natrii Cefpiramidum; Натрий Цефпирамид.

$C_{25}H_{23}N_8NaO_7S_2$=634.6

CAS — 74849-93-7.
ATC — J01DD11.
ATC Vet — QJ01DD11.
UNII — 137KB7GYKB.

Pharmacopoeias. In *Jpn*.

Profile

Cefpiramide is a third-generation cephalosporin antibacterial related to cefoperazone (p. 243.1) and with similar activity against *Pseudomonas aeruginosa*, but possibly less active against Enterobacteriaceae. Cefpiramide is also active against staphylococci and streptococci and marginal activity against enterococci *in vitro* has been reported. Like cefamandole (p. 236.2), cefpiramide contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia, alcohol intolerance, and potentiation of anticoagulants.

Cefpiramide is given by intravenous injection or infusion as the sodium salt in the treatment of susceptible infections but doses are expressed in terms of cefpiramide; 1.04 g of cefpiramide sodium is equivalent to about 1 g of cefpiramide. The usual dose is 1 to 2 g daily in 2 divided doses.

References.

1. Wang H, *et al.* In-vitro antibacterial activities of cefpiramide and other broad-spectrum antibiotics against 440 clinical isolates in China. *J Infect Chemother* 2000; **6:** 81–5.

Sodium content. Each g of cefpiramide sodium contains about 1.6 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tailixin (泰力信); Tamicin (泰吡信); ***Jpn***: Sepatren†.

Pharmacopoeial Preparations
USP 36: Cefpiramide for Injection.

Cefpirome Sulfate *(BANM, USAN, rINNM)*

Cefpiroma, sulfato de; Cefpirome, Sulfate de; Cefpirome Sulphate; Cefpiromi Sulfas; Cefpiromsulfat; HR-810 (cefpirome or cefpirome sulfate); Kefpiromisulfaatti; Sulfato de cefpiroma; Цефпирома Сульфат.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-pyrindiniomethyl)-3-cephem-4-carboxylate sulphate.

$C_{22}H_{22}N_6O_5S_2$,H_2SO_4=612.6

CAS — 84957-29-9 (cefpirome); 98753-19-6 (cefpirome sulfate).
ATC — J01DE02.
ATC Vet — QJ01DE02.
UNII — BA5ALU2ZT9.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Cefpirome is a fourth-generation cephalosporin antibacterial used in the treatment of infections due to susceptible organisms. They include infections of the urinary tract, respiratory tract, and skin, and also septicaemia. It is effective against *Pseudomonas aeruginosa* and may be given to treat infections in neutropenic patients. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefpirome is given by intravenous injection over 3 to 5 minutes or infusion over 20 to 30 minutes as the sulfate, but doses are expressed in terms of the base; 1.19 g of cefpirome sulfate is equivalent to about 1 g of cefpirome. The usual dose is the equivalent of 1 or 2 g of cefpirome every 12 hours. For details of reduced doses to be used in renal impairment, see p. 249.3.

References.

1. Brown EM, *et al.* eds. Cefpirome: a novel extended spectrum cephalosporin. *J Antimicrob Chemother* 1992; **29** (suppl A): 1–104.
2. Wiseman LR, Lamb HM. Cefpirome: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy in the treatment of severe nosocomial infections and febrile neutropenia. *Drugs* 1997; **54:** 117–40.

Administration in renal impairment. Intravenous doses of cefpirome should be modified in renal impairment; after a loading dose of 1 or 2 g depending on the severity of infection, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of infection:

- CC 20 to 50 mL/minute: 0.5 or 1 g twice daily
- CC 5 to 20 mL/minute: 0.5 or 1 g once daily
- CC 5 mL/minute or less (in haemodialysis patients): 0.5 or 1 g once daily plus a half-dose after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin, p. 235.2.

Cefpirome is reported to interfere with the Jaffé method of measuring creatinine concentrations to determine renal function.

References.

1. Rubinstein E, *et al.* A review of the adverse events profile of cefpirome. *Drug Safety* 1993; **9:** 340–5.

Interactions

Probenecid reduces the renal clearance of cefpirome.

Antimicrobial Action

Cefpirome is a fourth-generation cephalosporin that is stable to many beta-lactamases. It has a spectrum of activity similar to that of the third-generation cephalosporin cefotaxime (p. 244.3), but it appears to be more active *in vitro* against staphylococci, some enterococci, some Enterobacteriaceae, and *Pseudomonas aeruginosa*. Cefpirome may be less active than ceftazidime (p. 253.3) against *Ps. aeruginosa*.

Pharmacokinetics

Cefpirome is given by injection as the sulfate. Mean peak serum concentrations of 80 to 90 micrograms/mL are attained after a single intravenous 1-g dose. The elimination half-life is about 2 hours and is prolonged in patients with renal impairment. Cefpirome is less than 10% bound to plasma proteins.

Cefpirome is widely distributed into body tissues and fluids and appears in breast milk. It is mainly excreted by the kidneys and 80 to 90% of a dose is recovered unchanged in the urine. Significant amounts are removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cefrom†; ***Austria***: Cefrom; ***China***: Cefrom (派新); Luobang (罗邦); ***Fr.***: Cefrom; ***Gr.***: Cefrom; ***India***: Allard; Bacirom; C-Rome; Cef-4; Ceforth; Cefph; Cefrom; Cepirom; Forgen; Forom; Ivcef; Ivirome; Neopirome; Nispirome; Nitpirome; Omnirom; Opirom; Tafrom; ***Indon.***: Bactirom; Bioprom; Caprocef; Cefir; Cefmer 1; Cefnos; Cefrin; Cefrom; Ethirom; Interome; Lanpirome; Lapirom; Mor-

cef; Nufirom; Rime; Romicef; Sopirom; Xenoprom; Yarox; ***Mex.***: Cefrom; ***Neth.***: Cefrom†; ***Philipp.***: Cefrin; Sanprome†; Zeferom; ***Port.***: Cipiram; Farmocefe; ***Rus.***: Cefanorm (Цефанорм); ***S.Afr.***: Cefrom; ***Thai.***: Cefrom†; Ferome.

Cefpodoxime Proxetil

(BANM, USAN, rINNM)

Cefpodoxima proxetilo; Cefpodoxime proxétil; Cefpodoxime, Proxétil de; Cefpodoximi Proxetilum; Cefpodoximum proxetili; CS-807; R-3763 (cefpodoxime); U-76252; U-76253 (cefpodoxime); Цефподоксима Проксетил.

The 1-[(isopropoxycarbonyl)oxy]ethyl ester of (*Z*)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid.

$C_{21}H_{27}N_5O_9S_2$=557.6

CAS — 80210-62-4 (cefpodoxime); 87239-81-4 (cefpodoxime proxetil).

ATC — J01DD13.

ATC Vet — QJ01DD13.

UNII — 2TB00A1Z7N.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefpodoxime Proxetil). A white or pale yellow or light brown, amorphous powder. Very slightly soluble or practically insoluble in water; freely soluble in anhydrous ethanol; very soluble in acetonitrile and in methyl alcohol. Protect from light.

USP 36: (Cefpodoxime Proxetil). A white to light brownish-white powder, odourless or having a faint odour. Very slightly soluble in water; freely soluble in dehydrated alcohol; soluble in acetonitrile and in methyl alcohol; slightly soluble in ether. Store in airtight containers at a temperature not exceeding 25 degrees.

Uses and Administration

Cefpodoxime is a third-generation cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the respiratory and urinary tracts, skin and skin structure, and gonorrhoea. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefpodoxime is given orally as the proxetil ester, which is hydrolysed on absorption to cefpodoxime. Doses are expressed in terms of the equivalent amount of cefpodoxime; 130 mg of cefpodoxime proxetil is equivalent to about 100 mg of cefpodoxime. Absorption may be enhanced if cefpodoxime proxetil is given with food. The usual dose for adults is 100 to 200 mg every 12 hours for respiratory-tract and urinary-tract infections. A dose of 200 or 400 mg every 12 hours may be used for skin and soft-tissue infections.

For uncomplicated gonorrhoea, a single dose of 200 mg may be given.

The interval between doses of cefpodoxime may need to be extended in patients with renal impairment (see p. 250.1).

For details of doses in children, see p. 250.1.

References.

1. Moore EP, *et al.*, eds. Cefpodoxime proxetil: a third-generation oral cephalosporin. *J Antimicrob Chemother* 1990; **26** (suppl E): 1–101.
2. Adam D, *et al.*, eds. Cefpodoxime proxetil: a new third generation oral cephalosporin. *Drugs* 1991; **42** (suppl 3): 1–66.
3. Frampton JE, *et al.* Cefpodoxime proxetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; **44:** 889–917.
4. Chocas EC, *et al.* Cefpodoxime proxetil: a new, broad-spectrum, oral cephalosporin. *Ann Pharmacother* 1993; **27:** 1369–77.
5. Fulton B, Perry CM. Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. *Paediatr Drugs* 2001; **3:** 137–58.

Administration in children. Cefpodoxime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. In the UK, licensed product information recommends that children and infants aged 15 days and older may be given 4 mg/kg orally every 12 hours, up to a maximum of 200 mg daily. In the USA, children aged 2 months and older may be given oral doses of 5 mg/kg every 12 hours, up to a maximum of 200 mg daily for pharyngitis or tonsillitis or 400 mg daily for acute otitis media or maxillary sinusitis.

Administration in renal impairment. The interval between oral doses of cefpodoxime should be extended in patients with renal impairment to every 24 hours in those with creatinine clearance of 10 to 39 mL/minute, and to every 48 hours when the creatinine clearance is less than 10 mL/minute. In patients on haemodialysis the dose should be given after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The most frequently reported adverse effects of cefpodoxime are gastrointestinal disturbances, especially diarrhoea.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefpodoxime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Absorption of cefpodoxime is decreased by antacids or histamine H_2-receptor antagonists. Probenecid reduces the renal excretion of cefpodoxime.

Antimicrobial Action

As for Cefixime, p. 241.1, but cefpodoxime has greater activity against *Staphylococcus aureus*.

References.

1. Valentini S, *et al.* In-vitro evaluation of cefpodoxime. *J Antimicrob Chemother* 1994; **33:** 495–508.

Pharmacokinetics

Cefpodoxime proxetil is de-esterified in the intestinal epithelium after oral doses, to release active cefpodoxime in the bloodstream. Bioavailability is about 50% in fasting subjects and may be increased in the presence of food. Absorption is decreased in conditions of low gastric acidity. Peak plasma concentrations of about 1.5, 2.5, and 4.0 micrograms/mL have been achieved 2 to 3 hours after oral doses of 100, 200, and 400 mg cefpodoxime respectively. About 20 to 30% of cefpodoxime is bound to plasma proteins. The plasma half-life is about 2 to 3 hours and is prolonged in patients with renal impairment.

Cefpodoxime reaches therapeutic concentrations in the respiratory and genito-urinary tracts and bile. It has been detected in low concentrations in breast milk.

Cefpodoxime is excreted unchanged in the urine. Some is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Biocef; Otreon; ***Braz.***: Orelox; ***Chile***: Baxemin; Cefirax; ***China***: Banan (搏拿); Bo Man Xin (博曼欣); Bo Wo Xin (搏沃欣); Cepodem (施博); Chun Di (纯迪); Chun Xin (纯欣); Hai Ling Yi (海凌依); Heng Ze (恒泽); Jia Bo (加博); Kang Fei (抗菲); Liang Bo (亮博); Min Xin (敏新); Ou Shuang (欧爽); Shan Pu Lan (善普兰); Shi Rui Bo (士瑞泊); Shuai Fu (帅孚); Si Li Tai (司力泰); Tao Te (韬特); Weijiexin (维洁信); Xi Bo Te Xin (西博特欣); Yan Zhi (延知); ***Fr.***: Orelox; ***Ger.***: Orelox; Podomexef; ***Gr.***: Cefodox; Orelox; ***Hong Kong***: Banan; ***India***: Apodox; Aripdox; Arodox; Avicef-O; Bactogard; Banin; Baroxime; Belpro; Bioproxe; Bobcef; C-Prox; Cacef; Capadex; Capoten; Caspod; CCL; Cedon; Cedoxime; Cefakind-P; Cefdolife; Cefective; Cefetil; Cefmag; Cefoact; Cefobit; Cefolex; Cefoprox; Ceforiz; Cefpogard; Cefpolar; Ceftils; Ceftop-DT; Cefvig; Cefwar; Cepocef; Cepocor; Cepodem; Ceporiz; Cepotil; Cepotuf; Cepotus; Cepox; Codimol; CPod; Docsef; Doxinis; Doxiz; Edrigard; Epodox; Everpod; Expodox; Fixtan; GSProx; Hipodox; Ipod; Ipodex; Kefodime; Kefpod; Kinopox; Kudox; Kzidime; Maxipod; Metoxim; Microcef; Monocef-O; Monotax-O; Nayacef; Nolia; Nudoxim; Odop; Omnacefpo; Oripod; Pandox; Tambac; ***Indon.***: Banadoz; Banan†; ***Irl.***: Cefodox; ***Ital.***: Cefodox; Orelox; Otreon; ***Jpn***: Banan; ***Mex.***: Orelox; ***Neth.***: Otreon†; ***Philipp.***: Banan†; Cefadox; Zudem; ***Port.***: Orelox†; ***S.Afr.***: Cepodem; Orelox; ***Spain***: Instana†; Otreon†; ***Switz.***: Orelox; Podomexef; ***Thai.***: Banan†; ***Turk.***: Dokselin; Orelox; Sefpotec; Sefsidal; ***UK***: Orelox; ***Ukr.***: Cefodox (Цефодокс); Cepodem (Цеподем); Dokcef (Докцеф); ***USA***: Vantin.

Multi-ingredient Preparations. ***India***: C-Prox-LB; Cedon-LB; Cedon-P; Cedoxime-LB; Ceftop; Doxinis-CV; Gudcef; Infactum; Kinopox-CV; Novodoxim; Nupod-CV; Papcef-CV.

Pharmacopoeial Preparations

USP 36: Cefpodoxime Proxetil for Oral Suspension; Cefpodoxime Proxetil Tablets.

Cefprozil *(BAN, USAN, rINN)*

BMY-28100-03-800; BMY-28100 (*cis*-isomer); BMY-28167 (*trans*-isomer); Cefprozilo; Cefprozilum; Kefprotsiili; Sefprozil; Цефпрозил.

(6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-8-oxo-3-(1-propenyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate; 7-(D-4-Hydroxyphenylglycylamino)-3-[(*E*)prop-1-enyl]cephem-4-carboxylic acid monohydrate.

$C_{18}H_{19}N_3O_5S.H_2O$=407.4

CAS — 92665-29-7 (anhydrous cefprozil); 121123-17-9 (cefprozil monohydrate).

ATC — J01DC10.

ATC Vet — QJ01DC10.

UNII — 4W0459ZA4V (cefprozil monohydrate); 1M698F4H4E (anhydrous cefprozil); 51SDI2FJIY (anhydrous cefprozil, e-isomer); W5T767OA4G (anhydrous cefprozil, z-isomer); 3ADV90MJVU (cefprozil, e-isomer); 358K60B00H (cefprozil, z-isomer).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Cefprozil Monohydrate). A mixture of the diastereoisomers of cefprozil monohydrate. A white or yellow, slightly hygroscopic, crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in acetone. Store in airtight containers.

USP 36: (Cefprozil). pH of a 0.5% solution in water is between 3.5 and 6.5. Store in airtight containers.

Uses and Administration

Cefprozil is a cephalosporin antibacterial consisting of *cis*- and *trans*- isomers in a ratio of about 90:10. It should probably be classified as a second-generation cephalosporin and is used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the urinary and respiratory tracts and skin and skin structure. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefprozil is given orally as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefprozil; 523 mg of cefprozil monohydrate is equivalent to about 500 mg of anhydrous cefprozil. The usual adult dose is 500 mg daily (as a single dose or in two divided doses), increased to 500 mg twice daily if necessary.

The dose of cefprozil may need to be reduced in patients with renal impairment, see p. 250.3.

For details of doses in children, see p. 250.3.

Reviews.

1. Wiseman LR, Benfield P. Cefprozil: a review of its antibacterial activity, pharmacokinetic properties, and therapeutic potential. *Drugs* 1993; **45:** 295–317.
2. Barriere SL. Review of in vitro activity, pharmacokinetic characteristics, safety, and clinical efficacy of cefprozil, a new oral cephalosporin. *Ann Pharmacother* 1993; **27:** 1082–9.
3. Aronovitz G. Treatment of upper and lower respiratory tract infections: clinical trials with cefprozil. *Pediatr Infect Dis J* 1998; **17** (suppl): S83–S88.
4. Bhargava S, *et al.* Cefprozil: a review. *Indian J Pediatr* 2003; **70:** 395–400.

Administration in children. Cefprozil may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children from the age of 6 months may be given oral doses of 15 mg/kg every 12 hours for the treatment of otitis media, 7.5 or 15 mg/kg every 12 hours for acute sinusitis, and 7.5 mg/kg every 12 hours for pharyngitis or tonsillitis. Children from the age of 2 years may be given 20 mg/kg once daily for skin and skin structure infections. Total daily doses used in children should not exceed 1 g.

Administration in renal impairment. Oral doses of cefprozil should be reduced in patients with renal impairment; standard doses should be halved in patients with a creatinine clearance ≤30 mL/minute. In patients on haemodialysis the dose should be given after each dialysis session.

Adverse Effects and Precautions

As for Cefalexin, p. 234.2.

Breast feeding. A study[1] in 9 healthy women found that concentrations of cefprozil in breast milk corresponded to no more than 0.3% of a dose and concluded that cefprozil could be given safely during breast feeding. The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of cefprozil in breast-feeding mothers, and that it may be considered to be usually compatible with breast feeding.

1. Shyu WC, *et al.* Excretion of cefprozil into human breast milk. *Antimicrob Agents Chemother* 1992; **36:** 938–41.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Serum sickness-like reactions were reported in 4 patients, 3 of them children, given cefprozil.[1] Such reactions have been associated with cefaclor (p. 233.1), but whether they represent a class-related hypersensitivity reaction is not clear. Hypersensitivity vasculitis[2] and hepatitis[3] have also been reported with cefprozil.

1. Lowery N, *et al.* Serum sickness-like reactions associated with cefprozil therapy. *J Pediatr* 1994; **125:** 325–8.
2. Totan M, Islek I. Hypersensitivity vasculitis induced by cefprozil. *Ann Saudi Med* 2002; **22:** 269–70.
3. Bilici A, *et al.* A rare case of hepatitis associated with cefprozil therapy. *Scand J Infect Dis* 2007; **39:** 190–2.

Interactions

As for Cefalexin, p. 234.2.

Antimicrobial Action

Cefprozil is bactericidal and has a similar but wider range of antimicrobial activity than cefaclor (p. 233.1).

Pharmacokinetics

Cefprozil is well absorbed from the gastrointestinal tract with a reported bioavailability of 90 to 95%. Oral doses of 0.25, 0.5, and 1 g produce peak plasma concentrations of about 6, 10, and 18 micrograms/mL respectively at 1 to 2 hours. The presence of food is reported to have little or no effect on the absorption of cefprozil. A plasma half-life of 1 to 1.4 hours has been reported; it is increased in patients with renal impairment, up to about 6 hours in those with end-stage renal failure. About 35 to 45% of cefprozil is bound to plasma proteins.

Cefprozil is widely distributed in the body tissues. Concentrations of cefprozil in tonsillar and adenoidal tissue are reported to be about 40 to 50% of those in plasma, and less than 0.3% of a 1-g dose has been recovered in breast milk in 24 hours. About 60% of a dose is excreted unchanged in the urine in the first 8 hours by glomerular filtration and tubular secretion. Concentrations of cefprozil of 700, 1000, and 2900 micrograms/mL have occurred in the urine within 4 hours of doses of 0.25, 0.5, and 1 g respectively. Some cefprozil is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ceprof†; ***Braz.***: Cefzil; ***Canad.***: Cefzil; ***China***: Cefzil (施复捷); Kai Ke Zhi (凯可之); Xi Neng (希能); Yinlishu (银力舒); Yuanrui (元锐); ***Cz.***: Cefzil; ***Gr.***: Cefgram; Cefipra; Cefium; Cefpro; Cefzil; Cepius; Gramium; Mycoterb; Natrofen; Pricefil; Procef; Prozidil; Sanocef; Teliomon; Top 1; Tricef; Zamalin; ***Hong Kong***: Procef†; ***Hung.***: Cefzil; ***India***: Orprozil; Refzil-O; ***Indon.***: Cefzil†; Lizor; ***Ital.***: Cronocef; Procef†; Rozicel†; ***Mex.***: Procef; ***Philipp.***: Procef†; ***Pol.***: Cefzil†; ***Port.***: Procef; Radacefe; ***S.Afr.***: Auroprozil; Prozef; ***Singapore***: Procef; ***Spain***: Brisoral†; ***Switz.***: Procef; ***Thai.***: Procef†; ***Turk.***: Erasef; Prefix; Serozil; ***Venez.***: Procef.

Pharmacopoeial Preparations
USP 36: Cefprozil for Oral Suspension; Cefprozil Tablets.

Cefquinome Sulfate *(BANM, USAN, rINNM)*

Cefquinoma, sulfato de; Cefquinome, Sulfate de; Cefquinome Sulphate; Cefquinomi Sulfas; HR-111V; Sulfato de cefquinoma; Цефхинома Сульфат.

{6*R*-[6α,7β(*Z*)]}-1-[(7-[[(2-amino-4-thiazolyl)-(methoxyimino) acetyl]amino}-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-5,6,7,8,-tetrahydroquinolinium sulfate (1:1).

$C_{23}H_{24}N_6O_5S_2.H_2SO_4$=626.7

CAS — 84957-30-2 (cefquinome); 118443-89-3 (cefquinome sulfate); 123766-80-3 (cefquinome sulfate).

UNII — 3858K104DQ.

Profile

Cefquinome is a fourth-generation cephalosporin antibacterial used as the sulfate in veterinary medicine.

Cefradine *(BAN, rINN)*

Cefradin; Cefradina; Cefradinas; Céfradine; Cefradinum; Cefradyna; Cephradine (USAN); Cephradine; Kefradiini; Sefradin; SKF-D-39304; SQ-11436; SQ-22022 (cefradine dihydrate); Цефрадин.

(7*R*)-7-(α-D-Cyclohexa-1,4-dienylglycylamino)-3-methyl-3-cephem-4-carboxylic acid.

$C_{16}H_{19}N_3O_4S$=349.4

CAS — 38821-53-3 (anhydrous cefradine); 31828-50-9 (non-stoichiometric cefradine hydrate); 58456-86-3 (cefradine dihydrate).

ATC — J01DB09.

ATC Vet — QJ01DB09.

UNII — F1BC02I72W (cefradine); 9YA6SX5S4D (anhydrous cefradine); FUC0D711ZN (cefradine monohydrate); 56PPJ9MMPE (cefradine dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US* (which allows the anhydrous form, the monohydrate, or the dihydrate).

Ph. Eur. 8: (Cefradine). A white or slightly yellow, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol and in *n*-hexane. A 1% solution in water has a pH of 3.5 to 6.0. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Cephradine). A white to off-white crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in chloroform; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Incompatibility and stability. Commercially available injections contain sodium carbonate or arginine as neutralisers. Injections containing sodium carbonate are incompatible with solutions such as compound sodium lactate injection that contain calcium salts.

References.

1. Wang Y-C J, Monkhouse DC. Solution stability of cephradine neutralized with arginine or sodium bicarbonate. *Am J Hosp Pharm* 1983; **40:** 432.
2. Mehta AC, *et al*. Chemical stability of cephradine injection solutions. *Intensive Therapy Clin Monit* 1988; **9**: 195–6.

Uses and Administration

Cefradine is a first-generation cephalosporin antibacterial given orally or by the parenteral route in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria (including infections of the respiratory and urinary tracts, bones and joints, and of the skin and skin structure) and for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefradine is given orally in doses of 1 to 2 g daily in 2 to 4 divided doses; up to 4 g daily may be given by this route. It may be given parenterally, by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by intermittent or continuous infusion, in doses of 2 to 4 g daily in 4 divided doses; up to 8 g daily may be given parenterally.

For surgical infection prophylaxis, 1 to 2 g may be given pre-operatively by intramuscular or intravenous injection; subsequent parenteral or oral doses are given as appropriate.

The dose of cefradine may need to be reduced in patients with renal impairment, see also p. 251.2.

For details of doses in children, see also p. 251.2.

Administration in children. Cefradine may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given orally, by intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or intermittent or continuous infusion. The usual oral dose is 25 to 50 mg/kg daily in 2 or 4 divided doses; for otitis media 75 to 100 mg/kg daily in divided doses every 6 to 12 hours (to a maximum of 4 g daily) may be given. Cefradine is given parenterally in a dose of 50 to 100 mg/kg daily in 4 divided doses, increasing to 200 to 300 mg/kg daily in severe infections.

Although not licensed in the UK, for the prevention of *Staphylococcus aureus* lung infection in children with cystic fibrosis the *BNFC* recommends that those aged 7 years and older may be given an oral dose of 2 g twice daily.

Administration in renal impairment. Doses of cefradine should be reduced in patients with severe renal impairment. The following oral and parenteral doses are recommended in UK licensed product information according to creatinine clearance (CC):

- CC more than 20 mL/minute: 500 mg every 6 hours
- CC 5 to 20 mL/minute: 250 mg every 6 hours
- CC less than 5 mL/minute: 250 mg every 12 hours

Patients undergoing chronic, intermittent haemodialysis may be given a 250-mg dose at the start of the session, repeated after 6 to 12 hours, then again 36 to 48 hours after the initial dose, and again at the start of the next haemodialysis if more than 30 hours have elapsed since the previous dose.

Further dosage modification may be required in children with renal impairment.

Adverse Effects and Precautions

As for Cefalexin, p. 234.2. Intramuscular injections of cefradine can be painful and thrombophlebitis has occurred on intravenous injection.

Interactions

As for Cefalexin, p. 234.2.

Antimicrobial Action

As for Cefalexin, p. 234.2.

Pharmacokinetics

Cefradine is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Doses of 0.25, 0.5, and 1 g given orally have produced peak plasma concentrations of about 9, 17, and 24 micrograms/mL respectively at 1 hour and are similar to those achieved with cefalexin. Absorption is delayed by the presence of food although the total amount absorbed is not appreciably altered. After intramuscular injection peak plasma concentrations of about 6 and 14 micrograms/mL have occurred within 1 to 2 hours of doses of 500 mg and 1 g respectively.

Only about 8 to 12% is reported to be bound to plasma proteins. A plasma half-life of about 1 hour has been reported; this is prolonged in patients with renal impairment. Cefradine is widely distributed to body tissues and fluids, but does not enter the CSF in significant quantities. Therapeutic concentrations occur in the bile. It crosses the placenta into the fetal circulation and is distributed in small amounts into breast milk.

Cefradine is excreted unchanged in the urine by glomerular filtration and tubular secretion, over 90% of an oral dose or 60 to 80% of an intramuscular dose being recovered within 6 hours. Peak urinary concentrations of about 3 mg/mL have been achieved after a 500-mg oral dose. Probenecid delays excretion.

Cefradine is removed by haemodialysis and peritoneal dialysis.

References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
2. Schwinghammer TL, *et al*. Pharmacokinetics of cephradine administered intravenously and orally to young and elderly subjects. *J Clin Pharmacol* 1990; **30:** 893–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Velosef†; ***China***: Di La (迪拉); Kebili (克必力); Saifuding (赛福定); Shen You (申优); Taiding (泰迪定); Velosef (泛捷复); Xianyi (先宜); Xindadelei (新达德雷); ***Fr.***: Dexef; Kelsef†; Zeefra†; ***Gr.***: Ampisodex; Amritacicl; Bionovium; Nipredin; Opebrin; Sporobiotic; Tracilarin; Velosef; Vethisel; ***Hong Kong***: Qualisef; Velosef†; Zeefra†; ***Indon.***: Dynacef; Lovecef†; Velodine; Velodrom; Velosef†; ***Irl.***: Velosef†; ***Ital.***: Ecosporina; ***Mex.***: Veracef; ***Philipp.***: Altozef; Cefralon; Gramcep; Medrin; Racep; Sedinef; Senadex; Solphride; Tolzep†; Vamosef; Velodyne; Yudinef; Zefadin; Zepdril; Zolicef; ***Pol.***: Tafril; ***Port.***: Biocefra; Cefalmin; Cefradur; ***S.Afr.***: Cefril†; ***Spain***: Septacef†; Velocef†; ***UAE***: Eskacef†; Julphacef; ***UK***: Nicef; Velosef†; ***Venez.***: Veracef.

Pharmacopoeial Preparations
BP 2014: Cefradine Capsules; Cefradine Injection; Cefradine Oral Suspension;
USP 36: Cephradine Capsules; Cephradine for Injection; Cephradine for Oral Suspension; Cephradine Tablets.

Cefsulodin Sodium *(BANM, USAN, rINNM)*

Abbott-46811; Cefsulodina sódica; Cefsulodine Sodique; Cefsulodinnatrium; Cefsulodinum Natricum; CGP-7174E; Kefsulodiininatrium; Natrii Cefsulodinum; SCE-129; Sulcephalosporin Sodium; Натрий Цефсулодин.

Sodium 3-(4-carbamoylpyridiniomethyl)-7-[(2*R*)-2-phenyl-2-sulphoacetamido]-3-cephem-4-carboxylate.

$C_{22}H_{19}N_4NaO_8S_2$=554.5

CAS — 62587-73-9 (cefsulodin); 52152-93-9 (cefsulodin sodium).

ATC — J01DD03.

ATC Vet — QJ01DD03.

UNII — 2D087186PY.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Cefsulodin is a third-generation cephalosporin antibacterial with a narrow spectrum of activity that has been used similarly to ceftazidime (p. 253.1) for the treatment of infections caused by susceptible strains of *Pseudomonas aeruginosa.*

It is given as the sodium salt by intravenous injection. Doses are expressed in terms of the equivalent amount of cefsulodin; 1.04 g of cefsulodin sodium is equivalent to about 1 g of cefsulodin. The usual adult dose is 6 g daily in 4 divided doses; in less severe infections daily doses of 3 to 4 g may be given.

For details of doses in children and in those with renal impairment, see p. 251.3.

Administration in children. Cefsulodin may be given to children for the treatment of infections caused by susceptible organisms, in particular *Pseudomonas aeruginosa.* Children may be given an intravenous dose of 100 mg/kg daily; 50 mg/kg daily may be given in less severe infections.

Administration in renal impairment. The dosage of cefsulodin given intravenously should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 20 to 50 mL/minute: a loading dose of 1.5 g then 1 g every 8 hours

- CC 5 to 20 mL/minute: a loading dose of 1.5 g then 1 g every 12 hours
- CC less than 5 mL/minute: a loading dose of 1.5 g then 1 g every 24 hours; for those receiving haemodialysis, a 1-g dose is given before dialysis on dialysis days, followed by a second 1-g dose after the dialysis run

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Sodium content. Each g of cefsulodin sodium contains about 1.8 mmol of sodium.

Antimicrobial Action

Cefsulodin is a bactericidal antibiotic with activity against *Pseudomonas aeruginosa* as great as that of ceftazidime (p. 253.3), but no significant activity against other Gram-negative bacteria. Gram-positive bacteria and anaerobes are not very susceptible. Its activity against *Ps. aeruginosa* may be enhanced by aminoglycosides.

Cefsulodin is stable to hydrolysis by many beta-lactamases, but emergence of resistant *Ps. aeruginosa* has been reported.

Pharmacokinetics

Cefsulodin is given parenterally as the sodium salt. It has a plasma half-life of about 1.6 hours, which is prolonged in renal impairment. Up to 30% of cefsulodin in the circulation is bound to plasma proteins. Therapeutic concentrations have been reported in many body tissues and fluids. The major route of excretion of cefsulodin is via the urine, mainly by glomerular filtration. Clearance may be enhanced in cystic fibrosis, although there have been conflicting reports.

References.
1. Granneman GR, *et al.* Cefsulodin kinetics in healthy subjects after intramuscular and intravenous injection. *Clin Pharmacol Ther* 1982; **31:** 95–103.
2. Reed MD, *et al.* Single-dose pharmacokinetics of cefsulodin in patients with cystic fibrosis. *Antimicrob Agents Chemother* 1984; **25:** 579–81.
3. Hedman A, *et al.* Increased renal clearance of cefsulodin due to higher glomerular filtration rate in cystic fibrosis. *Clin Pharmacokinet* 1990; **18:** 168–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Ulfaret; ***Jpn***: Takesulin†.

Ceftaroline Fosamil Acetate

(BANM, USAN, rINNM)

Acetato de ceftarolina fosamilo; Ceftaroline Fosamil, Acétate de; Ceftarolini Fosamili Acetas; PPI-0903 (ceftaroline fosamil or ceftaroline fosamil acetate); TAK-599 (ceftaroline fosamil or ceftaroline fosamil acetate); Цефтаролина Фозамил Ацетат.

(6*R*,7*R*)-7-{[(2*Z*)-(Ethoxyimino)[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetyl}amino)-3-{[4-(1-methylpyridinium-4-yl) thiazol-2-yl}sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylate monoacetate monohydrate.

$C_{22}H_{21}N_8O_8PS_4.C_2H_4O_2.H_2O$=762.7

CAS — 229016-73-3 (ceftaroline fosamil); 400827-46-5 (anhydrous ceftaroline fosamil acetate); 400827-55-6 (ceftaroline fosamil acetate monohydrate).

ATC — J01DI02.

ATC Vet — QJ01DI02.

UNII — EZ9W6O5S09 (anhydrous ceftaroline fosamil acetate); P9VXV1408Y (ceftaroline fosamil acetate monohydrate).

Uses and Administration

Ceftaroline fosamil is a broad-spectrum cephalosporin antibacterial, sometimes described as a 'fifth-generation' cephalosporin, that is used in the treatment of community-acquired pneumonia and acute skin and skin structure infections caused by susceptible organisms; it may be of particular use for skin infections caused by MRSA.

Ceftaroline fosamil is given as the acetate salt by intravenous infusion over 1 hour. Doses are expressed in terms of the equivalent amount of ceftaroline fosamil; 1.11 g of ceftaroline fosamil acetate is equivalent to about 1 g of ceftaroline fosamil. The usual dose is the equivalent of 600 mg ever 12 hours. Doses may need to be reduced in renal impairment (see p. 252.2).

References.
1. Parish D, Scheinfeld N. Ceftaroline fosamil, a cephalosporin derivative for the potential treatment of MRSA infection. *Curr Opin Investig Drugs* 2008; **9:** 201–9.
2. Zhanel GG, *et al.* Ceftaroline: a novel broad-spectrum cephalosporin with activity against meticillin-resistant *Staphylococcus aureus*. *Drugs* 2009; **69:** 809–31.
3. Steed ME, Rybak MJ. Ceftaroline: a new cephalosporin with activity against resistant gram-positive pathogens. *Pharmacotherapy* 2010; **30:** 375–89.
4. Corey GR, *et al.* Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 2010; **51:** 641–50.

Administration in renal impairment. In patients with renal impairment, the following intravenous doses of ceftaroline fosamil are recommended, according to creatinine clearance (CC):
- CC 31 to 50 mL/minute: 400 mg every 12 hours
- CC 15 to 30 mL/minute: 300 mg every 12 hours
- CC < 15 mL/minute: 200 mg every 12 hours (for patients on haemodialysis, doses should be given after the dialysis run)

Adverse Effects and Precautions

As for Cefalotin Sodium (p. 235.2). Like other broad-spectrum cephalosporins (see Cefotaxime, p. 244.3), ceftaroline has the potential for promoting colonisation and superinfection with resistant organisms.

Antimicrobial Action

Ceftaroline fosamil is a fifth-generation cephalosporin with broad-spectrum bactericidal activity against many Gram-positive and Gram-negative organisms. Its activity is similar to that of cefotaxime (p. 244.3); however, it has an expanded spectrum of activity against Gram-positive bacteria that includes MRSA and multidrug-resistant *Streptococcus pneumoniae*. Enterococci are generally resistant, but there may be some susceptibility shown by *Enterococcus faecalis*.

Although ceftaroline has good activity against many Gram-negative bacteria, *Pseudomonas aeruginosa, Acinetobacter* spp., *Alcaligenes* spp., and *Stenotrophomonas maltophilia* have decreased susceptibility.

Ceftaroline has poor activity against Gram-negative anaerobes such as *Bacteroides fragilis* and *Prevotella* spp., however, Gram-positive anaerobes such as *Propionibacterium* spp. and *Peptostreptococcus* spp. are highly susceptible.

Pharmacokinetics

After infusion, ceftaroline fosamil is rapidly converted in the plasma to ceftaroline, the bio-active form of the drug. Mean peak plasma concentrations of 19 micrograms/mL have been reported after a single 600 mg dose of ceftaroline fosamil given intravenously over 1 hour. Ceftaroline is about 20% bound to plasma proteins, and in healthy patients, has a mean steady-state volume of distribution of about 20.3 litres.

Ceftaroline is metabolised in small amounts to the microbiologically-inactive metabolite ceftaroline M-1 via hydrolysis of the β-lactam ring.

Ceftaroline and its metabolite are excreted mainly by the kidneys, with about 88% of a dose recovered in the urine within 48 hours (mainly as unchanged drug); a small amount of drug is excreted in faeces. The elimination half-life of ceftaroline is about 2.66 hours. Ceftaroline exposure and half-life are significantly increased in renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Zinforo; ***Norw.***: Zinforo; ***UK***: Zinforo; ***USA***: Teflaro.

Ceftazidime *(BAN, USAN, rINN)*

Ceftazidim; Ceftazidim pentahydrát; Ceftazidima; Ceftazidimas; Ceftazidimum; Ceftazidimum Pentahydricum; Ceftazydym; GR-20263; Keftatsidiimi; LY-139381; Seftazidim; Цефтазидим.

(*Z*)-(7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-(1-pyridiniomethyl)-3-cephem-4-carboxylate pentahydrate.

$C_{22}H_{22}N_8O_7S_2.5H_2O$=636.6

CAS — 72558-82-8 (anhydrous ceftazidime); 78439-06-2 (ceftazidime pentahydrate).

ATC — J01DD02.

ATC Vet — QJ01DD02.

UNII — 9M416Z9QNR (ceftazidime pentahydrate); DZR1ENT301 (anydrous ceftazidime).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ceftazidime Pentahydrate). A semisynthetic product derived from a fermentation product. A white or almost white crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in alcohol and in acetone; it dissolves in acid and alkali solutions. A 0.5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

Ph. Eur. 8: (Ceftazidime Pentahydrate with Sodium Carbonate for Injection). A sterile mixture of ceftazidime pentahydrate and anhydrous sodium carbonate. A white or pale yellow powder. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light and humidity.

USP 36: (Ceftazidime). A white to cream-coloured crystalline powder. Slightly soluble in water, in dimethylformamide, and in methyl alcohol; insoluble in alcohol, in acetone, in chloroform, in dioxan, in ether, in ethyl acetate, and in toluene; soluble in alkali and in dimethyl sulfoxide. pH of a 0.5% solution in water is between 3.0 and 4.0. Store in airtight containers.

Formulation. Ceftazidime for injection is available as a dry powder containing ceftazidime with sodium carbonate. When reconstituted ceftazidime sodium is formed with the evolution of carbon dioxide. An alternative formulation, ceftazidime with arginine, appears to overcome the problems associated with effervescence.[1] In some countries a frozen injection containing ceftazidime sodium is also used.

1. Stiles ML, *et al.* Gas production of three brands of ceftazidime. *Am J Hosp Pharm* 1991; **48:** 1727–9.

Incompatibility. It has been reported that ceftazidime does not cause decreased activity when incubated in solution with *gentamicin*[1] or *tobramycin*[2] at 37 degrees, or when mixed with tobramycin in serum.[3] Ceftazidime and tobramycin[4] were also stable for up to 16 hours at room temperature when combined in a glucose-containing dialysis solution, and for a further 8 hours at 37 degrees. However, licensed product information recommends that ceftazidime, like most other beta lactams, should not be mixed with an aminoglycoside in the same giving set or syringe because of the potential for inactivation of either drug.

Ceftazidime is generally considered to be compatible with *metronidazole*, but degradation of ceftazidime has been reported.[5] Precipitation has occurred with *vancomycin*[6] and therefore the product information considers it prudent to flush giving sets and intravenous lines between giving the two drugs. However, in one study[7] ceftazidime and/or vancomycin were stable in a glucose-containing peritoneal dialysis solution when kept for 6 days in a refrigerator or 48 to 72 hours at room temperature, and in a further study[8] the two drugs were stable when combined in similar solutions containing 1.5% or 4.25% glucose for up to 12 hours when stored at 37 degrees and for 24 hours when stored at 4 degrees and 24 degrees. Ceftazidime and *teicoplanin*[9] were stable in combination in a peritoneal dialysis solution at 37 degrees for 8 hours when it had been previously stored at 4 degrees, but not when previously stored at 25 degrees. Ceftazidime was not stable when mixed in solution with *aminophylline*.[10] There was some evidence of possible incompatibility with *pentamidine*.[11]

1. Elliott TSJ, *et al.* Stability of gentamicin in combination with selected new β-lactam antibiotics. *J Antimicrob Chemother* 1984; **14:** 668–9.
2. Elliott TSJ, *et al.* Stability of tobramycin in combination with selected new β-lactam antibiotics. *J Antimicrob Chemother* 1986; **17:** 680–1.
3. Pennell AT, *et al.* Effect of ceftazidime, cefotaxime, and cefoperazone on serum tobramycin concentrations. *Am J Hosp Pharm* 1991; **48:** 520–2.
4. Mason NA, *et al.* Stability of ceftazidime and tobramycin sulfate in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; **49:** 1139–42.
5. Messerschmidt W. Pharmazeutische kompatibilität von ceftazidim und metronidazol. *Pharm Ztg* 1990; **135:** 36–8.
6. Cairns CJ, Robertson J. Incompatibility of ceftazidime and vancomycin. *Pharm J* 1987; **238:** 577.
7. Vaughan LM, Poon CY. Stability of ceftazidime and vancomycin alone and in combination in heparinized and nonheparinized peritoneal dialysis solution. *Ann Pharmacother* 1994; **28:** 572–6.
8. Stamatakis MK, *et al.* Stability of high-dose vancomycin and ceftazidime in peritoneal dialysis solutions. *Am J Health-Syst Pharm* 1999; **56:** 246–8.
9. Manduru M. *et al.* Stability of ceftazidime sodium and teicoplanin sodium in a peritoneal dialysis solution. *Am J Health-Syst Pharm* 1996; **53:** 2731–4.
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11. Lewis JD. El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1462–3.

Stability. References.

1. Richardson BL, *et al.* The pharmacy of ceftazidime. *J Antimicrob Chemother* 1981; **8** (suppl B): 233–6.
2. Brown AF, *et al.* Freeze thaw stability of ceftazidime. *Br J Parenter Ther* 1985; **6:** 43, 45, 50.
3. Walker SE, Dranitsaris G. Ceftazidime stability in normal saline and dextrose in water. *Can J Hosp Pharm* 1988; **41:** 65–6, 69–71.
4. Wade CS, *et al.* Stability of ceftazidime and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1991; **48:** 1515–19.
5. Stiles ML, *et al.* Stability of ceftazidime (with arginine) and of cefuroxime sodium in infusion-pump reservoirs. *Am J Hosp Pharm* 1992; **49:** 2761–4.
6. Stewart JT, *et al.* Stability of ceftazidime in plastic syringes and glass vials under various storage conditions. *Am J Hosp Pharm* 1992; **49:** 2765–8.
7. Nahata MC, *et al.* Stability of ceftazidime (with arginine) stored in plastic syringes at three temperatures. *Am J Hosp Pharm* 1992; **49:** 2954–6.
8. Bednar DA, *et al.* Stability of ceftazidime (with arginine) in an elastomeric infusion device. *Am J Health-Syst Pharm* 1995; **52:** 1912–14.

9. van Doorne H, *et al*. Ceftazidime degradation rates for predicting stability in a portable infusion-pump reservoir. *Am J Health-Syst Pharm* 1996; **53:** 1302–5.
10. Stendal TL, *et al*. Drug stability and pyridine generation in ceftazidime injection stored in an elastomeric infusion device. *Am J Health-Syst Pharm* 1998; **55:** 683–5.
11. Servais H, Tulkens PM. Stability and compatibility of ceftazidime administered by continuous infusion to intensive care patients. *Antimicrob Agents Chemother* 2001; **45:** 2643–7.

Uses and Administration

Ceftazidime is a third-generation cephalosporin antibacterial with enhanced activity against *Pseudomonas aeruginosa*. It is used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, especially infections due to *Pseudomonas* spp. They include biliary-tract infections, bone and joint infections, respiratory-tract infections, infections in immunocompromised patients (neutropenic patients), skin and skin structure infections, and urinary-tract infections. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftazidime is available as the pentahydrate but it is formulated with sodium carbonate, to form the sodium salt in solution, or with arginine. Doses are expressed in terms of anhydrous ceftazidime; ceftazidime pentahydrate 1.16 g is equivalent to about 1 g of anhydrous ceftazidime. It is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion over up to 30 minutes.

The usual dose for adults ranges from 1 to 6 g daily in divided doses every 8 or 12 hours. The higher doses are used in severe infections especially in immunocompromised patients. In adults with cystic fibrosis who have pseudomonal lung infections, high doses of 90 to 150 mg/kg daily in 3 divided doses are used; up to 9 g daily has been given to those with normal renal function. Single doses of more than 1 g should be given intravenously.

For surgical infection prophylaxis in patients undergoing prostatic surgery, a dose of 1 g may be given at induction of anaesthesia and repeated if necessary when the catheter is removed.

The dose of ceftazidime may need to be reduced in patients with renal impairment, see p. 253.2. For details of doses in children, see also p. 253.1.

Ceftazidime can be used with an aminoglycoside, another beta lactam such as piperacillin, or vancomycin in patients with severe neutropenia, or, if infection with *Bacteroides fragilis* is suspected, with an antimicrobial such as clindamycin or metronidazole. The drugs should generally be given separately (see also Incompatibility, p. 250.3).

References.
1. Rains CP, *et al*. Ceftazidime: an update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1995; **49:** 577–617.
2. Roberts JA, *et al*. Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; **29:** 117–28.
3. Hubert D, *et al*. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother* 2009; **53:** 3650–6.

Administration in children. Ceftazidime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion.

In the UK, the *BNFC* recommends that neonates and children may be given a dose of 25 mg/kg every 24 hours in neonates less than 7 days old, every 12 hours in those aged 7 to 21 days, and every 8 hours in older neonates and children. The dose may be doubled in severe infection, febrile neutropenia, and meningitis (to a maximum daily dose of 6 g in children 1 month of age and older).

For pseudomonal lung infection in cystic fibrosis in patients aged 1 month and older a dose of 50 mg/kg every 8 hours (to a maximum daily dose of 9 g) may be given.

In the USA, the American Academy of Pediatrics[1] suggests the following doses for ceftazidime:

- for neonates aged ⩽ 7 days (irrespective of body weight): 50 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ⩽ 2 kg: 50 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing > 2 kg: 50 mg/kg every 8 hours
- children 1 month and older: 90 to 150 mg/kg daily in 3 divided doses (to a maximum daily dose of 3 g) for mild to moderate infections, or 200 to 300 mg/kg daily in 3 divided doses (to a maximum daily dose of 6 g) in severe infections

Although not licensed for nebulisation in the UK, the *BNFC* suggests a dose of 1 g inhaled twice daily for the management of chronic *Burkholderia cepacia* infection in patients aged 1 month and older with cystic fibrosis.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. In patients with renal impairment parenteral doses of ceftazidime may need to be reduced. After a loading dose of 1 g, maintenance doses are based on the creatinine clearance (CC):

- CC 31 to 50 mL/minute: 1 g every 12 hours
- CC 16 to 30 mL/minute: 1 g every 24 hours
- CC 6 to 15 mL/minute: 500 mg every 24 hours
- CC less than 5 mL/minute: 500 mg every 48 hours

In severe infections these doses may need to be increased by 50%. In these patients ceftazidime trough serum concentrations should not exceed 40 micrograms/mL. In patients undergoing peritoneal dialysis a loading dose of 1 g may be given followed by 500 mg every 24 hours; ceftazidime sodium may also be added to the dialysis fluid, usually 125 to 250 mg of ceftazidime for 2 litres of dialysis fluid. In patients undergoing haemodialysis a loading dose of 1 g is given and then 1 g after each dialysis period.

For critically ill patients undergoing continuous renal replacement therapy, a loading dose of 2 g and the following maintenance doses, given intravenously, have been recommended:[1]

- for continuous venovenous haemodialysis (CVVHD) or haemodialfiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours; 2 g every 8 hours may be necessary for very resistant Gram-negative pathogens
- for continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours

Continuous infusion dosing regimens have also been suggested for use in patients undergoing CVVHDF[2] and CVVH.[3]

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.
2. Mariat C, *et al*. Continuous infusion of ceftazidime in critically ill patients undergoing continuous venovenous haemodiafiltration: pharmacokinetic evaluation and dose recommendation. *Crit Care* 2006; **10:** R26. Available at: http://ccforum.com/content/pdf/cc3993.pdf (accessed 24/06/10)
3. Moriyama B, *et al*. Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. *Ann Pharmacother* 2009; **43:** 1324–37.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Like cefotaxime (p. 244.3), ceftazidime has the potential to promote colonisation and superinfection with resistant organisms. The risk of superinfection with, for example, *Staphylococcus aureus* may be higher than with cefotaxime, since ceftazidime is less active against staphylococci.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ceftazidime, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the blood. References.

1. Hui CH, Chan LC. Agranulocytosis associated with cephalosporin. *BMJ* 1993; **307:** 484.

Effects on the nervous system. References.

1. Al-Zahawi MF, *et al*. Hallucinations in association with ceftazidime. *BMJ* 1988; **297:** 858.
2. Jackson GD, Berkovic SF. Ceftazidime encephalopathy: absence status and toxic hallucinations. *J Neurol Neurosurg Psychiatry* 1992; **55:** 333–4.
3. Chow KM, *et al*. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; **23:** 369–73.

Effects on the skin. References.

1. Vinks SATMM, *et al*. Photosensitivity due to ambulatory intravenous ceftazidime in cystic fibrosis patient. *Lancet* 1993; **341:** 1221–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ceftazidime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Unlike that of many other cephalosporins, the renal clearance of ceftazidime is not much affected by probenecid.

References.
1. Verhagen CA, *et al*. The renal clearance of cefuroxime and ceftazidime and the effect of probenecid on their tubular excretion. *Br J Clin Pharmacol* 1994; **37:** 193–7.

Antimicrobial Action

Ceftazidime has a bactericidal action and broad spectrum of activity similar to that of cefotaxime (p. 244.3), but increased activity against *Pseudomonas* spp.; it is less active against staphylococci and streptococci. Unlike cefotaxime it has no active metabolite.

Ceftazidime is highly stable to hydrolysis by most beta-lactamases.

- It is active *in vitro* against many Gram-negative bacteria including *Pseudomonas aeruginosa, Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), and Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli, Klebsiella* spp., both indole-positive and indole-negative *Proteus, Providencia, Salmonella, Serratia,* and *Shigella* spp. and *Yersinia enterocolitica.*
  Other susceptible Gram-negative bacteria include *Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria* spp.
- Among Gram-positive bacteria it is active against some staphylococci and streptococci, but meticillin-resistant staphylococci, enterococci, and *Listeria monocytogenes* are generally resistant.
- Ceftazidime is active against some anaerobes, although most strains of *Bacteroides fragilis* and *Clostridium difficile* are resistant.

The activity of ceftazidime against *Ps. aeruginosa* and some Enterobacteriaceae may be enhanced by aminoglycosides. Antagonism has been reported *in vitro* between ceftazidime and chloramphenicol.

Resistance. As with cefotaxime, resistance may develop during treatment due to the derepression of chromosomally mediated beta-lactamases. It has been noted particularly in *Pseudomonas* spp. and in Enterobacteriaceae including *Citrobacter, Enterobacter* spp. and *Proteus vulgaris.* Resistance may also occur due to the production of plasmid-mediated extended-spectrum beta-lactamases, particularly in *Klebsiella* spp. and *E. coli.*

Pharmacokinetics

Ceftazidime is given by injection as the sodium salt or in solution with arginine. Mean peak plasma concentrations of 17 and 39 micrograms/mL have been reported about 1 hour after intramuscular doses of 0.5 and 1 g of ceftazidime, respectively. Five minutes after intravenous bolus injections of 0.5, 1, and 2 g of ceftazidime, mean plasma concentrations of 45, 90, and 170 micrograms/mL, respectively, have been reported. The plasma half-life of ceftazidime is about 2 hours, but this is prolonged in patients with renal impairment and in neonates. Clearance may be enhanced in patients with cystic fibrosis. It is about 10% bound to plasma proteins.

Ceftazidime is widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF when the meninges are inflamed. It crosses the placenta and is distributed into breast milk.

Ceftazidime is passively excreted in bile, although only a small proportion is eliminated by this route. It is mainly excreted by the kidneys, almost exclusively by glomerular filtration; probenecid has little effect on the excretion. About 80 to 90% of a dose appears unchanged in the urine within 24 hours. It is removed by haemodialysis and peritoneal dialysis.

Critically ill patients. References.

1. Georges B, *et al*. Population pharmacokinetics of ceftazidime in intensive care unit patients: influence of glomerular filtration rate, mechanical ventilation, and reason for admission. *Antimicrob Agents Chemother* 2009; **53:** 4483–9.

Cystic fibrosis. References.

1. Leeder JS, *et al*. Ceftazidime disposition in acute and stable cystic fibrosis. *Clin Pharmacol Ther* 1984; **36:** 355–62.
2. Hedman A, *et al*. Influence of the glomerular filtration rate on renal clearance of ceftazidime in cystic fibrosis. *Clin Pharmacokinet* 1988; **15:** 57–65.
3. Vinks AATMM, *et al*. Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. *J Antimicrob Chemother* 1997; **40:** 125–33.
4. Bulitta JB, *et al*. Population pharmacokinetic comparison and pharmacodynamic breakpoints of ceftazidime in cystic fibrosis patients and healthy volunteers. *Antimicrob Agents Chemother* 2010; **54:** 1275–82.

The elderly. References.

1. LeBel M, *et al*. Pharmacokinetics of ceftazidime in elderly volunteers. *Antimicrob Agents Chemother* 1985; **28:** 713–15.
2. Higbee MD, *et al*. Pharmacokinetics of ceftazidime in elderly patients. *Clin Pharm* 1989; **8:** 59–62.
3. Sirgo MA, Norris S. Ceftazidime in the elderly: appropriateness of twice-daily dosing. *DICP Ann Pharmacother* 1991; **25:** 284–8.

Hepatic impairment. References.

1. El Touny M, *et al*. Pharmacokinetics of ceftazidime in patients with liver cirrhosis and ascites. *J Antimicrob Chemother* 1991; **28:** 95–100.

Neonates. References.

1. van den Anker JN, *et al*. Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther* 1995; **58:** 650–9.

2. van den Anker JN, *et al.* Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. *Br J Clin Pharmacol* 1995; **40:** 439–43.
3. van den Anker JN, *et al.* Once-daily versus twice-daily administration of ceftazidime in the preterminfant. *Antimicrob Agents Chemother* 1995; **39:** 2048–50.

Renal impairment. References.

1. Welage LS, *et al.* Pharmacokinetics of ceftazidime in patients with renal insufficiency. *Antimicrob Agents Chemother* 1984; **25:** 201–4.
2. Leroy A, *et al.* Pharmacokinetics of ceftazidime in normal and uremic subjects. *Antimicrob Agents Chemother* 1984; **25:** 638–42.
3. Ackerman BH, *et al.* Effect of decreased renal function on the pharmacokinetics of ceftazidime. *Antimicrob Agents Chemother* 1984; **25:** 785–6.
4. Lin N-S, *et al.* Single- and multiple-dose pharmacokinetics of ceftazidime in infected patients with varying degrees of renal function. *J Clin Pharmacol* 1989; **29:** 331–7.
5. Kinowski J-M, *et al.* Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. *Antimicrob Agents Chemother* 1993; **37:** 464–73.
6. Demotes-Mainard F, *et al.* Pharmacokinetics of intravenous and intraperitoneal ceftazidime in chronic ambulatory peritoneal dialysis. *J Clin Pharmacol* 1993; **33:** 475–9.
7. Kim K, *et al.* Pharmacokinetic profiles of ceftazidime after intravenous administration in patients undergoing automated peritoneal dialysis. *Antimicrob Agents Chemother* 2011; **55:** 2523–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crima; Fortum; Pluseptic; Tinacef; Zidima†; ***Austral.***: Fortum; ***Austria***: Fortum; Kefazim; ***Belg.***: Glazidim; Kefadim; ***Braz.***: Ceftazidon; Ceften; Cetaz; Fortaz; Intracef†; Kefadim; ***Canad.***: Fortaz; ***Chile***: Ceftiol; Fortum; ***China***: Ansaiding (安塞定); Dalishu (达力舒); Deding (得定); Fengdaxin (锋达欣); Fortum (复达欣); Kangliding (康力啶); Kefadim (凯复定); Lizhu Ruixin (丽珠锐欣); Ruitading (瑞他定); Shuerxin (舒而欣); Tazime (泰得欣); Xianding (先定); Xintianxin (新天欣); ***Cz.***: Fortum; ***Denm.***: Fortum; Solvetan; ***Fin.***: Glazidim; ***Fr.***: Fortum; Fortumset; ***Ger.***: Fortum; InfectoZidim†; ***Gr.***: Cefin; Ceftaridem; Ftazidime; Lemoxol; Limozidim; Malocef; Novocral; Septax; Sipiel; Solvetan; ***Hong Kong***: Fortum; ***Hung.***: Cetazime†; Fortum; ***India***: Afzid; Ailzid; Amceft; Aritaz; Azid; Bectozid; Betasys; Binzid; C-Zid; Cadzid; Cef-G; Cefazid; Cefcure; Cefdina; Cefid; Ceftabit; Ceftariz; Ceftavir; Ceftaz; Ceftidin; Cefzid; Cefzidime; Cefzy; Cuzid; Czidnate; Efta; Eutum; Fasst; Fectim; Fobidime; Fortacef; Fortum; Forzid; Fotaran; Glifest; Indozid; Izid; Kayzid; Laboceta; Larzid; Lazid; Magnazide; Manzid; Megazid; N-Ciz; Nanocef; Neceft; Nepocef; Nidim; NKCefta; Novazidim; Omnazide; Orzid; Oszid; Zytaz; ***Indon.***: Biozim; Caltum; Cefdime; Ceftamax; Ceftum; Cetazum; Extimon; Fortum; Lacedim; Pharodime; Sodime; Thidim; Veltadim; Yadim; Zefidim; Zibac; Zidifec; ***Irl.***: Fortum; ***Israel***: Fortum†; Septax; ***Ital.***: Ceftim†; Deltazime; Dizatec; Etazim; Fribat; Glazidim; Liotixil; Panzid; Spectrum; Starcef; Tazidif; Tottizim; ***Malaysia***: Cef-4; Cefatum; Fortum; Tazid; Vaxcel Ceftazidime; ***Mex.***: Fenit; Fortum; Izadima; Tagal; Taloken†; Taxifur†; Teczidima; Zadolina; Zidicef†; ***Neth.***: Fortum; Tazalux; ***Norw.***: Fortum; ***NZ***: Fortum; ***Philipp.***: Bactizef; Baxidyme; Ceftaz; Ceftazivit; Ceftibac; Clovizeme; Dimzef; Fivtum; Flazidem; Fortazep†; Fortum; Forzid; Hacef; Megacef; Onetazid; Romacef; Spexil; Tazicef; Tazid; Tazidan; Tazidem; Tazim; Uniranz; Vinsef; Zadim; Zeptrigen; Ziamid; ***Pol.***: Biotum; Fortum; Mirocef†; ***Port.***: Cefortam; Ceftazim; Ceftim; Zidimox; ***Rus.***: Bestum (Бестум); Ceftidin (Цефтидин); Cefzid (Цефзид); Fortoferin (Фортоферин); Fortum (Фортум); Lorazidime (Лоразидим); Orzid (Орзид); Tizime (Тизим); Vicef (Вицеф); ***S.Afr.***: Fortum; Keftaz; Orzid; Tazject; ***Singapore***: Cefazime; Cetazine; Fortum; Parzidim; Tazime; ***Spain***: Fortam; Kefamin†; ***Swed.***: Fortum; ***Switz.***: Fortam; ***Thai.***: Cef-4; Cef-Dime; Cefodime; Ceftime; Dimase†; Fortadim†; Fortum; Forzid†; Tazid†; Zedim; Zeftam; ***Turk.***: Fortum; Iesetum; Zidim; ***UAE***: Negacef; ***UK***: Fortum; Kefadim; ***Ukr.***: Biotum (Бифиформ)†; Ceftadime (Цефтадим); Ceftum (Цефтум); Fortum (Фортум); Orzid (Орзид)†; Zacef (Зацеф); ***USA***: Ceptaz; Fortaz; Tazicef; Tazidime†; ***Venez.***: Betazidim; Biozidima; Cefgram; Fortum.

Multi-ingredient Preparations. ***India***: Combitaz; Fobidime-TZ.

Pharmacopoeial Preparations
BP 2014: Ceftazidime Injection;
USP 36: Ceftazidime for Injection; Ceftazidime Injection.

Cefteram Pivoxil *(rINNM)*

Ceftéram, Pivoxil de; Cefteram pivoxilo; Cefterami Pivoxil; T-2588; Цефтерама Пивоксил.
Pivaloyloxymethyl (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-methyl-2*H*-tetrazol-2-ylmethyl)-3-cephem-4-carboxylic acid.
$C_{22}H_{27}N_9O_7S_2$=593.6
CAS — 82547-58-8 (cefteram); 82547-81-7 (cefteram pivoxil).
UNII — 0OD86RT58C.

Pharmacopoeias. In *Jpn.*

Profile

Cefteram is a cephalosporin antibacterial used for the treatment of susceptible infections. It is given orally as the pivaloyloxymethyl ester, cefteram pivoxil, and doses are expressed in terms of cefteram; 186 mg of cefteram pivoxil is equivalent to about 150 mg of cefteram. The usual dose is 150 to 300 mg daily in 3 divided doses after meals. For severe infections, up to 600 mg daily may be given.

For reference to carnitine deficiency occurring after the administration of some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tomiron (富山龙); ***Jpn***: Tomiron.

Ceftezole Sodium *(rINNM)*

Ceftezol sódico; Ceftézole Sodique; Natrii Ceftezolum; Натрий Цефтезол.
Sodium (7*R*)-7-[2-(1*H*-tetrazol-1-yl)acetamido]-3-(1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylate.
$C_{13}H_{11}N_8NaO_4S_3$=462.5
CAS — 26973-24-0 (ceftezole); 41136-22-5 (ceftezole sodium).
ATC — J01DB12.
ATC Vet — QJ01DB12.
UNII — 3NHZ4Y117H.

Pharmacopoeias. In *Chin.*

Profile

Ceftezole is a cephalosporin antibacterial with properties similar to those of cefalotin (p. 235.1). It is given as the sodium salt but doses are expressed in terms of the base; 1.05 g of ceftezole sodium is equivalent to about 1 g of ceftezole. The usual dose is 2 to 4 g daily by intramuscular injection in 2 or 3 divided doses.

Sodium content. Each g of ceftezole sodium contains about 2.16 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi An Lai (必安来); Luohao (罗昊); Tezacef (特子社复); Yi Ti Xin (益替欣).

Ceftibuten *(BAN, USAN, rINN)*

Ceftibutène; Ceftibuteno; Ceftibutenum; Keftibuteeni; 7432-S; Sch-39720; Цефтибутен.
7-[2-(2-Amino-1,3-thiazol-4-yl)-4-carboxyisocrotonamide]-3-cephem-4-carboxylic acid.
$C_{15}H_{14}N_4O_6S_2$=410.4
CAS — 97519-39-6.
ATC — J01DD14.
ATC Vet — QJ01DD14.
UNII — IW71N46B4Y (ceftibuten); 62F4443RWP (ceftibuten dihydrate).

Pharmacopoeias. *Jpn* includes the dihydrate.

Uses and Administration

Ceftibuten is a third-generation cephalosporin antibacterial used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria including urinary-tract and respiratory-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftibuten is given orally as the dihydrate, but doses are expressed in terms of anhydrous ceftibuten; 435 mg of ceftibuten dihydrate is equivalent to about 400 mg of anhydrous ceftibuten. The usual adult dose is 400 mg once daily on an empty stomach.

The dose of ceftibuten may need to be reduced in patients with renal impairment, see p. 254.3.

For details of doses in children, see p. 254.2.

Reviews.

1. Wiseman LR, Balfour JA. Ceftibuten: review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1994; **47:** 784–808.
2. Nelson JD, McCracken GH (eds). Ceftibuten: a new orally active cephalosporin for pediatric infections. *Pediatr Infect Dis J* 1995; **14** (suppl): S76–S133.
3. Guay DRP. Ceftibuten: a new expanded-spectrum oral cephalosporin. *Ann Pharmacother* 1997; **31:** 1022–33.
4. Owens RC, *et al.* Ceftibuten: an overview. *Pharmacotherapy* 1997; **17:** 707–20.

Administration in children. Ceftibuten may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children over 6 months of age and weighing 45 kg or less may be given 9 mg/kg daily as a single oral dose.

In studies,[1] the same dose for 10 days has proved safe and effective for the management of urinary-tract infection in children from 1 month of age.

1. Mårild S, *et al.* Ceftibuten versus trimethoprim-sulfamethoxazole for oral treatment of febrile urinary tract infection in children. *Pediatr Nephrol* 2009; **24:** 521–6.

Administration in renal impairment. Doses of ceftibuten should be reduced in patients with moderate to severe renal impairment. The following oral doses based on creatinine clearance (CC) may be used:

- CC 30 to 49 mL/minute: 200 mg once daily
- CC 5 to 29 mL/minute: 100 mg once daily

Patients undergoing haemodialysis 2 or 3 times weekly may be given a dose of 400 mg after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The most frequently reported adverse effects of ceftibuten are gastrointestinal disturbances, especially diarrhoea, and headache.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ceftibuten as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Antimicrobial Action

As for Cefixime, p. 241.1. It is less active *in vitro* against *Streptococcus pneumoniae.*

References.

1. Shawar R, *et al.* Comparative in vitro activity of ceftibuten (Sch-39720) against bacterial enteropathogens. *Antimicrob Agents Chemother* 1989; **33:** 781–4.
2. Bragman SGL, Casewell MW. The in-vitro activity of ceftibuten against 475 clinical isolates of Gram-negative bacilli, compared with cefuroxime and cefadroxil. *J Antimicrob Chemother* 1990; **25:** 221–6.
3. Wise R, *et al.* Ceftibuten—in-vitro activity against respiratory pathogens, β-lactamase stability and mechanism of action. *J Antimicrob Chemother* 1990; **26:** 209–13.
4. Maioli E, *et al.* In vitro activity of ceftibuten at sub-inhibitory concentrations in comparison with other antibiotics against respiratory and urinary tract pathogens. *J Chemother* 2007; **19:** 152–60.

Pharmacokinetics

Ceftibuten is rapidly absorbed from the gastrointestinal tract, although the rate and extent of absorption are somewhat decreased by the presence of food. Peak plasma concentrations of about 17 micrograms/mL occur about 2 hours after a 400-mg dose. The plasma half-life of ceftibuten is about 2.0 to 2.3 hours and is prolonged in patients with renal impairment. Ceftibuten is 65 to 77% bound to plasma proteins.

Ceftibuten distributes into middle-ear fluid and bronchial secretions. About 10% of a dose is converted to the *trans*-isomer, which has about one-eighth of the activity of the *cis*-isomer. Ceftibuten is excreted mainly in the urine and also in the faeces. Significant amounts are removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Keimax; ***Gr.***: Caedax; ***Hong Kong***: Cedax; ***Hung.***: Cedax; ***India***: Procadax; ***Ital.***: Cedax; Isocef; ***Jpn***: Seftem; ***Malaysia***: Cedax; ***Mex.***: Cedax; ***Neth.***: Cedax; ***Philipp.***: Cedax†; ***Pol.***: Cedax; ***Port.***: Caedax; ***Rus.***: Cedax (Цедекс); ***Singapore***: Cedax; ***Spain***: Biocef†; Cedax; ***Swed.***: Cedax; ***Switz.***: Cedax; ***Thai.***: Cedax; ***Turk.***: Cedax; ***Ukr.***: Cedax (Цедекс); ***USA***: Cedax; ***Venez.***: Cedax.

Ceftiofur *(BAN, rINN)*

Ceftiofurum; Keftiofuuri; Цефтиофур.
CAS — 80370-57-6.
ATC Vet — QJ01DD90; QJ51DA91.
UNII — 83JL932I1C.

Ceftiofur Hydrochloride *(BANM, USAN, rINNM)*

Ceftiofur, Chlorhydrate de; Ceftiofuri Hydrochloridum; Hidrocloruro de ceftiofur; U-64279A; Цефтиофура Гидрохлорид.
(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)-glyoxylamido]-3-mercaptomethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7²-(*Z*)-(*O*-methyloxime), 2-furoate (ester), monohydrochloride.
$C_{19}H_{17}N_5O_7S_3$.HCl=560.0
CAS — 103980-44-5.
ATC Vet — QJ01DD90; QJ51DA91.
UNII — 6822A07436.

Ceftiofur Sodium *(BANM, USAN, rINNM)*

Ceftiofur sódico; Ceftiofur Sodique; Ceftiofurum natricum; CM-31-916; Natrii Ceftiofurum; U-64279E; Натрий Цефтиофур.

$C_{19}H_{16}N_5NaO_7S_3$=545.5

CAS — 104010-37-9.

ATC Vet — QJ01DD90; QJ51DA91.

UNII — NHI34IS56E.

Profile

Ceftiofur is a cephalosporin antibacterial used as the hydrochloride and sodium salts in veterinary practice.

Ceftizoxime Sodium *(BANM, USAN, rINNM)*

Ceftizoxima sódica; Ceftizoxime Sodique; Ceftizoximnatrium; Ceftizoximum Natricum; FK-749; FR-13749; Keftitsoksiiminatrium; Natrii Ceftizoximum; Seftizoksim Sodyum; SKF-88373-Z; Натрий Цефтизоксим.

Sodium (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate.

$C_{13}H_{12}N_5NaO_5S_2$=405.4

CAS — 68401-81-0 (ceftizoxime); 68401-82-1 (ceftizoxime sodium).

ATC — J01DD07.

ATC Vet — QJ01DD07.

UNII — 26337D5X88.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Ceftizoxime Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Stability. References.

1. Lesko AB, *et al.* Ceftizoxime stability in iv solutions. *DICP Ann Pharmacother* 1989; **23**: 615–18.

Uses and Administration

Ceftizoxime is a third-generation parenteral cephalosporin antibacterial used for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structures, genito-urinary and respiratory tracts, and gynaecological infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftizoxime is given as the sodium salt by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion. If 2 g of ceftizoxime is injected intramuscularly the dose should be divided between sites.

Doses are expressed in terms of the equivalent amount of ceftizoxime; 1.06 g of ceftizoxime sodium is equivalent to about 1 g of ceftizoxime. It is usually given in an adult dose of 1 to 2 g every 8 to 12 hours. In severe infections 2 to 4 g may be given intravenously every 8 hours; doses up to 2 g every 4 hours have been given in life-threatening infections.

For the treatment of uncomplicated urinary-tract infections, a dose of 500 mg every 12 hours is used. A single intramuscular dose of 1 g has been given in uncomplicated gonorrhoea.

The dose of ceftizoxime may need to be reduced in patients with renal impairment, see p. 255.1. For details of doses in children, see also p. 255.1.

References.

1. Richards DM, Heel RC. Ceftizoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1985; **29:** 281–329.

Administration in children. Ceftizoxime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion. The American Academy of Pediatrics[1] recommends that children aged 1 month and older may be given 150 mg/kg daily in 3 divided doses (to a maximum daily dose of 3 to 4 g) for mild to moderate infections; the dose may be increased to 150 to 200 mg/kg daily in 3 or 4 divided doses (to a maximum daily dose of 6 to 12 g) in severe infections.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of ceftizoxime should be modified in renal impairment; after a loading dose of 0.5 to 1 g, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of the infection:

- CC 50 to 79 mL/minute: 0.5 to 1.5 g every 8 hours
- CC 5 to 49 mL/minute: 0.25 to 1 g every 12 hours
- CC less than 5 mL/minute: 250 to 500 mg every 24 hours or 0.5 to 1 g every 48 hours, after dialysis.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p. 244.3.

Sodium content. Each g of ceftizoxime sodium contains about 2.5 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of ceftizoxime.

Antimicrobial Action

As for Cefotaxime Sodium, p. 244.3, although ceftizoxime has no active metabolite.

Pharmacokinetics

After intramuscular injection of 0.5 and 1 g of ceftizoxime, mean peak plasma concentrations of about 14 and 39 micrograms/mL respectively have been reported after 1 hour. The plasma half-life of ceftizoxime is about 1.7 hours and is prolonged in neonates and in renal impairment. Ceftizoxime is 30% bound to plasma proteins.

Ceftizoxime is widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF when the meninges are inflamed. It crosses the placenta and low concentrations have been detected in breast milk.

Nearly all of a dose is excreted unchanged in the urine within 24 hours of dosage, thus achieving high urinary concentrations. Ceftizoxime is excreted by tubular secretion as well as glomerular filtration and giving it with probenecid results in higher and more prolonged plasma concentrations. Some ceftizoxime is removed by haemodialysis.

Neonates. References.

1. Fujii R. Investigation of half-life and clinical effects of ceftizoxime in premature and newborn infants. *Drug Invest* 1990; **2:** 143–9.
2. Reed MD, *et al.* Ceftizoxime disposition in neonates and infants during the first six months of life. *DICP Ann Pharmacother* 1991; **25:** 344–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Dalijing (达力净); Daliqing (达力清); Epocelin (益保世灵); Zhuobisha (卓必沙); ***India***: Cefizox; Eldcef; Epocelin; ***Indon.***: Cefim; Cefizox; Tizos; ***Ital.***: Eposerin; ***Jpn***: Epocelin; ***Philipp.***: Tergecin†; Unizox; Zoxim; ***Port.***: Cefizox; ***Turk.***: Cefizox; ***USA***: Cefizox†.

Pharmacopoeial Preparations

USP 36: Ceftizoxime for Injection; Ceftizoxime Injection.

Ceftobiprole Medocaril *(USAN, rINN)*

BAL-5788-001; BAL-5788; BAL-9141 (ceftobiprole); Ceftobiprol medocarilo; Ceftobiprole Médocaril; Ceftobiprolum Medocarilum; Ro-65-5788; Ro-63-9141 (ceftobiprole); Цефтобипрол Медокарил.

(6*R*,7*R*)-7-[(2*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetamido]-3-({(*E*){(3′*R*)-1′-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]-2-oxo-(1,3′-bipyrrolidin)-3-ylidene}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{26}H_{26}N_8O_{11}S_2$=690.7

CAS — 209467-52-7 (ceftobiprole); 376653-43-9 (ceftobiprole medocaril); 252188-71-9 (ceftobiprole medocaril sodium).

ATC — J01DI01.

ATC Vet — QJ01DI01.

UNII — N99027V28J.

NOTE. Ceftobiprole medocaril is normally formulated as ceftobiprole medocaril sodium ($C_{26}H_{25}N_8NaO_{11}S_2$=712.6).

Profile

Ceftobiprole is a broad-spectrum cephalosporin antibacterial used in the treatment of complicated skin and skin structure infections caused by susceptible organisms, including meticillin-resistant *Staphylococcus aureus*.

It is given by intravenous infusion over 1 to 2 hours as the prodrug, ceftobiprole medocaril (formulated as its sodium salt); doses are expressed in terms of ceftobiprole; 1.33 g of ceftobiprole medocaril sodium is equivalent to about 1 g of ceftobiprole. The usual dose is the equivalent of 500 mg every 8 or 12 hours. The dose of ceftobiprole may need to be reduced in patients with renal impairment, see p. 255.3.

References.

1. Noel GJ. Clinical profile of ceftobiprole, a novel beta-lactam antibiotic. *Clin Microbiol Infect* 2007; **13** (suppl 2): 25–9.
2. Murthy B, Schmitt-Hoffmann A. Pharmacokinetics and pharmacodynamics of ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity. *Clin Pharmacokinet* 2008; **47:** 21–33.
3. Zhanel GG, *et al.* Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol* 2008; **9:** 245–54.
4. Deresinski SC. The efficacy and safety of ceftobiprole in the treatment of complicated skin and skin structure infections: evidence from 2 clinical trials. *Diagn Microbiol Infect Dis* 2008; **61:** 103–9.
5. Anderson SD, Gums JG. Ceftobiprole: an extended-spectrum anti-methicillin-resistant Staphylococcus aureus cephalosporin. *Ann Pharmacother* 2008; **42:** 806–16.
6. Vidaillac C, Rybak MJ. Ceftobiprole: first cephalosporin with activity against methicillin-resistant Staphylococcus aureus. *Pharmacotherapy* 2009; **29:** 511–25.
7. Barbour A, *et al.* Ceftobiprole: a novel cephalosporin with activity against Gram-positive and Gram-negative pathogens, including methicillin-resistant Staphylococcus aureus (MRSA). *Int J Antimicrob Agents* 2009; **34:** 1–7.

Administration in renal impairment. Reduced doses of ceftobiprole may be necessary in patients with moderate to severe renal impairment. Suggested intravenous doses should be given over 2 hours and are based on creatinine clearance (CC):

- CC 30 to 49 mL/minute: 500 mg every 12 hours
- CC less than 30 mL/min: 250 mg every 12 hours

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Zeftera†; ***Rus.***: Zeftera (Зефтера).

Ceftriaxone Sodium *(BANM, USAN, rINNM)*

Ceftriakson sodowy; Ceftriaksono natrio druska; Ceftriaxon-Dinatrium; Ceftriaxon sodná sůl trihemihydrát; Ceftriaxona sódica; Ceftriaxone sodique; Ceftriaxonnatrium; Ceftriaxonnátrium; Ceftriaxonum natricum; Ceftriaxonum Natricum Trihemihydricum; Keftriaksoninatrium; Natrii Ceftriaxonum; Ro-13-9904; Ro-13-9904/000 (ceftriaxone); Seftriakson Sodyum; Натрий Цефтриаксон.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl) thiomethyl]-3-cephem-4-carboxylic acid, disodium salt, sesquaterhydrate.

$C_{18}H_{16}N_8Na_2O_7S_3{,}3½H_2O$=661.6

CAS — 73384-59-5 (ceftriaxone); 74578-69-1 (anhydrous ceftriaxone sodium); 104376-79-6 (ceftriaxone sodium sesquaterhydrate).

ATC — J01DD04.

ATC Vet — QJ01DD04.

UNII — 023Z5BR09K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ceftriaxone Sodium). A semisynthetic product derived from a fermentation product. An almost white to yellowish, slightly hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in methyl alcohol. A 12% solution in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Ceftriaxone Sodium). A white to yellowish-orange crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Incompatibility. UK licensed product information warns of incompatibility if ceftriaxone sodium is mixed with calcium-containing solutions or with aminoglycosides, amsacrine, fluconazole, labetalol, or vancomycin. Published reports of incompatibility have included that between ceftriaxone and vancomycin[1] or pentamidine.[2]

1. Pritts D, Hancock D. Incompatibility of ceftriaxone with vancomycin. *Am J Hosp Pharm* 1991; **48:** 77.
2. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.

Stability. References.

1. Nahata MC. Stability of ceftriaxone sodium in peritoneal dialysis solutions. *DICP Ann Pharmacother* 1991; **25:** 741–2.
2. Canton E, Esteban MJ. Stability of ceftriaxone solution. *J Antimicrob Chemother* 1992; **30:** 397–8.
3. Bailey LC, *et al.* Stability of ceftriaxone sodium in injectable solutions stored frozen in syringes. *Am J Hosp Pharm* 1994; **51:** 2159–61.
4. Plumridge RJ, *et al.* Stability of ceftriaxone sodium in polypropylene syringes at -20, 4, and 20 degreesC. *Am J Health-Syst Pharm* 1996; **53:** 2320–3.

Uses and Administration

Ceftriaxone is a third-generation cephalosporin antibacterial used for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structures, genito-urinary tract (including gonorrhoea), respiratory tract, gynaecological infections, and early Lyme disease. It is also used for infections in

neutropenic patients and surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftriaxone is given as the sodium salt by slow intravenous injection over at least 2 to 4 minutes, by intermittent intravenous infusion over at least 30 minutes, or by deep intramuscular injection. If more than 1 g is to be injected intramuscularly then the dose should be divided between more than one site. Doses are expressed in terms of the equivalent amount of ceftriaxone; 1.19 g of ceftriaxone sodium is equivalent to about 1 g of ceftriaxone.

The usual dose is 1 to 2 g daily as a single dose or in two divided doses; in severe infections up to 4 g daily may be given. A single intramuscular dose of 250 mg is recommended for the treatment of uncomplicated gonorrhoea.

For surgical infection prophylaxis, a single dose of 1 g may be given 0.5 to 2 hours before surgery; a 2-g dose is suggested before colorectal surgery.

Although not licensed for the prevention of secondary cases of meningococcal meningitis, the *BNF* suggests a single intramuscular dose of 250 mg may be used.

The dose of ceftriaxone may need to be modified in patients with renal impairment, see p. 256.1. For details of doses in children, see also p. 256.1.

References.
1. Brogden RN, Ward A. Ceftriaxone: a reappraisal of its antibacterial activity and pharmacokinetic properties, and an update on its therapeutic use with particular reference to once-daily administration. *Drugs* 1988; **35:** 604–45.
2. Lamb HM, *et al*. Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. *Drugs* 2002; **62:** 1041–89.
3. Bijie H, *et al*. In vitro activity, pharmacokinetics, clinical efficacy, safety and pharmacoeconomics of ceftriaxone compared with third and fourth generation cephalosporins: review. *J Chemother* 2005; **17:** 3–24.
4. Woodfield JC, *et al*. A meta-analysis of randomized, controlled trials assessing the prophylactic use of ceftriaxone; a study of wound, chest, and urinary infections. *World J Surg* 2009; **33:** 2538–50.

Administration in children. Ceftriaxone may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by deep intramuscular injection, or intravenously as a slow injection over 2 to 4 minutes, or by intermittent intravenous infusion over 30 to 60 minutes; intravenous doses in neonates should be given over 60 minutes.

The *BNFC* recommends the following doses:

- neonates: 20 to 50 mg/kg once daily
- children 1 month of age and older and weighing less than 50 kg: 50 mg/kg once daily, increased to up to 80 mg/kg daily in severe infections and meningitis
- older children and those weighing more than 50 kg: 1 g daily, increased to 2 to 4 g daily in severe infections and meningitis

In the USA, the American Academy of Pediatrics[1] suggests neonates may be given a dose of 50 mg/kg every 24 hours. Children 1 month and older may be given a dose of 50 to 75 mg/kg (maximum 1 g) once daily for mild to moderate infections, or 100 mg/kg daily in 1 or 2 divided doses (to a maximum daily dose of 2 to 4 g) in severe infections.

The *BNFC* also permits the use of ceftriaxone in the following unlicensed indications:

for the prevention of secondary cases of meningococcal meningitis

- children from 1 month to 12 years of age may be given 125 mg as a single intramuscular dose
- those older than 12 years may be given 250 mg as a single intramuscular dose

for the prevention of secondary cases of *Haemophilus influenzae* type b in children who cannot take rifampicin

- from 1 month to 12 years of age ceftriaxone may be given by intravenous infusion at a dose of 50 mg/kg (to a maximum of 1 g) once daily for 2 days
- those older than 12 years may be given 1 g once daily for 2 days either by intramuscular injection or intravenously

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in hepatic and renal impairment. A reduction in dosage of ceftriaxone may be necessary in patients with severe renal impairment (creatinine clearance below 10 mL/minute), in whom the daily parenteral dose should not exceed 2 g. In patients undergoing dialysis, and in those with both renal and hepatic impairment, plasma concentrations of ceftriaxone should be monitored to determine whether dose adjustment is needed.

Meningitis. A meta-analysis[1] of randomised controlled studies to evaluate the effectiveness and safety of short-course antibacterial treatment for community-acquired bacterial meningitis in children reported no difference between short-course (4 to 7 days) and standard long-course (7 to 14 days) treatment with intravenous ceftriaxone in terms of clinical success, long-term neurological complications, long-term hearing impairment, total adverse events, or secondary nosocomial infections.

An international, placebo-controlled, study[2] of 5 or 10 days of treatment with intravenous ceftriaxone in 1004 children aged 2 months to 12 years (including those with HIV infection) with bacterial meningitis concluded that parenteral ceftriaxone could be safely discontinued in those children who are stable by day 5 of treatment. The authors considered that prompt treatment with antibacterials were probably more important in reducing morbidity and mortality than a long-course treatment regimen.

1. Karageorgopoulos DE, *et al*. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. *Arch Dis Child* 2009; **94:** 607–14.
2. Molyneux E, *et al*. CSF 5 Study Group. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. *Lancet* 2011; **377:** 1837–45.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p. 244.3. Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of ceftriaxone; diarrhoea may occur more often, especially in children.

Biliary sludge or pseudolithiasis due to a precipitate of calcium ceftriaxone has been seen occasionally in patients given ceftriaxone. Similarly, deposition of the calcium salt has occurred rarely in the urine. Isolated cases of death in term or premature neonates have been associated with precipitation of calcium ceftriaxone in lungs and kidneys, and in some of these cases a calcium-containing product has been given by a different route or line, or at a different time. The FDA therefore contra-indicates the use of ceftriaxone and intravenous calcium-containing products in neonates 28 days of age and younger. In older patients they consider the risk of precipitation to be low and ceftriaxone and calcium-containing products may be given sequentially, provided the infusion lines are thoroughly flushed between infusions. Ceftriaxone should not be given together with intravenous calcium-containing solutions via a Y-site in any age group.

Ceftriaxone is highly protein bound and is able to displace bilirubin from albumin binding sites, causing hyperbilirubinaemia; its use should be avoided in jaundiced neonates. Use is also contra-indicated in premature neonates (postmenstrual age less than 41 weeks).

Neutropenia has been reported with most cephalosporins; a complex mechanism has been attributed to that associated with ceftriaxone. There have been rare reports of fatal haemolysis associated with ceftriaxone.

Although ceftriaxone has an *N*-methylthiotriazine ring rather than an *N*-methylthiotetrazole side-chain, it might still have the potential to cause hypoprothrombinaemia.

Breast feeding. A study of drug distribution and protein binding between maternal blood and breast milk post partum in a 26-year-old woman given ceftriaxone 2 g daily by intravenous infusion for 10 days found that penetration of ceftriaxone into breast milk increased at these doses as protein binding capacity was saturated, although no adverse effects occurred in the infant.[1] The authors advised caution in breast-feeding mothers given acidic drugs which also have high protein binding such as ceftriaxone[1] although, on the basis that no adverse effects have been seen in breast-fed infants whose mothers were receiving ceftriaxone, the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Bourget P, *et al*. Ceftriaxone distribution and protein binding between maternal blood and milk postpartum. *Ann Pharmacother* 1993; **27:** 294–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the biliary tract. Using abdominal ultrasonography, biliary sludge or pseudolithiasis was found in about 40% of severely ill children being treated with high doses of ceftriaxone[1] and was later reported in adults.[2-5] The sludge has been identified as a calcium salt of ceftriaxone.[6] Patients are often asymptomatic and the sludge usually dissolves once ceftriaxone is stopped. Gallstones with ceftriaxone as a major component have been identified in a patient given long-term high-dose treatment.[7] Similarly, a bile-duct stone composed of ceftriaxone occurred with high-dose ceftriaxone in a child.[8] In another report, intractable hiccups were associated with ceftriaxone-related pseudolithiasis in a 10-year-old boy.[9]

1. Schaad UB, *et al*. Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet* 1988; **ii:** 1411–13.
2. Pigrau C, *et al*. Ceftriaxone-associated biliary pseudolithiasis in adults. *Lancet* 1989; **ii:** 165.
3. Heim-Duthoy KL, *et al*. Apparent biliary pseudolithiasis during ceftriaxone therapy. *Antimicrob Agents Chemother* 1990; **34:** 1146–9.
4. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy* 2005; **25:** 1389–95.
5. Rienstra M, *et al*. Ceftriaxone-associated biliary pseudolithiasis. *Neth J Med* 2009; **67:** 113–4.
6. Park HZ, *et al*. Ceftriaxone-associated gallbladder sludge: identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology* 1991; **100:** 1665–70.
7. Lopez AJ, *et al*. Ceftriaxone-induced cholelithiasis. *Ann Intern Med* 1991; **115:** 712–14.
8. Robertson FM, *et al*. Ceftriaxone choledocholithiasis. *Pediatrics* 1996; **98:** 133–5.
9. Bonioli E, *et al*. Pseudolithiasis and intractable hiccups in a boy receiving ceftriaxone. *N Engl J Med* 1994; **331:** 1532.

Effects on the blood. References.
1. Haubenstock A, *et al*. Hypoprothrombinaemic bleeding associated with ceftriaxone. *Lancet* 1983; **i:** 1215–16.
2. Rey D, *et al*. Ceftriaxone-induced granulopenia related to a peculiar mechanism of granulopoiesis inhibition. *Am J Med* 1989; **87:** 591–2.
3. Bernini JC, *et al*. Fatal hemolysis induced by ceftriaxone in a child with sickle cell anemia. *J Pediatr* 1995; **126:** 813–15.
4. Lascari AD, Amyot K. Fatal hemolysis caused by ceftriaxone. *J Pediatr* 1995; **126:** 816–17.
5. Scimeca PG, *et al*. Hemolysis after treatment with ceftriaxone. *J Pediatr* 1996; **128:** 163.
6. Moallem HJ, *et al*. Ceftriaxone-related fatal hemolysis in an adolescent with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1998; **133:** 279–81.
7. Meyer O, *et al*. Fatal immune haemolysis due to a degradation product of ceftriaxone. *Br J Haematol* 1999; **105:** 1084–5.
8. Viner Y, *et al*. Severe hemolysis induced by ceftriaxone in a child with sickle-cell anemia. *Pediatr Infect Dis J* 2000; **19:** 83–5.
9. Seltsam A, Salama A. Ceftriaxone-induced immune haemolysis: two case reports and a concise review of the literature. *Intensive Care Med* 2000; **26:** 1390–4.
10. Citak A, *et al*. Ceftriaxone-induced haemolytic anaemia in a child with no immune deficiency or haematological disease. *J Paediatr Child Health* 2002; **38:** 209–10.

Effects on the pancreas. References.
1. Zimmermann AE, *et al*. Ceftriaxone-induced acute pancreatitis. *Ann Pharmacother* 1993; **27:** 36–7.
2. Maranan MC, *et al*. Gallstone pancreatitis caused by ceftriaxone. *Pediatr Infect Dis J* 1998; **17:** 662–3.

Neonates. References to the displacement of bilirubin by ceftriaxone in neonates.
1. Gulian J-M, *et al*. Bilirubin displacement by ceftriaxone in neonates: evaluation by determination of 'free' bilirubin and erythrocyte-bound bilirubin. *J Antimicrob Chemother* 1987; **19:** 823–9.
2. Fink S, *et al*. Ceftriaxone effect on bilirubin-albumin binding. *Pediatrics* 1987; **80:** 873–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ceftriaxone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of ceftriaxone sodium contains about 3.0 mmol of sodium.

Interactions

Ceftriaxone has an *N*-methylthiotriazine side-chain and may have the potential to increase the effects of anticoagulants and to cause a disulfiram-like reaction with alcohol. For contra-indications to the use of ceftriaxone with calcium-containing products see Adverse Effects and Precautions, above.

Unlike that of many cephalosporins, the renal excretion of ceftriaxone is not affected by probenecid.

Antimicrobial Action

As for Cefotaxime Sodium, p. 244.3, although ceftriaxone has no active metabolite.

References.
1. Goldstein FW, *et al*. Resistance to ceftriaxone and other β-lactams in bacteria isolated in the community. *Antimicrob Agents Chemother* 1995; **39:** 2516–19.

Pharmacokinetics

Ceftriaxone has nonlinear dose-dependent pharmacokinetics because of its protein binding; about 85 to 95% is bound to plasma proteins depending on the concentration of ceftriaxone.

Mean peak plasma concentrations of about 40 and 80 micrograms/mL have been reported 2 hours after intramuscular injection of 500 mg and 1 g of ceftriaxone respectively. The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 and 9 hours; it may be prolonged in neonates. The half-life does not change appreciably in patients with moderate renal impairment, but it may be prolonged in severe impairment especially when there is also hepatic impairment.

Ceftriaxone is widely distributed in body tissues and fluids. It crosses both inflamed and non-inflamed meninges, generally achieving therapeutic concentrations in the CSF. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations occur in bile.

About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found

in the faeces as unchanged drug and microbiologically inactive compounds.

Reviews.
1. Hayton WL, Stoeckel K. Age-associated changes in ceftriaxone pharmacokinetics. *Clin Pharmacokinet* 1986; **11:** 76–86.
2. Yuk JH, *et al*. Clinical pharmacokinetics of ceftriaxone. *Clin Pharmacokinet* 1989; **17:** 223–35.
3. Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. *Clin Pharmacokinet* 2001; **40:** 685–94.
4. Garot D, *et al*. Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. *Br J Clin Pharmacol* 2011; **72:** 758–67.

Hepatic impairment. References.
1. Stoeckel K, *et al*. Single-dose ceftriaxone kinetics in liver insufficiency. *Clin Pharmacol Ther* 1984; **36:** 500–9.
2. Hary L, *et al*. The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; **36:** 613–16.
3. Toth A, *et al*. Pharmacokinetics of ceftriaxone in liver-transplant recipients. *J Clin Pharmacol* 1991; **31:** 722–8.

Pregnancy. References.
1. Bourget P, *et al*. Pharmacokinetics and protein binding of ceftriaxone during pregnancy. *Antimicrob Agents Chemother* 1993; **37:** 54–9.

Renal impairment. The pharmacokinetics of ceftriaxone are not markedly altered in mild to moderate renal impairment,[1] but the half-life can be prolonged in severe or end-stage renal disease.[1-4] Ceftriaxone is generally not removed by peritoneal dialysis[4] or by haemodialysis[1-3] although a decrease in half-life has been reported during haemodialysis.[5] In many patients no alteration in dosage is necessary, but some individuals have reduced non-renal clearance despite apparently normal hepatic function.[2,3] It is advisable to monitor plasma ceftriaxone in patients with severe renal impairment and unknown non-renal clearance.

1. Patel IH, *et al*. Ceftriaxone pharmacokinetics in patients with various degrees of renal impairment. *Antimicrob Agents Chemother* 1984; **25:** 438–42.
2. Stoeckel K, *et al*. Single-dose ceftriaxone kinetics in functionally anephric patients. *Clin Pharmacol Ther* 1983; **33:** 633–41.
3. Cohen D, *et al*. Pharmacokinetics of ceftriaxone in patients with renal failure and in those undergoing hemodialysis. *Antimicrob Agents Chemother* 1983; **24:** 529–32.
4. Ti T-Y, *et al*. Kinetic disposition of intravenous ceftriaxone in normal subjects and patients with renal failure on hemodialysis or peritoneal dialysis. *Antimicrob Agents Chemother* 1984; **25:** 83–7.
5. Garcia RL, *et al*. Single-dose pharmacokinetics of ceftriaxone in patients with end-stage renal disease and hemodialysis. *Chemotherapy* 1988; **34:** 261–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acantex; Bioteral; Cefomax; Ceftriaz; Exempla; Rivacefin; Soltrimox; ***Austral.***: Rocephin; ***Austria***: Cefotrix; Rocephin; ***Belg.***: Rocephine; ***Braz.***: Ceftriax; Glicocef†; Keftron; Mesporan†; Neocefotriona; Prodoxin†; Rocefin; Triaxin; Triaxon; Triaxton; Trioxina; ***Canad.***: Rocephin†; ***Chile***: Acantex; Grifotriaxona; ***China***: Ansailong (安塞隆); Cefin (泛生舒复); Dezhi (得治); Likang Kesong (丽康可松); Livzonphin (丽珠芬); Locekin (罗塞秦); Oframax (果复每); Rocephin (罗氏芬); Xianqin (先嗪); ***Cz.***: Lendacin; Megion†; Samixon; ***Denm.***: Cefotrix; Rocephalin; ***Fin.***: Rocephalin; ***Fr.***: Rocephine; Triacefan; ***Ger.***: Cefotrix; Rocephin; ***Gr.***: Antibacin; Azatyl; Bresec; Ceftrixon; Ceriaxon; Farcef; Fredofol; Gladius; Glorixone; Infeflox; Labilex; Medaxone; Riaxon; Rocephin; Rolisporin; Travilan; Ugotrex; Veracol; ***Hong Kong***: Medaxonum; Mesporin; Rocephin; Zoxon; ***Hung.***: Cefotrix†; Lendacin; Megion; Rocephin; ***India***: Acticef; Afzone; Alitax; Alkaceff; Alnacef; Amcef; Arixon; Avcef; Axocare; Axone; Axtrum; Becef; Bintrax; Broadcef; Brucef; C Tri; C-Tech; C-Tri; Cadizone; Cafage; Cafzone; Cameo; Cebay TRX; Cef; Cefa Kit; Cefaday; Cefamed; Cefast; Cefaxone; Cefcin; Cefera; Cefezone; Cefmac; Cefmol; Cefoat; Cefocef; Cefogram; Cefotec; Cefritz-S; Cefritz; Cefs; Cefset; Cefsine; Ceftraset; Ceftrax; Ceftrian; Ceftril; Ceftrisone; Ceftrol; Ceftron; Cefwon; Cefxi; Cefzox; Cepoxit-CX; Ceptradin; Cetazone; Cetriax; Cetzone; Cezone; Champione; Chuncif; Ciforion; Ciplacef; Comtrix; Controx; Costrex; Cotyx; Cruzone; CSI; CT Ceff; CT-Xone; CTX; Cucef; Cuxone; CX-One; D-Cef; Daltrix; Deczone; Dewcef; E-Cef; Efectal; Efoceft; Eftanu; Ekcef; Emtri; Emtriaxone; Eracef; Estxone; Extacef-I; Fexon; Finetriax; Fixi; Forone; Geminate; Glen; Glicef; Gloriax; Gramocef; Gutencef; Hicef; Hocef; I-Tone; Ifytrox; Incef; Indocef; Indoxone; Infoxon; Intax; Ivixone; Kafi; Keftra; Kexone; Labxone; Lezone; Lifecare; Lisel; Lyceft; Magtrax; Marcef; Mediceft; Mepcef; Mintrax; Mocef; Monocef; Monotax; Multi-Xone; Nefzon; Nexef-O; Nizotrax; NKCef; Nosocef; Novaceft; Novatrax; Nu Axiom; Nutracip; O-Cef; Oframax; Omisafe; Omna One; Oncef; Opticef; Ostri; Oxy; Pancef; Parcef; Powercef; Safelo; ***Indon.***: Betrix; Biotriax; Bioxon; Broadced; Brospec; Cefaxon; Cefriex; Cefsix; Ceftrox; Cefxon; Cephaflox; Cocefin; Criax; Ecotrixon; Elpicef; Erocef; Foricef; Gracef; Intricef; Intrix; Renxon; Rixone; Rocephin; Socef; Starxon; Terfacef; Termicef; Tricefin; Trijec; Trixon; Tyason; Zeftrix; ***Irl.***: Rocephin; ***Israel***: Keftriaxone; Pan-Ceftriaxone; Rocephin; Triax†; ***Ital.***: Axobat; Bixon; Cefrag; Davixon; Daytrix; Deixim; Diaxone; Eftry; Eraxitron; Fidato; Frineg; Kocefan; Monoxar; Nilson; Panatrix; Pantoxon; Ragex; Rocefin; Setriox; Sirtap; Valexime; ***Jpn***: Rocephin; ***Malaysia***: Cefaxone; Ceftrex; Eftriax†; Mesporin; Rocephin; Trixone; Unocef; Vaxcel Ceftriaxone; ***Mex.***: Amcef; Asepzona; Aurofox; Axtar; Benaxona; Cefaxona; Cefraden; Ceftrex; Ceftrilem; Centrifal; Limiprol; Megion; Oframax; Primotox; Rocephin; Tacex; Terbac†; Tindortec; Triaken; Triox; Xonatil; ***Neth.***: Exogran; Lopratin†; Rocephin; ***Norw.***: Rocephalin†; ***NZ***: Rocephin†; Veracol; ***Philipp.***: Acrexon; Afrixon; Armak; Auroxone; Bactrias; Bettrix; CEF-3; Cefotrim; Ceftrialis; Ceftrox; Ceptrocin; Cikedrix; Clovizone; Cotenzo; Cryaxon; Dintri; Efekton; Eroxet; Eurosef†; Fazactin; Fenadef; Forgram; Haxon; Hoftrex; Kenaxef; Keptrix; Maxeftin; Medzef; Megion; Monocrin; Norcephin; Novosef; Noxoram; Onizef; Panjecxone; Pantrixon; Pneumosolv; Recephin; Retrokor; Roceftin; Rocephin; Rolaphin; Roxifen; Roxon; Samjizon; Seltroz; Sergimax; Supraxone; Torocef; Triax; Triaxon; Tricexone; Trixophin; Tyoxone; Unixone; Xtenda; Zerone; ***Pol.***: Biotrakson; Lendacin; Oframax; Rocephin†; Tartriakson; ***Port.***: Betasporina; Cefilan; Ceriax; Kemudin; Mesporin; Rocephin; ***Rus.***: Axone (Аксоне); Azaran (Азаран); Betasporina (Бетаспорина); Biotrakson (Биотраксон); Cefatrin (Цефатрин); Cefaxone (Цефаксон); Cefogram (Цефограм); Cefson (Цефсон); Ceftriabol (Цефтриабол); Ceftrifin (Цефтрифин); Hizone (Хизон); Ificef (Ифицеф); Lendacin (Лендацин); Lifaxon (Лифаксон); Loraxone (Лораксон); Medaxone (Медаксон); Megion (Мегион); Movigip (Мовигип); Novosef (Новосеф); Oframax (Офрамакс); Rocepherin (Роцеферин); Rocephin (Роцефин); Stericef (Стерицеф); Tercef (Терцеф); Torocef (Тороцеф); Triaxone (Триаксон); ***S.Afr.***: Kocef; Medaxone; Oframax; Rocephin; Rocicect; Triaphin; Triaxiphin; ***Singapore***: Antibacin; Cefaxone; Ceftriphine; Oframax; Rocephin; Trexofin; Triaxone; Tricefin; Trizon; ***Spain***: Rocefalin†; ***Swed.***: Cefonova†; Rocephalin; ***Switz.***: Rocephin; ***Thai.***: CEF-3; Cef-Zone; Ceftrex; Ceftriphin; Gomcephin; Oframax; Rinxofay†; Rocephin; Sedalin; Triacef†; Tricephin†; Trixone; Trixophin; Utofin; Zefaxone; ***Turk.***: Armaseft; Baktisef; Cefaday; Cefridem; Cephaxon; Desefin; Equiceft; Forsef; Iesef; Nevakson; Novosef; Rocephin; Triaxon; Unacefin; ***UAE***: Triaxone; ***UK***: Rocephin; ***Ukr.***: Cefaxone (Цефаксон); Cefogram (Цефограм); Lendacin (Лендацин)†; Noraxon (Нораксон); Oframax (Офрамакс); Parcef (Парцеф)†; ***USA***: Rocephin; ***Venez.***: Bioceftrax; Cefin; Cefix; Ceftrialin; Ciplacef; Eftrival; Megion; Rocephin; Strixone; Tricefi.

Multi-ingredient Preparations. ***China***: Xin Junbizhi (新君必治); ***India***: Acticef-SB; Adesul; Afzone-S; Alitax-S; Alkaceff-S; Alnacef-S; Alnacef-T; Amceft-S; Arixon-SB; Arixon-TZB; Augtaz; Avcef-S; Avcef-TZ; Axocare-S; Axocare-T; Axon-SB; Axone-SB; Axtrum-S; Bactosul; Big-Tum; Broadcef-S; Broadcef-T; C-Fort; C-Tab-SB; C-Tum; Cadizone-S; Cadizone-XP; Cafage-S; Cameo-S; Cearium; Cebactum; Cef-S; Cefa-T Kit; Cefaday-S; Cefaday-TZ; Cefcin-SB; Cefcin-TJ; Cefirone T; Cefirone-V; Cefjoy; Cefmol-SF; Cefmol-TZ; Cefritz-TZ; Cefrose-S; Cefs-T; Cefset-S; Cefset-TX; Cefsine-S; Cefsine-TZ; Ceftichek; Ceftraset-S; Ceftril-S; Ceftrimax; Ceftrol-S; Cefurin; Cefwon-S; Cefzone-S; Cefzox-SF; Cefzox-TZ; Cepoxit-S; Cesafe-TZ; Cetriax-S; Cetzone-S; Cetzone-TZ; Cezone Plus; Champione-S; Chuncif-S; Corcef-SB; Cotyx-S; Crucef; CSI-S; CT Ceff SM; CT Ceff-TZ; CTMor-TZ; CTrisana-SB; CTX-TZ; Cucef-S; Cuxone-SL; Deczone-S; Deczone-T; Deczone-TP; Dewcef-S; Dibact; Eftanu-S; Ekcef-S; Emtri-S; Estxone-SB; Extacef-Tazo; Extacef-XL; Finecef-T; Finetriax-S; Formic; Forone-SB; Geminate Plus; Glen-SB; Glen-TZB; Glicef-S; Glicef-T; Gloriax-SB; Gramocef-S; Hicef-T; Hocef-S; Hocef-T; Ifytrox-SB; Ifytrox-TB; Incef-SB; Incef-TZ; Indocef-SB; Indoxone-S; Infoxon-S; Infoxon-T; Kafi-S; Kafi-TBZ; Keftragard; Kexone Plus; Kxone-SL; Labxone-SB; Lezone-S; Lezone-XP; Lifecare-A; Lifecare-C; Lifecare-SB; Lifecare-T; Lisel-S; Lisel-TBZ; Lyceft Plus; Mahacef-SB; Mat-CS; Mepef-S; Mintrax-S; Mocef-S; Mocef-TZ; Monobact; Montaz; Nexef-SB; Nexef-TBZ; Nizotrax-S; NKCef+S; Novaceft-S; Nutracip-SB; Oframax Forte; Onbact; Opticef-S; Oritiz; Oxy-S; Pancef-S.

Pharmacopoeial Preparations
BP 2014: Ceftriaxone Injection;
USP 36: Ceftriaxone for Injection; Ceftriaxone Injection.

Cefuroxime *(BAN, USAN, rINN)*

640/359; Cefuroxim; Cefuroxima; Céfuroxime; Cefuroximum; Kefuroksiimi; Sefuroksim; Цефуроксим.

(*Z*)-3-Carbamoyloxymethyl-7-[2-(2-furyl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid.

$C_{16}H_{16}N_4O_8S$=424.4

CAS — 55268-75-2.

ATC — J01DC02; S01AA27.

ATC Vet — QJ01DC02; QJ51DA06; QS01AA27.

UNII — O1R9FJ93ED.

Cefuroxime Axetil *(BANM, USAN, rINNM)*

CCI-15641; Cefuroksimas aksetilas; Cefuroksymu aksetyl; Cefuroxima axetilo; Cefuroxim-axetil; Cefuroximaxetil; Céfuroxime axétil; Céfuroxime, Axétil de; Cefuroximi Axetilum; Cefuroximum Axetili; Cefuroximum Axetilum; Kefuroksiimiaksetiili; Sefuroksim Aksetil; Цефуроксима Аксетил.

$C_{20}H_{22}N_4O_{10}S$=510.5

CAS — 64544-07-6.

ATC — J01DC02; S01AA27.

ATC Vet — QJ01DC02; QS01AA27.

UNII — Z49QDT0J8Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefuroxime Axetil). A white or almost white powder. Slightly soluble in water and in alcohol; soluble in acetone, in ethyl acetate, and in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Cefuroxime Axetil). A mixture of the diastereoisomers of cefuroxime axetil. A white or almost white powder. The amorphous form is insoluble in water and in ether; slightly soluble in dehydrated alcohol; freely soluble in acetone; soluble in chloroform, in ethyl acetate, and in methyl alcohol. The crystalline form is insoluble in water and in ether; slightly soluble in dehydrated alcohol; freely soluble in acetone; sparingly soluble in chloroform, in ethyl acetate, and in methyl alcohol. Store in airtight containers.

Cefuroxime Sodium *(BANM, rINNM)*

Cefuroksimo natrio druska; Cefuroksym sodowy; Cefuroxim-Natrium; Cefuroxim sodná sůl; Cefuroxima sódica; Céfuroxime Sodique; Cefuroximnatrium; Cefuroxim-nátrium; Cefuroximum Natricum; Kefuroksiiminatrium; Natrii Cefuroximum; Sefuroksim Sodyum; Натрий Цефуроксим.

$C_{16}H_{15}N_4NaO_8S$=446.4

CAS — 56238-63-2.

ATC — J01DC02; S01AA27.

ATC Vet — QJ01DC02; QS01AA27.

UNII — R8A7M9MY61.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefuroxime Sodium). A white or almost white slightly hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.5 to 8.5. Store in airtight containers.

USP 36: (Cefuroxime Sodium). A white or faintly yellow powder. Freely soluble in water; very slightly soluble in alcohol, in chloroform, in ether, and in ethyl acetate; soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.5. Store in airtight containers.

Incompatibility and stability. Cefuroxime sodium may be incompatible with aminoglycosides.

References.
1. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; **15:** 187–96.
2. Stiles ML, *et al*. Stability of ceftazidime (with arginine) and of cefuroxime sodium in infusion-pump reservoirs. *Am J Hosp Pharm* 1992; **49:** 2761–4.
3. Hebron B, Scott H. Shelf life of cefuroxime eye-drops when dispensed in artificial tear preparations. *Int J Pharm Pract* 1993; **2:** 163–7.

Uses and Administration

Cefuroxime is a second-generation cephalosporin antibacterial used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the bones and joints, CNS, skin and skin structures, respiratory tract, genito-urinary tract (including gonorrhoea), and Lyme disease. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefuroxime is given orally as the acetoxyethyl ester, cefuroxime axetil, in the form of tablets or suspension with or after food, or by injection as the sodium salt. Cefuroxime sodium may be given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion; it can also be given by intracameral injection. Doses of cefuroxime axetil and cefuroxime sodium are expressed in terms of the equivalent amount of cefuroxime; 1.20 g of cefuroxime axetil and 1.05 g of cefuroxime sodium are each equivalent to about 1 g of cefuroxime.

The usual oral dose is 250 mg twice daily; for uncomplicated urinary-tract infections 125 mg twice daily may be adequate and for respiratory-tract infections 250 to 500 mg twice daily is recommended. For Lyme disease an oral dose of 500 mg is given twice daily for 20 days.

By injection the usual dose is 750 mg of cefuroxime every 8 hours but in more severe infections 1.5 g may be given intravenously every 8, or in some cases every 6 hours.

Those with pneumonia or with acute exacerbations of chronic bronchitis may respond to sequential therapy with parenteral cefuroxime 1.5 g twice daily or 750 mg twice daily respectively, followed by oral cefuroxime 500 mg twice daily in each case.

For the treatment of meningitis due to sensitive strains of bacteria, cefuroxime is given intravenously in doses of 3 g every 8 hours.

In the treatment of gonorrhoea, a single dose of 1.5 g by intramuscular injection, divided between 2 injection sites, has been used. A single 1-g oral dose of cefuroxime has been given for uncomplicated gonorrhoea. In each case an oral dose of probenecid 1 g may be given with cefuroxime.

For surgical infection prophylaxis, the usual dose is 1.5 g of cefuroxime intravenously before the procedure; this may be supplemented by 750 mg intramuscularly every 8 hours for up to 24 to 48 hours depending upon the procedure. For

total joint replacement, 1.5 g of cefuroxime powder may be mixed with the methylmethacrylate cement.

Cefuroxime may be given by intracameral injection for the prophylaxis of postoperative endophthalmitis; a dose of 1 mg is slowly injected into the anterior chamber of the eye at the end of cataract surgery.

The dose of cefuroxime may need to be reduced in patients with renal impairment, see p. 258.1. For details of doses in children, see also p. 258.1.

Reviews.

1. Perry CM, Brogden RN. Cefuroxime axetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1996; **52:** 125–58.
2. Scott LJ, *et al*. Cefuroxime axetil: an updated review of its use in the management of bacterial infections. *Drugs* 2001; **61:** 1455–1500.
3. Keating GM. Intracameral cefuroxime: prophylaxis of postoperative endophthalmitis after cataract surgery. *Drugs* 2013; **73:** 179–86.

Administration in children. Cefuroxime may be given to neonates and children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical prophylaxis. It is given orally as cefuroxime axetil; the sodium salt is given parenterally either by intramuscular injection or intravenously, by slow injection over 3 to 5 minutes, or intermittent or continuous infusion.

The *BNFC* suggests the following treatment doses for cefuroxime:

given *orally*

- children 3 months to 2 years of age: 10 mg/kg (to a maximum dose of 125 mg) twice daily
- those over 2 years of age: 15 mg/kg (to a maximum dose of 250 mg) twice daily, *or*

given *parenterally*

- neonates under 7 days of age: 25 mg/kg every 12 hours
- neonates 7 to 21 days of age: 25 mg/kg every 8 hours
- neonate 21 to 28 days of age: 25 mg/kg every 6 hours
- these doses may be doubled in neonates with severe infections, but should be given intravenously
- children from 1 month of age: 20 mg/kg (to a maximum dose of 750 mg) every 8 hours; this dose may be increased to 50 to 60 mg/kg (to a maximum dose of 1.5 g) every 6 or 8 hours in severe infection and cystic fibrosis

For surgical prophylaxis the *BNFC* suggests that children from the age of 1 month may be given a dose of 50 mg/kg (to a maximum dose of 1.5 g) intravenously before the procedure; this may be supplemented by up to 3 further doses of 30 mg/kg (to a maximum dose of 750 mg) intramuscularly or intravenously at 8-hour intervals for high-risk procedures.

In the USA, the American Academy of Pediatrics[1] suggests the following doses:

orally

- children 1 month and older: 20 to 30 mg/kg daily in 2 divided doses (to a maximum daily dose of 0.5 to 1 g) for mild to moderate infections

intravenously or *intramuscularly*

- for neonates aged ⩽ 7 days (irrespective of body weight): 50 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ⩽ 2 kg: 50 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing > 2 kg: 50 mg/kg every 8 hours
- children 1 month and older: 75 to 100 mg/kg daily in 3 divided doses (to a maximum daily dose of 2.25 to 4.5 g) for mild to moderate infections, or 100 to 200 mg/kg daily in 3 or 4 divided doses (to a maximum daily dose of 3 to 6 g) in severe infections

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of cefuroxime may need to be reduced in renal impairment. Licensed product information suggests the following doses based on creatinine clearance (CC):

- CC 10 to 20 mL/minute: 750 mg twice daily
- CC less than 10 mL/minute: 750 mg once daily

Patients undergoing haemodialysis should receive an additional 750-mg dose following each dialysis; those undergoing continuous peritoneal dialysis may be given 750 mg twice daily.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Gastrointestinal disturbances, including diarrhoea, nausea, and vomiting, have occurred in some patients receiving cefuroxime axetil. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Mild to moderate hearing loss has been reported in some children given cefuroxime for the treatment of meningitis.

Antibiotic-associated colitis. For reports of pseudomembranous colitis associated with cefuroxime axetil, see Cefalotin, p. 235.2.

Hypersensitivity. A report[1] of a serum sickness-like reaction to cefuroxime. Similar reactions have occurred with cefaclor (p. 233.1), although it is unclear whether they represent a class effect.

A patient who developed a type-1 hypersensitivity reaction to cefuroxime, characterised by itchy maculopapular rash, exhibited cross-sensitivity to cefotaxime and ceftriaxone on patch testing, possibly because of similarities in the side-chain;[2] no cross-sensitivity to cefazolin, cefepime, cefoxitin, or ceftazidime, or to various penicillins, was seen on testing and the patient subsequently tolerated doses of amoxicillin and ceftazidime. The authors noted that cefuroxime had been found in another study to be the most frequent cause of immediate-type hypersensitivity reactions to cephalosporins.

1. Katta R, Anusuri V. Serum sickness-like reaction to cefuroxime: a case report and review of the literature. *J Drugs Dermatol* 2007; **6:** 747–8.
2. Varela Losada S, *et al*. Immediate-type allergic reaction to cefuroxime: cross-reactivity with other cephalosporins, and good tolerance to ceftazidime. *J Investig Allergol Clin Immunol* 2009; **19:** 164–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefuroxime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/10/11)

Sodium content. Each g of cefuroxime sodium contains about 2.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefuroxime.

Antimicrobial Action

Cefuroxime is bactericidal and has a similar spectrum of antimicrobial action and pattern of resistance to those of cefamandole (p. 237.1). It is more resistant to hydrolysis by beta-lactamases than cefamandole, and therefore may be more active against beta-lactamase-producing strains of, for example, *Haemophilus influenzae* and *Neisseria gonorrhoeae*. However, treatment failures have occurred in patients with *H. influenzae* meningitis given cefuroxime and might be associated with a relatively high minimum bactericidal concentration when compared with the minimum inhibitory concentration or with a significant inoculum effect. Reduced affinity of penicillin-binding proteins for cefuroxime has also been reported to be responsible for resistance in a beta-lactamase-negative strain of *H. influenzae*.

References.

1. Arditi M, *et al*. Cefuroxime treatment failure and Haemophilus influenzae meningitis: case report and review of literature. *Pediatrics* 1989; **84:** 132–5.
2. Mendelman PM, *et al*. Cefuroxime treatment failure of nontypable Haemophilus influenzae meningitis associated with alteration of penicillin-binding proteins. *J Infect Dis* 1990; **162:** 1118–23.
3. Brown NM, *et al*. Cefuroxime resistance in Haemophilus influenzae. *Lancet* 1992; **340:** 552.

Pharmacokinetics

Cefuroxime axetil is absorbed from the gastrointestinal tract and is rapidly hydrolysed in the intestinal mucosa and blood to cefuroxime; absorption is enhanced in the presence of food. Peak plasma concentrations occur about 2 to 3 hours after an oral dose. The sodium salt is given by intramuscular or intravenous injection. Peak plasma concentrations of about 27 micrograms/mL have been achieved 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose. Up to 50% of cefuroxime in the circulation is bound to plasma proteins. The plasma half-life is about 70 minutes and is prolonged in patients with renal impairment and in neonates.

Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. It crosses the placenta and has been detected in breast milk.

Cefuroxime is excreted unchanged, by glomerular filtration and renal tubular secretion, and high concentrations occur in the urine. On injection, most of a dose of cefuroxime is excreted within 24 hours, the majority within 6 hours. Probenecid competes for renal tubular secretion with cefuroxime resulting in higher and more prolonged plasma concentrations of cefuroxime. Small amounts of cefuroxime are excreted in bile.

Plasma concentrations are reduced by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefurox; ***Austral.***: Zinnat; ***Austria***: Curocef; Zinnat; ***Belg.***: Cefurim; Doccefuro†; Kefurox; Zinacef; Zinnat; ***Braz.***: Keroxime; Medcef; Monocef; Zinacef; Zinnat; ***Canad.***: Ceftin; ***Chile***: Cerevax; Curocef; Zinnat; ***China***: AoShu (澳舒); Axetine (安可欣); Ba Xin (巴欣); Ceroxim (协诺信); Dalixin (达力新); Fulexin (伏乐新); Jia Nuo Xin (嘉诺欣); Jin Mao (金茂); Kaidixin (凯帝欣); Ku Xin (库欣); Li Fu Xin (丽扶欣); Li Jian Xin (立健新); Lifurox (力复乐); Monacef (明可欣); Pai Wei Xin (派威欣); Rui Fu Xin (瑞呋欣); Sipeiding (司佩定); Supero (舒贝洛); Xi Lu Xin (希路信); Xin Li Xin (信立欣); Xin Lu Xin (欣路信); Xinfuxin (新福欣); Yaxing (亚星); Youlexin (优乐新); Yun Tai (运泰); Zinacef (西力欣); ***Cz.***: Axetine; Medoxin; Miksor; Xorimax; Zinacef; Zinnat; Zinoxime†; ***Denm.***: Zinacef; Zinnat; ***Fin.***: Aprokam; Zinacef; Zinnat; ***Fr.***: Cepazine†; Zinnat; ***Ger.***: Cefuhexal†; Cefuro-Puren†; Cefurox-Wolff†; Cefurox†; Elobact; Zinnat†; ***Gr.***: Anaptivan; Cefoprim; Cefur; Cefuretil; Cefuroprol; Cerofene; Ceruxim; Cupax; Ecoline; Feacef; Foucacillin; Fredyr; Furaxil; Galemin; Genephoxal; Gonif; Helatocil; Interbion; Lyprovir; Medoxem; Mevecan; Mosalan; Nelabocin; Nipogalin; Normafenac; Receant; Saxetil; Sedopan; Vekfazolin; Yokel; Zagorine; Zetagal; Zilisten; Zinacef; Zinadol; ***Hong Kong***: Axacef; Axim; Ceflour; Quali-Cefurnat; Sefuxim; Xorimax; Zinacef; Zinnat; ***Hung.***: Cefurin†; Ceroxim; Xorim; Xorimax; Zinacef; Zinnat; ***India***: Actum; Adexim; Altacef; Altum; Anorex; Arixime; Atom; Aucee; Axacef; Axeptil; Axeris; Axetim; Axtl; Bacticef; Barocef; Bencef; Bigcef; Biocef; Bullcef; C-Furo; C-Tri-T; Cascef; Ceax; Cef-Vepan; Cefakind; Cefam; Cefar; Cefasyn; Cefexl; Cefies; Cefking; Ceflet; Cefob; Cefogen; Cefoprim; Ceforim; Ceforox; Cefos; Cefoxim; Cefpil; Cefta; Ceftab; Ceftal; Ceftra; Ceftum; Cefu; Cefubir; Cefucin; Cefucos; Cefunis; Cefupet; Cefurin; Cefusym; Cefutab-O; Cefuvik; Cefyrex; Cefzim; Ceplex; Cepokem; Cerom; Ceroxitum; Cesai; Cetil; Ceurox; Cilixem; CTrox; Curoxim; Cutil; Cuxim; Daltum; Dericef; Difu; Duxim; Edrucef; Ethicef; Evercef; Exeption; Exime; Flamicef; Forcef; Forcez; Forex; Forkem; Fucef; Furion; Furobid; Furomax; Furome; Furox; Furoxil; Fydoroxim; Glyph-ZM; Gocef; I-M-Sure; Iflacef; Insifu; Intracef; Iviroxime; Jaxe; Joxcy; Kaircef; Kaxitel; Kefstar; Kefuel; Kem; Kincef; Klime; L-Tum; Lazocin; Luroxime; Magna; Magnacef; Martec; Maxim; Maxtum; Metump; Milcef; Neftum-AXT; Neroxim; Nifoxime; Novaroxim; Ocef; Omnixim; Oruf; Supacef; ***Indon.***: Anbacim; Cefurox†; Celocid; Cethixim; Kalcef; Kenacef†; Oxtercid; Roxbi†; Sharox; Soxime; Zinacef†; Zinnat; ***Irl.***: Ceftal; Zinacef; Zinnat; ***Israel***: Cefurax; Ceroxim†; Kefurim; Pan-Cefuroxime; Zinacef; Zinnat; ***Ital.***: Biociclin†; Cefoprim†; Cefurin; Curoxim; Duxima; Itorex; Lafurex†; Oraxim; Supero; Tilexim; Zinnat; Zinocep; Zoref; ***Malaysia***: Altacef; Anikef; Ceflour; Efurox; Furoxime; Vaxcel Cefuroxime; Xorimax; Xylid; Zinacef; Zinnat; Zocef; ***Mex.***: Cefabiot; Cefagen; Cefuracet; Cetoxil; Froxal; Fucerox; Furobioxin; Magnaspor; Novador; Ximaken; Xorufec; Zinnat; ***Neth.***: Aprokam; Zinacef; Zinnat; ***Norw.***: Zinacef; ***NZ***: Axetine; Zinacef; Zinnat; ***Philipp.***: Aeruginox; Altacef; Ambixime; Axet; Axurocef; Bactipoz; Betcef; C-Tri T; Cefogen; Ceftil; Cefucil†; Cefumax; Cefurex; Cefuzime; Cervin; Cesavess; Cidokez; Cimex; Clovixime; Curecef; Darcef; Ecocef; Educef; Elixime; Emixor; Eoroxime; Eroxmit; Eurimax; Finax; Fubaxyn†; Furocef; Furocem; Furomax; Furoxim†; Furoxy; Harox; Ifurax; Infekor; Jectocef; Kaftax; Kefezy; Kefox; Kefstar; Kefsyn; Kefurox; Keunzef; Lasuzef; Laxinat; Loxatrel†; Medxil; Medxime; Medzyme; Microzef; Panaxim; Panjecxime; Pheoronex; Plerozef; Profurex; Rexofen; Rezafil; Robisef; Rocef; Romicef; Rovix; Roxetil; Roxicef; Roxime; Roxym†; Rucef; Ruxim; Sharox†; Shincef; Teikeden; Unoximed; Vitaroxima; Xorimax; Zefcid; Zefsur; Zefur; Zefuxim; Zegen; Zenoxim; Zinacef; Zinaf; Zinnat; Zoltax; Zurenix; ***Pol.***: Biofuroksym; Bioracef; Ceroxim; Novocef; Plixym†; Tarsime; Xelacef; Xorim†; Xorimax; Zamur; Zinacef; Zinnat; Zinoxx; ***Port.***: Antibioxime; Axacef; Cefofix†; Condronac; Curoxime; Famicef; Lusocef†; Saracef; Zipos; Zoref; ***Rus.***: Antibioxim (Антибиоксим); Axetine (Аксетин); Cefurabol (Цефурабол); Cefurus (Цефурус); Cetyl (Цетил); Kefstar (Кефстар); Ketocef (Кетоцеф); Proxime (Проксим); Supero (Суперо); Xorim (Ксорим); Zinacef (Зинацеф); Zinnat (Зиннат); ***S.Afr.***: Auroxime; Betaroxime; Cefasyn; Cefu-Hexal; Ceroxim; Cipofix; CuroAx; Intracef†; Medaxime; Zefroxe; Zefurime; Zinacef; Zinnat; Zinoxime; ***Singapore***: Bearcef; Ceftil; Cefxin; Shincef; Xorimax; Zinacef; Zinnat; ***Spain***: Curoxima†; Nivador†; Selan†; Zinnat; ***Swed.***: Zinacef; Zinnat†; ***Switz.***: Cefurim; Zinacef; Zinat; ***Thai.***: Axurocef†; C-Tri T; Cefamar†; Cefurim; Farmacef; Furoxime; Magnaspor; Neurox; Sefuxim; Zinacef; Zinnat; Zocef; Zonef†; ***Turk.***: Aksef; Cefaks; Cefatin; Cefurol; Enfexia; Multisef; Oraceftin; Sefaktil; Seffur; Sefuroks; Zinnat; ***UAE***: Cefuzime; ***UK***: Aprokam; Zinacef; Zinnat; ***Ukr.***: Aksef (Аксеф); Biofuroksym (Биофуроксим)†; Cefoctam (Цефоктам); Cefumax (Цефумакс); Cefutil (Цефутил); Cetil (Цетил); Enfexia (Энфексия); Kimacef (Кимацеф); Mikrex (Микрекс); Spizef (Спизеф); Zinacef (Зинацеф); Zinnat (Зиннат); ***USA***: Ceftin; Zinacef; ***Venez.***: Xorim; Zencef; Zinacef; Zinnat.

Multi-ingredient Preparations. ***India***: Bactocef; C-Tri EM; Cefos-S; Covatil-CV; Intracef-CV; Ocef-CV.

Pharmacopoeial Preparations

BP 2014: Cefuroxime Axetil Oral Suspension; Cefuroxime Axetil Tablets; Cefuroxime Eye Drops; Cefuroxime Injection; Cefuroxime Intracameral Injection;

USP 36: Cefuroxime Axetil for Oral Suspension; Cefuroxime Axetil Tablets; Cefuroxime for Injection; Cefuroxime Injection.

Cethromycin *(USAN, rINN)*

A-195773; Abbott-195773; ABT-773; Céthromycine; Cethromycinum; Cetromicina; Цетромицин.

(3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyl-3a,7,9,11,13,15-hexamethyl-11-{[3-(quinolin-3-yl)prop-2-enyl]oxy}-10-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy} octahydro-2*H*-oxacyclotetradecino[4,3-*d*]oxazole-2,6,8,14 (1*H*,7*H*,9*H*)-tetrone.

$C_{42}H_{59}N_3O_{10}$=765.9

CAS — 205110-48-1.

UNII — J0086219X6.

Profile

Cethromycin is a ketolide antibacterial under investigation for the treatment of susceptible respiratory-tract infections.

References.

1. Dougherty TJ, Barrett JF. ABT-773: a new ketolide antibiotic. *Expert Opin Invest Drugs* 2001; **10:** 343–51.
2. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; **62:** 1771–1804.
3. Zhanel GG, *et al.* Ketolides: an emerging treatment for macrolide-resistant respiratory infections, focusing on S. pneumoniae. *Expert Opin Emerg Drugs* 2003; **8:** 297–321.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; **53:** 918–27.
5. Anonymous. Cethromycin: A-195773, A-195773-0, A-1957730, Abbott-195773, ABT 773. *Drugs R D* 2007; **8:** 95–102.
6. Hammerschlag MR, Sharma R. Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. *Expert Opin Invest Drugs* 2008; **17:** 387–400.
7. Rafie S, *et al.* Cethromycin: a promising new ketolide antibiotic for respiratory infections. *Pharmacotherapy* 2010; **30:** 290–303.

Chloramphenicol *(BAN, rINN)*

Chloramfenikol; Chloramfenikolis; Chloramphénicol; Chloramphenicolum; Chloranfenicol; Cloranfenicol; Kloramfenikol; Klóramfenikol; Kloramfenikoli; Laevomycetinum; Хлорамфеникол.

2,2-Dichloro-*N*-[(α*R*,β*R*)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide.

$C_{11}H_{12}Cl_2N_2O_5$=323.1

CAS — 56-75-7.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QJ51BA01; QS01AA01; QS02AA01; QS03AA08.

UNII — 66974FR9Q1.

NOTE. CPL is a code approved by the BP 2014 for use on single unit doses of eye drops containing chloramphenicol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chloramphenicol). A substance produced by the growth of certain strains of *Streptomyces venezuelae*, but now mainly prepared synthetically. A white, greyish-white or yellowish-white, fine crystalline powder or fine crystals, needles, or elongated plates. Slightly soluble in water; freely soluble in alcohol and in propylene glycol. Protect from light.

USP 36: (Chloramphenicol). Fine, white to greyish-white or yellowish-white, needle-like crystals or elongated plates. Soluble 1 in 400 of water; freely soluble in alcohol, in acetone, in ethyl acetate, and in propylene glycol. pH of a 2.5% suspension in water is between 4.5 and 7.5. Its solutions are practically neutral to litmus. It is reasonably stable in neutral or moderately acid solutions. Store in airtight containers.

Chloramphenicol Palmitate *(BANM, rINNM)*

Chloramfenikolio palmitatas; Chloramfenikol-palmitát; Chloramfenikolu palmitynian; Chloramphenicol α-Palmitate; Chloramphénicol, Palmitate de; Chloramphenicoli Palmitas; Chloramphenicolpalmitat; Cloranfenicol, palmitato de; Kloramfenikolipalmitaatti; Kloramfenikolpalmitat; Klóramfenikol-palmitát; Palmitato de cloranfenicol; Palmitylchloramphenicol; Хлорамфеникола Пальмитат.

$C_{27}H_{42}Cl_2N_2O_6$=561.5

CAS — 530-43-8.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QS01AA01; QS02AA01; QS03AA08.

UNII — 43VU4207NW.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chloramphenicol Palmitate). A fine, white or almost white, unctuous, powder. M.p. 87 degrees to 95 degrees. Chloramphenicol palmitate shows polymorphism and the thermodynamically stable form has low bioavailability following oral administration. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone; very slightly soluble in hexane. Protect from light.

USP 36: (Chloramphenicol Palmitate). A fine, white, unctuous, crystalline powder, having a faint odour. M.p. 87 degrees to 95 degrees. Insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in chloroform; soluble in ether; very slightly soluble in hexane. Store in airtight containers.

Chloramphenicol Sodium Succinate

(BANM, rINNM)

Chloramfenikolio natrio sukcinatas; Chloramfenikol-sukcinát sodná sůl; Chloramphenicol α-Sodium Succinate; Chloramphénicol, Succinate Sodique de; Chloramphenicolhydrogensuccinat-Natrium; Chloramphenicoli Natrii Succinas; Cloranfenicol, succinato sódico de; Kloramfenikol Süksinat Sodyum; Klóramfenikol-hidrogénszukcinátnátrium; Kloramfenikolinatriumsuksinaatti; Kloramfenikolnatriumsuccinat; Succinato sódico de cloranfenicol; Хлорамфеникола Натрия Сукцинат.

$C_{15}H_{15}Cl_2N_2NaO_8$=445.2

CAS — 982-57-0.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QS01AA01; QS02AA01; QS03AA08.

UNII — 872109HX6B.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet. Chin.* includes Chloramphenicol Hydrogen Succinate.

Ph. Eur. 8: (Chloramphenicol Sodium Succinate). A white or yellowish-white hygroscopic powder. Very soluble in water; freely soluble in alcohol. A 25% solution in water has a pH of 6.4 to 7.0. Store in airtight containers. Protect from light.

USP 36: (Chloramphenicol Sodium Succinate). A light yellow powder. Freely soluble in water and in alcohol. pH of a solution in water containing the equivalent of chloramphenicol 25% is between 6.4 and 7.0. Store in airtight containers.

Incompatibility. Incompatibility or loss of activity has been reported between chloramphenicol and many other substances. Other factors, especially drug concentration, may play a part and incompatibilities are most often seen with concentrated solutions.

Uses and Administration

The risk of life-threatening adverse effects, particularly bone-marrow aplasia, has severely limited the clinical usefulness of chloramphenicol, although it is still widely used in some countries. It should never be given systemically for minor infections and regular blood counts are usually advisable during treatment. The third-generation cephalosporins replaced chloramphenicol for many of its former uses, and there are consequently few unambiguous indications for its use. It has been used in severe typhoid and other salmonellal infections, although it does not eliminate the carrier state. Chloramphenicol is an alternative to a third-generation cephalosporin in the treatment of bacterial meningitis, both empirically and against sensitive organisms such as *Haemophilus influenzae*. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. It has been used in the treatment of severe anaerobic infections, particularly in brain abscesses, and in infections below the diaphragm where *Bacteroides fragilis* is often implicated; however, other drugs are usually preferred. Although the tetracyclines remain the treatment of choice in rickettsial infections such as typhus and the spotted fevers, chloramphenicol is also used as an alternative where the tetracyclines cannot be given.

Other bacterial infections in which chloramphenicol may be used as an alternative or adjunct to other drugs include actinomycosis, ehrlichiosis, cystic fibrosis, severe gastroenteritis (including *Salmonella* enteritis, cholera, and *Yersinia* enteritis), gas gangrene, granuloma inguinale, severe *Haemophilus influenzae* infections (for example in epiglottitis), severe melioidosis, pelvic inflammatory disease, plague (especially if meningitis develops), pneumonia, psittacosis, Q fever, relapsing fever, tularaemia (especially when meningitis is suspected), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Chloramphenicol is extensively used in the topical treatment of ear and, in particular, eye infections, despite the fact that many of these are mild and self-limiting. It has also been used topically in the treatment of skin infections.

When given *systemically*, chloramphenicol is usually used orally as capsules or as a suspension of chloramphenicol palmitate. When oral use is not feasible, water-soluble chloramphenicol sodium succinate may be given intravenously, but oral therapy should be substituted as soon as possible; an intravenous dose should be injected over at least 1 minute or given by slow intravenous infusion. Intramuscular injection is controversial because of doubts whether absorption is adequate.

Doses are expressed in terms of chloramphenicol base and are similar whether given orally or intravenously. Chloramphenicol palmitate 1.7 g and chloramphenicol sodium succinate 1.4 g are each equivalent to about 1 g of chloramphenicol base.

The usual dose is 50 mg/kg daily in divided doses every 6 or 8 hours; up to 100 mg/kg daily may be given in meningitis or severe infections due to moderately resistant organisms, although these higher doses should be reduced as soon as possible. It has been recommended that treatment should be continued after the patient's temperature has returned to normal for a further 4 days in rickettsial diseases, and for 8 to 10 days in typhoid fever, to minimise the risk of relapse.

In the *topical* treatment of eye infections, chloramphenicol is usually applied as a 0.5% solution or as a 1% ointment. Generally, drops are applied up to 6 times daily. Severe infections may need more frequent dosing initially, reducing gradually once the infection is controlled. When ointment is used, it may be applied once daily at night if drops are used during the day, or 3 or 4 times daily if used alone.

For bacterial infections in otitis externa, chloramphenicol has been given as ear drops in a strength of 5 or 10%. A dose of 2 or 3 drops to the affected ear 2 or 3 times daily has been used.

Chloramphenicol has also been used in the form of *other derivatives* including the glycinate, the palmitoylglycolate, the pantothenate, the steaglate, the stearate, and the hydrogen succinate.

Administration. When parenteral use of chloramphenicol is necessary the intravenous route is generally preferred, although the intramuscular route has been advocated. Adequate serum concentrations after intramuscular injection have been reported,[1,2] although this is contrary to the widely held belief that chloramphenicol sodium succinate is poorly absorbed by this route. Pain on injection was also claimed to be minimal.[1] After a study in children with bacterial meningitis,[3] treatment with intramuscular chloramphenicol for 2 or 3 days followed by oral therapy has been suggested, although a later study[2] found that the intramuscular route produced therapeutic concentrations when the oral route did not. However, it has been said[4] that children describe intramuscular chloramphenicol as amongst the worst treatments they ever receive, and certainly much worse than the insertion of intravenous cannulae.

1. Shann F, *et al.* Absorption of chloramphenicol sodium succinate after intramuscular administration in children. *N Engl J Med* 1985; **313:** 410–14.
2. Weber MW, *et al.* Chloramphenicol pharmacokinetics in infants less than three months of age in the Philippines and The Gambia. *Pediatr Infect Dis J* 1999; **18:** 896–901.
3. Shann F, *et al.* Chloramphenicol alone versus chloramphenicol plus penicillin for bacterial meningitis in children. *Lancet* 1985; **ii** 681–3.
4. Coulthard MG, Lamb WH. Antibiotics: intramuscular or intravenous? *Lancet* 1985; **ii:** 1015.

Administration in children. Because of metabolic differences, neonates and premature infants will generally require lower **systemic** doses than older infants and children. Where there is no alternative to the use of chloramphenicol, the doses recommended according to age and maturity are as follows:

- *all neonates up to 2 weeks old:* 25 mg/kg daily in divided doses (the *BNFC* suggests 2 divided doses at intervals of 12 hours) by intravenous injection
- *full-term neonates 2 weeks of age and older:* 25 to 50 mg/kg daily given in divided doses of 12.5 mg/kg every 6 to 12 hours
- *premature neonates 2 weeks of age or older, and infants with suspected immature metabolic processes:* 25 mg/kg daily intravenously in divided doses
- *infants and children aged 1 month to 18 years:* where metabolic processes are mature, as for adults (see Uses and Administration, above). Where immature metabolic processes are suspected a reduced dose of 25 mg/kg daily in divided doses has again been recommended

Blood concentration monitoring is recommended when using parenteral or oral chloramphenicol in neonates, children with immature metabolic processes, and for children receiving higher dose ranges for serious infections. It is also preferred for those under 4 years of age. For details of recommended plasma concentrations, see Precautions, p. 260.2.

Chloramphenicol **topical** eye and ear preparations are used similarly to use in adults (see Uses and Administration, p. 257.2).

Enterococcal infections. The emergence of resistance to vancomycin among enterococcal isolates has required the development of new therapeutic options such as linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin for the treatment of vancomycin-resistant enterococcal infections (p. 181.1). There is, however, no standard treatment and choice of antibacterial depends on local patterns of resistance and antibacterial sensitivity tests. Some reports have indicated that chloramphenicol may be effective against vancomycin-resistant *Enterococcus faecium*.[1-3] Although no significant effect of chloramphenicol on mortality was found in one small study,[4] a retrospective analysis[5] of the outcomes of 6 patients with bacteraemia due to vancomycin-resistant *Enterococcus faecium* concluded that chloramphenicol was effective and should be considered as a treatment option. However, vancomycin-resistant enterococci also resistant to chloramphenicol have been reported.[6]

1. Norris AH, *et al.* Chloramphenicol for the treatment of vancomycin-resistant enterococcal infections. *Clin Infect Dis* 1995; **20:** 1137–44.
2. Papanicolaou GA, *et al.* Nosocomial infections with vancomycin-resistant Enterococcus faecium in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996; **23:** 760–6.
3. Mato SP, *et al.* Vancomycin-resistant Enterococcus faecium meningitis successfully treated with chloramphenicol. *Pediatr Infect Dis J* 1999; **18:** 483–4.
4. Lautenbach E, *et al.* The role of chloramphenicol in the treatment of bloodstream infection due to vancomycin-resistant Enterococcus. *Clin Infect Dis* 1998; **27:** 1259–65.
5. Ricaurte JC, *et al.* Chloramphenicol treatment for vancomycin-resistant Enterococcus faecium bacteremia. *Clin Microbiol Infect* 2001; **7:** 17–21.
6. Lautenbach E, *et al.* Emergence of resistance to chloramphenicol among vancomycin-resistant enterococcal (VRE) bloodstream isolates. *Int J Antimicrob Agents* 2004; **23:** 200–3.

Adverse Effects and Treatment

Chloramphenicol may cause severe and sometimes fatal adverse effects. The most serious of these is bone-marrow depression, which can take two different forms. The first is a fairly common dose-related reversible depression occurring usually when plasma-chloramphenicol concentrations exceed 25 micrograms/mL or when adult doses are greater than 4 g daily, and is characterised by morphological changes in the bone marrow, decreased iron utilisation, reticulocytopenia, anaemia, leucopenia, and thrombocytopenia. This effect may be due to inhibition of protein synthesis in the mitochondria of bone marrow cells.

The second and apparently unrelated form of bone-marrow toxicity is severe irreversible aplastic anaemia. This is fairly rare, with a suggested incidence of about 1:18 000 to 1:50 000, although the incidence varies throughout the world, and is not considered to be dose-related. The aplasia usually develops after a latent period of weeks or even months and has been suggested to be the result of a nitrated benzene radical produced *in vivo*. It is considered that there may be some genetic or biochemical predisposition, but there is no way of identifying susceptible patients. Although most cases follow oral use, aplasia has also occurred after intravenous and topical (eye drops) use of chloramphenicol. Survival is most likely in those with early onset aplasia, but they may subsequently develop acute myeloid leukaemia.

A toxic manifestation—the 'grey syndrome' or 'grey baby syndrome'—characterised by abdominal distension, vomiting, ashen colour, hypothermia, progressive pallid cyanosis, irregular respiration, and circulatory collapse, followed by death in a few hours or days, has occurred in premature and other newborn infants given large doses of chloramphenicol. The syndrome is associated with high plasma concentrations of chloramphenicol, due to reduced capacity for glucuronidation and decreased glomerular filtration in children of this age, leading to drug accumulation. Recovery is usually complete if the drug is withdrawn early enough after onset, but up to 40% of infants with the full-blown syndrome may die. The syndrome has also been reported in infants born to mothers given chloramphenicol in late pregnancy or labour. A similar syndrome has been reported in adults and older children given very high doses.

Prolonged oral use of chloramphenicol may induce bleeding, either by bone-marrow depression or by reducing the intestinal flora with consequent inhibition of vitamin K synthesis. Haemolytic anaemia has occurred in some patients with the Mediterranean form of glucose 6-phosphate dehydrogenase deficiency, but is rare in patients with milder forms of the deficiency. Paroxysmal nocturnal haemoglobinuria has also been reported.

Peripheral as well as optic neuritis has been reported, usually in patients treated over prolonged periods. Although ocular symptoms are often reversible if treatment is withdrawn early, permanent visual impairment or blindness has occurred.

Other neurological symptoms have included encephalopathy with confusion and delirium, depression, and headache. Ototoxicity has also occurred, especially after the use of ear drops.

Hypersensitivity reactions including rashes, fever, and angioedema may occur especially after topical use; anaphylaxis has occurred but is rare. Jarisch-Herxheimer reactions may also occur. Gastrointestinal symptoms including nausea, vomiting, and diarrhoea can follow oral use. Disturbances of the oral and intestinal flora may cause stomatitis, glossitis, and rectal irritation. Patients may experience an intensely bitter taste after rapid intravenous use of chloramphenicol sodium succinate.

Aplastic anaemia. A review[1] of the toxicity of chloramphenicol and related drugs, including the potential role of the *p*-nitro group in producing aplastic anaemia, indicated that derivatives such as thiamphenicol, which lack this grouping, are not associated with increased incidence of aplastic anaemia.

For a discussion of the risk of aplastic anaemia associated with topical use of chloramphenicol eye drops, see under Ocular Use, p. 260.3.

1. Yunis AA. Chloramphenicol: relation of structure to activity and toxicity. *Ann Rev Pharmacol Toxicol* 1988; **28:** 83–100.

Effects on the liver. Isolated cases of hepatotoxicity, including hepatitis and jaundice, have been reported after systemic use of chloramphenicol.

In a case report[1] hepatitis also occurred in a 37-year-old patient after a 5-day course of chloramphenicol 0.5% eye drops; the patient presented 7 days after the end of treatment with lethargy, pruritus, dark urine, scleral icterus, and elevated liver-transaminase values. A liver biopsy 6 weeks after stopping chloramphenicol was highly suggestive of drug-induced hepatitis, and transaminase values returned to normal within 10 months of stopping the eye drops.

1. Doshi B, Sarkar S. Topical administration of chloramphenicol can induce acute hepatitis. *BMJ* 2009; **339:** 574.

Overdosage. Charcoal haemoperfusion was found to be far superior to exchange transfusion in the removal of chloramphenicol from blood, although it did not prevent death in a 7-week-old infant with the 'grey syndrome' after a dosage error.[1]

1. Freundlich M, *et al.* Management of chloramphenicol intoxication in infancy by charcoal hemoperfusion. *J Pediatr* 1983; **103:** 485–7.

Precautions

Chloramphenicol is contra-indicated in patients with a history of hypersensitivity or toxic reaction to the drug. It should never be given systemically for minor infections, prophylaxis, or where less toxic antibacterials could be used. Repeated courses and prolonged treatment should be avoided and it should not be used in patients with pre-existing bone-marrow depression or blood dyscrasias. Routine periodic blood examinations are advisable in all patients, but will not warn of aplastic anaemia.

Use of chloramphenicol with other drugs liable to depress bone-marrow function should be avoided.

Excessive blood concentrations may occur after usual doses in patients with hepatic or renal impairment, or in premature and full-term neonates who have immature metabolic processes. Licensed product information recommends dose reduction in such patients, based on monitoring of serum chloramphenicol concentrations; a suggested range for peak plasma concentrations is 10 to 25 micrograms/mL, and for trough concentrations, 5 to 15 micrograms/mL. In addition, specific dosage guidance is given for neonates (see Administration in Children, p. 257.3), although they should never be given chloramphenicol systemically (unless it may be life-saving and there is no alternative treatment) because of the risk of 'grey syndrome'.

Chloramphenicol readily crosses the placenta and US licensed product information recommends that use during pregnancy or at term should be undertaken with caution due to potential toxic effects on the fetus. Equivalent UK information lists pregnancy as a contra-indication to the systemic use of chloramphenicol. However, see also p. 260.3

Chloramphenicol may interfere with the development of immunity and it should not be given during active immunisation.

Breast feeding. Chloramphenicol is distributed into breast milk[1] and the last available guidance from the American Academy of Pediatrics[2] considered that its use by mothers during breast feeding might be of concern, since there have been reports of possible idiosyncratic bone-marrow suppression in the infant.

1. Havelka J, *et al.* Excretion of chloramphenicol in human milk. *Chemotherapy* 1968; **13:** 204–11.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Ocular use. Ocular chloramphenicol is widely used in the UK for the treatment of superficial eye infections. In view of the potential for serious toxicity, such as aplastic anaemia, after systemic absorption some, particularly in the USA, have advised that its ocular use should be restricted to situations where there is no alternative treatment.[1] However, apart from patients with a personal or family history of blood dyscrasias, the use, particularly of short courses, was defended by several specialists in the UK,[2-4] and the arguments have been the subject of several reviews.[5-7] Prospective case-control studies were considered necessary to clarify the risk.[8] One such study,[9] involving 145 patients with aplastic anaemia and 1226 controls, found that only 3 of the patients had been exposed to ocular chloramphenicol, and calculated that the absolute risk was no more than 0.5 cases per million treatment courses. Similarly, data[10] from 2 other studies revealed that none of 426 patients with aplastic anaemia and 7 of 3118 controls had used chloramphenicol eye drops. In a survey[11] of patients who received prescriptions for chloramphenicol eye drops the risk of serious haematological toxicity was 3 per 442 543 patients or 3 per 674 148 prescriptions.

1. Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? *BMJ* 1995; **310:** 1217–18.
2. Mulla RJ, *et al.* Is it time to stop using chloramphenicol on the eye: fears are based on only six cases. *BMJ* 1995; **311:** 450.
3. Buckley RJK, *et al.* Is it time to stop using chloramphenicol on the eye: safe in patients with no history of blood dyscrasia. *BMJ* 1995; **311:** 450.
4. Hall AV, *et al.* Is it time to stop using chloramphenicol on the eye: risk is low in short courses. *BMJ* 1995; **311:** 450–1.
5. McGhee CNJ, Anastas CN. Widespread ocular use of topical chloramphenicol: is there justifiable concern regarding idiosyncratic aplastic anaemia? *Br J Ophthalmol* 1996; **80:** 182–4.
6. Rayner SA, Buckley RJ. Ocular chloramphenicol and aplastic anaemia: is there a link? *Drug Safety* 1996; **14:** 273–6.
7. Titcomb L. Ophthalmic chloramphenicol and blood dyscrasias: a review. *Pharm J* 1997; **258:** 28–35.
8. Gordon-Smith EC, *et al.* Is it time to stop using chloramphenicol on the eye: prospective study of aplastic anaemia should give definitive answer. *BMJ* 1995; **311:** 451.
9. Laporte J-R, *et al.* Possible association between ocular chloramphenicol and aplastic anaemia—the absolute risk is very low. *Br J Clin Pharmacol* 1998; **46:** 181–4.
10. Wiholm B-E, *et al.* Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ* 1998; **316:** 666.
11. Lancaster T, *et al.* Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database. *BMJ* 1998; **316:** 667.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chloramphenicol as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Pregnancy. A case-control study involving 22865 women whose babies had congenital abnormalities and 38 151 controls found that 52 of the former and 51 of the latter had taken oral chloramphenicol (usually with other drugs) during pregnancy.[1] There was no evidence of a teratogenic effect of chloramphenicol, and it was thought to pose little risk in early pregnancy.

1. Czeizel AE, *et al.* A population-based case-control teratologic study of oral chloramphenicol treatment during pregnancy. *Eur J Epidemiol* 2000; **16:** 323–7.

Sodium content. Each g of chloramphenicol sodium succinate represents about 2.2 mmol of sodium.

Interactions

The use of chloramphenicol with other drugs that can cause bone-marrow depression may increase the risk of haematological toxicity, and should be avoided.

Chloramphenicol is inactivated in the liver and may, therefore, interact with drugs that are metabolised by hepatic microsomal enzymes. For example, it enhances the effects of coumarin anticoagulants, such as dicoumarol and warfarin, some hypoglycaemics such as chlorpropamide and tolbutamide, and antiepileptics such as phenytoin. Conversely, the metabolism of chloramphenicol may be increased by inducers of hepatic enzymes such as phenobarbital or rifampicin. Some other interactions affecting the activity of chloramphenicol are discussed below.

Chloramphenicol may decrease the effects of iron and vitamin B_{12} in anaemic patients and has occasionally impaired the action of oral contraceptives.

For the effects of chloramphenicol on the activity of other antibacterials, see Antimicrobial Action, p. 261.1.

Analgesics. A report of an increase in chloramphenicol half-life from 3.25 to 15 hours when intravenous *paracetamol* was given to 6 patients in intensive care 2 hours after intravenous chloramphenicol[1] was not confirmed by subsequent studies in patients receiving oral paracetamol. A study in 5 children found that the half-life of intravenous

chloramphenicol was reduced from 3 to 1.2 hours, with an increase in clearance, when oral paracetamol was given 30 minutes beforehand.[2] Furthermore, a study in 26 children found no evidence of altered disposition when oral paracetamol was given to patients receiving intravenous chloramphenicol,[3] and no significant change in chloramphenicol pharmacokinetics was found in 5 patients given oral chloramphenicol and paracetamol.[4]

1. Buchanan N, Moodley GP. Interaction between chloramphenicol and paracetamol. *BMJ* 1979; **2:** 307–8.
2. Spika JS, *et al*. Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* 1986; **61:** 1121–4.
3. Kearns GL, *et al*. Absence of a pharmacokinetic interaction between chloramphenicol and acetaminophen in children. *J Pediatr* 1985; **107:** 134–9.
4. Stein CM, *et al*. Lack of effect of paracetamol on the pharmacokinetics of chloramphenicol. *Br J Clin Pharmacol* 1989; **27:** 262–4.

Antiepileptics. Serum concentrations of chloramphenicol are usually reduced by the hepatic enzyme induction that occurs with *phenobarbital*,[1,2] and similar reductions have been reported in a case study during *phenytoin* use.[3] Conversely, elevated and potentially toxic serum-chloramphenicol concentrations have resulted during phenytoin use,[2] apparently due to competition for binding sites, although increased metabolism may alternatively lead to decreased serum-chloramphenicol concentrations.

For reference to the effects of chloramphenicol on phenobarbital and phenytoin, see p. 537.2 and p. 542.3, respectively.

1. Bloxham RA, *et al*. Chloramphenicol and phenobarbitone—a drug interaction. *Arch Dis Child* 1979: **54:** 76–7.
2. Krasinski K, *et al*. Pharmacologic interactions among chloramphenicol, phenytoin and phenobarbital. *Pediatr Infect Dis* 1982; **1:** 232–5.
3. Powell DA, *et al*. Interactions among chloramphenicol, phenytoin, and phenobarbital in a pediatric patient. *J Pediatr* 1981; **98:** 1001–3.

Antineoplastics. For the effect of chloramphenicol on *cyclophosphamide*, see p. 773.2.

Gastrointestinal drugs. Fatal aplastic anaemia of rapid onset has occurred in 2 patients who received intravenous chloramphenicol and *cimetidine*.[1,2] As there is usually a latent period of 2 weeks to 12 months before aplastic anaemia develops after chloramphenicol therapy it is plausible that an additive or synergistic effect may have occurred between the 2 drugs to cause bone-marrow toxicity.

1. Farber BF, Brody JP. Rapid development of aplastic anemia after intravenous chloramphenicol and cimetidine therapy. *South Med J* 1981; **74:** 1257–8.
2. West BC, *et al*. Aplastic anemia associated with parenteral chloramphenicol: review of 10 cases, including the second case of possible increased risk with cimetidine. *Rev Infect Dis* 1988; **10:** 1048–51.

Immunosuppressants. For the effect of chloramphenicol on *ciclosporin* and on *tacrolimus*, see p. 1956.1 and p. 1977.3, respectively.

Oral contraceptives. For the effect of chloramphenicol on oral contraceptives, see Hormonal Contraceptives, p. 2243.1.

Antimicrobial Action

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum of action against both Gram-positive and Gram-negative bacteria, as well as some other organisms.

Mechanism of action. Chloramphenicol is thought to enter sensitive cells by an active transport process. Within the cell it binds to the 50S subunit of the bacterial ribosome at a site adjacent to the site of action of the macrolides and clindamycin, and inhibits bacterial protein synthesis by preventing attachment of aminoacyl transfer RNA to its acceptor site on the ribosome, thus preventing peptide bond formation by peptidyl transferase. The block in protein synthesis results in a mainly bacteriostatic action, although it may be bactericidal to some organisms, including *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, at higher concentrations.

Spectrum of activity. Chloramphenicol has activity against many types of bacteria, although in most cases there are less toxic alternatives available. The following pathogens are usually susceptible (but see also Resistance, below):

- Gram-positive cocci including streptococci such as *Str., pneumoniae*, *Str. pyogenes*, and the viridans streptococci. Strains of *Staphylococcus aureus* may be less susceptible, and meticillin-resistant staphylococci are commonly found to be resistant. Enterococcal species are often resistant, but activity against some strains of vancomycin-resistant enterococci has been reported
- other Gram-positive species including *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Listeria monocytogenes*, and anaerobes such as *Actinomyces* spp., *Peptococcus*, and *Peptostreptococcus* spp. are usually susceptible. While most *Clostridium* spp. are susceptible, many strains of *C. difficile*, particularly those of serogroup C, are resistant
- Gram-negative cocci such as *Neisseria meningitidis* and *N. gonorrhoeae* are usually highly sensitive, as are *Haemophilus influenzae* and a variety of other Gram-negative bacteria including *Bordetella pertussis*, *Brucella abortus*, *Campylobacter* spp., *Pasteurella*, and *Vibrio* spp. Despite good *in-vitro* activity against *Legionella* spp., chloramphenicol is not as active *in-vivo* as many other antibacterials (particularly macrolides and fluoroquinolones) against *L. pneumophila*

The Enterobacteriaceae vary in their susceptibility, and many strains have shown acquired resistance (see below). The susceptibility of *Escherichia coli* has marked geographic variability, but other Enterobacteriaceae, including *Citrobacter*, *Enterobacter*, *Klebsiella*, *Proteus*, *Shigella*, *Salmonella*, and *Yersinia* spp. are generally susceptible. Chloramphenicol has poor activity against *Serratia* spp., and *Pseudomonas aeruginosa* are invariably resistant, although *Burkholderia* (formerly *Pseudomonas*) spp. are often susceptible

- Gram-negative anaerobes are generally susceptible including *Bacteroides fragilis*, *Veillonella*, and *Fusobacterium* spp.
- other susceptible organisms include *Leptospira* spp., spirochaetes such as *Treponema pallidum*, Chlamydiaceae, Mycoplasma spp., and Rickettsia spp.
- *Nocardia* spp. are resistant
- Chloramphenicol is ineffective against protozoa and viruses. However, its reported activity against *Batrachochytrium dendrobatitis*, a fungus affecting frogs, has suggested the possibility of activity against other fungi

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility exists of an antagonistic effect if chloramphenicol is given with a bactericidal drug, and some antagonism has been shown *in vitro* between chloramphenicol and various beta lactams and aminoglycosides. The clinical significance of most of these interactions is usually held to be doubtful, but care is advisable where patient factors or infection severity make bactericidal activity desirable. Chloramphenicol may competitively inhibit the effects of macrolides or lincosamides such as clindamycin because of the adjacency of their binding sites on the ribosome.

Resistance. Acquired resistance has been widely reported, although the prevalence of resistance has tended to decline where use of the drug has become less frequent. The most commonly seen form of resistance has been the production of an acetyltransferase that inactivates the drug. Such resistance is usually plasmid-mediated and may be associated with resistance to other drugs such as the tetracyclines. Other mechanisms that may reduce sensitivity to chloramphenicol include reduced permeability or uptake, and ribosomal mutation.

The actual incidence of resistance varies considerably in different countries and different centres. Epidemics of chloramphenicol-resistant *Salmonella* and *Shigella* spp. have occurred in many areas of the world, particularly in South and South-east Asia and Central and South America, and often reflect local usage patterns of chloramphenicol. Greater use of alternative antibacterials has more recently resulted in a decline in chloramphenicol resistance in some countries where it was formerly common. Resistance among *Haemophilus* and *Neisseria* spp. occurs, and the latter may be problematic in developing countries, although it does not yet seem to be widespread. Acquired resistance has also been reported in *Staph. aureus*, *Str. pneumoniae*, and *Str. pyogenes*.

Pharmacokinetics

Chloramphenicol is readily absorbed when given orally. Blood concentrations of 10 micrograms/mL or more may occur about 1 or 2 hours after a single oral dose of 1 g. Chloramphenicol palmitate is hydrolysed to chloramphenicol in the gastrointestinal tract before absorption, and the sodium succinate, which is given parenterally, is probably hydrolysed to free drug mainly in the liver, lungs, kidneys, and plasma; such hydrolysis may be incomplete in infants and neonates, contributing to the variable pharmacokinetics in this age group. Chloramphenicol sodium succinate is, even in adults, only partially and variably hydrolysed, so that blood concentrations of chloramphenicol obtained after the sodium succinate is given parenterally are often lower than those obtained after oral chloramphenicol, with up to 30% of a dose excreted unchanged in the urine before hydrolysis can take place (but see under Administration, p. 257.3).

Chloramphenicol is widely distributed in body tissues and fluids; it enters the CSF, giving concentrations of about 50% of those existing in the blood even in the absence of inflamed meninges; it diffuses across the placenta into the fetal circulation, into breast milk, and into the aqueous and vitreous humours of the eye. It also enters the aqueous humour after topical application. Up to about 60% in the circulation is bound to plasma protein. The half-life of chloramphenicol has been reported to range from 1.5 to 4 hours; the half-life is prolonged in patients with severe hepatic impairment and is also much longer in neonates. Renal impairment has relatively little effect on the half-life of the active drug, due to its extensive metabolism, but may lead to accumulation of the inactive metabolites.

Chloramphenicol is excreted mainly in the urine but only 5 to 10% of an oral dose appears unchanged; the remainder is inactivated in the liver, mostly by conjugation with glucuronic acid. About 3% is excreted in the bile. However, most is reabsorbed and only about 1%, mainly in the inactive form, is excreted in the faeces.

The absorption, metabolism, and excretion of chloramphenicol are subject to considerable interindividual variation, especially in infants and children, making monitoring of plasma concentrations necessary to determine pharmacokinetics in a given patient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anuar; Bioticaps; Chloromycetin; Farmicetina; Isopto Fenicol; Klonalfenicol; Pluscloran†; Poenfenicol; Quemicetina†; ***Austral.***: Chloromycetin; Chlorsig; ***Austria***: Halomycetin; Kemicetin†; Oleomycetin†; ***Braz.***: Arifenicol; Clorafenil; Neo Fenicol; Profenicol†; Quemicetina; Sintomicetina; Uni Fenicol†; Visalmin; Vixmicina; ***Canad.***: Ak-Chlor; Chloromycetin; Chloroptic†; Diochloram; Pentamycetin; ***Chile***: Chloromycetin†; Clorampast; Gemitin; ***China***: Moisten (润舒); ShuEr (舒尔); Tianli Runzhu (天力润珠); ***Fin.***: Chloromycetin; Oftan Akvakol; Oftan Chlora; ***Ger.***: Posifenicol C; ***Gr.***: Chloranic; Chlorocollyre; Chloromyk; Chloroptic; Kemicetine; Kemipen; Kramerin; Maltogen; Niamycetine; Ursa-Fenol; ***Hong Kong***: Aristophen; Chloroph; Chlorsig; Elisca; Europhenicol; Isopto Fenicol†; Kemicetine; Optivis; Venicol†; Xepanicol; ***India***: Aglomycetin; Andrecin; Biophenicol; Chemocetin; Chloraxin; Chlormet; Chlorocin; Chloromycetin; Daclor; Decol; Dexoren; Enclor; Enteromycetin; Eptico; Fencol; Kemicetine; Labchlor; Larmycetin; Ocuchlor; Oculor; Optocol; Paraxin; Reclor; Vanmycetin; Vitamycetin; ***Indon.***: Chloramex; Chlorbiotic†; Cloramidina; Colain†; Colme; Colsancetine; Combicetin; Empeecetin; Enkacetyn; Fenicol; Ikamicetin; Isotic Salmicol; Kalmicetine; Kemicetine; Lanacetine; Licoklor; Microtina†; Neophenicol†; Palmicol; RECO; Ribocine; Spersanicol†; Suprachlor; Xepanicol; ***Irl.***: Chloromycetin; ***Israel***: Chlorphenicol; Phenicol; Synthomycine; ***Ital.***: Chemicetina; Mycetin; Sificetina; Vitamfenicolo; ***Malaysia***: Beaphenicol; Chloramex; Nicol; Xepanicol†; ***Mex.***: Abefen; Bariclor†; Brocil; Chloromycetin; Clomicin†; Clorafen†; Cloramed†; Cloramfeni; Clorampler; Cloran; Cloranmicron; Cloratenol; Clorazin; Clordil†; Clorfenil†; Clorofunon; Clorotan; Diarman; Dilclor†; Enteromicin; Estreptopal; Exacol; Fenicol; Fenisol; Fenizzard†; Lebrocetin; Leclor A†; Naxo†; Oftadil; Omycet†; Palcol†; Palmiclor; Palmifer; Palmisol; Procloril†; Pronicol; Quemicetina; Solvaris; Uniclor; ***NZ***: Chlorafast; Chloromycetin; Chlorsig; ***Philipp.***: Alphagram Otic; Anpheclor; Aphrenil; Biomycetin; C-Phenicol; Chloro-S; Chloro-V; Chlorocaire; Chloromycetin; Chlorsig; CLM; Clovicol; Esnicol†; Fen-Alcon†; Forastrol†; Genphenil; Gerafen; Kemicetine†; Klorfen; Klornik; Medimycetin; Medoptic; Metrophenicol; Oliphenicol; Optomycin; Pediachlor; Penachlor; Septicyn; Typhiclor; Venimicetin; Vistachlor; ***Pol.***: Detreomycyna; ***Port.***: Clorocil; Micetinoftalmina; ***Rus.***: Levomycetin (Левомицетин); Synthomycin (Синтомицин); ***S.Afr.***: Chloramex; Chlorchol; Chlorcol; Chlornicol; Chloromycetin; Chlorphen; Lennacol†; Spersanicol; ***Singapore***: Beaphenicol; Enclor; Isopto Fenicol; Kemicetine†; Optichlor; Xepanicol; ***Swed.***: Chloromycetin; ***Switz.***: Septicol†; ***Thai.***: Antibi-Otic; Archifen; Chlor-Pyrad; Chloracil; Chloram-P; Chloramno†; Chloroph; Chlorosin†; Cogenate†; Cogetine; Fenicol; Genercin†; Levornycetin†; Med-Chloramp; Mycochlorin†; Pharmacetin; Pisalin; Silmycetin; Synchlolim; Unison Ointment; Vanafen; ***Turk.***: Armisetin†; Kemicetine; Klorasuksinat; ***UK***: Brochlor; Chloromycetin; Clorogen; Golden Eye; Kemicetine; Optrex Infected Eyes; ***Ukr.***: Laevomycetin (Левомицетин); ***USA***: Chloromycetin†; ***Venez.***: Cloftal.

Multi-ingredient Preparations. ***Arg.***: Acnoxin; Antiflogol; Bioftal; Clorfibrase; Colirio Antibiotico CNH; Colirio Oftalmico; Esodar; Fluoropoen; Iruxol; Klonovan; Neocortizul†; Oftal-D; Poenbioptal; Quemicetina con Hidrocortisona; Quemicetina Nasal Compuesta; ***Austria***: Cortison Kemicetin†; Oleomycetin-Prednison†; ***Belg.***: De Icol; ***Braz.***: Dexafenicol; Epitezan; Fenidex; Fibrase; Fibrinase c/Cloranfenicol; Gino Fibrase; Gino Kollagenase; Gyno Iruxol; Iruxol; Kollagenase com cloranfenicol; Naxogin Composto; Otomicina; Ouvidonal; Profenicol†; Regencel; Regenom; Sulnil; ***Canad.***: Pentamycetin-HC; ***Chile***: Gemitin con Prednisolona; Naxogin Compositum†; Otandrol; Sintoftona; ***China***: Fukexin (复可欣); ***Cz.***: Spersadex Compositum; ***Denm.***: Spersadex Comp; ***Fin.***: Iruxol†; Oftan C-C; Oftan Dexa-Chlora; ***Fr.***: Cebedexacol†; ***Ger.***: Aquapred†; Ichthoseptal†; ***Gr.***: Chlorapred; Cortiphenol H; Dexachlor; Dispersadron-C; Geypirina; Neo-Otil; Nezefib; Otenor; Spersadexoline; Sulfachlor; Sulfachloramphenicol; Sulfanicole; ***Hong Kong***: Anlina†; Cortiphenol H†; Dexanicol†; Eurodron; Neo-Dex (Improved); Sonexa-C; Spersadex Comp; ***India***: A-Cof; Adcort; Advin-NC; Arima; Bactisone; Beclocin-O; Belmycetin-C†; Bestec; Biomycetin; Candibiotic; CBL; Chloramsone; Chlormet-DM; Chlormixin†; Chloromycetin Ear Drops; CLCD; Clobiotic; Deco-AT; Deco; Decol-C; Decol-P; Denclor; Dexamon; Dexoren-S; Dexosyn-C†; Eligao; Enteromycetin Otic; Eptico-D; Excan; Eyclor-Dexa; Eyclor; Flubichlor; Fungi-BC; Infabact; Kemicetine Antiozena; LBC; Mycin; Mycotic; Ocupol-D; Ocupol; Olotic; Otek-AC Plus; Otiden; Otiderm; Otina; Otocin; Otocos; Otosym; Perfocyn†; Pyrimon; ***Indon.***: Chloramphecort-H; Chloramphecort;

Gynoxa; Indoson; Kemiderm; Kloramixin D; Kloramixin; Klorfeson; Naxogin Complex; Otolin; Particol†; Ramicort; Spersadex Comp; ***Israel***: Phenimixin; Tarocidin D; Tarocidin; Threolone; ***Ital.***: Antibioptal; Betabioptal; Cloradex; Colbiocin; Colbiocin; Cortison Chemicetina; Cosmiciclina; Eubetal Antibiotico; Eubetal Antibiotico; Idracemi; Iruxol; Vasofen; Xantervit Antibiotico; ***Malaysia***: De Icol; Spersadexoline†; ***Mex.***: Cloramfeni Otico; Cloran Otico†; Cloxona-O; Fibrase; Levodexan; Levofenil; Nispil; Ofodex; Otalgan; Otifar; Otiser; Poral; Pre Clor; Soldrin; Solfranicol; Sulfa Cloran; Trecloran†; Ulcoderma†; ***Norw.***: Spersadex med kloramfenikol; ***Philipp.***: Dexanicol; Iclodex; Ipecor; Spersadex Compound; ***Port.***: Predniftalmina; ***Rus.***: Candibiotic (Кандибиотик); Colbiocin (Колбиоцин); Colbiocin (Колбиоцин); Cortomycetin (Кортомицетин); Iruxol (Ируксол)†; Levomecol (Левомеколь); Levometil (Левометил); Levosin (Левосин); Netran (Нетран); Olasol (Олазоль); Saledez (Саледез); ***S.Afr.***: Covomycin-D; Covomycin; Covotop†; Spersadex Comp; Spersadexoline†; ***Singapore***: Spersadex Comp; Spersadexoline; ***Spain***: Blefarida†; Cloram Hemidex†; Cloram Zinc†; Cortison Chemicet Topica; Dermisone Epitelizante†; Icol; Medrivas Antib; ***Switz.***: Spersadex Comp; ***Thai.***: Archifen; CD-Oph; Chlorotracin†; Dermasol; Levoptin; Spersadexoline†; Vagicin; ***UK***: Actinac†; ***Ukr.***: Candibiotic (Кандибиотик); Micogynax (Микожинакс); ***Venez.***: Clorasona.

Pharmacopoeial Preparations

BP 2014: Chloramphenicol Capsules; Chloramphenicol Ear Drops; Chloramphenicol Eye Drops; Chloramphenicol Eye Ointment; Chloramphenicol Sodium Succinate Injection;

USP 36: Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Prednisolone Ophthalmic Ointment; Chloramphenicol Capsules; Chloramphenicol Cream; Chloramphenicol for Ophthalmic Solution; Chloramphenicol Ophthalmic Ointment; Chloramphenicol Ophthalmic Solution; Chloramphenicol Otic Solution; Chloramphenicol Palmitate Oral Suspension; Chloramphenicol Sodium Succinate for Injection; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment.

Chloroxine *(USAN)*

Cloroxinum; 5,7-Dichlorochinolin-8-ol; 5,7-Dichloroquinolin-8-ol; Kloroxin; Хлороксин.

$C_9H_5Cl_2NO$=214.0

CAS — 773-76-2.

UNII — 2I8BD5OI8B.

Profile

Chloroxine is a halogenated hydroxyquinoline with antibacterial and antifungal properties similar to those of clioquinol (p. 275.1). It is given orally in preparations for acute infectious diarrhoea. It has also been used topically in the treatment of dandruff and seborrhoeic dermatitis of the scalp.

Chloroxine is a component of halquinol (p. 311.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Endiaron; Endioderm; ***USA***: Capitrol†.

Multi-ingredient Preparations. ***Cz.***: Triaderm†; Triamcinolon E; ***Ital.***: Beben Clorossina.

Chlorquinaldol *(BAN, rINN)*

Chlorochinaldol; Chlorquinaldolum; Clorquinaldol; Kloorikinaldoli; Klorkinaldol; Хлорхинальдол.

5,7-Dichloro-2-methylquinolin-8-ol.

$C_{10}H_7Cl_2NO$=228.1

CAS — 72-80-0.

ATC — D08AH02; G01AC03; P01AA04; R02AA11.

ATC Vet — QD08AH02; QG01AC03; QR02AA11.

UNII — D6VHC87LLS.

Pharmacopoeias. In *Pol.*

Profile

Chlorquinaldol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p. 275.1). It is mainly applied topically in infected skin conditions and in vaginal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Gynosan; ***Ukr.***: Chinofucin-LH (Хинофуцин-ЛХ); Chlorchinaldin (Хлорхинальдин)†.

Multi-ingredient Preparations. ***Arg.***: Nerisona C; ***Braz.***: Bi-Nerisona; ***Chile***: Bi-Nerisona†; ***China***: Colposeptine (可宝净); ***Denm.***: Locoidol†; ***Fr.***: Nerisone C; ***Gr.***: Nerisona C; ***Hong Kong***: Colposeptine; Nerisone C; ***Indon.***: Nerisona Combi; ***Irl.***: Locoid C†; ***Israel***: Multiderm; ***Ital.***: Impetex; Nerisona C; ***Mex.***: Bi-Nerisona; ***Mon.***: Colposeptine; ***Norw.***: Locoidol†; ***NZ***: Locoid C; Nerisone C; ***Philipp.***: Nerisona Combi; ***Pol.***: Chlorchinaldin H; Gynalgin; Laticort-CH†; ***Port.***: Nerisona C; Trophoseptine; ***Rus.***: Gynalgin (Гиналгин); ***Spain***: Claral Plus; ***Switz.***: Anginazol; ***Turk.***: Colposeptine; Impetex; Nerisona C; ***Ukr.***: Colposeptine (Колпосептин); Gynalgin (Гиналгин); ***Venez.***: Binerisona.

Chlortetracycline *(BAN, rINN)*

Chlortetracyclin; Chlortétracycline; Chlortetracyclinum; Chlortetracyklin; Clortetraciclina; Klooritetrasykliini; Klortetracyclin; Хлортетрациклин.

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide; 7-Chlorotetracycline.

$C_{22}H_{23}ClN_2O_8$=478.9

CAS — 57-62-5.

ATC — A01AB21; D06AA02; J01AA03; S01AA02.

ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QJ51AA03; QS01AA02.

UNII — WCK1KIQ23Q.

Chlortetracycline Bisulfate *(BANM, rINNM)*

Bisulfato de clortetraciclina; Chlortétracycline, Bisulfate de; Chlortetracycline Bisulphate; Chlortetracyclini Bisulfas; Clortetraciclina, bisulfato de; Хлортетрациклина бисульфат.

UNII — 1D06KZ672I.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Chlortetracycline Bisulfate). Store in airtight containers. Protect from light.

Chlortetracycline Hydrochloride

(BANM, rINNM)

Chlorotetrackliny chlorowodorek; Chlortetraciklino hidrochloridas; Chlortétracycline, Chlorhydrate de; Chlortetracyclinhydrochlorid; Chlortetracyclini Hydrochloridum; Chlortetracyklin-hydrochlorid; Clortetraciclina, hidrocloruro de; Hidrocloruro de clortetraciclina; Klooritetrasykliinihydrokloridi; Klórtetraciklin-hidroklorid; Klortetracyklinhydroklorid; Хлортетрациклина гидрохлорид.

$C_{22}H_{23}ClN_2O_8HCl$=515.3

CAS — 64-72-2.

ATC — A01AB21; D06AA02; J01AA03; S01AA02.

ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QS01AA02.

UNII — O1GX33ON8R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Chlortetracycline Hydrochloride). The hydrochloride of a substance produced by the growth of certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Slightly soluble in water and in alcohol; it dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.3 to 3.3. Protect from light.

USP 36: (Chlortetracycline Hydrochloride). A yellow, odourless crystalline powder. Soluble 1 in 75 of water and 1 in 560 of alcohol; practically insoluble in acetone, in chloroform, in dioxan, and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.3 and 3.3. Store in airtight containers. Protect from light.

Profile

Chlortetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p. 375.1) and is used as the hydrochloride, more often topically than orally. It is used as a 1% ophthalmic ointment and as a 3% ointment for application to the skin. It is poorly absorbed from the gastrointestinal tract compared with other tetracyclines but it has sometimes been given orally with other tetracycline derivatives.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlortetracycline as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Aureomycin; Aureomycine†; ***Fr.***: Aureomycine; ***Ger.***: Aureomycin; ***Gr.***: Aureomycin; ***Hong Kong***: Chlortralim; ***Ital.***: Aureomicina; ***Malaysia***: Chlortralim; ***Pol.***: Chlorocyclinum; ***Singapore***: Chlortralim; ***Spain***: Aureomicina; Dermosa Aureomicina; ***Thai.***: Aureomycin†; Chlortralim.

Multi-ingredient Preparations. ***Austria***: Aureocort; ***Braz.***: Corticlen; ***Ital.***: Aureocort; Aureomix; ***S.Afr.***: Tritet†; ***UK***: Aureocort.

Pharmacopoeial Preparations

BP 2014: Chlortetracycline Eye Ointment; Chlortetracycline Ointment;

USP 36: Chlortetracycline Hydrochloride Ointment; Chlortetracycline Hydrochloride Ophthalmic Ointment.

Ciclacillin *(BAN, rINN)*

Ciclacilina; Ciclacilline; Ciclacillinum; Ciklacillin; Cyclacillin (USAN); Siklasilliini; Wy-4508; Циклациллин.

(6*R*)-6-(1-Aminocyclohexanecarboxamido)penicillanic acid.

$C_{15}H_{23}N_3O_4S$=341.4

CAS — 3485-14-1.

UNII — 72ZJ154X86.

Pharmacopoeias. In *Jpn*.

Profile

Ciclacillin is an aminopenicillin with properties similar to those of ampicillin (p. 218.2), although it is generally less active *in vitro*.

Cilastatin Sodium *(BANM, USAN, rINNM)*

Cilastatin-Natrium; Cilastatin sodná sůl; Cilastatina sódica; Cilastatine Sodique; Cilastatinnatrium; Cilastatino natrio druska; Cilastatinum Natricum; Cilasztatin-nátrium; L-642957; MK-791; Natrii Cilastatinas; Natrii Cilastatinum; Natriumsilastatinaatti; Natriumsilastatinat; Silastatiininatrium; Silastatin Sodyum; Натрий Циластатин.

(*Z*)-(*S*)-6-Carboxy-6-[(*S*)-2,2-dimethylcyclopropanecarboxamido]hex-5-enyl-L-cysteine, monosodium salt.

$C_{16}H_{25}N_2NaO_5S$=380.4

CAS — 82009-34-5 (cilastatin); 81129-83-1 (cilastatin sodium).

UNII — 5428WXZ74M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cilastatin Sodium). A white or light yellow, hygroscopic, amorphous powder. Very soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone and in dichloromethane; very slightly soluble in dimethyl sulfoxide. A 1% solution in water has a pH of 6.5 to 7.5. Store at a temperature not exceeding 8 degrees in airtight containers.

USP 36: (Cilastatin Sodium). A white to tan-coloured powder. Soluble in water and in methyl alcohol. pH of a 1% solution in water is between 6.5 and 7.5. Store at a temperature less than 8 degrees.

Profile

Cilastatin is an inhibitor of dehydropeptidase I, an enzyme found in the brush border of the renal tubules. It is given as the sodium salt with the antibacterial imipenem (p. 311.2) to prevent its renal metabolism to microbiologically inactive and potentially nephrotoxic products. This increases the concentrations of imipenem achieved in the urine and protects against any nephrotoxic effects, which were seen with high doses of imipenem given experimentally to *animals*.

Cilastatin has no antibacterial activity itself, and does not affect the antibacterial activity of imipenem.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Dixabiox; Imipecil; Imistatin; Klonam; Zienam; ***Austral.***: Primaxin; ***Austria***: Zienam; ***Belg.***: Tienam; ***Braz.***: Tienam; Tiepem; ***Canad.***: Primaxin; ***Chile***: Inem; Tienam; ***China***: Bacqure (齐佩能); Prepenem (谱能); Tienam (泰能); ***Cz.***: Cilanem; Imecitin; Tienam; ***Fin.***: Tienam; ***Fr.***: Tienam; ***Ger.***: Zienam; ***Gr.***: Imicil; Nimedine; Primagal; Primalix; Primaxin; ***Hong Kong***: Prepenem; Tienam; ***Hung.***: Cilanem; Tienam; ***India***: Cilanem; Cilaspene; Cimispect; Flaminim; I-Nem; Ime-Cila; Imelastin; Imi-Cila; Iminem; Imitop; Lastinem; ***Indon.***: Elastyn; Pelastin; Tienam; Timipen; ***Israel***: Tienam; ***Ital.***: Imipem; Tenacid; Tienam; ***Malaysia***: Bacqure; Tienam; ***Mex.***: Arzomeba; Iminen†; Lemibet†; Opostibac; Tienam; ***Neth.***: Tienam; ***Norw.***: Tienam; ***NZ***: Primaxin; ***Philipp.***: Anipen; Penam; Plastin; Tienam; ***Pol.***: Ransetron; Tienam; ***Port.***: Tienam; ***Rus.***: Cilaspen (ЦИЛАСПЕН); Grimipenem (Гримипенем); Tienam (Тиенам); ***S.Afr.***: Tienam; ***Singapore***: Tienam; ***Spain***: Tienam; ***Swed.***: Tienam; ***Switz.***: Tienam; ***Thai.***: Bacqure; Cilapenem; Prepenem; Tienam; ***Turk.***: Silanem; Tienam; ***UAE***: Maxinem; ***UK***: Primaxin; ***Ukr.***: Lastinem (Ластинем)†; Sinerpen (Синерпен); Tienam (Тиенам); ***USA***: Primaxin; ***Venez.***: Zienam.

Pharmacopoeial Preparations

USP 36: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Cinoxacin *(BAN, USAN, rINN)*

64716; Azolinic Acid; Cinoxacine; Cinoxacino; Cinoxacinum; Compound 64716; Sinoksasiini; Циноксацин.

1-Ethyl-1,4-dihydro-4-oxo-1,3-dioxolo[4,5-g]cinnoline-3-carboxylic acid.

$C_{12}H_{10}N_2O_5$=262.2

CAS — 28657-80-9.

ATC — J01MB06.

ATC Vet — QJ01MB06.

UNII — LMK22VUH23.

Pharmacopoeias. In *US.*

USP 36: (Cinoxacin). A white to yellowish-white, odourless crystalline solid. Insoluble in water and in most common organic solvents; soluble in alkaline solution. Store in airtight containers.

Uses and Administration

Cinoxacin is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p. 330.3). In the treatment of urinary-tract infections the usual oral dose is 500 mg twice daily; for prophylaxis 500 mg is given at bedtime.

Administration in renal impairment. Cinoxacin should be used in reduced dosage, or not at all, in patients with renal impairment.

Adverse Effects and Precautions

As for Nalidixic Acid, p. 331.1.

Caution is needed in patients with renal impairment (see above).

References.

1. Stricker BHC, *et al.* Anaphylactic reactions to cinoxacin. *BMJ* 1988; **297:** 1434–5.

Interactions

As for Nalidixic Acid, p. 331.2.

Antimicrobial Action

As for Nalidixic Acid, p. 331.2. Cross-resistance with nalidixic acid has been shown.

Pharmacokinetics

Cinoxacin is rapidly and almost completely absorbed after oral doses. Peak serum concentrations of about 15 micrograms/mL occur 2 to 3 hours after a 500-mg dose. The plasma half-life is about 1 to 2 hours. Cinoxacin is more than 60% bound to plasma proteins.

Cinoxacin appears to be metabolised in the liver and is excreted via the kidney. Over 95% of a dose appears in the urine within 24 hours, over half as unaltered drug and the remainder as inactive metabolites. Mean urinary concentrations of about 300 micrograms/mL have been achieved during the first 4 hours after a 500-mg oral dose. Urinary excretion is reduced by probenecid and in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Cinobactin; Fleryl; Iristan-V; Londolife; Panafen; Simarlen; ***Ital.***: Cinobac; Cinocil; Cinoxen†; Uroc†; Urocinox.

Pharmacopoeial Preparations

USP 36: Cinoxacin Capsules.

Ciprofloxacin *(BAN, USAN, rINN)*

Bay-q-3939; Ciprofloksacinas; Ciprofloxacine; Ciprofloxacino; Ciprofloxacinum; Siprofloksasiini; Siprofloksasin; Siprofloxacin; Ципрофлоксацин.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

$C_{17}H_{18}FN_3O_3$=331.3

CAS — 85721-33-1.

ATC — J01MA02; S01AE03; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AE03; QS02AA15; QS03AA07.

UNII — 5E8K9I0O4U.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Ciprofloxacin). An almost white or pale yellow, slightly hygroscopic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Ciprofloxacin). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Avoid temperatures above 40 degrees. Protect from light.

Ciprofloxacin Hydrochloride

(BANM, USAN, rINNM)

Bay-o-9867; Ciprofloksacino hidrochloridas; Ciprofloxacine, chlorhydrate de; Ciprofloxacin-hidroklorid; Ciprofloxacin-hydrochlorid; Ciprofloxacinhydrochlorid; Ciprofloxacinhydroklorid; Ciprofloxacini Hydrochloridum; Ciprofloxacino, hidrocloruro de; Cyprofloksacyny chlorowodorek; Hidrocloruro de ciprofloxacino; Siprofloksasiinihydrokloridi; Siprofloksasin Hidroklorür; Ципрофлоксацина гидрохлорид.

Ciprofloxacin hydrochloride monohydrate.

$C_{17}H_{18}FN_3O_3$,HCl,H_2O=385.8

CAS — 86483-48-9 (anhydrous ciprofloxacin hydrochloride); 86393-32-0 (ciprofloxacin hydrochloride monohydrate).

ATC — J01MA02; S01AE03; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AE03; QS02AA15; QS03AA07.

UNII — 4BA73M5E37.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US*, and *Viet.*

Ph. Eur. 8: (Ciprofloxacin Hydrochloride). A pale yellow, slightly hygroscopic, crystalline powder. It contains a variable quantity of water. Soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in dichloromethane, and in ethyl acetate; slightly soluble in methyl alcohol. A 2.5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Ciprofloxacin Hydrochloride). Faintly yellowish to light yellow crystals. Sparingly soluble in water; very slightly soluble in dehydrated alcohol; slightly soluble in acetic acid and in methyl alcohol; practically insoluble in acetone, in acetonitrile, in dichloromethane, in ethyl acetate, and in hexane. pH of a 2.5% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Ciprofloxacin Lactate *(BANM, rINNM)*

Ciprofloxacine, Lactate de; Ciprofloxacini Lactas; Ciprofloxacino, lactato de; Lactato de ciprofloxacino; Ципрофлоксацина Лактат.

$C_{17}H_{18}FN_3O_3$,$C_3H_6O_3$=421.4

CAS — 97867-33-9.

ATC — J01MA02; S01AE03; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AE03; QS02AA15; QS03AA07.

UNII — UEY6XFC224.

Incompatibility. Ciprofloxacin infusion is stated in UK licensed product information to have a pH of 3.9 to 4.5 and to be incompatible with injections chemically or physically unstable at this pH range. Incompatibility has been reported between ciprofloxacin and other drugs including some antibacterials.[1-5]

1. Lyall D, Blythe J. Ciprofloxacin lactate infusion. *Pharm J* 1987; **238:** 290.
2. Janknegt R, *et al.* Quinolones and penicillins incompatibility. *DICP Ann Pharmacother* 1989; **23:** 91–2.
3. Goodwin SD, *et al.* Compatibility of ciprofloxacin injection with selected drugs and solutions. *Am J Hosp Pharm* 1991; **48:** 2166–71.
4. Jim LK. Physical and chemical compatibility of intravenous ciprofloxacin with other drugs. *Ann Pharmacother* 1993; **27:** 704–7.
5. Elmore RL, *et al.* Stability and compatibility of admixtures of intravenous ciprofloxacin and selected drugs. *Clin Ther* 1996; **18:** 246–55.

Stability. For mention of loss of activity in ciprofloxacin solutions exposed to ultraviolet light see under Precautions, p. 266.2.

Uses and Administration

Ciprofloxacin is a fluorinated 4-quinolone or fluoroquinolone antibacterial with a wider spectrum of activity than nalidixic acid (see Antimicrobial Action, p. 267.2) and more favourable pharmacokinetics allowing its use in systemic infections. It has been used in the treatment of infections caused by susceptible bacteria, including in anthrax, biliary-tract infections, infected bites and stings, bone and joint infections, cat scratch disease, chancroid, exacerbations of cystic fibrosis, ear, nose, and throat infections (including otitis externa, otitis media, and sinusitis), HACEK endocarditis, gastro-enteritis (including travellers' diarrhoea and campylobacter enteritis, cholera, salmonella enteritis, shigellosis, and yersinia enteritis), gonorrhoea, granuloma inguinale, infections in immunocompromised patients (neutropenia), legionnaires' disease, pelvic inflammatory disease, peritonitis, plague, lower respiratory-tract infections (including pseudomonal infections in cystic fibrosis, but excluding infections due to *Streptococcus pneumoniae* such as pneumococcal pneumonia), rickettsial infections (including Q fever, spotted fevers, and typhus), septicaemia, typhoid and paratyphoid fever, and urinary-tract infections including chronic bacterial prostatitis. It may be used for infections of skin or skin structures due to Gram-negative bacteria, although a fluoroquinolone which also has good activity against Gram-positive organisms may be preferred. Ciprofloxacin is also used for meningococcal meningitis prophylaxis, surgical infection prophylaxis, and in the treatment of nontuberculous mycobacterial infections; it has also been used to treat tuberculosis, but has largely been replaced in this role by more effective fluoroquinolones (see p. 264.2). Ciprofloxacin is used topically in the treatment of eye and ear infections.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Administration and dosage. Ciprofloxacin is given orally as the hydrochloride or base, by intravenous infusion as the lactate, and in eye drops, eye ointment, or ear drops as the hydrochloride. Doses and strengths are expressed in terms of the base. Ciprofloxacin hydrochloride 291.1 mg is equivalent to about 250 mg of ciprofloxacin. Ciprofloxacin lactate 127 mg is equivalent to about 100 mg of ciprofloxacin.

The usual oral dose of ciprofloxacin ranges from 250 to 750 mg twice daily depending on the severity and nature of the infection. Modified-release preparations for once-daily dosage are available in some countries. The usual intravenous dose is 200 mg twice daily to 400 mg 3 times daily, generally given over 60 minutes as a solution containing the equivalent of 1 to 2 mg/mL. A 28-day course of treatment with an oral dose of 500 mg twice daily or an intravenous dose of 400 mg twice daily should be given for chronic bacterial prostatitis. Bone and joint infections should be treated with an oral dose of 500 to 750 mg twice daily or an intravenous dose of 400 mg two or three times daily for 4 to 12 weeks; for malignant otitis externa, the higher doses are recommended for up to 3 months. Intravenous infusions of 400 mg three times daily have also been recommended in severe or complicated lower respiratory tract or skin infections, nosocomial pneumonia, and with piperacillin for empirical treatment of febrile neutropenic patients.

For treatment and postexposure prophylaxis of inhalation **anthrax**, a 60-day course of treatment with either intravenous doses of 400 mg twice daily or oral doses of 500 mg twice daily is recommended; although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of 500 to 750 mg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

Doses should be reduced in patients with severe renal impairment (see p. 264.1).

Single oral doses of 500 mg may be used for the treatment of **gonorrhoea**, depending upon patterns of resistance. A single oral dose of 750 mg has been used for surgical infection prophylaxis, given 60 minutes before the procedure. For **meningococcal meningitis** prophylaxis a single oral dose of 500 mg is recommended.

For details of doses in children, including adolescents, see p. 263.3.

For corneal ulcers and superficial **ocular infections** caused by susceptible strains of bacteria ciprofloxacin is given as the hydrochloride in eye drops and eye ointment containing the equivalent of 0.3% of ciprofloxacin.

Ciprofloxacin is also used topically as the hydrochloride in ear drops containing the equivalent of 0.2 or 0.3% of ciprofloxacin, usually with a corticosteroid such as dexamethasone or hydrocortisone, for the treatment of otitis externa and chronic suppurative otitis media caused by susceptible strains of bacteria.

General references to fluoroquinolones[1-8] including ciprofloxacin specifically.[9-12]

1. Balfour JA, Goa KL, eds. Proceedings of the 5th International symposium on new quinolones. *Drugs* 1995; **49** (suppl 2): 1–505.
2. Walker RC. The fluoroquinolones. *Mayo Clin Proc* 1999; **74:** 1030–7.
3. Smith A, *et al.* Fluoroquinolones: place in ocular therapy. *Drugs* 2001; **61:** 747–61.
4. Schaeffer AJ. The expanding role of fluoroquinolones. *Am J Med* 2002; **113** (suppl 1A): 45S–54S.
5. Zhanel GG, *et al.* A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* 2002; **62:** 13–59.
6. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. *Drugs* 2004; **64:** 1359–73.
7. Shams WE, Evans ME. Guide to selection of fluoroquinolones in patients with lower respiratory tract infections. *Drugs* 2005; **65:** 949–91.
8. Andriole VT. The quinolones: past, present, and future. *Clin Infect Dis* 2005; **41** (suppl 2): S113–S119.
9. Davis R, *et al.* Ciprofloxacin: an updated review of its pharmacology, therapeutic efficacy and tolerability. *Drugs* 1996; **51:** 1019–74.
10. Campoli-Richards DM, *et al.* Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1998; **35:** 373–447.
11. Gould FK, *et al.* , eds. Ten years of ciprofloxacin: the past, present and future. *J Antimicrob Chemother* 1999; **43** (suppl A): 1–134.
12. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 2004; **64:** 61 1–28.

Administration in children. Ciprofloxacin is not recommended for general use in children and adolescents (see

under Precautions, p. 266.1) but, if considered essential, it may be given orally or by intravenous infusion over 60 minutes. UK licensed product information recommends that for serious infections, oral doses of 20 mg/kg (maximum 750 mg) twice daily, or intravenous doses of 10 mg/kg (maximum 400 mg) three times daily may be used in those aged 1 year and older. For younger children, the *BNFC* recommends the following doses:

- neonates: 15 mg/kg orally, or 10 mg/kg intravenously, both twice daily
- from 1 month to 18 years: 20 mg/kg (maximum 750 mg) orally twice daily or 10 mg/kg (maximum 400 mg) three times daily

Ciprofloxacin is also licensed in different doses for specific indications as outlined below.

In the UK and the USA ciprofloxacin is licensed for the treatment and postexposure prophylaxis of inhalation **anthrax** in children and adolescents. A 60-day course of treatment with either intravenous doses of 10 mg/kg (to a maximum of 400 mg) twice daily or oral doses of 15 mg/kg (to a maximum of 500 mg) twice daily is recommended; the *BNFC* suggests that similar doses may be given to those as young as 1 month of age. Although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of up to 15 mg/kg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

It is also licensed in the UK for acute exacerbations of **cystic fibrosis** associated with *Pseudomonas aeruginosa* infection in those aged 1 year and older. An oral dose of 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 10 mg/kg (to a maximum of 400 mg) three times daily is recommended. Although not licensed for younger children, the *BNFC* suggests these doses are suitable for those aged 1 month and older.

Ciprofloxacin is also licensed in the UK and the USA for complicated **urinary-tract infections** or **pyelonephritis** in those aged 1 year and older. An oral dose of 10 to 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 6 to 10 mg/kg (to a maximum of 400 mg) three times daily is recommended. The *BNFC* suggests the following doses for younger children:

- neonates: 10 mg/kg orally or 6 mg/kg intravenously, both twice daily
- children from 1 month to 18 years of age: 10 to 20 mg/kg (maximum 750 mg) orally twice daily or 6 to 10 mg/kg intravenously (maximum 400 mg) three times daily

Although unlicensed in the UK, the *BNFC* suggests a single oral dose of 125 mg for **meningococcal meningitis prophylaxis** in children aged 1 month to 5 years; children aged 5 to 12 years may be given a single oral dose of 250 mg, and those aged over 12 years a single oral dose of 500 mg. Single oral doses of 500 mg have also been suggested for the treatment of **gonorrhoea** in those over 12 years of age.

Administration in renal impairment. The dose of ciprofloxacin should be reduced in ***adult patients*** with renal impairment by either reducing the total daily dose and/or by increasing the dosage interval in accordance with their creatinine clearance (CC); ideally plasma concentrations of ciprofloxacin should be monitored.

In the UK, usual doses may be used for those with a CC greater than 60 mL/minute; for lower CC, up to 500 mg orally or up to 400 mg intravenously may be given at the following intervals:

- CC 30 to 60 mL/minute: twice daily
- CC less than 30 mL/minute: once daily

For haemodialysis or peritoneal dialysis patients, up to 500 mg orally or 400 mg intravenously every 24 hours has been recommended; for haemodialysis patients, doses should be given after the dialysis run.

Alternatively, in the USA the following doses are recommended:

- CC 30 to 50 mL/minute: up to 500 mg orally every 12 hours or the usual dose intravenously
- CC 5 to 29 mL/minute: up to 500 mg orally every 18 hours or up to 400mg intravenously every 18 to 24 hours

A pharmacokinetic study in 10 critically ill patients undergoing continuous renal replacement therapy with continuous venovenous haemofiltration or haemodiafiltration suggested that an intravenous dose of ciprofloxacin 400 mg every 24 hours would be suitable in such situations.[1] Other authors have suggested that up to 400 mg twice daily may be necessary for patients undergoing continuous venovenous haemodialysis or haemofiltration.[2]

1. Malone RS, *et al.* Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother* 2001; **45:** 2949–54.
2. Trotman RL, *et al.* Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis* 2005; **41:** 1159–66.

Inflammatory bowel disease. Ciprofloxacin has been given, sometimes with metronidazole, in the management of active Crohn's disease[1,2] (see Inflammatory Bowel Disease, p. 1811.3), particularly for perianal fistulae.[3,4]

1. Prantera C, *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91:** 328–32.
2. Ishikawa T, *et al.* Metronidazole plus ciprofloxacin therapy for active Crohn's disease. *Intern Med* 2003; **42:** 318–21.
3. West RL, *et al.* Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2004; **20:** 1329–36.
4. Thia KT, *et al.* Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009; **15:** 17–24.

Tuberculosis. Although the newer fluoroquinolones are reported to have good *in-vitro* (levofloxacin, gatifloxacin, moxifloxacin) and *in-vivo* (gatifloxacin and moxifloxacin) bactericidal activity against *Mycobacterium tuberculosis*,[1] reviews[1,2] of data obtained from controlled studies, cohorts, and case series, published up to March 2006, evaluating the clinical efficacy of fluoroquinolones for the treatment of tuberculosis (p. 210.2) concluded that substituting or adding fluoroquinolones (in particular the older fluoroquinolones such as ciprofloxacin or ofloxacin) to established first-line treatment regimens did not confer additional benefits. In a later study,[3] substitution of moxifloxacin for ethambutol in a first-line treatment regimen (including isoniazid, rifampicin, and pyrazinamide) resulted in a significantly higher rate of negative culture conversion at 8 weeks, suggesting that use of moxifloxacin with other first-line drugs might shorten the time needed to cure tuberculosis by several months, although further study is needed.

There are very few controlled studies evaluating the use of fluoroquinolones in multidrug-resistant tuberculosis (MDR-TB), but 2 retrospective studies support their efficacy.[1] WHO guidelines[4,5] recommend that patients with suspected or confirmed MDR-TB should receive second-line antituberculous drugs as part of a DOTS-plus regimen; such drugs include ofloxacin, levofloxacin, and moxifloxacin. The usual recommended oral doses are as follows:[5]

- moxifloxacin: 400 mg daily
- levofloxacin: 750 mg to 1 g daily
- ofloxacin: 800 mg to 1 g daily

Because of its relatively weak efficacy compared with other fluoroquinolones, ciprofloxacin is no longer recommended by WHO for the treatment of either susceptible or drug-resistant tuberculosis.

1. Moadebi S, *et al.* Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs* 2007; **67:** 2077–99.
2. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/07/08).
3. Sellier P, *et al.* Moxifloxacin versus ethambutol in initial tuberculosis treatment. *Lancet* 2009; **373:** 1183–9.
4. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/02/10)
5. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008.* Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 08/02/10)

Adverse Effects

Ciprofloxacin is generally well tolerated. The range of adverse effects associated with ciprofloxacin and the other fluoroquinolones is broadly similar to that of earlier quinolones such as nalidixic acid (p. 331.1). They most often involve the gastrointestinal tract, CNS, or skin.

Gastrointestinal disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia and are the most frequent adverse effects. Pseudomembranous colitis, pancreatitis, and dysphagia have been reported rarely.

Headache, dizziness, confusion, insomnia, and restlessness are among the commonest effects on the CNS. Others include tremor, drowsiness, nightmares, visual and other sensory disturbances, hallucinations, psychotic reactions, depression, convulsions, and intracranial hypertension. Paraesthesia and peripheral neuropathy have also been reported.

In addition to rash and pruritus, hypersensitivity-type reactions affecting the skin have included, rarely, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity has occurred, although it may be more frequent with some other fluoroquinolones such as lomefloxacin and sparfloxacin. Anaphylaxis has been associated with ciprofloxacin and some other quinolones. As with other quinolones, reversible arthralgia or myalgia has sometimes occurred and joint erosions have been documented in immature *animals*. Tendon damage has also been reported.

Fluoroquinolones have neuromuscular-blocking activity, which may exacerbate muscle weakness in patients with myasthenia gravis. In rare cases, severe exacerbations leading to respiratory failure or death have occurred.

Other adverse effects reported with ciprofloxacin include crystalluria, transient increases in serum creatinine or blood urea nitrogen and, rarely, acute renal failure secondary to interstitial nephritis. Elevated liver enzyme values, jaundice, and hepatitis have occurred, as have haematological disturbances including eosinophilia, leucopenia, thrombocytopenia and, very rarely, pancytopenia, haemolytic anaemia or agranulocytosis. Cardiovascular adverse effects include tachycardia, hypotension, oedema, syncope, hot flushes, and sweating. Some fluoroquinolones may rarely cause prolongation of the QT interval and ventricular arrhythmias, including torsade de pointes (see p. 264.3).

As with other antibacterials, superinfection with organisms not very susceptible to ciprofloxacin is possible. Such organisms include *Candida, Clostridium difficile*, and *Streptococcus pneumoniae*. There is some evidence that fluoroquinolone use may be associated with an increased risk of colonisation by MRSA.

Pain and irritation may occur at the site of infusion accompanied rarely by phlebitis or thrombophlebitis.

Adverse effects reported after ocular use of ciprofloxacin include local burning or discomfort, keratopathy, corneal staining, corneal precipitates or infiltrates, and photophobia.

Local discomfort, pain, or pruritus have occurred after use of ear drops containing ciprofloxacin.

General reviews of the adverse effects of fluoroquinolones[1-7] and ciprofloxacin specifically.[8,9]

1. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999; **28:** 352–64.
2. Ball P, *et al.* Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Safety* 1999; **21:** 407–21.
3. Rubinstein E. History of quinolones and their side effects. *Chemotherapy* 2001; **47** (suppl 3): 3–8.
4. Leone R, *et al.* Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Safety* 2003; **26:** 109–20.
5. Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. *Drugs Aging* 2003; **20:** 289–302.
6. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005; **41** (suppl 2): S144–S157.
7. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007; **41:** 1859–66.
8. Segev S, *et al.* Safety of long-term therapy with ciprofloxacin: data analysis of controlled clinical trials and review. *Clin Infect Dis* 1999; **28:** 299–308.
9. Heyd A, Haverstock D. Retrospective analysis of the safety profile of oral and intravenous ciprofloxacin in a geriatric population. *Clin Ther* 2000; **22:** 1239–50.

Effects on the blood. Haematological disturbances including thrombocytopenia,[1] eosinophilia,[2] leucopenia, and, very rarely, pancytopenia,[3] haemolytic anaemia,[4] or agranulocytosis have been reported with ciprofloxacin and some other fluoroquinolones. There has also been a case report[5] of haemolytic-uraemic syndrome associated with ciprofloxacin therapy; the patient recovered with routine supportive treatment (haemodialysis and plasma exchange) after the drug was stopped. In addition, transient reductions in factor VIII and von Willebrand's factor leading to bleeding in 2 patients receiving ciprofloxacin has been reported.[6] Neutropenia that developed in an elderly patient a few days after starting treatment with intravenous moxifloxacin resolved on stopping the drug.[7]

1. Starr JA, Ragucci KR. Thrombocytopenia associated with intravenous ciprofloxacin. *Pharmacotherapy* 2005; **25:** 1030–4.
2. Mofredj A, *et al.* Norfloxacin-induced eosinophilia in a cirrhotic patient. *Ann Pharmacother* 2002; **36:** 1107–8.
3. Deng JY, Tovar JM. Pancytopenia with levofloxacin therapy for pelvic inflammatory disease in an otherwise healthy young patient. *Ann Pharmacother* 2006; **40:** 1692–3.
4. Oh YR, *et al.* Levofloxacin-induced autoimmune hemolytic anemia. *Ann Pharmacother* 2003; **37:** 1010–13.
5. Allan DS, *et al.* Ciprofloxacin-associated hemolytic-uremic syndrome. *Ann Pharmacother* 2002; **36:** 1000–1002.
6. Castaman G, Rodeghiero F. Acquired transitory von Willebrand syndrome with ciprofloxacin. *Lancet* 1994; **343:** 492.
7. Chang C-M, *et al.* Moxifloxacin-associated neutropenia in a cirrhotic elderly woman with lower extremity cellulitis. *Ann Pharmacother* 2008; **42:** 580–3.

Effects on the cardiovascular system. Prolongation of the QT interval,[1,2] sometimes progressing to torsade de pointes,[3-8] has been associated with ciprofloxacin and other fluoroquinolones although a review[9] considered that ciprofloxacin was least likely to produce this effect. A subsequent observational, population-based, case-control study[10] of patients who had had ventricular arrhythmia or cardiac arrest supported an association between an increased risk of these events and the recent use of a fluoroquinolone. Licensed product information recommends that gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, and sparfloxacin should be avoided in patients with predisposing factors or who are also receiving other drugs that are known to cause this effect and that norfloxacin should be used with caution in such situations.

1. Noel GJ, *et al.* Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003; **73:** 292–303.
2. Nykamp DL, *et al.* QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. *Ann Pharmacother* 2005; **39:** 543–6.

3. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001; **21:** 1468–72.
4. Owens RC, Ambrose PG. Torsades de pointes associated with fluoroquinolones. *Pharmacotherapy* 2002; **22:** 663–8.
5. Bertino JS, *et al.* Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. *Clin Infect Dis* 2002; **34:** 861–3.
6. Amankwa K, *et al.* Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. *Clin Pharmacol Ther* 2004; **75:** 242–7.
7. Dale KM, *et al.* Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007; **41:** 336–40.
8. Knorr JP, *et al.* Ciprofloxacin-induced Q-T interval prolongation. *Am J Health-Syst Pharm* 2008; **65:** 547–51.
9. Owens RC. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; **64:** 1091–1124.
10. Zambon A, *et al.* Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Safety* 2009; **32:** 159–67.

Effects on the gastrointestinal tract. There have been several case reports and studies supporting an association between pseudomembranous colitis or superinfection with *Clostridium difficile* and use of ciprofloxacin[1,2] and other fluoroquinolones.[3-7]

1. McFarland LV, *et al.* Ciprofloxacin-associated Clostridium difficile disease. *Lancet* 1995; **346:** 977–8.
2. Angel CA, *et al.* Severe ciprofloxacin-associated pseudomembranous colitis in an eight-year-old child. *J Pediatr Surg* 2004; **39:** 1590–2.
3. Dan M, Samra Z. Clostridium difficile colitis associated with ofloxacin therapy. *Am J Med* 1989; **87:** 479.
4. Ortiz-de-Saracho J, *et al.* Moxifloxacin-induced Clostridium difficile diarrhea. *Ann Pharmacother* 2003; **37:** 452–3.
5. Gaynes R, *et al.* Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis* 2004; **38:** 640–5.
6. Pépin J, *et al.* Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; **41:** 1254–60.
7. Gallagher JC, *et al.* Severe pseudomembranous colitis after moxifloxacin use: a case series. *Ann Pharmacother* 2009; **43:** 123–8.

Effects on glucose metabolism. For the effects of fluoroquinolones (in particular gatifloxacin) on blood glucose see under Gatifloxacin, p. 305.3.

Effects on the kidneys. A review[1] of case reports of renal toxicity (including interstitial nephritis, acute renal failure, acute tubular necrosis, and crystalluria) associated with ciprofloxacin and other fluoroquinolones indicated that such toxicity, although potentially serious, was rare. It was also noted that nearly all patients developing acute renal failure were over 50 years of age. Another review,[2] confirming that the problem remained rare, noted that risk factors for quinolone-induced nephrotoxicity seemed to include the particular quinolone chosen, with ciprofloxacin the most often involved, as well as the use of high doses, patient age, inadequate hydration, and use of other nephrotoxic drugs or the presence of other processes likely to contribute to renal damage such as diabetes.

1. Lomaestro BM. Fluoroquinolone-induced renal failure. *Drug Safety* 2000; **22:** 479–85.
2. Montagnac R, *et al.* Les insuffisances rénales aiguës aux quinolones: revue générale à propos d'une observation avec cristallisation liée à la ciprofloxacine. *Nephrol Ther* 2005; **1:** 44–51.

Effects on the liver. Fluoroquinolones, including ciprofloxacin, may cause elevated liver enzyme values. In most patients this effect is transient and reversible without stopping the drug.

More serious cases of hepatotoxicity, including fatalities, have been reported both with ciprofloxacin[1-6] and with other fluoroquinolones[4,7-15] but they are rare. In many cases the patients were elderly and had comorbid conditions.

1. Grassmick BK, *et al.* Fulminant hepatic failure possibly related to ciprofloxacin. *Ann Pharmacother* 1992; **26:** 636–9.
2. Sherman O, Beizer JL. Possible ciprofloxacin-induced acute cholestatic jaundice. *Ann Pharmacother* 1994; **28:** 1162–4.
3. Villeneuve J-P, *et al.* Suspected ciprofloxacin-induced hepatotoxicity. *Ann Pharmacother* 1995; **29:** 257–9.
4. Jones SE, Smith RH. Quinolones may induce hepatitis. *BMJ* 1997; **314:** 869.
5. Contreras MÁ, *et al.* Severe ciprofloxacin-induced acute hepatitis. *Eur J Clin Microbiol Infect Dis* 2001; **20:** 434–5.
6. Dichiara AJ, *et al.* Ciprofloxacin-induced acute cholestatic liver injury and associated renal failure: case report and review. *Minerva Gastroenterol Dietol* 2008; **54:** 307–15.
7. González Carro P, *et al.* Fatal subfulminant hepatic failure with ofloxacin. *Am J Gastroenterol* 2000; **95:** 1606.
8. Björnsson E, *et al.* Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. *Am J Gastroenterol* 2000; **95:** 3662–4.
9. Spahr L, *et al.* Acute fatal hepatitis related to levofloxacin. *J Hepatol* 2001; **35:** 308–9.
10. Karim A, *et al.* Possible levofloxacin-induced acute hepatocellular injury in a patient with chronic obstructive lung disease. *Clin Infect Dis* 2001; **33:** 2088–90.
11. Soto S, *et al.* Moxifloxacin-induced acute liver injury. *Am J Gastroenterol* 2002; **97:** 1853–4.
12. Coleman CI, *et al.* Possible gatifloxacin-induced fulminant hepatic failure. *Ann Pharmacother* 2002; **36:** 1162–7.
13. Schwalm J-D, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. *CMAJ* 2003; **168:** 847–8.
14. Cheung O, *et al.* Gatifloxacin-induced hepatotoxicity and acute pancreatitis. *Ann Intern Med* 2004; **140:** 73–4.
15. Çoban Ş, *et al.* Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. *Ann Pharmacother* 2005; **39:** 1737–40.

Effects on the musculoskeletal system. Reversible arthralgia has sometimes occurred with the fluoroquinolones;[1] joint erosions have been documented in immature *animals*. In a report,[2] treatment with pefloxacin may have contributed to the destructive arthropathy that occurred in a 17-year-old youth. For a discussion of the use of fluoroquinolones in children and adolescents, see Administration in Children, under Precautions, p. 266.1.

There have been reports[3-7] of tendinitis and tendon rupture associated with fluoroquinolones. By July 1995, the UK CSM[5] had received 21 reports of tendon damage, often of the Achilles tendon, associated with these antibacterials—11 with ciprofloxacin and 10 with ofloxacin. In a later case-control study[8] of a cohort of 46 776 users of fluoroquinolones between July 1992 to June 1998, 704 had Achilles tendinitis and 38 had Achilles tendon rupture; the adjusted relative risk of Achilles tendon disorders with current use was 1.9. The risk of tendon damage is increased by use with corticosteroids and is more common with increasing age:[5] the case-control study[8] found that the relative risk for current users rose to 3.2 among those aged 60 and over, and to 6.2 in those in this age group also using corticosteroids. Another case-control study[9] using data from 1988 to 1998 held on a different UK general practice database reported similar findings and concluded that ofloxacin was associated with a higher risk of tendon damage than other fluoroquinolones. A review[10] of the literature between 1966 and 2001 revealed 98 case reports of fluoroquinolone-associated tendon damage. Of these, 36 were associated with pefloxacin therapy and 25 with ciprofloxacin; ofloxacin was associated with 6 cases. Renal disease or impairment was also considered as a risk factor.

Onset may be rapid: rupture has occurred within 48 hours of starting therapy.[11] It can, however, also occur after therapy has been completed, in some cases up to several months later. The CSM[5] warned that at the first sign of pain or inflammation the fluoroquinolone should be withdrawn and the affected limb rested until the tendon symptoms had resolved. Similar warnings have been issued in other countries, but some cases have continued to be reported.[12,13] In the USA the FDA has required a warning to be added to prescribing information for the fluoroquinolones stating that there is an increased risk in patients over 60, in kidney, heart, and lung transplant recipients, and with use of concomitant corticosteroid therapy.[14]

There have been reports[15,16] of rhabdomyolysis in patients given fluoroquinolones, including one fatality associated with levofloxacin therapy.[15] Acute myalgia without signs of rhabdomyolysis has also been reported with ciprofloxacin.[17]

1. Alfaham M, *et al.* Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. *BMJ* 1987; **295:** 699.
2. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; **7:** 310–14.
3. Huston KA. Achilles tendinitis and tendon rupture due to fluoroquinolone antibiotics. *N Engl J Med* 1994; **331:** 748.
4. Szarfman A, *et al.* More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995; **332:** 193.
5. CSM/MCA. Tendon damage associated with quinolone antibiotics. *Current Problems* 1995; **21:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20156196&RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
6. Carrasco JM, *et al.* Tendinitis associated with ciprofloxacin. *Ann Pharmacother* 1997; **31:** 120.
7. Mathis AS, *et al.* Levofloxacin-associated Achilles tendon rupture. *Ann Pharmacother* 2003; **37:** 1014–17.
8. van der Linden PD, *et al.* Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ* 2002; **324:** 1306–7.
9. van der Linden PD, *et al.* Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003; **163:** 1801–7.
10. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 2003; **36:** 1404–10.
11. CSM/MCA. Reminder: fluoroquinolone antibiotics and tendon disorders. *Current Problems* 2002; **28:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
12. Adverse Drug Reactions Advisory Committee (ADRAC). Fluoroquinolone antibiotics: remember tendon disorders. *Aust Adverse Drug React Bull* 2006; **25:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 12/07/06)
13. Akali AU, Niranjan NS. Management of bilateral Achilles tendon rupture associated with ciprofloxacin: a review and case presentation. *J Plast Reconstr Aesthet Surg* 2008; **61:** 830–4.
14. FDA. Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (marketed as Cipro and generic ciprofloxacin), ciprofloxacin extended release (marketed as Cipro XR and Proquin XR), gemifloxacin (marketed as Factive), levofloxacin (marketed as Levaquin), moxifloxacin (marketed as Avelox), norfloxacin (marketed as Noroxin), and ofloxacin (marketed as Floxin and generic ofloxacin)] (issued 8th July, 2008). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm (accessed 12/08/08)
15. Petitjeans F, *et al.* A case of rhabdomyolysis with fatal outcome after a treatment with levofloxacin. *Eur J Clin Pharmacol* 2003; **59:** 779–80.
16. Hsiao S-H, *et al.* Acute rhabdomyolysis associated with ofloxacin/levofloxacin therapy. *Ann Pharmacother* 2005; **39:** 146–9.
17. Eisele S, *et al.* Ciprofloxacin-related acute severe myalgia necessitating emergency care treatment: a case report and review of the literature. *Int J Clin Pharmacol Ther* 2009; **47:** 165–8.

Effects on the nervous system. By 1991 the UK CSM[1] had received 26 reports of convulsions associated with ciprofloxacin, 1 with norfloxacin, and 1 with ofloxacin. It was noted that convulsions could occur both in patients with epilepsy and in those with no history of convulsions. Generalised seizures have been reported in patients given gatifloxacin[2] and levofloxacin.[3,4] Seizures have also been associated with the use of ear drops containing ciprofloxacin.[5] All 5 case reports[2-5] involved patients aged 65 years and over; of these, 1 had a history (although unclear) of seizures,[2] 3 had chronic renal impairment,[3-5] and 1 had neither.[3] Ciprofloxacin-associated seizures have also been reported[6] in a patient with thyrotoxicosis.

Other reports of CNS toxicity associated with ciprofloxacin have included eosinophilic meningitis,[7] delirium,[8] and acute psychoses.[9,10] Peripheral neuropathy,[11] dysaesthesia,[12] catatonia[13] (also with levofloxacin[14]), hemiparesis,[15] and tinnitus[16] have also been reported. Acute psychosis occurred[17] in a patient using ciprofloxacin eye drops. A review[18] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials including ciprofloxacin and ofloxacin. Levofloxacin has also been reported to have possibly unmasked a hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease).[19]

There have also been reports of sleep disturbances[20] and of a Tourette-like syndrome[21] associated with ofloxacin. Ataxia[22] and hallucinations[23] have been reported with the use of gatifloxacin. In one case report, acute encephalopathy occurred in an elderly woman after ingestion of a single dose of gemifloxacin.[24]

A literature review[25] (up to 31st October 2010) found that the most commonly reported psychiatric adverse events with the fluoroquinolones were mania, insomnia, acute psychosis, and delirium, while the most commonly reported neurological events were convulsions (including grand mal convulsion), confusional state, and myoclonus.

1. CSM. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)
2. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. *Ann Pharmacother* 2004; **38:** 235–7.
3. Kushner JM, *et al.* Seizures associated with fluoroquinolones. *Ann Pharmacother* 2001; **35:** 1194–8.
4. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39:** 953–5.
5. Orr CF, Rowe DB. Eardrop attacks: seizures triggered by ciprofloxacin eardrops. *Med J Aust* 2003; **178:** 343.
6. Agbaht K, *et al.* Ciprofloxacin-associated seizures in a patient with underlying thyrotoxicosis: case report and literature review. *Int J Clin Pharmacol Ther* 2009; **47:** 303–10.
7. Asperilla MO, *et al.* Eosinophilic meningitis associated with ciprofloxacin. *Am J Med* 1989; **87:** 589–90.
8. Jay GT, Fitzgerald JM. Ciprofloxacin-induced delirium. *Ann Pharmacother* 1997; **31:** 252.
9. McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. *Am J Med* 1991; **90:** 528–9.
10. Reeves RR. Ciprofloxacin-induced psychosis. *Ann Pharmacother* 1992; **26:** 930–1.
11. Aoun M, *et al.* Peripheral neuropathy associated with fluoroquinolones. *Lancet* 1992; **340:** 127.
12. Zehnder D, *et al.* Painful dysaesthesia with ciprofloxacin. *BMJ* 1995; **311:** 1204.
13. Akhtar S, Ahmad H. Ciprofloxacin-induced catatonia. *J Clin Psychiatry* 1993; **54:** 115–16.
14. Youssef NA, *et al.* Levofloxacin-induced catatonia. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33:** 741–2.
15. Rosolen A, *et al.* Acute hemiparesis associated with ciprofloxacin. *BMJ* 1994; **309:** 1411.
16. Paul J, Brown NM. Tinnitus and ciprofloxacin. *BMJ* 1995; **311:** 232.
17. Tripathi A, *et al.* Acute psychosis following the use of topical ciprofloxacin. *Arch Ophthalmol* 2002; **120:** 665–6.
18. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; **22:** 71–81.
19. Panas M, *et al.* Hereditary neuropathy unmasked by levofloxacin. *Ann Pharmacother* 2011; **45:** 1312–13.
20. Upton C. Sleep disturbance in children treated with ofloxacin. *BMJ* 1994; **309:** 1411.
21. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. *Ann Pharmacother* 1996; **30:** 138–41.
22. Mohan N, *et al.* Oral gatifloxacin-induced ataxia. *Am J Health-Syst Pharm* 2002; **59:** 1894.
23. Adams M, Tavakoli H. Gatifloxacin-induced hallucinations in a 19-year-old man. *Psychosomatics* 2006; **47:** 360.
24. Barrett MJ, Login IS. Gemifloxacin-associated neurotoxicity presenting as encephalopathy. *Ann Pharmacother* 2009; **43:** 782–4.
25. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. *Drug Safety* 2011; **34:** 465–88.

Hypersensitivity. Hypersensitivity and skin reactions have been associated with ciprofloxacin and other fluoroquinolones. Reports have included anaphylaxis (which has sometimes been fatal, and may occur after the first dose),[1-4] serum sickness,[5] Stevens-Johnson syndrome,[6] toxic epidermal necrolysis (sometimes fatal),[7-13] laryngeal oedema,[14] and vasculitis.[15-17] Fatal vasculitis has been reported with ofloxacin.[18] Radiation recall reactions have also been reported.[19,20]

1. Assouad M, *et al.* Anaphylactoid reactions to ciprofloxacin. *Ann Intern Med* 1995; **122:** 396–7.
2. Smythe MA, Cappelletty DM. Anaphylactoid reaction to levofloxacin. *Pharmacotherapy* 2000; **20:** 1520–3.
3. Ho DY, *et al.* Anaphylactoid reaction to ciprofloxacin. *Ann Pharmacother* 2003; **37:** 1018–23.
4. Sachs B, *et al.* Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Safety* 2006; **29:** 1087–1100.

5. Slama TG. Serum sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother* 1990; **34:** 904–5.
6. Hällgren J, *et al.* Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug. *J Am Acad Dermatol* 2003; **49** (suppl): S267–S269.
7. YerasiAB, Oertel MD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1996; **30:** 297.
8. Livasy CA, Kaplan AM. Ciprofloxacin-induced toxic epidermal necrolysis: a case report. *Dermatology* 1997; **195:** 173–5.
9. Melde SL. Ofloxacin: a probable cause of toxic epidermal necrolysis. *Ann Pharmacother* 2001; **35:** 1388–90.
10. Sahin MT, *et al.* Norfloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39:** 768–70.
11. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39:** 953–5.
12. Islam AFMS, Rahman MS. Levofloxacin-induced fatal toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39:** 1136–7.
13. Davila G, *et al.* Toxic epidermal necrolysis induced by levofloxacin. *Ann Allergy Asthma Immunol* 2009; **102:** 441–2.
14. Baciewicz AM, *et al.* Laryngeal edema related to ciprofloxacin therapy. *Ann Pharmacother* 1992; **26:** 1456.
15. Choe U, *et al.* Ciprofloxacin-induced vasculitis. *N Engl J Med* 1989; **320:** 257–8.
16. Stubbings J, *et al.* Cutaneous vasculitis due to ciprofloxacin. *BMJ* 1992; **305:** 29.
17. Drago F, *et al.* Henoch-Schönlein purpura induced by fluoroquinolones. *Br J Dermatol* 1994; **131:** 448.
18. Pace JL, Gatt P. Fatal vasculitis associated with ofloxacin. *BMJ* 1989; **299:** 658.
19. Cho S, *et al.* Radiation recall reaction induced by levofloxacin. *J Drugs Dermatol* 2008; **7:** 64–7.
20. Jain S, *et al.* Radiation recall dermatitis with gatifloxacin: a review of literature. *J Med Imaging Radiat Oncol* 2008; **52:** 191–3.

Superinfection. Superinfection with *Streptococcus pneumoniae* has been reported in patients receiving ciprofloxacin.[1-3] For references to superinfection with *Clostridium difficile* and associated pseudomembranous colitis, see under Effects on the Gastrointestinal Tract, p. 263.1.

Fungal otitis externa is also associated with the use of ear drops containing fluoroquinolones.[4]

1. Righter J. Pneumococcal meningitis during intravenous ciprofloxacin therapy. *Am J Med* 1990; **88:** 548.
2. Gordon JJ, Kauffman CA. Superinfection with Streptococcus pneumoniae during therapy with ciprofloxacin. *Am J Med* 1990; **89:** 383–4.
3. Lee BL, *et al.* Infectious complications with respiratory pathogens despite ciprofloxacin therapy. *N Engl J Med* 1991; **325:** 520–1.
4. Schrader N, Isaacson G. Fungal otitis externa: its association with fluoroquinolone eardrops. *Pediatrics* 2003; **111:** 1123.

Precautions

Ciprofloxacin should be used with caution in patients with epilepsy or a history of CNS disorders. Care is also necessary in those with renal impairment or G6PD deficiency (see also p. 266.2). An adequate fluid intake should be maintained during treatment with ciprofloxacin and excessive alkalinity of the urine avoided because of the risk of crystalluria.

Since ciprofloxacin and related fluoroquinolones have, like nalidixic acid, been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these drugs should not generally be used in patients aged under 18 years (see also p. 266.1), pregnant women, or breast-feeding mothers (but see also p. 266.2) unless the benefits outweigh the risks. Tendon damage may occur rarely with fluoroquinolones (see Effects on the Musculoskeletal System, p. 263.2) and treatment should be stopped if patients have tendon pain, inflammation, or rupture; subsequent use of fluoroquinolones is contra-indicated in these patients. Fluoroquinolones should also be avoided in patients with a history of myasthenia gravis, as severe muscle weakness may occur (see Adverse Effects, p. 262.2).

Exposure to strong sunlight or sunlamps should be avoided during treatment with ciprofloxacin. The ability to drive or operate machinery may be impaired, especially when alcohol is also taken.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, p. 262.3) and should be avoided or used with caution in patients with QT prolongation or relevant risk factors such as uncorrected electrolyte disturbances, bradycardia, or pre-existing cardiac disease. Certain drugs may also increase the risk (see Interactions, p. 266.3).

Ciprofloxacin and other fluoroquinolones should be avoided in MRSA infections because of the high level of resistance.

Administration in children. Since ciprofloxacin and other fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks.[1-4] For example, ciprofloxacin is licensed in some countries for use in the prophylaxis and treatment of inhalational anthrax and also in the treatment of certain infections in those under 18 years of age (see under Uses and Administration, p. 261.3). A systematic review[4] of the use of ciprofloxacin in more than 16 000 children (7 months to 17 years) found that musculoskeletal adverse events were most frequent; 258 events were reported in 232 patients, giving an estimated risk of 1.6%. Of these musculoskeletal events 50% were arthralgia, 19% tendon or joint disorder, and 15% reduced movement or stiffness. The review also found no dose-dependent or duration-dependent risk of toxicity and no significant effect on growth; adverse events were reversible on stopping medication.

A comparative cohort study[2] involving about 500 children and adolescents found that the incidence of musculoskeletal adverse effects was higher (10 cases out of 264 patients) in those taking fluoroquinolones (ciprofloxacin, ofloxacin, or pefloxacin) than in those taking other antibacterials (1 out of 237). In the former group of patients, these adverse effects, mainly arthralgias, were reversible and were most frequent with pefloxacin therapy.

1. Burstein GR, *et al.* Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002; **35** (suppl 2): S191–S199.
2. Chalumeau M, *et al.* Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Abstract: *Pediatrics* 2003; **111:** 1427–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/6/e714 (accessed 01/11/06)
3. American Academy of Pediatrics Committee on Infectious Diseases. The use of systemic fluoroquinolones. *Pediatrics* 2006; **118:** 1287–92.
4. Adefurin A, *et al.* Ciprofloxacin safety in paediatrics: a systematic review. *Arch Dis Child* 2011; **96:** 874–80.

Breast feeding. Ciprofloxacin was found to be undetectable in the serum of a breast-fed infant whose mother took ciprofloxacin 500 mg daily for 10 days.[1] In another study[2] involving 30 women who underwent termination of pregnancy, 10 each were given ciprofloxacin, ofloxacin, or pefloxacin respectively, and all 3 drugs were found to be highly concentrated in breast milk with ratios exceeding 75% of the simultaneous serum concentrations 2 hours after a dose. It was concluded that, because fluoroquinolones had been shown to cause arthropathy in young *animals*, their potential benefits should be weighed against the risk to the infant before they were considered for use in breast-feeding women. The American Academy of Pediatrics[3] considers that the use of ciprofloxacin is usually compatible with breast feeding.

1. Gardner DK, *et al.* Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant. *Clin Pharm* 1992; **11:** 352–4.
2. Giamarellou H, *et al.* Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; **87** (suppl 5A): 49S–51S.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Exposure to UV light. Loss of antibacterial activity has been reported after irradiation of ciprofloxacin solutions by UV light.[1] In addition to the possible hazard of photosensitivity reactions, a reduction in both cutaneous and circulating levels of ciprofloxacin was predicted in patients exposed to sunlight through window glass or the longer wavelength UVA radiation from sunbeds.[1]

1. Phillips G, *et al.* The loss of antibiotic activity of ciprofloxacin by photodegradation. *J Antimicrob Chemother* 1990; **26:** 783–9.

G6PD deficiency. Licensed product information for ciprofloxacin and other fluoroquinolones advises that these drugs be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency as there may be a risk of haemolysis. This cautionary advice is based on similar warnings for nalidixic acid, a non-fluorinated quinolone. However, a review[1] found no reports of haemolysis in G6PD-deficient patients given fluoroquinolones.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.

Myasthenia gravis. Caution is advised in patients with myasthenia gravis given fluoroquinolones after a few reports of the possible exacerbation of symptoms[1,2] or unmasking of subclinical myasthenia gravis[3] by ciprofloxacin. Exacerbation of myasthenia gravis is considered to be a class effect;[2] it has also been reported with other fluoroquinolones including norfloxacin, ofloxacin, pefloxacin, gatifloxacin, levofloxacin, and moxifloxacin.[2,4-6] Exacerbations usually occurred within 1 to 2 days of systemic fluoroquinolone use, but have not been reported with non-systemic formulations. Dyspnoea was the most commonly reported adverse event (50% of cases) followed by muscle weakness or fatigue (48%). More serious, although less frequent, were cases of respiratory failure requiring mechanical ventilation (30% of reports). Nearly all patients improved when the fluoroquinolone dose was reduced or stopped, although some required additional supportive treatment.

1. Moore B, *et al.* Possible exacerbation of myasthenia gravis by ciprofloxacin. *Lancet* 1988; **i:** 882.
2. Jones SC, *et al.* Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. *Drug Safety* 2011; **34:** 839–47.
3. Mumford CJ, Ginsberg L. Ciprofloxacin and myasthenia gravis. *BMJ* 1990; **301:** 818.
4. Rauser EH, *et al.* Exacerbation of myasthenia gravis by norfloxacin. *DICP Ann Pharmacother* 1990; **24:** 207–8.
5. Azevedo E, *et al.* Probable exacerbation of myasthenia gravis by ofloxacin. *J Neurol* 1993; **240:** 508.
6. Vial T, *et al.* Aggravation d'une myasthénie sous péfloxacine. *Rev Neurol (Paris)* 1995; **151:** 286–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ciprofloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Although there are no controlled studies on the use of ciprofloxacin in pregnant women, data available shows no increased risk of congenital malformations or other adverse fetal events. However, the UK teratology information service (UKTIS) and the US Teratogen Information System (TERIS) consider the data to be too limited to state that there is no increased risk of adverse outcomes. UK licensed product information recommends that it is preferable to avoid the use of ciprofloxacin during pregnancy.

Interactions

Fluoroquinolones, including ciprofloxacin, are known to inhibit the cytochrome P450 isoenzyme CYP1A2 and may increase plasma concentrations of drugs, such as clozapine, ropinirole, theophylline, and tizanidine, that are metabolised by this isoenzyme. Use of ciprofloxacin with tizanidine is contra-indicated, although theophylline may be used providing its dose is reduced and concentrations monitored. Clozapine or ropinirole may also be used, providing appropriate clinical surveillance occurs with subsequent dose adjustment where necessary.

Ciprofloxacin is reported to enhance the effect of oral anticoagulants such as warfarin and the oral antidiabetic glibenclamide. Severe hypoglycaemia, sometimes fatal, has occurred in patients also taking glibenclamide. Renal tubular secretion of methotrexate may be inhibited by ciprofloxacin, potentially increasing its toxicity.

The excretion of ciprofloxacin or related drugs is reduced and plasma concentrations may be increased by probenecid. Cations such as aluminium, calcium, magnesium, or iron reduce the absorption of oral ciprofloxacin or related drugs when given together. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H_2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance.

Transient increases in serum creatinine have occurred when ciprofloxacin is given with ciclosporin; monitoring of serum creatinine concentrations is recommended. Altered serum concentrations of phenytoin have been reported in patients also receiving ciprofloxacin.

Further details concerning some of these interactions, and others, are given below.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, p. 262.3) and should be avoided in patients also receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmics (such as amiodarone and sotalol). In addition, caution should be exercised when they are used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants).

For physical or chemical incompatibilities with ciprofloxacin, see p. 261.2.

Analgesics. Use of *fenbufen* with fluoroquinolones may increase the incidence of fluoroquinolone CNS adverse effects. Reviews[1,2] have noted cases of convulsions associated with the use of fenbufen and enoxacin reported to the Japanese regulatory authorities. The UK CSM[3] has recognised that convulsions may occur due to an interaction between the fluoroquinolones and *NSAIDs*; by 1991, 3 such interactions had been reported to them. Adverse neurological effects have also been reported in a patient receiving *naproxen* and chloroquine when ciprofloxacin was given, which abated when the antirheumatic drugs were stopped.[4]

Ciprofloxacin also interacts with *opioid analgesics*; peak serum concentrations of oral ciprofloxacin given preoperatively were significantly reduced when intramuscular *papaveretum* was injected.[5] In the UK, licensed product information for ciprofloxacin tablets recommends that opioid premedication should not be used if ciprofloxacin is given for surgical infection prophylaxis.

1. Janknegt R. Drug interactions with quinolones. *J Antimicrob Chemother* 1990; **26** (suppl D): 7–29.
2. Christ W. Central nervous system toxicity of quinolones: human and animal findings. *J Antimicrob Chemother* 1990; **26** (suppl B): 219–25.
3. CSM. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)

4. Rollof J, Vinge E. Neurologic adverse effects during concomitant treatment with ciprofloxacin, NSAIDs, and chloroquine: possible drug interaction. *Ann Pharmacother* 1993; **27:** 1058–9.
5. Morran C, *et al.* Brief report: pharmacokinetics of orally administered ciprofloxacin in abdominal surgery. *Am J Med* 1989; **87** (suppl 5A): 86S–88S.

Antacids and metal ions. The absorption of ciprofloxacin and other fluoroquinolones is reduced by *antacids* containing *aluminium* or *magnesium* and also by *calcium, iron,* and *zinc* salts.[1] *Sucralfate* releases aluminium ions in the stomach and thereby reduces the absorption of ciprofloxacin[2,3] and other fluoroquinolones, including norfloxacin,[4] ofloxacin, and sparfloxacin.[5] In addition, antacids or oral iron preparations might antagonise the antibacterial activity of fluoroquinolones within the gut lumen.[6] *Dairy products* with a high calcium content may also interfere with the absorption of some fluoroquinolones.[7-9] *Enteral feeds,* which contain cations, have also been found to reduce absorption of ciprofloxacin.[10] Exposure to ciprofloxacin was also reduced by *lanthanum carbonate,* and was thought to be due to the lanthanum ion forming a non-absorbable complex with ciprofloxacin.[11] A reduction in ciprofloxacin bioavailability has also been reported after *chewable tablets* of didanosine which contain aluminium and magnesium ion buffering agents.[12]

It is recommended that oral ciprofloxacin should be given at least 2 hours before or 6 hours after such products; similar advice also applies to other fluoroquinolones.

1. Lomaestro BM, Bailie GR. Absorption interactions with fluoroquinolones: 1995 update. *Drug Safety* 1995; **12:** 314–33.
2. Garrelts JC, *et al.* Sucralfate significantly reduces ciprofloxacin concentrations in serum. *Antimicrob Agents Chemother* 1990; **34:** 931–3.
3. Van Slooten AD, *et al.* Combined use of ciprofloxacin and sucralfate. *DICP Ann Pharmacother* 1991; **25:** 578–82.
4. Parpia SH, *et al.* Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob Agents Chemother* 1989; **33:** 99–102.
5. Kamberi M, *et al.* The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. *Br J Clin Pharmacol* 2000; **49:** 98–103.
6. Lewin CS, Smith JT. 4-Quinolones and multivalent ions. *J Antimicrob Chemother* 1990; **26:** 149.
7. Neuvonen PJ, *et al.* Interference of dairy products with the absorption of ciprofloxacin. *Clin Pharmacol Ther* 1991; **50:** 498–502.
8. Kivistö KT, *et al.* Inhibition of norfloxacin absorption by dairy products. *Antimicrob Agents Chemother* 1992; **36:** 489–91.
9. Neuvonen PJ, Kivistö KT. Milk and yoghurt do not impair the absorption of ofloxacin. *Br J Clin Pharmacol* 1992; **33:** 346–8.
10. Healy DP, *et al.* Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother* 1996; **40:** 6–10.
11. How PP, *et al.* Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clin J Am Soc Nephrol* 2007; **2:** 1235–40.
12. Sahai J, *et al.* Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* 1993; **53:** 292–7.

Antibacterials. The simultaneous use of parenteral ciprofloxacin and *azlocillin* has resulted in higher and more prolonged serum concentrations of ciprofloxacin.[1] Steady-state plasma concentrations of moxifloxacin are significantly reduced when given with *rifampicin* and *isoniazid* for the treatment of tuberculosis.[2]

1. Barriere SL, *et al.* Alteration in the pharmacokinetic disposition of ciprofloxacin by simultaneous administration of azlocillin. *Antimicrob Agents Chemother* 1990; **34:** 823–6.
2. Nijland HMJ, *et al.* Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007; **45:** 1001–7.

Anticoagulants. For reports of ciprofloxacin and other fluoroquinolones enhancing the effect of oral anticoagulants, see under *Warfarin,* p. 1531.1.

Antidiabetics. For reference to elevated *glibenclamide* concentrations in patients who were also given ciprofloxacin, see p. 505.3.

Antiepileptics. For conflicting reports of the effect of ciprofloxacin on serum-*phenytoin* concentrations, see p. 542.3.

Antifungals. Both *fluconazole* and levofloxacin can prolong the QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; **60:** 2479–83.

Antimigraine drugs. For a recommendation to reduce the dosage of *zolmitriptan* when given with ciprofloxacin, see p. 682.3.

Antineoplastics. Absorption of oral ciprofloxacin appears to be reduced after cytotoxic chemotherapy.[1]

For reference to the effect of ciprofloxacin on the pharmacokinetics of *cyclophosphamide,* see p. 773.2.

1. Johnson EJ, *et al.* Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. *J Antimicrob Chemother* 1990; **25:** 837–42.

Antivirals. Both ciprofloxacin and *foscarnet* can cause convulsions and 2 patients developed generalised tonic-clonic seizures while receiving the drugs together.[1]

For reference to reduction of ciprofloxacin bioavailability due to the antacid content of chewable *didanosine* tablets, see under Antacids and Metal Ions, above.

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; **28:** 869–72.

Anxiolytics. For reference to the effect of ciprofloxacin on the pharmacokinetics of *diazepam, midazolam,* and *temazepam,* see under Diazepam, p. 1068.2.

Immunosuppressants. For reference to possible interaction between fluoroquinolones and *ciclosporin,* see Quinolones, p. 1956.1. For a pharmacokinetic study reporting reduced exposure to *mycophenolate mofetil* when given with norfloxacin or norfloxacin plus metronidazole, see p. 1968.2.

Muscle relaxants. For a report of ciprofloxacin increasing the plasma concentrations of *tizanidine,* see p. 2027.1.

Sevelamer. The bioavailability of ciprofloxacin was decreased by about 50% when it was given with sevelamer.[1] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Kays MB, *et al.* Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis* 2003; **42:** 1253–9.

Xanthines. Ciprofloxacin and other fluoroquinolones (to a greater or lesser extent) decrease the clearance of *theophylline* (p. 1234.2) and *caffeine* (p. 1206.1) from the body. Seizures have occurred in patients given ciprofloxacin and theophylline and in one such report[1] serum-theophylline concentrations were normal.

1. Bader MB. Role of ciprofloxacin in fatal seizures. *Chest* 1992; **101:** 883–4.

Antimicrobial Action

Ciprofloxacin is bactericidal and acts by inhibiting DNA gyrase and topoisomerase IV, which are essential enzymes in the reproduction of bacterial DNA. It has a broader spectrum of activity and is more potent *in vitro* than the non-fluorinated quinolone nalidixic acid although resistance to many species or strains previously sensitive is emerging. Activity may be reduced in acid media and in the presence of urine but not of serum.

Spectrum of activity.

- Among Gram-negative aerobic bacteria, ciprofloxacin may be active *in vitro* against Enterobacteriaceae, including *Escherichia coli* and *Citrobacter, Enterobacter, Klebsiella, Proteus, Providencia, Salmonella, Serratia, Shigella,* and *Yersinia* spp.
  It may also have activity against *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae. H. influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*), and *N. meningitidis* are all sensitive.
  Other Gram-negative aerobic bacteria reported to be sensitive to ciprofloxacin have included *Gardnerella vaginalis, Helicobacter pylori, Legionella* spp., *Pasteurella multocida,* and *Vibrio* spp.
  Variable activity has been reported against *Acinetobacter* spp., *Brucella melitensis,* and *Campylobacter* spp.
- Among Gram-positive aerobic bacteria, ciprofloxacin is active against staphylococci, including penicillinase-producing and penicillinase-nonproducing strains, and against some MRSA. Streptococci, in particular *Streptococcus pneumoniae* and enterococci, are less susceptible.
  Other Gram-positive bacteria sensitive to ciprofloxacin *in vitro* are *Bacillus* spp.; variable activity has been noted for *Corynebacterium* spp.
- Most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile,* are resistant to ciprofloxacin, although some other *Clostridium* spp. may be susceptible.
- Ciprofloxacin has some activity against mycobacteria, mycoplasmas, rickettsias, *Chlamydia trachomatis,* and *Ureaplasma urealyticum.*

Acquired resistance. Resistant strains, particularly of MRSA, *Ps. aeruginosa, E. coli, Klebsiella pneumoniae, C. jejuni, N. gonorrhoeae,* and *Str. pneumoniae* have emerged during treatment with ciprofloxacin although there are widely differing patterns of resistance geographically. Resistance to ciprofloxacin has usually been chromosomally mediated although plasma-mediated resistance has recently been noted.

Pharmacokinetics

Ciprofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70 to 80% and a peak serum concentration of about 2.4 micrograms/mL occurs 1 to 2 hours after a 500-mg oral dose. Absorption of ciprofloxacin tablets may be delayed by the presence of food, but is not substantially affected overall.

Plasma protein binding ranges from 20 to 40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. It appears in the CSF, but concentrations are only about 10% of those in serum when the meninges are not inflamed. Ciprofloxacin crosses the placenta and is also distributed into breast milk. High concentrations occur in bile.

The elimination half-life is about 3 to 5 hours and there is evidence of modest accumulation. Half-life may be prolonged in renal impairment (a value of 8 hours has been reported in end-stage renal disease) and to some extent in the elderly. However, no dose adjustment is usually necessary in patients with renal impairment unless it is severe; similarly, usual doses can be given to the elderly except in those with severe renal impairment. There is limited information on the effect of hepatic impairment; the half-life of ciprofloxacin has been reported to be slightly prolonged in patients with severe cirrhosis of the liver. With one or two exceptions, most studies have shown that the pharmacokinetics of ciprofloxacin are not markedly affected by cystic fibrosis.

Ciprofloxacin is eliminated principally by urinary excretion, but non-renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa. At least 4 active metabolites have been identified. Oxociprofloxacin appears to be the major urinary metabolite and sulfociprofloxacin the primary faecal metabolite. Urinary excretion is by active tubular secretion as well as glomerular filtration and is reduced by probenecid; it is virtually complete within 24 hours. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as metabolites. Up to 70% of a parenteral dose may be excreted unchanged within 24 hours and 10% as metabolites. Faecal excretion over 5 days has accounted for 20 to 35% of an oral dose and 15% of an intravenous dose.

Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

General pharmacokinetics. Reviews of the pharmacokinetics of ciprofloxacin[1] and the fluoroquinolones in general.[2,3]

1. Vance-Bryan K, *et al.* Clinical pharmacokinetics of ciprofloxacin. *Clin Pharmacokinet* 1990; **19:** 434–61.
2. Aminimanizani A, *et al.* Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 2001; **40:** 169–187.
3. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 2005; **41** (suppl 2): S127–S135.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Argeflox; Atibax C; Biotic; Ciapar; Ciloxan; Cipro Otico; Cipro; Ciprolabsa; Cipromed; Ciprotenk; Cirflox-G; Ciriax; Crisacide; Exertial; Floraxina; Gino Ciriax†; Golysine; Lorbifloxacina; Medaflox; Microsulf; Neflox†; Nexofloxacin; Novidat; Ocefax; Omaflaxina; Quisegen; Rexner; Safoxen; Septicide; Ultramicina; ***Austral.***: C-Flox; Cifran; Ciloquin; Ciloxan; Ciprol; Ciproxin; Profloxin; Proquin†; ***Austria***: Ciflox; Ciloxan; Cipromed; Ciprostad; Ciproxin; Otanol; Utiminx; Vegarex†; ***Belg.***: Ciloxan; Ciprobel; Ciproflomed†; Ciproxine; Docciproflo†; ***Braz.***: Biamotil; Ciclatry; Ciflox†; Cifloxatil; Cifloxtron; Ciloxan; Cinoflax; Ciprix; Cipro; Ciprocilin; Ciprodine; Ciprofar; Ciprofloxil; Ciproxin; Ciprocin; Ciproxen; Ductocina; Floxan†; Floxocip; Maxiflox; Nixin†; Ofoxin; Otofoxin; Proflox; Proxacin; Quiflox; Quinoflox; ***Canad.***: Apo-Ciproflox; Ciloxan; Cipro; ***Chile***: Baycip; Cifloxin; Ciloxacin; Ciproval; Ciproxino; Grifociprox; Oflono; Oftaciprox†; Sophixin; Tigina; ***China***: Bei Si Te (贝斯特); Cifran (悉复欢); Ciprobay (西普乐); Da Wei Bang (达维邦); Guang Yi Sha (广易沙); Huayu (华昱); Jia Ke (佳可); Kuinuoxian (奎诺仙); Kun Ning (坤宁); Lin Qing (林青); Qiu Lu (秋露); Rui Kang (瑞康); Rui Xin Chao (瑞欣超); Sai Ke Xing (赛克星); Shi Pu Huan (世普欢); Xin Jie Ming (新洁明); Xipofuxing (希珀福星); Xipuxing (希普欣); ***Cz.***: Cifloxinal; Cifran†; Ciloxan; Ciphin; Ciplox; Ciprinol; Ciprobay; Ciprum†; ***Denm.***: Cifin; Ciloxan; Ciprinomyl; Ciproflomyl†; Ciproscope; Ciproten; Ciproxin†; ***Fin.***: Cetraxal; Cipromed†; Ciproxin; Siprion; ***Fr.***: Ciflox; Ciloxan; Uniflox; ***Ger.***: Ciloxan; Cipro-Q†; Cipro-saar; Cipro†; Ciprobay; Ciprobeta; Ciprodoc†; Ciprofat†; Ciproflox-Puren†; Ciproflox†; Ciprohexal†; Gyracip†; InfectoCipro†; Keciflox; Panotile cipro; ***Gr.***: Afenoxin; Alciprocin; Aristin-C; Balepton; Biocipro; Bivorilan; Cidrops; Cifloxacin; Ciloxan; Ciprocton; Ciprofal; Cipromycin; Ciprospes; Ciprovian; Ciproxin; Citrovenot; Droll; Edestis; Flociprin; Forterra; Ginorectol; Glossyfin; Grenis-Cipro; Infectina; Labentrol; Ladinin; Limox; Nafloxin; Ravalton; Remena; Revion; Revionorm; Superspor; Topistin; Ufexil; Uritent; Urodixin; Utiminx; ***Hong Kong***: Aprocin; Cifloxin; Cifran†; Ciloxan; Cipide†; Ciplox†; Cipmax; Ciprofrankin†; Ciprol; Ciproxin; Ciproxyl; Cirok†; Cyfloxin†; Duflomex†; Enoxin; Gonning; Hippro†; Medociprin; Proxacin; Quidex†; Quinocin†; Uroxin; Utahzone†; Viprolox†; ***Hung.***: Cifloxin; Cifran; Ciloxan; Ciphin†; Ciplox; Ciprinol; Ciprobay; Ciprolen; Ciropharm†; Ciprum; Cydonin; ***India***: Abact; Adcip; Adiflox; Alcip; Alcipro; Alquin; Aniflox; Aricip; Atocip; Avcip; Avilox; Bactoquin; Baycip; Bekaycin; Bicipro;

Bio Cipron; Biocip; C-Flox; C-Lox; C-OD; C-Plus; C-Pro; Cadiwin; Caniron; Caspro; Cbic; Cebect; Cebran; Ceepro; Ceeptalib; Ceflox; Cefobac; Celox; Ceplox; Ceprolen; Cibiotic; Cif; Ciflon; Cifomed; Cifran; Cigram; Cina; Cinant; Cinodin; Cip; Cipact; Cipad; Cipcin; Cipcot; Cipgen; Cipglow; Cipic; Cipkind; Ciporic; Ciprex; Cipride; Ciprind; Cipro-Cent; Ciproace; Ciprobid; Ciprobiotic; Ciprocap; Ciprocure; Ciprodac; Ciprodel; Ciprodex; Ciprofen; Ciprolar; Ciproleb; Ciprolen; Ciprolet; Cipromark; Cipromax; Cipromed; Cipromycetine; Cipronat; Cipronex-E; Cipronova; Ciropan; Ciropet; Ciproquin; Ciprosia; Ciprosym; Ciprotek; Ciprotum; Ciprova; Ciprovar; Ciprovec; Ciprovit; Ciprowin; Ciprox; Ciprozen; Ciprozet; Ciprozol; Cips; Ciptam; Ciptar; Ciptec; Cipure; Cipven; Cipwin; Cipzone; Cipzy; Ciral; Ciwi; Coflox; Corgard; Cosflox; Coutim; Cymex; Cyprin; Depci; Disquin; E-Cip; Eldequin; Elquin; Flocin; Flocy; Floxaquin-C; Floxip; Fulgram; Glocip; Hicip; Icip; K-Cip; Kaicip; Kera; Kocip; Kurecip; Lacipron; Lakcip; Lexflox; Locip; Lucipro; Lypro; Maflo; Mapci; Mencip; Mericip; Microcip; Microflox; Mintocip; Miz; Nayacip; Neocip; Nexcip; NTBec; Nucip; Omibact; Omniflox; Orpic; Panzer; Quinobact; Strox; Zoxan; ***Indon.***: Bactiprox; Baquinor; Bernoflox; Bidiprox†; Cetafloxo; Ciflos; Cilox; Ciprec; Ciproxin; Civell; Coroflox; Corsacin; Cylowam†; Disfabac†; Duflomex†; Etacin; Floksid; Floxbio; Floxigra; Giraboc†; Interflox; Isotic Renator; Jayacin; Kifarox; Lapiflox; Licoprox; Meflosin; Mensipox; Nilaflox; Phaproxin; Poncoflox; Proxcip; Proxitor; Qinox; Quamiprox; Quidex; Quinobiotic; Renator; Rindoflox; Scanax; Siflox; Tequinol; Vidintal†; Viflox; Vioquin; Volinol; Wiaflox; Ximex Cylowam; Zeniflox; Zumaflox; ***Irl.***: Biofloxcin; Cifloxager; Cifox; Ciloxan; Ciproxin; Profloxin; Truoxin; ***Israel***: Cifran; Ciloxan; Ciplox; Cipro†; Ciprodex; Ciprogis; Ciproxin; Giroflox; Ufexil; ***Ital.***: Battizer; Chinocid; Ciperus; Ciprosol; Ciproxin; Cuspis; Eoxin; Flontalexin; Generflon; Ibixacin; Kinox; Macar; Oftacilox; Prociflor; Samper; Uni-cexal; ***Jpn***: Ciproxan; ***Malaysia***: Bactiflox; Cifloxin; Cifran; Ciloxan; Ciprobay; Ciproflo; Ciprox; Ciproxol; Enoxin; Serviflox; ***Mex.***: Antimed; Apoflox; Arfloxina; Bacproin; Bioflox; Ci-Sons; Cifran; Ciloxan; Cimogal; Ciprain; Cipro; Ciprobac; Ciprobiotic; Ciproflox; Ciprofur†; Ciprohexal†; Ciproser; Ciprotec; Ciproxina; Ciqfadin; Ciriax; Dinaflox; Eni; Eufloxin; Flovin; Floxager; Floxantina; Floxelena†; Floxitul; Gibac; Infloxa†; Italnik; Kenzoflex; Lemiflox; Lemyflox†; Liferxina; Microrgan; Mitroken; Novoquin; Opthaflox; Patox; Pharcina; Profluxol; Provay; Quinoflox; Rancif; Rictor†; Sinfexina†; Sophixin; Suiflox; Trigen; Vifloxina; Wasiprobil; Z-Xin; Zipra; ***Neth.***: Cetraxal; Ciloxan†; Ciprinol; Ciproxin; Otiflox; ***Norw.***: Cilox; Ciproxin; ***NZ***: Cifran; Ciloxan; Cipflox; Ciproxin; DP-Cipro; Topistin; Ufexil; ***Philipp.***: Alcipro; Bacipro; Baxolyn; Brelcip†; Ciclodin; Cidrolex; Cidroxal†; Ciflodal; Cifloxin; Ciloxan; Ciplox; Cipro-V; Ciprobach; Ciprobay; Ciprobet; Ciprobiotic; Ciprofen; Ciproflox; Ciproglen; Ciprolet; Cipromac; Cipromax; Cipromet; Ciprotal; Ciprotor; Ciproxel; Ciprozef; Cirok; Floroc†; Flosicron; Floxacef; Floxil; Floxzu†; Genoflox; Holdestin; Hyprocel; Ifloxin; Inoxzel; Iprobac; Iprolan; Ipromax; Kinogen; Kinoves; Laitun; Nexproxyn; Oflobay; Optaflox; Probact; Profilox; Proseloc; Proviflox; Proxazin; Proxco; Proxidin; Proxivex; Prozin; Qinosyn; Quidex; Quilox; Quinocip; Quinoryl; Quiprime; Rancif; Rapiqure; Rexfobys; Savedar; Sigmacip; Sutid; Uniflox; Uticin; Vistaflox; Xenoflox; Xipro; Xypen; Xyprody; Zalvos; Ziprocap; Zomrac; Zyflox; ***Pol.***: Cifran†; Ciloxan; Ciphin; Ciprinol; Ciprobay; Cipronex; Ciropol; Ciproquin; Ciprum†; Proxacin; ***Port.***: Ciflan†; Ciplox; Ciproxina; Colintil; Estecina; Giroflox; ISINO; Megaflox; Nivoflox; Nixin; Oftacilox; Quinox; ***Rus.***: Cifloxinal (Ципфлоксинал); Cifran (Ципфран); Ciloxan (Цилоксан); Ciplox (Ципплокс); Cipraz (Ципраз); Ciprex (Ципрекс); Ciprinol (Ципринол); Ciprobay (Ципробай); Ciprobid (Ципробид); Ciprobrin (Ципробрин); Ciprocin (Ципросин); Ciprodox (Ципродокс); Ciprolacare (Ципролакэр); Ciprolet (Ципролет); Ciprolone (Ципролон); Cipromed (Ципромед); Cipronat (Ципронат); Ciprosun (Ципросан)†; Ciprova (Ципрова); Ificipro (Ифиципро); Medociprin (Медоциприн); Procipro (Проципро); Quintor (Квинтор); Sifloks (Сифлокс); ***S.Afr.***: Adco-Ciprin; Biocip; Cifloc; Cifran; Cilofloc; Ciloxan; Ciplox; Cipro-Hexal; Ciprobay; Ciprocina; Ciprogen; Ciprol; Dynafloc; Loxip; Orpic; Spec-Topistin; ***Singapore***: Ciloxan; Ciprobay; Ciprohexal; Ciprolet; Cycin; Enoxin; Ginorectol; Microflox; Neofloxin; Novaflox; Qupron; Serviflox; Topistin; Uroxin; ***Spain***: Aceoto; Araxacina; Baycip; Belmacina†; Cetraflux; Cetraxal; Ciflot; Ciprenit Otico†; Ciproactin; Ciproctal†; Ciproxina Simple; Cunesin; Doriman; Estecina; Felixene; Giroflox†; Globuce; Numen; Oftacilox; Otociprin; Otosat; Piprol†; Rigoran; Sepcen; Septocipro; Tam†; Ultramicina; ***Swed.***: Ciloxan; Ciproxin; ***Switz.***: Ciloxan; Cip eco; Ciproflox; Ciproxine; ***Thai.***: C-Floxacin†; Ciflex; Ciflo; Ciflolan; Cifloxin; Cifloxno; Cifolox; Cifran; Cilab†; Ciloxan; Cinfloxine; Cipflocin; Cipon; Cipro; Ciprobay; Ciprobid; Ciprocep; Ciprofex; Ciprofin; Ciprogen; Ciprohof; Ciprolet†; Ciprom-M; Ciproquin; Ciprovid†; Ciproxan; Ciproxin; Ciproxyl; Cobay; Cyflox; Enoxin; Forexin; Hippro; Ificipro; Microflox†; Optal-Pro; Pharproxin; Poli-Cifloxin; Proflox; Supraflox; Tulipt†; Ultraflox†; Uroxin; Vesprocin; Xyrocin; ***Turk.***: Ciflosin; Cifluron; Ciloxan; Ciprasid; Cipro; Ciproktan; Cipronatin; Ciproxin; Loxasid; Proxacin; Roflazin; Roxin; Sanfloks; Sanset; Sifloks; Siprobel; Siprogut; Siprosan; Sispres†; UroCiproxin†; ***UAE***: Sarf; ***UK***: Ciloxan; Ciproxin; ***Ukr.***: Bactiflox (Бактифлокс)†; Cifran (Цифран); Ciprinol (Ципринол); Cipro (Ципро); Ciprobay (Ципробай); Ciprobel (Ципробел); Ciprofarm (Ципрофарм); Ciprohexal (Ципрогексал)†; Cipromed (Ципромед); Ciproxol (Ципроксол); Floximed (Флоксимед); Ificipro (Ифиципро); Sifloks (Сифлокс); ***USA***: Cetraxal; Ciloxan; Cipro; ***Venez.***: Bacipro; Baflox; Ciflox; Ciloxan; Ciprivax; Ciproflox; Cipronax; Ciproquin; Ciproxina; Cirok; Cypral; Iproxin; Lisipin; Oxtin; Quinoftal; Quinotic; Serviflox; Sophixin; Zolina.

Multi-ingredient Preparations. ***Arg.***: Aibrex; Ciloxadex; Cipro HC; Ciproflox-Otic†; Ciprofloxacina D; Cirflox Oftal; Cirflox Otic; Ciriax Otic L; Ciriax Otic; Decadron con Ciprofloxina; Delos Otic; Fotamicin; Labsa Otic L; Labsa Otic; Medaflox Dol; Omaflaxina D; Otex HC; Oto Biotaer†; Otobiotic; Otocipro; Otolef HC; Otosporin C; Otosporin Dexa; Procalm; Prootocipro; Quidex; Tacines; ***Austral.***: Ciproxin HC; ***Braz.***: Biamotil-D; Biancort; Cilodex; Ciprixin Dexa; Cipro HC; Cylocort; Maxiflox D; Otociriax; ***Canad.***: Ciprodex; ***Chile***: Cilodex; Ciprodex; Oflono-D; Otex HC; ***Cz.***: Ciprobay HC Otic†; ***Denm.***: Ciflox; Cilodex; ***Fin.***: Cetraxal Comp; Ciproxin-Hydrocortison; ***Gr.***: Ciprobay; Otospon; ***Hong Kong***: Cipro HC; ***India***: AC; Adcip-TZ; Alcip-TZ; Alcipro-TN; Aricip-TZ; Atocip-TZ; Avilox-M; Avilox-TZ; Baycip-TZ; Biocip-TZ; Caniron-TZ; Caspro-TZ; Cbic-TZ; Cebect-TZ; Cebran-TN; Ceepro-TZ; Ceflox-CF; Ceflox-D; Ceflox-TZ; Cefobac-TD; Cefobac-TDH; Ceplox-TZ; Ceprolen-D; Cidalox-TZ; Ciflon-TZ; Cifomed-D; Cifomed-TZ; Cifran-CT-H; Cifran-CT; Cifran-OZ; Cina-TZ; Cinant-TZ; Cinodin-TZ; Cip-TZ; Cipcin-TNZ; Cipcot-TZ; Cipflox-TZ; Cipgen TZ; Cipglow-TZ; Ciplox D; Ciplox TZ; Ciplox; Cipnet-OZ; Cipro-TZ; Ciprobid-TZ; Ciprobiotic-FC; Ciprobiotic-TN; Ciprodac-TZ; Ciprodex-TZ; Ciprogyl; Ciprolar-F; Ciprolar-FC; Ciprolar-T; Ciprolet-A; Ciprolet-AH; Cipromark-DX; Cipronat-TZ; Cipronij-TZ; Ciropet-TZ; Ciprosia-D; Ciprosym-TZ; Ciprotini; Ciprotiz; Ciprotum-TZ; Ciprova-T; Ciprovec-TZ; Ciprowin-TZ; Ciprozee-TZ; Ciprozen-D; Ciptam-CT; Ciptech-CT; Cipti; Ciptini; Cipure-TZ; Cipven-TZ; Cipwin-TZ; Cipzone-TN; Cipzy-TZ; Ciral-TZ; Citi; Citibid; Citizol; Ciwi-TZ; CPF-TZ; CT-Robes; Cymex-TZ; Cyprin-D; Cyprin-TD; Depci-TZ; Diarlop-CT; Donnagyl-H; E-Cip-TZ; Elquin-TZ; Flocin-TZ; Flocipron-T; Flocy TZ; Flucocip; Formax; Gastrogyl Plus; Gastrogyl; Glocip-TZ; Hicip-TZ; K-Cip-TZ; Kurecip-TZ; Labocip-TZ; Lexflox-TZ; Locip-TZ; Lomet-CT; Loxitin; Lucipro-T; Mapci-TZ; Microcip-TZ; Microflox-CT; Microflox-DX; Miflox-DM; Mini-Citizol; Mintocip-TZ; Neocip FC; Neocip M; Nexcip-TZ; Normide-CZ; Nucip-TZ; Nugen Eye/Ear; Ocimix; Odicip-OZ; Omibact-TZ; Omniflox-CT; Orpic-T; Panzer-TZ; Tinvista-CF; ***Israel***: Cilodex†; Ciproxin HC†; ***Ital.***: Mediflox; ***Mex.***: Cilodex; Ciproxina HC; Ciriax D; Combiquine-C; Dinill-D; Oto Eni; Quinoflox Otico; Sodrimax; Softramc; Sophixin DX; Vodelan; ***NZ***: Cilodex; Ciproxin HC; ***Rus.***: Ciprolet A (Ципролет А); Kombinil-Duo (Комбинил-Дуо); ***S.Afr.***: Cilodex; Ciprobay HC; ***Singapore***: Cilodex; Ciprobay HC; ***Spain***: Aceoto Plus; Cetraxal Plus; Ciproxina; Synalotic; Ultramicina Plus; ***Switz.***: Ciproxin HC; ***Ukr.***: Cetraxal Plus (Цетраксал Плюс); Cifran CT (Цифран CT); Orcipol (Орципол); ***USA***: Cipro HC; Ciprodex; ***Venez.***: Otalex; Quinocort; Quinotic HC.

Pharmacopoeial Preparations

BP 2014: Ciprofloxacin Infusion; Ciprofloxacin Tablets;
USP 36: Ciprofloxacin and Dexamethasone Otic Suspension; Ciprofloxacin Extended-Release Tablets; Ciprofloxacin Injection; Ciprofloxacin Ophthalmic Ointment; Ciprofloxacin Ophthalmic Solution; Ciprofloxacin Tablets.

Clarithromycin *(BAN, USAN, rINN)*

A-56268; Abbott-56268; Clarithromycine; Clarithromycinum; Claritromicina; Klarithromycin; Klaritromicinas; Klaritromisin; Klaritromycin; Klaritromysiini; TE-031; Кларитромицин.

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-3-(2,6-Dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)pentadecan-13-olide; 6-*O*-Methylerythromycin.

$C_{38}H_{69}NO_{13}$=748.0

CAS — *81103-11-9.*

ATC — *J01FA09.*

ATC Vet — *QJ01FA09.*

UNII — *H1250JIK0A.*

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clarithromycin). A white or almost white, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; slightly soluble in methyl alcohol.

USP 36: (Clarithromycin). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol, in methyl alcohol, and in acetonitrile; soluble in acetone; slightly soluble in phosphate buffer at pH values of 2 to 5. pH of a 0.2% suspension in a mixture of water and methyl alcohol (19:1) is between 8.0 and 10.0. Store in airtight containers.

Uses and Administration

Clarithromycin is a macrolide derived from erythromycin with similar actions and uses (p. 294.1). It is given in the treatment of respiratory-tract infections (including otitis media) and in skin and soft-tissue infections. Clarithromycin is also used for the prophylaxis and treatment of nontuberculous mycobacterial infections and has been used as a second-line drug in the treatment of leprosy. It is used in some countries as an alternative to penicillins for prophylaxis of endocarditis.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Clarithromycin may be given to eradicate *Helicobacter pylori* in treatment regimens for peptic ulcer disease (p. 1816.2). It is used with pyrimethamine as an alternative regimen in the treatment of toxoplasmosis (p. 926.1).

Clarithromycin is given orally or by intravenous infusion. Some clarithromycin preparations are prepared with the aid of lactobionic acid and may be stated to contain clarithromycin lactobionate; others may contain clarithromycin citrate. Doses are expressed in terms of the equivalent amount of clarithromycin.

Usual oral doses in adults are 250 mg twice daily, increased to 500 mg twice daily if necessary in severe infection. Modified-release tablets allowing once-daily use are available in some countries.

The usual intravenous dose is 500 mg twice daily, given as an infusion over 60 minutes using a solution containing about 0.2% of clarithromycin. Intravenous treatment may continue for 2 to 5 days, but should be changed to oral clarithromycin when possible.

For treatment and prophylaxis of disseminated infection due to *Mycobacterium avium* complex, clarithromycin may be given in an oral dose of 500 mg twice daily; for treatment, it should be given with other antimycobacterials. For leprosy, oral clarithromycin 500 mg daily has been given as part of an alternative multidrug therapy regimen.

For the eradication of *H. pylori* associated with peptic ulcer disease, clarithromycin, usually in an oral dose of 500 mg twice daily, is given with another antibacterial and either a proton pump inhibitor or a histamine H_2-receptor antagonist, for 7 to 14 days.

Doses may need to be reduced in patients with severe renal impairment (see p. 268.3).

For details of doses in children, see p. 268.3.

Reviews.

1. Peters DH, Clissold SP. Clarithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; **44:** 117–64.
2. Barradell LB, *et al.* Clarithromycin: a review of its pharmacological properties and therapeutic use in Mycobacterium avium-intracellulare complex infection in patients with acquired immune deficiency syndrome. *Drugs* 1993; **46:** 289–312.
3. Markham A, McTavish D. Clarithromycin and omeprazole: as Helicobacter pylori eradication therapy in patients with H. pylori-associated gastric disorders. *Drugs* 1996; **51:** 161–78.
4. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc* 1999; **74:** 613–34.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.
6. Anonymous. Clarithromycin. *Tuberculosis (Edinb)* 2008; **88:** 92–5.

Administration in children. The usual oral dose of clarithromycin for infants and children is 7.5 mg/kg twice daily; this dose has also been suggested by the *BNFC* for neonates. Those over 12 years of age may be given the usual adult dose (see Uses and Administration, above).

Although intravenous use is not licensed for children in the UK the *BNFC* suggests a dose of 7.5 mg/kg twice daily for those aged from 1 month to 12 years; older children may be given the adult dose (see Uses and Administration, above).

For prophylaxis of disseminated infection due to *Mycobacterium avium* complex, US guidelines suggest clarithromycin may be given in an oral dose of 7.5 mg/kg twice daily; when used for treatment, it should be given with other antimycobacterials and the dose may be increased to 15 mg/kg (to a maximum of 500 mg) twice daily.[1]

For the **prevention of secondary cases of pertussis** the *BNFC* suggests that clarithromycin may be given twice daily for 7 days in the following oral doses:

- neonates: 7.5 mg/kg
- children 1 month to 12 years of age, according to bodyweight:
  - under 8 kg: 7.5 mg/kg
  - 8 to 11 kg: 62.5 mg
  - 12 to 19 kg: 125 mg
  - 20 to 29 kg: 187.5 mg
  - 30 to 40 kg: 250 mg
- children from 12 years of age: 500 mg

For the eradication of *Helicobacter pylori* associated with peptic ulcer disease, the *BNFC* suggests that 7.5 mg/kg (to a maximum of 500 mg) twice daily may also be given orally with another antibacterial and a proton pump inhibitor for 7 days to children aged 1 year and over.

1. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 09/12/13)

Administration in renal impairment. Licensed product information states that in patients with severe renal impairment (creatinine clearance of less than 30 mL/minute) oral and intravenous doses of clarithromycin may need to be halved or the dosing interval doubled.

Ischaemic heart disease. For mention of studies investigating clarithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p. 222.1.

Multiple myeloma. Clarithromycin 500 mg orally twice daily has been added[1] to a regimen of lenalidomide and dexamethasone in treatment-naive patients with multiple myeloma (p. 699.2). The regimen (BiRD) was considered effective and well tolerated, with a higher response rate at lower dexamethasone doses than had been previously reported with lenalidomide and dexamethasone alone. A regimen of clarithromycin, low-dose thalidomide, and dexamethasone (BLT-D) has also been evaluated.[2]

1. Niesvizky R, *et al.* BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood* 2008; **111:** 1101–9.
2. Coleman M, *et al.* BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenström's macroglobulinemia. *Leuk Lymphoma* 2002; **43:** 1777–82.

Respiratory disorders. For reference to the use of clarithromycin in the management of respiratory disorders, see under Erythromycin, p. 294.3.

Adverse Effects and Precautions

As for Erythromycin, p. 295.1. Gastrointestinal disturbances are the most frequent adverse effect but are usually mild and less frequent with clarithromycin than with erythromycin. Smell and taste disturbances, stomatitis, glossitis, tongue and tooth discoloration, and headache have occurred. There have also been reports of transient CNS effects. Other adverse effects include arthralgia, myalgia, hypoglycaemia, leucopenia, and thrombocytopenia. Interstitial nephritis and renal failure have been reported rarely. Clarithromycin may aggravate muscle weakness in patients with myasthenia gravis and new onset of myasthenic syndromes has been reported.

Intravenous doses may cause phlebitis and pain at the injection site.

Caution is required in patients with hepatic or renal impairment and doses should be reduced in those with renal impairment (see under Uses and Administration p. 266.3). It should not be used during pregnancy if possible as high doses have been associated with embryotoxicity in *animal* studies.

Effects on the blood. Single cases of thrombocytopenia[1] and thrombocytopenic purpura[2,3] associated with clarithromycin have been reported. Cases of agranulocytosis have also been reported.[4] A case of thrombocytopenia accompanied by interstitial nephritis, hepatitis, and elevated serum amylase levels was attributed to an allergic reaction to clarithromycin.[5] Toxic epidermal necrolysis and subsequent death due to aplastic anaemia have been reported in a patient after taking clarithromycin for 3 days.[6]

1. Price TA, Tuazon CU. Clarithromycin-induced thrombocytopenia. *Clin Infect Dis* 1992; **15:** 563–4.
2. Oteo JA, *et al.* Clarithromycin-induced thrombocytopenic purpura. *Clin Infect Dis* 1994; **19:** 1170–1.
3. Alexopoulou A, *et al.* Thrombotic thrombocytopenic purpura in a patient treated with clarithromycin. *Eur J Haematol* 2002; **69:** 191–2.
4. Jacobs P, *et al.* Immune agranulocytosis and clarithromycin. *Hematology* 2004; **9:** 291–6.
5. Baylor P, Williams K. Interstitial nephritis, thrombocytopenia, hepatitis, and elevated serum amylase levels in a patient receiving clarithromycin therapy. *Clin Infect Dis* 1999; **29:** 1350–1.
6. Baz K, *et al.* Fatal aplastic anaemia in a patient with clarithromycin-induced toxic epidermal necrolysis. *J Eur Acad Dermatol Venereol* 2004; **18:** 104–5.

Effects on the cardiovascular system. QT prolongation and torsade de pointes were associated with use of clarithromycin in 2 patients.[1] Renal impairment in 1 of the patients and hepatic impairment and organic heart disease in both could have increased their susceptibility to these effects.

For mention of an unexpected increase in cardiovascular mortality in patients with stable coronary heart disease given clarithromycin, see Ischaemic Heart Disease, in Uses and Administration of Azithromycin, p. 222.1.

1. Lee KL, *et al.* QT prolongation and torsades de pointes associated with clarithromycin. *Am J Med* 1998; **104:** 395–6.

Effects on the eyes. Corneal opacities, reversible on stopping treatment, were reported in a patient receiving oral clarithromycin as part of a regimen for disseminated *Mycobacterium avium* complex infection.[1] Corneal subepithelial deposits have also been reported in a patient after prolonged use of clarithromycin eye drops for *Mycobacterium avium* complex keratitis. The deposits did not cause any ocular discomfort and resolved on stopping therapy.[2]

1. Dorrell L, *et al.* Toxicity of clarithromycin in the treatment of Mycobacterium avium complex infection in a patient with AIDS. *J Antimicrob Chemother* 1994; **34:** 605–6.
2. Tyagi AK, *et al.* An unreported side effect of topical clarithromycin when used successfully to treat Mycobacterium avium-intracellulare keratitis. *Cornea* 1999; **18:** 606–7.

Effects on the gastrointestinal tract. Pseudomembranous colitis associated with *Clostridium difficile* developed in a child receiving clarithromycin.[1]

1. Braegger CP, Nadal D. Clarithromycin and pseudomembranous enterocolitis. *Lancet* 1994; **343:** 241–2.

Effects on the liver. Progressive cholestatic jaundice, which subsequently proved fatal, developed in a 59-year-old woman after 3 days of clarithromycin therapy for acute maxillary sinusitis.[1] Fulminant hepatic failure in another patient, which developed during clarithromycin therapy, resolved once the drug was withdrawn.[2] Clarithromycin itself was considered responsible although there was the possibility that it had increased concentrations of isradipine, another known hepatotoxic drug that the patient was also receiving.

1. Fox JC, *et al.* Progressive cholestatic liver disease associated with clarithromycin treatment. *J Clin Pharmacol* 2002; **42:** 676–80.
2. Tietz A, *et al.* Fulminant liver failure associated with clarithromycin. *Ann Pharmacother* 2003; **37:** 57–60.

Effects on the lungs. On 2 occasions fever and pulmonary infiltration with eosinophilia occurred in a patient given clarithromycin.[1] Another patient developed eosinophilic pneumonia 3 days after starting clarithromycin; symptoms improved when the drug was stopped.[2]

1. Terzano C, Petroianni A. Clarithromycin and pulmonary infiltration with eosinophilia. *BMJ* 2003; **326:** 1377–8.
2. Ohnishi H, *et al.* Clarithromycin-induced eosinophilic pneumonia. *Intern Med* 2004; **43:** 231–5.

Effects on mental state. Acute psychoses occurred in 2 patients receiving clarithromycin as part of prophylactic treatment for *Helicobacter pylori* infection and were similar to 3 previously reported cases in either AIDS patients or elderly subjects.[1] Delirium[2] has also been associated with clarithromycin monotherapy in an elderly patient, and visual hallucinations have occurred in a 37-year-old woman being treated with ceftriaxone and clarithromycin for suspected pneumonia;[3] and in 2 children taking standard doses of clarithromycin.[4] Mania associated with clarithromycin use has also been reported in a child.[5] A review[6] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials; clarithromycin was found to be the antibacterial most frequently implicated.

1. Gómez-Gil E, *et al.* Clarithromycin-induced acute psychoses in peptic ulcer disease. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 70–1.
2. Özsoylar G, *et al.* Clarithromycin monotherapy-induced delirium. *J Antimicrob Chemother* 2007; **59:** 331.
3. Fernández Arenas O, *et al.* Alucinaciones por administración de una pauta estándar de claritromicina. *Farm Hosp* 2007; **31:** 315–16.
4. Erkek N, *et al.* Visual hallucinations possibly associated with clarithromycin administration at therapeutic dosage in two children. *Med Princ Pract* 2009; **18:** 332–4.
5. Fidan T, Fidan V. Clarithromycin-induced mania in a child. *Int J Clin Pharmacol Ther* 2009; **47:** 402–4.
6. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; **22:** 71–81.

Effects on the pancreas. Pancreatitis has been reported in patients receiving clarithromycin.[1-3]

1. Liviu L, *et al.* Pancreatitis induced by clarithromycin. *Ann Intern Med* 1996; **125:** 701.
2. Schouwenberg BJJW, Deinum J. Acute pancreatitis after a course of clarithromycin. *Neth J Med* 2003; **61:** 266–7.
3. González Carro P, *et al.* Acute pancreatitis and modified-release clarithromycin. *Ann Pharmacother* 2004; **38:** 508–509.

Hypersensitivity. In addition to rashes and other hypersensitivity reactions, which occasionally occur in patients receiving macrolides, leucocytoclastic vasculitis,[1] Henoch-Schönlein purpura,[2] and toxic epidermal necrolysis[3,4] have been reported in patients receiving clarithromycin.

1. Gavura SR, Nusinowitz S. Leukocytoclastic vasculitis associated with clarithromycin. *Ann Pharmacother* 1998; **32:** 543–5.
2. Borrás-Blasco J, *et al.* Henoch-Schönlein purpura associated with clarithromycin: case report and review of literature. *Int J Clin Pharmacol Ther* 2003; **41:** 213–16. Correction. *ibid.*; 420.
3. Khaldi N, *et al.* Toxic epidermal necrolysis and clarithromycin. *Can J Clin Pharmacol* 2005; **12:** e264–e268.
4. Clayton TH, *et al.* Clarithromycin suspension-associated toxic epidermal necrolysis in a 2-year-old girl. *Clin Exp Dermatol* 2007; **32:** 755–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clarithromycin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 296.2.

Antidepressants. For a report of delirium following use of clarithromycin with *fluoxetine*, see Antibacterials, p. 426.1.

Antidiabetics. For reference to hypoglycaemia resulting from the addition of clarithromycin to *glibenclamide* or *glipizide*, see Antibacterials, p. 505.3.

Antigout drugs. For mention of fatal *colchicine* toxicity associated with concomitant use of clarithromycin, see Macrolides, p. 606.3.

Antivirals. Due to its effect on the cytochrome P450 isoenzyme CYP3A4, *ritonavir* markedly inhibits the metabolism of clarithromycin to its 14-hydroxy metabolite; other HIV-protease inhibitors are expected to interact similarly, albeit to lesser degrees. Clarithromycin becomes more dependent on renal clearance when hepatic metabolism is strongly inhibited; as a result, interactions may be more significant for those with renal impairment. Licensed product information for clarithromycin recommends an extra reduction in dose in patients with renal impairment receiving ritonavir, over and above any reduction that may be needed for the renal impairment alone: doses of clarithromycin should be reduced by 50% in patients with a creatinine clearance (CC) of 30 to 60 mL/minute and reduced by 75% in those with a CC below 30 mL/minute; the daily dose should not exceed 1 g.

Similar dose reductions have been recommended when given with most other ritonavir-boosted HIV-protease inhibitors. However, US licensed product information for *atazanavir* advises considering a 50% dose reduction of clarithromycin, regardless of renal status, to reduce the risk of QT-interval prolongation. It should be noted that this reduction may also substantially reduce levels of the active metabolite 14-hydroxyclarithromycin (which may be of clinical relevance in the treatment of Gram-negative infections such as those due to *Haemophilus influenzae*), and therefore alternatives to clarithromycin should be considered for treatment of infections other than those caused by *Mycobacterium avium complex* (MAC).

The NNRTI *delavirdine* may have similar effects on clarithromycin to those of the HIV-protease inhibitors, and clarithromycin doses should be reduced in patients with renal impairment as above. Use of *efavirenz*, *etravirine*, or *nevirapine* with clarithromycin may decrease plasma concentrations of the macrolide while increasing its hydroxy metabolite. UK licensed information for etravirine and nevirapine advises that alternatives to clarithromycin should be considered for treatment of MAC infections, given the reduced activity of the hydroxy metabolite against this organism. Co-administration of efavirenz with clarithromycin has been associated with a high incidence of rash.

Decreased concentrations of *zidovudine* (p. 1026.2) have been reported in patients also taking clarithromycin and clarithromycin product information recommends that doses of the two drugs should be separated by 1 to 2 hours.

Disulfiram. For a report of an interaction between clarithromycin and disulfiram, see Macrolides, p. 2496.3.

Gastrointestinal drugs. In a study[1] in healthy subjects, concentrations of clarithromycin and its active metabolite were increased in gastric tissue and mucus and, to a lesser extent, in plasma during use of *omeprazole*. In addition, use of clarithromycin with omeprazole resulted in higher and more prolonged plasma concentrations of omeprazole. The investigators suggest that this interaction could account for the synergistic action seen with this combination when used for eradication of *Helicobacter pylori*. However, licensed product information for clarithromycin states that no dosage adjustment to either drug is necessary.

Although a study[2] in healthy subjects suggested that some pharmacokinetic parameters of clarithromycin are altered by *cimetidine*, the clinical significance of such changes are unknown.

1. Gustavson LE, *et al.* Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; **39:** 2078–83.
2. Amsden GW, *et al.* Oral cimetidine prolongs clarithromycin absorption. *Antimicrob Agents Chemother* 1998; **42:** 1578–80.

Antimicrobial Action

As for Erythromycin, p. 297.1.

Clarithromycin is reported to be more active than erythromycin against susceptible streptococci and staphylococci *in vitro*, as well as against some other species including *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Legionella* spp., *Chlamydia trachomatis*, and *Ureaplasma urealyticum*. Clarithromycin is reported to be more active than erythromycin or azithromycin against some mycobacteria, including *Mycobacterium avium* complex and *M. leprae*. It is reported to have some *in-vitro* activity against the protozoan *Toxoplasma gondii*. The major metabolite, 14-hydroxyclarithromycin, is also active, and may enhance the activity of clarithromycin *in vivo*, notably against *Haemophilus influenzae*. The MICs of this metabolite are equal or twofold higher than those of the parent drug; the former is twofold more active than the latter against *H. influenzae*.

Activity with other antimicrobials. Clarithromycin has been reported to enhance the activity of some antimycobacterials including ethambutol, isoniazid, pyrazinamide, and rifampicin against *Mycobacterium tuberculosis*.[1,2]

1. Cavalieri SJ, *et al*. Synergistic activities of clarithromycin and antituberculous drugs against multi drug-resistant Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 1995; **39:** 1542–5.
2. Mor N, Esfandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; **41:** 2035–6.

Resistance. Erythromycin-resistant isolates of *Streptococcus pneumoniae* are commonly cross-resistant to clarithromycin.[1] The incidence of resistance to clarithromycin and other macrolides is higher among penicillin-resistant strains than among penicillin-sensitive strains.[2] Clarithromycin-resistant isolates of *Helicobacter pylori* have also emerged.[3-7] Genetic mutations responsible for clarithromycin resistance have been identified in *H. pylori*[8] and in *Mycobacterium* spp.[9,10] Since resistance develops rapidly in *M. avium* during clarithromycin monotherapy, combination therapy is usually recommended. However, resistance to clarithromycin in an AIDS patient with systemic *M. avium* complex infection, despite combined treatment with clofazimine, has been described.[11]

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2. Barry AL, *et al*. Macrolide resistance among Streptococcus pneumoniae and Streptococcus pyogenes isolates from out-patients in the USA. *J Antimicrob Chemother* 1997; **40:** 139–40.
3. López-Brea M, *et al*. Evolution of resistance to metronidazole and clarithromycin in Helicobacter pylori clinical isolates from Spain. *J Antimicrob Chemother* 1997; **40:** 279–81.
4. Hultén K, *et al*. Macrolide resistance in Helicobacter pylori: mechanism and stability in strains from clarithromycin-treated patients. *Antimicrob Agents Chemother* 1997; **41:** 2550–3.
5. Kalach N, *et al*. High levels of resistance to metronidazole and clarithromycin in Helicobacter pylori strains in children. *J Clin Microbiol* 2001; **39:** 394–7.
6. Grove DI, Koutsouridis G. Increasing resistance of Helicobacter pylori to clarithromycin: is the horse bolting? *Pathology* 2002; **34:** 71–3.
7. Megraud F, *et al*. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013 **62:** 34–42.
8. Versalovic J, *et al*. Mutations in 23S rRNA are associated with clarithromycin resistance in Helicobacter pylori. *Antimicrob Agents Chemother* 1996; **40:** 477–80.
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10. Wallace RJ, *et al*. Genetic basis for clarithromycin resistance among isolates of Mycobacterium chelonae and Mycobacterium abscessus. *Antimicrob Agents Chemother* 1996; **40:** 1676–81.
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Pharmacokinetics

Clarithromycin is rapidly absorbed from the gastrointestinal tract, and undergoes first-pass metabolism; the bioavailability of the parent drug is about 55%. The extent of absorption is relatively unaffected by the presence of food. Peak plasma concentrations occur 2 to 3 hours after an oral dose. Steady-state concentrations are reached within 3 to 4 days and peak plasma concentrations of clarithromycin and its principal active metabolite, 14-hydroxyclarithromycin, are then about 1 and 0.6 micrograms/mL, respectively, after 250 mg orally every 12 hours as tablets. The same dose given as a suspension to fasting subjects produces steady-state plasma concentrations of about 2 micrograms/mL of clarithromycin and about 0.7 micrograms/mL of 14-hydroxyclarithromycin.

The pharmacokinetics of clarithromycin are non-linear and dose dependent; high doses may produce disproportionate increases in peak concentrations of the parent drug, due to saturation of the metabolic pathways. However, the non-linearity is slight at the recommended doses of 250 to 500 mg every 8 to 12 hours.

Clarithromycin and 14-hydroxyclarithromycin are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. Plasma protein binding has been reported to be about 80%. Clarithromycin has been detected in breast milk. It is extensively metabolised in the liver, and excreted in faeces via the bile; 5 to 10% of the parent drug is recovered from the faeces. At steady state, about 20% and 30% of a 250-mg or 500-mg dose as tablets, respectively, and about 40% of a 250-mg dose as suspension, is excreted in the urine as unchanged drug. 14-Hydroxyclarithromycin as well as other metabolites are also excreted in the urine, accounting for 10 to 15% of the dose. The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are about 3 to 4 and 5 to 6 hours, respectively in patients receiving 250 mg every 12 hours, and about 5 to 7 and 7 to 9 hours, respectively, in those receiving 500 mg every 8 to 12 hours. The half-life is prolonged in renal impairment.

Reviews.

1. Rodvold KA. Clinical pharmacokinetics of clarithromycin. *Clin Pharmacokinet* 1999; **37:** 385–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aeroxina; Claribiotic; Claricina; Clarimax; Clarimid†; Clarovil; Corixa; Fadamicina; Finasept; Ira; Iset; Kailasa; Klaricid; Klonacid; Macromicina; Quotal; Soferax; Windar; ***Austral.***: Clarac; Clarihexal; Clarithro; Kalixocin; Klacid; ***Austria***: Klacid; Maclar†; ***Belg.***: Biclar; Clarithromed†; Heliclar; Maclar; Monoclarium; ***Braz.***: Clamicin; Clarineo; Claritromax†; Klaricid; Klaroxil; ***Canad.***: Biaxin; ***Chile***: Clarimax; Clarosip†; Clatic; Euromicina; Infex; Klaricid; Mus-TC; Pre-Clar; ***China***: A Rui (阿瑞); Ai Er Bei (艾尔贝); An Ji Er Ning (安吉尔宁); An Ji Er Shu (安吉尔舒); Ang Ke (昂克); Ao Fu An (澳扶安); Ao Ni Ya (奥尼亚); Baihongyou (百红优); Bao Nuo (保诺); Bing Ke (冰克); Chang Di (长迪); Claricin (甲力); Feng Rui (锋锐); Fu Ke Xing (福可星); Gui Long Nuo Ke (桂龙诺克); Jia Ji Ning (甲吉宁); Jia Nuo Qi (佳诺奇); Jin Yang Bo Tai (金阳博泰); Jun Ran (君然); Ka Mai (卡迈); Ka Rui Si (卡瑞斯); Ka Tai Ka (卡太卡); Kai Mai (开迈); Kang Ka (康卡); Kasimaixin (卡斯迈欣); Ke Li Xian (柯力仙); Ke Man Xin (科曼欣); Ke Mei Xin (可枚辛); Ke Ni Bang (克尼邦); Klabax (卡碧士); Klacid (克拉仙); Li Xin (立辛); Limaixian (利迈先); Lu Xian Tong (路仙同); Lv Shu (绿舒); Mei Bo (美博); Mo Xin (莫欣); Nai Er (奈尔); Nuo Bang (诺邦); Nuo Sha (诺沙); Pi Ke (匹刻); Pu Mai (普迈); Rui Yuan (瑞源); Sai Hong (赛红); Sang Mei (桑美); Sen Ke (森克); Sha Di (沙迪); Shen Mai Qi (申迈奇); Sheng Nuo De (圣诺得); Shuang Chuan (双川); Tai Bi Jie (泰必捷); Tai Fei (泰菲); Tai Mei La (泰每拉); Wei Peng (维朋); Wo Ka (沃卡); Yi Chuang (怡川); Yi Ren (宜仁); Yu Jun Xian (裕君先); Zhen Ke (臻克); ZhenKe (珍可); ***Cz.***: Clarexid†; Clarosip†; Fromilid; Klabax; Klacid; Lekoklar; ***Denm.***: Klacid; Klaricid; ***Fin.***: Clarium; Cymoklar; Klacid; Zeclar; ***Fr.***: Mononaxy; Monozeclar; Naxy; Zeclar; ***Ger.***: Biaxin†; Clarithrobeta; Clarosip†; Cyllind†; Klacid; Mavid†; ***Gr.***: Althromicin; Arecid; Brevil; Chlamydicin; Claribactron; Claridus; Clarimex; Clarimil; Claripen; Clarithrocin; Claromycin; Derizic; Egelif; Eliben; Ezumycin; Geromycin; Glartin; Klaretop; Klarexyl; Klaribros; Klaricid; Klarifar; Klarifect; Klarimac; Klarithrin; Klaroxin; Klazidem; Larithro; Laromin; Lyoclar; Macladin; Maxigan; Maxilin; Mythrocin; Odycin; Pharicid; Pharlemyron; Primocid; Riclemed; Rithroprol; Ritran; Sanicet; Sythro; Thriamox; Tromypen; Zeclar; Zeclaren; ***Hong Kong***: Binoclar; Clacin; Claricin; Clarsin; Cleron†; Fascar; Klacid; Klerimed; Synclar; Vick-Clarcid; ***Hung.***: Cidoclar†; Fromilid; Klabax; Klacid; Klarigen; Lekoklar; ***India***: Acem; Acgel; Acnesol-CL; Bioclar; Celex-OD; Celex; Clamycin; Clar; Clarbact; Claribid; Claricin; Claricip; Clarics; Claridase; Clarie; Clarigen; Clarigo; Clarimac; Clarithro; Clarivir; Clariwin; Clear; Clycin; Crixan; F-Clar; Heliclar; Klacid; Klacin; Klarim; Larit; Maclar; Macmax; Macroclar; Monoclar; Mythro; Mythrocin; Neuclar; Novaclar; Synclar; ***Indon.***: Abbotic; Bicrolid; Binoklar†; Clacine; Clapharma†; Comtro; Hecobac; Orixal; ***Irl.***: Clarie; Claripsine; Clarosip†; Claryl; Clonocid; Clorom; Klacid; Klaram; Klariger; ***Israel***: Karin; Klacid; Klaridex; ***Ital.***: Klacid; Macladin; Madiclar; Soriclar; Veclam; Winclar; ***Jpn***: Clarith; ***Malaysia***: Avexus; Binocular; Clarem; Clarimycin; Crixan; Klacid; Klerimed; Maclar; ***Mex.***: Adel; Arlecyn-K; Claritral; Clatrocin†; Collitred; Crixan†; Crolisil; Doycur; Fhisfal; Gervaken; Klabet; Klaricid; Klarix; Klarmyn; Klarpharma; Krobicin; Mabicrol; Neo-Clarosip; Quedox; Rolicytin; Torvic†; Trimeba; Vikrol; Xuclamin; ***Neth.***: Biaxin†; Clarosip†; Klacid; Klaricid†; Kloreniss; ***Norw.***: Klacid; ***NZ***: Clarac; Klacid; Klamycin; ***Philipp.***: Baclecin; Bysclas; Clabet; Clamycin; Clarianta; Clarie; Clariget; Clarithrocid; Clariwin; Claryl; Clistanex; Galemin; Hamun; Klaret; Klargen; Klaricid; Klarid; Klarimac; Klarix; Klarmyn; Klaryz; Klaz; Larizin; Maclar; Macrodin; Macrolin; Macronox; Maxulid; Neo-klar; Onexid; Oracid; Rithrocin†; Ritromax; Supalide†; ***Pol.***: Fromilid; Klabax; Klabion; Klacid; Klarigen; Klarmin; Lekoklar; Taclar; ***Port.***: Ciclinil; Clacina; Cladia; Clarbac; Clarobiotico; Klacid; Zeclar†; Zocid; ***Rus.***: Arvicin (Арвицин); Binoclar (Биноклар); Clarbact (Кларбакт); Clarithrosin (Кларитросин); Clarosip (Кларосип); Ecozitrin (Экозитрин); Fromilid (Фромилид); Klabax (Клабакс); Klacid (Клацид); Klarexid (Кларексид); Klaricin (Кларицин); Klaricit (Кларицит); Klaromin (Кларомин); Klasine (Класине); Klerimed (Клеримед); Lekoklar (Лекоклар); Seidon (Сейдон); ***S. Afr.***: Clacee; ClariHexal; Klacid; Klarithran; Klarizon; ***Singapore***: Bicrolid; Clari; Claripen; Clariwin; Cleron; Crixan; Klacid; Klerimed; Monoclarium; ***Spain***: Bremon; Klacid; Kofron; ***Swed.***: Klacid; ***Switz.***: Clamycin†; Clarithrocine; Claromycine; Klacid; Klaciped; ***Thai.***: Clacina; Clacinia; Clarith; Claron; Crixan; Fascar; Klacid; ***Turk.***: Clabel; Claricide; Cleanomisin; Deklarit; Klacid; Klamaxin; Klamer; Klarolid; Klaromin; Klasol; Klax; Klerant; Laricid; Macrol; Maxiclar; Megasid; Uniklar; ***UAE***: Clamycin; ***UK***: Clarosip†; Febzin; Klaricid; Mycifor; ***Ukr.***: Clabax (Клабакс OD); Clabel (Клабел); Fromilid (Фромилид); Klacid (Клацид); Kleron (Клерон); Lekoklar (Лекоклар)†; ***USA***: Biaxin; ***Venez.***: Binoclar; Claranta; Claritic; Claritron; Clarivax; Klaricid.

Multi-ingredient Preparations. ***Austral.***: Klacid HP 7; Losec Hp 7†; Nexium Hp; Probitor Hp7; Pylorid-KA†; ***Braz.***: Erradic; H Bacter; Helicopac; Heliklar; Omepramix; Pylorikit; Pyloripac; Pyloriset; Pyloritrat; ***Canad.***: Hp-Pac; Losec 1-2-3 A; Losec 1-2-3 M; Nexium 1-2-3 A; ***Chile***: Lanzopral Heli-Pack; Pylopac; ***China***: Weisanlian (胃三联); Yi Hong (怡弘); ***Fin.***: Helipak K; ***Ger.***: ZacPac; ***India***: Claridase; GI Kit; Heligo; L-Cot; LTC-Kit; OTC HP Kit; Pantocid-HP; Pantop-HP Kit; Pantop-HP; Pylokit; ***Malaysia***: Klacid HP 7; Pylobact Combi; ***Mex.***: Pylopac; Rezplen; ***Neth.***: PantoPAC; ***NZ***: Losec Hp7; ***Philipp.***: OAC Hp7+; ***Rus.***: Pylobact (Пилобакт); ***Swed.***: Nexium Hp; ***Turk.***: Helipak; Trio; ***Ukr.***: β-Klatinol (β-КЛАТИНОЛ); Clamed (Кламед); Esoxium Combi (Эзоксиум Комби); Onristat (Орністат)†; Pylobact Neo (Пилобакт Нео); ***USA***: Omeclamox-Pak; Prevpac.

Pharmacopoeial Preparations

BP 2014: Clarithromycin for Infusion; Clarithromycin Tablets; Prolonged-release Clarithromycin Tablets;
USP 36: Clarithromycin Extended-Release Tablets; Clarithromycin for Oral Suspension; Clarithromycin Tablets.

Clavulanic Acid *(BAN, rINN)*

Acide Clavulanique; Ácido clavulánico; Acidum Clavulanicum; BRL-14151; Clavulánico, ácido; Klavulanik Asit; MM-14151; Клавулановая Кислота.

(*Z*)-(2*R*,5*R*)-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

$C_8H_9NO_5$=199.2

CAS — 58001-44-8 (clavulanic acid); 57943-81-4 (sodium clavulanate).

UNII — 23521W1S24.

Potassium Clavulanate *(BANM, rINNM)*

Potasu klavulanian; BRL-14151K; Clavulanate de Potassium; Clavulanate Potassium (USAN); Clavulanato potásico; Kalii Clavulanas; Kalio klavulanatas; Kaliumclavulanat; Kaliumklavulanaatti; Kaliumklavulanat; Kalium-klavulanát; Káliumklavulanát; Potassium, clavulanate de; Калия Клавуланат.

$C_8H_8KNO_5$=237.3

CAS — 61177-45-5.

UNII — Q42OMW3AT8.

NOTE. Compounded preparations of potassium clavulanate may be represented by the following names:

- Co-amoxiclav *x*/*y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Eur. also includes Diluted Potassium Clavulanate.

Ph. Eur. 8: (Potassium Clavulanate). The potassium salt of a substance produced by the growth of certain strains of *Streptomyces clavuligerus* or by any other means. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

Ph. Eur. 8: (Potassium Clavulanate, Diluted; Kalii Clavulanas Dilutus). A dry mixture of potassium clavulanate and microcrystalline cellulose or anhydrous or hydrated colloidal silicon dioxide. A white or almost white, hygroscopic, powder. A suspension corresponding to 1% of potassium clavulanate in water has a pH of 4.8 to 8.0. Store in airtight containers.

USP 36: (Clavulanate Potassium). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol with decomposition. Stability in aqueous solutions is not good, optimum stability at a pH of 6.0 to 6.3. pH of a 1% solution in water is between 5.5 and 8.0. Store in airtight containers.

Profile

Clavulanic acid is produced by cultures of *Streptomyces clavuligerus*. It has a beta-lactam structure resembling that of the penicillin nucleus, except that the fused thiazolidine ring of the penicillins is replaced by an oxazolidine ring. In general, clavulanic acid has only weak antibacterial activity. It is a potent progressive inhibitor of plasmid-mediated and some chromosomal beta-lactamases produced by Gram-negative bacteria including *Haemophilus ducreyi*, *H. influenzae*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Bacteroides fragilis*, and some Enterobacteriaceae. It is also an inhibitor of the beta-lactamases produced by *Staphylococcus aureus*. Clavulanic acid can permeate bacterial cell walls and can therefore inactivate both extracellular enzymes and those that are bound to the cell. Its mode of action depends on the particular enzyme inhibited, but it generally acts as a competitive, and often irreversible, inhibitor. Clavulanic acid consequently enhances the activity of penicillin and cephalosporin antibacterials against many resistant strains of bacteria. However, it is generally less effective against chromosomally mediated type 1 beta-lactamases; therefore, many *Citrobacter*, *Enterobacter*, *Morganella*, and *Serratia* spp., and *Pseudomonas aeruginosa* remain resistant. Some plasmid-mediated extended-spectrum beta-lactamases in *Klebsiella pneumoniae*, some other Enterobacteriaceae, and *Ps. aeruginosa* are also not inhibited by beta-lactamase inhibitors.

All cross-references refer to entries in Volume A

Clavulanic acid is given as potassium clavulanate orally and by injection with amoxicillin (co-amoxiclav) (p. 216.2), and by injection with ticarcillin (p. 380.2).

Use of clavulanate with penicillins has been associated with the development of cholestatic jaundice and hepatitis (see under Adverse Effects of Amoxicillin, p. 217.2) and therefore restrictions on the use of co-amoxiclav have been suggested in some countries (see p. 271.1).

Because of the risk of cholestatic jaundice the UK CSM[1] recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant beta-lactamase-producing strains and that treatment should not usually exceed 14 days. It may be considered for the following main indications:

- sinusitis, otitis media, recurrent tonsillitis
- acute exacerbations of chronic bronchitis
- bronchopneumonia
- urinary-tract infections, especially when recurrent or complicated, but not prostatitis
- septic abortion, pelvic or puerperal sepsis, and intra-abdominal sepsis
- cellulitis, animal bites, and severe dental abscess with spreading cellulitis.

1. CSM/MCA. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23**: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Optamox; ***Austral.***: Moxiclav; ***Indon.***: Aclam; ***Philipp.***: Agpen; Koact; ***Thai.***: Clanoxy; Rapiclav; ***Turk.***: Amoksilav.

Multi-ingredient Preparations. ***Arg.***: Aclav†; Amixen Clavulanico; Amoclav Duo; Amoclav; Amoxi Plus; Amoxigrand Compuesto; Amoxitenk Plus; Bi Moxal Duo; Bi Moxal; Bioclavid; Bioxilina Plus; Clamoxol Bio; Clamoxol; Clavulox Duo; Clavulox; Cloximar Duo†; Darzitil Plus Duo; Darzitil Plus; Dibional; Fabamox Duo; Grinsil Clavulanico; Klonalmox; Nobactam Clavulanico; Optamox Duo; Plenobiotic Duo; Ultrabiotic Duo; Ultrabiotic; ***Austral.***: Augmentin; Clamohexal†; Clamoxyl; Clavulin; Clavycillin; Curam; GA-Amclav; Timentin; ***Austria***: AmoclanHexal; AmoxiClavulan; Amoxicomp; Amoxiplus; Amoxistad plus; Augmentin; Clavamox; Xiclav; ***Belg.***: Amoclane; Amoxiclav; Augmentin; Clavucid; Co-Amoxi†; Docamoclaf†; Timentin; ***Braz.***: Amplamox AC; Augmentin†; Betaclav†; Clavulin; Claxam; Novamox; Policlavumoxil; Sigma Clav; Timentin; ***Canad.***: Apo-Amoxi Clav; Clavulin; Novo-Clavamoxin; ratio-Aclavulanate; Timentin; ***Chile***: Ambilan Bid; Ambilan; Amolex; Augmentin Bid; Augmentin; Clavinex Duo; Clavinex; Clavoxilina Bid; ***China***: A Le Xian (阿乐仙); Aikeer (艾克儿); Amoksiklav (莱得怡); An Ke (安克); An Qi (安奇); Anmiejun (安灭菌); Ao Ge Men Ding (奥格门汀); Ao Xian (奥先)†; Augmentin (力百汀); Bang Lin (棒林); Bi Lin (毕林); Bi Qi Er (比奇尔); Chao Qing (超青); Curam (克瑞兰); Fengkelin (锋克林); Haikela (海可拉); Jian Ao (健澳); Jin Li Chen (今利辰); Jin Li Shu (金力舒); Ju Tai (巨泰); Jun Er Qing (君尔清); Keng Qiang (铿锵); Lieqi (列其); Luo De (洛得); Nuoke (诺可); Rui Si (瑞思); Sheng Ai (胜艾); Sheng Xi Kai (盛西凯); Shu Xian Lin (舒仙琳); Te Di (特迪); Timentin (特美汀); Wei An Ke Xin (维安可欣); You Lin Jia (尤林加); ***Cz.***: Amoclabene; Amoksiklav; Augmentin Duo; Augmentin; Betaklav†; Clamox; Curam; Enhancin†; Forcid†; Medoclav; Megamox; Timentin†; ***Denm.***: Bioclavid; Spektraforte; Spektramox; ***Fin.***: Amorion Comp; Amoxin Comp; Augmentin; Bioclavid; Clavumed†; Clavurion†; Yamoxiclav†; ***Fr.***: Augmentin; Ciblor†; Claventin; ***Ger.***: Amoclav†; Amoxclav†; Amoxi-Clavulan†; Amoxi-saar plus; Amoxicillin comp; Amoxiclav; Augmentan; InfectoSupramox; ***Gr.***: Augmentin; Bioclavid; Forcid; Frolicin; Fugentin; Moxiclav; Tenervan; Timentin; ***Hong Kong***: Amoksiklav; Augmentin; Clamovid; Curam; Fleming; Moxiclav; Quali-Mentin; Timentin; ***Hung.***: Aktil; Amoclav; Augmentin-Duo; Augmentin-Extra†; Augmentin; Co-Amoxi; Curam; Enhancin; Forcid; ***India***: Aclav; Acticlav; Adclav; Adpax; Advent; Aelxim-CL; Afixim Clav; Afymox-Clav; Alepam; Alfi-CV; Amclaid; Ament; Amo-C Plus; Amo-Nate; Amoclavs-LB; Amoclavs; Amonit Plus; Amoxytek; Amstar-Clav; Arclav; Ariclav; Astute-CV; Atmox-CL; Augclav; Augmentin; Augmexx; Augnic; Augpen-LB; Augpen; Augpod; Aulanic; Avclav; Bactoclav; Belfix-CV; Benzoclav; Bestomax 375; Bestomax; Betmox-CV; Bilactam-XL; Bilin Plus; Bixigard-C; Blumox-CA; Bodimox-CV; Boostim-LB; Boostim; C Mox; C-Fix-XT; C-Moxy; Cadmentin; Cafage-CL; Canmox; Capiclav; Casclav; CDCV; Cefchamp; Cefexy-CV; Cefit-XL; Cefix-CV; Cefoclav; Ceftyl-CV; Cefupop-CV; Ceme-CV; Cexime-CL; CGV-DS; Cifilac-CV; Cinclav; Clafel; Clamchek; Clamox; Clamoxy A; Clamoxy; Clamp; Clanex; Clanic; Clanoxy; Clapex; Clatimox Syr; Clatimox; Clauvmentin; Clav-II; Clavactum; Clavage; Clavam; Clavbel; Claver; Clavid-A; Clavimox; Clavipen; Clavitrax; Clavnic; Clavogard; Clavotrol; Clavox; Clavtax-O; Clavter-LB; Clavu-M; Clavunate; Cleblo-CL; Cleblo-CL; Cliver-A; Clomid-CL; Co-Symoxyl; Coax; Cobex-CL; Comentin; Cosmoxyl; Covatil-CV; Cuclav; Curam; CV-Cef; Daczim-CL; Demoxin-CB; Dewmox-CV; Doxiclav; Doxinis-CV; Droxyl Clav; Duclav; E-Amox CL; Edoxim-CV; Elclav; Emclav; Emtax-CL; Enhancin; Esclox-CL; Etoclav; Everclav; Exario; Exlla-CV; Expodox-CV; Fightox; Fimi-CV; Finecef-CV; Fixcef-CL; Fixx Clav; Flamclov; Flemiclav-LB; Flemiclav; Forticlav; Geclave; Germox; Glomox-C; Glyph-C; Goclav; Gramclav; Gramocef-CV; GSClav; Hibrid; Hifen-CV; Hofim-C; Hosiclav; Incef-CV; Indcel; Indclav; Infactum; Inmox Clav; Intracef-CV; Ipodex-CV; IV Augclav; Jidox-C; Kalmox; Kindclav; Kinopox-CV; Kistan; Klamoric; Klavoclav; Krusade; Labocef-CV; Labzone; Laciclav; Lacom-CV 625; Lacom-CV; Lactoclav; Lakmox-CL; Lamna-C; Laxclav-LB; Laxclav; Laximo-XL; Lebzone; Leclav; Lemna-C Kid; Letix-C; Lexime-CV; Linaox-Clav; LMX Forte; Logcef-CV; M-Clav; M-Klav; Mahacef-CV; Maxclav; Maximizin; MDCef-CV; Mediclav; Mega-CV; Megaclav; Megamentin; Megox; Mikclav; Miliximx-CV; Minoclav; Mintclav; Mintodox-CL; Monamox-CL; Mordica; Mordica; Moxclav; Moxifast-CV; Moxigem; Moxikare; Moxikind-CV; Moxinova CV; Moxiphar-CV; Moxipil-CL; Moxipil-CV; Moxiplus-CV; Moxitrac-CV; Moxiz CV; Moxnic; Moxsav; Moxspen-CL; Moxtive-Clav; Moxxil-Duo; Moxy Plus-CV; Moxycare; Moxyclav; Moxynic; Moxyvent; Mpx-CV; Mucoclav; Myclav; Nayaclav; Neclav; Netclav; Netflox-OZ; Neucomox; Nikomox-CV; Nipp-CA; Nismentin; Nizoclav; Noir; Novaclav; Novamox-CV; Nuclav; Nufex Beta; Nupod-CV; O-Moxy-CL; Ocef-CV; Oclam; Ogmen; Omlar-CV; Omnapil-CV; Omnataxcv; Onamox-CL; One Clav; Opox-CV; Orgamox-CL BD; Orgamox-CL; Osclav; Oxipod-CV; Pamclav; Papcef-CV; Timentin†; ***Indon.***: Amocomb; Ancla; Augmentin; Auspilic; Bellamox; Betaclav; Biditin†; Capsinat; Clabat; Claneksi; Clavamox; Claxy; Comsikla; Danoclav; Daxet; Dexyclav; Ikamoxyl Plus; Improvox; Lansiclav; Nufaclav; Nuvoclav; Palentin; Prafamoct; Protamox; Surpas; Syneclav; Viaclav; Vibranat; Vulamox; Zumafen†; ***Irl.***: Amoclav; Augmentin; Bellmentin†; Clavamel; Germentin; Pinaclav; ***Israel***: Amoxiclav; Augmentin; Clavamox; Clavenir; Claventin; Moclav; Timentin; ***Ital.***: Abba; Acadimox; Aklav; Anival; Augmentin; Aveggio; Clavulin; Euticlavir; Homer; Klavux; Kruxade; Levantes; Mondex; Moxivul; Neoduplamox; Puriclav; Servamox†; Timentin; Xinamod; ***Malaysia***: Augmentin; Cavumox; Clamentin; Clamovid; Clavam; Clavomid; Curam; Enhancin; Moxiclav; Myclav; ***Mex.***: Acarbixin; Acimox AC; Alvi-Tec; Amobay CL; Amoxiclav; Amoxiclide; Ampliron Duo; Apoclavox; Augmentin; Avuxilan; Clambusil; Clamoxin; Clavant; Clavucyd; Clavulin; Clavuser; Crizmat; Enhancin; Gramaxin; Moxlin CLV; Rapiclav; Riclasip; Servamox CLV; Sinufin; Timentin; Valclan†; ***Neth.***: Amoclan†; Amuclan†; Augmentin; Bioclavid; Forcid; Zymolav; ***NZ***: Alpha-Amoxyclav†; Augmentin; Curam; Synermox; Timentin; ***Philipp.***: Addex; Agcomen; Alvonal; Amoclav; Anbicyn; Atadar; Augmentin; Augmex†; Augurcin; Bactiv; Bactoclav; Bioclav; Bioclavid; Cax; Clamovid; Clamoxil; Claneksi; Clavasul; Claventin; Clavimox; Clavmex; Clavomax; Clavorex; Clavox; Clavoxel; Clavoxin; Clovimax; CO-AX; Comxicla; Duotak; Enhamox; Enhancin; Exten; Globantin; Gloclav; Julmentin; Klavic; Luvmox; Natravox; Nexilav; Penhance; Proxiclav; Rafonex; Sanmox†; Solclav; Sovlan; Sullivan; Suplentin†; Ticarcin; Timentin; Valmocel†; Vamox; Xilanic; ***Pol.***: Amoclan; Amoksiklav; Augmentin; Curam†; Forcid; Ramoclav†; Taromentin; Timentin; ***Port.***: Amoclavam; Amplamox Plus†; Augmentin; Betamox; Clavamox; Clavepen; Forcid; Noprilam; Penilan; ***Rus.***: Amoclan (Амоклан)†; Amoksiklav (Амоксиклав); Arlet (Арлет); Augmentin (Аугментин); Clamosar (Кламосар); Ecoclav (Экоклав); Flemoclav (Флемоклав); Liclav (Ликлав); Medoclav (Медоклав); Panklav (Панклав); Ranclav (Ранклав); Rapiclav (Рапиклав); Timentin (Тиментин); ***S.Afr.***: Adco-Amoclav; Amoclan; Apex-Clavutin; AugMaxcil; Augmentin; Auro-Amoxiclav; Bindoclav; Bio-Amoksiclav; Bio-Amoksiklav; Clamentin; Clavumox; Co-Amoxyclav; Curam; Forcid; Ranclav; Rolab-Amoclav†; ***Singapore***: Amocla; Augmentin; Clamonex; Clamovid; Curam; Enhancin; Fugentin†; Moxiclav; ***Spain***: Amoclave†; Augmentine; Duonasa; Odontobiotic; ***Swed.***: Bioclavid; Spektramox; ***Switz.***: Augmentin; Aziclav; Clavamox†; Co-Amoxi; Co-Amoxicillin; Co-Amoxicilline; CoAmox; ***Thai.***: AMK; Amocla†; Amoksiklav; Anbicyn; Augclav; Augmentin; Augpen†; Biclav; Cavumox; Clavmoxy; Clavomid; Curam; Ind Clav; Klamoks†; Manclamine; Moxiclav; Moxicle; Pencla†; Ranclav; Verclav; ***Turk.***: Amoklavin; Augmentin; Bioment; Croxilex; Klamoks; Klavunat; Klavupen; Timentin; ***UAE***: Julmentin; ***UK***: Augmentin-Duo; Augmentin; Timentin; ***Ukr.***: Amoksiklav (Амоксиклав); Amoxicomb (Амоксикомб); Amoxil-K (Амоксилу-К); Augmentin (Аугментин); Bactoklav (Бактоклав); Betaklav (Бетаклав)†; Clavam (Клавам); Flemoclav (Флемоклав); Klamox (Кламокс)†; Panclav (Панклав)†; Timentin (Тиментин); ***USA***: Amoclan; Augmentin; Timentin; ***Venez.***: Augmentin; Clavumox; Curam; Fulgram.

Pharmacopoeial Preparations

BP 2014: Co-amoxiclav Injection; Co-amoxiclav Oral Suspension; Co-amoxiclav Tablets; Dispersible Co-amoxiclav Tablets; Ticarcillin and Clavulanic Acid Infusion;

USP 36: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Amoxicillin and Clavulanic Acid Extended-Release Tablets; Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection.

Clemizole Penicillin *(BAN, rINN)*

Clemizol penicilina; Clemizole Benzylpenicillin; Clémizole Pénicilline; Clemizolum Penicillinum; Klemitsolipenisilliini; Klemizolpenicillin; Penicillin G Clemizole; Клемизол Пенициллин.

1-[1-(4-Chlorobenzyl)benzimidazol-2-ylmethyl]pyrrolidinium (6*R*)-6-(2-phenylacetamido)penicillanate.

$C_{16}H_{18}N_2O_4S,C_{19}H_{20}ClN_3$=660.2

CAS — 6011-39-8.

UNII — 5UL276H6TF.

Profile

Clemizole penicillin is a long-acting preparation of benzylpenicillin (p. 228.1) with similar properties and uses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Prevepen†; ***Mex.***: Megapenil†.

Multi-ingredient Preparations. ***Chile***: Prevepen Forte; ***Mex.***: Alivin Plus; Anapenil; Megapenil Forte†.

Clindamycin *(BAN, USAN, rINN)*

Clindamicina; Clindamycine; Clindamycinum; Klindamisin; Klindamycin; Klindamysiini; U-21251; Клиндамицин.

Methyl 6-amino-7-chloro-6,7,8-trideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-L-*threo*-D-*galacto*-octopyranoside.

$C_{18}H_{33}ClN_2O_5S$=425.0

CAS — 18323-44-9.

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

UNII — 3U02EL437C.

NOTE. The name Clinimycin, which was formerly used for clindamycin, has also been used for a preparation of oxytetracycline.

Clindamycin Hydrochloride *(BANM, rINNM)*

(7*S*)-Chloro-7-deoxylincomycin Hydrochloride; Chlorodeoxylincomycin Hydrochloride; Clindamicina, hidrocloruro de; Clindamycine, Chlorhydrate de; Clindamycinhydrochlorid; Clindamycini Hydrochloridum; Hidrocloruro de clindamicina; Klindamicin-hidroklorid; Klindamicino hidrocloridas; Klindamisin Hidroklorür; Klindamycin-hydrochlorid; Klindamycinhydroklorid; Klindamycyny chlorowodorek; Klindamysiinihydrokloridi; Клиндамицина Гидрохлорид.

$C_{18}H_{33}ClN_2O_5S,HCl$=461.4

CAS — 21462-39-5 (anhydrous clindamycin hydrochloride); 58207-19-5 (clindamycin hydrochloride monohydrate).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

UNII — T20OQ1YN1W (clindamycin hydrochloride); ZNC153389R (clindamycin hydrochloride monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clindamycin Hydrochloride). A white or almost white, crystalline powder. It contains a variable quantity of water. Very soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 3.0 to 5.0. Store in airtight containers.

USP 36: (Clindamycin Hydrochloride). A white or practically white crystalline powder, odourless or has a faint mercaptan-like odour. Freely soluble in water, in dimethylformamide, and in methyl alcohol; soluble in alcohol; practically insoluble in acetone. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Clindamycin Palmitate Hydrochloride

(BANM, USAN, rINNM)

Clindamicina, hidrocloruro del palmitato de; Clindamycine, Chlorhydrate de Palmitate de; Clindamycini Palmitatis Hydrochloridum; Hidrocloruro del palmitato de clindamicina; U-25179E; Клиндамицина Палмитата Гидрохлорид.

Clindamycin 2-palmitate hydrochloride.

$C_{34}H_{63}ClN_2O_6S,HCl$=699.9

CAS — 36688-78-5 (clindamycin palmitate); 25507-04-4 (clindamycin palmitate hydrochloride).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

UNII — VN9A8JM7M7.

Pharmacopoeias. In *US*.

USP 36: (Clindamycin Palmitate Hydrochloride). A white to off-white amorphous powder having a characteristic odour. Freely soluble in water, in chloroform, in ether, and in benzene; soluble 1 in 3 of alcohol and 1 in 9 of ethyl acetate; very soluble in dimethylformamide. pH of a 1% solution in water is between 2.8 and 3.8. Store in airtight containers.

Clindamycin Phosphate *(BANM, USAN, rINNM)*

Clindamicina, fosfato de; Clindamycin-2-dihydrogenphosphat; Clindamycine, Phosphate de; Clindamycini Dihydrogenophosphas; Clindamycini Phosphas; Fosfato de clindamicina; Klindamicin-foszfát; Klindamicino fosfatas; Klindamisin Fosfat; Klindamycin dihydrogen fosfát; Klindamycinfosfat; Klindamysiinifosfaatti; U-28508; Клиндамицина Фосфат.

Clindamycin 2-(dihydrogen phosphate).
$C_{18}H_{34}ClN_2O_8PS$=505.0
CAS — 24729-96-2.
ATC — D10AF01; G01AA10; J01FF01.
ATC Vet — QD10AF01; QG01AA10; QJ01FF01.
UNII — EH6D711318.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Clindamycin Phosphate). A white or almost white, slightly hygroscopic powder. It shows polymorphism. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding 30 degrees in airtight containers.

USP 36: (Clindamycin Phosphate). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Soluble 1 in 2.5 of water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform, in ether, and in benzene. pH of a 1% solution in water is between 3.5 and 4.5. Store in airtight containers.

Incompatibility. Solutions of clindamycin salts have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Licensed product information for the injectable solution of clindamycin states that incompatibility has been reported between clindamycin and the following drugs: ampicillin, aminophylline, barbiturates, calcium gluconate, ceftriaxone, ciprofloxacin, idarubicin, magnesium sulfate, phenytoin, and ranitidine.

Clindamycin phosphate is incompatible with natural rubber closures.

Uses and Administration

Clindamycin is a chlorinated derivative of the lincosamide antibacterial lincomycin. It is a mainly bacteriostatic drug used in the treatment of serious anaerobic infections, notably due to *Bacteroides fragilis*. Clindamycin is also used for some Gram-positive infections due to pneumococci, staphylococci (including meticillin-resistant forms), and streptococci. However, because of its potential for causing pseudomembranous colitis (see Adverse Effects, p. 273.2) it is usually used only when alternative drugs are unsuitable.

Amongst the conditions that it may be used to treat (either alone, or with other antibacterials) are liver abscess, actinomycosis, biliary-tract infections, staphylococcal bone and joint infections, the carrier state of diphtheria, endophthalmitis, gas gangrene, various gynaecological infections including bacterial vaginosis, endometritis, and pelvic inflammatory disease, intra-abdominal infections including secondary peritonitis, streptococcal pharyngitis (usually to treat the carrier state), serious respiratory-tract infections including empyema and pneumonia (especially lung abscess), septicaemia, and skin and soft-tissue infections involving heavy colonisation with streptococci or anaerobes such as necrotising fasciitis. It is used in the prophylaxis of endocarditis in penicillin-allergic patients, in the prevention of perinatal streptococcal infections, and with other drugs for the prophylaxis of surgical infection. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax.

For details of these bacterial infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Clindamycin is also applied topically in the treatment of acne (see Skin Disorders, p. 273.1) and rosacea (see Skin Disorders, p. 273.1).

Clindamycin has some antiprotozoal actions, and has been used, usually with other antiprotozoals, in various infections including babesiosis (p. 272.3), malaria (p. 272.3), and toxoplasmosis (p. 273.1). It may also be used with primaquine in the treatment of pneumocystis pneumonia (p. 273.1).

Clindamycin is given **orally** as capsules containing the hydrochloride or as oral liquid preparations containing the palmitate hydrochloride. The capsules should be taken with a glass of water. Doses are expressed in terms of the base; 1.1 g of clindamycin hydrochloride and 1.6 g of clindamycin palmitate hydrochloride are each equivalent to about 1 g of clindamycin. The usual adult oral dose is 150 to 300 mg every 6 hours; in severe infections the dose may be increased to 450 mg every 6 hours.

Clindamycin is given **parenterally** as the phosphate by deep intramuscular injection or by intermittent or continuous intravenous infusion. Doses are again expressed in terms of the base; 1.2 g of clindamycin phosphate is equivalent to about 1 g of clindamycin. For intravenous use, the concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL and the rate of infusion should be not more than 30 mg/minute with a maximum of 1.2 g given in a single one-hour infusion. Continuous intravenous infusions may begin with a single rapid infusion of the first dose (generally over 30 minutes), followed by a continuous infusion of 0.75 to 1.25 mg/minute. Not more than 600 mg should be given as a single intramuscular injection.

The usual parenteral dose is the equivalent of 0.6 to 1.2 g of clindamycin daily in two to four divided doses; in severe infections the dose may be increased to 2.7 g daily and up to 4.8 g daily may be given intravenously in life-threatening situations.

For *prophylaxis* in adult patients at high risk of developing endocarditis and who cannot be given a penicillin, US experts suggest a single 600 mg dose of clindamycin, given orally, intramuscularly, or by intravenous infusion, 30 to 60 minutes before dental procedures involving manipulation of the gums, perforation of the oral mucosa, or work on the periapical areas of the teeth. However, in the UK the *BNF* and NICE now suggest that such prophylaxis is unnecessary (see p. 179.2).

For details of doses in children, including infants and adolescents, see p. 272.2.

Topical formulations containing clindamycin phosphate equivalent to 1% of clindamycin are used for the treatment of acne. The hydrochloride may be applied similarly, but systemic absorption may be greater (see Pharmacokinetics, p. 274.2). Clindamycin phosphate is also available in combination preparations with adapalene, benzoyl peroxide, and tretinoin.

Clindamycin phosphate may be given **intravaginally** as pessaries or as a 2% cream for the treatment of bacterial vaginosis; the equivalent of about 100 mg of clindamycin is given at night for 3 to 7 days.

Administration. Some studies have suggested that a parenteral regimen of clindamycin 600 mg three times daily is as effective as giving the same dose four times daily,[1] or as giving 900 mg three times daily.[2,3] In a meta-analysis[4] of parenteral clindamycin dosing regimens, 600 or 900 mg three times daily were similarly effective in the treatment of pelvic infection. For intra-abdominal infections, the two regimens showed similar rates of clinical success (defined as either improvement or cure), but the 600-mg regimen showed a significantly lower rate of definitive cure. The authors suggested that, although 600 mg three times daily was likely to be acceptable for most pelvic infections, dose recommendations for intra-abdominal infections should remain patient specific.

A population *pharmacokinetic model* in 50 patients treated with either oral or intravenous clindamycin for osteomyelitis found that clindamycin clearance increases with body weight; it was suggested that for patients weighing more than 75 kg a dose of 900 mg three times daily may be considered.[5]

1. Buchwald D, *et al.* Effect of hospitalwide change in clindamycin dosing schedule on clinical outcome. *Rev Infect Dis* 1989; **11:** 619–24.
2. Chin A, *et al.* Cost analysis of two clindamycin dosing regimens. *DICP Ann Pharmacother* 1989; **23:** 980–3.
3. Chatwani A, *et al.* Clindamycin dosage scheduling for acute pelvic infection. *Am J Obstet Gynecol* 1990; **163:** 240.
4. Rovers JP, *et al.* Meta-analysis of parenteral clindamycin dosing regimens. *Ann Pharmacother* 1995; **29:** 852–8.
5. Bouazza N, *et al.* Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. *Br J Clin Pharmacol* 2012; **74:** 971–7.

INTRAVITREAL ROUTE. Intravitreal injection of clindamycin 1 mg, alone or with surgical intervention, was successfully used in 6 patients with toxoplasmic retinochoroiditis.[1] Favourable outcomes and good tolerance were also noted in patients treated with intravitreal clindamycin and dexamethasone.[2,3] Intravitreal injection of clindamycin with gentamicin has been reported[4] to be of benefit in preventing acute bacterial endophthalmitis in patients with retained intra-ocular foreign bodies after penetrating eye injury.

1. Sobrin L, *et al.* Intravitreal clindamycin for toxoplasmic retinochoroiditis. *Retina* 2007; **27:** 952–7.
2. Kishore K, *et al.* Intravitreal clindamycin and dexamethasone for toxoplasmic retinochoroiditis. *Ophthalmic Surg Lasers* 2001; **32:** 183–92.
3. Lasave AF, *et al.* Intravitreal clindamycin and dexamethasone for zone 1 toxoplasmic retinochoroiditis at twenty-four months. *Ophthalmology* 2010; **117:** 1831–8.
4. Soheilian M, *et al.* Prophylaxis of acute posttraumatic bacterial endophthalmitis: a multicenter, randomized clinical trial of intraocular antibiotic injection, report 2. *Arch Ophthalmol* 2007; **125:** 460–5.

SUBCONJUNCTIVAL ROUTE. It has been suggested, should periocular use of clindamycin be necessary, that the injection solution can be given in doses of 15 to 50 mg by subconjunctival injection.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006.* London: Moorfields Pharmaceuticals, 2006.

Administration in children. The usual **oral** dose for infants and children under 12 years of age is the equivalent of 3 to 6 mg/kg of clindamycin every 6 hours; children over 12 years of age may be given the usual adult dose (see Uses and Administration, above). In the UK, the *BNFC* suggests that neonates aged 14 to 28 days may also be given an oral dose of 3 to 6 mg/kg every 6 hours while those aged under 14 days may be given this dose every 8 hours. US authorities recommend that neonates are given oral clindamycin in the same doses as those used parenterally (see below).

The usual **parenteral** dose for infants and children aged from 1 month to 12 years is the equivalent of 15 to 25 mg/kg of clindamycin daily in 3 or 4 divided doses; in severe infections the dose may be increased to 40 mg/kg daily and a minimum dose of 300 mg daily should be given regardless of body-weight. Children over 12 years of age may be given the usual adult dose (see Uses and Administration, above). In the USA, the following parenteral doses have been suggested by the American Academy of Pediatrics[1] for use in those aged less than 1 month; these doses may also be given orally:

- for neonates aged ⩽7 days and weighing ⩽2 kg: 5 mg/kg every 12 hours
- for neonates aged ⩽7 days and weighing >2 kg: 5 mg/kg every 8 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 5 mg/kg every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birthweight neonates (those weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 5 mg/kg every 6 hours

It should be borne in mind that some parenteral formulations contain benzyl alcohol, which may cause fatal 'gasping syndrome' in neonates (see p. 1741.1).

For the treatment of staphylococcal lung infection in children aged from 1 month to 18 years with cystic fibrosis, the *BNFC* recommends oral doses of 5 to 7 mg/kg (to a maximum of 600 mg) every 6 hours.

For children's doses in babesiosis, malaria, and toxoplasmosis, see below.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Babesiosis. Clindamycin, given with quinine, both for 7 to 10 days, is recommended by some experts in the USA[1] for the treatment of babesiosis (p. 922.2) caused by *Babesia microti*. Dosage regimens include:

- clindamycin 1.2 g intravenously twice daily, with quinine 650 mg orally three or four times daily
- clindamycin 300 to 600 mg intravenously every 6 hours, with quinine as above
- clindamycin 600 mg orally three times daily, with quinine as above

Children may be given clindamycin 20 to 40 mg/kg daily intravenously or orally in 3 or 4 divided doses with quinine 25 mg/kg daily orally in 3 divided doses, both for 7 to 10 days.

1. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Correction. *ibid.* 2007; **45:** 941. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 23/03/09)

Malaria. Quinine sulfate plus follow-on treatment with doxycycline, tetracycline, or clindamycin are recommended regimens for the treatment of chloroquine-resistant falciparum malaria (p. 644.1) in non-endemic malaria areas. Doxycycline is generally preferred because it can be given once daily, and there are more data on the efficacy of quinine combined with the tetracyclines than with clindamycin.[1] However, tetracyclines are contra-indicated in children under 8 years of age and in pregnant women, and these groups may be given clindamycin. Clindamycin is given in a usual *adult* dose of 20 mg/kg daily in 3 divided doses (or 450 mg 3 times daily) for 7 days with quinine sulfate 600 to 650 mg 3 times daily for 3 or 7 days (depending on where the infection was acquired), both orally.[1-5] Parenteral quinine (or quinidine) plus follow-on treatment with a tetracycline or clindamycin may be used for severe falciparum malaria in both endemic and non-endemic malaria areas.[1,3-6] Patients unable to tolerate oral treatment may begin follow-on therapy intravenously.[6]

In the UK[5] public health authorities recommend that *children* be given clindamycin at a dose of 7 to 13 mg/kg 3 times daily for 7 days; US[1] public health authorities recommend giving 20 mg/kg daily in 3 divided doses.

1. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (updated April 2011). Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 27/07/11)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. British Infection Society. Algorithm for initial assessment and management of malaria in adults (issued February 2007). Available at: http://www.britishinfection.org/drupal/sites/default/files/MalariaAlgorithm07.pdf (accessed 17/01/11)
4. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 18/08/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
5. Lalloo DG, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; **54:** 111–21. Correction. [primaquine dose]. Corrected version available at: http://

www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947343507 (accessed 25/05/10)
6. CDC. Guidelines for treatment of malaria in the United States: based on drugs currently available for use in the United States (updated 18th May, 2009). Available at: http://www.cdc.gov/malaria/pdf/treatmenttable.pdf (accessed 18/08/10)

Pneumocystis pneumonia. Clindamycin may be used with primaquine as an alternative to co-trimoxazole for the **treatment** of pneumocystis pneumonia (p. 567.2). In the USA, some experts[1,2] recommend giving clindamycin 600 to 900 mg intravenously, or 300 to 450 mg orally, every 6 or 8 hours with primaquine 30 mg orally once daily, both for 21 days. In the UK the *BNF* suggests giving clindamycin 600 mg every 8 hours with primaquine 30 mg daily, both orally, for mild to moderate disease (but notes that this combination is associated with considerable toxicity).

A meta-analysis[3] of literature published between January 1975 to August 1999 found that, when compared with other salvage agents (such as atovaquone, co-trimoxazole, eflornithine, pentamidine, and trimetrexate), clindamycin with primaquine was the most effective regimen in patients unresponsive to conventional treatment. The authors also concluded that this latter regimen was effective as primary treatment of mild to moderately severe disease and suggested that it had fewer adverse effects than co-trimoxazole. However, a later systematic review[4] of second-line salvage treatments for AIDS-related pneumocystis pneumonia considered co-trimoxazole to be the drug of choice in most settings; clindamycin with primaquine was recommended as a suitable salvage option where initial treatment with co-trimoxazole has failed or been poorly tolerated.

Clindamycin with primaquine is not normally recommended for **prophylaxis** although there are reports of it being tried.[5] A retrospective examination[6] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 12/09/13)
3. Smego RA, *et al.* A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. *Arch Intern Med* 2001; **161:** 1529–33.
4. Benfield T, *et al.* Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr* 2008; **48:** 63–7.
5. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
6. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Skin disorders. *ACNE.* Clindamycin is one of the most widely used topical antibacterials in the treatment of acne vulgaris (p. 1682.2), usually with other topical drugs to reduce the development of resistance.

Some references.

1. Schlessinger J, *et al.* ZIANA Study Group. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol* 2007; **6:** 607–15.
2. Guay DR. Topical clindamycin in the management of acne vulgaris. *Expert Opin Pharmacother* 2007; **8:** 2625–64.
3. McKeage K, Keating GM. Clindamycin/benzoyl peroxide gel (BenzaClin): a review of its use in the management of acne. *Am J Clin Dermatol* 2008; **9:** 193–204.
4. Korting HC, Schöllmann C. Management der Acne vulgaris: Fokus auf Clindamycin und Zink. *Hautarzt* 2009; **60:** 42–7.
5. Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis* 2010; **85:** 15–24.

ROSACEA. Topical clindamycin[1] has improved inflammatory episodes of rosacea (p. 1688.3), although other features of the skin disorder may not respond. A small study[2] showed that once-daily application of clindamycin 1% plus benzoyl peroxide 5% was effective in the treatment of moderate to severe rosacea.

1. Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol* 1993; **32:** 65–7.
2. Breneman D, *et al.* Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol* 2004; **43:** 381–7.

Toxoplasmosis. Clindamycin with pyrimethamine has been used for the treatment and secondary prophylaxis (chronic maintenance) of toxoplasmosis (p. 926.1) instead of the more usual treatment with pyrimethamine plus sulfadiazine, in patients unable to tolerate sulfonamides; folinic acid is also given to counteract the megaloblastic anaemia associated with pyrimethamine. In adult patients with AIDS and toxoplasmic encephalitis, US recommendations[1] are:

- *treatment* with clindamycin 600 mg every 6 hours orally or intravenously for at least 6 weeks, *then*
- *chronic maintenance* therapy with oral clindamycin 600 mg every 8 hours

For corresponding doses of pyrimethamine, see under Pyrimethamine p. 663.1.

Children may be given oral or intravenous clindamycin 5 to 7.5 mg/kg 4 times daily for at least 6 weeks, followed by chronic maintenance therapy.[2]

Two studies have found acute therapy with pyrimethamine and oral clindamycin, 600 mg 4 times daily[3] or 1200 mg every 6 hours intravenously,[4] to be as effective as pyrimethamine and sulfadiazine. Oral maintenance therapy with pyrimethamine and clindamycin 300 mg 4 times daily was, however, found to be less effective than pyrimethamine and sulfadiazine at preventing relapses in a population followed for 3 years or more[3] and consequently higher maintenance doses of clindamycin are now recommended (see above). Clindamycin with fluorouracil produced beneficial responses in a study involving 16 patients.[5]

In contrast, another study, comparing clindamycin alone (in lower oral doses—300 mg twice daily) with pyrimethamine alone for prophylaxis of toxoplasmic encephalitis, reported an unacceptably high incidence of adverse effects with clindamycin, which forced premature termination of the clindamycin arm—see AIDS under Precautions, p. 273.3.

Intravitreal injections of clindamycin have also been used to treat toxoplasmic retinochoroiditis, usually where systemic therapy has failed or been poorly tolerated—see Intravitreal Route, p. 270.2.

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5804.pdf (accessed 11/05/09)
2. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; **58** (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 10/11/10)
3. Katlama C, *et al.* Pyrimethamine-clindamycin vs pyrimethamine-sulphadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996; **22:** 268–75.
4. Dannemann B, *et al.* Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992; **116:** 33–43.
5. Dhiver C, *et al.* 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS* 1993; **7:** 143–4.

Adverse Effects and Treatment

Use of clindamycin has been associated with the development of diarrhoea in up to 20% of patients; symptoms have occurred with topical as well as oral or parenteral formulations. In about 2 to 10% of patients severe or even fatal antibiotic-associated or pseudomembranous colitis may develop during therapy or up to several weeks afterwards. Early reports showed that it occurred more frequently in middle-aged and elderly women, particularly after abdominal surgery; it may also occur rarely after vaginal use. Clindamycin should be stopped immediately if significant diarrhoea or colitis occurs; recovery usually occurs within 3 weeks of stopping the drug. Protein supplementation and use of an antibacterial active against *Clostridium* spp. should be considered for severe antibiotic-associated colitis. For further information on the treatment of antibiotic-associated colitis see p. 183.1.

Other gastrointestinal effects include nausea, vomiting, abdominal pain or cramps; an unpleasant or metallic taste has occasionally been reported after high intravenous doses. Oesophagitis and oesophageal ulceration has been reported particularly after ingestion of capsules with insufficient water. Taste disturbances may also be associated with oral and topical use of clindamycin.

Rashes and urticaria, the most common hypersensitivity reactions, occur in up to 10% of patients usually after 1 to 2 weeks of therapy. Erythema multiforme, Stevens-Johnson syndrome, and exfoliative and vesiculobullous dermatitis have been reported rarely, and a few cases of anaphylaxis have occurred.

Other adverse effects include transient leucopenia or occasionally agranulocytosis, eosinophilia, thrombocytopenia, polyarthritis, and abnormalities of liver function tests; in some cases overt jaundice and hepatic damage have been reported. Renal dysfunction, shown by azotaemia, oliguria, and/or proteinuria, has been reported rarely.

Although local irritation is rare, intramuscular injection has led to induration and sterile abscess, and thrombophlebitis may occur after intravenous use. Too rapid intravenous infusion can result in rare instances of cardiopulmonary arrest and hypotension. Some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p. 1741.1).

Topical application may be associated with local irritation, skin dryness, and contact dermatitis; sufficient clindamycin may be absorbed to produce systemic effects. Cervicitis, vaginitis, vaginal candidiasis, and vulvovaginal irritation have been reported with intravaginal use; a small amount of systemic absorption also occurs.

Effects on the cardiovascular system. Cardiac arrest occurred in a 50-year-old woman after rapid injection of 600 mg of undiluted clindamycin phosphate into a central intravenous line. Further injections were given over 30 minutes without cardiovascular complications.[1] There has also been a case of severely prolonged QT interval attributed to the addition of clindamycin to therapy in an elderly woman;[2] the patient developed AV block and subsequent torsade de pointes, and required resuscitation. When clindamycin was stopped, signs of heart block resolved, and the QT interval returned to normal over several days.

1. Aucoin P, *et al.* Clindamycin-induced cardiac arrest. *South Med J* 1982; **75:** 768.
2. Gabel A, *et al.* Ventricular fibrillation due to long QT syndrome probably caused by clindamycin. *Am J Cardiol* 1999; **83:** 813–15.

Effects on the ears. A 14-year-old boy who was treated with topical clindamycin for acne vulgaris developed unilateral tinnitus during therapy and unilateral sensorineural hearing loss 2 months later;[1] symptoms subsequently recurred upon 2 rechallenges.

1. Scissors B, Shwayder T. Topical clindamycin reproducibly causing tinnitus in a 14-year-old boy. *J Am Acad Dermatol* 2006; **54** (suppl): S243–S244.

Effects on the lymphatic system. Lymphadenopathy was reported in a 54-year-old woman given intravenous clindamycin as part of an antibacterial regimen for osteomyelitis. Symptoms resolved when clindamycin was stopped, but recurred on rechallenge with the drug.[1]

1. Southern PM. Lymphadenitis associated with the administration of clindamycin. *Am J Med* 1997; **103:** 164–5.

Effects on the skin. Toxic epidermal necrosis was reported in a patient about 7 days after starting an oral course of clindamycin; with treatment, the condition resolved within 4 weeks.[1] Acute generalised exanthematous pustulosis associated with oral clindamycin use has also been reported in some patients.[2-4]

Acute febrile neutrophilic dermatosis, or Sweet's syndrome, has been reported in patients given oral, or oral and intravenous, clindamycin for dental infections.[5,6]

1. Paquet P, *et al.* Toxic epidermal necrolysis following clindamycin treatment. *Br J Dermatol* 1995; **132:** 665–6.
2. Valois M, *et al.* Clindamycin-associated acute generalized exanthematous pustulosis. *Contact Dermatitis* 2003; **48:** 169.
3. Kapoor R, *et al.* Acute generalized exanthematous pustulosis induced by clindamycin. *Arch Dermatol* 2006; **142:** 1080–81.
4. Sulewski RJ, *et al.* Acute generalized exanthematous pustulosis due to clindamycin. *Dermatol Online J* 2008; **14:** 14. Available at: http://dermatology.cdlib.org/147/case_presentation/agep/blyumin.html (accessed 06/05/09)
5. Clark BM, *et al.* Clindamycin-induced Sweet's syndrome. *Pharmacotherapy* 2007; **27:** 1343–6.
6. Kandula S, *et al.* Clindamycin-induced Sweet syndrome. *J Am Acad Dermatol* 2010; **62:** 898–900.

Precautions

Clindamycin should not be given to patients hypersensitive to it or to the closely related drug lincomycin. It should be used with caution in patients with a history of gastrointestinal disease, particularly colitis, and stopped immediately if significant diarrhoea or colitis occurs. Middle-aged and elderly female patients may be at greater risk of severe diarrhoea or pseudomembranous colitis, especially after abdominal surgery. Caution has also been advised in atopic patients. Periodic tests of liver and kidney function and blood counts have been recommended in patients on prolonged therapy, and in infants. Caution is required during parenteral use in neonates, since some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' (see p. 1741.1).

AIDS. Clindamycin was poorly tolerated by patients with AIDS in a study of its use for *prophylaxis* of toxoplasmic encephalitis.[1] Despite the use of relatively low doses of clindamycin (300 mg twice daily), 23 of 52 patients reported adverse effects that necessitated temporary or permanent withdrawal of the drug, the most frequent adverse reactions being diarrhoea and rash. The clindamycin arm of the study had to be terminated prematurely. Nevertheless, clindamycin has been used successfully in patients with AIDS for the *treatment* of both toxoplasmic encephalitis (see Toxoplasmosis, above) and pneumocystis pneumonia (above).

1. Jacobson MA, *et al.* Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. *Lancet* 1992; **339:** 333–4.

Breast feeding. US licensed product information states that concentrations of clindamycin in breast milk were 0.7 to 3.8 micrograms/mL after doses of 150 mg orally to 600 mg intravenously. The last available guidance from the American Academy of Pediatrics[1] considered that use

of clindamycin was usually compatible with breast feeding. Nevertheless, UK product information states that although it is unlikely that a breast-fed infant could absorb significant amounts, caution should be exercised when clindamycin is given during breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clindamycin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Interactions

Clindamycin has neuromuscular blocking activity and may enhance the effect of other drugs with this action (see Atracurium, p. 2032.1), leading to a potential danger of respiratory depression. Clindamycin may antagonise the effects of parasympathomimetics.

Clindamycin may competitively inhibit the effects of macrolides, ketolides, streptogramins, linezolid, and chloramphenicol because they all bind to the same subunit of the ribosome. Antagonism between clindamycin and erythromycin has been shown *in vitro*.

Adsorbents. In 16 healthy subjects given clindamycin alone and with a *kaolin-pectin* suspension it was found that the suspension had no effect on the extent of clindamycin absorption but did markedly reduce the absorption rate.[1]

1. Albert KS, *et al.* Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycin. *J Pharm Sci* 1978; **67:** 1579–82.

Immunosuppressants. For the effect of clindamycin on *ciclosporin* disposition, see Lincosamides, under Interactions of Ciclosporin, p. 1956.1.

Antimicrobial Action

Clindamycin is a lincosamide antibacterial with a mainly bacteriostatic action against Gram-positive aerobes and many anaerobic bacteria.

Mechanism of action. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome, similarly to macrolides such as erythromycin (p. 297.1), and inhibit the early stages of protein synthesis. The action of clindamycin is mainly bacteriostatic, although high concentrations may be slowly bactericidal against sensitive strains.

Spectrum of activity. Clindamycin is active against:

- most aerobic Gram-positive bacteria including streptococci, staphylococci, *Bacillus anthracis*, *Nocardia* spp., and *Corynebacterium diphtheriae;* enterococci are generally resistant, but clindamycin has some activity against *Enterococcus durans*
- many Gram-positive anaerobes including *Bifidobacterium, Lactobacillus, Eubacterium, Propionibacterium, Peptococcus,* and *Peptostreptococcus* spp., and many strains of *Actinomyces* spp., *Clostridium perfringens,* and *Cl. tetani.* The susceptibility of *Cl. difficile* varies widely, but during outbreaks of diarrhoea associated with *Cl. difficile,* the strains are usually resistant to clindamycin
- Gram-negative anaerobes such as *Fusobacterium* spp. (although *F. varium* is usually resistant), *Prevotella* spp., and *Bacteroides* spp., including the *B. fragilis* group

Most Gram-negative aerobic bacteria, including the Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp., are intrinsically resistant to clindamycin; unlike erythromycin, *Neisseria gonorrhoeae, N. meningitidis,* and *Haemophilus influenzae* are generally resistant. *Mycoplasma* spp. are also generally resistant to clindamycin. *Mycobacterium tuberculosis* is resistant, but clindamycin has some activity against *M. leprae.* Fungi, yeasts, and viruses are also resistant; however, clindamycin has been reported to have some antiprotozoal activity against *Toxoplasma gondii* and *Plasmodium* spp.

Resistance. The mechanisms of acquired resistance are the same as those for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein, and, in a few staphylococcal isolates, enzymic inactivation by a plasmid-mediated adenyltransferase. Methylation of the ribosome leads to cross-resistance between the lincosamides and macrolides and streptogramins (the MLS_B phenotype); this type of resistance is usually plasmid-mediated and inducible. Another resistance pattern (the M phenotype), which is common in the macrolide-resistant streptococci spp. found in the US, does not impart cross-resistance to clindamycin. Complete cross-resistance exists between clindamycin and lincomycin.

The incidence of resistance varies with the organism and the geographical location; it is more frequent in organisms that are also erythromycin-resistant, and some strains of meticillin-resistant *Staph. aureus* are also resistant to clindamycin. In some countries and institutions there is evidence of an increase in resistance amongst the *B. fragilis* group to about 25% of strains or more. Resistance to clindamycin by anaerobes has also been reported in 10 to 20% of *Clostridium* spp. other than *C. perfringens,* 8% of peptostreptococci, 9% of *Fusobacterium* spp., and 11% of *Prevotella* strains.

Action. References suggesting that clindamycin may reduce microbial adherence and enhance phagocytosis by its effects on bacterial slime (glycocalyx)[1-3] and that its antibacterial effects may be independent of plasma concentrations.[4,5]

1. Veringa EM, *et al.* Enhancement of opsonophagocytosis of Bacteroides spp by clindamycin in subinhibitory concentrations. *J Antimicrob Chemother* 1981; **23:** 577–87.
2. Veringa EM, *et al.* The role of glycocalyx in surface phagocytosis of Bacteroides spp, in the presence and absence of clindamycin. *J Antimicrob Chemother* 1989; **23:** 711–20.
3. Khardori N, *et al.* Effect of subinhibitory concentrations of clindamycin and trospectomycin on the adherence of Staphylococcus epidermidis in an in vitro model of vascular catheter colonization. *J Infect Dis* 1991; **164:** 108–13.
4. Xue IB, *et al.* Variation in postantibiotic effect of clindamycin against clinical isolates of Staphylococcus aureus and implications for dosing of patients with osteomyelitis. *Antimicrob Agents Chemother* 1996; **40:** 1403–7.
5. Klepser ME, *et al.* Bactericidal activity of low-dose clindamycin administered at 8- and 12-hour intervals against Staphylococcus aureus, Streptococcus pneumoniae, and Bacteroides fragilis. *Antimicrob Agents Chemother* 1997; **41:** 630–5.

Pharmacokinetics

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastrointestinal tract; concentrations of 2 to 3 micrograms/mL occur within 1 hour after a 150-mg oral dose, with average concentrations of about 700 nanograms/mL after 6 hours. After doses of 300 and 600 mg, peak plasma concentrations of 4 and 8 micrograms/mL, respectively, have been reported. Absorption is not significantly diminished by food but the rate of absorption may be reduced. Clindamycin palmitate hydrochloride is rapidly hydrolysed to free clindamycin on oral use.

When given parenterally, the biologically inactive clindamycin phosphate is also hydrolysed to clindamycin. When the equivalent of 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 micrograms/mL occurs within 3 hours; 600 mg gives a peak concentration of 9 micrograms/mL. In children, peak concentrations may occur within 1 hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms/mL occur by the end of infusion.

Small amounts of clindamycin may be absorbed after topical application to the skin; absorption of clindamycin hydrochloride from the skin is about 4 to 5%. Systemic absorption of the phosphate is lower and it is therefore preferred for topical use. About 5% of a dose may be absorbed systemically from an intravaginal cream formulation; systemic absorption appears to be slower in women with bacterial vaginosis than in healthy women. Absorption from vaginal pessaries is reported to be about 30%.

Clindamycin is widely distributed in body fluids and tissues, including bone, but it does not reach the CSF in significant concentrations. It diffuses across the placenta into the fetal circulation and has been reported to appear in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, but may be prolonged in preterm neonates and in patients with severe renal impairment.

Clindamycin undergoes metabolism, presumably in the liver, to the active *N*-demethyl and sulfoxide metabolites, and also to some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow, and takes place over several days. It is not effectively removed from the blood by dialysis.

AIDS patients. Clindamycin was reported to have higher bioavailability, lower plasma clearance, and a lower volume of distribution in patients with AIDS than in healthy subjects.[1] This may partly be explained by increased binding to plasma proteins.[2]

Although it is generally considered that penetration of clindamycin into the CSF is insignificant, parasiticidal CSF concentrations against *Toxoplasma gondii* were achieved with intravenous clindamycin in patients with AIDS.[3]

1. Gatti G, *et al.* Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. *Antimicrob Agents Chemother* 1993; **37:** 1137–43.
2. Flaherty JF, *et al.* Protein binding of clindamycin in sera of patients with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 1134–8.
3. Gatti G, *et al.* Penetration of clindamycin and its metabolite N-demethylclindamycin into cerebrospinal fluid following intravenous infusion of clindamycin phosphate in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42:** 3014–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acnestop; Clidan; Clindacin; Clindalaf; Clindopax; Clintopic; Dalacin C; Dalacin T; Naxoclinda; Torgyn; ***Austral.***: Cleocin; Clindatech; Dalacin C; Dalacin T; Dalacin V; Zindaclin; ***Austria***: Clindac; Dalacin C; Dalacin; Lanacine; ***Belg.***: Dalacin C; Dalacin; Dalacin; Zindaclin; ***Braz.***: Anaerocid; Clinagel; Clindabiotic; Clindacne; Clindamin C; Clindarix; Dalacin C; Dalacin T; Dalacin V; ***Canad.***: Clinda-T; Clindets; Dalacin C; Dalacin T; Dalacin Vaginal; ***Chile***: Biomicin; Clidets; Clinacnyl; Cluvax; Daclin; Dalacin C; Dalacin T; Dalacin V†; Dalacin; Dermabel; Divanon; ***China***: Ao Di (傲地); Ao Li Xian (奥丽先); Bang Wei Lin Xin (邦韦林欣); Bei He (倍禾); Bin Ke (滨可); Bo Le (博乐); Bo Shi Duo Ta (博士多他); Da Fen Rong (达芬蓉); Dalacin C (特丽仙 C); Dalacin T (特丽仙 T); De Bao Sheng (德宝生); Fu Bang (孚帮); Fu Si Ka (福司卡); Heng Xin (恒新); Huashu (华舒); Jianqi (健奇); Jie Li (捷立); Jin Ge Duo Na (金格多那); Jing Dan (景丹); Kai Fu Fei (凯甫菲); Ke Er Sheng (可尔生); Ke Ran Fu (恪然福); Ke Su (克宿); Ke Xin Lin (可欣林); Li Bang Te (力邦特); Li Shen (力深); Lipai (力派); LiTai (力泰); Lizhuling (丽珠灵); Long Ge Xin (隆格新); Long Ke Duo (龙可多); Luoqing (洛庆); Mei Di Xing (美迪星); Pu Nai Tong (普耐同); Pu Yuan Xin (普源欣); Qi Er Su (奇尔速); Qin Lin (沁林); Rong Da (容大); She Xin (舍欣); She Yue (舍悦); Shuai Ke Jia Er (帅克佳尔); Shuaijie (帅洁); Tadixian (他迪仙); Tang Ni Wei (汤尼威); Te Na Si (特纳斯); Wei Kang (维康); Xianqing (先清); Xin Fu Neng (欣复能); Xin Lai (信徕); Xin Pu Feng (欣普风); Xin Qi (馨琦); Xin Yi Kang (欣忆康); Xu Luo (旭洛); Yan Le (颜乐); Yi Jun Ding (益君定); You Ni Ling (尤尼灵); ZaiXing (再欣); Zha Wei (札威); Zhi Fu Bao (知芙保); Zhuo Li (卓力); ***Cz.***: Dalacin C; Dalacin T; Dalacin; Klimicin; Zindaclin†; ***Denm.***: Dalacin C; Dalacin; Myclin†; ***Fin.***: Dalacin; Klindagol†; Myclin†; ***Fr.***: Dalacine T; Dalacine; Zindacline; ***Ger.***: Basocin; Clin-Sanorania; Clinda-saar; Clinda; Clindabeta; Clindahexal†; Clindasol; Clindastad†; Dentomycin†; Jutaclin†; Sobelin; Turimycin†; ***Gr.***: Arfarel; Borophen; Botamycin-N; Clidacin; Climycen; Clindagel; Clindamed; Dalacin C; Edason; Esteria; Fleminosan; Fouch; Lindasol; Paradis; Skinasol; Sotomycin; Toliken; Upderm; Vagiclin; Veldom; Velkaderm; Ygielle; ***Hong Kong***: Bittle; Claribel; Clinac; Clindatech; Clinex; Dalacin C; Dalacin T; Delta T†; Frankacin-T†; Kolincin; Qualiclinda; T3 Mycin; Tidact†; Zindaclin; ***Hung.***: Dalacin C; Dalacin T; Dalacin; Klimicin; ***India***: Acneclin; Acneris; Clear Gel; Clenz; Clid; Climycin; Clin-Gold; Clincin; Clindac-A; Clindatec; Clindaz; Clinderm; Clindol; Clingard; Clinscar; CTop; Daklin; Dalacin C; Dalacin; Dalcap†; Dalcinex; Daltrex; Erytop; Gynasafe; Labomycin; Magclin; Mimosee; ***Indon.***: Albiotin; Anerocid; Biodasin; Cindala†; Clidacor; Climadan; Clinbercin; Clindexcin; Clinex; Clinidac; Clinika; Clinium; Clinjos; Clinmas; Comdasin; Dacin; Daclin; Dalacin C; Ethidan; Indanox; Lando; Librodan†; Lindacyn; Lindan; Mediklin; Milorin; Niladacin; Nufaclind; Opiclam; Probiotin; Prolic; Zumatic; ***Irl.***: Dalacin C; Dalacin T; Dalacin; Zindaclin; ***Israel***: Dalacin C; Dalacin Vaginal; Dalagis T; Zindaclin; ***Ital.***: Cleocin; Dalacin C; Dalacin T; Zindaclin; ***Malaysia***: Clindac; Dalacin C; Dalacin T; T3 Mycin; Tidact; Topicil; Zindaclin; ***Mex.***: Aktufoam; Ancine†; Apomiclin; Biodaclin; Cigmadil†; Clendazaf; Clendix; Clidets; Clinamsa†; Clindazyn†; Clindazyn; Cliran†; Cobatin; Cutaclin; Dalacin C; Dalacin T; Dalacin V; Dalafar; Dalatina V; Dalatina; Damiclin†; Destralina; Feisclin; Foshlenn; Galecin; Indamid†; Klyndaken†; Lindacil; Lisiken; Losertrin; Lyrfhis; Trexen; Ulmicy; ***Neth.***: Dalacin C; Dalacin T; ***Norw.***: Dalacin; ***NZ***: Clindatech; Dalacin C; Topicil; ***Philipp.***: Abanxl; Acresil; Anerocin; Clin-D; Clindal; Clindamit; Clindatech; Clinderm; Cliz; Daklin; Dalace; Dalacin C; Dalaclin; Inprosyn-HP; Klincyn; Klindex; Lincyn; Myclin; Potecin; T3 Mycin; Tidact; Zindal; ***Pol.***: Clindacin†; Clindacne; Clindo†; Dalacin C; Dalacin T; Dalacin; Klimicin; Klindacin T; Normaclin; Zindaclin; ***Port.***: Clincina; Dalacin C; Dalacin T; Dalacin V; Zindaclin; ***Rus.***: Clindacin (Клиндацин); Clindovit (Клиндовит); Dalacin (Далацин); Klimicin (Климицин)†; ***S.Afr.***: Clindac†; Clindahexal; Dalacin C; Dalacin T; Dalacin VC; ***Singapore***: Climadan; Clindagel; Clindatech; Dalacin C; Dalacin T; T3Mycin; Tidact; Topicil; Zindaclin; ***Spain***: Clinwas; Dalacin; Zindaclin; ***Swed.***: Dalacin; ***Switz.***: Dalacin C; Dalacin T; Dalacin V; ***Thai.***: Acnegon; Acnocin; Cedelin; Chinacin-T; Clinda VC; Clinda; Clindacne; Clindalin; Clindaman; Clindavid; Clinott; Dacin-F; Dalacin C; Dalacin T; Klimicin†; Klinda; Klindan†; Klinna; Lacin†; Millda†; Rosil; Todacin; ***Turk.***: Clamine-T; Cleocin T; Clin; Klindan; Klindaver; Klinoksin; Klitopsin; Meneklin; ***UK***: Dalacin C; Dalacin T; Dalacin; Zindaclin; ***Ukr.***: Clindahexal (Клиндагексал)†; Clindesse (Клиндес); Dalacin (Далацин); Dalacin C (Далацин Ц); Milagin (Милагин); Vagicin (Вагицин-Здоровье); ***USA***: Cleocin T; Cleocin; Clindagel; ClindaMax; Clindesse; Clindets†; Evoclin; ***Venez.***: Bioclindax; Clindaval; Clindox; Clinfol; Dalacin.

Multi-ingredient Preparations. ***Arg.***: Clidan B; Clindacur; Clindoxyl; Colposan; CP-Acne Duo; Dermaclean†; Duo Clindacin; Ovogin; Perclin; Peroxiclin Duo; Torgyn Duo; Z-Clindacin; ***Austral.***: ClindaBenz; Duac; ***Austria***: Indoxyl; ***Braz.***: Adacne Clin; Clindoxyl; Vitacid Acne; ***Canad.***: Benzaclin; Biacna; Clindasol; Clindoxyl; ***Chile***: Indoxyl; Klina; Taripel; ***Cz.***: Duac; ***Denm.***: Clindoxyl; ***Fin.***: Clindoxyl; ***Ger.***: Duac; Refobacin Revision; ***Gr.***: Indoxyl; ***Hong Kong***: Benzolac Cl; Duac; ***Hung.***: Duac; ***India***: Aclin; Acneris-AD; Acrub; Acsolve-C; Adacin; Alesa; Candid-CL; Canison-C; Clevyx; Clima-V; Clin-3; Clinagel; Clindapene; Clinderm-A; Clingen Plus; Clingen; Clinicare; Clinmide; Clinsoft; Convoy; Deriva-C; Deriva-CMS; Epilene C; Faceclin-A;

Faceclin; Feiz; Femcinol-A; Imidil-CV; Labopene-C; Nicolin; Nisacne; Nuforce-CD; ***Indon.***: Benzolac Cl; Climadan; Medi-Klin TR; ***Irl.***: Duac; ***Israel***: Benzaclin†; Duac; ***Ital.***: Duac; ***Malaysia***: Duac; ***Mex.***: Benzaclin†; Clindapack; Femisan; Gynoclin-V; Indoxyl; Loffymix†; Trexen Duo; ***Neth.***: Duac; ***NZ***: Duac; ***Philipp.***: Duac; ***Pol.***: Duac; ***Port.***: Duac; ***Rus.***: Clenzit-C (Клензит-С); ***Singapore***: Clindoxyl; ***Spain***: Duac; ***Swed.***: Duac; ***Switz.***: Duac; ***Thai.***: Duac; ***Turk.***: Benzaclin; Cleocin; Clindoxyl; ***UK***: Duac Once Daily; ***Ukr.***: Cliran Zinc (Клиран Цинк); Duac (Дуак); Vagiklin (Вагиклин); ***USA***: Acanya; Benzaclin; Clindacin ETZ; Clindacin P; Duac; PledgaClin; Ziana.

Pharmacopoeial Preparations

BP 2014: Clindamycin Capsules; Clindamycin Injection;

USP 36: Clindamycin for Injection; Clindamycin Hydrochloride Capsules; Clindamycin Hydrochloride Oral Solution; Clindamycin Injection; Clindamycin Palmitate Hydrochloride for Oral Solution; Clindamycin Phosphate Gel; Clindamycin Phosphate Topical Solution; Clindamycin Phosphate Topical Suspension; Clindamycin Phosphate Vaginal Cream; Clindamycin Phosphate Vaginal Inserts.

Clioquinol *(BAN, rINN)*

Chinoform; Chloroiodoquine; Cliochinolum; Clioquinolum; Iodochlorhydroxyquin; Iodochlorhydroxyquinoline; Kliochinol; Kliokinol; Kliokinoli; Kliokvinolis; PBT-1; Quiniodochlor; Клиохинол.

5-Chloro-7-iodoquinolin-8-ol.

C_9H_5ClINO=305.5

CAS — 130-26-7.

ATC — D08AH30; D09AA10; G01AC02; P01AA02; S02AA05.

ATC Vet — QD08AH30; QD09AA10; QG01AC02; QS02AA05.

UNII — 7BHQ856EJ5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Clioquinol). An almost white, light yellow, brownish-yellow, or yellowish-grey powder. Practically insoluble in water; very slightly soluble or slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Clioquinol). A voluminous, spongy, yellowish-white to brownish-yellow powder having a slight characteristic odour. It darkens on exposure to light. Practically insoluble in water; soluble 1 in 3500 of alcohol, 1 in 120 of chloroform, and 1 in 4500 of ether; soluble in hot ethyl acetate and in hot glacial acetic acid. Store in airtight containers. Protect from light.

Uses and Administration

Clioquinol is a halogenated hydroxyquinoline with antibacterial and antifungal activity and is used in creams and ointments, usually containing 3%, in the treatment of skin infections. It is applied with a corticosteroid in inflammatory skin conditions complicated by bacterial or fungal infections. It is also used in ear drops for otitis externa. The treatment of bacterial and of fungal skin infections is described on p. 207.1 and p. 568.1 respectively.

For a discussion of the risks from topical application of clioquinol, see Adverse Effects and Precautions, p. 275.2.

Clioquinol has been given orally in the treatment of intestinal amoebiasis. It has also been used for the prophylaxis and treatment of traveller's diarrhoea and similar infections but is of doubtful value. Oral preparations have now generally been withdrawn because of neurotoxicity (see Adverse Effects and Precautions, p. 275.1). However, oral clioquinol has been investigated for its action as a chelator of copper and zinc in the treatment of Alzheimer's disease (see p. 275.1).

Alzheimer's disease. A systematic review[1] to evaluate the efficacy of metal protein attenuating compounds, such as clioquinol, for the treatment of cognitive impairment due to Alzheimer's disease, evaluated only one small randomised controlled study comparing clioquinol and placebo; no significant differences were found. Further studies with clioquinol have now been stopped, but studies are ongoing with a successor compound, PBT2.

1. Sampson E, *et al.* Metal protein attenuating compounds for the treatment of Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 03/04/09).

Adverse Effects and Precautions

Clioquinol, which contains iodine, may rarely cause iodism in sensitive patients or interfere with certain thyroid function tests. Local application of clioquinol in ointments or creams may occasionally cause severe irritation or hypersensitivity and there may be cross-sensitivity with other halogenated hydroxyquinolines.

Clioquinol stains clothing and linen yellow on contact and may stain the skin and discolour fair hair.

Clioquinol given orally has been associated with severe neurotoxicity. In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods, and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are mainly those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms, which include paraesthesias in the legs progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. A characteristic green pigment, a chelate of clioquinol with iron, is often seen on the tongue and in the urine and faeces. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disability.

It was suggested that the Japanese epidemic might be due to genetic susceptibility, but a few similar cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, such as broxyquinoline or diiodohydroxyquinoline have been reported from other countries. Oral preparations of clioquinol have now been banned in most countries.

General references.

1. Mao X, Schimmer AD. The toxicology of clioquinol. *Toxicol Lett* 2008; **182:** 1–6.

Hypersensitivity. Clioquinol is classified as a contact allergen that can commonly cause sensitisation, especially when applied to eczematous skin; chlorquinaldol can also cause sensitisation, although less frequently.[1] Cross-sensitivity between the two has been reported, and may also exist between clioquinol and some oral quinolines, such as amodiaquine, chloroquine, or quinine, used to treat malaria.[2] It is important to include clioquinol and chlorquinaldol in routine patch testing since the clinical reaction may be relatively mild and sensitivity easily missed, particularly in the presence of a corticosteroid which suppresses or attenuates the reaction.

1. Anonymous. Skin sensitisers in topical corticosteroids. *Drug Ther Bull* 1986; **24:** 57–9.
2. Rodríguez A, *et al.* Contact cross-sensitization among quinolines. *Allergy* 2001; **56:** 795.

Topical application. Absorption of clioquinol through the skin has been noted on topical application.[1,2] Last available guidance from the Committee on Drugs of the American Academy of Pediatrics[3] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

1. Fischer T, Hartvig P. Skin absorption of 8-hydroxyquinolines. *Lancet* 1977; **i:** 603.
2. Stohs SJ, *et al.* Percutaneous absorption of iodochlorhydroxyquin in humans. *J Invest Dermatol* 1984; **82:** 195–8.
3. Kauffman RE, *et al.* American Academy of Pediatrics. Clioquinol (iodochlorhydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; **86:** 797–8.[Re-affirmed October 2006, Retired January 2011] Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;86/5/797.pdf (accessed 15/02/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ke Ai Lin (珂艾林); ***Ger.***: Linola-sept; ***India***: Dermo Quinol; Derino Quinol; Enteroquinol; Entrozyme Plain; ***Mex.***: Bagton; Bionder-C; Cortifung-C; Lasalar-Y Simple; Luzolona Simple; Nolil; Vioformo.

Multi-ingredient Preparations. ***Arg.***: Betnovate-C; ***Austral.***: Hydroform; Locacorten Vioform; ***Austria***: Betnovate-C†; ***Braz.***: Betnovate-Q; Cliotisona; Cremederme; Dreniformio; Hidrocorte; Locorten Vioformio; Permut; Polideрms; Predmicin; Quadribeta; Quadriderm; Quadrihexal; Quadrikin†; Quadrilon; Quadriplus†; Qualiderm; Tetraderm; Vioformio-Hidrocortisona; ***Canad.***: Locacorten Vioform; Vioform-Hydrocortisone; ***Denm.***: Betnovat med Chinoform; Locacorten Vioform; Synalar med Chinoform; ***Fin.***: Bemetson-K; Betnovat-C†; Locacorten Vioform; ***Fr.***: Alkocortenbioform†; Locacortene Vioforme†; ***Ger.***: Locacorten Vioform; ***Gr.***: Betnovate-C; Helpogen; Locacorten Vioform; Myco-Synalar; ***Hong Kong***: Aplosyn-C†; Cliocort†; Clobeta-G; Dermafacte†; Quadriderm; ***Hung.***: Lorinden C; Prednisolon J†; ***India***: ABC Derm; Alcoderm; Balderm; Beclate-C; Becloderm-C; Benda; Betnederm C; Betnovate-C; Clobequad; Clobquad; Corge-C; Cortoquinol; Daredeгm; Derminol; Dermitop; Dexaquin; Dipform; Esgiderm; Fourderm; Fubac; Millicorten-Vioform; Quiss; ***Indon.***: Benoson V†; Krimbeson; Viohydrocort; Visancort; ***Irl.***: Betnovate-C; Vioform-Hydrocortisone†; ***Israel***: Betnovate-C†; ***Ital.***: Diproform; Locorten Vioformio†; Locorten; ***Mex.***: Bentix; Cetoquina Y; Clio-Betnovate; Clioderm-H†; Cortifung-Y; Cortilona Compuesta; Dealan; Dermatofin; Diprosone Y; Ditayod; Farmacorti YC; Lasalar-Y; Luzolona Y; Sebryl Plus; Sebryl; Sebstopp; Solfurol; Suyodil; Synalar C; Topsyn-Y; Ultracortin†; Vioformo-Cort; Yderm; Yodozona; ***Neth.***: Locacorten Vioform; ***Norw.***: Betnovat med Chinoform; Synalar med Chinoform; ***NZ***: Betnovate-C; Locacorten Vioform; Locorten Vioform; ***Philipp.***: Aplosyn C; Betnovate-C; Dermalin†; Diproform; Quadriderm; Quadrotopic; ***Pol.***: Betnovate-C; Lorinden C; Viosept†; ***Port.***: Betnovate-C; Dexaval V; Quinodermil-AS; ***Rus.***: Dermosolon (Дермозолон); Lorinden C (Лоринден С); ***S.Afr.***: Betnovate-C†; Cortoderm-C†; Locacorten Vioform; Quadriderm; Synalar C; ***Singapore***: Dermanol-C; Hydroderm-C; ***Spain***: Cuatroderm; Menaderm Clio; Menaderm Otologico; ***Swed.***: Betnovat med Chinoform; Locacorten Vioform; ***Switz.***: Betnovate-C; ***Thai.***: Banocin; Beta-C; Betnovate-C†; Betosone-CE; Chlorotracin†; Dermaheu; Dertec; Endothalyl; Genquin; Patarvate-C; Quadriderm; Spectroderm; ***Turk.***: Betnovate-C; Kortisetin; Locacortene Vioform; Prednol-A; ***UK***: Betnovate-C; Locorten Vioform; Synalar C; Vioform-Hydrocortisone†; ***Ukr.***: Dermosolon (Дермозолон)†; Lorinden C (Лоринден С); Viosept (Виосепт)†; ***USA***: 1 + 1-F; Corque; Hysone; ***Venez.***: Dermosupril C; Diproformo; Locorten Vioformo; Quadriderm; Tridetarmon.

Pharmacopoeial Preparations

BP 2014: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment;

USP 36: Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone Ointment; Clioquinol Cream; Clioquinol Ointment; Compound Clioquinol Topical Powder.

Clofazimine *(BAN, USAN, rINN)*

B-663; Clofazimin; Clofazimina; Clofaziminum; G-30320; Klofatsimiini; Klofatzimin; Klofazimin; Klofaziminas; NSC-141046; Клофазимин.

3-(4-Chloroanilino)-10-(4-chlorophenyl)-2,10-dihydro-2-phenazin-2-ylideneisopropylamine.

$C_{27}H_{22}Cl_2N_4$=473.4

CAS — 2030-63-9.

ATC — J04BA01.

ATC Vet — QJ04BA01.

UNII — D959AE5USF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Clofazimine). A fine reddish-brown powder. It shows polymorphism. Practically insoluble in water; very slightly soluble in alcohol; soluble in dichloromethane.

USP 36: (Clofazimine). Dark red crystals. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in ethyl acetate; soluble in chloroform and in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Clofazimine is an antimycobacterial and is used as part of multidrug regimens for the treatment of multibacillary leprosy (p. 188.3). It has anti-inflammatory properties and has been given in chronic Type 2 lepra reactions (erythema nodosum leprosum) and in a variety of skin disorders.

Clofazimine is given orally with, or immediately after, food or milk for optimum absorption.

For multibacillary leprosy the most common regimen is that recommended by WHO, in which rifampicin 600 mg and clofazimine 300 mg are both given *once a month*, with *daily* doses of clofazimine 50 mg and dapsone 100 mg; this treatment continues for 12 months.

For details of doses in children, see p. 275.3.

Clofazimine 50 mg daily is given with ofloxacin and minocycline in patients unable to take rifampicin. Clofazimine is not usually given in paucibacillary leprosy (p. 188.3). However, it may be used in the treatment regimen as a replacement for dapsone when the latter has caused severe toxicity. The clofazimine dose in such regimens is the same as that in multibacillary leprosy, i.e. 300 mg once a month (with rifampicin 600 mg), plus 50 mg clofazimine daily, but is only continued for 6 months.

Clofazimine has been used in the treatment of chronic Type 2 lepra reactions, although the effect may not be evident for 4 to 6 weeks. A dose of up to 300 mg daily has been suggested but it should not be given for longer than 3 months. Corticosteroids may be given with clofazimine, and standard antileprosy treatment should be continued. Clofazimine is not used in Type 1 lepra reactions.

References.

1. Anonymous. Clofazimine. *Tuberculosis (Edinb)* 2008; **88:** 96–9.
2. Gurfinkel P, *et al.* Use of clofazimine in dermatology. *J Drugs Dermatol* 2009; **8:** 846–51.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral clofazimine 150 mg, rifampicin 450 mg, and dapsone 50 mg *once a month*, plus dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*. For children less than 10 years of age the dose should be adjusted according to body-weight. As for adults, treatment is given for 12 months.

Adverse Effects

Adverse effects to clofazimine are dose related, the most common being red to brown discoloration of the skin especially on areas exposed to sunlight; leprotic lesions may

become mauve to black. These changes are more noticeable in light-skinned people and may limit its acceptance. The conjunctiva and cornea may also show some signs of red to brown pigmentation. The generalised discoloration may take months to years to disappear after stopping therapy. Discoloration of hair, tears, sweat, sputum, breast milk, urine, and faeces may occur, as may nail discoloration with high doses of 300 mg daily. Severe depression related to skin discoloration has been reported rarely.

Gastrointestinal effects are uncommon for doses of clofazimine less than 100 mg daily and usually are not severe. Symptoms of nausea, vomiting, and abdominal pain occurring shortly after the start of treatment may be due to direct irritation of the gastrointestinal tract and such symptoms usually disappear on dose reduction. Use of doses of 300 mg daily or more for several months sometimes produces abdominal pain, diarrhoea, weight loss, gastrointestinal bleeding, and in severe cases the small bowel may become oedematous and symptoms of bowel obstruction may develop. This may be due to deposition of crystals of clofazimine in the wall of the small bowel and in the mesenteric lymph nodes. Crystal deposition may also occur in other organs including the liver and spleen and there have been rare reports of splenic infarction. Symptoms usually regress on withdrawal of treatment although fatalities have been reported.

Clofazimine may produce a dryness of the skin and ichthyosis as well as decreased sweat production and rashes. Pruritus, acneiform eruptions, and photosensitivity reactions have also been reported.

Eye irritation and decreased tear production may occur.

Headache, drowsiness, dizziness, taste disorders, and elevation of blood glucose levels have been reported rarely.

Incidence of adverse effects. The incidence of adverse effects was reviewed in 65 patients[1] who were receiving, or had received, clofazimine in weekly doses of either 700 mg or less as antimycobacterial therapy, or more than 700 mg as anti-inflammatory therapy. Length of treatment ranged from 1 to 83 months. Adverse effects on the skin included discoloration (20% of patients), pigmentation (64.6%), dry skin (35.4%), and pruritus (5%). Ocular adverse effects were conjunctival pigmentation (49.2%), subjective dimness of vision (12.3%), and dry eyes, burning, and other ocular irritation (24.6%). Gastrointestinal adverse effects included abdominal pain (33.8%), nausea (9.2%), diarrhoea (9.2%), and weight loss, vomiting, or loss of appetite (13.8%). The different dose regimens for antimycobacterial therapy or anti-inflammatory effect had similar incidences of adverse effects. Skin pigmentation in 8 patients disappeared on average 8.5 months after stopping therapy with clofazimine, the maximum time required being one year. Adverse effects of clofazimine were considered to be well tolerated.

In another report covering 540 patients receiving clofazimine 100 mg on alternate days or 300 mg daily, the most common adverse effect was skin pigmentation, which occurred in 77.8% of the patients. Ichthyotic changes were reported in 66.7% and pruritus in 20.2%. Gastrointestinal symptoms occurred in 20 patients (about 4%); other effects such as discoloration of sweat, urine, and tears were minor.[2]

1. Moore VJ. A review of side-effects experienced by patients taking clofazimine. *Lepr Rev* 1983; **54:** 327–35.
2. Kumar B, *et al*. More about clofazimine—3 years experience and review of the literature. *Indian J Lepr* 1987; **59:** 63–74.

Effects on the eyes. Accumulation of clofazimine crystals in the eye can lead to pigmentation of the cornea and conjunctiva. Degeneration of the retinal pigment epithelium has also been attributed to clofazimine therapy in a patient.[1] Slight repigmentation was seen after withdrawal of clofazimine.

1. Forster DJ, *et al*. Bull's eye retinopathy and clofazimine. *Ann Intern Med* 1992; **116:** 876–7.

Effects on the gastrointestinal tract. Gastrointestinal effects are uncommon at doses of clofazimine less than 100 mg daily. However, there have been some reports of severe gastrointestinal adverse events, including fatalities, in patients taking clofazimine.[1-4] An 11-year-old child given clofazimine (150 mg daily) for graft-versus-host disease developed severe enteropathy 2 years after starting treatment.[1] Clofazimine was stopped and symptoms resolved after 5 weeks. Enteropathy has also been reported in a 20-year-old patient who had taken 200 mg of clofazimine daily for 4 years.[2] Clofazimine was stopped but his symptoms did not resolve; he developed peripheral oedema and hypoalbuminaemia and died 2 years later due to cerebral thrombosis. In another report,[4] partial intestinal obstruction developed in a patient after 12 months of treatment with clofazimine 100 mg daily for the treatment of multidrug-resistant tuberculosis. The patient recovered 3 weeks after stopping clofazimine. Splenic infarction has been reported after 11 months treatment with high-dose clofazimine for the management of pyoderma gangrenosum.[5] Chronic abdominal pain due to crystal-storing histiocytosis of mesenteric lymph nodes is well recognised, and may mimic the symptoms of gastrointestinal lymphoma or myeloma.[3]

1. Parizhskaya M, *et al*. Clofazimine enteropathy in a pediatric bone marrow transplant recipient. *J Pediatr* 2001; **138:** 574–6.
2. Hameed A, *et al*. A case of clofazimine enteropathy. *Int J Clin Pract* 1998; **52:** 439–40.
3. Sukpanichnant S, *et al*. Clofazimine-induced crystal-storing histiocytosis producing chronic abdominal pain in a leprosy patient. *Am J Surg Pathol* 2000; **24:** 129–35.
4. Üsküdar O, *et al*. Partial intestinal obstruction due to clofazimine in a patient with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; **9:** 703–4.
5. McDougall AC, *et al*. Splenic infarction and tissue accumulation of crystals associated with the use of clofazimine (Lamprene; B663) in the treatment of pyoderma gangrenosum. *Br J Dermatol* 1980; **102:** 227–30.

Effects on the heart. Ventricular tachycardia, thought to be probably torsade de pointes, was reported to be associated with clofazimine.[1]

1. Choudhri SH, *et al*. Clofazimine induced cardiotoxicity—a case report. *Lepr Rev* 1995; **66:** 63–8.

Precautions

Clofazimine should be used with caution in patients with gastrointestinal symptoms such as abdominal pain and diarrhoea. If gastrointestinal symptoms develop during treatment, the dose should be reduced and, if necessary, the interval between doses increased, or the drug should be stopped. Daily doses of more than 100 mg should not be used for more than 3 months because of dose-related adverse effects on the gastrointestinal tract; patients receiving doses above 100 mg daily should be under medical supervision.

Patients should be warned that clofazimine may cause a reddish-brown discoloration of breast milk, hair, skin, conjunctiva, tears, sputum, sweat, urine, and faeces. Nails may be discoloured at higher doses.

As clofazimine crosses the placental barrier, neonates of women receiving clofazimine may have skin discoloration at birth.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that the use of clofazimine by mothers during breast feeding may be of concern, since there is the possibility of transfer of a high percentage of the maternal dose and a possible increase in skin pigmentation in the infant. A small study in 8 women calculated that up to 30% of a maternal dose may be ingested by a breast-fed infant.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Venkatesan K, *et al*. Excretion of clofazimine in human milk in leprosy patients. *Lepr Rev* 1997; **68:** 242–6.

Pregnancy. Two successful pregnancies in women who received clofazimine throughout pregnancy have been reported[1] but a literature review revealed 3 neonatal deaths in 13 pregnancies, although the deaths could not be directly attributed to clofazimine. However, WHO[2] states that its recommended multiple drug therapy regimens for leprosy, which may include clofazimine, are safe during pregnancy.

1. Farb H, *et al*. Clofazimine in pregnancy complicated by leprosy. *Obstet Gynecol* 1982; **59:** 122–3.
2. WHO. *Guide to eliminate leprosy as a public health problem.* 1st ed. Geneva: WHO,2000. Also available at: http://www.who.int/lep/resources/Guide_Int_E.pdf (accessed 28/07/08)

Interactions

Some preliminary data have suggested that the anti-inflammatory action of clofazimine in Type 2 lepra reactions may be reduced by dapsone, although US licensed product information (*Lamprene; Novartis, USA*) states that these findings have not been confirmed; the antimycobacterial effect was not affected.

Elevated plasma and urine concentrations of clofazimine have been detected in patients receiving high doses of clofazimine with isoniazid, although skin concentrations were found to be lower.

For a report of the effect of clofazimine on rifampicin absorption, see p. 355.2.

Antimicrobial Action

Clofazimine is bacteriostatic and weakly bactericidal against *Mycobacterium leprae*. Tissue antimicrobial activity in humans cannot be found until after about 50 days of therapy. Clofazimine is active *in vitro* against various other species of *Mycobacterium*. Resistance has been reported rarely and no cross-resistance occurs with rifampicin or dapsone.

Pharmacokinetics

Clofazimine is absorbed from the gastrointestinal tract in amounts varying from 45 to 70%. Absorption is greatest when clofazimine is given in microcrystalline formulations and when it is taken immediately after food. The time to steady-state plasma concentrations has not been determined but exceeds 42 days.

Average plasma concentrations in leprosy patients receiving 100 or 300 mg daily are reported as 700 nanograms/mL and 1.0 microgram/mL, respectively.

Because of its lipophilic nature, clofazimine is mainly distributed to fatty tissue and reticuloendothelial cells, including macrophages. Clofazimine is distributed to most organs and tissues and into breast milk; it crosses the placenta but not the blood-brain barrier.

The tissue half-life after a single dose has been reported to be about 10 days; that after multiple oral doses has been variously estimated to be between 25 and 90 days. Clofazimine accumulates in the body and is largely excreted unchanged in the faeces, both as unabsorbed drug and via biliary excretion. About 1% of the dose is excreted in 24 hours in the urine as unchanged clofazimine and metabolites. A small amount of clofazimine is also excreted through sebaceous and sweat glands, and in sputum.

References.

1. Holdiness MR. Clinical pharmacokinetics of clofazimine: a review. *Clin Pharmacokinet* 1989; **16:** 74–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Lamprene; ***Braz.***: Neozimina; ***Cz.***: Lamprene; ***Fr.***: Lamprene; ***Gr.***: Lamprene; ***India***: Clofozine; Hansepran; ***Jpn***: Lampren; ***Neth.***: Lampren; ***NZ***: Lamprene; ***Spain***: Lampren†; ***Thai.***: Lamcoin; ***USA***: Lamprene.

Multi-ingredient Preparations. ***Thai.***: Lepromix MB.

Pharmacopoeial Preparations
BP 2014: Clofazimine Capsules;
USP 36: Clofazimine Capsules.

Clofoctol *(rINN)*

Clofoctolum; Клофоктол.
2-(2,4-Dichlorobenzyl)-4-(1,1,3,3-tetramethylbutyl)phenol.
$C_{21}H_{26}Cl_2O$=365.3
CAS — 37693-01-9.
ATC — J01XX03.
ATC Vet — QJ01XX03.
UNII — 704083NI0R.

Profile

Clofoctol has bacteriostatic or bactericidal activity against Gram-positive organisms such as staphylococci and streptococci. It is given in doses of 750 mg twice daily rectally in the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Gramplus.

Clometocillin Potassium *(rINNM)*

Clometocilina potásica; Clométocilline Potassique; 3,4-Dichloro-α-methoxybenzylpenicillin Potassium; Kalii Clometocillinum; Penicillin 356 (clometocillin); Калия Клометоциллин.
Potassium (6*R*)-6-[2-(3,4-dichlorophenyl)-2-methoxyacetamido]penicillanate.
$C_{17}H_{17}Cl_2KN_2O_5S$=471.4
CAS — 1926-49-4 (clometocillin); 15433-28-0 (clometocillin potassium).
ATC — J01CE07.
ATC Vet — QJ01CE07.
UNII — 7C71K33PDJ.

Profile

Clometocillin is a penicillin given orally as the potassium salt in the treatment of susceptible bacterial infections. Doses are expressed in terms of the base. The usual adult dose is 500 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Rixapen.

Cloxacillin *(BAN, rINN)*

Cloxacilina; Cloxacilline; Cloxacillinum; Kloksasilliini; Kloxacillin; Клоксациллин.
(6*R*)-6-[3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

$C_{16}H_{18}ClN_3O_5S$=435.9
CAS — 61-72-3.
ATC — J01CF02.
ATC Vet — QJ01CF02; QJ51CF02; QS01AA90.
UNII — O6X5QGC2VB.

Cloxacillin Benzathine *(BANM, rINNM)*

Cloxacilina benzatina; Cloxacilline Benzathine; Cloxacillinum Benzathinum; Клоксациллин Бензатин.
The *N,N'*-dibenzylethylenediamine salt of cloxacillin.
$C_{16}H_{20}N_2,(C_{19}H_{18}ClN_3O_5S)_2$=1112.1
CAS — 23736-58-5; 32222-55-2.
ATC — J01CF02.
ATC Vet — QJ01CF02.
UNII — AC79L7PV2G.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet)*.

BP(Vet) 2014: (Cloxacillin Benzathine). A white or almost white powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers.

USP 36: (Cloxacillin Benzathine). White or almost white, almost odourless, crystals or crystalline powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; sparingly soluble in acetone; soluble in chloroform and in methyl alcohol. pH of a 1% suspension in water is between 3.0 and 6.5. Store in airtight containers.

Cloxacillin Sodium *(BANM, USAN, rINNM)*

BRL-1621; Cloxacilina sódica; Cloxacillin-Natrium; Cloxacilline sodique; Cloxacillinum Natricum; Cloxacillinum Natricum Monohydricum; Kloksacilino natrio druska; Kloksacylina sodowa; Kloksasilliininatrium; Kloxacilin sodná sůl monohydrát; Kloxacillinnatrium; Kloxacillin-nátrium; Natrii Cloxacillinum; P-25; Натрий Клоксациллин.
$C_{19}H_{17}ClN_3NaO_5S,H_2O$=475.9
CAS — 642-78-4 (anhydrous cloxacillin sodium); 7081-44-9 (cloxacillin sodium monohydrate).
ATC — J01CF02.
ATC Vet — QJ01CF02.
UNII — MWQ645MKMF (anhydrous cloxacillin sodium); 65LCB0084Y (cloxacillin sodium monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cloxacillin Sodium). Semisynthetic product derived from a fermentation product. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25 degrees in airtight containers.

USP 36: (Cloxacillin Sodium). A white, odourless, crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers at a temperature not exceeding 25 degrees.

Incompatibility. Cloxacillin sodium has been reported to be incompatible with aminoglycosides and several other antimicrobials.

Uses and Administration

Cloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p. 301.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Cloxacillin is given orally, intramuscularly, or by intravenous injection or infusion as the sodium salt and doses are expressed in terms of the equivalent amount of cloxacillin; 1.09 g of cloxacillin sodium is equivalent to about 1 g of cloxacillin.

Usual oral doses are 250 to 500 mg four times daily and should be given 1 hour before, or 2 hours after meals as the presence of food in the stomach reduces absorption. Parenteral doses usually range from 1 to 2 g every 6 hours; for more severe infections such as meningitis or endocarditis, 2 g every 4 hours may be used. Other routes have included intra-articular or intrapleural injection, and inhalation.

For details of doses in children, see p. 277.1.

Cloxacillin may be used with other antibacterials, including ampicillin, to produce a wider spectrum of activity.

Cloxacillin benzathine is used in veterinary medicine.

Administration in children. Cloxacillin may be given to neonates and children for the treatment of infections caused by susceptible bacteria, particularly beta-lactamase-producing staphylococci, in the following doses:

- neonates 7 days of age and younger, weighing less than 2 kg: 25 mg/kg *orally* or *intravenously* every 12 hours
- neonates 7 to 28 days of age, weighing less than 2 kg, or, neonates 7 days of age and younger weighing 2 kg or more: 25 mg/kg *orally* or *intravenously* every 8 hours
- neonates 7 to 28 days of age weighing 2 kg or more: 25 mg/kg every 6 hours, *orally* or *intravenously*
  For treatment of meningitis, the above doses should be doubled, and given *intravenously*.
- children from 1 month of age, weighing less than 20 kg: 50 to 100 mg/kg daily (maximum 4 g) divided every 6 hours; *orally*, *intravenously*, or *intramuscularly*. For severe infection, up to 200 mg/kg daily (maximum 12 g) in divided doses may be given *intravenously*
- children from 1 month of age, weighing 20 kg or more: as for adults (see Uses and Administration, above)

Adverse Effects and Precautions

As for Flucloxacillin, p. 301.3.

Effects on the kidneys. References.
1. García-Ortiz R, *et al.* Cloxacillin-induced acute tubulo interstitial nephritis. *Ann Pharmacother* 1992; **26:** 1241–2.

Effects on the liver. References.
1. Enat R, *et al.* Cholestatic jaundice caused by cloxacillin: macrophage inhibition factor test in preventing rechallenge with hepatotoxic drugs. *BMJ* 1980; **280:** 982–3.
2. Konikoff F, *et al.* Cloxacillin-induced cholestatic jaundice. *Am J Gastroenterol* 1986; **81:** 1082–3.
3. Goland S, *et al.* Severe cholestatic hepatitis following cloxacillin treatment. *Postgrad Med J* 1998; **74:** 59–60.

Phlebitis. For a study indicating that dicloxacillin is associated with a higher incidence of phlebitis than cloxacillin, see p. 288.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cloxacillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]
1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of cloxacillin sodium contains about 2.1 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

As for Flucloxacillin, p. 302.1.

Pharmacokinetics

Cloxacillin is incompletely absorbed from the gastrointestinal tract, and absorption is reduced by the presence of food in the stomach. After an oral dose of 500 mg, a peak plasma concentration of 7 to 15 micrograms/mL is attained in fasting subjects in 1 to 2 hours. Absorption is more complete when given by intramuscular injection and peak plasma concentrations of about 15 micrograms/mL have occurred 30 minutes after a dose of 500 mg. Doubling the dose can double the plasma concentration. About 94% of cloxacillin in the circulation is bound to plasma proteins. Cloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

Cloxacillin crosses the placenta and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Therapeutic concentrations can be achieved in pleural and synovial fluids and in bone.

Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 35% of an oral dose is excreted in the urine and up to 10% in the bile. Cloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations in patients with cystic fibrosis have been attributed to both enhanced tubular secretion and enhanced nonrenal clearance of cloxacillin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Apo-Cloxi; Novo-Cloxin; Nu-Cloxi; ***China***: An Mei Lin (安美林); Gaofen (高芬); ***Fin.***: Staflocil; ***Fr.***: Orbenine; ***Gr.***: Anaclosil; Orbenin; Staphyclox; ***Hong Kong***: Apo-Cloxi; Cloxa†; Cloxcin; Lidoxin; Monoclox†; Prostaphlin-A†; ***India***: Aclox; Bioclox; Clocilin; Clopen; Klox; Neoclox; ***Indon.***: Meixam; ***Israel***: Loxavit; Orbenil; ***Malaysia***: Monoclox; ***Norw.***: Ekvacillin; ***Philipp.***: Avastoph; Caxin; Ciclox†; Clocsamed; Clopen; Clox; Cloxaco; Cloxal; Cloxigen†; Cloxil; Cloxin; CLX; Eloxil; Encloxil; Eraclox; Excelox†; Jogen; Kloxitas; Lewinex; Medaclox; Medix; Noxylen; Orbenin; Oxaclen; Pannox; Patriflex; Prostaphilin-A†; Secloxin; Solaze; Vamcloxil; ***Pol.***: Syntarpen; ***S.Afr.***: Cloxin; Orbenin†; ***Singapore***: Apo-Cloxi; Cloxacap; Cloxcin; Lidoxin; Procap-C; ***Spain***: Anaclosil; Orbenin; ***Swed.***: Ekvacillin; ***Thai.***: Clox†; Cloxa; Cloxacel; Cloxalin; Cloxam; Cloxamed; Cloxan; Cloxanbin†; Cloxasian; Cloxgen; Cloxil; Cloxillin; Cloxin; Cloxino†; Cloxpac; Cloxstar†; Coclox†; Corbin; Greater-Gloxa†; K-Cil; Lidoxin; Lincox; Loxzalin; Meiclox; Orbenin†; Panoxilin; Procloxin; S-Cloxin; Sanoclox; Socloxin†; Syntoclox†; Theraclox†; Vaclox†; Vicloxa.

Multi-ingredient Preparations. ***China***: Jielite (洁利特); Kaifa (凯法); ***Hong Kong***: Cloxamp†; Cloxampi†; Cloxampilin†; Co-Amclox†; Lampicin†; Pamedox†; Roscilox†; ***India***: ABClox; ACL; Adilox; Afymox-CL; AK-60; Alclox; Amci-Clox; Amclo; Amclominus; Amclox-LB; Amclox-LBS; Amclox; Amcloxin; Amiclox Plus; Amolac Plus DT; Amolac Plus; Amphy; Ampicloxa; Ampifort; Ampilox-LB; Ampilox; Amplus; Amplus; Ampoxin-LB; Ampoxin; Ampy C; Ampylox; Amyclox-LB; Amyclox; Axcel-L; Axcel-LS; Baciclox; Bacimox; Bactimox Plus; Bactimox; Baxin-LB; Baxin; Bclomox; Betaclox; Bicidal Plus; Bicil-P; Biclopen; Bilactam; Bilin-CS; Biplox-SL; Bluclox; Blumox-XL; Broadcure; Broadiclox-LB; Broadiclox; C-Clox; C-Tax-O XL; Cadmoxin-CS; Campilox-LB; Campilox; Capilac XP; Capilac; Cefglobe; Cefi XL; Cefo-LX; Cefocef-XL; Cilclox; Clacin; Clax; Climox; Climpen; Clodax-L; Clomentin; Clompic; Clotrop; Cloxam Plus; Cloxapene; Cloxcin; Cluster; Cobacta-S; Combilox-LB; Combilox; Combipen; Cynox; Dabcilox; Daze-MX; DC-Ped; DC; Dualcillin; Duoclox; Dupen Ped; Dynaclox; Edomox-C; Elclox Plus; Elclox; Elfi-XL; Emulox; Eradiclox; Eudase-MX; Euphoclox; Famclox; Flemiklox-LBX; G-Clox; Geniclox; Glocef-CL; Glymox-Plus; Glymox-Plus; Glymox; Gudcef; Himox Plus; Himox-LS; Hipenox LB; Hipenox; Imox-Clo LB†; Imox-Clo; Inloxy-LB Kid; Inloxy-SLB; Inloxy; Klomox; Kloxamp; Laclomox; Lacom; LC-Mox; Leemoxin-CS; Magclox-LB; Magnacillin; Mahacef-XL; Mediclox Plus; Megaclox LB; Megaclox; Megamox; Megapen; Mikilac Kidtab; Mikilac Plus; Milixim-LX; Moclox; Mokcan-C LB; Mokcan-C; Moxiclox; Moxlox-L; Moxlox; Moxtid-CS; Moxyplus-SL; Mytimox; Nataclox; Nepoclox; Nodimox Plus-LB; Nodimox Plus; Novaclox LB; Novaclox; Nuclox; Numox-LB; Numox; Oleclox; Omnipen; Osoclox; Oxylac; Suprimox; Symbiotik; ***Ital.***: Amplium; ***S.Afr.***: Ampiclox†; Ampoxin; Apen; Cloxam; Megamox; ***Thai.***: Ampcoxin; Ampiclox†; Viccillin-S†.

Pharmacopoeial Preparations
USP 36: Cloxacillin Sodium Capsules; Cloxacillin Sodium for Oral Solution.

Colistin Sulfate *(BANM, pINNM)*

Colistin Sulphate; Colistina, sulfato de; Colistine, Sulfate de; Colistini Sulfas; Colistinsulfat; Kolistiinisulfaatti; Kolistino sulfatas; Kolistinsulfat; Kolistin-sulfát; Kolistyny siarczan; Kolisztin-szulfát; Polymyxin E Sulphate; Sulfato de colistina; Колистина Сульфат.
CAS — 1066-17-7 (colistin); 1264-72-8 (colistin sulfate).
ATC — A07AA10; J01XB01.
ATC Vet — QA07AA10; QJ01XB01.
UNII — WP15DXU577.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Colistin Sulfate). A mixture of the sulfates of polypeptides produced by certain strains of *Bacillus polymyxa* var. *colistinus* or obtained by any other means. It contains not less than 19 000 International Units/mg, calculated with reference to the dried drug. A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Colistin Sulfate). The sulfate salt of an antibacterial substance produced by the growth of *Bacillus polymyxa* var. *colistinus*. It has a potency of not less than 500 micrograms of colistin per mg. A white to slightly yellow, odourless, fine powder. Freely soluble in water; insoluble in acetone and in ether; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 7.0. Store in airtight containers.

Stability. Colistin base is precipitated from aqueous solution above pH 7.5.

Colistimethate Sodium *(BANM, USAN, rINN)*

Colistimetato de Sódio; Colistimetato de sodio; Colistimetato sódico; Colistimethat-Natrium; Colistiméthate Sodique; Colistimethatum natricum; Colistimethatum Natrium; Colistin Sulphomethate Sodium; Colistinéméthanesulfonate Sodique; Kolistimetaattinatrium; Kolistimetatnatrium; Kolistimetato natrio druska; Kolistimethát sodná sůl; Kolistymetat sodowy; Kolisztimetát-nátrium; Pentasodium Colistinmethanesulfonate; Sodium Colistimethate; Sodium Colistinmethanesulphonate; W-1929; Колистиметат Натрий.
CAS — 30387-39-4 (colistimethate); 8068-28-8 (colistimethate sodium).
ATC — A07AA10; J01XB01.

ATC Vet — QA07AA10; QJ01XB01.
UNII — XW0E5YS77G.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Colistimethate Sodium). It is prepared from colistin by the action of formaldehyde and sodium bisulfite. The potency is not less than 11 500 units/mg, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.

USP 36: (Colistimethate Sodium). A white to slightly yellow, odourless, fine powder. It has a potency equivalent to not less than 390 micrograms of colistin per mg. Freely soluble in water; insoluble in acetone and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 6.5 and 8.5.

Stability. After the death of a patient with cystic fibrosis who had been given a liquid solution of colistimethate premixed for inhalation with a nebuliser (see Cystic Fibrosis, under Adverse Effects, p. 279.1) the US FDA warned[1] that such premixing of colistimethate in an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution and increases the potential for lung toxicity. When colistimethate is mixed with water and buffer it undergoes spontaneous hydrolysis to colistin; polymyxin E1, a component of colistin, has been shown to cause pulmonary inflammation in *animal* studies. Inhalation solutions of colistimethate should therefore be given promptly after preparation.

1. FDA. Colistimethate (marketed as Coly-Mycin M and generic products) (issued 28 June 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/colistimethateHCP.htm (accessed 18/01/08)

Units

The first International Standard Preparation (1968) for colistin contains 20 500 units/mg of colistin sulfate and the first International Reference Preparation (1968) for colistimethate contains 12 700 units/mg of colistimethate. Pure colistin base has been assigned a potency of 30 000 units/mg.

Differences in how doses of colistimethate sodium are expressed in different parts of the world (for example, as international units in the UK, or as colistin base in the USA) may cause considerable confusion; it should be noted that doses reported in clinical studies or case reports may vary depending on the country of origin and the preparation used. To avoid confusion, some have suggested that doses of colistimethate sodium be expressed in terms of international units.

Uses and Administration

Colistin is a polymyxin antibacterial that has been used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*, although other drugs are usually preferred. Colistimethate sodium is used by inhalation in the management of respiratory infections in patients with cystic fibrosis (p. 177.2). Colistin has been given orally as the sulfate for the treatment of gastrointestinal infections, although in the UK, the *BNF* has advised against its use for this indication. Colistin sulfate is also given orally for bowel preparation before abdominal surgery, and with other drugs in regimens for selective digestive tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p. 187.3).

The usual oral dose of colistin sulfate is 1.5 to 3 million units given 3 times daily. For bowel preparation, the same dose is given for 24 hours with the course being completed 12 hours before surgery.

Colistin is given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units given 3 times daily (maximum dose 6 million units in 24 hours) for patients weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients (see Adverse Effects and Precautions, p. 278.3).

Colistimethate sodium may also be given by inhalation in respiratory infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis. A nebulised solution is used in a usual dose of 1 to 2 million units given 2 or 3 times daily. A 3-week course of 2 million units twice daily may be given with other systemic antibacterials for initial colonisation, increased to a maximum of 2 million units given 3 times daily for up to 3 months in frequent recurrent infections; 1 to 2 million units twice daily may be given for chronic infection. Solutions for inhalation should be freshly prepared (see Stability, above). Alternatively, a dry-powder inhaler can be used in the management of chronic infections; a dose of 1.6625 million units is inhaled twice daily.

Doses and dosage intervals should be adjusted in patients with renal impairment (see p. 278.2).

For details of doses in children, see p. 278.2.

Colistimethate sodium has also been given by subconjunctival injection and as a bladder instillation. Both colistin sulfate and colistimethate sodium have been applied topically, often with other antibacterials, in the management of ear, eye, and skin infections.

Reviews.

1. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; **40:** 1333–41. Correction. *ibid.* 2006; **42:** 1819. [dose]
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Li J, *et al.* Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6:** 589–601.
4. Michalopoulos A, Falagas ME. Colistin and polymyxin B in critical care. *Crit Care Clin* 2008; **24:** 377–91.
5. Petrosillo N, *et al.* Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies. *Clin Microbiol Infect* 2008; **14:** 816–27.
6. Falagas ME, Rafailidis PI. Re-emergence of colistin in today's world of multidrug-resistant organisms: personal perspectives. *Expert Opin Invest Drugs* 2008; **17:** 973–81.

Administration in children. Colistin sulfate may be used orally in children for selective digestive tract decontamination. Although it is licensed for use in the treatment of gastrointestinal infections caused by Gram-negative bacteria, the *BNFC* has advised against this practice. The following doses may be given **orally** according to weight:

- up to 15 kg: 250 000 to 500 000 units 3 times daily
- 15 to 30 kg: 0.75 to 1.5 million units 3 times daily
- over 30 kg: the usual adult dose (see Uses and Administration, above)

Colistimethate sodium may be used parenterally in children for the treatment of serious infections caused by susceptible Gram-negative bacteria;[1,2] it may also be used by inhalation for management of *Pseudomonas aeruginosa* infection in cystic fibrosis. **Parenteral** doses may vary between countries.

UK according to weight:

- up to 60 kg: 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 60 kg: the usual adult dose (see above)

USA:

- children may be given the usual adult dose, equivalent to colistin base, of 2.5 to 5 mg/kg daily in 2 to 4 divided doses

Monitoring of plasma concentrations is required in some patients (see Adverse Effects, Treatment, and Precautions, p. 278.3).

For **inhalation** colistimethate sodium may be given as a nebulised solution in the following doses according to age:

- under 2 years: 0.5 to 1 million units twice daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age and that the dose may be increased to 1 million units three times daily in subsequent infections)
- over 2 years: the usual adult dose (see Uses and Administration, above)

Colistimethate sodium may alternatively be given by dry-powder inhaler for chronic *Pseudomonas aeruginosa* infection in children aged 6 years and older with cystic fibrosis; doses are as for adults (see above).

Doses and dosage intervals should be adjusted in patients with renal impairment (see p. 278.2).

1. Rosanova M, *et al.* Use of colistin in a pediatric burn unit in Argentina. *J Burn Care Res* 2009; **30:** 612–5.
2. Falagas ME, *et al.* Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. *Int J Antimicrob Agents* 2009; **33:** 503.e1–503.e13.

Administration in renal impairment. Dosage of **parenteral** colistimethate sodium must be adjusted in renal impairment; both reduction in dose and decreased frequency of dosing may be required.

In the UK, the following intravenous doses of colistimethate sodium, based on creatinine clearance (CC), have been suggested with one preparation (*Colomycin; Forest, UK*) for patients weighing 60 kg or more:

- CC 20 to 50 mL/minute: 1 to 2 million units every 8 hours
- CC 10 to 20 mL/minute: 1 million units every 12 to 18 hours
- CC less than 10 mL/minute: 1 million units every 18 to 24 hours

Licensed product information for another preparation (*Promixin; Profile, UK*) recommends the following intravenous dose modifications:

- mild impairment: 1 to 1.5 million units twice daily
- moderate impairment: 1 million units once or twice daily
- severe impairment: 1 to 1.5 million units every 36 hours

US licensed product information suggests the following intravenous or intramuscular doses (equivalent to colistin base) for adults with renal impairment in terms of plasma-creatinine concentrations:

- 1.3 to 1.5 mg/100 mL: 150 to 230 mg given daily in two divided doses
- 1.6 to 2.5 mg/100 mL: 133 to 150 mg given daily as a single dose or in 2 divided doses
- 2.6 to 4.0 mg/100 mL: 100 to 150 mg given every 36 hours

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy recommends an intravenous dose (equivalent to colistin base) of 2.5 mg/kg every 48 hours for patients undergoing continuous renal replacement therapy (CRRT). The authors note that a shorter dosing interval may be appropriate depending on patient specific factors including the specific type of CRRT used (as well as filter type and flow rate), the site of infection, and the level of antibacterial resistance of the infecting organism, and that close monitoring of pharmacological response, adverse effects, and serum-drug concentrations (where possible) should guide dosing. Other authors have suggested that a dose (equivalent to colistin base) of around 2 to 3 mg/kg intravenously every 12 hours may be required to achieve acceptable serum-drug concentrations for resistant Gram-negative bacteria in patients receiving continuous venovenous haemodiafiltration (CVVHDF) specifically.[2]

For critically ill patients undergoing intermittent haemodialysis, a dose (equivalent to colistin base) of 1.5 mg/kg every 24 to 48 hours has been suggested.[1]

Although high colistimethate sodium serum concentrations are considered unlikely during **inhaled** therapy, monitoring of serum concentrations has been suggested in those with renal impairment given nebulised drug.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.
2. Li J, *et al.* Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 2005; **49:** 4814–5.

Multidrug-resistant Gram-negative infections. A systematic review[1] of 6 controlled studies comparing nebulised or intravenous colistimethate sodium for the treatment of ventilator-associated pneumonia with other antibacterials found that colistin may be as safe and effective as standard antibacterial therapy, and suggested that it could be an alternative treatment for multidrug-resistant Gram-negative organisms. A high-dose extended-interval regimen[2] of intravenous colistimethate sodium has also been used to treat such infections. The dosing schedule was based on a loading dose of colistimethate sodium 9 million units by intravenous infusion, followed by subsequent doses of 4.5 million units, with the dosing interval adjusted according to renal function: every 12 hours for those with a creatinine clearance (CC) above 50 mL/min, every 24 hours for a CC 20 to 50 mL/min, or every 48 hours for a CC below 20 mL/min. High efficacy was seen without significant renal toxicity.

1. Florescu DF, *et al.* What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. *Clin Infect Dis* 2012; **54:** 670–80.
2. Dalfino L, *et al.* High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis* 2012; **54:** 1720–6.

Adverse Effects, Treatment, and Precautions

As for Polymyxin B Sulfate, p. 345.1.

Colistin sulfate is poorly absorbed from the gastrointestinal tract and adverse effects do not normally occur with usual oral doses. However, gastrointestinal absorption is limited and unpredictable in infants under 6 months of age and systemic adverse effects such as transient sensory disturbances may occur in this patient group.

Cough and bronchospasm are very common following inhalation of colistimethate sodium, but usually disappear or diminish with continued use. Reactions can be treated with an inhaled beta$_2$ agonist used before or after treatment, but withdrawal may be required if symptoms remain problematic. Cases of sore throat or sore mouth, possibly due to hypersensitivity or superinfection with *Candida* spp., have also been reported. After inhalation the mouth may be rinsed with water and the water expelled. Other adverse effects reported after inhalation include tinnitus, haemoptysis, dysphonia, dysgeusia, epistaxis, pharyngolaryngeal pain, gastrointestinal disturbances, and arthralgia.

Neurotoxic reactions such as dizziness, confusion, and visual disturbances can occur during parenteral therapy and patients so affected should not drive or operate machinery. Pain and local irritation are reported to be less troublesome after intramuscular injection of colistimethate sodium than with colistin sulfate or polymyxin B. Overgrowth of

non-susceptible organisms, particularly *Proteus* spp., may occur after prolonged use.

Plasma-concentration monitoring during systemic treatment is recommended in neonates, patients with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre (about 125 to 200 units/mL) are recommended.

Cystic fibrosis. Intravenous colistin sulfate was reported to be associated with a lower rate of severe nephrotoxicity among 19 patients with cystic fibrosis than has been previously reported in other patient populations.[1] However, fatal acute respiratory distress syndrome (ARDS) has been reported in a cystic fibrosis patient after inhalation of colistimethate sodium 75 mg twice daily.[2] The solution used had been compounded 5 weeks previously, and it was considered that ARDS was caused by the conversion of colistimethate sodium to the active form colistin which may cause airway or alveolar injury. The FDA subsequently warned that inhalation solutions should be used promptly after preparation (see Stability, p. 276.1).

1. Bosso JA, *et al.* Toxicity of colistin in cystic fibrosis patients. *DICP Ann Pharmacother* 1991; **25:** 1168–70.
2. McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med* 2007; **357:** 2310–1.

Effects on the cardiovascular system. Significant, but transient, hypotension occurred in a patient after starting aerosolised colistin inhalation.[1] Intravenous colistin, alone or with aerosolised amikacin, had no such effect on blood pressure.

1. Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrug-resistant Pseudomonas aeruginosa. *Ann Pharmacother* 2006; **40:** 1677–80.

Effects on the kidneys. The rates of colistin-associated nephrotoxicity previously reported in the literature have varied from around 50% in older studies to no toxicity in more recent reports,[1] which may, in part, be due to variable definitions of toxicity.[2] In a retrospective study[1] evaluating the incidence of nephrotoxicity defined by a standardised criteria, intravenous colistimethate sodium was associated with some degree of renal dysfunction in 45% of patients, with 21% subsequently stopping therapy as a result. The risk of toxicity was increased fourfold in those given colistimethate sodium for more than 14 days. A similar rate of nephrotoxicity (43%) was reported from a retrospective study of patients who had received intravenous colistin for 48 hours or longer.[3] Nephrotoxicity occurred in a dose-dependent manner; more than 30% of patients who received between 3 and 4.9 mg/kg of colistin daily (based on ideal body weight) had nephrotoxicity and this increased to 69% when daily doses of 5 mg/kg or more were given. In most patients nephrotoxicity occurred within the first week of therapy and no clear association was seen between cumulative colistin doses and nephrotoxicity. None of the patients had long-term renal failure or required haemodialysis after their treatment with colistin.[3] Another retrospective cohort study of 30 patients treated with intravenous colistin for 48 hours or longer reported that nephrotoxicity occurred in 33% of patients within the first 5 days of treatment. Nephrotoxicity was associated with excessive colistin dosing which was usually due to the daily mg/kg dose of colistin being calculated according to the actual body weight in obese patients rather than the ideal body weight.[4]

See Cystic Fibrosis, above, for the suggestion that nephrotoxicity may be less frequent in this patient group.

1. Hartzell JD, *et al.* Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin Infect Dis* 2009; **48:** 1724–8.
2. Falagas ME, Rafailidis PI. Nephrotoxicity of colistin: new insight into an old antibiotic. *Clin Infect Dis* 2009; **48:** 1729–31.
3. Pogue JM, *et al.* Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis* 2011; **53:** 879–84.
4. Deryke CA, *et al.* Colistin dosing and nephrotoxicity in a large community teaching hospital. *Antimicrob Agents Chemother* 2010; **54:** 4503–5.

Occupational asthma. Occupational asthma has been reported in a 24-year-old man working in a pharmaceutical company transporting and storing raw materials.[1] Three months after starting his job, he developed rhinitis which improved over the weekends; 9 months later, exposure to colistin had caused him to develop a sudden cough, wheeze, and dyspnoea. A specific inhalation challenge confirmed the diagnosis of occupational asthma to colistin and the patient stopped working in the colistin-exposed environment. He was asymptomatic at 6-months follow-up.

1. Gómez-Ollés S, *et al.* Occupational asthma due to colistin in a pharmaceutical worker. *Chest* 2010; **137:** 1200–2.

Porphyria. Although the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden offers no classification for colistin,[1] UK-licensed product information advises that colistin should be used with extreme caution in patients with porphyria.

1. The Drug Database for Acute Pophyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Polymyxin B Sulfate, p. 345.2.

Antimicrobial Action

The antimicrobial spectrum and mode of action of colistin is similar to that of polymyxin B (p. 345.2) but colistin sulfate is slightly, and colistimethate significantly, less active.

Pharmacokinetics

Colistin sulfate and colistimethate sodium are poorly absorbed from the gastrointestinal tract of adults and children; however, limited and unpredictable gastrointestinal absorption occurs in infants under 6 months of age. The drugs are not absorbed through mucous membranes, or intact or denuded skin. Transpulmonary absorption of colistimethate sodium is variable following inhalation of nebulised solution or dry powder. Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Plasma protein binding of colistin is reported to be more than 50% but that of colistimethate sodium is low. Colistin is reversibly bound to body tissues, but binding does not occur with colistimethate. Some colistimethate sodium may be hydrolysed to colistin *in vivo*. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment; values of 10 to 20 hours have been reported in patients with a creatinine clearance of less than 20 mL/minute. See also Half-life p. 279.2. Half-life may initially be prolonged in neonates but has been reported to fall to 2 to 3 hours after 3 or 4 days.

Colistimethate is mainly excreted by glomerular filtration as changed and unchanged drug and up to 80% of a parenteral dose may be recovered in the urine within 24 hours. Excretion is more rapid in children than in adults; it is reduced in patients with renal impairment. Colistin crosses the placenta but diffusion into the CSF is negligible. It is distributed into breast milk.

Cystic fibrosis. References.

1. Reed MD, *et al.* The pharmacokinetics of colistin in patients with cystic fibrosis. *J Clin Pharmacol* 2001; **41:** 645–54.
2. Li J, *et al.* Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. *J Antimicrob Chemother* 2003; **52:** 987–92.
3. Ratjen F, *et al.* Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006; **57:** 306–11.

Half-life. A study involving 18 critically-ill patients given intravenous colistimethate sodium found that the pharmacokinetics fitted a single-compartment model with an estimated half-life of 14.4 hours.[1] It was considered that the pharmacokinetics implied that plasma concentrations of the drug would be inadequate in this group until steady state was reached; loading doses might be of benefit in critically-ill patients.

1. Plachouras D, *et al.* Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. *Antimicrob Agents Chemother* 2009; **53:** 3430–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfacolin; Alficetin; Nolisim; Toliscrin; ***Austral.***: Coly-Mycin M†; Tadim; ***Belg.***: Colistineb; ***Canad.***: Coly-Mycin M; ***China***: Colmycin (可利迈仙); ***Cz.***: Colomycin; ***Denm.***: Promixin; ***Fr.***: Colimycine; ***Ger.***: ColiFin; Diaront mono; Promixin; ***Gr.***: Colimycine; Colomycin; Tadim; ***Hong Kong***: Colomycin; ***Hung.***: Colomycin; ***India***: Colgit; Coligyl; Colistop; GDSafe; Harmless; Walamycin; ***Indon.***: Colistine; ***Irl.***: Colomycin; Promixin; ***Israel***: Coliracin; ***Ital.***: Colimicina†; Colimicina; ***Mex.***: Colmesdant; ***Neth.***: ColiFin; Colobreathe; Tadim; ***Norw.***: Promixin; ***Port.***: Colixin; ***Spain***: Colimicina†; Promixin; ***Swed.***: Tadim; ***Switz.***: ColiFin; ***Thai.***: Colistate; ***Turk.***: Colistimicin; ***UK***: Colobreathe; Colomycin; Promixin; ***Ukr.***: Colomycin (Коломицин); ***USA***: Coly-Mycin M.

Multi-ingredient Preparations. ***Arg.***: Clarex Compuesto; Eristin; ***Fr.***: Bacicoline; ***Ger.***: Ecolicin; ***Ital.***: Colbiocin; Colbiocin; Eubetal Antibiotico; Eubetal Antibiotico; ***Mex.***: Colfur†; Colistin Magma†; ***Neth.***: Bacicoline-B; ***NZ***: Antibiotic Simplex; ***Philipp.***: Elicocin; ***Rus.***: Colbiocin (Колбиоцин); Colbiocin (Колбиоцин); ***USA***: Coly-Mycin S Otic; Cortisporin-TC.

Pharmacopoeial Preparations

BP 2014: Colistimethate Injection; Colistimethate Sodium Powder for Nebuliser Solution; Colistin Tablets;

USP 36: Colistimethate for Injection; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Colistin Sulfate for Oral Suspension.

Co-tetroxazine *(BAN)*

CAS — 73173-12-3.

Profile

Co-tetroxazine, a mixture of tetroxoprim (p. 378.3) and sulfadiazine (p. 363.3) in the proportion of 2:5, has properties similar to those of co-trimoxazole (p. 279.3). It has been given orally, mainly in the treatment of infections of the urinary and respiratory tracts, including pneumocystis pneumonia.

Co-trifamole *(BAN)*

CN-3123; Cotrifamol.

ATC — J01EE04.

Profile

Co-trifamole, a mixture of 5 parts of sulfamoxole (p. 370.1) and 1 part of trimethoprim (p. 383.2), has properties similar to those of co-trimoxazole (p. 279.3) and has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Supristol.

Co-trimoxazole *(BAN)*

Cotrimossazolo; Co-trimoxazol; Cotrimoxazol; Ko-trimoksazol; Kotrimoksazol; Kotrimoxazol; SMX-TMP; SMZ-TMP; TMP-SMX; TMP-SMZ; Ко-тримоксазол.

CAS — 8064-90-2.

ATC — J01EE01.

Description. Co-trimoxazole is defined as a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim.

Preparation and stability. Co-trimoxazole concentrate for injection must be diluted before being given as an intravenous infusion. Each 5 mL (80 mg of trimethoprim and 400 mg of sulfamethoxazole) of the concentrate is usually diluted in 125 mL of infusion solution. The recommended diluent is glucose 5%, although other solutions, including sodium chloride 0.9%, may be compatible for adequate periods. In patients who are fluid restricted, each 5 mL of the concentrate may be diluted in 75 mL of glucose 5%.

Diluted infusion solutions of co-trimoxazole have limited stability and eventually form a precipitate: this occurs more rapidly at higher concentrations. If the solution is cloudy or crystallisation appears at any time before or during an infusion, the solution should be discarded. Dilution is best carried out immediately before use; prepared solutions should be kept at room temperature and used within 2 hours of preparation if diluted in 75 mL of diluent, within 4 hours if in 100 mL, or within 6 hours if in 125 mL.

Uses and Administration

Co-trimoxazole is a mixture of the medium-acting sulfonamide, sulfamethoxazole, and the diaminopyrimidine, trimethoprim, in the proportion of 5 parts of sulfamethoxazole to 1 part of trimethoprim. It is used in infections caused by susceptible bacteria, particularly those of the urinary, respiratory, and gastrointestinal tracts, although the indications for its use are restricted in the UK (see p. 280.1). It is used to treat nocardiosis (p. 280.3) and is usually the drug of choice for the management of pneumocystis pneumonia (see p. 280.3).

Its other uses have included the treatment of acne, biliary-tract infections, brucellosis (generally with other drugs), cat scratch disease, *Burkholderia cepacia* (*Pseudomonas cepacia*) infections in cystic fibrosis, granuloma inguinale, listeriosis, melioidosis, mycetoma, otitis media, pertussis, typhoid and paratyphoid fever, and Whipple's disease. It has also been used for the prophylaxis of infections in immunocompromised patients. For details of the bacterial infections listed above and their treatment, see under Choice of Antibacterial, p. 172.2.

Co-trimoxazole is also used in the management of toxoplasmosis (p. 280.3), as well as many other protozoal infections, including blastocystis infection (p. 280.2), cyclosporiasis (p. 280.2), and isosporiasis (p. 280.2). It also may be used in the management of certain granulomatous disorders (p. 280.2).

Co-trimoxazole is usually given orally in a standard dose of 960 mg (trimethoprim 160 mg and sulfamethoxazole 800 mg) twice daily; in severe infections 2.88 g daily in 2 divided doses has been given. Lower doses are given for

long-term treatment and in patients with renal impairment (see Administration in Renal Impairment, p. 280.2).

Higher doses of co-trimoxazole of up to 120 mg/kg daily given in 2 to 4 divided doses for 14 to 21 days are used in the treatment of pneumocystis pneumonia; serum concentrations should be monitored and folate supplementation possibly considered (but see Pneumocystis Pneumonia, p. 280.3). For prophylaxis of pneumocystis pneumonia, the following dose regimens may be used: 960 mg once daily (7 days each week); 960 mg once daily on alternate days (3 days each week); or 960 mg twice daily on alternate days (3 days each week).

For details of doses in children, see p. 280.1.

For serious infections, if oral use is not possible, treatment may begin by intravenous infusion. Each ampoule (containing 480 mg of co-trimoxazole in 5 mL) is typically added to 125 mL of a suitable diluent immediately before use (see also p. 277.3), and the solution infused over 60 to 90 minutes. Doses given are similar to recommended oral doses.

The place of co-trimoxazole in therapy was reviewed by the UK CSM in 1995 (see also Incidence of Adverse Effects, p. 281.1).[1] As a result they recommended that its use should be limited to: pneumocystis pneumonia, toxoplasmosis, and nocardiosis; urinary-tract infections and acute exacerbations of chronic bronchitis, but only when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer it to a single antibacterial; and acute otitis media in children, but again only when there is good reason to prefer it.

In other countries co-trimoxazole continues to be used for susceptible infections without restriction.

1. CSM. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Administration in children. Co-trimoxazole may be used in children for the treatment of infections caused by susceptible organisms, or for the prophylaxis of pneumocystis infection in those who are immunocompromised. It may be given orally or by intravenous infusion. Doses are expressed as the total amount of sulfamethoxazole and trimethoprim.

In the UK, co-trimoxazole is generally not recommended for use in infants younger than 6 weeks because of the risk of kernicterus from the sulphonamide component (see under Precautions of Sulfamethoxazole, p. 368.1), although it may be used in infants from 4 weeks of age for the treatment and prophylaxis of pneumocystis pneumonia. For the treatment of most infections, the *BNFC* recommends an *oral* dose of 24 mg/kg twice daily or the following *standard* doses:

- children 6 weeks to 6 months of age: 120 mg twice daily
- children 6 months to 6 years of age: 240 mg twice daily
- children 6 to 12 years of age: 480 mg twice daily

When used *intravenously*, doses of 18 mg/kg every 12 hours are recommended, although in severe infection up to 27 mg/kg (to a maximum of 1.44 g) every 12 hours may be used.

Alternatively, in the USA the American Academy of Pediatrics[1] recommends that children from 1 month of age may be given 48 to 72 mg/kg daily, orally in 2 divided doses.

For ***treatment*** of **pneumocystis pneumonia**, 120 mg/kg daily in 2 to 4 divided doses is recommended, either orally or intravenously for 14 to 21 days. For ***prophylaxis***, a few different regimens have been suggested. The *BNFC* suggests that an oral dose of 450 mg/m^2 (to a maximum of 960 mg) may be given twice daily on 3 alternate or consecutive days each week. US guidelines for prophylaxis of opportunistic infection in HIV-infected children suggest that a dose of 15 to 30 mg/kg twice daily may be given on 2 or 3 days of the week; the dose may be given on consecutive or alternate days of the week. Alternatively, the total daily dose may be given as a single dose on every day of the week.[2] In children with leukaemia or lymphoma, co-trimoxazole 30 mg/kg daily given in 2 divided doses on 2 consecutive days each week has been reported to be an effective alternative regimen.[3]

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 13/12/13)
3. Lindemulder S, Albano E. Successful intermittent prophylaxis with trimethoprim/sulfamethoxazole 2 days per week for Pneumocystis carinii (jiroveci) pneumonia in pediatric oncology patients. Abstract: *Pediatrics* 2007; **120:** 158. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/1/e47 (accessed 14/08/09)

Administration in renal impairment. Doses of co-trimoxazole, both orally and intravenously, should be reduced in patients with renal impairment. The following recommendations for adults and children over 12 years of age are based on creatinine clearance (CC):

- CC above 30 mL/minute: the standard dose
- CC 15 to 30 mL/minute: half the standard dose
- CC below 15 mL/minute: not recommended.

In a review,[1] the following doses of co-trimoxazole (based on the trimethoprim component) were recommended for critically ill patients undergoing different types of renal replacement therapy:

- intermittent haemodialysis: 2.5 to 10 mg/kg every 24 hours or 5 to 20 mg/kg three times weekly (given after dialysis on dialysis days)
- continuous renal replacement therapy: 2.5 to 7.5 mg/kg every 12 hours; up to 10 mg/kg may be needed for patients with pneumocystis pneumonia who are undergoing continuous venovenous haemodiafiltration (CVVHDF)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Blastocystis infection. For a mention of the use of co-trimoxazole in the treatment of *Blastocystis hominis* infection, see p. 922.3.

Cyclosporiasis. Patients with *Cyclospora* infection (p. 923.2) have responded to treatment with co-trimoxazole.[1,2]

1. Hoge CW, *et al.* Placebo-controlled trial of co-trimoxazole for cyclospora infections among travellers and foreign residents in Nepal. *Lancet* 1995; **345:** 691–3. Correction. *ibid.:* 1060.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 885–8.

Granulomatous diseases. Although co-trimoxazole appears to be effective in reducing the incidence of bacterial infection in patients with chronic granulomatous disease,[1-3] a disorder of leucocyte function associated with recurrent life-threatening infection and granuloma formation, its use in systemic vasculitis is much more controversial. There have been some reports of benefit from co-trimoxazole in patients with Wegener's granulomatosis (p. 1615.2),[4-7] but relapse appears to be common,[6] and an analysis[8] of the experience of the USA National Institutes of Health in 158 patients, was sceptical of its value: only 1 of 9 patients given 960 mg twice daily orally had any prolonged improvement.

Some evidence later emerged that addition of co-trimoxazole to maintenance regimens in patients already in remission reduces the incidence of relapse,[9] although another study suggested that it might actually increase the risk of relapse.[10]

1. Mouy R, *et al.* Incidence, severity, and prevention of infections in chronic granulomatous disease. *J Pediatr* 1989; **114:** 555–60.
2. Margolis DM, *et al.* Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. *J Infect Dis* 1990; **162:** 723–6.
3. Gallin JI, Malech HL. Update on chronic granulomatous diseases of childhood: immunotherapy and potential for gene therapy. *JAMA* 1990; **263:** 1533–7.
4. DeRemee RA, *et al.* Wegener's granulomatosis: observations on treatment with antimicrobial agents. *Mayo Clin Proc* 1985; **60:** 27–32.
5. Bowden FJ, Griffiths H. Co-trimoxazole in the treatment of Wegener's granulomatosis. *Med J Aust* 1989; **151:** 303–4.
6. Valeriano-Marcet J, Spiera H. Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. *Arch Intern Med* 1991; **151:** 1649–52.
7. Ohtake T, *et al.* Generalized Wegener's granulomatosis responding to sulfamethoxazole-trimethoprim monotherapy. *Intern Med* 2001; **40:** 666–70.
8. Hoffman GS, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116:** 488–98.
9. Stegeman CA, *et al.* Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996; **335:** 16–20.
10. de Groot K, *et al.* Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996; **39:** 2052–61.

Isosporiasis. A regimen of oral co-trimoxazole 960 mg four times daily for 10 days followed by 960 mg twice daily for 3 weeks was reported to be initially effective in patients with AIDS suffering from isosporiasis (p. 923.3), and produced resolution of diarrhoea within 2 days of beginning treatment; it was, however, associated with a high rate of recurrence.[1] A shorter regimen followed by indefinite prophylaxis may be preferable in persons with AIDS; in a small randomised controlled study, co-trimoxazole 960 mg twice daily for 7 days, followed by 10 weeks of prophylaxis, was effective in HIV-infected patients with isosporiasis.[2]

1. DeHovitz JA, *et al.* Clinical manifestations and therapy of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1986; **315:** 87–90.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 885–8.

Nocardiosis. Co-trimoxazole is used in the treatment of nocardiosis (p. 193.3). There is no consensus on the optimum dosage; doses of 2.88 to 3.84 g daily in divided doses for up to 3 months have been used.

Pneumocystis pneumonia. Co-trimoxazole is the preferred drug for both the treatment and prophylaxis of pneumocystis pneumonia (p. 567.2). A single dose of 480 mg daily may be effective and better tolerated for prophylaxis than a daily dose of 960 mg.[1] However, some still prefer the latter dose schedule[2] which is also the one preferred by the CDC in the USA[3] and is a licensed dose for prophylaxis in both the UK and USA. Various studies[1,2,4-8] have shown intermittent dosing is also effective for the prophylaxis of pneumonia and is better tolerated than daily dosing; the dose has usually been 960 mg three times each week on alternate days[1,2,4-7] although 960 mg twice daily three times each week has also been given.[8] The addition of folinic acid has no effect on tolerability and may be associated with a higher rate of therapeutic failure (see HIV Infection and AIDS, p. 2067.3).

1. Ioannidis JPA, *et al.* A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med* 1996; **156:** 177–88.
2. El-Sadr WM, *et al.* A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. *Clin Infect Dis* 1999; **29:** 775–83.
3. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 09/07/09)
4. Wormser GP, *et al.* Low-dose intermittent trimethoprim-sulfamethoxazole for prevention of Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *Arch Intern Med* 1991; **151:** 688–92.
5. Stein DS, *et al.* Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1991; **35:** 1705–9.
6. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus disease. *Lancet* 1991; **337:** 468–71.
7. Bozzette SA, *et al.* The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98:** 177–82.
8. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.

Toxoplasmosis. There is some evidence that giving co-trimoxazole for prophylaxis of pneumocystis pneumonia produces an additional benefit in acting prophylactically against toxoplasmic encephalitis in persons with HIV infection or AIDS,[1-5] but the evidence (as for other drugs) has been largely anecdotal or from small retrospective studies. In the USA, the CDC recommends[1] that co-trimoxazole 960 mg daily (as for pneumocystis pneumonia prophylaxis, above) be given to HIV-infected patients who are seropositive for *Toxoplasma* and have a CD4+ count below 100 cells/microlitre.

Co-trimoxazole has also produced promising results in preliminary studies for the treatment of toxoplasmic encephalitis in patients with AIDS,[6] and a systematic review[7] considered it an effective treatment, particularly in resource-poor settings where alternatives such as pyrimethamine with sulfadiazine might not be available.

For a discussion of toxoplasmosis and its management, see p. 926.1.

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 14/09/09)
2. Zangerle R, Allerberger F. Effect of prophylaxis against Pneumocystis carinii on toxoplasma encephalitis. *Lancet* 1991; **337:** 1232.
3. Carr A, *et al.* Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992; **117:** 106–11.
4. Beaman MH, *et al.* Prophylaxis for toxoplasmosis in AIDS. *Ann Intern Med* 1992; **117:** 163–4.
5. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.
6. Torre D, *et al.* Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42:** 1346–9.
7. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/07/08).

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its components; most effects can be attributed to sulfamethoxazole (p. 367.3), although some, including potentially

serious hyperkalaemia, may be caused by trimethoprim (see p. 384.1). Gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

A high incidence of adverse effects has been reported in AIDS patients; desensitisation may sometimes be considered (see Immunocompromised Patients under Precautions, p. 281.2).

Incidence of adverse effects. There has been concern over the safety of co-trimoxazole. In 1985, reporting on 85 deaths associated with the use of co-trimoxazole,[1] mainly due to blood dyscrasias (50 reports) and skin reactions (14 reports), the UK CSM found that fatalities showed a marked increase with age: below 40 years, there were 0.25 reported deaths per million prescriptions, but for patients over 65 years of age the number of reported deaths per million prescriptions was more than 15-fold greater. However, at that time the CSM felt that it would be unwise to assume that trimethoprim was substantially less liable than co-trimoxazole to cause fatal adverse reactions.[1] Others suggested[2] that most of the deaths associated with the use of co-trimoxazole were typical of sulfonamide toxicity and that the indications for the use of co-trimoxazole should be reduced; this included the suggestion that it should be contra-indicated in the elderly. The CSM stated that their main message was that the risks of treatment with co-trimoxazole were more apparent in the elderly, but that there was no significant difference between the numbers of reports received for serious adverse reactions to trimethoprim and co-trimoxazole when corrected for prescription volumes.[3] In practice, despite further occasional reports of fatalities in elderly patients,[4] there did not appear to have been a marked reduction in the use of this drug in the UK.[5] A similar warning of increased risk from co-trimoxazole in elderly patients was issued by the Adverse Drug Reactions Advisory Committee in Australia.[6]

A large population-based follow-up study in the UK[7] indicated that the risks of serious liver, blood, skin, and kidney disorders with either co-trimoxazole, trimethoprim, or cefalexin were small and were similar to those with many other antibacterials. Although in 1995 the CSM did restrict the use of co-trimoxazole on the grounds that its place in therapy had changed[8] (see under Uses and Administration, p. 278.1), they also noted that co-trimoxazole continued to show a similar pattern of serious suspected adverse reactions to that reported 10 years earlier and that adverse drug reactions with trimethoprim were similar; blood dyscrasias and generalised skin disorders were the most serious reactions in each case and occurred mainly in elderly patients.

1. CSM. Deaths associated with co-trimoxazole, ampicillin and trimethoprim. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. Lacey RW, *et al*. Co-trimoxazole toxicity. *BMJ* 1985; **291:** 481.
3. Goldberg A. Co-trimoxazole toxicity. *BMJ* 1985; **291**: 673.
4. Whittington RM. Toxic epidermal necrolysis and co-trimoxazole. *Lancet* 1989; **ii**: 574.
5. Carmichael AJ, Tan CY. Fatal toxic epidermal necrolysis associated with co-trimoxazole. *Lancet* 1989; **ii**: 808–9.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Trimethoprim-sulphamethoxazole warning on elderly. *Aust Adverse Drug React Bull* February 1990.
7. Jick H, Derby LE. Is co-trimoxazole safe? *Lancet* 1995; **345:** 1118–19.
8. CSM. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Effects on the CNS. Higher-level gait disorder and nocturnal delirium were reported in an elderly man given oral co-trimoxazole, up to 1.92 g every 12 hours, for lung infection;[1] dramatic improvement occurred shortly after the drug was stopped. Tremor associated with co-trimoxazole use has also been reported in a patient treated for suspected pneumocystis pneumonia.[2] The trimethoprim component has been proposed as the most likely cause of adverse effects involving the CNS.[2]

1. Dakin LE. Probable trimethoprim/sulfamethoxazole-induced higher-level gait disorder and nocturnal delirium in an elderly man. *Ann Pharmacother* 2009; **43:** 129–33.
2. Floris-Moore MA, *et al*. Adverse reactions to trimethoprim/sulfamethoxazole in AIDS. *Ann Pharmacother* 2003; **37:** 1810–3.

Precautions

As for Sulfamethoxazole, p. 368.1 and Trimethoprim, p. 384.2.

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of a rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects (see Incidence of Adverse Effects, above). Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were taking co-trimoxazole, and the last available guidance from the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding. Studies have shown that significant concentrations of trimethoprim and sulfamethoxazole are present in breast milk after maternal doses;[2,3] however, the calculated dose to the infant was deemed unlikely to lead to clinical effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Arnauld R, *et al*. Étude du passage de la triméthoprime dans le lait maternel. *Ouest Med* 1972; **25**: 959–64.
3. Miller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. *Hell Soc Chemother* 1974; **1:** 687–91.

G6PD deficiency. It has been suggested by some that co-trimoxazole should be avoided by people with G6PD deficiency.[1] Others suggest that therapeutic doses may be given without causing haemolytic anaemia.[2] However, a healthy, 37-year-old man developed haemolytic anaemia, hepatitis, orthostatic hypotension, and aseptic meningitis after taking co-trimoxazole for a urinary-tract infection; the patient was later found to have G6PD deficiency and this was considered to have increased his risk for a co-trimoxazole hypersensitivity reaction as well as for developing haemolytic anaemia.[3]

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67**: 601–11.
2. Youngster I, *et al*. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.
3. Chisholm-Burns MA, *et al*. Aseptic meningitis, hemolytic anemia, hepatitis, and orthostatic hypotension in a patient treated with trimethoprim-sulfamethoxazole. *Am J Health-Syst Pharm* 2010; **67:** 123–7.

Immunocompromised patients. An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in **patients with AIDS** being treated for pneumocystis pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS.[1] Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and hepatitis, may be 80% or more.[2-4] Adverse reactions also appear to be unusually frequent when prophylactic doses are used.[4] A lower frequency of cutaneous reactions has been reported among African, Haitian, and American black AIDS patients compared with white AIDS patients, suggesting a genetic susceptibility to such reactions.[5]

High serum concentrations of trimethoprim and sulfamethoxazole may contribute to the incidence of adverse effects,[6,7] and it was noted[6] that adverse effects, and in particular myelosuppression, were kept to tolerable levels in a group of patients in whom the **dose** of co-trimoxazole was adjusted to maintain serum-trimethoprim concentrations at 5 to 8 micrograms/mL. In a study in HIV-infected patients given co-trimoxazole for the prophylaxis of pneumocystis pneumonia,[8] a gradual start to therapy (increased over 2 weeks to the full therapeutic dose) was found to improve the tolerability of co-trimoxazole, when compared with patients started on full therapeutic doses. However, others[9] found no difference in the frequency of adverse effects when the sulfamethoxazole dose was modified.

It was suggested[10] that it was the reactive hydroxylamine **metabolites** of sulfamethoxazole that produced the adverse effects in HIV-infected individuals, but later work by the same authors[11] cast some doubt on this hypothesis.

Some workers have used diphenhydramine alone or with adrenaline to manage hypersensitivity reactions associated with co-trimoxazole therapy, thus allowing continuation of treatment,[12,13] while other workers have tried **desensitisation** to co-trimoxazole in patients with AIDS.[14-19] A systematic review[20] based on 3 small studies concluded that desensitisation was a more effective strategy than continuation. For mention of desensitisation to sulfonamides in patients with AIDS, see under Sulfamethoxazole, p. 368.2.

An increased incidence of myelosuppression, although not, apparently, of other adverse effects, has been reported in **patients with leukaemia** receiving maintenance chemotherapy.[21,22] Multifocal myoclonus and bilateral asterixis occurred in an immunocompromised lymphoma patient 4 days after starting treatment with high dose co-trimoxazole for the treatment of *Nocardia asteroides*. Symptoms resolved completely after stopping co-trimoxazole treatment.[23]

1. Masur H. Treatment of infections and immune defects. In: Fauci AS, moderator. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; **100**: 92–106.
2. Gordin FM, *et al*. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **100**: 495–9.
3. Jaffe HS, *et al*. Complications of co-trimoxazole in treatment of AIDS-associated Pneumocystis carinii pneumonia in homosexual men. *Lancet* 1983; **ii**: 1109–11.
4. Mitsuyasu R, *et al*. Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535.
5. Colebunders R, *et al*. Cutaneous reactions to trimethoprim-sulfamethoxazole in African patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; **107**: 599–600.
6. Sattler FR, *et al*. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; **109**: 280–7.
7. Stevens RC, *et al*. Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; **35**: 1884–90.
8. Para MF, *et al*. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr* 2000; **24:** 337–43.
9. McLean I, *et al*. Modified trimethoprim-sulphamethoxazole doses in Pneumocystis carinii pneumonia. *Lancet* 1987; **ii**: 857–8.
10. van der Ven AJAM, *et al*. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
11. ter Hofstede HJM, *et al*. Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
12. Gibbons RB, Lindauer JA. Successful treatment of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole in hypersensitive AIDS patients. *JAMA* 1985; **253**: 1259–60.
13. Toma E, Fournier S. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 954.
14. Kreuz W, *et al*. "Treating through" hypersensitivity to co-trimoxazole in children with HIV infection. *Lancet* 1990; **336**: 508–9.
15. Carr A, *et al*. Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; **7:** 65–71.
16. Absar N, *et al*. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; **93:** 1001–5.
17. Cortese LM, *et al*. Trimethoprim/sulfamethoxazole desensitization. *Ann Pharmacother* 1996; **30:** 184–6.
18. Caumes E, *et al*. Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; **133:** 465–9.
19. Demoly P, *et al*. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998; **102:** 1033–6.
20. Lin D, *et al*. Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/07/08).
21. Woods WG, *et al*. Myelosuppression associated with co-trimoxazole as a prophylactic antibiotic in the maintenance phase of childhood acute lymphocytic leukemia. *J Pediatr* 1984; **105**: 639–44.
22. Drysdale HC, Jones LF. Co-trimoxazole prophylaxis in leukaemia. *Lancet* 1982; **i**: 448.
23. Dib EG, *et al*. Multifocal myoclonus induced by trimethoprim-sulfamethoxazole therapy in a patient with nocardia infection. *N Engl J Med* 2004; **350:** 88–9.

Interference with diagnostic tests. Co-trimoxazole has been reported[1,2] to cause a small reduction in serum-thyroxine and tri-iodothyronine concentrations, probably due to the sulfonamide component.[2] Although co-trimoxazole had not been shown to be a cause of hypothyroidism (since all concentrations remained within the normal range), tests of thyroid function might need to be interpreted with care in patients on such treatment.

1. Cohen HN, *et al*. Effects on human thyroid function of sulphonamide and trimethoprim combination drugs. *BMJ* 1980; **281**: 646–7.
2. Cohen HN, *et al*. Trimethoprimand thyroid function. *Lancet* 1981; **i**: 676–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the combination of sulfamethoxazole and trimethoprim as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/08/11)

Interactions

Any of the drug interactions reported with sulfamethoxazole (p. 368.2) or trimethoprim (p. 384.2) may occur with co-trimoxazole.

Antibacterials. For reference to potential interaction between co-trimoxazole and *rifampicin*, see p. 355.2.

Antimicrobial Action

The actions and spectrum of activity of co-trimoxazole are essentially those of its components, sulfamethoxazole (p. 368.3) and trimethoprim (p. 384.3).

Because they act at different points of the folate metabolic pathway a potent synergy exists between its components *in vitro* with an increase of up to about tenfold in antibacterial activity, and a frequently bactericidal action where the components individually are generally bacteriostatic. The optimum effect against most organisms is seen at a ratio of 1 part trimethoprim to 20 of sulfamethoxazole; although co-trimoxazole is formulated as a 1 to 5 ratio, differences in the pharmacokinetics of the two drugs mean that the ratio of the peak concentrations is about 1:20. However, it is not clear that the optimum ratio is achieved at all sites and, given that both drugs are present in therapeutic concentrations, the contribution of synergy to the effects of co-trimoxazole *in vivo* is uncertain.

Although it was originally thought that combining trimethoprim and sulfamethoxazole would prevent resistance developing to either of the two components, this has not proved correct and resistance to co-trimoxazole (in both Gram-positive and Gram-negative organisms) is now widespread. Rates of resistance vary depending on the bacterial species, the type of infection being treated, and geographic location. Resistance is generally chromosomeor plasmid-mediated. Although resistant organisms are usually resistant to both components of the mixture, strains resistant to either the sulfonamide or trimethoprim, and with a reduced sensitivity to co-trimoxazole, have been reported; resistance to co-trimoxazole develops more slowly *in vitro* than to either component alone. Resistance has occurred notably among Enterobacteriaceae; resistant *Salmonella* and *Shigella* are common in many countries, while resistance in *Haemophilus influenzae, H. ducreyi*, and *Streptococcus pneumoniae* tends to vary according to geographic location. Resistance in *Moraxella catarrhalis* has been reported rarely.

References.

1. Martin JN, *et al.* Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era. *J Infect Dis* 1999; **180:** 1809–18.
2. Huovinen P. Resistance to trimethoprim-sulfamethoxazole. *Clin Infect Dis* 2001; **32:** 1608–14.

Pharmacokinetics

As for sulfamethoxazole (p. 369.1) and trimethoprim (p. 384.3). Co-trimoxazole is rapidly and well absorbed from the gastrointestinal tract and peak plasma concentrations are reached between 1 to 4 hours after an oral dose; effective plasma concentrations are maintained for up to 24 hours after an oral therapeutic dose. Steady-state concentrations are reached after dosing for 2 to 3 days. Plasma concentrations of trimethoprim and sulfamethoxazole are generally around the optimal ratio of 1:20, although they may vary from 1:20 to 1:30 or more. The ratio of the two drugs is usually much lower in the tissues (often around 1:2 to 1:5) since trimethoprim, the more lipophilic drug, penetrates many tissues better than sulfamethoxazole and has a much larger volume of distribution. In urine the ratio may vary from 1:1 to 1:5 depending on the pH. Co-trimoxazole is excreted mainly by the kidneys through both glomerular filtration and tubular secretion; about 50% is excreted in the urine within 24 hours as unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adrenol; Bacticel; Bactrim; Cotrizol-G; Danferane; Dosulfin Fuerte; Netocur; Novidrine; Sulfagrand; Tritenk; Urisept NF; ***Austral.***: Bactrim; Respim; Septrin; Trimoxazole†; ***Austria***: Bactrim; Cotribene; Eusaprim; Oecotrim†; ***Belg.***: Bactrim; Cotrim†; Eusaprim; ***Braz.***: Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Belfactrim F; Benectrin; Dientrin; Ectrin; Gamactrin†; Imuneprim†; Infectrin; Metoprin; Neotrin; Pulkrin†; Qiftrim; Roytrin; Selectrin†; Teutrin; Tricban; Trimexazol; Uropol†; ***Canad.***: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Protrin; Septra; Trisulfa; ***Chile***: Bacterol; Bactrimel; Septrin; Trelibec; ***China***: Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (奎建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Yu An Li Qing (玉安立清); ***Cz.***: Biseptol; Bismoral†; Primotren†; Sumetrolim; ***Fin.***: Cotrim; ***Fr.***: Bactrim; ***Ger.***: Berlocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; ***Gr.***: Bactrimel; Bioprim; Blaxezan; Blexon; Epahol; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; ***Hong Kong***: Chemoprim; Cotrim; Dhatrin; Letus; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; ***Hung.***: Cotripharm; Sumetrolim; ***India***: Alcorim-F; Antrima; Bactrim; Ciplin; Colizole; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Methoxaprim; Moly Kid; Mountrim; Okatrim DS; Oriprim; Otrim; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.***: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.***: Septrin; ***Israel***: Diseptyl; Resprim; Septrin; ***Ital.***: Bactrim; Chemitrim; Eusaprim†; ***Jpn***: Bactramin; Baktar; ***Malaysia***: Bacin; Bactrim; Chemix; Cotrim; Resprim†; Trimexazole; Trizole; ***Mex.***: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric†; Bactide†; Bactilen; Bactiver; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimzol; TS-Bac; Vanadyl; ***Neth.***: Bactrimel; ***Norw.***: Bactrim; ***NZ***: Apo-Sulfatrim†; Deprim; Trisul; ***Philipp.***: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim†; Zolmed; ***Pol.***: Bactrim; Biseptol; Septrin†; Two-Septol; ***Port.***: Bactrim; Microcetim†; Septrin; ***Rus.***: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гроseптол); Oriprim (Ориприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); ***S.Afr.***: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac; Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac; Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; ***Singapore***: Apo-Sulfatrim; Bacin; BS; Chemix; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; ***Spain***: Momentol†; Septrin; ***Swed.***: Bactrim; Eusaprim; ***Switz.***: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; ***Thai.***: Actin; Actrim; Addtrim; Agsulfa; Babytrim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Conprim†; Coprim; Cotamox; Cotrim; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Zoleprim; ***Turk.***: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Septrin; Sulfaprim; Trifen; Trimoks; ***UAE***: Trimol; ***UK***: Fectrim; Septrin; ***Ukr.***: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гроseптол); Soluseptol (Солюseптол); Sumetrolim (Суметролим); ***USA***: Bactrim; Cotrim†; Septra; SMZ-TMP; Sulfatrim; ***Venez.***: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Multi-ingredient Preparations. ***Arg.***: Bacti-Uril; Bactrim Balsamico; Dosulfin Bronquial; Enterobacticel; Netocur Balsamico; Neumobacticel; ***Braz.***: Assepium Balsamico; Benectrin Balsamico; Diazol; Dispeptrin†; Ectrin Balsamico; Metoprin Balsamico†; Selectrin Balsamico; Urectrim; ***Chile***: Entero Micinovo; Uro-Micinovo; ***China***: Xiaoke (消刻); ***India***: Chemotrin; Neoprim; ***Mex.***: Bactrim Compositum; Brogamax; Guayaprin; Octex; Sadocin; Trimexole Compositum; ***Singapore***: Co-Trimexazole; Trimaxazole; ***Spain***: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets;

USP 36: Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets.

Cycloserine *(BAN, rINN)*

Cicloserina; D-Cycloserin; Cycloserine; D-Cycloserine; Cycloserinum; Cykloserin; SC-49088; Sikloserin; Sykloseriini; Циклосерин.

(+)-(*R*)-4-Aminoisoxazolidin-3-one.

$C_3H_6N_2O_2$=102.1

CAS — 68-41-7.

ATC — J04AB01.

ATC Vet — QJ04AB01.

UNII — 95IK5KI84Z.

Description. Cycloserine is an antimicrobial substance produced by the growth of certain strains of *Streptomyces orchidaceus* or *S. garyphalus*, or obtained by synthesis.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cycloserine). A white to pale yellow, crystalline powder, odourless or has a faint odour. It is hygroscopic and deteriorates upon absorbing water. Freely soluble in water. pH of a 10% solution in water is between 5.5 and 6.5. Store in airtight containers.

Uses and Administration

Cycloserine is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p. 210.2) as part of a multidrug regimen when resistance to primary drugs has developed. It has been used in urinary-tract infections, although less toxic drugs are preferred.

The usual adult oral dose in tuberculosis is 250 mg twice daily for 2 weeks, followed by 0.5 to 1 g daily in divided doses. Dosage in patients with mild to moderate renal impairment should be reduced and doses for all patients should be adjusted by monitoring plasma concentrations (see Precautions, p. 282.3).

For details of doses in children, see p. 282.3.

Cycloserine has been tried for the adjunctive treatment of schizophrenia and anxiety disorders (see p. 282.3). L-Cycloserine has been investigated for the treatment of Gaucher disease (p. 2433.3).

References.

1. Anonymous. Cycloserine. *Tuberculosis (Edinb)* 2008; **88:** 100–1.

Administration in children. Use of cycloserine is licensed in both the UK and USA for children, although age ranges are not specified in licensed product information. For the treatment of drug-resistant tuberculosis the American Academy of Pediatrics[1] suggests an oral dose of 5 to 10 mg/kg twice daily, to a maximum dose of 1 g daily.

Doses are adjusted according to blood concentrations and response.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Psychological disorders. Cycloserine has been tried as an adjunct in the management of schizophrenia (p. 1031.3) and anxiety disorders (p. 1028.1).

References.

1. Duncan EJ, *et al.* Effects of D-cycloserine on negative symptoms in schizophrenia. *Schizophr Res* 2004; **71:** 239–48.
2. Hofmann SG, *et al.* Augmentation treatment of psychotherapy for anxiety disorders with D-cycloserine. *CNS Drug Rev* 2006; **12:** 208–17.
3. Tuominen HJ, *et al.* Glutamatergic drugs for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 02/07/10).
4. Otto MW, *et al.* Clinical perspectives on the combination of D-cycloserine and cognitive-behavioral therapy for the treatment of anxiety disorders. *CNS Spectr* 2007; **12:** 51–61.
5. Wilhelm S, *et al.* Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165:** 335–41.
6. Goff DC, *et al.* Once-weekly D-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. *Schizophr Res* 2008; **106:** 320–7.
7. Otto MW, *et al.* Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biol Psychiatry* 2010; **67:** 365–70.
8. Heaton LJ, *et al.* Propranolol and D-cycloserine as adjunctive medications in reducing dental fear in sedation practice. *SAAD Dig* 2010; **26:** 27–35.

Adverse Effects and Treatment

The most frequent adverse effects with cycloserine involve the CNS and include anxiety, confusion, disorientation, depression, psychoses possibly with suicidal tendencies, aggression, irritability, and paranoia. Vertigo, headache, drowsiness, speech difficulties, tremor, paresis, hyperreflexia, dysarthria, paraesthesia, coma, and convulsions may also occur. Neurological reactions are dose related and may be reduced by keeping plasma concentrations below 30 micrograms/mL. It has been reported that up to 30% of patients have adverse effects, but these usually subside when cycloserine is stopped or the dosage is reduced. Pyridoxine has been used in an attempt to treat or prevent neurological reactions but its value is unproven.

Hypersensitivity reactions including skin reactions and photosensitivity occur rarely. Serum aminotransferase values may be raised, especially in patients with a history of liver disease. Folate and vitamin B_{12} deficiency, megaloblastic anaemia, and sideroblastic anaemia have been reported occasionally when cycloserine has been used with other antituberculous drugs. Heart failure has occurred in patients receiving daily doses of 1 g or more.

Precautions

Cycloserine is contra-indicated in patients with epilepsy, depression, psychosis, severe anxiety, severe renal impairment, or in those who misuse alcohol. Cycloserine should be stopped, or the dose reduced, if skin reactions or symptoms of CNS toxicity develop.

Cycloserine has a low therapeutic index, and dosage should be adjusted according to plasma concentrations, which should be monitored at least weekly in patients with renal impairment, in those taking doses greater than 500 mg daily, and in patients showing signs of neurotoxicity. Plasma concentrations should be maintained below 30 micrograms/mL. Haematological, renal, and hepatic function should be monitored. Patients with mild to moderate renal impairment require lower doses.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cycloserine,[1] and the last available guidance from the American Academy of Pediatrics considered[2] that it is therefore usually compatible with breast feeding.

1. Morton RF, *et al.* Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. UK licensed product information for cycloserine notes that its use has been associated with clinical exacerbations of porphyria and it is not recommended in porphyric patients.

Interactions

Patients receiving cycloserine and taking alcohol are at increased risk of convulsions; for reference to increased blood-alcohol concentrations in patients receiving cycloserine, see p. 1736.2.

Neurotoxic effects may be potentiated by use of cycloserine with ethionamide, and concurrent use of cycloserine and isoniazid may result in increased CNS toxicity, such as dizziness and drowsiness.

Antimicrobial Action

Cycloserine interferes with bacterial cell wall synthesis by competing with D-alanine for incorporation into the cell wall. It has variable activity against Gram-positive and Gram-negative bacteria including *Escherichia coli* and *Staphylococcus aureus*.

Cycloserine is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistance develops if cycloserine is used alone.

Pharmacokinetics

Cycloserine is readily and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations of 10 micrograms/mL have been obtained 3 to 4 hours after a dose of 250 mg, rising to 20 to 30 micrograms/mL on repeating the dose every 12 hours. The plasma half-life is about 10 hours and is prolonged in patients with renal impairment.

Cycloserine is widely distributed into body tissues and fluids, including the CSF, placenta, and breast milk, producing fetal blood concentrations approaching those in maternal serum.

Cycloserine is excreted largely unchanged by glomerular filtration. About 50% of a single 250-mg dose is excreted unchanged in the urine within 12 hours and about 70% is excreted within 72 hours. As negligible amounts of cycloserine appear in the faeces, it is assumed that the remainder of a dose is metabolised to unidentified metabolites. It is removed by haemodialysis.

Pregnancy and breast feeding. Cycloserine has been shown to pass to the fetus, into amniotic fluid,[1] and into breast milk.[2] Concentrations in breast milk after 250 mg four times daily have been reported to range from 6 to 19 micrograms/mL.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Morton RF, *et al.* Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Closina†; ***Gr.***: D-cycloserin†; Seromycin; ***Hong Kong***: Seromycin†; ***India***: Coxerin; Cyclokox; Cyclorine; Cyclotec; Cyserin; MDSerine; Myser; Pamserine; ***Rus.***: Coxerin (Коксерин); Coxerin Plus (Коксерин Плюс); Myzer (Майзер); ***Thai.***: Proserine†; ***Turk.***: Siklocap; ***UK***: Cycloserine; ***USA***: Seromycin.

Multi-ingredient Preparations. ***Rus.***: Cyclo Plus (Цикло Плюс).

Pharmacopoeial Preparations

USP 36: Cycloserine Capsules.

Dalbavancin *(BAN, USAN, rINN)*

A-A-1; BI-397; Dalbavancina; Dalbavancine; Dalbavancinum; MDL-63397; VER-001; V-Glycopeptide; Дальбаванцин.

5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl]carbamoyl]-42-*O*-α-D-mannopyranosyl-15-*N*-methyl(ristomycin A aglicone) (main component).

$C_{88}H_{100}Cl_2N_{10}O_{28}$=1816.7

CAS — 171500-79-1.

ATC — J01XA04.

ATC Vet — QJ01XA04.

UNII — 808UI9MS5K.

NOTE. The name Zeven has been used as a trade mark for dalbavancin.

Profile

Dalbavancin is a lipoglycopeptide antibacterial under investigation for the treatment of severe infections due to Gram-positive bacteria, including complicated infections of the skin and soft tissues. It has a prolonged terminal elimination half-life and has been given intravenously in a regimen of two doses at an interval of one week.

References.[1-7] See also under Uses and Administration of Telavancin, p. 373.1.

1. Lin S-W, *et al.* Dalbavancin: a new option for the treatment of gram-positive infections. *Ann Pharmacother* 2006; **40:** 449–60.
2. Billeter M, *et al.* Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. *Clin Infect Dis* 2008; **46:** 577–83.
3. Anderson VR, Keating GM. Dalbavancin. *Drugs* 2008; **68:** 639–48.
4. Bailey J, Summers KM. Dalbavancin: a new lipoglycopeptide antibiotic. *Am J Health-Syst Pharm* 2008; **65:** 599–610.
5. Dowell JA, *et al.* Pharmacokinetic-pharmacodynamic modeling of dalbavancin, a novel glycopeptide antibiotic. *J Clin Pharmacol* 2008; **48:** 1063–8.
6. Marbury T, *et al.* Pharmacokinetics of dalbavancin in patients with renal or hepatic impairment. *J Clin Pharmacol* 2009; **49:** 465–76.
7. Zhanel GG, *et al.* New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; **70:** 859–86.

Danofloxacin Mesilate *(BANM, rINNM)*

CP-76136-27 (danofloxacin mesilate); CP-76136 (danofloxacin); Danofloksasiinimesilaatti; Danofloxacin Mesylate (USAN); Danofloxacine, Mésilate de; Danofloxacini Mesilas; Danofloxacinmesilat; Danofloxacino, mesilato de; Mesilato de danofloxacino; Данофлоксацина Мезилат.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-oxo-3-quinolinecarboxylic acid monomethanesulphonate.

$C_{19}H_{20}FN_3O_3.CH_4O_3S$=453.5

CAS — 112398-08-0 (danofloxacin); 119478-55-6 (danofloxacin mesilate).

UNII — 94F3SX3LEM.

Profile

Danofloxacin is a fluoroquinolone antibacterial used as the mesilate in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Dapsone *(BAN, USAN, rINN)*

DADPS; Dapson; Dapsona; Dapsonas; Dapsoni; Dapsonum; Dapszon; DDS; Diaminodiphenylsulfone; Diaphenylsulfone; Disulone; NSC-6091; Sulphonyldianiline; Дапсон; 4,4′-Sulfonylbis-benzenamine.

Bis(4-aminophenyl) sulphone.

$C_{12}H_{12}N_2O_2S$=248.3

CAS — 80-08-0.

ATC — D10AX05; J04BA02.

ATC Vet — QD10AX05; QJ04BA02.

UNII — 8W5C518302.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Dapsone). A white or slightly yellowish-white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves freely in dilute mineral acids. Protect from light.

USP 36: (Dapsone). A white or creamy-white, odourless crystalline powder. Very slightly soluble in water, freely soluble in alcohol; soluble in acetone and in dilute mineral acids. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dapsone prepared from commercially available tablets found them to be stable for 3 months when stored at 4 degrees and at 25 degrees.

1. Nahata MC, *et al.* Stability of dapsone in two oral liquid dosage forms. *Ann Pharmacother* 2000; **34:** 848–50.

Uses and Administration

Dapsone is used as part of multidrug regimens in the treatment of all forms of leprosy (p. 188.3). It has also been used in the prophylaxis of leprosy and in the management of household contacts of leprosy patients. Dapsone is used as an alternative to co-trimoxazole or pentamidine for the treatment and prophylaxis of pneumocystis pneumonia (p. 284.1), and has been used with pyrimethamine for the prophylaxis of malaria (see under Pyrimethamine, p. 662.3). It is also used in dermatitis herpetiformis and other dermatoses (see Skin Disorders, p. 284.1) and is applied topically in acne. It is used for the prophylaxis of toxoplasmosis (p. 926.1) and for the treatment of actinomycetoma (see Mycetoma, p. 193.1). It has been tried alone or with topical imiquimod for the treatment of cutaneous leishmaniasis (p. 283.3).

Systemic dapsone is usually given orally. There are some reports of it being given by intramuscular injection, but such injections can be painful and cause abscess formation.

The most common regimens for **leprosy** are those recommended by WHO. For multibacillary leprosy, rifampicin 600 mg and clofazimine 300 mg are both given *once a month* with dapsone 100 mg and clofazimine 50 mg both *daily* for 12 months. Adults weighing less than 35 kg receive reduced doses of rifampicin and dapsone, and in such patients the dapsone dose is 50 mg or 1 to 2 mg/kg daily.

The WHO regimen for paucibacillary leprosy consists of rifampicin 600 mg once a month and dapsone 100 mg daily; both are given for 6 months. Doses are reduced in low-weight patients as for multibacillary leprosy.

The doses of dapsone used for the prophylaxis and treatment of **pneumocystis pneumonia** are discussed in more detail under pneumocystis pneumonia, p. 284.1.

The dose needed to treat **dermatitis herpetiformis** has to be titrated for individual patients, but it is usual to start with an oral dose of 50 mg daily, gradually increased to 300 mg daily or more if required. This dose should be reduced to a minimum as soon as possible. Maintenance dosage can often be reduced in patients receiving a gluten-free diet.

In the treatment of **acne**, dapsone is applied topically as a 5% gel twice daily.

For details of doses in children, see p. 283.3.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral dapsone 50 mg plus rifampicin 450 mg and clofazimine 150 mg *once a month*, together with dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*; both are given for 12 months. For paucibacillary leprosy WHO recommends oral dapsone 50 mg plus rifampicin 450 mg *once a month*, together with dapsone 50 mg *daily*; both are given for 6 months. For children less than 10 years of age the dose should be adjusted according to body weight.

For details of doses for the treatment of pneumocystis pneumonia in children, see p. 284.1.

Connective tissue disorders. Relapsing polychondritis (p. 1610.3) has responded to dapsone, as has Behçet's syndrome (p. 1601.1) and SLE. Vasculitic syndromes such as hypersensitivity vasculitis (p. 1606.1) have also improved following dapsone.

Immune thrombocytopenia. Dapsone has been reported[1-5] to be of benefit in some patients, including children, with refractory immune thrombocytopenia (p. 1606.1).

1. Radaelli F, *et al.* Adult refractory chronic idiopathic thrombocytopenic purpura: can dapsone be proposed as second-line therapy? *Br J Haematol* 1999; **104:** 641–2.
2. Dutta TK, *et al.* Dapsone in treatment of chronic idiopathic thrombocytopenic purpura in adults. *J Assoc Physicians India* 2001; **49:** 421–5.
3. Meeker ND, *et al.* Dapsone therapy for children with immune thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003; **25:** 173–5.
4. Damodar S, *et al.* Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults—a report on 90 patients. *Eur J Haematol* 2005; **75:** 328–31.
5. Vancine-Califani SM, *et al.* Efficacy and safety of dapsone as a second-line treatment in non-splenectomized adults with immune thrombocytopenic purpura. *Platelets* 2008; **19:** 489–95.

Leishmaniasis. In early reports from India, treatment of cutaneous leishmaniasis (p. 924.1) with oral dapsone 2 mg/kg daily for several weeks led to cure rates in excess of 80%.[1] However, an open-label study of 11 patients in Columbia[2] reported favourable clinical response in only 2 of 6 patients who completed a 13-week course of oral dapsone 200 mg daily.

In a later study in Kuwait,[3] good or excellent response to therapy was reported for about 43% of patients given oral dapsone, and for about 57% of those given a combination of oral dapsone and topical imiquimod 5%.

1. Mahajan VK, Sharma NL. Therapeutic options for cutaneous leishmaniasis. *J Dermatolog Treat* 2007; **18:** 97–104.

2. Osorio LE, *et al.* Treatment of cutaneous leishmaniasis in Colombia with dapsone. *Lancet* 1998; **351:** 498–9.
3. Al-Mutairi N, *et al.* Tropical medicine rounds: Treatment of Old World cutaneous leishmaniasis with dapsone, itraconazole, cryotherapy, and imiquimod, alone and in combination. *Int J Dermatol* 2009; **48:** 862–9.

Pneumocystis pneumonia. Oral dapsone is used alone or with oral pyrimethamine[1] for *primary and secondary prophylaxis* of pneumocystis pneumonia (p. 567.2) in patients unable to tolerate co-trimoxazole. In adults a dose of dapsone 100 mg daily in one or two doses is commonly used[1] and has been reported to have similar efficacy to co-trimoxazole.[2] Dapsone has also been given with pyrimethamine in various regimens including:

- dapsone 50 mg daily with pyrimethamine 50 mg once weekly[1,3]
- dapsone 100 mg plus pyrimethamine 50 mg both given twice weekly[4]
- dapsone 200 mg plus pyrimethamine 75 mg both given once weekly[1,5]

In children from 1 month of age the recommended dose of dapsone is 2 mg/kg daily (to a maximum of 100 mg daily) or 4 mg/kg weekly (to a maximum of 200 mg weekly).[6]

For *treatment* of adults and adolescents, an oral regimen of dapsone 100 mg once daily with trimethoprim 5 mg/kg three times daily, for 21 days, has been suggested for mild to moderate disease in patients unable to tolerate co-trimoxazole.[1] Infants and children under 13 years of age may be given a dose of dapsone of 2 mg/kg once daily (to a maximum of 100 mg daily) plus trimethoprim 5 mg/kg three times daily.[6]

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1 207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 01/07/09)
2. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; **332:** 693–9.
3. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; **328:** 1514–20.
4. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.
5. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; **20:** 531–41.
6. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; **58** (RR-11): 1–166. Available at: http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf (accessed 07/06/10)

Skin disorders. Dapsone is used for the suppression of skin lesions in dermatitis herpetiformis (p. 1683.2). The mechanism of action is unknown but is unrelated to its antimicrobial activity. Reports, generally involving small numbers of patients, suggest that dapsone may also be beneficial for bullous or mucous membrane pemphigoid (p. 1687.1), pyoderma gangrenosum (p. 1688.3), recurrent erythema multiforme (p. 1684.3), and urticaria (p. 1689.2).

References.
1. Gürcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. *Am J Clin Dermatol* 2009; **10:** 383–96.

ACNE. Dapsone is available in the USA as a 5% topical gel for the treatment of acne (p. 1682.2). The use of topical dapsone for acne has been reviewed.[1-5]

1. Stotland M, *et al.* Dapsone 5% gel: a review of its efficacy and safety in the treatment of acne vulgaris. *Am J Clin Dermatol* 2009; **10:** 221–7.
2. Pickert A, Raimer S. An evaluation of dapsone gel 5% in the treatment of acne vulgaris. *Expert Opin Pharmacother* 2009; **10:** 1515–21.
3. Scheinfeld N. Aczone, a topical gel formulation of the antibacterial, anti-inflammatory dapsone for the treatment of acne. *Curr Opin Investig Drugs* 2009; **10:** 474–81.
4. Webster GF. Is topical dapsone safe in glucose-6-phosphate dehydrogenase-deficient and sulfonamide-allergic patients? *J Drugs Dermatol* 2010; **9:** 532–6.
5. Kircik LH. Harnessing the anti-inflammatory effects of topical dapsone for management of acne. *J Drugs Dermatol* 2010; **9:** 667–71.

Spider bites. As discussed on p. 2420.1, necrotic araneism resulting from the bite of spiders of the genus *Loxosceles* is usually treated conservatively with surgical repair of any persistent defect. A prospective clinical study[1] of 31 patients with brown recluse spider bites indicated that treatment with oral dapsone 100 mg daily for 14 days followed by delayed surgical intervention if necessary reduced the incidence of wound complications and residual scarring compared with treatment by immediate surgical excision. A dose of 100 mg twice daily has also been given for 14 days.[2] An evaluation[3] of the management of brown recluse spider bites found that common treatments did not reduce healing time or scarring; dapsone was associated with slower healing rate and an increased risk of scarring.

1. Rees RS, *et al.* Brown recluse spider bites: a comparison of early surgical excision versus dapsone and delayed surgical excision. *Ann Surg* 1985; **202:** 659–63.
2. King LE, Rees RS. Dapsone treatment of a brown recluse bite. *JAMA* 1983; **250:** 648.
3. Mold JW, Thompson DM. Management of brown recluse spider bites in primary care. *J Am Board Fam Pract* 2004; **17:** 347–52.

Toxoplasmosis. For mention of the use of dapsone in the primary prevention of toxoplasmosis, see under Pyrimethamine, p. 663.1.

Adverse Effects

Varying degrees of dose-related haemolysis and methaemoglobinaemia are the most frequently reported adverse effects of dapsone, and occur in most patients given oral doses of more than 200 mg daily; doses of up to 100 mg daily do not cause significant haemolysis, but patients with G6PD deficiency are affected by doses above about 50 mg daily.

Although agranulocytosis has been reported rarely with dapsone when used alone, reports have been more common when it has been used with other drugs in the prophylaxis of malaria. Deaths due to agranulocytosis, aplastic anaemia, and other blood dyscrasias have been reported.

Rash and pruritus may develop. Serious cutaneous hypersensitivity reactions occur rarely and include maculopapular rash, exfoliative dermatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Fixed drug eruptions have occurred.

A 'dapsone syndrome' may occur after 4 to 8 weeks of treatment and resembles mononucleosis in its presentation (see Hypersensitivity, p. 285.1).

Peripheral neuropathy with motor loss has been reported in patients on dapsone for dermatological conditions. Peripheral neuropathy may occur as part of leprosy reaction states and is not an indication to stop dapsone.

Other adverse effects occur infrequently and include nausea, vomiting, anorexia, headache, hepatitis, insomnia, psychosis, and tachycardia.

Carcinogenicity. A survey of 1678 leprosy patients admitted for treatment to the National Hansen's Disease Center in the USA between 1939 and 1977 indicated that, although dapsone has been implicated as a carcinogen in *animals*, the use of dapsone did not appear to affect significantly the risk of cancer in these patients.[1] The International Agency for Research on Cancer concluded[2] that there was limited evidence for the carcinogenicity of dapsone in *animals* and insufficient data to be able to classify the carcinogenic risk in humans. A subsequent retrospective cohort study[3] also found no significantly increased risk of death or death from cancer among patients who received dapsone for treatment of ocular inflammatory disorders.

1. Brinton LA, *et al.* Cancer mortality among patients with Hansen's disease. *J Natl Cancer Inst* 1984; **72:** 109–14.
2. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 24* 1980 (updated 07/04/98). Also available at: http://monographs.iarc.fr/ENG/Monographs/vol24/volume24.pdf (accessed 16/07/10)
3. Kempen JH, *et al.* Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. Abridged version: *BMJ* 2009; **339:** b2480. Full version: http://www.bmj.com/cgi/content/full/339/jul03_1/b2480?view=long&pmid=19578087 (accessed 07/06/10)

Effects on the blood. *Haemolysis* is the most frequent serious adverse effect of dapsone and may occur at oral doses of 200 mg or higher daily.[1] Red blood cells may contain Heinz bodies and there is a reduction in their life span.[2] Well-known risk factors include G6PD deficiency,[3] methaemoglobin reductase deficiency, and haemoglobin M trait; haemoglobin E trait may also increase susceptibility to haemolytic reactions.[2] Haemolytic anaemia has been reported in a neonate after ingestion of dapsone in breast milk.[4] Clinically relevant haemolysis or anaemia was not reported in patients treated with topical dapsone gel 5% for acne, including patients with G6PD deficiency.[5] However, US licensed product information states that some individuals with G6PD deficiency using dapsone gel have developed laboratory changes suggestive of mild haemolysis.

Methaemoglobinaemia,[6] although common, is rarely symptomatic.[1] However, severe cyanosis was associated with methaemoglobinaemia after an inadvertent overdose with dapsone in an HIV-positive patient with suspected pneumocystis pneumonia.[7] Methaemoglobinaemia has also been reported in an HIV-negative patient with severe renal impairment, who had previously undergone liver and kidney transplantations and who was receiving dapsone for prophylaxis of pneumocystis pneumonia.[8] The metabolite dapsone hydroxylamine is probably responsible for the methaemoglobinaemia and haemolysis associated with dapsone.[3] Studies have shown[9,10] that use of dapsone with cimetidine, which inhibits production of the *N*-hydroxy metabolite, has resulted in a decrease in methaemoglobin levels, at least in the short term.

Agranulocytosis has occurred rarely on use of dapsone in leprosy and skin disease. More cases have been seen with use for malaria prophylaxis[11] (see also under Pyrimethamine, p. 663.2) and dermatitis herpetiformis.[12] The reaction is usually self-limiting once the drug is withdrawn, but fatalities have occurred.[12,13]

Aplastic anaemia has been reported.[14,15] Of 11 fatalities attributed to dapsone reported to the British and Swedish adverse reaction registers[16] between 1968 and 1988, seven were due to white blood cell dyscrasias; none were attributed to red cell dyscrasias, although such reactions formed almost half of all serious reactions reported for dapsone.

Pure red cell aplasia has been reported in an elderly patient taking oral dapsone daily for granuloma annulare.[17]

Thrombocytosis was reported in a patient with AIDS receiving dapsone prophylactically.[18]

See also Hypoalbuminaemia, p. 285.2.

1. Jopling WH. Side-effects of antileprosy drugs in common use. *Lepr Rev* 1983; **54:** 261–70.
2. Lachant NA, Tanaka KR. Case report: dapsone-associated Heinz body hemolytic anemia in a Cambodian woman with hemoglobin E trait. *Am J Med Sci* 1987; **294:** 364–8.
3. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.
4. Sanders SW, *et al.* Hemolytic anemia induced by dapsone transmitted through breast milk. *Ann Intern Med* 1982; **96:** 465–6.
5. Piette WW, *et al.* Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. *Arch Dermatol* 2008; **144:** 1564–70.
6. Ashurst JV, *et al.* Pathophysiologic mechanisms, diagnosis, and management of dapsone-induced methemoglobinemia. *J Am Osteopath Assoc* 2010; **110:** 16–20.
7. Seaton RA, *et al.* Blue and breathless. *Hosp Med* 1999; **60:** 530.
8. Ward KE, McCarthy MW. Dapsone-induced methemoglobinemia. *Ann Pharmacother* 1998; **32:** 549–53.
9. Coleman MD, *et al.* The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. *Br J Clin Pharmacol* 1990; **30:** 761–7.
10. Rhodes LE, *et al.* Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol* 1995; **132:** 257–62.
11. Firkin FC, Mariani AF. Agranulocytosis due to dapsone. *Med J Aust* 1977; **2:** 247–51.
12. Cockburn EM, *et al.* Dapsone-induced agranulocytosis: spontaneous reporting data. *Br J Dermatol* 1993; **128:** 702–3.
13. Barss P. Fatal dapsone agranulocytosis in a Melanesian. *Lepr Rev* 1986; **57:** 63–6.
14. Foucauld J, *et al.* Dapsone and aplastic anemia. *Ann Intern Med* 1985; **102:** 139.
15. Meyerson MA, Cohen PR. Dapsone-induced aplastic anaemia in a woman with bullous systemic lupus erythematosus. *Mayo Clin Proc* 1994; **69:** 1159–62.
16. Björkman A, Phillips-Howard PA. Adverse reactions to sulfa drugs: implications for malaria chemotherapy. *Bull WHO* 1991; **69:** 297–304.
17. Borrás-Blasco J, *et al.* Pure red cell aplasia associated with dapsone therapy. *Ann Pharmacother* 2005; **39:** 1137–8.
18. Wynn RF, *et al.* Case report of dapsone-related thrombocytosis in an AIDS patient. *Am J Med* 1995; **98:** 602.

Effects on the eyes. There have been rare reports[1-4] of ocular toxicity, usually resulting in permanent loss of visual acuity, after overdoses with dapsone. Toxic effects included blurring of vision,[1,2] optic atrophy,[1] ischaemic retinopathy, ischaemic optic neuropathy,[3] and bilateral macular infarction.[4] These effects were thought to be due to acute hypoxia and obstruction with red cell fragments. A case of anterior ischaemic optic neuropathy[5] has also been reported in a patient taking usual doses of dapsone for dermatitis herpetiformis.

1. Daneshmend TK. The neurotoxicity of dapsone. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 43–58.
2. Alexander TA, *et al.* Presumed DDS ocular toxicity. *Indian J Ophthalmol* 1989; **37:** 150–1.
3. Seo M-S, *et al.* Dapsone maculopathy. *Korean J Ophthalmol* 1997; **11:** 70–3.
4. Chakrabarti M, *et al.* Bilateral macular infarction due to diaminodiphenyl sulfone (4,4′ DDS) toxicity. *Retina* 1999; **19:** 83–4.
5. Chalioulias K, *et al.* Anterior ischaemic optic neuropathy associated with Dapsone. *Eye* 2006; **20:** 943–5.

Effects on the liver. Toxic hepatitis and cholestatic jaundice have been reported by licensed product information to occur early in dapsone therapy. Jaundice may also form part of the dapsone syndrome (see Hypersensitivity, p. 285.1). Deterioration in liver function tests during dapsone treatment has been noted in a patient with dermatitis herpetiformis and primary sclerosing cholangitis.[1]

1. Kirby B, *et al.* Abnormal liver function tests induced by dapsone in a patient with dermatitis herpetiformis and primary sclerosing cholangitis. *Br J Dermatol* 1999; **141:** 172–3.

Effects on the lungs. Hypersensitivity reactions to dapsone usually affect the skin, but there have been rare reports of dapsone hypersensitivity presenting with fever, wheezing, and pulmonary eosinophilia.[1-4] Pulmonary eosinophilia occurred in one patient taking dapsone for urticaria[1] and in another taking dapsone as part of the WHO multidrug treatment regimen for leprosy.[2] In both patient symptoms resolved when dapsone was stopped and occurred again on rechallenge. Another patient[3] known to develop fever and wheezing when taking dapsone for leprosy was given a dapsone challenge for 5 days. He became acutely ill and

had a high absolute eosinophil count; symptoms resolved 2 weeks after stopping dapsone.

1. Jaffuel D, *et al*. Eosinophilic pneumonia induced by dapsone. *BMJ* 1998; **317:** 181.
2. Kaur J, *et al*. Dapsone-induced eosinophilic pneumonitis in a leprosy patient. *Indian J Lepr* 2005; **77:** 267–71.
3. Arunthathi S, Raju S. Dapsone induced pulmonary eosinophilia without cutaneous allergic manifestations—an unusual encounter—a case report. *Acta Leprol* 1998; **11:** 3–5.
4. Janier M, *et al*. Pulmonary eosinophilia associated with dapsone. *Lancet* 1994; **343:** 860–1.

Effects on mental state. Psychiatric adverse effects have been reported in leprosy patients receiving dapsone, but the role of dapsone in this effect is poorly defined.[1-4] Manic-depressive reactions have been reported in 2 patients[2,3] with skin disorders and psychosis[4] was reported in a patient being treated for leprosy. These reactions appeared to be idiosyncratic reactions to dapsone. In all cases symptoms resolved when dapsone was stopped.

1. Daneshmend T. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; **299:** 324.
2. Carmichael AJ, Paul CJ. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; **298:** 1524. Correction. *ibid.*; **299:** 56.
3. Gawkrodger D. Manic depression induced by dapsone in patient with dermatitis herpetiformis. *BMJ* 1989; **299:** 860.
4. Balkrishna, Bhatia MS. Dapsone-induced psychosis. *J Indian Med Assoc* 1989; **87:** 120–1.

Effects on the nervous system. A case review[1] of 21 patients who had dapsone-induced neuropathy reported that the median time to onset of symptoms was about 1 year; with a range of 11 days to 18 years. Symptoms occurred in patients taking doses varying from 25 to 800 mg/day and after a total cumulative dose of 4 to 1500 g. Most patients had either pure motor or mixed sensory-motor neuropathies, while pure sensory neuropathy was rarely reported. Patients generally recovered, either partially or completely, within one year of stopping dapsone. Progressive multifocal leukoencephalopathy has been reported in a patient with SLE treated with a dapsone-containing regimen, although it was unclear what role dapsone had played.[2]

1. Méry L, *et al*. Polynévrite sensitive induite par la dapsone (Disulone). *Ann Dermatol Venereol* 2003; **130:** 447–9.
2. Stahl NI. Progressive multifocal leukoencephalopathy in a minimally immunosuppressed patient with systemic lupus erythematosus treated with dapsone. *J Rheumatol* 2008; **35:** 725–7.

Effects on the pancreas. Acute pancreatitis has been associated with the use of dapsone to treat dermatitis herpetiformis in an 87-year-old man.[1] Symptoms resolved on stopping dapsone but recurred upon rechallenge.

1. Jha SH, *et al*. Dapsone-induced acute pancreatitis. *Ann Pharmacother* 2003; **37:** 1438–40.

Effects on taste. A persistent sweet taste and tingling of the face and lips was described in a patient receiving dapsone for ocular cicatricial pemphigoid.[1] The symptoms resolved when dapsone was stopped.

1. Stafanous SN, Morgan SJ. A previously unrecognised side effect of dapsone. *Br J Ophthalmol* 1997; **81:** 1113–14.

Hyperpigmentation. Hyperpigmented macules were reported in 32 of about 800 children given dapsone with pyrimethamine for 3 months or more for malaria prophylaxis.[1] The reaction was attributed to dapsone.

1. David KP, *et al*. Hyperpigmented dermal macules in children following the administration of Maloprim for malaria chemoprophylaxis. *Trans R Soc Trop Med Hyg* 1997; **91:** 204–8.

Hypersensitivity. Dapsone syndrome is a rare idiosyncratic hypersensitivity reaction, although it has been suggested[1-3] that the incidence has increased since the introduction of multidrug therapy for leprosy. It usually occurs in the first 4 to 8 weeks of therapy, is not dose-related, and resolves within 14 days on stopping dapsone. Dapsone syndrome may also occur within 1 to 2 weeks of stopping the drug, due to its long elimination half-life and high protein binding.[4] Common clinical symptoms may include exanthematous rash, fever, hepatitis (cholestatic and hepatocellular injuries), eosinophilia, lymphadenopathy, and mononucleosis. The syndrome has occurred in leprosy patients,[5,6] in patients with skin disorders,[7] in patients with AIDS taking dapsone for prophylaxis of pneumocystis pneumonia,[4] and in patients taking weekly dapsone (with pyrimethamine) for malaria prophylaxis.[8] Fatalities have occurred.[9,10] Desensitisation has been successfully carried out in several patients with AIDS who had hypersensitivity to dapsone.[11,12]

1. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Lepr Rev* 1989; **60:** 267–73.
2. Kumar RH, *et al*. Dapsone syndrome—a five year retrospective analysis. *Indian J Lepr* 1998; **70:** 271–6.
3. Rao PN, Lakshmi TSS. Increase in the incidence of dapsone hypersensitivity syndrome—an appraisal. *Lepr Rev* 2001; **72:** 57–62.
4. Lee KB, Nashed TB. Dapsone-induced sulfone syndrome. *Ann Pharmacother* 2003; **37:** 1044–6.
5. Alves-Rodrigues EN, *et al*. Dapsone syndrome with acute renal failure during leprosy treatment: case report. *Braz J Infect Dis* 2005; **9:** 84–6.
6. Bucaretchi F, *et al*. Dapsone hypersensitivity syndrome in an adolescent during treatment during [sic] of leprosy. *Rev Inst Med Trop Sao Paulo* 2004; **46:** 331–4.
7. Sener O, *et al*. Severe dapsone hypersensitivity syndrome. *J Investig Allergol Clin Immunol* 2006; **16:** 268–70.
8. Tee AKH, *et al*. Dapsone hypersensitivity syndrome masquerading as a viral exanthem: three cases and a mini-review. *Ann Acad Med Singapore* 2004; **33:** 375–8.
9. Frey HM, *et al*. Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; **94:** 777–9.
10. Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. *J Dermatol* 2005; **32:** 883–9.
11. Metroka CE, *et al*. Desensitization to dapsone in HIV-positive patients. *JAMA* 1992; **267:** 512.
12. Cook DE, Kossey JL. Successful desensitization to dapsone for Pneumocystis carinii prophylaxis in an HIV-positive patient. *Ann Pharmacother* 1998; **32:** 1302–5.

Hypoalbuminaemia. Severe and often life-threatening hypoalbuminaemia has been reported rarely in patients taking dapsone for long periods for dermatitis herpetiformis.[1-3] Hypoalbuminaemia usually resolves rapidly once dapsone is withdrawn.

1. Kingham JGC, *et al*. Dapsone and severe hypoalbuminaemia. *Lancet* 1979; **ii:** 662–4 and 1018.
2. Foster PN, Swan CHJ. Dapsone and fatal hypoalbuminaemia. *Lancet* 1981; **ii:** 806–7.
3. Sinclair SA, *et al*. Life threatening hypoalbuminaemia associated with dapsone therapy. *Br J Dermatol* 1996; **135** (suppl 47): 45.

Photosensitivity. Dapsone-induced photosensitivity is rare and has been reported mainly among patients being treated for leprosy.[1,2] Among 11 reported cases, skin lesions occurred after 5 to 34 weeks (mean 13 weeks) of dapsone therapy; in 8 cases, the severity required that dapsone be stopped. Systemic corticosteroids, antihistamines, and sunscreen lotions have typically been the mainstay of treatment.[1]

Dapsone-induced photosensitivity can be mimicked by polymorphous light eruption, chronic actinic dermatitis, pellagra, and rarely porphyria cutanea tarda or SLE; it may also occur as part of dapsone syndrome (see under Hypersensitivity, above).[1,2]

1. De D, *et al*. Dapsone induced acute photosensitivity dermatitis; a case report and review of literature. *Lepr Rev* 2007; **78:** 401–4.
2. Kar BR. Dapsone-induced photosensitivity: a rare clinical presentation. *Photodermatol Photoimmunol Photomed* 2008; **24:** 270–1.

Treatment of Adverse Effects

In severe overdosage, repeated oral doses of activated charcoal should be given with the aim of preventing absorption of dapsone but also to aid the elimination of dapsone and its monoacetyl metabolite. Methaemoglobinaemia has been treated with slow intravenous injections of methylthioninium chloride 1 to 2 mg/kg repeated after 30 to 60 minutes if necessary; due to the long half-life of dapsone and its metabolites, serious overdoses will usually require regular dosing every 6 to 8 hours for 2 to 3 days. Methylthioninium chloride should not be given to patients with G6PD deficiency since it will not be effective. Haemolysis has been treated by infusion of concentrated human red blood cells to replace the damaged cells. Supportive therapy includes giving oxygen and fluids.

Patients who develop dapsone syndrome (see Hypersensitivity, above) may require several weeks of corticosteroid therapy.

Overdosage. References.

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; **4:** 387–92.
2. Endre ZH, *et al*. Successful treatment of acute dapsone intoxication using charcoal hemoperfusion. *Aust N Z J Med* 1983; **13:** 509–12.
3. Hoetelmans RMW, *et al*. Combined dapsone and clofazimine intoxication. *Hum Exp Toxicol* 1996; **15:** 625–8.
4. Ferguson AJ, Lavery GG. Deliberate self-poisoning with dapsone: a case report and summary of relevant pharmacology and treatment. *Anaesthesia* 1997; **52:** 359–63.
5. Southgate HJ, Masterson R. Lessons to be learned: a case study approach: prolonged methaemoglobinaemia due to inadvertent dapsone poisoning; treatment with methylene blue and exchange transfusion. *J R Soc Health* 1999; **119:** 52–5.
6. Park KH, *et al*. Dapsone intoxication: clinical course and characteristics. *Clin Toxicol* 2010; **48:** 516–21.

Precautions

Dapsone should not be used in patients with severe anaemia. It is recommended that regular blood counts be performed during treatment. Patients deficient in G6PD or methaemoglobin reductase, or with haemoglobin M are more susceptible to the haemolytic effects of dapsone. Dapsone contains the sulfa moiety ($-SO_2NH_2$) and the UK licensed product information states that it is contra-indicated in patients with a sulfonamide (sulfa) or sulfone allergy. For further information on cross-reactivity between sulfa-containing drugs see Hypersensitivity, under Sulfamethoxazole, p. 367.3.

Where possible, liver function should be monitored during treatment.

The benefits of dapsone in the treatment of leprosy during pregnancy are thought to outweigh any potential risks to the pregnant patient or fetus. Some recommend folic acid 5 mg daily for leprosy patients receiving dapsone during pregnancy.

Breast feeding. Dapsone is distributed into breast milk and the last available guidance from the American Academy of Pediatrics[1] stated that, although usually compatible with breast feeding, use of dapsone in a breast-feeding mother has resulted in sulfonamide detected in the infant's urine.[2] There has also been a report of haemolytic anaemia in a breast-fed infant (see Effects on the Blood, under Adverse Effects, p. 282.2). A study in 3 women who were given a single dose of dapsone 100 mg plus pyrimethamine and chloroquine estimated that if their infants were breast-fed they would receive 4.6, 10, or 14.3%, respectively, of the maternal dose in the 9-day period after it was given.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Dreisbach JA. Sulphone levels in breast milk of mothers on sulphone therapy. *Lepr Rev* 1952; **23:** 101–6.
3. Edstein MD, *et al*. Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22:** 733–5.

Porphyria. Although dapsone has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] both Porphyria South Africa[2] and the European Porphyria Network[3] classify dapsone as unsafe and recommend it be avoided in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)
2. Porphyria South Africa. Available at: http://web.uct.ac.za/depts/porphyria/ (accessed 12/10/11)
3. European Porphyria Network. Available at: http://www.porphyria-europe.com (accessed 12/10/11)

Pregnancy. References.

1. Brabin BJ, *et al*. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Safety* 2004; **27:** 633–48.

Interactions

Serum concentrations of dapsone are increased, with a consequent increased risk of adverse effects, when given with probenecid, probably as a result of reduced renal excretion of dapsone. Increased dapsone and trimethoprim concentrations have also been reported in patients receiving both drugs, who may similarly be at greater risk of dapsone toxicity. Rifampicin reduces serum concentrations of dapsone to a level that may compromise efficacy in infections other than leprosy. Rifampicin concentrations are generally unaffected. Dapsone may reduce the anti-inflammatory effects of clofazimine (p. 274.2).

Antibacterials. In a study of AIDS patients with pneumocystis pneumonia, the mean peak serum concentrations of dapsone after 7 days were 1.5 micrograms/mL after 100 mg daily and 2.1 micrograms/mL after the same dose with *trimethoprim* 20 mg/kg daily; concentrations of trimethoprim were also increased.[1] Elevated dapsone concentrations may contribute to the toxicity and the efficacy of this combination.

1. Lee BL, *et al*. Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of Pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989; **110:** 606–11.

Antimalarials. Although some licensed product information has warned that dapsone-induced haematotoxicity could be potentiated by folic acid antagonists such as *pyrimethamine*, the tolerability of dapsone plus pyrimethamine was similar to dapsone alone when each treatment was given on a once-weekly basis to patients with HIV infection.[1] Dapsone concentrations were not significantly higher in patients receiving dapsone plus pyrimethamine than in those receiving dapsone alone.

1. Falloon J, *et al*. Pharmacokinetics and safety of weekly dapsone and dapsone plus pyrimethamine for prevention of pneumocystis pneumonia. *Antimicrob Agents Chemother* 1994; **38:** 1580–7.

Gastrointestinal drugs. *Cimetidine* has been reported to increase the area under the curve for dapsone, but to decrease the area under the curve for the metabolite dapsone hydroxylamine. Haematotoxicity is thought to be related to production of this metabolite (see Effects on the Blood, p. 282.2).

Antimicrobial Action

Dapsone is a sulfone active against many bacteria and some protozoa, but it is mainly used for its action against *Mycobacterium leprae*. Like the sulfonamides it may inhibit folic acid synthesis in susceptible organisms although this is not considered to be the mechanism of action in *M. leprae*. It is usually considered to be bacteriostatic against *M. leprae*, although it may also possess weak bactericidal activity. As with the sulfonamides, antibacterial activity is inhibited by

p-aminobenzoic acid. Dapsone is also active against *Pneumocystis jirovecii*. *Plasmodium falciparum* is generally only moderately susceptible, but the drug's antiplasmodial activity is markedly increased when used with a dihydrofolate reductase inhibitor such as pyrimethamine (p. 662.3).

Secondary (acquired) dapsone resistance of *M. leprae* is mainly associated with dapsone being used on its own. Primary dapsone resistance has also been reported with increasing frequency in areas with secondary resistance. Resistance of *M. leprae* to dapsone should be suspected whenever a patient relapses clinically and bacteriologically.

Drug resistance. Monotherapy with dapsone was the standard of treatment for all forms of leprosy until the 1980's, when concerns about dapsone resistance led WHO to introduce a multidrug treatment (MDT) regimen consisting of dapsone, rifampicin, and clofazimine. Long-term follow-up studies[1,2] designed to evaluate the efficacy of WHO MDT regimen reported relapse rates of 1.1 to 9% after a minimum of 2 years treatment. Drug sensitivity analyses were reported for 15 of these patients; no resistance to clofazimine or rifampicin was reported, while isolates from 3 patients showed dapsone resistance.[1] An evaluation of drug resistance after the introduction of WHO MDT regimen in Nepal[3] concluded that secondary resistance to dapsone does not develop under this regimen. In a 25-year follow-up study,[4] re-treatment with an alternative dapsone-containing MDT (rifampicin 1.2 g plus clofazimine 1.2 g given *once a month*, plus dapsone 100 mg daily for 1 year) significantly reduced the rate of relapse among multibacillary leprosy patients previously treated with dapsone monotherapy. Strains of *Mycobacterium leprae* with multiple resistance to rifampicin, ofloxacin, and dapsone have been isolated from a patient who had previously received dapsone monotherapy followed by treatment with rifampicin plus ofloxacin for 28 days.[5]

1. Cellona RV, *et al.* Long-term efficacy of 2 year WHO multiple drug therapy (MDT) in multibacillary (MB) leprosy patients. *Int J Lepr Other Mycobact Dis* 2003; **71:** 308–19.
2. Norman G, *et al.* Relapses in multibacillary patients treated with multidrug therapy until smear negativity: findings after twenty years. *Int J Lepr Other Mycobact Dis* 2004; **72:** 1–7.
3. Roche PW, *et al.* Dapsone drug resistance in the MDT era. *Int J Lepr Other Mycobact Dis* 2000; **68:** 323–5.
4. Jing Z, *et al.* Twenty five years follow up of MB leprosy patients retreated with a modified MDT regimen after a full course of dapsone monotherapy. *Lepr Rev* 2009; **80:** 170–6.
5. Cambau E, *et al.* Multidrug-resistance to dapsone, rifampicin, and ofloxacin in Mycobacterium leprae. *Lancet* 1997; **349:** 103–4.

Pharmacokinetics

Dapsone is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 8 hours after a dose. Steady-state concentrations are not attained until after at least 8 days of daily dosage; doses of 100 mg daily provide trough concentrations of 500 nanograms/mL, which are well in excess of the MIC for *M. leprae*. About 70 to 90% of dapsone in the circulation is bound to plasma proteins and nearly 100% of its monoacetylated metabolite is bound. Only very small amounts are absorbed after topical application.

Dapsone undergoes enterohepatic recycling. It is widely distributed; it is present in saliva and breast milk and crosses the placenta. The half-life ranges from 10 to 50 hours; with a mean of 20 to 30 hours.

Dapsone is acetylated to monoacetyldapsone, the major metabolite, and other mono and diacetyl derivatives. Acetylation shows genetic polymorphism. Hydroxylation is the other major metabolic pathway resulting in hydroxylamine dapsone, which may be responsible for dapsone-associated methaemoglobinaemia and haemolysis.

Dapsone is mainly excreted in the urine, only 20% of a dose as unchanged drug.

References.
1. Zuidema J, *et al.* Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet* 1986; **11:** 299–315.
2. May DG, *et al.* The disposition of dapsone in cirrhosis. *Clin Pharmacol Ther* 1992; **51:** 689–700.
3. Mirochnick M, *et al.* Pharmacokinetics of dapsone in children. *J Pediatr* 1993; **122:** 806–9.
4. Opravil M, *et al.* Levels of dapsone and pyrimethamine in serum during once-weekly dosing for prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Antimicrob Agents Chemother* 1994; **38:** 1197–9.
5. Gatti G, *et al.* Penetration of dapsone into cerebrospinal fluid of patients with AIDS. *J Antimicrob Chemother* 1997; **40:** 113–15.
6. Mirochnick M, *et al.* Pharmacokinetics of dapsone administered daily and weekly in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1999; **43:** 2586–91.
7. Mirochnick M, *et al.* Population pharmacokinetics of dapsone in children with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2001; **70:** 24–32.
8. Thiboutot DM, *et al.* Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. *Clin Pharmacokinet* 2007; **46:** 697–712.

Metabolism. Measurement of the relative activity of the two main routes of dapsone metabolism (acetylation and hydroxylation) suggests that the risk of adverse effects is greater in individuals in whom the *N*-hydroxylation route predominates.[1] This is consistent with the hypothesis that the toxicity of dapsone is related to production of an active metabolite. See also Effects on the Blood, p. 282.2.

1. Bluhm RE, *et al.* Development of dapsone toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapsone as risk factors. *Clin Pharmacol Ther* 1999; **65:** 598–605.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daps†; ***Canad.***: Aczone; ***Gr.***: Sulfona; ***India***: Acnesone; ***Mex.***: Dapsoderm-X; ***Philipp.***: Lepravir; ***Port.***: Sulfona; ***Spain***: Sulfona†; ***Thai.***: Dopsan; ***USA***: Aczone.

Multi-ingredient Preparations. ***Austral.***: Maloprim†; ***Austria***: Isoprodian†; ***Fr.***: Disulone; ***Singapore***: Pyrisone; ***Thai.***: Lepromix MB; Lepromix PB.

Pharmacopoeial Preparations
BP 2014: Dapsone Tablets;
USP 36: Dapsone Oral Suspension; Dapsone Tablets.

Daptomycin *(BAN, USAN, rINN)*

Daptomicina; Daptomycine; Daptomycinum; LY-146032; Даптомицин.

N-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonyl-glycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine 1.13-3,4-lactone.

$C_{72}H_{101}N_{17}O_{26}$=1620.7

CAS — 103060-53-3.
ATC — J01XX09.
ATC Vet — QJ01XX09.
UNII — NWQ5N31VKK.

Uses and Administration

Daptomycin is given for the treatment of complicated Gram-positive infections of the skin and skin structures, and *Staphylococcus aureus* bacteraemia, including right-sided endocarditis, caused by meticillin-susceptible and meticillin-resistant strains.

For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

For the treatment of skin and soft-tissue infections, daptomycin is given by intravenous infusion over 30 minutes, or by intravenous injection over 2 minutes, in a dose of 4 mg/kg once daily for 7 to 14 days. A higher dose of 6 mg/kg once daily is given for 2 to 6 weeks in the treatment of bacteraemia.

For details of dosage modification in patients with renal impairment, see p. 286.2.

Daptomycin has also been investigated for use in other indications, including vancomycin-resistant enterococcal infections and complicated urinary-tract infections.

References.
1. Fenton C, *et al.* Daptomycin. *Drugs* 2004; **64:** 445–55.
2. Steenbergen JN, *et al.* Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 2005; **55:** 283–8.
3. Schriever CA, *et al.* Daptomycin: a novel cyclic lipopeptide antimicrobial. *Am J Health-Syst Pharm* 2005; **62:** 1145–58.
4. French GL. Bactericidal agents in the treatment of MRSA infections—the potential role of daptomycin. *J Antimicrob Chemother* 2006; **58:** 1107–17.
5. Hair PI, Keam SJ. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs* 2007; **67:** 1483–1512.
6. Enoch DA, *et al.* Daptomycin. *J Infect* 2007; **55:** 205–13.
7. Weis F, *et al.* Daptomycin, a lipopeptide antibiotic in clinical practice. *Curr Opin Investig Drugs* 2008; **9:** 879–84.
8. Forrest GN, *et al.* Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother* 2008; **42:** 213–17.
9. Levine DP. Clinical experience with daptomycin: bacteraemia and endocarditis. *J Antimicrob Chemother* 2008; **62** (suppl 3): iii35–iii39.
10. Warren RE. Daptomycin in endocarditis and bacteraemia: a British perspective. *J Antimicrob Chemother* 2008; **62** (suppl 3): iii25–iii33.
11. Gould IM. Who's winning the war? *J Antimicrob Chemother* 2008; **62** (suppl 3): iii3–iii6.
12. Sakoulas G. Clinical outcomes with daptomycin: a post-marketing, real-world evaluation. *Clin Microbiol Infect* 2009; **15** (suppl 6): 11–6.
13. Bliziotis IA, *et al.* Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections: a meta-analysis. *Ann Pharmacother* 2010; **44:** 97–106.
14. Kosmidis C, Levine DP. Daptomycin: pharmacology and clinical use. *Expert Opin Pharmacother* 2010; **11:** 615–25.

Administration in renal impairment. Licensed product information recommends that in patients with a creatinine clearance of less than 30 mL/minute, including those receiving haemodialysis or peritoneal dialysis, the intravenous dosage of daptomycin should be modified to 4 mg/kg once every 48 hours in the treatment of skin and soft-tissue infections, and to 6 mg/kg once every 48 hours in the treatment of bacteraemia.

Alternatively, a review[1] has suggested that critically ill patients undergoing intermittent haemodialysis be given a dose of 4 to 6 mg/kg every 48 to 72 hours (after dialysis). For those undergoing continuous renal replacement therapy, 4 to 6 mg/kg every 48 hours is recommended, although a dose of 4 to 6 mg/kg every 24 hours or 8 mg/kg every 48 hours can be considered for patients with deep-seated infections, or those who do not respond to standard doses; serum-drug concentration measurements and frequent monitoring of serum-creatinine kinase levels should be considered when these larger doses are used.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

High-dose therapy. Due to concerns regarding clinical failure and emergence of resistance, some have questioned whether the standard 4- to 6-mg/kg daily dose for daptomycin is sufficient,[1,2] particularly for deep-seated infections with heavy bacterial load.[3] In some case reports,[4,5] clinical success occurred after higher doses where standard doses had failed. In a retrospective study[6] of 61 patients treated with daptomycin, a mean dose of 8 mg/kg daily (range 7 to 11 mg/kg daily) for a median duration of 25 days was well tolerated; although 3 patients (4.9%) had symptomatic elevations in creatine phosphokinase, all cases resolved once the drug was stopped.

1. Cosgrove SE, Corey GR. A balancing act: microbe versus muscle. *Clin Infect Dis* 2009; **49:** 181–3.
2. Moise PA, *et al.* Safety and clinical outcomes when utilizing high-dose (≥8 mg/kg) daptomycin therapy. *Ann Pharmacother* 2009; **43:** 1211–9.
3. Livermore DM. Future directions with daptomycin. *J Antimicrob Chemother* 2008; **62** (suppl 3): iii41–iii49.
4. Cunha BA, *et al.* Pacemaker-induced Staphylococcus aureus mitral valve acute bacterial endocarditis complicated by persistent bacteremia from a coronary stent: cure with prolonged/high-dose daptomycin without toxicity. *Heart Lung* 2006; **35:** 207–11.
5. Cunha BA, *et al.* Methicillin-resistant Staphylococcus aureus (MRSA) mitral valve acute bacterial endocarditis (ABE) in a patient with Job's syndrome (hyperimmunoglobulin E syndrome) successfully treated with linezolid and high-dose daptomycin. *Heart Lung* 2008; **37:** 72–5.
6. Figueroa DA, *et al.* Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. *Clin Infect Dis* 2009; **49:** 177–80.

Adverse Effects and Precautions

The most common adverse effects associated with daptomycin are gastrointestinal effects including nausea and vomiting, constipation, diarrhoea, and dyspepsia. Headache, insomnia, dizziness, and fever may occur. Injection site reactions have occurred. Effects on the skin have included rash and pruritus. Abnormal liver function tests and jaundice have been reported. Other reported adverse effects include hypertension or hypotension, renal failure, dyspnoea, and anaemia. There have been rare cases of hypersensitivity, anaphylaxis, infusion reactions, and eosinophilic pneumonia.

Elevated plasma creatine phosphokinase (CPK) concentrations during daptomycin therapy may be associated with muscle pain and/or weakness, myositis, myopathy, and rarely rhabdomyolysis; patients with renal impairment or taking other drugs known to cause myopathy (see Interactions, p. 287.1) may be at increased risk. All patients should be monitored for the development of muscle pain or weakness, and plasma CPK concentrations measured once weekly. More frequent measurements should be performed in those with an increased risk of myopathy, or with a baseline CPK concentration greater than 5 times the upper limit of normal (ULN), or who develop signs of myopathy. Daptomycin should be stopped in patients with signs of myopathy and CPK concentrations greater than 5 times the ULN, or in those without reported signs of myopathy but with CPK concentrations greater than 10 times the ULN.

Daptomycin should be given with caution and in reduced dosage to patients with renal impairment; clinical response and renal function should be monitored closely.

Consideration should be given to stopping daptomycin therapy in patients who develop signs or symptoms of peripheral neuropathy.

Effects on the lungs. Bronchiolitis obliterans organising pneumonia with eosinophilic infiltration has been reported in an 84-year-old man after 4 weeks of daptomycin therapy;[1] clinical improvement occurred after the drug was stopped. The mechanism of toxicity was unknown and the authors suggested that it might be associated with epithelial injury caused by daptomycin accumulating in the alveolar spaces.

A 60-year-old man receiving daptomycin developed eosinophilic pneumonia resulting in respiratory failure that required mechanical ventilation;[2] he improved after stopping the drug and starting corticosteroid therapy. Chronic corticosteroid-dependent pneumonitis has also been reported in two elderly patients after they developed eosinophilic pneumonia during daptomycin therapy.[3]

The FDA identified 7 cases of eosinophilic pneumonia between 2004 and 2010 that were most likely associated with daptomycin. The ages of the patients ranged from 60 to 87 years. Eosinophilic pneumonia generally developed 2 to 4 weeks after starting treatment and all patients reported improvement or resolution of symptoms when daptomycin

was stopped; 5 patients were also given systemic corticosteroid therapy. Two patients were rechallenged with daptomycin and eosinophilic pneumonia recurred.[4]

1. Cobb E, *et al.* Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. *Ann Pharmacother* 2007; **41:** 696–701.
2. Hayes D, *et al.* Eosinophilic pneumonia induced by daptomycin. *J Infect* 2007; **54:** e211–e213.
3. Lal Y, Assimacopoulos AP. Two cases of daptomycin-induced eosinophilic pneumonia and chronic pneumonitis. *Clin Infect Dis* 2010; **50:** 737–40.
4. FDA. FDA drug safety communication: eosinophilic pneumonia associated with the use of Cubicin (daptomycin) (issued 29th July, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220273.htm (accessed 15/10/10)

Pregnancy. Intravenous daptomycin, 4 mg/kg daily for 14 days, was successfully used to treat pyelonephritis associated with vancomycin-resistant enterococci (VRE) in a 27-week pregnant woman; no neonatal abnormalities were reported.[1]

1. Shea K, *et al.* Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. *Ann Pharmacother* 2008; **42:** 722–5.

Interactions

There may be an increased risk of myopathy if daptomycin is given with other drugs also known to have this adverse effect, such as statins, fibrates, and ciclosporin. Licensed product information recommends stopping the latter if possible; otherwise, plasma creatine phosphokinase concentrations should be measured more than once weekly in addition to the usual precautions (see Adverse Effects and Precautions, p. 284.3).

Daptomycin is mainly excreted by renal filtration and caution is advised if given with drugs that reduce renal filtration, such as NSAIDs and selective inhibitors of cyclooxygenase-2, since plasma concentrations of daptomycin may be increased.

Daptomycin has been reported to interact with a particular reagent used in some assays of PT-INR resulting in apparent prolongation of PT and elevation of INR.

Antimicrobial Action

Daptomycin is a lipopeptide antibacterial that is reported to have a spectrum of antibacterial activity similar to that of vancomycin (p. 389.1) and greater potency against most Gram-positive bacterial strains *in vitro*; it is inactive against Gram-negative bacteria. Daptomycin disrupts the bacterial cell membrane potential by binding to the cell membranes in a calcium-dependent process, but without entering the cytoplasm, thus inhibiting the synthesis of protein, DNA, and RNA.

Daptomycin has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci.

It is reported to show antimicrobial synergy *in vitro* with aminoglycosides, beta lactams, and rifampicin against *Staph. aureus* (including meticillin-resistant strains) and enterococci (including vancomycin-resistant strains).

Resistance to daptomycin has been shown in clinical studies but only rarely; the mechanism of resistance has not been identified.

Reviews.

1. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in Staphylococcus aureus. *Clin Infect Dis* 2007; **45:** 601–8.

Pharmacokinetics

Daptomycin is not absorbed to any significant extent after oral doses. The pharmacokinetics of daptomycin are generally linear at intravenous doses ranging from 4 to 12 mg/kg once daily. Peak plasma concentrations occur within 0.5 to 0.8 hours. It is distributed mainly into the extracellular space with a volume of distribution of about 0.1 litres/kg. Daptomycin crosses the blood-brain barrier and the placenta. It is about 90% bound to plasma proteins, mainly serum albumin.

In-vitro studies indicate that daptomycin is not metabolised by, and does not affect, the cytochrome P450 isoenzyme system. Little or no metabolism is thought to take place although 4 minor metabolites have been detected in the urine.

Daptomycin is excreted mainly via renal filtration with about 78% and 6% of a dose recovered in the urine and faeces, respectively. It has an elimination half-life of about 8 hours after an intravenous dose of 4 mg/kg once daily for 7 days and is prolonged in patients with renal impairment; a two- to threefold increase has been reported in those with severe impairment or end-stage renal disease.

Daptomycin is removed by haemodialysis or peritoneal dialysis.

References.

1. Dvorchik B, *et al.* Population pharmacokinetics of daptomycin. *Antimicrob Agents Chemother* 2004; **48:** 2799–2807.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cubicin; ***Austral.***: Cubicin; ***Austria***: Cubicin; ***Braz.***: Cubicin; ***Canad.***: Cubicin; ***China***: Cubicin (克必信); ***Cz.***: Cubicin; ***Denm.***: Cubicin; ***Fr.***: Cubicin; ***Ger.***: Cubicin; ***Gr.***: Cubicin; ***Hong Kong***: Cubicin; ***Irl.***: Cubicin; ***Israel***: Cubicin; ***Ital.***: Cubicin; ***Jpn***: Cubicin; ***Malaysia***: Cubicin; ***Neth.***: Cubicin; ***Norw.***: Cubicin; ***NZ***: Cubicin; ***Philipp.***: Cubicin; ***Pol.***: Cubicin; ***Port.***: Cubicin; ***Rus.***: Cubicin (Кубицин); ***Singapore***: Cubicin; ***Spain***: Cubicin; ***Swed.***: Cubicin; ***Switz.***: Cubicin; ***Thai.***: Cubicin; ***Turk.***: Cubicin; ***UK***: Cubicin; ***Ukr.***: Cubicin (Кубицин); ***USA***: Cubicin.

Delamanid *(USAN, rINN)*

Délamanid; Delamanidum; OPC-67683; Деламанид.

(2*R*)-2-Methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*]oxazole.

$C_{25}H_{25}F_3N_4O_6$=534.5

CAS — 681492-22-8.

UNII — 8OOT6M1PC7.

Profile

Delamanid is an antimycobacterial under investigation for the treatment of multidrug-resistant tuberculosis. It is an orally active imidazole derivative that inhibits mycolic acid synthesis.

References.

1. Gler MT, *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; **366:** 2151–60.

Demeclocycline *(BAN, rINN)*

Demeclociclina; Demeclocyclin; Déméclocycline; Demeclocyclinum; Demeklocyklin; Demeklosiklin; Demeklosykliini; Demethylchlortetracycline; Демеклоциклин.

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyltetracycline.

$C_{21}H_{21}ClN_2O_8$=464.9

CAS — 127-33-3 (demeclocycline); 13215-10-6 (demeclocycline sesquihydrate).

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.

UNII — 5R5W9ICI6O.

Pharmacopoeias. In *US.*

USP 36: (Demeclocycline). A yellow, odourless crystalline powder. Sparingly soluble in water; soluble 1 in 200 of alcohol and 1 in 40 of methyl alcohol; dissolves readily in 3N hydrochloric acid and in alkaline solutions. pH of a 1% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Demeclocycline Hydrochloride *(BANM, rINNM)*

Demeclociclina, hidrocloruro de; Déméclocycline, Chlorhydrate de; Demeclocyclinhydrochlorid; Demeclocyclini hydrochloridum; Demeklociklin-hidroklorid; Demeklociklino hidrochloridas; Demeklocyklin-hydrochlorid; Demeklocyklin-hydroklorid; Demeklocykliny chlorowodorek; Demeklosiklin Hidroklorür; Demeklosykliinihydrokloridi; Demethylchlortetracycline Hydrochloride; Hidrocloruro de demeclociclina; Демеклоциклина Гидрохлорид.

$C_{21}H_{21}ClN_2O_8$,HCl=501.3

CAS — 64-73-3.

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.

UNII — 29O079NTYT.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Demeclocycline Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Soluble or sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

USP 36: (Demeclocycline Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 60 of water and 1 in 50 of methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone and in chloroform; sparingly soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Uses and Administration

Demeclocycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.3). It is excreted more slowly and effective blood concentrations are maintained for a longer period.

Demeclocycline is given orally as the hydrochloride; the usual adult dose for susceptible **infections** is 600 mg daily in 2 or 4 divided doses, preferably 1 hour before or 2 hours after meals. For atypical pneumonia, 900 mg daily in 3 divided doses may be given. It has also sometimes been given orally with other tetracycline derivatives.

For details of doses in children, and in patients with hepatic impairment, see p. 287.3.

Demeclocycline may also be given to adults in the treatment of chronic **hyponatraemia** associated with the syndrome of inappropriate antidiuretic hormone secretion, when water restriction has proved ineffective. Initially 900 to 1200 mg is given daily in divided doses, reducing to maintenance doses of 600 to 900 mg daily. For further information see p. 287.3.

The calcium and magnesium salts of demeclocycline have also been used.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential; demeclocycline (given as the hydrochloride) may be used for the treatment of susceptible infections. In the UK, it is licensed for use in children aged 12 years and over; the usual adult dose (see Uses and Administration, above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 7 to 13 mg/kg (maximum 600 mg) daily in 2 or 4 divided doses.

Administration in hepatic impairment. UK licensed product information states that the oral dosage of demeclocycline should not exceed 1 g daily in patients with known liver disease.

Syndrome of inappropriate ADH secretion. Demeclocycline may be given to reduce hyponatraemia in the treatment of the syndrome of inappropriate ADH (antidiuretic hormone) secretion (SIADH—p. 2351.2) by antagonising the effect of ADH on the renal tubules; lithium has been given as an alternative. Both lithium and demeclocycline act by interfering with the cellular action of ADH to produce nephrogenic diabetes insipidus. Demeclocycline was reported to be superior to lithium[1] and may be better tolerated than urea for chronic SIADH, although fluid restriction is probably still the treatment of choice.[2] However, since nephrotoxicity has been reported in patients with cardiac or hepatic disease, the usefulness of demeclocycline in the treatment of hyponatraemic states might be limited; this view was supported by studies in patients with heart failure[3] and cirrhosis.[4]

1. Forrest JN, *et al.* Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978; **298:** 173–7.
2. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356:** 2064–72.
3. Zegers de Beyl D, *et al.* Demeclocycline treatment of water retention in congestive heart failure. *BMJ* 1978; **1:** 760.
4. Miller PD, *et al.* Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *JAMA* 1980; **243:** 2513–15.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Phototoxic reactions occur more frequently with demeclocycline than with other tetracyclines and patients should avoid direct exposure to sunlight or artificial ultraviolet light.

Reversible nephrogenic diabetes insipidus with polyuria, polydipsia, and weakness may occur in patients treated with demeclocycline, particularly with prolonged treatment and/or high doses. Plasma creatinine should be monitored in patients receiving demeclocycline for long periods for the treatment of inappropriate secretion of antidiuretic hormone, since tetracycline-induced renal impairment may not otherwise be apparent in the absence of oliguria. For a comment that the usefulness of demeclocycline for this indication may be limited by nephrotoxicity in patients with cardiac or hepatic disease, see Syndrome of Inappropriate ADH Secretion under Uses and Administration, above.

Interactions

As for Tetracycline, p. 377.3.

Antimicrobial Action

As for Tetracycline, p. 377.3.

Demeclocycline is stated to be somewhat more active against certain strains of some organisms including *Neisseria gonorrhoeae* and *Haemophilus influenzae*, as well as to being the most active of the tetracyclines *in vitro* against *Brucella* spp.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

About 60 to 80% of a dose of demeclocycline is absorbed from the gastrointestinal tract. Peak plasma concentrations of about 1.5 to 1.7 micrograms/mL have been reported 3 to 4 hours after a single oral dose of 300 mg, but higher plasma concentrations may be achieved with repeated dosage. Its plasma elimination half-life is about 12 hours, although this may be prolonged in patients with renal impairment; values of 42 to 68 hours have been reported in severe impairment. The renal clearance of demeclocycline is about half that of tetracycline.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Alkonatrem; ***Gr.***: Ledermycin; ***India***: Ledermycin; ***Neth.***: Ledermycin; ***UK***: Ledermycin†; ***USA***: Declomycin.

Multi-ingredient Preparations. ***Ger.***: Ledermix; ***Hong Kong***: Ledermix; ***Irl.***: Ledermix; ***Israel***: Ledermix; ***S.Afr.***: Tritet†; ***Switz.***: Ledermix; ***UK***: Ledermix.

Pharmacopoeial Preparations

BP 2014: Demeclocycline Capsules;
USP 36: Demeclocycline Hydrochloride Capsules; Demeclocycline Hydrochloride Tablets; Demeclocycline Oral Suspension.

Dibekacin Sulfate *(BANM, rINNM)*

Dibekacin Sulphate; Dibekacina, sulfato de; Dibékacine, Sulfate de; Dibekacini Sulfas; Sulfato de dibekacina; Дибекацина Сульфат; 3′,4′-Dideoxykanamycin B.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl)-streptamine sulphate.

$C_{18}H_{37}N_5O_8.xH_2SO_4$

CAS — 34493-98-6 (dibekacin); 58580-55-5 (dibekacin sulfate).
ATC — J01GB09.
ATC Vet — QJ01GB09.
UNII — A08691992Z.

Pharmacopoeias. In *Jpn*.

Profile

Dibekacin is an aminoglycoside antibacterial derived from kanamycin with actions and uses similar to those of gentamicin (p. 306.2). It has been given intramuscularly as the sulfate in doses equivalent to dibekacin 1 to 3 mg/kg daily in divided doses. It has also been given in similar doses by slow intravenous infusion. Dosage should be adjusted based on serum-dibekacin concentration monitoring. It has also been used topically for eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Pratonil; Rolimycin; ***Jpn***: Panimycin; ***Venez.***: Dibekan.

Dicloxacillin *(BAN, USAN, rINN)*

BRL-1702; Dicloxacilina; Dicloxacilline; Dicloxacillinum; Diklоksasilfiini; Diklоksacillin; R-13423; Диклоксациллин.

(6*R*)-6-[3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

$C_{19}H_{17}Cl_2N_3O_5S$=470.3

CAS — 3116-76-5.
ATC — J01CF01.
ATC Vet — QJ01CF01; QJ51CF01.
UNII — COF19H7WBK.

Dicloxacillin Sodium *(BANM, USAN, rINNM)*

Dicloxacilina sódica; Dicloxacillin-Natrium; Dicloxacilline sodique; Dicloxacillinum natricum; Dicloxacillinum Natricum Monohydricum; Diklоksasilino natrio druska; Diklоksasilfiini-natrium; Diklоksasilin sodná sůl monohydrát; Dikloxacillinnatrium; Diklоksasillin-nátrium; Natrii Dicloxacillinum; P-1011; Натрий Диклоксациллин.

Sodium dicloxacillin monohydrate.

$C_{19}H_{16}Cl_2N_3NaO_5S.H_2O$=510.3

CAS — 343-55-5 (anhydrous dicloxacillin sodium); 13412-64-1 (dicloxacillin sodium monohydrate).
ATC — J01CF01.
ATC Vet — QJ01CF01.
UNII — 4HZT2V9KX0.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Dicloxacillin Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25 degrees in airtight containers.

USP 36: (Dicloxacillin Sodium). A white to off-white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers.

Uses and Administration

Dicloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p. 301.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Dicloxacillin is given intravenously and orally as the sodium salt. All doses are expressed in terms of the equivalent amount of dicloxacillin; 1.09 g of dicloxacillin sodium is equivalent to about 1 g of dicloxacillin. Oral doses should be taken at least 1 hour before, or 2 hours after, meals since the presence of food in the stomach reduces absorption. The usual adult oral dose is 250 mg every 6 hours. Doses may be doubled in severe infections. Similar doses may be given by slow intravenous injection or, preferably, by intravenous infusion, although intravenous doses of up to 2 g every 4 or 6 hours, may be required for serious infections such as endocarditis or osteomyelitis.

Adverse Effects and Precautions

As for Flucloxacillin, p. 301.3.

Effects on the liver. References.

1. Kleinman MS, Presberg JE. Cholestatic hepatitis after dicloxacillin-sodium therapy. *J Clin Gastroenterol* 1986; **8**: 77–8.

Phlebitis. Phlebitis has been associated with infusion of cloxacillin and dicloxacillin; a small study[1] in patients with peripheral venous catheters indicated that the incidence was higher with the latter drug (phlebitis occurred in 21% of cases with cloxacillin, and 38% with dicloxacillin). The risk was greater in catheters inserted in the forearm or antecubital fossa than those in the hand or wrist, but greater infusion time or concentration were not associated with increased risk.

1. Lanbeck P, *et al.* Dicloxacillin: a higher risk than cloxacillin for infusion phlebitis. *Scand J Infect Dis* 2003; **35**: 397–400.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dicloxacillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of dicloxacillin sodium contains about 2 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

As for Flucloxacillin, p. 302.1.

Pharmacokinetics

Dicloxacillin is better absorbed from the gastrointestinal tract than cloxacillin but absorption is reduced by the presence of food in the stomach. Peak plasma concentrations of 10 to 18 micrograms/mL have been reported in fasting subjects 1 hour after a 500-mg oral dose. Doubling the dose can double the plasma concentration. About 97% of dicloxacillin in the circulation is bound to plasma proteins. Dicloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

The distribution of dicloxacillin in body tissues and fluids is similar to that of cloxacillin (p. 275.2).

Dicloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 60% of an oral dose is excreted in the urine. Only small amounts are excreted in the bile. Dicloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations have been reported in patients with cystic fibrosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Diclocil; Dicloxsig; Distaph; ***Denm.***: Dicillin; Diclocil; ***Fin.***: Diclocil; ***Gr.***: Diclocil; ***Hong Kong***: Odicoza; ***India***: Klox-D; ***Mex.***: Amifarin†; Antiben; Brispen; Butimaxil; Cilpen†; Clobioxal; Dic-FHI; Dicleophen; Diclo-Tecno; Dicloxaquim; Diluxina; Dimicin; Ditterolina; Dixen; Doxil†; Pardix; Penclox; Posipen; ***Norw.***: Diclocil; ***NZ***: Diclocil†; ***Port.***: Diclocil; ***Swed.***: Diclocil†; ***Thai.***: Amcidil†; Cloxydin†; Di-K-Cil; Dicillin; Diclex; Diclocil†; Diclocillin; Diclohof; Diclono†; Diclonox; Dicloson; Diclox; Dicloxa; Dicloxane; Dicloxcin; Dicloxgen; Dicloxia; Dicloxilin; Dicloxin†; Dicloxman; Dicloxno; Dicloxpac; Diloxin; Dixocillin; Dorox; U-Diclox; ***Venez.***: Diclocil.

Multi-ingredient Preparations. ***China***: Diclomox (澳广); Kai Li Da (凯力达); Wei Jing (纬净); ***India***: ADC; Alcilox; Alclox-D; Alnaclox; Amclosym; Amclox DL; Amdiclox; Amklok; Amoclox-D; Amoxytek D; Ampoxin Plus; Amsat; Arimox-D; Baxin-D-LB+; Baxin-D-LB; Baxin-D; Betadac-DC; Bicil-P; Bicil; Blox-DC; Blumox-DXL; Calmox; Cefocef-DXL; Cefupop-XL; Checkmox-DX; Cinmox-DC; Clobimox; Clodax; Clos-DX; Clospen; Cloxinova; Clynox; Coax-DX; Combo-AD; Cosclox; D-Clox; Dicam; Dicloxa-MX; Dicmoxy; Dimotic; Discloxy; Dixi; Ethiclox-LB; Flemiklox-DX; Formic-XL; Hclox; Hifen-LXX; Incef-CL; Intaclox-D; Intamox-D; Jinclox; Kemox Plus; Lexmox-DC; Lizamox-D; Lomox-D; Lupimox Forte; Monomox-DX; Moxifact; Moxikind Plus; Moxipil-LB; Moxitrac-DX; Moxklok; Moxtid-D; Moxyplus-DC; Napi-D; NBMox-DC; Nugen-XL; O-Moxy-DC; Odimox-DL; ***Mex.***: Ampiclox-D†; Anglotex†; Brucilina; Diamprex†; Doxapen†; Panac K†; Panac; Pentidix.

Pharmacopoeial Preparations

USP 36: Dicloxacillin Sodium Capsules; Dicloxacillin Sodium for Oral Suspension.

Difloxacin Hydrochloride *(USAN, rINNM)*

A-56619; Abbott-56619; Difloxacine, Chlorhydrate de; Difloxacini hydrochloridum; Difloxacino, hidrocloruro de; Hidrocloruro de difloxacino; Дифлоксацина Гидрохлорид.

6-Fluoro-1-(*p*-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride.

$C_{21}H_{19}F_2N_3O_3.HCl$=435.9

CAS — 98106-17-3 (difloxacin); 91296-86-5 (difloxacin hydrochloride).
UNII — XJ0260HJ0O.

Pharmacopoeias. In *Eur.* (see p. vii) as the trihydrate for veterinary use.

Ph. Eur. 8: (Difloxacin Hydrochloride Trihydrate for Veterinary Use). A white or light yellow, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; very slightly soluble in dichloromethane.

Profile

Difloxacin is a fluoroquinolone antibacterial used as the hydrochloride in veterinary medicine for the treatment of susceptible infections in poultry. It was formerly used in humans but was associated with an unacceptable incidence of adverse CNS effects.

Dihydrostreptomycin Sulfate *(BANM, rINNM)*

Dihidroestreptomicina, sulfato de; Dihidrosztreptomicin-szulfát; Dihydrostreptomycin sulfát; Dihydrostreptomycin Sulphate; Dihydrostreptomycine, Sulfate de; Dihydrostreptomycini Sulfas; Dihydrostreptomycinsulfat; Dihydrostreptomysiinisulfaatti; Sulfato de dihidroestreptomicina; Дигидрострептомицина Сульфат.

O-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-hydroxymethyl-α-L-lyxofuranosyl-(1→4)-N^1,N^3-diamidino-D-streptamine sulphate.

$(C_{21}H_{41}N_7O_{12})_2.3H_2SO_4$=1461.4

CAS — 128-46-1 (dihydrostreptomycin); 5490-27-7 (dihydrostreptomycin sulfate).
ATC — S01AA15.
ATC Vet — QS01AA15.
UNII — T7D4876IUE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, both for veterinary use only.

Ph. Eur. 8: (Dihydrostreptomycin Sulfate for Veterinary Use; Dihydrostreptomycin Sulfate BP(Vet) 2014). The sulfate of a substance obtained by catalytic hydrogenation of streptomycin or by any other means. The semisynthetic product is derived from a fermentation product. Stabilisers may be added. A white or almost white, hygroscopic powder. It contains a maximum of 2.0% streptomycin sulfate calculated with reference to the dried drug. Freely soluble in water; practically insoluble in alcohol, in acetone, and in methyl alcohol. A 25% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 36: (Dihydrostreptomycin Sulfate). A white or almost white amorphous or crystalline powder; the amorphous form is hygroscopic. Freely soluble in water; practically insoluble in acetone, in chloroform, and in methyl alcohol. pH of a solution in water containing the equivalent of dihydrostreptomycin 20% is between 4.5 and 7.0, except that if it is labelled as being solely for oral use, the pH is between 3.0 and 7.0. Store in airtight containers.

Profile

Dihydrostreptomycin is an aminoglycoside antibacterial with actions similar to those of streptomycin (p. 361.1). Since it is more likely than streptomycin to cause partial or complete loss of hearing it is not used parenterally in humans. It is not absorbed after oral doses, and has been given by this route for gastrointestinal infections. It is also used as the sulfate in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain:*** Citrocil.

Multi-ingredient Preparations. ***Arg.:*** Vagisan Compuesto; Vagisan; ***Mex.:*** Estrefen; ***Spain:*** Cilinafosal Dihidroestreptomicina†; Salitanol Estreptomicina†; Sulfintestin Neomicina.

Dirithromycin *(BAN, USAN, rINN)*

ASE-136BS; Dirithromycine; Dirithromycinum; Diritromicin; Diritromicina; Diritromicinas; Diritromisin; Diritromycin; Diritromysiini; LY-237216; Диритромицин.

(1*R*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,15*R*,17*S*)-7-(2,6-Dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-3-ethyl-2,10-dihydroxy-15-(2-methoxyethoxymethyl)-2,6,8,10,12,17-hexamethyl-9-(3,4,6-trideoxy-3-dimethylamino-β-L-*xylo*-hexopyranosyloxy)-4,16-dioxa-14-azabicyclo[11.3.1]heptadecan-5-one; (9*S*)-9-Deoxo-11-deoxy-9,11-[imino[(1*R*)-2-(2-methoxyethoxy)-ethylidene]oxy]erythromycin.

$C_{42}H_{78}N_2O_{14}$=835.1

CAS — 62013-04-1.

ATC — J01FA13.

ATC Vet — QJ01FA13.

UNII — 1801D76STL.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. & (Dirithromycin). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

USP 36: (Dirithromycin). A white or practically white powder. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

Uses and Administration

Dirithromycin is a prodrug of the macrolide antibacterial erythromycylamine, which has similar properties to those of erythromycin (p. 293.2) and is used in respiratory-tract, skin, and soft-tissue infections caused by susceptible organisms.

Dirithromycin is given orally as enteric-coated tablets in a usual dose of 500 mg once daily.

References.
1. Various. Dirithromycin: a new once-daily macrolide. *J Antimicrob Chemother* 1993; **31** (suppl C): 1–185.
2. Brogden RN, Peters DH. Dirithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **48:** 599–616.
3. Wintermeyer SM, *et al.* Dirithromycin: a new macrolide. *Ann Pharmacother* 1996; **30:** 1141–9.
4. McConnell SA, Amsden GW. Review and comparison of advanced-generation macrolides clarithromycin and dirithromycin. *Pharmacotherapy* 1999; **19:** 404–15.

Adverse Effects and Precautions

As for Erythromycin, p. 295.1.

The most frequent adverse effects of dirithromycin are gastrointestinal disturbances; headache has also occurred. Dirithromycin should be used with caution in patients with moderate to severe hepatic impairment since its active metabolite erythromycylamine is mainly eliminated in the bile. It should also be used with caution in those with severe renal impairment.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 296.2.

Cytochrome P450 isoenzymes. Dirithromycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p. 296.2). The lack of interactions between dirithromycin and theophylline, terfenadine, or warfarin would appear to support this.

Antimicrobial Action

As for Erythromycin, p. 297.1.

Dirithromycin is reported to be generally less active than erythromycin *in vitro*, but may show greater activity *in vivo* than is indicated by *in-vitro* studies and may exert a postantibiotic effect.

Pharmacokinetics

Dirithromycin is readily absorbed after oral doses and undergoes rapid non-enzymatic hydrolysis to its active metabolite erythromycylamine. Absorption is enhanced by food. Bioavailability is about 10%. Daily doses of dirithromycin 500 mg produce peak plasma concentrations of erythromycylamine of about 400 nanograms/mL.

Erythromycylamine is widely distributed and tissue concentrations exceed those in plasma. Protein binding is 15 to 30%. Erythromycylamine is mainly excreted unchanged in the bile with only about 2% in the urine. The mean plasma half-life is about 8 hours and the mean urinary terminal elimination half-life is about 44 hours.

Distribution into milk has been found in studies in *rodents.*

References.
1. Sides GD, *et al.* Pharmacokinetics of dirithromycin. *J Antimicrob Chemother* 1993; **31** (suppl C): 65–75.
2. LaBreque D, *et al.* Pharmacokinetics of dirithromycin in patients with impaired hepatic function. *J Antimicrob Chemother* 1993; **32:** 741–50.
3. Mazzei T, *et al.* Pharmacokinetics of dirithromycin in patients with mild or moderate cirrhosis. *Antimicrob Agents Chemother* 1999; **43:** 1556–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China:*** Bi Zheng (毕正); Di Hong (迪红); Di Mai Xin (迪迈欣); Hongjidi (红极第); Lu Di (路迪); Luo Ke Xin (罗可辛); Pai Sheng (派盛); Ping Li Da (平立达); Qi Li Tuo (奇立妥); Yan Jin (严尽); Yi Li Xin (怡力昕); Yu Da (域大); ***Fr.:*** Dynabac†; ***Gr.:*** Dynabac; ***Turk.:*** Dynabac.

Pharmacopoeial Preparations
USP 36: Dirithromycin Delayed-Release Tablets.

Doripenem *(USAN, rINN)*

Doripénem; Doripénème; Doripenemum; S-4661; Дорипенем.

(+)-(4*R*5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({(3*S*,5*S*)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

$C_{15}H_{24}N_4O_6S_2$, H_2O=438.5

CAS — 148016-81-3 (doripenem); 364622-82-2 (doripenem monohydrate).

ATC — J01DH04.

ATC Vet — QJ01DH04.

UNII — BHV525JOBH (doripenem); 4B035T6NKT (doripenem monohydrate).

Uses and Administration

Doripenem is a carbapenem antibacterial similar to imipenem (p. 311.2). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections such as hospital-acquired pneumonia, and complicated intra-abdominal or urinary-tract infections, including pyelonephritis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Doripenem is given as the monohydrate, but doses are expressed in terms of the amount of anhydrous doripenem; 1.04 g of doripenem monohydrate is equivalent to about 1 g of anhydrous doripenem. In the treatment of susceptible infections, doripenem is given by intravenous infusion over 1 hour, in a usual dose of 500 mg every 8 hours. For some patients with hospital-acquired pneumonia, this dose may be insufficient and a dose of 1 g every 8 hours has been recommended (see p. 289.3 for further details). An extended infusion over 4 hours may be more suitable for very severe infections, or those caused by less susceptible organisms and UK licensed product information allows this as an option in the management of hospital-acquired pneumonia. Doripenem treatment is usually given for 5 to 14 days; all patients with hospital-acquired pneumonia should be treated for at least 10 days.

For details of reduced doses in renal impairment, see p. 289.3.

References.
1. Lister PD. Carbapenems in the USA: focus on doripenem. *Expert Rev Anti Infect Ther* 2007; **5:** 793–809.
2. Poulakou G, Giamarellou H. Doripenem: an expected arrival in the treatment of infections caused by multidrug-resistant Gram-negative pathogens. *Expert Opin Invest Drugs* 2008; **17:** 749–71.
3. Chastre J, *et al.* Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 2008; **36:** 1089–96.
4. Lucasti C, *et al.* Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, non-inferiority study. *Clin Ther* 2008; **30:** 868–83.
5. Keam SJ. Doripenem: a review of its use in the treatment of bacterial infections. *Drugs* 2008; **68:** 2021–57.
6. Paterson DL, Depestel DD. Doripenem. *Clin Infect Dis* 2009; **49:** 291–8.
7. Naber KG, *et al.* Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. *Antimicrob Agents Chemother* 2009; **53:** 3782–92.
8. Mandell L. Doripenem: a new carbapenem in the treatment of nosocomial infection. *Clin Infect Dis* 2009; **49** (suppl 1): S1–S3.
9. Chahine EB, *et al.* Doripenem: a new carbapenem antibiotic. *Am J Health-Syst Pharm* 2010; **67:** 2015–24.
10. Overturf GD. Doripenem: an early look at a carbapenem not yet approved for pediatrics. *Pediatr Infect Dis J* 2010; **29:** 163–5.

Administration in renal impairment. Doses of doripenem given by intravenous infusion should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 50 mL/minute: 250 mg every 8 hours
- CC greater than 10 to less than 30 mL/minute: 250 mg every 12 hours

The pharmacokinetics of doripenem have been examined in a small study[1] in 11 dialysis-dependent patients with end-stage renal disease who were undergoing continuous renal replacement therapy (CRRT), either via 12-hour continuous venovenous haemofiltration (CVVH) or continuous venovenous haemodiafiltration (CVVHDF). The study found that despite significant removal of doripenem and the active metabolite (doripenem-M1) by CRRT, a single 500-mg doripenem dose infused over 1 hour produced significantly higher plasma concentrations of doripenem, higher systemic exposure, and longer half-life in those undergoing CRRT than in healthy subjects. During CVVH and CVVHDF, respectively, the percentages of administered doripenem dose removed were 38 and 29%, and clearances of doripenem were 22 and 25 mL/minute. It was recommended that dosage regimens for doripenem in patients receiving CRRT should be adjusted. The results of another small study[2] in patients with end-stage renal disease (CC less than 10 mL/minute) who were receiving 3-times weekly haemodialysis suggested that an intravenous dose of doripenem 500 mg once every 24 hours would provide adequate serum concentrations.

1. Cirillo I, *et al.* Influence of continuous venovenous hemofiltration and continuous venovenous hemodiafiltration on the disposition of doripenem. *Antimicrob Agents Chemother* 2011; **55:** 1187–93.
2. Heil EL, *et al.* Validation of doripenem dosing in patients with end-stage renal disease receiving hemodialysis. *Ann Pharmacother* 2011; **45:** 1455–6.

Pneumonia. Regulatory authorities in Europe[1] and the USA[2] have recently issued safety alerts after a study evaluating the use of doripenem in the treatment of ventilator-associated pneumonia was stopped early. Preliminary results had shown a lower cure rate and an excess mortality in patients receiving an unlicensed dose of doripenem (1 g every 8 hours for 7 days) when compared with treatment with imipenem-cilastatin for 10 days. Based on the available data, it was considered that the shorter duration of treatment, augmented renal clearance, and infection with some specific types of bacteria had all contributed to the outcome.

In view of these findings, the EMEA[1] has made the following recommendations when giving doripenem to patients with hospital-acquired pneumonia, which includes ventilator-associated pneumonia:

- The dose of doripenem should be increased to 1 g every 8 hours and infused over 4 hours for patients with augmented renal clearance or with infections by non-fermenting, Gram-negative pathogens such as *Pseudomonas* spp. and *Acinetobacter* spp..
- If non-fermenting Gram-negative pathogens are confirmed, concomitant treatment with an aminoglycoside should be considered.
- For all patients, treatment should be for 10 to 14 days and is usually in the upper range for infections with non-fermenting, Gram-negative pathogens.

In the USA, doripenem is not licensed for the treatment of pneumonia.

1. EMA. Questions and answers on the review of Doribax (doripenem) (issued 21st June, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/06/WC500129084.pdf (accessed 16/08/12)
2. Chang P. Doripenem dear healthcare professional letter (issued 3rd January, 2012). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM286277.pdf (accessed 16/08/12)

Adverse Effects and Precautions

As for Imipenem, p. 312.1.

Doripenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the

enzyme, is not required. Excess mortality has been reported in patients with ventilator-associated pneumonia given inappropriate doses of doripenem; for further information, see under Uses and Administration, p. 287.2.

Effects on the nervous system. Doripenem appears to carry a relatively low risk of inducing seizures.[1]

1. Zhanel GG, *et al.* Overview of seizure-inducing potential of doripenem. *Drug Safety* 2009; **32:** 709–16.

Interactions

Probenecid inhibits the renal excretion of doripenem thereby increasing its plasma concentrations and prolonging its elimination half-life; co-administration is not recommended.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to carbapenem antibacterials, see p. 557.2.

Antimicrobial Action

Like other carbapenems (see Imipenem, p. 312.2), doripenem is active against most Gram-positive and Gram-negative bacteria (including aerobes and anaerobes) with the exception of *Stenotrophomonas maltophilia, Burkholderia cepacia, Enterococcus faecium,* and MRSA. It is reported to have good activity *in vitro* against a broader range of such organisms than other carbapenems.

Doripenem is a particularly potent inhibitor of Gram-negative bacteria that have a high potential for drug resistance, such as *Pseudomonas aeruginosa,* and the Enterobacteriaceae. Compared with other carbapenems, doripenem also appears to have a relatively weak ability to promote the emergence of antibacterial resistance *in vitro.*

References.

1. Sahm D. In vitro activity of doripenem. *Clin Infect Dis* 2009; **49** (suppl 1): S11–S16.

Pharmacokinetics

After intravenous infusion of doripenem 500 mg over 1 hour, a mean peak plasma concentration of 23 micrograms/mL is attained, falling to 10 micrograms/mL after 1.5 hours and 1 microgram/mL after 6 hours.

Doripenem is less than 10% bound to plasma proteins and is widely distributed into body tissues and fluids. It is metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite (doripenem-M1). The plasma elimination half-life is about 1 hour in adults; the half-life may be prolonged in patients with renal impairment. Doripenem is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% and 15% of a dose is recovered as unchanged drug and metabolite, respectively, in the urine within 48 hours. Less than 1% is excreted in faeces.

Doripenem is removed by haemodialysis.

References.

1. Cirillo I, *et al.* Pharmacokinetics, safety, and tolerability of doripenem after 0.5-, 1-, and 4-hour infusions in healthy volunteers. *J Clin Pharmacol* 2009; **49:** 798–806.
2. Nandy P, *et al.* Population pharmacokinetics of doripenem based on data from phase 1 studies with healthy volunteers and phase 2 and 3 studies with critically ill patients. *Antimicrob Agents Chemother* 2010; **54:** 2354–9.
3. Samtani MN, *et al.* Pharmacokinetic-pharmacodynamic-model-guided doripenem dosing in critically ill patients. *Antimicrob Agents Chemother* 2010; **54:** 2360–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Doribax; ***Austral.***: Doribax; ***Austria***: Doribax; ***Belg.***: Doribax; ***Canad.***: Doribax; ***Cz.***: Doribax; ***Denm.***: Doribax; ***Fr.***: Doribax; ***Ger.***: Doribax; ***Gr.***: Doribax; ***Hong Kong***: Doribax; ***Hung.***: Doribax; ***Irl.***: Doribax; ***Israel***: Doribax; ***Jpn***: Finibax; ***Malaysia***: Doribax; ***Neth.***: Doribax; ***Norw.***: Doribax; ***NZ***: Doribax; ***Philipp.***: Doribax; ***Pol.***: Doribax; ***Port.***: Doribax; ***Rus.***: Doriprex (Дорипрекс); ***Singapore***: Doribax; ***Spain***: Doribax; ***Swed.***: Doribax; ***Thai.***: Doribax; ***Turk.***: Doribax; ***UK***: Doribax; ***USA***: Doribax.

Doxycycline *(BAN, USAN, rINN)*

Doksiciklinas monohidratas; Doksisiklin; Doksisykliini; Doksisykliinimonohydraatti; Doksycyklina; Doxiciclina; Doxiciklin; Doxycyclin; Doxycyclin-Monohydrat; Doxycycline Monohydrate; Doxycycline monohydratée; Doxycyclinum; Doxycyclinum Monohydricum; Doxycyklin monohydrát; Doxycyklinmonohydrat; GS-3065; Доксициклин.

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide monohydrate; 6-Deoxy-5β-hydroxytetracycline monohydrate.

$C_{22}H_{24}N_2O_8,H_2O$=462.5

CAS — 564-25-0 (anhydrous doxycycline); 17086-28-1 (doxycycline monohydrate).

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — N12000U13O (doxycycline monohydrate); 334895S862 (anhydrous doxycycline).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Doxycycline Monohydrate). A yellow crystalline powder. Very slightly soluble in water and in alcohol. It dissolves in dilute solutions of mineral acids and in solutions of alkali hydroxides and carbonates. A 1% suspension in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Doxycycline). A yellow crystalline powder. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; freely soluble in dilute acid and in alkali hydroxide solutions. pH of a 1% suspension in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Doxycycline Calcium *(BANM, rINNM)*

Calcii Doxycyclinum; Doxiciclina cálcica; Doxycycline Calcique; Кальций Доксициклин.

CAS — 94088-85-4.

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — 8ZL07I20SB.

Doxycycline Fosfatex *(BAN, USAN)*

AB-08; DMSC; Doxiciclina fosfatex.

6-Deoxy-5β-hydroxytetracycline—metaphosphoric acid—sodium metaphosphate in the ratio 3:3:1.

$(C_{22}H_{24}N_2O_8)_3(HPO_3)_3NaPO_3$=1675.2

CAS — 83038-87-3.

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — 2IQ26U2DZQ.

Doxycycline Hyclate *(BANM, rINNM)*

Doksiciklino hiklatas; Doksisykliinihyklaatti; Doksycykliny hyklan; Dossiciclina Iclato; Doxiciclina, hiclato de; Doxiciklin-hiklát; Doxycycline, Hyclate de; Doxycycline Hydrochloride; Doxycyclinhyclat; Doxycyclini Hyclas; Doxycyklinhyklat; Doxycyklin-hyklát; Hiclato de doxiciclina; Доксициклина Гиклат.

Doxycycline hydrochloride hemiethanolate hemihydrate.

$C_{22}H_{24}N_2O_8,HCl,½C_2H_5OH,½H_2O$=512.9

CAS — 10592-13-9 (doxycycline hydrochloride); 24390-14-5 (doxycycline hyclate).

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — 19XTS3T51U (doxycycline hyclate); 4182Z6T2ET (doxycycline hydrochloride).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Doxycycline Hyclate). A yellow hygroscopic crystalline powder. Freely soluble in water and in methyl alcohol; sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides and of carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Store in airtight containers. Protect from light.

USP 36: (Doxycycline Hyclate). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of doxycycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Preparations of doxycycline hyclate have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Uses and Administration

Doxycycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.3). It is usually preferred to other tetracyclines in the treatment of susceptible infections because of its fairly reliable absorption and a long half-life that permits less frequent (often once daily) dosing. It also has the advantage that with care it can be given to patients with renal impairment. However, relatively high doses may need to be given for urinary-tract infections because of its low renal excretion.

Doxycycline has antiprotozoal actions and may be given with quinine in the management of falciparum malaria resistant to chloroquine (p. 644.1).

Solutions of doxycycline are also used for malignant effusions (p. 700.1).

Doxycycline is usually given orally as the base or its various salts, usually the hyclate. Doses are expressed in terms of doxycycline; doxycycline hyclate 115 mg is equivalent to about 100 mg of anhydrous doxycycline. Doxycycline capsules and tablets should be given with plenty of fluid, with the patient in an upright position, and well before going to bed. Doxycycline may be given with food or milk if gastric irritation occurs. Dispersible tablets or liquid formulations are advisable in elderly patients.

In patients in whom oral therapy is not feasible, doxycycline hyclate may be given by slow intravenous infusion of a solution containing 0.1 to 1 mg/mL, in equivalent doses. Infusions should be given over 1 to 4 hours.

The usual adult dose, either orally or intravenously, in susceptible **infections** is 200 mg of doxycycline on the first day (as a single dose or in divided doses), followed by 100 mg daily. In severe infections the initial dosage is maintained throughout the course of treatment. For details of doses in children and adolescents, see p. 291.1.

In patients with uncomplicated gonococcal infections (p. 204.2), doxycycline 100 mg twice daily for 7 days is given orally, although it has occasionally been given in a single dose of 300 mg followed by a second similar dose 1 hour later. For syphilis (p. 205.2) in penicillin-allergic patients, doxycycline 100 to 200 mg twice daily is given orally for at least 14 days; some authorities suggest giving the same dose for 28 to 30 days to patients with late latent disease and those with long-standing syphilis of more than a year should be given 100 mg twice daily for 28 days.

For relapsing fever (p. 202.2) and louse-borne typhus (p. 212.3), doxycycline 100 or 200 mg may be given as a single oral dose. For prophylaxis of scrub typhus, 200 mg may be taken as a single oral dose. For the prophylaxis of leptospirosis (p. 189.3), 200 mg may be given orally once a week throughout exposure for up to 21 days and 200 mg is also given when leaving the area of infection risk.

Doxycycline is used in non-endemic areas for the treatment of chloroquine-resistant falciparum malaria in an oral dose of 200 mg daily for at least 7 days with or after treatment with quinine. Doxycycline 100 mg daily may be used for prophylaxis in areas of high risk or where multidrug resistance exists, and can be used prophylactically for up to 2 years.

For treatment of inhalation anthrax (p. 173.2), a 60-day course of treatment with oral doses of 100 mg twice daily may be used; one or two other antibacterials should also be given. Although unlicensed, the same regimen is recommended by UK and US public health authorities for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of doxycycline 100 mg twice daily is recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure. If there are signs of systemic involvement, extensive oedema, or lesions on the head and neck, intravenous therapy and a multidrug approach is recommended. For postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with oral doses of doxycycline 100 mg twice daily may be used. Alternatively prophylaxis may be started with oral ciprofloxacin for 5 days and then oral doxycycline (100 mg twice daily) may be substituted to complete the 60-day course.

In the treatment of acne vulgaris, an oral dose of 50 mg daily for 6 to 12 weeks may be adequate, although the *BNF* advocates a dose of 100 mg daily. It is also given in low doses of 40 mg once daily as a modified-release preparation for the treatment of inflammatory lesions associated with rosacea in adults.

Doxycycline may be given orally in low, **subantimicrobial doses** of 20 mg twice daily for 3 months as an adjunct to supragingival and subgingival scaling and root planing to adults with periodontitis. For chronic periodontitis, a modified-release subgingival gel containing doxycycline hyclate 10% (released over 7 days) has been inserted into the periodontal pocket.

For further information on the use of subantimicrobial doses of doxycycline for the treatment of acne, rosacea, and peridontal disease, see p. 290.3.

Administration. *SUBANTIMICROBIAL DOSES.* Doxycycline is given in doses of 20 mg orally twice daily, which are not sufficient to achieve antimicrobial concentrations in the body, as an adjunct in the treatment of periodontal disease (p. 192.3). The benefits of treatment are believed to be due to its ability to downregulate the actions of matrix metalloproteinases, enzymes involved in the breakdown of collagen and which play a key role in the inflammatory and destructive processes of periodontitis.[1-3]

Similar subantimicrobial doses have been investigated, and produced apparent benefit, in patients with acne (p. 1682.2) or rosacea (p. 1688.3);[4] there was no evidence that even quite prolonged therapy at these doses influenced the development of antibacterial resistance in bacterial flora. A low-dose modified-release preparation containing

doxycycline 40 mg is available in some countries for the treatment of inflammatory lesions associated with rosacea.

1. Preshaw PM, *et al*. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis: a review. *J Clin Periodontol* 2004; **31:** 697–707.
2. Gapski R, *et al*. Systemic MMP inhibition for periodontal wound repair: results of a multi-centre randomized-controlled clinical trial. *J Clin Periodontol* 2009; **36:** 149–56.
3. Caton J, Ryan ME. Clinical studies on the management of periodontal diseases utilizing subantimicrobial dose doxycycline (SDD). *Pharmacol Res* 2011; **63:** 114–20.
4. Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. *Cutis* 2004; **74:** 118–122.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, doxycycline is licensed for low-dose, **subantimicrobial**, and standard dose, **antibacterial use** in children aged 12 years and over only; the usual adult dose (see Uses and Administration, p. 288.2) may be given orally. However, in the USA, it may be given to children over 8 years old; those weighing 45 kg or less may be given usual oral or intravenous doses of 4.4 mg/kg on the first day (as a single dose or in divided doses), followed by 2.2 mg/kg daily and those weighing over 45 kg may be given the usual adult dose (see above).

In the USA, doxycycline is also licensed in children over 8 years old for prophylaxis of chloroquine-resistant falciparum **malaria** in areas of high risk or where multidrug resistance exists. The recommended oral dose is 2 mg/kg (to a maximum of 100 mg) once daily.

US public health authorities suggest that doxycycline may also be given to children under 8 years old for the treatment of inhalation, gastrointestinal, or cutaneous **anthrax**,[1] and for postexposure prophylaxis of inhalation anthrax.[2] For the treatment and postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with doses of 2.2 mg/kg (to a maximum of 100 mg) twice daily is suggested; the same regimen is also recommended for the treatment of gastrointestinal anthrax. As for adult treatment regimens, one or two other antibacterials should also be given when treating established infection. For treatment, antibacterials are initially given intravenously and then switched to oral therapy when clinically appropriate.[2,3] In the treatment of cutaneous anthrax, a 7-to 10-day course of treatment with an oral dose of 2.2 mg/kg twice daily is recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.[2,3] In the UK[3] public health authorities only recommend doxycycline for those older than 8 years old and weighing over 45 kg who may be given the usual adult dose (see above).

Doxycycline can also be used to treat children with **Rocky Mountain spotted fever** (p. 208.1). US[4] public health authorities have suggested a dose of 2.2 mg/kg twice daily in children weighing less than about 45 kg, given either orally or intravenously.

1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* 2001; **50:** 909–19. Correction. *ibid.*; 962. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm (accessed 02/02/11)
2. CDC. Update: Investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR* 2001; **50:** 889–93. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5041.pdf (accessed 02/02/11)
3. Health Protection Agency. *Anthrax: guidelines for action in the event of a deliberate release.* Version 6.2; issued 21/12/10. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947401128 (accessed 02/02/11)
4. Chapman AS, *et al*. Tickborne Rickettsial Diseases Working Group. CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. A practical guide for physicians and other health-care and public health professionals. *MMWR* 2006; **55:** 1–27. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5504.pdf (accessed 28/01/09)

Lymphatic filariasis. Filaria have been shown to contain *Wolbachia* endobacteria, which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of individuals with lymphatic filariasis (p. 146.3). A double-blind, randomised, placebo-controlled study[1] of 72 patients infected with *Wuchereria bancrofti* found that those given oral doxycycline 200 mg daily for 8 weeks had a significant reduction in the number of adult worms at 14 months; ultrasonography detected adult worms in 22% of those given doxycycline and in 88% of those given placebo. Microfilaraemia was almost completely eliminated at 8 to 14 months follow-up. A small, double-blind, randomised, placebo-controlled study[2] also in patients infected with *W. bancrofti*, reported that a 3-week course of doxycycline 200 mg daily with a single dose of ivermectin (150 microgram/kg) plus albendazole (400 mg), given 4 months after starting treatment with doxycycline, is more effective in inducing long-term amicrofilaraemia than standard treatment with ivermectin plus albendazole, but is insufficient to kill adult worms. Similarly, courses of doxycycline for either 6 or 4 weeks (plus single doses of ivermectin with or without albendazole given 4 months after starting treatment) have been shown to decrease *Wolbachia* load and have strong microfilarial activity.[3,4] Another double-blind, randomised, placebo-controlled study[5] in persons infected with *Brugia malayi* found that doxycycline 100 mg daily for 6 weeks either alone or with a single dose of diethylcarbamazine (6 mg/kg) plus albendazole (400 mg), given 4 months after starting treatment with doxycycline, significantly reduced *Wolbachia* levels. Furthermore, after 1 year the prevalence of microfilaraemia was reduced by 77% in patients given doxycycline alone and by 87.5% in those given doxycycline and diethylcarbamazine plus albendazole; a 26.7% reduction of microfilaraemia was reported for those given placebo and diethylcarbamazine plus albendazole.

See also Onchocerciasis, p. 291.2.

1. Taylor MJ, *et al*. Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial. *Lancet* 2005; **365:** 2116–21.
2. Turner JD, *et al*. A randomized, double-blind clinical trial of a 3-week course of doxycycline plus albendazole and ivermectin for the treatment of Wuchereria bancrofti infection. *Clin Infect Dis* 2006; **42:** 1081–9.
3. Debrah AY, *et al*. Doxycycline reduces plasma VEGF-C/sVEGFR-3 and improves pathology in lymphatic filariasis. *PLoS Pathog* 2006; **2:** e92.
4. Debrah AY, *et al*. Macrofilaricidal effect of 4 weeks of treatment with doxycycline on *Wuchereria bancrofti*. *Trop Med Int Health* 2007; **12:** 1433–41.
5. Supali T, *et al*. Doxycycline treatment of Brugia malayi-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. *Clin Infect Dis* 2008; **46:** 1385–93.

For the use of doxycycline in the treatment of malaria see under Tetracycline, p. 376.1.

Mansonella infections. As with other filaria, *Mansonella perstans* have been shown to rely on a symbiotic relationship with *Wolbachia* endobacteria, leading to hopes that *M. perstans* infections (see p. 147.2) might be effectively treated with antibacterials. In a randomised open-label study[1] of patients with *M. perstans* microfilaraemia, [oral] doxycycline 200 mg daily given for 6 weeks led to significantly reduced levels of *M. perstans* at 12 months, and sustained suppression 36 months after treatment.

1. Coulibaly YI, *et al*. A randomized trial of doxycycline for *Mansonella perstans* infection. *N Engl J Med* 2009; **361:** 1448–58.

Multiple sclerosis. Matrix metalloproteinases (MMPs) have been shown to play a role in the pathogenesis of multiple sclerosis and may also reduce the efficacy of therapy by degrading interferon beta. Tetracyclines have immunomodulatory and neuroprotective effects, and are also potent inhibitors of MMPs. Doxycycline has been evaluated in an open label study in a few patients with remitting-relapsing multiple sclerosis and breakthrough disease;[1] adding oral doxycycline to their intramuscular interferon beta-1a therapy was reported to be safe and associated with disease stabilisation in most.

1. Minagar A, *et al*. Combination therapy with interferon beta-1a and doxycycline in multiple sclerosis: an open-label trial. *Arch Neurol* 2008; **65:** 199–204.

Musculoskeletal and joint disorders. For reference to the use of doxycycline in the management of various musculoskeletal and joint disorders, see under Tetracycline, p. 376.2.

Onchocerciasis. As in lymphatic filariasis (above), *Onchocerca volvulus* worms rely on a symbiotic relationship with *Wolbachia* endobacteria, and this has provided a new approach in the treatment of individuals with onchocerciasis (p. 147.2). A 4-month controlled clinical study[1] of 35 patients with onchocerciasis found that those given oral doxycycline 100 mg daily for 6 weeks showed a trend toward more frequent degeneration or death of adult worms and suppressed embryonic development at early stages for the duration of the study period. A subsequent study[2] of 88 patients found that embryogenesis was interrupted for at least 18 months in those given a single standard dose of ivermectin (150 micrograms/kg) plus oral doxycycline 100 mg daily for 6 weeks compared with those given only the standard dose of ivermectin.

1. Hoerauf A, *et al*. Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* 2000; **355:** 1242–3.
2. Hoerauf A, *et al*. Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001; **357:** 1415–16.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Gastrointestinal disturbances with doxycycline are reported to be less frequent than with tetracycline and doxycycline may also cause less tooth discoloration.

Oesophageal ulceration or sometimes rupture may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: doxycycline should be taken with at least half a glass of water, in an upright position, and well before going to bed. Dispersible tablets or liquid formulations should be used in elderly patients, who may be at greater risk of oesophageal injury.

Hypersensitivity reactions are uncommon with doxycycline, although the Jarisch-Herxheimer reaction may occur when it is used to treat spirochetal infections. Doxycycline is considered one of the most potent photosensitisers among the tetracyclines, and photosensitivity is common; photoonycholysis may rarely occur without an associated skin rash.

Unlike many tetracyclines, doxycycline does not appear to accumulate in patients with impaired renal function, and aggravation of impairment may be less likely. Similarly, there is also no evidence that doxycycline causes severe hepatitis.

Incidence of adverse effects. For the suggestion that doxycycline may cause fewer adverse effects than minocycline, see p. 327.2.

Anosmia. Anosmia or dysosmia (absent or impaired sense of smell) have occasionally been reported in patients receiving doxycycline, although the association has not been definitely established.[1]

1. Bleasel AF, *et al*. Anosmia after doxycycline use. *Med J Aust* 1990; **152:** 440.

Breast feeding. See Pharmacokinetics, p. 291.3, for a suggestion that doxycycline has a greater potential for toxicity in breast-fed infants than other tetracyclines.

Effects on intracranial pressure. Doxycycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p. 377.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies doxycycline as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

As for Tetracycline, p. 377.3.

Doxycycline has a lower affinity for binding with calcium than many tetracyclines. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc; even intravenous doxycycline may be affected, although less so than when given orally.

Doxycycline is a substrate of the cytochrome P450 isoenzyme CYP3A4 and a moderate inhibitor of the same cytochrome system. Its metabolism may therefore be accelerated by drugs that induce hepatic enzymes such as alcohol (chronic use), rifampicin, and antiepileptics including carbamazepine, phenobarbital, phenytoin, and primidone.

It has been suggested that doxycycline could increase ciclosporin concentrations, but evidence for this seems to be scant.

Antimicrobial Action

As for Tetracycline, p. 377.3.

Doxycycline is more active than tetracycline against many bacterial species including *Streptococcus pyogenes*, enterococci, *Nocardia* spp., *Yersinia pestis*, and various anaerobes. Cross-resistance is common although no resistance to doxycycline has been found in *Chlamydia* or *Rickettsia* spp.. Doxycycline is also more active against protozoa, particularly *Plasmodium* spp.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

Doxycycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of milk or food in the stomach or duodenum. Mean peak plasma concentrations of 2.6 micrograms/mL have been reported 2 hours after a 200-mg oral dose, falling to 1.45 micrograms/mL at 24 hours. After intravenous infusion of the same dose peak plasma concentrations ranging from 5 to 10 micrograms/mL occur; these fall slowly and concentrations of 1 to 2 micrograms/mL persist for 24 hours.

Doxycycline is more lipid-soluble than tetracycline. It is widely distributed in body tissues and fluids, with excellent penetration into the liver, kidney, and sinuses. Penetration into CSF is only moderate, and CSF concentrations are not more than 1 microgram/mL in those with non-inflamed meninges. It crosses the placenta and is distributed into breast milk with concentrations of up to 40% of plasma. The potential for toxicity in a breast-fed infant may be greater than with the other tetracyclines because doxycycline is less bound to calcium. About 80 to 95% of doxycycline in the

circulation is reported to be bound to plasma proteins. Its biological half-life varies from about 12 to 24 hours.

In patients with normal renal function about 40% of a dose is slowly excreted in the urine, although more is excreted by this route if the urine is made alkaline. However, the majority of a dose of doxycycline is excreted in the faeces after chelation in the intestines. Although doxycycline has been reported to undergo partial inactivation in the liver, some sources consider this doubtful; however, the kinetics of doxycycline have been reportedly altered in patients receiving drugs that induce hepatic metabolism.

Doxycycline is stated not to accumulate significantly in patients with renal impairment, although excretion in the urine is reduced; increased amounts of doxycycline are excreted in the faeces in these patients. Nevertheless, there have been reports of some accumulation in renal failure. Removal of doxycycline by haemodialysis is insignificant.

Reviews.
1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15:** 355–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asolmicina.dox; Atridox†; Ciclidoxan; Doxibiot†; Granudoxy; Verboril; Vibramicina; ***Austral.***: Doryx; Doxsig; Doxy; Doxyhexal; Doxylin; Frakas; Vibra-Tabs; Vibramycin; ***Austria***: Dotur; Doxybene; Doxyderm; Doxydyn; Doxyhexal†; Doxystad; Vibramycin; Vibravenos; ***Belg.***: Docdoxycy†; Doxylets; Doxytab; Vibratab; ***Braz.***: Ciclisan†; Clordox; Doxilegrand†; Neo Doxicilin; Protectina; Uni Doxiciclin; Vibradoxin; Vibramicina; ***Canad.***: Apo-Doxy; Atridox; Doxycin; Doxytab; Novo-Doxylin; Periostat; Vibra-Tabs; Vibramycin; ***Chile***: Abraxil; Dentarec; Doryx†; Doxithal; Sigadoxin; Tolexine; Vibramicina; ***China***: Ai Rui De An (艾瑞得安); Duo Di (多迪); Wan Shi Qi (万士奇); Yong Xi (永喜); ***Cz.***: Deoxymykoin; Doxybene; Doxyhexal; ***Denm.***: Dotur†; Oracea; Vibradox; ***Fin.***: Atridox†; Doximed; Doximycin; Doxitin; Oracea; ***Fr.***: Doxy; Doxylis; Doxypalu; Granudoxy; Spanor; Tolexine; Vibramycine N; Vibraveineuse; ***Ger.***: Aknefug Doxy†; Antodox†; Doxakne; Doxy Komb†; Doxy M; Doxy-HP†; Doxy-N-Tablinen†; Doxy-Wolff†; Doxy; Doxyderma; Doxydoc†; Doxyhexal†; Doxymono†; Ligosan; Oraycea; ***Gr.***: Anfadox†; Atridox; Combaforte; Impalamycin; Ivamycin; Lentomyk; Microvibrate; Novimax; Otosal; Relyomycin; Smilitene; Vibrabiotic; Vibramycin; Vibravenos; Vibravenosa; Visubiotic; ***Hong Kong***: Amermycin; Doxat†; Doxitab†; Doxy; Doxycap†; Doxylin†; Doxymycin; Medomycin; Plemex†; Synvibra†; Vibramycin; Wanmycin; ***Hung.***: Doxitidin; Doxypharm; Doxyprotect; Huma-Doxylin; Tenutan; ***India***: Apidox; Bidox-DT; Biodoxi; Ceedox; Chemedox-HT; Codox; Dedoxyn; Dobid; Dox-M DT; Doxicip; Doxina; Doxipil; Doxitab; Doxodin-TR; Doxt; Doxy; Doxycap; Doxyleb; Doxylin-DT; Doxyn; Doxypal-DR; Doxyric; Doxytop; Duradox; DX-24; Emdox; Geeox; Ginadox; Idoxy; LAA; Lenteclin; Lupidox; M-Dox; Martidox-M; Microdox; Minicycline; Nab-DT; Nee; Novadox; Nudoxy; Solomycin; Vibazine; ***Indon.***: Dohixat; Dotur; Doxacin; Doxicor; Doxin†; Dumoxin; Interdoxin; Siclidon; Viadoxin; Vibramycin; ***Irl.***: Atridox†; By-Mycin; Efracea; Periostat; Vibramycin; ***Israel***: Doxibiotic†; Doxy; Doxylin; Periostat†; Vibramycin†; ***Ital.***: Atridox; Bassado; Miraclin; Periostat; ***Malaysia***: Doline†; Domycine; Doxycillin; Doxymycin; Medomycin; Vibramycin; ***Mex.***: Bioximicina; Domiken; Doranbax†; Doxinonflam; Kenciclen; Periosan; Roxidolin; Vibramicina; Vivradoxil; ***Neth.***: Atridox†; Doxy†; Efracea; Periostat; Unidox; Vibramycin; ***Norw.***: Doxylin; Vibramycin†; Vibranord; ***NZ***: Doxine; Doxy; ***Philipp.***: Bactidox; Comxin; Cytragen; Doxicon; Doxin; Doxylyn; Dyna; Harvellin; Quedox; Vibramycin; ***Pol.***: Dotur†; Doxicin; Doxyratio M; Supracyclin†; Unidox; ***Port.***: Actidox; Atridox†; Doxytrex; Periostat; Pluridoxina; Sigadoxin; Vibramicina; ***Rus.***: Doxal (Доксал); Medomycin (Медомицин)†; Unidox (Юнидокс); Vibramycin (Вибрамицин)†; Vidokcine (Видокцин); Xedocine (Кседоцин); ***S.Afr.***: Cyclidox; Doximal; Doxitab; Doxyclin†; Doxycyl; Doxyhexal†; Doxymycin†; Doxytet; Dumoxin; Noritet†; Vibramycin†; ***Singapore***: Apo-Doxy; Bronmycin; Domycine; Doryx†; Doxine†; Doxycap; Doxyline; Doxymycin; Medomycin; Microdox; Remycin; Tetradox; Vibramycin; Wanmycin†; ***Spain***: Atridox†; Dosil; Doxiclat; Doxicrisol†; Doxipil; Doxiten Bio; Mededoxi†; Peledox†; Proderma; Retens†; Rexilen; Vibracina; Vibravenosa; ***Swed.***: Atridox†; Doxyferm; Oracea; Vibramycin†; Vibranord; ***Switz.***: Doxycline; Doxylag; Doxysol; Oracea; Periostat†; Rudocyclin; Supracycline; Tasmacyclin Akne; Vibramycine; Vibraveineuse; Zadorin; ***Thai.***: Amermycin; Bronmycin†; Cin-Doxy; Docline; Docyl; Doxin; Doxine; Doxinin; Doxinpac; Doxxo†; Doxy-P; Doxy; Doxyclate; Doxycline; Doxycom; Doxyhof; Doxylcap; Doxylin; Doxyman; Doxymed; Madoxy; Medomycin; Medoxin†; Poli-Cycline; Pondoxcycline; Servidoxyne†; Siadocin; Tetradox; Torymycin; Veemycin; Vibramycin; Viprocin; ***Turk.***: Doksin; Monodoks; Tetradox; ***UAE***: DuraDox; ***UK***: Atridox; Doxylar; Efracea; Periostat; Vibramycin†; Vibramycin; ***Ukr.***: Doxy-M (Докси-М); Doxybene (Доксибене); Unidox (Юнидокс); ***USA***: Adoxa†; Alodox; Atridox; Avidoxy; Doryx; Monodox; Morgidox; NutriDox†; Ocudox; Oracea; Oraxyl†; Periostat; Vibra-Tabs†; Vibramycin; ***Venez.***: Doxiclival; Tremesal; Vibramicina C.

Multi-ingredient Preparations. ***Cz.***: Doxycyclin Al Comp; ***Ger.***: Ambrodoxy†; Ambroxol AL comp†; Ambroxol comp; Doxy Comp†; Doxy Plus†; ***India***: Acnedox-LB; Avidox-LB; Avidox-OZ; Avidox-SP; Dox-M ST; Dox-M TZ; Dox-M-A; Dox-M-OZ; Doxy-1 L-DR Forte; Doxyguard; Doxylin-TZ; Emdox-TZ; Glodox-LB; Microdox; ***Spain***: Dosil Enzimatico; Doxiten Enzimatico; ***USA***: Avidoxy DK.

Pharmacopoeial Preparations
BP 2014: Dispersible Doxycycline Tablets; Doxycycline Capsules; **USP 36:** Doxycycline Calcium Oral Suspension; Doxycycline Capsules; Doxycycline for Injection; Doxycycline for Oral Suspension; Doxycycline Hyclate Capsules; Doxycycline Hyclate Delayed-release Capsules; Doxycycline Hyclate Delayed-Release Tablets; Doxycycline Hyclate Tablets; Doxycycline Tablets.

Enoxacin *(BAN, USAN, rINN)*

AT-2266; CI-919; Enoksasiini; Enoksasin; Énoxacine; Enoxacino; Enoxacinum; PD-107779; Эноксацин.
1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid.
$C_{15}H_{17}FN_4O_3$=320.3
CAS — 74011-58-8.
ATC — J01MA04.
ATC Vet — QJ01MA04.
UNII — 325OGW249P.

Pharmacopoeias. *Chin.* and *Jpn* include the sesquihydrate.

Uses and Administration

Enoxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2). It is used mainly in the treatment of urinary-tract infections (p. 213.1) and gonorrhoea (p. 204.2).

For urinary-tract infections, enoxacin is given orally in doses of 200 or 400 mg twice daily.

For details of reduced doses in renal impairment, see p. 292.2.

A single 200-mg or 400-mg dose may be given for uncomplicated gonorrhoea.

References.
1. Patel SS, Spencer CM. Enoxacin: a reappraisal of its clinical efficacy in the treatment of genitourinary tract infections. *Drugs* 1996; **51:** 137–60.

Administration in renal impairment. When the creatinine clearance is 30 mL/minute or less urinary concentrations of enoxacin may be too low to have a therapeutic effect in urinary-tract infections. In other infections, half the usual oral dose of enoxacin is recommended.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Reduced dosage may be needed in renal impairment—see Administration in Renal Impairment, under Uses and Administration, above.

Interactions

As for Ciprofloxacin, p. 264.3.

Of the fluoroquinolones, enoxacin has been reported to cause the most marked interaction with theophylline (p. 1234.2) and with caffeine (p. 1206.1).

Antimicrobial Action

As for Ciprofloxacin, p. 265.2, although enoxacin is generally less potent *in vitro*.

Pharmacokinetics

Peak plasma concentrations of 2 to 3 micrograms/mL occur 1 to 2 hours after a 400-mg oral dose of enoxacin. The plasma half-life is about 3 to 6 hours. Plasma protein binding ranges from 18 to 67%. Enoxacin appears to be widely distributed in the body and concentrations higher than those in plasma have been reported in tissues such as lung, kidney, and prostate. High concentrations occur in bile, but the extent of biliary excretion is not clear.

Enoxacin is eliminated from the body mainly by urinary excretion, but also by metabolism. The major metabolite, 3-oxo-enoxacin, has some antibacterial activity. Urinary excretion of enoxacin is by both tubular secretion and glomerular filtration and may be reduced by probenecid. High concentrations occur in the urine since about 60% of an oral dose of enoxacin appears unchanged in the urine within 24 hours; about 10% is recovered as 3-oxo-enoxacin. In renal impairment the half-life of enoxacin may be prolonged and the oxometabolite may accumulate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi Cai Ni (必采尼); De Xing Li (的星力); Jiu Nuo (久诺); Kai Quan (凯全); Li De Jia (力得佳); Mei Feng (美风); Nuojia (诺佳); ***Fr.***: Enoxor; ***Ger.***: Enoxor; ***Gr.***: Enoxor; ***Ital.***: Enoxen; ***Jpn***: Flumark†; ***Turk.***: Enoksetin.

Enrofloxacin *(BAN, USAN, rINN)*

Bay-Vp-2674; Enrofloksasiini; Enrofloxacine; Enrofloxacino; Enrofloxacinum; Энрофлоксацин.
1-Cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.
$C_{19}H_{22}FN_3O_3$=359.4
CAS — 93106-60-6.
ATC Vet — QJ01MA90.
UNII — 3DX3XEK1BN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Enrofloxacin for Veterinary Use). A pale yellowish or light yellow, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Enrofloxacin). A pale yellow to light yellow crystalline powder. Very slightly soluble in water at pH 7.0. Store in airtight containers. Protect from light.

Profile

Enrofloxacin is a fluoroquinolone antibacterial that is used in veterinary practice.

Ertapenem Sodium *(BANM, USAN, rINNM)*

Ertapenem sódico; Ertapénem Sodique; L-749345; MK-0826; MK-826; Natrii Ertapenemum; ZD-4433; Натрий Эртапенем.
Sodium (4*R*,5*S*,6*S*)-3-{[(3*S*,5*S*)-5-[(*m*-Carboxyphenyl)carbamoyl]-3-pyrrolidinyl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.
$C_{22}H_{24}N_3NaO_7S$=497.5
CAS — 153832-46-3 (ertapenem); 153832-38-3 (ertapenem disodium); 153773-82-1 (ertapenem sodium).
ATC — J01DH03.
ATC Vet — QJ01DH03.
UNII — 2T90KE67L0.

Incompatibility and stability. References.
1. McQuade MS, *et al.* Stability and compatibility of reconstituted ertapenem with commonly used iv infusion and coinfusion solutions. *Am J Health-Syst Pharm* 2004; **61:** 38–45.

Uses and Administration

Ertapenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p. 311.3). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria including intra-abdominal infections, acute gynaecological infections, complicated urinary-tract infections, skin and skin-structure infections (in particular, diabetic foot infections), and respiratory-tract infections. It is also used prophylactically in colorectal surgery. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ertapenem is given as the sodium salt, but doses are expressed in terms of the base; 1.04 g of ertapenem sodium is equivalent to about 1 g of ertapenem. For treatment, it is given by intravenous infusion over 30 minutes or by intramuscular injection, in a usual dose of 1 g once daily. For prophylaxis, a single 1-g dose is given intravenously 1 hour before the start of surgery.

The dose of ertapenem may need to be reduced in renal impairment, see p. 292.3.

For details of doses in infants and children, see p. 292.3.

References.
1. Keating GM, Perry CM. Ertapenem: a review of its use in the treatment of bacterial infections. *Drugs* 2006; **65:** 2151–78.
2. Rogers LC, *et al.* Ertapenem for diabetic foot infections. *Drugs Today* 2006; **42:** 695–701.
3. Burkhardt O, *et al.* Ertapenem: the new carbapenem 5 years after first FDA licensing for clinical practice. *Expert Opin Pharmacother* 2007; **8:** 237–56.
4. Falagas ME, *et al.* Meta-analysis: ertapenem for complicated intra-abdominal infections. *Aliment Pharmacol Ther* 2008; **27:** 919–31.
5. Nielsen MD, *et al.* The use of ertapenem for the treatment of lower extremity infections. *J Foot Ankle Surg* 2009; **48:** 135–41.
6. Congeni BL. Ertapenem. *Expert Opin Pharmacother* 2010; **11:** 669–72.

Administration in children. Ertapenem may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by intravenous infusion over 30 minutes or if appropriate by intramuscular injection. For children from 3 months of age the usual recommended dose is 15 mg/kg twice daily (up to a maximum of 1 g daily).

Administration in renal impairment. US licensed product information indicates that parenteral doses of ertapenem should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

All cross-references refer to entries in Volume A

- CC 30 mL or less per minute per 1.73 m² (including end-stage disease where CC is 10 mL or less per minute per 1.73 m²): 500 mg daily for adults
- haemodialysis: if the 500-mg dose is given in the 6-hour period before dialysis an additional 150 mg should be given after the dialysis session

The UK product information, however, states that in advanced renal insufficiency and haemodialysis there are inadequate data to make recommendations and that ertapenem should not be used in these patients.

Adverse Effects and Precautions

As for Imipenem, p. 312.1. There have been reports of DRESS syndrome (drug rash with eosinophilia and systemic symptoms) after the use of ertapenem.

Ertapenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the enzyme, is not required.

Effects on the nervous system. Unusual mental status changes were reported in 2 elderly men after 5 to 7 days of treatment with ertapenem.[1] The first, a 79-year-old man, developed garbled speech and miosis that resolved after ertapenem was stopped but recurred upon rechallenge. The second patient, a 70-year-old man with cachexia and acute renal insufficiency, developed delirium that resolved the day after ertapenem was stopped. There have also been postmarketing reports of aggression, hallucinations, dyskinesia, myoclonus, and tremor after the use of ertapenem.

1. Duquaine S, *et al.* Central nervous system toxicity associated with ertapenem use. Abstract: *Ann Pharmacother* 2011; **45:** 127. Full version: http://www.theannals.com/cgi/reprint/45/1/e6 (accessed 24/06/11)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ertapenem as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Probenecid inhibits the renal excretion of ertapenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to ertapenem, and the view that carbapenems should not be used with valproates, see p. 557.2.

Antimicrobial Action

As for Imipenem, p. 312.2.

Ertapenem is reported to be slightly more active overall *in vitro* than imipenem but is less active against Gram-positive bacteria and has a narrower spectrum of activity. It is generally not active against *Acinetobacter* spp., *Pseudomonas aeruginosa*, MRSA, or enterococci.

Pharmacokinetics

After intravenous infusion of ertapenem 1 g over 30 minutes, a mean plasma concentration of 155 micrograms/mL is attained, falling to 9 micrograms/mL after 12 hours and 1 microgram/mL after 24 hours. After the same dose intramuscularly, a plasma concentration of 67 micrograms/mL is achieved after 2 hours. Bioavailability after intramuscular injection is about 90%.

Ertapenem is more than 90% bound to plasma proteins. It is distributed into breast milk. The plasma half-life is about 4 hours in adults and 2.5 hours in infants and in children aged 3 months to 12 years; the half-life may be prolonged in patients with renal impairment.

Ertapenem is partially metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite. About 80% of a dose is excreted in the urine as both unchanged drug and metabolite. About 10% is excreted in faeces.

Ertapenem is removed by haemodialysis.

References.

1. Mistry GC, *et al.* Pharmacokinetics of ertapenem in patients with varying degrees of renal insufficiency and in patients on hemodialysis. *J Clin Pharmacol* 2006; **46:** 1128–38.
2. Brink AJ, *et al.* Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. *Int J Antimicrob Agents* 2009; **33:** 432–6.
3. Frasca D, *et al.* Pharmacokinetics of ertapenem following intravenous and subcutaneous infusions in patients. *Antimicrob Agents Chemother* 2010; **54:** 924–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Invanz; ***Austral.***: Invanz; ***Austria***: Invanz; ***Braz.***: Invanz; ***Canad.***: Invanz; ***Chile***: Invanz; ***China***: Invanz (怡万之); ***Cz.***: Invanz; ***Denm.***: Invanz; ***Fin.***: Invanz; ***Fr.***: Invanz; ***Ger.***: Invanz; ***Gr.***: Invanz; ***Hong Kong***: Invanz; ***Hung.***: Invanz; ***India***: Invanz; ***Indon.***: Invanz; ***Irl.***: Invanz; ***Israel***: Invanz; ***Ital.***: Invanz; ***Malaysia***: Invanz; ***Neth.***: Invanz; ***Norw.***: Invanz; ***NZ***: Invanz; ***Philipp.***: Invanz; ***Pol.***: Invanz; ***Port.***: Invanz; ***Rus.***: Invanz (Инванз); ***S.Afr.***: Invanz; ***Singapore***: Invanz; ***Spain***: Invanz; ***Swed.***: Invanz; ***Switz.***: Invanz; ***Thai.***: Invanz; ***Turk.***: Invanz; ***UK***: Invanz; ***Ukr.***: Invanz (Инванз); ***USA***: Invanz; ***Venez.***: Invanz.

Erythromycin *(BAN, rINN)*

Eritromicin; Eritromicina; Eritromicinas; Eritromisin; Érythromycine; Erythromycinum; Erytromycin; Erytromycyna; Erytromysiini; Эритромицин.

Erythromycin A is (2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-5-(3-amino-3,4,6-trideoxy-*N*,*N*-dimethyl-β-D-*xylo*-hexopyranosyloxy)-3-(2,6-dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-13-ethyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethyl-9-oxotridecan-13-olide.

$C_{37}H_{67}NO_{13}$=733.9

CAS — 114-07-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QJ51FA01; QS01AA17.

UNII — 63937KV33D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Erythromycin). It is produced by the growth of a strain of *Streptomyces erythreus* and is a mixture of macrolide antibiotics consisting largely of erythromycin A. It occurs as a white or slightly yellow powder or colourless or slightly yellow crystals; slightly hygroscopic. Slightly soluble in water but less soluble at higher temperatures; freely soluble in alcohol; soluble in methyl alcohol. Protect from light.

USP 36: (Erythromycin). It consists primarily of erythromycin A. A white or slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 1000 of water; soluble in alcohol, in chloroform, and in ether. Store in airtight containers.

Erythromycin Estolate *(BAN, USAN, rINNM)*

Eritromicina, estolato de; Eritromicin-esztolát; Eritromicino estolatas; Erythromycin Propionate Lauryl Sulfate; Erythromycin Propionate Lauryl Sulphate; Érythromycine, Estolate d'; Erythromycinestolat; Erythromycin-estolát; Erythromycini Estolas; Erytromycinestolat; Erytromycyny estolan; Erytromysiiniestolaatti; Estolato de eritromicina; Propionylerythromycin Lauryl Sulphate; Эритромицина Эстолат.

Erythromycin 2′-propionate dodecyl sulphate.

$C_{40}H_{75}NO_{14}.C_{12}H_{26}O_4S$=1056.4

CAS — 3521-62-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — XRJ2P631HP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Erythromycin Estolate). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; practically insoluble in dilute hydrochloric acid. Protect from light.

USP 36: (Erythromycin Estolate). A white, odourless or practically odourless, crystalline powder. It has a potency equivalent to not less than 600 micrograms of erythromycin per mg, calculated on the anhydrous basis. Practically insoluble in water; soluble 1 in 20 of alcohol, 1 in 15 of acetone, and 1 in 10 of chloroform. Store in airtight containers.

Erythromycin Ethyl Succinate *(BANM)*

Eritromicina, etilsuccinato de; Eritromicin-etilszukcinát; Eritromicino etilsukcinatas; Erythromycin Ethylsuccinate; Érythromycine, éthylsuccinate d'; Erythromycinethylsuccinat; Erythromycin-ethylsukcinát; Erythromycini ethylsuccinas; Erytromycinetylsuccinat; Erytromycyny etylobursztynian; Erytromysiinietyylisuksinaatti; Эритромицина Этилсукцинат.

Erythromycin 2′-(ethylsuccinate).

$C_{43}H_{75}NO_{16}$=862.1

CAS — 41342-53-4.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — 1014KSJ86F.

NOTE. Compounded preparations of erythromycin ethyl succinate may be represented by the following names:

- Co-erynsulfisox (*PEN*)—erythromycin ethyl succinate and acetyl sulfafurazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Erythromycin Ethylsuccinate; Erythromycin Ethyl Succinate BP 2014). A white or almost white, hygroscopic crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Erythromycin Ethylsuccinate). A white or slightly yellow, odourless or practically odourless, crystalline powder. It has a potency equivalent to not less than 765 micrograms of erythromycin per mg, calculated on the anhydrous basis. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in macrogol 400. Store in airtight containers.

Erythromycin Gluceptate *(BANM, rINNM)*

Eritromicina, gluceptato de; Érythromycine, Gluceptate d'; Erythromycini Gluceptas; Gluceptato de eritromicina; Эритромицина Глюцептат.

Erythromycin glucoheptonate.

$C_{37}H_{67}NO_{13}.C_7H_{14}O_8$=960.1

CAS — 304-63-2; 23067-13-2.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — 2AY21R0U64.

Pharmacopoeias. In *US*.

USP 36: (Sterile Erythromycin Gluceptate). It is erythromycin gluceptate suitable for parenteral use. It has a potency equivalent to not less than 600 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a 2.5% solution in water is between 6.0 and 8.0.

Erythromycin Lactobionate *(BANM, rINNM)*

Eritromicina, lactobionato de; Eritromicin-laktobionát; Eritromicino laktobionatas; Érythromycine, Lactobionate d'; Erythromycini Lactobionas; Erythromycinlactobionat; Erythromycin-laktobionát; Erytromycinlaktobionat; Erytromycyny laktobionian; Erytromysiinilaktov; Éthylèneglycol, monostéarate d'; Lactobionato de eritromicina; Эритромицина Лактобионат.

Erythromycin mono(4-*O*-β-D-galactopyranosyl-D-gluconate).

$C_{37}H_{67}NO_{13}.C_{12}H_{22}O_{12}$=1092.2

CAS — 3847-29-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — 33H58I7GLQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Erythromycin Lactobionate). Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*. White or slightly yellow, hygroscopic powder. Soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very slightly soluble in acetone and in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5. Store in airtight containers.

USP 36: (Sterile Erythromycin Lactobionate). It has a potency equivalent to not less than 525 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a solution in water containing the equivalent of erythromycin 5% is between 6.5 and 7.5.

Erythromycin Propionate *(BANM, USAN, rINNM)*

Eritromicina, propionato de; Erythromycin Propanoate; Érythromycine, Propionate d'; Erythromycini Propionas; Propionato de eritromicina; Propionylerythromycin; Эритромицина Пропионат.

Erythromycin 2′-propionate.

$C_{40}H_{71}NO_{14}$=790.0

CAS — 134-36-1.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — H875CIT999.

Pharmacopoeias. In *Fr*.

Erythromycin Stearate *(BANM, rINNM)*

Eritromicina, estearato de; Eritromicino stearatas; Eritromicin-sztearát; Eritromisin Stearat; Érythromycine, Stéarate d'; Erythromycini Stearas; Erythromycinstearat; Erythromycin-stearát; Erytromycinstearat; Erytromycyny stearynian; Erytromysiinistearaatti; Estearato de eritromicina; Эритромицина Стеарат.

Erythromycin octadecanoate.

$C_{37}H_{67}NO_{13}.C_{18}H_{36}O_2$=1018.4

CAS — 643-22-1.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — LXW024X05M.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Erythromycin Stearate). A mixture of the stearates of erythromycin and stearic acid. A white or almost white crystalline powder. Practically insoluble in water;

soluble in acetone and in methyl alcohol. Solutions may be opalescent.

USP 36: (Erythromycin Stearate). The stearic acid salt of erythromycin with an excess of stearic acid. White or slightly yellow crystals or powder, odourless or may have a slight, earthy odour. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, and in methyl alcohol. Store in airtight containers.

Incompatibility and stability. The stability of erythromycin derivatives is dependent upon pH, with particularly rapid degradation occurring at a pH greater than 10 or less than 5.5. Incompatibility might reasonably be expected, therefore, when erythromycin preparations are mixed with drugs or preparations that have a highly acidic or alkaline pH. In practice, reports of incompatibility are not always consistent, and other factors such as the temperature and concentration of solutions, and the diluents used, may play a role.

Solutions for infusion. For the preparation of solutions of erythromycin lactobionate for infusion, a primary solution containing not more than 5% of erythromycin should be prepared first; only water for injection should be used in preparing the primary solution. It should be further diluted with sodium chloride 0.9% or other suitable intravenous fluid before use. Acidic solutions, such as glucose, should only be used if neutralised with sodium bicarbonate.

Uses and Administration

Erythromycin is a macrolide antibacterial with a wide spectrum of activity, that is used in the treatment of infections caused by susceptible organisms.

Its uses have included the treatment of severe campylobacter enteritis, chancroid, diphtheria, legionnaires' disease and other *Legionella* infections, neonatal conjunctivitis, pertussis, respiratory-tract infections including bronchitis, pneumonia (mycoplasmal and other atypical pneumonias as well as streptococcal), and sinusitis, and trench fever, and, combined with neomycin, for the prophylaxis of surgical infection in patients undergoing bowel surgery. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. It is also used in the prevention of diphtheria in non-immune patients and of pertussis in non- or partially immune patients.

Erythromycin is used as an alternative to penicillin in penicillin-allergic patients with various conditions including actinomycosis, leptospirosis, listeriosis, mouth infections, otitis media (usually with a sulfonamide such as sulfafurazole), pelvic inflammatory disease caused by *Neisseria gonorrhoeae*, pharyngitis, and staphylococcal and streptococcal skin infections. It has been used in the treatment of penicillin-allergic patients with syphilis, but there are doubts about its efficacy. It is also used in the prevention of perinatal or Group A streptococcal infections, rheumatic fever, and infections in splenectomised patients. In penicillin-allergic patients in the early stages of Lyme disease, erythromycin may be used as an alternative to a tetracycline; this use is generally restricted to pregnant women and young children, since it is less effective than other drugs. It is also used as an alternative to the tetracyclines in patients with cholera, *Chlamydia* or *Chlamydophila* infections (such as epididymitis, lymphogranuloma venereum, nongonococcal urethritis, pneumonia, psittacosis, and trachoma), Q fever, and spotted fevers.

For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Both oral and topical erythromycin may be used in acne (see Skin Disorders, p. 295.1) and rosacea (p. 1688.3).

Erythromycin may be given as the base or its salts or esters; doses are expressed in terms of the base. Each 1 g of erythromycin is equivalent to about the following amounts of each salt or ester:

- erythromycin estolate 1.44 g
- erythromycin ethyl succinate 1.17 g
- erythromycin gluceptate 1.31 g
- erythromycin lactobionate 1.49 g
- erythromycin propionate 1.08 g
- erythromycin stearate 1.39 g

The usual oral adult dose is the equivalent of erythromycin 1 to 2 g daily in 2 to 4 divided doses; for severe infections this may be increased to up to 4 g daily in divided doses. Daily doses higher than 1 g should be given in more than 2 divided doses.

For the prevention of streptococcal infections in patients with evidence of rheumatic fever or heart disease, who are unable to take penicillin or sulfonamides, a dose of 250 mg twice daily may be given.

For the management of acne, maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNF* recommends a dose of 500 mg twice daily.

In patients who are unable to take erythromycin orally and in those who are severely ill, in whom it is necessary to attain an immediate high blood concentration, erythromycin may be given intravenously as the lactobionate, in doses equivalent to those given orally. The gluceptate has also been used intravenously. To reduce the risk of venous irritation it should be given only by continuous or intermittent intravenous infusion of a solution containing not more than 0.5% of erythromycin. Intermittent infusions should be given every 6 hours over 20 to 60 minutes.

Doses may need to be limited in patients with renal impairment (see p. 294.3).

For details of doses in children, see p. 294.2.

Erythromycin was formerly given by intramuscular injection, but such injections are painful and are no longer generally recommended. Erythromycin is used as a 0.5% eye ointment for the treatment of superficial ocular infections, including neonatal conjunctivitis, caused by susceptible strains of bacteria and for the prophylaxis of neonatal conjunctivitis caused by *N. gonorrhoeae* or *C. trachomatis*. It may also be applied topically as a 2 to 4% gel or solution for the treatment of acne vulgaris and is also available in combination preparations with benzoyl peroxide, ichthammol, isotretinoin, tretinoin, and zinc acetate.

Erythromycin acistrate, erythromycin cyclocarbonate, and propionyl erythromycin mercaptosuccinate have also been used. Erythromycin thiocyanate and erythromycin phosphate are used in veterinary medicine.

Reviews.

1. Zhanel GG, *et al.* Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 2001; **61:** 443–98.

Administration. A discussion of the significance of different formulations and salts used for oral preparations of erythromycin concluded that there was no clear evidence that any was superior in terms of clinical effect.[1]

1. Anonymous. Giving erythromycin by mouth. *Drug Ther Bull* 1995; **33:** 77–9.

Administration in children. Erythromycin may be given orally or by continuous or intermittent intravenous infusion for the treatment of **infections** caused by susceptible organisms. The usual dose for infants and children is the equivalent of about 30 to 50 mg/kg of erythromycin daily in 2 to 4 divided doses although it may be doubled in severe infections. Based on age, the usual dose in children 2 to 8 years old is 1 g daily and in infants and children up to 2 years old 500 mg daily. Those over 8 years of age may be given the usual adult dose (see Uses and Administration, above).

The following doses have been suggested for use in neonates:

- In the UK, the *BNFC* suggests an oral dose of 12.5 mg/kg, or an intravenous dose of 10 to 12.5 mg/kg, every 6 hours
- In the USA, the American Academy of Pediatrics[1] suggests that neonates of 1 week of age or less may be given 10 mg/kg orally or intravenously every 12 hours. All neonates more than 1 week of age may be given the same dose every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birthweight neonates (weighing less than 1 kg)

For the **prevention of recurrence of rheumatic fever** the *BNFC* suggests that erythromycin may be given orally in penicillin allergic children in the following doses:

- children 1 month to 2 years of age: 125 mg twice daily
- children from 2 years of age: 250 mg twice daily

For the **prevention of secondary cases of group A streptococcal infection** the *BNFC* suggests that erythromycin may be given orally for 10 days in penicillin allergic children in the following doses:

- children 1 month to 2 years of age: 125 mg every 6 hours
- children 2 to 8 years of age: 250 mg every 6 hours
- children from 8 years of age: 250 to 500 mg every 6 hours

For the **prevention of secondary cases of diphtheria** in non-immune patients the *BNFC* suggests that erythromycin may be given orally for 7 days:

- children 1 month to 2 years of age: 125 mg every 6 hours
- children 2 to 8 years of age: 250 mg every 6 hours
- children from 8 years of age: 500 mg every 6 hours

If nasopharyngeal swabs for *Corynebacterium diphtheriae* are positive after the first 7 days, treatment should be continued for a further 10 days.

For the management of **acne**, oral maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNFC* recommends a dose of 500 mg twice daily in those over 12 years of age. It also suggests a dose of 250 mg daily in 1 or 2 divided doses for infants with acne.

Although unlicensed in the UK for use in **gastrointestinal stasis**, the *BNFC* suggests a dose of 3 mg/kg given orally or by intravenous infusion, 4 times daily for neonates and children up to 18 years of age (see also p. 294.3).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. A maximum dose of erythromycin 1.5 g daily has been suggested by the *BNF* for adult patients with severe renal impairment.

Decreased gastrointestinal motility. Erythromycin stimulates gut motility, apparently by acting as a motilin receptor agonist, although it has been suggested that it may have other actions as well.[1] It has been tried, with some success, for its prokinetic action in a small number of patients with decreased gastrointestinal motility (p. 1808.2) including those with functional dyspepsia,[2] gastroparesis,[3] reflux ileus,[4] acute colonic pseudo-obstruction (Ogilvie's syndrome),[4,5] delayed gastric emptying after pancreatic-duodenal surgery,[6] and neonatal postoperative intestinal dysmotility.[7] It has also been used to increase gastrointestinal motility in critically ill, mechanically ventilated patients[8,9] and in preterm very low birth-weight infants.[10,11] However, the prophylactic or routine use of erythromycin in such circumstances has been cautioned against,[9,10] and a systematic review[12] of neonatal use also suggested that erythromycin should be reserved for a very small subset of high-risk preterm neonates with persistent or severe feed intolerance. Although another systematic review[13] reported more positive effects on feeding tolerance when erythromycin was given at higher doses (40 to 50 mg/kg daily) or to infants more than 32 weeks of gestational age, it concluded that there was insufficient evidence to recommend the use of erythromycin (at low or high doses) for preterm infants with or at risk of feeding intolerance. Adverse effects associated with the long-term use of erythromycin that is necessary in, for example, diabetic gastroparesis, may also be problematic.[14]

For suggested doses in the treatment of children with gastrointestinal stasis, see Administration in Children, above.

1. Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut* 1992; **33:** 397–401.
2. Arts J, *et al.* Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; **54:** 455–60.
3. Maganti K, *et al.* Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003; **98:** 259–63.
4. Armstrong DN, *et al.* Erythromycin for reflux ileus in Ogilvie's syndrome. *Lancet* 1991; **337:** 378.
5. Bonacini M, *et al.* Erythromycin as therapy for acute colonic pseudo-obstruction (Ogilvie's syndrome). *J Clin Gastroenterol* 1991; **13:** 475–6.
6. Yeo CJ, *et al.* Erythromycin accelerates gastric emptying after pancreaticoduodenectomy: a prospective, randomized, placebo-controlled trial. *Ann Surg* 1993; **218:** 229–38.
7. Simkiss DE, *et al.* Erythromycin in neonatal postoperative intestinal dysmotility. *Arch Dis Child* 1994; **71:** F128–9.
8. Chapman MJ, *et al.* Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. *Crit Care Med* 2000; **28:** 2334–7.
9. Hawkyard CV, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *J Antimicrob Chemother* 2007; **59:** 347–58.
10. Ng PC, *et al.* Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F177–F182.
11. Nuntnarumit P, *et al.* Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006; **148:** 600–605.
12. Patole S, *et al.* Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F301–F306.
13. Ng E, Shah VS. Erythromycin for the prevention and treatment of feeding intolerance in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 14/07/09).
14. Tanis AA, *et al.* Side-effects of oral erythromycin for treatment of diabetic gastroparesis. *Lancet* 1993; **342:** 1431.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that the 14-membered ring macrolides (such as clarithromycin, erythromycin, and roxithromycin) and the 15-membered ring macrolides (such as azithromycin) also have immunomodulatory and anti-inflammatory effects that could be useful in the management of respiratory diseases including asthma (p. 1195.2), bronchiectasis, chronic obstructive pulmonary disease (p. 1199.1), cystic fibrosis (p. 177.2), desquamative interstitial pneumonia, diffuse panbronchiolitis, and sinusitis (p. 206.2).[1-6] However, a systematic review[7] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further studies were warranted. A systematic review[8] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear and further studies were needed. A randomised, double-blind, placebo-controlled study[9] to evaluate the use of oral azithromycin given three times a week for 12 months for the treatment of cystic fibrosis in children, reported a significant reduction in the number of pulmonary exacerbations needing treatment with antibacterials,

even in the absence of infection with *Pseudomonas aeruginosa*. In another study, in patients with chronic obstructive pulmonary disease, oral azithromycin 250 mg taken daily for 12 months, in addition to their usual treatment, decreased the frequency of exacerbations and improved quality of life;[10] a reduction in hearing was noted in a small percentage of patients. Azithromycin has also been investigated[11-13] in the management of bronchiolitis obliterans in patients who have undergone lung transplantation (p. 1941.3), although its role has yet to be defined.

1. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. *Chest* 2004; **125** (suppl 2): 52S–61S.
2. Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2004; **125** (suppl 2): 70S–78S.
3. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; **54:** 21–8.
4. King P. Is there a role for inhaled corticosteroids and macrolide therapy in bronchiectasis? *Drugs* 2007; **67:** 965–74.
5. Knyazhitskiy A, *et al.* Beneficial response to macrolide antibiotic in a patient with desquamative interstitial pneumonia refractory to corticosteroid therapy. *Chest* 2008; **134:** 185–7.
6. Giamarellos-Bourboulis EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. *Int J Antimicrob Agents* 2008; **31:** 12–20.
7. Richeldi L, *et al.* Macrolides for chronic asthma. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/03/07).
8. Southern KW, *et al.* Macrolide antibiotics for cystic fibrosis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 02/03/07).
9. Clement A, *et al.* Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006; **61:** 895–902.
10. Albert RK, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; **365:** 689–98.
11. Gottlieb J, *et al.* Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2008; **85:** 36–41.
12. Porhownik NR, *et al.* Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. *Can Respir J* 2008; **15:** 199–202.
13. Fietta AM, Meloni F. Lung transplantation: the role of azithromycin in the management of patients with bronchiolitis obliterans syndrome. *Curr Med Chem* 2008; **15:** 716–23.

Skin disorders. *ACNE.* Erythromycin may be used topically or orally in the treatment of acne (p. 1682.2). Topical erythromycin may be used for mild inflammatory acne if benzoyl peroxide is ineffective or poorly tolerated. It is also used as adjunctive treatment in more severe acne. Erythromycin is also available as a complex with zinc acetate that has been reported to be more effective than topical erythromycin alone[1] or oral minocycline.[2] However, development of resistance by the skin flora is an increasing problem. Combination therapy with benzoyl peroxide and erythromycin has been reported to be helpful in preventing the selection of resistant mutants[3,4] and to be more effective than topical clindamycin alone.[5] Combination with azelaic acid has also been tried.[6] Alternatively, short intervening courses of benzoyl peroxide during antibacterial therapy may help to eliminate any resistant bacteria that have been selected.[7] It has also been recommended that courses of topical antibacterials be continued for no longer than necessary (although treatment should be used for at least 6 months), that the same drug be used if further treatment is required, and that treatment with different oral and topical antibacterials or antibacterial rotation be avoided.[7]

Oral erythromycin has been used as an alternative to a tetracycline in moderate acne. However, resistance to erythromycin is becoming widespread among propionibacteria, and response may be poor, although it may perhaps be an option for those patients in whom other antibacterials are unsuitable.

1. Habbema L, *et al.* A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. *Br J Dermatol* 1989; **121:** 497–502.
2. Stainforth J, *et al.* A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. *J Dermatol Treat* 1993; **4:** 119–22.
3. Eady EA, *et al.* Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; **131:** 331–6.
4. Eady EA, *et al.* The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996; **134:** 107–13.
5. Packman AM, *et al.* Treatment of acne vulgaris: combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. *Int J Dermatol* 1996; **35:** 209–11.
6. Pazoki-Toroudi H, *et al.* Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris. *J Dermatolog Treat* 2010; **21:** 212–16.
7. Eady EA, *et al.* Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *BMJ* 1993; **306:** 555–6.

Adverse Effects

Erythromycin and its salts and esters are generally well tolerated and serious adverse effects are rare. Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are fairly common after both oral and parenteral use, probably because of the stimulant activity of erythromycin on the gut. Gastrointestinal effects are dose related and appear to be more common in young than in older patients. Superinfection with resistant organisms may occur and pseudomembranous colitis has been reported.

Hypersensitivity reactions appear to be uncommon, having been reported in about 0.5% of patients, and include pruritus, urticaria, and skin rash as well as occasional cases of anaphylaxis. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported very rarely. Hypersensitivity or irritation may occur after topical application of erythromycin.

A hypersensitivity reaction is thought to be responsible for the hepatotoxicity sometimes reported in patients receiving erythromycin or its derivatives but this has been disputed by some. Most reports of cholestatic hepatitis have been in patients receiving the estolate, and it has been suggested that the propionyl ester linkage is particularly associated with hepatotoxicity, but symptoms have also been reported in patients given the base and most of the other derivatives, both orally and parenterally. Symptoms indicative of cholestasis, including upper abdominal pain (sometimes very severe), nausea and vomiting, abnormal liver function values, raised serum bilirubin, and usually jaundice, may be accompanied by rash, fever, and eosinophilia. Symptoms usually occur in patients who have been taking the drug for more than 10 days, although they may develop more quickly in patients given the drug previously. Hepatic dysfunction seems to be rare in children under 12 years of age. The effects of erythromycin on the liver are generally reversible on stopping treatment. Erythromycin may interfere with tests for serum aspartate aminotransferase, which might make diagnosis of hepatotoxicity more difficult.

A generally reversible sensorineural deafness, sometimes with tinnitus, has been reported in patients given erythromycin and appears to be related to serum concentration, with an increased likelihood of such effects in patients given doses of 4 g or more daily of base or its equivalent, in those given intravenous therapy, and in those with renal or hepatic impairment.

Other adverse effects that have been reported in patients given erythromycin include agranulocytosis, aggravation of muscular weakness in myasthenia gravis patients, and pancreatitis. Prolongation of the QT interval and other arrhythmias, sometimes fatal, including torsade de pointes have been reported particularly with intravenous use. There have also been isolated reports of transient CNS adverse effects including confusion, hallucinations, seizures, and vertigo.

Parenteral formulations of erythromycin are irritant and intravenous dosage may produce thrombophlebitis, particularly at high doses. Intramuscular injection is generally avoided as it may produce severe pain.

General reviews.

1. Periti P, *et al.* Adverse effects of macrolide antibacterials. *Drug Safety* 1993; **9:** 346–64.
2. Principi N, Esposito S. Comparative tolerability of erythromycin and newer macrolide antibacterials in paediatric patients. *Drug Safety* 1999; **20:** 25–41.
3. Rubinstein E. Comparative safety of the different macrolides. *Int J Antimicrob Agents* 2001; **18** (suppl 1): S71–S76.

Effects on body temperature. A report of hypothermia associated with oral erythromycin in 2 children.[1] Symptoms resolved on stopping the drug. The children were cousins, perhaps indicating a genetic predisposition to the effect. There has also been a similar report of hypothermia in 3 children given azithromycin orally.[2]

1. Hassel B. Hypothermia from erythromycin. *Ann Intern Med* 1991; **115:** 69–70.
2. Kavukçu S, *et al.* Hypothermia from azithromycin. *J Toxicol Clin Toxicol* 1997; **35:** 225 6.

Effects on the cardiovascular system. There have been several reports[1-6] of QT prolongation or torsade de pointes associated with erythromycin, particularly with intravenous use.

A review[7] of reports of torsade de pointes received by the FDA Adverse Event Reporting System between 1987 and December 2000 identified 156 cases associated with use of azithromycin, clarithromycin, dirithromycin, or erythromycin. Of these reports, half involved the use of other drugs known to prolong the QT interval; comorbid diseases and physiological abnormalities, including cardiac abnormalities, were also commonly reported. A retrospective analysis[8] of a cohort of patients who suffered sudden death from cardiac causes found that the rate of sudden cardiac death was twice as high among current users of erythromycin as in those not using antibacterials; there was no such increase among former users, nor among current users of amoxicillin. The greatest increase in risk was seen in patients using erythromycin with inhibitors of the cytochrome P450 isoenzyme subfamily CYP3A; such patients had more than 5 times the risk of sudden cardiac death of patients who took neither. Findings from an observational population-based case-control study[9] in patients who had had ventricular arrhythmia or cardiac arrest supported the association between recent use of macrolides and increased risk of these events. Another observational study[10] of data from a US cohort reported that treatment with oral azithromycin for 5 days was associated with a small absolute increase in deaths from cardiovascular causes; this was most pronounced among patients with a high baseline risk of cardiovascular disease. The risk of death was significantly greater with azithromycin than with amoxicillin or ciprofloxacin but did not differ significantly from the risk with levofloxacin.

1. McComb JM, *et al.* Recurrent ventricular tachycardia associated with QT prolongation after mitral valve replacement and its association with intravenous administration of erythromycin. *Am J Cardiol* 1984; **54:** 922–3.
2. Schoenenberger RA, *et al.* Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ* 1990; **330:** 1375–6.
3. Nattel S, *et al.* Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med* 1990; **89:** 235–8.
4. Gitler B, *et al.* Torsades de pointes induced by erythromycin. *Chest* 1994; **105:** 368–72.
5. Gouyon JB, *et al.* Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994; **13:** 840–1.
6. Drici M-D, *et al.* Cardiac actions of erythromycin: influence of female sex. *JAMA* 1998; **280:** 1774–6.
7. Shaffer D, *et al.* Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis* 2002; **35:** 197–200.
8. Ray WA, *et al.* Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; **351:** 1089–96.
9. Zambon A, *et al.* Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Safety* 2009; **32:** 159–67.
10. Ray WA, *et al.* Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; **366:** 1881–90.

Effects on the gastrointestinal tract. Comparison in patients with upper respiratory-tract infections has suggested that erythromycin ethyl succinate may be associated with less **abdominal pain** than an equivalent dosage of erythromycin base.[1] Another study has indicated that there was no significant difference in gastrointestinal symptoms between plain and enteric-coated formulations of erythromycin base.[2] Severe **nausea and vomiting** after rapid intravenous infusion of erythromycin lactobionate stopped in 2 patients who transferred to oral erythromycin base or ethyl succinate.[3] However, the adverse effects may have been due to the rate of infusion, since in 2 further patients symptoms resolved when the lactobionate was given more slowly as a more dilute solution.[3]

Studies have suggested an association between erythromycin and infantile **hypertrophic pyloric stenosis**.[4-6] A retrospective cohort study of 469 infants who had received erythromycin found that 43 were diagnosed with the condition including 36 male infants, although erythromycin had been prescribed almost equally for males and females.[5] All the infants in whom stenosis developed were given erythromycin in the first 2 weeks of life. In another study,[6] involving 7138 infants given erythromycin between 3 and 90 days of life, use of the drug between 3 and 13 days of life was associated with an almost eightfold increased risk of infantile hypertrophic pyloric stenosis. However, it was believed that the evidence did not support a generalisation of this association to the whole class of macrolides[7] although pyloric stenosis has been reported in breast-fed infants associated with the use of erythromycin or several other macrolides in their mothers (see under Precautions, p. 296.1). Hypertrophic pyloric stenosis has also been reported in 2 of 3 premature triplets treated with azithromycin.[8]

A case of black **hairy tongue** has been reported[9] associated with long-term erythromycin treatment.

For reference to the stimulant effects of erythromycin on the gastrointestinal tract, see Decreased Gastrointestinal Motility under Uses and Administration, p. 292.3.

1. Saloranta P, *et al.* Erythromycin ethylsuccinate, base and acistrate in the treatment of upper respiratory tract infection: two comparative studies of tolerability. *J Antimicrob Chemother* 1989; **24:** 455–62.
2. Ellsworth AJ, *et al.* Prospective comparison of patient tolerance to enteric-coated vs non-enteric-coated erythromycin. *J Fam Pract* 1990; **31:** 265–70.
3. Seifert CF, *et al.* Intravenous erythromycin lactobionate-induced severe nausea and vomiting. *DICP Ann Pharmacother* 1989; **23:** 40–4.
4. Honein MA, *et al.* Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet* 1999; **354:** 2101–5. Correction. *ibid.* 2000; **355:** 758.
5. Mahon BE, *et al.* Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. *J Pediatr* 2001; **139:** 380–4.
6. Cooper WO, *et al.* Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 2002; **156:** 647–50.
7. Hauben M, Amsden GW. The association of erythromycin and infantile hypertrophic pyloric stenosis: causal or coincidental? *Drug Safety* 2002; **25:** 929–42.
8. Morrison W. Infantile hypertrophic pyloric stenosis in infants treated with azithromycin. *Pediatr Infect Dis J* 2007; **26:** 186–8.
9. Pigatto PD, *et al.* Black hairy tongue associated with long-term oral erythromycin use. *J Eur Acad Dermatol Venereol* 2008; **22:** 1269–70.

Effects on the neonate. For a suggestion that erythromycin or other macrolides might be associated with an increased risk of infantile hypertrophic pyloric stenosis in

neonates, see under Effects on the Gastrointestinal Tract, p. 293.3.

Effects on the skin. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have rarely been reported with macrolides.[1,2]

1. Lestico MR, Smith AD. Stevens-Johnson syndrome following erythromycin administration. *Am J Health-Syst Pharm* 1995; **52:** 1805–7.
2. Sullivan S, *et al*. Stevens-Johnson syndrome secondary to erythromycin. *Ann Pharmacother* 1999; **33:** 1369.

Overdosage. Acute pancreatitis was reported in a 12-year-old girl after ingestion of about 5 g of erythromycin base.[1] Transient pancreatitis has also been reported in another 15-year-old girl who took 5.328 g of erythromycin base.[2] Erythromycin produces contraction of the sphincter of Oddi resulting in reflux of bile into the pancreas but the resulting pancreatitis is self-limited and remits when sphincter tone returns to normal after the erythromycin is eliminated from the body.

1. Berger TM, *et al*. Acute pancreatitis in a 12-year-old girl after an erythromycin overdose. *Pediatrics* 1992; **90:** 624–6.
2. Tenenbein MS, Tenenbein M. Acute pancreatitis due to erythromycin overdose. *Pediatr Emerg Care* 2005; **21:** 675–6.

Precautions

Erythromycin and its derivatives should be avoided in those known to be hypersensitive to it, or in those who have previously developed jaundice. All forms of erythromycin should be used with care in patients with existing liver disease or hepatic impairment, and the estolate is best avoided in such patients; liver function should be monitored. Repeated courses of the estolate or use for longer than 10 days increases the risk of hepatotoxicity.

The lactobionate should be used with caution in patients with severe renal impairment; dosage reduction may be necessary particularly in those who develop toxicity. A reduced dose of the estolate has also been recommended in severe renal impairment.

Erythromycin may aggravate muscle weakness in patients with myasthenia gravis.

Erythromycin should be used with care in patients with a history of arrhythmias or a predisposition to QT interval prolongation. Certain medications may also increase the risk of arrhythmias (see Interactions, p. 296.2).

Erythromycin may interfere with some diagnostic tests including measurements of urinary catecholamines and 17-hydroxycorticosteroids. It has also been associated with falsely-elevated serum aspartate aminotransferase values when measured colorimetrically, although genuine elevations of this enzyme, due to hepatotoxicity, also occur, particularly with the estolate.

Erythromycin is irritant; solutions for parenteral use should be suitably diluted and given by intravenous infusion over 20 to 60 minutes to reduce the incidence of thrombophlebitis. Rapid infusion is also more likely to be associated with arrhythmias or hypotension.

Breast feeding. There has been a report[1] of a breast-fed infant who developed pyloric stenosis thought to be associated with use of erythromycin by the mother. However, the American Academy of Pediatrics[2] states that, although erythromycin is concentrated in human breast milk, no adverse effects have been seen in breast-fed infants whose mothers were receiving erythromycin and it is therefore usually compatible with breast feeding. A large Danish population-based cohort study[3] later concluded that the use of macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin, or spiramycin) during breast feeding increased the risk of infantile hypertrophic pyloric stenosis. (See also Effects on the Gastrointestinal Tract, p. 293.3.) A milk-to-plasma ratio of 0.5 has been reported for erythromycin.[4]

1. Stang H. Pyloric stenosis associated with erythromycin ingested through breastmilk. *Minn Med* 1986; **69:** 669–70, 682.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/04/07)
3. Sørensen HT, *et al*. Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. *Scand J Infect Dis* 2003; **35:** 104–106.
4. *et al. Drugs in pregnancy and lactation.* 8th ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2008.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies erythromycin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. Of 298 pregnant women who took erythromycin estolate, clindamycin, or placebo for 3 weeks or longer, about 14, 4, and 3% respectively had abnormally high serum aspartate aminotransferase values.[1] Erythromycin estolate should probably not be given to pregnant women.

A study[2] of data from the Swedish Medical Birth Registry of infants born between July 1995 and December 2002 examined details of infants exposed to erythromycin or phenoxymethylpenicillin during early pregnancy. Of 1844 exposed to erythromycin, 103 (5.6%) had congenital malformations compared with 420 of 9110 (4.7%) for phenoxymethylpenicillin. Of these, 34 (1.8%) and 86 (0.9%) respectively had a cardiovascular malformation, the rate being considered high for erythromycin. This contrasted with a previous study based on a 1980–96 dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities which found no signs of teratogenicity for erythromycin.[3] Although an increased risk for cardiovascular abnormalities was initially apparent when analysing erythromycin usage throughout pregnancy as reported by the mother, this was not confirmed when assessing usage only in the second or third month nor in the entire pregnancy for medically documented intake. The Swedish data also revealed a possible association between infant pyloric stenosis and early prenatal exposure to erythromycin[2] although others had previously failed to confirm such a risk[4] (see also Effects on the Gastrointestinal Tract, p. 293.3).

For information on the use of antibacterials, including erythromycin, as adjuncts in the management of premature labour, see p. 201.3.

1. McCormack WM, *et al*. Hepatotoxicity of erythromycin estolate during pregnancy. *Antimicrob Agents Chemother* 1977; **12:** 630–5.
2. Källén BAJ, *et al*. Is erythromycin therapy teratogenic in humans? *Reprod Toxicol* 2005; **20:** 209–14.
3. Czeizel AE, *et al*. A population-based case-control teratologic study of oral erythromycin treatment during pregnancy. *Reprod Toxicol* 1999; **13:** 531–6.
4. Hussain N, Herson VC. Erythromycin use during pregnancy in relation to pyloric stenosis. *Am J Obstet Gynecol* 2002; **187:** 821–2.

Interactions

Erythromycin and other macrolides have the potential to interact with many drugs through their action on hepatic cytochrome P450 isoenzymes, particularly CYP1A2 and CYP3A4. Macrolides competitively inhibit drug metabolism by these microsomal cytochromes, and also form inactive complexes with them. Enzyme inhibition is reported to be particularly pronounced with macrolides such as erythromycin and troleandomycin. Other macrolides such as azithromycin and dirithromycin are reported to have little or no effect on hepatic cytochromes, and consequently may produce fewer interactions (see also Mechanism, p. 296.2).

Macrolide-induced inhibition of metabolism can result in severe adverse effects, including ventricular arrhythmias with astemizole, cisapride, and terfenadine. Macrolides themselves have been reported rarely to prolong the QT interval and should in any case be used with caution with other drugs known to also have this effect.

Other mechanisms by which macrolides cause interactions include suppression of the gastrointestinal flora responsible for the intraluminal metabolism of digoxin and possibly oral contraceptives, and the stimulant effect of macrolides on gastrointestinal motility which is believed to be responsible for the interaction between spiramycin and levodopa. An alternative mechanism by which macrolides increase serum concentrations of digoxin is thought to be via the inhibition of intestinal or renal P-glycoprotein transport of digoxin.

Few drugs are reported to affect erythromycin but cimetidine may increase and theophylline may decrease erythromycin concentrations (see p. 296.3).

The effect on antimicrobial action when erythromycin is given with other antimicrobials is discussed under Antimicrobial Action, p. 297.1.

General references[1-4] to interactions associated with macrolide antibacterials.

1. von Rosenstiel N-A, Adam D. Macrolide antibacterials: drug interactions of clinical significance. *Drug Safety* 1995; **13:** 105–22.
2. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; **50:** 285–95.
3. Pai MP, *et al*. Macrolide drug interactions: an update. *Ann Pharmacother* 2000; **34:** 495–513.
4. Shakeri-Nejad K, Stahlmann R. Drug interactions during therapy with three major groups of antimicrobial agents. *Expert Opin Pharmacother* 2006; **7:** 639–51.

Mechanism

In *rats* and humans, troleandomycin, and erythromycin and some of its derivatives, induce microsomal enzymes; the nitrosoalkane metabolites so formed produce stable inactive complexes with the iron of cytochrome P450. Eventually the oxidative metabolism of other drugs may be decreased. These effects are marked after troleandomycin, moderate after erythromycin, small after oleandomycin, and absent or negligible after josamycin, midecamycin, or spiramycin.[1,2]

1. Pessayre D, *et al*. Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* 1985; **16** (suppl A): 181–94.
2. Periti P, *et al*. Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 1992; **23:** 106–31.

Drugs

For reference to the effects of erythromycin and other macrolides on other drugs, see

- alfentanil (p. 19.3)
- bromocriptine (p. 900.1)
- carbamazepine (p. 516.2)
- ciclosporin (p. 1956.1)
- clozapine (p. 1061.2)
- colchicine (p. 606.3)
- conivaptan (p. 2486.2)
- digoxin (p. 1356.3)
- dihydroergotamine and ergotamine (p. 675.2)
- disopyramide (p. 1365.2)
- levodopa (p. 908.1)
- midazolam and triazolam (p. 1068.2)
- oxycodone (p. 113.3)
- phenytoin (p. 542.3)
- pimozide (p. 1052.1)
- quetiapine (p. 1102.2)
- quinidine (p. 1483.1)
- repaglinide (p. 498.1)
- rifabutin (p. 351.3)
- sertraline (see under Fluoxetine, p. 426.1)
- sildenafil (p. 2366.3)
- simvastatin and other statins (p. 1494.3)
- tacrolimus (p. 1977.3)
- terfenadine (p. 641.2)
- theophylline (p. 1234.1)
- tolvaptan (p. 2633.1)
- valproate (p. 557.2)
- verapamil (p. 1525.1)
- vinblastine (p. 882.3)
- warfarin (p. 1531.1)
- zopiclone (p. 1118.3)

In the case of astemizole, cisapride, and terfenadine the UK CSM has warned that there is a risk of inducing ventricular arrhythmias if erythromycin, or possibly other macrolides, are also given,[1,2] and that, in particular, cisapride should not be used with macrolides.[3] The CHM[4] later advised that amisulpride, ergotamine, dihydroergotamine, mizolastine, pimozide, simvastatin, and tolterodine should not be given with erythromycin. A warning was also issued that increased erythromycin concentrations may occur when used with other inhibitors of the cytochrome P450 CYP3A isoenzymes such as the azole antifungals, some calcium-channel blockers including diltiazem and verapamil, and HIV-protease inhibitors. For a report of an increased risk of sudden cardiac death associated with such combinations see Effects on the Cardiovascular System, p. 293.2.

1. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
2. CSM/MCA. Cisapride (Prepulsid, Alimax): interactions with antifungals and antibiotics can lead to ventricular arrhythmias. *Current Problems* 1996; **22:** 1. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
3. CSM/MCA. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; **24:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
4. CHM/MHRA. Erythromycin and other macrolides: focus on interactions. *Current Problems* 2006; **31:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/01/07)

Bronchodilators. Intravenous *theophylline* has been reported[1,2] to decrease serum concentrations of oral erythromycin although other studies[3,4] using intravenous or oral theophylline with intravenous erythromycin did not show any significant pharmacokinetic changes.

For reference to the effects of erythromycin on theophylline, see Macrolides, under Interactions of Theophylline, p. 1234.1.

1. Iliopoulou A, *et al*. Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; **14:** 495–9.
2. Paulsen O, *et al*. The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; **32:** 493–8.
3. Hildebrandt R, *et al*. Influence of theophylline on the renal clearance of erythromycin. *Int J Clin Pharmacol Ther Toxicol* 1987; **25:** 601–4.
4. Pasic J, *et al*. The interaction between chronic oral slow-release theophylline and single-dose intravenous erythromycin. *Xenobiotica* 1987; **17:** 493–7.

Gastrointestinal drugs. *Cimetidine* may increase plasma concentrations of erythromycin and deafness occurred in a patient taking both drugs.[1]

1. Mogford N, *et al*. Erythromycin deafness and cimetidine treatment. *BMJ* 1994; **309:** 1620.

Antimicrobial Action

Erythromycin is a macrolide antibacterial with a broad and essentially bacteriostatic action against many Gram-positive and to a lesser extent some Gram-negative bacteria, as well as other organisms including some *Mycoplasma* spp., Chlamydiaceae, *Rickettsia* spp., and spirochaetes.

Mechanism of action. Erythromycin and other macrolides bind reversibly to the 50S subunit of the ribosome, resulting in blockage of the transpeptidation or translocation reactions, inhibition of protein synthesis, and hence inhibition of cell growth. Its action is mainly bacteriostatic, but high concentrations are slowly bactericidal against the more sensitive strains. Because macrolides penetrate readily into white blood cells and macrophages there has been some interest in their potential synergy with host defence mechanisms *in vivo*. The actions of erythromycin are increased at moderately alkaline pH (up to about 8.5), particularly in Gram-negative species, probably because of the improved cellular penetration of the nonionised form of the drug.

Spectrum of activity. Erythromycin has a broad spectrum of activity. The following pathogenic organisms are usually sensitive to erythromycin:

- Gram-positive cocci, particularly streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes*. However, resistance has been increasingly reported in both organisms, particularly in penicillin-resistant *Str. pneumoniae*.
  Most strains of *Staphylococcus aureus* remain susceptible, although resistance can emerge rapidly, and some enterococcal strains are also susceptible.
- Other Gram-positive organisms including *Bacillus anthracis, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae*, and *Listeria monocytogenes*. Anaerobic *Clostridium* spp. are also usually susceptible, as is *Propionibacterium acnes*. *Nocardia* spp. vary in their susceptibility.
- Gram-negative cocci including *Neisseria meningitidis* and *N. gonorrhoeae*, and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are usually sensitive.
- Other Gram-negative organisms vary in their susceptibility, but *Bordetella* spp., some *Brucella* strains, and *Flavobacterium* and *Legionella* spp. are usually susceptible. *Haemophilus ducreyi* is reportedly susceptible, but *H. influenzae* is somewhat less so. The Enterobacteriaceae are usually resistant, although some strains may respond at alkaline pH. *Helicobacter pylori* and most strains of *Campylobacter jejuni* are sensitive (about 1% of the latter are reported to be resistant in the USA).
- Among the Gram-negative anaerobes most strains of *Bacteroides fragilis* and many *Fusobacterium* strains are resistant.
- Other organisms usually sensitive to erythromycin include *Actinomyces*, Chlamydiaceae, rickettsias, spirochaetes such as *Treponema pallidum* and *Borrelia burgdorferi*, some mycoplasmas (notably *Mycoplasma pneumoniae*), and some of the opportunistic mycobacteria: *Mycobacterium scrofulaceum* and *M. kansasii* are usually susceptible, but *M. intracellulare* is often resistant and *M. fortuitum* usually so.

Fungi, yeasts, and viruses are not susceptible to erythromycin.

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility of an antagonistic effect if erythromycin is given with a bactericide exists, and some antagonism has been shown *in vitro* between erythromycin and various penicillins and cephalosporins or gentamicin. However, in practice the results of such concurrent use are complex, and depend on the organism; in some cases synergy has been seen. Because of the adjacency of their binding sites on the ribosome, erythromycin may competitively inhibit the effects of chloramphenicol or lincosamides such as clindamycin or lincomycin.

Resistance. Several mechanisms of acquired resistance to erythromycin have been reported of which the most common is a plasmid-mediated ability to methylate ribosomal RNA, resulting in decreased binding of the antimicrobial drug. This can result in cross-resistance between erythromycin, other macrolides, lincosamides, and streptogramin B, because they share a common binding site on the ribosome and this pattern of resistance is referred to as the MLS_B phenotype. It is seen in staphylococci, and to a somewhat lesser extent in streptococci, as well as in a variety of other species including *B. fragilis, Clostridium perfringens, Corynebacterium diphtheriae*, and *Listeria* and *Legionella* spp.

Decreased binding of antimicrobial to the ribosome may also occur as a result of a chromosomal mutation, resulting in an alteration of the ribosomal proteins in the 50S subunit, which conveys one-step high-level erythromycin resistance. This form of resistance has been found in some strains of *Str. pneumoniae, H. pylori, M. pneumoniae, Escherichia coli, Str. pyogenes, Staph. aureus*, and *Campylobacter* spp.

Other forms of erythromycin resistance may be due to the production of a plasmid-determined erythromycin esterase that can inactivate the drug, or to decreased drug penetration. The latter may be partly responsible for the intrinsic resistance of Gram-negative bacteria like the Enterobacteriaceae, but has also been shown to be acquired as a plasmid-mediated determinant in some organisms; production of a protein which increases drug efflux from the cell is thought to explain the M phenotype resistance, in which organisms are resistant to 14-and 15-carbon ring macrolides, but retain sensitivity to 16-carbon ring macrolides, lincosamides, and streptogramins.

The incidence of resistance varies greatly with the area and the organism concerned and, although the emergence of resistance is rarely a problem in the short-term treatment of infection, it is quite common in conditions requiring prolonged treatment such as endocarditis due to *Staph. aureus*. The incidence of resistance in streptococci is generally lower than in *Staph. aureus* but shows geographical variation and may be increasing in some countries, including the UK. In addition, localised outbreaks of resistant strains may occur and produce a much higher incidence of resistance.

Antipseudomonal activity. Although macrolides have limited direct antibacterial activity against *Pseudomonas aeruginosa*, prolonged exposure at sub-MICs has produced antipseudomonal effects *in vitro*[1-3] and synergy has been shown with other antipseudomonals.[4] Erythromycin and clarithromycin appear to have the greatest activity. This action has been partly attributed to the ability of macrolides to reduce the protective biofilm produced by some strains of *P. aeruginosa*.[3,5] Other proposed mechanisms of action include modification of the inflammatory response to infection and direct inhibition of other virulence factors such as twitching motility.[3]

1. Tateda K, *et al*. Effects of sub-MICs of erythromycin and other macrolide antibiotics on serum sensitivity of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1993; **37:** 675–80.
2. Tateda K, *et al*. Direct evidence of antipseudomonal activity of macrolides: exposure-dependent bactericidal activity and inhibition of protein synthesis by erythromycin, clarithromycin, and azithromycin. *Antimicrob Agents Chemother* 1996; **40:** 2271–5.
3. Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on Pseudomonas aeruginosa. *Chest* 2004; **125** (suppl 2): 62S–69S.
4. Bui KQ, *et al*. In vitro and in vivo influence of adjunct clarithromycin on the treatment of mucoid Pseudomonas aeruginosa. *J Antimicrob Chemother* 2000; **45:** 57–62.
5. Yasuda H, *et al*. Interaction between biofilms formed by Pseudomonas aeruginosa and clarithromycin. *Antimicrob Agents Chemother* 1993; **37:** 1749–55.

Resistance. A meta-analysis[1] found that reported macrolide resistance in *Streptococcus pneumoniae* varied greatly from country to country. The percentage of erythromycin-resistant *Str. pneumoniae* in the USA (20.7%) was less than that in Europe (32.0%) although this difference was not considered statistically significant, and higher levels of resistance were found in Asia (57.3%). In Europe, *Str. pyogenes* showed greater resistance to erythromycin (36.8%) than *Str. pneumoniae*. However, across all regions, the mean resistance of *Str. pneumoniae* was statistically equivalent (30.4%) and also similar to that of *Str. pyogenes* (30.0%).

1. Halpern MT, *et al*. Meta-analysis of bacterial resistance t o macrolides. *J Antimicrob Chemother* 2005; **55:** 748–57.

Pharmacokinetics

Erythromycin base is unstable in gastric acid, and absorption is therefore variable and unreliable. Consequently, the base is usually given in film- or enteric-coated preparations, or one of the more acid-stable salts or esters is used. Food may reduce absorption of the base or the stearate, although this depends to some extent on the formulation; the esters are generally more reliably and quickly absorbed and their absorption is little affected by food, so that the timing of doses in relation to food intake is unimportant.

Peak plasma concentrations generally occur between 1 and 4 hours after a dose and have been reported to range from about 0.3 to 1.0 micrograms/mL after 250 mg of erythromycin base, and from 0.3 to 1.9 micrograms/mL after 500 mg. Similar concentrations have been seen after equivalent doses of the stearate. Peak concentrations may be somewhat higher after repeated use 4 times daily. Higher total concentrations occur after oral doses of the estolate or ethyl succinate, but only about 20 to 30% of estolate or 55% of ethyl succinate is present as the active base, the rest being present as the inactive ester (in the case of the estolate as the propionate). Peak concentrations of about 500 nanograms/mL of erythromycin base have been reported after 250 mg of the estolate or 500 mg of the ethyl succinate. A peak of 3 to 4 micrograms/mL results after 200 mg of gluceptate or lactobionate intravenously.

Erythromycin is widely distributed throughout body tissues and fluids, although it does not cross the blood-brain barrier well and concentrations in CSF are low. Relatively high concentrations are found in the liver and spleen, and some is taken up into polymorphonuclear lymphocytes and macrophages. Around 70 to 75% of the base is protein bound, but after doses as the estolate the propionate ester is stated to be about 95% protein bound. Erythromycin crosses the placenta: fetal plasma concentrations are variously stated to be 5 to 20% of those in the mother. It is distributed into breast milk.

Erythromycin is partly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 via *N*-demethylation to inactive, unidentified metabolites. It is excreted in high concentrations in the bile and undergoes intestinal reabsorption. About 2 to 5% of an oral dose is excreted unchanged in the urine and as much as 12 to 15% of an intravenous dose may be excreted unchanged by the urinary route. The half-life of erythromycin is usually reported to be about 1.5 to 2.5 hours, although this may be slightly longer in patients with renal impairment and has been reported to be between 4 to 7 hours in severe impairment.

Erythromycin is not removed by haemodialysis or peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Algiderm; Ambamida; Atlamicin; Clarex; Cuartal; Eri; Erigrand; Erisine; Erisol; Erit; Eritroderm; Eritrofarm; Eritromed; Eritrovis; Eryacne; Eryfluid; Etisux; Iloticina; Ingelets†; Kitacne; Oftalmolets; Pantomicina; Pentoclave; Stiemycin; Toperit; Trixne; Wemid; ***Austral.***: E-Mycin; EES; Eryacne; Eryc; Eryhexal†; Erythrocin; ***Austria***: Akne Cordes†; Eryaknen; Erystad†; Erythrocin; Meromycin; Stiemycine†; ***Belg.***: Acneryne; Aknemycin; Erythrocine; Erythroforte; Inderm; Stimycine; ***Braz.***: Eribiotic; Eritrex; Eryacnen; Ilosone; Kanazima†; Pantomicina; Stiemycin; Valmicin; ***Canad.***: Ak Mycin; Apo-Erythro; Diomycin; EES; Erybid; Eryc; Erysol; Erythro; Erythrocin; Novo-Rythro; PCE; ***Chile***: Cinactiv; Eryacnen; Erypark†; Gelerit; Labocne†; Mercina; Pantomicina; ***China***: Ai Jia Xing (艾加星); AoShuDa (澳抒达); AoShuXin (澳抒欣); Davercin (达发新); Guansha (冠沙); Ke Te Jia (科特加); Lijunsha (利君沙); Mei Hong (美红); San Jiu Jun Bi Sha (三九君必沙); Xin Hong Kang (新红康); Yi Hu Wei Mei Su Chong Ji (乙琥威); ***Cz.***: Aknefug-EL†; Aknemycin; Eryfluid; Erythrocin†; ***Denm.***: Abboticin; Erycin; Escumycin; Hexabotin; ***Fin.***: Abboticin; Ermysin; ***Fr.***: Abboticine; Egery; Ery; Eryacne; Eryfluid; Erythrocine; Erythrogel; Stimycine; ***Ger.***: Aknederm Ery†; Aknefug-EL; Aknemycin; Ery-Diolan†; Ery†; Eryaknen; Erybeta†; Erycinum; Erydermec; Eryhexal†; Erythro; Erythrocin; Inderm; InfectoMycin; Paediathrocin†; Sanasepton; Stiemycine; ***Gr.***: Acne Hermal; Dankit; Eryacne; Erycream; Erygel; Erymyk; Erythrocin; Erythrogel; Erythropen; Erythroskin; Lederpax; Rotacin; Roug-Mycin; ***Hong Kong***: Aknemycin; E-Mycin†; EES†; Erismycine†; Erogran†; Erotab†; Erymycin†; Erythro; Erythrocin†; Oracin†; Rycin†; Stiemycin; ***Hung.***: Aknefug-EL; Aknemycin; Davercin; Eryc†; Erythrotrop; Meromycin; ***India***: Acnederm; Acnelak; Acnesol; Acnet; Althrocin; Aritomycin; Calthrox; Citamycin; E-Mycin; EES; Eltocin; Elucin; Erase; Eroate; Erocyn; Erolcid; Eroma; Eromed; Ery; Eryacne; Erycin; Erycip; Erypal; Erysafe†; Erysoft; Eryspans; Eryster; Erythrocin; Erythrokem; Erythrolar; Erytop; Etomin; Floramycin; Gery; Inderyth; Okamycin; ***Indon.***: Cetathrocin†; Corsatrocin; Dothrocyn; Duramycin†; EES†; Erphathrocin; Erycoat; Eryderm; Erymed; Erysanbe; Erythrin; Erythrocin; Jeracin; Narlecin; Opithrocin; Pharothrocin; ***Irl.***: Erymax; Erythrocin; Erythroped; Primacine; Stiemycin; ***Israel***: Acnetrim; Aknemycin; Erythro-Teva; Erythrocin; ***Ital.***: Eritrocina; Eryacne; Lauromicina; ***Malaysia***: Aknemycin†; EES; Erycin; Eryderm; Eryped†; Eryson; Erythrocin†; Oftalmolosa Cusi; Sathrocin; Stiemycin; ***Mex.***: Apo-Trina; Benitrom†; Bestocin; Biotril; Eribec†; Eriber; Erisuspen; Eritrolat; Eritropharma; Eritrosol; Eritrovier; Eritrowel†; Eryacnen; Eryderm; Erylar; Iliocin†; Ilosin†; Ilosone; Iqfamicina; Lantrom; Latotryd; Lauricin; Laurimicina†; Lauritran; Optomicin; Pantomicina; Pertrosom; Procephal†; Promicin; Quimolauril; Sansacne; Stiemycin; T-Stat; Tropharma; Witromin†; ***Neth.***: Aknemycin†; Eryacne; Eryderm; Eryfluid†; Erythrocine; Erytrolyve†; Inderm; Stiemycin†; ***Norw.***: Abboticin; Ery-Max; ***NZ***: E-Mycin; EES; Era; Eryacne; Erythrocin; Stiemycin; ***Philipp.***: Aldricin; Ery-Max†; Ery-V; Eryzar; Erylide; Erythrocin; Fildrocin; Ilosone; Medripol; Optryl; Pertustat; Romaxin; Sansacne; Sorestin; Stiemycin; Upperzin; ***Pol.***: Aknemycin; Davercin; ***Port.***: Akne-Mycin; Clinac; Eritrazon; Eritrocel; Eritrocina; Eryfluid; ESE; ***S. Afr.***: Acu-Erylate S†; Betamycin; Erycette†; Eryderm; Eryko†; Erymycin; Erystat†; Erythrocin; Estomycin†; Ilosone; Ilotycin TS; Purmycin; Rubimycin†; Spectrasone; Stiemycin; Xeramel; ***Singapore***: Akne-Mycin; EES; Ermycin; Erogran; Erotab; Eryacne; Eryc; Erycyn; Eryderm; Eryped; Erysol; Eryson; Erythro; Ranthrocin; Stiemycin; ***Spain***: Bronsema†; Deripil; Eridosis; Eritrogobens; Eritroveinte; Euskin; Lagarmicin; Loderm; Pantomicina; ***Swed.***: Abboticin; Ery-Max; ***Switz.***: Akne-Mycin; Aknilox; Erios†; Eryaknen; Eryderm†; Erythrocine; ***Thai.***: E S; Erathrom; Ericin; Erimit; Erimycin; Ery-Tab†; Eryacne; Erycin; Erycon; Erymin; Eryo; Erypac; Erysate; Erysil; Eryth-mycin; Erythorate; Erythrocin†; Erythromed; Erytomin; Etrola†; Etrolate†; Ilosone†; Malocin; Medthrocin; Pocin; Redrocin†; Rintacap; Rintacin; Rytho-Cap; Rythocin†; Servitrocin†; Stacin; Stiemycin; Suthrocin; Tomcin; ***Turk.***: Aknilox; Erimicin; Eritro; Eritrosif; Eryacne; Erythrocin; ***UAE***: Eromycin; ***UK***: Eryacne; Erymax; Erythrocin; Erythroped; Stiemycin; Tiloryth; ***USA***: Akne-Mycin; ATS; Del-Mycin; E-Base; E-Mycin; EES; Eramy-

cin; Ery-Tab; Eryc; Erycette; Eryderm; Erygel; Eryped; Erythrocin; Ilotycin; PCE; Robimycin Robitabs; ***Venez.***: Eryacne; Ilosone; Inderm; Leda-Rix; Pantomicina; Yisadin.

Multi-ingredient Preparations. ***Arg.***: Acneout; Acnepas E; Clarex Compuesto; Ecnagel E; Erimicin; Eristin; Eritrobron; Pentoclave Combi; Peroximicina; Stievamycin; Tratacne; Zineryt; ***Austria***: Aknemycin compositum; Isotrexin; ***Belg.***: Benzaderinine; Benzamycin†; Zineryt; ***Braz.***: Eritrex A; Isotrexin; ***Canad.***: Benzamycin; Pediazole; Stievamycin; ***Chile***: Benzac Plus; Bioquin; Dermodan Plus; Erimicin; Erylik; Stievamycin; ***China***: Benzamycin (必麦森); Fuqing (芙晴); ***Cz.***: Aknemycin Plus; Isotrexin; Zineryt; ***Fr.***: Antibiotrex; Erylik; Pediazole; ***Ger.***: Aknemycin Plus; Aknemycin†; Ecolicin; Isotrexin; Zineryt; ***Gr.***: Benzamycin; Erybenz; Pediazole; Zarcad; ***Hong Kong***: Aknemycin Plus; Erylik; ***Hung.***: Isotrexin; Zineryt; ***India***: Acnebenz; Acnelak-Z; Acrub; Aknemycin Plus; Calthrox; Eltocin-BR; Ero-B; Erysia; ***Indon.***: Erymed Plus; ***Irl.***: Benzamycin†; Isotrexin; Zineryt; ***Israel***: Aknemycin Plus; Aknemycin; Benzamycin; Pediazole†; ***Ital.***: Isotrexin; Lauromicina; Zineryt; ***Malaysia***: Aknemycin Plus; Efasol; ***Mex.***: Benzac Plus†; Benzamycin†; Bisolvon E; Eriwest; Pantobron; Pediazole; Quimobrom; Stievamycin; ***Neth.***: Zineryt; ***NZ***: Antibiotic Simplex; ***Philipp.***: Elicocin; ***Pol.***: Aknemycin Plus; Isotrexin; Zineryt; ***Port.***: Isotrexin; Zineryt; ***Rus.***: Isotrexin (Изотрексин); Zineryt (Зинерит); ***S.Afr.***: Zineryt; ***Singapore***: Aknemycin Plus; Benzamycin†; Isotrexin; ***Spain***: Isotrex Eritromicina; Loderm Retinoico†; Zineryt; ***Switz.***: Akne-Mycin†; ***Thai.***: Isotrexin; ***Turk.***: Benzamycin; Eritretin; Isotrexin; ***UK***: Aknemycin Plus; Isotrexin; Zineryt; ***Ukr.***: Isotrexin (Изотрексин); Macrotussin (Макротуссин); Zineryt (Зинерит); ***USA***: Benzamycin; Pediazole†.

Pharmacopoeial Preparations

BP 2014: Erythromycin and Zinc Acetate Lotion; Erythromycin Estolate Capsules; Erythromycin Ethyl Succinate Oral Suspension; Erythromycin Ethyl Succinate Tablets; Erythromycin Lactobionate Infusion; Erythromycin Stearate Tablets; Gastro-resistant Erythromycin Capsules; Gastro-resistant Erythromycin Tablets;

USP 36: Erythromycin and Benzoyl Peroxide Topical Gel; Erythromycin Delayed-release Capsules; Erythromycin Delayed-release Tablets; Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Estolate Capsules; Erythromycin Estolate for Oral Suspension; Erythromycin Estolate Oral Suspension; Erythromycin Estolate Tablets; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Erythromycin Ethylsuccinate for Oral Suspension; Erythromycin Ethylsuccinate Injection; Erythromycin Ethylsuccinate Oral Suspension; Erythromycin Ethylsuccinate Tablets; Erythromycin Lactobionate for Injection; Erythromycin Ointment; Erythromycin Ophthalmic Ointment; Erythromycin Pledgets; Erythromycin Stearate Tablets; Erythromycin Tablets; Erythromycin Topical Gel; Erythromycin Topical Solution; Sterile Erythromycin Ethylsuccinate; Sterile Erythromycin Gluceptate; Sterile Erythromycin Lactobionate.

Ethambutol Hydrochloride

(BANM, USAN, rINNM)

CL-40881; Etambutol, hidrocloruro de; Etambutol Hidroklorür; Etambutol-hidroklorid; Etambutolhydroklorid; Etambutolihydrokloridi; Etambutolio hidroclorídas; Etambutolo; Etambutolu chlorowodorek; Éthambutol, Chlorhydrate d'; Ethambutol-dihydrochlorid; Ethambutoldihydrochlorid; Ethambutoli Dihydrochloridum; Ethambutoli Hydrochloridum; Ethambutolo; Hidrocloruro de etambutol; Этамбутола Гидрохлорид.

(*S,S*)-*N,N'*-Ethylenebis(2-aminobutan-1-ol) dihydrochloride.

$C_{10}H_{24}N_2O_2.2HCl$=277.2

CAS — 74-55-5 (ethambutol); 1070-11-7 (ethambutol hydrochloride).

ATC — J04AK02.

ATC Vet — QJ04AK02.

UNII — QE4VW5FO07.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ethambutol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. A 2% solution in water has a pH of 3.7 to 4.0. Store in airtight containers.

USP 36: (Ethambutol Hydrochloride). A white crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol; slightly soluble in chloroform and in ether.

Uses and Administration

Ethambutol is used with other antituberculous drugs in the primary treatment of pulmonary and extrapulmonary tuberculosis (p. 210.2) to suppress emergence of resistance to the other drugs used in the regimens. It is also used as a component of regimens for the treatment of nontuberculous mycobacterial infections (p. 194.1).

In the treatment of tuberculosis, ethambutol is given, as the hydrochloride, usually with isoniazid, rifampicin, and pyrazinamide in the initial 8-week phase and sometimes in the continuation phase. It is given orally in a single daily dose of 15 mg/kg, or 30 mg/kg three times weekly. Initial doses of ethambutol 25 mg/kg daily for 60 days may be given to patients who have previously had antimycobacterial therapy, reduced to 15 mg/kg daily thereafter.

For details of doses in children, see p. 298.2.

Doses may require adjustment in patients with renal impairment, for details see p. 298.2.

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing ethambutol with isoniazid, isoniazid and rifampicin, or isoniazid, rifampicin, and pyrazinamide are available in some countries.

References.

1. Anonymous. Ethambutol. *Tuberculosis (Edinb)* 2008; **88:** 102–5.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an oral dose of ethambutol of 20 mg/kg daily or 50 mg/kg (to a maximum of 2.5 g) twice weekly.

For *congenitally acquired* tuberculosis in neonates the *BNFC* suggests a dose of 20 mg/kg once daily. For the treatment of children 1 month and older a dose of 20 mg/kg once daily or 30 mg/kg three times a week for the 2 month initial treatment phase is suggested.

See also Children, under Precautions p. 299.1

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Licensed product information advises that ethambutol doses be adjusted based on serum concentrations (see Precautions, p. 299.1) for patients with renal impairment.

Alternatively, for patients with severe renal impairment (creatinine clearance < 30 mL/minute) an empirical dose adjustment may be considered; WHO guidelines for the treatment of tuberculosis[1] recommend a dose of 15 mg/kg orally 3 times weekly, while the *BNF* recommends a dose of 15 to 25 mg/kg depending on serum-ethambutol concentrations (to a maximum of 2.5 g) orally 3 times weekly.

1. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 02/12/10)

Adverse Effects and Treatment

The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red colour blindness. One or both eyes may be affected. The degree of visual impairment appears to depend on the dose and duration of therapy; toxicity occurs most frequently at daily doses of 25 mg/kg or more and after at least 2 months of therapy. Recovery of vision usually takes place over a period of a few weeks or months, but in rare cases it may take up to a year or more or the effect may be permanent. Retinal haemorrhage has occurred rarely.

Renal clearance of urate may be reduced and acute gout has been precipitated rarely.

Hypersensitivity reactions including rashes, pruritus, leucopenia, fever, and joint pains have occurred but appear to be rare with ethambutol. Other adverse effects which have been reported include confusion, disorientation, hallucinations, headache, dizziness, malaise, jaundice or transient liver dysfunction, peripheral neuropathy, thrombocytopenia, pulmonary infiltrates, eosinophilia, and gastrointestinal disturbances such as nausea, vomiting, anorexia, and abdominal pain.

Teratogenicity has been seen in *animals* (but see also Precautions, p. 299.1).

Blood concentrations of ethambutol after overdosage may be reduced by haemodialysis or peritoneal dialysis.

Effects on the blood. Neutropenia has been reported in a patient on ethambutol, isoniazid, and rifampicin.[1] Each drug induced neutropenia individually on rechallenge. In another patient also receiving mixed antituberculous therapy, eosinophilia and neutropenia were associated with ethambutol; the effects recurred only on rechallenge with this drug.[2] Rash, blood eosinophilia, and pulmonary infiltrates occurred in a patient after 8 weeks of multidrug therapy for miliary tuberculosis. Rechallenge again attributed the adverse event to ethambutol.[3] Thrombocytopenia attributable to ethambutol has been reported in 2 patients.[4,5]

1. Jenkins PF, *et al.* Neutropenia with each standard antituberculosis drug in the same patients. *BMJ* 1980; **280:** 1069–70.
2. Wong CF, Yew WW. Ethambutol-induced neutropenia and eosinophilia. *Chest* 1994; **106:** 1638–9.
3. Wong PC, *et al.* Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. *Eur Respir J* 1995; **8:** 866–8.
4. Rabinovitz M, *et al.* Ethambutol-induced thrombocytopenia. *Chest* 1982; **81:** 765–6.
5. Prasad R, Mukerji PK. Ethambutol-induced thrombocytopaenia. *Tubercle* 1989; **70:** 211–12.

Effects on the CNS. A 40-year-old man with advanced HIV infection had rapid cognitive decline, hallucinations, and delusions within 2 weeks of starting oral ethambutol treatment for *Mycobacterium avium* complex infection; symptoms resolved on stopping treatment.[1]

1. Martin SJ, Bowden FJ. Ethambutol toxicity manifesting as acute onset psychosis. *Int J STD AIDS* 2007; **18:** 287–8.

Effects on the eyes. The ocular toxicity of ethambutol has been reviewed.[1-3] One such review[1] reported that when ethambutol is taken for more than 2 months the incidence of retrobulbar neuritis is about 18% in patients receiving a daily dose of more than 35 mg/kg, reducing to 5 to 6% with a daily dose of 25 mg/kg, and less than 1% with a daily dose of 15 mg/kg. An earlier study reported ophthalmic effects in 10 of 2184 patients taking ethambutol in doses of 25 mg/kg or less daily, although few of the 10 patients complained of symptoms.[4] In 9 of the 10 patients, ocular changes occurred after the second month of treatment. In the 928 patients who only had 2 months of ethambutol therapy, ocular toxicity was not reported. A prospective study[5] of 229 patients taking ethambutol for *Mycobacterium avium* complex lung disease reported that ocular toxicity was more common in patients given daily doses rather than intermittent (3 times a week) therapy.

While short-term use of ethambutol is usually safe, deterioration of vision leading to long-term blindness has been reported after only a few doses;[6] it was suspected that this was an idiosyncratic reaction. Rapid onset reversible ocular toxicity has also occurred.[7]

Visual defects occurring with ethambutol generally resolve when the drug is stopped.

1. Chan RYC, Kwok AKH. Ocular toxicity of ethambutol. *Hong Kong Med J* 2006; **12:** 56–60.
2. Fraunfelder FW, *et al.* Update on ethambutol optic neuropathy. *Expert Opin Drug Safety* 2006; **5:** 615–8.
3. Vistamehr S, *et al.* Ethambutol neuroretinopathy. *Semin Ophthalmol* 2007; **22:** 141–6.
4. Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax* 1986; **41:** 737–9.
5. Griffith DE, *et al.* Ethambutol ocular toxicity in treatment regimens for Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2005; **172:** 250–3.
6. Karnik AM, *et al.* A case of ocular toxicity to ethambutol—an idiosyncratic reaction? *Postgrad Med J* 1985; **61:** 811–13.
7. Schild HS, Fox BC. Rapid-onset reversible ocular toxicity from ethambutol therapy. *Am J Med* 1991; **90:** 404–6.

Effects on the kidneys. Interstitial nephritis has been reported[1,2] in 5 patients receiving ethambutol and isoniazid; 3 were also receiving other antimycobacterials. In another patient, acute renal failure occurred secondary to interstitial nephritis, which was thought to have been induced by ethambutol.[3]

1. Collier J, *et al.* Two cases of ethambutol nephrotoxicity. *BMJ* 1976; **2:** 1105–6.
2. Stone WJ, *et al.* Acute diffuse interstitial nephritis related to chemotherapy of tuberculosis. *Antimicrob Agents Chemother* 1976; **10:** 164–72.
3. García-Martín F, *et al.* Acute interstitial nephritis induced by ethambutol. *Nephron* 1991; **59:** 679–80.

Effects on the liver. Although transient abnormalities in liver function commonly occur during the early stages of antituberculosis treatment, drugs other than ethambutol are generally considered responsible. Ethambutol has generated fewer reports of hepatotoxicity to the UK CSM than rifampicin, isoniazid, or pyrazinamide,[1] and the use of regimens containing ethambutol has been recommended for patients unable to tolerate standard regimens due to hepatotoxicity.[1-3]

1. Ormerod LP, *et al.* Hepatotoxicity of antituberculosis drugs. *Thorax* 1996; **51:** 111–13.
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005: **53:** 1203. [dose]

Effects on the skin. Toxic epidermal necrolysis[1] and lichenoid[2] and erythema multiforme-type drug eruptions[3] have been associated with the use of ethambutol. Delayed hypersensitivity reactions have also been reported.[4] Licensed product information notes that Stevens-Johnson syndrome and dermatitis have also occurred.

1. Pegram PS, *et al.* Ethambutol-induced toxic epidermal necrolysis. *Arch Intern Med* 1981; **141:** 1677–8.
2. Grossman ME, *et al.* Lichenoid eruption associated with ethambutol. *J Am Acad Dermatol* 1995; **33:** 675–6.
3. Kurokawa I, *et al.* Erythema multiforme-type drug eruption due to ethambutol with eosinophilia and liver dysfunction. *Int J Antimicrob Agents* 2003; **21:** 596–7.
4. Bakkum RSLA, *et al.* Delayed-type hypersensitivity reaction to ethambutol and isoniazid. *Contact Dermatitis* 2002; **46:** 359.

Hyperuricaemia. In a controlled study of 71 patients taking ethambutol 20 mg/kg daily orally with other antimycobacterials, serum-uric acid concentrations increased in 66, mainly in the first 2 weeks of treatment.[1] One patient developed arthralgia and another acute gouty arthritis. Serum-uric acid concentrations did not change in 60 control patients receiving other antimycobacterials.

1. Khanna BK, Gupta VP. Ethambutol-induced hyperuricaemia. *Tubercle* 1984; **65:** 195–9.

Precautions

Ethambutol is generally contra-indicated in patients with optic neuritis. It should be used with great care in patients with visual defects, the elderly, and in children in whom evaluation of changes in visual acuity may be difficult (see also Children, p. 299.1). Ocular examination is recommended before treatment with ethambutol and some consider that regular examinations are necessary during treatment, especially in children. Patients should be advised to report visual disturbances immediately and to stop ethambutol pending visual evaluation.

Ethambutol should be given in reduced dosage to patients with renal impairment and dosage adjustments may need to be made according to serum concentrations (but see also Administration in Renal Impairment, p. 296.2). *BNF* recommends peak concentrations of 2 to 6 mg/litre and trough concentrations of less than 1 mg/litre.

Ethambutol may precipitate attacks of gout.

Although ethambutol crosses the placenta and may be teratogenic in *animals*, problems in humans have not been documented. The benefits of ethambutol in the treatment of tuberculosis are thought to outweigh any potential risks in pregnancy.

Breast feeding. Ethambutol distributes into breast milk to produce concentrations similar to those in plasma. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving ethambutol, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Children. Due to the possible difficulty of evaluating changes in visual acuity that may be induced in children receiving ethambutol, the *BNFC* advises that it should be used with caution in children under 5 years of age and unable to report visual changes accurately, whereas in the USA licensed product information has advised against use in those under 13 years of age.

The authors of a review of the use of ethambutol in children concluded that no extra precautions were necessary in children aged 5 years or more, and that it could also be used in younger children without undue fear of adverse effects.[1] Another review suggested that visual toxicity is not a particular problem except perhaps when CNS infection is involved.[2] A literature review[3] on the use of ethambutol in children reported almost no ocular toxicity at daily doses of 15 to 30 mg/kg. Ethambutol is therefore considered safe in children of all ages at a daily dose of 20 mg/kg (range 15 to 25 mg/kg) or a three times weekly dose of 30 mg/kg.

1. Trébucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int J Tuberc Lung Dis* 1997; **1:** 12–15.
2. Graham SM, *et al*. Ethambutol in tuberculosis: time to reconsider? *Arch Dis Child* 1998; **78:** 274–8.
3. WHO. *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children.* Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf (accessed 03/10/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ethambutol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/07/11)

Antimicrobial Action

Ethambutol is active against *Mycobacterium tuberculosis* and some other mycobacteria, including some strains of *M. avium* complex, *M. kansasii*, *M. fortuitum*, and *M. intracellulare*. Activity seems to be limited against many isolates of *Mycobacterium avium* complex, but, synergistic activity occurs when used with clarithromycin, azithromycin, rifampicin, rifabutin, ciprofloxacin, amikacin, or streptomycin in 2- (or preferably) 3-drug regimens. Resistant strains of *M. tuberculosis* are readily produced if ethambutol is used alone.

Pharmacokinetics

About 80% of an oral dose of ethambutol is absorbed from the gastrointestinal tract. Absorption is not significantly impaired by food (but see also Bioavailability, p. 299.2). After a single dose of 25 mg/kg peak plasma concentrations of up to 5 mg/L occur within 4 hours, and are less than 1 mg/L by 24 hours.

Ethambutol is distributed to most tissues, including the lungs, kidneys, and erythrocytes. About 10 to 50% may diffuse into the CSF when the meninges are inflamed. It has been reported to cross the placenta and is distributed into breast milk. The elimination half-life after oral doses is about 3 to 4 hours.

Ethambutol is partially metabolised in the liver to the aldehyde and dicarboxylic acid derivatives, which are inactive. Most of a dose appears in the urine within 24 hours as unchanged drug and 8 to 15% as the inactive metabolites. About 20% of the dose is excreted unchanged in the faeces.

Bioavailability. Although the absorption of ethambutol is not generally regarded as being impaired by food, a study in 14 healthy subjects[1] suggested that giving it with a high-fat meal or an antacid could delay absorption and reduce the peak plasma concentration.

1. Peloquin CA, *et al*. Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* 1999; **43:** 568–72.

HIV-infected patients. Malabsorption of ethambutol and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see under Rifampicin, p. 356.1.

Pregnancy and breast feeding. Ethambutol crosses the placenta and is present in fetal tissue in amounts of at least 74.5% of the maternal serum concentration.[1] Ethambutol distributes into breast milk to produce concentrations similar to those in plasma.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Snider DE, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144:** 589–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Myambutol; ***Austria***: Etibi; Myambutol; ***Belg.***: Myambutol; ***Canad.***: Etibi; ***Cz.***: Sural; ***Denm.***: Myambutol; ***Fin.***: Oributol; ***Fr.***: Myambutol; ***Ger.***: EMB-Fatol; Myambutol; ***Gr.***: Althocin; Blomison; Dexambutol; Myambutol; ***Hong Kong***: EMB; ***Hung.***: Sural; ***India***: Albutol; Anbutol; Colbutol; Combutol; Ebutol; Ecox; EMTB; Etibi; Isotol; Koxi; Myambutol; Mycoback; Mycobact; Mycobutol; Mycostat; Rifacom-EZ; Themibutol; Tibitol; ***Indon.***: Arsitam; Bacbutol; Cetabutol†; Corsabutol; ETH Ciba†; Parabutol†; Santibi; Tibigon†; Tibitol; ***Ital.***: Etapiam; Miambutol; ***Mex.***: Dovalem; Etadotbal; Tambutec; ***Mon.***: Dexambutol; ***Neth.***: Myambutol; ***NZ***: Myambutol; ***Philipp.***: Danbutol; E-tol; Holtresis; Odetol; Triambutol; ***Port.***: Turresis; ***Rus.***: Combutol (Комбутол); Ebutol (Эбутол); EMB (ЕМБ); Ly-Butol (Ли-Бутол); Upbutol (Апбутол)†; ***S.Afr.***: Purderal†; ***Singapore***: E-Butol; Ebutol; ***Spain***: Myambutol; ***Switz.***: Myambutol; ***Thai.***: ATB; Etham; Ethbutol; Lambutol; Myrin-P†; Servambutol†; Tibitab; Tobutol; ***Turk.***: Dimbutol; Miambutol; ***Ukr.***: Inbutol (Инбутол); ***USA***: Myambutol.

Multi-ingredient Preparations. ***China***: An Si Nuo Kang (安斯诺康); Ke Lao Er Kang (克劳尔康); Yi Nuo Ni Kang (怡诺尼康); ***Denm.***: Rimstar; ***Fin.***: Rimstar; ***Gr.***: Myambutol-INH; ***India***: AFB3; AFB4; Akt-3; Akt-4; Akt-FD; Akurit-3; Akurit-4; Becox Forte Kit; Bicox-E; Binex DT; Binex E; Binex ZE; Cavitar RHE; Caviter FD; Combunex; Confez-3; Coxina-3; Coxina-4; Coxkit-3; Coxrid; Coxter-4; Cx-4; Cx-5; Emrif Kit; Eufacin Plus; Forecox; Inabutol Forte†; Infez-4; Isokoxi; Lifebutol-H; Monto-3; Monto-4; Mycocox-4; Mycocox-E; Mycodot-4; Mycodot-E; Myconex; Mycurit-3; Mycurit-4; RHZ Plus; Rifa E; Wokex-3; Wokex-4; Xeed 3E; Xeed 4; ***Indon.***: bacbutINH; Erabutol Plus; Meditam-6†; Metham; Mycothambin-INH†; Niazitol; Pulna; Rimstar; Santibi Plus; ***Irl.***: Rimstar; ***Ital.***: Etanicozid B6; Rimstar; ***Mex.***: Dotbal; ***Mon.***: Dexambutol-INH†; ***Neth.***: Rimstar†; ***Norw.***: Rimstar; ***Philipp.***: 4D; AKuriT-4; Continukit Plus†; Continukit; Ebutol; Econofix; Econokit-MDR; Econokit; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; Myrin-P; Myrin; Quadmax; Quadtab; Rimstar; Sthamizide; SVM-Polypac-A†; Tres; Tritab; Viper†; ***Rus.***: Combitub (Комбитуб); Combitub-Neo (Комбитуб-Нео); Forecox (Форкокс); Isocomb (Изокомб); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Phthizoetham (Фтизоэтам); Protiocomb (Протиокомб); Protub-4 (Протуб-4); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе); Protubetham (Протубэтам); Repin B_6 (Репин B_6); Rimstar 4-FDC (Римстар 4-ФДС)†; ***S.Afr.***: Rifafour; Rimstar; ***Singapore***: Merip; ***Spain***: Rimstar; ***Swed.***: Rimstar; ***Switz.***: Rimstar; ***Thai.***: Rifafour; Rimstar†; ***UK***: Rimstar; Voractiv.

Pharmacopoeial Preparations

BP 2014: Ethambutol Tablets;

USP 36: Ethambutol Hydrochloride Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Ethionamide *(BAN, USAN, rINN)*

Ethionamid; Éthionamide; Ethionamidum; 2-Ethylthioisonicotinamide; Etionamid; Etionamida; Etionamidas; Etionamide; Etionamidi; 1314-TH; Этионамид.

2-Ethylpyridine-4-carbothioamide.

$C_8H_{10}N_2S$=166.2

CAS — 536-33-4.

ATC — J04AD03.

ATC Vet — QJ04AD03.

UNII — OAY8ORS3CQ.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ethionamide). Small yellow crystals or a yellow crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

USP 36: (Ethionamide). A bright yellow powder having a faint to moderate sulfide-like odour. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol and in propylene glycol; soluble in methyl alcohol. pH of a 1% slurry in water is between 6.0 and 7.0. Store in airtight containers.

Uses and Administration

Ethionamide is a thioamide derivative considered to be interchangeable with protionamide. It is used with other antituberculous drugs for the treatment of tuberculosis (p. 210.2) when resistance to primary drugs has developed. It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p. 188.3) but less toxic alternatives are now preferred.

In the treatment of resistant tuberculosis, adults may be given 15 to 20 mg/kg daily (maximum 1 g daily) orally. Ethionamide may be given in divided doses with meals, or as a single daily dose after the evening meal, or at bedtime, to minimise gastrointestinal adverse effects. For details of doses in infants, children, and adolescents, see p. 299.3.

Similar doses were used for the treatment of leprosy.

Ethionamide has also been used as rectal suppositories; the hydrochloride has been given intravenously.

References.

1. Anonymous. Ethionamide. *Tuberculosis (Edinb)* 2008; **88:** 106–8.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an oral dose of ethionamide 15 to 20 mg/kg (to a maximum of 1 g) daily, given in 2 to 3 divided doses.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Treatment

Many patients cannot tolerate therapeutic doses of ethionamide and have to stop treatment. The most common adverse effects are dose-related gastrointestinal disturbances, including nausea, vomiting, diarrhoea, anorexia, excessive salivation, a metallic taste, stomatitis, and abdominal pain. Tolerance may be improved by reducing the dose, adjusting the timing of dosage, or giving an antiemetic.

Mental disturbances including depression, anxiety, and psychosis have been provoked. Dizziness, drowsiness, headache, orthostatic hypotension, and asthenia may also occur occasionally. Peripheral and optic neuropathy, diplopia and blurred vision, and a pellagra-like syndrome have occurred. Pyridoxine or nicotinamide have been suggested for the treatment or prevention of neurotoxic effects.

Hepatitis may occur occasionally, with or without jaundice. The incidence of hepatotoxicity is increased when ethionamide is given with rifampicin.

Other adverse effects reported include hypersensitivity reactions, thrombocytopenia and purpura, alopecia, dermatitis (including photodermatitis), endocrine disturbances, hypoglycaemia, and hypothyroidism with or without goitre.

Teratogenic effects have been reported in *animals*.

Effects on the liver. Use of ethionamide or protionamide with rifampicin for the treatment of multibacillary leprosy has been associated with a high incidence of hepatotoxicity. A hepatitis incidence of 4.5 to 5% has been reported for patients on ethionamide or protionamide, rifampicin, and either dapsone or clofazimine.[1,2] In these studies, diagnosis of hepatitis was based on clinical assessment. When laboratory monitoring was used, an incidence of 13% was reported with a regimen of ethionamide or pro-

tionamide with rifampicin and dapsone.[3] A regimen of protionamide, dapsone, rifampicin, and clofazimine has been associated with a 22% incidence based on laboratory monitoring.[4] Use of ethionamide with pyrazinamide has also resulted in a high incidence of abnormal liver function tests.[5]

In the above studies rifampicin was given daily during part or all of the regimens. The incidence of hepatotoxicity when ethionamide or protionamide is used with once-monthly rifampicin may be lower; hepatotoxicity was not reported in patients receiving monthly rifampicin and daily protionamide, isoniazid, and dapsone.[6]

1. Pattyn SR, *et al.* Hepatotoxicity of the combination of rifampin-ethionamide in the treatment of multibacillary leprosy. *Int J Lepr* 1984; **52:** 1–6.
2. Pattyn SR, *et al.* Combined regimens of one year duration in the treatment of multibacillary leprosy—II: combined regimens with rifampicin administered during 6 months. *Lepr Rev* 1989; **60:** 118–23.
3. Cartel J-L, *et al.* Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampin, and a thioamide. *Int J Lepr* 1983; **51:** 461–5.
4. Ji B, *et al.* Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev* 1984; **55:** 283–9.
5. Schless JM, *et al.* The use of ethionamide in combined drug regimens in the re-treatment of isoniazid-resistant pulmonary tuberculosis. *Am Rev Respir Dis* 1965; **91:** 728–37.
6. Ellard GA, *et al.* Long-term prothionamide compliance: a study carried out in India using a combined formulation containing prothionamide, dapsone and isoniazid. *Lepr Rev* 1988; **59:** 163–75.

Precautions

Ethionamide should not be used in severe hepatic impairment. Liver function tests should be carried out before, and regularly during, treatment with ethionamide.

Caution is necessary in patients with depression or other psychiatric illness. Difficulty may occur in the management of diabetes mellitus. Periodic monitoring of blood glucose, thyroid function, and visual function is desirable.

Ethionamide is teratogenic in *animals*.

Interactions

The adverse effects of other antimycobacterials may be increased when ethionamide is used (see Effects on the Liver, p. 297.3, and under Cycloserine, Interactions, p. 281.1).

Alcohol. A psychotic reaction has been reported in a patient receiving ethionamide after excessive intake of alcohol.[1]

1. Lansdown FS, *et al.* Psychotoxic reaction during ethionamide therapy. *Am Rev Respir Dis* 1967; **95:** 1053–5.

Antimicrobial Action

Ethionamide is active only against mycobacteria including *Mycobacterium tuberculosis*, *M. kansasii*, *M. leprae*, *M. malmoense*, and some strains of *M. avium* complex.

Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and protionamide. Cross-resistance has also been reported with isoniazid and with *in vitro* thioacetazone.

Cross-resistance. References.

1. Schaaf HS, *et al.* Ethionamide cross- and co-resistance in children with isoniazid-resistant tuberculosis. *Int J Tuberc Lung Dis* 2009; **13:** 1355–9.

Pharmacokinetics

Ethionamide has been given as a sugar-coated tablet or more recently as a more stable film-coated tablet. Both formulations are readily absorbed from the gastrointestinal tract: after an oral dose of 250 mg, sugar-coated tablets produce a peak plasma concentration of about 1.5 micrograms/mL after 1.5 hours, while film-coated tablets give a peak plasma concentration of 2.16 micrograms/mL after about 1 hour. Distribution of ethionamide from the film-coated tablet into body tissues and fluids was expected to be similar to that of the sugar-coated tablets. Ethionamide from sugar-coated tablets is widely distributed throughout body tissues and fluids. It crosses the placenta and penetrates the uninflamed meninges, appearing in the CSF in concentrations equivalent to those in serum. It is about 30% bound to plasma proteins. The half-life for the sugar-coated tablet is reported to be 2 to 3 hours and 1.92 hours for the film-coated tablet. Ethionamide is extensively metabolised, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

Distribution. After single doses of ethionamide 15 or 20 mg/kg as an oral suspension in children with tuberculous meningitis, the peak spinal fluid concentration was reached in 1½ to 2½ hours.[1] A wide range of concentrations was reported but doses of 20 mg/kg were more likely to produce spinal fluid concentrations above 2.5 micrograms/mL, the concentration considered by the authors to be essential for therapeutic success.

1. Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr* 1989; **115:** 483–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Trecator; ***India***: E-Thio; Enamide; Ethide; Ethimax; Ethiobin; Ethiocid; Ethiokox; Ethionam; Ethomid; Etomide; Etumide; MDThide; Mycotuf; Myobid; ***Rus.***: Ethide (Этид); Ethomid (Этомид); Myobid (Миобид); Reginicid (Региницид); ***S.Afr.***: Ethatyl; ***Thai.***: Eton; ***Turk.***: Etyomid; ***USA***: Trecator.

Pharmacopoeial Preparations
USP 36: Ethionamide Tablets.

Etimicin Sulfate

Antibiotic 89-07; E-402.
1-*N*-Ethyl gentamicin C_{1a} sulfate.
$(C_{21}H_{43}N_5O_7)_2,5H_2SO_4$=1445.6
CAS — 59711-96-5 (etimicin); 362045-44-1 (etimicin sulfate).

Pharmacopoeias. In *Chin.*

Profile

Etimicin, a derivative of gentamicin C_{1a}, is an aminoglycoside antibacterial with actions similar to those of gentamicin (p. 306.2). It is given intravenously as the sulfate.

References.

1. Zhao C, *et al.* A randomized controlled clinical trial on etimicin, a new aminoglycoside antibiotic, versus netilmicin in the treatment of bacterial infections. *Chin Med J (Engl)* 2000; **113:** 1026–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ai Yi (爱益); Aida (爱大); Chuang Cheng (创成); Ge Mei Da (格美达); Pan Nuo (潘诺); XiNeng (悉能); Yi Qing (亦清).

Faropenem Sodium *(rINNM)*

ALP-201; Faropenem sódico; Faropénem Sodique; Fropenem Sodium; Furopenem; Natrii Faropenemum; SUN-5555; SY-5555; Wy-49605; YM-044; Натрий Фаропенем.
Sodium (+)-(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydro-2-furyl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.
$C_{12}H_{14}NaNO_5S$=307.3
CAS — 106560-14-9 (faropenem); 141702-36-5 (faropenem medoxomil); 122547-49-3 (faropenem sodium).
ATC — J01DI03.
ATC Vet — QJ01DI03.
UNII — 7O46G914RQ.

Pharmacopoeias. *Jpn* includes the hemipentahydrate.

Profile

Faropenem is a penem antibacterial that is given orally as the sodium salt for the treatment of susceptible infections.

Faropenem medoxomil (*USAN*) (A-0026; Bay-56-6854; SUN-A0026; SUN-208) has been investigated for the treatment of respiratory-tract infections and uncomplicated skin and skin-structure infections. NOTE. Faropenem medoxomil has also been referred to as faropenem daloxate although such use of the term daloxate is not in keeping with *INN* nomenclature conventions.

References.

1. Critchley IA, *et al.* Activities of faropenem, an oral β-lactam, against recent US isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. *Antimicrob Agents Chemother* 2002; **46:** 550–5.
2. von Eiff C, *et al.* Comparative in vitro activity of faropenem against staphylococci. *J Antimicrob Chemother* 2002; **50:** 277–80.
3. Milatovic D, *et al.* In vitro activity of faropenem against 5460 clinical bacterial isolates from Europe. *J Antimicrob Chemother* 2002; **50:** 293–9.
4. Wexler HM, *et al.* In vitro activities of faropenem against 579 strains of anaerobic bacteria. *Antimicrob Agents Chemother* 2002; **46:** 3669–75.
5. Jones ME, *etal.* Activity of faropenem, a new furanem, against European respiratory pathogens collected during 2000-2001: a comparison with other beta-lactam agents. *J Antimicrob Chemother* 2003; **51:** 196–9.
6. Gettig JP, *et al.* Faropenem medoxomil. *Ann Pharmacother* 2008; **42:** 80–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Di Pai (迪哌); Gaoyi (高益); Jun Di (君迪); Peifu (蓓芙); ***India***: Duonem; Faronem; Farozet; ***Jpn***: Farom.

Fidaxomicin *(USAN, rINN)*

Fidaxomicina; Fidaxomicine; Fidaxomicinum; Lipiarmycin; OPT-80; PAR-101; Tiacumicin B; Фидаксомицин.
(3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-3-({[6-Deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl-β-D-mannopyranosyl]oxy}methyl)-12-{[6-deoxy-5-*C*-methyl-4-*O*-(2-methylpropanoyl)-β-D-*lyxo*-hexopyranosyl]oxy}-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyloxacyclooctadeca-3,5,9,13,15-pentaen-2-one.
$C_{52}H_{74}Cl_2O_{18}$=1058
CAS — 873857-62-6.
ATC — A07AA12.
ATC Vet — QA07AA12.
UNII — Z5N076G8YQ.

Uses and Administration

Fidaxomicin is a nonabsorbed, narrow-spectrum macrocyclic antibacterial used in the treatment of *Clostridium difficile*-associated diarrhoea (see Antibiotic-associated Colitis, p. 183.1). It is given orally in a dose of 200 mg twice daily for 10 days.

References.

1. Sullivan KM, Spooner LM. Fidaxomicin: a macrocyclic antibiotic for the management of *Clostridium difficile* infection. *Ann Pharmacother* 2010; **44:** 352–9.
2. Miller M. Fidaxomicin (OPT-80) for the treatment of *Clostridium difficile* infection. *Expert Opin Pharmacother* 2010; **11:** 1569–78.
3. Louie TJ, *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; **364:** 422–31.
4. Mullane KM, Gorbach S. Fidaxomicin: first-in-class macrocyclic antibiotic. *Expert Rev Anti Infect Ther* 2011; **9:** 767–77.
5. Mullane KM, *et al.* Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis* 2011; **53:** 440–7.

Adverse Effects and Precautions

Adverse effects occurring with oral use of fidaxomicin are mainly gastrointestinal in nature and include nausea, vomiting, and abdominal pain. Anaemia, neutropenia, and gastrointestinal haemorrhage may also occur.

Since there is only minimal systemic absorption, oral fidaxomicin should not be used for the treatment of systemic infections. Use of oral fidaxomicin in the absence of a proven or strongly suspected *Clostridium difficile* infection is unlikely to provide benefit and may lead to the development of drug resistant bacteria.

Antimicrobial Action

Fidaxomicin has potent bactericidal activity against *Clostridium difficile in vitro* through its inhibition of RNA synthesis by RNA polymerases. It has more limited activity against other Gram-positive bacteria, and no activity against Gram-negative bacteria.

Pharmacokinetics

Fidaxomicin is essentially nonabsorbed from the gastrointestinal tract after an oral dose. It undergoes hydrolysis in the gut to form the main metabolite, OP-1118, which is microbiologically active. Over 92% of a dose is excreted in the faeces as either fidaxomicin or OP-118, although very small amounts of OP-118 have been recovered in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Dificid; ***Denm.***: Dificlir; ***Irl.***: Dificlir; ***Norw.***: Dificlir; ***Spain***: Dificlir; ***Swed.***: Dificlir; ***UK***: Dificlir; ***USA***: Dificid.

Fleroxacin *(BAN, USAN, rINN)*

AM-833; Fleroksasiini; Fléroxacine; Fleroxacino; Fleroxacinum; Ro-23-6240; Ro-23-6240/000; Флероксацин.
6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.
$C_{17}H_{18}F_3N_3O_3$=369.3
CAS — 79660-72-3.
ATC — J01MA08.
ATC Vet — QJ01MA08.
UNII — N804LDH51K.

Pharmacopoeias. In *Chin.*

Profile

Fleroxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.1), but is reported to have greater systemic bioavailability and a longer half-life. It is given orally for the treatment of susceptible infections in usual doses of 200 to 300 mg once daily. It has also been given by intravenous infusion.

The incidence of adverse effects associated with fleroxacin has been relatively high.

General references.
1. Balfour JA, *et al*. Fleroxacin: a review of its pharmacology and therapeutic efficacy in various infections. *Drugs* 1995; **49:** 794–850.

Adverse effects. References[1-3] to adverse effects associated with fleroxacin.

1. Bowie WR, *et al*. Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. *Antimicrob Agents Chemother* 1989; **33:** 1778–82.
2. Geddes AM. Safety of fleroxacin in clinical trials. *Am J Med* 1993; **94** (suppl 3A): 201S–203S.
3. Kimura M, *et al*. Photosensitivity induced by fleroxacin. *Clin Exp Dermatol* 1996; **21:** 46–7.

Breast feeding. The American Academy of Pediatrics[1] states that fleroxacin is usually compatible with breast feeding. However, in a study,[2] in which women were given a single 400-mg dose and breast feeding was withheld for 48 hours, it was concluded that although a breast-fed infant would only receive a moderate amount (maximum 10 mg daily), fleroxacin should not be used in breast-feeding mothers due to the potential for adverse effects such as arthropathy in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Dan M, *et al*. Penetration of fleroxacin into breast milk and pharmacokinetics in lactating women. *Antimicrob Agents Chemother* 1993; **37:** 293–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bang Lai Li Xin (邦来立欣); Chen Long Luo Xin (辰龙罗欣); Ding Ke Si (定克斯); Duo Mi Te Ding (多米特定); Fu Lu Xin (福路新); Fu Luo Ke (富络克); Fu Nuo Ding (复诺定); Fuluxing (芙璐星); Hu Kang (护康); Jimin FuXin (济民福欣); Luo Fei (洛菲); Nuo Er (诺尔); Nuo Tong (诺同); Qian Le An (千乐安); Si Tong Tuo Luo (四通佗罗); Wo Er De (沃尔得); Yan Li Da (严力达); ***Jpn***: Megalocin†.

Flomoxef Sodium *(rINNM)*

Flomoxef sódico; Flomoxef Sodique; Natrii Flomoxefum; 6315-S; Натрий Фломоксеф.

7*R*-7-[2-(Difluoromethylthio)acetamido]-3-[1-(2-hydroxyethyl)-1*H*-tetrazol-5-ylthiomethyl]-7-methoxy-1-oxa-3-cephem-4-carboxylic acid sodium.

$C_{15}H_{17}F_2N_6NaO_7S_2$=518.4

CAS — 99665-00-6 (flomoxef); 92823-03-5 (flomoxef sodium).

UNII — 445HIB8XNF.

Pharmacopoeias. In *Jpn*.

Profile

Flomoxef is an oxacephalosporin or oxacephem antibacterial with properties similar to latamoxef (p. 317.2). It is given intravenously as the sodium salt and doses are expressed in terms of flomoxef; 1.04 g of flomoxef sodium is equivalent to about 1 g of flomoxef. The usual dose is 1 to 2 g daily in two divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Flumarin (氟吗宁); ***Jpn***: Flumarin.

Florfenicol *(BAN, USAN, rINN)*

Florfénicol; Florfenicolum; Florfenikol; Florfenikoli; Sch-25298; Флорфеникол.

2,2-Dichloro-*N*-[(αS,β-α*R*)-(fluoromethyl)-β-hydroxy-4-methanesulfonylphenethyl]acetamide.

$C_{12}H_{14}Cl_2FNO_4S$=358.2

CAS — 76639-94-6.

ATC Vet — QJ01BA90; QJ51BA90.

UNII — 9J97307Y1H.

Profile

Florfenicol, a fluorinated analogue of chloramphenicol, is an antibacterial used in veterinary medicine.

Flucloxacillin *(BAN, rINN)*

BRL-2039; Floxacillin (USAN); Flucloxacilina; Flucloxacilline; Flucloxacillinum; Flukloksasilin; Flukloksasilliini; Flukloxacillin; Флуклоксациллин.

(6*R*)-6-[3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

$C_{19}H_{17}ClFN_3O_5S$=453.9

CAS — 5250-39-5.

ATC — J01CF05.

ATC Vet — QJ01CF05; QJ51CF05.

UNII — 43B2M34G2V.

NOTE. Compounded preparations of flucloxacillin may be represented by the following names:
- Co-fluampicil (*BAN*)—flucloxacillin 1 part and ampicillin 1 part (w/w).

Flucloxacillin Magnesium *(BANM, rINNM)*

Flucloxacilina magnésica; Flucloxacilline Magnesique; Flucloxacilline-magnésium; Flucloxacillinum magnesicum; Magnesii Flucloxacillinum; Магния Флуклоксациллин.

$(C_{19}H_{16}ClFN_3O_5S)_2Mg,8H_2O$=1074.1

CAS — 58486-36-5.

ATC — J01CF05.

ATC Vet — QJ01CF05.

UNII — 4Z8782KMVT.

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Flucloxacillin Magnesium Octahydrate). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 6.5.

Flucloxacillin Sodium *(BANM, rINNM)*

Flucloxacilina sódica; Flucloxacillin-Natrium; Flucloxacilline Sodique; Flucloxacillinum natricum; Flucloxacillinum Natricum Monohydricum; Flukloksasilino natrio druska; Flukloksasilin Sodyum; Flukloksasiliininatrium; Flukloxacilin sodná sůl monohydrát; Flukloxacillinnatrium; Flukloxacillin-nátrium; Natrii Flucloxacillinum; Натрий Флуклоксациллин.

$C_{19}H_{16}ClFN_3NaO_5S,H_2O$=493.9

CAS — 1847-24-1 (anhydrous flucloxacillin sodium); 34214-51-2 (flucloxacillin sodium monohydrate).

ATC — J01CF05.

ATC Vet — QJ01CF05.

UNII — 05F65O42VK (anhydrous flucloxacillin sodium); LMG7C674WJ (flucloxacillin sodium monohydrate).

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Flucloxacillin Sodium). A white or almost white, crystalline hygroscopic, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25 degrees in airtight containers.

Incompatibility. As with other penicillins, flucloxacillin sodium is incompatible with aminoglycosides. Incompatibility has also been reported with many other drugs given parenterally including antibacterials such as ciprofloxacin, erythromycin lactobionate, and ofloxacin, cardiac drugs such as amiodarone, atropine sulfate, dobutamine hydrochloride, and verapamil hydrochloride, and others including buprenorphine, calcium gluconate, chlorpromazine hydrochloride, diazepam, metoclopramide hydrochloride, morphine sulfate, papaveretum, pethidine hydrochloride, prochlorperazine edisilate, and promethazine hydrochloride.

Flucloxacillin should not be mixed with blood products or other proteinaceous fluids, or with intravenous lipid emulsions.

Uses and Administration

Flucloxacillin is an isoxazolyl penicillin used primarily for the treatment of infections due to staphylococci resistant to benzylpenicillin. These include bone and joint infections, endocarditis, pneumonia, skin infections (including soft-tissue infections), and toxic shock syndrome. For discussions of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Flucloxacillin is given parenterally and orally as the sodium or magnesium salt. All doses are expressed as flucloxacillin; 1.18 g of flucloxacillin magnesium and 1.09 g of flucloxacillin sodium are each equivalent to about 1 g of flucloxacillin.

The usual adult dose orally or by intramuscular injection is 250 mg four times daily. Oral doses should be taken at least 30 minutes before meals as the presence of food in the stomach reduces absorption. Flucloxacillin is given intravenously in a dose of 0.25 to 1 g four times daily by slow injection over 3 to 4 minutes or by intravenous infusion. All systemic doses may be doubled in severe infections. Up to 8 g daily in 3 or 4 divided doses may be given for osteomyelitis; in endocarditis a dose of 8 g daily in 4 divided doses may be given to patients weighing up to 85 kg, and 12 g daily in 6 divided doses may be used in those weighing more. In severe renal impairment a reduction in dosage may be necessary.

Flucloxacillin has been given by other routes in conjunction with systemic therapy. It has been given in a dose of 250 to 500 mg daily by intra-articular injection, dissolved if necessary in a 0.5% solution of lidocaine hydrochloride, or by intrapleural injection in a dose of 250 mg daily. Using powder for injection, 125 to 250 mg has been dissolved in 3 mL of sterile water and inhaled by nebuliser 4 times daily.

For details of doses in children, see p. 301.3.

Flucloxacillin may be used with other antibacterials, including ampicillin (known as co-fluampicil), to produce a wider spectrum of activity. If flucloxacillin is given with an aminoglycoside the two drugs should not be mixed.

Administration in children. Flucloxacillin may be given to neonates and children for the treatment of infections caused by susceptible organisms and may be given orally, by intramuscular or slow intravenous injection, or by intermittent intravenous infusion over 30 to 60 minutes.

In the UK, the *BNFC* suggests the following:

For infections due to beta-lactamase-producing staphylococci including in **otitis externa, pneumonia, impetigo, and cellulitis**:
- neonates: 25 mg/kg *orally* or *intravenously*, given twice daily for those under 7 days of age, 3 times daily for those 7 to 21 days of age, and 4 times daily for those 21 to 28 days of age; intravenous doses may be doubled for severe infection
- children from 1 month to 2 years of age: 62.5 to 125 mg; 2 to 10 years, 125 to 250 mg; 10 years and older, 250 to 500 mg; all doses to be given *orally* 4 times daily
  or
  children from 1 month of age: 12.5 to 25 mg/kg *intramuscularly* (to a maximum of 500 mg) or *intravenously* (to a maximum of 1 g) every 6 hours; intravenous dose may be doubled for severe infection

For **osteomyelitis, cerebral abscess, and staphylococcal meningitis**:
- neonates: 50 to 100 mg/kg *intravenously*, given every 12 hours for those under 7 days of age, every 8 hours for those 7 to 21 days of age, and every 6 hours for those 21 to 28 days of age
- children from 1 month of age: 50 mg/kg (maximum 2 g) *intravenously* every 6 hours

For **endocarditis**:
- children from 1 month of age: 50 mg/kg (maximum 2 g) *intravenously* every 6 hours

For *prevention* of **staphylococcal lung infection in cystic fibrosis**:
- for the primary prevention, flucloxacillin is given orally to neonates and children in a dose of 125 mg twice daily
- for secondary prevention in children from 1 month of age an oral dose of 50 mg/kg (to a maximum of 1 g) twice daily is given

For the *treatment* of staphylococcal lung infection, infants and children from 1 month of age may be given an oral dose of 25 mg/kg (to a maximum dose of 1 g) in 3 or 4 divided doses; alternatively, it may be given intravenously in a dose of 50 mg/kg (to a maximum of 2 g) every 6 hours.

In children with severe renal impairment (creatinine clearance less than 10 mL/min), the normal dose should be given no more frequently than every 8 hours.

Adverse Effects and Precautions

As for Benzylpenicillin p. 229.2.

Hepatitis and cholestatic jaundice have been reported occasionally with flucloxacillin and may be delayed in onset for up to 2 months after treatment has been stopped; older patients and those receiving flucloxacillin for more than 2 weeks are at greater risk. Fatalities have occurred, usually in patients with serious underlying hepatic disease. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis associated with flucloxacillin. Agranulocytosis and neutropenia have been associated rarely with isoxazolyl penicillins such as flucloxacillin. Haemolytic anaemia has also been reported. Phlebitis has followed intravenous infusion.

Effects on the liver. In October 2004, the UK CSM issued a reminder[1] that flucloxacillin is associated rarely with an increased risk of hepatitis and cholestatic jaundice. In some patients, almost always those with serious underlying hepatic disease, fatalities have occurred. The onset of hepatic adverse effects may be delayed for up to 2 months after stopping treatment, and is not related to the dose or to the route. Older patients and those receiving flucloxacillin for more than 2 weeks are at increased risk. Flucloxacillin should not be used in patients with a history of hepatic dysfunction related to its use, and should be used only with caution in patients with evidence of other hepatic impairment. Careful enquiry should be made concerning previous hypersensitivity to beta lactams. A cohort study[2] using UK prescription data found that the risk of developing cholestatic liver disease in the 45 days after

starting flucloxacillin was 6.1 per 100 000. In contrast to other countries, flucloxacillin continued to be seen as a first-line drug in the UK. The potential genetic mechanisms of flucloxacillin-induced liver injury have been reviewed.[3]

1. CSM. Reminder: flucloxacillin and serious hepatic disorders. *Current Problems* 2004; **30:** 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)
2. Li L, *et al*. Updated study on risk of cholestatic liver disease and flucloxacillin. *Br J Clin Pharmacol* 2009; **68:** 269–70.
3. Andrews E, Daly AK. Flucloxacillin-induced liver injury. *Toxicology* 2008; **254:** 158–63.

Effects on metabolism. Use of flucloxacillin, often with paracetamol, has been associated with accumulation of pyroglutamic acid resulting in pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.[1-3]

1. Croal BL, *et al*. Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult receiving antibiotic therapy. *Clin Chem* 1998; **44:** 336–40.
2. Peter JV, *et al*. An unusual cause of severe metabolic acidosis. *Med J Aust* 2006; **185:** 223–5. Correction. *ibid*.; 528.
3. Rolleman EJ, *et al*. Guilty as charged: unmeasured urinary anions in a case of pyroglutamic acidosis. *Neth J Med* 2008; **66:** 351–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flucloxacillin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of flucloxacillin sodium contains about 2 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterials. In a small randomised study in healthy subjects,[1] *piperacillin* was found to decrease both renal and non-renal clearance of flucloxacillin to 45 and 66% respectively. The extent of the interaction was larger at higher doses, and considered clinically significant by the authors. The pharmacokinetics of piperacillin were not significantly affected by flucloxacillin.

1. Landersdorfer CB, *et al*. Inhibition of flucloxacillin tubular renal secretion by piperacillin. *Br J Clin Pharmacol* 2008; **66:** 648–59.

Antimicrobial Action

Flucloxacillin is bactericidal with a mode of action similar to that of benzylpenicillin, but is resistant to staphylococcal penicillinase. It is active therefore against penicillinase-producing and non-penicillinase-producing staphylococci. Its activity against streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* is less than that of benzylpenicillin, but sufficient to be useful when these organisms are present with penicillin-resistant staphylococci. Flucloxacillin is virtually ineffective against *Enterococcus faecalis*.

Resistance. The resistance of staphylococci to flucloxacillin and other penicillinase-resistant penicillins is described under meticillin (p. 325.3).

Pharmacokinetics

Flucloxacillin is better absorbed from the gastrointestinal tract than cloxacillin, but absorption is reduced by the presence of food in the stomach. After an oral dose of 0.25 to 1 g, in fasting subjects, peak plasma concentrations in about 1 hour are usually in the range of 5 to 15 micrograms/mL. Plasma concentrations after intramuscular injection of flucloxacillin sodium are similar, but peak concentrations occur after about 30 minutes. Doubling the dose can double the plasma concentration. About 95% of flucloxacillin in the circulation is bound to plasma proteins. Flucloxacillin has been reported to have a plasma half-life of about 1 hour. The half-life is prolonged in neonates.

The distribution of flucloxacillin into body tissues and fluids is similar to that of cloxacillin (p. 275.2).

Flucloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 66% of an oral dose and 76% of a parenteral dose is excreted in the urine within 8 hours. Only small amounts are excreted in the bile. Flucloxacillin is not removed by haemodialysis or peritoneal dialysis.

Plasma concentrations are enhanced by probenecid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Flopen; Floxapen†; Floxsig; Flubiclox; Flucil; Staphylex; ***Austria***: Floxapen; ***Belg.***: Floxapen; Staphycid; ***Chile***: Fluxacina†; Vitalpen; ***China***: Aofolin (奥佛林); Kun Te (昆特); Yifen (伊芬); ***Denm.***: Heracillin; ***Ger.***: Fluclox; Staphylex; ***Gr.***: Floxapen; Itaclox; ***Hong Kong***: Floxapen†; Fluckoxil†; ***India***: Neoflox; ***Indon.***: Floxapen†; ***Irl.***: Floxapen; Flucillin; Fluclon; Geriflox; ***Ital.***: Cloxillin; Evercid; Faifloc; Fareclox; Flucacid; Flucef; Flucinal; Fluclox; Fluxacil; Liderclox; Nepenic; Pantaflux; Recaflux; ***Malaysia***: Flucloxil; Staphlex†; ***Mex.***: Floxapen†; ***Neth.***: Floxapen; ***NZ***: Floxapen; Flucloxin; Staphlex†; ***Philipp.***: Fluclox; Fluxin; Stafloxin; ***Port.***: Floxapen; ***S.Afr.***: Floxapen†; Flupen; ***Singapore***: Staphlex†; ***Swed.***: Heracillin; ***Switz.***: Floxapen; ***Thai.***: Staphycid†; ***Turk.***: Flix; Floksin; ***UK***: Floxapen; Fluclomix; Ladropen; ***Venez.***: Floxapen.

Multi-ingredient Preparations. ***China***: Fu Wei (弗威); Kun Bai (昆柏); ***Ger.***: Flanamox; ***S.Afr.***: Macropen; Megapen; Suprapen; ***UK***: Magnapen†; Magnapen; Magnapen.

Pharmacopoeial Preparations

BP 2014: Co-fluampicil Capsules; Co-fluampicil Oral Suspension; Flucloxacillin Capsules; Flucloxacillin Injection; Flucloxacillin Oral Solution; Flucloxacillin Oral Suspension.

Flumequine *(BAN, USAN, rINN)*

Flumechin; Flumekiini; Flumekin; Flumekvinas; Flumequin; Flumequina; Fluméquine; Flumequinum; R-802; Флумехин.

9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid.

$C_{14}H_{12}FNO_3$=261.3

CAS — 42835-25-6.

ATC — J01MB07.

ATC Vet — QJ01MB07.

UNII — UVG8VSP25J.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flumequine). A white or almost white microcrystalline powder. Practically insoluble in water; sparingly soluble in dichloromethane; very slightly soluble in methyl alcohol; freely soluble in dilute solutions of alkali hydroxides.

Profile

Flumequine is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p. 330.3). It may be more active *in vitro* against some Enterobacteriaceae. In the treatment of urinary-tract infections doses of 400 mg are given orally 3 times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Apurone.

Flurithromycin Ethyl Succinate *(rINNM)*

Etilsuccinato de fluritromicina; Flurithromycin Ethylsuccinate; Flurithromycine, Éthylsuccinate de; Flurithromycini Ethylsuccinas; Fluritromicina, etilsuccinato de [erINNM]; Флуритромицина Этилсукцинат.

(8*S*)-8-Fluoroerythromycin mono(ethyl butanedioate) ester.

$C_{43}H_{74}FNO_{16}$=880.1

CAS — 82664-20-8 (flurithromycin); 82730-23-2 (flurithromycin ethyl succinate).

ATC — J01FA14.

ATC Vet — QJ01FA14.

Profile

Flurithromycin is a fluorinated macrolide antibacterial derived from erythromycin (p. 291.2). It is given orally as the ethyl succinate but doses are expressed in terms of the base. The usual dose in the treatment of susceptible infections is the equivalent of 375 mg of flurithromycin twice daily, after meals.

References.

1. Saverino D, *et al*. Antibacterial profile of flurithromycin, a new macrolide. *J Antimicrob Chemother* 1992; **30:** 261–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Flurizic; Mizar; Ritro.

Formosulfathiazole

Formaldehyde-sulphathiazole; Formosulfatiazol; Formosulphathiazole; Methylenesulfathiazole.

$(C_9H_9N_3O_2S_2.CH_2O)_x$

CAS — 12041-72-4; 13968-86-0.

ATC Vet — QA07A890; QD06BA90; QG51AA09.

Profile

Formosulfathiazole, a condensation product of sulfathiazole with formaldehyde, has properties similar to those of sulfamethoxazole (p. 367.2). It is poorly absorbed and has been given for its antibacterial action in the gastrointestinal tract, often with other antibacterials.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Pol.***: Sterovag†; ***Spain***: Sulfintestin Neomicina.

Fosfomycin *(BAN, USAN, rINN)*

Fosfomicina; Fosfomycine; Fosfomycinum; Fosfomysiini; MK-955; Phosphomycin; Phosphonomycin; Фосфомицин.

(1*R*,2*S*)-1,2-Epoxypropylphosphonic acid.

$C_3H_7O_4P$=138.1

CAS — 23155-02-4.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 2N81MY12TE.

Description. Fosfomycin is an antibacterial isolated from *Streptomyces fradiae* and other *Streptomyces* spp. or produced synthetically.

Fosfomycin Calcium *(BANM, rINNM)*

Calcii Fosfomycinum; Fosfomicina cálcica; Fosfomicina cálcical; Fosfomicino kalcio druska; Fosfomycin-Calcium; Fosfomycin vápenatá sůl monohydrát; Fosfomycine Calcique; Fosfomycinkalcium; Fosfomycinum Calcicum; Fosfomycinum Calcicum Monohydricum; Fosfomysiinikalsium; Foszfomicin-kalcium; Кальций Фосфомицин.

$C_3H_5CaO_4P,H_2O$=194.1

CAS — 26016-98-8; 26469-67-0.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 76EIK6888N (fosfomycin calcium); T330QG2NYS (fosfomycin calcium hydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Fosfomycin Calcium). A white or almost white powder. Slightly soluble in water; practically insoluble in acetone, in dichloromethane, and in methyl alcohol. A 0.1% solution in water has a pH of 8.1 to 9.6. Store in airtight containers. Protect from light.

Fosfomycin Sodium *(BANM, rINNM)*

Fosfomicina sódica; Fosfomicino natrio druska; Fosfomycin disodná sůl; Fosfomycin-Natrium; Fosfomycine Sodique; Fosfomycinnatrium; Fosfomycinum Dinatricum; Fosfomycinum Natricum; Fosfomysiininatrium; Foszfomicin-nátrium; Natrii Fosfomycinum; Натрий Фосфомицин.

$C_3H_5Na_2O_4P$=182.0

CAS — 26016-99-9.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 97MMO19FNO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Fosfomycin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; practically insoluble in dehydrated alcohol and in dichloromethane; sparingly soluble in methyl alcohol. A 5% solution in water has a pH of 9.0 to 10.5. Store in airtight containers. Protect from light.

Fosfomycin Trometamol *(BANM, rINNM)*

Fosfomicina trometamol; Fosfomicinas trometamolis; Fosfomisin Trometamol; Fosfomycin Tromethamine (USAN); Fosfomycine Trométamol; Fosfomycintrometamol; Fosfomycin-trometamol; Fosfomycinum Trometamol; Fosfomycinum Trometamolum; Fosfomycyna z trometamolem; Fosfomysiinitrometamoli; Foszfomicin-trometamol; FZ-588; Z-1282; Фосфомицин Трометамол.

$C_3H_7O_4P,C_4H_{11}NO_3$=259.2

CAS — 78964-85-9.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 7FXW6U30GY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Fosfomycin Trometamol). A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Fosfomycin Tromethamine). pH of a 5% solution in carbon dioxide-free water is 3.5 to 5.5. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Fosfomycin is a phosphonic acid antibacterial given orally as the trometamol or calcium salt and intramuscularly or intravenously as the disodium salt in the treatment of a variety of bacterial infections due to susceptible organisms. Doses are expressed in terms of the base; fosfomycin calcium 1.4 g, fosfomycin sodium 1.3 g, and fosfomycin trometamol 1.9 g are each equivalent to about 1 g of fosfomycin.

In the treatment of acute uncomplicated infections of the urinary tract (p. 213.1), fosfomycin trometamol is given orally as a single dose equivalent to 3 g of fosfomycin. Fosfomycin trometamol has also been used for the prophylaxis of infection in transurethral surgical procedures. For a discussion of surgical infections and their prophylaxis and treatment, see p. 209.1.

The usual oral dose of fosfomycin calcium is the equivalent of 0.5 to 1 g of fosfomycin every 8 hours. Higher doses have been given parenterally as the sodium salt, with up to 20 g daily having been given intravenously in severe infection.

Fosfomycin has also been used with beta lactam antibacterials.

References.

1. Reeves DS. Fosfomycin trometamol. *J Antimicrob Chemother* 1994; **34:** 853–8.
2. Patel SS, *et al*. Fosfomycin tromethamine: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997; **53:** 637–56.
3. Stein GE. Single-dose treatment of acute cystitis with fosfomycin tromethamine. *Ann Pharmacother* 1998; **32:** 215–19.
4. Schito GC. Why fosfomycin trometamol as first line therapy for uncomplicated UTI? *Int J Antimicrob Agents* 2003; **22** (suppl 2): 79–83.
5. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol: double blind, randomized, parallel group, placebo controlled study. *Arzneimittelforschung* 2005; **55:** 420–7.
6. Sádaba-Díaz de Rada B, *et al*. Fosfomicina trometamol: dosis múltiples como pauta larga en el tratamiento de las infecciones urinarias bajas. *Enferm Infecc Microbiol Clin* 2006; **24:** 546–50.
7. Pullukcu H, *et al*. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. *Int J Antimicrob Agents* 2007; **29:** 62–5.
8. Falagas ME, *et al*. Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008; **46:** 1069–77.
9. Falagas ME, *et al*. Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies. *Int J Antimicrob Agents* 2009; **34:** 111–20.
10. Falagas ME, *et al*. Fosfomycin for the treatment of infections caused by Gram-positive cocci with advanced antimicrobial drug resistance: a review of microbiological, animal and clinical studies. *Expert Opin Invest Drugs* 2009; **18:** 921–44.
11. Falagas ME, *et al*. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010; **10:** 43–50.
12. Popovic M, *et al*. Fosfomycin: an old, new friend? *Eur J Clin Microbiol Infect Dis* 2010; **29:** 127–42.

Adverse Effects and Precautions

Gastrointestinal disturbances including nausea and diarrhoea, transient increases in serum concentrations of aminotransferases, headache, visual disturbances, and skin rashes have been reported after use of fosfomycin. Eosinophilia and, rarely, angioedema, aplastic anaemia, exacerbation of asthma, cholestatic jaundice, hepatic necrosis, and toxic megacolon, have also occurred.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fosfomycin as probably not porphyrinogenic; it may be used as a drug of first-choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Antimicrobial Action

Fosfomycin is a bactericidal antibacterial. After active uptake into the cell it is reported to interfere with the first step in the synthesis of bacterial cell walls. It is active *in vitro* against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, some streptococci, most Enterobacteriaceae, *Haemophilus influenzae*, *Neisseria* spp., and some strains of *Pseudomonas aeruginosa* although some are resistant. *Bacteroides* spp. are not sensitive.

Bacterial resistance to fosfomycin has been reported and can be chromosomal or, in some organisms, transferred by plasmids encoding multiple resistance (for example in *Serratia marcescens*). However, there appears to be little cross-resistance with other antibacterials.

Fosfomycin has been reported to show antimicrobial synergy with many antibacterials against organisms such as enterococci, meticillin-resistant *Staph. aureus*, and the enterobacteria. Such synergistic effects have been reported particularly with the beta lactams, but also with aminoglycosides, macrolides, tetracyclines, chloramphenicol, rifamycin, and lincomycin. Antimicrobial antagonism with a beta lactam has also been reported.

There is some suggestion that use of fosfomycin with an aminoglycoside may also reduce the nephrotoxicity of the latter *in vivo*.

References.

1. Barry AL, Brown SD. Antibacterial spectrum of fosfomycin trometamol. *J Antimicrob Chemother* 1995; **35:** 228–30.

Pharmacokinetics

Fosfomycin or fosfomycin calcium are poorly absorbed from the gastrointestinal tract. Peak plasma concentrations 4 hours after a 1-g dose of fosfomycin calcium are about 7 micrograms/mL, and bioavailability has been calculated at about 30 to 40%. Similar bioavailability has been reported for the trometamol salt, and plasma concentrations of about 22 to 32 micrograms/mL have been reported 2 hours after an oral dose equivalent to 3 g fosfomycin. Fosfomycin disodium is given intramuscularly or intravenously: intravenous infusion of a 4-g dose results in peak plasma concentrations of around 120 micrograms/mL. The plasma half-life is about 2 hours. Fosfomycin does not appear to be bound to plasma proteins. It crosses the placenta and is widely distributed in body fluids including the CSF; small amounts have been found in breast milk and bile. The majority of a parenteral dose is excreted unchanged in the urine, by glomerular filtration, within 24 hours.

Urinary concentrations of up to 3 mg/mL have been reported within 2 to 4 hours of an oral dose of fosfomycin trometamol equivalent to 3 g of fosfomycin; therapeutic concentrations of 200 to 300 micrograms/mL remained in urine after 48 hours.

References.

1. Bergan T, *et al*. Pharmacokinetic profile of fosfomycin trometamol. *Chemotherapy* 1993; **39:** 297–301.
2. Roussos N, *et al*. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *Int J Antimicrob Agents* 2009; **34:** 506–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Veramina; ***Austria***: Monuril; ***Belg.***: Monuril; ***Braz.***: Monuril; ***Canad.***: Monurol; ***Chile***: Monurol†; ***China***: Fu An Xin (复安欣); Fumeixin (复美欣); Monurol (美乐力); Vnikon (维尼康); ***Fin.***: Monurol†; ***Fr.***: Fosfocine; Monuril; Uridoz; ***Ger.***: InfectoFos; Monuril; ***Gr.***: Monurol; ***Hong Kong***: Monurol; ***Hung.***: Monural; ***Indon.***: Fosmicin; Fosmidex; Monuril; ***Irl.***: Monuril; ***Israel***: Monurol; ***Ital.***: Fosfocin; Monuril; ***Jpn***: Fosmicin-S; Fosmicin; ***Malaysia***: Monurol; ***Mex.***: Fosfocil; Monurol; ***Neth.***: Monuril; ***Philipp.***: Monurol; ***Pol.***: Monural; ***Port.***: Monuril; ***Rus.***: Monural (Монурал); Urofosfabol (Урофосфабол); ***S.Afr.***: Urizone; ***Singapore***: Monurol; ***Spain***: Fosfocina; Monurol; Solufos; Uroseptic; ***Switz.***: Monuril; ***Thai.***: Fosfomin; Fosmicin; Monurol; ***Turk.***: Monurol; Urocare; Uromisin; ***Ukr.***: Monural (Монурал); ***USA***: Monurol.

Framycetin Sulfate *(BANM, rINNM)*

Framicetina, sulfato de; Framicetino sulfatas; Framicetinszulfát; Framycetin Sulphate; Framycétine, Sulfate de; Framycetini Sulfas; Framycetinsulfat; Framycetin-sulfát; Framysetiinisulfaatti; Neomycin B Sulphate; Sulfato de framicetina; Sulfato de neomicina B; Фрамицетина Сульфат.

2-Deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]streptamine sulphate.

$C_{23}H_{46}N_6O_{13}.xH_2SO_4$

CAS — 119-04-0 (framycetin); 4146-30-9 (framycetin sulfate).

ATC — D09AA01; R01AX08; S01AA07.

ATC Vet — QD09AA01; QJ01GB91; QR01AX08; QS01AA07.

UNII — Y3720KZ4TQ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Framycetin Sulfate). A substance produced by growth of selected strains of *Streptomyces fradiae* or *S. decaris* or obtained by any other means. It contains not more than 3% of neomycin C (p. 331.3) and loses not more than 8% of its weight on drying. A white or yellowish-white, hygroscopic powder. The potency is not less than 630 units of neomycin B per mg, calculated with reference to the dried substance. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Framycetin is an aminoglycoside antibacterial that forms the major component of neomycin (p. 331.3) and has similar actions and uses. Framycetin sulfate is used topically in usual concentrations of 1% for the treatment of infections of the skin, and in concentrations of 0.5% for infections of the eye and ear. It is often used with other antibacterials and corticosteroids in topical preparations.

Framycetin sulfate is poorly absorbed from the gastrointestinal tract and has been given orally for the treatment of gastrointestinal infections and pre-operatively for bowel preparation. It has sometimes been given prophylactically as part of regimens for the selective decontamination of the digestive tract in patients in intensive care.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Sofra-Tulle†; Soframycin; ***Belg.***: Soframycine; ***Canad.***: Sofra-Tulle; Soframycin; ***Ger.***: Leukase N; ***India***: Frade; Sofra-Tulle; Soframycin; ***Indon.***: Daryant-Tulle; Sofra-Tulle; ***Irl.***: Soframycin†; ***NZ***: Soframycin; ***Philipp.***: Steri-Tin; ***Rus.***: Isofra (Изофра); ***S.Afr.***: Sofra-Tulle†; Soframycin†; ***Singapore***: Fracitin; Soframycin; ***Switz.***: Soframycin†; ***Thai.***: Sofra-Tulle; ***UK***: Sofra-Tulle†; ***Ukr.***: Isofra (Изофра).

Multi-ingredient Preparations. ***Arg.***: Biotaer Nasal†; ***Austral.***: Otodex; Sofradex; Soframycin†; ***Austria***: Leukase†; ***Belg.***: Frakidex; Sofraline; Sofrasolone; ***Braz.***: Fonergin; ***Canad.***: Opticort; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; Sofracort; Soframycin; Soframycin; ***Cz.***: Pulpomixine†; Septomixine; ***Denm.***: Proctosedyl; Sofradex; ***Fin.***: Proctosedyl; ***Fr.***: Arthrisone†; Cortexan Framycetine; Corticetine†; Frakidex; Framyxone; Polyfra†; Pulpomixine; Septomixine; ***Ger.***: Leukase N; ***Gr.***: Sofradex; ***Hong Kong***: Frakidex; Frazoline†; Sofradex; ***India***: Proctosedyl; Sofracort; Sofradex-F; Sofradex; ***Indon.***: Blecidex; Sofradex; ***Irl.***: Proctosedyl; Sofradex; ***Malaysia***: Proctosedyl; Sofradex; ***Neth.***: Proctosedyl; Sofradex; ***Norw.***: Proctosedyl; Sofradex; ***NZ***: Sofradex; Soframycin†; ***Philipp.***: Proctosedyl; ***Pol.***: Caridenf; Dexadent; ***Port.***: Frakidex; ***Rus.***: Proctosedyl (Проктоседил); Proctosedyl M (Проктоседил М); Sofradex (Софрадекс); ***S.Afr.***: Proctosedyl; Sofradex; ***Singapore***: Frakidex; Proctosedyl; Sofradex; ***Spain***: Abrasone; Aldoderma; Nesfare; Otomidrin; ***Swed.***: Proctosedyl†; ***Switz.***: Dexalocal-F; Frakidex; Septomixine; Sofradex†; ***Thai.***: Proctosedyl; Sofradex; Topifram; ***UK***: Sofradex; ***Ukr.***: Proctosedyl (Проктоседил); Sofradex (Софрадекс)†.

Ftivazide *(rINN)*

Ftivazida; Ftivazidum; Phthivazid; Phthivazidum; Фтивазид.

2′-Vanillylideneisonicotinohydrazide monohydrate.

$C_{14}H_{13}N_3O_3.H_2O$=289.3

CAS — 149-17-7 (anhydrous ftivazide).

UNII — 40Q4C3O4V0.

Pharmacopoeias. In *Chin.* and *Int.*

Profile

Ftivazide is an antimycobacterial given orally in the treatment of tuberculosis. It is a derivative of isoniazid.

Furaltadone Hydrochloride *(BANM, rINNM)*

Furaltadone, Chlorhydrate de; Furaltadoni Hydrochloridum; Hidrocloruro de furaltadona; Фуральтадона Гидрохлорид.

(±)-5-Morpholinomethyl-3-(5-nitrofurylideneamino)oxazolidin-2-one hydrochloride.

$C_{13}H_{16}N_4O_6.HCl$=360.8

CAS — 139-91-3 (furaltadone); 59302-14-6 (±-furaltadone).

UNII — 37Q02H7JT2.

Pharmacopoeias. *Fr.* includes Furaltadone for veterinary use.

Profile

Furaltadone was formerly given orally as an antibacterial but was later withdrawn owing to its toxic effects. Furaltadone hydrochloride is still used topically in preparations for ear disorders.

Furaltadone has been used in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Thai.***: Otosamthong†; SM Oto.

Furazidin

Akritoin; Furagin; Furazidine; Фуразидин.

1-{[3-(5-Nitro-2-furyl)allylidene]amino}hydantoin.

$C_{10}H_8N_4O_5$=264.2

CAS — 1672-88-4.

UNII — K2R4N34Y9I.

Profile

Furazidin is a nitrofuran antibacterial with properties similar to those of nitrofurantoin. It is used in the treatment of urinary-tract infections. A usual oral dose is 100 mg given

four times daily for one day followed by 100 mg given three times daily for 7 to 8 days.

It has been used similarly as the potassium salt.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Furaginum; ***Rus.***: Furamag (Фурамаг); Furasol (Фурасол); ***Ukr.***: Furamag (Фурамаг); Furasol (Фурасол).

Fusafungine *(BAN, rINN)*

Fusafungin; Fusafungina; Fusafunginum; Фузафунгин.

CAS — 1393-87-9.

ATC — R02AB03.

ATC Vet — QR02AB03.

UNII — 65DD690W0C.

Profile

Fusafungine is a depsipeptide antibacterial produced by *Fusarium lateritium* strain 437. It is active against some Gram-positive and Gram-negative organisms, *Candida albicans*, and *Mycoplasma pneumoniae*. It has also been stated to possess anti-inflammatory activity.

It is used in the form of an aerosol spray in the treatment of infections of the upper respiratory tract, inhaled in usual doses of 500 micrograms every 4 hours into each nostril or via the mouth. These routes may be used simultaneously if necessary.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Locabiosol; ***Belg.***: Locabiotal; ***Braz.***: Locabiotal; ***Cz.***: Bioparox; ***Ger.***: Locabiosol; ***Gr.***: Locabiotal; ***Hung.***: Bioparox; ***Irl.***: Locabiotal; ***Ital.***: Locabiotal; ***Malaysia***: Locabiotal; ***Philipp.***: Locabiotal†; ***Pol.***: Bioparox; ***Port.***: Locabiosol; ***Rus.***: Bioparox (Биопарокс); ***S.Afr.***: Locabiotal†; ***Spain***: Fusaloyos; ***Switz.***: Locabiotal; ***Turk.***: Locabiotal; ***Ukr.***: Bioparox (Биопарокс).

Fusidic Acid *(BAN, USAN, rINN)*

Acide Fusidique; Ácido fusídico; Acidum Fusidicum; Acidum Fusidicum Hemihydricum; Fucidinsyra; Fusídico, ácido; Fusidiinihappo; Fusidik Asit; Fusidinsyra; Fuzidinsav; Fuzido rūgštis; Kyselina fusidová hemihydrát; SQ-16603; Фэузидовая Кислота.

ent-16α-Acetoxy-3β-dihydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-(17*Z*)-17(20),24-dien-21-oic acid hemihydrate.

$C_{31}H_{48}O_6,½H_2O$=525.7

CAS — 6990-06-3 (anhydrous fusidic acid); 172343-30-5 (fusidic acid hemihydrate).

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fusidic Acid). An antimicrobial substance produced by the fermentation of certain strains of *Fusidium coccineum* or by any other means. A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Sodium Fusidate *(BANM, rINNM)*

Fusidate de Sodium; Fusidate Sodium (USAN); Fusidato sódico; Natrii Fusidas; Natrio fuzidatas; Natriumfusidaatti; Natriumfusidat; Natrium-fusidát; Nátrium-fuzidát; Sodium, fusidate de; Sodyum Fusidat; SQ-16360; Натрий Фэузидат.

$C_{31}H_{47}NaO_6$=538.7

CAS — 751-94-0.

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

UNII — J7P3696BCQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Sodium Fusidate). An antimicrobial substance produced by the fermentation of certain strains of *Fusidium coccineum* or by any other means. A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol. A 1.25% solution in water has a pH of 7.5 to 9.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Incompatibility. UK licensed product information states that reconstituted sodium fusidate injection is incompatible with infusion solutions containing glucose 20% or more, lipid infusions, and peritoneal dialysis fluids; precipitation may occur in solutions with a pH of less than 7.4.

Uses and Administration

Fusidic acid and its salts are antibacterials used mainly in the treatment of susceptible staphylococcal infections, often with other anti-staphylococcal antibacterials to prevent the emergence of resistance (see Resistance, under Antimicrobial Action, p. 305.1). They have been used systemically mainly in infections caused by penicillin-resistant strains, including in osteomyelitis and endocarditis, and topically in eye infections and superficial infections of the skin. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

The fusidates are given orally or topically as fusidic acid or sodium fusidate, or intravenously as sodium fusidate. Sodium fusidate 1 g is equivalent to about 980 mg of fusidic acid. Because of differences in absorption (see Pharmacokinetics, p. 305.1) 250 mg of fusidic acid is therapeutically equivalent to only 175 mg of the sodium salt, so doses of fusidic acid suspension (commonly used in children) appear relatively higher (see p. 304.2). The diolamine salt was formerly used intravenously in humans but is still used in topical preparations in veterinary medicine.

Sodium fusidate is given as tablets in a usual oral adult dose of 500 mg every 8 hours, although this dose may be doubled in severe infection. For cutaneous staphylococcal infections, a dose of 250 mg twice daily is suitable. When given orally as the suspension the usual adult dose is 750 mg of fusidic acid three times daily.

In severe infections in adults weighing over 50 kg, sodium fusidate 500 mg is given three times daily by slow intravenous infusion. Each 500-mg dose is usually given as a buffered solution (pH 7.4 to 7.6) diluted to 500 mL with sodium chloride or other suitable intravenous solution. For those weighing less than 50 kg, a dose of 6 to 7 mg/kg three times daily is used. For details of doses in children, see p. 304.2.

Sodium fusidate as a 2% ointment or medicated dressing, or fusidic acid as a 2% cream or gel, are used in the local treatment of skin infections. Eye drops containing fusidic acid 1% are used in eye infections. Topical use may lead to problems of resistance (see Antimicrobial Action, p. 304.3).

References.

1. García-Rodríguez JA, *et al.* Acido fusídico. *Rev Esp Quimioter* 2003; **16:** 161–71.
2. Doughty MJ, Dutton GN. Fusidic acid viscous eyedrops—an evaluation of pharmacodynamics, pharmacokinetics and clinical use for UK optometrists. *Ophthalmic Physiol Opt* 2006; **26:** 343–61.
3. Schöfer H, Simonsen L. Fusidic acid in dermatology: an updated review. *Eur J Dermatol* 2010; **20:** 6–15.

Administration in children. Fusidic acid and its salt may be used in neonates and children for the treatment of susceptible staphylococcal infections, particularly those due to penicillin-resistant strains. *Oral* doses of **fusidic acid suspension**, given three times daily, are:

- up to 1 year old: about 16 mg/kg
- 1 to 5 years: 250 mg
- 5 to 12 years: 500 mg
- over 12 years: usual adult doses (see above)

Suggested doses of **sodium fusidate** by *intravenous* infusion are:

- 1 month and above: if weighing less than 50 kg, 6 to 7 mg/kg three times daily; heavier children may be given usual adult doses (see Uses and Administration, above)

Adverse Effects and Precautions

Apart from mild gastrointestinal upsets, fusidic acid or sodium fusidate appear to be well tolerated when given orally. Treatment with fusidates, orally or especially by the intravenous route, has been associated with jaundice and changes in liver function; normal liver function is usually restored when treatment is stopped. Therefore, fusidates should be given with caution to patients with hepatic impairment, and periodic monitoring of hepatic function is recommended in these patients and in those receiving high or prolonged oral doses. Caution is also required in biliary disease or biliary obstruction.

Venospasm, thrombophlebitis, and haemolysis have occurred in patients given fusidates intravenously. To reduce this it is recommended that solutions be buffered and that the solution should be given as a slow infusion into a large vein where there is a good blood flow. Hypocalcaemia has occurred after use of intravenous doses above those recommended, and has been attributed to the phosphate-citrate buffer in the preparation. Intramuscular or subcutaneous use may lead to tissue necrosis and is contra-indicated.

Hypersensitivity reactions in the form of rashes and irritation may occur with topical fusidates; rash is rare after systemic use.

Fusidic acid competes with bilirubin for binding to albumin *in vitro* and caution has been advised if it is given to premature, jaundiced, acidotic, or seriously-ill neonates because of the risk of kernicterus.

Effects on the blood. There have been occasional reports of granulocytopenia[1-3] and thrombocytopenia[3] after the use of fusidic acid systemically. Sideroblastic anaemia has also been reported.[4] UK licensed product information also states that there have been isolated cases of neutropenia, agranulocytosis, and pancytopenia.

1. Revell P, *et al.* Granulocytopenia due to fusidic acid. *Lancet* 1988; **ii:** 454–5.
2. Evans DIK. Granulocytopenia due to fusidic acid. *Lancet* 1988; **ii:** 851.
3. Leibowitz G, *et al.* Leukopenia and thrombocytopenia due to fusidic acid. *Postgrad Med J* 1991; **67:** 591–2.
4. Vial T, *et al.* Sideroblastic anaemia during fusidic acid treatment. *Eur J Haematol* 2004; **72:** 358–60.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fusidic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Although the exact metabolic pathways of fusidic acid are not known, an interaction has been suspected with drugs metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4, and UK licensed product information suggests avoiding their use with fusidic acid.

Antivirals. An HIV-infected patient had fusidic acid toxicity after taking fusidic acid orally for one week with his usual antiretroviral treatment of *ritonavir*, *saquinavir*, and stavudine.[1] The plasma-fusidic acid concentration was about twice that expected and the ritonavir and saquinavir concentrations were also elevated. Fusidic acid was stopped and the patient initially improved. However, 4 days later he presented with jaundice, nausea, weakness, and further increases in liver function tests and hence all medications were stopped. The fusidic acid concentration, as well as those of ritonavir and saquinavir, were found to be still significantly elevated 6 days after fusidic acid had been stopped. The patient was able to restart his antiretroviral therapy later with no problems. The authors suggested that this interaction may be due to mutual inhibition of metabolism between the HIV-protease inhibitors and fusidic acid, and recommended that use of fusidic acid with either saquinavir or ritonavir should be avoided.

1. Khaliq Y, *et al.* A drug interaction between fusidic acid and a combination of ritonavir and saquinavir. *Br J Clin Pharmacol* 2000; **50:** 82–3.

Lipid regulating drugs. For reference to the effect of fusidic acid in patients receiving *statins*, see p. 1494.3.

Antimicrobial Action

Fusidic acid is a steroidal antibacterial with a bacteriostatic or bactericidal activity, mainly against Gram-positive bacteria.

Fusidic acid inhibits bacterial protein synthesis although, in contrast to drugs such as the macrolides or tetracyclines, it does not bind to the bacterial ribosome, but inhibits a factor necessary for translocation of peptide subunits and elongation of the peptide chain. It is capable of inhibiting protein synthesis in mammalian cells but exerts a selective action against susceptible infecting organisms because of poor penetration into the host cell.

- Fusidic acid is very active against staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains). *Nocardia asteroides* and many clostridial strains are also highly susceptible. The streptococci and enterococci are less susceptible.
- Most Gram-negative bacteria are intrinsically resistant but fusidic acid is active against *Neisseria* spp. and *Bacteroides fragilis*.
- It has some activity against strains of *Mycobacterium tuberculosis* and is highly active against *M. leprae*.
- Fungi are resistant, but fusidic acid has some activity against a range of protozoa including *Giardia lamblia* and *Plasmodium falciparum*.
- High concentrations of fusidate are reported to inhibit viral growth *in vitro*, including that of HIV, although it is unclear whether this represents a surfactant effect, a general cytotoxic effect, or a genuine antiviral action.

No synergy has been shown *in vitro* in most studies between fusidic acid and rifampicin or vancomycin, and antagonism of the effects of ciprofloxacin has been reported. Interactions with the penicillins are complex, with either antagonism of the effect of one or both drugs, or no interaction. However, use of an antistaphylococcal penicillin with fusidic acid may prevent the emergence of fusidic acid-resistant staphylococcal mutants, and such combinations may be clinically effective.

Resistance. Resistance may be chromosomally mediated, representing altered protein synthesis, or plasmid-mediated, which appears to be due to reduced penetration of active

drug into the cell. For further details on the increase of resistance to fusidic acid, see p. 305.1.

Resistance. There has been an increase in the number of reports of fusidic acid resistance in *Staphylococcus aureus* particularly in dermatological isolates. The number of clinical isolates of initially resistant staphylococci has historically been low at about 1 to 2% overall.[1-3] However, in the UK the rate of fusidic acid resistance in staphylococcal isolates increased by up to 200% during the 1990s, and over half of all isolates are resistant in some samples.[3] This has been attributed to the widespread topical use of fusidic acid.[1-3] Resistance may remain high for some time, even where use of fusidates has been restricted to preserve activity.[4]

The rate of resistance to short courses of fusidic acid used in systemic monotherapy is reported to be about 5%. In contrast, when given systemically with other antibacterials, the rate of resistance remains low at 0.8%.[5] Therefore, it has been suggested that systemic fusidic acid should be restricted to use with other antibacterial agents where clinically indicated in order to reduce the rate of resistance.[3,5]

1. Livermore D, *et al*. Fusidic-acid use and resistance. *Lancet* 2002; **360:** 806.
2. Mason BW, *et al*. Fusidic acid resistance in community isolates of methicillin-susceptible Staphylococcus aureus and fusidic acid prescribing. *J Antimicrob Chemother* 2003; **51:** 1033–6.
3. Dobie D, Gray J. Fusidic acid resistance in Staphylococcus aureus. *Arch Dis Child* 2004; **89:** 74–7.
4. Mitra A, *et al*. High levels of fusidic acid-resistant Staphylococcus aureus despite restrictions on antibiotic use. *Clin Exp Dermatol* 2009; **34:** 136–9.
5. Howden BP, Grayson ML. Dumb and dumber—the potential waste of a useful antistaphylococcal agent: emerging fusidic acid resistance in Staphylococcus aureus. *Clin Infect Dis* 2006; **42:** 394–400.

Pharmacokinetics

Sodium fusidate is well absorbed from the gastrointestinal tract, and a single oral 500-mg dose is reported to produce mean plasma concentrations of about 30 micrograms/mL within 2 to 4 hours, although there is considerable interindividual variation. Oral suspensions of fusidic acid are less well absorbed, with a bioavailability reported to be about 70% of that for sodium fusidate. Absorption may be delayed by food and may be more rapid in children than adults. Some accumulation occurs with repeated dosage and plasma concentrations of 100 micrograms/mL or more have been reported after 500 mg of sodium fusidate given three times daily for 4 days.

Fusidate is widely distributed into tissues and body fluids, including bone, pus, and synovial fluid; it penetrates cerebral abscesses but does not enter CSF in appreciable amounts. It has been found in the fetal circulation and in breast milk. About 95% or more of fusidate in the circulation is bound to plasma proteins.

Fusidate has a plasma half-life of about 10 to 15 hours. It is excreted in the bile, almost entirely as metabolites, some of which have weak antimicrobial activity. About 2% appears unchanged in the faeces. Little is excreted in the urine or removed by haemodialysis.

References.

1. Reeves DS. The pharmacokinetics of fusidic acid. *J Antimicrob Chemother* 1987; **20:** 467–76.
2. Peter J-D, *et al*. Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. *Antimicrob Agents Chemother* 1993; **37:** 501–6.
3. Brown NM, *et al*. The pharmacokinetics and protein-binding of fusidic acid in patients with severe renal failure requiring either haemodialysis or continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1997; **39:** 803–9.
4. Turnidge J. Fusidic acid pharmacology, pharmacokinetics and pharmacodynamics. *Int J Antimicrob Agents* 1999; **12** (suppl 2): S23–S34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acifusin; Arzimol; Biofucid; Drum; Fucidin; Fucithalmic; Fusitop; Gelbiotic; ***Austral.***: Fucidin; ***Austria***: Fucidin; Fucithalmic; ***Belg.***: Affusine; Fucidin; Fucithalmic; ***Braz.***: Verutex; ***Canad.***: Fucidin; Fucithalmic; ***Chile***: Fucidin; Fucithalmic; ***China***: Fucidin (立思丁); Fucithalmic (夫司名); Phudicin (奥络); ***Cz.***: Fucidin; Fucithalmic; ***Denm.***: Fucidin; Fucidine; Fucithalmic; ***Fin.***: Fucidin; Fucithalmic; ***Fr.***: Diacutis†; Fucidine; Fucithalmic; ***Ger.***: Fucidine; Fucithalmic; Fusicutan; ***Gr.***: Flusterix; Fucidin; Fusindac; ***Hong Kong***: Foban; Fucidin; Fucithalmic; Fusidate; Qualifutin; ***Hung.***: Fucidin; Fucithalmic†; ***India***: Fucidin; Fucin; Fucinex; Fucithalmic; Fudec; Fudic; Fusa; Fusibact; Fusid; Fusiderm; Fusigen; Fusital; Fusiwal; Fuson; Futop; Noboyle; ***Indon.***: Afucid; Fucidin; Fucilex; Fucithalmic; Fuladic; Fuson; Fusycom; Futaderm; ***Irl.***: Fucidin; Fucithalmic; ***Israel***: Fucidin; Fucithalmic; Staphiderm; ***Ital.***: Dermomycin; Fucidin; Fucithalmic; ***Malaysia***: Foban; Fucidin Intertulle; Fucidin; Fucithalmic; ***Mex.***: Aceler; Fucidin; Uniderm; ***Neth.***: Affusine; Fucidin; Fucidine; Fucithalmic; ***Norw.***: Fucidin; Fucithalmic; ***NZ***: Foban; Fucidin; Fucithalmic; ***Philipp.***: Flexid; Fucidin; Fucithalmic; Fusigen; Fuson; Hoebenate; Hopaq; Woncare; ***Pol.***: Fucidin; Fusacid; ***Port.***: Fucidine; Fucithalmic; Fusextrine; Infloc; Nadiclox; ***Rus.***: Fucidin (Фуцидин); Fucithalmic (Фуциталмик); ***S.Afr.***: Fucidin; Fucithalmic; ***Singapore***: Duzen; Foban; Forsuderm; Fucidin; Fucithalmic†; Fudikin; ***Spain***: Fucidine; Fucithalmic; ***Swed.***: Fucidin; Fucithalmic; ***Switz.***: Fucidin; Fucithalmic; Fusicutan; ***Thai.***: Difusin; Foban; Fucidin; Fucithalmic; Fusid; ***Turk.***: Fucidin; Fucithalmic; Robisid; Stafeks; Stafine; ***UAE***: Futasole; ***UK***: Fucidin; Fucithalmic; ***Ukr.***: Fusiderm (Фузидерм).

Multi-ingredient Preparations. ***Arg.***: Acifusin B; Arzimol B; Drum B; Fucicort; Fucidin H; Fusimed B; Fusimed; Gelbiotic Plus; ***Belg.***: Fucicort; Fucidin Hydrocortisone; ***Braz.***: Veruderm B; Verutex B; ***Canad.***: Fucidin H; ***Chile***: Fucicort; Fucidin H; ***Cz.***: Fucicort; Fucidin H; ***Denm.***: Fucibet; Fucicort; Fucidin-Hydrocortison; ***Fin.***: Fucicort; Fucidin-Hydrocortison; ***Ger.***: Fucicort; Fucidine H; ***Gr.***: Alpider; Befucil; Betacort; Betafusin; Betasid; Betfu; Fubecot; Fucicort; Fucicream; Fucidin H; Fusibet; Fusindac-H; Hydrofusin; Roseti; Sensibio; Staficort; ***Hong Kong***: Fobancort; Fucicort; Fucidin H; ***Hung.***: Fucicort; Fucidin H; ***India***: Clonate-F; Fucibet; Fucidin H; Fucin-B; Fudec-B; Fudec-M; Fusacort; Fusibact-B; Fusiderm B; Fusigen-B; Fusiwal-B; Fuson-B; Fuson-H; Halostrol-F; Halovate-F; Mecloma-F; Momoz-F; ***Indon.***: Fucicort; ***Irl.***: Fucibet; Fucidin H; ***Israel***: Fucicort; Fucidin H; ***Ital.***: Dermomycin Cort; Fucicort; Fucidin H; Piodermina; ***Malaysia***: Axcel Fusi-Corte†; Foban-Hydro; Fobancort; Fucicort; Fucidin H; Fusidic B; ***Mex.***: Aceler-Co; Fucicort; ***Neth.***: Fucidin + Hydrocortisone†; ***Norw.***: Fucidin-Hydrocortison; ***NZ***: Fucicort; ***Philipp.***: Fucicort; Fucidin H; Hoebedic; ***Port.***: Fucicort; Fucidine H; ***Rus.***: Fucicort (Фуцикорт); Fucidin H (Фуцидин Г); Fugentin (Фугентин); ***S.Afr.***: Fucidin H; ***Singapore***: Fobancort; Fucicort; Fucidin H; ***Spain***: Fucibet; Fucidine H; ***Swed.***: Fucidin-Hydrocortison; ***Switz.***: Fucicort; Fucidin H; ***Thai.***: Fobancort; Fucicort; Fucidin H; ***Turk.***: Fucicort; Fucidin H; ***UAE***: Futasone; ***UK***: Fucibet; Fucidin H; ***Ukr.***: Fusiderm B (Фузидерм Б).

Pharmacopoeial Preparations

BP 2014: Fusidic Acid Cream; Fusidic Acid Eye Drops; Fusidic Acid Oral Suspension; Sodium Fusidate Ointment.

Garenoxacin Mesilate *(BANM, rINNM)*

BMS-284756-01; Garenoxacin Mesylate (USAN); Garénoxacine, Mésilate de; Garenoxacini Mesilas; Mesilato de garenoxacino; T-3811ME; Гареноксацина Мезилат.

1-Cyclopropyl-8-(difluoromethoxy)-7-[(1*R*)-1-methyl-2,3-dihydro-1*H*-isoindol-5-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methanesulfonate monohydrate.

$C_{23}H_{20}F_2N_2O_4,CH_4O_3S,H_2O$=540.5

CAS — 194804-75-6 (garenoxacin); 223652-82-2 (garenoxacin mesilate); 223652-90-2 (garenoxacin mesilate monohydrate).

ATC — J01MA19.

ATC Vet — QJ01MA19.

UNII — OXI6EF55FR.

Profile

Garenoxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.2). Garenoxacin is used as the mesilate but doses are given in terms of the base: about 507 mg of the mesilate is equivalent to 400 mg of garenoxacin. It is given orally in the treatment of susceptible infections in usual doses equivalent to 400 mg of garenoxacin daily.

Reviews.

1. Takagi H, *et al*. Clinical studies of garenoxacin. *Int J Antimicrob Agents* 2008; **32:** 468–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Geninax.

Gatifloxacin *(USAN, rINN)*

AM-1155; BMS-206584-01; CG-5501; Gatifloxacine; Gatifloxacino; Gatifloxacinum; Гатифлоксацин.

(±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

$C_{19}H_{22}FN_3O_4,1½H_2O$=402.4

CAS — 160738-57-8 (anhydrous gatifloxacin); 180200-66-2 (gatifloxacin sesquihydrate).

ATC — J01MA16; S01AE06.

ATC Vet — QJ01MA16; QS01AE06.

UNII — L4618BD7KJ (gatifloxacin sesquihydrate); 81485Y3A9A (anhydrous gatifloxacin).

Uses and Administration

Gatifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It has been given orally, or by intravenous infusion as a 2 mg/mL solution over 60 minutes, for the treatment of susceptible infections, in a usual adult dose of 400 mg once daily. However, systemic products have now been withdrawn in most countries due to safety concerns.

For details of reduced doses to be used in renal impairment, see p. 305.3.

Gatifloxacin is also used as either a 0.3 or 0.5% eye drop for the treatment of bacterial conjunctivitis.

Reviews.

1. Keam SJ, *et al*. Gatifloxacin: a review of its use in the treatment of bacterial infections in the US. *Drugs* 2005; **65:** 695–724.
2. Gatifloxacin. *Tuberculosis (Edinb)* 2008; **88:** 109–11.

Administration in renal impairment. Oral and intravenous doses of gatifloxacin should be reduced in patients with renal impairment; the usual initial dose of 400 mg should be followed by reduced maintenance doses of 200 mg daily in those with a creatinine clearance of less than 40 mL/minute and in those on haemodialysis or continuous peritoneal dialysis.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported in patients (usually diabetics) taking gatifloxacin. However, hypoglycaemia, and particularly hyperglycaemia, have occurred in non-diabetic patients. Severe life-threatening events, including hyperosmolar nonketotic hyperglycaemic coma, diabetic ketoacidosis, hypoglycaemic coma, convulsions, and mental status changes have been reported very rarely. Although in most cases the blood-glucose disturbance was reversible, fatalities have been reported. Gatifloxacin should not be given to diabetic patients. Other risk factors for developing blood-glucose disturbances include older age (patients 65 years of age or over), renal impairment, or use of other drugs that alter blood-glucose concentrations, particularly hypoglycaemics. Patients with risk factors should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, gatifloxacin should be stopped.

Effects on glucose metabolism. Hypoglycaemia and hyperglycaemia have been associated with gatifloxacin in both diabetic and non-diabetic patients.[1-6] A review[7] of spontaneous adverse effects reported to the FDA in the USA between November 1997 and September 2003 found the rate of blood-glucose disturbances with gatifloxacin to be tenfold higher when compared with ciprofloxacin, levofloxacin, and moxifloxacin. Subsequent population-based case-control studies[8] in elderly patients given fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, or moxifloxacin), second-generation cephalosporins, or macrolides also found an increased risk of blood-glucose disturbances with gatifloxacin.

While blood-glucose disturbances appear to be mainly associated with gatifloxacin, the possibility that they may also be a class effect of fluoroquinolones cannot be excluded; patients most at risk are the elderly, those with diabetes and/or those taking hypoglycaemic drugs, and patients with impaired renal function.[9] Twenty two case reports of dysglycaemia associated with the use of levofloxacin were received by Health Canada between January 1997 and June 2006; reported cases included 15 diabetic patients.[10] In a retrospective cohort study,[11] the odds of severe hypo- or hyperglycaemia among diabetics treated with levofloxacin was significantly higher than in those treated with azithromycin, although the risk from gatifloxacin was found to be greater still.

In contrast, the same study[11] found no significant difference in the odds of severe dysglycaemia between ciprofloxacin and azithromycin, or for non-diabetic patients, between any of the antibacterials studied. A review of the effects of moxifloxacin on blood glucose, including data from large postmarketing studies, suggests it also has no significant effect.[12]

1. Baker SE, Hangii MC. Possible gatifloxacin-induced hypoglycemia. *Ann Pharmacother* 2002; **36:** 1722–6.
2. Donaldson AR, *et al*. Possible gatifloxacin-induced hyperglycemia. *Ann Pharmacother* 2004; **38:** 602–5.
3. Happe MR, *et al*. Gatifloxacin-induced hyperglycemia. *Ann Intern Med* 2004; **141:** 968–9.
4. Khovidhunkit W, Sunthornyothin S. Hypoglycemia, hyperglycemia, and gatifloxacin. *Ann Intern Med* 2004; **141:** 969.
5. Greenberg AL, *et al*. Gatifloxacin therapy associated with hypoglycemia. *Clin Infect Dis* 2005; **40:** 1210–11.
6. Blommel AL, Lutes RA. Severe hyperglycemia during renally adjusted gatifloxacin therapy. *Ann Pharmacother* 2005; **39:** 1349–52.
7. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. *Clin Infect Dis* 2005; **41:** 1269–76.
8. Park-Wyllie LY, *et al*. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006; **354:** 1352–61.
9. Lewis RJ, Mohr JF. Dysglycaemias and fluoroquinolones. *Drug Safety* 2008; **31:** 283–92.
10. Health Canada. Levofloxacin: dysglycemia and liver disorders. *Can Adverse React News* 2007; **17:** 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n1-eng.pdf (accessed 17/06/08)
11. Aspinall SL, *et al*. Severe dysglycemia with the fluoroquinolones: a class effect? *Clin Infect Dis* 2009; **49:** 402–8.
12. Gavin JR, *et al*. Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. *Drug Safety* 2004; **27:** 671–86.

Interactions

As for Ciprofloxacin, p. 264.3.

Use of gatifloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Antidiabetics. Given the adverse effects of gatifloxacin, pharmacodynamic interactions with antidiabetics might reasonably be anticipated. Severe and persistent hypoglycaemia occurred in 3 patients taking oral hypoglycaemics (*repaglinide*, *glibenclamide* and *pioglitazone*, and *glimepiride*) when gatifloxacin was added to their therapy.[1]

1. Menzies DJ, *et al.* Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. *Am J Med* 2002; **113:** 232–4.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Gatifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

References.

1. Stein GE, *et al.* Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. *Antimicrob Agents Chemother* 2003; **47:** 1308–12.

Pharmacokinetics

Gatifloxacin is readily absorbed from the gastrointestinal tract with an absolute bioavailability of 96%. Peak plasma concentrations occur within 1 to 2 hours of an oral dose. Gatifloxacin is widely distributed into body tissues and is about 20% bound to plasma proteins. It undergoes limited metabolism and has an elimination half-life of 7 to 14 hours. Gatifloxacin is excreted mainly unchanged in the urine with less than 1% as metabolites. About 5% is also excreted unchanged in the faeces. Distribution into milk occurs in *animals*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gatif; Zymaran; ***Braz.***: Zymar; ***Canad.***: Zymar; ***Chile***: Gatif; Zymar; ***China***: Ai Er Jia (艾尔嘉); Ao Lai Ke (澳莱克); Ba Ti (巴替); Bai Ke Sha (百科沙); Bi Zhi (必致); Chen Li (辰立); Chen Zheng (辰正); Di Na Ke (地纳克); Diyou (迪友); Fudixing (芙蒂星); Fuqi (福奇); Gan Nuo Xin (敢诺新); Gatilox (加西); Haichao (海超); Heng Sen (恒森); Jia Di Fu (嘉迪福); Jia Heng Xing (加恒兴); Jia Kui Long (加葵龙); Jia Li (珈力); Jia Luo Ling (佳洛灵); Jia Mai Xin (加迈欣); Jia Tai (加泰); Jia Yi Xin (加益新); Kai Ze (凯泽); Kui Er Tai (奎尔泰); Kui Tai (奎泰); Kui Yan (葵严); Lai Di (莱迪); Lai Fu Le Xin (来福乐欣); Lai Mei Qing (莱美清); Laijia (来佳); Le Pai (乐派); Li Ou (利欧); Lin Ke Jia (林可佳); Luo Ka Nuo (洛卡诺); Luoxin Yanda (罗欣严达); Nuo Li Er (诺丽尔); Ou Nuo (欧诺); Ou Te Luo Kang (欧特罗康); Pa Te La (帕特拉); Qian Yi (千意); Shang Bang (尚邦); Sheng Di Feng (圣迪锋); Shu Pu Ren (舒普仁); Tequin (天坤); Tong Bo (同博); Tong Nuo Xin (同诺欣); Wan Yue (万悦); Xian Kui Sha (先奎莎); Xindite (欣灿特); Yan Ke Xian (严克仙); Yan Li Fei (严立菲); Yu Kuai (誉快); Yue Bo (悦博); Zhe Peng (哲朋); Zhu Ning; ***India***: Adflox; Adgat; Alex; Algat; Arigat; Armflox; Avigat; Biogat; Comigat; Cugat; Dasikon; E-Gati; Ecogat BCD; Engatt; Exagt; Fatiflox; Floxigat; Fugat; Fydogat; G-Cebran; G-Flox; G-Quin; G2K; Gabact; Gabee; Gabir; Gaity; Gale; Gate; Gateme; Gatex; Gati-OD; Gatiba; Gatibenz; Gaticad; Gaticare; Gaticas; Gaticin; Gatifect; Gatigo; Gatigram; Gatik; Gatikind; Gatilab; Gatilex; Gatilink; Gatilox; Gatimac; Gatimore; Gatin; Gatina; Gatinex; Gatinova; Gatiom; Gatiospi; Gatipan; Gatiquin; Gatisia; Gatispan; Gatistac; Gatistal; Gatitoon; Gativar; Gatix; Gatiz; Gatizen; Gatlak; Gatme; Gatmor; Gatnic; Gatomed; Gator; Gatox; Gatri; Gatrid; Gatrital; Gatt; Gatven; Gatymal; Gatz; Getflox; Getoli; Getready; GF; Giflexcin; Giftum; Glyph; Gofel; Granaz; Gres; Gulf; Guts; Gutts; Intragat; K-Gat; KGT; Lyflox; Mach-X; Meris; Microgat; Multigat; Oxigat; Zyquin; ***Indon.***: Gaticin†; Gatimax†; ***Israel***: Zymar; Zymaxid; ***Jpn***: Gatiflo; ***Malaysia***: Zymar; ***Mex.***: Zymar; ***NZ***: Tequin†; ***Philipp.***: Itiflox; Zymar; ***Rus.***: Gatispan (Гатиспан); Zarquin (Зарквин); ***S.Afr.***: Zymar; ***Singapore***: Zymar; ***Thai.***: Zymar; ***Turk.***: Zymar; ***Ukr.***: Bigaflon (Бигафлон); Dasikon (Дасикон)†; Gatibact (Гатибакт); Gatijem (Гатиджем)†; Gatonova (Гатинова)†; ***USA***: Zymar; Zymaxid.

Multi-ingredient Preparations. ***Braz.***: Zypred; ***India***: Amgat; Diragyl; Ecogat A; Engatt-DX; Fatiflox-OZ; Floxigat M; Garnid; Gate-DX; Gatigram-OZ; Gatikind-AM; Gatikind-OZ; Gatilox-DM; Gatimore-OZ; Gatiquin Oz Kit; Gatri-OZ; Gatrich; Gatrid-OZ; Gatrix; Gatus; Getoli D; Inogat-O; Intragat-AM; Intragat-O; Meris-D; Microgat-DX.

Gemifloxacin Mesilate *(rINNM)*

Gemifloxacin Mesylate (USAN); Gémifloxacine, Mésilate de; Gemifloxacini Mesilas; Gemifloxacino, mesilato de; LB-20304 (gemifloxacin); LB-20304a; Mesilato de gemifloxacino; SB-265805 (gemifloxacin); SB-265805S; Гемифлоксацина Мезилат.

(±)-7-[3-(Aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid 7⁴-(*Z*)-(*O*-methyloxime) methanesulfonate.

$C_{18}H_{20}FN_5O_4,CH_4O_3S$=485.5

CAS — 204519-64-2 (gemifloxacin); 204519-65-3 (gemifloxacin mesilate).

ATC — J01MA15.

ATC Vet — QJ01MA15.

UNII — X459F8RL01.

Uses and Administration

Gemifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It is given orally, as the mesilate, for the treatment of community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis. Doses are expressed in terms of the base; 399 mg of gemifloxacin mesilate is equivalent to about 320 mg of gemifloxacin. The usual dose is 320 mg once daily for 5 days in patients with bronchitis or for 7 days in those with pneumonia.

For details of reduced doses in patients with renal impairment, see p. 306.2.

Reviews.

1. Lowe MN, Lamb HM. Gemifloxacin. *Drugs* 2000; **59:** 1137–47.
2. Yoo BK, *et al.* Gemifloxacin: a new fluoroquinolone approved for treatment of respiratory infections. *Ann Pharmacother* 2004; **38:** 1226–35.
3. File TM, Tillotson GS. Gemifloxacin: a new, potent fluoroquinolone for the therapy of lower respiratory tract infections. *Expert Rev Anti Infect Ther* 2004; **2:** 831–43.
4. Bhavnani SM, Andes DR. Gemifloxacin for the treatment of respiratory tract infections: in vitro susceptibility, pharmacokinetics and pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2005; **25:** 717–40.
5. Blondeau JM, Tillotson G. Role of gemifloxacin in the management of community-acquired lower respiratory tract infections. *Int J Antimicrob Agents* 2008; **31:** 299–306.
6. Lode HM, *et al.* Gemifloxacin for community-acquired pneumonia. *Expert Opin Invest Drugs* 2008; **17:** 779–86.
7. Tillotson GS. Role of gemifloxacin in community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2008; **6:** 405–18.
8. Jivcu C, Gotfried M. Gemifloxacin use in the treatment of acute bacterial exacerbation of chronic bronchitis. *Int J Chron Obstruct Pulmon Dis* 2009; **4:** 291–300.

Administration in renal impairment. Oral doses of gemifloxacin should be halved in patients with a creatinine clearance of 40 mL/minute or less, including those receiving haemodialysis or continuous peritoneal dialysis.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Rashes may be more common with gemifloxacin and treatment should be stopped if they occur.

Interactions

As for Ciprofloxacin, p. 264.3.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Gemifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

References.

1. Morrissey I, Tillotson G. Activity of gemifloxacin against Streptococcus pneumoniae and Haemophilus influenzae. *J Antimicrob Chemother* 2004; **53:** 144–8.

Pharmacokinetics

Gemifloxacin is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of about 71%. Peak plasma concentrations occur 0.5 to 2 hours after an oral dose. Gemifloxacin is widely distributed into body tissues including the bronchial mucosa and lungs, and is about 55 to 73% bound to plasma proteins. It undergoes limited hepatic metabolism and has an elimination half-life of about 7 hours. It is excreted as unchanged drug and metabolites in the faeces and urine. Urinary excretion is by active tubular secretion and is reduced by probenecid. Distribution into milk has been found in *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Factive; ***Canad.***: Factive†; ***China***: Factive (吉速星); ***India***: Floxigem; G-Floren; Gembax; Gemistar; Gemitab; Graptor; ***Mex.***: Factive-5; ***Rus.***: Factiv (Фактив); ***S.Afr.***: Factive; ***Turk.***: Factive; ***USA***: Factive.

Gentamicin Sulfate *(BANM, USAN, pINNM)*

Gentamicin sulfát; Gentamicin Sulphate; Gentamicina, sulfato de; Gentamicine, Sulfate de; Gentamicini sulfas; Gentamicino sulfatas; Gentamicinsulfat; Gentamicin-szulfát; Gentamisiinisulfaatti; Gentamisin Sülfat; Gentamycyny siarczan; NSC-82261; Sch-9724; Sch-13706 (gentamicin C_1); Sulfato de gentamicina; Гентамицина Сульфат.

CAS — 1403-66-3 (gentamicin); 1405-41-0 (gentamicin sulfate).

ATC — D06AX07; J01GB03; S01AA11; S02AA14; S03AA06.

ATC Vet — QD06AX07; QJ01GB03; QS01AA11; QS02AA14; QS03AA06.

UNII — 8X7386QRLV (gentamicin sulfate); 1904Y9FPPV (gentamicin C_1).

NOTE. GNT is a code approved by the BP 2014 for use on single unit doses of eye drops containing gentamicin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Gentamicin Sulfate). A mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*, the main components being gentamicins C1, C1a, C2, C2a, and C2b. It contains 20 to 40% of gentamicin C1, 10 to 30% of gentamicin C1a; the sum of gentamicins C2, C2a, and C2b is 40 to 60%. The potency is not less than 590 units/mg, calculated with reference to the anhydrous substance. A white or almost white hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Gentamicin Sulfate). The sulfate salt, or a mixture of such salts, of antibiotic substances produced by the growth of *Micromonospora purpurea*. The content of gentamicin C1 is between 25 and 50%, the content of gentamicin C1a is between 10 and 35%, and the sum of the contents of gentamicin C2a and gentamicin C2 is between 25 and 55%. It has a potency equivalent to not less than 590 micrograms of gentamicin per mg, calculated on the dried basis. A white to buff powder. Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 4% solution in water is between 3.5 and 5.5. Store in airtight containers.

Incompatibility. The aminoglycosides are inactivated *in vitro* by various penicillins and cephalosporins via an interaction with the beta-lactam ring, the extent of inactivation depending on temperature, concentration, and duration of contact. The different aminoglycosides vary in their stability, with amikacin apparently the most resistant and tobramycin the most susceptible to inactivation; gentamicin and netilmicin are of intermediate stability. The beta lactams also vary in their ability to produce inactivation, with ampicillin, benzylpenicillin, and antipseudomonal penicillins such as carbenicillin and ticarcillin producing marked inactivation. Inactivation has also been reported with clavulanic acid.

Gentamicin is also incompatible with furosemide, heparin, sodium bicarbonate (the acid pH of gentamicin solutions may liberate carbon dioxide), and some solutions for parenteral nutrition. Interactions with preparations having an alkaline pH (such as aciclovir or sulfadiazine sodium), or drugs unstable at acid pH (for example erythromycin salts), might reasonably be expected.

Given their potential for incompatibility, gentamicin and other aminoglycosides should not generally be mixed with other drugs in syringes or infusion solutions nor given through the same intravenous line. When aminoglycosides are given with a beta lactam, they should generally be given at separate sites.

General references.

1. Henderson JL, *et al.* In vitro inactivation of gentamicin, tobramycin, and netilmicin by carbenicillin, azlocillin, or mezlocillin. *Am J Hosp Pharm* 1981; **38:** 1167–70.
2. Tindula RJ, *et al.* Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; **17:** 906–8.
3. Navarro AS, *et al.* In-vitro interaction between dibekacin and penicillins. *J Antimicrob Chemother* 1986; **17:** 83–9.
4. Courcol RJ, Martin GR. Comparative aminoglycoside inactivation by potassium clavulanate. *J Antimicrob Chemother* 1986; **17:** 682–4.
5. Canann D, *et al.* Visual compatibility of i.v. medications routinely used in bone marrow transplant recipients. *Am J Health-Syst Pharm* 2009; **66:** 727–9. Correction. *ibid.*; 1431.

Stability. There was an average 16% potency loss of gentamicin sulfate from solutions containing 10 and 40 mg/mL when stored at 4 degrees or 25 degrees in plastic disposable syringes for 30 days, and a brown precipitate formed in several. Storage in glass disposable syringes for 30 days produced an average 7% potency loss, which was considered acceptable, but storage for longer resulted in precipitate formation in some cases and was not recommended.[1]

1. Weiner B, *et al.* Stability of gentamicin sulfate injection following unit dose repackaging. *Am J Hosp Pharm* 1976; **33:** 1254–9.

Uses and Administration

Gentamicin is an aminoglycoside antibacterial used, often with other antibacterials, to treat severe systemic infections due to sensitive Gram-negative and other organisms (see

Antimicrobial Action, p. 309.2). Such infections include abscesses, biliary-tract infections (acute cholecystitis or cholangitis), brucellosis, cat scratch disease, cystic fibrosis, endocarditis (in the treatment and prophylaxis of endocarditis due to streptococci, enterococci, or staphylococci), endometritis, gastro-enteritis, granuloma inguinale, listeriosis, meningitis, otitis externa, otitis media, pelvic inflammatory disease, peritonitis, plague, pneumonia, septicaemia, skin infections such as in burns or ulcers (given systemically for pseudomonal and other Gram-negative infections), trench fever, tularaemia, and urinary-tract infections (acute pyelonephritis), as well as in the prophylaxis of surgical infection and the treatment of immunocompromised patients and those in intensive care. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. Gentamicin is also applied topically for localised infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Gentamicin is often used with other antibacterials to extend its spectrum of activity or increase its efficacy, e.g. with a penicillin for enterococcal and streptococcal infections, or an antipseudomonal beta lactam for pseudomonal infections, or with metronidazole or clindamycin for mixed aerobic-anaerobic infections.

Administration and dosage. Gentamicin is used as the sulfate but doses are expressed in terms of gentamicin base. For many of the infections above it is given *intramuscularly* every 8 hours to provide a total daily dose of 3 to 5 mg/kg. Intramuscular (or intravenous—see below) doses have traditionally played an important role in regimens for the treatment and prophylaxis of bacterial endocarditis, although the need for prophylaxis has largely been re-evaluated in recent years (see Endocarditis, p. 179.2, for details and doses). For urinary-tract infections, if renal function is not impaired, 160 mg once daily may be used.

Gentamicin sulfate may also be given *intravenously* in similar doses to those used intramuscularly, but there is some disagreement as to the appropriate method, since intravenous infusion has been associated with both subtherapeutic and excessive trough concentrations of gentamicin, while bolus intravenous injection may increase the risk of neuromuscular blockade. In the USA, intravenous infusion of the recommended dose diluted in 50 to 200 mL and given over 30 minutes to 2 hours is favoured, while UK licensed product information recommends infusion over no more than 20 to 30 minutes, in a limited fluid volume (100 mL), or slow bolus injection over at least 2 to 3 minutes.

The course of treatment should generally be limited to 7 to 10 days. As gentamicin is poorly distributed into fatty tissue it has been suggested that dosage calculations should be based on an estimate of lean body-weight.

For details of use in children, see p. 307.3.

Dose adjustment and monitoring. Dosage should be adjusted in all patients according to plasma-gentamicin concentrations, and this is discussed in more detail under Administration and Dosage, p. 307.2.

Once-daily dosage. The total daily requirement may be given as a single dose (see Once-daily Dosage, p. 307.2). In suitable patients this appears to be as safe and effective as conventional regimens, and is more convenient. However, it is not suitable for all patients, especially those with endocarditis, extensive burns, or renal impairment (creatinine clearance less than 20 mL/minute). The *BNF* recommends a once-daily dose regimen for gentamicin, of 5 to 7 mg/kg by intravenous infusion and then adjusted according to serum-gentamicin concentration. With once-daily dosage, traditional methods of monitoring peak and trough plasma concentrations may not be applicable and local guidelines on dosage and plasma concentrations should be consulted.

Other routes. Gentamicin has sometimes been given orally for enteric infections and to suppress intestinal flora and has occasionally been given by inhalation of nebulised solution in cystic fibrosis. In meningitis it has been given intrathecally or intraventricularly usually in doses of 1 to 5 mg daily with intramuscular therapy. Gentamicin has also been given by subconjunctival injection.

A bone cement impregnated with gentamicin is used in orthopaedic surgery. Acrylic beads containing gentamicin and threaded on to surgical wire are implanted in the management of bone infections.

Gentamicin has also been applied topically for skin infections in concentrations of 0.1%, but such use may lead to the emergence of resistance and is considered inadvisable. Concentrations of 0.3% are used in preparations for topical application to the eyes and ears.

A liposomal formulation of gentamicin is under investigation.

Reviews.

1. Edson RS, Terrell CL. The aminoglycosides. *Mayo Clin Proc* 1999; **74:** 519–28.

Administration and dosage. *CONCENTRATION MONITORING.* Measurements of aminoglycoside plasma concentrations are routinely performed to individualise dosage regimens, both in terms of dose given and dosing interval, in order to attain the desired therapeutic range as quickly as possible.[1] This entails measurement of both peak concentrations to monitor efficacy and trough concentrations to avoid accumulation and thereby prevent toxicity. Dosage should be adjusted in all patients according to these concentrations, but this is of particular importance where factors such as age, renal impairment, or high dosage may predispose to toxicity. Although there has been some dispute about the relationship between plasma concentrations and toxicity it is generally recommended that, for multiple daily dosing with gentamicin, trough plasma concentrations (measured just before the next dose) should be less than 2 micrograms/mL, and peak concentrations should reach at least 4 micrograms/mL but not exceed 10 micrograms/mL. In the UK, peak concentrations are generally measured 1 hour after intramuscular and intravenous doses, but practice has varied between centres and countries and this may lead to difficulties when comparing figures.

Methods exist for calculating aminoglycoside dosage requirements, though none has been universally accepted. Simple pharmacokinetic methods involve linear dosage adjustment based on peak or trough concentrations or area under the concentration-time curve, or the use of predictive nomograms.[1] For most patients receiving once-daily dosage (see p. 307.2), the nomogram is the method of choice, mainly because of its simplicity. However, it has not been validated for children and does not work in patients with either a very high clearance of aminoglycosides or a high volume of distribution, such as those with ascites, burns, or cystic fibrosis, or in other conditions such as pregnancy where the fixed dose assumed in the construction of the nomogram is irrelevant. When a nomogram cannot be applied, a more sophisticated pharmacokinetic method is required, using either Bayesian statistics or non-Bayesian methods such as that of Sawchuk and Zaske.[2,3] Bayesian methods are favoured when the patient population's pharmacokinetic parameters are well known because of their good predictive performance. Otherwise, the Sawchuk and Zaske method is the method of choice because of its robustness and the lack of requirement for prior information about the distribution of parameters within the population.[1]

1. Tod MM, *et al.* Individualising aminoglycoside dosage regimens after therapeutic drug monitoring: simple or complex pharmacokinetic methods? *Clin Pharmacokinet* 2001; **40:** 803–14.
2. Sawchuk RJ, Zaske DE. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm* 1976; **4:** 183–95.
3. Sawchuk RJ, *et al.* Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther* 1977; **21:** 362–9.

IN PATIENTS WITH NON-IDEAL BODY-WEIGHT. **References.**

1. Traynor AM, *et al.* Aminoglycoside dosing weight correction factors for patients of various body sizes. *Antimicrob Agents Chemother* 1995; **39:** 545–8.

ONCE-DAILY AND EXTENDED-INTERVAL DOSE REGIMENS. Parenteral aminoglycosides have been given in multiple daily dose regimens (usually 2 or 3 doses daily); these are usually the dose regimens included in most licensed product information. However, current practice is to give the same total daily dose of the aminoglycosides once-daily in selected patients. The rationale for preferring single daily dose regimens and therefore higher intermittent plasma concentrations includes the prolonged postantibiotic effect of aminoglycosides (persistent antibacterial activity after plasma concentrations have fallen below the MIC), potentially higher antibacterial concentrations at the site of infection, and theoretical reductions in the incidence of adaptive resistance, with no apparent increase in oto- or nephrotoxicity. Such regimens are also attractive on the grounds of convenience and economy. Clinical studies have generally included small numbers of patients with uncomplicated infections and have excluded patients with altered pharmacokinetic profiles, but several meta-analyses have been published which have concluded that once-daily administration appears to be at least as effective as, and no more toxic than, multiple daily dosing in such patient populations.[1-7] Similar results have been seen in children and neonates;[8] once-daily and extended-interval dose regimens respectively have been suggested for amikacin, gentamicin, and tobramycin.

Several methods for calculating doses and monitoring treatment have been proposed.[9-11] There is insufficient information for pregnant or breast-feeding women, or patients with burns or impaired renal or hepatic function.[11-13] However, preliminary reports suggest that once-daily use may be practical in trauma patients[14] and children with neutropenia.[15] A systematic review[16] also concluded that once-daily tobramycin was as effective in the treatment of patients with cystic fibrosis as the multiple dose regimens. Once-daily dosage may, though, be inappropriate for elderly patients[17] (due to an increased incidence of nephrotoxicity), patients in whom the volume of drug distribution or clearance is difficult to predict or markedly abnormal,[18] and in the treatment of enterococcal endocarditis.[11] In the UK, the *BNF* states that a once-daily high dose regimen should be avoided in patients with endocarditis, extensive burns, or creatinine clearance less than 20 mL/minute. For mention of an increase in endotoxin reactions associated with the use of single daily doses see under Adverse Effects, p. 308.3.

1. Barza M, *et al.* Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996; **312:** 338–45.
2. Hatala R, *et al.* Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med* 1996; **124:** 717–25.
3. Ferriols-Lisart R, Alos-Almiñana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health-Syst Pharm* 1996; **53:** 1141–50.
4. Munckhof WJ, *et al.* A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother* 1996; **37:** 645–63.
5. Bailey TC, *et al.* A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; **24:** 786–95.
6. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; **24:** 796–809.
7. Hatala R, *et al.* Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. *Clin Infect Dis* 1997; **24:** 810–15.
8. Rao SC, *et al.* One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 19/12/08).
9. Begg EJ, *et al.* A suggested approach to once-daily aminoglycoside dosing. *Br J Clin Pharmacol* 1995; **39:** 605–9.
10. Prins JM, *et al.* Validation and nephrotoxicity of a simplified once-daily aminoglycoside dosing schedule and guidelines for monitoring therapy. *Antimicrob Agents Chemother* 1996; **40:** 2494–9.
11. Freeman CD, *et al.* Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. *J Antimicrob Chemother* 1997; **39:** 677–86.
12. Rodvold KA, *et al.* Single daily doses of aminoglycosides. *Lancet* 1997; **350:** 1412.
13. Anonymous. Aminoglycosides once daily? *Drug Ther Bull* 1997; **35:** 36–7.
14. Finnell DL, *et al.* Validation of the Hartford nomogram in trauma surgery patients. *Ann Pharmacother* 1998; **32:** 417–21.
15. Tomlinson RJ, *et al.* Once daily ceftriaxone and gentamicin for the treatment of febrile neutropenia. *Arch Dis Child* 1999; **80:** 125–31.
16. Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 16/07/10).
17. Koo J, *et al.* Comparison of once-daily versus pharmacokinetic dosing of aminoglycosides in elderly patients. *Am J Med* 1996; **101:** 177–83.
18. Gerberding JL. Aminoglycoside dosing: timing is of the essence. *Am J Med* 1998; **105:** 256–8.

Administration in children. For severe infections caused by susceptible bacteria in children beyond the newborn period the American Academy of Pediatrics (AAP)[1] suggests an intravenous or intramuscular dose equivalent to 3 to 7.5 mg/kg daily of gentamicin, in 3 divided doses.

For *septicaemia, CNS infections and meningitis, biliary-tract infection, acute pyelonephritis, endocarditis, and pneumonia* in infants and children the *BNFC* suggests:

- a **once-daily** dose regimen (not for endocarditis or meningitis) by intravenous infusion of 7 mg/kg and then adjusted according to serum-gentamicin concentration in those from 1 month of age, *or*
- a **multiple daily dose regimen** by intramuscular or by slow intravenous injection over at least 3 minutes
  - those 1 month to 12 years of age: 2.5 mg/kg every 8 hours
  - children from 12 years of age: 2 mg/kg every 8 hours

For the treatment of pseudomonal lung infection in *cystic fibrosis* the *BNFC* suggests:

- a **multiple daily dose regimen** of gentamicin given by slow intravenous injection or by intravenous infusion of 3 mg/kg every 8 hours in those from 1 month of age

For the treatment of *bacterial ventriculitis* and *CNS infection* the *BNFC* suggests that in addition to systemic treatment an **intrathecal** or **intraventricular** injection of a suitable preparation of gentamicin in a dose of 1 mg daily (increasing to 5 mg daily if necessary) may be given in those from 1 month of age.

For *neonatal sepsis* the *BNFC* suggests an **extended-interval dose regimen** of gentamicin by slow intravenous injection or intravenous infusion as follows:

- for neonates aged ⩽7 days: 5 mg/kg every 36 hours
- for neonates aged >7 days: 5 mg/kg every 24 hours

An alternative regimen also based on the age and birth-weight of the neonate is suggested by the AAP;[1] doses should be given by intramuscular or intravenous injection:

- for neonates aged ⩽7 days and weighing ⩽2 kg: 5 mg/kg every 48 hours
- for neonates aged ⩽7 days and weighing >2 kg: 4 mg/kg every 24 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 4 to 5 mg/kg every 24 to 48 hours; a dosing interval of 48 hours may be used until 2 weeks of life in extremely low birth-weight neonates (those weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 4 mg/kg every 12 to 24 hours

Many studies have been carried out in neonates and infants to evaluate the use and determine the dose of aminoglycosides when used in once-daily or in extended-interval dosing regimens.[2-17]

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Isemann BT, *et al*. Optimal gentamicin therapy in preterm neonates includes loading doses and early monitoring. *Ther Drug Monit* 1996; **18:** 549–55.
3. Logsdon BA, Phelps SJ. Routine monitoring of gentamicin serum concentrations in pediatric patients with normal renal function is unnecessary. *Ann Pharmacother* 1997; **31:** 1514–18.
4. Murphy JE, *et al*. Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. *Am J Health-Syst Pharm* 1998; **55:** 2280–9.
5. Yeung MY, Smyth JP. Targeting gentamicin concentrations in babies: the younger the baby, the larger the loading dose and the longer the dose interval. *Aust J Hosp Pharm* 2000; **30:** 98–101.
6. Stickland MD, *et al*. An extended interval dosing method for gentamicin in neonates. *J Antimicrob Chemother* 2001; **48:** 887–93.
7. Rastogi A, *et al*. Comparison of two gentamicin dosing schedules in very low birth weight infants. *Pediatr Infect Dis J* 2002; **21:** 234–40.
8. Chattopadhyay B. Newborns and gentamicin—how much and how often? *J Antimicrob Chemother* 2002; **49:** 13–16.
9. English M, *et al*. A randomised, controlled trial of once daily and multidose daily gentamicin in young Kenyan infants. *Arch Dis Child* 2004; **89:** 665–9.
10. Lanao JM, *et al*. Pharmacokinetic basis for the use of extended interval dosage regimens of gentamicin in neonates. *J Antimicrob Chemother* 2004; **54:** 193–8.
11. Contopoulos-Ioannidis DG, *et al*. Extended-interval aminoglycoside administration for children: a meta-analysis. Abstract: *Pediatrics* 2004; **114:** 248. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/1/e111 (accessed 23/03/09)
12. Smyth A, *et al*. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial. *Lancet* 2005; **365:** 573–8.
13. Nestaas E, *et al*. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F294–300.
14. Murphy JE. Prediction of gentamicin peak and trough concentrations from six extended-interval dosing protocols for neonates. *Am J Health-Syst Pharm* 2005; **62:** 823–7.
15. Hale LS, Durham CR. A simple, weight-based, extended-interval gentamicin dosage protocol for neonates. *Am J Health-Syst Pharm* 2005; **62:** 1613–16.
16. Khan AM, *et al*. Extended-interval gentamicin administration in malnourished children. *J Trop Pediatr* 2006; **52:** 179–84.
17. Hennig S, *et al*. Target concentration intervention is needed for tobramycin dosing in paediatric patients with cystic fibrosis–a population pharmacokinetic study. *Br J Clin Pharmacol* 2008; **65:** 502–10.

Administration in renal impairment. Although many nomograms, schedules, and rules have been devised for the calculation of aminoglycoside dosage in renal impairment, where possible dosage modification should be based on the monitoring of individual pharmacokinetic parameters. Standard dosage calculation methods should not be used for patients undergoing dialysis as they may require supplementary post-dialysis doses.

A review[1] of antimicrobial dosing in critically ill patient undergoing renal replacement therapy, suggests that such patients should receive a loading dose of 2 to 3 mg/kg (except for synergy dosing in those on intermittent haemodialysis), with the following empirical maintenance doses, dependent on the clinical indication, type of renal replacement therapy, and serum-gentamicin concentrations:

- intermittent haemodialysis: 1 mg/kg (for synergy or mild urinary-tract infections), 1 to 1.5 mg/kg (for moderate to severe urinary-tract infections), or 1.5 to 2 mg/kg (for systemic Gram-negative infections) every 48 to 72 hours
- continuous renal replacement therapy: 1 mg/kg (for synergy or mild urinary-tract infections) or 1 to 1.5 mg/kg (for moderate to severe urinary-tract infections) every 24 to 36 hours, or 1.5 to 2.5 mg/kg every 24 to 48 hours (for systemic Gram-negative infections)

Serum-gentamicin concentration measurements (drawn before the run for those on haemodialysis) should be used to further adjust the dosing interval. The next maintenance dose should be given when serum-gentamicin concentrations are within the following ranges:[1]

- for synergy or mild urinary-tract infections: < 1 mg/litre
- for moderate to severe urinary-tract infections: < 1.5 to 2 mg/litre
- for systemic Gram-negative bacterial infections: < 3 to 5 mg/litre

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Ménière's disease. Gentamicin and streptomycin have been used for medical ablation in advanced Ménière's disease (p. 611.2). Although gentamicin given systemically is considered to be more ototoxic than streptomycin, evidence from *animal* studies suggests that intratympanic use may be less ototoxic. This, and a higher incidence of adverse effects with streptomycin, has meant that intratympanic gentamicin is now preferred. Intratympanic gentamicin has been reported to control vertigo symptoms in the majority of patients, although some have a worsening of their hearing loss immediately after treatment.[1-9] However, the ideal regimen for intratympanic gentamicin has yet to be defined.

1. Nedzelski JM, *et al*. Chemical labyrinthectomy: local application of gentamicin for the treatment of unilateral Meniere's disease. *Am J Otol* 1992; **13:** 18–22.
2. Pyykkö I, *et al*. Intratympanic gentamicin in bilateral Meniere's disease. *Otolaryngol Head Neck Surg* 1994; **110:** 162–7.
3. Quaranta A, *et al*. Intratympanic therapy for Ménière's disease: high-concentration gentamicin with round-window protection. *Ann N Y Acad Sci* 1999; **884:** 410–24.
4. Longridge NS, Mallinson AI. Low-dose intratympanic gentamicin treatment for dizziness in Meniere's disease. *J Otolaryngol* 2000; **29:** 35–9.
5. Quaranta A, *et al*. Intratympanic therapy for Ménière's disease: effect of administration of low concentration of gentamicin. *Acta Otolaryngol* 2001; **121:** 387–92.
6. Marzo SJ, Leonetti JP. Intratympanic gentamicin therapy for persistent vertigo after endolymphatic sac surgery. *Otolaryngol Head Neck Surg* 2002; **126:** 31–3.
7. Cohen-Kerem R, *et al*. Intratympanic gentamicin for Menière's disease: a meta-analysis. *Laryngoscope* 2004; **114:** 2085–91.
8. Postema RJ, *et al*. Intratympanic gentamicin therapy for control of vertigo in unilateral Menière's disease: a prospective, double-blind, randomized, placebo-controlled trial. *Acta Otolaryngol* 2008; **128:** 876–80.
9. Pullens B, van Benthem PP. Intratympanic gentamicin for Ménière's disease or syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 17/06/13).

Adverse Effects

The aminoglycosides can produce irreversible, cumulative ototoxicity. This affects both the cochlea (manifest as hearing loss, initially of higher tones, and which, because speech recognition relies greatly on lower frequencies, may not be at first apparent) and the vestibular system (manifest as dizziness or vertigo). The incidence and relative toxicity with different aminoglycosides is a matter of some dispute, but netilmicin is probably less cochleotoxic than gentamicin or tobramycin, and amikacin more so. Netilmicin also exhibits less vestibular toxicity than gentamicin, tobramycin, or amikacin, while streptomycin produces a high incidence of vestibular damage. Vestibular damage is more common than hearing loss in patients receiving gentamicin.

Reversible nephrotoxicity may occur and acute renal failure has been reported, often in association with the use of other nephrotoxic drugs. Renal impairment is usually mild, although acute tubular necrosis and interstitial nephritis have occurred. Decreased glomerular filtration rate is usually seen only after several days, and may even occur after therapy has stopped. Electrolyte disturbances (notably hypomagnesaemia, but also hypocalcaemia and hypokalaemia) have occurred. The nephrotoxicity of gentamicin is reported to be largely due to the gentamicin C_2 component.

Although particularly associated with high plasma concentrations, many risk factors have been suggested for ototoxicity and nephrotoxicity in patients receiving aminoglycosides—see Precautions p. 308.3.

Aminoglycosides possess a neuromuscular-blocking action and respiratory depression and muscular paralysis have been reported, notably after absorption from serous surfaces. Neomycin has the most potent action and deaths have been associated with its use.

Hypersensitivity reactions have occurred, especially after local use, and cross-sensitivity between aminoglycosides may occur. Very rarely, anaphylactic reactions to gentamicin have occurred. Some hypersensitivity reactions have been attributed to the presence of sulfites in parenteral formulations, and endotoxic shock has also been reported.

Infrequent effects reported for gentamicin include blood dyscrasias, purpura, nausea and vomiting, stomatitis, and signs of liver dysfunction such as increased serum-aminotransferase values and increased serum-bilirubin concentrations. Neurotoxicity has occurred, with both peripheral neuropathies and central symptoms being reported including encephalopathy, confusion, lethargy, hallucinations, convulsions, and mental depression.

Atrophy or fat necrosis has been reported at injection sites. There have been isolated reports of meningeal irritation, arachnoiditis, polyradiculitis, and ventriculitis after intrathecal, intracisternal, or intraventricular use of aminoglycosides. Subconjunctival injection of gentamicin may lead to pain, hyperaemia, and conjunctival oedema, while severe retinal ischaemia has followed intra-ocular injection.

Effects on the ears. Reviews and references to aminoglycoside-induced ototoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5:** 155–62.
2. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
3. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33:** 797–800.
4. Mattie H, *et al*. Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24:** 281–93.
5. Schacht J. Aminoglycoside ototoxicity: prevention in sight? *Otolaryngol Head Neck Surg* 1998; **118:** 674–7.
6. Nakashima T, *et al*. Vestibular and cochlear toxicity of aminoglycosides—a review. *Acta Otolaryngol* 2000; **120:** 904–11.
7. Darlington CL, Smith PF. Vestibulotoxicity following aminoglycoside antibiotics and its prevention. *Curr Opin Investig Drugs* 2003; **4:** 841–6.
8. Rizzi MD, Hirose K. Aminoglycoside ototoxicity. *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 352–7.
9. Ariano RE, *et al*. Aminoglycoside-induced vestibular injury: maintaining a sense of balance. *Ann Pharmacother* 2008; **42:** 1282–9.
10. Mulrennan SA, *et al*. Aminoglycoside ototoxicity susceptibility in cystic fibrosis. *Thorax* 2009; **64:** 271–2.
11. Bitner-Glindzicz M, *et al*. Aminoglycoside-induced deafness during treatment of acute leukaemia. *Arch Dis Child* 2010; **95:** 153–5.

Effects on the kidneys. Reviews and references to aminoglycoside-induced nephrotoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5:** 155–62.
2. Lietman PS, Smith CR. Aminoglycoside nephrotoxicity in humans. *Rev Infect Dis* 1983; **5** (suppl 2): S284–93.
3. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
4. Kohlhepp SJ, *et al*. Nephrotoxicity of the constituents of the gentamicin complex. *J Infect Dis* 1984; **149:** 605–14.
5. Mattie H, *et al*. Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24:** 281–93.
6. Appel GB. Aminoglycoside nephrotoxicity. *Am J Med* 1990; **88** (suppl 3C): 16S–20S.
7. Bertino JS, *et al*. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis* 1993; **167:** 173–9.
8. Swan SK. Aminoglycoside nephrotoxicity. *Semin Nephrol* 1997; **17:** 27–33.
9. Baciewicz AM, *et al*. Aminoglycoside-associated nephrotoxicity in the elderly. *Ann Pharmacother* 2003; **37:** 182–6.
10. Rougier F, *et al*. Aminoglycoside nephrotoxicity. *Curr Drug Targets Infect Disord* 2004; **4:** 153–62.
11. Martínez-Salgado C, *et al*. Glomerular nephrotoxicity of aminoglycosides. *Toxicol Appl Pharmacol* 2007; **223:** 86–98.
12. Oliveira JFP, *et al*. Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units. *Antimicrob Agents Chemother* 2009; **53:** 2887–91.

Effects on the skin. Periocular ulcerative dermatitis has been reported in some newborn infants following the routine use of gentamicin ointment for ocular infection prophylaxis. The dermatitis was thought to be due to a direct vaso-occlusive effect of gentamicin on the blood vessels of the eyelid; however, the possibility of a hypersensitivity reaction or the synergistic action of gentamicin and the preservative could not be excluded.[1]

1. Binenbaum G, *et al*. Periocular ulcerative dermatitis associated with gentamicin ointment prophylaxis in newborns. *J Pediatr* 2010; **156:** 320–1.

Endotoxin reactions. Reports of endotoxin reactions associated with intravenous gentamicin have been received by the CDC and the FDA in the USA.[1] Although endotoxin concentrations in the injections used were within USP limits, giving a single daily dose rather than divided doses was thought to have resulted in toxic serum concentrations of endotoxins.[1,2]

1. CDC. Endotoxin-like reactions associated with intravenous gentamicin—California, 1998. *MMWR* 1998; **47:** 877–80.
2. Krieger JA, Duncan L. Gentamicin contaminated with endotoxin. *N Engl J Med* 1999; **340:** 1122.

Treatment of Adverse Effects

Aminoglycosides may be removed by haemodialysis or to a much lesser extent by peritoneal dialysis. Calcium salts given intravenously have been used to counter neuromuscular blockade; the efficacy of neostigmine has been variable.

For reference to the potential for calcium-channel blockers to reduce aminoglycoside-related nephrotoxicity, see Kidney Disorders, under Uses of Verapamil, p. 1523.1.

Precautions

Gentamicin is contra-indicated in patients with a history of hypersensitivity to it, and probably in those hypersensitive to other aminoglycosides. It should be avoided in patients with myasthenia gravis, and great care is required in patients with parkinsonism and other conditions characterised by muscular weakness.

The risk of ototoxicity and nephrotoxicity from aminoglycosides is increased at high plasma concentrations and it is therefore generally desirable to determine dosage requirements by individual monitoring. In patients receiving standard multiple daily dose regimens of gentamicin, dosage should be adjusted to avoid peak plasma concentrations above 10 micrograms/mL, or trough concentrations (immediately before next dose) exceeding 2 micrograms/mL. Local guidelines on serum concentration should be consulted where once-daily dosage regimens are used. Monitoring is particularly important in patients receiving high doses or prolonged courses, in infants and the elderly, and in patients with renal impairment, who generally require reduced doses. It is also important in patients with cystic fibrosis or significant obesity; again, altered doses may be required. See Pharmacokinetics p. 309.3 for other patient groups in whom pharmacokinetics may be altered. Impaired hepatic function or auditory function, bacteraemia, fever, and perhaps exposure to loud

noises have also been reported to increase the risk of ototoxicity, while circulatory volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity. Regular assessment of auditory and renal function is particularly necessary in patients with additional risk factors.

Topical application of gentamicin into the ear is contra-indicated in patients with known or suspected perforation of the ear drum.

Use of aminoglycosides during pregnancy may damage the eighth cranial nerve of the fetus.

Breast feeding. A study[1] involving 10 mothers given gentamicin and their breast-fed infants found measurable gentamicin concentrations in the serum of 5 of the 10 neonates, indicating that appreciable gastrointestinal absorption had occurred. It was, however, considered that these low concentrations would not cause clinical effects and the American Academy of Pediatrics[2] also considers that the use of gentamicin is usually compatible with breast feeding.

1. Celiloglu M, *et al.* Gentamicin excretion and uptake from breast milk by nursing infants. *Obstet Gynecol* 1994; **84:** 263–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interference with assay procedures. The implications of drug interference with assays for aminoglycosides have been reviewed.[1] Other antimicrobials and antineoplastics may alter the results of microbiological assays but this can be overcome by selection of an appropriate assay organism.

Microbiological assays for aminoglycosides in samples also containing *imipenem* could be accomplished by using cysteine hydrochloride to inactivate imipenem, which is stable to most beta-lactamases.[2] Because aminoglycosides may be inactivated by *penicillins* and *cephalosporins*, it has been recommended that aminoglycoside sampling times should be chosen to coincide with a trough plasma concentration for the beta lactam. Samples should be frozen if there is to be a delay before they are assayed[3] or a penicillinase added. However, one group of workers have reported loss of gentamicin activity after storage at -60 degrees before assay.[4] Furthermore, there have been reports that concentrations of aminoglycosides in patients also given beta lactams have been overestimated using a homogeneous enzyme immunoassay, probably because of an inability to differentiate between active drug and inactivated products.[5,6]

The radionuclide *gallium-67* interferes with radioenzymatic assays, and it has been suggested that an agar diffusion method should be used in patients who have received a gallium scan.[7,8]

Heparin has been shown to produce underestimation of aminoglycoside concentrations when using microbiological, enzymatic, or immunoassays.[9-11] It has been recommended either that serum should be used or that blood samples should not be collected in heparinised tubes or from indwelling catheter lines. Some consider that concentrations of heparin in the blood of patients receiving heparin are too low to affect gentamicin.[12]

Falsely low concentrations of aminoglycoside have also been reported in microbiological assays in the presence of *zinc* salts.[13]

Heat treatment of whole *blood* to inactivate human immunodeficiency virus leads to an increase in the concentration of gentamicin subsequently found on assay.[14]

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–87.
2. McLeod KM, *et al.* Gentamicin assay in the presence of imipenem. *J Antimicrob Chemother* 1986; **17:** 828–9.
3. Tindula RJ, *et al.* Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; **17:** 906–8.
4. Carlson LG, *et al.* Potential liabilities of gentamicin homogeneous enzyme immunoassay. *Antimicrob Agents Chemother* 1982; **21:** 192–4.
5. Ebert SC, Clementi WA. In vitro inactivation of gentamicin by carbenicillin, compared by Emit and microbiological assays. *Drug Intell Clin Pharm* 1983; **17:** 451.
6. Dalmady-Israel C, *et al.* Ticarcillin and assay of tobramycin. *Ann Intern Med* 1984; **100:** 460.
7. Bhattacharya I, *et al.* Effects of radiopharmaceuticals on radioenzymatic assays of aminoglycoside antibiotics: interference by gallium-67 and its elimination. *Antimicrob Agents Chemother* 1978; **14:** 448–53.
8. Shannon K, *et al.* Interference with gentamicin assays by gallium-67. *J Antimicrob Chemother* 1980; **6:** 285–300.
9. Nilsson L. Factors affecting gentamicin assay. *Antimicrob Agents Chemother* 1980; **17:** 918–21. Correction. *ibid.;* **18:** 839.
10. Nilsson L, *et al.* Inhibition of aminoglycoside activity by heparin. *Antimicrob Agents Chemother* 1981: **20:** 155–8.
11. O'Connell MB, *et al.* Heparin interference with tobramycin, netilmicin, and gentamicin concentrations determined by Emit. *Drug Intell Clin Pharm* 1984; **18:** 503–4.
12. Regamey C, *et al.* Inhibitory effect of heparin on gentamicin concentrations in blood. *Antimicrob Agents Chemother* 1972; **1:** 329–32.
13. George RH, Healing DE. The effect of zinc on aminoglycoside assay. *J Antimicrob Chemother* 1978; **4:** 186.
14. Eley A, *et al.* Effect of heat on gentamicin assays. *Lancet* 1987; **ii:** 335–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gentamicin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Use of other nephrotoxic drugs (including other aminoglycosides, vancomycin, some cephalosporins, ciclosporin, cisplatin, and fludarabine), or of potentially ototoxic drugs such as etacrynic acid and perhaps furosemide, may increase the risk of aminoglycoside toxicity. It has been suggested that use of an antiemetic such as dimenhydrinate may mask the early symptoms of vestibular ototoxicity. Care is also required if other drugs with a neuromuscular-blocking action are used (see Atracurium, p. 2032.1). The neuromuscular-blocking properties of aminoglycosides may be sufficient to provoke severe respiratory depression in patients given general anaesthetics or opioids.

There is a theoretical possibility that the antibacterial effects of aminoglycosides could be reduced by bacteriostatic antibacterials, but such combinations have been used successfully in practice.

Since aminoglycosides have been shown to be incompatible with some beta lactams *in vitro* (see Incompatibility, p. 304.3), these antibacterials should be given separately if both are required; antagonism *in vivo* has been reported only in a few patients with severe renal impairment, in whom aminoglycoside activity was diminished. Aminoglycosides have synergistic activity with some beta lactams *in vivo* (see Antimicrobial Action, p. 309.2).

Renal excretion of zalcitabine may be reduced by aminoglycosides.

For reports of severe hypocalcaemia in patients treated with aminoglycosides and bisphosphonates, see p. 1177.2.

Gentamicin may inhibit α-galactosidase activity and should not be used with agalsidase alfa or beta.

Antimicrobial Action

Gentamicin is an aminoglycoside antibiotic and has a bactericidal action against many Gram-negative aerobes and against some strains of staphylococci.

Mechanism of action. Aminoglycosides are taken up into sensitive bacterial cells by an active transport process which is inhibited in anaerobic, acidic, or hyperosmolar environments. Within the cell they bind to the 30S, and to some extent to the 50S, subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is imperfectly understood, and other mechanisms may contribute, including effects on membrane permeability.

Spectrum of activity. The following pathogenic organisms are usually sensitive to gentamicin (but see also Resistance, below).

- Many strains of Gram-negative bacteria including species of *Brucella, Calymmatobacterium, Campylobacter, Citrobacter, Escherichia, Enterobacter, Francisella, Klebsiella, Proteus, Providencia, Pseudomonas, Serratia, Vibrio,* and *Yersinia.* Some activity has been reported against isolates of *Neisseria,* although aminoglycosides are rarely used clinically in neisserial infections.
- Among the Gram-positive organisms many strains of *Staphylococcus aureus* are highly sensitive to gentamicin. *Listeria monocytogenes* and some strains of *Staph. epidermidis* may also be sensitive to gentamicin, but enterococci and streptococci are usually insensitive to gentamicin.
- Some actinomycetes and mycoplasmas have been reported to be sensitive to gentamicin, but mycobacteria are insensitive at clinically achievable concentrations.
- Anaerobic organisms, yeasts, and fungi are resistant.

Activity with other antimicrobials. Gentamicin has synergy with beta lactams, probably because the effects of the latter on bacterial cell walls enhance aminoglycoside penetration. Enhanced activity has been shown with a penicillin (such as ampicillin or benzylpenicillin) and gentamicin against the enterococci, and gentamicin has been combined with an antipseudomonal penicillin such as ticarcillin for enhanced activity against *Pseudomonas* spp., and with vancomycin for enhanced activity against staphylococci and streptococci.

Resistance to the aminoglycosides may be acquired by three main mechanisms. The first is by mutation of ribosomal target sites leading to reduced affinity for binding; this type of resistance is generally only relevant for streptomycin and, even then, it appears to be rare in Gram-negative bacteria. Secondly, penetration of aminoglycosides into bacterial cells is by an oxygen-dependent active transport process and resistance may occur because of elimination or reduction of this uptake; when it occurs this generally results in cross-resistance to all aminoglycosides. Thirdly, and by far the most important cause of resistance to the aminoglycosides, is inactivation by enzymatic modification.

Three main classes of enzyme conferring resistance have been found, operating by phosphorylation, acetylation, or addition of a nucleotide group, usually adenyl. Enzyme production is usually plasmid-determined and resistance can therefore be transferred between bacteria, even of different species. Resistance to other antibacterials may be transferred at the same time. In *Staph. aureus,* transfer of resistance is more likely when these drugs are used topically.

Each type of enzyme produces characteristic patterns of resistance, but their overlapping and variable affinities for their substrates result in many permutations of cross-resistance to the different aminoglycosides. The different enzymes vary in their distribution and prevalence in different locations, and at different times, presumably with variations in antibacterial usage, but relationships to the use of specific aminoglycosides are difficult to establish. These variations in drug sensitivity require local testing to determine resistance and establish susceptibility of bacteria to the aminoglycoside being used, but such local variations mean that estimates of the incidence of resistance are of limited value.

In general, the occurrence of resistant pathogens seems to have been greater in southern than in northern Europe, and perhaps greater in the USA than in Europe. There has been particular concern over the increasing incidence of high-level gentamicin resistance among enterococci (in up to 50% of isolates from some centres), since they already possess inherent or acquired resistance to many drugs, including vancomycin in some cases. A similar problem exists with gentamicin resistance in meticillin-resistant strains of *Staph. aureus.* Such multiply-resistant strains pose a major therapeutic problem in those centres where they occur, since the usual synergistic combinations with other antibacterials are ineffective. However, results from some centres indicate that rational use of a wider range of aminoglycosides (including amikacin which is not affected by most of the aminoglycoside-degrading enzymes) has resulted in a modest decline in overall aminoglycoside resistance.

References.

1. Mingeot-Leclercq M-P, *et al.* Aminoglycosides: activity and resistance. *Antimicrob Agents Chemother* 1999; **43:** 727–37.
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4. Magnet S, Blanchard JS. Molecular insights into aminoglycoside action and resistance. *Chem Rev* 2005; **105:** 477–98.

Pharmacokinetics

Gentamicin and other aminoglycosides are poorly absorbed from the gastrointestinal tract but are rapidly absorbed after intramuscular injection. Average peak plasma concentrations of about 4 micrograms/mL have been attained in patients with normal renal function 30 to 60 minutes after an intramuscular dose equivalent to gentamicin 1 mg/kg, which is similar to concentrations achieved after intravenous infusion. There may be considerable individual variation. Several doses are required before plasma equilibrium concentrations occur and this may represent the saturation of binding sites in body tissues such as the kidney. Binding of gentamicin to plasma proteins is usually low.

On parenteral use, gentamicin and other aminoglycosides diffuse mainly into extracellular fluids. However, there is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved; diffusion into the eye is also poor. Aminoglycosides diffuse readily into the perilymph of the inner ear. They cross the placenta but only small amounts have been reported in breast milk.

Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and on instillation into, and irrigation of, wounds, body-cavities (except the urinary bladder), and joints.

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration. At steady state at least 70% of a dose may be recovered in the urine in 24 hours and urine concentrations in excess of 100 micrograms/mL may be achieved. However, gentamicin and the other aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney, although the relative degree to which this occurs may vary with different aminoglycosides. Release from these sites is slow and small amounts of aminoglycosides may be detected in the urine for up to 20

days or more after treatment stops. Small amounts of gentamicin appear in the bile.

The pharmacokinetics of the aminoglycosides are affected by many factors, which may become significant because of the relatively small difference between therapeutic and toxic concentrations, reinforcing the need for monitoring.

- Absorption from intramuscular sites may be reduced in critically ill patients, especially in conditions that reduce perfusion such as shock, resulting in **reduced plasma concentrations**. Plasma concentrations may also be reduced in patients with conditions which expand extracellular fluid volume or increase renal clearance including ascites, cirrhosis, heart failure, malnutrition, spinal cord injury, burns, cystic fibrosis, and possibly leukaemia. Clearance is also reportedly increased in intravenous drug abusers, and in patients who are febrile.
- In contrast, renal impairment or reduced renal clearance for any reason (for example in neonates with immature renal function, or in the elderly in whom glomerular function tends to decline with age) can result in markedly **increased plasma concentrations** and/or prolonged half-lives. However, in neonates initial plasma concentrations may actually be reduced, due to a larger volume of distribution. Plasma concentrations may also be higher than expected for a given dose in obese patients (in whom extracellular volume is low relative to weight), and in patients with anaemia.

Renal clearance, and hence plasma concentrations, of aminoglycosides may vary according to a circadian cycle, and it has been suggested that this should be taken into account when determining and comparing plasma aminoglycoside concentrations.

References.
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2. Hilmer SN, *et al*. Gentamicin pharmacokinetics in old age and frailty. *Br J Clin Pharmacol* 2011; **71:** 224–31.

Pharmacokinetics in neonates. References

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2. Hale LS, Durham CR. A simple, weight-based, extended-interval gentamicin dosage protocol for neonates. *Am J Health-Syst Pharm* 2005; **62:** 1613–16.
3. García B, *et al*. Population pharmacokinetics of gentamicin in premature newborns. *J Antimicrob Chemother* 2006; **58:** 372–9.
4. Murphy JE, Roether AM. Two nomograms for determining extended-dosing intervals for gentamicin in neonates. *Am J Health-Syst Pharm* 2008; **65:** 624–30. Correction. *ibid.;* 795.
5. Touw DJ, *et al*. Therapeutic drug monitoring of aminoglycosides in neonates. *Clin Pharmacokinet* 2009; **48:** 71–88. Correction. *ibid.;* 209–10. [dose]
6. Nielsen EI, *et al*. Developmental pharmacokinetics of gentamicin in preterm and term neonates: population modelling of a prospective study. *Clin Pharmacokinet* 2009; **48:** 253–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gentaderm; Gentamina; Gentapharma; Gentaren; Gentoler†; Glevomicina; Plurisemina; Provisual; Rupegen; Sintepul†; ***Austral.***: Genoptic; ***Austria***: Gentax; Refobacin; Sulmycin; ***Belg.***: Geomycine; ***Braz.***: Emisgenta; Garacin; Garamicina; Garamin†; Gentagran; Gentamicil; Gentamil; Gentamisan; Gentaron; Vitamicin†; ***Canad.***: Diogent; Garamycin; Gentak; ***Chile***: Gentalyn; Gentisal; Oftagen; ***China***: Jie Li Tai (杰力泰); Rui Bei Ke (瑞贝克); Wei Lun (维伦); ***Cz.***: Garamycin; ***Denm.***: Garamycin†; Gentacoll; Hexamycin; ***Fin.***: Gensumycin; Gentacoll; ***Fr.***: Gentalline; ***Ger.***: Gencin; Gent-Ophtal; Genta†; Gentamytrex†; InfectoGenta; Refobacin; Sulmycin; Terramycin N†; ***Gr.***: Anfomilan; Centaurin; Cortolexan; Dabroson; Diakarmon; Epabe; Fripeintil; Garamycin; Garbilocin; Gentagen; Gentamedin; Octoret; Septospes; Yedoc; ***Hong Kong***: Garamycin; Genoptic†; Miramycin; ***Hung.***: Garamycin†; ***India***: Andregen†; Bactigen; Biogaracin; Emugent; G Mycin; G-Mycin; G20/80; Garamax; Garamycin; Genka; Genkind; Genmycin; Gensat; Genster; Gentacip; Gentact; Gentalab; Gentam; Gentaril; Gentasia; Gentasporin; Gentate; Genticyn Eye/Ear; Genticyn; Gentina; Genty; Gentyric; Gerocin; Indogenta; Ingen; Intagenta; Intragen; Ketajet; Lyramycin; Mycin; Mygenta; Optocin; ***Indon.***: Balticin; Bioderm†; Dermabiotik†; Dermagen; Ethigent; Garabiotic†; Garamycin; Garapon; Garexin; Gentacyl†; Gentamerck; Gentamisin†; Ikagen; Isotic Timact; Konigen†; Licogenta; Nichogencin; Ottogenta; Sagestam; Salgen; Salticin; Timact; Ximex Konigen; ***Irl.***: Cidomycin; Genoptic†; Genticin; ***Israel***: Gentatrim; Lacromycin; Opti-Genta; ***Ital.***: Ciclozinil; Eutopic; Gentacream; Gentalyn; Genticol; Gentomil; Nemalin; Ribomicin; Tacigen; ***Malaysia***: Beagenta; Garamycin; Garasent; Miramycin; ***Mex.***: Beramicina; Fustermicina†; G-I†; Garacoll†; Garakacin; Garalen†; Garamicina; Geclicin; Genemicin; Genkova; Genrex; Genser; Genta-Micron; Genta; Gentamil; Gentapat; Gentazaf Z; Gentazol; Gentialoquin†; Geracin; Ikatin; Lifegram; Progen†; Quilagen; Servigenta; Tamicin-G; Tamigen; Tondex; Tremax; Yectamicina; ***Neth.***: Garacol; Gentamytrex†; ***Norw.***: Garamycin†; Gensumycin; ***NZ***: Genoptic; ***Philipp.***: Agentam; Bellagen; Garamycin; Garazin; Gecitam; Genom; Gentamytrex†; Gentaxin; Gentrobex; Klontar; Migentax; Minoglen†; Mycin; Obogen; Opthagen; Orimed; Rocygen; Servigenta; Tangyn; Topigen; ***Pol.***: Garamycin; ***Port.***: Cronocol; Garalone; Genta Gobens; Gentalin; Gentocil; Ophtagram; Septopal; ***S.Afr.***: Cidomycin†; Garamycin; Sabax Gentamix; Sterisol Fermentmycin†; ***Singapore***: Colircusi; Dermogen; Garasent; Genoptic†; Gentamytrex; Gentapro; Gentasol; Miramycin; Optigen; ***Spain***: Genta Gobens; Gevramycin†; Rexgenta; ***Swed.***: Garamycin; Gensumycin; ***Switz.***: Garamycin; Ophtagram; ***Thai.***: Garamycin; Gencidal; Genta-Oph; Genta; Gentacin; Gentaderm; Gental; Gentawin; Gentrex; Grammicin; Grammixin; Miramycin; Skinfect; Versigen; ***Turk.***: Genmisin; Genta†; Gentagut; Gentamed; Genthaver; Gentreks; Getamisin; Getasin†; ***UAE***: Gental; ***UK***: Cidomycin; Genticin; ***USA***: Garamycin; Genoptic; Gentacidin†; Gentak; Gentasol; Ocu-Mycin; ***Venez.***: Gentalyn; Gentamilan; Gentisul; Solgenta.

Multi-ingredient Preparations. ***Arg.***: Adenil; Anginotrat; Bacticort Complex; Bacticort; Bactisona†; Becortin; Betacort Plus; Blamy; Butimerin Complex; Calmurid; Cevaderm; Cicatrizol; Ciprocort; Cuta Crema; Denvercrem; Dercotex; Dermizol G; Dermizol Trio; Dermoperative; Dermosona; Dexamytrex; Dicasone Complex; Diprogenta; Factor Dermico; Filoderma Plus; Filoderma; Genamic†; Gentacler; Gentacort Plus; Gentasol; Griseocrem; Hifamonil Crema; Lazar-Cort Complex; Lichensa; Linfol Dermico; Lisoderma; Macril; Magicrem; Microsona C; Miklogen; Monizol Cort Crema; Otalex G; Otonorthia; Pancutan; Provisual Compuesto; Quadriderm; Quiacort G Plus; Quiacort G; Sirotamicin BG; Tribiocort; Tricifa; Tricur; Tridermal; Triliver; Triplex; Vitacortil; ***Austral.***: Palacos E with Garamycin†; Palacos R with Garamycin†; Septopal†; ***Austria***: Decoderm Compositum; Decoderm trivalent†; Dexagenta; Diprogenta; Septopal; Voltamicin†; ***Belg.***: Decoderm Compositum†; Dexagenta-POS; Duracoll; Infectoflam†; Septopal; ***Braz.***: Betogenta; Cauterex; Cremederme; Diprogenta; Diprozil; Duotrat; Garasone; Gentacort; Gino Cauterex; Permut; Poliderms; Quadribeta; Quadriderm; Quadrihexal; Quadrikin†; Quadrilon; Quadriplus†; Qualiderm; Septopal; Tetraderm; ***Canad.***: Diprogen; Garasone; Pentasone; Valisone-G; ***Chile***: Diprospan G; Gentasone; Labosona G; Mixgen; Oftagen Compuesto; Palacos E con Gentamicina†; Palacos R con Gentamicina†; Perlas De PMMA con Gentamicina†; ***China***: Chanyanling (肠炎灵); Guan Xin Ke (贯新克); Infectoflam (易妥芬); Jinquan (金泉); Muli (目力); Qiyu (奇钰); Septopal (塞透派勒); Voltamicin (复美新); ***Cz.***: Belogent; Dexa-Gentamicin; Garasone; ***Denm.***: Septopal†; ***Fin.***: Celestoderm cum Garamycin; Septopal; ***Fr.***: Indobiotic; Septopal†; ***Ger.***: Cibaflam†; Decoderm Comp; Dexa-Gentamicin; Dexagent-Ophtal; Dexamytrex; Diprogenta; Heraeus PMMA Kette G; Inflanegent; Palasept G†; Refobacin Bone Cement R; Refobacin Plus Bone Cement; Refobacin Revision; Septocoll; Septopal; Smart-Mix Cemvac GHV; SmartSet GHV; Sulmycin mit Celestan-V; Terracortril Dexagenta†; ***Gr.***: BV 17G; Celestoderm-V with Garamycin; Dermobeta; Dexamytrex; Garamat; Gentadex; Helpogen; Luzin; Palacos R with Gentamycin; Propiogenta; Septopal; Upanil; ***Hong Kong***: Beta-Genta†; Clobert-G†; Clobeta-G; Clotrim-B†; Cobetsol†; Conazole; Dermaclof†; Dermafacte†; Dermal G; Diprogenta; Garasone; Lycobeta-G; Quadriderm; Septopal†; Triderm; Tridewel†; Triditol-G; ***Hung.***: Garasone; Gentason†; Septopal†; ***India***: ABC Derm; Alclos-GM; Alcoderm; Aliderma; Aloederm-G; Atderm; Baclasia-CG; Balderm; BC-Zole; Beclasone-GM; Beclex-GM; Beclocid-G; Beclolab-CG; Beclotis-CG; Beclozen; Becmet-CG; Becmet-CG; Becmet-G; Becmet-GM; Belar-G; Benda; Bestopic; Betagel-G; Betamil-GM; Betanate G; Betanate GM; Betaspi-GM; Betnederm GM; Betnovate-GM; Betzee-G; Betzee-GM; Caltec; Candiderma; Candigen-BG; Canoderma; CGM; Clobaderm-GM; Clobasia-GM; Clobecos-GM; Clobequad; Cloberis-GM; Clobesym-GM; Clobeta-CF; Clobetamil-G; Clobquad; Cloby; Cloderm-GM; Clodip-GM; Clofung GM; Clofung-G; Clogem; Clomax-BG; Clomycin†; Clonate-G; Clonate-GM; Clop-G; Clop-MG; Clos-GM; Clotof-G; Clotof-GM; Corge-C; Cortiderm-G; Cortiderm-GM; Cortisol-G; Cosvate-G; Cosvate-GM; Cutasol-GM; Cuticare; Cutivate-GT; Darederm; Decand BG; Dermaspan; Derminol; Dermitop; Dermocrat Plus; Dermonit; Dermotriad; Dermowin-GM; Diclogenta; Dipgenta; Diprogen; Diprovate-G; Drep; E-Derm; Ecodax-G; Ecziclo-G; Ecziclo-GM; Ecziclo-M; Enderm-GM; Epicort-GC; Esgiderm; Etan-G; Etan-GM; Eumosone-G; Flunec; Fourderm AF; Fourderm; Fubac; GCB; Gem; Genta Cort B; Genta Cort D; Genta Swift-D; Genta Swift; Gentacip D; Gentacort-FC; Gentacort-MF; Gentalene-C; Gentasia-D; Gentasporin-HC; Gentate-B; Genticyn B; Genticyn HC; Gentopic; Gentyl-DM; Gerocin-BM; GMF; Hyton; IFB; Ifyclo-G; Imidil Plus; Intragen-D; Kloryl-G; Labosol-GM; Lamonte-BG; Leobet-GM; Leobet-GZ; Leta-GM; Lobate-G; Lotril-BG; Lupiderm-G; Lupiderm-GM; Magclo-G; Mediron; Miclogenta; Micocort-G; Nuforce-GM; Quiss; Septopal†; Sigmaderm; Tenovate G; Translipo-Triple; ***Indon.***: Benoson G; Betagentam; Betasin; Biocort†; Celestoderm-V with Garamycin; Cinogenta; Digenta; Diprogenta; Diprosta†; Garasone; Genolon; Gentacortin†; Gentasolon; Isotic Betaracin; Mastroson†; Salgen Plus; Sinobiotik†; Skilone; Skinal†; Sonigen; Synalten; Zensoderm; ***Irl.***: Gentisone HC; ***Israel***: Aflumycin; Betacorten-G; Cicloderm-C; Diprogenta; Triderm; ***Ital.***: Betacream; Citrizan Antibiotico; Dermabiolene; Egerian; Fidagenbeta; Genalfa†; Gentacort†; Gentalyn Beta; Kamelyn; Sterozinil; Vasosterone Oto†; ***Malaysia***: B-Mycin; Beprogent; Betagen; Betamethasone G; Diprogenta; Garasone; Genta-Dex; Gentadexa; Joysun; ***Mex.***: Barmicil Compuesto; Beclogen; Beclotrin; Betrigen; Clotricina; Diprosone G; Garamicina-V†; Garasone; Miclobet; Prubagen; Quadriderm NF; Quadermin; Triderm; ***Neth.***: Dexagenta-POS; Dexamytrex; Septopal; ***Norw.***: Septopal; ***NZ***: CMW Gentamicin; Palacos with Garamycin; Smartmix; Smartset; Vacu-Mix Plus with CMW gentamicin; ***Philipp.***: Combiderm; Dexamytrex; Diprogenta; Garasone; Infectoflam; Ophtasone; Quadriderm; Quadrotopic; Septopal; Triderm; Xetam-Opta; ***Pol.***: Bedicort G; Belogent; Dexamytrex; Diprogenta; Triderm; ***Port.***: Dexamytrex; Diprogenta; Epione; Gentadexa; Indobiotic; Quadriderme; ***Rus.***: Akriderm Genta (Акридерм Гента); Akriderm GK (Акридерм ГК); Belogent (Белогент); Betaderm (Бетадерм); Betagenot (Бетагенот); Candiderm (Кандидерм); Canison Plus (Канизон Плюс); Celestoderm-V with Garamycin (Целестодерм-В с Гарамицином); Dexa-Gentamicin (Декса-Гентамицин); Fugentin (Фугентин); Garasone (Гаразон); Triderm (Тридерм); ***S.Afr.***: Diprogenta; Palacos R with Garamycin; Quadriderm; Septopal; ***Singapore***: Antasone; B-Tasone-G; Beprogent; Combiderm; Conazole; Dexa-Gentamicin; Dexamytrex†; Diprogenta; Garasone†; Gentriderm; Gentrisone; Infectoflam; Modaderm; Neoderm; Refobacin Bone Cement R†; Saerogenta-A; Septopal; Tri-Micon; Triderm; ***Spain***: Celestoderm Gentamicina; Cuatroderm; Diprogenta; Epitelizante; Flugen†; Flutenal Gentamicina†; Gentadexa; Interderm; Novoter Gentamicina; ***Swed.***: Celeston valerat med gentamicin†; ***Switz.***: Dexagenta-POS; Diprogenta; Infectoflam†; Ophtasone; Septopal; Triderm; Voltamicin; ***Thai.***: Beprogent; Beprogenta; Betagen; Betagram; Dermaheu; Dertec; Dexamytrex†; Genquin; Gental-F; Infectoflam†; Pred Oph; Quadriderm; Refobacin Bone Cement R; Septopal; Skinfect-B; Spectroderm; ***Turk.***: Belogent; Indobiotic; ***UK***: Collatamp EG; Gentisone HC; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal; Vipsogal; ***Ukr.***: Betaderm (Бетадерм); Candiderm (Кандидерм); Clotrex (Клотрекс); Cremgen (Кремген); Gentaxan (Гентаксан); Triacutan (Триакутан); Triderm (Тридерм); ***USA***: Pred G; ***Venez.***: Betaderm con Gentamicina; Celestoderm con Gentalyn; Diprogenta; Garabet; Garasone; Gentidexa; Gentidexa; Quadriderm; Triderm; Tridetarmon.

Pharmacopoeial Preparations

BP 2014: Gentamicin and Hydrocortisone Acetate Ear Drops; Gentamicin Cream; Gentamicin Ear Drops; Gentamicin Eye Drops; Gentamicin Injection; Gentamicin Ointment;

USP 36: Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Gentamicin Injection; Gentamicin Sulfate Cream; Gentamicin Sulfate Ointment; Gentamicin Sulfate Ophthalmic Ointment; Gentamicin Sulfate Ophthalmic Solution.

Gramicidin *(BAN, rINN)*

Gramicidin D; Gramicidin (Dubos); Gramicidina; Gramicidinas; Gramicidine; Gramicidinum; Gramisidiini; Gramisidin; Грамицидин.

CAS — 1405-97-6.
ATC — R02AB30.
ATC Vet — QR02AB30.
UNII — 5IE62321P4.

NOTE. The name gramicidin was formerly applied to tyrothricin.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Gramicidin). It consists of a family of antimicrobial linear polypeptides usually obtained by extraction from tyrothricin, the complex isolated from the fermentation broth of *Bacillus brevis*. The main component is gramicidin A1, together with gramicidins A2, B1, C1, and C2 in particular. The potency is not less than 900 units/mg calculated with reference to the dried substance. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Gramicidin). An antibacterial substance produced by the growth of *Bacillus brevis* (Bacillaceae); it may be obtained from tyrothricin. It has a potency of not less than 900 micrograms of gramicidin per mg, calculated on the dried basis. A white or practically white, odourless, crystalline, powder. Insoluble in water; soluble in alcohol. Store in airtight containers.

Profile

Gramicidin has properties similar to those of tyrothricin (p. 386.1) and is too toxic to be given systemically. It is used topically for the local treatment of susceptible infections usually with other antibacterials such as neomycin and polymyxin B, and often with a corticosteroid as well.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gramicidin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Neo-Argicilline.

Multi-ingredient Preparations. ***Arg.***: Antibiocort; Aseptobron N; Aseptobron N; Biotaer Nasal†; Bucoangin N; Caext; Carnot Colutorio; Collubiazol N; Expectosan Caramelos; Gargaletas;

Graneodin N; Graneodin; Gripaben Caramelos; Kenacomb; Nasomicina; Neo Coltirot; Pantometil†; Proetztotal; Tosedrin NF; ***Austral.***: Kenacomb; Neosporin†; Otocomb Otic; Otodex; Sofradex; Soframycin†; ***Austria***: Volon A antibiotikahaltig†; ***Belg.***: Mycolog; Polyspectran Gramicidine†; ***Braz.***: Fonergin; Londerm-N†; Mud; Neolon D; Omcilon-A M; Oncibel; Oncileg; Onciplus†; ***Canad.***: Ak Spor; Antibiotic Cream; Antibiotic Plus; Complete Antibiotic Ointment; Diosporin†; Neosporin; Opticort; Optimyxin Plus; Optimyxin; Polysporin Complete; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polysporin; Polytopic; ratio-Triacomb; Sofracort; Soframycin; Soframycin; Triple Antibiotic Ointment; Viaderm-KC; ***Chile***: Oftabiotico; ***China***: Kenacomb (复方康纳乐霜); ***Denm.***: Kenalog Comp med Mycostatin†; Sofradex; ***Fin.***: Bafucin; Polysporin†; ***Ger.***: Polyspectran; ***Gr.***: Neo-Priphen; Neosporin; Sofradex; Thilodexine-N; ***Hong Kong***: Centacomb; Dermawell†; In-quadeicren; Kenacomb†; Neosporin; Polyneospin†; Polyoph; Polyspectran†; Sofradex; Triacomb†; ***Hung.***: Polyspor†; ***India***: Kenacomb; Kenalog-S; Neosporin; Sofracort; ***Indon.***: Blecidex; Isotic Enpigi; Neosyd; Sofradex; ***Irl.***: Graneodin†; Kenacomb†; Sofradex; ***Israel***: Dermacombin; ***Ital.***: Eta Biocortilen VC; ***Malaysia***: Kenacomb; Pocin G†; Sofradex; ***Mex.***: Biotarson N†; Biotarson O†; Graneodin D; Kenacomb; Neosporin; Polixin; Poly-Micron; Septilisin; Soperil; Sulned; ***Neth.***: Mycolog†; Sofradex; ***Norw.***: Sofradex; ***NZ***: Kenacomb; Sofradex; Soframycin†; Viaderm-KC; ***Philipp.***: Iporam; Kenacomb†; Lidex NGN; Neosporin; Novasorin; Oticom; Trispec; ***Pol.***: Dicortineff; Triacomb; ***Port.***: Dropcina; ***Rus.***: Sofradex (Софрадекс); ***S.Afr.***: Kenacomb†; Sofradex; ***Singapore***: Sofradex; ***Spain***: Flodermol; Fludronef†; Midacina; Oftalmowell; Tivitis†; ***Swed.***: Bafucin; ***Switz.***: Angidine†; Mycolog N; Neosporin; Sofradex†; Topsym polyvalent; Tyrothricine + Gramicidine†; ***Thai.***: Dermacombin; Kenacomb†; Polyoph; Sofradex; Topifram; Xanalin; ***Turk.***: Neosporin; ***UAE***: Panderm; ***UK***: Neosporin†; Sofradex; ***Ukr.***: Grammidin with Anaesthetic Neo (Граммидин С Анестетиком Нео); ***USA***: Neosporin; Ocu-Spor-G; Ocutricin; Polymycin; ***Venez.***: Kenacomb.

Pharmacopoeial Preparations

USP 36: Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Gramicidin Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Gramicidin S *(rINN)*

Gramicidin C; Gramicidina S; Gramicidine S; Gramicidinum S; Soviet Gramicidin; Грамицидин С.

$C_{60}H_{92}N_{12}O_{10}$=1141.5

CAS — 113-73-5.

UNII — WHM29QA23F.

Profile

Gramicidin S is an antibacterial polypeptide, produced by *Bacillus brevis*, and has similar properties to tyrothricin (p. 386.1). It is unsuitable for systemic use and is used topically for the local treatment of susceptible infections and as lozenges for infections of the mouth and throat. The hydrochloride is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Grammidin (Граммидин).

Multi-ingredient Preparations. ***Indon.***: FG Ointment†; FG Troches; ***Rus.***: Grammidin Neo (Граммидин Нео); Grammidin with Anesthetic Neo (Граммидин с АнестетикОм Нео); ***Ukr.***: Grammidin (Граммидин); Grammidin Neo (Граммидин Нео); Sofradex (Софрадекс)†.

Halquinol *(BAN)*

Chlorhydroxyquinoline; Chlorquinol; Halquinols (USAN); SQ-16401.

A mixture of the chlorinated products of quinolin-8-ol containing 57 to 74% of 5,7-dichloroquinolin-8-ol (chloroxine, p. 260.1), 23 to 40% of 5-chloroquinolin-8-ol (cloxiquine, p. 577.1), and not more than 4% of 7-chloroquinolin-8-ol.

CAS — 8067-69-4.

UNII — Z7Z4BX535U.

Profile

Halquinol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p. 273.1). It is used topically in infected skin conditions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Valpeda.

Ibafloxacin *(BAN, USAN, rINN)*

Ibafloksasiini; Ibafloxacine; Ibafloxacino; Ibafloxacinum; R-835; S-25930; Ибафлоксацин.

9-Fluoro-6,7-dihydro-5,8-dimethyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

$C_{15}H_{14}FNO_3$=275.3

CAS — 91618-36-9.

ATC Vet — QJ01MA96.

UNII — 53VPK9R0T5.

Profile

Ibafloxacin is a fluoroquinolone antibacterial that is used in veterinary medicine for the treatment of susceptible infections in cats and dogs.

Iclaprim *(USAN, rINN)*

AR-100; Iclaprime; Iclaprimum; Ro-48-2622; Иклаприм.

5-[(2*RS*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-chromen-5-ylmethyl]pyrimidine-2,4-diamine.

$C_{19}H_{22}N_4O_3$=354.4

CAS — 192314-93-5.

ATC — J01EA03.

ATC Vet — QJ01EA03.

UNII — 42445HUU0O.

Iclaprim Mesilate *(rINNM)*

AR-100.001; Iclaprim Mesylate (USAN); Iclaprime, Mésilate d'; Iclaprimi Mesilas; Mesilato de iclaprim; Иклаприма Мезилат.

5-[[(2*RS*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-yl]methyl]pyrimidine-2,4-diamine methanesulfonate.

$C_{19}H_{22}N_4O_3,CH_4O_3S$=450.5

CAS — 474793-41-4.

ATC — J01EA03.

ATC Vet — QJ01EA03.

UNII — 7U972CJ5AT.

NOTE. The name Mersarex has been used as a trade mark for iclaprim mesylate.

Profile

Iclaprim is a diaminopyrimidine antibacterial similar to trimethoprim (p. 383.2) that has been investigated for the treatment of complicated infections of the skin and skin structure caused by Gram-positive bacteria, including MRSA.

References.

1. Sincak CA, Schmidt JM. Iclaprim, a novel diaminopyrimidine for the treatment of resistant gram-positive infections. *Ann Pharmacother* 2009; **43:** 1107–14.
2. Sader HS, *et al.* Potency and bactericidal activity of iclaprim against recent clinical Gram-positive isolates. *Antimicrob Agents Chemother* 2009; **53:** 2171–5.
3. Krievins D, *et al.* Multicenter, randomized study of the efficacy and safety of intravenous iclaprim in complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2009; **53:** 2834–40.

Imipenem *(BAN, USAN, rINN)*

N-Formimidoyl Thienamycin; Imipemide; Imipeneemi; Imipénem; Imipenem monohydrát; Imipenemas; Imipenemum; Imipenemum Monohydricum; MK-0787; MK-787; Имипенем.

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-(2-iminomethylaminoethylthio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

$C_{12}H_{17}N_3O_4S,H_2O$=317.4

CAS — 64221-86-9 (anhydrous imipenem); 74431-23-5 (imipenem monohydrate).

UNII — 71OTZ9ZE0A (imipenem monohydrate); Q20IM7HE75 (anhydrous imipenem).

Description. Imipenem is the *N*-formimidoyl derivative of thienamycin, an antibiotic produced by *Streptomyces cattleya.*

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Imipenem Monohydrate). A white, almost white, or pale yellow slightly hygroscopic powder. Slightly soluble in water and in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 7.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Imipenem). A white to tan-coloured crystalline powder. Slightly soluble in water and in methyl alcohol. Store at a temperature not exceeding 8 degrees.

Incompatibility and stability. Imipenem is unstable at alkaline or acidic pH and the commercially available injection of imipenem with cilastatin sodium for intravenous use is buffered to provide, when reconstituted, a solution with pH 6.5 to 7.5. Licensed product information advises against mixing with other antibacterials.

References.

1. Bigley FP, *et al.* Compatibility of imipenem-cilastatin sodium with commonly used intravenous solutions. *Am J Hosp Pharm* 1986; **43**: 2803–9.
2. Smith GB, *et al.* Stability and kinetics of degradation of imipenem in aqueous solution. *J Pharm Sci* 1990; **79**: 732–40.
3. Pourroy B, *et al.* Incompatibility of imipenem-cilastatin and amoxicillin. *Am J Health-Syst Pharm* 2009; **66:** 1253–4.

Uses and Administration

Imipenem is a carbapenem beta-lactam antibacterial, differing from the penicillins in that the 5-membered ring is unsaturated and contains a carbon rather than a sulfur atom. Since imipenem is metabolised in the kidney by the enzyme dehydropeptidase I it is always given with cilastatin (p. 260.3), an inhibitor of the enzyme; this enhances urinary concentrations of active drug and was found to protect against the nephrotoxicity of high doses of imipenem seen in *animal* studies.

Imipenem is used for the treatment of infections caused by susceptible Gram-positive and Gram-negative organisms; because of its broad spectrum of activity, it may also be given in the treatment of polymicrobial infections or as empirical therapy before the identification of causative organisms. Such infections include infections in immunocompromised patients (with neutropenia), intra-abdominal infections, bone and joint infections, lower-respiratory-tract infections, skin and skin-structure infections, urinary-tract infections and biliary-tract infections; it is not indicated for CNS infections. It may also be used for surgical infection prophylaxis. Imipenem may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Commercial preparations contain imipenem and cilastatin, as the sodium salt, in a ratio of 1 to 1. Doses of the combination are expressed in terms of the amount of anhydrous imipenem. Imipenem is given by intravenous infusion; doses of 250 or 500 mg are infused over 20 to 30 minutes, and doses of 750 mg or 1 g over 40 to 60 minutes. Products for intramuscular use are available in some countries.

The usual intravenous dose is 1 to 2 g daily in divided doses every 6 or 8 hours, depending on the severity of the infection. Usual doses are based on a body-weight of at least 70 kg; proportionate reduction of the dose is recommended for patients weighing less than this. Up to a maximum daily dose of 50 mg/kg (not exceeding 4 g) has been given in life-threatening infections or infections due to less sensitive organisms.

Imipenem may be given intramuscularly in adults with mild to moderate infections in doses of 500 or 750 mg every 12 hours.

The dose of imipenem should be reduced in renal impairment and in those weighing less than 70 kg, see p. 312.1. See also p. 311.3 for details of doses in children.

General reviews.

1. Balfour JA, *et al.* Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 1996; **51:** 99–136.
2. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.
3. Norrby SR. Carbapenems in serious infections: a risk-benefit assessment. *Drug Safety* 2000; **22:** 191–4.
4. Rodloff AC, *et al.* Two decades of imipenem therapy. *J Antimicrob Chemother* 2006; **58:** 916–29.
5. Zhanel GG, *et al.* Comparative review of the carbapenems. *Drugs* 2007; **67:** 1027–52.
6. Lo TS, *et al.* A review of the carbapenems in clinical use and clinical trials. *Recent Pat Antiinfect Drug Discov* 2008; **3:** 123–31.
7. Kattan JN, *et al.* New developments in carbapenems. *Clin Microbiol Infect* 2008; **14:** 1102–11.
8. Masterton RG. The new treatment paradigm and the role of carbapenems. *Int J Antimicrob Agents* 2009; **33:** 105–110.

Administration. For the suggestion that extended infusion of imipenem with cilastatin might increase its efficacy see under Meropenem, p. 323.3.

Administration in children. Imipenem (with cilastatin, see Uses and Administration, above) may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by intravenous infusion; doses less than or equal to 500 mg are infused over 15 to 30 minutes, and doses more than 500 mg over 40 to 60 minutes.

Although not licensed for use in children less than 1 year of age in the UK, the *BNFC* recommends the following doses of imipenem:

- neonates under 7 days: 20 mg/kg every 12 hours
- neonates 7 to 21 days: 20 mg/kg every 8 hours
- neonates 21 to 28 days: 20 mg/kg every 6 hours
- children 1 to 3 months: 20 mg/kg every 6 hours

- children 3 months of age and over: 15 mg/kg (to a maximum dose of 500 mg) every 6 hours; for infection caused by Pseudomonas or other less sensitive organisms, life-threatening infection, or for empirical treatment of infection in febrile patients with neutropenia, 25 mg/kg (to a maximum dose of 1 g) is given every 6 hours

For the treatment of *cystic fibrosis* the *BNFC* recommends that children from 1 month of age may be given 25 mg/kg (to a maximum dose of 1 g) every 6 hours.

It should be noted that these recommendations potentially result in higher doses being given to larger children than would be given to an adult of comparable body-weight if the dose in the latter were reduced for being below 70 kg.

US licensed product information recommends the following doses for neonates and children weighing 1.5 kg or more:

- neonates less than 1 week of age: 25 mg/kg every 12 hours
- neonates 1 to 4 weeks of age: 25 mg/kg every 8 hours
- children 1 to 3 months of age: 25 mg/kg every 6 hours
- children 3 months of age and older: 15 to 25 mg/kg every 6 hours to a maximum daily dose of 2 g for fully susceptible organisms or 4 g for moderately susceptible organisms (mainly for strains of *Pseudomonas aeruginosa*). Up to 90 mg/kg daily has been given to older children with cystic fibrosis.

Administration in renal impairment. Intravenous doses of imipenem are generally reduced in patients with renal impairment (creatinine clearance less than 70 mL/minute per 1.73 m^2) regardless of body-weight. A further proportionate reduction in dose is recommended for patients weighing less than 70 kg. Tables to calculate appropriate reductions depending on body-weight, creatinine clearance, and infection characteristics are available in the licensed product information.

Patients with a creatinine clearance of 5 mL/minute or less should only be given imipenem if haemodialysis is started within 48 hours. Imipenem and cilastatin are cleared from the body by haemodialysis and doses should be given after a dialysis session and then every 12 hours.

For critically ill patients undergoing continuous renal replacement therapy, a loading dose of 1 g, and the following maintenance doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 500 mg every 8 hours
- continuous venovenous haemodialysis (CVVHD): 500 mg every 6 to 8 hours
- continuous venovenous haemodiafiltration (CVVHDF): 500 mg every 6 hours

Information is lacking on the safety or efficacy of the *intramuscular* route in patients with renal impairment.

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects

Imipenem is always given with the enzyme inhibitor cilastatin and thus clinical experience relates to the combination.

Adverse effects with imipenem-cilastatin are similar in general to those with other beta lactams (see Benzylpenicillin, p. 229.2, and Cefalotin, p. 235.2). Hypersensitivity reactions such as rashes, urticaria, eosinophilia, fever, and, rarely, anaphylaxis may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea, tooth or tongue discoloration, and altered taste. Superinfection with non-susceptible organisms such as *Enterococcus faecium*, strains of *Pseudomonas aeruginosa* with acquired resistance, and *Candida* may also occur. Pseudomembranous colitis may develop. Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Increases in liver enzymes and abnormalities in haematological parameters, including a positive Coombs' test, have been noted.

Local reactions such as pain or thrombophlebitis may occur after injection.

Seizures or convulsions have been reported with imipenem-cilastatin, particularly in patients with a history of CNS lesions and/or poor renal function, but sometimes in those without predisposing factors for seizures given recommended doses; it is generally considered to be more epileptogenic than other carbapenems. Mental disturbances and confusion have also been reported.

Cilastatin has protected against the nephrotoxicity seen with high doses of imipenem given experimentally to *animals*. A harmless reddish coloration of urine has been seen in children.

Effects on the nervous system. References.

1. Eng RH, *et al*. Seizure propensity with imipenem. *Arch Intern Med* 1989; **149**: 1881–3.
2. Brown RB, *et al*. Seizure propensity with imipenem. *Arch Intern Med* 1990; **150**: 1551.
3. Job ML, Dretler RH. Seizure activity with imipenem therapy: incidence and risk factors. *DICP Ann Pharmacother* 1990; **24**: 467–9.
4. Leo RJ, Ballow CH. Seizure activity associated with imipenem use: clinical case reports and review of the literature. *DICP Ann Pharmacother* 1991; **25**: 351–4.
5. Duque A, *et al*. Vertigo caused by intravenous imipenem/cilastatin. *DICP Ann Pharmacother* 1991; **25**: 1009.
6. Lucena M, *et al*. Imipenem/cilastatin-associated hiccups. *Ann Pharmacother* 1992; **26:** 1459.
7. Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Safety* 1996; **15:** 87–90.

Hypersensitivity. A retrospective analysis[1] involving a total of 211 patients appeared to show that those with a history of reported or documented penicillin allergy had an 11% incidence of hypersensitivity reactions when treated with a carbapenem antibacterial compared with 2.7% for those without such a history of penicillin allergy. There was no difference in the occurrence of allergic-type reactions between imipenem-cilastatin and meropenem. A study[2] in patients with cell-mediated allergy to beta lactams reported a 5.5% rate of cross-sensitivity with imipenem. Others, however, have reported very low rates of cross-sensitivity to imipenem-cilastatin (less than 1%) in adults[3] and children[4] with documented hypersensitivity to penicillins. Similarly low rates of cross-sensitivity to meropenem have been reported[5,6] in patients with IgE-mediated hypersensitivity to penicillins. Based on available data, the authors of a review[7] recommended that penicillin-allergic patients who require a carbapenem first be skin-tested to the carbapenem; if the results are negative, a carbapenem may be safely given in a graded dose challenge.

1. Prescott WA, *et al*. Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004; **38:** 1102–7.
2. Schiavino D, *et al*. Cross-reactivity and tolerability of imipenem in patients with delayed-type, cell-mediated hypersensitivity to beta-lactams. *Allergy* 2009; **64:** 1644–8.
3. Romano A, *et al*. Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med* 2006; **354:** 2835–7.
4. Atanasković-Marković M, *et al*. Tolerability of imipenem in children with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol* 2009; **124:** 167–9.
5. Romano A, *et al*. Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Ann Intern Med* 2007; **146:** 266–9.
6. Atanasković-Marković M, *et al*. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy* 2008; **63:** 237–40.
7. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother* 2009; **43:** 304–15.

Precautions

Imipenem-cilastatin should not be given to patients known to be hypersensitive to it, and should be given with caution to patients known to be hypersensitive to penicillins, cephalosporins, or other beta lactams because of the possibility of cross-sensitivity (see Hypersensitivity, above).

It should be given with caution to patients with renal impairment, and the dose reduced appropriately. Particular care is necessary in patients with CNS disorders such as epilepsy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imipenem-cilastatin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Seizures have been reported in patients given ganciclovir with imipenem-cilastatin.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to imipenem, and the view that carbapenems should not be used with valproates, see p. 557.2.

Antimicrobial Action

Imipenem is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of activity *in vitro*, including activity against Gram-positive and Gram-negative aerobic and anaerobic organisms, and is stable to hydrolysis by beta-lactamases produced by most bacterial species. Cilastatin, the enzyme inhibitor given with imipenem, appears to have no antibacterial activity.

- Most Gram-positive cocci are sensitive to imipenem including most streptococci, and both penicillinase- and non-penicillinase-producing staphylococci, although MRSA is typically resistant.
  Imipenem generally has good inhibitory (but not bactericidal) activity against *Enterococcus faecalis*, but most *E. faecium* are resistant. *Nocardia*, *Rhodococcus*, *Listeria*, *Bacillus*, and *Corynebacterium* spp. (with the exception of *C. jeikeium* and *C. urealyticum*) are also sensitive.
- Among Gram-negative bacteria, imipenem is active against many of the Enterobacteriaceae including strains that produce extended-spectrum beta-lactamases (ESBLs). Sensitive organisms may include *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. Imipenem is also active against *Burkholderia pseudomallei* and *B. mallei*, *Campylobacter jejuni*, *Haemophilus influenzae*, and *Neisseria* spp., including beta-lactamase-producing strains. *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are resistant to imipenem.
- Many anaerobic bacteria, including *Bacteroides* spp., are sensitive to imipenem, but *Clostridium difficile* is only moderately susceptible.
- Rapidly-growing mycobacteria including *Mycobacterium fortuitum*, *M. chelonae*, *M. abscessus*, and *M. marinum* are variably susceptible to imipenem.
- Imipenem is not active against *Chlamydia trachomatis*, *Mycoplasma* spp., fungi, or viruses.

There have been reports of antagonism between imipenem and other beta lactams *in vitro*. Imipenem and aminoglycosides often act synergistically against some isolates of *Ps. aeruginosa*.

Imipenem is a potent inducer of beta-lactamases of some Gram-negative bacteria, but generally remains stable to them.

Resistance. Imipenem resistance, which generally results from a combination of porin loss with expression of either AmpC-type enzymes or ESBLs, or from the production of carbapenemases (such as the class B metallo-β-lactamases) is increasing among the Enterobacteriaceae. Genes for the expression of carbapenemases tend to be found on plasmids that already contain mutations conferring resistance to other antibacterials such as fluoroquinolones and aminoglycosides; as a result, carbapenemase-producing Enterobacteriaceae are typically extremely drug-resistant and their spread is a cause for significant concern. Carbapenemase production has also contributed to widespread resistance among *Ps. aeruginosa* and *Acinetobacter baumannii*, both of which have historically been susceptible to imipenem.

Resistance. References.

1. Rasmussen BA, Bush K. Carbapenem-hydrolyzing β-lactamases. *Antimicrob Agents Chemother* 1997; **41:** 223–32.
2. Livermore DM. Acquired carbapenemases. *J Antimicrob Chemother* 1997; **39:** 673–6.
3. Modakkas EM, Sanyal SC. Imipenem resistance in aerobic gram-negative bacteria. *J Chemother* 1998; **10:** 97–101.
4. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. *JAMA* 2008; **300:** 2911–3.
5. Zilberberg MD, *et al*. Imipenem resistance of *Pseudomonas* in pneumonia: a systematic literature review. *BMC Pulm Med* 2010; **10:** 45.
6. Cornaglia G, *et al*. Metallo-β-lactamases: a last frontier for β-lactams? *Lancet Infect Dis* 2011; **11:** 381–93.

Pharmacokinetics

Imipenem is not appreciably absorbed from the gastrointestinal tract and is given parenterally.

Imipenem is excreted mainly in the urine by glomerular filtration and, to a lesser extent, by tubular secretion. It undergoes partial metabolism in the kidneys by dehydropeptidase I, an enzyme in the brush border of the renal tubules, to inactive, nephrotoxic metabolites, with only about 5 to 40 or 45% of a dose excreted in the urine as unchanged active drug. Consequently, imipenem is given with cilastatin sodium (p. 260.3), a dehydropeptidase inhibitor, to ensure adequate urinary-imipenem concentrations. While cilastatin may slightly increase serum concentrations of imipenem, half-life is not appreciably affected.

The pharmacokinetics of imipenem and cilastatin are similar and both have plasma half-lives of about 1 hour; half-lives, especially those of cilastatin, may be prolonged in neonates and in patients with renal impairment. Intravenous infusion over 20 to 30 minutes of 500 mg or 1 g of imipenem with cilastatin results in peak plasma-imipenem concentrations of 21 to 58 micrograms/mL and 41 to 83 micrograms/mL respectively. Imipenem is incompletely absorbed after intramuscular injection with a bioavailability of about 60 to 75%, and peak-plasma concentrations occur later and are more prolonged than those after intravenous administration. When imipenem with cilastatin is given in doses of 500 or 750 mg intramuscularly, peak plasma-imipenem concentrations of 10 and 12 micrograms/mL respectively occur at about 2 hours and prolonged absorption results in plasma-imipenem concentrations of above 2 micrograms/mL for 6 to 8 hours. Up to 20% of imipenem and 40% of cilastatin is bound to plasma proteins. Imipenem is widely distributed in body tissues and fluids and crosses the placenta, but concentrations in CSF are only about 1 to 10% of concurrent serum concentrations.

When given with cilastatin about 70% of an intravenous dose of imipenem is recovered unchanged in the urine within 10 hours. A total of 50% of an intramuscular dose is recovered in the urine and urinary concentrations above 10 micrograms/mL are maintained for 12 hours after a dose of 500 or 750 mg. Cilastatin is also excreted mainly in the urine, the majority as unchanged drug and about 12% as *N*-acetyl cilastatin. Both imipenem and cilastatin are removed by haemodialysis.

Less than 1% of imipenem is excreted via the bile in the faeces.

Reviews.
1. Drusano GL. An overview of the pharmacology of imipenem/cilastatin. *J Antimicrob Chemother* 1986; **18** (suppl E): 79–92.
2. Watson ID, *et al*. Clinical pharmacokinetics of enzyme inhibitors in antimicrobial chemotherapy. *Clin Pharmacokinet* 1988; **15**: 133–64.
3. Mouton JW, *et al*. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet* 2000; **39:** 185–201.

The elderly. References.
1. Finch RG, *et al*. Pharmacokinetic studies of imipenem/cilastatin in elderly patients. *J Antimicrob Chemother* 1986; **18** (suppl E): 103–7.

Hepatic impairment. References.
1. Rolando N, *et al*. The penetration of imipenem/cilastatin into ascitic fluid in patients with chronic liver disease. *J Antimicrob Chemother* 1994; **33:** 163–7.

Pregnancy and the neonate. References.
1. Reed MD, *et al*. Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990; **34:** 1172–7.
2. Heikkilä A, *et al*. Pharmacokinetics and transplacental passage of imipenem during pregnancy. *Antimicrob Agents Chemother* 1992; **36:** 2652–5.

Renal impairment. References.
1. Verbist L, *et al*. Pharmacokinetics and tolerance after repeated doses of imipenem/cilastatin in patients with severe renal failure. *J Antimicrob Chemother* 1986; **18** (suppl E): 115–20.
2. Alarabi AA, *et al*. Pharmacokinetics of intravenous imipenem/cilastatin during intermittent haemofiltration. *J Antimicrob Chemother* 1990; **26:** 91–8.
3. Pietroski NA, *et al*. Steady-state pharmacokinetics of intramuscular imipenem-cilastatin in elderly patients with various degrees of renal function. *Antimicrob Agents Chemother* 1991; **35:** 972–5.
4. Konishi K, *et al*. Removal of imipenem and cilastatin by hemodialysis in patients with end-stage renal failure. *Antimicrob Agents Chemother* 1991; **35:** 1616–20.
5. Chan CY, *et al*. Pharmacokinetics of parenteral imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1991; **27:** 225–32.
6. Tegeder I, *et al*. Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 1997; **41:** 2640–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Dixabiox; Imipecil; Imistatin; Klonam; Zienam; ***Austral.***: Primaxin; ***Austria***: Zienam; ***Belg.***: Tienam; ***Braz.***: Tienam; Tiepem; ***Canad.***: Primaxin; ***Chile***: Inem; Tienam; ***China***: Bacqure (齐佩能); Prepenem (谱能); Tienam (泰能); ***Cz.***: Cilanem; Imecitin; Tienam; ***Fin.***: Tienam; ***Fr.***: Tienam; ***Ger.***: Zienam; ***Gr.***: Imicil; Nimedine; Primagal; Primalix; Primaxin; ***Hong Kong***: Prepenem; Tienam; ***Hung.***: Cilanem; Tienam; ***India***: Cilanem; Cilaspene; Cimispect; Flaminim; I-Nem; Ime-Cila; Imelastin; Imi-Cila; Iminem; Imitop; Lastinem; ***Indon.***: Elastyn; Pelastin; Tienam; Timipen; ***Israel***: Tienam; ***Ital.***: Imipem; Tenacid; Tienam; ***Malaysia***: Bacqure; Tienam; ***Mex.***: Arzomeba; Iminen†; Lemibet†; Opostibac; Tienam; ***Neth.***: Tienam; ***Norw.***: Tienam; ***NZ***: Primaxin; ***Philipp.***: Anipen; Penam; Plastin; Tienam; ***Pol.***: Ransetron; Tienam; ***Port.***: Tienam; ***Rus.***: Cilaspen (ЦИЛАСПЕН); Grimipenem (Гримипенем); Tienam (Тиенам); ***S.Afr.***: Tienam; ***Singapore***: Tienam; ***Spain***: Tienam; ***Swed.***: Tienam; ***Switz.***: Tienam; ***Thai.***: Bacqure; Cilapenem; Prepenem; Tienam; ***Turk.***: Silanem; Tienam; ***UAE***: Maxinem; ***UK***: Primaxin; ***Ukr.***: Lastinem (Ластинем)†; Sinerpen (Синерпен); Tienam (Тиенам); ***USA***: Primaxin; ***Venez.***: Zienam.

Pharmacopoeial Preparations
USP 36: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Isepamicin *(BAN, USAN, rINN)*

HAPA-B; Isepamicina; Isépamicine; Isepamicinum; Sch-21420; Изепамицин.

4-*O*-(6-Amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-(3-amino-L-lactoyl)-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine; 1*N*-(*S*-3-Amino-2-hydroxypropionyl)-gentamicin B.

$C_{22}H_{43}N_5O_{12}$=569.6

CAS — 58152-03-7; 67479-40-7.

ATC — J01GB11.

ATC Vet — QJ01GB11.

UNII — G7K224460P.

Isepamicin Sulfate *(BANM, rINNM)*

Isepamicin Sulphate; Isepamicina, sulfato de; Isépamicine, Sulfate d'; Isepamicini Sulfas; Isepamisin Sülfat; Sulfato de isepamicina; Изепамицина Сульфат.

$C_{22}H_{43}N_5O_{12}.2H_2SO_4$=765.8

CAS — 68000-78-2.

ATC — J01GB11.

ATC Vet — QJ01GB11.

UNII — U606Y00EWE.

Pharmacopoeias. In *Jpn*, which specifies a variable amount of H_2SO_4.

Profile

Isepamicin is a semisynthetic aminoglycoside antibacterial with actions and uses similar to those of gentamicin (p. 304.2). It is reported not to be degraded by many of the enzymes responsible for aminoglycoside resistance. Isepamicin sulfate has been given by intramuscular injection or intravenous infusion in a dose of up to 15 mg/kg daily in 2 divided doses. Once-daily dosage may be possible in selected patients. Dosage should be adjusted based on serum-isepamicin concentration monitoring. In adults, the total daily dose should not exceed 1.5 g.

References.
1. Tod M, *et al*. Clinical pharmacokinetics and pharmacodynamics of isepamicin. *Clin Pharmacokinet* 2000; **38:** 205–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Exacin (依克沙); ***Hong Kong***: Isepacin†; ***Jpn***: Exacin; ***Turk.***: Isepacine.

Isoniazid *(BAN, pINN)*

INAH; INH; Isoniatsidi; Isoniazida; Isoniazide; Isoniazidum; Isonicotinic Acid Hydrazide; Isonicotinylhydrazide; Isonicotinylhydrazine; Izoniazid; Izoniazidas; Izoniazyd; Tubazid; Изониазид.

Isonicotinohydrazide.

$C_6H_7N_3O$=137.1

CAS — 54-85-3.

ATC — J04AC01.

ATC Vet — QJ04AC01.

UNII — V83O1VOZ8L.

NOTE. The name Isopyrin, which has been applied to isoniazid, has also been applied to ramifenazone.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Isoniazid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 6.0 to 8.0.

USP 36: (Isoniazid). Colourless, or white, odourless crystals, or white crystalline powder. Soluble 1 in 8 of water and 1 in 50 of alcohol; slightly soluble in chloroform; very slightly soluble in ether. pH of a 10% solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. It has been recommended that sugars such as glucose, fructose, and sucrose should not be used in isoniazid syrup preparations because the absorption of the drug was impaired by the formation of a condensation product.[1] Sorbitol may be a suitable substitute if necessary.
1. Rao KVN, *et al*. Inactivation of isoniazid by condensation in a syrup preparation. *Bull WHO* 1971; **45:** 625–32.

Sterilisation. Solutions of isoniazid should be sterilised by autoclaving.

Uses and Administration

Isoniazid is a hydrazide derivative that is the mainstay of the primary treatment of pulmonary and extrapulmonary tuberculosis (p. 210.2). It is used with other antituberculous drugs usually in regimens including rifampicin, ethambutol, and pyrazinamide. Isoniazid is also used in high-risk subjects for the prophylaxis of tuberculosis.

Isoniazid is given in the initial and continuation phases of short-course tuberculosis regimens. The usual oral adult dose is 5 mg/kg, to a maximum of 300 mg, daily on an empty stomach. For intermittent therapy, WHO recommends 10 mg/kg three times a week, to a maximum of 900 mg per dose, while the recommended dose in the UK is 15 mg/kg three times a week and in the USA 15 mg/kg once weekly or two or three times a week is recommended. Caution is required in patients with hepatic impairment and doses may need to be reduced in those with severe renal impairment.

Similar doses to those used orally may be given by intramuscular injection when isoniazid cannot be taken orally; it may also be given by intravenous injection. Isoniazid has also been given intrathecally and intrapleurally.

In the treatment of latent tuberculosis, daily doses of 300 mg for 6 months are recommended by WHO and in the UK, while in the USA the preferred treatment regimen is oral isoniazid 5 mg/kg (to a maximum of 300 mg) daily or 15 mg/kg (to a maximum of 900 mg) twice weekly for 9 months. As an alternative to such regimens, isoniazid may be given with rifampicin for 3 months.

For details of doses in children, see p. 313.3.

Isoniazid aminosalicylate (pasiniazid) and isoniazid sodium glucuronate have also been used in the treatment of tuberculosis.

Fixed-dose combination products containing 2, 3, or 4 drugs have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing isoniazid in various combinations with rifampicin, ethambutol, and pyrazinamide are available in some countries.

References.
1. Anonymous. Isoniazid. *Tuberculosis (Edinb)* 2008; **88:** 112–6.

Administration in children. A study[1] in 56 hospitalised children (median age of 3.22 years and interquartile range of 1.58 to 5.38 years) given isoniazid daily as part of their antituberculosis treatment found that peak concentrations of isoniazid were less than 3 mg/L in 70% of children prescribed a dose of 4 to 6 mg/kg, while those given a dose of 8 to 12 mg/kg had peak concentrations similar to those in adults taking 300 mg of isoniazid daily. The authors concluded that younger children need higher doses of isoniazid per kilogram of body weight to achieve isoniazid concentrations similar to those in adults and recommended a daily dose of 8 to 12 mg/kg.

WHO now therefore recommends[2,3] isoniazid 10 mg/kg daily (replacing an earlier recommendation[4] for 5 mg/kg daily). Specific guidance[3] has also been issued for the use of fixed-dose combinations of isoniazid 30, 60 or 150 mg plus rifampicin (with or without pyrazinamide and ethambutol) to achieve this in children weighing between 5 and 30 kg. Similarly, for the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP)[5] suggests an oral dose of isoniazid 10 to 15 mg/kg daily or 20 to 30 mg/kg twice weekly, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests oral doses of 10 mg/kg once daily or 15 mg/kg three times a week.

For the treatment of *latent* tuberculosis the American Thoracic Society[6] suggests oral doses of 10 to 20 mg/kg (maximum 300 mg) daily or 20 to 40 mg/kg (maximum 900 mg) twice weekly for 9 months. Similar doses have been suggested by the AAP. For children 1 month and older the *BNFC* suggests a dose of 10 mg/kg once daily for 6 months when used alone or for 3 months when given with rifampicin; WHO recommends 5 mg/kg once daily for 6 months.

For daily dosing regimens the maximum oral dose of isoniazid is 300 mg and for intermittent regimens the maximum dose is 900 mg per dose.

1. McIlleron H, *et al*. Isoniazid plasma concentrations in a cohort of South African children with tuberculosis: implications for international pediatric dosing guidelines. *Clin Infect Dis* 2009; **48:** 1547–53.
2. WHO. *WHO model formulary for children: based on the second model list of essential medicines for children 2009*. Geneva: WHO, 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 21/01/11)
3. WHO. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf (accessed 19/01/11)
4. WHO. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf (accessed 07/06/10)
5. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
6. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; **49:** 1–51. Also published in *Am J RespirCrit Care Med* 2000; **111:** S221–S247. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm (accessed 07/06/10)

Adverse Effects

Isoniazid is generally well tolerated at currently recommended doses. However, patients who are slow acetylators of isoniazid and those with advanced HIV disease appear to have a higher incidence of some adverse effects. Also patients whose nutrition is poor are at risk of peripheral neuritis which is one of the commonest adverse effects of isoniazid. Other neurological adverse effects include psychotic reactions and convulsions. Pyridoxine may be given to prevent or treat these adverse effects. Optic neuritis has also been reported.

Transient increases in liver enzymes occur in 10 to 20% of patients during the first few months of treatment and usually return to normal despite continued treatment. Symptomatic hepatitis occurs in about 0.1 to 0.15% of patients given isoniazid as monotherapy, but this can increase with age, regular alcohol consumption, and in those with chronic liver disease. The influence of acetylator status is uncertain. Elevated liver enzymes associated with clinical signs of hepatitis such as nausea and vomiting, or fatigue may indicate hepatic damage; in these circumstances, isoniazid should be stopped pending evaluation and should only be reintroduced cautiously once hepatic function has recovered. Fatalities have occurred due to liver necrosis.

Haematological effects reported on use of isoniazid include various anaemias, agranulocytosis, thrombocytopenia, and eosinophilia.

Hypersensitivity reactions occur infrequently and include skin eruptions (including erythema multiforme), fever, and vasculitis.

Other adverse effects include nausea, vomiting, dry mouth, constipation, pellagra, purpura, hyperglycaemia, lupus-like syndrome, vertigo, hyperreflexia, urinary retention, and gynaecomastia.

Symptoms of overdosage include slurred speech, metabolic acidosis, hallucinations, hyperglycaemia, respiratory distress or tachypnoea, convulsions, and coma; fatalities can occur.

Carcinogenicity. Concern about the carcinogenicity of isoniazid arose in the 1970s when an increased risk of bladder cancer in patients treated with isoniazid was reported.[1-3] However, no evidence to support a carcinogenic effect of isoniazid was found in more than 25 000 patients followed up for 9 to 14 years in studies organised by the USA Public Health Service[4] and in 3842 patients followed up for 16 to 24 years in the UK.[5]

1. Miller CT. Isoniazid and cancer risks. *JAMA* 1974; **230:** 1254.
2. Kerr WK, Chipman ML. The incidence of cancer of bladder and other sites after INH therapy. *Am J Epidemiol* 1976; **104:** 335–6.
3. Miller CT, *et al.* Relative importance of risk factors in bladder carcinogenesis. *J Chron Dis* 1978; **31:** 51–6.
4. Glassroth JL, *et al.* An assessment of the possible association of isoniazid with human cancer deaths. *Am Rev Respir Dis* 1977; **116:** 1065–74.
5. Stott H, *et al.* An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. *Tubercle* 1976; **57:** 1–15.

Effects on the blood. In addition to the effects mentioned on p. 311.3, rare reports of adverse effects of isoniazid on the blood include bleeding associated with acquired inhibition of fibrin stabilisation[1] or of factor XIII,[2] and red cell aplasia.[3-5]

For a reference to neutropenia, see Effects on the Blood, under Ethambutol Hydrochloride, p. 296.2.

1. Otis PT, *et al.* An acquired inhibitor of fibrin stabilization associated with isoniazid therapy: clinical and biochemical observations. *Blood* 1974; **44:** 771–81.
2. Krumdieck R, *et al.* Hemorrhagic disorder due to an isoniazid-associated acquired factor XIII inhibitor in a patient with Waldenström's macroglobulinemia. *Am J Med* 1991; **90:** 639–45.
3. Claiborne RA, Dutt AK. Isoniazid-induced pure red cell aplasia. *Am Rev Respir Dis* 1985; **131:** 947–9.
4. Lewis CR, Manoharan A. Pure red cell hypoplasia secondary to isoniazid. *Postgrad Med J* 1987; **63:** 309–10.
5. Veale KS, *et al.* Pure red cell aplasia and hepatitis in a child receiving isoniazid therapy. *J Pediatr* 1992; **120:** 146–8.

Effects on the CNS. In addition to the peripheral neuropathy that is a well-established adverse effect of isoniazid, effects on the CNS have also been reported, including ataxia and cerebellar toxicity,[1,2] psychotic reactions[3-5] (generally characterised by delusions, hallucinations, and confusion), and seizures, particularly after overdosage.[6] Encephalopathy has been reported in dialysis patients.[7,8] Encephalopathy may also be a symptom of pellagra, which may be associated with isoniazid treatment.[9]

1. Blumberg EA, Gil RA. Cerebellar syndrome caused by isoniazid. *DICP Ann Pharmacother* 1990; **24:** 829–31.
2. Lewin PK, McGreal D. Isoniazid toxicity with cerebellar ataxia in a child. *CMAJ* 1993; **148:** 49–50.
3. Pallone KA, *et al.* Isoniazid-associated psychosis: case report and review of the literature. *Ann Pharmacother* 1993; **27:** 167–70.
4. Alao AO, Yolles JC. Isoniazid-induced psychosis. *Ann Pharmacother* 1998; **32:** 889–91.
5. Witkowski AE, *et al.* Isoniazid-associated psychosis. *Gen Hosp Psychiatry* 2007; **29:** 85–6.
6. Shah BR, *et al.* Acute isoniazid neurotoxicity in an urban hospital. *Pediatrics* 1995; **95:** 700–4.
7. Cheung WC, *et al.* Isoniazid induced encephalopathy in dialysis patients. *Tubercle Lung Dis* 1993; **74:** 136–9.
8. Wang HY, *et al.* Encephalopathy caused by isoniazid in a patient with end stage renal disease with extrapulmonary tuberculosis. *Ren Fail* 2003; **25:** 135–8.
9. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48:** 628–34.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with isoniazid and other first-line antituberculous drugs, but sometimes **hepatotoxicity** may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Isoniazid and pyrazinamide are thought to have a greater potential for hepatotoxicity than rifampicin.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1] Speculation that fast acetylators of isoniazid could be at increased risk of hepatotoxicity due to production of a hepatotoxic hydrazine metabolite has not been supported;[2] in fact, slow acetylators have generally been found to have a higher risk than fast acetylators.[3,4] This could reflect a reduced rate of subsequent metabolism to non-toxic compounds. In addition, concentrations of hydrazine in the blood have not been found to correlate with acetylator status.[5,6]

A multicentre study[7] considered the **incidence** of hepatotoxicity from a short-term regimen of daily isoniazid, rifampicin, and pyrazinamide for 8 weeks in the initial phase followed by daily isoniazid and rifampicin for 16 weeks in the continuing phase. Analysis from 617 patients showed an incidence of hepatotoxic reactions of 1.6%; the incidence of elevated aspartate aminotransferase was 23.2%. In the same study, 445 patients on a 9-month regimen of daily isoniazid and rifampicin had a 1.2% incidence of hepatotoxicity and 27.1% incidence of elevated liver enzymes. A similar incidence of hepatitis of 1.4% among 350 patients on a 9-month regimen of rifampicin and isoniazid has also been reported.[8] A retrospective analysis[9] of 430 children on isoniazid and rifampicin revealed hepatotoxic reactions in 3.3%, the highest incidence being in children with severe disease.

The incidence of hepatotoxicity is lower in patients receiving isoniazid for *prophylaxis* than in those receiving treatment for active disease. During a 7-year period[10] an incidence of 0.15% was recorded in 11 141 patients who started prophylactic therapy, whereas it was 1.25% amongst 1427 patients receiving treatment. A similar study[11] in a slightly older patient population reported an incidence of 0.56%. Between 2004 and 2008, the CDC received 17 reports of severe liver injury (leading to hospitalisation or death) in patients receiving isoniazid for treatment of latent tuberculosis infection;[12] injury occurred mainly between the second and ninth month of therapy. Of these 17 patients, 5 subsequently required liver transplantation, and 5 died (including 1 transplant recipient). No cases of hepatotoxicity were reported in 556 HIV-infected patients taking a 3-month prophylactic regimen of isoniazid and rifampicin for latent tuberculosis.[13] A meta-analysis[14] concluded that daily isoniazid and rifampicin for 3 months appeared to be as safe as treatment with isoniazid alone for 6 to 12 months.

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[15] for initial measurement of liver function in all patients and regular **monitoring** in patients with known chronic liver disease. Details are given concerning the response to deteriorating liver function depending on the clinical situation, and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced in the USA.[16,17]

For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Rifampicin, p. 354.1 and Pyrazinamide, p. 347.3.

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11:** 699–707.
2. Gurumurthy P, *et al.* Lack of relationship between hepatic toxicity and acetylator phenotype in three thousand South Indian patients during treatment with isoniazid for tuberculosis. *Am Rev Respir Dis* 1984; **129:** 58–61.
3. Dickinson DS, *et al.* Risk factors for isoniazid (INH)-induced liver dysfunction. *J Clin Gastroenterol* 1981; **3:** 271–9.
4. Pande JN, *et al.* Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; **51:** 132–6.
5. Gent WL, *et al.* Factors in hydrazine formation from isoniazid by paediatric and adult tuberculosis patients. *Eur J Clin Pharmacol* 1992; **43:** 131–6.
6. Donald PR, *et al.* Hydrazine production in children receiving isoniazid for the treatment of tuberculous meningitis. *Ann Pharmacother* 1994; **28:** 1340–3.
7. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
8. Dutt AK, *et al.* Short-course chemotherapy for extrapulmonary tuberculosis: nine years' experience. *Ann Intern Med* 1986; **104:** 7–12.
9. O'Brien RJ, *et al.* Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. *Pediatrics* 1983; **72:** 491–9.
10. Nolan CM, *et al.* Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; **281:** 1014–18.
11. Fountain FF, *et al.* Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest* 2005; **128:** 116–23.
12. CDC. Severe isoniazid-associated liver injuries among persons being treated for latent tuberculosis infection - United States, 2004-2008. *MMWR* 2010; **59:** 224–9. Also available at: http://www.cdc.gov/mmwr/pdf/wk/mm5908.pdf (accessed 07/06/10)
13. Whalen CC, *et al.* A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997; **337:** 801–8.
14. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005; **40:** 670–6.
15. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
16. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
17. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 16/07/10)

Effects on the pancreas. Cases of isoniazid-induced pancreatitis have been rarely reported;[1-4] pancreatitis resolved in these patients once treatment with isoniazid was stopped, and recurred on rechallenge. It is recommended if isoniazid-induced pancreatitis is proven that the drug should be permanently avoided.[4] Chronic pancreatic insufficiency, after an acute episode, was reported in a patient given isoniazid, rifampicin, ethambutol, and pyrazinamide and was considered to be a drug hypersensitivity reaction.[5]

1. Chan KL, *et al.* Recurrent acute pancreatitis induced by isoniazid. *Tubercle Lung Dis* 1994; **75:** 383–5.
2. Rabassa AA, *et al.* Isoniazid-induced acute pancreatitis. *Ann Intern Med* 1994; **121:** 433–4.
3. Stephenson I, *et al.* Acute pancreatitis induced by isoniazid in the treatment of tuberculosis. *Am J Gastroenterol* 2001; **96:** 2271–2.
4. Chow KM, *et al.* Recurrent acute pancreatitis after isoniazid. *Neth J Med* 2004; **62:** 172–4.
5. Liu BA, *et al.* Pancreatic insufficiency due to antituberculous therapy. *Ann Pharmacother* 1997; **31:** 724–6.

Effects on the skin and hair. Isoniazid causes cutaneous drug reactions in less than 1% of patients.[1,2] These reactions include urticaria, purpura, acneform syndrome,[3] a lupus erythematosus-like syndrome[4] (see p. 314.3), and exfoliative dermatitis.[5] Pellagra is also associated with isoniazid.[6] Isoniazid was considered the most likely cause of alopecia in 5 patients receiving antituberculosis regimens which also included rifampicin, ethambutol, and pyrazinamide.[7]

1. Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976; **235:** 918–23.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.
3. Thorne N. Skin reactions to systemic drug therapy. *Practitioner* 1973; **211:** 606–13.
4. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; **136:** 508–11.
5. Rosin MA, King LE. Isoniazid-induced exfoliative dermatitis. *South Med J* 1982; **75:** 81.
6. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48:** 628–34.
7. FitzGerald JM, *et al.* Alopecia side-effect of antituberculosis drugs. *Lancet* 1996; **347:** 472–3.

Lupus. Antinuclear antibodies have been reported to occur in up to 22% of patients receiving isoniazid; however, patients are usually asymptomatic and overt lupoid syndrome is rare.[1,2] The incidence of antibody induction has been reported to be higher in slow acetylators than in fast acetylators,[3] but the difference was not statistically significant and acetylator phenotype is not considered an important determinant of the risk of isoniazid-induced lupus.[1,4,5] The syndrome appeared to be due to isoniazid itself rather than its metabolite acetylisoniazid.[6]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; **123:** 460–3.
2. Siddiqui MA, Khan IA. Isoniazid-induced lupus erythematosus presenting with cardiac tamponade. *Am J Ther* 2002; **9:** 163–5.
3. Alarcon-Segovia D, *et al.* Isoniazid acetylation rate and development of antinuclear antibodies upon isoniazid treatment. *Arthritis Rheum* 1971; **14:** 748–52.
4. Clark DWJ. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs* 1985; **29:** 342–75.
5. Rychlik-Sych M, *et al.* Acetylation genotype and phenotype in patients with systemic lupus erythematosus. *Pharmacol Rep* 2006; **58:** 22–9.
6. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; **ii:** 422–4.

Treatment of Adverse Effects

Pyridoxine hydrochloride 10 mg daily is usually recommended for prophylaxis of peripheral neuritis associated with isoniazid although up to 50 mg daily may be used. A dose of 50 mg three times daily may be given for treatment of peripheral neuritis if it develops. In children the *BNFC* recommends the following oral doses according to age:

- 1 month to 12 years: 5 to 10 mg daily (prophylaxis), or 10 to 20 mg 2 or 3 times daily (treatment)
- 12 to 18 years: 10 mg daily (prophylaxis) or 30 to 50 mg 2 or 3 times daily (treatment)

Nicotinamide has been given, usually with pyridoxine, to patients who develop pellagra.

Isoniazid doses of 1.5 g or more are potentially toxic and doses of 10 to 15 g may be fatal without appropriate treatment. Treatment of overdosage is symptomatic and supportive and consists of activated charcoal, correction of metabolic acidosis, and control of convulsions. In addition to a benzodiazepine, large doses of pyridoxine may be needed intravenously for control of convulsions (see Overdose, p. 315.1). Isoniazid is removed by haemodialysis or peritoneal dialysis.

Overdosage. In adults with isoniazid-induced convulsions the UK National Poisons Information Service recommends management with an initial intravenous dose of diazepam or lorazepam; in resistant cases, patients should also be given an intravenous dose of pyridoxine hydrochloride equivalent to the estimated amount of isoniazid ingested (to a maximum of 5 g); this maximum dose should also be used when the amount of isoniazid ingested is unknown. For children the recommended dose of pyridoxine hydrochloride is 70 mg/kg (to a maximum of 5 g). If convulsions continue or recur, this dose may be repeated. Oral activated charcoal (50 g for adults and 1 g/kg for children) may be considered if this is given within 1 hour of an ingestion of isoniazid of more than 20 mg/kg.

Pyridoxine deficiency. Pyridoxine deficiency associated with isoniazid in doses of 5 mg/kg daily is uncommon. Patients at risk of developing pyridoxine deficiency include those with diabetes, uraemia, alcoholism, HIV infection, and malnutrition.[1,2] Supplementation with pyridoxine should be considered for these at-risk groups as well as for pregnant women and patients with seizure disorders.[1] For the prophylaxis of peripheral neuritis it is common practice to give pyridoxine 10 mg daily, although 6 mg daily might be sufficient.[3] However, in one patient a dose of pyridoxine 10 mg daily failed to prevent psychosis, the symptoms of which only resolved after stopping isoniazid and increasing the pyridoxine dosage to 100 mg daily.[4]

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. Snider DE. Pyridoxine supplementation during isoniazid therapy. *Tubercle* 1980; **61:** 191–6.
4. Chan TYK. Pyridoxine ineffective in isoniazid-induced psychosis. *Ann Pharmacother* 1999; **33:** 1123–4.

Precautions

Isoniazid should be used with caution in patients with convulsive disorders, a history of psychosis, or hepatic or renal impairment. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, usually in a dose of 10 mg daily, although up to 50 mg daily may be used. If symptoms of hepatitis develop, such as malaise, fatigue, anorexia, and nausea, isoniazid should be stopped pending evaluation.

Liver function should be checked before treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease. Regular monitoring of liver function is recommended in patients with pre-existing liver disease, and the British Thoracic Society has recommended that isoniazid treatment be suspended if serum aminotransferase concentrations are elevated to more than 5 times the normal upper limit or the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. Careful monitoring should be considered for black and Hispanic women, in whom there may be an increased risk of fatal hepatitis.

When visual symptoms occur during isoniazid treatment periodic eye examinations have been suggested.

Breast feeding. Peak concentrations of isoniazid in breast milk were 6 micrograms/mL after a dose of 5 mg/kg and were 16.6 micrograms/mL after a 300-mg dose.[1] However, drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. Adverse effects on breast-fed infants have not been reported and the last available guidance from the American Academy of Pediatrics thus considered isoniazid to be usually compatible with breast feeding,[2] although such infants should be monitored for toxic reactions.

1. Snider D, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144:** 589–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isoniazid as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Pregnancy and the neonate. In a review[1] of antituberculous treatment in pregnant patients it was reported that over 95% of 1480 pregnancies in which isoniazid had been given resulted in a normal term infant. Slightly more than 1% of the infants/fetuses were abnormal and many of these abnormalities were CNS related. Isoniazid is therefore recognised as being suitable for use in regimens for the **treatment** of tuberculosis in pregnant patients.[2,3] Pyridoxine supplementation is recommended[2] (see Pyridoxine Deficiency under Treatment of Adverse Effects, above). **Preventive therapy** with isoniazid is generally delayed until after delivery unless other risk factors are present.

1. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122:** 65–79.
2. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)

Interactions

The risk of hepatotoxicity may be increased in patients receiving isoniazid with a rifamycin or other potentially hepatotoxic drugs, including alcohol.

Isoniazid can inhibit the hepatic metabolism of some drugs, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine (p. 516.2), ethosuximide (p. 521.2), primidone, and phenytoin (p. 542.3), the benzodiazepines diazepam and triazolam (p. 1068.2), chlorzoxazone (p. 2023.1), theophylline (p. 1234.1), and disulfiram. The metabolism of enflurane (see Effects on the Kidneys, p. 1903.1) may be increased in patients receiving isoniazid, resulting in potentially nephrotoxic levels of fluoride. Isoniazid has been associated with increased concentrations and enhanced effects or toxicity of clofazimine (p. 274.2), cycloserine (p. 281.1), and warfarin (p. 1531.1).

For interactions affecting isoniazid, see below.

Alcohol. The metabolism of isoniazid may be increased in chronic alcoholics: this may lead to reduced isoniazid efficacy.[1] These patients may also be at increased risk of developing isoniazid-induced peripheral neuropathies and hepatic damage (see Precautions, above).

1. Anonymous. Interaction of drugs with alcohol. *Med Lett Drugs Ther* 1981; **23:** 33–4.

Antacids. Oral absorption of isoniazid is reduced by aluminium-containing antacids; isoniazid should be given at least 1 hour before the antacid.[1]

1. Hurwitz A, Schluzman DL. Effects of antacids on gastrointestinal absorption of isoniazid in rat and man. *Am Rev Respir Dis* 1974; **109:** 41–7.

Antifungals. Serum concentrations of isoniazid were below the limits of detection in a patient also receiving rifampicin and *ketoconazole*.[1] For the effect of isoniazid on ketoconazole, see p. 587.1.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; **109:** 844–5. Correction. *ibid.* 1989; **111:** 96.

Antivirals. The clearance of isoniazid was approximately doubled when *zalcitabine* was given to 12 HIV-positive patients.[1] In addition, care is needed since *stavudine* and zalcitabine may also cause peripheral neuropathy; use of isoniazid with stavudine has been reported to increase its incidence.[2]

1. Lee BL, *et al.* The effect of zalcitabine on the pharmacokinetics of isoniazid in HIV-infected patients. *Intersci Conf Antimicrob Agents Chemother* 1994; **34:** 3(A4).
2. Breen RAM, *et al.* Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals. *AIDS* 2000; **14:** 615.

Corticosteroids. Giving *prednisolone* 20 mg to 13 slow acetylators and 13 fast acetylators receiving isoniazid 10 mg/kg reduced plasma concentrations of isoniazid by 25 and 40% respectively.[1] Renal clearance of isoniazid was also enhanced in both acetylator phenotypes and the rate of acetylation increased in slow acetylators only.[1]

The clinical significance of this effect is not established.

1. Sarma GR, *et al.* Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother* 1980; **18:** 661–6.

Food. Palpitations, headache, conjunctival irritation, severe flushing, tachycardia, tachypnoea, and sweating have been reported in patients taking isoniazid after ingestion of *cheese*,[1,2] *red wine*,[1] and some *fish*.[3,4] Accumulation of tyramine[1] or histamine[3] has been proposed as the cause of these food-related reactions, and they could be mistaken for anaphylaxis.[4]

1. Toutoungi M, *et al.* Cheese, wine, and isoniazid. *Lancet* 1985; **ii:** 671.
2. Carvalho ACC, *et al.* Reaction to cheese during TB treatment. *Thorax* 2004; **59:** 635.
3. Kottegoda SR. Cheese, wine and isoniazid. *Lancet* 1985; **ii:** 1074.
4. O'Sullivan TL. Drug-food interaction with isoniazid resembling anaphylaxis. *Ann Pharmacother* 1997; **31:** 928.

Opioid analgesics. For a report of an interaction between isoniazid and *pethidine*, attributed to isoniazid's inhibitory actions on monoamine oxidase, see p. 123.2.

Antimicrobial Action

Isoniazid is highly active against *Mycobacterium tuberculosis* and may have activity against some strains of other mycobacteria including *M. kansasii*.

Although it is rapidly bactericidal against actively dividing *M. tuberculosis*, it is considered to be only bacteriostatic against semi-dormant organisms and has less sterilising activity than rifampicin or pyrazinamide.

Resistance of *M. tuberculosis* to isoniazid develops rapidly if it is used alone in the *treatment* of clinical infection, and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by the combination of isoniazid with other antimycobacterials which appears to be highly effective in preventing emergence of resistance to other antituberculous drugs. Resistance does not appear to be a problem when isoniazid is used alone in *prophylaxis*, probably because the bacillary load is low.

Mycobacterium avium complex. Synergistic activity of isoniazid plus streptomycin and, to a lesser degree, isoniazid plus clofazimine, against *Mycobacterium avium* complex (MAC) has been shown *in vitro* and *in vivo*.[1]

1. Reddy MV, *et al.* In vitro and in vivo synergistic effect of isoniazid with streptomycin and clofazimine against Mycobacterium avium complex (MAC). *Tubercle Lung Dis* 1994; **75:** 208–12.

Pharmacokinetics

Isoniazid is readily absorbed from the gastrointestinal tract and after intramuscular injection. Peak concentrations of about 3 to 7 micrograms/mL appear in blood 1 to 2 hours after an oral fasting dose of 300 mg. The rate and extent of absorption of isoniazid is reduced by food. Isoniazid is not considered to be bound appreciably to plasma proteins and distributes into all body tissues and fluids, including the CSF. It appears in fetal blood if given during pregnancy (see p. 316.1), and is distributed into breast milk (see under Precautions, above).

The plasma half-life for isoniazid ranges from about 1 to 6 hours, with shorter half-lives in fast acetylators. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by *N*-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised isoniazid is conjugated to hydrazones. The metabolites of isoniazid have no tuberculostatic activity and, apart from possibly monoacetylhydrazine, they are also less toxic. The rate of acetylation of isoniazid and monoacetylhydrazine is genetically determined and there is a bimodal distribution of persons who acetylate them either slowly or rapidly. Ethnic groups differ in their proportions of these genetic phenotypes. When isoniazid is given daily or 2 or 3 times weekly, clinical efficacy is not influenced by acetylator status.

In patients with normal renal function, over 75% of a dose appears in the urine in 24 hours, mainly as metabolites. Small amounts of drug are also excreted in the faeces. Isoniazid is removed by haemodialysis.

Distribution. Therapeutic concentrations of isoniazid have been detected in CSF[1,2] and synovial fluid[3] several hours after an oral dose. Diffusion into saliva is good and it has been suggested that salivary concentrations could be used in place of serum concentrations in pharmacokinetic studies.[4]

1. Forgan-Smith R, *et al.* Pyrazinamide and other drugs in tuberculous meningitis. *Lancet* 1973; **ii:** 374.

2. Miceli JN, *et al.* Isoniazid (INH) kinetics in children. *Fedn Proc* 1983; **42:** 1140.
3. Mouries D, *et al.* Passage articulaire de l'isoniazide et de l'éthambutol: deux observations de synovite tuberculeuse du genou. *Nouv Presse Med* 1975; **4:** 2734.
4. Gurumurthy P, *et al.* Salivary levels of isoniazid and rifampicin in tuberculous patients. *Tubercle* 1990; **71:** 29–33.

HIV-infected patients. Malabsorption of isoniazid and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p. 356.1.

Pregnancy. Isoniazid crosses the placenta and average fetal concentrations of 61.5 and 72.8% of maternal serum or plasma concentration have been reported.[1] The half-life of isoniazid may be prolonged in neonates.[1]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Isoniac; Nicotibina; ***Belg.***: Nicotibine; ***Canad.***: Isotamine B; Isotamine; ***China***: Jieheqing (结核清); Pi Jin (匹金); Sheng Jun (胜君); ***Cz.***: Nidrazid; ***Fin.***: Tubilysin; ***Fr.***: Rimifon; ***Ger.***: Isozid comp N; Isozid; tebesium-s; tebesium; ***Gr.***: Cemidon; Dianicotyl; Nicozid†; ***Hong Kong***: Trisofort†; ***Hung.***: Isonicid; ***India***: Iso-Rifa; Isokin; Isonex; Rifacom-EZ; ***Indon.***: INH-Ciba; INHA; Inoxin; Kapedoxin; Medinh-OD†; Niacifort-6; Nufadoxin; Pehadoxin; Pulmolin†; Pyravit; Pyrifort†; Suprazid; TB Vit 6; ***Ital.***: Nicozid; ***Jpn***: Hydra; Hydrazide†; ***Mex.***: Hidrasix; Isodo Tbal; Valifol; ***Philipp.***: Comprilex; Curazid (Reformulated); Eurocoxin; Isodexid; Isonid; Isoprim; Isoxin; Nicetal†; Odinah; Pulmodrin; Techxafort; Terozid; Trisofort†; Vamsoxid†; Zidrid; ***Pol.***: Nidrazid; ***Port.***: Hidrazida; ***Rus.***: Isozid (Изозид); Isozid Comp (Изозид Комп); ***Singapore***: Rimifon; ***Spain***: Cemidon B6; Cemidon; ***Swed.***: Tibinide; ***Switz.***: Rimifon; ***Thai.***: Antimic; Myrin-P†; ***Turk.***: INH; Isovit; ***USA***: Laniazid; Nydrazid.

Multi-ingredient Preparations. ***Arg.***: Bacifim†; Rifinah; ***Austria***: Isoprodian†; Rifater; Rifoldin mit INH; ***Braz.***: Isoniaton†; ***Canad.***: Rifater; ***China***: An Si Nuo Kang (安斯诺康); Chang Wei Rui Da Xin (长威瑞达欣); Dai Fei Lin (戴菲林); Fei An (费安); Fei Lu De (菲路得); Fei Ning (费宁); Fei Su (菲苏); Fei Ting (菲亭); Hu Fei Te (护菲特); Ke Lao Er Kang (克劳尔康); Pi Lv (匹律); Rui Fu An Kang (瑞福安康); Rui Qing (瑞清); Ti Bi (缇碧); Wei Bao (维葆); Wei Fei (维菲); Yi Bi Fu (依比福); Yi Nuo Ni Kang (怡诺尼康); Yi Ti Bi (伊缇碧); ***Denm.***: Rimactazid; Rimcure; Rimstar; ***Fin.***: Rimactazid; Rimstar; ***Fr.***: Rifater; Rifinah; ***Ger.***: Iso-Eremfat; Rifater†; Rifinah†; tebesium Duo; tebesium Trio; ***Gr.***: Myambutol-INH; Oboliz; Rifater; Rifinah; Rimactazid; ***Hong Kong***: Rifater; Rifinah; ***Hung.***: Rifazid; ***India***: AFB3; AFB4; Akt-2; Akt-3; Akt-4; Akt-FD; Akurit-3; Akurit-4; Akurit-Z; Akurit; Antibin; Arzade; Arzide†; Becox Forte Kit; Becox RH; Bicox Kid; Bicox-E; Bicox; Binex DT; Binex E; Binex Kid; Binex Z; Binex ZE; Binex; Cavidin INH; Cavirip; Cavitar RHE; Caviter FD; Caviter; Combunex; Confez-3; Coxina-3; Coxina-4; Coxinex; Coxkit-3; Coxpic; Coxrid; Coxter-2; Coxter-3; Coxter-4; Cx-3; Cx-4; Cx-5; Emrif Kit; Emrif; Eufacin Inh; Eufacin Plus; Eufazid; Famcin H; Faminex Forte; Faminex; Forecox; Gocox Compound; Gocox-3; Inabutol Forte†; Inapas; Infez-4; Ipcacin Kid†; Ipcacin; Ipcazide; Iso-Ripharmed; Isokin-300; Isokin-T Forte; Isokoxi; Isorifam; Lifebutol-H; Macox Plus; Macox-ZH; Monto-2; Monto-3; Monto-4; Montonex Forte; Montorip; Mycocox-4; Mycocox-E; Mycocox-Z; Mycocox; Mycodot Kit; Mycodot-4; Mycodot-E; Mycodot-Z; Myconex; Mycospas; Mycurit-3; Mycurit-4; Mycurit-Z; Optirifa Plus; R-Cinex Z; R-Cinex; RHZ Plus; RHZ; Rifa E; Rifa; Rimactazid + Z; Rimpazid; Siticox-INH†; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed 2; Xeed 3E; Xeed 4; ***Indon.***: bacbutINH; Erabutol Plus; Meditam-6†; Metham; Mycothambin-INH†; Niazitol; Pulna; Ramicin-ISO†; Rimactazid; Rimcure; Rimstar; Santibi Plus; ***Irl.***: Rifater; Rifinah; Rimactazid; Rimcure†; Rimstar; ***Ital.***: Etanicozid B6; Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; ***Malaysia***: Rimactazid; Rimcure; ***Mex.***: Arpisen†; Dotbal-S; Dotbal; Finater†; Finateramida†; Rifater; Rifinah; ***Mon.***: Dexambutol-INH†; ***Neth.***: Rifinah; Rimactazid†; Rimcure†; Rimstar†; ***Norw.***: Rimactazid; Rimcure; Rimstar; ***NZ***: Rifinah; ***Philipp.***: 4D; AKuriT-4; AKuriT; Bifix; CombiKids†; CombiPack; Continukit Plus†; Continukit; Continupack†; Duomax; Ebutol; Econofix; Econokit-MDR; Econokit; Econopack; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; HR Pedia Kit; HRZ Pedia Kit; Kidz Kit 2; Kidz Kit 3; Myrin-P; Myrin; Quadmax; Quadtab; Refam Duo†; Refam Pedia Kit†; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; Sthamizide; SVM-Polypac-A†; Tres; Triofix; Tritab; Viper†; ***Pol.***: Rifamazid; ***Port.***: Rifater; Rifinah; ***Rus.***: Combitub (Комбитуб); Forecox (Форкокс); Iso-Eremfat (Изо-Эремфат); Isocomb (Изокомб); Isopask (Изопаск); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Mac-Pas Plus (Мак-Пас Плюс); Phthizoetham (Фтизоэтам); Phthizopiram (Фтизопирам); Protub-2 (Протуб-2); Protub-3 (Протуб-3); Protub-4 (Протуб-4); Protub-Lome (Протуб-Ломе); Protubetham (Протубэтам); Protubpira (Протубпира); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс)†; Rimactazid (Римактазид)†; Rimecure 3-FDC (Римкур 3-ФДС)†; Rimstar 4-FDC (Римстар 4-ФДС)†; Tubavit (Тубавит); ***S.Afr.***: Rifafour; Rifater†; Rifinah; Rimactazid; Rimcure; Rimstar; ***Singapore***: Merip; Rimactazid; ***Spain***: Amiopia†; Duplicalcio B12†; Rifater; Rifinah; Rimactazid†; Rimcure†; Rimstar; Tisobrif†; ***Swed.***: Rimactazid; Rimcure; Rimstar; ***Switz.***: Rifater; Rifinah; Rimactazid; Rimstar; ***Thai.***: Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid†; Rimcure 3-FDC; Rimstar†; ***UK***: Rifater; Rifinah; Rimstar; Voractiv; ***USA***: IsonaRif; Rifamate; Rifater; ***Venez.***: Rimactazid; Rimcure.

Pharmacopoeial Preparations
BP 2014: Isoniazid Injection; Isoniazid Oral Solution; Isoniazid Tablets;
USP 36: Isoniazid Injection; Isoniazid Syrup; Isoniazid Tablets; Rifampin and Isoniazid Capsules; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Josamycin *(BAN, USAN, rINN)*

EN-141; Josamicina; Josamicinas; Josamycine; Josamycinum; Josamysiini; Jozamicin; Leucomycin A_3; Джозамицин.
A stereoisomer of 7-(formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′-acetate 4″-isovalerate.
$C_{42}H_{69}NO_{15}$=828.0
CAS — 16846-24-5; 56689-45-3.
ATC — J01FA07.
ATC Vet — QJ01FA07.
UNII — HV13HFS217.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Josamycin). A macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic powder. It contains a minimum of 900 units/mg calculated with reference to the dried substance. Very slightly soluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Josamycin Propionate *(BANM, rINNM)*

Josamicina, propionato de; Josamicino propionatas; Josamycine, Propionate de; Josamycini Propionas; Josamycinpropionat; Josamycin-propionát; Josamysiinipropionaatti; Jozamicin-propionát; Propionato de josamicina; YS-20P; Джозамицина Пропионат.
Josamycin 10-propionate.
$C_{45}H_{73}NO_{16}$=884.1
CAS — 56111-35-4; 40922-77-8.
ATC — J01FA07.
ATC Vet — QJ01FA07.
UNII — 053VA4B06Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Josamycin Propionate). It is derived from a macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic, crystalline powder. It contains a minimum of 843 units/mg, calculated with reference to the dried substance. Practically insoluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Uses and Administration

Josamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p. 292.1). It is given orally as the base or the propionate but doses are expressed in terms of the base; 1.07 g of josamycin propionate is equivalent to about 1 g of josamycin. Usual doses in the treatment of susceptible infections are the equivalent of 1 to 2 g of josamycin daily in 2 or more divided doses.

Adverse Effects and Precautions

As for Erythromycin, p. 293.1. Josamycin is reported to produce less gastrointestinal disturbance than erythromycin.

Oedema. A report of josamycin-induced oedema of the foot.[1]

1. Bosch X, *et al.* Josamycin-induced pedal oedema. *BMJ* 1993; **307:** 26.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 294.2.

Cytochrome P450 isoenzymes. Josamycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore interact less than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p. 294.2). The general absence of an interaction between josamycin and theophylline would appear to support this.

Antimicrobial Action

As for Erythromycin, p. 295.1. Some reports suggest that josamycin may be more active against some strains of anaerobic species such as *Bacteroides fragilis*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Josalid; ***China***: Beibeisha (贝贝莎); Josamy (娇莎); ***Fr.***: Josacine; ***Ital.***: Iosalide; ***Jpn***: Josamy; ***Rus.***: Wilprafen (Вильпрафен); ***Spain***: Josamina; ***Ukr.***: Wilprafen (Вильпрафен).

Multi-ingredient Preparations. ***Ital.***: Corti-Fluoral.

Kanamycin Acid Sulfate *(BANM)*

Kanamicina, sulfato ácido de; Kanamicino rūgštusis sulfatas; Kanamycin Acid Sulphate; Kanamycin sulfát kyselý; Kanamycine, sulfate acide de; Kanamycini sulfas acidus; Kanamycinsulfat, Saures; Kanamycinsyrasulfat; Kanamysiinihapposulfaatti; Savanyú kanamicin-szulfát; Канамицина Кислого Сульфат.
ATC — A07AA08; J01GB04; S01AA24.
ATC Vet — QA07AA08; QJ01GB04; QS01AA24.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Kanamycin Acid Sulfate). A form of kanamycin sulfate prepared by adding sulfuric acid to a solution of kanamycin sulfate and drying by a suitable method. A white or almost white, hygroscopic powder containing not less than 670 units/mg and 23 to 26% of sulfate, calculated with reference to the dried material. Soluble 1 in about 1 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 5.5 to 7.5.

Kanamycin Sulfate *(BANM, rINNM)*

Kanamicina, sulfato de; Kanamicin-monoszulfát; Kanamicino monosulfatas; Kanamycin A Sulphate; Kanamycin monosulfát monohydrát; Kanamycin Monosulphate; Kanamycin Sulphate; Kanamycine, monosulfate de; Kanamycine, Sulfate de; Kanamycini monosulfas; Kanamycini Monosulfas Monohydricus; Kanamycini Sulfas; Kanamycinmonosulfat; Kanamycyny siarczan; Kanamysiinimonosulfaatti; Sulfato de kanamicina; Канамицина Сульфат.
6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine sulphate monohydrate.
$C_{18}H_{36}N_4O_{11},H_2SO_4,H_2O$=600.6
CAS — 59-01-8 (kanamycin); 25389-94-0 (anhydrous kanamycin sulfate).
ATC — A07AA08; J01GB04; S01AA24.
ATC Vet — QA07AA08; QJ01GB04; QS01AA24.
UNII — OW1N4G4R9W (kanamycin sulfate); J80EX28SMQ (kanamycin A sulfate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Jpn includes the anhydrous substance.

Ph. Eur. 8: (Kanamycin Monosulfate; Kanamycin Sulfate BP 2014). The sulfate of an antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus*. A white or almost white, crystalline powder containing not less than 750 units/mg and 15.0 to 17.0% of sulfate, calculated with reference to the dried material. Soluble 1 in about 8 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 6.5 to 8.5.

USP 36: (Kanamycin Sulfate). A white, odourless crystalline powder. It has a potency equivalent to not less than 750 micrograms of kanamycin per mg, calculated on the dried basis. Freely soluble in water; insoluble in acetone, in ethyl acetate, and in benzene. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides such as kanamycin with beta lactams, see under Gentamicin Sulfate, p. 304.3. Kanamycin is also reported to be incompatible with various other drugs including some other antimicrobials as well as with some electrolytes.

Uses and Administration

Kanamycin is an aminoglycoside antibacterial with actions similar to those of gentamicin (p. 304.3). It has been used in the treatment of susceptible Gram-negative and staphylococcal infections, including gonorrhoea (p. 204.2) and neonatal gonococcal eye infections (p. 193.2), although its use has declined in many centres because of the

development of resistance. As with gentamicin it may be used with penicillins and with cephalosporins; the injections should be given at separate sites. Kanamycin has also been used as a second-line drug in tuberculosis (p. 210.2), but other, safer drugs are usually preferred.

The sulfate or acid sulfate salts are often used: in the USA, preparations containing the bisulfate ($C_{18}H_{36}N_4O_{11},2H_2SO_4$), but referred to as the sulfate, are available. Doses are expressed in terms of kanamycin base; 1.2 g of kanamycin sulfate, and 1.34 g of kanamycin acid sulfate, are each equivalent to about 1 g of kanamycin. It is usually given by intramuscular injection, and in acute infections adults may be given 15 mg/kg daily, to a maximum of 1.5 g daily, in 2 to 4 divided doses. The same doses may be given by intravenous infusion of a 0.25 to 0.5% solution over 30 to 60 minutes; in the UK, up to 30 mg/kg daily has been given in 2 or 3 divided doses by this route. Treatment of acute infections should preferably not continue for longer than 7 to 10 days or exceed a cumulative dose of 10 g kanamycin. A dose of 3 to 4 g weekly, given as 1 g on alternate days or as 1 g twice daily on 2 days each week, was formerly suggested in the UK for chronic bacterial infections, up to a maximum cumulative dose of 50 g, but prolonged use increases the risk of nephrotoxicity and is not generally recommended.

A single intramuscular dose of 2 g of kanamycin has been used when other, first-line drugs are not available in the treatment of gonococcal eye infections.

For details of doses in children, see p. 317.1.

Peak plasma concentrations greater than 30 micrograms/mL and trough concentrations greater than 10 micrograms/mL should be avoided. It is recommended that dosage should be adjusted in all patients according to plasma-kanamycin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p. 305.2.

Kanamycin has been used orally similarly to neomycin (p. 332.1), for the suppression of intestinal flora. For preoperative use, 1 g may be given every hour for 4 hours, then 1 g every 6 hours for 36 to 72 hours. In the management of hepatic encephalopathy, 8 to 12 g daily in divided doses may be given.

Kanamycin has also been given in doses of 250 mg as a nebulised inhalation, 2 to 4 times daily. Solutions of kanamycin 0.25% have been used for the irrigation of body cavities.

Kanamycin tannate has also been used.

Administration in children. For severe infections caused by susceptible bacteria in children beyond the newborn period the American Academy of Pediatrics[1] suggests an intravenous or intramuscular dose equivalent to kanamycin 15 to 30 mg/kg daily, in 3 divided doses.

For prophylaxis in neonates born to mothers with gonococcal infections *or* for the treatment of gonococcal neonatal conjunctivitis, WHO recommends kanamycin 25 mg/kg, up to a maximum of 75 mg, as a single intramuscular dose, if first-line drugs are not available.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2.

For patients given standard regimens, peak plasma concentrations of kanamycin >30 micrograms/mL, and trough concentrations >10 micrograms/mL, should be avoided. Auditory (cochlear) toxicity is more frequent than vestibular toxicity.

Local pain and inflammation, as well as bruising and haematoma, have been reported at the site of intramuscular injections.

Gastrointestinal disturbances and a malabsorption syndrome, similar to that seen with oral neomycin (p. 332.2), have occurred after oral kanamycin. Oral kanamycin should be avoided in patients with gastrointestinal ulceration.

Breast feeding. Although kanamycin is distributed into breast milk[1] the American Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers were receiving kanamycin, and therefore considers[2] that its use is usually compatible with breast feeding.

1. Chyo N, *et al.* Clinical studies of kanamycin applied in the field of obstetrics and gynecology. *Asian Med J* 1962; **5:** 265–75.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 307.2. It is active against a similar range of organisms although it is not active against *Pseudomonas* spp. Some strains of *Mycobacterium tuberculosis* are sensitive.

Resistance has been reported in strains of many of the organisms normally sensitive to kanamycin, and at one time was widespread, but a decline in the use of kanamycin has meant that resistance has become somewhat less prevalent. Cross-resistance occurs between kanamycin and neomycin, framycetin, and paromomycin, and partial cross-resistance has been reported between kanamycin and streptomycin.

References.

1. Ho YH, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3.

Less than 1% of an oral dose is absorbed, although this may be significantly increased if the gastrointestinal mucosa is inflamed or ulcerated.

After intramuscular injection peak plasma concentrations of kanamycin of about 20 and 30 micrograms/mL occur about 1 hour after doses of 0.5 and 1 g respectively. A plasma half-life of about 3 hours has been reported. Absorption after intraperitoneal instillation is similar to that from intramuscular doses.

Kanamycin is rapidly excreted by glomerular filtration and most of a parenteral dose appears unchanged in the urine within 24 hours. It has been detected in cord blood and in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cristalomicina; ***Ger.***: Kan-Ophtal†; Kana-Stulln; Kanamytrex; ***Gr.***: Eye-Cure Ph-C†; ***India***: Efficin; Kanamac; Kancin; Kaycin; Neokanyn; ***Indon.***: Kanabiotic†; Kanarco; Kanoxin†; ***Ital.***: Keimicina; ***Malaysia***: Kancin; ***Mex.***: Cancina†; Kanapat; Kantrex; Solkan; Sulmyn†; ***Singapore***: Kancin-L; ***Thai.***: Anbikan†; Kancin†; Kangen; KMH; ***USA***: Kantrex†; ***Venez.***: Kantrex.

Multi-ingredient Preparations. ***Arg.***: Cristalomicina; ***Ital.***: Dermaflogil; ***Rus.***: Gelplastan (Желпластан); ***S.Afr.***: Kantrexil; ***Spain***: Kanafosal Predni†; Kanafosal†; Kanapomada†; Naso Pekamin†; ***Thai.***: KA-Cilone†; ***Venez.***: Monosulpa; Rinomax.

Pharmacopoeial Preparations

USP 36: Kanamycin Injection; Kanamycin Sulfate Capsules.

Kitasamycin *(BAN, USAN, rINN)*

Kitasamicina; Kitasamycine; Kitasamycinum; Leucomycin; Китазамицин.

CAS — 1392-21-8 (kitasamycin); 37280-56-1 (kitasamycin tartrate); 178234-32-7 (kitasamycin acetate).

ATC Vet — QJ01FA93.

Pharmacopoeias. In *Chin.* and *Jpn.*

Jpn also includes Kitasamycin Acetate (Acetylkitasamycin) and Kitasamycin Tartrate.

Profile

Kitasamycin is a macrolide antibacterial produced by *Streptomyces kitasatoensis*, consisting mainly of kitasamycins A_4 and A_5. It has actions and uses similar to those of erythromycin (p. 291.2) and has been given orally as the base or intravenously as the tartrate in the treatment of susceptible infections. Kitasamycin acetate has also been given orally.

Kitasamycin has been added to animal feed stuffs in some countries as a growth promotor for pigs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Ji Er Le (安吉儿乐); Le Pu Mei Xin (乐普美欣); Shuang Ning (爽宁); Tian Cao (田草); Xiaojun (小军).

Latamoxef Disodium *(BANM, rINNM)*

Latamoksefidinatrium; Latamoxef disódico; Latamoxef Disodique; Latamoxef Sodium; Latamoxefdinatrium; Latamoxefum Dinatricum; LY-127935; Moxalactam Disodium (USAN); 6059-S; Динатрий Латамоксеф.

(7*R*)-7-[2-Carboxy-2-(4-hydroxyphenyl)acetamido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-1-oxa-3-cephem-4-carboxylic acid, disodium salt.

$C_{20}H_{18}N_6Na_2O_9S$=564.4

CAS — 64952-97-2 (latamoxef); 64953-12-4 (latamoxef disodium).

ATC — J01DD06.

ATC Vet — QJ01DD06.

UNII — 5APW73W3QZ.

Pharmacopoeias. In *Jpn.*

Profile

Latamoxef is an oxacephalosporin antibacterial that has been given intramuscularly or intravenously as the disodium salt in the treatment of susceptible infections. It differs from the cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by oxygen. Like cefamandole (p. 236.2) it has an *N*-methylthiotetrazole side-chain and may cause hypoprothrombinaemia. Serious bleeding episodes have been reported with latamoxef and prophylaxis with vitamin K and monitoring of bleeding time have been recommended during treatment. In addition to hypoprothrombinaemia, inhibition of platelet function and more rarely immune-mediated thrombocytopenia may be responsible for interference with haemostasis. As with the methylthiotetrazole-containing cephalosporins, a disulfiram-like reaction with alcohol may occur.

Latamoxef has antimicrobial activity similar to that of the third-generation cephalosporin cefotaxime (p. 244.3), although it is generally less active against Gram-positive bacteria and more active against *Bacteroides fragilis*.

Breast feeding. The authors of a pharmacokinetic study[1] in 8 women given latamoxef cautioned that there was a possibility of colonisation of the infant's bowel with Gram-positive bacteria and in consequence a risk of enterocolitis. They therefore advised against breast feeding during maternal use of the drug. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving latamoxef, and the last available guidance from the American Academy of Pediatrics considered[2] that it was therefore usually compatible with breast feeding.

1. Miller RD, *et al.* Human breast milk concentration of moxalactam. *Am J Obstet Gynecol* 1984; **148:** 348–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Shiomarin (噻吗灵); ***Jpn***: Shiomarin.

Lenampicillin Hydrochloride *(rINNM)*

Hidrocloruro de lenampicilina; KBT-1585; Lénampicilline, Chlorhydrate de; Lenampicillini Hydrochloridum; Ленампициллина Гидрохлорид.

2,3-Dihydroxy-2-butenyl(2*S*,5*R*,6*R*)-6-[(*R*)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, cyclic carbonate, hydrochloride.

$C_{21}H_{23}N_3O_7S,HCl$=497.9

CAS — 86273-18-9 (lenampicillin); 80734-02-7 (lenampicillin hydrochloride).

Pharmacopoeias. In *Jpn.*

Profile

Lenampicillin is an ester of the beta-lactam antibacterial ampicillin to which it is hydrolysed *in vivo*. It is used, as the hydrochloride, in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: ZhenXin (珍欣).

Levofloxacin *(BAN, USAN, rINN)*

DR-3355; HR-355; Levofloksasiini; Levofloksasin; Lévofloxacine; Levofloxacino; Levofloxacinum; *S*-(-)-Ofloxacin; RWJ-25213; Левофлоксацин.

(-)-(*S*)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid.

$C_{18}H_{20}FN_3O_4$=361.4

CAS — 100986-85-4 (levofloxacin); 138199-71-0 (levofloxacin hemihydrate).
ATC — J01MA12; S01AE05.
ATC Vet — QJ01MA12; QS01AE05.
UNII — 6GNT3Y5LMF.

Pharmacopoeias. In *US.*

USP 36: (Levofloxacin). A light yellowish-white to yellow-white crystals or crystalline powder. Sparingly soluble in water, in acetone, and in methyl alcohol; soluble in acetic acid and in dimethyl sulfoxide; practically insoluble in glycerol and in *n*-octanol. Store in airtight containers. Protect from light.

Uses and Administration

Levofloxacin is the *S*-(-)-isomer of the fluoroquinolone antibacterial ofloxacin (p. 336.3). It is given orally, or by intravenous infusion as a 5 mg/mL solution over 30 to 90 minutes, to treat susceptible infections including tuberculosis (but see under Uses and Administration of Ciprofloxacin, p. 262.2). Levofloxacin is given as the hemihydrate but doses are expressed in terms of the base; levofloxacin hemihydrate 256 mg is equivalent to about 250 mg of levofloxacin. Usual doses range from 250 to 500 mg once or twice daily for 7 to 14 days depending on the severity and nature of the infection. A dose of 250 mg once daily for 3 days may be given for uncomplicated urinary-tract infections. A 28-day course of treatment with a dose of 500 mg once daily should be given for chronic bacterial prostatitis. In the USA, doses of 750 mg once daily for 7 to 14 days may be used for complicated skin infections and for hospital-acquired pneumonia; a shorter course of 750 mg once daily for 5 days may be given for community-acquired pneumonia, acute bacterial sinusitis, complicated urinary-tract infections, and acute pyelonephritis. A 60-day course of treatment with a dose of 500 mg once daily is also licensed in the USA for treatment and postexposure prophylaxis of inhalation anthrax.

Doses should be reduced in patients with renal impairment (see p. 318.1).

Levofloxacin is also used topically as the hemihydrate in eye drops. A solution containing the equivalent of 0.5% of levofloxacin is used for the treatment of bacterial conjunctivitis and 1.5% for corneal ulcers caused by susceptible strains of bacteria. The hemihydrate is also being studied for use by inhalation in the treatment of lung infections in patients with cystic fibrosis.

Reviews.

1. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. *Drugs* 1994; **4:** 677–700.
2. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32:** 320–36.
3. Martin SJ, *et al.* A risk-benefit assessment of levofloxacin in respiratory, skin and skin structure, and urinary tract infections. *Drugs* 2001; **24:** 199–222.
4. Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs* 2003; **63:** 2769–2802.
5. Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008; **68:** 535–65.
6. Anonymous. Levofloxacin. *Tuberculosis (Edinb)* 2008; **88:** 119–21.
7. Keating GM. Levofloxacin 0.5% ophthalmic solution: a review of its use in the treatment of external ocular infections and in intraocular surgery. *Drugs* 2009; **69:** 1267–86.

Administration in children. Since fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks. In the USA levofloxacin is licensed for use in children 6 months of age and older only for treatment and postexposure prophylaxis of inhalation anthrax. The following doses, based on body-weight, may be given orally or intravenously[1] for 60 days:

- less than 50 kg: 8 mg/kg (maximum 250 mg) every 12 hours
- 50 kg or more: 500 mg once every 24 hours

1. Li F, *et al.* Pharmacometrics-based dose selection of levofloxacin as a treatment for postexposure inhalational anthrax in children. *Antimicrob Agents Chemother* 2010; **54:** 375–9.

Administration in renal impairment. Although initial intravenous and oral doses (see Uses and Administration, above) remain unchanged in patients with renal impairment, subsequent doses of levofloxacin should be adjusted according to creatinine clearance (CC).

In the UK, the following doses are recommended:

- CC 20 to 50 mL/minute: subsequent doses are halved
- CC 10 to 19 mL/minute: subsequent doses are reduced to one-quarter of the usual dose; a regimen of 250 mg daily should be reduced to 125 mg every 48 hours
- CC less than 10 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): usual doses of 250 mg or 500 mg daily are reduced to 125 mg every 48 or 24 hours respectively; a regimen of 500 mg twice daily is reduced to 125 mg every 24 hours

In the USA, the following dose modifications are recommended:

After an initial dose of 750 mg daily,

- CC 20 to 49 mL/minute: subsequent doses are 750 mg every 48 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 500 mg every 48 hours

After an initial dose of 500 mg daily,

- CC 20 to 49 mL/minute: subsequent doses are 250 mg every 24 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 250 mg every 48 hours

After an initial dose of 250 mg daily,

- CC 10 to 19 mL/minute: subsequent doses are 250 mg every 48 hours (although no dose adjustment is required for the short-course, low-dose regimen used in uncomplicated urinary-tract infection)

In critically ill patients undergoing continuous renal replacement therapy (CRRT), a loading dose of 500 to 750 mg has been recommended, followed by maintenance doses dependent on the type of CRRT:[1]

- continuous venovenous haemofiltration (CVVH): 250 mg every 24 hours
- continuous venovenous haemodialysis (CVVHD): 250 to 500 mg every 24 hours
- continuous venovenous haemodiafiltration (CVVHDF): 250 to 750 mg every 24 hours

For critically ill patients undergoing intermittent haemodialysis, a dose of 250 to 500 mg every 48 hours (given after the dialysis run) has been recommended.[1]

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Peptic ulcer disease. For mention of the potential use of levofloxacin in eradication regimens for *Helicobacter pylori*, see p. 1816.2.

References.

1. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2006; **23:** 35–44.
2. Gisbert JP, *et al.* First-line triple therapy with levofloxacin for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2007; **26:** 495–500.
3. Rispo A, *et al.* Levofloxacin in first-line treatment of Helicobacter pylori infection. *Helicobacter* 2007; **12:** 364–5.
4. Perna F, *et al.* Levofloxacin-based triple therapy for Helicobacter pylori re-treatment: role of bacterial resistance. *Dig Liver Dis* 2007; **39:** 1001–5.
5. Zullo A, *et al.* Helicobacter pylori eradication with either quadruple regimen with lactoferrin or levofloxacin-based triple therapy: a multicentre study. *Dig Liver Dis* 2007; **39:** 806–10.
6. Yee YK, *et al.* Clinical trial: levofloxacin-based quadruple therapy was inferior to traditional quadruple therapy in the treatment of resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2007; **26:** 1063–7.
7. Gisbert JP, *et al.* H. pylori Study Group of the Asociación Española de Gastroenterología. Second-line rescue therapy with levofloxacin after H. pylori treatment failure: a Spanish multicenter study of 300 patients. *Am J Gastroenterol* 2008; **103:** 71–6.
8. Castro-Fernández M, *et al.* Efficacy of triple therapy with a proton pump inhibitor, levofloxacin, and amoxicillin as first-line treatment to eradicate Helicobacter pylori. *Rev Esp Enferm Dig* 2009; **101:** 395–8, 399–402.
9. Schrauwen RW, *et al.* Seven-day PPI-triple therapy with levofloxacin is very effective for Helicobacter pylori eradication. *Neth J Med* 2009; **67:** 96–101.
10. Di Caro S, *et al.* Second-line levofloxacin-based triple schemes for Helicobacter pylori eradication. *Dig Liver Dis* 2009; **41:** 480–5.

Tuberculosis. For mention of the use of levofloxacin in the treatment of tuberculosis, see under Ciprofloxacin, p. 262.2.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, levofloxacin should be stopped.

Effects on glucose metabolism. See also under Gatifloxacin, p. 303.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levofloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Use of levofloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Levofloxacin does not appear to interact significantly with theophylline or ciclosporin.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Levofloxacin is generally considered to be about twice as active as ofloxacin (p. 337.1), the racemic substance. Levofloxacin has a broad spectrum of activity which includes Gram-positive bacteria.

References.

1. Brown DFJ, *et al.*, eds. Levofloxacin: an extended spectrum 4-quinolone agent. *J Antimicrob Chemother* 1999; **43** (suppl C): 1–90.

Pharmacokinetics

Levofloxacin is rapidly and almost completely absorbed after oral doses and peak plasma concentrations occur within 1 to 2 hours. It is widely distributed into body tissues including the bronchial mucosa and lungs, but penetration into CSF is relatively poor. Levofloxacin is about 30 to 40% bound to plasma proteins. Only small amounts are metabolised, to inactive metabolites. The elimination half-life of levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted largely unchanged, mainly in the urine with less than 5% as metabolites. It is not removed by haemodialysis or peritoneal dialysis.

References.

1. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet* 1997; **32:** 101–19.
2. Piscitelli SC, *et al.* Pharmacokinetics and safety of high-dose and extended-interval regimens of levofloxacin in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; **43:** 2323–7.
3. Chien S, *et al.* Levofloxacin pharmacokinetics in children. *J Clin Pharmacol* 2005; **45:** 153–60.
4. Lee CKK, *et al.* Levofloxacin pharmacokinetics in adult cystic fibrosis. *Chest* 2007; **131:** 796–802.
5. Zhang J, *et al.* Permeability and concentration of levofloxacin in epithelial lining fluid in patients with lower respiratory tract infections. *J Clin Pharmacol* 2010; **50:** 922–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anuar; Bacfuron; Bactifren; Bactocilina; Benur; Ceplene Plus; Fentaxina; Floxlevo; Grepiflox; Leflumax; Levaquin; Lexobron; Misile; Quinomed L; Septibiotic; Tavanic; Teraquin; Ultraquin; Uniflox; Valiflox; Voflox; Xaflo; Zenic; ***Austria***: Oftaquix; Tavanic; ***Belg.***: Tavanic; ***Braz.***: Levaquin; Levcin; Levotac; Levoxin; Tamiram; Tavagran; Tavanic; Vonax; ***Canad.***: Levaquin; ***Chile***: Auxxil; Medibiox; Novacilina; Quinobiot; Recamicina; Tavanic; ***China***: An Li Lai (安理莱); Cravit (可乐必妥); Laiwoxing (莱沃幸); Qi Si Ding (齐斯丁); ***Cz.***: Aflobax; Oftaquix; Tavanic; ***Denm.***: Felvosin†; Oftaquix; Voflan†; ***Fin.***: Oftaquix; Tavanic; ***Fr.***: Tavanic; ***Ger.***: Oftaquix; Tavanic; ***Gr.***: Floxator; Levolacin; Levoprolin; Lexacin; Talerin; Tavanic; Zirotan; Zoclix; ***Hong Kong***: Cravit; Levicin†; Levoxin; ***Hung.***: Leflokin; Levoxa; Oftaquix; Savulin; Tavanic; ***India***: Acquire; Adlox; Aflevo; Albactin; Aleflox; Alevo; Alvox; Apoflox; Balleo; Bat; Brilevo; C-Livo; Cuflox; Cutiflox; Day-5; Defox; E-Livo; Eklevo; Elof; Elone; Elvo; Elvox; Enatome; Evabit; Evopic; Flavo; Floquin; Floroxin; Flostar; Fydoliv; Fyflox; Fynal; Gevoflox; Glevo; Gyraze; Hawk; Hileflox; Idalev; Klever; Kylevo; L-Asiflox; L-Cin; L-Flo; L-Flox; L-Oxo; L-Sig; Laffter; Lamiwin; Lavaza; Lavoflox; LCR; Lebact; Lecourse; Ledor; Ledric; Lee; Leefbid; Leeflox; Lefosym; Lek; Lemed; Leocip; Leof; Leoflox; Leon; Leroy; Levace; Levact; Levator; Levend; Levloc; Levoact; Levobact; Levobenz; Levobos; Levobus; Levocad; Levocas; Levocide; Levocos; Levodak; Levoday; Levoden; Levoff; Levoflow; Levoflox; Levofox; Levogram; Levogrm; Levohill; Levokab; Levokem; Levola; Levolab; Levolak; Levolife; Levolon; Levom; Levomag; Levoman; Levomed; Levon; Levonez; Levopet; Levophar; Levopil; Levoquin; Levorax; Levosh; Levosidh; Levosip; Levospan; Levospi; Levosym; Levotab; Levotas; Levotec; Levotech; Levotoz; Levotran; Levotum; Levowal; Levowok; Levox; Levoxin; Levrea; Lewel; Lexacin; Lexiflox; Lexoquin; LF; LFC Med; Liflo; Lift; Lin; Lina; Lipep; Livbest; Livbid; Livestar; Livocin; Livoric; Livota; Livoven; Livox; LMG; Lofel; Lofo; Lotor; Loxof; LQueen; Lufi; LV Flox; LVM; LVX; LXN; Lypestar; Lzen; Mevof; Milivo; Mintoflox; Monoflox; Morelevo; Multivox; NBLox; Novaflox; Novocin; Nutlevo; Olevo; Osibact; Tavanic; ***Indon.***: Armolev; Corvox; Cravit; Cravox; Difloxin; Elvacin; Farlev; Floxacap; Floxacom; Lecrav; Lefos; Lekuicin; Levocin; Levonic; Levores; Levovid; Levoxal; Lexa; Lovequin; LQ-500; Mosardal; Nislev; Nufalev; Prolecin; Prolevox; Reskuin; Rinvox; Tevox; Volequin; VoLox; Voxin; Zenilev; Zidalev; ***Irl.***: Refaz; Tavager; Tavanic; ***Israel***: Levo; Tavanic; ***Ital.***: Agilev; Alvand; Batiflox; Lemaxil; Levoxacin; Levoxigram; Oftaquix; Prixar; Refrain; Sineflox; Summaflox; Tavanic; Trissil; ***Jpn***: Cravit; ***Malaysia***: Cravit; Glevo; Loxof; ***Mex.***: Bredelin; Cina†; Elequine; Evocs-III; Flevox; Lefloxin; Prosxaflo; Ran-Levo; Tavanic; Tevotev; Voflaxin; ***Neth.***: Oftaquix†; Prixar†; Tavanic; ***Philipp.***: Day Five; Flevoxcin; Floxel; Glevo; Lefloxin; Levan; Levex; Levobact; Levobet; Levocin; Levoflox; Levomax; Levonox; Levoprime; Levoquin; Levostran; Levox; Levoxin; Levoxl; Levozef; Lexi; Lexyl; Lexzin; Lezasin; Lotor; Loxeva; Oftaquix; Omnivox; Pneumocal; Pravox; Quinolev; Qumic; Santis; Teravox; Terlev; Voflox; Voleca; Wilovex; ***Pol.***: Aflobax; Levoxa; Oftaquix; Oroflocina; Tavanic; ***Port.***: Foxitina†; Oftaquix; Tavanic; ***Rus.***: Ecolevid (Эколевид); Eleflox (Элефлокс); Flexid (Флексид); Floracid (Флорацид); Glevo (Глево); Leflobact (Лефлобакт); Lefoxin (Лефоксин); Levolet (Леволет); Maclevo (Маклево); Oftaquix (Офтаквикс); Remedia

(Ремедиа); Signicef (Сигницеф); Tanflomed (Танфломед); Tavanic (Таваник); ***S.Afr.***: Lintrip; Tavaloxx; Tavanic; ***Singapore***: Cravit; ***Spain***: Asey; Tavanic; ***Swed.***: Oftaquix; Tavanic; ***Switz.***: Levex; Tavanic; ***Thai.***: Cravit; Lefloxin; Levocin; Levoflox; Levox; Loxof; Olfovel; ***Turk.***: Cravit; Floxilevo; Lebel; Lefosin; Levokuin; Levolon; Levonat; Levonidin; Levoteva; Lexacin; Nevotek; Potant; Ravivo; Tavanic; Voleflok; ***UAE***: Jenoquine†; ***UK***: Evoxil; Oftaquix; Tavanic; ***Ukr.***: Floxium (Флоксиум); Lefloc (Лефлок); Leflocin (Лефлоцин); Levo-FQ (Лево-ФК); Levobact (Левобакт); Levolet (Леволет); Loxof (Локсоф); Tavanik (Таваник); Taxacin (Таксацин); Zolev (Золев); ***USA***: Iquix; Levaquin; Quixin; ***Venez.***: Levaquin; Proxime; Tavanic.

Multi-ingredient Preparations. ***Braz.***: Pyloripac Retrat; ***India***: Aleflox-OZ; Evopic-OZ; Fynal-OZ; Kylevo-OZ; L-Cin-A; L-Cin-OZ; Lebact-AM; Lebact-O; Lefosym-OZ; Lek-OZ; Levact-OZ; Levocide-OZ; Levocos-OZ; Levoflox Oz; Levogyl; Levospan-OZ; Levosym-OZ; Livbest-AM; Novaflox-OZ.

Pharmacopoeial Preparations
USP 36: Levofloxacin Oral Solution.

Lincomycin *(BAN, USAN, rINN)*

Lincomicina; Lincomycine; Lincomycinum; Linkomycin; Linkomysiini; U-10149; Линкомицин.

Methyl 6-amino-6,8-dideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-α-D-*erythro*-D-*galacto*-octopyranoside.

$C_{18}H_{34}N_2O_6S$=406.5

CAS — 154-21-2.

ATC — J01FF02.

ATC Vet — QJ01FF02.

UNII — BOD072YW0F.

Lincomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lincomicina; Lincomicina, hidrocloruro de; Lincomycine, Chlorhydrate de; Lincomycinhydrochlorid-Monohydrat; Lincomycini hydrochloridum; Lincomycini Hydrochloridum Monohydricum; Linkomicin-hidroklorid; Linkomicino hidrochloridas; Linkomisin Hidroklorür; Linkomycin hydrochlorid monohydrát; Linkomycinhydroklorid; Linkomycyny chlorowodorek; Linkomysiinihydrokloridi; Lyncomycini Hydrochloridum; NSC-70731; Линкомицина Гидрохлорид.

Lincomycin hydrochloride monohydrate.

$C_{18}H_{34}N_2O_6S,HCl,H_2O$=461.0

CAS — 859-18-7 (anhydrous lincomycin hydrochloride); 7179-49-9 (lincomycin hydrochloride, monohydrate).

ATC — J01FF02.

ATC Vet — QJ01FF02.

UNII — M6T05Z2B68 (lincomycin hydrochloride monohydrate); GCWBY9936L (anhydrous lincomycin hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Lincomycin Hydrochloride). A mixture of antibiotics produced by *Streptomyces lincolnensis* var. *lincolnensis* or obtained by any other means, the main component being lincomycin hydrochloride monohydrate. A white or almost white crystalline powder. It contains not more than 5% of lincomycin B. Very soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30 degrees. If the substance is sterile, store in airtight containers.

USP 36: (Lincomycin Hydrochloride). A white or practically white crystalline powder, odourless or with a faint odour. Freely soluble in water; very slightly soluble in acetone; soluble in dimethylformamide. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Solutions of lincomycin hydrochloride have an acid pH and incompatibility may be expected with alkaline preparations, or with drugs unstable at low pH. Licensed product information for the injectable solution states that physical incompatibility has been reported with novobiocin, kanamycin, and phenytoin.

Uses and Administration

Lincomycin is a lincosamide antibacterial with actions and uses similar to those of its chlorinated derivative, clindamycin (p. 270.1). Clindamycin is usually preferred to lincomycin because of its greater activity and better absorption, although the usefulness of both drugs is limited by the risk of pseudomembranous colitis.

Lincomycin is given orally or parenterally as the hydrochloride but doses are expressed in terms of the base; 1.13 g of lincomycin hydrochloride is equivalent to about 1 g of lincomycin. The usual adult oral dose is 500 mg 3 or 4 times daily, taken at least 1 or 2 hours before or after food. It is given parenterally by intramuscular injection in a dose of 600 mg once or twice daily, or by slow intravenous infusion in a dose of 0.6 to 1 g two or three times daily. Higher intravenous doses have been given in very severe infections, up to a total daily dose of about 8 g. For intravenous use, lincomycin 1 g should be diluted in not less than 100 mL of diluent and infused over at least 1 hour.

For details of reduced doses in renal impairment, see p. 319.2.

For details of doses in infants and children, see p. 319.2.

Lincomycin hydrochloride may be given by subconjunctival injection in a dose equivalent to 75 mg of lincomycin.

Administration in children. The usual oral dose of lincomycin for infants and children aged 1 month and over is 30 to 60 mg/kg daily in divided doses. It is given parenterally to those over 1 month old in a dose of 10 to 20 mg/kg daily in divided doses by intramuscular injection or intravenous infusion.

For suggested doses in children with renal impairment see p. 319.2.

Administration in renal impairment. Oral and parenteral doses of lincomycin may need to be reduced in patients with severe renal impairment; a reduction down to 25 to 30% of the usual dose (see Uses and Administration, above) may be appropriate.

Adverse Effects, Treatment, and Precautions

As for Clindamycin, p. 271.2.

Hypersensitivity reactions such as rashes, urticaria, and angioedema may be less frequent with lincomycin than with clindamycin. Other adverse effects reported rarely with lincomycin include aplastic anaemia, pancytopenia, tinnitus, and vertigo.

Lincomycin should be used with caution in patients with hepatic or renal impairment; consideration should be given to decreasing the dosage frequency and serum concentrations should be monitored during high-dose therapy. Reduced doses may be necessary in those with severe renal impairment (see above).

Interactions

As for Clindamycin, p. 272.1.

Absorption of lincomycin is reduced by adsorbent antidiarrhoeals and cyclamate sweeteners.

Antimicrobial Action

As for Clindamycin, p. 272.1, but it is less potent. There is complete cross-resistance between clindamycin and lincomycin. Some cross-resistance with erythromycin, including the phenomenon known as dissociated cross-resistance or inducible MLS_B phenotype, has been reported.

Pharmacokinetics

About 20 to 35% of an oral dose of lincomycin is rapidly absorbed from the gastrointestinal tract; after a 500-mg dose, peak plasma concentrations of about 2 to 3 micrograms/mL are reached within 2 to 4 hours. Food markedly reduces the rate and extent of absorption. An intramuscular injection of 600 mg produces average peak plasma concentrations of between 11 and 12 micrograms/mL at 60 minutes and a 2-hour intravenous infusion of 600 mg produces an average of about 16 micrograms/mL.

The biological half-life of lincomycin is about 5 hours and may be prolonged in hepatic or renal impairment. Serum half-life may be doubled in patients with hepatic impairment and up to 3 times longer in those with severe renal impairment. Lincomycin is widely distributed in the tissues including bone and body fluids but diffusion into the CSF is poor, although it may be slightly better when the meninges are inflamed. It diffuses across the placenta and is distributed into breast milk.

Lincomycin is partially inactivated in the liver; unchanged drug and metabolites are excreted in the urine, bile, and faeces. Lincomycin is not effectively removed from the blood by haemodialysis or peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Frademicina; ***Austral.***: Lincocin; ***Belg.***: Lincocin; ***Braz.***: Farmicina; Frademicina; Linatron; Lincoflan; Lincomiral; Lincovax; Lindemicina; Neo Linco; ***Canad.***: Lincocin; ***Chile***: Lincocin; ***China***: Hu Gu (护谷); LiKe (力克); Lincocin (丽可胜); ***Cz.***: Neloren; ***Fr.***: Lincocine; ***Gr.***: Lincocin; Pecasolin; ***Hong Kong***: Lincocin; ***India***: Admycin-L; Amlinc; Lincocin; Lincosa; Lincozin; Lincy; Lines; Link; Linka; Linkam; Lintop; Liod; Lycin; Lynx; ***Indon.***: Biolincom; Ethilin; Linco†; Lincocin; Lincophar; Lincyn; Lintropsin; Nichomycin; Nolipo; Percocyn; Pritalinc; Tamcocin; Tismamisin; Zencocin; Zumalin; ***Ital.***: Lincocin; ***Malaysia***: Linco; Lincosa; ***Mex.***: Bactokina; Libiocid; Limidrax; Linbac; Lincocin; Lincopat; Lincover; Lisonin; Loriz; Princol†; Rimsalin; Yectolin; ***NZ***: Lincocin; ***Philipp.***: Adlynx; Lincocin; ***Pol.***: Lincocin; Neloren; ***Port.***: Lincocina; ***Rus.***: Neloren (Нелорен)†; ***S.Afr.***: Lincocin; ***Singapore***: Lincocin; ***Spain***: Cillimicina†; Lincocin; ***Thai.***: Linco-P; Linco; Lincocilin; Lincocin; Lincolan; Lincomax†; Lincono; Lincosa; Lingo; Linmycin; Unolin; Uto Lincomycin; ***Turk.***: Lincocin; Linkoles; Linkomed; Linkosol; Linosin; ***Ukr.***: Lincocin (Линкоцин)†; ***USA***: Lincocin; ***Venez.***: Formicina; Lincocin.

Multi-ingredient Preparations. ***Arg.***: Nicozinc.

Pharmacopoeial Preparations
BP 2014: Lincomycin Capsules; Lincomycin Injection;
USP 36: Lincomycin Hydrochloride Capsules; Lincomycin Hydrochloride Syrup; Lincomycin Injection.

Linezolid *(BAN, USAN, rINN)*

Linetsolidi; Linézolide; Linezolidum; PNU-100766; U-100766; Линезолид.

N-{[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl}acetamide.

$C_{16}H_{20}FN_3O_4$=337.4

CAS — 165800-03-3.

ATC — J01XX08.

ATC Vet — QJ01XX08.

UNII — ISQ9I6J12J.

Incompatibility and stability. References.
1. Zhang Y, *et al.* Compatibility and stability of linezolid injection admixed with three quinolone antibiotics. *Ann Pharmacother* 2000; **34:** 996–1001.

Uses and Administration

Linezolid is an oxazolidinone antibacterial used for the treatment of Gram-positive infections of the skin and respiratory tract, including those due to vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*.

It is given, orally or by intravenous infusion (over 30 to 120 minutes), in a usual adult dose of 600 mg every 12 hours for 10 to 14 days; treatment for up to 28 days may be necessary if there is vancomycin resistance. In uncomplicated skin and skin structure infections an oral dose of 400 mg every 12 hours for 10 to 14 days is usually sufficient.

For doses in children, see p. 319.3.

Reviews.
1. Plouffe JF. Emerging therapies for serious gram-positive bacterial infections: a focus on linezolid. *Clin Infect Dis* 2000; **31** (suppl 4): S144–S149.
2. Perry CM, Jarvis B. Linezolid: a review of its use in the management of serious gram-positive infections. *Drugs* 2001; **61:** 525–51.
3. Bain KT, Wittbrodt ET. Linezolid for the treatment of resistant gram-positive cocci. *Ann Pharmacother* 2001; **35:** 566–75.
4. Paladino JA. Linezolid: an oxazolidinone antimicrobial agent. *Am J Health-Syst Pharm* 2002; **59:** 2413–25.
5. Birmingham MC, *et al.* Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003; **36:** 159–68.
6. Wilcox MH. Efficacy of linezolid versus comparator therapies in Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii27–ii35.
7. Falagas ME, *et al.* Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother* 2006; **58:** 273–80.
8. Ntziora F, Falagas ME. Linezolid for the treatment of patients with central nervous system infection. *Ann Pharmacother* 2007; **41:** 296–308.
9. Falagas ME, *et al.* Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents* 2007; **29:** 233–9.
10. Manfredi R. Le prospettive terapeutiche di linezolid nelle infezioni da patogeni Gram-positivi multiresistenti. *Recenti Prog Med* 2007; **98:** 143–54.
11. Falagas ME, *et al.* Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. *Lancet Infect Dis* 2008; **8:** 53–66.
12. Falagas ME, Vardakas KZ. Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. *Drug Safety* 2008; **31:** 753–68.
13. Di Paolo A, *et al.* Pharmacological issues of linezolid: an updated critical review. *Clin Pharmacokinet* 2010; **49:** 439–47.

Administration in children. UK licensed product information does not recommend the use of linezolid in children and adolescents below 18 years of age. However, the *BNFC* suggests the following doses of linezolid in the treatment of pneumonia or *complicated* skin and soft-tissue infections, given orally or by intravenous infusion over 30 to 120 minutes:

- neonates up to 7 days old: 10 mg/kg every 12 hours, increasing to every 8 hours if response is poor
- 7 days to 12 years of age: 10 mg/kg (to a maximum of 600 mg) every 8 hours
- 12 to 18 years: usual adult doses (see Uses and Administration, above).

Similar doses are licensed in the USA. US licensed product information also suggests that in the treatment of *uncomplicated skin* and *skin structure* infections, oral doses given every 12 hours are sufficient in those aged 5 to 11 years.

Further references.
1. Cuzzolin L, Fanos V. Linezolid: a new antibiotic for newborns and children? *J Chemother* 2006; **18:** 573–81.
2. Velissariou IM. Use of linezolid in children: an overview of recent advances. *Expert Rev Anti Infect Ther* 2006; **4:** 947–52.
3. Chiappini E, *et al.* Clinical efficacy and tolerability of linezolid in pediatric patients: a systematic review. *Clin Ther* 2010; **32:** 66–88.

Administration in renal impairment. Linezolid should be used with caution in patients with renal impairment (creatinine clearance less than 30 mL/minute). Although no dosage adjustment is required, licensed product information states that peak plasma concentrations of linezolid's two major metabolites were about tenfold higher in such patients after several days of treatment. As about 30% of a dose is removed during 3 hours of haemodialysis it is recommended that linezolid should be given after dialysis.

Mycobacterial infections. A systematic review[1] noted that linezolid has been used with some success as an adjunct in the treatment of multidrug-resistant tuberculosis (p. 210.2); it has also been tried in nontuberculous mycobacterial infections (p. 194.1). Usual initial doses were 600 mg twice daily. However, serious adverse effects such as peripheral or optic neuropathy (in 11 of 24 patients), and anaemia (10 of 24) occurred. The review concluded that although there was limited evidence suggesting linezolid may be effective as second-line adjunct therapy for patients with mycobacterial infections, its usefulness is limited by the frequent potentially severe complications of prolonged linezolid use.

A subsequent case series[2] reported that treatment with a linezolid-containing regimen (600 mg twice daily) resulted in sputum conversion as well as clinical and radiographical improvement in 7 patients with extensively drug-resistant tuberculosis; the average time to sputum conversion was 53 days. However, 3 patients developed reversible neutropenia, and 2 developed peripheral neuropathy. Lower dose linezolid-containing regimens (600 mg daily) were better tolerated in a retrospective study of 30 patients with multidrug-resistant tuberculosis;[3] adverse effects (such as peripheral and optic neuropathy, anaemia/thrombocytopenia, rash and diarrhoea) occurred in 9 patients but linezolid needed to be stopped in only 3.

1. Ntziora F, Falagas ME. Linezolid for the treatment of patients with mycobacterial infections: a systematic review. *Int J Tuberc Lung Dis* 2007; **11:** 606–11. Correction. *ibid.*; 936. (title change)
2. Condos R, *et al.* Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. *Chest* 2008; **134:** 187–92.
3. Schecter GF, *et al.* Linezolid in the treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2010; **50:** 49–55.

Adverse Effects and Precautions

The adverse effects most frequently reported in patients given linezolid include diarrhoea, nausea and vomiting, metallic taste, headache, insomnia, constipation, rashes, dizziness, fever, oral and vaginal candidiasis, and abnormal liver function tests. Superficial discoloration of the teeth has occurred in some patients. Lactic acidosis has been reported. Convulsions have also been reported in patients treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported. There have been rare reports of bullous skin eruptions including Stevens-Johnson syndrome. Peripheral and optic neuropathy, sometimes progressing to loss of vision, have occurred rarely, mainly in patients given linezolid for more than 28 days. Visual blurring has been reported in some patients given less than 28 days of treatment.

Reversible myelosuppression including anaemia, leucopenia, pancytopenia and, in particular, thrombocytopenia has been reported and blood counts should be monitored weekly in patients receiving linezolid. Patients particularly at risk are those who have received linezolid for more than 10 to 14 days, who are receiving other bone marrow suppressant drugs, or who have pre-existing myelosuppression or severe renal impairment.

Patients with mixed (Gram-negative and Gram-positive) infections are at a higher risk of mortality when linezolid is given as monotherapy (see Increased Mortality, p. 320.3); linezolid must therefore be used with appropriate antibacterial cover for Gram-negative organisms in such patients.

References.

1. Rubinstein E, *et al.* Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* 2003; **47:** 1824–31.
2. Bishop E, *et al.* Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006; **50:** 1599–1602.
3. Falagas ME, Vardakas KZ. Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. *Drug Safety* 2008; **31:** 753–68.
4. Metaxas EI, Falagas ME. Update on the safety of linezolid. *Expert Opin Drug Safety* 2009; **8:** 485–91.
5. Vinh DC, Rubinstein E. Linezolid: a review of safety and tolerability. *J Infect* 2009; **59** (suppl 1): S59–S74.

Effects on the blood. Reversible myelosuppression with red cell hypoplasia occurred in 3 patients treated with linezolid.[1] Features of the myelosuppression were considered by some[1,2] to be similar to those associated with chloramphenicol, although this was disputed by the manufacturers.[3]

There have been reports of thrombocytopenia occurring at a higher incidence than that reported by the manufacturers; in one study,[4] 6 of 19 patients who had been treated with linezolid developed thrombocytopenia, while another[5] found that it occurred in 23 of 48 patients given the drug for more than 5 days.

During the initial 8 months of licensed use in the UK 12 reports of haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) were received by the UK CSM.[6]

Studies have shown that the risk of thrombocytopenia and anaemia is increased in patients on prolonged linezolid therapy with pre-existing myelosuppression[7,8] or severe renal impairment.[9]

1. Green SL, *et al.* Linezolid and reversible myelosuppression. *JAMA* 2001; **285:** 1291.
2. Lawyer MC, Lawyer EZ. Linezolid and reversible myelosuppression. *JAMA* 2001; **286:** 1974.
3. Arellano FM. Linezolid and reversible myelosuppression. *JAMA* 2001; **286:** 1973–4.
4. Attassi K, *et al.* Thrombocytopenia associated with linezolid therapy. *Clin Infect Dis* 2002; **34:** 695–8.
5. Orrick JJ, *et al.* Thrombocytopenia secondary to linezolid administration: what is the risk? *Clin Infect Dis* 2002; **35:** 348–9.
6. CSM/MCA. Reminder: linezolid (Zyvox) and myelosuppression. *Current Problems* 2001; **27:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)
7. Senneville E, *et al.* Risk factors for anaemia in patients on prolonged linezolid therapy for chronic osteomyelitis: a case-control study. *J Antimicrob Chemother* 2004; **54:** 798–802.
8. Grau S, *et al.* Linezolid: low pre-treatment platelet values could increase the risk of thrombocytopenia. *J Antimicrob Chemother* 2005; **56:** 440–1.
9. Wu V-C, *et al.* High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. *Clin Infect Dis* 2006; **42:** 66–72.

Effects on the eyes. See under Effects on the Nervous System, p. 320.2.

Effects on mitochondria. Linezolid appears to inhibit mitochondrial protein synthesis when given for prolonged courses. This decreases cellular energy production in tissues that are highly dependent on oxidative phosphorylation, such as the optic nerve, skeletal muscles, liver, and kidneys, leading to adverse effects such as lactic acidosis[1] or hyperlactataemia,[1,2] rhabdomyolysis,[3] and optic[4] and/or peripheral neuropathy[1] (see also p. 320.2). Encephalopathy, lactic acidosis, optic neuropathy, skeletal myopathy, and renal failure were reported[1] in a 63-year-old woman after a 4-month course of linezolid. The symptoms resolved when linezolid was stopped; however, the patient remained blind and disorientated. In contrast, bilateral mitochondrial optic neuropathy seen[4] in a 6-year-old boy after a 1-year course of oral linezolid resolved 3 months after linezolid treatment was stopped. In another study[2] reversible hyperlactataemia was reported in 5 patients given linezolid for 1 to 3 months. Mitochondrial activity and lactic acid levels returned to normal when linezolid therapy was stopped.

1. De Vriese AS, *et al.* Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis* 2006; **42:** 1111–1117.
2. Garrabou G, *et al.* Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. *Antimicrob Agents Chemother* 2007; **51:** 962–7.
3. Carroll MW, *et al.* Rhabdomyolysis in a patient treated with linezolid for extensively drug-resistant tuberculosis. *Clin Infect Dis* 2012; **54:** 1624–7.
4. Javaheri M, *et al.* Linezolid-induced optic neuropathy: a mitochondrial disorder? *Br J Ophthalmol* 2007; **91:** 111–15. Correction. *ibid.*; 403.

Effects on the nervous system. The Australian Adverse Drug Reactions Advisory Committee[1] stated in February 2003 that it had received 4 reports of *peripheral neuropathy* in patients who had taken linezolid for 6 to 9 months; none of these cases had resolved at the time of the report. They suggested that the risk of peripheral neuropathy should be considered when treatment was extended beyond 28 days. There have been several published reports of peripheral and *optic neuropathy* associated with linezolid,[2-9] with some attributing these effects to the inhibition of mitochondrial protein synthesis by linezolid. For further discussion see Effects on Mitochondria, above. The regulatory authority in the UK has warned that patients should be advised to report any symptoms of visual impairment immediately, including changes in visual acuity or colour vision, blurred vision, or visual field defects.[10] Any linezolid-treated patient with new visual symptoms should be evaluated promptly and referred to an ophthalmologist if necessary; regular monitoring is advised in all patients who may require treatment for more than 28 days.

In one case report, deterioration of *seizure* control occurred in an epileptic woman treated with linezolid, leading to complex partial status epilepticus. A subsequent rechallenge also led to more prolonged and frequent seizures. The authors suggest that linezolid should be used with caution in patients with a history of epilepsy.[11]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Linezolid and peripheral neuropathy. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0302.htm (accessed 11/01/08)
2. Corallo CE, Paull AE. Linezolid-induced neuropathy. *Med J Aust* 2002; **177:** 332.
3. Rho JP, *et al.* Linezolid-associated peripheral neuropathy. *Mayo Clin Proc* 2004; **79:** 927–30.
4. Lee E, *et al.* Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis* 2003; **37:** 1389–91.
5. Bressler AM, *et al.* Peripheral neuropathy associated with prolonged use of linezolid. *Lancet Infect Dis* 2004; **4:** 528–31.
6. Health Canada. Linezolid (Zyvoxam) and neuropathy. *Can Adverse React News* 2005; **15** (1): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15neng.pdf (accessed 24/07/09)
7. Zivkovic SA, Lacomis D. Severe sensory neuropathy associated with long-term linezolid use. *Neurology* 2005; **64:** 926–7.
8. Legout L, *et al.* Linezolid-induced neuropathy. *Clin Infect Dis* 2004; **38:** 767–8.
9. Rucker JC, *et al.* Linezolid-associated toxic optic neuropathy. *Neurology* 2006; **66:** 595–8.
10. CHM/MHRA. Linezolid (Zyvox): severe optic neuropathy. *Current Problems* 2006; **31:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)
11. Shneker BF, *et al.* Linezolid inducing complex partial status epilepticus in a patient with epilepsy. *Neurology* 2009; **72:** 378–9.

Increased mortality. In March 2007, the FDA[1] issued an alert advising that an open-label, randomised study comparing linezolid to vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections, including catheter-site infections, had found that death rates were significantly higher in patients treated with linezolid (78 of 363) than in the comparator arm (58 of 363), particularly in those with Gram-negative or mixed infections. Mortality did not differ for patients with purely Gram-positive infections.

The FDA[1] and the UK manufacturer[2] therefore advised that linezolid should not be used in infections caused by Gram-negative bacteria and should only be used in mixed Gram-positive and Gram-negative infections when appropriate cover for Gram-negative organisms is given at the same time. Licensed product information now reflects these warnings.

1. FDA. Information for healthcare professionals: linezolid (marketed as Zyvox) (issued 16th March 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/linezolidHCP.pdf (accessed 11/01/08)
2. Pfizer, UK. Important safety information (issued 28th February, 2007). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con2030646&RevisionSelectionMethod=Latest (accessed 11/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies linezolid as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Linezolid is a reversible, nonselective MAOI and therefore has the potential to interact with adrenergic and serotonergic drugs. Enhanced pressor activity has been reported in patients receiving linezolid with phenylpropanolamine or pseudoephedrine and initial doses of dopamine or adrenaline should be reduced. There have also been cases of serotonin syndrome when linezolid was taken with serotonin reuptake inhibitors, and similar symptoms when it was taken with dextromethorphan. The interactions of conventional MAOIs, both with other drugs and with foods, are described under Phenelzine, p. 446.3 and p. 447.1.

The peak plasma concentration and AUC of linezolid were decreased by about 20 and 30% respectively in healthy subjects given concomitant rifampicin, possibly due to the induction of hepatic enzymes; other strong inducers of hepatic enzymes may therefore also cause decreases in linezolid exposure.

Antidepressants. Serotonin syndrome has been reported in patients taking linezolid with serotonergic antidepressants such as *venlafaxine* (see p. 458.3) and *SSRIs* (though concomitant use may be possible, see p. 426.1).

Opioid analgesics. For a report of an interaction between linezolid and *pethidine*, attributed to linezolid's inhibitory actions on monoamine oxidase, see p. 123.2.

Antimicrobial Action

Linezolid is an oxazolidinone antibacterial with activity against a range of aerobic Gram-positive bacteria including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is less active against Gram-negative bacteria, but has some *in-vitro* activity against *Haemophilus influenzae*, *Legionella* spp., *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *Pasteurella* spp. It is not active against *Acinetobacter* spp., Enterobacteriaceae, or *Pseudomonas* spp.

Oxazolidinone antibacterials are bacteriostatic and act by inhibition of ribosomal protein synthesis. Cross-resistance between oxazolidinones and other classes of antibacterial is considered unlikely.

Resistant strains of enterococci and meticillin-resistant *Staph. aureus* have been reported.

References.

1. Noskin GA, *et al.* In vitro activities of linezolid against important Gram-positive bacterial pathogens including vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 1999; **43:** 2059–62.
2. Cercenado E, *et al.* In vitro activity of linezolid against multiply resistant Gram-positive clinical isolates. *J Antimicrob Chemother* 2001; **47:** 77–81.
3. Gemmell CG. Susceptibility of a variety of clinical isolates to linezolid: a European inter-country comparison. *J Antimicrob Chemother* 2001; **48:** 47–52.
4. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii9–ii16.
5. Jones RN, *et al.* Activity of linezolid against 3,251 strains of uncommonly isolated Gram-positive organisms: report from the SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* 2007; **51:** 1491–3.

Resistance. There have been reports of linezolid resistance in enterococci, involving both *Enterococcus faecium*[1-4] and *E. faecalis*.[2] There is also concern over the emergence of linezolid resistance in staphylococci, such as meticillin-resistant *Staphylococcus aureus*,[5-7] *Staph. auricularis*,[8] and *Staph. epidermidis*.[8,9] A survey[10] of reported resistance to linezolid in the USA found that it was still rare but was no longer limited to enterococci having also occurred in *Staph. epidermidis* and *Streptococcus oralis*.

1. Gonzales RD, *et al.* Infections due to vancomycin-resistant Enterococcus faecium resistant to linezolid. *Lancet* 2001; **357:** 1179.
2. Auckland C, *et al.* Linezolid-resistant enterococci: report of the first isolates in the United Kingdom. *J Antimicrob Chemother* 2002; **50:** 743–6.
3. Herrero IA, *et al.* Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. *N Engl J Med* 2002; **346:** 867–9.
4. Seedat J, *et al.* Rapid emergence of resistance to linezolid during linezolid therapy of an Enterococcus faecium infection. *Antimicrob Agents Chemother* 2006; **50:** 4217–19.
5. Tsiodras S, *et al.* Linezolid resistance in a clinical isolate of Staphylococcus aureus. *Lancet* 2001; **358:** 207–8.
6. Wilson P, *et al.* Linezolid resistance in clinical isolates of Staphylococcus aureus. *J Antimicrob Chemother* 2003; **51:** 186–8.
7. Morales G, *et al.* Resistance to linezolid is mediated by the cfr gene in the first report of an outbreak of linezolid-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2010; **50:** 821–5.
8. Cieloszyk K, *et al.* Linezolid resistance in three isolates of coagulase-negative staphylococci. *Ann Pharmacother* 2007; **41:** 526–7.
9. Kelly S, *et al.* Linezolid resistance in coagulase-negative staphylococci. *J Antimicrob Chemother* 2006; **58:** 898–9.
10. Mutnick AH, *et al.* Linezolid resistance since 2001: SENTRY Antimicrobial Surveillance Program. *Ann Pharmacother* 2003; **37:** 769–74.

Pharmacokinetics

Linezolid is rapidly and extensively absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is about 31% bound to plasma proteins. Linezolid is reported to be distributed into bone, fat, lungs, muscle, skin blister fluids, and into the CSF. It is metabolised mainly by oxidation to 2 main inactive metabolites, the hydroxyethyl glycine metabolite (PNU-142586) and the aminoethoxyacetic acid metabolite (PNU-142300); other minor inactive metabolites have also been identified. About 40% of a dose is excreted in the urine as PNU-142586, 30% as linezolid, and 10% as PNU-142300. Small amounts of metabolites are excreted in the faeces. The elimination half-life of linezolid is about 5 to 7 hours.

Children exhibit more rapid clearance of linezolid than adults; half-life is reported to range from about 2 to 4 hours, increasing with age.

References.

1. MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii17–ii25.
2. Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. *Clin Pharmacokinet* 2003; **42:** 1129–40.
3. Whitehouse T, *et al.* Pharmacokinetic studies of linezolid and teicoplanin in the critically ill. *J Antimicrob Chemother* 2005; **55:** 333–40.
4. Vardakas KZ, *et al.* Association of pharmacokinetic and pharmacodynamic aspects of linezolid with infection outcome. *Curr Drug Metab* 2009; **10:** 2–12.
5. Santos RP, *et al.* Pharmacokinetics and pharmacodynamics of linezolid in children with cystic fibrosis. *Pediatr Pulmonol* 2009; **44:** 148–54.
6. Abe S, *et al.* Population pharmacokinetic analysis of linezolid in patients with infectious disease: application to lower body weight and elderly patients. *J Clin Pharmacol* 2009; **49:** 1071–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Litrecan; Zyvox; ***Austral.***: Zyvox; ***Austria***: Zyvoxid; ***Belg.***: Zyvoxid; ***Braz.***: Zyvox; ***Canad.***: Zyvoxam; ***Chile***: Zyvox; ***China***: Zyvox; ***Cz.***: Zyvoxid; ***Denm.***: Zyvoxid; ***Fin.***: Zyvoxid; ***Fr.***: Zyvoxid; ***Ger.***: Zyvoxid; ***Gr.***: Antizolid; Zyvoxid; ***Hong Kong***: Zyvox; ***India***: Alzolid; Anzolid; Infulid; Limet; Linid; Linoplus; Linosept; Linospan; Linox; Lintran; Linzid; Lizbid; Lizemox; Lizoforce; Lizolid; Lizomed; ***Indon.***: Zyvox; ***Irl.***: Zyvox; ***Israel***: Zyvoxid; ***Ital.***: Zyvoxid; ***Malaysia***: Zyvox; ***Mex.***: Zyvoxam; ***Neth.***: Zyvoxid; ***Norw.***: Zyvoxid; ***NZ***: Zyvox; ***Philipp.***: Zyvox; ***Pol.***: Zyvoxid; ***Port.***: Zyvoxid; ***Rus.***: Zyvox (Зивокс); ***S.Afr.***: Zyvoxid; ***Singapore***: Zyvox; ***Spain***: Zyvoxid; ***Swed.***: Zyvoxid; ***Switz.***: Zyvoxid; ***Thai.***: Zyvox; ***Turk.***: Linoxid; Zizolid; Zyvoxid; ***UK***: Zyvox; ***Ukr.***: Zyvox (Зивокс); ***USA***: Zyvox; ***Venez.***: Zyvox.

Lomefloxacin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lomefloxacino; Lomefloksasiinihydrokloridi; Lomefloksasin Hidroklorür; Lométloxacine, Chlorhydrate de; Lomefloxacinhydroklorid; Lomefloxacini Hydrochloridum; Lomefloxacino, hidrocloruro de; NY-198; SC-47111; SC-47111A (lomefloxacin); Ломефлоксацина Гидрохлорид.

(*RS*)-1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

$C_{17}H_{19}F_2N_3O_3$,HCl=387.8

CAS — 98079-51-7 (lomefloxacin); 98079-52-8 (lomefloxacin hydrochloride).

ATC — J01MA07; S01AE04.

ATC Vet — QJ01MA07; QS01AE04.

UNII — 9VC7S3ZXXB.

Uses and Administration

Lomefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It is given orally for the treatment of susceptible infections, including bronchitis due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), and urinary-tract infections. It is also used for surgical infection prophylaxis. Lomefloxacin is given as the hydrochloride but doses are expressed in terms of the base; lomefloxacin hydrochloride 441.5 mg is equivalent to about 400 mg of lomefloxacin. Dosage in the evening may minimise the risk of phototoxic reactions.

The usual dose is 400 mg once daily for 10 to 14 days. A dose of 400 mg once daily for 3 days is suitable in women with acute uncomplicated cystitis. For details of reduced doses in renal impairment, see p. 321.2.

For surgical infection prophylaxis a single 400-mg dose is given 1 to 6 hours before the procedure.

Lomefloxacin is also used topically as the hydrochloride in eye drops and ear drops containing the equivalent of 0.3% of lomefloxacin for the treatment of bacterial conjunctivitis and for the treatment of otitis externa and otitis media, respectively.

General references.

1. Wadworth AN, Goa KL. Lomefloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1991; **42:** 1018–60.
2. Neu HC, ed. Lomefloxacin: development of a once-a-day quinolone. *Am J Med* 1992; **92** (suppl 4A): 1S–137S.

Administration in renal impairment. Oral doses of lomefloxacin should be reduced in patients with renal impairment; the initial dose of 400 mg should be followed by maintenance doses of 200 mg daily in those with a creatinine clearance of 10 to 40 mL/minute per 1.73 m^2 and in those on haemodialysis.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

A relatively high incidence of phototoxic reactions has been seen in patients taking lomefloxacin. Patients should be advised to avoid exposure to sunlight during, and for a few days after, lomefloxacin therapy, and to stop the drug immediately if phototoxicity occurs. Risk of phototoxicity may be reduced by taking lomefloxacin in the evening.

Effects on the skin. Lomefloxacin has been associated with a higher incidence of phototoxic reactions, particularly in patients over 60 years of age and/or with a history of fluoroquinolone treatment; the incidence was also high when used for 30 days or longer.[1] *In-vitro* results[2] suggest that use of sunscreens to protect against lomefloxacin-induced phototoxicity may be feasible.

1. Arata J, *et al.* Photosensitivity reactions caused by lomefloxacin hydrochloride: a multicenter survey. *Antimicrob Agents Chemother* 1998; **42:** 3141–5.
2. Reinhardt P, *et al.* Broad-spectrum sunscreens prevent the secretion of proinflammatory cytokines in human keratinocytes exposed to ultraviolet A and phototoxic lomefloxacin. *Can J Physiol Pharmacol* 2006; **84:** 221–6.

Interactions

As for Ciprofloxacin, p. 264.3.

Lomefloxacin does not appear to interact significantly with theophylline or caffeine.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Most streptococci, including *Streptococcus pneumoniae*, are relatively resistant to lomefloxacin.

Pharmacokinetics

Lomefloxacin is rapidly and almost completely absorbed after oral doses and peak plasma concentrations of about 3 micrograms/mL occur about 1.5 hours after a 400-mg dose. Lomefloxacin is about 10% bound to plasma proteins. It is widely distributed into body tissues including the lungs and prostate.

The elimination half-life of lomefloxacin is about 7 to 8 hours, and is prolonged in patients with renal impairment. Lomefloxacin is excreted in the urine, about 65% as unchanged drug, 9% as the glucuronide, and less than 0.5% as other metabolites. Small amounts (about 10%) are also eliminated unchanged in the faeces. Negligible amounts of lomefloxacin are removed by haemodialysis or peritoneal dialysis.

References.

1. Freeman CD, *et al.* Lomefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 6–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Okacin; ***Austria***: Okacin; Uniquin†; ***Belg.***: Okacin†; ***Braz.***: Maxaquin; ***China***: Ai Bang (爱邦); Ao Mei Xin (奥每欣); Bai De (百德); Bai Ye Xing (百夜星); Bei Luo Te (贝洛特); Duo Long (多龙); Fu Yue (孚悦); Ge Tai (哥台); Ji Ping (吉平); Keqi (科奇); KuiTai (喹泰); Le Bei Xin (乐贝新); Lefen (乐芬); Long Hua Su (龙化素); Luo Wei (洛威); Nuo Ling Dun (诺灵盾); Qi Mi Gao (奇米高); Qian Di (迁迪); Qiluoxian (奇洛先); Qing Xing (庆兴); Shajunda (沙君达); Wanfuluo (万夫洛); Wei Pu (维普); Xin Li Wei (欣立威); Xingfuxin (兴福欣); Yi Lin (逸林); Yi Lu (益禄); Zhong Bao Luo Tai (中宝洛泰); Zhuo Yue (卓悦); ***Cz.***: Okacin†; ***Fr.***: Decalogiflox; Logiflox; ***Ger.***: Okacin†; ***Gr.***: Okacin; ***Hong Kong***: Lomeflox; Maxaquin; Okacin; ***Hung.***: Okacin†; ***India***: Floxaday; Foxil; Gynalom; Lomaday; Lomedon; Lomef; Lomewon; Lomexel; Lomflox; Lomibact; Lomitas; Loxipen; Mahaquin; Okacin; Ontop†; ***Israel***: Okacin†; ***Ital.***: Chimono; Lomebact; Maxaquin; Okacin; Uniquin; ***Jpn***: Bareon; Lomeflon; ***Mex.***: Lomacin; Maxaquin; ***Philipp.***: Okacin; ***Pol.***: Okacin†; ***Port.***: Loransil; Maxaquin; Okacin; Uniquin†; ***Rus.***: Ksenakvin (Ксенаквин); Lofox (Лофокс); Lomacin (Ломацин); Lomflox (Ломфлокс); Okacin (Окацин)†; ***S.Afr.***: Maxaquin†; Okacyn†; Uniquin†; ***Singapore***: Lomflox; Okacin; ***Spain***: Ocacin†; ***Switz.***: Maxaquin†; Okacin†; ***Thai.***: Okacin†; ***Turk.***: Okacin; ***UAE***: Lomax; ***Ukr.***: Ksenakvin (Ксенаквин)†; Lomaday (Ломадей)†; Okacin (Окацин)†; ***USA***: Maxaquin†; ***Venez.***: Loflox; Lomex; Maxaquin; Okacin.

Multi-ingredient Preparations. ***Rus.***: Combitub-Neo (Комбитуб-Нео); Lomecomb (Ломекомб); Protiocomb (Протиокомб); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе).

Loracarbef *(BAN, USAN, rINN)*

KT-3777; Loracarbefum; Lorakarbef; Lorakarbefi; LY-163892; Лоракарбеф.

(6*R*,7*S*)-3-Chloro-8-oxo-7-D-phenylglycylamino-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

$C_{16}H_{16}ClN_3O_4,H_2O$=367.8

CAS — 76470-66-1 (anhydrous loracarbef); 121961-22-6 (loracarbef monohydrate).

ATC — J01DC08.

ATC Vet — QJ01DC08.

UNII — 3X11EVM5SU (loracarbef); W72I5ZT78Z (anhydrous loracarbef).

Pharmacopoeias. In *US.*

USP 36: (Loracarbef). pH of a 10% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Uses and Administration

Loracarbef is an oral carbacephem antibacterial. The carbacephems are closely related to the cephalosporins, but replacement of the sulfur atom in the 7-aminocephalosporanic acid nucleus by a methylene group is said to enhance stability. It is used similarly to cefaclor in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria including infections of the respiratory and urinary tracts and of skin and skin-structures. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Loracarbef should be given 1 hour before food or on an empty stomach. Loracarbef is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous loracarbef. The usual adult dose is 200 to 400 mg every 12 hours. In uncomplicated urinary-tract infections, a dose of 200 mg daily may be adequate.

The dose of loracarbef may need to be reduced in renal impairment, see p. 322.1. For details of doses in children, see also p. 322.1.

General references.

1. Moellering RC, Jacobs NF. Advances in outpatient antimicrobial therapy: loracarbef. *Am J Med* 1992; **92** (suppl 6A): 1S–103S.
2. Brogden RN, McTavish D. Loracarbef: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 716–36.
3. Roos K, Larsson P. Loracarbef versus phenoxymethylpenicillin in the treatment of recurrent streptococcal pharyngotonsillitis. *Scand J Infect Dis* 1997; **29:** 141–5.
4. Gooch WM, *et al.* Loracarbef versus clarithromycin in children with acute otitis media with effusion. *Clin Ther* 1999; **21:** 711–22.

Administration in children. Loracarbef may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. A usual dose for children weighing 7 kg or more is 7.5 mg/kg every 12 hours for uncomplicated infections or 15 mg/kg every 12 hours for acute otitis media or acute maxillary sinusitis.

Administration in renal impairment. Oral doses of loracarbef should be reduced in patients with renal impairment; patients with a creatinine clearance of 10 to 49 mL/minute may be given half the usual dose at the usual dosage interval or the full usual dose at twice the usual interval; patients with a creatinine clearance of less than 10 mL/minute may be treated with the usual dose given every 3 to 5 days. Patients on haemodialysis should receive another dose following dialysis.

Adverse Effects and Precautions

Adverse effects of loracarbef are generally similar to those of other beta lactams (see Benzylpenicillin, p. 229.2, and Cefalotin, p. 235.2). They include gastrointestinal disturbances, particularly diarrhoea, and hypersensitivity reactions such as skin rashes. Increases in liver enzymes and abnormalities in haematological parameters have been reported.

Loracarbef should not be given to patients known to be hypersensitive to it or to other beta lactams because of the possibility of cross-sensitivity. It should be given with caution, with appropriate dosage reduction, in patients with renal impairment.

Effects on the kidneys. References.

1. Thieme RE, *et al.* Acute interstitial nephritis associated with loracarbef therapy. *J Pediatr* 1995; **127:** 997–1000.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies loracarbef as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Probenecid decreases the renal excretion of loracarbef thereby increasing its plasma concentrations.

Antimicrobial Action

Loracarbef is bactericidal with antibacterial activity similar to that of cefaclor (p. 233.1).

Pharmacokinetics

Loracarbef is well absorbed from the gastrointestinal tract with a bioavailability of 90%. Peak plasma concentrations after 200- and 400-mg doses as capsules are about 8 and 14 micrograms/mL respectively at 1.2 hours. Peak concentrations occur more rapidly after an oral suspension and a paediatric dose of 15 mg/kg produces a concentration of about 19 micrograms/mL within 40 to 60 minutes. Absorption is delayed by the presence of food. A plasma half-life of about 1 hour has been reported which is prolonged in renal impairment. About 25% is bound to plasma proteins.

Loracarbef is excreted largely unchanged in the urine, and therapeutic concentrations are maintained in the urine for up to 12 hours. Probenecid delays excretion. Loracarbef is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Lorafem†; ***Gr.***: Lorbef; ***S. Afr.***: Lorabid; ***Swed.***: Lorabid†; ***Turk.***: Lorabid.

Pharmacopoeial Preparations
USP 36: Loracarbef Capsules; Loracarbef for Oral Suspension.

Lymecycline *(BAN, rINN)*

Limeciclina; Limeciklin; Limesiklin; Lymecyclin; Lymécycline; Lymecyclinum; Lymecyklin; Lymecyklina; Lymesykliini; Tetracyclinemethylene lysine; Лимециклин.

(+)-*N*-(5-Amino-5-carboxypentylaminomethyl)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonapthacene-2-carboxamide; N^2-{[(+)-5-Amino-5-carboxypentylamino]methyl}tetracycline.

$C_{29}H_{38}N_4O_{10}$=602.6

CAS — 992-21-2.

ATC — J01AA04.

ATC Vet — QJ01AA04.

UNII — 7D6EM3S13P.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lymecycline). A reaction product of formaldehyde, lysine, and tetracycline. A yellow, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.8 to 8.2. Store in airtight containers. Protect from light.

Profile

Lymecycline is a tetracycline derivative with general properties similar to those of tetracycline (p. 375.1). Although its absorption is not significantly affected by moderate amounts of milk, it is still affected by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc.

Lymecycline is given orally and doses are expressed in terms of the equivalent amount of tetracycline base. Lymecycline 407 mg is equivalent to about 300 mg of tetracycline and to about 325 mg of tetracycline hydrochloride. The usual adult dose is the equivalent of 300 mg of tetracycline base twice daily. In severe infections total daily doses of up to the equivalent of 1.2 g may be given. In the treatment of acne, the equivalent of 300 mg is given daily for at least 8 weeks.

For details of use in children and adolescents, see p. 322.2.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, lymecycline is licensed for use in children aged 12 years and over; the usual oral adult dose (see above) may be given. However, in some countries, it is licensed for use in those over 8 years old.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lymecycline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Skin disorders. For reference to the use of lymecycline in the treatment of acne, see under Tetracycline, p. 376.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Eficiclina; Tetralysal; ***Belg.***: Tetralysal; ***Braz.***: Tetralysal; ***Chile***: Tetralysal; ***Denm.***: Tetralysal; ***Fin.***: Tetralysal; ***Fr.***: Tetralysal; ***Hong Kong***: Tetralysal; ***Hung.***: Tetralysal; ***Irl.***: Tetralysal; ***Ital.***: Tetralysal; ***Mex.***: Tetralisal; ***Norw.***: Tetralysal; ***NZ***: Tetralysal; ***Philipp.***: Tetralysal; ***S.Afr.***: Tetralysal; ***Swed.***: Tetralysal; ***Switz.***: Tetralysal; ***UK***: Tetralysal; ***Venez.***: Tetralysal.

Pharmacopoeial Preparations
BP 2014: Lymecycline Capsules.

Mafenide *(BAN, USAN, rINN)*

Mafenid; Mafenida; Maféníde; Mafenidi; Mafenidum; NSC-34632; Мафенид.

α-Aminotoluene-*p*-sulphonamide.

CAS — 138-39-6.

ATC — D06BA03.

ATC Vet — QD06BA03.

UNII — 5844758P4L.

Mafenide Acetate *(BANM, rINNM)*

Acetato de mafenida; Mafenida, acetato de; Maféníde, Acétate de; Mafenidi Acetas; Мафенида Ацетат.

$C_7H_{10}N_2O_2S,C_2H_4O_2$=246.3

CAS — 13009-99-9.

ATC — D06BA03.

ATC Vet — QD06BA03.

UNII — RQ6LP6Z0WY.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Mafenide Acetate). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.4 and 6.8. Store in airtight containers. Protect from light.

Uses and Administration

Mafenide is a short-acting sulfonamide that is not inactivated by *p*-aminobenzoic acid or by pus and serum. The acetate is used as a cream, containing the equivalent of mafenide 8.5%, for the prevention and treatment of infection, including *Pseudomonas aeruginosa*, in second- and third-degree burns (p. 1683.1). A solution containing mafenide acetate 5% is also available for use under moist dressings in burns. Mafenide hydrochloride and mafenide propionate have also been used.

Adverse Effects, Treatment, and Precautions

Mafenide is absorbed to some extent after topical application and may produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p. 367.3). Fatal haemolytic anaemia with disseminated intravascular coagulation, related to G6PD deficiency, has been reported.

Mafenide cream may cause pain or a burning sensation on application to the burnt area, with occasional bleeding or excoriation. The separation of the eschar may be delayed and fungal invasion of the wound has been reported. By its action in inhibiting carbonic anhydrase, mafenide may cause metabolic acidosis and hyperventilation; acid–base balance should therefore be monitored, particularly in patients with extensive burns, or with pulmonary or renal impairment. If persistent acidosis occurs, mafenide treatment should be temporarily suspended and fluid therapy continued.

Hypersensitivity. References.

1. Firoz EF, *et al.* Allergic contact dermatitis to mafenide acetate: a case series and review of the literature. *J Drugs Dermatol* 2007; **6:** 825–8.

Pharmacokinetics

Mafenide is absorbed from wounds into the circulation and is metabolised to *p*-carboxybenzenesulfonamide, which is excreted in the urine. The metabolite has no antibacterial action but retains the ability to inhibit carbonic anhydrase.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Sulfamylon.

Multi-ingredient Preparations. ***Indon.***: FG Ointment†.

Pharmacopoeial Preparations
USP 36: Mafenide Acetate Cream; Mafenide Acetate for Topical Solution.

Magainins

Magaininas; Магаинины.

Profile

The magainins are a group of antibacterial peptides derived from amphibians. Several semisynthetic derivatives including pexiganan acetate (MSI-78), MSI-93, and MSI-94 have been investigated as topical anti-infectives.

References.

1. Lamb HM, Wiseman LR. Pexiganan acetate. *Drugs* 1998; **56:** 1047–52.
2. Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. *Drugs* 2007; **67:** 195–214.
3. Andrès E, Dimarcq JL. Peptides antimicrobiens cationiques: de l'étude de l'immunité innée à la production de médicaments. Mise à jour. *Med Mal Infect* 2007; **37:** 194–9.
4. Lipsky BA, *et al.* Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. *Clin Infect Dis* 2008; **47:** 1537–45.

Mandelic Acid

Ácido fenilglicólico; Ácido mandélico racémico; Amygdalic Acid; Mandélico, ácido; Phenylglycolic Acid; Racemic Mandelic Acid; Миндальная Кислота.

2-Hydroxy-2-phenylacetic acid.

$C_8H_8O_3$=152.1

CAS — 90-64-2; 17199-29-0 ((+)-mandelic acid); 611-71-2 ((-)-mandelic acid); 611-72-3 ((±)-mandelic acid).

ATC — B05CA06; J01XX06.

ATC Vet — QB05CA06; QJ01XX06.

UNII — NH496X0UJX.

Profile

Mandelic acid has bacteriostatic properties and is used as a 1% flushing solution for the maintenance of indwelling urinary catheters. Mandelic acid and acetyl mandelic acid are used topically in preparations for the treatment of acne. It was formerly given orally in the treatment of urinary-tract infections, usually as the ammonium or calcium salt.

Mandelic acid is a component of methenamine mandelate (p. 325.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Rolip.

Multi-ingredient Preparations. ***Chile***: NeoStrata; ***Fr.***: Zeniac LP Fort; Zeniac LP; Zeniac; Zeniac; ***Ital.***: Neoceuticals Clear Skin†; Neoceuticals Spot Treatment†.

Marbofloxacin *(BAN, rINN)*

Marbofloksasiini; Marbofloxacine; Marbofloxacino; Marbofloxacinum; Марбофлоксацин.

9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid.

$C_{17}H_{19}FN_4O_4$=362.4

CAS — 115550-35-1.

ATC Vet — QJ01MA93.

UNII — 8X09WU898T.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Marbofloxacin for Veterinary Use). A light yellow, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; sparingly soluble or slightly soluble in dichloromethane. Protect from light.

Profile

Marbofloxacin is a fluoroquinolone antibacterial used in veterinary medicine.

Mecillinam *(BAN, rINN)*

Amdinocillin (USAN); FL-1060; Mecilinam; Mécillinam; Mecillinamum; Mesillinaami; Ro-10-9070; Мециллинам.

(6*R*)-6-(Perhydroazepin-1-ylmethyleneamino)penicillanic acid.

$C_{15}H_{23}N_3O_3S$=325.4

CAS — 32887-01-7.

ATC — J01CA11.

ATC Vet — QJ01CA11.

UNII — V10579P3QZ.

Uses and Administration

Mecillinam is a semisynthetic penicillin with a substituted amidino group at the 6-position of the penicillanic acid nucleus. It is given by slow intravenous injection, by intravenous infusion, or intramuscularly, in the treatment of susceptible Gram-negative infections (see under Antimicrobial Action, p. 323.1).

For urinary-tract infections a dose of 800 mg is given every 6 to 8 hours. A total dose of up to 60 mg/kg daily may be used in very severe infections.

Mecillinam has been used with other beta lactams to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

The pivaloyloxymethyl ester of mecillinam, pivmecillinam, is used orally (see p. 344.2).

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mecillinam as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

Mecillinam is a derivative of amidinopenicillanic acid. Unlike benzylpenicillin and related antibacterials, it is active against many Gram-negative bacteria.

- Sensitive organisms include Enterobacteriaceae such as *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Salmonella*, and *Shigella* spp. The susceptibility of *Proteus* spp. varies; *Serratia marcescens* is generally resistant.
- It is less active against *Neisseria* spp. and *Haemophilus influenzae*. *Pseudomonas aeruginosa* and *Bacteroides* spp. are considered to be resistant.
- It is much less active against Gram-positive bacteria; enterococci including *Enterococcus faecalis* are resistant.

Mecillinam interferes with the synthesis of the bacterial cell wall by binding with a different penicillin-binding protein from benzylpenicillin. This difference in mode of action may explain the synergism against many Gram-negative organisms that has been reported *in vitro* between mecillinam and various penicillins or cephalosporins.

Mecillinam is inactivated by beta-lactamases, but is more stable than ampicillin.

Pharmacokinetics

Mecillinam is poorly absorbed from the gastrointestinal tract. Peak plasma concentrations of about 6 and 12 micrograms/mL have been achieved half an hour after intramuscular doses of 200 and 400 mg, respectively. The usual plasma half-life of about 1 hour has been reported to be prolonged to 3 to 5 hours or more in severe renal impairment. Between 5 and 10% of mecillinam is bound to plasma proteins. Mecillinam is widely distributed into body tissues and fluids; little passes into the CSF unless the meninges are inflamed. It crosses the placenta into the fetal circulation; little appears to be distributed into breast milk.

Mecillinam is metabolised to only a limited extent. From 50 to 70% of a parenteral dose may be excreted in the urine within 6 hours by glomerular filtration and tubular secretion. Renal tubular secretion can be reduced by probenecid. Some mecillinam is excreted in bile where high concentrations occur.

Mecillinam is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Selexid; ***Gr.***: Selexid.

Meclocycline *(BAN, USAN, rINN)*

GS-2989; Meclociclina; Meclocyclin; Méclocycline; Meclocyclinum; Meklocyklin; Meklosykliini; NSC-78502; Меклоциклин.

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

$C_{22}H_{21}ClN_2O_8$=476.9

CAS — 2013-58-3.

ATC — D10AF04.

ATC Vet — QD10AF04.

UNII — 23Q8M2HE6S.

Meclocycline Sulfosalicylate *(USAN)*

Meclociclina, sulfosalicilato de; Meclocycline Sulphosalicylate; Меклоциклина Сульфосалицилат.

Meclocycline 5-sulphosalicylate.

$C_{22}H_{21}ClN_2O_8.C_7H_6O_6S$=695.0

CAS — 73816-42-9.

ATC — D10AF04.

ATC Vet — QD10AF04.

UNII — 46VZA7RX28.

Pharmacopoeias. In *US.*

USP 36: (Meclocycline Sulfosalicylate). pH of a 1% solution in water is between 2.5 and 3.5. Store in airtight containers. Protect from light.

Profile

Meclocycline is a tetracycline antibacterial (p. 375.1) that is applied topically as the sulfosalicylate for the treatment of acne vulgaris (p. 1682.2) and superficial skin infections (p. 207.1). Potency is expressed in terms of meclocycline. Preparations containing the equivalent of 1 or 2% are available. Meclocycline sulfosalicylate has also been given as a pessary in the treatment of vulvovaginal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Meclosorb; ***Ital.***: Mecloderm Ovuli; Mecloderm.

Multi-ingredient Preparations. ***Ital.***: Anti-Acne; Mecloderm F.

Pharmacopoeial Preparations

USP 36: Meclocycline Sulfosalicylate Cream.

Meleumycin

Pharmacopoeias. In *Chin.*

Profile

Meleumycin, a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens*, consists of a mixture of midecamycin A_1 and kitasamycin A_6. It has actions and uses similar to those of erythromycin (p. 291.2) and is given orally in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Si Qi Le (司奇乐).

Meropenem *(BAN, USAN, rINN)*

ICI-194660; Meropeneemi; Meropeném; Méropénem; Meropenemum; SM-7338; Меропенем.

(4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-Dimethylcarbamoylpyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

$C_{17}H_{25}N_3O_5S.3H_2O$=437.5

CAS — 96036-03-2 (meropenem); 119478-56-7 (meropenem trihydrate).

ATC — J01DH02.

ATC Vet — QJ01DH02.

UNII — FV9J3JU8B1 (meropenem); YOP6PX08AO (anhydrous meropenem).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Meropenem Trihydrate). A white or light yellow, crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 4.0 to 6.0.

USP 36: (Meropenem). Colourless to white crystals. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone and in ether; soluble in dimethylformamide and in 5% monobasic potassium phosphate solution. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Uses and Administration

Meropenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p. 309.3). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria including intra-abdominal infections, gynaecological infections, meningitis, respiratory-tract infections, skin and skin-structure infections, urinary-tract infections, and infections in immunocompromised patients. It may also be of use for initial empirical treatment of such conditions because of its broad spectrum of action. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Meropenem is given intravenously as the trihydrate, but doses are expressed in terms of the amount of anhydrous meropenem; 1.14 g of meropenem trihydrate is equivalent to about 1 g of anhydrous meropenem. It is given as an infusion over 15 to 30 minutes in a usual adult dose of 0.5 to 1 g every 8 hours; 2 g every 8 hours is recommended for meningitis and for bronchopulmonary infections in cystic fibrosis. Doses of up to 1 g may alternatively be given by slow intravenous injection over 3 to 5 minutes.

The dose of meropenem may need to be reduced in renal impairment, see p. 324.1. See also p. 323.3 for details of doses in infants and children.

Reviews.

1. Wiseman LR, *et al.* Meropenem: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1995; **50:** 73–101.
2. Finch RG, *et al.* eds. Meropenem: focus on clinical performance. *J Antimicrob Chemother* 1995; **36** (suppl A): 1–223.
3. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.
4. Hurst M, Lamb HM. Meropenem: a review of its use in patients in intensive care. *Drugs* 2000; **59:** 653–80.
5. Lowe MN, Lamb HM. Meropenem: an updated review of its use in the management of intra-abdominal infections. *Drugs* 2000; **60:** 619–46.
6. Edwards SJ, *et al.* Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin* 2005; **21:** 785–94.
7. Linden P. Safety profile of meropenem: an updated review of over 6000 patients treated with meropenem. *Drug Safety* 2007; **30:** 657–68.
8. Baldwin CM, *et al.* Meropenem: a review of its use in the treatment of serious bacterial infections. *Drugs* 2008; **68:** 803–38.
9. Perrott J, *et al.* Comparing outcomes of meropenem administration strategies based on pharmacokinetic and pharmacodynamic principles: a qualitative systematic review. *Ann Pharmacother* 2010; **44:** 557–64.

Administration. Similarly to doripenem (see p. 287.2) extended infusion of meropenem or imipenem with cilastatin over 3 hours rather than 30 minutes has been suggested[1] as a way of increasing the efficacy of these drugs, particularly against severe or resistant infections.

1. Lee LS, *et al.* Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. *Diagn Microbiol Infect Dis* 2010; **68:** 251–8.

Administration in children. Meropenem may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is usually given by intravenous infusion over 15 to 30 minutes but

doses of up to 20 mg/kg may alternatively be given by slow intravenous injection over 3 to 5 minutes. Meropenem is licensed in both the UK and the USA for infants and children aged 3 months and over. The usual dose is 10 to 20 mg/kg every 8 hours. A dose of 40 mg/kg is given every 8 hours for meningitis and for bronchopulmonary infections in cystic fibrosis. Children weighing over 50 kg should be dosed as for adults (see Uses and Administration, p. 321.3).

In addition, the *BNFC* suggests the following doses for those under 3 months of age:

- neonates under 7 days of age: 20 mg/kg every 12 hours (or 40 mg/kg every 12 hours in severe infections and in meningitis)
- neonates 7 to 28 days of age: 20 mg/kg every 8 hours (or 40 mg/kg every 8 hours in severe infections and in meningitis)
- infants 1 to 3 months of age: 10 to 20 mg/kg every 8 hours (or 40 mg/kg every 8 hours in meningitis and for bronchopulmonary infections in cystic fibrosis)

Administration in renal impairment. Intravenous doses of meropenem should be reduced in patients with renal impairment. The following doses may be given to adults based on creatinine clearance (CC):

- CC 26 to 50 mL/minute: the usual dose given every 12 hours
- CC 10 to 25 mL/minute: one-half the usual dose every 12 hours
- CC less than 10 mL/minute: one-half the usual dose every 24 hours
- haemodialysis patients: the usual dose after the dialysis session

Alternatively, a review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy has recommended that those undergoing intermittent haemodialysis receive a dose of 500 mg every 24 hours (given after the dialysis run). For those undergoing continuous renal replacement therapy, the authors suggest a loading dose of 1 g, with the following maintenance doses:

- continuous venovenous haemofiltration (CVVH): 500 mg to 1 g every 12 hours (although 500 mg every 8 hours can also be considered). Other authors[2] have suggested that patients on high-volume CVVH will require doses of 1 g every 8 hours to treat infections caused by less susceptible bacteria
- continuous venovenous haemodialysis (CVVHD) and haemodiafiltration (CVVHDF): 500 mg to 1 g every 8 to 12 hours (500 mg every 6 to 8 hours can also be considered for CVVHDF)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.
2. Bilgrami I, *et al.* Meropenem dosing in critically ill patients with sepsis receiving high-volume continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 2010; **54:** 2974–8.

Adverse Effects and Precautions

As for Imipenem, p. 310.1.

Meropenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have less potential to induce seizures than imipenem (see p. 324.1).

Effects on the liver. Vanishing bile-duct syndrome, a potentially life-threatening cause of cholestatic liver injury, has been associated with the use of meropenem.[1]

1. Schumaker AL, Okulicz JF. Meropenem-induced vanishing bile duct syndrome. *Pharmacotherapy* 2010; **30:** 953.

Effects on the nervous system. *Animal* studies have indicated that meropenem induces fewer seizures than imipenem-cilastatin and clinical data from the manufacturer have confirmed this.[1] Comparison of data[2] from 4872 patients with a variety of infections (including meningitis) treated with meropenem with that from 4752 patients given other antibacterials, mainly cephalosporin-based regimens or imipenem-cilastatin, showed that meropenem was not associated with any greater risk of seizures than the other antibacterials and was likely to have less neurotoxic potential than imipenem-cilastatin, making it suitable to use in the treatment of meningitis.

1. Norrby SR, *et al.* Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother* 1995; **36** (suppl A): 207–23.
2. Norrby SR, Gildon K M. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. *Scand J Infect Dis* 1999; **31:** 3–10.

Hypersensitivity. For suggestions that the rate of cross-sensitivity to carbapenems, including meropenem, in patients with penicillin hypersensitivity may be lower than previously thought, see p. 310.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies meropenem as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to meropenem, and the view that carbapenems should not be used with valproates, see p. 557.2.

Antimicrobial Action

As for Imipenem, p. 310.2.

Meropenem is slightly more active than imipenem against Enterobacteriaceae and slightly less active against Gram-positive organisms.

Pharmacokinetics

After intravenous injection of meropenem 0.5 and 1 g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively.

Meropenem has a mean plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.

Meropenem is removed by haemodialysis.

References.

1. Mouton JW, Van den Anker JN. Meropenem clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **28:** 275–86.
2. Thalhammer F, Horl WH. Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. *Clin Pharmacokinet* 2000; **39:** 271–9.
3. Ververs TF, *et al.* Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. *Crit Care Med* 2000; **28:** 3412–16.
4. van Enk JG, *et al.* Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001; **23:** 198–201.
5. Goldstein SL, *et al.* Meropenem pharmacokinetics in children and adolescents receiving hemodialysis. *Pediatr Nephrol* 2001; **16:** 1015–18.
6. Ariano RE, *et al.* Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39:** 32–8.
7. Novelli A, *et al.* Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet* 2005; **44:** 539–49.
8. Du X, *et al.* Population pharmacokinetics and pharmacodynamics of meropenem in pediatric patients. *J Clin Pharmacol* 2006; **46:** 69–75.
9. Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin Infect Dis* 2008; **47** (suppl 1): S32–S40.
10. van den Anker JN, *et al.* Meropenem pharmacokinetics in the newborn. *Antimicrob Agents Chemother* 2009; **53:** 3871–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Meroefectil; Merotenk; Merozen; Merpem; ***Austral.***: Merrem; ***Austria***: Merinfec; Optinem; ***Belg.***: Meronem; ***Braz.***: Mepenox; Meronem; Zylpen; ***Canad.***: Merrem; ***Chile***: Acus; Meronem; ***China***: Meite (美特); Mepem (美平); Painon (倍能); ***Cz.***: Menoinfex; Meronem; ***Denm.***: Meronem; Merospira; ***Fin.***: Meronem; ***Fr.***: Meronem; ***Ger.***: Meronem; ***Gr.***: Carbenem; Merobact; Meronem; Merovia; Merozan; Nemerop; Ronepem; Rulmenem; Santamer; ***Hong Kong***: Meronem; ***Hung.***: Meronem; ***India***: Ameropem; Amropenem; Aripnem; Cosmor; Curepin; Erope; Etopen; Exmer; Feropenem; Geriopen; Gonem; Inlife; Inpenam; Insomer; Kanam; Map; Marnif; Marzipan; Maxinem; Maxopem; Maxopen; Medinumm; Medipenam; Menem; Merenz; Merobact; Merobest; Merobus; Merocad; Merocrit; Merod; Merofact; Merofit; Merokem; Meromate; Meromer; Meronem; Meronis; Meropam; Meroplan; Merosan; Merospect; Merotec; Merotop; Merotrol; Merover; Merowor; Meroza; Mery; Micon; Moira; Morep; MPenem; Myopan; Neumer; Onmero; Open; Pacetaker; ***Indon.***: Caprenem; Eradix; Lanmer; Merem; Merobat; Merocef; Merofen; Meronem; Meropex; Merosan; Merotik; Propenem; Rindonem; Ronem; Sefanem; Tripenem; ***Irl.***: Merapem; Meronem; ***Israel***: Meronem; ***Ital.***: Meperost; Merrem; Reopemest; ***Jpn***: Meropen; ***Malaysia***: Meronem; ***Mex.***: Lusantem; Merrem; Pisapem; Strinem; ***Neth.***: Mepereost; Meronem; Reopemest†; ***Norw.***: Meronem; ***NZ***: Merrem; ***Philipp.***: Mepenem; Merix; Meromax; Meronem; Merop; Meropen; Ropen; Ropenem; ***Pol.***: Mepereost; Meronem; Reopemest; ***Port.***: Meronem; ***Rus.***: Merexid (Мерексид); Meronem (Меронем); Meropenabol (Меропенабол); Syronem (Сайронем); ***S.Afr.***: Mercide; Meronem; ***Singapore***: Meronem; ***Spain***: Meronem; ***Swed.***: Meronem; ***Switz.***: Meronem; ***Thai.***: Bestinem; Enem; Mapenem; Mero; Meronem; Monem; Penem; Romenem; Zaxter; ***Turk.***: Meronem; Merosid; Merozan; Mopem; ***UAE***: Miran; ***UK***: Meronem; ***Ukr.***: Мерепам (Мепенам); Meronem (Меронем); Mezonex (Мезонекс)†; Panlactam (Панлактам); Ronem (Ронем); ***USA***: Merrem; ***Venez.***: Meronem.

Pharmacopoeial Preparations

USP 36: Meropenem for Injection.

Methacycline *(BAN, USAN)*

GS-2876; Metaciclina; Metacycline (pINN); Métacycline; Metacyclinum; Metacyklin; Metasykliini; Метациклин.

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

$C_{22}H_{22}N_2O_8$=442.4

CAS — 914-00-1.

ATC — J01AA05.

ATC Vet — QJ01AA05.

UNII — IR235I7C5P.

Methacycline Hydrochloride *(BANM)*

Hidrocloruro de metaciclina; Metaciclina, hidrocloruro de; Métacycline, Chlorhydrate de; Metacycline Hydrochloride (pINNM); Metacyclini Chloridum; Metacyclini Hydrochloridum; Metacykliny chlorowodorek; Méthylènecycline Chlorhydrate; 6-Methyleneoxytetracycline Hydrochloride; Метациклина Гидрохлорид.

$C_{22}H_{22}N_2O_8$,HCl=478.9

CAS — 3963-95-9.

ATC — J01AA05.

ATC Vet — QJ01AA05.

UNII — 9GJ0N7ZAP0.

Pharmacopoeias. In *Chin.*, *Pol.*, and *US.*

USP 36: (Methacycline Hydrochloride). A yellow to dark yellow crystalline powder. Soluble 1 in 100 of water, 1 in 300 of alcohol, and 1 in 25 of 0.1N sodium hydroxide; very slightly soluble in chloroform and in ether. pH of a solution in water containing the equivalent of methacycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Profile

Methacycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.1). Like demeclocycline, it is excreted more slowly than tetracycline and effective blood concentrations are maintained for longer periods; the plasma elimination half-life is about 14 hours.

Methacycline hydrochloride is given orally in a usual adult dose of 600 mg daily in 2 divided doses, preferably 1 hour before or 2 hours after meals.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Zuobenneng (佐本能); ***Fr.***: Lysocline; Physiomycine; ***Ital.***: Esarondil; Rotilen.

Pharmacopoeial Preparations

USP 36: Methacycline Hydrochloride Capsules; Methacycline Hydrochloride Oral Suspension.

Methenamine *(rINN)*

Aminoform; E239; Esametilentetrammina; Esammina; Formine; Heksamin; Hexamethylenamine; Hexamine; Metenamiini; Metenamin; Meténamin; Metenamina; Metenaminas; Metenammina; Methenamin; Méthénamine; Methenaminum; Urotropine; Метенамин.

Hexamethylenetetramine; 1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane.

$C_6H_{12}N_4$=140.2

CAS — 100-97-0.

ATC — J01XX05.

ATC Vet — QJ01XX05.

UNII — J50OIX95QV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Methenamine). A white, or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Methenamine). Colourless, practically odourless, lustrous crystals or white crystalline powder. Soluble 1 in 1.5 of water, 1 in 12.5 of alcohol, 1 in 10 of chloroform, and 1 in 320 of ether. Its solutions are alkaline to litmus.

Methenamine Hippurate *(BAN, USAN, rINNM)*

Heksamin Hippurat; Hexamine Hippurate; Hipurato de metenamina; Metenamin Hippurat; Metenamina, hipurato de; Méthénamine, Hippurate de; Methenamini Hippuras; Метенамина Гиппурат.

Hexamethylenetetramine hippurate.

$C_6H_{12}N_4,C_9H_9NO_3$=319.4

CAS — 5714-73-8.

ATC — J01XX05.

ATC Vet — QJ01XX05.

UNII — M329791L57.

Pharmacopoeias. In *US.*

Methenamine Mandelate *(rINNM)*

Heksamin Mandelat; Hexamine Amygdalate; Hexamine Mandelate; Mandelato de metenamina; Metenamin Mandelat; Metenamina, mandelato de; Méthénamine, Mandelate de; Methenamini Mandelas; Метенамина Манделат.

Hexamethylenetetramine mandelate.

$C_6H_{12}N_4,C_8H_8O_3$=292.3

CAS — 587-23-5.

ATC — J01XX05.

ATC Vet — QJ01XX05.

UNII — 695N30CINR.

Pharmacopoeias. In *US.*

USP 36: (Methenamine Mandelate). A white, practically odourless crystalline powder. Very soluble in water; soluble 1 in 10 of alcohol, 1 in 20 of chloroform, and 1 in 350 of ether. Its solutions have a pH of about 4.

Uses and Administration

Methenamine is used, usually as the hippurate or mandelate, in the prophylaxis and long-term suppression of chronic or recurrent, uncomplicated, lower urinary-tract infections and asymptomatic bacteriuria. It has been considered suitable for long-term use because acquired resistance does not appear to develop.

Methenamine and its salts should not be used in upper urinary-tract infections because it is eliminated too rapidly to exert an effect, nor in acute urinary infections. It is only active in acidic urine, when formaldehyde is released, and although hippuric or mandelic acid helps to acidify the urine, ammonium chloride or ascorbic acid may be tried. If urea-splitting bacteria such as *Proteus* or some *Pseudomonas* spp. are present they may produce so much ammonia that the urine cannot be acidified (see also Antimicrobial Action, p. 325.2).

The usual oral adult dose of methenamine or methenamine mandelate is 1 g given four times daily. Methenamine hippurate is given orally in a usual dose of 1 g twice daily; the dose may be increased to three times daily in catheterised patients.

For details of doses in children, see p. 325.1.

Methenamine has been used topically in deodorant preparations, since in the presence of acid sweat it liberates formaldehyde. Methenamine calcium thiocyanate has been used in combination preparations for upper respiratory-tract disorders.

Reviews.

1. Schiøtz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. *Acta Obstet Gynecol Scand* 2002; **81:** 743–6.
2. Lee BB, *et al.* Methenamine hippurate for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 11/01/08).

Administration in children. In children, methenamine and its salts may be given orally for prophylaxis and long-term suppression of chronic or recurrent, uncomplicated lower urinary-tract infections and asymptomatic bacteriuria.

In the USA, the usual recommended dose of methenamine mandelate in children up to 6 years old is about 18 mg/kg given four times daily; those aged 6 to 12 years may be given methenamine or methenamine mandelate 500 mg four times daily.

In the UK, methenamine hippurate may be given in a usual oral dose of 500 mg twice daily in children aged 6 to 12 years. Doses of up to 1 g twice daily have been given in the USA.

Adverse Effects and Precautions

Methenamine and its salts are generally well tolerated but may cause gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. Skin rashes, pruritus, and occasionally other hypersensitivity reactions, may occur.

Comparatively large amounts of formaldehyde may be formed during prolonged use or when large doses are given. This may produce irritation and inflammation of the urinary tract, especially the bladder, as well as painful and frequent micturition, haematuria, and proteinuria. The effect of the formaldehyde may be reduced by alkalinising drugs, such as sodium bicarbonate, or large quantities of water, but it is then less effective.

Methenamine and its salts are contra-indicated in patients with hepatic impairment because of the liberation of ammonia in the gastrointestinal tract. Although methenamine itself is not contra-indicated in renal impairment, its salts should be avoided in severe impairment because of the risk of mandelate or hippurate crystalluria. They should also be avoided in patients with severe dehydration, metabolic acidosis, or gout.

Interference with laboratory estimations for catecholamines, 17-hydroxycorticosteroids, and oestrogens in the urine has been reported.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methenamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The use of drugs that alkalinise the urine, including some antacids, potassium citrate, and diuretics such as acetazolamide or the thiazides, should be avoided because the activation of methenamine to formaldehyde may be inhibited (but see above).

Use of methenamine with sulfonamides may increase the risk of crystalluria since methenamine requires low urinary pH for its effect, at which sulfonamides and their metabolites are poorly soluble; methenamine may also form poorly soluble compounds with some sulfonamides.

Antimicrobial Action

Methenamine owes its antibacterial properties to formaldehyde, a non-specific bactericide, which is slowly liberated by hydrolysis at acid pH. Most Gram-positive and Gram-negative organisms and fungi are susceptible. Hippuric and mandelic acids have some antibacterial activity *in vitro*, but their contribution to the antibacterial action of the salts *in vivo*, beyond assisting the maintenance of low urinary pH, is uncertain. Urea-splitting organisms such as *Proteus* and some *Pseudomonas* spp. tend to increase urinary pH and inhibit the release of formaldehyde, thereby decreasing the efficacy of methenamine. Use with acetohydroxamic acid, a potent inhibitor of bacterial urease, has been suggested for urinary infections due to these organisms. True resistance to formaldehyde does not appear to be a problem in clinical use.

Pharmacokinetics

Methenamine is readily absorbed from the gastrointestinal tract and widely distributed in the body. Under acid conditions methenamine is slowly hydrolysed to formaldehyde and ammonia: about 10 to 30% of an oral dose may be converted in the stomach unless it is given as an enteric-coated preparation. Almost no hydrolysis of methenamine takes place at physiological pH, and it is therefore virtually inactive in the body. The half-life is reported to be about 4 hours. Methenamine is rapidly and almost completely eliminated in the urine, and provided this is acidic (preferably below pH 5.5) bactericidal concentrations of formaldehyde occur. Because of the time taken for hydrolysis, however, these do not occur until the urine reaches the bladder, with peak concentrations occurring up to 2 hours after an oral dose. Absorption, and hence excretion, may be somewhat delayed in patients given enteric-coated formulations.

Methenamine crosses the placenta and small amounts may be distributed into breast milk.

The mandelate and hippurate moieties are also rapidly absorbed and are excreted in urine by tubular secretion as well as glomerular filtration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hiprex; ***Canad.***: Dehydral; Mandelamine; Urasal†; ***Denm.***: Haiprex; ***Fin.***: Hipeksal; Hiprex; ***Ger.***: Antihydral; ***Gr.***: Amigdalin; ***Hong Kong***: Antihydral; ***India***: Mandelamin; ***Israel***: Hiprex; ***Malaysia***: Hiprex; ***Mex.***: Bioran; ***Neth.***: Reflux; ***Norw.***: Hiprex; ***NZ***: Hiprex; ***Philipp.***: Hiprex†; ***Pol.***: Stoppot; ***Swed.***: Hiprex; ***Turk.***: Helpa; Hipurin; Manuprin; Neturone; Purinol; Uron; ***UK***: Hiprex; ***USA***: Hiprex; Mandelamine; Urex; ***Venez.***: Mandelamine.

Multi-ingredient Preparations. ***Belg.***: Carbobel; Mictasol; ***Braz.***: Acridin; Cystex; Sepurin; ***Chile***: Uroknop; ***Hung.***: Aknesol; ***Pol.***: Dezorol; Pedipur; Urosal; ***Rus.***: Teimurov (Теймурова); ***Turk.***: Helmo-Blue; Helmobleu; ***USA***: Atrosept; Cystex; Darpaz†; Hyophen; MHP-A; MSP-Blu; Phosphasal; Prosed/DS; UAA; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Urogesic Blue; Uryl; Ustell; Utac; Uticap; Utira; Utrona-C; ***Venez.***: Azo-Mandelamine.

Homoeopathic Preparations. ***Fr.***: L 8.

Pharmacopoeial Preparations

USP 36: Methenamine Elixir; Methenamine Hippurate Tablets; Methenamine Mandelate Delayed-release Tablets; Methenamine Mandelate for Oral Solution; Methenamine Mandelate Oral Suspension; Methenamine Mandelate Tablets; Methenamine Tablets.

Meticillin Sodium *(rINNM)*

BRL-1241; Dimethoxyphenecillin Sodium; Dimethoxyphenyl Penicillin Sodium; Methicillin Sodium (USAN); Methicillin Sodium (BANM); Meticilina sódica; Méticilline Sodique; Meticillinum Natricum; Natrii Meticillinum; SQ-16123; X-1497; Натрий Метициллин.

Sodium (6*R*)-6-(2,6-dimethoxybenzamido)penicillanate monohydrate.

$C_{17}H_{19}N_2NaO_6S,H_2O$=420.4

CAS — 61-32-5 (meticillin); 132-92-3 (anhydrous meticillin sodium); 7246-14-2 (meticillin sodium monohydrate).

ATC — J01CF03.

ATC Vet — QJ01CF03.

UNII — AO9YF4MN30.

Incompatibility. Meticillin sodium has been reported to be incompatible with aminoglycosides and some other antimicrobials. It has also been reported to be incompatible with acidic and alkaline drugs.

Uses and Administration

Meticillin is a penicillinase-resistant penicillin and has been used similarly to flucloxacillin (p. 299.2) in the treatment of staphylococcal infections resistant to benzylpenicillin. It is not active orally and has been given by injection as the sodium salt.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Meticillin is the penicillin most commonly associated with acute interstitial nephritis.

Effects on the kidneys. References.

1. Sanjad SA, *et al.* Nephropathy, an underestimated complication of methicillin therapy. *J Pediatr* 1974; **84:** 873–7.
2. Galpin JE, *et al.* Acute interstitial nephritis due to methicillin. *Am J Med* 1978; **65:** 756–65.

Sodium content. Each g of meticillin sodium contains about 2.4 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

Meticillin has a mode of action similar to that of benzylpenicillin (p. 230.1) but it is resistant to staphylococcal penicillinase. There is evidence that meticillin is more stable to staphylococcal penicillinase than the other penicillinase-resistant penicillins.

Meticillin is active against both penicillinase-producing and non-penicillinase-producing staphylococci, and also against *Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Str. pneumoniae*, and some viridans streptococci. Its activity against penicillin-sensitive staphylococci and streptococci is less than that of benzylpenicillin. It is virtually ineffective against *Enterococcus faecalis*.

Resistance of staphylococci to meticillin is due to the expression of an altered penicillin-binding protein and is not dependent on penicillinase production. There is cross-resistance with other penicillins, including the penicillinase-resistant penicillins cloxacillin, dicloxacillin, flucloxacillin, nafcillin, and oxacillin, and with the cephalosporins. Meticillin-resistant staphylococci are also frequently resistant to other antibacterials, including aminoglycosides, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, and tetracycline. The incidence of such resistance has varied considerably. However, both endemic (restricted to one hospital) and epidemic (affecting more than one hospital) strains of meticillin-resistant *Staphylococcus aureus* (MRSA) are now recognised and infections are a problem in many hospitals. Community-acquired strains of MRSA have also been recognised, but are generally susceptible to a wider range of antibacterials than strains acquired in hospital.

There have been fewer studies on coagulase-negative staphylococci, but patterns of meticillin resistance in *Staph. epidermidis* are similar to those for MRSA and the frequency of resistance may be higher.

For further details on meticillin-resistant staphylococci and the management of infections, see under Staphylococcal Infections, p. 208.2.

Resistance. References to meticillin-resistant staphylococci.

1. Rybak MJ, Akins RL. Emergence of methicillin-resistant Staphylococcus aureus with intermediate glycopeptide resistance: clinical significance and treatment options. *Drugs* 2001; **61:** 1–7.
2. Stapleton PD, Taylor PW. Methicillin resistance in Staphylococcus aureus: mechanisms and modulation. *Sci Prog* 2002; **85:** 57–72.
3. Berger-Bächi B, Rohrer S. Factors influencing methicillin resistance in staphylococci. *Arch Microbiol* 2002; **178:** 165–71.
4. Eady EA, Cove JH. Staphylococcal resistance revisited: community-acquired methicillin resistant Staphylococcus aureus—an emerging problem for the management of skin and soft tissue infections. *Curr Opin Infect Dis* 2003; **16:** 103–24.
5. Boyce JM, *et al.* Meticillin-resistant Staphylococcus aureus. *Lancet Infect Dis* 2005; **5:** 653–63.
6. Martins A, Cunha M de LRS. Methicillin resistance in Staphylococcus aureus and coagulase-negative staphylococci: epidemiological and molecular aspects. *Microbiol Immunol* 2007; **51:** 787–95.
7. Millar BC, *et al.* Proposed definitions of community-associated meticillin-resistant Staphylococcus aureus (CA-MRSA). *J Hosp Infect* 2007; **67:** 109–13.
8. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. *Clin Infect Dis* 2008; **46** (suppl 5): S344–S349.
9. Deurenberg RH, Stobberingh EE. The molecular evolution of hospital- and community-associated methicillin-resistant Staphylococcus aureus. *Curr Mol Med* 2009; **9:** 100–15.

Pharmacokinetics

Meticillin is inactivated by gastric acid and must be given by injection. Peak plasma concentrations occur within 0.5 to 1 hour of an intramuscular injection; concentrations of up to 18 micrograms/mL occur after a dose of 1 g. A half-life of 0.5 to 1 hour has been reported, although this may be increased to 3 to 6 hours in renal impairment. About 40% of the meticillin in the circulation is bound to plasma proteins. It is widely distributed in body fluids and in tissues, but there is little diffusion into the CSF unless the meninges are inflamed. Meticillin also crosses the placenta and appears in breast milk. Relatively high concentrations occur in bile compared with plasma, although only small amounts are excreted in bile. The majority is rapidly excreted by tubular secretion and glomerular filtration; up to 80% of an injected dose has been detected unchanged in the urine.

Plasma concentrations are enhanced by probenecid. They may be reduced in patients with cystic fibrosis.

Mezlocillin *(BAN, USAN, rINN)*

Metslosilliini; Mezlocilina; Mezlocilline; Mezlocillinum; Мезлоциллин.

6-[*N*-(3-Methylsulfonyl-2-oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

$C_{21}H_{25}N_5O_8S_2$=539.6

CAS — 51481-65-3.

ATC — J01CA10.

ATC Vet — QJ01CA10.

UNII — OH2O403D1G.

Mezlocillin Sodium *(BANM, rINNM)*

Bay-f-1353; Mezlocilina sódica; Mezlocilline Sodique; Natrii Mezlocillinum; Натрий Мезлоциллин.

Sodium (6*R*)-6-[D-2-(3-mesyl-2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate monohydrate.

$C_{21}H_{24}N_5NaO_8S_2.H_2O$=579.6

CAS — 42057-22-7 (anhydrous mezlocillin sodium); 80495-46-1 (mezlocillin sodium monohydrate).

ATC — J01CA10.

ATC Vet — QJ01CA10.

UNII — 3CWW8B5904 (mezlocillin sodium monohydrate); RX227TP94U (mezlocillin sodium).

Pharmacopoeias. In *US.*

USP 36: (Mezlocillin Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 4.5 and 8.0. Store in airtight containers.

Incompatibility. Mezlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Uses and Administration

Mezlocillin is a ureidopenicillin with uses similar to those of piperacillin (p. 342.1). It is commonly used with an aminoglycoside; however they should be given separately as they have been shown to be incompatible.

Mezlocillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of mezlocillin; 1.07 g of mezlocillin sodium is equivalent to about 1 g of mezlocillin. Dosage may need to be reduced in renal impairment. It may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 30 minutes, or by deep intramuscular injection. Single intramuscular doses should not exceed 2 g.

For the treatment of serious infections, 200 to 300 mg/kg daily in divided doses may be given intravenously. For life-threatening infections, up to 350 mg/kg daily may be used, but the total daily dose should not normally exceed 24 g. For uncomplicated urinary-tract infections, a dose of 1.5 to 2 g may be given intramuscularly or intravenously every 6 hours.

Uncomplicated gonorrhoea may be treated by a single intramuscular or intravenous dose of mezlocillin 1 to 2 g. Probenecid 1 g orally may be given at the same time or up to 30 minutes before the injection.

For the prophylaxis of infection during surgery, an intravenous pre-operative dose of mezlocillin 4 g, repeated at 6-hourly intervals for 2 further doses, may be given.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 232.1.

Prolongation of bleeding time has been less frequent and less severe with mezlocillin than with carbenicillin.

Sodium content. Each g of mezlocillin sodium contains about 1.7 mmol of sodium. As mezlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterial. For the effect of mezlocillin on the clearance of *cefotaxime*, see p. 244.3.

Neuromuscular blockers. Mezlocillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p. 2032.1).

Antimicrobial Action

Mezlocillin has a similar antimicrobial action to piperacillin (p. 343.1). Its activity against *Pseudomonas aeruginosa* is less than that of azlocillin or piperacillin.

Pharmacokinetics

Mezlocillin is not absorbed from the gastrointestinal tract to any significant extent. It is well absorbed after intramuscular injection, with peak plasma concentrations of 15 to 25 micrograms/mL 45 to 90 minutes after a single dose of 1 g. It is reported to have nonlinear dose-dependent pharmacokinetics. Between 16 and 42% of mezlocillin in the circulation is bound to plasma proteins. Mezlocillin is reported to have a plasma half-life of about 1 hour; this is slightly prolonged in neonates, and in patients with renal impairment half-lives of up to about 6 hours have been reported.

Mezlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into CSF except when the meninges are inflamed.

Mezlocillin is reported to be metabolised to a limited extent. About 55% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 6 hours of a dose, hence achieving high urinary concentrations. High concentrations are also found in the bile; up to 30% of a dose has been reported to be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Mezlocillin is removed by haemodialysis, and to some extent by peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Baypen; ***China***: Baypen (拜朋); Li Yang (力扬); Meige (美各); Nuomei (诺美); Yi Mei (亿美); ***Fr.***: Baypen†; ***Ger.***: Baypen†; ***Ital.***: Baypen.

Multi-ingredient Preparations. ***China***: Han Guang (汉光); Jia Luo Tan (佳洛坦); Kai Wei Ke (凯韦可); KaiLin (开林).

Pharmacopoeial Preparations

USP 36: Mezlocillin for Injection.

Micronomicin Sulfate *(pINNM)*

Gentamicin C_{2B} Sulphate; KW-1062 (micronomicin); Micronomicin Sulphate; Micronomicina, sulfato de; Micronomicine, Sulfate de; Micronomicini Sulfas; Sagamicin Sulphate; Sulfato de micronomicina; Микрономицина Сульфат; 6′*N*-Methylgentamicin C_{1A} Sulphate.

O-2-Amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-*erythro*-hexopyranosyl-(1→4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)]-2-deoxy-D-streptamine hemipentasulphate.

$(C_{20}H_{41}N_5O_7)_2.5H_2SO_4$=1417.5

CAS — 52093-21-7 (micronomicin).

ATC — S01AA22.

ATC Vet — QS01AA22.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Micronomicin is an aminoglycoside antibacterial with general properties similar to those of gentamicin (p. 304.2). It is given as the sulfate and doses are expressed in terms of micronomicin; 183 mg of micronomicin sulfate is equivalent to about 120 mg of micronomicin. It is given by intramuscular injection or by intravenous infusion over 30 minutes to 1 hour in doses of 120 to 240 mg daily in 2 or 3 divided doses. Dosage should be adjusted based on serum-micronomicin concentration monitoring. It is also used topically as eye drops or ointment in a concentration of 0.3% for infections of the eye.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jun Jia (君佳); Jun Wei (君为); LuoYi (洛意); Mei Luo Ke (美罗克); Rui Nuo Mei Xin (瑞诺美新); ***Ital.***: Luxomicina; ***Jpn***: Sagamicin†; ***Singapore***: Sagamicin.

Midecamycin *(rINN)*

Midecamicina; Midecamycin A_1; Midécamycine; Midecamycinum; Mydecamycin; Мидекамицин.

7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16,-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′,4″-dipropionate.

$C_{41}H_{67}NO_{15}$=814.0

CAS — 35457-80-8.

ATC — J01FA03.

ATC Vet — QJ01FA03.

UNII — N34Z0Y5UH7.

Pharmacopoeias. In *Jpn.*

Midecamycin Acetate *(rINNM)*

Acecamycin; Acetato de midecamicina; Midecamicina, acetato de; Midecamycin Diacetate; Midécamycine, Acétate de; Midecamycini Acetas; Miocamycin; Miokamycin; MOM; Ponsinomycin; 1532-RB; Мидекамицина Ацетат.

9,3″-Diacetylmidecamycin; Leucomycin V 3^B, 9-diacetate $3,4^B$-dipropanoate.

$C_{45}H_{71}NO_{17}$=898.1

CAS — 55881-07-7.

ATC — J01FA11.

ATC Vet — QJ01FA11.

Pharmacopoeias. In *Jpn.*

Profile

Midecamycin is a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens* with actions and uses similar to those of erythromycin (p. 291.2) but it is somewhat less active. It is given orally for the treatment of susceptible infections as the acetate in usual doses of 0.9 to 1.8 g daily in 2 or 3 divided doses. It has also been given as the base.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Merced; ***China***: Mei Jia Xin (美加欣); Mei Ou Ka (美欧卡); Meilitai (美力泰); ***Fr.***: Mosil; ***Gr.***: Miocacin; Miocamen; ***Hong Kong***: Medemycin; ***Ital.***: Macroral; Midecin†; Miocamen; Miokacin; ***Jpn***: Medemycin; Miocamycin; ***Port.***: Miocacin; ***Rus.***: Macropen (Макропен); ***Spain***: Momicine; Myoxam; ***Thai.***: Miotin; ***Ukr.***: Macropen (Макропен).

Minocycline *(BAN, USAN, rINN)*

Minociclina; Minocyclin; Minocyclinum; Minocyklin; Minocyklina; Minosiklin; Minosykliini; Миноциклин.

(4*S*,4a*S*,5a*R*,12a*S*)4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-7-dimethylaminotetracycline.

$C_{23}H_{27}N_3O_7$=457.5

CAS — 10118-90-8.

ATC — A01AB23; J01AA08.

ATC Vet — QA01AB23; QJ01AA08.
UNII — FYY3R43WGO.

Minocycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de minociclina; Minociclina, hidrocloruro de; Minociklin-hidroklorid; Minociklino hidrochloridas; Minocycline, Chlorhydrate de; Minocyclini hydrochloridum; Minocyklin-hydrochlorid; Minocyklinhydroklorid; Minocykliny chlorowodorek; Minosykliinihydrokloridi; Миноциклина Гидрохлорид.

$C_{23}H_{27}N_3O_7$,HCl=493.9
CAS — 13614-98-7.
ATC — A01AB23; J01AA08.
ATC Vet — QA01AB23; QJ01AA08.
UNII — 0020414E5U.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpm,* and *US.*

Ph. Eur. 8: (Minocycline Hydrochloride Dihydrate). A yellow, hygroscopic, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Minocycline Hydrochloride). A yellow crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of minocycline 1% is between 3.5 and 4.5. Store in airtight containers. Protect from light.

Incompatibility. Preparations of minocycline hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Uses and Administration

Minocycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.3). It is also a component of multidrug regimens for the treatment of leprosy (p. 188.3) and has been used in the prophylaxis of meningococcal infection to eliminate the carrier state, but the high incidence of vestibular disturbances means that it is not the drug of choice for the latter.

Minocycline is usually given orally as the hydrochloride; doses are expressed in terms of the base. Minocycline hydrochloride 108 mg is equivalent to about 100 mg of minocycline. Minocycline capsules and tablets should be taken with plenty of fluid, with the patient in an upright position, and well before going to bed.

In patients in whom oral therapy is not feasible, minocycline hydrochloride has been given by slow intravenous infusion in doses equivalent to those given orally. In some countries it has also been given by intramuscular injection.

The usual adult oral dose is 200 mg daily in divided doses, usually every 12 hours; an initial loading dose of 200 mg may be given.

An oral dose of 50 mg twice daily or 100 mg once daily is used for the treatment of acne; alternatively, a dose of about 1 mg/kg once daily is also given as a modified-release preparation to patients weighing 45 kg and over. In asymptomatic meningococcal carriers, 100 mg has been given orally twice daily for 5 days, usually followed by a course of rifampicin.

For multibacillary leprosy an oral dose of minocycline 100 mg daily with clofazimine and ofloxacin *or* 100 mg monthly with rifampicin and ofloxacin have been recommended by WHO as alternative multidrug therapy regimens. As an alternative regimen for patients with single-lesion paucibacillary leprosy WHO suggests a single dose of minocycline 100 mg with rifampicin and ofloxacin.

For details of doses in children and adolescents, see p. 327.1.

For dosage recommendations in patients with renal impairment, see p. 327.2.

In adults with periodontitis (p. 192.3), a modified-release subgingival gel containing minocycline hydrochloride has been inserted into the periodontal pocket as an adjunct to scaling and root planing; each cartridge contains the equivalent of 1 mg of minocycline and the total used depends on the size, shape, and number of pockets being treated. Minocycline has also been applied as a 2% gel for periodontal infections.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, minocycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Administration in renal impairment. US licensed product information states that pharmacokinetics in patients with renal impairment have not been fully characterised and therefore recommends that no more than 200 mg in any 24-hour period should be given to these patients.

Asthma. For reference to the use of minocycline in the treatment of asthma, see under Tetracycline, p. 376.1.

Musculoskeletal and joint disorders. For reference to the use of minocycline in the treatment of rheumatoid arthritis, see under Tetracycline, p. 376.2.

Neuroprotective effect. Minocycline has been shown to have a neuroprotective effect[1] in *animal* models of stroke (p. 1269.2), brain and spinal cord injury, and neurodegenerative disorders such as Huntington's chorea (p. 1029.3), multiple sclerosis (p. 998.3), Parkinson's disease (p. 890.1), and amyotrophic lateral sclerosis (ALS, a form of motor neurone disease, p. 2605.2); however it is unclear whether it can produce clinical benefits. Clinical studies in a few patients with **Huntington's chorea** indicated that minocycline was well tolerated[2] and had a neuroprotective effect.[3] Similarly, an open-label study[4] in 152 patients with acute ischaemic **stroke** suggested that giving minocycline at the acute stage improved the outcome. However, a randomised placebo-controlled study[5] in 412 patients with **ALS**, given minocycline in escalating doses (up to 400 mg daily) for 9 months reported a harmful effect. Minocycline has also been proposed[6,7] as an adjunct in the management of schizophrenia (p. 1031.3).

1. Plane JM, *et al.* Prospects for minocycline neuroprotection. *Arch Neurol* 2010; **67:** 1442–8.
2. Huntington Study Group. Minocycline safety and tolerability in Huntington disease. *Neurology* 2004; **63:** 547–9.
3. Bonelli RM, *et al.* Neuroprotection in Huntington's disease: a 2-year study on minocycline. *Int Clin Psychopharmacol* 2004; **19:** 337–42.
4. Lampl Y, *et al.* Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. *Neurology* 2007; **69:** 1404–10.
5. Gordon PH, *et al.* Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial. *Lancet Neurol* 2007; **6:** 1045–53.
6. Miyaoka T. Clinical potential of minocycline for schizophrenia. *CNS Neurol Disord Drug Targets* 2008; **7:** 376–81.
7. Levkovitz Y, *et al.* A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry* 2010; **71:** 138–49.

Skin disorders. For reference to the use of minocycline in the treatment of various skin disorders, see under Tetracycline, p. 376.3.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Gastrointestinal disturbances with minocycline are reported to be less frequent than with the less well absorbed tetracyclines.

Oesophageal ulceration has occurred and may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: minocycline should be taken with at least half a glass of water, in an upright position, and well before going to bed.

Vestibular adverse effects including dizziness or vertigo may occur with minocycline, particularly in women. Patients should be advised not to drive or operate machinery if affected. Tinnitus and decreased hearing have been reported rarely.

There have also been reports, some fatal, of a hypersensitivity syndrome (comprising eosinophilia, fever, rash, and varying additional symptoms), a lupus-like syndrome, and a serum-sickness-like syndrome (both comprising arthralgia, fever, and joint stiffness or swelling, amongst other symptoms).

Minocycline may also cause hyperpigmentation of the skin (see p. 328.1).

Although minocycline, unlike many tetracyclines, does not appear to accumulate in patients with renal impairment, usual doses can lead to higher serum concentrations resulting in possible liver toxicity; reduced doses and monitoring of renal function may be necessary, particularly in those with severe impairment.

The *BNF* recommends that if treatment continues for longer than 6 months patients should be monitored every 3 months for hepatotoxicity, pigmentation, and SLE.

Incidence of adverse effects. Severe complications have been reported in patients given minocycline for acne, including serum-sickness-like disease,[1,2] lupus erythematosus,[3] and hepatitis.[3,4] The number of cases reported probably reflects the widespread use of this drug and the true incidence of such adverse effects is difficult to assess.[5] A study of 700 patients receiving minocycline for acne revealed adverse effects in 13.6%, mostly benign.[6] Gastrointestinal disturbances and vestibular disturbances were the most common, each occurring in about 2% of patients, and pigmentation in up to 4% of patients.

Another problem is that of assessing the efficacy of minocycline and the incidence of severe adverse effects relative to other antibacterials commonly used in acne such as tetracycline and erythromycin. A systematic review[7] suggested that the incidence of adverse effects might be greater with minocycline than with doxycycline. A retrospective analysis[8] of a UK population database found that minocycline was associated with an increased risk for drug-induced lupus erythematosus; no increased risk was reported for the other tetracyclines. Other systematic reviews[9,10] concluded that minocycline should not be used as a first-line oral tetracycline in patients with acne since there is no compelling evidence that it is more effective than some other tetracyclines or commonly used treatments; the risk of rare but serious adverse effects also makes it less suitable.[10]

1. Knowles SR, *et al.* Serious adverse reactions induced by minocycline: report of 13 patients and review of the literature. *Arch Dermatol* 1996; **132:** 934–9.
2. Harel L, *et al.* Serum-sickness-like reaction associated with minocycline therapy in adolescents. *Ann Pharmacother* 1996; **30:** 481–3.
3. Gough A, *et al.* Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996; **312:** 169–72.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and the liver, the CNS, the skin. *Aust Adverse Drug React Bull* 1996; **15:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 11/08/08)
5. Seukeran DC, *et al.* Benefit-risk assessment of acne therapies. *Lancet* 1997; **349:** 1251–2.
6. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134:** 693–5.
7. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther* 2005; **27:** 1329–42.
8. Margolis DJ, *et al.* Association or lack of association between tetracycline class antibiotics used for acne vulgaris and lupus erythematosus. *Br J Dermatol* 2007; **157:** 540–6.
9. Garner SE, *et al.* Minocycline for acne vulgaris: efficacy and safety. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/05/05).
10. McManus P, Iheanacho I. Don't use minocycline as first line oral antibiotic in acne. *BMJ* 2007; **334:** 154.

Effects on intracranial pressure. Minocycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p. 377.2.

Effects on the liver. A systematic review[1] considered 65 published case reports of hepatitis or liver damage associated with the use of minocycline for acne, including 4 fatalities, and also data held by WHO concerning 493 reactions involving the liver in 393 patients in whom the indication for the use of minocycline was largely unspecified.

Of the 65 published cases, 38 occurred in females and 61 in patients under 40 years of age. These cases appeared to be of the following types:

- 16 cases appeared to be attributable to a hypersensitivity reaction, with a rapid onset usually within 1 month of starting treatment and sometimes associated with eosinophilia and exfoliative dermatitis
- 29 cases of hepatitis (of which 20 were in females) appeared to be of an auto-immune nature, occurring after 1 year or more of therapy and sometimes associated with lupus-like symptoms
- 20 cases could not be definitively classified into either group

The 393 patients described by the WHO data had 22 different types of hepatic reaction that could be broadly grouped into 4 categories:

- hepatic dysfunction (32% of patients)
- hepatitis (26%)
- abnormal liver function tests (24%)
- hyperbilirubinaemia or jaundice (14%)

There were, in addition, several other reactions, including hepatic damage or necrosis in 11 patients and fatty liver in 7. Gender distribution was almost even. Of the 393 patients, 14 also had lupus-like symptoms. The outcome of the hepatic reactions was reported in less than half of the patients, although it was apparent that there had been at least 3 fatalities.

Despite these findings, the reviewers concluded[1] that there was no clear information regarding the absolute or relative risks of hepatitis in patients given minocycline, and that it was inappropriate to comment as to whether monitoring would be worthwhile. A study of the comparative rates of hepatitis in people exposed to minocycline compared with those who were not was required.

1. Lawrenson RA, *et al.* Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. *Drug Safety* 2000; **23:** 333–49.

Effects on the lungs. Hypersensitivity pneumonitis, characterised by pulmonary infiltrates and eosinophilia, has been reported[1-6] with minocycline. In most cases, the pneumonitis resolved after stopping minocycline but some required corticosteroid therapy; however, residual lung

damage can occur. In one case[6] relapsing acute respiratory failure that required mechanical ventilation was reported.

1. Guillon J-M, *et al.* Minocycline-induced cell-mediated hypersensitivity pneumonitis. *Ann Intern Med* 1992; **117:** 476–81.
2. Bridges AJ. Minocycline-induced pneumonia. *Ann Intern Med* 1993; **118:** 749–50.
3. Sigmann P. Minocycline-induced pneumonia. *Ann Intern Med* 1993; **118:** 750.
4. Sitbon O, *et al.* Minocycline pneumonitis and eosinophilia: a report on 8 patients. *Arch Intern Med* 1994; **154:** 1633–40.
5. Dykhuizen RS, *et al.* Minocycline and pulmonary eosinophilia. *BMJ* 1995; **310:** 1520–1.
6. Oddo M, *et al.* Relapsing acute respiratory failure induced by minocycline. *Chest* 2003; **123:** 2146–8.

Hyperpigmentation. Minocycline has been associated with pigmentation of the skin and other tissues.[1-5] Three patterns of skin pigmentation have been described:[1] blue-black macules occurring in areas of inflammation and scarring, possibly due to an iron chelate of minocycline within macrophages; blue-grey macules or hyperpigmentation affecting normal skin, which may be due to a breakdown product of minocycline; or a greyish-brown discoloration occurring particularly in sun-exposed areas of skin ('muddy skin syndrome'), apparently due to melanin deposition. In general, pigmentation results from long-term use of minocycline at cumulative doses greater than 100 g; however, skin or oral mucosal pigmentation may occur regardless of dose or duration of therapy.[2] Indeed, there have been reports[3] of skin pigmentation developing after short-term use ranging from 3 to 28 days. Pigmentation of the skin and oral mucosa usually appears to resolve slowly on stopping the drug although recovery may be incomplete; pigmentation is often permanent when other sites are involved.[2]

1. Basler RSW. Minocycline-related hyperpigmentation. *Arch Dermatol* 1985; **121:** 606–8.
2. Eisen D, Hakim MD. Minocycline-induced pigmentation: incidence, prevention and management. *Drug Safety* 1998; **18:** 431–40.
3. Nakamura S, *et al.* Acute pigmentation due to minocycline therapy in atopic dermatitis. *Br J Dermatol* 2003; **148:** 1073–4.
4. Geria AN, *et al.* Minocycline-induced skin pigmentation: an update. *Acta Dermatovenerol Croat* 2009; **17:** 123–6.
5. Youssef S, *et al.* Minocycline-induced pigmentation mimicking persistent ecchymosis. *Cutis* 2009; **84:** 22–6.

Minocycline-induced autoimmunity. It has been suggested that some rare adverse effects of minocycline, such as drug-induced lupus, auto-immune hepatitis, serum sickness, and vasculitis, with or without the development of antinuclear antibodies or other autoantibodies, might all represent aspects of a single process, referred to as minocycline-induced autoimmunity (MIA). Patients usually show constitutional symptoms such as fever, malaise, loss of appetite, rash, arthralgia, myalgia, and auto-immune hepatitis; most cases occur in young women being treated for acne.[1,2]

In a retrospective cohort study[2] (from September 1996 to September 2006) that identified 27 children (19 female) with MIA, symptoms on stopping minocycline resolved rapidly in 14 of the children and within 12 months in another 6 but 7 had chronic auto-immune disease 13 to 48 months later. All patients with chronic disease had evidence of arthritis at presentation and required long-term treatment with immunosuppressives. No association was found between the duration of use, cumulative dose, and clinical outcomes. Long-term immune system alteration, after a drug hypersensitivity reaction, has also been reported in a 15-year-old girl given minocycline for the treatment of acne vulgaris. She developed auto-immune hyperthyroidism 7 weeks after stopping the minocycline and auto-immune type 1 diabetes mellitus 7 months after stopping the minocycline. In addition, she developed elevated titres of several markers of systemic auto-immune disease, including antinuclear, anti-Sjögren syndrome A, and anti-Smith antibodies.[3]

A retrospective literature review from 1966 to April 1998 identified more than 60 cases of minocycline-induced SLE and 24 cases of minocycline-induced auto-immune hepatitis after long-term use of minocycline (4 to 120 months).[4] Thirteen patients (10 female) with both auto-immune disorders were reviewed. Symptoms in all these patients included symmetrical polyarthralgias and polyarthritis, raised liver enzyme values, and positive antinuclear antibodies; 10 patients reported constitutional symptoms. Four patients received treatment with corticosteroids, alone or with hydroxychloroquine and/or azathioprine, but symptoms resolved, and laboratory results normalised or significantly improved in all patients after minocycline was stopped.[4]

1. Moore TL. Autoimmunity and minocycline. *J Pediatr* 2008; **153:** 303–4.
2. El-Hallak M, *et al.* Chronic minocycline-induced autoimmunity in children. *J Pediatr* 2008; **153:** 314–9.
3. Brown RJ, *et al.* Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol* 2009; **145:** 63–6.
4. Angulo JM, *et al.* Coexistent minocycline-induced systemic lupus erythematosus and autoimmune hepatitis. *Semin Arthritis Rheum* 1998; **28:** 187–92.

Interactions

As for Tetracycline, p. 377.3.

Minocycline has a lower affinity for binding with calcium than tetracycline. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc.

Antimicrobial Action

Minocycline has a spectrum of activity and mode of action similar to that of tetracycline (p. 377.3) but it is more active against many species including *Staphylococcus aureus*, streptococci, *Neisseria meningitidis*, various enterobacteria, *Acinetobacter*, *Bacteroides*, *Haemophilus*, *Nocardia*, and some mycobacteria, including *M. leprae*.

Partial cross-resistance exists between minocycline and other tetracyclines but some strains resistant to other drugs of the group remain sensitive to minocycline, perhaps because of better cell-wall penetration.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

Minocycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of food or moderate amounts of milk. After an oral loading dose of 200 mg peak plasma concentrations ranging from 2 to 4 micrograms/mL occur after 2 to 4 hours and fall to about 1 microgram/mL after 24 hours; a maintenance dose of 100 mg every 12 hours keeps the plasma concentration at about 2.3 to 3.5 micrograms/mL. On intravenous infusion of a dose of 100 mg a mean peak plasma concentration of 8.75 micrograms/mL is produced, and falls to 1.32 micrograms/mL after 24 hours; after daily infusions of a dose of 200 mg plasma concentrations of 1 to 4 micrograms/mL are maintained.

Minocycline is more lipid-soluble than doxycycline and the other tetracyclines and is widely distributed in body tissues and fluids with high concentrations being achieved in the hepatobiliary tract, lungs, sinuses and tonsils, as well as in tears, saliva, and sputum. Penetration into the CSF is relatively poor, although a higher ratio of CSF to blood concentrations has been reported with minocycline than with doxycycline and other tetracyclines. It crosses the placenta and is distributed into breast milk. About 75% of minocycline in the circulation is bound to plasma proteins. The plasma half-life is about 16 hours after the first dose and 21 hours after repeated doses.

It has a low renal clearance: only about 8 to 13% of a dose is excreted unchanged in the urine and up to about 20 to 30% is excreted unchanged in the faeces. However, in contrast to most tetracyclines it appears to undergo some metabolism in the liver, mainly to 9-hydroxyminocycline. Sources differ as to whether the normal plasma half-life is prolonged in patients with renal impairment, with a consequent risk of accumulation; hepatic impairment does not appear to lead to accumulation. Little minocycline is removed by haemodialysis and peritoneal dialysis.

Reviews.

1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15:** 355–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acneclin; Clinax; Meibi; Minocin†; Pimple†; Seboclear; ***Austral.***: Akamin; Minomycin; ***Austria***: Auramin†; Minostad; Udima; ***Belg.***: Klinotab; Mino-50; Minocin; Minotab; ***Braz.***: Minoderm; ***Canad.***: Arestin; Enca†; Minocin; ***Chile***: Bagomicina; Pracne; ***China***: Kang Ni (康尼); Mei Nong (美侬); Mei Nuo Xing (美诺星); Meikewei (美克威); Minocin (玫满); Periocline (派丽奥); ***Fr.***: Mestacine; Minolis†; Mynocine; Parocline; Zacnan†; ***Ger.***: Aknefug Mino†; Aknosan; Klinomycin†; Minakne; Minoclir; Minoplus†; Skid; Skinocyclin†; Udima; ***Gr.***: Cycline; Minocin; Periocline; ***Hong Kong***: Minaxen†; Minocin†; ***India***: CNN; Cynomycin; Divaine; Minolox; Minoz; ***Indon.***: Minocin†; ***Irl.***: Aknemin; Dentomycin; Minocin; Minodene; Minosil; Minox; ***Israel***: Arestin; Minoclin; ***Ital.***: Minocin; Minotek; ***Jpn***: Periocline; ***Malaysia***: Borymycin; Minoclin; ***Mex.***: Banimed; Micromycin; Minocin; Ranminо†; ***Neth.***: Aknemin; Minocin†; Minotab†; Minotek; Peritrol†; ***NZ***: Minomycin; Minotabs; ***Philipp.***: Minocin; ***Port.***: Arestin; Cipancin; Minocin; Minotrex; ***S.Afr.***: Cyclimycin; Minotabs; Triomin†; ***Singapore***: Borymycin; Minocin; ***Spain***: Minocin; ***Swed.***: Arestin†; ***Switz.***: Aknin-N†; Aknoral†; Minac 50; Minocin; ***Thai.***: Minocin; ***UK***: Aknemin; Dentomycin; Minocin; Sebomin; Sebren; ***USA***: Arestin; Cleeravue-M; Dynacin; Minocin; Myrac†; Solodyn; Ximino.

Pharmacopoeial Preparations

BP 2014: Minocycline Tablets; Prolonged-release Minocycline Capsules;

USP 36: Minocycline for Injection; Minocycline Hydrochloride Capsules; Minocycline Hydrochloride Oral Suspension; Minocycline Hydrochloride Tablets; Minocycline Periodontal System.

Morinamide *(pINN)*

Morfazinamide; Morinamida; Morinamidum; Morphazinamide; Моринамид.

N-Morpholinomethylpyrazine-2-carboxamide.

$C_{10}H_{14}N_4O_2$=222.2

CAS — 952-54-5.

ATC — J04AK04.

ATC Vet — QJ04AK04.

UNII — 8CFL28PA3W.

Profile

Morinamide is an antimycobacterial that has been given orally as the hydrochloride in the treatment of tuberculosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Morfozid.

Moxifloxacin Hydrochloride

(BANM, USAN, rINNM)

Bay-12-8039; Hidrocloruro de moxifloxacino; Moxifloxacine, chlorhydrate de; Moxifloxacinhydrochlorid; Moxifloxacini Hydrochloridum; Moxifloxacino, hidrocloruro de; Моксифлоксацина Гидрохлорид.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid hydrochloride.

$C_{21}H_{24}FN_3O_4$,HCl=437.9

CAS — 151096-09-2 (moxifloxacin); 186826-86-8 (moxifloxacin hydrochloride).

ATC — J01MA14; S01AE07.

ATC Vet — QJ01MA14; QS01AE07.

UNII — C53598599T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Moxifloxacin Hydrochloride). Produced using a method validated to show the satisfactory enantiomeric purity of the final product. A light yellow or yellow powder or crystals, slightly hygroscopic. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 0.2% solution in water has a pH of 3.9 to 4.6. Store in airtight containers. Protect from light.

USP 36: (Moxifloxacin Hydrochloride). Slightly yellow to yellow powder or crystals. Sparingly soluble in water and in methyl alcohol; slightly soluble in alcohol, in dimethylformamide, and in 0.1N hydrochloric acid; practically insoluble in acetone, in dichloromethane, in ethyl acetate, and in toluene; soluble in 0.1N sodium hydroxide; insoluble in *n*-heptane and in methyl *tert*-butyl ether. Store in airtight containers. Protect from light.

Uses and Administration

Moxifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It may be given orally, or by intravenous infusion over 60 minutes, for the treatment of susceptible infections including respiratory, skin and skin structure, and intra-abdominal infections. However, due to safety concerns, its use has now been restricted in the EU to the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, or community-acquired pneumonia only when other medicines cannot be prescribed or have failed. Moxifloxacin is given as the hydrochloride but doses are expressed in terms of the base; moxifloxacin hydrochloride 436.3 mg is equivalent to about 400 mg of moxifloxacin. The usual dose is 400 mg once daily.

Moxifloxacin is also used topically as the hydrochloride in eye drops containing the equivalent of 0.5% of moxifloxacin for the treatment of bacterial conjunctivitis.

Reviews.

1. Keating GM, Scott LJ. Moxifloxacin: a review of its use in the management of bacterial infections. *Drugs* 2004; **64:** 2347–77.
2. O'Brien TP. Evidence-based review of moxifloxacin. *Int Ophthalmol Clin* 2006; **46:** 61–72.
3. Miravitlles M, *et al.* Eficacia clínica del moxifloxacino en el tratamiento de las agudizaciones de la bronquitis crónica: revisión sistemática y metaanálisis. *Arch Bronconeumol* 2007; **43:** 22–8.
4. Miravitlles M. Moxifloxacin in the management of exacerbations of chronic bronchitis and COPD. *Int J Chron Obstruct Pulmon Dis* 2007; **2:** 191–204.
5. O'Brien TP, *et al.* Perspectives on antibiotics for postoperative endophthalmitis prophylaxis: potential role of moxifloxacin. *J Cataract Refract Surg* 2007; **33:** 1790–800.
6. Anonymous. Moxifloxacin. *Tuberculosis (Edinb)* 2008; **88:** 127–31.
7. Ludlam HA, Enoch DA. Doxycycline or moxifloxacin for the management of community-acquired pneumonia in the UK? *Int J Antimicrob Agents* 2008; **32:** 101–5.

Eye infections. In order to attain therapeutic concentrations most antibacterials used in the treatment of bacterial endophthalmitis need to be given by the intravitreal route but moxifloxacin given systemically may produce adequate concentrations. An oral dose of moxifloxacin 400 mg daily may be given for 10 days.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006*. London: Moorfields Pharmaceuticals, 2006.

Tuberculosis. For mention of the use of moxifloxacin in the treatment of tuberculosis, see under Ciprofloxacin, p. 262.2.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

References.

1. Faich GA, *et al.* Clinical experience with moxifloxacin in patients with respiratory tract infections. *Ann Pharmacother* 2004; **38:** 749–54.
2. Ball P, *et al.* Safety profile of oral and intravenous moxifloxacin: cumulative data from clinical trials and postmarketing studies. *Clin Ther* 2004; **26:** 940–50.
3. Andriole VT, *et al.* Retrospective analysis of the safety profile of oral moxifloxacin in elderly patients enrolled in clinical trials. *Drug Safety* 2005; **28:** 443–52.
4. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Safety* 2009; **32:** 359–78.

Effects on the liver. Like other fluoroquinolones (p. 263.1) moxifloxacin has been associated with rare cases of severe and even fatal liver toxicity.[1-3] Although a review of the relative toxicities of moxifloxacin and other fluoroquinolones and antibacterials considered that the incidence of such reactions with moxifloxacin was not significantly different than with other fluoroquinolones, and less than that reported with amoxicillin plus clavulanic acid,[3] an analysis by regulatory authorities in the EU[4] considered that they were of sufficient concern that use of moxifloxacin should be restricted (see Uses and Administration, p. 326.3).

1. Soto S, *et al.* Moxifloxacin-induced acute liver injury. *Am J Gastroenterol* 2002; **97:** 1853–4.
2. Nori S, *et al.* Moxifloxacin-associated drug hypersensitivity syndrome with toxic epidermal necrolysis and fulminant hepatic failure. *Arch Dermatol* 2004; **140:** 1537–8.
3. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Safety* 2009; **32:** 359–78.
4. EMEA/CHMP. European Medicines Agency recommends restricting the use of oral moxifloxacin-containing medicines (issued 24/07/08). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/38292708en.pdf (accessed 18/09/09)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moxifloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Moxifloxacin does not appear to interact significantly with theophylline or probenecid.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Moxifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

References.

1. Stein GE, *et al.* Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. *Antimicrob Agents Chemother* 2003; **47:** 1308–12.
2. Pletz MWR, *et al.* Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob Agents Chemother* 2004; **48:** 780–2.

Pharmacokinetics

Moxifloxacin is readily absorbed from the gastrointestinal tract after oral doses with an absolute bioavailability of about 90%. It is widely distributed throughout the body tissues and is about 30 to 50% bound to plasma proteins. Moxifloxacin has an elimination half-life of about 12 hours, allowing once-daily dosing. It is metabolised mainly via sulfate and glucuronide conjugation, and is excreted in the urine and the faeces as unchanged drug and as metabolites, the sulfate conjugate mainly in the faeces and the glucuronide exclusively in the urine. Distribution into milk has been found in *animals*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avelox; Moflag; Vigamox; ***Austral.***: Avelox; ***Austria***: Actira; Avelox; Octegra; ***Belg.***: Avelox; Kanavig; Proflox; ***Braz.***: Avalox; Vigamox; ***Canad.***: Avelox; Vigamox; ***Chile***: Avelox; Flovacil; Imix; Moxaval; Moxicino; Moxof; Vigamox; ***China***: Avelox (拜复乐); ***Cz.***: Avelox; Vigamox; ***Denm.***: Avelox; Infekt; Vigamox; ***Fin.***: Avelox; Vigamox; ***Fr.***: Izilox; ***Ger.***: Avalox; Vigamox; ***Gr.***: Avelox; Mikrobiel; Octegra; Proflox; Rucela; Vigamox; ***Hong Kong***: Avelox; Vigamox; ***Hung.***: Avelox; Octegra†; ***India***: Apdrops; Emef; Eye-Quin; Floxsafe; Hinemox; Inmox; L-Floxin; M-Moflo; Mediflox; Mo-Floren; Mofil; Mosi; Moxiblu; Moxicip; Moxif; Moxigram; Moximycin; Moxl; Otymox-MF; ***Indon.***: Avelox; Vigamox; ***Irl.***: Avelox; Moxivig; Vigamox†; ***Israel***: Megaxin; Vigamox; ***Ital.***: Actira; Avalox; Octegra; ***Jpn***: Avelox; ***Malaysia***: Avelox; Vigamox; ***Mex.***: Avelox; Vigamoxi; ***Neth.***: Avelox; Octegra†; Vigamox; ***NZ***: Avelox; Vigamox; ***Philipp.***: Avelox; Moxiflox; Vigamox; ***Pol.***: Avelox; Vigamox; ***Port.***: Avelox; Proflox; ***Rus.***: Avelox (Авелокс); Moximac (Моксимак); Plevilox (Плевилокс); Vigamox (Вигамокс); ***S.Afr.***: Avebact; Avelon; Litares; Moxibay; Numoxx; Vigamox; ***Singapore***: Avelox; Vigamox; ***Spain***: Actira; Havelox†; Octegra†; Proflox; Vigamox; ***Swed.***: Avelox; Vigamox; ***Switz.***: Avalox; Vigamox; ***Thai.***: Avelox; Vigamox; ***Turk.***: Atafloks; Avelox; Mofelox; Moxai; Moxifor; Moxitec; Pitoxil; Vigamox; ***UK***: Avelox; Moxivig; ***Ukr.***: Avelox (Авелокс); Maxicin (Максицин); ***USA***: Avelox; Moxeza; Vigamox; ***Venez.***: Avelox; Vigamox.

Multi-ingredient Preparations. ***Arg.***: Moflag D; Vigadexa; ***India***: Milflox Plus; Mosi-D; Moxi-Mep-D; Moxiblu-D; Moxigram-DX; ***Thai.***: Vigadexa.

Pharmacopoeial Preparations

USP 36: Moxifloxacin Ophthalmic Solution.

Mupirocin *(BAN, USAN, rINN)*

BRL-4910A; Mupirocina; Mupirocinas; Mupirocine; Mupirocinum; Mupirosiini; Pseudomonic Acid; Мупироцин.

9-[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxypyran-2-yl]-3-methylbut-2-enoyloxy]nonanoic acid; (2*S*-{2α(*E*),3β,4β,5α[2*R**,3*R**(1*R**,2*R**)]}-9-{[3-Methyl-1-oxo-4-(tetrahydro-3,4-dihydroxy-5-{[3-(2-hydroxy-1-methyl-propyl)oxiranyl]methyl}-2*H*-pyran-2-yl)-2-butenyl]oxy}nonanoic acid.

$C_{26}H_{44}O_9$=500.6

CAS — 12650-69-0.

ATC — D06AX09; R01AX06.

ATC Vet — QD06AX09; QR01AX06.

UNII — D0GX863OA5.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8 (Mupirocin). A white or almost white powder. It shows polymorphism. Slightly soluble in water; freely soluble in dehydrated alcohol, in acetone, and in dichloromethane. The pH of a freshly prepared saturated solution in water is 3.5 to 4.0. Protect from light.

USP 36: (Mupirocin). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in dehydrated alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ether. pH of a saturated solution in water is between 3.5 and 4.5. Store in airtight containers.

Mupirocin Calcium *(BANM, USAN, rINNM)*

BRL-4910F; Calcii Mupirocinum; Mupirocin-Calcium; Mupirocin vápenatá sůl dihydrát; Mupirocina cálcica; Mupirocine Calcique; Mupirocinkalcium; Mupirocin-kalcium; Mupirocino kalcio druska; Mupirocinum calcicum; Mupirocinum Calcicum Dihydricum; Mupirosiinikalsium; Кальций Мупироцин.

$C_{52}H_{86}O_{18}Ca,2H_2O$=1075.4

CAS — 104486-81-9 (anhydrous mupirocin calcium); 115074-43-6 (mupirocin calcium dihydrate).

ATC — D06AX09; R01AX06.

ATC Vet — QD06AX09; QR01AX06.

UNII — RG38I2P540.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8 (Mupirocin Calcium). A white or almost white powder. Very slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane.

USP 36: (Mupirocin Calcium). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens*. It is applied topically as a 2% ointment in a macrogol base, or as a cream containing mupirocin calcium equivalent to 2% mupirocin, in the treatment of various bacterial skin infections. These preparations should be applied up to 3 times daily for up to 10 days; treatment should be re-evaluated if there is no response after 3 to 5 days. They are not suitable for application to mucous membranes, and therefore a nasal ointment containing mupirocin calcium equivalent to 2% mupirocin in a paraffin basis is used for eradication of the nasal carriage of *Staphylococcus aureus*, particularly epidemic meticillin-resistant strains. The nasal ointment should be applied into each nostril 2 or 3 times daily for a maximum of 7 days.

For further details of skin infections and staphylococcal infections and their treatment, see under Choice of Antibacterial, p. 207.1 and p. 208.2 respectively.

References.

1. Roth VR, *et al.* Should we routinely use mupirocin to prevent staphylococcal infections? *Infect Control Hosp Epidemiol* 2000; **21:** 745–9.
2. Perl TM, *et al.* Mupirocin and the Risk of Staphylococcus Aureus Study Team. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med* 2002; **346:** 1871–7.
3. Takahashi S, *et al.* The preventive effects of mupirocin against nasotracheal intubation-related bacterial carriage. *Anesth Analg* 2003; **97:** 222–5.
4. Laupland KB, Conly JM. Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. *Clin Infect Dis* 2003; **37:** 933–8.
5. Tacconelli E, *et al.* Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. *Clin Infect Dis* 2003; **37:** 1629–38.
6. Wertheim HF, *et al.* Mupirocin prophylaxis against nosocomial Staphylococcus aureus infections in nonsurgical patients: a randomized study. *Ann Intern Med* 2004; **140:** 419–25.
7. Kallen AJ, *et al.* Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005; **26:** 916–22.
8. Unemura Y, *et al.* Impact of prophylactic mupirocin for radical esophagectomy. *J Infect Chemother* 2006; **12:** 257–63.
9. Sit D, *et al.* Prophylactic intranasal mupirocin ointment in the treatment of peritonitis in continuous ambulatory peritoneal dialysis patients. *Adv Therapy* 2007; **24:** 387–93.
10. van Rijen M, *et al.* Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 02/09/09).
11. Coates T, *et al.* Nasal decolonization of Staphylococcus aureus with mupirocin: strengths, weaknesses and future prospects. *J Antimicrob Chemother* 2009; **64:** 9–15.
12. Xu G, *et al.* Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. *Nephrol Dial Transplant* 2010; **25:** 587–92.

Adverse Effects and Precautions

Mupirocin is usually well tolerated but local reactions such as burning, stinging, and itching may occur after the application of mupirocin to the skin.

Some mupirocin products are formulated in a macrogol base: such formulations are not suitable for application to mucous membranes and should be used with caution in patients with extensive burns or wounds because of the possibility of macrogol toxicity. Care is also required in patients with renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mupirocin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Antimicrobial Action

Mupirocin is an antibacterial that inhibits bacterial protein synthesis by binding to isoleucyl transfer RNA synthetase. It is mainly bacteriostatic at low concentrations, although it is usually bactericidal in the high concentrations achieved by topical application to the skin. At these concentrations it may have some activity against organisms reported to be relatively resistant to mupirocin *in vitro*.

- It is mainly active against Gram-positive aerobes. Most strains of staphylococci (including meticillin-resistant and multiply-resistant *Staph. aureus*) and streptococci are susceptible *in vitro*, although the enterococci are relatively resistant.
  Mupirocin is also active against *Listeria monocytogenes* and *Erysipelothrix rhusiopathiae*.
- The Gram-negative organisms are generally insensitive, but *Haemophilus influenzae*, *Neisseria* spp. and a few others are sensitive.
- Anaerobic organisms, both Gram-positive and Gram-negative, are generally resistant, and activity against fungi is low.

Mupirocin is more active *in vitro* at acid pH than in alkaline conditions.

Naturally resistant strains of *Staph. aureus* occur rarely but resistance, including high-level plasmid-mediated transferable resistance, has emerged, particularly during long-term use. There has been some concern that inappropriate prescribing of mupirocin has led to this steadily increasing resistance.

Activity against fungi. Activity of mupirocin 2% *in vitro* against *Candida albicans* was comparable to that of other commonly used topical antifungals. Although MICs were considerably in excess of those reported for susceptible bacteria, clinical responses in 10 patients suggested that

adequate concentrations of mupirocin were achieved after topical application.[1]

1. Rode H, *et al.* Efficacy of mupirocin in cutaneous candidiasis. *Lancet* 1991; **338:** 578.

Resistance. References.

1. Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. *J Antimicrob Chemother* 1998; **41:** 11–18.
2. Schmitz F-J, *et al.* The prevalence of low- and high-level mupirocin resistance in staphylococci from 19 European hospitals. *J Antimicrob Chemother* 1998; **42:** 489–95.
3. Upton A, *et al.* Mupirocin and Staphylococcus aureus: a recent paradigm of emerging antibiotic resistance. *J Antimicrob Chemother* 2003; **51:** 613–17.
4. Kresken M, *et al.* Prevalence of mupirocin resistance in clinical isolates of Staphylococcus aureus and Staphylococcus epidermidis: results of the Antimicrobial Resistance Surveillance Study of the Paul-Ehrlich-Society for Chemotherapy, 2001. *Int J Antimicrob Agents* 2004; **23:** 577–81.
5. Walker ES, *et al.* A decline in mupirocin resistance in methicillin-resistant Staphylococcus aureus accompanied administrative control of prescriptions. *J Clin Microbiol* 2004; **42:** 2792–5.
6. Patel JB, *et al.* Mupirocin resistance. *Clin Infect Dis* 2009; **49:** 935–41.

Pharmacokinetics

Only very small amounts of topically applied mupirocin are absorbed into the systemic circulation where it is rapidly metabolised to monic acid, which is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bactroban; Dimsa; Mupax; Mupirox; Paldar; Quemicetina Nasal NF; Vidox; ***Austral.***: Bactroban; ***Austria***: Bactroban; ***Belg.***: Bactroban; ***Braz.***: Bacrocin; Bactocin; Bactroban; Bactroneo; Dermoban; Supirocin; ***Canad.***: Bactroban; ***Chile***: Bactroban; Bantix; Paldar; Ultrabiotic; Underan; ***China***: Bactroban (百多邦); ***Cz.***: Bactroban; ***Denm.***: Bactroban; ***Fin.***: Bactroban; ***Fr.***: Bactroban; Mupiderm; ***Ger.***: InfectoPyoderm; Turixin; ***Gr.***: Bactroban; Bactrocine; Hevronaz; Micoban; Mupider; Mupiran; Veltion; ***Hong Kong***: Bactroban; Muprin; ***Hung.***: Bactroban; ***India***: Bactroban; Brodisym; I-Bact; MPower; Mu-Oint; Mufect; Mupiban; Mupinova; Mupirax; Muroci; Supirocin; ***Indon.***: Bactoderm; Bactroban; Pibaksin; ***Irl.***: Bactroban; ***Israel***: Bactroban; ***Ital.***: Bactroban; Mupiskin; ***Jpn***: Bactroban; ***Malaysia***: Bactroban; Muprin; Supirocin; ***Mex.***: Backskin; Bactroban; Sinpebac; ***Neth.***: Bactroban; ***NZ***: Bactroban; ***Philipp.***: Bactifree; Bactroban; Bactrocin; Foskina; Mupicin; Mupiderm; Muprin; ***Pol.***: Bactroban; Mupirox; ***Port.***: Bactroban; ***Rus.***: Bactroban (Бактробан); Supirocin (Супироцин); ***S.Afr.***: Bactroban; Supiroban; ***Singapore***: Bactroban; Mupider; Mupirax; Supirocin; ***Spain***: Bactroban; Plasimine; ***Swed.***: Bactroban; ***Switz.***: Bactroban; ***Thai.***: Bacidal; Bactex; Bactokil; Bactroban; Banbact; Muporin; ***Turk.***: Bactroban; ***UK***: Bactroban; ***Ukr.***: Bactroban (Бактробан); ***USA***: Bactroban; Centany; ***Venez.***: Bactroban.

Multi-ingredient Preparations. ***India***: Flutibact; Mupimet; Supirocin-B; ***Mex.***: Dermucor-H; ***Philipp.***: Foskina-B; ***Rus.***: Supirocin-B (Супироцин-Б).

Pharmacopoeial Preparations

BP 2014: Mupirocin Cream; Mupirocin Nasal Ointment; Mupirocin Ointment;

USP 36: Mupirocin Cream; Mupirocin Nasal Ointment; Mupirocin Ointment.

Nadifloxacin *(BAN, rINN)*

Jinofloxacin; Nadifloxacine; Nadifloxacino; Nadifloxacinum; OPC-7251; Надифлоксацин.

(±)-9-Fluoro-6,7-dihydro-8-(4-hydroxypiperidino)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

$C_{19}H_{21}FN_2O_4$=360.4

CAS — 124858-35-1.

UNII — 6CL9Y5YZEQ.

Profile

Nadifloxacin is a fluoroquinolone antibacterial used in topical treatment of acne. It is applied twice daily as a 1% cream or ointment.

Reviews.

1. Jacobs MR, Appelbaum PC. Nadifloxacin: a quinolone for topical treatment of skin infections and potential for systemic use of its active isomer, WCK 771. *Expert Opin Pharmacother* 2006; **7:** 1957–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Pingfu (萍敷); Xin Ke Fei (欣可菲); Yi You Ning (依尤宁); ***Ger.***: Nadixa; ***Gr.***: Nadixa; ***India***: Nadibact; Nadicin; Nadiderm; Nadiflox; Nadim; Nadiskin; Nadoxin; ***Indon.***: Acuatim; ***Ital.***: Nadixa; ***Jpn***: Acuatim; ***Mex.***: Nadixa; ***Philipp.***: Nadoxin; ***Port.***: Nadixa; ***Spain***: Nadixa; ***Turk.***: Nadixa; ***Ukr.***: Nadoxin (Надоксин).

Multi-ingredient Preparations. ***India***: Metazole; Motoso; Nadicin-C; Nadoxin-C.

Nafcillin Sodium *(BANM, USAN, rINNM)*

Nafcilina sódica; Nafcilline Sodique; Nafcillinnatrium; Nafcillinum Natricum; Nafsilliininatrium; Natrii Nafcillinum; Wy-3277; Натрий Нафциллин.

Sodium (6*R*)-6-(2-ethoxy-1-naphthamido)penicillanate monohydrate.

$C_{21}H_{21}N_2NaO_5S,H_2O$=454.5

CAS — 147-52-4 (nafcillin); 985-16-0 (anhydrous nafcillin sodium); 7177-50-6 (nafcillin sodium monohydrate).

ATC — J01CF06.

UNII — SY07234TTS (anhydrous nafcillin sodium); 49G3001BCK (nafcillin sodium monohydrate).

Pharmacopoeias. In *US*.

USP 36: (Nafcillin Sodium). A white to yellowish-white powder having not more than a slight characteristic odour. Freely soluble in water and in chloroform; soluble in alcohol. pH of a 3% solution in water is between 5.0 and 7.0. Store in airtight containers.

Incompatibility. Nafcillin sodium has been reported to be incompatible with aminoglycosides and some other antibacterials. It has also been reported to be incompatible with acidic and alkaline drugs.

Uses and Administration

Nafcillin is a penicillinase-resistant penicillin used similarly to flucloxacillin (p. 299.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

It is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of nafcillin; 1.1 g of nafcillin sodium is equivalent to about 1 g of nafcillin. Nafcillin sodium may be given intravenously by slow injection over 5 to 10 minutes or by slow infusion over at least 30 to 60 minutes; usual adult doses are 0.5 to 1 g of nafcillin every 4 hours, although it is usually recommended that it be used for not more than 24 to 48 hours because of the risk of thrombophlebitis. Up to 12 g daily, in divided doses, has been used in deep-seated infections such as endocarditis and osteomyelitis. It has also been given by intramuscular injection in doses of 0.5 to 1 g of nafcillin every 4 to 6 hours.

For details of doses in children, see p. 330.2.

Nafcillin sodium has also been given orally but other penicillinase-resistant penicillins are preferred.

Administration in children. Nafcillin may be given to neonates and children for the treatment of infections caused by susceptible strains of penicillinase-producing staphylococci by intramuscular injection, slow intravenous injection over 5 to 10 minutes, or by intravenous infusion over 30 to 60 minutes.

In the USA, the American Academy of Pediatrics[1] recommends the following doses:

- all neonates with a birth-weight of less than 1.2 kg, and neonates less than 1 week of age with a birth-weight of 1.2 to 2 kg: 25 mg/kg every 12 hours
- neonates less than 1 week of age with a birth-weight of more than 2 kg: 25 mg/kg every 8 hours
- neonates 1 week of age or older with a birth-weight of 1.2 to 2 kg: 25 mg/kg every 8 hours
- neonates 1 week of age or older with a birth-weight of more than 2 kg: 25 to 35 mg/kg every 6 hours
- children 1 month and older: 50 to 100 mg/kg daily in 4 divided doses; 100 to 150 mg/kg daily may be used for severe infections

1. American Academy of Pediatrics. *2009 Red Book: Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2009.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Thrombophlebitis may occur when nafcillin is given by intravenous injection, and tissue damage has been reported on extravasation.

Effects on the kidneys. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; **26:** 985–90.
2. Guharoy SR, *et al.* Suspected nafcillin-induced interstitial nephritis. *Ann Pharmacother* 1993; **27:** 170–3.
3. Hoppes T, *et al.* Four cases of nafcillin-associated acute interstitial nephritis in one institution. *Nat Clin Pract Nephrol* 2007; **3:** 456–61.

Effects on the liver. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; **26:** 985–90.
2. Presti ME, *et al.* Nafcillin-associated hepatotoxicity: report of a case and review of the literature. *Dig Dis Sci* 1996; **41:** 180–4.

Lupus erythematosus. A report[1] of apparent drug-induced lupus erythematosus associated with nafcillin.

1. Blazes DL, Martin GJ. Drug-induced lupus erythematosus secondary to nafcillin: the first reported case. *Rheumatol Int* 2004; **24:** 242–3.

Sodium content. Each g of nafcillin sodium contains about 2.2 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Immunosuppressants. For the effect of nafcillin on *ciclosporin*, see p. 1956.2.

Antimicrobial Action

As for Flucloxacillin, p. 300.1.

Pharmacokinetics

Nafcillin is incompletely and irregularly absorbed from the gastrointestinal tract, especially when given after food. After intramuscular injection it is absorbed more reliably, an injection of 0.5 to 1 g producing peak plasma concentrations of 5 to 8 micrograms/mL within about 0.5 to 1 hour. Up to 90% of nafcillin in the circulation is bound to plasma proteins. Nafcillin has been reported to have a plasma half-life of about 0.5 to 1.5 hours. The half-life is prolonged in neonates.

Nafcillin crosses the placenta into the fetal circulation and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Nafcillin is distributed into pleural and synovial fluids and into bone.

Nafcillin differs from most other penicillins in that it is largely inactivated by hepatic metabolism. It is excreted via the bile although some reabsorption takes place in the small intestine. Only about 10% of a dose given orally before food, and about 30% of a dose given intramuscularly, is excreted in the urine.

Plasma concentrations are enhanced by probenecid.

Preparations

Pharmacopoeial Preparations

USP 36: Nafcillin for Injection; Nafcillin Injection; Nafcillin Sodium Capsules; Nafcillin Sodium for Oral Solution; Nafcillin Sodium Tablets.

Nalidixic Acid *(BAN, USAN, rINN)*

Acide Nalidixique; Ácido nalidíxico; Acidum Nalidixicum; Kwas nalidyksowy; Kyselina nalidixová; Nalidiksiinihappo; Nalidiksik Asit; Nalidikso rūgštis; Nalidíxico, ácido; Nalidixinic Acid; Nalidixinsäure; Nalidixinsyra; Nalidixsav; NSC-82174; Win-18320; Налидиксовая Кислота.

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

$C_{12}H_{12}N_2O_3$=232.2

CAS — 389-08-2.

ATC — J01MB02.

ATC Vet — QJ01MB02.

UNII — 3B91HWA56M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nalidixic Acid). An almost white or pale yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Nalidixic Acid). A white to very pale yellow, odourless crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 910 of alcohol and 1 in 29 of chloroform; slightly soluble in acetone, in methyl alcohol, and in toluene; soluble in dichloromethane and in solutions of fixed alkali hydroxides and carbonates. Store in airtight containers.

Uses and Administration

Nalidixic acid is a 4-quinolone antibacterial used in the treatment of urinary-tract infections due to Gram-negative bacteria other than *Pseudomonas* spp. (p. 213.1) and in the treatment of selected gastrointestinal infections caused by susceptible organisms. It has also been used to treat shigellosis (bacillary dysentery) (p. 186.1), although widespread resistance has now limited its usefulness.

The usual oral dose is 900 mg 4 times daily for at least 7 days in acute infections, reducing thereafter to 600 mg 4 times daily in chronic infections. Since bacterial resistance may develop rapidly it has been suggested that if treatment with nalidixic acid has not resulted in a negative urine culture within 48 hours another antimicrobial should be used.

For details of reduced doses in renal impairment, see p. 331.1. See also p. 331.1 for details of doses in infants and children.

Although the antibacterial activity of nalidixic acid does not appear to be influenced by urinary pH, the use of

sodium bicarbonate or sodium citrate does increase the concentration of active drug in the urine. Commercial preparations containing nalidixic acid, sodium bicarbonate, and sodium citrate have been used in some countries.

It is also used with the analgesic phenazopyridine.

Administration in children. Although nalidixic acid is not generally recommended for use in patients under 18 years of age (see Precautions, p. 331.1), it may be used for the treatment of urinary-tract or selected gastrointestinal infections caused by susceptible Gram-negative bacteria in infants and children over 3 months of age. The usual oral dose is 55 to 60 mg/kg daily in 4 divided doses for at least 7 days, reducing thereafter to about 30 mg/kg daily in 4 divided doses for prolonged treatment.

In addition, the *BNFC* suggests that a dose of 30 mg/kg daily in 2 divided doses may be given for prophylaxis of urinary-tract infections.

Administration in renal impairment. In the UK, some products of nalidixic acid have been licensed for use at half the usual oral dose in patients with a creatinine clearance below 20 mL/minute. However, other licensed product information does not include this information and suggests that nalidixic acid should not be used in patients with severe renal impairment. The *BNF* suggests avoiding use in those with a estimated glomerular filtration rate less than 20 mL/minute per 1.73 m^2.

Adverse Effects

The most frequent adverse reactions to nalidixic acid involve the gastrointestinal tract, skin, and CNS. Gastrointestinal effects have been reported in about 8% of patients and include nausea, vomiting, diarrhoea, and abdominal pain.

Adverse effects on the skin include photosensitivity reactions with erythema and bullous eruptions, allergic rashes, urticaria, and pruritus. Erythema multiforme and Stevens-Johnson syndrome have been reported rarely. Eosinophilia, fever, angioedema, and, rarely, anaphylactoid reactions have occurred.

Neurological effects include visual disturbances, headache, dizziness or vertigo, drowsiness, and sometimes confusion, depression, excitement, and hallucinations. Toxic psychoses or convulsions have occurred, especially after large doses; convulsions are most likely in patients with predisposing factors such as cerebral arteriosclerosis or epilepsy. There have been reports of intracranial hypertension, especially in infants and young children, and also of metabolic acidosis.

Peripheral neuropathies, muscular weakness, and myalgia are occasional adverse effects. Sixth cranial nerve palsy has been reported rarely.

Arthralgia has been reported (degenerative changes in weight-bearing joints of young *animals* are documented). Tendon damage has occasionally been associated with nalidixic acid and related compounds, the fluoroquinolones (see Effects on the Musculoskeletal System, under Ciprofloxacin, p. 263.2).

Cholestatic jaundice, thrombocytopenia, and leucopenia have occurred rarely, as has haemolytic anaemia in patients who may or may not have G6PD deficiency. There have been isolated reports of fatal auto-immune haemolytic anaemia in elderly patients.

Precautions

Nalidixic acid is contra-indicated in patients with a history of convulsive disorders and in those with severe renal impairment. It should be given with care to patients with hepatic or moderate renal impairment, severe cerebral arteriosclerosis, or G6PD deficiency. Blood counts and renal and hepatic function should be monitored if treatment continues for more than 2 weeks.

It should be avoided in infants less than 3 months old. Since nalidixic acid and related antimicrobials have been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these compounds should not generally be used in patients aged under 18 years, pregnant women, or during breast feeding (but see also p. 331.1) unless the benefits outweigh the risks. Treatment should be stopped if symptoms of neuropathy or arthralgia occur. Tendon damage may occur rarely and treatment should be stopped if patients have tendon pain, inflammation, or rupture.

Exposure to strong sunlight or sunlamps should be avoided during treatment with nalidixic acid.

Nalidixic acid may cause false-positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics[1] states that nalidixic acid is usually compatible with breast feeding, although haemolytic anaemia has been reported[2] in a breast-fed infant, with no evidence of G6PD deficiency, whose mother had received nalidixic acid.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)
2. Belton EM, Jones RV. Haemolytic anaemia due to nalidixic acid. *Lancet* 1965; **ii:** 691.

G6PD deficiency. Licensed product information for nalidixic acid advises that it should be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency as there may be a risk of haemolysis. However, a review[1] found only 3 reports of haemolysis in G6PD-deficient patients given nalidixic acid; the scarcity of reports despite its wide use, suggested that nalidixic acid could be given in therapeutic doses to patients with G6PD deficiency.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.

Porphyria. Although nalidixic acid has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] UK licensed product information contra-indicates its use in patients with a history of porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Interactions

The absorption of nalidixic acid is reduced by sucralfate, and divalent and trivalent cations such as aluminium, calcium, iron, magnesium, and zinc, and therefore use of nalidixic acid with antacids, iron preparations, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. It is recommended that such products should not be given within 2 hours before or after nalidixic acid.

The excretion of nalidixic acid is reduced and plasma concentrations increased by probenecid. Other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline have been shown to antagonise the action of nalidixic acid *in vitro* and should not be used together.

Fatal haemorrhagic enterocolitis has been associated with the use of nalidixic acid and high-dose intravenous melphalan in children; use with other alkylating antineoplastics is also contra-indicated. There is a possible risk of increased nephrotoxicity when nalidixic acid is given with ciclosporin.

Nalidixic acid is reported to enhance the effect of oral anticoagulants such as warfarin (see p. 1531.1); this may be due in part to displacement of anticoagulant from its plasma binding sites. The dose of anticoagulant may need to be reduced.

The effect of some quinolone antibacterials on xanthines is discussed under Caffeine, p. 1206.1, and Theophylline, p. 1234.2.

Convulsions may be precipitated by the use of some quinolones with NSAIDs (see Analgesics, under Interactions of Ciprofloxacin, p. 264.3), although this has not been reported with nalidixic acid.

Antimicrobial Action

Nalidixic acid is considered to act by interfering with the replication of bacterial DNA, probably by inhibiting DNA gyrase (topoisomerase) activity. It is active against Gram-negative bacteria including *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Salmonella* spp., and *Shigella* spp., and is usually bactericidal. *Pseudomonas aeruginosa*, Gram-positive bacteria, and anaerobes are not generally susceptible.

Bacterial resistance may develop rapidly, sometimes within a few days of starting treatment, but it does not appear to be transferable or R-plasmid mediated (see also p. 331.2). Cross-resistance occurs with oxolinic acid and cinoxacin.

The antibacterial activity of nalidixic acid is not significantly affected by differences in urinary pH. Antagonism between nalidixic acid and other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline has been shown *in vitro*.

Resistance. Bacterial plasmid-mediated resistance to quinolones had not been seen by the late 1980s.[1] A report[2] of such resistance to nalidixic acid in *Shigella dysenteriae* responsible for an epidemic of shigellosis in Bangladesh in 1987, was questioned at the time.[3] On reinspection of the data, chromosomal mutation rather than plasmid-mediated resistance was confirmed as the mechanism responsible so far for resistance to quinolones.[1] Subsequent data[4] in an isolate of *Klebsiella pneumoniae* have, however, suggested that plasma-mediated resistance to quinolones may be possible.

1. Courvalin P. Plasmid-mediated 4-quinolone resistance: a real or apparent absence? *Antimicrob Agents Chemother* 1990; **34:** 681–4.
2. Munshi MH, *et al.* Plasmid-mediated resistance to nalidixic acid in Shigella dysenteriae type 1. *Lancet* 1987; **ii:** 419–21.
3. Crumplin GC. Plasmid-mediated resistance to nalidixic acid and new 4-quinolones? *Lancet* 1987; **ii:** 854–5.
4. Martínez-Martínez L, *et al.* Quinolone resistance from a transferable plasmid. *Lancet* 1998; **351:** 797–9.

Pharmacokinetics

Nalidixic acid is rapidly and almost completely absorbed from the gastrointestinal tract, and peak plasma concentrations of 20 to 40 micrograms/mL have been reported 1 to 2 hours after a 1-g oral dose. Plasma half-lives of about 1 to 2.5 hours have been reported (but see p. 331.3).

Nalidixic acid is partially metabolised to hydroxynalidixic acid, which has antibacterial activity similar to that of nalidixic acid and accounts for about 30% of active drug in the blood. About 93% of nalidixic acid and 63% of hydroxynalidixic acid are bound to plasma proteins. Both nalidixic acid and hydroxynalidixic acid are rapidly metabolised to inactive glucuronide and dicarboxylic acid derivatives; the major inactive metabolite 7-carboxynalidixic acid is usually only detected in urine.

Nalidixic acid and its metabolites are excreted rapidly in the urine, nearly all of a dose being eliminated within 24 hours. More than 80% of the drug excreted in the urine is as inactive metabolites, but peak urinary concentrations of active drug averaging about 150 to 200 micrograms/mL occur 3 to 4 hours after a single 1-g dose. Hydroxynalidixic acid accounts for about 80 to 85% of activity in the urine. Urinary excretion is reduced by probenecid. About 4% of a dose is excreted in the faeces.

Traces of nalidixic acid are distributed into breast milk and appear to cross the placenta.

Half-life. Although a plasma half-life of 1 to 2.5 hours is generally cited for nalidixic acid, values of 6 to 7 hours have been reported for active drug (nalidixic acid and hydroxynalidixic acid) after using more specific and sensitive assay techniques and longer sampling periods than previously.[1]

The elimination rate of nalidixic acid appears to be not markedly altered by renal impairment, but the elimination of hydroxynalidixic acid is significantly reduced. 7-Carboxynalidixic acid has appeared in the plasma of patients with renal impairment.[2] Plasma concentrations of active drug were higher and the half-life prolonged in elderly subjects.[3]

1. Ferry N, *et al.* Nalidixic acid kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1981; **29:** 695–8.
2. Cuisinaud G, *et al.* Nalidixic acid kinetics in renal insufficiency. *Br J Clin Pharmacol* 1982; **14:** 489–93.
3. Barbeau G, Belanger P-M. Pharmacokinetics of nalidixic acid in old and young volunteers. *J Clin Pharmacol* 1982; **22:** 490–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Naluril; Wintomylon; ***Gr.***: Nal-acid; Uridril; Wintomylon; ***Hong Kong***: Wintomylon†; ***Hung.***: Nevigramon; ***India***: Diarlop; Dix; Gramoneg; Nadix; Negadix; ***Indon.***: Urineg; ***Irl.***: Negram†; ***Mex.***: A-N-Dix†; Acidix; Kamilon; Nalix; Nalomin; Pronal Dix; Uronalin; Wintomylon†; ***Pol.***: Nevigramon†; ***Rus.***: Negram (Нерам); Nevigarmon (Невиграмон); ***S.Afr.***: Puromylon; Winlomylon†; ***UK***: Uriben; ***USA***: NegGram†.

Multi-ingredient Preparations. ***India***: Abdogyl-N; Aldiagram; Amibex-NA; Bactomet; Darmed; Diarlop Plus; Entrozyme-M; Gramogyl; Gramoneg-M; Matrix-MN; Nalidys; Negadix-M; ***Mex.***: Azo-Uronalin; Azo-Wintomylon; Azogen; Azuron; Nalixone; Naxilan-Plus; Pirifur.

Pharmacopoeial Preparations
BP 2014: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets;
USP 36: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets.

Neomycin *(BAN, rINN)*

Neomicina; Néomycine; Neomycinum; Neomysiini; Неомицин.

CAS — 1404-04-2 (neomycin); 3947-65-7 (neomycin A); 119-04-0 (neomycin B); 66-86-4 (neomycin C).

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

UNII — 116QD7X297 (neomycin); 5981U00LY0 (neomycin A).

Description. A mixture of 2 isomers, neomycin B ($C_{23}H_{46}N_6O_{13}$ = 614.6) and neomycin C ($C_{23}H_{46}N_6O_{13}$ = 614.6) with neomycin A (neamine, $C_{12}H_{26}N_4O_6$ = 322.4); neomycins B and C are glycoside esters of neamine and neobiosamines B and C. Framycetin (p. 301.2) consists of neomycin B.

Neomycin Sulfate *(BANM, rINNM)*

Fradiomycin Sulfate; Neomicina, sulfato de; Neomicino sulfatas; Neomicin-szulfát; Neomisin Sülfat; Neomycin Sulphate; Néomycine, sulfate de; Neomycini Sulfas; Neomycinsulfat; Neomycin-sulfát; Neomycyny siarczan; Neomysiinisulfaatti; Sulfato de neomicina; Неомицина Сульфат.

CAS — 1405-10-3.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

UNII — 057Y626693.

NOTE. NEO is a code approved by the BP 2014 for use on single unit doses of eye drops containing neomycin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Neomycin Sulfate). A mixture of the sulfates of substances produced by the growth of certain selected strains of *Streptomyces fradiae*, the main component being the sulfate of neomycin B. The potency is not less than 680 units/mg, calculated with reference to the dried substance. A white or yellowish-white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

USP 36: (Neomycin Sulfate). The sulfate salt of a kind of neomycin, an antibacterial substance produced by the growth of *Streptomyces fradiae* (Streptomycetaceae), or a mixture of two or more such salts. It has a potency equivalent to not less than 600 micrograms of neomycin per mg, calculated on the dried basis. A white to slightly yellow powder, or cryodesiccated solid. It is odourless or practically so, and is hygroscopic. Soluble 1 in 1 of water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether. pH of a solution in water containing the equivalent of neomycin 3.3% is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Neomycin Undecenoate *(BANM)*

Neomicina, undecilenato de; Neomycin Undecylenate (rINNM); Neomycin Undecylenate (USAN); Néomycine, Undécylénate de; Neomycini Undecylenas; Undecilenato de neomicina; Неомицина Ундециленат.

The 10-undecenoate salt of neomycin.

CAS — 1406-04-8.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

Uses and Administration

Neomycin is an aminoglycoside antibacterial used topically in the treatment of infections of the skin, ear, and eye due to susceptible staphylococci and other organisms. Most preparations contain the sulfate, but neomycin undecenoate is also used. Neomycin is often used with another antibacterial such as bacitracin, colistin, gramicidin, or polymyxin B. Such combinations have been used topically in the eye before ophthalmic surgery for infection prophylaxis and, with propamidine isetionate, in the treatment of acanthamoeba keratitis (p. 921.2). A cream containing neomycin sulfate and chlorhexidine hydrochloride has been used for application to the nostrils in the treatment of staphylococcal nasal carriers (p. 208.2) but, as with other topical antibacterial preparations, development of resistance may be a problem. Neomycin is often used with topical corticosteroids, but such preparations should be used with caution because of the risk that signs of resistant infection may be suppressed. Care must also be taken where there is skin trauma because of the risk of increased absorption and toxicity (see Adverse Effects, p. 332.2). For details of bacterial skin infections and their treatment, see p. 207.1.

Because neomycin sulfate is poorly absorbed from the gastrointestinal tract, it has been given orally for bowel preparation before abdominal surgery, often with erythromycin (p. 209.1). Neomycin sulfate is also given orally with other antibacterials and antifungals in the selective decontamination of the digestive tract in patients in intensive care (p. 187.3).

Neomycin is rarely used in the treatment of existing gastrointestinal infections. Although it has been used in the treatment of diarrhoea due to infection with enteropathogenic *Escherichia coli* (EPEC) (p. 184.3), the use of neomycin in children with acute diarrhoea is generally not recommended.

Neomycin sulfate may be given orally to patients with incipient hepatic encephalopathy (p. 1811.2) to reduce the flora of the gastrointestinal tract.

Neomycin has also been used for the irrigation of wounds and body cavities but such use is no longer recommended because of the risk of toxicity.

Oral administration. For pre-operative use, 1 g of neomycin sulfate has been given hourly for 4 hours and then every 4 hours for 2 or 3 days before surgery.

As an adjunct in the management of hepatic encephalopathy, 4 to 12 g may be given daily in divided doses, usually for 5 to 7 days; up to 4 g daily may be given over an indefinite period to those with chronic hepatic insufficiency. Prolonged use may cause malabsorption.

For details of doses in children, see p. 332.2.

Topical preparations typically contain the equivalent of 0.35% neomycin base.

Neomycin hydrochloride has also been used.

Administration in children. Neomycin sulfate has been given orally for *bowel preparation* before abdominal surgery, often with erythromycin. UK licensed product information recommends the following doses, taken every 4 hours for 2 or 3 days before the operation:

- in those 6 to 12 years of age: 250 to 500 mg
- in those over 12 years of age: 1 g

As an adjunct in the management of *hepatic encephalopathy* children may be given oral neomycin sulfate 50 to 100 mg/kg daily in divided doses for 5 to 7 days.

For some *enteric infections* caused by susceptible bacteria in children beyond the newborn period the American Academy of Pediatrics[1] suggests oral doses of 100 mg/kg daily in 4 divided doses.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Treatment

As for Gentamicin Sulfate, p. 306.2.

Neomycin has particularly potent nephrotoxic and ototoxic properties and so is generally no longer given parenterally. However, enough may be absorbed after use by other routes (e.g. orally, instillation into cavities or open wounds, or topical application to damaged skin) to produce irreversible partial or total deafness. The effect is dose-related and is enhanced by renal impairment. Nephrotoxic effects may also occur.

Large oral doses of neomycin cause nausea, vomiting, and diarrhoea. Prolonged oral use can lead to a potentially severe malabsorption syndrome with steatorrhoea and diarrhoea. Superinfection may occur, especially with prolonged treatment.

Neomycin has a stronger neuromuscular-blocking action than other aminoglycosides, and respiratory depression and arrest has followed the intraperitoneal instillation of neomycin. Fatalities have occurred.

Hypersensitivity reactions, such as rashes, pruritus, and sometimes drug fever or even anaphylaxis, can develop during local treatment with neomycin and may be masked by the combined use of a corticosteroid. Cross-sensitivity with other aminoglycosides may occur.

Precautions

As for Gentamicin Sulfate, p. 306.3. Parenteral use of neomycin, or its use for irrigation of wounds or serous cavities such as the peritoneum, is no longer recommended.

Neomycin is contra-indicated for intestinal disinfection when an obstruction is present, in patients with a history of allergy to aminoglycosides, and in infants under 1 year. It should be used with great care in patients with renal or hepatic impairment, or with neuromuscular disorders, and in those with impaired hearing. The topical use of neomycin in patients with extensive skin damage or perforated tympanic membranes may result in deafness.

Prolonged local use should be avoided as it may lead to skin sensitisation and possible cross-sensitivity to other aminoglycosides.

Hypersensitivity and vaccination. Neomycin was thought to be responsible for a hypersensitivity reaction[1] in a child given measles, mumps, and rubella vaccine containing neomycin 25 micrograms. However, there is also a report of successful vaccination with measles, mumps, and rubella vaccine in a neomycin-sensitive child.[2] Although the vaccine may contain small amounts of neomycin or kanamycin, and sensitivity to either is considered a contra-indication to its use, it is only rarely necessary to withhold it once appropriate expert advice has been taken. There is little logic to intradermal testing since test solutions contain 4 to 40 times as much neomycin as the vaccine.[2]

1. Kwittken PL, *et al.* MMR vaccine and neomycin allergy. *Am J Dis Child* 1993; **147:** 128–9.
2. Elliman D, Dhanraj B. Safe MMR vaccination despite neomycin allergy. *Lancet* 1991; **337:** 365.

Interactions

As for Gentamicin Sulfate, p. 307.2. Absorption after oral or local use may be sufficient to produce interactions with other drugs given systemically.

Neomycin orally has been reported to impair the absorption of other drugs including phenoxymethylpenicillin, digoxin, and methotrexate; the efficacy of oral contraceptives might be reduced. The effects of acarbose may be enhanced by oral neomycin.

Antimicrobial Action

Neomycin has a mode of action and spectrum of activity similar to that of gentamicin (p. 307.2) but it lacks activity against *Pseudomonas aeruginosa.* It is reported to be active against *Mycobacterium tuberculosis.*

Because of its extensive topical use, resistance has been reported to be relatively widespread, notably among staphylococci, and some *Salmonella*, *Shigella*, and *Escherichia coli* strains. Cross-resistance with kanamycin, framycetin, and paromomycin occurs.

Pharmacokinetics

Neomycin is poorly absorbed from the gastrointestinal tract, about 97% of an oral dose being excreted unchanged in the faeces. Doses of 3 g orally produce peak plasma concentrations of up to 4 micrograms/mL and absorption is similar after an enema. Absorption may be increased in conditions which damage or inflame the mucosa. Absorption has also been reported to occur from the peritoneum, respiratory tract, bladder, wounds, and inflamed skin.

Once neomycin is absorbed it is rapidly excreted by the kidneys in active form. It has been reported to have a half-life of 2 to 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Concatag; Neomas; ***Austral.***: Neosulf; ***Braz.***: Cinaderm; Nemicina; Neocina†; Neodermicina; Neomed; Neomicon; Pomicina; ***China***: Xian Ke Xin (显克欣); ***Ger.***: Cysto-Myacyne N; Myacyne; Uro-Nebacetin N†; Vagicillin†; ***Gr.***: Nivemycin; ***Hong Kong***: Neoate†; Uni-Neoderm†; ***India***: Methacin; ***Israel***: Neocin; ***Jpn***: Francetin; ***Mex.***: Neomixen; ***Port.***: Enteromicina; Oto-Synalar N; ***Thai.***: Myneocin; ***UK***: Nivemycin; ***USA***: Neo-fradin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Dexamethasone and Neomycin Ear Spray; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone and Neomycin Cream; Neomycin Eye Drops; Neomycin Eye Ointment; Neomycin Tablets;

USP 36: Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin for Injection; Neomycin Sulfate and Bacitracin Ointment; Neomycin Sulfate and Bacitracin Zinc Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream; Neomycin Sulfate and

Dexamethasone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution; Neomycin Sulfate and Fluocinolone Acetonide Cream; Neomycin Sulfate and Fluorometholone Ointment; Neomycin Sulfate and Flurandrenolide Cream; Neomycin Sulfate and Flurandrenolide Lotion; Neomycin Sulfate and Flurandrenolide Ointment; Neomycin Sulfate and Gramicidin Ointment; Neomycin Sulfate and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Lotion; Neomycin Sulfate and Hydrocortisone Acetate Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin Sulfate and Hydrocortisone Cream; Neomycin Sulfate and Hydrocortisone Ointment; Neomycin Sulfate and Hydrocortisone Otic Suspension; Neomycin Sulfate and Methylprednisolone Acetate Cream; Neomycin Sulfate and Prednisolone Acetate Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Triamcinolone Acetonide Cream; Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment; Neomycin Sulfate Cream; Neomycin Sulfate Ointment; Neomycin Sulfate Ophthalmic Ointment; Neomycin Sulfate Oral Solution; Neomycin Sulfate Tablets; Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Netilmicin Sulfate *(BANM, USAN, rINNM)*

Netilmicin Sulphate; Netilmicina, sulfato de; Nétilmicine, Sulfate de; Netilmicini Sulfas; Netilmicino sulfatas; Netilmicinsulfat; Netilmicin-sulfát; Netilmicin-szulfát; Netilmisiinisulfaatti; Netilmisin sülfat; Netylmycyny siarczan; Sch-20569; Sulfato de netilmicina; N^1-Ethylsissomicin; Нетилмицина Сульфат.

4-*O*-[(2*R*,3*R*)-*cis*-3-Amino-6-aminomethyl-3,4-dihydro-2*H*-pyran-2-yl]-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)-1-*N*-ethylstreptamine sulphate.

$(C_{21}H_{41}N_5O_7)_2.5H_2SO_4$=1441.5

CAS — 56391-56-1 (netilmicin); 56391-57-2 (netilmicin sulfate).

ATC — J01GB07; S01AA23.

ATC Vet — QJ01GB07; QS01AA23.

UNII — S741ZJS97U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Netilmicin Sulfate). A substance obtained by synthesis from sisomicin. The potency is not less than 650 units/mg, calculated with reference to the dried substance. A white or yellowish-white, very hygroscopic, powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Netilmicin Sulfate). The potency is equivalent to not less than 595 micrograms of netilmicin per milligram, calculated on the dried basis. A white to pale yellowish-white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. pH of a solution in water containing the equivalent of netilmicin 4% is between 3.5 and 5.5. Store in airtight containers. Protect from moisture.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including netilmicin, with beta lactams, see under Gentamicin Sulfate, p. 304.3. Netilmicin is also reported to be incompatible with furosemide, heparin, and vitamin B complex.

Uses and Administration

Netilmicin is a semisynthetic aminoglycoside antibacterial with actions and uses similar to those of gentamicin (p. 304.3). It may be used as an alternative to amikacin (p. 214.2) in the treatment of infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. As with gentamicin, netilmicin may be used with penicillins and with cephalosporins; the injections should be given separately.

Netilmicin is given as the sulfate but doses are expressed in terms of the equivalent amount of base; 1.5 g of netilmicin sulfate is equivalent to about 1 g of netilmicin. It is usually given intramuscularly in doses of 4 to 6 mg/kg daily as a single dose; alternatively, it may be given in equally divided doses every 8 or 12 hours; for the control of life-threatening infections, up to 7.5 mg/kg may be given daily in divided doses every 8 hours for short periods.

The same doses may be given by slow intravenous injection over 3 to 5 minutes or infused intravenously over 0.5 to 2 hours in 50 to 200 mL of infusion fluid.

Peak plasma concentrations below 12 micrograms/mL and troughs below 2 micrograms/mL have been recommended for divided daily dose regimens.

Dosage should be adjusted in all patients according to plasma-netilmicin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p. 305.2.

For details of doses in children, see p. 333.2.

Administration in children. Dosage recommendations for netilmicin in infants and children vary somewhat. One regimen is 7.5 to 9 mg/kg daily in infants and neonates older than 1 week, and 6 to 7.5 mg/kg daily in children aged 12 months and over, both given in divided doses every 8 hours. Premature infants and neonates less than 1 week old may be given 3 mg/kg every 12 hours.

Doses may be given by intramuscular or slow intravenous injection or by intravenous infusion.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2. Some studies suggest that netilmicin is less nephrotoxic and ototoxic than gentamicin or tobramycin, although others have not found any significant differences in their toxicity.

It has been suggested that peak plasma concentrations of netilmicin should not exceed 12 micrograms/mL for prolonged therapy, and troughs should be below 2 micrograms/mL.

Effects on the cardiovascular system. Severe hypotension was associated with netilmicin in a patient undergoing artificial ventilation.[1] Hypotensive episodes were of short duration and coincided with netilmicin injection. They almost disappeared when sedation was stopped.

1. Rygnestad T. Severe hypotension associated with netilmicin treatment. *BMJ* 1997; **315:** 31.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies netilmicin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 307.2. It is active against a similar range of organisms although it is also reported to have some activity against *Nocardia*. It may be somewhat less effective against *Pseudomonas aeruginosa*. It is not degraded by all of the enzymes responsible for aminoglycoside resistance, and may be active against some strains resistant to gentamicin or tobramycin, but this is less marked than with amikacin: for example, gentamicin-resistant *Providencia, Pseudomonas*, and *Serratia* are usually also netilmicin-resistant. Between about 5 and 20% of Gram-negative isolates are reported to be resistant to netilmicin.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3.

After intramuscular injection of netilmicin, peak plasma concentrations occur within 0.5 to 1 hour, and concentrations of about 7 micrograms/mL have been reported after doses of 2 mg/kg; similar concentrations are obtained after intravenous infusion of the same dose over 1 hour. Peak concentrations after rapid intravenous injection may transiently be 2 or 3 times higher than those after infusion. Standard, once-daily doses may produce transient peak concentrations of 20 to 30 micrograms/mL. In multiple dosing studies, netilmicin in usual doses every 12 hours produced steady-state concentrations on the second day which were less than 20% higher than those seen after the first dose.

The half-life of netilmicin is usually 2.0 to 2.5 hours. About 80% of a dose is excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Certomycin; ***Braz.***: Netromicina; ***China***: Ai Hong (爱宏); Ai Jia Xin (艾佳欣); An Jie Xing (安捷星); Ao Guang Su (奥广素); Ao Tian Yu (奥天禹); Changfu TianXin (长富天欣); De Luo Jia (德洛佳); Fei Te (菲特); Feng Ke Nai (锋可耐); Fu Yin (孚茵); Heng Shi (衡实); Jia Nai (佳奈); Jie Nai (洁奈); JunXin (君欣); Kai Bao Min (凯保敏); Kang Li Xing (康力星); Lang Fan (浪凡); Luoji (洛吉); Nai Di (乃迪); Nai Kang (奈康); Nai Te (奈特); Nai Xing Long (耐兴龙); Nai Yi (奈怡); Naidufuxing (奈狄福星); Netromycin (力确兴); Pu Nai Xin (普奈新); Puqi (普奇); Rui Peng (瑞朋); Rui Shan (瑞杉); Sheng Di (圣迪); Sheng Di Xin (圣迪新); Shensuo (深索); Su Meng (苏盟); Tian Quan Tai Ning (天泉泰宁); Tuo Xing (妥星); Yan Pa Rui (延帕瑞); ***Cz.***: Netromycine; Nettacin†; ***Fin.***: Netilyn†; ***Fr.***: Netromicine; ***Ger.***: Certomycin†; ***Gr.***: Netromycin; Rizaldon; Zaby; ***Hong Kong***: Netromycin; ***Hung.***: Netromycine†; ***India***: Neticin; Netilcin; Netmicin; Netromax; Netromycin; Netspan; ***Indon.***: Hypobhac; Netromycin; ***Ital.***: Nettacin; Nettavisc; Zetamicin; ***Malaysia***: Lotifar; Netromycin; ***Mex.***: Netira; Netromicina; ***Philipp.***: Keunmixin; Netilcin; Netromycin†; Netrozin; ***Pol.***: Netromycine; ***Port.***: Netromicina; Tilcin; ***Rus.***: Netromycin (Нетромицин); ***S.Afr.***: Netromycin; ***Singapore***: Netromycin; ***Swed.***: Netilyn†; ***Switz.***: Netromycine†; ***Thai.***: Bactrocin; Nelin; Netil; Netromycin; ***Turk.***: Netira; Netromycin; ***Venez.***: Netromicina.

Multi-ingredient Preparations. ***China***: Bei Xing (倍兴); ***Ital.***: Netildex; Xanternet; ***Turk.***: Netildex.

Pharmacopoeial Preparations

USP 36: Netilmicin Sulfate Injection.

Nifuroxazide *(BAN, rINN)*

Nifuroksatsidi; Nifuroksazid; Nifuroksazidas; Nifuroxazid; Nifuroxazida; Nifuroxazidum; Нифуроксазид.

2′-(5-Nitrofurfurylidene)-4-hydroxybenzohydrazide.

$C_{12}H_9N_3O_5$=275.2

CAS — 965-52-6.

ATC — A07AX03.

ATC Vet — QA07AX03.

UNII — PM5LI0P38J.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nifuroxazide). A bright yellow crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Profile

Nifuroxazide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It is given orally in a dose of 800 mg daily in divided doses in the treatment of colitis and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Passifuril; ***Cz.***: Endiex; Ercefuryl; ***Fr.***: Bacterix; Bifix†; Diafuryl; Diarmonis; Ediston; Ercefuryl; Imoseptyl; Panfurex; Perabacticel; ***Gr.***: Enorep; Ercefuryl; Kaofuryl; ***Hong Kong***: Ercefuryl; Panfurex; ***Indon.***: Fuzide; Nifudiar; Nifural; ***Mex.***: Akabar; Eskapar†; Topron; ***Philipp.***: Ercefuryl; ***Pol.***: Endiex; ***Rus.***: Enterofuryl (Энтерофурил); Ersefuryl (Эрсефурил); ***Singapore***: Ercefuryl; Niraben; ***Thai.***: Debby; Ercefuryl†; Erfuzide; Mifuzide; ***Turk.***: Diafuryl; Durisal; Endosin; Ercefuryl; Erfulyn; Furil†; Nifuryl†; Nufro; ***Ukr.***: Enterofuril (Энтерофурил); Lecor (Лекор).

Multi-ingredient Preparations. ***Chile***: Diaren; Enterol Con Nifuroxacida; Esancol; Imecol; Liracol; Liracol; Nifurat; Testisan; ***Mex.***: Dia-Par Compuesto; Eskapar Compuesto.

Nifurpirinol *(USAN, rINN)*

Furpirinol; Nifurpirinolum; P-7138; Нифурпиринол.

$C_{12}H_{10}N_2O_4$=246.2

CAS — 13411-16-0.

UNII — 7O5A98XY8U.

Profile

Nifurpirinol is a nitrofuran antimicrobial used in veterinary medicine for the treatment of bacterial and fungal infections in ornamental fish.

Nifurtoinol *(rINN)*

Hydroxymethylnitrofurantoin; Nifurtoïnol; Nifurtoinolum; Нифуртоинол.

3-Hydroxymethyl-1-(5-nitrofurfurylideneamino)hydantoin.

$C_9H_8N_4O_6$=268.2

CAS — 1088-92-2.

ATC — J01XE02.

ATC Vet — QJ01XE02.

UNII — 980688H13O.

Profile

Nifurtoinol is a nitrofuran antibacterial with properties similar to those of nitrofurantoin (p. 334.1) and is used in the treatment of urinary-tract infections. It is given orally in doses of up to 300 mg daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Urfadyn PL.

Nifurzide *(rINN)*

Nifurzida; Nifurzidum; Нифурзид.
5-Nitro-2-thiophenecarboxylic acid [3-(5-nitro-2-furyl)allylidene]hydrazide.
$C_{12}H_8N_4O_5S$=336.3
CAS — 39978-42-2.
ATC — A07AX04.
ATC Vet — QA07AX04.
UNII — Z35R6K4C26.

Profile

Nifurzide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It has been given orally in the treatment of diarrhoea.

Nisin

E234; Nisina; Низин.
CAS — 1414-45-5.
UNII — EN8XKG133D.

Profile

Nisin is a polypeptide antibacterial produced by *Lactococcus lactis* (*Streptococcus lactis*). It is used as a food preservative.

It has been investigated for the treatment of various infections, including those caused by *Helicobacter pylori* and *Clostridium difficile*.

Nitrofurantoin *(BAN, rINN)*

Furadoninum; Nitrofurantoiini; Nitrofurantoina; Nitrofurantoína; Nitrofurantoinas; Nitrofurantoïne; Nitrofurantoinum; Нитрофурантоин.
1-(5-Nitrofurylideneamino)hydantoin; 1-(5-Nitrofurylideneamino)imidazolidine-2,4-dione.
$C_8H_6N_4O_5$=238.2
CAS — 67-20-9 (anhydrous nitrofurantoin); 17140-81-7 (nitrofurantoin monohydrate).
ATC — J01XE01.
ATC Vet — QJ01XE01.
UNII — 927AH8112L (nitrofurantoin); E1QI2CQQ1I (nitrofurantoin monohydrate).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Int. and *US* specify anhydrous or monohydrate.

Ph. Eur. 8: (Nitrofurantoin). A yellow, crystalline powder or crystals. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Nitrofurantoin). It is anhydrous or contains one molecule of water of hydration. Lemon-yellow, odourless crystals or fine powder. Nitrofurantoin and its solutions are discoloured by alkalis and by exposure to light, and are decomposed on contact with metals other than stainless steel or aluminium. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store in airtight containers. Protect from light.

Uses and Administration

Nitrofurantoin is a nitrofuran antibacterial that is used in the treatment of uncomplicated lower urinary-tract infections (p. 213.1), including prophylaxis or long-term suppressive therapy in recurrent infection.

It is given orally, in a usual dose of 50 to 100 mg four times daily, with food or milk. Treatment is usually continued for 7 days. A dual-release formulation, consisting of macrocrystalline nitrofurantoin and nitrofurantoin monohydrate, is available in some countries and is given in a dose of 100 mg twice daily. A usual long-term prophylactic dose is 50 to 100 mg at bedtime.

For details of doses in children, see p. 334.1.

Reviews.

1. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs* 2001; **61:** 353–64.

Administration in children. In the UK, nitrofurantoin may be given to children aged 3 months to 12 years for the *treatment* of urinary-tract infection in a usual oral dose of 3 mg/kg daily given in 4 divided doses; 1 mg/kg may be given at night for long-term *prophylactic* therapy. However, a systematic review[1] concluded, on the basis of the rather low-grade evidence available, that the adverse effects of nitrofurantoin may outweigh its benefits and render it unacceptable for long-term therapy.

Higher oral doses of 5 to 7 mg/kg daily in 4 divided doses are recommended for the *treatment* of urinary-tract infection in the USA in children aged 1 month and above; for long-term *prophylactic* therapy 1 mg/kg daily given in one or two divided doses is considered adequate.

Older children may be given usual adult doses (see Uses and Administration, above).

1. Williams GJ, *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/01/08).

Adverse Effects

The estimated incidence of adverse effects with nitrofurantoin has varied enormously, but may be around 10% overall; an incidence of serious reactions of about 0.001% for pulmonary, and 0.0007% for neurological reactions has been suggested. The most common adverse effects of nitrofurantoin involve the gastrointestinal tract. They are dose-related and generally include nausea, vomiting, and anorexia; abdominal pain and diarrhoea occur less frequently. It has been reported that adverse effects on the gastrointestinal tract are less common when nitrofurantoin is given in a macrocrystalline form or with food.

Neurological adverse effects include headache, drowsiness, vertigo, dizziness, nystagmus, and benign intracranial hypertension. Severe and sometimes irreversible peripheral neuropathy has developed, particularly in patients with renal impairment and in those given prolonged therapy.

Hypersensitivity reactions such as skin rashes, urticaria, pruritus, fever, sialadenitis, and angioedema may occur. Anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pancreatitis, a lupus-like syndrome, myalgia, and arthralgia have also been reported. Patients with a history of asthma may have acute asthmatic attacks.

Acute pulmonary sensitivity reactions characterised by sudden onset of fever, chills, eosinophilia, cough, chest pain, dyspnoea, pulmonary infiltration or consolidation, and pleural effusion may occur within hours to a few days of beginning therapy, but they usually resolve on stopping treatment.

Subacute or chronic pulmonary symptoms including interstitial pneumonitis and pulmonary fibrosis may develop more insidiously in patients on long-term therapy and the latter are not always reversible, particularly if therapy is continued after onset of symptoms.

Hepatotoxicity including cholestatic jaundice, hepatitis, and hepatic necrosis may develop rarely, particularly in women, and may represent a hypersensitivity reaction. Other adverse effects include megaloblastic anaemia, leucopenia, granulocytopenia or agranulocytosis, thrombocytopenia, aplastic anaemia, and haemolytic anaemia in persons with a genetic G6PD deficiency. Transient alopecia has been reported.

Nitrofurantoin may cause a brownish discoloration of the urine.

There is limited evidence from *animal* studies that nitrofurantoin may be carcinogenic, although this has not been shown conclusively in humans.

References.

1. Koch-Weser J, *et al.* Adverse reactions to sulfisoxazole, sulfamethoxazole, and nitrofurantoin: manifestations and specific reaction rates during 2118 courses of therapy. *Arch Intern Med* 1971; **128:** 399–404.
2. Holmberg L, *et al.* Adverse reactions to nitrofurantoin: analysis of 921 reports. *Am J Med* 1980; **69:** 733–8.
3. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. *BMJ* 1982; **284:** 1440–2.
4. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* 1985; **19:** 540–7.
5. Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol (Baltimore)* 2004; **172:** 448–53.

Effects on the lungs. References[1,2] to pulmonary toxicity associated with long-term nitrofurantoin treatment, and to acute pulmonary reactions.[3] Sporadic cases of chronic lung disease continue to be reported,[4-10] and the importance of monitoring during long-term therapy has been stressed.[8]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Pulmonary toxicity with long-term nitrofurantoin. *Aust Adverse Drug React Bull* 2004; **23:** 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.htm (accessed 11/01/08)
2. Mendez JL, *et al.* Chronic nitrofurantoin-induced lung disease. *Mayo Clin Proc* 2005; **80:** 1298–1302.
3. Williams EM, Triller DM. Recurrent acute nitrofurantoin-induced pulmonary toxicity. *Pharmacotherapy* 2006; **26:** 713–8.
4. Hargett CW, *et al.* Giant cell interstitial pneumonia associated with nitrofurantoin. *Lung* 2006; **184:** 147–9.
5. Bhullar S, *et al.* Severe nitrofurantoin lung disease resolving without the use of steroids. *J Postgrad Med* 2007; **53:** 111–3.
6. Koulaouzidis A, *et al.* Nitrofurantoin-induced lung- and hepatotoxicity. *Ann Hepatol* 2007; **6:** 119–21.
7. Lin DC, Bhally H. Nitrofurantoin-induced interstitial lung disease. *N Z Med J* 2007; **120:** U2753.
8. Mrozek N, *et al.* Pneumopathie à la nitrofurantoïne: à propos de deux observations. *Rev Med Interne* 2008; **29:** 149–51.
9. Martins RR, *et al.* Chronic eosinophilic pneumonia secondary to long-term use of nitrofurantoin: high-resolution computed tomography findings. *J Bras Pneumol* 2008; **34:** 181–4.
10. Fenton ME, *et al.* Nitrofurantoin-associated bronchiolitis obliterans organizing pneumonia: report of a case. *Can Respir J* 2008; **15:** 31 1–2.

Precautions

Nitrofurantoin should not be given to patients with renal impairment since antibacterial concentrations in the urine may not be attained and toxic concentrations in the plasma can occur. Nitrofurantoin is also contra-indicated in patients known to be hypersensitive to nitrofurans, in those with G6PD deficiency, and in infants (in the UK it is contra-indicated below 3 months of age, though the USA permits use from 1 month old).

Nitrofurantoin should be used with care in the elderly, who may be at increased risk of toxicity, particularly acute pulmonary reactions. All patients undergoing prolonged therapy should be monitored for changes in pulmonary function, and the drug withdrawn at the first signs of pulmonary damage. Care is required in patients with pre-existing pulmonary, hepatic, neurological, or allergic disorders, and in those with conditions (such as anaemia, diabetes mellitus, electrolyte imbalance, debility, or vitamin B deficiency) which may predispose to peripheral neuropathy. Nitrofurantoin should be withdrawn if signs of peripheral neuropathy develop. Although hepatic reactions such as hepatitis, cholestatic jaundice, and hepatic necrosis rarely occur, fatalities have been reported. Patients should be monitored, and the drug stopped immediately if hepatitis occurs.

Nitrofurantoin may cause false positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics considers that, although nitrofurantoin appears in breast milk, it is usually compatible with breast feeding, but caution is necessary in breast-fed infants with G6PD deficiency.[1] The *BNFC* suggests that the amount ingested may be enough to produce haemolysis in G6PD-deficient infants; it recommends that nitrofurantoin should be avoided in mothers who are breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 11/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nitrofurantoin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Pregnancy. Licensed product information contra-indicates the use of nitrofurantoin in pregnant patients at term (38 to 42 weeks), or during labour and delivery, because of the possibility of producing haemolytic anaemia in the neonate.

Interactions

Nitrofurantoin and the quinolone antibacterials are antagonistic *in vitro* but the clinical significance is unknown. The antibacterial activity of nitrofurantoin may be decreased in the presence of carbonic anhydrase inhibitors and other drugs that alkalinise the urine.

Probenecid or sulfinpyrazone should not be given with nitrofurantoin as they may reduce its excretion. Magnesium trisilicate may reduce the absorption of nitrofurantoin but it is not clear whether this applies to other antacids.

Antiepileptics. For reference to the effect of nitrofurantoin on *phenytoin* concentrations, see p. 542.3.

Antifungals. An elderly patient who had been taking nitrofurantoin daily for 5 years developed combined hepatic and pulmonary toxicity 2 months after also starting *fluconazole* therapy.[1] Although either drug may have caused the hepatic toxicity, possible pharmacokinetic changes induced by an interaction with fluconazole may have precipitated the nitrofurantoin-induced pulmonary toxicity.

1. Linnebur SA, Parnes BL. Pulmonary and hepatic toxicity due to nitrofurantoin and fluconazole treatment. *Ann Pharmacother* 2004; **38:** 612–16.

Hormonal contraceptives. For mention of a possible decrease in contraceptive efficacy when nitrofurantoin was used with oral contraceptives, see under Hormonal Contraceptives, p. 2243.1.

Antimicrobial Action

Nitrofurantoin is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens. The mode of action is uncertain but appears to depend on the formation of reactive intermediates by reduction; this process occurs more efficiently in bacterial than in mammalian cells.

It is effective against the enterococci *in vitro*, as well as various other Gram-positive species including staphylococci, streptococci, and corynebacteria, although this is of little clinical significance. Most strains of *Escherichia coli* are particularly sensitive to nitrofurantoin but *Enterobacter* and *Klebsiella* spp. are less susceptible and some may be resistant. *Pseudomonas aeruginosa* is resistant as are most strains of *Proteus*spp.

Nitrofurantoin is most active in acid urine, and if the pH exceeds 8 most of the antibacterial activity is lost. Resistance rarely develops during nitrofurantoin treatment but may occur during prolonged treatment. Plasmid-encoded resistance has been reported in *E. coli*. Resistance may be due to the loss of nitrofuran reductases which generate the active intermediates.

Pharmacokinetics

Nitrofurantoin is readily absorbed from the gastrointestinal tract. The absorption rate is dependent on crystal size. The macrocrystalline form has slower dissolution and absorption rates, produces lower serum concentrations than the microcrystalline form, and takes longer to achieve peak concentrations in the urine. The presence of food in the gastrointestinal tract may increase the bioavailability of nitrofurantoin and prolong the duration of therapeutic urinary concentrations. Preparations of nitrofurantoin from different sources may not be bioequivalent, and care may be necessary if changing from one brand to another.

On absorption, concentrations in blood and body tissues are low because of rapid elimination, and antibacterial concentrations are not achieved. Nitrofurantoin crosses the placenta and the blood-brain barrier and traces have been detected in breast milk. There is some disagreement about the degree of protein binding, and although figures of up to about 60% are quoted by some sources, others suggest that the figure should be as much as 90%. The plasma half-life is reported to range from 0.3 to 1 hour.

Nitrofurantoin is metabolised in the liver and most body tissues while about 30 to 40% of a dose is excreted rapidly in the urine as unchanged nitrofurantoin. Some tubular reabsorption may occur in acid urine. Average doses give a concentration of 50 to 200 micrograms/mL in the urine in patients with normal renal function.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Furadantina; Uratina; Urodantina; Urofuran; ***Austral.***: Furadantin†; Macrodantin; ***Austria***: Furadantin; ***Belg.***: Furadantine; ***Braz.***: Hantina; Macrodantina; Nitrofen; Urogem†; ***Canad.***: Macrobid; Macrodantin†; Novo-Furantoin†; ***Chile***: Macrodantina; Macrosan; Matidan; ***China***: Tanding (坦啶); ***Fin.***: Nitrofur-C; ***Fr.***: Furadantine; Furadoine; Microdoine; ***Ger.***: Furadantin; Nifurantin; Nifuretten; Uro-Tablinen; ***Gr.***: Furolin; Londofurol; Nitrotoin; ***India***: Furadantin; Furasoz; Martifur; Niftas; Niftran; ***Irl.***: Furadantin; Macrobid; Macrodantin; ***Israel***: Uvamin; ***Ital.***: Furedan; Furil†; Macrodantin†; Neo-Furadantin; ***Mex.***: Biofurin; Furadantina; Furitex; Futroken; Macrodantina; Macrofurin; Promac†; Suronit; ***Neth.***: Furabid; Furadantine MC; ***Norw.***: Furadantin; ***NZ***: Furadantin†; Nifuran; ***Philipp.***: Macrodantin; ***Pol.***: Siraliden†; ***Port.***: Furadantina; ***Rus.***: Furadonin (Фурадонин); ***S.Afr.***: Furadantin†; Macrodantin; ***Spain***: Furantoina; Furobactina†; ***Swed.***: Furadantin; ***Switz.***: Furadantine; Urodin†; Uvamine retard; ***Turk.***: Piyeloseptyl; ***UK***: Furadantin†; Macrobid; Macrodantin; ***USA***: Furadantin; Macrobid; Macrodantin; ***Venez.***: Macrodantina.

Multi-ingredient Preparations. ***Arg.***: Bagociletas con Anestesia†; ***Braz.***: Uropac; ***Ger.***: Nifurantin B 6; ***Hong Kong***: Urobilin†; ***India***: Nephrogesic; ***Turk.***: Uriseptin.

Pharmacopoeial Preparations

BP 2014: Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets;

USP 36: Nitrofurantoin Capsules; Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets.

Nitrofurazone *(BAN)*

Furacilinum; Nitrofuraali; Nitrofural (pINN); Nitrofural; Nitrofurál; Nitrofuralis; Nitrofuralum; Nitrofuratsoni; Nitrofurazon; Nitrofurazonum; Нитрофурал.

5-Nitro-2-furaldehyde semicarbazone.

$C_6H_6N_4O_4$=198.1

CAS — 59-87-0.

ATC — B05CA03; D08AF01; D09AA03; P01CC02; S01AX04; S02AA02.

ATC Vet — QB05CA03; QD08AF01; QD09AA03; QG01AX90; QP51AC02; QS01AX04; QS02AA02.

UNII — X8XI7085Z6.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Nitrofural; Nitrofurazone BP 2014). A yellow or brownish-yellow, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.0. Protect from light.

USP 36: (Nitrofurazone). A lemon-yellow, odourless crystalline powder. It darkens slowly on exposure to light. Soluble 1 in 4200 of water, 1 in 590 of alcohol, and 1 in 350 of propylene glycol; practically insoluble in chloroform and in ether; soluble in dimethylformamide; slightly soluble in polyethylene glycol mixtures. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Sterilisation. Autoclaving gauze dressings impregnated with nitrofurazone, as recommended by the US manufacturer, resulted in over 10% loss of the drug.[1] Since the spectroscopic assay used may not have distinguished between nitrofurazone and some of its degradation products, the degree of degradation might have been greater than this.

1. Phillips C, Fisher E. Effect of autoclaving on stability of nitrofurazone soluble dressing. *Am J Health-Syst Pharm* 1996; **53:** 1169–71.

Uses and Administration

Nitrofurazone is a nitrofuran derivative that is used topically for wounds, burns, ulcers, and skin infections, and for the preparation of surfaces before skin grafting. It is usually applied in a concentration of 0.2% in a water-soluble or water-miscible basis. A solution of nitrofurazone is used for bladder irrigation.

Urinary catheters impregnated with nitrofurazone, to reduce bacterial colonisation and infection, are available in some countries.

Adverse Effects

Sensitisation and generalised allergic skin reactions may be produced by topical nitrofurazone.

Nitrofurazone is a toxic drug when given orally and serious adverse effects include severe peripheral neuropathy; haemolysis may occur in patients with G6PD deficiency. Nitrofurazone in high oral doses is carcinogenic in *rats.*

Precautions

Nitrofurazone is contra-indicated in patients with known hypersensitivity. Preparations containing macrogols should be used with caution in patients with renal impairment since macrogols can be absorbed and their accumulation in such patients may result in symptoms of further impairment.

Oral nitrofurazone should be used with caution in patients with G6PD deficiency because of the risk of haemolysis.

Antimicrobial Action

Nitrofurazone is a nitrofuran derivative with a broad spectrum of antibacterial activity, but with little activity against *Pseudomonas* spp. It also has antitrypanosomal activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Furacin; NitroMed; ***Belg.***: Furacine; ***Braz.***: Caziderm; Furacin; Sensiderme; ***Chile***: Furacin; ***Ger.***: Furacin-Sol; ***India***: Emfurazone; Furacin; ***Mex.***: Furacin; Kufro†; Nifurol; Probizal; Vulnizol; ***Philipp.***: Furacin; ***Port.***: Rayonfur; ***S.Afr.***: Furacin†; Furasept; Furex; Germex†; ***Spain***: Botinit; Furacin; ***Thai.***: Bactacin; Mytrocin; Polycin; ***Turk.***: Dermikolin; Furacin; Furaderm; Furazol; ***Venez.***: Furacin; Furfuril; Fuxal.

Multi-ingredient Preparations. ***Arg.***: Fadanasal; O-Biol; Vagicural; Vagisan Compuesto; Vagisan; Vislus; ***Braz.***: Nitrileno; ***India***: Furacin-S†; ***Ital.***: Furotricina; ***Mex.***: Madecassol C; Madecassol N; ***Spain***: Dertrase; ***Thai.***: Denson†.

Pharmacopoeial Preparations

USP 36: Nitrofurazone Ointment; Nitrofurazone Topical Solution.

Nitroxoline *(BAN, pINN)*

Nitroxolina; Nitroxolinum; Нитроксолин.

5-Nitroquinolin-8-ol.

$C_9H_6N_2O_3$=190.2

CAS — 4008-48-4.

ATC — J01XX07.

ATC Vet — QJ01XX07.

UNII — A8M33244M6.

Profile

Nitroxoline has antibacterial and antifungal properties and is used in the treatment of urinary-tract infections in oral doses of 400 to 600 mg daily given in divided doses after meals. It has also been given with sulfamethizole.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Cysto-Saar†; Nilox; ***Rus.***: 5-Nitrox (5-Нитрокс)†; 5-Nok (5-Нок); ***S.Afr.***: Nicene N†; ***Ukr.***: 5-NOK (5-НОК).

Multi-ingredient Preparations. ***Braz.***: Minazol.

Norfloxacin *(BAN, USAN, rINN)*

AM-715; *N*-Desmethylpefloxacin; MK-366; Norfloksacinas; Norfloksacyna; Norfloksasiini; Norfloksasin; Norfloxacine; Norfloxacino; Norfloxacinum; Норфлоксацин.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

$C_{16}H_{18}FN_3O_3$=319.3

CAS — 70458-96-7.

ATC — J01MA06; S01AE02.

ATC Vet — QJ01MA06; QS01AE02.

UNII — N0F8P22L1P.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Norfloxacin). A white or pale yellow, hygroscopic, photosensitive, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone. Store in airtight containers. Protect from light.

USP 36: (Norfloxacin). A white to pale yellow crystalline powder. Slightly soluble in water, in alcohol, and in acetone; freely soluble in acetic acid; sparingly soluble in chloroform; practically insoluble in ether; very slightly soluble in ethyl acetate and in methyl alcohol. Store in airtight containers. Protect from light.

Norfloxacin Pivoxil *(BANM, rINNM)*

Norfloxacine, Pivoxil de; Norfloxacini Pivoxil; Norfloxacino pivoxilo; Норфлоксацина Пивоксил.

Pivaloyloxymethyl 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

$C_{22}H_{28}FN_3O_5$=433.5

ATC — J01MA06; S01AE02.

ATC Vet — QJ01MA06; QS01AE02.

Uses and Administration

Norfloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1), but it is generally less potent *in vitro.*

Norfloxacin is used mainly in the treatment of urinary-tract infections (p. 213.1), although based on concerns regarding efficacy, regulatory authorities in the EU have advised against its use for treatment of complicated pyelonephritis specifically. It may also be used for the treatment of gonorrhoea (p. 204.2).

Norfloxacin is given orally at least 1 hour before, or 2 hours after, food or milk.

In urinary-tract infections the usual dose is 400 mg twice daily for 3 to 10 days. Treatment may need to be continued for up to 12 weeks in chronic relapsing urinary-tract infections; it may be possible to reduce the dose to 400 mg once daily if there is an adequate response within the first 4 weeks. A 28-day course of treatment with a dose of 400 mg twice daily should be given for acute or chronic bacterial prostatitis.

Doses may need to be reduced in renal impairment, see p. 335.3.

A single oral dose of 800 mg is given in the treatment of uncomplicated gonorrhoea.

Eye drops containing 0.3% of norfloxacin are used to treat eye infections.

The pivaloyloxymethyl salt of norfloxacin, norfloxacin pivoxil, is also used in some countries.

Administration in renal impairment. Oral doses of norfloxacin may need to be reduced in renal impairment; for urinary-tract infections, 400 mg once daily should be given to patients with a creatinine clearance of 30 mL/minute per 1.73 m^2 or less.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies norfloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2, although norfloxacin is less potent *in vitro*. Norfloxacin is not active against Chlamydiaceae, mycoplasmas, or mycobacteria.

Pharmacokinetics

About 30 to 40% of an oral dose of norfloxacin is absorbed. Peak plasma concentrations of about 1.5 micrograms/mL occur about 1 to 2 hours after a 400-mg oral dose; the presence of food can delay absorption. Norfloxacin is about 14% bound to plasma proteins. It is probably widely distributed, but information is limited. Norfloxacin penetrates well into tissues of the genito-urinary tract. It crosses the placenta. Relatively high concentrations occur in bile.

The plasma half-life is 3 to 4 hours and may be prolonged in renal impairment; a value of 6.5 hours or more has been reported when creatinine clearance is below 30 mL/minute per 1.73 m^2. About 30% of a dose is excreted unchanged in the urine within 24 hours, producing high urinary concentrations; norfloxacin is least soluble at a urinary pH of 7.5. Urinary excretion is by tubular secretion and glomerular filtration and is reduced by probenecid, although plasma concentrations of norfloxacin are not generally affected. Some metabolism occurs, possibly in the liver, and several metabolites, some with antibacterial activity, have been identified in urine. About 30% of an oral dose appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bio Tarbun; Floxamicin; Floxatral; Frifloxacina; Memento NF; Nefronet; Norflol; Noroxin; Norsol; Parcetin; Ritromine; Uro-Linfol; Urofos; Uronovag; Uroseptal; Urotem; Uroxacin; Wenflox; ***Austral.***: Insensye†; Norflohexal†; Noroxin; Nufloxib; Roxin; ***Austria***: Floxacin; Zoroxin; ***Belg.***: Zoroxin; ***Braz.***: Androfloxin; Flox; Floxacin; Floxanor; Floxinol; Genitoflox†; Neofloxin; Norf; Norflox†; Norfloxasan; Norfloxil; Norfloxmed; Norxin; Quinoform; Respexil; Uni Norflox; Uritrat; Uroseptal; Urotrobel; Uroxazol-N; ***Canad.***: Apo-Norflox; ***Chile***: Fulgram; ***China***: Ai Li Ke (艾立克); Jin Ya Jie (金娅捷); ***Cz.***: Gyrablock; Nolicin; ***Fr.***: Chibroxine; Noroxine; ***Ger.***: Bactracid†; Barazan; Chibroxin†; Firin†; Norflohexal†; Norflosal†; Norflox†; Norfluxx; ***Gr.***: Alenbit; Azoxina; Constilax; Dirunez; Fluseminal; Grenis; Lemorcan; Lorcamin; Norocin; Ovinol; Pistofil; Setanol; Sinobid; Sofasin; Steinaclox; Urisold; Urobacid; Urospes-N; Vetamol; Zolmic; ***Hong Kong***: Floxen†; Janacin†; Lexiflox†; Mitatonin; Surflox; Uroctal†; ***Hung.***: Nolicin; ***India***: Actiflox-400; Alflox; Anquin; Bacigyl; Biofloxin; Denar; Enteroflox; Flox; Floxiren; Gyrax; Harflox; Loxone; Meriflox; N-Flox; Negaflox; Nitdin; Nor-U; Noralox; Norbactin; Norbid; Norflox; Norigyl; Norilet; Norin; Normax; Nornij; Norrit; Norvit; Norzen; Nox; Optoflox; ***Indon.***: Pyrflox†; ***Israel***: Apirol†; ***Ital.***: Diperflox; Flossac; Naflox; Norflox; Noroxin; Renoxacin; Sebercim; Theanorf; Uticina; Utinor; ***Jpn***: Baccidal; ***Malaysia***: Janacin; Norfloxin; Rexacin; Trizolin; Urinox; Urobacid; ***Mex.***: Baxamed; Difoxacil; Floxacin; Microxin; Noflorox; Norbactin†; Noroxin; Norquinol; Oranor; ***Neth.***: Chibroxol†; Noroxin†; ***NZ***: Noroxin†; ***Philipp.***: Euroflox†; Fasqilon†; Flamorel; Heiwin; Jaydisyn; Lexiflox; Lexinor†; Norbactin†; Norex; Nortram†; NRX; Septinor; Uritracin; Urobacid†; Utiflox; Utinor; Winaflox†; ***Pol.***: Chibroxin; Nolicin; Norsept; ***Port.***: Besflox; Chibroxol; Noroxin; Uroflox; ***Rus.***: Gyrablock (Гираблок)†; Locsone (Локсон); Negaflox (Негафлокс)†; Nolicin (Нолицин); Norbactin (Норбактин); Norfacin (Норфацин); Norilet (Норилет); Normax (Нормакс); Sofasin (Софазин); Utibid (Ютибид); ***S.Afr.***: Floxin; Noroxin†; Utifloxa; Utin; ***Singapore***: Bexinor; Foxgoria; Gyrablock; Loxone; Norbactin; Sefnor; Trizolin; ***Spain***: Amicrobin; Chibroxin; Esclebin†; Espeden†; Nalion†; Norflok†; Noroxin†; Senro†; Uroctal†; Xasmun; ***Swed.***: Lexinor†; ***Switz.***: Norflocin; Noroxin; Norsol; ***Thai.***: Crossa; Floximed; Foxin; Foxinon; Gonorcin; Janacin; Lexfor; Lexinor†; Loxone†; M-Flox; Manoflox; Medic Nor; Myfloxin; Noracin; Norbactin; Norcin; Norfa; Norfan; Norfass†; Norfcin; Norflacil; Norflo; Norflocin; Norflox; Norfloxin; Norfloxpac; Norfloxyl; Norfox; Norxacin; Norxia; Noxine; Noxinor; Proxacin; Proxinor; Rexacin; Sanorflox; Sefnor; Snoffocin; Solexin; Urinox; Uritracin†; Vesxacin†; Xacin; Zinor; ***Turk.***: Noroxin; ***UAE***: Uroxin; ***UK***: Utinor; ***Ukr.***: Norbactin (Норбактин); Norfloxal (Норфлогексал)†; ***USA***: Noroxin; ***Venez.***: Danilon; Noroxin.

Multi-ingredient Preparations. ***Arg.***: Nor 2; Urotem Dol; ***India***: Actiflox-T; Actinor-MZ; Actinor-TZ; Amibex-TZ; Bioflox-TZ; C-Dial; C-Nor Plus; Cinzole; Conaz; Dazonor; Diaba-M; Diaba; Digyl; Duonor; Dysnilox; Elnor-TZ; Emflox-TZ; Entamizole TN; Enteroflox-T; Fenigyl; Flontin; Gastogyl-M; Gramogyl; Gramoneg-TN; Harflox-T; Klassak; Lotinor; Loxamet; Loxitin-P; Loxone-T; Mangogyl; Mapgyl; Mapgyl; Matinor; Matrix; Meganeg; Metnox; Metronor-P; N-Flox D; N-Flox TZ; N-Tiz; N-TZ; Nedge; Neflox-TZ; Nex-M; Nitdin-TZ; NM Power; Nogit-M; Nor T; Nor-Metrogyl; Nor-T; Noragyl-OZ; Noragyl; Noragyl; Norazol; Norbactin-Z; Norbit; Nordys; Norfagyl; Norfazole; Norfen TZ; Norflox TZ; Norgrade; Norilet-A; Norin-MZ; Norin-TD; Norlex-TZ; Norlon; Normax TZ; Normide; Normint; Nornij-TZ; Norrit-Ord; Norrit; Nort; Norzee-TZ; Notisym-LB; Notty; Nox-TZ; Noxigyl; NT-Z; NTD; NTD; Nugit-M; Okagyl; Oniflox; Parabact†; Powergyl; Tinvista-NF; ***Mex.***: Mictasol; Norflen.

Pharmacopoeial Preparations

BP 2014: Norfloxacin Eye Drops; Norfloxacin Tablets;
USP 36: Norfloxacin Ophthalmic Solution; Norfloxacin Tablets.

Norvancomycin Hydrochloride

56-Demethylvancomycin; *N*-Demethylvancomycin.
(S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-[[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(amino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride.
$C_{65}H_{73}Cl_2N_9O_{24}$,HCl=1471.7
CAS — 91700-98-0 (norvancomycin).

Pharmacopoeias. In *Chin.*

Profile

Norvancomycin is a glycopeptide antibacterial with properties similar to those of vancomycin (p. 386.2).

Novobiocin *(BAN, rINN)*

Crystallinic Acid; Novobiocina; Novobiocine; Novobiocinum; Novobiosiini; Novobiosin; PA-93; Streptonivicin; U-6591; Новобиоцин.
4-Hydroxy-3-[4-hydroxy-3-(3-methylbut-2-enyl)benzamido]-8-methylcoumarin-7-yl 3-*O*-carbamoyl-5,5-di-*C*-methyl-α-L-lyxofuranoside.
$C_{31}H_{36}N_2O_{11}$=612.6
CAS — 303-81-1.
UNII — 17EC19951N.

Description. Novobiocin is an antimicrobial substance produced by the growth of *Streptomyces niveus* and *S. spheroides* or related organisms.

Novobiocin Calcium *(BANM, rINNM)*

Calcii Novobiocinum; Calcium Novobiocin; Novobiocina cálcica; Novobiocine Calcique; Novobiocinum Calcium; Кальций Новобиоцин.
$(C_{31}H_{35}N_2O_{11})_2Ca$=1263.3
CAS — 4309-70-0.
UNII — RHW5BU180N.

Novobiocin Sodium *(BANM, rINNM)*

Natrii Novobiocinum; Novobiocina sódica; Novobiocine Sodique; Novobiocinum Natricum; Sodium Novobiocin; Натрий Новобиоцин.
$C_{31}H_{35}N_2NaO_{11}$=634.6
CAS — 1476-53-5.
UNII — Q9S9NQ5YIY.

Pharmacopoeias. In *Fr.* and *US.*

USP 36: (Novobiocin Sodium). A white or yellowish-white, odourless, hygroscopic crystalline powder. Freely soluble in water, in alcohol, in methyl alcohol, in glycerol, and in propylene glycol; practically insoluble in acetone, in chloroform, and in ether; slightly soluble in butyl acetate. pH of a 2.5% solution in water is between 6.5 and 8.5. Store in airtight containers.

Profile

Novobiocin is an antibacterial which is structurally related to coumarin. It is active against Gram-positive bacteria such as *Staphylococcus aureus* (including meticillin-resistant strains) and other staphylococci; *Enterococcus faecalis* is usually resistant but *E. faecium* may be sensitive. Some Gram-negative organisms including *Haemophilus influenzae* and *Neisseria* spp. are also susceptible, as are some strains of *Proteus*, but most of the Enterobacteriaceae are resistant. Its action is primarily bacteriostatic, although it may be bactericidal against more sensitive species at high concentrations. It is an inhibitor of DNA gyrase and is effective in eliminating plasmids, but resistance to novobiocin develops readily *in vitro* and during therapy.

Although novobiocin has been used alone or with other drugs such as rifampicin or sodium fusidate in the treatment of infections due to staphylococci and other susceptible organisms, it has been largely superseded by other drugs because of the problems of resistance and toxicity.

Novobiocin is a potent sensitiser and hypersensitivity reactions are relatively common; they include rashes, fever, and pruritus, and more serious reactions such as Stevens-Johnson syndrome and pneumonitis. Jaundice and liver damage have occurred, although apparent jaundice may be due to a yellow metabolite of the drug rather than hyperbilirubinaemia. Other adverse effects include eosinophilia, leucopenia, thrombocytopenia, agranulocytosis, and haemolytic anaemia; gastrointestinal disturbances are common.

Ofloxacin *(BAN, USAN, rINN)*

DL-8280; Hoe-280; Ofloksacinas; Ofloksasiini; Ofloksasin; Ofloxacine; Ofloxacino; Ofloxacinum; RU-43280; Офлоксацин.
(±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid.
$C_{18}H_{20}FN_3O_4$=361.4
CAS — 82419-36-1; 83380-47-6.
ATC — J01MA01; S01AE01; S02AA16.
ATC Vet — QJ01MA01; QS01AE01; QS02AA16.
UNII — A4P49JAZ9H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Ofloxacin). A pale yellow or bright yellow crystalline powder. Slightly soluble in water and in methyl alcohol; slightly soluble to soluble in dichloromethane; soluble in glacial acetic acid. Store in airtight containers. Protect from light.

USP 36: (Ofloxacin). Pale yellowish-white to light yellowish-white crystals or crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Ofloxacin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de ofloxacino; Ofloxacine, Chlorhydrate d'; Ofloxacini Hydrochloridum; Офлоксацина Гидрохлорид.
$C_{18}H_{20}FN_3O_4$,HCl=397.8
ATC — J01MA01; S01AE01; S02AA16.
ATC Vet — QJ01MA01; QS01AE01; QS02AA16.
UNII — I2UWV315WA.

Uses and Administration

Ofloxacin is a fluoroquinolone antibacterial used similarly to ciprofloxacin (p. 261.2). It is also used in *Chlamydia* or *Chlamydophila* infections including nongonococcal urethritis (p. 177.1 and p. 212.3) and in mycobacterial infections such as leprosy (p. 188.3) and tuberculosis (see under Uses and Administration of Ciprofloxacin, p. 262.2).

Ofloxacin is given orally as the base or by intravenous infusion as the hydrochloride. All doses are expressed in terms of the base; ofloxacin hydrochloride 220.2 mg is equivalent to about 200 mg of ofloxacin.

The usual oral or intravenous dose ranges from 200 mg daily to 400 mg twice daily depending on the severity and the nature of the infection. Oral doses of up to 400 mg may be given as a single dose, preferably in the morning. For intravenous use a 0.2% solution is infused over 30 minutes.

An oral dose of 200 mg twice daily for 3 days is suitable in women with acute uncomplicated cystitis. A 6-week course of treatment with an oral dose of 300 mg twice daily should be given for chronic bacterial prostatitis. A single 400-mg dose of ofloxacin may be given orally for uncomplicated gonorrhoea.

Oral doses of 400 mg *daily* given with clofazimine and minocycline or 400 mg *monthly* given with rifampicin and minocycline have been recommended by WHO as alternative multidrug therapy regimens for multibacillary leprosy. As an alternative regimen for single-lesion paucibacillary leprosy WHO suggests a single dose of ofloxacin 400 mg with rifampicin and minocycline.

Ofloxacin is used topically as 0.3% eye drops for the treatment of conjunctivitis and corneal ulcers caused by susceptible strains of bacteria. It is also used as 0.3% ear drops for the treatment of otitis externa and otitis media.

For details of reduced doses in hepatic or renal impairment, see p. 337.1.

Reviews.
1. Todd PA, Faulds D. Ofloxacin: a reappraisal of its antimicrobial activity, pharmacology and therapeutic use. *Drugs* 1991; **42:** 825–76.
2. Onrust SV, *et al*. Ofloxacin: a reappraisal of its use in the management of genitourinary tract infections. *Drugs* 1998; **56:** 895–928.
3. Simpson KL, Markham A. Ofloxacin otic solution: a review of its use in the management of ear infections. *Drugs* 1999; **58:** 509–31.
4. Wai TKH, Tong MCF. A benefit-risk assessment of ofloxacin otic solution in ear infection. *Drug Safety* 2003; **26:** 405–20.

Administration in hepatic impairment. The clearance of ofloxacin is reduced in patients with severe hepatic impairment or cirrhosis and lower doses should be used; a maximum oral dose of 400 mg daily has been recommended.

Administration in renal impairment. Lower doses of ofloxacin may be necessary in patients with renal impairment. After the usual initial oral dose (see Uses and Administration, p. 334.3), subsequent doses are adjusted according to creatinine clearance (CC):
- CC 20 to 50 mL/minute: doses halved to 100 to 200 mg daily or the usual dose is given every 24 hours
- CC less than 20 mL/minute: dose reduced to 100 mg every 24 hours
- patients on haemodialysis or peritoneal dialysis: 100 mg every 24 hours

BCG toxicity. For mention of the possible use of ofloxacin to reduce the incidence of toxicity after BCG intravesicular instillation, see p. 2379.3.

Tuberculosis. For mention of the use of ofloxacin in the treatment of tuberculosis, see under Ciprofloxacin, p. 262.2.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, ofloxacin should be stopped.

A reduction in blood pressure may occur rarely after intravenous infusion. Similarly, sudden reductions in blood pressure may occur when intravenous ofloxacin is given with hypotensive drugs. Cardiovascular function should be monitored in such patients and in those also receiving barbiturate anaesthetics.

Ofloxacin eye drops may increase the risk of corneal perforation in those with pre-existing corneal ulcers or epithelial defects.

Breast feeding. The American Academy of Pediatrics has stated that no adverse effects have been seen in breast-fed infants whose mothers were receiving ofloxacin and that it is therefore usually compatible with breast feeding.[1] However, in a study[2] of 10 women given ofloxacin after termination of pregnancy, drug concentrations in breast milk were sufficiently high to recommend that the use of ofloxacin in lactating women should be avoided.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)
2. Giamarellou H, *et al*. Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; **87** (suppl 5A): 49S–51S.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ofloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Use of ofloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Ofloxacin is more active than ciprofloxacin against *Chlamydia trachomatis*. It is also active against *Mycobacterium leprae* as well as *M. tuberculosis* and some other *Mycobacterium* spp. Synergistic activity against *M. leprae* has been reported between ofloxacin and rifabutin.

The optically active *S*-(-)-isomer levofloxacin (p. 315.3) has twice the activity of the racemate ofloxacin.

Resistance has been reported in some strains of *Neisseria gonorrhoeae*.

Pharmacokinetics

Ofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is almost 100% and a peak plasma concentration of about 3 to 5 micrograms/mL occurs 1 to 2 hours after an oral 400-mg dose. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected.

About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile.

The elimination of ofloxacin is biphasic; half-lives of about 4 to 5 and 20 to 25 hours have been reported for the 2 phases, respectively. In renal impairment values of 15 to 60 hours have been reported. There is limited metabolism to desmethyl and *N*-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations. Less than 5% is excreted in the urine as metabolites. From 4 to 8% of a dose may be excreted in the faeces.

Only small amounts of ofloxacin are removed by haemodialysis or peritoneal dialysis.

References.
1. Lamp KC, *et al*. Ofloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **22:** 32–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Floxil; Ingeflox†; Klonalflox; Newflox; Oflox; Otoflox; Quinomed; Rafocilina; ***Austral.***: Ocuflox; ***Austria***: Floxal; Oflox†; Tarivid; ***Belg.***: Docofloxacine†; Tarivid; Trafloxal; ***Braz.***: Flogirax; Floxina; Floxstat; Genoxacin; Nostil; Oflox; ***Canad.***: Apo-Oflox†; Ocuflox; ***Chile***: Oflox; Poenflox†; ***China***: An Fu Le (安福乐); Anli (安利); Ao Di Fu Kang (奥迪扶康); Ao Wei Te (奥卫特); Aofuxing (奥复星); Bei Li De (贝立德); Di Ke Luo (迪可罗); Dong Kang Ming (东康明); Fei Ning Da (菲宁达); Geiluoxian (盖洛仙); Hao Te (浩特); Heng Run (恒润); JieFu (捷孚); Nuo Qing (诺青); Pu Guang (普光); Rui Da (瑞达); Tai Fu Kang (泰福康); Tarivid (泰利必妥); Xin Long (信龙); Xinlituo (信利妥); Yan Hua Xing (延华星); Yang Da Ning (阳达宁); Zanocin (赞诺欣); ***Cz.***: Floxal; Ofloxin; Tarivid†; Taroflox; Zanocin; ***Denm.***: Exocin; Tarivid†; ***Fin.***: Exocin; Tarivid; ***Fr.***: Exocine; Monoflocet; Oflocet; ***Ger.***: Floxal; Gyroflox†; Oflohexal†; Oflox†; Ofloxbeta†; Tarivid; Uro-Tarivid; ***Gr.***: Ermofan; Exocin; Grenis-Oflo; Hetacloxacin; Oflocollyre; Tabrin; Urimax; ***Hong Kong***: Flovid; Floxan†; Lessin; Maproxacin†; Marfloxacin†; Ofus; Puiritol; Quotavil; Tarivid; Viotisone; ***Hung.***: Floxal; Oflogen; Tarivid; Zanocin; ***India***: Abof; Aflox; Agroflox; Alocin; Alof; Alox; Alproxen; Ariflox; Arviflox; Asiflox-OZ; Asiflox; Atoflox; Aviflox; B-Flox; Bacter; Bactof; Bactoff; Bekker; Bestoflox; Bidoflox; Bio Flo; Biofast; Bioff; Bioz; Broflox; Bru-O; C-Flox; Cadof; Canocin; Casflox; CG Flox; Chekmet; Cinflox; Clofcin; Covax; Cozan; Crof; Cucin; Curadex; Cyflox; Denof; Doact; Duflox; E-Flox; Ecoflox; Eflobid; Emucin; Entof DPS; Essasin; Esterflox; Eufox; Exocin; Falcon; Festive; Fixiflox; Flex; Flobacin; Flogard; Florida; Flow; Flox-200; Flox-O; Floxar; Floxicontin; Floxil-O; Floxine; Floxole; Floxur; Floxzen; GBO; Genflox; GFlox; Gilflox; Glofty; Gyroflox; Harpoon; Hineoflox; Hoflo; Indocin; Indof; Inflobact; Inflobid; Inflox; Infoxin; Jflo; Jox; Kaiflox; Kureflox; Laflox; Lexof; Loft; Logflox; Loxin; Magof; Megaflox; Mep-Orva; Meuflox; Mintof; Mofcare; Moflo; Monoflox; NBox; Neobid; Neva; Nida; Niolox; Noff; Novofran; O-Cebran; O-Fact; O-Quin; O-Tab; OA; Obactin; Obid-ER; Obit; Ocin; Ociz; Ocucin; Oculone; Of Plus; Of; Ofac; Ofacin; Ofal; Ofax; Ofbid; Ofcare; Ofcura; Ofel; Ofelder; Ofet; Offy; Ofia; Ofkab; Ofkair; OFL; Ofla; Oflabin; Oflacin; Oflact; Oflagard; Oflage; Oflahill; Oflak; Oflamed; Oflaquin; Oflas; Oflaset; Oflatoon-OZ; Oflatoon; Oflavid; Oflawin; Oflee; Oflem; Ofler; Oflex; Oflict; Oflin; Oflo; Oflocos; Ofloday; Ofloden; Oflog; Ofloine; Oflomac; Oflomil; Oflomits; Oflon; Oflopar; Oflopip; Ofloren; Oflostar; Oflotas; Oflotec; Ofloter; Oflovid; Oflox; Oflozen; Oflxcin; Ofly; Ofmed; Ofnet; Ofnij; Ofnis; Ofo; Ofor; Ofoxin; Ofpil; Ofral; Ofran; Ofras; Ofsis; Ofspan; Ofspin; Oftacin; Oftar; Oftarx; Oftec; Oftum; Ofven; Ofwin; Ofzac; Ofzen; Ojen; Okaflox; Okil; Oks; Ol; Olfi; Olfic; Olfo; Olife; Olpit; Oltaur; Olumpil; Omeflox; Opeq; Opex; Ophar; OQN; Oqueen; Orixa; Osani-DS; Osani-M; Osani; Oseflox; Osflox; Oshflox; Osiflox; Otago; Otic; Oxal; Oxalic; Oxdrin; Oxiflox; Oxit; Oxo; Oxoism; Oxop; Oxwal; Oza; Tariflox; Tarivid; Zanocin; ***Indon.***: Akilen; Danoflox; Efexin†; Ethiflox; Flotavid; Floxan†; Floxika; Loxinter; Mefoxa; Nilavid; Nufafloqo; Ostrid; Pharflox; Poncoquin; Qipro; Quinovid; Rilox; Tariflox; Tarivid; Tarivid; Zelavel; Zyflox; ***Irl.***: Biravid; Exocin; Tarivid; ***Israel***: Oflodex; Oflox; Ofloxacina; Tarivid; Uro-Tarivid†; ***Ital.***: Exocin; Oflocin; ***Jpn***: Tarivid; ***Malaysia***: Evaflox; Healox†; Inoflox†; Medofloxine; Ofcin; Ofloxol; Tarivid; Zanocin; ***Mex.***: Bactocin; Flonacin; Flosep; Floxil; Floxstat; Forxanix; Loxtev†; Ocuflox; Oxken; Quiflural; Rixivoc; Zanocin†; ***Neth.***: Tarivid; Trafloxal; ***Norw.***: Tarivid; ***Philipp.***: Cinoflox; Delbysen; Dizoflox; Dolocep; Effexin; Exogan; Flodemex; Flovid; Flox; Floxagen; Floxwin; Floxy; Fluraxid; Gonocin; Gyros; Iflox; Imoflox; Inoflex; Inoflox; Iquinol Otic; Iquinol; Itex; Keftil; Lofection; Loxin; Mergexin; Ofbeat; Ofcin; Ofladon; Oflosyn; Onexacin; Otoflox; Oxyflox; Ponebac; Prozu†; Qiflon; Qinolon; Sensoflox; Terioxan; Vioson; Zofex; ***Pol.***: Floxal; Tarivid; ***Port.***: Bactoflox; Bioquil; Exocin; Floxedol; Oflocet; Tarivid; ***Rus.***: Dancil (Данцил); Floxal (Флоксал); Geoflox (Джеофлокс); Oflo (Офло); Oflocide (Офлоцид); Ofloxabol (Офлоксабол); Ofloxin (Офлоксин); Taricin (Тарицин); Tariferid (Тариферид); Tarivid (Таривид); Uniflox (Унифлокс); Zanocin (Заноцин); Zoflox (Зофлокс); ***S.Afr.***: Exocin; Octin; Tafloc; Tarivid; Zanocin; ***Singapore***: Aflacin; Akilen; Flovid; Fugacin; Ofcin; Tarivid; ***Spain***: Exocin; Oflovir; Surnox; ***Swed.***: Tarivid; ***Switz.***: Floxal; Tarivid; ***Thai.***: Exocin; Floxy†; Hyflox; Konovid; Mifloxin; O-Flox; Occidal; Ocin; Ofacin; Ofla; Oflo; Oflobac; Oflocee; Oflomet; Oflox; Ofloxa; Ofloxcin; Orivid; Qinolon; Seracin; Tarivid; Travid; Vesoflox; Viotisone; ***Turk.***: Drovid; Exocin; Girasid†; Kozoksin; Menefloks; Menofloks; Ofkozin; Oflocide; Ofloks; Tarivid; Urosin; ***UK***: Exocin; Tarivid; ***Ukr.***: Floksan (Флоксан); Floxal (Флоксал); Oflo (Офло); Oflohexal (Офлогексал)†; Ofloxin (Офлоксин); Zanocin (Заноцин); ***USA***: Floxin Otic; Floxin; Ocuflox; ***Venez.***: Floxstat; Norlamine; Oflox; Poenflox.

Multi-ingredient Preparations. ***India***: A-Flox M; A-Flox-OZ; A-Flox; Abof-NZ; Abof-OZ; Adeflox-O; Aflox-OZ; AFlox-TZ; Alocin-OZ; Alocin; Alof-T; Alox-OD; Ariflox-OZ; Arilif-OZ; Arinbid OZ; Arviflox-OZ; Atasol; Atoflox-OZ; Aviflox-M; Aviflox-OZ; Aviflox-ST; Aviflox-TZ; Bacter-M; Bacter-NZ; Bacter-OZ; Bacter-TZ; Bactezoa-LB; Bactoff-OZ; Baseflox OZ; Bekker-M; Bekker-OZ; Bestoflox N; Biofast-OZ; Biosin; Bonflox; Brakke; Broflox Plus; Bru-OZ; C-Flox-M; C-Flox-OZ; Canocin-OZ; Casflox-OZ; Casflox-TZ; Chekmet-O; Cinflox-OZ; Clofcin-M; Clofcin-T; Covax-OZ; Cozan-O; Cozan-T; Cucin-O; Cucin-T; Diof; Doact-TZ; Doloket-O; DTO; Ducidal-OZ; Duochek; Ecoflox-OZ; Edilox-OZ; Edilox-S; Emucin-TN; Essasin-OZ; Esterflox-OZ; Eufox-O; Eufox-TZ; Exopred; Falcon-TZ; Fern; Festive B; Festive D; Festive-OZ; Festive-TZ; Fixiflox-D; Fixiflox-H; Fixiflox-OZ; Flagynor; Flex-OZ; Flexril-Ord; Flobacin-OZ; Flobacin-TZ; Flogard-O; Florida-T; Flow-OZ; Floxaquin-O; Floxar-OZ; Floxine-NT; Floxine-OZ; Floxole-MZ; Floxole-NT; Floxole-OZ; Floxur-TZ; Floxzen-M; Floxzen-OZ; Floxzen-ST; Fouz; Ftz; Fydof; Gazal-O; Genflox TZ; Geryl-O; GFlox-OZ; Gic-O; Glofty-D; Glofty-OZ; Harpoon-DD; Harpoon-TZ; Hoflo-O; Hoflox-O; Indocin-D; Indocin-OZ; Indof OZ; Inflobact-D; Inflobact-OZ; Inflobid TZ; Inflobid-D; Inflobid-NXT; Inflobid-OZ; Inflox-OZ; Infoxin-OZ; Jflo-OZ; Jox-TZ; Kareof-OZ; Ketlur Plus; Ketoflox; Kooz; Kureflox-OZ; Laflox-O; Lamizol-O; Lexof-OZ; Lexof-TZ; Logflox-OZ; Loobid; Lumigard; Magof-OZ; MCFlox-OZ; Megaflox-M; Megaflox-TZ; Meganor; Meuflox-OZ; Mintof-OZ; Mof-OZ; Mofcare-TZ; Moflo-OZ; NBox-OZ; Netazox-OF; Netflox-OZ; Neva-OZ; Niolox-D; Niolox-OZ; Nita-O; Nitazet-O; Nitzix-O; Nizonide-O; Noff-OR; Normet; O & O; O-Cebran-O; O-Cebran-OZ; O-Dex; O-Fact-OZ; O2; O2H; Obactin-OZ; Obactin-TZ; Obid-OZ; Obid; Obit-M; Obit-OZ; Obit-TZ; Ocepred; Ociz-OR; Of-M; Ofac-O; Ofac-T; Ofacin-M; Ofacin-O; Ofacin-TZ; Ofal-M; Ofal-OZ; Ofal-TZ; Ofax-TZ; Ofbid-OZ; Ofcare-NT; Ofcare-OD; Ofcura-OZ; Ofdaz; Ofdex; Ofelder-D; Ofelder-PA; Ofet-D; Ofet-H; Ofet-O; Ofet-T; Ofia-OZ; Ofkab-OZ; Ofkair-OZ; Ofla-OZ; Ofla-TZ; Oflab-OZ; Oflab; Oflabin+LB; Oflabin-TZ; Oflacin-DX; Oflacin-P; Oflact-M; Oflact-OZ; Oflagard-O; Oflagard-OL; Oflage-OZ; Oflamed-MN; Oflamed-OZ; Oflamed-TZ; Oflaquin-M; Oflaquin-OZ; Oflark-O; Oflas-OZ; Oflaset-OZ; Oflatoon-MZ; Oflavid-TZ; Oflavid; Oflawin-OZ; Oflawin-TZ; Oflee-M; Oflee-NT; Oflee-OZ; Oflem-D; Oflem-OZ; Ofler-TZ; Oflict-OZ; Oflin-TZ; Oflina-OZ; Oflo-D; Oflo-DT; Oflo-M; Oflo-OZ; Oflo-TZ; Oflocos-OZ; Oflocos-TZ; Ofloday-OZ; Ofloden-O; Ofloden-T; Ofloine-OZ; Oflomac-TZ; Oflomet; Oflomil-OZ; Oflon-OZ; Oflon-TZ; Ofloparl-OR; Oflopip-O; Ofloren-OZ; Ofloren-TZ; Oflostar-D; Oflostar-M; Oflostar-OZ; Oflostar-TZ; Oflotas-OZ; Oflotec-OZ; Oflox D; Oflox TZ; Oflozen-D; Oflxcin-TZ; Ofly-OZ; OFM; Ofmed-OZ; Ofnet-OZ; Ofnida-LB; Ofnida; Ofnis-OZ; Ofo-OZ; Ofo-TZ; Ofor-OZ; Ofpil-O; Ofpil-TZ; Ofral-OZ; Ofral-TZ; Ofran-OZ; Ofsis-OZ; Ofspan-OZ; Ofspan-TZ; Ofspin-OZ; Oft; Oftacin-OZ; Oftec-M; Oftech-OZ; Oftini; Oftum-OZ; Oftum-TZ; Oftwo; Ofven-TZ; Ofwin-OZ; Ofzac-OZ; Ofzen-OZ; Ofzo; Ojen-OZ; Ojen-TZ; Okaflox M; Okaflox-TZ; Okil-OZ; Oks-OZ; Oley-OZ; Olfi TZ; Olfi-O; Olfic-OZ; Olfon-OR; Olife-M; Olife-OZ; Olife-TZ; Olife; Olpit-NZ; Olpit-OZ; Oltaur-TZH; Omeflox-KT; On-OZ; Oniz-O; Opeq-OZ; Ophar-OZ; OQN-O; Oqueen-OZ; Orflo; Orflo; Orin-O; Orni-O; Ornidox; Orniflox; Ornilox; Ornof; Oroflox-OZ; Osani-D; Osani-NT; Osani-O; Osani-T; Osflox-OR; Osiflox-OZ; Osiflox-TZ; Ospol-OZ; Ot; Otago-O; Otek-O; Otic-O; Otichek; Otiflox; Otocin-O; Oxacin-OZ; Oxalic-NZ; Oxcin-Ord; Oxdrin-D; Oxdrin-Ord; Oxiflox-OZ; Oxiflox-TZ; Oxit-OZ; Oxo-D; Oxo-M; Oxo-Ord; Oxo-TZ; Oxoism-OZ; Oxop-D; Oxwal-OZ; Oxwal-TZ; Oxyna; Oza-O; Satrogyl-O; Satromax-O; Tariflox Plus; ***Mex.***: Orecil NF; ***Philipp.***: Exopred; ***Rus.***: Oflomelid (Офломелид); ***Thai.***: Exopred; ***Ukr.***: Oflocain (Офлокаин); Ofor (Офор); Tiflox (Тифлокс)†.

Pharmacopoeial Preparations
USP 36: Ofloxacin Ophthalmic Solution; Ofloxacin Tablets.

Oleandomycin Phosphate *(BANM, rINNM)*

Fosfato de oleandomicina; Oleandomicina, fosfato de; Oléandomycine, Phosphate d'; Oleandomycini Phosphas; PA-105 (oleandomycin); Олеандомицина Фосфат.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*R*,13*R*)-3-(2,6-Dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyloxy)-8,8-epoxymethano-11-hydroxy-2,4,6,10,12,13-hexamethyl-9-oxo-5-(3,4,6-tri-

deoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)tridecan-13-olide phosphate.
$C_{35}H_{61}NO_{12},H_3PO_4$=785.9
CAS — 3922-90-5 (oleandomycin); 7060-74-4 (oleandomycin phosphate).
ATC — J01FA05.
ATC Vet — QJ01FA05.
UNII — 8681H0C27P.

Profile

Oleandomycin is a macrolide antibacterial produced by the growth of certain strains of *Streptomyces antibioticus* with actions and uses similar to those of erythromycin (p. 291.2). It has antimicrobial activity weaker than that of erythromycin. It has been given orally or intravenously as the phosphate in the treatment of susceptible infections.

Troleandomycin (p. 385.2) is the triacetyl ester.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Oletetrin (Олететрин).

Orbifloxacin *(BAN, rINN)*

Orbifloksasiini; Orbifloxacine; Orbifloxacino; Orbifloxacinum; Орбифлоксацин.
1-Cyclopropyl-7-(*cis*-3,5-dimethyl-1-piperazinyl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.
$C_{19}H_{20}F_3N_3O_3$=395.4
CAS — 113617-63-3.
ATC Vet — QJ01MA95.
UNII — 660932TPY6.

Pharmacopoeias. In *US*. In *Eur*. (see p. vii) for veterinary use only.

Ph. Eur. 8: (Orbifloxacin for Veterinary Use). White or pale yellow, crystals or crystalline powder. It exhibits polymorphism. Very slightly soluble in water; practically insoluble dehydrated alcohol; soluble in glacial acetic acid.

USP 36: (Orbifloxacin). White to pale yellow, odourless crystals or crystalline powder. Very slightly soluble in water, in methyl alcohol, and in chloroform; practically insoluble in alcohol and in diethyl ether; soluble in acetic acid. pH of a 1% solution in water is between 6.5 and 7.8.

Profile

Orbifloxacin is a fluoroquinolone antibacterial used in veterinary medicine for the treatment of susceptible infections in dogs.

Preparations

Pharmacopoeial Preparations
USP 36: Orbifloxacin Tablets.

Oritavancin *(rINN)*

LY-333328; Oritavancina; Oritavancine; Oritavancinum; Оритаванцин.
(4″*R*)-22-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-*N*$^{3''}$-[*p*-(*p*-chlorophenyl)benzyl]vancomycin.
$C_{86}H_{97}Cl_3N_{10}O_{26}$=1793.1
CAS — 171099-57-3.
ATC — J01XA05.
ATC Vet — QJ01XA05.
UNII — PUG62FRZ2E.

Oritavancin Phosphate *(rINNM)*

Fosfato de oritavancina; Oritavancin Diphosphate (USAN); Oritavancine, Phosphate d'; Oritavancini Phosphas; Оритаванцина Фосфат.
$C_{86}H_{97}Cl_3N_{10}O_{26},2H_3PO_4$=1989.1
CAS — 192564-14-0.
ATC — J01XA05.
UNII — VL1P93MKZN.

Profile

Oritavancin is a lipoglycopeptide antibacterial under investigation for the treatment of complicated infections of the skin and soft tissues due to Gram-positive bacteria.

References.[1-6] See also under Uses and Administration of Telavancin, p. 373.1.

1. Van Bambeke F, *et al*. Glycopeptide antibiotics: from conventional molecules to new derivatives. *Drugs* 2004; **64:** 913–36.
2. Ward KE, *et al*. Oritavancin—an investigational glycopeptide antibiotic. *Expert Opin Invest Drugs* 2006; **15:** 417–29.
3. Poulakou G, Giamarellou H. Oritavancin: a new promising agent in the treatment of infections due to Gram-positive pathogens. *Expert Opin Invest Drugs* 2008; **17:** 225–43.
4. Crandon J, Nicolau DP. Oritavancin: a potential weapon in the battle against serious Gram-positive pathogens. *Future Microbiol* 2008; **3:** 251–63.
5. Rubino CM, *et al*. Oritavancin population pharmacokinetics in healthy subjects and patients with complicated skin and skin structure infections or bacteremia. *Antimicrob Agents Chemother* 2009; **53:** 4422–8.
6. Zhanel GG, *et al*. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; **70:** 859–86.

Ormetoprim *(USAN, rINN)*

NSC-95072; Ormetoprima; Ormétoprime; Ormetoprimum; Ro-5-9754; Орметоприм.
5-(4,5-Dimethoxy-2-methylphenyl)methyl-2,4-pyrimidinediamine.
$C_{14}H_{18}N_4O_2$=274.3
CAS — 6981-18-6.
UNII — M3EFS94984.

Profile

Ormetoprim is a diaminopyrimidine antibacterial used similarly to trimethoprim (p. 383.2) as a sulfonamide potentiator, in veterinary medicine. Preparations usually contain 1 part of ormetoprim to 5 parts of sulfonamide.

Oxacillin Sodium *(BANM, USAN, rINNM)*

(5-Methyl-3-phenyl-4-isoxazolyl)penicillin Sodium; Natrii Oxacillinum; Oksacylina sodowa jednowodna; Oksasilliininatriummonohydraatti; Oxacilin sodná sůl monohydrát; Oxacilina sódica; Oxacilline Sodique; Oxacilline sodique monohydratée; Oxacillinnatriummonohydrat; Oxacillinum natricum monohydricum; Oxacillinum Natrium; P-12; SQ-16423; Натрий Оксациллин.
Sodium (6*R*)-6-(5-methyl-3-phenylisoxazole-4-carboxamido) penicillanate monohydrate.
$C_{19}H_{18}N_3NaO_5S,H_2O$=441.4
CAS — 66-79-5 (oxacillin); 1173-88-2 (anhydrous oxacillin sodium); 7240-38-2 (oxacillin sodium monohydrate).
ATC — J01CF04.
ATC Vet — QJ01CF04.
UNII — G0V6C994Q5 (oxacillin monohydrate); 4TWD2995UP (anhydrous oxacillin sodium).

Pharmacopoeias. In *Chin*., *Eur*. (see p. vii), and *US*.

Ph. Eur. 8: (Oxacillin Sodium Monohydrate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 3.0% solution in water has a pH of 4.5 to 7.5.

USP 36: (Oxacillin Sodium). A fine white crystalline powder, odourless or having a slight odour. Freely soluble in water, in dimethyl sulfoxide, and in methyl alcohol; slightly soluble in dehydrated alcohol, in chloroform, in methyl acetate, and in pyridine; insoluble in ether, in ethyl acetate, in ethylene chloride, and in benzene. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers at a mean temperature not exceeding 25 degrees.

Incompatibility. Oxacillin sodium has been reported to be incompatible with aminoglycosides and tetracyclines.

Uses and Administration

Oxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p. 299.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Oxacillin is given orally or by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of oxacillin; 1.1 g of oxacillin sodium is equivalent to about 1 g of oxacillin. Oral doses should preferably be given at least 1 hour before, or 2 hours after, meals. The usual oral dose is 1 g of oxacillin twice daily. Oxacillin may be given by intramuscular injection, by slow intravenous injection over about 10 minutes, or by intravenous infusion. Usual parenteral doses are 250 to 500 mg every 4 to 6 hours. Doses may be increased to 1 g every 4 to 6 hours for severe infections, although total daily doses of up to 12 g have been used for deep-seated infections such as endocarditis and osteomyelitis.

For details of doses in children, see p. 338.2.

Administration in children. Oxacillin may be given to neonates and children for the treatment of infections caused by susceptible strains of penicillinase-producing staphylococci by intramuscular or intravenous injection, or by intravenous infusion.

In the USA, the American Academy of Pediatrics[1] recommends the following *parenteral* doses:

- all neonates with a birth-weight less than 1.2 kg: 25 mg/kg every 12 hours
- neonates less than 1 week of age with a birth-weight of 1.2 to 2 kg: 25 to 50 mg/kg every 12 hours
- neonates less than 1 week of age with a birth-weight more than 2 kg, or neonates 1 week of age or older with a birth-weight of 1.2 to 2 kg: 25 to 50 mg/kg every 8 hours
- neonates 1 week of age or older with a birth-weight of more than 2 kg: 25 to 50 mg/kg every 6 hours
- children 1 month and older: 100 to 150 mg/kg daily in 4 divided doses; 150 to 200 mg/kg daily in 4 or 6 divided doses may be used for severe infections

In infants and children, the *oral* route has also been used in some countries in the following doses:

- infants: 125 mg for every 5 kg of body-weight, twice daily
- children: 500 mg twice daily

1. American Academy of Pediatrics. *2009 Red Book: Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2009.

Adverse Effects and Precautions

As for Flucloxacillin, p. 299.3.

Effects on the liver. References.

1. Onorato IM, Axelrod JL. Hepatitis from intravenous high-dose oxacillin therapy: findings in an adult inpatient population. *Ann Intern Med* 1978; **89:** 497–500.
2. Saliba B, Herbert PN. Oxacillin hepatotoxicity in HIV-infected patients. *Ann Intern Med* 1994; **120:** 1048.
3. Maraqa NF, *et al*. Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. *Clin Infect Dis* 2002; **34:** 50–4.
4. Lee CY, *et al*. Reversible oxacillin-associated hepatitis in a 9-month-old boy. *J Paediatr Child Health* 2008; **44:** 146–8.

Sodium content. Each g of oxacillin sodium contains about 2.3 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

As for Flucloxacillin, p. 300.1.

Resistance. The isolation of pneumococci resistant to oxacillin but sensitive to benzylpenicillin has been reported.[1,2] The resistance was due to acquisition of a low-affinity penicillin-binding protein and conferred cross-resistance to meticillin and cloxacillin, and, to a lesser degree, to cefotaxime.

1. Johnson AP, *et al*. Oxacillin-resistant pneumococci sensitive to penicillin. *Lancet* 1993; **341:** 1222.
2. Dowson CG, *et al*. Genetics of oxacillin resistance in clinical isolates of Streptococcus pneumoniae that are oxacillin resistant and penicillin susceptible. *Antimicrob Agents Chemother* 1994; **38:** 49–53.

Pharmacokinetics

Oxacillin is incompletely absorbed from the gastrointestinal tract. Absorption is reduced by the presence of food in the stomach and is less than with cloxacillin. Peak plasma concentrations of 3 to 6 micrograms/mL occurred 1 hour after an oral dose of 500 mg given to fasting subjects. After intramuscular injection of 500 mg, peak plasma concentrations of up to 15 micrograms/mL have been achieved by 30 minutes. Doubling the dose can double the plasma concentration. About 93% of the oxacillin in the circulation is bound to plasma proteins. Oxacillin has been reported to have a plasma half-life of about 0.5 hours. The half-life is prolonged in neonates.

The distribution of oxacillin into body tissues and fluids is similar to that of cloxacillin (p. 275.2).

Oxacillin undergoes some metabolism, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion.

About 20 to 30% of an oral dose, and more than 40% of an intramuscular dose, is rapidly excreted in the urine. Oxacillin is also excreted in the bile.

Plasma concentrations are enhanced by probenecid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Penstapho; ***Braz.***: Oxanon; Oxapen; Prodoxacilina†; Roxacilin; Staficilin N; ***Cz.***: Prostaphlin; ***Fr.***: Bristopen; ***Ger.***: InfectoStaph†; ***Ital.***: Penstapho; ***Philipp.***: Oxal; Oxapen; Oxatalis; Panadox; Prostaphlin†; Stafcil; Wydox; ***Venez.***: Biocilina; OxiPen; Prostafilina.

Multi-ingredient Preparations. ***Rus.***: Oxamp (Оксамп); Oxampicine (Оксампицин); Oxamsar (Оксамсар).

Pharmacopoeial Preparations
USP 36: Oxacillin for Injection; Oxacillin Injection; Oxacillin Sodium Capsules; Oxacillin Sodium for Oral Solution.

Oxolinic Acid *(BAN, USAN, rINN)*

Acide Oxolinique; Ácido oxolínico; Acidum Oxolinicum; Kyselina oxolinová; NSC-110364; Oksoliinihappo; Oksolinik

Asit; Oksolino rūgštis; Oxolínico, ácido; Oxolinsäure; Oxolinsav; Oxolinsyra; W-4565; Оксолиновая Кислота.
5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid.
$C_{13}H_{11}NO_5$=261.2
CAS — 14698-29-4.
ATC — J01MB05.
ATC Vet — QJ01MB05.
UNII — L0A22B22FT.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oxolinic Acid). An almost white or pale yellow crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

Profile

Oxolinic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p. 328.3), although adverse effects on the CNS may be more frequent. It has been given orally in the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Oksolin.

Oxytetracycline *(BAN, rINN)*

Glomycin; Hydroxytetracycline; Oksitetraciklinas; Oksitetrasiklin; Oksitetrasykliini; Oksytetracyklina; Ossitetraciclina; Oxitetraciclina; Oxitetraciklin; Oxitetracyklin; Oxytetracyclin; Oxytétracycline; Oxytetracyclinum; Oxytetracyklin; Riomitsin; Terrafungine; Окситетрациклин.
4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 5β-Hydroxytetracycline.
$C_{22}H_{24}N_2O_9$=460.4
CAS — 79-57-2 (anhydrous oxytetracycline); 6153-64-6 (oxytetracycline dihydrate).
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QG51AA01; QJ01AA06; QJ51AA06; QS01AA04.
UNII — SLF0D9077S (anhydrous oxytetracycline); X20I9EN955 (oxytetracycline dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*, which specify the dihydrate ($C_{22}H_{24}N_2O_9,2H_2O$ = 496.5); *US* allows the anhydrous substance or the dihydrate.

Ph. Eur. 8: (Oxytetracycline Dihydrate). A substance produced by the growth of certain strains of *Streptomyces rimosus* or obtained by any other means. A yellow, crystalline powder. Very slightly soluble in water; dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 4.5 to 7.5. Store in airtight containers. Protect from light.

USP 36: (Oxytetracycline). A pale yellow to tan, odourless crystalline powder, that darkens on exposure to strong sunlight. Soluble 1 in 4150 of water, 1 in 66 of dehydrated alcohol, and 1 in 6250 of ether; sparingly soluble in alcohol; practically insoluble in chloroform; freely soluble in 3N hydrochloric acid and in alkaline solutions. pH of a 1% suspension in water is between 4.5 and 7.0. It loses potency in solutions of pH below 2 and is rapidly destroyed by alkali hydroxide solutions. Store in airtight containers. Protect from light.

Oxytetracycline Calcium *(BANM, rINNM)*

Calcii Oxytetracyclinum; Oxitetraciclina cálcica; Oxytétracycline Calcique; Кальций Окситетрациклин.
$C_{44}H_{46}CaN_4O_{18}$=958.9
CAS — 15251-48-6 (xCa).
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QJ01AA06; QS01AA04.
UNII — C8MRZ07FDV.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Oxytetracycline Calcium). A pale yellow to greenish-fawn, crystalline powder. Practically insoluble in water; soluble in dilute acids; dissolves slowly in dilute ammonia solution. A 2.5% suspension in water has a pH of 6.0 to 7.5. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Oxytetracycline Calcium). A yellow to light brown crystalline powder. Insoluble in water; soluble 1 in more than 1000 of alcohol, of chloroform, and of ether, and 1 in 15 of 0.1N sodium hydroxide. pH of a 2.5% suspension in water is between 6.0 and 8.0. Store in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light.

Oxytetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de oxitetraciclina; Oksitetraciklino hidrochloridas; Oksitetrasiklin Hidroklorür; Oksitetrasykliinihydrokloridi; Oksytetracykliny chlorowodorek; Oxitetraciclina, hidrocloruro de; Oxitetraciklin-hidroklorid; Oxitetracyklinhydroklorid; Oxytétracycline, Chlorhydrate d'; Oxytetracyclinhydrochlorid; Oxytetracyclini Hydrochloridum; Oxytetracyklin-hydrochlorid; Окситетрациклина Гидрохлорид.
$C_{22}H_{24}N_2O_9$,HCl=496.9
CAS — 2058-46-0.
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QJ01AA06; QS01AA04.
UNII — 4U7K4N52ZM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Oxytetracycline Hydrochloride). A yellow, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Solutions in water become turbid on standing owing to the precipitation of oxytetracycline. A 1% solution in water has a pH of 2.3 to 2.9. Store in airtight containers. Protect from light.

USP 36: (Oxytetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline powder. It decomposes at temperatures exceeding 180 degrees, and exposure to strong sunlight or temperatures exceeding 90 degrees in moist air causes it to darken. Its potency is diminished in solutions having a pH below 2, and it is rapidly destroyed by alkali hydroxide solutions. Freely soluble in water, but crystals of oxytetracycline separate as a result of partial hydrolysis of the hydrochloride; sparingly soluble in alcohol and in methyl alcohol, and even less soluble in dehydrated alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Oxytetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts.

Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Uses and Administration

Oxytetracycline is a tetracycline derivative with actions and uses similar to those of tetracycline (p. 375.3).

Oxytetracycline dihydrate or hydrochloride are usually used in tablets, capsules, and injections, and the calcium salt in aqueous oral suspensions; all three are also used in topical preparations. Doses have been expressed as anhydrous oxytetracycline, the dihydrate, or the hydrochloride but in practice this appears to make little difference. Oxytetracycline dihydrate and oxytetracycline hydrochloride 269.8 mg, and oxytetracycline calcium 260.3 mg, are each equivalent to about 250 mg of oxytetracycline.

Oxytetracycline is usually given orally in adult doses of 250 to 500 mg four times daily, usually 1 hour before or 2 hours after food. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects.

Doses of oxytetracycline 250 to 500 mg daily have been used in acne, although the *BNF* advocates a dose of 500 mg twice daily.

Oxytetracycline is sometimes given intramuscularly, in doses of 250 mg once daily or 300 mg daily in 2 or 3 divided doses, but this route may be painful and produces lower blood concentrations than recommended oral doses. As intramuscular injections are painful, lidocaine is usually included in the solution. Oxytetracycline has also been given intravenously.

For details of doses in children and adolescents, see p. 339.2.

Oxytetracycline and its salts have been applied topically, often with other agents, as a variety of eye and ear drops, ointments, creams, and sprays.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, oxytetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in some other countries, it may be given to those over 8 years old in usual oral doses of 25 to 50 mg/kg (to a maximum of 1 g) daily in 4 divided doses or by intramuscular injection in usual doses of 15 to 25 mg/kg daily in 2 or 3 divided doses (maximum of 250 mg per dose).

Skin disorders. For reference to the use of oxytetracycline in the treatment of various skin disorders, see under Tetracycline, p. 376.3.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Oxytetracycline may produce less tooth discoloration than some other tetracyclines but gastrointestinal symptoms tend to be more severe.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxytetracycline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

As for Tetracycline, p. 377.3.

Antimicrobial Action

As for Tetracycline, p. 377.3.

Oxytetracycline is somewhat less active against many organisms.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

An oral dose of 500 mg every 6 hours is reported to produce steady-state plasma concentrations of 3 to 4 micrograms/mL. Plasma protein binding is reported to be about 20 to 40% and the half-life to be about 9 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Terramicina; ***Braz.***: Terramicina; ***Denm.***: Oxytetral†; ***Gr.***: Oxacycle; Terramycin; ***Hong Kong***: Oxylim; Syntermycin†; ***Hung.***: Tetran; ***India***: Oxter; Oxyteracin; Oxytetra; Terramycin; ***Indon.***: Chemotrex†; Corsamycin; Terramycin; ***Irl.***: Clinimycin†; ***Malaysia***: Oxylim; ***Mex.***: Metrecina; Oxitraklin; Terrados; Terramicina; ***Norw.***: Oxytetral†; ***Philipp.***: Noxebron; ***Port.***: Terricil; ***S.Afr.***: Acu-Oxytet†; Adco-Oxypan; Adco-Roxy; Be-Oxytet; Cotet†; Dynoxytet; Nucotet; O-4 Cycline; Oxymycin†; Pharmatet; Spectratet†; Tetracem; ***Singapore***: Oxylim; Syntermycin; ***Spain***: Terramicina; ***Swed.***: Oxytetral†; ***Thai.***: O-Tetra; Oxycide; Oxycline; Oxylim; Oxynutra; ***Turk.***: Neocol†; ***UK***: Oxymycin; ***Venez.***: Terramicina.

Multi-ingredient Preparations. ***Arg.***: Terra-Cortril; ***Austria***: Tetra-Gelomyrtol†; ***Belg.***: Terra-Cortril + Polymyxine B; Terra-Cortril; Terramycine + Polymyxine B; ***Braz.***: Terra-Cortril; Terramicina c/Polimixina; ***Denm.***: Hydrocortison med Terramycin og Polymyxin-B; Hydrocortison med Terramycin; Terramycin Polymyxin B; ***Fin.***: Terra-Cortril P; Terra-Cortril; ***Fr.***: Auricularum; Sterdex; ***Ger.***: Corti Biciron N; Tetra-Gelomyrtol; ***Gr.***: Auricularum; Oxacycle-P; Terra-Cortril; Terramycin w Polymyxin Otic; Terramycin with Polymyxin; ***Hong Kong***: Terramycin with Polymyxin B; ***Hung.***: Oxycort; Tetran-Hydrocortison; ***India***: Terramycin SF; ***Indon.***: Sancortmycin; Terra-Cortril; Terramycin Poly†; ***Israel***: Terramycin†; ***Ital.***: Cosmiciclina; ***Malaysia***: Terramycin; ***Mex.***: Terramicina; Terraxin; ***Neth.***: Terra-Cortril met polymyxine-B; ***Norw.***: Terra-Cortril Polymyxin B; Terra-Cortril; Terramycin Polymyxin B; ***Philipp.***: Terramycin; ***Pol.***: Atecortin; Oxycort; ***Rus.***: Gioxyson (Гиоксизон); Oxycort (Оксикорт); ***S.Afr.***: Terra-Cortril†; Terramycin†; ***Singapore***: Terramycin; ***Spain***: Terra-Cortril; Terra-Cortril; Terramicina; ***Swed.***: Terracortril med polymyxin B; Terracortril; Terramycin Polymyxin B†; ***Thai.***: Terramycin; ***Turk.***: Geotril†; Heksa; Polimisin; Sekamisin†; Terramycin; Vitacillin; ***UK***: Terra-Cortril; Trimovate; ***Ukr.***: Aprolat (Апролат); Oxycort (Оксикорт); ***USA***: Terak; Terra-Cortril; Terramycin with Polymyxin B; Urobiotic-250; ***Venez.***: Ofterra; Terramicina con Polimixina B.

Pharmacopoeial Preparations

BP 2014: Oxytetracycline Capsules; Oxytetracycline Tablets;

USP 36: Oxytetracycline and Nystatin Capsules; Oxytetracycline and Nystatin for Oral Suspension; Oxytetracycline Calcium Oral Suspension; Oxytetracycline for Injection; Oxytetracycline Hydrochloride and Hydrocortisone Acetate Ophthalmic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Oxytetracycline Hydrochloride Capsules; Oxytetracycline Injection; Oxytetracycline Tablets.

Panipenem *(rINN)*

CS-533; Panipénem; Panipenemum; RS-533; Панипенем.
(+)-(5*R*,6*S*)-3{[(*S*)-1-Acetimidoyl-3-pyrrolidinyl]thio}-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.
$C_{15}H_{21}N_3O_4S$=339.4

CAS — 87726-17-8.
UNII — W9769W09JF.

Pharmacopoeias. In *Jpn.*

Profile

Panipenem is a carbapenem beta-lactam antibacterial similar to imipenem (p. 309.2). It is given intravenously with betamipron (p. 231.1), which reduces its adverse renal effects.

References.
1. Goa KL, Noble S. Panipenem/betamipron. *Drugs* 2003; **63:** 913–25.
2. Tajima N, *et al.* Population pharmacokinetic analysis of panipenem/betamipron in patients with various degrees of renal function. *Chemotherapy* 2006; **52:** 245–53.
3. Kwon KT, *et al.* Panipenem versus cefepime as empirical monotherapy in adult cancer patients with febrile neutropenia: a prospective randomized trial. *Jpn J Clin Oncol* 2008; **38:** 49–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***China***: Carbenin (克倍宁); ***Jpn***: Carbenin.

Pazufloxacin Mesilate

Mesilato de pazufloxacino (rINNM); Mesilato de pazufloxacino; Pazufloxacine, Mésilate de; Pazufloxacini Mesilas; Pazufloxacino, mesilato de; T-3761 (pazufloxacin); T-3762; Пазуфлоксацина Мезилат.

(-)-(3*S*)-10-(1-Aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid methanesulfonate.

$C_{16}H_{15}FN_2O_4$, CH_3SO_3H=414.4

CAS — 127045-41-4 (pazufloxacin); 163680-77-1 (pazufloxacin mesilate).
ATC — J01MA18.
ATC Vet — QJ01MA18.
UNII — 2XI226J1HS.

Profile

Pazufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1). It is given by intravenous infusion as the mesilate in the treatment of susceptible infections in a usual dose equivalent to 1 g of pazufloxacin daily in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Ti (安替); Ao Er Man (奥尔曼); Ba Hong (巴红); BoXin (博信); Fa Duo Lin (法多琳); Fei Xun Qi (菲迅奇); Fengzhuxin (锋珠新); Fengzhuye (锋珠烨); Fu Li Te (伏立特); Heng Mu (恒沐); Jia Le Tong Xin (佳乐同欣); Jia Yi Ni (加易尼); Jun Ke Duo (君克多); Jun Pu (君普); Lai Mei Jing (莱美净); Mi Si Long (米斯龙); Min Xing (敏星); Ni Sai Xin (尼赛信); Nuo Jun Xin (诺君欣); Pa Di Xing (帕迪星); Pai Shu Ke (派抒可); Pai Si Xin (派斯欣); Qi Ruo Da (齐若达); Ren Ge Duo Na (仁格多那); Tong Qi (通琦); Wei Li Xian (威利仙); Wei Yu Qing (维予清); Xu Yuan (旭原); Xuan Bo (宣搏); Ya Zheng Li (亚征利); Yanlei (严雷); ***Jpn***: Pasil; Pazucross.

Pefloxacin Mesilate *(BANM, rINNM)*

EU-5306 (pefloxacin); Mesilato de pefloxacino; Pefloksacino mesilatas dihidratas; Pefloksacyny mezylan dwuwodny; Pefloksasiinimesilaattidihydraatti; Pefloxacin Mesilate Dihydrate; Pefloxacin mesylát dihydrát; Pefloxacin Mesylate; Pefloxacin Mesylate (USAN); Péfloxacine, Mésilate de; Péfloxacine (mésilate de) dihydraté; Pefloxacini Mesilas; Pefloxacini Mesilas Dihydricus; Pefloxacinmesilat-Dihydrat; Pefloxacinmesilatdihydrat; Pefloxacin-mezilát-dihidrát; Pefloxacino, mesilato de; 1589-RB (pefloxacin); 41982-RP; Пефлоксацина Мезилат.

1-Ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid methanesulphonate dihydrate.

$C_{17}H_{20}FN_3O_3.CH_4O_3S.2H_2O$=465.5

CAS — 70458-92-3 (pefloxacin); 70458-95-6 (pefloxacin mesilate); 149676-40-4 (pefloxacin mesilate dihydrate).
ATC — J01MA03.
ATC Vet — QJ01MA03.
UNII — 5IAD0UV3FH.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Pefloxacin Mesilate Dihydrate). A fine, white or almost white powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Profile

Pefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.1). It also has bactericidal activity against *Mycobacterium leprae* and has been tried in the treatment of leprosy (p. 188.3).

Pefloxacin has a longer plasma half-life than ciprofloxacin (about 8 to 13 hours) and is also extensively metabolised, the main metabolite being *N*-desmethylpefloxacin (norfloxacin, p. 333.3).

Pefloxacin is given orally or by intravenous infusion as the mesilate in the treatment of susceptible infections. Doses are expressed in terms of the base; pefloxacin mesilate 558.5 mg is equivalent to about 400 mg of pefloxacin. The usual dose is 400 mg twice daily; the first dose may be doubled if effective serum concentrations need to be attained quickly. A single oral dose of 800 mg may be used in the treatment of gonococcal urethritis in men and acute uncomplicated cystitis in women.

Fluoroquinolones have caused adverse effects on the musculoskeletal system (see under Adverse Effects of Ciprofloxacin, p. 263.2) and in the case of pefloxacin this has led to restrictions in some countries.

Adverse effects. References to adverse effects with pefloxacin.

1. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; **7:** 310–14.
2. Al-Hedaithy MA, Noreddin AM. Hypersensitivity anaphylactoid reaction to pefloxacin in a patient with AIDS. *Ann Pharmacother* 1996; **30:** 612–14.
3. Chang H, *et al.* Pefloxacin-induced arthropathy in an adolescent with brain abscess. *Scand J Infect Dis* 1996; **28:** 641–3.

Pharmacokinetics. References to the pharmacokinetics of pefloxacin.

1. Bressolle F, *et al.* Pefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **27:** 418–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Peflacin; ***China***: Beining (倍宁); Da Fu Ming (达福明); Wei Li Ke (威力克); Wei Ning Jia (维宁佳); ***Cz.***: Abaktal; ***Fr.***: Peflacine; ***Gr.***: Idrostamin; Labocton; Londoman; Obergan; Peflacine; ***Hung.***: Abaktal†; Peflacine†; ***India***: Cylox; Hinepox; Pefbid; Pelox; Proflox; Qucin; ***Indon.***: Dexaflox; Felox; Noflexin; Oxaflox; Peflacine; ***Ital.***: Peflacin; Peflox; ***Malaysia***: Quilaxin; ***Mex.***: Peflacina†; ***Philipp.***: Floxin†; Floxol; Peraxin; ***Pol.***: Abaktal; Peflacine; ***Port.***: Peflacine†; ***Rus.***: Abaktal (Абактал); Pefloxabol (Пефлоксабол); Pelox (Пелокс); Perti (Перти)†; Unikpef (Юникпеф); ***Thai.***: Peflacine; ***Turk.***: Peflacine; ***Ukr.***: Abaktal (Абктал); Peflocin (Пефлоцин)†; Pelox (Пелокс)†.

Penethamate Hydriodide *(BAN)*

Diethylaminoethyl Penicillin G Hydroiodide; Penetamato, hidroioduro de; Pénéthamate, iodhydrate de; Penethamati hydroiodidum.

2-Diethylaminoethyl (6*R*)-6-(2-phenylacetamido)penicillanate hydriodide.

$C_{22}H_{31}N_3O_4S$,HI=561.5

CAS — 3689-73-4 (penethamate); 808-71-9 (penethamate hydriodide).
ATC Vet — QJ01CE90; QJ51CE90.
UNII — GA14AS9QOK.

Profile

Penethamate is a penicillin antibacterial used as the hydriodide in veterinary medicine.

Pheneticillin Potassium *(BANM, rINNM)*

Feneticilina potásica; Kalii Pheneticillinum; Penicillin B; Phenethicillin Potassium; Phénéticilline Potassique; Pheneticillinum Kalicum; Potassium α-Phenoxyethylpenicillin; Калия Фенетициллин.

A mixture of the D(+)- and L(-)-isomers of potassium (6*R*)-6-(2-phenoxypropionamido)penicillanate.

$C_{17}H_{19}KN_2O_5S$=402.5

CAS — 147-55-7 (pheneticillin); 132-93-4 (pheneticillin potassium).
ATC — J01CE05.
ATC Vet — QJ01CE05.
UNII — 70978WUK7C.

Pharmacopoeias. In *Jpn.*

Profile

Pheneticillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p. 340.3). It is given orally in a usual dose of 250 mg three times daily, as the potassium salt, for the treatment of susceptible mild to moderate infections. Pheneticillin sodium has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Broxil.

Phenoxymethylpenicillin *(BAN, rINN)*

Fenoksimetilpenicilinas; Fenoksimetyylipenisilliini; Fenoksymetylopenicylina; Fenoximetilpenicilina; Fenoximetilpenicillin; Fenoximetylpenicillin; Fenoxymethylpenicilin; Penicillin, Phenoxymethyl; Penicillin V (USAN); Penisilin V; Phénomycilline; Phenoxymethyl Penicillin; Phénoxyméthylpénicilline; Phenoxymethylpenicillinum; Феноксиметилпенициллин.

(6*R*)-6-(2-Phenoxyacetamido)penicillanic acid.

$C_{16}H_{18}N_2O_5S$=350.4

CAS — 87-08-1.
ATC — J01CE02.
ATC Vet — QJ01CE02.
UNII — Z61I075U2W.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Phenoxymethylpenicillin). A substance produced by the growth of certain strains of *Penicillium notatum* or related organisms on a culture medium containing an appropriate precursor, or obtained by any other means. A white or almost white, slightly hygroscopic, crystalline powder. Very slightly soluble in water; soluble in alcohol. A 0.5% suspension in water has a pH of 2.4 to 4.0. Store in airtight containers.

USP 36: (Penicillin V). A white, odourless crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in acetone; insoluble in fixed oils. pH of a 3% suspension in water is between 2.5 and 4.0. Store in airtight containers.

Phenoxymethylpenicillin Calcium

(BANM, rINNM)

Calcii Phenoxymethylpenicillinum; Fenoximetilpenicilina cálcica; Penicillin V Calcium; Phénoxyméthylpénicilline Calcique; Phenoxymethylpenicillinum Calcicum; Кальций Феноксиметилпенициллин.

$(C_{16}H_{17}N_2O_5S)_2Ca.2H_2O$=774.9

CAS — 147-48-8 (anhydrous phenoxymethylpenicillin calcium); 73368-74-8 (phenoxymethylpenicillin calcium dihydrate).
ATC — J01CE02.
ATC Vet — QJ01CE02.
UNII — 3750YH4NM7.

Pharmacopoeias. In *Int.*

Phenoxymethylpenicillin Potassium

(BANM, rINNM)

Fenoksimetil Penisilin Potasyum; Fenoksimetilpenicilino kalio druska; Fenoksimetyylipenisilliinikalium; Fenoksymetylopenicylina potasowa; Fenoximetilpenicilina potásica; Fenoximetilpenicilina Potássica; Fenoximetilpenicillinkálium; Fenoximetylpenicillin kalium; Fenoxymethylpenicilin draselná sůl; Kalii Phenoxymethylpenicillinum; Penicillin V Potassium (USAN); Phenoxymethylpenicillin-Kalium; Phénoxyméthylpénicilline Potassique; Phenoxymethylpenicillinum Kalicum; Калия Феноксиметилпенициллин.

$C_{16}H_{17}KN_2O_5S$=388.5

CAS — 132-98-9.
ATC — J01CE02.
ATC Vet — QJ01CE02.
UNII — 146T0TU1JB.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Phenoxymethylpenicillin Potassium). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.5 to 7.5.

USP 36: (Penicillin V Potassium). A white, odourless crystalline powder. Very soluble in water; soluble 1 in 150 of alcohol; insoluble in acetone. pH of a 3% solution in water is between 4.0 and 7.5. Store in airtight containers.

Units

The first International Standard Preparation (1957) of phenoxymethylpenicillin contained 1695 units/mg but was withdrawn in 1968. Despite this, doses of phenoxymethylpenicillin are still expressed in units in some countries.

Phenoxymethylpenicillin 250 mg is equivalent to about 400 000 units.

Uses and Administration

Phenoxymethylpenicillin is used similarly to benzylpenicillin (p. 228.3) in the treatment or prophylaxis of infections caused by susceptible organisms, especially streptococci. It is used only for the treatment of mild to moderate infections, and not for chronic, severe, or deep-seated infections since absorption can be unpredictable. Patients treated initially with parenteral benzylpenicillin may continue treatment with oral phenoxymethylpenicillin once a satisfactory clinical response has been obtained. Specific indications for phenoxymethylpenicillin include anthrax (mild uncomplicated infections), Lyme disease (early stage in pregnant women or young children), pharyngitis or tonsillitis, rheumatic fever (primary and secondary prophylaxis), streptococcal skin infections, and spleen disorders (pneumococcal infection prophylaxis). For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Phenoxymethylpenicillin is given orally, usually as the potassium or calcium salt, preferably at least 30 minutes before, or 2 hours after, food. Benzathine phenoxymethylpenicillin (p. 228.1) is also used.

Doses are expressed in terms of the equivalent amount of phenoxymethylpenicillin; 1.1 g of phenoxymethylpenicillin calcium and 1.1 g of phenoxymethylpenicillin potassium are each equivalent to about 1 g of phenoxymethylpenicillin.

Usual adult doses have been 250 to 500 mg every 6 hours but in severe infections the *BNF* recommends up to 1 g every 6 hours. Dosage may need to be modified in severe renal impairment.

To prevent recurrences of rheumatic fever the *BNF* recommends 250 mg twice daily, while WHO suggests a dose of 500 mg twice daily. The *BNF* also recommends 250 to 500 mg every 6 hours for 10 days to prevent secondary cases of invasive group A streptococcal infection, and 250 mg every 12 hours for long-term prophylaxis of pneumococcal infection in asplenia, or in patients with sickle-cell disease.

For details of doses in children, see p. 341.1.

Administration in children. Phenoxymethylpenicillin may be given orally to children for the treatment of infections caused by susceptible bacteria, as well as for prevention of recurrent rheumatic fever and pneumococcal infection in some patient populations. It may also be used in neonates and children to prevent secondary group A streptococcal infection.

In the UK, the *BNFC* suggests the following doses:

For susceptible infections including **oral infections, tonsillitis, otitis media, erysipelas, and cellulitis**:

- children 1 month to 1 year of age: 62.5 mg 4 times daily
- children 1 to 6 years of age: 125 mg 4 times daily
- children 6 to 12 years of age: 250 mg 4 times daily

For **severe infection**, children should receive at least 12.5 mg/kg (maximum 1 g) 4 times daily.

For **prevention of pneumococcal infection** in asplenia or sickle-cell disease:

- children less than 1 year of age: 62.5 mg twice daily
- children 1 year to 5 years of age: 125 mg twice daily
- children from 5 years of age: 250 mg twice daily

To **prevent recurrence of rheumatic fever**:

- children 1 month to 6 years of age: 125 mg twice daily
- children from 6 years of age: 250 mg twice daily

To **prevent secondary cases of group A streptococcal infection, phenoxymethylpenicillin is given for 10 days in the following doses**:

- neonates: 12.5 mg/kg (maximum 62.5 mg) every 6 hours
- children 1 month to 1 year of age: 62.5 mg every 6 hours
- children 1 to 6 years of age: 125 mg every 6 hours
- children from 6 to 12 years of age: 250 mg every 6 hours

In the USA, the American Academy of Pediatrics (AAP)[1] makes the following alternative dosing recommendations for the treatment of **mild to moderate infections**:

- children from 1 month of age: 25 to 50 mg/kg daily, orally in 3 or 4 divided doses (maximum 2 g)

The AAP considers phenoxymethylpenicillin to be inappropriate for treatment of severe infections.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Phenoxymethylpenicillin is usually well tolerated but may occasionally cause transient nausea and diarrhoea.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenoxymethylpenicillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Potassium content. Each g of phenoxymethylpenicillin potassium contains about 2.6 mmol of potassium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterials. Reduced absorption was reported when phenoxymethylpenicillin was given after an oral course of *neomycin*.[1]

1. Cheng SH, White A. Effect of orally administered neomycin on the absorption of penicillin V. *N Engl J Med* 1962; **267:** 1296–7.

Beta blockers. Fatal anaphylactic reactions to phenoxymethylpenicillin in 2 patients on *nadolol* and *propranolol* respectively, might have been potentiated by the beta blocker.[1]

1. Berkelman RL, *et al.* Beta-adrenergic antagonists and fatal anaphylactic reactions to oral penicillin. *Ann Intern Med* 1986; **104:** 134.

Antimicrobial Action

Phenoxymethylpenicillin has a range of antimicrobial activity similar to that of benzylpenicillin (p. 230.1) and a similar mode of action. It may be less active against some susceptible organisms, particularly Gram-negative bacteria.

The mechanisms and patterns of resistance to phenoxymethylpenicillin are similar to those of benzylpenicillin.

Pharmacokinetics

Phenoxymethylpenicillin is more resistant to inactivation by gastric acid and is more completely absorbed than benzylpenicillin from the gastrointestinal tract. Absorption is usually rapid, although variable, with about 60% of an oral dose being absorbed. The calcium and potassium salts are better absorbed than the free acid. Peak plasma concentrations of 3 to 5 micrograms/mL occur 30 to 60 minutes after a dose of 500 mg. The effect of food on absorption appears to be slight. The plasma half-life of phenoxymethylpenicillin is about 30 to 60 minutes and may be increased to about 4 hours in severe renal impairment. About 80% is reported to be protein bound. The distribution and elimination of phenoxymethylpenicillin is similar to that of benzylpenicillin (p. 230.2). It is metabolised in the liver to a greater extent than benzylpenicillin; several metabolites have been identified including penicilloic acid. The unchanged drug and metabolites are excreted rapidly in the urine. Only small amounts are excreted in the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Grampenil NF; Pen Oral; Penagrande†; Penfantil; Penicina†; ***Austral.***: Abbocillin-VK; Cilicaine VK; Cilopen VK; LPV; Penhexal VK†; ***Austria***: Ospen; Pen-V; Penbene; Penstad; Star-Pen†; ***Belg.***: Peni-Oral; ***Braz.***: Meracilina; Oracilin; Pen-V-Cil†; Pen-Ve-Oral; Pencilin-V; Penicigran; ***Canad.***: Apo-Pen-VK; Novo-Pen-VK; Nu-Pen-VK; ***China***: Bangning ShaJi (邦宁沙吉); Kai Lai Li Ke (凯莱立克); Li Te Er Xin (力特尔新); Weibaisi (维百斯); ***Cz.***: Ospen; Penbene; Pencid†; ***Denm.***: Pancillin; Primcillin; Rocilin†; Vepicombin; ***Fin.***: Medicillin; Milcopen; V-Pen; ***Fr.***: Oracilline; ***Ger.***: Arcasin; InfectoCillin; Isocillin; Ispenoral; Megacillin oral†; P-Mega-Tablinen; Pen Mega†; Penbeta†; Penhexal†; ***Gr.***: Ospen; ***Hung.***: Ospen; ***India***: Kaypen; ***Indon.***: Fenocin; Ospen; ***Irl.***: Calvepen; Kopen; ***Israel***: Pen-Rafa VK; Rafapen Mega; Rafapen V-K†; ***Malaysia***: Beapen; Ospen; ***Mex.***: Anapenil; Kavipen; Pen-Vi-K; Pota-Vi-Kin; ***Neth.***: Acipen†; ***Norw.***: Apocillin; Weifapenin; ***NZ***: Cilicaine VK; ***Philipp.***: Sumapen; ***Pol.***: Ospen; ***Rus.***: Star-Pen (Стар-Пен); ***S.Afr.***: Betapen; In Cil-Vk; Incil†; Len VK; Spec-Pen-V-K†; ***Singapore***: Ospen†; Penopen; ***Spain***: Penilevel; ***Swed.***: Kavepenin; Peceve†; Tikacillin; ***Switz.***: Ospen; Phenocillin†; Stabicilline; ***Thai.***: Medic-V; Metro-V†; P-Cillin V; Pen-V; Pener; Penvedon; Penvelin; Penveno; Semicillin; Suveelin; ***Turk.***: Cilacil†; Cliacil; Penoksil; ***USA***: Pen-Vee K; Veetids†; ***Venez.***: Ospen.

Multi-ingredient Preparations. ***Spain***: Penilevel Retard.

Pharmacopoeial Preparations

BP 2014: Phenoxymethylpenicillin Oral Solution; Phenoxymethylpenicillin Tablets;

USP 36: Penicillin V for Oral Suspension; Penicillin V Potassium for Oral Solution; Penicillin V Potassium Tablets; Penicillin V Tablets.

Phthalylsulfacetamide *(BAN)*

Phthalylsulphacetamide; Sulfanilacetamidum Phthalylatum.

4′-(Acetylsulphamoyl)phthalanilic acid.

$C_{16}H_{14}N_2O_6S$=362.4

CAS — 131-69-1.

UNII — 24PUW23GRX.

Profile

Phthalylsulfacetamide is a sulfonamide antibacterial. It is poorly absorbed when given orally and has been used for gastrointestinal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Enterol Con Nifuroxacida; Enterol†; ***Mex.***: Facetin-D.

Phthalylsulfathiazole *(BAN, rINN)*

Ftalazol; Ftalilsulfatiazol; Ftalilsulfatiazolas; Ftálilszulfatiazol; Ftalylsulfathiazol; Ftalylsulfatiazol; Ftalyylisulfatiatsoli; Phtalylsulfathiazol; Phthalazol; Phthalazolum; Phthalylsulfathiazol; Phthalylsulfathiazolum; Phthalylsulphathiazole; Sulfaphtalylthiazol; Фталилсульфатиазол.

4′-(1,3-Thiazol-2-ylsulphamoyl)phthalanilic acid.

$C_{17}H_{13}N_3O_5S_2$=403.4

CAS — 85-73-4.

ATC — A07AB02.

ATC Vet — QA07AB02.

UNII — 6875L5852V.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Phthalylsulfathiazole). A white or yellowish-white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; freely soluble in dimethylformamide. Protect from light.

Profile

Phthalylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is poorly absorbed, about 95% remaining in the intestine and only about 5% being slowly hydrolysed to sulfathiazole and absorbed.

It is given, with other antibacterials, for its antibacterial action in the gastrointestinal tract in the treatment of infections and for bowel decontamination before surgery.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Enterosulfa; ***Thai.***: Thalatex.

Multi-ingredient Preparations. ***Arg.***: Carbon Tabs; Colistop; Diarrocalmol; Estreptocarbocaftiazol; Estreptocarbocaftiazol; Opocarbon; ***Braz.***: Parenterin; ***Chile***: Esancol; Imecol; Liracol; Testisan; ***Gr.***: Enteromyk; ***Mex.***: Bontal; Ditayod; ***Thai.***: Chlorotracin†; Coccila; Diaropect; Disento; Endothalyl.

Pipemidic Acid *(BAN, rINN)*

Acide Pipémidique; Ácido pipemídico; Acidum Pipemidicum; Acidum pipemidicum trihydricum; Kyselina pipemidová trihydrát; Pipemídico, ácido; Pipemidihappo; Pipemidiinihappotrihydraatti; Pipemidinsav-trihidrát; Pipemidinsyratrihydrat; Pipémidique (acide) trihydraté; Pipemido rūgštis trihidratas; Pipemidsyra; Piperamic Acid; 1489-RB; Пипемидовая Кислота.

8-Ethyl-5,8-dihydro-5-oxo-2-(piperazin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

$C_{14}H_{17}N_5O_3$=303.3

CAS — 51940-44-4 (anhydrous pipemidic acid); 72571-82-5 (pipemidic acid trihydrate).

ATC — J01MB04.

ATC Vet — QJ01MB04.

UNII — LT12J5HVR8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn* (all as the trihydrate).

Ph. Eur. 8: (Pipemidic Acid Trihydrate). A pale yellow or yellow crystalline powder. Very slightly soluble in water and in dichloromethane; practically insoluble in alcohol. It dissolves in dilute solutions of acids and of alkali hydroxides. Protect from light.

Profile

Pipemidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p. 328.3), but is more active *in vitro* against some bacteria, including *Pseudomonas aeruginosa*. It is used (as the trihydrate) in the treatment of urinary-tract infections in oral doses equivalent to 400 mg of the anhydrous substance twice daily.

Interactions. For the effect of pipemidic acid on the clearance of xanthines, see under Caffeine, p. 1206.1, and Theophylline, p. 1234.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Finuret; Memento; Priper; ***Braz.***: Balurol; Elofuran; Pipram; Pipurol; Uroxina; ***Chile***: Purid; Uropimide; ***Fr.***: Pipram; ***Ger.***: Deblaston†; ***Gr.***: Diflogin; Pipram; ***Hong Kong***: Urotractin; ***Indon.***: Impresial; Urinter; Urixin; Urotractin; Utrex†; ***Ital.***: Biosoviran†; Cistomid; Diperpen; Faremid; Pipefort; Pipemid; Pipram; Pipurin; Urodene†; Uropimid; Urosan; Urotractin; ***Jpn***: Dolcol; ***Malaysia***: Urotractin; ***Mex.***: Uripiser; Uronovag; Uropipemid; ***Neth.***: Pipram; ***Philipp.***: Urixin†; ***Pol.***: Palin; Urolin†; ***Rus.***: Palin (Палин); Pilamin (Пиламин); Pimidel (Пимидель); Pipegal (Пипегал); Pipelin (Пипелин); Uropimid (Уропимид); Urotractin (Уротрактин); ***S. Afr.***: Deblaston; ***Singapore***: Urotractin; ***Spain***: Galusan; Nuril; Urisan; Uropipedil†; ***Thai.***: Pipedic; Urotractin; ***Ukr.***: Palin (Палин); Pimidel (Пимидел); Pipemidin (Пипемидин).

Multi-ingredient Preparations. ***Arg.***: Priper Plus.

Piperacillin *(BAN, rINN)*

Piperacilin monohydrát; Piperacilina; Piperacilinas; Pipéracilline; Piperacillinum; Piperacillinum Monohydricum; Piperasilliini; Пиперациллин.

(6*R*)-6-[*R*-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]penicillanic acid monohydrate; 3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate.

$C_{23}H_{27}N_5O_7S,H_2O$=535.6

CAS — 61477-96-1 (anhydrous piperacillin); 66258-76-2 (piperacillin monohydrate).

ATC — J01CA12.

ATC Vet — QJ01CA12.

UNII — X00B0D5O0E (piperacillin); 9I628532GX (anhydrous piperacillin).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Piperacillin). A white or almost white powder. Slightly soluble in water and in ethyl acetate; freely soluble in methyl alcohol.

USP 36: (Piperacillin). A white to off-white crystalline powder. Practically insoluble to very slightly soluble in water; very slightly soluble in ethyl acetate; slightly soluble in isopropyl alcohol; very soluble in methyl alcohol.

Piperacillin Sodium *(BANM, USAN, rINNM)*

CL-227193; Natrii Piperacillinum; Piperacilin sodná sůl; Piperacilina sódica; Piperacilino natrio druska; Piperacillin-Natrium; Pipéracilline Sodique; Piperacillin-nátrium; Piperacillinnatrium natricum; Piperacillinum; Piperacillinum natricum; Piperacylina sodowa; Piperasilin Sodyum; Piperasilliininatrium; T-1220; Натрий Пиперациллин.

$C_{23}H_{26}N_5NaO_7S$=539.5

CAS — 59703-84-3.

ATC — J01CA12.

ATC Vet — QJ01CA12.

UNII — M98T69Q7HP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Piperacillin Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in ethyl acetate. A 10% solution in water has a pH of 5.0 to 7.0. Store in airtight containers.

USP 36: (Piperacillin Sodium). A white to off-white solid. Freely soluble in water and in alcohol. pH of a 40% solution in water is between 5.5 and 7.5. Store in airtight containers.

Incompatibility. Piperacillin sodium has been reported to be incompatible with aminoglycosides and sodium bicarbonate.

A formulation of piperacillin plus tazobactam containing edetic and citric acids (*Tazocin, Zosyn*) is considered compatible with lactated Ringer's solution, as well as some aminoglycosides at specific concentrations, whereas formulations without these additives are not compatible.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; **35:** 1360–3.

Uses and Administration

Piperacillin is a ureidopenicillin that is used similarly to ticarcillin (p. 380.2) for the treatment of infections caused by *Pseudomonas aeruginosa*, and also infections due to other susceptible bacteria. It has been used particularly in immunocompromised patients (neutropenic patients) and for biliary-tract infections (cholangitis). Other indications have included uncomplicated gonorrhoea due to penicillin-sensitive gonococci, and urinary-tract infections. It has also been used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2. For the treatment of serious infections piperacillin is commonly used with an aminoglycoside, but they should be given separately because of possible incompatibility.

Piperacillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of piperacillin; 1.04 g of piperacillin sodium is equivalent to about 1 g of piperacillin. Doses should generally be reduced in moderate to severe renal impairment (see p. 342.3).

Piperacillin may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 20 to 30 minutes, or by deep intramuscular injection. Single doses of more than 2 g should not be given by the intramuscular route. For information on extended infusions of piperacillin with tazobactam see p. 342.2.

For the treatment of serious or complicated infections, piperacillin 200 to 300 mg/kg daily may be given in divided doses intravenously; the usual dose is 3 to 4 g every 4 or 6 hours. In life-threatening infections, particularly those caused by *Pseudomonas* or *Klebsiella* spp., it should be given in a dose of not less than 16 g daily. The usual maximum daily dose is 24 g, although this has been exceeded.

For mild or uncomplicated infections, 100 to 125 mg/kg daily may be given; usual doses are 2 g every 6 or 8 hours, or 4 g every 12 hours, intravenously, or 2 g every 8 or 12 hours intramuscularly.

Uncomplicated gonorrhoea may be treated by a single intramuscular dose of 2 g. Probenecid 1 g may be given orally 30 minutes before the injection.

For the prophylaxis of infection during surgery, 2 g just before the procedure, or when the umbilical cord is clamped in caesarean section, followed by at least 2 doses of 2 g at intervals of 4 or 6 hours within 24 hours of the procedure, may be given.

Piperacillin with tazobactam. Piperacillin is frequently used with tazobactam (p. 371.3), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. The combination is given intravenously in a ratio of piperacillin (as the sodium salt) 8 parts to 1 part of tazobactam (as the sodium salt). The usual recommended dose (expressed as the combined amount of piperacillin and tazobactam) is 4.5 g given every 8 hours or 3.375 g given every 6 hours. For nosocomial pneumonia, bacterial infections in neutropenic patients, and other severe infections a dose of 4.5 g may be given every 6 hours.

For details of dosing in children for both piperacillin and piperacillin plus tazobactam, see p. 342.2.

References.

1. Greenwood D, Finch RG, eds. Piperacillin/tazobactam: a new β-lactam/β-lactamase inhibitor combination. *J Antimicrob Chemother* 1993; **31** (suppl A): 1–124.
2. Schoonover LL, *et al*. Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother* 1995; **29:** 501–14.
3. Perry CM, Markham A. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs* 1999; **57:** 805–43.
4. Kotapati S, *et al*. The clinical and economic benefits of administering piperacillin-tazobactam by continuous infusion. *Intensive Crit Care Nurs* 2005; **21:** 87–93.
5. Gin A, *et al*. Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. *Expert Rev Anti Infect Ther* 2007; **5:** 365–83.

Administration. There is evidence from *in-vitro*, *animal*, and some small clinical studies that intravenous infusions of piperacillin-tazobactam given over extended periods (4 hours instead of the recommended 30 minutes) enhances the pharmacodynamic profile of piperacillin-tazobactam, by extending the time the free drug level remains above the minimum inhibitory concentration. For these studies a dose regimen of 3.375 g every 8 hours as a 4-hour infusion was commonly given.[1] This dose may, however, not be adequate for isolates with minimum inhibitory concentrations of ≥32 micrograms/mL (such as *Pseudomonas aeruginosa*), and for these organisms a dose of 4.5 g given every 6 hours as a 3-hour infusion has been suggested.[1]

1. Kaufman SE, *et al*. Rationale and evidence for extended infusion of piperacillin-tazobactam. *Am J Health-Syst Pharm* 2011; **68:** 1521–6.

Administration in children. Piperacillin has been given alone, or with tazobactam to neonates and children for the treatment of infections caused by susceptible organisms.

Piperacillin. Although it is not licensed for use in children under 12 years of age in the USA, the American Academy of Pediatrics (AAP)[1] suggests intramuscular or intravenous doses of 200 mg/kg daily in 3 or 4 divided doses for mild to moderate infections in children 1 month of age and older; for severe infections, the dose may be increased to 300 to 400 mg/kg daily in 4 to 6 divided doses.

Piperacillin plus tazobactam. Piperacillin has also been given with tazobactam to paediatric patients.[2] In the UK, the combination of piperacillin plus tazobactam is not licensed for use in children under 12 years of age *except* for those with neutropenia or complicated intra-abdominal infections. Despite this, it has been used for a number of other indications. The *BNFC* recommends the following doses (expressed as the combined amount of piperacillin and tazobactam) by intravenous infusion over 30 minutes.

For **hospital-acquired pneumonia, septicaemia, complicated infections involving the urinary-tract or skin and soft tissues**:

- neonates: 90 mg/kg every 8 hours
- children 1 month to 12 years of age: 90 mg/kg every 6 to 8 hours (maximum 4.5 g every 6 hours)
- children from 12 years of age: 4.5 g every 8 hours, increased to 4.5 g every 6 hours in severe infection

For infections in children with **neutropenia**:

- children from 1 month of age: 90 mg/kg (maximum 4.5 g) every 6 hours

For **complicated intra-abdominal infections**:

- children from 2 to 12 years of age: 112.5 mg/kg (maximum 4.5 g) every 8 hours
- children from 12 years of age: 4.5 g every 8 hours, increased to 4.5 g every 6 hours in severe infection

Alternatively, the AAP[1] recommends the following intravenous doses [based on piperacillin component]:

- for neonates aged 7 days or less: 100 mg/kg every 12 hours
- for neonates aged 8 to 28 days: 100 mg/kg every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for children beyond the newborn period: 300 mg/kg daily in 3 divided doses; a lower daily dose of 240 mg/kg is recommended for those 2 to 9 months of age.

The AAP[1] does not recommend the use of piperacillin plus tazobactam in mild to moderate infection.

Doses of piperacillin plus tazobactam may need to be adjusted in children with renal impairment; for further information see p. 342.3.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Wolf MF, Simon A. The use of piperacillin-tazobactam in neonatal and paediatric patients. *Expert Opin Drug Metab Toxicol* 2009; **5:** 57–69.

Administration in renal impairment. Doses of *piperacillin* should be reduced in moderate to severe renal impairment; for serious infections in adults, the following maximum doses for intravenous or intramuscular use have been recommended based on creatinine clearance (CC):

- CC 20 to 40 mL/min: 4 g every 8 hours
- CC less than 20 mL/min: 4 g every 12 hours
- haemodialysis patients: 2 g every 8 hours, with an additional dose of 1 g given after each haemodialysis run

For *piperacillin plus tazobactam*, UK licensed product information recommends the following maximum intravenous doses (expressed as the combined amount of piperacillin and tazobactam) in renal impairment, based on CC:

Adults:

- CC 20 to 40 mL/min: 4.5 g every 8 hours
- CC less than 20 mL/min: 4.5 g every 12 hours
- haemodialysis patients: an additional 2.25-g dose should be given after each dialysis run

Children:

- CC ≤ 50 mL/min: 78.75 mg/kg every 8 hours
- haemodialysis patients: an additional 45-mg/kg dose should be given after each dialysis run

In a review,[1] the following doses, expressed as the combined amount of piperacillin and tazobactam, were recommended for critically ill adults undergoing different types of renal replacement therapy:

- continuous venovenous haemofiltration (CVVH): 2.25 to 3.375 g every 6 to 8 hours
- continuous venovenous haemodialysis (CVVHD): 2.25 to 3.375 g every 6 hours
- continuous venovenous haemodiafiltration (CVVHDF): 3.375 g every 6 hours
- intermittent haemodialysis: 2.25 g every 8 to 12 hours

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 232.1.

Prolongation of bleeding time has been less frequent and less severe with piperacillin than with carbenicillin. Like other penicillins, piperacillin may interfere with some diagnostic tests (see Precautions for Benzylpenicillin, p. 229.3); additionally, false-positive tests for *Aspergillus* infection have been reported in patients given piperacillin plus tazobactam.

Effects on the blood. References.

1. Peralta FG, *et al*. Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis* 2003; **37:** 1568–72.
2. Scheetz MH, *et al*. Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; **30:** 295–306.
3. Garcia Gala JM, *et al*. Immune hemolysis due to piperacillin/tazobactam. *Transfus Apher Sci* 2009; **40:** 97–8.

4. Mayer B, *et al*. Piperacillin-induced immune hemolysis: new cases and a concise review of the literature. *Transfusion* 2010; **50:** 1135–8.

Hypersensitivity. In the mid 1980s there were reports of a relatively high incidence of adverse reactions to piperacillin, especially fever, in patients with cystic fibrosis.[1-3] However, the manufacturers[4] considered such patients to be particularly prone to allergy and cited reactions with other semisynthetic penicillins including carbenicillin and azlocillin.

Similar apparent hypersensitivity reactions have been reported in patients taking high doses of piperacillin and other ureidopenicillins, over long periods for other indications,[5] and with other penicillins in patients with cystic fibrosis,[6] although piperacillin does appear to be most frequently implicated.[6]

1. Stead RJ, *et al*. Adverse reactions to piperacillin in cystic fibrosis. *Lancet* 1984; **i:** 857–8.
2. Strandvik B. Adverse reactions to piperacillin in patients with cystic fibrosis. *Lancet* 1984; **i:** 1362.
3. Stead RJ, *et al*. Adverse reactions to piperacillin in adults with cystic fibrosis. *Thorax* 1985; **40:** 184–6.
4. Brock PG, Roach M. Adverse reactions to piperacillin in cystic fibrosis. *Lancet* 1984; **i:** 1070–1.
5. Lang R, *et al*. Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. *Rev Infect Dis* 1991; **13:** 68–72.
6. Pleasants RA, *et al*. Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. *Chest* 1994; **106:** 1124–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piperacillin as not porphyrinogenic and the combination of piperacillin with tazobactam as probably not porphyrinogenic; both may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of piperacillin sodium contains about 1.85 mmol of sodium. As piperacillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Products containing piperacillin plus tazobactam contain about 2.36 mmol of sodium for each g of the piperacillin component; when the product is formulated with edetic acid the sodium content is higher (about 2.36 mmol sodium per g).

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterials. For the effect of piperacillin on *flucloxacillin*, see p. 300.1.

Neuromuscular blockers. Piperacillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p. 2032.1).

Antimicrobial Action

Piperacillin has a similar antimicrobial action to carbenicillin (p. 232.1) and ticarcillin (p. 381.1), but is active against a wider range of Gram-negative organisms, including *Klebsiella pneumoniae*. It is also generally more active *in vitro*, especially against *Pseudomonas aeruginosa* and the Enterobacteriaceae, against Gram-positive *Enterococcus faecalis*, and possibly against *Bacteroides fragilis*. There is, however, an inoculum effect, i.e. minimum inhibitory concentrations of piperacillin increase with the size of the inoculum.

Combinations of piperacillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae. The effect of using piperacillin with other beta lactams has been less predictable.

The activity of piperacillin against some organisms, resistant because of the production of beta-lactamases, may be restored by tazobactam, a beta-lactamase inhibitor. Such organisms include beta-lactamase-producing strains of staphylococci, *Escherichia coli*, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of piperacillin against *Ps. aeruginosa* is not enhanced by tazobactam.

Resistance has developed in *Ps. aeruginosa* during treatment with piperacillin, especially when used alone. There may be some cross-resistance with other antipseudomonal penicillins.

References.

1. Higashitani F, *et al*. Inhibition of β-lactamases by tazobactam and in-vitro antibacterial activity of tazobactam combined with piperacillin. *J Antimicrob Chemother* 1990; **25:** 567–74.
2. Mehtar S, *et al*. The in-vitro activity of piperacillin/tazobactam, ciprofloxacin, ceftazidime and imipenem against multiple resistant Gram-negative bacteria. *J Antimicrob Chemother* 1990; **25:** 915–19.
3. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; **26:** 598–9.
4. Kadima TA, Weiner JH. Mechanism of suppression of piperacillin resistance in enterobacteria by tazobactam. *Antimicrob Agents Chemother* 1997; **41:** 2177–83.
5. Klepser ME, *et al*. Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; **41:** 435–9.
6. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing Enterobacteriaceae: the role of piperacillin-tazobactam. *Clin Microbiol Infect* 2008; **14** (suppl 1): 181–4. Correction. *ibid.*; (suppl 5): 21–4.

Pharmacokinetics

Piperacillin is not absorbed from the gastrointestinal tract. It is well absorbed after intramuscular use and peak plasma concentrations of 30 to 40 micrograms/mL occur 30 to 50 minutes after a 2-g dose. The pharmacokinetics of piperacillin are reported to be nonlinear and dose-dependent. The plasma half-life is about 1 hour, but is prolonged in neonates. In patients with severe renal impairment there may be a threefold increase in half-life; in those with end-stage renal failure half-lives of 4 to 6 hours have been reported, and in those with both renal and hepatic impairment much longer half-lives may result. About 20% of piperacillin in the circulation is bound to plasma proteins.

Piperacillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

About 60 to 80% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours, achieving high concentrations. High concentrations also occur in the bile and up to 20% of a dose may be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Piperacillin is removed by haemodialysis.

Piperacillin with tazobactam. The pharmacokinetics of piperacillin do not appear to be altered by tazobactam, but piperacillin reduces the renal clearance of tazobactam.

References.

1. Heikkilä A, Erkkola R. Pharmacokinetics of piperacillin during pregnancy. *J Antimicrob Chemother* 1991; **28:** 419–23.
2. Wise R, *et al*. Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. *Antimicrob Agents Chemother* 1991; **35:** 1081–4.
3. Johnson CA, *et al*. Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. *Clin Pharmacol Ther* 1992; **51:** 32–41.
4. Dupon M, *et al*. Plasma levels of piperacillin and vancomycin used as prophylaxis in liver transplant patients. *Eur J Clin Pharmacol* 1993; **45:** 529–34.
5. Sörgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J Antimicrob Chemother* 1993; **31** (suppl A): 39–60.
6. Reed MD, *et al*. Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother* 1994; **38:** 2817–26.
7. Bourget P, *et al*. Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. *Antimicrob Agents Chemother* 1996; **40:** 139–45.
8. Occhipinti DJ, *et al*. Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. *Antimicrob Agents Chemother* 1997; **41:** 2511–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Petezam; ***Gr.***: Pipril; Zobactam; Zoracilin; ***India***: Pipracil; ***Israel***: Pipracin; ***Ital.***: Cilpier; Ecosette; Farecillin; Peracil; Picillin; Piperital; Pipersal; Pipertex; Reparcillin; Semipenil; ***Jpn***: Pentcillin; ***Thai.***: Peracin†; Pipracil; ***Turk.***: Pipraks.

Multi-ingredient Preparations. ***Arg.***: Pipetexina; Tazonam; Vredian; ***Austral.***: PiperTaz; Tazocin; Tazopip; ***Austria***: Pipitaz; Tazonam; ***Belg.***: Tazocin; ***Braz.***: Tazocilina; Tazocin; ***Canad.***: Tazocin; ***Chile***: Aurotaz-P; Tazonam; ***China***: An Di Tai (安迪泰); Bai Ding (百定); Bang Da (邦达); Caryn (凯伦); Fengtailing (锋泰灵); Haitaxin (海他欣); Kang De Li (康得力); Li Ke Duo (力可多); Pai Shu (派纾); Tazocin (特治星); Xintemie (新特灭); Yi Jun (一君); Yi Tan (益坦); ***Cz.***: Tazabax; Tazip; Tazocin; Tazopet; Tazoratio; Tebranic; ***Denm.***: Tazocin; ***Fin.***: Tazocin; ***Fr.***: Tazocilline; ***Ger.***: Tazobac; ***Gr.***: Bactalin; Gramenox; Oliten; Tavoctame; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong***: Tazocin; ***Hung.***: Tazocin; ***India***: Adzopip; Ampip-T; Baclin; Boxter; Cadipip; Cidal; Cinpip-TZ; Combiwin; Cureact; Durataz; Elzox; Europep-T; Everpip-TZ; Forpep; Gotaz; Gramotaz; Hoslin; Infocer; Inforcer; Ip-Taz; Jope; Kombat; KPT; Lazocin Forte; Lazopip; Lintaz; Lupitaz; Matlin; Medipip; Megacillin; Mezobact-P; Microtaz; Monal; Olin; Pactum; Tazact; Tazofast; Tazopen; Zosyn; ***Indon.***: Tazocin; ***Irl.***: Pipercin; Piperin; Tazocin; ***Israel***: Tazocillin; Tazocin; Tazopip; Tazorex; ***Ital.***: Ibitazina; Limerick; Tazobac; Tazocin; Tazopenil; ***Jpn***: Zosyn; ***Malaysia***: Tazocin; ***Mex.***: Tasovak; Tazocin; Tazpen; ***Neth.***: Tazocin; ***Norw.***: Piptazira; Tazocin; ***NZ***: Tazocin; ***Philipp.***: Bactaz; Peprasan-T; Piptaz; Pizobac; Pletzolyn; Tanzo; Tapimycin; Tazobak; Tazocin; Tazolin†; Tazopen; Tazotaz; Tebranic; Vigocid; ***Pol.***: Tazacylin; Tazocin; Tazoratio; ***Port.***: Tazobac; ***Rus.***: Tacillin-J (Тациллин ДЖ); Tazocin (Тазоцин); ***S.Afr.***: Curitaz; Tazobax; Tazocin; ***Singapore***: Tazocin; Tazpen; ***Spain***: Tazocel; ***Swed.***: Tazocin†; ***Switz.***: Tazobac; ***Thai.***: Astaz-P; Pipertaz; Tazocin; Tazrobida; Tebranic; ***Turk.***: Tazocin; Tazoper; ***UK***: Tazocin; ***Ukr.***: Tazar (Тазар); Zopercin (Зоперцин); ***USA***: Zosyn; ***Venez.***: Tazopril; Tazpen.

Pharmacopoeial Preparations

BP 2014: Piperacillin Infusion;

USP 36: Piperacillin and Tazobactam for Injection; Piperacillin for Injection.

Pirlimycin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de pirlimicina; Pirlimicina, hidrocloruro de; Pirlimycine, Chlorhydrate de; Pirlimycinhydroklorid; Pirlimycini Hydrochloridum; Pirlimysiinihydrokloridi; U-57930E; Пирлимицина Гидрохлорид.

Methyl 7-chloro-6,7,8-trideoxy-6-(*cis*-4-ethyl-L-pipecolamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside monohydrochloride monohydrate.

$C_{17}H_{31}ClN_2O_5S,HCl,H_2O$=465.4

CAS — 79548-73-5 (pirlimycin); 77495-92-2 (pirlimycin hydrochloride).

UNII — 8S09O559AQ.

NOTE. The name Pirsue has been used as a trade mark for pirlimycin hydrochloride.

Profile

Pirlimycin is a lincosamide antibacterial used in veterinary medicine.

Piromidic Acid *(rINN)*

Acide Piromidique; Ácido piromídico; Acidum Piromidicum; PD-93; Piromídico, ácido; Piromidihappo; Piromidsyra; Пиромидовая Кислота.

8-Ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

$C_{14}H_{16}N_4O_3$=288.3

CAS — 19562-30-2.

ATC — J01MB03.

ATC Vet — QJ01MB03.

UNII — 3I12WH4EWF.

Profile

Piromidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p. 328.3). It has been used in the treatment of susceptible infections. There have been several reports of acute renal failure associated with piromidic acid.

Pivampicillin *(BAN, rINN)*

MK-191; Pivampicilin; Pivampicilina; Pivampicilinas; Pivampicilline; Pivampicillinum; Pivampisilliini; Пивампициллин.

Pivaloyloxymethyl (6*R*)-6-(α-D-phenylglycylamino)penicillanate.

$C_{22}H_{29}N_3O_6S$=463.5

CAS — 33817-20-8.

ATC — J01CA02.

ATC Vet — QJ01CA02.

UNII — 0HLM346LL7.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pivampicillin). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in methyl alcohol. It dissolves in dilute acids. Store in airtight containers.

Pivampicillin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de pivampicilina; Pivampicilina, hidrocloruro de; Pivampicilline, Chlorhydrate de; Pivampicillini Hydrochloridum; Пивампициллина Гидрохлорид.

$C_{22}H_{29}N_3O_6S,HCl$=500.0

CAS — 26309-95-5.

ATC — J01CA02.

ATC Vet — QJ01CA02.

UNII — V9HOC53L7L.

Uses and Administration

Pivampicillin is the pivaloyloxymethyl ester of ampicillin (p. 218.3) and has similar uses; 1.3 g of pivampicillin and 1.43 g of pivampicillin hydrochloride are each equivalent to about 1 g of ampicillin. Pivampicillin is given in usual oral doses of 350 to 700 mg 3 or 4 times daily; if necessary, the dose may be increased to 1 g orally 3 times daily.

In areas where gonococci remain sensitive a single dose of 1.4 g is given for gonorrhoea, with probenecid 1 g.

For details of doses in children, see p. 344.1.

Pivampicillin hydrochloride has been used in some countries.

Pivampicillin has also been given with pivmecillinam (p. 344.1).

Administration in children. Pivampicillin may be used orally in children for the treatment of susceptible infections. An oral dose of 35 to 70 mg/kg daily in 3 divided doses has been suggested for children up to 6 years of age; those older than 6 years may be dosed as for adults (see p. 341.3).

Adverse Effects and Precautions

As for Ampicillin, p. 219.2. Pivampicillin is reported to cause a lower incidence of diarrhoea than ampicillin. Upper gastrointestinal discomfort may be more frequent when pivampicillin is taken on an empty stomach.

Pivaloyloxymethyl esters such as pivampicillin have been associated with the induction of carnitine deficiency (see p. 344.1).

Carnitine deficiency. Carnitine deficiency (see p. 2053.3) has been reported after the use of pivampicillin and pivmecillinam.[1] It is thought that the pivalic acid liberated on hydrolysis of these pivaloyloxymethyl esters *in vivo* is excreted as pivaloyl-carnitine with a consequent depletion in plasma and muscle concentrations of carnitine.[2] Low plasma-carnitine concentrations persisted in a patient after stopping pivampicillin, despite 6 weeks of replacement therapy with oral carnitine 1g daily. She had originally presented with skeletal myopathy when given pivampicillin for 3 months. A more intensive carnitine replacement regimen might be necessary in such patients.[3]

1. Holme E, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy. *Lancet* 1989; **ii:** 469–73.
2. Anonymous. Carnitine deficiency. *Lancet* 1990; **335:** 631–3.
3. Rose SJ, *et al.* Carnitine deficiency associated with long-term pivampicillin treatment: the effect of a replacement therapy regime. *Postgrad Med J* 1992; **68:** 932–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pivampicillin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Benzylpenicillin, p. 230.1.

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving pivampicillin (or pivmecillinam) and valproate; use of either antibacterial with valproate or medications that liberate pivalic acid should be avoided.

Antimicrobial Action

Pivampicillin has the antimicrobial activity of ampicillin to which it is hydrolysed *in vivo* (p. 219.3).

Pharmacokinetics

Pivampicillin is acid-stable and is readily absorbed from the gastrointestinal tract. On absorption it is rapidly and almost completely hydrolysed to ampicillin, pivalic acid, and formaldehyde. Plasma-ampicillin concentrations 1 hour after a dose are 2 to 3 times those attained after an equivalent dose of ampicillin. The absorption of pivampicillin is generally not significantly affected by food. About 70% of a dose is excreted in the urine as ampicillin within 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Pondocillin; ***Fr.***: Proampi†.

Pivmecillinam *(BAN, rINN)*

Amdinocillin Pivoxil (USAN); FL-1039; Pivamdinocillin; Pivmecilinam; Pivmécillinam; Pivmecillinamum; Pivmesillinaami; Ro-10-9071; Пивмециллинам.

Pivaloyloxymethyl (6*R*)-6-(perhydroazepin-1-ylmethyleneamino)penicillanate.

$C_{21}H_{33}N_3O_5S$=439.6

CAS — 32886-97-8.

ATC — J01CA08.

ATC Vet — QJ01CA08.

UNII — 1WAM1OQ30B.

Pivmecillinam Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pivmecilinam; Pivmecilinam, hidrocloruro de; Pivmecilinam-hydrochlorid; Pivmecilinamo hidrochloridas; Pivmécillinam, Chlorhydrate de; Pivmecillinám-hidroklorid; Pivmecillinamhydrochlorid; Pivmecillinamhydroklorid; Pivmecillinami Hydrochloridum; Pivmesillinaamihydrokloridi; Пивмециллинама Гидрохлорид.

$C_{21}H_{33}N_3O_5S,HCl$=476.0

CAS — 32887-03-9.

ATC — J01CA08.

ATC Vet — QJ01CA08.

UNII — 48FX7N21H2.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Pivmecillinam Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in dehydrated alcohol, and in methyl alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 2.8 to 3.8. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Pivmecillinam is the pivaloyloxymethyl ester of mecillinam (p. 321.1), to which it is hydrolysed after oral dosage. It is used in the treatment of urinary-tract infections (p. 213.1).

Doses of pivmecillinam have often been expressed in a confusing manner since no differentiation has been made between the hydrochloride, used in tablets, and the base, used in suspensions for oral use. Pivmecillinam 1.35 g and pivmecillinam hydrochloride 1.46 g are each equivalent to about 1 g of mecillinam.

Pivmecillinam should preferably be taken with food (see also Administration, under Adverse Effects and Precautions, p. 344.2).

In acute uncomplicated cystitis, the initial dose is 400 mg orally followed by 200 mg three times daily for 8 doses. In chronic or recurrent bacteriuria, 400 mg may be given 3 or 4 times daily.

For details of doses in children, see p. 344.2.

Pivmecillinam has been given with other beta lactams, particularly pivampicillin (p. 341.3), to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro.*

For parenteral use, mecillinam is given.

References.

1. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000; **46** (suppl S1): 35–9.

Administration in children. Pivmecillinam may be used orally in children 3 months of age and older for the treatment of urinary-tract infections. In the UK, the *BNFC* recommends that for all urinary-tract infections in children weighing less than 40 kg, a dose of 5 to 10 mg/kg every 6 hours may be used; alternatively the total daily dose may be given in 3 divided doses. Children weighing more than 40 kg may be treated as for adults (see Uses and Administration, above).

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Pivaloyloxymethyl esters such as pivmecillinam have been associated with the induction of carnitine deficiency (see Pivampicillin, above).

Administration. Oesophageal injury has been associated rarely with pivmecillinam tablets.[1,2] Patients are advised to take them during a meal, while sitting or standing, and with at least half a glass of water.[3]

1. CSM. Pivmecillinam and oesophageal injury. *Current Problems 19* 1987. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024426&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)
2. Mortimer Ö, Wiholm B-E. Oesophageal injury associated with pivmecillinam tablets. *Eur J Clin Pharmacol* 1989; **37:** 605–7.
3. Anonymous. CSM warning on pivmecillinam. *Pharm J* 1987; **238:** 443.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pivmecillinam as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Pivampicillin, above.

Antimicrobial Action

Pivmecillinam has the antimicrobial activity of mecillinam (p. 321.1) to which it is hydrolysed *in vivo.*

Pharmacokinetics

Pivmecillinam is well absorbed from the gastrointestinal tract and is rapidly hydrolysed to the active drug mecillinam (p. 321.2), pivalic acid, and formaldehyde. The presence of food in the stomach does not appear to have a significant effect on absorption. Peak plasma concentrations of mecillinam of 5 micrograms/mL have been achieved 1 to 2 hours after a 400-mg dose of pivmecillinam.

About 45% of a dose may be excreted in the urine as mecillinam, mainly within the first 6 hours.

References.

1. Heikkilä A, *et al.* The pharmacokinetics of mecillinam and pivmecillinam in pregnant and non-pregnant women. *Br J Clin Pharmacol* 1992; **33:** 629–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Selexid; ***Canad.***: Selexid†; ***Denm.***: Penomax; Selexid; ***Fin.***: Penomax; Selexid; ***Fr.***: Selexid; ***Gr.***: Selexid; ***Norw.***: Penomax; Selexid; ***NZ***: Selexid; ***Port.***: Selexid; ***Swed.***: Penomax; Selexid; ***UK***: Selexid.

Polymyxin B Sulfate *(BANM, rINNM)*

Polimiksin B Sülfat; Polimiksino B sulfatas; Polimixin-B-szulfát; Polimixina B, sulfato de; Polimyksyny B siarczan; Polimyxini b sulfas; Polymyksiini-B-sulfaatti; Polymyxin B sulfat; Polymyxin B Sulphate; Polymyxin-B-sulfat; Polymyxin-B-sulfát; Polymyxine B, Sulfate de; Polymyxini B Sulfas; Polymyxinum B Sulfas; Sulfato de polimixina B; Полимиксина В Сульфат.

CAS — 1404-26-8 (polymyxin B); 1405-20-5 (polymyxin B sulfate); 4135-11-9 (polymyxin B1); 34503-87-2 (polymyxin B2); 71140-58-4 (polymyxin B3).

ATC — A07AA05; J01XB02; S01AA18; S02AA11; S03AA03.

ATC Vet — QA07AA05; QJ01XB02; QS01AA18; QS02AA11; QS03AA03.

UNII — 19371312D4 (polymyxin B sulfate); 57VAB21ZLF (polymyxin B1 sulfate); WTC2W6JDTU (polymyxin B2 sulfate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Polymyxin B Sulfate). A mixture of the sulfates of polypeptides produced by the growth of certain strains of *Bacillus polymyxa* or obtained by any other means. A white or almost white, hygroscopic powder. Soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 36: (Polymyxin B Sulfate). The sulfate salt of a kind of polymyxin, a substance produced by the growth of *Bacillus polymyxa* (Bacillaceae), or a mixture of two or more such salts. A white to buff-coloured, powder, odourless or has a faint odour. It has a potency of not less than 6000 Polymyxin B units/mg, calculated on the dried substance. Freely soluble in water; slightly soluble in alcohol. pH of a 0.5% solution in water is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported with many other drugs including antibacterials. Polymyxin B sulfate is rapidly inactivated by strong acids and alkalis.

Units

The second International Standard Preparation (1969) of polymyxin B sulfate contains 8403 units/mg.

NOTE. The available forms of polymyxin B sulfate are generally less pure than the International Standard Preparation. Doses have sometimes been stated in terms of pure polymyxin base; 100 mg of pure polymyxin B is considered to be equivalent to 1 million units (1 mega unit).

Uses and Administration

Polymyxin B sulfate is used topically, often with other drugs, in the treatment of skin, ear, and eye infections due to susceptible organisms. Eye drops containing polymyxin B with neomycin and gramicidin have been used for the prophylaxis of infection in patients undergoing ocular surgery and, with propamidine isetionate, for the treatment of acanthamoeba keratitis (p. 921.2). Polymyxin B has been given orally with other drugs in regimens for selective digestive-tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p. 187.3). Polymyxin B is also used parenterally for the treatment of infections due to susceptible Gram-negative bacteria, especially *Pseudomonas aeruginosa;* other drugs have generally been preferred but its use is increasing due to the emergence of multidrug resistant Gram-negative organisms. Polymyxin B has been given intrathecally in meningeal infection, by subconjunctival injection for eye infections, and by inhalation for the treatment of pneumonia.

For topical application polymyxin B is usually available as a 0.1% solution or ointment (10 000 units per mL or per g respectively) combined with other drugs. Intravenous doses

range from 15 000 to 25 000 units/kg daily, by infusion and may be given every 12 hours. The intramuscular route has also been used despite the severe pain which may be associated with it; doses range from 25 000 to 30 000 units/kg daily, and may be given every 4 or 6 hours.

Doses should be reduced in patients with renal impairment (see p. 345.1).

Intrathecal doses of 50 000 units may be given once daily for 3 to 4 days, then on alternate days for at least 2 weeks after the CSF cultures become negative.

For details of doses in children, see p. 345.1.

For subconjunctival injection, doses of up to 100 000 units daily may be used for infections of the cornea and conjunctiva.

References.

1. Evans ME, *et al*. Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant Gram-negative bacteria. *Ann Pharmacother* 1999; **33:** 960–7.
2. Falagas ME, *et al*. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Arnold TM, *et al*. Polymyxin antibiotics for gram-negative infections. *Am J Health-Syst Pharm* 2007; **64:** 819–26.
4. Zavascki AP, *et al*. Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. *J Antimicrob Chemother* 2007; **60:** 1206–15.
5. Kwa A, *et al*. Polymyxin B: similarities to and differences from colistin (polymyxin E). *Expert Rev Anti Infect Ther* 2007; **5:** 811–21.
6. Nation RL, Li J. Optimizing use of colistin and polymyxin B in the critically ill. *Semin Respir Crit Care Med* 2007; **28:** 604–14.
7. Michalopoulos A, Falagas ME. Colistin and polymyxin B in critical care. *Crit Care Clin* 2008; **24:** 377–91.
8. Yuan Z, Tam VH. Polymyxin B: a new strategy for multidrug-resistant Gram-negative organisms. *Expert Opin Invest Drugs* 2008; **17:** 661–8.
9. Molina J, *et al*. New information about the polymyxin/colistin class of antibiotics. *Expert Opin Pharmacother* 2009; **10:** 2811–28.
10. Velkov T, *et al*. Structure-activity relationships of polymyxin antibiotics. *J Med Chem* 2010; **53:** 1898–916.

Administration in children. Polymyxin B may be used parenterally in neonates and children for the treatment of infections caused by susceptible bacteria, particularly *Pseudomonas aeruginosa*, and intrathecally for the treatment of meningitis. Up to 40 000 units/kg daily of polymyxin sulfate may be given to infants with normal renal function by intravenous infusion or by intramuscular injection, although the latter is not recommended routinely because of severe pain at injection sites. Doses as high as 45 000 units/kg daily have been tried in premature and full-term neonates. For suggested doses in children with renal impairment see p. 345.1.

In children under 2 years of age, intrathecal doses of 20 000 units once daily for 3 to 4 days or 25 000 units on alternate days may be given, followed by the latter dose for at least 2 weeks after the CSF cultures become negative.

Older children may be given the usual adult dose (see Uses and Administration, p. 342.3).

Administration in renal impairment. Licensed product information recommends that parenteral doses of polymyxin sulfate should be reduced in adults and children with renal impairment; a maximum intravenous dose of 15 000 units/kg daily has been suggested. However, a small study[1] of 8 critically ill patients reported that polymyxin B given intravenously was eliminated mainly by non-renal pathways, and that total body clearance appears to be relatively insensitive to renal function. Others have suggested that the dose and/or frequency of intravenous polymyxin B do not need to be adjusted in patients with renal impairment.[2]

1. Zavascki AP, *et al*. Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin Infect Dis* 2008; **47:** 1298–1304.
2. Kwa AL, *et al*. Pharmacokinetics of polymyxin B in a patient with renal insufficiency: a case report. *Clin Infect Dis* 2011; **52:** 1280–1.

Adverse Effects, Treatment, and Precautions

When given parenterally, the major adverse effects of the polymyxins are dose-related neurotoxicity and nephrotoxicity. Hypersensitivity reactions are rare, although rashes and fever have been reported, and polymyxins cause histamine release, which may lead to bronchoconstriction and other anaphylactoid symptoms. Polymyxins should be avoided in patients with a history of hypersensitivity to any of the group.

Neurotoxic reactions can occur in up to 7% of patients with normal renal function and include peripheral effects such as circumoral and 'stocking-glove' pattern paraesthesias, visual disturbances, and dizziness, ataxia, confusion, drowsiness, and other CNS effects. The polymyxins are potent neuromuscular blockers, and respiratory paralysis and apnoea may result, especially in overdosage and in patients with renal impairment or pre-existing disorders of neuromuscular transmission such as myasthenia gravis, in whom particular care is needed; certain medications may also increase the risk (see Interactions, p. 345.2). Neostigmine or calcium salts are usually of little value in reversing neuromuscular blockade and artificial ventilation may be required if it develops.

Nephrotoxicity may occur in up to 20% of patients after parenteral use and may be marked by nitrogen retention, haematuria, proteinuria, and tubular necrosis. Electrolyte disturbances are common. Baseline renal function levels should be established before starting parenteral polymyxin B therapy and renal function and blood concentrations of polymyxins should be monitored frequently during therapy. Patients with pre-existing renal impairment and nitrogen retention are at particular risk and require dosage reduction. Signs of decreasing urine output and increasing nitrogen retention are an indication for stopping the drug in all patients. Although polymyxin B is said to be more nephrotoxic than colistin on a weight-for-weight basis, their effects on the kidney seem to be similar at therapeutically equivalent doses.

Polymyxin B is irritant; pain after intramuscular injection may be severe and thrombophlebitis can occur after intravenous injection. Meningeal irritation, manifest as fever, headache, stiff neck, and increased cell count and protein levels in the CSF, may follow intrathecal doses.

Ear drops containing polymyxins should not be used in patients with perforated ear drums, due to the increased risk of ototoxicity. Topical application to large areas of skin should be avoided because of the risk of systemic absorption resulting in neurotoxicity and nephrotoxicity, particularly in children, the elderly, and patients with renal impairment.

References.

1. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006; **10:** R27.
2. Wunsch H, *et al*. Polymyxin use associated with respiratory arrest. *Chest* 2012; **141:** 515–17.

Interactions

Polymyxins may enhance the action of neuromuscular blockers (p. 2032.1) possibly resulting in respiratory depression and apnoea, and concurrent use should be avoided. Additive neurotoxicity and/or nephrotoxicity may occur if polymyxins are given with other potentially neurotoxic and/or nephrotoxic drugs including aminoglycosides; concurrent use should also be avoided.

Antimicrobial Action

Polymyxin B and the other polymyxin antibacterials act primarily by binding to membrane phospholipids and disrupting the bacterial cytoplasmic membrane. Polymyxin B has a bactericidal action on most Gram-negative bacilli except *Proteus* spp. It is particularly effective against *Pseudomonas aeruginosa*. Of the other Gram-negative organisms, *Acinetobacter* spp., *Escherichia coli*, *Enterobacter* and *Klebsiella* spp., *Haemophilus influenzae*, *Bordetella pertussis*, *Salmonella*, and *Shigella* spp. are sensitive. Classical *Vibrio cholerae* 01 is sensitive but the El Tor and O139 biotypes are resistant. *Serratia*, *Burkholderia*, and *Providencia* spp., and *Bacteroides fragilis* are usually resistant. It is not active against *Neisseria* spp., obligate anaerobes, and Gram-positive bacteria. Some fungi such as *Coccidioides immitis* are susceptible but most are resistant.

Antimicrobial synergy has been reported with other drugs, including chloramphenicol, tetracyclines, and the sulfonamides and trimethoprim.

The action of polymyxin B is reduced by divalent cations such as calcium and magnesium, and so activity *in vivo* is less marked than *in vitro*.

Acquired resistance to polymyxin B is uncommon, although adaptive resistance may develop in enterobacteria exposed to sublethal concentrations. There is complete cross-resistance between polymyxin B and colistin.

Pharmacokinetics

Polymyxin B sulfate is not absorbed from the gastrointestinal tract, except in infants who may absorb up to 10% of a dose. It is not absorbed through mucous membranes, or intact or denuded skin.

Peak plasma concentrations after intramuscular injection usually occur within 2 hours, but are variable and polymyxin B sulfate is partially inactivated by serum. It is widely distributed and extensively bound to cell membranes in the tissues; it does not appear to be highly bound to serum proteins. Accumulation may occur after repeated doses. There is no diffusion into the CSF and it does not cross the placenta. Polymyxin B is reported to have a serum half-life of about 6 hours but this is prolonged in renal impairment; values of 2 to 3 days have been reported in patients with a creatinine clearance of less than 10 mL/minute.

Polymyxin B sulfate is excreted mainly by the kidneys by glomerular filtration, about 60% of a dose being recovered unchanged in the urine, but there is a time lag of 12 to 24 hours before polymyxin B is recovered in the urine.

Polymyxin B is not removed to an appreciable extent by peritoneal dialysis or haemodialysis.

References.

1. Zavascki AP, *et al*. Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin Infect Dis* 2008; **47:** 1298–304.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Aerosporin; ***Philipp.***: Aerosporin; ***Port.***: Oto-Synalar N.

Multi-ingredient Preparations. ***Arg.***: Belbar; Cristalomicina NF; Fangan Plus; Ginal Cent; Ginkan; Irix Biotic; Isoptomax; Linfol Cicatrizante; Mailen; Mini O; Neo Pelvicillin; Neoftalm Dexa; Neoftalm; Neolag; O-Biol P†; Otosporin L; Otosporin; Ovufem; Ovumix; Pantometil†; Pentol; Poenbioptal NF; Polygynax; Polyplex; Septigyn; Sincerum Biotic L; Trimepol D†; Trimepol†; Vagicural Plus; ***Austral.***: Neosporin†; ***Austria***: Otosporin; ***Belg.***: Dexa-Polyspectran New†; Maxitrol; Neobacitracine; Panotile; Polydexa; Polyspectran Gramicidine†; Polytrim; Predmycin P; Statrol†; Synalar Bi-Otic; Terra-Cortril + Polymyxine B; Terramycine + Polymyxine B; ***Braz.***: Anaseptil; Colpolase†; Elotin; Ginec; Lidosporin; Maxinom; Maxitrol; Nepodex; Otomixyn; Otosporin; Otosynalar; Panotil; Poliginax; Polipred; Polysporin†; Predmicin; Terramicina c/Polimixina; ***Canad.***: Ak Spor; Ak Trol; Antibiotic Cold Sore Ointment†; Antibiotic Cream; Antibiotic Ointment; Antibiotic Plus; Antibiotique Onguent†; Bacimyxin; Band-Aid Antibiotic Adhesive Bandages plus Antibiotic; Bioderm; Complete Antibiotic Ointment; Cortimyxin; Cortimyxin; Cortisporin; Cortisporin; Dioptrol; Diosporin†; Diosporin; Lidomyxin; Maxitrol; Neosporin; Neosporin; Neosporin; Optimyxin Plus; Optimyxin; Optimyxin; Ozonol Antibiotic Plus; PMS-Polytrimethoprim; Polyderm; Polysporin Complete; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polysporin; Polysporin; Polytopic; Polytopic; Polytrim; Spor-HC; Triple Antibiotic Ointment; ***Chile***: Dermabiotico; Gotalgic; Grifoftal-D†; Maxitrol†; Oftabiotico; Oftabiotico; Oticum; Otolisan; Otoseptil; ***China***: Poly Pred (帕利百); ***Cz.***: Maxitrol; Otosporin†; Polygynax; Pulpomixine†; ***Denm.***: Hydrocortison med Terramycin og Polymyxin-B; Terramycin Polymyxin B; ***Fin.***: Maxitrol; Polysporin†; Terra-Cortril P; ***Fr.***: Antibio-Synalar; Atebemyxine; Auricularum; Cebemyxine; Framyxone; Maxidrol; Panotile; Polydexa; Polyfra†; Polygynax Virgo; Polygynax; Pulpomixine; ***Ger.***: Dexa Polyspectran; Isopto Max; Polyspectran HC; Polyspectran; Polyspectran; ***Gr.***: Auricularum; Fotocollyre; Isopto Maxitrol; Neo-Dexacanol; Neopolymyx; Neosporin; Oxacycle-P; Paroticin; Polypictine; Statrol; Synalar; Terramycin w Polymyxin Otic; Terramycin with Polymyxin; Thilodexine-N; ***Hong Kong***: Aplosyn-Otic; Bacimyxin†; Cebemyxine; Maxitrol; Neosporin; Otosporin; Otozambon; Polycin†; Polydex-N; Polydexa; Polygynax; Polyneospin†; Polyoph; Polyspectran†; Terramycin with Polymyxin B; ***Hung.***: Otosporin; Polysport†; ***India***: Cadiprim; Chlormixin†; Decol-P; Derbec-N; Dexosyn Plus†; Eyclor-Dexa; Eyclor; Mycin; Neosporin-H; Neosporin-H; Neosporin; Neosporin; Ocupol-D; Ocupol; Oriprim-P; ***Indon.***: Inmatrol; Isotic Enpigi; Isotic Neolyson; Isotic Nepafrin†; Kenetrol†; Kloramixin D; Kloramixin; Liposin; Maxitrol; Nelicort; Neocortic; Neofen; Neosyd; Oregan; Osatrol†; Otilon; Otolin; Otopain; Otopraf; Otozambon; Polidemisin; Polifrisin; Terramycin Poly†; Tigalin; Ximex Optixitrol; ***Irl.***: Maxitrol; Otosporin; Polyfax; Predmycin-P; ***Israel***: Bamyxin; Desoren; Dex-Otic; Maxitrol; Phenimixin; Tarocidin D; Tarocidin; Terramycin†; ***Ital.***: Anauran; Cicatrene; Mixotone; ***Malaysia***: Bacitracin-N; Maxitrol; Oftalmotrim; Pocin G†; Pocin H; Terramycin; ***Mex.***: Alosol; Biodexan; Biofrin; Biotriamin†; Cortisporin; Dexsul; Hidropolicin†; Maxitrol; Neobacigrin; Neosporin; Neosporin; Polixin; Polixin; Poly-Micron; Rinadex Compuesto; Septilisin; Soperil; Soxaron; Sulned; Synalar N; Synalar O; Synalar Oftalmico†; Terramicina; Terraxin; Tribiot; ***Neth.***: Maxitrol†; Otosporin; Panotile; Polytrim; Synalar; Terra-Cortril met polymyxine-B; ***Norw.***: Maxitrol; Terra-Cortril Polymyxin B; Terramycin Polymyxin B; ***NZ***: Maxitrol; ***Philipp.***: Aceflo; Aplosyn-Otic; BNP Ointment; Cortisporin; Hydrospor; Ipodex; Iporam; Ircos; Isonep H; Isonep; Isore; Maxirap; Maxitrol; Maxoptic; Neodex-V; Neosporin; Novasorin; Postop; Postotic; Predmycin-P; Rapidax; Statrol†; Supravis; Synalar Otic; Syntemax; Terramycin Plus; Terramycin; Trimycin-H; Trimycin; Trispec; Vistacom; ***Pol.***: Atecortin; Dexadent; Maxibiotic; Maxitrol; Multibiotic; Neotopic†; Tribiotic; ***Port.***: Conjunctilone-S; Conjunctilone; Oftalmotrim; Otosporin; Polisulfade; Polydexa; ***Rus.***: Anauran (Анауран); Maxitrol (Макситрол); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилефрином); Polygynax (Полижинакс); ***S.Afr.***: Maxitrol; Otosporin; Polysporin†; Terra-Cortril†; Terramycin†; ***Singapore***: Maxitrol; Otosporin; Polybamycin; Polydexa; Polygynax; Predmycin-P†; Terramycin; ***Spain***: Bacisporin†; Blastoestimulina; Creanolona; Dermisone Tri Antibiotic; Liquipom Dexa Antibiotico†; Maxitrol; Oftalmotrim; Oftalmowell; Otix; Panotile†; Phonal; Poly Pred; Pomada Antibiotica; Synalar Nasal; Synalar Otico; Terra-Cortril; Terramicina; Tivitis†; Tulgrasum Antibiotico; Vinciseptil Otico; ***Swed.***: Terracortril med polymyxin B; Terramycin Polymyxin B†; ***Switz.***: Baneopol†; Maxitrol; Mycinopred†; Neosporin; Otosporin†; Panotile; Polydexa; Spersapolymyxin; ***Thai.***: Banocin; Maxitrol; My-B; Otosamthong†; Polyoph; Predmycin P; SM Oto; Spersapolymyxin†; Terramycin; Xanalin; ***Turk.***: Cebemyxine; Geotril†; Heksa; Neosporin; Oftalmotrim†; Polimisin; Polycilline†; Polytrim; Sekamisin†; Terramycin; Vitacillin; ***UK***: Maxitrol; Neosporin†; Otosporin†; Polyfax; ***Ukr.***: Aprolat (Апролат); Maxitrol (Макситрол); Neladex (Неладекс); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилэфрином); Polygynax (Полижинакс); ***USA***: Ak-Poly-Bac; Cortatrigen; Cortimycin; Cortimycin; Cortisporin; Dexasporin†; Ear-Eze†; LazerSporin-C; Maxitrol; Neocin; Neopolydex; Neosporin + Pain Relief; Neosporin + Pain Relief; Neosporin GU; Neosporin; Neotricin HC†; Ocu-Spor-B; Ocu-Spor-G; Ocu-Trol; Ocutricin;

Ocutricin; Otic-Care; OtiTricin; Otobiotic; Otocort; Otomycin-HPN; Otosporin; Pediotic†; Poly-Dex; Poly-Pred†; Polycin-B; Polymycin; Polymycin; Polysporin; Polytracin; Polytrim; ProCo-Mycin; Terak; Terramycin with Polymyxin B; Tri-Biozene; UAD-Otic; ***Venez.***: Dermabiotic; Maxicort; Maxitrol; Ofterra; Otocort; Poli-Otico; Terramicina con Polimixina B.

Pharmacopoeial Preparations

BP 2014: Polymyxin and Bacitracin Eye Ointment; Polymyxin and Bacitracin Ointment;

USP 36: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Polymyxin B for Injection; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder; Polymyxin B Sulfate and Hydrocortisone Otic Solution; Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution.

Pristinamycin *(BAN, rINN)*

Pristinamicina; Pristinamycine; Pristinamycinum; RP-7293; Пристинамицин.

CAS — 270076-60-3.
ATC — J01FG01.
ATC Vet — QJ01FG01.

Profile

Pristinamycin is a streptogramin antibacterial produced by the growth of *Streptomyces pristina spiralis*, with actions and uses similar to those of virginiamycin (p. 389.3). It is given orally in the treatment of susceptible infections, particularly staphylococcal infections, in a dose of 2 to 4 g daily in divided doses.

Pristinamycin is a naturally occurring mixture of two synergistic components, pristinamycin I which is a macrolide, and pristinamycin II which is a depsipeptide.[1] It has been available for many years as an oral antistaphylococcal drug, and also acts against streptococci. It is effective against strains showing resistance to erythromycin; resistance to pristinamycin is rare,[2,3] although resistance in staphylococci has been reported in the past.[4,5] It is effective against meticillin-resistant *Staphylococcus aureus* (MRSA)[6,7] and other multidrug-resistant Gram-positive organisms,[8] but its usefulness in severe infection is limited by its poor solubility, which prevents development of an intravenous formulation. Oral pristinamycin has been shown to be as effective as standard therapy with intravenous then oral penicillin in the treatment of erysipelas.[9]

Mixtures of water-soluble derivatives of pristinamycins I and II, such as quinupristin/dalfopristin (p. 349.1), are in clinical use or under investigation.

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2. Weber P. Streptococcus pneumoniae: absence d'émergence de résistance à la pristinamycine. *Pathol Biol (Paris)* 2001; **49:** 840–5.
3. Leclercq R, *et al.* Activité in vitro de la pristinamycine vis-àvis des staphylocoques isolés dans les hôpitaux français en 1999-2000. *Pathol Biol (Paris)* 2003; **51:** 400–4.
4. Loncle V, *et al.* Analysis of pristinamycin-resistant Staphylococcus epidermidis isolates responsible for an outbreak in a Parisian hospital. *Antimicrob Agents Chemother* 1993; **37:** 2159–65.
5. Allignet J, *et al.* Distribution of genes encoding resistance to streptogramin A and related compounds among staphylococci resistant to these antibiotics. *Antimicrob Agents Chemother* 1996; **40:** 2523–8.
6. Dancer SJ, *et al.* Oral streptogramins in the management of patients with methicillin-resistant Staphylococcus aureus (MRSA) infections. *J Antimicrob Chemother* 2003; **51:** 731–5.
7. Ng J, Gosbell IB. Successful oral pristinamycin therapy for osteoarticular infections due to methicillin-resistant Staphylococcus aureus (MRSA) and other Staphylococcus spp. *J Antimicrob Chemother* 2005; **55:** 1008–12.
8. Ruparelia N, *et al.* Pristinamycin as adjunctive therapy in the management of Gram-positive multi-drug resistant organism (MDRO) osteoarticular infection. *J Infect* 2008; **57:** 191–7.
9. Bernard P, *et al.* Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial. *BMJ* 2002; **325:** 864–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Pyostacine.

Procaine Benzylpenicillin *(BAN, rINNM)*

Bensylpenicillinprokain; Bentsyylipenisilliiniprokaiini; Benzilpenicilinas prokainas; Benzilpenicillin-prokain; Benzylopenicylina prokainowa; Benzylpenicillin Novocaine; Benzylpénicilline Procaïne; Benzylpenicillinum Procainum; Penicillin G Procaine; Procaína bencilpenicilina; Procaína penicilina; Procaïne Benzylpénicilline; Procaine Penicillin; Procaine Penicillin G; Procaini Benzylpenicillinum; Procainum Benzylpenicillinum; Prokain Benzilpenisilin; Prokain Penisilin G; Prokain-benzylpenicilin; Прокаин Бензилпенициллин.

2-(4-Aminobenzoyloxy)ethyldiethylammonium (6*R*)-6-(2-phenylacetamido)penicillanate monohydrate.

$C_{13}H_{20}N_2O_2,C_{16}H_{18}N_2O_4S,H_2O$=588.7

CAS — 54-35-3 (anhydrous procaine benzylpenicillin); 6130-64-9 (procaine benzylpenicillin monohydrate).
ATC — J01CE09.
ATC Vet — QJ01CE09; QJ51CE09.
UNII — 17R794ESYN.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Benzylpenicillin, Procaine). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol. A 0.33% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

USP 36: (Penicillin G Procaine). White crystals or white, very fine, microcrystalline powder, odourless or practically odourless. Slightly soluble in water; soluble in alcohol and in chloroform. It is rapidly inactivated by acids, by alkali hydroxides, and by oxidising agents. pH of a saturated solution in water is between 5.0 and 7.5.

Uses and Administration

Procaine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p. 230.1) to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations produced, its use should be restricted to infections caused by micro-organisms that are highly sensitive to penicillin. Procaine benzylpenicillin should not be used as the sole treatment for severe acute infections, or when bacteraemia is present.

Procaine benzylpenicillin is used mainly in the treatment of syphilis; other indications have included pneumonia (in children in developing countries), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Doses of procaine benzylpenicillin may sometimes be expressed in terms of equivalent units of benzylpenicillin. Procaine benzylpenicillin 600 mg is equivalent to about 360 mg of benzylpenicillin (600 000 units). Procaine benzylpenicillin is given by deep intramuscular injection in usual doses of 0.6 to 1.2 g daily. For dosing regimens used in the treatment of syphilis, see p. 205.2.

Procaine benzylpenicillin is also used in combined preparations with other penicillins, including benzylpenicillin and benzathine benzylpenicillin.

For details of doses in children, see p. 346.2.

Administration in children. Procaine benzylpenicillin may be given by deep intramuscular injection to infants and children for the treatment of susceptible bacterial infections, including pneumonia and congenital syphilis.

If used for the treatment of **pneumonia**, WHO suggests a dose of 50 mg/kg daily for 10 days.

For doses used to treat **congenital syphilis** in infants, see p. 205.2.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Procaine benzylpenicillin should not be given to patients known to be hypersensitive to either of its components. Procaine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Severe, usually transient, reactions with symptoms of severe anxiety and agitation, confusion, psychotic reactions including visual and auditory hallucinations, seizures, tachycardia and hypertension, cyanosis, and a sensation of impending death have occasionally been reported with procaine benzylpenicillin and may be due to accidental intravascular injection. Since similar reactions have also occurred with other depot penicillin preparations that do not contain procaine, its presence is unlikely to be the major cause of such reactions, but may be a contributory factor, especially after injection of high doses. These reactions have been termed non-allergic, pseudoallergic, pseudoanaphylactic, or Hoigné's syndrome; the term 'embolic-toxic reaction' has also been proposed.

Interactions

As for Benzylpenicillin, p. 230.1.

Pharmacokinetics

When procaine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in 1 to 4 hours, and effective concentrations of benzylpenicillin are usually maintained for 12 to 24 hours. However, plasma concentrations are lower than those after an equivalent dose of benzylpenicillin potassium or sodium.

Distribution into the CSF is reported to be poor.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cilicaine Syringe; ***Cz.***: Pendepon Compositum; ***Hung.***: Retardillin; ***Mex.***: Benzotripen; Farmabep; Promizol; Sodilin†; Unicil 3/1; Unicil 6:3:3; ***NZ***: Cilicaine; ***S.Afr.***: Bio-Cillin; Procillin; ***Spain***: Farmaproina; ***Turk.***: Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Penadur 6.3.3; Penkain-K†; Procillin†; ***USA***: Crysticillin.

Multi-ingredient Preparations. ***Austria***: Retarpen compositum; ***Braz.***: Benapen; Benzapen G; Despacilina; Pencil 400†; Penkaron; Wycillin; ***Ger.***: Retacillin compositum; ***Hong Kong***: Pan-Fort Procaine†; Penicillin G Procaine Fortified†; ***Hung.***: Promptcillin Forte; ***India***: Bistrepen; Fortified PP; Fortified Procaine Peni; FPP; ***Malaysia***: Procaine Penicillin; ***Mex.***: Bencelin Combinado; Benzanil Compuesto†; Benzetacil Combinado; Hidrocilina; Lugaxil; Pecivax; Pendiben Compuesto†; Penicil; Penipot; Penisodina; Penprocilina†; Procilin†; Respicil; Robencaxil; Suipen; ***Port.***: Atralcilina†; Lentocilin; ***Rus.***: Benzycillin 3 (Бензициллин 3); Benzycillin 5 (Бензициллин 5); Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.***: Ultracillin†; ***Spain***: Benzetacil Compuesta; Cepacilina 633†; ***Turk.***: Pencain K; Pronapen; ***Ukr.***: Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***USA***: Bicillin C-R; ***Venez.***: Benzetacil 3-3; Benzetacil 6-3-3; Pronapen.

Pharmacopoeial Preparations

USP 36: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Procaine for Injectable Suspension; Penicillin G Procaine Injectable Suspension.

Propicillin Potassium *(BANM, pINNM)*

Kalii Propicillinum; Potassium α-Phenoxypropylpenicillin; Propicilina potásica; Propicilline Potassique; Propicillinum Kalicum; Калия Пропициллин.

A mixture of the D(+)- and L(-)-isomers of potassium (6*R*)-6-(2-phenoxybutyramido)penicillanate.

$C_{18}H_{21}KN_2O_5S$=416.5

CAS — 551-27-9 (propicillin); 1245-44-9 (propicillin potassium).
ATC — J01CE03.
ATC Vet — QJ01CE03.
UNII — 75RXW2P83Y.

Profile

Propicillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p. 338.3). Propicillin potassium is given orally for the treatment of susceptible mild to moderate infections in a usual dose of 700 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Baycillin†.

Protionamide (BAN, rINN)

Prothionamide; Protionamid; Protionamida; Protionamidi; Protionamidum; RP-9778; TH-1321; Протионамид.

2-Propylpyridine-4-carbothioamide.

$C_9H_{12}N_2S$=180.3

CAS — 14222-60-7.

ATC — J04AD01.

ATC Vet — QJ04AD01.

UNII — 76YOO33643.

Pharmacopoeias. In *Chin.*, *Int.*, and *Jpn*.

Uses and Administration

Protionamide is a thioamide derivative considered to be interchangeable with ethionamide (p. 297.3) and is used as a second-line drug in the treatment of multidrug-resistant tuberculosis (p. 210.2). It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p. 188.3) but less toxic alternatives are now preferred. Complete cross-resistance occurs between the two drugs. In the treatment of resistant tuberculosis, adults may be given 15 to 20 mg/kg daily (maximum 1 g daily) orally; typically treatment in such patients is given in divided doses with meals, or as a single daily dose. It has also been given as rectal suppositories; protionamide hydrochloride has been given intravenously. Like ethionamide, it has generally been replaced by less toxic antimycobacterials.

References.

1. Anonymous. Prothionamide. *Tuberculosis (Edinb)* 2008; **88:** 139–40.

Adverse Effects, Precautions, and Antimicrobial Action

As for Ethionamide, p. 297.3.

Pharmacokinetics

Protionamide is readily absorbed from the gastrointestinal tract and produces peak plasma concentrations about 2 hours after an oral dose. It is widely distributed throughout body tissues and fluids, including the CSF. Protionamide is metabolised to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

References.

1. Lee HW, *et al.* Pharmacokinetics of prothionamide in patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2009; **13:** 1161–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: ektebin†; Peteha; ***Hong Kong***: Peteha; ***India***: MDPride; Mycotuf P; Prothicid; ***Rus.***: Peteha (Петеха); Pronicid (Проницид); ***Turk.***: Promid†; Tionamid.

Multi-ingredient Preparations. ***Austria***: Isoprodian†; ***Rus.***: Combitub-Neo (Комбитуб-Нео); Protiocomb (Протиокомб); Protub-5 (Протуб-5).

Prulifloxacin (rINN)

NM-441; Prulifloxacine; Prulifloxacino; Prulifloxacinum; Прулифлоксацин.

(±)-7-{4-[(*Z*)-2,3-Dihydroxy-2-butenyl]-1-piperazinyl}-6-fluoro-1-methyl-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid cyclic carbonate.

$C_{21}H_{20}FN_3O_6S$=461.5

CAS — 123447-62-1.

ATC — J01MA17.

ATC Vet — QJ01MA17.

UNII — J42298IESW.

Profile

Prulifloxacin is the prodrug of ulifloxacin (AF-3013; NM-394), a fluoroquinolone antibacterial. It is given for the treatment of susceptible infections in a usual oral dose of 600 mg daily.

Reviews.

1. Keam SJ, Perry CM. Prulifloxacin. *Drugs* 2004; **64:** 2221–34.
2. Prats G, *et al.* Prulifloxacin: a new antibacterial fluoroquinolone. *Expert Rev Anti Infect Ther* 2006; **4:** 27–41.
3. Blasi F, *et al.* Prulifloxacin: a brief review of its potential in the treatment of acute exacerbation of chronic bronchitis. *Int J Chron Obstruct Pulmon Dis* 2007; **2:** 27–31.
4. Giannarini G, *et al.* Prulifloxacin: clinical studies of a broad-spectrum quinolone agent. *Future Microbiol* 2009; **4:** 13–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Unidrox; ***China***: Aifude (艾弗德); Jiaxin (加欣); Tian Zan (天赞); Xun Ao (迅奥); Yi Qi Di (易启迪); ***Cz.***: Unidrox; ***Gr.***: Chinoplus; Glimbax; Prixina; ***Hung.***: Unidrox; ***Ital.***: Chinoplus; Keraflox; Unidrox; ***Pol.***: Chinoplus; Prixina; ***Port.***: Keraflox; Oliflox; Unidrox; ***Thai.***: Darflox.

Pyrazinamide (BAN, rINN)

Pirazinamid; Pirazinamida; Pirazinamidas; Pirazynamid; Pyratsiiniamidi; Pyrazinamid; Pyrazinamidum; Pyrazinoic Acid Amide; Пиразинамид.

Pyrazine-2-carboxamide.

$C_5H_5N_3O$=123.1

CAS — 98-96-4.

ATC — J04AK01.

ATC Vet — QJ04AK01.

UNII — 2KNI5N06TI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Pyrazinamide). A white or almost white, crystalline powder. It shows polymorphism. Sparingly soluble in water, slightly soluble in alcohol and in dichloromethane.

USP 36: (Pyrazinamide). A white to practically white, odourless or practically odourless, crystalline powder. Soluble 1 in 67 of water, 1 in 175 of dehydrated alcohol, 1 in 135 of chloroform, 1 in 1000 of ether, and 1 in 72 of methyl alcohol; slightly soluble in alcohol.

Uses and Administration

Pyrazinamide is used as part of multidrug regimens for the treatment of tuberculosis (p. 210.2), mainly in the initial 8-week phase of short-course treatment. Pyrazinamide is usually given daily or 3 times weekly. In the UK, usual recommended oral doses for adults under 50 kg are 1.5 g daily, or 2 g three times weekly. The usual dose for those 50 kg or more is 2 g daily, or 2.5 g three times weekly. The recommended doses in the USA are 20 to 25 mg/kg daily (maximum 2 g) or 1.5 to 3 g three times weekly or 2 to 4 g twice weekly. WHO recommends 25 mg/kg daily or 35 mg/kg three times weekly.

For details of doses in children, see p. 347.2.

Pyrazinamide has also been used in the chemoprophylaxis of tuberculosis (see p. 347.3).

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy; thereby decreasing the risk of acquired drug resistance. Combination products containing pyrazinamide with isoniazid, isoniazid and rifampicin, or isoniazid, rifampicin, and ethambutol are available in some countries.

References.

1. Anonymous. Pyrazinamide. *Tuberculosis (Edinb)* 2008; **88:** 141–4.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an oral dose of pyrazinamide of 30 to 40 mg/kg daily or 50 mg/kg (to a maximum of 2 g) twice weekly, for the initial treatment phase. For children 1 month and older the *BNFC* suggests a dose of 35 mg/kg (to a maximum of 1.5 g in those under 50 kg and 2 g in those over 50 kg) once daily or 50 mg/kg (to a maximum of 2 g in those under 50 kg and 2.5 g in those over 50 kg) three times a week. WHO now recommends[2] 30 to 40 mg/kg once daily; in children weighing between 5 and 30 kg, specific guidance has been issued on achieving this using available fixed dose combination products. Heavier children are treated as adults (see Uses and Administration, above).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. WHO. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf (accessed 19/01/11)

Administration in hepatic impairment. See Precautions, p. 348.2.

Administration in renal impairment. Oral pyrazinamide is mainly metabolised in the liver, but its metabolites are excreted in the urine, therefore the CDC[1] suggests that the dose may need to be reduced in patients with renal impairment; alternatively, WHO[2] recommends a dose of 25 mg/kg be given three times a week. The Joint Tuberculosis Committee of the British Thoracic Society[3] consider that standard dosage may be used in such patients. Dialysis affects the clearance of pyrazinamide and CDC recommends reducing the dose to 25 to 35 mg/kg three times a week after dialysis.

In a study[4] of 6 patients on haemodialysis, the average amount of pyrazinamide and its metabolites removed during a dialysis session was 926 mg after an oral dose of 1700 mg. It was recommended that the usual pyrazinamide dose be given to patients on dialysis as the risk of accumulation was negligible, and that the dose on dialysis days be given after the procedure.

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
2. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 06/12/10)
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
4. Lacroix C, *et al.* Haemodialysis of pyrazinamide in uraemic patients. *Eur J Clin Pharmacol* 1989; **37:** 309–11.

Tuberculosis chemoprophylaxis. In the USA, the American Thoracic Society and the CDC recommended an oral dose of pyrazinamide 15 to 20 mg/kg daily (maximum 2 g daily) with rifampicin 600 mg daily as an alternative to isoniazid monotherapy for the treatment of latent tuberculosis infection.[1] (In those unable to take rifampicin, it was substituted with rifabutin 300 mg daily.) However, owing to reports of serious and fatal liver damage (see Effects on the Liver, under Adverse Effects, p. 347.3) the CDC and the American Thoracic Society now recommend that the combination of pyrazinamide with rifampicin should not be offered to persons with latent tuberculosis.[2]

1. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; **49:** 1–51. Also published in *Am J Respir Crit Care Med* 2000; **111:** S221–S247. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm (accessed 07/06/10)
2. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; **52:** 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)

Adverse Effects and Treatment

Hepatotoxicity is the most serious adverse effect of pyrazinamide therapy and its frequency appears to be dose related. However, in currently recommended doses, when given with isoniazid and rifampicin, the incidence of hepatitis has been reported to be less than 3%. Patients may have a transient increase in liver enzyme values; more seriously hepatomegaly, splenomegaly, and jaundice may develop and on rare occasions death has occurred.

Hyperuricaemia commonly occurs and may lead to attacks of gout.

Other adverse effects are anorexia, nausea, vomiting, aggravation of peptic ulcer, arthralgia, malaise, fever, sideroblastic anaemia, thrombocytopenia, and dysuria. Photosensitivity, pellagra, and rashes have been reported on rare occasions.

Effects on the cardiovascular system. Acute hypertension was associated with pyrazinamide in a previously normotensive woman.[1]

1. Goldberg J, *et al.* Acute hypertension as an adverse effect of pyrazinamide. *JAMA* 1997; **277:** 1356.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with pyrazinamide and other first-line antituberculous drugs, but sometimes hepatotoxicity may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Pyrazinamide and isoniazid are thought to have a greater potential for hepatotoxicity than rifampicin.[1]

The risk of hepatitis with antituberculous regimens containing pyrazinamide may be lower than suggested by early studies, in which large doses were used, often for long periods (the influence of dose on hepatotoxicity has, however, been questioned[2]). The **incidence** of hepatitis in studies[3] of short-course regimens containing pyrazinamide has ranged from 0.2% in Africa, to 0.6% in Hong Kong, to 2.8% in Singapore. These and later studies[4-6] have shown that hepatotoxicity is not increased when pyrazinamide is added to the *initial phase* of short-term chemotherapy containing rifampicin and isoniazid. Nevertheless, a report[7] of 4 cases of fulminant hepatic failure in patients given triple therapy with the potentially hepatotoxic drugs rifampicin, isoniazid, and pyrazinamide (1 patient also received ethambutol) highlighted the importance of strict liver function monitoring and this was reinforced by others. The addition of pyrazinamide to a *continuation-phase* regimen of isoniazid and/or rifampicin was found to considerably increase the risk of hepatotoxicity; after 12 weeks or more of treatment, the estimated risk of hepatotoxicity was 2.6% for regimens with pyrazinamide plus isoniazid and/or rifampicin compared with 0.8% for isoniazid plus rifampicin.[8]

The incidence of severe hepatotoxicity was found to be lower in patients receiving isoniazid, rifampicin, and pyrazinamide for initial treatment of active disease, than in those receiving rifampicin and pyrazinamide for 2 months for latent tuberculosis infection. For further information on hepatotoxicity caused by rifampicin and pyrazinamide for the management of latent tuberculosis infection see Effects on the Liver, under Rifampicin, p. 354.1.

The Joint Tuberculosis Committee of the British Thoracic Society has produced recommendations[9] for initial measurement of liver function in all patients and regular **monitoring** in patients with pre-existing liver disease, as well as the response to deteriorating liver function; prompt re-introduction of appropriate antituberculosis therapy is recommended once normal liver function is restored. Similar guidelines have been produced for the USA.[10,11] For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p. 312.1.

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11:** 699–707.
2. Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. *Antimicrob Agents Chemother* 2010; **54:** 2847–54.
3. Girling DJ. The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle* 1984; **65:** 1–4.
4. Parthasarathy R, *et al*. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle* 1986; **67:** 99–108.
5. Combs DL, *et al*. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
6. le Bourgeois M, *et al*. Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; **64:** 177–8.
7. Mitchell I, *et al*. Anti-tuberculous therapy and acute liver failure. *Lancet* 1995; **345:** 555–6.
8. Chang KC, *et al*. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. *Am J Respir Crit Care Med* 2008; **177:** 1391–6.
9. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
10. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
11. Saukkonen JJ, *et al*. American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 16/07/10)

Effects on the nervous system. Convulsions that developed in a 2-year-old child receiving antituberculous therapy appeared to be due to pyrazinamide, given in a dose of 250 mg daily.[1]

1. Herlevsen P, *et al*. Convulsions after treatment with pyrazinamide. *Tubercle* 1987; **68:** 145–6.

Hyperuricaemia. Hyperuricaemia in patients taking pyrazinamide may be due to pyrazinoic acid, the main metabolite of pyrazinamide, inhibiting uric acid excretion.[1]

In a large multicentre study,[2] the incidence of elevated serum concentrations of uric acid for patients taking rifampicin, isoniazid, and pyrazinamide was 52.2% at 8 weeks while the incidence for patients given rifampicin and isoniazid was 5.4%. Arthralgia was reported in 6 of 617 patients taking rifampicin, isoniazid, and pyrazinamide, but in none of 445 patients given rifampicin and isoniazid.

Slight increases in plasma concentrations of uric acid occurred in 9 of 43 children after one month's treatment with rifampicin, isoniazid, ethambutol, and pyrazinamide. Arthralgias and gout did not occur. Uric acid concentrations were normal on completion of treatment with pyrazinamide.[3] Some studies[4] have suggested a relationship between elevated serum uric acid levels and arthralgia, but this has not been confirmed.[5]

1. Ellard GA, Haslam RM. Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamide. *Tubercle* 1976; **57:** 97–103.
2. Combs DL, *et al*. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
3. le Bourgeois M, *et al*. Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; **64:** 177–8.
4. Hong Kong Tuberculosis Treatment Services/British MRC. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. *Tubercle* 1976; **57:** 81–95.
5. Jenner PJ, *et al*. Serum uric acid concentrations and arthralgia among patients treated with pyrazinamide-containing regimens in Hong Kong and Singapore. *Tubercle* 1981; **62:** 175–9.

Pellagra. Pellagra, probably due to pyrazinamide, developed in a 26-year-old woman receiving antituberculous therapy.[1] Symptoms regressed, despite continued therapy, on giving nicotinamide.

1. Jørgensen J. Pellagra probably due to pyrazinamide: development during combined chemotherapy of tuberculosis. *Int J Dermatol* 1983; **22:** 44–5.

Precautions

Pyrazinamide should be used with caution in patients with liver disorders and is contra-indicated in established chronic or severe liver disease. In patients with liver disorders, liver function should be assessed before and regularly during treatment. The British Thoracic Society has recommended that pyrazinamide treatment should be suspended if serum aminotransferase concentrations are elevated to 5 times the normal upper limit or if the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. WHO recommends that pyrazinamide not be reintroduced if the hepatitis produced a clinical jaundice.

Pyrazinamide should not be given to patients with acute gout or hyperuricaemia and should be used with caution in patients with a history of gout. Caution should also be observed in patients with renal impairment. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Porphyria. Pyrazinamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Although detailed teratogenicity data are not available, WHO,[1] the IUATLD,[2] the British Thoracic Society,[3] and the CDC[4] do not contra-indicate pyrazinamide in pregnant patients.

1. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/06/10)
2. Caminero Luna JA. *A tuberculosis guide for specialist physicians.* Paris: International Union Against Tuberculosis and Lung Disease (IUATLD), 2004. Available at: http://www.tbrieder.org/publications/specialists_en.pdf (accessed 03/10/07)
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
4. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]

Interactions

Antigout drugs. The complex interactions occurring when pyrazinamide and *probenecid* are given to patients with gout have been studied.[1] Urinary excretion of urate depends on the relative size and timing of doses of the two drugs. Probenecid is known to block the excretion of pyrazinamide. A pharmacokinetic study[2] in 6 healthy subjects found that *allopurinol*, a xanthine oxidase inhibitor, increases concentrations of pyrazinoic acid (the main metabolite of pyrazinamide) thereby worsening pyrazinamide-induced hyperuricaemia. Allopurinol would therefore also appear to be unsuitable for treating pyrazinamide-induced hyperuricaemia.

1. Yü TF, *et al*. The effect of the interaction of pyrazinamide and probenecid on urinary uric acid excretion in man. *Am J Med* 1977; **63:** 723–8.
2. Lacroix C, *et al*. Interaction between allopurinol and pyrazinamide. *Eur Respir J* 1988; **1:** 807–11.

Antiretrovirals. Concentrations of pyrazinamide were low or undetectable in 4 patients also taking *zidovudine*.[1] In the same study, 6 of 7 patients with HIV infection taking pyrazinamide without zidovudine had normal serum pyrazinamide concentrations.

1. Peloquin CA, *et al*. Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; **30:** 919–25.

Antimicrobial Action

Pyrazinamide has a bactericidal effect on *Mycobacterium tuberculosis* but appears to have no activity against other mycobacteria or micro-organisms *in vitro*. It is almost completely inactive at a neutral pH, but is effective against persisting tubercle bacilli within the acidic intracellular environment of the macrophages. The initial inflammatory response to chemotherapy increases the number of organisms in the acidic environment. As inflammation subsides and pH increases, the sterilising activity of pyrazinamide decreases. This pH-dependent activity explains the clinical efficacy of pyrazinamide as part of the initial 8-week phase in short-course treatment regimens.

Resistance to pyrazinamide rapidly develops when it is used alone.

Action. Although the antimicrobial activity of pyrazinamide has been recognised since the 1950s, the mode of action is still unclear. One proposal is that pyrazinoic acid is the active moiety. Pyrazinamidase produced by the tubercle bacilli is known to convert pyrazinamide to pyrazinoic acid. A further proposal[1] is that the pyrazinoic acid formed within the macrophage would be trapped, thereby lowering intracellular pH to levels toxic to tubercle bacilli.

A review[2] has suggested that pyrazinoic acid depends on pH-based passive diffusion to enter the mycobacterial cell whereas its removal from the cell via an efflux pump requires energy; under conditions of dormancy, when bacterial metabolism decreases, pyrazinoic acid tends to accumulate in the bacterium, accounting for the value of pyrazinamide in preferentially killing dormant organisms and thus its role in combination therapy. Because relatively small changes in local pH could affect this accumulation, it was hypothesised that adjunctive inhalation of pyrazinoic acid might greatly enhance the efficacy of oral pyrazinamide therapy.

1. Salfinger M, *et al*. Pyrazinamide and pyrazinoic acid activity against tubercle bacilli in cultured human macrophages and in the BACTEC system. *J Infect Dis* 1990; **162:** 201–7.
2. Mitchison DA, Fourie PB. The near future: improving the activity of rifamycins and pyrazinamide. *Tuberculosis (Edinb)* 2010; **90:** 177–81.

Activity with other antimicrobials. Synergistic activity against *Mycobacterium tuberculosis* has been reported with pyrazinamide and clarithromycin.[1]

1. Mor N, Esfandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; **41:** 2035–6.

Pharmacokinetics

Pyrazinamide is readily absorbed from the gastrointestinal tract. Peak serum concentrations occur about 2 hours after an oral dose and have been reported to be about 33 micrograms/mL after 1.5 g, and 59 micrograms/mL after 3 g. Pyrazinamide is widely distributed in body fluids and tissues and diffuses into the CSF. The half-life has been reported to be about 9 to 10 hours. It is metabolised mainly in the liver by hydrolysis to the major active metabolite pyrazinoic acid, which is subsequently hydroxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted via the kidneys mainly by glomerular filtration. About 70% of a dose appears in the urine within 24 hours mainly as metabolites and about 4% as unchanged drug. Pyrazinamide is removed by dialysis. Pyrazinamide is distributed into breast milk.

A short distribution phase and an elimination phase of 9.6 hours in healthy subjects after a single oral dose of pyrazinamide 27 mg/kg has been reported;[1] the half-life for the major metabolite pyrazinoic acid was 11.8 hours.

In the major metabolic pathway, pyrazinamide was deaminated to pyrazinoic acid which was hydroxylated to hydroxypyrazinoic acid; in the minor pathway, pyrazinamide was hydroxylated to hydroxypyrazinamide which was then deaminated to hydroxypyrazinoic acid. The limiting step was deamination; oxidation by xanthine oxidase occurred very quickly.

1. Lacroix C, *et al*. Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. *Eur J Clin Pharmacol* 1989; **36:** 395–400.

Bioavailability. The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[1] However, another report[2] showed slightly reduced peak serum concentrations when pyrazinamide was given with a high-fat meal, and the authors suggested that pyrazinamide should preferably be given on an empty stomach.

1. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; **76:** 109–13.
2. Peloquin CA, *et al*. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* 1998; **18:** 1205–11.

Breast feeding. The peak concentration of pyrazinamide in breast milk of a 29-year-old woman was 1.5 micrograms/mL 3 hours after a 1-g dose.[1] The peak plasma concentration was 42 micrograms/mL after 2 hours.

1. Holdiness MR. Antituberculosis drugs and breast-feeding. *Arch Intern Med* 1984; **144:** 1888.

Distribution. Pyrazinamide was given to 28 patients with suspected tuberculous meningitis in doses of 34 to 41 mg/kg. The mean concentration of pyrazinamide in the CSF after 2 hours was 38.6 micrograms/mL and represented about 75% of that in serum; concentrations at 5 and 8 hours were 44.5 and 31.0 micrograms/mL respectively and were about 10% higher than those in serum.[1] The use of corticosteroids appeared to have no influence on penetration of pyrazinamide into the CSF of patients with tuberculous meningitis.[2]

1. Ellard GA, *et al*. Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis. *BMJ* 1987; **294:** 284–5.
2. Woo J, *et al*. Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; **42:** 235–42.

Hepatic impairment. A study[1] of the pharmacokinetics of pyrazinamide was carried out in 10 patients with cirrhosis of the liver. After a dose of about 19.3 mg/kg, the elimina-

tion phase was about 15 hours for pyrazinamide and 24 hours for the major metabolite pyrazinoic acid.

1. Lacroix C, *et al*. Pharmacokinetics of pyrazinamide and its metabolites in patients with hepatic cirrhotic insufficiency. *Arzneimittelforschung* 1990; **40:** 76–9.

HIV-infected patients. Malabsorption of pyrazinamide and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p. 356.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zinamide†; ***Austria***: Pyrafat; ***Belg.***: Tebrazid; ***Braz.***: Pirazinon†; ***Canad.***: Tebrazid; ***Fin.***: Tisamid; ***Fr.***: Pirilene; ***Ger.***: Pyrafat; ***Hong Kong***: Pyrafat; ***India***: Actizid; Antizide; Copyrazin; Eumide; Isomide; Macrozide; Montozin; P-Zide; Parazid; Pyzina; PZA-Ciba; Rifacom-EZ; ***Indon.***: Corsazinamid; Neotibi; Pezeta-Ciba; Prazina; Sanazet; Siramid; TB ZET; ***Ital.***: Piraldina; ***Malaysia***: PZA; ***Mex.***: Nizamyl; ***NZ***: Zinamide†; ***Philipp.***: Midazen; Pyramin; Pyrasol†; Pyrazin; PZA-Ciba; Zapedia†; Zcure; Zinaplex; Zinaprim; ***Port.***: Pramide; ***Rus.***: Lynamid (Линамид); Macrozide (Макрозид); Pyrafat (Пирафат); Pyzina (Пизина); ***S.Afr.***: Pyrazide; ***Singapore***: PZA; ***Thai.***: Myrin-P†; Pyramide; PZA†; TZM†; ***Turk.***: Pirazinid; ***UK***: Zinamide.

Multi-ingredient Preparations. ***Austria***: Rifater; ***Canad.***: Rifater; ***China***: Chang Wei Rui Da Xin (长威瑞达欣); Dai Fei Lin (戴菲林); Fei Ning (费宁); Fei Su (菲苏); Hu Fei Te (护菲特); Ke Lao Er Kang (克劳尔康); Pi Lv (匹律); Rui Fu An Kang (瑞福安康); Rui Qing (瑞清); Wei Bao (维葆); Yi Bi Fu (依比福); Yi Nuo Ni Kang (怡诺尼康); Yi Ti Bi (伊缇碧); ***Denm.***: Rimcure; Rimstar; ***Fin.***: Rimstar; ***Fr.***: Rifater; ***Ger.***: Rifater†; tebesium Trio; ***Gr.***: Rifater; ***Hong Kong***: Rifater; ***India***: AFB4; Akt-4; Akt-FD; Akurit-4; Akurit-Z; Becox Forte Kit; Binex Z; Binex ZE; Cavirip; Caviter FD; Caviter; Coxina-4; Coxter-3; Coxter-4; Cx-5; Emrif Kit; Eufacin Plus; Eufazid; Faminex Forte; Forecox; Gocox-3; Infez-4; Macox-ZH; Monto-4; Montorip; Mycocox-4; Mycocox-Z; Mycodot-4; Mycodot-Z; Mycurit-4; Mycurit-Z; R-Cinex Z; RHZ Plus; RHZ; Rimactazid + Z; Tricox; Wokex-4; Xeed 4; ***Indon.***: Rimcure; Rimstar; ***Irl.***: Rifater; Rimcure†; Rimstar; ***Ital.***: Rifater; Rimcure; Rimstar; ***Malaysia***: Rimcure; ***Mex.***: Arpisen†; Dotbal; Finateramida†; Rifater; ***Neth.***: Rimcure†; Rimstar†; ***Norw.***: Rimcure; Rimstar; ***Philipp.***: 4D; AKuriT-4; CombiKids†; CombiPack; Econofix; Econokit-MDR; Econokit; Econopack; Fixcom 4; HRZ Pedia Kit; Kidz Kit 3; Myrin-P; Quadmax; Quadtab; Refam Pedia Kit†; Rifater; Rimcure; Rimstar; SVM-Polypac-A†; Triofix; Viper†; ***Port.***: Rifater; ***Rus.***: Combitub (Комбитуб); Combitub-Neo (Комбитуб-Нео); Forecox (Форкокс); Isocomb (Изокомб); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Phthizopiram (Фтизопирам); Protiocomb (Протиокомб); Protub-3 (Протуб-3); Protub-4 (Протуб-4); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе); Protubpira (Протубпира); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rifacomb Plus (Рифакомб Плюс)†; Rimecure 3-FDC (Римкур 3-ФДС)†; Rimstar 4-FDC (Римстар 4-ФДС)†; ***S.Afr.***: Rifafour; Rifater†; Rimcure; Rimstar; ***Singapore***: Merip; ***Spain***: Rifater; Rimcure†; Rimstar; ***Swed.***: Rimcure; Rimstar; ***Switz.***: Rifater; Rimstar; ***Thai.***: Rifafour; Rifampyzid; Rifater; Rimcure 3-FDC; Rimstar†; ***UK***: Rifater; Rimstar; Voractiv; ***USA***: Rifater; ***Venez.***: Rimcure.

Pharmacopoeial Preparations

BP 2014: Pyrazinamide Oral Suspension; Pyrazinamide Tablets; **USP 36:** Pyrazinamide Oral Suspension; Pyrazinamide Tablets; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Quinupristin/Dalfopristin

Dalfopristin (rINN); Dalfopristin (USAN); Dalfopristin (BAN); Kinupristiini/dalfopristiini; Kinupristin/dalfopristin; Quinupristin (BAN); Quinupristin (rINN); Quinupristin (USAN); Quinupristina/dalfopristina; Quinupristine/dalfopristine; Quinupristinum/Dalfopristinum; RP-59500; Хинупристин/Дальфопристин.

CAS — 126602-89-9 (quinupristin/dalfopristin); 176861-85-1 (quinupristin/dalfopristin).

ATC — J01FG02.

ATC Vet — QJ01FG02.

UNII — R9M4FJE48E (dalfopristin); 23OW28RS7P (quinupristin).

Dalfopristin Mesilate *(BANM, rINNM)*

Dalfopristin Mesylate; Dalfopristina, mesilato de; Dalfopristine, Mésilate de; Dalfopristini Mesilas; Mesilato de dalfopristina; RP-54476 (dalfopristin); Дальфопристина Мезилат.

(3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-{[2-(Diethylamino)ethyl]sulfonyl}-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2.1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone methanesulphonate; (26*R*,27*S*)-26-{[2-(Diethylamino)-ethyl]sulfonyl}-26,27-dihydrovirginiamycin M_1 methanesulphonate.

$C_{34}H_{50}N_4O_9S,CH_4O_3S$=787.0

CAS — 112362-50-2 (dalfopristin).

UNII — R9M4FJE48E (dalfopristin).

Quinupristin Mesilate *(BANM, rINNM)*

Mesilato de quinupristina; Quinupristin Mesylate; Quinupristina, mesilato de; Quinupristine, Mésilate de; Quinupristini Mesilas; RP-57669 (quinupristin); Хинупристина Мезилат.

N-{(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(Dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-{[(3*S*)-3-quinuclidinylthio]methyl}-12*H*-pyrido[2,1-*f*]pyrrolo[2,1-*l*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide methanesulphonate; 4-[4-(Dimethylamino)-*N*-methyl-L-phenylalamine]-5-(*cis*-5-{[(*S*)-1-azabicyclo[2.2.2]oct-3-ylthio]methyl}-4-oxo-L-2-piperidinecarboxylic acid)-virginiamycin S_1 methanesulphonate.

$C_{53}H_{67}N_9O_{10}S,CH_4O_3S$=1118.3

CAS — 120138-50-3 (quinupristin).

UNII — 23OW28RS7P (quinupristin).

Uses and Administration

Quinupristin/dalfopristin is a streptogramin antibacterial related to pristinamycin. Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin I and pristinamycin IIA respectively, and are used in the ratio 3:7. Quinupristin/dalfopristin is active against a range of Gram-positive and some Gram-negative organisms, but it is reserved for the treatment of serious infections with multidrug-resistant Gram-positive bacteria, specifically MRSA and vancomycin-resistant *Enterococcus faecium*.

Quinupristin/dalfopristin is given as the mesilate salts by intravenous infusion, in glucose 5% over 60 minutes, in a dose of 7.5 mg/kg (equivalent to quinupristin 2.25 mg/kg and dalfopristin 5.25 mg/kg) every 8 or 12 hours for at least 7 days. To minimise venous irritation, the vein should be flushed with glucose 5% after each infusion; alternatively, the infusion may be given through a central venous catheter. The injection should not be diluted with saline solutions since it is incompatible with sodium chloride.

Doses may need to be reduced in patients with hepatic impairment (see p. 349.2).

References.

1. Bayston R, *et al.* , eds. Quinupristin/dalfopristin—update on the first injectable streptogramin. *J Antimicrob Chemother* 1997; **39** (suppl A): 1–151.
2. Wood MJ (ed). Quinupristin/dalfopristin–a novel approach for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 1999; **44** (suppl A): 1–46.
3. Lamb HM, *et al*. Quinupristin/dalfopristin: a review of its use in the management of serious Gram-positive infections. *Drugs* 1999; **58:** 1061–97.
4. Drew RH, *et al*. Treatment of methicillin-resistant Staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy: for the Synercid Emergency-Use Study Group. *J Antimicrob Chemother* 2000; **46:** 775–84.
5. Allington DR, Rivey MP. Quinupristin/dalfopristin: a therapeutic review. *Clin Ther* 2001; **23:** 24–44.
6. Linden PK, *et al*. Treatment of vancomycin-resistant Enterococcus faecium infections with quinupristin/dalfopristin. *Clin Infect Dis* 2001; **33:** 1816–23.
7. Goff DA, Sierawski SJ. Clinical experience of quinupristin-dalfopristin for the treatment of antimicrobial-resistant gram-positive infections. *Pharmacotherapy* 2002; 748–58.
8. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis* 2003; **36:** 473–81.
9. Brown J, Freeman BB. Combining quinupristin/dalfopristin with other agents for resistant infections. *Ann Pharmacother* 2004; **38:** 677–85.
10. Manfredi R. A re-emerging class of antimicrobial agents: streptogramins (quinupristin/dalfopristin) in the management of multiresistant gram-positive nosocomial cocci in hospital setting. *Mini Rev Med Chem* 2005; **5:** 1075–81.

Administration in hepatic impairment. Licensed product information states that in clinical studies of quinupristin/dalfopristin the incidence of adverse effects in patients with chronic liver impairment or cirrhosis was similar to that in patients with normal liver function. However, pharmacokinetic studies have shown that systemic exposure to quinupristin/dalfopristin and their metabolites may be increased in those with hepatic impairment. In some countries it has therefore been recommended that quinupristin/dalfopristin should be avoided in patients with severe hepatic impairment, and that for those with moderate impairment a dose reduction to 5 mg/kg intravenously (equivalent to quinupristin 1.5 mg/kg and dalfopristin 3.5 mg/kg) should be considered if 7.5 mg/kg is not tolerated.

Adverse Effects and Treatment

The adverse effects most frequently reported in patients receiving quinupristin/dalfopristin include nausea and vomiting, diarrhoea, skin rash, pruritus, headache, and pain. Myalgia and arthralgia have occurred and may be severe; symptoms may be improved by decreasing the dose frequency. Eosinophilia, anaemia, leucopenia, and neutropenia are also common. Individual cases of severe thrombocytopenia and pancytopenia have been reported. Pseudomembranous colitis has also been reported.

Hyperbilirubinaemia and raised liver enzyme values may occur.

Pain and inflammation at the injection site is common, and thrombophlebitis has occurred.

Quinupristin/dalfopristin is not removed by peritoneal dialysis, and removal by haemodialysis is considered unlikely.

Effects on the musculoskeletal system. References.

1. Olsen KM, *et al*. Arthralgias and myalgias related to quinupristin-dalfopristin administration. Abstract: *Clin Infect Dis* 2001; **32:** 674. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/318702 (accessed 12/08/08)
2. Carver PL, *et al*. Risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin therapy. *Pharmacotherapy* 2003; **23:** 159–64.
3. Raad I, *et al*. Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. *J Antimicrob Chemother* 2004; **53:** 1105–8.
4. Gupte G, *et al*. Quinupristin-dalfopristin use in children is associated with arthralgias and myalgias. *Pediatr Infect Dis J* 2006; **25:** 281.

Precautions

Quinupristin/dalfopristin should be used with caution in patients with hepatic impairment and avoided in severe impairment, as elevated plasma concentrations of quinupristin and dalfopristin and their metabolites have been found in patients with hepatic dysfunction, and elevated concentrations of quinupristin metabolites have occurred in patients with hyperbilirubinaemia. The combination is contra-indicated in patients who have plasma-bilirubin concentrations greater than 3 times the normal upper limit.

Prolongation of the QT interval has been seen in *animals* given quinupristin/dalfopristin; therefore caution is advised in patients at risk of cardiac arrhythmias.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinupristin/dalfopristin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Quinupristin/dalfopristin inhibits the cytochrome P450 isoenzyme CYP3A4 and it may therefore inhibit the metabolism of several drugs. In particular, there is a theoretical possibility of serious ventricular arrhythmias when given with drugs that prolong the QT interval, such as astemizole, cisapride, and terfenadine. Quinupristin/dalfopristin has been shown to increase plasma concentrations of ciclosporin, midazolam, nifedipine, and tacrolimus. The use of ergot alkaloids with quinupristin/dalfopristin should be avoided.

Antimicrobial Action

Quinupristin/dalfopristin is a semisynthetic streptogramin antibacterial. Quinupristin and dalfopristin each have bacteriostatic activity and in combination usually act synergistically to produce bactericidal activity. The streptogramins act on the ribosome to block protein synthesis.

Quinupristin/dalfopristin is active against a range of Gram-positive bacteria including meticillin- and multidrug-resistant strains of *Staphylococcus aureus* and *S. epidermidis*, vancomycin-resistant *Enterococcus faecium* (but not *E. faecalis*), and penicillin- and macrolide-resistant *Streptococcus pneumoniae*. It is also active against the anaerobe *Clostridium perfringens*, and Gram-negative bacteria *Legionella pneumophila*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Mycoplasma pneumoniae*, and *Neisseria meningitidis*.

References.

1. Schouten MA, Hoogkamp-Korstanje JAA. Comparative in-vitro activities of quinupristin-dalfopristin against Gram-positive bloodstream isolates. *J Antimicrob Chemother* 1997; **40:** 213–19.
2. Pankuch GA, *et al*. Postantibiotic effect and postantibiotic sub-MIC effect of quinupristin-dalfopristin against Gram-positive and negative organisms. *Antimicrob Agents Chemother* 1998; **42:** 3028–31.
3. Johnson AP, *et al*. Susceptibility to quinupristin/dalfopristin and other antibiotics of vancomycin-resistant enterococci from the UK, 1997 to mid-1999. *J Antimicrob Chemother* 2000; **46:** 125–8.
4. Ling TK, *et al*. In vitro activity and post-antibiotic effect of quinupristin/dalfopristin (Synercid). *Chemotherapy* 2001; **47:** 243–9.
5. Eliopoulos GM, Wennersten CB. Antimicrobial activity of quinupristin-dalfopristin combined with other antibiotics against vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 2002; **46:** 1319–24.
6. Hancock RE. Mechanisms of action of newer antibiotics for Gram-positive pathogens. *Lancet Infect Dis* 2005; **5:** 209–18.

Resistance. Although uncommon, isolated reports of *E. faecium* resistant to quinupristin/dalfopristin have

emerged,[1-8] and have included a link to the use of the streptogramin virginiamycin as an animal food additive.[3,4]

1. Eliopoulos GM, *et al.* Characterization of vancomycin-resistant Enterococcus faecium isolates from the United States and their susceptibility in vitro to dalfopristin-quinupristin. *Antimicrob Agents Chemother* 1998; **42:** 1088–92.
2. Bozdogan B, *et al.* Plasmid-mediated coresistance to streptogramins and vancomycin in Enterococcus faecium HM1032. *Antimicrob Agents Chemother* 1999; **43:** 2097–8.
3. Werner G, *et al.* Association between quinupristin/dalfopristin resistance in glycopeptide-resistant Enterococcus faecium and the use of additives in animal feed. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 401–2.
4. Hershberger E, *et al.* Quinupristin-dalfopristin resistance in gram-positive bacteria: mechanism of resistance and epidemiology. *Clin Infect Dis* 2004; **38:** 92–8.
5. Oh WS, *et al.* High rate of resistance to quinupristin-dalfopristin in Enterococcus faecium clinical isolates from Korea. *Antimicrob Agents Chemother* 2005; **49:** 5176–8.
6. Donabedian SM, *et al.* Quinupristin-dalfopristin resistance in Enterococcus faecium isolates from humans, farm animals, and grocery store meat in the United States. *J Clin Microbiol* 2006; **44:** 3361–5.
7. Karanika M, *et al.* Reduced susceptibility to quinupristin/dalfopristin in Enterococcus faecium in Greece without prior exposure to the agent. *Int J Antimicrob Agents* 2008; **31:** 55–7.
8. Chong YP, *et al.* Quinupristin-dalfopristin versus linezolid for the treatment of vancomycin-resistant Enterococcus faecium bacteraemia: efficacy and development of resistance. *Scand J Infect Dis* 2010; **42:** 491–9.

Pharmacokinetics

After parenteral doses, quinupristin and dalfopristin are rapidly metabolised. At steady state, the half-life of quinupristin and its metabolites is about 3 hours and that of dalfopristin and its metabolites about 1 hour. Elimination half-lives of unchanged quinupristin and dalfopristin are 0.9 and 0.75 hours, respectively. Protein binding ranges from 55 to 78% for quinupristin and 11 to 26% for dalfopristin. The main route of excretion is biliary, with 75 to 77% of a dose detectable in the faeces. Urinary excretion accounts for 15% of the quinupristin and 19% of the dalfopristin dose. Negligible amounts are removed by peritoneal dialysis and probably also by haemodialysis.

Distribution into milk has been found in studies in *rats*.

References.
1. Bearden DT. Clinical pharmacokinetics of quinupristin/dalfopristin. *Clin Pharmacokinet* 2004; **43:** 239–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Synercid†; ***Braz.***: Synercid; ***Cz.***: Synercid†; ***Fr.***: Synercid†; ***Gr.***: Synercid; ***Hung.***: Synercid†; ***Irl.***: Synercid†; ***Ital.***: Synercid; ***Neth.***: Synercid; ***NZ***: Synercid; ***Pol.***: Synercid†; ***Port.***: Synercid†; ***UK***: Synercid; ***USA***: Synercid.

Ramoplanin *(USAN, rINN)*

A-16686; MDL-62198; Ramoplanina; Ramoplanine; Ramoplaninum; Рамопланин.

CAS — 76168-82-6.
UNII — 0WX9996O2G.

Profile

Ramoplanin is a lipoglycodepsipeptide antibacterial with a spectrum of activity *in vitro* similar to that of vancomycin (p. 389.1) but considerably more potent. It is also active against *Bacteroides* spp. It is under investigation, notably for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for use in the prevention of systemic infection in patients colonised with vancomycin-resistant enterococci.

Reviews.
1. Farver DK, *et al.* Ramoplanin: a lipoglycodepsipeptide antibiotic. *Ann Pharmacother* 2005; **39:** 863–8.
2. Fulco P, Wenzel RP. Ramoplanin: a topical lipoglycodepsipeptide antibacterial agent. *Expert Rev Anti Infect Ther* 2006; **4:** 939–45.

Retapamulin *(BAN, USAN, rINN)*

Retapamulina; Rétapamuline; Retapamulinum; SB-275833; Ретапамулин.

(3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-Ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propanocyclopenta[8]annulen-8-yl{[(1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]sulfanyl}acetate.

$C_{30}H_{47}NO_4S$=517.8

CAS — 224452-66-8.
ATC — D06AX13.
ATC Vet — QD06AX13.
UNII — 4MG6O8991R.

Uses and Administration

Retapamulin is a pleuromutilin antibacterial isolated from the fungus *Clitopilus passeckerianus*. It is applied topically as a 1% ointment in the treatment of impetigo and other bacterial skin infections due to meticillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. The preparation should be applied twice daily for 5 days; treatment should be re-evaluated if there is no response within about 3 days. It is not suitable for application to mucous membranes.

For further details of skin infections and staphylococcal infections and their treatment, see p. 207.1 and p. 208.2 respectively.

References.
1. Parish LC, *et al.* Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. *J Am Acad Dermatol* 2006; **55:** 1003–1013.
2. Oranje AP, *et al.* Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. *Dermatology* 2007; **215:** 331–40.
3. Yang LPH, Keam SJ. Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. *Drugs* 2008; **68:** 855–73.
4. Anonymous. Retapamulin for impetigo and other infections. *Drug Ther Bull* 2008; **46:** 76–9. Correction. *ibid.*; 88.
5. Yang LP, Keam SJ. Spotlight on retapamulin in impetigo and other uncomplicated superficial skin infections. *Am J Clin Dermatol* 2008; **9:** 411–13.
6. Shawar R, *et al.* Topical retapamulin in the management of infected traumatic skin lesions. *Ther Clin Risk Manag* 2009; **5:** 41–9.

Adverse Effects and Precautions

Retapamulin is usually well tolerated; the most common reported adverse effect is application site irritation. Other local reactions such as erythema, pain, and pruritus occur rarely. Retapamulin ointment contains butylated hydroxytoluene (p. 1742.1), which may cause local adverse effects such as contact dermatitis, or irritation to the eyes and mucous membranes. It should not be applied to abscesses.

Retapamulin has proved ineffective in infections caused by meticillin-resistant *Staphylococcus aureus*, and should not be used in their treatment.

Antimicrobial Action

Retapamulin is an antibacterial that selectively inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It is mainly bacteriostatic against meticillin-susceptible *Staphylococcus aureus*, and streptococci such as *Strep. pyogenes*. Although *in vitro* activity has been shown against meticillin-resistant *Staph. aureus*, the *in vivo* efficacy of retapamulin was found to be inadequate in clinical studies.

References.
1. Pankuch GA, *et al.* Activity of retapamulin against Streptococcus pyogenes and Staphylococcus aureus evaluated by agar dilution, microdilution, E-test, and disk diffusion methodologies. *Antimicrob Agents Chemother* 2006; **50:** 1727–30.
2. Jones RN, *et al.* Activity of retapamulin (SB-275833), a novel pleuromutilin, against selected resistant Gram-positive cocci. *Antimicrob Agents Chemother* 2006; **50:** 2583–6.
3. Rittenhouse S, *et al.* Selection of retapamulin, a novel pleuromutilin for topical use. *Antimicrob Agents Chemother* 2006; **50:** 3882–5.
4. Champney WS, Rodgers WK. Retapamulin inhibition of translation and 50S ribosomal subunit formation in Staphylococcus aureus cells. *Antimicrob Agents Chemother* 2007; **51:** 3385–7.
5. Woodford N, *et al.* In vitro activity of retapamulin against Staphylococcus aureus isolates resistant to fusidic acid and mupirocin. *J Antimicrob Chemother* 2008; **62:** 766–8.

Pharmacokinetics

Only very small amounts of topically applied retapamulin are absorbed into the systemic circulation. It is about 94% bound to plasma proteins and has been shown to be metabolised by mono-oxygenation and N-demethylation *in vitro*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Altargo; ***Austria***: Altargo; ***Belg.***: Altargo; ***Braz.***: Altargo; ***Chile***: Altargo; ***Cz.***: Altargo; ***Denm.***: Altargo; ***Ger.***: Altargo; ***Gr.***: Altargo; ***Hung.***: Altargo; ***Irl.***: Altargo; ***Ital.***: Altargo; ***Neth.***: Altargo; ***Norw.***: Altargo; ***Pol.***: Altargo; ***Port.***: Altargo; ***Singapore***: Altargo; ***Spain***: Altargo; ***Swed.***: Altargo; ***UK***: Altargo; ***USA***: Altabax.

Ribostamycin Sulfate *(BANM, rINNM)*

Ribostamycin Sulphate; Ribostamycine, Sulfate de; Ribostamycini Sulfas; SF-733 (ribostamycin); Sulfato de ribostamicina; Рибостамицина Сульфат.

2-Deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-(β-D-ribofuranosyl)-streptamine sulphate.

$C_{17}H_{34}N_4O_{10}xH_2SO_4$

CAS — 25546-65-0 (ribostamycin); 53797-35-6 (ribostamycin sulfate).
ATC — J01GB10.
ATC Vet — QJ01GB10.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Ribostamycin is an aminoglycoside with actions and uses similar to those of gentamicin (p. 304.2). It is given as the sulfate by intramuscular injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn.*** Vistamycin.

Rifabutin *(BAN, USAN, rINN)*

Ansamicin; Ansamycin; Ansamycinum; Ansamysiini; LM-427; Rifabutiini; Rifabutina; Rifabutinas; Rifabutine; Rifabutinum; Рифабутин.

(9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo-[2′,3′:7,8]naphth[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate.

$C_{46}H_{62}N_4O_{11}$=847.0

CAS — 72559-06-9.
ATC — J04AB04.
ATC Vet — QJ04AB04.
UNII — 1W306TDA6S.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Rifabutin). A reddish-violet amorphous powder. Slightly soluble in water and in alcohol; soluble in methyl alcohol.

USP 36: (Rifabutin). An amorphous red-violet powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol. Store at a temperature not exceeding 40 degrees. Protect from light.

Stability. Study of the stability of two extemporaneous oral liquid preparations of rifabutin.[1]

1. Haslam JL, *et al.* Stability of rifabutin in two extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1999; **56:** 333–6.

Uses and Administration

Rifabutin is a rifamycin antibacterial used as an alternative to the macrolides for the prophylaxis of *Mycobacterium avium* complex (MAC) infection in immunocompromised patients. It is also used for the treatment of other nontuberculous mycobacterial infections (including those due to MAC) (p. 194.1) and tuberculosis (p. 210.2). When used for treatment rifabutin, like rifampicin, should be used with other antibacterials to prevent the emergence of resistant organisms.

Rifabutin is given as a single oral daily dose. The dose for the prophylaxis of MAC infection is 300 mg daily. For the treatment of nontuberculous mycobacterial infections the dose is 450 to 600 mg daily in a multidrug regimen for up to 6 months after negative cultures are obtained. For pulmonary tuberculosis the usual dose is 300 mg daily for at least 6 months as part of a multidrug regimen; it can also be given intermittently (usually 3 times each week) as an alternative to daily use.

For details of doses in children, see p. 350.3.

Doses should be reduced to 300 mg daily in patients also receiving macrolides or azole antifungals (see under Adverse Effects, Effects on the Eyes, p. 351.2). Dosage alterations may also be necessary in patients receiving HIV-protease inhibitors (see under Tuberculosis, p. 351.1) and in those with severe renal impairment (see p. 351.1).

Reviews.
1. Brogden RN, Fitton A. Rifabutin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 983–1009.
2. Anonymous. Rifabutin. *Tuberculosis (Edinb)* 2008; **88:** 145–7.

Administration in children. For the prophylaxis of MAC in HIV-infected infants and children with low CD4+ counts, the American Academy of Pediatrics (AAP)[1] suggests an oral dose of rifabutin 5 mg/kg daily in those older than 6 years; the *BNFC* suggests the same dose may be given from 1 year of age and those 12 years of age and older may be given the usual adult dose (see Uses and Administration, above). The maximum oral dose of rifabutin is 300 mg daily.

For the treatment of nontuberculous mycobacterial disease in children aged 1 month to 12 years the *BNFC* suggests a dose of 5 mg/kg once daily as part of a multidrug regimen for up to 6 months after negative cultures are obtained; those 12 years of age and older may be given the usual adult dose.

For the treatment of pulmonary tuberculosis in those 12 years of age and older the *BNFC* suggests a dose of 150 to

450 mg once daily for at least 6 months as part of a multidrug regimen.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Oral doses of rifabutin should be reduced by 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/minute).

Cryptosporidiosis. Rifabutin may have a potential prophylactic effect against cryptosporidiosis (p. 923.1).

Mycobacterium avium complex infections. Alterations in rifabutin dosage may be necessary in patients receiving antiretrovirals for the management of HIV infection; further details are given under Tuberculosis, p. 351.1.

Peptic ulcer disease. For mention of the use of rifabutin in eradication regimens for *Helicobacter pylori* see p. 1816.2.

References.

1. Borody TJ, *et al.* Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2006; **23:** 481–8. Correction. *ibid.*; **24:** 439.
2. Miehlke S, *et al.* Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther* 2006; **24:** 395–403.
3. González Carro P, *et al.* Efficacy of rifabutin-based triple therapy in Helicobacter pylori infected patients after two standard treatments. *J Gastroenterol Hepatol* 2007; **22:** 60–3.
4. Navarro-Jarabo JM, *et al.* Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate helicobacter pylori infection. *BMC Gastroenterol* 2007; **7:** 31. Available at: http://www.biomedcentral.com/1471-230X/7/31 (accessed 12/11/07)

Toxoplasmosis. A beneficial response to rifabutin used with pyrimethamine was reported in a patient with AIDS-related *Toxoplasma gondii* encephalitis.[1] The patient was allergic to sulfonamides and clindamycin, which are commonly used (see p. 926.1).

1. Schürmann D, *et al.* Rifabutin appears to be a promising agent for combination treatment of AIDS-related toxoplasma encephalitis. *J Infect* 1998; **36:** 352–3.

Tuberculosis and HIV infection. A systematic review[1] noted that although there was no evidence to support a general replacement of rifampicin by rifabutin in regimens for tuberculosis, persons with HIV were the most likely to benefit from such an alternative because of the reduced risk of interactions with antiretroviral therapy, and had been underrepresented in studies. Rifabutin has nonetheless been used in place of rifampicin in short-course therapy for tuberculosis in patients given antiretroviral drugs for HIV infection and may be preferred for patients unable to take efavirenz.[2,3] However, dose modifications are often necessary; additionally, some combinations, notably rifabutin with delavirdine, or saquinavir alone, should not be used, although rifabutin may be given with ritonavir-boosted saquinavir.

- In patients taking ritonavir-boosted HIV-protease inhibitors the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week.[2,3] It should be noted, however, that there have been reports of inadequate serum-rifabutin concentrations (leading to rifamycin resistance) with the three times weekly regimen among patients taking ritonavir-boosted lopinavir; serum-rifabutin concentration monitoring should be considered[4]
- In patients taking unboosted atazanavir the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week[2,3]
- In those taking unboosted amprenavir, fosamprenavir, indinavir, or nelfinavir the daily dose of rifabutin should be decreased from 300 mg to 150 mg, and the dose for intermittent therapy should be 300 mg three times weekly. The dose of indinavir may need to be increased[5]
- In patients taking efavirenz (without a coadministered HIV-protease inhibitor), the dose of rifabutin should be increased from 300 mg daily or intermittently to 450 to 600 mg daily or 600 mg three times each week[2,3]
- In patients taking nevirapine the usual dose of rifabutin is given (300 mg daily or 300 mg three times each week)
- Rifabutin should not be used in patients taking etravirine plus a ritonavir-boosted HIV-protease inhibitor; if etravirine is given without a ritonavir-boosted HIV-protease inhibitor, rifabutin may be given at a dose of 300 mg once daily[3]
- Delavirdine plasma concentrations are significantly decreased by rifabutin and therefore its use with rifabutin is not recommended.

1. Davies GR, *et al.* Rifabutin for treating pulmonary tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 08/07/09).
2. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 11/04/11)
4. Boulanger C, *et al.* Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis* 2009; **49:** 1305–11.
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 2009. accessed 07/12/10.

Adverse Effects and Precautions

As for Rifampicin, p. 353.3.

Rifabutin is usually well tolerated. The most common adverse effects include rash, gastrointestinal disturbances, and neutropenia. It produces a syndrome of polyarthralgia-arthritis at doses greater than 1 g daily. Uveitis has been reported, especially in patients also receiving clarithromycin or other macrolides and possibly also with fluconazole. Asymptomatic corneal opacities have been reported after long-term use.

Rifabutin should be used with caution in patients with severe hepatic or renal impairment.

An orange-tan skin pigmentation has been reported to occur in most patients taking rifabutin.[1] Urine may also be discoloured.[2] A flu-like syndrome has been reported in 2 of 12 patients given 300 mg daily for Crohn's disease,[3] in 8 of 15 HIV-infected patients given increasing doses of rifabutin,[2] and in 1 of 16 HIV-infected patients on continuous rifabutin.[1]

Other reported adverse effects include hepatitis,[1] leucopenia[2] (including neutropenia[4]), epigastric pain,[3] rash,[3] erythema,[2] and ageusia.[5]

Rash, fever, and vomiting occurred in 1 of 2 children receiving 6.5 mg/kg daily.[6]

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.
2. Torseth J, *et al.* Evaluation of the antiviral effect of rifabutin in AIDS-related complex. *J Infect Dis* 1989; **159:** 1115–18.
3. Basilisco G, *et al.* Controlled trial of rifabutin in Crohn's disease. *Curr Ther Res* 1989; **46:** 245–50.
4. Apseloff G, *et al.* Severe neutropenia caused by recommended prophylactic doses of rifabutin. *Lancet* 1996; **348:** 685.
5. Morris JT, Kelly JW. Rifabutin-induced ageusia. *Ann Intern Med* 1993; **119:** 171–2.
6. Levin RH, Bolinger AM. Treatment of nontuberculous mycobacterial infections in pediatric patients. *Clin Pharm* 1988; **7:** 545–51.

Effects on the eyes. Uveitis may occur a few weeks or months after starting rifabutin, and generally necessitates withdrawal of the drug and treatment with topical or systemic corticosteroids and cycloplegics.[1] In 1994, the UK CSM was aware of 48 reports of uveitis in patients taking rifabutin.[2] Most patients were also receiving clarithromycin for treatment of AIDS-related *Mycobacterium avium* complex (MAC) infection and many were also receiving fluconazole (see Interactions, p. 351.3). A dosage reduction to 300 mg rifabutin daily is now recommended in patients also receiving macrolides or triazole antifungals[2,3] and is reported to produce a satisfactory response in MAC infections.[4] Panuveitis and retinal vasculitis has been reported[5] in 4 patients with active tuberculosis given rifabutin, and was thought to be a result of activation of the immune system by *Mycobacterium tuberculosis* and the very low weight of the patients.

Rifabutin-associated uveitis in children is less commonly reported probably because they may not notice or complain about visual changes, therefore monitoring of their vision while on treatment is advised.[6]

Persistent corneal deposits have been reported[7] in patients given rifabutin for Crohn's disease.

1. Tseng AL, Walmsley SL. Rifabutin-associated uveitis. *Ann Pharmacother* 1995; **29:** 1149–55.
2. CSM. Rifabutin (Mycobutin)—uveitis. *Current Problems* 1994; **20:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
3. CSM. Revised indications and drug interactions of rifabutin. *Current Problems* 1997; **23:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
4. Shafran SD, *et al.* A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS; rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996; **335:** 377–83.
5. Skolik S, *et al.* Rifabutin-associated panuveitis with retinal vasculitis in pulmonary tuberculosis. *Ocul Immunol Inflamm* 2005; **13:** 483–5.
6. Olesen HH, Krag S. Rifabutin-associated uveitis in a child. *Pediatr Infect Dis J* 2005; **24:** 1023–5.
7. Williams K, Ilari L. Persistent corneal endothelial deposits associated with rifabutin therapy for Crohn's disease. *Cornea* 2010; **29:** 706–7.

Effects on the joints. A polyarthralgia-arthritis syndrome was reported in an initial dose finding study[1] in 9 of 10 patients taking rifabutin, as monotherapy, at doses greater than 1 g. The syndrome did not occur in patients given less than 1 g daily and disappeared on drug withdrawal. Two patients with polyarthralgia-arthritis symptoms developed uveitis (see also under Effects on the Eyes, above) and aphthous stomatitis at doses of about 1.8 g daily. However, a later study[2] and case reports[3] have reported polyarthralgia-arthritis syndrome when rifabutin was given at doses of 300 to 600 mg daily as part of a multidrug regimen, including a macrolide (azithromycin or clarithromycin), for the treatment of *Mycobacterium avium* complex infection. Concentrations of rifabutin were increased as a result of inhibition of cytochrome P450 isoenzymes by the macrolide and some have suggested a maximum dose of rifabutin of 300 mg daily when used with a macrolide.[2] Higher doses of 450 to 600 mg daily may be considered for large patients or those who have failed to respond to initial treatment with a lower dose.

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.
2. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21:** 594–8.
3. Le Gars L, *et al.* Polyarthralgia-arthritis syndrome induced by low doses of rifabutin. *J Rheumatol* 1999; **26:** 1201–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rifabutin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for Rifampicin, p. 355.1.

Rifabutin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme CYP3A4). It is a less potent inducer of cytochrome P450 isoenzymes than rifampicin, but similar interactions should nevertheless be anticipated. Use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of rifabutin, and possibly adverse effects.

Plasma concentrations of rifabutin are increased by clarithromycin (and possibly other macrolides) or fluconazole, resulting in increased rifabutin toxicity, in particular uveitis, (see Effects on the Eyes, above), neutropenia, and polyarthralgia-arthritis syndrome (see Effects on the Joints, above).

Some other interactions affecting the activity of rifabutin are discussed below.

General references.

1. Baciewicz AM, *et al.* Update on rifampin and rifabutin drug interactions. *Am J Med Sci* 2008; **335:** 126–36.

Antibacterials. As discussed under Effects on the Eyes, above, most patients developing uveitis during rifabutin treatment are also receiving *clarithromycin* and it may also be implicated in the polyarthralgia-arthritis syndrome (see Effects on the Joints, above). In a study[1] of the treatment of *Mycobacterium avium* complex infection in AIDS patients, uveitis or pseudojaundice or both were noted in those receiving rifabutin, ethambutol, and clarithromycin, but not in those receiving rifabutin, ethambutol, ciprofloxacin, and clofazimine. A retrospective study[2] after an outbreak of uveitis in a similar patient population also found clarithromycin to be a risk factor, with a trend towards greater risk at higher rifabutin doses, although patient numbers were small. In 26 patients taking rifabutin with either clarithromycin or *azithromycin*,[3] the incidence and severity of adverse effects in general was similar, although the 2 patients who developed uveitis were both receiving clarithromycin.

Pharmacokinetic studies have found increased rifabutin concentrations when clarithromycin is also used. A study in healthy subjects[4] was terminated prematurely because of the high incidence of adverse effects, including neutropenia, fevers, and myalgia, particularly in subjects receiving rifabutin with azithromycin or clarithromycin. Mean serum concentrations of rifabutin and its 25-*O*-deacetyl metabolite in subjects also receiving clarithromycin were more than 4 times and 37 times those in subjects receiving rifabutin alone. Plasma concentrations were unaffected by azithromycin. Similar effects on rifabutin concentrations were found in HIV-infected subjects receiving clarithromycin[5] and reductions in clarithromycin concentrations were also noted. A study[6] to determine the tolerance and pharmacokinetic interactions of rifabutin and azithromycin in subjects with or without HIV infection found no significant drug interaction; however, the combination was poorly tolerated, mainly because of a high incidence of gastrointestinal symptoms and neutropenia.

1. Shafran SD, *et al.* Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. *N Engl J Med* 1994; **330:** 438–9.
2. Kelleher P, *et al.* Uveitis associated with rifabutin and macrolide therapy for Mycobacterium avium intracellulare infection in AIDS patients. *Genitourin Med* 1996; **72:** 419–21.

3. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21:** 594–8.
4. Apseloff G, *etal.* Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 830–5.
5. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998; **42:** 631–9.
6. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob Agents Chemother* 2001; **45:** 1572–7.

Antifungals. Rifabutin concentrations are increased by triazole antifungals and patients are at increased risk of rifabutin toxicity, specifically uveitis (see under Effects on the Eyes, p. 349.2). Rifabutin also markedly reduces the plasma concentrations of *itraconazole*, *posaconazole*, and *voriconazole*, but does not affect the metabolism of *fluconazole*.

The area under the concentration-time curve (AUC) for rifabutin and its active 25-deacetyl metabolite were increased by 82% and 216% respectively when fluconazole was given to 12 HIV-infected patients.[1] Another study[2] in 10 patients with HIV infection, found that fluconazole increased the AUC of rifabutin by 76% and by 152% when the patients were also given clarithromycin. Raised plasma-rifabutin concentrations were reported in a patient who developed uveitis while also receiving itraconazole.[3] The mechanism of the interaction remains uncertain but could involve microsomal cytochrome P450 isoenzyme CYP3A4 (see Metabolism under Pharmacokinetics, p. 352.3).

1. Trapnell CB, *et al.* Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. *Ann Intern Med* 1996; **124:** 573–6.
2. Jordan MK, *et al.* Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *Antimicrob Agents Chemother* 2000; **44:** 2170–2.
3. Lefort A, *et al.* Uveitis associated with rifabutin prophylaxis and itraconazole therapy. *Ann Intern Med* 1996; **125:** 939–40.

Antiretrovirals. Rifabutin may be used as a substitute for rifampicin in the treatment of tuberculosis.[1,2] It has little effect on the serum concentrations of unboosted *HIV-protease inhibitors* (except indinavir, nelfinavir, and saquinavir) and ritonavir-boosted HIV-protease inhibitors, although it has been reported to *increase* plasma concentrations of ritonavir-boosted lopinavir (see p. 1005.1). However, HIV-protease inhibitors, particularly if boosted with ritonavir, significantly increase serum concentrations and toxicity of rifabutin. The dose of rifabutin is therefore usually substantially decreased when given with HIV-protease inhibitors (see Tuberculosis and HIV infection under Uses, p. 349.1). Rifabutin should not be given with unboosted saquinavir; but saquinavir may be given with rifabutin if boosted with ritonavir.[2] Increases in the dose of indinavir are also required.[2]

Serum concentrations of rifabutin may be increased or decreased in those taking *NNRTIs*, however, rifabutin may usually be given to patients taking nevirapine without the need for any dose modifications. US licensed product information advises that etravirine should not be used with rifabutin if combined with ritonavir-boosted darunavir, ritonavir-boosted lopinavir, or ritonavir-boosted saquinavir; however, US guidelines[3] advise avoiding combination with any ritonavir-boosted HIV-protease inhibitor. Rifabutin is not recommended in patients taking delavirdine. In patients taking efavirenz, the dose of rifabutin should be increased by at least 50% (see Tuberculosis and HIV infection under Uses, p. 349.1).

No clinically significant interactions are expected with the integrase inhibitor *raltegravir* or the CCR-5 receptor antagonist *maraviroc*.[2]

Although rifabutin is reported to reduce the plasma concentrations of *zidovudine*, studies have shown that the effect is not marked (see p. 1026.2), and licensed product information for rifabutin suggests that the reduction may not be clinically relevant.

1. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 16/07/10)
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 11/04/11)

Antimicrobial Action

Rifabutin possesses a spectrum of antibacterial activity similar to that of rifampicin (p. 355.3). However, most investigations have concentrated on its action against mycobacteria. Cross-resistance with rifampicin is common.

Antimycobacterial action. Rifabutin possesses activity against most species of mycobacteria. It may be more active *in vivo* than *in vitro* studies suggest, as a result of its favourable pharmacokinetic profile and prolonged postantibiotic effect.[1]

Rifabutin has been reported to be active in *animal* assays against *Mycobacterium leprae*,[2] including a rifampicin-resistant strain.[3] Synergistic activity against *M. leprae* has been reported[4] *in vitro* for rifabutin with sparfloxacin.

1. Kunin CM. Antimicrobial activity of rifabutin. *Clin Infect Dis* 1996; **22** (suppl 1): S3–S14.
2. Hastings RC, Jacobson RR. Activity of ansamycin against Mycobacterium leprae in mice. *Lancet* 1983; **ii:** 1079–80. Correction. *ibid.*; 1210.
3. Hastings RC, *et al.* Ansamycin activity against rifampicin-resistant Mycobacterium leprae. *Lancet* 1984; **i:** 1130.
4. Dhople AM, Ibanez MA. In-vitro activity of three new fluoroquinolones and synergy with ansamycins against Mycobacterium leprae. *J Antimicrob Chemother* 1993; **32:** 445–51.

Resistance. Rifampicin-resistant strains of *Mycobacterium tuberculosis* have been identified in 2 patients receiving rifabutin alone as prophylaxis against *M. avium* complex.[1,2] It is therefore important to exclude *M. tuberculosis* infection before beginning rifabutin prophylaxis.

Rifampicin-resistant *M. kansasii* has also been reported in a patient receiving rifabutin.[3]

Acquired resistance has been reported in HIV-infected persons receiving highly intermittent regimens (once- or twice-weekly) of rifabutin for the treatment of active tuberculosis,[4,5] and the CDC has advised that such patients receive daily treatment during the intensive phase of therapy and daily or 3 times-weekly treatment during the continuation phase.

1. Weltman AC, *et al.* Rifampicin-resistant Mycobacterium tuberculosis. *Lancet* 1995; **345:** 1513.
2. Bishai WR, *et al.* Brief report: rifampin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. *N Engl J Med* 1996; **334:** 1573–6.
3. Meynard JL, *et al.* Rifampin-resistant Mycobacterium kansasii infection in a patient with AIDS who was receiving rifabutin. *Clin Infect Dis* 1997; **24:** 1262–3.
4. CDC. Notice to readers: acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *MMWR* 2002; **51:** 214–15.
5. Burman W, *et al.* Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med* 2006; **173:** 350–6.

Pharmacokinetics

Rifabutin is readily but incompletely absorbed from the gastrointestinal tract and peak plasma concentrations of about 250 to 600 nanograms/mL have been reported 2 to 4 hours after an oral dose of 300 mg; doubling the dose increases the peak plasma concentration. Food may delay absorption but does not affect the extent of absorption. Rifabutin is about 70% bound to plasma proteins. Rifabutin is lipophilic and therefore is widely distributed in body tissues and fluids.

Rifabutin is rapidly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 mainly to active 25-O-deacetyl and 31-hydroxy metabolites. Rifabutin induces its own metabolism resulting in a lower area under the curve after 4 weeks of continuous treatment than after the first few doses.

About 53% of a dose is found in the urine, mainly as metabolites and about 30% of a dose is excreted in the faeces. The mean half-life for rifabutin is reported to be about 40 hours, with a range of 16 to 69 hours.

References.
1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; **33:** 1237–41.

HIV-infected patients. Malabsorption of rifabutin and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p. 356.1.

The pharmacokinetics of rifabutin were studied in HIV-infected patients with normal renal and hepatic function.[1] A two-compartment open pharmacokinetic model was proposed. Rifabutin was rapidly but incompletely absorbed from the gastrointestinal tract and bioavailability was poor, being 20% on day 1 of the study and 12% on day 28. Mean peak plasma concentrations occurred 2 to 3 hours after oral doses and were about 350, 500, and 900 nanograms/mL after doses of 300, 600, and 900 mg respectively. The peak and trough concentrations after 600 mg twice daily were about 900 and 200 nanograms/mL respectively. Rifabutin was about 70% bound to plasma proteins. The area under the curve showed a decrease on repeated dosage which might be explained by the induction of drug-metabolising liver enzymes. A large volume of distribution of 8 to 9 litres/kg, indicative of extensive tissue distribution, and a mean terminal half-life of 32 to 38 hours were reported.

This study[1] also showed that the peak plasma concentration of the major metabolite, 25-deacetylrifabutin, was 10% of the parent compound. Only 4% of unchanged rifabutin was excreted in the urine after oral use and between 6 to 14% after intravenous use. Total urinary excretion of rifabutin and metabolite 72 hours after intravenous use was 44%; total faecal excretion was between 30 and 49%.

Peak and trough concentrations at steady state were reported as 900 and 200 nanograms/mL respectively in a patient with tuberculosis given rifabutin 450 mg daily.[2] While these figures were the same as those previously reported with 600 mg twice daily,[1] the earlier study showed that there was considerable interpatient variability.

CSF concentrations in 5 patients with AIDS on rifabutin 450 mg daily ranged from 36 to 70% of serum concentrations.[3]

1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; **33:** 1237–41.
2. Gillespie SH, *et al.* The serum rifabutin concentrations in a patient successfully treated for multi-resistant mycobacterium tuberculosis infection. *J Antimicrob Chemother* 1990; **25:** 490–1. Correction. *ibid.* 1991; **27:** 877.
3. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.

Metabolism. Five metabolites of rifabutin were identified in an *in-vitro* study[1] using human hepatic and enterocyte microsomes. Cytochrome P450 isoenzyme CYP3A4 was involved in the formation of all metabolites except 25-*O*-deacetylrifabutin. Deacetylation of rifabutin was apparently mediated by microsomal cholinesterase,[1] although another study[2] showed that further metabolism of 25-*O*-deacetylrifabutin is dependent on CYP3A4. The results[1] also suggested that metabolism by intestinal CYP3A4 contributes significantly to presystemic metabolism of rifabutin (and consequently its low bioavailability) and to drug interactions with azole antifungals (see above) and with macrolides (see p. 349.3).

1. Iatsimirskaia E, *et al.* Metabolism of rifabutin in human enterocyte and liver microsomes: kinetic parameters, identification of enzyme systems, and drug interactions with macrolides and antifungal agents. *Clin Pharmacol Ther* 1997; **61:** 554–62.
2. Trapnell CB, *et al.* Metabolism of rifabutin and its 25-desacetyl metabolite, LM565, by human liver microsomes and recombinant human cytochrome P-450 3A4: relevance to clinical interaction with fluconazole. *Antimicrob Agents Chemother* 1997; **41:** 924–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mycobutin; ***Austria***: Mycobutin; ***Belg.***: Mycobutin; ***Canad.***: Mycobutin; ***Cz.***: Mycobutin; ***Fin.***: Ansatipin; ***Fr.***: Ansatipine; ***Gr.***: Ansatipin; Mycobutin; ***Hong Kong***: Mycobutin; ***Irl.***: Mycobutin; ***Israel***: Mycobutin; ***Ital.***: Mycobutin; ***Neth.***: Mycobutin; ***NZ***: Mycobutin; ***Port.***: Mycobutin; ***Rus.***: Mycobutin (Микобутин); ***S.Afr.***: Mycobutin; ***Spain***: Ansatipin; ***Swed.***: Ansatipin; ***Switz.***: Mycobutin; ***Turk.***: Mycobutin; ***UK***: Mycobutin; ***Ukr.***: Mycobutin (Микобутин); ***USA***: Mycobutin.

Pharmacopoeial Preparations

USP 36: Rifabutin Capsules; Rifabutin Oral Suspension.

Rifampicin *(BAN, rINN)*

Ba-41166/E; L-5103; NSC-113926; Rifaldazine; Rifampicina; Rifampicinas; Rifampicine; Rifampicinum; Rifampin (USAN); Rifampisiini; Rifampisin; Rifamycin AMP; Ryfampicyna; Рифампицин.

3-(4-Methylpiperazin-1-yliminomethyl)rifamycin SV; (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-1,2-Dihydro-5,6,9,17,19-pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methylpiperazin-1-yliminomethyl)-1,11-dioxo-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-21-yl acetate.

$C_{43}H_{58}N_4O_{12}$=823.0

CAS — 13292-46-1.

ATC — J04AB02.

ATC Vet — QJ04AB02; QJ54AB02.

UNII — VJT6J7R4TR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Rifampicin). A reddish-brown or brownish-red, crystalline powder. Slightly soluble in water, in alcohol, and in acetone; soluble in methyl alcohol. A 1% suspension has a pH of 4.5 to 6.5. Store at a temperature not exceeding 25 degrees in an atmosphere of nitrogen in airtight containers. Protect from light.

USP 36: (Rifampin). A red-brown crystalline powder. Very slightly soluble in water; freely soluble in chloroform; soluble in ethyl acetate and in methyl alcohol. A 1% suspension in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Uses and Administration

Rifampicin belongs to the rifamycin group of antimycobacterials (p. 169.1) and is used in the treatment of various infections due to mycobacteria and other susceptible organisms (see Antimicrobial Action, p. 355.3). It is usually

given with other antibacterials to prevent the emergence of resistant organisms.

Rifampicin is used, mainly with isoniazid and pyrazinamide, as a component of multidrug regimens for the treatment of tuberculosis, and with dapsone and clofazimine in the treatment of leprosy. For the treatment of nontuberculous mycobacterial infections it is usually used with clarithromycin and ethambutol as part of a multidrug regimen.

Other uses include the treatment of brucellosis, Legionnaires' disease, mycetoma, penicillin-resistant pneumococcal meningitis, Q-fever, and various staphylococcal infections, including endocarditis. Rifampicin is used for the prophylaxis of epiglottitis and meningitis due to *Haemophilus influenzae* and for meningococcal meningitis. It is also used for the eradication of pharyngeal streptococcal carriage in pharyngitis, to reduce staphylococcal carriage, and to eliminate the carrier states for meningococcal and *H. influenzae* meningitis. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. For discussions of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

The usual oral adult dose of rifampicin is 8 to 12 mg/kg (to a maximum of 600 mg) daily, preferably on an empty stomach, or the same dose by intravenous infusion as the base or the sodium salt; higher doses are sometimes used (see below).

Rifampicin is given in the initial and continuation phases of short-course **tuberculosis** regimens (p. 210.2) with other antimycobacterials. Rifampicin is given orally on an empty stomach in adult doses of 10 mg/kg (maximum 600 mg) daily or two or three times weekly. (WHO does not recommend twice-weekly regimens as there is an increased risk of treatment failure if a dose is missed.) Alternatively, doses may be expressed as follows: with daily use, adults weighing less than 50 kg receive 450 mg and those over 50 kg receive 600 mg; with intermittent use, adults receive 600 to 900 mg three times weekly. The maximum recommended dose is considered to be 900 mg because a greater incidence of adverse effects may occur with doses above 900 mg.

For the treatment of latent tuberculosis oral rifampicin 10 mg/kg (to a maximum dose of 600 mg) may be given once daily with isoniazid for 3 months. If the contact is infected with isoniazid-resistant tuberculosis then rifampicin monotherapy may be given daily for 4 to 6 months.

In **leprosy** regimens (p. 188.3), rifampicin is usually given with dapsone for paucibacillary leprosy, and with dapsone and clofazimine for multibacillary leprosy. WHO recommends that rifampicin is given once monthly in a usual oral adult dose of 600 mg. Single-dose treatment with rifampicin, ofloxacin, and minocycline may be an alternative in patients with single-lesion paucibacillary leprosy.

In the treatment of **brucellosis**, **Legionnaires' disease**, and serious **staphylococcal infections** a dose of 600 to 1200 mg daily, orally or by intravenous infusion, in divided doses has been recommended in combination with other antibacterials.

For **prophylaxis** against meningococcal meningitis and the treatment of meningococcal carriers, rifampicin is usually given in an oral dose of 600 mg twice daily for 2 days. For prophylaxis against meningitis due to *Haemophilus influenzae*, an oral dose of 20 mg/kg once daily (to a maximum dose of 600 mg daily) for 4 days is given to adults.

For details of doses in children see p. 353.1.

Fixed-dose combination products for antimycobacterial therapy have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing rifampicin with isoniazid, isoniazid and pyrazinamide, isoniazid and ethambutol, or isoniazid, ethambutol, and pyrazinamide are available in some countries.

Doses of rifampicin should be reduced in patients with hepatic impairment (see p. 353.2).

References.
1. Anonymous. Rifampin. *Tuberculosis (Edinb)* 2008; **88:** 151–4.
2. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev* 2010; **23:** 14–34.

Administration in children. For the treatment of **tuberculosis** in infants, children, and adolescents the American Academy of Pediatrics (AAP)[1] suggests an oral dose of rifampicin of 10 to 20 mg/kg (to a maximum of 600 mg) daily or twice weekly, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests an oral dose of 15 mg/kg once daily (to a maximum of 450 mg in those under 50 kg or 600 mg in those over 50 kg); alternatively, 15 mg/kg (to a maximum of 900 mg) three times a week. WHO now recommends 10 to 20 mg/kg once daily in children weighing between 5 and 30 kg; specific recommendations have been issued on achieving this using available fixed dose combination products. Heavier children are treated as adults (see Uses and Administration, p. 350.3).[2]

For the treatment of *latent* tuberculosis the *BNFC* suggests that children 1 month and older are given oral rifampicin 15 mg/kg (to a maximum of 450 mg in those under 50 kg or 600 mg in those over 50 kg) once daily with isoniazid for 3 months. If the contact is infected with isoniazid-resistant tuberculosis then rifampicin monotherapy should be given daily for 6 months. The AAP, however, suggest oral rifampicin 10 to 20 mg/kg daily for 6 months; if daily treatment is not possible the same dose may be given twice a week for 6 months.

In **leprosy** regimens rifampicin is usually given with dapsone for the treatment of paucibacillary leprosy, and with dapsone and clofazimine for the treatment of multibacillary leprosy. WHO recommends that rifampicin is given once monthly in an oral dose of 450 mg to children 10 years of age and older.

In the treatment of **brucellosis, Legionnaires' disease**, and serious **staphylococcal infections** doses recommended by the *BNFC* are 5 to 10 mg/kg twice daily in neonates and infants up to 12 months of age, and 10 mg/kg (maximum 600 mg) twice daily in those older than one year of age. Doses are given orally or by intravenous infusion and in combination with other antibacterials.

For doses used in the treatment of human granulocytic anaplasmosis, see Ehrlichiosis, p. 353.2.

For prophylaxis against meningococcal **meningitis** the AAP recommends infants less then 1 month old are given 5 mg/kg, while infants and children aged 1 month or more are given 10 mg/kg (to a maximum of 600 mg), both given orally twice daily for 2 days. The *BNFC* recommends doses of 5 mg/kg for neonates and infants up to 12 months of age and 10 mg/kg (maximum 600 mg) for children between 1 and 12 years of age, each given orally twice daily for 2 days.

For prophylaxis against meningitis due to *Haemophilus influenzae* the AAP suggests that infants less than 1 month old may be given 10 mg/kg once daily orally for 4 days, while the *BNFC* suggests that this dose should be given to infants aged 1 to 3 months. For older infants and children both the AAP and the *BNFC* recommend an oral dose of 20 mg/kg (to a maximum of 600 mg) once daily for 4 days.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. WHO. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf (accessed 19/01/11)

Administration in hepatic impairment. Reduced oral and intravenous doses of rifampicin are recommended for patients with hepatic impairment and a maximum of 8 mg/kg daily has been suggested. See also Precautions, p. 354.3.

Ehrlichiosis. Beneficial responses to rifampicin were reported[1] in 2 women with human granulocytic anaplasmosis (see Ehrlichiosis, p. 179.1), who were pregnant and in whom the usual treatment (a tetracycline) was contra-indicated.

US guidelines[2] recommend rifampicin as a treatment alternative for patients with mild human granulocytic ehrlichiosis in whom doxycycline is contra-indicated; a dose of 300 mg orally twice daily for 7 to 10 days is recommended. Children may be given 10 mg/kg (to a maximum of 300 mg) twice daily for the same duration.

1. Buitrago MI, *et al.* Human granulocytic ehrlichiosis during pregnancy treated successfully with rifampin. *Clin Infect Dis* 1998; **27:** 213–15.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 09/12/10)

Meningitis prophylaxis. *HAEMOPHILUS INFLUENZAE MENINGITIS PROPHYLAXIS.* Meningeal infection with *Haemophilus influenzae* type b (Hib) in children is associated with substantial morbidity, but the incidence has decreased since the introduction of immunisation with *H. influenzae* type b vaccine. Although a worldwide problem, the disease (p. 191.1) and its prophylaxis has been studied mainly in the USA, where it was shown that children under 4 years of age formed the highest risk group for primary infection while children under 2 years of age formed the highest risk group for secondary infection.[1] The goal of prophylaxis in close contacts is to eliminate carriage of the organism to prevent spread to young children. Risk of infection to young children with recent household contact to the primary case of infection with *H. influenzae* type b is increased 600- to 800-fold,[1,2] but only increased 20-fold[3] from day-care or school contact. The risk may be higher when more than 1 index patient is identified.

Rifampicin given orally in doses of 20 mg/kg once daily for 4 days (maximum dose 600 mg) has been shown to eradicate Hib nasopharyngeal carriage in at least 95% of contacts of the primary case.[4] There is some evidence from a study involving 68 families of patients with Hib infection that rifampicin 20 mg/kg daily for 2 days may be as effective as a 4-day course in eradicating Hib pharyngeal colonisation.[5] Rifampicin prophylaxis appears to be successful in preventing infection in household contacts, but benefit in school settings where there has been a single index case has not been established.[3]

Recommendations have been made for rifampicin prophylaxis.[6,7] The American Academy of Pediatrics (AAP) recommends[6] that all household contacts be given rifampicin prophylaxis where there is at least 1 vulnerable contact person (considered to be a child younger than 4 years of age who is not or incompletely immunised against Hib, an incompletely immunised child younger than 12 months of age, or an immunocompromised child, regardless of vaccine status) in the household. Similar recommendations have been made in the UK (although a vulnerable contact is considered to be a child under 10 years old, or any immunocompromised person, regardless of age).[7] The AAP[6] also recommends rifampicin prophylaxis when 2 or more cases of Hib disease have occurred within 60 days in a day-care or school. In the UK,[7] prophylaxis has been recommended for all room contacts when 2 or more cases of disease have occurred within 120 days. Rifampicin prophylaxis is not recommended for pregnant women.[6]

For recommended *doses* see Uses and Administration (p. 350.3) and Administration in Children, above.

Rifampicin should also be given to the primary case since treatment of the infection does not eradicate nasopharyngeal carriage.[2,6,7]

1. Casto DT, Edwards DL. Preventing Haemophilus influenzae type b disease. *Clin Pharm* 1985; **4:** 637–48.
2. Cartwright KAV, *et al.* Chemoprophylaxis for Haemophilus influenzae type b: rifampicin should be given to close contacts. *BMJ* 1991; **302:** 546–7.
3. ASHP Commission on Therapeutics. ASHP therapeutic guidelines on nonsurgical antimicrobial prophylaxis. *Clin Pharm* 1990; **9:** 423–45.
4. Band JD, *et al.* Prevention of Hemophilus influenzae type b disease. *JAMA* 1984; **251:** 2381–6.
5. Green M, *et al.* Duration of rifampin chemoprophylaxis for contacts of patients infected with Haemophilus influenzae type B. *Antimicrob Agents Chemother* 1992; **36:** 545–7.
6. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
7. DoH, Public Health England. Revised recommendations for the prevention of secondary Haemophilus influenzae type b (Hib) disease (updated 1 July, 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/231009/ Revised_recommendations_for_the_preventions_of_secondary_Haemophilus_influenzae_type_b_disease.pdf (accessed 11/09/13)

MENINGOCOCCAL MENINGITIS PROPHYLAXIS. Neisseria meningitidis is an important cause of bacterial meningitis (p. 191.1); all age groups are at risk during epidemics but children are usually at highest risk during endemic outbreaks. Vaccines are available for meningococci groups A, C, Y, and W135 but not usually for group B, therefore antimicrobial prophylaxis remains important in preventing the spread of the disease. The aim of prophylaxis is to eliminate nasopharyngeal carriage of the organism. Sulfadiazine and minocycline are no longer used because of resistance and adverse effects. A 2-day course of oral rifampicin (for doses see Uses and Administration (p. 350.3) and Administration in Children, above) is one of the recommended regimens for prophylaxis (although ciprofloxacin is usually preferred).[1] Antibacterial prophylaxis should be given as soon as possible to close contacts (ideally within 24 hours of diagnosis of the index case). It is also recommended for child care or nursery school contacts in the USA,[2] but is not usually advised for this group in the UK after a single case.[1] The index patient should also receive antibacterial prophylaxis for 2 days before hospital discharge since treatment with penicillin does not eliminate nasopharyngeal carriage.

1. Health Protection Agency. Guidance for public health management of meningococcal disease in the UK (updated January 2011). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947389261 (accessed 12/05/11)
2. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): prevention and control of meningococcal disease. *MMWR* 2005; **54** (RR-7): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5407.pdf (accessed 05/10/07)

Naegleria infections. For mention of the use of rifampicin in primary amoebic meningoencephalitis, see p. 922.1.

Adverse Effects

Rifampicin is usually well tolerated. Adverse effects are more common during intermittent therapy or after restarting interrupted treatment.

Some patients may have a cutaneous syndrome that presents 2 to 3 hours after a daily or intermittent dose as facial flushing and itching, with or without a rash, or rarely eye irritation and visual disturbances. A flu-like syndrome characterised by episodes of fever, chills, headache, dizziness, bone pain, shortness of breath, and malaise has been associated with intermittent use. It usually occurs after 3 to 6 months of intermittent treatment and has a higher incidence with doses of 25 mg/kg or more given once weekly than with more frequent dosage regimens. Anaphylaxis or shock has occurred rarely.

Gastrointestinal adverse effects include nausea, vomiting, anorexia, diarrhoea, and epigastric distress. Taking doses on an empty stomach is recommended for maximal absorption, but dosage after a meal will minimise gastrointestinal intolerance. Pseudomembranous colitis has been reported. Rifampicin produces transient abnormalities in liver function and hepatitis. Fatalities due to hepatotoxicity have been reported occasionally (see Effects on the Liver, p. 354.1).

Rifampicin can cause thrombocytopenia and purpura, usually when given as an intermittent regimen, and if this occurs further use of rifampicin is contra-indicated. Other haematological adverse effects include eosinophilia, leucopenia, and haemolytic anaemia.

Alterations in kidney function and renal failure have occurred, particularly during intermittent therapy. Menstrual disturbances have been reported.

Nervous system adverse effects include headache, drowsiness, ataxia, dizziness, and numbness.

Oedema, myopathy, and muscular weakness have been reported.

Thrombophlebitis has occurred after prolonged intravenous infusion. Extravasation during intravenous infusion may cause local irritation and inflammation.

Rifampicin causes a harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears, and other body fluids. Soft contact lenses may become permanently stained.

Effects on the blood. Thrombocytopenia may occur in patients taking rifampicin, most commonly as intermittent therapy, and probably has an immunological basis. The platelet count may fall within 3 hours of a dose and return to normal within 36 hours, if additional doses are not given.[1] There may also be a risk of thrombocytopenia when re-introducing rifampicin to patients who have interrupted their treatment.[2] Thrombocytopenia has also been reported in a patient taking rifampicin for the first time for meningococcal prophylaxis.[3] Thrombotic thrombocytopenic purpura has been reported in a patient after two weeks of treatment with oral rifampicin and intravenous vancomycin for an infection with MRSA.[4] Fatalities have occurred when rifampicin was not withdrawn once thrombocytopenic purpura had developed or when treatment with rifampicin was resumed in patients who had experienced purpura.[1] However, there is a report of the successful re-introduction of rifampicin in a patient who developed thrombocytopenia without rifampicin-dependent antibodies.[5]

Bleeding from the oral cavity not associated with thrombocytopenia has been reported in a patient taking rifampicin.[6] Leucopenia,[7,8] haemolysis or haemolytic anaemia,[9] and red cell aplasia[10] have occurred. Disseminated intravascular coagulation has been reported in a patient receiving intermittent rifampicin therapy.[11] The incidence of deep-vein thrombosis increased in one group of hospitalised tuberculosis patients when rifampicin was introduced as standard therapy,[12] but data from others have not supported a causal relationship.[13]

1. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1982; **23:** 56–74.
2. Burnette PK, *et al*. Rifampin-associated thrombocytopenia secondary to poor compliance. *Drug Intell Clin Pharm* 1989; **23:** 382–4.
3. Hall AP, *et al*. New hazard of meningococcal chemoprophylaxis. *J Antimicrob Chemother* 1993; **31:** 451.
4. Gupta R, Wargo KA. Rifampin-induced thrombotic thrombocytopenic purpura. *Ann Pharmacother* 2005; **39:** 1761–2.
5. Bhasin DK, *et al*. Can rifampicin be restarted in patients with rifampicin-induced thrombocytopenia? *Tubercle* 1991; **72:** 306–7.
6. Sule RR. An unusual reaction to rifampicin in a once monthly dose. *Lepr Rev* 1996; **67:** 227–33.
7. Van Assendelft AHW. Leucopenia in rifampicin chemotherapy. *J Antimicrob Chemother* 1985; **16:** 407–8.
8. Vijayakumaran P, *et al*. Leucocytopenia after rifampicin and ofloxacin therapy in leprosy. *Lepr Rev* 1997; **68:** 10–15.
9. Lakshminarayan S, *et al*. Massive haemolysis caused by rifampicin. *BMJ* 1973; **2:** 282–3.
10. Mariette X, *et al*. Rifampicin-induced pure red cell aplasia. *Am J Med* 1989; **87:** 459–60.
11. Souza CS, *et al*. Disseminated intravascular coagulopathy as an adverse reaction to intermittent rifampin schedule in the treatment of leprosy. *Int J Lepr* 1997; **65:** 366–71.
12. White NW. Venous thrombosis and rifampicin. *Lancet* 1989; **ii:** 434–5.
13. Cowie RL, *et al*. Deep-vein thrombosis and pulmonary tuberculosis. *Lancet* 1989; **ii:** 1397.

Effects on the gastrointestinal tract. In addition to symptoms of gastrointestinal intolerance, there have been reports of gastrointestinal bleeding and erosive gastritis,[1] ulcerative colitis,[2] and eosinophilic colitis[3] in patients receiving rifampicin.

1. Zargar SA, *et al*. Rifampicin-induced upper gastrointestinal bleeding. *Postgrad Med J* 1990; **66:** 310–11.
2. Tajima A, *et al*. Rifampicin-associated ulcerative colitis. *Ann Intern Med* 1992; **116:** 778–9.
3. Lange P, *et al*. Eosinophilic colitis due to rifampicin. *Lancet* 1994; **344:** 1296–7.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with rifampicin and other first-line antituberculous drugs, but sometimes the **hepatotoxicity** may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Rifampicin is thought to have a lower potential for hepatotoxicity than isoniazid or pyrazinamide.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1]

The **incidence** of severe hepatotoxicity was found to be lower in patients taking isoniazid, rifampicin, and pyrazinamide for initial treatment of active tuberculosis, than in those given rifampicin and pyrazinamide for 2 months for latent infection. Management of latent disease with the rifampicin plus pyrazinamide regimen was also associated with a higher incidence of severe hepatotoxicity than was isoniazid monotherapy for 6 months.[2] Severe and sometimes fatal hepatotoxicity has been associated with a regimen of rifampicin and pyrazinamide for the treatment of latent tuberculosis in a mainly HIV-negative study population.[2-6] In the USA, the CDC and the American Thoracic Society[7] now recommend that a regimen of rifampicin with pyrazinamide should not generally be offered to persons with latent tuberculosis. However, an evaluation of studies[8] for the prevention of tuberculosis, involving HIV-infected patients, reported very little evidence of hepatotoxicity among patients taking rifampicin plus pyrazinamide and among those taking isoniazid.

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[9] for initial measurement of liver function in all patients and regular **monitoring** in patients with pre-existing liver disease. Details are given concerning the response to deteriorating liver function and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced for the USA.[10,11]

For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p. 312.1 and Pyrazinamide, p. 345.3.

Hepatitis and liver dysfunction have also been reported in patients taking rifampicin, in the absence of other hepatotoxic drugs, for the treatment of pruritus associated with primary biliary cirrhosis.[12]

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11:** 699–707.
2. van Hest R, *et al*. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. *Clin Infect Dis* 2004; **39:** 488–96.
3. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. *MMWR* 2001; **50:** 733–5. Also available at http://www.cdc.gov/mmwr/PDF/wk/mm5034.pdf (accessed 05/10/07)
4. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide treatment for latent tuberculosis infection. *MMWR* 2002; **51:** 998–9. Also available at http://www.cdc.gov/mmwr/PDF/wk/mm5144.pdf (accessed 05/10/07)
5. Jasmer RM, *et al*. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002; **137:** 640–7.
6. Ijaz K, *et al*. Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. *Clin Infect Dis* 2006; **42:** 346–55.
7. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; **52:** 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)
8. Gordin FM, *et al*. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? *Clin Infect Dis* 2004; **39:** 561–5.
9. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
10. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 05/10/07) Correction. *ibid*. 2005; **53:** 1203. [dose]
11. Saukkonen JJ, *et al*. American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 16/07/10)
12. Prince MI, *et al*. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut* 2002; **50:** 436–9.

Effects on the lungs. Pulmonary fibrosis[1] in one elderly man and pneumonitis[2] in another were attributed to rifampicin.

1. Umeki S. Rifampicin and pulmonary fibrosis. *Arch Intern Med* 1988; **148:** 1663, 7.
2. Kunichika N, *et al*. Pneumonitis induced by rifampicin. *Thorax* 2002; **57:** 1000–1001.

Effects on the pancreas. Chronic pancreatic insufficiency has been reported in a patient after use of rifampicin, isoniazid, ethambutol, and pyrazinamide.[1]

1. Liu BA, *et al*. Pancreatic insufficiency due to antituberculosis therapy. *Ann Pharmacother* 1997; **31:** 724–6.

Effects on the skin. Skin reactions to rifampicin are usually mild, irrespective of it being given daily or intermittently.[1] However, there have been a few isolated reports of severe reactions such as toxic epidermal necrolysis,[2] exfoliative dermatitis,[3] fixed drug eruptions,[4,5] and acute generalised exanthematous pustulosis.[6] Contact dermatitis has been seen after handling rifampicin powder.[7]

1. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother* 1977; **3:** 115–32.
2. Okano M, *et al*. Toxic epidermal necrolysis due to rifampicin. *J Am Acad Dermatol* 1987; **17:** 303–4.
3. Goldin HM, *et al*. Rifampin and exfoliative dermatitis. *Ann Intern Med* 1987; **107:** 789.
4. Mimouni A, *et al*. Fixed drug eruption following rifampin treatment. *DICP Ann Pharmacother* 1990; **24:** 947–8.
5. John SS. Fixed drug eruption due to rifampin. *Lepr Rev* 1998; **69:** 397–9.
6. Azad A, Connelly N. Case of rifampicin-induced acute generalized exanthematous pustulosis. *Intern Med J* 2006; **36:** 619–20.
7. Anker N, Da Gunha Bang F. Long-term intravenous rifampicin treatment: advantages and disadvantages. *Eur J Respir Dis* 1981; **62:** 84–6.

Hypersensitivity. References.

1. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother* 1977; **3:** 115–32.
2. Wurtz RM, *et al*. Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients. *Lancet* 1989; **i:** 955–6.
3. Harland RW, *et al*. Anaphylaxis from rifampin. *Am J Med* 1992; **92:** 581–2.
4. Cnudde F, Leynadier F. The diagnosis of allergy to rifampicin confirmed by skin test. *Am J Med* 1994; **97:** 403–4.
5. Sharma VK, *et al*. Rifampicin-induced urticaria in leprosy. *Lepr Rev* 1997; **68:** 331–2.
6. Martínez E, *et al*. Shock and cerebral infarct after rifampin re-exposure in a patient infected with human immunodeficiency virus. *Clin Infect Dis* 1998; **27:** 1329–30.

Lupus. Symptoms including malaise, arthralgia, arthritis, and oedema of the extremities, occurring in 4 patients taking rifampicin and 3 taking rifabutin, were considered to be due to drug-induced lupus syndrome.[1] Cutaneous lupus erythematosus was reported in a patient receiving rifampicin with clarithromycin and ethambutol.[2] All patients had positive anti-nuclear antibody titres.[1,2]

1. Berning SE, Iseman MD. Rifamycin-induced lupus syndrome. *Lancet* 1997; **349:** 1521–2.
2. Patel GK, Anstey AV. Rifampicin-induced lupus erythematosus. *Clin Exp Dermatol* 2001; **26:** 260–2.

Overdosage. Cases of skin pigmentation induced by rifampicin overdose have been reviewed.[1] Reddish-orange discoloration of the skin appeared within a few hours of taking the drug; urine, mucous membranes, and sclera were also discoloured. Periorbital or facial oedema, pruritus, and gastrointestinal intolerance occurred in most patients. Treatment was supportive and clinical symptoms resolved in most patients over 3 to 4 days, although fatalities occurred with doses over 14 g.

1. Holdiness MR. A review of the redman syndrome and rifampicin overdosage. *Med Toxicol Adverse Drug Exp* 1989; **4:** 444–51.

Precautions

Liver function should be checked before treatment with rifampicin and special care should be taken in alcoholic patients or those with pre-existing liver disease who require regular monitoring during therapy. UK licensed product information states that use is contra-indicated in patients with jaundice. A self-limiting hyperbilirubinaemia may occur in the first 2 or 3 weeks of treatment. Alkaline phosphatase values may be raised moderately due to rifampicin's enzyme-inducing capacity. Isolated results showing hyperbilirubinaemia in the first few weeks and/or moderately elevated transaminase values are not indications to withdraw rifampicin. However, dose adjustment is necessary when there is other evidence of hepatic impairment and treatment should be suspended when there is evidence of more serious liver toxicity.

Blood counts should be monitored during prolonged treatment and in patients with hepatic disorders. Should thrombocytopenia or purpura occur then rifampicin should be withdrawn permanently. UK product information also recommends such withdrawal in patients who develop haemolytic anaemia or renal failure.

Use of rifampicin after interruption of treatment has been associated with increased risk of serious adverse effects.

The enzyme-inducing properties of rifampicin (see Interactions, p. 355.1) can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormone, and vitamin D. Management of diabetes mellitus may be more difficult, and rifampicin should be used with caution in diabetic patients.

Patients should be advised that rifampicin may colour faeces, saliva, sputum, sweat, tears, urine, and other body-

fluids orange-red. Soft contact lenses may become permanently stained.

Rifampicin should not be given by the intramuscular or subcutaneous route. When given by intravenous infusion care should be taken to avoid extravasation.

Adrenocortical insufficiency. Adrenal insufficiency has been associated with tuberculosis and induction of microsomal enzymes by rifampicin may accelerate the metabolism of cortisol and precipitate an acute adrenal crisis in such patients.[1] Induction of microsomal enzymes may be enough to compromise even patients with mildly impaired cortisol production. Critical hypotension has also developed in non-Addisonian patients within a week to 10 days of starting rifampicin therapy. However, it has not been necessary to suspend the use of rifampicin if patients are treated with corticosteroids.[2] The efficacy of corticosteroid therapy can be reduced by rifampicin.

1. Elansary EH, Earis JE. Rifampicin and adrenal crisis. *BMJ* 1983; **286:** 1861–2.
2. Boss G. Rifampicin and adrenal crisis. *BMJ* 1983; **287:** 62.

Breast feeding. Rifampicin is excreted into breast milk. No adverse effects have been seen in breast-fed infants whose mothers were taking rifampicin, and the last available guidance from the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/10/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rifampicin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Pregnancy. Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] have recommended treatment of pregnant patients with the same rifampicin-containing multidrug regimens as would be used in non-pregnant patients. While use of rifampicin in pregnant patients is generally considered to be safe, the drug does cross into the fetus[4] and malformations and bleeding tendencies have been reported.[5] A literature review[5] revealed 386 normal term infants and 29 elective terminations out of 446 pregnancies in patients who took rifampicin with other antimycobacterial drugs. A variety of malformations were reported; there were 14 abnormal infants or fetuses, 2 premature births, 9 still-births and 7 spontaneous abortions. It was considered that rifampicin did not increase the overall risk of congenital malformations.

Rifampicin treatment can increase the metabolism of vitamin K, resulting in clotting disorders associated with vitamin K deficiency. Bleeding disorders in 2 mothers shortly after delivery, and scalp haemorrhage, anaemia, and shock in one of the infants have been reported.[6] The authors recommended blood coagulation monitoring and giving prophylactic vitamin K to mothers and neonates when the mother has received rifampicin during pregnancy.

1. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/12/10)
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 05/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
4. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
5. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122:** 65–79.
6. Chouraqui JP, *et al.* Hémorragie par avitaminose K chez la femme enceinte et le nouveau-né: rôle éventuel de la rifampicine: a propos de 2 observations. *Therapie* 1982; **37:** 447–50.

Interactions

Rifampicin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme family CYP3A) or drug transporter proteins (such as p-glycoprotein). Drugs so affected may require an increase in dosage to maintain efficacy and patients should be monitored closely when starting or stopping concurrent rifampicin treatment. Women taking oral contraceptives should use additional precautions or change to a non-hormonal form of contraception (see Rifamycins, p. 2243.1).

The absorption of rifampicin may be reduced by antacids, but this interaction can be overcome by giving rifampicin an hour before any antacid. Similarly, rifampicin and preparations containing bentonite (for example some aminosalicylic acid preparations) should be given 8 hours apart. Isoniazid and halothane may increase the potential for hepatotoxicity when given with rifampicin. Atovaquone may increase the concentration of rifampicin, while rifampicin decreases the concentration of atovaquone. Some other interactions affecting the activity of rifampicin are discussed below.

Reviews.

1. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. *Drug Safety* 2002; **25:** 111–33.
2. Niemi M, *et al.* Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet* 2003; **42:** 819–50.
3. Baciewicz AM, *et al.* Update on rifampin and rifabutin drug interactions. *Am J Med Sci* 2008; **335:** 126–36.

Antibacterials. Use of *clofazimine* in leprosy patients receiving rifampicin with or without dapsone may decrease the rate of absorption of rifampicin and increase the time to peak plasma concentration.[1] In patients receiving clofazimine, rifampicin, and dapsone, the area under the curve for rifampicin was reduced.[1] However, a multiple dose study[2] showed that the pharmacokinetics of rifampicin were similar after 7 days of treatment with rifampicin and dapsone or rifampicin, dapsone, and clofazimine.

In 15 patients receiving therapy including rifampicin for tuberculosis, a course of *co-trimoxazole* resulted in increases in peak plasma concentrations and in the area under the concentration-time curve for rifampicin.[3] No adverse effects were seen and the clinical implications of this observation remain unclear. In another study,[4] significant reductions in the area under the plasma concentration-time curves for trimethoprim and sulfamethoxazole occurred after therapy including rifampicin was given to 10 HIV-infected patients on co-trimoxazole prophylaxis. Again, the clinical significance of this interaction is unclear.

There is little significant pharmacokinetic interaction between rifampicin and *isoniazid*.[5] Although lower blood concentrations of rifampicin have been reported with isoniazid, the effect is not considered clinically significant.[6] Since both drugs are hepatotoxic, there could be an increased incidence of hepatic damage, although the benefits of using this combination are considered to outweigh any potential risks.

1. Mehta J, *et al.* Effect of clofazimine and dapsone on rifampicin (Lositril) pharmacokinetics in multibacillary and paucibacillary leprosy cases. *Lepr Rev* 1986; **57** (suppl 3): 67–76.
2. Venkatesan K, *et al.* The effect of clofazimine on the pharmacokinetics of rifampicin and dapsone in leprosy. *J Antimicrob Chemother* 1986; **18:** 715–18.
3. Bhatia RS, *et al.* Drug interaction between rifampicin and cotrimoxazole in patients with tuberculosis. *Hum Exp Toxicol* 1991; **10:** 419–21.
4. Ribera E, *et al.* Rifampin reduces concentrations of trimethoprim and sulfamethoxazole in serum in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2001; **45:** 3238–41.
5. Acocella G, *et al.* Kinetics of rifampicin and isoniazid administered alone and in combination to normal subjects and patients with liver disease. *Gut* 1972; **13:** 47–53.
6. Mouton RP, *et al.* Blood levels of rifampicin, desacetylrifampicin and isoniazid during combined therapy. *J Antimicrob Chemother* 1979; **5:** 447–54.

Antifungals. Giving rifampicin, *ketoconazole*, and isoniazid together has produced low serum concentrations of each drug resulting in failure of antifungal treatment.[1] Rifampicin serum concentrations are reduced when rifampicin is given with ketoconazole;[2] separation of the doses by 30 minutes[3] to 12 hours[2] may result in similar rifampicin concentrations to those attained when rifampicin is given alone, although serum concentrations of ketoconazole remain depressed regardless of the timing of doses.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; **109:** 844–5. Correction. *ibid.* 1989; **111:** 96.
2. Engelhard D, *et al.* Interaction of ketoconazole with rifampin and isoniazid. *N Engl J Med* 1984; **311:** 1681–3.
3. Doble N, *et al.* Pharmacokinetic study of the interaction between rifampicin and ketoconazole. *J Antimicrob Chemother* 1988; **21:** 633–5.

Antigout drugs. Although a study[1] showed that *probenecid* could increase serum-rifampicin concentrations, another[2] subsequently found that the effect was uncommon and inconsistent and concluded that probenecid had no place as an adjunct to routine rifampicin therapy.

1. Kenwright S, Levi AJ. Impairment of hepatic uptake of rifamycin antibiotics by probenecid and its therapeutic implications. *Lancet* 1973; **ii:** 1401–5.
2. Fallon RJ, *et al.* Probenecid and rifampicin serum levels. *Lancet* 1975; **ii:** 792–4.

Antiretrovirals. Rifamycins can induce the metabolism of *zidovudine*, the NNRTIs delavirdine, efavirenz, etravirine, and nevirapine, and *HIV-protease inhibitors*, resulting in potentially subtherapeutic plasma concentrations. In addition HIV-protease inhibitors inhibit the metabolism of rifamycins resulting in elevated plasma-rifamycin concentrations and an increased incidence of adverse effects.[1,2]

Guidelines in the UK[3] and the USA[2] recommend that rifampicin should not be used with the *NNRTIs* delavirdine and etravirine but opinion varies on whether it should be used with nevirapine. Patients taking rifampicin-based tuberculosis treatment when antiretroviral therapy (ART) was started were found to have a higher probability of an elevated viral load or virological failure in the first 2 years if they started treatment with a nevirapine-based regimen compared with those who started efavirenz-based ART.[4] However, virological outcomes for those given a nevirapine-based regimen were good, with 80% of them being virologically suppressed after 18 months of ART. Similarly, a prospective, controlled study of 142 HIV and tuberculosis co-infected Thai patients[5] found plasma-efavirenz concentrations to be less compromised by rifampicin than plasma-nevirapine concentrations; low NNRTI concentrations were predictive of HAART failure. Based on these data, the authors suggested that efavirenz-based ART should be preferred for HIV-infected patients who require treatment with rifampicin. Licensed product information for nevirapine and etravirine advise against the use of either drug with rifampicin. Rifampicin decreases the serum concentration of efavirenz and if they are used together, consideration should be given to increasing the dose of the antiretroviral (see Uses and Administration of Efavirenz, p. 977.1); no dose modification is needed for rifampicin.

It is also recommended that rifampicin should not be used with unboosted or low-dose ritonavir-boosted *HIV-protease inhibitor* regimens.

Rifampicin significantly decreases the serum concentration of the CCR-5 receptor antagonist, *maraviroc*, and it is recommended that the dose of maraviroc be increased (see Uses and Administration of Maraviroc, p. 1005.2); no dose modification is needed for rifampicin. Similarly, a dose increase should be considered for the integrase inhibitor *raltegravir* if coadministration with rifampicin cannot be avoided (see Uses and Administration of Raltegravir, p. 1011.3). No clinically significant interactions are expected with the HIV fusion inhibitor *enfuvirtide*.[6] See also p. 350.1 for comment on the interaction of antiretrovirals with rifabutin.

1. Anonymous. Clinical update: impact of HIV protease inhibitors on the treatment of HIV-infected tuberculosis patients with rifampin. *MMWR* 1996; **45:** 921–5.
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 16/07/10)
3. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)
4. Boulle A, *et al.* Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; **300:** 530–9.
5. Manosuthi W, *et al.* A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N_2R Study. *Clin Infect Dis* 2009; **48:** 1752–9.
6. Boyd MA, *et al.* Lack of enzyme-inducing effect of rifampicin on the pharmacokinetics of enfuvirtide. *J Clin Pharmacol* 2003; **43:** 1382–91.

Antimicrobial Action

Rifampicin is bactericidal against a wide range of microorganisms and interferes with their synthesis of nucleic acids by inhibiting DNA-dependent RNA polymerase. It has the ability to kill intracellular organisms. It is active against mycobacteria, including *Mycobacterium tuberculosis*, *M. avium*, and *M. leprae* and, having high sterilising activity against these organisms, it possesses the ability to eliminate semi-dormant or persisting organisms.

Rifampicin is also active against Gram-positive bacteria, especially staphylococci, but less active against Gram-negative organisms. The most sensitive Gram-negative bacteria include *Neisseria meningitidis*, *N. gonorrhoeae*, *Haemophilus influenzae*, and *Legionella* spp. Rifampicin also has activity against *Chlamydia trachomatis* and some anaerobic bacteria. At high concentrations it is active against some viruses.

Strains of *M. tuberculosis*, *M. leprae*, and other susceptible bacteria (such as *N. meningitidis*) have shown resistance, both initially and during treatment. Acquired resistance to rifampicin develops rapidly if it is used alone in the treatment of clinical infection, and resistance is thought to be due to a single-step mutation of the DNA-dependent RNA polymerase. Thus in tuberculosis and leprosy treatment regimens, rifampicin is used with other antimycobacterials to delay or prevent the development of rifampicin resistance. Resistance does not appear to be a problem when rifampicin is used alone in the management of latent tuberculosis, probably because the bacillary load is low. Cross-resistance has been shown between rifampicin and other rifamycins. Strains of *M. tuberculosis* resistant to both rifampicin and isoniazid (termed multidrug-resistant tuberculosis) are increasingly being reported; some strains are also resistant to second-line antimycobacterials (termed extensively drug-resistant tuberculosis).

Pharmacokinetics

Rifampicin is readily absorbed from the gastrointestinal tract and peak plasma concentrations varying from 4 to 32 micrograms/mL (average 7 micrograms/mL) have been reported after a dose of 600 mg. Food may reduce and delay absorption. Rifampicin is about 80% bound to plasma proteins. It is widely distributed in body tissues and fluids and diffusion into the CSF is increased when the meninges are inflamed. Rifampicin is distributed into breast milk and crosses the placenta (see Breast Feeding, p. 353.1, and Pregnancy, p. 353.1, under Precautions). Half-lives for rifampicin have been reported to range initially from 2 to 5 hours, the longest elimination times occurring after the largest doses. However, as rifampicin induces its own metabolism, elimination time may decrease by up to 40% during the first 2 weeks, resulting in half-lives of about 2 to 3 hours. The half-life is prolonged in patients with severe hepatic impairment.

Rifampicin is rapidly metabolised in the liver mainly to active 25-*O*-deacetylrifampicin and excreted in the bile. Deacetylation diminishes intestinal reabsorption and increases faecal excretion, although significant enterohepatic circulation still takes place. About 60% of a dose eventually appears in the faeces. The amount excreted in the urine increases with increasing doses and up to 30% of a dose may be excreted in the urine, about half of it being unchanged drug. The metabolite formylrifampicin is also excreted in the urine. In patients with renal impairment the half-life of rifampicin is not prolonged at doses of 600 mg or less.

Distribution. Rifampicin is widely distributed in most body tissues and fluids after oral or intravenous use.[1] Rifampicin is also able to penetrate into polymorphonuclear leucocytes to kill intracellular pathogens.[2] Rifampicin does not appear to diffuse well through the uninflamed meninges[3] but therapeutic concentrations have been attained in the CSF after daily doses of 600 and 900 mg when the meninges are inflamed;[4] concentrations in the CSF are about 10 to 20% of simultaneous serum concentrations, and approximately represent the fraction unbound to plasma proteins. Corticosteroids do not appear to influence the penetration of rifampicin into the CSF of patients with tuberculous meningitis.[5]

1. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.
2. Prokesch RC, Hand WL. Antibiotic entry into human polymorphonuclear leukocytes. *Antimicrob Agents Chemother* 1982; **21:** 373–80.
3. Sippel JE, *et al*. Rifampin concentrations in cerebrospinal fluid of patients with tuberculous meningitis. *Am Rev Respir Dis* 1974; **109:** 579–80.
4. D'Oliveira JJG. Cerebrospinal fluid concentrations of rifampin in meningeal tuberculosis. *Am Rev Respir Dis* 1972; **106:** 432–7.
5. Woo J, *et al*. Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; **42:** 235–42.

HIV-infected patients. Malabsorption of rifampicin and other antituberculous drugs has been reported in some patients with HIV infection and tuberculosis,[1-6] and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. It is not clear whether this is related to the HIV infection itself or associated diarrhoea. A pilot study[2] in 26 HIV-positive patients undergoing multidrug antituberculosis treatment found that serum concentrations of isoniazid were generally regarded as adequate; serum concentrations of rifampicin and ethambutol were low. A study[3] in patients with HIV infection but not co-infected with tuberculosis reported reduced absorption for rifampicin and pyrazinamide compared with healthy subjects; isoniazid was generally well absorbed. A pharmacokinetic study[4] reported malabsorption of all first-line antituberculous drugs in patients who had advanced HIV infection with diarrhoea and cryptosporidial infection. A further pharmacokinetic study,[5] in a similar subject population, found a significant degree of malabsorption of rifampicin and isoniazid in HIV-infected patients with or without diarrhoea. Low serum concentrations of rifabutin were reported in HIV-infected patients co-infected with tuberculosis treated with an intermittent (twice-weekly) tuberculosis regimen.[6] However, others found that HIV infection either did not affect[7,8] or uncommonly affected[9] the pharmacokinetics of antituberculous drugs.

Some authorities[10,11] consider that HIV-infected patients (including children) with tuberculosis have a similar response to short-course multidrug therapy as HIV-negative tuberculosis patients, and that most can be treated with the standard 6-month regimen. US[11,12] and UK[13] guidelines recommend that highly intermittent (once or twice weekly) tuberculosis regimens should not be used for co-infected patients with CD4+ cell counts less than 100 cells/microlitre.

1. Patel KB, *et al*. Drug malabsorption and resistant tuberculosis in HIV-infected patients. *N Engl J Med* 1995; **332:** 336–7.
2. Peloquin CA, *et al*. Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; **30:** 919–25.
3. Sahai J, *et al*. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann Intern Med* 1997; **127:** 289–93.
4. Gurumurthy P, *et al*. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob Agents Chemother* 2004; **48:** 4473–5.
5. Gurumurthy P, *et al*. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis* 2004; **38:** 280–3.
6. Weiner M, *et al*. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005; **40:** 1481–91.
7. Choudhri SH, *et al*. Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea. *Clin Infect Dis* 1997; **25:** 104–11.
8. Taylor B, Smith PJ. Does AIDS impair the absorption of antituberculosis agents? *Int J Tuberc Lung Dis* 1998; **2:** 670–5.
9. Perlman DC, *et al*. The clinical pharmacokinetics of pyrazinamide in HIV-infected persons with tuberculosis. *Clin Infect Dis* 2004; **38:** 556–64.
10. WHO. *TB/HIV. A clinical manual*. 2nd ed. Geneva: WHO, 2004. Available at: http://whqlibdoc.who.int/publications/2004/9241546344.pdf (accessed 05/10/07)
11. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1 207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 01/07/09)
12. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; **58** (RR-11): 1–166. Available at http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf (accessed 16/07/10)
13. Pozniak AL, *et al*. British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)

Intravenous administration. Mean peak plasma concentrations of 10 micrograms/mL have been reported after rifampicin 600 mg by intravenous infusion over 3 hours. Peak plasma concentrations declined with repeated doses but to a less marked extent than occurs with oral use.[1] Mean peak plasma concentrations of 27 micrograms/mL have been reported in children after doses of 11.5 mg/kg infused over 30 minutes. Mean concentrations of 1.9 micrograms/mL were reported 8 hours after the dose.[2]

1. Acocella G, *et al*. Serum and urine concentrations of rifampicin administered by intravenous infusion in man. *Arzneimittelforschung* 1977; **27:** 1221–6.
2. Koup JR, *et al*. Pharmacokinetics of rifampin in children I. Multiple dose intravenous infusion. *Ther Drug Monit* 1986; **8:** 11–16.

Oral administration. Gastrointestinal absorption of rifampicin is considered good. However, analysis of serum-rifampicin concentrations in children indicated that only 50 ± 22% of a freshly prepared oral suspension was absorbed.[1] Varying oral bioavailability from capsule formulations has also been reported and could result in ineffective therapy[2] or higher than needed serum concentrations.[3]

The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[4] Another report[5] also showed reduced peak serum concentrations when rifampicin was given with a high-fat meal, and it was suggested that rifampicin should preferably be given on an empty stomach.

1. Koup JR, *et al*. Pharmacokinetics of rifampin in children II. Oral bioavailability. *Ther Drug Monit* 1986; **8:** 17–22.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.
3. Ganiswarna SG, *et al*. Bioavailability of rifampicin caplets (600 mg and 450 mg) in healthy Indonesian subjects. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 60–4.
4. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; **76:** 109–13.
5. Peloquin CA, *et al*. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. *Chest* 1999; **115:** 12–18. Correction. *ibid.*; 1485.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Moxina†; Rifadin; Rifalep; ***Austral.***: Rifadin; Rimycin; ***Austria***: Eremfat; Rifoldin; Rimactan; ***Belg.***: Rifadine; ***Braz.***: Monicil†; Rifaldin; Rifamp; ***Canad.***: Rifadin; Rofact; ***Chile***: Rifadin; Rifaldin†; ***China***: Fuhe (复和); Pi Jin (匹金); Shu Lan Xin (舒兰新); Wei Fu Xin (维夫欣); ***Cz.***: Arficin; Benemicin; Eremfat; ***Denm.***: Rimactan; ***Fin.***: Rimapen; ***Fr.***: Rifadine; Rimactan; ***Ger.***: Eremfat; Rifa†; ***Gr.***: Declobiotic; Maximicetin; Rifadin; Rifaldin; ***Hong Kong***: Ricin; Rifacap†; Rifadin; Rifasynt; Rimactane†; Rimycin†; ***Hung.***: Rifamed; ***India***: Coxid; Eufacin; Famcin; Iso-Rifa; Kemorifa; LS Rif; Macox; Monocin; Montomycin; R-Cin; Rifacilin; Rifacom-EZ; Rifamycin; Rimactane; Siticox†; ***Indon.***: Corifam; Famri; Lanarif; Medirif†; Merimac; Prolung†; Ramicin†; RIF; Rifabiotic†; Rifacin†; Rifamtibi; Rimactane; ***Irl.***: Rifadin; Rimactane†; ***Israel***: Rimactan; ***Ital.***: Rifadin; ***Malaysia***: Rifasynt; Rimactane; ***Mex.***: Alfiral; Eurifam; Finamicina†; Pestarin†; Rifadin; Rimactan; Turifam; ***Neth.***: Rifadin; ***Norw.***: Rimactan; ***NZ***: Rifadin; ***Philipp.***: Crisarfam; Fampisec; Framacin†; Medifam; Natricin; Odifam†; Refam†; Rexilan; Ricyn†; Rifacin; Rifadin; Rifamax; Rifanid; Rimactane; Rimaped; Riprocin; ***Port.***: Rifadin; Rifex†; ***Rus.***: Benemicin (Бенемицин)†; Eremfat (Эремфат); Farbutin (Фарбутин); Macox (Макокс); Rimactane (Римактан); Rimpin (Римпин); ***S.Afr.***: Rifadin; Rimactane; ***Singapore***: Rifaren; Rimactane†; ***Spain***: Rifaldin; Rimactan; ***Swed.***: Rifadin; Rimactan; ***Switz.***: Rimactan; ***Thai.***: Manorifcin; Myrin-P†; Ricin; Rifacin-A; Rifadin; Rifagen; Rifam-P; Rifam; Rifamcin; Rimaccin; Rimactane†; Rimecin; Ripin; ***Turk.***: Rifadin; Rifcap; Rifex†; ***UK***: Rifadin; Rimactane; ***USA***: Rifadin; Rimactane; ***Venez.***: Rifadin; Rimactan.

Multi-ingredient Preparations. ***Arg.***: Bacifim†; Rifaprim; Rifinah; ***Austria***: Rifater; Rifoldin mit INH; ***Braz.***: Isoniaton†; ***Canad.***: Rifater; ***China***: An Si Nuo Kang (安斯诺康); Chang Wei Rui Da Xin (长威瑞达欣); Dai Fei Lin (戴菲林); Fei An (费安); Fei Lu De (菲路得); Fei Ning (费宁); Fei Su (菲苏); Fei Ting (菲亭); Hu Fei Te (护菲特); Ke Lao Er Kang (克劳尔康); Pi Lv (匹律); Rui Fu An Kang (瑞福安康); Rui Qing (瑞清); Ti Bi (缇碧); Wei Bao (维葆); Wei Fei (维菲); Yi Bi Fu (依比福); Yi Nuo Ni Kang (怡诺尼康); Yi Ti Bi (伊缇碧); ***Denm.***: Rimactazid; Rimcure; Rimstar; ***Fin.***: Rimactazid; Rimstar; ***Fr.***: Rifater; Rifinah; ***Ger.***: Iso-Eremfat; Rifater†; Rifinah†; tebesium Duo; tebesium Trio; ***Gr.***: Oboliz; Rifater; Rifinah; Rimactazid; ***Hong Kong***: Rifater; Rifinah; ***Hung.***: Rifazid; ***India***: AFB3; AFB4; Akt-2; Akt-3; Akt-4; Akt-FD; Akurit-3; Akurit-4; Akurit-Z; Akurit; Antibin; Arzade; Arzide†; Becox Forte Kit; Becox RH; Bicox Kid; Bicox-E; Bicox; Binex DT; Binex E; Binex Kid; Binex Z; Binex ZE; Binex; Cavidin INH; Cavirip; Cavitar RHE; Caviter FD; Caviter; Confez-3; Coxina-3; Coxina-4; Coxinex; Coxkit-3; Coxpic; Coxter-2; Coxter-3; Coxter-4; Cx-3; Cx-4; Cx-5; Emrif Kit; Emrif; Eufacin Inh; Eufacin Plus; Eufazid; Famcin H; Faminex Forte; Faminex; Forecox; Gocox Compound; Gocox-3; Infez-4; Ipcacin Kid†; Ipcacin; Iso-Ripharmed; Isorifam; Macox Plus; Macox-ZH; Monto-2; Monto-3; Monto-4; Montonex Forte; Montorip; Mycocox-4; Mycocox-E; Mycocox-Z; Mycocox; Mycodot Kit; Mycodot-4; Mycodot-E; Mycodot-Z; Mycurit-3; Mycurit-4; Mycurit-Z; Optirifa Plus; R-Cinex Z; R-Cinex; RHZ Plus; RHZ; Rifa E; Rifa; Rimactazid + Z; Rimpazid; Siticox-INH†; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed 2; Xeed 3E; Xeed 4; ***Indon.***: Ramicin-ISO†; Rimactazid; Rimcure; Rimstar; ***Irl.***: Rifater; Rifinah; Rimactazid; Rimcure†; Rimstar; ***Ital.***: Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; ***Malaysia***: Rimactazid; Rimcure; ***Mex.***: Arpisen†; Dotbal-S; Dotbal; Finater†; Finateramida†; Rifaprim; Rifater; Rifinah; ***Neth.***: Rifinah; Rimactazid†; Rimcure†; Rimstar†; ***Norw.***: Rimactazid; Rimcure; Rimstar; ***NZ***: Rifinah; ***Philipp.***: 4D; AKuriT-4; AKuriT; Bifix; CombiKids†; CombiPack; Continukit Plus†; Continukit; Continupack†; Duomax; Econofix; Econokit-MDR; Econokit; Econopack; Fixcom 3; Fixcom 4; HR Pedia Kit; HRZ Pedia Kit; Kidz Kit 2; Kidz Kit 3; Myrin-P; Myrin; Quadmax; Quadtab; Refam Duo†; Refam Pedia Kit†; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; SVM-Polypac-A†; Tres; Triofix; Tritab; Viper†; ***Pol.***: Rifamazid; ***Port.***: Rifater; Rifinah; ***Rus.***: Combitub (Комбитуб); Forecox (Форкокс); Iso-Eremfat (Изо-Эремфат); Isocomb (Изокомб); Laslonvita (Ласлонвита); Protub-2 (Протуб-2); Protub-3 (Протуб-3); Protub-4 (Протуб-4); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс)†; Rimactazid (Римактазид)†; Rimecure 3-FDC (Римкур 3-ФДС)†; Rimstar 4-FDC (Римстар 4-ФДС)†; Tubavit (Тубавит); ***S.Afr.***: Rifafour; Rifater†; Rifinah; Rimactazid; Rimcure; Rimstar; ***Singapore***: Merip; Rimactazid; ***Spain***: Rifater; Rifinah; Rimactazid†; Rimcure†; Rimstar; Tisobrif†; ***Swed.***: Rimactazid; Rimcure; Rimstar; ***Switz.***: Rifater; Rifinah; Rimactazid; Rimstar; ***Thai.***: Lepromix MB; Lepromix PB; Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid†; Rimcure 3-FDC; Rimstar†; ***UK***: Rifater; Rifinah; Rimstar; Voractiv; ***USA***: IsonaRif; Rifamate; Rifater; ***Venez.***: Rimactazid; Rimcure.

Pharmacopoeial Preparations

BP 2014: Rifampicin Capsules; Rifampicin Oral Suspension;
USP 36: Rifampin and Isoniazid Capsules; Rifampin Capsules; Rifampin for Injection; Rifampin Oral Suspension; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Rifamycin Sodium *(BANM, USAN, rINNM)*

CB-01-11; M-14 (rifamycin); Natrii Rifamycinum; Rifamicina sódica; Rifamicin-nátrium; Rifamicino natrio druska; Rifamycin-Natrium; Rifamycin sodná sůl; Rifamycin SV; Rifamycin SV Sodium; Rifamycine sodique; Rifamycinnatrium; Rifamycinum Natricum; Rifamysiininatrium; Ryfamycinum Natricum; Ryfamycyna sodowa; Натрий Рифамицин.

Sodium (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-21-acetoxy-1,2-dihydro-6,9,17,19-tetrahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,11-dioxo-2,7-(epoxypentadeca-1,11,13-trienimino)-naphtho[2,1-*b*]furan-5-olate.

$C_{37}H_{46}NNaO_{12}$=719.8

CAS — 6998-60-3 (rifamycin); 14897-39-3 (rifamycin sodium); 15105-92-7 (rifamycin sodium).

ATC — J04AB03; S01AA16; S02AA12.

ATC Vet — QJ04AB03; QS01AA16; QS02AA12.

UNII — 32086GS35Z.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rifamycin Sodium). The monosodium salt of rifamycin SV, a substance obtained by chemical transformation of rifamycin B which is produced during growth of certain strains of *Amycolatopsis mediterranei*. Rifamycin SV may also be obtained directly from certain mutants of *A. mediterranei*. The potency is not less than 900 units/mg calculated with reference to the anhydrous substance. A red, fine or slightly granular powder. Soluble in water; freely soluble in dehydrated alcohol. A 5% solution in water

has a pH of 6.5 to 8.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Rifamycin is a rifamycin antibacterial that has been used in the treatment of infections caused by susceptible organisms including Gram-positive organisms such as staphylococci. It has been given as the sodium salt by intramuscular injection and by slow intravenous infusion and is also given by local instillation and topical application.

Adverse Effects and Precautions

Some gastrointestinal adverse effects have occurred after injections of rifamycin. High doses may produce alterations in liver function. Hypersensitivity reactions including rashes, pruritus, and anaphylaxis have occurred rarely, but prolonged use increases the risk of sensitisation. A reddish coloration of the urine and other body fluids has been reported. Rifamycin should be used with care in patients with hepatic dysfunction.

Antimicrobial Action

Rifamycin has similar antimicrobial actions to those of rifampicin (p. 353.3).

Pharmacokinetics

Rifamycin is not effectively absorbed from the gastrointestinal tract. Plasma concentrations of 2 micrograms/mL occur 2 hours after a dose of 250 mg by intramuscular injection; concentrations of about 11 micrograms/mL have been achieved 2 hours after an intravenous dose of 500 mg. Rifamycin is about 80% bound to plasma proteins and has a plasma half-life of about 1 hour.

Rifamycin is excreted mainly in the bile and only small amounts appear in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rifocina; ***Austria***: Rifocin; ***Belg.***: Rifocine; ***Braz.***: Arrif; Rifan; Rifasan; Rifocina; ***China***: De Ji Jin Fei Ke (德济金菲克); Feng Li Fu (蜂立复); Fu An Er (夫安尔); Lan Qi (澜琪); Sai Rui Chen (赛瑞辰); Xing Suo Ning (星索宁); ***Fr.***: Otofa; ***Ital.***: Rifocin; ***Mex.***: Rifocyna; ***Port.***: Rifocina; ***Rus.***: Otofa (Отофа); ***Switz.***: Otofa; ***Turk.***: Rif; Rifateral; Rifocin; ***Ukr.***: Otofa (Отофа); Rifonat (Рифонат); ***Venez.***: Rifocina.

Multi-ingredient Preparations. ***Braz.***: Rifocort.

Rifapentine *(BAN, USAN, rINN)*

DL-473; DL-473-IT; L-11473; MDL-473; Rifapentina; Rifapentinum; Рифапентин.

3-[*N*-(4-Cyclopentyl-1-piperazinyl)formimidoyl]rifamycin.

$C_{47}H_{64}N_4O_{12}$=877.0

CAS — 61379-65-5.

ATC — J04AB05.

ATC Vet — QJ04AB05.

UNII — XJM390A33U.

Uses and Administration

Rifapentine is a rifamycin antibacterial (see Rifampicin, p. 350.3) that is used, with other antimycobacterials, for the treatment of tuberculosis (p. 210.2).

For drug-susceptible organisms rifapentine is given orally in a dose of 600 mg twice weekly during the initial intensive phase of short-course tuberculosis regimens, then once weekly during the continuation phase.

General references.

1. Jarvis B, Lamb HM. Rifapentine. *Drugs* 1998; **56:** 607–16.
2. Munsiff SS, *et al.* Rifapentine for the treatment of pulmonary tuberculosis. *Clin Infect Dis* 2006; **43:** 1468–75.
3. Anonymous. Rifapentine. *Tuberculosis (Edinb)* 2008; **88:** 155–8.

Adverse Effects

As for Rifampicin, p. 351.3.

A higher incidence of hyperuricaemia has been reported with rifapentine than with rifampicin.

Precautions

As for Rifampicin, p. 352.3.

Rifapentine is only licensed for use in once- or twice-weekly regimens, and should not be given to HIV-infected patients because of potential interactions with HIV-protease inhibitors; an increased risk of developing resistance to rifamycins with highly intermittent (once- or twice-weekly) dosing regimens may occur in these patients.

Rifapentine is teratogenic in *animals*.

Interactions

As for Rifampicin, p. 353.1.

Enzyme induction studies have suggested that rifapentine is a more potent inducer of cytochrome P450 isoenzymes than rifabutin, but less potent than rifampicin. It should not be used with HIV-protease inhibitors because of the risk of developing resistance, see Precautions, above.

Antimicrobial Action

As for Rifampicin, p. 353.3.

Cross-resistance is common between rifapentine and rifampicin in *Mycobacterium tuberculosis*.

Antimycobacterial action. References.

1. Mor N, *et al.* Comparison of activities of rifapentine and rifampin against Mycobacterium tuberculosis residing in human macrophages. *Antimicrob Agents Chemother* 1995; **39:** 2073–7.
2. Vernon A, *et al.* Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 1999; **353:** 1843–7.

Pharmacokinetics

Rifapentine is absorbed after oral doses. Absorption is enhanced by between about 35 and 85% when rifapentine is taken with food. Peak plasma concentrations occur 5 to 6 hours after a single dose of 600 mg and steady-state concentrations are reached by day 10 during daily use. A half-life of about 13 hours has been reported. Rifapentine undergoes nonoxidative metabolism and does not induce its own metabolism. Rifapentine and its active metabolite 25-deacetylrifapentine are 98% and 93% bound to plasma proteins, respectively.

Rifapentine and 25-deacetylrifapentine are excreted mainly in the faeces with a small amount appearing in the urine.

References.

1. Keung ACF, *et al.* Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunction. *J Clin Pharmacol* 1998; **38:** 517–24.
2. Keung AC-F, *et al.* Pharmacokinetics of rifapentine in subjects seropositive for the human immunodeficiency virus: a phase I study. *Antimicrob Agents Chemother* 1999; **43:** 1230–3.
3. Conte JE, *et al.* Single-dose intrapulmonary pharmacokinetics of rifapentine in normal subjects. *Antimicrob Agents Chemother* 2000; **44:** 985–90.
4. Weiner M, *et al.* Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med* 2004; **169:** 1191–7.
5. Langdon G, *et al.* Population pharmacokinetics of rifapentine and its primary desacetyl metabolite in South African tuberculosis patients. *Antimicrob Agents Chemother* 2005; **49:** 4429–36.
6. Blake MJ, *et al.* Pharmacokinetics of rifapentine in children. *Pediatr Infect Dis J* 2006; **25:** 405–9.
7. Zvada SP, *et al.* Effects of four different meal types on the population pharmacokinetics of single-dose rifapentine in healthy male volunteers. *Antimicrob Agents Chemother* 2010; **54:** 3390–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ming Jia Xin (明佳欣); ***Rus.***: Rifapex (Рифапекс); ***USA***: Priftin.

Rifaximin *(BAN, USAN, rINN)*

L-105; Rifaxidin; Rifaximina; Rifaximine; Rifaximinum; Рифаксимин.

(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-Pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazole-1,15(2*H*)-dione 25-acetate.

$C_{43}H_{51}N_3O_{11}$=785.9

CAS — 80621-81-4.

ATC — A07AA11; D06AX11.

ATC Vet — QA07AA11; QD06AX11; QG51AA06; QJ51XX01.

UNII — L36O5T016N.

NOTE. The code L-105 has also been applied to the cephalosporin cefuzonam.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rifaximin). A semisynthetic product derived from a fermentation product. A red-orange, crystalline, hygroscopic powder. It exhibits polymorphism. Practically insoluble in water; soluble in acetone and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Rifaximin is a synthetic, nonabsorbed, derivative of rifamycin used orally for the treatment of travellers' diarrhoea (see Gastro-enteritis, p. 182.2) caused by noninvasive strains of *Escherichia coli* and to reduce the risk of recurrence of hepatic encephalopathy (see p. 1811.2). It has also been tried for other infectious diarrhoea in nontravellers, abdominal distension, bloating, and flatulence, small bowel bacterial overgrowth, and for surgical infection prophylaxis, as well as in some of those conditions discussed under Gastrointestinal Disorders (p. 1807.2), including diverticulitis, Crohn's disease, and non-constipation irritable bowel syndrome.

For the treatment of travellers' diarrhoea in those 12 years of age and older, the recommended oral dose is 200 mg three times daily for 3 days. A dose of 550 mg orally twice daily is recommended to reduce the risk of overt hepatic encephalopathy recurrence among patients 18 years of age and older. Doses given for other indications range from 400 to 1200 mg daily, in 2 to 4 divided doses.

Rifaximin has also been used topically as a 5% ointment.

General references.

1. Gillis JC, Brogden RN. Rifaximin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential in conditions mediated by gastrointestinal bacteria. *Drugs* 1995; **49:** 467–84.
2. Ojetti V, *et al.* Rifaximin pharmacology and clinical implications. *Expert Opin Drug Metab Toxicol* 2009; **5:** 675–82.
3. Bajaj JS, Riggio O. Drug therapy: rifaximin. *Hepatology* 2010; **52:** 1484–8.
4. Dupont HL. Biologic properties and clinical uses of rifaximin. *Expert Opin Pharmacother* 2011; **12:** 293–302.

Gastrointestinal disorders. References.

1. DuPont HL, *et al.* Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis* 2001; **33:** 1807–15.
2. Pakyz AL. Rifaximin: a new treatment for travelers' diarrhea. *Ann Pharmacother* 2005; **39:** 284–9.
3. Robins GW, Wellington K. Rifaximin: a review of its use in the management of traveller's diarrhoea. *Drugs* 2005; **65:** 1697–1713.
4. Adachi JA, DuPont HL. Rifaximin: a novel nonabsorbed rifamycin for gastrointestinal disorders. *Clin Infect Dis* 2006; **42:** 541–7. Correction. *ibid.*; 896. [dose frequency]
5. Pimentel M, *et al.* The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med* 2006; **145:** 557–63.
6. Fumi AL, Trexler K. Rifaximin treatment for symptoms of irritable bowel syndrome. *Ann Pharmacother* 2008; **42:** 408–12.
7. Shafran I, Burgunder P. Rifaximin for the treatment of newly diagnosed Crohn's disease: a case series. *Am J Gastroenterol* 2008; **103:** 2158–60.
8. Jiang Q, *et al.* Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol* 2008; **20:** 1064–70.
9. Lauritano EC, *et al.* Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. *Eur Rev Med Pharmacol Sci* 2009; **13:** 111–16.
10. Peralta S, *et al.* Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with rifaximin. *World J Gastroenterol* 2009; **15:** 2628–31.
11. Maclayton DO, Eaton-Maxwell A. Rifaximin for treatment of hepatic encephalopathy. *Ann Pharmacother* 2009; **43:** 77–84.
12. Bass NM, *et al.* Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362:** 1071–81.
13. Hong KS, *et al.* Efficacy of rifaximin compared with ciprofloxacin for the treatment of acute infectious diarrhea: a randomized controlled multicenter study. *Gut Liver* 2010; **4:** 357–62.
14. Tannous G, *et al.* Therapeutic success of rifaximin for *Clostridium difficile* infection refractory to metronidazole and vancomycin. *Case Rep Gastroenterol* 2010; **4:** 404–409.
15. Patrick Basu P, *et al.* Rifaximin therapy for metronidazole-unresponsive *Clostridium difficile* infection: a prospective pilot trial. *Therap Adv Gastroenterol* 2010; **3:** 221–5.
16. Pimentel M, *et al.* TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011; **364:** 22–32.

Diverticular disease. Rifaximin may be used in the management of diverticular disease (p. 1809.2); for reference to its use with mesalazine see p. 1862.3.

Adverse Effects and Precautions

Since rifaximin is poorly absorbed from the gastrointestinal tract, adverse effects have generally been restricted to gastrointestinal disturbances such as abdominal pain, diarrhoea, and nausea. Headache may also occur. Hypersensitivity reactions, including exfoliative dermatitis and angioedema have been reported.

Because of its poor systemic absorption (see p. 357.3) rifaximin should not be used to treat systemic bacterial infections. It should not be given to patients with travellers' diarrhoea complicated by fever or blood in the stool and should be used with caution in patients with severe (Child-Pugh Class C) hepatic impairment because of the risk of increased systemic exposure.

References.

1. Ericsson CD. Safety and tolerability of the antibacterial rifaximin in the treatment of travellers' diarrhoea. *Drug Safety* 2006; **29:** 201–7.

Antimicrobial Action

Rifaximin has a mechanism of action and spectrum of antibacterial activity similar to that of rifampicin (see p. 353.3). Among Gram-negative bacteria, it is particularly active against the Enterobacteriaceae, and has good activity against *Vibrio cholera*. It also has pH-dependent activity against *Helicobacter pylori* (including clarithromycin-resistant strains); activity is improved at basic pH.

Rifaximin also appears to have activity against some protozoa, such as *Blastocystis hominis* and *Cryptosporidium parvum*.

Pharmacokinetics

Rifaximin is essentially nonabsorbed from the gastrointestinal tract, having a bioavailability of less than 0.4%. After a

single 400-mg oral dose serum concentrations up to 5.3 nanograms/mL have been found at 4 hours. Rifaximin is moderately bound to human plasma proteins. No excretion in breast milk has been noted.

Systemically available rifaximin is believed to be metabolised in the liver, similarly to other rifamycin derivatives; the systemic exposure of rifaximin is markedly elevated in patients with hepatic impairment; after the same dosing regimen, AUCs were 10-, 13-, and 20-fold higher in those with Child-Pugh Class A, B, and C hepatic impairment, respectively, than in healthy patients.

Rifaximin concentrates, and is mainly excreted unchanged in the faeces; less than 1% of a dose is recovered in the urine within the first 24 hours, mostly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Coloximina; Rifadom; ***Austria***: Colidimin; ***China***: Bang Yi (邦益); Fu Jie Ting (弗皆亭); Fu Te (抚特); Ji Li Qing (及利晴); Jinxili (金喜利); Lai Li Qing (莱利青); Ou Ke Shuang (欧克双); Qian Er Fen (倩儿芬); Sa Fen (萨芬); Xi Jie (希捷); Xifushen (昔服申); Zi Jun (紫军); ***Cz.***: Normix; ***Denm.***: Faxinorm; Saftra; Xifaxan; ***Fin.***: Targaxan; ***Ger.***: Xifaxan; ***Gr.***: Lormyx; Rifacol; ***Hung.***: Normix; ***Ital.***: Colrifax; Diamixin; Normix; Redactiv; Rifacol; Sanecol; ***Mex.***: Flonorm; ***Neth.***: Xifaxan; ***Pol.***: Xifaxan; ***Port.***: Xifaxan; ***Rus.***: Alfa Normix (Альфа Нормикс); ***Spain***: Spiraxin; Zaxine†; ***Turk.***: Colidur; Normix; ***UK***: Targaxan; Xifaxanta; ***USA***: Xifaxan.

Rokitamycin *(rINN)*

M-19-Q; Rikamycin; Rokitamicina; Rokitamycine; Rokitamycinum; TMS-19Q; Рокитамицин; 3″-Propionyl-leucomycin A_5.

[(4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxooxacyclohexadeca-11,13-dien-6-yl]-3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4″-butyrate 3″-propionate.

$C_{42}H_{69}NO_{15}$=828.0

CAS — 74014-51-0.

ATC — J01FA12.

ATC Vet — QJ01FA12.

UNII — ZPT03UEM0E.

Pharmacopoeias. In *Jpn.*

Profile

Rokitamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p. 291.2). It has been given orally in usual doses of 400 mg twice daily in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Paidocin; Rokital; ***Jpn***: Ricamycin.

Rolitetracycline *(BAN, USAN, rINN)*

PMT; Pyrrolidinomethyltetracycline; Rolitetraciclina; Rolitétracycline; Rolitetracyclinum; Rolitetracyklin; Rolitetrasykliini; SQ-15659; Ролитетрациклин.

N^2-(Pyrrolidin-1-ylmethyl)tetracycline.

$C_{27}H_{33}N_3O_8$=527.6

CAS — 751-97-3.

ATC — J01AA09.

ATC Vet — QJ01AA09.

UNII — GH9IW85221.

Profile

Rolitetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p. 375.1). It is included in some topical eye preparations used for the treatment of susceptible infections. It has also been given by injection, when it has been associated with shivering and, more rarely, rigor, due to a Jarisch-Herxheimer reaction. Injection has also been followed by a peculiar taste sensation, often similar to ether.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Colbiocin; Eubetal Antibiotico; ***Rus.***: Colbiocin (Колбиоцин).

Rosoxacin *(BAN, USAN, rINN)*

Acrosoxacin; Rosoksasiini; Rosoxacine; Rosoxacino; Rosoxacinum; Win-35213; Розоксацин.

1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid.

$C_{17}H_{14}N_2O_3$=294.3

CAS — 40034-42-2.

ATC — J01MB01.

ATC Vet — QJ01MB01.

UNII — 3Y1OT3J4NW.

Uses and Administration

Rosoxacin is a 4-quinolone antibacterial with actions similar to those of nalidixic acid (p. 328.3). It is active against *Neisseria gonorrhoeae* and has been given as single-dose oral treatment for gonorrhoea. It has also been used in the treatment of urinary-tract infections.

Adverse Effects and Precautions

As for Nalidixic Acid, p. 329.1.

Dizziness, drowsiness, and visual disturbances occur relatively frequently, and patients should be advised not to drive or operate machinery if affected.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Eradacil; ***Mex.***: Eradacil†.

Roxithromycin *(BAN, USAN, rINN)*

Roksitromicinas; Roksitromisin; Roksitromysiini; Roxithromycine; Roxithromycinum; Roxitromicin; Roxitromicina; Roxitromycin; RU-965; RU-28965; Рокситромицин.

Erythromycin 9-[*O*-[(2-methoxyethoxy)methyl]oxime].

$C_{41}H_{76}N_2O_{15}$=837.1

CAS — 80214-83-1.

ATC — J01FA06.

ATC Vet — QJ01FA06.

UNII — 21KOF230FA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Roxithromycin). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane; slightly soluble in dilute hydrochloric acid. Store in airtight containers.

Uses and Administration

Roxithromycin is a macrolide antibacterial given for the treatment of susceptible infections; its actions and uses are similar to those of erythromycin (p. 292.1). It is given orally to adults in a usual dose of 150 mg twice daily or sometimes 300 mg once daily, at least 15 minutes before meals, for 5 to 10 days.

Dosage may need to be modified in patients with hepatic or renal impairment (see p. 358.2).

For doses in infants and children, see p. 358.2.

References.

1. Williams JD, Sefton AM. Comparison of macrolide antibiotics. *J Antimicrob Chemother* 1993; **31** (suppl C): 11–26.
2. Markham A, Faulds D. Roxithromycin: an update of its antimicrobial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **48**: 297–326.
3. Young LS, Lode H, eds. Roxithromycin: first of a new generation of macrolides: update and perspectives. *Infection* 1995; **23** (suppl 1): S1–S52.
4. Lovering AM, *et al.*, eds. Roxithromycin—additional therapeutic potential. *J Antimicrob Chemother* 1998; **41** (suppl B): 1–97.

Administration in children. Roxithromycin may be given orally to children for the treatment of susceptible infections. In those weighing from 6 to 40 kg, a dose of 5 to 8 mg/kg daily may be used.

Administration in hepatic impairment. The licensed product information for roxithromycin notes that safety in hepatic impairment has not been established and advises halving the usual daily oral dose (see above) if used.

Administration in renal impairment. The licensed product information for roxithromycin notes that safety in renal impairment has not been established and dosage adjustment details are not specified.

A pharmacokinetic study[1] in 20 subjects (10 with normal renal function and 10 with severely impaired function) suggested that doubling the dosage interval of oral roxithromycin would be suitable in those with a creatinine clearance of less than 15 mL/minute.

1. Halstenson CE, *et al.* Disposition of roxithromycin in patients with normal and severely impaired renal function. *Antimicrob Agents Chemother* 1990; **34**: 385–9.

Alopecia. Results of a study *in vitro* and *in vivo*[1] suggested that topical roxithromycin might be of benefit in restoring hair loss in individuals with androgenetic alopecia.

1. Ito T, *et al.* Roxithromycin antagonizes catagen induction in murine and human hair follicles: implication of topical roxithromycin as hair restoration reagent. *Arch Dermatol Res* 2009; **301**: 347–55.

Hyperplasia. Gingival hyperplasia is a well recognised adverse effect of ciclosporin treatment; a small study[1] indicated that roxithromycin could reduce overgrowth, possibly by an effect on transforming growth factor-β. For the use of another macrolide, azithromycin, for this indication see Hyperplasia, p. 1954.3.

1. Condé SAP, *et al.* Roxithromycin reduces cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc* 2008; **40**: 1435–8.

Ischaemic heart disease. For mention of studies investigating roxithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p. 222.1.

Respiratory disorders. For reference to the use of roxithromycin in the management of respiratory disorders, see under Erythromycin, p. 292.3.

Adverse Effects and Precautions

As for Erythromycin, p. 293.1.

Gastrointestinal disturbances are the most frequent adverse effect, but are less frequent than with erythromycin.

The dose of roxithromycin may need to be reduced in patients with hepatic or renal impairment.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in a patient given roxithromycin; renal function improved over several days after the drug was stopped.

1. Akcay A, *et al.* Acute renal failure and hepatotoxicity associated with roxithromycin. *Ann Pharmacother* 2004; **38**: 721–2.

Effects on the lungs. Acute eosinophilic pneumonia was attributed in a patient to the use of roxithromycin.[1] The condition resolved after treatment with methylprednisolone.

1. Pérez-Castrillón JL, *et al.* Roxithromycin-induced eosinophilic pneumonia. *Ann Pharmacother* 2002; **36**: 1808–9.

Effects on the pancreas. Acute pancreatitis, with duodenal inflammation, pain, pancreatic enlargement, and raised serum-amylase developed in a patient within 24 hours of substituting roxithromycin for erythromycin ethyl succinate.[1] Symptoms resolved rapidly once roxithromycin was stopped.

1. Souweine B, *et al.* Acute pancreatitis associated with roxithromycin therapy. *DICP Ann Pharmacother* 1991; **25**: 1137.

Hypersensitivity. For a report of an eosinophilic syndrome in a patient after treatment with azithromycin or roxithromycin, see Azithromycin, p. 222.3. See also under Effects on the Lungs, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies roxithromycin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 294.2.

Roxithromycin has a much lower affinity for cytochrome P450 isoenzymes than erythromycin and therefore has fewer interactions. It does not appear to interact with antacids, carbamazepine, oral contraceptives, prednisolone, or ranitidine.

Antimicrobial Action

As for Erythromycin, p. 295.1. It is reported to be as active or slightly less active than erythromycin.

Pharmacokinetics

Roxithromycin is absorbed after oral doses with a bioavailability of about 50%. Peak plasma concentrations of about 6 to 8 micrograms/mL occur around 2 hours after a single 150-mg dose. The mean peak plasma concentration at steady state after a dose of 150 mg twice daily is 9.3 micrograms/mL. Absorption is reduced when taken after a meal. It is widely distributed into tissues and body fluids; high concentrations are taken up into white blood cells. Small amounts of roxithromycin are distributed into breast milk. It is about 96% bound to plasma proteins

(mainly α_1-acid glycoprotein) at trough concentrations, but binding is saturable, and only about 87% is bound at usual peak concentrations. Small amounts of roxithromycin are metabolised in the liver, and the majority of a dose is excreted in the faeces as unchanged drug and metabolites; about 7 to 10% is excreted in urine, and up to 15% via the lungs. The elimination half-life is reported to range from about 8 to 13 hours, but may be more prolonged in patients with hepatic or renal impairment and in children. It has been reported that roxithromycin is not substantially removed by peritoneal dialysis.

References.
1. Puri SK, Lassman HB. Roxithromycin: a pharmacokinetic review of a macrolide. *J Antimicrob Chemother* 1987; **20** (suppl B): 89–100.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Delos; Klomicina; Rulid†; ***Austral.***: Biaxsig; Roxar; Roxide†; Roximycin; Rulide; ***Austria***: Roxithrostad; Rulide; ***Belg.***: Rulid; ***Braz.***: Floxid; Rotram; Roxina; Roxitran; Roxitrom; Rulid; ***Chile***: Ramivan; ***China***: Ai Luo Xin (爱罗欣); Ao Ge Shen (奥格申); Bei Ke (蓓克); Bei Sha (倍沙); Bi Ai Di (毕埃帝); Fu Xin (芙欣); Heng Te (恒特); Lang Su (朗素); Le Er Tai (乐尔泰); Le Xi Qing (乐喜清); Li Fu (力弗); Lizhuxing (丽珠星); Luo Jun Qing (罗君青); Luo Li Sa (罗立萨); Luo Shi Li (逻施立); Luo Si Mei (洛司美); Pinsheng (品圣); Pu Hong (浦虹); Qi Wei (齐威); Ren Su (仁苏); Romycin (罗迈新); Rulide (罗力得); Sai Le Lin (赛乐林); Tai Luo (泰罗); Techne (德依); Tian Kai (天凯); Wei Man (维曼); Xi Shi Ning (西适宁); Xin Mei Luo (欣美罗); Xinhong (信虹); Ya Li Xi (亚力希); Yan Di (严迪); ***Denm.***: Roximstad; Surlid; ***Fin.***: Surlid; ***Fr.***: Claramid; Rulid; Subroxine†; ***Ger.***: Infectoroxit†; Roxi-Puren†; Roxi-Q†; Roxi-saar†; Roxi†; Roxibeta; Roxigamma†; Roxigrun†; RoxiHexal†; Roxithro-Lich†; Rulid†; ***Gr.***: Acevor; Anti-Bio; Aristomycin; Asmetic; Azuril; Bazuctril; Bicofen; Delitroxin; Erybros; Hobatmycine; Macrolid-S; Neo-Suxigal; Nirox; Oxetine; Redotrin; Roxibron; Roxicillin; Roxicur; Roximin; Roxitazon; Roxivinol; Roxuril; Roxy-Due; Roxyspes; Rulid; Seide; Siguon; Thriostaxil; Tirabicin; Toscamycin-R; Uramilon; Vaselpin; Vomitoran; ***Hong Kong***: Roxicin; Roxinox†; Rudin; Rulid; Ruxitex; Uonin; ***Hung.***: Renicin†; Rulid; ***India***: Actirox; Arbid; Artirox; Atrox; Aurox 150; Aurox-Kid; Avirox; Bd-Rox; Bio-Throx; Biorox; C-Rox; Canrox; Curox; Cyrox; Derox; E-Rox; Emrox; Entrox-P; Geerox; Hirox; Hycin; Inrox; Kevrox; Leolide; Luprex; Maclong; Macrox; Medirox; MGrox; Myrox; N-Rox; Nuroxy; Odirox; Roxee; Roxem; Roxeptin; Roxibid; Roxid; Roxivista; Roxyrol; Unorox; ***Indon.***: Anbiolid; Biostatik; Ixor; Rolexit; Rulid; Ruxcine†; Simacron; Sitro; Uplores; Xorin; ***Israel***: Roxo; Rulid; ***Ital.***: Assoral; Overal; Rossitrol; Rulid; ***Malaysia***: Roxcin; Roxinox; Rulid; Uonin; ***Mex.***: Crolix; Kensodic†; Rulid; Sertrom; ***Neth.***: Rulide†; ***NZ***: Romicin†; ***Philipp.***: Dorolid; Guamil; Macrol; Marulide; Plethirox; Rocin; Roxid; Roxil; Roximed; Roxitaz†; Roxithro; Roxl; Rulid; Ruthison; Thromyn; Trodex; Troxolid; Xithrom; ***Pol.***: Renicin; Rolicyn; Roxiratio; Roxitron; Rulid; Xitrocin; ***Port.***: Inferoxin; Odonticina; Roxitron; Rulide; ***Rus.***: Elrox (Элрокс); Remora (Ремора); Roksolit (Роксолит); Romyk (Ромик); Rovenal (Ровенал); Roxeptin (Роксептин); Roxihexal (Роксигексал); Roxybel (Роксибел); Roxylor (Роксилор); Rulicin (Рулицин); Rulid (Рулид); ***S.Afr.***: Roxulide†; Roxxibid; Rulide; Throsyn; ***Singapore***: Roxid; Uplores; ***Spain***: Rulide; ***Swed.***: Surlid; ***Switz.***: Rulid†; ***Thai.***: Ammirox; Coroxin; Eroxade; I-Throcin; Manroxin; Neolid†; Poliroxin; Rocitro; Romed; Rothricin; Roxamycin; Roxcin; Roxicin; Roxifect; Roxilan; Roximed; Roximin; Roxino; Roxinox; Roxinpac; Roxithro; Roxithroxyl; Roxitin; Roxitop; Roxitron; Roxlecon; Roxomycin†; Roxthomed; Roxthrin; Roxto; Roxtrocin; Roxxo†; Roxy; Roxydin†; Rucin; Rulid; Rulosone; Ruxitex; Saroxxo; Uonin; Utolid; V-Rox; Vesthromycin; ***Turk.***: Remora; Ritosin; Roksimin; Roksolit; Rulid; ***Ukr.***: Renicin (Реніцин)†; Roxid (Роксид); Roxihexal (Роксигексал)†; Roxilid (Роксилид); Xitrocin (Кситроцин); ***Venez.***: Roxicure; Roxitrol; Rulid.

Multi-ingredient Preparations. ***India***: Ambroxit; Arbid-A; Artirox-SP; Aurox 50; Avirox-AM; Avirox-ST; Canrox-A; Flanzen-RX; Kevrox-S; Kevrox-SA; Medirox-A; Roxeptin-ME.

Rufloxacin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de rufloxacino; MF-934 (rufloxacin); Rufloxacine, Chlorhydrate de; Rufloxacini Hydrochloridum; Rufloxacino, hidrocloruro de; Руфлоксацина Гидрохлорид.

9-Fluoro-2,3-dihydro-10-[4-methylpiperazin-1-yl]-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid hydrochloride.

$C_{17}H_{18}FN_3O_3S$,HCl=399.9

CAS — 101363-10-4 (rufloxacin); 106017-08-7 (rufloxacin hydrochloride).

ATC — J01MA10.

ATC Vet — QJ01MA10.

UNII — 1643374N6L.

Profile

Rufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1). It is given orally as the hydrochloride in the treatment of susceptible infections in a usual initial dose of 400 mg on the first day followed by 200 mg daily thereafter. A plasma half-life of 30 hours or more has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kang Zan (康赞); Qari (卡力); ***Ital.***: Monos; Qari; Tebraxin†; ***Mex.***: Uroflox; ***Philipp.***: Uroclar; ***Thai.***: Uroflox.

Sarafloxacin Hydrochloride *(BANM, USAN, rINNM)*

A-56620 (sarafloxacin or sarafloxacin hydrochloride); A-57135 (sarafloxacin); Abbott-56620 (sarafloxacin or sarafloxacin hydrochloride); Hidrocloruro de sarafloxacino; Sarafloxacine, Chlorhydrate de; Sarafloxacini Hydrochloridum; Sarafloxacino, hidrocloruro de; Сарафлоксацина Гидрохлорид.

6-Fluoro-1-(*p*-fluorophenyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride.

$C_{20}H_{17}F_2N_3O_3$,HCl=421.8

CAS — 98105-99-8 (sarafloxacin); 91296-87-6 (sarafloxacin hydrochloride).

UNII — I36JP4Q9DF.

Profile

Sarafloxacin is a fluoroquinolone antibacterial that has been used as the hydrochloride in veterinary medicine.

Sisomicin Sulfate *(BANM, USAN, rINNM)*

Antibiotic 6640 (sisomicin); Rickamicin Sulphate; Sch-13475 (sisomicin); Sisomicin Sulphate; Sisomicina, sulfato de; Sisomicine, Sulfate de; Sisomicini Sulfas; Sissomicin Sulphate; Sulfato de sisomicina; Сизомицина Сульфат.

4-*O*-[(2*R*,3*R*)-*cis*-3-Amino-6-aminomethyl-3,4-dihydro-2*H*-pyran-2-yl]-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine sulphate; 2-Deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-D-*glycero*-hex-4-enopyranosyl)streptamine sulphate.

$(C_{19}H_{37}N_5O_7)_2.5H_2SO_4$=1385.4

CAS — 32385-11-8 (sisomicin); 53179-09-2 (sisomicin sulfate).

ATC — J01GB08.

ATC Vet — QJ01GB08.

UNII — K14444371C.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Sisomicin Sulfate). It loses not more than 15% of its weight on drying. 1 mg of sisomicin sulfate has a potency equivalent to not less than 580 micrograms of sisomicin calculated on the dried basis. A 4% solution in water of sisomicin has a pH of 3.5 to 5.5. Store in airtight containers.

Profile

Sisomicin, an antibacterial produced by *Micromonospora inyoensis* and closely related to gentamicin C_{1A}, is an aminoglycoside with general properties similar to those of gentamicin (p. 304.2). It is given as the sulfate but doses are expressed in terms of the base; 1.5 g of sisomicin sulfate is equivalent to about 1 g of sisomicin. The usual dose for adults is 3 mg/kg daily given intramuscularly in 2 or 3 divided doses. It may be given by intravenous infusion if necessary.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Jia Xi (奥加西); De Bao Yi (德宝益); Lai Sai (莱赛); Li Sui (利岁); Luo Li (洛利); ***Gr.***: Geonyn; Somazinal; Sosialon; Udolin; ***India***: Ensamycin; Sisoptin.

Pharmacopoeial Preparations

USP 36: Sisomicin Sulfate Injection.

Sitafloxacin *(USAN, rINN)*

DU-6859 (anhydrous sitafloxacin); DU-6859a (sitafloxacin sesquihydrate); Sitafloxacine; Sitafloxacino; Sitafloxacinum; Ситафлоксацин.

(-)-7-[(7*S*)-7-Amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

$C_{19}H_{16}ClF_2N_3O_3$=409.8

CAS — 127254-12-0 (anhydrous sitafloxacin); 163253-37-0 (sitafloxacin monohydrate); 163253-35-8 (sitafloxacin sesquihydrate).

ATC — J01MA21.

ATC Vet — QJ01MA21.

UNII — 9TD681796G (sitafloxacin); 3GJC60U4Q8 (sitafloxacin anhydrous).

NOTE. Sitafloxacin exists in several hydration states; the name sitafloxacin has been used to refer to both the anhydrous substance and the sesquihydrate ($C_{19}H_{18}ClF_2N_3O_3$,1½H_2O=436.8); the latter is known in Japan as sitafloxacin hydrate.

Profile

Sitafloxacin is a fluoroquinolone that is given orally in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Gracevit; ***Thai.***: Gracevit.

Sparfloxacin *(BAN, USAN, rINN)*

AT-4140; CI-978; Esparfloxacino; PD-131501; RP-64206; Sparfloksasiini; Sparfloxacine; Sparfloxacinum; Спарфлоксацин.

5-Amino-1-cyclopropyl-7-(*cis*-3,5-dimethylpiperazin-1-yl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.

$C_{19}H_{22}F_2N_4O_3$=392.4

CAS — 110871-86-8.

ATC — J01MA09.

ATC Vet — QJ01MA09.

UNII — Q90AGA787L.

Pharmacopoeias. In *Chin.*

Uses and Administration

Sparfloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2). It is given orally for the treatment of susceptible infections in a usual dose of 100 to 300 mg in 1 or 2 divided doses daily. It has also been tried in tuberculosis. For further information on the use of other fluoroquinolones in the treatment of tuberculosis, see under Uses and Administration of Ciprofloxacin, p. 262.2.

General references.
1. Finch RG, *et al.* , eds. Sparfloxacin: focus on clinical performance. *J Antimicrob Chemother* 1996; **37** (suppl A): 1–167.
2. Goa KL, *et al.* Sparfloxacin: a review of its antibacterial activity, pharmacokinetic properties, clinical efficacy and tolerability in lower respiratory tract infections. *Drugs* 1997; **53:** 700–25.
3. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32:** 320–36.
4. Schentag JJ. Sparfloxacin: a review. *Clin Ther* 2000; **22:** 372–87.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Concern over phototoxicity associated with sparfloxacin has led to restriction of its use in some countries; patients should be advised to avoid exposure to sunlight during, and for a few days after, sparfloxacin therapy, and to stop the drug immediately if phototoxicity occurs.

Photosensitivity. In a survey[1] of the reporting rate for phototoxicity associated with sparfloxacin in France, the manufacturer or the French Pharmacovigilance System received 371 reports of severe phototoxic reactions during the first 9 months after marketing of the drug; this approximated to between 4 and 25 times the rate reported for other fluoroquinolones. In addition to photodermatitis, photo-onycholysis has also been reported with sparfloxacin.[2]

1. Pierfitte C, *et al.* The link between sunshine and phototoxicity of sparfloxacin. *Br J Clin Pharmacol* 2000; **49:** 609–12.
2. Mahajan VK, Sharma NL. Photo-onycholysis due to sparfloxacin. *Australas J Dermatol* 2005; **46:** 104–5.

Interactions

As for Ciprofloxacin, p. 264.3.

Sparfloxacin does not appear to interact with theophylline or caffeine, nor with warfarin or cimetidine. Probenecid does not alter the pharmacokinetics of sparfloxacin.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Sparfloxacin is reported to be more active *in vitro* than ciprofloxacin against mycobacteria and against Gram-positive bacteria, including *Streptococcus pneumoniae* and other streptococci and staphylococci.

Pharmacokinetics

Sparfloxacin is well absorbed from the gastrointestinal tract with a bioavailability of about 90%. Peak plasma

concentrations occur 3 to 6 hours after a dose. Sparfloxacin is widely distributed into body tissues and fluids, including respiratory tissues, but is only about 45% bound to plasma proteins. It is metabolised in the liver by glucuronidation and has an elimination half-life of about 20 hours. It is excreted in equal amounts in the faeces and urine as unchanged drug and as the glucuronide metabolite.

References.
1. Shimada J, *et al.* Clinical pharmacokinetics of sparfloxacin. *Clin Pharmacokinet* 1993; **25:** 358–69.
2. Montay G. Pharmacokinetics of sparfloxacin in healthy volunteers and patients: a review. *J Antimicrob Chemother* 1996; **37** (suppl A): 27–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ba Sha (巴沙); Lang Rui (朗瑞); Sen Ao Xin (森奥欣); SenAoXin (森澳欣); Shi Bao Fu (世保扶); Spara (司巴乐); Sparca (立特); ***India***: Actiflox; Acuspar; Alps; Artispar; Aspar; Atospar; Bal-Spar; Bluspar; Canspar; Cinospar; Dinor; E-Spar; Efospar; Flotome; Floxpar; Guspar; Inspar; Jugam; Kespar; Klaspar; Novospar; Onespar; Ospar; Paar; Parcy; Scat; Sparbact; Sparcip; Spardac; Spardrops; Sparquin; Sparvista; Sparx; ***Indon.***: Newspar; Resflok; Sparos; ***Jpn***: Spara†; ***Rus.***: Respara (Респара); Sparbact (Спарбакт); Sparflo (Спарфло); ***Ukr.***: Sparflo (Спарфло).

Spectinomycin *(BAN, rINN)*

Actinospectacin; Espectinomicina; Spectinomycine; Spectinomycinum; Spektinomycin; Spektinomysiini; Спектиномицин.

Perhydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino) pyrano[2,3-*b*][1,4]benzodioxin-4-one.

$C_{14}H_{24}N_2O_7$=332.4

CAS — 1695-77-8.

ATC — J01XX04.

ATC Vet — QJ01XX04.

UNII — 93AKI1U6QF.

Description. Spectinomycin is an antimicrobial substance produced by the growth of *Streptomyces spectabilis* or by any other means.

Spectinomycin Hydrochloride

(BANM, USAN, rINNM)

Espectinomicina, hidrocloruro de; Hidrocloruro de espectinomicina; M-141; Spectinomycine, Chlorhydrate de; Spectinomycine (dichlorhydrate de) pentahydraté; Spectinomycini dihydrochloridum pentahydricum; Spectinomycini Hydrochloridum; Spektinomicin-hidroklorid; Spektinomicino hidrochloridas; Spektinomycin hydrochlorid; Spektinomycindihydrokloridpentahydrat; Spektinomysiinidihydrokloridipentahydraatti; Spektynomycyny chlorowodorek; Spektynomycyny dichlorowodorek pięciowodny; U-18409AE; Спектиномицина Гидрохлорид.

Spectinomycin dihydrochloride pentahydrate.

$C_{14}H_{24}N_2O_7$,2HCl,5H_2O=495.3

CAS — 21736-83-4 (anhydrous spectinomycin hydrochloride); 22189-32-8 (spectinomycin hydrochloride pentahydrate).

ATC — J01XX04.

ATC Vet — QJ01XX04.

UNII — HWT06H303Z (spectinomycin hydrochloride pentahydrate); 296JEI210Z (anhydrous spectinomycin hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Spectinomycin Dihydrochloride Pentahydrate). A substance produced by *Streptomyces spectabilis* or by any other means. A white or almost white, slightly hygroscopic, powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 3.8 to 5.6. Store in airtight containers.

USP 36: (Spectinomycin Hydrochloride). A white to pale buff crystalline powder. 1 mg of monograph substance has a potency equivalent to not less than 603 micrograms of spectinomycin. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. A 1% solution in water has a pH of 3.8 to 5.6. Store in airtight containers.

Uses and Administration

Spectinomycin is used as an alternative to cephalosporins or fluoroquinolones in the treatment of gonorrhoea (p. 204.2) although poor distribution into saliva limits its usefulness in pharyngeal infections. It has also been used in the treatment of chancroid (p. 204.2).

Spectinomycin is given as the hydrochloride but doses are expressed in terms of the base. Spectinomycin hydrochloride 1.5 g is equivalent to about 1 g of spectinomycin. In the treatment of gonorrhoea it is given by deep intramuscular injection as a single dose equivalent to 2 g of spectinomycin, although a dose of 4 g may sometimes be required, divided between two injection sites. Multiple-dose courses have been used for the treatment of disseminated infections.

Spectinomycin is not effective against syphilis or chlamydial infections and additional therapy for these infections may also be needed.

For details of doses in children, see p. 360.2.

Administration in children. Parenteral spectinomycin is generally not recommended in neonates because of the presence of benzyl alcohol, a preservative that has been associated with fatalities in neonates due to the 'gasping syndrome' (see Neonates, p. 1741.1).

For prophylaxis in neonates born to mothers with gonorrhoea WHO permits a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg) as an alternative to ceftriaxone. The CDC recommends spectinomycin as an alternative to cephalosporins in the treatment of uncomplicated gonorrhoea (p. 204.2) in children beyond the newborn period and weighing under 45 kg; a single intramuscular dose equivalent to 40 mg/kg of spectinomycin may be given.

Adverse Effects and Precautions

Nausea, dizziness, fever and chills, insomnia, and urticaria have occasionally occurred with single doses of spectinomycin. Anaphylaxis has occurred rarely. Mild to moderate pain has been reported after intramuscular injections. Alterations in kidney and liver function and a decrease in haemoglobin and haematocrit have occasionally been seen with repeated doses. Although a reduction in urine output has been seen after single and multiple doses, spectinomycin has not been noted to produce functional changes indicative of nephrotoxicity.

Spectinomycin is ineffective in the treatment of syphilis and patients being treated for gonorrhoea should be observed for evidence of syphilis.

Interactions

Lithium. For the effect of spectinomycin in patients receiving lithium, see Antimicrobials, under Interactions of Lithium, p. 433.3.

Antimicrobial Action

Spectinomycin is an aminocyclitol antibacterial that acts by binding to the 30S subunit of the bacterial ribosome and inhibiting protein synthesis. Its activity is generally modest, particularly against Gram-positive organisms. Anaerobic organisms are mostly resistant. Various Gram-negative organisms are sensitive, including many enterobacteria and also *Haemophilus ducreyi*, and it is particularly effective against *Neisseria gonorrhoeae*. Although generally bacteriostatic, spectinomycin is bactericidal against susceptible gonococci at concentrations not much above the MIC.

Resistance may develop by chromosomal mutation or may be plasmid-mediated in some organisms; resistant gonococci have been reported clinically, notably in the Far East, but in most parts of the world resistant neisserial strains have been uncommon to date.

Pharmacokinetics

Spectinomycin is poorly absorbed orally but is rapidly absorbed after the intramuscular injection of the hydrochloride. A 2-g dose produces peak plasma concentrations of about 100 micrograms/mL at 1 hour while a 4-g dose produces peak concentrations of about 160 micrograms/mL at 2 hours. Therapeutic plasma concentrations are maintained for up to 8 hours. Distribution into saliva is poor (which limits its value in pharyngeal gonorrhoea). It is poorly bound to plasma proteins. Spectinomycin is excreted in an active form in the urine and up to 100% of a dose has been recovered within 48 hours. A half-life of about 1 to 3 hours has been reported; it is prolonged in patients with renal impairment. Spectinomycin is partially removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Trobicin†; ***Belg.***: Trobicin; ***China***: Shubeitinuo (舒贝替诺); Trobicin (曲必星); Zhuo Qing (卓青); ***Fr.***: Trobicine; ***Gr.***: Trobicin; ***Hong Kong***: Kirin; Trobicin; ***India***: Myspec; Spectin; Trobicin; ***Mex.***: Trobicin; ***Rus.***: Kirin (Кирин); Trobicin (Тробицин); ***S.Afr.***: Trobicin†; ***Singapore***: Trobicin; ***Spain***: Kempi†; ***Thai.***: Trobicin; Vabicin†.

Pharmacopoeial Preparations

USP 36: Spectinomycin for Injectable Suspension.

Spiramycin *(BAN, USAN, rINN)*

Espiramicina; IL-5902; NSC-55926; NSC-64393 (spiramycin hydrochloride); RP-5337; Spiramicin; Spiramicinas; Spiramisin; Spiramycine; Spiramycinum; Spiramysiini; Спирамицин.

A mixture comprised principally of (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,16*R*)-(11*E*,13*E*)-6-[(*O*-2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-(1→4)-(3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyl)oxy]-7-formylmethyl-4-hydroxy-5-methoxy-9,16-dimethyl-10-[(2,3,4,6-tetradeoxy-4-dimethylamino-D-*erythro*-hexopyranosyl)oxy]oxacyclohexadeca-11,13-dien-2-one (Spiramycin I).

$C_{43}H_{74}N_2O_{14}$=843.1

CAS — 8025-81-8.

ATC — J01FA02.

ATC Vet — QJ01FA02; QJ51FA02.

UNII — 71ODY0V87H (spiramycin); 033ECH6IFG (spiramycin I); 05298J5WMU (spiramycin II); 0NHE9TRJ93 (spiramycin III).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *BP(Vet)*. *Jpn* includes Acetylspiramycin.

Ph. Eur. 8: (Spiramycin). A macrolide antibiotic produced by the growth of certain strains of *Streptomyces ambofaciens* or obtained by any other means. The potency is not less than 4100 units/mg, calculated with reference to the dried substance. A white or slightly yellowish, slightly hygroscopic powder. Slightly soluble in water; freely soluble in alcohol, in acetone, and in methyl alcohol. A 0.5% solution in methyl alcohol and water has a pH of 8.5 to 10.5. Store in airtight containers.

Uses and Administration

Spiramycin is a macrolide antibacterial that is used similarly to erythromycin (p. 292.1) in the treatment of susceptible bacterial infections. It has also been used in the protozoal infections cryptosporidiosis (p. 923.1) and toxoplasmosis (p. 926.1).

Spiramycin is given orally as the base or intravenously as the adipate; it has also been given rectally as the adipate. The usual oral adult dose is 6 to 9 million units daily, in 2 or 3 divided doses. Doses of up to 15 million units have been given daily in divided doses for severe infections. A dose of 1.5 million units of spiramycin may be given by slow intravenous infusion every 8 hours; in severe infection the dose may be doubled.

Spiramycin is available in combination preparations with metronidazole in some countries.

Acetylspiramycin is also used.

Reviews.
1. Rubinstein E, Keller N. Spiramycin renaissance. *J Antimicrob Chemother* 1998; **42:** 572–6.

Adverse Effects and Precautions

As for Erythromycin, p. 293.1.

The most frequent adverse effects are gastrointestinal disturbances. Transient paraesthesia has been reported during parenteral use.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies spiramycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 294.2.

Spiramycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p. 294.2). The lack of interactions between spiramycin and theophylline and ciclosporin would appear to support this. Nevertheless, a report of torsade de pointes in a patient with a congenital long QT syndrome during treatment with spiramycin and *mequitazine*[1] suggests that caution is still needed.

Reduced plasma concentrations of *levodopa* have been reported when given with spiramycin (see p. 908.1).

1. Verdun F, *et al.* Torsades de pointes sous traitement par spiramycine et méquitazine: à propos d'un cas. *Arch Mal Coeur Vaiss* 1997; **90:** 103–6.

Antimicrobial Action

As for Erythromycin, p. 295.1, although it is somewhat less active *in vitro* against many species. It is active against *Toxoplasma gondii*.

Pharmacokinetics

Spiramycin is incompletely absorbed from the gastrointestinal tract and absorption is reduced by food. It is widely distributed into tissues, although it does not cross the blood-brain barrier. Spiramycin crosses the placenta and is distributed into breast milk. Plasma protein binding ranges from 10 to 25%. An oral dose of 6 million units produces peak blood concentrations of 3.3 micrograms/mL after 1.5 to 3 hours; the half-life is about 5 to 8 hours. High tissue concentrations occur and persist long after the plasma concentration has fallen to low levels.

Spiramycin is metabolised in the liver to active metabolites; substantial amounts are excreted in the bile and about 10% in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rovamycine; ***Austria***: Rovamycin; ***Belg.***: Rovamycine; ***Braz.***: Rovamicina; ***Canad.***: Rovamycine; ***China***: Fa Luo (法罗); Fuluxian (芙露仙); Yi Nuo Xin (伊诺欣); ***Cz.***: Rovamycine; ***Fr.***: Rovamycine; ***Ger.***: Rovamycine; Selectomycin; ***Gr.***: Rovamycine; ***Hong Kong***: Rovamycine; ***Hung.***: Rovamycine; ***India***: Rovamycin; ***Indon.***: Ethirov; Hypermycin†; Ismacrol; Medirov†; Osmycin; Provamed; Rofacin; Rovadin; Rovamycine; Sorov; Spirabiotic; Spiradan; Spiranter; Spirasin; Varoc; Vipram; ***Israel***: Rovamycine; ***Ital.***: Rovamicina; Spiromix†; ***Malaysia***: Rovamycine; ***Mex.***: Provamicina; ***Neth.***: Rovamycine; ***Norw.***: Rovamycin; ***Philipp.***: Rovamax; ***Pol.***: Rovamycine; ***Port.***: Rovamycine; ***Rus.***: Rovamycine (Ровамицин); ***Singapore***: Rovamycine; ***Spain***: Dicorvin; Rovamycine; ***Switz.***: Rovamycine†; ***Thai.***: Rovamycine; Spiracin†; ***Turk.***: Rovagyl; Rovamycine; ***Ukr.***: Rovacid (Ровацид)†; Rovamycine (Ровамицин); Starket (Старкет); ***Venez.***: Provamicina.

Multi-ingredient Preparations. ***Arg.***: Estilomicin; ***Braz.***: Periodontil; ***Fr.***: Bi Missilor; Birodogyl; Missilor; Rodogyl; ***Malaysia***: Rodogyl; ***Mex.***: Rodogyl; ***Spain***: Rhodogil.

Streptomycin *(BAN, rINN)*

Estreptomicina; Streptomisin; Streptomycine; Streptomycinum; Streptomysiini; Стрептомицин.

O-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1→4)-N^3,N^3-diamidino-D-streptamine.

$C_{21}H_{39}N_7O_{12}$=581.6

CAS — 57-92-1.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

UNII — Y45OSO73OB.

Description. An antimicrobial organic base produced by the growth of certain strains of *Streptomyces griseus*, or by any other means.

Streptomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de estreptomicina; Streptomycine, Chlorhydrate de; Streptomycini Hydrochloridum; Стрептомицина Гидрохлорид.

$C_{21}H_{39}N_7O_{12}$,3HCl=691.0

CAS — 6160-32-3.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

UNII — 8P331B9592.

Streptomycin Sulfate *(BANM, rINNM)*

Estreptomicina, sulfato de; Streptomicino sulfatas; Streptomycin Sesquisulphate; Streptomycin sulfát; Streptomycin Sulphate; Streptomycine, Sulfate de; Streptomycini sulfas; Streptomycinsulfat; Streptomycyny siarczan; Streptomysiinisulfaatti; Sulfato de estreptomicina; Sztreptomicin-szulfát; Стрептомицина Сульфат.

$(C_{21}H_{39}N_7O_{12})_2$,$3H_2SO_4$=1457.4

CAS — 3810-74-0.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

UNII — CW25IKJ202.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Streptomycin Sulfate). A white or almost white, hygroscopic powder. The potency is not less than 720 units/mg, calculated with reference to the dried substance. Very soluble in water; practically insoluble in dehydrated alcohol. A 25% solution in water has a pH of 4.5 to 7.0. Store in airtight containers.

USP 36: (Streptomycin Sulfate). A white or practically white, hygroscopic powder; odourless or with not more than a faint odour. It has a potency equivalent to not less than 650 micrograms and not more than 850 micrograms of streptomycin per mg. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform. A solution in water containing the equivalent of streptomycin 20% has a pH of 4.5 to 7.0. Store in airtight containers.

Incompatibility. Streptomycin sulfate is incompatible with acids and alkalis.

Uses and Administration

Streptomycin is an aminoglycoside antibacterial mainly used with other antimycobacterials, in the treatment of nontuberculous mycobacterial infections and tuberculosis. It is given during the initial phase of treatment in those with tuberculous meningitis and in those previously treated for tuberculosis. Streptomycin has been used, with a penicillin, as an alternative to gentamicin in the treatment of bacterial endocarditis. Streptomycin is effective in the treatment of plague, tularaemia, and, with a tetracycline, in brucellosis. It has also been used, with other drugs, in various other infections including mycetoma and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Streptomycin is mostly used as the sulfate but doses are expressed in terms of the base; 1.25 g of streptomycin sulfate is equivalent to about 1 g of streptomycin. It is given by intramuscular injection.

In the treatment of **tuberculosis**, streptomycin is given in usual adult doses of 15 mg/kg daily, up to a maximum of 1 g daily. The maximum daily dose should be reduced to 500 to 750 mg in adults aged over 40 years, and in those weighing less than 50 kg. Dosage should also be reduced in those with renal impairment, in whom plasma-drug concentration should be monitored. Streptomycin may also be given at the same dose as part of an intermittent regimen 2 or 3 times weekly. It has been given by the intrathecal route, together with intramuscular dosage, for tuberculous meningitis, but this is no longer recommended.

In the treatment of **other infections**, streptomycin has been given in usual adult doses of 1 to 2 g daily in divided doses, depending on the susceptibility and severity of infection.

For details of doses in children, see p. 361.2.

In all patients dosage should preferably be adjusted according to plasma-streptomycin concentrations, and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity. The course of treatment (other than in tuberculosis) should usually be limited to 7 to 14 days, and peak plasma concentrations should be between 15 and 40 micrograms/mL and trough concentrations below 3 to 5 micrograms/mL or below 1 microgram/mL in renal impairment or in those over 50 years of age. For discussion of the methods used to calculate aminoglycoside dosage requirements, see Administration and Dosage under Gentamicin Sulfate, p. 305.2.

Streptomycin has also been used as the hydrochloride, the pantothenate, and as a complex with calcium chloride.

Administration in children. For the treatment of *tuberculosis* in children from 1 month of age, streptomycin is given by intramuscular injection and with other antimycobacterial drugs. The American Academy of Pediatrics[1] suggests a dose of streptomycin of 20 to 40 mg/kg (to a maximum of 1 g) daily, while the *BNFC* suggests a dose of 15 mg/kg (also to a maximum of 1 g) once daily. WHO recommends a dose of streptomycin of 12 to 18 mg/kg once daily or three times a week.

Streptomycin is given with doxycycline for the treatment of *brucellosis*. In children aged 1 month and older the *BNFC* suggests a dose of streptomycin of 5 to 10 mg/kg every 6 hours or the total daily dose may be given in 2 or 3 divided doses.

Streptomycin is given by intramuscular injection for the treatment of *other infections* in children in doses of up to 40 mg/kg daily (to a maximum of 1 g daily) in divided doses for 3 to 7 days, depending on the susceptibility and severity of infection.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Ménière's disease. Streptomycin and gentamicin have been used for medical ablation in advanced Ménière's disease (p. 611.2). Systemic treatment has generally been limited by the development of chronic ataxia and oscillopsia (oscillating vision). However, streptomycin sulfate 1 g twice daily by intramuscular injection on 5 days each week for 2 weeks, repeated as necessary to a total dose of up to 60 g,[1,2] or 1 g twice daily for 5 days, followed if necessary by a further 3 days of treatment in the second week,[3] has produced improvements in vestibular symptoms without hearing loss in patients with Ménière's disease. Local (intratympanic) injections have also been tried,[4] but gentamicin is considered to be less toxic and is now generally preferred.

1. Shea JJ, *et al.* Long-term results of low dose intramuscular streptomycin for Ménière's disease. *Am J Otol* 1994; **15:** 540–4.
2. Balyan FR, *et al.* Titration streptomycin therapy in Meniere's disease: long-term results. *Otolaryngol Head Neck Surg* 1998; **118:** 261–6.
3. Graham MD. Bilateral Meniere's disease: treatment with intramuscular titration streptomycin sulfate. *Otolaryngol Clin North Am* 1997; **30:** 1097–1100.
4. Beck C, Schmidt CL. 10 Years of experience with intratympanally applied streptomycin (gentamycin) in the therapy of Morbus Menière. *Arch Otorhinolaryngol* 1978; **221:** 149–52.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2. Like gentamicin the ototoxic effects of streptomycin are mainly vestibular rather than auditory. Ototoxicity has been seen in infants whose mothers had been given streptomycin during pregnancy. However, streptomycin is reported to be somewhat less nephrotoxic than the other aminoglycosides.

Paraesthesia in and around the mouth is not uncommon after intramuscular injection of streptomycin, and other neurological symptoms, including peripheral neuropathies, optic neuritis, and scotoma have occasionally occurred. Intrathecal use has resulted in symptoms of meningeal inflammation including radiculitis, arachnoiditis, nerve root pain, and paraplegia, and some recommend that it be avoided. The risk of neurotoxic reactions is greater in patients with renal impairment or pre-renal azotaemia.

Hypersensitivity skin reactions are reported in about 5% of patients, and eosinophilia may occur. There have been reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, severe exfoliative dermatitis, and anaphylaxis. Sensitisation is common among those who handle streptomycin occupationally. Topical and inhalational use of streptomycin should be avoided. If necessary, hypersensitivity can usually be overcome by desensitisation. Aplastic anaemia and agranulocytosis have been reported rarely.

Although sources differ, it is usually suggested that peak plasma concentrations should be between 15 and 40 micrograms/mL, and trough concentrations below 3 to 5 micrograms/mL; in the UK the *BNF* recommends that trough concentrations in excess of 1 microgram/mL should be avoided in those over 50 years of age or those with renal impairment. A total cumulative dose in excess of 100 g may be associated with a higher incidence of adverse effects and should only be exceeded in exceptional circumstances.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving streptomycin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Handling. Streptomycin may cause severe dermatitis in sensitised persons, and pharmacists, nurses, and others who handle the drug frequently should wear masks and rubber gloves.

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

Streptomycin has a mode of action and antimicrobial spectrum similar to that of gentamicin (p. 307.2), although most strains of *Pseudomonas aeruginosa* are resistant. It is effective against *Yersinia pestis*, *Francisella tularensis*, and *Brucella* spp. Streptomycin has particular activity against *Mycobacterium tuberculosis*.

Resistance to streptomycin has often been reported and may develop in strains which are initially sensitive within a few days or weeks of beginning therapy. The widespread emergence of resistance has largely halted its use in infections due to the common Gram-negative aerobes. Primary resistance in *M. tuberculosis* is relatively uncommon in the UK and USA but may be seen in a third or more of cases in the Far East.

Both low-level and high-level resistance have been reported; the latter is thought to be due to mutation of the ribosomal binding site of the antibiotic and cannot be overcome by the synergistic use of another drug such as a beta lactam, whereas strains with moderate resistance due to decreased uptake or permeability of streptomycin may respond to combined use.

Organisms resistant to framycetin, kanamycin, neomycin, and paromomycin usually show cross-resistance to streptomycin, although streptomycin-resistant strains sometimes respond to one of these drugs.

References.

1. Cooksey RC, *et al.* Characterization of streptomycin resistance mechanisms among Mycobacterium tuberculosis isolates from patients in New York City. *Antimicrob Agents Chemother* 1996; **40:** 1186–8.
2. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3. After intramuscular injection of streptomycin, peak plasma concentrations occur in 0.5 to 2 hours but the time taken and the concentration attained, which may be as high as about 50 micrograms/mL after a dose of 1 g, vary considerably. The half-life of streptomycin is about 2.5 hours. About one-third of streptomycin in the circulation is bound to plasma proteins. It is rapidly excreted by glomerular filtration and the concentration of streptomycin in the urine is often very high, with about 30 to 90% of a dose usually being excreted within 24 hours. It is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Strepto-Fatol; ***Ger.***: Strepto-Fatol†; Strepto-Hefa†; ***India***: Ambistryn-S; Cipstryn; Isos; ***Mex.***: Bucomicina†; Sulfestrep; ***S.Afr.***: Bio-Strep; Solustrep; ***Thai.***: Strepto.

Multi-ingredient Preparations. ***Arg.***: Estreptocarbocaftiazol; Estreptocarbocaftiazol; ***Gr.***: Polypictine; ***Mex.***: Aguipental; ***Port.***: Bienterico†.

Pharmacopoeial Preparations
BP 2014: Streptomycin Injection;
USP 36: Streptomycin for Injection; Streptomycin Injection.

Succinylsulfathiazole *(BAN, rINN)*

Succinilsolfatiazolo; Succinilsulfatiazol; Succinylsulfathiazol; Succinylsulfathiazolum; Succinylsulfathiazolum Monohydricum; Succinylsulfatiazol; Succinylsulphathiazole; Sukcinilsulfatiazolas; Sukcinylsulfathiazol monohydrát; Suksinyylisulfatiatsoli; Szukcinilszulfatiazol; Сукцинилсульфатиазол.

4′-(1,3-Thiazol-2-ylsulphamoyl)succinanilic acid monohydrate.

$C_{13}H_{13}N_3O_5S_2,H_2O$=373.4

CAS — 116-43-8 (anhydrous succinylsulfathiazole).

ATC — A07AB04.

ATC Vet — QA07AB04.

UNII — RSS8647O4S (succinylsulfathiazole); HM7K18OJZ9 (succinylsulfathiazole monohydrate).

Profile

Succinylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is poorly absorbed and has been given for its antibacterial activity in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Venez.***: Guanicar.

Sulbactam *(BAN, rINN)*

CP-45899; Sulbactamum; Sulbaktaami; Sulbaktam; Сульбактам.

Penicillanic acid 1,1-dioxide; (2*S*,5*R*)-3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide.

$C_8H_{11}NO_5S$=233.2

CAS — 68373-14-8.

ATC — J01CG01.

ATC Vet — QJ01CG01.

UNII — S4TF6I2330.

Pivsulbactam *(BAN)*

CP-47904; Sulbactam Pivoxil (USAN); Пивсульбактам.

Pivaloyloxymethyl penicillanate 1,1-dioxide.

$C_{14}H_{21}NO_7S$=347.4

CAS — 69388-79-0.

UNII — 2X0WTA96KX.

Sulbactam Sodium *(BANM, USAN, rINNM)*

CP-45899-2; Natrii Sulbactamum; Sulbactam-Natrium; Sulbactam sódico; Sulbactam Sodique; Sulbactamum natricum; Sulbaktaaminatrium; Sulbaktam sodná sůl; Sulbaktam sodowy; Sulbaktamnatrium; Натрий Сульбактам.

$C_8H_{10}NNaO_5S$=255.2

CAS — 69388-84-7.

ATC — J01CG01.

ATC Vet — QJ01CG01.

UNII — DKQ4T82YE6.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulbactam Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in ethyl acetate. It is freely soluble in diluted acids. A 5.0% solution in water has a pH of 4.5 to 7.2; if the substance is sterile: 5.2 to 7.2. Store in airtight containers.

USP 36: (Sulbactam Sodium). A white to off-white crystalline powder. It contains not less than 886 micrograms and not more than 941 microgram of sulbactam per mg, calculated on the anhydrous basis. Freely soluble in water and in dilute acid; sparingly soluble in acetone, in chloroform, and in ethyl acetate. Store in airtight containers.

Profile

Sulbactam is a penicillanic acid sulfone with beta-lactamase inhibitory properties. It is active against Neisseriaceae and *Acinetobacter baumanii*, but generally has only weak antibacterial activity against other organisms. It is an irreversible inhibitor of many plasmid-mediated and some chromosomal beta-lactamases and has a similar spectrum of beta-lactamase inhibition to clavulanic acid (p. 268.3), although it is regarded as less potent. Sulbactam can therefore enhance the activity of penicillins and cephalosporins against many resistant strains of bacteria.

It is given with ampicillin (p. 218.2) in the treatment of infections where beta-lactamase production is suspected. Sulbactam is poorly absorbed from the gastrointestinal tract and is given by injection as the sodium salt. The pharmacokinetics of parenteral sulbactam and ampicillin are similar. For oral use the mutual prodrug sultamicillin (p. 371.1) is available in some countries. Sulbactam is also given orally as the pivoxil derivative, pivsulbactam, with amoxicillin. Sulbactam has also been given with cefoperazone.

References.

1. Lee NLS, *et al.* β-Lactam antibiotic and β-lactamase inhibitor combinations. *JAMA* 2001; **285:** 386–8.
2. Lode H. Role of sultamicillin and ampicillin/sulbactam in the treatment of upper and lower bacterial respiratory tract infections. *Int J Antimicrob Agents* 2001; **18:** 199–209.
3. Kanra G. Experience with ampicillin/sulbactam in severe infections. *J Int Med Res* 2002; **30** (suppl 1): 20A–30A.
4. Lee N, *et al.* Clinical role of β-lactam/β-lactamase inhibitor combinations. *Drugs* 2003; **63:** 1511–24.
5. Rafailidis PI, *et al.* Ampicillin/sulbactam: current status in severe bacterial infections. *Drugs* 2007; **67:** 1829–49.
6. Akova M. Sulbactam-containing beta-lactamase inhibitor combinations. *Clin Microbiol Infect* 2008; **14** (suppl 1): 185–8.

Breast feeding. Although sulbactam is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Foulds G, *et al.* Sulbactam kinetics and excretion into breast milk in postpartum women. *Clin Pharmacol Ther* 1985; **38:** 692–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Combactam; ***China***: Lianke (联可); ***Ger.***: Combactam; ***India***: Cefritz-S; ***Indon.***: Cefoject; ***Spain***: Betamaz; ***Turk.***: Ampisid; B-Laktam.

Multi-ingredient Preparations. ***Arg.***: Aminoxidin Sulbactam; Ampi-Bis Plus; Ampigen SB; Darzitil SB; Prixin; Trifamox IBL Duo; Trifamox IBL; Unasyna†; ***Austria***: Unasyn; ***Braz.***: Combactan; Sulbamox; Trifamox; Unasyn; ***Chile***: Auropennz; Sulbamox; Sulperazon; Unasyn; ***China***: Bai Ding (百定); Bei Shu Lin (倍舒林); Dalipaitan (达力哌坦); Dexiao (得消); Fanlin (凡林); Fengpaixin (锋派新); Fumaixin (孚麦欣); Haishubi (海舒必); Han Guang (汉光); Jia Luo Tan (佳洛坦); Kai Wei Ke (凯韦可); KaiLin (开林); Kaisheng (凯生); Kang Li Shu (康力舒); Lai Qie Li (来切利); Li Ke Duo (力可多); Lijunpaishu (利君派舒); Linglanxin (铃兰欣); Litan (力坦); Pai Shu (派纾); Pu Shu (普舒); Ruipuxin (瑞普欣); Shu An Xin (舒氨新); Shu Sa Lin (舒萨林); Shuanxilin (舒氨西林); Shudi (舒敌); Shutabituo (舒他必妥); Stanyn (施坦宁); Sulperazon (舒普深); Trifamox IBL (特福猛); Unasyn (优立新); Wei Qi Da (威奇达); Xi Lin (悉林); Xian Qiang (先强); Xianjie (先捷); Xianpu (先普); Xianshu (先舒); Xidilin (西迪林); Xin An Lin (欣安林); Xin Junbizhi (新君必治); Xinkuaixin (新快欣); Xinruipuxin (新瑞普欣); Xintemie (新特灭); Xinzhijun (新治君); Yi Jun (一君); Yi Tan (益坦); Zetong (泽同); ***Cz.***: Bitammon; Sulperazon; Unasyn; ***Fr.***: Unacim; ***Ger.***: Ampicillin comp†; Unacid; ***Gr.***: Begalin-P; Demotine; ***Hong Kong***: Sulperazon; Unasyn; ***Hung.***: Unasyn; ***India***: Acticef-SB; Adesul; Afzone-S; Alitax-S; Alkaceff-S; Alnacef-S; Amceft-S; Amisul; Ampitum; Ampy S; Ampysul; Apozone-S; Arifzon-SB; Arixon-SB; Atozon-S; Augtax; Avcef-S; Avicef-S; Axocare-S; Axon-SB; Axone-SB; Axtrum-S; Bacticid-CS; Bactocef; Bactonis; Bactorus; Bactosul; Bahutcef-SL; Betamp; Big-Tum; Broadcef-S; Burnex; C-Bact; C-Bactum; C-Fort; C-Lactum; C-Tab-SB; C-Tum; Cadcef-S; Cadizone-S; Cafage-S; Cafazone-S; Cameo-S; Cearium; Cebac; Cebactum; Cebanex; Cebect; Cef-S; Cefac; Cefactam; Cefaday-S; Cefalin-S; Cefantral-S; Cefasul; Cefbect; Cefcin-SB; Cefdinex-SB; Cefglobe-S; Cefina-SB; Cefjoy; Cefla; Cefmate; Cefmol-SF; Cefobac; Cefobel-S; Cefobeta; Cefoden-SB; Cefogard-S; Cefom-S; Cefonet-S; Cefonex; Ceforex; Cefos-S; Cefosal; Cefosul; Cefosun S; Cefozed-S; Cefpar SB; Cefrobactum; Cefrosan; Cefrose-S; Cefset-S; Cefsine-S; Ceftichek; Ceftocin; Ceftop; Ceftraset-S; Ceftril-S; Ceftrimax; Ceftrol-S; Cefum; Cefup; Cefurax-D; Cefurin; Cefwon-S; Cefzon SB; Cefzone-S; Cefzox-SF; Cepoxit-S; Ceprazo-S; Ceprozone-S; Cerazone-S; Cesal; Cetriax-S; Cetzone-S; Cezon-S; Cezone Plus; Champione-S; Chuncif-S; Cinclox-S; Cis-SL; Cizon-SB; Corcef-SB; Cotyx-S; CSI-S; CT Ceff SM; CT Spar SM; CTrisana-SB; Cucef-S; Cucef-S; Curemax; Cuxone-SL; Dalcefa-SB; Decef; Deczone-S; Dewcef-S; Duotax; Duozone; Effimax Plus; Eftanu-S; Ekcef-S; Emtri-S; Estxone-SB; Evacef-S; Extacef-XL; Finetriax-S; Fofone-S; Formic; Forone-SB; Fro-Cef; Frone-SL; Fuzosul; Fytobact; Geminate Plus; Glen-SB; Glicef-S; Gloriax-SB; Gramocef-S; Hocef-S; Hosizone; Ifytrox-SB; Imex; Inbac Kit; Incef-SB; Indobact; Indocef-SB; Indoxone-S; Infoxon-S; Iszu; Ivimax; Kafi-S; Kaircef-S; Kefbactam; Kefchek; Kefsurge; Keftragard; Kephazon-S; Kexone Plus; Krasule; Kxone-SL; L-Cef; Labicef-S; Labxone-SB; Lactagard; Lezone-S; Lifecare-SB; Lisel-S; Lyceft Plus; Magnatax; Magnazone; Magnex; Magtam; Mahacef-SB; Mat-CS; Maxitax; Mecef-S; Medinex; Mepef-S; Mintrax-S; Mocef-S; Monoact; Monobact; Montero; Mutax Plus; Nebect; Nefsul; Neftum-SB; Nexef-SB; Nizotrax-S; NKCef+S; Nosobac; Novaceft-S; Novacip-S; Nubact; Nuperazone Plus; Nutaxin-S; Nutracip-SB; Ocefa-SB; Odospi-S; Ofirex; Oframax Forte; Onbact; Opticef-S; Oramax; Oritaximax; Orozone-SB; Osocillin-S; Osotax-S; Osul-S; Over-SB; Oxy-S; Pancef-S; Parabact; Sulbacef; Sulbacin; Sultax; Zosul; ***Indon.***: Bactazon; Ferotam; Fosular; Soperam; Stabactam; Sulbacef; Sulperazon; Zotam; ***Israel***: Unasyn; ***Ital.***: Bethacil; Loricin; Unasyn; ***Jpn***: Unasyn-S; ***Malaysia***: Easyn; Shinasyn; Sulbacin; Sulbamp; Sulperazon; Unasyn; ***Mex.***: Megamox; Trifamox IBL; Unasyna; ***Philipp.***: Ambacitam; Ampimax; Ampisul; Dinocin; Silgram; Subacillin; Sulbacin; Sulperazone; Sultacillin; Ultramox; Unasan; Unasyn; ***Pol.***: Sulperazon; Unasyn; ***Rus.***: Bacperazone (Бакперазон); Cebanex (Цебанекс); Cephpar (Цефпар); Libakcil (Либакцил); Sulbacin (Сульбацин); Sulcef (Сульцеф); Sulcefazon (Сульцефазон); Sulmover (Сульмовер); Sulperacef (Сульперацеф); Sulperason (Сульперазон); Sultasin (Сультасин); Sulzoncef (Сульзонцеф); Trifamox IBL (Трифамокс ИБЛ); Unasyn (Уназин)†; ***Singapore***: Unasyn; ***Thai.***: Bacticep; Cebactam; Cefpar; Cefper; Prazone-S; Sulam; Sulbaccin; Sulbacilline; Sulcef; Sulperazon; Sulpermed; Unasyn; Zonbactam; ***Turk.***: Alfasid; Combicid; Devasid; Duobak; Duobaktam; Duocid; Nobecid; Primaseft†; Probicid; Sefbaktam; Sulbaksit; Sulcid; Sulperazon; Sultasid; Sultibac; ***Ukr.***: Ampisid (Амписид); Ampisulbin (Амписульбин); Cebanex (Цебанекс); Cefoperazone Plus (Цефоперазон плюс); Cefosulbin (Цефосульбин); Cesulpin (Цесульпин); Gepacef Combi (Гепацеф Комби); Prazone-S (Празон-С); Sulperasone (Сульперазон); Taxtam (Тактам); Unasyn (Уназин)†; ***USA***: Unasyn; ***Venez.***: Ampibactan; Fipexiam; Sinif; Sulperazon; Unasyn.

Pharmacopoeial Preparations
USP 36: Ampicillin and Sulbactam for Injection.

Sulbenicillin Sodium *(rINNM)*

Natrii Sulbenicillinum; Sulbenicilina sódica; Sulbénicilline Sodique; α-Sulfobenzylpenicillin Sodium; Sulfocillin Sodium; Натрий Сульбеницциллин.

The disodium salt of (6*R*)-6-(2-phenyl-2-sulphoacetamido) penicillanic acid.

$C_{16}H_{16}N_2Na_2O_7S_2$=458.4

CAS — 34779-28-7 (sulbenicillin); 41744-40-5 (sulbenicillin); 36417-90-0 (sulbenicillin sodium).

ATC — J01CA16.

ATC Vet — QJ01CA16.

UNII — 29SO9LIM1Q.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Sulbenicillin sodium has actions and uses similar to those of carbenicillin sodium (p. 232.1). It is given by intramuscular or intravenous injection or infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Kedacillin; ***Mex.***: Kedacillin†; ***Philipp.***: Kedacillin.

Sulfabenzamide *(BAN, USAN, rINN)*

Sulfabensamid; Sulfabentsamidi; Sulfabenzamida; Sulfabenzamidum; Sulfabenzide; Сульфабензамид.

N-Sulphanilylbenzamide.

$C_{13}H_{12}N_2O_3S$=276.3

CAS — 127-71-9.

UNII — G58F8OPL4I.

Pharmacopoeias. In *US*.

USP 36: (Sulfabenzamide). A fine, white, practically odourless powder. Insoluble in water and in ether; soluble

in alcohol, in acetone, and in sodium hydroxide 4% solution. Protect from light.

Profile

Sulfabenzamide is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is reported to exert an optimal bacteriostatic action at pH 4.6. It has been used with sulfacetamide and sulfathiazole in pessaries or a vaginal cream for the treatment of bacterial vaginosis, although its value has been questioned. The vaginal cream has also been used for the prevention of bacterial infection after cervical and vaginal surgery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Vagi-Sulfa; ***Gr.***: Kronoderm; Sultrin; ***Philipp.***: Sultrin†; ***S.Afr.***: Sultrin†; ***USA***: Sultrin†.

Pharmacopoeial Preparations
USP 36: Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Sulfacarbamide *(BAN, rINN)*

Sulfacarbamida; Sulfacarbamidum; Sulfakarbamid; Sulfanilcarbamide; Sulfaurea; Sulphacarbamide; Sulphanilylurea; Sulphaurea; Urosulphanum; Сульфакарбамид.
Sulphanilylurea monohydrate.
$C_7H_9N_3O_3S,H_2O$=233.2
CAS — 547-44-4 (anhydrous sulfacarbamide); 6101-35-5 (sulfacarbamide monohydrate).
UNII — W6CD25Z4QR.

Pharmacopoeias. In *Pol.*

Profile

Sulfacarbamide is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It has been used in the treatment of urinary-tract infections, sometimes with other drugs.

Sulfacetamide *(BAN, rINN)*

Acetosulfaminum; Sulfacetamid; Sulfacetamida; Sulfacétamide; Sulfacetamidum; Sulfatsetamidi; Sulphacetamide; Сульфацетамид.
N-Sulphaniloylacetamide.
$C_8H_{10}N_2O_3S$=214.2
CAS — 144-80-9.
ATC — S01AB04.
ATC Vet — QJ01EQ21; QS01AB04.
UNII — 4965G3J0F5.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Sulfacetamide). A white, odourless, crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides; practically insoluble in benzene. Solutions in water are acid to litmus and sensitive to light; they are unstable when acidic or strongly alkaline. Protect from light.

Sulfacetamide Sodium *(BANM, rINNM)*

Natrii Sulfacetamidum; Soluble Sulphacetamide; Sulfacetamid-Natrium; Sulfacetamid sodná sůl monohydrát; Sulfacetamid sodowy; Sulfacetamida sódica; Sulfacétamide Sodique; Sulfacetamidnatrium; Sulfacetamido natrio druska; Sulfacetamidum natricum; Sulfacetamidum Natricum Monohydricum; Sulfacylum; Sülfasetamid Sodyum; Sulfasetamidinatrium; Sulphacetamide Sodium; Sulphacetamidum Sodium; Szulfacetamid-nátrium; Натрий Сульфацетамид.
$C_8H_9N_2NaO_3S,H_2O$=254.2
CAS — 127-56-0 (anhydrous sulfacetamide sodium); 6209-17-2 (sulfacetamide sodium monohydrate).
ATC — S01AB04.
ATC Vet — QJ01EQ21; QS01AB04.
UNII — 4NRT660KJQ.

NOTE. SULF is a code approved by the BP 2014 for use on single unit doses of eye drops containing sulfacetamide sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US,* and *Viet.*

Ph. Eur. 8: (Sulfacetamide Sodium). A white or yellowish-white, crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. A 5% solution in water has a pH of 8.0 to 9.5. Protect from light.

USP 36: (Sulfacetamide Sodium). A white odourless crystalline powder. Soluble 1 in 2.5 of water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 8.0 to 9.5. Store in airtight containers. Protect from light.

Stability. When solutions of sulfacetamide sodium are heated, hydrolysis occurs forming sulfanilamide which may be deposited as crystals, especially from concentrated solutions and under cold storage conditions.

Uses and Administration

Sulfacetamide is a short-acting sulfonamide antibacterial that is used with sulfabenzamide and sulfathiazole in preparations for vaginal use, and is applied, as the sodium salt, in infections or injuries of the eyes, although it is rarely of much value. Eye drops containing sulfacetamide sodium 10 to 30% and eye ointments containing 10% have been used. The sodium salt is also applied topically in the treatment of skin infections, and with sulfur in the management of rosacea.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Local application of sulfacetamide sodium to the eye may cause burning or stinging but this is rarely severe enough to require stopping treatment.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

When sulfacetamide sodium is applied to the eye it penetrates into ocular tissues and fluids and may be absorbed into the blood when the conjunctiva is inflamed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermaseb; ***Austral.***: Acetopt†; Bleph-10; ***Austria***: Cetazin; ***Belg.***: Anginamide; Antebor; Sulfa 10; ***Braz.***: Queimalive; ***Canad.***: Ak-Sulf; Bleph-10†; Cetamide†; Diosulf; Sodium Sulamyd; ***Fr.***: Antebor†; ***Hong Kong***: Sulfex; ***India***: Albucid; Alektra; Andremide; Bleph; Locula; Ocu-Sulf; Optacd; ***Indon.***: Albucid; Isotic Cetride†; ***Irl.***: Bleph-10†; ***Israel***: Klaron†; Optisol†; Sulfacid; ***Mex.***: Blef-10; Cetapred; Examida; Isoftalmol†; Sodamida; Sul 10; ***NZ***: Acetopt; Bleph-10; ***Philipp.***: Acetopt; Facetam; Sensocet; Vistasulf; ***S.Afr.***: Spersamide†; ***Singapore***: Sulfex; ***Thai.***: Bleph-10; Optal; ***Turk.***: Optamid; Sivex; ***Ukr.***: Sulfacyl (Сульфацил); ***USA***: Ak-Sulf; Bleph-10; Carmol Scalp Treatment†; Isopto Cetamide†; Klaron; Mexar; Ocusulf†; Ovace; Seb-Prev Wash; Sodium Sulamyd†; Sulf-10; Sulfac; Sulster; Vanocin; ***Venez.***: Sulfacet.

Multi-ingredient Preparations. ***Arg.***: Blefamide; ***Braz.***: Isopto Cetapred; Paraqueimol; Sulnil; Vagi-Sulfa; ***Canad.***: Ak-Cide; Blephamide; Dioptimyd; Sulfacet-R; ***Chile***: Blefamide†; Blefamide; Deltamid; ***Ger.***: Blephamide; ***Gr.***: Blephamide; Eyecort; Geypirina; Isopto Cetapred; Kronoderm; Otenor; Sulfachlor; Sulfachloramphenicol; Sulfanicole; Sultrin; ***India***: Cortola-M; Nebasulf; Neotop; Zinco Sulpha†; ***Israel***: Blephamide; ***Ital.***: Antisettico Astringente Sedativo; Aureomix; Brumeton Colloidale S; Cosmiciclina; Visublefarite; ***Mex.***: Axel; Blefamide-F; Blefamide; Deltamid; Isopto Cetapred; Premid; Sulfa Cloran; Sulfa Hidro†; Sulvi; ***NZ***: Blephamide†; ***Philipp.***: Cetapred†; Isopto Cetapred†; Lonace; Sterilid-V; Sultrin†; ***Port.***: Meocil; ***S. Afr.***: Covancaine; Covosan†; Sultrin†; ***Singapore***: Blephamide†; ***Spain***: Celestone S†; Denticelso; ***Switz.***: Blephamide; ***Turk.***: Blephamide; Brumeton; Suprenil; ***USA***: Avar; Blephamide; BP Cleansing Wash; Cerisa; Claris; Clenia†; FML-S†; Garimide; Metimyd†; Nicosyn; Plexion; Rosac†; Rosaderm; Rosanil; Rosula NS†; Rosula†; SE SS; SSS; Sulfacet-R; SulfaCleanse; Sulfamide; Sultrin†; SulZee†; Sumadan; Sumaxin; Suphera; Vasocidin; Vasocine; Vasosulf†; Virti-Sulf; Zencia; Zetacet†; ***Venez.***: Sulfacort.

Pharmacopoeial Preparations
USP 36: Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Suspension; Sulfacetamide Sodium Ophthalmic Ointment; Sulfacetamide Sodium Ophthalmic Solution; Sulfacetamide Sodium Topical Suspension; Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Sulfachlorpyridazine *(BAN, rINN)*

Sulfachlorpyridazin; Sulfachlorpyridazinum; Sulfaclorpiridazina; Sulphachlorpyridazine; Сульфахлорпиридазин.
N^1-(6-Chloropyridazin-3-yl)sulphanilamide.
$C_{10}H_9ClN_4O_2S$=284.7
CAS — 80-32-0.
ATC Vet — QJ01EQ12.
UNII — P78D9P90C0.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Sulfachlorpyridazine). Protect from light.

Profile

Sulfachlorpyridazine is a sulfonamide antibacterial used in veterinary medicine.

Sulfachrysoidine *(rINN)*

Carboxysulfamidochrysoidine; Sulfachrysoïdine; Sulfachrysoidinum; Sulfacrisoidina; Сульфахризоидин.
3,5-Diamino-2-(*p*-sulfamoylphenylazo) benzoic acid.
$C_{13}H_{13}N_5O_4S$=335.3
CAS — 485-41-6.
UNII — 39O1389K38.

Profile

Sulfachrysoidine is a sulfonamide antibacterial that has been used topically as the sodium salt for infections of the oral mucosa.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Collubiazol.

Sulfaclozine *(rINN)*

Sulfaclozin; Sulfaclozina; Sulfaclozinum; Sulfaklotsiini; Sulfaklozin; Сульфаклозин.
N^1-(6-Chloropyrazinyl)sulfanilamide.
$C_{10}H_9ClN_4O_2S$=284.7
CAS — 102-65-8; 27890-59-1.
ATC Vet — QP51AG04.
UNII — 69YP7Z48CW.

Profile

Sulfaclozine is a sulfonamide antibacterial that has been used in veterinary medicine.

Sulfadiazine *(BAN, rINN)*

Solfadiazina; Solfapirimidina; Sulfadiatsiini; Sülfadiazin; Sulfadiazin; Sulfadiazina; Sulfadiazinas; Sulfadiazinum; Sulphadiazine; Szulfadiazin; Сульфадиазин.
N^1-(Pyrimidin-2-yl)sulphanilamide.
$C_{10}H_{10}N_4O_2S$=250.3
CAS — 68-35-9.
ATC — J01EC02.
ATC Vet — QJ01EQ10.
UNII — 0N7609K889.

NOTE. Compounded preparations of sulfadiazine may be represented by the following names:
- Co-tetroxazine (*BAN*)—sulfadiazine 5 parts and tetroxoprim 2 parts (see p. 277.3)
- Co-trimazine (*BAN*)—sulfadiazine 5 parts and trimethoprim 1 part.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *US,* and *Viet.*

Ph. Eur. 8: (Sulfadiazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Practically insoluble in water; very slightly soluble in alcohol; slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfadiazine). White or slightly yellow, odourless or nearly odourless, powder, slowly darkening on exposure to light. Soluble 1 in 13 000 of water; sparingly soluble in alcohol and in acetone; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides, and ammonia. Protect from light.

Sulfadiazine Sodium *(BANM, rINN)*

Sodium Sulfadiazine; Soluble Sulphadiazine; Sulfadiazina de sodio; Sulfadiazina sódica; Sulfadiazine sodique; Sulfadiazinum Natricum; Sulphadiazine Sodium; Сульфадиазин Натрий.
$C_{10}H_9N_4NaO_2S$=272.3
CAS — 547-32-0.
ATC — J01EC02.
UNII — 84CS1P306F.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Sulfadiazine Sodium). A white powder. Soluble 1 in 2 of water; slightly soluble in alcohol. On prolonged exposure to humid air it absorbs carbon dioxide with the liberation of sulfadiazine and becomes incompletely soluble in water. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Solutions of sulfadiazine sodium are alkaline, and incompatibility may reasonably be expected with acidic drugs or with preparations unstable at high pH. In the UK, licensed product information has stated that sulfadiazine sodium injection is incompatible with fructose, iron salts, and salts of heavy metals.

Uses and Administration

Sulfadiazine is a short-acting sulfonamide that has been used similarly to sulfamethoxazole (p. 367.2) in the treatment of infections due to susceptible organisms. It has been used in the treatment of nocardiosis and lymphogranuloma venereum, and has been given for the prophylaxis of rheumatic fever in penicillin-allergic patients. For details of these infections and their treatment, see Choice of Antibacterial, p. 172.2. Sulfadiazine is also given with pyrimethamine for the treatment and prevention of relapse of toxoplasmosis (p. 926.1) and has been tried in disseminated *Acanthamoeba* infection (p. 921.3).

In the treatment of susceptible infections, sulfadiazine may be given orally in usual doses of 2 to 4 g daily in divided doses.

Immunocompromised patients who have toxoplasmosis should be given a dose of 4 to 6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2 to 4 g daily, which should continue indefinitely. Pyrimethamine should always be given as well.

For the prophylaxis of rheumatic fever, patients weighing less than about 30 kg are given 500 mg once daily, while those over 30 kg may receive 1 g once daily.

For details of doses in children, see p. 364.1.

Where oral use is not possible, treatment has also been begun intravenously using the sodium salt. Sulfadiazine sodium 1.09 g is equivalent to about 1 g of sulfadiazine. Intravenous doses of sulfadiazine sodium are given by infusion or by slow intravenous injection of a solution containing up to 5% sulfadiazine. It may be diluted with sodium chloride 0.9%. The usual dose is the equivalent of sulfadiazine 2 to 3 g initially, then 1 g four times daily for 2 days; subsequent treatment is given orally.

Sulfadiazine sodium has been given by deep intramuscular injection, but great care must be taken to prevent damage to subcutaneous tissues; the intravenous route is preferred.

Sulfadiazine has been used with trimethoprim as cotrimazine. Sulfadiazine has also been used with other sulfonamides, particularly sulfamerazine and sulfadimidine, to reduce the problems of low solubility in urine.

Administration in children. Sulfadiazine may be used in children for the management of infections caused by susceptible organisms, including toxoplasmosis, for which it may also be used in neonates. It is also used for prophylaxis of rheumatic fever. Although parenteral preparations may be available in some countries, the oral route is preferred.

In the UK, licensed product information recommends that children beyond the neonatal period may receive an initial oral dose of 75 mg/kg followed by a maintenance dose of 150 mg/kg daily in divided doses. Alternatively, in the USA, the American Academy of Pediatrics (AAP)[1] recommends 120 to 150 mg/kg daily in 4 to 6 divided doses. The maximum total daily dose should not exceed 6 g.

For treatment of **congenital toxoplasmosis**, the *BNFC* recommends that neonates may receive sulfadiazine 50 mg/kg twice daily for 12 months, *plus* pyrimethamine 1 mg/kg twice daily for 2 days, once daily for 6 months, then 3 times a week for 6 months.

For the treatment of **acquired toxoplasmosis** in HIV-infected children, US guidelines[2] suggest the following regimen for at least 6 weeks, followed by chronic suppressive therapy:

- sulfadiazine 25 to 50 mg/kg (to a maximum of 1.5 g) 4 times daily *plus*
- pyrimethamine 2 mg/kg (to a maximum of 50 mg) once daily for 3 days, then 1 mg/kg (to a maximum of 25 mg), once daily

For **chronic suppression of toxoplasmosis** in HIV-infected children, US guidelines[2] suggest sulfadiazine 85 to 120 mg/kg (to a maximum of 4 g) daily in 2 to 4 divided doses *plus* pyrimethamine 1 mg/kg (to a maximum of 25 mg) once daily.

In the prevention of recurrent **rheumatic fever**, sulfadiazine is dosed in children according to weight, similarly to adults (see Uses and Administration, above).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 13/12/13)

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Because of the low solubilities of sulfadiazine and its acetyl derivative in urine, crystalluria is more likely after use of sulfadiazine than after sulfamethoxazole.

Sulfadiazine sodium solution is strongly alkaline and it should therefore be given intravenously in a strength not exceeding 5%, over at least 10 minutes. For the same reason, intramuscular injections are painful and sulfadiazine sodium should not be given by intrathecal or subcutaneous injection.

Carnitine deficiency. Hyperammonaemia and carnitine deficiency developed in an immunocompromised patient given sulfadiazine and pyrimethamine for the treatment of toxoplasmosis.[1]

1. Sekas G, Harbhajan SP. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95:** 112–13.

Effects on the eyes. Numerous white stone-like concretions of sulfadiazine occurred in the conjunctiva of a woman who had used sulfadiazine eye drops for about 1 year.[1]

1. Boettner EA, *et al.* Conjunctival concretions of sulfadiazine. *Arch Ophthalmol* 1974; **92:** 446–8.

Effects on the kidneys. There have been reports of crystalluria and renal failure associated with the use of sulfadiazine in immunocompromised patients,[1-8] including the suggestion that AIDS patients may be particularly prone to sulfadiazine-induced renal toxicity.[3] Renal failure and leucopenia in a patient treated with sulfadiazine silver for pyoderma gangrenosum were thought to be due to systemic absorption of the silver component.[9]

1. Goadsby PJ, *et al.* Acquired immunodeficiency syndrome (AIDS) and sulfadiazine-associated acute renal failure. *Ann Intern Med* 1987; **107:** 783–4.
2. Ventura MG, *et al.* Sulfadiazine revisited. *J Infect Dis* 1989; **160:** 556–7.
3. Simon DI, *et al.* Sulfadiazine crystalluria revisited: the treatment of Toxoplasma encephalitis in patients with acquired immunodeficiency syndrome. *Arch Intern Med* 1990; **150:** 2379–84.
4. Díaz F, *et al.* Sulfadiazine-induced multiple urolithiasis and acute renal failure in a patient with AIDS and Toxoplasma encephalitis. *Ann Pharmacother* 1996; **30:** 41–2.
5. Guitard J, *et al.* Sulfadiazine-related obstructive urinary tract lithiasis: an unusual cause of acute renal failure after kidney transplantation. *Clin Nephrol* 2005; **63:** 405–7.
6. Solano Remírez M, *et al.* Insuficiencia renal por sulfadiazina en paciente VIH con toxoplasmosis cerebral. *An Med Interna* 2005; **22:** 395–6.
7. Hyvernat H, *et al.* Insuffisance rénale aiguë obstructive lors d'un traitement par sulfadiazine. *Presse Med* 2006; **35:** 423–4.
8. de la Prada Alvarez FJ, *et al.* Insuficiencia renal aguda por depósito de cristales de sulfadiacina. *An Med Interna* 2007; **24:** 235–8.
9. Chaby G, *et al.* Insuffisance rénale aiguë après application topique de sulfadiazine argentique. *Ann Dermatol Venereol* 2005; **132:** 891–3.

Effects on the liver. A case of severe hepatotoxicity and probable hepatorenal syndrome occurred in a patient about 14 days after taking sulfadiazine as part of a treatment regimen for toxoplasmosis retinitis. The patient stopped all medicines after 3 weeks. She made a complete recovery with supportive management which included haemodialysis, and treatment with acetylcysteine.[1]

1. Khalili H, *et al.* Severe hepatotoxicity and probable hepatorenal syndrome associated with sulfadiazine. *Am J Health-Syst Pharm* 2011; **68:** 888–92.

Effects on the salivary glands. Enlargement of the salivary glands (sialadenitis) has been reported[1] in a patient who received a preparation containing sulfadiazine; complete recovery followed within 3 days of stopping therapy. Rechallenge confirmed that sulfadiazine was the causative agent.

1. Añíbarro B, Fontela JL. Sulfadiazine-induced sialadenitis. *Ann Pharmacother* 1997; **31:** 59–60.

Interactions

As for Sulfamethoxazole, p. 368.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

Sulfadiazine is readily absorbed from the gastrointestinal tract and peak blood concentrations occur 3 to 6 hours after a single dose; 20 to 55% has been reported to be bound to plasma proteins. It penetrates into the CSF within 4 hours of an oral dose to produce therapeutic concentrations, which may be more than half those in the blood. Up to 40% of sulfadiazine in the blood is present as the acetyl derivative. The half-life of sulfadiazine is about 10 hours; it is prolonged in renal impairment.

About 50% of a single dose of sulfadiazine given orally is excreted in the urine in 24 hours; 15 to 40% is excreted as the acetyl derivative.

The urinary excretion of sulfadiazine and the acetyl derivative is dependent on pH. About 30% is excreted unchanged in both fast and slow acetylators when the urine is acidic whereas about 75% is excreted unchanged by slow acetylators when the urine is alkaline. The half-life of sulfadiazine ranges from 7 to 12 hours and that of its metabolite from 8 to 12 hours.[1]

1. Vree TB, *et al.* Determination of the acetylator phenotype and pharmacokinetics of some sulphonamides in man. *Clin Pharmacokinet* 1980; **5:** 274–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Suladrin†; ***Fr.***: Adiazine; ***Gr.***: Adiazine†; ***Mex.***: Bioarginol-C; Hebermin; Sularyn†; ***Port.***: Labdiazina; ***Thai.***: Odiazine; Rediazine; Sul BCO; Sulfazine-M.

Multi-ingredient Preparations. ***Arg.***: Afonisan; Anginotrat; Pastillas Lorbi†; ***Austria***: Rhinon; ***Braz.***: Triglobe; ***China***: Zengxiao Lianhuangpian (增效联磺); ***Fin.***: Ditrim; Trimetin Duplo†; ***India***: Aubril; Zad-G; ***Indon.***: Trisulfa; ***Malaysia***: Balin; Beaglobe; Trizine; ***Mex.***: Agin; Estrefen; ***Philipp.***: Triglobe†; Trizine; ***Port.***: Broncodiazina†; ***Singapore***: Balin; Trizine; ***Thai.***: Sulfatril†; Triple Sulphas; Trisulfa Co-P; Trisulfapyrimidines; ***Turk.***: Sulfatrim†.

Pharmacopoeial Preparations

BP 2014: Sulfadiazine Injection;
USP 36: Sulfadiazine Sodium Injection; Sulfadiazine Tablets; Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Sulfadiazine Silver *(BANM, rINNM)*

Argenti Sulfadiazinum; Gümüş Sülfadiazin; Hopeasulfadiatsiini; Silbersulfadiazin; Silver Sulfadiazine (USAN); Silver Sulfadiazine; Silver Sulphadiazine; Silversulfadiazin; Sulfadiazina argéntica; Sulfadiazina de plata; Sulfadiazine Argentique; Sulfadiazinum Argenticum; Sulfadiazinum Argentum; Sulphadiazine Silver; Zilversulfadiazine; Сульфадиазин Серебра.

$C_{10}H_9AgN_4O_2S$=357.1

CAS — 22199-08-2.

ATC — D06BA01.

ATC Vet — QD06BA01.

UNII — W46JY43EJR.

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.

USP 36: (Silver Sulfadiazine). A white to creamy-white, odourless or almost odourless crystalline powder. It becomes yellow on exposure to light. Practically insoluble in alcohol, in chloroform, and in ether; slightly soluble in acetone; freely soluble in 30% ammonia solution. It decomposes in moderately strong mineral acids. Protect from light.

Uses and Administration

Sulfadiazine silver is a sulfonamide that is used as a 1% cream for the prevention and treatment of infection in severe burns (p. 1683.1).

Sulfadiazine silver has also been used in other skin conditions, such as leg ulcers (p. 1690.1), where infection may prevent healing and for the prophylaxis of infection in skin grafting. It has also been applied to the eyes in the treatment of superficial *Aspergillus* infections.

Catheters impregnated with sulfadiazine silver have been used to reduce catheter colonisation and related bloodstream infection (p. 1733.1).

Adverse Effects, Treatment, and Precautions

Sulfadiazine silver may be absorbed after topical application and produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p. 367.3).

Local pain or irritation are uncommon; the separation of the eschar may be delayed and fungal invasion of the wound may occur.

Transient leucopenia does not usually require withdrawal of sulfadiazine silver, but blood counts should be monitored to ensure they return to normal within a few days. Systemic absorption of silver, resulting in argyria, can occur when sulfadiazine silver is applied to large area wounds or over prolonged periods.

References.

1. Fuller FW. The side effects of silver sulfadiazine. *J Burn Care Res* 2009; **30:** 464–70.

Argyria. Argyria, with discoloration of the skin and sensorimotor neuropathy, has been reported after excessive application of sulfadiazine silver 1% cream to extensive leg ulcers.[1] Systemic argyria associated with loss of proprioception and impaired coordination has also been

reported with long-term use of the 1% cream under occlusive dressing in a patient with severe generalised dystrophic epidermolysis bullosa.[2]

1. Payne CMER, *et al.* Argyria from excessive use of topical silver sulphadiazine. *Lancet* 1992; **340**: 126.
2. Flohr C, *et al.* Topical silver sulfadiazine-induced systemic argyria in a patient with severe generalized dystrophic epidermolysis bullosa. *Br J Dermatol* 2008; **159**: 740–1.

Effects on the kidneys. For mention of renal failure and leucopenia associated with the use of sulfadiazine silver see under Sulfadiazine, p. 362.2.

Interactions

As for Sulfamethoxazole, p. 368.2.

Sulfadiazine silver is not antagonised by *p*-aminobenzoic acid or related compounds. The silver content of sulfadiazine silver may inactivate enzymatic debriding agents.

Antimicrobial Action

Sulfadiazine silver has broad antimicrobial activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, and some yeasts and fungi. Sulfadiazine silver has a bactericidal action; in contrast to sulfadiazine, the silver salt acts mainly on the cell membrane and cell wall and its action is not antagonised by *p*-aminobenzoic acid. Resistance to sulfadiazine silver has been reported and may develop during therapy.

Pharmacokinetics

Sulfadiazine silver slowly releases sulfadiazine when in contact with wound exudates. Up to about 10% of the sulfadiazine may be absorbed; concentrations in blood of 10 to 20 micrograms/mL have been reported, although higher concentrations may occur when extensive areas of the body are treated. Some silver may also be absorbed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sulfatral; ***Austral.***: Allevyn Ag; Flamazine; ***Austria***: Flammazine; ***Belg.***: Flammazine; Sedoflame; Sulfasil; ***Braz.***: Dermazine; Gino Dermazine†; Silglos; Sulfaderm†; ***Canad.***: Dermazin; Flamazine; ***Cz.***: Dermazin†; ***Denm.***: Flamazine; Flammazine; ***Fin.***: Flamazine; ***Fr.***: Flammazine; Sicazine†; ***Ger.***: Brandiazin†; Flammazine; InfectoFlam; ***Gr.***: Brandiazin; Flammazine; Sedoflame; Sylfio; ***Hong Kong***: Dermazin; Flamazine†; Silvederma; Silvex; ***Hung.***: Dermazin; ***India***: Burn Aid; Ceptidar; SSZ; ***Indon.***: Burnazin; ***Irl.***: Flamazine; ***Israel***: Silverol; ***Ital.***: Bacternil; Sofargen; ***Mex.***: Argemol; Argentafil; Argental; Silvadene†; Zitep†; ***Neth.***: Flammazine; ***Norw.***: Flamazine; ***NZ***: Flamazine; ***Philipp.***: Burnsil; Flammazine; Innoxiderm; Silvex; Sterizol; Sulfadin; Synvodex; ***Pol.***: Dermazin†; ***Port.***: Flammazine; Sicazine; Silvederma; Silvespray†; ***Rus.***: Dermazin (Дермажин); Silvederma (Сильведерм); Sulphargin (Сульфаргин); ***S.Afr.***: Argent-Eze†; Bactrazine; Flamazine; Silbecor; ***Spain***: Flammazine; Silvederma; ***Switz.***: Flammazine; Silvertone†; ***Thai.***: Dermazin; Flamazine; Silverderm; Silverol; Silvex; ***Turk.***: Silder; Silvaden; Silvadiazin; Silvamed; Silverdin; ***UAE***: Silvadiazin; ***UK***: Flamazine; ***Ukr.***: Argedin (Аргедин); Dermazin (Дермазин); Sulfargin (Сульфаргин); ***USA***: Silvadene; SSD; Thermazene; ***Venez.***: Menaderm; Protosulfil; Silvederma.

Multi-ingredient Preparations. ***Arg.***: Fisioderm; Iuronico Biotic; Platsul A; Sulfadiazina de Plata; Sulfaplat; ***Austral.***: Silvazine†; ***Belg.***: Flammacerium; ***Braz.***: Dermacerium; ***Chile***: FCE; Platsul A; ***Cz.***: Ialugen Plus; ***Fr.***: Altreet Ag; Flammacerium; Ialuset Plus; Urgotul S.Ag; ***Ger.***: Physiotulle-Ag; Urgotul S.Ag; ***Gr.***: Flammacerium; ***Hong Kong***: Flammacerium; ***Hung.***: Ialugen Plus; ***India***: AG-X; Aloederm-B; Alorex; Argisept; Burnheal; Burnil; Burnkul; Burnoff; Burnosym; Burnowin; Dermogard; Dibact; Drez-S; Glosilex; Heal; Silverex; ***Ital.***: Altergen; Connettivina Plus; ***Neth.***: Flammacerium; ***NZ***: Silvazine†; ***Philipp.***: Flammacerium; ***Pol.***: Flammacerium†; ***Singapore***: Silvazine†; Silvin; ***Spain***: Flammazine Cerio; ***Switz.***: Ialugen Plus; ***UK***: Flammacerium; Physiotulle-Ag; ***Ukr.***: Ebermin (Эбермин).

Pharmacopoeial Preparations
USP 36: Silver Sulfadiazine Cream.

Sulfadicramide *(rINN)*

Sulfadicramid; Sulfadicramida; Sulfadicramidum; Sulfadikramid; Sulfadikramidi; Сульфадикрамид.
N′-(3,3-Dimethylacroyl)sulphanilamide.
$C_{11}H_{14}N_2O_3S$=254.3
CAS — 115-68-4.
ATC — S01AB03.
ATC Vet — QS01AB03.
UNII — 7WZ5EG263C.

Profile

Sulfadicramide is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It has been applied as a 15% ointment for superficial infections of the eye.

Sulfadimethoxine *(BAN, rINN)*

Solfadimetossina; Solfadimetossipirimidina; Sulfadimethoxin; Sulfadiméthoxine; Sulfadimethoxinum; Sulfadimetoksiini; Sulfadimetoxin; Sulfadimetoxina; Sulphadimethoxine; Сульфадиметоксин.
N^1-(2,6-Dimethoxypyrimidin-4-yl)sulphanilamide.
$C_{12}H_{14}N_4O_4S$=310.3
CAS — 122-11-2.
ATC — J01ED01.
ATC Vet — QJ01EQ09; QP51AG02.
UNII — 30CPC5LDEX.

Pharmacopoeias. In *Fr.* and *It.* In *US* for veterinary use only.

USP 36: (Sulfadimethoxine). Practically white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, in ether, and in hexane; soluble in 2N sodium hydroxide; sparingly soluble in 2N hydrochloric acid. Store in airtight containers. Protect from light.

Profile

Sulfadimethoxine is a long-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is used in preparations for the treatment of skin infections and was formerly used for the treatment of urinary-tract infections. It is also used in veterinary medicine, sometimes with baquiloprim or ormetoprim.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Levosin (Левосин); ***Thai.***: D-Med; Ximeprim.

Sulfadimidine *(BAN, rINN)*

Solfametazina; Sulfadimerazine; Sulfadimezinum; Sulfadimidiini; Sulfadimidin; Sulfadimidina; Sulfadimidinas; Sulfadimidinum; Sulfamethazine; Sulphadimethylpyrimidine; Sulphadimidine; Sulphamethazine; Szulfadimidin; Сульфадимидин.
N^1-(4,6-Dimethylpyrimidin-2-yl)sulphanilamide.
$C_{12}H_{14}N_4O_2S$=278.3
CAS — 57-68-1.
ATC — J01EB03.
ATC Vet — QJ01EQ03; QP51AG01.
UNII — 48U51W007F.

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulfisomidine (p. 371.1). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.* Also in *BP(Vet)*.

Ph. Eur. 8: (Sulfadimidine). White or almost white powder or crystals. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfamethazine). White to yellowish-white, practically odourless, powder. It may darken on exposure to light. Very slightly soluble in water and in ether; slightly soluble in alcohol; soluble in acetone. Protect from light.

Sulfadimidine Sodium *(BANM, rINNM)*

Natrii Sulfadimidinum; Soluble Sulphadimidine; Sulfadimidina sódica; Sulfadimidine Sodique; Sulfamethazine Sodium; Sulphadimidine Sodium; Натрий Сульфадимидин.
$C_{12}H_{13}N_4NaO_2S$=300.3
CAS — 1981-58-4.
ATC — J01EB03.
UNII — 7Z13P9Q95C.

Pharmacopoeias. In *Int.*

Profile

Sulfadimidine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2).

It is well absorbed from the gastrointestinal tract and is about 80 to 90% bound to plasma proteins. Reported half-lives have ranged from 1.5 to 4 hours in fast and 5.5 to 8.8 hours in slow acetylators. Because of the relatively high solubility of the drug and its acetyl metabolite, crystalluria may be less likely than with sulfamethoxazole.

In the treatment of susceptible infections, sulfadimidine has been given orally in an initial dose of 2 g, followed by 0.5 to 1.0 g every 6 to 8 hours. It has also been given parenterally as the sodium salt.

Sulfadimidine has also been used with other sulfonamides, particularly sulfamerazine and sulfadiazine. It is also used in veterinary medicine, sometimes with baquiloprim or trimethoprim.

Because its pharmacokinetics differ in fast and slow acetylators, sulfadimidine has been used to determine acetylator status.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Septosyl; ***Thai.***: Famidine.

Multi-ingredient Preparations. ***Indon.***: Trisulfa; ***Thai.***: Sulfatril†; Triple Sulphas; Trisulfa Co-P; Trisulfapyrimidines.

Pharmacopoeial Preparations
USP 36: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Sulfadoxine *(BAN, USAN, rINN)*

Ro-4-4393; Sulfadoksiini; Sulfadoksinas; Sulfadossina; Sulfadoxin; Sulfadoxina; Sulfadoxinum; Sulformethoxine; Sulforthomidine; Sulphormethoxine; Sulphorthodimethoxine; Szulfadoxin; Сульфадоксин.
N^1-(5,6-Dimethoxypyrimidin-4-yl)sulphanilamide.
$C_{12}H_{14}N_4O_4S$=310.3
CAS — 2447-57-6.
ATC Vet — QJ01EQ13.
UNII — 88463U4SM5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Sulfadoxine). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfadoxine). Protect from light.

Uses and Administration

Sulfadoxine is an ultra-long-acting sulfonamide that has been used in the treatment of various infections but is now rarely used alone.

It is given as a fixed-dose combination of 20 parts sulfadoxine with 1 part pyrimethamine (*Fansidar*, *Roche*) in the treatment of falciparum malaria (p. 644.1), usually with artesunate. Although the combination has been used in the prophylaxis of malaria, the risk of toxicity is now generally considered to outweigh its value.

In the treatment of malaria, the usual oral dose is 1.5 g of sulfadoxine with 75 mg of pyrimethamine as a single dose.

For details of doses in children, see p. 365.3.

Sulfadoxine with pyrimethamine has also been given intramuscularly.

Sulfadoxine with pyrimethamine has also been tried in the treatment of actinomycetomas (see Mycetoma p. 193.1), and for prophylaxis of pneumocystis pneumonia in immunocompromised patients (see p. 567.2 for the more usual prophylactic regimens).

A mixture of 5 parts of sulfadoxine with 1 part trimethoprim is used in veterinary medicine.

Administration in children. Sulfadoxine may be used in children, with pyrimethamine, for the treatment of falciparum malaria. It may be given as a single oral dose to children 2 months of age and older according to bodyweight as follows:

- 5 to 10 kg: 250 mg, with 12.5 mg pyrimethamine
- 11 to 20 kg: 500 mg, with 25 mg pyrimethamine
- 21 to 30 kg: 750 mg, with 37.5 mg pyrimethamine
- 31 to 45 kg: 1 g, with 50 mg pyrimethamine
- over 45 kg: as for adults (see Uses and Administration, above)

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3. For reference to the adverse effects of a combination of sulfadoxine and pyrimethamine, see Pyrimethamine, p. 663.3.

If adverse effects occur, sulfadoxine has the disadvantage that several days are required for elimination from the body.

References.

1. Peters PJ, *et al.* Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety* 2007; **30**: 481–501.

Interactions

As for Sulfamethoxazole, p. 368.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3. Synergy exists between sulfadoxine and pyrimethamine, which act against folate metabolism at different points of the metabolic cycle.

Resistance to the combination of sulfadoxine and pyrimethamine in plasmodia, first noted in Thailand in the late 1970s, has become widespread in many malarious areas of the world. For further details of resistance to antimalarial drugs, see p. 644.1.

Pharmacokinetics

Sulfadoxine is readily absorbed from the gastrointestinal tract and peak concentrations of about 60 micrograms/mL occur about 4 hours after a 500-mg dose. It has an elimination half-life of about 200 hours. About 90 to 95% is reported to be bound to plasma proteins.

Sulfadoxine is widely distributed to body tissues and fluids; it passes into the fetal circulation and has been detected in low concentrations in breast milk. Sulfadoxine is excreted in urine, mainly unchanged.

References.
1. Karunajeewa HA, *et al.* Pharmacokinetic properties of sulfadoxine-pyrimethamine in pregnant women. *Antimicrob Agents Chemother* 2009; **53:** 4368–76.
2. Nyunt MM, *et al.* Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. *Clin Pharmacol Ther* 2010; **87:** 226–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Malaysia***: Fansidar.

Multi-ingredient Preparations. ***Austral.***: Fansidar†; ***Braz.***: Fansidar; ***Fr.***: Fansidar; ***Gr.***: Fansidar; ***India***: Amalar; Croydox-in-FM; Domine; Laridox; Larinate Kit; Malasulf; Malcidal; Malocide; Masunate; Metasulfin; Onli-2; Pyralfin; Rimodar; ***Indon.***: Fansidar; Plasmodin; Suldox; ***Irl.***: Fansidar†; ***Israel***: Fansidar†; ***Malaysia***: Madomine; Malafon; ***Philipp.***: Fansidar; ***Rus.***: Fansidar (Фансидар); ***S.Afr.***: Fansidar; ***Switz.***: Fansidar†; ***Thai.***: Vinsilar; ***UK***: Fansidar; ***Ukr.***: Fansidar (Фансидар)†; ***USA***: Fansidar†.

Pharmacopoeial Preparations
USP 36: Sulfadoxine and Pyrimethamine Tablets.

Sulfafurazole *(BAN, plNN)*

Sulfafuratsoli; Sulfafurazol; Sulfafurazolas; Sulfafurazolo; Sulfafurazolum; Sulfisossazolo; Sulfisoxazole; Sülfizoksazol; Sulphafuraz; Sulphafurazole; Szulfafurazol; Сульфафуразол.

N^1-(3,4-Dimethylisoxazol-5-yl)sulphanilamide.

$C_{11}H_{13}N_3O_3S$=267.3

CAS — 127-69-5.

ATC — J01EB05; S01AB02.

ATC Vet — QJ01EQ05; QS01AB02.

UNII — 740T4C525W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulfafurazole). White or yellowish-white, crystalline powder or crystals. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfisoxazole). A white to slightly yellowish, odourless crystalline powder. Soluble 1 in 7700 of water and 1 in 10 of boiling alcohol; soluble in 3N hydrochloric acid. Store in airtight containers. Protect from light.

Acetyl Sulfafurazole

Acetilsulfafurazol; Acetyl Sulphafurazole; Sulfisoxazole Acetyl; Ацетилсульфафуразол.

N^1-Acetyl Sulphafurazole; *N*-(3,4-Dimethylisoxazol-5-yl)-*N*-sulphanilylacetamide.

$C_{13}H_{15}N_3O_4S$=309.3

CAS — 80-74-0.

ATC — J01EB05; S01AB02.

ATC Vet — QJ01EB05; QS01AB02.

UNII — WBT5QH3KED.

NOTE. Acetyl sulfafurazole is to be distinguished from the N^4-acetyl derivative formed from sulfafurazole by conjugation in the body.

Compounded preparations of acetyl sulfafurazole may be represented by the following name:

- Co-erynsulfisox (*PEN*)—acetyl sulfafurazole and erythromycin ethyl succinate.

Pharmacopoeias. In *US*.

USP 36: (Sulfisoxazole Acetyl). A white or slightly yellow crystalline powder. Practically insoluble in water; soluble 1 in 176 of alcohol, 1 in 35 of chloroform, 1 in 1064 of ether, and 1 in 203 of methyl alcohol. Store in airtight containers. Protect from light.

Sulfafurazole Diolamine *(plNNM)*

NU-445; Sulfafurazol diolamina; Sulfafurazol, Diolamine de; Sulfafurazoli Diolaminum; Sülfisoksazol Dietanolamin; Sulfisoxazole Diolamine (USAN); Sulphafurazole Diethanolamine; Sulphafurazole Diolamine; Сульфафуразола Диоламин.

The 2,2′-iminobisethanol salt of sulphafurazole.

$C_{11}H_{13}N_3O_3S.C_4H_{11}NO_2$=372.4

CAS — 4299-60-9.

ATC — J01EB05; S01AB02.

ATC Vet — QS01AB02.

UNII — 30S4B46J8B.

Uses and Administration

Sulfafurazole is a short-acting sulfonamide that has been used similarly to sulfamethoxazole (p. 367.2), notably in the treatment of urinary-tract infections, pneumonia due to *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), nocardiosis, and trachoma. It is also used, usually with erythromycin, in the treatment of otitis media. For details of these infections and their treatment see Choice of Antibacterial, p. 172.2.

Sulfafurazole is usually given orally. In the treatment of susceptible infections, it has been given in an initial dose of 2 to 4 g, followed by 4 to 8 g daily in divided doses every 4 to 6 hours. Dosage modification may be necessary in patients with renal impairment. For details of doses in children, see p. 366.2. Acetyl sulfafurazole is tasteless and is used in liquid oral preparations of the drug; doses are expressed in terms of sulfafurazole. 1.16 g of acetyl sulfafurazole is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has been used, as an ophthalmic ointment or solution containing the equivalent of 4% of sulfafurazole, in the topical treatment of susceptible eye infections. Sulfafurazole diolamine 1.39 g is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has also been given parenterally.

Administration in children. Sulfafurazole may be used in infants and children 2 months of age and older for the treatment of infections caused by susceptible organisms, and is usually given orally. It is usually given in an initial dose of 75 mg/kg, followed by a maintenance dose of 150 mg/kg daily (to a maximum of 6 g) in 4 to 6 divided doses.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Sulfafurazole and its acetyl derivative are relatively soluble in urine and the risk of crystalluria is generally slight, but nevertheless adequate fluid intake is recommended.

Breast feeding. A study[1] in 6 women given sulfafurazole concluded that the amount of drug appearing in breast milk posed no risk to the healthy infant beyond the immediate newborn period, but potential risk in breast-fed infants with jaundice or G6PD deficiency, or who are ill, stressed, or premature, was more difficult to evaluate. Based on this evidence, the last available guidance from the American Academy of Pediatrics[2] stated that sulfafurazole was usually compatible with breast feeding, but caution was required in the infants mentioned above.

1. Kauffman RE, *et al.* Sulfisoxazole secretion into human milk. *J Pediatr* 1980; **97:** 839–41.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Interactions

As for Sulfamethoxazole, p. 368.2.

Sulfafurazole has been reported to increase the anaesthetic effect of thiopental.

Eye preparations of sulfafurazole diolamine should not be applied with preparations of silver salts.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

Sulfafurazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 4 hours after an oral dose. Acetyl sulfafurazole (the N^1-acetyl derivative) is broken down to sulfafurazole in the gastrointestinal tract before absorption, resulting in delayed and somewhat lower peak concentrations. Sulfafurazole is about 85 to 90% is bound to plasma proteins. It readily diffuses into extracellular fluid, but very little diffuses into cells. Concentrations in the CSF are about one-third of those in the blood. Sulfafurazole crosses the placenta into the fetal circulation and is distributed into breast milk. About 30% of sulfafurazole in the blood and in the urine is in the form of the N^4-acetyl derivative.

Sulfafurazole is excreted rapidly in the urine, up to 97% of a single dose being eliminated in 48 hours. The half-life is reported to range from about 5 to 8 hours. Both sulfafurazole and its N^4-acetyl derivative are more soluble than many other sulfonamides in urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Gansol; ***USA***: Gantrisin†; ***Venez.***: Ganticol.

Multi-ingredient Preparations. ***Canad.***: Pediazole; ***Chile***: Bioquin; ***Fr.***: Pediazole; ***Gr.***: Pediazole; ***Israel***: Pediazole†; ***Mex.***: Pediazole; Urovec†; ***Thai.***: Pyrizole; ***Turk.***: Azo Gantrisin; ***USA***: Pediazole†.

Pharmacopoeial Preparations
USP 36: Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Sulfisoxazole Acetyl Oral Suspension; Sulfisoxazole Tablets.

Sulfaguanidine *(BAN, rINN)*

Solfaguanidina; Sulfaguanidiini; Sulfaguanidin; Sulfaguanidina; Sulfaguanidinas; Sulfaguanidinum; Sulfaguanidyna; Sulfamidinum; Sulginum; Sulphaguanidine; Szulfaguanidin; Сульфагуанидин.

1-Sulphanilylguanidine; *N*′-Amidinosulphanilamide.

$C_7H_{10}N_4O_2S$=214.2

CAS — 57-67-0 (anhydrous sulfaguanidine); 6190-55-2 (sulfaguanidine monohydrate).

ATC — A07AB03.

ATC Vet — QA07AB03.

UNII — 15XQ8043FN.

Pharmacopoeias. In *Eur.* (see p. vii).

Viet. includes the monohydrate.

Ph. Eur. 8: (Sulfaguanidine). A white or almost white, fine crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in dichloromethane. It dissolves in dilute solutions of mineral acids. Protect from light.

Profile

Sulfaguanidine is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is absorbed to a limited extent from the gastrointestinal tract and may therefore be more likely to cause systemic effects than less well absorbed drugs such as phthalylsulfathiazole and succinylsulfathiazole. It is used, usually with other drugs, in the treatment of gastrointestinal infections, and has also been applied locally to the skin and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Enteropathyl†; ***Rus.***: Sulgin (Сульгин); ***Thai.***: Sulfayel.

Multi-ingredient Preparations. ***Chile***: Carbon Sulfaguanidina; ***India***: Enteroguanidine; ***Mex.***: Neopecsul; ***Thai.***: Biodan.

Sulfamerazine *(BAN, rINN)*

RP-2632; Solfamerazina; Sulfamerasinum; Sulfameratsiini; Sulfamerazin; Sulfamerazina; Sulfamerazinas; Sulfamérazine; Sulfamerazinum; Sulfamethyldiazine; Sulfamethylpyrimidine; Sulphamerazine; Szulfamerazin; Сульфамеразин.

N^1-(4-Methylpyrimidin-2-yl)sulphanilamide.

$C_{11}H_{12}N_4O_2S$=264.3

CAS — 127-79-7.

ATC — D06BA06; J01ED07.

ATC Vet — QD06BA06.

UNII — UR1SAB295F.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *BP(Vet)*.

Ph. Eur. 8: (Sulfamerazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Sulfamerazine Sodium *(BANM, rINN)*

Soluble Sulphamerazine; Sulfamerazina de sodio; Sulfamerazina sódica; Sulfamérazine sodique; Sulfamerazinum Natricum; Sulphamerazine Sodium; Сульфамеразин Натрий.

$C_{11}H_{11}N_4NaO_2S$=286.3
CAS — 127-58-2.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.
UNII — JOV4UJY07O.

Profile

Sulfamerazine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It has usually been given with other sulfonamides, or with trimethoprim.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Trisulfa; ***Thai.***: Sulfatril†; Triple Sulphas; Trisulfa Co-P; Trisulfapyrimidines.

Pharmacopoeial Preparations
USP 36: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Sulfamethizole *(BAN, rINN)*

Sulfamethizol; Sulfaméthizol; Sulfamethizolum; Sulfametitsoli; Sulfametizol; Sulfametizolas; Sulfametizolo; Sulphamethizole; Szulfametizol; Сульфаметизол.
N^1-(5-Methyl-1,3,4-thiadiazol-2-yl)sulphanilamide.
$C_9H_{10}N_4O_2S_2$=270.3
CAS — 144-82-1.
ATC — B05CA04; D06BA04; J01EB02; S01AB01.
ATC Vet — QB05CA04; QD06BA04; QJ01EQ02; QS01AB01.
UNII — 25W8454H16.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulfamethizole). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfamethizole). Practically odourless, white crystals or powder. Soluble 1 in 2000 of water, 1 in 38 of alcohol, 1 in 13 of acetone, and 1 in 1900 of chloroform and of ether; freely soluble in solutions of ammonium, potassium, and sodium hydroxides; soluble in dilute mineral acids; practically insoluble in benzene. Protect from light.

Uses and Administration

Sulfamethizole is a short-acting sulfonamide that is given orally in the treatment of infections of the urinary tract, sometimes with other antibacterials; it is unsuitable for the treatment of systemic infection since only relatively low concentrations of drug occur in the blood and tissues.

It is given in usual adult doses of 1 g twice daily. For details of doses in children, see p. 367.1.

Sulfamethizole monoethanolamine has also been used.

Administration in children. Sulfamethizole has been used orally in infants and children 2 months of age and older for the treatment of urinary-tract infections due to susceptible organisms, in a typical dose of 50 mg/kg daily in 2 to 4 divided doses.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Sulfamethizole and its acetyl derivative are relatively soluble in urine, and the risk of crystalluria is quite low, but an adequate fluid intake should generally be maintained.

Interactions

As for Sulfamethoxazole, p. 368.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

Sulfamethizole is readily absorbed from the gastrointestinal tract; about 90% has been reported to be bound to plasma proteins. Its half-life has been reported to range from about 1.5 to 3 hours. It is only slightly acetylated in the body and is rapidly excreted, about 60% of a dose being eliminated in the urine in 5 hours and around 90% within 10 hours. Sulfamethizole and its acetyl derivative are readily soluble in urine over a wide pH range. Concentrations in blood and tissues are low because of its rapid excretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Lucosil; ***Fr.***: Rufol.

Multi-ingredient Preparations. ***Spain***: Micturol Sedante; ***USA***: Urobiotic-250; ***Venez.***: Bacteval.

Pharmacopoeial Preparations
USP 36: Sulfamethizole Oral Suspension; Sulfamethizole Tablets.

Sulfamethoxazole *(BAN, USAN, rINN)*

Ro-4-2130; SMX; SMZ; Sulfamethoxazol; Sulfaméthoxazole; Sulfamethoxazolum; Sulfametoksatsoli; Sulfametoksazol; Sulfametoksazolas; Sulfametoxazol; Sulfametoxazolo; Sulfisomezole; Sulphamethoxazole; Szulfametoxazol; Сульфаметоксазол.
N^1-(5-Methylisoxazol-3-yl)sulphanilamide.
$C_{10}H_{11}N_3O_3S$=253.3
CAS — 723-46-6.
ATC — J01EC01.
ATC Vet — QJ01EQ11.
UNII — JE42381TNV.

NOTE. Compounded preparations of sulfamethoxazole may be represented by the following names:
- Co-trimoxazole (*BAN*)—sulfamethoxazole 5 parts and trimethoprim 1 part (see p. 277.3)
- Co-trimoxazole (*PEN*)—sulfamethoxazole and trimethoprim.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sulfamethoxazole). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves in dilute solutions of sodium hydroxide and in dilute acids. Protect from light.

USP 36: (Sulfamethoxazole). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 3400 of water, 1 in 50 of alcohol, and 1 in 1000 of chloroform and of ether; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; freely soluble in acetone and in dilute solutions of sodium hydroxide. Protect from light.

Uses and Administration

The use of sulfamethoxazole and other sulfonamides has been limited by the increasing incidence of resistant organisms. Their main use has been in the treatment of acute, uncomplicated urinary-tract infections, particularly those caused by *Escherichia coli*. They have also been used in nocardiosis, and in some other bacterial infections such as otitis media, *Chlamydia* and *Chlamydophila* infections, and prophylaxis of meningococcal meningitis, but have largely been replaced by other drugs: even where pathogens retain some sensitivity to sulfonamides, a combination such as co-trimoxazole (sulfamethoxazole with trimethoprim) has often been preferred. The usual treatment of these infections is discussed under Choice of Antibacterial, p. 172.2.

Sulfonamides are also used, often with pyrimethamine or trimethoprim, in the treatment of protozoal infections, particularly malaria (p. 644.1) and toxoplasmosis (p. 926.1). They are also used similarly in pneumocystis pneumonia (p. 567.2).

Sulfamethoxazole is a medium-acting sulfonamide that has been given orally in a usual dose of 2 g initially, followed by 1 g twice daily. In severe infections 1 g three times daily has been given.

For details of doses in children, see p. 367.2.

Reduction of dosage may be required in patients with renal impairment.

For the uses and dosage of sulfamethoxazole with trimethoprim, see Co-trimoxazole, p. 277.3.

Sulfamethoxazole lysine has also been used.

Administration. US licensed product information for a former product of sulfamethoxazole recommended that blood concentrations be measured in patients receiving sulfonamides for serious infections. The following concentrations of free sulfonamide in the blood were considered to be therapeutically effective:
- for most infections, 50 to 150 micrograms/mL
- for serious infections, 120 to 150 micrograms/mL

Concentrations of 200 micrograms/mL should not be exceeded since the incidence of adverse reactions might be increased.

Administration in children. Sulfamethoxazole may be used orally in children for the treatment of infections caused by susceptible organisms. It has been given in an initial dose of 50 to 60 mg/kg, followed by a maintenance dose of 25 to 30 mg/kg twice daily (to a maximum daily dose of 75 mg/kg).

Adverse Effects and Treatment

Nausea, vomiting, anorexia, and diarrhoea are relatively common after use of sulfamethoxazole and other sulfonamides.

Hypersensitivity reactions to sulfonamides have proved a problem. Fever is relatively common, and reactions involving the skin may include rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum. Severe, potentially fatal, skin reactions including toxic epidermal necrolysis and the Stevens-Johnson syndrome have occurred in patients treated with sulfonamides. Dermatitis may also occur from contact of sulfonamides with the skin. SLE, particularly exacerbation of pre-existing disease, has also been reported.

Nephrotoxic reactions including interstitial nephritis and tubular necrosis, which may result in renal failure, have been attributed to hypersensitivity to sulfamethoxazole. Lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine of sulfamethoxazole or its less soluble acetylated metabolite. The risk of crystalluria can be reduced by giving fluids to maintain a high urine output. If necessary, alkalinisation of the urine with sodium bicarbonate may increase solubility and aid the elimination of sulfonamides.

Blood disorders have occasionally occurred during treatment with the sulfonamides including sulfamethoxazole, and include agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, hypoprothrombinaemia, and eosinophilia. Many of these effects on the blood may result from hypersensitivity reactions. Sulfonamides may rarely cause cyanosis due to methaemoglobinaemia. Acute haemolytic anaemia is a rare complication which may be associated with G6PD deficiency.

Other adverse effects that may be manifestations of a generalised hypersensitivity reaction to sulfonamides include a syndrome resembling serum sickness, hepatic necrosis, hepatomegaly and jaundice, myocarditis, pulmonary eosinophilia and fibrosing alveolitis, and vasculitis including polyarteritis nodosa. Anaphylaxis has been reported only very rarely.

Other adverse reactions reported after sulfamethoxazole or other sulfonamides include hypoglycaemia, hypothyroidism, neurological reactions including aseptic meningitis, ataxia, benign intracranial hypertension, convulsions, dizziness, drowsiness, fatigue, headache, insomnia, mental depression, peripheral or optic neuropathies, psychoses, tinnitus, vertigo, and pancreatitis.

Sulfonamides may displace serum-bound bilirubin, resulting in kernicterus in premature neonates.

As with other antimicrobials, sulfamethoxazole may cause alterations of the bacterial flora in the gastrointestinal tract. There is, therefore, the possibility, although it appears to be small, that pseudomembranous colitis may occur.

Slow acetylators of sulfamethoxazole may be at greater risk of adverse reactions than fast acetylators.

For further information on the adverse effects of sulfamethoxazole when used with trimethoprim, see Co-trimoxazole, p. 278.3.

Hypersensitivity. Adverse effects to sulfonamide antibacterials are a relatively common problem, occurring in about 3% of courses; about 3% of these are true hypersensitivity reactions some of which can be severe or life-threatening.[1]

The sulfa moiety ($-SO_2NH_2$) which is contained in the chemical structure of sulfonamide antibacterials is also part of many other drugs, including the carbonic anhydrase inhibitors (such as acetazolamide), the thiazide diuretics (such as hydrochlorothiazide and indapamide), loop diuretics (such as furosemide), sulfonylurea antidiabetics (such as tolbutamide and glyburide), selective cyclooxygenase-2 inhibitors (such as celecoxib), serotonin agonists (such as sumatriptan), HIV-protease inhibitors (amprenavir and fosamprenavir), dapsone, and probenecid.[1-3] However, chemical differences between the sulfonamide antibacterials and these others mean that the latter are less likely to cause severe hypersensitivity reactions.[1,4,5] The immunological determinant of type I immunologic reaction to sulfonamide antibacterials is the N1 heterocyclic ring, and nonantibacterial sulfonamides do not have this structural feature. Many non-type I hypersensitivity responses to sulfonamide antibacterials are due to reactive metabolites; metabolite formation is stereospecific to the N4 amino nitrogen of the sulfonamide antibacterials and this structure is also not found on any nonantibacterial sulfonamides.[4,5] Although severe cases of presumed cross-hypersensitivity have been reported rarely,[1] the chemical differences and the stereospecificity of these reactions makes true cross-reactivity between antibacterial and nonantibacterial sulfonamides extremely unlikely.[1-5]

Even though the risk of cross-reactivity is low, concerns about it continue to complicate treatment as patients who have had a reaction after taking a sulfonamide are thought to be at increased risk for another reaction or a cross-

hypersensitivity reaction and prescribers are often warned that all sulfonamides should be contra-indicated in those with a history of sulfa allergy, even though data supporting this advice are mainly limited to a few case reports. A retrospective cohort study in the UK[2] found that while allergy to a sulfonamide antibacterial was a risk factor for a subsequent allergic reaction to nonantibacterial sulfonamide-containing drugs, a history of penicillin allergy was also at least as strong a risk factor. This finding was thought to be due to a general tendency to allergic reactions among certain patients rather than a specific cross-reactivity with drugs containing the sulfa moiety. The authors therefore considered that patients with a history of any type of allergic reaction after taking sulfonamides or penicillins should be regarded as at increased general risk of reactions to other drugs, rather than specifically contra-indicating sulfonamides.

A review of case reports and observational studies of cross-reactivity between antibacterial and nonantibacterial sulfonamides published in the literature between 1966 and March 2004[3] also found that the concerns about cross-reactivity between the two groups were not supported by the published data. The authors suggested that except for patients with serious allergic reactions and/or multiple drug allergies, all other patients with a sulfa allergy might be given sulfonamide-containing drugs provided there is no alternative drug available and they were appropriately monitored while on treatment. Others have suggested giving a test dose, preferably orally and in a monitored environment.[1]

1. Ponka D. Approach to managing patients with sulfa allergy: use of antibiotic and nonantibiotic sulfonamides. *Can Fam Physician* 2006; **52:** 1434–8.
2. Strom BL, *et al*. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; **349:** 1628–35.
3. Johnson KK, *et al*. Sulfonamide cross-reactivity: fact or fiction? *Ann Pharmacother* 2005; **39:** 290–301.
4. Brackett CC, *et al*. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. *Pharmacotherapy* 2004; **24:** 856–70.
5. Brackett CC. Sulfonamide allergy and cross-reactivity. *Curr Allergy Asthma Rep* 2007; **7:** 41–8.

Precautions

In patients given sulfamethoxazole, adequate fluid intake is necessary to reduce the risk of crystalluria; the daily urine output should be 1200 mL or more. Compounds that render the urine acidic may increase the risk of crystalluria; the risk may be reduced with alkaline urine.

Treatment with sulfonamides should be stopped immediately a rash appears because of the danger of severe allergic reactions such as the Stevens-Johnson syndrome.

Sulfamethoxazole should be given with care to patients with renal or hepatic impairment and is contra-indicated in patients with severe impairment or with blood disorders. Dosage reduction may be necessary in renal impairment. Complete blood counts and urinalyses with microscopic examination should be carried out, particularly during prolonged therapy. Sulfamethoxazole should not be given to patients with a history of hypersensitivity to sulfonamides as cross-sensitivity may occur between drugs of this group. Care is generally advisable in patients with a history of allergy or asthma. Caution is also needed in the elderly, who may be more likely to have other risk factors for reactions. Some consider sulfamethoxazole to be contra-indicated in lupus erythematosus as it may exacerbate the condition. Patients with glucose 6-phosphate dehydrogenase deficiency may be at risk of haemolytic reactions.

Sulfamethoxazole and other sulfonamides are not usually given to infants within 1 to 2 months of birth because of the risk of producing kernicterus; for the same reason, they are generally contra-indicated in pregnant women before delivery (see p. 368.2).

Patients with AIDS may be particularly prone to adverse reactions, especially when sulfamethoxazole is given with trimethoprim as co-trimoxazole.

Sulfonamides have been reported to interfere with some diagnostic tests, including those for urea, creatinine, and urinary glucose and urobilinogen.

Breast feeding. Sulfonamides are distributed into breast milk in low concentrations and, although they are generally contra-indicated in the USA in breast-feeding women because of the risk of kernicterus, they are usually thought to pose a negligible risk to healthy neonates. However, sulfonamides should be used with caution in breast-feeding mothers of ill, stressed, or premature infants and of infants with jaundice, hyperbilirubinaemia or G6PD deficiency.

The last available guidance from the American Academy of Pediatrics considered sulfamethoxazole, when given with trimethoprim, to be compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Immunocompromised patients. Sulfamethoxazole is mainly conjugated in the liver to the N^4-acetyl derivative, but is also oxidised, to a limited extent, to the hydroxylamine metabolite.[1-5] Although this metabolite was originally implicated[6] in the development of adverse reactions to sulfonamides, recent work[7] has cast some doubt on this hypothesis. The metabolite appears to be produced through cytochrome P450 oxidative metabolism, and it has been suggested that slow acetylators of sulfamethoxazole show increased oxidation compared with other metabolic routes.[1] AIDS patients also have increased oxidation, since they may be depleted of substrates such as acetylcoenzyme A or glutathione necessary for acetylation or detoxification, and this may explain their susceptibility to sulfamethoxazole toxicity.[2,3]

There have been attempts to inhibit the formation of the hydroxylamine metabolite by competitive inhibition of cytochrome P450 enzymes, notably with fluconazole and ketoconazole.[4,5] Encouraging results have been obtained with fluconazole in healthy subjects, but the potential for clinical benefit in AIDS patients requires further study.[5]

However, one successful method of overcoming adverse effects in AIDS patients has been **desensitisation**. Desensitisation by use of initial doses of 4 mg of sulfamethoxazole or 5 mg of sulfadiazine every 6 hours, doubled at 24-hour intervals until the desired dose was reached, was uneventful in 9 of 13 patients with AIDS requiring sulfonamide treatment for opportunistic infections.[8] The remaining 4 had cutaneous reactions with fever, but in 2 of these the reactions were successfully managed with an antihistamine. Although there is a risk of anaphylaxis, patients with AIDS can be successfully treated with sulfonamides after desensitisation.

See also Immunocompromised Patients under Precautions of Co-trimoxazole, p. 279.2.

1. Cribb AE, Spielberg SP. Sulfamethoxazole is metabolized to the hydroxylamine in humans. *Clin Pharmacol Ther* 1992; **51:** 522–6.
2. Lee BL, *et al*. The hydroxylamine of sulfamethoxazole and adverse reactions in patients with acquired immunodeficiency syndrome. *Clin Pharmacol Ther* 1994; **56:** 184–9.
3. van der Ven AJA, *et al*. Urinary recovery and kinetics of sulphamethoxazole and its metabolites in HIV-seropositive patients and healthy volunteers after a single oral dose of sulphamethoxazole. *Br J Clin Pharmacol* 1995; **39:** 621–5.
4. Mitra AK, *et al*. Inhibition of sulfamethoxazole hydroxylamine formation by fluconazole in human liver microsomes and healthy volunteers. *Clin Pharmacol Ther* 1996; **59:** 332–40.
5. Gill HJ, *et al*. The effect of fluconazole and ketoconazole on the metabolism of sulphamethoxazole. *Br J Clin Pharmacol* 1996; **42:** 347–53.
6. van der Ven AJAM, *et al*. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 431–3.
7. ter Hofstede HJM, *et al*. Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
8. Torgovnick J, Arsura E. Desensitization to sulfonamides in patients with HIV infection. *Am J Med* 1990; **88:** 548–9.

Pregnancy. Some sulfonamides have been shown to cause fetal abnormalities including cleft palate in *animals*, but fears of **teratogenic effects** in humans do not appear to be substantiated. Sulfonamides are probably safe in the first trimester of pregnancy, although throughout pregnancy they should be used only in the absence of a suitable alternative drug.[1]

Sulfonamides may displace serum-bound bilirubin and they should be avoided close to delivery because of the risk of kernicterus in the neonate. The risk of drug-induced **bilirubin displacement** has been reviewed.[2] The initial evidence suggesting a kernicterus-promoting effect of drugs in neonates was reported for sulfafurazole, and this drug now serves as a standard displacing agent against which other drugs are evaluated. Although all sulfonamides are highly protein bound, each has a different capacity to displace bilirubin. Sulfadiazine and sulfanilamide have been found to be the least displacing of the sulfonamides and the effects of sulfadiazine on bilirubin may not be clinically significant; an increased incidence of hyperbilirubinaemia and kernicterus has not been shown after use for prophylaxis of rheumatic fever during pregnancy. Sulfasalazine should theoretically cause significant bilirubin displacement, but studies suggest that the drug may be given to patients with Crohn's disease who are pregnant or breast feeding. Metabolites of sulfonamides have also been evaluated for kernicterus-promoting effects; glucuronide metabolites are expected to compete for binding sites less effectively than the parent compound, whereas acetylated metabolites of some sulfonamides appear to be more potent bilirubin displacers.

1. Wise R. Prescribing in pregnancy: antibiotics. *BMJ* 1987; **294:** 42–4.
2. Walker PC. Neonatal bilirubin toxicity: a review of kernicterus and the implications of drug-induced bilirubin displacement. *Clin Pharmacokinet* 1987; **13:** 26–50.

Interactions

The action of sulfonamides may be antagonised by *p*-aminobenzoic acid and its derivatives, particularly potassium aminobenzoate and the procaine group of local anaesthetics.

Sulfamethoxazole and other sulfonamides may potentiate the effects of some drugs, such as oral anticoagulants (p. 1531.1), methotrexate (p. 827.3), and phenytoin (p. 542.3); this may be due to displacement of the drug from plasma protein binding sites or to inhibition of metabolism. However, the clinical significance of these interactions appears to depend on the particular sulfonamide involved. The possibility of interactions with other highly protein-bound drugs, such as NSAIDs, should be considered.

High doses of sulfonamides have been reported to have a hypoglycaemic effect; the antidiabetic effect of the sulfonylurea compounds may be enhanced by sulfonamides (p. 505.3). Some sulfonamides have been associated with a decrease in plasma-ciclosporin concentrations when used together (p. 1956.2). Isolated reports have described possible failures of hormonal contraceptives resulting in pregnancy in patients given sulfonamides (p. 2243.1).

The use of compounds that render the urine acidic may increase the risk of crystalluria.

Antimicrobial Action

Sulfamethoxazole and other sulfonamides have a similar structure to *p*-aminobenzoic acid and interfere with the synthesis of nucleic acids in sensitive micro-organisms by blocking the conversion of *p*-aminobenzoic acid to the coenzyme dihydrofolic acid, a reduced form of folic acid; in man, dihydrofolic acid is obtained from dietary folic acid so sulfonamides do not affect human cells. Their action is mainly bacteriostatic, although they may be bactericidal where concentrations of thymine are low in the surrounding medium. The sulfonamides have a broad spectrum of action, but the development of widespread resistance (see below) has greatly reduced their usefulness, and susceptibility often varies widely even among nominally sensitive pathogens.

- Gram-positive cocci, such as *Staphylococcus aureus*, *S. saprophyticus*, *Streptococcus pyogenes*, *Str. pneumoniae*, and the viridans streptococci are susceptible to sulfonamides, but enterococci are resistant.
  Gram-positive bacilli reported to be susceptible include *Bacillus anthracis*, *Clostridium perfringens*, *C. tetani*, and most strains of *B. cereus*.
  Actinomycetes spp. and *Nocardia* spp. are generally susceptible, while *Listeria monocytogenes* shows variable susceptibility.
- Among the Gram-negative organisms, most of the Enterobacteriaceae including *Enterobacter*, *Escherichia coli*, *Klebsiella*, *Proteus*, *Salmonella*, *Shigella*, and *Yersinia* species are susceptible to sulfonamides (but see Resistance below); *Providencia* are, however, often resistant.
  Although pathogenic *Neisseria* spp. were formerly extremely susceptible to sulfonamides, many strains are now resistant.
  Haemophilus influenza type b is susceptible but susceptibility rates for *H. ducreyi* vary.
  Sulfonamides may be effective against most strains of *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*) and some strains of *Pseudomonas aeruginosa*.
  Other Gram-negative organisms that have been reported to be susceptible include *Acinetobacter* spp., *Legionella pneumophila*, and most *Bacteroides fragilis* strains.
- Some serotypes of *Chlamydia trachomatis* are susceptible to sulfonamides but *C. psittaci* and *C. pneumonia* are resistant. *Mycoplasma*, *Ureaplasma urealyticum*, *Treponema*, *Leptospira*, *Rickettsia*, and *Coxiella burnetii* are resistant to sulfonamides.
- Atypical mycobacteria show variable susceptibility to sulfonamides while the long-acting sulfonamides are bacteriostatic against *Mycobacterium leprae*.
- Although sulfonamides have some *in vitro* activity against the protozoa *Plasmodium falciparum* and *P. vivax*, malaria parasites may become resistant to sulfonamides. Some sulfonamides may be active against *Toxoplasma gondii* and *Pneumocystis jirovecii*.
- The fungi *Paracoccidioides brasiliensis* is usually susceptible to sulfonamides, although resistant strains occur naturally and resistance may also develop during treatment. Sulfonamides (alone or with trimethoprim) have been effective in the treatment of histoplasmosis.

Sulfamethoxazole and other sulfonamides show synergy with the dihydrofolate reductase inhibitors pyrimethamine and trimethoprim which inhibit a later stage in folic acid synthesis. For reports of the antimicrobial activity of sulfamethoxazole with trimethoprim, see Co-trimoxazole, p. 280.1.

The *in-vitro* antimicrobial activity of sulfamethoxazole is very dependent on both the culture medium and size of inoculum used.

Resistance. Acquired resistance to sulfonamides is common and widespread among formerly susceptible organisms, particularly *Neisseria* spp., *Pseudomonas* spp.,

Enterobacteriaceae (such as *Shigella, Escherichia coli,* and *Salmonella*), staphylococci, and streptococci.

There appear to be several mechanisms of resistance including alteration of dihydropteroate synthetase, the enzyme inhibited by sulfonamides, to a less sensitive form, or an alteration in folate biosynthesis to an alternative pathway; increased production of *p*-aminobenzoic acid; or decreased uptake or enhanced metabolism of sulfonamides.

Resistance may result from chromosomal alteration, or may be plasmid-mediated and transferable, as in many resistant strains of enterobacteria. High-level resistance is usually permanent and irreversible. There is complete cross-resistance between the different sulfonamides.

Pharmacokinetics

Sulfamethoxazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 2 hours. Blood concentrations of up to 100 micrograms/mL occur after a single 2-g oral dose. About 70% is bound to plasma proteins. The plasma half-life is about 6 to 12 hours; it is prolonged in patients with severe renal impairment.

Sulfamethoxazole, like most sulfonamides, diffuses freely throughout the body tissues and may be detected in the urine, saliva, sweat, and bile, in the cerebrospinal, peritoneal, ocular, and synovial fluids, and in pleural and other effusions. It crosses the placenta into the fetal circulation and low concentrations have been detected in breast milk.

Sulfamethoxazole undergoes conjugation mainly in the liver, chiefly to the inactive N^4-acetyl derivative; this metabolite represents about 15% of the total amount of sulfamethoxazole in the blood. Metabolism is increased in patients with renal impairment and decreased in those with hepatic impairment. Elimination in the urine is dependent on pH. About 80 to 100% of a dose is excreted in the urine, of which about 60% is in the form of the acetyl derivative, with the remainder as unchanged drug and glucuronide.

Sulfamethoxazole is also oxidised to the hydroxylamine, a metabolite that has been implicated in adverse reactions to sulfonamides (see also Immunocompromised Patients, under Precautions, p. 366.2), although some doubt has been cast upon this hypothesis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Adrenol; Bacti-Uril; Bacticel; Bactrim Balsamico; Bactrim; Cotrizol-G; Danferane; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Netocur Balsamico; Netocur; Neumobacticel; Novidrine; Sulfagrand; Tritenk; Urisept NF; ***Austral.***: Bactrim; Resprim; Septrin; Trimoxazole†; ***Austria***: Bactrim; Cotribene; Eusaprim; Oecotrim†; ***Belg.***: Bactrim; Cotrim†; Eusaprim; ***Braz.***: Assepium Balsamico; Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Belfactrim F; Benectrin Balsamico; Benectrin; Diazol; Dientrin; Dispeptrin†; Ectrin Balsamico; Ectrin; Gamactrin†; Imuneprim†; Infectrin; Metoprin Balsamico†; Metoprin; Neotrin; Pulkrin†; Qiftrim; Roytrin; Selectrin Balsamico; Selectrin†; Teutrin; Tricban; Trimexazol; Urocrim; Uropol†; ***Canad.***: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Protrin; Septra; Trisulfa; ***Chile***: Bacterol; Bactrimel; Entero Micinovo; Septrin; Trelibec; Uro-Micinovo; ***China***: Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (奎建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Xiaoke (消刻); Yu An Li Qing (玉安立清); Zengxiao Lianhuangpian (增效联磺); ***Cz.***: Biseptol; Bismoral†; Primotren†; Sumetrolim; ***Fin.***: Cotrim; ***Fr.***: Bactrim; ***Ger.***: Berlocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; ***Gr.***: Bactrimel; Bioprim; Blaxezan; Blexon; Epahol; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; ***Hong Kong***: Chemoprim; Cotrim; Dhatrin; Letus; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; ***Hung.***: Cotripharm; Sumetrolim; ***India***: Alcorim-F; Antrima; Bactrim; Chemotrin; Ciplin; Colizole; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Malarwin; Methoxaprim; Moly Kid; Mountrim; Neoprim; Okatrim DS; Oriprim; Otrim; Pyramet; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.***: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.***: Septrin; ***Israel***: Diseptyl; Resprim; Septrin; ***Ital.***: Bactrim; Chemitrim; Eusaprim†; ***Jpn***: Bactramin; Baktar; ***Malaysia***: Bacin; Bactrim; Chemix; Cotrim; Resprim†; Trimexazole; Trizole; ***Mex.***: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric†; Bactide†; Bactilen; Bactiver; Bactrim Compositum; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Guayaprin; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octex; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole Compositum; Trimexole; Trimzol; TS-Bac; Vanadyl; ***Neth.***: Bactrimel; ***Norw.***: Bactrim; ***NZ***: Apo-Sulfatrim†; Deprim; Trisul; ***Philipp.***: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim†; Zolmed; ***Pol.***: Bactrim; Biseptol; Septrin†; Two-Septol; ***Port.***: Bactrim; Microcetim†; Septrin; ***Rus.***: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гросептол); Oriprim (Оприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); ***S.Afr.***: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac; Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac; Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; ***Singapore***: Apo-Sulfatrim; Bacin; BS; Chemix; Co-Trimexazole; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; Trimaxazole; ***Spain***: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†; Momentol†; Septrin; Soltrim; ***Swed.***: Bactrim; Eusaprim; ***Switz.***: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; ***Thai.***: Actin; Actrim; Addtrim; Agsulfa; Babytrim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Conprim†; Coprim; Cotamox; Cotrim; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Zoleprim; ***Turk.***: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Septrin; Sulfaprim; Trifen; Trimoks; ***UAE***: Trimol; ***UK***: Fectrim; Septrin; ***Ukr.***: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гросептол); Soluseptol (Солюсептол); Sumetrolim (Суметролим); ***USA***: Bactrim; Cotrim†; Septra; SMZ-TMP; Sulfatrim; ***Venez.***: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets;

USP 36: Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Sulfamethoxazole Oral Suspension; Sulfamethoxazole Tablets.

Sulfamethoxypyridazine *(BAN, rINN)*

Solfametossipiridazina; Sulfamethoxypyridazin; Sulfaméthoxypyridazine; Sulfamethoxypyridazinum; Sulfamethoxypyridazinum ad usum veterinarium; Sulfametoksipyridatsiini; Sulfametoxipiridazina; Sulfametoxipyridazin; Sulphamethoxypyridazine; Szulfametoxipiridazin; Сульфаметоксипиридазин.

N^1-(6-Methoxypyridazin-3-yl)sulphanilamide.

$C_{11}H_{12}N_4O_3S$=280.3

CAS — 80-35-3.

ATC — J01ED05.

ATC Vet — QJ01EQ15.

UNII — T034E4NS2Z.

Pharmacopoeias. In *Int.* and *Viet.* In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Sulfamethoxypyridazine for Veterinary Use; Sulfametoxypyridazine BP(Vet) 2014). A white or slightly yellowish crystalline powder which colours slowly on exposure to light. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; very slightly soluble in dichloromethane; dissolves in dilute mineral acids and solutions of alkali hydroxides. Protect from light.

Profile

Sulfamethoxypyridazine is a long-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2) and has been used for the treatment of susceptible infections. It is rapidly absorbed from the gastrointestinal tract and excreted slowly in urine, partly as the N^4-acetyl metabolite; it remains detectable for up to 7 days after a dose. It has also been used with trimethoprim similarly to co-trimoxazole.

Acetyl sulfamethoxypyridazine, which is hydrolysed in the gastrointestinal tract forming sulfamethoxypyridazine, and sulfamethoxypyridazine sodium have also been used.

Skin disorders. Sulfamethoxypyridazine has been used in the treatment of pemphigoid,[1,2] and also in the management of dermatitis herpetiformis.[3]

1. Thornhill M, *et al.* An open clinical trial of sulphamethoxypyridazine in the treatment of mucous membrane pemphigoid. *Br J Dermatol* 2000; **143:** 117–26.
2. Gach JE, *et al.* Sulfamethoxypyridazine-responsive pemphigoid nodularis: a report of two cases. *J Am Acad Dermatol* 2005; **53** (2 suppl 1): S101–S104.
3. Fry L. Dermatitis herpetiformis. *Baillieres Clin Gastroenterol* 1995; **9:** 371–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Uropac.

Sulfamethylthiazole

Methylsulfathiazole; Sulfametiltiazol; Sulphamethylthiazole; Сульфаметилтиазол.

4-Amino-*N*-(4-methyl-2-thiazolyl)benzenesulfonamide.

$C_{10}H_{11}N_3O_2S_2$=269.3

CAS — 515-59-3.

Profile

Sulfamethylthiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It is applied topically with tetracycline in the treatment of eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Pensulvit.

Sulfametopyrazine *(BAN)*

AS-18908; NSC-110433; Sulfametopirazina; Sulfametossipirazina; Sulfaleeni; Sulfalen; Sulfalene (pINN); Sulfalene (USAN); Sulfalène; Sulfaleno; Sulfalenum; Sulfamethoxypyrazine; Sulfapirazinmetossina; Sulfapyrazin Methoxyne; Sulphalene; Сульфален.

N^1-(3-Methoxypyrazin-2-yl)sulphanilamide.

$C_{11}H_{12}N_4O_3S$=280.3

CAS — 152-47-6.

ATC — J01ED02.

ATC Vet — QJ01EQ19.

UNII — T6BL4ZC15G.

Pharmacopoeias. In *It.*

Uses and Administration

Sulfametopyrazine is a long-acting sulfonamide that has been used orally in the treatment of respiratory- and urinary-tract infections due to sensitive organisms.

Sulfametopyrazine is given with pyrimethamine (p. 662.3) in the treatment of malaria.

It has also been given in the ratio 4 parts of sulfametopyrazine to 5 parts of trimethoprim as a combination with uses similar to those of co-trimoxazole (p. 277.3).

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 365.3.

If adverse effects occur, sulfametopyrazine has the disadvantage that several days are required for its elimination from the body.

Interactions

As for Sulfamethoxazole, p. 366.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 366.3.

Pharmacokinetics

Sulfametopyrazine is readily absorbed from the gastrointestinal tract; 60 to 80% is bound to plasma proteins. Only about 5% of a dose is metabolised to the acetyl derivative. It is slowly excreted in the urine. The biological half-life has been reported to be about 60 to 65 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Kelfizine W; ***Thai.***: Eadazine.

Multi-ingredient Preparations. ***Belg.***: Co-Arinate; Dafrafin†; ***India***: Metakelfin; ***Ital.***: Metakelfin.

Sulfametrole *(BAN, rINN)*

Sulfametrol; Sulfamétrole; Sulfametrolo; Sulfametrolum; Сульфаметрол.

N^1-(4-Methoxy-1,2,5-thiadiazol-3-yl)sulphanilamide.

$C_9H_{10}N_4O_3S_2$=286.3

CAS — 32909-92-5.

UNII — F5AK41IPQG.

Profile

Sulfametrole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It is given in the ratio of 5 parts of sulfametrole to 1 part of trimethoprim as a combination with uses similar to those of co-trimoxazole (p. 277.3). Usual oral doses are 960 mg (800 mg of sulfametrole and 160 mg of trimethoprim) twice daily; for severe infections, the dose may be doubled. It has also been given as the sodium salt by intravenous infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Lidaprim; ***Gr.***: Lidaprim; ***Hong Kong***: Lidaprim; ***Neth.***: Lidatrim†; Rokiprim; ***Rus.***: Lidaprim (Лидаприм)†.

Sulfamonomethoxine *(BAN, USAN, rINN)*

DJ-1550; DS-36; ICI-32525; Ro-4-3476; Sulfamonomethoxin; Sulfamonométhoxine; Sulfamonomethoxinum; Sulfamonometoxina; Сульфамонометоксин.

N^1-(6-Methoxypyrimidin-4-yl)sulphanilamide monohydrate.

$C_{11}H_{12}N_4O_3S,H_2O$=298.3

CAS — 1220-83-3 (anhydrous sulfamonomethoxine).

ATC Vet — QJ01EQ18.

UNII — U700P169W2.

Pharmacopoeias. In *Jpn.*

Profile

Sulfamonomethoxine is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p. 365.2). It is used in veterinary medicine.

Sulfamoxole *(BAN, USAN, rINN)*

Sulfamoksoli; Sulfamoxol; Sulfamoxolo; Sulfamoxolum; Sulphadimethyloxazole; Sulphamoxole; Сульфамоксол.

N^1-(4,5-Dimethyloxazol-2-yl)sulphanilamide.

$C_{11}H_{13}N_3O_3S$=267.3

CAS — 729-99-7.

ATC — J01EC03.

UNII — HGG82XE020.

NOTE. Compounded preparations of sulfamoxole may be represented by the following name:

- Co-trifamole (*BAN*)—sulfamoxole 5 parts and trimethoprim 1 part (see p. 277.3).

Pharmacopoeias. In *Fr.*

Profile

Sulfamoxole is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p. 365.2). It has been used with trimethoprim as co-trifamole (p. 277.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Cortina; Supristol.

Sulfanilamide *(rINN)*

Solfammide; Streptocidum; Sulfaminum; Sulfaniiliamidi; Sulfanilamid; Sulfanilamida; Sulfanilamidas; Sulfanilamidum; Sulphanilamide; Szulfanilamid; Сульфаниламид.

4-Aminobenzenesulphonamide; *p*-Sulphamidoaniline.

$C_6H_8N_2O_2S$=172.2

CAS — 63-74-1.

ATC — D06BA05; J01EB06.

ATC Vet — QD06BA05; QJ01EQ06.

UNII — 21240MF57M.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *BP(Vet)*.

Ph. Eur. 8: (Sulfanilamide). White or yellowish-white crystals or fine powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone; practically insoluble in dichloromethane; dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Sulfanilamide is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). Its antibacterial activity is less than that of sulfamethoxazole. It has been used topically, including vaginally, for the treatment of susceptible infections, often with other drugs. The sodium, sodium mesilate, and camsilate salts have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Streptocide (Стрептоцид); ***Spain***: Azol.

Multi-ingredient Preparations. ***Arg.***: Clinal; ***Belg.***: Polyseptol; Sulfa-Sedemol; ***Rus.***: Inhalipt (Ингалипт); Novoinhalipt (Новоингалипт); Osarcid (Осарцид); ***S.Afr.***: Achromide; Daromide†; Ung Vernleigh; ***Spain***: Buco Regis; Cilinafosal Dihidroestreptomicina†; Cilinafosal Hidrocortisona†; Cilinafosal†; Kanafosal Predni†; Kanafosal†; Nasopomada†; Vitavox†; ***Ukr.***: Nitacid (Нитацид); Streptonitol (Стрептонитол); ***USA***: Alasulf; Deltavac; DIT1-2.

Sulfapyridine *(BAN, rINN)*

Sulfapiridina; Sulfapyridiini; Sulfapyridin; Sulfapyridinum; Sulphapyridine; Сульфапиридин.

N^1-(2-Pyridyl)sulphanilamide.

$C_{11}H_{11}N_3O_2S$=249.3

CAS — 144-83-2.

ATC — J01EB04.

ATC Vet — QJ01EQ04.

UNII — Y5V2N1KE8U.

Pharmacopoeias. In *Fr.* and *US*.

USP 36: (Sulfapyridine). White or faintly yellowish-white, odourless or practically odourless, crystals, granules, or powder. It slowly darkens on exposure to light. Soluble 1 in 3500 of water, 1 in 440 of alcohol, 1 in 65 of acetone; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides. Protect from light.

Profile

Sulfapyridine is a short- or intermediate-acting sulfonamide, with properties similar to those of sulfamethoxazole (p. 365.2). It is slowly and incompletely absorbed from the gastrointestinal tract and excreted in urine; sulfapyridine and its acetyl metabolite are poorly soluble in urine and the risk of crystalluria is relatively high. Adverse effects are common, and gastrointestinal disturbances may preclude continued therapy. Because of its toxicity, sulfapyridine is now seldom used except occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment is unsuitable; oral doses of up to 1 g four times daily have been given initially, reduced to the minimum effective maintenance dose once improvement occurs.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] stated that, although sulfapyridine was usually compatible with breast feeding, caution was required in breast-fed infants with jaundice or G6PD deficiency, or who were ill, stressed, or premature.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Pemphigoid. Benefit has been seen with sulfapyridine in ocular cicatricial pemphigoid.[1]

1. Elder MJ, *et al.* Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. *Br J Ophthalmol* 1996; **80:** 549–52.

Preparations

Pharmacopoeial Preparations

USP 36: Sulfapyridine Tablets.

Sulfaquinoxaline *(BAN, rINN)*

Sulfabenspyrazin; Sulfabentspyratsiini; Sulfabenzpyrazine; Sulfabenzpyrazinium; Sulfabenzpyrazinum; Sulfachinossalina; Sulfaquinoxalin; Sulfaquinoxalina; Sulfaquinoxalinum; Sulphaquinoxalina; Sulphaquinoxaline; Сульфахиноксалин.

N^1-(Quinoxalin-2-yl)sulphanilamide.

$C_{14}H_{12}N_4O_2S$=300.3

CAS — 59-40-5 (sulfaquinoxaline); 967-80-6 (sulfaquinoxaline sodium).

ATC Vet — QJ01EQ16; QP51AG03.

UNII — WNW8115TM9.

Pharmacopoeias. In *Fr.* Also in *BP(Vet)* and in *US* for veterinary use only.

Fr. also includes Sulfaquinoxaline Sodium, $C_{14}H_{11}N_4NaO_2S$ = 322.3.

BP(Vet) 2014: (Sulfaquinoxaline). A yellow powder. Practically insoluble in water and in ether; very slightly soluble in alcohol. It dissolves in aqueous solutions of alkalis. Protect from light.

USP 36: (Sulfaquinoxaline). Protect from light.

Profile

Sulfaquinoxaline is a sulfonamide antibacterial used in veterinary medicine, sometimes with trimethoprim.

Sulfathiazole *(BAN, rINN)*

M&B-760; Norsulfazole; RP-2090; Solfatiazolo; Sulfanilamidothiazolum; Sulfathiazol; Sulfathiazolum; Sulfatiatsoli; Sulfatiazol; Sulfatiazolas; Sulfatiazolo; Sulfonazolum; Sulphathiazole; Szulfatiazol; Сульфатиазол.

N^1-(1,3-Thiazol-2-yl)sulphanilamide.

$C_9H_9N_3O_2S_2$=255.3

CAS — 72-14-0.

ATC — D06BA02; J01EB07.

ATC Vet — QD06BA02; QJ01EQ07.

UNII — Y7FKS2XWQH.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Sulfathiazole). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfathiazole). A white or faintly yellowish-white, practically odourless, fine powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone, in dilute mineral acids, in solutions of alkali hydroxides, and in 6N ammonium hydroxide. Protect from light.

Sulfathiazole Sodium *(BANM, rINNM)*

Natrii Sulfathiazolum; Soluble Sulphathiazole; Sulfathiazol Sodique; Sulfathiazolum Natricum; Sulfatiazol sódico; Sulphathiazole Sodium; Натрий Сульфатиазол.

$C_9H_8N_3NaO_2S_2,5H_2O$=367.4

CAS — 144-74-1 (anhydrous sulfathiazole sodium); 6791-71-5 (sulfathiazole sodium pentahydrate).

ATC — D06BA02; J01EB07.

ATC Vet — QD06BA02.

UNII — PV16N742VM.

Pharmacopoeias. In *BP(Vet)* ($1\frac{1}{2}H_2O$ or $5H_2O$).

BP(Vet) 2014: (Sulfathiazole Sodium). A white or yellowish-white crystalline powder or granules. Freely soluble in water; soluble in alcohol. A solution in water containing the equivalent of 1% of the anhydrous substance has a pH of 9.0 to 10.0. Protect from light.

Profile

Sulfathiazole is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It is now rarely used systemically due to its toxicity.

Sulfathiazole is used with other sulfonamides, usually sulfabenzamide and sulfacetamide, in preparations for the topical treatment of vaginal infections and is also used with other drugs in the treatment of skin infections.

Sulfathiazole sodium has been applied topically with other drugs in the treatment of eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Blefarosan†; Welt-Sulfazol; ***Rus.***: Norsulfazol (Норсульфазол).

Multi-ingredient Preparations. ***Arg.***: Otocuril; ***Braz.***: Vagi-Sulfa; ***Chile***: Indocalm; Tru; ***Gr.***: Kronoderm; Sultrin; ***Ital.***: Streptosil con Neomicina; ***Mex.***: Unguento Cruz; Unguento Sulfatiazol Rojtier; ***Philipp.***: Sultrin†; ***Pol.***: Sulfarinol; ***Rus.***: Inhalipt (Ингалипт); Novoinhalipt (Новоингалипт); ***S.Afr.***: Sultrin†; ***Spain***: Cremsol†; Salitanol Estreptomicina†; ***USA***: Sultrin†.

Pharmacopoeial Preparations

USP 36: Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Sulfathiazole Silver *(BANM, rINNM)*

Argenti Sulfathiazolum; Sulfathiazol Argentique; Sulfatiazol argéntica; Серебра Сульфатиазол.

4-Amino-*N*-2-thiazolylbenzenesulfonamide monosilver(1+).
$C_9H_9N_3O_2S_2Ag$=363.2
CAS — 24342-30-1.
UNII — TG8Z82ZC56.

Profile

Sulfathiazole silver is a sulfonamide antibacterial used topically for burns, ulcers, and other infections of the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Argosulfan; ***Pol.***: Argosulfan; ***Rus.***: Argosulfan (Аргосульфан); ***Ukr.***: Argosulphan (Аргосульфан).

Sulfatroxazole *(BAN, rINN)*

Sulfatroxazol; Sulfatroxazolum; Сульфатроксазол.
N^1-(4,5-Dimethyl-1,2-oxazol-3-yl)sulfanilamide.
$C_{11}H_{13}N_3O_3S$=267.3
CAS — 23256-23-7.
ATC Vet — QJ01EQ14.
UNII — ZXC0PT8FFS.

Profile

Sulfatroxazole is a sulfonamide antibacterial used with trimethoprim in veterinary medicine.

Sulfisomidine *(BAN, rINN)*

Sulfa-isodimérazine; Sulfaisodimidiini; Sulfaisodimidin; Sulfaisodimidine; Sulfaisodimidinum; Sulfasomidine; Sulfisomidiini; Sulfisomidin; Sulfisomidina; Sulfisomidinum; Sulfizomidinas; Sulphasomidine; Szulfizomidin; Сульфизомидин.
N^1-(2,6-Dimethylpyrimidin-4-yl)sulphanilamide.
$C_{12}H_{14}N_4O_2S$=278.3
CAS — 515-64-0.
ATC — J01EB01.
UNII — W03L3ODK6E.

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulfisomidine, and sulphadimethylpyrimidine is sometimes used as a synonym for sulfadimidine (p. 363.2). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Profile

Sulfisomidine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It has been used topically for skin or vaginal infections and has also been given orally. The sodium salt has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Aristamid.

Sultamicillin *(BAN, USAN, rINN)*

CP-49952; Sultamicilin; Sultamicilina; Sultamicilline; Sultamicillinum; Sultamisilin; Sultamisilliini; Sultamycylina; VD-1827; Сультамициллин.
Penicillanoyloxymethyl (6*R*)-6-(D-2-phenylglycylamino)penicillanate *S*′,*S*′-dioxide.
$C_{25}H_{30}N_4O_9S_2$=594.7
CAS — 76497-13-7.
ATC — J01CR04.
ATC Vet — QJ01CR04.
UNII — 65DT0ML581.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sultamicillin). A semisynthetic product derived from a fermentation product. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in methyl alcohol. Store in airtight containers.

Sultamicillin Tosilate *(BANM, rINNM)*

Sultamicilina, tosilato de; Sultamicilin-tosylát; Sultamicillin Tosylate; Sultamicilline, tosilate de; Sultamicillini Tosilas; Sultamicillintosilat; Sultamisilliinitosilaatti; Sultamycyliny tozylan; Tosilato de sultamicilina; Сультамициллина Тозилат.
Sultamicillin toluene-4-sulphonate.
$C_{25}H_{30}N_4O_9S_2.C_7H_8O_3S$=766.9
CAS — 83105-70-8.
UNII — 46940LU8EO (anhydrous sultamicillin tosilate); 2M66QX49ZZ (sultamicillin tosilate dihydrate).

Pharmacopoeias. In *Chin.*

Eur. (see p. vii) and *Jpn* include the dihydrate.

Ph. Eur. 8: (Sultamicillin Tosilate Dihydrate; Sultamicillini Tosilas Dihydricus). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Sultamicillin is a prodrug of ampicillin (p. 218.2) and of the beta-lactamase inhibitor sulbactam (p. 360.1); it consists of the two compounds linked as a double ester. During absorption from the gastrointestinal tract it is hydrolysed, releasing equimolar quantities of ampicillin and sulbactam.

Sultamicillin is given orally as tablets containing sultamicillin tosilate or as oral suspension containing sultamicillin. It is used in the treatment of infections where beta-lactamase-producing organisms might occur, including uncomplicated gonorrhoea, otitis media, and respiratory-tract and urinary-tract infections. The usual dose is 375 to 750 mg of sultamicillin (equivalent to 147 to 294 mg of sulbactam and 220 to 440 mg of ampicillin) twice daily. A single dose of sultamicillin 2.25 g with probenecid 1 g may be used for uncomplicated gonorrhoea.

When parenteral therapy is necessary a combined preparation of ampicillin with sulbactam is given.

References.

1. Friedel HA, *et al.* Sultamicillin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1989; **37:** 491–522.
2. Lode H. Role of sultamicillin and ampicillin/sulbactam in the treatment of upper and lower bacterial respiratory tract infections. *Int J Antimicrob Agents* 2001; **18:** 199–209.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ampigen SB; Unasyna; ***Austria***: Unasyn; ***Braz.***: Unasyn; ***Chile***: Unasyna; ***China***: Bei Zong (倍宗); BeiLong (贝隆); Bo De (博德); Caderyn (凯德林); Kailanxin (凯兰欣); Shilijing (施利静); Shu An (舒氨); Shutaxian (舒他仙); Si Hai Neng (思海能); Su Ke (苏克); Yin Shu (垠舒); ***Ger.***: Unacid PD; ***Gr.***: Begalin; ***Hong Kong***: Unasyn; ***Hung.***: Unasyn; ***India***: Sulbacin; ***Indon.***: Bactesyn; Cinam; Picyn; Unasyn; Viccillin-SX; ***Ital.***: Unasyn; Unasyn; ***Malaysia***: Sulbacin; Unasyn; ***Mex.***: Pentrexyl-S12-H; Unasyna; ***Philipp.***: Sulbacillin; Sulmicil; Unasyn; Unicilin; Zunamyn; ***Pol.***: Unasyn; ***Singapore***: Unasyn; ***Thai.***: Ambacitam; Ampitam†; Amsubac; Sulam; Unasyn; ***Turk.***: Alfasid; Ampisid; Combicid; Devasid; Duobak; Duobaktam; Duocid; Nobecid; Sulcid; Sultamat; Sultasid; Sultibac; ***Venez.***: Fipexiam; Sinif; Sulamp; Sultamilan; Unasyn.

Multi-ingredient Preparations. ***Cz.***: Unasyn.

Taurolidine *(BAN, rINN)*

Taurolidina; Taurolidinum; Тауролидин.
4,4′-Methylenebis(perhydro-1,2,4-thiadiazine 1,1-dioxide).
$C_7H_{16}N_4O_4S_2$=284.3
CAS — 19388-87-5.
ATC — B05CA05.
ATC Vet — QB05CA05.
UNII — 8OBZ1M4V3V.

Profile

Taurolidine is a broad-spectrum antibacterial. It is hydrolysed in aqueous solution to its monomeric form taurultam and other metabolites, with the release of what was originally thought to be formaldehyde but are now considered to be activated methylene glycol or methylol groups, from which it is believed to derive its activity. Its antibacterial activity *in vitro* is modest but is reported to be enhanced in the presence of serum or urine; it is active against pathogens including *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Taurolidine is also reported to inactivate bacterial endotoxin.

Taurolidine is used in peritonitis; a solution containing 0.5% is used for irrigation and a 2% solution is available for instillation. The drug has been given experimentally as an intravenous infusion in the treatment of severe sepsis or endotoxic shock and in pancreatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Taurolin; ***Ger.***: Taurolin; ***Irl.***: Taurolin; ***Neth.***: Taurolin; ***Switz.***: Taurolin; ***Turk.***: Taurolin.

Tazobactam Sodium *(BANM, USAN, rINNM)*

CL-298741 (tazobactam); CL-307579; Natrii Tazobactamum; Tazobactam sódico; Tazobactam Sodique; Tazobactamum natricum; Tazobaktam Sodyum; YTR-830; YTR-830H (tazobactam); Натрий Тазобактам.
Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate 4,4-dioxide.
$C_{10}H_{11}N_4NaO_5S$=322.3
CAS — 89786-04-9 (tazobactam); 89785-84-2 (tazobactam sodium).
ATC — J01CG02.
ATC Vet — QJ01CG02.
UNII — UXA545ABTT.

Profile

Tazobactam is a penicillanic acid sulfone derivative with beta-lactamase inhibitory properties similar to those of sulbactam (p. 360.2) although it is regarded as more potent. It has the potential to enhance the activity of beta-lactam antibacterials against beta-lactamase-producing bacteria.

Tazobactam sodium is given intravenously with piperacillin sodium (p. 340.1) for the treatment of bacterial infections. The pharmacokinetics of tazobactam and piperacillin are similar.

References.

1. Bush K, *et al.* Kinetic interactions of tazobactam with β-lactamases from all major structural classes. *Antimicrob Agents Chemother* 1993; **37:** 851–8.
2. Payne DJ, *et al.* Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important β-lactamases. *Antimicrob Agents Chemother* 1994; **38:** 767–72.
3. Lee NLS, *et al.* β-Lactam antibiotic and β-lactamase inhibitor combinations. *JAMA* 2001; **285:** 386–8.
4. Lee N, *et al.* Clinical role of β-lactam/β-lactamase inhibitor combinations. *Drugs* 2003; **63:** 1511–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Petezam; ***Gr.***: Zobactam; Zoracilin.

Multi-ingredient Preparations. ***Arg.***: Pipetexina; Tazonam; Vredian; ***Austral.***: PiperTaz; Tazocin; Tazopip; ***Austria***: Pipitaz; Tazonam; ***Belg.***: Tazocin; ***Braz.***: Tazocilina; Tazocin; ***Canad.***: Tazocin; ***Chile***: Aurotaz-P; Tazonam; ***China***: An Di Tai (安迪泰); Bang Da (邦达); Caryn (凯伦); Fengtailing (锋泰灵); Haitaxin (海他欣); Kai Si (凯斯); Kang De Li (康得力); Tazocin (特治星); Xian Bi Ta (仙必他); ***Cz.***: Tazabax; Tazip; Tazocin; Tazopet; Tazoratio; Tebranic; ***Denm.***: Tazocin; ***Fin.***: Tazocin; ***Fr.***: Tazocilline; ***Ger.***: Tazobac; ***Gr.***: Bactalin; Gramenox; Oliten; Tavoctame; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong***: Tazocin; ***Hung.***: Tazocin; ***India***: Adzopip; Alnacef-T; Ampip-T; Arixon-TZB; Augtaz; Avcef-TZ; Axocare-T; Baclin; Boxter; Broadcef-T; C-Pime-T; Cadipip; Cadizone-XP; Cefa-T Kit; Cefaday-TZ; Cefcin-TJ; Cefirone T; Cefmol-TZ; Cefritz-TZ; Cefs-T; Cefset-TX; Cefsine-TZ; Cefzox-TZ; Cesafe-TZ; Cetzone-TZ; Cidal; Cinpip-TZ; Combitaz; Combiwin; Crucef; CT Ceff-TZ; CTMor-TZ; CTX-TZ; Cureact; Deczone-T; Deczone-TP; Dibact; Durataz; Elzox; Europep-T; Everpip-TZ; Extacef-Tazo; Finecef-T; Fobidime-TZ; Forpep; Glen-TZB; Glicef-T; Gotaz; Gramotaz; Hicef-T; Hocef-T; Hoslin; Ifytrox-TB; Incef-TZ; Infocer; Inforcer; Infoxon-T; Ip-Taz; Jope; Kafi-TBZ; Kombat; KPT; Lazocin Forte; Lazopip; Lezone-XP; Lifecare-A; Lifecare-C; Lifecare-T; Lintaz; Lisel-TBZ; Lupitaz; Magnova; Matlin; Medipip; Megacillin; Mezobact-P; Microtaz; Mocef-TZ; Monal; Montaz; Nexef-TBZ; Olin; Oritiz; Pactum; Tazact; Tazofast; Tazopen; Zosyn; ***Indon.***: Tazocin; ***Irl.***: Pipercin; Piperin; Tazocin; ***Israel***: Tazocillin; Tazocin; Tazopip; Tazorex; ***Ital.***: Ibitazina; Limerick; Tazobac; Tazocin; Tazopenil; ***Jpn***: Zosyn; ***Malaysia***: Tazocin; ***Mex.***: Tasovak; Tazocin; Tazpen; ***Neth.***: Tazocin; ***Norw.***: Piptazira; Tazocin; ***NZ***: Tazocin; ***Philipp.***: Bactaz; Peprasan-T; Piptaz; Pizobac; Pletzolyn; Tanzo; Tapimycin; Tazobak; Tazocin; Tazolin†; Tazopen; Tazotaz; Tebranic; Vigocid; ***Pol.***: Tazacylin; Tazocin; Tazoratio; ***Port.***: Tazobac; ***Rus.***: Tacillin-J (Тациллин ДЖ); Tazocin (Тазоцин); ***S.Afr.***: Curitaz; Tazobax; Tazocin; ***Singapore***: Tazocin; Tazpen; ***Spain***: Tazocel; ***Swed.***: Tazocin†; ***Switz.***: Tazobac; ***Thai.***: Astaz-P; Pipertaz; Tazocin; Tazrobida; Tebranic; ***Turk.***: Tazocin; Tazoper; ***UK***: Tazocin; ***Ukr.***: Tazar (Тазар); Zopercin (Зоперцин); ***USA***: Zosyn; ***Venez.***: Tazopril; Tazpen.

Pharmacopoeial Preparations

USP 36: Piperacillin and Tazobactam for Injection.

Teicoplanin *(BAN, USAN, rINN)*

A-8327; DL-507-IT; L-12507; MDL-507; Teichomycin A_2; Teicoplanina; Téicoplanine; Teicoplaninum; Teikoplaniini; Teikoplanin; Тейкопланин.
CAS — 61036-62-2 (teichomycin); 61036-64-4 (teichomycin A_2).
ATC — J01XA02.
ATC Vet — QJ01XA02.
UNII — 4U3D3YY81M.

Description. A glycopeptide antibacterial obtained from cultures of *Actinoplanes teichomyceticus* or the same substance obtained by any other means.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Teicoplanin). A fermentation product that is a mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus*. The 6 principal components of the mixture are teicoplanin A_{2-1} to A_{2-5} and teicoplanin A_{3-1}. The anhydrous and sodium chloride-free substance has a minimum potency of 900 units/mg.

A yellowish, amorphous powder. Freely soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 5% solution in water has a pH of 6.5 to 7.5. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Teicoplanin is a lipoglycopeptide antibacterial that may be used as an alternative to vancomycin (p. 386.3) in the treatment or prophylaxis of serious staphylococcal or other Gram-positive infections where other drugs cannot be used. Teicoplanin, given orally, has been suggested as a possible alternative to vancomycin or metronidazole in antibiotic-associated colitis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Teicoplanin is given intravenously, as a bolus dose or by infusion over 30 minutes, or by intramuscular injection. The usual mean dose is 6 mg/kg intravenously or intramuscularly initially, followed by 3 mg/kg intravenously or intramuscularly on each subsequent day of treatment (in practice this equates to a usual dose of 400 mg initially followed by 200 mg daily, except in patients weighing more than 85 kg in whom it is adapted accordingly). In more severe infections, 6 mg/kg may be given every 12 hours for the first 3 doses, followed by 6 mg/kg daily. Higher doses have been given (see Administration, p. 372.1). The duration of therapy should not exceed 4 months.

In the treatment of antibiotic-associated colitis caused by *Clostridium difficile* teicoplanin may be given orally at a dose of 200 mg twice daily for 10 days.

For the prophylaxis of Gram-positive infection in high-risk patients undergoing surgical procedures who are unable to receive penicillin, teicoplanin may be given in a single intravenous dose of 400 mg at induction of anaesthesia; a dose of 800 mg has been recommended by the *BNF* for those undergoing skeletal stabilisation and definitive soft-tissue closure.

Although no relationship between plasma concentrations and toxicity has been established, the *BNF* suggests that the former may sometimes be used as a guide to optimise treatment: trough concentrations should be above 10 micrograms/mL (above 20 micrograms/mL in patients with endocarditis or with deep-seated infections such as those of the bones and joints) but less than 60 micrograms/mL.

For CAPD-associated peritonitis, teicoplanin may be added to the dialysis solution at a concentration of 20 mg/litre; this dose should be given in each bag of solution in the first week, in alternate bags in the second week, and in the overnight dwell bag only during the third week. Patients may be given an initial loading dose of 400 mg intravenously if they are febrile.

Dosage should be adjusted in patients with impaired renal function (see Administration in Renal Impairment, p. 372.2). For doses in children and neonates see Administration in Children, p. 372.2.

The use of teicoplanin has been reviewed.[1-6] Two systematic reviews[5,6] comparing teicoplanin and vancomycin found that teicoplanin was at least as effective as the other drug, and was associated with a lower incidence of adverse effects, particularly nephrotoxicity. It was suggested that teicoplanin might be preferred in patients at higher risk of acute kidney injury.[6]

1. Murphy S, Pinney RJ. Teicoplanin or vancomycin in the treatment of Gram-positive infections? *J Clin Pharm Ther* 1995; **20:** 5–11.
2. de Lalla F, Tramarin A. A risk-benefit assessment of teicoplanin in the treatment of infections. *Drug Safety* 1995; **13:** 317–28.
3. Periti P, *et al*. Antimicrobial prophylaxis in orthopaedic surgery: the role of teicoplanin. *J Antimicrob Chemother* 1998; **41:** 329–40.
4. Schaison G, *et al*. Teicoplanin in the treatment of serious infection. *J Chemother* 2000; **12** (suppl 5): 26–33.
5. Svetitsky S, *et al*. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. *Antimicrob Agents Chemother* 2009; **53:** 4069–79.
6. Cavalcanti AB, *et al*. Teicoplanin versus vancomycin for proven or suspected infection. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 09/12/10).

Administration. It has been suggested that increased loading doses or maintenance doses of teicoplanin may be needed in severe or deep-seated infections. In patients with bone and joint infection standard daily maintenance doses of 400 mg intravenously have been reported to result in trough concentrations above the recommended 20 micrograms/mL in only about 40% of cases, whereas of those given 600 mg intravenously once daily, over 70% achieved the desired trough concentration.[1] Others have found that an intravenous dose of 6 mg/kg (400 mg) twice daily achieved trough concentrations of 20 micrograms/mL only after 4 days of treatment;[2] it was pointed out that some have advocated loading doses of 12 mg/kg or even 15 mg/kg every 12 hours for at least 3 doses in patients with bone and joint infections. A conventional regimen with a loading dose of 6 mg/kg twice daily for 48 hours followed by 6 mg/kg daily was thought appropriate for most infections with sensitive organisms other than infective endocarditis, septic arthritis, or osteomyelitis.

UK licensed product information notes that in some clinical situations, such as in infected, severely burnt patients or those with *Staphylococcus aureus* endocarditis, unit maintenance doses of up to 12 mg/kg have been given intravenously.

1. Matthews PC, *et al*. Teicoplanin levels in bone and joint infections: are standard doses subtherapeutic? *J Infect* 2007; **55:** 408–13.
2. Brink AJ, *et al*. Gauteng Understanding Teicoplanin Serum levels (GUTS) study group. Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. *Int J Antimicrob Agents* 2008; **32:** 455–8.

Administration in children. In the UK, teicoplanin is licensed for use in *children* from the age of 2 months to treat Gram-positive infections, but the *BNFC* considers that the same doses may be given from one month of age. It is given preferably by intravenous injection or infusion over 30 minutes, but the intramuscular route may be used if necessary after the first 3 doses. For moderate infections a loading dose of 10 mg/kg (maximum 400 mg) every 12 hours for three doses is followed by a daily dose of 6 mg/kg (maximum 400 mg). For severe infections or neutropenic patients the daily dose is maintained at 10 mg/kg.

The recommended dosage regimen for *neonates* is a loading dose of 16 mg/kg followed by a maintenance dose of 8 mg/kg once daily. The *BNFC* specifies that it should be given by intravenous infusion in this age group.

Administration in renal impairment. Doses of teicoplanin should be adjusted in patients with renal impairment, though reduction is not required until the fourth day of treatment. Teicoplanin should be given in usual intravenous or intramuscular doses (see Uses and Administration, above) for the first 3 days of therapy, thereafter the dose is adjusted according to creatinine clearance (CC):

- CC 40 to 60 mL/minute: half initial dose given daily or initial dose given every 2 days
- CC less than 40 mL/minute and for haemodialysed patients: one-third initial dose given daily or initial dose given every 3 days

Critically ill patients undergoing continuous venovenous haemofiltration (CVVH) may require higher than standard doses of teicoplanin, as considerable amounts of the drug are removed by CVVH. After a 1.2-g intravenous loading dose, daily maintenance doses of 0.6 to 1.8 g were required to produce adequate trough concentrations (defined by the authors as 15 to 25 micrograms/mL) in a pharmacokinetic study;[1] the authors considered that serum-drug concentration monitoring was essential for patients on CVVH, as teicoplanin elimination can be variable depending on patient condition and individual filtration protocols.

1. Bellmann R, *et al*. Teicoplanin pharmacokinetics in critically ill patients on continuous veno-venous hemofiltration. *Int J Clin Pharmacol Ther* 2010; **48:** 243–9.

Adverse Effects and Precautions

Fever, rash and pruritus, and occasional bronchospasm and anaphylaxis have been reported with teicoplanin, but, in comparison with vancomycin (p. 388.1), it appears to be better tolerated when given by rapid intravenous injection and, although erythema and flushing of the upper body have occurred, the 'red-man syndrome' has been reported less often. In addition, unlike vancomycin, teicoplanin does not appear to cause tissue necrosis and can be given by intramuscular injection. Other hypersensitivity reactions have included rigors, angioedema, and, rarely, severe skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Other reported reactions include gastrointestinal disturbances, dizziness, headache, thrombocytopenia (especially at high doses), leucopenia, neutropenia, eosinophilia, disturbances in liver enzyme values, and pain, erythema, and thrombophlebitis or abscess at the injection site. Rare cases of agranulocytosis have occurred. Renal impairment and ototoxicity have been reported but both appear to be less frequent than with vancomycin.

Renal and auditory function should be monitored during prolonged therapy in patients with pre-existing renal impairment, and in those receiving other ototoxic or nephrotoxic drugs, although opinions conflict as to whether increased risk of nephrotoxicity exists with combined therapy with drugs such as the aminoglycosides. In general, periodic blood counts and liver- and renal-function tests are advised during treatment.

No relationship has yet been established between plasma concentration and toxicity, and plasma-concentration monitoring is not generally considered necessary, although it may be used to optimise therapy (see Uses and Administration, above). Dosage adjustment is required in renal impairment.

Hypersensitivity. Although there have been occasional reports of cross-sensitivity to teicoplanin in patients hypersensitive to vancomycin,[1-5] the majority of reports suggest that cross-sensitivity is very rare and teicoplanin can usually be used in patients intolerant of vancomycin.[6-9]

1. McElrath MJ, *et al*. Allergic cross-reactivity of teicoplanin and vancomycin. *Lancet* 1986; **i:** 47.
2. Grek V, *et al*. Allergic cross-reaction of teicoplanin and vancomycin. *J Antimicrob Chemother* 1991; **28:** 476–7.
3. Marshall C, *et al*. Glycopeptide-induced vasculitis—cross-reactivity between vancomycin and teicoplanin. *J Infect* 1998; **37:** 82–3.
4. Kwon HS, *et al*. A case of hypersensitivity syndrome to both vancomycin and teicoplanin. *J Korean Med Sci* 2006; **21:** 1108–10.
5. Hsiao SH, *et al*. Teicoplanin-induced hypersensitivity syndrome with a preceding vancomycin-induced neutropenia: a case report and literature review. *J Clin Pharm Ther* 2010; **35:** 729–32.
6. Schlemmer B, *et al*. Teicoplanin for patients allergic to vancomycin. *N Engl J Med* 1988; **318:** 1127–8.
7. Smith SR, *et al*. Teicoplanin administration in patients experiencing reactions to vancomycin. *J Antimicrob Chemother* 1989; **23:** 810–12.
8. Wood G, Whitby M. Teicoplanin in patients who are allergic to vancomycin. *Med J Aust* 1989; **150:** 668.
9. Hung YP, *et al*. Tolerability of teicoplanin in 117 hospitalized adults with previous vancomycin-induced fever, rash, or neutropenia: a retrospective chart review. *Clin Ther* 2009; **31:** 1977–86.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies teicoplanin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Red-man syndrome. Although teicoplanin is believed[1,2] to be less likely than vancomycin to induce the red-man syndrome, symptoms consistent with the syndrome have nevertheless been reported after intravenous use.[3]

1. Sahai J, *et al*. Comparison of vancomycin- and teicoplanin-induced histamine release and "red man syndrome". *Antimicrob Agents Chemother* 1990; **34:** 765–9.
2. Rybak MJ, *et al*. Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; **36:** 1204–7.
3. Dubettier S, *et al*. Red man syndrome with teicoplanin. *Rev Infect Dis* 1991; **13:** 770.

Antimicrobial Action

As for Vancomycin Hydrochloride, p. 389.1, although in general teicoplanin is more active against susceptible strains. In particular, it may be more active *in vitro* against enterococci and some anaerobic organisms, including strains of *Clostridium*. However, some coagulase-negative staphylococci are less sensitive to teicoplanin than to vancomycin.

Acquired resistance to teicoplanin has developed in staphylococci during treatment with teicoplanin. Cross-resistance with vancomycin has occurred in staphylococci and enterococci. See also under Antimicrobial Action of Vancomycin, p. 389.1.

Pharmacokinetics

Teicoplanin is poorly absorbed from the gastrointestinal tract. After a 400-mg intravenous dose, peak plasma concentrations 1 hour later are reported to be in the range 20 to 50 micrograms/mL. It is well absorbed on intramuscular injection with a bioavailability of about 90%; after a dose of 3 mg/kg intramuscularly, peak plasma concentrations of 5 to 7 micrograms/mL have been reported after 2 to 4 hours.

The pharmacokinetics of teicoplanin are triphasic, with a biphasic distribution and a prolonged elimination. Penetration into the CSF is poor. It is taken up into white blood cells, and about 90 to 95% of teicoplanin in plasma is protein bound. It is excreted almost entirely by glomerular filtration in the urine, as unchanged drug. The terminal half-life is prolonged, but reported half-lives have ranged from about 30 to 190 hours or longer, depending on the sampling time; an effective clinical half-life of about 60 hours has been suggested for use in calculating dosage regimens. Half-life is increased progressively with increasing degrees of renal impairment. Teicoplanin is not removed by haemodialysis.

Teicoplanin is a mixture of several components, the pharmacokinetics of which have been shown to vary slightly, depending on their lipophilicity.

Reviews.

1. Wilson APR. Clinical pharmacokinetics of teicoplanin. *Clin Pharmacokinet* 2000; **39:** 167–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Targocid; Teicox; Teiklonal; Terbiox; ***Austral.***: Targocid; ***Austria***: Targocid; ***Belg.***: Targocid; ***Braz.***: Bactomax; Kirom; Targocid; Teicon†; Teicoston; Teicozid†; Teiplan; Toplanina; ***Chile***: Targocid; ***China***: Jialixin (加立信); Tapocin (大贝辛); Targocid (他格适); ***Cz.***: Targocid; ***Denm.***: Targocid; ***Fin.***: Targocid; ***Fr.***: Targocid; ***Ger.***: Targocid; ***Gr.***: Talinac; Targocid; Targoplanin; ***Hong Kong***: Targocid; ***Hung.***: Targocid; ***India***: Icop; Targocid; Ticocin; ***Indon.***: Targocid; ***Irl.***: Targocid; ***Israel***: Targocid; ***Ital.***: Targosid; Teicomid; ***Jpn***: Targocid; ***Malaysia***: Targocid; ***Mex.***: Tarbiglem; Targocid; Teripol; ***Neth.***: Targocid; ***Norw.***: Targocid; ***NZ***: Targocid; ***Pol.***: Targocid; ***Port.***: Targosid; ***S.Afr.***: Targocid; ***Singapore***: Targocid; ***Spain***: Targocid; ***Swed.***: Targocid; ***Switz.***: Targocid; ***Thai.***: Targocid; ***Turk.***: Targocid; Tekosit; ***UK***: Targocid; ***Ukr.***: Norteic (Нортейк); Targocid (Таргоцид); Teico (Тейко); ***Venez.***: Targocid.

Multi-ingredient Preparations. ***Ger.***: Targobone†.

Telavancin *(rINN)*

Telavancina; Télavancine; Telavancinum; Телаванцин.

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-3-(2-Amino-2-oxoethyl)-10,19-dichloro-44-[(3-{[2-(decanylamino)ethyl]amino}-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-(1→2)-β-D-glucopyranosyl)oxy]-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)pentanamido]-2,5,24,38,39-pentaoxo-29-{[(phosphonomethyl)amino]methyl}-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-1*H*,22*H*-23,36-(epiminomethano)-8,11:18,21-dietheno-13,16:31,35-bis(metheno)[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid.

$C_{80}H_{106}Cl_2N_{11}O_{27}P$=1755.7

CAS — 372151-71-8.

ATC — J01XA03.

ATC Vet — QJ01XA03.

UNII — XK134822Z0.

Telavancin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de telavancina; TD-6424; Télavancine, Chlorhydrate de; Telavancini Hydrochloridum; Телаванцина Гидрохлорид.

$C_{80}H_{106}Cl_2N_{11}O_{27}P,HCl$=1792.1

CAS — 560130-42-9.

UNII — 0701472ZG0.

NOTE. Telavancin hydrochloride used commercially has been stated to be a mixture of the mono-, di-, and trihydrochlorides.

Uses and Administration

Telavancin is a lipoglycopeptide antibacterial with properties similar to those of vancomycin (p. 386.3). It is used for the treatment of complicated skin and skin structure infections caused by susceptible Gram-positive bacteria and of nosocomial pneumonia (including ventilator associated pneumonia) known or suspected to be caused by MRSA.

Telavancin is given as a mixture of the mono-, di-, and tri hydrochloride salts but doses are expressed in terms of the base. It is given by intermittent intravenous infusion over 60 minutes to reduce the risk of infusion-related reactions such as the red-man syndrome. For infusion, a concentrated solution containing the equivalent of telavancin 15 mg/mL in sterile water, glucose 5%, or sodium chloride 0.9% is prepared and then further diluted in an appropriate infusion solution (such as glucose 5%, sodium chloride 0.9%, or lactated Ringer's solution) to a final concentration of 0.6 to 8 mg/mL.

The usual recommended dose in patients 18 years of age and older is the equivalent of telavancin 10 mg/kg once every 24 hours. Dose adjustment may be required in patients with renal impairment (see p. 373.2).

Reviews.[1-4] A review[3] of dalbavancin, oritavancin, and telavancin noted that the lipophilic side-chain of such lipoglycopeptides prolonged their half-life and helped to anchor the drug to the cell membrane and increase its activity against Gram-positive cocci. In addition to their common activity against cell-wall synthesis, oritavancin and telavancin can alter cell-membrane permeability; oritavancin may also inhibit RNA synthesis and has some activity against vanA resistant enterococci. Phase III studies have suggested that all 3 are effective in complicated skin and skin-structure infections. The half-life of dalbavancin is between 147 and 258 hours, which would allow for once-weekly dosing, while that of oritavancin (393 hours) might allow for a single dose per treatment course. However, the authors noted that only telavancin had gained regulatory approval, and the status of the other lipoglycopeptide antibacterials was unclear.

1. Charneski L, *et al.* Telavancin: a novel lipoglycopeptide antibiotic. *Ann Pharmacother* 2009; **43:** 928–38.
2. Saravolatz LD, *et al.* Telavancin: a novel lipoglycopeptide. *Clin Infect Dis* 2009; **49:** 1908–14.
3. Lyseng-Williamson KA, Blick SKA. Telavancin. *Drugs* 2009; **69:** 2607–20.
4. Zhanel GG, *et al.* New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; **70:** 859–86.

Administration in renal impairment. The dose of telavancin intravenous infusion should be adjusted in renal impairment according to creatinine clearance (CC):

- greater than 50 mL/minute: 10 mg/kg every 24 hours
- 30 to 50 mL/minute: 7.5 mg/kg every 24 hours
- 10 to less than 30 mL/minute: 10 mg/kg every 48 hours

No recommendations have been made for those with end-stage renal disease or undergoing haemodialysis, due to insufficient data.

Adverse Effects and Precautions

The most common adverse effects of telavancin are transient taste disturbance, mild nausea and vomiting, and foamy urine. As with vancomycin (see p. 388.1), infusion-related reactions (so-called 'red-neck' or 'red-man' syndrome) may occur but often can be alleviated by stopping or slowing the rate of the infusion.

Nephrotoxicity may occur more frequently with telavancin than with vancomycin. Adverse renal effects are more likely to occur in patients with comorbidities predisposing them to renal dysfunction such as pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension, and are also more frequent in the elderly. Serum-creatinine concentration and creatinine clearance should be measured before starting telavancin, periodically throughout treatment, and when the treatment course is complete. Decreased clinical efficacy of telavancin has been noted in patients with moderate or severe baseline renal impairment (creatinine clearance ≤ 50 mL/minute).

Telavancin may prolong the QT-interval and should be avoided in patients with pre-existing risk factors such as congenital long QT syndrome, known prolongation of the QT-interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Although telavancin does not interfere with coagulation, it may interfere with certain monitoring tests such as prothrombin time, international normalised ratio, activated partial thromboplastin time, activated clotting time, and coagulation based factor Xa tests. Blood samples for such tests should ideally be collected at trough serum-telavancin concentrations, as shortly as possible before the next dose of telavancin.

Interactions

Risk of renal toxicity with telavancin is increased in patients using other drugs known to affect kidney function (including NSAIDs, ACE inhibitors, and loop diuretics).

Because telavancin may prolong the QT interval, it should be used with caution in patients taking other drugs known to have this effect.

Antimicrobial Action

Telavancin, a lipoglycopeptide, is a semisynthetic derivative of vancomycin with concentration-dependent bactericidal activity against Gram-positive aerobic and anaerobic bacteria; it has no activity against Gram-negative organisms.

Mechanism of action. While telavancin shares the mechanism of action of vancomycin (see p. 389.1) it differs in that it also potently inhibits cross-linking of peptidoglycan in a similar manner to the penicillins. The rapid bactericidal activity of telavancin is thought to be a result of its novel ability to bind and depolarise the bacterial cell membrane, altering cell permeability.

Spectrum of activity. Like vancomycin (see p. 389.1), telavancin has good *in-vitro* activity against most *Staphylococcus* and *Streptococcus* spp., including meticillin-resistant *Staph. aureus*. Enterococci are also susceptible, although vancomycin-resistant strains have reduced susceptibility to telavancin. Telavancin is also active against anaerobic Gram-positive bacteria including *Corynebacterium* and *Clostridium* spp. *In-vitro* studies indicate that telavancin has a post-antibiotic effect ranging from 1 to 6 hours against clinically relevant Gram-positive pathogens.

Pharmacokinetics

Telavancin is not absorbed to any significant extent after oral doses. The pharmacokinetics of telavancin in adults are generally linear for intravenous doses ranging from 7.5 to 15 mg/kg once daily for up to 7 days. Steady-state concentrations occur by the third day. Telavancin is about 90% bound to plasma proteins, mainly albumin. Protein binding is concentration-independent and unaffected by renal or hepatic impairment.

In-vitro studies indicate that telavancin is not metabolised by the cytochrome P450 isoenzyme system. Although hydroxylated metabolites have been detected in the urine and plasma of patients given telavancin, the metabolic pathway that produces them has not been identified.

Telavancin is excreted mainly by the kidneys, with about 76% of a dose recovered from the urine; the elimination half-life is about 8 hours after a dose of 10 mg/kg once daily. Telavancin exposure is significantly increased in renal impairment, and dose adjustment is required for patients with creatinine clearance ≤ 50 mL/minute (see Administration in Renal Impairment, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Vibativ†; ***USA***: Vibativ.

Telithromycin *(BAN, USAN, rINN)*

HMR-3647; RU-66647; Télithromycine; Telithromycinum; Telitromicina; Telitromisin; Телитромицин.

(3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyloctahydro-11-methoxy-3a,7,9,11,13,15-hexamethyl-1-{4-[4-(3-pyridyl)imidazol-1-yl]butyl}-10-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-2*H*-oxacyclotetradecino[4,3-*d*][1,3]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone.

$C_{43}H_{65}N_5O_{10}$=812.0

CAS — 173838-31-8; 191114-48-4.

ATC — J01FA15.

ATC Vet — QJ01FA15.

UNII — KI8H7H19WL.

Uses and Administration

Telithromycin is a ketolide antibacterial used for the treatment of susceptible respiratory-tract infections in adults including mild to moderate community-acquired pneumonia. In some countries it is also licensed for use in the treatment of acute sinusitis and acute bacterial exacerbations of chronic bronchitis when resistance to beta-lactam and/or macrolide antibacterials is known or suspected; and as an alternative to beta-lactam antibacterials for tonsillitis or pharyngitis caused by Group A *beta streptococci* in patients over 12 years of age. It is given orally in a usual dose of 800 mg once daily.

Doses may need to be reduced in patients with renal impairment (see p. 373.3).

References.

1. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; **62:** 1771–1804.
2. Zhanel GG, Hoban DJ. Ketolides in the treatment of respiratory infections. *Expert Opin Pharmacother* 2002; **3:** 277–97.
3. Ackermann G, Rodloff AC. Drugs of the 21st century: telithromycin (HMR 3647)—the first ketolide. *J Antimicrob Chemother* 2003; **51:** 497–511.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; **53:** 918–27.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.
6. Wellington K, Noble S. Telithromycin. *Drugs* 2004; **64:** 1683–94.
7. Kasbekar N, Acharya PS. Telithromycin: the first ketolide for the treatment of respiratory infections. *Am J Health-Syst Pharm* 2005; **62:** 905–16.
8. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40:** 1657–64.
9. Nguyen M, Chung EP. Telithromycin: the first ketolide antimicrobial. *Clin Ther* 2005; **27:** 1144–63.
10. Brown SD. Benefit-risk assessment of telithromycin in the treatment of community-acquired pneumonia. *Drug Safety* 2008; **31:** 561–75.

Administration in renal impairment. Doses of telithromycin should be reduced in severe renal impairment (creatinine clearance of less than 30 mL/minute):

- UK licensed product information states that alternating daily oral doses of 800 mg and 400 mg, starting with 800 mg may be given whether or not hepatic function is also impaired
- US licensed product information recommends a dose of 600 mg once daily if there is no hepatic impairment but a dose of 400 mg once daily if there is co-existing impairment

Doses should be given after dialysis sessions to patients on haemodialysis.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases (see also Respiratory Disorders, under Uses of Erythromycin, p. 292.3). Ketolides also appear to have such effects: a 10-day course of oral telithromycin 800 mg daily, started with standard treatment for acute asthma (p. 1195.2) in adults, was reported to improve asthma symptoms regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[1] The mechanism of this effect is unclear, however, and further studies are needed.

1. Johnston SL, *et al.* The TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006; **354:** 1589–1600.

Adverse Effects

Diarrhoea and other gastrointestinal disturbances such as nausea, vomiting, abdominal pain, and flatulence are among the most common adverse reactions after use of telithromycin. Severe, but usually reversible, hepatic dysfunction, including elevation of liver enzymes and hepatitis, with or without jaundice has been reported; however, there have been cases of fatal hepatotoxicity including fulminant hepatitis, hepatic necrosis, and hepatic failure. Effects on the CNS may include dizziness, headache, vertigo, and, occasionally, insomnia or drowsiness. Taste, and very rarely smell, disturbances may occur. Other less commonly reported adverse effects include paraesthesia, eosinophilia, rashes, and cardiovascular effects such as arrhythmias, hypotension, and bradycardia. Visual disturbances, particularly affecting accommodation, have occurred. Syncope, usually associated with the vagal syndrome, has been noted. Very rarely reported adverse effects include angioedema and anaphylaxis. There have been isolated cases of erythema multiforme, pseudomembranous colitis, and muscle cramps. Life-threatening acute respiratory failure has been reported in patients with myasthenia gravis (see also Precautions, p. 374.2).

Effects on the eyes. Visual disturbances, namely blurred vision, difficulty with focusing, and diplopia have been associated with telithromycin. These have been reported to be more common in females under the age of 40 years and to occur in 1.1% of patients compared with 0.28% in those receiving a comparable antibacterial.[1] Licensed product information reports that symptoms are fully reversible, mostly mild to moderate in severity, and typically occur within a few hours of the first or second dose, lasting for several hours and recurring upon subsequent dosing. They have not been associated with any ocular abnormality.

1. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40:** 1657–64.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in an 18-year-old man who received telithromycin for 5 days. Complete recovery of renal function occurred 2 weeks after starting symptomatic treatment with methylprednisolone.

1. Tintillier M, *et al*. Telithromycin-induced acute interstitial nephritis: a first case report. *Am J Kidney Dis* 2004; **44:** e25–e27.

Effects on the liver. Hepatotoxicity, including raised liver enzymes,[1] is an established adverse effect of telithromycin and may be severe or fatal.[2] A spontaneous-report case-control study[3] of hepatotoxicity in patients who had taken telithromycin estimated an 82% increased risk of hepatotoxicity compared with users of other drugs; the risk was greater in men than in women. However, this study also estimated an 85% increased risk among users of macrolide antibacterials in general. The association between the reporting of hepatotoxicity and the use of telithromycin was further confirmed by using 4 data mining algorithms.[4]

A subsequent expert review[5] of 42 cases of telithromycin-associated hepatotoxicity reported to the FDA noted that 5 had a severe outcome (4 deaths and 1 liver transplant). Typical clinical features were considered to be short latency (a median of 10 days but as short as 2 days in some cases), and abrupt onset of fever, abdominal pain, and jaundice; ascites occurred in some, even if liver injury was only moderately severe. Because of the short latency, monitoring of liver enzyme values was thought to be unhelpful in preventing severe toxicity.

1. Bolesta S, Roslund BP. Elevated hepatic transaminases associated with telithromycin therapy: a case report and literature review. *Am J Health-Syst Pharm* 2008; **65:** 37–41.
2. Clay KD, *et al*. Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann Intern Med* 2006; **144:** 415–20.
3. Dore DD, *et al*. Telithromycin use and spontaneous reports of hepatotoxicity. *Drug Safety* 2007; **30:** 697–703.
4. Chen Y, *et al*. Risk of hepatotoxicity associated with the use of telithromycin: a signal detection using data mining algorithms. *Ann Pharmacother* 2008; **42:** 1791–6.
5. Brinker AD, *et al*. Telithromycin-associated hepatotoxicity: Clinical spectrum and causality assessment of 42 cases. *Hepatology* 2009; **49:** 250–7.

Effects on the skin. A 26-year-old woman with a history of rash to penicillin and sulfonamides developed toxic epidermal necrolysis after 13 doses of oral telithromycin for treatment of sinusitis; she was discharged 4 weeks after admission to hospital but had scars on her face and body and had lost her eyelashes.[1]

1. Health Canada. Telithromycin (Ketek): suspected association with toxic epidermal necrolysis. *Can Adverse React News* 2007; **17** (2): 2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 18/06/08)

Precautions

Telithromycin should not be given to patients with known hypersensitivity to it or to the macrolides; similarly, a history of hepatitis and/or jaundice associated with telithromycin or macrolides is a contra-indication.

Telithromycin is contra-indicated in patients with myasthenia gravis because it may exacerbate symptoms of the disease; exacerbations usually occur within 1 to 3 hours of the first dose. Fatalities have been reported.

Patients with a congenital or family history of QT interval prolongation should not receive telithromycin; it should be used with care in those with coronary heart disease, cardiac arrhythmias, and in those with hypokalaemia or hypomagnesaemia, due to its potential to prolong the QT interval. Certain medications may also increase the risk of cardiac arrhythmias and prolong the QT interval (see Interactions, p. 374.2).

Patients or their carers should be informed about signs and symptoms of hepatitis. Should any of these develop during treatment with telithromycin, they should stop taking the drug and consult their doctor. It should be used with caution in patients with hepatic impairment; however, this is based on limited data in such patients. Reduced doses may be necessary in those with severe renal impairment (see p. 371.3).

Since telithromycin can produce visual disturbances or loss of consciousness caution is advised when driving, operating machinery, or undertaking similar hazardous activities.

Breast feeding. Telithromycin has been shown in *animal* studies to be excreted in breast milk at concentrations about 5 times greater than those in maternal plasma, although corresponding data for humans are not available.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies telithromycin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. Reproductive toxicity, but not teratogenicity, has been seen in *animals*; the potential risk for humans is unknown.

Interactions

Telithromycin is an inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Although there have been few clinical reports, drug interactions with telithromycin may be expected to be similar to those seen with erythromycin (see p. 294.2). In particular, caution is required when telithromycin is given with drugs that may prolong the QT interval. Use of telithromycin with cisapride, ergot alkaloid derivatives, pimozide, astemizole, or terfenadine is usually contra-indicated. Caution is usually necessary with benzodiazepines such as alprazolam, midazolam, and triazolam, and with metoprolol. Telithromycin should not be given with drugs that induce the cytochrome P450 isoenzyme CYP3A4, such as rifampicin, phenytoin, carbamazepine, or St John's wort. Telithromycin increases plasma concentrations of some statins and hence the risk of myopathy; it should not be given with atorvastatin, lovastatin, or simvastatin.

Antimicrobial Action

Telithromycin is a ketolide antibacterial with a bactericidal action and is highly active against certain Gram-positive bacteria, including multidrug-resistant strains of *Streptococcus pneumoniae*. Some strains of *Streptococcus pyogenes* and of *Staphylococcus aureus* are also sensitive.

Telithromycin also shows good activity against the Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*). Activity against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) is comparable with macrolides, and it shows greater activity than erythromycin and roxithromycin against *Legionella* spp. *Mycobacterium* spp. are reported to be moderately susceptible.

Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp. are not susceptible.

References.

1. Hammerschlag MR, *et al*. Activity of telithromycin, a new ketolide antibacterial, against atypical and intracellular respiratory tract pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 25–31.
2. Felmingham D, *et al*. Activity of the ketolide antibacterial telithromycin against typical community-acquired respiratory pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 33–42.
3. Felmingham D, *et al*. Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999-2000). *J Infect* 2004; **48:** 39–55.
4. Drago L, *et al*. Selection of resistance of telithromycin against Haemophilus influenzae, Moraxella catarrhalis and streptococci in comparison with macrolides. *J Antimicrob Chemother* 2004; **54:** 542–5.
5. Farrell DJ, Felmingham D. Activities of telithromycin against 13,874 Streptococcus pneumoniae isolates collected between 1999 and 2003. *Antimicrob Agents Chemother* 2004; **48:** 1882–4.

Pharmacokinetics

Telithromycin is rapidly absorbed after an oral dose, with a bioavailability of 57%. Peak plasma concentrations of about 2 micrograms/mL occur about 1 to 3 hours after an 800-mg dose. Food does not affect the absorption of telithromycin.

Telithromycin is widely distributed in body fluids and tissues, including those of the respiratory tract, and plasma protein binding is 60 to 70%. Concentrations in target tissues are reported to be higher than plasma concentrations, suggesting the drug may remain effective when the plasma concentration has fallen below the MIC.

About two-thirds of a dose is metabolised in the liver to inactive metabolites and the remaining third is eliminated unchanged in the urine and faeces. Metabolism is mediated both by cytochrome P450 isoenzymes (mainly CYP3A4) and non-cytochrome P450 enzymes. The pharmacokinetics of telithromycin are triphasic with a biphasic elimination phase; the elimination half-life is 2 to 3 hours and the terminal half-life about 10 hours.

Distribution into milk has been found in *animal* studies.

References.

1. Muller-Serieys C, *et al*. Tissue kinetics of telithromycin, the first ketolide antibacterial. *J Antimicrob Chemother* 2004; **53:** 149–57.
2. Shi J, *et al*. Clinical pharmacokinetics of telithromycin, the first ketolide antibacterial. *Clin Pharmacokinet* 2005; **44:** 915–34.
3. Ong CT, *et al*. Intrapulmonary concentrations of telithromycin: clinical implications for respiratory tract infections due to Streptococcus pneumoniae. *Chemotherapy* 2005; **51:** 339–46.
4. Zeitlinger M, *et al*. Ketolides—the modern relatives of macrolides: the pharmacokinetic perspective. *Clin Pharmacokinet* 2009; **48:** 23–38.
5. Traunmüller F, *et al*. Multiple-dose pharmacokinetics of telithromycin in peripheral soft tissues. *Int J Antimicrob Agents* 2009; **34:** 72–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ketek†; ***Belg.***: Ketek; ***Braz.***: Ketek; ***Canad.***: Ketek†; ***Cz.***: Ketek; ***Fin.***: Ketek; ***Fr.***: Ketek; ***Ger.***: Ketek; ***Gr.***: Ketek; ***Irl.***: Ketek; ***Ital.***: Ketek; ***Jpn***: Ketek†; ***Mex.***: Ketek; ***Neth.***: Ketek; ***Pol.***: Ketek; ***Port.***: Ketek; ***S. Afr.***: Ketek; ***Spain***: Ketek; ***Swed.***: Ketek; ***Thai.***: Ketek†; ***Turk.***: Ketek; ***UK***: Ketek; ***USA***: Ketek; ***Venez.***: Ketek.

Temocillin *(BAN, USAN, rINN)*

Temocilina; Témocilline; Temocillinum; Темоциллин.
(6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.
$C_{16}H_{18}N_2O_7S_2$=414.4
CAS — 66148-78-5.
ATC — J01CA17.
ATC Vet — QJ01CA17.
UNII — 03QB156W6I.

Temocillin Sodium *(BANM, rINNM)*

BRL-17421; Natrii Temocillinum; Temocilina sódica; Temocillin Disodium; Témocilline Sodique; Натрий Темоциллин.
The disodium salt of (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.
$C_{16}H_{16}N_2Na_2O_7S_2$=458.4
CAS — 61545-06-0.
ATC — J01CA17.
ATC Vet — QJ01CA17.
UNII — 96IIP39ODH.

Profile

Temocillin is a semisynthetic penicillin that is highly resistant to many beta-lactamases and is used for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative aerobic bacteria, including those resistant to third-generation cephalosporins.

It is given as the sodium salt and doses are expressed in terms of the base; 1.11 g of temocillin sodium is equivalent to about 1 g of temocillin. It is given by intramuscular injection, slow intravenous injection over 3 to 4 minutes, or by intravenous infusion over 30 to 40 minutes.

The usual dose is 1 g every 12 hours; this dose may be doubled in severe infections but should be given intravenously.

For doses used in children, and in renal impairment, see p. 375.1.

A brief review[1] suggesting that for Gram-negative infections where co-infection with Gram-positive organisms, anaerobes, or *Pseudomonas* spp. is unlikely, temocillin

may have a useful niche role in sparing the use of more broadly effective drugs such as the carbapenems.

1. Livermore DM, Tulkens PM. Temocillin revived. *J Antimicrob Chemother* 2009; **63:** 243–5.

Administration in children. Temocillin may be used in children for the treatment of infections caused by susceptible organisms, and may be given by intramuscular injection, slow intravenous injection over 3 to 4 minutes, or by intravenous infusion over 30 to 40 minutes.

The recommended dose for children is 25 mg/kg daily in 2 divided doses; in severe infections, 50 mg/kg daily in 2 divided doses may be given intravenously.

Administration in renal impairment. Parenteral doses of temocillin should be modified in patients with moderate to severe renal impairment. In adults, the following parenteral doses are recommended based on creatinine clearance (CC):

- CC 30 to 60 mL/min: 1 g every 12 hours
- CC 10 to 30 mL/min: 1 g every 24 hours
- CC less than 10 mL/min: 1 g every 48 hours or 500 mg every 24 hours
- haemodialysis patients: 1 g every 48 hours; the dose should normally be given at the end of the dialysis run. In patients who are dialysed daily, 500 mg should be given after each dialysis session

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Negaban; ***UK***: Negaban.

Terizidone *(rINN)*

B-2360; Terizidona; Térizidone; Terizidonum; Теризидон.

4,4′-[*p*-Phenylenebis(methyleneamino)]bis(isoxazolidin-3-one).

$C_{14}H_{14}N_4O_4$=302.3

CAS — 25683-71-0.

ATC — J04AK03.

ATC Vet — QJ04AK03.

UNII — 1199LEX5N8.

Profile

Terizidone has been used in the treatment of infections of the urinary tract and of pulmonary and extrapulmonary tuberculosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Terizidex; ***Rus.***: Rezonisate (Резонизат); Rezonisate Plus (Резонизат Плюс); ***S.Afr.***: Terividin.

Tetracycline *(BAN, rINN)*

Tetraciclina; Tetraciklin; Tetraciklinas; Tetracyclin; Tétracycline; Tetracyclinum; Tetracyklin; Tetracyklina; Tetrasiklin; Tetrasykliini; Тетрациклин.

A variably hydrated form of (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide.

$C_{22}H_{24}N_2O_8$=444.4

CAS — 60-54-8 (anhydrous tetracycline); 6416-04-2 (tetracycline trihydrate).

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QG01AA90; QG51AA02; QJ01AA07; QJ51AA07; QS01AA09; QS02AA08; QS03AA02.

UNII — F8VB5M810T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tetracycline). A yellow crystalline powder. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 3.5 to 6.0. Protect from light.

USP 36: (Tetracycline). A yellow, odourless, crystalline powder. It darkens in strong sunlight. Soluble 1 in 2500 of water and 1 in 50 of alcohol; practically insoluble in chloroform and in ether; soluble in methyl alcohol; freely soluble in dilute acids and in alkali hydroxide solutions. It loses not more than 13% of its weight on drying. A 1% suspension in water has a pH of 3.0 to 7.0. The potency of tetracycline is reduced in solutions having a pH below 2 and it is rapidly destroyed in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Tetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tetraciclina; Tetraciclina, hidrocloruro de; Tetraciklinhidroklorid; Tetraciklino hidrochloridas; Tétracycline, Chlorhydrate de; Tetracyclinhydrochlorid; Tetracyclini hydrochloridum; Tetracyklin hydrochlorid; Tetracyklinhydroklorid; Tetracykliny chlorowodorek; Tetrasiklin Hidroklorür; Tetrasykliinihydrokloridi; Тетрациклина Гидрохлорид.

$C_{22}H_{24}N_2O_8$.HCl=480.9

CAS — 64-75-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

UNII — P6R62377KV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes Epitetracycline Hydrochloride.

Ph. Eur. 8: (Tetracycline Hydrochloride). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline. A 1% solution in water has a pH of 1.8 to 2.8. Protect from light.

USP 36: (Tetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline, powder. Tetracycline hydrochloride darkens in moist air when exposed to strong sunlight. Soluble 1 in 10 of water and 1 in 100 of alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates, although it is rapidly destroyed by alkali hydroxide solutions. A 1% solution in water has a pH of 1.8 to 2.8. The potency of tetracycline hydrochloride is reduced in solutions having a pH below 2. Store in airtight containers. Protect from light.

Tetracycline Phosphate Complex *(BAN)*

Tetraciclina, complejo con fosfato.

CAS — 1336-20-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

UNII — 6B7BK5H33B.

Description. A complex of sodium metaphosphate and tetracycline.

Incompatibility. Tetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts. Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Tetracycline undergoes reversible epimerisation in *solution* to the less active 4-epitetracycline;[1,2] the degree of epimerisation is dependent on pH, and is greatest at a pH of about 3, with conversion of some 55% to the epimer at equilibrium.[1] The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.[1] Intravenous solutions of tetracycline hydrochloride with a pH between 3 and 5 have been reported to be stable for 6 hours, but to lose about 8 to 12% of their potency in 24 hours at room temperature.[3] Although epimerisation is the dominant degradation reaction at pH 2.5 to 5, outside this pH range other reactions become important, with the pH-dependent formation of anhydrotetracycline at very low pH, and oxidation to isotetracycline at alkaline pH.[4]

In contrast to the case in solution, *suspensions* of tetracycline hydrochloride with a pH between 4 and 7 are stable for at least 3 months.[2] This is because epimerisation, which continues until an equilibrium is achieved between tetracycline and its epimer, depends only on the portion in solution, and the solubility of tetracycline at this pH range is low.

The stability of *solid* dosage forms and powder at various temperatures and humidities has also been studied; tetracycline hydrochloride was fairly stable when stored at 37 degrees and 66% humidity for 2 months, with about a 10% loss of potency, but the phosphate was rather less stable, with potency losses of 25 to 40% and the formation of potentially toxic degradation products.[5] Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.[5] However, although this study, and an accelerated stability study carried out by WHO[6] indicate that there is a risk of deterioration of solid dose tetracycline, in practice a study of its stability during shipment to the tropics found that deterioration was not a problem.[7]

1. Remmers EG, *et al.* Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; **52:** 752–6.
2. Grobben-Verpoorten A, *et al.* Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; **7:** 104–8.
3. Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; **24:** 434–9.
4. Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chemi (Sci)* 1978; **6:** 201–14.
5. Walton VC, *et al.* Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; **59:** 1160–4.
6. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 18/05/07)
7. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304:** 210–14.

Uses and Administration

The tetracyclines are bacteriostatic antibacterials with a wide spectrum of activity. They have been used in the treatment of many infections but emergence of bacterial resistance and the development of other antibacterials have limited their value. They are the drugs of choice or effective alternatives in treatment of rickettsial and coxiella infections (including Q fever, spotted fevers, and typhus), some chlamydial infections (including psittacosis, trachoma, lymphogranuloma venereum, and non-gonococcal urethritis), *Chlamydophila pneumonia* and mycoplasmal infections (especially pneumonia caused by *Mycoplasma pneumoniae*), as well as some other bacterial infections (such as brucellosis, cat-scratch disease, ehrlichiosis, Lyme disease, melioidosis, plague, relapsing fever, and trench fever). They are used as part of regimens for pelvic inflammatory disease and for gastritis and peptic ulcer disease caused by *Helicobacter pylori*. Tetracyclines are used as an alternative to other drugs in the treatment of actinomycosis, infected animal bites, chronic bronchitis, gas gangrene, gastro-enteritis (due to *Campylobacter* or *Yersinia enterocolitica*), granuloma inguinale, leptospirosis, syphilis, tularaemia, Whipples disease, *Vibrio* and *Aeromonas* spp. infections (including water-associated cellulitis), and infections due to *Mycobacterium marinum*. A tetracycline is often used with fluid and electrolyte replacement in the treatment of cholera. They may be used for mouth infections, especially in destructive forms of periodontal disease. There are now relatively few areas where tetracycline-resistant gonococci are uncommon, which limits the value of tetracyclines in gonorrhoea, but they are often given with antigonorrhoeal therapy to treat concomitant chlamydial infections, and they retain some value in the prophylaxis of neonatal gonococcal conjunctivitis by topical application. Tetracyclines are also recommended for the treatment and prophylaxis of anthrax.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Tetracyclines are also used in the oral treatment of acne and rosacea (see Skin Disorders, p. 376.3).

Tetracyclines have antiprotozoal actions and tetracycline or doxycycline may be given with quinine in the management of falciparum malaria resistant to chloroquine (p. 376.1). Tetracyclines are the usual treatment for balantidiasis (p. 922.3).

Tetracycline has been used in the management of malabsorption syndromes such as tropical sprue.

Tetracycline has been instilled as a sclerosant solution for pleurodesis and in the management of malignant effusions (p. 700.1).

Administration and dosage. In the treatment of systemic infections the tetracyclines are usually given orally. They should be taken with plenty of fluid while sitting or standing, and well before going to bed, to avoid the risk of oesophageal ulceration. In severe acute infections they have been given by slow intravenous infusion or, rarely, by intramuscular injection; parenteral therapy should be substituted by oral dosage as soon as practicable.

Doses of tetracycline base and tetracycline hydrochloride are expressed in terms of the hydrochloride. Tetracycline (anhydrous) 231 mg is equivalent to about 250 mg of tetracycline hydrochloride. The usual adult oral dosage of tetracycline hydrochloride is 250 or 500 mg every 6 hours, preferably 1 hour before or 2 hours after meals. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects. It is also sometimes given orally with other tetracycline derivatives.

Tetracycline hydrochloride has been given by slow intravenous infusion or by intramuscular injection in severe infections. Intravenous products of tetracycline itself are no longer marketed in many countries because of the risk of hepatotoxicity, although other intravenous tetracyclines may be available. As intramuscular injections were painful,

procaine hydrochloride was usually included in the solution.

For details of doses in children and adolescents, see p. 376.1.

Care is required if tetracyclines are given to the elderly. They should be avoided if possible in renal impairment (with the exception of doxycycline and minocycline) and doses reduced if they must be used. For dosage recommendations in patients with hepatic impairment, see p. 376.1.

Other routes. Although topical application carries the risk of sensitisation and may contribute to the development of resistance, tetracycline hydrochloride has been used as a 3% ointment; a 0.2% solution has been used in acne but systemic treatment appears to produce better results. A 1% eye ointment or eye drops have been used in the treatment of ocular infections due to susceptible organisms. For the treatment of pleural effusions, 500 mg of tetracycline hydrochloride has been dissolved in 30 to 50 mL of sodium chloride 0.9% and instilled into the pleural space. For periodontal disease, fibres that release tetracycline have been inserted into the periodontal pocket.

Reviews.

1. Chopra I, *et al.* Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother* 1992; **29:** 245–77.
2. Smilack JD. The tetracyclines. *Mayo Clin Proc* 1999; **74:** 727–9.
3. Voils SA, *et al.* Use of macrolides and tetracyclines for chronic inflammatory diseases. *Ann Pharmacother* 2005; **39:** 86–94.
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5. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; **54:** 258–65.
6. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin* 2007; **25:** 133–5.
7. Orsucci D, *et al.* Neuroprotective effects of tetracyclines: molecular targets, animal models and human disease. *CNS Neurol Disord Drug Targets* 2009; **8:** 222–31.
8. Griffin MO, *et al.* Tetracyclines: a pleitropic family of compounds with promising therapeutic properties; Review of the literature. *Am J Physiol Cell Physiol* 2010; **299:** C539–C548.
9. Monk E, *et al.* Clinical applications of non-antimicrobial tetracyclines in dermatology. *Pharmacol Res* 2011; **63:** 130–45.
10. Richards C, *et al.* Antimicrobial and non-antimicrobial tetracyclines in human cancer trials. *Pharmacol Res* 2011; **63:** 151–6.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, tetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see Uses and Administration, p. 373.3), to a maximum of 2 g daily, may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 25 to 50 mg/kg daily in 4 divided doses.

Administration in hepatic impairment. Some licensed product information has stated that the oral dosage of tetracycline should not exceed 1 g daily in patients with known liver disease.

Asthma. The observed anti-inflammatory effects of tetracyclines have led to interest in their use for treatment of asthma or other allergic disorders. In a preliminary, randomised, placebo-controlled study of 17 adult asthmatics, the addition of minocycline 150 mg orally twice daily for 8 weeks to usual asthma therapy had a significant corticosteroid-sparing effect, leading to a 30% reduction in mean daily prednisone dose. Minocycline treatment also led to significant improvement in asthma symptoms brought on by environmental triggers.

1. Daoud A, *et al.* Minocycline treatment results in reduced oral steroid requirements in adult asthma. *Allergy Asthma Proc* 2008; **29:** 286–94.

Diabetic complications. The *BNF* notes that diabetic diarrhoea in patients with autonomic neuropathy can often be managed with 2 or 3 doses of oral tetracycline 250 mg.

Malaria. Tetracyclines (particularly doxycycline) may be given for the treatment and prophylaxis of falciparum malaria and the non-falciparum malarias (usually caused by *Plasmodium vivax* or, less commonly, by *P. ovale* or *P. malariae*) (p. 644.1). The action of tetracyclines is relatively slow and they should never be used alone to treat malaria. They are active against both blood and tissue forms of the parasite, and high cure rates have been obtained when given with other antimalarials.[1]

For the treatment of falciparum malaria a usual oral regimen is a 3- or 7-day course of quinine given with or followed by 7 days of a tetracycline. The dose of tetracycline itself usually recommended is 250 mg four times daily, although 500 mg twice daily may be more practical. The dose of doxycycline given orally with or after quinine is 100 mg twice daily for at least 7 days. If the patient is too ill for oral medication quinine should be given parenterally until oral therapy can be begun to complete the course; US guidelines also suggest that doxycycline (100 mg every 12 hours) may be given intravenously until the patient can take oral therapy. A 2-week course of primaquine should be added when treating a non-falciparum malaria to kill hypnozoites. Although tetracycline therapy is normally contra-indicated in pregnant women and children, it may have to be given if the risk of withholding the drug is judged to outweigh the risk to developing teeth and bones.

Chemoprophylaxis with doxycycline has been shown to be effective against *Plasmodium falciparum* and *P. vivax* and short-term prophylaxis with oral doxycycline 100 mg daily is an option in areas of high risk where other drugs are likely to be ineffective. Chemoprophylaxis should be started 1 to 2 days before exposure to malaria and should continue throughout exposure and for at least 4 weeks after leaving the malarious area. Although long-term prophylaxis with doxycycline has not been specifically studied, use for up to 2 years is thought to be safe.

1. Tan KR, *et al.* Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC Expert Meeting on Malaria Chemoprophylaxis. *Am J Trop Med Hyg* 2011; **84:** 517–31.

Mouth ulceration. Tetracyclines may be used as mouthwashes in recurrent aphthous stomatitis (p. 1814.2) and reportedly reduce ulcer pain and duration,[1,2] but their potential for adverse effects if swallowed must be borne in mind, and their acidity can damage tooth enamel if poorly formulated. The results from a small crossover study[3] showed that 0.2% minocycline oral rinses (used 4 times daily for up to 10 days or until lesions and symptoms resolved) significantly reduced the severity and duration of pain compared with 0.25% tetracycline rinses for management of recurrent aphthous stomatitis. Benefit has also been reported with the use of a dental paste containing 3% chlortetracycline.[2] Topical application of a tetracycline has been tried for oral ulceration associated with Behçet's syndrome (p. 1601.1).

1. Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendium dentifrice. *Acta Odontol Scand* 1985; **43:** 47–52.
2. Altenburg A, Zouboulis CC. Current concepts in the treatment of recurrent aphthous stomatitis. *Skin Therapy Lett* 2008; **13:** 1–4.
3. Gorsky M, *et al.* Topical minocycline and tetracycline rinses in treatment of recurrent aphthous stomatitis: a randomized cross-over study. *Dermatol Online J* 2007; **13:** 1. Available at: http://dermatology.cdlib.org/132/original/tcn/gorsky.html (accessed 09/02/11)

Musculoskeletal and joint disorders. Tetracyclines, usually minocycline, are among the wide range of drugs tried in rheumatoid arthritis (p. 13.2). Studies[1,2] indicate that minocycline can produce modest beneficial effects in patients with advanced disease, but the clinical significance of these improvements has been questioned.[3] Greater symptomatic improvements have been obtained with minocycline when it is used in patients with early rheumatoid arthritis;[4,5] continued treatment with minocycline may also reduce the need for disease-modifying antirheumatic drugs (DMARDs).[6] A systematic review,[7] which included these and some other studies, reported that the use of tetracyclines (doxycycline, minocycline, or tetracycline) for 3 months or longer was associated with a reduction in disease activity but not in joint damage when compared with placebo or a DMARD (hydroxychloroquine or methotrexate); the authors also noted that patients with early onset disease responded better to tetracyclines. There has been speculation over the role of infection as a cause of rheumatoid arthritis.[3,8] A later study[9] in patients with early seropositive disease found that initial therapy with methotrexate plus doxycycline was superior to methotrexate alone. It was also noted that therapeutic responses to doxycycline 100 mg twice daily and 20 mg twice daily were similar, suggesting that its anti-inflammatory effects were more important; however, further studies are needed.

Although there has been little convincing clinical evidence that any treatment can slow the progression of osteoarthritis (p. 12.3), a placebo-controlled study involving 431 women with unilateral osteoarthritis of the knee found that treatment with doxycycline 100 mg twice daily over 30 months was associated with a reduction in the rate of joint space narrowing.[10] It had no effect on the contralateral knee, and did not reduce pain scores, although these were low at baseline. A systematic review[11] did not support the use of doxycycline for the treatment of osteoarthritis of the knee or hip, and concluded that small benefits in terms of joint space narrowing were of questionable clinical relevance and outweighed by the adverse effects of doxycycline.

The role of antibacterials is also uncertain in reactive arthritis (see Bone and Joint Infections, p. 175.1), although long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[12] However, another small study[13] found that treatment with a 4-month course of doxycycline 100 mg twice daily was not superior to a 10-day course.

1. Kloppenburg M, *et al.* Minocycline in active rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 629–36.
2. Tilley BC, *et al.* Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **122:** 81–9.
3. McKendry RJR. Is rheumatoid arthritis caused by an infection? *Lancet* 1995; **345:** 1319–20.
4. O'Dell JR, *et al.* Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized double-blind, placebo-controlled trial. *Arthritis Rheum* 1997; **40:** 842–8.
5. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001; **44:** 2235–41.
6. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis with minocycline: four-year follow-up of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; **42:** 1691–5.
7. Stone M, *et al.* Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol* 2003; **30:** 2112–22.
8. O'Dell JR. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? *Drugs* 1999; **57:** 279–82.
9. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum* 2006; **54:** 621–7.
10. Brandt KD, *et al.* Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005; **52:** 2015–25.
11. Nüesch E, *et al.* Doxycycline for osteoarthritis of the knee or hip. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 02/06/10).
12. Lauhio A. Reactive arthritis: consider combination treatment. *BMJ* 1994; **308:** 1302–3.
13. Putschky N, *et al.* Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial. *Ann Rheum Dis* 2006; **65:** 1521–4.

Peptic ulcer disease. Tetracycline has been used as part of triple therapy to eradicate *Helicobacter pylori* in patients with peptic ulcer disease (p. 1816.2). The usual dose of tetracycline in these regimens has been 500 mg four times daily for 2 weeks.

Periodontal disease. For the use of doxycycline in subantimicrobial doses as an adjunct in the treatment of periodontal disease, see Administration, Subantimicrobial Doses, p. 288.3.

Skin disorders. *ACNE.* Tetracyclines may be used topically or orally in the treatment of acne (p. 1682.2). In acne, antibacterials appear to act by suppressing the growth of *Propionibacterium acnes*, but also by suppressing inflammation. Topical tetracycline is used for mild inflammatory acne and as an adjunct to systemic treatment in more severe forms. Tetracyclines, given orally, are the drugs of choice for moderate acne and may be considered, in high doses, for severe acne. Licensed doses in the UK are:

- doxycycline 50 mg daily (the *BNF* advocates 100 mg daily)
- lymecycline equivalent to 300 mg of tetracycline daily
- minocycline 100 mg daily
- oxytetracycline 250 to 500 mg daily (the *BNF* advocates 500 mg twice daily)
- tetracycline 1 g daily

Treatment should be changed to another antibacterial if there has been no improvement in the first 3 months. Maximum improvement is said to occur after 4 to 6 months, but treatment may need to continue for 2 or more years.

Minocycline has been reported to have superior antibacterial activity against *P. acnes* and a reduced incidence of resistance compared with tetracycline;[1] it has also been reported to be more effective than erythromycin against oxytetracycline-resistant acne.[2] However, a later randomised study[3] found minocycline to be comparable in efficacy to oxytetracycline, topical erythromycin with benzoyl peroxide, and topical benzoyl peroxide alone in the treatment of mild to moderate acne; in another randomised study[4] lymecycline also showed comparable efficacy and safety. Doxycycline also appears to have similar efficacy to minocycline.[5] However, minocycline can cause skin pigmentation and may be associated rarely with immunologically-mediated reactions,[5,6] and some[5] therefore favour the use of doxycycline as the first-line systemic antibacterial in acne. An enteric-coated formulation may reduce adverse effects and improve compliance. For the use of doxycycline in subantimicrobial doses in patients with acne, see Administration, Subantimicrobial Doses, p. 288.3. Although the usual dose of minocycline is 100 mg daily in one or two divided doses some patients may need up to 200 mg daily.[7]

1. Eady EA, *et al.* Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol* 1990; **122:** 233–44.
2. Knaggs HE, *et al.* The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne—a retrospective study and a review. *J Dermatol Treat* 1993; **4:** 53–6.
3. Ozolins M, *et al.* Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* 2004; **364:** 2188–95.
4. Bossuyt L, *et al.* Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol* 2003; **13:** 130–35.
5. Kircik LH. Doxycycline and minocycline for the management of acne: a review of efficacy and safety with emphasis on clinical implications. *J Drugs Dermatol* 2010; **9:** 1407–11.
6. Ferner RE, Moss C. Minocycline for acne. *BMJ* 1996; **312:** 138.
7. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134:** 693–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are generally given to control the blistering in pemphigus and pemphigoid (p. 1687.1), although there have been reports[1-8] suggesting that a tetracycline (often minocycline) may be of

value in controlling the lesions associated with various types of pemphigus and pemphigoid.

1. Sawai T, *et al*. Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132:** 668–70.
2. Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* 1995; **132:** 784–9.
3. Kolbach DN, *et al*. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133:** 88–90.
4. Loo WJ, *et al*. Minocycline as a therapeutic option in bullous pemphigoid. *Clin Exp Dermatol* 2001; **26:** 376–9.
5. Amato L, *et al*. Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13:** 143–6.
6. Assmann T, *et al*. Therapieresistenter pemphigus vulgaris: Kombinationstherapie mit Methylprednisolon und Doxycyclin. *Hautarzt* 2003; **54:** 979–81.
7. Kakurai M, *et al*. Localized pemphigoid (pretibial type) with IgG antibody to BP180 NC16a domain successfully treated with minocycline and topical corticosteroid. *Clin Exp Dermatol* 2007; **32:** 759–61.
8. Carrozzo M, *et al*. Minocycline in combination with mycophenolate mofetil in oral mucous membrane pemphigoid. *Eur J Dermatol* 2008; **18:** 198–200.

ROSACEA. Tetracyclines are commonly used[1] in the treatment of rosacea (p. 1688.3). Long-term treatment is usually necessary.

Tetracycline and doxycycline have also been shown to improve ocular manifestations of rosacea.[2] However, a review[3] of the literature concluded that the treatment effect and optimal dose and duration of these 2 drugs have yet to be established; oxytetracycline was found to be of moderate benefit.

For the use of doxycycline in subantimicrobial doses in patients with rosacea, see p. 288.3.

1. Alikhan A, *et al*. The role of tetracyclines in rosacea. *Am J Clin Dermatol* 2010; **11:** 79–87.
2. Frucht-Pery J, *et al*. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; **116:** 88–92.
3. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. *Cornea* 2004; **23:** 106–9.

Adverse Effects

The adverse effects of tetracycline are common to all tetracyclines. Gastrointestinal effects including nausea, vomiting, and diarrhoea are common especially with high doses and most are attributed to irritation of the mucosa. Oesophageal ulceration has been reported with doxycycline, minocycline, and tetracycline, particularly after ingestion of capsules or tablets with insufficient water at bedtime. Other effects that have been reported include glossitis, stomatitis, and dysphagia.

Oral candidiasis, vulvovaginitis, and pruritus ani occur, mainly due to overgrowth with *Candida albicans*, and there may be overgrowth of resistant coliform organisms, such as *Pseudomonas* spp. and *Proteus* spp., causing diarrhoea. More seriously, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported. It has been suggested that disturbances in the intestinal flora are more common with tetracycline than with better absorbed derivatives such as doxycycline.

Renal dysfunction has been reported with tetracyclines, particularly exacerbation of dysfunction in those with pre-existing renal impairment. Usual therapeutic doses given to patients with renal impairment increase the severity of uraemia with increased excretion of nitrogen and loss of sodium, accompanied by acidosis and hyperphosphataemia, and may lead to excessive systemic accumulation of the tetracycline and possible liver toxicity. These effects are related to the dose and the severity of renal impairment and are probably due to the anti-anabolic effects of the tetracycline. Acute renal failure and interstitial nephritis have occurred rarely. Dialysis and renal transplantation have been required for tetracycline-induced renal failure.

Increases in liver enzyme values have been reported with tetracyclines. In some cases severe and sometimes fatal hepatotoxicity, associated with fatty changes in the liver and pancreatitis, has occurred in pregnant women and in patients with renal impairment or those given high doses (particularly intravenous) tetracycline. Intravenous products of tetracycline itself are no longer marketed in many countries because of the risk of hepatotoxicity, although other intravenous tetracyclines may be available. However, hepatotoxicity has also occurred in patients without these predisposing factors but is rarely reported in those given oral tetracycline in standard doses for up to 10 days, or in those given doxycycline.

Tetracyclines are deposited both in deciduous teeth (milk teeth; primary teeth) and in permanent teeth during their formation, causing permanent discoloration and enamel hypoplasia. The darkening effect of tetracyclines on permanent teeth appears to be related to the total dose given. Doxycycline binds less with calcium compared with other tetracyclines and these changes may occur less frequently. Tetracyclines are also deposited in calcifying areas in bone and the nails and interfere with bone growth when given in therapeutic doses to young infants or pregnant women.

Nail discoloration and onycholysis may occur. Abnormal pigmentation of the skin, conjunctiva, oral mucosa, tongue, and internal organs such as the thyroid has occurred rarely. Permanent discoloration of the cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy.

Intracranial hypertension with headache, dizziness, tinnitus, visual disturbances, and papilloedema has been reported. The use of tetracyclines in infants has been associated with a bulging fontanelle. If raised intracranial pressure occurs tetracycline treatment should be stopped. Transient myopia in patients taking tetracyclines may be due to changes in refractive power of the lens. Other adverse effects that have occasionally been reported with tetracyclines include increased muscle weakness in patients with myasthenia gravis and exacerbation of SLE.

Hypersensitivity to the tetracyclines is much less common than to the beta lactams, but hypersensitivity reactions, including rashes, fixed drug eruptions, exfoliative dermatitis, toxic epidermal necrolysis, drug fever, pericarditis, angioedema, urticaria, and asthma have been reported; anaphylaxis has occurred very rarely. Photosensitivity, which has been reported with most tetracyclines, occurs most frequently with demeclocycline and other long-acting derivatives, less with chlortetracycline, and very rarely with oxytetracycline and tetracycline; it appears to be phototoxic rather than photoallergic in nature. Paraesthesia may be an early sign of impending phototoxicity.

Local pain and irritation can occur when tetracyclines are given parenterally and thrombophlebitis may follow intravenous injections. A Jarisch-Herxheimer reaction occurs commonly in patients with relapsing fever treated with tetracyclines.

Although rare, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, neutropenia, and thrombocytopenia have been reported. Tetracyclines may produce hypoprothrombinaemia. They have also been associated with reductions in serum-vitamin B concentrations, including a case of folate deficiency and concomitant megaloblastic anaemia.

The use of tetracyclines that are out-of-date or which have deteriorated has been associated with the development of a reversible Fanconi-type syndrome characterised by polyuria and polydipsia with nausea, glycosuria, aminoaciduria, hyperphosphaturia, hypokalaemia, and hyperuricaemia with acidosis and proteinuria; these effects have been attributed to the presence of degradation products, in particular anhydroepitetracycline.

Effects on intracranial pressure. Raised intracranial pressure has been described in patients given tetracyclines.[1] Tetracycline is most commonly implicated, usually in patients being treated for acne; the syndrome has also been associated with doxycycline[2-4] and minocycline.[5,6] Presenting symptoms, such as headaches, tinnitus, visual loss, diplopia, nausea, and vomiting, usually develop from within 2 weeks to 1 year or more of starting a tetracycline. Most cases resolved when the drug was stopped although some required symptomatic treatment with diuretics (including acetazolamide), corticosteroids, and/or lumbar puncture. Nevertheless, permanently decreased visual acuity and irreversible visual-field defects have been reported.[2,7]

1. Digre KB. Not so benign intracranial hypertension. *BMJ* 2003; **326:** 613–14.
2. Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *BMJ* 2003; **326:** 641–2.
3. Friedman DI, *et al*. Doxycycline and intracranial hypertension. *Neurology* 2004; **62:** 2297–9.
4. Roux X, *et al*. Hypertension intracrânienne bénigne secondaire à la prise de doxycycline. *Rev Med Interne* 2009; **30:** 1058–60.
5. Weese-Mayer DE, *et al*. Minocycline and pseudotumor cerebri: the well-known but well-kept secret. *Pediatrics* 2001; **108:** 519–20.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and not so benign intracranial hypertension. *Aust Adverse Drug React Bull* 2003; **22:** 2–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0302.pdf (accessed 07/02/07)
7. Altinbas A, *et al*. Intracraniële hypertensie met ernstige en blijvende visusdaling en gezichtsvelduitval na gebruik van orale tetracycline. *Ned Tijdschr Geneeskd* 2005; **149:** 1908–12.

Precautions

The tetracyclines are contra-indicated in patients hypersensitive to any of this group of antibacterials, since cross-sensitivity may occur.

Tetracyclines should not be used during pregnancy because of the risk of hepatotoxicity in the mother as well as the effects on the developing fetus. They should also be avoided during breast feeding and in children up to the age of 8, or according to the *BNF*, 12, years. Use in pregnancy, potentially during breast feeding, or in childhood, may result in impaired bone growth and permanent discoloration of the child's teeth.

In general the tetracyclines, with the exception of doxycycline, should be used with caution in those with renal impairment and, if they must be given, doses should be reduced. However, the *BNF* advises avoiding tetracyclines, except doxycycline and minocycline, even in mild impairment. Care should also be taken if tetracyclines are given to patients with hepatic impairment and high doses should be avoided.

Patients who may be exposed to direct sunlight should be warned of the risk of photosensitivity. Care is advisable in patients with myasthenia gravis, who may be at risk of neuromuscular blockade. Tetracyclines should be avoided in those with SLE.

Serum monitoring of tetracyclines may be helpful in patients with risk factors given prolonged therapy: it has been suggested that serum concentrations of tetracycline should not exceed 15 micrograms/mL. To avoid the risk of oesophageal ulceration oral tetracyclines (notably doxycycline, see p. 289.2) should be taken with plenty of fluid while sitting or standing, and well before going to bed.

Tetracycline may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] stated that, after use of tetracycline by breast-feeding mothers, there was negligible absorption by the infant and that tetracycline was therefore usually compatible with breast feeding. However, licensed product information states that adverse effects including permanent tooth discoloration and enamel hypoplasia may occur in breast-fed infants and that breast feeding is contra-indicated during treatment with tetracyclines.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetracycline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

The absorption of the tetracyclines is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc, and therefore use of tetracyclines with antacids, iron preparations, some foods such as milk and dairy products, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. Sodium bicarbonate, colestipol, colestyramine, and kaolin-pectin are also reported to reduce tetracycline absorption, but potential reductions due to cimetidine or sucralfate are probably of little clinical significance. These interactions can be minimised by giving such products at least 1 to 3 hours apart from tetracyclines. Strontium ranelate should not be given with tetracyclines because of possible complex formation.

The nephrotoxic effects of tetracyclines may be exacerbated by diuretics, methoxyflurane, or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be used with caution in patients receiving tetracyclines. An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together; such use should be avoided. Tetracyclines have been reported to produce increased concentrations of lithium, digoxin, halofantrine, and theophylline (although these interactions are not strongly established); the effects of oral anticoagulants have also been increased in a few patients. There have been occasional reports of tetracyclines increasing the toxic effects of ergot alkaloids and methotrexate. Tetracyclines may decrease plasma-atovaquone concentrations. Ocular inflammation has occurred after the use of ocular preparations preserved with thiomersal in some patients receiving tetracyclines. Tetracyclines may decrease the efficacy of oral contraceptives.

Because of possible antagonism of the action of the penicillins by the mainly bacteriostatic tetracyclines it has been recommended that the two types of drug should not be used together, especially when a rapid bactericidal action is necessary.

Antimicrobial Action

The tetracyclines are mainly bacteriostatic, with a broad spectrum of antimicrobial activity including Chlamydiaceae, *Mycoplasma* spp., *Rickettsia* and *Coxiella* spp., *Mycobacteria* spp., spirochaetes, many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

Mechanism of action. Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis, and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective activity against the infecting organism.

Spectrum of activity. The following pathogenic organisms are usually sensitive to tetracyclines:

- Gram-positive cocci including some strains of *Staphylococcus aureus* and coagulase-negative staphylococci, and streptococci including *Str. pneumoniae*, *Str. pyogenes* (group A), and some viridans streptococci
  Enterococci are essentially resistant
- Other Gram-positive bacteria including strains of *Actinomyces israelii*, *Bacillus anthracis*, *Erysipelothrix rhusiopathiae*, *Listeria monocytogenes*, and among the anaerobes some *Clostridium* spp.
  Nocardia spp. are generally much less susceptible although some are sensitive to minocycline
  Propionibacterium acnes is susceptible although the action of the tetracyclines in acne is complex and benefit may be seen even at subinhibitory concentrations
- Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *N. gonorrhoeae* (gonococci), although some strains are resistant, and *Moraxella catarrhalis* (*Branhamella catarrhalis*)
  Acinetobacter spp. may be resistant to tetracycline, but most strains are susceptible to doxycycline and minocycline
- other sensitive Gram-negative aerobes including *Bartonella* spp., *Bordetella pertussis*, *Brucella* spp., *Klebsiella granulomatis*, *Campylobacter* spp., *Eikenella corrodens*, *Francisella tularensis*, *Helicobacter pylori*, *Haemophilus influenzae* and some strains of *H. ducreyi*, *Legionella* spp., *Pasteurella multocida*, *Streptobacillus moniliformis*, and various members of the Vibrionaceae including *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Vibrio cholerae*, *V. vulnificus*, *V. alginolyticus*, and *V. parahaemolyticus*
  although many of the Enterobacteriaceae, including *Salmonella*, *Shigella*, and *Yersinia* spp., are susceptible, resistant strains are common; however, doxycycline remains a treatment choice for *Y. pestis*. *Proteus* and *Providencia* spp. are not susceptible. *Pseudomonas aeruginosa* is not susceptible either, although some other species formerly classified as *Pseudomonas* respond, including *Burkholderia mallei*, *B. pseudomallei*, and *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*)
- Among the Gram-negative anaerobes *Bacteroides fragilis* may sometimes be susceptible, although wild strains are often resistant; *Fusobacterium* and *Prevotella* spp. may also be sensitive
- Other organisms usually sensitive to tetracyclines include Chlamydiaceae (such as *Chlamydia trachomatis* and *Chlamydophila pneumonia*), *Rickettsia* and *Coxiella* spp., many spirochaetes (including *Borrelia burgdorferi*, *Leptospira* spp., and *Treponema pallidum*), atypical mycobacteria (such as *Mycobacterium marinum*, *M. abscessus*, *M. chelonae*, and *M. fortuitum*), and mycoplasmas (including *Mycoplasma pneumoniae*, *M. hominis*, and *Ureaplasma urealyticum*)
- in addition the tetracyclines are active against some protozoa including *Plasmodium falciparum* and *Entamoeba histolytica*
- fungi, yeasts, and viruses are generally resistant

Resistance. Resistance to the tetracyclines is usually plasmid-mediated and transferable. It is often inducible, and appears to be associated with the ability to prevent accumulation of the antibacterial within the bacterial cell, both by decreasing active transport of the drug into the cell and by increasing tetracycline efflux.

Unsurprisingly, given the widespread use of the tetracyclines (including as components of animal feeds, although this is now banned in some countries), resistant strains of the majority of sensitive species have now been reported. Resistance has increased particularly among Enterobacteriaceae such as *Escherichia coli*, *Enterobacter*, *Salmonella*, and *Shigella* spp., especially in hospital isolates, and multiple resistance is common. Staphylococci are commonly resistant, although doxycycline or minocycline are occasionally effective against tetracycline-resistant strains. Resistance is now also common among group A streptococci, and even more so among group B streptococci; there is also resistance among pneumococci, which often show multiple drug resistance. Emergence of high-level tetracycline-resistant strains of *Neisseria gonorrhoeae* is common in some areas. Frequent resistance is also seen in clostridia, and in *Bacteroides fragilis* (among more than 60% of isolates in some countries), while increasing resistance amongst *Haemophilus ducreyi* has limited the value of tetracyclines in chancroid. Tetracycline resistance in *H. pylori* and *V. cholerae* has been reported. Rates of tetracycline resistance among *H. pylori* vary from less than 2% to about 56% depending on geographic area, while in other areas surveys of clinical isolates have reported no tetracycline-resistant strains. Resistance in *V. cholerae* fluctuates significantly under the selective pressure of antibacterial use.

Pharmacokinetics

Most tetracyclines (except minocycline and doxycycline) are incompletely absorbed from the gastrointestinal tract, about 60 to 80% of a dose of the drug usually being available. Doxycycline and minocycline are more lipophilic and are almost completely (90 to 100%) absorbed. The degree of absorption is reduced by the presence of divalent and trivalent metal ions and also certain drugs, with which tetracyclines form stable insoluble complexes, and to a variable degree by milk or food (see Interactions p. 375.3). However, the more lipophilic derivatives are little affected by food. Formulation with phosphate may enhance the absorption of tetracycline. Peak plasma concentrations of tetracycline occur about 1.5 to 4 hours after oral use. Higher concentrations occur after intravenous use; concentrations may be higher in women than in men.

Tetracyclines may be differentiated on the basis of their half-lives. Doxycycline and minocycline are long-acting; demeclocycline is intermediate-acting, while tetracycline and oxytetracycline are short-acting. The half-life of tetracyclines (except chlortetracycline) are generally determined by the rate of excretion by the kidneys. In the circulation, tetracyclines are bound to plasma proteins to varying degrees; protein binding tends to be higher for the intermediate- and long-acting drugs. Reported values range from about 20 to 40% for oxytetracycline, 20 to 65% for tetracycline, about 45% for chlortetracycline, 35 to 90% for demeclocycline, 75% for minocycline, and about 80 to 95% for methacycline and for doxycycline. Of the 'short-acting' analogues, chlortetracycline has a reported half-life of about 6 hours, oxytetracycline 9 hours, and tetracycline 8 hours, although reported values for the latter two range from about 6 to 12 hours. The 'intermediate-acting' tetracyclines, demeclocycline and methacycline, have reported half-lives of about 12 and 14 hours respectively, although various sources cite values of 7 to 17 hours, and the 'long-acting' minocycline and doxycycline have half-lives of about 16 and 18 hours, with reported values anywhere between 11 to 26 and 12 to 24 hours respectively.

The tetracyclines are widely distributed throughout the body tissues and fluids. Concentrations in CSF are relatively low, but may be raised if the meninges are inflamed, and small amounts appear in saliva and in the fluids of the eye; higher concentrations occur with more lipid-soluble derivatives such as minocycline and doxycycline. Tetracyclines appear in breast milk, but bioavailability to the infant is low because they form an insoluble complex with calcium. They diffuse across the placenta and reach concentrations in the amniotic fluid and umbilical cord plasma of 20% and 60% of the concentration in the maternal blood, respectively. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth.

The tetracyclines are excreted in the urine and in the faeces. Renal clearance is by glomerular filtration. Up to 60% of an intravenous dose of tetracycline, and up to 55% of an oral dose, is eliminated unchanged in the urine; tetracycline concentrations in the urine of up to 300 micrograms/mL may be reached 2 hours after a usual dose is taken and be maintained for up to 12 hours. Usually about 40 to 70% of a dose is excreted in the urine, but for chlortetracycline, doxycycline, and minocycline, rather less is eliminated by this route since chlortetracycline and minocycline undergo metabolism, and doxycycline is excreted mainly in the faeces. Urinary excretion is increased if urine is alkalinised.

The tetracyclines are excreted in the bile, where concentrations 5 to 25 times those in plasma can occur. Since there is some enterohepatic reabsorption complete elimination is slow. Considerable quantities occur in the faeces after oral doses.

Tetracyclines are slowly removed by haemodialysis, except for doxycycline which is not removed; they are not removed by peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ciclotetryl; ***Austral.***: Achromycin; Latycin†; Tetrex†; ***Braz.***: Ambra-Sinto T; Aureciclina; Cinatrex; Infex†; Parenzyme Tetraciclina; Prociclina†; Tetraben; Tetracaps†; Tetracilil; Tetracina; Tetraclin; Tetragel†; Tetraxil; Tetrex; ***Canad.***: Apo-Tetra; Jaa Tetra; Nu-Tetra; ***Fin.***: Apocyclin; Oricyclin; ***Ger.***: Imex; Tefilin; ***Gr.***: Cliten; Hostacyclin; Imex; Muvito; Tetrac; Tracyclin; ***Hong Kong***: Akotid†; Medocycline; Tetraclin†; ***India***: Achromycin; Hostacycline; Idilin; Ingacycline; Lupiterra; Resteclin; Subamycin; Tetrabact; ***Indon.***: Cetacycline-P†; Conmycin; Corsatet; Dumocycline; Ikacycline; Indocycline; Licoklin; Sanlin; Spectrocycline†; Super Tetra; Tetra†; Tetrarco; Tetrin; ***Irl.***: Topicycline†; ***Israel***: Recycline; Tevacycline†; ***Ital.***: Ambramicina; ***Malaysia***: Beatacycline; Dhatracin; ***Mex.***: Acromicina; Ambotetra; Berciclina; Biotricina; Dibaterr†; Educiclina; Miciclin; Neoprobal; Ofticlin†; Oxi-T†; Profalin CPS; Quimocyclar; Senociclin; Solclin; Te-Br†; Teclizima; Terrakal†; Tetra-Zil; Tetra; Tetrapar; Tetrapres; Tetrex; Tetrim; ***Philipp.***: Metrocycline; Moncycline; Traxetrine; ***Rus.***: Polcortolon TC (Полькортолон ТС); ***S.Afr.***: Tetrex†; ***Singapore***: Apo-Tetra; Beatacycline; Biotine; Dhatracin; Tetracap; Xepacycline; ***Spain***: Quimpe Antibiotico; ***Thai.***: Achromycin; Bioman; Bomcin; Boramycin†; Forbiotin; Forcycline; Ganospec; Heromycin; Hydromycin; Lenocin; Pantocycline; Piccomycin; T-Buffer; TC-Mycin; TC-Ointment; Tetra Central; Tetra Frx; Tetra HCl; Tetrafilm; Tetralim; Tetraman; Tetrana; Tetrano†; Tetraphos; Tetrasin; TM Mycin; Utomycin; ***Turk.***: Acnedur; Imex; Tetra; Tetralet; Tetramin; Vitasilin†; ***UK***: Topicycline†; ***USA***: Bristacycline; Sumycin†; Tetrex; ***Venez.***: Alfaciclina.

Multi-ingredient Preparations. ***Arg.***: Papasine; Solustres; ***Austria***: Fluorex Plus; Mysteclin; ***Braz.***: Anfoterin; Gino-Teracin; Monocetin†; Novasutin; Talsutin; Tericin AT; Tricangine; Tricocilin B; Vagiklin†; ***Fin.***: Helipak T; ***Ger.***: Mysteclin; ***Hong Kong***: Talsutin†; ***Hung.***: Polcortolon TC†; ***India***: Antibic-DF; Atrocin; Corteyclin; Entakon-M; Meklin; ***Indon.***: Enpicortyn; Talsutin†; ***Irl.***: Pylera; ***Ital.***: Alfaflor; Betafloroto; Colbiocin; Eubetal Antibiotico; Flumeciclina†; Mictasone†; Pensulvit; ***Mex.***: Berciclina Enzimatica; Ditral; Pharbrix; Quimotrip†; Solfranicol; Treclorán†; Urovec†; ***Philipp.***: Vagimycin†; ***Pol.***: Polcortolon TC; ***Rus.***: Colbiocin (Колбиоцин); Oletetrin (Олететрин); ***S.Afr.***: Riostatin†; Tetrex-F†; Tritet†; Vagmycin†; ***Spain***: Nasopomada†; ***USA***: First Mary's Mouthwash; Helidac; Pylera.

Pharmacopoeial Preparations

BP 2014: Tetracycline Capsules; Tetracycline Tablets;

USP 36: Tetracycline Hydrochloride and Nystatin Capsules; Tetracycline Hydrochloride Capsules; Tetracycline Hydrochloride for Injection; Tetracycline Hydrochloride for Topical Solution; Tetracycline Hydrochloride Ointment; Tetracycline Hydrochloride Ophthalmic Ointment; Tetracycline Hydrochloride Ophthalmic Suspension; Tetracycline Hydrochloride Oral Suspension; Tetracycline Hydrochloride Tablets; Tetracycline Oral Suspension.

Tetroxoprim *(BAN, USAN, rINN)*

Tetroxoprima; Tétroxoprime; Tetroxoprimum; Тетроксоприм.

5-[3,5-Dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine-2,4-diyldiamine.

$C_{16}H_{22}N_4O_4$=334.4

CAS — 53808-87-0.

UNII — 5R6712AY0K.

NOTE. Compounded preparations of tetroxoprim may be represented by the following name:

- Co-tetroxazine (*BAN*)—tetroxoprim 2 parts and sulfadiazine 5 parts (see p. 277.3).

Profile

Tetroxoprim is a diaminopyrimidine antibacterial that acts as a dihydrofolate reductase inhibitor similar to, but less active than, trimethoprim (p. 383.2). It has been used, with sulfadiazine, as co-tetroxazine (p. 277.3).

Tetroxoprim embonate has been used similarly.

Thenoic Acid

Tenoic Acid; Tenoico, ácido; 2-Thiophenic Acid; Тиофенкарбоновая Кислота.

Thiophene-2-carboxylic acid.

$C_5H_4O_2S$=128.1

CAS — 527-72-0.

Profile

Thenoic acid has been given orally, rectally, or intranasally as the sodium salt, and orally as the lithium salt, in the treatment of respiratory-tract infections. The monoethanolamine salt has been used sublingually as a mucolytic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Dolirhume; Gelutrophyl; Rhinotrophyl.

Multi-ingredient Preparations. ***Fr.***: Glossithiase; Trophires Compose; Trophires†; Trophires.

Thiamphenicol *(BAN, USAN, rINN)*

CB-8053; Dextrosulphenidol; Thiamfenicol; Thiamfenikol; Thiamphénicol; Thiamphenicolum; Thiophenicol; Tiamfenicolo; Tiamfenikol; Tiamfenikoli; Tiamfenikolis; Tianfenicol; Win-5063-2; Win-5063 (racephenicol); Тиамфеникол.

(αR,βR)-2,2-Dichloro-*N*-(β-hydroxy-α-hydroxymethyl-4-methylsulphonylphenethyl)acetamide.
$C_{12}H_{15}Cl_2NO_5S$=356.2
CAS — 15318-45-3 (thiamphenicol); 847-25-6 (racephenicol).
ATC — J01BA02.
ATC Vet — QJ01BA02; QJ51BA02.
UNII — FLQ7571NPM.

NOTE. Racephenicol, the racemic form of thiamphenicol, is *USAN*.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Thiamphenicol). A fine, white or yellowish-white, crystalline powder or crystals. Slightly soluble in water and in ethyl acetate; sparingly soluble in dehydrated alcohol and in acetone; freely soluble in acetonitrile and in dimethylformamide; very soluble in dimethylacetamide; soluble in methyl alcohol. Protect from light and moisture.

Thiamphenicol Glycinate Hydrochloride

Thiamphenicol Aminoacetate Hydrochloride; Tiamfenicolo Glicinato Cloridrato; Tianfenicol, hidrocloruro del glicinato de.
$C_{14}H_{18}Cl_2N_2O_6S,HCl$=449.7
CAS — 2393-92-2 (thiamphenicol glycinate); 2611-61-2 (thiamphenicol glycinate hydrochloride).
ATC — J01BA02.
ATC Vet — QJ01BA02.
UNII — 88VGC22BWE.

Pharmacopoeias. In *It.*

Uses and Administration

Thiamphenicol has been used similarly to chloramphenicol (p. 257.2) in the treatment of susceptible infections, including sexually transmitted diseases. The usual oral dose is 1.5 g daily in divided doses; up to 3 g daily has been given initially in severe infections. Equivalent doses, expressed in terms of thiamphenicol base, may be given by intramuscular or intravenous injection as the more water soluble glycinate hydrochloride; 1.26 g of thiamphenicol glycinate hydrochloride is equivalent to about 1 g of thiamphenicol. A maximum daily dose of 1 g has been suggested for elderly patients. Doses should also be reduced in patients with renal impairment (see p. 379.1).

For the treatment of gonorrhoea, oral doses of thiamphenicol have ranged from 2.5 g daily for 1 or 2 days through to 2.5 g on the first day followed by 2 g daily on each of 4 subsequent days. The single daily dose may be most appropriate for male patients with uncomplicated gonorrhoea.

Thiamphenicol glycinate hydrochloride may also be given by inhalation, or by endobronchial or intracavitary instillation.

Thiamphenicol has also been used as thiamphenicol glycinate acetylcysteinate and thiamphenicol sodium glycinate isophthalolate.

For details of doses in children, see p. 379.1.

Administration in children. In children, oral doses may range from 30 to 100 mg/kg daily according to age and severity of infection. Similar doses may also be given by intramuscular or intravenous injection.

Administration in renal impairment. Doses of thiamphenicol should be reduced in patients with renal impairment according to creatinine clearance (CC). For the oral preparation, suggested reduced doses are:

- CC 30 to 60 mL/minute: 500 mg twice daily
- CC 10 to 30 mL/minute: 500 mg once daily

Alternatively, for parenteral use the following doses have been suggested:

- CC 50 to 75 mL/minute: 500 mg every 12 hours
- CC 25 to 50 mL/minute: 500 mg every 18 hours
- CC 20 mL/minute: 500 mg every 24 hours
- CC 10 mL/minute: 500 mg every 48 hours

Adverse Effects and Precautions

As for Chloramphenicol, p. 258.1.

Thiamphenicol is probably more liable to cause dose-dependent reversible depression of the bone marrow than chloramphenicol, particularly in the elderly or in those with impaired renal function, but it is not usually associated with aplastic anaemia. Thiamphenicol also appears to be less likely to cause the 'grey syndrome' in neonates.

Doses of thiamphenicol should be reduced in patients with renal impairment. It is probably not necessary to reduce doses in patients with hepatic impairment.

Interactions

As for Chloramphenicol, p. 258.3.

Although thiamphenicol is not metabolised in the liver and might not be expected to be affected by drugs that induce hepatic enzymes, it is reported to inhibit hepatic microsomal enzymes and may affect the metabolism of other drugs.

Antimicrobial Action

Thiamphenicol has a broad spectrum of activity resembling that of chloramphenicol (p. 259.1). Although in general it is less active than chloramphenicol it is reported to be equally effective, and more actively bactericidal, against *Haemophilus* and *Neisseria* spp.

Cross-resistance occurs between thiamphenicol and chloramphenicol. However, some strains resistant to chloramphenicol may be susceptible to thiamphenicol.

Pharmacokinetics

Thiamphenicol is absorbed from the gastrointestinal tract after oral doses and peak serum concentrations of 3 to 6 micrograms/mL occur about 2 hours after a 500-mg dose.

Thiamphenicol diffuses into the CSF, across the placenta, into breast milk, and penetrates well into the lungs. About 10% is bound to plasma proteins. The half-life of thiamphenicol is around 2 to 3 hours; the half-life is increased in patients with renal impairment. It is excreted in the urine, about 70% of a dose being excreted in 24 hours as unchanged drug. Despite undergoing little or no conjugation with glucuronic acid in the liver, prolonged half-life and raised plasma concentrations may occur in patients with hepatitis or cirrhosis. A small amount is excreted in the bile and the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Fluimucil Antibiotic; Urfamycine; ***Braz.***: Glitisol; ***China***: Jiangke (将克); Pushijie (普施捷); Vicemycetin (赛美欣); ***Fr.***: Thiophenicol; ***Hong Kong***: Urfamycin; ***Indon.***: Biothicol; Canicol; Cetathiacol; Comthycol; Conucol; Corsafen; Daiticin; Dexycol; Fosicol; Genicol; Ipibiofen; Kalticol; Lacophen; Lanacol; Nikolam; Nilacol; Nufathiam; Opiphen; Phenobiotic†; Promixin; Renamoca†; Rindofen; Sendicol; Thiambiotic†; Thiamet; Thiamfilex; Thiamika; Thiamycin; Thislacol; Troviakol; Urfamycin; Urfekol†; Venacol; Zumatab; ***Ital.***: Fluimucil Antibiotico; Glitisol; ***Mex.***: Tiofeniclin†; ***Rus.***: Fluimucil Antibiotic (Флуимуцил антибиотик); ***Thai.***: Doqua; Mycochlorin-T; Thiam-P; Thiamcin; Treomycin; Urfamycin; ***Turk.***: Thiophenicol†; Tiofen; Urfamycin†; Urfetem.

Multi-ingredient Preparations. ***Thai.***: Fluimucil Antibiotic†.

Thioacetazone *(BAN, rINN)*

Amithiozone; Amitiozon; TBI/698; Tebezonum; Thiacetazone; Thioacétazone; Thioacetazonum; Tiasetazon; Tioacetazona; Тиоацетазон.
4-Acetamidobenzaldehyde thiosemicarbazone.
$C_{10}H_{12}N_4OS$=236.3
CAS — 104-06-3.
UNII — MMG78X7SSR.

Pharmacopoeias. In *Int.*

Uses and Administration

Thioacetazone has been used with other antimycobacterials in the treatment of tuberculosis (p. 210.2). Thioacetazone-containing regimens are less effective than the short-course regimens recommended by WHO but are used in long-term regimens with isoniazid in some developing countries to reduce drug costs. Thioacetazone has been used as a second-line drug for multidrug-resistant tuberculosis but is no longer considered appropriate for routine use; in particular, it is not generally recommended for use in HIV-positive patients because of the risk of severe adverse reactions (but see Effects on the Skin, p. 379.3).

Thioacetazone has been used in the treatment of leprosy (p. 188.3), but WHO now considers that such use is no longer justified.

In the treatment of tuberculosis, thioacetazone has been given orally in doses of 150 mg daily. Daily use is recommended as the drug is less effective when given intermittently.

Adverse Effects

Gastrointestinal disturbances, hypersensitivity reactions including rashes, conjunctivitis, and vertigo are the adverse effects most frequently reported with thioacetazone although the incidence appears to vary between countries. Toxic epidermal necrolysis, exfoliative dermatitis (which has sometimes been fatal), and the Stevens-Johnson syndrome have been reported; the incidence of severe skin reactions is especially high in patients with HIV infection (see p. 379.3). Thioacetazone may cause bone-marrow depression with leucopenia, agranulocytosis, and thrombocytopenia. Acute haemolytic anaemia may occur and a large percentage of patients will have some minor degree of anaemia. Hepatotoxicity with jaundice may also develop and acute hepatic failure has been reported. Cerebral oedema has been reported. Dose-related ototoxicity may occur rarely.

Incidence of adverse effects. In a 10-year series of 1212 patients with tuberculosis who were treated with a regimen of streptomycin, isoniazid, and thioacetazone, 171 (14%) had adverse reactions associated with thioacetazone. The most common adverse effects were giddiness (10%), occurring mainly when used with streptomycin, and rashes (3%) including exfoliation and the Stevens-Johnson syndrome.[1]

1. Pearson CA. Thiacetazone toxicity in the treatment of tuberculosis patients in Nigeria. *J Trop Med Hyg* 1978; **81:** 238–42.

Effects on the nervous system. Acute peripheral neuropathy which occurred in a 50-year-old man on 2 separate occasions within 15 minutes of a dose of thioacetazone may have been due to an allergic reaction.[1]

1. Gupta PK, *et al.* Acute severe peripheral neuropathy due to thiacetazone. *Indian J Tuberc* 1984; **31:** 126–7.

Effects on the skin. A high incidence of severe and sometimes fatal cutaneous hypersensitivity reactions to thioacetazone has been reported in patients with HIV infection being treated for tuberculosis.[1,2] WHO advised that thioacetazone should be avoided in such patients.[3] Unfortunately, thioacetazone has been one of the mainstays of tuberculosis treatment in the developing world because of its relatively low cost.[4] Some have supported a change to rifampicin-based regimens in, for example, parts of Africa with a high incidence of HIV infection.[5] Others have found a lower frequency of fatalities from adverse cutaneous reactions to thioacetazone than reported previously and have suggested that improved management might allow retention of thioacetazone in tuberculosis programmes.[6] This was rejected by other workers who considered that better and more cost-effective regimens were available than those containing thioacetazone.[7] A pragmatic approach may be to adopt a strategy depending upon the prevailing incidence of HIV infection in the population.[8] Thus, where the incidence of HIV infection is high, ethambutol should be substituted for thioacetazone; where the incidence is moderate, routine HIV testing could be used to identify patients at risk; and where the incidence is low, education of patients on the risks of skin reaction would be adequate.

1. Nunn P, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337:** 627–30.
2. Chintu C, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-I. *Arch Dis Child* 1993; **68:** 665–8.
3. Raviglione MC, *et al.* HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment. *Bull WHO* 1992; **70:** 515–26.
4. Nunn P, *et al.* Thiacetazone—avoid like poison or use with care? *Trans R Soc Trop Med Hyg* 1993; **87:** 578–82.
5. Okwera A, *et al.* Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994; **344:** 1323–8.
6. Ipuge YAL *et al.* Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; **346:** 657–60.
7. Elliott AM, *et al.* Treatment of tuberculosis in developing countries. *Lancet* 1995; **346:** 1098–9.
8. van Gorkom J, Kibuga DK. Cost-effectiveness and total costs of three alternative strategies for the prevention and management of severe skin reactions attributable to thiacetazone in the treatment of human immunodeficiency virus positive patients with tuberculosis in Kenya. *Tubercle Lung Dis* 1996; **77:** 30–6.

Hypertrichosis. Hypertrichosis occurred in 2 children receiving thioacetazone.[1]

1. Nair LV, Sugathan P. Thiacetazone induced hypertrichosis. *Indian J Dermatol Venereol* 1982; **48:** 161–3.

Precautions

The efficacy and toxicity of a regimen of treatment which includes thioacetazone should be determined in a community before it is used widely since there appear to be geographical differences.

Thioacetazone should not be given to patients with hepatic impairment. It has also been suggested that, because thioacetazone has a low therapeutic index and is excreted mainly in the urine, it should not be given to patients with renal impairment. Treatment should be stopped if rash or other signs of hypersensitivity occur. It should probably be avoided in HIV-positive patients because they are at increased risk of severe adverse effects (see Effects on the Skin, above).

Interactions

Thioacetazone may enhance the ototoxicity of streptomycin.

Antimicrobial Action

Thioacetazone is bacteriostatic. It is effective against most strains of *Mycobacterium tuberculosis*, although sensitivity varies in different parts of the world.

Thioacetazone is also bacteriostatic against *M. leprae*. Resistance to thioacetazone develops when used alone. Cross-resistance can develop between thioacetazone and ethionamide or protionamide.

Pharmacokinetics

Thioacetazone is absorbed from the gastrointestinal tract and peak plasma concentrations of 1 to 2 micrograms/mL have been obtained about 4 to 5 hours after a 150-mg dose. About 20% of a dose is excreted unchanged in the urine. A half-life of about 12 hours has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Citazon.

Multi-ingredient Preparations. *India*: Isokin-T Forte.

Thiostrepton

Thiostreptonum; Tiostreptón; Tiostrepton; Tiostreptoni; Тиострептон.

$C_{72}H_{85}N_{19}O_{18}S_5$=1664.9

CAS — 1393-48-2.

UNII — HR4S203Y18.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Thiostrepton). An antibacterial substance produced by the growth of strains of *Streptomyces azureus*. It has a potency of not less than 900 units/mg, calculated on the dried basis. A white to off-white crystalline solid. Practically insoluble in water, in the lower alcohols, in nonpolar organic solvents, and in dilute aqueous acids or alkalis; soluble in glacial acetic acid, in chloroform, in dimethylformamide, in dimethyl sulfoxide, in dioxan, and in pyridine. Store in airtight containers.

Profile

Thiostrepton is an antibacterial produced by strains of *Streptomyces azureus*. It is included in topical antibacterial preparations for veterinary use.

Tiamulin *(BAN, rINN)*

SQ-14055; Tiamuliini; Tiamulina; Tiamuline; Tiamulinum; Тиамулин.

{[2-(Diethylamino)ethyl]thio}acetic acid 8-ester with octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one.

$C_{28}H_{47}NO_4S$=493.7

CAS — 55297-95-5.

ATC Vet — QJ01XQ01; QP51AX15.

UNII — E38WZ4U54R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Tiamulin for Veterinary Use; Tiamulin BP(Vet) 2014). A sticky, translucent, slightly hygroscopic, yellowish mass. Practically insoluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Tiamulin). Protect from light.

Tiamulin Fumarate *(BANM, USAN, rINNM)*

Fumarato de tiamulina; 81723-hfu; SQ-22947; Tiamuliinivetyfumaraatti; Tiamulina, fumarato de; Tiamuline, Fumarate de; Tiamuline, hydrogénofumarate de; Tiamulin-fumarát; Tiamulini Fumaras; Tiamulini Hydrogenofumaras; Tiamulinvätefumarat; Тиамулина Фумарат.

$C_{28}H_{47}NO_4S,C_4H_4O_4$=609.8

CAS — 55529796-6.

UNII — ION1Q02ZCX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Tiamulin Hydrogen Fumarate for Veterinary Use; Tiamulin Hydrogen Fumarate BP(Vet) 2014). A white or light yellow, crystalline powder. Soluble in water and in methyl alcohol; freely soluble in dehydrated alcohol. A 1% solution in water has a pH of 3.1 to 4.1. Protect from light.

USP 36: (Tiamulin Fumarate). A 1.0% solution in water has a pH of 3.1 to 4.1. Store in airtight containers. Protect from light.

Profile

Tiamulin fumarate is an antibacterial used in veterinary medicine.

Ticarcillin Monosodium *(BANM, rINNM)*

Ticarcilina monosódica; Ticarcilline Monosodique; Ticarcillinum Mononatricum; Мононатрий Тикарциллин.

Monosodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido] penicillanate monohydrate.

$C_{15}H_{15}N_2NaO_6S_2,H_2O$=424.4

CAS — 34787-01-4 (ticarcillin); 3973-04-4 (ticarcillin); 74682-62-5 (ticarcillin monosodium).

UNII — SM6JM116PM (anhydrous ticarcillin monosodium); 34GZ64SH49 (ticarcillin monosodium monohydrate).

Pharmacopoeias. In *US*.

USP 36: (Ticarcillin Monosodium). Store in airtight containers.

Ticarcillin Sodium *(BANM, rINNM)*

BRL-2288; Natrii Ticarcillinum; Ticarcilina sódica; Ticarcillin Disodium (USAN); Ticarcillin-Natrium; Ticarcilline sodique; Ticarcillinum Dinatricum; Ticarcillinum natricum; Tikarcilin disodná sůl; Tikarcilin sodná sůl; Tikarcilino natrio druska; Tikarcillinnatrium; Tikarcillin-nátrium; Tikarsilliininatrium; Tykarcylina sodowa; Натрий Тикарциллин.

Disodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido]penicillanate.

$C_{15}H_{14}N_2Na_2O_6S_2$=428.4

CAS — 4697-14-7; 29457-07-6.

ATC — J01CA13.

ATC Vet — QJ01CA13.

UNII — G8TVV6DSYG.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ticarcillin Sodium). A white or slightly yellow, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Ticarcillin Disodium). A white to pale yellow powder or solid. 1 mg of monograph substance has a potency equivalent to not less than 800 micrograms of ticarcillin, calculated on the anhydrous basis. Freely soluble in water. A 1% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. Ticarcillin sodium has been reported to be incompatible with aminoglycosides.

References.

1. Swenson E, *et al*. Compatibility of ticarcillin disodium clavulanate potassium with commonly used intravenous solutions. *Curr Ther Res* 1990; **48**: 385–94.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; **35**: 1360–3.

Uses and Administration

Ticarcillin is a carboxypenicillin used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*. Pseudomonal infections where ticarcillin is used include those in cystic fibrosis (respiratory-tract infections), immunocompromised patients (neutropenia), peritonitis, and septicaemia. Other infections that may be due to *Ps. aeruginosa* include bone and joint infections, meningitis, otitis media (chronic), skin infections (burns, ecthyma gangrenosum, ulceration), and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ticarcillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ticarcillin; 1.1 g of ticarcillin sodium is equivalent to about 1 g of ticarcillin. Doses may need to be reduced in renal impairment (see p. 380.3).

Ticarcillin is usually given in doses of 200 to 300 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours.

In adults the use of oral probenecid 500 mg four times daily may produce higher and more prolonged plasma concentrations of ticarcillin, but caution is advised in patients with renal impairment.

In the treatment of complicated urinary-tract infections, a dose of ticarcillin 150 to 200 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours may be used. For uncomplicated urinary-tract infections, the usual dose is ticarcillin 1 g every 6 hours intramuscularly or by slow intravenous injection.

In patients with cystic fibrosis, ticarcillin has been given by nebuliser in the management of respiratory-tract infections.

Ticarcillin is often used with an aminoglycoside but the injections must be given separately because of possible incompatibility.

Ticarcillin with clavulanic acid. Ticarcillin is often used with clavulanic acid (p. 268.3), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. This combination is given by intravenous infusion in a ratio of 15 or 30 parts of ticarcillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses have been variably described both in terms of the combined content of ticarcillin and clavulanic acid, and in terms of the ticarcillin content alone. In terms of the latter, usual adult doses range from 9 to 18 g daily in 3 to 6 divided doses.

For details of doses in children for both ticarcillin and ticarcillin plus clavulanic acid, see p. 380.3.

Administration in children. Ticarcillin, alone or more commonly with clavulanic acid, has been given to neonates and children for the treatment of infections caused by susceptible Gram-negative organisms. In the UK, the combination of ticarcillin plus clavulanic acid is licensed for use in neonates and children weighing more than 2 kg; in the USA licensed use is restricted to children 3 months of age and older.

In the UK, the *BNFC* recommends the following doses (expressed as the combined amount of ticarcillin and clavulanic acid) by intravenous infusion:

For infections due to *Pseudomonas* and *Proteus spp*.:

- preterm neonates weighing less than 2 kg: 80 mg/kg every 12 hours
- all other neonates: 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections
- children from 1 month of age: 80 mg/kg (maximum 3.2 g) every 6 to 8 hours; may be increased to every 4 hours in those weighing over 40 kg with more severe infections

In the USA, doses are expressed as the ticarcillin component. An intravenous dose of 200 mg/kg daily in divided doses every 6 hours is suggested for mild to moderate infections. However, the American Academy of Pediatrics[1] considers that it should only be used for severe infections; they recommend a dose of 200 to 300 mg/kg daily in 4 to 6 divided doses (to a maximum of 12 to 18 g daily).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Doses of ticarcillin may need to be reduced in patients with renal impairment. After an initial intravenous loading dose of 3 g, the intravenous maintenance dosage should be adjusted according to the patient's creatinine clearance (CC):

- CC 30 to 60 mL/minute: 2 g every 4 hours
- CC 10 to 30 mL/minute: 2 g every 8 hours
- CC less than 10 mL/minute: 2 g every 12 hours (or 1 g intramuscularly every 6 hours)
- CC less than 10 mL/minute in presence of *hepatic impairment*: 2 g intravenously every 24 hours or 1 g intramuscularly every 12 hours
- peritoneal dialysis patients: 3 g every 12 hours
- haemodialysis patients: 2 g every 12 hours plus an additional dose of 3 g after each dialysis session

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 232.1.

Cholestatic jaundice and hepatitis have been reported when ticarcillin was used with clavulanic acid; the clavulanic acid component has been implicated.

Ticarcillin should be given with caution to patients with renal impairment.

Breast feeding. Although ticarcillin is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. von Kobyletzki D, *et al*. Ticarcillin serum and tissue concentrations in gynecology and obstetrics. *Infection* 1983; **11**: 144–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Effects on the bladder. The Australian Adverse Drug Reactions Advisory Committee had received 15 reports of haemorrhagic cystitis associated with ticarcillin or ticarcillin-clavulanic acid between 1980 and June 2002, mainly in

paediatric cystic fibrosis patients.[1] Almost all patients recovered quickly after the withdrawal of ticarcillin.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Haemorrhagic cystitis with ticarcillin in cystic fibrosis patients. *Aust Adverse Drug React Bull* 2002; **21:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 29/07/08)

Effects on the liver. Cholestatic jaundice and hepatitis have been associated with combined preparations of a penicillin and clavulanic acid (see Amoxicillin, p. 217.2) and as of February 1993, 2 cases had been reported to the UK CSM with ticarcillin and clavulanic acid.[1] It appeared that the clavulanic acid was probably responsible.

1. CSM/MCA. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)

Sodium content. Each g of ticarcillin sodium contains about 4.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Immunosuppressants. For the effect of ticarcillin on *ciclosporin* disposition, see p. 1956.2.

Antimicrobial Action

Ticarcillin is bactericidal and has a mode of action and range of activity similar to that of carbenicillin (p. 232.1), but is reported to be 2 to 4 times more active against *Pseudomonas aeruginosa*.

Combinations of ticarcillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae.

The activity of ticarcillin against organisms usually resistant because of the production of certain beta-lactamases is enhanced by clavulanic acid, a beta-lactamase inhibitor. Such organisms have included staphylococci, many Enterobacteriaceae, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of ticarcillin against *Ps. aeruginosa* is not enhanced by clavulanic acid. Resistance to ticarcillin with clavulanic acid has been reported.

There is cross-resistance between carbenicillin and ticarcillin.

References.

1. Pulverer G, *et al.* In-vitro activity of ticarcillin with and without clavulanic acid against clinical isolates of Gram-positive and Gram-negative bacteria. *J Antimicrob Chemother* 1986; **17** (suppl C): 1–5.
2. Masterton RG, *et al.* Timentin resistance. *Lancet* 1987; **ii:** 975–6.
3. Fass RJ, Prior RB. Comparative in vitro activities of piperacillin-tazobactam and ticarcillin-clavulanate. *Antimicrob Agents Chemother* 1989; **33:** 1268–74.
4. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; **26:** 598–9.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; **41:** 435–9.

Pharmacokinetics

Ticarcillin is not absorbed from the gastrointestinal tract. After intramuscular injection of 1 g peak plasma concentrations in the range of 22 to 35 micrograms/mL occur after 0.5 to 1 hour. About 50% of ticarcillin in the circulation is bound to plasma proteins. A plasma half-life of 70 minutes has been reported. A shorter half-life in patients with cystic fibrosis (about 50 minutes in one study) has been attributed to increased renal and non-renal elimination. The half-life is prolonged in neonates and also in patients with renal impairment, especially if hepatic function is also impaired. A half-life of about 15 hours has been reported in severe renal impairment.

Distribution of ticarcillin in the body is similar to that of carbenicillin. Relatively high concentrations have been reported in bile, but ticarcillin is excreted principally by glomerular filtration and tubular secretion. Concentrations of 2 to 4 mg/mL occur in the urine after the intramuscular injection of 1 or 2 g. Ticarcillin is metabolised to a limited extent. Up to 90% of a dose is excreted unchanged in the urine, mostly within 6 hours after a dose. Plasma concentrations are enhanced by probenecid.

Ticarcillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Ticarcillin crosses the placenta and small amounts are distributed into breast milk.

Ticarcillin with clavulanic acid. The pharmacokinetics of ticarcillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

References.

1. Staniforth DH, *et al.* Pharmacokinetics of parenteral ticarcillin formulated with clavulanic acid: Timentin. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 123–9.
2. Brogard JM, *et al.* Biliary elimination of ticarcillin plus clavulanic acid (Claventin): experimental and clinical study. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 135–44.
3. de Groot R, *et al.* Pharmacokinetics of ticarcillin in patients with cystic fibrosis: a controlled prospective study. *Clin Pharmacol Ther* 1990; **47:** 73–8.
4. Wang J-P, *et al.* Disposition of drugs in cystic fibrosis IV: mechanisms for enhanced renal clearance of ticarcillin. *Clin Pharmacol Ther* 1993; **54:** 293–302.
5. Burstein AH, *et al.* Ticarcillin-clavulanic acid pharmacokinetics in preterm neonates with presumed sepsis. *Antimicrob Agents Chemother* 1994; **38:** 2024–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ticarpen; ***USA***: Ticar†.

Multi-ingredient Preparations. ***Austral.***: Timentin; ***Belg.***: Timentin; ***Braz.***: Timentin; ***Canad.***: Timentin; ***China***: A Le Xian (阿乐仙); Lieqi (列其); Timentin (特美汀); ***Cz.***: Timentin†; ***Fr.***: Claventin; ***Gr.***: Timentin; ***Hong Kong***: Timentin; ***India***: Timentin†; ***Israel***: Timentin; ***Ital.***: Timentin; ***Mex.***: Timentin; ***NZ***: Timentin; ***Philipp.***: Ticarcin; Timentin; ***Pol.***: Timentin; ***Rus.***: Timentin (Тиментин); ***Turk.***: Timentin; ***UK***: Timentin; ***Ukr.***: Timentin (Тиментин); ***USA***: Timentin.

Pharmacopoeial Preparations

BP 2014: Ticarcillin and Clavulanic Acid Infusion;
USP 36: Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection; Ticarcillin for Injection.

Tigecycline *(BAN, USAN, rINN)*

GAR-936; TBG-MINO; Tigeciclina; Tigécycline; Tigecyclinum; WAY-GAR-936; Тигециклин.

(4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

$C_{29}H_{39}N_5O_8$=585.7

CAS — 220620-09-7.

ATC — J01AA12.

ATC Vet — QJ01AA12.

UNII — 70JE2N95KR.

Stability and compatibility. In the UK, it is recommended that solutions of tigecycline be used immediately after reconstitution, however US licensed product information states that it may be stored at room temperature for up to 24 hours after reconstitution (up to 6 hours in the vial and the remaining time in the infusion bag), or up to 45 hours at 2 to 8 degrees after reconstitution and transfer to an infusion bag.

Tigecycline is compatible when given via a Y-site with amikacin, dobutamine, dopamine hydrochloride, gentamicin, haloperidol, lidocaine hydrochloride, morphine, noradrenaline, piperacillin with tazobactam (formulated with edetic acid), potassium chloride, propofol, ranitidine hydrochloride, theophylline, and tobramycin. It is incompatible with amphotericin B, diazepam, esomeprazole, omeprazole, or any intravenous solution that may result in a pH above 7.

Uses and Administration

Tigecycline is a glycylcycline antibacterial used in adults for the intravenous treatment of complicated skin and skin structure infections or complicated intra-abdominal infections caused by susceptible organisms. In the USA, tigecycline is also licensed for use in community-acquired pneumonia, including in cases with concurrent bacteraemia. Tigecycline is given by intravenous infusion over 30 to 60 minutes in an initial loading dose of 100 mg followed by 50 mg every 12 hours. For details of reduced dosage to be given in severe hepatic impairment, see p. 381.2.

Reviews.

1. Zhanel GG, *et al.* The glycylcyclines: a comparative review with the tetracyclines. *Drugs* 2004; **64:** 63–88.
2. Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. *Drugs* 2005; **65:** 1317–36.
3. Frampton JE, Curran MP. Tigecycline. *Drugs* 2005; **65:** 2623–35.
4. Kasbekar N. Tigecycline: a new glycylcycline antimicrobial agent. *Am J Health-Syst Pharm* 2006; **63:** 1235–43.
5. Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis* 2006; **43:** 518–24.
6. Slover CM, *et al.* Tigecycline: a novel broad-spectrum antimicrobial. *Ann Pharmacother* 2007; **41:** 965–72.
7. Grolman DC. Therapeutic applications of tigecycline in the management of complicated skin and skin structure infections. *Int J Infect Dis* 2007; **11** (suppl 1): S7–S15.
8. Karageorgopoulos DE, *et al.* Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) Acinetobacter infections: a review of the scientific evidence. *J Antimicrob Chemother* 2008; **62:** 45–55.
9. Curcio D. Tigecycline for treating bloodstream infections: a critical analysis of the available evidence. *Diagn Microbiol Infect Dis* 2008; **61:** 358–9.
10. Mullangi PK, Pankey GA. Tigecycline in critical care. *Crit Care Clin* 2008; **24:** 365–75.
11. McKeage K, Keating GM. Tigecycline: in community-acquired pneumonia. *Drugs* 2008; **68:** 2633–44.
12. Nicolau DP. Management of complicated infections in the era of antimicrobial resistance: the role of tigecycline. *Expert Opin Pharmacother* 2009; **10:** 1213–22. Correction. *ibid.*; 1527.

Administration in hepatic impairment. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (Child-Pugh category C); the initial intravenous loading dose should be 100 mg with reduced maintenance doses of 25 mg every 12 hours.

Adverse Effects

Tigecycline is a glycylcycline antibacterial with structural similarity to the tetracyclines and adverse effects similar to those of tetracyclines may potentially occur (see p. 375.1). The most common adverse effects associated with tigecycline have been nausea, vomiting, and diarrhoea. Other common adverse effects include abscess, abdominal pain, anorexia, dyspepsia, dizziness, headache, phlebitis, pruritus, and rash. Infection-related serious adverse events, including sepsis or septic shock have been reported; however, a causal relationship could not be established. Raised liver enzymes, bilirubinaemia, increased serum amylase, and increased blood urea nitrogen have also been reported. Occasionally, significant liver impairment, including fatal liver failure, has occurred. Local reactions have been reported at the infusion site and thrombocythaemia, anaemia, and leucocytosis may occur. Acute pancreatitis has been reported, usually after at least one week of treatment; symptoms generally resolve on stopping tigecycline. Potentially life-threatening anaphylaxis or anaphylactoid reactions have also been reported.

Precautions

Due to the potential for similar adverse effects, precautions applicable to the tetracyclines (see p. 375.2) should be taken with tigecycline. In particular, tigecycline should not be given in pregnancy as it has caused fetal harm in *animal* studies. Distribution into milk has also been found in *animal* studies. It should also not be given during tooth development (up to 8 years of age) as it may cause permanent tooth discoloration. Caution should be exercised when using tigecycline as monotherapy in patients with complicated intra-abdominal infections secondary to intestinal perforation. Patients taking anticoagulants should be closely monitored as tigecycline may prolong both the prothrombin time and the activated partial thromboplastin time. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (see above).

The FDA has issued a warning that tigecycline has been associated with an increased mortality risk when used to treat a variety of serious infections and has recommended that an alternative should be considered in patients with severe infections.[1]

1. FDA. Tygacil (tigecycline): label change - increased mortality risk (issued 1st September 2010). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm224626.htm (accessed 02/09/10)

Interactions

Immunosuppressants. For mention of increased serum concentrations of *ciclosporin* associated with concomitant tigecycline treatment, see p. 1956.2.

Antimicrobial Action

Tigecycline is generally bacteriostatic and acts by binding to the 30S subunit of the ribosome and preventing the binding of aminoacyl transfer RNA, similarly to tetracyclines (see p. 375.3). It has activity against a broad range of Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobic organisms. Tigecycline has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci. Gram-negative organisms that have proven susceptible include *Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, and some *Klebsiella* spp. Tigecycline also has activity against some anaerobic bacteria including *Bacteroides fragilis* and some other *Bacteroides* spp., *Clostridium perfringens*, and *Peptostreptococcus micros*. Some activity has also been reported against plasmodia.

Pharmacokinetics

After intravenous doses tigecycline is widely distributed into the tissues. Binding to plasma proteins has been reported to be 71 to 89% *in vitro*. Tigecycline is not thought to be extensively metabolised, although some trace metabolites have been identified including a glucuronide, an *N*-acetyl metabolite, and a tigecycline epimer. Tigecycline is primarily eliminated (about 60%) via biliary excretion of unchanged drug and some metabolites with a reported half-life of about 42 hours after multiple doses. About 22% is excreted unchanged in the urine.

Reviews.

1. Meagher AK, *et al.* The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 2005; **41** (suppl 5): S333–S340.
2. Rello J. Pharmacokinetics, pharmacodynamics, safety and tolerability of tigecycline. *J Chemother* 2005; **17** (suppl 1): 12–22.

3. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother* 2006; **58:** 256–65.
4. MacGowan AP. Tigecycline pharmacokinetic/pharmacodynamic update. *J Antimicrob Chemother* 2008; **62** (suppl 1): i11–i16.
5. Barbour A, *et al*. Clinical pharmacokinetics and pharmacodynamics of tigecycline. *Clin Pharmacokinet* 2009; **48:** 575–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tygacil; ***Austral.***: Tygacil; ***Austria***: Tygacil; ***Belg.***: Tygacil; ***Braz.***: Tygacil; ***Canad.***: Tygacil; ***Chile***: Tygacil; ***China***: Tygacil (泰阁); ***Cz.***: Tygacil; ***Denm.***: Tygacil; ***Fr.***: Tygacil; ***Ger.***: Tygacil; ***Gr.***: Tygacil; ***Hong Kong***: Tygacil; ***Hung.***: Tygacil; ***Indon.***: Tygacil; ***Irl.***: Tygacil; ***Israel***: Tygacil; ***Ital.***: Tygacil; ***Jpn***: Tygacil; ***Malaysia***: Tygacil; ***Mex.***: Tygacil; ***Neth.***: Tygacil; ***Norw.***: Tygacil; ***NZ***: Tygacil; ***Philipp.***: Tygacil; ***Pol.***: Tygacil; ***Port.***: Tygacil; ***Rus.***: Tigacil (Тигацил); ***Singapore***: Tygacil; ***Spain***: Tygacil; ***Swed.***: Tygacil; ***Switz.***: Tygacil; ***Thai.***: Tygacil; ***Turk.***: Tygacil; ***UK***: Tygacil; ***Ukr.***: Tygacil (Тигацил); ***USA***: Tygacil; ***Venez.***: Tygacil.

Tilmicosin *(BAN, USAN, rINN)*

EL-870; LY-177370; Tilmicosina; Tilmicosine; Tilmicosinum; Тильмикозин.

4″-*O*-De(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-20-deoxo-20-(*cis*-3,5-dimethyl-piperidino)tylosin.

$C_{46}H_{80}N_2O_{13}$=869.1

CAS — 108050-54-0.

ATC Vet — QJ01FA91.

UNII — XL4103X2E3.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Tilmicosin). White to off-white amorphous solid. Slightly soluble in water and in *n*-hexane. Store at a temperature not exceeding 40 degrees. Protect from light.

Tilmicosin Phosphate *(BANM, USAN, rINNM)*

Fosfato de tilmicosina; Tilmicosina, fosfato de; Tilmicosine, Phosphate de; Tilmicosini Phosphas; Тильмикозина Фосфат.

$C_{46}H_{80}N_2O_{13},H_3O_4P$=967.1

CAS — 137330-13-3.

UNII — SMH7U1S683.

Profile

Tilmicosin is a macrolide antibacterial used as the base or the phosphate in veterinary medicine.

Adverse effects. Accidental self-injection of tilmicosin by a farm worker, resulted in asthenia and temporary pulmonary, gastrointestinal, and neuromuscular toxicity.[1] A review[2] of human exposures to tilmicosin injection reported between March 1992 and March 2005 suggested that the overall risk of serious adverse effects was about 2 cases per million doses. Serious cardiovascular adverse effects, including bradycardia, hypertension, hypotension, tachycardia, and tachypnoea, occurred in 156 of 3168 reported cases and, of these, fatalities occurred in 13.

1. Crown LA, Smith RB. Accidental veterinary antibiotic injection into a farm worker. *Tenn Med* 1999; **92:** 339–40.
2. Veenhuizen MF, *et al*. Analysis of reports of human exposure to Micotil 300 (tilmicosin injection). *J Am Vet Med Assoc* 2006; **229:** 1737–42.

Handling. Contact with tilmicosin should be avoided. It is irritating to the eyes and may cause allergic reactions.

Tobramycin *(BAN, USAN, rINN)*

47663; Nebramycin Factor 6; Tobramicin; Tobramicina; Tobramicinas; Tobramisin; Tobramycine; Tobramycinum; Tobramycyna; Tobramysiini; Тобрамицин.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)streptamine.

$C_{18}H_{37}N_5O_9$=467.5

CAS — 32986-56-4.

ATC — J01GB01; S01AA12.

ATC Vet — QJ01GB01; QS01AA12.

UNII — VZ8RRZ51VK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tobramycin). A substance produced by *Streptomyces tenebrarius* or obtained by any other means. A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 9.0 to 11.0.

USP 36: (Tobramycin). A white to off-white, hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. Contains not more than 8.0% w/w of water. A 10% solution in water has a pH of 9.0 to 11.0. Store in airtight containers.

Tobramycin Sulfate *(BANM, rINNM)*

Sulfato de tobramicina; Tobramicina, sulfato de; Tobramycin Sulphate; Tobramycine, Sulfate de; Tobramycini Sulfas; Tobramycyny siarczan; Тобрамицина Сульфат.

$(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$=1425.4

CAS — 49842-07-1 ($C_{18}H_{37}N_5O_9,xH_2SO_4$); 79645-27-5 ($(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$).

ATC — J01GB01; S01AA12.

ATC Vet — QJ01GB01; QS01AA12.

UNII — HJT0RXD7JK.

Pharmacopoeias. In *Pol.* and *US*.

USP 36: (Tobramycin Sulfate). It has a potency of not less than 634 micrograms and not more than 739 micrograms of tobramycin per mg. A 4% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including tobramycin, with beta lactams, see under Gentamicin Sulfate, p. 304.3. Tobramycin is also reported to be incompatible with various other drugs and, as injections have an acid pH, incompatibility with alkaline preparations or with drugs unstable at acid pH may reasonably be expected.

Uses and Administration

Tobramycin is an aminoglycoside antibacterial with actions and uses similar to those of gentamicin (p. 304.3). It is used, usually as the sulfate, particularly in the treatment of pseudomonal infections.

As with gentamicin, tobramycin may be used with penicillins or cephalosporins; the injections should be given separately.

Tobramycin sulfate is given by intramuscular injection, or by intravenous infusion over 20 to 60 minutes in 50 to 100 mL of sodium chloride 0.9% or glucose 5% injection; proportionately less fluid should be given to children. It has also been given slowly by direct intravenous injection. Doses are expressed in terms of tobramycin base; 1.5 g of tobramycin sulfate is equivalent to about 1 g of tobramycin.

Doses of tobramycin are similar to those of gentamicin, with the usual adult dose ranging from 3 to 5 mg/kg daily in 3 or 4 divided doses. For mild to moderate urinary-tract infections in adults, a single intramuscular dose of 2 to 3 mg/kg may be effective.

For details on dosage in children, including discussion of the use of tobramycin in the management of cystic fibrosis, see Administration in Children; p. 382.2.

Treatment should generally be limited to 7 to 10 days, and peak plasma concentrations greater than 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) or trough concentrations greater than 2 micrograms/mL should be avoided. In all patients, dosage should be adjusted according to plasma-tobramycin concentrations and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity.

For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage under Uses and Administration of Gentamicin Sulfate, p. 305.2. As with some other aminoglycosides, once-daily and extended-interval dose regimens have been used successfully in selected patients for the treatment of other infections without increasing toxicity but local guidelines should be consulted for dosage and serum concentrations (see also Once-daily and Extended-interval Dose Regimens, under Gentamicin, p. 305.2).

Tobramycin may be used as a 0.3% eye ointment or eye drops in the treatment of eye infections.

Reviews.

1. Cheer SM, *et al*. Inhaled tobramycin (TOBI): a review of its use in the management of pseudomonas aeruginosa infections in patients with cystic fibrosis. *Drugs* 2003; **63:** 2501–20.

Administration in children. Tobramycin is licensed for use in children and may be given by intramuscular or intravenous injection, or by inhalation.

For *septicaemia, meningitis and other CNS infections, biliary-tract infection, acute pyelonephritis,* and *pneumonia* (in hospital patients) in infants and children the *BNFC* suggests:

- a **multiple daily dose regimen** of tobramycin by slow intravenous injection over at least 3 to 5 minutes
  - those 1 month to 12 years of age: 2 to 2.5 mg/kg every 8 hours
  - children 12 to 18 years of age: 1 mg/kg every 8 hours; in severe infections the dose may be increased up to 5 mg/kg daily in divided doses every 6 to 8 hours but should be reduced to 3 mg/kg daily as soon as clinically indicated, *or*
- a **once daily dose regimen** given by intravenous infusion of 7 mg/kg adjusted according to serum-tobramycin concentration in those from 1 month of age

For severe infections caused by susceptible bacteria in infants and children beyond the newborn period the American Academy of Pediatrics (AAP)[1] suggests an intravenous or intramuscular dose of tobramycin of 3 to 7.5 mg/kg daily, in 3 divided doses.

For the treatment of pseudomonal lung infection in *cystic fibrosis* the *BNFC* suggests:

- a **multiple daily dose regimen** of tobramycin by slow intravenous injection of 8 to 10 mg/kg daily in 3 divided doses in those from 1 month of age, *or*
- a **once daily dose regimen** by intravenous infusion over 30 minutes of 10 mg/kg (to a maximum of 660 mg) adjusted according to serum-tobramycin concentration in children from 1 month of age
- **inhalation** of tobramycin, as either a powder or nebulised solution, may be given for chronic infections in children aged 6 years and older. The powder is given in a dose of 112 mg while the dose for the nebulised solution is 300 mg. Both formulations are given every 12 hours for 28 days, after which treatment is stopped for 28 days before being started for another 28-day course; this cycle may be repeated indefinitely

The AAP[1] recommends an intravenous or intramuscular dose of 8 to 10 mg/kg daily for pulmonary exacerbations in those with cystic fibrosis.

For *neonatal sepsis* the *BNFC* suggests:

- an **extended-interval dose regimen** by slow intravenous injection or intravenous infusion
  - those with a postmenstrual age of less than 32 weeks: 4 to 5 mg/kg every 36 hours
  - those with a postmenstrual age of 32 weeks and over: 4 to 5 mg/kg every 24 hours, *or*
- a **multiple daily dose regimen** by slow intravenous injection or intravenous infusion
  - those less than 7 days old: 2 mg/kg every 12 hours
  - those 7 to 28 days old: 2 to 2.5 mg/kg every 8 hours

An alternative regimen based on the age and body-weight of the neonate is suggested by the AAP;[1] doses should be given by intramuscular or intravenous injection:

- for neonates ⩽7 days of age and weighing ⩽2 kg: 5 mg/kg every 48 hours
- for neonates ⩽7 days of age and weighing >2 kg: 4 mg/kg every 24 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 4 to 5 mg/kg every 24 to 48 hours; the longer dosing interval may be needed in extremely low birth-weight neonates (weighing <1 kg) until 2 weeks of life
- for neonates aged 8 to 28 days and weighing >2 kg: 4 mg/kg every 12 to 24 hours

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2. Some studies suggest that tobramycin is slightly less nephrotoxic than gentamicin, but others have not found any significant difference in their effects on the kidneys.

Peak plasma-tobramycin concentrations above 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) and trough concentrations above 2 micrograms/mL should be avoided.

When tobramycin is given by inhalation with other inhaled drugs, they should be given first before the dose of tobramycin. After the first inhaled dose of tobramycin, patients should be monitored for bronchospasm and if it occurs, the test should be repeated using a bronchodilator. Peak flow should be measured before nebulisation and again after it. Caution should be exercised in the presence of severe haemoptysis. Renal function should be monitored before treatment and every six months during use.

Effects on the ear. Reversible vestibular toxicity (ataxia, dizziness, and oscillopsia) occurred in a patient on haemodialysis after about 3 weeks of treatment with inhaled tobramycin for bronchiectasis due to colonisation with *Pseudomonas aeruginosa*.[1]

1. Edson RS, *et al*. Vestibular toxicity due to inhaled tobramycin in a patient with renal insufficiency. *Mayo Clin Proc* 2004; **79:** 1185–91.

Effects on the kidneys. Irreversible acute renal failure requiring haemodialysis occurred in a high-risk patient with chronic renal failure after being treated for 4 weeks with inhaled tobramycin for *Pseudomonas aeruginosa* pneumonia.[1]

1. Cannella CA, Wilkinson ST. Acute renal failure associated with inhaled tobramycin. *Am J Health-Syst Pharm* 2006; **63:** 1858–61.

Effects on the liver. A case[1] of possible tobramycin-induced hepatotoxicity was reported in a 20-year-old patient receiving antibacterial treatment for *Pseudomonas aeruginosa* bacteraemia and osteomyelitis. Liver enzyme values started to increase when empirical treatment was changed to intravenous tobramycin and ceftazidime, and markedly increased when the regimen was changed, increasing the dose of tobramycin and replacing ceftazidime with piperacillin/tazobactam and then later

aztreonam. Enzyme values began to decrease after all treatment was stopped on day 12.

1. Nisly SA, *et al.* Tobramycin-induced hepatotoxicity. *Ann Pharmacother* 2007; **41:** 2061–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tobramycin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 307.2. Tobramycin is reported to be somewhat more active *in vitro* than gentamicin against *Pseudomonas aeruginosa* and less active against *Serratia*, staphylococci, and enterococci; however these differences do not necessarily translate into differences in clinical efficacy.

Cross-resistance between tobramycin and gentamicin is generally seen, but about 10% of strains resistant to gentamicin are susceptible to tobramycin.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3.

After intramuscular use of tobramycin, peak plasma concentrations occur within 30 to 90 minutes and concentrations of about 4 micrograms/mL have been reported following doses of 1 mg/kg. Usual doses by slow intravenous injection may result in plasma concentrations which briefly exceed 12 micrograms/mL. A plasma half-life of 2 to 3 hours has been reported. Sufficient tobramycin may be absorbed after inhalation to produce systemic adverse effects (see Effects on the Ear, p. 380.3).

Inhalation. References.

1. Touw DJ, *et al.* Pharmacokinetics of aerosolized tobramycin in adult patients with cysticfibrosis. *Antimicrob Agents Chemother* 1997; **41:** 184–7.
2. Beringer PM, *et al.* Pharmacokinetics of tobramycin in adults with cystic fibrosis: implications for once-daily administration. *Antimicrob Agents Chemother* 2000; **44:** 809–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alveoterol; Belbarmicina; Bideon Biotic; Bioptic; Fotex; Gotabiotic D; Gotabiotic; Klonamicin; Oftalbrax; Pulbronkal; Radina; Tobi; Tobrabiotic; Tobradosa; Tobragan; Tobral; Tobralep; Tobraler; Tobranet†; Tobrex; Tofib; Toflamixina†; Tuberbut; Xao T; Xibrax; ***Austral.***: Nebcin†; Tobi; Tobra-Day; Tobrex; ***Austria***: Bramitob; Cromycin; Tobi; Tobrasix; Tobrex; ***Belg.***: Obracin; Tobi; Tobravisc; Tobrex; ***Braz.***: Bramitob; Tobracin; Tobracular; Tobraftal; Tobragan; Tobralox; Tobramina; Tobranom†; Tobrex; ***Canad.***: Tobi; Tobrex; ***Chile***: Notrix; Tobragan; Tobrex; Tobrin; Trazil; Tuberbut; Xolof; Zoteon; ***China***: Eyebrex (艾若); Jia Nuo Tai (佳诺泰); Rui Nuo Sai (瑞诺赛); Tai Tuo (泰托); Tai Xing (泰星); Tobrex (托百士); Tuo Xin (妥欣); ***Cz.***: Bramitob; Brulamycin†; Tobi; Tobrex; ***Denm.***: Nebcina; Tobi; Tobrex; ***Fin.***: Tobi; Tobrex; Tomycin; ***Fr.***: Nebcine; Tobi; Tobrabact; Tobrex; ***Ger.***: Bramitob; Gernebcin; Tobi; Tobra-cell†; Tobramaxin; ***Gr.***: Bramitob; Brulamycin; Colther; Eyebrex; Eyetobrin; Ikobel; Monobracin; Monotobrin; Nebcin; Thilo-micine; Tirselon; Tobi; Tobrex; Zerodiar; ***Hong Kong***: Tobrex; Toracin†; ***Hung.***: Bramitob; Brulamycin; Tobi; Tobrex; ***India***: Bactob; Eltol; Eyebrex; Fytobra; Glytob; Ibrex; Intob; MDas; Mytob; Mytobra; Nutob; Obra; Ocutob; Tobacin; Tobazon†; Tobraneg; ***Indon.***: Bralifex; Dartobcin†; Isotic Tobryne; Tobrex; Tobryne†; ***Irl.***: Bramitob; Tobi; Tobravisc†; ***Israel***: Bramitob; Tobi; Tobrex; ***Ital.***: Bramicil; Bramitob; Nebicina; Tobi; Tobrabact; Tobral; Tobrastill; ***Jpn***: Tobi; ***Malaysia***: Tobrex; ***Mex.***: Eyebrex; Isenia; Micitrex†; Obry; Poentobral; Tobrex; Trazil; Verbram; ***Neth.***: Bramitob; Nebris; Obracin; Tobi; Tobrabact; Tobrex; ***Norw.***: Nebcina; Tobi; Tobrex; ***NZ***: Nebcin; Tobra-Day; Tobrex; ***Philipp.***: Consac; Ramitop; Tobra-V; Tobrex; ***Pol.***: Bramitob; Tobi; Tobrex; Tobrexan; Tobrosopt; ***Port.***: Bramitob; Tobi; Tobra-Gobens; Tobrex; Tobrexan; Tobridavi†; Tobrineb; ***Rus.***: Bramitob (Брамитоб); Brulamycin (Бруламицин); Nebcin (Небцин); Tobi (Тоби); Tobrex (Тобрекс); Tobropt (Тобропт); ***S.Afr.***: Nebcin; Tobi; Tobrex; ***Singapore***: Ocusyn; Tobrex; ***Spain***: Bramitob; Tobi; Tobra Gobens; Tobrabact; Tobrex; Tobrineb; ***Swed.***: Nebcina; Tobi; Tobrex; ***Switz.***: Bramitob; Obracin; Tobi; Tobrex; ***Thai.***: Tobrex; ***Turk.***: Nebcin; Promesin; Thilomaxine; Tobel; Tobi; Tobrased; Tobrex; Tobrinex; Tobsin; ***UK***: Bramitob; Tobi; Tobravisc; ***Ukr.***: Tobrex (Тобрекс); Tobrimed (Тобримед); ***USA***: AkTob; Bethkis; Tobi; Tobrasol; Tobrex; ***Venez.***: Poentobral; Tobranax; Tobrasol; Tobrex.

Multi-ingredient Preparations. ***Arg.***: Antibioptal; Bicrinol; Bideon Biotic Plus; Biocort; Bioptic DX; Decadron con Tobramicina; Fotadex; Gotabiotic F; Ingebrax†; Klonamicin Compuesto; Larsen; Lotemicin; Polioftal; Purpumicina; Radina Dex; Tobrabiotic D; Tobracort†; Tobradex; Tobradiclo†; Tobragan D; Tobralep DX; Tobraler DX; Tobratlas Dexa; Tobratlas; Toflam Plus; Toflam; Toflamixina Plus†; Vistadex; Xibradex; Zylet; ***Austria***: Tobradex; ***Belg.***: Ocubrax; Tobradex; ***Braz.***: Tobracin D; Tobracort; Tobradex; Zylet; ***Canad.***: Tobradex; ***Chile***: Poentobral Plus; Tobradex; Tobragan D; Tobrin-D; Todexona; Trazidex; Xolof D; ***China***: Dian Shu (典舒); Jia Ming (佳名); TobraDex (典必殊); ***Cz.***: Tobradex; ***Denm.***: Tobradex; ***Fin.***: Tobrasone; ***Fr.***: Tobradex; ***Ger.***: Tobradex; ***Gr.***: Dexamycin; Eyebrex-Dexa; Lofoto; O-Biotic; Thilomicine Dex; Tobradex; Tobrafen; ***Hong Kong***: Tobradex; ***Hung.***: Tobradex; ***India***: FML-T; Glytob-D; LT-Cin; Mogitob-D; Nutob-F; Obra-D; Obra-F; Obrasone; Ocutob-D; Tobazon DM†; ***Indon.***: Bralifex Plus; Isotic Tobrizon; Tobradex; ***Israel***: Zylet; ***Ital.***: Tobradex; ***Malaysia***: Tobradex; ***Mex.***: Iseni-Dex; Obrydex; Obrypre; Poentobral D; Poentobral F; Tobracort; Tobradex; Trazidex; Trazinac; Zyleth; ***Neth.***: Tobradex; ***Norw.***: Tobrasone; ***NZ***: Tobradex; ***Philipp.***: Duocom; Mydexin; Mytodex; Ramtrex; Rapidex; Tobradex; ***Pol.***: Tobradex; ***Port.***: Tobradex; ***Rus.***: Tobradex (Тобрадекс); Tobrasone (Тобразон); ***S.Afr.***: Tobradex; ***Singapore***: Tobradex; Zylet; ***Spain***: Ocubrax; Tobradex; ***Swed.***: Tobrasone; ***Switz.***: Tobradex; Tobrafen; ***Thai.***: Tobradex; Zylet; ***Turk.***: Combidex; Ocubrax; Tobradex; ***UK***: Tobradex; ***Ukr.***: Ocubrax (Окубракс)†; Tobradex (Тобрадекс); ***USA***: Tobradex; Zylet; ***Venez.***: Poentobral Plus; Tobracort; Tobradex; Tobragan D; Todenac; Todex; Trazidex; Trazinac.

Pharmacopoeial Preparations

BP 2014: Tobramycin Injection;

USP 36: Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension; Tobramycin for Injection; Tobramycin Inhalation Solution; Tobramycin Injection; Tobramycin Ophthalmic Ointment; Tobramycin Ophthalmic Solution.

Tosufloxacin *(USAN, rINN)*

A-61827; Abbott-61827; Tosufloxacine; Tosufloxacino; Tosufloxacinum; Тосуфлоксацин.

(±)-7-(3-Amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

$C_{19}H_{15}F_3N_4O_3$=404.3

CAS — 100490-36-6 (anhydrous tosufloxacin); 108138-46-1 (anhydrous tosufloxacin); 107097-79-0 (tosufloxacin monohydrate).

UNII — GHJ553KQPS (tosufloxacin); 6239812J7L (tosufloxacin monohydrate).

Tosufloxacin Tosilate *(rINNM)*

A-64730; T-3262; Tosilato de tosufloxacino; Tosufloxacin Tosylate; Tosufloxacine, Tosilate de; Tosufloxacini Tosilas; Tosufloxacino, tosilato de; Тосуфлоксацина Тозилат.

Tosufloxacin toluene-4-sulphonate monohydrate.

$C_{19}H_{15}F_3N_4O_3,C_7H_8O_3S,H_2O$=594.6

CAS — 115964-29-9; 144742-63-2.

UNII — NO6NM634EH.

Profile

Tosufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1). It is given orally as the tosilate in the treatment of susceptible infections in usual doses of 300 to 450 mg daily in 2 or 3 divided doses.

For blepharitis, conjunctivitis, corneal ulcers, and other eye infections caused by susceptible strains of bacteria, eye drops containing 0.3% of tosufloxacin tosilate are used.

References.

1. Niki Y. Pharmacokinetics and safety assessment of tosufloxacin tosilate. *J Infect Chemother* 2002; **8:** 1–18.
2. Takahama H, Tazaki H. Tosufloxacin tosilate-induced thrombocytopenic purpura. *J Dermatol* 2007; **34:** 465–7.
3. Kamiya K, *et al.* Corneal deposits after topical tosufloxacin in a patient with poor tear secretion. *Cornea* 2009; **28:** 114–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ang Te (昂特); Ci Er Tai (赐尔泰); Nuo Li Si (诺力思); ***Jpn***: Ozex.

Trimethoprim *(BAN, USAN, rINN)*

BW-56-72; NSC-106568; TMP; Triméthoprime; Trimethoprimum; Trimethoxyprim; Trimetopriimi; Trimetoprim; Trimetoprima; Trimetoprimas; Trimetoprym; Триметоприм.

5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine.

$C_{14}H_{18}N_4O_3$=290.3

CAS — 738-70-5.

ATC — J01EA01.

ATC Vet — QJ01EA01; QJ51EA01.

UNII — AN164J8Y0X.

NOTE. Compounded preparations of trimethoprim may be represented by the following names:

- Co-trifamole (*BAN*)—trimethoprim 1 part and sulfamoxole 5 parts (see p. 277.3)
- Co-trimazine (*BAN*)—trimethoprim 1 part and sulfadiazine 5 parts
- Co-trimoxazole (*BAN*)—trimethoprim 1 part and sulfamethoxazole 5 parts (see p. 277.3)
- Co-trimoxazole (*PEN*)—trimethoprim and sulfamethoxazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Trimethoprim). A white or yellowish-white powder. Very slightly soluble in water; slightly soluble in alcohol.

USP 36: (Trimethoprim). White to cream-coloured, odourless crystals or crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone; soluble in benzyl alcohol; practically insoluble in carbon tetrachloride and in ether; sparingly soluble in chloroform and in methyl alcohol. Store in airtight containers. Protect from light.

Trimethoprim Sulfate *(BANM, USAN, rINNM)*

BW-72U; Sulfato de trimetoprima; Trimethoprim Sulphate; Triméthoprime, Sulfate de; Trimethoprimi Sulfas; Trimetoprim Sülfat; Trimetoprima, sulfato de; Триметоприма Сульфат.

$(C_{14}H_{18}N_4O_3)_2.H_2SO_4$=678.7

CAS — 56585-33-2.

UNII — E377MF8EQ8.

Pharmacopoeias. In *Viet.* and *US.*

USP 36: (Trimethoprim Sulfate). A white to off-white crystalline powder. Soluble in water, in alcohol, in dilute mineral acids, and in fixed alkalis. pH of a 0.05% solution in water is between 7.5 and 8.5. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Trimethoprim is a diaminopyrimidine antibacterial that is used for the treatment of infections due to sensitive organisms, including gastro-enteritis and respiratory-tract infections, and in particular for the treatment and prophylaxis of urinary-tract infections. For details of these infections and their treatment, see Choice of Antibacterial, p. 172.2.

Trimethoprim is also used with sulfonamides. The most common combination is co-trimoxazole (trimethoprim with sulfamethoxazole) (p. 277.3). Other combinations are co-trimazine (with sulfadiazine) and co-trifamole (with sulfamoxole) (see p. 277.3); trimethoprim has also been used with sulfamerazine, sulfametopyrazine, sulfametrole, and sulfamethoxypyridazine, and, in veterinary practice, with sulfadiazine, sulfadoxine, sulfamethoxazole, and sulfaquinoxaline.

Trimethoprim with sulfamethoxazole (co-trimoxazole) or with dapsone is used in the management of pneumocystis pneumonia (p. 567.2).

The usual oral dose of trimethoprim in acute infection is 100 or 200 mg twice daily; doses of 200 or 300 mg daily as a single dose are also used. For the dosage of trimethoprim when given with sulfamethoxazole, see under Co-trimoxazole, p. 277.3. Up to 20 mg/kg daily may be given with dapsone for the treatment of pneumocystis pneumonia. For long-term prophylaxis the usual dose is 100 mg at night.

Trimethoprim has been given intravenously by injection or infusion as the lactate although doses are in terms of the base. The usual dose has been 200 mg every 12 hours; initial doses may be higher or given more frequently in severely ill patients.

Care should be taken in patients with moderate to severe renal impairment and doses generally should be reduced.

For doses used in renal impairment, and for details of use in children, see p. 384.1.

Trimethoprim with polymyxin B has been used topically in the treatment and prophylaxis of eye infections. Trimethoprim sulfate and trimethoprim hydrochloride are also used.

Administration. *SINGLE-DOSE THERAPY.* Although there are obvious advantages to a single-dose regimen, one study[1] found that there was about a 1 in 4 risk of recurrence of urinary-tract infection within 10 days in 50 children given, according to age, a single oral dose of 75 to 450 mg of trimethoprim. The problems with a single-dose regimen were confirmed by others[2] in a study involving 344 evaluated cases of cystitis in 306 women. Only 122 of 173 cases treated with trimethoprim 320 mg as a single oral dose were evaluated as cured after 5 weeks, compared with 149 of 171 given 160 mg twice daily for 1 week (71 versus

87%). Again, these results suggest that about 1 patient in 4 would have to be re-treated.

1. Nolan T, *et al.* Single dose trimethoprim for urinary tract infection. *Arch Dis Child* 1989; **64:** 581–6.
2. Österberg E, *et al.* Efficacy of single-dose versus seven-day trimethoprim treatment of cystitis in women: a randomized double-blind study. *J Infect Dis* 1990; **161:** 942–7.

Administration in children. Trimethoprim may be used in children for the treatment of infections caused by susceptible organisms. Although in the UK, trimethoprim is only licensed for oral use in those 6 weeks of age and older, the *BNFC* provides the following dose recommendations:

For **treatment** of urinary- or respiratory-tract infections:

- neonates: initially 3 mg/kg as a single dose, followed by 1 to 2 mg/kg twice daily
- children from 1 month of age: 4 mg/kg (to a maximum of 200 mg) twice daily

  or

  children 6 weeks to 6 months of age: 25 mg twice daily
  children 6 months to 6 years of age: 50 mg twice daily
  children from 6 years of age: 100 mg twice daily

For the **prophylaxis** of urinary-tract infections:

- neonates and children: 2 mg/kg (to a maximum of 100 mg) at night

Administration in renal impairment. Oral doses of trimethoprim should generally be reduced in patients with moderate to severe renal impairment according to the estimated glomerular filtration rate (eGFR):

- eGFR 15 to 30 mL/minute per 1.73m^2: normal dose for 3 days reduced to one-half thereafter
- eGFR below 15 mL/minute per 1.73m^2: half the normal dose from the start of treatment

Plasma concentrations should be monitored in patients with severe renal impairment.

Adverse Effects and Treatment

Trimethoprim is reasonably well tolerated in general, and the most frequent adverse effects at usual doses are pruritus and rash (in about 3 to 7% of patients) and mild gastrointestinal disturbances including nausea, vomiting, and glossitis. Adverse effects, including hypersensitivity reactions, are more common in patients with AIDS, about 50 to 60% of whom will need to change their treatment due to adverse effects.

Rarely, more severe effects have been reported. Sulfonamide-like skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Disturbances of liver enzyme values and cholestatic jaundice have been associated with trimethoprim. Rises in serum creatinine and blood-urea nitrogen have been reported although it is unclear whether this represents genuine renal dysfunction or inhibition of tubular secretion of creatinine. Photosensitivity has been reported. Fever is not uncommon but occasionally hypersensitivity reactions may be severe and anaphylaxis and angioedema have been reported. Cases of aseptic meningitis have also occurred.

Trimethoprim may cause a depression of haematopoiesis due to interference of the drug in the metabolism of folic acid, particularly when given over a prolonged period or in high doses. This may manifest as megaloblastic anaemia, or as thrombocytopenia and leucopenia; methaemoglobinaemia has also been seen. Folinic acid may be given to counter this effect; for details of the folinic acid dose regimen, see Uses and Administration of Folinic Acid, p. 2067.1. Trimethoprim is teratogenic in *animals*.

For further information on the adverse effects of trimethoprim when used with sulfamethoxazole, see Co-trimoxazole, p. 278.3.

Effects on the eyes. There have been isolated reports of bilateral anterior uveitis associated with trimethoprim.[1-4] The reaction has recurred on rechallenge with trimethoprim.[1,2] In one case a patient developed uveitis after co-trimoxazole, and subsequently uveitis with retinal haemorrhage after trimethoprim alone.[3] In one report,[2] uveitis was associated with arthritis and Stevens-Johnson syndrome.

1. Gilroy N, *et al.* Trimethoprim-induced aseptic meningitis and uveitis. *Lancet* 1997; **350:** 112.
2. Arola O, *et al.* Arthritis, uveitis, and Stevens-Johnson syndrome induced by trimethoprim. *Lancet* 1998; **351:** 1102.
3. Kristinsson JK, *et al.* Bilateral anterior uveitis and retinal haemorrhages after administration of trimethoprim. *Acta Ophthalmol Scand* 1997; **75:** 314–15.
4. Pathak S, Power B. Bilateral acute anterior uveitis as a side effect of trimethoprim. *Eye* 2007; **21:** 252–3.

Hyperkalaemia. Hyperkalaemia is a common complication of both high- and standard-dose trimethoprim therapy,[1] and in some cases may be serious or life-threatening. The drug is thought to have potassium-sparing properties similar to amiloride, with hyperkalaemia usually developing in the first 3 to 10 (usually 4 to 5) days of therapy. Although clinically important hyperkalaemia may develop in the absence of any predisposing factors, those at highest risk appear to be patients with renal impairment or other conditions affecting potassium homoeostasis (such as hypoaldosteronism), those taking other potassium-altering medications (including ACE inhibitors, NSAIDs, and potassium-sparing diuretics), or those taking high doses of trimethoprim.

1. Perazella MA. Trimethoprim-induced hyperkalaemia: clinical data, mechanism, prevention and management. *Drug Safety* 2000; **22:** 227–36.

Precautions

Trimethoprim should not be given to patients with a history of hypersensitivity to the drug, and it should be stopped if a rash appears. Care is necessary in giving trimethoprim to patients with renal impairment to avoid accumulation and toxicity: it should not be given in severe renal impairment unless blood concentrations can be monitored. It should be used with caution in patients with severe hepatic damage as changes may occur in the absorption and metabolism of trimethoprim.

It is suggested that regular haematological examination should be made during prolonged courses of treatment although the *BNF* considers evidence of their practical value to be unsatisfactory; patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. Trimethoprim should not usually be given to patients with serious haematological disorders and particularly not in megaloblastic anaemia secondary to folate depletion. Care should be taken in patients with actual, or possible, folate deficiency and use of folinic acid should be considered. Trimethoprim should be avoided during pregnancy. Elderly patients may be more susceptible to adverse effects and a lower dosage may be advisable.

Trimethoprim may interfere with some diagnostic tests, including serum-methotrexate assay where dihydrofolate reductase is used and the Jaffé reaction for creatinine.

For further information on precautions for trimethoprim given with sulfamethoxazole, see Co-trimoxazole, p. 279.1.

Breast feeding. Trimethoprim appears in breast milk and the US licensed product information has stated that care is required when it is used in breast-feeding mothers.

The last available guidelines from the American Academy of Pediatrics considered trimethoprim, when given with sulfamethoxazole, to be compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Fragile X syndrome. A warning that trimethoprim and other folate antagonists should be avoided in children with the fragile X chromosome, which is associated with mental retardation and is folate sensitive.[1]

1. Hecht F, Glover TW. Antibiotics containing trimethoprim and the fragile X chromosome. *N Engl J Med* 1983; **308:** 285–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trimethoprim as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

Trimethoprim may increase serum concentrations of some drugs, including phenytoin, digoxin, procainamide, rosiglitazone, and repaglinide, potentiating their effect. This may be due to competitive inhibition of renal excretion, decreased metabolism, or both. It has been suggested that trimethoprim may potentiate the effects of warfarin. Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine, and lamivudine. Trimethoprim and dapsone increase each other's serum concentrations, whereas rifampicin may decrease trimethoprim concentrations.

An increased risk of nephrotoxicity has been reported with the use of trimethoprim or co-trimoxazole and ciclosporin. Intravenous use of trimethoprim and sulfonamides may reduce ciclosporin concentrations in blood. Hyponatraemia has been reported in patients given trimethoprim with diuretics. An increased risk of thrombocytopenia has been seen in elderly patients given co-trimoxazole with diuretics, although it is unclear which component of the antibacterial is responsible.

Use of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression, and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors, such as pyrimethamine or methotrexate.

Severe hyperkalaemia has been noted in patients given trimethoprim (or co-trimoxazole) with an ACE inhibitor.

Antimicrobial Action

Trimethoprim is a dihydrofolate reductase inhibitor. It inhibits the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid which is necessary for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA. It acts in the same metabolic pathway as the sulfonamides. It exerts its selective action because of a far greater affinity for the bacterial than the mammalian enzyme. Trimethoprim may be bacteriostatic or bactericidal depending on growth conditions; pus, for example, may inhibit the action of trimethoprim because of the presence of thymine and thymidine.

Spectrum of activity. Trimethoprim is active against many Gram-negative and Gram-positive aerobes, as well as some protozoa. The following species are usually susceptible (but see also Resistance, below).

- Many Gram-positive cocci are sensitive, including *Staphylococcus aureus*, streptococci including *Streptococcus pyogenes*, *Str. pneumoniae* (although resistance has been reported worldwide), and the viridans streptococci, and to a variable extent enterococci, although their sensitivity is reduced in the presence of folate. Trimethoprim is bactericidal against most strains of *Listeria monocytogenes* and some strains of *Nocardia* spp. are susceptible.
- Other sensitive Gram-positive organisms include strains of *Listeria*, *Corynebacterium diphtheriae*, and the Gram-positive bacilli.
- Among the Gram-negative organisms, most of the Enterobacteriaceae are susceptible, or moderately so, including *Citrobacter*, *Enterobacter*, *Escherichia*, *Hafnia*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* species. *Vibrio cholerae* are generally susceptible but resistant strains are well documented. *Haemophilus influenzae* and *H. ducreyi* are usually susceptible, however, *H. ducreyi* strains with increased resistance to trimethoprim have been reported. Pathogenic *Neisseria* spp. are moderately resistant, while strains of *Helicobacter pylori*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and *Bacteroides* spp. are generally resistant.
- Anaerobic species are usually resistant.
- *Chlamydiaceae*, *Mycoplasma*, and *Ureaplasma* species and *Treponema pallidum* are generally resistant.
- *Mycobacterium tuberculosis* and *M. haemophilum* are resistant although *M. marinum* may not be.
- Trimethoprim has some activity against *Pneumocystis jirovecii* and against some protozoa such as *Naegleria*, *Plasmodium*, and *Toxoplasma*.

Activity with other antimicrobials. Because their modes of action are complementary, affecting different stages in folate metabolism, a potent synergistic effect exists between trimethoprim and sulfonamides against many organisms *in vitro*.

Fixed-dose combinations of trimethoprim with various sulfonamides are available, of which co-trimoxazole (trimethoprim with sulfamethoxazole in a 1:5 mixture) is the most widely used. For further details on the antimicrobial action of co-trimoxazole, see p. 280.1.

Synergy has also been reported with rifampicin, and with the polymyxins.

Resistance. Resistance to trimethoprim may be due to several mechanisms. Clinical resistance is often due to plasmid-mediated dihydrofolate reductases that are resistant to trimethoprim: such genes may become incorporated into the chromosome via transposons. Resistance may also be due to overproduction of dihydrofolate reductase, changes in cell permeability, or bacterial mutants which are intrinsically resistant to trimethoprim because they depend on exogenous thymine and thymidine for growth. Despite fears of a rapid increase in resistance if trimethoprim was used alone there is little evidence that this has been any worse than in areas where it has been used with sulfonamides. Nonetheless, trimethoprim resistance has been reported in many species, and very high frequencies of resistance have been seen in some developing countries, particularly among the Enterobacteriaceae.

References.

1. Huovinen P, *et al.* Trimethoprim and sulfonamide resistance. *Antimicrob Agents Chemother* 1995; **39:** 279–89.

Pharmacokinetics

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations occur about 1 to 4 hours after an oral dose; peak plasma concentrations of about 1 microgram/mL have been reported after a single 100-mg dose. About 45% is bound

to plasma proteins. Trimethoprim is widely distributed to various tissues and fluids including kidneys, liver, lung and bronchial secretions, saliva, aqueous humour, prostatic tissue and fluid, and vaginal secretions; concentrations in many of these tissues are reported to be higher than serum concentrations but concentrations in the CSF are about one-quarter to one-half of those in serum. Trimethoprim readily crosses the placenta and it appears in breast milk. The half-life is about 8 to 10 hours in adults and somewhat less in children, but is prolonged in severe renal impairment and in neonates, whose renal function is immature.

Trimethoprim is excreted mainly by the kidneys through glomerular filtration and tubular secretion. About 10 to 20% of trimethoprim is metabolised in the liver and small amounts are excreted in the faeces via the bile, but most, about 40 to 60% of a dose, is excreted in urine, mainly as unchanged drug, within 24 hours. Trimethoprim is removed from the blood by haemodialysis to some extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Alprim; Triprim; ***Austria***: Infectotrimet; Motrim; Solotrim†; Triprim; ***Cz.***: Triprim; ***Denm.***: Trimopan; ***Fin.***: Trimetin; Trimex†; Trimopan; ***Ger.***: InfectoTrimet; ***Hong Kong***: Primsol; ***Irl.***: Monotrim; Trimoptin; ***Malaysia***: Alprim†; ***NZ***: TMP; ***Pol.***: Trimesan; Urotrim; ***S.Afr.***: Purium†; ***Singapore***: Alprim; ***Spain***: Tediprima; ***Swed.***: Idotrim; ***Thai.***: Trimethop; Utisept†; ***UAE***: Trimol-A; ***UK***: Monotrim; Trimopan; ***USA***: Primsol; Proloprim; Trimpex.

Multi-ingredient Preparations. ***Arg.***: Adrenol; Bacti-Uril; Bacticel; Bactrim Balsamico; Bactrim; Cotrizol-G; Danferane; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Neoftalm Dexa; Neoftalm; Neolag; Netocur Balsamico; Netocur; Neumobacticel; Novidrine; Rifaprim; Sulfagrand; Trimepol D†; Trimepol†; Tritenk; Urisept NF; ***Austral.***: Bactrim; Resprim; Septrin; Trimoxazole†; ***Austria***: Bactrim; Cotribene; Eusaprim; Lidaprim; Oecotrim†; ***Belg.***: Bactrim; Cotrim†; Eusaprim; Polytrim; ***Braz.***: Assepium Balsamico; Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Belfactrim F; Benectrin Balsamico; Benectrin; Diazol; Dientrin; Dispeptrin†; Ectrin Balsamico; Ectrin; Gamactrin†; Imuneprim†; Infectrin; Metoprin Balsamico†; Metoprin; Neotrin; Pulkrin†; Qiftrim; Roytrin; Selectrin Balsamico; Selectrin†; Teutrin; Tricban; Triglobe; Trimexazol; Urocrim; Uropol†; ***Canad.***: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; PMS-Polytrimethoprim; Polytrim; Protrin; Septra; Trisulfa; ***Chile***: Bacterol; Bactrimel; Entero Micinovo; Septrin; Trelibec; Uro-Micinovo; ***China***: An Li Kang (安立康); Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (奎建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Pixian (彼先); Xiaoke (消刻); Xindabao (新达宝); Yu An Li Qing (玉安立清); Zengxiao Lianhuangpian (增效联磺); ***Cz.***: Biseptol; Bismoral†; Primotren†; Sumetrolim; ***Fin.***: Cotrim; Ditrim; Trimetin Duplo†; ***Fr.***: Bactrim; ***Ger.***: Berlocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; ***Gr.***: Bactrimel; Bioprim; Blaxezan; Blexon; Epahol; Lidaprim; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; ***Hong Kong***: Chemoprim; Cotrim; Dhatrin; Letus; Lidaprim; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; ***Hung.***: Cotripharm; Sumetrolim; ***India***: Alcorim-F; Antrima; Aubril; Bactrim; Cadiprim; Chemotrin; Ciplin; Colizole; Cortina; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Methoxaprim; Moly Kid; Mountrim; Neoprim; Okatrim DS; Oriprim-P; Oriprim; Otrim; Sepmax; Septran; Supristol; Tabrol; Trisulfose; ***Indon.***: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.***: Septrin; ***Israel***: Diseptyl; Resprim; Septrin; ***Ital.***: Bactrim; Chemitrim; Eusaprim†; ***Jpn***: Bactramin; Baktar; ***Malaysia***: Bacin; Bactrim; Balin; Beaglobe; Chemix; Cotrim; Oftalmotrim; Resprim†; Trimexazole; Trizine; Trizole; ***Mex.***: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric†; Bactide†; Bactilen; Bactiver; Bactrim Compositum; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Guayaprin; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octex; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Rifaprim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole Compositum; Trimexole; Trimzol; TS-Bac; Vanadyl; ***Neth.***: Bactrimel; Lidatrim†; Polytrim; Rokiprim; ***Norw.***: Bactrim; ***NZ***: Apo-Sulfatrim†; Deprim; Trisul; ***Philipp.***: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Triglobe†; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizine; Trizole; Xanazole; Zamboprim†; Zolmed; ***Pol.***: Bactrim; Biseptol; Septrin†; Two-Septol; ***Port.***: Bactrim; Microcetim†; Oftalmotrim; Septrin; ***Rus.***: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гроseптол); Lidaprim (Лидаприм)†; Oriprim (Ориприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); ***S.Afr.***: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac; Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac; Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; ***Singapore***: Apo-Sulfatrim; Bacin; Balin; BS; Chemix; Co-Trimexazole; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; Trimaxazole; Trizine; ***Spain***: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†; Momentol†; Oftalmotrim; Otix; Septrin; Soltrim; ***Swed.***: Bactrim; Eusaprim; ***Switz.***: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; ***Thai.***: Actin; Actrim; Addtrim; Agsulfa; Babytrim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Conprim†; Coprim; Cotamox; Cotrim; D-Med; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Ximeprim; Zoleprim; ***Turk.***: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Oftalmotrim†; Polycillin†; Polytrim; Septrin; Sulfaprim; Sulfatrim†; Trifen; Trimoks; ***UAE***: Trimol; ***UK***: Fectrim; Septrin; ***Ukr.***: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гроseптол); Soluseptol (Солюсептол); Sumetrolim (Суметролим); ***USA***: Bactrim; Cotrim†; Polytrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.***: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; Trimethoprim Oral Suspension; Trimethoprim Tablets;

USP 36: Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution; Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Trimethoprim Tablets.

Troleandomycin *(BAN, USAN, rINN)*

NSC-108166; Triacetyloleandomycin; Troleandomicina; Troleandomisin; Troléandomycine; Troleandomycinum; Troleandomysiini; Тролеандомицин.

The triacetyl ester of oleandomycin .

$C_{41}H_{67}NO_{15}$=814.0

CAS — 2751-09-9.

ATC — J01FA08.

ATC Vet — QJ01FA08.

UNII — C4DZ64560D.

Pharmacopoeias. In *Fr.*

Profile

Troleandomycin is a prodrug of the macrolide antibacterial oleandomycin that has actions similar to those of erythromycin (p. 291.2). It has been given orally in the treatment of susceptible infections although more effective antibacterials are generally preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Triocetin†; ***Turk.***: Tekmisin.

Tulathromycin *(USAN, rINN)*

CP-472295 (component A); CP-547272 (component B); Tulathromycine; Tulathromycinum; Tulatromicina; Тулатромицин.

$C_{41}H_{79}N_3O_{12}$=806.1

CAS — 217500-96-4 (component A); 280755-12-6 (component B).

ATC Vet — QJ01FA94.

UNII — Q839I13422 (tulathromycin); 897A3KN7AP (tulathromycin component A); T5PDD839DA (tulathromycin component B).

NOTE. The name Draxxin has been used as a trade mark for tulathromycin.

Profile

Tulathromycin is a macrolide antibacterial used in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Tylosin *(BAN, rINN)*

Tilosina; Tilozin; Tylosiini; Tylosine; Tylosinum; Tylozyna; Тилозин.

$C_{46}H_{77}NO_{17}$=916.1

CAS — 1401-69-0.

ATC Vet — QJ01FA90; QJ51FA90.

UNII — YEF4JXN031.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, both for veterinary use.

Ph. Eur. 8: (Tylosin for Veterinary Use; Tylosin BP 2014; Tylosin BP(Vet) 2014). A mixture of macrolide antibiotics produced by a strain of *Streptomyces fradiae* or by any other means. The main component of the mixture is tylosin A, but tylosin B (desmycosin), tylosin C (macrocin), and tylosin D (relomycin) may also be present. An almost white or slightly yellow powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane. It dissolves in dilute solutions of mineral acids. A 2.5% suspension in water has a pH of 8.5 to 10.5. Protect from light.

USP 36: (Tylosin). A macrolide antibiotic substance or mixture of such substances produced by the growth of *Streptomyces fradiae* or by any other means. A white to buff-coloured powder. Slightly soluble in water; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; freely soluble in methyl alcohol. It loses not more than 5% of its weight on drying. Protect from light, moisture, and temperatures exceeding 40 degrees.

Tylosin Tartrate *(BANM, rINNM)*

Tartrato de tilosina; Tilosina, tartrato de; Tilozin-tartarát; Tylosiinitartraatti; Tylosin tartarát; Tylosine, Tartrate de; Tylosini tartras; Tylosintartrat; Tylozyny winian; Тилозина Тартрат.

$(C_{46}H_{77}NO_{17})_2,C_4H_6O_6$=1982.3

CAS — 1405-54-5.

UNII — 5P4625C51T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use.

Ph. Eur. 8: (Tylosin Tartrate for Veterinary Use; Tylosin Tartrate BP 2014; Tylosin Tartrate BP(Vet) 2014). An almost white or slightly yellow hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in dehydrated alcohol. It dissolves in dilute solutions of mineral acids. A 2.5% solution in water has a pH of 5.0 to 7.2. Store in airtight containers. Protect from light.

USP 36: (Tylosin Tartrate). A tartrate of a mixture of macrolide antibiotic substances, or the mixture of such substances, produced by the growth of *Streptomyces fradiae*, or by any other means. Its potency is not less than 800 micrograms of tylosin per mg, calculated on the dried basis.

An almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids. pH of a 2.5% solution in water is between 5.0 and 7.2. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Tylosin is a macrolide antibacterial with actions similar to those of erythromycin (p. 291.2). Tylosin and its phosphate and tartrate salts are used in veterinary medicine in the prophylaxis and treatment of infections caused by susceptible organisms.

Tylosin and tylosin phosphate have been added to animal feeding stuffs as growth promotors for pigs.

Tylvalosin Tartrate *(USAN, rINNM)*

Acetyl Isovaleryl Tylosin Tartrate; Acetylisovaleryltylosin Tartrate; Tartrato de tilvalosina; Tylvalosine, Tartrate de; Tylvalosini Tartras; Тильвалозина Тартрат.

(4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-{[(6-Deoxy-2,3-di-*O*-methyl-β-*D*-allopyranosyl)oxy]methyl}-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate (2*R*,3*R*)-2,3-dihydroxybutanedioate.

$C_{53}H_{87}NO_{19}xC_4H_6O_6$

CAS — 63409-12-1 (tylvalosin); 63428-13-7 (tylvalosin tartrate).

ATC Vet — QJ01FA92.

UNII — AL5667FY0W.

The symbol † denotes a preparation no longer actively marketed

Profile

Tylvalosin is a derivative of tylosin (p. 383.3) and is used similarly as the tartrate in veterinary medicine.

Tyrothricin *(BAN, rINN)*

Tirotricina; Tirotricinas; Tirotrisin; Tyrothricine; Tyrothricinum; Tyrotricin; Tyrotrisiini; Тиротрицин.

CAS — 1404-88-2.
ATC — D06AX08; R02AB02; S01AA05.
ATC Vet — QD06AX08; QR02AB02; QS01AA05.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tyrothricin). A mixture of antimicrobial linear and cyclic polypeptides, isolated from the fermentation broth of *Bacillus brevis*. It consists mainly of gramicidins and tyrocidins; other related compounds may be present in smaller amounts. The potency is 180 to 280 international units/mg, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Tyrothricin). An antibacterial substance produced by the growth of *Bacillus brevis*. It is a mixture consisting chiefly of gramicidin and tyrocidine, the latter being usually present as the hydrochloride. Store in airtight containers.

Uses and Administration

Tyrothricin is unsuitable for systemic use. It is active *in vitro* against many Gram-positive bacteria and has been used either alone or with other antibacterials in the local treatment of infections mainly of the skin and mouth.

Adverse Effects and Precautions

Tyrothricin is too toxic to be used systemically; effects that have been reported include hepatic and renal toxicity as well as Stevens-Johnson syndrome. It damages the sensory epithelium of the nose and instances of prolonged loss of smell have occurred after its use as a nasal spray or instillation. Tyrothricin should not be instilled into the nasal cavities or into closed body cavities.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Tyrosur; ***Gr.***: Triciderm; Tyrex Dermose; ***Ital.***: Faringotricina; Hydrotricine; Rinotricina; ***Port.***: Hydrotricine; ***Turk.***: Hydrotricine; ***Ukr.***: Tyrosur (Тирозур).

Multi-ingredient Preparations. ***Arg.***: Acemuk L; Algiodent; Aseptobron Caramelos; Bagociletas; Biotaer an Caramelos; Biotaer Nebulizable; Bucotricin; Caramelos Antibioticos Lefmar; Caramelos Antibioticos; Caramelos Antibioticos; Collubiazol; Fanaletas; Filotricin A; Fonergine; Gineseptina; Oralsone C; Pulmosan Caramelos; Solumerin; Sulfanoral T; Tavinex; Vagicural; Vagisan Compuesto; Vagisan; ***Austria***: Dorithricin; Lemocin; Limexx†; Tyrothricin comp; ***Belg.***: Lemocin; Tyro-Drops†; ***Braz.***: Amidalin; Amigdagen†; Amigdalol; Anapyon; Anginotricin; Auritricin; Colpagex-N†; Colpolase†; Gynax-N; Lacto Vagin; Malvatricin Ginecologico†; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvatricin; Oturga; Trivagel N; Vagitrin-N; ***Canad.***: Antibiotic Cold Sore Ointment†; Soropon†; ***China***: Deq (得益); ***Ger.***: Dorithricin; Lemocin†; Tyrosur; ***Gr.***: Evex; Oulogram; Trachisan; ***Hong Kong***: Deq; Tyricine; Tyrocaine†; Tyrothricin Co; ***Hung.***: Dorithricin; Tyrosur; ***India***: Tytin; ***Indon.***: Lemocin; ***Irl.***: Tyrozets; ***Israel***: Clearocin; Kalgaron; Lemocin; Rafathricin with Benzocaine; ***Ital.***: Bioarscolloid; Deltavagin; Furotricina; Golamixin; Kinogen; Rinocidina; ***Malaysia***: Deq; Upha Lozenges; ***Mex.***: Angenovag; ***Port.***: Mebocaina; Medifon†; Mentocaina R; ***Singapore***: Beathricin; Deq; Dorithricin; Trachisan; Tyrocaine; ***Spain***: Anginovag; Bucometasana; Cicatral; Cohortan; Denticelso; Diformiltricina†; Miozets; Pastillas Koki Mentol Tirotricina; Piorlis†; Roberfarin; Viberol Tirotricina; ***Switz.***: Citropain nouvelle formule; Gem nouvelle formule contre le mal de gorge; Impuls†; Lemocin; Mebu; Mebucaine; Mebucasol f†; Otothricinol; Rotpunkt Apotheke nouvelle formule pastilles contre le mal de gorge†; Sangerol; Solmucaine; Swidro nouvelle formule pastilles contre le mal de gorge†; Tyroqualine; Tyrothricin†; Tyrothricine + Gramicidine†; Zurcher Bahnhof Apotheke pastilles contre le mal de gorge nouvelle formule†; ***Thai.***: Deq; Iwazin; Jawkepta; Sigatricin†; Tonsilon; Trocacin; Troneo; ***Turk.***: Neolet; ***UAE***: B-Cool; ***UK***: Tyrozets; ***Ukr.***: Anginovag (Ангиноваг); Trachisan (Трахисан); ***Venez.***: Otan.

Valnemulin *(BAN, rINN)*

Valnemuliini; Valnemulina; Valnémuline; Valnemulinum; Вальнемулин.

({2-[(*R*)-2-Amino-3-methylbutyramido]-1,1-dimethylethyl}thio)acetic acid 8-ester with (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one.

$C_{31}H_{52}N_2O_5S$=564.8

CAS — 101312-92-9 (valnemulin); 133868-46-9 (valnemulin hydrochloride).
ATC Vet — QJ01XQ02.
UNII — 2AHC415BQG.

Pharmacopoeias. *Eur.* (see p. vii) includes the hydrochloride for veterinary use.

Profile

Valnemulin is an antibacterial used as the hydrochloride in veterinary medicine.

Vancomycin *(BAN, rINN)*

Vancomicina; Vancomycine; Vancomycinum; Vankomycin; Vankomysiini; Ванкомицин.

(S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-{[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid.

$C_{66}H_{75}Cl_2N_9O_{24}$=1449.3

CAS — 1404-90-6.
ATC — A07AA09; J01XA01.
ATC Vet — QA07AA09; QJ01XA01.
UNII — 6Q205EH1VU.

Description. A glycopeptide antimicrobial substance or mixture of glycopeptides produced by the growth of certain strains of *Amycolatopsis orientalis* (*Nocardia orientalis*, *Streptomyces orientalis*), or by any other means.

Pharmacopoeias. In *US.*

USP 36: (Vancomycin). Store in airtight containers.

Vancomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de vancomicina; Vancomicina, hidrocloruro de; Vancomycine, Chlorhydrate de; Vancomycinhydrochlorid; Vancomycin-hydrochlorid; Vancomycini Hydrochloridum; Vankomicinhidroklorid; Vankomicino hidrochloridas; Vankomisin Hidroklorür; Vankomycinhydroklorid; Vankomysiinihydrokloridi; Wankomycyny chlorowodorek; Ванкомицина Гидрохлорид.

$C_{66}H_{75}Cl_2N_9O_{24}$.HCl=1485.7

CAS — 1404-93-9.
ATC — A07AA09; J01XA01.
ATC Vet — QA07AA09; QJ01XA01.
UNII — 71WO621TJD.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Vancomycin Hydrochloride). A mixture of related glycopeptides, consisting mainly of vancomycin B, a substance produced by certain strains of *Amycolatopsis orientalis* or obtained by any other means. A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Vancomycin Hydrochloride). A substance or mixture of substances produced by the growth of *Streptomyces orientalis*. A white, almost white, or tan to brown, odourless, free-flowing powder. Freely soluble in water; insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers.

Incompatibility. Solutions of vancomycin hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Reports of incompatibility are not always consistent, and other factors such as the composition of the vehicles used may play a part.

Strength of solution may also be important; evidence of physical incompatibility was seen in solutions containing citrate 4% and vancomycin 20 mg/mL (as may be used in catheter lock solutions), but when the concentration of vancomycin was reduced to either 10 mg/mL or 5 mg/mL, no evidence of incompatibility was seen.[1]

1. Dotson B, *et al.* Physical compatibility of 4% sodium citrate with selected antimicrobial agents. *Am J Health-Syst Pharm* 2010; **67:** 1195–8.

Stability. Although licensed product information recommends storage at 2 degrees to 8 degrees, solutions of vancomycin hydrochloride in various diluents (sodium chloride 0.9%, glucose 5%, and peritoneal dialysis solution) have been found to be stable for at least 14 days at room temperature.[1-3]

The stability of vancomycin in ophthalmic solution has also been studied.[4]

1. Das Gupta V, *et al.* Stability of vancomycin hydrochloride in 5% dextrose and 0.9% sodium chloride injections. *Am J Hosp Pharm* 1986; **43:** 1729–31.
2. Walker SE, Birkhans B. Stability o f intravenous vancomycin. *Can J Hosp Pharm* 1988; **41:** 233–8.
3. Mauhinuey WM, *et al.* Stability of vancomycin hydrochloride in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; **49:** 137–9.
4. Fuhrman LC, Stroman RT. Stability of vancomycin in an extemporaneously compounded ophthalmic solution. *Am J Health-Syst Pharm* 1998; **55:** 1386–8.

Uses and Administration

Vancomycin is a glycopeptide antibacterial that is used intravenously in the treatment and prophylaxis of serious staphylococcal or other susceptible Gram-positive infections, traditionally when other drugs cannot be used because of resistance or patient intolerance. It is used particularly in the treatment of MRSA infections (p. 208.2). It may also be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax, and orally in the treatment of antibiotic-associated colitis. For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Vancomycin may be used with other antibacterials to extend or increase efficacy notably with gentamicin or other aminoglycosides, or with rifampicin (but see Antimicrobial Action, p. 389.1).

Administration and dosage. Vancomycin is given as the hydrochloride but doses are expressed in terms of the base. 1.03 g of vancomycin hydrochloride is equivalent to about 1 g of vancomycin. It is given intravenously, preferably by intermittent infusion, although continuous infusion has been used. For intermittent infusion, a concentrated solution containing the equivalent of 500 mg of vancomycin in 10 mL of water is prepared and then added to glucose 5% or sodium chloride 0.9% to produce a diluted solution containing not more than 5 mg/mL; this diluted solution is then infused over at least 60 minutes for a 500-mg dose or 100 minutes for a 1-g dose. Final concentrations of up to 10 mg/mL may be used for patients requiring fluid restriction, although there is an increased risk of adverse events. For continuous intravenous infusion when intermittent infusion is not feasible, the equivalent of 1 to 2 g is added to a sufficiently large volume of glucose or sodium chloride to permit the daily dose to be given over a period of 24 hours.

The usual adult dose is the equivalent of 500 mg of vancomycin every 6 hours or 1 g every 12 hours (but see also Administration, p. 387.1). Response is generally seen within 48 to 72 hours in sensitive infections. In patients with staphylococcal endocarditis, treatment for at least 3 weeks has been recommended.

Where vancomycin is required for surgical infection prophylaxis, a single 1-g dose given by intravenous infusion is recommended by the *BNF*.

For doses in children and neonates, see p. 387.2.

Dose adjustment and monitoring. It has been recommended that dosage should be adjusted if necessary according to plasma-vancomycin concentrations, and this is particularly important where factors such as age or renal impairment (see also p. 388.1) may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. There has been some dispute about the relationship between plasma concentrations and toxicity, and this, complicated by differences in the sampling time after the end of infusion and by differences in the regimens and assay method used, has meant that suggested peak and trough concentrations have varied considerably (see Precautions, p. 388.3).

Other routes. Vancomycin hydrochloride is given orally in the treatment of staphylococcal enterocolitis and antibiotic-associated colitis, including pseudomembranous colitis associated with the overgrowth of *Clostridium difficile*. It is given in a dose of 0.5 to 2 g daily in 3 or 4 divided doses for 7 to 14 days; the lowest dose of 500 mg daily is often considered adequate.

In meningitis or other CNS infections, vancomycin has sometimes been given by the intrathecal or intraventricular route in order to ensure adequate CSF concentrations of antibiotic. Vancomycin has also been applied topically to the eye or given by subconjunctival or intravitreal injection; it has also been given by inhalation. Vancomycin has been added to dialysis solutions in the treatment of peritonitis associated with continuous ambulatory peritoneal dialysis.

General references.

1. Stevens DL. The role of vancomycin in the treatment paradigm. *Clin Infect Dis* 2006; **42** (suppl 1): S51–S57.
2. Deresinski S. Vancomycin: does it still have a role as an antistaphylococcal agent? *Expert Rev Anti Infect Ther* 2007; **5:** 393–401.
3. Cunha BA. Vancomycin revisited: a reappraisal of clinical use. *Crit Care Clin* 2008; **24:** 393–420.
4. Levine DP. Vancomycin: understanding its past and preserving its future. *South Med J* 2008; **101:** 284–91.
5. Niu SC, *et al.* Modified vancomycin dosing protocol for treatment of diabetic foot infections. *Am J Health-Syst Pharm* 2008; **65:** 1740–3.

Administration. A consensus review[1] considered that, for most patients with normal renal function, doses of 15 to 20 mg/kg (based on actual body-weight) given every 8 to 12 hours will be necessary for adequate serum-vancomycin trough concentrations. For seriously ill patients an initial loading dose of 25 to 30 mg/kg can be considered so that optimal serum-vancomycin trough concentrations will occur more quickly. For patients infected with strains having an MIC of 2 micrograms/mL or more this was not likely to be adequate, and alternative therapies should be considered. Trough concentrations should always be maintained above 10 micrograms/mL to avoid the development of resistance in *Staph. aureus*. When individual doses exceed 1 g the infusion period should be extended to 1.5 to 2 hours.

Weight-based dosing is particularly important for obese patients. A multicentre study in patients of various bodyweights indicated that although fixed doses of vancomycin 1 g twice daily achieved satisfactory initial dosing (determined as 10 mg/kg or more per dose) in underweight, normal, and overweight patients, only about 28% of obese patients could be considered to be adequately dosed.[2] If more stringent dose limits of at least 15 mg/kg per dose were used as recommended in several guidelines, less than 1% of obese patients were given adequate initial doses, and this was rarely corrected in the subsequent 24 hours. It has therefore been recommended[1] that initial doses for all patients, including the obese, should be calculated based on absolute body-weight, and then adjusted based on serum-vancomycin concentrations.

1. Rybak M, *et al*. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2009; **66:** 82–98. Correction. *ibid.*; 887. Also available at: http://www.ajhp.org/cgi/reprint/66/1/82 (accessed 12/11/10)
2. Hall RG, *et al*. Multicenter evaluation of vancomycin dosing: emphasis on obesity. *Am J Med* 2008; **121:** 515–18.

Administration in children. Vancomycin is licensed for use in children. In children and infants over 1 month of age, an *intravenous* dose of 10 mg/kg four times a day or 15 mg/kg three times a day, up to the usual adult maximum of 1 to 2 g daily, may be given for mild to moderate infections; for severe infections, the daily dose may be increased to 60 mg/kg daily up to a maximum of 2 to 4 g daily.

In neonates, various dosage schedules have been suggested. UK licensed product information states that neonates up to 1 month old may be given an initial intravenous dose of 15 mg/kg; this is followed by 10 mg/kg every 12 hours in the first week of life or by 10 mg/kg every 8 hours in those aged 1 week to 1 month. The *BNFC* recommends the following intravenous doses for neonates:

- less than 29 weeks postmenstrual age: 15 mg/kg every 24 hours
- 29 to 35 weeks postmenstrual age: 15 mg/kg every 12 hours
- over 35 weeks postmenstrual age: 15 mg/kg every 8 hours

In the USA, the American Academy of Pediatrics[1] suggests that intravenous doses for neonates are based are on serum-creatinine concentrations as follows:

- serum-creatinine concentrations < 0.7 mg/dL: 15 mg/kg every 12 hours
- serum-creatinine concentrations 0.7 to 0.9 mg/dL: 20 mg/kg every 24 hours
- serum-creatinine concentrations 1 to 1.2 mg/dL: 15 mg/kg every 24 hours
- serum-creatinine concentrations 1.3 to 1.6 mg/dL: 10 mg/kg every 24 hours
- serum-creatinine concentrations > 1.6 mg/dL: 15 mg/kg every 48 hours

Note. For neonates with a gestation of 28 weeks or less, a value of 0.2 is added to the measured serum-creatinine concentration when the algorithm is used.

One group of workers,[2] found that continuous infusion of vancomycin in premature neonates could achieve the required therapeutic range in most cases and had produced good bacteriological efficacy. The regimen they proposed for the first 48 hours was 20 mg/kg daily in premature neonates with a serum-creatinine concentration of more than 90 micromol/litre and 30 mg/kg daily in those with a serum-creatinine concentration of 90 micromol/litre or less. Thereafter the dosage was increased or decreased if necessary by 5 mg/kg daily to maintain serum-vancomycin concentrations between 10 and 25 micrograms/mL.

Vancomycin may also be given *orally* to treat staphylococcal enterocolitis and antibiotic-associated colitis. A suggested dose for children in licensed product information is 40 mg/kg daily in 3 or 4 divided doses; the *BNFC* suggests the following doses given four times daily, usually for 10 to 14 days:

- 1 month up to 5 years: 5 mg/kg
- 5 to 12 years: 62.5 mg
- over 12 years: 125 mg

Higher oral doses may be considered if the infection is life-threatening or fails to respond to treatment.

Review[3] of the use of vancomycin in neonates.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Plan O, *et al*. Continuous-infusion vancomycin therapy for preterm neonates with suspected or documented Gram-positive infections: a new dosage schedule. *Arch Dis Child Fetal Neonatal Ed* 2008; **93:** F418–21.
3. de Hoog M, *et al*. Vancomycin: pharmacokinetics and administration regimens in neonates. *Clin Pharmacokinet* 2004; **43:** 417–40.

Administration in renal impairment. Various methods, including predictive nomograms based on creatinine clearance and pharmacokinetic methods such as those using Bayesian statistics, have been suggested for calculating vancomycin dosage requirements in patients with reduced renal function. One suggested approach has been a loading dose of 15 mg/kg followed by a daily dose in mg equivalent to about 15 times the glomerular filtration rate in mL/minute; or in anuric patients a dose of 1 g every 7 to 10 days. However, individualised dosage based on plasma concentrations is generally to be preferred.

Vancomycin is significantly dialysable via high-flux intermittent haemodialysis and it has been suggested that once-weekly vancomycin dosing in this setting will result in inadequate trough concentrations. A review[1] of antimicrobial dosing in renal replacement therapy has recommended that patients on intermittent haemodialysis should receive a loading dose of 15 to 25 mg/kg intravenously on day 1, followed by a 5 to 10 mg/kg maintenance dose after each dialysis run; dose adjustments should be made based on both the targeted, and reported serum-vancomycin concentrations.

For critically ill patients undergoing continuous renal replacement therapy, the same loading dose is recommended; maintenance doses (which should be adjusted based on serum-vancomycin concentration) are as follows:[1]

- continuous venovenous haemofiltration (CVVH): 10 to 15 mg/kg every 24 to 48 hours
- continuous venovenous haemodialysis (CVVHD): 10 to 15 mg/kg every 24 hours (7.5 mg/kg every 12 hours may be required when higher serum-vancomycin concentrations are needed)
- continuous venovenous haemodiafiltration (CVVHDF): 7.5 to 10 mg/kg every 12 hours

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Adverse Effects

The intravenous use of vancomycin may be associated with the so-called 'red-neck' or 'red-man' syndrome, characterised by erythema, flushing, or rash over the face and upper torso, and sometimes by hypotension and shock-like symptoms. The effect appears to be due in part to the release of histamine and is usually related to rapid infusion.

Hypersensitivity reactions may occur in about 5% of patients and include rashes, fever, chills, and rarely, anaphylactoid reactions, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) has also been reported. Many reactions have become less frequent with the availability of more highly purified preparations. Reversible neutropenia, eosinophilia, and rarely thrombocytopenia and agranulocytosis have been reported; neutropenia is stated to be more common in patients who have received a total dose of 25 g or more. Nephrotoxicity, including rare cases of interstitial nephritis, may occur, particularly at high doses or in patients with predisposing factors, but has declined in frequency with greater awareness of the problem and appropriate monitoring of plasma concentrations and renal function.

Ototoxicity is also associated with vancomycin, and is more likely in patients with high plasma concentrations, or with renal impairment or pre-existing hearing loss. It may progress after drug withdrawal, and may be irreversible. Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.

Vancomycin is irritant; intravenous use may be associated with thrombophlebitis, although this can be minimised by the slow infusion of dilute solutions, and by using different infusion sites. Extravasation may cause tissue necrosis.

Because of its poor absorption, relatively few adverse effects have been reported after the oral use of vancomycin, although mild gastrointestinal disturbances have occurred.

Effects on the ears. Reviews[1,2] of ototoxicity associated with vancomycin therapy have indicated that the actual number of cases is quite small, and close examination suggests that in most cases where hearing loss occurred patients had also received an aminoglycoside. The degree, and the reversibility, of ototoxicity associated with vancomycin alone is uncertain.

1. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity: a review. *Med Toxicol* 1988; **3:** 376–86.
2. Brummett RE, Fox KE. Vancomycin- and erythromycin-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33:** 791–6.

Effects on the gastrointestinal tract. Exposure to antibacterials, particularly broad-spectrum antibacterials, is the most significant risk factor for development of antibiotic-associated colitis (AAC). Antibacterials usually used to treat the disease such as vancomycin and metronidazole have also been shown to cause AAC. A 25-year-old woman developed AAC after a course of vancomycin and metronidazole, both orally, for pelvic inflammatory disease.[1] The condition resolved after treatment with vancomycin given alone. In another case,[2] *C. difficile* colitis developed after the use of intravenous vancomycin in a patient who had recently had other antibacterial treatment. For further reports on AAC caused by metronidazole see under Metronidazole, p. 940.1.

1. Bingley PJ, Harding GM. Clostridium difficile colitis following treatment with metronidazole and vancomycin. *Postgrad Med J* 1987; **63:** 993–4.
2. Szczesny A, *et al*. Incidence of pseudomembranous colitis after vancomycin-treated MRSA infection. *Clin Microbiol Infect* 2002; **8:** 58–9.

Effects on the heart. Cardiac arrest associated with an inadvertent rapid intravenous dose of vancomycin 150 mg has been reported[1] in a neonate.

1. Boussemart T, *et al*. Cardiac arrest associated with vancomycin in a neonate. *Arch Dis Child* 1995; **73:** F123.

Effects on the kidneys. In a study,[1] nephrotoxicity was seen in 14 of 101 patients given vancomycin 1 g before and after vascular surgery for infection prophylaxis compared with 2 of 99 given saline placebo, suggesting that even short regimens of vancomycin can affect renal function. In another study involving 224 patients, nephrotoxicity was seen in 8 of 168 given vancomycin alone, 14 of 63 given vancomycin with an aminoglycoside, and 11 of 103 given an aminoglycoside without vancomycin.[2] This latter study found that use with aminoglycosides, trough serum concentrations of vancomycin greater than 10 micrograms/mL, and prolonged vancomycin therapy (for more than 21 days) were associated with an increased risk of nephrotoxicity. A later retrospective study[3] suggested that a relationship between exposure and nephrotoxicity existed, and that the most useful measure of the former was trough concentration of vancomycin. (In these studies nephrotoxicity was defined in terms of increased serum creatinine.) The use of high-dose vancomycin, in an effort to overcome resistance in meticillin-resistant staphylococci, has therefore led to concerns that aggressive dosing may increase the risk of nephrotoxicity; however, a review[4] has pointed out that the risk of nephrotoxicity with the drug remains minimal in patients without other risk factors.

1. Gudmundsson GH, Jensen LJ. Vancomycin and nephrotoxicity. *Lancet* 1989; **i:** 625.
2. Rybak MJ, *et al*. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; **25:** 679–87.
3. Lodise TP, *et al*. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis* 2009; **49:** 507–14.
4. Hazlewood KA, *et al*. Vancomycin-associated nephrotoxicity: grave concern or death by character assassination? *Am J Med* 2010; **123:** 182.e1–e7.

Effects on the liver. A 57-year-old man with multiple medical conditions developed raised liver enzyme values, on 5 different occasions, while being treated with oral vancomycin for episodes of *Clostridium difficile*-associated enterocolitis; liver enzymes returned to normal values each time the vancomycin was stopped.[1]

1. Cadle RM, *et al*. Vancomycin-induced elevation of liver enzyme levels. *Ann Pharmacother* 2006; **40:** 1186–9.

Effects on the nervous system. Encephalopathy[1] (associated with high CSF concentrations after oral doses) and peripheral neuropathy[2] has been associated with vancomycin.

1. Thompson CM, *et al*. Absorption of oral vancomycin—possible associated toxicity. *Int J Pediatr Nephrol* 1983; **4:** 1–4.
2. Leibowitz G, *et al*. Mononeuritis multiplex associated with prolonged vancomycin treatment. *BMJ* 1990; **300:** 1344.

Effects on the skin. Rashes, erythema, or pruritus are the most common skin reactions associated with vancomycin but there have also been reports of linear IgA dermatosis,[1-4] Stevens-Johnson-like reaction,[5] bullous eruption,[6] local skin necrosis,[7] and exfoliative dermatitis.[6] In an analysis, risk factors for adverse cutaneous reactions were suggested to be age under 40 years and duration of therapy greater than 7 days.[6] See also under Hypersensitivity, p. 388.3.

1. Piketty C, *et al*. Linear IgA dermatosis related to vancomycin. *Br J Dermatol* 1994; **130:** 130–1.
2. Nousari HC, *et al*. Vancomycin-associated linear IgA bullous dermatosis. *Ann Intern Med* 1998; **129:** 507–8.

3. Bernstein EF, Schuster M. Linear IgA bullous dermatosis associated with vancomycin. *Ann Intern Med* 1998; **129:** 508–9.
4. Danielsen AG, Thomsen K. Vancomycin-induced linear IgA bullous disease. *Br J Dermatol* 1999; **141:** 756–7.
5. Laurencin CT, *et al.* Stevens-Johnson-like reaction with vancomycin treatment. *Ann Pharmacother* 1992; **26:** 1520–1.
6. Korman TM, *et al.* Risk factors for adverse cutaneous reactions associated with intravenous vancomycin. *J Antimicrob Chemother* 1997; **39:** 371–81.
7. Hoelen DW, *et al.* Severe local vancomycin induced skin necrosis. *Br J Clin Pharmacol* 2007; **64:** 553–4.

Hypersensitivity. Skin reactions to vancomycin are common (see Effects on the Skin, p. 385.3), and may occur as part of a hypersensitivity reaction. The DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has been reported rarely,[1] in patients given vancomycin. In general, the onset of DRESS occurred within 2 to 5 weeks of starting treatment, and was associated with hepatitis (and sometimes nephritis and pneumonitis); all patients survived after immediate withdrawal of vancomycin and treatment with intravenous corticosteroids.

1. Vaubey L, *et al.* Vancomycin-induced DRESS syndrome in a female patient. *Pharmacology* 2008; **82:** 138–41.

Red-man syndrome. References[1-3] to the 'red-man syndrome', and evidence that pretreatment with an antihistamine can provide significant protection against it.[4,5] Similar reactions appear to be much less of a problem with teicoplanin and substitution of teicoplanin for vancomycin may be a viable alternative in patients at risk.[2,3,6] Skin tests are reported[7] to be of little value in predicting the severity of 'red-man syndrome'.

1. Wallace MR, *et al.* Red man syndrome: incidence, etiology, and prophylaxis. *J Infect Dis* 1991; **164:** 1180–5.
2. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. *J Antimicrob Chemother* 1991; **27** (suppl B): 17–29.
3. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; **36:** 1204–7.
4. Renz CL, *et al.* Oral antihistamines reduce the side effects from rapid vancomycin infusion. *Anesth Analg* 1998; **87:** 681–5.
5. Renz CL, *et al.* Antihistamine prophylaxis permits rapid vancomycin infusion. *Crit Care Med* 1999; **27:** 1732–7.
6. Smith SR. Vancomycin and histamine release. *Lancet* 1990; **335:** 1341.
7. Polk RE, *et al.* Vancomycin skin tests and prediction of "red man syndrome" in healthy volunteers. *Antimicrob Agents Chemother* 1993; **37:** 2139–43.

AFTER ORAL ADMINISTRATION. Reports of rash[1] and 'red-man syndrome'[2,3] after oral vancomycin.

1. McCullough JM, *et al.* Oral vancomycin-induced rash: case report and review of the literature. *DICP Ann Pharmacother* 1991; **25:** 1326–8.
2. Killian AD, *et al.* Red man syndrome after oral vancomycin. *Ann Intern Med* 1991; **115:** 410–11.
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Precautions

Vancomycin should not be given again to patients who have had a hypersensitivity reaction to it. It should not be given intramuscularly, and care should be taken when it is given intravenously to avoid extravasation, because of the risk of tissue necrosis. The adverse effects of infusion may be minimised by dilution of each 500 mg of vancomycin in at least 100 mL of fluid, and by infusion of doses over not less than 60 minutes. Infusion sites should be changed regularly.

Because the risk of ototoxicity and nephrotoxicity is thought to be increased at high plasma concentrations it may be desirable to adjust dosage requirements according to plasma-vancomycin concentrations. However, uncertainty about the optimum methods and sampling times for monitoring, as well as some uncertainty about the degree of risk, means that there is less general agreement than for the aminoglycosides. UK licensed product information suggests that peak concentrations should be kept below 30 micrograms/mL and trough concentrations should not exceed 5 to 10 micrograms/mL, although the *BNF* suggests trough concentrations of 10 to 15 micrograms/mL, or 15 to 20 micrograms/mL when treating endocarditis or less susceptible strains of MRSA. It is generally agreed, however, that vancomycin should be avoided in patients with a history of impaired hearing and that particular care is necessary in patients with renal impairment, in neonates (especially if premature), and in the elderly, all of whom may be at increased risk of toxicity. Renal function and blood counts should be monitored regularly in all patients, and monitoring of auditory function is advisable, especially in high-risk patients. Vancomycin should be stopped in patients who develop tinnitus.

Since vancomycin is poorly absorbed, toxicity is much less of a problem after oral use than with the intravenous route, but care is required in patients with inflammatory gastrointestinal disorders, including antibiotic-associated colitis, in whom absorption may be enhanced.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vancomycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Interactions

Other ototoxic or nephrotoxic drugs, such as aminoglycosides, polymyxins, ciclosporin, cisplatin, and loop diuretics, are likely to increase the risk of toxicity and if they need to be given with vancomycin caution and appropriate monitoring are recommended.

Some of the adverse effects of vancomycin may be enhanced by the use of general anaesthetics; it has been suggested that, where patients require both, vancomycin infusions should be completed before the induction of anaesthesia.

Vancomycin may increase neuromuscular blockade produced by drugs such as suxamethonium or vecuronium.

Antimicrobial Action

Vancomycin is a glycopeptide antibacterial with a mainly bactericidal action against a variety of Gram-positive bacteria.

Mechanism of action. Vancomycin exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall. Unlike penicillins, which act mainly to prevent the cross-linking of peptidoglycans which gives the cell wall its strength, vancomycin prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself. Vancomycin may also exert some effects by damaging the cytoplasmic membrane of the protoplast, and by inhibiting bacterial RNA synthesis.

Spectrum of activity. Staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains), *Streptococcus pneumoniae*, *Str. pyogenes*, some strains of Group B streptococci, and the viridans streptococci are reported to be susceptible to vancomycin. Enterococci such as *Enterococcus faecalis*, are often 'tolerant', i.e. inhibition, but no bactericidal effect, can be achieved at usual plasma concentrations (but see Activity with other Antimicrobials and Resistance, below).

Clostridium difficile is usually highly susceptible as are most other clostridia. *Actinomyces* spp., *Bacillus anthracis*, *Corynebacterium* spp., some lactobacilli, and *Listeria* are usually susceptible. Virtually all Gram-negative organisms, as well as mycobacteria and fungi, are intrinsically resistant.

Activity with other antimicrobials. Vancomycin exhibits synergy with the aminoglycosides against enterococci; such combinations are usually bactericidal, even against vancomycin-tolerant strains. The synergistic effect is reported to be greater with gentamicin than with streptomycin. Combinations with an aminoglycoside are also reported to show synergy against *Staph. aureus*; however, variable results, including antimicrobial antagonism, or lack of synergy, have been reported against strains of *Staph. aureus* when vancomycin was combined with rifampicin. Synergy has been reported with the third-generation cephalosporins against *Staph. aureus* and enterococci.

Resistance to vancomycin in normally susceptible organisms has until recently remained relatively uncommon, although high-level intrinsic resistance has been seen in some species of *Lactobacillus*, *Leuconostoc*, and *Erysipelothrix*. However, there are an increasing number of reports of high-level acquired resistance amongst enterococci, apparently plasmid-mediated and transferable to other Gram-positive organisms, notably *Staph. aureus*, which are causing considerable concern (see p. 389.1).

Resistance to vancomycin among enterococci, possibly driven in part by the use of antibiotics as growth promotors for livestock (see under Avoparcin, p. 221.1) has been well established.[1,2] Six resistance patterns have been reported, known as VanA, VanB, VanC, VanD, VanE, and VanG. VanA strains are inducibly resistant to high concentrations of vancomycin and teicoplanin; VanB strains retain susceptibility to teicoplanin. VanC strains have constitutive resistance to low concentrations of vancomycin, but not teicoplanin. VanE and VanG strains acquire low level resistance to vancomycin but again, may retain some susceptibility to teicoplanin.[3] Many genes may produce resistance, but they generally do so by resulting in production of cell-wall peptidoglycans with variant end chains that have a reduced affinity for vancomycin.[3]

Enterococci are capable of transferring resistance genes to other bacteria. Because of the first-line role played by vancomycin in the management of infections due to MRSA there is particular concern about the emergence of vancomycin resistance among staphylococci. Strains of *Staph. aureus* with intermediate resistance to vancomycin and/or other glycopeptide antibacterials (VISA or GISA), now usually defined as an MIC of 4 to 8 micrograms/mL, have been reported from several countries,[3-8] and there have been some reports of high-level resistance (vancomycin-resistant *Staph. aureus*, VRSA; MIC greater than 16 micrograms/mL), thought to result from transferred VanA resistance.[9,10] The emergence of heteroresistant strains (hVISA, in which most of a population is susceptible but it contains subpopulations that have intermediate resistance) appears to be increasing, and is of some concern since it is likely to result in selection of more resistant organisms.[3,11]

Guidelines have been issued[12,13] in an attempt to reduce the spread of vancomycin resistance.

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Pharmacokinetics

Vancomycin is only poorly absorbed from the gastrointestinal tract, although absorption may be somewhat greater when the gastrointestinal tract is inflamed. Infusion of a 1-g dose intravenously over 60 minutes has reportedly been associated with plasma concentrations of up to about 60 micrograms/mL immediately after completion of the infusion, and about 25 micrograms/mL 2 hours later, falling to under 10 micrograms/mL after 11 hours. However, there may be considerable interindividual variation in the pharmacokinetics of vancomycin: a range of half-lives between 3 and 13 hours has been reported, with an average of about 6 hours, in patients with normal renal function. Half-life may be prolonged in patients with renal impairment, to 7 days or more in anephric patients. About 55% is bound to plasma proteins, although large variations have been reported.

Vancomycin diffuses into extracellular fluid, including pleural, pericardial, ascitic, and synovial fluid. Small amounts are found in bile. Vancomycin concentration in lung tissue is relatively low, accounting for 20 to 30% of serum concentration. There is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved. Vancomycin crosses the peritoneal cavity; about 60% of an intraperitoneal dose is reported to be absorbed in 6 hours. It is reported to cross the placenta. It is also distributed into breast milk.

Little or no metabolism of vancomycin is thought to take place. It is excreted unchanged by the kidneys, mostly by glomerular filtration. Some 80 to 90% of the dose is excreted in urine within 24 hours. There appears to be a small amount of non-renal clearance, although the mechanism for this has not been determined.

The pharmacokinetics of vancomycin may be altered by conditions which affect renal clearance: clearance of vancomycin has been reported to be enhanced in burn patients, whereas in those with renal impairment, or reduced renal function (such as neonates or the elderly), clearance is reduced and plasma-concentrations and half-lives increased. Dosage adjustment is often necessary in patients with reduced or impaired renal function; ideally, this should be based on plasma-concentration monitoring. Although clearance is also altered in hepatic impairment, it has been suggested that dosage adjustment is not necessary in the absence of other factors.

Plasma concentrations of vancomycin are reported to be little affected by conventional haemodialysis, although the use of high-flux membranes may significantly reduce vancomycin concentrations. Peritoneal dialysis, although it may decrease concentrations, is also thought not to do so by significant amounts, but haemoperfusion or haemofiltration effectively removes vancomycin from the blood.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fabomicina†; Icoplax; Rivervan; Vancomax; Vancotenk; Varedet; ***Austral.***: Vancocin; ***Austria***: Vancocin; ***Belg.***: Vamysin; Vancocin; ***Braz.***: Amplobac†; Vanclomin; Vancoabbott; Vancocina; Vancoson; Vancotrat; ***Canad.***: Val-Vanco†; Vancocin; ***Chile***: Kovan; ***China***: Laikexin (来可信); Vancocin (稳可信); Vanconal (万君雅); Vancorin (方刻林); ***Cz.***: Edicin; Vancocin; ***Denm.***: Vancocin; ***Fin.***: Vancosan; ***Ger.***: Vanco-ratiopharm; Vanco-saar; Vanco; ***Gr.***: Rulvon; Vamistol; Vancosan; Voncon; Vondem; Voxin; ***Hong Kong***: Lyphocin; Vancocin†; ***Hung.***: Vancocin; ***India***: Covancin; Cytovan; Forstaf; Vancocin; Vancogram; Vanlid; ***Indon.***: Vancep; ***Irl.***: Vancocin; ***Israel***: Vanco-Teva; ***Ital.***: Copovan; Farmaciclin; Levovanox; Maxivanil; Vancocina; Vancotex; Zengac; ***Malaysia***: Vancotex; ***Mex.***: Estavam; Ifavac†; Vacsol; Vanaurus; Vancocin; Vancox; ***Neth.***: Norimko; Vancocin; ***Philipp.***: Kavocil; Vakocil†; Vancin; Vancocin; Vancomet; Vanosyn; ***Pol.***: Acviscin; Edicin; Vancocin†; Vancotex; ***Port.***: Glipep†; ***Rus.***: Edicin (Эдицин); Vancocin (Ванкоцин); Vancomabol (Ванкомабол); Vancorus (Ванкорус); ***S.Afr.***: Vancocin; ***Singapore***: Dhacocin; ***Swed.***: Vancocin; ***Switz.***: Vancocin; ***Thai.***: Edicin; Vancin-S; Vancogen; ***Turk.***: Edicin; Vancocin; Vancorin; Vancotek; ***UAE***: Vancolon; ***UK***: Vancocin; ***Ukr.***: Edicin (Эдицин); Tancofeto (Танкофето); Vancogen (Ванкоген)†; ***USA***: Lyphocin; Vancocin; Vancoled†; ***Venez.***: Vagran.

Multi-ingredient Preparations. ***India***: Cefirone-V.

Pharmacopoeial Preparations

BP 2014: Vancomycin Capsules; Vancomycin Infusion; Vancomycin Oral Solution;

USP 36: Vancomycin Hydrochloride Capsules; Vancomycin Hydrochloride for Injection; Vancomycin Hydrochloride for Oral Solution; Vancomycin Injection.

Virginiamycin *(BAN, USAN, rINN)*

Antibiotic 899; SKF-7988; Virgimycin; Virginiamicina; Virginiamycine; Virginiamycinum; Виргиниамицин.

CAS — 11006-76-1; 21411-53-0 (virginiamycin M_1); 23152-29-6 (virginiamycin S_1).

ATC — D06AX10.

ATC Vet — QD06AX10; QJ01FG90.

UNII — C49WS9N75L.

Profile

Virginiamycin is a streptogramin antibacterial mixture consisting mainly of 2 antimicrobial substances, virginiamycin M_1, and virginiamycin S_1, produced by the growth of *Streptomyces virginiae*. It has been used for the treatment of infections due to sensitive organisms, particularly Gram-positive cocci. It has been given orally and applied locally. It may cause gastrointestinal disturbances including diarrhoea and vomiting. A few instances of hypersensitivity have been seen.

Virginiamycin has been used in animal feeding stuffs as a growth promotor.

Xibornol *(BAN, rINN)*

1BX; 1HP; CP3H; Xibornolum; Ксиборнол.

6-(Isoborn-2-yl)-3,4-xylenol; 6-[(1*R*,2*S*,4*S*)-Born-2-yl]-3,4-xylenol.

$C_{18}H_{26}O$=258.4

CAS — 38237-68-2; 13741-18-9.

ATC — J01XX02.

ATC Vet — QJ01XX02.

UNII — RQ12GMY0FZ.

Profile

Xibornol is an antibacterial that is reported to have a bacteriostatic action on Gram-positive organisms such as staphylococci and streptococci, as well as activity against *Haemophilus influenzae*. It has been given orally, as an oral spray, and rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Bornilene.

Antidementia Drugs

This chapter includes some drugs used or promoted in the management of dementia, including centrally acting anticholinesterases such as donepezil, galantamine, rivastigmine, and tacrine, the *N*-methyl-D-aspartate receptor antagonist memantine, and drugs considered to have nootropic properties, such as piracetam and idebenone.

Many other drugs have been tried in various forms of dementia (see p. 390.1) and are discussed elsewhere in *Martindale*.

Dementia

Dementia is a syndrome in which impairment of cortical or subcortical function leads to deterioration of cognitive processes or intellectual abilities including memory, judgement, language, communication, and abstract thinking. Unlike delirium there is no gross clouding of consciousness. There may be changes in personality and behaviour disturbances. Dementia is usually progressive, though not always irreversible, and loss of social and other skills often leads to complete dependence on others.

Although dementia is more prevalent in the elderly it is not an inevitable consequence of ageing. Dementia can result from many conditions including:

- *neurodegenerative diseases*: Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Lewy-body disease, multiple sclerosis, progressive supranuclear palsy
- *vascular diseases*: multiple cerebral infarcts, occlusion of carotid artery, cranial arteritis
- *trauma*: subdural haematoma
- *neoplasms*
- *CNS infections*: encephalitis, syphilis, toxoplasmosis, AIDS, Creutzfeldt-Jakob disease
- *endocrine/metabolic disorders*: hypothyroidism, uraemia, hepatic failure, cardiac failure, respiratory failure, hypoxia, hyponatraemia
- *toxic insults*: alcohol, solvents, heavy metals, drug therapy
- *hydrocephalus*
- *nutritional deficiency*: vitamin B_{12}, folic acid, thiamine
- *depression*
- *sleep disorders*: obstructive sleep apnoea, narcolepsy

Alzheimer's disease is the most common cause of dementia and accounts for over half of all patients; about one-third of dementia cases are due to vascular disease.

Treatment of dementia can be broadly divided into control of disturbed behaviour (p. 1030.2) and attempts to improve or preserve cognitive function (see below). Although many drugs have been tried in the management of cognitive impairment most have produced little or no benefit.

Alzheimer's disease is a progressive degenerative condition affecting mainly patients over 65 years of age. The rare early-onset form of Alzheimer's disease (familial Alzheimer's disease) has been referred to as pre-senile dementia. Death usually occurs within 10 years of onset.[1] Apart from age other risk factors include Down's syndrome and a family history of Alzheimer's disease.[1-3] Presence of the ε4 allele of apolipoprotein E is another risk factor; it correlates with prevalence and age of onset in some forms of Alzheimer's disease but use for routine clinical or predictive testing is not recommended.[2,4-6] Elevated levels of plasma homocysteine have been linked with the development of dementia and Alzheimer's disease.[7] Cardiovascular risk factors such as diabetes, hypercholesterolaemia, hypertension, and obesity have also been associated with an increased risk.[2,8] Dialysis dementia, an irreversible condition which has occurred in dialysis patients, has been associated with excess aluminium in the dialysing fluid but the role of aluminium in Alzheimer's disease, if any, is unclear.[4]

Deficiencies in numerous neurotransmitters have been found in patients with Alzheimer's disease but reduced choline acetyltransferase activity leading to reduced synthesis of acetylcholine remains the most consistent defect correlating with the severity of the condition.[9-12] Attempts to increase acetylcholine concentrations in the brain have included use of *cholinesterase inhibitors*, *acetylcholine precursors*, *enhancers of acetylcholine release*, and *cholinergic agonists*. However, none replace lost cholinergic neurones and therefore none affect overall progression of the disease.

Donepezil, galantamine, and rivastigmine are the main *cholinesterase inhibitors*.[3,5,6,8,11-20] All have produced modest improvement in cognition and global clinical impression in patients with mild to moderately severe disease. However, there is a lack of long-term studies and little evidence of their effectiveness in advanced disease although donepezil is licensed for the treatment of severe dementia in many countries. A systematic review found no evidence of any difference between these 3 drugs with regard to efficacy although there appeared to be fewer adverse effects associated with donepezil compared with rivastigmine.[21] In the UK, NICE[22] states that donepezil, galantamine, and rivastigmine may be used in patients with mild to moderate dementia if given under the following conditions:

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Tacrine was formerly used but is often poorly tolerated and may cause serious hepatotoxicity. Other cholinesterase inhibitors that have been tried in Alzheimer's disease include metrifonate and physostigmine.

Treatments using *precursors of acetylcholine* such as lecithin or choline alone are not generally considered to produce useful improvements,[10-12] although it has been suggested that choline alfoscerate may be of some benefit.

Fampridine, which *enhances acetylcholine release from nerve terminals* has also been tried in Alzheimer's disease but there is little evidence of clinical benefit.

Limited improvement has been reported with some *cholinergic agonists* and pilocarpine may even exacerbate the dementia. Muscarinic M_1 agonists such as cevimeline and xanomeline have been investigated[12,23] on the basis that muscarinic M_1 receptors appear to be preserved throughout the course of Alzheimer's disease. However, these drugs have not been successful in improving symptoms of the disease. An alternative line of investigation has been the *stimulation of nicotinic receptors* using nicotine.[12]

The *N-methyl-D-aspartate (NMDA) receptor antagonist* memantine has shown some benefit in various dementias[3,6,8,14,19,20,24,25] and is recommended in the treatment of moderate to severe Alzheimer's disease.[6,22] In the UK, NICE[22] recommends that in moderate disease memantine is used only in patients who cannot take acetylcholine esterase inhibitors. It is thought to act through modulation of the effects of the neurotransmitter glutamate.

A hypothesis that free radicals may initiate and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease has prompted the investigation of drugs such as vitamin E (e.g. α-tocopherol), ginkgo biloba, idebenone, and selegiline for *antoxidant* therapy but their value remains to be confirmed.[6,10,15,24,26] Although some older US guidelines[12] have suggested consideration of vitamin E supplementation in an attempt to slow progression of the disease, more recent US[27] and European guidelines[6] do not recommend it for the treatment of cognitive symptoms because of limited evidence of efficacy as well as safety concerns. Selegiline has produced mixed results in a large number of controlled studies and US guidelines[27] note that few clinicians actually use the drug in clinical practice. A systematic review[28] has found no convincing evidence that ginkgo biloba is effective in the treatment of dementia or cognitive impairment; its use is not recommended in European guidelines.[6]

Neurotropic or *nootropic drugs* such as piracetam are considered to enhance memory and cognition. They have been tried in preventing cognitive deficits associated with Alzheimer's disease and other dementias but there is little convincing evidence of clinical usefulness.[6,12]

Many drugs with *vasodilator activity* were originally tried in dementia when it was believed that the condition was due to 'cerebrovascular insufficiency' (p. 1269.2), but overall there was little convincing evidence of benefit.[29] Ergot derivatives such as codergocrine mesilate and nicergoline have been the most commonly used; however, any effectiveness is now attributed to their action as metabolic enhancers or nootropic drugs and their place in therapy has still to be established.[30]

The *calcium-channel blocker* nimodipine has been of benefit in dementia of various aetiologies but its role in therapy remains unclear.[25,30]

Observations have suggested that *oestrogens* may reduce the risk and delay the onset of Alzheimer's disease in postmenopausal women receiving HRT.[3,5,6,12] However, a large controlled study found that combined HRT increased the risk of substantial decline in global cognitive function, did not prevent the development of mild cognitive impairment, and doubled the risk of dementia. A beneficial effect of oestrogens on cognitive function in postmenopausal women who already have mild or moderate Alzheimer's disease has not been shown in controlled studies (see p. 2244.3).

Some retrospective studies also indicate an inverse association between the use of *anti-inflammatory drugs* such as NSAIDs and the risk of developing Alzheimer's disease.[6,12,14] However, there is currently insufficient evidence to support the use of NSAIDs in the treatment of Alzheimer's disease.[3,6,8,14,31]

The possibility of an association between *statin* therapy and a reduced risk of developing dementia has also been mooted. However, a systematic review[32] concluded that there was good evidence that statins given in later life have no effect in preventing Alzheimer's disease and dementia, and that they should not be prescribed to that end.

Other drugs under investigation for Alzheimer's disease include latrepirdine dihydrochloride, an antihistamine that is reported to also have neuroprotective effects, and methylthioninium chloride, which is thought to dissolve and prevent the aggregation of tau protein filaments in the brain. It is hoped that these and other immune-based therapies in development will have disease-modifying effects.[33] A vaccine for Alzheimer's disease is being investigated.[8,14,27]

A less marked degree of impaired memory, without dementia, is seen in some patients. Many, but not all, patients with such **mild cognitive impairment** (MCI) go on to develop Alzheimer's disease, and there has been considerable interest in treating them, in the hope of retarding progression to the more severe condition.[20,34,35] However, appropriate strategies for management are unclear: although treatment with cholinesterase inhibitors, antoxidants, and other drugs used for Alzheimer's disease has been investigated, there has been some concern about a possibly increased risk of death in patients with MCI treated with galantamine (see Effects on the Cardiovascular and Cerebrovascular Systems, p. 394.2). In the UK, NICE[36] does not recommend the use of cholinesterase inhibitors in patients with MCI.

Vascular dementia[25,37-39] is a syndrome produced by ischaemic, hypoxic, or haemorrhagic brain lesions. Vessel occlusion is the most common cause of vascular dementia and produces a variety of cognitive deficits depending on the site of ischaemia. Among the major forms of dementia recognised are those due to multiple infarcts, single strategic infarcts, and subcortical white matter ischaemia (Binswanger's disease). Vascular dementia has a more acute onset than dementia due to Alzheimer's disease and in contrast to the continuous progression of Alzheimer's disease often has a stepwise progression. Risk factors for vascular dementia parallel those for stroke (p. 1269.2) and similar methods for prevention and treatment may be of use but there is a lack of evidence from adequately controlled trials. Cholinergic deficits are well documented in patients with vascular dementia; cholinesterase inhibitors such as *donepezil* and *galantamine* have been found to be well tolerated and effective in these patients. Positive results have also been seen with the NMDA receptor antagonist *memantine*.[25,39] However, in the UK, NICE[36] does not recommend the use of cholinesterase inhibitors or memantine for cognitive decline in vascular dementia.

Lewy-body dementia[37,40-42] is distinguished from other types of dementia by a state of fluctuating cognitive impairment and confusion; hallucinations, paranoid delusions, a tendency to fall for no apparent reason, and transient clouding or loss of consciousness are also characteristic symptoms. In addition, mild extrapyramidal symptoms may be present and there is increased susceptibility to the extrapyramidal adverse effects of antipsychotics (see the Elderly, under Precautions of Chlorpromazine on p. 1051.1). Severe cholinergic deficits in patients with Lewy-body dementia have prompted treatment with cholinesterase inhibitors. *Donepezil* and *rivastigmine* have been shown to be well tolerated and effective, but further studies are needed to establish their role.

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41. Swanberg MM, Cummings JL. Benefit-risk considerations in the treatment of dementia with Lewybodies. *Drug Safety* 2002; **25:** 511–23.
42. McKeith IG, *et al*. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; **65:** 1863–72.

Aniracetam *(USAN, rINN)*

Aniracétam; Aniracetamum; Ro-13-5057; Анирацетам.

1-(4-Methoxybenzoyl)-2-pyrrolidinone.

$C_{12}H_{13}NO_3$=219.2

CAS — 72432-10-1.

ATC — N06BX11.

ATC Vet — QN06BX11.

UNII — 5L16LKN964.

Profile

Aniracetam is a nootropic drug that has been tried in senile dementia (p. 388.1). It is given orally in usual doses of 1.5 g daily.

References.

1. Lee CR, Benfield P. Aniracetam: an overview of its pharmacodynamic and pharmacokinetic properties, and a review of its therapeutic potential in senile cognitive disorders. *Drugs Aging* 1994; **4:** 257–73.
2. Nakamura K. Aniracetam: its novel therapeutic potential in cerebral dysfunctional disorders based on recent pharmacological discoveries. *CNS Drug Rev* 2002; **8:** 70–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aniran; Pergamid; ***China***: Bi Si Ling (毕思灵); Bo Bang Lin (博邦邻); San Le Xi (三乐喜); Shuntan (顺坦); Yi Ling Shu (益灵舒); ***Gr.***: Memodrin; Referan; ***Ital.***: Ampamet.

Bifemelane *(rINN)*

Bifémélane; Bifemelano; Bifemelanum; MCI-2016 (bifemelane hydrochloride); Бифемелан.

N-Methyl-4-[(α-phenyl-*o*-tolyl)oxy]butylamine.

$C_{18}H_{23}NO$=269.4

CAS — 90293-01-9 (bifemelane); 62232-46-6 (bifemelane hydrochloride).

ATC — N06AX08.

ATC Vet — QN06AX08.

UNII — Z4501GN13G.

Profile

Bifemelane is a nootropic that has been given orally in a usual dose of 150 mg of the hydrochloride daily in divided doses for the treatment of cerebrovascular disorders including some forms of dementia (p. 388.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cordinal; Neurocine.

Choline Alfoscerate *(rINN)*

Alfoscerato de colina; Choline, Alfoscérate de; Choline Alphoscerate; Choline Glycerophosphate; Cholini Alfosceras; Colina, alfoscerato de; L-α-Glycerylphosphorylcholine; Холина Альфосцерат.

Choline hydroxide, (*R*)-2,3-dihydroxypropyl hydrogen phosphate, inner salt.

$C_8H_{20}NO_6P$=257.2

CAS — 28319-77-9.

ATC — N07AX02.

ATC Vet — QN07AX02.

UNII — 60M225GW66.

Profile

Choline alfoscerate is a precursor of acetylcholine and has been tried in the treatment of Alzheimer's disease and other dementias (p. 391.2). The usual oral dose is 0.8 to 1.2 g daily in divided doses; doses of 1 g daily have been given by intramuscular or slow intravenous injection.

Dementia. Treatment with precursors of acetylcholine is not generally thought to be of benefit in dementia (p. 388.1). However, in an analysis[1] of 8 controlled clinical studies the use of choline alfoscerate shared some benefit in patients with Alzheimer's disease or vascular dementia or with acute cerebrovascular disease. Results of a further 3 uncontrolled studies in the same review suggested that it might favour functional recovery in patients with cerebral stroke.

1. Parnetti L, *et al*. Choline alphoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. *Mech Ageing Dev* 2001; **122:** 2041–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Gliatilin; Noebra; ***Ital.***: Brezal; Delecit; Gliatilin; ***Pol.***: Gliatilin; ***Rus.***: Cerepro (Церепро); Cereton (Церетон); Cholitilin (Холитилин); Cholitiline (Холитилин); Gleacer (Глеацер); Gliatilin (Глиатилин); ***Ukr.***: Gliatilin (Глиатилин).

Codergocrine Mesilate *(BAN)*

Codergocrina, mesilato de; Co-dergocrine Mesilate; Codergocrine, mésilate de; Co-dergocrine Mesylate; Co-dergocrine Methanesulphonate; Codergocrini Mesilas; Codergocrinmesilat; Dihydroergotoxine Mesylate; Dihydroergotoxine Methanesulphonate; Dihydrogenated Ergot Alkaloids; Ergoloid Mesylates (USAN); Hydrogenated Ergot Alkaloids; Kodergokriinimesilaatti; Ko-dergokrin Mesilat; Kodergokrinmesilat; Kodergokrin-mesylát; Kodergokrino mesilatas.

CAS — 11032-41-0 (codergocrine); 8067-24-1 (codergocrine mesilate).

ATC — C04AE01.

ATC Vet — QC04AE01.

UNII — X3S33EX3KW.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Codergocrine Mesilate). A mixture of dihydroergocornine mesilate ($C_{31}H_{41}N_5O_5$, CH_4O_3S = 659.8), dihydroergocristine mesilate, α-dihydroergocryptine mesilate, and β-dihydroergocryptine mesilate (epicriptine mesilate). It contains 30 to 35% of dihydroergocornine, 30 to 35% of dihydroergocristine, 20 to 25% of α-dihydroergocryptine, and 10 to 13% of β-dihydroergocryptine. A white or yellowish powder. Sparingly soluble in water; sparingly soluble to soluble in alcohol; slightly soluble in dichloromethane. A 0.5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Ergoloid Mesylates). A mixture of the methanesulfonate salts of the three hydrogenated alkaloids, dihydroergocristine, dihydroergocornine, and dihydroergocryptine, in an approximate weight ratio of 1:1:1. Dihydroergocryptine mesilate exists as a mixture of alpha- and beta-isomers. The ratio of alpha- to beta-isomers is not less than 1.5:1.0 and not more than 2.5:1.0. A white to off-white, microcrystalline or amorphous, practically odourless powder. Slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. A 0.5% solution in water has a pH of 4.2 to 5.2. Store in airtight containers. Protect from light.

Uses and Administration

Unlike the natural ergot alkaloids (see Ergotamine, p. 674.2), codergocrine mesilate has only limited vasoconstrictor effects.

A mixture of hydrogenated ergot alkaloids, codergocrine mesilate is used as an adjunct in the symptomatic treatment of mild to moderate dementia in the elderly (see also p. 391.3). It is given in oral doses of 1 mg three times daily or 4.5 mg once daily in the morning, preferably before meals. Higher doses have also been used. It has been given sublingually, intramuscularly, subcutaneously, or by intravenous infusion.

In some countries, codergocrine mesilate has been used in the treatment of hypertension, migraine, and in peripheral vascular disease.

Codergocrine esilate has been used similarly to the mesilate.

Dementia. Codergocrine has been used for many years in dementia (p. 388.1) but its value is not established.[1-3] Originally its effects were thought to be mediated through peripheral and cerebral vasodilatation but it is now classified as a metabolic enhancer.

1. Wadworth AN, Chrisp P. Co-dergocrine mesylate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in age-related cognitive decline. *Drugs Aging* 1992; **2:** 153–73.
2. Schneider LS, Olin JT. Overview of clinical trials of Hydergine in dementia. *Arch Neurol* 1994; **51:** 787–98.
3. Schneider L, *et al*. Hydergine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 13/02/06).

Erectile dysfunction. For reference to the use of creams containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p. 1392.3.

Adverse Effects

Adverse effects occasionally reported with codergocrine mesilate include abdominal cramps, nausea, vomiting, headache, blurred vision, skin rashes, nasal congestion, flushing of the skin, dizziness, bradycardia, and orthostatic hypotension.

Local irritation has occurred after sublingual use.

Effects on the cardiovascular system. Of 8 patients given codergocrine mesilate 1.5 mg three times daily for the treatment of dementia, 3 developed severe sinus bradycardia associated with general deterioration in their condition, necessitating withdrawal of the treatment.[1] However, no sinus bradycardia had been seen in 40 elderly patients in whom the dose was built up to 1.5 mg three times daily over 3 weeks.[2]

1. Cayley ACD, *et al*. Sinus bradycardia following treatment with Hydergine for cerebrovascular insufficiency. *BMJ* 1975; **4:** 384–5.
2. Cohen C. Sinus bradycardia following treatment with Hydergine. *BMJ* 1975; **4:** 581.

Precautions

Codergocrine mesilate should be used with caution in patients with severe bradycardia.

Interactions

Ticlopidine. Codergocrine mesilate reduces plasma concentrations of ticlopidine, see p. 1513.1.

Pharmacokinetics

Codergocrine is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are reached in about 1 to 2 hours after an oral dose. Oral bioavailability is low; this has been attributed to incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism. It is 81% bound to plasma proteins. Elimination is biphasic with a short half-life of 1.5 to 2.5 hours (α phase) and a longer half-life of 13 to 15 hours (β phase). Codergocrine is mainly excreted with bile in the faeces, although small amounts are eliminated in the urine as metabolites and unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Coplexina; Ergoxina; Hydergina; Vimotadine; ***Austria***: Dorehydrin†; Ergomed; Hydergin; ***Belg.***: Hydergine; Ibexone; Stofilan; ***Braz.***: Codergine; Hydergine; ***Canad.***: Hydergine; ***China***: Hydergine (喜得镇); Perenan (培磊能); Si Qing (思清); Trigogine (弟哥静); ***Cz.***: Secatoxin Forte; ***Fin.***: Hydergin; ***Fr.***: Capergyl†; Hydergine; ***Ger.***: DCCK†; Hydergin; Hydro-Cebral; Orphol†; ***Gr.***: Bordersin†; Ecuor; Engestol-Hyd; Hidrosan; Huperloid; Hydergine; Ibergal; Iresolamin; Kerasex; Normanomin; Nulin; Pallotrinate; Phenyramon; Primarocin; Resinat; Santamin; Uvu; Zidrol; Zinvalon; Zodalin; ***Hong Kong***: Headgen†; Hydergine; Stofilan†; Trigogine; ***India***: Cereloid; Hydergine; ***Indon.***: Cirloid; Ergotika; Exergin; Fontula; Hydergin; Procere; Xepadergin; ***Israel***: Hydergine; ***Ital.***: Hydergina; ***Malaysia***: Headgen; Hydergine; ***Mex.***: Hydergina; ***Philipp.***: Hydergine; ***Port.***: Hydergine; ***Singapore***: Headgen; Hydergine; Trigogine; ***Spain***: Hydergina; ***Swed.***: Hydergin; ***Switz.***: Ergohydrine†; Hydergine; ***Thai.***: Alergot; Helcon; Hyceral; Hydergine; Hydrine; Hymed; Naline; Togine; Trigogine; Vasculin†; Vasian; ***Turk.***: Segol; ***USA***: Gerimal†; Hydergine; ***Venez.***: Astergina.

Multi-ingredient Preparations. ***Arg.***: Difusil; Reagin Vascular; ***Ukr.***: Distonin (Дистонин)†.

Pharmacopoeial Preparations
BP 2014: Codergocrine Tablets;
USP 36: Ergoloid Mesylates Capsules; Ergoloid Mesylates Oral Solution; Ergoloid Mesylates Tablets.

Dihydroergocristine Mesilate *(BANM)*

Dihidroergocristina, mesilato de; Dihidroergokristino mesilatas; Dihidroergokrisztin-mezilát; Dihydroergocristine, mésilate de; Dihydroergocristine Mesylate; Dihydroergocristine Methanesulphonate; Dihydroergocristini Mesilas; Dihydroergocristinmesilat; Dihydroergokristiinimesilaatti; Dihydroergokristinmesilat; Dihydroergokristin-mesylát.

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-isopropyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulphonate.

$C_{35}H_{41}N_5O_5,CH_4O_3S$=707.8

CAS — 17479-19-5 (dihydroergocristine); 24730-10-7 (dihydroergocristine mesilate).

ATC — C04AE04.

ATC Vet — QC04AE04.

UNII — DS7CL18UAM.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dihydroergocristine Mesilate). A white or almost white, fine crystalline powder. Slightly soluble in water; soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

Profile

Dihydroergocristine mesilate is a component of codergocrine mesilate (p. 389.2) and has similar actions. In some countries it has been given orally in doses of 3 to 6 mg daily in divided doses in the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency. It has also been given by intramuscular or intravenous injection.

References.

1. Franciosi A, Zavattini G. Dihydroergocristine in the treatment of elderly patients with cognitive deterioration: a double-blind, placebo-controlled, dose-response study. *Curr Ther Res* 1994; **55:** 1391–1401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nehydrin†; ***Braz.***: Iskemil; ***Gr.***: Agiobita; Alfacrist; Ancef; Beytina; Cristil; Diertina; Ergobel; Ergocrist; Ergofil; Fenitina; Guadal; Memotil; Mentidose; Normocedon; Thriolan; Tonergon; ***Port.***: Diertina; ***Spain***: Diertine; Ergodavur†.

Multi-ingredient Preparations. ***Arg.***: Cervilane; Cinacris; Micerfin; ***Austria***: Brinerdin; ***Braz.***: Isketam; Norogil; Vertizine D; ***Chile***: Cervilane; ***Cz.***: Anavenol; Crystepin†; Ersilan; Neocrystepin†; ***Fr.***: Iskedyl; ***Ital.***: Brinerdina; ***Mex.***: Cervilan; ***Pol.***: Anavenol†; Normatens; Venacorn; ***Rus.***: Anavenol (Анавенол); Brinerdin (Бринердин); Crystepin (Кристепин); Normatens (Нормотенс); ***S.Afr.***: Brinerdin; ***Spain***: Clinadil; Diemil; ***Switz.***: Brinerdine; ***Thai.***: Bedin; Brinerdin; Briscotin†; ***Ukr.***: Normatens (Нормотенс).

Dihydroergocryptine Mesilate

Dihidroergocriptina, mesilato de; Dihydroergocryptine Mesylate; Dihydroergocryptine Methanesulphonate; Dihydroergokryptine Mesylate.

$C_{32}H_{43}N_5O_5,CH_4O_3S$=673.8

CAS — 25447-66-9 (dihydroergocryptine, α-isomer); 19467-62-0 (dihydroergocryptine, β-isomer); 14271-05-7 (dihydroergocryptine mesilate, α-isomer); 65914-79-6 (dihydroergocryptine mesilate, β-isomer).

ATC — N04BC03.

ATC Vet — QN04BC03.

UNII — 5AAV003TAQ (dihydroergocryptine mesilate); Z4I7BU58DN (dihydroergocryptine mesilate α-isomer); 79Y4U49I29 (dihydroergocryptine mesilate β-isomer).

Profile

Dihydroergocryptine mesilate is a component of codergocrine mesilate (p. 389.2) and has similar actions. It has been given orally in doses of up to 20 mg daily for migraine, and in maintenance doses of up to 60 to 120 mg daily for parkinsonism. It has also been used for age-related dementia and to inhibit lactation. In some countries it has been given with caffeine for cerebrovascular and peripheral vascular disorders.

References.

1. Scarzella L, *et al*. Dihydroergocryptine in the management of senile psycho-organic syndrome. *Int J Clin Pharmacol Res* 1992; **12:** 37–46.
2. Battistin L, *et al*. Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. *Acta Neurol Scand* 1999; **99:** 36–42.
3. Bergamasco B, *et al*. Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double-blind, placebo-controlled study. *Acta Neurol Scand* 2000; **101:** 372–80.
4. Micieli G, *et al*. Alpha-dihydroergocryptine and predictive factors in migraine prophylaxis. *Int J Clin Pharmacol Ther* 2001; **39:** 144–51.
5. Tergau F, *et al*. Treatment of restless legs syndrome with the dopamine agonist alpha-dihydroergocryptine. *Mov Disord* 2001; **16:** 731–5.
6. Albanese A, Colosimo C. Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists. *Acta Neurol Scand* 2003; **107:** 349–55.
7. Mailland E, *et al*. Alpha-dihydroergocryptine in the long-term therapy of Parkinson's disease. *Arzneimittelforschung* 2004; **54:** 647–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Cripar (克瑞帕); ***Cz.***: Almirid†; ***Ger.***: Almirid†; Cripar†; ***Gr.***: Daverium; ***Irl.***: Almirid†; ***Ital.***: Daverium; Myrol; ***Mex.***: Diamin; ***Pol.***: Almirid; ***Port.***: Striatal; ***Rus.***: Vasobral (Вазобрал); ***Switz.***: Cripar†.

Multi-ingredient Preparations. ***China***: Vasobral (洛斯宝); ***Fr.***: Vasobral; ***Hong Kong***: Vasobral.

Donepezil Hydrochloride

(BANM, USAN, rINNM)

BNAG; Donépézil, Chlorhydrate de; Donepezil Hidroklorür; Donepezili Hydrochloridum; Donepezilo, hidrocloruro de; E-2020; ER-4111 (donepezil); Hidrocloruro de donepezilo; Донепезила Гидрохлорид.

(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride.

$C_{24}H_{29}NO_3,HCl$=416.0

CAS — 120014-06-4 (donepezil); 142057-79-2 (donepezil); 120011-70-3 (donepezil hydrochloride); 142057-77-0 (donepezil hydrochloride).

ATC — N06DA02.

ATC Vet — QN06DA02.

UNII — 3O2T2PJ89D.

Pharmacopoeias. In *US.*

USP 36: (Donepezil Hydrochloride). A white to off-white, crystalline powder. Soluble in water and in glacial acetic acid; slightly soluble in alcohol and in acetonitrile; freely soluble to soluble in chloroform; practically insoluble in ethylacetate and in *n*-hexane. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Donepezil hydrochloride, a piperidine derivative, is a reversible and selective inhibitor of acetylcholinesterase with actions similar to those of neostigmine (p. 687.2). It is highly selective for the CNS and is used for the symptomatic treatment of dementia in Alzheimer's disease (p. 392.3). In the UK, the licensed use of donepezil is limited to those patients with mild to moderately severe dementia (but see p. 392.3); in the USA it is also licensed for use in those with severe symptoms.

Regardless of severity, donepezil hydrochloride is given in an initial oral dose of 5 mg once daily increased if necessary after 4 to 6 weeks to 10 mg once daily; the dose should be taken just before bedtime. In those with severe symptoms, after 3 months, a further increase to a dose of 23 mg once daily may be considered. Clinical benefit should be reassessed on a regular basis.

In some countries, donepezil is also licensed for use in patients with vascular dementia (p. 392.3); doses are similar to those used for the treatment of mild to moderate dementia in Alzheimer's disease.

Dementia. Donepezil hydrochloride is used in the symptomatic treatment of dementia in *Alzheimer's disease* (p. 388.1). In individual studies, it appears to produce modest benefits in some patients with mild to moderately severe dementia.[1-4] These findings are also supported by a systematic review[5] which concluded that, for treatment periods of up to 1 year, donepezil produces modest improvements in cognitive function and global clinical state. Benefit has also been reported in patients with more severe dementia.[5-8]

In the UK, NICE states that donepezil may be used in patients with mild to moderate dementia if given under the following conditions:[9]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Donepezil has also been tried in patients with *mild cognitive impairment* (MCI).[10,11] Findings from a double-blind study[11] have suggested that although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first year of treatment when compared with placebo, the rate of progression after 3 years of therapy was not lower than that of the placebo group. The authors of a systematic review[12] of these 2 studies found no evidence to support the use of donepezil in patients with MCI. Any benefits were considered to be minor, short-lived, and associated with significant adverse effects. A more recent study[13] conducted over 48 weeks found a small but significant improvement in the score of one cognitive measure with donepezil when compared with placebo; however, there were no changes in other measures of global impairment or function. The authors considered that such measures may not be sensitive enough to detect changes in patients with MCI.

Donepezil may be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[14] have shown an improvement in cognition and global function in patients with probable or possible vascular dementia. A systematic review also concluded that donepezil improved mild to moderate vascular cognitive impairment in the short term (treatment for 6 months).[15] The manufacturer has reported[16] that out of a total of 3 studies of donepezil in vascular dementia, one (Study 319) showed an apparently increased mortality compared with placebo: 1.7% and 0%, respectively. In a combined analysis of the other 2 studies, the mortality rate was 1.7% in the donepezil group and 2% in the placebo group. Combined analysis of all 3 studies showed no statistically significant difference in the mortality rates between the donepezil (1.7%) and placebo (1.1%) groups; the risk of vascular events such as stroke and myocardial infarction was also similar for each group. The unexpectedly low mortality rate with placebo in Study 319 was unusual given the age and pathology of the subjects. An increased risk of death has also been reported with another acetylcholinesterase inhibitor, *galantamine*, when used in patients who did not have Alzheimer's disease (see Effects on the Cardiovascular and Cerebrovascular Systems, p. 394.2).

1. Rogers SL, *et al*. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; **50:** 136–45.
2. Mohs RC, *et al*. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001; **57:** 481–8.

3. Winblad B, *et al*. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; **57:** 489–95.
4. Holmes C, *et al*. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 2004; **63:** 214–19.
5. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 13/02/06).
6. Feldman H, *et al*. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; **57:** 613–20.
7. Winblad B, *et al*. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet* 2006; **367:** 1057–65.
8. Black SE, *et al*. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology* 2007; **69:** 459–69.
9. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
10. Salloway S, *et al*. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* 2004; **63:** 651–7.
11. Petersen RC, *et al*. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352:** 2379–88.
12. Birks J, Flicker L. Donepezil for mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 09/08/07).
13. Doody RS, *et al*. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology* 2009; **72:** 1555–61.
14. Black S, *et al*. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003; **34:** 2323–30.
15. Malouf R, Birks J. Donepezil for vascular cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 13/02/06).
16. Eisai, Jpn. Eisai reports results from latest donepezil study in vascular dementia (issued 16th March, 2006). Available at: http://www.eisai.co.jp/enews/enews200609pdf.pdf (accessed 09/08/07)

Parkinsonism. Although acetylcholinesterase inhibitors such as donepezil hydrochloride may theoretically worsen parkinsonism symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p. 1030.2).

Adverse Effects and Treatment

Adverse effects of acetylcholinesterase inhibitors such as donepezil notably include nausea, vomiting, anorexia, diarrhoea, fatigue, and dizziness. Other common adverse effects include abdominal pain, dyspepsia, rash, pruritus, headache, somnolence, muscle cramps, insomnia, sweating, tremor, and syncope; upper-respiratory-tract and urinary-tract infections have been noted. Rare cases of angina, sinoatrial and AV blocks, bradycardia, peptic ulcers, gastrointestinal haemorrhage, extrapyramidal symptoms, and seizures have been observed. Psychiatric disturbances, including depression, hallucinations, agitation, aggressive behaviour, and confusion have also been reported. There is a potential for bladder outflow obstruction. Minor increases in serum-creatine kinase have also occurred with donepezil.

Increased liver transaminases have been noted with acetylcholinesterase inhibitors; hepatotoxicity may be severe with the acetylcholinesterase inhibitor tacrine (see p. 398.3).

The use of acetylcholinesterase inhibitors has been associated with weight loss and consequently some licensed product information has recommended that a patient's weight is monitored during treatment. Female patients have been found to be more susceptible to nausea, vomiting, anorexia, and weight loss.

Overdosage with cholinesterase inhibitors may result in 'cholinergic crisis', the details of which are described under Adverse Effects of Neostigmine, p. 688.2.

Reviews of the safety profile of donepezil.

1. CSM/MCA. Donepezil (Aricept). *Current Problems* 1999; **25:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 13/08/07)
2. Jackson S, *et al*. The safety and tolerability of donepezil in patients with Alzheimer's disease. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 1–8.

Effects on the cardiovascular system. The Australian Adverse Drug Reactions Advisory Committee noted in October 2004 that it had received 32 reports of cardiac arrhythmias associated with donepezil (14 of bradycardia, 1 bundle branch block, 5 AV blocks, 10 cases of syncope, and 2 unspecified), as well as 7 cases of myocardial infarction or cardiac arrest.[1] There had been 7 reports of similar cardiovascular effects with rivastigmine and 6 with galantamine; the larger number with donepezil was almost certainly due to wider usage of this drug. Most patients recovered when the drug was stopped or the dose reduced, though many were hospitalised and in 4 cases a pacemaker was required.

One study in vascular dementia reported an increased death rate with donepezil (see Dementia, p. 390.3) but no increase in vascular events.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cholinesterase inhibitors and cardiac arrhythmias. *Aust Adverse Drug React Bull* 2004; **23:** 19–20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.pdf (accessed 13/02/06)

Effects on the nervous system. Restless legs, mumbling, and stuttering developed in an elderly patient after increasing the dose of donepezil to 10 mg daily.[1] Symptoms resolved when donepezil was withdrawn and recurred on rechallenge.

1. Amouyal-Barkate K, *et al*. Abnormal movements with donepezil in Alzheimer disease. *Ann Pharmacother* 2000; **34:** 1347.

Effects on the urinary tract. Urinary incontinence is a recognised adverse effect of the older anticholinesterases such as neostigmine; not unexpectedly there have also been cases associated with donepezil.[1]

1. Hashimoto M, *et al*. Urinary incontinence: an unrecognised adverse effect with donepezil. *Lancet* 2000; **356:** 568.

Precautions

Donepezil and other acetylcholinesterase inhibitors should be used with caution, if at all, in patients with gastrointestinal or urinary-tract obstruction; their use is not recommended in patients recovering from bladder or gastrointestinal surgery. Care is also required in patients with a history of asthma, obstructive pulmonary disease, Parkinson's disease, or seizures, and in those, with, or at risk of developing, peptic ulcer disease. Patients with cardiovascular conduction disorders such as sick-sinus syndrome may be susceptible to the vagotonic effects of acetylcholinesterase inhibitors.

Dizziness, somnolence, fatigue, and muscle cramps may occur especially when starting treatment with or increasing the dose of acetylcholinesterase inhibitors; the performance of skilled tasks such as driving may be affected.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies donepezil as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Neostigmine, p. 688.3. Hepatic metabolism of donepezil via the cytochrome P450 system has been demonstrated; plasma concentrations of donepezil may be raised by drugs that inhibit the isoenzyme CYP3A4 such as ketoconazole, itraconazole, and erythromycin, and by those that inhibit the isoenzyme CYP2D6 such as fluoxetine and quinidine. Conversely, plasma-donepezil concentrations may be reduced by enzyme inducers such as rifampicin, phenytoin, carbamazepine, and alcohol.

Antimuscarinics. Although antimuscarinics are expected to antagonise the effects of anticholinesterases, such combinations are sometimes used in patients with dementia who are distressed by symptoms of urge incontinence.[1] There have been, however, a few cases[2] of agitation, anxiety, confusion, aggression, and delusion precipitated by *tolterodine* in patients who had been stable on donepezil or rivastigmine. The interaction appeared to cause a state of cholinergic neurogenic hypersensitivity, similar to sudden withdrawal of the anticholinesterase.

1. Siegler EL, Reidenberg M. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. *Clin Pharmacol Ther* 2004; **75:** 484–8.
2. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc* 2002; **50:** 1165–6.

Pharmacokinetics

Donepezil hydrochloride is well absorbed from the gastrointestinal tract, maximum plasma concentrations being achieved within 3 to 4 hours after ingestion. It is about 95% bound to plasma proteins, mainly albumin. Donepezil undergoes partial metabolism via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6, to 4 major metabolites. About 11% of a dose is present in plasma as 6-*O*-desmethyldonepezil, which has similar activity to the parent compound. Over 10 days, about 57% of a dose is recovered from the urine as unchanged drug and metabolites, and about 15% from the faeces; 28% remains unrecovered suggesting accumulation. The elimination half-life is about 70 hours. Steady-state concentrations are achieved within 3 weeks of the start of therapy.

References.

1. Tiseo PJ, *et al*. Metabolism and elimination of ^{14}C-donepezil in healthy volunteers: a single-dose study. *Br J Clin Pharmacol* 1998; **46** (suppl 1): 19–24.
2. Reyes JF, *et al*. Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 9–17.
3. Nagy CF, *et al*. Steady-state pharmacokinetics and safety of donepezil HCl in subjects with moderately impaired renal function. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 18–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alzaimax; Cebrocal; Crialix; Cristaclar; Donepes; Donnox; Donpex; Donzeimer†; Endoclar; Eranz; Lirpan; Oldinot; Onefin; Valpex; ***Austral.***: Aricept; ***Austria***: Aricept; ***Belg.***: Aricept; ***Braz.***: Epez; Eranz; Ziledon; ***Canad.***: Aricept; ***Chile***: Dazolin; Dopaben; Eranz; Evimal; Fincip; ***China***: A Rui Si (阿瑞斯); Aricept (安理申); Fang Qing (方清); Fu Si Ke (扶斯克); Gai Fei (盖菲); Jia Qi (加奇); Nuo Chong (诺冲); Sai Ling Si (赛灵斯); Si Bo Hai (思博海); ***Cz.***: Adonep; Alzhedon†; Alzil; Aricept; Calofra; Dobedipil; Donpethon; Dospelin; Ezida; Landex; Mazil; Nepla; Oneza; Promemore; Tolerdilan; Yasnal; ***Denm.***: Aricept; Dobedipil†; Domethan; Doneprion; Doneratio†; Donespes; Memac†; ***Fin.***: Aricept; Doneratio; Yasnal; ***Fr.***: Aricept; ***Ger.***: Aricept; ***Gr.***: Aricept; Aripezil; Dementis; Donegal; Donelet; Donesan; Donester; Donopez; Dozilax; Hania; Kibilis; Nepezil; Penezil; Pezale; Razil; Sulbenin; Tactrol; Venaxen; ***Hong Kong***: Aricept; ***Hung.***: Aricept; Donecept; Donectil; Donesyn; Palixid; ***India***: Aricep; Deppzil; Donasure; Donaz; Donecept; Donep; Dopezil; Dorent; Nozil; ***Indon.***: Aldomer; Alzim; Aricept; Fordesia; ***Irl.***: Aricept; Aripez; Aripil; Arizime; Dentap; Donecept; Donelinn; Donesyn; Dozept; ***Israel***: Aricept; Asenta; Memorit; ***Ital.***: Aricept; Lizidra; Memac; Yasnoro; ***Jpn***: Aricept; ***Malaysia***: Aricept; ***Mex.***: Eranz; ***Norw.***: Aricept; ***NZ***: Aricept; Concorda; Donaccord; Donezil; ***Philipp.***: Aricept; Done; Donezel; ***Pol.***: Alzdone; Alzepezil; Apo-Doperil; Aricept; Cogiton; Cognezil; Dobedipil; Donecept; Donecleus; Donectil; Donemed; Donepex; Doneprion; Donesyn; Memocept; Mensapex; Redumas; Ricordo; Symepezil; Yasnal; ***Port.***: Alizil; Alkimus; Aricept; Damzipil†; Dilpeze†; Dizil; Dolizi†; Fremptel; Paxel†; ***Rus.***: Aricept (Арисепт); Yasnal (Яснал); ***S. Afr.***: Aricept; Ariknow; Donecept; ***Singapore***: Aricept; ***Spain***: Aricept; Lixben; Yasnal; ***Swed.***: Aricept; Azepezil; ***Switz.***: Aricept; ***Thai.***: Aricept; Donept; Tonizep; ***Turk.***: Alzancer; Aricept; Arypez; Dement; Divare; Doenza; Dozyl; Nopez; Zhedon; ***UK***: Aricept; ***Ukr.***: Almer (Альмер); Alzepil (Алзепил); ***USA***: Aricept; ***Venez.***: Eranz.

Pharmacopoeial Preparations

USP 36: Donepezil Hydrochloride Orally Disintegrating Tablets; Donepezil Hydrochloride Tablets.

Fonturacetam *(rINN)* ⊗

BRN-5030440; *N*-Carbamoyl-methyl-4-phenyl-2-pyrrolidone; Carphedon; Fonturacétam; Fonturacetamum; Karfedon; 4-Phenylpiracetam; Фонтурацетам.

rac-2-(2-Oxo-4-phenylpyrolidin-1-yl)acetamide.

$C_{12}H_{14}N_2O_2$=218.3

CAS — 77472-70-9.

UNII — 99QW5JU66Y.

Profile

Fonturacetam is a nootropic and has been used in the management of various cerebrovascular disorders. It has also been abused in sport.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Phenotropil (Фенотропил); ***Ukr.***: Entrop (Энтроп); Phenotropil (Фенотропил).

Galantamine Hydrobromide

(BANM, USAN, rINNM)

Galantamina, hidrobromuro de; Galantamine, Bromhydrate de; Galantaminhydrobromid; Galantamini hydrobromidum; Galanthamine Hydrobromide; Galanthamini Hydrobromidum; Hidrobromuro de galantamina; Галантамина Гидробромид.

(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide.

$C_{17}H_{21}NO_3$,HBr=368.3

CAS — 357-70-0 (galantamine); 1953-04-4 (galantamine hydrobromide).

ATC — N06DA04.

ATC Vet — QN06DA04.

UNII — MJ4PTD2VVW.

Description. The hydrobromide of galantamine, an alkaloid which has been obtained from the Caucasian snowdrop (Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae), and related species.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Galantamine Hydrobromide). A white or almost white, crystalline or amorphous powder. Sparingly soluble in water; very slightly soluble in dehydrated alcohol; it dissolves in dilute solutions of alkali hydroxides. pH of a 2% solution in water is 4.0 to 5.5.

USP 36: (Galantamine Hydrobromide). A white to almost white powder. Sparingly soluble in water; very slightly

soluble in alcohol; soluble in 0.1N sodium hydroxide; insoluble in propyl alcohol.

Uses and Administration

Galantamine hydrobromide is a reversible inhibitor of acetylcholinesterase activity, with actions similar to those of neostigmine (p. 687.2). It also has an intrinsic action on nicotinic receptors. It is used in the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (but see p. 394.1).

Galantamine is given as the hydrobromide although doses are expressed in terms of the base; 5.1 mg of galantamine hydrobromide is equivalent to about 4 mg of galantamine. An initial oral dose of 4 mg is given twice daily with food for 4 weeks, then increased to 8 mg twice daily. This dose should be maintained for at least 4 weeks; thereafter, the dose may be further increased to 12 mg twice daily according to response and tolerance. A modified-release preparation is also available for once-daily use. The clinical benefit of galantamine should be reassessed, preferably within the first 3 months, and thereafter on a regular basis. Reductions in dose may be necessary in patients with hepatic or renal impairment (see p. 394.1) or in those also taking certain cytochrome P450 isoenzyme inhibitors (see Interactions, p. 394.2).

Galantamine hydrobromide has also been used in various neuromuscular disorders, and to curtail the muscle relaxation produced by competitive neuromuscular blockers.

Administration in hepatic impairment. No dose adjustment of galantamine is necessary in mild hepatic impairment. Patients with moderate impairment should begin with an oral dose of 4 mg once daily (or 8 mg every other day if using a modified-release preparation), preferably taken in the morning, for at least one week; thereafter the dose may be increased to 4 mg twice daily (or its once-daily equivalent if using a modified-release preparation) for at least 4 weeks, with subsequent increases up to a maximum of 8 mg twice daily (or its once-daily equivalent if using a modified-release preparation). Galantamine is contra-indicated in severe impairment (Child-Pugh score greater than 9) due to lack of data.

Administration in renal impairment. UK licensed product information states that no dose adjustment is necessary for galantamine in mild or moderate renal impairment. However, US licensed product information recommends that the dose should not exceed 16 mg daily in patients with moderate impairment.

Galantamine is contra-indicated in severe impairment (creatinine clearance less than 9 mL/minute) due to lack of data.

Dementia. Reviews[1-3] suggest that galantamine is of benefit in patients with mild to moderate symptoms of *Alzheimer's disease* (p. 388.1); evidence in more severely impaired subjects is lacking. In the UK, NICE states that galantamine may be used in patients with mild to moderate dementia if given under the following conditions:[4]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Galantamine may also be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[5] have shown a trend towards improved cognition in patients with probable vascular dementia, although patients numbers were too small for this to be significant. A more recent multicentre study[6] in patients with probable vascular dementia found cognitive improvement with galantamine to be greater than with placebo; however, improvement in daily activities with galantamine was similar to that seen with placebo.

A systematic review[3] concluded that galantamine could not be recommended for treatment in patients with *mild cognitive impairment* because of limited clinical benefit and an unexplained association with an excess death rate (see also Effects on the Cardiovascular and Cerebrovascular Systems, p. 394.2).

1. Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. *Drugs* 2000; **60:** 1095–1122.
2. Pearson VE. Galantamine: a new Alzheimer drug with a past life. *Ann Pharmacother* 2001; **35:** 1406–13.
3. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 14/02/06).
4. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
5. Erkinjuntti T, *et al.* Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002; **359:** 1283–90.
6. Auchus AP, *et al.* Galantamine treatment of vascular dementia: a randomized trial. *Neurology* 2007; **69:** 448–58.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p. 391.1. Hypertension has also been reported with galantamine.

For details regarding dose adjustments in moderate hepatic or renal impairment, see under Uses and Administration, above. There are no data on the use of galantamine in patients with severe hepatic or renal impairment and consequently in the licensed product information it is contra-indicated in such patients; it should also not be given to patients with both significant hepatic and renal impairment.

Effects on the cardiovascular and cerebrovascular systems. Results from 2 studies of the use of galantamine in mild cognitive impairment (an unlicensed indication) have suggested that there may be an increased risk of death in patients given galantamine compared with those on placebo: out of a total of about 2000 patients, 13 died in the galantamine groups with only 1 death reported in the placebo groups.[1,2] About half of the deaths were caused by cardiovascular or cerebrovascular events.

For a suggestion of possibly increased mortality with *donepezil* in patients with vascular dementia, see Dementia, p. 390.3.

1. Janssen-Ortho Inc. Safety information from investigational studies with Reminyl (galantamine hydrobromide) in mild cognitive impairment (MCI) (issued 18th April, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/reminyl_hpc-eng.pdf (accessed 05/08/08)
2. Ortho-McNeil Neurologics, Inc. Important prescribing information: deaths in subjects with mild cognitive impairment (MCI) (issued 31st March, 2005). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164870.pdf (accessed 19/08/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies galantamine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Neostigmine, p. 688.3. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Consequently its bioavailability may be increased by drugs that inhibit CYP2D6, such as quinidine, fluoxetine, fluvoxamine, and paroxetine, and by those that inhibit CYP3A4, such as ketoconazole and ritonavir. Dose reduction of galantamine may be required when given with such drugs.

Pharmacokinetics

Galantamine is well absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in about 1 hour after ingestion from conventional formulations; with modified-release formulations, peak concentrations occur about 4 to 5 hours after a dose and are somewhat lower. The absolute oral bioavailability of galantamine is about 90%. The presence of food delays the rate of absorption although the extent of absorption is not affected. Protein binding is about 18%. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; a number of active metabolites are formed. The elimination half-life is about 7 to 8 hours. After 7 days, the majority of a single oral dose is recovered in the urine with up to about 6% detected in the faeces; about 20 to 30% of the dose is excreted in the urine as unchanged galantamine. Clearance is reported to be 20% lower in females than in males and 25% lower in poor metabolisers than in extensive metabolisers.

References.
1. Zhao Q, *et al.* Pharmacokinetics and safety of galantamine in subjects with hepatic impairment and healthy volunteers. *J Clin Pharmacol* 2002; **42:** 428–36.
2. Piotrovsky V, *et al.* Galantamine population pharmacokinetics in patients with Alzheimer's disease: modeling and simulations. *J Clin Pharmacol* 2003; **43:** 514–23.
3. Farlow MR. Clinical pharmacokinetics of galantamine. *Clin Pharmacokinet* 2003; **42:** 1383–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Intelec; Memolos; Numencial; Reminyl; ***Austral.***: Galantyl; Reminyl; ***Austria***: Reminyl; ***Belg.***: Reminyl; ***Braz.***: Reminyl; ***Canad.***: Reminyl; ***Chile***: Galamed; Reminyl; ***China***: Hui Min (慧敏); Jin Kang Ling Li (金康灵力); Qi Er Neng (奇尔能); Reminyl (力益临); Shi Wei Bao (施维宝); Yi You Li Ning (易优利宁); ***Cz.***: Apo-Galant; Flashemel†; Galamed†; Kurоment†; OxyGal†; Reminyl; ZapTron†; ***Denm.***: Reminyl; ***Fin.***: Reminyl; ***Fr.***: Reminyl; ***Ger.***: Galnora; Reminyl; ***Gr.***: Aneprosil; Galanyl; Memo-Farmellas; Memoton Life; Reminyl; Riminyl; Zoroflog; ***Hong Kong***: Reminyl; ***India***: Galamer; ***Indon.***: Reminyl; ***Irl.***: Galsya; Reminyl; ***Israel***: Reminyl; ***Ital.***: Galema; Reminyl; ***Jpn***: Reminyl; ***Malaysia***: Reminyl; ***Mex.***: Reminyl; ***Neth.***: Bergal; Galantagen; Galantex; Reminyl; ***Norw.***: Reminyl; ***NZ***: Galantyl; Reminyl; ***Philipp.***: Reminyl; ***Pol.***: Nivalin; ***Port.***: Reminyl; ***Rus.***: Nivalin (Нивалин); Reminyl (Реминил); ***S.Afr.***: Reminyl; ***Singapore***: Reminyl; ***Spain***: Galnora; Reminyl; ***Swed.***: Reminyl; ***Switz.***: Reminyl; ***Thai.***: Reminyl; ***Turk.***: Reminyl; ***UK***: Elmino; Galsya; Gatalin; Lotprosin; Reminyl; ***Ukr.***: Nivalin (Нивалин); ***USA***: Razadyne; ***Venez.***: Proneurax.

Pharmacopoeial Preparations
USP 36: Galantamine Tablets.

Idebenone *(rINN)*

CV-2619; Idebenona; Idébénone; Idebenonum; Идебенон.
2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.
$C_{19}H_{30}O_5$=338.4
CAS — 58186-27-9.
ATC — N06BX13.
ATC Vet — QN06BX13.
UNII — HB6PN45W4J.

Profile

Idebenone has been described as a nootropic and an antioxidant. It is used in the treatment of mental impairment associated with cerebrovascular disorders. A dose of 90 mg daily has been given orally in 2 divided doses after food. Idebenone has also been tried in Alzheimer's disease.

Idebenone is used in the symptomatic management of various clinical manifestations of Friedreich's ataxia in patients aged 8 years and over. Doses are given orally with food according to body-weight: initial doses of 300 mg three times daily in patients weighing over 45 kg or of 150 mg three times daily in those weighing 45 kg or under are recommended. After at least 6 months this may be increased, according to response and tolerance, to 750 mg three times daily in patients over 45 kg or 450 mg three times daily in those weighing 45 kg or under. If no additional improvement is seen after 6 months on the higher dose, the dosage should be reduced to the initial dose.

Alternatively, in some countries, idebenone may be licensed specifically for the treatment of cardiomyopathy associated with Friedreich's ataxia; for example, in Switzerland, a dose of 5 mg/kg daily in 3 divided doses is recommended for such use in patients aged 4 years and over.

Leucocytopenia and agranulocytosis have been reported rarely with the use of idebenone. Some licensed product information recommends that a complete blood cell count and liver function tests should be performed before starting treatment and regularly thereafter, and also before and after dose increases. Idebenone should not be used in patients with moderate or severe hepatic impairment and used with caution in those with mild impairment.

Idebenone is also being investigated for the treatment of Duchenne muscular dystrophy, Leber's optic atrophy, and the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Idebenone is available as a 1% cream for the cosmetic treatment of wrinkles.

Dementia. Idebenone was found to be safe and effective in patients with mild to moderate Alzheimer's disease (p. 388.1) when followed for up to 2 years.[1,2] In a further study,[3] its safety and efficacy were comparable to tacrine. However, another study[4] found no clinically significant slowing of cognitive decline in patients with Alzheimer's disease treated with idebenone.

1. Weyer G, *et al.* Efficacy and safety of idebenone in the long-term treatment of Alzheimer's disease: a double-blind, placebo controlled multicentre study. *Hum Psychopharmacol Clin Exp* 1996; **11:** 53–65.
2. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm* 1998; **54** (suppl): 301–10.
3. Gutzmann H, *et al.* Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. *Pharmacopsychiatry* 2002; **35:** 12–18.
4. Thal LJ, *et al.* Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology* 2003; **61:** 1498–1502.

Friedreich's ataxia. Preliminary studies of idebenone in the treatment of Friedreich's ataxia.[1-7]

1. Hausse AO, *et al.* Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart* 2002; **87:** 346–9.
2. Artuch R, *et al.* Friedreich's ataxia: idebenone treatment in early stage patients. *Neuropediatrics* 2002; **33:** 190–3.
3. Mariotti C, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; **60:** 1676–9.

4. Buyse G, *et al*. Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology* 2003; **60:** 1679–81.
5. Rustin P, *et al*. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2004; **62:** 524–5.
6. Di Prospero NA, *et al*. Safety, tolerability, and pharmacokinetics of high-dose idebenone in patients with Friedreich ataxia. *Arch Neurol* 2007; **64:** 803–8.
7. Di Prospero NA, *et al*. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. *Lancet Neurol* 2007; **6:** 878–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Esanic†; Geniceral; Idesole; Nemocebral; Pavertrin; Sicoplus; Ulcourona; ***Canad.***: Catena; ***China***: Jin Bo Rui (金博瑞); ***Ital.***: Mnesis; ***Mex.***: Lucebanol; ***Port.***: Amizal; Cerestabon; Idecortex; ***Rus.***: Neiromet (Нейромет); Noben (Нобен); ***Switz.***: Mnesis†; ***USA***: Prevage.

Multi-ingredient Preparations. ***Arg.***: Idenimo; Idesole Plus; Nemocebral Plus; ***India***: Hi-Q Plus; Hi-Q.

Memantine Hydrochloride

(BANM, USAN, rINNM)

1-Amino-3,5-dimethyladamantane Hydrochloride; D-145 (memantine); 3,5-Dimethyl-1-adamantanamine hydrochloride; DMAA (memantine); Hidrocloruro de memantina; Memantin Hidroklorür; Memantina, hidrocloruro de; Mémantine, Chlorhydrate de; Memantini Hydrochloridum; Мемантина Гидрохлорид.

3,5-Dimethyltricyclo[3.3.1.1.^{3,7}]decan-1-amine hydrochloride.

$C_{12}H_{21}N,HCl$=215.8

CAS — 19982-08-2 (memantine); 41100-52-1 (memantine hydrochloride).

ATC — N06DX01.

ATC Vet — QN06DX01.

UNII — JY0WD0UA60.

Uses and Administration

Memantine is a derivative of amantadine (p. 891.3) and is likewise an antagonist of *N*-methyl-D-aspartate receptors. It is given in the treatment of moderate to severe Alzheimer's disease (see Dementia, p. 395.1). Memantine has also been given in the treatment of parkinsonism and central spasticity, and in other disorders such as brain injury or comatose states. It is given orally as the hydrochloride.

In the treatment of **Alzheimer's disease**, the initial dose of memantine hydrochloride is 5 mg once daily for the first week; this should be increased in weekly increments of 5 mg to a maximum dose of 20 mg daily. In the USA, licensed product information states that doses of 10 mg daily and over should be taken in 2 divided doses; however, once-daily dosing is recommended in the UK. Dosage adjustment may be required in patients with renal impairment (see p. 395.1). Clinical benefit should be reassessed on a regular basis.

Memantine hydrochloride has also been given by slow intravenous injection.

Memantine is under investigation in the treatment of glaucoma and peripheral neuropathy.

Administration in renal impairment. UK licensed product information advises that no dose adjustment is needed when memantine hydrochloride is given for Alzheimer's disease in patients with mild renal impairment (creatinine clearance [CC] 50 to 80 mL/minute). However, in those with moderate impairment (CC 30 to 49 mL/minute) an oral dose of 10 mg daily may be used (after starting at 5 mg daily) and if well tolerated for at least 7 days, it may be increased to 20 mg daily as described above (see above). In those with severe impairment (CC 5 to 29 mL/minute) the maximum daily dose is 10 mg. In the USA, licensed product information states that no dose reduction is required in those with mild or moderate impairment; a target dose of 10 mg daily is recommended in patients with severe impairment (CC 5 to 29 mL/minute).

Dementia. A systematic review[1] of the use of memantine in dementia (p. 388.1) concluded that it did have a small beneficial effect on cognitive and functional decline at 6 months in patients with moderate to severe Alzheimer's disease; the effects were not clinically discernible in those with mild to moderate vascular dementia but were discernible in those with mild to moderate Alzheimer's disease. In the UK, NICE[2] has recommended memantine in the treatment of moderate disease in patients who cannot take acetylcholine esterase inhibitors, and also in the treatment of severe disease. A general review, including a safety profile, of memantine in Alzheimer's disease has also been published.[3]

1. McShane R, *et al*. Memantine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).
2. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
3. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. *Drugs* 2006; **66:** 1515–34.

Adverse Effects and Precautions

Common adverse effects with memantine include constipation, dizziness, headache, hypertension, and somnolence. Less common reactions such as anxiety, hallucinations, confusion, fatigue, abnormal gait, hypertonia, vomiting, fungal infections, cystitis, thromboembolism, and increased libido have also occurred. Isolated cases of psychotic reactions and pancreatitis have been reported.

Dosage adjustment may be required in renal impairment, but recommendations vary (see under Uses and Administration, above).

Only limited clinical data are available for patients with recent myocardial infarction, uncompensated congestive heart failure, and uncontrolled hypertension and use of memantine in these patients should be closely monitored. Seizures have occurred rarely and caution is recommended in patients at risk of convulsions. Conditions that increase urinary pH, such as drastic changes in diet, renal tubular acidosis, or severe infections of the urinary tract, may decrease elimination of memantine resulting in increased plasma levels; patient monitoring is recommended in such cases.

References.

1. Farlow MR, *et al*. Memantine for the treatment of Alzheimer's disease: tolerability and safety data from clinical trials. *Drug Safety* 2008; **31:** 577–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies memantine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Use of other *N*-methyl-D-aspartate antagonists such as amantadine, ketamine, or dextromethorphan with memantine may increase both the incidence and severity of adverse effects and should be avoided. The effects of dopaminergics and antimuscarinics may also be enhanced whereas memantine may reduce the actions of barbiturates and antipsychotics.

Memantine may alter the effects of the antispasmodics baclofen and dantrolene. The clearance of memantine is reduced under alkaline urine conditions and drugs such as carbonic anhydrase inhibitors and sodium bicarbonate should be used with caution.

Pharmacokinetics

Memantine is well absorbed after oral doses. Peak plasma concentrations are achieved in about 3 to 8 hours. Plasma protein binding is about 45%. Memantine undergoes partial hepatic metabolism; the main metabolites include *N*-3,5-dimethyl-gludantan and 1-nitroso-3,5-dimethyl-adamantane. The majority of a dose is excreted unchanged via the kidney; some active renal tubular secretion and reabsorption occurs. The terminal half-life ranges from 60 to 100 hours although under alkaline conditions the rate of elimination is reduced.

References.

1. Periclou A, *et al*. Pharmacokinetic study of memantine in healthy and renally impaired subjects. *Clin Pharmacol Ther* 2006; **79:** 134–43.
2. Kornhuber J, *et al*. Memantine pharmacotherapy: a naturalistic study using a population pharmacokinetic approach. *Clin Pharmacokinet* 2007; **46:** 599–612. Correction. *ibid.*; 712.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Akatinol; Carrier; Conexine; Ebixa; Fentina; Lucidex; Merital; Neuroplus; Prilben; Pronervon; Tonibral; ***Austral.***: Ebixa; Memanxa; Memanxa; ***Austria***: Axura; Ebixa; ***Belg.***: Ebixa; ***Braz.***: Alois; Clomenac; Ebix; Heimer; ***Canad.***: Ebixa; ***Chile***: Ebixa; Eutebrol; Lindex; Memax; Mimetix; Vivimex; ***China***: Ebixa (易倍申); ***Cz.***: Axura; Ebixa; ***Denm.***: Axura; Ebixa; ***Fin.***: Ebixa; Mentixa; ***Fr.***: Ebixa; ***Ger.***: Axura; Ebixa; ***Gr.***: Ebixa; ***Hong Kong***: Ebixa; ***Hung.***: Ebixa; ***India***: Admenta; Mentadem; Mentra; ***Irl.***: Axura; Ebixa; ***Israel***: Ebixa; Memox; ***Ital.***: Ebixa; ***Jpn***: Memary; ***Malaysia***: Ebixa; ***Mex.***: Akatinol; Ebixa; Eutebrol; ***Neth.***: Axura; Ebixa; ***Norw.***: Ebixa; ***NZ***: Ebixa; ***Philipp.***: Abixa; Zimerz; ***Pol.***: Axura; Ebixa; ***Port.***: Axura; Ebixa; ***Rus.***: Akatinol (Акатинол); Noojerone (Ноожерон); ***S.Afr.***: Ebixa; ***Singapore***: Ebixa; ***Spain***: Axura; Ebixa; ***Swed.***: Axura; Ebixa; ***Switz.***: Axura; Ebixa; ***Thai.***: Ebixa; Neumantine; ***Turk.***: Alzant; Alzmex; Cogito; Demax; Ebitex; Ebixa; Korint; Melanda; Memanzaks; Memorix; Mexia; ***UK***: Ebixa; Maruxa; Nemdatine; ***Ukr.***: Abixa (Абикса); Mema (Мема); ***USA***: Namenda.

Nizofenone *(rINN)*

Nizofenona; Nizofénone; Nizofenonum; Y-9179; Низофенон.

2′-Chloro-2-[2-[(diethylamino)methyl]imidazol-1-yl]-5-nitrobenzophenone.

$C_{21}H_{21}ClN_4O_3$=412.9

CAS — 54533-85-6.

ATC — N06BX10.

ATC Vet — QN06BX10.

UNII — 7A2NOC3R88.

Nizofenone Fumarate *(rINNM)*

Fumarato de nizofenona; Midafenone Fumarate; Nizofénone, Fumarate de; Nizofenoni Fumaras; Низофенона Фумарат.

$C_{21}H_{21}ClN_4O_3,C_4H_4O_4$=528.9

CAS — 54533-86-7; 93929-95-4.

ATC — N06BX10.

ATC Vet — QN06BX10.

UNII — 1I1Z517Z3Y.

Profile

Nizofenone has been described as a nootropic and cerebral vasodilator. It is used parenterally, as the fumarate, to minimise cerebral ischaemic damage after subarachnoid haemorrhage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Ekonal.

Oxiracetam *(BAN, rINN)*

CGP-21690E; CT-848; ISF-2522; Oksirasetaami; Oxiracétam; Oxiracetamum; Oxracetam; Оксирацетам.

4-Hydroxy-2-oxo-1-pyrrolidineacetamide.

$C_6H_{10}N_2O_3$=158.2

CAS — 62613-82-5.

ATC — N06BX07.

ATC Vet — QN06BX07.

UNII — P7U817352G.

Profile

Oxiracetam has been used as a nootropic in organic brain syndromes and senile dementia.

Dementia. Clinical benefit has been reported in patients with dementia (p. 388.1) given oxiracetam,[1] but in the USA it was withdrawn from phase II clinical studies in patients with Alzheimer's disease due to lack of efficacy.[2]

1. Maina G, *et al*. Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. *Neuropsychobiology* 1990; **21:** 141–5.
2. Parnetti L. Clinical pharmacokinetics of drugs for Alzheimer's disease. *Clin Pharmacokinet* 1995; **29:** 110–29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bei Qing Xing (倍清星); Jian Lang Xing (健朗星); Ou Lai Ning (欧来宁); Ou Lan Tong (欧兰同).

Piracetam *(BAN, USAN, rINN)*

CI-871; Piracétam; Piracetamas; Piracetamum; Pirasetaami; Pirasetam; Pyrrolidone Acetamide; UCB-6215; Пирацетам.

2-(2-Oxopyrrolidin-1-yl)acetamide.

$C_6H_{10}N_2O_2$=142.2

CAS — 7491-74-9.

ATC — N06BX03.

ATC Vet — QN06BX03.

UNII — ZH516LNZ10.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Piracetam). A white or almost white powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol. Protect from light.

Uses and Administration

Piracetam acts on the CNS and has been described as a nootropic; it is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood viscosity at high doses. Piracetam is used as an adjunct in the treatment of myoclonus of cortical origin, and has also been used in dementia (see also p. 396.2). Other disorders or states in which it has been tried (on the basis of a supposed 'cerebrocortical insufficiency' responsive to piracetam) include alcoholism, vertigo,

cerebrovascular accidents, dyslexia, behavioural disorders in children, and after trauma or surgery.

In cortical myoclonus, piracetam is given in oral doses of 7.2 g daily increasing by 4.8 g daily every 3 or 4 days up to a maximum of 24 g daily. It is given in 2 or 3 divided doses. Once the optimal dose of piracetam has been established, attempts should be made to reduce the dose of other drugs. For dosage in renal impairment see p. 396.1.

Piracetam has been given for various other disorders in a usual oral dose of up to 2.4 g daily in 2 or 3 divided doses; doses of up to 4.8 g daily or higher have been used in severe cases. In severe disorders it has also been given by intramuscular or intravenous injection.

General references.

1. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. *CNS Drug Rev* 2005; **11:** 169–82.
2. Malykh AG, Sadaie MR. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. *Drugs* 2010; **70:** 287–312.

Administration in renal impairment. The usual oral dose of piracetam (see p. 393.3) should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC between 50 and 79 mL/minute: two-thirds of the usual dose, given in 2 or 3 divided doses
- CC between 30 and 49 mL/minute: one-third of the usual dose, given in 2 divided doses
- CC between 20 and 29 mL/minute: one-sixth of the usual dose, given as a single dose

Use of piracetam is contra-indicated in those with a CC of less than 20 mL/minute.

Dementia. Although piracetam is used in some countries in the management of cognitive impairment and dementia (p. 388.1), a systematic review[1] concluded that the evidence from the published literature did not support this use.

1. Flicker L, Grimley Evans J. Piracetam for dementia or cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/02/06).

Myoclonus. A review[1] of 62 case reports, 3 open studies, and 2 double-blind studies concluded that piracetam is beneficial in the treatment of disabling myoclonus (p. 511.3), either as adjunctive treatment or as monotherapy. Similar conclusions were made in another review[2] in which experience of 12 patients with progressive myoclonus epilepsy, 8 of whom benefited from piracetam in doses of up to 45 g daily without significant adverse effects, was described.

1. Van Vleymen B, Van Zandijcke M. Piracetam in the treatment of myoclonus: an overview. *Acta Neurol Belg* 1996; **96:** 270–80.
2. Genton P, *et al*. Piracetam in the treatment of cortical myoclonus. *Pharmacopsychiatry* 1999; **32** (suppl): 49–53.

Stroke. Piracetam did not influence the outcome if given within 12 hours of the onset of acute ischaemic stroke in a multicentre, randomised, double-blind study,[1] although post hoc analyses suggested that it might confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate to severe degree. Further analyses of the same data concluded that piracetam did not produce significant adverse effects when given in high doses to patients with acute stroke,[2] and significantly more patients had recovered from aphasia on piracetam than placebo.[3] The results of two further randomised, double-blind, placebo-controlled studies supporting the role of piracetam as an adjunct to intensive speech therapy in improving aphasia following stroke were also reported.[3] In contrast, a systematic review including the first study considered that the trend towards an increased risk of early death in patients allocated to piracetam was of concern, and concluded that the data did not support routine use of piracetam in acute ischaemic stroke.[4]

1. De Deyn PP, *et al*. Treatment of acute and ischemic stroke with piracetam. *Stroke* 1997; **28:** 2347–52.
2. De Reuck J, Van Vleymen B. The clinical safety of high-dose piracetam—its use in the treatment of acute stroke. *Pharmacopsychiatry* 1999; **32** (suppl): 33–7.
3. Huber W. The role of piracetam in the treatment of acute and chronic aphasia. *Pharmacopsychiatry* 1999; **32** (suppl): 38–43.
4. Ricci S, *et al*. Piracetam for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).

Vertigo. Piracetam has been reported to be of benefit in patients with vertigo (p. 612.3) of both central or peripheral origin.[1]

1. Oosterveld WJ. The effectiveness of piracetam in vertigo. *Pharmacopsychiatry* 1999; **32** (suppl): 54–60.

Adverse Effects and Precautions

Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness, and depression. Other reported adverse effects include gastrointestinal disorders such as abdominal pain, diarrhoea, nausea and vomiting, hypersensitivity reactions, ataxia, vertigo, confusion, hallucinations, angioedema, and rashes. Piracetam should not be given to patients with hepatic impairment or severe renal impairment; dosage reduction is recommended for those with mild to moderate renal impairment (see under Uses and Administration, above). Therapy with piracetam should not be withdrawn abruptly in myoclonic patients due to the risk of inducing seizures. When used to treat cortical myoclonus, piracetam is contra-indicated in patients with cerebral haemorrhage, and should be used with caution after major surgery and in those with haemostatic disorders or severe haemorrhage.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piracetam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Anticoagulants. For reference to the effect of piracetam on *warfarin* therapy, see p. 1535.1.

Pharmacokinetics

Piracetam is rapidly and extensively absorbed from the gastrointestinal tract; peak plasma concentrations are reached within 1.5 hours after oral doses. The plasma half-life is reported to be 5 hours and it crosses the blood-brain barrier. Piracetam is excreted almost completely in the urine. It crosses the placenta and is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Noostan; ***Austria***: Cerebryl; Nootropil; Novocephal; Pirabene; ***Belg.***: Braintop; Docpiracet†; Geratam; Noodis; Nootropil; Piracemed†; Piracetop†; ***Braz.***: Cintilan; Nootron; Nootropil; ***Chile***: Nootropyl; ***China***: Hong Wei Li Di (宏威利迪); Kang Ling (康灵); Kang Rong (康容); Lu Si Qi (路思齐); Ning Xiu Xin (宁秀欣); Qing Da (庆达); Si Bi Ke (斯必克); Si Tai (思泰); Tan Fu (坦复); Tong Tan Kang (通坦康); Xin Ao Xin (欣奥欣); Yi An Nuo (益安诺); YiTing (易汀); Zhen Xi (真昔); ***Cz.***: Geratam; Kalicor†; Nootropil; Oikamid; Pirabene; ***Fin.***: Nootropil; ***Fr.***: Gabacet; Nootropyl; ***Ger.***: Cerepar N†; Nootrop; Normabrain†; Piracebral†; Piracetrop†; ***Gr.***: Aminotrophylle-88; Arterosol; Cebragil; Celebral; Centracetam; Cetrop; Cosmoxim; Espritam; Latys; Lobelo; Logofren; Lowtens; Meclivin; Meditam; Noforit; Nootrop†; Oxynium; Piracem; Psycoton; Stamin; Zalipan; ***Hong Kong***: Nootropil; Piratin; ***Hung.***: Cerebryl; Lucetam; Memoril; Nootropil; Pirabene; ***India***: Alcetam; Amritam; Axetam; Brentor; Ceact; Cerecetam; Cetam; E-Tam; Enpir; Etotam; Floracetam; Gencephal; Mincetam; Neopiram; Neurocetam; Neuropil; Nicetam; Nootropil; Normabrain; Normenta†; Nupic; Nurest; Nutam; Orotam; Pirament; Piratam; ***Indon.***: Antikun; Benocetam; Brenaris; Cervas; Cetoros; Chepamed; Ciclobrain; Cytropil; Encebion†; Ethopil; Fepiram; Gotropil; Gracetam; Latropil; Lutrotam; Mersitropil; Neurocet; Neurotam; Noocephal; Noocetam; Nootropil; Notrotam; Nufacetam; Piratrof; Pratropil; Primatam; Procetam; Resibron; Revolan; Scantropil; Sevotam; Sotropil; Tropilex; ***Irl.***: Nootropil†; ***Ital.***: Nootropil; Psycoton; ***Jpn***: Myocalm; Nootropil†; ***Malaysia***: Cebrotonin; Ceretam; Knowful; Nootropil; Syntam; ***Mex.***: Dinagen†; Nootropil; ***Neth.***: Nootropil; ***Norw.***: Nootropil; ***Philipp.***: Irahex; Neurocetam; Neuroton; Nootrocet; Nootropil; Normabrain; Nurocer; Pirasam†; ***Pol.***: Biotropil; Lucetam; Memotropil; Nootropil; ***Port.***: Acetar; Noostan; Nootropil†; Oxibran; ***Rus.***: Eskotropil (Эскотропил); Lucetam (Луцетам); Memotropil (Мемотропил); Nootropil (Ноотропил); Phezam (Фезам); Piratropil (Пиратропил); ***S.Afr.***: Nootropil†; ***Singapore***: Cebrotonin; Cetam; Neurocetam; Nootropil; Piratam; Racetam; ***Spain***: Ciclofalina; Nootropil; ***Swed.***: Nootropil; ***Switz.***: Nootropil; Pirax†; ***Thai.***: Embol; Knoful†; Mancetam; Mempil; Noocetam; Nootropil; Scarda; ***Turk.***: Cerebrofil; Nootropil; Norotrop; ***UK***: Nootropil; ***Ukr.***: Lucetam (Луцетам); Nootropil (Ноотропил); ***Venez.***: Breinox.

Multi-ingredient Preparations. ***Braz.***: Energiclin†; Energivit; Exit; Isketam; ***India***: Neuromin-M; Nutam Plus; ***Port.***: Anacervix; ***Rus.***: Combitropil (Комбитропил); NooCam (НооКам); Omaron (Омарон); Piracezine (Пирацезин); Vinpotropile (Винпотропил); ***Spain***: Anacervix; Devincal†; Diemil; ***Ukr.***: Cinatropil (Цинатропил)†; Evrisam (Эвризам); Memosam (Мемозам); Neuro-Norm (Нейро-Норм); Olatropil (Олатропил); Omaron (Омарон); Phezam (Фезам); Tiocetam (Тиоцетам).

Pramiracetam Sulfate *(USAN, rINNM)*

Amacetam Sulphate; CI-879; Pramiracétam, Sulfate de; Pramiracetam, sulfato de; Pramiracetam Sulphate; Pramiracetami Sulfas; Sulfato de pramiracetam; Прамирацетама Сульфат.

N-[2-(Diisopropylamino)ethyl]-2-oxo-1-pyrrolidineacetamide sulphate.

$C_{14}H_{27}N_3O_2,H_2SO_4$=367.5

CAS — 68497-62-1 (pramiracetam); 72869-16-0 (pramiracetam sulfate).

ATC — N06BX16.

ATC Vet — QN06BX16.

UNII — OP7O7MNS9P.

Profile

Pramiracetam sulfate has been used in age-related memory impairment and senile dementia. It has also been tried, without much success, as an adjunct to ECT in severe depression.

References.

1. McLean A, *et al*. Placebo-controlled study of pramiracetam in young males with memory and cognitive problems resulting from head injury and anoxia. *Brain Inj* 1991; **5:** 375–80.
2. Auteri A, *et al*. Pharmacokinetics of pramiracetam in healthy volunteers after oral administration. *Int J Clin Pharmacol Res* 1992; **12:** 129–32.
3. Scarpazza P, *et al*. Multicenter evaluation of pramiracetam for the treatment of memory impairment of probable vascular origin. *Adv Therapy* 1993; **10:** 217–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ukr.***: Pramistar (Прамистар).

Pyritinol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de piritinol; Piritinol, hidrocloruro de; Pirytynolu dichlorowodorek; Pyrithioxine Hydrochloride; Pyritinol, Chlorhydrate de; Pyritinoli Dihydrochloridum; Pyritinoli Hydrochloridum; Пиритинола Гидрохлорид.

5,5-Dihydroxy-6,6-dimethyl-3,3-dithiodimethylenebis(4-pyridylmethanol) dihydochloride monohydrate.

$C_{16}H_{20}N_2O_4S_2,2HCl,H_2O$=459.4

CAS — 1098-97-1 (pyritinol); 10049-83-9 (anhydrous pyritinol hydrochloride).

ATC — N06BX02.

ATC Vet — QN06BX02.

UNII — 0OE436N2Y2.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Pyritinol hydrochloride has been described as a nootropic that promotes the uptake of glucose by the brain. It has been used in the treatment of various cerebrovascular and mental function disorders. It has been given in a usual oral dose of 600 mg daily in 3 divided doses. Pyritinol hydrochloride has also been given as an alternative to penicillamine in rheumatoid arthritis. It is also an ingredient of various preparations promoted as tonics.

References.

1. Knezevic S, *et al*. Pyritinol treatment of SDAT patients: evaluation by psychiatric and neurological examination, psychometric testing and rCBF measurements. *Int Clin Psychopharmacol* 1989; **4:** 25–38.
2. Lemmel EM. Comparison of pyritinol and auranofin in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1993; **32:** 375–82.
3. Straumann A, *et al*. Acute pancreatitis due to pyritinol: an immune-mediated phenomenon. *Gastroenterology* 1998; **115:** 452–4.
4. Maria V, *et al*. Severe cholestatic hepatitis induced by pyritinol. *BMJ* 2004; **328:** 572–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Encephabol; ***Chile***: Encefabol; ***China***: Ai Nao Xing (爱瑙幸); An Jie De Xin (安洁德欣); Ling Bo Kang (灵博康); Tian Shu Qing (天叔清); Xin Te (信特); Yi Shou (益首); Ying Luo En (英罗恩); ***Cz.***: Encephabol; Enerbol†; ***Ger.***: Encephabol; ***Gr.***: Encephabol; ***Hong Kong***: Encephabol; ***India***: Encephabol; ***Indon.***: Encepan; Encephabol; Enerbol; ***Malaysia***: Pyritil; ***Mex.***: Encephabol; ***Philipp.***: Encephabol; ***Port.***: Cerbon; ***Rus.***: Encephabol (Энцефабол); Enerbol (Энербол)†; ***S.Afr.***: Encephabol†; ***Thai.***: Encephabol; Memonol; Pyritil; ***Ukr.***: Encephabol (Энцефабол); ***Venez.***: Acon; Bonifen; Bonitrop; Fitina.

Multi-ingredient Preparations. ***Arg.***: Ciprovit Energizante; Gabimex Plus; Levantol Procaina; ***Spain***: Refulgin†; Tomevit†.

Rivastigmine *(BAN, USAN, rINN)*

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Rivastigmiini; Rivastigmin; Rivastigmina; Rivastigminum; SDZ-212-713; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Ривастигмин.

(-)-*m*-[(*S*)-1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate.

$C_{14}H_{22}N_2O_2$=250.3

CAS — 123441-03-2.

ATC — N06DA03.

ATC Vet — QN06DA03.
UNII — PKI06M3IW0.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Rivastigmine). A viscous, clear, colourless or yellow or very slightly brown, hygroscopic liquid. Sparingly soluble in water; very soluble in dehydrated alcohol and in heptane. Store in airtight containers under an inert gas at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Rivastigmine). Store in airtight containers under an inert gas at a temperature of 2 degrees to 8 degrees. Protect from light.

Rivastigmine Hydrogen Tartrate

(BANM, rINNM)

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Hidrogenotartrato de rivastigmina; Rivastigmina, hidrogenotartrato de; Rivastigmine Bitartrate; Rivastigmine, Hydrogénotartrate de; Rivastigmine Tartrate; Rivastigmini Hydrogenotartras; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Ривастигмина Гидротартрат.

$C_{14}H_{22}N_2O_2.C_4H_6O_6$=400.4
CAS — 129101-54-8.
ATC — N06DA03.
ATC Vet — QN06DA03.
UNII — 9IY2357JPE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Rivastigmine Hydrogen Tartrate). A white or almost white, very hygroscopic, crystalline or fine crystalline powder. It shows polymorphism. Very soluble in water; soluble in methyl alcohol; very slightly soluble in ethyl acetate. Store in airtight containers. Protect from light.

USP 36: (Rivastigmine Tartrate). A white to off-white powder. Very soluble in water and in methyl alcohol; very slightly soluble in ethyl acetate. Store in airtight containers.

Uses and Administration

Rivastigmine is a carbamate type reversible acetylcholinesterase inhibitor; it also inhibits butyrylcholinesterase. Rivastigmine is selective for the CNS and is used for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (but see p. 398.1) and idiopathic Parkinson's disease (p. 398.1). It is given orally as the hydrogen tartrate or in transdermal patches as the base. For both routes doses are expressed in terms of the base; 2.4 mg of rivastigmine hydrogen tartrate is equivalent to about 1.5 mg of rivastigmine.

An initial oral dose is 1.5 mg given twice daily with food. Thereafter, the dose may be increased according to response and tolerance by increments of 1.5 mg twice daily at intervals of at least 2 weeks to a maximum dose of 6 mg twice daily. In the USA, licensed product information recommends dose increments at intervals of at least 4 weeks when treating dementia associated with Parkinson's disease.

Transdermal patches delivering 4.6, 9.5, or 13.3 mg of rivastigmine over 24 hours are also available for once-daily application. In the USA, rivastigmine patches are licensed for use in the treatment of dementia in Alzheimer's disease or Parkinson's disease; however, in the UK, the licensed use is restricted to dementia in Alzheimer's disease. An initial transdermal dose is 4.6 mg daily; after at least 4 weeks and if well tolerated, the dose should be increased to 9.5 mg daily. US licensed product information states that the dose may be further increased to 13.3 mg daily after at least another 4 weeks; UK licensed product information states that this increase should only be considered after a minimum of 6 months of treatment at the lower dose. A maintenance dose of 4.6 mg daily may be sufficient for patients with a low body-weight (below 50 kg) who develop adverse effects; conversely, those who weigh more than 100 kg may need doses higher than 9.5 mg daily.

Patients already taking oral rivastigmine may be changed to the patches as follows:

- those taking 6 mg daily or less of oral rivastigmine may be switched to patches delivering 4.6 mg over 24 hours
- those taking more than 6 mg daily orally may be switched to patches delivering 9.5 mg over 24 hours

The first patch should be applied on the day following the last oral dose. The patch should be applied to intact skin on the upper or lower back, or on the upper arm or chest; it should not be applied to the abdomen or thigh due to decreased bioavailability. Re-application to the same site should be avoided for 14 days. Only one patch should be applied at a time.

Doses may need to be adjusted in those with hepatic or renal impairment (see p. 398.1).

If treatment with oral or transdermal rivastigmine is interrupted for more than a few days, it should be restarted at the low initial dose, and then increased as described above. Clinical benefit should be reassessed on a regular basis; treatment should be stopped if there is no improvement after 3 months.

Administration in hepatic impairment. Exposure to rivastigmine is increased in patients with hepatic impairment and those with significant impairment may experience more adverse reactions. Recommendations to titrate the dose of rivastigmine to patients' requirements should be closely followed.

Based on pharmacokinetic studies with oral rivastigmine, licensed product information for rivastigmine transdermal patches suggests to consider a dose of 4.6 mg daily as both initial and maximum therapy in patients with mild to moderate hepatic impairment (Child Pugh score of 5 to 9). There is a lack of data on its use in severe hepatic impairment.

Administration in renal impairment. Exposure to rivastigmine may be increased in patients with renal impairment and those with significant impairment may experience more adverse reactions. Recommendations to titrate the dose of rivastigmine to patients' requirements should be closely followed.

Based on pharmacokinetic studies with oral rivastigmine, UK licensed product information for rivastigmine transdermal patches suggests to consider a dose of 4.6 mg daily as both initial and maximum therapy in patients with significant renal impairment. However, US product information does not consider dose adjustment to be necessary in this patient group due to the lack of a clear effect of creatinine clearance on the steady state concentrations of rivastigmine or its metabolite.

Dementia. Rivastigmine may be of benefit in the management of patients with mild to moderate dementia in *Alzheimer's disease*[1,2] (see Dementia, p. 388.1). In the UK, NICE states that it may be used in patients with mild to moderate dementia if given under the following conditions:[3]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Rivastigmine given in titrated doses of up to 6 mg twice daily was also found to be well tolerated, and to produce some improvement in behavioural and psychiatric symptoms, in a group of patients with *Lewy-body dementia.*[4] However, a systematic review[5] that included this study noted that rivastigmine did not have significant benefit in cognitive function compared with placebo; the authors considered that the evidence for its use in such patients was weak and that further trials were needed.

Rivastigmine has also been tried in the treatment of *vascular dementia.* A systematic review[6] concluded that although there is some evidence of benefit in these patients, available data are inadequate and further trials were warranted before rivastigmine could be recommended.

For the use of rivastigmine in the treatment of dementia in Parkinson's disease, see p. 398.1.

1. Birks J, *et al.* Rivastigmine for Alzheimer's disease. Available in The John Wiley; 2009 (accessed 01/03/10).
2. Dhillon S. Rivastigmine transdermal patch: a review of its use in the management of dementia of the Alzheimer's type. *Drugs* 2011; **71:** 1209–31.
3. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
4. McKeith I, *et al.* Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000; **356:** 2031–36.
5. Wild R, *et al.* Cholinesterase inhibitors for dementia with Lewy bodies. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 14/02/06).
6. Craig D, Birks J. Rivastigmine for vascular cognitive impairment. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Parkinsonism. Although acetylcholinesterase inhibitors such as rivastigmine may theoretically worsen parkinsonian symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p. 1030.2). In 2 large studies,[1,2] rivastigmine was found to produce some improvement in symptoms of dementia associated with Parkinson's disease when compared with placebo. Furthermore, a retrospective analysis[3] that included one of these studies concluded that rivastigmine did not induce clinically significant exacerbation of motor dysfunction in this patient group; emergent or worsening rest tremor had been reported, however, this effect was transient and associated with dose titration.

1. Emre M, *et al.* Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004; **351:** 2509–18.
2. Wesnes KA, *et al.* Benefits of rivastigmine on attention in dementia associated with Parkinson disease. *Neurology* 2005; **65:** 1654–6.
3. Oertel W, *et al.* Effects of rivastigmine on tremor and other motor symptoms in patients with Parkinson's disease dementia: a retrospective analysis of a double-blind trial and an open-label extension. *Drug Safety* 2008; **31:** 79–94.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p. 391.1. Application site reactions such as erythema, pruritus, rash, and vesicles have been seen with transdermal use of rivastigmine. Serious adverse effects, including fatalities, have occurred after incorrect use of transdermal patches, the most frequent causes being the failure to remove the previous patch before applying a new one and application of more than one patch at a time. In such cases of overdose all patches should be removed immediately and no further patch applied for the next 24 hours.

Rivastigmine blood levels are dependent on body-weight and careful titration of dosage is recommended in those with a low or high body-weight; for further details, see under Uses and Administration, above.

Rivastigmine should be used with care in patients with impaired hepatic or renal function.

Reviews.

1. Darreh-Shori T, Jelic V. Safety and tolerability of transdermal and oral rivastigmine in Alzheimer's disease and Parkinson's disease dementia. *Expert Opin Drug Safety* 2010; **9:** 167–76.
2. Greenspoon J, *et al.* Transdermal rivastigmine: management of cutaneous adverse events and review of the literature. *CNS Drugs* 2011; **25:** 575–83.

Effects on the gastrointestinal tract. A 67-year-old woman experienced severe vomiting after rivastigmine, in an oral dose of 4.5 mg, was mistakenly reintroduced without the recommended titration phase;[1] the vomiting was so severe that the patient also suffered a rupture of the oesophagus that needed corrective surgery. The authors commented that careful dose titration of rivastigmine is necessary even when restarting treatment.

1. Babic T, *et al.* Spontaneous rupture of oesophagus (Boerhaave's syndrome) related to rivastigmine. *Age Ageing* 2000; **29:** 370–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rivastigmine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Neostigmine, p. 688.3. See also Antimuscarinics, under Donepezil, p. 391.2, for mention of an interaction between rivastigmine and tolterodine.

Pharmacokinetics

Rivastigmine is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached in about 1 hour after oral doses. Food delays absorption by about 1.5 hours and reduces maximum plasma concentrations. Absorption from transdermal patches is slow and peak plasma concentrations are reached in 10 to 16 hours after applying the first patch; with subsequent patches, peak concentrations are reached in about 8 hours. Exposure to rivastigmine is highest when the patch is applied to the upper back, chest, or upper arm, and about 20 to 30% lower when applied to the abdomen or thigh. Rivastigmine is about 40% bound to plasma proteins and readily crosses the blood-brain barrier; it is widely distributed throughout the body. Rivastigmine is rapidly and extensively metabolised, primarily by cholinesterase-mediated hydrolysis to the weakly active decarbamylated metabolite. The plasma half-life is about 1 hour after oral doses and about 3 hours after patch removal. After oral use, more than 90% of a dose is excreted in the urine within 24 hours; no unchanged rivastigmine is detected in the urine. Less than 1% of a dose appears in the faeces.

References.

1. Hossain M, *et al.* Estimation of the absolute bioavailability of rivastigmine in patients with mild to moderate dementia of the Alzheimer's type. *Clin Pharmacokinet* 2002; **41:** 225–34.
2. Kurz A, *et al.* Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review. *Int J Clin Pract* 2009; **63:** 799–805.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Donadox; Exelon; Luneste; Remizeral; Rivasmina; ***Austral.***: Exelon; ***Austria***: Exelon; ***Belg.***: Exelon; ***Braz.***: Exelon; Prometax; ***Canad.***: Exelon; ***Chile***: Exelon; Probrain; ***China***: Exelon (艾斯能); ***Cz.***: Evertas; Exelon; Ivagalmin; Kerstipon; Nimvastid; Prometax; Ristidic; Vastigmex; ***Denm.***: Exelon; Nimvastid; Prometax; ***Fin.***: Exelon; ***Fr.***: Exelon; ***Ger.***: Exelon; ***Gr.***: Exelon; Prometax; ***Hong Kong***: Exelon; ***Hung.***: Exelon; ***India***: Exelon; ***Indon.***: Exelon; ***Irl.***: Exelon; Nimvastid; Prometax; ***Israel***: Exelon; ***Ital.***: Exelon; Prometax; ***Jpn***: Exelon; Rivastach; ***Malaysia***: Exelon; ***Mex.***: Exelon; ***Neth.***:

Exelon; Ivagalmin; Niddastig†; Nimvastid; Prometax; Ristidic; Rivalong; Rivarlau; Rivaxon; Signelon†; ***Norw.***: Exelon; ***NZ***: Exelon; Rimane; ***Philipp.***: Exelon; ***Pol.***: Exelon; Ivagalmin; Nimvastid; Prometax; Ristidic; Rivaller; Rivastinorm; Riveka; Symelon; Velastina; ***Port.***: Exelon; Nimvastid; Prometax; ***Rus.***: Exelon (Экселон); ***S.Afr.***: Exelon; ***Singapore***: Exelon; ***Spain***: Exelon; Prometax; ***Swed.***: Exelon; Nimvastid; ***Switz.***: Exelon; ***Thai.***: Exelon; ***Turk.***: Altigmin; Exelon; Ristart; Rivaxel; ***UK***: Exelon; ***USA***: Exelon; ***Venez.***: Exelon.

Pharmacopoeial Preparations
USP 36: Rivastigmine Tartrate Capsules.

Tacrine Hydrochloride

(BANM, USAN, rINNM)

CI-970; Hidrocloruro de tacrina; Hidrocloruro de tetrahidroaminoacridina; Tacrina, hidrocloruro de; Tacrine, Chlorhydrate de; Tacrini hydrochloridum; Tetrahydroaminoacridine Hydrochloride; THA; Такрина Гидрохлорид.

1,2,3,4-Tetrahydroacridin-9-ylamine hydrochloride.

$C_{13}H_{14}N_2$,HCl=234.7

CAS — 321-64-2 (tacrine); 1684-40-8 (tacrine hydrochloride).

ATC — N06DA01.

ATC Vet — QN06DA01.

UNII — 4966RNG0BU.

Pharmacopoeias. In *US* as the monohydrate.

USP 36: (Tacrine Hydrochloride). The monohydrate occurs as a white powder. Freely soluble in water, in alcohol, in dimethyl sulfoxide, in methyl alcohol, in propylene glycol, and in 0.1N hydrochloric acid; sparingly soluble in linoleic acid and in macrogol 400.

Profile

Tacrine hydrochloride is a centrally acting reversible inhibitor of acetylcholinesterase activity that has been used in the treatment of mild to moderately severe dementia in Alzheimer's disease. However, hepatotoxicity was common and sometimes severe (see under Adverse Effects, p. 398.3).

Tacrine has also been used intravenously to antagonise competitive neuromuscular blockers and as a postoperative respiratory stimulant.

Adverse effects. *EFFECTS ON THE LIVER.* Examination of data from 2446 patients who were at least 50 years old and received tacrine for Alzheimer's disease suggested that raised serum-alanine aminotransferase (ALT) concentrations are likely to occur in about 50% of patients.[1] Most cases developed within the first 12 weeks of therapy,[1] but an asymptomatic increase in ALT concentrations has been reported in a patient after more than 80 weeks of therapy.[2] The increase is usually asymptomatic and mild, and resolves upon dosage reduction or stopping treatment. However, a small percentage of patients may develop unpredictable life-threatening hepatotoxicity although frequent monitoring of ALT concentrations during the first 12 weeks of therapy can identify susceptible individuals. No significant correlation has been found between plasma-tacrine concentrations and hepatotoxicity.[3]

1. Watkins PB, *et al.* Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994; **271:** 992–8.
2. Terrell PS, *et al.* Late-onset alanine aminotransferase increase with tacrine. *Ann Pharmacother* 1996; **30:** 301.
3. Ford JM, *et al.* Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. *Clin Pharmacol Ther* 1993; **53:** 691–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Talem; ***Austral.***: THA†; ***Gr.***: Cognex†; ***USA***: Cognex†.

Pharmacopoeial Preparations
USP 36: Tacrine Capsules.

Xanomeline *(USAN, rINN)*

LY-246708; NNC-11-0232; Xanomelina; Xanoméline; Xanomelinum; Ксаномелин.

3-[4-(Hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridine.

$C_{14}H_{23}N_3OS$=281.4

CAS — 131986-45-3.

UNII — 9ORI6L73CJ.

Profile

Xanomeline is a selective muscarinic M_1 agonist. Xanomeline tartrate has been studied in the management of Alzheimer's disease but drugs of this type have not generally produced benefit.

References.

1. Sramek JJ, *et al.* The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. *J Clin Pharmacol* 1995; **35:** 800–806.
2. Bodick NC, *et al.* Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; **54:** 465–73.

Antidepressants

Bipolar disorder, p. 399
Depression, p. 400
Mania, p. 402

This chapter describes drugs used principally in the treatment of affective disorders. Affective disorders are disorders of mood that may manifest as ***depression*** or ***mania*** or, in some cases, as ***mixed affective states*** in which depressive and manic or hypomanic episodes may coexist or rapidly alternate.

- The core features of ***depressive disorders*** are low mood, anhedonia (the loss of interest in former pleasures or activities), pessimism, and lethargy. They were formerly classified either as ***endogenous***, in which the symptoms were independent of external factors and considered to be a consequence of factors within the patient, or ***reactive***, in which depressive symptoms were a result of external stressors (i.e. exogenous). It is now recognised that depressive disorders are composed of both endogenous and reactive factors. Similarly, the classification of ***neurotic depression*** is no longer considered useful because it encompasses several different syndromes.
  Depressive episodes generally last for at least 2 weeks and are classified according to severity as mild, moderate, severe, or severe with psychosis. ***Recurrent brief depression*** is defined as depressive episodes that last a few days and recur regularly. Depression is often accompanied by characteristic ***somatic*** symptoms, including anorexia, weight loss, insomnia, early morning waking, and psychomotor retardation. Symptoms associated with ***atypical depression*** include overeating and oversleeping. Some classifications distinguish between major depressive episodes and minor (and hence ***major*** or ***minor depression***) based on the number and type of symptoms.
- The main symptoms of ***mania*** are overactivity, mood changes ranging from elation to irritability, expansive ideas, and inflated self-importance. Manic episodes are classified according to severity in a similar manner to depressive disorders: namely, mild, moderate, severe, or severe with psychosis. ***Hypomania*** is differentiated from mania in terms of a reduction in intensity of symptoms and social incapacity.
- Alternating episodes of mania or hypomania and depression are termed ***bipolar disorder (bipolar affective disorder)***. (To differentiate between alternating episodes of depression and mania or depression and hypomania, some classification systems use the terms ***bipolar I disorder*** and ***bipolar II disorder***, respectively.) Since it is very rare for repeated episodes of mania to occur without alternating episodes of depression, it is accepted practice to include mania without depression within the bipolar category. The term ***unipolar disorder*** (***unipolar depression***) is reserved for depressive disorders without mania.
- States of persistent but mild disturbances of mood exist in which the symptoms are not severe enough to meet the criteria for classification as a major depressive or hypomanic disorder, but may nevertheless cause considerable suffering to the patient. ***Subthreshold depressive symptoms*** and ***dysthymia*** are terms used to describe a milder depressive state whereas ***cyclothymia*** has some similarity to bipolar disorder, the instability characterised by long periods of hypomania and mild depression.
- The term ***seasonal affective disorder*** has been applied to depressive disorders repeatedly occurring seasonally, but not related to seasonal stressful life events; the depressive symptoms usually occur during the autumn and winter months. There have also been reports of patients developing seasonal bipolar disorder with hypomania or mania occurring in the summer months.
- Anxiety is often associated with depressive disorders at all levels of severity and it may be difficult to distinguish between the two conditions, especially in the milder forms. ***Mixed anxiety and depressive disorder*** defines a state in which anxiety and depressive symptoms coexist but neither component is severe enough to merit classification as an anxiety disorder or a depressive disorder.

Classification of antidepressants. Antidepressants are classified into different groups either structurally or depending on which central neurotransmitters they act upon. The older tricyclic (e.g. amitriptyline) and related cyclic antidepressants and the monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine) have now been joined by the selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine), the reversible inhibitors of monoamine oxidase type A (RIMAs) (e.g. moclobemide), and more recently by the serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g. venlafaxine). Other antidepressants that do not fit exactly into these groups include bupropion, the herbal preparation St John's wort, mirtazapine, reboxetine, and trazodone.

Lithium salts provide a source of lithium ions that compete with sodium ions at various sites in the body and thus have an action and adverse effects distinct and separate from those of other antidepressants.

Bipolar disorder

Bipolar disorder (manic depression) is a mixed affective disorder in which the patient has alternating episodes of hypomania or mania and depression. Although isolated episodes of mania may occur, they are more usually part of bipolar disorder; for the purposes of classification, mania without depression is therefore included in the bipolar category. Manic episodes usually start suddenly and last on average for about 4 months. The depressive phase may last longer with an average duration of 6 months. The course of the illness is unpredictable; most patients will suffer a relapse after an initial manic episode, and of these, probably 10 to 20% will have more than 3 episodes a year with partial or full remission in between, or switch to the alternative phase (rapid cycling). The diagnosis of bipolar disorder can be difficult, particularly if patients are only seen during the depressive phase. The morbidity of the disorder is often substantial especially during the depressive phase. Suicide is a significant risk and up to one-third of patients may attempt to take their own life.

The treatment of bipolar disorder is generally divided into the following phases:

- acute manic or mixed episode
- acute depressive episode
- maintenance and long-term treatment

Guidelines have been issued in the UK[1-3] and USA[4,5] to facilitate treatment choice in the management of bipolar disorder; international guidelines and expert consensus statements are also available.[6-9] The choice of drug therapy should be guided by severity, the type of episode (including associated symptoms), and patient preference.

In patients with severe **manic** or mixed episodes, initial treatment with an antipsychotic or the mood stabiliser valproate should be considered because of their rapid onset of action; for less severe cases lithium, another mood stabiliser, may also be appropriate.[1,3,6,8] The choice between lithium or valproate as first-line treatment has been a matter of debate: although there is more reliable evidence for the use of lithium, its narrow therapeutic index and monitoring requirements[10-12] (see Pharmacokinetics of Lithium, p. 434.3) have led to the increased use of valproate in some countries.[10] Lithium must also be given in high doses in acute mania and its antimanic actions may be delayed by at least a week.[11,13] Nonetheless, lithium is still widely used[11] and may be most effective in pure euphoric mania.[6,8] However, valproate may be a better first-choice drug in rapid cycling bipolar disorder, for which it is particularly effective, and in mixed or dysphoric states.[1,4,6-8] Carbamazepine and its derivative oxcarbazepine are sometimes used as alternatives to lithium or valproate although their efficacy is not as well established and they are considered a second-line choice by most guidelines.[3,4,6,8] Treatment with carbamazepine is also complicated by its numerous drug interactions.[10,12,13]

Patients with mania and co-existing psychotic features usually require treatment with an antipsychotic to produce a rapid tranquillising effect.[4] Traditionally, classical antipsychotics such as the phenothiazine chlorpromazine and the butyrophenone haloperidol have been used although most guidelines now recommend the atypical antipsychotics, particularly olanzapine, quetiapine, and risperidone, because of their more favourable adverse effect profile.[1,3-6,8] Nevertheless, classical antipsychotics still appear to be widely used in the treatment of mania although high-dose therapy should be avoided because of the risk of extrapyramidal effects.[8] If sedation is required the short-term use of a benzodiazepine such as clonazepam or lorazepam should be considered instead of high-dose antipsychotics;[1,3,4] however, such treatments should be stopped as soon as symptoms subside in order to reduce the risk of dependence.[12]

The initial treatment should be continued at an optimal dose for at least 1 week before making any change to the regimen if the patient is unresponsive; if there is a partial response it may be appropriate to wait at least another week before considering the treatment ineffective. Options for patients who are inadequately controlled on optimised first-line treatment include a trial of lithium or valproate with an antipsychotic.[1,3,4,6,8] (Combination therapy has also been recommended as first-line treatment in patients with particularly severe symptoms.[3,4]) Another option is to try an alternative mood stabiliser or antipsychotic.[6] Clozapine may be considered in more refractory cases[3,4] and ECT is effective in patients who are severely ill or resistant to treatment.[1,3,4,8]

The treatment of the acute **depressive phase** of bipolar disorder depends on the severity of the depression and whether any psychotic symptoms are still present. Less severe cases may be adequately controlled by lithium, which has a modest antidepressant action.[3] Alternatively, treatment with lamotrigine or an antidepressant may be considered although most guidelines[1,3,6,9] recommend that antidepressants should be given with a mood stabiliser such as lithium or valproate to reduce the risk of antidepressant-induced switching (see below). The atypical antipsychotic quetiapine also has an antidepressant action and is another monotherapy alternative for managing the acute depressive phase.[3,9]

The selection of an antidepressant for bipolar depression generally involves the same considerations as those for unipolar depression (see p. 400.1) although the risk of switching to mania should also be taken into account. Antidepressants have also been implicated in the induction of rapid cycling;[4,12] they should be tapered and stopped if either switching or rapid cycling occurs.[1,3,6] The SSRIs and possibly bupropion are usually first-choice antidepressants as they have a low risk of switching when compared with other antidepressants.[3,4,6,9,14] Tricyclic antidepressants should only be used in resistant cases as the risk of switching to mania is higher than with other antidepressant groups.[1,3] Data for the newer antidepressants such as nefazodone and venlafaxine are limited; it has been suggested that the risk of switching with venlafaxine is increased.[6,9] MAOIs may be less likely to induce mania than other antidepressants, but troublesome adverse effects and safety issues have limited their use.

As with the manic phase, treatment should be tried at an optimal dose and for an adequate time before it is considered ineffective.[6,9] If there is no response, second-line options include adding an antidepressant or lamotrigine in those patients on monotherapy with a mood stabiliser such as lithium, or in those patients already on an antidepressant, an alternative antidepressant may be tried or a second mood stabiliser added.[4,6,9] Additional treatment with an antipsychotic may be necessary if psychotic symptoms are also present.[3,4] In addition, some atypical antipsychotics have been shown to be of benefit in non-psychotic bipolar depression when given with an antidepressant[6,9] and one such combination preparation (olanzapine with fluoxetine) is available in some countries. Quetiapine is another atypical antipsychotic that may be added to therapy.[2,3] ECT is a valuable alternative and should be considered for resistant or severe bipolar depression.[1,3,4,9]

Once the acute phase has been brought under control, drug therapy should be continued until the patient is thought unlikely to suffer a relapse; this might entail **maintaining treatment** for several months.[3,4,15] When full remission has been achieved treatment should be gradually stopped over several weeks unless long-term treatment is planned (see below). Antipsychotics and antidepressants are usually stopped unless residual symptoms persist.

Some guidelines[3,4] recommend that **long-term** treatment should be started after a single episode of mania although others generally wait until a patient has had at least 2 manic episodes.[6] Lithium is often the drug of choice for the long-term treatment of bipolar disorder.[1,3,4] It reduces the risk of relapse, particularly mania,[3] although its prophylactic effects on depression are less obvious.[16] Long-term lithium treatment has also been associated with an anti-suicide effect.[3,15] Other treatment options include valproate, lamotrigine (particularly if bipolar depression is a burden), aripiprazole olanzapine, quetiapine, and possibly carbamazepine or oxcarbazepine.[1,3-7] Combination therapy may be necessary in those who fail on monotherapy; ECT and clozapine have also been tried in treatment-resistant patients.[3,7] However, it is usual practice for patients to continue with their acute treatment, given at the same doses, if effective.[3,4,6]

There is no consensus on the appropriate duration of long-term treatment and in some patients with severe

disorders it may be necessary to continue treatment indefinitely.

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Depression

Clinical depression (unipolar depression) is a disturbance of mood that is distinguishable from the usual mood fluctuations of everyday life. A depressed mood is usually the major symptom, which may be accompanied by other mental or somatic symptoms representing several depressive syndromes (see p. 397.1). Suicide is a significant risk and up to half of all patients with depression may attempt suicide during their lifetime. Risk factors for developing depression include female gender and a positive family history.

The aetiology of depression is unknown but it may represent an interaction between psychological and biochemical mechanisms rather than any single factor. The symptoms appear to be mediated through alterations in levels of some central neurotransmitters, although it is not certain that this represents a cause of the disorder. However, it is at this level that the antidepressant drugs currently in clinical use exert their action.

Guidelines have been issued nationally in, for example, the UK[1,2] and the USA,[3-5] and internationally,[6,7] which provide evidence-based recommendations for the treatment of depression. The decision to start treatment should be based on the severity of the condition and the risks to the patient.

- Patients with *subthreshold depressive symptoms* do not routinely require treatment with antidepressants unless symptoms have been present for a long period, typically 2 years or more.[1,2]
- Patients with *mild depression* may improve while being monitored without any additional help; in others simple interventions such as problem-solving, counselling, or exercise may be effective.[2] The evidence for the efficacy of antidepressants in mild depression is lacking and initial treatment with antidepressants is not recommended;[1,2,4] however, patients with persistent mild depression or those with a history of depression may benefit from antidepressant treatment.[1,2]
- Patients with *moderate* depression should be treated with an antidepressant; psychological treatments (particularly cognitive behavioural therapy) are also effective.[1,2]
- A combination of antidepressants and psychological treatments should be considered in patients with *severe* depression.[1,2] ECT may also be of value, particularly when a rapid improvement of symptoms is essential (e.g. in patients at high risk of suicide) or in patients with depressive psychosis or psychomotor retardation.[8,9]
- For patients with *psychotic depression*, an antipsychotic may be required in addition to any antidepressant treatment;[1,2,4] ECT should also be considered.[4]
- Light therapy appears to be effective in patients with *seasonal affective disorder*.[10,11] Exposure to bright artificial light may take place at any time of the day, and the therapy should continue until the natural seasonal remission of the disorder; antidepressant drugs may also be used.

Choice of antidepressant. In more recent years many newer drugs have been licensed and added to the original treatments for depression. The role of these drugs relative to the older drugs is established for some of the newer drug groups, particularly the SSRIs, and evidence suggests that efficacy is comparable. In addition, many new drugs have been promoted on the basis of superior tolerability and this is also supported by clinical studies (see below for further details). The improved choice of treatment options offered by the newer antidepressants has meant that therapy is increasingly tailored to individual patient requirements.

- Tricyclic antidepressants have long been preferred over MAOIs because of the problem of drug interactions and the need for strict dietary precautions with the latter group. Tricyclics with sedative properties may be more suitable for agitated and anxious patients, whereas those with less sedative properties may be preferred for withdrawn and apathetic patients. Unfortunately, the traditional tricyclics such as amitriptyline have antimuscarinic and cardiotoxic adverse effects that can limit their use. Their cardiotoxicity also means that they are associated with a high risk of fatality in patients taking overdoses (see toxicity in overdosage, below).
- Continuing development produced lofepramine and drugs related to the tricyclic group such as mianserin that are less cardiotoxic than the earlier tricyclics.
- The subsequent introduction of SSRIs such as fluoxetine provided a group of drugs with still fewer antimuscarinic and cardiotoxic adverse effects. However, the SSRIs themselves have characteristic adverse effects; gastrointestinal symptoms such as nausea and vomiting may be a problem, and sleep disturbances and anxiety may be exacerbated at the start of treatment. Moreover, those in current clinical use interact to varying degrees with cytochrome P450 isoenzymes, which carries a potential for interaction with many drugs.
- More recently serotonin and noradrenaline reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine have been developed, as well as reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide. RIMAs offer a safer alternative to the MAOIs and fewer dietary restrictions are necessary. Nefazodone, mirtazapine, and reboxetine, which have slightly different biochemical profiles from the major groups, are also more recent introductions. Bupropion, another unrelated antidepressant, is also available in some countries. With the exception of nefazodone, which causes hepatotoxicity and venlafaxine, which is cardiotoxic, most of these newer drugs seem to be associated with fewer severe adverse effects; their efficacy is also comparable to that of the tricyclics and SSRIs.[12-14]
- Other drugs used in the treatment of depression include flupentixol, the antidepressant dose of which is lower than that used for the treatment of psychoses. Agomelatine, an agonist at melatonergic MT_1 and MT_2 receptors and an antagonist at 5-HT_{2C} receptors, is used in the treatment of depression. Ademetionine, the active derivative of methionine, has been tried in depressive disorders, and extracts of the plant St John's wort are widely used in some countries for depression. Transdermal patches containing selegiline, an irreversible inhibitor of monoamine oxidase type B, are available in the USA for the treatment of depression. Lithium may be used for the prophylaxis of recurrent unipolar depression as an alternative to standard antidepressants, although it is more commonly used in the management of bipolar disorder (see p. 397.2); its role in unipolar depression is more usually to augment the effect of standard antidepressants in treatment-resistant disease.

An area of particular concern with regard to initial choice of an antidepressant is the most appropriate drug for patients considered to be a high suicide risk.[15] It is important to remember that suicide is an inherent risk in depression; it is generally accepted that with all antidepressant therapies the risk of suicide may increase in the early stages of recovery (for further details, see Effects on Mental State, under Fluoxetine, p. 422.2). Varying relative risks of **toxicity in overdosage** for different groups of antidepressant have been assessed:[16-19]

- older tricyclics and the tetracyclic maprotiline[20] appear to be more toxic in overdosage than the tetracyclic mianserin[21] and the SSRIs[18,22]
- MAOIs have an intermediate risk[22,23]
- within the tricyclic group, desipramine[16,17,22] has been reported to be associated more frequently with fatal overdosage although some[24] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage; lofepramine[19,22,25] may be one of the safer tricyclics
- toxicity of the SNRI venlafaxine in overdose appears to be greater than other new serotonergic antidepressants and comparable to some of the less toxic tricyclics[22]

Although such analyses cannot determine to what extent the data reflect prescribing patterns and patient selection as opposed to drug toxicity[16,17,25] it is widely accepted that the older tricyclics are more toxic in overdosage, and that the SSRIs[26,27] and the newer tricyclic and related cyclic antidepressants are safer.[27] In practice, it is often difficult to identify patients at high risk for suicide, and it has therefore been suggested that a routine strategy should be to begin antidepressant therapy in all patients with drugs that have low toxicity in overdose.[15,27] However, whichever antidepressant is chosen, all patients should be closely monitored during early therapy until significant improvement in depression occurs and limited quantities of antidepressants should be prescribed at any one time.

Current guidelines recommend that choice of antidepressant should be based on superior tolerability, safety in overdose, and efficacy at prescribed doses.[1,2,4,6] Meta-analyses[28-31] comparing the efficacy of SSRIs and tricyclics in general find no difference in efficacy although there is the suggestion of a greater efficacy for some tricyclics when given to inpatients. However, drop-out rates due to adverse effects have generally been higher in patients receiving tricyclics than in those taking SSRIs. Based on these findings, most guidelines recommend that an SSRI[1,2,4,6] should be used as first-line treatment. In addition some consider that lofepramine, nortriptyline, or newer antidepressants such as mirtazapine or reboxetine are suitable alternatives.[1,4,6] Bupropion, which is marketed as an antidepressant in the USA, is considered to be a first-line choice in US guidelines.[4] Older tricyclics may, however, be more appropriate in severely ill patients or in other situations where maximising efficacy is important.[1] The use of an MAOI may be considered in patients with atypical depression[4,6] although, in practice, SSRIs are often tried initially because of their more favourable adverse effects profile.[4]

The sedative properties of some of the antidepressants may adversely affect the performance of potentially hazardous tasks such as driving and the operation of machinery. One of the less sedative antidepressants should be used where appropriate, although care is needed with all psychotropic drugs, especially at the start of treatment.

Regardless of antidepressant choice, certain principles of management apply when **starting antidepressant therapy**.

- A low initial dose will minimise adverse effects; this is then increased until an adequate response occurs.[4] When the newer antidepressants, including the SSRIs, are used the dose can generally be increased after a few days; for the tricyclics the increase should be more gradual.[32] Gradual introduction of treatment is of particular importance in the elderly who may be more susceptible to adverse effects.
- Although some adverse effects of antidepressant drugs appear soon after treatment is started, there is a delay of about 2 weeks before any therapeutic benefit is seen, and at least 6 weeks before maximum improvement in depressive symptoms occurs.[33] Claims of a fast onset of action have been made for several antidepressants, but in a review[34] of data relating to onset of action with currently available antidepressants, none have been shown conclusively to work faster than any other. This delay in benefit may relate to a combination of pharmacokinetic and neurochemical factors.
- A patient's response to the chosen drug should not be considered inadequate until they have been maintained at an adequate dose for at least 3 to 4 weeks[1,2] (the *BNF* has recommended 6 weeks in the elderly). Patients with a partial response should continue for a further 2 to 4 weeks (possibly longer in the elderly) before considering further adjustments in therapy. Treatment failure is often due to subtherapeutic doses,[1] particularly with the older tricyclics whose adverse effects limit maximum tolerable doses in many patients.[35] Where lack of compliance leads to subtherapeutic doses therapeutic drug monitoring may be of value.[6]

In those who show little or no response to an adequate trial of the first-choice antidepressant the following options exist:

- switching to an alternative antidepressant
- adding another drug (augmentation), particularly if there has been a partial response
- introducing psychological treatments such as cognitive behavioural therapy if not previously used

Guidelines generally consider it preferable to try an alternative single antidepressant before giving combinations of drugs (augmentation).[1-4,6]

If **switching antidepressants** the choice is between a drug from the same pharmacological group or one from a different group.[1-4,6] In the UK, venlafaxine is usually reserved for patients with more severe depression, or when two different SSRIs have failed, because of its adverse cardiovascular effects and toxicity in overdose.[1,2] MAOIs can also be tried in patients who are refractory to or intolerant of treatment with other antidepressants.[1,2,4]

When changing a patient from one type of antidepressant to another an appropriate drug-free interval may be needed. An MAOI (including a RIMA and selegiline) should not be started until at least one week after stopping a tricyclic antidepressant, an SSRI, or any related antidepressant; in the case of bupropion, mirtazapine, and the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine to 5 weeks, because of their longer half-lives. For the tricyclics clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. Conversely, 2 weeks should elapse between stopping MAOI (including selegiline) therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, or any related antidepressant. No treatment-free period is necessary between stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI or another antidepressant.

Drugs that have been used in **augmentation strategies** for resistant depression include lithium,[1,2,4,6] thyroid hormones (liothyronine),[1,4,6,36] and central stimulants[4,36] such as methylphenidate. Atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine, and risperidone may be added to therapy.[1,2,37] Pindolol has also been studied as an augmentation agent with several SSRIs and other serotonergic antidepressants.[6,36] Another method is to combine different classes of antidepressants. Although this has been used successfully in the treatment of drug-resistant depression,[2,4,6,36] it may result in enhanced adverse reactions or interactions and should only be done under expert supervision. For further details of the interactions between different antidepressants, see under Interactions of Phenelzine, p. 447.2.

If the response to treatment is good, the patient should continue with the same treatment for at least 4 to 6 months after full remission,[1-4] and perhaps 12 months in the elderly;[6] symptoms are likely to recur if treatment is stopped too soon.[38-40] In general, the dose should not be reduced for this **continuation phase**.[1,3,4,7] Continuing therapy beyond this phase[1,2,4,7,41] is a matter of clinical judgement and should take into account the number of prior episodes, any residual symptoms, and the severity of the episode. **Maintenance therapy** should be considered for recurrent depressive disorders,[1,2,4,7,38,40,42] and may be necessary for several years, if not indefinitely, in some cases. Again, full therapeutic doses are recommended for prophylaxis rather than reduced doses.[1,2,4,7,39,42]

Suddenly **stopping antidepressant therapy** after regular use for 8 weeks or more may precipitate withdrawal symptoms.[43-45] Common symptoms seen after antidepressant withdrawal include headache, anorexia, nausea, insomnia, and anxiety; the SSRIs have also been associated with episodes of dizziness and paraesthesia which are rarely seen with the tricyclics.[46] Withdrawal reactions may be more severe with the MAOIs especially tranylcypromine.[46] To minimise symptoms, most guidelines[1,2,4] and authorities such as the *BNF* recommend reducing the dose over a period of about 4 weeks, although considerably longer periods (6 months) may be required when withdrawing maintenance therapy.

Depressive disorders may arise in **childhood and adolescence**, the prevalence increasing with age.[6] Concerns about a possible increased risk of suicide with antidepressant treatment, have led to considerable uncertainty about appropriate management in young patients.[47-51] In the UK, guidelines issued by NICE state that the mainstay of treatment for this patient group should be psychological therapy;[47] treatment with antidepressants should only be offered alongside psychological therapy. For children and adolescents with mild depression, as for adults, a period of watchful waiting may be appropriate before starting any treatment. If symptoms have not resolved after several weeks, patients should be started on an appropriate course of psychological therapy such as group cognitive behavioural therapy or guided self-help which should be continued for 2 to 3 months. Antidepressants should not be used for the initial treatment of mild depression. Children or adolescents with moderate to severe depression (or those with mild depression unresponsive to the above measures) should be given more specific psychological treatment such as individual cognitive behavioural therapy, interpersonal therapy, or short-term family therapy. Combined treatment with an antidepressant (which, as in adults, appears more effective than either alone[52]) should only be considered if there is a lack of response to psychotherapy alone.[47] The SSRI fluoxetine is considered the first-choice antidepressant in children aged 12 and over because of proven efficacy and low toxicity in overdose;[6,47] although the evidence for its efficacy in younger children has been questioned,[47] a review by the EMEA concluded that studies showed a positive effect and approved its use throughout the EU in children from 8 years of age.[53] In the USA, escitalopram and fluoxetine are the only SSRIs licensed for the treatment of depression in young patients. The other SSRIs should not be used in children (but see below) because of unproven efficacy and/or an increased risk of a harmful outcome (see Effects on Mental State under Fluoxetine, p. 422.2 for further details). Similar recommendations have been made for the SNRI venlafaxine (see p. 457.2) and the serotonergic antidepressant, mirtazapine (see p. 438.2). Patients who remain unresponsive to combined treatment should be initially tried on an alternative psychological therapy.[47] A change in antidepressant may also be warranted and NICE guidelines have suggested that citalopram and sertraline may be appropriate, provided certain criteria have been met.[47] (Paroxetine and venlafaxine should not be used.[47]) Lithium has also been tried[6] and ECT may be considered for older children with severe, unresponsive depression.[6,47] Tricyclics may have a modest effect in the treatment of depression in adolescents; however, they are not effective in the treatment of younger children.[54] In practice they have often been reserved for refractory cases in adolescents[55] although evidence to support this role is lacking[54] and NICE guidelines[47] do not recommend their use. There have also been reports of death due to cardiotoxicity in children taking tricyclic antidepressants, in particular desipramine and imipramine.

Following the concerns raised about the possible increased risk of suicide in children and adolescents treated with antidepressants, the FDA undertook a meta-analysis of 372 studies in adults. From 295 studies in psychiatric patients, the overall risk of suicide was not increased, but there was a trend toward increased risk with younger age. Although the effect was not statistically significant, the FDA considered the trend sufficiently convincing to warn that, like children and adolescents, **young adults** (aged 18 to 24 years) treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[56] In the UK, an Expert Working Group of the CSM found no clear evidence that use of SSRIs in young adults increased the risk of self-harm or suicidal thoughts;[57] however, it was noted that such patients have a higher background risk of suicidal behaviour than older adults and consequently should be closely monitored during treatment.

Depression in the **elderly** is not uncommon and may affect up to 4% of this population.[58] Suicide is also more frequent in the elderly than in the general population and depressive symptoms are present in about 80% of patients aged over 74 years who commit suicide.[58] Depression in the elderly is often undertreated and prognosis is poor; treatment is also often complicated by co-existing medical conditions.[4,6,58,59] SSRIs are often the first choice of treatment in the elderly because of their favourable adverse effect profile and low toxicity in overdose.[4,6,58,59] They may be especially appropriate in patients with an existing cardiovascular disease or in those taking other medications that may lower the blood pressure. Tricyclics such as amitriptyline and imipramine are probably best avoided in the elderly as their cardiotoxic, antimuscarinic, and sedative effects may be particularly troublesome. However, the tricyclics desipramine and nortriptyline are considered by some[4,6,58] to be an alternative first-choice as they are less cardiotoxic and have fewer antimuscarinic and sedative actions compared with amitriptyline or imipramine. Other newer antidepressants may also be useful in specific situations; bupropion, which has the advantage of a relative lack of cardiotoxicity and drug interactions, may be an appropriate option.[4] Lower initial doses of antidepressant drugs are often recommended in the elderly to minimise adverse effects but individual differences in metabolism and excretion may mean that some patients are undertreated. The elderly tend to respond more slowly to antidepressants than younger patients[6] and additional psychosocial or psychotherapeutic management is often warranted.[4,58] The management of inadequate responses to initial therapies in elderly patients should follow the same principles as in younger patients.[6,58] ECT is also safe and effective in the elderly, and should be considered in those at high risk for suicide or who are refractory to or intolerant of antidepressant drugs.[6,58] Depression late in life may require long-term antidepressant treatment beyond the recovery phase, even after first episodes of depression and should be a continuation of the treatment that was successful in the initial acute phase (see above).

Treatment of women with depressive disorders during and after **pregnancy** raises concerns about the risk of teratogenicity, fetal growth retardation, or perinatal problems (see also individual drug monographs); the ratio of risk to the child versus the benefit to the mother must therefore be considered very carefully.[6,60,61] It should also be remembered that untreated depression during pregnancy has been associated with poor neonatal outcomes such as low birth-weight.[61] In some cases starting treatment with an antidepressant will be appropriate although psychotherapy and ECT should also be considered as alternatives.[6,61] Treatment should not be stopped as a matter of routine in early pregnancy in women who become pregnant while taking an antidepressant.[60] Maternal mood disorders in the immediate postpartum period are related to hormonal changes, particularly falling progesterone levels; the symptoms are mild and resolve spontaneously after several days, therefore no treatment is required.[4,6] Of greater concern are major depressive episodes that occur beyond this initial phase, which are clinically identical to depressive disorders in general and call for the same principles of management[60] (although there are few studies to support this[62]). These depressive episodes have been found to be related to the presence of immediate postpartum mood disorders, although no hormonal basis to this association has been identified.[60] Nevertheless, there has been interest in the use of oestrogen as a treatment.

As with use of any medicine in women who **breastfeed**, the risks to the infant from drugs distributed into breast milk must be considered. The American Academy of Pediatrics[63] considers that the effect of all antidepressants on nursing infants could be of concern.

Symptoms of **anxiety and depression** often coexist and it may be difficult to distinguish which is the predominant disorder, especially in milder forms. Depression is generally treated before anxiety,[2] using antidepressants such as SSRIs that also have anxiolytic effects.[64] Where anxiety predominates, comorbid mild depression may also respond to psychological treatment of anxiety.[64] Anxiolytics and antipsychotics can be useful adjuncts in agitated depression, but a sedative antidepressant might be preferable. Combination preparations of antidepressants with antipsychotics or anxiolytics should not be used because the dosage of the individual components should be adjusted separately. Also, anxiolytics should only be prescribed on a short-term basis whereas antidepressants are given for longer periods.

The efficacy of antidepressants in **chronic fatigue syndrome** in clinical studies have been equivocal although it has been suggested that antidepressant therapy should be tried in patients with co-existing depression.[65] Cognitive therapy may also be useful.

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Mania

Although isolated episodes of mania (see p. 397.1) may occur, mania is usually followed by depression when it is considered to be part of bipolar disorder. It is accepted practice to include mania without depression within the bipolar category. The treatment and prophylaxis of acute mania are therefore described under Bipolar Disorder, p. 397.2.

Agomelatine *(BAN, rINN)*

Agomelatina; Agomélatine; Agomelatinum; S-20098; Агомелатин.

N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide.

$C_{15}H_{17}NO_2$=243.3

CAS — 138112-76-2.

ATC — N06AX22.

ATC Vet — QN06AX22.

UNII — 137R1N49AD.

Uses and Administration

Agomelatine is an agonist at melatonergic MT_1 and MT_2 receptors, and an antagonist at 5-HT_{2C} receptors. It is given orally in the treatment of depression (p. 398.1) at a dose of 25 mg once daily at bedtime. After 2 weeks, the dose may be increased to 50mg at bedtime if necessary. Unlike many other antidepressants, there is no need to taper the dose of agomelatine when treatment is stopped.

Agomelatine is under investigation in the management of anxiety.

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Adverse Effects and Precautions

The most common adverse effects that occur in the first few weeks of agomelatine treatment are transient nausea and dizziness, which are usually mild or moderate. Other gastrointestinal disturbances, headache, somnolence, insomnia, migraine, hyperhidrosis, back pain, and fatigue are also reported as being common adverse effects. There have been cases of paraesthesia, blurred vision, and eczema.

Increases in serum transaminases are common during agomelatine therapy, and the drug is contra-indicated in patients with hepatic impairment. Liver function should be tested before starting agomelatine, and after about 6, 12, and 24 weeks of treatment. Liver function tests should be repeated within 48 hours in any patient who has increased serum transaminase values. The drug should be stopped if values increase to more than 3 times the upper limit of normal, and liver function should be monitored until they return to normal. Liver function should also be tested in any patient who develops symptoms of hepatic dysfunction, and agomelatine should be stopped if jaundice occurs.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is noted because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions followed when treating patients with depression should therefore be followed when treating patients with other disorders.

Agomelatine should be used with caution in patients with bipolar disorder because of the risk of precipitating mania.

As with other antidepressants, agomelatine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Children. Agomelatine has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age is not recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on Mental State, under Fluoxetine, p. 422.2).

Interactions

Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP1A2 have the potential to interact with agomelatine. By this mechanism, fluvoxamine can markedly inhibit the metabolism of agomelatine and increase systemic exposure by about sixtyfold. The use of agomelatine with potent CYP1A2 inhibitors is therefore contra-indicated. Moderate CYP1A2 inhibitors, such as oestrogens, may also increase exposure to agomelatine, and such combinations should be used with caution.

Pharmacokinetics

Agomelatine is rapidly and well absorbed after oral dosage and peak plasma concentrations occur within 1 to 2 hours; however, it has a low absolute bioavailability of less than 5% with substantial interindividual variability. It is about 95% bound to plasma proteins. Systemic exposure increases proportionally with dose, and first-pass metabolism becomes saturated at higher doses. Agomelatine is rapidly metabolised, mainly by the hepatic cytochrome P450 isoenzyme CYP1A2; the isoenzymes CYP2C9 and CYP2C19 also make a minor contribution. It has a mean plasma half-life of between 1 and 2 hours and is mainly excreted in the urine as inactive metabolites. Systemic exposure to agomelatine is substantially increased in patients with liver impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Valdoxan; ***Austral.***: Valdoxan; ***Austria***: Valdoxan; ***Belg.***: Valdoxan; ***Braz.***: Valdoxan; ***China***: Valdoxan (维度新); ***Cz.***: Thymanax; Valdoxan; ***Denm.***: Valdoxan; ***Fr.***: Valdoxan; ***Ger.***: Valdoxan; ***Gr.***: Valdoxan; ***Hong Kong***: Valdoxan; ***Hung.***: Valdoxan; ***Irl.***: Thymanax; Valdoxan; ***Malaysia***: Valdoxan; ***Neth.***: Thymanax; Valdoxan; ***Pol.***: Thymanax; Valdoxan; ***Port.***: Thymanax; Valdoxan; ***Rus.***: Valdoxan (Вальдоксан); ***Singapore***: Valdoxan; ***Spain***: Thymanax; Valdoxan; ***Swed.***: Valdoxan; ***Switz.***: Valdoxan; ***Thai.***: Valdoxan; ***Turk.***: Valdoxan; ***UK***: Valdoxan; ***Ukr.***: Melitor (Мелитор).

Amineptine Hydrochloride *(rINNM)*

Amineptina, hidrocloruro de; Amineptine, Chlorhydrate d'; Amineptini Hydrochloridum; Hidrocloruro de amineptina; S-1694; Аминептина Гидрохлорид.

7-[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)amino] heptanoic acid hydrochloride.

$C_{22}H_{27}NO_2$,HCl=373.9

CAS — 57574-09-1 (amineptine); 30272-08-3 (amineptine hydrochloride).

ATC — N06AA19.

ATC Vet — QN06AA19.

UNII — A5P604A12R.

Profile

Amineptine hydrochloride is a tricyclic antidepressant (see Amitriptyline, p. 403.1). It has been given orally in the treatment of depression.

Hepatic adverse effects seem to be more common than with most other tricyclic antidepressants (see Effects on the Liver, p. 405.3). Also amineptine has been subject to abuse and withdrawal has been both prolonged and difficult; for these reasons, it is no longer marketed in many countries.

Adverse effects. In 5 patients very severe acne-type lesions were associated with the chronic self-increased use of high doses of amineptine (0.2 to 1 g daily).[1] Unusual lactam metabolites were found in all patients and in 2 these were still present, along with the lesions, 3 months after stopping therapy. In another case, a 48-year-old woman developed acne-like eruptions after long-term use of amineptine 400 mg daily.[2] There was no clinical improvement 6 months after amineptine withdrawal.

1. Vexiau P, *et al*. Severe acne-like lesions caused by amineptine overdose. *Lancet* 1988; **i:** 585.
2. De Gálvez Aranda MV, *et al*. Acneiform eruption caused by amineptine: a case report and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15:** 337–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Survector.

Amitriptyline *(BAN, rINN)*

Amitriptilina; Amitriptyliini; Amitriptylin; Amitriptylinum; Амитриптилин.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene) propyldimethylamine; 10,11-Dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine.

$C_{20}H_{23}N$=277.4

CAS — 50-48-6.

ATC — N06AA09.

ATC Vet — QN06AA09.

UNII — 1806D8D52K.

Amitriptyline Embonate *(BANM, rINNM)*

Amitriptilina, embonato de; Amitriptyline, Embonate d'; Amitriptylini Embonas; Embonato de amitriptilina; Амитриптилина Эмбонат.

$(C_{20}H_{23}N)_2C_{23}H_{16}O_6$=943.2

CAS — 17086-03-2.

Pharmacopoeias. In *Br.*

BP 2014: (Amitriptyline Embonate). A pale yellow to brownish-yellow, odourless or almost odourless powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in chloroform. Protect from light.

Amitriptyline Hydrochloride *(BANM, rINNM)*

Amitriptilin Hidroklorür; Amitriptilina, hidrocloruro de; Amitriptilin-hidroklorid; Amitriptilino hidrochloridas; Amitriptyliinihydrokloridi; Amitriptyline, chlorhydrate d'; Amitriptylinhydrochlorid; Amitriptylin-hydrochlorid; Amitriptylinhydroklorid; Amitriptylini Hydrochloridum; Amitryptyliny chlorowodorek; Hidrocloruro de amitriptilina; Амитриптилина Гидрохлорид.

$C_{20}H_{23}N$,HCl=313.9

CAS — 549-18-8.

UNII — 26LUD4JO9K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Amitriptyline Hydrochloride). A white or almost white powder or colourless crystals. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Amitriptyline Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.0.

Stability. Decomposition occurred when solutions of amitriptyline hydrochloride in water or phosphate buffers were autoclaved at 115 degrees to 116 degrees for 30 minutes in the presence of excess oxygen.[1]

The decomposition of amitriptyline as the hydrochloride in buffered aqueous solution stored at 80 degrees in the dark was accelerated by metal ions.[2] Disodium edetate 0.1% significantly reduced the decomposition rate of these amitriptyline solutions but propyl gallate and hydroquinone were less effective. Sodium metabisulfite produced an initial lowering of amitriptyline concentration and subsequently an acceleration of decomposition. The rate of decomposition was also much greater in amber glass ampoules than in clear glass ones (the metal ion content of amber glass is higher than that of clear glass). However, there were considerable variations between different batches of amber glass and, since amitriptyline is photolabile, its solutions are likely to be stored in amber containers.

Solutions of amitriptyline hydrochloride in water are stable for at least 8 weeks at room temperature if protected from light either by storage in a cupboard or in amber containers.[3] Decomposition to ketone and, to a lesser extent, other unidentified products was found to occur on exposure to light.

1. Enever RP, *et al.* Decomposition of amitriptyline hydrochloride in aqueous solution: identification of decomposition products. *J Pharm Sci* 1975; **64:** 1497–9.
2. Enever RP, *et al.* Factors influencing decomposition rate of amitriptyline hydrochloride in aqueous solution. *J Pharm Sci* 1977; **66:** 1087–9.
3. Buckles J, Walters V. The stability of amitriptyline hydrochloride in aqueous solution. *J Clin Pharm* 1976; **1:** 107–12.

Uses and Administration

Tricyclic antidepressants such as amitriptyline were developed from phenothiazine compounds related to chlorpromazine and, as the name suggests, possess a 3-ring molecular structure. They inhibit the neuronal reuptake of noradrenaline in the CNS; some, in addition, inhibit the reuptake of serotonin (5-HT). Prevention of the reuptake of these monoamine neurotransmitters, which potentiates their action in the brain, appears to be associated with antidepressant activity. Tricyclic antidepressants also possess affinity for muscarinic and histamine H_1 receptors to varying degrees, see under Adverse Effects, p. 404.3. Amitriptyline is one of the more sedating tricyclics. Antidepressants with one, two, or four rings have also been developed, and these share only some of the properties of the tricyclics.

While the sedative action and other adverse effects of amitriptyline and other tricyclics are soon apparent, it may be several weeks before any antidepressant effect is seen. After a response has been obtained, maintenance therapy should be continued at the optimum dose for at least 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects.

Amitriptyline, a dibenzocycloheptadiene, is usually given orally as the hydrochloride and doses are expressed in terms of this salt. Amitriptyline hydrochloride is also given by intramuscular or slow intravenous injection; doses may be expressed in terms of the base or the hydrochloride. Amitriptyline hydrochloride 75 mg is equivalent to about 66.3 mg of the base. Amitriptyline has also been given orally as the embonate and as the oxide (amitriptylinoxide).

In the treatment of **depression**, amitriptyline hydrochloride is given initially in a daily dose of 50 to 75 mg orally in divided doses (or as a single dose at night). Thereafter, the dose may be gradually increased, if necessary, to 150 mg daily, the additional doses being given in the late afternoon or evening. Doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

Adolescent and elderly patients often have reduced tolerance to tricyclic antidepressants and UK licensed product information states that initial doses of amitriptyline hydrochloride as low as 25 mg daily may be used in these groups, given either in divided doses or as a single dose, preferably at bedtime. The *BNF* suggests a minimum initial dose of 30 mg daily. In the UK, the use of amitriptyline in children under 16 years for the treatment of depression is not recommended.

In the initial stages of treatment, if oral dosage is impracticable or inadvisable, amitriptyline hydrochloride may be given by intramuscular injection, but the oral route should be substituted as soon as possible. Doses are similar to those usually given orally. The intravenous route has also been used.

Dose adjustments have been suggested for patients with genetic polymorphisms in the cytochrome P450 isoenzymes CYP2D6 and CYP2C19 (see Administration in Genetic Variation, p. 403.2).

Tricyclic antidepressants, including amitriptyline, may be helpful in some **anxiety disorders** such as panic disorder, and in the management of **neuropathic pain** (see p. 404.2). For the uses of amitriptyline in children, see p. 403.2.

Amitriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. Amitriptyline is used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for when other methods have failed and should preferably only be given to cover periods away from home. Tricyclic antidepressants are not recommended in children under 6 years of age. For a discussion of tricyclic use in nocturnal enuresis, see Micturition Disorders, p. 404.1.

Oral doses of amitriptyline hydrochloride that may be used are:

- 10 to 20 mg for children aged 6 to 10 years
- 25 to 50 mg for children 11 years and over

The dose should be given at night and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination, including an ECG, is recommended before a further course.

For the use of amitriptyline in children with **neuropathic pain**, see p. 404.2.

Administration in genetic variation. The effect of cytochrome P450 isoenzymes CYP2D6 and CYP2C19 genotypes on tricyclic antidepressant dosage has been reviewed,[1] and the following adjustments, based on phenotype, have been suggested for their use in depression:

CYP2D6 phenotype and amitriptyline or nortriptyline use

- ultrarapid metaboliser: avoid due to potential lack of efficacy; if use is warranted, consider increasing the initial dose (see Uses and Administration, above) and use therapeutic drug monitoring to guide dose adjustments
- extensive metaboliser (77 to 92% of Caucasian population): the usual initial dose may be given
- intermediate metaboliser: consider reducing the initial dose by 25% and use therapeutic drug monitoring to guide dose adjustments
- poor metaboliser: avoid due to increased potential for adverse effects; if use is warranted, consider decreasing the initial dose by 50% and use therapeutic drug monitoring to guide dose adjustments

CYP2C19 phenotype and amitriptyline use

- ultrarapid metaboliser: consider alternative drug; if use is warranted, use therapeutic drug monitoring to guide dose adjustments
- extensive metaboliser (35 to 50% of multiethnic population): the usual initial dose may be given
- intermediate metaboliser: the usual initial dose may be given
- poor metaboliser: consider decreasing the initial dose by 50% and use therapeutic drug monitoring to guide dose adjustments

The authors suggested that because tricyclics have comparable pharmacokinetic profiles, the above guidance may be applied to other tricyclics including clomipramine, desipramine, doxepin, imipramine, and trimipramine; however, it was noted that there are fewer data to support such dosage adjustments in these drugs.

1. Hicks JK, *et al.* Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther* 2013; **93:** 402–8.

Anxiety disorders. For the use of tricyclic antidepressants in anxiety disorders, see under Clomipramine, p. 414.2.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Antidepressants can help to reduce the frequency of overeating and some other symptoms of bulimia but relapse tends to occur when stopped. Many antidepressants have been tried, but the tricyclic desipramine and the SSRI fluoxetine have been the most commonly used and are considered to be well tolerated.

References.

1. Hay PPJ, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/07/10).
2. Bacaltchuk J, Hay PPJ. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 28/07/10).

Ciguatera poisoning. Amitriptyline has relieved some of the neurological symptoms associated with ciguatera poisoning (see Mannitol, p. 1428.2).

Cocaine dependence. For the use of tricyclic antidepressants in cocaine dependence, see under Desipramine, p. 415.2.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Although less well tolerated than the newer antidepressants, tricyclic antidepressants may still be chosen because of wide experience with their use and familiarity with their pharmacological actions. The more sedating tricyclics such as amitriptyline, clomipramine, dosulepin, doxepin, and trimipramine may be of value in depression with associated agitation or anxiety. The less sedating tricyclics such as amoxapine, desipramine, imipramine, lofepramine, nortriptyline, and protriptyline may be of value for withdrawn or apathetic depressed patients. However, the *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage and not recommended for treatment of depression, and that dosulepin should only be prescribed by specialists.

Combination therapy with differing classes of antidepressants, including the tricyclics, has been used in the treatment of refractory or drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and requires expert supervision. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2.

References.

1. Deisenhammer EA, *et al.* Intravenous versus oral administration of amitriptyline in patients with major depression. *J Clin Psychopharmacol* 2000; **20:** 417–22.
2. Guaiana G, *et al.* Amitriptyline for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).

Headache. Tricyclic antidepressants can be effective in the management of some types of headache and, although they are especially useful when the headache is accompanied by depression, their beneficial effects appear to be independent of their antidepressant action. They are used for the prophylaxis of migraine (p. 670.3) when drugs such as propranolol have proved ineffective. Amitriptyline is the tricyclic usually used but others have been tried. It

has also been investigated in children. The *BNF* suggests an initial adult dosage for amitriptyline hydrochloride in the prophylaxis of migraine of 10 mg orally at night, increased if necessary to a dose of 50 to 75 mg (maximum of 150 mg) at night; the need for continuing prophylaxis should be reviewed at intervals of about 6 months. Tricyclics are also used prophylactically in the control of chronic tension-type headache (p. 671.3) although benefit is rarely complete. Improvement is generally seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression. Amitriptyline may be used in the management of symptoms during withdrawal in patients with medication-overuse headache (p. 670.2).

References.
1. Mathew NT. Prophylaxis of migraine and mixed headache: a randomized controlled study. *Headache* 1981; **21:** 105–9.
2. Pfaffenrath V, *et al*. Combination headache: practical experience with a combination of a β -blocker and an antidepressive. *Cephalalgia* 1986; **6** (suppl 5): 25–32.
3. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; **1:** 216–23.
4. Ziegler DK, *et al*. Propranolol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. *Arch Neurol* 1993; **50:** 825–30.
5. Pfaffenrath V, *et al*. Efficacy and tolerability of amitriptylinoxide in the treatment of chronic tension-type headache: a multi-centre controlled study. *Cephalalgia* 1994; **14:** 149–55.
6. Hershey AD, *et al*. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache* 2000; **40:** 539–49.
7. Holroyd KA, *et al*. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001; **285:** 2208–15.
8. Descombes S, *et al*. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. *Headache* 2001; **41:** 178–82.
9. Jackson JL, *et al*. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ* 2010; **341:** c5222.

Hiccup. Amitriptyline is one of many drugs for which there are anecdotal reports[1] of success in the treatment of intractable hiccup (p. 1046.3).

1. Stalnikowicz R, *et al*. Amitriptyline for intractable hiccups. *N Engl J Med* 1986; **315:** 64–5.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p. 2314.1), initial treatment is usually with a central stimulant. Tricyclic antidepressants such as imipramine or desipramine are reserved for patients who fail to respond to or who are intolerant of stimulants. They may also be of use for selected patients with certain co-existing disorders.

Interstitial cystitis. Tricyclic antidepressants have been found to be of benefit in the treatment of interstitial cystitis (p. 2348.1). In a placebo-controlled study in 48 patients with interstitial cystitis, amitriptyline treatment (in doses ranging from 25 to 100 mg daily) significantly reduced the symptom score and improved pain and urgency when compared with placebo;[1] however, in some patients the antimuscarinic adverse effects of amitriptyline were troublesome. Amitriptyline or imipramine have also been given at night, with methenamine hippurate during the day, in the treatment of interstitial cystitis.[2]

1. van Ophoven A, *et al*. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol (Baltimore)* 2004; **172:** 533–6.
2. Cardozo L. Postmenopausal cystitis. *BMJ* 1996; **313:** 129.

Irritable bowel syndrome. A tricyclic antidepressant may be tried in irritable bowel syndrome (p. 1813.3), particularly where diarrhoea and abdominal pain are presenting symptoms.

Micturition disorders. Tricyclic antidepressants are among the drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of **nocturnal enuresis** in children (p. 2349.1) in whom organic pathology has been excluded. However, because of their potentially fatal toxicity in overdosage, there has been concern over the safety of using tricyclics in households with children. Most experience in nocturnal enuresis has been with imipramine, but other tricyclics such as amitriptyline, nortriptyline, and clomipramine have also been used. Their mechanism of action in nocturnal enuresis is unclear. It may be the result of their antimuscarinic and antispasmodic actions as well as their effect on sleep patterns and possible stimulation of antidiuretic hormone secretion. Imipramine appears to be most effective in older children, but many patients develop tolerance and increasingly higher doses are required.

Tricyclic antidepressants are also sometimes used in the management of **urinary incontinence** (p. 2349.2).

References.
1. Glazener CMA, *et al*. Tricyclic and related drugs for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 24/11/05).

Narcoleptic syndrome. Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis associated with narcolepsy (p. 2314.3). Imipramine has been widely used for these symptoms although some consider clomipramine more effective. The onset of action is quicker than when used for depression and doses required appear to be lower (typically 10 to 75 mg of imipramine daily) although tolerance may develop. Doses should be titrated to provide maximal protection for the time of day when symptoms usually occur.

Pain. Tricyclic antidepressants, usually amitriptyline, are useful in alleviating some types of pain when given in subantidepressant doses. An initial oral dose of amitriptyline hydrochloride 10 mg at night increased gradually if necessary to about 75 mg daily has been suggested by the *BNF* for the management of neuropathic pain in adults. Similar doses of amitriptyline hydrochloride are also suggested by the *BNFC* for the treatment of neuropathic pain, either chronic or in palliative care, in children aged 12 years and over; in addition, younger children aged 2 years and above may receive an initial dose of 200 to 500 micrograms/kg (to a maximum of 10 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily on specialist advice.

Chronic neuropathic pain as seen in cancer (p. 7.1), central post-stroke pain (p. 7.3), diabetic neuropathy (p. 8.2), phantom limb pain (p. 10.3), and postherpetic neuralgia (p. 10.3) responds to therapy with tricyclics. Tricyclics are also often of benefit in the treatment of idiopathic orofacial pain (p. 10.2), and may be of value for patients with complex regional pain syndrome (p. 8.1). Pain and sleep quality may be improved by tricyclics in patients with fibromyalgia (see Soft-tissue Rheumatism, p. 14.2), a condition that responds poorly to analgesics and anti-inflammatory drugs. See also Choice of Analgesic on p. 4.2. Patients with migraine or chronic tension-type headache may also benefit from tricyclics (see Headache, p. 401.3). There is little evidence for an analgesic effect of tricyclics in acute or arthritic pain.

References.
1. Onghena P, Van Houdenhove, B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992; **49:** 205–19.
2. McQuay HJ, *et al*. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68:** 217–27.
3. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; **156:** 1047–52.
4. McQuay HJ, Moore RA. Antidepressants and chronic pain. *BMJ* 1997; **314:** 763–4.
5. Joss JD. Tricyclic antidepressant use in diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 996–1000.
6. Arnold LM, *et al*. Antidepressant treatment of fibromyalgia: a meta-analysis and review. *Psychosomatics* 2000; **41:** 104–13.
7. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci* 2001; **26:** 30–6.
8. Reisner L. Antidepressants for chronic neuropathic pain. *Curr Pain Headache Rep* 2003; **7:** 24–33.

Pathological crying or laughing. Pathological crying or laughing can result from lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressants and favourable results have been reported in double-blind studies with amitriptyline[1] and nortriptyline.[2]

1. Schiffer RB, *et al*. Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985; **312:** 1480–2.
2. Robinson RG, *et al*. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry* 1993; **150:** 286–93.

Premenstrual syndrome. For reference to the tricyclic antidepressant, clomipramine, in premenstrual syndrome, see p. 414.3.

Schizophrenia. Antidepressants such as the tricyclics are considered worth trying as an adjunct in the treatment of patients with schizophrenia (p. 1031.3) who develop depression during the recovery phase after an acute episode of psychosis. There is, however, no clear evidence that they are effective during acute psychotic episodes or for depression during periods of remission in patients with chronic schizophrenia.[1]

1. Anonymous. The drug treatment of patients with schizophrenia. *Drug Ther Bull* 1995; **33:** 81–6.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of tricyclic antidepressants (see Effects on Sexual Function in Adverse Effects, p. 406.1). Such properties have been studied as a potential form of treatment for men with premature ejaculation (see Clomipramine, p. 414.3).

Skin disorders. See under Doxepin, p. 416.3, for use of tricyclic antidepressants in skin disorders.

Smoking cessation. Tricyclic antidepressants are among the drugs that have been tried with varying degrees of success as alternatives to nicotine replacement therapy (NRT) to alleviate the withdrawal syndrome associated with smoking cessation (p. 2570.2). Nortriptyline is recommended by some as a second-line treatment in those patients who cannot tolerate or relapse after NRT.

References.
1. Hughes JR, *et al*. Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Adverse Effects

Many adverse effects of amitriptyline and similar tricyclic antidepressants are caused by their antimuscarinic actions. Antimuscarinic effects are relatively common and occur before an antidepressant effect is obtained. They include dry mouth, constipation occasionally leading to paralytic ileus, urinary retention, blurred vision and disturbances in accommodation, increased intra-ocular pressure, and hyperthermia. Tolerance is often achieved if treatment is continued and adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Drowsiness may also be common, although a few tricyclic antidepressants possess little or no sedative potential and may produce nervousness and insomnia. Other neurological adverse effects include headache, peripheral neuropathy, tremor, ataxia, epileptiform seizures, tinnitus, and occasional extrapyramidal symptoms including speech difficulties (dysarthria). Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Gastrointestinal complaints include sour or metallic taste, stomatitis, and gastric irritation with nausea and vomiting.

Effects on the cardiovascular system are discussed in more detail below (p. 405.1). Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported and, rarely, cholestatic jaundice and blood disorders, including eosinophilia, bone-marrow depression, thrombocytopenia, leucopenia, and agranulocytosis.

Endocrine effects include testicular enlargement, gynaecomastia and breast enlargement, and galactorrhoea. Sexual dysfunction may also occur. Changes in blood sugar concentrations may also occur, and, very occasionally, hyponatraemia associated with inappropriate secretion of antidiuretic hormone.

Other adverse effects that have been reported are increased appetite with weight gain (or occasionally anorexia with weight loss). Sweating may be a problem.

Symptoms of **overdosage** may include excitement and restlessness with marked antimuscarinic effects, including dryness of the mouth, hot dry skin, dilated pupils, tachycardia, urinary retention, and intestinal stasis. Severe symptoms include unconsciousness, convulsions and myoclonus, hyperreflexia, hypothermia, hypotension, metabolic acidosis, and respiratory and cardiac depression, with life-threatening cardiac arrhythmias that may recur some days after apparent recovery. Delirium, with confusion, agitation and hallucinations, is common during recovery.

Antimuscarinic and antihistaminic properties. Studies *in vitro*[1] showed antidepressant affinities for human muscarinic acetylcholine receptors and therefore the likelihood of antimuscarinic effects to be, in descending order:

- amitriptyline
- protriptyline
- clomipramine
- trimipramine
- doxepin
- imipramine
- nortriptyline
- desipramine
- amoxapine
- maprotiline
- trazodone

The effect of affinities for other receptor sites was less certain, although those antidepressants with high affinity for histamine H_1 receptors might be expected to be more sedating. Affinities for *murine* histamine H_1 receptors in descending order were:

- doxepin
- trimipramine
- amitriptyline
- maprotiline
- amoxapine
- nortriptyline
- imipramine
- clomipramine
- protriptyline

- trazodone
- desipramine

1. Richelson E. Antimuscarinic and other receptor-blocking properties of antidepressants. *Mayo Clin Proc* 1983; **58:** 40–6.

Effects on the blood. After a case report of agranulocytosis linked with imipramine, review of the literature suggested that agranulocytosis associated with tricyclic antidepressant use was a rare idiosyncratic condition, resulting from a direct toxic effect rather than an allergic mechanism, and particularly affected the elderly from 4 to 8 weeks after beginning treatment.[1]

Between 1963 and 1993 the UK CSM received 912 reports of drug-induced agranulocytosis of which 38 were due to tricyclic antidepressants (12 fatal) and 1499 cases of neutropenia of which 46 were due to tricyclics (none fatal).[2] In a report[3] on a patient who developed aplastic anaemia associated with use of remoxipride and dosulepin it was noted that up to May 1993 the CSM had also received 11 reports of aplastic anaemia secondary to use of dosulepin.

Neutropenia reported[4] in a patient after separate exposure to imipramine and nortriptyline, indicated that there might be cross-intolerance between the tricyclic antidepressants and if neutropenia developed with one member of the group the use of others on future occasions should be avoided.

1. Albertini RS, Penders TM. Agranulocytosis associated with tricyclics. *J Clin Psychiatry* 1978; **39:** 483–5.
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
3. Philpott NJ, *et al*. Aplastic anaemia and remoxipride. *Lancet* 1993; **342:** 1244–5.
4. Draper BM, Manoharan A. Neutropenia with cross-intolerance between two tricyclic antidepressant agents. *Med J Aust* 1987; **146:** 452–3.

Effects on bone. A review of 9 epidemiological studies, mainly in patients aged 50 years or older, found an increased risk of fracture in those receiving tricyclic antidepressants. However, no definite conclusions could be made about a dose-response relationship, time relationship, or the possible mechanism.[1]

1. MHRA/CHM. Antidepressants: risk of fractures. *Drug Safety Update* 2010; **3** (10): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON081866&RevisionSelectionMethod=LatestReleased (accessed 28/07/10)

Effects on the cardiovascular system. The cardiotoxic potential of tricyclic antidepressants after **overdosage** is widely acknowledged; symptoms include arrhythmias, conduction defects, and hypotension. This factor was, in part, responsible for the development of antidepressants with different chemical structures and pharmacological properties that are less cardiotoxic. It also led to some concern over whether tricyclic antidepressants had adverse effects on the heart or cardiovascular system when used in usual therapeutic doses.

Since the introduction of the tricyclic antidepressants, reports, often anecdotal, have been published of adverse cardiovascular effects at **therapeutic doses** and have included malignant hypertension with amitriptyline,[1] and cardiomyopathy in a patient given amitriptyline and imipramine.[2] QT prolongation, which in some cases progressed to torsade de pointes, has also been associated with some tricyclics.[3,4] Sudden cardiac death in patients with pre-existing cardiac disease has been linked with amitriptyline[5-7] or imipramine,[6] although the Boston Collaborative Drug Surveillance Program failed to confirm these findings.[8] In a more recent analysis, it has been suggested that the risk of sudden cardiac death may increase with high doses of tricyclic antidepressants.[9] Using patient medication records, it was found that the rate of sudden cardiac death in patients taking less than 100 mg of amitriptyline or its equivalent, [presumably as a daily dose although this is not specified], did not differ from that among non-users of antidepressants even in those with cardiovascular disease or other conditions considered to increase the risk of sudden death; however, the risk was significantly increased in those patients on doses of 100 mg or more when compared with non- users, regardless of any predisposing conditions.

There have also been reports of sudden death in children given desipramine[10-12] or imipramine;[12-14] in at least some of these cases plasma concentrations were not elevated and the children had no cardiac abnormality. Again, however, evaluation of much of the evidence suggests the association is weak;[15] nonetheless, the American Heart Association recommends baseline ECG monitoring in children who are to be treated with tricyclic antidepressants, and a repeat ECG when steady-state dosage is achieved.[16]

Re-evaluations and reviews of this topic[17,18] concluded that the only significant or serious cardiovascular adverse effects, seen in *patients with no history* of cardiovascular disease given therapeutic doses of tricyclic antidepressants, are orthostatic hypotension and tachycardia, and that these effects may be particularly troublesome in elderly patients. However, a later study[19] also considered that prolongation of the QT interval might occur with therapeutic doses of tricyclics in non-risk patients.

In *patients with overt heart disease* it was considered[17] that increased risk was likely in those with intraventricular conduction abnormalities; in patients with a history of myocardial infarction or angina, but free of conduction defects, the use of tricyclics appeared to be mainly limited by how often they developed orthostatic hypotension and to what degree. In a re-evaluation of the risks and benefits of tricyclics in patients with ischaemic heart disease no consensus was reached.[20] In practice the authors used SSRIs or bupropion as first-choice therapy in patients with ischaemic heart disease who were mildly or moderately depressed; tricyclics were reserved for unresponsive patients and were also used as first-choice therapy for patients with more severe depression despite cardiac risks. More recently an increased risk of myocardial infarction has been found in patients taking tricyclic antidepressants (but not SSRIs) with treatment for heart disease.[21] Results of a later case-control study[22] examining the risk of ischaemic heart disease for different types of antidepressants and individual antidepressants support these findings. After adjustment for confounders and use of other antidepressants the risk of ischaemic heart disease was significantly raised in patients who had ever taken tricyclics but not in those given other antidepressants. When the risk was calculated for the tricyclics amitriptyline, dosulepin, and lofepramine, and confounders had been adjusted for, an increased risk of ischaemic heart disease remained only for dosulepin with evidence of a dose-response relationship.

1. Dunn FG. Malignant hypertension associated with use of amitriptyline hydrochloride. *South Med J* 1982; **75:** 1124–5.
2. Howland JS, *et al*. Cardiomyopathy associated with tricyclic antidepressants. *South Med J* 1983; **76:** 1455–6.
3. Baker B, *et al*. Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. *J Clin Psychopharmacol* 1997; **17:** 15–21.
4. Vieweg WVR, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics* 2004; **45:** 371–7.
5. Coull DC, *et al*. Amitriptyline and cardiac disease. *Lancet* 1970; **ii:** 590–1.
6. Moir DC, *et al*. Cardiotoxicity of amitriptyline. *Lancet* 1972; **ii:** 561–4.
7. Moir DC, *et al*. Medicines evaluation and monitoring group: a follow-up study of cardiac patients receiving amitriptyline. *Eur J Clin Pharmacol* 1973; **6:** 98–101.
8. Boston Collaborative Drug Surveillance Program. Adverse reactions to the tricyclic-antidepressant drugs: report from Boston Collaborative Drug Surveillance Program. *Lancet* 1972; **i:** 529–31.
9. Ray WA, *et al*. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; **75:** 234–41.
10. Anonymous. Sudden death in children treated with a tricyclic antidepressant. *Med Lett Drugs Ther* 1990; **32:** 53.
11. Riddle MA, *et al*. Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 792–7.
12. Varley CK, McClellan J. Case study: two additional sudden deaths with tricyclic antidepressants. *J Am Acad Child Adolesc Psychiatry* 1997; **36:** 390–4.
13. Swanson JR, *et al*. Death of two subjects due to imipramine and desipramine metabolite accumulation during chronic therapy: a review of the literature and possible mechanisms. *J Forensic Sci* 1997; **42:** 335–9.
14. Varley CK. Sudden death of a child treated with imipramine: case study. *J Child Adolesc Psychopharmacol* 2000; **10:** 321–5.
15. Biederman J, *et al*. Estimation of the association between desipramine and the risk for sudden death in 5- to 14-year-old children. *J Clin Psychiatry* 1995; **56:** 87–93.
16. Gutgesell H, *et al*. Cardiovascular monitoring of children and adolescents receiving psychotropic drugs: a statement for healthcare professionals from the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1999; **99:** 979–82. Also available at: http://circ.ahajournals.org/cgi/reprint/99/7/979 (accessed 24/11/05)
17. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu RevMed* 1984; **35:** 503–11.
18. Mortensen SA. Cyclic antidepressants and cardiotoxicity. *Practitioner* 1984; **228:** 1180–3.
19. Reilly JG, *et al*. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355:** 1048–52.
20. Glassman AH, *et al*. The safety of tricyclic antidepressants in cardiac patients: risk-benefit reconsidered. *JAMA* 1993; **269:** 2673–5.
21. Cohen HW, *et al*. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med* 2000; **108:** 2–8.
22. Hippisley-Cox J, *et al*. Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care. *BMJ* 2001: **323:** 666–9.

EFFECTS ON THE PERIPHERAL CIRCULATION. Painful vasospastic episodes, characterised by cold and blue hands and feet, occurred in a woman each time she received imipramine 150 mg daily and also with amitriptyline, but only when the dose was increased to 200 mg daily.[1] This suggested that the ability of tricyclic antidepressants to induce vasospasm was not limited to imipramine and that the effect might be partly dose-dependent. Additionally, acrocyanosis of the hands and feet has been reported in a child receiving imipramine for nocturnal enuresis.[2]

1. Appelbaum PS, Kapoor W. Imipramine-induced vasospasm: a case report. *Am J Psychiatry* 1983; **140:** 913–15.
2. Anderson RP, Morris BAP. Acrocyanosis due to imipramine. *Arch Dis Child* 1988; **63:** 204–5.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion with hyponatraemia* has been reported in patients receiving tricyclics and other antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.[1] Case reports of hyponatraemia in 24 patients treated with tricyclics and 20 patients treated with other antidepressants have been summarised.[2]

In a review covering the effects of drugs on *prolactin secretion*[3] it was stated that antidepressants could affect prolactin secretion by disturbing the balance of catecholaminergic inhibition and serotonergic stimulation of prolactin release, although any change is less than with antipsychotic therapy. Clomipramine and nortriptyline had been reported to stimulate prolactin release whereas amitriptyline, desipramine, and imipramine had been reported to be without effect. Such stimulation may account for symptoms of galactorrhoea or amenorrhoea reported with some tricyclics.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
3. Hell K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; **3:** 463–98.

Effects on the gastrointestinal tract. Rare cases of ileus and pseudo-obstruction have apparently resulted from the antimuscarinic effects of tricyclic antidepressants.[1-4] An early report[1] from the UK CSM noted no evidence that any tricyclic was especially liable to cause ileus.

1. CSM. Tricyclic antidepressants and ileus. *Current Problems 3* 1978. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024410&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. McMahon AJ. Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J* 1989; **65:** 948–9.
3. Sood A, Kumar R. Imipramine induced acute colonic pseudo-obstruction (Ogilvie's syndrome): a report of two cases. *Indian J Gastroenterol* 1996; **15:** 70–1.
4. Ross JP, *et al*. Imipramine overdose complicated by toxic megacolon. *Am Surg* 1998; **64:** 242–4.

Effects on the kidneys and urine. Haematuria has been seen in a patient receiving amitriptyline and carbamazepine;[1] carbamazepine had previously been taken alone for a long period without producing this effect.

Amitriptyline may have produced a blue-green colour in urine,[2] although it was considered to be a rare phenomenon.

1. Gillman MA, Sandyk R. Hematuria following tricyclic therapy. *Am J Psychiatry* 1984; **141:** 463–4.
2. Beeley L. *BMJ* 1986; **293:** 750.

Effects on the liver. In a report of 91 cases of hepatitis due to antidepressant therapy, 63 occurred in patients receiving the tricyclic antidepressant amineptine, sometimes with other psychotropic drugs; in about 50% of these amineptine cases, benzodiazepines had also been taken and it was postulated that the benzodiazepines may have increased the oxidation of amineptine to a toxic metabolite.[1] Most patients presented with abdominal pain and mixed liver damage with predominant cholestasis. One died after myocardial infarction, but all the others recovered. The mean amineptine dosage was 200 mg daily. In comparison, only a few cases were attributed to other tricyclic antidepressants—amitriptyline (4 cases), clomipramine (3 cases), and dibenzepin (1 case). Cross-hepatotoxicity between amineptine and clomipramine has also been reported in a patient.[2]

Hepatotoxicity has also been noted with lofepramine. The UK CSM had by the end of 1987 received 57 reports of abnormal liver function tests associated with lofepramine.[3] They included hepatic failure (1 case), jaundice (9 cases), and hepatitis (5 cases). All reactions occurred within the first 8 weeks of treatment and all were reversible on stopping the drug.

1. Lefebure B, *et al*. Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.
2. Larrey D, *et al*. Cross hepatotoxicity between tricyclic antidepressants. *Gut* 1986; **27:** 726–7.
3. CSM. Lofepramine (Gamanil) and abnormal blood tests of liver function. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the mouth. The inhibition of salivation caused by tricyclic antidepressants (in this case clomipramine) has been implicated in dental caries formation.[1]

1. deVries MW, Peeters F. Dental caries with longterm use of antidepressants. *Lancet* 1995; **346:** 1640.

Effects on the nervous system. Effects on the nervous system attributed to tricyclic antidepressants include drowsiness (especially with those with antihistaminic activity), peripheral neuropathy, tremor, ataxia, confusion, and delirium. Of particular concern is a reduction in the seizure threshold (see Epileptogenic Effect, p. 406.1). Extrapyramidal effects (p. 406.1) and neuroleptic malignant syndrome (see p. 406.2) may also occasionally occur.

Effects on sexual function. Loss of libido and impotence are common in depression, often making the role of drugs in producing sexual dysfunction difficult to assess.[1]

Sedation due to tricyclic antidepressants may lead to loss of libido and many of the tricyclics have been reported to cause impotence.[1,2] Amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, and trimipramine have been stated to delay or inhibit ejaculation, and amoxapine, imipramine, and protriptyline, also to cause painful ejaculation. However, some tricyclics have been used for their effect on ejaculation in the management of premature ejaculation (see Sexual Dysfunction under Clomipramine, p. 414.3).

In women, anorgasmia or delayed orgasm has been reported with amitriptyline, amoxapine, clomipramine, and imipramine,[1-3] although spontaneous orgasm associated with yawning has been reported with clomipramine.[4]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Anonymous. Drugs that cause sexual dysfunction. *Med Lett Drugs Ther* 1987; **29:** 65–70.
3. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; **28:** 497–9.
4. McLean JD, *et al.* Unusual side effects of clomipramine associated with yawning. *Can J Psychiatry* 1983; **28:** 569–70.

Effects on the skin. Hypersensitivity reactions to tricyclic antidepressants are said to be uncommon.[1] Urticaria and angioedema have occurred, the urticaria occasionally clearing without drug withdrawal. Pruritus is also uncommon, but may be associated with transient erythema. Photosensitivity reactions are far less common than with phenothiazines; protriptyline has been the tricyclic most frequently implicated.[2,3] Rarely, exfoliative dermatitis has developed, and purpura, pigmentation, and lichen planus have been noted in isolated reports. In some cases pigmentation changes may be permanent.[4] Toxic epidermal necrolysis has been reported in a patient 2 weeks after starting therapy with amoxapine.[5] Hypersensitivity reactions to tricyclic antidepressants usually occur between 14 and 60 days after the start of treatment.[6]

Amitriptyline and fluoxetine have been implicated in the development of atypical cutaneous lymphoid hyperplasia in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[7] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to lesional resolution.

1. Almeyda J. Drug reactions XIII: cutaneous reactions to imipramine and chlordiazepoxide. *Br J Dermatol* 1971; **84:** 298–9.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; **136** (June): 508–11.
3. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; **14:** 252–9.
4. Dean CE, Grund FM. Imipramine-associated hyperpigmentation. *Ann Pharmacother* 2003; **37:** 825–8.
5. Camisa C, Grines C. Amoxapine: a cause of toxic epidermal necrolysis? *Arch Dermatol* 1983; **119:** 709–10.
6. Quitkin F. Cross-tolerance of tricyclic antidepressant drugs. *JAMA* 1979; **241:** 1625.
7. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131:** 925–9.

Epileptogenic effect. Seizures have been reported after therapeutic doses of tricyclic antidepressants as well as after overdosage, although the mechanism by which the seizures are induced is unclear.[1] Seizures usually appear within a few days of starting the drug or changing to a higher dose but in patients with no history of epilepsy or no predisposing medical condition the frequency seems[1] to be very low with an incidence of about 1 in 1000. An incidence of 0.4 per 1000 was reported[2] based on 16 cases out of an estimated group of 42 000 patients receiving tricyclics and who had no predisposing factors, but in another review[3] a reasonable estimate of the incidence was considered to be 3 to 6 per 1000. However, it is widely agreed that tricyclics should be used very cautiously in patients with epilepsy or those with a low convulsive threshold.

In a retrospective analysis of 1313 cases[4] of overdosage involving cyclic antidepressants, seizures occurred more commonly with the tricyclics amoxapine (24.5%) and desipramine (17.9%), and the tetracyclic maprotiline (12.2%). In another analysis of 302 consecutive cases of tricyclic overdosage a higher rate of seizures was seen with dosulepin in overdosage (13%) than other tricyclics.[5]

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Jick SS, *et al.* Antidepressants and convulsions. *J Clin Psychopharmacol* 1992; **12:** 241–5.
3. Rosenstein DL, *et al.* Seizures associated with antidepressants: a review. *J Clin Psychiatry* 1993; **54:** 289–99.
4. Wedin GP, *et al.* Relative toxicity of cyclic antidepressants. *Ann Emerg Med* 1986; **15:** 797–804.
5. Buckley NA, *et al.* Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet* 1994: **343:** 159–62.

Extrapyramidal effects. Extrapyramidal effects such as orofacial and choreoathetoid movements, and dyskinesias have been attributed to treatment with tricyclic antidepressants. Dysarthria has also been reported[1] and was said to be not uncommon in those taking higher doses of tricyclic antidepressants, but unusual at lower doses.[2]

Some patients with panic disorder may be sensitive to imipramine, developing symptoms of insomnia, jitteriness, and irritability.[3] Symptoms have also been seen in patients with panic disorder treated with low doses of desipramine although the symptoms usually subsided when the dose of the tricyclic was gradually increased. It has been suggested[4] that these symptoms may be related to akathisia and are more likely to occur with those tricyclics that have a more potent effect on inhibition of noradrenaline reuptake.

Reviews of adverse effects of drugs on the nervous system have also listed acute torsion dystonias and tremors[5] as being caused or exacerbated by tricyclic antidepressants.

1. Quader SE. Dysarthria: an unusual side effect of tricyclic antidepressants. *BMJ* 1977; **2:** 97.
2. Saunders M. Dysarthria with tricyclic antidepressants. *BMJ* 1977; **2:** 317.
3. Yeragani VK, *et al.* Tricyclic induced jitteriness—a form of akathisia? *BMJ* 1986; **292:** 1529.
4. Cole JO, Bodkin JA. Antidepressant drug side effects. *J Clin Psychiatry* 1990; **51** (suppl): 21–6.
5. Llau M-E, *et al.* Mouvements anormaux d'origine médicamenteuse: l'expérience d'un centre de pharmacovigilance sur cinq ans. *Therapie* 1995; **50:** 425–7.

Hypersensitivity. A hypersensitivity syndrome developed in a 24-year-old woman 3 weeks after starting amitriptyline 50 mg daily for the treatment of depression;[1] symptoms included generalised erythroderma with mild scaling, sinus tachycardia, haematological abnormalities such as eosinophilia, and raised liver enzyme values. The patient recovered after drug withdrawal and treatment with intravenous prednisolone.

See also under Effects on the Skin, above.

1. Milionis HJ, *et al.* Hypersensitivity syndrome caused by amitriptyline administration. *Postgrad Med J* 2000; **76:** 361–3.

Hyponatraemia. See Effects on the Endocrine System, p. 403.2.

Neuroleptic malignant syndrome. Of 16 cases of neuroleptic malignant syndrome reported to the UK CSM by July 1986, 3 cases occurred in patients receiving a tricyclic antidepressant; amitriptyline with perphenazine had been taken by one patient and dosulepin or clomipramine alone by 2 other patients. The clomipramine case was fatal.[1] Other reports have been associated with amoxapine,[2] clomipramine alone,[3] clomipramine with triazolam,[4] and nortriptyline.[5]

1. CSM. Neuroleptic malignant syndrome—an underdiagnosed condition? *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024425&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Madakasira S. Amoxapine-induced neuroleptic malignant syndrome. *DICP Ann Pharmacother* 1989; **23:** 50–1.
3. Haddow AM, *et al.* Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin. *BMJ* 2004; **329:** 1333–5.
4. Domingo P, *et al.* Benign type of malignant syndrome. *Lancet* 1989; **i:** 50.
5. June R, *et al.* Neuroleptic malignant syndrome associated with nortriptyline. *Am J Emerg Med* 1999; **17:** 736–7.

Overdosage. In a 1993 report[1] tricyclic antidepressants were associated with a higher risk of fatality after suicide attempts by drug overdose compared with the non-tricyclics available at the time. Some reports[2] have considered desipramine to be associated more frequently than other tricyclic antidepressants with fatal overdosage, although others[3] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage.

Later reviews continue to cite tricyclic antidepressants as one of the most commonly ingested substances in fatal cases of self-poisoning.[3,4]

1. Anonymous. Antidepressant drugs and the risk of suicide. *WHO Drug Inf* 1993; **7:** 18–20.
2. Amitai Y, Frischer H. The toxicity and dose of desipramine hydrochloride. *JAMA* 1994; **272:** 1719–20.
3. Kerr GW, *et al.* Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001; **18:** 236–41.
4. Glauser J. Tricyclic antidepressant poisoning. *Cleve Clin J Med* 2000; **67:** 704–19.

Treatment of Adverse Effects

The basis of the management of tricyclic antidepressant poisoning is intensive supportive care and symptomatic therapy.

Since tricyclic antidepressants slow gastrointestinal transit time, absorption may be delayed in overdosage. Activated charcoal may be given if a toxic dose of a tricyclic antidepressant has been ingested (see p. 406.3) and the patient presents within 1 hour, provided the airway can be protected; a second dose may be considered after 1 to 2 hours in patients with central features of toxicity. Gastric lavage is rarely used but may be considered in life-threatening overdoses.

The patient should be monitored for cardiac arrhythmias. UK authorities consider that although cardiac arrhythmias are of concern they are best treated by correction of hypoxia and acidosis with intravenous sodium bicarbonate; the use of antiarrhythmic drugs is best avoided. Intravenous sodium bicarbonate should also be given to treat arrhythmias or significant ECG abnormalities even in the absence of acidosis.

Convulsions can be managed by giving diazepam, lorazepam, or midazolam intravenously. Phenytoin should be avoided because it may increase the risk of arrhythmias. Oral or intravenous diazepam may be given to sedate agitated patients; if ineffective, oral or parenteral haloperidol may be considered.

Forced diuresis, haemodialysis, and haemoperfusion are not of value in tricyclic antidepressant poisoning, and charcoal haemoperfusion is of doubtful benefit.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with tricyclic antidepressants to be uncertain. However, it is suggested that activated charcoal given orally or by nasogastric tube may be considered if this is given within 1 hour of ingestion of any amount of tricyclic antidepressant in children, and the following amounts or more in adults, provided that the airway can be protected:

- amitriptyline: 3 mg/kg
- clomipramine: 4 mg/kg
- desipramine: 3 mg/kg
- dosulepin: 3 mg/kg
- doxepin: 4 mg/kg
- imipramine: 4 mg/kg
- lofepramine: 15 mg/kg
- nortriptyline: 3 mg/kg
- trimipramine: 5 mg/kg

Precautions

The antimuscarinic effects of tricyclic antidepressants warrant care in patients with urinary retention, prostatic hyperplasia, or chronic constipation; caution has also been advised in untreated angle-closure glaucoma and in phaeochromocytoma.

The epileptogenic potential of tricyclic antidepressants requires care in patients with a history of epilepsy. In addition, because of their potential cardiotoxicity, tricyclics should be used with caution in patients with cardiovascular disease and avoided in those with heart block, cardiac arrhythmias, or in the immediate recovery period after myocardial infarction. Caution has also been recommended in patients with hyperthyroidism as tricyclics may increase the risk of developing cardiac arrhythmias.

Blood-sugar concentrations may be altered in diabetic patients.

Because tricyclic antidepressants are metabolised and inactivated in the liver they should be used with caution in patients with hepatic impairment and avoided in severe liver disease.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be followed when treating patients with other disorders.

If tricyclic antidepressants are used for the depressive component of bipolar disorder, mania may be precipitated; similarly, psychotic symptoms may be aggravated if tricyclics are used for a depressive component of schizophrenia.

Drowsiness often occurs, particularly at the start of therapy, and patients, if affected, should not drive or operate machinery.

Tricyclic antidepressants may inhibit salivation and regular dental check-ups are recommended for patients on long-term therapy, particularly when taking those with marked antimuscarinic actions.

Elderly patients can be particularly sensitive to the adverse effects of tricyclic antidepressants and a reduced dose, especially initially, should be used.

Tricyclic antidepressants are not recommended for depression in children. If they are used for nocturnal enuresis in children they should be limited to short courses with a full physical examination before subsequent courses.

Tricyclic antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms (see p. 407.3).

Licensed product information recommends that, where possible, tricyclic antidepressants should be stopped several days before elective surgery, and that they should be used with caution in patients requiring ECT; however, see also under Anaesthesia, p. 406.3.

Anaesthesia. Patients receiving tricyclic antidepressants are at an increased risk of developing hypotension or car-

diac arrhythmias during anaesthesia. Tricyclics may also dangerously potentiate the cardiovascular effects of vasopressor drugs such as sympathomimetics that may be required during anaesthesia. Although some licensed product information recommends stopping tricyclics several days before elective surgery where possible, the *BNF* advises that this is unnecessary as long as the anaesthetist is informed.

Commenting on the anaesthetic considerations relevant to ECT,[1] it was considered that therapy with tricyclic antidepressants should not be a contra-indication to anaesthesia for ECT. A major consideration, though, was said to be the interaction of tricyclics with barbiturates resulting in increased sleep time and duration of anaesthesia. This meant that lower doses of barbiturate anaesthetics should be used.

Antidepressants with significant serotonergic effects such as the tricyclic clomipramine may increase the risk of bleeding during surgery; for further details see under Precautions in Fluoxetine, p. 425.3.

1. Gaines GY, Rees DI. Electroconvulsive therapy and anesthetic considerations. *Anesth Analg* 1986; **65:** 1345–56.

Breast feeding. In general, only small amounts of tricyclic antidepressants are distributed into breast milk. Nevertheless, the American Academy of Pediatrics[1] considers that the effect of all antidepressants, including tricyclics, on nursing infants is unknown but may be of concern. In addition, most manufacturers advise that tricyclics should be avoided by women during breast feeding.

Case reports indicate that amitriptyline and its metabolite (nortriptyline),[2,3] clomipramine,[4] desipramine and its metabolite (2-hydroxydesipramine),[5] dosulepin and its primary metabolites (nordothiepin, dothiepin-*S*-oxide, and nordothiepin-*S*-oxide),[6] doxepin and its metabolite (*N*-desmethyldoxepin),[7-9] imipramine and its metabolite (desipramine),[10] and maprotiline[11] are all present in breast milk in concentrations similar to those in maternal blood; amoxapine and its metabolite (8-hydroxyamoxapine)[12] have also been found in breast milk but in concentrations lower than in maternal blood. In all but 2 of the above cases the infants were breast fed without having adverse effects and tricyclics were undetectable in the infant's blood or present only in minute amounts. In one of the affected infants,[8] adverse effects included sedation and shallow respiration. Although the doxepin given to the mother was almost undetectable in the infant's serum, its desmethyl metabolite appeared to have accumulated. In the other infant, drowsiness, poor suckling, and difficulty in swallowing were noted[9] but the concentrations of both doxepin and its desmethyl metabolite were below the lower level of quantification. However, it was considered that the infant may have been at a greater risk for adverse effects because he had also developed hyperbilirubinaemia. There were no data for the effects of amoxapine on breast-fed infants because the case reported[12] involved samples of milk taken from a woman who had galactorrhoea as an adverse effect of tricyclic use. No adverse effects were seen during a 27-month follow-up of 14 breast-fed infants whose mothers had taken imipramine 100 to 225 mg daily for 4 to 24 weeks.[13]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1980; **137:** 855–6.
3. Brixen-Rasmussen L, *et al.* Amitriptyline and nortriptyline excretion in human breast milk. *Psychopharmacology (Berl)* 1982; **76:** 94–5.
4. Schimmell MS, *et al.* Toxic neonatal effects following maternal clomipramine therapy. *Clin Toxicol* 1991; **29:** 479–84.
5. Stancer HC, Reed KL. Desipramine and 2-hydroxydesipramine in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1986; **143:** 1597–1600.
6. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.
7. Kemp J, *et al.* Excretion of doxepin and N-desmethyldoxepin in human milk. *Br J Clin Pharmacol* 1985; **20:** 497–9.
8. Matheson I, *et al.* Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* 1985; **ii:** 1124.
9. Frey OR, *et al.* Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. *Ann Pharmacother* 1999; **33:** 690–3.
10. Sovner R, Orsulak PJ. Excretion of imipramine and desipramine in human breast milk. *Am J Psychiatry* 1979; **136:** 451–2.
11. Lloyd AH. Practical considerations in the use of maprotiline (Ludiomil) in general practice. *J Int Med Res* 1977; **5** (suppl 4): 122–38.
12. Gelenberg AJ. Amoxapine, a new antidepressant, appears in human milk. *J NervMent Dis* 1979; **167:** 635–6.
13. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 1991; **21:** 157–71.

Cardiovascular disease. For comments on the potential cardiotoxicity of tricyclic antidepressants and precautions to be observed in patients with pre-existing cardiovascular disorders, see under Effects on the Cardiovascular System in Adverse Effects, p. 403.1.

Contact lenses. Based on reports involving amitriptyline[1] and maprotiline[2] it has been considered that the antimuscarinic action of tricyclic antidepressants may decrease tear flow enough to cause corneal drying and staining of contact lenses.[3]

1. Litovitz GL. Amitriptyline and contact lenses. *J Clin Psychiatry* 1984; **45:** 188.
2. Troiano G. Amitriptyline and contact lenses. *J Clin Psychiatry* 1985; **46:** 199.
3. Anonymous. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; **17:** 55–6.

Diabetes mellitus. The fact that tricyclic antidepressants may cause alterations in blood-glucose concentrations has led to the recommendation that these drugs should be used with caution in diabetic patients. Amitriptyline has also been reported[1] to cause hypoglycaemic unawareness; a patient did not have the usual adrenergic symptoms that preceded or accompanied her hypoglycaemic episodes.

1. Sherman KE, Bornemann M. Amitriptyline and asymptomatic hypoglycemia. *Ann Intern Med* 1988; **109:** 683–4.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects both of which are more pronounced at the start of treatment; sedative tricyclics, such as amitriptyline and doxepin, are likely to cause greater psychomotor impairment than less sedative tricyclics such as imipramine and nortriptyline.[1] However, an epidemiological study[3] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs. In healthy subjects fluoxetine (an SSRI) and dosulepin appeared to have a similar but apparently small potential for impairing psychomotor and driving performance.[4]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that drugs such as the older tricyclic antidepressants may have pronounced antimuscarinic and antihistaminic effects, which may impair driving.[5] In addition, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J HospMed* 1986; **35:** 193–5.
3. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
4. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; **39:** 397–404.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

ECT. For comments concerning precautions in patients receiving ECT, see under Anaesthesia, p. 404.3.

Epilepsy. For comments on the epileptogenic effect of tricyclic antidepressants and the need for caution in patients with a history of epilepsy or other risk factors for development of seizures, see under Epileptogenic Effect in Adverse Effects, p. 404.1.

Food. A high-fibre diet reduced or abolished the efficacy of doxepin in 2 patients and desipramine in one.[1]

1. Stewart DE. High-fiber diet and serum tricyclic antidepressant levels. *J Clin Psychopharmacol* 1992; **12:** 438–40.

Gastro-oesophageal reflux disease. The antimuscarinic action of tricyclic antidepressants may cause relaxation of the lower oesophageal sphincter and could aggravate nocturnal symptoms of gastro-oesophageal reflux if given in the late evening.[1]

1. Atkinson M. Use and misuse of drugs in the treatment of gastro-oesophageal reflux. *Prescribers' J* 1982; **22:** 129–36.

Glaucoma. Manufacturers have stated that, because of their antimuscarinic actions, tricyclic antidepressants should be used with caution in patients with angle-closure glaucoma or raised intra-ocular pressure. There have been few reports of glaucoma associated with tricyclics, although acute angle-closure glaucoma was reported in 4 patients with narrow angles while taking imipramine in usual doses,[1] and in another patient taking clomipramine.[2] In the latter case, the presenting sign was amaurosis fugax, caused by the combination of raised intra-ocular pressure and an abnormally large drop in blood pressure on standing.

1. Ritch R, *et al.* Oral imipramine and acute angle closure glaucoma. *Arch Ophthalmol* 1994; **112:** 67–8.
2. Schlingemann RO, *et al.* Amaurosis fugax on standing and angle-closure glaucoma with clomipramine. *Lancet* 1996; **347:** 465.

Phaeochromocytoma. Use of imipramine[1,2] or desipramine[3] has caused adverse effects such as seizures and cardiovascular abnormalities (tachycardia and hypertension or hypotension) in patients with previously undiagnosed phaeochromocytoma. It has been suggested[3] that imipramine and its metabolite, desipramine, may be particularly effective in unmasking phaeochromocytoma and that this may be a reflection of their relative potency in inhibiting the noradrenaline reuptake mechanism.

1. Kaufmann JS. Pheochromocytoma and tricyclic antidepressants. *JAMA* 1974; **229:** 1282.
2. Mok J, Swann I. Diagnosis of phaeochromocytoma after ingestion of imipramine. *Arch Dis Child* 1978; **53:** 676–7.
3. Achong MR, Keane PM. Pheochromocytoma unmasked by desipramine therapy. *Ann Intern Med* 1981; **94:** 358–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amitriptyline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Management of depression during pregnancy can be difficult, and one report[1] on experience in 8 pregnant women being treated with a tricyclic antidepressant suggested that the dose might need to be increased during the second half of pregnancy to achieve a response. There are obvious concerns about such treatment (see also Depression, p. 398.1). However, although there have been isolated reports[2] attributing *congenital malformations* to the use of tricyclic antidepressants during pregnancy, large-scale studies and case-control data[3,4] have failed to substantiate any association.

The effects of tricyclics on *fetal neurodevelopment* were studied[5] in 80 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to tricyclics *in utero* in the first trimester compared with those exposed to fluoxetine or no adverse developmental influences. A subsequent study indicated that exposure to tricyclic antidepressants or fluoxetine throughout gestation did not appear to adversely affect cognition.[6]

Fetal tachyarrhythmia detected at 37 weeks of gestation was attributed to maternal use of dosulepin during pregnancy. When this was stopped, no abnormalities in fetal heart rate were found and an uneventful labour led to a healthy infant being delivered. However, the authors expressed concern that fetal tachycardias might result in *in-utero* cardiac failure and considered that tricyclic antidepressants should be used during pregnancy only if there were compelling reasons.[7]

Withdrawal syndromes manifesting as hypothermia and jitteriness,[8] convulsions,[9,10] or myoclonus[11] have been reported in neonates whose mothers took clomipramine during pregnancy. Management has been with phenobarbital or clomipramine. Licensed product information advises that if it is justifiable to do so, clomipramine should be withdrawn at least 7 weeks before the calculated date of delivery.

1. Wisner KL, *et al.* Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 1993; **150:** 1541–2.
2. Barson AJ. Malformed infant. *BMJ* 1972; **2:** 45.
3. Greenberg G, *et al.* Maternal drug histories and congenital abnormalities. *BMJ* 1977; **2:** 853–6.
4. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
5. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336:** 258–62.
6. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; **159:** 1889–95.
7. Prentice A, Brown R. Fetal tachyarrhythmia and maternal antidepressant treatment. *BMJ* 1989; **298:** 190.
8. Musa AB, Smith CS. Neonatal effects of maternal clomipramine therapy. *Arch Dis Child* 1979; **54:** 405.
9. Cowe L, *et al.* Neonatal convulsions caused by withdrawal from maternal clomipramine. *BMJ* 1982; **284:** 1837–8.
10. Bromiker R, Kaplan M. Apparent intrauterine fetal withdrawal from clomipramine hydrochloride. *JAMA* 1994; **272:** 1722–3.
11. Bloem BR, *et al.* Clomipramine withdrawal in newborns. *Arch Dis Child Fetal Neonatal Ed* 1999; **81:** F77–F79.

Surgery. For comments regarding precautions in patients undergoing surgery, see under Anaesthesia, p. 404.3.

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more may precipitate withdrawal symptoms. The symptoms associated with withdrawal of tricyclic antidepressants appear to form 4 distinct syndromes:[1]

- gastrointestinal disturbances and generalised somatic symptoms such as malaise, chills, headache, and increased perspiration, which may also be accompanied by anxiety and agitation
- sleep disturbances characterised by insomnia followed by excessive and vivid dreams
- parkinsonism or akathisia
- hypomania or mania

Tricyclic withdrawal has also resulted in cardiac arrhythmias in some patients. Withdrawal symptoms seem to be more common and more severe in children.[2]

Many of the symptoms associated with stopping tricyclics may be produced by cholinergic rebound[1] and can be minimised by a gradual reduction in dosage. The *BNF* recommends that any antidepressant, including a tricyclic, that has been given regularly for 8 weeks or more should be stopped gradually over a period of at least 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy. If withdrawal symptoms do occur, they can be managed by restarting at a dose sufficient to eliminate them, and then stopping gradually.[1,2] On the occasions that it may be necessary to stop a tricyclic abruptly, the withdrawal symptoms can be treated with a centrally active antimuscarinic such as atropine or benzatropine,[1] or alternatively, if withdrawal symptoms are just gastrointestinal, an antimuscarinic that does not cross the blood-brain barrier such as propantheline.[1] Awareness of the possibility of withdrawal syndromes helps to avoid misinterpreting new symptoms after withdrawal as evidence of relapse.

Tricyclic antidepressants have been included in some classifications as drugs of dependence because of their potential to produce withdrawal syndromes, but a review[3] of several substance abuse studies challenged this on finding no evidence of abuse or dependence of the barbiturate type developing with the tricyclics.

For reports of withdrawal symptoms in neonates born to mothers who took tricyclic antidepressants during pregnancy, and their management, see under Pregnancy, p. 405.3.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.
2. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; **24:** 29–30.
3. Lichtigfeld FJ, Gillman MA. The possible abuse of and dependence on major tranquillisers and tricyclic antidepressants. *S Afr Med J* 1994; **84:** 5–6.

Interactions

Interactions involving tricyclic antidepressants often result from additive toxicity or from altered metabolism of one drug by the other. Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP2D6 may affect tricyclic metabolism and produce marked alterations in plasma concentrations.

Adverse effects may be enhanced by antimuscarinic drugs or CNS depressants, including alcohol. Barbiturates and other enzyme inducers such as rifampicin and some antiepileptics can increase the metabolism of tricyclic antidepressants and may lower plasma concentrations and reduce antidepressant response. Cimetidine, methylphenidate, antipsychotics, and calcium-channel blockers can reduce the metabolism of the tricyclics, leading to the possibility of increased plasma concentrations and accompanying toxicity.

Patients taking thyroid preparations may show an accelerated response to tricyclic antidepressants and occasionally liothyronine has been used to produce this effect in patients with refractory depression. However, the use of tricyclics with thyroid hormones may precipitate cardiac arrhythmias.

The antihypertensive effects of debrisoquine, guanethidine, and clonidine may be reduced by tricyclic antidepressants. The pressor effects of sympathomimetics, especially those of the direct-acting drugs adrenaline and noradrenaline, can be enhanced by tricyclic antidepressants; however, there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and tricyclic antidepressants. Great care should, however, be taken to avoid inadvertent intravenous injection of the local anaesthetic preparation.

Drugs that prolong the QT interval, including antiarrhythmics such as amiodarone or quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, and thioridazine), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants. This may be exacerbated where the interacting drug (such as quinidine or some antipsychotics) also reduces tricyclic metabolism.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the serotonin syndrome (see p. 445.2) may occur. For this reason an appropriate drug-free interval should elapse between stopping some types of antidepressant and starting another. Tricyclic antidepressants should not generally be given to patients receiving MAOIs or for at least 2 weeks (3 weeks if starting clomipramine or imipramine) after their withdrawal. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting a tricyclic. At least 1 to 2 weeks (3 weeks in the case of clomipramine or imipramine) should elapse between withdrawing a tricyclic antidepressant and starting any drug liable to provoke a serious reaction (e.g. phenelzine).

Further details concerning some of the above interactions, and others, are given below.

Alcohol. For reference to the effect of alcohol on amitriptyline, see under CNS depressants, p. 409.1.

Analgesics. Doubling of plasma-doxepin concentrations with associated lethargy has been reported in a patient after the addition of *dextropropoxyphene* to the tricyclic.[1] This was consistent with previous studies indicating that dextropropoxyphene can impair the hepatic metabolism of other drugs.

For general reference to the effect of tricyclic antidepressants, notably amitriptyline and clomipramine, on *opioid analgesics*, see under Morphine, p. 95.3.

1. Abernethy DR, *et al.* Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; **97:** 223–4.

Antiarrhythmics. Antiarrhythmics that prolong the QT interval may increase the likelihood of ventricular arrhythmias when given with tricyclic antidepressants. This includes various class I antiarrhythmics such as *disopyramide, flecainide, procainamide, propafenone,* and *quinidine,* and the class III antiarrhythmic *amiodarone.*

Raised serum-desipramine concentrations and signs of toxicity were noted[1] in a patient taking desipramine after starting treatment with digoxin and propafenone for paroxysmal atrial fibrillation. It was considered that propafenone probably reduced the metabolism and clearance of desipramine.

1. Katz MR. Raised serum levels of desipramine with the antiarrhythmic propafenone. *J Clin Psychiatry* 1991; **52:** 432–3.

Anticoagulants. For the effect of tricyclic antidepressants on anticoagulants, see under Warfarin, p. 1531.3.

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in interactions or enhanced adverse reactions, and should be used only under expert supervision. For further details of the interactions between different antidepressants when used together, see Phenelzine, p. 447.2. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p. 445.2.

Antidiabetics. For the effect of tricyclic antidepressants on *sulfonylureas* and *insulin*, see Interactions, p. 504.3 and p. 488.3, respectively.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

A review[1] of drug interactions with *phenytoin* noted that although there had been reports of interactions between antiepileptics and tricyclic or related antidepressants, most involved enzyme-inducing antiepileptics other than phenytoin or phenytoin with other drugs. In the only report where phenytoin could be identified as the sole antiepileptic used, 2 patients required high doses of desipramine to achieve an antidepressant effect and to maintain plasma-desipramine concentrations in the range usually associated with therapeutic efficacy.

Carbamazepine has been reported to induce the metabolism of several tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, and nortriptyline) and to reduce their plasma concentrations. The clinical importance of the interaction is unclear. Use of nortriptyline with carbamazepine in a patient led to a decrease in serum-nortriptyline concentration requiring an increase in nortriptyline dose.[2] In another patient a prolonged QT interval was noted after use of desipramine with carbamazepine;[3] the authors hypothesised that the accelerated metabolism of desipramine had resulted in high levels of a cardiotoxic metabolite.

Valproate has been reported to increase plasma concentrations of amitriptyline,[4] clomipramine,[5] and nortriptyline.[4,6]

For the effect of the cyclic antidepressants desipramine and viloxazine on carbamazepine, see p. 516.2. For the effects of tricyclic antidepressants on phenytoin, see p. 543.1.

See also under Barbiturates, p. 408.3.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; **18:** 131–50.
2. Brøsen K, Kragh-Sørensen P. Concomitant intake of nortriptyline and carbamazepine. *Ther Drug Monit* 1993; **15:** 258–60.
3. Baldessarini RJ, *et al.* Anticonvulsant cotreatment may increase toxic metabolites of antidepressants and other psychotropic drugs. *J Clin Psychopharmacol* 1988; **8:** 381–2.
4. Wong SL, *et al.* Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. *Clin Pharmacol Ther* 1996; **60:** 48–53.
5. Fehr C, *et al.* Increase in serum clomipramine concentrations caused by valproate. *J Clin Psychopharmacol* 2000; **20:** 493–4.
6. Fu C, *et al.* Valproate/nortriptyline interaction. *J Clin Psychopharmacol* 1994; **14:** 205–6.

Antifungals. Increased serum concentrations of nortriptyline[1] or amitriptyline[2,3] have occurred in patients also taking *fluconazole.* In some patients the use of amitriptyline with fluconazole has led to syncope[3] or torsade de pointes.[4] Raised serum concentrations of nortriptyline and associated symptoms of intoxication have been reported in 2 patients during treatment with *terbinafine;*[5,6] the interaction was confirmed on rechallenge. In another case, dizziness, dry mouth, and muscle twitching were reported in a patient on long-term imipramine treatment after starting terbinafine;[7] serum imipramine concentrations were found to be elevated and symptoms subsided after the dose of imipramine was reduced. A study in healthy subjects also indicated that terbinafine similarly inhibited the metabolism of desipramine.[8]

1. Gannon RH. Fluconazole-nortriptyline drug interaction. *Ann Pharmacother* 1992; **26:** 1456.
2. Newberry DL, *et al.* A fluconazole/amitriptyline drug interaction in three male adults. *Clin Infect Dis* 1997; **24:** 270–1.
3. Robinson RF, *et al.* Syncope associated with concurrent amitriptyline and fluconazole therapy. *Ann Pharmacother* 2000; **34:** 1406–1409.
4. Dorsey ST, Biblo LA. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. *Am J Emerg Med* 2000; **18:** 227–9.
5. van der Kuy P-HM, *et al.* Nortriptyline intoxication induced by terbinafine. *BMJ* 1998; **316:** 441.
6. van der Kuy P-HM, *et al.* Pharmacokinetic interaction between nortriptyline and terbinafine. *Ann Pharmacother* 2002; **36:** 1712–14.
7. Teitelbaum ML, Pearson VE. Imipramine toxicity and terbinafine. *Am J Psychiatry* 2001; **158:** 2086.
8. Madani S, *et al.* Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. *J Clin Pharmacol* 2002; **42:** 1211–18.

Antihypertensives. In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but there may be antagonism of the effect of *adrenergic neurone blockers* and of *clonidine.*

Antimigraine drugs. For the effects when some tricyclics are used with *dihydroergotamine*, see p. 675.2.

Antineoplastics. For the effects when tricyclic antidepressants are used with *altretamine*, see p. 739.1.

Antiprotozoals. Toxic psychosis developed in a patient on amitriptyline after starting *furazolidone,* an antiprotozoal with monoamine oxidase inhibiting activity.[1]

1. Aderhold RM, Muniz CE. Acute psychosis with amitriptyline and furazolidone. *JAMA* 1970; **213:** 2080.

Antipsychotics. For a discussion of interactions between antipsychotics and tricyclic antidepressants, see *Chlorpromazine* (p. 1052.1). For details of a possible interaction between clomipramine and *clozapine,* see p. 1061.3.

Antivirals. HIV-protease inhibitors may increase the plasma concentrations of tricyclic antidepressants whose metabolism is mediated through common cytochrome P450 isoenzymes. *Ritonavir* has produced moderate increases in the plasma concentrations of desipramine and a lower initial dose of desipramine may be appropriate. Licensed product information for ritonavir has warned that a similar increase may occur for other tricyclics; monitoring of therapeutic and adverse effects is recommended when tricyclics are used with ritonavir.

Anxiolytics. For a suggestion that *benzodiazepines* may increase the oxidation of amineptine to a toxic metabolite, see under Effects on the Liver in Adverse Effects, p. 403.3. For a possible interaction of desipramine and other antidepressants with *zolpidem* see p. 1117.2.

Barbiturates. Antidepressants may antagonise the antiepileptic activity of some barbiturates by lowering the convulsive threshold.

Barbiturates can increase the metabolism of tricyclic antidepressants and thereby produce lower plasma concentrations.

For details of the interaction of tricyclic antidepressants with barbiturate anaesthetics, see under Anaesthesia in Precautions, p. 404.3.

Beta blockers. Raised imipramine plasma concentrations were noted in two 9-year-old children also given *propranolol;*[1] in both cases, no significant adverse effects were reported. *Labetalol* has also increased the bioavailability of imipramine in healthy subjects and inhibited its metabolism.[2]

The risk of ventricular arrhythmias may be increased when tricyclic antidepressants are taken with *sotalol.*

1. Gillette DW, Tannery LP. Beta blocker inhibits tricyclic metabolism. *J Am Acad Child Adolesc Psychiatry* 1994; **33:** 223–4.
2. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; **32:** 176–83.

Calcium-channel blockers. *Diltiazem* and *verapamil* each increased the bioavailability of imipramine in healthy subjects; second-degree heart block developed in 2 subjects.[1] Diltiazem also increased the bioavailability of nortriptyline in one patient,[2] probably by reducing the first-pass metabolism of nortriptyline. Increased serum concentrations of trimipramine have been reported when taken with diltiazem,[3] although there was no evidence of toxicity.

1. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; **32:** 176–83.
2. Krähenbühl S, *et al.* Pharmacokinetic interaction between diltiazem and nortriptyline. *Eur J Clin Pharmacol* 1996; **49:** 417–19.
3. Cotter PA, *et al.* Asymptomatic tricyclic toxicity associated with diltiazem. *Ir J Psychol Med* 1996; **13:** 168–9.

CNS depressants. Drugs with depressant actions on the CNS may be expected to enhance the drowsiness and related effects produced by the sedating type of tricyclic antidepressants. Such an interaction may occur between *alcohol* and tricyclic antidepressants and a study has shown that alcohol decreases the hepatic first-pass extraction of amitriptyline resulting in increased free plasma-amitriptyline concentrations, especially during the period of drug absorption.[1]

The problems that may be encountered with *barbiturate anaesthetics* are discussed under Anaesthesia in Precautions, p. 404.3.

1. Dorian P, *et al.* Amitriptyline and ethanol: pharmacokinetic and pharmacodynamic interaction. *Eur J Clin Pharmacol* 1983; **25:** 325–31.

Disulfiram. Acute organic brain syndrome has been reported in 2 patients after the addition of amitriptyline to their disulfiram treatment.[1] It was suspected that the syndrome was potentiated by the combined action of the drugs and the synergistic elevation in dopamine concentration.

For a report of the enhancement of the disulfiram-alcohol reaction by amitriptyline, see p. 2496.3.

1. Maany I, *et al.* Possible toxic interaction between disulfiram and amitriptyline. *Arch Gen Psychiatry* 1982; **39:** 743–4.

Dopaminergics. Serious adverse effects have been reported[1] when *selegiline*, an irreversible selective inhibitor of monoamine oxidase type B, was used with tricyclic antidepressants. In some instances effects resembled the potentially fatal serotonin syndromes reported when tricyclics are given with non-selective MAOIs (see under Phenelzine, p. 445.2).

Some manufacturers of selegiline advise that tricyclic antidepressants should not generally be given at the same time, or for at least 2 weeks after it has been discontinued. Similarly, at least one week should elapse before withdrawing a tricyclic antidepressant and starting selegiline.

For reference to the effect when tricyclic antidepressants are taken with *levodopa*, see p. 908.2.

1. Anonymous. Selegiline and antidepressants: risk of serious interactions. *WHO Drug Inf* 1995; **9:** 160–1.

General anaesthetics. For the effect of amitriptyline on *enflurane*, see p. 1903.2. For the effects of using tricyclic antidepressants with *barbiturates* see under Anaesthesia in Precautions, p. 404.3.

Histamine. For the effect of tricyclic antidepressants on histamine given exogenously, see p. 2525.3.

Histamine H_2-antagonists. *Cimetidine* is a known inhibitor of hepatic metabolism of drugs and symptoms of tricyclic toxicity have been reported in patients given cimetidine with desipramine,[1] doxepin,[2] or imipramine;[1] there has been a report of psychosis developing in a patient given imipramine and cimetidine.[3] Elevated tricyclic concentrations during combined therapy or reductions in tricyclic concentrations after withdrawal of cimetidine have been reported for imipramine[4] and nortriptyline.[5] Studies in healthy subjects have also indicated increased bioavailability and/or impaired hepatic metabolism of amitriptyline,[6] doxepin,[7,8] and imipramine[9] during cimetidine therapy. Adjustment of tricyclic antidepressant dosage may therefore be required if cimetidine therapy is begun or stopped.

Ranitidine has been reported not to alter the pharmacokinetics of amitriptyline,[10] doxepin,[8] or imipramine.[9]

1. Miller DD, Macklin M. Cimetidine-imipramine interaction: a case report. *Am J Psychiatry* 1983; **140:** 351–2.
2. Brown BA, *et al.* Cimetidine-doxepin interaction. *J Clin Psychopharmacol* 1985; **5:** 245–7.
3. Miller ME, *et al.* Psychosis in association with combined cimetidine and imipramine treatment. *Psychosomatics* 1987; **28:** 217–19.
4. Shapiro PA. Cimetidine-imipramine interaction: case report and comments. *Am J Psychiatry* 1984; **141:** 152.
5. Miller DD, *et al.* Cimetidine's effect on steady-state serum nortriptyline concentrations. *Drug Intell Clin Pharm* 1983; **17:** 904–5.
6. Curry SH, *et al.* Cimetidine interaction with amitriptyline. *Eur J Clin Pharmacol* 1985; **29:** 429–33.
7. Abernethy DR, Todd EL. Doxepin-cimetidine interaction: increased doxepin bioavailability during cimetidine treatment. *J Clin Psychopharmacol* 1986; **6:** 8–12.
8. Sutherland DL, *et al.* The influence of cimetidine versus ranitidine on doxepin pharmacokinetics. *Eur J Clin Pharmacol* 1987; **32:** 159–64.
9. Wells BG, *et al.* The effect of ranitidine and cimetidine on imipramine disposition. *Eur J Clin Pharmacol* 1986; **31:** 285–90.
10. Curry SH, *et al.* Lack of interaction of ranitidine with amitriptyline. *Eur J Clin Pharmacol* 1987; **32:** 317–20.

Muscle relaxants. There has been an isolated report[1] of a patient taking *baclofen* for spasticity who had weakness in his legs and was unable to stand after starting treatment with nortriptyline. Symptoms improved on stopping nortriptyline but recurred when imipramine was given.

1. Silverglat MJ. Baclofen and tricyclic antidepressants: possible interaction. *JAMA* 1981; **246:** 1659.

Sex hormones. There have been anecdotal reports of interactions between tricyclic antidepressants and *oestrogens*[1-3] resulting in a lack of antidepressant response and/or tricyclic toxicity but the significance of these interactions is unknown.

1. Prange AJ, *et al.* Estrogen may well affect response to antidepressant. *JAMA* 1972; **219:** 143–4.
2. Khurana RC. Estrogen-imipramine interaction. *JAMA* 1972; **222:** 702–3.
3. Somani SM, Khurana RC. Mechanism of estrogen-imipramine interaction. *JAMA* 1973; **223:** 560.

Smoking. Tobacco smoke has been reported to reduce the plasma levels of tricyclic antidepressants.[1-3] The clinical significance is not, however, fully established as the plasma concentration of unbound drug may not be affected.[3] The mechanism is probably by stimulation of hepatic drug metabolism by components present in cigarette smoke.

1. Perel JM, *et al.* Pharmacodynamics of imipramine in depressed patients. *Psychopharmacol Bull* 1975; **11:** 16–18.
2. John VA, *et al.* Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing. *J Int Med Res* 1980; **8** (suppl 3): 88–95.
3. Perry PJ, *et al.* Effects of smoking on nortriptyline plasma concentrations in depressed patients. *Ther Drug Monit* 1986; **8:** 279–84.

Sympathomimetics. The pressor effects of sympathomimetics can be enhanced by tricyclic antidepressants.

For prescribing precautions in patients on tricyclic therapy who may require sympathomimetics during anaesthesia, see under Anaesthesia in Precautions, p. 404.3.

Thyroid hormones. An increase in receptor sensitivity to catecholamines produced by thyroid hormones has been proposed as the reason for an increase in response to tricyclic antidepressants given with *liothyronine*.[1,2]

1. Banki CM. Cerebrospinal fluid amine metabolites after combined amitriptyline-triiodothyronine treatment of depressed women. *Eur J Clin Pharmacol* 1977; **11:** 311–15.
2. Goodwin FK, *et al.* Potentiation of antidepressant effects by L-triiodothyronine in tricyclic nonresponders. *Am J Psychiatry* 1982; **139:** 34–8.

Pharmacokinetics

Amitriptyline is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 6 hours after oral doses.

Amitriptyline undergoes extensive first-pass metabolism and is demethylated in the liver by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6 to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation (possibly to active metabolites) by CYP2D6 and *N*-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have an elimination half-life ranging from about 9 to 25 hours, which may be considerably extended in overdosage. Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

Amitriptyline and nortriptyline cross the placenta and are distributed into breast milk (see Breast Feeding under Precautions, p. 405.1).

References.

1. Schulz P, *et al.* Discrepancies between pharmacokinetic studies of amitriptyline. *Clin Pharmacokinet* 1985; **10:** 257–68.
2. Brøsen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J Clin Pharmacol* 1989; **36:** 537–47.
3. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; **18:** 434–59.
4. Wood AJJ, Zhou HH. Ethnic differences in drug disposition and responsiveness. *Clin Pharmacokinet* 1991; **20:** 350–73.
5. Llerena A, *et al.* Debrisoquin and mephenytoin hydroxylation phenotypes and CYP2D6 genotype in patients treated with neuroleptic and antidepressant agents. *Clin Pharmacol Ther* 1993; **54:** 606–11.
6. Ghahramani P, *et al.* Cytochromes P450 mediating the N-demethylation of amitriptyline. *Br J Clin Pharmacol* 1997; **43:** 137–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fiorda; Tryptalgin; Tryptanol; Uxen; ***Austral.***: Endep; Tryptanol†; ***Austria***: Saroten; Tryptizol†; ***Belg.***: Redomex; ***Braz.***: Amytril; Neurotrypt; Protanol; Tripsol; Trisomatol; Tryptanol; ***Canad.***: Elavil; Levate; Novo-Triptyn; ***Denm.***: Saroten; ***Fin.***: Triptyl; ***Fr.***: Elavil; Laroxyl; ***Ger.***: Amineurin†; Amiovid; Equilibrin; Saroten; Syneudon; ***Gr.***: Maxivalet; Saroten; Stelminal; Thymontil; ***Hong Kong***: Endep†; Qualitriptine; ***Hung.***: Teperin; ***India***: Amit; Amitone; Amitor; Amitrip; Amrea; Amypres; Crypton; Eliwel; Gentrip; Kamitrin; Latilin; Mitryp-10; Odep; Sarotena; Tryptomer; ***Israel***: Elatrol; Elatrolet; Tryptal†; ***Ital.***: Adepril; Laroxyl; Triptizol; ***Malaysia***: Tripta; Tryptanol†; ***Mex.***: Anapsique; Tryptanol; ***Neth.***: Sarotex; Tryptizol; ***Norw.***: Sarotex; ***NZ***: Amirol; Amitrip; ***Port.***: ADT; Tryptizol; ***Rus.***: Amyzol (Амизол)†; Eliwel (Эливел)†; Saroten (Саротен); ***S.Afr.***: Noriline†; Saroten†; Trepiline; Tryptanol; ***Singapore***: Tripta; ***Spain***: Deprelio; Tryptizol; ***Swed.***: Saroten; Tryptizol; ***Switz.***: Saroten; Tryptizol†; ***Thai.***: Amitec; Amitryn; Conmitrip; Polytanol; Tripsyline; Tripta; Triptyline; Tripzol; Tryptanol; ***Turk.***: Laroxyl; Triptilin; ***UK***: Elavil; ***Ukr.***: Saroten (Саротен); ***Venez.***: Tryptanol.

Multi-ingredient Preparations. ***Austria***: Limbitrol; ***Braz.***: Limbitrol; ***Canad.***: Apo-Peram†; PMS-Levazine; ***Chile***: Antalin; Limbatrilin; Morelin; Tiperin; ***Fin.***: Klotriptyl; Limbitrol; Pertriptyl; ***Gr.***: Minitran; Triphenaze; ***India***: Amichlor; Amixide H; Amize; Amizep; Amrea-C; Amypres-C; Chlotrip; Emotrip; Febl; Gentrip Forte; Gentrip Plus; Libotryp; Librodep; Limbitrol; Limbival; Mirip; Mitryp; Normaline Plus; Normaline-H; ***Indon.***: Limbitrol; Mutabon-D; Mutabon-M; ***Ital.***: Diapatol; Limbitryl; Mutabon; Sedans; ***Mex.***: Adepsique; ***Port.***: Mutabon; ***Rus.***: Amixide (Амиксид); ***S.Afr.***: Limbitrol†; ***Spain***: Mutabase; Nobritol; ***Switz.***: Limbitrol; ***Thai.***: Neuragon†; Polybon; ***UK***: Triptafen; ***USA***: Etrafon†; Limbitrol.

Pharmacopoeial Preparations

BP 2014: Amitriptyline Tablets;
USP 36: Amitriptyline Hydrochloride Injection; Amitriptyline Hydrochloride Tablets; Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Perphenazine and Amitriptyline Hydrochloride Tablets.

Amoxapine *(BAN, USAN, rINN)*

Amoksapiini; Amoksapin; Amoxapin; Amoxapina; Amoxapinum; CL-67772; Амоксапин.

2-Chloro-11-(piperazin-1-yl)dibenz[*b,f*][1,4]oxazepine.

$C_{17}H_{16}ClN_3O$=313.8

CAS — *14028-44-5.*

ATC — *N06AA17.*

ATC Vet — *QN06AA17.*

UNII — *R63VQ857OT.*

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Amoxapine). A white to yellowish crystalline powder. Practically insoluble in water; slightly soluble in acetone; freely soluble in chloroform; sparingly soluble in methyl alcohol and in toluene; soluble in tetrahydrofuran. Store in airtight containers.

Uses and Administration

Amoxapine, the *N*-desmethyl derivative of loxapine (p. 1082.2), is a dibenzoxazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). Amoxapine is one of the less sedating tricyclics and its antimuscarinic effects are mild; it also inhibits the reuptake of dopamine.

In the treatment of depression (p. 398.1) amoxapine is given in oral doses of 50 mg two or three times daily initially, gradually increased as necessary up to 100 mg two or three times daily by the end of the first week. Higher doses of up to 600 mg daily may also be given, if required, in severely depressed patients in hospital. A suggested dose for the elderly is 25 mg two or three times daily initially, increased as necessary up to 50 mg two or three times daily by the end of the first week; further increases to a maximum of 300 mg daily are permitted, if required.

Once-daily dosage regimens, usually given at night, are suitable for amoxapine up to 300 mg daily once an effective dosage has been established; divided-dosage regimens are recommended for doses above 300 mg daily.

It has been claimed that, in the treatment of depression, amoxapine has a more rapid onset of action than amitriptyline or imipramine with a clinical effect possibly appearing 4 to 7 days after starting therapy, although this has been disputed.

Amoxapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Amoxapine has also been investigated for its potential as an antipsychotic.

References.

1. Jue SG, *et al.* Amoxapine: a review of its pharmacology and efficacy in depressed states. *Drugs* 1982; **24:** 1–23.

2. Sa DS, *et al*. Amoxapine shows an antipsychotic effect but worsens motor function in patients with Parkinson's disease and psychosis. *Clin Neuropharmacol* 2001; **24:** 242–4.
3. Apiquian R, *et al*. Amoxapine shows atypical antipsychotic effects in patients with schizophrenia: results from a prospective open-label study. *Schizophr Res* 2003; **59:** 35–9.
4. Fitzgerald PB, *et al*. Amoxapine in schizophrenia: a negative double-blind controlled trial. *J Clin Psychopharmacol* 2004; **24:** 448–50.
5. Apiquian R, *et al*. Amoxapine as an atypical antipsychotic: a comparative study vs risperidone. *Neuropsychopharmacology* 2005; **30:** 2236–44.
6. Chaudhry IB, *et al*. Amoxapine as an antipsychotic: comparative study versus haloperidol. *J Clin Psychopharmacol* 2007; **27:** 575–81.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Rare cases of tardive dyskinesias and the neuroleptic malignant syndrome have been reported with amoxapine.

Antidopaminergic effects. Amoxapine is a derivative of the antipsychotic loxapine (p. 1082.2) and possesses some antipsychotic activity. It also has dopamine-receptor blocking properties as do its hydroxylated metabolites. Adverse effects that are symptoms of such blockade have been reported and reviewed[1,2] and include akinesia, akathisia, withdrawal dyskinesia, reversible tardive dyskinesia, persistent dyskinesia, elevated serum concentration of prolactin, and galactorrhoea. Chorea[3] and oculogyric crisis[4] have also been reported.

1. Tao GK, *et al*. Amoxapine-induced tardive dyskinesia. *Drug Intell Clin Pharm* 1985; **19:** 548–9.
2. Devarajan S. Safety of amoxapine. *Lancet* 1989; **ii:** 1455.
3. Patterson JF. Amoxapine-induced chorea. *South Med J* 1983; **76:** 1077.
4. Hunt-Fugate AK, *et al*. Adverse reactions due to dopamine blockade by amoxapine. *Pharmacotherapy* 1984; **4:** 35–9.

Antimuscarinic effects. Amoxapine therapy has been reported to produce adverse effects associated with antimuscarinic activity (such as constipation, blurred vision, and dry mouth), but such reports did not reflect *in-vitro* findings that amoxapine had considerably less affinity for muscarinic binding sites than amitriptyline;[1] this was supported by results in healthy subjects. The adverse effects described as antimuscarinic could possibly be explained by amoxapine affecting noradrenergic mechanisms.

1. Bourne M, *et al*. A comparison of the effects of single doses of amoxapine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 57–62.

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on the endocrine system. Reversible nonketotic hyperglycaemia developed in a 49-year-old woman with no history of diabetes mellitus within 5 days of oral therapy with amoxapine 50 mg three times daily.[1] She had previously had nonketotic hyperglycaemic coma after loxapine 150 mg daily. 7-Hydroxyamoxapine, a metabolite common to both amoxapine and loxapine, was implicated.

See also Antidopaminergic Effects, above, for mention of galactorrhoea and hyperprolactinaemia.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Overdosage. In overdosage, amoxapine is reported to cause acute renal failure with rhabdomyolysis,[1,2] coma, and seizures.[3-5] Although there has been some debate as to whether the incidence of seizures and death is higher with overdosage of amoxapine than with other tricyclic antidepressants, some[6] consider that evidence does seem to favour increased neurological consequences.

It has been reported that amoxapine is not cardiotoxic in overdosage[3] but later evidence would suggest that there is cardiotoxic potential.[6,7]

1. Pumariega AJ, *et al*. Acute renal failure secondary to amoxapine overdose. *JAMA* 1982; **248:** 3141–2.
2. Jennings AE, *et al*. Amoxapine-associated acute renal failure. *Arch Intern Med* 1983; **143:** 1525–7.
3. Kulig K, *et al*. Amoxapine overdose: coma and seizures without cardiotoxic effects. *JAMA* 1982; **248:** 1092–4.
4. Litovitz TL, Troutman WG. Amoxapine overdose: seizures and fatalities. *JAMA* 1983; **250:** 1069–71.
5. Jefferson JW. Convulsions associated with amoxapine. *JAMA* 1984; **251:** 603–4.
6. Leonard BE. Safety of amoxapine. *Lancet* 1989; **ii:** 808.
7. Sørensen MR. Acute myocardial failure following amoxapine intoxication. *J Clin Psychopharmacol* 1988; **8:** 75.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Amoxapine is readily absorbed from the gastrointestinal tract. It bears a close chemical relationship to loxapine (p. 1082.2) and is similarly metabolised by hydroxylation. It is excreted in the urine, mainly as its metabolites in conjugated form as glucuronides.

Amoxapine has been reported to have a plasma half-life of 8 hours and its major metabolite, 8-hydroxyamoxapine, has been reported to have a biological half-life of 30 hours; 7-hydroxyamoxapine has been identified as another metabolite. Both metabolites are pharmacologically active. Amoxapine is about 90% bound to plasma proteins.

Amoxapine and its metabolite 8-hydroxyamoxapine are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Defanyl; ***India***: Amolife; Demolox; Oxamine; Oxcap; ***Indon.***: Asendin†.

Pharmacopoeial Preparations
USP 36: Amoxapine Tablets.

Benactyzine Hydrochloride *(BANM, rINNM)*

Amizylum; Benacticina, hidrocloruro de; Bénactyzine, Chlorhydrate de; Benactyzini Hydrochloridum; Hidrocloruro de benacticina; Бенактизина Гидрохлорид.
2-Diethylaminoethyl benzilate hydrochloride.
$C_{20}H_{25}NO_3$,HCl=363.9
CAS — 302-40-9 (benactyzine); 57-37-4 (benactyzine hydrochloride).
UNII — 26R628272Q.

Profile

Benactyzine has antidepressant and antimuscarinic activity. It has been used as the hydrochloride in the management of depression and associated anxiety. It is also used as a pharmacological tool. Methylbenactyzium bromide (p. 1864.3), the methobromide of benactyzine, has been used for its antimuscarinic activity in the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Dimaval.

Bupropion *(BAN, rINN)*

Amfebutamone; Bupropión; Bupropione; Bupropionum; Бупропион.
(±)-2-(*tert*-Butylamino)-3′-chloropropiophenone.
$C_{13}H_{18}ClNO$=239.7
CAS — 34911-55-2.
ATC — N06AX12.
ATC Vet — QN06AX12.
UNII — 01ZG3TPX31.

Bupropion Hydrobromide *(BANM, USAN, rINNM)*

Bupropione, Bromhydrate de; Bupropioni Hydrobromidum; BVF-033; Hidrobromuro de bupropión; Бупропиона Гидробромид.
(2*RS*)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]propan-1-one hydrobromide.
$C_{13}H_{18}ClNO$,HBr=320.7
CAS — 905818-69-1.
ATC — N06AX12.
ATC Vet — QN06AX12.
UNII — E70G3G5863.

Bupropion Hydrochloride *(BANM, USAN, rINNM)*

Amfebutamone Hydrochloride; Bupropión, hidrocloruro de; Bupropione, Chlorhydrate de; Bupropionhydroklorid; Bupropioni Hydrochloridum; Bupropionihydrokloridi; BW-323; Hidrocloruro de anfebutamona; Hidrocloruro de bupropión; Бупропиона Гидрохлорид.
(±)-2-(*tert*-Butylamino)-3′-chloropropiophenone hydrochloride.
$C_{13}H_{18}ClNO$,HCl=276.2
CAS — 31677-93-7.
ATC — N06AX12.
ATC Vet — QN06AX12.
UNII — ZG7E5POY8O.

Pharmacopoeias. In *US*.

USP 36: (Bupropion Hydrochloride). A white powder. Soluble in water, in alcohol, and in 0.1N hydrochloric acid. Protect from light.

Uses and Administration

Bupropion is a chlorpropiophenone antidepressant chemically unrelated to other classes of antidepressants but similar in structure to the central stimulant diethylpropion (p. 2321.1). It is a weak blocker of neuronal reuptake of serotonin and noradrenaline compared with tricyclic antidepressants; it also inhibits the neuronal reuptake of dopamine. The antidepressant effect may not be evident until after 4 weeks of therapy. Bupropion is also used as an aid to smoking cessation.

Bupropion is given orally as the hydrochloride or the hydrobromide; 150 mg of bupropion hydrochloride is equivalent to about 174 mg of the hydrobromide. To minimise agitation, anxiety, and insomnia that often occur at the start of therapy, and to reduce the risk of seizures, doses should be increased gradually; the total daily dose should be given in equally divided doses and the maximum recommended single and total daily doses should not be exceeded. Insomnia at the start of therapy may be minimised by avoiding bedtime doses. Patients with hepatic or renal impairment should be given reduced doses and monitored for toxic effects (see p. 410.3).

In the treatment of **depression** bupropion hydrochloride is given in initial doses of 100 mg twice daily increased, if necessary, after at least 3 days to 100 mg three times daily. In severe cases, if no improvement has occurred after several weeks of therapy, the dose may be increased further to a maximum of 150 mg three times daily. Bupropion hydrochloride is also available as a modified-release preparation given in an initial dose of 150 mg once daily in the morning increased, if necessary, after at least 3 days to 150 mg twice daily; in severe cases, the dose of the modified-release preparation may be increased further after several weeks to 200 mg twice daily. A modified-release preparation that is given once daily is also available; the maximum daily dose for this preparation is 450 mg as a single dose in the morning. Bupropion hydrobromide is also given as a modified-release preparation for once-daily use; doses are equivalent to those of the hydrochloride, when given once daily.

A modified-release preparation of bupropion hydrochloride is also licensed for the prevention of depression in patients with **seasonal affective disorder**; the maximum dose for this disorder is 300 mg once daily. A once-daily modified-release preparation of bupropion hydrobromide is also given in doses equivalent to those of the hydrochloride for this indication.

Bupropion hydrochloride is given as a modified-release preparation as an aid to **smoking cessation** in an initial dose of 150 mg once daily for 6 days, increasing to 150 mg twice daily on day 7. In the USA, the dose may be increased after 3 days. In the UK, the maximum recommended dose in the elderly, or in patients with predisposing risk factors for seizure (see Precautions, p. 412.1), is 150 mg daily. Treatment should be started about 1 to 2 weeks before the patient attempts to stop smoking, to allow steady-state blood concentrations of bupropion to be reached, and normally continues for 7 to 12 weeks; if there is no significant progress towards smoking abstinence by the seventh week, then therapy should be stopped. Use with nicotine transdermal patches may be warranted in some patients, although there is a risk of hypertension with such therapy (see Interactions, p. 412.2).

Administration in hepatic impairment. When used as an aid to *smoking cessation* in patients with mild to moderate hepatic impairment, bupropion hydrochloride should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily. The use of bupropion hydrochloride in patients with severe hepatic cirrhosis is contra-indicated in the UK although doses of 150 mg every other day are permitted in the USA.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered in patients with mild to moderate impairment. In patients with severe hepatic cirrhosis the dose varies according to the preparation given. For modified-release bupropion hydrochloride (or its equivalent as the hydrobromide) the suggested maximum oral dose is 100 mg once daily or 150 mg every other day, while the maximum dose of immediate-release bupropion hydrochloride is 75 mg once daily. Similar recommendations apply to modified-release preparations when used for the prevention of depression in *seasonal affective disorder*.

Administration in renal impairment. When used as an aid to *smoking cessation* in patients with renal impairment, bupropion hydrochloride should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Bupropion has a different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, it may be safer in overdosage than the older tricyclics.

References.
1. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001; **35:** 1608–13.
2. Weihs KL, *et al.* Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry* 2002; **51:** 753–61.
3. Glod CA, *et al.* Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs* 2003; **16:** 123–30.
4. Rush AJ, *et al.* The STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; **354:** 1231–42.
5. Trivedi MH, *et al.* The STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006; **354:** 1243–52.
6. Papakostas GI, *et al.* Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. *J Clin Psychiatry* 2007; **68:** 1907–12.
7. Dhillon S, *et al.* Bupropion: a review of its use in the management of major depressive disorder. *Drugs* 2008; **68:** 653–89.
8. Papakostas GI, *et al.* Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. *J Clin Psychiatry* 2008; **69:** 1287–92.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p. 2314.1) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants. Data from open and controlled studies involving small numbers of patients suggest that bupropion is effective in adults and children.[1,2]

1. Cantwell DP. ADHD through the life span: the role of bupropion in treatment. *J Clin Psychiatry* 1998; **59** (suppl 4): 92–4.
2. Wilens TE, *et al.* A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 2001; **158:** 282–8.

Obesity. Bupropion is under investigation in the management of obesity. It is being studied as combination therapy with naltrexone (see Eating Disorders, p. 1565.3) or zonisamide (see Obesity, p. 561.1).

Smoking cessation. Bupropion is effective in the management of smoking cessation (p. 2570.2) and may be used as a first-line alternative to nicotine replacement therapy (NRT); its action is said to be independent of its antidepressant activity. Bupropion with NRT has also been used successfully although there is an increased risk of hypertension with this combination (see Interactions, p. 412.2).

References:
1. Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. *Drugs* 2000; **59:** 1007–1024.
2. Tashkin DP, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; **357:** 1571–5.
3. Gonzales DH, *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001; **69:** 438–44.
4. Hays JT, *et al.* Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. *Ann Intern Med* 2001; **135:** 423–33.
5. Fagerström K, *et al.* Smoking cessation treatment with sustained-release bupropion: optimising approaches to management. A seminar-in-print. *Drugs* 2002; **62** (suppl 2): 1–70.
6. Hays JT, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. *Mayo Clin Proc* 2003; **78:** 1020–4.
7. Tonnesen P, *et al.* A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; **254:** 184–92.
8. Simon JA, *et al.* Bupropion for smoking cessation: a randomized trial. *Arch Intern Med* 2004; **164:** 1797–1803.
9. Roddy E. ABC of smoking cessation: bupropion and other non-nicotine pharmacotherapies. *BMJ* 2004; **328:** 509–11.
10. Paluck EC, *et al.* Outcomes of bupropion therapy for smoking cessation during routine clinical use. *Ann Pharmacother* 2006; **40:** 185–90.
11. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Adverse Effects and Treatment

Agitation, anxiety, and insomnia often occur during the initial stages of bupropion therapy. Other relatively common adverse effects reported with bupropion include fever, dry mouth, headache or migraine, dizziness, urinary frequency, nausea and vomiting, constipation, tremor, sweating, and skin rashes. Hypersensitivity reactions, ranging from pruritus and urticaria to, less commonly, angioedema, dyspnoea, and anaphylactoid reactions, have occurred, as have symptoms suggestive of serum sickness. There have been rare reports of Stevens-Johnson syndrome and erythema multiforme. Tachycardia, chest pain, and hypertension (sometimes severe), or occasionally vasodilatation, orthostatic hypotension, palpitations, and syncope have been reported. Psychotic episodes, confusion, nightmares, impaired memory, dysgeusia, anorexia with weight loss, paraesthesia, tinnitus, and visual disturbances have also been reported.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Seizures, which appear to be partially dose-related, may occur with bupropion and have been particularly notable in patients with anorexia nervosa or bulimia nervosa; the risk is also increased in patients with a history of seizure disorders or other predisposing factor. The manufacturers state that the overall incidence of seizure in patients receiving bupropion at recommended doses is about 0.1 to 0.4%.

Symptoms of overdosage include hallucinations, nausea and vomiting, tachycardia, loss of consciousness, and death (following massive overdose); seizures have occurred in about one-third of all bupropion overdose cases. Activated charcoal should be considered in adult patients who have taken more than 450 mg and in all children, if they present within 1 hour of ingestion and provided the airway can be protected; gastric lavage may also be used to decrease absorption. Treatment is supportive. Benzodiazepines may be tried for seizures. Diuresis, dialysis, and haemoperfusion are unlikely to be of benefit.

Incidence of adverse effects. Up to 24 July 2002 (the first 25 months of marketing), the UK CSM had received 7630 reports of suspected adverse reactions associated with the use of bupropion.[1] Of these reports, 60 were associated with a fatal outcome although in most cases underlying conditions could have been responsible. Cardiovascular and cerebrovascular disorders such as myocardial infarction and stroke were reported as the cause of death in 70% of cases. The CSM also commented that adverse reactions were mainly recognised ones and listed in the licensed product information.

In January 2005 the German pharmacovigilance network reviewed[2] 273 reports of adverse effects associated with bupropion, received between June 2000 and September 2004. The most frequent adverse effects were: psychiatric disorders (79.3%), including suicide attempts (17.6%), and tachycardia (11.15%), seizures (8.8%), and dyspnoea (8.8%). There were also 4 cases of pancreatitis and one of raised pancreatic enzyme activity three times greater than normal.

1. CSM/MCA. Zyban (bupropion hydrochloride) - safety update (issued 26th July, 2002). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019524&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
2. Arzneimittelkommission der deutschen Ärzteschaft. Erhöhte Pankreasenzyme oder akute Pankreatitis unter Bupropion (Zyban) (aus der UAW-Datenbank; issued 10th January, 2005). Available at: http://www.akdae.de/Arzneimittelsicherheit/Bekanntgaben/Archiv/2005/800_20050110.html (accessed 28/07/10)

Effects on the cardiovascular system. Up to the end of December 2001 the national pharmacovigilance centre in the Netherlands had received 591 adverse reaction reports associated with the use of bupropion for smoking cessation since its marketing 2 years earlier;[1] of these, 45 concerned cardiac complaints such as palpitations (21 reports), arrhythmias (7 reports), myocardial infarction (3 reports), anginal pain (2 reports), and cardiac arrest (1 report). Twenty-two reports also mentioned chest pain or tightness, although these were considered to be of noncardiac origin. In another report a 43-year-old male suffered an acute myocardial infarction 2 weeks after starting bupropion for smoking cessation;[2] he had experienced central chest and arm pain 3 days before the infarction. The authors of the report said that up to 30 April 2001 the UK CSM had received 238 reports of chest pain and 134 reports of chest tightness associated with bupropion use.

1. de Graaf L, Diemont WL. Chest pain during use of bupropion as an aid in smoking cessation. *Br J Clin Pharmacol* 2003; **56:** 451–2.
2. Patterson RN, Herity NA. Acute myocardial infarction following bupropion (Zyban). *Q J Med* 2002; **95:** 58–9.

Effects on the cerebrovascular system. A 67-year-old male had paraesthesia, dizziness, tinnitus, confusion, and gait impairment after taking bupropion for smoking cessation.[1] Although a transient ischaemic attack was suspected symptoms resolved on stopping bupropion and recurred on rechallenge.

1. Humma LM, Swims MP. Bupropion mimics a transient ischemic attack. *Ann Pharmacother* 1999; **33:** 305–7.

Effects on the pancreas. See under Incidence of Adverse Effects, above.

Effects on the skin. *Erythema multiforme* developed in a 31-year-old woman several weeks after starting modified-release bupropion for depression.[1] Symptoms resolved on drug withdrawal. In another report, 3 patients with controlled *psoriasis* had an exacerbation of their psoriatic symptoms after starting bupropion for smoking cessation.[2] All 3 patients required hospitalisation to control their symptoms. There have also been several reports of patients developing *generalised acute urticaria*;[3,4] systemic symptoms resembling serum sickness were also reported in 1 case[4] (see also Hypersensitivity, p. 411.3).

1. Lineberry TW, *et al.* Bupropion-induced erythema multiforme. *Mayo Clin Proc* 2001; **76:** 664–6.
2. Cox NH, *et al.* Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; **146:** 1061–3.
3. Fays S, *et al.* Bupropion and generalized acute urticaria: eight cases. *Br J Dermatol* 2003; **148:** 177–8.
4. Loo WJ, *et al.* Bupropion and generalized acute urticaria: a further case. *Br J Dermatol* 2003; **149:** 660.

Extrapyramidal effects. A 44-year-old man had acute head and neck dystonia while taking buspirone and modified-release bupropion.[1] No recurrence was noted on rechallenge with buspirone although symptoms did develop on rechallenge with bupropion when the dose was increased from 150 mg once daily to 150 mg twice daily. In another case, a 42-year-old woman had gross involuntary movements of her torso, arms, and legs (diagnosed as ballism) 8 days after starting bupropion for smoking cessation;[2] the dose had been increased from 150 mg once daily to 150 mg twice daily on the fourth day. She recovered when bupropion was stopped and treatment with haloperidol and oxazepam was given.

1. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. *Ann Pharmacother* 2002; **36:** 251–4.
2. de Graaf L, *et al.* Ballism associated with bupropion use. *Ann Pharmacother* 2003; **37:** 302–3.

Hypersensitivity. Eosinophilia has been reported[1] in a patient 12 days after bupropion was added to her existing treatment regimen of glibenclamide and tolmetin. The eosinophil count returned to normal after all medication was stopped. Bupropion appeared to be the causative drug.

Serum sickness or symptoms suggestive of serum sickness has also been associated with bupropion use.[2-5] In one case,[5] although the initial presentation resembled serum sickness, the patient went on to develop multisystem complications that included hepatitis, cholestasis, and myocarditis.

Angioedema affecting the feet, hands, arms, lower lip, and tongue occurred in a patient about 20 days after starting bupropion.[6] He also had a pruritic rash and urticaria, and developed watery diarrhoea and slight swelling and soreness of the knees and heals. The reaction was treated symptomatically and bupropion therapy was stopped.

See also Effects on the Skin, above.

1. Malesker MA, *et al.* Eosinophilia associated with bupropion. *Ann Pharmacother* 1995; **29:** 867–8.
2. Yolles JC, *et al.* Serum sickness induced by bupropion. *Ann Pharmacother* 1999; **33:** 931–3.
3. McCollom RA, *et al.* Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; **34:** 471–3.
4. Benson E. Bupropion-induced hypersensitivity reactions. *Med J Aust* 2001; **174:** 650–1.
5. Bagshaw SM, *et al.* Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. *Ann Allergy Asthma Immunol* 2003; **90:** 572–5.
6. Tackett AE, Smith KM. Bupropion-induced angioedema. *Am J Health-Syst Pharm* 2008; **65:** 1627–30.

Overdosage. Unlike the tricyclic antidepressants, bupropion appears to lack any significant cardiovascular or antimuscarinic adverse effects when taken in overdose. In an early review[1] of 58 overdose cases involving immediate-release bupropion alone, the most common symptoms were sinus tachycardia, lethargy, tremor, and seizures; other effects included confusion, lightheadedness, hallucinations, paraesthesias, and vomiting. Most patients had minor effects or none at all. Similar symptoms have also been noted in reviews of overdose cases involving modified-release bupropion.[2,3] UK licensed prescribing information for bupropion also lists ECG changes such as conduction disturbances, arrhythmias, and tachycardia although a literature review[4] concluded that cardiotoxicity appeared to be rare with bupropion overdosage. Although rare, there have been fatalities after overdose; in some cases other drugs may have been involved.[3,5,6]

More recent case reports and reviews with modified-release preparations have highlighted that seizures are a particular feature of bupropion overdose.[2,3,7,8]

1. Spiller HA, *et al.* Bupropion overdose: a 3-year multi-center retrospective analysis. *Am J Emerg Med* 1994; **12:** 43–5.
2. Balit CR, *et al.* Bupropion poisoning: a case series. *Med J Aust* 2003; **178:** 61–3.
3. Shepherd G, *et al.* Intentional bupropion overdoses. *J Emerg Med* 2004; **27:** 147–51.
4. Druteika D, Zed PJ. Cardiotoxicity following bupropion overdose. *Ann Pharmacother* 2002; **36:** 1791–5.
5. Friel PN, *et al.* Three fatal drug overdoses involving bupropion. *J Anal Toxicol* 1993; **17:** 436–8.
6. Harris CR, *et al.* Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997; **35:** 321–4.
7. Bhattacharjee C, *et al.* Bupropion overdose: a potential problem with the new 'miracle' anti-smoking drug. *Int J Clin Pract* 2001; **55:** 221–2.
8. Paoloni R, Szekely I. Sustained-release bupropion overdose: a new entity for Australian emergency departments. *Emerg Med (Fremantle)* 2002; **14:** 109–12.

Precautions

Bupropion may induce seizures and consequently its use is contra-indicated in patients with epilepsy. It is also contra-indicated in patients with a history of anorexia nervosa or bulimia nervosa, as a higher incidence of seizures has been noted in such patients treated with bupropion, and in those undergoing abrupt withdrawal from alcohol or benzodiazepines. It should be used with extreme caution, if at all, in patients with a history of seizure disorders or other predisposing factors such as severe hepatic cirrhosis or a CNS tumour. The use of bupropion in patients with other risk factors for seizures (for example, alcohol abuse, a history of head trauma, diabetes, and drugs known to lower the seizure threshold) should only be undertaken when there are compelling clinical reasons.

Bupropion should be used with caution in patients with bipolar disorder or psychoses because of the risk of precipitating mania; use for smoking cessation in such patients may be contra-indicated. It should also be used cautiously in patients with a recent history of myocardial infarction or unstable heart disease, and in hepatic or renal impairment.

When bupropion is used for depression, patients should be closely monitored during early therapy until significant improvement occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other CNS-active drugs, the ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by bupropion, and patients, if affected, should not drive or operate machinery.

Breast feeding. The American Academy of Pediatrics considers[1] that the effect of bupropion on nursing infants is unknown but may be of concern.

In a study[2] in 10 women, bupropion and its active metabolites were found in breast milk, and the average breast milk to plasma bupropion ratio was 2.8. The authors estimated that for a breast-fed infant the total exposure to bupropion and its metabolites would be 2% of the weight-normalised maternal bupropion dose, and that this should not be of concern for most infants. No adverse effects were noted in an infant breast fed twice daily by a mother who had breast-milk concentrations of bupropion higher than those in her plasma;[3] neither bupropion nor its metabolites were detected in the infant's plasma. Similar findings were noted in a study in 2 breast-fed infants whose mothers took bupropion for postpartum depression.[4] Bupropion was found in the urine of 1 of 4 breast-fed infants whose mothers were taking bupropion; the infant was reported to be nearly 6 weeks premature.[5] In these women, the average milk to serum ratio of bupropion was 1.30, and the infant dose estimated to be 5.7% of the maternal dose. In this report, too, the authors considered the risk of systemic exposure in the infants to be minimal. However, in another report, a 6-month-old infant had a seizure after being fed breast milk that had been expressed and stored 2 days earlier, after the infant's mother had taken a single dose of bupropion.[6] Before the seizure, the mother had taken 2 doses of bupropion and breast fed the infant several times with no adverse effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Haas JS, *et al.* Bupropion in breast milk: an exposure assessment for potential treatment to prevent post-partum tobacco use. *Tob Control* 2004; **13:** 52–6.
3. Briggs GC, *et al.* Excretion of bupropion in breast milk. *Ann Pharmacother* 1993; **27:** 431–3.
4. Baab SW, *et al.* Serum bupropion levels in 2 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2002; **63:** 910–11.
5. Davis MF, *et al.* Bupropion levels in breast milk for 4 mother-infant pairs: more answers to lingering questions. *J Clin Psychiatry* 2009; **70:** 297–8.
6. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry* 2004; **65:** 881–2.

Children. Bupropion has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age, regardless of indication, is not recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p. 422.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bupropion as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The safety of bupropion in pregnancy has not been established. In a study of 136 women who took bupropion for either depression or smoking cessation in at least the first trimester of pregnancy, there were 105 live births, 20 spontaneous abortions, 10 therapeutic abortions, 1 still-birth, and 1 neonatal death; no major congenital malformations were reported.[1] Compared with a control group not exposed to teratogens, the rate of spontaneous abortions was significantly higher in the bupropion group when both indications were considered; however, there was no difference in the rate when women taking bupropion for depression were compared with this control group and another control group of women taking other antidepressants.

Complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding have been reported with some of the newer antidepressants such as bupropion.[2] Other reported symptoms have included seizures, muscle rigidity, jitteriness, and prolonged crying. It is unknown whether such symptoms represent a direct toxicity of bupropion or a possible withdrawal syndrome.

1. Chun-Fai-Chan B, *et al.* Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 2005; **192:** 932–6.
2. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Bupropion should not be given with or within 14 days of stopping an MAOI; however, no treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting bupropion.

The use of alcohol with bupropion should be minimised or avoided completely because it may alter the seizure threshold. Similarly, extreme caution is needed if other drugs that lower the seizure threshold, such as other antidepressants, antimalarials, antipsychotics, sedating antihistamines, quinolones, tramadol, theophylline, or systemic corticosteroids are used with bupropion. In the UK, where it is licensed as a modified-release product for smoking cessation, a maximum dose of 150 mg daily is recommended if patients are also taking such drugs.

Use of nicotine transdermal patches with bupropion has been associated with hypertension, and patients using both should therefore have their blood pressure monitored.

Caution has been advised in patients receiving either amantadine or levodopa with bupropion because of reports of a higher incidence of adverse effects in patients receiving these combinations.

Animal studies have indicated that bupropion may induce drug-metabolising enzymes and pharmacokinetic interactions with other drugs are therefore a possibility. Bupropion is itself metabolised by hepatic enzyme systems and drugs known to affect such systems may interact with bupropion. For example carbamazepine, phenobarbital, or phenytoin may induce the metabolism of bupropion while other drugs such as cimetidine or valproate may inhibit its metabolism. *In-vitro* studies have shown that bupropion is metabolised by the cytochrome P450 isoenzyme CYP2B6. Consequently interactions may occur between bupropion and drugs that affect this isoenzyme, for example orphenadrine, cyclophosphamide, and ifosfamide.

In-vitro studies have also shown that bupropion is also an inhibitor of the isoenzyme CYP2D6; caution should be exercised when it is given with drugs metabolised by this isoenzyme and they should be started at the lower end of their dose range. Such drugs include some antidepressants, antipsychotics, beta blockers, and type Ic antiarrhythmics.

Antiepileptics. Plasma-bupropion concentrations became undetectable in 2 patients who were also receiving *carbamazepine*; plasma concentrations of hydroxybupropion, an active metabolite of bupropion, were high.[1]

1. Popli AP, *et al.* Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiatry* 1995; **7:** 99–101.

Antivirals. There is some evidence from study *in vitro* that the antivirals *efavirenz*, *nelfinavir*, and *ritonavir* can inhibit the cytochrome P450 isoenzyme CYP2B6.[1] However, evidence of clinically significant interaction with bupropion is lacking: a small case series of 10 patients who took bupropion with low-dose ritonavir (100 mg twice daily), or efavirenz or nelfinavir, did not note any episodes of seizures.[2] A study[3] in 7 healthy male subjects also found that 2 days of low-dose ritonavir (200 mg twice daily) had little impact on the pharmacokinetics of a single bupropion dose.

In contrast, UK licensed product information for bupropion states that studies in healthy subjects found that ritonavir (100 mg or 600 mg, twice daily) reduced the exposure to bupropion and its major metabolites in a dose-dependent manner, possibly by inducing its metabolism. In another study[4] in healthy subjects, the plasma concentrations and AUC of bupropion and its active metabolite hydroxybupropion, from a single dose of bupropion, were reduced by about 50% after 14 days of a *lopinavir/ritonavir* combination (400 mg/100 mg twice daily). This effect was attributed to induction of CYP2B6 and UDP-glucuronosyltransferase by the HIV-protease inhibitor combination. In discussing the contrasting results that have been reported, the authors suggested that the higher ritonavir concentrations achieved *in-vitro* had an inhibitory effect, compared with the inducing effect of lower steady-state concentrations achieved *in-vivo*. In practice, UK licensed product information for bupropion suggests that the dose may need to be increased in patients also taking ritonavir, but that the maximum dose of bupropion should not be exceeded.

1. Hesse LM, *et al.* Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* 2001; **29:** 100–102.
2. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series. *AIDS* 2003; **17:** 638–40.
3. Hesse LM, *et al.* Ritonavir has minimal impact on the pharmacokinetic disposition of a single dose of bupropion administered to human volunteers. *J Clin Pharmacol* 2006; **46:** 567–76.
4. Hogeland GW, *et al.* Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2007; **81:** 69–75.

Histamine H_2-antagonists. A randomised controlled study in 24 subjects found that *cimetidine* had no effect on the pharmacokinetics of modified-release bupropion or its active metabolite, hydroxybupropion.[1]

1. Kustra R, *et al.* Lack of effect of cimetidine on the pharmacokinetics of sustained-release bupropion. *J Clin Pharmacol* 1999: **39:** 1184–8.

Pharmacokinetics

Bupropion is well absorbed from the gastrointestinal tract but may undergo extensive first-pass metabolism. Several metabolites of bupropion are pharmacologically active and have longer half-lives, and achieve higher plasma concentrations, than the parent compound. Hydroxybupropion is the major metabolite, produced by the metabolism of bupropion by the cytochrome P450 isoenzyme CYP2B6; in *animal* studies hydroxybupropion was one-half as potent as bupropion. Threohydrobupropion and erythrohydrobupropion are produced by reduction and are about one-fifth the potency of the parent compound. Bupropion is 80% or more bound to plasma proteins. The terminal plasma half-life of immediate-release bupropion is about 14 hours; the terminal plasma half-life of modified-release bupropion is about 20 hours. The metabolites of bupropion are excreted mainly in the urine; less than 1% of the parent drug is excreted unchanged. Bupropion and its metabolites cross the placenta and are distributed into breast milk.

References.
1. Sweet RA, *et al.* Pharmacokinetics of single- and multiple-dose bupropion in elderly patients with depression. *J Clin Pharmacol* 1995; **35:** 876–84.

Smoking. No clinically significant differences were seen between the pharmacokinetics of bupropion or its metabolites in cigarette smokers and non-smokers.[1]

1. Hsyu P-H, *et al.* Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* 1997; **37:** 737–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lung; Odranal†; Wellbutrin; ***Austral.***: Clorprax†; Prexaton; Zyban; ***Austria***: Elontril; Wellbutrin; Zyban; ***Belg.***: Wellbutrin; Zyban; ***Braz.***: Bup; Wellbutrin; Zetron; Zyban; ***Canad.***: Wellbutrin; Zyban; ***Chile***: Buxon; Wellbutrin; ***China***: Le Fu Ting (乐孚亭); Yue Ting (悦亭); ***Cz.***: Elontril; Wellbutrin; Zyban†; ***Denm.***: Wellbutrin; Zyban; ***Fin.***: Voxra; Zyban; ***Fr.***: Zyban; ***Ger.***: Elontril; Zyban; ***Gr.***: Wellbutrin; Zyban; ***Hong Kong***: Wellbutrin; Zyban; ***Hung.***: Elontril; Wellbutrin; ***India***: Bupep; Bupisure; Bupron; Ession; Nicotex; Zyban; ***Irl.***: Zyban; ***Israel***: Wellbutrin; Zyban; ***Ital.***: Elontril; Wellbutrin; Zyban; ***Malaysia***: Zyban; ***Mex.***: Butrew; Wellbutrin; ***Neth.***: Elontril; Quomem; Wellbutrin; Zyban; Zyntabac; ***Norw.***: Wellbutrin; Zyban; ***NZ***: Zyban; ***Pol.***: Wellbutrin; Zyban; ***Port.***: Elontril; Wellbutrin; Zyban; Zyntabac†; ***S.Afr.***: Wellbutrin; Zyban; ***Singapore***: Wellbutrin; Zyban†; ***Spain***: Elontril; Quomem†; Zyntabac; ***Swed.***: Voxra; Zyban; ***Switz.***: Wellbutrin; Zyban; ***Thai.***: Quomem; Wellbutrin; ***Turk.***: Wellbutrin; Zyban; ***UK***: Zyban; ***USA***: Aplenzin; Budeprion†; Buproban; Forfivo; Wellbutrin; Zyban; ***Venez.***: Wellbutrin.

Pharmacopoeial Preparations

USP 36: Bupropion Hydrochloride Extended-Release Tablets; Bupropion Hydrochloride Tablets.

Citalopram *(BAN, rINN)*

Citalopramum; Lu-10-171; Sitalopraami; Циталопрам.
1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.
$C_{20}H_{21}FN_2O$=324.4
CAS — 59729-33-8.
ATC — N06AB04.
ATC Vet — QN06AB04.
UNII — 0DHU5B8D6V.

Citalopram Hydrobromide
(BANM, USAN, rINNM)

Citalopram, Bromhydrate de; Citalopram, hidrobromuro de; Citalopramhydrobromid; Citaloprami Hydrobromidum; Hidrobromuro de citalopram; Lu-10-171B; Nitalapram Hydrobromide; Sitalopram Hidrobromür; Циталопрама Гидробромид.
$C_{20}H_{21}FN_2O,HBr$=405.3
CAS — 59729-32-7.
UNII — I1E9D14F36.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Citalopram Hydrobromide). A white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol.

USP 36: (Citalopram Hydrobromide). A white to almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; soluble in alcohol. A 0.5% solution in water has a pH of 5.5 to 6.5.

Citalopram Hydrochloride *(BANM, rINNM)*

Citalopram, Chlorhydrate de; Citalopram, hidrocloruro de; Citalopramhydrochlorid; Citaloprami hydrochloridum; Hidrocloruro de citalopram; Циталопрама Гидрохлорид.
$C_{20}H_{21}FN_2O,HCl$=360.9
UNII — 4DY48G26JY.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Citalopram Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in dehydrated alcohol.

Uses and Administration

Citalopram, a phthalane derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 419.1). Citalopram is given orally as the hydrobromide or hydrochloride, usually as a single daily dose. Doses are expressed in terms of citalopram; citalopram hydrobromide 25.0 mg and citalopram hydrochloride 22.3 mg are each equivalent to about 20.0 mg of citalopram.

In the treatment of **depression**, the initial oral dose (given as tablets or a liquid) is the equivalent of 20 mg daily. After at least one week, the dose may be increased to a maximum of 40 mg daily. In some countries citalopram is also given as the hydrochloride in the form of concentrated oral drops containing the equivalent of 40 mg/mL of citalopram. The bioavailability of the drops is about 25% greater than that of the tablets and consequently daily doses appear to be lower: a 20-mg tablet dose is equivalent to a 16-mg (8 drops) dose of the concentrate. Citalopram hydrochloride has also been given by intravenous infusion in doses of 20 to 40 mg when the oral route is impracticable.

In the treatment of **panic disorder** with or without agoraphobia, the initial oral dose is 10 mg (or the equivalent as the concentrate) daily increasing to 20 mg daily after one week. The dose may be increased thereafter as required up to a maximum of 40 mg daily. In some countries citalopram is also used in the treatment of **obsessive-compulsive disorder** in doses similar to those used in depression (see above).

Elderly patients should be given half the recommended adult doses, up to a maximum of 20 mg (or their equivalents as the concentrate) daily. In addition, patients who are poor CYP2C19 metabolisers should be given an initial dose of 10 mg daily for the first 2 weeks of treatment, increasing to a maximum of 20 mg daily thereafter, according to response. Similarly, a maximum dose of 20 mg daily is recommended in those also taking CYP2C19 inhibitors. For dosage in hepatic and renal impairment, see p. 413.2, and for doses used in children, see p. 413.2.

Citalopram should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

The *S*-enantiomer of citalopram, escitalopram (p. 418.2) is given for the treatment of depression and some anxiety disorders.

Reviews.

1. Milne RJ, Goa KL. Citalopram: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. *Drugs* 1991; **41**: 450–77.

Administration in children. There are concerns about the use of SSRIs in children (see Effects on Mental State, under Adverse Effects of Fluoxetine, p. 422.2) and citalopram therapy is unlicensed in those under 18 years of age. Nonetheless, the *BNFC* suggests that it may be used by specialists for the treatment of major depression in those aged 12 years and over. The initial oral dose is 10 mg daily, increased if necessary to 20 mg daily over 2 to 4 weeks; the maximum dose is 40 mg daily. It may also be given in the form of concentrated oral drops, see Uses and Administration, above for details of equivalence and bioavailability.

Administration in hepatic or renal impairment. Citalopram should be used with caution in patients with hepatic impairment, particularly those with severe impairment. An initial oral dose of 10 mg (or the equivalent as the concentrate) daily is recommended for the first 2 weeks of treatment in those with mild or moderate impairment; thereafter, the dose may be increased, according to response, to a maximum of 20 mg daily.

There is no need for dose adjustment in mild to moderate renal impairment although information is lacking on appropriate dosage in severe impairment.

Anxiety disorders. Citalopram has been given in anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1), obsessive-compulsive disorder (p. 1028.2), post-traumatic stress disorder (p. 1029.2), and social anxiety disorder (see under Phobic Disorders, p. 1029.1).

References.

1. Bouwer C, Skin DJ. Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. *J Affect Disord* 1998; **49:** 79–82.
2. Lepola UM, *et al.* A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. *J Clin Psychiatry* 1998; **59:** 528–34.
3. Seedat S, *et al.* Open trial of citalopram in adults with post-traumatic stress disorder. *Int J Neuropsychopharmacol* 2000; **3:** 135–40.
4. Montgomery SA, *et al.* Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2001; **16:** 75–86.
5. Perna G, *et al.* A comparison of citalopram and paroxetine in the treatment of panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2001; **34:** 85–90.
6. Marazziti D, *et al.* Citalopram in refractory obsessive-compulsive disorder: an open study. *Int Clin Psychopharmacol* 2001; **16:** 215–19.
7. Atmaca M, *et al.* Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings. *Hum Psychopharmacol* 2002; **17:** 401–5.
8. Varia I, Rauscher F. Treatment of generalized anxiety disorder with citalopram. *Int Clin Psychopharmacol* 2002; **17:** 103–7.
9. Mukaddes NM, *et al.* Citalopram treatment of children and adolescents with obsessive-compulsive disorder: a preliminary report. *Psychiatry Clin Neurosci* 2003; **57:** 405–8.
10. Lenze EJ, *et al.* Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. *Am J Psychiatry* 2005; **162:** 146–50.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as citalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Montgomery SA, *et al.* The optimal dosing regimen for citalopram—a meta-analysis of nine placebo-controlled studies. *Int Clin Psychopharmacol* 1994; **9** (suppl 1): 35–40.
2. Keller MB. Citalopram therapy for depression: a review of 10 years of European experience and data from US trials. *J Clin Psychiatry* 2000; **61:** 896–908.
3. Parker NG, Brown CS. Citalopram in the treatment of depression. *Ann Pharmacother* 2000; **34:** 761–71.
4. Guelfi JD, *et al.* Efficacy of intravenous citalopram compared with oral citalopram for severe depression. Safety and efficacy data from a double-blind, double-dummy trial. *J Affect Disord* 2000; **58:** 201–9.
5. Hochstrasser B, *et al.* Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 2001; **178:** 304–10.
6. Klysner R, *et al.* Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 2002; **181:** 29–35.
7. Roose SP, *et al.* Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004; **161:** 2050–9.
8. Trivedi MH, *et al.* The STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006; **163:** 28–40.
9. McGrath PJ, *et al.* Response to a selective serotonin reuptake inhibitor (citalopram) in major depressive disorder with melancholic features: a STAR*D report. *J Clin Psychiatry* 2008; **69:** 1847–55.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Favourable results with citalopram have been reported in a double-blind placebo-controlled study[1] and in case reports.[2-4]

1. Andersen G, *et al.* Citalopram for post-stroke pathological crying. *Lancet* 1993; **342:** 837–9.
2. Andersen G, *et al.* Citalopram treatment of traumatic brain damage in a 6-year-old boy. *J Neurotrauma* 1999; **16:** 341–4.
3. Kaschka WP, *et al.* Treatment of pathological crying with citalopram. *Pharmacopsychiatry* 2001; **34:** 254–8.
4. Giacobbe P, Flint A. Pharmacological treatment of post-stroke pathological laughing and crying. *J Psychiatry Neurosci* 2007; **32:** 384.

Schizophrenia. The treatment of schizophrenia consists mainly of a combination of social therapy and antipsychotic drugs (see p. 1031.3). Like other antidepressants, citalopram has been examined for its potential value as an adjuvant in schizophrenia.[1-4] In a preliminary placebo-controlled study[1] in 15 patients with chronic schizophrenia who had signs of impulsive aggression, adding citalopram to existing antipsychotic therapy significantly reduced the frequency, but not the average severity, of aggressive incidents. In a subsequent study involving 90 patients, citalopram appeared to improve subjective well-being but had no clear effect on psychopathological symptoms.[2]

1. Vartiainen H, *et al.* Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; **91:** 348–51.
2. Salokangas RKR, *et al.* Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. *Acta Psychiatr Scand* 1996; **94:** 175–80.
3. Taiminen TJ, *et al.* Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. *Int Clin Psychopharmacol* 1997; **12:** 31–5.
4. Kasckow JW, *et al.* Citalopram augmentation of antipsychotic treatment in older schizophrenia patients. *Int J Geriatr Psychiatry* 2001; **16:** 1163–7.

Sexual dysfunction. SSRIs have been tried in the treatment of premature ejaculation, but results with citalopram have been conflicting, see under Fluoxetine, p. 421.1.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 421.1) although increased appetite and weight gain have also been reported with citalopram.

Citalopram may cause dose-dependent prolongation of the QT interval and torsade de pointes has been reported. It should be used with caution, if at all, in patients at risk of developing such arrhythmias including those with congenital QT prolongation, congestive heart failure, bradycardia, or a predisposition to hypokalaemia or hypomagnesaemia. ECG and/or electrolyte monitoring is recommended in these patients; citalopram should be stopped in those with a persistent QTc of greater than 500 milliseconds. Use with other drugs that may prolong the QT interval or inhibit the metabolism of citalopram may also increase the risk (see Interactions, p. 413.3).

Citalopram may be more cardiotoxic in overdosage than other SSRIs; for further details, see Overdosage, under Fluoxetine, p. 423.3.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p. 424.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 422.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies citalopram as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 426.1.

The use of citalopram with other drugs that may prolong the QT interval is contra-indicated, and a maximum oral dose of citalopram 20 mg daily is recommended in patients also taking inhibitors of the cytochrome P450 isoenzyme CYP2C19.

Pharmacokinetics

Citalopram is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral doses. Citalopram is widely distributed throughout the body; protein binding is less than 80%. Citalopram is metabolised by demethylation, deamination, and oxidation to active and inactive metabolites. The demethylation of citalopram to one of its active metabolites, demethylcitalopram, involves the cytochrome P450 isoenzymes CYP3A4 and CYP2C19; the metabolism of citalopram is also partly dependent on CYP2D6. Didemethylcitalopram has also been identified as a metabolite of citalopram. The elimination half-life of citalopram is reported to be about 36 hours. It is excreted mainly via the liver (85%) with the remainder via the kidneys. About 12% of the daily dose is excreted in the urine as unchanged drug. Citalopram is distributed into breast milk in very low concentrations (see Breast Feeding under Precautions in Fluoxetine, p. 424.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Humorap; Psiconor; Seropram; Zentius; ***Austral.***: Celapram; Celica; Ciazil; Cipramil; Citalo; Talam; Talohexal†; ***Austria***: Citalostad; Eostar†; Pram; Seropram; ***Belg.***: Cipramil; ***Braz.***: Alcytam; Celapram; Cipramil; Citaforin; Citagran; Citaprass; Citta; Denyl; Maxapran; Procimax; Tensiopax; Zoxipan; Zycitapran; ***Canad.***: Celexa; CTP; Ran-Citalo; ***Chile***: Actipram; Cimal; Cipramil; Cortran; Finap†; Pramcil; Prisma; Setronil; Temperax; Zebrak; Zentius; ***China***: Cipramil (喜普妙); Duo Fo (多弗); Te Lin Na (特林那); Wang You (望悠); Yi Tai Na (一泰纳); YiTeAn (易特安); ***Cz.***: Apo-Cital; Cerotor; Cipram†; Cita; Citalec; Citalon; Citaratio†; Dalsan; Pram; Seropram; Zyloram; ***Denm.***: Akarin†; Cipramil; Citacip; Citaham†; Citalonte; Seropram; ***Fin.***: Cipramil; Sepram; ***Fr.***: Seropram; ***Ger.***: Cipramil; CitaLich†; Citalo-Q†; Citalogamma†; Citalon; Futuril†; Serital†; ***Gr.***: A-Depress-Therapy; Acelopram; Adeprenal; Alepram; Atinorm; Belmazol; Bibien†; Bivien; Celius; Cilopress; Cinapen; Cipram; Cipraned; Citalgert; Citaloprol; Citopram; Decilop; Depretal; Ecloram; Erlicon; Espinal; Etapiam; Eumitol; Exenadil; Galopran; Goldamit; Kylipram; Lodeprem; Lopracil; Lopraxer; Loptar; Malicon; Pralotam; Pramital; Prefucet; Pricital; Renevil; Ropramin; Selon; Seproc; Seretover; Serocel; Seropram; Seror; Siloam; Sitaleau; Sotovon; Talopram; Talopron; Taloram; Talosin; Taprocil; Tasonade; Unstress; Varom; Verus; Vesema; Xadorek; Zanipram; Zeclicid; ***Hong Kong***: Arpolax; Cipram; Cital; Talam†; ***Hung.***: Citagen; Citalodep; Citalon†; Citalowin†; Citapram; Dalsan; Oropram†; Seropram; Serotor; Zyloram; ***India***: C-Pram; C-Talo; Celepra; Celica; Citadep; Citalomine; Citalop; Citara; Citola; Citopam; Cytop; Feliz; Lopram; Madam; Nevdep; Palocit; ***Indon.***: Cipram†; ***Irl.***: Bellcital; Ciprager; Cipralam†; Cipramil; Ciprapine; Ciprotan; Citrol; ***Israel***: Cipramil; Recital; ***Ital.***: Elopram; Felipram; Feliximir; Frimaind; Kaidor; Lampopram†; Marpram; Percitale; Pramexyl†; Return; Ricap; Seropram; Sintopram; Verisan; ***Malaysia***: Cipram; Cital†; ***Mex.***: Cibrom; Citox; Norecsero; Prepram; Seropram; Xyloranе†; ***Neth.***: Cipramil; Ciprapine†; Lontax†; ***Norw.***: Cipramil; ***NZ***: Celapram; Cipramil; ***Philipp.***: Feliz; Lupram; Tazen; ***Pol.***: Aurex; Cilon†; Cilonast; Cipramil; Citabax; Cital; Citaratio; Citaxin†; Citronil; Oropram; ***Port.***: Citadep†; Zitolex; ***Rus.***: Cipramil (Ципрамил); Citalift (Циталифт); Citalon (Циталон); Citalorin (Циталорин); Citol (Цитол); Humorap (Уморап); Opra (Опра); Pram (Прам); Sedopram (Седопрам); Siozam (Сиозам); ***S.Afr.***: Adco-Talomil; Cilate; Cilift; Ciloram; Cipramil; CitaloHexal; Depramil; ***Singapore***: Cipram; ***Spain***: Calton; Citalvir; Genprol†; Prisdal; Relapaz; Seregra; Seropram; Somac†; ***Swed.***: Cipramil; ***Switz.***: Claropram; Seropram; ***Thai.***: Cipram†; ***Turk.***: Atopran; Cipram; Citara; Citexam; Citol; Citolap; Citolixin; Citrex; Copsam; Eslopram; Laira; Pasilopram; Relaxol; Sintab; Vodelax; ***UK***: Cipramil; ***Ukr.***: Cipramil (Ципрамил); Cita Sandoz (Цита Сандоз); ***USA***: Celexa; ***Venez.***: Seropram.

Pharmacopoeial Preparations

USP 36: Citalopram Oral Solution; Citalopram Tablets.

Clomipramine Hydrochloride

(BANM, USAN, rINNM)

Chlorimipramine Hydrochloride; Clomipramina, hidrocloruro de; Clomipramine, chlorhydrate de; Clomipraminhydrochlorid; Clomipramini Hydrochloridum; G-34586; Hidrocloruro de clomipramina; Hidrocloruro de monoclorimipramina; Klomipramiinihydrokloridi; Klomipramin Hidroklorür; Klomipramin hydrochlorid; Klomipramin-hidroklorid; Klomipraminhydroklorid; Klomipramino hidrochloridas; Monochlorimipramine Hydrochloride; Кломипрамина Гидрохлорид.

3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyldimethylamine hydrochloride.

$C_{19}H_{23}ClN_2$,HCl=351.3

CAS — 303-49-1 (clomipramine); 17321-77-6 (clomipramine hydrochloride).

ATC — N06AA04.

ATC Vet — QN06AA04.

UNII — 2LXW0L6GWJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clomipramine Hydrochloride). A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in dichloromethane; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.0. Protect from light.

USP 36: (Clomipramine Hydrochloride). A white to faintly yellow crystalline powder. Very soluble in water. pH of a 10% solution in water is between 3.5 and 5.0.

Uses and Administration

Clomipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It has antimuscarinic properties and is also a potent serotonin reuptake inhibitor. Clomipramine is one of the more sedating tricyclics. It is used as the hydrochloride.

In the treatment of **depression**, clomipramine hydrochloride is given in oral doses of 10 mg daily initially, increasing gradually to 30 to 150 mg daily if required; up to 250 mg daily or higher may be given in severe cases or in patients who also have obsessional or phobic disorders. A suggested initial dose for the elderly is 10 mg daily increasing gradually over 10 days to 30 to 75 mg daily if required. Clomipramine may be given in divided doses throughout the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

In the treatment of **obsessive-compulsive disorder** and **phobias**, clomipramine hydrochloride may be given in an initial oral dose of 25 mg daily (or 10 mg daily for elderly patients or those sensitive to tricyclics). The dose may be increased gradually over two weeks to 100 to 150 mg daily; in some countries, maximum doses of 250 mg daily have been used. Similar doses have also been used in the management of **panic disorder**. Clomipramine hydrochloride may also be used for the treatment of obsessive-compulsive disorder in children and adolescents aged 10 years and over (see p. 414.2 for doses).

Clomipramine has been given for depression or obsessive-compulsive disorder by the intramuscular or intravenous routes if giving it orally is impracticable or inadvisable. The initial dose of clomipramine hydrochloride by intramuscular injection is 25 to 50 mg daily, increasing to a maximum of 100 to 150 mg daily; oral dosage should be substituted as soon as possible. Clomipramine hydrochloride may also be given by intravenous infusion in doses of 50 to 75 mg daily diluted in 250 to 500 mL of sodium chloride 0.9% or glucose 5% and infused over 1.5 to 3 hours. When a satisfactory response to parenteral doses has been obtained oral therapy should be substituted, initially giving double the parenteral dose by mouth and subsequently adjusting if necessary. Patients must be carefully supervised during intravenous infusion of clomipramine hydrochloride and the blood pressure carefully monitored owing to the risk of hypotension.

In the adjunctive treatment of **cataplexy associated with narcolepsy**, clomipramine hydrochloride is given in an initial oral dose of 10 mg daily and gradually increased until a satisfactory response occurs, usually within the range of 10 to 75 mg daily.

For all indications, an oral modified-release preparation, containing clomipramine hydrochloride 75 mg, may be given once daily for maintenance.

Clomipramine has also been used in the management of **nocturnal enuresis** in children (see p. 414.2 for doses).

Clomipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. In the UK, the use of clomipramine in children under 18 years is not recommended in the treatment of depressive states, phobias, or cataplexy associated with narcolepsy. However, in some countries clomipramine hydrochloride is licensed for the treatment of **obsessive-compulsive disorder** in children and adolescents aged 10 years and over. Initial oral doses are 25 mg daily, increased gradually during the first 2 weeks to a maximum daily dose of 3 mg/kg or 100 mg, whichever is smaller, and given in divided doses. Further increases are permitted, over several weeks to a maximum daily dose of 3 mg/kg or 200 mg, whichever is smaller. Once titration has been achieved the dose may be given as a single dose at bedtime.

Clomipramine hydrochloride is also licensed for oral use in the management of **nocturnal enuresis** in some countries (for a discussion of tricyclic use in nocturnal enuresis see Micturition Disorders under Amitriptyline, p. 402.1). The age ranges and licensed doses vary somewhat from country to country, however. For example, in *France*, use is licensed in children over 6 years of age, at a daily dose of 10 to 30 mg, or 0.5 to 1 mg/kg, whereas in *Austria* and *Switzerland* the licensed dose is: 6 to 8 years, 20 to 30 mg; 9 to 12 years, 25 to 50 mg; over 12 years, 25 to 75 mg.

Anxiety disorders. Tricyclic antidepressants that inhibit serotonin reuptake, such as clomipramine and imipramine, have been given in the management of anxiety disorders (p. 1028.1) including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), post-traumatic stress disorder (p. 1029.2), and trichotillomania.

References.

1. Swedo SE, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N Engl J Med* 1989; **321:** 497–501.
2. McTavish D, Benfield P. Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs* 1990; **39:** 136–53.
3. Kelly MW, Myers CW. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. *DICP Ann Pharmacother* 1990; **24:** 739–44.
4. Papp LA, *et al.* Clomipramine treatment of panic disorder: pros and cons. *J Clin Psychiatry* 1997; **58:** 423–5.
5. Fallon BA, *et al.* Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry* 1998; **55:** 918–24.
6. Sasson Y, *et al.* A double-blind crossover comparison of clomipramine and desipramine in the treatment of panic disorder. *Eur Neuropsychopharmacol* 1999; **9:** 191–6.

Autism. Clomipramine reduced adventitious movements when tried in 5 boys with autistic disorder.[1] However, in a small study in 7 children no improvement in symptoms was noted and adverse effects were common and serious.[2] In another study,[3] although clomipramine was found to be as effective as haloperidol in the treatment of some autistic symptoms, patients on clomipramine were significantly less likely to complete the study for reasons that included the onset of adverse effects.

1. Brasic JR, *et al.* Clomipramine ameliorates adventitious movements and compulsions in prepubertal boys with autistic disorder and severe mental retardation. *Neurology* 1994; **44:** 1309–12.
2. Sanchez LE, *et al.* A pilot study of clomipramine in young autistic children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 537–44.
3. Remington G, *et al.* Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol* 2001; **21:** 440–4.

Micturition disorders. In some countries, clomipramine is used in children for the treatment of nocturnal enuresis; for further details, see Administration in Children, above.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2). In several countries, clomipramine hydrochloride is licensed for the treatment of chronic pain; oral doses range from 10 to 150 mg daily. Parenteral doses may also be given.

Premenstrual syndrome. Clomipramine reduced premenstrual irritability and depressed mood when given during the luteal phase;[1] oral doses of clomipramine ranged from 25 to 75 mg daily. It was postulated that the efficacy of clomipramine in relieving premenstrual symptoms is related to its serotonin reuptake inhibitor activity. For the overall management of premenstrual syndrome, see p. 2272.3.

1. Sundblad C, *et al.* Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology* 1993; **9:** 133–45.

Sexual dysfunction. Clomipramine has been used for its inhibitory effect on ejaculation in the management of premature ejaculation[1-5] (p. 2350.2). In some men with very short latencies (less than 1 minute) continuous therapy with a low daily dose of clomipramine, typically 20 or 30 mg, may be more effective than taking 25 mg as required.[5] Any benefits may relate to its effect as a serotonin reuptake inhibitor; other antidepressants with serotonin reuptake inhibiting actions, such as fluoxetine and sertraline, have also been tried in this condition.[4]

1. Hawton K. Erectile dysfunction and premature ejaculation. *Br J Hosp Med* 1988; **40:** 428–36.
2. Althof SE, *et al.* A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry* 1995; **56:** 402–7.
3. Haensel SM, *et al.* Clomipramine and sexual function in men with premature ejaculation and controls. *J Urol (Baltimore)* 1996; **156:** 1310–15.
4. Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol (Baltimore)* 1998; **159:** 425–7.
5. Rowland DL, *et al.* Effective daily treatment with clomipramine in men with premature ejaculation when 25 mg (as required) is ineffective. *BJU Int* 2001; **87:** 357–60.

Stuttering. Clomipramine was of modest success in a controlled study[1] of 17 patients with developmental stuttering (p. 1078.1). It was suggested that its efficacy may be related to its serotonin reuptake inhibitor activity.

1. Gordon CT, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56:** 238–42.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clomipramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

MAOIs. The combination of clomipramine and *tranylcypromine* is considered particularly hazardous.

The serotonin syndrome (p. 445.2) has occurred in patients receiving clomipramine and *moclobemide* (see under Interactions of Antidepressants in Phenelzine, p. 447.2).

Pharmacokinetics

Clomipramine is readily absorbed from the gastrointestinal tract, and extensively demethylated during first-pass metabolism in the liver to its primary active metabolite, desmethylclomipramine.

Clomipramine and desmethylclomipramine are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Clomipramine has been estimated to have a plasma elimination half-life of about 21 hours, which may be considerably extended in overdosage; that of desmethylclomipramine is longer (about 36 hours).

Paths of metabolism of both clomipramine and desmethylclomipramine include hydroxylation and *N*-oxidation. About two-thirds of a single dose of clomipramine is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; the remainder of the dose appears in the faeces. Clomipramine crosses the placenta and is distributed into breast milk.

References.

1. Gex-Fabry M, *et al.* Clomipramine metabolism: model-based analysis of variability factors from drug monitoring data. *Clin Pharmacokinet* 1990; **19:** 241–55.
2. Balant-Gorgia AE, *et al.* Clinical pharmacokinetics of clomipramine. *Clin Pharmacokinet* 1991; **20:** 447–62.
3. Nielsen KK, *et al.* Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther* 1994; **55:** 518–27.
4. Herrera D, *et al.* Pharmacokinetics of a sustained-release dosage form of clomipramine. *J Clin Pharmacol* 2000; **40:** 1488–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anafranil; ***Austral.***: Anafranil; Clopram†; Placil; ***Austria***: Anafranil; ***Belg.***: Anafranil; ***Braz.***: Anafranil; Clo; Clomipran; Fenatil; ***Canad.***: Anafranil; Novo-Clopamine; ***Chile***: Anafranil; Atenual; Ausentron; Deprelin†; ***China***: Anafranil (安拿芬尼); ***Cz.***: Anafranil; ***Denm.***: Anafranil; ***Fin.***: Anafranil; ***Fr.***: Anafranil; ***Ger.***: Anafranil; ***Gr.***: Anafranil; ***Hong Kong***: Anafranil; Clopress†; Zoiral†; ***Hung.***: Anafranil; ***India***: Anafranil; Clofranil; Clom; Clomine; Clomip; Clomistar; Clomizil; Clonil; Depnil; Mario; Ocifril; ***Indon.***: Anafranil; ***Irl.***: Anafranil; ***Israel***: Anafranil; Maronil; ***Ital.***: Anafranil; ***Malaysia***: Anafranil; Denapranil; ***Mex.***: Anafranil; ***Neth.***: Anafranil; ***Norw.***: Anafranil; ***NZ***: Clopress†; ***Philipp.***: Anafranil; ***Pol.***: Anafranil; Hydiphen†; ***Port.***: Anafranil; ***Rus.***: Anafranil (Анафранил); Clofranil (Клофранил); ***S.Afr.***: Anafranil; Clomidep; Equinorm; ***Singapore***: Anafranil; Depranil; ***Spain***: Anafranil; ***Swed.***: Anafranil; ***Switz.***: Anafranil; ***Thai.***: Anafranil; Clofranil; ***Turk.***: Anafranil; ***UK***: Anafranil; ***Ukr.***: Anafranil (Анафранил); ***USA***: Anafranil; ***Venez.***: Anafranil.

Pharmacopoeial Preparations
BP 2014: Clomipramine Capsules; Prolonged-release Clomipramine Tablets;
USP 36: Clomipramine Hydrochloride Capsules.

Desipramine Hydrochloride

(BANM, USAN, rINNM)

Desipramiinihydrokloridi; Desipramina, hidrocloruro de; Désipramine, chlorhydrate de; Desipramin-hydrochlorid; Desipraminhydrochlorid; Desipraminhydroklorid; Desipramini Hydrochloridum; Desmethylimipramine Hydrochloride; Dezipramin-hidroklorid; Dezipramino hidrochloridas; Dezypraminy chlorowodorek; DMI; EX-4355; G-35020; Hidrocloruro de desipramina; Hidrocloruro de desmetilimipramina; JB-8181; NSC-114901; RMI-9384A; Дезипрамина Гидрохлорид.

3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl(methyl) amine hydrochloride.

$C_{18}H_{22}N_2$,HCl=302.8

CAS — 50-47-5 (desipramine); 58-28-6 (desipramine hydrochloride).

ATC — N06AA01.

ATC Vet — QN06AA01.

UNII — 1Y58DO4MY1.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Desipramine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. Protect from light.

USP 36: (Desipramine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 12 of water, 1 in 14 of alcohol, and 1 in 3.5 of chloroform; insoluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Desipramine, the principal active metabolite of imipramine (p. 428.2), is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is one of the less sedating tricyclics and its antimuscarinic effects are mild. Desipramine is used as the hydrochloride.

In the treatment of depression, desipramine hydrochloride is given orally in daily doses of 100 to 200 mg; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. Lower doses should be used in adolescents and the elderly and are usually 25 to 100 mg daily; up to 150 mg daily may be required for severe depression. Initial doses should be low and gradually increased according to tolerance and clinical response. Therapy may initially be given as a single daily dose or in divided doses; maintenance therapy may be given as a single daily dose usually at night.

Desipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Cocaine dependence. Since dopamine depletion may be the cause of the depression often associated with cocaine craving and with relapse, drugs such as desipramine that interact with dopaminergic systems have been tried in managing cocaine withdrawal symptoms (see p. 1990.1). However, a systematic review[1] was unable to find evidence to support the use of antidepressants in the treatment of cocaine dependence although the efficacy of desipramine was suggested in some individual studies.

1. Lima MS, *et al.* Antidepressants for cocaine dependence [withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 24/11/05).

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (see p. 2314.1) tricyclic antidepressants such as imipramine or desipramine[1-4] are usually reserved for patients who fail to respond to, or who are intolerant of, stimulants. They may also be of use for selected patients with co-existing disorders such as Tourette's syndrome, anxiety, and enuresis.

1. Rapport MD, *et al.* Methylphenidate and desipramine in hospitalized children: I. separate and combined effects on cognitive function. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 333–42.
2. Pataki CS, *et al.* Side effects of methylphenidate and desipramine alone and in combination in children. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1065–72.
3. Singer HS, *et al.* The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 1995; **95:** 74–81.
4. Spencer T, *et al.* A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2002; **59:** 649–56.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2) when given in subantidepressant doses.

References to the use of desipramine.

1. Kishore-Kumar R, *et al.* Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47:** 305–12.
2. Max MB, *et al.* Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326:** 1250–6.
3. Coquoz D, *et al.* Central analgesic effects of desipramine, fluvoxamine, and moclobemide after single oral dosing: a study in healthy volunteers. *Clin Pharmacol Ther* 1993; **54:** 339–44.
4. Gordon NC, *et al.* Temporal factors in the enhancement of morphine analgesia by desipramine. *Pain* 1993; **53:** 273–6.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Desipramine is the principal active metabolite of imipramine (p. 429.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Distonal; ***Ger.***: Petylyl†; ***Israel***: Deprexan; ***Ital.***: Nortimil; ***Pol.***: Petylyl†; ***Turk.***: Desipram; ***USA***: Norpramin.

Pharmacopoeial Preparations
BP 2014: Desipramine Tablets;
USP 36: Desipramine Hydrochloride Tablets.

Desvenlafaxine Succinate *(BANM, USAN, rINNM)*

O-Desmethylvenlafaxine succinate; Dèsvenlafaxine, Succinate de; Desvenlafaxini Succinas; DVS-233 (base or succinate); Succinato de desvenlafaxina; Wy-45233; Десвенлафаксина Сукcинат.

1-[(1*RS*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate.

$C_{16}H_{25}NO_2.C_4H_6O_4.H_2O$=399.5

CAS — 93413-62-8 (desvenlafaxine); 386750-22-7 (desvenlafaxine succinate).

ATC — N06AX23.

ATC Vet — QN06AX23.

UNII — ZB22ENF0XR.

Profile

Desvenlafaxine, the major active metabolite of venlafaxine, is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p. 456.2). It is given orally as the succinate but doses are expressed in terms of the base; desvenlafaxine succinate 75.8 mg is equivalent to about 50 mg of desvenlafaxine. The succinate is given in the treatment of depression (p. 398.1) as a modified-release preparation providing a dose equivalent to desvenlafaxine 50 mg once daily. Higher doses of up to 400 mg daily have been studied, but provide no additional benefit and are associated with more frequent adverse effects. The dose may need to be reduced in patients with hepatic or renal impairment (see p. 415.3).

Desvenlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

Desvenlafaxine is under investigation in the management of menopausal vasomotor symptoms, neuropathic pain, and fibromyalgia.

References.

1. DeMartinis NA, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* 2007; **68:** 677–88.
2. Septien-Velez L, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 2007; **22:** 338–47.
3. Liebowitz MR, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry* 2007; **68:** 1663–72.
4. Archer DF, *et al.* A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. *Am J Obstet Gynecol* 2009; **200:** 172.e1–172.e10.

Administration in hepatic or renal impairment. The usual desvenlafaxine oral dose of 50 mg daily may be given to patients with moderate to severe hepatic impairment; doses above 100 mg daily are not recommended.

Patients with moderate renal impairment (creatinine clearance [CC] of 30 to 50 mL/min) may be given a maximum dose of 50 mg daily. In severe impairment (CC less than 30 mL/min) or end-stage renal disease, 50 mg may be given on alternate days. Supplemental doses should not be given after dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pristiq; ***Austral.***: Pristiq; ***Braz.***: Pristiq; ***Canad.***: Pristiq; ***Chile***: Pristiq; ***Hong Kong***: Pristiq; ***Israel***: Pristiq; ***Malaysia***: Pristiq; ***Singapore***: Pristiq; ***Thai.***: Pristiq; ***USA***: Pristiq.

Dibenzepin Hydrochloride

(BANM, USAN, rINNM)

Dibenzepina, hidrocloruro de; Dibenzépine, Chlorhydrate de; Dibenzepini Hydrochloridum; HF-1927; Hidrocloruro de dibenzepina; Дибензепина Гидрохлорид.

10-(2-Dimethylaminoethyl)-5,10-dihydro-5-methyl-dibenzo[*b*,*e*][1,4]diazepin-11-one hydrochloride.

$C_{18}H_{21}N_3O$,HCl=331.8

CAS — 4498-32-2 (dibenzepin); 315-80-0 (dibenzepin hydrochloride).

ATC — N06AA08.

ATC Vet — QN06AA08.

UNII — JLN027354Z.

Profile

Dibenzepin hydrochloride is a tricyclic antidepressant (see Amitriptyline, p. 401.1).

In the treatment of depression dibenzepin hydrochloride is given in oral doses of 480 mg daily; higher doses of up to 720 mg daily may be required in some patients with severe depression. Elderly patients should be given reduced doses of 240 mg daily initially, increased to a maximum of 480 mg daily if required.

Dibenzepin hydrochloride has also been given by intravenous infusion.

In some countries it has also been used for nocturnal enuresis.

Dibenzepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

References.
1. Wirtheim E, Bloch Y. Dibenzepin overdose causing pulmonary edema. *Ann Pharmacother* 1996; **30:** 789–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Noveril†; ***Cz.***: Noveril; ***Hung.***: Noveril†; ***Israel***: Noveril†; ***Pol.***: Noveril†; ***Switz.***: Noveril.

Dosulepin Hydrochloride *(BANM, rINNM)*

Dosulepiinihydrokloridi; Dosulepina, hidrocloruro de; Dosulépine, Chlorhydrate de; Dosulepin-hydrochlorid; Dosulepinhydrochlorid; Dosulepinhydroklorid; Dosulepini hydrochloridum; Dosulepino hidrochloridas; Doszulepinhidroklorid; Dothiepin Hydrochloride (USAN); Dothiepin Hydrochloride; Hidrocloruro de dosulepina; Hidrocloruro de dotiepina; Досулепина Гидрохлорид.

3-(Dibenzo[*b*,*e*]thiepin-11-ylidene)propyldimethylamine hydrochloride.

$C_{19}H_{21}NS,HCl$=331.9

CAS — 113-53-1 (dosulepin); 897-15-4 (dosulepin hydrochloride).

ATC — N06AA16.

ATC Vet — QN06AA16.

UNII — 3H0042311V.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dosulepin Hydrochloride). A white or faintly yellow crystalline powder. It consists chiefly of the *E*-isomer. Freely soluble in water, in alcohol, and in dichloromethane. A 10% solution in water has a pH of 4.2 to 5.2. Protect from light.

Uses and Administration

Dosulepin hydrochloride is a tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is one of the more sedating tricyclics. In the UK, the MHRA suggests that the use of dosulepin for depression should be limited, because of the small margin of safety between the maximum therapeutic dose and potentially fatal overdose. It advises that treatment should only be started by a specialist-care prescriber, and that the quantity issued per prescription should be limited. In patients with increased risk factors for suicide at the start of treatment, during dose adjustment, and until improvement occurs, the MHRA suggests a maximum supply equivalent to 2 weeks of treatment with 75 mg daily.

In the treatment of depression, dosulepin hydrochloride is given in oral doses of 25 mg three times daily initially, gradually increased to 50 mg three times daily if necessary; alternatively a single dose at night may be given. Higher doses of up to 225 mg daily have been given to severely depressed patients in hospital. The recommended initial dose for the elderly is 50 to 75 mg daily.

Dosulepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on the cardiovascular system. For reference to an increased risk of ischaemic heart disease in patients treated with dosulepin, see under Amitriptyline, p. 403.1.

Overdosage. After an overdose of 1 g of dosulepin, the ECG of a 41-year-old man showed cardiac abnormalities mimicking an acute myocardial infarction.[1] However, as cardiac enzymes did not confirm an ischaemic event, the abnormalities were thought to be due to either the quinidine-like effect of dosulepin or changes in potassium membrane permeability.

1. Steeds RP, Muthusamy R. Abnormal ventricular conduction following dothiepin overdose simulating acute myocardial infarction. *Heart* 2000; **83:** 289.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Dosulepin hydrochloride is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (also termed northiaden). Paths of metabolism also include *S*-oxidation.

Dosulepin is excreted in the urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces. Elimination half-lives of about 14 to 24 and 23 to 46 hours have been reported for dosulepin and its metabolites, respectively.

Dosulepin is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p. 405.1).

References.
1. Maguire KP, *et al.* Clinical pharmacokinetics of dothiepin: single-dose kinetics in patients and prediction of steady-state concentrations. *Clin Pharmacokinet* 1983; **8:** 179–85.
2. Yu DK, *et al.* Pharmacokinetics of dothiepin in humans: a single dose dose-proportionality study. *J Pharm Sci* 1986; **75:** 582–5.
3. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dothep; Prothiaden; ***Belg.***: Prothiaden; ***Cz.***: Prothiaden; ***Denm.***: Prothiaden; ***Fr.***: Prothiaden; ***Ger.***: Idom†; ***Hong Kong***: Prothiaden†; Qualiaden; Vick-Thiaden; ***India***: Dothcin; Dothip; Othtric; Prothiaden; ***Irl.***: Dothep; Prothiaden; ***Ital.***: Protiaden; ***Malaysia***: Depropin; Dothep†; Prothiaden; ***Neth.***: Prothiaden; ***NZ***: Dopress; Prothiaden†; ***Philipp.***: Prothiaden†; ***Port.***: Protiadene; ***S.Afr.***: Prothiaden; Thaden; ***Singapore***: Espin; Prothiaden; ***Spain***: Prothiaden†; ***UK***: Prepadine; Prothiaden.

Multi-ingredient Preparations. ***Austria***: Harmomed.

Pharmacopoeial Preparations
BP 2014: Dosulepin Capsules; Dosulepin Oral Solution; Dosulepin Tablets.

Doxepin Hydrochloride

(BANM, USAN, rINNM)

Doksepiinihydrokloridi; Doksepin Hidroklorür; Doksepino hidrochloridas; Doksepiny chlorowodorek; Doxepina, hidrocloruro de; Doxépine, Chlorhydrate de; Doxepin-hidroklorid; Doxepinhydrochlorid; Doxepin-hydrochlorid; Doxepinhydroklorid; Doxepini hydrochloridum; Hidrocloruro de doxepina; NSC-108160; P-3693A; Доксепина Гидрохлорид.

(*E*)-3-(Dibenz[*b*,*e*]oxepin-11-ylidene)propyldimethylamine hydrochloride.

$C_{19}H_{21}NO,HCl$=315.8

CAS — 1668-19-5 (doxepin); 1229-29-4 (doxepin hydrochloride); 4698-39-9 (doxepin hydrochloride, E-isomer); 25127-31-5 (doxepin hydrochloride, Z-isomer).

ATC — N06AA12.

ATC Vet — QN06AA12.

UNII — 3U9A0FE9N5 (doxepin hydrochloride); CU61C5RH24 (E-doxepin hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Doxepin Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Doxepin Hydrochloride). It consists of a mixture of *Z*- and *E*-isomers.

Uses and Administration

Doxepin is a dibenzoxepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It has moderate antimuscarinic and marked sedative properties and has serotonin reuptake inhibitor activity.

In the treatment of **depression** doxepin is given orally as the hydrochloride although doses are expressed in terms of the base; doxepin hydrochloride 84.8 mg is equivalent to about 75 mg of doxepin. The initial dose is 75 mg daily, gradually adjusted according to response. Doses of up to 300 mg daily may be required in severely depressed patients; mildly affected patients may respond to as little as 25 to 50 mg daily. Lower doses may be required in the elderly who may be more susceptible to developing adverse effects. Daily doses up to 100 mg may be given in divided doses or as a single dose at bedtime. If the total daily dose exceeds 100 mg, it should be given in 3 divided doses, although the largest portion, up to a maximum of 100 mg, may be given at bedtime. In the USA, the recommended maximum single dose is 150 mg.

Doxepin hydrochloride has also been given by intramuscular or intravenous injection.

Doxepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Low doses of doxepin may be used in the management of **insomnia** characterised by difficulty in sleep maintenance. Doxepin hydrochloride is given orally to provide a dose equivalent to doxepin 6 mg once daily at night; the dose should be taken within 30 minutes of bedtime. A dose of 3 mg may be sufficient for some patients, which is also the recommended starting dose for elderly patients aged 65 years and older. It is recommended that the dose should not be taken within 3 hours of a meal, to minimise the potential for effects continuing into the next day.

Doxepin has histamine H_1- and H_2-antagonist activity and is used topically in a cream containing 5% of the hydrochloride for the short-term (up to 8 days) relief of moderate pruritus associated with various types of dermatitis (see p. 416.3). A thin film should be applied 3 or 4 times daily to the affected area. To reduce the incidence of drowsiness, maximum coverage should be less than 10% of the body-surface; this equates to no more than 12 g of the cream daily. Occlusive dressings should be used with caution, if at all.

Headache. Tricyclic antidepressants can be effective in the management of some types of headache—see p. 401.3.

References to the use of doxepin.
1. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; **1:** 216–23.

Insomnia. Doxepin is used in low doses in the management of insomnia (p. 1033.2).[1,2]

1. Roth T, *et al.* Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep* 2007; **30:** 1555–61.
2. Scharf M, *et al.* Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2008; **69:** 1557–64.

Skin disorders. Tricyclic antidepressants have several pharmacological activities and some drugs in this group have notable antihistaminic actions. Doxepin in particular has very potent antihistaminic activity. It has been shown to be an effective oral alternative to conventional antihistamines in the treatment of chronic urticaria,[1-3] and to be an effective oral treatment for idiopathic cold urticaria.[4,5] In the case of cold urticaria doxepin may act by inhibiting release of a platelet-activating factor-like lipid.[5]

For an overview of the possible treatments for the various urticarias, including mention of the use of doxepin, see p. 1689.2.

As with conventional antihistamines (p. 612.1) doxepin has also been used topically for the relief of pruritus (see also p. 1687.3) associated with various types of allergic and inflammatory skin disorders[6,7] although some authorities remain to be convinced of its efficacy.[8,9] Topical application of doxepin can also produce contact dermatitis (see Effects on the Skin, p. 416.3) and drowsiness and other systemic effects.

1. Greene SL, *et al.* Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol* 1985; **12:** 669–75.
2. Harto A, *et al.* Doxepin in the treatment of chronic urticaria. *Dermatologica* 1985; **170:** 90–3.
3. Goldsobel AB, *et al.* Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986; **78:** 867–73.
4. Neittaanmäki H, *et al.* Comparison of cinnarizine, cyproheptadine, doxepin, and hydroxyzine in treatment of idiopathic cold urticaria: usefulness of doxepin. *J Am Acad Dermatol* 1984; **11:** 483–9.
5. Grandel KE, *et al.* Association of platelet-activating factor with primary acquired cold urticaria. *N Engl J Med* 1985; **313:** 405–9.
6. Drake LA, *et al.* Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Am Acad Dermatol* 1994; **31:** 613–16.
7. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. *Ann Pharmacother* 1997; **31:** 633–5.
8. Anonymous. Doxepin cream for pruritus. *Med Lett Drugs Ther* 1994; **36:** 99–100.
9. Anonymous. Doxepin cream for eczema? *Drug Ther Bull* 2000; **38:** 31–2.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3). Drowsiness and other systemic effects can also occur after topical application. In addition, local effects, most commonly burning and stinging, have been reported.

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on the skin. Up to January 2002 the FDA was aware of 26 cases of allergic contact dermatitis associated with the use of doxepin 5% cream;[1] manifestations included eczema, urticaria, purpura, and papulovesicular lesions. Of the 20 cases where details were known, 13 occurred after use for more than the recommended 8 days. Patch testing was positive in the 21 cases where it was performed, supporting an allergic reaction rather than an exacerbation of the original condition.

1. Bonnel RA, *et al.* Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 2003; **48:** 294–6.

Overdosage. An infant became difficult to arouse after the application of doxepin cream 5% to about 50% of her body-surface; an entire 30-g tube of the cream was used in only 2 applications.[1] The cream is not recommended for use in children.

1. Zell-Kanter M, *et al.* Doxepin toxicity in a child following topical application. *Ann Pharmacother* 2000; **34:** 328–9.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Doxepin is readily absorbed from the gastrointestinal tract after oral doses, and is extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desmethyldoxepin. Doxepin is also absorbed through the skin after topical application.

Paths of metabolism of both doxepin and desmethyldoxepin include hydroxylation and *N*-oxidation. Doxepin is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Doxepin and desmethyldoxepin are widely distributed throughout the body; the plasma protein binding of doxepin is about 76%. Doxepin has been estimated to have a plasma elimination half-life ranging from 8 to 24 hours, which may be considerably extended in overdosage; that of desmethyldoxepin is longer.

Doxepin crosses the blood-brain barrier and the placenta. It is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p. 405.1).

References.

1. Faulkner RD, *et al.* Multiple-dose doxepin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **34:** 509–15.
2. Joyce PR, Sharman JR. Doxepin plasma concentrations in clinical practice: could there be a pharmacokinetic explanation for low concentrations? *Clin Pharmacokinet* 1985; **10:** 365–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Deptran; Sinequan; ***Austria***: Sinequan†; ***Belg.***: Sinequan; ***Canad.***: Sinequan; Zonalon; ***China***: Li Ke Ning (丽科宁); ***Denm.***: Sinequan; ***Fin.***: Doxal; ***Fr.***: Quitaxon; ***Ger.***: Aponal; Doneurin†; Doxe†; Mareen; ***Gr.***: Sinequan; ***Hong Kong***: Qualiquan; Sinequan; ***India***: Doxedep; Doxetar; Doxin; Doxyril; Noctaderm; Spectra; ***Indon.***: Sagalon; ***Irl.***: Sinequan†; Xepin†; ***Israel***: Gilex; ***Mex.***: Sinequan; ***Neth.***: Sinequan; ***Norw.***: Sinequan; ***NZ***: Anten; ***Pol.***: Sinequan†; ***Spain***: Sinequan; ***Switz.***: Sinquane; ***Thai.***: Sinequan; ***Turk.***: Antimax; ***UK***: Sinepin; Xepin; ***USA***: Prudoxin; Silenor; Sinequan†; Zonalon.

Multi-ingredient Preparations. ***India***: Doxure.

Pharmacopoeial Preparations

BP 2014: Doxepin Capsules;
USP 36: Doxepin Hydrochloride Capsules; Doxepin Hydrochloride Oral Solution.

Duloxetine Hydrochloride

(BANM, USAN, rINNM)

Duloxetina, hidrocloruro de; Duloxétine, Chlorhydrate de; Duloxetini Hydrochloridum; Hidrocloruro de duloxetina; LY-248686 (duloxetine); Дулоксетина Гидрохлорид.

(+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride.

$C_{18}H_{19}NOS,HCl=333.9$

CAS — 116539-59-4 (duloxetine); 136434-34-9 (duloxetine hydrochloride).

ATC — N06AX21.

ATC Vet — QN06AX21.

UNII — 9044SC542W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Duloxetine Hydrochloride). A white or almost white powder. Sparingly soluble in water; freely soluble in methyl alcohol; practically insoluble in hexane. Protect from light.

USP 36: (Duloxetine Hydrochloride). A white to brownish-white solid. Slightly soluble in water. Protect from light.

Uses and Administration

Duloxetine hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p. 456.2). It is given orally as the hydrochloride although doses are expressed in terms of the base; duloxetine hydrochloride 22.5 mg is equivalent to about 20 mg of duloxetine.

Duloxetine is used in the treatment of **depression** in usual initial doses of 20 or 30 mg twice daily, or 60 mg once daily. A lower starting dose of 30 mg once daily for the first week may be suitable for some patients, to allow them to adjust to the effects of duloxetine before increasing the dose. Patients should be continued on a dose of 60 mg once daily. Those with a history of repeated episodes of depression who respond to duloxetine may require long-term treatment using 60 to 120 mg daily.

Duloxetine is also used in the treatment of **generalised anxiety disorder**, in a usual initial dose of 30 or 60 mg once daily. A dose of 60 mg daily is usually adequate, but doses of 90 or 120 mg daily may be needed in some patients.

In the treatment of diabetic **peripheral neuropathic pain** the usual dose is 60 mg once daily. Some patients who respond insufficiently to this dose may benefit from up to 120 mg daily in divided doses. Response to therapy should be evaluated after 2 months and every 3 months thereafter.

In **fibromyalgia**, an initial dose of 30 mg daily is given for the first week to allow patients to adjust to the effects of duloxetine, then increased to 60 mg once daily. A similar dose is used in the management of **chronic musculoskeletal pain** such as low back pain and pain due to osteoarthritis.

Duloxetine is also used in the treatment of moderate to severe **stress urinary incontinence** in women. Usual initial doses are 40 mg twice daily; however, some patients may benefit from an initial dose of 20 mg twice daily for 2 weeks before increasing to 40 mg twice daily.

For dosage in hepatic or renal impairment, see p. 417.2.

Duloxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, p. 417.3).

Administration in hepatic or renal impairment. Duloxetine should not be used in patients with hepatic impairment.

UK licensed product information for duloxetine states that no dosage adjustment is necessary in mild to moderate renal impairment (creatinine clearance 30 mL/min or above). However, US information suggests that a lower starting dose and gradual dose increase may be warranted for patients, such as diabetics, with renal impairment. Both UK and US information recommend that duloxetine should not be used in more severe renal impairment (creatinine clearance less than 30 mL/min).

Anxiety disorders. Duloxetine is used in the treatment of generalised anxiety disorder (p. 1028.1).

References.

1. Koponen H, *et al.* Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry* 2007; **9:** 100–107.
2. Endicott J, *et al.* Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. *J Clin Psychiatry* 2007; **68:** 518–24. Corrections. *ibid.* 2007; 518, 806.
3. Hartford J, *et al.* Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol* 2007; **22:** 167–74.
4. Allgulander C, *et al.* Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 2007; **23:** 1245–52.
5. Rynn M, *et al.* Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety* 2008; **25:** 182–9.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage. Similar properties may also favour the use of serotonin and noradrenaline reuptake inhibitors such as duloxetine.

References.

1. Goldstein DJ, *et al.* Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002; **63:** 225–31.
2. Detke MJ, *et al.* Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; **63:** 308–15.
3. Raskin J, *et al.* Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry* 2003; **64:** 1237–44.
4. Goldstein DJ, *et al.* Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 2004; **24:** 389–99.
5. Detke MJ, *et al.* Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol* 2004; **14:** 457–70.
6. Dugan SE, Fuller MA. Duloxetine: a dual reuptake inhibitor. *Ann Pharmacother* 2004; **38:** 2078–85.
7. Whitmyer VG, *et al.* A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *J Clin Psychiatry* 2007; **68:** 1921–30.
8. Perahia DGS, *et al.* Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70:** 706–16.

Micturition disorders. Duloxetine is used[1-3] to increase urethral tone in the treatment of women with moderate to severe stress urinary incontinence (p. 2349.2). A systematic review[3] concluded that duloxetine treatment reduced the frequency of incontinence episodes and significantly improved the patient's quality of life; however, it was unclear if these benefits were sustained. In addition, the review showed that adverse effects, particularly nausea, were common with duloxetine and led some patients to stop treatment.

1. McCormack PL, Keating GM. Duloxetine in stress urinary incontinence. *Drugs* 2004; **64:** 2567–73.
2. Ghoniem GM, *et al.* A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol (Baltimore)* 2005; **173:** 1647–53.
3. Mariappan P, *et al.* Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 14/09/06).

Pain. Duloxetine is used[1-5] in the treatment of diabetic peripheral neuropathic pain (p. 8.2) and fibromyalgia (see Soft-tissue Rheumatism, p. 14.2), a condition that responds poorly to analgesics and anti-inflammatory drugs. It is also used in the management of chronic musculoskeletal pain such as low back pain (p. 9.2) and pain due to osteoarthritis (p. 12.3).

1. Lunn MPT, *et al.* Duloxetine for treating painful neuropathy or chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 01/03/11).
2. Chappell AS, *et al.* Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain* 2009; **146:** 253–60.
3. Skljarevski V, *et al.* Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine* 2010; **35:** E578–E585.
4. Skljarevski V, *et al.* Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain* 2010; **11:** 1282–90.
5. Chappell AS, *et al.* A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract* 2011; **11:** 33–41.

Adverse Effects and Treatment

Adverse effects reported most frequently with duloxetine include nausea, headache, insomnia, fatigue, somnolence, dry mouth, dizziness, and constipation. Other common adverse effects include anorexia, diarrhoea, dyspepsia, vomiting, anxiety, visual disturbances, tremor, weight gain or loss, sexual dysfunction, nervousness, lethargy, yawning, hot flushes, increased sweating, and pruritus. Dose-related increases in blood pressure have also been seen in some patients. Reports of tachycardia, ecchymosis, urinary hesitation, rashes, and photosensitivity reactions are less common, and convulsions and activation of mania or hypomania have occurred rarely. Increases in liver enzyme values, hepatitis, and acute liver injury are uncommon, usually occurring within a few months of starting duloxetine. There have been reports of hepatic failure with or without jaundice (sometimes fatal), with a mixed or hepatocellular pattern of damage. Cases of orthostatic hypotension and syncope, serotonin syndrome, and akathisia have also been reported. Suicidal ideation may occur in some patients.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In the treatment of overdosage the value of gastric decontamination is uncertain; however, oral activated charcoal should be considered if more than 5 mg/kg of duloxetine has been ingested and the patient presents within 1 hour of ingestion. Symptomatic and supportive therapy should be given thereafter as necessary. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Incidence of adverse effects. References.

1. Brunton S, *et al.* Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. *Drug Safety* 2010; **33:** 393–407.

Precautions

Duloxetine should not be used in patients with hepatic or severe renal impairment and is contra-indicated in patients with uncontrolled narrow-angle glaucoma or hypertension. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Blood pressure should also be monitored because of the risk of hypertension. Increases in fasting blood glucose and in total cholesterol have been reported in diabetic patients. It should be used with caution in patients with a history of seizures, of bleeding disorders, or of hypomania or mania.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, duloxetine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Symptoms reported when duloxetine therapy was stopped abruptly include headache, nausea, vomiting, dizziness, insomnia, anxiety, and paraesthesia. It is therefore recommended that duloxetine should be withdrawn gradually and the patient monitored to minimise the risk of withdrawal reactions (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

Children. Duloxetine has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age is not generally recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts

and behaviour in such patients (see Effects on the Mental State, under Fluoxetine, p. 422.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies duloxetine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Neonatal behavioural syndrome developed about 3 days after birth in an infant whose mother had taken duloxetine during pregnancy.[1] The infant developed jerky rhythmic movements, twitching, and episodes of shaking, which were managed with phenobarbital for about 7 weeks. At 2 years of age, the child was healthy with normal neurobehavioural development.

1. Eyal R, Yaeger D. Poor neonatal adaptation after in utero exposure to duloxetine. *Am J Psychiatry* 2008; **165:** 651.

Interactions

Duloxetine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with duloxetine. At least 5 days should elapse between stopping duloxetine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). The use of duloxetine with other antidepressants including the SSRIs, other serotonin and noradrenaline reuptake inhibitors, and the reversible inhibitors of monoamine oxidase is not recommended. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2.

Caution is advised when using duloxetine with other centrally acting drugs including alcohol and those with sedative properties.

Duloxetine is metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6. It should not be given with potent inhibitors of CYP1A2 such as fluvoxamine, ciprofloxacin, and enoxacin as such combinations are likely to result in increased duloxetine concentrations. Similarly, caution is recommended when duloxetine is given with potent CYP2D6 inhibitors such as paroxetine. Duloxetine itself is also a moderate inhibitor of CYP2D6 and, consequently, licensed product information recommends that it should be used cautiously with drugs that have a narrow therapeutic index and are extensively metabolised by this isoenzyme. In particular, use with thioridazine is contra-indicated because of the risk of serious ventricular arrhythmias and sudden death associated with raised thioridazine concentrations.

As duloxetine may increase the risk of bleeding, caution is advised when it is given with warfarin or drugs known to affect platelet function.

Duloxetine is highly protein bound and adverse effects may occur if given with other highly protein-bound drugs.

References.

1. Skinner MH, *et al*. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther* 2003; **73:** 170–7.
2. Lobo ED, *et al*. In vitro and in vivo evaluations of cytochrome P450 1A2 interactions with duloxetine. *Clin Pharmacokinet* 2008; **47:** 191–202.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p. 681.3).

Pharmacokinetics

Duloxetine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 6 hours after an oral dose. Food delays the time to reach peak concentrations to 10 hours. Protein binding is about 96%, mainly to albumin and $alpha_1$-acid glycoprotein. Duloxetine is extensively metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6; two major, but inactive, metabolites are formed, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. These and other metabolites are mainly excreted in the urine; about 20% is excreted in the faeces. Less than 1% of a dose is excreted in the urine as unchanged duloxetine. The elimination half-life of duloxetine is 8 to 17 hours with an average of about 12 hours. Duloxetine is distributed into breast milk.

References.

1. Lantz RJ, *et al*. Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. *Drug Metab Dispos* 2003; **31**: 1142–50.
2. Skinner MH, *et al*. Effect of age on the pharmacokinetics of duloxetine in women. *Br J Clin Pharmacol* 2004; **57:** 54–61.
3. Lobo ED, *et al*. Population pharmacokinetics of orally administered duloxetine in patients: implications for dosing recommendation. *Clin Pharmacokinet* 2009; **48:** 189–97.
4. Lobo ED, *et al*. Effects of varying degrees of renal impairment on the pharmacokinetics of duloxetine: analysis of a single-dose phase I study and pooled steady-state data from phase II/III trials. *Clin Pharmacokinet* 2010; **49:** 311–21.

Distribution into breast milk. A study in 6 women, who were given duloxetine 40 mg orally twice daily, found that the drug was distributed into breast milk.[1] The concentration of duloxetine was consistently lower in milk than in plasma, at a ratio of about 0.25. No infants were breast fed during the study, but the dose they would have been likely to receive was calculated to be about 2 micrograms/kg daily, or about 0.14% of the maternal dose.

1. Lobo ED, *et al*. Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clin Pharmacokinet* 2008; **47:** 103–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cymbalta; Duxetin; ***Austral.***: Cymbalta; ***Austria***: Cymbalta; Yentreve; ***Belg.***: Cymbalta; Yentreve; ***Braz.***: Cymbalta; ***Canad.***: Cymbalta; ***Chile***: Cymbalta; Duceten; Lervitan; Nitexol; Yentreve; ***China***: Ao Si Ping (奥思平); Cymbalta (欣百达); ***Cz.***: Ariclaim; Cymbalta; Xeristar; Yentreve; ***Denm.***: Cymbalta; Xeristar; Yentreve; ***Fin.***: Cymbalta; Yentreve; ***Fr.***: Cymbalta; ***Ger.***: Ariclaim; Cymbalta; Yentreve; ***Gr.***: Ariclaim; Cymbalta; Xeristar; Yentreve; ***Hong Kong***: Cymbalta; ***Hung.***: Cymbalta; ***India***: C-Pact; Delok; Dulife; Dumore; Duvanta; Duxet; Duzela; Nudep; ***Indon.***: Cymbalta; ***Irl.***: Ariclaim; Cymbalta; Xeristar; Yentreve; ***Israel***: Cymbalta; Yentreve; ***Ital.***: Cymbalta; Xeristar; Yentreve; ***Jpn***: Cymbalta; ***Malaysia***: Cymbalta; ***Mex.***: Cymbalta; Yentreve; ***Neth.***: Ariclaim; Cymbalta; Xeristar; Yentreve; ***Norw.***: Cymbalta; ***Philipp.***: Cymbalta; ***Pol.***: Ariclaim; Cymbalta; Xeristar; Yentreve; ***Port.***: Ariclaim; Cymbalta; Xeristar; Yentreve; ***Rus.***: Cymbalta (Симбалта); ***S.Afr.***: Cymbalta; ***Singapore***: Cymbalta; ***Spain***: Cymbalta; Xeristar; ***Swed.***: Ariclaim; Cymbalta; Yentreve; ***Switz.***: Cymbalta; ***Thai.***: Cymbalta; ***Turk.***: Cymbalta; ***UK***: Cymbalta; Yentreve; ***USA***: Cymbalta.

Multi-ingredient Preparations. ***India***: Duzela-M.

Pharmacopoeial Preparations
USP 36: Duloxetine Delayed-Release Capsules.

Escitalopram Oxalate

(BANM, USAN, rINNM)

S-Citalopram Oxalate; Escitalopram, Oxalate d'; Escitalopram, oxalato de; Escitalopramі Oxalas; Lu-26-054/0; Oxalato de escitalopram; Эсциталопрама Оксалат.

(+)-(*S*)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate.

$C_{20}H_{21}FN_2O,C_2H_2O_4$=414.4

CAS — 128196-01-0 (escitalopram); 219861-08-2 (escitalopram oxalate).

ATC — N06AB10.

ATC Vet — QN06AB10.

UNII — 5U85DBW7LO.

Pharmacopoeias. In *US*.

USP 36: (Escitalopram Oxalate). A fine, white to slightly yellow powder. Sparingly soluble in water and in alcohol; freely soluble in methyl alcohol and in dimethyl sulfoxide; very slightly soluble in ethyl acetate and in isopropyl alcohol; insoluble in heptane.

Uses and Administration

Escitalopram, the *S*-enantiomer of citalopram (p. 411.1), is an SSRI with actions and uses similar to those of fluoxetine (p. 419.1). It is given orally as the oxalate although doses are expressed in terms of the base; escitalopram oxalate 12.8 mg is equivalent to about 10 mg of escitalopram.

In the treatment of **depression**, the usual dose is 10 mg once daily increased, after at least a week, to a maximum of 20 mg once daily if necessary.

Escitalopram is also used in the treatment of **panic disorder** with or without agoraphobia. Initial doses are 5 mg once daily, increased after a week to 10 mg once daily; further increases up to a maximum of 20 mg daily may be necessary in some patients.

Doses of escitalopram used in the treatment of **generalised anxiety disorder**, **social anxiety disorder**, and **obsessive-compulsive disorder** are similar to those used in depression.

Initial treatment with half the usual recommended dose and a lower maximum dose should be considered in elderly patients; a maximum of 10 mg daily has been recommended. Patients with hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 may also require lower doses (see p. 418.3). For doses in children, see p. 418.2.

Escitalopram should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

Administration in children. There are concerns about the use of SSRIs in children (see Effects on Mental State, under Adverse Effects of Fluoxetine, p. 422.2) and, in the UK, escitalopram therapy is unlicensed in those under 18 years of age. In the USA, however, escitalopram may be given for the treatment of major depression in children and adolescents aged 12 years and over. Initial oral doses of 10 mg once daily can be increased, if necessary, to 20 mg once daily after at least 3 weeks.

Administration in hepatic impairment. Increases of 51% and 69% in the area under the concentration-time curve occurred in a single-dose study of escitalopram in patients with mild and moderate hepatic impairment (Child-Pugh score 5 or 6, and 7 to 9, respectively).[1] This study also reported that activity of the cytochrome P450 isoenzyme CYP2C19 was a better predictor of escitalopram clearance than the Child-Pugh classification.

UK licensed product information for escitalopram suggests that patients with mild to moderate hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 should receive an initial oral dose of 5 mg daily, increased to 10 mg daily after 2 weeks depending on response; more careful dose titration is advised in those with severe impairment. US licensed product information recommends 10 mg daily as a suitable dose for patients with hepatic impairment.

1. Areberg J, *et al*. The pharmacokinetics of escitalopram in patients with hepatic impairment. *AAPS J* 2006; **8:** E14–E19.

Anxiety disorders. Escitalopram has been given in anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1), obsessive-compulsive disorder (p. 1028.2), and social anxiety disorder (see under Phobic Disorders, p. 1029.1).

References.

1. Stahl SM, *et al*. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2003; **64:** 1322–7.
2. Davidson JR, *et al*. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004; **19:** 234–40.
3. Lader M, *et al*. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 2004; **19:** 241–8.
4. Kasper S, *et al*. Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. *Br J Psychiatry* 2005; **186:** 222–6.
5. Stein DJ, *et al*. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 2007; **23:** 701–11.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as escitalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Burke WJ, *et al*. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002; **63:** 331–6.
2. Wade A, *et al*. Escitalopram 10mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2002; **17:** 95–102.
3. Lepola UM, *et al*. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003; **18:** 211–17.
4. Rapaport MH, *et al*. Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 2004; **65:** 44–9.
5. Montgomery SA, *et al*. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004; **50:** 57–64.
6. Murdoch D, Keam SJ. Escitalopram: a review of its use in the management of major depressive disorder. *Drugs* 2005; **65:** 2379–2404.
7. Cipriani A, *et al*. Escitalopram versus other antidepressive agents for depression. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 07/08/09).

Adverse Effects, Treatment, and Precautions

As for Citalopram, p. 411.3.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 422.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies escitalopram as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pharmacokinetics

Escitalopram has similar pharmacokinetics to those of racemic citalopram (p. 411.3).

References.

1. Søgaard B, *et al*. The pharmacokinetics of escitalopram after oral and intravenous administration of single and multiple doses to healthy subjects. *J Clin Pharmacol* 2005; **45:** 1400–6.
2. Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 2007; **46:** 281–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aramix; Axiomat; Beaplen; Citalax; Esciprox; Esciterokam; Ex3; Lexapro; Lextor; Meridian; Novo Humorap; Talpram; Zenvas; ***Austral.***: Esipram; Esitalo; Lexam; Lexapro; Loxalate; ***Austria***: Cipralex; ***Belg.***: Sipralexa; ***Braz.***: Espran; Exodus; Lexapro; Reconter; ***Canad.***: Cipralex; ***Chile***: Celtium; Eciprax; Ectiban; Ipran; Lexapro; Neopresol; Neozentius; Nexipram; Reposil; Zepaz; ***China***: Lexapro (来士普); ***Cz.***: Anxila; Cipralex; Depresinal; Despra; Elicea; Escirdec; Escitil; Escitralix; Esoprex; Esprolan; Isozyloram; Itakem; Lenuxin; ***Denm.***: Cipralex; Entact; Escinapram†; Esertia; Lideropram; Lorepram†; Mylopram; Scippa†; Seroplex; Solatcit; Talogen; Talomam; ***Fin.***: Cipralex; Esipral; ***Fr.***: Seroplex; ***Ger.***: Cipralex; ***Gr.***: Cipralex; Entact; ***Hong Kong***: Lexapro; ***Hung.***: Cipralex; ***India***: Alivate-E; Alwel; Ambulax-AD; Articalm; C-Pram-S; Cilentra; Cipralex; Cita-S; Citalop-S; Citel; Citofast; Deplam-S; Deptune; Ecitalop; Elcit; Emdes; Escin; Escita; Escitapax; Escitrac; Esdep; Esfancy; Esfany; Esitonic; Esitor; Esjoy; Espam; Espar; Estomine; Feliz-S; Firsito; Jolivel; Jopram; Monopram; Nestilo; Nexito; Recita; S-Citadep; ***Indon.***: Cipralex†; ***Irl.***: Esciprex; Escitasan; Escitomar; Escitotab; Etalopro; Lexapro; Scippa; ***Israel***: Cipralex; Esto; ***Ital.***: Cipralex; Entact; ***Jpn***: Lexapro; ***Malaysia***: Lexapro; ***Mex.***: Lexapro; ***Neth.***: Cipralex†; Escitaburg†; Escitafloc†; Escitalis†; Escitalodeon†; Escitalofi†; Lexapro; ***Norw.***: Cipralex; ***NZ***: Lexapro; Loxalate; ***Philipp.***: Jovia; Lexapro; ***Pol.***: Depralin; Deprigen; Elicea; Escertal; Escitasan; Escitil; Lenuxin; Lexapro; Mozarin; Pramatis; ***Port.***: Aloce†; Cipralex; Depart†; Ecitrix†; Escitaham†; Espax†; Rasec; Sades; Sciprал; Tacipram†; Tacipram; Ticofarma; Zecidec†; Zocital†; ***Rus.***: Cipralex (Ципралекс); Selectra (Селектра); ***S.Afr.***: Cipralex; Citraz; Lexamil; Zytomil; ***Singapore***: Lexapro; ***Spain***: Cipralex; Entact†; Escilan; Escimylan; Esertia; Heipram; ***Swed.***: Cipralex; Premalex; ***Switz.***: Cipralex; ***Thai.***: Lexapro; ***Turk.***: Avertyn; Cipralex; Citoles; Eslorex; Esmax; Esram; Losiram; Secita; Tiopram†; Zendor; ***UK***: Cipralex; ***Ukr.***: Cipralex (Ципралекс); Esopram (Эзопрам); Essobel (Эссобел); ***USA***: Lexapro; ***Venez.***: Lexapro.

Multi-ingredient Preparations. ***India***: C-Pram-S Plus; Cita-S Forte; Cita-S Plus; Ecitalop-C; Escin Plus; Escita Plus; Escitrac-CZ; Esfany-CZ; Esitor Forte; Esjoy Plus; Espar-CL; Estomine Zee; Estomine-SF; Feliz-S Plus; Nexito Forte; Nexito-Plus.

Pharmacopoeial Preparations
USP 36: Escitalopram Tablets.

Fluoxetine Hydrochloride

(BANM, USAN, rINNM)

Fluoksetiinihydrokloridi; Fluoksetin Hidroklorür; Fluoksetino hidrochloridas; Fluoksetyny chlorowodorek; Fluoxetina, hidrocloruro de; Fluoxétine, chlorhydrate de; Fluoxetin-hidroklorid; Fluoxetinhydrochlorid; Fluoxetin-hydrochlorid; Fluoxetinhydroklorid; Fluoxetini hydrochloridum; Hidrocloruro de fluoxetina; Lilly-103472; LY-110140; Флуоксетина Гидрохлорид.

(±)-*N*-Methyl-3-phenyl-3-(α,α,α-trifluoro-*p*-tolyloxy)propylamine hydrochloride.

$C_{17}H_{18}F_3NO,HCl$=345.8

CAS — 54910-89-3 (fluoxetine); 59333-67-4 (fluoxetine hydrochloride).

ATC — N06AB03.

ATC Vet — QN06AB03.

UNII — I9W7N6B1KJ (fluoxetine hydrochloride); 7C4D25ST1T (R-fluoxetine hydrochloride).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of fluoxetine:

Distas; Green and whites; Greens; Limes; Pros; Zacs.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fluoxetine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.5.

USP 36: (Fluoxetine Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in alcohol and in methyl alcohol; practically insoluble in ether. Store in airtight containers.

Uses and Administration

Prevention of the reuptake of monoamine transmitters such as serotonin, which potentiates their action in the brain, appears to be associated with antidepressant activity. SSRIs such as fluoxetine preferentially inhibit the reuptake of serotonin compared with noradrenaline, and have limited direct action at other neurotransmitter sites, including muscarinic receptors. They therefore cause fewer antimuscarinic or sedative adverse effects than the tricyclic antidepressants and are less cardiotoxic. Citalopram is the most selective of the SSRIs currently available, whereas paroxetine is the most potent.

SSRIs provide an alternative to the tricyclics for the treatment of depression. As with the tricyclics, it may be several weeks before an antidepressant effect is seen. Once depression has then resolved, maintenance therapy should be continued for at least 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years.

Some SSRIs are also used as part of the management of generalised anxiety disorder, obsessive-compulsive disorder, panic disorders with or without agoraphobia, social phobia, and post-traumatic stress disorder, and as part of the management of bulimia nervosa. Fluoxetine is also used in the treatment of premenstrual dysphoric disorder.

Fluoxetine, a phenylpropylamine derivative, is given orally as the hydrochloride, but doses are expressed in terms of the base; fluoxetine hydrochloride 22.4 mg is equivalent to about 20 mg of fluoxetine.

In the treatment of **depression** the usual initial dose of fluoxetine is 20 mg once daily; US licensed product information recommends giving this dose in the morning. If no clinical response is seen after several weeks, the daily dose may be gradually increased, up to a maximum of 80 mg daily (60 mg in the elderly). Doses above 20 mg daily may be given in 2 divided doses, for example in the morning and at noon, or as a once daily dose. A once-weekly, modified-release preparation equivalent to 90 mg of fluoxetine is available in the USA for use in patients whose depressive symptoms have stabilised, and who require long-term treatment; it is recommended that weekly dosing is started 7 days after the last daily dose of fluoxetine. Fluoxetine may also be given as a combination preparation with olanzapine (p. 1089.3) in the management of depressive episodes associated with bipolar disorder, and in treatment-resistant depression. The daily dose of fluoxetine is usually within the range of 20 to 50 mg, and the combination is given as a single dose in the evening.

Fluoxetine is used in the management of **bulimia nervosa** in a dose of 60 mg daily, which may be given as a single morning dose or in divided doses.

In the management of **obsessive-compulsive disorder** the initial dose of fluoxetine is 20 mg once daily increased after several weeks if there is no response to up to 60 mg daily. Up to 80 mg daily has been used, sometimes divided into 2 doses.

Fluoxetine may be used in the treatment of **panic disorder** in initial doses of 10 mg once daily. After a week the dose should be increased to 20 mg daily; further increases to 60 mg daily may be considered after several weeks if no improvement is seen.

A dose of 20 mg daily is used in the treatment of **premenstrual dysphoric disorder**. Intermittent dosing is also permitted: for each new cycle, fluoxetine should be started 14 days before the onset of menstruation and continued until the first full day of menstruation. Treatment may be continued for 6 months; benefit should then be reassessed before continuing further.

A lower or less frequent dosage is recommended in elderly patients. For dose adjustment in hepatic or renal impairment, see p. 419.2, and for doses in children, see p. 419.2.

It should be noted that because fluoxetine and norfluoxetine have prolonged half-lives several weeks of therapy are required before steady-state concentrations are attained; similarly after dosage adjustments a time lag will occur before steady-state concentrations are again achieved. Although SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms, the long half-life may reduce the need for dose tapering with fluoxetine.

Administration in children. Fluoxetine may be used for the treatment of **depression** in children aged 8 years and over. Initial oral doses of 10 mg daily can be increased to 20 mg daily after 1 to 2 weeks (except in low-weight children when such increases should not be made for several weeks, and then only if the clinical response is insufficient). Because of concerns about the use of SSRIs in children (see Effects on Mental State, p. 422.2), fluoxetine is licensed in the EU only as an adjunct to psychological therapy in children and adolescents with moderate to severe depression who have not responded to psychological therapy alone.

Fluoxetine is also licensed in the USA for the management of **obsessive-compulsive disorder** in children aged 7 years and over, starting with an oral dose of 10 mg daily. In low-weight children this may be increased after several weeks to 20 to 30 mg daily, if required. The dose in adolescents and heavier children may be increased to 20 mg daily after 2 weeks; further increases to 60 mg daily may be made after several weeks, as necessary.

Administration in hepatic or renal impairment. Fluoxetine is subject to hepatic metabolism, and, therefore, lower doses, such as alternate-day dosing, have been recommended in patients with significant hepatic impairment.

It is also excreted by the kidneys and licensed information for some UK products recommends a similar dose reduction in patients with mild to moderate renal impairment and that fluoxetine should be avoided in those with severe impairment. However, other UK and US product information states that plasma concentrations of fluoxetine or its metabolite norfluoxetine in patients with severe impairment requiring dialysis did not differ from those in controls with normal renal function when given fluoxetine 20 mg daily for 2 months.

Anorexia nervosa. Counselling and psychotherapy form the major part of treatment of anorexia nervosa and there is little or no role for specific drug therapy. Antidepressants may be indicated when there is co-existing depression or obsessive-compulsive disorder but malnourished anorexic patients may be more susceptible to adverse effects and less responsive than other patients with depression. Fluoxetine has been studied in the prevention of relapse once weight gain has been achieved, with mixed results.

References.

1. Bergh C, *et al.* Selective serotonin reuptake inhibitors in anorexia. *Lancet* 1996; **348:** 1459–60.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
3. Kaye WH, *et al.* Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001; **49:** 644–52.
4. Kim SS. Role of fluoxetine in anorexia nervosa. *Ann Pharmacother* 2003; **37:** 890–2.
5. Walsh BT, *et al.* Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA* 2006; **295:** 2605–12. Corrections. *ibid.*; **296:** 934 and 2007; **298:** 2008.

Anxiety disorders. SSRIs have been given in a variety of anxiety disorders but their role in these disorders is most well established in the treatment of *obsessive-compulsive disorder* (p. 1028.2). Efficacy in obsessive-compulsive disorder appears to have been best shown for fluvoxamine and fluoxetine but other SSRIs are also effective and patients unresponsive to one SSRI may respond to another. SSRIs are also of use in the treatment of *generalised anxiety disorder* (p. 1028.1), *panic disorder* (p. 1029.1), and *post-traumatic stress disorder* (p. 1029.2). SSRIs are considered to be the first choice for the treatment of *social anxiety disorder* (see under Phobic Disorders, p. 1029.1). Fluoxetine is one of the SSRIs that has been tried in the treatment of *trichotillomania.*

References.

1. Tollefson GD, *et al.* A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1994; **51:** 559–67.
2. Yanchick JK, *et al.* Efficacy of fluoxetine in trichotillomania. *Ann Pharmacother* 1994; **28:** 1245–6.
3. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *Int Clin Psychopharmacol* 1995; **10:** 45–9.
4. Michelson D, *et al.* Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. *Br J Psychiatry* 1999; **174:** 213–18.
5. Connor KM, *et al.* Fluoxetine in post-traumatic stress disorder: randomised, double-blind study. *Br J Psychiatry* 1999; **175:** 17–22.
6. Meltzer-Brody S, *et al.* Symptom-specific effects of fluoxetine in post-traumatic stress disorder. *Int Clin Psychopharmacol* 2000; **15:** 227–31.
7. Geller DA, *et al.* Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 773–9.
8. Romano S, *et al.* Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. *J Clin Psychopharmacol* 2001; **21:** 46–52.
9. Barnett SD, *et al.* Tolerability of fluoxetine in posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26:** 363–7.
10. Liebowitz MR, *et al.* Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1431–8.
11. Birmaher B, *et al.* Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2003; **42:** 415–23.
12. Davidson JR, *et al.* Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 2004; **61:** 1005–13.

Bipolar disorder. Treatment of the depressive phase of bipolar disorder (p. 397.2) with antidepressants needs caution since these drugs may precipitate mania or hypomania. SSRIs such as fluoxetine have nonetheless been used in bipolar disorder with some success. In some countries, fluoxetine is also available as a fixed-dose combination with the atypical antipsychotic olanzapine for use in the depressive phase of bipolar disorder.

References.

1. Amsterdam JD, *et al.* Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol* 1998; **18:** 435–40.
2. Megna JL, Devitt PJ. Treatment of bipolar depression with twice-weekly fluoxetine: management of antidepressant-induced mania. *Ann Pharmacother* 2001; **35:** 45–7.
3. Tohen M, *et al.* Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003; **60:** 1079–88. Correction. *ibid.* 2004; **61:** 176.
4. Amsterdam JD, *et al.* Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate. *Bipolar Disord* 2004; **6:** 75–81.
5. Deeks ED, Keating GM. Olanzapine/fluoxetine: a review of its use in the treatment of acute bipolar depression. *Drugs* 2008; **68:** 1115–37.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Fluoxetine and the tricyclic desipramine have been suggested as the antidepressants of choice because they have been used extensively and are considered to be well tolerated. Other SSRIs that have been tried include sertraline, fluvoxamine, and paroxetine. Antidepressants in general do not appear to alter the patient's disturbed self-image, although disturbed attitudes might improve during short-term therapy with fluoxetine.

References.

1. Goldbloom DS, Olmsted MP. Pharmacotherapy of bulimia nervosa with fluoxetine: assessment of clinically significant attitudinal change. *Am J Psychiatry* 1993; **150:** 770–4.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
3. Hay PPJ, *et al*. Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 29/07/10).
4. Bacaltchuk J, Hay PPJ. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 29/07/10).

Congenital myasthenia. Fluoxetine may be used as an alternative to quinidine sulfate in the treatment of the slow-channel congenital myasthenic syndrome (p. 685.1).

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as fluoxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

Combination therapy with differing classes of antidepressants, including the SSRIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions, and should be used only under expert supervision. For further details see Antidepressants, under Interactions of Phenelzine, p. 447.2.

References to the use of SSRIs in general and to the use of fluoxetine are given below.

1. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995; **310:** 1433–8.
2. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry* 1995; **56:** 30–4.
3. Fava M, *et al*. Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. *J Clin Psychiatry* 1995; **56:** 52–5.
4. Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. *Drug Safety* 1998; **18:** 57–82.
5. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998; **7** (suppl 1): 11–17.
6. Cheer SM, Goa KL. Fluoxetine: a review of its therapeutic potential in the treatment of depression associated with physical illness. *Drugs* 2001; **61:** 81–110.
7. Sampson SM. Treating depression with selective serotonin reuptake inhibitors: a practical approach. *Mayo Clin Proc* 2001; **76:** 739–44.
8. Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs* 2001; **61:** 2221–8.
9. Bull SA, *et al*. Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother* 2002 **36:** 578–84.
10. Emslie GJ, *et al*. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1205–15.
11. March J, *et al*. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; **292:** 807–20.
12. Devanand DP, *et al*. Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. *Am J Geriatr Psychiatry* 2005; **13:** 59–68.
13. Trivedi MH, *et al*. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry* 2009; **70:** 387–96.

Disturbed behaviour. SSRIs appear to have been of some benefit in controlling symptoms such as impulsiveness and aggression[1-4] when tried in various disorders for the management of disturbed behaviour (see p. 1030.2). There have been several case reports of fluoxetine being used with some success in the control of fantasies associated with various paraphilias.[5]

1. Cornelius JR, *et al*. Fluoxetine trial in borderline personality disorder. *Psychopharmacol Bull* 1990; **26:** 151–4.
2. Vartiainen H, *et al*. Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; **91:** 348–51.
3. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry* 1997; **54:** 1081–8.
4. Coccaro EF, *et al*. A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *J Clin Psychiatry* 2009; **70:** 653–62.
5. Richer M, Crismon ML. Pharmacotherapy of sexual offenders. *Ann Pharmacother* 1993; **27:** 316–19.

Headache. A systematic review[1] of 13 studies found that the SSRIs were no better than placebo in the prevention of migraine or tension-type headache; when compared with the tricyclic antidepressants, the SSRIs were as effective for migraine but less effective for tension-type headache. However, it was noted that studies were small, of short duration (8 to 12 weeks), and most had methodological faults.

Guidelines for the management of migraine or tension-type headache (see p. 670.3 and p. 671.3, respectively) do not recommend the use of SSRIs for prophylaxis.

1. Moja L, *et al*. Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 27/01/09).

Hot flushes. HRT with oestrogens is usually the mainstay of acute treatment for symptoms such as hot flushes associated with the menopause (see Menopausal Disorders, p. 2245.1); however, HRT has potentially tumour-stimulating effects and may be unsuitable in some patients, particularly those with a history of breast cancer (see Malignant Neoplasms, under Precautions of HRT, p. 2250.2). Preliminary studies have shown that some SSRIs (fluoxetine, paroxetine, and sertraline) have a modest effect on alleviating hot flushes and may be an alternative to HRT in peri- and postmenopausal women and in women with a history of breast cancer.[1-4] Indeed, low-dose paroxetine is used for the treatment of moderate to severe vasomotor symptoms associated with the menopause;[5] however, there is some concern that paroxetine may interact with tamoxifen treatment in patients with breast cancer (see Antidepressants under Interactions in Tamoxifen, p. 863.3 for details).

In addition, paroxetine has been tried in the treatment of hot flushes in men receiving anti-androgen therapy for prostate cancer.[6]

The serotonergic antidepressant venlafaxine has also been tried with some success in men and women with hot flushes in whom other treatments were unsuitable.[7]

1. Stearns V, *et al*. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003; **289:** 2827–34.
2. Kockler DR, McCarthy MW. Antidepressants as a treatment for hot flashes in women. *Am J Health-Syst Pharm* 2004; **61:** 287–92.
3. De Sloover Koch Y, Ernst ME. Selective serotonin-reuptake inhibitors for the treatment of hot flashes. *Ann Pharmacother* 2004; **38:** 1293–6.
4. Stearns V, *et al*. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005; **23:** 6919–30. Correction. *ibid.*; 8549.
5. Simon JA, *et al*. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause* 2013; **20:** 1027–35.
6. Loprinzi CL, *et al*. Pilot evaluation of paroxetine for treating hot flashes in men. *Mayo Clin Proc* 2004; **79:** 1247–51.
7. Schober CE, Ansani NT. Venlafaxine hydrochloride for the treatment of hot flashes. *Ann Pharmacother* 2003; **37:** 1703–7.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (ADHD—p. 2314.1) initial treatment is usually with a central stimulant. SSRIs such as fluoxetine have produced beneficial effects as an adjunct to central stimulants in small numbers of patients with comorbid disorders such as depression or obsessive-compulsive disorder;[1-3] although there is insufficient evidence to assess their efficacy in ADHD alone.

1. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. *J Child Adolesc Psychopharmacol* 1993; **3:** 1–10.
2. Bussing R, Levin GM. Methamphetamine and fluoxetine treatment of a child with attention-deficit hyperactivity disorder and obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 1993; **3:** 53–8.
3. Finding RL. Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents and adults: a case series. *J Child Adolesc Psychopharmacol* 1996; **6:** 165–75.

Hypochondriasis. SSRIs may be of benefit in patients with hypochondriasis.[1] Fluoxetine in an initial dose of 20 mg daily gradually increased up to 80 mg daily produced some beneficial results in 10 of 14 patients with hypochondriasis (p. 1030.2) who completed 12 weeks of treatment.[2] Fluvoxamine[3] and paroxetine[4] have also been tried.

1. Fallon BA, *et al*. The pharmacotherapy of hypochondriasis. *Psychopharmacol Bull* 1996; **32:** 607–11.
2. Fallon BA, *et al*. Fluoxetine for hypochondriacal patients without major depression. *J Clin Psychopharmacol* 1993; **13:** 438–41.
3. Fallon BA, *et al*. An open trial of fluvoxamine for hypochondriasis. *Psychosomatics* 2003; **44:** 298–303.
4. Oosterbaan DB, *et al*. An open study of paroxetine in hypochondriasis. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; **25:** 1023–33.

Hypotension. SSRIs have been used in patients with neurally mediated hypotension refractory to standard treatment (see p. 1277.2), although evidence of benefit is mainly anecdotal. However, a small study[1] found that paroxetine reduced the incidence of both tilt-induced and spontaneous syncope.

See also Orthostatic Hypotension, p. 420.3.

1. Di Girolamo E, *et al*. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999; **33:** 1227–30.

Obesity. Fluoxetine has been tried with some success as part of the management of obesity (p. 2315.1). Fluoxetine's mechanism of action in obesity is unknown. Serotonin is believed to be involved in the regulation of satiety[1] but fluoxetine has also been shown to increase resting energy expenditure and raise basal body temperature.[2] A common dose for fluoxetine in the management of obesity has been 60 mg daily; it appears that fluoxetine has a dose-related effect on weight loss.[3] Reviews[1,4,5] agree that fluoxetine can aid weight reduction in the short term but after 16 to 20 weeks some patients have started to regain weight and its long-term efficacy is unknown. Troublesome adverse effects can occur.[1] Some patients treated with fluoxetine for depression have had an increase of appetite and some have gained weight. There has been a report[6] of a patient who lost weight during treatment with fluoxetine for depression despite an increased appetite and food intake.

1. Anonymous. Fluoxetine (Prozac) and other drugs for treatment of obesity. *Med Lett Drugs Ther* 1994; **36:** 107–8.
2. Bross R, Hoffer LJ. Fluoxetine increases resting energy expenditure and basal body temperature in humans. *Am J Clin Nutr* 1995; **61:** 1020–5.
3. Levine LR, *et al*. Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study. *Int J Obes* 1989; **13:** 635–45.
4. Bray GA. Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann Intern Med* 1993; **119:** 707–13.
5. Mayer LE, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
6. Fichtner CG, Braun BG. Hyperphagia and weight loss during fluoxetine treatment. *Ann Pharmacother* 1994; **28:** 1350–2.

Orthostatic hypotension. Although orthostatic hypotension has been reported in some patients taking SSRIs, there has been a report[1] that fluoxetine 20 mg daily for 6 to 8 weeks produced beneficial effects in 4 of 5 patients with chronic symptomatic orthostatic hypotension (p. 1634.3) refractory to other treatment. Modest benefits have also been seen in patients with orthostatic hypotension associated with parkinsonism.[2]

1. Grubb BP, *et al*. Fluoxetine hydrochloride for the treatment of severe refractory orthostatic hypotension. *Am J Med* 1994; **97:** 366–8.
2. Montastruc JL, *et al*. Fluoxetine in orthostatic hypotension of Parkinson's disease: a clinical and experimental pilot study. *Fundam Clin Pharmacol* 1998; **12:** 398–402.

Pain. SSRIs have been tried in the treatment of painful disorders including fibromyalgia and diabetic neuropathy.

See also Headache, above.

References.

1. Goldenberg D, *et al*. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996; **39:** 1852–9.
2. Jung AC, *et al*. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997; **12:** 384–9.
3. Smith AJ. The analgesic effects of selective serotonin reuptake inhibitors. *J Psychopharmacol* 1998; **12:** 407–13.
4. Anderberg UM, *et al*. Citalopram in patients with fibromyalgia–a randomized, double-blind, placebo-controlled study. *Eur J Pain* 2000; **4:** 27–35.
5. Shimodozono M, *et al*. Reduction of central poststroke pain with the selective serotonin reuptake inhibitor fluvoxamine. *Int J Neurosci* 2002; **112:** 1173–81.
6. Arnold LM, *et al*. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med* 2002; **112:** 191–7.

Parkinsonism. It has been suggested that fluoxetine might be of use in the management of selected patients with Parkinson's disease (p. 890.1) who have levodopa-induced dyskinesias unresponsive to other measures.[1] However, although fluoxetine has been reported to have produced beneficial results in such patients[2] there has also been a report of increased disability in patients with Parkinson's disease given fluoxetine.[3] Extrapyramidal effects have also been reported in other patients taking fluoxetine (see under Adverse Effects, p. 423.2). Fluoxetine has been tried in parkinsonism-related orthostatic hypotension (above).

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.
2. Durif F, *et al*. Levodopa-induced dyskinesias are improved by fluoxetine. *Neurology* 1995; **45:** 1855–8.
3. Steur ENHJ. Increase of Parkinson disability after fluoxetine medication. *Neurology* 1993; **43:** 211–3.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Beneficial effects have been claimed for fluoxetine in several uncontrolled studies and reports.[1-4]

1. Seliger GM, *et al*. Fluoxetine improves emotional incontinence. *Brain Inj* 1992; **6:** 267–70.
2. Sloan RL, *et al*. Fluoxetine as a treatment for emotional lability after brain injury. *Brain Inj* 1992; **6:** 315–19.
3. Hanger HC. Emotionalism after stroke. *Lancet* 1993; **342:** 1235–6.
4. Tsai WC, *et al*. Treatment of emotionalism with fluoxetine during rehabilitation. *Scand J Rehabil Med* 1998; **30:** 145–9.

Peripheral vascular disease. Anecdotal reports[1,2] and a small pilot study[3] of fluoxetine (in a daily dose of 20 to 60 mg) suggest it may produce favourable therapeutic responses in patients with Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3).

1. Bolte MA, Avery D. Case of fluoxetine-induced remission of Raynaud's phenomenon—a case report. *Angiology* 1993; **44:** 161–3.
2. Jaffe IA. Serotonin reuptake inhibitors in Raynaud's phenomenon. *Lancet* 1995; **345:** 1378.

3. Coleiro B, *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)* 2001; **40:** 1038–43.

Premenstrual syndrome. Fluoxetine is used to control both the psychological and somatic symptoms of women with premenstrual dysphoric syndrome, a severe form of premenstrual syndrome (p. 2272.3). Other SSRIs also appear to be useful.

References.

1. Carr RR, Ensom MHH. Fluoxetine in the treatment of premenstrual dysphoric disorder. *Ann Pharmacother* 2002; **36:** 713–17.
2. Pearlstein T. Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard? *Drugs* 2002; **62:** 1869–85.
3. Luisi AF, Pawasauskas JE. Treatment of premenstrual dysphoric disorder with selective serotonin reuptake inhibitors. *Pharmacotherapy* 2003; **23:** 1131–40.
4. Brown J, *et al.* Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 30/07/10).

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs (see Effects on Sexual Function in Adverse Effects, p. 423.1). Such properties of the SSRIs have been studied as a potential form of treatment for men with premature ejaculation[1-3] (p. 2350.2). The relative effects of the SSRIs on delaying ejaculation have also been studied.[4] Paroxetine was found to cause the strongest delay, followed by fluoxetine and then sertraline; fluvoxamine caused a slight delay although the effect was not significantly different from that seen with placebo. (Citalopram was unavailable at the time of the study; later studies of its effect have been conflicting.[3])

1. Waldinger MD, *et al.* Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 1994; **151:** 1377–9.
2. Mendels J, *et al.* Sertraline treatment for premature ejaculation. *J Clin Psychopharmacol* 1995; **15:** 341–6.
3. Moreland AJ, Makela EH. Selective serotonin-reuptake inhibitors in the treatment of premature ejaculation. *Ann Pharmacother* 2005; **39:** 1296–1301.
4. Waldinger MD, *et al.* Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine and sertraline. *J Clin Psychopharmacol* 1998; **18:** 274–81.

Adverse Effects

SSRIs such as fluoxetine are less sedating than tricyclic antidepressants and have fewer antimuscarinic and cardiotoxic effects. Adverse effects reported with SSRIs include dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhoea. Anorexia and weight loss may also occur. Neurological adverse effects have included either anxiety, restlessness, nervousness, and insomnia, or drowsiness and fatigue; headache, tremor, dizziness, seizures, hallucinations, confusion, agitation, extrapyramidal effects, depersonalisation, mania, panic attacks, sexual dysfunction, and symptoms suggestive of a serotonin syndrome (p. 445.2) have also occurred. The concern that SSRIs may be associated with increased suicidal ideation is discussed under Effects on Mental State, p. 422.2.

Excessive sweating, pruritus, rashes, alopecia, photosensitivity, and urticaria have also been reported. Angioedema and anaphylactoid reactions have occurred. In some patients who have developed rashes while taking fluoxetine, systemic hypersensitivity reactions involving the lungs, kidneys, or liver, and possibly related to vasculitis, have developed; it has therefore been advised that fluoxetine therapy should be stopped in any patient who develops a skin rash.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly. Hyperprolactinaemia and galactorrhoea have occurred, as have changes in blood sugar, in patients receiving SSRIs.

Arthralgia and myalgia have been reported and there have also been cases of orthostatic hypotension, yawning, urinary retention, and abnormal vision including blurred vision and mydriasis. Abnormal liver function tests have been reported rarely. SSRIs have occasionally been associated with bleeding disorders such as ecchymosis and purpura and other effects on the blood.

In overdosage nausea, vomiting, and excitation of the CNS are considered to be prominent features; death has been reported.

Incidence of adverse effects. In June 1992 the UK CSM had received 1236 reports of adverse effects with fluvoxamine (from about 280 000 prescriptions) compared with 2422 for fluoxetine (from about 480 000 prescriptions).[1] The overall patterns of adverse effects were similar but dermatological reactions were more likely with fluoxetine and gastrointestinal reactions with fluvoxamine. Reports of attempted suicide increased after adverse publicity about SSRIs in 1990, and the number of reports per million prescriptions were similar for the 2 drugs (25 for fluoxetine and 20 for fluvoxamine); at that time such figures were not considered disconcerting given that features of depression, including attempted suicide, can worsen after the introduction of any antidepressant (see also Effects on Mental State, p. 422.2). A later review[2] by the CSM of the 5 SSRIs available in the UK (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) found that the SSRIs were broadly similar with respect to their safety profile. A list of adverse reactions common to all SSRIs was provided.

A review[3] of 1861 adverse reactions to citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline reported to the Swedish Adverse Drug Reactions Advisory Committee found that the most commonly reported reactions were neurological (22.4% of all reports), psychiatric (19.5%), and gastrointestinal (18.0%). Compared with other SSRIs, gastrointestinal symptoms were more common with fluvoxamine, psychiatric symptoms with sertraline, and dermatological symptoms with fluoxetine.

A later meta-analysis[4] has compared the adverse effect profile of fluoxetine with other antidepressants including the tricyclics and other SSRIs. The overall risk of any adverse effect with fluoxetine was less than that for the tricyclic antidepressants; however, there was no difference in risk when fluoxetine was compared with other SSRIs. When considering individual adverse reactions, fluoxetine was more likely to cause activating effects such as insomnia, agitation, tremor, and anxiety, and gastrointestinal disturbances such as nausea, vomiting, diarrhoea, weight loss, and anorexia than other antidepressants. In contrast, the tricyclics were associated with a greater risk of sedation, antimuscarinic effects (such as dry mouth, dizziness, and blurred vision), constipation, and weight gain, than fluoxetine.

1. CSM. Safety of fluoxetine (Prozac): comparison with fluvoxamine (Faverin). *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 27/11/05)
3. Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. *Drug Safety* 1999; **20:** 277–87.
4. Brambilla P, *et al.* Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry* 2005; **38:** 69–77.

Effects on the blood. Abnormalities in platelet aggregation were associated with fluoxetine given to a severely underweight patient.[1] Platelet activity returned to normal when fluoxetine was stopped. Fluoxetine was also suspected of being the cause of bruising in a patient whose blood clotting parameters were within normal limits.[2] Purpura and bruising have been reported to be the commonest adverse blood effects associated with fluoxetine, paroxetine, or sertraline although cases of thrombocytopenia have been recorded for all three antidepressants.[3] The suggested mechanism was inhibition of uptake of serotonin into platelets, thereby disrupting platelet aggregation; caution was recommended when treating patients with a history of bleeding disorders with SSRIs. However, a subsequent cohort study based on prescription-event monitoring provided only weak evidence of a link between the use of SSRIs and the development of bleeding disorders.[4] A similar study[5] found no evidence of a major increased risk of intracranial haemorrhage with the use of SSRIs, although smaller increases in risk could not be ruled out.

For mention of a possibly increased risk of gastrointestinal bleeding, see Effects on the Gastrointestinal Tract, p. 422.1.

1. Alderman CP, *et al.* Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother* 1992; **26:** 1517–19.
2. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. *Ann Pharmacother* 1996; **30:** 786–8.
3. Anonymous. Bruising and bleeding with SSRIs. *Aust Adverse Drug React Bull* 1998; **17:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9808.pdf (accessed 14/08/08)
4. Layton D, *et al.* Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. *Eur J Clin Pharmacol* 2001; **57:** 167–76.
5. de Abajo FJ, *et al.* Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol* 2000; **50:** 43–7.

Effects on bone. A review of 9 epidemiological studies, mainly in patients aged 50 years or older, found an increased risk of fracture in those receiving SSRIs. However, no definite conclusions could be made about a dose-response relationship, time relationship, or the possible mechanism.[1]

1. MHRA/CHM. Antidepressants: risk of fractures. *Drug Safety Update* 2010; **3** (10): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON081866&RevisionSelectionMethod=LatestReleased (accessed 28/07/10)

Effects on the cardiovascular system. SSRIs are not usually associated with the same degree of cardiotoxicity as the tricyclic antidepressants (see p. 403.1), although orthostatic hypotension has been reported in some patients. A decrease in heart rate with ECG changes has been noted with fluvoxamine. However, a study[1] on long-term fluvoxamine treatment in 311 patients followed for 1 year revealed no significant effect on ECG findings compared with patients given placebo.

Concern over the use of sertraline in patients with coronary heart disease was raised after a report[2] of a 53-year-old man with a history of coronary heart disease who had attacks of sudden precordial chest pain on starting treatment with sertraline. The pain responded to glyceryl trinitrate. The manufacturers[3] pointed out that there had been no ECG changes confirming an ischaemic origin of the disorder in this patient and that in studies sertraline had had no demonstrable clinical effects on intraventricular conduction or ECG intervals. Furthermore, no significant changes in cardiovascular indices had been recorded in patients who had taken overdoses of up to 6 g of sertraline. It was suggested that this might have been an effect on the gastrointestinal tract possibly at the oesophageal level.

Citalopram has been associated with dose-dependent prolongation of the QT interval and torsade de pointes; for further details, see Adverse Effects, Treatment, and Precautions of Citalopram, p. 411.3.

1. Hochberg HM, *et al.* Electrocardiographic findings during extended clinical trials of fluvoxamine in depression: one years experience. *Pharmacopsychiatry* 1995; **28:** 253–6.
2. Iruela LM. Sudden chest pain with sertraline. *Lancet* 1994; **343:** 1106.
3. Berti CA, Doogan DP. Sudden chest pain with sertraline. *Lancet* 1994; **343:** 1510–11.

Effects on the cerebrovascular system. There have been rare reports of cerebral ischaemic events associated with the use of SSRIs. In one case[1] a 57-year-old man receiving long-term treatment for atrial fibrillation and hypercholesterolaemia presented with a facial droop and slurred speech 3 days after starting paroxetine 20 mg twice daily. Symptoms resolved after anticoagulant therapy and stopping paroxetine but recurred when paroxetine was reintroduced at a dose of 10 mg twice daily. Paroxetine was stopped and no further episodes had occurred within 4 months at follow-up.

For a report that there is no major increased risk of intracranial haemorrhage associated with the SSRIs, see Effects on the Blood, above.

1. Manos GH, Wechsler SM. Transient ischemic attack reported with paroxetine use. *Ann Pharmacother* 2004; **38:** 617–20.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion (SIADH)* with *hyponatraemia* has been reported in patients receiving antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant, and usually involved elderly patients.[1] However, the results of a later study[2] have suggested that cases are more likely to occur with serotonergic antidepressants such as the SSRIs, clomipramine, and venlafaxine. Case reports of hyponatraemia in 16 patients treated with SSRIs have been summarised.[3] A further review[4] of reports on 15 patients with hyponatraemia with SIADH induced by fluoxetine (12 cases), fluvoxamine (2 cases), and paroxetine (1 case) showed that the risk was greatest during the early treatment phase. This is borne out by single-case reports[5-12] of hyponatraemia with SIADH in elderly patients receiving either citalopram, paroxetine, or sertraline. A retrospective study[13] of hyponatraemia associated with either fluoxetine or paroxetine use also showed the early onset of the condition and identified low body-weight as being another risk factor for developing hyponatraemia. Not unexpectedly, replacing one SSRI with another has resulted in a recurrence of hyponatraemia; however, in one report,[14] the symptoms of hyponatraemia did not recur until about 16 months after switching SSRIs.

SSRI-associated *hyperprolactinaemia* has been reported.[15] Lactation and raised prolactin levels occurred in a teenager 3 days after fluoxetine was added to her existing therapy which included pimozide. Stopping fluoxetine had no effect on lactation, which only ceased after withdrawing pimozide. In another report,[16] hyperprolactinaemia and galactorrhoea in an elderly woman receiving fluoxetine resolved on stopping the drug.

Gynaecomastia, unrelated to prolactin concentrations, was associated with the start of fluoxetine therapy in a 49-year-old man. Symptoms subsided 10 months after withdrawing fluoxetine.[17]

Although SSRIs may be favoured for the management of depression in patients with diabetes, there is some evidence that sertraline and fluoxetine can induce *hypoglycaemia*.[18,19] Licensed product information for other SSRIs also warns of similar risks with these products.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?

IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Movig KLL, *et al*. Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly. *Eur J Clin Pharmacol* 2002; **58:** 143–8.
3. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
4. Canadian Medical Association. Hyponatraemia and selective serotonin reuptake inhibitors. *Can Med Assoc J* 1996; **154:** 63.
5. Bluff DD. SIADH in a patient receiving sertraline. *Ann Intern Med* 1995; **123:** 811.
6. Adverse Drug Reactions Advisory Committee. Selective serotonin reuptake inhibitors and SIADH. *Med J Aust* 1996; **164:** 562.
7. Kessler J, Samuels SC. Sertraline and hyponatremia. *N Engl J Med* 1996; **335:** 524.
8. Robinson D, *et al*. SIADH—compulsive drinking or SSRI influence? *Ann Pharmacother* 1996; **30:** 885.
9. Monmany J, *et al*. Syndrome of inappropriate secretion of antidiuretic hormone induced by paroxetine. *Arch Intern Med* 1999; **159:** 2089–90.
10. Odeh M, *et al*. Severe life-threatening hyponatremia during paroxetine therapy. *J Clin Pharmacol* 1999; **39:** 1290–1.
11. Barclay TS, Lee AJ. Citalopram-associated SIADH. *Ann Pharmacother* 2002; **36:** 1558–63.
12. Flores G, *et al*. Severe symptomatic hyponatremia during citalopram therapy–a case report. *BMC Nephrol* 2004; **5:** 2.
13. Wilkinson TJ, *et al*. Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 1999; **47:** 211–17.
14. Arinzon ZH, *et al*. Delayed recurrent SIADH associated with SSRIs. *Ann Pharmacother* 2002; **36:** 1175–7.
15. Arya DK, *et al*. Lactation associated with fluoxetine treatment. *Aust N Z J Psychiatry* 1995; **29:** 697.
16. Peterson MC. Reversible galactorrhea and prolactin elevation related to fluoxetine use. *Mayo Clin Proc* 2001; **76:** 215–16.
17. Sahin M, *et al*. A possible case of gynecomastia with fluoxetine. *Ann Pharmacother* 2005; **39:** 1369.
18. Deeg MA, Lipkin EW. Hypoglycemia associated with the use of fluoxetine. *West J Med* 1996; **164:** 262–3.
19. Pollak PT, *et al*. Sertraline-induced hypoglycemia. *Ann Pharmacother* 2001; **35:** 1371–4.

Effects on the eyes. Symptoms of glaucoma that developed in a patient receiving fluoxetine subsided within 2 days of drug withdrawal.[1] Similar symptoms have been reported with citalopram,[2] fluvoxamine,[3] paroxetine,[2,4] and sertraline.[2] In some cases, the SSRI may have aggravated pre-existing glaucoma.[2,3] Intra-ocular pressure after oral doses of fluoxetine was recorded in 20 patients in a placebo-controlled crossover double-blind study.[5] Significant increases were found in all patients 2 hours after receiving fluoxetine; some patients still had raised intraocular pressure after 8 hours. A review of case reports documenting SSRI-associated changes in intra-ocular pressure concluded that such changes were difficult to predict;[6] however, it was recommended that those with risk factors for glaucoma, such as elderly patients with a family history, should be considered for ophthalmic consultations before starting an SSRI and regularly throughout treatment.

Anisocoria (uneven pupillary dilatation) has been reported[7] in a patient taking paroxetine and in another taking sertraline. It was noted that the UK CSM had received 21 reports of mydriasis associated with paroxetine but it appeared that noticeably asymmetrical mydriasis as seen in these 2 patients had not previously been reported.

1. Ahmad S. Fluoxetine and glaucoma. *DICP Ann Pharmacother* 1991; **25:** 436.
2. Anonymous. SSRIs and increased intraocular pressure. *Aust Adverse Drug React Bull* 2001; **20:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0102.pdf (accessed 14/08/08)
3. Jiménez-Jiménez FJ, *et al*. Aggravation of glaucoma with fluvoxamine. *Ann Pharmacother* 2001; **35:** 1565–6.
4. Eke T, Carr S. Acute glaucoma, chronic glaucoma, and serotoninergic drugs. *Br J Ophthalmol* 1998; **82:** 976–7.
5. Costagliola C, *et al*. Fluoxetine oral administration increases intraocular pressure. *Br J Ophthalmol* 1996; **80:** 678.
6. Costagliola C, *et al*. SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs* 2004; **18:** 475–84.
7. Barrett J. Anisocoria associated with selective serotonin reuptake inhibitors. *BMJ* 1994; **309:** 1620.

Effects on the gastrointestinal tract. A case-control study[1] suggested that treatment with SSRIs produced a moderately increased risk of upper gastrointestinal bleeding (adjusted relative risk 3.0). The risk was greatly increased if SSRIs were given with NSAIDs (relative risk 15.6). Treatment with SSRIs did not appear to increase the risk of ulcer perforation. The absolute risk of bleeding was estimated at one case per 8000 prescriptions, a risk similar to that of low-dose ibuprofen. A more recent cohort study[2] found a similar increase in risk. However, others have questioned whether such an association exists.[3]

A retrospective cohort study[4] in *elderly* patients found that there was an increasing risk of upper gastrointestinal bleeding as the extent of inhibition of serotonin reuptake by the antidepressant used increased. The effect was considered to be clinically important for patients with a high risk of such bleeding, namely the very elderly and those with a history of previous upper gastrointestinal bleeding.

Some[5] consider that gastroprotection is unlikely to be justified in those given SSRIs alone and furthermore there are no studies to suggest that gastroprotective drugs reduce the risk of SSRI-associated haemorrhage. However, it has been recommended[5] that such protection should be considered when SSRIs and NSAIDs are used together because of the increased risk.

1. de Abajo FJ, *et al*. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999; **319:** 1106–9.
2. Dalton SO, *et al*. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003; **163:** 59–64.
3. Dunn NR, *et al*. Association between SSRIs and upper gastrointestinal bleeding. *BMJ* 2000; **320:** 1405–6.
4. van Walraven C, *et al*. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001; **323:** 655–8.
5. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. *BMJ* 2005; **331:** 529–30.

Effects on the hair. A report[1] on 2 patients who had hair loss associated with the use of fluoxetine noted 4 other published cases and stated that, up to the end of 1991, the US manufacturers had received 498 reports of fluoxetine-associated alopecia.

1. Ogilvie AD. Hair loss during fluoxetine treatment. *Lancet* 1993; **342:** 1423.

Effects on the liver. Acute hepatitis occurred in 2 patients after several months of fluoxetine treatment;[1] it was noted that 5 other cases of acute hepatitis with fluoxetine had been reported.

Abnormal liver function tests were seen in a patient after a suicide attempt with sertraline and cefalexin.[2] The patient was then started on venlafaxine but, again abnormal liver function tests were noted. When these abnormal values had decreased, sertraline was restarted at therapeutic doses, with a subsequent increase in liver function tests. Values returned to normal once all medications were stopped. Auto-immune hepatitis has been reported after therapeutic doses of sertraline;[3] rechallenge in this case was also positive.

Hepatotoxicity has also been rarely associated with citalopram[4] and with paroxetine use.[5]

1. Cai Q, *et al*. Acute hepatitis due to fluoxetine therapy. *Mayo Clin Proc* 1999; **74:** 692–4.
2. Kim KY, *et al*. Acute liver damage possibly related to sertraline and venlafaxine ingestion. *Ann Pharmacother* 1999; **33:** 381–2.
3. Persky S, Reinus JF. Sertraline hepatotoxicity: a case report and review of the literature on selective serotonin reuptake inhibitor hepatotoxicity. *Dig Dis Sci* 2003; **48:** 939–44.
4. López-Torres E, *et al*. Hepatotoxicity related to citalopram. *Am J Psychiatry* 2004; **161:** 923–4.
5. Azaz-Livshits T, *et al*. Paroxetine associated hepatotoxicity: a report of 3 cases and a review of the literature. *Pharmacopsychiatry* 2002; **35:** 112–15.

Effects on mental state. As early as 1990 there was concern that the SSRIs increased the risk of *suicidal ideation* after the publication of a case series of such events with fluoxetine.[1] Meta-analyses[2,3] performed around that time (criticism of statistical power notwithstanding[4]) did not confirm an increased risk and this was supported by the results of prescription-event monitoring.[5] Nevertheless, reports of suicidal ideation as well as suicide and self-harm have continued to be published for the SSRIs and the issue remains controversial. A subsequent meta-analysis[6] of 702 randomised controlled studies found an increased risk for attempted suicide in those taking SSRIs when compared with placebo but not when compared with tricyclic antidepressants.

Risk analysis of suicidal behaviour with any antidepressant is confounded by the rarity of suicide even in patients with depression, and by the possibility that such behaviour is a manifestation of the underlying disease. Furthermore, the more favourable safety profile of the SSRIs, particularly in overdosage (see Depression, p. 398.1), when compared with the older MAOIs and tricyclic antidepressants may have resulted in the SSRIs being prescribed to those patients at greater risk of suicidal behaviour.

In 2003, the UK CSM established an Expert Working Group to address increasing public concerns regarding the safety of the SSRIs. The serotonergic antidepressants venlafaxine and mirtazapine were also included and the conclusions given below also apply to these drugs. In its final report[7] issued in December 2004, the Working Group concluded that the risk of suicide may increase in the early stages of treatment for depression in **adults** and consequently careful and frequent monitoring is important, particularly if a patient has worsening of symptoms or new symptoms after starting therapy. However, the Working Group noted that increases in the prescribing of SSRIs have not been associated with an increase in suicide rates, although they acknowledged that the interpretation of these findings was difficult. They could not rule out that there might be a modest increase in the risk of suicidal ideation and self-harm with the SSRIs when compared with placebo. However, there was insufficient evidence from clinical studies to determine any differences between the SSRIs as a group, or between the SSRIs and other antidepressants regarding the risk of suicidal behaviour; evidence from the General Practice Research database has suggested that there is no increased risk of such behaviour with the SSRIs when compared with the tricyclic antidepressants. The Working Group also concluded that the evidence for a relationship between suicidal behaviour and a change in dose was not robust; however, patients should be monitored for any new symptoms or worsening of disease around the time of any dose change.

The Expert Working Group of the CSM has also commented[7] on the use of SSRIs in **young adults**. They concluded that although there was no clear evidence of an increased risk of self-harm or suicidal thoughts in young adults of 18 years or over, such patients have a higher background risk of suicidal behaviour than older adults and consequently those treated with SSRIs should be closely monitored. Furthermore, the results of a meta-analysis undertaken by the FDA found that although the overall risk of suicide was not increased in adult patients receiving antidepressants, there was a non-significant trend toward increased risk with younger age. The FDA considered the trend sufficiently convincing to warn that, like children and adolescents, young adults aged between 18 and 24 years treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[8]

In 2003 the CSM recommended (on the basis of their Expert Working Group's finding) that paroxetine should not be used to treat depressive illness in **children under 18 years old**. Data from studies received by CSM in May 2003 failed to show that paroxetine was effective in depressive illness in this age group and indicated that the risk of harmful outcome, including self-harm and potentially suicidal behaviour, was 1.5 to 3.2 times greater in those given paroxetine when compared with placebo.[9] Following a further review,[10] the CSM extended their recommendation to include the SSRIs citalopram, escitalopram, and sertraline; subsequent analysis had also associated these antidepressants with an unfavourable risk to benefit ratio in the treatment of depression in children under 18. The CSM also included fluvoxamine in their recommendation as its risk to benefit ratio was unassessable. Fluoxetine was not included and the CSM acknowledged that clinical studies had shown a favourable risk to benefit ratio for fluoxetine in the treatment of depression in young patients. The European Medicines Agency (EMEA) has also recommended that serotonergic antidepressants, including the SSRIs, should not be used in children and adolescents except within their approved indications,[11] but considered[12] that studies with fluoxetine in children and adolescents have shown a positive effect that outweighs any potential risks, and recommended that it should be licensed for use where needed, as an adjunct to psychological therapies in children from 8 years of age. Nevertheless, it is recognised that specialists may decide to use these drugs according to clinical need and, although unlicensed, guidelines issued by NICE suggest that citalopram and sertraline may be given for the treatment of depression in those aged 12 years and over (for further details, see Depression, p. 398.1).

The FDA has not issued advice contra-indicating the use of these antidepressants in those under 18 years old in the USA, although they have stressed that all patients, including adolescents and children, should be closely monitored for worsening depression or suicidal behaviour, especially at the beginning of treatment. Apart from escitalopram and fluoxetine, the SSRIs are not licensed in the USA for the treatment of depression in young patients.

The use of SSRIs has been associated with the development of *akathisia*, *restlessness*, and *psychomotor agitation* such as an inability to sit or stand still, particularly in the first few weeks of treatment.[13] In some patients these symptoms have precipitated suicidal behaviour. However, the Expert Working Group of the CSM considered that it was not possible to draw any conclusions on the link between the development of these symptoms and the risk of suicidal behaviour, as such data were not included in the majority of cases.[7]

There have been suggested links between the use of fluoxetine and *irritability, hostility, and aggression*.[14] However, one review[15] noted that an unpublished analysis had indicated that patients taking fluoxetine for a variety of disorders were not more likely to be aggressive than those taking placebo. Prescription-event monitoring has also found no evidence to suggest that fluoxetine increases the frequency of aggression.[5]

Initiation of antidepressant therapy with paroxetine or sertraline has been associated with either worsening or a new onset of *flashback syndrome* in 2 patients with a history of lysergide abuse.[16]

There have been isolated reports of *memory loss* associated with the use of SSRIs.[17]

For further effects on mental function, see also under Withdrawal (p. 425.3) and under Mania in Precautions, p. 425.1.

1. Teicher MH, *et al*. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990; **147:** 207–10.
2. Beasley CM, *et al*. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991; **303:** 685–92. Correction. *ibid.*; 968.

3. Goldstein DJ, *et al.* Analyses of suicidality in double-blind, placebo-controlled trials of pharmacotherapy for weight reduction. *J Clin Psychiatry* 1993; **54:** 309–16.
4. Li Wan Po A. Fluoxetine and suicide: meta-analysis and Monte-Carlo simulations. *Pharmacoepidemiol Drug Safety* 1993; **2:** 79–84.
5. Nakielny J. Fluoxetine and suicide. *Lancet* 1994; **343:** 1359.
6. Fergusson D, *et al.* Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; **330:** 396. Correction. *ibid.*; 653.
7. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
8. Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; **356:** 2343–6.
9. MHRA. Safety of Seroxat (paroxetine) in children and adolescents under 18 years - contraindication in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th June, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019507.pdf (accessed 14/08/08)
10. MHRA. Selective Serotonin Reuptake Inhibitors - use in children and adolescents with major depressive disorder. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th December, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019492.pdf (accessed 08/09/10)
11. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf (accessed 29/07/10)
12. Committee for Medicinal Products for Human Use, European Medicines Agency. European Medicines Agency adopts a positive opinion for the use of Prozac in the treatment of children and adolescents suffering from depression (issued 6th June, 2006). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/12/WC500017468.pdf (accessed 29/07/10)
13. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998; **12:** 192–214.
14. Anonymous. Fluoxetine, suicide and aggression. *Drug Ther Bull* 1992; **30**: 5–6.
15. Power AC, Cowen PJ. Fluoxetine and suicidal behaviour; some clinical and theoretical aspects of a controversy. *Br J Psychiatry* 1992; **161:** 735–41.
16. Markel H, *et al.* LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *J Pediatr* 1994; **125:** 817–19.
17. Joss JD, *et al.* Memory loss in a patient treated with fluoxetine. *Ann Pharmacother* 2003; **37:** 1800–3.

Effects on sexual function. Sexual dysfunction is often noted in patients with depression and may be due to their antidepressant medication or to the disease itself. Complaints include a decrease in or loss of libido, delayed ejaculation, erectile difficulty, or anorgasmia in men;[1] loss of libido, delayed orgasm, or anorgasmia have been reported in women.[1,2] Early identification is important since drug-induced sexual dysfunction is a common cause of non-compliance; in addition, it may adversely affect the quality of life of patients and hamper their recovery.[3,4]

It has been considered that sexual dysfunction occurs in up to 1.9% of patients taking fluoxetine, with impotence or ejaculatory problems occurring in less than 1% of patients.[5] However, these figures, which were based on information supplied by the US manufacturer, have been disputed[6,7] and the incidence of sexual dysfunction may be higher than the manufacturer's data suggest. Earlier studies and anecdotal reports quoted rates of 7.8 to 75% for sexual dysfunction with fluoxetine but it appears that only small numbers of men were studied.[8] A later review[9] also estimated the incidence of SSRI-induced sexual dysfunction at between 10 and 75%.

The incidence of sexual dysfunction may differ between types of antidepressants. A large, observational study[3] found the rate of sexual dysfunction to be higher with the SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) and the SNRI venlafaxine than with bupropion or nefazodone. However, no significant difference in rate was found among the SSRIs as a group. The study also identified other risk factors for developing sexual dysfunction which included increasing age, the use of high doses, and use with other medications. Gender, race, and length of treatment were not associated with an increased risk.

Suggested[1,4,10] strategies for managing SSRI-induced sexual dysfunction include reducing the dosage of the SSRI or altering the timing of doses, or changing to another antidepressant. In some cases tolerance may develop, particularly if the dysfunction occurred early in treatment. One small study[11] has indicated that spontaneous improvement may occur even up to 6 months after the start of therapy.[11] Evidence of efficacy for drug treatments is mainly anecdotal. Cyproheptadine seems to have been tried most often, but the SSRI may become less effective (see Antihistamines, under Interactions, p. 426.2) and patients should be monitored for worsening symptoms of depression.

The effects of the SSRIs on sexual function have been studied as a potential form of treatment for men with premature ejaculation (see Sexual Dysfunction in Uses, p. 419.1).

1. Frye CB, Berger JE. Treatment of sexual dysfunction induced by selective serotonin-reuptake inhibitors. *Am J Health-Syst Pharm* 1998; **55:** 1167–9.
2. Feiger A, *et al.* Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996; **57** (suppl 2): 53–62.
3. Clayton AH, *et al.* Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002; **63:** 357–66.
4. Hirschfeld RMA. Long-term side effects of SSRIs: sexual dysfunction and weight gain. *J Clin Psychiatry* 2003; **64** (suppl 18): 20–4.
5. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1994; **272:** 242.
6. Balon R. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1489.
7. Hopkins HS, Gelenberg AJ. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1489–90.
8. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1490.
9. Gregorian RS, *et al.* Antidepressant-induced sexual dysfunction. *Ann Pharmacother* 2002; **36:** 1577–89.
10. Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacother* 1998; **32:** 1209–15.
11. Haberfellner EM, Rittmannsberger H. Spontaneous remission of SSRI-induced orgasm delay. *Pharmacopsychiatry* 2004; **37:** 127–30.

Effects on the skin. *Toxic epidermal necrolysis* developed in a 16-year-old girl 8 days after beginning fluvoxamine therapy.[1] Other drugs, which included metoclopramide, clorazepate, and clomipramine were discounted as possible causes.

Amitriptyline and fluoxetine have been implicated in the development of *atypical cutaneous lymphoid hyperplasia* in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[2] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to the improvement.

Bullous pemphigoid induced by fluoxetine has been reported in a 75-year-old woman.[3] Spontaneous resolution followed within 3 weeks of stopping the drug.

Paroxetine treatment has been associated with the development of *cutaneous vasculitis*, which involved several fingers, in a 20-year-old woman;[4] rechallenge was positive. On both occasions the patient recovered when paroxetine was withdrawn.

A severe *bullous reaction with full-thickness skin necrosis* has been reported in a 48-year-old woman after 6 months of treatment with sertraline.[5] The lesions required extensive skin grafts and recovery was prolonged, with drug-induced scleroderma developing in the affected area.

1. Wolkenstein P, *et al.* Toxic epidermal necrolysis after fluvoxamine. *Lancet* 1993; **342:** 304–5.
2. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131:** 925–9.
3. Rault S, *et al.* Bullous pemphigoid induced by fluoxetine. *Br J Dermatol* 1999; **141:** 755–6.
4. Margolese HC, *et al.* Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry* 2001; **158:** 497.
5. Kirkup ME, *et al.* Delayed onset of bullous reaction with severe deep skin necrosis in association with sertraline. *Br J Dermatol* 2004; **150:** 164–6.

Epileptogenic effect. Generalised seizures have been reported in 2 patients with no history of seizures after starting fluoxetine therapy.[1,2] Although convulsions have been noted in patients taking fluvoxamine (see Incidence of Adverse Effects, p. 428.1), a small clinical study involving 35 depressed epileptic patients[3] found no change in the number of seizures or in their nature when fluvoxamine was given in doses of up to 200 mg daily.

1. Weber JJ. Seizure activity associated with fluoxetine therapy. *Clin Pharm* 1989; **8:** 296–8.
2. Ware MR, Stewart RB. Seizures associated with fluoxetine therapy. *DICP Ann Pharmacother* 1989; **23:** 428.
3. Harmant J, *et al.* Fluvoxamine: an antidepressant with low (or no) epileptogenic effect. *Lancet* 1990; **336:** 386.

Extrapyramidal effects. Extrapyramidal effects, such as tics[1] and akathisia,[2,3] have been reported with fluoxetine. By 1993, the UK CSM had received 39 reports of extrapyramidal reactions with paroxetine including 15 of dystonia of the face and mouth.[4] Although extrapyramidal effects might occur with other SSRIs, orofacial dystonias appeared to be more common with paroxetine. However, evidence from monitoring prescriptions within the UK showed that the overall incidence of extrapyramidal effects was the same for paroxetine as for other SSRIs.[5] Orofacial dystonias (teeth clenching) or dyskinesias (teeth grinding), resulting in severe damage to teeth and gums in many cases, have been reported[6] in 6 patients receiving fluoxetine, fluvoxamine, paroxetine, or sertraline. The authors concluded that these adverse effects were not specific for any particular SSRI. Analysis of spontaneous adverse reaction reports received by the national pharmacovigilance centre in The Netherlands found that there had been 41 reports of extrapyramidal effects associated with the SSRIs over a period of nearly 15 years;[7] parkinsonism and dystonia were the most frequently reported effects. Over the same time period, 14 reports had been received in total for other antidepressants. The authors commented that the results might be biased by the selective reporting of adverse reactions to the SSRIs.

Dyskinesia associated with withdrawal of citalopram and risperidone has been reported in a patient.[8]

The onset of akathisia may be linked to suicidal ideation; for further details, see Effects on Mental State, p. 420.2.

1. Eisenhauer G, Jermain DM. Fluoxetine and tics in an adolescent. *Ann Pharmacother* 1993; **27:** 725–6.
2. Lipinski JF, *et al.* Fluoxetine-induced akathisia: clinical and theoretical implications. *J Clin Psychiatry* 1989; **50:** 339–42.
3. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry* 1991; **52:** 491–3.
4. CSM/MCA. Dystonia and withdrawal symptoms with paroxetine (Seroxat). *Current Problems* 1993; **19:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Choo V. Paroxetine and extrapyramidal reactions. *Lancet* 1993; **341:** 624.
6. Fitzgerald K, Healy D. Dystonias and dyskinesias of the jaw associated with the use of SSRIs. *Hum Psychopharmacol Clin Exp* 1995; **10:** 215–19.
7. Schillevoort I, *et al.* Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case-control study using spontaneous reports. *Int Clin Psychopharmacol* 2002; **17:** 75–9.
8. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; **34:** 269.

Hypersensitivity. Hypersensitivity reactions to SSRIs are well documented. Interestingly, despite structural dissimilarities, there have been a few reports of cross-sensitivity between SSRIs. A young man who had previously developed a maculopapular rash while taking paroxetine suffered a similar reaction after starting sertraline;[1] both episodes resolved after the SSRI was withdrawn.

1. Warnock CA, Azadian AG. Cross-sensitivity between paroxetine and sertraline. *Ann Pharmacother* 2002; **36:** 631–3.

Hyponatraemia. See Effects on the Endocrine System, p. 419.3.

Overdosage. SSRIs are generally regarded as being less toxic in overdosage than tricyclic antidepressants or MAOIs. A review[1] of SSRI overdosage, covering the period 1985 to 1997, noted that there had been remarkably few fatal overdoses when taken alone. Moderate overdoses (up to about 30 times the usual daily dose) were generally associated with minor symptoms at most; only at very high doses (more than 75 times the usual daily dose) did more serious effects such as seizures, ECG abnormalities, and decreased consciousness tend to occur. Toxicity was greatly increased, however, when overdoses of SSRIs were taken with alcohol or other drugs. There was no evidence of a difference in the various SSRIs with respect to safety in overdosage. The results of a more recent cohort study[2] have also confirmed the relative safety of the SSRIs in overdosage. However, the study also found that citalopram was potentially more cardiotoxic than other SSRIs in overdose, causing significant prolongation of the QT interval (see below). In addition, serotonin syndrome was noted as being a common feature of SSRI overdosage although in most cases symptoms were not severe or life-threatening.

- Fatal overdose was reported with *citalopram* in 6 patients,[3] although the suggested cause of death as cardiac dysfunction rather than seizures was disputed.[4] Nonetheless, cases[2,5] of cardiac abnormalities (including prolongation of the QT interval) associated with citalopram overdose have continued to be reported, and routine ECG monitoring may be necessary in the management of overdosage. Some authors consider that a metabolite, didemethylcitalopram, rather than citalopram itself, may be responsible for the cardiotoxicity seen with citalopram overdose.[5] At therapeutic doses, concentrations of didemethylcitalopram are much lower than those of citalopram and, in general, significant cardiotoxicity is not seen; however, in overdosage the amount of didemethylcitalopram may be sufficient to induce cardiac conduction abnormalities.
- A report involving 87 cases in which *fluoxetine* was taken in overdosage without other drugs found that the main symptoms were tachycardia, drowsiness, tremor, and nausea and vomiting.[6] These were considered relatively minor, and were of short duration, and supportive care was considered to be the only intervention necessary.
- Of 41 cases of self-poisoning with *fluvoxamine*, only one patient died and even here fluvoxamine was not implicated.[7] Prolonged cerebral depression occurred in a patient after fluvoxamine overdose,[7] but this may have been due to an interaction with temazepam which the patient also took in overdose.
- One hour after taking 2 g of *sertraline* in a suicide attempt a 42-year-old woman was flushed, angry, emotionally labile, and easily distracted but not psychotic.[8] Apart from watery bowel movements recovery was mainly uneventful after treatment with gastric lavage, oral activated charcoal with sorbitol, and intravenous hydration. In another case,[9] symptoms resembling serotonin syndrome developed in a 51-year-old woman after an overdose attempt with sertraline; it was believed that the patient may have taken as much as 8 g of sertraline. She recovered with supportive treatment. Abnormal liver function tests have also been noted after

a suicide attempt with sertraline (see Effects on the Liver, p. 420.2).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p. 398.1.

1. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry* 1998; **59** (suppl 15): 42–8.
2. Isbister GK, *et al.* Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; **42:** 277–85.
3. Öström M, *et al.* Fatal overdose with citalopram. *Lancet* 1996; **348:** 339–40.
4. Brion F, *et al.* Fatal overdose with citalopram? *Lancet* 1996; **348:** 1380.
5. Catalano G, *et al.* QTc interval prolongation associated with citalopram overdose: a case report and literature review. *Clin Neuropharmacol* 2001; **24:** 158–62.
6. Borys DJ, *et al.* Acute fluoxetine overdose: a report of 234 cases. *Am J Emerg Med* 1992; **10:** 115–20.
7. Banerjee AK. Recovery from prolonged cerebral depression after fluvoxamine overdose. *BMJ* 1988; **296:** 1774.
8. Brown DF, Kerr HD. Sertraline overdose. *Ann Pharmacother* 1994; **28:** 1307.
9. Brendel DH, *et al.* Massive sertraline overdose. *Ann Emerg Med* 2000; **36:** 524–6.

Treatment of Adverse Effects

Treatment of overdosage with an SSRI involves appropriate symptomatic and supportive therapy. Activated charcoal may be given orally if the amount ingested was large (see p. 424.1) and treatment is within an hour of ingestion, provided the airway can be protected. Dialysis, haemoperfusion, exchange transfusion, and measures to increase urine production are considered unlikely to be of benefit.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with SSRIs to be uncertain. However, it is suggested that oral activated charcoal may be considered in adults and children if this is given within 1 hour of ingestion and the quantity of SSRI exceeds the following amount, provided that the airway can be protected:

- citalopram: 2 mg/kg
- escitalopram: 1 mg/kg
- fluoxetine: 6 mg/kg
- fluvoxamine maleate: 15 mg/kg
- paroxetine: 3 mg/kg
- sertraline: 7 mg/kg

Precautions

Because of their epileptogenic effect SSRIs should be used with caution in patients with epilepsy or a history of such disorders (and should be avoided if the epilepsy is poorly controlled). Treatment should be stopped if seizures develop or when there is an increase in seizure frequency. Care is advised in patients receiving ECT as prolonged seizures have occurred rarely. SSRIs should also be used with caution in patients with cardiac disease or a history of bleeding disorders. Although SSRIs are preferred to tricyclics for the treatment of depression in patients with diabetes, they may alter glycaemic control and therefore caution is also warranted in diabetic subjects. SSRIs should be used with caution in patients with angle-closure glaucoma.

Fluoxetine should be stopped in patients who develop a rash since systemic effects, possibly related to vasculitis, have occurred in such patients. Fluoxetine undergoes hepatic metabolism and should be used with caution and in reduced doses in patients with impaired hepatic function.

Patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. For a discussion of the concern that SSRIs may increase suicidal ideation, and concerns about their use for depression in children and adolescents, see Effects on Mental State in Adverse Effects, p. 420.2. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders. If SSRIs are given for the depressive component of bipolar disorder, mania may be precipitated. Symptoms may also worsen during the initial treatment of panic disorder with SSRIs.

SSRIs may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Some licensed product information recommends reduced or less frequent dosage of SSRIs for elderly patients.

SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms although this may be unnecessary for fluoxetine because of its long half-life.

Abuse. There have been occasional reports of individuals abusing fluoxetine.[1,2]

1. Pagliaro LA, Pagliaro AM. Fluoxetine abuse by an intravenous drug user. *Am J Psychiatry* 1993; **150:** 1898.
2. Tinsley JA, *et al.* Fluoxetine abuse. *Mayo Clin Proc* 1994; **69:** 166–8.

Blood disorders. For a reference recommending cautious use of SSRIs in patients with a history of bleeding disorders, see Effects on the Blood in Adverse Effects, p. 419.2.

Breast feeding. The American Academy of Pediatrics[1] considers that the effect of all antidepressants, including SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) on nursing infants is unknown but may be of concern. In addition, most licensed product information advises that SSRIs should be avoided by women during breast feeding.

- *Citalopram* and its metabolites have been detected in breast milk; however, in one study, the plasma concentrations in exposed infants were either very low or undetectable and no adverse effects were reported.[2] In another study, 3 out of 31 breast-fed infants whose mothers were taking citalopram had adverse effects, specifically one case each of colic, decreased feeding, and irritability.[3] However, there was no significant increase in the risk of adverse events in this group of infants when compared with either infants of depressed mothers not taking citalopram, or infants of healthy controls.
- Symptoms of colic were reported[4] in a 6-week-old infant whose mother was taking *fluoxetine* 20 mg daily. The concentrations of fluoxetine and its active metabolite norfluoxetine were 69 nanograms/mL and 90 nanograms/mL respectively in breast milk, and 340 nanograms/mL and 208 nanograms/mL respectively in the infant's plasma. The infant's symptoms resolved when he was formula fed. Post-natal weight gain has been reduced in infants exposed to fluoxetine during breast feeding, although in all cases the reduction was less than 2 standard deviations below the norm.[5] In another report,[6] several seizure-like episodes occurred in a breast-fed infant whose mother was taking fluoxetine in addition to carbamazepine and buspirone; however, plasma drug concentrations in the infant were significant only for fluoxetine and norfluoxetine. In a study[7] of 10 women taking fluoxetine while breast feeding 11 infants, breast milk concentrations of fluoxetine ranged from 17.4 to 293 nanograms/mL and of norfluoxetine from 23.4 to 379.1 nanograms/mL. No adverse effects were noted in the infants. Similar concentrations have occurred in other breast-fed infants without any apparent drug-induced adverse effects.[8-10] Fluoxetine and norfluoxetine were detected in the milk of 14 nursing women.[11] Blood samples were taken from 9 of the infants in the study, and of these, fluoxetine was detected in the plasma of 5 and norfluoxetine in 7. Although it was felt that many infants would tolerate the mean combined dose of fluoxetine and norfluoxetine transmitted via breast milk in this study, there was considerable interpatient variability in estimated infant dose and caution should be exercised; neonates in particular had higher concentrations of norfluoxetine than older infants. Moreover, since both fluoxetine and norfluoxetine have long half-lives, neonates already exposed *in utero* may have an additional risk of adverse effects during breast feeding.
- The excretion of *fluvoxamine* into breast milk was studied[12] in a woman who had been receiving fluvoxamine maleate 100 mg twice daily for 2 weeks. The concentration of fluvoxamine base 4.75 hours after a dose was 310 nanograms/mL in maternal plasma and 90 nanograms/mL in breast milk. It was estimated that an infant would ingest only 0.5% of the daily maternal intake. It was considered that these data supported the notion that the use of fluvoxamine by nursing mothers posed little risk to the infant. A subsequent study[13] found no detectable drug concentrations in the plasma of breast-fed infants exposed to fluvoxamine; the authors suggested that fluvoxamine was a reasonable choice for nursing mothers requiring treatment for depression.
- Although *paroxetine* was detected in measurable concentrations in the breast milk of a group of 10 nursing mothers receiving paroxetine no adverse effects were reported in any of their breast-fed infants.[14] Paroxetine could not be detected in the plasma of 7 of the 8 infants from whom samples were obtained and in the other infant, concentrations were not quantifiable. Another study involving 7 women suggested that the dose of paroxetine to suckling infants would be 0.7 to 2.9% of the weight-adjusted maternal dose.[15] A later study[13] also found no detectable drug concentrations in the plasma of breast-fed infants exposed to paroxetine; the authors suggested that paroxetine was a reasonable choice for nursing mothers requiring treatment for depression. In a prospective cohort study, weight gain at 6 and 12 months of age in infants whose mothers took paroxetine during breast feeding was not adversely affected when compared with the infants of mothers who either did not breast feed or breast fed without taking any drugs during lactation;[16] in addition, there was no difference in reaching the usual developmental milestones between the infants of the 3 groups.
- Plasma concentrations of *sertraline* were undetectable in a breast-fed infant despite the presence of concentrations in the mother's breast milk ranging from 8.8 to 43 nanograms/mL over a 24-hour period.[17] However, the authors pointed out that metabolite concentrations were not measured and that sertraline may have been present in the infant at a concentration below the level of sensitivity of the assay. Other studies[13,18-21] have found desmethylsertraline in breast milk, which was also detected in the plasma of some of the infants in several studies[13,18,20,21] but not all.[19] The authors of at least one study[13] suggested that sertraline was a reasonable choice for nursing mothers requiring treatment for depression. In addition, some authors recommend expressing and discarding breast milk 8 to 9 hours after a maternal dose, when levels of desmethylsertraline and sertraline are maximal, in order to significantly reduce infant exposure to sertraline.[21]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Heikkinen T, *et al.* Citalopram in pregnancy and lactation. *Clin Pharmacol Ther* 2002; **72:** 184–91.
3. Lee A, *et al.* Frequency of infant adverse events that are associated with citalopram use during breast-feeding. *Am J Obstet Gynecol* 2004; **190:** 218–21.
4. Lester BM, *et al.* Possible association between fluoxetine hydrochloride and colic in an infant. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1253–5.
5. Chambers CD, *et al.* Weight gain in infants breastfed by mothers who take fluoxetine. *Pediatrics* 1999; **104:** 1120–1.
6. Brent NB, Wisner KL. Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. *Clin Pediatr (Phila)* 1998; **37:** 41–4.
7. Taddio A, *et al.* Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 1996; **36:** 42–7.
8. Isenberg KE. Excretion of fluoxetine in human breast milk. *J Clin Psychiatry* 1990; **51:** 169.
9. Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics* 1992; **89:** 676–7.
10. Yoshida K, *et al.* Fluoxetine in breast-milk and developmental outcome of breast-fed infants. *Br J Psychiatry* 1998; **172:** 175–9.
11. Kristensen JH, *et al.* Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol* 1999; **48:** 521–7.
12. Wright S, *et al.* Excretion of fluvoxamine in breast milk. *Br J Clin Pharmacol* 1991; **31:** 209.
13. Hendrick V, *et al.* Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry* 2001; **179:** 163–6.
14. Begg EJ, *et al.* Paroxetine in human milk. *Br J Clin Pharmacol* 1999; **48:** 142–7.
15. Öhman R, *et al.* Excretion of paroxetine into breast milk. *J Clin Psychiatry* 1999; **60:** 519–23.
16. Merlob P, *et al.* Paroxetine during breast-feeding: infant weight gain and maternal adherence to counsel. *Eur J Pediatr* 2004; **163:** 135–9.
17. Altshuler LL, *et al.* Breastfeeding and sertraline: a 24-houranalysis. *J Clin Psychiatry* 1995; **56:** 243–5.
18. Stowe ZN, *et al.* Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiatry* 1997; **154:** 1255–60.
19. Kristensen JH, *et al.* Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br J Clin Pharmacol* 1998; **45:** 453–7.
20. Epperson N, *et al.* Maternal sertraline treatment and serotonin transport in breast-feeding mother-infantpairs. *Am J Psychiatry* 2001; **158:** 1631–7.
21. Stowe ZN, *et al.* The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry* 2003; **64:** 73–80.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, p. 420.2.

Diabetes mellitus. A patient with type 1 diabetes mellitus lost hypoglycaemic awareness after starting therapy with fluoxetine.[1] Awareness returned on tapered withdrawal of fluoxetine. Changes in blood sugar concentrations may occur in patients with diabetes treated for depression with SSRIs (see also Effects on the Endocrine System, p. 419.3); however, these may represent an improvement in glycaemic control.[2]

1. Sawka AM, *et al.* Loss of hypoglycemia awareness in an adolescent with type 1 diabetes mellitus during treatment with fluoxetine hydrochloride. *J Pediatr* 2000; **136:** 394–6.
2. Lustman PJ, *et al.* Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000; **23:** 618–23.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressants can also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects. These are more pronounced with older antidepressants such as the tricyclic antidepressants than with the SSRIs, but a comparative study[3] of fluoxetine (an SSRI) and dosulepin (a tricyclic) in healthy subjects showed a similar but apparently small potential for impairing psychomotor and driving performance. A later epidemiological study[4] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs.

In the UK, the Driver and Vehicle Licensing Authority (DVLA)[5] considers that drugs such as SSRIs may have fewer adverse effects on drivers than antidepressants with pronounced antimuscarinic or antihistaminic adverse

effects, such as tricyclic antidepressants. However, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should also cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
3. Ramaekers JG, *et al*. A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; **39:** 397–404.
4. Barbone F, *et al*. Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

Gastrointestinal disorders. For the opinion that the SSRIs may produce a clinically important increase in the risk of upper gastrointestinal bleeding in patients with a high risk of such bleeding, see under Effects on the Gastrointestinal Tract, p. 420.1.

Glaucoma. For reference to SSRIs precipitating or exacerbating symptoms of glaucoma, see Effects on the Eyes, p. 420.1.

Mania. Hypomania or mania have been reported with the SSRIs; consequently, UK licensed product information recommends that SSRIs should be withdrawn in any patient entering a manic phase.

Fluvoxamine was associated with manic behaviour in 8 patients who were being treated for major depression;[1] 3 also had obsessive-compulsive disorder. Daily doses of fluvoxamine ranged from 75 to 300 mg and duration of therapy to development of manic behaviour from 2 to 6 weeks. The authors were unable to determine whether fluvoxamine had induced mania or unmasked latent bipolar disorder in these patients. However, they recommended that fluvoxamine-treated patients should be monitored for manic behaviour.

Symptoms of manic behaviour also developed in a 7-year-old girl after taking *sertraline* for about 2 weeks for the treatment of major depression.[2] She recovered within a few weeks of stopping sertraline.

1. Dorevitch A, *et al*. Fluvoxamine-associated manic behavior: a case series. *Ann Pharmacother* 1993; **27:** 1455–7.
2. Ghaziuddin M. Mania induced by sertraline in a prepubertal child. *Am J Psychiatry* 1994; **151:** 944.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluoxetine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. In an early prospective study[1] comparing 128 pregnant women exposed to a mean daily dose of about 26 mg of fluoxetine during their first trimester with control groups given tricyclic antidepressants or non-teratogens, the incidence of **neonatal malformations** was similar in all groups and did not exceed that in the general population. However, there was a tendency to a higher incidence of **miscarriages** in the groups given fluoxetine or tricyclics. A later prospective study[2] comparing 228 pregnant women taking fluoxetine with a control group taking non-teratogens also failed to find a significant increased incidence in major fetal abnormalities in the fluoxetine group; it also did not reveal an increased risk of miscarriage. There was an increase in the incidence of minor fetal abnormalities in infants exposed to fluoxetine during the first trimester. Also, infants exposed to fluoxetine during the third trimester had more perinatal complications such as prematurity, low full-term birthweight and length, and poor neonatal adaptation compared with infants exposed only during the first and second trimesters. However, the design of this study was criticised[3] because of several methodological problems such as unmatched controls and a higher maternal age in the fluoxetine group, which may partly explain the excess of poor perinatal outcomes.

The manufacturer evaluated the outcome of 796 pregnancies in which the mother received fluoxetine during the first trimester and considered that it was unlikely that fluoxetine increased the risk of miscarriage or fetal malformation.[4] A prospective controlled study[5] on pregnancy outcome in women exposed to fluvoxamine, paroxetine, or sertraline also found that, when used in recommended doses, there appeared to be no increase in the risk of major congenital malformations, miscarriages, or still-births when compared with women exposed to non-teratogens. Nonetheless, the results from a more recent meta-analysis which included some of the above studies have suggested that maternal exposure to antidepressant treatment (specifically SSRIs, tricyclics, nefazodone, trazodone, or venlafaxine) may significantly increase the risk of miscarriage in comparison to women not exposed to antidepressants.[6] However, the authors acknowledged that the underlying depression itself might be a contributing factor to the increased risk.

There is some evidence that paroxetine may be more teratogenic than other antidepressants. In 2005, the manufacturer *GlaxoSmithKline* commented[7] on the results of 2 studies on the use of antidepressants in pregnant women. Data from a retrospective US epidemiological study showed a non-significant, 1.5-fold increase in the risk of cardiovascular malformations, particularly ventricular septal defects, in the infants of mothers who had taken paroxetine during pregnancy when compared with those whose mothers had taken other antidepressants. The data also showed a significant increase in the overall risk of major congenital malformations (including cardiovascular defects) in those infants exposed to paroxetine. A second study using data from the Swedish national birth registry also found a twofold increase in the risk of cardiovascular malformations in infants exposed to paroxetine when compared with the general population; however, this study did not find an increase in the overall risk of major congenital malformations in those infants exposed to paroxetine. Based on these findings, the manufacturer revised the product literature for paroxetine to strengthen the warnings on its use in pregnancy. More recently, a Danish study[8] concluded that there was a significant, twofold increase in the risk of septal heart defects with the SSRIs as a group (specifically citalopram, fluoxetine, paroxetine, and sertraline) when compared with a general population of pregnant women. However, when considered individually, the increase in risk was only statistically significant for citalopram and sertraline. The risk of major congenital malformations overall was not increased in this study. These somewhat conflicting results may be explained by methodological differences between the studies.

Maternal use of SSRIs has been associated with **neonatal complications**. CNS toxicity and an increased heart rate were reported in a neonate whose mother had received 20 mg of fluoxetine daily throughout most of her pregnancy.[9] The neonate's symptoms resolved 96 hours after delivery. In another neonate whose mother took up to 30 mg daily of fluoxetine throughout the third trimester cardiac arrhythmias were noted.[10] In a matched-control study[11] the rate of complications after delivery in 55 infants exposed to paroxetine during the third trimester was higher than in a control group who had been exposed to paroxetine or non-teratogenic agents during the first or second timesters. Complications that occurred in the infants exposed in the third trimester included respiratory distress (9 cases), hypoglycaemia (2 cases), bradycardia (1 case), jaundice (1 case), and suckling problems (1 case). More recently, another matched-control study[12] has suggested that exposure to SSRIs (in this case fluoxetine, paroxetine, and sertraline) after the 20th week of gestation may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Of 377 infants with a confirmed diagnosis of PPHN, the mothers of 14 (3.7%) had taken an SSRI after the 20th week of gestation, compared with only 6 out of 836 infants (0.7%) in the matched-control group. Although these figures represent about a sixfold increase in the risk of PPHN in infants exposed to SSRIs *in utero*, the absolute risk remains relatively low (about 6 to 12 per 1000 women).

Several reports[2,13-17] have described symptoms such as jitteriness, irritability, sleep disturbances, and altered muscle tone in neonates who had been exposed to SSRIs *in utero*, especially during the third trimester; in the majority of cases the symptoms are mild and self-limiting. Although withdrawal symptoms have been reported with most SSRIs, they have been more commonly reported in those neonates exposed to paroxetine.[18] More recently, some authors have used the term neonatal behavioural syndrome to refer to such symptoms.[16] It is unclear whether the symptoms represent a withdrawal syndrome or direct serotonin toxicity;[15,17,19] however, it has been suggested by some that *in-utero* exposure to SSRIs with a short half-life such as paroxetine may lead to a neonatal withdrawal syndrome whereas exposure to an SSRI with a long half-life, particularly fluoxetine, may manifest as neonatal serotonin toxicity.[16] There have been case reports of intraventricular haemorrhage in neonates whose mothers took SSRIs during late pregnancy but there is currently not enough data to determine whether the frequency of such bleeds in infants exposed to SSRIs is higher than normal.[17]

The effects of fluoxetine on fetal **neurodevelopment** were studied[20] in 55 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to fluoxetine *in utero* during the first trimester compared with those exposed to tricyclic antidepressants or adverse developmental influences. A subsequent study indicated that exposure to fluoxetine or tricyclic antidepressants throughout gestation did not appear to affect cognition adversely.[21] In another follow-up study, subtle differences in motor development and control, in particular tremulousness and inappropriate fine motor movements, were noted in the infants and children of depressed mothers who had taken SSRIs during pregnancy when compared with the infants of depressed mothers who had not taken any medication.[22] However, in other measures of mental development no differences between the two groups were seen.

1. Pastuszak A, *et al*. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993; **269:** 2246–8.
2. Chambers CD, *et al*. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996; **335:** 1010–15.
3. Robert E. Treating depression in pregnancy. *N Engl J Med* 1996; **335:** 1056–8.
4. Goldstein DJ, *et al*. Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 1997; **89:** 713–18.
5. Kulin NA, *et al*. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998; **279:** 609–10.
6. Hemels MEH, *et al*. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005; **39:** 803–9.
7. GlaxoSmithKline USA. Important prescribing information (issued December 2005). Available at: http://www.gsk.com/media/paroxetine/pregnancy_hcp_letter.pdf (accessed 23/02/10)
8. Pedersen LH, *et al*. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009; **339:** b3569.
9. Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. *Pediatrics* 1993; **92:** 721–2.
10. Abebe-Campino G, *et al*. Cardiac arrhythmia in a newborn infant associated with fluoxetine use during pregnancy. *Ann Pharmacother* 2002; **36:** 533–4.
11. Costei AM, *et al*. Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 2002; **156:** 1129–32.
12. Chambers CD, *et al*. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006; **354:** 579–87.
13. Nijhuis IJM, *et al*. Withdrawal reactions of a premature neonate after maternal use of paroxetine. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F77.
14. Stiskal JA, *et al*. Neonatal paroxetine withdrawal syndrome. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F134–F135.
15. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 2004; **113:** 368–75.
16. Moses-Kolko EL, *et al*. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; **293:** 2372–83.
17. Nordeng H, Spigset O. Treatment with selective serotonin reuptake inhibitors in the third trimester of pregnancy: effects on the infant. *Drug Safety* 2005; **28:** 565–81.
18. Sanz EJ, *et al*. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet* 2005; **365:** 482–7.
19. Isbister GK, *et al*. Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F147–F148.
20. Nulman I, *et al*. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336:** 258–62.
21. Nulman I, *et al*. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; **159:** 1889–95.
22. Casper RC, *et al*. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003; **142:** 402–8.

Surgery. In patients undergoing orthopaedic surgery, the risk of perioperative blood loss was significantly increased in those taking serotonergic antidepressants (specifically clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine) when compared with those on non-serotonergic antidepressants.[1] In addition, there was a significant increase in the need for blood transfusion during surgery in those on serotonergic antidepressants compared with those not receiving antidepressant medication.

1. Movig KLL, *et al*. Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med* 2003; **163:** 2354–8.

Withdrawal. Withdrawal reactions have been reported for all SSRIs and the related antidepressants mirtazapine and venlafaxine on dosage reduction or stopping treatment, although the frequency of such reactions may vary.[1-5] Paroxetine and venlafaxine have been associated with withdrawal reactions more often than other serotonergic antidepressants; in the case of paroxetine this may be due, in part, to its short half-life. Fluvoxamine also has a short half-life and has been shown in some studies to have a high risk of withdrawal reactions. The apparent lower risk of withdrawal reactions with fluoxetine may be due to its long half-life. Other factors that increase the risk of withdrawal reactions include abrupt withdrawal, the use of high doses, and prolonged therapy.[5]

In general, withdrawal reactions tend to occur within 3 days of stopping an SSRI or related antidepressant,[1,4,5] although a delay of up to 2 weeks may be noted with fluoxetine.[5] Common symptoms include dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety, and sleep disorders. In some cases withdrawal symptoms may be severe and disabling. There has also been a report[6] of 2

patients without a history of major psychiatric disorder who developed severe behavioural symptoms when paroxetine was withdrawn. Withdrawal was abrupt in one patient and more gradual, over a 12-day period, in the other. Symptoms were mainly hypomanic over the first few days, followed by a period of escalated ego-dystonic aggression, behavioural dyscontrol, and suicidal ideation.

Antidepressant dose tapering appears to reduce the frequency and severity of withdrawal reactions.[5] The *BNF* recommends that any antidepressant, including an SSRI, that has been taken regularly for 8 weeks or more should be stopped gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The withdrawal syndrome of the SSRIs is not considered to be a consequence of dependence.[4,5]

See also Extrapyramidal Effects under Adverse Effects, p. 421.2. For debate about whether a withdrawal syndrome exists in neonates whose mothers have received SSRIs see Pregnancy, p. 423.1.

1. Price JS, *et al.* A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996; **42:** 757–63.
2. Adverse Drug Reactions Advisory Committee (ADRAC). SSRI's and withdrawal syndrome. *Aust Adverse Drug React Bull* 1996; **15:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9602.htm (accessed 14/08/08)
3. Coupland NJ, *et al.* Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol* 1996; **16:** 356–62.
4. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)
5. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
6. Bloch M, *et al.* Severe psychiatric symptoms associated with paroxetine withdrawal. *Lancet* 1995; **346:** 57.

Interactions

SSRIs interact with other drugs mainly as a result of their inhibitory activity on hepatic cytochrome P450 isoenzymes. Individual SSRIs do not all show the same degree of inhibition nor do they react with the same isoenzymes. The drugs inhibited by specific SSRIs depends on the isoenzyme affected.

As SSRIs have occasionally been associated with bleeding disorders and other effects on the blood, caution is advised when they are given with drugs known to affect platelet function.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, adverse reactions including the *serotonin syndrome* (see p. 445.2) may occur; in its more severe form, serotonin syndrome can resemble neuroleptic malignant syndrome. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. SSRIs should not generally be given to patients receiving MAOIs or for at least 2 weeks after their use. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI. At least one week should elapse between withdrawing an SSRI and starting any drug liable to provoke a serious reaction (e.g. phenelzine); in the case of the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine 5 weeks, because of their longer half-lives. (For fluoxetine, the interval may need to be further extended if therapy has been prolonged or if high doses have been given.) Adverse effects such as the serotonin syndrome may also occur when the SSRIs are given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Further details concerning some of these interactions, and others, are given below.

References.

1. Mitchell PB. Drug interactions of clinical significance with selective serotonin reuptake inhibitors. *Drug Safety* 1997; **17:** 390–406.
2. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33:** 454–71.
3. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; **3:** 13–37.

Antibacterials. Rapid development of delirium was reported[1] in a patient when *clarithromycin* was added to his existing regimen of fluoxetine and nitrazepam. It was suggested that his delirium was a result of increased plasma-fluoxetine concentrations produced by the inhibition of cytochrome P450 enzymes by clarithromycin. Serotonin syndrome developed in a patient given *erythromycin* in addition to sertraline;[2] this was attributed to inhibition of CYP3A4 by the antibacterial, resulting in accumulation of the SSRI. There have also been reports of serotonin syndrome when *linezolid* was given with fluoxetine,[3] sertraline,[4] paroxetine,[5] and citalopram[6]; in the latter case the patient developed complications including metabolic acidosis and ultimately fatal cardiac arrest.[6] Reviews of serotonin syndrome associated with the use of linezolid suggest that serotonergic antidepressants such as the SSRIs are the interacting drug most often implicated.[7-9] However, it has been suggested that if warranted, linezolid may be given to patients receiving serotonergic antidepressants provided the patient is carefully monitored for signs and symptoms of serotonin syndrome.[8]

1. Pollak PT, *et al.* Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* 1995; **29:** 486–8.
2. Lee DO, Lee CD. Serotonin syndrome in a child associated with erythromycin and sertraline. *Pharmacotherapy* 1999; **19:** 894–6.
3. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. *Am J Health-Syst Pharm* 2007; **64:** 59–62.
4. Lavery S, *et al.* Linezolid and serotonin syndrome. *Psychosomatics* 2001; **42:** 432–4.
5. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. *Clin Infect Dis* 2002; **34:** 1651–2.
6. Bernard L, *et al.* Serotonin syndrome after concomitant treatment with linezolid and citalopram. *Clin Infect Dis* 2003; **36:** 1197.
7. Lawrence KR, *et al.* Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* 2006; **42:** 1578–83.
8. Taylor JJ, *et al.* Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis* 2006; **43:** 180–7.
9. FDA. Drug Safety Communication: updated information about the drug interaction between linezolid (Zyvox) and serotonergic psychiatric medications (issued 20th October, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm276251.htm (accessed 06/11/12)

Anticoagulants. SSRIs may increase the anticoagulant activity of some anticoagulants including *acenocoumarol* and *warfarin* (see p. 1531.3).

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in enhanced adverse reactions or interactions, and should be used only under expert supervision. For further details of the interactions between different antidepressants when given together, see Phenelzine, p. 447.2. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p. 445.2.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

There has been a report of the serotonin syndrome (see p. 445.2) developing in a patient 14 days after fluoxetine had been added to *carbamazepine* therapy.[1]

Phenobarbital has been reported to reduce serum concentrations of paroxetine.[2] Steady-state serum concentrations of paroxetine were found to be lower in patients taking *phenytoin* than in those taking carbamazepine or valproate.[3]

Low serum concentrations of citalopram have been reported in 2 patients also taking carbamazepine.[4] Serum concentrations increased when carbamazepine was changed to oxcarbazepine.

Some SSRIs have been reported to increase plasma concentrations of carbamazepine (see p. 516.2) and phenytoin (see p. 543.1). For conflicting reports of the effect of fluoxetine on serum-*valproate* concentrations, see p. 557.2.

1. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342:** 442–3.
2. Greb WH, *et al.* The effect of liver enzyme inhibition by cimetidine and enzyme induction by phenobarbitone on the pharmacokinetics of paroxetine. *Acta Psychiatr Scand* 1989; **80** (suppl 350): 95–8.
3. Andersen BB, *et al.* No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. *Epilepsy Res* 1991; **10:** 201–4.
4. Leinonen E, *et al.* Substituting carbamazepine with oxcarbazepine increases citalopram levels. A report on two cases. *Pharmacopsychiatry* 1996; **29:** 156–8.

Antihistamines. *Cyproheptadine* given to male and female patients as treatment for sexual dysfunction induced by fluoxetine or paroxetine has produced re-emergence of previously controlled depressive symptoms[1,2] or bulimia nervosa[3] in some patients.

Citalopram, fluoxetine, and fluvoxamine may increase plasma concentrations of *astemizole* or *terfenadine* by inhibition of their hepatic cytochrome P450 metabolism, increasing the risk of ventricular arrhythmias; use together should be avoided.

1. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. *J Clin Psychiatry* 1991; **52:** 163–4.
2. Christensen RC. Adverse interaction of paroxetine and cyproheptadine. *J Clin Psychiatry* 1995; **56:** 433–4.
3. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J Clin Psychiatry* 1991; **52:** 261–2.

Antimalarials. For mention of the effect of the SSRI fluvoxamine on the metabolism of *proguanil*, see p. 662.2.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of SSRIs with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p. 681.3). Fluvoxamine may inhibit the metabolism of *frovatriptan* and *zolmitriptan* (see p. 676.3 and p. 682.3, respectively). For the effects when some SSRIs are used with *dihydroergotamine*, see p. 675.2.

Antimuscarinics. For the effect when SSRIs were taken with *benzatropine*, see p. 896.1. For the effect of paroxetine on *procyclidine*, see p. 913.3.

Antineoplastics. Paroxetine may inhibit the metabolism of *tamoxifen*; for further details, see p. 863.3.

Antipsychotics. For reports of adverse effects in patients treated with SSRIs and antipsychotics, see under *Chlorpromazine*, p. 1052.1. Interactions between SSRIs and atypical antipsychotics are also mentioned under *clozapine*, p. 1061.3, *olanzapine*, p. 1092.1, *risperidone*, p. 1105.3, and *sertindole*, p. 1107.3.

Antivirals. Plasma concentrations of fluoxetine and other SSRIs are possibly increased by HIV-protease inhibitors, such as *ritonavir*, which may inhibit metabolism of the SSRI. Unexpectedly, however, total exposure to paroxetine was about halved by a *ritonavir-boosted fosamprenavir* combination in a study in healthy subjects.[1] Although the free fraction of paroxetine in plasma was increased, suggesting that it had been displaced from protein binding, the maximum concentration of free paroxetine was reduced.

The serotonin syndrome has been described[2] in a few patients given regimens that included fluoxetine and antiretroviral-dose ritonavir. The reaction also occurred in another patient given fluoxetine and *efavirenz*.

1. van der Lee MJ, *et al.* Interaction study of the combined use of paroxetine and fosamprenavir-ritonavir in healthy subjects. *Antimicrob Agents Chemother* 2007; **51:** 4098–4104.
2. DeSilva KE, *et al.* Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* 2001; **15:** 1281–5.

Anxiolytics. Fluoxetine and fluvoxamine increase plasma concentrations of some *benzodiazepines* (see under Diazepam, p. 1068.3). For mention of possible interactions between some SSRIs and *buspirone*, see p. 1043.2.

Beta blockers. For the effect when fluoxetine or fluvoxamine was taken with beta blockers, see p. 1321.3.

Ciclosporin. For the effect when fluoxetine or fluvoxamine was taken with ciclosporin, see p. 1956.2.

Cough suppressants. For the effects when using fluoxetine or paroxetine with *dextromethorphan*, see p. 1661.2.

Dopaminergics. *Selegiline* is an irreversible selective inhibitor of monoamine oxidase type B. Serious adverse effects have been reported when selegiline and SSRIs have been used together (see p. 917.1). In some instances, these reactions resemble the potentially fatal serotonin syndromes reported when SSRIs are given with non-selective MAOIs (see p. 445.2).

SSRIs should not generally be given to patients receiving selegiline, or for at least 2 weeks after it has been stopped. Similarly, at least one week should elapse between withdrawing an SSRI and starting selegiline; this interval should be increased to 2 weeks for sertraline, and to 5 weeks for fluoxetine because of their longer half-lives.

Gastrointestinal drugs. Acute dystonia has been noted in a patient given fluvoxamine and *metoclopramide*.[1] Similar reports have been published for other SSRIs (fluoxetine[2] or sertraline[3]) and metoclopramide. Involuntary twitching, tremor, and stiffness of the jaw and tongue occurred on both occasions after the use of intravenous metoclopramide in a patient also taking sertraline.[4] The authors considered the adverse effects to be features of the serotonin syndrome.

For the effect of fluvoxamine on *alosetron*, and a recommendation that the combination be avoided, see p. 1820.1.

For the effect of fluvoxamine on proton pump inhibitors, including *omeprazole*, see p. 1874.1.

1. Palop V, *et al.* Acute dystonia associated with fluvoxamine-metoclopramide. *Ann Pharmacother* 1999; **33:** 382.
2. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* 1995; **152:** 122–5.
3. Christensen RC, Byerly MJ. Mandibular dystonia associated with the combination of sertraline and metoclopramide. *J Clin Psychiatry* 1996; **57:** 596.
4. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36:** 67–71.

General anaesthetics. For a report of a generalised tonic-clonic seizure in a patient receiving paroxetine and *methohexital sodium*, see p. 1910.2.

Hypnotics. For reference to visual hallucinations in patients receiving an SSRI concomitantly with *zolpidem*, see p. 1117.2.

Levothyroxine. For mention of a decreased effect of levothyroxine in patients given sertraline concomitantly, see p. 2341.2.

Local anaesthetics. For the effect of fluvoxamine on *ropivacaine*, see p. 1996.3.

Muscle relaxants. For a report of QT prolongation in a patient taking fluoxetine and *cyclobenzaprine*, see p. 2023.3.

For the effect of fluvoxamine on *tizanidine*, see p. 2027.1.

NSAIDs. For reference to an increased risk of upper gastrointestinal bleeding in patients taking SSRIs and NSAIDs together, see under Effects on the Gastrointestinal Tract, p. 420.1.

Opioid analgesics. A possible case of serotonin syndrome (p. 445.2) has been reported with *tramadol* and sertraline,[1] and another when sertraline was given with high doses of *oxycodone*.[2] There have also been occasional reports of the syndrome in patients given tramadol with citalopram,[3] fluoxetine,[4] or paroxetine.[5,6] Other reports of serotonin syndrome were associated with use of oxycodone and fluvoxamine,[7] *pethidine* and fluoxetine,[8] and citalopram with *fentanyl*[9] or pethidine.[10] For reference to SSRIs enhancing the effects and toxicity of *methadone*, see p. 90.3.

1. Mason BJ, Blackburn KH. Possible serotonin syndrome associated with tramadol and sertraline coadministration. *Ann Pharmacother* 1997; **31:** 175–7.
2. Rosebraugh CJ, *et al.* Visual hallucination and tremor induced by sertraline and oxycodone in a bone marrow transplant patient. *J Clin Pharmacol* 2001; **41:** 224–7.
3. Mahlberg R, *et al.* Serotonin syndrome with tramadol and citalopram. *Am J Psychiatry* 2004; **161:** 1129.
4. Kesavan S, Sobala GM. Serotonin syndrome with fluoxetine plus tramadol. *J R Soc Med* 1999; **92:** 474–5.
5. Egberts ACG, *et al.* Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *Int Clin Psychopharmacol* 1997; **12:** 181–2.
6. Lantz MS, *et al.* Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry* 1998; **13:** 343–5.
7. Karunatilake H, Buckley NA. Serotonin syndrome induced by fluvoxamine and oxycodone. *Ann Pharmacother* 2006; **40:** 155–7.
8. Tissot TA. Probable meperidine-induced serotonin syndrome in a patient with a history of fluoxetine use. *Anesthesiology* 2003; **98:** 1511–12.
9. Ailawadhi S, *et al.* Serotonin syndrome caused by interaction between citalopram and fentanyl. *J Clin Pharm Ther* 2007; **32:** 199–202.
10. Altman EM, Manos GH. Serotonin syndrome associated with citalopram and meperidine. *Psychosomatics* 2007; **48:** 361–3.

Parasympathomimetics. For the effect of some SSRIs on *galantamine*, see p. 392.2.

Sibutramine. There is a risk of CNS toxicity due to synergistic serotonergic actions when an SSRI is given with sibutramine.

Smoking. Serum concentrations of fluvoxamine were lower in smokers than non-smokers in a single-dose study.[1] It was proposed that the polycyclic hydrocarbons present in cigarette smoke stimulated hepatic metabolism of fluvoxamine by cytochrome P450 isoenzymes.

1. Spigset O, *et al.* Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 1995; **58:** 399–403.

Stimulants. For the effect of paroxetine on the metabolism of *atomoxetine*, see p. 2317.3.

Theophylline. For the effect of fluvoxamine on theophylline, see p. 1234.3.

Pharmacokinetics

Fluoxetine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 6 to 8 hours after oral doses. Systemic bioavailability does not appear to be affected by food. Fluoxetine is extensively metabolised, by demethylation, in the liver to its primary active metabolite norfluoxetine. Excretion is mainly via the urine. Protein binding is reported to be about 95%.

Fluoxetine used clinically is a racemic mixture consisting of *R*- and *S*-enantiomers in equal amounts. Both enantiomers are active according to *animal* studies, but *S*-fluoxetine is eliminated more slowly. Metabolism is believed to be mediated by cytochrome P450 isoenzyme CYP2D6 (but see p. 427.2), and leads to *R*- and *S*-enantiomers of norfluoxetine, with the *S*-enantiomer being considered as active as the parent drug; the *R*-enantiomer is considered to be much less active. This metabolism is subject to genetic polymorphism. While the small proportion of the population known as slow metabolisers do show a different spectrum of parent drug and metabolite, the overall activity does not appear to be altered.

Fluoxetine is widely distributed throughout the body.

Fluoxetine has a relatively long elimination half-life of about 1 to 3 days after acute use and 4 to 6 days after long-term use; that of its metabolite, norfluoxetine, is even longer, being about 4 to 16 days. These long half-lives have clinical implications. Steady-state plasma concentrations will only be attained after several weeks. Additionally, fluoxetine and its metabolites may persist for a considerable time after treatment, and this has led to precautions concerning the subsequent use of other serotonergic drugs (see Interactions, p. 424.1).

Fluoxetine and norfluoxetine are distributed into breast milk (see Breast Feeding under Precautions, p. 422.2).

References.

1. Altamura AC, *et al.* Clinical pharmacokinetics of fluoxetine. *Clin Pharmacokinet* 1994; **26:** 201–14.
2. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 1996; **31:** 444–69.
3. Greenblatt DJ, *et al.* Inhibition of human cytochrome P450-3A isoforms by fluoxetine and norfluoxetine: in vitro and in vivo studies. *J Clin Pharmacol* 1996; **36:** 792–8.
4. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; **60:** 512–21.
5. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997; **32** (suppl 1): 1–21.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Metabolism. Although fluoxetine is stated by the manufacturers to be metabolised by the cytochrome P450 isoenzyme CYP2D6, which is supported by studies[1] indicating that its disposition is altered in poor metabolisers of debrisoquine (a substrate for this enzyme), others have suggested that CYP2C19, and perhaps CYP2C9, play an important role.[2]

1. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; **60:** 512–21.
2. Liu Z-Q, *et al.* Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol* 2001; **52:** 96–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alental; Animex-On; Anzolden†; Captaton; Eburnate; Equilibrane; Faboxetina; Felixina; Fibrotina†; Fluopiram†; Fluoxiram; Foxetin; Lapsus; Mitilase; Nervosal; Neupax; Neuro Laz; Prozac; Saurat; ***Austral.***: Auscap; Fluohexal†; Fluoxebell†; Lovan; Prozac; Zactin; ***Austria***: Felicium; Floccin†; Fluctine; Fluoxibene; Flux; Fluxil†; FluxoMed; Mutan; Positivum; ***Belg.***: Docfluoxetine†; Fluox†; Fluoxemed†; Fluoxone; Fontex; Prosimed†; Prozac; ***Braz.***: Daforin; Deprax; Depress; Eufor; Fluox; Fluxene; Nortec; Prozac; Prozen; Psiquial; Verotina; Zyfloxin; ***Canad.***: FXT†; Prozac; ***Chile***: Actan; Alentol; Anisimol; Aprinol; Clinium; Dominium; Nerbet; Pragmaten; Prozac; Sostac; Ultiflox; ***China***: Ao Mai Lun (奥麦伦); Jin Kai Ke (金开克); Kai Ke (开克); Prozac (百优解); Youke (优克); Zactin (艾旭); ***Cz.***: Defluox; Deprex; Floxet; Fluoxin†; Fluzak; Magrilan; Portal†; Prozac; ***Denm.***: Flutin†; Fondur†; Fontex; ***Fin.***: Fluoxone; Seromex; Seronil; ***Fr.***: Prozac; ***Ger.***: Fluctin; Fluox-Puren†; Fluoxe-Q†; FluoxeLich; Fluoxgamma; Fluxet; ***Gr.***: Dagrilan; Dinalexin; Exostrept; Flonital; Fluocalm; Fluxadir; Fokeston; Hapilux; Ladose; Orthon; Sartuzin; Sofelin; Stephadilat-S; Stressless; Thiramil; Zinovat; ***Hong Kong***: Anzac†; CP-Fluoxet; Dawnex†; Deprexin†; Floxet; Fluxetin; Fluxil; Nopres; Prozac; Qualisac; ***Hung.***: Deprexin; Floxet; FluWinox†; Portal; Prozac; ***India***: Afzot; Alivate; Barozac; Curix; Dawnex; Depten; Depzac; Faa; Fadep; Faxtin; Floxikair; Fluchem; Fludac; Fludawn; Fludep; Flugen; Flumusa-20; Flunat; Flunil; Fluriv; Flutin; Flutine; Flutinol; Flutop; Flutrac; Flutric; Flux; Fluxal; Fluxin; Fluze; Fulx; Griloc; HT; Loftil; Molux; Nedep; Noc; Nuzac; Platin; ***Indon.***: Andep†; Ansi†; Antiprestin; Courage; Deprezac; Elizac; Foransi; Kalxetin; Lodep†; Nopres; Noxetine; Oxipres; Prozac; ZAC; Zactin†; ***Irl.***: Affex; Bellzac; Biozac; Fluzac; Gerozac; Norzac; Prozac; Prozamel; Prozatan†; Prozit; ***Israel***: Flutine; Prizma; Prozac; ***Ital.***: Azur; Clexiclor; Cloriflox; Diesan; Flotina; Fluoxeren; Ipsumor; Prozac; Xeredien; ***Malaysia***: Fluovex; Fluran; Fluxetil; Prozac; Salipax; Sinzac; ***Mex.***: Aniup; Auroken; Axtin; Deprozin; F-Exina; Farmaxetina; Flocet†; Florexal; Fluctine†; Fluneurin; Fluoxac; Fluralex; Flutinax†; Fusum; Indozul; Lebensart; Ovisen; Pisaurit; Prozac; Quanilene; Regultron; Siquial; Teczac; Ulmely; Zatin; ***Neth.***: Flustad; Prozac; ***Norw.***: Fontex; ***NZ***: Fluox; Plinzene†; Prozac; ***Philipp.***: Adep; Adepssir; Deprexone; Deprizac; Motivest; Neuxetin; Oxedep; Prodin; Prozac; ***Pol.***: Andepin; Bioxetin; Deprexetin; Salipax†; Seronil; Xetiran; ***Port.***: Digassim; Prozac; Psipax; Salipax; Selectus; Tuneluz; ***Rus.***: Apo-Fluoxetine (Апо-Флуоксетин); Flunisan (Флунисан); Fluval (Флувал); Framex (Фрамекс)†; Portal (Портал); Prodep (Продеп); Proflusak (Профлузак); Prozac (Прозак); ***S.Afr.***: Deprozan; Flutinol; Lorien; Nuzak; ProHexal; Prozac; Prozyn; Ranflocs; Rezak; Trizac†; ***Singapore***: Fluoxone; Fluxetin; Fluxil; Foxtin; Magrilan; Prozac; Zactin; ***Spain***: Adofen; Lecimar†; Luramon; Prozac; Reneuron; ***Swed.***: Fontex; ***Switz.***: Fluctine; Fluocim†; Fluoxifar†; ***Thai.***: Actisac; Anzac; Dawnex†; Deproxin; F-ZAC; Flulox; Flumed; Fluoxine; Flusac; Flutine; Fluxetil; Fluxetin; Fluzac; Foxetin; Hapilux; Loxetine; Magrilan; Oxetine; Oxsac; Prodep†; Prozac; Unprozy; Xetin; Zezac; ***Turk.***: Depreks; Depset; Florak; Foxeteva; Fulsac; Loksetin; Prozac; Seronil; Zedprex; ***UAE***: Flutin; ***UK***: Prozac; Prozep; Prozit; ***Ukr.***: Fluxen (Флуксен); Portal (Портал)†; ***USA***: Prozac; Sarafem; Selfemra; ***Venez.***: Anoxen; Antipres; Fluxet; Fluzac; Prozac; Psiquial.

Multi-ingredient Preparations. ***Chile***: Symbyax; ***India***: Alamflu; Alp-FT; Altin; Ateez-F; Azo-F; Cinol Forte; Cinol Plus; Cooltime; Coral-F; Depten-AZ; Depten-OZ; Depwell; Exiten Plus; Faa Plus; Faxtin-A; Fiden-AZ; Fludep Plus; Fludep-AZ; Flumusa; Fluwel; Fluxin-AL; Fluzolam; Kurelam-F; L-Peez F; M-Olan Plus; Oladay-F; Olanex-F; Olapin Forte; Olapin Plus; Olorest-F; ***Mex.***: Symbyax; ***USA***: Symbyax.

Pharmacopoeial Preparations

BP 2014: Fluoxetine Capsules; Fluoxetine Oral Solution;
USP 36: Fluoxetine Capsules; Fluoxetine Delayed-Release Capsules; Fluoxetine Oral Solution; Fluoxetine Tablets; Olanzapine and Fluoxetine Capsules.

Fluvoxamine Maleate

(BANM, USAN, rINNM)

DU-23000; Fluvoksamiinimaleaatti; Fluvoksamin Maleat; Fluvoxamina, maleato de; Fluvoxamine, Maléate de; Fluvoxamini Maleas; Fluvoxaminmaleat; Maleato de fluvoxamina; MK-264; SME-3110; Флувоксамина Малеат.

(*E*)-5-Methoxy-4′-trifluoromethylvalerophenone *O*-2-aminoethyloxime maleate.

$C_{15}H_{21}F_3N_2O_2.C_4H_4O_4$=434.4

CAS — 54739-18-3 (fluvoxamine); 61718-82-9 (fluvoxamine maleate).

ATC — N06AB08.

ATC Vet — QN06AB08.

UNII — 5LGN83G74V.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fluvoxamine Maleate). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in methyl alcohol.

USP 36: (Fluvoxamine Maleate). A white to off-white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in solvent ether. Protect from light.

Uses and Administration

Fluvoxamine, an aralkylketone derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 417.1).

In the treatment of **depression** fluvoxamine maleate is given in an initial oral dose of 50 or 100 mg once daily, preferably in the evening; in some patients the dose may need to be gradually increased to a maximum of 300 mg daily. It is recommended that daily dosages exceeding 150 mg should be given in 2 or 3 divided doses.

Fluvoxamine maleate is also used in the management of **obsessive-compulsive disorder**. In the UK, doses are similar to those used in the treatment of depression. The recommended starting dose in the USA is 50 mg once daily at bedtime; this dose may be increased by increments of 50 mg every 4 to 7 days to a maximum of 300 mg daily. Doses above 100 mg daily should be given in 2 divided doses. It is recommended that if no improvement occurs within 10 weeks, treatment with fluvoxamine should be reassessed.

In the USA, a modified-release preparation of fluvoxamine maleate is available for the treatment of obsessive-compulsive disorder. The initial dose is 100 mg once daily at bedtime increased, as necessary, by increments of 50 mg at weekly intervals to a maximum of 300 mg once daily.

US licensed product information recommends that dosage modification be considered in elderly patients, in whom clearance may be decreased. For dosage in renal and hepatic impairment, see p. 427.3, and for doses used in children, see p. 427.3.

It has also been used for the treatment of **social anxiety disorder**.

Fluvoxamine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Administration in children. Fluvoxamine maleate may be used in the management of **obsessive-compulsive disorder** in children aged 8 years and over, including adolescents. The recommended starting dose is 25 mg given orally, once daily at bedtime. This may be increased in increments of 25 mg every 4 to 7 days to a maximum daily dose of 200 mg for children (8 to 11 years old) or 300 mg for adolescents. Daily doses of more than 50 mg should be given as 2 divided doses; if the 2 doses are unequal, the larger dose should be given at bedtime.

Administration in hepatic or renal impairment. UK licensed product information recommends that patients with hepatic or renal impairment should begin therapy with a low dose of fluvoxamine maleate and be carefully monitored. US product information only recommends that dosage modification be considered in hepatic impairment,

since it considers evidence of accumulation in renal impairment to be lacking.

Anxiety disorders. Fluvoxamine has been given in a variety of anxiety disorders including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), and social anxiety disorder (see under Phobic Disorders, p. 1029.1).

References.

1. van Vliet IM, *et al.* Psychopharmacological treatment of social phobia: a double blind placebo controlled study with fluvoxamine. *Psychopharmacology (Berl)* 1994; **115:** 128–34.
2. Freeman CPL, *et al.* Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. *J Clin Psychiatry* 1994; **55:** 301–5.
3. Greist JH, *et al.* Efficacy of fluvoxamine in obsessive-compulsive disorder: results of a multicentre, double blind, placebo-controlled trial. *Eur J Clin Res* 1995; **7:** 195–204.
4. Stein MB, *et al.* Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind placebo-controlled study. *Am J Psychiatry* 1999; **156:** 756–60.
5. Figgitt DP, McClellan KJ. Fluvoxamine: an updated review of its use in the management of adults with anxiety disorders. *Drugs* 2000; **60:** 925–54.
6. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 2001; **344:** 1279–85.
7. Asnis GM, *et al.* Fluvoxamine in the treatment of panic disorder: a multicenter, double-blind, placebo-controlled study in outpatients. *Psychiatry Res* 2001; **103:** 1–14.
8. Hollander E, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64:** 640–7.
9. Stein DJ, *et al.* Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. *Int J Neuropsychopharmacol* 2003; **6:** 317–23.

Hypochondriasis. For reference to the use of SSRIs, including fluvoxamine, in hypochondriasis, see under Fluoxetine, p. 418.2.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 419.1).

Bradycardia with ECG changes has been noted with fluvoxamine (but see also Effects on the Cardiovascular System in Adverse Effects of Fluoxetine, p. 419.2).

It is recommended that fluvoxamine should be withdrawn in patients who have increased serum liver enzyme concentrations.

Fluvoxamine may need to be given with caution to patients with hepatic or renal impairment, and to the elderly.

Incidence of adverse effects. The UK CSM has reported[1] that between 25 September 1986 and 23 March 1988 it had received 961 reports of adverse reactions, including 5 deaths, associated with the use of fluvoxamine. The most frequently reported reactions were nausea (183 reports) and vomiting (101 reports). Other reactions included dizziness, somnolence, agitation, headache, tremor, and, during the first few days, worsening of anxiety. There were 13 reports of convulsions. Reports of appetite stimulation and antimuscarinic reactions were unusual. The effects sometimes resolved with time or dose reduction.

The safety profile of fluvoxamine has been reviewed.[2] For a comparison of the adverse reaction profiles of other SSRIs including fluoxetine with that of fluvoxamine, see Incidence of Adverse Effects, under Adverse Effects of Fluoxetine, p. 419.1.

1. CSM. Fluvoxamine (Faverin): adverse reaction profile. *Current Problems 22* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024429&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Wagner W, *et al.* Fluvoxamine: a review of its safety profile in worldwide studies. *Int Clin Psychopharmacol* 1994; **9:** 223–7.

Breast feeding. For comments on the use of SSRIs in breast-feeding patients, see under Precautions for Fluoxetine, p. 422.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 420.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluvoxamine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 424.1.

Fluvoxamine can greatly increase plasma concentrations of theophylline (see p. 1234.3), and they should not be given together, or, if this is unavoidable, the dose of theophylline should be halved and plasma-theophylline concentrations monitored more closely.

For the effect of fluvoxamine on melatonin, see p. 2552.2, and on pirfenidone, see p. 2592.1.

References.

1. Wagner W, Vause EW. Fluvoxamine: a review of global drug-drug interaction data. *Clin Pharmacokinet* 1995; **29** (suppl 1): 26–32.

Pharmacokinetics

Fluvoxamine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 3 to 8 hours after a dose. Systemic bioavailability does not appear to be affected by food. It is extensively metabolised in the liver by oxidative demethylation and deamination, to inactive metabolites. Excretion is mainly in the urine; about 2% of a dose is excreted as unchanged drug. Fluvoxamine is widely distributed throughout the body and protein binding is reported to be about 80%; it has a plasma-elimination half-life of about 15 hours. Fluvoxamine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p. 422.2).

References.

1. Perucca E, *et al.* Clinical pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1994; **27:** 175–90.
2. van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1995; **29** (suppl 1): 1–9.
3. Xu Z-H, *et al.* In vivo inhibition of CYP2C19 but not CYP2D6 by fluvoxamine. *Br J Clin Pharmacol* 1996; **42:** 518–21.
4. DeVane CL, Gill HS. Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. *J Clin Psychiatry* 1997; **58** (suppl 5): 7–14.
5. Spigset O, *et al.* Non-linear fluvoxamine disposition. *Br J Clin Pharmacol* 1998; **45:** 257–63.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Faverin; Luvox; Movox; Voxam; ***Austria***: Floxyfral; ***Belg.***: Floxyfral; ***Braz.***: Luvox; ***Canad.***: Luvox; Riva-Fluvox; ***Chile***: Luvox; ***China***: Luvox (兰释); Ruibile; ***Cz.***: Fevarin; ***Denm.***: Dumirox; Fevarin; ***Fin.***: Fevarin†; Fluvosol; ***Fr.***: Floxyfral; ***Ger.***: Fevarin; Fluvohexal†; ***Gr.***: Dumyrox; Myroxine; ***Hong Kong***: Faverin; ***Hung.***: Fevarin; ***India***: Fluvator; Fluvoxin; Foxa; Sorest; Uvox; ***Indon.***: Luvox; ***Irl.***: Faverin; ***Israel***: Favoxil; ***Ital.***: Dumirox; Fevarin; Maveral; ***Jpn***: Luvox; ***Malaysia***: Luvox; ***Mex.***: Luvox; Vuminix; ***Neth.***: Fevarin; ***Norw.***: Fevarin; ***Philipp.***: Faverin†; Voxamine; ***Pol.***: Fevarin; ***Port.***: Dumyrox; ***Rus.***: Fevarin (Феварин); ***S.Afr.***: Faverin; Luvox; ***Singapore***: Faverin; ***Spain***: Dumirox; ***Swed.***: Fevarin; ***Switz.***: Flox-ex; Floxyfral; ***Thai.***: Faverin; Fluvoxin; ***Turk.***: Faverin; Fluvamteva; Revoxin; ***UK***: Faverin; ***Ukr.***: Deprivox (Депривокс); Fevarin (Феварин); ***USA***: Luvox; ***Venez.***: Luvox.

Pharmacopoeial Preparations
BP 2014: Fluvoxamine Tablets;
USP 36: Fluvoxamine Maleate Tablets.

Imipramine *(BAN, rINN)*

Imipramiini; Imipramin; Imipramina; Imipraminum; Имипрамин.

3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyldimethylamine.

$C_{19}H_{24}N_2$=280.4

CAS — 50-49-7.

ATC — N06AA02.

ATC Vet — QN06AA02.

UNII — OGG85SX4E4.

Imipramine Embonate *(BANM, rINNM)*

Embonato de imipramina; Imipramina, embonato de; Imipramine, Embonate d'; Imipramine Pamoate; Imipramini Embonas; Имипрамина Эмбонат.

$(C_{19}H_{24}N_2)_2C_{23}H_{16}O_6$=949.2

CAS — 10075-24-8.

UNII — MC34P30298.

Imipramine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de imipramina; Imipram. Hydrochlor.; Imipramiinihydrokloridi; Imipramin Hidroklorür; Imipramina, hidrocloruro de; Imipramine, chlorhydrate d'; Imipraminhidroklorid; Imipraminhydrochlorid; Imipramin-hydrochlorid; Imipraminhydroklorid; Imipramini Chloridum; Imipramini hydrochloridum; Imipramino hidrochloridas; Imipraminy chlorowodorek; Imizine; Имипрамина Гидрохлорид.

$C_{19}H_{24}N_2$,HCl=316.9

CAS — 113-52-0.

UNII — BKE5Q1J60U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Imipramine Hydrochloride). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 10% solution in water has a pH of 3.6 to 5.0. Protect from light.

USP 36: (Imipramine Hydrochloride). A white to off-white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; insoluble in ether and in benzene. Store in airtight containers.

Uses and Administration

Imipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). Imipramine is one of the less sedating tricyclics and has moderate antimuscarinic activity. Imipramine is usually given orally as the hydrochloride or embonate, with doses expressed in terms of the hydrochloride. Imipramine embonate 149.8 mg and imipramine base 88.5 mg are both equivalent to about 100 mg of imipramine hydrochloride.

In the treatment of **depression**, the usual daily dose of imipramine hydrochloride is up to 75 mg in divided doses initially, gradually increased to 150 to 200 mg daily as necessary; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. A suggested initial dose for the elderly in the UK is 10 mg daily, gradually increasing to 30 to 50 mg daily. In the USA, daily doses of 25 to 50 mg are recommended for initial therapy in the elderly and adolescents, increasing to a maximum of 100 mg daily as required. Since imipramine has a prolonged half-life, once-daily dosage regimens may also be suitable, usually given at night.

Imipramine, as the hydrochloride, has also been given by intramuscular injection in the treatment of depression.

For the uses of imipramine in children, see p. 428.3.

Imipramine oxide hydrochloride (imipraminoxide hydrochloride) has also been used as an antidepressant and for nocturnal enuresis.

Imipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. Imipramine is used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home. Tricyclic antidepressants are not recommended in children under 6 years of age. For a discussion of tricyclic use in nocturnal enuresis, see Micturition Disorders under Amitriptyline, p. 402.1.

Suggested oral doses of imipramine hydrochloride are:

- 25 mg for children aged 6 to 7 years (20 to 25 kg)
- 25 to 50 mg for children aged 8 to 11 years (25 to 35 kg)
- 50 to 75 mg for children over 11 years (35 to 54 kg)

The dose should be taken just before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Imipramine has also been used in children with **attention deficit hyperactivity disorder** (see p. 428.3).

Anxiety disorders. See under Clomipramine, p. 412.2. In some countries, imipramine hydrochloride is licensed for the treatment of panic disorder in an initial oral dose of 10 mg daily; this dose may be increased as necessary to between 75 to 150 mg daily although doses of 200 mg daily may be needed in some patients.

Some references to the use of imipramine in anxiety disorders are given below.

1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160:** 191–202.
2. Lepola UM, *et al.* Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; **8:** 115–18.
3. Rickels K, *et al.* Antidepressants for the treatment of generalised anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 1993; **50:** 884–95.
4. Clark DM, *et al.* A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. *Br J Psychiatry* 1994; **164:** 759–69.
5. Barlow DH, *et al.* Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000; **283:** 2529–36. Correction. *ibid.*; **284:** 2597.

Hyperactivity. Although not licensed in the UK for use in children with attention deficit hyperactivity disorder, the *BNFC* has suggested that imipramine hydrochloride may be given to those aged 6 years and over in an oral dose of 10 to 30 mg twice daily.

See also under Desipramine, p. 413.2.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2). In some countries, imipramine hydrochloride is also available for the treatment of chronic pain; the usual recommended oral dose is 25 to

75 mg daily, although doses of up to 300 mg daily may be necessary.

Some references to the use of imipramine are given below.

1. Walsh TD. Controlled study of imipramine and morphine in chronic pain due to advanced cancer. *Proc Am Soc Clin Oncol* 1986; **5:** 237.
2. Sindrup SH, *et al*. Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990; **47:** 509–15.
3. Hummel T, *et al*. A comparison of the antinociceptive effects of imipramine, tramadol and anpirtoline. *Br J Clin Pharmacol* 1994; **37:** 325–33.
4. Cannon RO, *et al*. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994; **330:** 1411–17.
5. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; **156:** 1047–52.
6. Minotti V, *et al*. Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* 1998; **74:** 133–7.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imipramine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Imipramine is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desipramine.

Paths of metabolism of both imipramine and desipramine include hydroxylation and *N*-oxidation. Imipramine is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; small amounts are excreted in the faeces via the bile.

Imipramine and desipramine are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Imipramine has been estimated to have an elimination half-life ranging from 9 to 28 hours, which may be considerably extended in overdosage. Plasma concentrations of imipramine and desipramine vary very widely between individuals but some correlation with therapeutic response has been established.

Imipramine and desipramine cross the blood-brain barrier and placenta and are distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p. 405.1).

References.
1. Sallee FR, Pollock BG. Clinical pharmacokinetics of imipramine and desipramine. *Clin Pharmacokinet* 1990; **18:** 346–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Elepsin†; Tofranil; ***Austral.***: Melipramine†; Tofranil; Tolerade; ***Belg.***: Tofranil; ***Braz.***: Depramina; Imipra; Mepramin; Praminan; Tofranil; Uni Imiprax; ***Canad.***: Impril; Novo-Pramine; Tofranil†; ***Cz.***: Melipramin; ***Fr.***: Tofranil; ***Ger.***: Pryleugan†; Tofranil; ***Gr.***: Depramine; Venefon; ***Hung.***: Melipramin; ***India***: Antidep; Antipres; Depik; Depranil; Depsol; Depsonil; Diamin; Elamin; Eldep; Impramine; Imprine; Microdep; ***Indon.***: Tofranil; ***Irl.***: Tofranil†; ***Israel***: Primonil†; Tofranil; ***Ital.***: Tofranil; ***Mex.***: Fixon; Talpramin; Tofranil; ***NZ***: Tofranil; ***Philipp.***: Tofranil; ***Port.***: Tofranil; ***Rus.***: Melipramin (Мелипрамин); ***S.Afr.***: Ethipramine; Mipralin†; Tofranil; ***Spain***: Tofranil; ***Switz.***: Tofranil; ***Thai.***: Celamine; Inpramine; Mipramine; Sermonil; Topramine; ***Turk.***: Tofranil; ***Ukr.***: Melipramin (Мелипрамин); ***USA***: Tofranil; ***Venez.***: Tofranil.

Multi-ingredient Preparations. ***India***: Anxitab; Depik Forte; Depik Plus; Depranil Plus; Depsodep; Depsol Forte; Depsol Plus; Depsonil-DZ; Diamin Plus; Eldep Forte; Eldep-M; Eldep-Plus; Imipam.

Pharmacopoeial Preparations

BP 2014: Imipramine Tablets;
USP 36: Imipramine Hydrochloride Injection; Imipramine Hydrochloride Tablets.

Iproniazid Phosphate *(BANM, rINNM)*

Fosfato de iproniazida; Iproniazida, fosfato de; Iproniazide, Phosphate d'; Iproniazidi Phosphas; Ипрониазида Фосфат.

2′-Isopropylisonicotinohydrazide phosphate.

$C_9H_{13}N_3O,H_3PO_4$=277.2

CAS — 54-92-2 (iproniazid); 305-33-9 (iproniazid phosphate).

ATC — N06AF05.

ATC Vet — QN06AF05.

UNII — 8DE00V62TV.

Profile

Iproniazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p. 444.1). It has been given orally in the treatment of depression.

Iproniazid is the isopropyl derivative of isoniazid (see p. 311.2) and was developed for use in tuberculosis, but owing to its toxicity is no longer used for this purpose.

Effects on the liver. Of 91 cases of hepatitis due to antidepressant therapy, cytolytic reactions occurred in 11 treated with iproniazid.[1] Five patients died, 3 of them after involuntary rechallenge. High levels of antimitochondrial antibody were found in 5 patients.

1. Lefebure B, *et al*. Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Marsilid.

Isocarboxazid *(BAN, rINN)*

Isocarboxazida; Isocarboxazide; Isocarboxazidum; Isokarboksatsidi; Isokarboxazid; Ro-50831; Изокарбоксазид.

2′-Benzyl-5-methylisoxazole-3-carbohydrazide.

$C_{12}H_{13}N_3O_2$=231.3

CAS — 59-63-2.

ATC — N06AF01.

ATC Vet — QN06AF01.

UNII — 34237V843T.

Pharmacopoeias. In *Chin.*

Uses and Administration

Isocarboxazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p. 444.1).

Isocarboxazid is used in the treatment of depression but because of the risks associated with irreversible non-selective MAOIs (see p. 398.1) usually other antidepressants are preferred. It is given in an initial oral dose of 30 mg daily in single or divided doses. If no improvement occurs after 4 weeks, doses of up to 60 mg daily can be tried for up to 4 to 6 weeks. Once a response has been obtained the dosage may be gradually reduced to a maintenance dose of 10 to 20 mg daily, although doses of up to 40 mg daily may be needed in some patients. Half the normal maintenance dose may be adequate in the elderly.

Isocarboxazid should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p. 444.2).

Interactions

For interactions associated with MAOIs, see Phenelzine, p. 446.3 and p. 447.1.

Pharmacokinetics

Isocarboxazid is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 3 to 5 hours after ingestion. It is metabolised by the liver, and is excreted in the urine mainly in the form of metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Marplan; ***USA***: Marplan.

Levomilnacipran *(USAN, rINN)*

F-2695 (levomilnacipran or levomilnacipran hydrochloride); Levomilnaciprán; Lévomilnacipran; Levomilnacipranum; Левомилнаципран.

(1*S*,2*R*)-2-(Aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide.

$C_{15}H_{22}N_2O$=246.4

CAS — 96847-54-0; 96847-55-1.

UNII — UGM0326TXX.

Levomilnacipran Hydrochloride

(USAN, rINNM)

F-2695 (levomilnacipran or levomilnacipran hydrochloride); Hidrocloruro de levomilnaciprán; Lévomilnacipran, Chlorhydrate de; Levomilnacipranı Hydrochloridum; Левомилнаципрана Гидрохлорид.

$C_{15}H_{22}N_2O$,HCl=282.8

CAS — 175131-60-9.

UNII — 371U2ZK31U.

Profile

Levomilnacipran is the 1*S*,2*R*-enantiomer of milnacipran (p. 437.3), a serotonin and noradrenaline reuptake inhibitor (SNRI), and is used for the treatment of depression (p. 398.1). It is given orally as the hydrochloride although doses are expressed in terms of the base; levomilnacipran hydrochloride 45.9 mg is equivalent to about 40 mg of levomilnacipran. The usual initial dose is 20 mg once daily, increased to 40 mg daily after 2 days; thereafter, the dose may be further increased, according to response, in steps of 40 mg at intervals of 2 days or more, to a maximum of 120 mg once daily.

Levomilnacipran is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and the dose in those who are also taking potent CYP3A4 inhibitors should not exceed 80 mg daily. For doses in patients with renal impairment, see p. 429.3.

Levomilnacipran should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

References.
1. Mago R, *et al*. Safety and tolerability of levomilnacipran ER in major depressive disorder: results from an open-label, 48-week extension study. *Clin Drug Investig* 2013; **33:** 761–71. Correction. *ibid.*; 861.
2. Hair P, *et al*. Levomilnacipran extended release: first global approval. *Drugs* 2013; **73:** 1639–45.
3. Citrome L. Levomilnacipran for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 2013; **67:** 1089–1104.
4. Bakish D, *et al*. Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. *J Psychiatry Neurosci* 2013; **38:** 130040.

Administration in renal impairment. Usual oral doses of levomilnacipran may be given to patients with mild renal impairment (creatinine clearance [CC] of 60 to 89 mL/min). The maximum daily dose should not exceed 80 mg in those with moderate (CC of 30 to 59 mL/min), or 40 mg in those with severe (CC of 15 to 29 mL/min), impairment. Levomilnacipran should not be used in end-stage renal disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Fetzima.

Lithium Carbonate *(USAN)*

CP-15467-61; Dilithium Carbonate; Ličio karbonatas; Lithii Carbonas; Lithium Carb.; Lithium, carbonate de; Lithiumcarbonat; Litio, carbonato de; Litiumkarbonaatti; Litiumkarbonat; Lítium-karbonát; Litu węglan; Lityum Karbonat; NSC-16895; Uhličitan lithný; Карбонат Лития.

Carbonic acid, dilithium salt.

Li_2CO_3=73.89

CAS — 554-13-2.

ATC — N05AN01.

ATC Vet — QN05AN01.

UNII — 2BMD2GNA4V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Lithium Carbonate). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol.

USP 36: (Lithium Carbonate). A white odourless granular powder. Sparingly soluble in water, very slightly soluble in alcohol; dissolves, with effervescence, in dilute mineral acids.

Lithium Citrate

Citronan lithný tetrahydrát; Ličio citratas; Lithii Citras; Lithii Citras Tetrahydricus; Lithium, citrate de; Lithiumcitrat; Litio, citrato de; Litiumcitrat; Lítium-citrát; Litiumsitraatti; Lityum Sitrat; Лития Цитрат.

$C_6H_5Li_3O_7$,4H_2O=282.0

CAS — 919-16-4 (anhydrous lithium citrate); 6080-58-6 (lithium citrate tetrahydrate).
UNII — 5Z6E9K79YV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

US also includes lithium hydroxide.

Ph. Eur. 8: (Lithium Citrate). A white or almost white fine crystalline powder. Freely soluble in water; slightly soluble in alcohol.

USP 36: (Lithium Citrate). A white odourless deliquescent powder or granules. Freely soluble in water; slightly soluble in alcohol. pH of a 5% solution in water is between 7.0 and 10.0. Store in airtight containers.

Uses and Administration

Lithium, given as one of its salts, provides a source of lithium ions, which compete with sodium ions at various sites in the body. It thus has an action and adverse effects distinct and separate from those of other antidepressants. Its mode of action is not understood, but it is effective in the management of **mania**, **bipolar disorder**, and **recurrent unipolar depression**. Since the margin between therapeutic and toxic serum concentrations is narrow the decision to give lithium is usually based on specialist advice; lithium should not be prescribed unless facilities for monitoring serum concentrations are available.

Treatment with lithium needs to be monitored by measurement of serum concentrations, which must be adjusted for each patient to give a clinical response without evidence of toxicity. There is evidence that patients are most likely to respond to concentrations of 0.8 mmol/litre or above, but individual patients may respond to concentrations as low as 0.4 mmol/litre, and it is impossible to identify these patients beforehand. Because toxic effects are associated with concentrations above 1.5 mmol/litre, and may occur with concentrations as low as 1 mmol/litre in susceptible patients such as the elderly, it is therefore recommended that doses are adjusted to provide a serum-lithium concentration of 0.4 to 1 mmol/litre (at the lower end of this range for maintenance therapy and elderly patients). Patients must be taught to recognise the symptoms of early lithium intoxication (see Adverse Effects, p. 430.3) in order to omit further doses of lithium and seek medical care should it be impending.

The dose of lithium given depends on the preparation chosen since different preparations of lithium salts vary widely in bioavailability. This can be illustrated by the recommended doses for some UK preparations:

- *Camcolit* tablets (*Norgine, UK*) containing lithium carbonate; for treatment, initially 1 to 1.5 g daily; for prophylaxis, initially 300 to 400 mg daily
- *Li-Liquid* syrup (*Rosemont, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.018 to 3.054 g daily in two divided doses (elderly or patients less than 50 kg, 509 mg twice daily)
- *Liskonum* tablets (*GlaxoSmithKline, UK*) containing lithium carbonate; for treatment, initially 450 to 675 mg twice daily (elderly, 225 mg twice daily); for prophylaxis, initially 450 mg twice daily (elderly, 225 mg twice daily)
- *Priadel* tablets (*Sanofi, UK*) containing lithium carbonate; for treatment and prophylaxis, initially 400 mg to 1.2 g daily as a single dose or in two divided doses (elderly or patients less than 50 kg, 200 to 400 mg daily)
- *Priadel* syrup (*Sanofi, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.04 to 3.12 g daily in two divided doses (elderly or patients less than 50 kg, 520 mg to 1.04 g daily)

Doses of lithium are initially divided throughout the day; however, when serum-lithium concentrations are stabilised once-daily dosage may be preferred.

The initial dose given is adjusted after 4 to 7 days according to the results of serum-lithium estimations obtained under controlled conditions (samples being taken 12 hours after the preceding dose). Serum-lithium concentrations are then checked once a week until the dosage has remained constant for 4 weeks. The frequency of estimations can then be reduced to about once every 3 months. Should the patient's circumstances change such that the lithium pharmacokinetics or requirements might be affected, close control of serum concentrations should be reinstated until the concentrations stabilise once more. Such circumstances could involve a change of lithium preparation, an intercurrent illness (including a urinary-tract infection), a manic or depressive phase, a change in dietary regimen or body temperature, pregnancy, or use of other drugs (in particular, sodium-containing preparations and diuretics). For further details see Precautions, p. 432.2 and Interactions, p. 433.2. Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Therefore, long-term treatment should only be undertaken if it is definitely indicated. Patients need to be regularly assessed and treatment should only continue after 3 to 5 years if the benefit persists.

Lithium is also used for the management of **aggressive or self-mutilating behaviour**. The doses are similar to those used in the prophylaxis of recurrent affective disorders described above.

Lithium is not licensed in the UK for use in children, although some preparations may be used in patients aged 12 years and over. The *BNFC* suggests that it may be considered, on the advice of a specialist, in the management of mania, bipolar disorder, recurrent depression, and aggressive or self-mutilating behaviour. Suggested doses are similar to those given above.

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse. For further details, see Withdrawal under Precautions, p. 433.2.

Other lithium salts have been used in the treatment of psychiatric disorders and these include the acetate, gluconate, glutamate, and sulfate.

Homoeopathy

Lithium carbonate has been used in homoeopathic medicines under the following names: Lithium carbonicum; Lithium carb; Lith. carb.

Lithium citrate has been used in homoeopathic medicines under the following names: Lithium citricum.

Anxiety disorders. Lithium has been tried as augmentation therapy in the treatment of obsessive-compulsive disorder (p. 1028.2).

Bipolar disorder. Lithium's main role in the management of bipolar disorder is for prophylaxis (see p. 397.2). It is sometimes used in the control of the acute manic stage, but, because of its slow onset of action, usually with an antipsychotic.

References.

1. Aronson JK, Reynolds DJM. Lithium. *BMJ* 1992; **305:** 1273–6.
2. Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994; **331:** 591–8.
3. Jensen HV, *et al.* Lithium prophylaxis of manic-depressive disorder: daily lithium dosing schedule versus every second day. *Acta Psychiatr Scand* 1995; **92:** 69–74.
4. Jensen HV, *et al.* Twelve-hour brain lithium concentration in lithium maintenance treatment of manic-depressive disorder: daily versus alternate-day dosing schedule. *Psychopharmacology (Berl)* 1996; **124:** 275–8.
5. Maj M, *et al.* Late non-responders to lithium prophylaxis in bipolar patients: prevalence and predictors. *J Affect Disord* 1996; **39:** 39–42.
6. Burgess S, *et al.* Lithium for maintenance treatment of mood disorders. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 24/11/05).
7. Sproule B. Lithium in bipolar disorder: can drug concentrations predict therapeutic effect? *Clin Pharmacokinet* 2002; **41:** 639–60.
8. Geddes JR, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; **161:** 217–22.
9. Severus WE, *et al.* What is the optimal serum lithium level in the long-term treatment of bipolar disorder—a review? *Bipolar Disord* 2008; **10:** 231–7.
10. Berghöfer A, *et al.* Long-term effectiveness of lithium in bipolar disorder: a multicenter investigation of patients with typical and atypical features. *J Clin Psychiatry* 2008; **69:** 1860–8.
11. Coryell W. Maintenance treatment in bipolar disorder: a reassessment of lithium as the first choice. *Bipolar Disord* 2009; **11** (suppl 2): 77–83.
12. Tondo L, Baldessarini RJ. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. *Epidemiol Psichiatr Soc* 2009; **18:** 179–83.

Depression. Lithium may be used in the treatment and prophylaxis of recurrent unipolar depression, usually when standard antidepressants have failed (p. 398.1). Lithium is also used to augment the efficacy of other antidepressants in refractory cases.

References.

1. Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry* 1998; **59** (suppl 6): 28–33.
2. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol* 1999; **19:** 427–34. Correction. *ibid.* 2000; **20:** 287.
3. Sackeim HA, *et al.* Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* 2001; **285:** 1299–1307.
4. Guzzetta F, *et al.* Lithium treatment reduces suicide risk in recurrent major depressive disorder. *J Clin Psychiatry* 2007; **68:** 380–3.
5. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry* 2007; **68:** 935–40.

Disturbed behaviour. For mention of lithium in the management of children with disturbed behaviour see p. 1030.2.

Headache. Lithium is one of many drugs that have been tried in cluster headache (p. 670.1) to prevent headache attacks during cluster periods. In a double-blind study[1] lithium and verapamil were found to be of similar efficacy for cluster headache prophylaxis although verapamil appeared to produce fewer adverse effects. However, a later placebo-controlled study[2] was stopped early when lithium was found to be no more effective than placebo.

1. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30:** 411–17.
2. Steiner TJ, *et al.* Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997; **17:** 673–5.

Hyperthyroidism. Lithium may be used in hyperthyroidism (p. 2332.2), though its practical value is a matter of debate and, rarely, it may even cause hyperthyroidism (see Effects on the Endocrine System in Adverse Effects, p. 431.1). Pretreatment with lithium has also been reported to prolong the exposure of the thyroid to radioactive iodine in patients with Graves' thyrotoxicosis.[1]

1. Bogazzi F, *et al.* Treatment with lithium prevents serum thyroid hormone increase after thionamide withdrawal and radioiodine therapy in patients with Graves' disease. *J Clin Endocrinol Metab* 2002; **87:** 4490–5.

Schizophrenia. The addition of lithium to antipsychotic treatment has been tried in patients with schizophrenia (p. 1031.3) or schizoaffective disorders who fail to respond to an antipsychotic alone. The results of a meta-analysis have suggested that lithium augmentation is of some benefit, particularly in those with schizoaffective disorders, although the evidence is inconsistent.[1] However, significantly more patients with lithium augmentation left the studies early, suggesting adverse effects may be problematic and the danger of an interaction between the drugs should also be borne in mind (see under Interactions, p. 433.3).

1. Leucht S, *et al.* Lithium for schizophrenia revisited: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2004; **65:** 177–86.

Skin disorders. Some salts or derivatives of lithium (notably lithium succinate, p. 1710.3, but also lithium gluconate) have been applied topically in preparations for seborrhoeic dermatitis.

References.

1. Dreno B, *et al.* Lithium gluconate 8% vs ketoconazole 2% in the treatment of seborrhoeic dermatitis: a multicentre, randomized study. *Br J Dermatol* 2003; **148:** 1230–6.
2. Dréno B, *et al.* Gluconate de lithium gel à 8 p. 100 dans le traitement de la dermatite séborrhéique. *Ann Dermatol Venereol* 2007; **134:** 347–51.

Adverse Effects

Many of the adverse effects of lithium are dose-related and the margin between the therapeutic and toxic dose is narrow.

Initial adverse effects of lithium therapy include nausea, diarrhoea, vertigo, muscle weakness, and a dazed feeling; these effects often abate with continued therapy. Fine hand tremors, polyuria, and polydipsia may, however, persist. Other adverse effects that may occur at therapeutic serum-lithium concentrations include weight gain and oedema (which should not be treated with diuretics). Hypercalcaemia, hypermagnesaemia, and hyperparathyroidism have been reported. Skin disorders such as acne, psoriasis, and rashes may be exacerbated by lithium therapy. Leucocytosis is a relatively common adverse effect. Long-term adverse effects include hypothyroidism and/or goitre, rarely hyperthyroidism, and mild cognitive and memory impairment. Histological and functional changes in the kidney have been noted after long-term use of therapeutic concentrations of lithium (but see under Effects on the Kidneys, p. 431.2).

Toxic effects may be expected at serum-lithium concentrations of about 1.5 mmol/litre, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously.

Signs of lithium toxicity include increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, giddiness with ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyperirritability, choreoathetoid movements, dysarthria, and drowsiness. Symptoms of severe overdosage at serum-lithium concentrations above 2 mmol/litre include hyperreflexia and hyperextension of limbs, syncope, toxic psychosis, seizures, polyuria, renal failure, electrolyte imbalance, dehydration, circulatory failure, coma, and occasionally death.

The hazards of lithium in pregnant patients are discussed under Pregnancy in Precautions, p. 433.1.

References.

1. McKnight RF, *et al.* Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012; **379:** 721–8.

Effects on the blood. A patient developed thrombocytopenia after restarting lithium therapy after a gap of some weeks.[1] Stopping lithium led to an improvement in platelet count, but the count fell when lithium therapy was tried again. This patient also had leucocytosis, a recognised effect of lithium. Although concerns about leukaemia induction have not been verified, the author noted earlier reports of aplastic and megaloblastic anaemia and a case of fatal haemolytic anaemia reported to the UK CSM.

1. Collings S. Thrombocytopenia associated with lithium carbonate. *BMJ* 1992; **305:** 159.

Effects on the cardiovascular system. Reports of adverse effects on the heart associated with lithium have included

bradycardia due to sinus node dysfunction,[1] which has persisted after stopping lithium,[2] premature ventricular contractions,[3] atrioventricular block,[4] and T-wave depression.[5] For the adverse cardiac effects associated with lithium intoxication, see under Overdosage, p. 432.1.

For mention of myocarditis possibly associated with lithium therapy, see under Effects on the Musculoskeletal System, p. 431.2.

1. Montalescot G, *et al.* Serious sinus node dysfunction caused by therapeutic doses of lithium. *Int J Cardiol* 1984; **5:** 94–6.
2. Palileo EV, *et al.* Persistent sinus node dysfunction secondary to lithium therapy. *Am Heart J* 1983; **106:** 1443–4.
3. Tangedahl TN, Gau GT. Myocardial irritability associated with lithium carbonate therapy. *N Engl J Med* 1972; **287:** 867–9.
4. Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry* 1985; **30:** 114–16.
5. Demers RG, Heninger GR. Electrocardiographic T-wave changes during lithium carbonate treatment. *JAMA* 1971; **218:** 381–6.

Effects on the endocrine system. There is a small, but definite, risk that patients taking lithium in therapeutic doses will develop *goitre*, clinical or subclinical *hypothyroidism*, or, rarely, both.[1-3] Published prevalence figures have varied widely although most studies have found an increased risk of hypothyroidism in patients treated with lithium when compared with the general population.[2] Prevalence also appears to be higher in women taking lithium than in men;[2] in addition, the increased risk in women may be greatest during the first 2 years of lithium therapy. Other risk factors identified include a family history of thyroid disorders.[3] However, a long-term, follow-up study[4,5] suggested that the incidence of thyroid abnormalities was no greater in lithium-treated patients than in the general population.

Early goitre and lithium-induced hypothyroidism are both reversible if lithium is withdrawn; if continued treatment with lithium is desirable the patient should be treated with levothyroxine.

There have been rare reports of *hyperthyroidism* in lithium-treated patients[6] and the association may only be one of coincidence, although it is important to realise that hyperthyroidism can precipitate mania and can also be mistaken for an attack of mania.

Increases in serum concentrations of calcium and parathyroid hormone have been described in patients receiving lithium therapy. Although generally considered to be slight, some patients have experienced *parathyroid hyperplasia*.[7,8]

Cases of *diabetes mellitus* developing in patients treated with lithium have been reported but may not be attributable to lithium.[9] A case of transient diabetes after withdrawal of lithium treatment has also been described, manifesting as excessive thirst and polyuria that progressed to diabetic ketoacidosis; insulin therapy was stopped after 7 months.[10]

1. Vincent A, *et al.* Lithium-associated hypothyroidism: a practical review. *Lithium* 1994; **5:** 73–4.
2. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism: prevalence and risk factors. *Br J Psychiatry* 1999; **175:** 336–9.
3. Ozpoyraz N, *et al.* Thyroid abnormalities in lithium-treated patients. *Adv Therapy* 2002; **19:** 176–84.
4. Bocchetta A, *et al.* Six-year follow-up of thyroid function during lithium treatment. *Acta Psychiatr Scand* 1996; **94:** 45–8.
5. Bocchetta A, *et al.* Ten-year follow-up of thyroid function in lithium patients. *J Clin Psychopharmacol* 2001; **21:** 594–8.
6. Yamagishi S-I, Yokoyama-Ohta M. A case of lithium-associated hyperthyroidism. *Postgrad Med J* 1999; **75:** 188–9.
7. Nordenström J, *et al.* Hyperparathyroidism associated with treatment of manic-depressive disorders by lithium. *Eur J Surg* 1992; **158:** 207–11.
8. Taylor JW, Bell AJ. Lithium-induced parathyroid dysfunction: a case report and review of the literature. *Ann Pharmacother* 1993; **27:** 1040–3.
9. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
10. Okosieme OE, *et al.* Transient diabetes associated with withdrawal of lithium therapy. *Diabetes Care* 2006; **29:** 1181.

Effects on the eyes. Decrease in accommodation has been reported in up to 10% of patients taking lithium; younger patients are most affected.[1] Blurred vision can also occur, most commonly early in therapy, but this may improve with time. Lithium can affect extra-ocular muscles and produce diplopia. A reduction in dosage or withdrawal of therapy may be required. It reduces lachrymal secretions and is excreted in tears in increased concentrations. In rare cases this may result in ocular irritation but this usually causes few problems when artificial tears are used. Photophobia, which occurs rarely with lithium therapy, may also be associated with the excretion of lithium in tears. Lithium can reduce dark adaptation due to a direct neural effect but whether this can progress further to cause irreversible macular or retinal degeneration is not proven. There are some rare but poorly documented reports of deposits in the cornea or conjunctiva. It was considered unlikely that lithium increased the risk of developing senile cataracts.

Lithium can cause nystagmus, many forms of which are reversible on reducing the dose or withdrawal of the drug. However, downbeat nystagmus is a serious adverse effect and is often irreversible. Irreversible oscillopsia can occur rarely secondary to nystagmus. Oculogyric crisis has been associated with lithium therapy and may be exacerbated by haloperidol.

Some ocular effects may be secondary to the effects of lithium on other systems. Exophthalmos and other thyroid-related eye disorders may occur rarely as a secondary effect of lithium on the thyroid. Lithium can also cause pseudotumor cerebri with papilloedema (benign intracranial hypertension). Most cases have occurred a few years after starting therapy but there has been a report of this condition after only 7 months of treatment. Ptosis has been reported, mainly associated with unmasking of myasthenia gravis.

1. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; **11:** 97–169.

Effects on the kidneys. Polyuria with associated polydipsia, due to drug-induced nephrogenic diabetes insipidus, is the most common result of the effects of lithium on the kidney; an early review[1] stated that the incidence ranged from 4 to 50%. In some patients, irreversible kidney damage, associated with renal histological changes that included tubular atrophy, focal interstitial nephropathy and focal fibrosis, and impairment of glomerular filtration rate, was reported. However, although patients on long-term maintenance lithium therapy did appear to be susceptible to the development of progressive impairment of urinary concentrating ability it was most noticeable in patients with a history of acute lithium toxicity. The risk of renal damage and impaired glomerular filtration rate was thought to be extremely small in patients on stable maintenance lithium therapy with no history of acute lithium intoxication.[1]

A similar review considered that, although it was necessarily an oversimplified view, many, and perhaps all, of the renal adverse effects of lithium were induced by excessive dosage.[2] Others have also defended lithium with respect to its renal toxicity and stated that long-term therapy, if properly controlled, does not necessarily lead to chronic or irreversible renal damage.[3-5]

1. Walker RG, Kincaid-Smith P. Kidneys and the fluid regulatory system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 206–13.
2. George CRP. Renal aspects of lithium toxicity. *Med J Aust* 1989; **150:** 291–2.
3. Schou M. Serum lithium monitoring of prophylactic treatment: critical review and updated recommendations. *Clin Pharmacokinet* 1988; **15:** 283–6.
4. Schou M. Lithium treatment of manic-depressive illness: past, present, and perspectives. *JAMA* 1988; **259:** 1834–6.
5. Gitlin M. Lithium and the kidney: an updated review. *Drug Safety* 1999; **20:** 231–43.

Effects on the musculoskeletal system. The effects of lithium on skeletal muscle are represented mainly by varying degrees of weakness and tremor (for further details see under Effects on the Nervous and Neuromuscular Systems, p. 431.2). Aggravation of myasthenia gravis has been reported. Acute or subacute painful proximal myopathy causing myalgia, cramps, myokymia, or weakness has also been described. An association with myocarditis has been proposed[1] but it is unclear whether this is causal.

1. Coulter DM, *et al.* Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ* 2001; **322:** 1207–9.

Effects on the nervous and neuromuscular systems. Neurotoxicity has long been recognised as a potential adverse effect of lithium. Minor effects of lithium on the nervous system can be minimised by reduction of lithium dose during maintenance therapy but severe effects warrant immediate and complete withdrawal of the drug.[1] Minor effects have been considered to include impaired concentration, comprehension, and short-term memory, restlessness and anxiety, depression, fine rapid tremors, and easy fatigue. Serious or severe effects might include declining cognition and mental status, gait disturbances, movement disorders such as choreoathetosis, myoclonus, and parkinsonism, seizures, cerebellar signs, pseudotumor cerebri (although this was rare), neuroleptic malignant syndrome, myopathy, axonal neuropathy, a myasthenic syndrome, and exacerbation of underlying neuromuscular disease. The cognitive effects of lithium such as mental slowing may be subtle.[2]

There are 2 types of lithium-induced tremor.[3] The first is a coarse tremor occurring with impending and actual lithium toxicity and appears to have both cerebellar and parkinsonian components. It is often associated with incoordination, facial spasms, twitching of muscles and limbs, hyperactive reflexes, and more general systemic signs of toxicity. With this type of tremor it was mandatory to stop or decrease the dose of lithium. The second type, which is more common, is a fine tremor, usually occurring within normal therapeutic concentrations, either transiently within a few days of starting treatment or later as a long-standing adverse effect. With this type of fine tremor there was evidence to show that a slight decrease in dose may be beneficial.

In addition to the effects mentioned above, impairment of taste perception (mainly involving butter and celery)[4] and speech disturbances with few other signs of toxicity[5-8] have been reported.

Neurotoxicity persisting for at least 2 months after stopping lithium therapy (SILENT; syndrome of irreversible lithium-effectuated neurotoxicity) has been described.[9] Common presentations included cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, and dementia with varying degrees of organic mental syndromes.

For further effects of lithium on the nervous system, see under Effects on the Eyes above, Effects on the Musculoskeletal System, above, and under Epileptogenic Effect, p. 431.3.

1. Sansone ME, Ziegler DK. Brain and nervous system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 240–5.
2. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. *Psychopharmacology (Berl)* 2003; **170:** 225–34.
3. Johns S, Harris B. Tremor. *BMJ* 1984; **288:** 1309.
4. Himmelhoch JM, Hanin I. Side effects of lithium carbonate. *BMJ* 1974; **4:** 233.
5. Solomon K, Vickers R. Dysarthria resulting from lithium carbonate: a case report. *JAMA* 1975; **231:** 280.
6. Worrall EP, Gillham RA. Lithium-induced constructional dyspraxia. *BMJ* 1983; **286:** 189.
7. McGovern GP. Lithium induced constructional dyspraxia. *BMJ* 1983; **286:** 646.
8. Netski AL, Piasecki M. Lithium-induced exacerbation of stutter. *Ann Pharmacother* 2001; **35:** 961.
9. Adityanjee, *et al.* The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; **28:** 38–49.

Effects on respiration. Lithium is not generally recognised as a respiratory depressant but an episode of reversible respiratory failure about 3 weeks after the start of lithium therapy has been described in a patient with stable chronic airways obstruction.[1] Recovery of consciousness and resolution of hypercapnia occurred within 24 to 36 hours of stopping lithium.

1. Weiner M, *et al.* Effect of lithium on the responses to added respiratory resistances. *N Engl J Med* 1983; **308:** 319–22.

Effects on sexual function and fertility. Lithium does not seem to interfere with sexual function in most patients, but there have been isolated reports of impotence and loss of libido attributed to lithium therapy.[1]

Studies *in vitro* have shown that lithium can inhibit sperm motility in concentrations comparable with those reported to be achieved in semen,[2] but concentrations found in cervico-vaginal mucus were considered unlikely to affect motility.[3]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Raoof NT, *et al.* Lithium inhibits human sperm motility in vitro. *Br J Clin Pharmacol* 1989; **28:** 715–17.
3. Salas IG, *et al.* Lithium carbonate concentration in cervico-vaginal mucus and serum after repeated oral dose administration. *Br J Clin Pharmacol* 1989; **28:** 751P.

Effects on the skin and hair. Patients taking lithium may develop skin disorders, though these are not necessarily serious or severe.[1-3] Male patients may be more susceptible to such effects than female, although early results suggested the reverse.[3] Onset can vary from 2 or 3 weeks to 7 or more years, but many reactions start to appear once optimal serum-lithium concentrations have been attained. Effects reported include psoriasis which may be severe and require lithium withdrawal. Seborrhoeic dermatitis and follicular keratosis also occur and can improve spontaneously or after stopping lithium. Acneform eruptions are found in areas not usually affected by acne vulgaris; in general the face is less affected or not affected at all.

Hair loss, not always severe, is more frequent than cutaneous effects. About 6% of patients may be affected and all forms of alopecias have been found. The onset occurs several weeks or months after the start of lithium therapy. The hair usually regrows despite continuing therapy but in some cases regrowth only occurs after withdrawal of lithium. In a review[4] of the effects on the ocular system, loss of eyebrows and eyelashes was noted as a rare event. Hair loss due to lithium-induced hypothyroidism can be corrected by thyroid replacement therapy.

For references to the association of lithium with lupus, see under Lupus, p. 432.1.

1. Lambert D, Dalac S. Skin, hair and nails. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 232–4.
2. Gupta AK, *et al.* Lithium therapy associated with hidradenitis suppurativa: case report and a review of the dermatologic side effects of lithium. *J Am Acad Dermatol* 1995; **32:** 382–6.
3. Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol* 2004; **5:** 3–8.
4. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; **11:** 97–169.

Epileptogenic effect. Seizures during lithium therapy usually indicate toxicity or impending toxicity. There have, however, been a few isolated reports of seizures in patients with serum-lithium concentrations within the normally accepted therapeutic range.[1,2]

1. Demers R, *et al.* Convulsion during lithium therapy. *Lancet* 1970; **ii:** 315–16.

2. Massey EW, Folger WN. Seizures activated by therapeutic levels of lithium carbonate. *South Med J* 1984; **77:** 1173–5.

Lupus. Studies have found that antinuclear antibodies were more common in patients taking lithium carbonate than in controls.[1,2] The absence of anti-DNA antibodies indicated that they did not have true SLE but it was considered that patients ingesting lithium might be at risk. Dermatological manifestations of lupus with the presence of antinuclear antibodies have been reported in a patient taking lithium.[3]

1. Johnstone EC, Whaley K. Antinuclear antibodies in psychiatric illness: their relationship to diagnosis and drug treatment. *BMJ* 1975; **2:** 724–5.
2. Presley AP, *et al*. Antinuclear antibodies in patients on lithium carbonate. *BMJ* 1976; **2:** 280–1.
3. Shukla VR, Borison RL. Lithium and lupuslike syndrome. *JAMA* 1982; **248:** 921–2.

Overdosage. Nausea, vomiting, and diarrhoea are common early features of lithium toxicity, and are followed by coarse tremor, increased muscle tone, cogwheel rigidity, fasciculation, and myoclonus.[1] Coma and convulsions may occur in serious cases and cardiac effects (first-degree heart block and QRS and QT prolongation) have been described rarely. A patient may appear to be aware with open eyes but have an expressionless face and be unable to move or speak (coma vigil). Acute renal failure and nephrogenic diabetes insipidus may develop.

In **acute overdosage**[2] vomiting often occurs within an hour of ingestion due to the high concentration of lithium in the stomach, but significant amounts of lithium can still reach the systemic circulation. The typical clinical symptoms often appear after a delay and gastrointestinal symptoms can re-appear at a later time. The symptoms of overdosage are reported to be mainly related to the gastrointestinal and nervous systems and include abdominal pain, anorexia, nausea, and vomiting, occasionally mild diarrhoea, giddiness, tremor, ataxia, slurring speech, myoclonus, twitching, asthenia, and depression; renal symptoms have also been noted by some investigators. Efficient detoxification procedures (see Treatment of Adverse Effects, p. 432.2) should be started as rapidly as possible.

Symptoms associated with **chronic intoxication** can be more severe and neurotoxicity may be a particular feature.[3,4] One reviewer considered that the majority of lithium intoxications reported had occurred in patients with renal impairment or in patients who had been given too high a dose.[2] The patient usually has a prodromal period of days to a few weeks with minor 'nervous' symptoms which are signs of a manifest slight intoxication. At an unpredictable point renal function starts to deteriorate and within hours or, at the most, a few days, the patient will become severely intoxicated. By this point lithium should have been stopped and efficient detoxification measures (see Treatment of Adverse Effects, p. 432.2) begun if the patient is to make a complete recovery. Other risk factors[3-5] for developing chronic intoxication include use with certain medications (see Interactions, p. 433.2), older age, and the presence of other conditions such as neurogenic diabetes insipidus and thyroid dysfunction (see also Precautions, p. 432.2).

In a series of 28 patients with lithium self-poisoning or therapeutic intoxication many of the features and symptoms mentioned above were noted.[6] Other workers[7,8] have also reported cases that illustrate the differences between acute and chronic toxicity encountered clinically.

Serum concentrations of lithium should be measured routinely throughout treatment to ensure that values do not rise to levels associated with toxicity. However, some patients may have concentrations considered to be toxic without showing any symptoms and others may develop signs of toxicity at therapeutic serum concentrations.[9]

Other symptoms that have been noted in case reports of lithium intoxication in individual patients include photophobia,[10] acute polyarthritis involving several large joints,[11] severe hypertension,[12] deep venous thrombophlebitis,[13] reduction of central temperature,[14] and severe leucopenia.[15]

1. Proudfoot AT. Acute poisoning with antidepressants and lithium. *Prescribers' J* 1986; **26:** 97–106.
2. Amdisen A. Clinical features and management of lithium poisoning. *Med Toxicol* 1988; **3:** 18–32.
3. Oakley PW, *et al*. Lithium toxicity: an iatrogenic problem in susceptible individuals. *Aust N Z J Psychiatry* 2001; **35:** 833–40.
4. Chen K-P, *et al*. Implication of serum concentration monitoring in patients with lithium intoxication. *Psychiatry Clin Neurosci* 2004; **58:** 25–9.
5. Montagnon F, *et al*. Lithium: poisonings and suicide prevention. *Eur Psychiatry* 2002; **17:** 92–5.
6. Dyson EH, *et al*. Self-poisoning and therapeutic intoxication with lithium. *Hum Toxicol* 1987; **6:** 325–9.
7. Ananth J, *et al*. Acute and chronic lithium toxicity: case reports and a review. *Lithium* 1992; **3:** 139–45.
8. Bailey B, McGuigan M. Lithium poisoning from a poison control center perspective. *Ther Drug Monit* 2000; **22:** 650–5.
9. Stern R. Lithium in the treatment of mood disorders. *N Engl J Med* 1995; **332:** 127–8.
10. Caplan RP, Fry AH. Photophobia in lithium intoxication. *BMJ* 1982; **285:** 1314–15.
11. Black DW, Waziri R. Arthritis associated with lithium toxicity: case report. *J Clin Psychiatry* 1984; **45:** 135–6.
12. Michaeli J, *et al*. Severe hypertension and lithium intoxication. *JAMA* 1984; **251:** 1680.
13. Lyles MR. Deep venous thrombophlebitis associated with lithium toxicity. *J Natl Med Assoc* 1984; **76:** 633–4.
14. Follézou J-Y, Bleibel J-M. Reduction of temperature and lithium poisoning. *N Engl J Med* 1985; **313:** 1609.
15. Green ST, Dunn FG. Severe leucopenia in fatal lithium poisoning. *BMJ* 1985; **290:** 517.

Treatment of Adverse Effects

In recent acute overdosage with lithium, consideration should be given to gastric lavage to empty the stomach if ingestion has occurred within 1 hour of presentation. However this may be of limited value after overdosage with modified-release preparations, which do not disintegrate in the stomach and may be too large to pass through a lavage tube. Activated charcoal is of no value. Whole-bowel irrigation has been suggested although there do not appear to be clinical studies to confirm efficacy.

Further measures may involve procedures to enhance the renal clearance of lithium or its active removal. Adequate hydration should be ensured and any electrolyte imbalance corrected, but forced diuresis or diuretics are contra-indicated. Appropriate supportive care may include measures to control hypotension and convulsions. Maintenance of fluid and electrolyte balance is particularly important because of the risk of hypernatraemia. The ECG should be monitored in symptomatic patients.

In severe poisoning, haemodialysis is the treatment of choice (particularly if there is renal impairment). Although effective in reducing serum-lithium concentrations, substantial rebound increases can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Peritoneal dialysis is less effective and only appropriate if haemodialysis facilities are not available. Haemofiltration has been tried to good effect.

Serum lithium concentrations should be monitored regularly throughout treatment. Once the serum and dialysis fluid are free of lithium, it has been recommended that serum-lithium concentrations should be monitored for at least another week so that allowance can be made for delayed diffusion from body tissues.

As a result of the narrow margin between therapeutic and toxic serum concentrations, lithium poisoning may also develop during the course of therapy. In some instances temporary withdrawal of lithium therapy and giving generous amounts of sodium and fluid may be all that is required while adverse effects abate. In any serious or severe case of intoxication active measures such as dialysis and supportive measures outlined above may need to be instituted. Gut decontamination is not useful.

References.
1. Smith SW, *et al*. Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 1991; **20:** 536–9.
2. Okusa MD, *et al*. Clinical manifestations and management of acute lithium intoxication. *Am J Med* 1994; **97:** 383–9.
3. Swartz CM, Jones P. Hyperlithemia correction and persistent delirium. *J Clin Pharmacol* 1994; **34:** 865–70.
4. Tyrer SP. Lithium intoxication: appropriate treatment. *CNS Drugs* 1996; **6:** 426–39.

Precautions

The margin between the therapeutic and the toxic concentration of lithium is narrow so therapy usually requires specialist advice, and serum concentrations should be monitored regularly under controlled conditions. Patients receiving lithium therapy should be taught to recognise the symptoms of early toxicity (see Adverse Effects, p. 428.3) and, should these occur, to stop therapy and request medical aid at once. They should be warned not to compensate for an omitted dose by subsequently taking a double dose. Additionally, patients should not be switched between different formulations or preparations of lithium without therapeutic monitoring, as bioavailability may be different.

Lithium should be avoided in patients with cardiac disease or renal impairment; cardiac and renal function should be monitored regularly during treatment. It should also be avoided in Addison's disease or other conditions with a sodium imbalance and in severely debilitated or dehydrated patients.

Patients receiving lithium should be examined periodically for abnormal thyroid function, since goitre and hypothyroidism may develop. Lithium should be avoided in untreated hypothyroidism. Lithium should be used with caution in patients with myasthenia gravis because exacerbation of this disorder has been reported (see Effects on the Musculoskeletal System in Adverse Effects, p. 429.2).

Lithium should be used with special care in the elderly since this group may be particularly susceptible to toxicity owing to reduced renal function.

Impaired driving performance or machine operating skills may occur in patients receiving lithium (see Driving, p. 432.3).

It may be necessary to temporarily reduce or stop lithium therapy in patients suffering from vomiting, diarrhoea, intercurrent infection, excessive sweating, or any other condition that causes excessive sodium loss and hence increased serum-lithium concentrations. Conversely, increased sodium levels are likely to reduce serum-lithium concentrations. Patients taking lithium should therefore maintain an adequate fluid intake and should avoid increasing or decreasing sodium intake through dietary changes or ingestion of sodium-containing medicaments. Significant changes in caffeine intake may affect serum-lithium concentrations (see Xanthines under Interactions, p. 434.3).

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse (see Withdrawal, p. 433.2).

The risks of using lithium in pregnant patients are described under Pregnancy, p. 433.1. If lithium is used during pregnancy then dose adjustments will be required to compensate for the altered renal handling.

Lithium should be temporarily stopped 24 hours before major surgery to safeguard the patient from accumulation (see Anaesthesia, p. 432.3).

Anaesthesia. The *BNF* states that lithium should be stopped 24 hours before major surgery, but the normal dose can be continued for minor surgery if fluids and electrolytes are carefully monitored. Lithium may accumulate because of reduced renal clearance associated with anaesthesia;[1] treatment should be resumed as soon as possible after surgery, when kidney function and fluid-electrolyte balance have become normal. Patients are often not allowed oral fluids or foods the night before surgery but patients with lithium-induced polyuria should be given fluids parenterally during the night before the operation, if they vomit copiously, or if they are unconscious for several hours.

There is no clinical evidence of interaction between lithium and anaesthetics, although lithium may prolong the action of neuromuscular blockers.[1]

1. Schou M, Hippus H. Guidelines for patients receiving lithium treatment who require major surgery. *Br J Anaesth* 1987; **59:** 809–10.

Breast feeding. Lithium is distributed into breast milk. Early reports suggested that serum concentrations in breast-fed infants were about one-third to one-half of those measured in mothers.[1] However, advice regarding the decision to breast feed remains equivocal. The American Academy of Pediatrics[2] considers that lithium should be given with caution to breast-feeding women but does not contra-indicate such use, and this is supported by some authors.[3,4] Conversely, most UK licensed product information and other authors[5,6] suggest that mothers receiving lithium should bottle feed their infants. It has been recommended[5] that if a mother did want to breast feed this should be done at times to avoid peak blood concentrations of lithium and the infant carefully monitored. Medication should be withheld or breast feeding stopped if the infant developed an infection or dehydration as they would be more susceptible to the adverse effects of lithium.

1. Schou M, Amdisen A. Lithium and pregnancy—III, lithium ingestion by children breast-fed by women on lithium treatment. *BMJ* 1973; **2:** 138.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
3. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; **51:** 410–13.
4. Sykes PA, *et al*. Lithium carbonate and breast-feeding. *BMJ* 1976; **2:** 1299.
5. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; **4:** 231–7.
6. Llewellyn A, *et al*. The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *J Clin Psychiatry* 1998; **59** (suppl 6): 57–64.

Cystic fibrosis. Reduced renal excretion of lithium was evident in 8 patients with cystic fibrosis compared with healthy subjects.[1] The authors recommended caution when prescribing standard doses of lithium to patients with cystic fibrosis until more definitive data were available.

1. Brager NPD, *et al*. Reduced renal fractional excretion of lithium in cystic fibrosis. *Br J Clin Pharmacol* 1996; **41:** 157–9.

Driving. In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.[1] Mania or hypomania is particularly dangerous and driving should cease during the acute illness. After an isolated episode, re-licensing can be reconsidered provided the patient has remained well and stable for at least 3 months, is compliant with treatment, and has regained insight; in addition, the patient should be free from any adverse effects of medication that would impair driving. If there have been 4 or

more episodes of mood swing within the previous 12 months, at least 6 months of stability will be required before re-licensing can be considered. Drivers of heavy goods and public service vehicles are normally required to be well and stable for 3 years before driving can resume.

Treatment with antidepressant drugs, including lithium, may also be hazardous,[2] although patients may be safer drivers with medication than without.[3] Lithium has been reported[2] to adversely affect the choice reaction time (a test to assess the time taken to respond correctly to some signals but not others) to a level considered dangerous for driving. Another study has found that elderly patients taking lithium may be at an increased risk of being involved in an injurious motor vehicle accident while driving when compared with a cohort of elderly, non-lithium users.[4]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)
2. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
3. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
4. Etminan M, *et al.* Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. *BMJ* 2004; **328:** 558–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lithium as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The decision whether to continue lithium treatment during pregnancy is difficult and should involve careful consideration of the risk-benefit ratio, which in some cases may favour treatment. Early case reports of mothers taking lithium during pregnancy pointed to an increased risk of congenital abnormalities with the baby's heart being mainly affected.[1] Support for this increased risk also came from a study[2] of the records of 59 children born to women who had taken lithium during pregnancy. However, another study[3] that prospectively followed 138 pregnant women being treated with lithium did not identify any difference in pregnancy outcome between them and a control group. The authors considered that lithium was not a major teratogen and felt that women with major affective disorders could continue lithium treatment during pregnancy provided that adequate fetal screening tests were carried out. A subsequent review[4] considered that the teratogenic risk was lower than previously thought, but that it would still be wise for women who wished to become pregnant to stop lithium if at all possible, at least during the period of embryogenesis. If lithium is stopped, withdrawal should be slow to prevent a relapse (see p. 433.2).

There is limited evidence that lithium treatment during pregnancy may increase the risk of fetal macrosomia, premature delivery, and perinatal mortality.[1,5] Polyhydramnios (an excess of amniotic fluid) in the last trimester of pregnancy has been reported and has been attributed to fetal lithium toxicity (polyuria and diabetes insipidus).[6,7]

Monitoring of serum-lithium concentrations is particularly important during pregnancy. The renal clearance of lithium by the mother is not constant during pregnancy; in the second half of the pregnancy clearance rises gradually by 30 to 50% but falls abruptly and significantly after delivery to pre-pregnancy values.[1,8] The increased doses of lithium that may be given during pregnancy to compensate for this increased clearance may result in lithium toxicity.[8] It is generally considered[1,9,10] advisable to stop lithium during the last few days of pregnancy to reduce the risk of maternal lithium toxicity due to accumulation of lithium but it should be started again a few days later after delivery at reduced dosage because of the increased postpartum risk of manic and depressive relapse.[1,10]

Reducing the dosage during the last few days of pregnancy also helps to reduce lithium concentrations in the neonate and avoid associated adverse effects.[1,9] Adverse effects that have been reported in neonates exposed *in utero* to lithium include cyanosis, lethargy, flaccidity, hypotonia, poor gag and sucking reflexes, feeding problems, bradycardia, tachycardia, goitre, hypothyroidism, nephrogenic diabetes, and jaundice;[9-12] withdrawal symptoms have also been seen.

1. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; **51:** 410–13.
2. Källén B, Tandberg A. Lithium and pregnancy: a cohort study on manic-depressive women. *Acta Psychiatr Scand* 1983; **68:** 134–9.
3. Jacobson SJ, *et al.* Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 1992; **339:** 530–3.
4. Cohen LS, *et al.* A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994; **271:** 146–50.
5. Troyer WA, *et al.* Association of maternal lithium exposure and premature delivery. *J Perinatol* 1993; **XIII:** 123–7.
6. Krause S, *et al.* Polyhydramnios with maternal lithium treatment. *Obstet Gynecol* 1990; **75:** 504–6.
7. Ang MS, *et al.* Maternal lithium therapy and polyhydramnios. *Obstet Gynecol* 1990; **76:** 517–19.
8. Lemoine J-M. Pregnancy, delivery and lactation. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 139–46.
9. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; **4:** 231–7.
10. Pinelli JM, *et al.* Case report and review of the perinatal implications of maternal lithium use. *Am J Obstet Gynecol* 2002; **187:** 245–9.
11. Frassetto F, *et al.* Goiter in a newborn exposed to lithium in utero. *Ann Pharmacother* 2002; **36:** 1745–8.
12. Kozma C. Neonatal toxicity and transient neurodevelopmental deficits following prenatal exposure to lithium: another clinical report and a review of the literature. *Am J Med Genet A* 2005; **132:** 441–4.

Surgery. For comments regarding the precautions to be considered in patients undergoing surgery, see under Anaesthesia, p. 430.3.

Withdrawal. Symptoms such as anxiety, tremor, fatigue, nausea, sweating, headache, sleep disturbances, diarrhoea, or blurred vision have developed within days of sudden cessation of treatment with lithium.[1] These symptoms may simply be a recurrence of the mood disorder. Uncontrolled studies of withdrawal symptoms have raised the possibility of a lithium-withdrawal state although controlled studies have been convincingly negative. It is, however, wise to reduce lithium dosage gradually rather than stop high-dosage treatment abruptly.

A frequent worry associated with stopping lithium therapy is that of relapse. Most evidence has supported the view that any relapses occurring in the first weeks after lithium withdrawal are simply part of a pattern of recurrence of bipolar disorder in general and are not indicative of a higher rate of recurrence. Some,[2] however, have found the proportion of patients relapsing on sudden withdrawal of lithium therapy to be 50%, a figure they consider to be too high to be accounted for by the natural history of the disease process. They and others[3] advise that this risk should be considered when prescribing lithium for bipolar disorder. In patients who previously had been stable on lithium for at least 18 months, the risk of early recurrence of bipolar disorder was higher when therapy was withdrawn rapidly in less than 2 weeks than when it was withdrawn gradually over 2 to 4 weeks.[4]

1. Goodnick PJ. Terminating treatment. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 115–17.
2. Mander AJ, Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. *Lancet* 1988; **ii:** 15–17.
3. Goodwin GM. Recurrence of mania after lithium withdrawal. *Br J Psychiatry* 1994; **164:** 149–52.
4. Faedda GL, *et al.* Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* 1993; **50:** 448–55.

Interactions

Some diuretics may reduce lithium excretion and result in toxicity (see p. 434.2 for further details). Thiazide diuretics may also show a paradoxical antidiuretic effect. Consequently, diuretics should be avoided or used with caution in those receiving lithium; if used together, a reduction in the lithium dose may be appropriate. Other drugs affecting electrolyte balance may also alter lithium excretion and should be avoided if possible or used with care.

Further interactions reported with lithium are discussed below.

Reviews.

1. Amdisen A. Lithium and drug interactions. *Drugs* 1982; **24:** 133–9.
2. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26:** 160–2.
3. Harvey NS, Merriman S. Review of clinically important drug interactions with lithium. *Drug Safety* 1994; **10:** 455–63.
4. Finley PR, *et al.* Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995; **29:** 172–91.

ACE inhibitors. Giving lithium with ACE inhibitors has been reported[1-5] to increase serum-lithium concentrations, resulting in some cases in lithium toxicity. ACE inhibitors such as *captopril*,[2] *enalapril*,[1,3,5] and *lisinopril*[4,5] have been implicated, although in a study[6] of enalapril and lithium in healthy subjects, the lithium levels remained unchanged. The mechanism is unclear but it has been suggested[7] that suppression of the renin-angiotensin-aldosterone system by ACE inhibitors may be responsible. Lithium excretion by the kidney is dependent on both glomerular filtration and sodium concentration in the proximal tubule, both of which are reduced by ACE inhibitors. It has also been suggested[5] that inhibition of angiotensin II production may lead to reduced fluid intake through lack of activation of the thirst stimulus and this would enhance the tendency to volume depletion caused by natriuresis. Patients considered[7] to be at risk from this reaction would include those whose renal function is largely dependent on the effect of angiotensin II, those with congestive heart failure, and those with volume depletion.

1. Douste-Blazy P, *et al.* Angiotensin converting enzyme inhibitors and lithium treatment. *Lancet* 1986; **i:** 1448.
2. Pulik M, Lida H. Interaction lithium-inhibiteurs de l'enzyme de conversion. *Presse Med* 1988; **17:** 755.
3. Navis GJ, *et al.* Volume homeostasis, angiotensin converting enzyme inhibition, and lithium therapy. *Am J Med* 1989; **86:** 621.
4. Baldwin CM, Safferman AZ. A case of lisinopril-induced lithium toxicity. *DICP Ann Pharmacother* 1990; **24:** 946–7.
5. Correa FJ, Eiser AR. Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am J Med* 1992; **93:** 108–9.
6. DasGupta K, *et al.* The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry* 1992; **53:** 398–400.
7. Mignat C, Unger T. Ace inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–47.

Analgesics. See NSAIDs and Opioid Analgesics, p. 434.2 and p. 434.3, respectively.

Angiotensin II receptor antagonists. There have been case reports of lithium intoxication occurring in patients after the addition of *candesartan*,[1] *losartan*,[2] or *valsartan*[3] to their therapy. The mechanism may be similar to that for ACE inhibitors (above).

1. Zwanzger P, *et al.* Lithium intoxication after administration of AT_1 blockers. *J Clin Psychiatry* 2001; **62:** 208–9.
2. Blanche P, *et al.* Lithium intoxication in an elderly patient after combined treatment with losartan. *Eur J Clin Pharmacol* 1997; **52:** 501.
3. Leung M, Remick RA. Potential drug interaction between lithium and valsartan. *J Clin Psychopharmacol* 2000; **20:** 392–3.

Antidepressants. Lithium has been used to augment the effect of other antidepressants in refractory depression. However, there have been reports of adverse reactions with some of these combinations. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2.

Antiepileptics. Severe CNS toxicity despite 'normal' serum-lithium concentrations has been described in a patient also taking *phenytoin* and *phenobarbital*.[1] Symptoms indicative of lithium toxicity have also been reported in a patient taking lithium with phenytoin alone;[2] again concentrations were not abnormal.

For reports of neurotoxicity in patients receiving *carbamazepine* and lithium, see p. 516.2. Carbamazepine-induced renal failure has also resulted in toxic serum-lithium concentrations.[3]

1. Speirs J, Hirsch SR. Severe lithium toxicity with "normal" serum concentrations. *BMJ* 1978; **1:** 815–16.
2. MacCallum WAG. Interaction of lithium and phenytoin. *BMJ* 1980; **280:** 610–11.
3. Mayan H, *et al.* Lithium intoxication due to carbamazepine-induced renal failure. *Ann Pharmacother* 2001; **35:** 560–2.

Antimicrobials. Lithium toxicity has been reported on isolated occasions in patients receiving *doxycycline*,[1] *metronidazole*,[2] *spectinomycin*,[3] and *tetracycline*.[4]

However, it has been noted that lithium and tetracycline have been used together without serious problems in many patients and that additionally tetracycline has been used to treat the acneform skin eruptions induced by lithium.[5] It has also been found[5] that in healthy subjects lithium concentrations were decreased, rather than increased, after the addition of tetracycline but this was probably of no clinical significance.

1. Miller SC. Doxycycline-induced lithium toxicity. *J Clin Psychopharmacol* 1997; **17:** 54–5.
2. Teicher MH, *et al.* Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 1987; **257:** 3365–6.
3. Anonymous. Possible adverse drug-drug interaction report: lithium intoxication in a spectinomycin-treated patient. *Int Drug Ther Newslett* 1978; **13:** 15.
4. McGennis AJ. Lithium carbonate and tetracycline interaction. *BMJ* 1978; **i:** 1183.
5. Fankhauser MP, *et al.* Evaluation of lithium-tetracycline interaction. *Clin Pharm* 1988; **7:** 314–17.

Antimigraine drugs. For comment on the suggestion that there may be a risk of increased CNS toxicity when *sumatriptan* and lithium are given together, see p. 681.3.

Antineoplastics. Transient decreases in serum-lithium concentration occurred in a patient given *cisplatin*.[1] The relative contributions of cisplatin itself, or the fluid loading procedure involving intravenous fluids and mannitol, or their combined effects were unclear. The interaction, however, had no apparent clinical significance in this patient although a risk of undertreatment with lithium may occur in other patients.

1. Pietruszka LJ, *et al.* Evaluation of cisplatin-lithium interaction. *Drug Intell Clin Pharm* 1985; **19:** 31–2.

Antipsychotics and anxiolytics. In the control of acute mania lithium is often too slow in onset to be used alone and therefore additional therapy with an antipsychotic may be necessary. It should be noted, however, that such combinations should be used with care as interactions and adverse reactions have occurred.

The renal excretion of lithium is increased by *chlorpromazine* treatment,[1] which means that subsequent withdrawal of chlorpromazine can result in an abrupt rise in serum-lithium concentrations.[2] The serum concentration of chlorpromazine can also be reduced by lithium,[3] and chlorpromazine toxicity may be precipitated by the abrupt withdrawal of lithium in patients previously stabilised on both drugs. Ventricular fibrillation has been described after withdrawal of lithium in a patient also taking chlorprom-

azine;[4] it was suggested that the chlorpromazine dose should be reduced if lithium is to be stopped.

There have been isolated reports of neurotoxicity or brain damage, characterised by delirium, seizures, encephalopathy, or an increased incidence of extrapyramidal symptoms in patients receiving lithium with *flupentixol decanoate*,[5] *fluphenazine decanoate*,[6] or high-dose *haloperidol*,[7-9] although two earlier retrospective studies of patients taking lithium with antipsychotics had failed to detect such adverse reactions.[10,11] Neurological reactions have also been reported in patients receiving lithium with *thioridazine*,[12,13] *sulpiride*,[14] *clozapine*,[15] and *risperidone*.[16] Although a causal relationship between these events and use of lithium with antipsychotics has not been fully established, patients should be monitored for signs of neurotoxicity if receiving such combinations.

A 1987 review considered that the neurotoxicity induced by lithium and antipsychotics was a rare entity.[17] Whether the combination produced any greater risk than either drug alone, and whether the neurotoxicity was a distinct diagnostic entity or simply represented atypical cases of lithium toxicity or the neuroleptic malignant syndrome, was debatable. The interaction between lithium and haloperidol might represent a form of neuroleptic malignant syndrome and that between lithium and the phenothiazines, especially thioridazine, a form of lithium toxicity. It was concluded that the risk from combination therapy was very small but that the clinician should, nevertheless, be aware of it.

Although lithium has been reported to interact with *diazepam* resulting in hypothermic episodes,[18] this may be an idiosyncratic response rather than a true drug interaction;[17] in general it was considered safe to use lithium with benzodiazepines.

1. Sletten I, *et al*. The effect of chlorpromazine on lithium excretion in psychiatric subjects. *Curr Ther Res* 1966; **8:** 441–6.
2. Pakes GE. Lithium toxicity with phenothiazine withdrawal. *Lancet* 1979; **ii:** 701.
3. Rivera-Calimlim L, *et al*. Effect of lithium on plasma chlorpromazine levels. *Clin Pharmacol Ther* 1978; **23:** 451–5.
4. Stevenson RN, *et al*. Ventricular fibrillation due to lithium withdrawal—an interaction with chlorpromazine? *Postgrad Med J* 1989; **65:** 936–8.
5. West A. Adverse effects of lithium treatment. *BMJ* 1977; **2:** 642.
6. Singh SV. Lithium carbonate/fluphenazine decanoate producing irreversible brain damage. *Lancet* 1982; **ii:** 278.
7. Cohen WJ, Cohen NH. Lithium carbonate, haloperidol, and irreversible brain damage. *JAMA* 1974; **230:** 1283–7.
8. Loudon JB, Waring H. Toxic reactions to lithium and haloperidol. *Lancet* 1976; **ii:** 1088.
9. Thomas C, *et al*. Lithium/haloperidol combinations and brain damage. *Lancet* 1982; **i:** 626.
10. Baastrup PC, *et al*. Adverse reactions in treatment with lithium carbonate and haloperidol. *JAMA* 1976; **236:** 2645–6.
11. Prakash R. Lithium-haloperidol combination and brain damage. *Lancet* 1982; **i:** 1468–9.
12. Standish-Barry HMAS, Shelly MA. Toxic neurological reaction to lithium/thioridazine. *Lancet* 1983; **i:** 771.
13. Cantor CH. Encephalopathy with lithium and thioridazine in combination. *Med J Aust* 1986; **144:** 164–5.
14. Dinan TG, O'Keane V. Acute extrapyramidal reactions following lithium and sulpiride co-administration: two case reports. *Hum Psychopharmacol Clin Exp* 1991; **6:** 67–9.
15. Blake LM, *et al*. Reversible neurologic symptoms with clozapine and lithium. *J Clin Psychopharmacol* 1992; **12:** 297–9.
16. Swanson CL, *et al*. Effects of concomitant risperidone and lithium treatment. *Am J Psychiatry* 1995; **152:** 1096.
17. Ross DR, Coffey CE. Neuroleptics and anti-anxiety agents. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 167–71.
18. Naylor GJ, McHarg A. Profound hypothermia on combined lithium carbonate and diazepam treatment. *BMJ* 1977; **2:** 22.

Benzodiazepines. See Antipsychotics and Anxiolytics, p. 431.3.

Calcium-channel blockers. Neurotoxicity has been reported in a patient receiving lithium after the addition of *verapamil*.[1] Serum-lithium concentrations were still inside the accepted therapeutic range and it was considered that the similar actions of lithium and verapamil on neurosecretory processes may have been responsible. Verapamil has also been reported to decrease serum-lithium concentrations.[2] Neurotoxicity has also been reported in a patient receiving lithium and *diltiazem*[3] as well as other drugs. Psychosis, possibly induced by the use of diltiazem and lithium together, has been reported in another patient.[4]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26:** 717–19.
2. Weinrauch LA, *et al*. Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108:** 1378–80.
3. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46:** 540–1.
4. Binder EF, *et al*. Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151:** 373–4.

Central stimulants. A woman who had been stabilised on lithium treatment for 15 months developed lithium toxicity within a few days of being given *mazindol*.[1]

There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *sibutramine*.

1. Hendy MS, *et al*. Mazindol-induced lithium toxicity. *BMJ* 1980; **280:** 684–5.

Diuretics. *Thiazide diuretics* produce sodium depletion by inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in serum-lithium concentrations.[1] Patients who are stabilised on lithium therapy and begin taking thiazide diuretics are at significant risk of developing lithium toxicity. Toxic lithium concentrations may be seen within 3 to 5 days of starting a diuretic. *Loop diuretics* (*furosemide*, *bumetanide*, and *etacrynic acid*) seem less likely to cause lithium retention, although caution is warranted, especially in patients whose dietary sodium is restricted.[1] *Amiloride*, and probably other potassium-sparing diuretics, have no effect on lithium excretion, but *acetazolamide* increases lithium excretion. However, the diuretic action of acetazolamide is short-lived and the interaction may therefore be transient.[1]

It has therefore been suggested that if diuretic therapy is necessary in patients stabilised on lithium, the lithium dose should be reduced by 25 to 50%,[1,2] lithium concentrations measured twice weekly until restabilisation occurs, and that perhaps loop diuretics such as bumetanide or furosemide would be preferable.

The topic of lithium-diuretic interaction and precautions to be considered has also been discussed.[3]

1. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26:** 160–3.
2. Ramsay LE. Interactions that matter: diuretics and antihypertensive drugs. *Prescribers' J* 1984; **24:** 60–5.
3. Grau E. Diuretics. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 180–3.

Gastrointestinal drugs. Giving *sodium bicarbonate* with lithium has led to reduced blood-lithium concentrations, attributed to increased renal excretion of the lithium cation in response to the extra load of bicarbonate anion to be excreted.[1] *Antacids* containing combinations of *aluminium and magnesium hydroxides* and *simeticone* had no effect on the dissolution and solubility of lithium carbonate *in vitro*[2] nor on its bioavailability *in vivo*.[3]

There has been a case report describing a possible interaction between lithium and *ispaghula* where low serum concentrations of lithium may have been due to ispaghula inhibiting intestinal absorption of lithium.[4]

Use of *cisapride* with lithium may increase the risk of ventricular arrhythmias.

1. McSwiggan C. A significant drug interaction. *Aust J Pharm* 1978; **59:** 6.
2. Schiessler DM, *et al*. Effect of antacids on lithium carbonate dissolution and solubility in vitro. *Am J Hosp Pharm* 1983; **40:** 825–8.
3. Goode DL, *et al*. Effect of antacid on the bioavailability of lithium carbonate. *Clin Pharm* 1984; **3:** 284–7.
4. Perlman BB. Interaction between lithium salts and ispaghula husk. *Lancet* 1990; **335:** 416.

Ion-exchange resins. The cation-exchange resin *sodium polystyrene sulfonate* may decrease the absorption of lithium salts.

Methyldopa. Lithium toxicity induced by methyldopa has been described on several occasions.[1-3] Symptoms of toxicity may occur even though serum-lithium concentrations remain within the therapeutic range.

1. Byrd GJ. Methyldopa and lithium carbonate: suspected interaction. *JAMA* 1975; **233:** 320.
2. O'Regan JB. Adverse interaction of lithium carbonate and methyldopa. *Can Med Assoc J* 1976; **115:** 385–6.
3. Osanloo E, Deglin JH. Interaction of lithium and methyldopa. *Ann Intern Med* 1980; **92:** 433–4.

Muscle relaxants. For reports of hypothermic episodes occurring with lithium and *diazepam*, see under Antipsychotics and Anxiolytics, p. 431.3.

Severe aggravation of hyperkinetic symptoms occurred in 2 patients with Huntington's chorea when *baclofen* was added to their treatment with lithium and haloperidol.[1]

1. Andén N-E, *et al*. Baclofen and lithium in Huntington's chorea. *Lancet* 1973; **ii:** 93.

Neuromuscular blockers. For reports of prolongation of neuromuscular blockade by lithium see under Atracurium, p. 2033.1. For further comments relating to surgery and anaesthesia, see under Anaesthesia in Precautions, p. 430.3.

NSAIDs. Decreased clearance and increased serum concentrations of lithium, resulting in toxicity on some occasions, have been reported after use of lithium with *celecoxib*,[1] *diclofenac*,[2] *ibuprofen*,[3,4] *indometacin*,[5,6] *ketorolac*,[7,8] *mefenamic acid*,[9,10] *naproxen*,[11] *piroxicam*,[12,13] *rofecoxib*,[14-16] and *tiaprofenic acid*;[17] secondary sources have also implicated *azapropazone*, *ketoprofen*,[18] *parecoxib*, and *phenylbutazone*.[18] However, serum-lithium concentration is not increased by *sulindac*.[11,19,20] Although serum-lithium concentrations were increased in a patient receiving *aspirin*[21] this has not been substantiated in others and an interaction is considered unlikely;[6,22] it has also been pointed out that control of sodium balance is necessary in such studies[22] and in the report purporting to show an interaction the diet had not been controlled.

It has been stated that for mild occasional aches, pains, and fever paracetamol was the preferred analgesic in patients receiving lithium, although occasional doses of aspirin were acceptable.[18] Sulindac appeared to be the safest NSAID for long-term use. Diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, phenylbutazone, and piroxicam should be avoided where possible but if it was necessary to use one of these drugs the maintenance dose of lithium should be reduced. It was also considered that perhaps other NSAIDs, for which no information was available at that time, should be regarded as having the potential to cause a rise in serum-lithium concentrations.

1. Slørdal L, *et al*. A life-threatening interaction between lithium and celecoxib. *Br J Clin Pharmacol* 2003; **55:** 413–14.
2. Reimann IW, Frölich JC. Effects of diclofenac on lithium kinetics. *Clin Pharmacol Ther* 1981; **30:** 348–52.
3. Kristoff CA, *et al*. Effect of ibuprofen on lithium plasma and red blood cell concentrations. *Clin Pharm* 1986; **5:** 51–5.
4. Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. *J Clin Psychiatry* 1987; **48:** 161–3.
5. Frölich JC, *et al*. Indomethacin increases plasma lithium. *BMJ* 1979; **1:** 1115–16.
6. Reimann IW, *et al*. Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* 1983; **40:** 283–6.
7. Langlois R, Paquette D. Increased serum lithium levels due to ketorolac therapy. *Can Med Assoc J* 1994; **150:** 1455–6.
8. Iyer V. Ketorolac (Toradol) induced lithium toxicity. *Headache* 1994; **34:** 442–4.
9. Shelley RK. Lithium toxicity and mefenamic acid: a possible interaction and the role of prostaglandin inhibition. *Br J Psychiatry* 1987; **151:** 847–8.
10. MacDonald J, Neale TJ. Toxic interaction of lithium carbonate and mefenamic acid. *BMJ* 1988; **297:** 1339.
11. Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol* 1986; **6:** 150–4.
12. Kerry RJ, *et al*. Possible toxic interaction between lithium and piroxicam. *Lancet* 1983; **i:** 418–19.
13. Walbridge DG, Bazire SR. An interaction between lithium carbonate and piroxicam presenting as lithium toxicity. *Br J Psychiatry* 1985; **147:** 206–7.
14. Sajbel TA, *et al*. Pharmacokinetic effects of rofecoxib therapy on lithium. *Pharmacotherapy* 2001; **21:** 380.
15. Lundmark J, *et al*. A possible interaction between lithium and rofecoxib. *J Clin Pharmacol* 2002; **53:** 403–4.
16. Rätz Bravo AE, *et al*. Lithium intoxication as a result of an interaction with rofecoxib. *Ann Pharmacother* 2004; **38:** 1189–93.
17. Alderman CP, Lindsay KSW. Increased serum lithium concentration secondary to treatment with tiaprofenic acid and fosinopril. *Ann Pharmacother* 1996; **30:** 1411–3.
18. Furnell MM. Non-steroidal anti-inflammatory drugs. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 183–6.
19. Furnell MM, Davies J. The effect of sulindac on lithium therapy. *Drug Intell Clin Pharm* 1985; **19:** 374–6.
20. Ragheb MA, Powell AL. Failure of sulindac to increase serum lithium levels. *J Clin Psychiatry* 1986; **47:** 33–4.
21. Bendz H, Feinberg M. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41:** 310–11.
22. Reimann I. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41:** 311.

Opioid analgesics. There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *tramadol*.

Parasympathomimetics. For the effect of lithium on parasympathomimetics, see Interactions of Neostigmine, p. 688.3.

Xanthines. It has been reported[1] that *theophylline* enhances the renal clearance of lithium, thus tending to reduce serum-lithium concentrations. Lithium blood concentrations increased by 24% when *caffeine* was eliminated from the diet of 11 patients taking lithium.[2] No toxicity was seen but these patients had been maintained on low baseline lithium concentrations; toxicity might occur in patients maintained at higher concentrations.

1. Cook BL, *et al*. Theophylline-lithium interaction. *J Clin Psychiatry* 1985; **46:** 278–9.
2. Mester R, *et al*. Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry* 1995; **37:** 348–50.

Pharmacokinetics

Lithium is readily and completely absorbed from the gastrointestinal tract when taken as one of its salts. Absorption can be affected by the formulation of the preparation taken. Peak serum concentrations occur between 0.5 and 3 hours after ingestion from conventional tablets, capsules, or liquids; with modified-release formulations peak concentrations are delayed and may occur between 2 and 12 hours after a dose. Lithium is distributed throughout the body and distribution is complete within about 6 to 10 hours; higher concentrations occur in the bones, the thyroid gland, and portions of the brain, than in the serum.

Lithium is excreted mainly in the urine; only a small amount can be detected in the faeces, saliva, and sweat. It is not bound to plasma proteins. It crosses the placenta and is distributed into breast milk. The elimination half-life in patients with normal renal function is about 12 to 24 hours, but increases with decreasing renal function; half-lives of up to 36 hours have been reported for elderly patients and 40 to 50 hours for patients with renal impairment. Steady-state concentrations may not, therefore, be attained until 4 to 7 days after starting treatment.

There is wide intersubject variation in the serum concentrations obtained after a given dose, and also in those required for therapeutic effect. Concentrations also vary considerably according to factors such as the dosage regimen (whether given in single or divided daily doses), renal function, the dietary regimen of the patient, the patient's state of health, the time at which the blood sample is taken, and other medication, such as sodium salts or diuretics, as well as by formulation and bioavailability. Moreover, there is only a narrow margin between the therapeutic and the toxic serum concentration of lithium. Therefore, not only is individual titration of lithium dosage essential to ensure constant appropriate concentrations for the patient, but the conditions under which the blood samples are taken for monitoring must be carefully controlled. In practice, a blood sample drawn 12 hours after the last dose of lithium following a consistent dosing schedule for 4 to 7 days is used for measurement of serum-lithium concentrations. Under these conditions the distribution of the last dose of lithium is complete, and steady-state concentrations will have been attained. The usual maintenance therapeutic serum concentrations of lithium are 0.4 to 1 mmol/litre; toxic effects may be expected at concentrations exceeding 1.5 mmol/litre. For further details regarding monitoring of serum concentrations of lithium, see Uses and Administration, p. 428.1. Estimation of lithium concentrations in other body fluids such as saliva has been investigated as a less invasive method of monitoring. However, results have been equivocal and these methods have not replaced serum monitoring in general practice.

References.
1. Ward ME, *et al.* Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 1994; **34:** 280–5.
2. Reiss RA, *et al.* Lithium pharmacokinetics in the obese. *Clin Pharmacol Ther* 1994; **55:** 392–8.
3. Thomsen K, Schou M. Avoidance of lithium intoxication: advice based on knowledge about the renal lithium clearance under various circumstances. *Pharmacopsychiatry* 1999; **32:** 83–6.
4. Sproule BA, *et al.* Differential pharmacokinetics of lithium in elderly patients. *Drugs Aging* 2000; **16:** 165–77.

Administration. References concerning the pharmacokinetic methods of predicting lithium dosage requirements.

1. Marken PA, *et al.* Preliminary comparison of predictive and empiric lithium dosing: impact on patient outcome. *Ann Pharmacother* 1994; **28:** 1148–52.
2. Taright N, *et al.* Nonparametric estimation of population characteristics of the kinetics of lithium from observational and experimental data: individualization of chronic dosing regimen using a new Bayesian approach. *Ther Drug Monit* 1994 **16:** 258–69.
3. Sproule BA, *et al.* Fuzzy logic pharmacokinetic modeling: application to lithium concentration prediction. *Clin Pharmacol Ther* 1997; **62:** 29–40.
4. Wright R, Crimson ML. Comparison of three a priori methods and one empirical method in predicting lithium dosage requirements. *Am J Health-Syst Pharm* 2000; **57:** 1698–1702.

Cystic fibrosis. For a reference to reduced renal excretion of lithium in patients with cystic fibrosis, see under Precautions, p. 430.3.

Distribution into breast milk. For references to the distribution of lithium into breast milk, see under Precautions, p. 430.3.

Pregnancy. For references to changes in renal clearance of lithium during pregnancy, see under Precautions, p. 431.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ceglution; Eskalit; Karlit; Lithiun; ***Austral.***: Lithicarb; Quilonum; ***Austria***: Neurolepsin; Quilonorm; ***Belg.***: Camcolit; Maniprex; Priadel; ***Braz.***: Carbolim; Carbolitium; Neurolithium; ***Canad.***: Carbolith; Lithane; ***Chile***: Cade L; Carbolit; Carboron; Psicolit; ***Denm.***: Litarex; ***Fin.***: Lito; ***Fr.***: Lithioderm; Neurolithium†; Teralithe; ***Ger.***: Hypnorex; Lithiofor; Quilonum; ***Gr.***: Lithiofor; Milithin; Priadel; ***Hong Kong***: Licarb; Lithicarb; Lithiofor; ***Hung.***: Liticarb; ***India***: Alkalith; Elcab; Genlith; Indlith; Licab; Lithocent; Lithopik; Lithosun; Staleth; ***Indon.***: Frimania; ***Irl.***: Camcolit; Priadel; ***Israel***: Licarbium; ***Ital.***: Carbolithium; ***Jpn***: Limas; ***Mex.***: Carbolit; Litheum; ***Neth.***: Camcolit; Litarex†; Priadel; ***Norw.***: Lithionit; ***NZ***: Lithicarb; Priadel; ***Phil.***: Quilonium-R; ***Port.***: Priadel; ***Rus.***: Sedalit (Седалит); ***S.Afr.***: Camcolit; Lentolith†; Quilonum; ***Singapore***: Camcolit; ***Spain***: Plenur; ***Swed.***: Lithionit; ***Switz.***: LiDCO; Litarex; Lithiofor; Priadel; Quilonorm; ***Thai.***: Licarb; Limed; Lit-300; Phanate†; ***Turk.***: Kilonum; Lithuril; ***UK***: Camcolit; Li-Liquid; Liskonum; Lithonate; Priadel; ***USA***: Lithobid.

Multi-ingredient Preparations. ***Austral.***: Caprilate†; ***Ger.***: Togal Classic†; ***Spain***: Citinoides†.

Homoeopathic Preparations. ***Chile***: Artroplex; ***Fr.***: Natrum Carbonicum Complexe No 10†; Rhus Toxicodendron Compose; Ricinus Compose; ***Ger.***: Arthriselect; Girheulit HM†; Girheulit HOM; Heweurat N; rheuma-loges; ***Neth.***: Rhodolith-Gastreu R46; ***Rus.***: Helidonium-Plus (Хелидониум-Плюс); Rhus-Plus (Рус-Плюс); ***Switz.***: Lithiumeel; Regenaplex Nr. 21c; Regenaplex Nr. 51c.

Pharmacopoeial Preparations
BP 2014: Lithium Carbonate Tablets; Lithium Citrate Oral Solution; Prolonged-release Lithium Carbonate Tablets;
USP 36: Lithium Carbonate Capsules; Lithium Carbonate Extended-release Tablets; Lithium Carbonate Tablets; Lithium Citrate Syrup.

Lofepramine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lofepramina; Leo-640; Lofepramina, hidrocloruro de; Lofépramine, Chlorhydrate de; Lofepramini Hydrochloridum; Lopramine Hydrochloride; WHR-2908A; Лофепрамина Гидрохлорид.

5-[3-[*N*-(Chlorophenacyl)-*N*-methylamino]propyl]-10,11-5*H*-dihydrodibenz[*b*,*f*]azepine hydrochloride.

$C_{26}H_{27}ClN_2O,HCl$=455.4

CAS — 23047-25-8 (lofepramine); 26786-32-3 (lofepramine hydrochloride).

ATC — N06AA07.

ATC Vet — QN06AA07.

UNII — Z24K96F991.

Pharmacopoeias. In *Br.*

BP 2014: (Lofepramine Hydrochloride). A fine, yellowish-white to green-yellow powder with a faint characteristic odour. It exhibits polymorphism. Very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Lofepramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). One of its metabolites is desipramine (p. 413.1). Lofepramine is one of the less sedating tricyclics.

In the treatment of depression (p. 398.1) lofepramine is given orally as the hydrochloride although doses are expressed in terms of the base. Lofepramine hydrochloride 76.1 mg is equivalent to about 70 mg of lofepramine. The usual dose is the equivalent of 70 mg two or three times daily.

Lofepramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in the elderly. UK licensed product information suggests that some elderly patients may respond to lower than usual doses of lofepramine, but in a study[1] involving 46 elderly patients with various grades of depression lofepramine 70 mg once daily was no more effective than placebo at the end of 28 days of treatment.

1. Tan RSH, *et al.* The effect of low dose lofepramine in depressed elderly patients in general medical wards. *Br J Clin Pharmacol* 1994; **37:** 321–4.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3) although it has a lower incidence of antimuscarinic adverse effects. Lofepramine should be avoided in patients with severe hepatic or severe renal impairment.

Effects on the liver. See under Amitriptyline, p. 403.3.

Overdosage. Lofepramine may be less toxic in overdosage than earlier tricyclics.[1] An analysis of data from the Office of National Statistics in England and Wales has also shown that the risk of death after an overdose with lofepramine was not significantly different from that associated with the SSRIs which, as a group, are considered to be safer in overdose than the tricyclics.[2]

1. Reid F, Henry JA. Lofepramine overdosage. *Pharmacopsychiatry* 1990; **23:** 23–27.
2. Mason J, *et al.* Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract* 2000; **50:** 366–70.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lofepramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Lofepramine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 hour of oral doses. Since lofepramine slows gastrointestinal transit time absorption can, however, be delayed, particularly in overdosage. It is extensively demethylated by first-pass metabolism in the liver to its active, primary metabolite, desipramine (p. 413.1). Paths of metabolism also include *N*-oxidation and hydroxylation. The plasma half-life is about 5 hours. Lofepramine is mainly excreted in the urine, chiefly in the form of its metabolites. Up to 99% of lofepramine is bound to plasma proteins. Lofepramine is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Gamonil; ***Irl.***: Gamanil; ***S. Afr.***: Emdalen; ***UK***: Lomont.

Pharmacopoeial Preparations
BP 2014: Lofepramine Tablets.

Maprotiline *(BAN, USAN, rINN)*

Maprotiliini; Maprotilin; Maprotilina; Maprotilinum; Манротилин.

3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)propyl(methyl) amine; *N*-Methyl-9,10-ethanoanthracene-9(10*H*)-propylamine.

$C_{20}H_{23}N$=277.4

CAS — 10262-69-8.

ATC — N06AA21.

ATC Vet — QN06AA21.

UNII — 2U1W68TROF.

Maprotiline Hydrochloride *(BANM, rINNM)*

Ba-34276; Hidrocloruro de maprotilina; Maprotiliinihydrokloridi; Maprotilin Hidroklorür; Maprotilina, hidrocloruro de; Maprotiline, chlorhydrate de; Maprotilin-hidroklorid; Maprotilinhydrochlorid; Maprotilin-hydrochlorid; Maprotilinhydroklorid; Maprotilini Hydrochloridum; Maprotilino hidrochloridas; Манротилина Гидрохлорид.

$C_{20}H_{23}N,HCl$=313.9

CAS — 10347-81-6.

UNII — 7C8J54PVFI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Maprotiline Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. Slightly soluble in water; soluble in alcohol; very slightly soluble in acetone; sparingly soluble in dichloromethane; freely soluble in methyl alcohol.

USP 36: (Maprotiline Hydrochloride). A fine white to off-white, practically odourless, crystalline powder. Slightly soluble in water; freely soluble in chloroform and in methyl alcohol; practically insoluble in isooctane. Store in airtight containers.

Uses and Administration

Maprotiline is a tetracyclic antidepressant with actions and uses similar to those of tricyclic antidepressants (see Amitriptyline, p. 401.1). It is one of the more sedating antidepressants but antimuscarinic effects are less marked. Like the tricyclics, maprotiline is an inhibitor of the reuptake of noradrenaline; it also has weak affinity for central adrenergic (α_1) receptors.

Maprotiline is usually given orally as the hydrochloride but it has also been given by injection as the mesilate and in oral drops as the resinate.

In the treatment of depression (p. 398.1) maprotiline hydrochloride is given orally, and the total daily dose may be given in single or divided doses. It is usually given in initial doses of 75 mg daily. After 2 weeks the dosage should be adjusted according to response, and may be gradually increased in steps of 25 mg up to a daily dose of 150 mg if necessary. Severely depressed, hospitalised patients may be given initial doses of 100 to 150 mg daily. Adjustment of the dose up to 225 mg daily may be required in some severely depressed patients. A suggested initial dose for elderly patients is 25 mg daily, gradually increased according to response to 50 to 75 mg daily.

Maprotiline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

Adverse effects with maprotiline, a tetracyclic antidepressant, are broadly similar to those with tricyclic antidepressants (see Amitriptyline, p. 402.3) but antimuscarinic effects are less frequent.

Rashes seem more common with maprotiline than with tricyclic antidepressants. Seizures have occurred in patients with no history of such disorders as well as in those with a history of epilepsy and the risk is increased if high doses of maprotiline are given. It should not be used in patients with epilepsy or a lowered seizure threshold.

Incidence of adverse effects. By March 1985 the UK CSM[1] had received reports of the following adverse reactions associated with maprotiline from a cumulative total of 2.5 million prescriptions: convulsions (124 cases), hepatic reactions (4 cases), and haematological reactions (8 cases). There had also been 454 reports of rashes.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the skin. In addition to many recorded instances of rashes with maprotiline (see Incidence of Adverse Effects, above) cutaneous vasculitis, which resolved on stopping therapy, has also been seen.[1]

1. Oakley AMM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust N Z J Med* 1985; **15:** 256–7.

Epileptogenic effect. In a retrospective review of 186 psychiatric patients with no history of seizures, 5 of 32 patients taking maprotiline developed generalised tonic-clonic seizures, compared with 1 of 45 receiving a tricyclic antidepressant.[1] There were no seizures in those patients who received other medications, or no drug treatment. Two of the 5 patients having seizures with maprotiline were taking doses of 75 to 150 mg daily, 2 were taking daily doses of 200 to 300 mg, and one patient had partial complex seizures with a daily dose of 150 mg and generalised tonic-clonic seizures after increasing the daily dose to 300 mg.

1. Jabbari B, *et al.* Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* 1985; **42:** 480–1.

Overdosage. Apart from seizures being more common with maprotiline, features of overdosage are similar to those seen with tricyclic antidepressant poisonings (see Adverse Effects of Amitriptyline, p. 402.3).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p. 398.1.

References.

1. Crome P, Newman B. Poisoning with maprotiline and mianserin. *BMJ* 1977; **2:** 260.
2. Curtis RA, *et al.* Fatal maprotiline intoxication. *Drug Intell Clin Pharm* 1984; **18:** 716–20.
3. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.
4. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies maprotiline as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

Interactions associated with maprotiline are similar to those associated with tricyclic antidepressants (see Amitriptyline, p. 406.1).

Pharmacokinetics

Maprotiline is slowly but completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur within 8 hours of an oral dose. It is widely distributed throughout the body and plasma protein binding is about 88 to 89%.

Maprotiline is extensively demethylated in the liver to its principal active metabolite, desmethylmaprotiline; paths of metabolism of both maprotiline and desmethylmaprotiline include *N*-oxidation, aliphatic and aromatic hydroxylation, and the formation of aromatic methoxy derivatives. In addition to desmethylmaprotiline, maprotiline-*N*-oxide is also reported to be pharmacologically active. The average elimination half-life of maprotiline is reported to be about 43 hours and that of its active metabolite even longer (range 60 to 90 hours). Maprotiline is excreted in the urine, mainly in the form of its metabolites, either in free or in conjugated form; appreciable amounts are also excreted in the faeces.

Maprotiline is distributed into breast milk (see Breast Feeding under Precautions of Amitriptyline, p. 405.1).

References.

1. Maguire KP, *et al.* An evaluation of maprotiline: intravenous kinetics and comparison of two oral doses. *Eur J Clin Pharmacol* 1980; **18:** 249–54.
2. Alkalay D, *et al.* Bioavailability and kinetics of maprotiline. *Clin Pharmacol Ther* 1980; **27:** 697–703.
3. Firkusny L, Gleiter H. Maprotiline metabolism appears to co-segregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br J Clin Pharmacol* 1994; **37:** 383–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ludiomil; ***Belg.***: Ludiomil; ***Braz.***: Ludiomil; ***Chile***: Mapromil†; ***China***: Ludiomil (路滴美); ***Cz.***: Ludiomil; Maprotibene†; ***Denm.***: Ludiomil; ***Fr.***: Ludiomil; ***Ger.***: Ludiomil; Maprolu†; ***Gr.***: Aprotilin; Klimastress; Ludiomil; Retinyl; ***Hung.***: Ludiomil; ***Indon.***: Ludiomil; Ludios; Sandepril; Tilsan; ***Israel***: Melodil; ***Ital.***: Ludiomil; ***Malaysia***: Ludiomil; Lunaline; ***Mex.***: Ludiomil; ***NZ***: Ludiomil; ***Pol.***: Ludiomil†; ***Port.***: Ludiomil; ***Rus.***: Ludiomil (Людиомил); ***S.Afr.***: Ludiomil; ***Singapore***: Ludiomil; Lunaline; ***Spain***: Ludiomil; ***Swed.***: Ludiomil; ***Switz.***: Ludiomil; ***Thai.***: Ludiomil†; ***Turk.***: Ludiomil; Maprotil; ***Ukr.***: Ludiomil (Людиомил); ***Venez.***: Ludiomil.

Pharmacopoeial Preparations

USP 36: Maprotiline Hydrochloride Tablets.

Melitracen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de melitraceno; Mélitracène, Chlorhydrate de; Melitraceni Hydrochloridum; Melitraceno, hidrocloruro de; N-7001; U-24973A; Мелитрацена Гидрохлорид.

3-(9,10-Dihydro-10,10-dimethyl-9-anthrylidene)propyldimethylamine hydrochloride.

$C_{21}H_{25}N,HCl$=327.9

CAS — 5118-29-6 (melitracen); 10563-70-9 (melitracen hydrochloride).

ATC — N06AA14.

ATC Vet — QN06AA14.

UNII — J3448GKP5W.

Profile

Melitracen is a tricyclic antidepressant (see Amitriptyline, p. 401.1). It is given orally as the hydrochloride although doses are expressed in terms of the base; melitracen hydrochloride 28.1 mg is equivalent to about 25 mg of melitracen.

Melitracen is given with flupentixol (p. 1074.1) in the management of depression with anxiety (p. 398.1). A combination of melitracen 10 mg and flupentixol 500 micrograms is given orally in the morning and at midday. In severe cases the morning dose may be doubled. The total daily dose should not exceed melitracen 40 mg and flupentixol 2 mg. Elderly patients may be given melitracen 10 mg with flupentixol 500 micrograms in the morning; in severe cases this dose may be given in the morning and at midday. Melitracen has also been used alone in the treatment of depression. It was given in initial doses of 25 mg two to three times daily, increased as necessary to a maximum of 225 mg daily.

Melitracen should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Novoxit.

Multi-ingredient Preparations. ***Austria***: Deanxit; ***Belg.***: Deanxit; ***China***: Deanxit (黛力新); ***Hong Kong***: Anfree; Danxipress; Deanxit; Quali-Xit; ***India***: Ambulax-FM; Deanxit; Delewal; Denxol; Flupen-M; Forcalm; Franxit; Fycida-M; Melicen-FP; Meliyos; Melthix; Metflu; ***Singapore***: Deanxit; ***Spain***: Deanxit; ***Switz.***: Deanxit; ***Thai.***: Deanxit.

Mianserin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de mianserina; Mianseriinihydrokloridi; Mianserin Hidroklorür; Mianserina, hidrocloruro de; Miansérine, Chlorhydrate de; Mianserinhydrochlorid; Mianserin-hydrochlorid; Mianserinhydroklorid; Mianserini Hydrochloridum; Mianserino hidrochloridas; Mianseryny chlorowodorek; Mianszerin-hidroklorid; Org-GB-94; Миансерина Гидрохлорид.

1,2,3,4,10,14b-Hexahydro-2-methyldibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine hydrochloride.

$C_{18}H_{20}N_2,HCl$=300.8

CAS — 24219-97-4 (mianserin); 21535-47-7 (mianserin hydrochloride).

ATC — N06AX03.

ATC Vet — QN06AX03.

UNII — 2X03TN217S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Mianserin Hydrochloride). A white or almost white crystalline powder or crystals. Sparingly soluble in water; slightly soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Mianserin is a tetracyclic antidepressant. It does not appear to have significant antimuscarinic properties, but has a marked sedative action. Unlike the tricyclic antidepressants (see Amitriptyline, p. 401.1), mianserin does not prevent the peripheral reuptake of noradrenaline; it blocks presynaptic adrenergic (α_2) receptors and increases the turnover of brain noradrenaline. Mianserin is also an antagonist of postsynaptic serotonin receptors in some parts of the brain.

In the treatment of depression (p. 398.1) mianserin hydrochloride is given in initial oral doses of 30 to 40 mg daily increased gradually thereafter as necessary. The effective daily dosage is usually between 30 and 90 mg. The daily dosage may be divided throughout the day or given as a single dose at night. Divided daily dosages of up to 200 mg have been given. The recommended initial daily dose in the elderly is not more than 30 mg, which may be slowly increased if necessary.

Mianserin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects

Antimuscarinic and cardiac adverse effects are fewer and milder with mianserin, a tetracyclic antidepressant, than with tricyclic antidepressants but effects are otherwise broadly similar (see Amitriptyline, p. 402.3); mianserin may be associated with a lower risk of cardiotoxicity in overdosage.

The most common adverse effect associated with mianserin is drowsiness. Mianserin also causes bone-marrow depression usually presenting as leucopenia, granulocytopenia, or agranulocytosis; aplastic anaemia has been reported. These adverse haematological reactions generally occur during the first few weeks of therapy and especially in the elderly.

Other adverse effects reported include disturbances of liver function and jaundice, breast disorders (gynaecomastia, nipple tenderness, and non-puerperal lactation), and polyarthropathy.

Effects on the blood. Between 1976 and the end of 1988 the UK CSM had received 239 reports of adverse haematological reactions associated with mianserin use.[1] The reports included 68 of agranulocytosis and 84 of granulocytopenia or leucopenia where mianserin was considered to be the probable or possible cause; there had been 17 fatalities. Allowing for the pattern of prescribing there was a greater number of reports of white blood cell disorders in patients over 65 years of age but there was no sex difference. The data also indicated that the adverse reactions were most likely to develop during the first 3 months of therapy. By the end of 1992 the number of reports of mianserin-induced agranulocytosis or neutropenia received by the CSM[2] had risen to 79 and 105, respectively.

A case of fatal aplastic anaemia associated with mianserin use has also been reported.[3]

Proposed mechanisms of mianserin haematotoxicity have included a direct toxicity[4] and an immunologically-mediated mechanism.[5] There is evidence from studies *in vitro* of a significant correlation between the desmethyl metabolite and cytotoxicity. Mianserin is given as a racemic preparation and the formation of metabolites was greater with the *R* (-)-enantiomer than with the *S*(+)-enantiomer.[6]

1. CSM. Mianserin and white blood cell disorders in the elderly. *Current Problems 25* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024441&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
3. Durrant S, Read D. Fatal aplastic anaemia associated with mianserin. *BMJ* 1982; **285:** 437.
4. O'Donnell JL, *et al.* Possible mechanism for mianserin induced neutropenia associated with saturable elimination kinetics. *BMJ* 1985; **291:** 1375–6.
5. Stricker BHC, *et al.* Thrombocytopenia and leucopenia with mianserin-dependent antibodies. *Br J Clin Pharmacol* 1985; **19:** 102–4.
6. Riley RJ, *et al.* A stereochemical investigation of the cytotoxicity of mianserin metabolites in vitro. *Br J Clin Pharmacol* 1989; **27:** 823–30.

Effects on the cardiovascular system. Although mianserin is considered to be less cardiotoxic than the tricyclic antidepressants adverse effects have been noted in individual patients. Two elderly patients developed signs of disturbed cardiac function (cardiac failure, atrial and ventricular fibrillation, bradycardia, and frequent ventricular ectopic beats) which resolved after the drug was stopped.[1] One of the patients also developed hypokalaemia which was possibly caused by mianserin. It was suggested that persons most likely to have problems were the elderly with a history of cardiovascular disorders. Further reports of mianserin-induced cardiac effects include recurrent ventricular fibrillation in a 61-year-old man after an overdose of mianserin[2] and bradycardia in a 50-year-old woman after a therapeutic dose.[3]

1. Whiteford H, *et al.* Disturbed cardiac function possibly associated with mianserin therapy. *Med J Aust* 1984; **140:** 166–7.
2. Haefeli WE, *et al.* Recurrent ventricular fibrillation in mianserin intoxication. *BMJ* 1991; **302:** 415–16.
3. Carcone B, *et al.* Symptomatic bradycardia caused by mianserin at therapeutic doses. *Hum Exp Toxicol* 1991; **10:** 383–4.

Effects on the liver. By March 1985 the UK CSM had received 57 reports of hepatic reactions associated with mianserin use from a total of 5 million prescriptions. Reactions had included jaundice and other abnormalities of liver function, but no fatalities had been reported.[1]

Case reports have also been published concerning jaundice;[2-5] liver function returned to normal after stopping mianserin or lowering the dose.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. Adverse Drug Reactions Advisory Committee. Mianserin: a possible cause of neutropenia and agranulocytosis. *Med J Aust* 1980; **2:** 673–4.
3. Goldstraw PW, *et al.* Mianserin and jaundice. *N Z Med J* 1983; **96:** 985.
4. Zarski J-P, *et al.* Toxicité hépatique des nouveaux anti-dépresseurs: a propos d'une observation. *Gastroenterol Clin Biol* 1983; **7:** 220–1.
5. Otani K, *et al.* Hepatic injury caused by mianserin. *BMJ* 1989; **299:** 519.

Effects on the musculoskeletal system. A patient developed an acute polyarthritis affecting the hands and feet 6 days after starting therapy with mianserin;[1] at that time the UK CSM had received 19 reports of arthritis and arthralgia associated with mianserin. For the suggestion that effects at serotonin receptors may be involved in such adverse effects see under Mirtazapine, p. 438.3.

1. Hughes A, Coote J. Arthropathy associated with treatment with mianserin. *BMJ* 1986; **292:** 1050.

Effects on the skin. Reports of adverse dermatological reactions in individual patients related to mianserin therapy have included toxic epidermal necrolysis[1] and erythema multiforme.[2,3]

1. Randell P. Tolvon and toxic epidermal necrolysis. *Med J Aust* 1979; **2:** 653.
2. Quraishy E. Erythema multiforme during treatment with mianserin—a case report. *Br J Dermatol* 1981; **104:** 481.
3. Cox NH. Erythema multiforme due to mianserin—a case against generic prescribing. *Br J Clin Pract* 1985; **39:** 293–4.

Effects on the tongue. Glossitis associated with mianserin therapy was reported in 2 patients.[1] Additionally, glossitis accompanied by severe facial oedema has been noted in another patient.[2] In all cases symptoms resolved after withdrawal of mianserin.

1. de la Fuente JR, Berlanga C. Glossitis associated with mianserin. *Lancet* 1984; **i:** 233.
2. Leibovitch G, *et al.* Severe facial oedema and glossitis associated with mianserin. *Lancet* 1989; **ii:** 871–2.

Epileptogenic effect. By March 1985 the UK CSM had received 64 reports of convulsions associated with mianserin use from a total of 5 million prescriptions.[1] In a previous review[2] concerning 40 of these cases it was considered that a causal connection could be established only in a minority. It was suggested that mianserin is no more epileptogenic than tricyclic antidepressants, an opinion that was also shared by other reviewers.[3]

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Edwards JG, Glen-Bott M. Mianserin and convulsive seizures. *Br J Clin Pharmacol* 1983; **15:** 299S–311S.
3. Richens A, *et al.* Antidepressant drugs, convulsions and epilepsy. *Br J Clin Pharmacol* 1983; **15:** 295S–298S.

Overdosage. Experience with 100 consecutive cases of intoxication with mianserin[1] revealed that when it was the only drug ingested symptoms were mild and neither deep coma nor convulsions occurred. More serious symptoms and 2 fatalities were seen in patients who had taken multiple drug overdoses. The results suggested that after an acute overdose mianserin is less toxic than the tricyclic antidepressants. This conclusion was also supported by a large follow-up study[2] comparing the outcome of suicide attempts among patients who had taken mianserin in overdose with those who had taken amitriptyline.

1. Chand S, *et al.* One hundred cases of acute intoxication with mianserin hydrochloride. *Pharmakopsychiatrie* 1981; **14:** 15–17.
2. Inman WHW. Blood disorders and suicide in patients taking mianserin or amitriptyline. *Lancet* 1988; **ii:** 90–2.

Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 404.3). Although mianserin is less cardiotoxic than the tricyclic antidepressants, it still should be used with caution in patients with cardiovascular disorders, such as heart block, or after recent myocardial infarction. Similarly, patients with angle-closure glaucoma or prostatic hyperplasia should be monitored even though antimuscarinic effects are rare. Mianserin should be used with caution in patients with diabetes mellitus, epilepsy, and hepatic or renal impairment; it should be avoided in severe hepatic disease.

Patients should be carefully monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

A full blood count is recommended every 4 weeks during the first 3 months of treatment with mianserin, because of the risk of bone-marrow depression. Similarly, if a patient receiving mianserin develops fever, sore throat, stomatitis, or other signs of infection, treatment should be stopped and a full blood count obtained. The elderly are considered to be at special risk of blood disorders from mianserin. For further details see Effects on the Blood under Adverse Effects, p. 434.3.

UK licensed product information recommends that mianserin should not be given during breast feeding, but the *BNF* considers the amount distributed into breast milk too small to be harmful.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mianserin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

It is recommended that mianserin should not be given to patients receiving MAOIs or for at least 14 days afterwards. At least one week should elapse between withdrawing mianserin and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Unlike the tricyclics (p. 406.1), mianserin does not diminish the effects of the antihypertensives guanethidine, hydralazine, propranolol, or clonidine. However, it is still recommended that blood pressure be monitored when mianserin is prescribed with antihypertensive therapy. Plasma-phenytoin concentrations should be monitored carefully in patients also treated with mianserin; phenytoin has also been reported to reduce concentrations of mianserin (see p. 437.2). There may be potentiation of effects when mianserin is given with CNS depressants such as alcohol, anxiolytics, or antipsychotics.

Antiepileptics. Reduced plasma concentrations and half-lives of mianserin and desmethylmianserin were seen in 6 patients also receiving antiepileptic therapy consisting of *phenytoin* with either *carbamazepine* or *phenobarbital*.[1] Carbamazepine alone may also reduce the plasma concentration of mianserin.[2,3]

Mianserin may antagonise the action of antiepileptics by lowering the convulsive threshold.

1. Nawishy S, *et al.* Kinetic interaction of mianserin in epileptic patients on anticonvulsant drugs. *Br J Clin Pharmacol* 1982; **13:** 612P–13P.
2. Leinonen E, *et al.* Effects of carbamazepine on serum antidepressant concentrations in psychiatric patients. *J Clin Psychopharmacol* 1991; **11:** 313–18.
3. Eap CB, *et al.* Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. *Ther Drug Monit* 1999; **21:** 166–70.

Pharmacokinetics

Mianserin is readily absorbed from the gastrointestinal tract, but its bioavailability is reduced by extensive first-pass metabolism in the liver.

Paths of metabolism of mianserin include aromatic hydroxylation, *N*-oxidation, and *N*-demethylation. Desmethylmianserin and 8-hydroxymianserin are pharmacologically active.

Mianserin is excreted in the urine, almost entirely as its metabolites, either free or in conjugated form; some is also found in the faeces.

Mianserin is widely distributed throughout the body and is extensively bound to plasma proteins. It has been found to have a biphasic plasma half-life with the duration of the terminal phase ranging from about 6 to 40 hours. Mianserin crosses the blood-brain barrier and the placenta. It is distributed into breast milk.

References.

1. Hrdina PD, *et al.* Mianserin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **33:** 757–62.
2. Pinder RM, Van Delft AML. The potential therapeutic role of enantiomers and metabolites of mianserin. *Br J Clin Pharmacol* 1983; **15:** 269S–276S.
3. Timmer CJ, *et al.* Absolute bioavailability of mianserin tablets and solution in healthy humans. *Eur J Drug Metab Pharmacokinet* 1985; **10:** 315–23.
4. Begg EJ, *et al.* Variability in the elimination of mianserin in elderly patients. *Br J Clin Pharmacol* 1989; **27:** 445–51.
5. Buist A, *et al.* Mianserin in breast milk. *Br J ClinPharmacol* 1993; **36:** 133–4.
6. Dahl M-L, *et al.* Stereoselective disposition of mianserin is related to debrisoquin hydroxylation polymorphism. *Clin Pharmacol Ther* 1994; **56:** 176–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lerivon; ***Austral.***: Lumin; Tolvon; ***Austria***: Tolvon; ***Belg.***: Lerivon; ***Braz.***: Tolvon; ***Chile***: Athimil; Prevalina; ***China***: Tolvon (特文); ***Cz.***: Lerivon; Miabene; ***Denm.***: Tolmin; Tolvon†; ***Fin.***: Miaxan†; Tolvon; ***Fr.***: Athymil†; ***Ger.***: Mianeurin†; Tolvin†; ***Gr.***: Tolvon; ***Hong Kong***: Tolvon†; ***Hung.***: Miagen; Tolvon; ***India***: Depnon; ***Irl.***: Tolvon†; ***Israel***: Bonserin; ***Ital.***: Lantanon; ***Mex.***: Tolvon; ***Neth.***: Tolvon; ***Norw.***: Tolvon; ***NZ***: Tolvon; ***Pol.***: Deprexolet; Lerivon; Miansec; Miansegen; Miansemerck; Norserin†; ***Port.***: Tolvon; ***Rus.***: Lerivon (Леривон); ***S.Afr.***: Lantanon; ***Spain***: Lantanon; ***Swed.***: Tolvon†; ***Switz.***: Tolvon; ***Thai.***: Mealin; Servin; Tolimed; Tolvon; ***Turk.***: Tolvon; ***Ukr.***: Lerivon (Леривон); Miaser (Миасер).

Pharmacopoeial Preparations
BP 2014: Mianserin Tablets.

Milnacipran Hydrochloride *(BANM, rINNM)*

F-2207 (milnacipran); Hidrocloruro de milnaciprán; Midalcipran Hydrochloride; Milnacipran, Chlorhydrate de; Milnaciprán, hidrocloruro de; Milnaciprani Hydrochloridum; Мильнаципрана Гидрохлорид.

(±)-*cis*-2-(Aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide hydrochloride.

$C_{15}H_{22}N_2O,HCl$=282.8

CAS — 92623-85-3 (milnacipran); 101152-94-7 (milnacipran hydrochloride); 175131-61-0 (milnacipran hydrochloride).

ATC — N06AX17.

ATC Vet — QN06AX17.

UNII — RNZ43O5WW5.

Profile

Milnacipran hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p. 456.2). It is used for the treatment of depression (p. 398.1) in usual oral doses of 50 mg twice daily. In the management of fibromyalgia (see Soft-tissue Rheumatism, p. 14.2), milnacipran hydrochloride is introduced gradually, starting with a single dose of 12.5 mg on the first day, 12.5 mg twice daily on days 2 and 3, then 25 mg twice daily on days 4 to 7, and 50 mg twice daily thereafter. The dose may need to be increased to 100 mg twice daily in some patients, according to response. For doses in renal impairment, see p. 437.3.

Milnacipran should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

References.

1. Tignol J, *et al.* Double-blind study of the efficacy and safety of milnacipran and imipramine in elderly patients with major depressive episode. *Acta Psychiatr Scand* 1998; **97:** 157–65.
2. Spencer CM, Wilde MI. Milnacipran: a review of its use in depression. *Drugs* 1998; **56:** 405–27.
3. Rouillon F, *et al.* Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. *Int Clin Psychopharmacol* 2000; **15:** 133–40.
4. Clerc G. Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine. *Int Clin Psychopharmacol* 2001; **16:** 145–51.
5. Fukuchi T, Kanemoto K. Differential effects of milnacipran and fluvoxamine, especially in patients with severe depression and agitated depression: a case-control study. *Int Clin Psychopharmacol* 2002; **17:** 53–8.
6. Clauw DJ, *et al.* Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther* 2008; **30:** 1988–2004. Correction. *ibid.* 2009; **31:** 446.
7. Mease PJ, *et al.* The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009; **36:** 398–409. Correction. *ibid.*; 661.

Administration in renal impairment. Usual doses of milnacipran hydrochloride may be given to patients with mild renal impairment, and used with caution in moderate impairment. An oral maintenance dose of 25 mg twice daily may be given to patients with severe impairment (creatinine clearance 5 to 29 mL/min), but can be increased to 50 mg twice daily according to response. The drug should not be used in end-stage renal disease.

Interactions. *ANTIMIGRAINE DRUGS.* There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p. 681.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dalcipran; Ixel; ***Austria***: Dalcipran†; Ixel; ***Braz.***: Ixel; ***Chile***: Ixel; Misulvan; ***Cz.***: Dalcipran†; Ixel; ***Fin.***: Ixel; ***Fr.***: Ixel; ***Hong Kong***: Ixel; ***India***: Milborn; Milnace; ***Israel***: Ixel; ***Jpn***: Toledomin; ***Pol.***: Ixel†; ***Port.***: Dalcipran; Ixel; ***Rus.***: Ixel (Иксел); ***Thai.***: Ixel; ***Turk.***: Ixel; ***USA***: Savella.

Mirtazapine *(BAN, USAN, rINN)*

6-Azamianserin; Mepirzapin; Mepirzepine; Mirtatsapiini; Mirtazapin; Mirtazapina; Mirtazapinum; Org-3770; Миртазапин.

(*RS*)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino-[2,1-*a*]pyrido[2,3-*c*][2]benzazepine.

$C_{17}H_{19}N_3$=265.4

CAS — 61337-67-5.

ATC — N06AX11.

ATC Vet — QN06AX11.

UNII — A051Q2099Q (mirtazapine); 8Z5UNK8A61 (mirtazapine hemihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mirtazapine). A white or almost white powder, slightly hygroscopic to hygroscopic. It exhibits polymorphism. Practically insoluble in water; freely soluble in anhydrous alcohol. Store in airtight containers.

USP 36: (Mirtazapine). It is anhydrous or contains one-half molecule of water of hydration. A white to creamy white, crystalline powder. Practically insoluble in water; soluble in solvent ether; sparingly soluble in *n*-hexane; freely soluble in methyl alcohol and in toluene. Store in airtight containers.

Uses and Administration

Mirtazapine, a piperazinoazepine, is an analogue of mianserin (p. 434.2); it is a noradrenergic and specific serotonergic antidepressant. It enhances the release of noradrenaline and, indirectly, serotonin through blockade of central presynaptic adrenergic (α_2) receptors. The effects of released serotonin are mediated via 5-HT_1 receptors as mirtazapine blocks both 5-HT_2 and 5-HT_3 receptors. Mirtazapine is given as a racemic mixture: the *S*(+)-enantiomer blocks α_2 and 5-HT_2 receptors whereas the *R* (-)-enantiomer blocks 5-HT_3 receptors. Mirtazapine is also a potent antagonist at histamine (H_1) receptors which gives it sedative properties; it has very little antimuscarinic activity.

In the treatment of depression (p. 398.1), mirtazapine is given in an initial oral daily dose of 15 or 30 mg, which may be increased gradually according to response. Changes in dose should be made at intervals of at least 1 to 2 weeks because of the long half-life. The usual effective daily dose lies within the range of 15 to 45 mg. Daily doses may be given as a single dose, preferably at bedtime, or in 2 divided doses with the larger portion taken at night. Mirtazapine may also be given by intravenous infusion.

Mirtazapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. Mirtazapine has been tried with some success in the treatment of anxiety disorders (p. 1028.1) including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), and post-traumatic stress disorder (p. 1029.2).

References.
1. Boshuisen ML, *et al.* The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol* 2001; **16:** 363–8.
2. Davidson JR, *et al.* Mirtazapine vs placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry* 2003; **53:** 188–91.
3. Chung MY, *et al.* Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. *Hum Psychopharmacol* 2004; **19:** 489–94.
4. Koran LM, *et al.* Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry* 2005; **66:** 515–20.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Mirtazapine is a central presynaptic adrenergic (α_2) receptor antagonist and has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, mirtazapine appears to have fewer unpleasant adverse effects in comparison with the older tricyclics.

References.
1. Kasper S, *et al.* A risk-benefit assessment of mirtazapine in the treatment of depression. *Drug Safety* 1997; **17:** 251–64.
2. Montgomery SA, *et al.* Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. *Int Clin Psychopharmacol* 1998; **13:** 63–73.
3. Puzantian T. Mirtazapine, an antidepressant. *Am J Health-Syst Pharm* 1998; **55:** 44–9.
4. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs* 1999; **57:** 607–31.
5. Schatzberg AF, *et al.* Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; **10:** 541–50.
6. Wade A, *et al.* A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. *Int Clin Psychopharmacol* 2003; **18:** 133–41.
7. Versiani M, *et al.* Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs* 2005; **19:** 137–46.
8. Watanabe N, *et al.* Multiple Meta-Analyses of New Generation Antidepressants (MANGA) Study Group. Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis. *J Clin Psychiatry* 2008; **69:** 1404–15.

Nausea and vomiting. Mirtazapine has been investigated in the management of severe nausea and vomiting (p. 1814.3). For mention of the successful use of mirtazapine to treat hyperemesis of pregnancy see Pregnancy, under Precautions, p. 438.3.

Further references.
1. Kast RE. Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy. *Support Care Cancer* 2001; **9:** 469–70.
2. Caldis EV, Gair RD. Mirtazapine for treatment of nausea induced by selective serotonin reuptake inhibitors. *Can J Psychiatry* 2004; **49:** 707.
3. Teixeira FV, *et al.* Mirtazapine (Remeron) as treatment for non-mechanical vomiting after gastric bypass. *Obes Surg* 2005; **15:** 707–9.

Adverse Effects

Adverse effects commonly reported with mirtazapine are an increase in appetite and weight, and oedema; drowsiness or sedation generally occur during the first few weeks of treatment. Dizziness, headache, and increases in liver enzyme levels have been reported less commonly; jaundice may occur. Other rarely reported adverse effects include orthostatic hypotension, rashes, nightmares, agitation, mania, hallucinations, paraesthesia, convulsions, tremor, myoclonus, psychomotor restlessness including akathisia, restless legs syndrome, arthralgia, myalgia, and reversible agranulocytosis, leucopenia, and granulocytopenia.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Incidence of adverse effects. The Australian Adverse Drug Reactions Advisory Committee has reported[1] that, up to October 2003, it had received 253 reports of adverse reactions associated with the use of mirtazapine. The most frequently reported reactions were oedema (33 reports), anxiety or agitation (24 reports), myalgia or arthralgia (24 reports), sedation (23 reports), and skin reactions (20 reports). Other reactions included hyperkinesis, diarrhoea, and nausea and vomiting. There were 16 cases of convulsions, all in patients without a history of epilepsy. Blood dyscrasias were also reported and included 8 cases of neutropenia, 6 of thrombocytopenia, and 1 each of lymphopenia and pancytopenia; in the majority of cases onset was within 2 months of starting mirtazapine.

A prescription-event monitoring study conducted in England identified 13 554 patients who had been prescribed mirtazapine during the first 2 years of marketing in the UK;[2] within this cohort, 807 adverse drug reactions were reported in 573 patients. The most common adverse reactions included drowsiness or sedation (116 reports), malaise (71 reports), dizziness (57 reports), nausea and vomiting (33 reports), weight gain (31 reports), and headache or migraine (21 reports). Facial oedema (5 reports), allergy (3 reports), bone marrow toxicity (2 reports), and myelodysplasia (1 report) were the more serious suspected adverse reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Convulsions and blood dyscrasias with mirtazapine. *Aust Adverse Drug React Bull* 2003; **22:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0310.pdf (accessed 24/11/05)
2. Biswas PN, *et al.* The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 554 patients in England. *J Psychopharmacol* 2003; **17:** 121–6.

Effects on the endocrine system. An elderly woman developed *hyponatraemia* within 4 days of starting mirtazapine at a dose of 15 mg at night.[1] Apart from her age, other risk factors for hyponatraemia included diuretic use and a previous episode while taking venlafaxine.

1. Roxanas MG. Mirtazapine-induced hyponatraemia. *Med J Aust* 2003; **179:** 453–4.

Effects on mental state. An Expert Working Group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs particularly the risk of suicidal behaviour in children; the safety of mirtazapine (another serotonergic antidepressant) was also considered. In its final report[1] in December 2004, the group concluded that data from studies received by the CSM had failed to show that mirtazapine was effective in the treatment of depression in **adolescents and children** under 18 years old, although the risk of suicidal behaviour was not increased. Consequently, it was considered that the balance of risks and benefits of mirtazapine for the treatment of depression in this group was unfavourable. Similar recommendations have also been issued in the EU.[2]

The risk of suicide and suicide-related events with serotonergic antidepressant treatment in **adults**, including young adults, are discussed under Fluoxetine, p. 420.2.

1. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf (accessed 30/07/10)

Effects on the musculoskeletal system. The Netherlands Pharmacovigilance Centre Lareb received 8 reports of arthralgia associated with the use of mirtazapine between May 1995 and October 2004; the effect usually developed within a short time of starting treatment and resolved once the drug was withdrawn.[1] The authors noted that of 4578 reported reactions to mirtazapine held in the WHO database up to March 2004, 110 concerned the development of arthralgia. Similar reactions have occurred with mianserin and nefazodone, and it was suggested that effects at serotonin 5-HT_1 or 5-HT_2 receptors might be involved.

1. Passier A, van Puijenbroek E. Mirtazapine-induced arthralgia. *Br J Clin Pharmacol* 2005; **60:** 570–2.

Extrapyramidal effects. Akathisia that developed in 2 patients given mirtazapine 30 mg at night[1] resolved in one after being treated with clonazepam and in the other patient after reducing the dose of mirtazapine to 15 mg at night.

1. Girishchandra BG, *et al.* Mirtazapine-induced akathisia. *Med J Aust* 2002; **176:** 242.

Serotonin syndrome. The serotonin syndrome (p. 445.2) is most commonly due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug has caused the syndrome. One such case[1] occurred in an elderly patient given mirtazapine 15 mg daily; he was also taking salbutamol, ipratropium, and nimodipine, although none of these are known to have serotonergic effects.

1. Hernández JL, *et al.* Severe serotonin syndrome induced by mirtazapine monotherapy. *Ann Pharmacother* 2002; **36:** 641–3.

Precautions

Mirtazapine should be used with caution in patients with epilepsy or a history of seizures, and it should be avoided completely if these disorders are unstable. Care is also required in hepatic or renal impairment, and cardiac disorders such as conduction disturbances, angina pectoris, and recent myocardial infarction; caution is further advised in patients with hypotension, diabetes mellitus, psychoses, and in those with a history of bipolar disorder. Treatment should be stopped if jaundice develops. Although mirtazapine has only weak antimuscarinic activity, it should nevertheless be used with care in patients with micturition disturbances, angle-closure glaucoma, and raised intra-ocular pressure.

Because of the risk of bone-marrow depression, patients should be advised to report any of the following symptoms during treatment: fever, sore throat, stomatitis, or other signs of infection; treatment should be stopped and a blood count performed.

Drowsiness often occurs at the start of therapy and patients, if affected, should not drive or operate machinery.

Patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Mirtazapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. Mirtazapine has been detected in breast milk;[1] however, the plasma concentration in a breast-fed infant was very low (200 picograms/mL) and no adverse events were detected.

1. Aichhorn W, *et al.* Mirtazapine and breast-feeding. *Am J Psychiatry* 2004; **161:** 2325.

Children. The use of mirtazapine in adolescents and children with depression is not recommended; for further details, see Effects on Mental State, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mirtazapine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. A small case series followed the pregnancies of 9 women exposed to mirtazapine during the first trimester;[1] in the majority of cases the women were also exposed to other drugs. Within the group there were 7

healthy deliveries, 1 induced abortion, and 1 spontaneous abortion. In another report a mother who was given mirtazapine twice during her pregnancy for the successful treatment of hyperemesis gravidarum bore healthy male twins.[2] A follow-up examination of the twins at 6 months was normal.

Health Canada has reported that some newborn infants of mothers who took newer antidepressants such as mirtazapine mainly during the third trimester of pregnancy have had complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding.[3] Reported symptoms included seizures, muscle rigidity, jitteriness, and constant crying. It was considered that these symptoms represented either direct toxicity of mirtazapine or a possible withdrawal syndrome.

1. Yaris F, *et al*. Newer antidepressants in pregnancy: prospective outcome of a case series. *Reprod Toxicol* 2004; **19:** 235–8.
2. Rohde A, *et al*. Mirtazapine (Remergil) for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy. *Arch Gynecol Obstet* 2003; **268:** 219–21.
3. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Mirtazapine should not be used with or within 2 weeks of stopping an MAOI; at least one week should elapse between stopping mirtazapine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Use of mirtazapine with alcohol or benzodiazepines may potentiate sedative effects.

The cytochrome P450 isoenzyme CYP3A4 is involved in the metabolism of mirtazapine and caution is advised when mirtazapine is given with potent inhibitors of this isoenzyme such as HIV-protease inhibitors, azole antifungals including ketoconazole, erythromycin, and nefazodone; raised plasma levels of mirtazapine have been noted after use with ketoconazole. Conversely, carbamazepine and other inducers of CYP3A4 increased the clearance of mirtazapine and the dose of mirtazapine may need to be increased when given with these drugs.

Cimetidine, which inhibits a range of cytochrome P450 isoenzymes, has more than doubled the bioavailability of mirtazapine; the dose of mirtazapine may need to be reduced if given with cimetidine.

Antihypertensives. For reports of hypertensive crisis occurring when mirtazapine was given with clonidine, see Antidepressants, p. 1342.1.

Pharmacokinetics

Mirtazapine is well absorbed from the gastrointestinal tract and peak plasma levels occur about 2 hours after oral use. Plasma protein binding is about 85%. Mirtazapine is extensively metabolised in the liver and the major biotransformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The *N*-desmethyl metabolite is pharmacologically active. Elimination is via urine (75%) and faeces (15%). The mean plasma elimination half-life is 20 to 40 hours. Data from *animal* studies indicate that mirtazapine crosses the placenta. Mirtazapine is distributed into breast milk.

References.

1. Timmer CJ, *et al*. Clinical pharmacokinetics of mirtazapine. *Clin Pharmacokinet* 2000; **38:** 461–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bilanz; Comenter; Mitaxind; Noxibel; Remeron; Tetrazic; ***Austral.***: Avanza; Axit; Mirtazon; Remeron; ***Austria***: Mirtabene; Mirtaron; Mirtel; Remeron; ***Belg.***: Remergon; ***Braz.***: Menelat; Razapina; Remeron; ***Canad.***: Remeron; ***Chile***: Amirel; Ciblex; Divaril; Promyrtil; Zuleptan; ***China***: Mi Er Ning (米尔宁); Paidisheng (派迪生); Remeron (瑞美隆); ***Cz.***: Calixta†; Esprital; Mirtabs†; Mirtastad†; Mirzaten; Remeron; Valdren†; ***Denm.***: Arintapin; Combar; Kompazin†; Miramerck†; Mirtazon†; Mirtin; Remeron; Zapatabs†; ***Fin.***: Mirtachem; Mirtaril; Mirtazon†; Remeron; Trimazimyl; ***Fr.***: Norset; ***Ger.***: Mirta TAD; Mirtagamma; MirtaLich; Mirtazelon; Remergil; ***Gr.***: Azapin; Depreram; Merdaten; Mirrador; Mirtamor; Mirtapil; Motofen; Remeron; Saxib; ***Hong Kong***: Remeron; ***Hung.***: Mirtadepi; Mirtel†; Mirzaten; Mizapin; Remeron; Yarocen; ***India***: Matiz; Maz; Miramind; Miraz; Mirazep; Mirnite; Mirpine; Mirstar; Mirt; Mirtacin; Mirtadep; Mirtaz; Mirzest; Mitocent; Nassa; Nutaz; ***Indon.***: Remeron; ***Irl.***: Bexmirt†; BexZis†; Mirap; Mirtall†; Mirtaz†; Mirzaten; Tazamel†; Zismirt; Zispin; ***Israel***: Miro; Remeron; ***Ital.***: Remeron; ***Malaysia***: Remeron; ***Mex.***: Comenter; Mirzalux; Remeron; Zapex; ***Neth.***: Azatrim†; Mirasol; Mirzasna; Mitabor; Remeron; ***Norw.***: Remeron; ***NZ***: Avanza; Remeron†; ***Philipp.***: Mirazep; Remeron; ***Pol.***: Esprital; Mirtagen; Mirtamerck; Mirtastad; Mirtor; Mirzaten; Remeron; Remirta; ***Port.***: Mirpax; Mirtazon; Psidep; Remeron; ***Rus.***: Mirtalan (Мирталан); Mirtazonal (Миртазонал); Mirzaten (Мирзатен); Noxibel (Ноксибел); Remeron (Ремерон); ***S.Afr.***: Adco-Mirteron; Beron; Mytra; Remeron; ***Singapore***: Remeron; ***Spain***: Afloyan; Mirpik†; Mirtamylan; Rexer; Vastat†; ***Swed.***: Mirtin; Remeron; ***Switz.***: Mirtazap; Remeron; ***Thai.***: Remeron; ***Turk.***: Minelza; Mirtaron; Redepra; Remeron; Velorin; Zestat; ***UK***: Zispin; ***Ukr.***: Esprital (Эспритал); Mirazep (Миразеп); Mirtastadin (Миртастадин); Remeron (Ремерон); ***USA***: Remeron; ***Venez.***: Comenter; Remeron.

Pharmacopoeial Preparations

BP 2014: Mirtazapine Oral Solution; Mirtazapine Tablets; Orodispersible Mirtazapine Tablets;

USP 36: Mirtazapine Orally Disintegrating Tablets; Mirtazapine Tablets.

Moclobemide *(BAN, USAN, rINN)*

Moclobemida; Moclobémide; Moclobemidum; Moklobemid; Moklobemidi; Ro-11-1163; Ro-11-1163/000; Моклобемид.

4-Chloro-*N*-(2-morpholinoethyl)benzamide.

$C_{13}H_{17}ClN_2O_2$=268.7

CAS — 71320-77-9.

ATC — N06AG02.

ATC Vet — QN06AG02.

UNII — PJ0Y7AZB63.

Pharmacopoeias. In *Chin.* and *Swiss.*

Uses and Administration

Moclobemide, a benzamide derivative, is a reversible inhibitor of monoamine oxidase type A (RIMA) (see under Phenelzine, p. 444.1) used for the treatment of depression and of social anxiety disorder.

In the treatment of **depression** the usual initial oral dose of moclobemide is 300 mg daily in divided doses. This may be increased up to 600 mg daily according to response. In some patients, a maintenance dose of 150 mg daily may be sufficient.

In the treatment of **social anxiety disorder**, the initial daily dose of moclobemide is 300 mg increased after 3 days to 600 mg given in 2 divided doses. Treatment should be continued for 8 to 12 weeks to assess efficacy; patients should be periodically re-evaluated thereafter to determine the need for further treatment.

Moclobemide should be taken after food.

Reduced doses may need to be given in hepatic impairment (see p. 439.2) and in patients also taking cimetidine (see p. 440.1).

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Reviews.

1. Bonnet U. Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev* 2003; **9:** 97–140.

Administration in hepatic impairment. UK licensed product information states that doses of moclobemide in patients with severe hepatic impairment may need to be reduced to half or one-third of the recommended dose (see above).

Anxiety disorders. The use of MAOIs in general in the management of anxiety disorders is discussed under Phenelzine on p. 444.2. For a discussion of the overall treatment of anxiety disorders, see p. 1028.1.

References.

1. Noyes R, *et al*. Moclobemide in social phobia: a controlled dose-response trial. *J Clin Psychopharmacol* 1997; **17:** 247–54.
2. Neal LA, *et al*. An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol* 1997; **12:** 231–7.
3. Schneier FR, *et al*. Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry* 1998; **172:** 70–7.
4. Tiller JW, *et al*. Moclobemide and fluoxetine for panic disorder. *Eur Arch Psychiatry Clin Neurosci* 1999; **249** (suppl 1): S7–S10.
5. Stein DJ, *et al*. Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. *Int Clin Psychopharmacol* 2002; **17:** 161–70.

Depression. As discussed on p. 398.1 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. The traditional MAOIs such as phenelzine are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide offer a safer alternative to the irreversible non-selective MAOIs and fewer dietary restrictions are necessary.

References.

1. Fitton A, *et al*. Moclobemide: a review of its pharmacological properties and therapeutic use in depressive illness. *Drugs* 1992; **43:** 561–96.
2. Angst J, Stabl M. Efficacy of moclobemide in different patient groups: a meta-analysis of studies. *Psychopharmacology (Berl)* 1992; **106** (suppl): S109–S113.
3. Lonnqvist J, *et al*. Moclobemide and fluoxetine in atypical depression: a double-blind trial. *J Affect Disord* 1994; **32:** 169–77.
4. Norman TR, Burrows GD. A risk-benefit assessment of moclobemide in the treatment of depressive disorders. *Drug Safety* 1995; **12:** 46–54.
5. Roth M, *et al*. Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. *Br J Psychiatry* 1996; **168:** 149–57.
6. Lotufo-Neto F, *et al*. Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology* 1999; **20:** 226–47.

Smoking cessation. In a preliminary double-blind, placebo-controlled parallel-group study in 88 smokers, moclobemide facilitated smoking cessation (p. 2570.2) in highly dependent smokers.[1]

1. Berlin I, *et al*. A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. *Clin Pharmacol Ther* 1995; **58:** 444–52.

Adverse Effects

Adverse effects reported to occur with moclobemide include sleep disturbances, dizziness, agitation, feelings of anxiety, restlessness, irritability, and headache. Gastrointestinal disturbances include dry mouth, diarrhoea, constipation, and nausea and vomiting. Paraesthesia, visual disturbances, and oedema have also been reported, and skin reactions include rash, pruritus, urticaria, and flushing. Confusional states have occurred but they disappear rapidly on stopping the drug. Raised liver enzymes and galactorrhoea have been reported rarely.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on the cardiovascular system. Hypertension has been reported[1,2] rarely in patients taking moclobemide, some of whom were also taking other drugs although moclobemide was suspected to be the cause. Blood pressure usually returned to normal after stopping moclobemide.

1. Coulter DM, Pillans PI. Hypertension with moclobemide. *Lancet* 1995; **346:** 1032.
2. Boyd IW. Hypertension with moclobemide. *Lancet* 1995; **346:** 1498.

Effects on the endocrine system. A prescription-event monitoring study found that galactorrhoea is significantly associated with the use of moclobemide.[1]

1. Dunn NR, *et al*. Galactorrhoea with moclobemide. *Lancet* 1998; **351:** 802.

Effects on the liver. An 85-year-old woman developed intrahepatic cholestasis after taking moclobemide for about 1 week;[1] she had previously been taking fluoxetine and was switched to moclobemide without a washout period. She died 12 days after the onset of jaundice despite prompt moclobemide withdrawal.

1. Timmings P, Lamont D. Intrahcpatic cholestasis associated with moclobemide leading to death. *Lancet* 1996; **347:** 762–3.

Overdosage. Several case series[1-3] have suggested that moclobemide is relatively safe when taken alone in overdose; symptoms such as gastrointestinal irritation, agitation, aggression, behavioural disturbances, and tachycardia have been noted. However, fatalities have been reported, particularly when taken with other serotonergic drugs.[3,4]

1. Hetzel W. Safety of moclobemide taken in overdose for attempted suicide. *Psychopharmacology (Berl)* 1992; **106:** S127–S129.
2. Myrenfors PG, *et al*. Moclobemide overdose. *J InternMed* 1993; **233:** 113–15.
3. Isbister GK, *et al*. Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* 2003; **56:** 441–50.
4. Giroud C, *et al*. Death following acute poisoning by moclobemide. *Forensic Sci Int* 2004; **140:** 101–7.

Precautions

Moclobemide is contra-indicated in patients with acute confusional states and in those with phaeochromocytoma. It should be avoided in excited or agitated patients, unless used with a sedative. Manic episodes may be provoked in patients with bipolar disorder. Care is also required in patients with thyrotoxicosis as moclobemide can theoretically precipitate a hypertensive reaction. Reduced doses should be used in patients with severe hepatic impairment.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Although impairment of mental alertness is generally not expected with moclobemide, caution should be exercised with respect to driving or operating machinery until individual reactions have been assessed.

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. In a study[1] of the distribution of moclobemide into the breast milk of 6 mothers given a single 300-mg dose of moclobemide, a mean of 0.057% of the dose appeared in breast milk as moclobemide and 0.031% as Ro-12-8095, its major metabolite, within 24 hours of a

dose. It was considered that this small amount of moclobemide was unlikely to be hazardous to breast-fed infants. UK licensed product information advises caution and consideration of the benefits of moclobemide therapy to the mother against possible risks to the infant.

1. Pons G, *et al*. Moclobemide excretion in human breast milk. *Br J Clin Pharmacol* 1990; **29:** 27–31.

Children. Moclobemide has not been adequately studied for the treatment of depression in children and its use is not recommended in UK licensed product information. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p. 420.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moclobemide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. UK licensed product information recommends that moclobemide should only be used during pregnancy if the benefits to the mother outweigh any possible risks to the fetus.

A patient who took at least 300 mg daily of moclobemide throughout her pregnancy delivered a healthy, full-term infant after an uncomplicated pregnancy.[1] The infant was monitored from birth, and psychomotor and somatic development for the first 14 months was found to be normal.

1. Rybakowski JK. Moclobemide in pregnancy. *Pharmacopsychiatry* 2001; **34:** 82–3.

Withdrawal. Withdrawal symptoms may occur if an antidepressant such as moclobemide is suddenly stopped after regular use for 8 weeks or more; the *BNF* recommends that the dose should be tapered gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

Despite reducing the dose of moclobemide over 3 days, symptoms such as muscle cramps, shivering, headache, nausea, and hot flushes developed in a 47-year-old woman on the day that moclobemide was completely stopped.[1] The patient had been taking moclobemide for about 15 months.

1. Curtin F, *et al*. Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *J Psychopharmacol* 2002; **16:** 271–2.

Interactions

The dietary restrictions that need to be followed with selective reversible inhibitors of monoamine oxidase type A such as moclobemide are less stringent than those for non-selective inhibitors of monoamine oxidase types A and B (see under Interactions of Phenelzine, p. 446.3). However, UK licensed product information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

Medicines containing *sympathomimetics, dextromethorphan,* or *anorectics* should not be taken with moclobemide. Moclobemide should not be given with *other antidepressants* although, owing to its short duration of action, a treatment-free period is generally considered unnecessary after its cessation. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2. Therapy with moclobemide should not be started until at least one week after cessation of a tricyclic or related antidepressant or an SSRI or related antidepressant (2 weeks in the case of paroxetine and sertraline; at least 5 weeks in the case of fluoxetine) or for at least one week after stopping treatment with non-selective MAOIs. CNS excitation or depression may occur if moclobemide is taken with *opioid analgesics,* and there is also a risk of CNS toxicity if taken with *serotonin ($5\text{-}HT_1$) agonists.* The metabolism of moclobemide is inhibited by *cimetidine,* leading to increased plasma concentrations and a need for reduced dosage (see p. 440.1).

Antimigraine drugs. For the effects of moclobemide on *serotonin ($5\text{-}HT_1$) agonists,* see under Sumatriptan, p. 681.3.

Cimetidine. Cimetidine 1 g daily for 2 weeks increased the mean peak plasma concentration of moclobemide in 8 healthy subjects from 575 nanograms/mL to 787 nanograms/mL; several other parameters associated with moclobemide absorption and disposition were also affected.[1] It was suggested that a reduction in the dosage of moclobemide might be required. UK licensed product information for moclobemide recommends reducing its dose by half in patients also receiving cimetidine.

1. Schoerlin M-P, *et al*. Cimetidine alters the disposition kinetics of the monoamine oxidase-A inhibitor moclobemide. *Clin Pharmacol Ther* 1991; **49:** 32–8.

Dopaminergics. Adverse effects including nausea, vomiting, and dizziness were noted in healthy subjects given moclobemide and *levodopa with benserazide*;[1] however, no significant hypertensive reactions were seen.

Caution is also required when *selegiline* and moclobemide are given together.[1] Dietary restrictions with this combination (see under Phenelzine, p. 446.3) are recommended by one manufacturer of selegiline, whereas others advise that this combination should be avoided (as does the manufacturer of moclobemide).

See also under Selegiline, p. 917.1.

1. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* 1993; **7:** 167–80.

Omeprazole. Omeprazole, which is an inhibitor of cytochrome P450 isoenzyme CYP2C19, increased plasma concentrations and elimination half-life of moclobemide in extensive metabolisers of the drug towards values seen in poor metabolisers.[1] It had little effect on pharmacokinetic parameters in poor metabolisers. The clinical effects were uncertain but extra care might be warranted if the 2 drugs are given together.

1. Yu K-S, *et al*. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; **69:** 266–73.

Opioid analgesics. Symptoms suggestive of a mild serotonin syndrome (p. 445.2) developed in a 73-year-old woman taking moclobemide, nortriptyline, and lithium after she was given *pethidine* intravenously.[1] Licensed product information recommends that moclobemide should not be given with pethidine.

1. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.

Pharmacokinetics

Moclobemide is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1 hour of ingestion. Absorption is virtually complete but first-pass metabolism reduces bioavailability of the drug. Moclobemide is widely distributed throughout the body and is 50% bound to plasma proteins. It undergoes extensive metabolism in the liver, in part by the cytochrome P450 isoenzymes CYP2C19 and CYP2D6. Metabolites of moclobemide and a small amount of unchanged drug are excreted in the urine. Moclobemide has a plasma elimination half-life of 2 to 4 hours. Moclobemide is distributed into breast milk.

References.

1. Mayersohn M, Guentert TW. Clinical pharmacokinetics of the monoamide oxidase-A inhibitor moclobemide. *Clin Pharmacokinet* 1995; **29:** 292–332.
2. Gram LF, *et al*. Moclobemide: a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. *Clin Pharmacol Ther* 1995; **57:** 670–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Amira; Arima†; Aurorix; Clobemix; Maosig; Mohexal; ***Austria***: Aurorix; ***Belg.***: Aurorix; ***Braz.***: Aurorix; ***Canad.***: Manerix; ***Chile***: Aurorix; Inpront†; ***China***: Bei Su (贝苏); Hai Bei Lin (海倍霖); Langtian (朗天); Tian Tai (恬泰); Ya Zheng (亚正); ***Cz.***: Apo-Moclob; Aurorix; ***Denm.***: Aurorix; Moclostad; ***Fin.***: Aurorix; ***Fr.***: Moclamine; ***Ger.***: Aurorix; Moclobeta; ***Gr.***: Aurorix; ***Hong Kong***: Aurorix†; ***Hung.***: Aurorix; Maorex†; Moclopharm†; Mocrim; ***India***: Morex; Rimarex; ***Indon.***: Aurorix†; ***Irl.***: Manerix; ***Israel***: Mobemide†; ***Malaysia***: Aurorix; ***Mex.***: Aurorex; Demobal; Feraken†; ***Neth.***: Aurorix; ***Norw.***: Aurorix; ***NZ***: Aurorix; ***Philipp.***: Aurorix†; ***Pol.***: Aurorix; Mobemid; Moclovil†; Moklar; ***Port.***: Aurorix; Zorix; ***Rus.***: Aurorix (Аурорикс); ***S.Afr.***: Aurorix†; Clorix†; Depnil; ***Singapore***: Aurorix; Mobemide; ***Spain***: Manerix; ***Swed.***: Aurorix; ***Switz.***: Aurorix; Moclo A; ***Thai.***: Aurorix†; ***Turk.***: Aurorix; Lobem; ***UK***: Manerix.

Nefazodone Hydrochloride

(BANM, USAN, rINNM)

BMY-13754; Hidrocloruro de nefazodona; MJ-13754-1; Nefazodona, hidrocloruro de; Néfazodone, Chlorhydrate de; Nefazodoni Hydrochloridum; Нефазодона Гидрохлорид.

2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-1,2,4-triazol-3-one monohydrochloride.

$C_{25}H_{32}ClN_5O_2,HCl$=506.5

CAS — 83366-66-9 (nefazodone); 82752-99-6 (nefazodone hydrochloride).

ATC — N06AX06.

ATC Vet — QN06AX06.

UNII — 27X63J94GR.

Pharmacopoeias. In *US.*

USP 36: (Nefazodone Hydrochloride). A non-hygroscopic white powder. Slightly soluble in water and in macrogols; freely soluble in chloroform; soluble in propylene glycol. Store in airtight containers at a temperature between 15 degrees and 30 degrees.

Uses and Administration

Nefazodone is a phenylpiperazine antidepressant structurally related to trazodone (see p. 453.1). It blocks the reuptake of serotonin at presynaptic neurones and is an antagonist at postsynaptic $5\text{-}HT_2$ receptors. Unlike trazodone, nefazodone inhibits the reuptake of noradrenaline. It blocks α_1-adrenoceptors but has no apparent effect on dopamine receptors. Nefazodone does not appear to have very significant antimuscarinic properties compared with tricyclic antidepressants.

Nefazodone hydrochloride has been given for the treatment of depression. One manufacturer (*Bristol-Myers Squibb*) has withdrawn nefazodone worldwide (see also Effects on the Liver, p. 440.3); however, nefazodone remains available in the USA, and possibly some other countries, as a generic preparation. The usual initial oral dose is 100 mg twice daily increased if necessary, in increments of 100 to 200 mg at intervals of at least a week, to a maximum of 300 mg twice daily. Doses are restricted in elderly patients: a recommended initial dose is 50 mg twice daily.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Nefazodone has been tried in anxiety disorders, but other drugs may now be preferred.

Adverse Effects and Treatment

The most common adverse effects seen with nefazodone are weakness, dry mouth, nausea, constipation, somnolence, dizziness, insomnia, and lightheadedness. Other effects which have occurred less frequently include chills, fever, orthostatic hypotension, incoordination, vasodilatation, arthralgia, paraesthesia, confusion, memory impairment, abnormal dreams, ataxia, and amblyopia and other visual disturbances. Syncope, priapism, and seizures have occurred rarely and there have been reports of sinus bradycardia. Hepatotoxicity has occurred (see p. 440.3).

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, the symptoms that have been reported most frequently include hypotension, dizziness, nausea, vomiting, and drowsiness. The value of gastric decontamination in the treatment of overdosage is uncertain. Activated charcoal should be considered if more than 1.5 g (in an adult) or 20 mg/kg (in a child) has been taken and treatment is within 1 hour of ingestion. US licensed product information recommends gastric lavage, although this technique is seldom practicable and should not be attempted unless the airway is protected. Supportive therapy should be given as necessary. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Reviews.

1. Robinson DS, *et al*. The safety profile of nefazodone. *J Clin Psychiatry* 1996; **57** (suppl 2): 31–8.

Effects on the liver. Subfulminant hepatic failure developed in 3 women given nefazodone for depression.[1] Two patients required liver transplantation although this was unsuccessful in one case and the patient died. Hepatitis, positive on rechallenge, has also been reported with nefazodone.[2]

The original US manufacturer (*Bristol-Myers Squibb*) of nefazodone have stated that rare events of raised liver enzymes, hepatitis, hepatic failure and necrosis have been reported since marketing but no causal relationship has been established. In the USA, a reported rate of about 1 case of hepatic failure resulting in death or transplantation per 250 000 to 300 000 patient years of nefazodone treatment has been estimated by the manufacturer; this rate is about 3 to 4 times greater than the background rate of hepatic failure.[3] Onset times for such cases ranged from 2 weeks to 6 months. The Canadian manufacturers have indicated[4] that as of June 2001 there had been 109 reports of serious hepatic adverse events associated with nefazodone from postmarketing surveillance worldwide. These included 23 cases of hepatic failure, of which 16 led to transplantation and/or death. Most cases occurred within 4 months of beginning treatment although a few were after continuous use for up to 2 years. After a review[5] of the data available to December 2002, it was decided to withdraw nefazodone from the Canadian market in November 2003. Subse-

quently, one manufacturer (*Bristol-Myers Squibb*) withdrew nefazodone worldwide.

1. Aranda-Michel J, *et al*. Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999; **130:** 285–8.
2. Schrader GD, Roberts-Thompson IC. Adverse effect of nefazodone: hepatitis. *Med J Aust* 1999; **170:** 452.
3. Jody DM [Bristol-Myers Squibb]. Important drug warning including black box information. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM171084.pdf (accessed 30/07/10)
4. Bristol-Myers Squibb Canada Inc/Linson Pharama Inc. Important safety information on nefazodone HCl: severe and serious hepatic events (issued June 2001). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)
5. Bristol-Myers Squibb Canada. Important safety information regarding the discontinuation of sales of nefazodone in Canada (issued October 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bms-nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)

Overdosage. A 27-year-old woman had no serious toxicity after taking 3 g of nefazodone in a suicide attempt.[1] Somnolence was the most severe effect noted. In another case, a 31-year-old woman attempted suicide with 16.8 g of nefazodone and an unknown quantity of verapamil.[2] The patient was lethargic, and developed significant bradycardia and hypotension; she recovered after supportive therapy. The authors reported that among the 7 cases of overdose occurring during clinical studies, there were no fatalities or permanent sequelae.

In a review of 1338 cases of nefazodone-only overdoses reported to the American Association of Poison Control Centers over a 2-year period, it was found that the majority of cases were either asymptomatic or mild in nature with symptoms such as nausea, vomiting, dizziness, and drowsiness.[3] More severe symptoms were noted in only 2 patients. In one case, an 11-year-old boy with a history of seizures suffered several seizures after starting nefazodone at a dose of 100 mg twice daily; the other case involved a 47-year-old man who developed premature ventricular contractions, bradycardia, agitation, and hypotension after an intentional overdose of an unknown quantity. No deaths were recorded in any of the cases where the outcome was known.

1. Gaffney PW, *et al*. Nefazodone overdose. *Ann Pharmacother* 1998; **32:** 1249–50.
2. Catalano G, *et al*. Nefazodone overdose: a case report. *Clin Neuropharmacol* 1999; **22:** 63–5.
3. Benson BE, *et al*. Toxicities and outcomes associated with nefazodone poisoning: an analysis of 1,338 exposures. *Am J Emerg Med* 2000; **18:** 587–92.

Precautions

Treatment with nefazodone should not generally be started in patients with active hepatic disease or elevated baseline serum transaminases. Patients who develop signs or symptoms of hepatic impairment such as jaundice, anorexia, abdominal pain, elevated transaminase levels, or malaise during treatment should be evaluated for hepatic damage and the drug withdrawn if necessary. Nefazodone is contra-indicated in patients previously withdrawn from the drug because of hepatotoxicity.

Nefazodone should be used with caution in patients with epilepsy, or a history of hypomania or mania. It should also be used with caution in cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (for example recent history of myocardial infarction, unstable heart disease, angina, or ischaemic stroke), and in any condition such as dehydration or hypovolaemia that may predispose patients to hypotension.

Since nefazodone is structurally related to trazodone which is known to have caused priapism (see Effects on Sexual Function, p. 454.1), US licensed product information recommends that any patient developing inappropriate or prolonged penile erections should stop nefazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Nefazodone may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. A study[1] in 2 nursing mothers receiving nefazodone for postpartum depression indicated that nefazodone, but not its major active metabolites, was distributed into breast milk in variable amounts; the quantity present did not seem to be dose-related. The calculated exposure of the two women's infants was 2.2% and 0.4% of the maternal dose respectively. Another report suggested that even such low exposures might result in clinically significant effects:[2] drowsiness, inability to maintain normal body temperature, and poor feeding were reported in the breast-fed infant of a woman receiving nefazodone. After breast feeding was stopped the symptoms resolved, suggesting an association between the two despite a calculated exposure in the infant of only 0.45% of the maternal dose.

1. Dodd S, *et al*. Nefazodone in the breast milk of nursing mothers: a report of two patients. *J Clin Psychopharmacol* 2000; **20:** 717–18.
2. Yapp P, *et al*. Drowsiness and poor feeding in a breast-fed infant: association with nefazodone and its metabolites. *Ann Pharmacother* 2000; **34:** 1269–72.

Children. US licensed product information considers that the safety and efficacy of nefazodone have not been established for the treatment of depression in adolescents and children. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p. 420.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nefazodone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Licensed product information states that nefazodone should only be used during pregnancy if the benefits to the mother outweigh the risks to the fetus.

In a multicentre study of 147 women who took either nefazodone or trazodone in at least the first trimester of pregnancy there were 121 live births, 20 spontaneous abortions, 6 therapeutic abortions, and 2 reports of major malformations (Hirschsprung disease and neural tube defect);[1] no still-births were recorded. There were no significant differences in pregnancy outcome in the nefazodone/trazodone group when compared with the 2 control groups (women with depression taking non-teratogenic antidepressants and women taking non-teratogenic drugs). The rate of spontaneous abortions was non-significantly higher in both the antidepressant groups than in the other control group. It was suggested that the rate of major malformations in all 3 groups was not greater than the baseline rate of 1 to 3%.

1. Einarson A, *et al*. A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 2003; **48:** 106–10.

Interactions

Nefazodone should not be given to patients receiving MAOIs or for at least 14 days after they are stopped; it has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping nefazodone therapy. For further details on the combined use of antidepressants, see Antidepressants under Interactions of Phenelzine, p. 447.2.

Orthostatic hypotension can be a problem with nefazodone, and therefore caution is required for any patient also on antihypertensive therapy.

Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 responsible for the metabolism of some benzodiazepines, and consequently it may produce clinically important increases in their plasma concentrations. Use with astemizole, cisapride, pimozide, and terfenadine (which are metabolised by the same isoenzyme) is best avoided because the potential also exists for increased plasma concentrations of these drugs, with the risk of inducing ventricular arrhythmias. Other substrates for this isoenzyme may also interact with nefazodone: atorvastatin, lovastatin, and simvastatin should be used with caution with nefazodone since there have been rare reports of rhabdomyolysis with such combinations. Increased serum concentrations of ciclosporin or tacrolimus, both substrates for CYP3A4, have been reported in patients also receiving nefazodone. Monitoring of serum ciclosporin or tacrolimus levels is recommended when either of these two drugs is given with nefazodone. Use of the vasopressin V_2-receptor antagonist tolvaptan with nefazodone is contra-indicated (see p. 2633.1).

Plasma concentrations of digoxin are increased by nefazodone, and because of digoxin's narrow therapeutic index, plasma concentrations of digoxin should be monitored if use with nefazodone is necessary.

Caution should be exercised when haloperidol is given with nefazodone as the clearance of haloperidol may be reduced. Plasma concentrations of carbamazepine are also increased when used with nefazodone. More importantly, carbamazepine may reduce nefazodone plasma concentrations to subtherapeutic levels and therefore use together is not recommended. Giving buspirone with nefazodone significantly increases the serum concentrations of buspirone; the manufacturers of nefazodone recommend that the initial dose of buspirone is reduced if these drugs are given together.

The potential for interaction between nefazodone and general anaesthetics exists and the manufacturer recommends that nefazodone should be stopped before elective surgery for as long as clinically feasible.

Benzodiazepines. For further details of interactions between nefazodone and benzodiazepines, see Diazepam, p. 1068.3.

Pharmacokinetics

Nefazodone is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 2 hours after oral doses. Absorption is delayed and reduced by food but this is not considered to be clinically significant. Nefazodone undergoes extensive first-pass metabolism and is more than 99% bound to plasma proteins; it is widely distributed. It is extensively metabolised by *N*-dealkylation and hydroxylation in the liver to several metabolites, two of which, hydroxynefazodone and *m*-chlorophenylpiperazine, are known to be pharmacologically active. Excretion is mainly as metabolites via the urine (about 55%) and the faeces (20 to 30%). The plasma elimination half-life is 2 to 4 hours. Pharmacokinetic parameters are reported to be non-linear with increasing doses. Nefazodone is distributed in small amounts into breast milk (see Breast Feeding, above).

Reviews.

1. Greene DS, Barbhaiya RH. Clinical pharmacokinetics of nefazodone. *Clin Pharmacokinet* 1997; **33:** 260–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Nefadon; Nefirel.

Pharmacopoeial Preparations

USP 36: Nefazodone Hydrochloride Tablets.

Nortriptyline Hydrochloride

(BANM, USAN, rINNM)

38489; Hidrocloruro de nortriptilina; Nortriptilina, hidrocloruro de; Nortriptilin-hidroklorid; Nortriptilino hidrochloridas; Nortriptyliinihydrokloridi; Nortriptyline, Chlorhydrate de; Nortriptylinhydrochlorid; Nortriptylin-hydrochlorid; Nortriptylinhydroklorid; Nortriptylini Hydrochloridum; Nortryptyliny chlorowodorek; Нортриптилина Гидрохлорид.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene) propyl(methyl)amine hydrochloride.

$C_{19}H_{21}N,HCl$=299.8

CAS — 72-69-5 (nortriptyline); 894-71-3 (nortriptyline hydrochloride).

ATC — N06AA10.

ATC Vet — QN06AA10.

UNII — 00FN6IH15D.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nortriptyline Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Nortriptyline Hydrochloride). A white to off-white powder having a slight characteristic odour. Soluble 1 in 90 of water, 1 in 30 of alcohol, 1 in 20 of chloroform, and 1 in 10 of methyl alcohol; practically insoluble in ether, in benzene, and in most other organic solvents. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Uses and Administration

Nortriptyline is a dibenzocycloheptadiene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is the principal active metabolite of amitriptyline. Nortriptyline is one of the less sedating tricyclics and its antimuscarinic effects are mild.

Nortriptyline is given orally as the hydrochloride although doses are expressed in terms of the base; nortriptyline hydrochloride 113.8 mg is equivalent to about 100 mg of nortriptyline. In the treatment of depression a low starting dose is given gradually increasing to the equivalent of 75 to 100 mg daily in 3 or 4 divided doses. Up to a maximum of 150 mg daily may be required in patients with severe depression. Licensed product information recommends that plasma concentrations of nortriptyline should be monitored when doses above 100 mg daily are given; however, the *BNF* considers that the evidence of any practical value is uncertain. Adolescents and the elderly may be given 30 to 50 mg daily in divided doses. Since nortriptyline has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

Dose adjustments have been suggested for patients with genetic polymorphisms in the cytochrome P450 isoenzyme CYP2D6 (see Administration in Genetic Variation, under Amitriptyline, p. 401.2).

For the use of nortriptyline in children, see p. 442.1.

Nortriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. Nortriptyline is used for the treatment of nocturnal enuresis in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home. Tricyclic antidepressants are not recommended in children under 6 years of age. For a discussion of tricyclic use in nocturnal enuresis see Micturition Disorders under Amitriptyline, p. 402.1.

Suggested oral doses of nortriptyline are:

- 10 mg for children aged 6 to 7 years (20 to 25 kg)
- 10 to 20 mg for children aged 8 to 11 years (25 to 35 kg)
- 25 to 35 mg for children aged over 11 years (35 to 54 kg)

The dose should be given 30 minutes before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination, including an ECG, is recommended before a further course.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2). Nortriptyline has also been tried and may produce fewer adverse effects than amitriptyline. In the management of neuropathic pain, the *BNF* has suggested an initial oral dose of 10 mg daily at night, increased if necessary to 75 mg daily.

References.
1. Atkinson JH, *et al.* A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. *Pain* 1998; **76:** 287–96.
2. Watson CP, *et al.* Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 1998; **51:** 1166–71.

Smoking cessation. For reference to the use of nortriptyline in management of smoking cessation, see under Amitriptyline, p. 402.2.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on ventilation. Severe hyperventilation developed in a 61-year-old man with end-stage renal disease after receiving nortriptyline 125 mg daily;[1] mechanical ventilation was necessary to correct severe respiratory alkalosis.

1. Sunderrajan S, *et al.* Nortriptyline-induced severe hyperventilation. *Arch Intern Med* 1985; **145:** 746–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nortriptyline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Nortriptyline is the main active metabolite of amitriptyline (p. 407.2). It has been reported to have a longer plasma half-life than amitriptyline. Nortriptyline is subject to extensive first-pass metabolism in the liver to 10-hydroxynortriptyline, which is active.

Metabolism. Individuals with a poor debrisoquine hydroxylation phenotype may be at greater risk of confusional states when taking nortriptyline.[1] This was thought to be because the polymorphic hydroxylation of debrisoquine and nortriptyline are mediated by similar enzymatic mechanisms [the cytochrome P450 isoenzyme CYP2D6], with poor oxidisers having higher plasma nortriptyline concentrations.[2,3] A nonlinear (dose-dependent) relationship between dose and plasma-nortriptyline concentrations has been seen during therapeutic drug monitoring[4] in subjects who were considered to be extensive metabolisers of debrisoquine; nonlinearity did not appear to occur in poor metabolisers. There was no significant correlation between hydroxylation phenotype and amitriptyline concentrations, suggesting that demethylation and hydroxylation of tricyclic antidepressants are mediated by different cytochrome P450 isoenzymes.[5]

The pharmacokinetics and pharmacological actions of 10-hydroxynortriptyline, the major active metabolite of nortriptyline, have been reviewed.[3]

1. Park BK, Kitteringham NR. Adverse reactions and drug metabolism. *Adverse Drug React Bull* 1987; **122:** 456–9.
2. Nordin C, *et al.* Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio. *Br J Clin Pharmacol* 1985; **19:** 832–5.
3. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants: emphasis on E-10-hydroxy-nortriptyline. *Clin Pharmacokinet* 1995; **28:** 26–40.
4. Jerling M, Alván G. Nonlinear kinetics of nortriptyline in relation to nortriptyline clearance as observed during therapeutic drug monitoring. *Eur J Clin Pharmacol* 1994; **46:** 67–70.
5. Bertilsson L, *et al.* Metabolism of various drugs in subjects with different debrisoquine and sparteine oxidation phenotypes. *Br J Clin Pharmacol* 1982; **14:** 602P.

Therapeutic plasma concentrations. Nortriptyline appears to have an optimum antidepressant effect at plasma concentrations between 50 and 150 nanograms/mL. Outside this range, there is a poor clinical response. Plasma concentration measurements are unequivocally useful in patients who do not respond to usual oral doses or in high-risk patients for whom, because of age or medical illness, it is especially important to use the lowest possible effective dose of the drug.[1]

It has been suggested[2] that within this range of total nortriptyline concentrations there is a probability of an antidepressant response of 68% or more with free concentrations of 7 to 10 nanograms/mL.

For reference to dose-dependent kinetics of nortriptyline seen in individuals with an extensive debrisoquine hydroxylation phenotype, see under Metabolism, above.

1. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; **142:** 155–62.
2. Perry PJ, *et al.* The relationship of free nortriptyline levels to antidepressant response. *Drug Intell Clin Pharm* 1984; **18:** 510.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Allegron; ***Belg.***: Nortrilen; ***Braz.***: Nortrip; Pamelor; ***Canad.***: Aventyl; Norventyl; ***Cz.***: Nortrilen; ***Denm.***: Noritren; ***Fin.***: Noritren; ***Ger.***: Nortrilen; ***Gr.***: Nortrilen; ***Hong Kong***: Nortrilen; ***India***: Sensival; ***Israel***: Nortylin; ***Ital.***: Noritren; ***Neth.***: Nortrilen; ***Norw.***: Noritren; ***NZ***: Norpress; ***Port.***: Norterol; ***Spain***: Norfenazin; Paxtibi; ***Swed.***: Sensaval; ***Switz.***: Nortrilen; ***Thai.***: N-Trip; Norline; Nortrilen†; Nortyline; Ortrip; ***UK***: Allegron; ***USA***: Aventyl; Pamelor.

Multi-ingredient Preparations. ***Arg.***: Karile; ***Chile***: Motitrel†; ***Indon.***: Motival†; ***Irl.***: Motival†; ***Ital.***: Dominans; ***Mex.***: Motival; ***S.Afr.***: Motival†; ***Spain***: Tropargal; ***Thai.***: Cetavol.

Pharmacopoeial Preparations
BP 2014: Nortriptyline Capsules; Nortriptyline Tablets;
USP 36: Nortriptyline Hydrochloride Capsules; Nortriptyline Hydrochloride Oral Solution.

Opipramol Hydrochloride *(BANM, USAN, rINNM)*

G-33040; Hidrocloruro de opipramol; Opipramol, Chlorhydrate d'; Opipramol, hidrocloruro de; Opipramol Hidroklorür; Opipramoli Dihydrochloridum; Opipramoli Hydrochloridum; Opipramolu dichlorowodorek; Опипрамола Гидрохлорид.

2-[4-(3-5*H*-Dibenz[*b*,*f*]azepin-5-ylpropyl)piperazin-1-yl]ethanol dihydrochloride.

$C_{23}H_{29}N_3O,2HCl$=436.4

CAS — 315-72-0 (opipramol); 909-39-7 (opipramol dihydrochloride).

ATC — N06AA05.

ATC Vet — QN06AA05.

UNII — B49OBI656M.

Pharmacopoeias. In *Pol.*

Profile

Opipramol hydrochloride is a dibenzazepine tricyclic antidepressant (see Amitriptyline, p. 401.1) given in oral doses of 50 to 300 mg daily in the treatment of depression.

It should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Insidon; ***Ger.***: Insidon†; Opipra†; Opipram; ***Gr.***: Insidon; ***Israel***: Oprimol†; ***Pol.***: Pramolan; Sympramol; ***Switz.***: Insidon; ***Turk.***: Deprenil; Insidon; Insomin; Inzeton; Opridon; Oprimol†.

Oxitriptan *(rINN)*

5-HTP; L-5-Hydroxytryptophan; Oxitriptán; Oxitriptanum; Ro-0783/B; Окситриптан.

L-2-Amino-3-(5-hydroxy-1*H*-indol-3-yl)propionic acid.

$C_{11}H_{12}N_2O_3$=220.2

CAS — 4350-09-8 (oxitriptan); 56-69-9 (DL-5-hydroxytryptophan).

ATC — N06AX01.

ATC Vet — QN06AX01.

UNII — C1LJO185Q9.

Profile

Oxitriptan is the L form of 5-hydroxytryptophan, a precursor of serotonin. Like tryptophan (p. 455.2) it is used in the treatment of depression; it is given in oral doses of up to 600 mg daily.

Oxitriptan is also used in doses of up to 1 g daily in myoclonic disorders, especially posthypoxic myoclonus (p. 511.3). It has also been used in neurological conditions including migraine, pain syndromes, and sleep disorders, and as an adjunct in epilepsy and parkinsonism.

DL-Oxitriptan has also been used as an antidepressant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Tript-OH; ***Fr.***: Levotonine; ***Ital.***: Tript-OH; ***Port.***: Cincofarm; ***Spain***: Cincofarm; ***Switz.***: Tript-OH†.

Multi-ingredient Preparations. ***Indon.***: Deprex; Menose; ***Ital.***: Pineal Notte; ***USA***: PowerSleep.

Paroxetine *(BAN, USAN, rINN)*

BRL-29060; FG-7051; Paroksetiini; Paroxetin; Paroxetina; Paroxétine; Paroxetinum; Пароксетин.

(-)-*trans*-5-(4-*p*-Fluorophenyl-3-piperidylmethoxy)-1,3-benzodioxole.

$C_{19}H_{20}FNO_3$=329.4

CAS — 61869-08-7.

ATC — N06AB05.

ATC Vet — QN06AB05.

UNII — 41VRH5220H.

Paroxetine Hydrochloride *(BANM, rINNM)*

BRL-29060A; Hidrocloruro de paroxetina; Paroksetiinihydrokloridihemihydraatti; Paroksetin Hidroklorür; Paroksetino hidrochloridas hemihidratas; Paroksetyny chlorowodorek; Paroxetin hydrochlorid; Paroxetina, hidrocloruro de; Paroxétine, chlorhydrate de; Paroxétine (chlorhydrate de) hémihydraté; Paroxetine Hydrochloride Hemihydrate; Paroxetinhydrochlorid-Hemihydrat; Paroxetinhydrokloridhemihydrat; Paroxetini Hydrochloridum; Paroxetini hydrochloridum hemihydricum; Пароксетина Гидрохлорид.

$C_{19}H_{20}FNO_3,HCl,½H_2O$=374.8

CAS — 78246-49-8 (anhydrous paroxetine hydrochloride); 110429-35-1 (paroxetine hydrochloride hemihydrate).

UNII — X2ELS050D8 (paroxetine hydrochloride, hemihydrate); 3I3T11UD2S (anhydrous paroxetine hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, which permit the anhydrous and hemihydrate forms.

Ph. Eur. 8: (Paroxetine Hydrochloride, Anhydrous). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers at a temperature not exceeding 25 degrees.

Ph. Eur. 8: (Paroxetine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. It exhibits pseudopolymorphism. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Paroxetine Hydrochloride). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white solid. Slightly soluble in water; soluble in alcohol and in methyl alcohol. Store the anhydrous form in airtight containers.

Paroxetine Mesilate *(BANM, rINNM)*

Mesilato de paroxetina; Paroxetina, mesilato de; Paroxétine, Mésilate de; Paroxetine Mesylate (USAN); Paroxetini Mesilas; Пароксетина Мезилат.

$C_{19}H_{20}FNO_3,CH_4O_3S$=425.5

CAS — 217797-14-3.

ATC — N06AB05.

ATC Vet — QN06AB05.
UNII — M711N184JE.

NOTE. The name Asimia has been used as a trade mark for paroxetine mesilate.

Uses and Administration

Paroxetine, a phenylpiperidine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 417.1); it is also used for the treatment of vasomotor symptoms associated with the menopause (see Hot Flushes, under Fluoxetine, p. 418.2). It is given orally usually as paroxetine hydrochloride or the mesilate. Doses are expressed in terms of the base; paroxetine hydrochloride 22.8 mg or paroxetine mesilate 25.8 mg are each equivalent to about 20 mg of paroxetine.

The licensed doses for **psychiatric disorders** given below refer to preparations containing paroxetine hydrochloride; similar doses are also used when paroxetine is given as the mesilate. Doses of paroxetine are given as a single dose in the morning. They may be increased in steps of 10 mg at intervals of at least 1 week; however, the efficacy of maximum licensed doses has been questioned (for further details, see Administration, p. 443.1).

In the treatment of *depression*, the usual dose of paroxetine is 20 mg daily, increased gradually, if necessary, to a maximum of 50 mg daily.

In the treatment of *generalised anxiety disorder*, the initial dose is 20 mg daily; further increases to a maximum of 50 mg have been given.

The initial dose in *obsessive-compulsive disorder* is 20 mg daily increased gradually to a usual maintenance dose of 40 mg daily; some patients may require up to 60 mg daily.

In the treatment of *panic disorder* with or without agoraphobia, the initial dose is 10 mg daily increased gradually to the usual recommended maintenance dose of 40 mg daily; some patients may benefit from 60 mg daily.

The recommended starting dose for the treatment of *post-traumatic stress disorder* is 20 mg daily; if necessary this may be increased gradually to a maximum of 50 mg daily.

The initial dose for the treatment of *social anxiety disorder* is 20 mg daily increased gradually, if necessary, to a maximum of 50 or 60 mg daily.

A suggested maximum daily dose in elderly or debilitated patients is 40 mg; US licensed product information also recommends a starting dose of 10 mg daily in such patients. Reduced doses should be given to patients with hepatic or renal impairment, see p. 443.1.

A modified-release preparation (as the hydrochloride) is also available in the USA for the treatment of depression, panic disorder, and social anxiety disorder; the maximum doses with this preparation may be slightly greater than those recommended with the immediate-release preparation. The modified-release preparation may also be used in the treatment of *premenstrual dysphoric disorder*. The initial dose is 12.5 mg once daily, usually in the morning, which may be increased to 25 mg once daily, if necessary, after an interval of at least one week. Treatment may be given throughout the menstrual cycle or limited to the luteal phase.

When used for psychiatric disorders, paroxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms; weekly decrements of 10 mg have been used (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Paroxetine mesilate is given for the treatment of moderate to severe **vasomotor symptoms associated with the menopause**; the usual dose is the equivalent of paroxetine 7.5 mg once daily at bedtime.

Reviews.

1. Wagstaff AJ, *et al*. Paroxetine: an update of its use in psychiatric disorders in adults. *Drugs* 2002; **62:** 655–703. Correction. *ibid.*; 1461.
2. Pae CU, Patkar AA. Paroxetine: current status in psychiatry. *Expert Rev Neurother* 2007; **7:** 107–20. Correction. *ibid.*; 313–14.
3. Tang SW, Helmeste D. Paroxetine. *Expert Opin Pharmacother* 2008; **9:** 787–94.

Administration. Although paroxetine is licensed in the UK at higher doses for psychiatric disorders, the UK CSM considers that there is a lack of evidence from clinical studies of additional efficacy with paroxetine when given above the following daily doses:

- depression, generalised anxiety disorder, social anxiety disorder, post-traumatic stress disorder: 20 mg
- obsessive-compulsive disorder, panic disorder: 40 mg

1. CSM/MCA Paroxetine prescribing advice. *Current Problems* 2004; **30:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)

Administration in hepatic or renal impairment. In the USA the recommended initial oral dose of paroxetine for psychiatric disorders in patients with severe renal or hepatic impairment is the equivalent of 10 mg daily, increased to a maximum of 40 mg daily as necessary. UK licensed product information recommends that doses in such patients are limited to the lower end of the range.

Anxiety disorders. Paroxetine is used in anxiety disorders including generalised anxiety disorder (p. 1028.1), obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), post-traumatic stress disorder (p. 1029.2), and social anxiety disorder (see under Phobic Disorders, p. 1029.1). It has also been tried for adult night terrors (see under Sleep-associated Movement Disorders, p. 1034.2).

References.

1. Oehrberg S, *et al*. Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1995; **167:** 374–9.
2. Zohar J, *et al*. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry* 1996; **169:** 468–74.
3. Lecrubier Y, *et al*. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatr Scand* 1997; **95:** 153–60.
4. Wilson SJ, *et al*. Adult night terrors and paroxetine. *Lancet* 1997; **350:** 185.
5. Stein MB, *et al*. Paroxetine treatment of generalized social phobia (social anxiety disorder). *JAMA* 1998; **280:** 708–13.
6. Baldwin D, *et al*. Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1999; **175:** 120–6.
7. Baldwin DS. Clinical experience with paroxetine in social anxiety disorder. *Int Clin Psychopharmacol* 2000; **15** (suppl): S19–24.
8. Marshall RD, *et al*. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 2001; **158:** 1982–8.
9. Tucker P, *et al*. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001; **62:** 860–8.
10. Liebowitz MR, *et al*. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry* 2002; **63:** 66–74.
11. Stein DJ, *et al*. Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. *Arch Gen Psychiatry* 2002; **59:** 1111–18.
12. Stocchi F, *et al*. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry* 2003; **64:** 250–8.
13. Hollander E, *et al*. Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry* 2003; **64:** 1113–21.
14. Lepola U, *et al*. Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *J Clin Psychiatry* 2004; **65:** 222–9.
15. Sheehan DV, *et al*. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *J Clin Psychiatry* 2005; **66:** 34–40.
16. Rickels K, *et al*. Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. *J Clin Psychiatry* 2006; **67:** 41–7.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as paroxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Leyman S, *et al*. Paroxetine: post-marketing experience on 4024 depressed patients in Belgium. *Eur J Clin Res* 1995; **7:** 287–96.
2. Rodríguez-Ramos P, *et al*. Effects of paroxetine in depressed adolescents. *Eur J Clin Res* 1996; **8:** 49–61.
3. Franchini L, *et al*. Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. *J Clin Psychiatry* 1998; **59:** 229–32.
4. Williams JW, *et al*. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000; **284:** 1519–26.
5. Golden RN, *et al*. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 2002; **63:** 577–84.
6. Rapaport MH, *et al*. Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J Clin Psychiatry* 2003; **64:** 1065–74.
7. Misri S, *et al*. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry* 2004; **65:** 1236–41.
8. Trivedi MH, *et al*. Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. *J Clin Psychiatry* 2004; **65:** 1356–64.
9. Dunner DL, *et al*. Efficacy and tolerability of controlled-release paroxetine in the treatment of severe depression: post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. *Clin Ther* 2005; **27:** 1901–11.
10. Katzman MA, *et al*. Paroxetine versus placebo and other agents for depressive disorders: a systematic review and meta-analysis. *J Clin Psychiatry* 2007; **68:** 1845–59.
11. Barbui C, *et al*. Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. *CMAJ* 2008; **178:** 296–305.

Hypochondriasis. For mention of the use of SSRIs, including paroxetine, in hypochondriasis, see under Fluoxetine, p. 418.2.

Premenstrual syndrome. Paroxetine (as a modified-release preparation) is used to control both the psychological and somatic symptoms of premenstrual syndrome (p. 2272.3).

References.

1. Cohen LS, *et al*. Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. *Psychosom Med* 2004; **66:** 707–13.
2. Landén M, *et al*. Placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder. *Neuropsychopharmacology* 2007; **32:** 153–61.
3. Steiner M, *et al*. Luteal phase administration of paroxetine for the treatment of premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled trial in Canadian women. *J Clin Psychiatry* 2008; **69:** 991–8.

Pruritus. Paroxetine has produced some benefit in the relief of non-dermatological pruritus.[1]

1. Zylicz Z, *et al*. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage* 2003; **26:** 1105–12.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the potential use of these effects in the management of premature ejaculation see Fluoxetine, p. 419.1.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 419.1).

Extrapyramidal reactions (including orofacial dystonias) and withdrawal symptoms associated with paroxetine have been reported to the UK CSM more commonly than with other SSRIs. For further details, see Extrapyramidal Effects under Adverse Effects of Fluoxetine, p. 421.2 and Withdrawal under Precautions, p. 423.3.

Breast feeding. For comments on the use of SSRIs in breast-feeding patients, see under Precautions for Fluoxetine, p. 422.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 420.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paroxetine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For discussion of the risks of SSRIs during pregnancy, and whether paroxetine is associated with a greater teratogenic risk than other SSRIs, see under Fluoxetine, p. 423.1.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 424.1.

Pharmacokinetics

Paroxetine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 5 hours of ingestion. It undergoes extensive first-pass metabolism in the liver. The main metabolic pathway is oxidation followed by methylation and formation of glucuronide and sulfate conjugates. The cytochrome P450 isoenzyme CYP2D6 is partly responsible for the metabolism of paroxetine. Paroxetine is widely distributed throughout body tissues and is about 95% bound to plasma proteins. The elimination half-life of paroxetine is reported to be about 21 hours. Excretion is via the urine (about 64%) and the faeces (about 36%), mainly as metabolites in both cases. Paroxetine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p. 422.2).

References.

1. Dalhoff K, *et al*. Pharmacokinetics of paroxetine in patients with cirrhosis. *Eur J Clin Pharmacol* 1991; **41:** 351–4.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.
3. Cristina Castelli M, *et al*. Pharmacokinetic properties of once-daily oral low-dose mesylate salt of paroxetine (LDMP 7.5 mg) following single and multiple doses in healthy postmenopausal women. *Clin Ther* 2013; **35:** 862–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Afenexil; Aropax; Datevan; Meplar; Neurotrox; Olane; Pamoxet; Paxil; Psicoasten; Sicopax†; Sicotral; Sostel; Tiarix; Xilanic†; ***Austral.***: Aropax; Extine; Oxetine†; Paxtine; ***Austria***: Allenopar; Ennos; Parocetan; Paroxat; Seroxat; ***Belg.***: Aropax; Seroxat; ***Braz.***: Aropax; Arotin; Benepax; Cebrilin; Depaxan; Moratus; Parox; Paxan; Paxil; Paxtrat; Pondera; Roxetin; Sertero; Zyparox; ***Canad.***: Paxil; ***Chile***: Aroxat; Bectam; Pamax; Posivyl; Roxepar; Seretran; Traviata; ***China***: Le You (乐友); Seroxat (赛乐特); ***Cz.***: Apo-Parox; Arketis; Parolex; Remood; Seroxat; ***Denm.***: Euplix; Optipar; Paroc; Paroxegen; Pasorex; Serorex; Seroxat; Seroxetabs; ***Fin.***: Optipar; Seroxat; ***Fr.***: Deroxat; Divarius; ***Ger.***: ParoLich†; Paroxalon; Paroxat†; Seroxat; Tagonis†; ***Gr.***: Noprilex; Parolet; Parosat; Paroxia; Paxinol; Prexat; Seroxat; Solben; Stiliden; Taberil; ***Hong Kong***: Parotin; Seroxat; ***Hung.***: Apodepi; Paretin; Parogen; Paroxat; Rexetin; Seroxat; Xetanor; ***India***: Cinpar-CR; Deprox; Leparox; Oxitine; Panex; Paradise; Pari; Parotin; Xet; ***Indon.***: Seroxat†; ***Irl.***: Meloxat; Paroser; Parox; Paxt; Seroxat; ***Israel***: Parotin; Paxxet; Seroxat; ***Ital.***: Dapagut; Daparox; Dropaxin; Eutimil; Serestill; Sereupin; Seroxat; Stiliden; ***Jpn***: Paxil; ***Malaysia***: Seroxat; ***Mex.***: Apo-Oxpar; Aropax; Ixicrol; Ontracel;

The symbol † denotes a preparation no longer actively marketed

Paxil; Tamcere; Xetroran; ***Neth.***: Seroxat; ***Norw.***: Seroxat; ***NZ***: Aropax; Loxamine; ***Philipp.***: Panex; Seroxat; ***Pol.***: Arketis; Deprozel†; ParoGen; Paromerck; Paroxinor; Paxeratio†; Paxtin; Rexetin; Seroxat; Xetanor; ***Port.***: Denerval; Dropax; Paxetil; Paxpar; Ritlemi; Seroxat; Stiliden; Voltak; Zanoxina; ***Rus.***: Actaparoxetine (Актапароксетин); Adepress (Адепресс); Paxil (Паксил); Plisil (Плизил); Rexetin (Рексетин); Serestill (Сиpестилл); ***S.Afr.***: Aropax; Deparoc; Parax; Paxil; Sedarin†; Serrapress; Xet; ***Singapore***: Seroxat; ***Spain***: Arapaxel; Casbol†; Daparox; Frosinor; Motivan; Paratonina†; Seroxat; Xetin; Zuria; ***Swed.***: Arketis; Paroxiflex; Seroxat; ***Switz.***: Deroxat; Parexat†; Paronex; Paroxetop†; ***Thai.***: Seroxat; ***Turk.***: Nokturn; Paroteva; Paxera; Paxil; Paxotin; Seroxat; Xetanor; Zoxapar; ***UK***: Seroxat; ***Ukr.***: Paroxin (Пароксин); Rexetin (Рексетин); ***USA***: Brisdelle; Paxil; Pexeva; ***Venez.***: Paxil.

Pharmacopoeial Preparations
BP 2014: Paroxetine Tablets;
USP 36: Paroxetine Tablets.

Phenelzine Sulfate *(BANM, pINNM)*

Fenelzina, sulfato de; Phénelzine, Sulfate de; Phenelzine Sulphate; Phenelzini Sulfas; Sulfato de fenelzina; Фенельзина Сульфат.

Phenethylhydrazine hydrogen sulphate.

$C_8H_{12}N_2H_2SO_4$=234.3

CAS — 51-71-8 (phenelzine); 156-51-4 (phenelzine sulfate).

ATC — N06AF03.

ATC Vet — QN06AF03.

UNII — 2681D7P965.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Phenelzine Sulfate). A white powder or pearly platelets with a pungent odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Protect from light.

USP 36: (Phenelzine Sulfate). A white to yellowish-white powder having a characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 1% solution in water is between 1.4 and 1.9. Store in airtight containers. Protect from heat and light.

Uses and Administration

Monoamine oxidase inhibitors (MAOIs) inhibit the action of monoamine oxidase, the enzyme responsible for the metabolism of several biogenic amines. Monoamine oxidase exists in two forms, type A and type B. Monoamine oxidase type A preferentially de-aminates adrenaline, noradrenaline, and serotonin whereas monoamine oxidase type B preferentially metabolises benzylamine and phenylethylamine; dopamine and tyramine are de-aminated by both forms of the enzyme.

- The traditional MAOIs such as phenelzine, iproniazid, isocarboxazid, and tranylcypromine are inhibitors of both types; apart from tranylcypromine, which produces a less prolonged inhibition of the enzyme than phenelzine, all are hydrazine derivatives and bind irreversibly.
- Selective inhibitors include selegiline (p. 915.2), an irreversible inhibitor of monoamine oxidase type B used in the treatment of Parkinson's disease and depression. Clorgiline, an irreversible selective type A inhibitor, was investigated for use as an antidepressant.
- Reversible inhibitors of monoamine oxidase type A (RIMAs) are used in treatment of depression and include moclobemide.

Antidepressant activity appears to reside mainly with inhibition of monoamine oxidase type A although the mode of action of these drugs in depression is not fully understood. Selective inhibitors are claimed to have fewer or less severe adverse effects than non-selective inhibitors. As tyramine is de-aminated by both monoamine oxidase types A and B, inhibiting only one of the enzymes allows for continued, albeit reduced, de-amination. Thus the dietary precautions that need to be observed with non-selective inhibitors are less stringent with the selective inhibitors.

Phenelzine and other antidepressant MAOIs are used in the treatment of atypical depression, particularly where phobic features or associated anxiety are present, or in patients who have not responded to other antidepressants. However, the risks associated with irreversible non-selective MAOIs usually mean that other antidepressants are preferred. Up to a month may elapse before an antidepressant response is obtained with MAOIs. After a response has been obtained maintenance therapy may need to be continued for at least 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years. Care should be taken in elderly patients because of an increased susceptibility to adverse effects. Moreover, therapy with the non-selective inhibitors is particularly unsuitable for patients considered unable to adhere to the strict dietary requirements necessary for safe usage. (For contra-indication in children, see under Precautions, p. 446.2).

Phenelzine is given orally as the sulfate although doses are expressed in terms of the base; phenelzine sulfate 25.8 mg is equivalent to about 15 mg of phenelzine. The usual initial dose is equivalent to phenelzine 15 mg three times daily; if no response has been obtained after 2 weeks the dosage may be increased to 15 mg four times daily; severely depressed patients in hospital may be given up to 30 mg three times daily. Once a response has been obtained the dosage may be gradually reduced for maintenance therapy; some patients may continue to respond to 15 mg on alternate days.

Phenelzine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. MAOIs have been used in the treatment of anxiety disorders. MAOIs appear to be effective in *panic disorder* (p. 1029.1). They also appear to be effective in *social anxiety disorder* (see under Phobic Disorders, p. 1029.1) and can improve anticipatory anxiety and functional disability. The main treatment for *post-traumatic stress disorder* (p. 1029.2) is psychotherapy but MAOIs are one of the alternatives that can help to reduce traumatic recollections and nightmares, and to repress flashbacks.

References.
1. Buigues J, Vallejo J. Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry* 1987; **48:** 55–9.
2. Frank JB, *et al.* A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. *Am J Psychiatry* 1988; **145:** 1289–91.
3. Heimberg RG, *et al.* Cognitive behavioural group therapy vs phenelzine therapy for social phobia: 12 week outcome. *Arch Gen Psychiatry* 1998; **55:** 1133–41.
4. Aarre TF. Phenelzine efficacy in refractory social anxiety disorder: a case series. *Nord J Psychiatry* 2003; **57:** 313–15.

Depression. As discussed on p. 398.1 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. MAOIs are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Even in depressed patients with atypical, hypochondriacal, hysterical, or phobic features, for which MAOIs are particularly effective, it is often recommended that another antidepressant type should be tried first. Reversible inhibitors of monoamine oxidase type A (RIMAs) offer an alternative to the MAOIs and less strict dietary restrictions are necessary. They may be effective in depressive disorders, although their relative efficacy in atypical depression remains to be established.

Combination therapy with differing classes of antidepressants, including the MAOIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and requires expert supervision. For further details, see Antidepressants under Interactions, p. 447.2.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p. 2314.1), initial treatment is usually with a central stimulant. MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use.

Migraine. Numerous drugs have been used for the prophylaxis of migraine (p. 670.3), although propranolol is generally preferred. Antidepressants such as the tricyclics can be useful alternatives when these drugs are ineffective or unsuitable. MAOIs are best reserved for severe cases refractory to other forms of prophylactic treatment.

Adverse Effects

Adverse effects commonly associated with phenelzine and other MAOIs include orthostatic hypotension and attacks of dizziness. Other common adverse effects include headache, dry mouth, constipation and other gastrointestinal disturbances (including nausea and vomiting), and oedema. Drowsiness, weakness, and fatigue are reported frequently although CNS stimulation may also occur and symptoms include agitation, nervousness, euphoria, restlessness, insomnia, and convulsions. Psychotic episodes, with hypomania or mania, confusion, hallucinations, or toxic delirium, may be induced in susceptible persons.

Sweating and muscle tremors, twitching, or hyperreflexia may occur, which in overdosage may present as extreme hyperpyrexia and neuromuscular irritability. Other reported reactions include blurred vision, nystagmus, urinary retention or difficulty in micturition, arrhythmias, rashes, leucopenia, sexual disturbances, and weight gain with inappropriate appetite. Jaundice has been reported with hydrazine MAOIs and, on rare occasions, fatal progressive hepatocellular necrosis. Peripheral neuropathies associated with the hydrazine derivatives may be caused by pyridoxine deficiency. Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of **overdosage** may be minor at first and progress over the ensuing 24 to 48 hours. After mild overdosage and symptomatic and supportive therapy, recovery may occur in 3 to 4 days, but after massive overdosage symptoms may persist for up to 2 weeks. CNS depression and drowsiness have been noted with overdosage, but CNS stimulation is more common, with irritability, hyperactivity, agitation, hallucinations, or convulsions. Respiratory depression and coma may ultimately occur. Cardiovascular effects include hypertension, sometimes with severe headache, although hypotension is more frequently reported; cardiac arrhythmias and peripheral collapse can also develop. Profuse sweating, hyperpyrexia, and neuromuscular excitation with hyperreflexia are also prominent features of overdosage.

MAOIs have been the most commonly implicated drugs in the serotonin syndrome (see p. 445.2). A severe hypertensive crisis, sometimes fatal, may occur if an MAOI is taken with some other drugs or certain foods (see Interactions, p. 447.1 and p. 446.3). These reactions are characterised by severe headache and a rapid and sometimes prolonged rise in blood pressure followed by intracranial haemorrhage or acute cardiac failure.

For the adverse effects of reversible inhibitors of monoamine oxidase type A (RIMAs), see Moclobemide, p. 437.3.

Incidence of adverse effects. A suspicion that the reported adverse effects of MAOIs were both exaggerated and over-emphasised prompted a comparative study in patients receiving phenelzine or imipramine.[1] The report noted that the dosages of phenelzine used were at the upper end of the usual therapeutic range (mean 77 mg daily) while those of imipramine were in the middle of the usual therapeutic range (mean 139 mg daily). The profile of adverse effects in the two groups was very similar. With the exception of significantly increased incidence of drowsiness in the phenelzine group, the 2 groups did not differ in the frequency of autonomic, CNS, cardiovascular, or psychological adverse effects. However, a significantly greater number of patients given phenelzine had to stop their treatment because of the severity of the adverse effects. Nonetheless it was considered that phenelzine was reasonably well-tolerated when compared with imipramine.

Others have also studied the adverse effect profile of phenelzine and made comparisons with tranylcypromine and imipramine.[2,3] A retrospective review involving 198 patients concluded that although phenelzine was more likely than the other two drugs to induce adverse effects, drug withdrawal because of adverse effects was less likely to occur. This was probably because phenelzine showed clear-cut clinical efficacy resulting in prescribers being reluctant to stop therapy.

1. Evans DL, *et al.* Early and late side effects of phenelzine. *J Clin Psychopharmacol* 1982; **2:** 208–10.
2. Rabkin J, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part I: a comparative study. *J Clin Psychopharmacol* 1984; **4:** 270–8.
3. Rabkin JG, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part II: treatment correlates and clinical management. *J Clin Psychopharmacol* 1985; **5:** 2–9.

Effects on the cardiovascular system. MAOIs are generally considered to be relatively free of adverse cardiovascular effects. The hypertensive reaction that may follow interactions of MAOIs with foods or other drugs is well known (see Interactions, p. 446.3 and p. 447.1) but orthostatic hypotension may also occur when these drugs are used on their own.

In a study[1] involving 14 patients it was found that phenelzine produced both a significant decrease in systolic blood pressure while lying down, and significant orthostatic hypotension; in 2 patients these effects on blood pressure meant treatment had to be altered. Differences between the effects of phenelzine and those reported for the tricyclic antidepressants were noted. Tricyclics were not known to affect lying systolic blood pressure and although both tricyclics and phenelzine could cause orthostatic hypotension, with the tricyclics it typically reaches a maximum within the first week of treatment whereas with phenelzine the maximum effect was noted after 4 weeks. Additionally, the study provided some indication that the blood pressure effects of phenelzine may attenuate with time, a phenomenon that is not known to occur with the tricyclics.

1. Kronig MH, *et al.* Blood pressure effects of phenelzine. *J Clin Psychopharmacol* 1983; **3:** 307–10.

Effects on the endocrine system. MAOIs may induce *hyperprolactinaemia*[1] and this has led to galactorrhoea in women.[2] Occasionally, MAOIs may cause *dilutional hyponatraemia* due to a reduction in the renal excretion of free water mediated by both enhanced vasopressin release and increased antidiuretic action on the renal tubule.[3] The UK CSM, commenting on reports[4] it had received of hyponatraemia with antidepressants (fluoxetine, paroxetine,

lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.

1. Slater SL, *et al*. Elevation of plasma-prolactin by monoamine-oxidase inhibitors. *Lancet* 1977; **ii:** 275–6.
2. Segal M, Heys RF. Inappropriate lactation. *BMJ* 1969; **4:** 236.
3. Baylis PH. Drug-induced endocrine disorders. *Adverse Drug React Bull* 1986; No 116: 432–5.
4. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the liver. Published case reports of hepatotoxic reactions to MAOIs have included jaundice in 4 patients[1] and hepatic failure progressing to encephalopathy in 2 patients;[2] this latter reaction was attributed to a hypersensitivity reaction.

Of 91 cases of hepatitis associated with antidepressants reported to French pharmacovigilance centres from 1977 to 1983, an MAOI (iproniazid) was implicated in 11. These 11 cases were associated with cytolytic reactions and 5 patients died.[3]

Two cases of fulminant hepatic failure have been reported[4] after use of phenelzine for 4 months; all other causes of acute liver damage were ruled out. Both patients recovered after emergency liver transplantation.

1. Holdsworth CD, *et al*. Hepatitis caused by the newer amine-oxidase-inhibiting drugs. *Lancet* 1961; **ii:** 621–3.
2. Wilkinson SP, *et al*. Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *BMJ* 1974; **1:** 186–9.
3. Lefebure B, *et al*. Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.
4. Gómez-Gil E, *et al*. Phenelzine-induced fulminant hepatic failure. *Ann Intern Med* 1996; **124:** 692–3.

Effects on the nervous system. MAOIs produce a variety of effects on the nervous system. Drowsiness is frequently reported but symptoms of CNS stimulation, including agitation, nervousness, and euphoria may also occur; psychotic episodes may be induced in susceptible individuals. Further adverse neurological reactions are described under Epileptogenic Effect, p. 445.1, and Extrapyramidal Effects, p. 445.2.

Peripheral neuropathies, sometimes associated with a documented pyridoxine deficiency, have been reported in patients receiving phenelzine.[1,2] In most of the patients the neuropathies developed 6 weeks to 4 months after starting phenelzine,[2] although in one case symptoms did not occur for 11 years.[1] The symptoms also generally disappeared when pyridoxine was given with continued phenelzine therapy.[2] The possibility that the dietary restrictions imposed on persons taking phenelzine might have contributed to a low pyridoxine intake was considered unlikely. The most probable mechanism for the induced pyridoxine deficiency was combination of the hydrazine moiety with the pyridoxal form of the vitamin to form an inactive compound.

Many drugs can inhibit transmission at the myoneural junction under experimental conditions and it has been said that phenelzine may cause postoperative respiratory depression, possibly through a combined action with neuromuscular blockers.[3] For further details, see Anaesthesia under Precautions, p. 446.1.

1. Heller CA, Friedman PA. Pyridoxine deficiency and peripheral neuropathy associated with long-term phenelzine therapy. *Am J Med* 1983; **75:** 887–8.
2. Stewart JW, *et al*. Phenelzine-induced pyridoxine deficiency. *J Clin Psychopharmacol* 1984; **4:** 225–6.
3. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Effects on sexual function. MAOIs such as phenelzine and tranylcypromine have been implicated in producing both impotence and failure of ejaculation.[1,2] Priapism has been reported with phenelzine.[3] There have also been several reports of female anorgasmia attributed to MAOIs, an effect which appears to be dose-related.[4] Loss of libido and impotence are common symptoms of depression, often making the role of drugs in producing sexual dysfunction difficult to assess.

1. Simpson GM, *et al*. Effects of anti-depressants on genito-urinary function. *Dis Nerv Syst* 1965; **26:** 787–9.
2. Wyatt RJ, *et al*. Treatment of intractable narcolepsy with a monoamine oxidase inhibitor. *N Engl J Med* 1971; **285:** 987–91.
3. Yeragani VK, Gershon S. Priapism related to phenelzine therapy. *N Engl J Med* 1987; **317:** 117–18.
4. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; **28:** 497–9.

Epileptogenic effect. Licensed product information indicates that convulsions represent one of the less common adverse effects of MAOIs; they may be a feature of overdosage.

A typical grand-mal seizure with tonic-clonic convulsions has been reported in a patient with no history of epilepsy or predisposing factors shortly after the start of phenelzine therapy.[1] The point was made that phenelzine-induced seizures had rarely been seen.

1. Bhugra DK, Kaye N. Phenelzine induced grand mal seizure. *Br J Clin Pract* 1986; **40:** 173–4.

Extrapyramidal effects. A parkinsonian syndrome developed in a patient about 5 weeks after the start of therapy with phenelzine. Symptoms gradually resolved over 10 days after the withdrawal of phenelzine. The mechanisms by which phenelzine could have induced these effects were discussed.[1]

1. Gillman MA, Sandyk R. Parkinsonism induced by a monoamine oxidase inhibitor. *Postgrad Med J* 1986; **62:** 235–6.

Hyponatraemia. See Effects on the Endocrine System, p. 442.3.

Lupus. A reversible lupus-like reaction has been reported in a patient who had been taking phenelzine sulfate for 8 months.[1]

1. Swartz C. Lupus-like reaction to phenelzine. *JAMA* 1978; **239:** 2693.

Overdosage. MAOIs in overdose rarely produce severe hypertension; the blood pressure may be high or low, or may alternate between the two. More commonly the patient gradually develops widespread muscle spasms, trismus, and opisthotonus with widely dilated pupils and a hot and sweating skin. About 16 to 24 hours after ingestion potentially fatal hyperthermia may develop; temperatures of 42.1 to 43.8 degrees have been recorded immediately before death. Disseminated intravascular coagulation, rhabdomyolysis, and acute tubular necrosis can also occur.[1]

1. Henry JA. Specific problems of drug intoxication. *Br J Anaesth* 1986; **58:** 223–33.

Serotonin syndrome. The serotonin syndrome is a drug-induced excess in serotonergic activity at central receptors.[1-10] It is characterised by the development of *at least three* of the following clinical features after a recent change in a treatment regimen involving serotonergic drugs:[1]

- agitation
- ataxia
- diaphoresis
- diarrhoea
- fever
- hyperreflexia
- myoclonus
- shivering
- changes in mental status

Strict application of these criteria may not identify early, mild, or subacute cases of serotonin syndrome and a simpler diagnostic approach focusing on neuromuscular features has also been suggested.[10] The syndrome should be distinguished from the hypertensive crises produced by the interaction between MAOIs and tyramine (see Interactions of MAOIs with Foods, p. 446.3), and from the neuroleptic malignant syndrome (see p. 1050.2).[3,8-10]

The onset of the syndrome is often within minutes of altering the regimen,[10] although some cases have occurred as much as several weeks later.[2] The occurrence and severity of the syndrome do not appear to be dose-related,[2] but to depend on the extent and duration of the rise in intrasynaptic serotonin.[5]

The serotonin syndrome is relatively uncommon and symptoms are usually mild. However, severe complications, including disseminated intravascular coagulation, severe hyperthermia, respiratory failure, and seizures have been reported; there have also been fatalities.

The serotonin syndrome may follow exposure to a single serotonergic drug or, more commonly, a combination of such drugs.[2,8-10] In the past, **MAOIs** have been the most commonly implicated drugs in this syndrome, particularly when taken with other antidepressants such as the tricyclics, SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs) including venlafaxine, trazodone, lithium, and tryptophan. (The use of combination therapy with serotonergic antidepressant drugs is discussed under Interactions of MAOIs with other Drugs, p. 447.2.) MAOIs combined with the opioids dextromethorphan and pethidine have also produced the serotonin syndrome. The interaction can occur with both irreversible and reversible MAOIs, and with those selective for monoamine oxidase type A such as moclobemide as well as with non-selective MAOIs.[11] The selective inhibitor of monoamine oxidase type B, selegiline, may also pose problems at high doses as its selectivity starts to diminish.

As usage of the **SSRIs** has increased, so too has the number of reports of adverse reactions when these drugs have been combined with other serotonergic drugs, including the herbal preparation St John's wort.

Other drugs that may potentially cause serotonin syndrome in certain circumstances include antiemetics such as ondansetron, buspirone, carbamazepine, dihydroergotamine, methylenedioxyamfetamine, sibutramine, selective serotonin (5-HT_1) agonists such as sumatriptan, and tramadol.[5,8-10]

Serotonergic potentiation may also occur if one serotonergic drug is used after another without allowing a sufficient **drug-free interval** after stopping the first. This is a particular problem when the first drug is an irreversible MAOI or a drug with a long half-life such as the SSRI fluoxetine.

Most cases of serotonin syndrome resolve within 24 hours after withdrawal of the offending drugs and giving supportive **therapy**,[1-4,8-10] including appropriate management of fever and hyperthermia (p. 11.3). Benzodiazepines may be of value to control agitation, myoclonus, and seizures. The non-specific serotonin antagonist cyproheptadine may be useful in more severe cases although its efficacy has not been established;[8,10] methysergide has also been used with some success.[2,3,6] Other drugs that have been tried include propranolol, chlorpromazine, and dantrolene[2,3,6,8-10] although adverse effects may limit their usefulness.

1. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; **148:** 705–13.
2. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. *Drug Safety* 1995; **13:** 94–104.
3. Corkeron MA. Serotonin syndrome—a potentially fatal complication of antidepressant therapy. *Med J Aust* 1995; **163:** 481–2.
4. Brown TM, *et al*. Pathophysiology and management of the serotonin syndrome. *Ann Pharmacother* 1996; **30:** 527–33.
5. Gillman PK. Serotonin syndrome: history and risk. *Fundam Clin Pharmacol* 1998; **12:** 482–91.
6. Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol* 1999; **13:** 100–109.
7. Mason PJ, *et al*. Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2000; **79:** 201–9.
8. Birmes P, *et al*. Serotonin syndrome: a brief review. *Can Med Assoc J* 2003; **168:** 1439–42.
9. Bilj D. The serotonin syndrome. *Neth J Med* 2004; **62:** 309–13.
10. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; **352:** 1112–20. Correction. *ibid.* 2007; **356:** 2437.
11. Livingston MG. Interactions with selective MAOIs. *Lancet* 1995; **345:** 533–4.

Treatment of Adverse Effects

In cases of overdosage with MAOIs the benefit of gastric decontamination is uncertain; however, in patients who present within 1 hour activated charcoal may be given orally, or, in potentially life-threatening cases, the stomach may be emptied by lavage. Management then largely involves intensive symptomatic and supportive therapy with particular attention being given to CNS effects, raised body temperature (which may develop into malignant hyperthermia), and cardiovascular effects. Delayed effects may develop some time after the overdose even in patients who are initially asymptomatic, and therefore prolonged monitoring for at least 12 hours is warranted. Other drugs taken with an overdose of MAOIs may complicate the features and result in the need for an even longer period of monitoring. Special care is needed with any drug therapy used in the management of MAOI overdosage in view of the many known interactions which occur with this class of drugs.

Muscle spasm, agitation, and convulsions should be treated with diazepam. Severe neuromuscular irritability may call for the use of a competitive neuromuscular blocker such as pancuronium and intubation with assisted ventilation. Hyperthermia may be a particular problem; if simple antipyretics such as paracetamol and external cooling measures fail a competitive neuromuscular blocker has often been advocated; dantrolene has also been suggested.

Hypotension, which is a fairly common feature, should be managed by intravenous fluid therapy and volume expansion; vasopressors should be avoided. Conversely, a hypertensive crisis may occasionally occur after an overdose with MAOIs and can be managed with phentolamine given by slow intravenous injection. Persistent hypertension may respond to intravenous nitrates.

Precautions

Phenelzine and other MAOIs should not be given to patients with liver disease or a history of abnormal liver function tests, or, because of their effects on blood pressure, to patients with congestive heart failure, cerebrovascular disease, or phaeochromocytoma. (Blood pressure should be monitored in all patients.) MAOIs should be avoided or only used with great caution in patients with blood disorders or cardiovascular disease, and in elderly or agitated patients who may be particularly susceptible to their adverse effects. They should be given with caution to epileptic patients. Caution has also been advised in diabetic patients because of conflicting evidence about whether glucose metabolism is altered or requirements for hypoglycaemics changed. MAOIs should be used with caution in patients with hyperthyroidism because of increased sensitivity to pressor amines.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when

treating patients with depression should therefore be observed when treating patients with other disorders.

Mania may be precipitated if MAOIs are used for the depressive component of bipolar disorder, and they are not usually indicated; similarly psychotic symptoms may be aggravated if they are used for a depressive component of schizophrenia.

MAOIs have a prolonged action so patients should not take any of the foods or drugs known to cause reactions (see Interactions, p. 446.3 and p. 447.1) for at least 14 days after stopping treatment. A similar drug-free period has been advised before any patient undergoes surgery since it may involve the use of drugs that can interact with MAOIs, although not all agree that this is necessary; caution has been advised in patients requiring MAOIs with ECT; for further details see under Anaesthesia, p. 446.1. Patients should carry cards giving details of their MAOI therapy; they and their relatives should be fully conversant with the implications of food and drug interactions and the precautions to be taken.

Patients liable to take charge of vehicles or other machinery should be warned that MAOIs may modify behaviour and state of alertness. Patients affected by drowsiness should not drive or operate machinery.

MAOIs should be withdrawn gradually to reduce the risk of withdrawal symptoms (see p. 446.2).

For the precautions to be observed with reversible inhibitors of monoamine oxidase A (RIMAs), see Moclobemide, p. 437.3.

Anaesthesia. The considerations given to patients taking tricyclic antidepressants before receiving anaesthesia for ECT or surgery (see Amitriptyline, p. 404.3) are also generally applicable to patients being treated with MAOIs; licensed product information for phenelzine also warns that transient respiratory and cardiovascular depression following ECT have been reported. The interactions of other drugs with MAOIs may be more numerous or more severe than those with tricyclics and the interaction with pethidine should not be forgotten.

A review[1] of the potential problems of anaesthesia in patients receiving MAOIs considered that stopping MAOIs about 2 weeks before anaesthesia was unreasonable, as there were safe and suitable anaesthetics available, although the dangers of sympathetic overactivity must always be remembered. This view, that it is safe to continue MAOIs throughout the period of anaesthesia, ECT, and surgery, is also held by others[2-4] although some disagree.[5]

Regardless of any decision, the anaesthetist should be informed of all drugs that the patient is or has been taking; this is particularly important when emergency surgery is required in a patient receiving MAOI therapy.

- It has been stated[1] that the interaction between MAOIs and *opioid analgesics* has two distinct forms: an excitatory form [serotonin syndrome—see p. 443.2]; and a depressive form consisting of respiratory depression, hypotension, and coma as a result of the inhibition of hepatic microsomal enzymes by the MAOI leading to accumulation of free opioid analgesic. *Pethidine* use during anaesthesia has elicited the excitatory response, which has frequently been severe and often fatal. For this reason, pethidine should never be given to patients receiving MAOIs. *Morphine* does not block neuronal serotonin uptake but its narcotic effects may be potentiated in the presence of MAOIs and a single case report of the depressive type of reaction has been described. Thus, morphine is the opioid analgesic of choice but must be given in reduced dosage and the dosage carefully titrated against clinical response. *Papaveretum* would appear to have no advantage over morphine. Although interactions of MAOIs with *pentazocine* have occurred in *animals*, it is not clear if this occurs in man. *Methadone* has been used in a patient without mishap and there is also anecdotal evidence to support the safety of *fentanyl*. A case report[6] described the successful use of *alfentanil* (with propofol and atracurium) mentioning that this was the first report of such use in patients receiving MAOIs. A further case report[7] has also described the safe use of alfentanil (with propofol and suxamethonium) for anaesthesia during ECT in 2 patients taking phenelzine. *Remifentanil* has also been used safely as part of an anaesthetic regimen (with sevoflurane, vecuronium, and isoflurane) in a patient also taking phenelzine.[8] In another case[9] a patient underwent successful anaesthesia with *sufentanil* (with thiopental, lidocaine, and vecuronium) while continuing to take an MAOI (tranylcypromine) as well as a tricyclic antidepressant (imipramine) and lorazepam.
- With regard to induction agents,[1] the use of *ketamine* in patients receiving MAOIs should be avoided on theoretical grounds, although no interactions have been reported. Potentiation of *barbiturates* may be expected.
- With neuromuscular blockers, phenelzine has been shown to decrease plasma cholinesterase concentrations and there have been case reports of a prolonged effect with *suxamethonium*; additionally this prolongation of the effect of suxamethonium may lead to apnoea and modification of the convulsion during ECT. However, a small case series of 4 patients taking tranylcypromine while undergoing ECT treatment (with suxamethonium as the neuromuscular blocker) found no difference in seizure length when compared with previous ECT courses when the patients were not taking an MAOI.[4] There may be a theoretical hazard with *pancuronium* since it releases stored adrenaline (although its use has been advocated in the treatment of symptoms of overdosage with MAOIs, see Treatment of Adverse Effects, p. 443.3), but *alcuronium*, *atracurium*, or *vecuronium* would all appear to be suitable alternatives.[1]
- *Enflurane*, *halothane*, *isoflurane*, and *nitrous oxide* are all safe in the presence of MAOIs, although there is a theoretical possibility of an increased risk of hepatic damage with halothane.
- *Indirect-acting sympathomimetics* pose the risk of a serious and possibly lethal hypertensive interaction but *direct-acting sympathomimetics*, such as *adrenaline*, *isoprenaline*, and *noradrenaline*, are reliable vasopressors in the presence of MAOIs although great care should be taken with their use because of enhanced receptor sensitivity.

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7. Beresford BJ, *et al.* Combination propofol-alfentanil anesthesia for electroconvulsive therapy in patients receiving monoamine oxidase inhibitors. *J ECT* 2004; **20:** 120–2.
8. Ure DS, *et al.* Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine. *Br J Anaesth* 2000; **84:** 414–16.
9. O'Hara JF, *et al.* Sufentanil-isoflurane-nitrous oxide anesthesia for a patient treated with monoamine oxidase inhibitor and tricyclic antidepressant. *J Clin Anesth* 1995; **7:** 148–50.

Children. Phenelzine is not recommended for the treatment of depression in children and adolescents less than 16 years of age. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on Mental State, under Fluoxetine, p. 420.2).

Driving. While affective disorders probably impair driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative properties and some MAOIs can adversely affect psychomotor performance.[1,2]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased;[3] driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.

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3. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

ECT. For comments concerning precautions in patients receiving ECT, see under Anaesthesia, above.

Surgery. For comments regarding precautions in patients undergoing surgery, see under Anaesthesia, above.

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more can precipitate withdrawal symptoms which may be very severe.

Symptoms associated with withdrawal of MAOIs[1,2] include gastrointestinal disturbances and generalised somatic symptoms such as nausea and vomiting, anorexia, chills, headache, and giddiness; sleep disturbances characterised by insomnia, severe nightmares, and somnolence; and CNS symptoms including panic, anxiety, restlessness, agitation, cognitive impairment, mood swings, depression and suicidal ideation, hypomania, delusions, and hallucinations. Some of the above may be controlled by restarting the MAOI in low doses, but the best management is considered to be prevention by gradually stopping the drug.[2] The *BNF* recommends reducing the dose over a period of 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The pathophysiology of the MAOI withdrawal syndrome is not fully known, although it has been hypothesised that some of the symptoms represent adrenergic hyperactivity[1] produced by the release of excessive amounts of dopamine and noradrenaline.[2]

With the exception of tranylcypromine, the withdrawal syndrome of MAOIs is not a consequence of drug dependence.[1] Tranylcypromine has been reported to produce dependence and tolerance in patients receiving high doses irrespective of whether or not they had a history of substance abuse. Tranylcypromine is similar in structure to amfetamine, which may be responsible for its addictive properties.[1]

1. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; **24:** 29–30.
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Interactions of MAOIs with Foods

A major disadvantage of MAOIs such as phenelzine is that by inhibiting monoamine oxidase they cause an accumulation of amine neurotransmitters. This means that the pressor effects of *tyramine*, which occurs in several common foods and is also metabolised by monoamine oxidase, can be dangerously enhanced. Reactions to foods rich in pressor amines such as tyramine can therefore occur in patients being treated with MAOIs, producing hypertensive crises. Cheese, especially aged or matured cheeses, meat or yeast extracts, pickled herrings, sauerkraut, dry sausage, smoked foods, and broad bean pods have caused such reactions. Patients should be warned not to eat any of these foods while being treated with an MAOI and for at least 14 days after its discontinuation. Some foods will only cause a reaction if large amounts are eaten, and foods may vary in tyramine content depending upon methods of manufacture and storage. Any protein-containing food such as meat, fish, or game subject to hydrolysis, fermentation, pickling, smoking, or spoilage could contain tyramine derived from tyrosine as a result of these processes or of deterioration. Patients taking MAOIs should therefore be advised to eat protein-containing foods only if fresh.

Alcoholic beverages, including wines, beers, and drinks that are de-alcoholised or are low in alcohol, contain variable amounts of tyramine and are best avoided.

The above dietary restrictions that need to be followed with MAOIs may be less stringent for reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (see p. 438.1), although licensed product information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

MAOIs can, when taken with certain foodstuffs, cause a potentially fatal hypertensive reaction. This effect is accepted and well documented and has led to the publication of many lists of prohibited foods and drinks. However, the dangers of the interaction may have been slightly overemphasised or exaggerated and published lists may have been overinclusive;[1-3] this may have led to reduced compliance in many patients.

A review and discussion[1] of the MAOI interaction with tyramine made the following observations and recommendations:

- the hyperadrenergic state resulting from this interaction consisted of three syndromes although significant overlap between them existed: paroxysmal headache of great severity; cardiovascular symptoms with paroxysmal hypertension; and intracerebral haemorrhage and death
- the most common offending drug reported had been tranylcypromine at doses of 20 to 50 mg daily although a few reports had involved phenelzine
- only 4 foodstuffs clearly warranted total prohibition: aged cheese, pickled herring or smoked fish, concentrated yeast extracts, and broad bean pods
- the ingestion of cheese was said to have been associated with 80% of all case reports and with virtually all fatalities. It was agreed that aged cheese should not be permitted, although cottage and cream cheese required no restriction. There was less agreement concerning dairy products such as yogurt and sour cream and it was suggested that limited amounts were permissible
- pickled herring or smoked fish were to be avoided because of several well-documented cases of hypertensive crisis as well as detection of high levels of tyramine. Any meat may become dangerous unless consumed while fresh as tyramine is formed from bacterial protein degradation
- concentrated yeast extracts have a significant tyramine content and yeast vitamin supplements may also constitute a hazard; baker's yeast was considered to be safe

- broad bean pods contain dopamine although the beans themselves were stated to have little pressor activity and carried no prohibition
- other foods which had been reported to have caused a hypertensive reaction but for which these authors considered that there was insufficient evidence to warrant dietary restriction were chocolate and caffeine-containing beverages, soy sauce, fresh fish, wild game, and fruits although caution was necessary with avocados and bananas.

Other reviews of foods[2,4,5] give broadly similar recommendations.

The consumption of alcoholic beverages, and in particular Chianti wine, has frequently been advised against. However, sources have differed on whether particular types of drink (white wine, red wine, spirits, or beer) are safe or not. A study[6] showed no significant differences in mean free tyramine concentration between white wine, red wine, Chianti, and beer although within each category of wine there could be up to a fiftyfold variation even if from the same grape stock. Mention has also been made[7,8] that alcohol-free or low-alcohol beers are likely to contain similar amounts of tyramine to alcoholic beers. The consumption of alcoholic drinks with MAOIs still appears to be controversial with some advocating total abstinence while others permit a modest intake.

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6. Hannah P, *et al*. Tyramine in wine and beer. *Lancet* 1988; **i:** 879.
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Interactions of MAOIs with other Drugs

MAOIs inhibit the metabolism of some *amine drugs* (notably indirect-acting sympathomimetics), which can lead to dangerous enhancement of their pressor effects. MAOIs also inhibit other drug-metabolising enzymes and are therefore responsible for a large number of *other drug interactions*. Moreover, they have an additive effect with serotonergic drugs which may result in the *serotonin syndrome* (see under Adverse Effects, p. 443.2). As in the case of foods, the danger of an interaction persists for at least 14 days after treatment with an MAOI has been stopped.

Severe hypertensive reactions due to enhancement of pressor activity have followed the use of sympathomimetics such as *amfetamines*, *dopamine*, *ephedrine*, *levodopa*, *phenylephrine*, *phenylpropanolamine*, and *pseudoephedrine*. Reactions may also follow the use of anorectics and stimulants with sympathomimetic activity such as *fenfluramine*, *methylphenidate*, *pemoline*, and *phentermine*. There have been case reports of fatalities in patients who took cough preparations containing *dextromethorphan*. There is no clinical evidence of dangerous interactions between *local anaesthetic preparations containing adrenaline* and MAOIs although they could occur if the preparation was accidentally given into a vein. Significant rises in blood pressure have been reported after the use of *buspirone* with MAOIs.

Inhibition of drug-metabolising enzymes by MAOIs may enhance the effects of *barbiturates* and possibly other *hypnotics*, *hypoglycaemics*, and possibly *antimuscarinics*. *Alcohol* metabolism may be altered and its effects enhanced; see also under Interactions of MAOIs with Foods, p. 444.3. Licensed product information suggests that the effects of various classes of *antihypertensives* may be enhanced by MAOIs, including *ACE inhibitors*, *beta blockers*, *calcium-channel blockers* and *thiazides*, with the potential for hypotension, although published evidence for most of these seems to be scanty. Some antihypertensives with direct actions on the sympathetic nervous system, such as *guanethidine*, *indoramin*, *methyldopa*, and, historically, *reserpine*, are suggested to be contra-indicated or used with great caution; both hypotensive and hypertensive reactions have been suggested.

Giving *pethidine* and possibly other *opioid analgesics* to patients taking an MAOI has also been associated with very severe and sometimes fatal reactions. When it is considered essential to use an opioid analgesic, one that does not inhibit serotonin reuptake should be chosen. The use of opioid analgesics and other drugs used during general anaesthesia in patients continuing to take MAOIs is discussed in Anaesthesia under Precautions, p. 444.1.

Clozapine may enhance the CNS effects of MAOIs.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions may occur. MAOIs should not generally be given to patients receiving *tricyclic antidepressants*, *SSRIs*, *serotonin and noradrenaline reuptake inhibitors (SNRIs)*, *bupropion*, *mirtazapine*, *nefazodone*, *reboxetine*, or *trazodone*. An appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. An MAOI should not be started until at least 1 or 2 weeks after stopping a tricyclic antidepressant. For the tricyclic antidepressants clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. For an SSRI, an SNRI, reboxetine, nefazodone, trazodone, or any related antidepressant the drug-free interval should be at least one week; in the case of bupropion, mirtazapine, and the SSRI sertraline, the interval is extended to 2 weeks, and for fluoxetine, at least 5 weeks because of their longer half-lives. Conversely, 2 weeks should elapse between stopping MAOI therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, an SNRI, bupropion, mirtazapine, reboxetine, or any related antidepressant. For further warnings on the combined use of antidepressants, see p. 447.2. Interactions can also occur between MAOIs themselves.

For details of the less severe interactions associated with reversible inhibitors of monoamine oxidase A (RIMAs), see Interactions of Moclobemide, p. 438.1.

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Antidepressants. Combination therapy with differing classes of antidepressants may result in interactions or enhanced adverse reactions such as the serotonin syndrome (see under Adverse Effects, p. 443.2). Despite these drawbacks certain combinations of drugs have been found to be beneficial in the treatment of drug-resistant depression, although others are considered unsuitable; absence of information documenting unsuitability or hazard does not necessarily imply that the two drugs may be used safely together but may merely reflect an untried combination. Because combination therapy poses increased risks it should be used only under expert supervision.

- MAOIs have been used fairly frequently under expert supervision with tricyclics in refractory depression and it has been stated[1] that the risk of serious problems in combining *tricyclic antidepressant and MAOI* antidepressant therapy is almost exclusively limited to sequential prescribing, in particular the addition of a tricyclic to established treatment with an MAOI. The recommended procedure was said to be to allow a drug-free interval of at least one week and then to start both drugs together at a low dosage. The dosage of both drugs is then gradually increased to around half that normally prescribed for the drugs when given on their own. The dietary restrictions for MAOIs alone apply equally to the combined antidepressant regimen.
  Amitriptyline and trimipramine were considered to be the tricyclics least likely to produce adverse effects with MAOIs, while phenelzine and isocarboxazid were the safest MAOIs. In contrast, clomipramine (a tricyclic with serotonin reuptake inhibiting activity) and imipramine are unsuitable for such use.[2,3] The combination of clomipramine with tranylcypromine is particularly dangerous. Symptoms suggestive of the serotonin syndrome occurred in an elderly patient due to an interaction between clomipramine and moclobemide, a reversible inhibitor of monoamine oxidase type A (RIMA).[4] Two fatalities due to serotonin syndrome have been reported after overdosage with clomipramine and moclobemide.[5] The syndrome has also developed when a patient was switched from clomipramine to moclobemide with no suitable drug-free interval.[6] A 39-year-old woman developed the serotonin syndrome while taking imipramine with moclobemide, although it was suggested that an excessive dose of the tricyclic may have been ingested accidentally.[7]
- The UK CSM has warned[8] that enhanced serotonergic effects may result from using *SSRIs with MAOIs* or other antidepressants. Although such an enhancement may be beneficial in some instances it can produce a life-threatening serotonin syndrome. Such reactions were later reported in patients taking sertraline with MAOIs.[9-11] Three fatalities due to serotonin syndrome have been reported after overdosage with citalopram and moclobemide.[5] A case of serotonin syndrome has been reported after switching from fluoxetine to moclobemide with no suitable drug-free interval.[6] Some authors[12] have reported good efficacy and tolerability with combinations of moclobemide and SSRIs. However, others[13] reported a high rate of adverse events although, as significant improvement in depressive symptoms was seen in some patients, it was suggested that giving moclobemide with SSRIs deserved consideration as an option for the treatment of refractory depression.
- Combination therapy with a *tricyclic antidepressant and an SSRI* has sometimes been used to treat resistant depression. Fluvoxamine[14] and fluoxetine[15] have been reported to increase plasma concentrations of the tricyclic, although to varying degrees. Fluoxetine has been reported to produce three- to fourfold increases in plasma concentrations of desipramine and imipramine. Fluvoxamine has a minimal effect on desipramine plasma levels but produces a three- to fourfold increase in concentrations of imipramine.[16] Plasma-desipramine concentrations are elevated threefold by paroxetine but increases of only 30% are produced by sertraline.[16] However, an inadequate interval of one day between stopping desipramine and starting paroxetine resulted in a case of serotonin syndrome.[6] Serotonin syndrome has also been reported[17] in a patient who received paroxetine and imipramine and in another given sertraline and amitriptyline.[18] A threefold increase in concentrations of trimipramine resulting in sedation and orthostatic hypotension has been reported[19] in 2 patients also given paroxetine. Additionally, norfluoxetine, the active metabolite of fluoxetine, has a long half-life and is responsible for the continuing interaction with tricyclics for several days or weeks after fluoxetine has been withdrawn. Citalopram was reported to have no effect on plasma-tricyclic concentrations in a patient although antidepressant effects were augmented.[20]
- *Lithium* and *tryptophan* have been used to augment the effect of other antidepressants in refractory depression. Phenelzine has been used successfully with lithium and tryptophan[21] in patients with treatment-resistant chronic depression although such a regimen has probably been used less since the reports of the eosinophilia-myalgia syndrome associated with tryptophan (see p. 455.3). There have, however, been several case reports of reactions similar to the serotonin syndrome in patients receiving MAOIs with tryptophan.[22,23]
  Although lithium is often added to tricyclic antidepressant therapy in patients with refractory depression, epileptic seizures have been reported in a patient receiving amitriptyline when lithium was added.[24] Serotonin syndrome has been reported[25] in a patient given clomipramine and lithium. Severe neurotoxicity has been reported[26,27] in some patients receiving lithium and tricyclic or tetracyclic antidepressants; adverse effects included tremor, memory impairment, disorganised thinking, and auditory hallucinations. One manufacturer of lithium preparations also reports symptoms of nephrogenic diabetes in patients receiving these combinations.
  By 1989 the CSM had received 19 reports of adverse reactions in patients treated with fluvoxamine and lithium; 5 reports concerned convulsions and 1 hyperthermia.[8] Tremor has been reported when lithium was given with paroxetine,[28] and in general the risk of CNS toxicity is increased when lithium is given with fluoxetine, fluvoxamine, paroxetine, or sertraline. There has been a report[29] of a fatality when fluoxetine was replaced by tranylcypromine and tryptophan with no drug-free period; the patient was also receiving other drugs concurrently.
- Use of the serotonin and noradrenaline reuptake inhibitor (SNRI) *venlafaxine with tricyclic antidepressants* has been associated with increased antimuscarinic adverse effects.[30,31] Seizures have also been reported with venlafaxine and trimipramine[32] and serotonin syndrome developed in a patient given amitriptyline, venlafaxine, and pethidine.[33] Similar antimuscarinic adverse effects have occurred in patients given *venlafaxine and the SSRI* fluoxetine;[31] serotonin syndrome has been reported in a patient who received venlafaxine and paroxetine.[6] The use of *venlafaxine with MAOIs* is contra-indicated by the manufacturers of venlafaxine because of the risk of life-threatening adverse reactions. Serious adverse reactions have been reported when venlafaxine was combined with isocarboxazid,[34] moclobemide,[6] phenelzine,[35] or tranylcypromine.[36]
- *Trazodone* is chemically unrelated to other antidepressants but does have serotonergic actions. Serotonin syndrome has been reported when trazodone was combined with the SSRI *paroxetine*.[37]
- Serotonin syndrome has been reported[38] in a patient who took *nefazodone* with *fluoxetine*. There has been a similar report[39] in a patient who received *paroxetine* 2 days after finishing gradual withdrawal from over 6 months of treatment with nefazodone.
- Symptoms resembling serotonin syndrome have occurred in a patient taking the noradrenergic and specific serotonergic antidepressant, *mirtazapine* with *fluvoxamine*;[40] another report[41] suggests that the plasma concentrations of mirtazapine may be increased as much as fourfold by fluvoxamine.
- Raised *nortriptyline* levels were noted in a patient also taking *bupropion*; the effect recurred on rechallenge.[42]

- In a report[43] of an interaction between *St John's wort* and *paroxetine*, a 50-year-old woman was found incoherent, groggy, and slow-moving after self-administering a single dose of paroxetine while taking St John's wort; recovery was uneventful. Use of St John's wort with the SSRIs may potentiate their serotonergic effects and increase the incidence of adverse reactions. The CSM has advised that patients should stop taking St John's wort if treatment with an SSRI is necessary.[44] Symptoms of serotonin syndrome have also been reported when St John's wort and *nefazodone* were taken.[45]

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32. Schlienger RG, *et al*. Seizures associated with therapeutic doses of venlafaxine and trimipramine. *Ann Pharmacother* 2000; **34:** 1402–5.
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39. John L, *et al*. Serotonin syndrome associated with nefazodone and paroxetine. *Ann Emerg Med* 1997; **29:** 287–9.
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43. Gordon JB. SSRIs and St. John's Wort: possible toxicity? *Am Fam Physician* 1998; **57:** 950, 953.
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45. Lantz MS, *et al*. St. John's Wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol* 1999; **12:** 7–10.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

UK licensed product information states that *carbamazepine* should be avoided with or within 2 weeks of a MAOI because of structural similarities with the tricyclic antidepressants; however, published evidence of adverse interactions is lacking. There is also a theoretical possibility of a similar interaction with *oxcarbazepine*.

Antimigraine drugs. For the effect of MAOIs on *serotonin (5-HT$_1$) agonists*, see under Sumatriptan, p. 681.3.

Antineoplastics. For the effect when MAOIs are used with *altretamine*, see p. 739.1.

Dopaminergics. For the effect of MAOIs with *amantadine*, see p. 893.2, with *levodopa*, see p. 908.2, and with *selegiline*, see p. 917.1.

General anaesthetics. The problems that may occur when patients receiving MAOIs are also given general anaesthetics are discussed under Anaesthesia in Precautions, p. 444.1.

Ginseng. There have been 2 reports[1,2] of adverse effects, including headaches, insomnia, tremulousness, and irritability when ginseng was taken with phenelzine.

1. Shader RI, Greenblatt DJ. Phenelzine and the dream machine—ramblings and reflections. *J Clin Psychopharmacol* 1985; **5:** 65.
2. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. *J Clin Psychopharmacol* 1987; **7:** 201–2.

Histamine. For the effect of MAOIs on histamine given exogenously, see p. 2525.3.

Insulin. For the effect of MAOIs on insulin, see p. 488.3.

Neuromuscular blockers. For the effects of MAOIs on the action of *suxamethonium*, see p. 2040.1. Problems that may be encountered with MAOIs and neuromuscular blockers used during anaesthesia are discussed under Anaesthesia in Precautions, p. 444.1.

Opioid analgesics. The problems that may occur with MAOIs and opioid analgesics used during anaesthesia are discussed under Anaesthesia in Precautions, p. 444.1.

Respiratory stimulants. For the effect of MAOIs with *doxapram*, see p. 2322.1.

Pharmacokinetics

Phenelzine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after ingestion. It is metabolised in the liver and is excreted in the urine almost entirely in the form of metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nardil; ***Belg.***: Nardelzine; ***Canad.***: Nardil; ***Irl.***: Nardil†; ***Ital.***: Margyl; ***NZ***: Nardil; ***UK***: Nardil; ***USA***: Nardil.

Pharmacopoeial Preparations
BP 2014: Phenelzine Tablets;
USP 36: Phenelzine Sulfate Tablets.

Pipofezine Hydrochloride *(rINNM)*

Hidrocloruro de pipofezina; Pipofézine, Chlorhydrate de; Pipofezine Dihydrochloride; Pipofezini Hydrochloridum; Пипофезина Гидрохлорид.

5-Methyl-3-(4-methyl-1-piperazinyl)-5*H*-pyridazino[3,4-*b*][1,4]benzoxazine dihydrochloride.

$C_{16}H_{19}N_5O,2HCl$=370.3

CAS — 24886-52-0 (pipofezine); 24853-80-3 (pipofezine hydrochloride).

Profile

Pipofezine is a tricyclic antidepressant (see Amitriptyline, p. 401.1).

In the treatment of depression (p. 398.1) pipofezine is usually given orally as the hydrochloride although doses are expressed in terms of the base; pipofezine hydrochloride 31.1 mg is equivalent to about 25 mg of pipofezine. An initial dose of 25 to 50 mg daily, given in 2 divided doses, is gradually increased as tolerated to a usual total daily dose of 150 to 200 mg given in 3 or 4 divided doses. If necessary, a maximum of 500 mg may be given daily in divided doses. For maintenance a modified-release preparation providing pipofezine 150 mg may be given once or twice daily.

Pipofezine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Azaphen (Азафен).

Pirlindole *(rINN)*

Pirlindol; Pirlindolum; Пирлиндол.

2,3,3a,4,5,6-Hexahydro-8-methyl-1*H*-pyrazino[3,2,1-*jk*]carbazole.

$C_{15}H_{18}N_2$=226.3

CAS — 60762-57-4.

UNII — V39YPH45FZ.

Profile

Pirlindole has been given orally in the treatment of depression.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Implementor; ***Rus.***: Normazidol (Нормазидол); Pyrazidol (Пиразидол); ***Ukr.***: Normazidol (Нормазидол)†.

Protriptyline Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de protriptilina; MK-240; Protriptilina, hidrocloruro de; Protriptyline, chlorhydrate de; Protriptylini Hydrochloridum; Протриптилина Гидрохлорид.

3-(5*H*-Dibenzo[*a*,*d*]cyclohept-5-enyl)propyl(methyl)amine hydrochloride.

$C_{19}H_{21}N,HCl$=299.8

CAS — 438-60-8 (protriptyline); 1225-55-4 (protriptyline hydrochloride).

ATC — N06AA11.

ATC Vet — QN06AA11.

UNII — 44665V00O8.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Protriptyline Hydrochloride). A white to yellowish-white, odourless or almost odourless, powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.5.

USP 36: (Protriptyline Hydrochloride). A white to yellowish powder. Is odourless or has not more than a slight odour. Soluble 1 in 2 of water, 1 in 3.5 of alcohol, and 1 in 2.5 of chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.5.

Uses and Administration

Protriptyline is a dibenzocycloheptatriene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is considerably less sedative than other tricyclics and may have a stimulant effect, thus making it particularly suitable for apathetic and withdrawn patients; its antimuscarinic effects are moderate.

In the treatment of depression, protriptyline hydrochloride is given in oral doses of 5 to 10 mg three or four times daily. It has been suggested that, because of its potential stimulant activity, any dosage increases should be added to the morning dose first and if insomnia occurs the last dose should be given no later than mid-afternoon. Higher doses of up to 60 mg daily may be required in severely depressed patients. A suitable initial dose for adolescents and the elderly is 5 mg three times daily; close monitoring of the cardiovascular system has been recommended if the dose exceeds a total of 20 mg daily in elderly subjects.

Protriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Since protriptyline may have some stimulant properties anxiety and agitation can occur more frequently; cardiovascular effects such as tachycardia and orthostatic hypotension may also be more frequent than with other tricyclics. Photosensitivity rashes have been noted more often with protriptyline than with other tricyclic antidepressants and patients taking it should avoid direct sunlight.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Protriptyline is well but slowly absorbed after oral doses: peak plasma concentrations occur only after 8 to 12 hours.

Paths of metabolism of protriptyline include *N*-oxidation and hydroxylation. Protriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Protriptyline is widely distributed throughout the body and extensively bound to plasma and tissue protein. Protriptyline has been estimated to have a very prolonged elimination half-life ranging from 55 to 198 hours, which may be further prolonged in overdosage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Vivactil.

Pharmacopoeial Preparations
BP 2014: Protriptyline Tablets;
USP 36: Protriptyline Hydrochloride Tablets.

Reboxetine Mesilate *(BANM, rINNM)*

FCE-20124 (reboxetine or reboxetine mesilate); Mesilato de reboxetina; PNU-155950E; Reboxetina, mesilato de; Réboxétine, Mésilate de; Reboxetine Mesylate (USAN); Reboxetine Mesylate; Reboxetini Mesilas; Ребоксетина Мезилат.

(±)-(2*RS*)-2-[(α*RS*)-α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulphonate.

$C_{19}H_{23}NO_3,CH_4O_3S$=409.5

CAS — 71620-89-8; 98769-81-4 (both reboxetine); 98769-82-5; 98769-84-7 (both reboxetine mesilate).

ATC — N06AX18.

ATC Vet — QN06AX18.

UNII — L94J81YNNY.

Uses and Administration

Reboxetine is a selective and potent inhibitor of the reuptake of noradrenaline; it also has a weak effect on serotonin reuptake. Reboxetine has no significant affinity for muscarinic receptors. It is given orally as the mesilate for the treatment of depression with doses expressed as the base; reboxetine mesilate 5.2 mg is equivalent to about 4 mg of reboxetine. The dose of reboxetine is 4 mg twice daily, which may be increased after 3 to 4 weeks, if necessary, to 10 mg daily; the maximum daily dose should not exceed 12 mg. Reduced doses should be given in hepatic or renal impairment, see p. 449.1. Reboxetine is not recommended for use in elderly patients (see under Precautions, p. 449.3).

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in hepatic or renal impairment. Lower initial oral doses equivalent to 2 mg of reboxetine twice daily are recommended by UK licensed product information in hepatic or renal impairment; doses may be increased thereafter according to tolerance.

Anxiety disorders. Reboxetine has been tried with some benefit in panic disorder (p. 1029.1) although it may be less effective than the SSRIs.

References.
1. Versiani M, *et al.* Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry* 2002; **63:** 31–7.
2. Seedat S, *et al.* Reboxetine and citalopram in panic disorder: a single-blind, cross-over, flexible-dose pilot study. *Int Clin Psychopharmacol* 2003; **18:** 279–84.
3. Bertani A, *et al.* Comparison of the treatment with paroxetine and reboxetine in panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2004; **37:** 206–10.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Reboxetine, a selective inhibitor of noradrenaline reuptake, has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, reboxetine appears to have fewer unpleasant adverse effects and to be safer in overdosage in comparison with the older tricyclics.

References.
1. Versiani M, *et al.* Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J Clin Psychiatry* 1999; **60:** 400–406.
2. Holm KJ, Spencer CM. Reboxetine: a review of its use in depression. *CNS Drugs* 1999; **12:** 65–83.
3. Scates AC, Doraiswamy PM. Reboxetine: a selective norepinephrine reuptake inhibitor for the treatment of depression. *Ann Pharmacother* 2000; **34:** 1302–12.
4. Versiani M, *et al.* Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. *J Clin Psychopharmacol* 2000; **20:** 28–34.
5. Ferguson JM, *et al.* Effects of reboxetine on Hamilton Depression Rating Scale factors from randomized, placebo-controlled trials in major depression. *Int Clin Psychopharmacol* 2002; **17:** 45–51.
6. Andreoli V, *et al.* Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. *J Clin Psychopharmacol* 2002; **22:** 393–9.
7. Montgomery S, *et al.* The antidepressant efficacy of reboxetine in patients with severe depression. *J Clin Psychopharmacol* 2003; **23:** 45–50.

Adverse Effects

Adverse effects most commonly seen with reboxetine include insomnia, dry mouth, constipation, and increased sweating. Disturbance of visual accommodation, loss of appetite, chills, vertigo, tachycardia, palpitations, vasodilatation, and orthostatic hypotension are reported as being common adverse reactions. Adverse urinary symptoms have also been reported as common and occur more frequently in men; effects include urinary hesitancy, frequency, and a sensation of incomplete bladder emptying. Erectile dysfunction, ejaculatory delay or pain, and testicular pain can also be common. There have been reports of allergic dermatitis, convulsions, agitation, anxiety, irritability, aggressive behaviour, hallucinations, cold extremities, paraesthesia, hypertension, and nausea and vomiting. Reduced plasma-potassium concentrations have been seen in elderly patients after prolonged use.

Hyponatraemia, possibly as a result of inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on body-weight. Body-weight fell from 55 to 43 kg over about 9 months in a woman given reboxetine.[1] She reported loss of appetite, without nausea or vomiting, although she continued eating three meals daily. High caloric dietary supplements did not reverse the weight loss. The effect started about 2 months after starting reboxetine, and weight was regained after stopping the drug. Weight loss occurred again when reboxetine was later restarted.

1. Lu TY-T, *et al.* Profound weight loss associated with reboxetine use in a 44-year-old woman. *Br J Clin Pharmacol* 2005; **60:** 218–20.

Effects on the CNS. Episodes of sleepwalking (somnambulism) were seen in an 18-year-old woman several weeks after starting reboxetine (at an initial dose of 2 mg daily gradually increased to 8 mg daily).[1] The patient had a history of childhood somnambulism that had resolved spontaneously; these particular episodes ceased after the dose of reboxetine was reduced to 4 mg daily.

1. Künzel HE, *et al.* Sleepwalking associated with reboxetine in a young female patient with major depression: a case report. *Pharmacopsychiatry* 2004; **37:** 307–8.

Effects on the endocrine system. Hyponatraemia thought to be associated with reboxetine therapy and to be due to the syndrome of inappropriate antidiuretic hormone secretion, has been reported in an elderly patient.[1]

1. Ranieri P, *et al.* Reboxetine and hyponatremia. *N Engl J Med* 2000; **342:** 215–16.

Effects on sexual function. The Australian Adverse Drug Reactions Advisory Committee has received 130 reports of adverse reactions associated with reboxetine use;[1] of these, 22 described male sexual dysfunction including ejaculation disorder (7 reports), erectile dysfunction (4 reports), and testicular pain or swelling (10 reports). In addition there were 2 reports of increased libido in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Effects on the urinary system. The Australian Adverse Drug Reactions Advisory Committee has received 26 reports of urinary symptoms such as hesitancy, reduced urine flow, and retention in patients taking reboxetine.[1] Although the majority of cases occurred in male patients, 6 reports mentioned such symptoms in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Treatment of Adverse Effects

The benefit of gastric decontamination after reboxetine overdose is uncertain; however, activated charcoal may be considered in adults and children who have ingested more than 1 mg/kg if they present within 1 hour of ingestion. Management thereafter mainly involves symptomatic and supportive therapy as required. Cardiac rhythm, blood pressure, and pulse rate should be monitored.

Genito-urinary disorders. Tamsulosin has been used successfully in the treatment of urinary hesitancy and painful ejaculation associated with reboxetine (see p. 2369.2).

Precautions

Reboxetine should be used with caution in patients with renal or hepatic impairment. It should also be used under close supervision in patients with bipolar disorder, urinary retention, benign prostatic hyperplasia, glaucoma, or a history of epilepsy or cardiac disorders.

Patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by reboxetine and patients, if affected, should not drive or operate machinery.

Breast feeding. Low concentrations of reboxetine were detected in the breast milk of 4 women being treated for post-natal depression.[1] There were also low concentrations in the plasma of 3 of the breast-fed infants, and the drug was not detected in the fourth. No adverse effects were seen in any of the 4 infants.

1. Hackett LP, *et al.* Transfer of reboxetine into breastmilk, its plasma concentrations and lack of adverse effects in the breastfed infant. *Eur J Clin Pharmacol* 2006; **62:** 633–8.

Children. Reboxetine has not been studied for the treatment of depression in children and UK licensed product information recommends that it should not be used for this indication in children and adolescents under 18 years of age. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in children and adolescents (see Effects on Mental State, under Fluoxetine, p. 420.2).

The elderly. Reboxetine is not recommended by UK licensed product information for use in elderly patients, because of a lack of experience in this patient group. However, reboxetine 2 mg orally twice daily was well tolerated in a study in 16 elderly patients (mean age 77.5 years) with post-stroke depression.[1]

1. Rampello L, *et al.* An evaluation of efficacy and safety of reboxetine in elderly patients affected by "retarded" post-stroke depression: a random, placebo-controlled study. *Arch Gerontol Geriatr* 2005; **40:** 275–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies reboxetine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. A review of pregnancy outcomes in the Swedish Medical Birth Registry found data on 15 infants born to women who had taken reboxetine in early pregnancy.[1] There was 1 report of ventricular septum defect.

1. Lennestål R, Källén B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. *J Clin Psychopharmacol* 2007; **27:** 607–13.

Interactions

Reboxetine should not be taken with, or within 2 weeks of stopping, an MAOI; at least one week should elapse after stopping reboxetine therapy before starting any drug liable to provoke a serious reaction (e.g. phenelzine). Caution should be taken when reboxetine is given with other drugs that lower blood pressure because orthostatic hypotension has occurred with reboxetine. However, the use of reboxetine with ergot derivatives may cause an increase in blood pressure. The possibility of hypokalaemia if reboxetine is given with potassium-depleting diuretics should also be considered.

Reboxetine is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4 and potent inhibitors of this isoenzyme may limit the elimination of reboxetine. Consequently, reboxetine should not be given with drugs known to inhibit CYP3A4 such as azole antifungals (e.g. ketoconazole), macrolide antibacterials (e.g. erythromycin) or fluvoxamine. Reboxetine in high concentrations has also been shown *in vitro* to inhibit CYP3A4 and CYP2D6; however, studies *in vivo* have suggested that interactions with drugs metabolised by these isoenzymes are unlikely.

Antifungals. Reboxetine's plasma concentrations were significantly increased when it was given with *ketoconazole*.[1]

The interaction was said to have involved the inhibition of the cytochrome P450 isoenzyme CYP3A4 by ketoconazole.

1. Herman BD, *et al.* Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin Pharmacol Ther* 1999; **66:** 374–9.

Pharmacokinetics

Reboxetine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 2 hours. Plasma protein binding is about 97% (92% in elderly subjects). *In-vitro* studies indicate that reboxetine is metabolised by the cytochrome P450 isoenzyme CYP3A4; the main metabolic pathways identified are dealkylation, hydroxylation, and oxidation followed by glucuronide or sulfate conjugation. Elimination is mainly via urine (78%) with 10% excreted as unchanged drug. The plasma elimination half-life is 13 hours. Data from *animal* studies indicate that reboxetine crosses the placenta. It is distributed into breast milk.

References.

1. Dostert P, *et al.* Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur Neuropsychopharmacol* 1997; **7** (suppl 1): S23–S35.
2. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet* 2000; **39:** 413–27.
3. Coulomb F, *et al.* Pharmacokinetics of single-dose reboxetine in volunteers with renal insufficiency. *J Clin Pharmacol* 2000; **40:** 482–7.
4. Poggesi I, *et al.* Pharmacokinetics of reboxetine in elderly patients with depressive disorders. *Int J Clin Pharmacol Ther* 2000; **38:** 254–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Edronax; ***Austria***: Edronax; ***Belg.***: Edronax; ***Braz.***: Prolift; ***Chile***: Prolift; ***China***: Yeluoshu (叶洛舒); Zuolexin (佐乐辛); ***Denm.***: Edronax; ***Fin.***: Edronax; ***Ger.***: Edronax; Solvex; ***Hung.***: Edronax; ***India***: Narebox; ***Irl.***: Edronax; ***Israel***: Edronax; ***Ital.***: Davedax; Edronax; ***Mex.***: Edronax; ***Norw.***: Edronax; ***NZ***: Edronax; ***Pol.***: Edronax; ***Port.***: Edronax; ***Rus.***: Edronax (Эдронакс); ***S.Afr.***: Edronax; ***Spain***: Irenor; Norebox; ***Swed.***: Edronax; ***Switz.***: Edronax; ***Thai.***: Edronax; ***Turk.***: Edronax; ***UK***: Edronax.

Sertraline Hydrochloride

(BANM, USAN, rINNM)

CP-51974-01; CP-51974-1; Hidrocloruro de sertralina; Sertralina, hidrocloruro de; Sertraline, Chlorhydrate de; Sertralinhydrochlorid; Sertralini Hydrochloridum; Сертралина Гидрохлорид.

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl (methyl)amine hydrochloride.

$C_{17}H_{17}Cl_2N,HCl$=342.7

CAS — 79617-96-2 (sertraline); 79559-97-0 (sertraline hydrochloride).

ATC — N06AB06.

ATC Vet — QN06AB06.

UNII — UT18907Y6X.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of sertraline:

Z's; Zloft; Zoomers.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Sertraline Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble or slightly soluble in anhydrous alcohol; slightly soluble in acetone and in isopropyl alcohol. Protect from light.

USP 36: (Sertraline Hydrochloride). White or off-white, crystalline powder. Slightly soluble in water, in acetone, and in isopropyl alcohol; freely soluble in absolute alcohol. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Sertraline, a naphthaleneamine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 417.1). It is given orally as sertraline hydrochloride as a single dose in the morning or evening. Doses are expressed in terms of the base; sertraline hydrochloride 56 mg is equivalent to about 50 mg of sertraline.

In the treatment of **depression**, the usual initial dose of sertraline is 50 mg daily increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

The usual initial dose of sertraline in **obsessive-compulsive disorder** is 50 mg daily. In the treatment of **panic disorder** with or without agoraphobia, **social anxiety disorder**, and **post-traumatic stress disorder**, the usual initial dose is 25 mg daily increased after one week to 50 mg daily. Thereafter, doses in all these disorders may be increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

In the treatment of **premenstrual dysphoric disorder**, sertraline is given in an initial dose of 50 mg daily either throughout the menstrual cycle or during the luteal phase only, as appropriate. Doses may be increased by 50 mg each menstrual cycle up to a maximum of 150 mg daily for continuous dosing or 100 mg daily when dosing during the luteal phase only. Those patients who require 100 mg daily during luteal phase-only dosing should initially be given 50 mg daily for the first 3 days of each luteal phase dosing period.

Once the optimal therapeutic response is obtained dosage should be reduced to the lowest effective level for maintenance.

For dosage adjustment in patients with hepatic impairment, and for doses used in children, see p. 450.2.

Sertraline should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Administration in children. There are concerns about the use of SSRIs in children (see Effects on Mental State, under Adverse Effects of Fluoxetine, p. 420.2) and the use of sertraline for the treatment of **depression** in those under 18 years of age is unlicensed. Nevertheless, the *BNFC* suggests that it may be used by specialists for the treatment of major depression in those aged 12 years and over; the usual adult dose (see Uses and Administration, above) may be given.

Sertraline may be given for the treatment of **obsessive-compulsive disorder** in children and adolescents aged 6 years and over. In children aged 6 to 12 years the usual initial oral dose is 25 mg once daily; adolescents may be started on 50 mg once daily. Increases in doses, if necessary, are similar to those in adults (see above); however, the lower body-weights of children should be considered in order to avoid excessive doses.

Administration in hepatic impairment. The clearance of sertraline was reduced in patients with liver cirrhosis, in a single-dose pharmacokinetic study.[1] US licensed product information states that in a small group of patients with chronic mild impairment (Child-Pugh scores of 5 to 8), given 50 mg daily for 21 days, exposure to sertraline was about 3 times that found in subjects with normal hepatic function. It also states that the effects of sertraline have not been studied in moderate and severe impairment. If sertraline is to be used in patients with hepatic impairment, it suggests that the drug should be used with caution and given at a lower dose or less frequently. UK product information considers sertraline to be contra-indicated in significant hepatic impairment, because of insufficient clinical experience.

1. Démolis J-L, *et al.* Influence of liver cirrhosis on sertraline pharmacokinetics. *Br J Clin Pharmacol* 1996; **42:** 394–7.

Anxiety disorders. Sertraline has been given in a variety of anxiety disorders (p. 1028.1) including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), social anxiety disorder (see under Phobic Disorders, p. 1029.1), and post-traumatic stress disorder (p. 1029.2).

References.

1. March JS, *et al.* Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA* 1998; **280:** 1752–6.
2. Londborg PD, *et al.* Sertraline in the treatment of panic disorder. A multisite, double-blind, placebo-controlled, fixed-dose investigation. *Br J Psychiatry* 1998; **173:** 54–60.
3. Brady K, *et al.* Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 2000; **283:** 1837–44.
4. Walker JR, *et al.* Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. *J Clin Psychopharmacol* 2000; **20:** 636–44.
5. Rynn MA, *et al.* Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry* 2001; **158:** 2008–14.
6. Rapaport MH, *et al.* Sertraline treatment of panic disorder: results of a long-term study. *Acta Psychiatr Scand* 2001; **104:** 289–98.
7. Rapaport MH, *et al.* Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. *J Clin Psychiatry* 2002; **63:** 59–65.
8. Koran LM, *et al.* Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. *Am J Psychiatry* 2002; **159:** 88–95.
9. Zohar J, *et al.* Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 190–5.
10. Liebowitz MR, *et al.* Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. *J Clin Psychiatry* 2003; **64:** 785–92.
11. Allgulander C, *et al.* Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 2004; **161:** 1642–9.
12. Friedman MJ, *et al.* Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry* 2007; **68:** 711–20.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as sertraline are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Stowe ZN, *et al.* Sertraline in the treatment of women with postpartum major depression. *Depression* 1995; **3:** 49–55.
2. Keller MB, *et al.* Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 1998; **280:** 1665–72.
3. Baca E, *et al.* Sertraline is more effective than imipramine in the treatment of non-melancholic depression: results from a multicentre, randomized study. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27:** 493–500.
4. Lepine JP, *et al.* A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. *Am J Psychiatry* 2004; **161:** 836–42.
5. Moscovitch A, *et al.* A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *Psychopharmacology (Berl)* 2004; **171:** 390–7.
6. Cipriani A, *et al.* Sertraline versus other antidepressive agents for depression. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 02/08/10).

Premenstrual syndrome. Sertraline throughout the menstrual cycle has produced beneficial effects in controlling both the psychological and somatic symptoms of women with premenstrual syndrome (p. 2272.3).[1-3] Giving sertraline solely during the luteal phase was also of benefit.[3-7]

1. Yonkers KA, *et al.* Sertraline in the treatment of premenstrual dysphoric disorder. *Psychopharmacol Bull* 1996; **32:** 41–6.
2. Yonkers KA, *et al.* Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment: a randomized controlled trial. *JAMA* 1997; **278:** 983–8.
3. Freeman EW, *et al.* Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. *Am J Psychiatry* 2004; **161:** 343–51.
4. Young SA, *et al.* Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. *J Clin Psychiatry* 1998; **59:** 76–80.
5. Jermain DM, *et al.* Luteal phase sertraline treatment for premenstrual dysphoric disorder: results of a double-blind, placebo-controlled, crossover study. *Arch Fam Med* 1999; **8:** 328–32.
6. Halbreich U, *et al.* Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2002; **100:** 1219–29.
7. Kornstein SG, *et al.* Low-dose sertraline in the treatment of moderate-to-severe premenstrual syndrome: efficacy of 3 dosing strategies. *J Clin Psychiatry* 2006; **67:** 1624–32.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the use of these effects as a potential form of management for premature ejaculation see Fluoxetine, p. 419.1.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 419.1). Menstrual irregularities and, rarely, erythema multiforme and pancreatitis have also been reported.

Sertraline should be used with caution in patients with hepatic or renal impairment; reduced doses should be considered in patients with hepatic impairment.

Breast feeding. For comments on the use of SSRIs in breast-feeding patients, see under Precautions for Fluoxetine, p. 422.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 420.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sertraline as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 424.1.

Pharmacokinetics

Sertraline is slowly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 4.5 to 8.4 hours after ingestion. It undergoes extensive first-pass metabolism in the liver. The main pathway is demethylation to inactive *N*-desmethylsertraline, a process that appears to involve multiple cytochrome P450 isoenzymes; further metabolism and glucuronide conjugation occurs. Sertraline is widely distributed throughout body tissues and is about 98% bound to plasma proteins. The plasma elimination half-life of sertraline is about 26 hours; steady-state concentrations occur after about one week with regular oral doses. Sertraline is excreted in about equal amounts in the urine and faeces, mainly as metabolites. Sertraline is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p. 422.2).

References.
1. Preskorn SH, ed. Sertraline: a pharmacokinetic profile. *Clin Pharmacokinet* 1997; **32** (suppl 1): 1–55.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.
3. Wang J-H, *et al*. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; **70:** 42–7.
4. DeVane CL, *et al*. Clinical pharmacokinetics of sertraline. *Clin Pharmacokinet* 2002; **41:** 1247–66.
5. Obach RS, *et al*. Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study. *Drug Metab Dispos* 2005; **33:** 262–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anilar; Atenix; Bicromil; Celonfex; Cratular; Deprecalm; Insertec; Irradial; Serlina; Servantax; Vunot; Zoloft; Zoxx; ***Austral.***: Concorz†; Eleva; Sertra; Sertracor; Setrona; Xydep; Zoloft; ***Austria***: Adjuvin; Gladem; Tresleen; ***Belg.***: Serlain; ***Braz.***: Assert; Cefelic; Dieloft; Novativ; Sered; Serenata; Seronip; Teuloft; Tolrest; Zoloft; Zoltralina; Zysertin; ***Canad.***: Zoloft; ***Chile***: Altruline; Deprax; Eleval; Emergen; Implicane; Lowfin; Sedoran; Serivo; Seronex; Sertac; Tralinser†; ***China***: Bei Yu (贝玉); JinDeSi (津得斯); Kuai Wu You (快五优); Leyuan (乐元); Pi Mai Le (彼迈乐); Wei Ta Ting (唯他停); Xi Tong Jing (西同静); Xinya Quling (新亚曲灵); Yi Suo Ming (伊素明); Ying Si Tiao (应思调); Yu Lang (愈朗); Yu Luo Xin (郁洛欣); Zoloft (左洛复); ***Cz.***: Adjuvin; Apo-Sertral; Asentra; Serlift; Sertivan; Setaloft; Stimuloton; Zoloft; ***Denm.***: Serlinan; Sertravis; Sertrix; Sertrone; Tralinan; Tralix; Zeelinax; Zeenix†; Zoloft; ***Fin.***: Zoloft; ***Fr.***: Zoloft; ***Ger.***: Gladem†; Sertra-Isis†; Sertra†; Sertralon; Zoloft; ***Gr.***: Certorun; Diticone; Enidap; Epilyd; Mycinil; Neurosedine; Positiva; Serolux; Serotyp; Sertral; Zoloft; Zolotrin; Zortal; ***Hong Kong***: Serdep; Stimuloton; Zoloft; ***Hung.***: Asentra; Camidlin†; Gerotralin†; Serlift; Serlosane†; Sertadepi; Sertagen; Sertwin†; Setaloft; Stimuloton; Zoloft; ***India***: Actiser; Aderta; Censir; Daxid; Dazolin; Deplin; Depsert; Episod; Inosert; Lindep; Line; Medisert; Mentolift; Obzin; Serdep; Serta; Xsert; ***Indon.***: Anexin; Antipres; Deptral; Fatral; Fridep; Iglodep; Nudep; Serlof; Sernade; Zerlin; Zoloft; ***Irl.***: Depreger; Lusert; Lustral; Seretral; Serimel; Serlan; Serlo; Sertraniche; ***Israel***: Lustral; Serenada; ***Ital.***: Tatig; Tralisen; Zoloft; ***Malaysia***: Serlift; Setrof; Zoloft; ***Mex.***: Acortral; Aleval; Altruline; Aluprex; Deptral; Equivac; Prosertin; Resteral; Serlift; Serolux; Sertex; ***Neth.***: Asentra; Enore; Zoloft; ***Norw.***: Zoloft; ***NZ***: Setrona; Zoloft; ***Philipp.***: Exulten; Serenata; Zolodin; Zoloft; Zotral; ***Pol.***: Antideprimal; Apresia†; Asentra; Asertin; Luxeta; Miravil; Sertagen; Sertahexal†; Sertranorm; Setaloft; Setaratio†; Stimuloton; Zoloft; Zotral; Zotral; ***Port.***: Aserin; Aserta; Deprilix; Eterim†; Gerlina; Luzina†; Psicotil; Serlin; Serpax; Sertabal; Sertralpharm†; Somidal; Tralin; Zoloft; ***Rus.***: Aleval (Алевал); Asentra (Асентра); Deprefolt (Депрефолт); Seralin (Сералин); Serenata (Серената); Serlift (Серлифт); Stimuloton (Стимулотон); Torin (Торин); Zoloft (Золофт); ***S.Afr.***: Adco-Zertra; Serdep; Serlife; Sermax; Sertra; Sertzol; Zolid; Zoloft; Zosert; Zylin; ***Singapore***: Zoloft; ***Spain***: Altisben; Aremis; Aserin; Besitran; Lustragen†; Lustramerck†; Sertrabrain†; Sertramerck†; ***Swed.***: Oralin; Sertrone; Zoloft; ***Switz.***: Seralin; Sertragen; Sertral†; Sertrin†; Zoloft; ***Thai.***: Serlift; Sertra; Starin; Zoloft; Zotaline; ***Turk.***: Lustec; Lustral; Misol; Selectra; Seralin; Serdep; Serotop; Serteva; Zeleft; ***UK***: Lustral; ***Ukr.***: Asentra (Асентра); Serlift (Серлифт); Sertraloft (Сертралофт)†; Stimuloton (Стимулотон); Zoloft (Золофт); ***USA***: Zoloft; ***Venez.***: Conexine; Lusedan; Satil; Serline; Serolux; Tialin; Zoloft.

Multi-ingredient Preparations. ***India***: Alltop-S; Alprax Forte; Alprax Plus; Altalin; Alzex Forte; Alzex Plus; Anxit Forte; Anxit Plus; Azo-S; Censir Forte; L-Peez S; Manorest Forte; Manorest Plus; MCalm; Mentolift-Plus; Restyl Forte; Restyl Plus.

Pharmacopoeial Preparations
BP 2014: Sertraline Tablets;
USP 36: Sertraline Hydrochloride Oral Solution; Sertraline Tablets.

Setiptiline *(rINN)*

Setiptilina; Sétiptiline; Setiptilinum; Teciptiline; Сетиптилин.

2,3,4,9-Tetrahydro-2-methyl-1*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*c*]pyridine.

$C_{19}H_{19}N$=261.4

CAS — 57262-94-9 (setiptiline); 85650-57-3 (setiptiline maleate).

UNII — 7L3810SZ6E.

Profile

Setiptiline is an antidepressant that has been used as the maleate in the treatment of depression.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Tecipul.

St John's Wort

Hierba de San Juan; Hipérico; Hiperikum; Hyperici Herba; Hypericum; Hypericum Perforatum; Johannesört; Johanniskraut; Jonažolių žolė; Mäkikuisma; Millepertuis; Orbáncfű; Třezalková nať; Ziele dziurawca; Зверобой Продырявленный.

CAS — 548-04-9 (hypericin).

*ATC Herb — HN06AW5001 (*Hypericum perforatum*: flower); HM01AW5010 (*Hypericum perforatum*: flower); HN06AW5002 (*Hypericum perforatum*: germ); HM01AW5011 (*Hypericum perforatum*: herb); HD03WX5008 (*Hypericum perforatum*: herb); HN06AW5003 (*Hypericum perforatum*: herb).*

*UNII — UFH8805FKA (*Hypericum perforatum *flowering top); XK4IUX8MNB (*Hypericum perforatum*); A6V4CUE7PV (*Hypericum perforatum *flower).*

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Eur. also includes the dry extract and a form for homoeopathic preparations.

Swiss also includes monographs for hypericum (fresh flowering tops) and hypericum oil.

Ph. Eur. 8: (St. John's Wort). The whole or fragmented, dried flowering tops of *Hypericum perforatum* gathered during flowering. It contains not less than 0.08% of total hypericins, expressed as hypericin ($C_{30}H_{16}O_8$ = 504.4) calculated with reference to the dried drug.

Ph. Eur. 8: (Hypericum for Homoeopathic Preparations; Hypericum Perforatum ad Praeparationes Homoeopathicas). The whole, fresh plant of *Hypericum perforatum*, at the beginning of the flowering period. Protect from light.

USP 36: (St. John's Wort). The dried flowering tops or aerial parts of *Hypericum perforatum* (Hypericaceae), gathered shortly before or during flowering. It contains not less than 0.04% of the combined total of hypericin ($C_{30}H_{16}O_8$ = 504.4) and pseudohypericin ($C_{30}H_{16}O_9$ = 520.4) and not less than 0.6% of hyperforin ($C_{35}H_{52}O_4$ = 536.8). Store in airtight containers. Protect from light.

Uses and Administration

Herbal preparations containing St John's wort are used, frequently for self-medication, in the treatment of depression. Such preparations are also promoted for the treatment of other nervous disorders such as insomnia and anxiety, particularly if associated with the menopause. St John's wort oil has also been used as an astringent.

The amount of active constituents can vary between different preparations and doses depend on the preparation being used.

Homoeopathy

St John's wort has been used in homoeopathic medicines under the following names: Hypericum; Hypericum perforatum; Hypericum perforatum ex herba; Hypericum, herba; Hyper.

References.
1. McIntyre M. A review of the benefits, adverse events, drug interactions, and safety of St John's Wort (Hypericum perforatum): the implications with regard to the regulation of herbal medicines. *J Altern Complement Med* 2000; **6:** 115–24.

Depression. St John's wort extracts are widely used in some countries for the treatment of depression (p. 398.1).

A systematic review[1] of randomised controlled studies found St John's wort extracts to be more effective than placebo in the treatment of mild to moderate depressive disorders. A later, more focused, systematic review[2] included only studies in which patients met the diagnostic criteria for major depression (ranging in severity from mild to severe). St John's wort was found to be superior to placebo, and to be of similar efficacy to standard antidepressants but with fewer adverse effects. However, studies mostly included patients with mild to moderate symptoms, and it was considered that evidence for the treatment of severe depression was still insufficient to draw conclusions. The doses of standard antidepressants were also generally at the lower limit of the recommended range. It was also notable that findings from studies in German-speaking countries were generally more favourable for St John's wort versus placebo, compared with studies performed elsewhere, a difference that the authors felt needed more investigation.

The mechanism of action of St John's wort extracts in the treatment of depression remains unclear. Extracts contain at least 10 active principles. Hypericin, one of the major constituents of St John's wort, was first thought responsible for the antidepressant effect since it had an inhibitory action on monoamine oxidase *in vitro*. However, it was later shown that this action was, at best, weak and it is now generally believed that monoamine oxidase inhibition is not responsible for the antidepressant effect of St John's wort. More recent studies have suggested that hyperforin may be one of the major constituents responsible for the antidepressant effect.[3] Although the evidence is mainly from *in vitro* studies, hyperforin inhibits the reuptake of several major neurotransmitters including serotonin, dopamine, and noradrenaline.[4]

1. Stevinson C, Ernst E. Hypericum for depression: an update of the clinical evidence. *Eur Neuropsychopharmacol* 1999; **9:** 501–5.
2. Linde K, *et al*. St John's wort for major depression. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/08/09).
3. Laakmann G, *et al*. St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998: **31** (suppl.): 54–9.
4. Chatterjee SS, *et al*. Hyperforin as a possible antidepressant component of hypericum extracts. *Life Sci* 1998; **63:** 499–510.

Adverse Effects and Precautions

Adverse effects reported with St John's wort have included gastrointestinal symptoms, dizziness, headache, confusion, urinary frequency, allergic reactions, and fatigue. Photosensitivity has also been reported; hypericin and pseudohypericin are the constituents of St John's wort thought to be responsible for this reaction.

Effects on the nervous system. Subacute polyneuropathy after sun exposure developed in a woman who had taken St John's wort for mild depression; she improved after drug withdrawal.[1] Seizures and confusion occurred in a 16-year-old girl after an overdose of St John's wort.[2] She had taken large daily doses for 2 weeks and an overdose just before presentation.

1. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's Wort. *Lancet* 1998; **352:** 1121–2.
2. Karalapillai DC, Bellomo R. Convulsions associated with an overdose of St John's wort. *Med J Aust* 2007; **186:** 213–14.

Effects on the skin. In addition to photosensitivity reactions associated with St John's wort use,[1] there has been a report of severe erythroderma in a patient who supplemented his regular antidepressant medication (dosulepin) with St John's wort.[2] The reaction was seen on both light-exposed and non-exposed areas, and was thought to be due to the St John's wort although there remained a possibility that it was due to an interaction between the 2 drugs.

1. Lane-Brown MM. Photosensitivity associated with herbal preparations of St John's wort (Hypericum perforatum). *Med J Aust* 2000; **172:** 302.
2. Holme SA, Roberts DL. Erythroderma associated with St John's wort. *Br J Dermatol* 2000; **143:** 1127–8.

Mania. Mania or hypomania has been associated with the use of St John's wort.[1-3]

1. Neirenberg AA, *et al*. Mania associated with St John's wort. *Biol Psychiatry* 1999; **46:** 1707–8.
2. Fahmi M, *et al*. A case of mania induced by hypericum. *World J Biol Psychiatry* 2002; **3:** 58–9.
3. Stevinson C, Ernst E. Can St John's wort trigger psychoses? *Int J Clin Pharmacol Ther* 2004; **42:** 473–80.

Withdrawal. A 58-year-old woman developed symptoms such as nausea, anorexia, dizziness, dry mouth, thirst, chills, and fatigue the day after stopping St John's wort;[1] she had taken the drug for 32 days. The symptoms, which the authors considered suggestive of a withdrawal syndrome, resolved within 8 days.

1. Dean AJ, *et al*. Suspected withdrawal syndrome after cessation of St John's wort. *Ann Pharmacother* 2003; **37:** 150.

Interactions

St John's wort has been shown to induce several drug metabolising enzymes including some cytochrome P450 isoenzymes (in particular CYP3A4) and the transport protein P-glycoprotein. Clinically important interactions resulting in decreased plasma concentrations of the interacting drug have been reported with ciclosporin, digoxin, HIV-protease inhibitors, NNRTIs, oral contraceptives, tacrolimus, theophylline, and warfarin. There is also a possibility of an interaction between St John's wort and antiepileptics. In addition, stopping St John's wort may result in increased, and possibly toxic, concentrations of the interacting drug.

In many countries, including the UK and USA, preparations of St John's wort are not required to be licensed as medicines, and the amount of active ingredient may vary widely between preparations. Changing preparations may therefore alter the degree of enzyme induction.

Use of St John's wort with drugs known to act on serotonergic neurotransmitters may result in synergistic interactions and an increased risk of adverse effects may also occur. Examples include the SSRIs and nefazodone (see Antidepressants, p. 445.2) and the selective serotonin (5-HT_1) agonists (see under Sumatriptan, p. 681.3) used to treat migraine.

References.
1. Roby CA, *et al*. St John's Wort: effect on CYP3A4 activity. *Clin Pharmacol Ther* 2000; **67:** 451–7.
2. CSM/MCA. Reminder: St John's Wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)

3. Dürr D, *et al.* St John's Wort induces intestinal p-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther* 2000; **68:** 598–604.
4. Wang Z, *et al.* The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001; **70:** 317–26.
5. Hennessy M, *et al.* St John's Wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol* 2002 **53:** 75–82.
6. Henderson L, *et al.* St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002; **54:** 349–56.
7. Mills E, *et al.* Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 2004; **329:** 27–30.
8. Mannel M. Drug interactions with St John's wort: mechanisms and clinical implications. *Drug Safety* 2004; **27:** 773–97.
9. Whitten DL, *et al.* The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br J Clin Pharmacol* 2006; **62:** 512–26.

Analgesics. For details of a possible interaction between St John's wort and the opioid analgesic *methadone*, see p. 90.3.

Anticoagulants. For mention of a possible interaction between St John's wort and *warfarin*, see p. 1535.2.

Antiepileptics. There is a possibility of an interaction between St John's wort and antiepileptics such as *carbamazepine* (see p. 516.2), *phenobarbital* (see p. 537.2), and *phenytoin* (see p. 543.1).

Antineoplastics. St John's wort may interact with some antineoplastics; examples include *aminolevulinic acid* (see p. 741.2), *imatinib* (see p. 809.2), and *irinotecan* (see p. 814.1).

Antivirals. For details of a possible interaction between St John's wort and *HIV-protease inhibitors* such as indinavir, see p. 989.3.

Anxiolytics. For mention of a possible interaction between St John's wort and *buspirone*, see p. 1043.2.

Cardiac glycosides. For details of a possible interaction between St John's wort and *digoxin*, see p. 1356.3.

Immunosuppressants. For details of possible interactions between St John's wort and *ciclosporin* or *tacrolimus*, see p. 1956.3 and p. 1977.3, respectively.

Oral contraceptives. For reports of a possible interaction between St John's wort and oral contraceptives, see p. 2243.2.

Verapamil. For details of a possible interaction between St John's wort and verapamil, see p. 1525.3.

Xanthines. For details of a possible interaction between St John's wort and *theophylline*, see p. 1234.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Amenicil; Hipax; Hiperinat; ***Austral.***: Remotiv; Stress-Relax†; ***Austria***: Esbericum; Hyperiforce; Jarsin; Johanicum; Kira; Laif; Perikan†; Psychotonin; Remotiv; ***Belg.***: Hyperiplant; Milperinol; Perika; Zibrine; ***Braz.***: Ciperico; Equilibrium; Felis†; Fiotan†; Fitovital†; Hiperex; Hipericin†; Hiperico†; Hipersac; Hyperigreen†; Iperisan; Motiven†; Prazen; Remotiv; Triativ; ***Canad.***: Hyperiforce†; Kira†; ***Chile***: Anxium; ***China***: Shuganjieyu Jiaonang (舒肝解郁); ***Cz.***: Felisio†; Helarium†; Hyperikan†; Jarsin; Laif; Nat Trezalky†; Remotiv†; Trezalka v Nalevovych Sacchich†; Trezalkova Nat; Trezalkovy Caj; ***Denm.***: Neurokan; ***Fin.***: Hyperiforce; ***Fr.***: Euphypertuis; Mildac; Procalmil; ***Ger.***: Cesradyston; Esbericum; Felis†; Hewepsychon uno†; Hyperforat; Jarsin; Kira; Laif; Neuroplant; Neurovegetalin; Psychotonin; Remotiv†; Spilan†; Texx; Tonizin†; ***Gr.***: Neukan†; ***Hung.***: Helarium†; Laif; Modigen; Myrall; Remotiv; ***India***: Depgard; J-Wort; Jovin; ***Indon.***: Preso†; ***Israel***: Laif; Remotiv; ***Ital.***: Nervaxon; Proserem†; Quiens; Remotive; ***Mex.***: Hiperikan; Remotiv†; ***Mon.***: Prosoft; ***Neth.***: Hyperiplant; Laif; ***Norw.***: Depasin†; Perika†; Velzina†; ***Pol.***: Apatinac; Deprim; Hypercaps; Hyperherba; Hyperosedat†; Perhip; Remotiv†; Silenil; ***Port.***: Alacre; Procalmil; ***Rus.***: Deprim (Деприм); Doppelherz Nervotonik (Доппельгерц Нервотоник); Helarium (Геларium); Negrustin (Негрустин); Novo-Passit (Ново-Пассит); ***Spain***: Animic†; Arkocapsulas Hiperico; Hipcedan; Hiperico†; Hyneurin; Livren†; Mediflor†; Perika†; Quetzal†; Vitalium†; ***Swed.***: Hypermin; Neurokan; ***Switz.***: Deprivita; Hyperiforce; HyperiMed; Hyperiplant; Hyperval; Jarsin; Lucilium; Mandal 425; ReBalance; Remotiv; Sanalum; Solevita; ***Thai.***: Hyperiforte; ***Turk.***: Felis†; ***UK***: Bettermood; Duchy Herbals Hyperi-Lift; Herbal Mood Relief; HRI Good Mood; Hyperi-Calm; Hypericon; Hyperidrine; Hyperiforce; Karma; Karmamood; Kira; Mood Boost; Moodeze; Neuropret; Ucalm; ***Ukr.***: Deprim (Деприм); Deprivit (Депривит); Helarium (Геларium); Herbion Hypericum (Гербион Гиперикум); Laif (Лайф); Neuroplant (Нейроплант); ***Venez.***: Hyperikan.

Multi-ingredient Preparations. ***Austral.***: 3B Beer Belly Buster†; Aloe Vera Gel; Cimicifuga Compound; Femi-Nan; Feminine Herbal Complex; Herbal Rest & Relax; Hernidisc; Irontona†; Joint & Muscle Cream; Lavandula Compound; Masculine Herbal Complex; Nappy Rash Relief Cream; Nevaton; Olf†; Vitatona†; Wild Yam Complex; ***Austria***: Magentee St Severin; Neroventee St Severin; Neurapas; Remifemin plus; Vulpuran; Wechseltee St Severin; ***Canad.***: Cystoforce†; Gallexier†; Salusan†; Trim-Fit†; ***Cz.***: Alvisan Neo; Cicaderma; Fytokliman Planta; Novo-Passit; Species Nervinae Planta; Stomaran; Zaludecni Cajova Smes; ***Ger.***: anabol-loges†; Dolo-cyl†; Gastritol; Hyperesa†; Neurapas; Psychotonin-sed†; Remifemin plus; Sedariston Konzentrat†; Sedariston plus†; ***Hung.***: Depsorin; Diabess; Gastrosol; Mensesyl; Remifemin Plus; Telma; ***Ital.***: Controller; Hiperogyn; Lenifren; Mithen; Skab 2†; Stressout; ***Malaysia***: Gyno-Plus; ***Mex.***: Nordimenty; ***Neth.***: Bioforce; ***Pol.***: Cholesol; Diges-Tonic; Doppelherz Energovital Tonik†; Fortestomachicae; Gastrobonisol; Guttae Stomachicae; Herbogastrin; Klosterfrau Aktiv; Krople Zoladkowe†; Krople Zoladkowe; Krople Zoladkowe; Melisal; Melissed; Nervomix; Perfocrat†; Prostapol; Psychotonisol†; Sedomix; Uroprost; ***Port.***: Cicaderma; ***Rus.***: Arfazetin-E (Арфазетин-Э); Brusniver (Бруснивер); Doppelherz Energotonik (Доппельгерц Энерготоник); Evalar (Эвалар); Polygemostat (Полигемостат); Prostanorm (Простанорм); Sibectan (Сибектан); ***Spain***: Neurapas; ***Switz.***: Huile de millepertuis A. Vogel (huile de St. Jean); Hyperiforce comp; Impuls a la consoude; Keppur; The d'avoine verte Vollmers†; Ziegella†; ***UK***: Botanova; DiaCalm; DiaMenoCalm; Menomood; Outlook; St Johnswort Compound; Tranquil; ***Ukr.***: Ambovit (Амбовит); Gastritol (Гастритол); Immuno-Ton (Іммуно-Тон); Novo-Passit (Ново-Пассит); Phytolyt (Фитолит); Sedavit (Седавит); Urochol (Урохол)†; Vitokan (Витокан); ***USA***: Sunnie.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Austria***: Arnica Komplex†; Globuli gegen Sonnenallergie; Memoria; Repisan; Traumeel; Tropfen bei Verletzungen; Valerianaheel; Wirbelsaule- und Gelenkstropfen Nr 2†; ***Canad.***: Aches & Pains; Arnica + Pain Relief; Arnicaid; Bumps and Bruises; Calendula +; Calendula Ointment†; Capsicum + Arthri-Cream; Cicaderma†; Den 141†; Formula DM 210†; Herpes Soothing Cream; Kids' Teething; Loprax†; Traumeel; Valerianaheel Comp†; ***Chile***: Bioactiv Z; ***Cz.***: Traumeel; ***Fr.***: Arnica Complexe no 1; Cicaderma; Hypericum Complexe No 26; Zincum Cyanidum Complexe No 101†; ***Ger.***: Cefakliman N†; Hewepsychon Mono†; Hyperforat Nervo; Hyperforat Vita; Infi-China; Levisticum S; Naranofem†; Nervoigen F; Nervoregin H; Phonix Urtica-Arsenicum spag; Roth's RKT Tropfen; Sedacalman; Sensiotin; Traumeel S; ***Hung.***: Traumeel; ***Neth.***: Achilite; Arnilite; Cephalite; Collite; Dermalite; Enulite; Gynaelite; Hepalite; Homeocare Nervo; Hyperilite; Mulimen H; Omnilite; Traumeel H; Traumeel S; ***Rus.***: Cicaderma (Цикадерма); Memoria (Мемория); Repisan (Реписан); Traumeel S (Траумель С); ***S.Afr.***: Berberis/Cantharis Comp†; Traumeel S; ***Switz.***: Nelsons Traumatica†; Regenaplex Nr. 12; Traumeel; ***UK***: Burns Cream; Hypercal; Pyrethrum Spray; ***Ukr.***: Memoria (Мемория); Traumeel S (Траумель С); ***USA***: Preferred Remedies Aches & Pains; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations

Ph. Eur.: St John's Wort Dry Extract, Quantified.

Tianeptine Sodium *(rINNM)*

Natrii Tianeptinum; Taneptinum Natricum; Tianeptiininatrium; Tianeptin-Natrium; Tianeptin sodná sůl; Tianeptin Sodyum; Tianeptina sódica; Tianeptine sodique; Tianeptinnatrium; Tianeptin-nátrium; Tianeptino natrio druska; Tianeptinum Natricum; Натрий Тианептин.

The sodium salt of 7-[(3-chloro-6,11-dihydro-6-methyldibenzo[*c,f*][1,2]thiazepin-11-yl)amino]heptanoic acid *S,S*-dioxide.

$C_{21}H_{24}ClN_2NaO_4S$=458.9

CAS — 66981-73-5 (tianeptine).

ATC — N06AX14.

ATC Vet — QN06AX14.

UNII — YG0E19592I.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tianeptine Sodium). A white or yellowish, very hygroscopic, powder. Freely soluble in water, in dichloromethane, and in methyl alcohol. Store in airtight containers.

Profile

Tianeptine sodium is an antidepressant reported to act by increasing (rather than inhibiting) the presynaptic reuptake of serotonin. It is given in oral doses of 12.5 mg three times daily in the treatment of depression (p. 398.1). Doses should be reduced to a total of 25 mg daily in elderly patients; for details of dosage in those with renal impairment, see p. 452.2.

Isolated cases of hepatitis have been reported during treatment with tianeptine.

Abuse. Reports of misuse of tianeptine.[1,2]

1. Leterme L, *et al.* Usage détourné de tianeptine: à propos de cinq cas de surconsommation. *Ann Med Interne (Paris)* 2003; **154:** 2S58–2S63.
2. Kisa C, *et al.* Is it possible to be dependent to tianeptine, an antidepressant? A case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31:** 776–8.

Administration in renal impairment. Licensed product information recommends that oral doses of tianeptine sodium should not exceed a total of 25 mg daily in patients with renal impairment.

Asthma. Tianeptine has been reported to improve symptoms in patients with asthma.[1] It was thought that reduction of raised levels of free serotonin found in such patients contributed to the beneficial effect of tianeptine.

1. Lechin F, *et al.* The serotonin uptake-enhancing drug tianeptine suppresses asthmatic symptoms in children: a double-blind, crossover, placebo-controlled study. *J Clin Pharmacol* 1998; **38:** 918–25.

Depression. References to the use of tianeptine in patients with depression (p. 398.1) are given below.

1. Wilde MI, Benfield P. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* 1995; **49:** 411–39.
2. Ginestet D. Efficacy of tianeptine in major depressive disorders with or without melancholia. *Eur Neuropsychopharmacol* 1997; **7** (suppl 3): S341–S345.
3. Wagstaff AJ, *et al.* Tianeptine: a review of its use in depressive disorders. *CNS Drugs* 2001; **15:** 231–59.
4. Kasper S, Olie JP. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Eur Psychiatry* 2002; **17** (suppl 3): 331–40.
5. Waintraub L, *et al.* Efficacy and safety of tianeptine in major depression: evidence from a 3-month controlled clinical trial versus paroxetine. *CNS Drugs* 2002; **16:** 65–75.
6. Nickel T, *et al.* Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol* 2003; **23:** 155–68.

Pharmacokinetics. References.

1. Royer RJ, *et al.* Tianeptine and its main metabolite: pharmacokinetics in chronic alcoholism and cirrhosis. *Clin Pharmacokinet* 1989; **16:** 186–91.
2. Carlhant D, *et al.* Pharmacokinetics and bioavailability of tianeptine in the elderly. *Drug Invest* 1990; **2:** 167–72.
3. Demotes-Mainard F, *et al.* Pharmacokinetics of the antidepressant tianeptine at steady state in the elderly. *J Clin Pharmacol* 1991; **31:** 174–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Stablon; ***Austria***: Stablon; ***Braz.***: Stablon; ***China***: Tatinol (达体朗); ***Cz.***: Coaxil; ***Fr.***: Stablon; ***Hung.***: Coaxil; ***India***: Stablon; ***Indon.***: Stablon; ***Malaysia***: Stablon; ***Mex.***: Stablon; ***Philipp.***: Stablon†; ***Pol.***: Coaxil; ***Port.***: Stablon; ***Rus.***: Coaxil (Коаксил); ***Singapore***: Stablon; ***Thai.***: Stablon; ***Turk.***: Stablon; ***Ukr.***: Coaxil (Коаксил); ***Venez.***: Stablon.

Tranylcypromine Sulfate *(BANM, rINNM)*

SKF-385; Sulfato de tranilcipromina; Tranilcipromina, sulfato de; Transamine Sulphate; Tranylcypromine, Sulfate de; Tranylcypromine Sulphate; Tranylcypromini Sulfas; Транилципромина Сульфат.

(±)-*trans*-2-Phenylcyclopropylamine sulphate.

$(C_9H_{11}N)_2,H_2SO_4$=364.5

CAS — 155-09-9 (tranylcypromine); 13492-01-8 (tranylcypromine sulfate).

ATC — N06AF04.

ATC Vet — QN06AF04.

UNII — 7ZAT6ES870.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Tranylcypromine Sulfate). A white or almost white crystalline powder; odourless or with a faint odour of cinnamaldehyde. Soluble in water; very slightly soluble in alcohol and in ether; insoluble in chloroform.

USP 36: (Tranylcypromine Sulfate). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in ether; practically insoluble in chloroform.

Uses and Administration

Tranylcypromine, a cyclopropylamine derivative, is an MAOI with actions and uses similar to those of phenelzine (p. 442.1). It produces a less prolonged inhibition of the enzymes than phenelzine.

Tranylcypromine is used in the treatment of depression, but as discussed on p. 398.1 the risks associated with traditional non-selective MAOIs such as tranylcypromine usually mean that other antidepressants are preferred. It is given orally as the sulfate although doses are expressed in terms of the base. Tranylcypromine sulfate 13.7 mg is equivalent to about 10 mg of tranylcypromine.

The usual initial dose is equivalent to tranylcypromine 10 mg in the morning and 10 mg in the afternoon; if the response is inadequate after a week, the afternoon dose may be increased to 20 mg or alternatively, 10 mg may be given additionally at midday. A dosage of 30 mg daily should only be exceeded with caution, although in the USA a maximum dose of 60 mg daily is allowed. Once a satisfactory response has been obtained the dosage may be gradually reduced for maintenance; some patients may continue to respond to 10 mg daily.

Tranylcypromine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p. 442.2).

Tranylcypromine has a stimulant action and insomnia is a common adverse effect if it is taken in the evening.

Hypertensive reactions are more likely to occur with tranylcypromine than with other MAOIs, but severe liver damage occurs less frequently.

Dependence. Dependence on tranylcypromine with tolerance has been reported in patients receiving high doses with or without a history of previous substance abuse. For further details, see Withdrawal under Precautions in Phenelzine, p. 444.2.

Effects on the cardiovascular system. Although orthostatic hypotension is more common, hypertension can occur with MAOIs. A hypertensive crisis has been described in 2 patients after only one dose of tranylcypromine.[1,2] In the first case it was thought possible that an autointeraction may have occurred between tranylcypromine and amfetamine to which it is partly metabolised. In the second case the provocation of hypertension led to the finding of a previously undiagnosed phaeochromocytoma and it was suggested this may have been a possibility in previous reports of hypertension induced by MAOIs.

1. Gunn J, *et al.* Hypertensive crisis and broad complex bradycardia after a single dose of monoamine oxidase inhibitor. *BMJ* 1989; **298:** 964.
2. Cook RF, Katritsis D. Hypertensive crisis precipitated by a monoamine oxidase inhibitor in a patient with phaeochromocytoma. *BMJ* 1990; **300:** 614.

Interactions

For interactions associated with MAOIs, see Phenelzine, p. 444.3 and p. 445.1.

The use of clomipramine with tranylcypromine is particularly hazardous.

Pharmacokinetics

Tranylcypromine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 3 hours after ingestion. It is excreted in the urine mainly in the form of metabolites. Tranylcypromine has a reported plasma elimination half-life of about 2.5 hours.

In 9 depressed patients, tranylcypromine absorption was rapid after oral dosing.[1] Absorption was biphasic in 7. Elimination was also rapid, with an elimination half-life of 1.54 to 3.15 hours. From 2 to 7 hours after dosing, standing systolic and diastolic blood pressures were lowered, and standing pulse was raised. The onset of the effect on standing systolic blood pressure correlated with the time of peak plasma tranylcypromine concentration. Maximum orthostatic drop of blood pressure and rise in pulse rate occurred 2 hours after dosing. Mean plasma-tranylcypromine concentrations correlated with mean orthostatic drop of systolic blood pressure and rise of pulse rate. Patients having clinically significant hypotensive reactions to tranylcypromine may benefit from changes in their dose regimen aimed at minimising peak concentrations.

1. Mallinger AG, *et al.* Pharmacokinetics of tranylcypromine in patients who are depressed: relationship to cardiovascular effects. *Clin Pharmacol Ther* 1986; **40:** 444–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Parnate; ***Braz.***: Parnate; ***Canad.***: Parnate; ***Ger.***: Jatrosom; ***Irl.***: Parnate; ***NZ***: Parnate; ***S. Afr.***: Parnate; ***Spain***: Parnate; ***USA***: Parnate.

Multi-ingredient Preparations. ***Arg.***: Cuait D; Stelapar; ***Ital.***: Parmodalin.

Pharmacopoeial Preparations
BP 2014: Tranylcypromine Tablets;
USP 36: Tranylcypromine Tablets.

Trazodone Hydrochloride

(BANM, USAN, rINNM)

AF-1161; Hidrocloruro de trazodona; Trazodon Hidroklorür; Trazodona, hidrocloruro de; Trazodone, Chlorhydrate de; Trazodoni Hydrochloridum; Тразодона Гидрохлорид.

2-[3-(4-*m*-Chlorophenylpiperazin-1-yl)propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.

$C_{19}H_{22}ClN_5O,HCl$=408.3

CAS — 19794-93-5 (trazodone); 25332-39-2 (trazodone hydrochloride).

ATC — N06AX05.

ATC Vet — QN06AX05.

UNII — 6E8ZO8LRNM.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of trazodone hydrochloride:

Sleepeasy.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Trazodone Hydrochloride). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 3.9 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Trazodone Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Trazodone is a triazolopyridine antidepressant chemically unrelated to other classes of antidepressants. It blocks the reuptake of serotonin at presynaptic neurones and has an action at 5-HT_1 receptors. Trazodone is also an antagonist at 5-$HT_{2A/2C}$ receptors. Unlike the tricyclic antidepressants, trazodone does not inhibit the peripheral reuptake of noradrenaline, although it may indirectly facilitate neuronal release. Trazodone blocks central α_1-adrenoceptors and appears to have no effect on the central reuptake of dopamine. It does not appear to have very significant antimuscarinic properties, but has a marked sedative action.

For the treatment of **depression** trazodone hydrochloride is given in oral doses of 150 mg daily initially; total daily dosage may be increased by 50 mg every 3 or 4 days up to 300 to 400 mg daily if necessary. The daily dosage may be divided throughout the day after food or be given as a single dose at night. Divided daily dosages of up to 600 mg may be given in severe depression in hospitalised patients. A suggested initial dose in elderly and other susceptible patients is 100 mg daily, and total daily doses above 300 mg are unlikely to be needed in these patients. A modified-release preparation that is given once daily is also available; the maximum daily dose for this preparation is 375 mg as a single dose at bedtime.

In the treatment of **anxiety** (p. 1028.1), trazodone hydrochloride is given in an initial oral dose of 75 mg daily increasing to 300 mg daily if necessary.

As with other antidepressants, trazodone should be withdrawn gradually.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Trazodone has a different biochemical profile from both the tricyclics and the SSRIs.

References.

1. Weisler RH, *et al.* Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994; **14:** 170–9.

Disturbed behaviour. Trazodone has produced beneficial results[1-3] when tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see p. 1030.2). Some[4] also consider that, in the management of dementia, trazodone might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant of or unresponsive to antipsychotics. However, the evidence for such use is poor; a systematic review on the use of trazodone in the treatment of behavioural and psychological symptoms of dementia found that the evidence from randomised, placebo-controlled studies was insufficient for any recommendations to be made.[5] The risk of adverse effects such as sedation and orthostatic hypotension, which may be particularly problematic in the elderly, should also be considered.[4]

1. Pasion RC, Kirby SG. Trazodone for screaming. *Lancet* 1993; **341:** 970.
2. Lebert F, *et al.* Behavioral effects of trazodone in Alzheimer's disease. *J Clin Psychiatry* 1994; **55:** 536–8.
3. Sultzer DL, *et al.* A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry* 1997; **5:** 60–9.
4. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
5. Martinon-Torres G, *et al.* Trazodone for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 24/11/05).

Sexual dysfunction. Priapism can occur as an adverse effect of trazodone (see Effects on Sexual Function in Adverse Effects, p. 454.1) and this has led to studies of oral trazodone for the treatment of erectile dysfunction (p. 2348.2). Positive responses have been reported, both with yohimbine[1] and alone.[2] However, there appear to have been few controlled studies and a systematic review[3] considered some of these to be either small, brief, or methodologically weak. Meta-analysis[3] of data from 6 studies did not find trazodone to be superior to placebo but subgroup analysis possibly suggested a better outcome in patients with psychogenic erectile dysfunction and in those given doses of 150 to 200 mg daily.

1. Montorsi F, *et al.* Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. *Urology* 1994; **44:** 732–6.
2. Lance R, *et al.* Oral trazodone as empirical therapy for erectile dysfunction: a retrospective review. *Urology* 1995; **46:** 117–20.
3. Fink HA, *et al.* Trazodone for erectile dysfunction: a systematic review and meta-analysis. *BJU Int* 2003; **92:** 441–6.

Substance dependence. The antidepressant, anxiolytic, and sedative properties of trazodone have been reported to have been useful when tried in patients having withdrawal syndromes from a variety of substances including alcohol (p. 1735.1),[1] cocaine (p. 1990.1),[2] and benzodiazepines (p. 1065.1).[3-5]

1. Le Bon O, *et al.* Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 2003; **23:** 377–83.
2. Small GW, Purcell JJ. Trazodone and cocaine abuse. *Arch Gen Psychiatry* 1985; **42:** 524.
3. Ansseau M, De Roeck J. Trazodone in benzodiazepine dependence. *J Clin Psychiatry* 1993; **54:** 189–91.
4. Rickels K, *et al.* Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berl)* 1999; **141:** 1–5.
5. Petrovic M, *et al.* A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. *Int J Geriatr Psychiatry* 1999; **14:** 754–60.

Adverse Effects and Treatment

Trazodone has sedative properties although drowsiness usually disappears on continuing treatment. Other adverse effects occasionally reported include dizziness, headache, nausea and vomiting, weakness, weight loss, tremor, dry mouth, bradycardia or tachycardia, orthostatic hypotension, oedema, constipation, diarrhoea, blurred vision, restlessness, confusional states, insomnia, and rash. Although some of these effects are typical of antimuscarinic activity it is reported that trazodone has little antimuscarinic activity compared with tricyclic antidepressants. *Animal* studies have also indicated that trazodone is less cardiotoxic than the tricyclics. Priapism has been reported.

Agranulocytosis, thrombocytopenia, and anaemia have been reported rarely. Adverse effects on hepatic function, including jaundice and hepatocellular damage, which may be severe, have also been reported rarely. There have been occasional reports of serotonin syndrome. Neuroleptic malignant syndrome has occurred rarely.

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of overdosage include drowsiness, dizziness, vomiting, priapism, respiratory arrest, seizures, and ECG changes. The value of gastric decontamination after overdosage is uncertain; however, activated charcoal may be considered in adults and children who have taken more than 15 mg/kg and present within 1 hour. Thereafter, symptomatic and supportive therapy should be given as appropriate.

Effects on the cardiovascular system. Although trazodone is considered to cause fewer adverse cardiovascular reactions than the tricyclic antidepressants, they have, nevertheless, been reported in individual patients. In therapeutic doses it has been associated with heart block in a patient with pre-existing cardiovascular disease,[1] as well as in a patient with no ECG abnormalities.[2] Similarly, ventricular arrhythmias have been associated with therapeutic doses of trazodone both in patients with a history of cardiac problems,[3,4] and with no history of cardiac abnormalities.[5] Atrial fibrillation has been reported in a patient with ischaemic heart disease.[6]

1. Rausch JL, *et al.* Complete heart block following a single dose of trazodone. *Am J Psychiatry* 1984; **141:** 1472–3.
2. Lippmann S, *et al.* Trazodone cardiotoxicity. *Am J Psychiatry* 1983; **140:** 1383.
3. Janowsky D, *et al.* Ventricular arrhythmias possibly aggravated by trazodone. *Am J Psychiatry* 1983; **140:** 796–7.
4. Vlay SC, Friedling S. Trazodone exacerbation of VT. *Am Heart J* 1983; **106:** 604.
5. Johnson BA. Trazodone toxicity. *Br J Hosp Med* 1985; **33:** 298.
6. White WB, Wong SHY. Rapid atrial fibrillation associated with trazodone hydrochloride. *Arch Gen Psychiatry* 1985; **42:** 424.

Effects on the eyes. A patient receiving clomipramine and trazodone orally noted excessive blinking whenever the dose of trazodone exceeded or equalled that of clomipramine.[1] When trazodone, but not clomipramine, was withdrawn, blinking became normal within 3 weeks.

1. Cooper MA, Dening TR. Excessive blinking associated with combined antidepressants. *BMJ* 1986; **293:** 1243.

Effects on the liver. A mixed hepatocellular-cholestatic liver enzyme pattern has been reported in a patient after about 3 weeks of treatment with trazodone in doses of up to 500 mg daily.[1] The enzyme abnormalities returned to normal 4 weeks after trazodone was stopped but it was suggested that liver enzyme values should be monitored

during the first 4 weeks of therapy. A similar case apparently presenting as obstructive jaundice and hepatocellular inflammation, in which the patient had only been taking 50 mg daily for 2 weeks, has also been described.[2] It was believed that the patient had had an idiosyncratic drug reaction to trazodone. Further reports of trazodone-induced liver injury include an elderly patient who developed chronic active hepatitis after taking trazodone 150 mg daily for about 8 months.[3] Fatal hepatic necrosis in another elderly patient was considered to be due to treatment with trazodone and antipsychotics.[4] The authors of the report[4] noted that up to August 1991 the UK CSM had received 14 reports of adverse effects on the liver associated with trazodone including one case of fatal hepatic necrosis. In one of 2 later reports of trazodone-induced hepatotoxicity,[5] a female patient with rheumatoid arthritis developed jaundice 18 months after trazodone was added to her existing therapy. All drugs were stopped and the patient improved; however, an inadvertent rechallenge with trazodone alone led to a recurrence of her symptoms, which again resolved after trazodone withdrawal. The second case[6] involved a HIV-positive male who was started on methadone, clonidine, and trazodone as part of a detoxification programme; 4 days later acute hepatitis and cholestasis was noted and trazodone and clonidine were withdrawn with subsequent resolution of symptoms. The authors considered that trazodone was the probable cause.

1. Chu AG, *et al.* Trazodone and liver toxicity. *Ann Intern Med* 1983; **99:** 128–9.
2. Sheikh KH, Nies AS. Trazodone and intrahepatic cholestasis. *Ann Intern Med* 1983; **99:** 572.
3. Beck PL, *et al.* Chronic active hepatitis associated with trazodone therapy. *Ann Intern Med* 1993; **118:** 791–2.
4. Hull M, *et al.* Fatal hepatic necrosis associated with trazodone and neuroleptic drugs. *BMJ* 1994; **309:** 378.
5. Fernandes NF, *et al.* Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am J Gastroenterol* 2000; **95:** 532–5.
6. Rettman KS, McClintock C. Hepatotoxicity after short-term trazodone therapy. *Ann Pharmacother* 2001; **35:** 1559–61.

Effects on mental state. There have been reports of mania,[1,2] and psychosis with hallucinations[3,4] associated with the use of trazodone in depressed patients; delirium[5] in patients with bulimia nervosa and possible psychosis or hypomania[6] in a patient receiving trazodone-tryptophan treatment for aggression have also been reported.

1. Warren M, Bick PA. Two case reports of trazodone-induced mania. *Am J Psychiatry* 1984; **141:** 1103–4.
2. Arana GW, Kaplan GB. Trazodone-induced mania following desipramine-induced mania in major depressive disorders. *Am J Psychiatry* 1985; **142:** 386.
3. Kraft TB. Psychosis following trazodone administration. *Am J Psychiatry* 1983; **140:** 1383–4.
4. Mizoguchi Y, Monji A. Low-dose-trazodone-induced disorganized type psychosis. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 253–4.
5. Damlouji NF, Ferguson JM. Trazodone-induced delirium in bulimic patients. *Am J Psychiatry* 1984; **141:** 434–5.
6. Patterson BD, Srisopark MM. Severe anorexia and possible psychosis or hypomania after trazodone-tryptophan treatment of aggression. *Lancet* 1989; **i:** 1017.

Effects on sexual function. Trazodone is notable for the number of reports of priapism associated with its use.[1,2] In most cases, priapism occurred during treatment with standard doses after 1 to 3 weeks of therapy. Several patients required surgery and recovery was not always complete.[1] A review[3] of priapism induced by psychotropic drugs proposed that the effect was related to blockade of alpha-adrenoceptors in the absence of sufficient antimuscarinic activity, criteria fulfilled by the pharmacological profile of trazodone.

Inhibition of ejaculation,[4] and an increase in libido in women[5] and men[6] have also been reported with trazodone therapy. There have also been reports of trazodone-associated priapism of the clitoris.[7,8]

1. CSM. Priapism and trazodone (Molipaxin). *Current Problems 13* 1984. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024420&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Anonymous. Priapism with trazodone (Desyrel). *Med Lett Drugs Ther* 1984; **26:** 35.
3. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
4. Jones SD. Ejaculatory inhibition with trazodone. *J Clin Psychopharmacol* 1984; **4:** 279–81.
5. Gartrell N. Increased libido in women receiving trazodone. *Am J Psychiatry* 1986; **143:** 781–2.
6. Sullivan G. Increased libido in three men treated with trazodone. *J Clin Psychiatry* 1988; **49:** 202–3.
7. Pescatori ES, *et al.* Priapism of the clitoris: a case report following trazodone use. *J Urol (Baltimore)* 1993; **149:** 1557–9.
8. Medina CA. Clitoral priapism: a rare condition presenting as a cause of vulvar pain. *Obstet Gynecol* 2002; **100:** 1089–91.

Effects on the skin. Individual reports of adverse dermatological reactions to trazodone have included leucocytoclastic vasculitis,[1] erythema multiforme,[2] and exacerbation of psoriasis.[3]

1. Mann SC, *et al.* Leukocytoclastic vasculitis secondary to trazodone treatment. *J Am Acad Dermatol* 1984; **10:** 699–70.
2. Ford HE, Jenike MA. Erythema multiforme associated with trazodone therapy: case report. *J Clin Psychiatry* 1985; **46:** 294–5.
3. Barth JH, Baker H. Generalized pustular psoriasis precipitated by trazodone in the treatment of depression. *Br J Dermatol* 1986; **115:** 629–30.

Epileptogenic effect. Tonic-clonic seizures related to trazodone therapy have been reported in 2 patients[1,2] with no history of seizure disorders.

1. Bowdan ND. Seizure possibly caused by trazodone hydrochloride. *Am J Psychiatry* 1983; **140:** 642.
2. Lefkowitz D, *et al.* Seizures and trazodone therapy. *Arch Gen Psychiatry* 1985; **42:** 523.

Overdosage. Reviews have indicated that the incidence of serious toxicity from trazodone overdose alone was low compared with tricyclic antidepressant overdose.[1-4]

In a review of 149 such cases,[1] only 10 deaths had been reported and in only 1 case was trazodone the sole agent reported taken; in this case autopsy revealed an acute myocardial infarction after the patient was stable. The other 9 patients also had histories of taking unknown quantities of alcohol, benzodiazepines, or other sedative-hypnotics that may have contributed to their death. In the surviving 139 patients there were 2 cases of respiratory arrest, 2 cases of right bundle branch block, and one case each of priapism, seizure, atrioventricular block, and T-wave inversion. The remaining patients had minor CNS-depressant effects.

In another review[2] of overdose no fatalities occurred in 39 cases where trazodone was taken alone, but there were 9 deaths in 49 cases where trazodone was taken with other drugs or alcohol.

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p. 398.1.

1. Hassan E, Miller DD. Toxicity and elimination of trazodone after overdose. *Clin Pharm* 1985; **4:** 97–100.
2. Gamble DE, Peterson LG. Trazodone overdose: four years of experience from voluntary reports. *J Clin Psychiatry* 1986; **47:** 544–6.
3. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.
4. Gallant DM. Antidepressant overdose: symptoms and treatment. *Psychopathology* 1987; **20** (suppl 1): 75–81.

Precautions

Trazodone should be used with caution in patients with cardiovascular disorders, such as ischaemic heart disease, and its use is not recommended in the immediate recovery phase after myocardial infarction. Similarly, it should be used with caution in patients with epilepsy and severe hepatic or renal impairment. Trazodone should be stopped immediately if patients develop signs of hepatic dysfunction or blood dyscrasias. Patients developing inappropriate or prolonged penile erections should also stop trazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Drowsiness often occurs at the start of trazodone therapy and patients, if affected, should not drive or operate machinery.

As with other antidepressants, trazodone therapy should be withdrawn gradually.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trazodone on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antidepressants do appear in breast milk and thus could conceivably alter infant CNS function both in the short and long term.

A study of 6 women each given a single 50-mg dose of trazodone concluded that the exposure of infants to trazodone via breast milk was very small.[2] However, trazodone has been reported to form an active metabolite and it was unknown to what extent this metabolite distributed into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Verbeeck RK, *et al.* Excretion of trazodone in breast milk. *Br J Clin Pharmacol* 1986; **22:** 367–70.

Pregnancy. UK licensed product information states that trazodone should be avoided during pregnancy; that for the USA indicates that trazodone should only be used if the benefits to the mother outweigh the risks to the fetus.

For details of outcome in a multicentre study on the use of trazodone during pregnancy, see under Nefazodone, p. 439.2.

Interactions

Trazodone should not be given to patients receiving MAOIs or for at least 14 days afterwards. It has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping trazodone therapy. For further details of combination antidepressant therapy, see Antidepressants under Interactions of Phenelzine, p. 445.2.

It is considered unlikely that trazodone will alter the effects of antihypertensives such as guanethidine; some interaction may, however, occur with clonidine. The dose of other antihypertensives may need to be reduced if used with trazodone.

The sedative effects of trazodone may be enhanced by alcohol or other CNS depressants. The potential for interaction between trazodone and general anaesthetics or muscle relaxants exists and some licensed product information recommends that trazodone should be stopped before elective surgery for as long as clinically feasible.

Trazodone may increase plasma concentrations of digoxin or phenytoin and some product information recommends monitoring their serum concentrations if used with trazodone.

Trazodone is metabolised by the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this isoenzyme may limit the elimination of trazodone. Consequently, trazodone may need to be given in reduced doses with drugs known to be potent inhibitors of CYP3A4 such as the azole antifungals itraconazole and ketoconazole, and the HIV-protease inhibitors. CYP3A4 inducers such as carbamazepine may reduce the plasma concentrations of trazodone.

Anticoagulants. For the effect of trazodone on *warfarin* dose requirement, see p. 1531.3.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

Trazodone may increase plasma concentrations of *carbamazepine* (see p. 516.2) and *phenytoin* (see p. 543.1). Some licensed product information recommends monitoring concentrations of phenytoin if used with trazodone.

Antivirals. In a small study in 10 subjects, the use of low-dose *ritonavir* (200 mg twice daily for 2 days) with trazodone (50 mg once daily) more than halved the clearance of trazodone resulting in significant increases in its peak plasma concentrations.[1] Adverse reactions were noted in 3 subjects and included dizziness, nausea, hypotension, and syncope.

1. Greenblatt DJ, *et al.* Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J Clin Pharmacol* 2003; **43:** 414–22.

Ginkgo biloba. Coma, reversible by flumazenil, developed in an 80-year-old woman with Alzheimer's disease 3 days after starting to take a preparation of ginkgo biloba with trazodone.[1]

1. Galluzzi S, *et al.* Coma in a patient with Alzheimer's disease taking low dose trazodone and gingko biloba. *J Neurol Neurosurg Psychiatry* 2000; **68:** 679–80.

Pharmacokinetics

Trazodone is readily absorbed from the gastrointestinal tract and when taken soon after a meal the amount absorbed may be increased. However, peak plasma concentrations, which may be reduced compared with the fasting state, occur about 1 hour after a dose taken on an empty stomach and after about 2 hours when taken with food. Protein binding is reported to be about 89 to 95%.

Trazodone is extensively metabolised in the liver and paths of metabolism include *N*-oxidation and hydroxylation. It is metabolised to its active metabolite *m*-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4. Trazodone is excreted mainly in the urine almost entirely in the form of its metabolites, either in free or in conjugated form: some is excreted in the faeces via biliary elimination. The elimination of trazodone from the plasma is biphasic, with a terminal elimination half-life of 5 to 9 hours.

Small amounts of trazodone are distributed into breast milk.

References.

1. Bayer AJ, *et al.* Pharmacokinetic and pharmacodynamic characteristics of trazodone in the elderly. *Br J Clin Pharmacol* 1983; **16:** 371–6.
2. Nilsen OG, Dale O. Single dose pharmacokinetics of trazodone in healthy subjects. *Pharmacol Toxicol* 1992; **71:** 150–3.
3. Nilsen OG, *et al.* Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Pharmacol Toxicol* 1993; **72:** 286–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Taxagon; ***Austria***: Trittico; ***Belg.***: Nestrolan; Trazolan; ***Braz.***: Donaren; ***Canad.***: Desyrel; Trazorel; ***Chile***: Diapresan; Trant; Trittico; Tronsalan; ***China***: Mei Su Yu (每素玉); Mesyrel (美抒玉); Shu Xu (舒绪); ***Cz.***: Trit-

tico AC; ***Fin.***: Azona; ***Ger.***: Thombran†; ***Gr.***: Trittico; ***Hong Kong***: Trittico; ***Hung.***: Trittico; ***India***: Depryl; ***Irl.***: Molipaxin; ***Israel***: Trazodil; Trittico†; ***Ital.***: Trittico; ***Mex.***: Sideril; ***Neth.***: Trazolan; ***Pol.***: Trittico; ***Port.***: Tranzelm†; Trazone; Triticum; Zameg†; ***Rus.***: Trittico (Триттико); ***S.Afr.***: Molipaxin; ***Singapore***: Trittico; ***Spain***: Deprax; ***Switz.***: Trittico; ***Thai.***: Desirel; Trazo; Zodonrel; Zorel; ***Turk.***: Desyrel; ***UK***: Molipaxin; ***Ukr.***: Trittico (Триттико); ***USA***: Oleptro; ***Venez.***: Trittico.

Pharmacopoeial Preparations
BP 2014: Trazodone Capsules; Trazodone Tablets;
USP 36: Trazodone Hydrochloride Tablets.

Trimipramine *(BAN, USAN, rINN)*

IL-6001; 7162-RP; Trimeprimine; Trimipramiini; Trimipramin; Trimipramina; Trimipraminum; Тримипрамин.

Dimethyl{3-(10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl-2-methyl)propyl}amine.

$C_{20}H_{26}N_2$=294.4

CAS — 739-71-9.

ATC — N06AA06.

ATC Vet — QN06AA06.

UNII — 6S082C9NDT.

Trimipramine Maleate *(BANM, USAN, rINNM)*

Maleato de trimipramina; Trimipramiinimaleaatti; Trimipramin maleinát; Trimipramina, maleato de; Trimipramine Hydrogen Maleate; Trimipramine, Maléate de; Trimipramini maleas; Trimipraminmaleat; Trimipramin-maleát; Trimipramino maleatas; Тримипрамина Малеат.

$C_{20}H_{26}N_2.C_4H_4O_4$=410.5

CAS — 521-78-8.

UNII — 269K6498LD.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Trimipramine Maleate). A white or almost white crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

USP 36: (Trimipramine Maleate). A white to almost white crystalline powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Uses and Administration

Trimipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It has marked antimuscarinic and sedative properties.

Trimipramine is given orally as the maleate although doses are expressed in terms of the base. Trimipramine maleate 34.9 mg is equivalent to about 25 mg of trimipramine. In the treatment of depression, the usual initial dose is the equivalent of trimipramine 50 to 75 mg daily, gradually increased as necessary to 150 to 300 mg daily. The recommended initial dose for the elderly in the UK is 30 to 75 mg daily, gradually increased as necessary. In the USA, the elderly and adolescents may be given 50 mg daily initially followed by gradual increments as necessary up to a maximum of 100 mg daily. Trimipramine may be given in divided doses during the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable and usually given at night.

Trimipramine has also been given orally as the hydrochloride and the mesilate; the mesilate has also been given intramuscularly.

Trimipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trimipramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Trimipramine is readily absorbed after oral doses and peak plasma concentrations occur in 2 hours. It is metabolised in the liver to its major metabolite desmethyltrimipramine, which is active. Trimipramine is excreted in the urine mainly in the form of its metabolites. It is about 95% bound to plasma proteins. The plasma elimination half-life is reported to be about 23 hours.

References.
1. Maurer H. Metabolism of trimipramine in man. *Arzneimittelforschung* 1989; **39**: 101–3.
2. Musa MN. Nonlinear kinetics of trimipramine in depressed patients. *J Clin Pharmacol* 1989; **29**: 746–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Surmontil; ***Canad.***: Apo-Trimip; Novo-Tripramine; ***Denm.***: Surmontil†; ***Fin.***: Surmontil; ***Fr.***: Surmontil; ***Ger.***: Herphonal; Stangyl; Trimineurin†; ***Hong Kong***: Surmontil; ***Hung.***: Sapilent; ***India***: Surmontil; ***Irl.***: Surmontil; ***Israel***: Surmontil; ***Ital.***: Surmontil; ***Norw.***: Surmontil; ***NZ***: Surmontil; Tripress†; ***Philipp.***: Surmontil; ***Port.***: Surmontil; ***S.Afr.***: Surmontil†; Tydamine; ***Singapore***: Apo-Trimip; ***Spain***: Surmontil; ***Switz.***: Surmontil; Trimine†; ***UK***: Surmontil; ***USA***: Surmontil.

Pharmacopoeial Preparations
BP 2014: Trimipramine Tablets.

Tryptophan *(BAN, USAN, rINN)*

Triptofán; Triptofanas; Triptófano; Tryptofaani; Tryptofan; L-Tryptophan; Tryptophane; Tryptophanum; W; Триптофан.

L-2-Amino-3-(indol-3-yl)propionic acid.

$C_{11}H_{12}N_2O_2$=204.2

CAS — 73-22-3.

ATC — N06AX02.

ATC Vet — QN06AX02.

UNII — 8DUH1N11BX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Tryptophan). A white or almost white crystalline or amorphous powder. Sparingly soluble in water; slightly soluble in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Tryptophan). White to slightly yellowish-white crystals or crystalline powder. Soluble in hot alcohol and in dilute hydrochloric acid. pH of a 1% solution in water is between 5.5 and 7.0.

Uses and Administration

Tryptophan is an amino acid that is an essential constituent of the diet. Tryptophan and DL-tryptophan have been used as dietary supplements.

Tryptophan is a precursor of serotonin. Because CNS depletion of serotonin is considered to be involved in depression, tryptophan has been used in its treatment. Although it has been given alone, evidence of efficacy is scant and tryptophan has generally been used as adjunctive therapy in depression. It has sometimes been given with pyridoxine and ascorbic acid, which are involved in its metabolism to serotonin (see Pharmacokinetics, p. 456.1).

In many countries preparations containing tryptophan have either been withdrawn from the market or their availability severely restricted or limited because of its association with the eosinophilia-myalgia syndrome. In the UK, tryptophan is restricted to use as an adjunct to other antidepressant medication or in patients who have failed to respond to an adequate trial of standard antidepressant drug treatment. Therapy should be started by hospital specialists; thereafter tryptophan may be prescribed in the community.

In the treatment of depression the usual oral dose of tryptophan is 1 g given three times daily, but some patients may require up to 6 g daily in divided doses. Lower doses may be required in the elderly especially those with renal or hepatic impairment.

Depression. Evidence of benefit for tryptophan when given alone for depression (p. 398.1) is lacking, though there is some suggestion of a weak antidepressant effect.[1] It has therefore mainly been used with other antidepressants in the belief that it would potentiate their effects. Although beneficial effects have been reported in some patients given tryptophan with SSRIs, tricyclic antidepressants, or MAOIs, either alone or with lithium, evidence of efficacy is mainly limited to case reports and small controlled studies.[2-4]

After the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, p. 455.3) preparations containing tryptophan for depression were withdrawn from the market or their use restricted. For details of UK restrictions see Uses and Administration, above.

1. Shaw K, *et al.* Tryptophan and 5-hydroxytryptophan for depression. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/11/05).
2. Barker WA, *et al.* The Newcastle chronic depression study: results of a treatment regime. *Int Clin Psychopharmacol* 1987; **2**: 261–72.
3. Smith S. Tryptophan in the treatment of resistant depression—a review. *Pharm J* 1998; **261**: 819–21.
4. Levitan RD, *et al.* Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J Psychiatry Neurosci* 2000; **25**: 337–46.

Dietary supplementation. The use of tryptophan as a dietary supplement has been reviewed.[1] However, because of its association with the eosinophilia-myalgia syndrome (see under Adverse Effects, p. 455.3), the addition of tryptophan to food intended for human consumption is prohibited in some countries.

1. Li Wan Po A, Maguire T. Tryptophan: useful dietary supplement or a health hazard? *Pharm J* 1990; **244**: 484–5.

Insomnia. Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity for the treatment of insomnia (p. 1033.2). However, in comparison with other hypnotics such as the benzodiazepines, the effects of tryptophan have been difficult to substantiate, and enthusiasm for tryptophan has waned considerably amongst sleep researchers.[1] It should also be noted that since the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, p. 455.3) preparations indicated for insomnia have been withdrawn from the market in many countries.

1. Lahmeyer HW. Tryptophan for insomnia. *JAMA* 1989; **262**: 2748.

Adverse Effects

Tryptophan-containing products have been associated with the eosinophilia-myalgia syndrome; for further details, see p. 455.3.

Other adverse effects that have been reported include nausea, headache, lightheadedness, and drowsiness.

An increased incidence of bladder tumours has been reported in *mice* given L-tryptophan orally as well as in cholesterol pellets embedded in the bladder lumen. However, there was no increase in tumour incidence when only high-dose, oral tryptophan was given.

Eosinophilia-myalgia syndrome. In late 1989 the first notification linking the eosinophilia-myalgia syndrome with the use of tryptophan-containing products was made in the USA.[1] There followed similar published case reports from the USA, Europe, and Japan. Reviews of tryptophan-associated eosinophilia-myalgia syndrome have noted that by early 1990 over 1500 cases were known in the USA.[2,3]

In early 1990 the CDC in the USA summarised the features and known reports concerning the syndrome.[4] As the name implies the characteristic features are an intense eosinophilia with disabling fatigue and muscle pain, although multisystem organ involvement and inflammatory disorders affecting the joints, skin, connective tissue, lungs, heart, and liver have also been recorded. Symptoms have generally developed over several weeks and the syndrome has occurred in patients who had been receiving tryptophan for many years previously with no untoward effect. In most patients slow and gradual improvement in the degree of eosinophilia and other clinical manifestations has followed the withdrawal of tryptophan, but in some patients the disease has progressed despite withdrawal and there have been fatalities.[5-7] The inflammatory condition has necessitated the use of corticosteroids in some patients.

The eosinophilia-myalgia syndrome has been reported in patients taking both tryptophan-containing prescription products for depression and non-prescription dietary supplements for disorders including insomnia, the premenstrual syndrome, and stress; it does not appear to have occurred in patients receiving amino-acid preparations containing tryptophan as part of total parenteral nutrition regimens. The recognition of this syndrome led to the withdrawal of tryptophan-containing products or severe restrictions being imposed upon their use in many countries during 1990.

Various theories were proposed as to the reason for the association of tryptophan with this syndrome. Confusion existed because the reports implicated a very wide range of products from different manufacturers. However, later evidence appeared to have confirmed that contaminated tryptophan had originated from a single manufacturer in Japan.[8-10] Bulk tryptophan was imported from Japan for manufacture into finished pharmaceutical dosage forms and it was noted in one of these reports[9] that a single product was often found to contain two or more lots of powdered tryptophan that were blended together during the production of tablets or capsules. Many trace contaminants have been found in batches of tryptophan associated with the syndrome.[11] One contaminant has been identified as 1,1′-ethylidenebis(tryptophan).[12] Its inclusion in bulk tryptophan powder appeared to coincide with alterations in the manufacturing conditions that involved a change in the strain of *Bacillus amyloliquefaciens* used in the fermentation process and a reduction in the amount of charcoal used for purification.[9] Other investigations indicated the presence of bacitracin-like peptides in batches

of the contaminated tryptophan.[13] However, further work[14] has provided only weak support for an association between the syndrome and any one particular contaminant and the causative agent remains to be confirmed. Nonetheless, since the syndrome only appeared to be associated with tryptophan from one manufacturer, tryptophan preparations were reintroduced in the UK in 1994 for restricted use under carefully monitored conditions.[15] In January 2005, the UK requirement for patient registration and monitoring was removed.

1. Anonymous. Eosinophilia-myalgia syndrome—New Mexico. *MMWR* 1989; **38:** 765–7.
2. Troy JL. Eosinophilia-myalgia syndrome. *Mayo Clin Proc* 1991; **66:** 535–8.
3. Milburn DS, Myers CW. Tryptophan toxicity: a pharmacoepidemiologic review of eosinophilia-myalgia syndrome. *DICP Ann Pharmacother* 1991; **25:** 1259–62.
4. Kilbourne EM, *et al.* Interim guidance on the eosinophilia-myalgia syndrome. *Ann Intern Med* 1990; **112:** 85–6.
5. Anonymous. Eosinophilia-myalgia syndrome associated with ingestion of L-tryptophan—United States, through August 24, 1990. *JAMA* 1990; **264:** 1655.
6. Kaufman LD, *et al.* Clinical follow-up and immunogenetic studies of 32 patients with eosinophilia-myalgia syndrome. *Lancet* 1991; **337:** 1071–4.
7. Hertzman PA, *et al.* The eosinophilia-myalgia syndrome: status of 205 patients and results of treatment 2 years after onset. *Ann Intern Med* 1995; **122:** 851–5.
8. Slutsker L, *et al.* Eosinophilia-myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990; **264:** 213–17.
9. Belongia EA, *et al.* An investigation of the cause of the eosinophilia-myalgia syndrome associated with tryptophan use. *N Engl J Med* 1990; **323:** 357–65.
10. Varga J, *et al.* The cause and pathogenesis of the eosinophilia-myalgia syndrome. *Ann Intern Med* 1992; **116:** 140–7.
11. Hill RH, *et al.* Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. *Arch Environ Contam Toxicol* 1993; **25:** 134–42.
12. Mayeno AN, *et al.* Characterization of "peak E", a novel amino acid associated with eosinophilia-myalgia syndrome. *Science* 1990; **250:** 1707–8.
13. Barnhart ER, *et al.* Bacitracin-associated peptides and contaminated L-tryptophan. *Lancet* 1990; **336:** 742.
14. Philen RM, *et al.* Tryptophan contaminants associated with eosinophilia-myalgia syndrome. *Am J Epidemiol* 1993; **138:** 154–9.
15. CSM/MCA. L-Tryptophan (Optimax): limited availability for resistant depression. *Current Problems* 1994; **20:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Precautions

Tryptophan has been associated with eosinophilia-myalgia syndrome (see p. 453.3); caution is advised in patients receiving the drug who develop some, but not all, of the symptoms of this syndrome. It should not be used in those with a history of eosinophilia-myalgia syndrome associated with tryptophan treatment.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be followed when treating patients with other disorders.

Patients taking tryptophan may experience drowsiness and, if affected, they should not drive or operate machinery. For further details of the effects of antidepressant therapy on driving see under Amitriptyline, p. 405.2.

Abnormal metabolism of tryptophan may occur in patients with pyridoxine deficiency and tryptophan is thus sometimes given with pyridoxine supplements.

Interactions

Although tryptophan has been given to patients receiving MAOIs in the belief that clinical efficacy may be improved, it should be noted that the adverse effects may also be potentiated. For further details, see Antidepressants under Interactions of Phenelzine, p. 445.2.

Use of tryptophan with drugs that inhibit the reuptake of serotonin may exacerbate the adverse effects of the latter and precipitate the serotonin syndrome (p. 443.2).

There have been occasional reports of sexual disinhibition in patients taking tryptophan with phenothiazines or benzodiazepines.

For a report of tryptophan reducing blood concentrations of levodopa, see Nutritional Agents under Interactions of Levodopa, p. 908.3.

Pharmacokinetics

Tryptophan is readily absorbed from the gastrointestinal tract. Tryptophan is extensively bound to plasma albumin. It is metabolised in the liver by tryptophan pyrrolase and tryptophan hydroxylase. Metabolites include hydroxytryptophan, which is then converted to serotonin, and kynurenine derivatives. Some tryptophan is converted to nicotinic acid and nicotinamide. Pyridoxine and ascorbic acid are cofactors in the decarboxylation and hydroxylation, respectively, of tryptophan; pyridoxine apparently prevents the accumulation of the kynurenine metabolites.

References.
1. Green AR, *et al.* The pharmacokinetics of L-tryptophan following its intravenous and oral administration. *Br J Clin Pharmacol* 1985; **20:** 317–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kalma; ***Canad.***: Tryptan; ***Ger.***: Ardeydorm; Ardeytropin; Kalma†; ***UK***: Optimax†.

Multi-ingredient Preparations. ***Braz.***: Organoneuro Optico; Profol; ***Fr.***: Fibromyalgine Fort; Neurobiane; Phytozac; Seroxyl; Vita-Dermacide; ***Ital.***: Brioplus; Fisioreve CM; Pineal; Promolax; Stressout; ***Mex.***: Aminoyodarsencal; ***Ukr.***: Gentaxan (Гентаксан); ***USA***: PDP Liquid Protein.

Venlafaxine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de venlafaxina; Venlafaxina, hidrocloruro de; Venlafaxine, chlorhydrate de; Venlafaxinhydrochlorid; Venlafaxin-hydrochlorid; Venlafaxini Hydrochloridum; Venlafaxinum Hydrochloridum; Wenlafaksyny chlorowodorek; Wy-45030; Венлафаксина Гидрохлорид.

(*RS*)-1-(2-Dimethylamino-1-*p*-methoxyphenylethyl)cyclohexanol hydrochloride.

$C_{17}H_{27}NO_2,HCl$=313.9

CAS — 93413-69-5 (venlafaxine); 99300-78-4 (venlafaxine hydrochloride).

ATC — N06AX16.

ATC Vet — QN06AX16.

UNII — 7D7RX5A8MO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Venlafaxine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol; slightly soluble or practically insoluble in acetone.

USP 36: (Venlafaxine Hydrochloride). An off-white to white crystalline powder. Soluble in water and in methyl alcohol. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Venlafaxine, a phenylethylamine derivative, is a serotonin and noradrenaline reuptake inhibitor (SNRI); it also weakly inhibits dopamine reuptake. It is reported to have little affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Venlafaxine is given orally as the hydrochloride although doses are expressed in terms of the base; venlafaxine hydrochloride 28.3 mg is equivalent to about 25 mg of venlafaxine. It should be taken with food.

Venlafaxine is used in the treatment of **depression**. The initial daily dose is equivalent to venlafaxine 75 mg in two or three divided doses. In the USA, it is suggested that some patients may be best started on 37.5 mg daily for the first 4 to 7 days before increasing the dose to 75 mg daily. The dose may be increased, if necessary, in steps of up to 75 mg and usually at intervals of 2 weeks or more. In some cases, because of disease severity, the dose may be increased more rapidly, but the interval between increases should be at least 4 days. Doses of up to 225 mg daily are usually effective for patients with moderate depression, but further increases up to a maximum daily dose of 375 mg, given in three divided doses, may be required in severely depressed patients. Modified-release preparations are available for once-daily dosing.

Venlafaxine is also used, as a modified-release preparation, in the treatment of **generalised anxiety disorder**. The recommended initial dose is 75 mg once daily. In the USA it is suggested that some patients may be best begun with 37.5 mg daily for 4 to 7 days initially, before increasing the dose to 75 mg daily. The dose may be subsequently increased, if necessary, in steps of up to 75 mg to a maximum of 225 mg daily. The interval between dose increases is usually 2 weeks or more, and should be at least 4 days.

Modified-release venlafaxine is licensed for the treatment of **social anxiety disorder** in doses similar to those used for generalised anxiety disorder (although licensed product information states that there is no evidence of additional benefit from doses above 75 mg daily). It is also licensed for **panic disorder** with or without agoraphobia in doses of 37.5 mg once daily for the first 7 days, then increasing to 75 mg daily. Subsequent increases in increments of up to 75 mg may be made to a maximum dose of 225 mg daily. The interval between dose increases is usually 2 weeks or more, and should be at least 7 days.

Reduced doses may need to be given in hepatic or renal impairment, see p. 456.3.

Venlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, p. 458.1).

Administration in hepatic impairment. In general, it is recommended that the usual dose of venlafaxine (see Uses and Administration, above) should be reduced by 50% in patients with mild to moderate hepatic impairment, and adjusted according to response. The drug should be used with caution, and even greater reductions in dose should be considered, for those with severe impairment or cirrhosis.

Administration in renal impairment. In the UK, licensed product information advises that patients with a glomerular filtration rate (GFR) of 30 mL/minute and above may be given the usual dose of venlafaxine (see Uses and Administration, above), although the drug should be used with caution. For patients with a GFR of less than 30 mL/minute, and those requiring haemodialysis, the usual dose should be reduced by 50%.

In the USA, it is suggested that the dose of venlafaxine should be reduced by 25% in patients with mild to moderate renal impairment, and by 50% in those requiring haemodialysis.

Anxiety disorders. Venlafaxine is used in the treatment of generalised anxiety disorder and social anxiety disorder (see under Phobic Disorders, p. 1029.1); it may also be of use in a variety of other types of anxiety disorders (p. 1028.1) including the treatment of obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), and post-traumatic stress disorder (p. 1029.2).

References.
1. Altamura AC, *et al.* Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. *Int Clin Psychopharmacol* 1999; **14:** 239–45.
2. Gelenberg AJ, *et al.* Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *JAMA* 2000; **283:** 3082–8.
3. Sheehan DV. Attaining remission in generalized anxiety disorder: venlafaxine extended release comparative data. *J Clin Psychiatry* 2001; **62** (suppl 19): 26–31.
4. Katz IR, *et al.* Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomised placebo-controlled clinical trials. *J Am Geriatr Soc* 2002; **50:** 18–25.
5. Hollander E, *et al.* Venlafaxine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64:** 546–50. Correction. *ibid.*; 972.
6. Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. *Br J Gen Pract* 2003; **53:** 772–7.
7. Boyer P, *et al.* Social adjustment in generalised anxiety disorder: a long-term placebo-controlled study of venlafaxine extended release. *Eur Psychiatry* 2004; **19:** 272–9.
8. Denys D, *et al.* A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. *J Clin Psychiatry* 2004; **65:** 37–43.
9. Liebowitz MR, *et al.* Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry* 2005; **62:** 190–8.
10. Liebowitz MR, *et al.* A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. *J Clin Psychiatry* 2005; **66:** 238–47.
11. Phelps NJ, Cates ME. The role of venlafaxine in the treatment of obsessive-compulsive disorder. *Ann Pharmacother* 2005; **39:** 136–40.
12. Bradwejn J, *et al.* Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry* 2005; **187:** 352–9.
13. Davidson J, *et al.* Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol* 2006; **26:** 259–67. Correction. *ibid.*; 473. [dose]
14. Davidson J, *et al.* Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 2006; **63:** 1158–65.
15. Ferguson JM, *et al.* Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry* 2007; **68:** 58–68.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. In December 2004 the UK CSM recommended that, because of the risk of adverse cardiovascular effects and toxicity in overdosage (see Adverse Effects and Treatment, p. 457.1), venlafaxine treatment should be begun and maintained under specialist supervision only. After an assessment of further safety evidence, these restrictions were revised in May 2006 and specialist supervision was considered only necessary when starting venlafaxine treatment in severely depressed or hospitalised patients who require doses of 300 mg daily or above. However, it was also advised that venlafaxine should be considered a second-line treatment, after the SSRIs.

The *O*-desmethyl metabolite of venlafaxine, desvenlafaxine (p. 413.2), is also used in depression.

References.
1. Morton WA, *et al.* Venlafaxine: a structurally unique and novel antidepressant. *Ann Pharmacother* 1995; **29:** 387–95.
2. Derivan A, *et al.* Venlafaxine: measuring the onset of antidepressant action. *Psychopharmacol Bull* 1995; **31:** 439–47.
3. Wellington K, Perry CM. Venlafaxine extended-release: a review of its use in the management of major depression. *CNS Drugs* 2001; **15:** 643–69.

4. Cohen LS, *et al.* Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry* 2001; **62:** 592–6.
5. Montgomery SA, *et al.* Venlafaxine versus placebo in the preventive treatment of recurrent major depression. *J Clin Psychiatry* 2004; **65:** 328–36.

Hot flushes. For the reference to the use of venlafaxine in the treatment of hot flushes, see under Fluoxetine, p. 418.2.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p. 2314.1) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants; in open studies venlafaxine has been reported to be effective in both adults[1-3] and children[4-6] although some individual patients had a worsening of symptoms.

1. Hedges D, *et al.* An open trial of venlafaxine in adult patients with attention deficit hyperactivity disorder. *Psychopharmacol Bull* 1995; **31:** 779–83.
2. Adler LA, *et al.* Open-label trial of venlafaxine in adults with attention deficit disorder. *Psychopharmacol Bull* 1995; **31:** 785–8.
3. Findling RL, *et al.* Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. *J Clin Psychiatry* 1996; **57:** 184–9.
4. Olvera RL, *et al.* An open trial of venlafaxine in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol* 1996; **6:** 241–50.
5. Motavalli Mukaddes N, Abali O. Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. *Psychiatry Clin Neurosci* 2004; **58:** 92–5.
6. Findling RL, *et al.* Venlafaxine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2007; **17:** 433–45.

Migraine. Retrospective analysis[1] in patients with tension-type headache (p. 671.3) or migraine (p. 670.3) indicated that venlafaxine, as a modified-release preparation, had potential for headache prophylaxis. A more recent randomised placebo-controlled study[2] also supports the use of modified-release venlafaxine in the prophylaxis of migraine.

1. Adelman LC, *et al.* Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: a retrospective study in a clinical setting. *Headache* 2000; **40:** 572–80.
2. Ozyalcin SN, *et al.* The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; **45:** 144–52.

Pain. Venlafaxine may be of benefit in the treatment of neuropathic pain syndromes (p. 10.1)[1,2] including painful diabetic neuropathy (p. 8.2).[3-5] It has also shown some promise in the treatment of fibromyalgia (see Soft-tissue Rheumatism, p. 14.2).[6]

1. Sumpton JE, Moulin DE. Treatment of neuropathic pain with venlafaxine. *Ann Pharmacother* 2001; **35:** 557–9.
2. Grothe DR, *et al.* Treatment of pain syndromes with venlafaxine. *Pharmacotherapy* 2004; **24:** 621–9.
3. Davis JL, Smith RL. Painful peripheral diabetic neuropathy treated with venlafaxine HCl extended release capsules. *Diabetes Care* 1999; **22:** 1909–10.
4. Kiayias JA, *et al.* Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. *Diabetes Care* 2000; **23:** 699.
5. Rowbotham MC, *et al.* Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004; **110:** 697–706. Correction. *ibid.* 2005; **113:** 248.
6. Sayar K, *et al.* Venlafaxine treatment of fibromyalgia. *Ann Pharmacother* 2003; **37:** 1561–5.

Adverse Effects and Treatment

Adverse effects that have been reported most frequently with venlafaxine include nausea, headache, insomnia, somnolence, dry mouth, dizziness, constipation, sexual dysfunction, asthenia, sweating, and nervousness. Other common adverse effects have included anorexia, diarrhoea, dyspepsia, abdominal pain, anxiety, urinary frequency, visual disturbances, mydriasis, vasodilatation, vomiting, tremor, paraesthesia, hypertonia, chills or fever, palpitations, weight gain or loss, increased serum-cholesterol, agitation, abnormal dreams, confusion, arthralgia, myalgia, tinnitus, pruritus, dyspnoea, yawning, and rashes. Dose-related increases in blood pressure have also been noted in some patients.

Less common effects have included reversible increases in liver enzymes, orthostatic hypotension, syncope, arrhythmias, tachycardia, mucous membrane bleeding, ecchymosis, hallucinations, bruxism, muscle spasm, myoclonus, alopecia, altered taste, urinary retention, menorrhagia, angioedema, and photosensitivity reactions.

Convulsions, galactorrhoea, haemorrhage including gastrointestinal bleeding, anaphylaxis, hepatitis, erythema multiforme, Stevens-Johnson syndrome, ataxia, dysarthria, extrapyramidal disorders including psychomotor restlessness and akathisia, and activation of mania or hypomania have been reported rarely. Other rare adverse effects include blood dyscrasias such as agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, and thrombocytopenia, prolongation of the QT interval and torsade de pointes, ventricular tachycardia or fibrillation, rhabdomyolysis, delirium, pancreatitis, and pulmonary eosinophilia.

Aggressive behaviour has developed with venlafaxine treatment particularly at the start and when stopping therapy. Suicidal ideation has been reported, particularly in children (see under Effects on Mental State, p. 457.2).

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, symptoms such as sweating, dizziness, somnolence, ECG changes, cardiac arrhythmias, and seizures may be noted. Treatment of overdosage includes consideration of the use of activated charcoal if 7 mg/kg or more has been ingested and the patient presents within 1 hour; this should be followed by symptomatic and supportive therapy. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Effects on the endocrine system. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatraemia may be more likely to occur with serotonergic antidepressants such as venlafaxine than with other antidepressants; for further details, see under Fluoxetine p. 419.3.

Effects on the eyes. Acute angle-closure glaucoma developed in a 45-year-old woman 3 days after starting venlafaxine;[1] she recovered after iridotomy. In another case, a 35-year-old man presented with bilateral acute angle-closure glaucoma 10 days after starting venlafaxine.[2] The patient had also had visual disturbances while on mirtazapine and sertraline.

1. Ng B, *et al.* Venlafaxine and bilateral acute angle closure glaucoma. *Med J Aust* 2002; **176:** 241.
2. de Guzman MHP, *et al.* Bilateral acute angle closure caused by supraciliary effusions associated with venlafaxine intake. *Med J Aust* 2005; **182:** 121–2.

Effects on the hair. Hair loss has been described in 3 women given venlafaxine. The effect was noticed by the patients within a few weeks[1] to 5 months[2] after starting treatment. One patient who noticed hair loss within 1 week of starting venlafaxine had the same problem during previous fluoxetine treatment.[3] In all 3 cases, hair loss abated soon after stopping venlafaxine. In 2 cases hair regrowth was reported within a few weeks,[2,3] but the third report was unclear as to whether regrowth occurred.[1]

1. Pitchot W, Ansseau M. Venlafaxine-induced hair loss. *Am J Psychiatry* 2001; **158:** 1159–60.
2. Pereira CE, Goldman-Levine JD. Extended-release venlafaxine-induced alopecia. *Ann Pharmacother* 2007; **41:** 1084.
3. O'Bryan EC, Albanese RP. A case report of fluoxetine- and venlafaxine-induced hair loss. *Prim Care Companion J Clin Psychiatry* 2004; **6:** 181.

Effects on the liver. Acute hepatitis developed in a 44-year-old woman about 6 months after starting venlafaxine;[1] she recovered once venlafaxine was withdrawn. In another report,[2] acute hepatitis developed in a 78-year-old man about a month after venlafaxine was added to therapy. Again, symptoms resolved when the drug was stopped. Hepatitis was noted in a 60-year-old woman about a month after starting low-dose venlafaxine (75 mg daily); symptoms resolved when the drug was stopped and recurred on rechallenge.[3] Hepatitis has also been attributed to low-dose venlafaxine (37.5 mg daily) in a patient with chronic hepatitis B; other causes of hepatitis and relapse of viral hepatitis were excluded.[4]

For a report of hepatotoxicity in patients taking venlafaxine subsequent to an attempted overdose with sertraline, see p. 420.2.

1. Horsmans Y, *et al.* Venlaxafine-associated [sic] hepatitis. *Ann Intern Med* 1999; **130:** 944.
2. Cardona X, *et al.* Venlafaxine-associated hepatitis. *Ann Intern Med* 2000; **132:** 417.
3. Phillips BB, *et al.* Hepatitis associated with low-dose venlafaxine for postmenopausal vasomotor symptoms. *Ann Pharmacother* 2006; **40:** 323–7.
4. Sencan I, *et al.* Low-dose venlafaxine-associated liver toxicity in chronic hepatitis. *Ann Pharmacother* 2004; **38:** 352–3.

Effects on mental state. An expert working group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs and, in particular, the risk of suicidal behaviour in children; the safety of venlafaxine (another serotonergic antidepressant) was also considered. An interim report issued in September 2003 concluded that data from studies received by the CSM failed to show that venlafaxine was effective in the treatment of depressive illness in **children under 18 years old** and indicated that the risk of harmful outcome including self-harm and suicidal ideation was increased in those receiving venlafaxine when compared with placebo.[1] The CSM recommended that venlafaxine should not be used to treat depressive illness in children under 18 years old. Similar warnings have also been issued in Canada,[2] the EU,[3] and the USA. (The final report[4] of the CSM's expert working group was published in December 2004.)

The risk of suicide and suicide-related events with antidepressant treatment in **adults** including young adults is discussed under Fluoxetine, p. 420.2.

1. MHRA. Safety of venlafaxine in children and adolescents under 18 years in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 19th September, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019501.pdf (accessed 14/08/08)
2. Wyeth Canada. Important safety information regarding the use of Effexor (venlafaxine HCl) tablets and Effexor XR (venlafaxine HCl) capsules in children and adolescents (issued 10th September, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/effexor_hpc-cps-eng.pdf (accessed 14/08/08)
3. EMEA. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf (accessed 02/08/10)
4. Weller IVD. *Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)

Effects on the skin. A patient developed Stevens-Johnson syndrome 12 days after starting therapy with venlafaxine for recurrent depression.[1] She had also been taking several other drugs for at least 6 months. Symptoms resolved on withdrawal of all medication and treatment with an intravenous corticosteroid. Other adverse dermatological effects that have been described in patients given venlafaxine include psoriasiform palmoplantar keratoderma with subungual hyperkeratosis,[2] and photodistributed eruptive telangiectasia.[3]

1. Weiss NT, *et al.* A possible case of venlafaxine-induced Stevens-Johnson syndrome. *J Clin Psychiatry* 2004; **65:** 1431–3.
2. Dalle S, *et al.* Venlafaxine-associated psoriasiform palmoplantar keratoderma and subungual hyperkeratosis. *Br J Dermatol* 2006; **154:** 999–1000.
3. Vaccaro M, *et al.* Photodistributed eruptive telangiectasia: an uncommon adverse drug reaction to venlafaxine. *Br J Dermatol* 2007; **157:** 822–4.

Overdosage. Rare serious events including seizures and ECG changes[1-3] have occurred after venlafaxine overdoses; in some cases, death has ensued.[4,5] Symptoms suggestive of serotonin toxicity may also develop.[6,7]

Venlafaxine may not be as safe in overdose as some other serotonergic antidepressants. A review[8] of UK data recording the number of deaths due to acute poisoning by a single drug, with or without alcohol, found the number of fatalities per million prescriptions (the fatal toxicity index) was higher for venlafaxine than for other serotonergic antidepressants, and was similar to that for some of the less toxic tricyclic antidepressants.

1. White CM, *et al.* Seizure resulting from a venlafaxine overdose. *Ann Pharmacother* 1997; **31:** 178–80.
2. Coorey AN, Wenck DJ. Venlafaxine overdose. *Med J Aust* 1998; **168:** 523.
3. Blythe D, Hackett LP. Cardiovascular and neurological toxicity of venlafaxine. *Hum Exp Toxicol* 1999; **18:** 309–13.
4. Banham NDG. Fatal venlafaxine overdose. *Med J Aust* 1998; **169:** 445, 448.
5. Mazur JE, *et al.* Fatality related to a 30-g venlafaxine overdose. *Pharmacotherapy* 2003; **23:** 1668–72.
6. Oliver JJ, *et al.* Venlafaxine poisoning complicated by a late rise in creatine kinase: two case reports. *Hum Exp Toxicol* 2002; **21:** 463–6.
7. Whyte IM, *et al.* Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *Q J Med* 2003; **96:** 369–74.
8. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002; **325:** 1332–3.

Serotonin syndrome. The serotonin syndrome (p. 443.2) is most often due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug may cause the syndrome. One such case[1] was reported to have occurred in a 29-year-old woman who developed symptoms suggestive of serotonin syndrome 3 days after starting low-dose venlafaxine. However, this patient had been switched to venlafaxine the day after stopping imipramine treatment; it is usually recommended that at least 3 weeks should elapse after stopping imipramine before starting another drug with serotonergic properties.

1. Pan J-J, Shen WW. Serotonin syndrome induced by low-dose venlafaxine. *Ann Pharmacother* 2003; **37:** 209–11.

Precautions

Venlafaxine should not be used in patients with an identified very high risk of a serious ventricular arrhythmia or uncontrolled hypertension. Caution is advised in those with a recent history of myocardial infarction or whose condition might be exacerbated by an increase in heart rate. Due to the risk of dose-related increases in blood pressure, blood pressure measurement should be performed regularly during therapy. Measurement of serum-cholesterol levels should also be considered with long-term treatment.

Venlafaxine should be used with caution in patients with moderate to severe hepatic or renal impairment and dosage adjustment may be necessary. It should also be used with caution in patients with a history of epilepsy and avoided in those with unstable disease; it should be stopped in any

patient developing a seizure or if there is an increase in seizure frequency. Caution is also advised in patients with a history of bleeding disorders or of hypomania or mania. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Patients who develop a rash, urticaria, or related allergic reaction with venlafaxine should be advised to contact their doctor.

Patients should be closely monitored during early antidepressant therapy until a significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, venlafaxine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery. Patients, especially the elderly, should be warned of the risk of dizziness or unsteadiness due to orthostatic hypotension.

Symptoms reported on abrupt withdrawal or dose reduction of venlafaxine include fatigue, somnolence, headache, nausea, vomiting, anorexia, palpitations, dizziness, dry mouth, diarrhoea, insomnia, agitation, anxiety, nervousness, confusion, hypomania, paraesthesia, sweating, and vertigo. It is therefore recommended that venlafaxine should be withdrawn gradually and the patient monitored to minimise the risk of withdrawal reactions (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Abuse. A patient had an amfetamine-like "high" after taking crushed modified-release tablets of venlafaxine in doses of up to 3600 mg daily.[1] He continued to ingest increasing amounts of venlafaxine until a 4050-mg dose produced chest pain. On evaluation he had a raised pulse and blood pressure but these returned to normal within a few days.

1. Sattar SP, *et al.* A case of venlafaxine abuse. *N Engl J Med* 2003; **348:** 764–5.

Breast feeding. Licensed product information recommends that venlafaxine should not be used in women who are breast feeding.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine were both detected in breast milk in significant quantities in 3 women[1] and concentrations of desmethylvenlafaxine were measurable in their infants' plasma. In another study[2] by the same group the mean milk-to-plasma ratio in 6 breast-feeding women was calculated to be 2.5 for venlafaxine and 2.74 for *O*-desmethylvenlafaxine. Detectable plasma concentrations of venlafaxine were found only in 1 of 7 breast-fed infants while 4 had detectable *O*-desmethylvenlafaxine levels; no adverse effects were reported in the infants. Nonetheless, the authors recommended caution when giving venlafaxine to breast-feeding women particularly for those feeding premature or very young neonates. The distribution of venlafaxine into breast milk and the presence of *O*-desmethylvenlafaxine in the serum of a further 5 breast-fed infants has also been reported.[3,4] There were no detectable adverse effects in the infants, and the authors of 1 report[4] suggested that women being treated for postpartum depression should not be generally discouraged from breast feeding. A study[5] of a further 13 women and their breast-fed infants also found venlafaxine and desvenlafaxine in both breast milk and infant plasma. No adverse effects were seen in the infants.

It has been suggested that venlafaxine in breast milk might alleviate a withdrawal syndrome in the neonate (see Pregnancy, p. 458.2).

1. Ilett KF, *et al.* Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 1998; **45:** 459–62.
2. Ilett KF, *et al.* Distribution of venlafaxine and its *O*-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 2002; **53:** 17–22.
3. Hendrick V, *et al.* Venlafaxine and breast-feeding. *Am J Psychiatry* 2001; **158:** 2089–90.
4. Berle JO, *et al.* Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes. *J Clin Psychiatry* 2004; **65:** 1228–34.
5. Newport DJ, *et al.* Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *J Clin Psychiatry* 2009; **70:** 1304–10.

Children. Venlafaxine is associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, p. 455.2.

US licensed product information also refers to studies that suggest that venlafaxine may adversely affect weight and height changes in children. In particular, the difference between the real and the expected growth rate was larger for those children under 12 years of age than for older children.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies venlafaxine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Licensed product information recommends that venlafaxine should not be used during pregnancy unless clearly necessary.

In a study of 150 women who took venlafaxine in the first trimester of pregnancy there were 125 live births, 18 spontaneous abortions, 7 therapeutic abortions, and 2 reports of major malformations (hypospadias and neural tube defect with club foot).[1] Although the rate of spontaneous abortions was non-significantly higher in the venlafaxine group than in historical controls, the rate of major malformations was not greater than the baseline rate of 1 to 3%.

A neonatal withdrawal syndrome developed in the infant of a mother who had taken venlafaxine throughout her pregnancy;[2] symptoms included restlessness, hypertonia, irritability, and poor feeding. The infant recovered within 8 days. Seizures have been described in 2 neonates whose mothers were taking venlafaxine.[3] Lip smacking and extensor limb posturing began at 30 minutes of age in 1 case, and multifocal myoclonic seizures occurred at 24 hours of age in the other; both recovered and were well at 1 year of age. Serum-venlafaxine concentrations had not been measured and the authors were unsure whether the adverse effects in the neonates were due to withdrawal or toxicity. In a retrospective study[4] of women who had taken SSRIs or venlafaxine during the third trimester (9 had taken venlafaxine), there were reports of adverse effects on the CNS and respiratory tract in the neonates, such as abnormal movements, tonus abnormalities, irritability, insomnia, indrawing, apnoea/bradycardia, and tachypnoea. The signs usually appeared on the first day of life and lasted for about 3 days in full-term neonates and about 5 days in those born prematurely.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine are distributed into breast milk (see Breast Feeding, above), and it has been suggested that breast feeding might have helped to alleviate symptoms of a withdrawal syndrome in a neonate whose mother took venlafaxine throughout her pregnancy.[5]

1. Einarson A, *et al.* Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 2001; **158:** 1728–30.
2. de Moor RA, *et al.* Withdrawal symptoms in a neonate following exposure to venlafaxine during pregnancy. *Ned Tijdschr Geneeskd* 2003; **147:** 1370–2.
3. Pakalapati RK, *et al.* Neonatal seizures from in utero venlafaxine exposure. *J Paediatr Child Health* 2006; **42:** 737–8.
4. Ferreira E, *et al.* Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 2007; **119:** 52–9.
5. Koren G, *et al.* Can venlafaxine in breast milk attenuate the norepinephrine and serotonin reuptake neonatal withdrawal syndrome? *J Obstet Gynaecol Can* 2006; **28:** 299–301.

Renal impairment. The mean terminal disposition half-life of venlafaxine was prolonged from a mean of 3.8 hours in 18 healthy subjects to 5.8 hours in 12 patients with mild to moderate renal impairment (creatinine clearance 10 to 70 mL/minute) and 10.6 hours in patients requiring haemodialysis;[1] corresponding values for *O*-desmethylvenlafaxine, the active major metabolite of venlafaxine, were 11.8, 16.8, and 28.5 hours, respectively. Because of the large intersubject variability, the change in disposition for venlafaxine and its active metabolite was evident only in patients with a creatinine clearance of less than 30 mL/minute; drug clearance in these patients was reduced by about 55% and half-life more than doubled. It was calculated that for these patients half the usual daily dose could be given once daily.

Similar recommendations are made in licensed product information, see under Uses and Administration, p. 454.3.

1. Troy SM, *et al.* The effect of renal disease on the disposition of venlafaxine. *Clin Pharmacol Ther* 1994; **56:** 14–21.

Surgery. Serotonergic antidepressants such as venlafaxine may be associated with an increased risk of blood loss during surgery; for further details, see under Fluoxetine, p. 423.3.

Withdrawal. Withdrawal reactions may be more common with venlafaxine than with some other serotonergic antidepressants; for further details, see under Fluoxetine, p. 423.3. Withdrawal reactions may also be seen in neonates after maternal venlafaxine use, see under Pregnancy above.

Some cases[1-3] of withdrawal reactions to venlafaxine have been reported.

1. Anonymous. Venlafaxine withdrawal reactions. *Med J Aust* 1998; **169:** 91–2.
2. Johnson H, *et al.* Withdrawal reaction associated with venlafaxine. *BMJ* 1998; **317:** 787.
3. Khazaal Y. Mania after venlafaxine withdrawal in a patient with generalized anxiety disorder. *Ann Pharmacother* 2007; **41:** 359–60.

Interactions

Although different antidepressants have been used together under expert supervision in refractory cases of depression, adverse reactions including the *serotonin syndrome* (see p. 443.2) may occur; in its more severe form, serotonin syndrome can resemble neuroleptic malignant syndrome. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. Venlafaxine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with venlafaxine. At least 7 days should elapse between stopping venlafaxine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). For further details, see Antidepressants under Interactions of Phenelzine, p. 445.2. Adverse effects such as the serotonin syndrome may also occur when venlafaxine is given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Venlafaxine has occasionally been associated with bleeding disorders and other effects on the blood; caution is advised when giving venlafaxine with other drugs known to affect platelet function.

Although cimetidine inhibits the first-pass hepatic metabolism of venlafaxine, it has no effect on the active metabolite *O*-desmethylvenlafaxine, which is present in the plasma in much greater concentrations. Licensed product information therefore considers that when cimetidine and venlafaxine are used together, clinical monitoring may only be necessary in elderly patients and in those with hepatic impairment or pre-existing hypertension.

Conversion of venlafaxine to its equally active metabolite *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore the potential exists for drugs that inhibit or act as a substrate for this enzyme to affect plasma concentrations of venlafaxine and its active metabolite. However, the US product information indicates that, as the total amount of active compounds is unaffected, no dosage adjustment is usually necessary for venlafaxine. Venlafaxine is also metabolised by CYP3A4 to the less active metabolite *N*-desmethylvenlafaxine. This is a relatively minor pathway and the potential for clinically significant interactions between venlafaxine and CYP3A4 inhibitors is considered to be small. However, potent inhibitors of CYP3A4 or drugs that inhibit both CYP2D6 and CYP3A4 could significantly increase venlafaxine concentrations in patients who are poor CYP2D6 metabolisers; such combinations should therefore be used with caution.

Venlafaxine itself is considered to be a relatively weak inhibitor of CYP2D6.

Antiarrhythmics. Psychosis with raised serum concentrations of venlafaxine and its metabolite *O*-desmethylvenlafaxine developed when *propafenone* therapy was started in a 67-year-old woman. There was improvement when venlafaxine was stopped and restarted at a reduced dose; 50 mg daily was sufficient to maintain therapeutic serum concentrations.[1]

1. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone interaction. *Int J Psychiatry Med* 2001; **31:** 427–32.

Antibacterials. Tingling in the tip of the tongue, intense paraesthesia in the fingers, severe abdominal cramps, profuse diarrhoea, cold sweats, and uncontrolled shivering and tremor occurred when *co-amoxiclav* was started in a man taking venlafaxine.[1] The reaction lasted for about 6 hours. It occurred again 2 months later after a single dose of co-amoxiclav. The patient reported that he had taken co-amoxiclav in the past without any reaction at a time when he was not taking venlafaxine. The mechanism for an interaction between venlafaxine and co-amoxiclav causing this serotonin syndrome is unknown. The author also suggested that many patients must have taken this combination without adverse effect, and found no other reports.

Serotonin syndrome has been reported in an elderly patient taking venlafaxine, after 20 days of antibacterial treatment including *linezolid*.[2] In another report, serotonin syndrome developed 8 days after starting treatment with intravenous linezolid in a patient taking venlafaxine.[3] For advice regarding the use of linezolid with serotonergic antidepressants such as venlafaxine, see under Interactions of Fluoxetine, p. 424.1.

1. Connor H. Serotonin syndrome after single doses of co-amoxiclav during treatment with venlafaxine. *J R Soc Med* 2003; **96:** 233–4.
2. Jones SL, *et al.* Serotonin syndrome due to co-administration of linezolid and venlafaxine. *J Antimicrob Chemother* 2004; **54:** 289–90.
3. Bergeron L, *et al.* Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* 2005; **39:** 956–61.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p. 681.3).

Antipsychotics. For mention of neuroleptic malignant syndrome developing in patients who received venlafaxine with antipsychotics see under Interactions in Chlorpromazine, p. 1052.1.

Gastrointestinal drugs. Signs suggestive of the serotonin syndrome that occurred after intravenous *metoclopramide* were attributed to an interaction with venlafaxine.[1] The 32-year-old woman experienced confusion, agitation, generalised shaking, myoclonus, facial twitching, diaphoresis, horizontal nystagmus, and dilated pupils, that resolved within 2 days after stopping both drugs and treatment with diazepam.

1. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36:** 67–71.

Selegiline. Although it is generally recommended that venlafaxine should not be started for at least 14 days after stopping an MAOI, there is a report[1] of serotonin syndrome developing when a patient began venlafaxine treatment 15 days after stopping selegiline, an MAO type B inhibitor.

1. Gitlin MJ. Venlafaxine, monoamine oxidase inhibitors, and the serotonin syndrome. *J Clin Psychopharmacol* 1997; **17:** 66–7.

Pharmacokinetics

Venlafaxine is readily absorbed from the gastrointestinal tract. After oral doses it undergoes extensive first-pass metabolism in the liver mainly to the active metabolite *O*-desmethylvenlafaxine; formation of *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. The isoenzyme CYP3A4 is also involved in the metabolism of venlafaxine. Other metabolites include *N*-desmethylvenlafaxine and *N,O*-didesmethylvenlafaxine. Peak plasma concentrations of venlafaxine and *O*-desmethylvenlafaxine occur about 2 and 4 hours after a dose, respectively. Venlafaxine is 27% and *O*-desmethylvenlafaxine 30% bound to plasma proteins. The mean elimination half-life of venlafaxine and *O*-desmethylvenlafaxine is about 5 and 11 hours, respectively. Venlafaxine is excreted mainly in the urine, mainly in the form of its metabolites, either free or in conjugated form; about 2% is excreted in the faeces. Venlafaxine and *O*-desmethylvenlafaxine have been detected in amniotic fluid and umbilical cord blood, and are distributed into breast milk.

References.

1. Troy SM, *et al.* The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 1995; **35:** 404–9.
2. Troy SM, *et al.* Pharmacokinetics and effect of food on the bioavailability of orally administered venlafaxine. *J Clin Pharmacol* 1997; **37:** 954–61.
3. Ball SE, *et al.* Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *Br J Clin Pharmacol* 1997; **43:** 619–26.
4. McAlpine DE, *et al.* Cytochrome P450 2D6 genotype variation and venlafaxine dosage. *Mayo Clin Proc* 2007; **82:** 1065–8.

Pregnancy. Venlafaxine and its metabolite, *O*-desmethylvenlafaxine, have been detected in amniotic fluid[1,2] and umbilical cord blood.[1,3] For adverse effects that have occurred in neonates of women who were taking venlafaxine during the third trimester, see Pregnancy, under Precautions, p. 456.2.

1. Hostetter A, *et al.* Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry* 2000; **48:** 1032–4.
2. Loughhead AM, *et al.* Antidepressants in amniotic fluid: another route of fetal exposure. *Am J Psychiatry* 2006; **163:** 145–7.
3. Rampono J, *et al.* A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol* 2004; **7:** 329–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfaxin; Efexor; Elafax; Ganavax; Mezine; Pramina; Quilarex; Sesaren; Sunvex; Venlifax; ***Austral.***: Efexor; Elaxine; Venla; Venlexor; ***Austria***: Efectin; Venaxibene; Venlafab; ***Belg.***: Efexor; Vennaxa†; ***Braz.***: Alenthus; Efexor; Novidat; Venforin; Venlaxin; Venlift; ***Canad.***: Effexor; ***Chile***: Axone; Depurol; Efexor; Lafaxin†; Nervix; Norpilen; Senexon; Sentidol; Sesaren†; Subelan; Venlacross; Venlax; ***China***: Blossom (博乐欣); Efexor (怡诺思); ***Cz.***: Argofan; Convalemin; Depant; Efectin; Elify; Faxiprol; Lafaxon†; Mollome; Nisaxin†; Nopekar; Olwexya; Prefaxine†; Ranfaxiran†; Tifaxin; Velaxin; Venlafab†; Venlagamma†; ***Denm.***: Efexor; Effexor†; Lavenax†; Nopekar; Panofen; Velaxatin†; Venladima; Venlakato; Venlamed†; Venlapete; Venlapol; Venlathen; ***Fin.***: Efexor; ***Fr.***: Effexor; ***Ger.***: Trevilor; Venlagamma; Venlasan; ***Gr.***: Arvifax; Deprevix; Efaxin; Efetrin; Efexor; Elify; Melocin; Memomax-S; Norafexine; Norezor; Serosmine; Tudor; Velept; Velpine; Ven-Fax; Venaxol; Venlasan; Voxafen; Xadevil; Zacalen; ***Hong Kong***: Efexor; Velaxin; Venxor; ***Hung.***: Arixen; Efectin†; Falven; Faxiprol; Fobiven; Jarvis; Nopekar; Olwexya; Velaxin; Venlaxgen; Ventadepress; ***India***: Dalium; Envelaf; Faxiven; Flavix; Venlor; Vexor; ***Indon.***: Efexor; ***Irl.***: Efaxil; Efexor; Ireven; Tonpular; Vedixal; Velexor; Venex; Venixaf; Venlafex; Venlalic; Venlift†; Venlofex; Vensir; ***Israel***: Efexor; Venla; Viepax; ***Ital.***: Efexor; Faxine; Zarelis; ***Malaysia***: Efexor; Venxor; ***Mex.***: Benolaxe; Efexor; Lafaxven; Odven SBK; ***Neth.***: Efexor; Elbfaxin†; Hafaxin†; Jarvis; Kofaxin†; Symfaxin†; Tifaxin†; Vendep†; Venfalex; Venlabacher; Venlaburg†; Venladem†; Venladoz; Venlamyl; Venlanofi; Venlaraf†; Venlaran†; Venlasand; Venlatif; Venlatio†; Venlexor; ***Norw.***: Efexor; Venlix; ***NZ***: Efexor; ***Philipp.***: Efexor; Venlift; ***Pol.***: Alventa; Axyven; Efectin; Efevelon; Faxigen; Faxolet; Jarvis; Lafactin; Oriven; Prefaxine; Symfaxin; Tonpular; Velafax; Velaxin; Venlectine; ***Port.***: Afax; Bexalov; Desinax; Efexor; Genexin; Pracet; Tubernax; Vedixal; Velax; Venxin; Xapnev; Zarelix; ***Rus.***: Alventa (Алвента); Efectin (Эфектин); Efevelone (Эфевелон); Velafax (Велафакс); Velaxin (Велаксин); Venlaxor (Венлаксор); ***S.Afr.***: Efegen; Efexor; Illovex; Odiven; Venlor; ***Singapore***: Efexor; ViePax†; ***Spain***: Arafaxina; Conervin; Dislaven; Dobupal; Flaxen; Levest; Vandral; Venlabrain; Venlamylan; Venlapine; Zarelis; ***Swed.***: Efexor; ***Switz.***: Efexor; Venlax; ***Thai.***: Efexor; Valosine; ***Turk.***: Efexor; Venfecto; Veniba; ***UK***: Depefex; Efexor; Foraven; Politid; Tifaxin; Tonpular; Venaxx; Venlalic; Winfex; ***Ukr.***: Velaxin (Велаксин); Venlaxor (Венлаксор); ***USA***: Effexor; ***Venez.***: Efexor; Idoxen; Sesaren.

Pharmacopoeial Preparations
BP 2014: Prolonged-release Venlafaxine Capsules; Prolonged-release Venlafaxine Tablets; Venlafaxine Tablets;
USP 36: Venlafaxine Hydrochloride Extended-Release Capsules; Venlafaxine Tablets.

Vilazodone *(USAN, rINN)*

EMD-515259; Vilazodona; Vilazodonum; Вилазодон.
5-{4-[4-(5-Cyanoindol-3-yl)butyl]-1-piperazinyl}-2-benzofurancarboxamide.
$C_{26}H_{27}N_5O_2$=441.5
CAS — 163521-12-8.
UNII — S23902OOV3.

Vilazodone Hydrochloride *(USAN, rINNM)*

EMD-68843; Hidrocloruro de vilazodona; SB-659746A; Vilazodone, Chlorhydrate de; Vilazodoni Hydrochloridum; Вилазодона Гидрохлорид.
$C_{26}H_{27}N_5O_2$,HCl=478.0
CAS — 163521-08-2.
UNII — U8HTX2GK8J.

Profile

Vilazodone is a selective serotonin reuptake inhibitor (see Fluoxetine, p. 417.1) and a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the $5\text{-}HT_{1A}$ subtype. It is given orally as the hydrochloride in the treatment of depression (p. 398.1). The initial dose is 10 mg once daily for 7 days, followed by 20 mg once daily for another 7 days, then increased to the usual dose of 40 mg once daily; it should be taken with food.

Vilazodone is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4; the usual dose should be reduced to 20 mg once daily in patients taking potent CYP3A4 inhibitors (e.g. ketoconazole), and in those taking moderate CYP3A4 inhibitors (e.g. erythromycin) who have intolerable adverse effects. CYP3A4 inducers may reduce the plasma concentrations of vilazodone although this has not been evaluated.

Vilazodone should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

References.

1. Rickels K, *et al.* Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70:** 326–33.
2. Dawson LA, Watson JM. Vilazodone: a $5\text{-}HT_{1A}$ receptor agonist/serotonin transporter inhibitor for the treatment of affective disorders. *CNS Neurosci Ther* 2009; **15:** 107–17.
3. Khan A. Vilazodone, a novel dual-acting serotonergic antidepressant for managing major depression. *Expert Opin Invest Drugs* 2009; **18:** 1753–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Viibryd.

Viloxazine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de viloxazina; ICI-58834; Viloxazina, hidrocloruro de; Viloxazine, Chlorhydrate de; Viloxazini Hydrochloridum; Вилоксазина Гидрохлорид.
2-(2-Ethoxyphenoxymethyl)morpholine hydrochloride.
$C_{13}H_{19}NO_3$,HCl=273.8
CAS — 46817-91-8 (viloxazine); 35604-67-2 (viloxazine hydrochloride).
ATC — N06AX09.
ATC Vet — QN06AX09.
UNII — OQW30I1332.

Profile

Viloxazine is a bicyclic antidepressant. Like the tricyclic antidepressants (see Amitriptyline, p. 401.1), viloxazine is an inhibitor of the reuptake of noradrenaline; it may also enhance the release of serotonin from neuronal stores. However, it does not have marked antimuscarinic, cardiotoxic, or sedative properties.

Viloxazine hydrochloride has been given for the treatment of depression. It should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Vortioxetine *(USAN, pINN)*

Lu-AA21004; Vortioxetina; Vortioxétine; Vortioxetinum; Вортиоксетин.
1-{2-[(2,4-Dimethylphenyl)sulfanyl]phenyl}piperazine.
$C_{18}H_{22}N_2S$=298.4
CAS — 508233-74-7.
UNII — 3O2K1S3WQV.

Vortioxetine Hydrobromide *(USAN, pINNM)*

Hidrobromuro de vortioxetina; Vortioxétine, Bromhydrate de; Vortioxetini Hydrobromidum; Вортиоксетина Гидробромид.
$C_{18}H_{22}N_2S$,HBr=379.4
CAS — 960203-27-4.
UNII — TKS641KOAY.

Profile

Vortioxetine inhibits the reuptake of serotonin (5-HT; see Fluoxetine, p. 417.1) and is an antagonist at $5\text{-}HT_3$ and an agonist at $5\text{-}HT_{1A}$ receptors. It is given orally as the hydrobromide in the treatment of depression (p. 398.1). Doses are expressed in terms of the base; vortioxetine hydrobromide 12.7 mg is equivalent to about 10 mg of vortioxetine. The initial dose is the equivalent of 10 mg once daily, increased to 20 mg once daily if tolerated. A dose of 5 mg daily may be considered in patients who do not tolerate higher doses.

The metabolism of vortioxetine is mediated by the cytochrome P450 isoenzymes, mainly CYP2D6: the dose should be halved in patients taking potent CYP2D6 inhibitors, and should also not exceed 10 mg daily in known poor CYP2D6 metabolisers. Conversely, the dose of vortioxetine may be increased to a maximum of 3 times the original dose in those taking potent inducers of CYP isoenzymes for longer than 14 days.

Although vortioxetine may be stopped abruptly, transient withdrawal symptoms such as headache and muscle tension have been reported after abruptly stopping therapy. Patients taking 15 or 20 mg daily should reduce their dose of vortioxetine to 10 mg daily for 1 week before stopping.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Brintellix.

Antidiabetics

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This chapter describes diabetes mellitus (type 1, type 2, and gestational diabetes mellitus) and its management with antidiabetics, including oral antidiabetic drugs and insulin.

Antidiabetic Drug Groups

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors act by delaying the absorption of glucose from the gastrointestinal tract. They are generally used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Acarbose, p. 468.2
- Miglitol, p. 493.3
- Voglibose, p. 505.3

Amylin analogues

Amylin is a pancreatic peptide hormone, thought to play a role in the regulation of glucose homoeostasis. The amylin analogue, pramlintide, slows the rate of gastric emptying, prevents the postprandial rise in glucagon concentrations, and reduces appetite. It is used with insulin in the management of both type 1 and type 2 diabetes mellitus.

Described in this chapter are
- Pramlintide, p. 496.3

Biguanides

Biguanide antidiabetics may have several actions, but are considered to act mainly by decreasing hepatic gluconeogenesis and increasing peripheral utilisation of glucose. Metformin is commonly used in type 2 diabetes mellitus, especially in overweight patients. Biguanide antidiabetics are described in more detail on p. 469.3.

Described in this chapter are
- Buformin, p. 471.2
- Metformin, p. 491.1
- Phenformin, p. 495.1

Dipeptidylpeptidase-4 inhibitors

Dipeptidylpeptidase-4 inhibitors (gliptins) impair the degradation of incretin hormones, which play a role in glucose homoeostasis by increasing insulin synthesis and release, and reducing glucagon secretion. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Alogliptin, p. 469.2
- Linagliptin, p. 490.1
- Saxagliptin, p. 501.2
- Sitagliptin, p. 502.1
- Teneligliptin, p. 504.1
- Vildagliptin, p. 504.3

Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 receptor agonists (incretin mimetics) enhance insulin secretion in the presence of raised glucose concentrations; they also suppress inappropriate glucagon secretion, and slow gastric emptying. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Exenatide, p. 473.1
- Liraglutide, p. 490.2
- Lixisenatide, p. 491.1

Insulin

Insulin therapy is essential in the management of type 1 diabetes mellitus, and may be used in some patients with type 2 disease. Human insulin (produced by modification of porcine insulin or by recombinant DNA technology) has generally replaced bovine and unmodified porcine insulins. Insulin analogues are also in use.

Described in this chapter are
- Insulin, p. 479.3

Meglitinides

Meglitinide antidiabetics (glinides), like sulfonylureas (p. 460.2), stimulate the release of insulin from the pancreas by the inhibition of ATP-sensitive potassium channels. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Mitiglinide, p. 493.3
- Nateglinide, p. 494.1
- Repaglinide, p. 497.2

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 inhibitor antidiabetics enhance urinary excretion of glucose by suppressing renal glucose reabsorption. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Canagliflozin, p. 471.2
- Dapagliflozin, p. 472.2

Sulfonylureas

Sulfonylurea antidiabetics stimulate the release of insulin from the pancreas, by inhibition of ATP-sensitive potassium channels. They are used in the management of type 2 diabetes mellitus. Sulfonylurea antidiabetics are described in more detail on p. 502.3.

Described in this chapter are
- Acetohexamide, p. 469.2
- Carbutamide, p. 471.3
- Chlorpropamide, p. 472.1
- Glibenclamide, p. 474.1
- Glibornuride, p. 474.3
- Gliclazide, p. 474.3
- Glimepiride, p. 475.2
- Glipizide, p. 476.1
- Gliquidone, p. 476.3
- Glisentide, p. 476.3
- Glyclopyramide, p. 479.1
- Glycyclamide, p. 479.1
- Tolazamide, p. 504.1
- Tolbutamide, p. 504.2

Thiazolidinediones

Thiazolidinedione antidiabetics (glitazones) act as selective agonists at the peroxisome proliferator-activated receptor gamma (PPARγ) to improve insulin sensitivity in adipose tissue, skeletal muscle, and the liver. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Pioglitazone, p. 495.1
- Rosiglitazone, p. 498.3

Diabetes mellitus

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity, or a combination of both factors. It is characterised by hyperglycaemia. As the disease progresses tissue or vascular damage ensues leading to severe complications such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and foot ulceration.

Diabetes mellitus may be categorised into several types but the two major types are type 1 (insulin-dependent diabetes mellitus; IDDM) and type 2 (non-insulin-dependent diabetes mellitus; NIDDM). The term juvenile-onset diabetes has sometimes been used for type 1 and maturity-onset diabetes for type 2.

Type 1 diabetes mellitus is present in patients who have little or no endogenous insulin secretory capacity and who therefore require exogenous insulin therapy for survival. This form of the disease has an auto-immune basis in most cases, and usually develops before adulthood. The associated hypoinsulinaemia and hyperglucagonaemia put such patients at risk of ketosis and ketoacidosis.

In **type 2 diabetes mellitus**, insulin secretion may appear normal or even excessive (and type 2 patients are thus less prone to ketosis) but it is insufficient to compensate for insulin resistance (p. 489.1). Obesity is present in the majority of type 2 patients; non-obese patients tend to have low insulin secretory capacity (although not as low as in type 1 diabetes) rather than appreciable insulin resistance. Type 2 diabetes typically develops later in life; it is rare in adolescents and children but is becoming more prevalent, related in part to the increase in obesity occurring particularly in westernised countries. It is closely associated with cardiovascular disease, and the 2 may arise from a common antecedent described as the metabolic syndrome.

See below for information on:
- Diagnosis of Diabetes Mellitus, p. 460.3
- Management of Diabetes Mellitus, p. 461.1
- Prevention of Diabetes Mellitus, p. 462.3
- Monitoring of Therapy in Diabetes Mellitus, p. 463.1
- Diabetes Mellitus and Pregnancy, p. 463.3
- Gestational Diabetes Mellitus, p. 464.1
- Diabetes Mellitus in Surgery or Critical Illness p. 464.2

Diagnosis of diabetes mellitus

Diagnosis is based upon blood-glucose concentrations or glycated haemoglobin (HbA_{1c}) exceeding set values under specified conditions. Patients with abnormal blood-glucose concentrations that do not reach the defined threshold for overt diabetes may be considered to have *impaired glucose tolerance (IGT)* or *impaired fasting glucose (IFG)*, which are risk factors for developing diabetes and cardiovascular disease.[1,2] The term *pre-diabetes* has been applied to IGT and IFG, but its use is discouraged by WHO.[1] Venous plasma glucose measurement is advocated as the preferred method for diagnostic blood-glucose testing. Capillary plasma glucose may still be reported in areas where only capillary sampling is available; venous and capillary samples will give the same result in the fasting state, but non-fasting glucose concentrations are higher in capillary samples than venous samples. Glucose results in whole blood can differ from those in plasma, depending on various factors, and the conversion of figures from whole blood glucose to plasma glucose can therefore be problematic.[1] Diagnosis can be confirmed using the *oral glucose tolerance test* (OGTT).[1] This test consists of a 12-hour fast followed by measurement of the fasting plasma-glucose concentration 10 minutes before the administration of a 75-g oral glucose load (in children 1.75 g/kg up to a maximum of 75 g), and further measurement of the plasma-glucose concentration 2 hours later.[3] There has been some confusion at an international level as to whether the glucose load should be 75 g of the anhydrous form or the monohydrate. Sources at WHO have therefore suggested that the form should be standardised as 75 g of anhydrous glucose (anhydrous dextrose), which would be equivalent to 82.5 g of the monohydrate (Glucose BP; dextrose monohydrate).[4]

Measurement of HbA_{1c} had not been recommended for routine diagnosis because of a lack of global standardisation and uncertainty about diagnostic thresholds.[1] However, this situation has been reviewed because of the development of a new reference method for standardised measurements (see under Monitoring of Therapy, p. 463.1) and growing evidence of a relationship between HbA_{1c} and long-term complications of diabetes, particularly retinopathy. An international expert committee[5] suggested that in non-pregnant individuals, diabetes should be diagnosed when HbA_{1c} is $\geq 6.5\%$; diagnosis should be confirmed with a repeat HbA_{1c} test unless clinical symptoms and glucose concentrations above 11.1 mmol/litre are present. The committee also considered that individuals with measures of ≥ 6.0 to $< 6.5\%$ were likely to be at high risk of progression to diabetes. The measurement of HbA_{1c} has therefore been incorporated into recommendations for diagnosis, but WHO points out that it is not available in many parts of the world and that results may be affected by a range of factors including haemoglobinopathies, certain anaemias, and disorders that affect red cell turnover such as malaria.[6]

The following diagnostic criteria have been recommended, although there are some slight differences between those of WHO[1,6] and the American Diabetes Association.[2]

Diabetes mellitus:
- classic symptoms of hyperglycaemia or hyperglycaemic crisis (including increased thirst and urine volume, and

unexplained weight loss), plus a random venous plasma glucose ≥ 11.1 mmol/litre[2]
or
- in the absence of symptoms and unequivocal hyperglycaemia, the following diagnostic results must be confirmed on a subsequent day:
  - fasting venous plasma glucose ≥ 7.0 mmol/litre[1,2] (the corresponding value for capillary plasma glucose is 7.0 mmol/litre[7])
    or
  - plasma glucose ≥ 11.1 mmol/litre after an OGTT[1,2] (the corresponding value for capillary plasma glucose is 12.2 mmol/litre[7])
    or
  - HbA_{1c} of ≥ 6.5%[2,6]

Impaired glucose tolerance (IGT):
- fasting venous plasma glucose < 7.0 mmol/litre *and* plasma glucose ≥ 7.8 mmol/litre to < 11.1 mmol/litre after an OGTT[1]
  or
- venous plasma glucose 7.8 to 11.0 mmol/litre after an OGTT[2]

Impaired fasting glucose (IFG):
- fasting venous plasma glucose 6.1 to 6.9 mmol/litre *and* (if measured) < 7.8 mmol/litre after an OGTT[1]
  or
- fasting venous plasma glucose 5.6 to 6.9 mmol/litre[2]

Raised HbA_{1c} indicating an increased risk of progression to diabetes:
- HbA_{1c} of 5.7 to 6.4%[2]

Other indicators, such as measurement of autoantibodies (to insulin or islet cells, for example) are not routinely used for diagnosis.

Once the presence of diabetes has been confirmed the distinction between type 1 and type 2 is made on clinical grounds.

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Management of diabetes mellitus

Diet, exercise, and the appropriate use of antidiabetic drugs including insulin, are all important aspects of the long-term management of diabetes mellitus. The main aims of management are to optimise glycaemic control and to reduce the risk of developing complications (see also Diabetic Complications, p. 464.2). For the management of diabetes mellitus in more specific groups, see also Diabetes Mellitus and Pregnancy, p. 463.3, Gestational Diabetes Mellitus, p. 464.1, and Diabetes Mellitus in Surgery or Critical Illness, p. 464.2.

DIETARY MODIFICATION. Dietary control is important in both type 1 and type 2 diabetes.[1-6] The goals of dietary modification are to maintain glucose concentrations in the normal range or as close to normal as possible, and a lipid and lipoprotein profile and blood pressure that reduce the risk of macrovascular disease. Correction of obesity is desirable in all patients, and weight loss in patients with type 2 diabetes can decrease insulin resistance, improve glycaemic and lipid measures, and reduce blood pressure. The influence of diet on diabetes is such that all diabetic patients need to be aware of the composition of foods and to be able to make adjustments to their diet, especially to counteract treatment-induced hypoglycaemia. However, neither protein restriction nor very low calorie diets are recommended.[4] A high fibre intake may lower blood-glucose concentrations and additional fibre is sometimes taken in the form of guar gum (see p. 479.2). Weight loss medication may be a useful adjunct to lifestyle changes in the management of overweight patients with type 2 diabetes.[4] There is some evidence that fluoxetine, orlistat, and sibutramine can achieve modest weight loss, and that fluoxetine and orlistat may contribute to a reduction in glycated haemoglobin, but long-term effects remain uncertain.[7] Some patients may be suitable candidates for bariatric surgery.[1,4]

EXERCISE. All diabetic patients should be encouraged to exercise, according to their age and physical capability.[1-3,5,6,8] Exercise improves carbohydrate metabolism, insulin sensitivity,[9] and cardiovascular function.[10] Small reductions in glycated haemoglobin (HbA_{1c}) can occur with exercise,[11,12] and a combination of aerobic and resistance training might be more effective than either alone.[13] It is also a useful component of any weight reduction programme although diet may be more effective in promoting weight loss and metabolic control.[10]

ORAL ANTIDIABETICS. For the majority of patients with *type 2* diabetes, diet and exercise are usually insufficient to control their disease in the long term, and the addition of an oral antidiabetic (oral hypoglycaemic) is needed to maintain glycaemic goals. Traditionally, patients with type 2 diabetes have been started on oral therapy after a suitable trial period of dietary modification and increased physical activity[2,6] (usually at least 3 months). The introduction and adjustment of drug therapy must be individualised, balancing the potential long-term benefits against other factors such as adverse effects and ease of use. The progressive nature of type 2 diabetes also means that many patients will eventually require combination oral therapy, and possibly the addition of insulin.[14] (The different antidiabetic drug groups are outlined p. 458.1.)

- Most patients with type 2 diabetes are overweight, and are preferably treated with the **biguanide** metformin.[5,6,14] It is generally well tolerated, does not cause hypoglycaemia on its own, and has either no effect on weight or promotes modest weight loss. However, it should not be used in patients with renal impairment in whom it has a rare tendency to cause lactic acidosis.[14] Although drug therapy is not normally not given in type 2 diabetes until diet and exercise have failed, a European/American consensus statement expressed the view that this generally occurred, and recommended that metformin be started, with lifestyle interventions, at diagnosis.[14]
- A **sulfonylurea** may be considered as an alternative for first-line oral monotherapy of type 2 diabetes. They are generally used in patients who are not overweight, when metformin is not tolerated or is contra-indicated, or if a rapid response is needed because of hyperglycaemic symptoms.[6] Sulfonylureas have a similar efficacy to metformin in terms of blood-glucose control, but can cause hypoglycaemia and are commonly associated with weight gain.[14] Chlorpropamide and glibenclamide have long half-lives and hence an increased tendency to cause hypoglycaemia, although a large study[15] reported that hypoglycaemic episodes were less frequent with chlorpropamide than glibenclamide. Nevertheless, shorter-acting sulfonylureas, such as gliclazide, glimepiride, and glipizide, are generally preferred.[14]
  A sulfonylurea may be added to therapy when glycaemic control is inadequate with metformin alone.[6,14] Alarming evidence[16] of an increased risk of death in patients enrolled in the UK Prospective Diabetes Study (UKPDS) given intensive therapy with metformin plus a sulfonylurea was not borne out by further analysis, and this combination is widely used (see also Metformin under Interactions of Sulfonylureas, p. 503.3).

Although other oral antidiabetics are often licensed for monotherapy of type 2 diabetes, their use is generally recommended when metformin and sulfonylureas are not sufficiently effective or cannot be used.

A **thiazolidinedione** may be added to either metformin or a sulfonylurea when a combination of these two is not feasible. Although initiation or intensification of insulin therapy is usually preferred to oral triple therapy,[14] adding a thiazolidinedione to both metformin and a sulfonylurea, may be considered when insulin would not be a suitable option.[6] Thiazolidinediones may cause weight gain, as well as fluid retention and exacerbation of heart failure, and they can increase the risk of bone fracture in women.[14,17] Although there is some evidence that pioglitazone may have beneficial effects on cardiovascular outcomes, risks may actually be increased with rosiglitazone (see Effects on the Cardiovascular System, p. 499.3) and the American Diabetes Association has advised against the use of this thiazolidinedione.[14]

- **Meglitinides** have a similar mechanism of action to sulfonylureas and are often used as alternatives. Repaglinide is almost as effective as metformin or the sulfonylureas, but nateglinide is considered to be somewhat less effective. The meglitinides are also associated with weight gain, but cause hypoglycaemia less frequently.[14] Their rapid onset and shorter duration of action may be advantageous in patients with erratic meal patterns.[6,17]
- The **dipeptidylpeptidase-4 (DPP-4) inhibitors** saxagliptin, sitagliptin, and vildagliptin, belong to a relatively new group of oral antidiabetics. They appear to be slightly less effective than other antidiabetics for glycaemic control,[18] but long-term comparative studies of efficacy and safety are lacking.[19] DPP-4 inhibitors may be added to either metformin or a sulfonylurea when a combination of these two is not appropriate.[6] Sitagliptin may be added to both metformin and a sulfonylurea when insulin would not be suitable. A DPP-4 inhibitor may be preferable to a thiazolidinedione if such therapy would be inappropriate.[6] DPP-4 inhibitors do not have a significant effect on weight, or cause hypoglycaemia when given alone.[14]
- The effects of **alpha-glucosidase inhibitors** are limited to reducing the rate of digestion and absorption of carbohydrates, and they are less effective than metformin and sulfonylureas.[14] They do not cause weight gain or hypoglycaemia, but adverse gastrointestinal effects can limit their use.[14,17] Acarbose may be considered as add-on therapy,[2] or for patients unable to use other oral antidiabetics.[6]

There is increasing interest in the use of oral antidiabetics as potential adjuncts to insulin therapy in children and adolescents with *type 1* diabetes. Drugs that have been tried include metformin and thiazolidinediones, which improve insulin sensitivity, and acarbose, as it alters carbohydrate absorption.[20] However, such therapy is not established and further research is needed.[3]

INSULIN THERAPY. In general, as *type 2* diabetes progresses, the majority of patients need multiple therapies to achieve glycaemic control.[21] Those who cannot be controlled adequately by oral drug therapy and diet need insulin either in addition to, or in place of, oral therapy. However, as insulin therapy is associated with more hypoglycaemic episodes and a greater tendency to weight gain, it remains reasonable to begin with oral therapy in type 2 diabetes before proceeding to insulin.[22] When insulin is added to oral treatment, metformin is generally continued.[6] Although some suggest that sulfonylureas may be continued and reviewed if hypoglycaemia occurs,[6] others advise that both sulfonylureas and meglitinides should be stopped (or tapered then stopped) when insulin is started.[14] The combination of insulin with a thiazolidinedione is generally avoided because it increases the risk of fluid retention and heart failure; nevertheless, UK guidelines suggest that the combination of insulin with pioglitazone may be considered in patients who previously had a marked response to a thiazolidinedione, or whose blood glucose is inadequately controlled on high-dose insulin.[6] Acarbose may also be continued when insulin is started.[6] Therapy is often started with basal insulin, given as a long-acting insulin analogue (such as insulin detemir or glargine) or intermediate-acting isophane insulin.[2,6,14] Combination of a single isophane insulin injection at bedtime (morning injection is less effective) with oral hypoglycaemics (either a sulfonylurea, metformin, or both) is as effective as insulin alone, and if metformin is used, is associated with less weight gain.[23] If HbA_{1c} is particularly high a biphasic insulin may be given twice daily.[2,6] Alternatively, multiple-injection regimens (basal insulin plus mealtime injections) may be used where blood glucose control is suboptimal or mealtime flexibility is desired.[2,6,14]

While insulin may not be a necessary part of the management of type 2 diabetes, it is essential in the treatment of patients with *type 1*, since they have little or no endogenous insulin secretory capacity. The aim of insulin therapy is to achieve the best possible control of blood-glucose concentrations, in order to reduce long-term complications of diabetes, without the risk of the hypoglycaemia that can occur if too fine a degree of control is attempted. The choice of insulin regimen will be influenced by several factors including age, lifestyle, patient preference, and metabolic targets. Many patients with type 1 diabetes have a temporary improvement in pancreatic beta-cell function soon after starting insulin treatment. This produces a period of partial remission known as the honeymoon phase, during which a small dose of insulin (0.5 units/kg or less daily) is sufficient to maintain good control.[3,24,25] However, as beta-cell destruction continues the dose of insulin needs to be increased to avoid hyperglycaemia;[24] insulin requirements also increase with growth during childhood, particularly during puberty.[24,25] Insulin doses are adjusted according to food intake, exercise, blood glucose monitoring, hypoglycaemic episodes, and HbA_{1c} measures[3,24,25] (see also Monitoring of Therapy, p. 463.1). Dosage schedules make use of the varying durations of action of insulin and insulin analogues.[3,24,25] One, two, or three injections daily of biphasic insulin may be suitable. Increasingly, however, basal-bolus regimens are advocated to improve glycaemic control. These regimens combine an intermediate- or long-acting basal insulin (usually at bedtime or twice daily) with multiple doses of a short- or rapid-acting insulin given before meals and snacks. Continuous subcutaneous insulin infusion therapy with mealtime boluses is a suitable alternative to multiple daily injections for a growing number of patients (for further details, see Intensive Administration Regimens under Uses of Insulin, p. 482.3). A rapid-acting insulin analogue given shortly after meals may be useful in very young children, to better match insulin dosing with erratic food intake.

OTHER DRUG TREATMENTS. Other less well established drugs may also be tried in the management of diabetes mellitus,

particularly when conventional therapy has proved unsuccessful.

- Addition of the **amylin analogue** pramlintide to insulin therapy can reduce postprandial hyperglycaemia and improve glycaemic control in patients with type 1 and type 2 diabetes.[14,17,26] It also contributes to weight loss, in contrast to the weight gain that usually occurs in patients treated with insulin. Like insulin, pramlintide is given subcutaneously, and it can increase the risk of insulin-induced hypoglycaemia.
- The glucagon-like peptide 1 (GLP-1) receptor agonist and **incretin mimic** exenatide may be added to oral antidiabetic treatment of type 2 diabetes.[6,14] As well as improving glycaemic control, it can contribute to weight loss, but must be given subcutaneously.[14] Hypoglycaemia can occur, particularly when exenatide is used with a sulfonylurea.[17,18] Liraglutide[17,18] is another GLP-1 agonist licensed to treat type 2 diabetes mellitus with other oral antidiabetics.
- The **sodium-glucose co-transporter 2 inhibitor**, dapagliflozin, enhances the urinary excretion of glucose by suppressing renal glucose reabsorption and is used in type 2 diabetes. It improves glycaemic control and can contribute to weight loss, and may be used as monotherapy or with other oral antidiabetics or insulin.[27-29] Similarly, canagliflozin may be used for the management of diabetes.[30]
- Colesevelam, an oral **bile-acid sequestrant**, may be added to metformin, a sulfonylurea, or insulin therapy in type 2 diabetes and may be of additional benefit in patients who also have hyperlipidaemia. It can enhance the reduction in HbA_{1c}, although the mechanism by which it does this is still unclear. Colesevelam is reported to have little effect on weight gain in diabetic patients.[31]
- The **dopamine agonist** bromocriptine may improve glycaemic control when used as an adjunctive therapy in type 2 diabetes.[32]
- There is some evidence that adjunctive supplementation with the **trace element** chromium may improve glycaemic control in type 2 diabetes.[33,34] However, a systematic review[34] found the quality of many studies to be poor, and analysis was hampered by the differences among chromium formulations. Long-term safety and efficacy have not been established. There are some reports of improved insulin sensitivity after treatment with the **vanadium** salt, vanadyl sulfate, in type 2 diabetes.[35,36]

PANCREATIC TRANSPLANTATION. Transplantation of the whole pancreas in patients with type 1 diabetes poorly controlled by insulin therapy has led to insulin independence, and has usually been carried out with kidney transplantation (see also Pancreatic Transplantation, p. 1942.1).[37] Transplantation of pancreatic islet cells has been developed as an alternative. Since the introduction of the so-called 'Edmonton Protocol'[38] and related regimens for immunosuppression, and improvements in techniques for harvesting and preparing islet cells, more experienced centres are now reporting some success in achieving insulin independence.[37] However, at present successful patients exchange life-long insulin therapy for life-long immunosuppression. The induction of tolerance, less toxic immunosuppression, and enhanced islet engraftment remain the focus of investigation.[39,40] Results in *animals* have suggested that a reasonable degree of glycaemic control may be achievable long term without immunosuppression, using a vascularised 'artificial pancreas' containing allogeneic or even xenogeneic islet cells.[41] Islet cell replacement and regeneration is another area of research.[42] *Haematopoietic stem cell transplantation* is also under investigation, and insulin independence has been reported in a small number of patients.[43]

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Prevention of diabetes mellitus. Because overt diabetes is the culmination of a prolonged process, methods to delay or prevent its development are being investigated, either by modifying risk factors in populations or groups, or by targeting individuals thought to be at high risk. Various strategies are under investigation to prevent the onset or progression of **type 1 diabetes**.[1,2] Antigen-specific tolerance is being studied using oral or intranasal insulin in individuals at risk, such as first- and second-degree relatives of patients with type 1 diabetes, although some evidence suggests that such a strategy might be useful only in particular subgroups of subjects. The use of non-specific immunomodulators has also been tried, but studies using nicotinamide or BCG vaccine have failed to show benefit. The role of early exposure to cow's milk protein in the diet, as a risk factor in the development of type 1 diabetes in infants at risk, is also under investigation. In patients with recent-onset type 1 diabetes, similar approaches are being studied in an attempt to prevent further pancreatic beta cell loss. There have been some positive results in the stimulation of immune tolerance using treatments based on heat shock protein and glutamic acid decarboxylase. Results from studies of anti-CD3 monoclonal antibodies[1,2] and the anti-CD20 antibody rituximab[3] are also of interest. There has been some success with immunosuppressants such as ciclosporin, but their use is limited by concerns about toxicity.[1,2]

Preventive strategies for **insulin resistance** and **type 2 diabetes** have tended to focus on weight loss, dietary modification, and exercise.[4,5] Smoking is also a known risk factor for type 2 diabetes,[6,7] although smoking cessation may itself lead to a higher short-term risk of the condition and should be coupled with strategies for diabetes prevention and early detection.[7]

Prophylactic drug therapy may also be possible. A systematic review concluded that there was good evidence for a reduced incidence of diabetes in patients treated with metformin, acarbose, or orlistat, although the attrition rates were high with orlistat; evidence of benefit from statins, oestrogen, and various antihypertensive drugs was more equivocal. It was considered likely that some of the benefits were indirect, due to drug-induced weight loss, and in no case was the benefit definitive enough that the drug could be recommended for diabetes prevention.[8] Recommendations for the prevention or delay of type 2 diabetes in individuals with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or a raised glycated haemoglobin (HbA_{1c}) suggest that although drug therapy should not be routinely used, metformin may be considered for those at highest risk for developing diabetes especially if they demonstrate progression of hyperglycaemia despite life style intervention.[9]

There are limited data to support the use of other drugs. Some suggest that acarbose may also be worth considering, while orlistat might be useful in obese patients.[5] Thiazolidinediones have been studied and rosiglitazone was found to reduce the incidence of type 2 diabetes in patients with IGT or IFG,[10] but the benefit was not sustained after the drug was stopped.[11] Pioglitazone has also been reported to reduce the risk of progression to type 2 diabetes, but to cause significant weight gain and oedema.[12]

There has also been interest in the effects of ACE inhibitors and angiotensin II receptor antagonists. In large studies that had mainly measured cardiovascular outcomes in patients with cardiovascular disease, secondary analyses showed reduced rates of new-onset diabetes,[13,14] suggesting that these drugs might have a potential role in preventing the onset of diabetes in patients at risk. However, ramipril did not prevent diabetes when it was studied over a median of 3 years in patients with IGT or IFG, and no history of cardiovascular disease.[15] Another study found a small reduction in the incidence of diabetes with the use of valsartan in patients with IGT.[16]

Screening for IGT, IFG, raised HbA_{1c}, and diabetes has been encouraged, particularly for those patients with risk factors.[9,17]

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Monitoring of therapy in diabetes mellitus. Monitoring of therapy is an integral part of the management of all diabetic patients.

Many patients monitor their **blood-glucose** concentrations regularly at home, and this is essential for those on intensified insulin regimens when tight control is required. Self-monitoring facilitates the detection of hyper- and hypoglycaemia, and can be used to guide insulin dose adjustment relative to meals and exercise.[1-3]

The value of self-monitoring of blood-glucose concentrations in patients who are not using insulin is less clear, and the optimal frequency and timing of self-monitoring in these patients has not been established.[1] It may be useful for providing information on hypoglycaemia associated with oral antidiabetics, to assess changes in glucose control when medications and lifestyle are altered, and to monitor changes during intercurrent illness.[4] However, it may have only a modest influence on improving long-term glycaemic control.[5]

Patients use a blood glucose meter to measure glucose concentrations in capillary blood taken from a finger prick. Frequency and timing must be individualised, but several tests are usually spread throughout the day.[1,3] Continuous glucose monitoring uses a subcutaneous sensor to measure interstitial glucose, which correlates well with plasma glucose.[1] These monitors can alert the user to impending episodes of hyper- or hypoglycaemia and provide additional data on the patterns of glucose change over time, which can be used to guide insulin dose adjustment and improve long-term glycated haemoglobin (HbA_{1c}) control. However, self-testing of capillary blood is still necessary for calibrating these devices and making acute treatment decisions.[1,6,7] Non-invasive glucose sensors have been developed, based on a range of technologies, but various shortcomings mean that few, if any, are available for clinical use.[7] Detection of urinary glucose has generally been superseded by the monitoring of blood glucose. However, as long as results are interpreted correctly, and the limitations understood, urine glucose monitoring can be a useful alternative where blood glucose testing is not possible.[8] For further information on glucose tests, see p. 2516.3.

For adequate diabetic control, various recommendations have been made for capillary blood-glucose targets, usually measured preprandially (in a fasting state) and postprandially (at the usual glucose peak 1 to 2 hours after the start of a meal).

- In the UK,[2] recommended goals for *adults* are a preprandial concentration within the range of 4.0 to 7.0 mmol/litre, and a postprandial concentration of less than 9.0 mmol/litre.
  In the USA,[1] slightly higher concentrations are considered acceptable at 3.9 to 7.2 mmol/litre preprandially, and less than 10.0 mmol/litre postprandially.
  Tighter recommendations have been made by the International Diabetes Federation (IDF),[9] which advocates lowering glucose measures to as near as normal as is safely possible, suggesting targets of 5.5 mmol/litre preprandially and 7.8 mmol/litre postprandially.
- Goals for *children* differ from those for adults. Although it would be ideal to achieve glucose control as near to normal as possible, young children have limited hypoglycaemic awareness and are at risk of permanent cognitive impairment after episodes of severe hypoglycaemia.[1]
  In the UK[2] recommended goals are preprandial concentrations of 4.0 to 8.0 mmol/litre and less than 10.0 mmol/litre postprandially.
  Guidance in the USA[1] advocates age-specific preprandial goals of 5.6 to 10.0 mmol/litre for children up to 6 years of age, 5.0 to 10.0 mmol/litre for those aged 6 to 12 years, and 5.0 to 7.2 mmol/litre for those aged 13 to 19 years.
  US guidance also recommends bedtime or overnight blood-glucose goals of 6.1 to 11.1 mmol/litre, 5.6 to 10.0 mmol/litre, and 5.0 to 8.3 mmol/litre, respectively, for these same age groups. It also suggests that postprandial measures should be monitored when there is a discrepancy between preprandial results and HbA_{1c} values, and to help assess glycaemia in children and adolescents on basal-bolus insulin regimens.
  The International Society for Pediatric and Adolescent Diabetes (ISPAD)[3] recommends 5.0 to 8.0 mmol/litre preprandially and 5.0 to 10.0 mmol/litre postprandially, and suggests a bedtime target of 6.7 to 10.0 mmol/litre and a nocturnal target of 4.5 to 9.0 mmol/litre.

Diabetic clinics also measure the degree of haemoglobin glycation (**HbA_{1c}**) as an indicator of longer term blood-glucose control and hence the risk of complications. Testing is generally recommended at least twice each year in patients meeting treatment goals, and more frequently when glycaemic control is unstable.[1,2,4] HbA_{1c} is expressed as the percentage of haemoglobin that is glycated or in units of mmol/mol. For some time, an assay established by the National Glycohemoglobin Standardization Program (NGSP), which was based on that used in the Diabetes Control and Complications Trial (DCCT), has been used.[10] A new reference method with increased specificity has been developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) for the calibration of laboratory instruments, which provides percentage results that are lower than those arrived at by the NGSP method but that can be converted to the equivalent NGSP value. It was suggested in 2007 that in order to avoid confusion in the clinical setting, HbA_{1c} results should continue to be reported as the NGSP (or DCCT-derived) percentage result, as well as the metrologically correct units of mmol/mol (millimoles of HbA_{1c} per mole of total haemoglobin).[10,11] In addition, a study[12] showing correlation between HbA_{1c} and average glucose concentrations has provided evidence to support recommendations for HbA_{1c} results to also be reported as an estimated average glucose (eAG) in mmol/litre.[1,11]

Like blood glucose, goals for HbA_{1c} vary. The usual non-diabetic reference range is 4.0 to 6.0%.

- In *adults*, UK guidelines[4] recommend that a general target of 6.5 to 7.5% should be used for HbA_{1c} in patients with type 2 diabetes. For patients with type 1 diabetes,[2] HbA_{1c} lower than 7.5% is suggested, while a goal of 6.5% or lower may be of benefit in patients at increased risk of arterial disease.
  In the USA,[1] a target of below 7.0% has been recommended for diabetic patients in general, and possibly lower for those with a short duration of diabetes, long life expectancy, and no significant cardiovascular disease.
  The IDF[9] advocates lowering glucose measures to as near to normal as safely possible, suggesting a target HbA_{1c} of less than 6.5%.
- For *children,* a target HbA_{1c} of less than 7.5% has been recommended in the UK[2] and by ISPAD.[3]
  As for blood-glucose, guidance in the USA[1] advocates age-specific targets for HbA_{1c} (< 8.5% for children up to 6 years of age, < 8.0% for those aged 6 to 12 years, < 7.5% for those aged 13 to 19 years).

Less stringent HbA_{1c} targets may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetic complications, extensive comorbid conditions, or where the general goal is difficult to attain in long-standing diabetes.[1,2] It has also been suggested, in the light of a retrospective cohort study involving almost 48 000 patients over 50 years old with type 2 diabetes which found that both low and high mean HbA_{1c} values were associated with increased all-cause mortality, that a minimum HbA_{1c} value might need to be specified.[13] Postprandial glucose may be targeted if HbA_{1c} goals are not met despite reaching preprandial glucose goals.[1,4]

Measurement of **glycated serum proteins**, particularly albumin, may be used to give an indication of glucose control, but covers a shorter period than haemoglobin. Such methods may be useful for measuring glycaemic control in patients with abnormal red cell survival-time.[3] Measurements of urinary or blood **ketones**, to detect impending ketoacidosis, should be monitored when there is uncontrolled hyperglycaemia, illness with fever and/or vomiting, episodes of drowsiness, abdominal pain, or rapid breathing. Blood ketone measurements are more accurate than urinary testing for diagnosing ketoacidosis.[3]

For more information on monitoring of diabetes mellitus in pregnancy, see p. 463.3, and in gestational diabetes mellitus, see p. 464.1.

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Diabetes mellitus and pregnancy

Adverse pregnancy outcomes, including spontaneous abortion, congenital malformation, and macrosomia, are more common in diabetic than in nondiabetic women. Improved management of the pregnant diabetic patient, particularly in early pregnancy, lessens the incidence of such events, but an increased risk still exists. Diabetic women are advised to plan their pregnancies so that glycaemic control can be improved before conception.[1-3] Recommendations for blood glucose and glycated haemoglobin (HbA_{1c}) are generally closer to normal than those recommended for nonpregnant patients (see below). Higher targets may be necessary for patients with hypoglycaemia unawareness or the inability to cope with intensified management.[3] Frequent self-monitoring is advised because of the increased potential for rapid-onset insulin-induced hypoglycaemia, and should be done both before and after meals, and at bedtime;[2,3] occasional measures taken between 2 and 4 a.m. have also been recommended.[3] (Pregnant diabetic patients are at risk of nocturnal hypoglycaemia owing to continued fetal glucose consumption while the mother is in a relatively fasting state.) Ketone testing is also advisable, particularly when there is persistent hyperglycaemia or the patient is unwell, as diabetic ketoacidosis can develop quickly and is associated with a high risk of fetal loss.[2,3]

- Preprandial capillary blood-glucose concentrations of between 3.5 and 5.9 mmol/litre, and 1-hour postprandial concentrations of below 7.8 mmol/litre, have been recommended in the UK.[2] In the USA,[1] a goal of 3.3 to 5.4 mmol/litre has been suggested for preprandial, bedtime, and overnight glucose, with a postprandial goal of 5.4 to 7.1 mmol/litre, and a mean daily glucose[3] of less than 6.2 mmol/litre. Tighter control (mean blood glucose less than 4.5 to 5.0 mmol/litre) should be avoided because of the risk of fetal growth restriction.[3]
- Suggested HbA_{1c} targets are below 6.1% in the UK[2] and below 6.0% in the USA.[3]

Insulin is the preferred treatment for both type 1 and type 2 diabetes mellitus in pregnancy. Insulin regimens are similar to those in non-pregnant patients, using a basal-bolus regimen or continuous subcutaneous insulin infusion.[3] As there is limited information about the safety of long-acting analogues, such as insulins detemir and glargine, isophane insulin should be used for the basal component. The rapid-acting insulin analogues, insulins aspart and lispro, are considered safe for use during pregnancy, and may produce better postprandial glucose control with less hypoglycaemia than regular insulin.[2,3] Insulin requirements may decrease during the first trimester, but then double or even triple during the course of the pregnancy.[3] Capillary blood-glucose concentrations should be monitored during labour and birth, and insulin doses will need to be reduced immediately after birth.[2]

Women with type 2 diabetes who have been taking oral antidiabetics are usually switched to insulin for the duration of the pregnancy.[3] However, there is increasing evidence to suggest that metformin might be used safely during pregnancy, and UK guidance[2] has suggested that it may be

used either as an adjunct or alternative to insulin if the likely benefits from improved glycaemic control outweigh the potential for harm. Nevertheless, the use of oral hypoglycaemics during pregnancy remains controversial; some argue that although there may be increasing evidence of fetal safety, oral treatments are not sufficiently effective to achieve the tight postprandial glycaemic control that is desirable during pregnancy.[4] Others suggest that oral treatments may have a role in poorly resourced settings where there is a lack of access to insulin.[5]

For information on gestational diabetes mellitus, see p. 464.1.

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Gestational diabetes mellitus. Gestational diabetes mellitus is defined as glucose intolerance with onset or first recognition during pregnancy, which generally resolves with delivery. However, increasing numbers of women with undiagnosed type 2 diabetes are being identified during screening for gestational diabetes.[1]

Initial screening is based on the assessment of risk factors such as age, body-mass index or body-weight, previous gestational diabetes, family history of diabetes, and ethnic origin with a high prevalence of diabetes. Various criteria have been used for gestational diabetes, but the American Diabetes Association suggests that those with risk factors should initially be screened for type 2 diabetes using standard diagnostic criteria (see Diagnosis of Diabetes Mellitus, p. 458.3). For women not found to have type 2 diabetes, a 75-g oral glucose tolerance test (OGTT) at 24 to 28 weeks of gestation is used to screen for gestational diabetes using criteria of:[1,2]

- fasting plasma glucose $\geqslant$ 5.1 mmol/litre
  or
- plasma glucose $\geqslant$ 10.0 mmol/litre at 1 hour after an OGTT
  or
- plasma glucose $\geqslant$ 8.5 mmol/litre at 2 hours after an OGTT

As shown for women with pre-existing diabetes, good glycaemic control in gestational diabetes reduces the risk of fetal macrosomia and other complications.[3-5]

- Glycaemic goals in the UK[3] are preprandial capillary blood-glucose concentrations of between 3.5 and 5.9 mmol/litre, and a 1-hour postprandial concentration of below 7.8 mmol/litre.
  In the USA,[2,4] a preprandial goal of less than 5.3 mmol/litre has been suggested, with a postprandial goal of less than 7.8 mmol/litre at 1 hour or 6.7 mmol/litre at 2 hours.

However, mean concentrations maintained below 4.8 mmol/litre can increase the risk of fetal growth impairment.[4]

Most women with gestational diabetes can be managed by diet and exercise alone.[3,4] However, if these are insufficient, insulin therapy may be given as for pregnant women with pre-existing diabetes.[3,4] UK guidance[3] also states that there is adequate evidence of efficacy and safety to consider metformin or glibenclamide as an adjunct or alternative to insulin.

Antidiabetic treatment should be stopped immediately after birth.[3] Most women will return to normal glucose tolerance, although follow-up is recommended because of an increased risk of developing type 2 diabetes in the future:[6] however, some women will remain diabetic or have ongoing impaired glucose tolerance.[2-4]

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Diabetes mellitus in surgery or critical illness

Stress-induced hyperglycaemia is associated with surgery, trauma, and critical illness, and will increase insulin requirements. Insulin-dependent diabetics who require **surgery** usually need to be managed with a continuous intravenous insulin infusion, and various algorithms have been developed with the goal of avoiding both hypo- and hyperglycaemia. Different blood-glucose targets have been suggested, usually to keep perioperative blood glucose below 10.0 or 11.0 mmol/litre, and to aim for near normoglycaemia.[1-3]

- In general, *insulin-dependent patients* should be given their normal regimen the day before the operation. On the day of surgery, patients may be given half their usual subcutaneous basal insulin dose, or the full basal dose for those using insulin glargine or a continuous subcutaneous insulin infusion.[1,2] Perioperative intravenous insulin in saline is given as a variable rate infusion via a syringe pump, with a separate 5 or 10% glucose infusion. Potassium chloride may be included in the glucose infusion[2] or given separately.[1] Alternatively, insulin may be added to the glucose infusion,[3] or a combined insulin-glucose-potassium infusion may be suitable.[2]
- *Non-insulin-dependent patients* should have any oral antidiabetic treatment omitted on the day of surgery; metformin should be stopped at least 24 hours before the procedure.[1,2] An intravenous insulin infusion may be indicated during major surgery[1,2] or when glycaemic control is poor.[2] Subsequent conversion back to subcutaneous insulin or oral antidiabetics should be undertaken as soon as the patient is able to resume eating and drinking normally,[1,2] although metformin should be withheld for 48 to 72 hours after surgery or iodinated radiocontrast media, and until normal renal function has been confirmed.[2]

The treatment of hyperglycaemia is also desirable for **critically ill** patients, including diabetics. However, as well as the risks of insulin-induced hypoglycaemia, there is some evidence that tight glycaemic control might increase mortality in these patients (see also Critically Ill Patients, under Insulin, p. 483.2). Guidelines[4,5] recommend starting an intravenous insulin infusion at a blood-glucose threshold of 10 mmol/litre for the treatment of persistent hyperglycaemia in most critically ill patients in the intensive care setting, with a maintenance range of 7.8 to 10.0 mmol/litre.

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Diabetic complications

Much of the increased mortality and morbidity seen in diabetic patients is the result of complications that develop with increasing duration of disease, particularly when glycaemic control is poor. Such complications may originate from increased glycation of proteins and other biological macromolecules in the hyperglycaemic environment, pathological activation of protein kinase C, or from increased accumulation of sorbitol and other polyols via the aldose reductase pathway,[1-3] but other factors play an important role in determining susceptibility. At the *macrovascular* level, diabetics are prone to hypertension and ischaemic heart disease, and heart disease is a major cause of death; control of blood pressure is now seen as being as important as glycaemic control in patients with type 2 diabetes. *Microvascular* tissue damage is an important factor in the development of diabetic nephropathy and retinopathy; it may also contribute to the other major complication, diabetic neuropathy. Collagen abnormalities are also seen. Diabetics with poor glycaemic control also have an increased liability to severe bacterial or fungal infection. Sometimes several factors may interact; thus neuropathy, infection, and impaired blood flow due to macro- or microvascular disease may all play a role in the development of diabetic foot disease, a complication which can ultimately lead to amputation.

For more information on these complications see under the headings Prevention of Diabetic Complications (p. 464.3), Diabetes-associated Cardiovascular Disease (p. 465.3), Diabetic Diarrhoea (p. 466.1), Diabetic Eye Disease (p. 466.2), Diabetic Foot Disease (p. 466.2), Diabetic Heart Disease (p. 466.3), Diabetic Nephropathy (p. 467.1), and Diabetic Neuropathy (p. 467.2).

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Prevention of diabetic complications. Much attention has been focused on whether strict or tight glycaemic control can modify the development or progression of diabetic complications. Tight glycaemic control has been shown to reduce microvascular complications of both type 1 and type 2 diabetes, but evidence for the prevention of macrovascular disease is less convincing.

The Diabetes Control and Complications Trial (DCCT)[1] compared the effects of conventional insulin therapy with those of continuous subcutaneous insulin infusion or multiple-injection regimens, on the development and progression of early complications in *type 1 diabetics*. The intensive treatment was aimed at keeping preprandial blood-glucose concentrations between 3.9 and 6.7 mmol/litre, postprandial concentrations at less than 10 mmol/litre, a weekly 3 a.m. measurement at greater than 3.6 mmol/litre, and the monthly glycated haemoglobin (HbA_{1c}) measurement at less than 6.05%. Intensive insulin therapy reduced the development and progression of retinopathy; it also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. There was also a risk reduction for combined cardiovascular and peripheral vascular events, but it was based on a small number of events in a relatively young study population, and was not statistically significant. The major disadvantage of intensive insulin therapy was a threefold greater risk of hypoglycaemia; weight gain was also significantly greater.

While it is accepted that some patients will benefit from intensive insulin regimens, this approach requires caution in patients at risk of hypoglycaemia. Also such intensive treatment may not always be necessary, for example in patients known to maintain good control by conventional dosage schedules, or where improvement can be obtained by setting achievable targets and improving patient education.[2] However, intensive therapy can help sustain endogenous insulin secretion in type 1 diabetes, which is associated with improved metabolic control;[3] this would favour starting intensive insulin therapy at an early stage. After the DCCT finished the patients returned to their own healthcare providers for diabetes care, but were followed in a cohort study for a further 11 years.[4] Although more than 90% of all patients went on to use intensive therapy, and glycated haemoglobin values became very similar for both groups during this time, there were fewer cardiovascular events and less microalbuminuria and albuminuria in the group that had received intensive treatment during the original DCCT, showing that the beneficial effects of intensive therapy were maintained long term. Thirty-year observational follow-up of some of the patients in the DCCT study[5] has shown that proliferative retinopathy, nephropathy and cardiovascular disease were all significantly reduced in those who had intensive diabetes therapy.

The reports of the UK Prospective Diabetes Study (UKPDS) have provided similar evidence in patients with newly diagnosed *type 2 diabetes*. This study has examined the benefits of intensive therapy, using a variety of drugs with diet and exercise. Intensive therapy, which aimed at producing fasting plasma-glucose concentrations of below 6 mmol/litre, substantially decreased the risk of microvascular complications (particularly retinopathy). There was no difference in benefit between intensive therapy with sulfonylureas and with insulin.[6] Metformin also produced benefit in the overweight patients who received it.[7] The UKPDS did not provide unequivocal evidence of a reduction in macrovascular disease with improved glycaemic control, although there was some suggestion of a reduction in risk of myocardial infarction. However, it did show that vigorous control of blood pressure, using captopril or atenolol as the first-line drugs in hypertension, reduced the risk of both macrovascular and microvascular complications,[8,9] suggesting that this should have a high priority in the treatment of type 2 diabetes. Patients returned to their own healthcare providers after the UKPDS finished, but were followed up for a further 10 years. Within a year, the difference in HbA_{1c} between the intensively and conventionally treated groups had disappeared, but a reduction in microvascular risk persisted over the decade and was particularly evident in those who had received a sulfonylurea or insulin. In addition, the risk reductions for myocardial infarction and death from any cause became statistically significant during follow-up.[10] The blood pressure differences between the groups also disappeared, within 2 years, and the associated risk reductions for both microvascular and macrovascular complications were not sustained after tight control of blood pressure was lost.[11]

The effect of tight glycaemic control has also been studied in type 2 diabetic patients with pre-existing diabetic complications. The intensive arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[12] was stopped early, after a mean of 3.5 years of follow-up, when it became apparent that tight glycaemic control in patients with type 2 diabetes and a history of cardiovascular disease, or multiple cardiovascular risk factors, did not significantly reduce major cardiovascular events and was associated with increased death from any cause. The reason for this increased mortality rate was unclear, but possible factors included the low HbA_{1c} goal (targeted to below 6.0%; a median of 6.4% was achieved), or the magnitude or speed of reduction in HbA_{1c}. Five-year outcomes from the ACCORD study[13] confirmed that there was an increased mortality rate associated with intensive multidrug therapy to reduce HbA_{1c} below 6% in patients with sub-optimally controlled long-standing diabetes and a high risk of cardiovascular disease. Subgroup analysis[14] indicated that intensive therapy was most likely to increase risk in patients with $HbA_{1c} \geq 8.5\%$, aspirin use at study entry, or in particular, self-reported history of neuropathy. Intensive therapy did delay the onset of albuminuria, and, by some measures, eye complications and neuropathy.[15]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) included patients with type 2 diabetes and a history of, or risk factors for, vascular disease. Results from a median follow-up of 5 years provided further evidence for an association between intensive glucose control (HbA_{1c} 6.5%) and a reduction in microvascular risks, particularly nephropathy, but found no significant effect on major macrovascular events.[16] In a separate component of ADVANCE, a fixed combination of perindopril and indapamide reduced the risk of a major microvascular or macrovascular complication compared with placebo, regardless of initial blood pressure; significant reductions were seen in total coronary and renal events, but not cerebrovascular or diabetic eye events.[17] Further analysis of the ADVANCE study showed that combined blood pressure lowering and intensive glycaemic control resulted in substantial reductions in major renal events and all-cause death.[18]

Another study of glycaemic control, the Veterans Affairs Diabetes Trial (VADT), found that lowering HbA_{1c} to 6.9% in patients with poorly controlled, long-standing type 2 diabetes had no significant effect on either microvascular or macrovascular complications.[19]

Pioglitazone has also been studied in patients with extensive macrovascular disease, based on the suggestion that it might have beneficial effects in addition to its effect on glycaemic control. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study targeted HbA_{1c} to below 6.5% and encouraged optimum lipid-lowering, antiplatelet, and antihypertensive therapy. Over 3 years it found no significant benefit in a broad composite end-point that included macrovascular outcomes as well as death from any cause, but did report significantly fewer events for a composite end-point that included only all-cause mortality, non-fatal myocardial infarction, and stroke.[20]

In an attempt to clarify the effects of intensive glycaemic control on cardiovascular outcomes in type 2 diabetes, a meta-analysis[21] combined data from UKPDS, PROactive, ADVANCE, VADT, and ACCORD, which included a total of more than 33 000 diabetic patients. Looking at separate end-points, there were significant reductions in non-fatal myocardial infarction and events of coronary heart disease, but the effects on stroke and all-cause mortality were not significant. Another meta-analysis[22] involving 13 studies and over 34 000 patients concluded that a benefit of intensive treatment on cardiovascular and all-cause mortality could not be shown, and although it was associated with modest improvements in the risk of non-fatal myocardial infarction and microalbuminuria, it also increased the risk of severe hypoglycaemia. A review of randomised controlled studies and meta-analyses of intensive versus conventional glycaemic control on microvascular and macrovascular complications in both type 1 and 2 diabetes[23] concluded that intensive therapy should be used at an early stage of diabetes and that for patients with long-standing well controlled diabetes it is more reasonable to use conventional glycaemic control.

The Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) study[24] included type 2 diabetics who were candidates for elective coronary revascularisation. While receiving antidiabetic therapy targeted to HbA_{1c} less than 7.0%, the study examined the effects of various treatment options on cardiovascular outcomes. After an average follow-up of about 5 years, the rates of survival and major cardiovascular events did not differ overall between groups allocated to either medical therapy alone or prompt revascularisation (percutaneous coronary intervention or coronary-artery bypass grafting as appropriate) plus medical therapy. In subgroup analysis, there were fewer major cardiovascular events in candidates for bypass grafting who underwent prompt surgery compared with those allocated to medical therapy. However, there was no significant difference for those who were candidates for percutaneous intervention when compared with medical therapy. The type of medical therapy (insulin-sensitising or insulin-providing drugs) also had no apparent effect on outcome.

The relationship between postprandial glucose concentrations and the development of diabetic complications is under investigation. Epidemiological studies in general populations have shown an association between macrovascular disease and hyperglycaemia after a glucose challenge. However, there are limited data about this relationship in diabetic patients. There is also some evidence that postprandial hyperglycaemia is associated with accelerated atherosclerosis. Whether targeting postprandial glucose concentrations can reduce or prevent cardiovascular complications is yet to be established.[25] The American Diabetes Association[26] has suggested that for patients with a raised HbA_{1c} despite preprandial glucose values within the target range, a postprandial target of lower than 10.0 mmol/litre (measured 1 to 2 hours after the start of the meal) may help to reduce HbA_{1c}. The International Diabetes Federation[27] has suggested a 2-hour postprandial goal closer to normal, at less than 7.8 mmol/litre. For details on recommended preprandial and HbA_{1c} goals, see Monitoring of Therapy, under Diabetes Mellitus, p. 459.1.

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Diabetes-associated cardiovascular disease. Diabetic patients are at increased risk of cardiovascular disease, and it is apparent that tight glycaemic control alone is not sufficient to avoid complications.[1] Diet and exercise are important components of cardiovascular risk reduction for diabetics, as well as the control of blood pressure and serum lipids, use of antiplatelet therapy, and the avoidance of smoking. For broader discussions about the management of cardiovascular disease, see Cardiovascular Risk Reduction (p. 1246.1), Hyperlipidaemias (p. 1248.1), and Hypertension (p. 1251.1). Peripheral arterial disease is more common in diabetics, is associated with an increased risk of cardiovascular and cerebrovascular events, and is a contributing factor to diabetic foot disease (see p. 466.2); cardiovascular risk reduction is therefore strongly advocated in diabetic patients with peripheral arterial disease.[2,3] The management of peripheral arterial disease is discussed on p. 1272.3. Diabetics are also prone to cardiomyopathy, see under Diabetic Heart Disease (p. 466.3).

Hypertension should be treated aggressively to prevent both microvascular and macrovascular complications of diabetes, and blood pressure is generally targeted to below 130/80 mmHg.[4-8] However, this may be unnecessarily stringent: evidence from the ACCORD study[9] suggested that a systolic blood-pressure target below 120 mmHg did not reduce rates of fatal and non-fatal cardiovascular events any further than one of 140 mmHg, and a subgroup analysis of the INVEST study indicated that no improved cardiovascular outcomes were seen from systolic blood pressure control below the range of 130 to 139 mmHg.[10] Although diet and exercise are recommended in the management of hypertension, most diabetics will require multidrug therapy. All of the main groups of antihypertensive drugs may be used, although an ACE inhibitor or angiotensin II receptor antagonist is usually recommended for first-line therapy. Calcium-channel blockers, diuretics, or beta blockers may be added as necessary.

Patients with diabetes are prone to develop elevated triglycerides and a serum-cholesterol profile associated with increased cardiovascular risk, and the management of ***dyslipidaemia*** is therefore advocated.[5,8] The American Diabetes Association[4] recommends a low-density-lipoprotein (LDL)-cholesterol target below 2.6 mmol/litre in patients without overt cardiovascular disease, and a lower goal of less than 1.8 mmol/litre in those with overt disease. Triglycerides of less than 1.7 mmol/litre are also suggested, with high-density-lipoprotein (HDL)-cholesterol above 1.0 mmol/litre in men and above 1.3 mmol/litre in women. Statins are the lipid lowering drugs of choice for LDL-cholesterol.[4,6,11] If statins are not tolerated or maximal doses do not achieve treatment goals, other drugs such as ezetimibe, bile-acid binding resins, or nicotinic acid may be tried; they are less effective than statins as monotherapy for lowering LDL-cholesterol, but may be added to statin therapy.[11] Fibrates, such as gemfibrozil, or nicotinic acid may be used for management of HDL-cholesterol and triglycerides. High doses of nicotinic acid can affect glycaemic control, but modest doses (0.75 to 2 g daily) may improve lipid profiles with manageable increases in blood-glucose concentrations.[4] Statins are also recommended regardless of baseline lipid levels for diabetics with overt cardiovascular disease, and for those without overt disease who are over the age of 40 years and have one or more other risk factors for cardiovascular disease.[4] A meta-analysis[12] of statin studies has shown cardiovascular benefits for diabetics similar to those seen in patients without diabetes, regardless of lipid profile and whether vascular disease was already present.[12] A possible beneficial effect from fibrates has also been suggested, and was studied in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[13] in patients with type 2 diabetes, with or without cardiovascular disease and without dyslipidaemia requiring treatment. After about 5 years of therapy, fenofibrate was not associated with a significant reduction in major coronary events, although there were reductions in non-fatal myocardial infarction and coronary revascularisations. However, follow-up of the FIELD study showed that fenofibrate may reduce the risk of both first myocardial infarction and further cardiovascular events after silent myocardial infarction.[14] A meta-analysis[15] that was dominated by the FIELD study concluded that fibrates reduced the incidence of cardiovascular events in type 2 diabetics, but the effect on mortality was not significant.

Antiplatelet therapy has also been recommended for cardiovascular risk reduction in diabetics. Aspirin is recommended for secondary prevention in diabetic patients with cardiovascular disease,[4,8] although some data suggest that there may be less benefit than in patients without diabetes.[6,7] It has also been recommended as primary

prevention in patients at increased risk, but the strength of evidence for this recommendation had been challenged because of extrapolation from studies of other high-risk groups, and limited benefit in diabetic subgroups within primary prevention studies.[16] Subsequent primary prevention studies specifically undertaken in diabetic patients have not definitively shown that low-dose aspirin reduced the risk of cardiovascular events,[17,18] although the Fremantle Diabetes Study in type 2 diabetics showed reduced cardiovascular and all-cause mortality in a primary prevention setting.[19] Despite a lack of conclusive evidence the American Diabetes Association, the American Heart Association, and the American College of Cardiology Foundation recommend that primary prevention be considered in most diabetic men over 50 years of age and women over 60 who have at least one additional major risk factor (a family history of cardiovascular disease, hypertension, smoking, dyslipidaemia, or albuminuria).[4,20] Clopidogrel is generally reserved for patients who are unable to take aspirin,[4,8] and the combination of aspirin and clopidogrel may be used for up to a year after an acute coronary syndrome.[4]

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Diabetic diarrhoea. Diabetic patients may develop intermittent bouts of watery diarrhoea, sometimes alternating with constipation; autonomic neuropathy and abnormalities of digestion and bowel flora may play a role.[1] Clonidine has been suggested for severe cases,[2] and octreotide has been used successfully,[3,4] but otherwise conventional management with antidiarrhoeal drugs (p. 1808.2) is advocated; a broad spectrum antibacterial (especially tetracycline[5]) may also be effective. The mechanism of action of tetracycline in diabetic diarrhoea is uncertain, but it has been suggested that 2 or 3 doses of tetracycline 250 mg can be tried at the start of an attack.

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Diabetic eye disease. Diabetic patients are prone to potentially blinding eye disease, usually in the form of cataract or diabetic retinopathy. Cataract generally requires surgical extraction, particular care being taken to avoid infection. Diabetic retinopathy may take a 'background', non-proliferative form, or become a more serious proliferative retinopathy associated with neovascularisation, vitreous haemorrhage and retinal detachment. Macular oedema, characterised by retinal thickening from leaky blood vessels, can develop at any stage of retinopathy.[1]

Aggressive glycaemic and blood pressure control is used to reduce the onset and progression of diabetic retinopathy.[1-3] Transient early worsening may occur in patients transferred to more intensive glycaemic regimens, which may be related to higher baseline HbA_{1c} values and a more rapid reduction of HbA_{1c}.[1] Although dyslipidaemia appears to increase the risk of retinopathy, it is still unclear whether lipid lowering therapy would be useful for prevention of diabetic retinopathy.[1] However, the ACCORD Eye Study Group showed that fenofibrate, when added to a statin, slowed the progression of diabetic retinopathy in type 2 diabetes.[3] The FIELD study[4] reported that fenofibrate reduced the need for laser treatment, but suggested that the mechanism of effect did not seem to be related to plasma-lipid concentrations.

Once severe nonproliferative or proliferative retinopathy has developed, pan-retinal laser photocoagulation is effective in limiting progression, while focal laser therapy may be used in macular oedema.[1,2] Surgical vitrectomy may be helpful for vitreous haemorrhage and areas of traction involving or threatening the macula in advanced proliferative retinopathy, and in widespread or diffuse macular oedema that has not responded to laser treatment.[1] Intravitreal injection of the corticosteroid triamcinolone acetonide may be useful for persistent diabetic macular oedema;[1,5,6] intravitreal implants that release fluocinolone acetonide or dexamethasone have also been studied.[1,6] However, cataract formation and raised intra-ocular pressure have been associated with intravitreal corticosteroids. Intravitreal ranibizumab, an inhibitor of vascular endothelial growth factor (VEGF), can improve visual acuity and appears to be more effective than laser therapy,[7,8] but the combination may be no better than ranibizumab alone.[8] It may be used alone or with laser therapy, but long-term efficacy is not yet proven. Other VEGF inhibitors that have been studied include bevacizumab and pegaptanib.[7]

Many drugs have been tried for the prevention or retardation of diabetic eye disease but mostly with indifferent results; these included aspirin, ticlopidine, aldose reductase inhibitors, ruboxistaurin, and octreotide.[1,9] There is some evidence that blockade of the renin-angiotensin system with an ACE inhibitor or angiotensin II receptor antagonist may be of benefit in retarding progression of early disease.[10]

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Diabetic foot disease. Peripheral arterial disease, neuropathy, collagen changes, and increased susceptibility to infection may contribute to the foot lesions to which diabetics are prone. Ulceration and tissue necrosis at pressure-points may be followed by tissue and bone infection, gangrene, and sepsis.

Management involves drainage and debridement of dead and infected tissue, pain care, and the use of antibacterials if necessary.[1,2] Surgical debridement of necrotic wound tissue has been shown to improve wound healing, and needs to be repeated if new necrotic tissue continues to form. Other, less well proven, methods include enzymatic debridement using collagenase, and larval (maggot) therapy.[3] While oral antibacterials with Gram-positive coverage may be adequate for mild to moderate infections, broad spectrum cover should be started intravenously if there is severe, limb-threatening infection; treatment should be adapted once the results of bacteriological culture are available.[1,3-6]

Various other adjunctive therapies that may be considered in the management of diabetic foot ulcers include becaplermin, bioengineered skin substitutes, hyperbaric oxygen therapy, and negative pressure wound therapy, although supporting evidence for these may be limited.[3,5,7,8] Granulocyte colony-stimulating factors given as adjunctive therapy with antibacterials may not accelerate wound healing or resolution of infection, but could reduce rates of amputation and other surgical procedures.[9] A retrospective cohort study[10] of over 2500 patients treated with advanced biological therapies has shown that wounds first treated with a bioengineered human skin equivalent (*Apligraf*) were more likely to heal than those treated with becaplermin or an autologous platelet-derived growth factor (platelet-rich plasma; platelet releasate *Procuren*).

Diabetic neuropathic osteoarthropathy (Charcot foot), characterised by joint dislocation, fracture, and destruction of the structures of the foot, is managed with immobilisation, stress reduction, and surgery; improvements in markers of bone turnover have been reported in small studies using bisphosphonates.[3]

Strict control of blood glucose is important and insulin should be given as required. Reduction of pressure to the ulcer (off-loading) should be offered to prevent further trauma and promote healing;[1] effective pain relief and bed rest may be needed, and surgical reconstruction to improve blood supply may be helpful in some cases.[3]

Ultimately, some patients require amputation of all or part of the foot.[3] Preventive care, with regular visits to a chiropodist, is therefore particularly important. The possibility that fenofibrate might reduce the risk of amputation in type 2 diabetics has been raised by results from the FIELD study.[11] Although lower limb vascular status was not routinely measured at baseline or in those who did not have an amputation, fenofibrate was associated with a reduction in the risk of first minor amputation in patients without documented large vessel (atherosclerotic) disease; the risk of either minor or major amputation was not reduced in those with large vessel disease.

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Diabetic heart disease. Diabetics may develop a form of cardiomyopathy, characterised by left ventricular hypertrophy with diastolic and systolic dysfunction in the absence of ischaemic heart disease and hypertension.[1,2] Tight glycaemic control might prevent or limit the development of heart disease, although data to confirm this are limited. Until more specific data become available, management strategies for associated heart failure (p. 1262.3) are based on those for non-diabetic patients, using ACE inhibitors, angiotensin II receptor antagonists, and beta blockers. Other conditions affecting the heart in diabetic patients include cardiovascular disease (see p. 463.3) and cardiac autonomic neuropathy (see Diabetic Neuropathy, p. 467.2)

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All cross-references refer to entries in Volume A

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Diabetic nephropathy. Nephropathic changes associated with microvascular disease develop in up to 30% of patients with type 1 diabetes and up to 40% of those with type 2 disease; diabetic nephropathy, of which the first clinical sign is albuminuria, is one of the major causes of end-stage renal disease (see Chronic Renal Failure, p. 1781.1).

Results from the DCCT indicate that strict glycaemic control reduces the incidence of microalbuminuria in type 1 diabetes[1] (with long-term renal benefits[2]), and smaller reductions were seen in the UKPDS[3] and ADVANCE[4] studies in patients with type 2 diabetes. It is also evident from the DCCT[1] and ADVANCE[4] that strict glycaemic control can slow the progression of nephropathy in patients who are already microalbuminuric.

An important approach to the management of diabetic nephropathy is optimal blood pressure control, because the treatment of hypertension can reduce the risk of developing microalbuminuria and delay progression.[5-7] The UKPDS[8] found atenolol and captopril to have similar effects on the progression of albuminuria in type 2 diabetics with hypertension. However, ACE inhibitors may have renoprotective effects independent of the patient's blood pressure[9,10] or the type of diabetes,[10] probably by inhibition of the renin-angiotensin system. Reduced progression to macroalbuminuria has been also found in normotensive patients with type 1 diabetes given ACE inhibitors.[11] As well as slowing progression, ACE inhibitors can normalise albumin excretion in patients with microalbuminuria.[10,11] There is also evidence for the efficacy of ACE inhibitors in the primary prevention of diabetic kidney disease,[12] although a 5-year study that measured structural changes in the kidney failed to find evidence that use of enalapril or losartan prevented development and progression of nephropathy.[13] For these reasons, ACE inhibitors are generally recommended as first-line therapy in diabetic patients with hypertension and albuminuria.[6]

Angiotensin II receptor antagonists have also been shown to reduce the progression of renal disease in type 2 patients with both microalbuminuria and macroalbuminuria,[7,10] and US recommendations consider them an equal first choice with ACE inhibitors;[6] UK guidelines suggest they may be used in those unable to tolerate ACE inhibitors.[14] Although direct comparisons are limited to small studies, the effects of ACE inhibitors and angiotensin II receptor antagonists on renal outcomes appear to be equivalent.[10] The combination of an ACE inhibitor with an angiotensin II receptor antagonist has been reported to reduce proteinuria more than an ACE inhibitor alone; however, most studies have been small and short-term, and there have been associated falls in glomerular filtration rate and raised serum potassium;[15] a larger multicentre study[16] suggested that combination therapy with telmisartan and ramipril, although it reduced proteinuria more than either drug alone, was associated with a higher incidence of renal events.

The renin inhibitor aliskiren has also been investigated as an addition to angiotensin II inhibitors, and improvements in albuminuria have been reported.[17] However, the combination of aliskiren with angiotensin II receptor inhibitors or ACE inhibitors has been contra-indicated because of an increased risk of adverse effects (see Diabetes Mellitus, under Precautions of Aliskiren Fumarate, p. 1296.1).

Addition of paricalcitol to treatment with ACE inhibitors or angiotensin II receptor antagonists also appears to lower residual albuminuria in patients with diabetic nephropathy,[18] and has been suggested as a possible novel approach to improve renal outcomes.

There has also been interest in the effects of fibrates on diabetic nephropathy. Tertiary outcome results from the FIELD study showed a reduced onset or progression of albuminuria in patients with type 2 diabetes given fenofibrate; there was also more regression of albuminuria in the fenofibrate group.[19] A substudy of the FIELD research[20] did not show a benefit on albumin excretion from using fenofibrate and noted increases in creatinine and cystatin-C measurements in patients, indicative of a negative effect on renal function However, further analysis of data from the main study[21] suggested that the effects of fenofibrate on plasma creatinine were reversible, and confirmed a reduction in albuminuria and a slowing of estimated decline in renal function over 5 years.

Dietary protein restriction (see Renal Failure, p. 2043.3) appears from several small studies to have a beneficial, although small, effect on disease progression.[22] It has been recommended for consideration particularly when nephropathy is progressing despite optimal glycaemic and blood pressure control and the use of an ACE inhibitor and/or angiotensin II receptor antagonist.[6]

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Diabetic neuropathy. Peripheral neuropathies are common complications of diabetes mellitus. The intensity and extent of neurological abnormalities are proportional to the degree and duration of hyperglycaemia. The manifestations of sensorimotor neuropathy (distal symmetrical polyneuropathy) classically progress from the fingers and toes in a symmetrical pattern. The most common symptom is sensory loss, which is a significant risk factor for the development of diabetic foot disease; neuropathic pain and paraesthesia can also occur. Autonomic neuropathy affecting the cardiovascular system can cause tachycardia and orthostatic hypotension, and may increase the risk of silent myocardial infarction. Other manifestations of autonomic neuropathy include gastroparesis, diarrhoea, bladder atony, and erectile dysfunction.[1,2] Focal neuropathies are less common, but may cause unilateral cranial nerve palsies, truncal pain or dysaesthesia, or proximal pain, sensory loss, muscle weakness, and atrophy of the thigh. Multifocal neuropathy affecting the lower limbs, trunk, and upper extremities is also less common.[2]

Results from the DCCT indicated that strict glycaemic control could substantially reduce the occurrence of clinical neuropathy in patients with type 1 diabetes,[3-5] a result which was not duplicated in the UKPDS in patients with type 2 diabetes.[6] Long-term follow-up studies from the DCCT/EDIC group showed that the benefits of intensive diabetes control on development of peripheral neuropathy still persisted 14 years later,[7] and that intensive therapy benefited type 1 patients with cardiac autonomic neuropathy over a similar period of time.[8]

Other treatments have also been studied in an attempt to prevent, treat, or slow the progression of diabetic neuropathy. Aldose reductase inhibitors such as epalrestat have been investigated, but a meta-analysis of 32 studies found no convincing evidence of benefit,[9] and serious adverse effects have halted development of several drugs in this class. The antioxidant thioctic acid has been studied in the treatment of diabetic neuropathy, and is promoted in some countries as a dietary supplement. Symptomatic improvements in sensorimotor neuropathy have been reported in some short-term studies using intravenous or high oral doses, but evidence of long-term efficacy and safety are lacking.[10,11] Results from another short-term study[12] have suggested slight improvement in cardiac autonomic neuropathy.

Other management of diabetic neuropathy is essentially symptomatic.[1,13,14] The management of diabetic neuropathic pain is discussed on p. 8.2. Tachycardia may require the use of beta blockers while orthostatic hypotension should be managed conventionally[1,15] (see under Fludrocortisone, p. 1634.3), although care may be required in the use of elastic stockings in patients with impaired blood flow to the feet. Diabetic gastroparesis may respond to prokinetic drugs such as metoclopramide, cisapride, domperidone, or erythromycin,[1,14,16,17] but their effects can be variable and long-term use may be limited by tachyphylaxis and adverse effects. Antiemetics may be used as adjuncts to prokinetic therapy, and endoscopic or surgical interventions may be needed when symptoms cannot be controlled. Management of diabetic diarrhoea is discussed p. 464.1. For the management of erectile dysfunction, see p. 2348.2.

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Diabetic emergencies

The most frequent complication of insulin therapy is **hypoglycaemia** and patients taking insulin need to be educated about its cause, symptoms, and treatment. Most patients can recognise the early warning signs of hypoglycaemia and by taking sugar immediately can prevent more serious symptoms developing. Comatose patients need to be given intravenous glucose or, if this is not practicable, subcutaneous, intramuscular, or intravenous glucagon (although glucose is still required if there is no response within 10 minutes). Hypoglycaemia can also develop in patients taking oral antidiabetics, notably the sulfonylureas.

Some patients report loss of the warning signs of hypoglycaemia after transferring from animal to human insulin and these patients, if appropriate, may need to be transferred back to animal insulin. However, the most significant factor in the loss of warning signs is exposure to hypoglycaemia itself, and loss of awareness is liable to be a particular problem in patients receiving intensive therapy. Hypoglycaemic unawareness can be reversed by avoiding

hypoglycaemia for 2 to 3 weeks, and there is limited evidence to suggest that caffeine can improve awareness of hypoglycaemia.[1,2]

Further details on drug-induced hypoglycaemia can be found in Hypoglycaemia under Insulin (p. 486.2) and Sulfonylurea Antidiabetics (p. 504.1), while management is discussed under Treatment of Insulin-induced Hypoglycaemia (p. 486.3) and Treatment of Adverse Effects (p. 504.1), respectively.

Diabetic ketoacidosis is caused by an absolute or relative lack of insulin, with an increase in counter-regulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone. The condition is characterised by hyperglycaemia, hyperketonaemia, metabolic acidosis, and glycosuria causing osmotic diuresis with subsequent dehydration and electrolyte abnormalities; death may result in up to 1% of cases overall.[3,4] Presenting symptoms include thirst, polyuria, weight loss, nausea, vomiting, diffuse abdominal pain, dehydration, weakness, and impaired mental status ranging from lethargy to coma.[4] Young children are also at increased risk of cerebral oedema.[3,5] Symptoms of poorly controlled diabetes may be present for several days before metabolic acidosis, which tends to develop quickly, typically over less than 24 hours.[4] Diabetic ketoacidosis is commonly precipitated by a failure to adjust insulin dosage in the presence of infection. Other precipitating factors include discontinuation of or inadequate insulin therapy, failure of a continuous subcutaneous insulin infusion pump, drugs that affect carbohydrate metabolism, and medical conditions such as pancreatitis, myocardial infarction, and stroke.[4] Diabetic ketoacidosis is often present when type 1 diabetes mellitus is diagnosed, particularly in younger children.[3] Pregnant diabetic women are also prone to the development of diabetic ketoacidosis, particularly in the second and third trimesters because of insulin resistance that increases insulin requirements.[6]

Diabetic ketoacidosis is a medical emergency. The basic principles of treatment are fluid replacement, insulin therapy, and correction of electrolyte imbalances.[3-5,7-9]

- Fluid requirements depend on individual needs, but treatment is generally started with sodium chloride 0.9% infusion, which is subsequently adjusted according to the hydration state, serum-electrolyte concentrations, and urinary output. Care should be taken to avoid overvigorous fluid replacement;[4] in children this can particularly exacerbate the risk of cerebral oedema.[3]
- Soluble regular insulin should be given once hypokalaemia (see below) has been excluded or treated, with doses adjusted to achieve a steady decline in plasma-glucose concentrations.[8,9] For details of insulin dosing recommendations, see Diabetic Emergencies under Insulin, p. 483.3. Large doses were formerly thought necessary, but lower dose regimens accompanied by adequate hydration and correction of hyperosmolarity have proven to be adequate and are now recommended.[3,4]

  Continuous intravenous infusion is the preferred method of insulin delivery for managing diabetic ketoacidosis. In the USA an initial intravenous bolus dose has been recommended in some regimens for adults;[4] it is considered unnecessary in children and may increase the risk of cerebral oedema.[3] Frequent subcutaneous injection is another option for giving regular insulin, but it has a delayed onset of action and prolonged half-life compared with intravenous infusion.[4] In the management of mild to moderate, uncomplicated diabetic ketoacidosis, the use of a subcutaneous rapid-acting insulin analogue may be considered.[3,4]

  Ketonaemia typically takes longer to clear than hyperglycaemia, and once plasma glucose has fallen to a suitable value, the dose of insulin is reduced and infusion of glucose is begun simultaneously,[4] allowing insulin to be continued in order to clear ketone bodies without inducing hypoglycaemia. Once glucose concentrations have been controlled and acidosis has completely cleared, transition to a maintenance subcutaneous dosage regimen of insulin can begin. However, intravenous insulin should not be stopped until this has taken effect, which may be 1 to 2 hours after starting subcutaneous regular insulin.[3,4] Any established therapy with a long-acting insulin analogue (insulin detemir or insulin glargine) should be continued during treatment for ketoacidosis.[8]
- Although total body stores of potassium are depleted in diabetic ketoacidosis, mainly from the intracellular pool, patients may present with serum concentrations that are normal, increased, or decreased.[3,4] Giving insulin and correcting acidosis will drive potassium back into the cells and lower the serum-potassium concentration; patients will generally need potassium replacement regardless of their serum concentration at presentation. Potassium is given by infusion and may be started after adequate renal function has been confirmed. In hyperkalaemic patients, potassium is given once serum concentrations have fallen to within normal limits.[4] For normokalaemic patients, it should be started when insulin therapy begins, after initial fluid expansion.[3] In the rare patient presenting with hypokalaemia, potassium replacement should begin with fluid replacement, and insulin withheld until potassium concentrations have risen to normal values.[4]

  Intravenous bicarbonate is now generally reserved for patients with severe acidaemia despite fluid replacement and insulin therapy. Some[3,4] have suggested that bicarbonate may be given to those with a pH of less than 6.9, aiming to achieve a pH above 7.0. Bicarbonate treatment can increase the risk of hypokalaemia, and potassium may be added to the infusion.

  Phosphate concentrations are affected in a similar manner to potassium concentrations in the ketoacidotic state, but there is less agreement on the need for routine doses of phosphate. Phosphate concentrations should be monitored and phosphate given if clinically significant hypophosphataemia occurs.[3,4]

The precipitating cause of diabetic ketoacidosis should also be identified and managed appropriately.

Hyperosmolar hyperglycaemic state (HHS) or hyperosmolar hyperglycaemic nonketotic coma (HONK) occurs mainly in elderly patients with type 2 diabetes and though much less common than diabetic ketoacidosis it carries a higher mortality.[10] HHS is an emerging problem in children and adolescents with type 2 diabetes.[11] Adult patients may present in coma with severe hyperglycaemia but with minimal ketosis; dehydration and renal impairment are common. Treatment is similar to that of diabetic ketoacidosis using intravenous insulin (see above), although the insulin dose should be reduced and glucose started once the plasma-glucose concentration has fallen to about 17 mmol/litre. A concentration of about 11 to 17 mmol/litre should be maintained until the patient is mentally alert and HHS resolves.[4] Features of HHS, such as dehydration and contracted vascular volume, low cardiac output, increased blood viscosity, and very high osmolarity may predispose the patient to thrombosis. Although prophylactic heparin may be considered in patients at high risk of thrombosis, there is a lack of evidence to confirm its safety or efficacy in this situation.[10] Treatment aims in children are similar to those for adults and although no definitive regimen is yet available suggested guidelines have been proposed.[12]

1. Dagogo-Jack S. Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. *Treat Endocrinol* 2004; **3:** 91–103.
2. de Galan BE, *et al*. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Neth J Med* 2006; **64:** 269–79.
3. Wolfsdorf J, *et al*. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; **29:** 1150–9. Also available at: http://care.diabetesjournals.org/content/29/5/1150.full.pdf (accessed 29/06/09)
4. Kitabchi AE, *et al*. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32:** 1335–43.
5. Dunger DB, *et al*. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. Abstract: *Pediatrics* 2004; **113:** 400–401. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/2/e133 (accessed 29/06/09)
6. Kamalakannan D, *et al*. Diabetic ketoacidosis in pregnancy. *Postgrad Med J* 2003; **79:** 454–7.
7. Wolfsdorf J, *et al*. International Society for Pediatric and Adolescent Diabetes. Diabetic ketoacidosis in children and adolescents with diabetes. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. *Pediatr Diabetes* 2009; **10** (suppl 12): 118–33. Also available at: http//www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20DKA.pdf (accessed 17/03/11)
8. *et al*. Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults. (issued March 2010). Also available at: http://www.diabetes.nhs.uk/document.php?o=212 (accessed 03/10/11)
9. Edge JA. British Society of Paediatric Endocrinology and Diabetes. Guidelines for the management of diabetic ketoacidosis. (issued November 2009). Available at: http://www.bsped.org.uk/professional/guidelines/docs/DKAGuideline.pdf (accessed 16/09/11)
10. Chiasson J-L, *et al*. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ* 2003; **168:** 859–66. Correction. *ibid.*; 1241.
11. Rosenbloom AL. Hyperglycemic hyperosmolar state: an emerging pediatric problem. *J Pediatr* 2010; **156:** 180–4.
12. Zeitler P, *et al*. Drugs and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. *J Pediatr* 2011; **158:** 9–14, 14.e1–14.e2.

Acarbose *(BAN, USAN, rINN)*

Acarbosa; Acarbosio; Acarbosum; AG-5421; Akarboosi; Akarbos; Akarbosa; Akarboz; Akarbozė; Akarboza; Bay-g-5421; Акарбоза.

O-{4-Amino-4,6-dideoxy-*N*-[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enyl]-α-D-glucopyranosyl}-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

$C_{25}H_{43}NO_{18}$=645.6

CAS — 56180-94-0.

ATC — A10BF01.

ATC Vet — QA10BF01.

UNII — T58MSI464G.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. & (Acarbose). A white or yellowish, amorphous, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 36: (Acarbose). Produced by certain strains of *Actinoplanes utahensis*. Store in airtight containers.

Uses and Administration

Acarbose is an inhibitor of alpha glucosidases, especially sucrase. This slows the digestion and absorption of carbohydrates in the small intestine and hence reduces the increase in blood-glucose concentrations after a carbohydrate load. It is given in the treatment of type 2 diabetes mellitus (p. 459.1) either alone or with a sulfonylurea, biguanide, or insulin. Acarbose treatment may be started with a low oral dose of 25 or 50 mg daily to minimise gastrointestinal disturbance. It is then gradually increased to a usual dose of 25 or 50 mg three times daily, immediately before food. After 4 to 8 weeks, the dose may be increased further if necessary, and doses up to 100 to 200 mg three times daily may be given. Licensed US product information recommends a maximum dose of 50 mg three times daily for patients weighing up to 60 kg, and a maximum of 100 mg three times daily for those weighing more. Some benefit has also been found when acarbose is used to supplement insulin therapy in type 1 diabetes mellitus.

Acarbose has also been studied for the treatment of reactive hypoglycaemia, the dumping syndrome, certain types of hyperlipoproteinaemia, and polycystic ovary syndrome.

References.

1. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin Pharmacokinet* 1996; **30:** 94–106.
2. Hoffman J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II study. *Am J Med* 1997; **103:** 483–90.
3. Hollander P, *et al*. Acarbose in the treatment of type I diabetes. *Diabetes Care* 1997; **20:** 248–53.
4. Buse J, *et al*. The PROTECT study: final results of a large multicenter postmarketing study in patients with type 2 diabetes. *Clin Ther* 1998; **20:** 257–69.
5. Scheen AJ. Clinical efficacy of acarbose in diabetes mellitus: a critical review of controlled trials. *Diabetes Metab* 1998; **24:** 311–20.
6. Holman RR, *et al*. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). *Diabetes Care* 1999; **22:** 960–4.
7. Riccardi G, *et al*. Efficacy and safety of acarbose in the treatment of type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study. *Diabet Med* 1999; **16:** 228–32.
8. Josse RG, *et al*. Acarbose in the treatment of elderly patients with type 2 diabetes. *Diabetes Res Clin Pract* 2003; **59:** 37–42.
9. Van de Laar FA, *et al*. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 13/01/09).
10. Hanefeld M, Schaper F. Acarbose: oral anti-diabetes drug with additional cardiovascular benefits. *Expert Rev Cardiovasc Ther* 2008; **6:** 153–63. Correction. *ibid.* 2009; **7:** 330.

Impaired glucose tolerance. A prospective study of patients with impaired glucose tolerance concluded that acarbose delayed the development of type 2 diabetes[1] and significantly reduced the incidence of cardiovascular disease and hypertension.[2] However, a systematic review,[3] which included this study, found that data were limited and that the quality of the other 4 included studies was poor. The authors of the review concluded that there was evidence that acarbose reduced the incidence of type 2 diabetes, but the effects on glycaemic control were limited and it was unclear whether the effect should be seen as prevention, delay, or masking of diabetes. They also felt that more study was needed to confirm whether acarbose prevented cardiovascular events in these patients.

1. Chiasson J-L, *et al*. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359:** 2072–7.
2. Chiasson J-L, *et al*. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290:** 486–94.
3. Van de Laar FA, *et al*. Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 12/01/09).

Adverse Effects

Acarbose often causes gastrointestinal disturbances, particularly flatulence due to bacterial action on non-absorbed carbohydrate in the colon. Abdominal distension, diarrhoea, and pain may occur. A decrease in dosage and improved dietary habits may reduce these adverse effects, and they generally diminish with time. Ileus has been rarely reported. Transient and reversible increases in liver enzyme values can occur, and acarbose should be withdrawn if the elevations persist; there have also been rare reports of jaundice and hepatitis including fatal fulminant hepatitis. Thrombocytopenia and pneumatosis cystoides intestinalis

have been reported. Skin reactions and oedema have been reported rarely.

Incidence of adverse effects. The manufacturers reported that adverse effects of acarbose were rarer in postmarketing surveillance studies than in previous clinical studies;[1,2] this was held to represent better tailoring of individual doses to patient tolerability.

1. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by postmarketing surveillance study. *Clin Invest Med* 1995; **18:** 325–31.
2. Mertes G. Safety and efficacy of acarbose in the treatment of type 2 diabetes: data from a 5-year surveillance study. *Diabetes Res Clin Pract* 2001; **52:** 193–204.

Effects on the gastrointestinal tract. Pneumatosis cystoides intestinalis has been reported after the use of alpha-glucosidase inhibitors including acarbose, miglitol, and voglibose.[1,2] The most common symptoms were abdominal distension and pain; haematochezia (blood in the stool) was also reported. The interval between starting therapy and onset of pneumatosis varied greatly, ranging from 7 days to 11 years.

1. Tsujimoto T, *et al.* Pneumatosis cystoides intestinalis following alpha-glucosidase inhibitor treatment: a case report and review of the literature. *World J Gastroenterol* 2008; **14:** 6087–92.
2. Kojima K, *et al.* Pneumatosis cystoides intestinalis induced by the alpha-glucosidase inhibitor miglitol. *Intern Med* 2010; **49:** 1545–8.

Effects on the liver. Hepatocellular liver damage and elevated serum aminotransferases, with or without jaundice, have been reported in patients receiving acarbose.[1-4] In these cases, symptoms resolved on stopping the drug; however, licensed product information states that there have been cases of fatal fulminant hepatitis.

1. Andrade RJ, *et al.* Hepatic injury caused by acarbose. *Ann Intern Med* 1996; **124:** 931.
2. Carrascosa M, *et al.* Acarbose-induced acute severe hepatotoxicity. *Lancet* 1997; **349:** 698–9.
3. Fujimoto Y, *et al.* Acarbose-induced hepatic injury. *Lancet* 1998; **351:** 340.
4. Hsiao S-H, *et al.* Hepatotoxicity associated with acarbose therapy. *Ann Pharmacother* 2006; **40:** 151–4.

Effects on the skin. Generalised erythema multiforme and eosinophilia occurred in a male diabetic patient 13 days after starting acarbose.[1] The hypersensitivity reaction was confirmed by rechallenge.

1. Kono T, *et al.* Acarbose-induced generalised erythema multiforme. *Lancet* 1999; **354:** 396–7.

Precautions

Acarbose is contra-indicated in inflammatory bowel disease, particularly where there is associated ulceration, and in gastrointestinal obstruction or patients predisposed to it. It should be avoided in patients with chronic intestinal diseases that significantly affect digestion or absorption, and in conditions which may deteriorate as a result of increased gas formation, such as hernia.

Acarbose is also contra-indicated in patients with hepatic impairment and liver enzyme values should be monitored, particularly during the first 6 to 12 months of therapy and at high doses.

Acarbose given alone should not cause hypoglycaemia, but may potentiate the effects of sulfonylureas and insulin. If hypoglycaemia doses develop in a patient receiving acarbose it needs to be treated with glucose, since the action of acarbose inhibits the hydrolysis of disaccharides.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acarbose as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Acarbose may enhance the effects of other antidiabetics, including insulin, and a reduction in their dosage may be needed. Use with gastrointestinal adsorbents and digestive enzyme preparations can diminish the effects of acarbose and should be avoided. Neomycin and colestyramine may enhance the effects of acarbose and a reduction in its dosage may be required. Acarbose may inhibit the absorption of digoxin (see Antidiabetics, under Interactions of Digoxin, p. 1356.3).

Pharmacokinetics

After ingestion of acarbose, the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity and is metabolised by intestinal enzymes and by the microbial flora. Less than 2% of a dose is absorbed unchanged, but about 35% is absorbed in the form of metabolites. Acarbose is excreted in the urine and faeces.

Renal impairment. Increased peak plasma concentrations of acarbose and areas under the concentration-time curve (of about 5 and 6 times normal, respectively) have been found in pharmacokinetic studies of patients with severe renal impairment (creatinine clearance less than 25 mL/min per 1.73 m^2). The clinical significance of these effects is unknown.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Glucobay; ***Austral.***: Glucobay; ***Austria***: Glucobay; ***Belg.***: Glucobay; ***Braz.***: Aglucose; Glucobay; ***Canad.***: Glucobay; Prandase†; ***Chile***: Glucobay; ***China***: Beixi (贝希); Glucobay (拜唐苹); Kaboping (卡博平); ***Cz.***: Glucobay; ***Denm.***: Glucobay; ***Fin.***: Glucobay; ***Fr.***: Glucor; ***Ger.***: Glucobay; ***Gr.***: Glucobay; ***Hong Kong***: Glucobay; ***Hung.***: Glucobay; ***India***: Abacus; Acarb; Acarbay; Acarex; Acarwin; Asucrose; Diabose; Diadose; Glubose; Glucar; Glucobay; Glucobose; Gludase; K-Carb; ***Indon.***: Eclid; Glucobay; ***Irl.***: Glucobay; ***Israel***: Acrose; Prandase; ***Ital.***: Glicobase; Glucobay; ***Malaysia***: Dibose; Garbose; Glucar; Glucobay; Glucorid; Precarbay; Precose†; ***Mex.***: Glemisal; Glucobay; Incardel; Sincrosa; ***Neth.***: Glucobay; ***Norw.***: Glucobay; ***NZ***: Glucobay; ***Philipp.***: Glucobay; Glyconase; ***Pol.***: Glucobay; ***Port.***: Alsucril; Bluecose; Establix; Glucobay; Linacal; ***Rus.***: Glucobay (Глюкобай); ***S.Afr.***: Glucobay; ***Singapore***: Glucobay; ***Spain***: Glucobay; Glumida; ***Swed.***: Glucobay; ***Switz.***: Glucobay; ***Thai.***: Glucobay; ***Turk.***: Acaris; Arokan; Glucar; Glucobay; Glynose; ***UK***: Glucobay; ***Ukr.***: Glucobay (Глюкобай)†; ***USA***: Precose; ***Venez.***: Glucobay.

Acetohexamide *(BAN, USAN, rINN)*

Acetohexamid; Acetohexamida; Acétohexamide; Acetohexamidum; Asetoheksamidi; Compound 33006; Ацетогексамид.

1-(4-Acetylbenzenesulphonyl)-3-cyclohexylurea.

$C_{15}H_{20}N_2O_4S$=324.4

CAS — 968-81-0.

ATC — A10BB31.

ATC Vet — QA10BB31.

UNII — QGC8W08I6I.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Acetohexamide). A white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 230 of alcohol and 1 in 210 of chloroform; soluble in pyridine and in dilute solutions of alkali hydroxides.

Profile

Acetohexamide is a sulfonylurea antidiabetic (p. 502.3). It has been given in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Dimelin.

Pharmacopoeial Preparations

USP 36: Acetohexamide Tablets.

Alogliptin Benzoate *(USAN, rINNM)*

Alogliptine, Benzoate de; Alogliptini Benzoas; Benzoato de alogliptina; SYR-322; Альоглиптина бензоат.

6-[(3*R*)-3-Aminopiperidin-1-yl]-1-(2-cyanobenzyl)-3-methylpyrimidin-2,4(1*H*,3*H*)-dione monobenzoate.

$C_{18}H_{21}N_5O_2.C_7H_6O_2$=461.5

CAS — 850649-61-5 (alogliptin); 850649-62-6 (alogliptin benzoate).

ATC — A10BH04.

ATC Vet — QA10BH04.

UNII — EEN99869SC.

Uses and Administration

Like sitagliptin (p. 502.1), alogliptin benzoate is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1).

Alogliptin is given as the benzoate, but doses are expressed in terms of the base; 34 mg of alogliptin benzoate is equivalent to about 25 mg of alogliptin. The usual oral dose is the equivalent of alogliptin 25 mg once daily with or without food. When given with metformin, alogliptin may be given in 2 divided doses. The dose of sulfonylurea or insulin may need to be lowered when used with alogliptin. Dosage should be adjusted in patients with renal impairment (see p. 469.3).

References.

1. Scott LJ. Alogliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2010; **70:** 2051–72. Correction. *ibid.*; 2475.
2. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; **71:** 1441–67.

Administration in renal impairment. Licensed product information suggests the following oral doses of alogliptin in patients with renal impairment, based on creatinine clearance (CC):

- mild impairment (CC 60 mL/min or more): no adjustment necessary, 25 mg once daily
- moderate impairment (CC 30 to less than 60 mL/min): 12.5 mg once daily
- severe impairment (CC 15 to less than 30 mL/min) or end-stage renal disease (CC less than 15 mL/min or requiring haemodialysis): 6.25 mg once daily. Alogliptin may be given without regard to the timing of haemodialysis but it has not been studied in peritoneal dialysis

Adverse Effects, Treatment, and Precautions

As for Sitagliptin Phosphate, p. 502.1.

There have been reports of fatal and non-fatal hepatic failure in patients taking alogliptin. It should be used with caution in patients with abnormal liver test results, and treatment interrupted in those who develop symptoms of liver injury and persistently elevated liver enzyme concentrations.

Interactions

The efficacy of alogliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Pharmacokinetics

Alogliptin is absorbed from the gastrointestinal tract, with a peak plasma concentration occurring about 1 to 2 hours after a single oral dose, and a bioavailability of almost 100%. Alogliptin is not extensively metabolised; about 76% is excreted in the urine and 13% in the faeces. Its terminal half-life is about 21 hours.

References.

1. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* 2010; **12:** 648–58.
2. Golightly LK, *et al.* Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet* 2012; **51:** 501–14. Correction. *ibid.*; 831.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Nesina; ***UK***: Vipidia; ***USA***: Nesina.

Multi-ingredient Preparations. ***Jpn***: Liovel; ***UK***: Vipdomet; ***USA***: Kazano; Oseni.

Biguanide Antidiabetics

Antidiabéticos biguanídicos; Бигуаниды Антидиабетические.

Uses and Administration

The biguanide antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p. 459.1). They are given to supplement treatment by diet modification when such modification has not proved effective on its own. In addition, because biguanides are not associated with weight gain, they are preferred in obese patients. In non-obese patients sulfonylureas (p. 502.3) may be preferred, although a biguanide is often added or given instead to patients who are not responding to a sulfonylurea.

The mode of action of biguanides is not clear. They do not stimulate insulin release but require that some insulin be present in order to exert their antidiabetic effect. Possible mechanisms of action include delay in the absorption of glucose from the gastrointestinal tract, an increase in insulin sensitivity and glucose uptake into cells, and inhibition of hepatic gluconeogenesis. Biguanides do not usually lower blood-glucose concentrations in non-diabetic subjects.

Hyperlipidaemias. The effect of biguanides on lipid metabolism is unclear, although some beneficial effects on serum-lipid profiles have been described. Study results in patients with type 2 diabetes have been reviewed.[1] Reductions in concentrations of total cholesterol and low-density-lipoprotein cholesterol can occur, an effect which may not necessarily depend on glycaemic control. Increases in high-density-lipoprotein cholesterol have not been significant. There is evidence for a reduction in serum-triglyceride levels, which may be related to glycaemic control and metformin dose. However, the review found that effects

on lipids were generally limited and not expected to result in major reductions in cardiovascular end-points.

1. Wulffelé MG, *et al*. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *J Intern Med* 2004; **256:** 1–14.

Polycystic ovary syndrome. For discussion of the potential of metformin in polycystic ovary syndrome, see p. 492.2.

Adverse Effects

Gastrointestinal adverse effects including anorexia, nausea, vomiting, and diarrhoea may occur with biguanides, often at the start of treatment. The effects generally resolve spontaneously, but can be minimised by introducing the drug gradually. Patients may have taste disturbance and there may be weight loss. Absorption of various substances including vitamin B_{12} may be impaired. Skin reactions have been reported rarely.

Hypoglycaemia is rare with a biguanide given alone, although it may occur if other contributing factors or drugs are present.

Lactic acidosis, sometimes fatal, has occurred with biguanides, mainly with phenformin. When it has occurred with metformin most cases have been in patients whose condition contra-indicated the use of the drug, particularly those with renal impairment.

Phenformin has been implicated in the controversial reports of excessive cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p. 503.2).

Reviews.

1. Paterson KR, *et al*. Undesired effects of biguanide therapy. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 173–82.
2. Howlett HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 1999; **20:** 489–503.

Effects on the blood. Megaloblastic anaemia has occurred with biguanide therapy (see Malabsorption, under Effects on the Gastrointestinal Tract, p. 470.1). A few cases of metformin-induced haemolysis resulting in hyperbilirubinaemia and jaundice have also been described,[1-3] including a case that progressed to massive haemolysis, shock, and death.[4]

1. Lin K-D, *et al*. Metformin-inducedhemolysis with jaundice. *N Engl J Med* 1998; **339:** 1860–1.
2. Kashyap AS, Kashyap S. Haemolytic anaemia due to metformin. *Postgrad Med J* 2000; **76:** 125–6.
3. Meir A, *et al*. Metformin-induced hemolytic anemia in a patient with glucose-6-phosphate dehydrogenase deficiency. *Diabetes Care* 2003; **26:** 956–7.
4. Packer CD, *et al*. Fatal hemolytic anemia associated with metformin: a case report. *J Med Case Reports* 2008; **2:** 300.

Effects on the gastrointestinal tract. *DIARRHOEA.* Diarrhoea is a well-known adverse effect of metformin.[1] It often occurs when treatment is started, but generally subsides with continued use; it can also be minimised by taking metformin with meals, starting with a low dose and increasing gradually. Chronic diarrhoea described as watery, often explosive, and frequently causing faecal incontinence, has been reported as an adverse effect of late onset in patients receiving metformin. Some patients had been on stable metformin therapy for several years before the onset of diarrhoea. Symptoms ceased upon withdrawal of metformin, and recurred in cases of rechallenge.[2,3]

1. Bytzer P, *et al*. Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther* 2001; **15:** 137–42.
2. Raju B, *et al*. Metformin and late gastrointestinal complications. *Am J Med* 2000; **109:** 260–1.
3. Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy* 2001; **21:** 1422–4.

MALABSORPTION. Megaloblastic anaemia due to vitamin B_{12} malabsorption in a 58-year-old woman was associated with long-term use of metformin.[1] Metformin also appeared to precipitate a fall in serum concentrations of vitamin B_{12} with megaloblastic anaemia, within 10 months of starting therapy, in a woman who had previously undergone gastrectomy.[2] She was successfully managed with mecobalamin supplementation and the use of nateglinide for the management of her diabetes.

In a survey of diabetic patients receiving biguanide therapy,[3] malabsorption of vitamin B_{12} was seen in 14 of 46 diabetics taking metformin or phenformin; metformin was more commonly to blame. Withdrawal of the drug resulted in normal absorption in only 7 of the 14. A placebo-controlled study[4] in 353 patients also found reduced vitamin B_{12} concentrations after 16 weeks of metformin, with associated decreases in serum-folate and increases in homocysteine. A study[5] in 390 patients has confirmed the effects of metformin on vitamin B_{12} and homocysteine concentrations. In a series of 10 patients[6] with vitamin B_{12} deficiency associated with metformin, vitamin B_{12} concentrations and blood count abnormalities were reported to have been corrected within 3 months of starting treatment with intramuscular or oral cyanocobalamin; 2 patients were transferred to treatment with other antidiabetic agents. Dietary advice on vitamin B_{12} intake has also been suggested as an intervention.[7]

1. Callaghan TS, *et al*. Megaloblastic anaemia due to vitamin B_{12} malabsorption associated with long-term metformin treatment. *BMJ* 1980; **280:** 1214–15.
2. Fujita H, *et al*. A case of megaloblastic anemia due to vitamin B_{12} deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy. *Endocr J* 2003; **50:** 483–4.
3. Adams JF, *et al*. Malabsorption of vitamin B_{12} and intrinsic factor secretion during biguanide therapy. *Diabetologia* 1983; **24:** 16–18.
4. Wulffelé MG, *et al*. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med* 2003; **254:** 455–63.
5. de Jager J, *et al*. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010; **340:** c2181.
6. Andrès E, *et al*. Metformin-associated vitamin B_{12} deficiency. *Arch Intern Med* 2002; **162:** 2251–2.
7. Vidal-Alaball J, Butler CC. Reduced serum vitamin B-12 in patients taking metformin. *BMJ* 2010; **340:** 1147–8.

Effects on the liver. Hepatotoxic reactions to metformin are rare, but several cases of cholestatic hepatitis have been described.[1-8] Generally, the reaction occurred less than 2 months after starting metformin, and resolved within about 3 months after stopping the drug.

1. Babich MM, *et al*. Metformin-induced acute hepatitis. *Am J Med* 1998; **104:** 490–2.
2. Desilets DJ, *et al*. Cholestatic jaundice associated with the use of metformin. *Am J Gastroenterol* 2001; **96:** 2257–8.
3. Nammour FE, *et al*. Metformin-induced cholestatic hepatitis. *Endocr Pract* 2003; **9:** 307–9.
4. Deutsch M, *et al*. Metformin hepatotoxicity. *Ann Intern Med* 2004; **140:** W25. Available at: http://www.annals.org/cgi/reprint/140/5/W-25.pdf (accessed 05/10/09)
5. Kutoh E. Possible metformin-induced hepatotoxicity. *Am J Geriatr Pharmacother* 2005; **3:** 270–3.
6. Barquero Romero J, Pérez Miranda M. Hepatitis colestásica inducida por metformina. *Gastroenterol Hepatol* 2005; **28:** 257–8.
7. Cone CJ, *et al*. Hepatotoxicity associated with metformin therapy in treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease. *Ann Pharmacother* 2010; **44:** 1655–9.
8. Miralles-Linares F, *et al*. Metformin-induced hepatotoxicity. *Diabetes Care* 2012; **35:** e21.

Effects on the pancreas. Although acute pancreatitis is more commonly associated with phenformin[1,2] there have also been a few cases of pancreatitis associated with metformin, in which renal failure may have precipitated metformin toxicity.[3,4] Pancreatitis has also occurred in a patient without renal impairment, about 48 hours after starting metformin for polycystic ovary syndrome.[5]

1. Wilde H. Pancreatitis and phenformin. *Ann Intern Med* 1972; **77:** 324.
2. Chase HS, Mogan GR. Phenformin-associated pancreatitis. *Ann Intern Med* 1977; **87:** 314–15.
3. Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. *Postgrad Med J* 2004; **80:** 239--40.
4. Fimognari FL, *et al*. Metformin-induced pancreatitis: a possible adverse drug effect during acute renal failure. *Diabetes Care* 2006; **29:** 1183.
5. Molina Infante J, *et al*. Pancreatitis aguda tóxica por metformina sin insuficiencia renal. *Med Clin (Barc)* 2008; **131:** 519.

Hypersensitivity. Vasculitis and pneumonitis in a 59-year-old woman was associated with use of metformin.[1] Symptoms improved on withdrawal of metformin, but reappeared on its reintroduction. Cutaneous vasculitis in a 33-year-old woman also resolved on withdrawal of metformin and recurred with its reintroduction.[2]

1. Klapholz L, *et al*. Leucocytoclastic vasculitis and pneumonitis induced by metformin. *BMJ* 1986; **293:** 483.
2. Salem CB, *et al*. Rare case of metformin-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2006; **40:** 1685–7.

Hypoglycaemia. Licensed product information for metformin states that hypoglycaemia does not occur with metformin alone, even in overdosage, although it may occur if given with alcohol or other hypoglycaemics. Interim 3-year results from the UK Prospective Diabetes Study[1] indicated that metformin therapy was associated with fewer hypoglycaemic episodes than sulfonylurea or insulin treatment, but more than with diet alone. In a follow-up study of 290 patients who were treated with metformin for at least 6 years, the annual percentage of patients reporting at least one hypoglycaemic episode was 1.7%, compared with 0.8% of 756 patients managed on diet alone.[2]

1. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for 3 years. *BMJ* 1995; **310:** 83–8.
2. Wright AD, *et al*. for the UKPDS Group. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. *J Diabetes Complications* 2006; **20:** 395–401.

Lactic acidosis. There is a small but definite risk of lactic acidosis associated with use of biguanide antidiabetics. Most early reports involved phenformin, which was consequently removed from the market in many countries although cases of phenformin-associated lactic acidosis still occur.[1-5] There has therefore been concern about the risks of lactic acidosis with metformin, which is still in wide use. However, lactic acidosis with metformin appears to be much less common:[6] a review suggested that the incidence was of the order of 3 cases per 100 000 patient years, which was 20 times less frequent than with phenformin.[7] This concurs with the findings of the FDA after the introduction of metformin to the US market: in the year after the marketing of metformin in the USA, the FDA had received reports of metformin-associated lactic acidosis in 66 patients,[8] the diagnosis being confirmed in 47. This represented a rate of about 5 cases per 100 000. Most patients who do develop lactic acidosis with metformin have one or more precipitating risk factors such as renal impairment, congestive heart failure, or other conditions predisposing to hypoxaemia or acute renal failure, including septicaemia, acute hepatic decompensation, alcohol abuse, acute myocardial infarction, and shock.[6,7] Dehydration might also be a contributing factor.[9-11] See also Heart Failure, p. 471.1, for further discussion on the risks of using metformin in patients with that condition. A systematic review,[12] which considered study results comprising over 70 000 patient years of treatment with metformin, concluded that provided metformin was prescribed taking into account the proper contra-indications, there was no evidence of an increased risk of lactic acidosis. The relationship between metformin and lactic acidosis has also been directly questioned in a review of 47 case reports.[13] The authors asserted that these patients had other risk factors that could account for the development of lactic acidosis, and that no relationship could be established between lactate concentration, metformin concentration, and mortality. They suggested, therefore, that the association between metformin use and lactic acidosis in these cases could have been coincidental rather than causal. Nonetheless, there have been a few reports of lactic acidosis developing in metformin-treated patients without apparent risk factors.[7,14,15]

1. Rosand J, *et al*. Fatal phenformin-associated lactic acidosis. *Ann Intern Med* 1997; **127:** 170.
2. Enia G, *et al*. Lactic acidosis induced by phenformin is still a public health problem in Italy. *BMJ* 1997; **315:** 1466–7.
3. Kwong SC, Brubacher J. Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 1998; **16:** 881–6.
4. Kumar A, *et al*. Severe acidosis in a patient with type 2 diabetes mellitus, hypertension, and renal failure. *Chest* 2003; **123:** 1726–9.
5. Fimognari FL, *et al*. Phenformin-induced lactic acidosis in an older diabetic patient: a recurrent drama (phenformin and lactic acidosis). *Diabetes Care* 2006; **29:** 950–1.
6. Lalau J-D. Lactic acidosis induced by metformin: incidence, management and prevention. *Drug Safety* 2010; **33:** 727–40.
7. Chan NN, *et al*. Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabet Med* 1999; **16:** 273–81.
8. Misbin RI, *et al*. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998; **338:** 265–6.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Metformin, dehydration and lactic acidosis. *Aust Adverse Drug React Bull* 2009; **28:** 11–12. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0906.pdf (accessed 11/02/11)
10. Fitzgerald E, *et al*. Metformin associated lactic acidosis. *BMJ* 2009; **339:** 1254–6.
11. Preiss DJ, Sattar N. Metformin and lactic acidosis. Metformin: framed again? *BMJ* 2010; **340:** 8–9.
12. Salpeter SR, *et al*. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 11/08/10).
13. Stades AME, *et al*. Metformin and lactic acidosis: cause or coincidence? A review of case reports. *J Intern Med* 2004; **255:** 179–87.
14. Silvestre J, *et al*. Metformin-induced lactic acidosis: a case series. *J Med Case Reports* 2007; **1:** 126.
15. Bruijstens LA, *et al*. Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. *Neth J Med* 2008; **66:** 185–90.

Treatment of Adverse Effects

Acute poisoning with biguanides may lead to the development of lactic acidosis (see Metabolic Acidosis, p. 1777.2) and calls for intensive supportive therapy. Glucose or glucagon may be required for hypoglycaemia, the general management of which is outlined in Insulin, p. 486.3. Activated charcoal may be given orally within 1 hour of overdose, provided the airway can be protected.

Overdosage. References.

1. Spiller HA, *et al*. Multicenter case series of pediatric metformin ingestion. *Ann Pharmacother* 2000; **34:** 1385–8.
2. Forrester MB. Adult metformin ingestions reported to Texas poison control centers, 2000—2006. *Hum Exp Toxicol* 2008; **27:** 575–83.

Precautions

Biguanides are inappropriate for patients with diabetic coma and ketoacidosis, or for those with severe infection, trauma, or other severe conditions where the biguanide is unlikely to control the hyperglycaemia; insulin should be used in such situations. Biguanides are generally avoided in patients with renal impairment, as it may predispose patients to lactic acidosis, and renal function should be monitored throughout therapy (see also Renal Impairment under Precautions of Metformin, p. 493.1). Dehydration may contribute to renal impairment. Conditions associated with hypoxia, such as acute heart failure, recent myocardial infarction, or shock, may increase the risk of lactic acidosis. Other conditions that may also predispose to lactic acidosis

in a patient taking a biguanide include excessive alcohol intake and hepatic impairment. Biguanides should be discontinued in patients undergoing surgery and only restarted once normal renal function has been established. They may also need to be temporarily stopped for examinations using contrast media in some patients (see under Interactions, p. 471.1).

Insulin is preferred for the treatment of diabetes in pregnancy (but see also p. 493.1 for reports of metformin use during pregnancy).

Owing to the possibility of decreased vitamin B_{12} absorption, annual monitoring of vitamin B_{12} concentrations is advisable during long-term treatment.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 487.2) for restrictions applied to diabetic patients in the UK.

Heart failure. Metformin has been contra-indicated in diabetic patients with heart failure, because of an increased risk of lactic acidosis. However, there is evidence from observational studies that although this contra-indication has been increasingly ignored, lactic acidosis in these patients is still rare.[1] A causal role for metformin in cases of lactic acidosis has also been questioned (see Lactic Acidosis, p. 468.2). Although heart failure is a common comorbidity in diabetics, controlled studies of metformin in these patients are lacking. Data from observational and retrospective studies, and a small prospective study, have shown no increase in risk of lactic acidosis with metformin, and have actually suggested that metformin may be associated with lower rates of morbidity and mortality, of any cause, in patients with heart failure.[1-4] It has therefore been suggested that metformin may be used, with caution, in diabetic patients with compensated, stable heart failure.[5] However, it is still contra-indicated in those with acute or unstable symptoms,[5] and in those with coexisting risk factors such as renal impairment.[1,3]

1. Tahrani AA, *et al.* Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *BMJ* 2007; **335:** 508–12.
2. Eurich DT, *et al.* Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. Abridged version: *BMJ* 2007; **335:** 497–501. Full version: http://www.bmj.com/cgi/reprint/335/7618/497 (accessed 23/02/09)
3. Roberts F, Ryan GJ. The safety of metformin in heart failure. *Ann Pharmacother* 2007; **41:** 642–6.
4. Khurana R, Malik IS. Metformin: safety in cardiac patients. *Heart* 2010; **96:** 99–102.
5. Inzucchi SE, *et al.* Metformin therapy in patients with type 2 diabetes complicated by heart failure. *Am Heart J* 2007; **154:** e45. Also published in:*Diabetes Care* 2007; **30:** e129.

Interactions

Use of a biguanide with other drugs that lower blood-glucose concentrations increases the risk of hypoglycaemia, while drugs that increase blood glucose may reduce the effect of biguanide therapy.

In general fewer drug interactions have been reported with biguanides than with sulfonylureas. Alcohol may increase the risk of lactic acidosis as well as of hypoglycaemia. Care should be taken if biguanides are given with drugs that may impair renal function.

Anticoagulants. For the effect of metformin on *phenprocoumon* activity, see Antidiabetics, p. 1531.3.

Antivirals. Fatal lactic acidosis has been reported[1] in a patient given metformin with *didanosine*, *stavudine*, and *tenofovir*.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Cimetidine. Cimetidine increased plasma-metformin concentrations in 7 healthy subjects.[1] The renal clearance of metformin was reduced; competition for proximal tubular secretion was considered responsible. A reduction in metformin dosage may be required in patients taking metformin and cimetidine, in order to reduce the risk of lactic acidosis. For a report of lactic acidosis in a patient given metformin, cimetidine, and orlistat, see Orlistat, p. 471.2.

1. Somogyi A, *et al.* Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; **23:** 545–51.

Contrast media. Caution is required when using iodinated contrast media in those receiving biguanides because of the risk of patients developing lactic acidosis. Licensed product information for some contrast media preparations warns that biguanides should be temporarily stopped 48 hours before the examination, and withheld until normal renal function is confirmed. However, several guidelines[1-4] that give advice on the use of iodinated contrast media in patients taking metformin, do not support such general restrictions for patients with normal serum creatinine and/or a glomerular filtration rate above 60 mL/minute. In general they recommend that for patients with:

- no comorbidities and normal renal function: there is no need to discontinue metformin before use of an iodinated contrast medium and no need to check serum creatinine afterwards
- multiple comorbidities and normal renal function: metformin should be discontinued at the time of the procedure and withheld for 48 hours. A repeat serum creatinine measurement is not mandatory before restarting metformin in such patients unless there are risk factors for renal damage
- renal dysfunction: metformin should be discontinued at the time of the procedure and should be restarted after at least 48 hours and then only if renal function remains stable

Canadian guidelines[1] also consider that metformin should be withheld in all patients for 48 hours if the volume of contrast medium is greater than 100 mL.

1. Benko A, *et al.* Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007; **58:** 79–87. Correction available at: http://www.car.ca/Files%5CNephropathy.pdf (accessed 22/05/09) [correct version]
2. European Society of Urogenital Radiology. ESUR guidelines on contrast media (version 7.0, issued August 2008). Available at: http://www.esur.org/ESUR_Guidelines_NEW.6.0.html (accessed 22/05/09)
3. Committee on Drugs and Contrast Media. American College of Radiology manual on contrast media (version 7, issued 2010). Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual/FullManual.aspx (accessed 24/08/10)
4. Board of the Faculty of Clinical Radiology; The Royal College of Radiologists. Standards for intravascular contrast agent administration to adult patients, second edition (issued April 2010). Available at: http://www.rcr.ac.uk/docs/radiology/pdf/BFCR%2810%294_Stand_contrast.pdf (accessed 24/08/10)

Ketotifen. Platelet counts in 10 diabetic patients receiving biguanides fell (markedly in 3 patients) when they were also given ketotifen.[1] Counts returned to normal a few days after the end of ketotifen therapy. However, the investigators did not consider the effect clinically significant.

1. Doleček R. Ketotifen in the treatment of diabetics with various allergic conditions. *Pharmatherapeutica* 1981; **2:** 568–74.

Orlistat. A study in healthy subjects found no significant interaction between orlistat and metformin.[1] However, lactic acidosis developed in a woman with diabetes mellitus given metformin, orlistat, and cimetidine.[2] The authors postulated that diarrhoea caused by orlistat may have led to renal impairment, and a subsequent impairment of metformin excretion. Alternatively, orlistat may have enhanced the absorption of metformin or increased the metformin-induced conversion of glucose to lactate in the gut. These possible interactions may have then been exacerbated by cimetidine, which may reduce renal clearance of metformin (see Cimetidine, above).

1. Zhi J, *et al.* Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. *J Clin Pharmacol* 2002; **42:** 1011–19.
2. Dawson D, Conlon C. Case study: metformin-associated lactic acidosis: could orlistat be relevant? *Diabetes Care* 2003; **26:** 2471–2.

Sulfonylureas. For reference to an apparent increase in mortality with an intensive regimen of metformin plus a sulfonylurea, see p. 503.3.

Buformin *(USAN, pINN)*

Buformina; Buformine; Buforminum; DBV; W-37; Буформин.

1-Butylbiguanide.

$C_6H_{15}N_5$=157.2

CAS — 692-13-7 (buformin); 1190-53-0 (buformin hydrochloride).

ATC — A10BA03.

ATC Vet — QA10BA03.

UNII — W2115E9C7B.

Profile

Buformin is a biguanide antidiabetic (p. 467.3). It has been given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of up to 300 mg daily. Buformin is also used as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Adebit.

Canagliflozin *(USAN, rINN)*

Canagliflozina; Canagliflozine; Canagliflozinum; JNJ-24831754ZAE; JNJ-28431754; JNJ-28431754AAA; TA-7284; Канаглифлозин.

(1*S*)-1,5-Anhydro-1-*C*-{3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl}-D-glucitol hemihydrate.

$C_{24}H_{25}FO_5S$,½H_2O=453.5

CAS — 842133-18-0 (anhydrous canagliflozin); 928672-86-0 (canagliflozin hemihydrate).

UNII — 0SAC974Z85.

NOTE. Canagliflozin (*INN*) is anhydrous, while Canagliflozin (*USAN*) refers to the hemihydrate.

Uses and Administration

Canagliflozin is a sodium-glucose co-transporter 2 inhibitor. It has similar actions to dapagliflozin (p. 472.2) and is used in the management of type 2 diabetes mellitus (p. 459.1).

Canagliflozin is given as the hemihydrate, but doses are expressed in terms of the anhydrous form; 102 mg of canagliflozin hemihydrate is equivalent to about 100 mg of anhydrous canagliflozin. An oral dose of 100 mg once daily is given before the first meal of the day. The dose may be increased to 300 mg once daily if necessary. In particular, patients taking inducers of uridine diphosphate glucuronosyltransferase (UGT), such as rifampicin, may need a daily dose of 300 mg. Doses of insulin, sulfonylurea, or other insulin secretagogues may need to be lowered when used with canagliflozin.

For the use of canagliflozin in renal impairment, see p. 471.3.

References.

1. Nisly SA, *et al.* Canagliflozin, a new sodium-glucose cotransporter 2 inhibitor, in the treatment of diabetes. *Am J Health-Syst Pharm* 2013; **70:** 311–19.

Administration in renal impairment. A canagliflozin dose of 100 mg orally once daily should not be exceeded in patients with moderate renal impairment (estimated GFR 45 to less than 60 mL/min per 1.73 m^2). It should not be used when estimated GFR is less than 45 mL/min per 1.73 m^2.

Adverse Effects and Precautions

As for Dapagliflozin, p. 472.3. Electrolyte disturbances associated with canagliflozin include increases in serum concentrations of potassium, magnesium, and phosphate. Hypersensitivity reactions have been reported.

Interactions

Rifampicin can decrease canagliflozin exposure by induction of uridine diphosphate glucuronosyltransferase (UGT) enzymes, including UGT1A9 and UGT2B4. See Uses and Administration, above, for canagliflozin dose adjustment in patients also given UGT inducers.

Canagliflozin may affect digoxin exposure (see Antidiabetics under Interactions of Digoxin, p. 1356.3).

Pharmacokinetics

Canagliflozin is absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 to 2 hours after a dose and an absolute bioavailability of about 65%. It is extensively bound to plasma proteins. Canagliflozin undergoes glucuronidation, mainly by the uridine diphosphate glucuronosyltransferases UGT1A9 and UGT2B4. There is minimal oxidative metabolism via the cytochrome P450 isoenzyme CYP3A4. About 52% of a dose is excreted in the faeces, mainly as unchanged canagliflozin; about 33% is found in the urine, mainly as *O*-glucuronide metabolites. It has a terminal half-life of about 10 to 13 hours. Removal of canagliflozin by haemodialysis is negligible.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Invokana; ***USA***: Invokana.

Carbutamide *(BAN, rINN)*

BZ-55; Ca-1022; Carbutamida; Carbutamidum; Glybutamide; Karbutamid; Karbutamidi; U-6987; Карбутамид.

1-Butyl-3-sulphanilylurea.

$C_{11}H_{17}N_3O_3S$=271.3

CAS — 339-43-5.

ATC — A10BB06.

ATC Vet — QA10BB06.

UNII — E3K8P4869P.

Profile

Carbutamide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in single daily doses of 0.5 to 1 g, but is more toxic than chlorpropamide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Glucidoral†.

Chlorpropamide *(BAN, rINN)*

Chloropropamid; Chlorpropamid; Chlorpropamidas; Chlorpropamidum; Clorpropamida; Klooripropamidi; Klorpropamid; Klórpropamid; Хлорпропамид.

1-(4-Chlorobenzenesulphonyl)-3-propylurea.

$C_{10}H_{13}ClN_2O_3S$=276.7

CAS — 94-20-2.

ATC — A10BB02.

ATC Vet — QA10BB02.

UNII — WTM2C3IL2X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Chlorpropamide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Chlorpropamide). A white crystalline powder having a slight odour. Practically insoluble in water; soluble in alcohol; sparingly soluble in chloroform.

Uses and Administration

Chlorpropamide is a sulfonylurea antidiabetic (p. 502.3). It has a duration of action of at least 24 hours, and is given orally in the treatment of type 2 **diabetes mellitus** (p. 459.1) in an initial daily dose of 250 mg as a single dose with breakfast. After 5 to 7 days the dose may be adjusted, in steps of 50 to 125 mg at intervals of 3 to 5 days, to achieve an optimum maintenance dose which is usually in the range 100 to 500 mg daily. Increasing the dose above 500 mg daily is unlikely to produce further benefit, and doses above 750 mg daily should be avoided. Although a reduced dose range has been proposed for the elderly, use of chlorpropamide is inadvisable in this group.

Chlorpropamide, though not the other sulfonylureas, is also sometimes used in cranial **diabetes insipidus** (p. 2348.2). It has been reported to act by sensitising the renal tubules to antidiuretic hormone. The dose has to be carefully adjusted to minimise the risk of hypoglycaemia. An initial oral dose of 100 mg daily, adjusted if necessary to a maximum of 350 mg daily has been recommended, although doses of up to 500 mg daily have been used.

Diabetes mellitus. Patients with type 2 diabetes whose blood glucose is adequately controlled at first by sulfonylureas often eventually have treatment failure and loss of diabetic control. Results from the UK Prospective Diabetes Study[1] have suggested that the 6-year failure rate was higher in patients treated with glibenclamide (48%) than in those given chlorpropamide (40%). This difference was equivalent to delaying the requirement for additional therapy for a year in chlorpropamide-treated patients.

1. Matthews DR, *et al.* UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. *Diabet Med* 1998; **15:** 297–303.

Adverse Effects and Treatment

As for sulfonylureas in general, p. 503.1 and p. 504.1.

Chlorpropamide may be more likely than other sulfonylureas to induce a syndrome of inappropriate secretion of antidiuretic hormone characterised by water retention, hyponatraemia, and CNS effects. Patients receiving chlorpropamide may develop facial flushing after drinking alcohol.

Precautions

As for sulfonylureas in general, p. 504.2.

Chlorpropamide should be avoided in the elderly and in renal or hepatic impairment because its long half-life increases the risk of hypoglycaemia. The antidiuretic effect of chlorpropamide may cause problems in patients with conditions associated with fluid retention.

Fasting. For the view that although some sulfonylurea antidiabetics may be able to be used with caution in fasting Muslim patients during Ramadan, chlorpropamide is contra-indicated, see under Precautions of Insulin, p. 487.3.

Thyroid disorders. Some manufacturers have recommended that chlorpropamide should not be used in patients with impaired thyroid function, but see under Sulfonylureas, p. 504.3.

Interactions

As for sulfonylureas in general, p. 504.3.

Chlorpropamide may produce profound facial flushing associated with alcohol ingestion.

Pharmacokinetics

Chlorpropamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. The half-life is about 35 hours. About 80% of a dose is metabolised in the liver; metabolites and unchanged drug are excreted in the urine. Chlorpropamide crosses the placenta and has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diabinese; Idle; Trane; ***Braz.***: Diabecontrol; Diabinese; Glicoben; Glicorp; Pramidalin; ***Canad.***: Novo-Propamide†; ***Chile***: Diabinese; ***Gr.***: Diabinese; ***Hong Kong***: Diabinese; ***India***: Copamide; ***Indon.***: Diabinese; ***Israel***: Diabitex†; ***Ital.***: Diabemide; ***Malaysia***: Propamide; ***Mex.***: Apoprod; Bioness; Diabiclor†; Diabinese; Insogen; ***Philipp.***: Diabinese†; ***S.Afr.***: Diabinese†; Diabitex; Hypomide; ***Singapore***: Anti-D; Propamide; ***Spain***: Diabinese†; ***Thai.***: Decose; Diabeedol†; Diabetese†; Diabinese; Dibecon; Dibemide; Glycemin†; Propamide; ***Turk.***: Diabinese; ***Venez.***: Dabinese.

Multi-ingredient Preparations. ***India***: Chlorformin; ***Ital.***: Bidiabe; Pleiamide; ***Mex.***: Apometoclor; Insogen Plus; Mellitron; Obinese; ***Switz.***: Diabiformine†.

Pharmacopoeial Preparations

BP 2014: Chlorpropamide Tablets;
USP 36: Chlorpropamide Tablets.

Dapagliflozin *(rINN)*

BMS-512148; Dapagliflozina; Dapagliflozine; Dapagliflozinum; Дапаглифлозин.

(1*S*)-1,5-Anhydro-1-*C*-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol.

$C_{21}H_{25}ClO_6$=408.9

CAS — 461432-26-8.

ATC — A10BX09.

ATC Vet — QA10BX09.

UNII — 1ULL0QJ8UC.

NOTE. Dapagliflozin (*USAN*) is the monohydrate of a compound of dapagliflozin with propanediol (see p. 472.2).

Dapagliflozin Propanediol *(rINNM)*

BMS-512148-05; Dapagliflozin (USAN).

(1*S*)-1,5-Anhydro-1-*C*-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol compound with (2*S*)-propane-1,2-diol (1:1) monohydrate.

$C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$=503.0

CAS — 960404-48-2.

ATC — A10BX09.

ATC Vet — QA10BX09.

UNII — 887K2391VH.

Uses and Administration

Dapagliflozin is a sodium-glucose co-transporter 2 inhibitor that enhances urinary excretion of glucose by suppressing renal glucose reabsorption. It is used as monotherapy or with other antidiabetic treatment, including insulin, in the management of type 2 diabetes mellitus (p. 459.1).

It is given as the monohydrate of a compound of dapagliflozin with propanediol, but doses are expressed in terms of dapagliflozin; 12.3 mg of dapagliflozin propanediol monohydrate is equivalent to about 10 mg of dapagliflozin. The usual oral dose is 10 mg once daily. Doses of insulin, sulfonylurea, and other insulin secretagogues may need to be lowered when used with dapagliflozin. The dose of dapagliflozin should be reduced in hepatic impairment (see p. 472.2).

References.
1. Anderson SL, Marrs JC. Dapagliflozin for the treatment of type 2 diabetes. *Ann Pharmacother* 2012; **46:** 590–8.
2. Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. *Diabetes Metab Syndr Obes* 2012; **5:** 313–27.
3. Clar C, *et al.* Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* 2012; **2:** e001007.

Administration in hepatic impairment. A starting oral dose of dapagliflozin 5 mg once daily is recommended in patients with severe hepatic impairment, which may be increased to 10 mg once daily if well tolerated. No dose adjustment is needed in mild and moderate impairment.

Adverse Effects and Precautions

The most common adverse effects of dapagliflozin are dysuria, polyuria, and genital and urinary-tract infections including vulvovaginitis and balanitis; the increase in rates of infection may be related to raised concentrations of urinary glucose. Dyslipidaemia and increased haematocrit are also common, and increases in blood concentrations of creatinine and urea have been reported. Other effects include back pain, hyperhidrosis, constipation, nausea, dizziness, and rash. Dapagliflozin increases diuresis, which can cause volume depletion and a fall in blood pressure; the effect may be greater in patients with very high blood-glucose concentrations. Dapagliflozin itself is unlikely to cause hypoglycaemia, but it may contribute to hypoglycaemia caused by other antidiabetics such as sulfonylureas and insulin.

Higher incidences of bladder, breast, and prostate cancers were recorded during clinical studies of dapagliflozin. However, risk factors and clinical characteristics of the cases were typical for these types of cancers, the duration of exposure to dapagliflozin before tumour diagnosis was short, and the small number of cases limited the assessment for statistical analysis of causality.

Dapagliflozin is less effective in patients with renal impairment; in addition the risk of adverse effects may also be greater in such patients. Although no dose adjustment is recommended in those with mild renal impairment, its use is not recommended in moderate to severe impairment (creatinine clearance < 60 mL/min). Renal function should be checked before starting dapagliflozin and monitored during treatment.

The dose of dapagliflozin should be reduced in hepatic impairment.

Pharmacokinetics

Peak plasma concentrations of dapagliflozin occur within 2 to 3 hours after an oral dose, with a bioavailability of about 78%. It is about 91% bound to plasma proteins. Dapagliflozin is extensively metabolised to inactive metabolites via uridine diphosphate glucuronosyltransferase UGT1A9 in the liver and kidney. It has a plasma terminal half-life of about 13 hours; about 75% of the dose is excreted in the urine and 21% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Forxiga; ***Neth.***: Forxiga; ***UK***: Forxiga; ***USA***: Farxiga.

Epalrestat *(rINN)*

Épalrestat; Epalrestatum; ONO-2235; Эпалрестат.

5-[(*Z*,*E*)-β-Methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.

$C_{15}H_{13}NO_3S_2$=319.4

CAS — 82159-09-9.

UNII — 424DV0807X.

NOTE. The name Aldonil has been used as a trade mark for epalrestat.

Profile

Epalrestat inhibits the enzyme aldose reductase which catalyses the conversion of glucose to sorbitol. It has been suggested that accumulation of sorbitol in certain cells, occurring only in conditions of hyperglycaemia and resulting in a hyperosmotic effect, may be involved in the pathogenesis of some diabetic complications. Aldose reductase inhibitors have no influence on blood-glucose concentrations. Epalrestat is given orally for the treatment of diabetic peripheral neuropathy (see p. 465.2), in a usual dose of 50 mg three times daily before meals.

References.
1. Goto Y, *et al.* A placebo-controlled double-blind study of epalrestat (ONO-2235) in patients with diabetic neuropathy. *Diabet Med* 1993; **10** (suppl 2): 39S–43S.
2. Uchida K, *et al.* Effect of 24 weeks of treatment with epalrestat, an aldose reductase inhibitor, on peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 1995; **17:** 460–6.
3. Hotta N, *et al.* Clinical investigation of epalrestat, an aldose reductase inhibitor, on diabetic neuropathy in Japan: multicenter study. *J Diabetes Complications* 1996; **10:** 168–72.
4. Ikeda T, *et al.* Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 1999; **43:** 193–8.
5. Iso K, *et al.* Long-term effect of epalrestat, an aldose reductase inhibitor, on the development of incipient diabetic nephropathy in type 2 diabetic patients. *J Diabetes Complications* 2001; **15:** 241–4.
6. Hotta N, *et al.* Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. *Diabetes Care* 2006; **29:** 1538–44.
7. Ramirez MA, Borja NL. Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy. *Pharmacotherapy* 2008; **28:** 646–55.

8. Maladkar M, *et al*. Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. *Int J Diabetes Dev Ctries* 2009; **29:** 28–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tang Lin (唐林); YiHeng (伊衡); ***Jpn***: Kinedak.

Exenatide *(BAN, USAN, rINN)*

AC-002993; AC-2993; AC-2993A; Eksenatyd; Exenatid; Exenatida; Exénatide; Exenatidum; LY-2148568; Synthetic Exendin-4; Эксенатид.

$C_{184}H_{282}N_{50}O_{60}S$=4186.6

CAS — 141758-74-9 (exenatide); 141732-76-5 (exendin-4).

ATC — A10BX04.

ATC Vet — QA10BX04.

UNII — 9P1872D4OL.

Uses and Administration

Exenatide is a synthetic form of exendin-4, a 39-amino acid peptide isolated from the venom of the Gila monster lizard (*Heloderma suspectum*, Helodermatidae). The drug is an incretin mimic that acts as an agonist at the glucagon-like peptide 1 receptor to enhance insulin secretion in the presence of raised glucose concentrations; it also suppresses inappropriate glucagon secretion and slows gastric emptying. Exenatide is used as adjunctive therapy in type 2 diabetes mellitus (p. 459.1) in patients who do not have adequate glycaemic control with metformin, a sulfonylurea, a thiazolidinedione, or dual therapy (metformin plus a sulfonylurea or thiazolidinedione). It is also used as adjunctive therapy to basal insulin with or without metformin and/or a thiazolidinedione. Exenatide is given by subcutaneous injection in an initial dose of 5 micrograms twice daily up to 60 minutes before the main morning and evening meals, which should be at least 6 hours apart. It should not be administered after a meal and if a dose is missed treatment should continue at the next scheduled dose. The dose of exenatide may be increased after 1 month to 10 micrograms twice daily if required.

A long-acting formulation of exenatide, for once-weekly dosing, is also available. A dose of 2 mg is given by subcutaneous injection on the same day each week (which can be changed if necessary provided the next dose is given at least 24 hours later) at any time of day, irrespective of meals.

For the use of exenatide in renal impairment, see p. 473.2.

References.

1. Gallwitz B. Benefit-risk assessment of exenatide in the therapy of type 2 diabetes mellitus. *Drug Safety* 2010; **33:** 87–100.
2. Shyangdan DS, *et al*. Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. *BMC Endocr Disord* 2010; **10:** 20. Available at: http://www.biomedcentral.com/1472-6823/10/20 (accessed 27/09/11)
3. Ratner R, *et al*. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. *Cardiovasc Diabetol* 2011; **10:** 22. Available at: http://www.cardiab.com/content/10/1/22 (accessed 27/09/11)
4. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 2011; **34** (suppl 2): S279–S284.
5. Esposito K, *et al*. GLP-1 receptor agonists and HBA1c target of < 7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Curr Med Res Opin* 2011; **27:** 1519–28.
6. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Pharmacother* 2011; **45:** 850–60.
7. Best JH, *et al*. Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. *Diabetes Care* 2011; **34:** 90–5.
8. Monami M, *et al*. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res* 2011; **2011:** 215764.
9. Gallwitz B. Glucagon-like peptide-1 analogues for type 2 diabetes mellitus: current and emerging agents. *Drugs* 2011; **71:** 1675–88.
10. Vilsbøll T, *et al*. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012; **344:** d7771. Available at: http://www.bmj.com/content/344/bmj.d7771?view=long&pmid=22236411 (accessed 13/08/12)
11. Berlie H, *et al*. Glucagon-like peptide-1 receptor agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review. *Diabetes Metab Syndr Obes* 2012; **5:** 165–74.

Action. Orally ingested glucose triggers a much greater secretion of insulin from the pancreas than when given intravenously, a phenomenon known as the 'incretin effect'. Two peptide hormones associated with the incretin effect are glucose-dependent insulin releasing polypeptide (GIP; formerly called gastric inhibitory peptide) and glucagon-like peptide 1 (GLP-1), which are both secreted by gastrointestinal cells in response to food ingestion, and act at specific receptors expressed on pancreatic and other tissue cells. Both stimulate insulin secretion and promote beta cell proliferation; GLP-1 also inhibits glucagon secretion, stimulates the biosynthesis of insulin, slows gastrointestinal transit, decreases the secretion of digestive enzymes, and enhances satiety to reduce food intake. Both GIP and GLP-1 are rapidly degraded by the cell-surface enzyme dipeptidylpeptidase-4 (DPP-4), which is found throughout the body.

In patients with type 2 diabetes the circulating levels of GIP are normal or slightly increased; however, its insulinotropic actions are reduced. Levels of GLP-1 appear to be reduced but response to its action is maintained. Consequently, research has focused on GLP-1 and two groups of drugs have been developed for use in type 2 diabetics: GLP-1 analogues (incretin mimetics), such as exenatide, have a prolonged agonist effect at GLP-1 receptors, while DPP-4 inhibitors, such as sitagliptin (p. 502.1), prevent the degradation of endogenous incretins.

Reviews.

1. Gautier JF, *et al*. Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes. *Diabetes Metab* 2005; **31:** 233–42.
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368:** 1696–1705.
3. Nauck MA. Unraveling the science of incretin biology. *Am J Med* 2009; **122** (6 suppl): S3–S10.

Administration in renal impairment. Exenatide should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, in whom clearance is reduced and risk of adverse gastrointestinal effects increased; it should be used with caution in patients with a renal transplant. Immediate-release exenatide may be used with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min); data on the use of a long-acting formulation of exenatide in such patients are very limited. Patients with mild impairment (creatinine clearance 50 to 80 mL/min) may take the recommended doses of either formulation (see Uses and Administration, above).

Nausea and vomiting with transient hypovolaemia that is caused by exenatide may worsen renal function.

Adverse Effects and Precautions

Hypoglycaemia can occur in patients given exenatide, particularly when given with a sulfonylurea (see also Interactions, p. 473.3). Exenatide commonly causes mild to moderate nausea, which is dose-dependent and tends to decrease with continued therapy in most patients. Other adverse effects include vomiting, diarrhoea, nervousness, dizziness, headache, and dyspepsia. Less frequent reports include asthenia, decreased appetite, gastro-oesophageal reflux, abdominal distension or pain, and hyperhidrosis. Mild injection site reactions may be common. Rashes and hypersensitivity reactions have occurred, and alopecia has also been reported. Acute pancreatitis has been reported, and in such cases exenatide should be stopped permanently.

There have been rare reports of altered renal function in patients given exenatide, including increased serum-creatinine concentrations, renal impairment, worsened chronic renal failure, and acute renal failure (sometimes requiring haemodialysis). Some of these patients also had nausea, vomiting, and/or diarrhoea, which may have affected hydration status, or were taking drugs known to affect renal function or hydration status.

Patients may develop antibodies to exenatide, but this does not usually affect glycaemic control and the antibody titres diminish with time. A small proportion of patients may develop high titres of antibodies, which may impair the efficacy of exenatide.

Exenatide should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use is not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, in whom clearance is reduced and risk of adverse gastrointestinal effects increased. It should be used with caution in moderate renal impairment (creatinine clearance 30 to 50 mL/min) and in patients with a renal transplant. Although exenatide has not been studied in patients with severe gastrointestinal disease, such as gastroparesis, the drug should probably be avoided in such cases because of the gastrointestinal adverse effects commonly associated with its use.

Transient increases in blood-glucose concentrations, that generally improve within the first 2 weeks of treatment, may occur in patients switching from the standard to the once-weekly formulation of exenatide.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 487.2) for restrictions applied to diabetic patients in the UK.

Effects on the pancreas. A 69-year-old man developed pancreatitis within a few days of starting exenatide therapy. Serum-lipase concentrations returned to normal and abdominal pain resolved rapidly when exenatide was stopped.[1] The FDA has also reviewed 30 reports of acute pancreatitis in patients treated with exenatide.[2,3] In 27 cases there was at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridaemia, and alcohol use. Improvement after stopping exenatide was confirmed in 22 reports, and in 3 cases of rechallenge there was a return of symptoms of acute pancreatitis. The FDA subsequently reported[4] in August 2008 that they had received reports of 6 cases of haemorrhagic or necrotising pancreatitis associated with exenatide; all patients required hospitalisation and 2 died. It was recommended that exenatide therapy should be stopped if signs or symptoms of pancreatitis develop and should not be restarted if pancreatitis is confirmed; other antidiabetic drugs should be considered for those with a history of pancreatitis. However, patients with type 2 diabetes may have a greater incidence of pancreatitis when compared with non-diabetic subjects,[5] and large cohort studies have not found a further increase in risk with exenatide itself.[6,7]

1. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. *Diabetes Care* 2006; **29:** 471.
2. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued October 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124712.htm (accessed 24/08/10)
3. Ahmad SR, Swann J. Exenatide and rare adverse events. *N Engl J Med* 2008; **358:** 1970–1.
4. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued August 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm (accessed 24/08/10)
5. Garg R, *et al*. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010; **33:** 2349–54.
6. Dore DD, *et al*. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 2009; **25:** 1019–27.
7. Dore DD, *et al*. A cohort study of acute pancreatitis in relation to exenatide use. *Diabetes Obes Metab* 2011; **13:** 559–66.

Interactions

A reduction in the sulfonylurea dose may be required when exenatide is added to therapy, because of an increased risk of hypoglycaemia with this combination. No increase in hypoglycaemia occurs when exenatide is used with metformin or a thiazolidinedione. The extent and rate of absorption of oral drugs may be reduced by exenatide. Where such an interaction would be undesirable, the oral medication should be given at least 1 hour before exenatide. If the oral medication must be taken with food, it should, where possible, be with a meal or snack when exenatide is not used. There may be an interaction between exenatide and warfarin (see Antidiabetics, under Interactions of Warfarin, p. 1531.3).

Pharmacokinetics

After subcutaneous injection, peak plasma concentrations of exenatide occur in about 2 hours. It is eliminated through the kidneys by glomerular filtration followed by proteolytic degradation, with a terminal half-life of about 2.4 hours. Clearance is reduced in patients receiving dialysis for end-stage renal disease.

References.

1. Kolterman OG, *et al*. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2005; **62:** 173–81.
2. Linnebjerg H, *et al*. Effect of renal impairment on the pharmacokinetics of exenatide. *Br J Clin Pharmacol* 2007; **64:** 317–27.
3. Kothare PA, *et al*. Pharmacokinetics, pharmacodynamics, tolerability, and safety of exenatide in Japanese patients with type 2 diabetes mellitus. *J Clin Pharmacol* 2008; **48:** 1389–99.
4. Iwamoto K, *et al*. Safety, tolerability, pharmacokinetics, and pharmacodynamics of exenatide once weekly in Japanese patients with type 2 diabetes. *Endocr J* 2009; **56:** 951–62.
5. Fineman M, *et al*. Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. *Clin Pharmacokinet* 2011; **50:** 65–74.
6. Linnebjerg H, *et al*. Exenatide—pharmacokinetics, pharmacodynamics, safety and tolerability in patients ≥ 75 years of age with type 2 diabetes. *Int J Clin Pharmacol Ther* 2011; **49:** 99–108.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Byetta; ***Austral.***: Byetta; ***Austria***: Byetta; ***Belg.***: Byetta; ***Braz.***: Byetta; ***Canad.***: Byetta; ***Chile***: Byetta; ***China***: Byetta (百泌达); ***Cz.***: Byetta; ***Denm.***: Bydureon; Byetta; ***Fr.***: Byetta; ***Ger.***: Bydureon; Byetta; ***Gr.***: Byetta; ***Hong Kong***: Byetta; ***Hung.***: Byetta; ***Irl.***: Bydureon; Byetta; ***Israel***: Bydureon; Byetta; ***Ital.***: Byetta; ***Jpn***: Bydureon; Byetta; ***Malaysia***: Byetta; ***Mex.***: Baietta; ***Neth.***: Bydureon; Byetta; ***Norw.***: Bydureon; Byetta; ***NZ***: Byetta; ***Philipp.***: Byetta; ***Pol.***: Byetta; ***Port.***: Byetta; ***Rus.***: Byetta (Баета); ***Singapore***: Byetta; ***Spain***: Byetta; ***Swed.***: Bydureon; Byetta; ***Switz.***: Bydureon; Byetta; ***Thai.***: Byetta; ***Turk.***: Byetta; ***UK***: Bydureon; Byetta; ***USA***: Bydureon; Byetta.

Glibenclamide *(BAN, rINN)*

Glibenclamid; Glibenclamida; Glibenclamidum; Glibenklamid; Glibenklamidas; Glibenklamidi; Glybenclamide; Glybenzcyclamide; Glyburide (USAN); HB-419; U-26452; Глибенкламид.

1-[4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulphonyl]-3-cyclohexylurea.

$C_{23}H_{28}ClN_3O_5S$=494.0

CAS — 10238-21-8.

ATC — A10BB01.

ATC Vet — QA10BB01.

UNII — SX6K58TVWC.

NOTE. The name glibornuride has frequently but erroneously been applied to glibenclamide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Glibenclamide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in dichloromethane. It shows polymorphism.

USP 36: (Glyburide). Store in airtight containers.

Uses and Administration

Glibenclamide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of up to 24 hours.

The usual initial dose of conventional formulations in type 2 diabetes mellitus is 2.5 to 5 mg daily with breakfast, adjusted every 7 days in steps of 2.5 mg daily up to 15 mg daily. Although increasing the dose above 15 mg is unlikely to produce further benefit, doses of up to 20 mg daily have been given. Doses greater than 10 mg daily may be given in 2 divided doses. Because of the relatively long duration of action of glibenclamide, it is best avoided in the elderly. For doses used in adolescents, see p. 474.1.

In some countries micronised preparations of glibenclamide are available, in which the drug is formulated with a smaller particle size, and which have enhanced bioavailability. The usual initial dose of one such preparation (*Glynase PresTab; Pharmacia Upjohn, USA*) is 1.5 to 3 mg daily, adjusted every 7 days in steps of 1.5 mg, up to a usual maximum of 12 mg daily. Doses greater than 6 mg daily may be given in 2 divided doses.

Action. References.
1. Gavin JR, ed. Glyburide: new insights into its effects on the beta cell and beyond. *Am J Med* 1990; **89** (suppl 2A): 1–53S.
2. Luzi L, Pozza G. Glibenclamide: an old drug with a novel mechanism of action? *Acta Diabetol* 1997; **34**: 239–44.

Administration in children. There is limited experience with the use of sulfonylureas in children with type 2 diabetes mellitus, and the biguanide, metformin, is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision, and that shorter-acting alternatives, such as tolbutamide, may be preferred to longer-acting sulfonylureas, such as glibenclamide, that have a greater risk of hypoglycaemia. Although not licensed for use in children in the UK, the *BNFC* suggests that glibenclamide may be given to adolescents, aged 12 to 18 years, in the management of type 2 diabetes mellitus and maturity-onset diabetes of the young. An initial oral dose of 2.5 mg daily, given with breakfast, may be adjusted according to response to a maximum of 15 mg daily.

For details of the use of glibenclamide in neonatal diabetes, see Diabetes Mellitus under Sulfonylureas, p. 503.1.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2.

For a suggestion that the failure rate in type 2 diabetics treated with glibenclamide may be higher than that for those treated with chlorpropamide, see Diabetes Mellitus under Uses and Administration of Chlorpropamide, p. 470.1.

Hypoglycaemia. Severe hypoglycaemia may occur in any patient given any sulfonylurea (see p. 504.1); glibenclamide which has a relatively prolonged duration of action, may cause severe hypoglycaemia more often than shorter-acting sulfonylureas.

In a 1983 review[1] of 57 instances of hypoglycaemia associated with glibenclamide the median age of patients affected was 70 years; only one was less than 60 years old. Median daily dosage was 10 mg. Coma or disturbed consciousness was seen in 46 patients. Ten of these remained comatose despite alleviation of their hypoglycaemia and died up to 20 days after presentation. The authors noted that, including their series of 57 cases, there had been published reports on 101 cases of severe hypoglycaemia with glibenclamide, 14 with a fatal outcome.

There has been a report[2] of hypoglycaemic coma associated with the inhalation of glibenclamide by a worker at a pharmaceutical plant.

1. Asplund K, *et al.* Glibenclamide-associated hypoglycaemia: a report on 57 cases. *Diabetologia* 1983; **24**: 412–17.
2. Albert F, *et al.* Hypoglycaemia by inhalation. *Lancet* 1993; **342**: 47–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glibenclamide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Sulfonylurea antidiabetics are generally avoided in the treatment of diabetes mellitus during pregnancy. However, glibenclamide may have a role in the management of gestational diabetes (see under Sulfonylureas, p. 504.3).

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Glibenclamide is readily absorbed from the gastrointestinal tract and peak plasma concentrations usually occur within 2 to 4 hours. It is extensively bound to plasma proteins. Absorption may be slower in hyperglycaemic patients and may differ according to the particle size of the preparation used. It is metabolised, almost completely, in the liver, the principal metabolite being only very weakly active. About 50% of a dose is excreted in the urine and 50% via the bile into the faeces.

References.
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2. Jaber LA, *et al.* The pharmacokinetics and pharmacodynamics of 12 weeks of glyburide therapy in obese diabetics. *Eur J Clin Pharmacol* 1993; **45**: 459–63.
3. Hoffman A, *et al.* The effect of hyperglycaemia on the absorption of glibenclamide in patients with non-insulin-dependent diabetes mellitus. *Eur J Clin Pharmacol* 1994; **47**: 53–5.
4. Rydberg T, *et al.* Concentration-effect relations of glibenclamide and its active metabolites in man: modelling of pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1997; **43**: 373–81.
5. Jönsson A, *et al.* Pharmacokinetics of glibenclamide and its metabolites in diabetic patients with impaired renal function. *Eur J Clin Pharmacol* 1998; **53**: 429–35.
6. Zhou L, *et al.* Contributions of human cytochrome P450 enzymes to glyburide metabolism. *Biopharm Drug Dispos* 2010; **31**: 228–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agobilina; Benclamid; Broi; Daonil; Diabe Pass; Diabemin; Dismiben; Euglucon; Gardoton; Glaturin; Glentor; Glibemida; Glidanil; Gliptid; Glitral; GON; Pira; Siruc; ***Austral.***: Daonil; Glimel; Semi-Daonil†; ***Austria***: Daonil; Euglucon†; Glucobene; Normoglucon; ***Belg.***: Bevoren†; Daonil; Euglucon; ***Braz.***: Aglucil†; Benclamin; Clamiben; Daonil; Diaben†; Diabexil†; Euglucon†; Glibenclamon; Glibendiab; Glibexil; Glicamin; Glimil; Glionil; Lisaglucon; Niclamida; ***Canad.***: DiaBeta; Euglucon; Gen-Glybe†; Med Glybe†; Mylan-Glybe; ***Chile***: Daonil; Euglusid†; Hipexal; Mezalit; ***China***: Pu Le Kang Ni (普乐康尼); ***Cz.***: Glucobene; Maninil; ***Denm.***: Daonil†; Hexaglucon; ***Fin.***: Euglamin; Euglucon†; Origlucon†; ***Fr.***: Daonil; Euglucan†; Hemi-Daonil; Miglucan†; ***Ger.***: Euglucon N; Glib-ratiopharm; Gliben†; Glibenbeta†; Glibendoc†; Glibenhexal†; Maninil; Semi-Euglucon N; ***Gr.***: Asugrin; Daonil; Deroctyl; Diabefar; Euglykon; Ozepal; ***Hong Kong***: Clamide; CP-Gliben†; Daonil; Euglucon†; Gliben†; Gliboral; Glimel; Glitisol; Marglucon†; Semi-Euglucon†; Xeltic; ***Hung.***: Gilemal; Glucobene; ***India***: Afdiex; Aviglen; Betanase; C-Mide; Codica; D-Con; Daonil; Diabetnil; Diolin; Euglucon; G-Nil; GLCO; Glibet; Glinil; Gluconil; Glucosafe; Glunil; Glyboral; Glybovin; Semi-Daonil; Semi-Euglucon; ***Indon.***: Condiabet; Daonil; Glidanil; Glimel; Gluconic; Glulo; Glyamid†; Libronil†; Padonil; Prodiabet†; Prodiamel; Renabetic; Semi-Daonil; Tiabet†; Trodeb; ***Irl.***: Daonil; Semi-Daonil; ***Israel***: Glibetic; Gluben; ***Ital.***: Daonil; Euglucon; Gliben; Gliboral; ***Jpn***: Euglucon; ***Malaysia***: Daonil; Dibelet; Euglucon; Gliben; Glibesyn; Glimide; ***Mex.***: Abuglib†; Apogly; Biojara; Biostin; Daonil; Dibetid; Diglexol; Euglucon; Gadinor; Glemicid†; Glibenil; Glibenval; Glicavin; Glicoxem; Glifarcal; Glihexal; Glipar; Glucal; Glucoven; Insusym; Mibeclag; Norboral; Ocrix; Reglusan; ***NZ***: Daonil; Gliben†; ***Philipp.***: Amecladin; Bendix; Benglycon; Daonil; Diabitor; Euglodin; Euglotab; Euglucon; Eundin; Gluban; Glymod†; Insol†; Lodulce; Orabetic; Semi-Euglucon; Sentionyl; Sucron†; ***Pol.***: Euclamin†; ***Port.***: Daonil; Semi-Daonil; ***Rus.***: Betanase (Бетаназ)†; Glibamide (Глибамид); Glibex (Глибекс); Glidanil (Глиданил); Glimidstada (Глимидстада); Maniglid (Маниглид); Maninil (Манинил); ***S.Afr.***: Daonil; Diacare; Glycomin; ***Singapore***: Benil; Clamide; Daonil; Dibelet; Glibesyn†; Glimel; Glimide; SP-Diatab; TO Nil; ***Spain***: Daonil; Euglucon; Glucolon; Norglicem; ***Swed.***: Daonil; Euglucon†; ***Switz.***: Daonil; Euglucon†; Glibenorm; Glibesifar; Melix; Semi-Daonil; ***Thai.***: Benclamin; BNIL†; Daonil; Daono; Debtan; Diabenol; Dibelet†; Dibesin; Diclanil†; Euglucon†; Glamide; Glibetic; Glibic; Gliclamin; Glicon; Glimide; Gluconil; Gluzo; Locose; Manoglucon; Semi-Diabenol; Sugril; TO Nil; Unil†; Xeltic; ***Turk.***: Dianorm; Diyaben†; Gliben; ***UAE***: Glynase; Mini-Glynase; ***UK***: Daonil; ***Ukr.***: Maninil (Манинил); ***USA***: DiaBeta; Glynase; Micronase†; ***Venez.***: Daonil; Euglucon; Gliciron.

Multi-ingredient Preparations. ***Arg.***: DBI Duo; Glucovance; Isloglib; Medobis G; Metformin Duo; Metglucon Duo; ***Austral.***: Glucovance; ***Belg.***: Glucovance; ***Braz.***: Glucovance; ***Chile***: Bi-Euglucon M; Diabetyl-G†; Diaglitab Plus; Fintaxim G; Glicenex Duo; Glidanil-G; Glifortex-G; Glimet†; Glucovance; Glukaut; Hipoglucin DA; ***China***: AnHe (安禾); Bai Kang (拜康); Gan Li Ke Fu (甘利可夫); Ge Shuang (格爽); Ge Wan Si (格万斯); Hui Luo Ping (惠络平); Jiang Xi (绛兮); Jin Ping Tang (金平唐); Jun Fu Le (君复乐); Ke Mai Ning (可麦宁); KeRuiTe (可瑞特); Li Jiang (立将); Li Li Le (利力乐); Li Li Nuo (利力诺); Li Sheng Yuan (立生源); Lian He Tang Ding (联合唐定); Lian Jiang (联将); Mei Jia Te (美佳特); Na Xun (拿迅); Qi Ting (齐亭); Rui Lian (瑞联); Shi Ke Yi (适可一); Shuang Ge Ning (双格宁); Shuang Li (双利); Shuang Ping Le (双平乐); Si Yi (思宜); Tai Bi (泰比); Tang Bei Kang (唐贝康); Tang Ke Jie (唐可捷); Tang Ke Ning (唐柯柠); Tang Li Ke (唐立克); Tang Ping (唐平); Tang Rui Ping (唐瑞平); Wan Su Qi (万苏琪); Wei Neng (威能); WeiYi (维夷); Yi Fu Yun (一孚芸); Yi Ke Fu (乙可夫); Yi Sha Ning (宜沙宁); Zhao Wei (兆威); ***Cz.***: Formaglyben; Glibomet; Glucovance; ***Fr.***: Glucovance; ***Gr.***: Daopar; Normell; ***Hong Kong***: Gliconorm; Glucovance; Mydiatab; ***India***: Aviglen-Forte; Aviglen-MF; Ben-Q-Met; Benclamet; Benformin; C-Mide Plus; Clamet; Combidos; Daocon-M; Daonil M; Diabetrol-3D; Diabetrol; Diaforte; Diolin-M; Dior Plus; Duotrol; Eumet-D; G-Formin; Glibact-M; Glibomet; Glifil M; Glinil M; Glitrac-M; Glucomin-Plus; Gluconil-M; Glucored; Glucotrac Plus; Glutowin Forte; Glycurb; Iscept-P; Iscept; Melitus; Metclam; Metica-G; ***Indon.***: Glucovance; ***Ital.***: Bi-Euglucon M; Diaglimet; Dialinax; Gliben F; Glibomet; Gliconorm; Glicorest; Glucomide; Suguan M; ***Malaysia***: Diamide; Glucovance; GlyMet; ***Mex.***: Apometglu; Bi-Dizalon†; Bi-Euglucon M; Bi-Pradia; Dibenmin; Dimefor-G; Duo-Anglucid; Glinorboral; Glucotec; Glucovance; Glunovag G; Gluxson; Imalet; Insusym-Forte; Kontroger; Maviglin; Metixor G; Midapharma; Mifelar-C; Nadib-M; Natisfar; Norfaben M; Sibet-C; Sil-Norboral; Wadil; ***Neth.***: Glucovance; ***Philipp.***: Euglo Plus; Glucovance; ***Pol.***: Glucovance; ***Port.***: Glucovance; ***Rus.***: Bagomet Plus (Багомет Плюс); Glibomet (Глибомет); Gluconorm (Глюконорм); Glucovance (Глюкован); ***S.Afr.***: Glucovance; ***Singapore***: Glucovance; ***Switz.***: Glucovance; ***Thai.***: Glucovance; ***Turk.***: Duplax; Glibomet; Glucovance; ***Ukr.***: Duotrol (Дуотрол); Glibofor (Глибофор); Glibomet (Глибомет); Glucovance (Глюкованс); ***USA***: Diofen; Glucovance; Glybofen; ***Venez.***: Bi-Euglucon; Diaformina Plus; Glucovance.

Pharmacopoeial Preparations

BP 2014: Glibenclamide Tablets;

USP 36: Glyburide and Metformin Hydrochloride Tablets; Glyburide Tablets.

Glibornuride *(BAN, USAN, rINN)*

Glibornurid; Glibornurida; Glibornuridi; Glibornuridum; Ro-6-4563; Глиборнурид.

1-[(2*S*,3*R*)-2-Hydroxyborn-3-yl]-3-tosylurea; 1-[(2*S*,3*R*)-2-Hydroxyborn-3-yl]-3-*p*-tolylsulphonylurea.

$C_{18}H_{26}N_2O_4S$=366.5

CAS — 26944-48-9.

ATC — A10BB04.

ATC Vet — QA10BB04.

UNII — VP83E7434R.

NOTE. The name glibornuride has frequently but erroneously been applied to glibenclamide.

Profile

Glibornuride is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of 12.5 to 75 mg daily. Daily doses of 50 mg or more are given in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Glutril†; ***Fr.***: Glutril†; ***Switz.***: Glutril; ***Turk.***: Glutril.

Gliclazide *(BAN, rINN)*

Gliclazid; Gliclazida; Gliclazidum; Gliklatsidi; Gliklazid; Gliklazidas; Gliklazyd; Glyclazide; SE-1702; Гликлазид.

1-(3-Azabicyclo[3.3.0]oct-3-yl)-3-tosylurea; 1-(3-Azabicyclo[3.3.0]oct-3-yl)-3-*p*-tolylsulphonylurea.

$C_{15}H_{21}N_3O_3S$=323.4

CAS — 21187-98-4.

ATC — A10BB09.

ATC Vet — QA10BB09.

UNII — G4PX8C4HKV.

NOTE. The names Crawnart, Diaglico, Glimiran, and Glutameal have been used as trade marks for gliclazide.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Gliclazide). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane.

Uses and Administration

Gliclazide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of 12 to 24 hours. Because its effects are less prolonged than those of chlorpropamide or glibenclamide it may be more suitable for elderly patients, who are prone to hypoglycaemia with longer-acting sulfonylureas. The usual initial dose is 40 to 80 mg daily with breakfast, gradually increased, if necessary, up to 320 mg daily. Doses of more than 160 mg daily are given in 2 divided doses. For doses used in adolescents, see p. 475.1. A modified-release tablet is also available: the usual initial dose is 30 mg once daily, increased if necessary in steps of 30 mg up to a maximum of 120 mg daily. The interval between dose increases of the modified-release preparation should be at least 1 month, but the dose may be increased after just 2 weeks in those patients who have not responded.

References.

1. Palmer KJ, Brogden RN. Gliclazide: an update of its pharmacological properties and therapeutic efficacy in non-insulin-dependent diabetes mellitus. *Drugs* 1993; **46:** 92–125.
2. Mailhot J. Efficacy and safety of gliclazide in the treatment of non-insulin-dependent diabetes mellitus: a Canadian multicenter study. *Clin Ther* 1993; **15:** 1060–8.
3. Ziegler O, Drouin P. Hemobiological properties of gliclazide. *J Diabetes Complications* 1994; **8:** 235–9.
4. Jennings PE. Vascular benefits of gliclazide beyond glycemic control. *Metabolism* 2000; **49** (suppl 2): 17–20.
5. Crepaldi G, Fioretto P. Gliclazide modified release: its place in the therapeutic armamentarium. *Metabolism* 2000; **49** (suppl 2): 21–5.
6. McGavin JK, *et al*. Gliclazide modified release. *Drugs* 2002; **62:** 1357–64.
7. Drouin P, Standl E. Diamicron MR Study Group. Gliclazide modified release: results of a 2-year study in patients with type 2 diabetes. *Diabetes Obes Metab* 2004; **6:** 414–21.
8. Ceriello A. Effects of gliclazide beyond metabolic control. *Metabolism* 2006; **55** (suppl 1): S10–S15.
9. Brown N. Is it time to re-assess the role of gliclazide? Targeting insulin resistance in type 2 diabetes patients suboptimally controlled with insulin. *Postgrad Med J* 2006; **82:** 471–5.
10. Zoungas S, *et al*. The efficacy of lowering glycated haemoglobin with a gliclazide modified release-based intensive glucose lowering regimen in the ADVANCE trial. *Diabetes Res Clin Pract* 2010; **89:** 126–33.

Administration in children. There is limited experience with the use of sulfonylureas in children with type 2 diabetes mellitus, and the biguanide, metformin, is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision and that shorter-acting alternatives may be preferred to longer-acting sulfonylureas that have a greater risk of hypoglycaemia. Although not licensed for use in children in the UK, the *BNFC* suggests that gliclazide may be given to adolescents, aged 12 to 18 years, in the management of type 2 diabetes mellitus and maturity-onset diabetes of the young. An initial oral dose of 20 mg once daily, given with breakfast, may be adjusted according to response to a maximum of 320 mg daily. Doses of more than 160 mg daily are given in 2 divided doses.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2.

The *BNF* suggests that gliclazide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential and that the smallest possible dose for adequate control should be used. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Gliclazide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. Gliclazide is extensively metabolised in the liver to metabolites that have no significant hypoglycaemic activity. Metabolites and a small amount of unchanged drug are excreted in the urine.

References.

1. Kobayashi K, *et al*. Pharmacokinetics of gliclazide in healthy and diabetic subjects. *J Pharm Sci* 1984; **73:** 1684–7.
2. Davis TME, *et al*. Pharmacokinetics and pharmacodynamics of gliclazide in Caucasians and Australian Aborigines with type 2 diabetes. *Br J Clin Pharmacol* 2000; **49:** 223–30.
3. Elliot DJ, *et al*. Identification of the human cytochromes P450 catalysing the rate-limiting pathways of gliclazide elimination. *Br J Clin Pharmacol* 2007; **64:** 450–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agluclide; Diamicron; Unava; ***Austral.***: Diamicron; Glyade; Mellihexal; Nidem; Oziclide; ***Austria***: Diabrezide; Diamicron; Gliclada; ***Belg.***: Diamicron; Uni Diamicron; ***Braz.***: Azukon; Diamicron; Erowgliz; Glicaron; ***Canad.***: Diamicron; ***Chile***: Dianormax; ***China***: Da Er De (达尔得); Diamicron (达美康); Hong Xu Yang (弘旭阳); Li Ning Ge (利宁格); Ruimai (瑞迈); ***Cz.***: Diadeon; Diaprel; Glyclada; Normodiab; Zeglydia; ***Denm.***: Altermicron†; Diamicron; Glizinoz†; Glizamed; Glucostabil; Glydium; Normodiab; Uni Diamicron; Zeglidia; ***Fr.***: Diamicron; Glydium; ***Ger.***: Diamicron; ***Gr.***: Diabezid; Diamicron; ***Hong Kong***: CP-Gliz; Diamicron; Diamitex†; Dianorm†; Efton†; Gliclada; Glimicron; Gluconox†; Glucozide; Glupozide†; Glyade†; Glyzyl; Licla; Marclazide†; Melicron†; Nidem; Pharlinde†; Qualizide; Suclear; Sun-Glizide; Vickamicron†; ***Hung.***: Diaprel; Gliclada; Gluctam; Normadiab; Zeglidia; ***India***: Alglid; Aviglic; Azukon; CGCron; Claz; Comzid; D-Clic; Debgone; Diabend; Diabic; Diagli; Diamicron; Dianorm; Diaob; Diatrol; Diazide; Dizide; Euclide; Fordib; Glatix; Glic; Glican; Glicla; Gliclafin; Gliclan; Gliclatan; Gliclaz; Glicron; Gliden; Glidiet; Glisafe; Glital; Glityx; Glix; Gliza; Glizid; Glucoact; Glucofit; Glucozid; Glurib; Glutide; Glyca; Glychek; Glycigon; Glycinorm; Glycor; Glycozide; Glygard; Glyloc; Glyneed; Glyred; Glysiss; Glyzee; GLZ; Intragly; Jozide; Kampex; Liz; Lo-G; Lycazid; Meglyde; Novozid; Nuzide; Semi-Glycigon; ***Indon.***: Diamicron; Fredam; Glicab; Glidabet; Glikamel; Glucodex; Glucored; Glukolos; Glycafor†; Linodiab†; Meltika; Nufamicron; Pedab; Tiaglib†; Xepabet; Zumadiac; ***Irl.***: Diabrezide; Diaclide; Diaglyc; Diamicron; Glydium; Myglyc; Vitile; ***Ital.***: Diabrezide; Diamicron; Dramion; Galtes; Glucobloc; ***Malaysia***: Diamicron; Diamitex; Dianid; Glimicron; Glucozide; Glyade; Medoclazide; Opglucon; Reclide; Remicron; Sun-Glizide; ***Mex.***: Diamicron; ***Neth.***: Diamicron; Glicacon; Gliclabore; Gliclalane; Gliclareze; Gliclatab; Glydium; ***NZ***: Diamicron; Glizon; ***Philipp.***: Clibite; Clizid; Diaclid; Diamicron; Dianorm; Glubitor; Gluconil; Glucoprime†; Succedin; Zebet; ***Pol.***: Diabezidum†; Diabrezide; Diagen; Diaprel; Diazidan; Glazide; Gliclada; Glinormax†; Glisan; Gluctam; Glydium; Normodiab; Norsulin†; ***Port.***: Diadeon; Diamicron; ***Rus.***: Diabefarm (Диабефарм); Diabest (Диабест)†; Diabeton (Диабетон); Diabinax (Диабинакс); Diabrezide (Диабрезид); Diatica (Диатика); Gliclada (Гликлада); Glucostabil (Глюкостабил); Glydiab (Глидиаб); Reclide (Реклид)†; ***S.Afr.***: Adco-Glucomed; Diaglucide; Diamicron; Diaran; Glycron; Glygard; Ziclin†; ***Singapore***: Diamicron; Dianorm; Diapro; Glimicron; Glizide; Glucozide; Glyade; Medoclazide; Melicron; Mexan; Nidem; SP-Glimed; Sun-Glizide; ***Spain***: Diamicron; Uni Diamicron†; ***Switz.***: Diamicron; ***Thai.***: Beclazide; Cadicon; Clazide; Diabeside; Diabetab; Diacose; Diamexon; Diamicron; Dianid; Diatica; Dicaron; Dicron; Diglucron; Dimetus; Gliclabit; Glicron†; Glucid; Glucocron; Gluconox; Glucozide†; Glycinorm; Glycon; Medoclazide; Ranclazide; Serviclazide†; ***Turk.***: Betanorm; Diamicron; Efikas; Glazid†; Glikron; Glumikron; Hipoglis; Oramikron; ***UAE***: Glyzide; ***UK***: Diaglyk; Diamicron; Laaglyda; Vitile; Zicron; ***Ukr.***: Diabeton (Диабетон); Diaglizide (Диаглизид); Glioral (Глиорал)†; Oziklid (Озиклид); ***Venez.***: Diamicron; Glidan.

Multi-ingredient Preparations. ***China***: Du He (度和); He Wei Yi (合维伊); Qi Zhi Ping (齐致平); ***India***: Alglid-M; Alnamet-G; Aviglic-MF; Azukon M; Best-M; Bigan-GC; Claformin; Claz-M; Comzid-M; Dabby; Debgone-M; Diabend-M; Diabic-M; Dianorm-M; Dianosis-MF; Diaob-M; Diatrol-M; Dizide-M; Elmet-G; Euclide-M; Evermet-G; Exermet Gz; Fordib MF; Gefor; Glatix-M; Glicamet; Glican-M; Glicas-M; Glicina-GM; Gliclafin-M; Gliclan M; Gliclastar M; Gliclaz-M; Glicmet; Gliden-MF; Glidiet-M; Glikare-M; Glim-C; Glim; Glisafe M; Glital-M; Glityx-M; Glitz-MF; Glix-M; Gliza-MF; Glizid-M; Glormin; Glucoact-M; Glucofit-M; Glucozid-M; Glurib-M; Glycard-M; Glycasia-MF; Glychek-M; Glycicon Mod; Glycigon-M; Glycinorm M; Glyclamin; Glycor-C; Glygard M; Glyhil; Glykind-M; Glyloc-M; Glymin; Glyneed-M; Glyni-M; Glyori; Glyred-M; Glyroz; Glysiss-M; Glyvik-M; Glyzee-M; GLZ Plus; Intragly-M; Jozide-M; K-Gem; Liz-M; Lodia; Lycazid-M; Melfor-G; Metfor-G; Mildim; Mintide Plus; Mintide; Nuzide-M; Obax; ***Rus.***: Glimekomb (Глимекомб); ***Thai.***: Glizid-M; ***Ukr.***: Dianorm-M (Діанорм-М).

Pharmacopoeial Preparations
BP 2014: Gliclazide Tablets.

Glimepiride *(BAN, USAN, rINN)*

Glimepirid; Glimepirida; Glimépiride; Glimepiridi; Glimepiridum; Glimepiryd; Hoe-490; Глимепирид.

1-({*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl}sulfonyl)-3-(*trans*-4-methylcyclohexyl)urea.

$C_{24}H_{34}N_4O_5S$=490.6

CAS — 93479-97-1.

ATC — A10BB12.

ATC Vet — QA10BB12.

UNII — 6KY687524K.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Glimepiride). A white to almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dichloromethane; soluble in dimethylformamide; very slightly soluble in methyl alcohol.

USP 36: (Glimepiride). A white to almost white powder. Practically insoluble in water; sparingly soluble in dichloromethane; soluble in dimethylformamide; slightly soluble in methyl alcohol. It dissolves in dilute alkali hydroxides and in dilute acids. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Glimepiride is a sulfonylurea antidiabetic (p. 502.3). It is given orally for the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of up to 24 hours. Initial doses of 1 to 2 mg daily may be increased if necessary, in steps of 1 to 2 mg at intervals of 1 to 2 weeks, to 4 mg daily for maintenance. The maximum recommended dose is 6 mg in the UK and 8 mg in the USA. Glimepiride is generally taken as a single dose with breakfast or the first main meal of the day. For the use of glimepiride in children, see p. 475.3.

References.

1. Massi-Benedetti M. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. *Clin Ther* 2003; **25:** 799–816.
2. Weitgasser R, *et al*. Effects of glimepiride on HbA(1c) and body weight in type 2 diabetes: results of a 1.5-year follow-up study. *Diabetes Res Clin Pract* 2003; **61:** 13–19.
3. Feinbock C, *et al*. Prospective multicentre trial comparing the efficacy of, and compliance with, glimepiride or acarbose treatment in patients with type 2 diabetes not controlled with diet alone. *Diabetes Nutr Metab* 2003; **16:** 214–21.
4. Briscoe VJ, *et al*. The role of glimepiride in the treatment of type 2 diabetes mellitus. *Expert Opin Drug Metab Toxicol* 2010; **6:** 225–35.

Administration in children. There is limited experience with the use of sulfonylureas in children, and the biguanide, metformin, is generally preferred. For further details on sulfonylurea use in children, see p. 502.3. Glimepiride was found to be safe and effective in children with type 2 diabetes (mean age 13.8 years), but associated with more weight gain than metformin.[1]

1. Gottschalk M, *et al*. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care* 2007; **30:** 790–4.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2. In some countries hepatic and haematological monitoring is recommended in patients receiving glimepiride; in the UK the *BNF* considers there is limited evidence of the clinical value of such monitoring.

Fasting. Glimepiride, given in unchanged doses but with the time of the single daily dose switched from morning to just before breaking fast after sunset, was used in Muslim patients during Ramadan without causing an increased incidence of hypoglycaemic episodes.[1]

For further advice on the management of diabetes mellitus in fasting Muslim patients during Ramadan see under Precautions of Insulin, p. 487.3.

1. The Glimepiride in Ramadan (GLIRA) Study Group. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. *Diabetes Care* 2005; **28:** 421–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glimepiride as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Glimepiride is completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur in 2 to 3 hours, and it is highly protein bound. The drug is extensively metabolised in the liver to two main metabolites. The cytochrome P450 isoenzyme CYP2C9 is involved in the formation of a hydroxy derivative, which is further metabolised to a carboxy derivative by cytosolic enzymes. The half-life after multiple doses is about 9 hours. About 60% of a dose is eliminated in the urine and 40% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adiuvan; Amaryl; Diabutil; Endial; Glemaz; Glimeplic; Gluceride; Glucopirida; Gretilab†; Hipoglut; Islopir; Lomet; Next Step; ***Austral.***: Amaryl; Aylide; Diapride; Dimirel; ***Austria***: Amaryl; Glimestad; ***Belg.***: Amarylle; ***Braz.***: Amapirida; Amaryl; Azulix; Bioglic; Diabemed; Diamellitis; Gliansor; Glimepibal; Glimepil; Glimeran; Glycopirida; Hipomeril; ***Canad.***: Amaryl; ***Chile***: Amaryl; Glemaz; Glix; Glucomet; Taboss; ***China***: Amaryl (亚莫利); Amoli (阿莱立); An Duo Mei (安多美); An Ni Ping (安尼平); Di Bei (迪北); Jia He Luo (佳和洛); Ke De Ping (科德平); Li Yi Ping (力贻苹); Pu Ren Ping (普仁平); Rui Ping (瑞平); Sheng Ping (圣平); Tang Fu (唐弗); Wan Su Ping (万苏平); Yi Rui (伊瑞); You Su (佑苏); ***Cz.***: Amarwin†; Amaryl; Amyx; Apo-Glimep†; Eglymad; Glemid; Glimegamma; GlimTek†; Glymexan; Medopirid; Melyd; Metis†; Oltar; ***Denm.***: Amaryl; Dibiglim; Glimeprisan; Glivasol; Limepisil†; Limezapine; Stapiride; Tineril; ***Fin.***: Amaryl; Dialosa; Gli-

mendin†; Glimespes; Oltar; Pirtad†; Priglide; ***Fr.***: Amarel; ***Ger.***: Amaryl†; Glimegamma; Magna†; ***Gr.***: Adinsulin-S; Anovis; Dia-Ban; Dialosa; Glidil; Glimepiron; Glimerid; Glimespes; Glimexin; Glimosa; Glincil; Gliperin; Glirid; Idesal; Mepirid; Nicordilen†; Penoza; Pharlecon; Raltone; Saccharofar; Solosa; Sucryl; Tetig; Tipo II; Toremol; Zutra; ***Hong Kong***: Amaryl; Diapride; Glimaryl; Glimeryl; ***Hung.***: Amagen; Amaryl; Dialosa; Diamitus; Glempid; Glibezid; Glimegamma; GlimeWin†; Glindia; Gliprex; Limeral; Melyd; Sintecal; ***India***: Adride; Amaryl; Asoride; Azulix; Bepride; Betaglim; Blisto; Capril; CGRyl; Chempride; Conpride; Daoride; Daoryl; Diaglim; Diapride; Diaset; Diaswich; Diazero; Dibiglim; Dipride; Elim; Emperide; Euglim; Euroglip; Flexiglim; Gadz; Gepride; Gimip; Gitae; Givov; Glador; Glamor; Gleam; Gli; Glimcare; Glimchek; Glimcip; Glimcom; Glimecure; Glimer; Glimestar; Glimetop; Glimfit; Glimid; Glimidot; Glimifix; Glimikare; Glimiprex; Glimiriv; Glimisave; Glimitab; Glimitan; Glimkap; Glimpax; Glimpid; Glimpil; Glimser; Glimsite; Glimtide; Glimulin; Glimy; Glimz; Glinidd; Glinorm; Glista-OD; Glisu; GLP; Glucoryl; Glucut; Glycirid; Glyfix; Glypride; Glyree M; Glyree; GMR; GP; Gride; Idapride; Ilet; Isryl; K-Glim; Karmelitus; Leride; Mepusulin; Mypride; Nabal; Novaride; Odiglim; ***Indon.***: Amadiab; Amaryl; Anpiride; Diaglime; Friladar; Glamarol; Glimexal; Gliperid; Glucoryl; Gluvas; Mapryl; Mepirilid; Metrix; Norizec; Paride; Relide; Simryl; ***Irl.***: Amaryl; ***Israel***: Amaryl; ***Ital.***: Amaryl; Diamel; Solosa; ***Malaysia***: Amaryl; Ameride; Diapride; Glenix; Glimaryl; Glimin; Glimpid; Glimulin; Miaryl; ***Mex.***: Amaryl; Diaglim; Diapride; Glimal; Glipiran†; Glupropan; Mepiritev; Redu-ST; Zukedib; ***Neth.***: Amaryl; Fertin; ***Norw.***: Amaryl; ***NZ***: Amaryl†; ***Philipp.***: Acotril; Aforglim; Arya; Azulix; Climeril; Diaberid; Diaglim; Diameride; Diamex; Diapride; Euglim; Geopride; Getryl; Glimarex; Glimaryl; Glimauno; Glimec; Glimed; Glimesyn; Gliperide; Glipiren; Glycobate; Glyper; Imerid; Mira; Neoglim; Norizec; Solodiab; Solosa; Sulfast; Syngly; ***Pol.***: Amaryl; Amyx; Apo-Glim; Avaron; Betaglid†; Diaril; Glemid†; Glibetic; Glibezid†; Glidiamid; Glimehexal; Glimesan†; GlimTeva†; Glindia†; Glipid; Limeral; Melyd; Oltar†; Pemidal; Symglic; ***Port.***: Amaryl; Andissa; Diapiride; Glimial; Gludon; Zopide; ***Rus.***: Amaryl (Амарил); Glemaz (Глемаз); Gliamal (Глиамал); Glumedex (Глюмедекс); Meglimid (Меглимид); ***S.Afr.***: Amaryl; Diaglim; Euglim; Glamaryl; Sulphonur; ***Singapore***: Amaryl; Dialosa; Diapride; ***Spain***: Amaryl; Roname; ***Swed.***: Amaryl; ***Switz.***: Amaryl; Glimerax†; Glimeryle; ***Thai.***: Amaryl; Diaglip; Dibiglim; ***Turk.***: Amaryl; Diaglin; Diameprid; Glimax; Glirid; Mepiriks; Sanprid; Tideca; ***UAE***: Glypride; ***UK***: Amaryl; Niddaryl; ***Ukr.***: Amapirid (Амапирид); Amaryl (Амарил); Diameprid (Диамеприд)†; Diapirid (Диапирид); Glianov (Глианов); Glibetic (Глибетик)†; Glipomar (Глипомар)†; Glirid (Глирид); Oltar (Олтар); ***USA***: Amaryl; ***Venez.***: Amaryl; Dimavyl; Glimerid.

Multi-ingredient Preparations. ***Arg.***: Amaryl M; Avandaryl; Endial Met; Hipoglut Met; ***Austria***: Avaglim†; Tandemact; ***Braz.***: Amaryl Flex; Meritor; ***Canad.***: Avandaryl†; ***Chile***: Amaryl M; Avandaryl; ***Cz.***: Avaglim†; Tandemact; ***Denm.***: Avaglim†; ***Fr.***: Tandemact†; ***Ger.***: Avaglim†; Tandemact; ***Gr.***: Avaglim†; ***Hung.***: Avaglim†; ***India***: Adride-M; Adride-P; Alnamet-GSR; Amaryl-M; Aroglim-M2; Azulix MF; Bepride-MF; Bepride-SF; Betaglim M; Betagrim-M; Bigan-GM; Bigonyl; Blisto-MF; Conpride M; Daoride-M; Daoride-PM; Daoryl-M; Deralin-M; Diakit-3; Diakit-4; Dianosis-P3; Diapex-M; Diaprid-M; Diapride Forte; Diapride Plus; Diaset-M; Diaswich M; Diazero-M; Diazero-PM; Dibiglim-P; Dipride-M; Euglim-M; Euglim-MP; Euglim-P; Euroglip Forte; Euroglip-M2; Evermet-GSR; Exermet GM; Forme; G-Tase G; Gemer P; Gemer; Gepride-M; Gimip-M; Gimip-PM; Gitae-M; Gitar; Glamor-M; Glamor-P; Glamor-PM; Glicon-M; Glicosi-M; Glimaday; Glimcare Forte; Glimcare Plus; Glimchek M; Glimestar PM; Glimestar-M; Glimi DM; Glimid-M; Glimidot-M; Glimifix-M; Glimikare-MSR; Glimiprex MF; Glimisave-M; Glimizide-M; Glimizide-PG; Glimkap M2; Glimpax-M; Glimpil-MF; Glimsite-M; Glimsite-MP; Glimtide Forte; Glimtide Plus; Glimulin-MF; Glimy-M; Glimy-MP; Glimy-P; Glinidd-M; Glinorm-M; Glip-MF; Glista; GLM; GLP-M; GLP-PM; Gluconorm-G; Glucut-GMP; Glucut-MT; Gluformin G; Glyciphage PG; Glyciphage-G; Glycomet-GP; GM; GMR-M; GMT; GPM; Gride-M; Idapride-M; Idapride-PM; Ilet-B; Ioglime; Isryl-M; K-Glim M; K-Pio-G; Matce-G; Matce-PG; Mepride-M; Metanorm G; Metapride; Metgli; Metride Plus; Metride; Minsugar-G; Obimet-GX; Odiglim-M; One Dia; ***Indon.***: Amaryl M; Avandaryl; ***Irl.***: Avaglim†; Tandemact; ***Ital.***: Avaglim†; Tandemact; ***Jpn***: Sonias; ***Malaysia***: Amaryl M; ***Mex.***: Amaryl M; Glimetal; Pime; Rangimet G; ***Neth.***: Avaglim†; Tandemact; ***Norw.***: Avaglim†; ***Philipp.***: Asenza Plus; Avandaryl†; Solosamet; ***Pol.***: Tandemact; ***Port.***: Avaglim†; Tandemact; ***Rus.***: Avandaglim (Авандаглим); ***Spain***: Avaglim†; Tandemact; ***Swed.***: Avaglim†; ***Thai.***: Amaryl M; Avandaryl†; ***Ukr.***: Amaryl M (Амарил М); Tripride (Трипрайд); ***USA***: Avandaryl; Duetact.

Pharmacopoeial Preparations
BP 2014: Glimepiride Tablets;
USP 36: Glimepiride Tablets; Pioglitazone and Glimepiride Tablets.

Glipizide *(BAN, USAN, pINN)*

CP-28720; Glipitsidi; Glipizid; Glipizida; Glipizidas; Glipizidum; Glipizyd; Glydiazinamide; K-4024; Глипизид.
1-Cyclohexyl-3-{4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzenesulphonyl}urea.
$C_{21}H_{27}N_5O_4S$=445.5
CAS — 29094-61-9.
ATC — A10BB07.
ATC Vet — QA10BB07.
UNII — X7WDT95N5C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Glipizide). A white or almost white crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Glipizide). Store in airtight containers. Protect from light.

Uses and Administration

Glipizide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of up to 24 hours. The usual initial dose is 2.5 to 5 mg daily given as a single dose about 30 minutes before breakfast. Dosage may be adjusted at intervals of several days by amounts of 2.5 to 5 mg daily, to a maximum of 20 mg daily. Doses up to 40 mg daily have been used, but see p. 476.2. Doses larger than 15 mg daily are given in two divided doses before meals. Modified-release formulations of glipizide are available in some countries; one such preparation (*Glucotrol XL; Pfizer, USA*) is given in usual doses of 5 to 10 mg daily as a single dose with breakfast.

Administration. Although glipizide may be given in doses up to a maximum of 40 mg daily, evidence for the benefits of high doses is scanty. A small study in patients with type 2 diabetes mellitus found that not only did increases in glipizide doses to more than 10 mg daily produce little or no benefit, but that the higher doses were associated with reduced rises in plasma-insulin concentrations and a lesser reduction in plasma-glucose concentrations.[1] There is, however, some evidence that glycaemic control and insulin sensitivity can be improved by the use of a modified-release rather than a conventional formulation of glipizide.[2,3]

1. Stenman S, *et al.* What is the benefit of increasing the sulfonylurea dose? *Ann Intern Med* 1993; **118:** 169–72.
2. Berelowitz M, *et al.* Comparative efficacy of once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care* 1994; **17:** 1460–4.
3. Leaf E, King JO. Patient outcomes after formulary conversion from immediate-release to extended-release glipizide tablets. *Am J Health-Syst Pharm* 1999; **56:** 454–6.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glipizide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Glipizide is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after a single dose. It is extensively bound to plasma proteins and has a half-life of about 2 to 4 hours. It is metabolised mainly in the liver and excreted chiefly in the urine, largely as inactive metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Minodiab; ***Austral.***: Melizide; Minidiab; ***Austria***: Glibenese; Minidiab; ***Belg.***: Glibenese; Minidiab; ***Braz.***: Minidiab; ***Chile***: Minidiab; Xiprine; ***China***: Ge Di (格迪); Glucotrol (瑞易宁); Glutrol (安吉); Jie Bei (捷贝); Li Da Mei (力达美); Meibida (美吡达); Mieteni (灭特尼); Minidiab (曼迪宝); Qin Su (秦苏); Si Le Ke (思乐克); Tonbac (唐贝克); Xiboge (西博格); Yi Ping (怡平); Yibida (怡必达); Youdaling (优哒灵); Yuan Tan (元坦); Yuelai (悦来); ***Cz.***: Minidiab; ***Denm.***: Glibenese†; Mindiab; Minodiab; ***Fin.***: Mindiab; ***Fr.***: Glibenese; Minidiab; Ozidia; ***Gr.***: Glibenese; Minodiab; ***Hong Kong***: Diasef; Glucotrol; Melizide†; Minidiab; Sunglucon; ***Hung.***: Minidiab; ***India***: Bimode-M; Bimode; D-Glip; Diacon; Diaglip; Dibizide; G-Trol; Glez; Glibetic; Glide; Glip; Glipiriv; Glipy; Glucolip; Glucotrol; Glylin; Glynase; Glytop; Glyzip; Godde; Lipi; ***Indon.***: Aldiab†; Glucotrol; Glyzid†; ***Irl.***: Glibenese; ***Israel***: Gluco-Rite; ***Ital.***: Minidiab; ***Malaysia***: Dipazide†; Glix; Melizide†; Minidiab; ***Mex.***: Luditec†; Minodiab; Pigloss; Prugal; Singloben; ***Norw.***: Mindiab; ***NZ***: Minidiab; ***Philipp.***: Brilizid; Glimax; Glix; Minidiab; ***Pol.***: Antidiab†; Glibenese; ***Port.***: Minidiab; ***Rus.***: Glibenese (Глибенез); Glynase (Глинез); ***S.Afr.***: Minidiab; ***Singapore***: Beapizide; Diasef; Dibizide; Glucotrol; Glynase; Melizide; Minidiab; Sunglucon; ***Spain***: Minodiab; ***Swed.***: Mindiab; ***Switz.***: Glibenese†; ***Thai.***: Depizide; Diabemin†; Diasef; Dipazide; Gipzide; Glibenil; Glimax†; Glipimed; Glipizon; Glizide; Glucodiab; Glucotrol; Glycediab; Glygen; GP-Zide; Manpizide; Melizide†; Minibit; Minidiab; Namedia; Neodiab†; Pezide; Phardiab; Topizide; Tozide; ***Turk.***: Glucotrol; Minidiab; ***UK***: Glibenese†; Minodiab; ***Ukr.***: Glynase (Глінез); ***USA***: Glucotrol; ***Venez.***: Minidiab.

Multi-ingredient Preparations. ***India***: Actizide-M; Bigan-GP; Diacon M; Diaglip M; Dibimet Plus; Dibizide-M; Glibetic-MF; Glicept; Gliformin; Glimet; Glipimet; Glipmet; Glucotrol MF; Glynase MF; Godde-M; Grip-M; Lipi-M; Metaglez; Metglib; ***Mex.***: Metdual; ***Philipp.***: Norsulin; ***Ukr.***: Dibizide-M (Дибизид-М); ***USA***: Metaglip†.

Pharmacopoeial Preparations
BP 2014: Glipizide Tablets;
USP 36: Glipizide and Metformin Hydrochloride Tablets; Glipizide Tablets.

Gliquidone *(BAN, rINN)*

ARDF-26; Glikidon; Glikidoni; Gliquidona; Gliquidonum; Гликвидон.
1-Cyclohexyl-3-{4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1*H*)-isoquinolyl)ethyl]benzenesulphonyl}urea.
$C_{27}H_{33}N_3O_6S$=527.6
CAS — 33342-05-1.
ATC — A10BB08.
ATC Vet — QA10BB08.
UNII — C7C2QDD75P.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Gliquidone). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dimethylformamide.

Profile

Gliquidone is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in a usual initial dosage of 15 mg daily given as a single dose up to 30 minutes before breakfast. Dosage may be adjusted by increments of 15 mg to a usual dose of 45 to 60 mg daily in 2 or 3 unequally divided doses, the largest dose being taken in the morning with breakfast. Single doses above 60 mg and daily doses above 120 mg are not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Glurenorm; ***Belg.***: Glurenorm; ***China***: Jie Shi (捷适); Ka Rui Lin (卡瑞林); Pu Yi (普怡); Tangshiping (糖适平); ***Cz.***: Glurenorm; ***Ger.***: Glurenorm; ***Gr.***: Devotan; ***Hung.***: Glurenorm; ***Indon.***: Fordiab; Glidiab; Glurenorm; Lodem; ***Ital.***: Glurenor; ***Pol.***: Glurenorm; ***Rus.***: Glurenorm (Глюренорм); ***Spain***: Glurenor; ***Thai.***: Glurenor; ***Turk.***: Glurenorm; ***Ukr.***: Glurenorm (Глюренорм).

Pharmacopoeial Preparations
BP 2014: Gliquidone Tablets.

Glisentide *(rINN)*

Glipentide; Glisentida; Glisentidum; Глизентид.
1-Cyclopentyl-3-[*p*-(2-*o*-anisamidoethyl)benzenesulphonyl]urea.
$C_{22}H_{27}N_3O_5S$=445.5
CAS — 32797-92-5.
UNII — 392TQL1E2Z.

Profile

Glisentide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of 2.5 to 20 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Staticum.

Glybuzole *(rINN)*

AN-1324; Désaglybuzole; Glibuzol; Glybuzolum; RP-7891; Глибузол.
N-(5-*tert*-Butyl-1,3,4-thiadiazol-2-yl)benzenesulphonamide.
$C_{12}H_{15}N_3O_2S_2$=297.4
CAS — 1492-02-0.
UNII — 1DJ2B6BM2C.

Profile

Glybuzole is an oral antidiabetic with a structure distinct from that of the sulfonylureas, biguanides, or sulfonamidopyrimidines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Gludiase†.

Glyclopyramide *(rINN)*

Gliclopiramida; Glyclopyramidum; Гликлопирамид.
1-(4-Chlorobenzenesulphonyl)-3-(pyrrolidin-1-yl)urea.
$C_{11}H_{14}ClN_3O_3S$=303.8
CAS — 631-27-6.
UNII — KE474IKG1W.

Profile

Glyclopyramide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of between 125 to 500 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Deamelin.

Glycyclamide *(rINN)*

Gliciclamida; Gliciclamide; Glycyclamidum; K-38; K-386; Tolcyclamide; Глицикламид.
1-Cyclohexyl-3-tosylurea; 1-Cyclohexyl-3-*p*-tolylsulphonylurea.
$C_{14}H_{20}N_2O_3S$=296.4
CAS — 664-95-9.
UNII — C40N4EJY68.

Profile

Glycyclamide is a sulfonylurea antidiabetic (p. 502.3). It has been given orally in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Diaborale.

Guar Gum

Cyamopsidis seminis pulvis; E412; Goma guar; Gomma di guar; Gomme de guar; Guar; Guar Flour; Guar Galactomannan; Guar, galactomannane du; Guar Galactomannanum; Guar galaktomanan; Guar galaktomannan; Guaran; Guaras; Guárbab galaktomannán; Guárbabmag-por; Guarbloem; Guargalactomannan; Guargalaktomannaani; Guargalaktomannan; Guargom; Gúargúmmí; Guarkärnmjöl; Guarkernmehl; Guarkumi; Guarmehl; Guarmjöl; Guaro galaktomananas; Guarpitmeel; Guma guar; Jaguar Gum; Гуаровая Смола; Гуаровая Камедь; Гуарова Гума.
CAS — 9000-30-0.
ATC — A10BX01.
ATC Vet — QA10BX01.
*ATC Herb — HA10BX5001 (*Cyamopsis tetragonoloba*: gum); HC10AW5005 (*Cyamopsis tetragonoloba*: gum); HA06AC5003 (*Cyamopsis tetragonoloba*: gum).*
UNII — E89I1637KE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Guar). Guar is obtained by grinding the endosperms of the seeds of *Cyamopsis tetragonolobus*. It consists mainly of guar galactomannan. Guar is a white or almost white powder, yielding a mucilage of variable viscosity when dissolved in water. Practically insoluble in alcohol.

Ph. Eur. 8: (Guar Galactomannan). A yellowish-white powder. It is soluble in cold and hot water; practically insoluble in organic solvents. Its main components are polysaccharides composed of D-galactose and D-mannose at molar ratios of 1:1.4 to 1:2. The molecules consist of a linear main chain of β-(1→4)-glycosidically linked mannopyranoses and single α-(1→6)-glycosidically linked galactopyranoses.

USNF 31: (Guar Gum). A gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, a galactomannan, composed of galactan and mannan units combined through glycosidic linkages. It is a white to yellowish-white, practically odourless, powder. Dispersible in hot or cold water forming a colloidal solution.

Uses and Administration

Guar gum is used in diabetes mellitus (see p. 479.2) as an adjunct to treatment with diet, insulin, or oral antidiabetics since it results in some reduction in both postprandial and fasting blood-glucose concentrations. It is given with or immediately before meals in doses of 5 g usually 3 times daily. Adverse gastrointestinal effects may be reduced by using a lower initial dose of 5 g once daily before breakfast for 1 week, then increasing to 5 g twice daily, then 3 times daily, as required. Each dose of guar gum granules should be taken stirred in about 200 mL of a cold drink.

Guar gum is also used as an adjunct in the treatment of hyperlipidaemias (see p. 479.2). It may be used to slow gastric emptying in some patients with the dumping syndrome (p. 1809.2).

Guar gum is used as a thickening and suspending agent, and as a tablet binder and disintegrant. It has been incorporated into processed foods.

Guar gum is an example of a soluble fibre.[1] On contact with water it forms a highly viscous gel, the viscosity of which varies with such factors as its plant source or the form in which it is given.[2]

Fibres such as guar gum reduce postprandial and fasting blood-glucose concentrations as well as plasma-insulin concentrations in healthy subjects and diabetic patients.[1,3,4] Such reductions in blood-glucose concentrations and in glycated haemoglobin have been found in both type 1 and type 2 **diabetes mellitus** (p. 459.1), but they have generally been small.[3] Possible mechanisms for these effects of guar gum include a delay in gastric emptying,[1,3-5] decreased small-bowel motility,[1,4] decreased glucose absorption resulting from increased viscosity of the contents of the gastrointestinal tract,[1,3] or inhibition of gastrointestinal hormones.[3]

Guar gum also lowers serum total cholesterol and low-density-lipoprotein (LDL) cholesterol concentrations; high-density-lipoprotein (HDL) cholesterol and triglyceride concentrations appear to be unaffected.[4] The most likely mechanism is binding of bile acids, reducing their enterohepatic circulation in a similar way to bile-acid sequestrants.[3,4] It might also interfere with absorption of dietary cholesterol.[4,6] When used alone in patients with **hypercholesterolaemia** guar gum has generally produced a modest reduction in plasma-cholesterol and LDL-cholesterol concentrations although some studies have been unable to find an effect. A few studies have suggested that the cholesterol-lowering effect is attenuated after 8 to 12 weeks of treatment but a long-term study saw a 17% decrease in total serum cholesterol that was maintained for 24 months.[7] Some studies have shown further reductions in cholesterol and LDL-cholesterol concentrations on addition of guar gum to therapy with other lipid regulating drugs.[4] The usual treatment of hyperlipidaemias is discussed on p. 1248.1.

There have been suggestions that guar gum reduces appetite by promoting a feeling of fullness, but a meta-analysis has indicated that it is not effective for reducing body-weight.[8] Products containing guar gum have, however, been promoted as **slimming aids**. Their use cannot be advocated because of the risk of tablets swelling before reaching the stomach and causing oesophageal obstruction.

1. Hockaday TDR. Fibre in the management of diabetes I: natural fibre useful as part of total dietary prescription. *BMJ* 1990; **300:** 1334–6.
2. Ellis PR, *et al.* Guar gum: the importance of reporting data on its physicochemical properties. *Diabet Med* 1986; **3:** 490–1.
3. Anonymous. Guar gum: of help to diabetics? *Drug Ther Bull* 1987; **25:** 65–7.
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5. Tattersall R, Mansell P. Fibre in the management of diabetes 2: benefits of fibre itself are uncertain. *BMJ* 1990; **300:** 1336–7.
6. Rideout TC, *et al.* Guar gum and similar soluble fibers in the regulation of cholesterol metabolism: current understandings and future research priorities. *Vasc Health Risk Manag* 2008; **4:** 1023–33.
7. Salenius J-P, *et al.* Long term effects of guar gum on lipid metabolism after carotid endarterectomy. *BMJ* 1995; **310:** 95–6.
8. Pittler MH, Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials. *Am J Med* 2001; **110:** 724–30.

Adverse Effects and Precautions

Guar gum can cause gastrointestinal disturbance with flatulence, diarrhoea, or nausea, particularly at the start of treatment.

Because guar gum swells on contact with liquid it should always be washed down carefully with water and should not be taken immediately before going to bed. It should not be used in patients with dysphagia, oesophageal disease, or intestinal obstruction.

Interactions

Guar gum may retard the absorption of other drugs; where this is likely to pose a problem the other drug should be taken at least an hour before guar gum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Benefibra; ***Cz.***: Benefibra; ***Fin.***: Guarem; ***Ger.***: Figur-Verlan; Guar Verlan; Urgo Hydrogel; ***India***: Nosulin; ***Ital.***: Benefibra; Novafibra†; ***NZ***: Guarcol; ***Spain***: Fibraguar; ***Switz.***: Leiguar; Vitaguarin; ***UK***: Resource OptiFibre; ***Ukr.***: Guarem (Гуарем).

Multi-ingredient Preparations. ***Arg.***: Desgras Complex; Desgras; Green Diet; ***Fr.***: Cyamox; Cyamox; Moxydar; Mucipulgite†; Mulkine†; Seroxydar†; ***Hung.***: Lipolest; ***India***: Fibrotin; ***Ital.***: Cruscasohn; Fibrovit; Resource Gelificata†; ***Singapore***: Bios Life; Chitosano; ***Switz.***: Mucipulgite†.

Insulin ⊗

B28-Asp-insulin (insulin aspart); HMR-1964 (insulin glulisine); Hoe-71GT (insulin glargine); Hoe-901 (insulin glargine); INA-X14 (insulin aspart); Inslin; Insulien; Insuliin; Insuliini; Insülin; Insúlín; Insulină; Insulin X14 (insulin aspart); Insulina; Insulinas; Insuline; Insulinin; Insulinum; Insulins; Inzulin; Inzulín; NN-304 (insulin detemir); NN-1250 (insulin degludec); Инсулин.
CAS — 9004-10-8 (insulin, neutral insulin); 11070-73-8 (bovine insulin); 12584-58-6 (porcine insulin); 11061-68-0 (human insulin); 8063-29-4 (biphasic insulin); 9004-21-1 (globin zinc insulin); 68859-20-1 (insulin argine); 8049-62-5 (insulin zinc suspensions); 53027-39-7 (isophane insulin); 9004-17-5 (protamine zinc insulin); 9004-12-0 (dalanated insulin); 51798-72-2 (bovine insulin defalan); 11091-62-6 (porcine insulin defalan); 116094-23-6 (insulin aspart); 844439-96-9 (insulin degludec); 169148-63-4 (insulin detemir); 160337-95-1 (insulin glargine); 207748-29-6 (insulin glulisine); 133107-64-9 (insulin lispro); 1200440-65-8 (insulin peglispro); 874442-57-6 (insulin tregopil).
ATC — A10AB01 (human); A10AB02 (beef); A10AB03 (pork); A10AB04 (lispro); A10AB05 (aspart); A10AB06 (glulisine); A10AC01 (human); A10AC02 (beef); A10AC03 (pork); A10AC04 (lispro); A10AE01 (human); A10AE02 (beef); A10AE03 (pork); A10AE04 (glargine); A10AE05 (detemir).
ATC Vet — QA10AB01 (human); QA10AB02 (beef); QA10AB03 (pork); QA10AB04 (lispro); QA10AB05 (aspart); QA10AB06 (glulisine); QA10AC01 (human); QA10AC02 (beef); QA10AC03 (pork); QA10AC04 (lispro); QA10AD01 (human); QA10AD02 (beef); QA10AD03 (pork); QA10AD04 (lispro); QA10AD05 (aspart); QA10AE01 (human); QA10AE02 (beef); QA10AE03 (pork); QA10AE04 (glargine); QA10AE05 (detemir); QA10AF01 (human).
UNII — D933668QVX (aspart); 576O9IZ534 (beef); 54Q18076QB (degludec); 4FT78T86XV (detemir); 2ZM8CX04RZ (glargine); 7XIY785AZD (glulisine); 1Y17CTI5SR (human); GFX7QIS1II (lispro); AVT680JB39 (pork).

Pharmacopoeias. Most pharmacopoeias have monographs for insulin and a variety of insulin preparations.

Ph. Eur. 8: (Insulin, Bovine). The natural antidiabetic principle obtained from beef pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at -20 degrees until released by the manufacturer. When thawed, insulin may be stored at 2 degrees to 8 degrees and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 8: (Insulin, Porcine). The natural antidiabetic principle obtained from pork pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at -20 degrees until released by the manufacturer. When thawed, insulin may be stored at 2 degrees to 8 degrees and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 8: (Insulin, Human). A protein having the structure of the antidiabetic hormone produced by the human pancreas. It is produced either by enzymatic modification and suitable purification of insulin obtained from the pancreas of the pig or by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and, with decomposition,

in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below -18 degrees or below until released by the manufacturer. When thawed, insulin is stored at 2 degrees to 8 degrees and used for manufacturing preparations within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 8: (Insulin Aspart; Insulinum Aspartum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, except that it has aspartic acid instead of proline at position 28 of the B-chain. As in human insulin, insulin aspart contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in aqueous solutions with a pH around 5.1. In aqueous solutions below pH 3.5 or above pH 6.5, the solubility is greater than or equal to 25 mg/mL. Store in airtight containers. Protect from light. It should be stored at or below -18 degrees until released by the manufacturer. When thawed, insulin aspart may be stored at 2 degrees to 8 degrees and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

Ph. Eur. 8: (Insulin Glargine; Insulinum Glarginum). It is a 2-chain peptide containing 53 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 32 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at position 21 in the A-chain and at the C-terminal end of the B-chain where it contains 2 additional amino acids. Human insulin is Asn(A21), whereas insulin glargine is Gly(A21), Arg(B31), Arg(B32). As in human insulin, insulin glargine contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white, hygroscopic powder. Practically insoluble in water and in anhydrous alcohol; soluble in dilute mineral acids. Store in airtight containers at a temperature of -20 degrees, excursions permitted between -15 degrees and -25 degrees. Protect from light.

Ph. Eur. 8: (Insulin Lispro; Insulinum Lisprum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B-chain. Human insulin is Pro(B28), Lys (B29), whereas insulin lispro is Lys(B28), Pro(B29). As in human insulin, insulin lispro contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below -18 degrees. When thawed, insulin lispro is used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

USP 36: (Insulin). A protein that affects the metabolism of glucose obtained from the pancreas of healthy bovine or porcine animals, or both, used for food by humans. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at -10 degrees to -25 degrees.

USP 36: (Insulin Human). A protein corresponding to the active principle elaborated in the human pancreas that affects the metabolism of carbohydrate (particularly glucose), fat, and protein. It is derived by enzymatic modification of insulin from pork pancreas in order to change its amino acid sequence appropriately, or produced by microbial synthesis via a recombinant DNA process. Store in airtight containers. Protect from light. It should be stored at -10 degrees to -25 degrees.

USP 36: (Insulin Lispro). Insulin Lispro is identical in structure to Insulin Human, except that it has lysine and proline at positions 28 and 29, respectively, of chain B, whereas this sequence is reversed in Insulin Human. It is produced by microbial synthesis via a recombinant DNA process. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at -10 degrees to -25 degrees.

Definitions and Terminology

Insulin is a hormone produced by the beta cells of the islets of Langerhans of the pancreas and consists of 2 chains of amino acids, the A and B chains, connected by 2 disulfide bridges. Insulin produced by different species conforms to the same basic structure but has different sequences of amino acids in the chains. **Porcine insulin** ($C_{256}H_{381}N_{65}O_{76}S_6$ = 5777.6) differs from **human insulin** ($C_{257}H_{383}N_{65}O_{77}S_6$ = 5807.6) in only one amino acid in the B chain, whereas **bovine insulin** ($C_{254}H_{377}N_{65}O_{75}S_6$ = 5733.6) differs from human insulin not only in this same amino acid in the B chain but also in 2 amino acids in the A chain.

The precursor of insulin in the pancreas is proinsulin which is a single polypeptide chain incorporating both the A and B chains of insulin connected by a peptide termed the C-peptide (or connecting-peptide). Although the insulins of various species may be similar in composition the proinsulins are not, in that the sequence and number of amino acids in the C-peptide may vary considerably.

Early commercial insulins were obtained by extraction from bovine or porcine or mixed bovine and porcine pancreases and were purified by recrystallisation only. Insulins obtained by such methods were often termed **'conventional insulins'** to distinguish them from insulins which have undergone further purification processes. An extract which has been recrystallised only once can be separated into 3 components or fractions termed the 'a', 'b', and 'c' components. The 'a' component consists of high molecular weight substances and is only usually found in very impure preparations since repeated recrystallisation will remove most of it. The 'b' component consists largely of proinsulin and insulin dimers, and the 'c' component consists of insulin, insulin esters, arginine insulin, and desamidoinsulin. Other pancreatic peptides such as glucagon, pancreatic polypeptide, somatostatin, and vasoactive intestinal peptide are also usually found in products which have not undergone further purification. Gel filtration will substantially reduce the content of proinsulin but will not significantly reduce the content of insulin derivatives or pancreatic peptides; products purified by gel filtration are often termed **'single-peak insulins'**. Addition of ion-exchange chromatography to the purification methods will further reduce the proinsulin content and also reduce the contamination by insulin derivatives and pancreatic peptides. In the UK **'highly purified insulins'** and **'monocomponent insulins'** are terms sometimes applied to insulins that have undergone both gel filtration and ion-exchange chromatography. In the USA the FDA has designated the term **'purified insulins'** for preparations similarly prepared and containing less than 10 ppm of proinsulin.

Much of the insulin now produced has an amino-acid sequence identical to that of human insulin. **Human insulin (emp)** is produced by the enzymatic modification of insulin obtained from the porcine pancreas; it is also sometimes called **semisynthetic human insulin**. The term **human insulin (crb)** is used for insulin produced by the chemical combination of A and B chains which have been obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (prb)** is produced from proinsulin obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (pyr)** is insulin produced from a precursor obtained from a yeast genetically modified by recombinant DNA technology. Human insulin obtained by recombinant DNA technology is sometimes termed **biosynthetic human insulin**.

Insulin or human insulin is supplied in a variety of forms in solution or suspension for injection (see Table 1, p. 477). Crystalline insulin may be prepared for therapeutic use merely by making a solution, either of acidic or neutral pH. **Soluble insulin** or **'neutral insulin'** is a short-acting preparation that can be given intravenously if necessary to cover emergencies. Soluble formulations are sometimes referred to as **'regular insulin'** or **'unmodified insulin'**; these names reflect the fact that the preparation has not been formulated to prolong its duration of action.

In order to prolong the duration of action of insulin, preparations may be formulated as suspensions in 2 general ways. The first involves complexing insulin with a protein from which it is slowly released; examples are **protamine zinc insulin**, which contains an excess of protamine, and **isophane insulin** (NPH insulin), which contains equimolecular amounts of insulin and protamine. The second method of prolonging the action of insulin is to modify the particle size and the various **insulin zinc suspensions** are in this category.

Biphasic insulins are mixtures providing for both immediate and prolonged action.

Chemical modification of the insulin molecule has resulted in insulins such as **dalanated insulin** (prepared by the removal of the C-terminal alanine from the B chain of insulin), **insulin defalan** (prepared by the removal of the terminal phenylalanine), and **sulfated insulin**, but these insulins have not been widely used.

More recently, recombinant DNA technology has enabled production of *insulin analogues* with altered pharmacokinetic profiles. **Insulin lispro** and **insulin aspart** are available as rapidly acting alternatives to soluble insulin and as intermediate-acting complexes with protamine. **Insulin glulisine** is another rapidly acting analogue. **Insulin glargine** is a long-acting form for once-daily use, and **insulin detemir** is used once or twice daily. **Insulin degludec** is described as an ultra-long acting analogue, which is used once daily. Further information on these can be found under the heading Insulin Analogues, in Uses, p. 482.1.

Stability and Storage

Both the Ph. Eur. 8 and the USP 36 recommend that insulin preparations be stored in a refrigerator at 2 degrees to 8 degrees and not be allowed to freeze. The Ph. Eur. 8 directs that insulin preparations should be protected from light, and the USP 36 that they should be protected from sunlight. It is recognised that patients may not follow such stringent storage guidelines and most manufacturers of commercial insulin preparations consider that storage by the patient at a temperature of up to 25 degrees would be acceptable for up to one month (individual product information should be consulted). Patients should still be advised not to expose their vials or cartridges to excessive heat or sunlight.

It is advisable to shake suspensions gently before a dose is withdrawn.

Insulin in powder form should be stored in airtight containers and protected from light. Storage at a low temperature is also recommended. The Ph. Eur. 8 advises storage at a temperature of -20 degrees for bovine and porcine insulin and Insulin Glargine and at -18 degrees or below for Human Insulin, and for Insulin Aspart and Insulin Lispro; the USP 36 requires storage at -10 degrees to -25 degrees for all types of insulin. It is stressed that this temperature is for the powder and not for the preparations; preparations should not be subjected to storage conditions that lead to freezing.

Adsorption. Insulin can be adsorbed onto glass and plastics used in giving sets, reducing the amount of insulin delivered by infusion before binding sites are saturated.[1,2] The tubing of giving sets are often primed using, for example, 50 mL of infusion containing insulin 1 unit/mL, but a smaller volume of 20 mL may be adequate.[1] In the past, albumin or polygeline were added to insulin solutions but this practice is no longer recommended.[3,4]

Variations in insulin dose delivery may be particularly problematic with the relatively dilute solutions and low flow rates used in neonatal hyperglycaemia.[5] Various methods have been investigated and found to reduce the amount of insulin lost by adsorption to the giving set, including flushing[6] or priming[7] the system with the insulin infusion, or using a concentrated insulin solution to prime the tubing.[5] A study[8] that compared different methods found wide variation in insulin delivery depending on solution concentration, flow rate, addition of albumin, catheter type, and priming or flushing of the system.

1. Goldberg PA, *et al.* "Waste not, want not": determining the optimal priming volume for intravenous insulin infusions. *Diabetes Technol Ther* 2006; **8:** 598–601.
2. Zahid N, *et al.* Adsorption of insulin onto infusion sets used in adult intensive care unit and neonatal care settings. *Diabetes Res Clin Pract* 2008; **80:** e11–e13.
3. Alberti KGMM. Diabetic emergencies. *Br Med Bull* 1989; **45:** 242–63.
4. Sanson TH, Levine SN. Management of diabetic ketoacidosis. *Drugs* 1989; **38:** 289–300.
5. Fuloria M, *et al.* Effect of flow rate and insulin priming on the recovery of insulin from microbore infusion tubing. *Pediatrics* 1998; **102:** 1401–6.
6. Simeon PS, *et al.* Continuous insulin infusions in neonates: pharmacologic availability of insulin in intravenous solutions. *J Pediatr* 1994; **124:** 818–20.
7. Avent M, Whitfield J. Insulin infusions in extremely low birth weight infants. *Pediatrics* 2000; **105:** 915–16.
8. Hewson MP, *et al.* Insulin infusions in the neonatal unit: delivery variation due to adsorption. *J Paediatr Child Health* 2000; **36:** 216–20.

Aggregation. For discussion of the problems of insulin aggregation, see Intensive Administration Regimens under Uses, p. 482.3.

Compatibility. The compatibility of insulin combinations is discussed in Mixing of Insulins under Uses, p. 483.1.

Units

One unit of *bovine insulin* is contained in 0.03891 mg of the first International Standard (1986). One unit of *porcine insulin* is contained in 0.03846 mg of the first International Standard (1986). One unit of *human insulin* is contained in 0.03846 mg of the first International Standard (1986).

Uses and Administration

Insulin is a hormone that plays a key role in regulating carbohydrate, protein, and fat metabolism. The main stimulus for its secretion is glucose, although many other factors including amino acids, catecholamines, glucagon, and somatostatin, are involved in its regulation. The secretion of insulin is not constant and peaks occur in response to the intake of food.

Table 1. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Soluble insulins (also known as regular or unmodified insulin)	Soluble Insulin Injection (Ph. Eur. 8)	Neutral Insulin Neutral Insulin Injection Soluble Insulin Insulin Injection	Solution of bovine, porcine, or human insulin	6.9 to 7.8				
	Insulin Injection (USP 36)		Solution of bovine or porcine, or a mixture of bovine and porcine, insulin	7.0 to 7.8	Short-acting	30 minutes to 1 hour	2 to 5 hours	6 to 8 hours
	Insulin Human Injection (USP 36)		Solution of human insulin	7.0 to 7.8				
Insulin analogues, rapid	Insulin Aspart Injection (BP 2014)		Solution of insulin aspart	6.9 to 7.8				
	Insulin Lispro Injection (BP 2014)		Solution of insulin lispro	6.9 to 7.8	Short-acting	5 to 20 minutes	1 to 3 hours	2 to 5 hours
	Insulin Lispro Injection (USP 36)		Solution of insulin lispro	7.0 to 7.8				
Biphasic insulins	Biphasic Insulin Injection (Ph. Eur. 8)	Biphasic Insulin	Suspension of crystals containing bovine insulin in a solution of porcine insulin	6.6 to 7.2				
	Biphasic Isophane Insulin Injection (Ph. Eur. 8)	Biphasic Isophane Insulin	Buffered suspension of porcine insulin or human insulin complexed with protamine sulfate or other suitable protamine, in a solution of porcine insulin or human insulin respectively.	6.9 to 7.8				
	Human Insulin Isophane Suspension and Human Insulin Injection (USP 36)		Buffered suspension of human insulin complexed with protamine sulfate, in a solution of human insulin	7.0 to 7.8				
Insulin suspensions	Isophane Insulin Injection (Ph. Eur. 8)	Isophane Insulin Isophane Insulin (NPH) Isophane Protamine Insulin Injection	Suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine. Contains 300 to 600 micrograms of protamine sulfate per 100 units of insulin	6.9 to 7.8				
	Isophane Insulin Suspension (USP 36)		Buffered aqueous suspension of zinc-insulin (bovine or porcine) crystals and protamine sulfate, combined in a manner such that the solid phase of the suspension consists of crystals composed of insulin, protamine, and zinc	7.0 to 7.8	Intermediate-acting	Within 2 hours	4 to 12 hours	Up to 24 hours
	Isophane Insulin Human Suspension (USP 36)		Buffered aqueous suspension of zinc-insulin human crystals and protamine sulfate, combined in such a manner that the solid phase of the suspension consists of crystals composed of insulin human, protamine, and zinc	7.0 to 7.5				
	Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 8)	Amorph. I.Z.S. Insulin Semilente Insulin Zinc Suspension (Amorphous)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				

Table 1. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Insulin suspensions *cont*	Prompt Insulin Zinc Suspension (USP 36)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is amorphous	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Ph. Eur. 8)	Insulin Lente I.Z.S. I.Z.S. (Mixed) Insulin Zinc Suspension (Mixed) Insulin Zinc Suspension	Suspension of bovine or porcine, or a mixture of bovine and porcine, or human insulin with a suitable zinc salt; the insulin is in a form practically insoluble in water. It may be produced by mixing Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 8) and Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 8) in a ratio of 3 to 7	6.9 to 7.8				
	Insulin Zinc Suspension (USP 36)	Insulin Zinc	Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8	Intermediate or long-acting	2 to 3 hours	6 to 15 hours	Up to 30 hours
	Insulin Human Zinc Suspension (USP 36)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 8)	Cryst. I.Z.S. Insulin Ultralente Insulin Zinc Suspension (Crystalline)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				
	Protamine Zinc Insulin Injection (BP 2014)	Protamine Zinc Insulin	Buffered suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine and zinc chloride or another suitable zinc salt	6.9 to 7.8				
	Extended Insulin Zinc Suspension (USP 36)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is predominantly crystalline	7.0 to 7.8	Long-acting	4 hours	10 to 20 hours	Up to 36 hours
	Extended Insulin Human Zinc Suspension (USP 36)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension is predominantly crystalline	7.0 to 7.8				

The major effects of insulin on carbohydrate homoeostasis follow its binding to specific cell-surface receptors on insulin-sensitive tissues, notably the liver, muscles, and adipose tissue. It inhibits hepatic glucose production and enhances peripheral glucose disposal thereby reducing blood-glucose concentration. It also inhibits lipolysis thereby preventing the formation of ketone bodies.

Therapy with insulin is essential for the long-term survival of all patients with type 1 diabetes mellitus. It may also be necessary in some patients with type 2 disease. The role of insulin is discussed further in the Management of Diabetes Mellitus (p. 459.1), Diabetes Mellitus and Pregnancy (p. 461.3), Gestational Diabetes Mellitus (p. 462.1), and Diabetes Mellitus in Surgery or Critical Care (p. 462.2).

Choice of insulin. The different types of insulin and their formulations are described under Definitions and Terminology, p. 476.1. In some countries including the UK the commercially available preparations have been standardised to a single **strength** containing 100 units/mL; a strength of 40 units/mL is still available in some other countries, and in others concentrated injections (500 units/mL) are available to enable high doses to be given subcutaneously in a small volume. The analogue insulin degludec may be available in strengths of 100 units/mL and 200 units/mL. All formulations can be given by subcutaneous injection, most by intramuscular injection, but only some soluble insulins and short-acting analogues can be given by the intravenous **route**. The long-term management of diabetic patients usually involves the subcutaneous route. Single-use syringes and needles, which are calibrated for the particular concentration of insulin being given, should preferably be used. Pen-injector devices which hold the insulin in cartridge form and meter the required dose are becoming increasingly popular. Soluble insulin is often given by the intraperitoneal route to patients on continuous ambulatory peritoneal dialysis. A product supplying short-acting insulin by inhalation (*Exubera; Pfizer*) was withdrawn from the market in late 2007, but the development of alternative inhaler products is continuing.

The various formulations of insulin are classified, according to their **duration of action** after subcutaneous injection, as short-, intermediate-, or long-acting. The exact duration of action for any particular preparation, however, is variable and may depend upon factors such as interindividual variation, the patient's antibody status, whether the insulin is identical to human insulin or of animal origin, the dose, and the site of injection.

- *Short-acting* insulins are the soluble insulins, which have an onset after about 30 minutes to 1 hour, a peak activity at about 2 to 5 hours, and a duration of about 6 to 8 hours. Some analogues, such as insulins lispro and aspart, are also short-acting, with a faster onset and shorter duration of action than soluble insulin and are often known as rapid-acting insulins.
- *Intermediate-acting* insulins include biphasic insulins, isophane insulins, and amorphous insulin zinc suspensions. In general these have an onset within about 2 hours, peak activity after about 4 to 12 hours, and a duration of up to 24 hours. Commercially available mixtures of soluble insulins and isophane insulins have activities which would normally place them within the intermediate-acting category.
- Mixed insulin zinc suspensions may be classified as either *intermediate- or long-acting* as the duration of action may be up to 30 hours; the onset of action is generally 2 to 3 hours and the time to peak activity 6 to 15 hours.
- *Long-acting* insulins include crystalline insulin zinc suspensions and protamine zinc insulins. These generally have an onset after about 4 hours, a peak activity at about 10 to 20 hours, and a duration of up to 36 hours. The insulin analogues insulin glargine and insulin detemir are also long-acting, but these show a more consistent absorption profile with little or no pronounced peak of activity. Insulin degludec is described as an ultra-long acting analogue.

After intramuscular injection, the onset of action of all insulins is generally more rapid and the duration of action shorter.

The type of formulation, its dose, and the frequency of administration are chosen to suit the needs of the individual patient. Whatever the formulation, human insulin or insulin analogues are generally used for all newly diagnosed diabetics.

Control. The **dosage** of insulin must be determined for each patient and although a precise dose range cannot be given, total daily subcutaneous doses up to about 1 unit/kg may be appropriate. Insulin requirements can be altered by various factors (see Precautions, p. 487.1) and very high doses may be necessary in patients with insulin resistance (p. 489.1). The dose should be adjusted as necessary according to the results of regular monitoring of blood concentrations (or occasionally urine concentrations) of glucose by the patient. In practice, the *BNF* suggests that it is generally acceptable for patients to aim for blood-glucose concentrations between 4 and 9 mmol/litre (4 to 7 mmol/litre preprandially, and less than 9 mmol/litre postprandially) with the understanding that occasional variations outside this range may occur. Long-term control is determined by monitoring glycated haemoglobin (HbA_{1c}) concentrations; ideally the aim is an HbA_{1c} level of 6.5 to 7.5% (48 to 59 mmol/mol) or less. However, recommendations vary between authorities, and may depend on factors such as age and comorbidities; for further details see Monitoring of Therapy in Diabetes Mellitus, p. 461.1.

The aim of any **regimen** should be to achieve the best possible control of blood glucose by attempting to mimic as closely as possible the pattern of optimum endogenous insulin secretion. Many regimens involve the use of a short-acting soluble insulin with an intermediate-acting insulin, such as isophane insulin or insulin zinc suspension, often given twice daily. Basal-bolus regimens, using multiple daily injections to improve glycaemic control, typically combine an intermediate- or long-acting basal insulin (in the evening or twice daily) with a dose of short-acting insulin before each meal. A continuous subcutaneous insulin infusion (CSII) can be a suitable alternative for intensive therapy in some patients. CSII delivers a constant basal infusion of insulin, with patient-activated bolus doses before each meal. A short-acting soluble insulin or insulin analogue is used, although some formulations of soluble insulin are unsuitable because of the risk of catheter obstruction; insulin suspensions and long-acting analogues are also unsuitable. Patients using CSII need to be well-motivated, able to monitor their own blood glucose, and have access to expert advice at all times. A once-daily injection of an intermediate-or long-acting insulin is now generally considered to be acceptable only for those patients with type 2 diabetes mellitus who still retain some endogenous insulin secretion but nevertheless require insulin therapy.

Ketoacidosis. Insulin is also an essential part of the emergency management of diabetic ketoacidosis. Only short-acting soluble insulins should be used. Treatment includes adequate fluid replacement, usually by infusing sodium chloride 0.9% initially, and the use of potassium salts to prevent or correct hypokalaemia. Insulin should be given by continuous intravenous infusion if possible, although other routes have also been used. Since insulin normally corrects hyperglycaemia before ketosis it is usually necessary to continue giving insulin once normoglycaemia has been achieved but to change the rehydration fluid to a glucose infusion so that the additional glucose prevents the development of hypoglycaemia. For details of regimens see Diabetic Emergencies, under Diabetes Mellitus, p. 483.3.

General reviews of insulin and its use.[1-6] It has been suggested that the plethora of insulin preparations available might sensibly be reduced,[2] although others dispute this.[7]

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Administration. *ADMINISTRATION ROUTES.* The long-term management of diabetic patients usually involves insulin injection by the **subcutaneous** route, using a syringe or insulin pen device. The *depth* of injection is important since insulin is absorbed more rapidly after intramuscular than subcutaneous injection; inadvertent intramuscular injection may therefore lead to greater day-to-day variability in blood-glucose control.[1] Full-depth vertical injection can increase the chance of intramuscular injection, particularly in lean patients. Techniques for minimising intramuscular administration include injecting into a raised skin fold, injecting at a 45 degree angle instead of perpendicular to the skin surface, and the use of a shorter needle.[2,3] Inconsistency in the time lapse before withdrawing the needle, and the possible reflux of insulin from the subcutaneous tissue if the needle is withdrawn too quickly, might also contribute to variability in the absorbed insulin dose.[1]

The anatomic *site* of subcutaneous insulin injection is usually rotated in an attempt to decrease local adverse effects (see Adverse Effects, p. 485.2). However, the rate of absorption varies between sites and such a practice may also contribute to day-to-day variability in blood-glucose concentrations.[4] For example, large variations in blood-glucose concentrations have been reported on subcutaneous injection into the thigh.[5] Some have suggested rotation of injection sites within an anatomic region, or possibly use of the same anatomic region for injections given at a specific time of day.[1,4]

Jet injectors deliver insulin at high pressure across the skin into the subcutaneous tissue without use of a needle.[6,7] The greater dispersion obtained gives more rapid absorption of short- and intermediate-acting insulins and consequently reduces the total duration of action.[6] Mild pain, bruising, and bleeding may be a problem.[6-8] Despite having been available for some years, there is little information about their benefits and risks and they are not widely used.[7] However, results in a small study in women with gestational diabetes have suggested that jet injection may be associated with less variation in postprandial blood-glucose concentration and a lower incidence of insulin antibodies.[9]

Insulin preparations may also be given by **intramuscular** injection. Absorption is more rapid than from a subcutaneous injection. However, exercise may produce considerable variations in insulin absorption after intramuscular injection.[10] Soluble insulins and rapid-acting soluble insulin analogues may be given **intravenously**; this route is used in diabetic ketoacidosis, and also in surgery and labour.

The subcutaneous and intravenous routes, and, rarely, the intramuscular route have all been used for the continuous administration of insulin (see Intensive Administration Regimens, p. 482.3).

Formulations of insulin for **intranasal** use are under investigation.[8,11-13] They have been tried in both type 1 and type 2 diabetes, but bioavailability is low and variable. Absorption enhancers have been used to facilitate uptake of insulin from the nasal mucosa and local adverse effects are dependent, in part, on their irritancy. Similarly, **buccal** formulations are under investigation,[8,13,14] and have become available in some countries for use as short-acting prandial doses of insulin (*Oral-lyn; Generex*).

Devices for delivering insulin to the lungs via oral **inhalation** have been developed.[8,15-18] Inhaled insulin is effective in maintaining glycaemic control in both type 1 and type 2 diabetes.[19-22] Although there is some evidence from longer-term studies that it is slightly less effective than subcutaneous injection, patient acceptability is higher with inhaled insulin.[19] It is given before meals as a short-acting insulin in patients also receiving intermediate or long-acting subcutaneous insulins or oral antidiabetics; in type 2 diabetes it has also been used alone. Data regarding the long-term safety of inhaled insulin need to be collected, given reports of pulmonary effects and higher levels of insulin antibodies in people with type 1 diabetes. A few cases of primary lung malignancies have occurred in clinical studies of inhaled insulin, at a higher incidence than in comparator-treated patients. However, the number of cases was too small to determine whether these events were related to inhaled insulin, and all affected patients had a history of cigarette smoking. The first licensed product for inhalation (*Exubera; Pfizer*) was withdrawn from the market in late 2007, although other products are still in development.

Endogenous insulin is delivered into the portal venous system, and then passes immediately to the liver where a large fraction of the insulin is extracted. The above routes of administration all deliver insulin into the peripheral circulation, with the risk of peripheral hyperinsulinaemia which has been considered a risk factor for atherosclerotic complications.[23] Giving insulin via the **intraperitoneal** or **oral** routes may overcome this problem to some extent. Peritoneal insulin is used routinely in diabetics undergoing chronic ambulatory peritoneal dialysis,[24,25] but has also been used for continuous administration (see Intensive Administration Regimens, p. 482.3). Various formulations of insulin for oral delivery are also under investigation.[8,12-14,26] **Transdermal**[8,13,27] insulin has also been tried.

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INSULIN ANALOGUES. Most of the insulin in pharmaceutical preparations is in the form of hexamers, which take time to dissociate into dimers and monomers that can be absorbed from a subcutaneous site. Substitution of amino-acid residues in the insulin molecule, using recombinant DNA technology, has produced insulin analogues such as insulin aspart and insulin lispro that form less stable hexamers and are therefore absorbed more rapidly. Similarly, structural changes have been made to develop long-acting basal analogues, such as insulin detemir and insulin glargine, as described below.

In the ***short-acting*** analogue **insulin lispro**, the B28 and B29 residues are replaced with lysine and proline, respectively. Compared with human regular insulin, it has a faster onset of action (within 15 minutes), peaks earlier, and has a shorter duration of action (2 to 5 hours). As a result, insulin lispro is given shortly before meals, but can alternatively be given immediately after eating if necessary. In diabetic patients, it controls postprandial glucose concentrations and glycated haemoglobin (HbA_{1c}) at least as well as regular insulin, without an increased risk of hypoglycaemia.[1] As well as adults, insulin lispro may be used in children and has been given during pregnancy. It is suitable for use in a continuous subcutaneous insulin infusion (CSII) and may be given intravenously in the treatment of ketoacidosis or during surgery.[1] Insulin lispro has also been complexed with protamine to produce an intermediate-acting form, which is available as a biphasic preparation.[1,2] A few cases of response to insulin lispro in patients with severe insulin resistance have been reported.[3,4]

Insulin aspart is another short-acting insulin analogue, with aspartic acid replacing proline at position B28.[5,6] It is also used immediately before meals and controls postprandial blood-glucose concentrations at least as well as regular human insulin, and may cause fewer hypoglycaemic episodes. Like insulin lispro, insulin aspart may be given to adults, children, and pregnant women, used in CSII, or given intravenously. It has also been formulated with protamine to create a biphasic preparation.[2,7]

Insulin glulisine is another insulin analogue, with asparagine at position B3 replaced by lysine, and lysine at B29 replaced by glutamic acid.[8] It also has a rapid onset (about 20 minutes) and short duration of action (4 hours), and is given about 15 to 20 minutes before meals or within 20 minutes after starting the meal.[9,10] Insulin glulisine has proven effective in the control of blood glucose in diabetic adults, but there is limited information about its use in young children and pregnant women. It may also be given by CSII or intravenously.

A systematic review[11] of studies comparing short-acting insulin analogues (aspart, glulisine, or lispro) with regular insulin found evidence of a minor benefit from analogues in improving HbA_{1c} values in adults with type 1 diabetes. The effect was more pronounced in studies using CSII and in studies with an intervention period of more than 3 months. No superiority could be shown in type 2 diabetics. Overall hypoglycaemia was similar, but severe episodes occurred less often in the analogue group. However, the effects of long-term analogue therapy on microvascular complications of diabetes remain to be studied. Another review[12] that included studies of biphasic insulin analogues in adults with type 2 diabetes concluded that they were similar to biphasic human insulin in controlling fasting glucose and HbA_{1c}, but more effective in lowering postprandial glucose concentrations. Premixed analogues may also provide better glycaemic control than long-acting insulin analogues and non-insulin antidiabetics.

Recombinant DNA technology has also been used to produce a ***long-acting*** basal insulin analogue, **insulin glargine**, in which glycine replaces asparagine at position A21 and two arginine molecules are added to the C-terminus of the B chain.[13-15] It is available as a solution at pH 4; on subcutaneous injection and neutralisation by tissue buffering processes, microprecipitates are formed that slowly release insulin glargine over 24 hours with no pronounced peak in concentration or in metabolic activity. As a result, insulin glargine is given once daily at any time, but should be given at the same time each day. The prolonged effects of insulin glargine may be advantageous in the management of patients who are susceptible to morning hyperglycaemia (see p. 488.1). Controlled studies have reported insulin glargine to be more effective than human isophane insulin in producing glycaemic control as part of a basal-bolus regimen, and to be associated with fewer hypoglycaemic episodes.[15] However, a systematic review[16] of studies in adults with type 2 diabetes did not find a significant advantage over human isophane insulin in glycaemic control. Insulin glargine was associated with fewer hypoglycaemic events reported by study participants, but confirmed and severe hypoglycaemia were not significantly different; there was slightly less weight gain with isophane insulin. Insulin glargine may be used in children over 2 years of age.

Insulin detemir is another long-acting insulin analogue. It is a neutral soluble human insulin analogue in which the terminal amino acid at B30 has been replaced by myristic acid, a 14-carbon fatty acid chain. This allows insulin detemir to bind reversibly to albumin, producing slow absorption and a prolonged and consistent metabolic effect for up to 24 hours, permitting once or twice daily dosing. It appears to be at least as effective as isophane insulin in maintaining overall glycaemic control but with less intrapatient variability, a similar or lower risk of hypoglycaemia, and less body-weight gain.[17] A systematic review[18] found no clinically relevant differences in efficacy between insulin glargine and insulin detemir although the former was associated with fewer injection-site reactions, and the latter with less weight gain. Insulin detemir may be used in children aged 2 years and older, and considered for use in pregnant women.

A systematic review[19] of studies in type 2 diabetics found that long-acting insulin analogues (detemir or glargine) had a similar effect to isophane insulin on glycaemic control, although they may be associated with less hypoglycaemia, including nocturnal events. The authors suggested a cautious approach to the use of these analogues until further efficacy and safety data become available.

Insulin degludec is an ultra-long-acting neutral soluble insulin analogue, in which the amino acid at position B30 is deleted and hexadecanoic acid is attached to the lysine at B29 via a glutamic acid spacer. After subcutaneous injection, molecules self-associate into multi-hexameric chains to form a depot, which slowly dissociates to release active monomers that are absorbed into the circulation. It has a duration of action of more than 42 hours, and is reported to have a flat, stable glucose-lowering effect; steady state occurs after 2 to 3 days of administration. Insulin degludec is used as a once daily injection, and although it should be given at the same time each day its long duration of action allows for some flexibility in dosing. It achieves similar glycaemic control to insulin glargine, but with less risk of nocturnal hypoglycaemia.[20-22] Insulin degludec has also been investigated in three times a week regimens.[22]

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INTENSIVE ADMINISTRATION REGIMENS. Intensive insulin regimens aim to mimic more closely the physiological insulin pattern in which a basal insulin concentration is supplemented by a preprandial boost of insulin. Such intensive regimens are used to provide tight control in an attempt to avoid long-term complications (see p. 462.3).

Intensified insulin regimens have the advantage of improving the patient's lifestyle and allowing flexibility in timing of meals. However, careful dietary control must still be maintained and regular monitoring of blood-glucose concentrations is an important component of such regimens. Therefore patients must be well-motivated, reliable, and able to monitor their own blood glucose, and must have access to expert 24-hour help.

In **multiple daily injection** regimens, the basal insulin is provided by injection of an intermediate- or long-acting insulin or insulin analogue, given usually at night, and soluble insulin or a short-acting analogue given before each main meal. Systems for **continuous administration** may be designed on an open-loop or closed-loop delivery system. *Open-loop systems* comprise an infusion pump with the infusion rate programmed or controlled manually according to blood-glucose monitoring carried out manually or continuously by a subcutaneous glucose sensor. *Closed-loop systems* (the 'artificial pancreas') consist of an insulin pump, a glucose sensor, and a computer for analysis of blood-glucose data and adjustment of insulin delivery. Systems for continuous administration have most commonly used the subcutaneous route, but intraperitoneal, intravenous, or intramuscular infusion have also been used.

The most extensively used **open-loop** system is *continuous subcutaneous insulin infusion* (CSII) using an external pump. A battery-powered pump infuses soluble insulin or a short-acting analogue via a subcutaneous catheter which is resited every 2 to 3 days. A background infusion is given at a predetermined rate, and preprandial bolus doses given using an override switch or manual drive.[1] CSII appears to provide better glycaemic control than conventional injection therapy.[2] It may be only slightly more effective than optimised multiple daily injection therapy in type 1 diabetics,[2-6] although the use of a continuous subcutaneous glucose sensor might further improve glycaemic control with pump therapy.[7] CSII may be used in all age groups including children,[3,4,6,8,9] and might be particularly useful in very young children because of their erratic food intake and reduced ability to convey symptoms of hypoglycaemia.[10]

Intensive regimens are associated with decreased hypoglycaemic awareness and more severe hypoglycaemic episodes compared with conventional therapy.[11] Although study results have been mixed as to whether CSII reduces the risk of severe hypoglycaemia compared with multiple daily injection therapy,[6,7,12] disabling hypoglycaemia associated with multiple daily injections may be an indication for changing to CSII.[6] Other complications include erythema, abscess, or cellulitis at the injection site and, rarely, contact dermatitis to components of the giving set, pump malfunction, or precipitation of insulin and catheter obstruction.[1] Pump therapy increases the risk of ketoacidosis if the pump fails or there is an acute increase in insulin requirements; the onset of ketoacidosis may be more rapid and more likely to be associated with dangerous hyperkalaemia than with conventional regimens because there is no depot of insulin.[1,13]

Further development of open-loop delivery systems has been in the design of *implantable insulin pumps* that deliver insulin intraperitoneally. Specially formulated insulin preparations have been developed to cope with the physical conditions of implanted pump therapy; for example Hoe-21PH is a highly concentrated insulin solution containing a stabilising agent. Some studies have shown improved glycaemic control, and fewer episodes of hypoglycaemia, compared with intensive subcutaneous delivery. The main associated problems are pump slow-down or catheter

obstruction due to aggregation of insulin within the device; these can normally be corrected by procedures to flush the pump and catheter. Problems at the implantation site can include infection, fluid accumulation, or skin thickening. The bulkiness of current pumps makes them unsuitable for children and adolescents who have not yet reached adult size.[14]

Closed-loop continuous infusion systems are generally confined to research and experimental work, although several prototypes have been studied in patients with type 1 diabetes.[15,16] Systems in development have been based on subcutaneous glucose monitoring and insulin delivery, or intravenous glucose monitoring with intraperitoneal insulin delivery from an implanted pump. Semiclosed-loop systems are also being considered, in which there is some manual input into prandial dose adjustment.[17,18]

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12. Fatourechi MM, *et al*. Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J Clin Endocrinol Metab* 2009; **94:** 729–40.
13. Knight G. Risks with continuous subcutaneous insulin infusion can be serious. *BMJ* 2001; **323:** 693–4.
14. Renard E, Schaepelynck-Bélicar P. EVADIAC Group. Implantable insulin pumps: a position statement about their clinical use. *Diabetes Metab* 2007; **33:** 158–66.
15. Nishida K, *et al*. What is artificial endocrine pancreas? Mechanism and history. *World J Gastroenterol* 2009; **15:** 4105–10.
16. Dassau E, *et al*. Closing the loop. *Int J Clin Pract* 2010; **64** (suppl 166): 20–5.
17. Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabet Med* 2006; **23:** 1–12.
18. Hanaire H. Continuous glucose monitoring and external insulin pump: towards a subcutaneous closed loop. *Diabetes Metab* 2006; **32:** 534–8.

MIXING OF INSULINS. Mixtures of insulin with differing durations of action may be used in order to produce a more normal pattern of blood glucose variation than can be achieved with a single insulin. However, physicochemical changes in the mixture may occur, either immediately on mixing or over time, and the physiological response to the mixture may therefore be different than if the components were given separately. An early review[1] suggested that insulins from different manufacturers should not be mixed, since formulation differences might render them incompatible. It is important that a consistent routine is followed in preparing and using such mixtures, and manufacturers advise that the shorter-acting insulin should be drawn into the syringe first, to avoid contamination of the vial with the longer-acting component. Pre-prepared mixtures are available from many manufacturers and may be preferable provided that the proportions are suited to the patient's needs.

The American Diabetes Association has issued guidelines[2] for mixing of insulins, including:

- patients well controlled on a particular mixed regimen should maintain their standard procedure for preparing doses
- no other medication or diluent should be mixed with insulin unless approved by the prescriber
- insulin glargine should not be mixed with other forms of insulin because of the low pH of its diluent
- currently available isophane and short-acting insulin formulations when mixed may be used immediately or stored for future use
- rapid-acting insulins (insulin aspart, insulin lispro) can be mixed with isophane, lente, and ultralente insulins. Ultralente insulins do not affect the onset of action of the rapid-acting component; a slight decrease in absorption rate but not bioavailability is seen if rapid-acting insulins are mixed with isophane insulin but postprandial blood-glucose response is similar to that seen with mixtures of rapid-acting and ultralente insulin
- mixtures of rapid-acting insulin with an intermediate- or long-acting insulin should be injected within 15 minutes before a meal
- mixing of short-acting (soluble) and lente or ultralente insulin is not recommended, as zinc ions present in the lente insulin may bind with the short-acting insulin and delay its effects. The degree and rate of binding vary with the insulins used, and may not reach equilibrium for 24 hours; if such mixtures are used the patient should standardise the interval between mixing and injection
- phosphate-buffered insulins (e.g. isophane insulin) should not be mixed with zinc-containing (lente or ultralente) insulins, as zinc phosphate may be precipitated, and the longer acting insulin may be partially and unpredictably converted to a short-acting form

Insulin formulations may change and the manufacturers should be consulted if their recommendations differ from those in the guidelines.

1. Fisher BM. Choosing an insulin. *Prescribers' J* 1988; **28:** 138–43. Correction. *ibid.*; 169.
2. American Diabetes Association. Insulin administration. *Diabetes Care* 2004; **27** (suppl 1): S106–S109. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s106.pdf (accessed 12/10/09)

Administration in children. Insulin is used for the management of type 1 diabetes mellitus in children, as it is in adults (see Uses, p. 476.3) and doses are adjusted similarly to achieve the desired control of blood sugar. The *BNFC* notes that most pre-pubertal children require insulin doses of around 0.6 to 0.8 units/kg daily once the initial temporary remission phase has ended. Unless the child has a very sedentary lifestyle a requirement for higher doses may indicate poor compliance or absorption, or the beginning of puberty. During puberty up to 1.5 to 2 units/kg daily may be required, especially during growth spurts; doses may subsequently require some adjustment to avoid excessive weight gain. There is less experience with insulin analogues in young children. Although type 2 diabetes is rare in children the incidence is rising, and insulin may be needed to maintain glycaemic control in some of these patients also.

Further details on the use of insulin in children can also be found in Diabetic Emergencies, p. 483.3, and Neonatal Hyperglycaemia, p. 485.1. See p. 486.3 for the treatment of insulin-induced hypoglycaemia in children.

Critically ill patients. Strict glycaemic control has been advocated for the management of stress-induced hyperglycaemia in critically ill patients, whether they are diabetic or not. However, a meta-analysis[1] of 29 studies, which included more than 8000 critically ill adult medical and surgical patients, did not confirm the beneficial results of an earlier influential study.[2] It found that using an insulin infusion to maintain tight control of glucose below 8.3 mmol/litre was not associated with reduced hospital mortality, but did increase hypoglycaemia. Another meta-analysis[3] that included only studies of the perioperative use of insulin (with or without glucose targets) found that it reduced mortality, but also increased hypoglycaemia. However, most of the effect was accounted for by the influential study[2] that had been stopped early because of an unexpectedly large treatment effect; when this study was removed from the meta-analysis, the beneficial effect of insulin on mortality was no longer statistically significant.

Subsequent to these analyses, a large randomised study (NICE-SUGAR)[4] compared the outcome of more than 6000 critically ill medical and surgical patients maintained in a target glucose range of either 4.5 to 6.0 mmol/litre, or up to 10.0 mmol/litre. In this study, intensive glucose control in the lower target range was actually associated with an increased risk of death in the 90 days after randomisation, as well as more hypoglycaemia. A further meta-analysis,[5] which incorporated the NICE-SUGAR results, found that intensive insulin therapy had no effect on the overall risk of death. Subgroup analysis showed a benefit for patients treated in a surgical intensive care unit, but the authors urged caution in the interpretation of this result because of low event rates in this group. The meta-analysis also confirmed an increased risk of hypoglycaemia from intensive insulin therapy. In another study[6] of 509 patients with septic shock who were given corticosteroid treatment, which can induce or exacerbate hyperglycaemia, the addition of intensive insulin therapy did not improve inpatient mortality when compared with conventional insulin therapy.

Although hyperglycaemia is known to be harmful in critically ill patients, there is uncertainty about which subgroups, if any, might benefit from the routine use of tight glycaemic control.[7,8] There is still controversy regarding the most appropriate blood-glucose target, how and when to measure blood-glucose concentrations, and the best method of insulin administration. The risks associated with insulin-induced hypoglycaemia also need to be considered. The effects of different feeding regimens might also be important.[5,9] Nevertheless, guidelines have been issued on the management of hyperglycaemia in critically ill patients. Some[10] have recommended starting insulin infusion therapy for persistent hyperglycaemia at a blood-glucose concentration threshold of no greater than 10.0 mmol/litre, with a target range of 7.8 to 10.0 mmol/litre, while others[11] have suggested a target range of 7.8 to 11.1 mmol/litre.

For a discussion of the management of hyperglycaemia in non-critically ill hospitalised patients, see Inpatient Hyperglycaemia, p. 484.3.

1. Wiener RS, *et al*. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008; **300:** 933–44. Correction. *ibid.*; **301:** 936.
2. Van den Berghe G, *et al*. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; **345:** 1359–67.
3. Gandhi GY, *et al*. Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic review and meta-analysis of randomized trials. *Mayo Clin Proc* 2008; **83:** 418–30.
4. Finfer S, *et al*. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360:** 1283–97.
5. Griesdale DEG, *et al*. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; **180:** 821–7.
6. Annane D, *et al*. COIITSS Study Investigators. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA* 2010; **303:** 341–8.
7. Lipshutz AKM, Gropper MA. Perioperative glycemic control: an evidence-based review. *Anesthesiology* 2009; **110:** 408–21.
8. Inzucchi SE, Siegel MD. Glucose control in the ICU—how tight is too tight? *N Engl J Med* 2009; **360:** 1346–9.
9. Van den Berghe G, *et al*. Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? *J Clin Endocrinol Metab* 2009; **94:** 3163–70.
10. Moghissi ES, *et al*. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; **32:** 1119–31. Also available at: http://care.diabetesjournals.org/content/32/6/1119.full.pdf (accessed 10/03/11) Also published in: *Endocr Pract* 2009; **15:** 353–69. Also available at: https://www.aace.com/sites/default/files/InpatientGlycemicControlConsensusStatement.pdf (accessed 10/08/11)
11. Qaseem A, *et al*. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2011; **154:** 260–7. Also available at: http://www.annals.org/content/154/4/260.full.pdf (accessed 10/03/11)

Diabetes mellitus. Insulin is the mainstay of the treatment of **type 1 diabetes mellitus**. For a discussion of the treatment of diabetes mellitus, including the contexts in which insulin is used, see p. 459.1. The possible role of tight glycaemic control with insulin to prevent the development of microvascular and macrovascular complications in patients with type 1 diabetes is discussed on p. 462.3, while further discussion of specific regimens and approaches to insulin therapy is given under Administration, p. 479.2.

DIABETIC EMERGENCIES. As discussed on p. 465.3, **diabetic ketoacidosis** and hyperosmolar hyperglycaemic state (HHS) are medical emergencies and should be treated immediately with fluid replacement and insulin. Potassium, and possibly phosphate, replacement may also be required, but bicarbonate should not be given unless acidaemia is very severe. In addition, potassium replacement, given by infusion, is generally necessary during insulin treatment to prevent insulin-induced hypokalaemia.

In the *UK* the *BNF* recommends that insulin be given by intravenous infusion for diabetic ketoacidosis, as a solution of soluble insulin 1 unit/mL in sodium chloride 0.9%. A fixed infusion rate of 0.1 units/kg per hour is recommended initially, with the rate adjusted so that the blood-ketone concentration falls by at least 0.5 mmol/litre per hour and the blood-glucose concentration falls by at least 3.0 mmol/litre per hour. When the blood-glucose concentration has fallen below 14 mmol/litre, glucose 10% infusion is started at a rate of 125 mL/hour in addition to the sodium chloride 0.9% infusion. The insulin infusion is continued until the blood-ketone concentration is below 0.3 mmol/litre and the blood pH is above 7.3. When the patient is able to eat and drink, subcutaneous fast-acting insulin should be given with a meal, and the insulin infusion may be stopped 1 hour later. Any established therapy with a long-acting insulin analogue (insulin detemir or insulin glargine) should be continued during treatment for ketoacidosis.

The *BNFC* gives some guidance on management of children with diabetic ketoacidosis. Children with mild ketoacidosis and less than 5% dehydration may be managed with oral rehydration and subcutaneous insulin. Those who do not respond, or are clinically unwell or more severely dehydrated are best managed with intravenous fluids and insulin. Rehydration should be with sodium chloride 0.9%,

at a rate that replaces deficit and provides maintenance over 48 hours; for those in shock an initial bolus of 10 mL/kg repeated up to twice, may be given. Fluid replacement may be changed to sodium chloride 0.45% with glucose 5% after 12 hours if response is adequate and plasma-sodium concentration stable. Potassium chloride should be included in rehydration fluids unless anuria is suspected. Insulin infusion should not be started until at least 1 hour after starting rehydration; soluble insulin 1 unit/mL in sodium chloride 0.9% is infused at a rate of 0.1 units/kg per hour. Once blood-glucose falls to 14.0 mmol/litre (and provided the blood pH is over 7.3) this rate can be reduced to 0.05 units/kg per hour; at the same time, glucose 5 or 10% should be added to the infusion fluids. This is continued until the patient is ready to take food orally. The insulin infusion should not be stopped until 1 hour after starting subcutaneous insulin or 10 minutes after starting a short-acting analogue.

Similar recommendations have been made in other UK guidelines on the management of diabetic ketoacidosis in adults and children.[1,2]

Intravenous insulin is also recommended in the *USA*. One set of recommendations[3] for diabetic ketoacidosis in adults suggests that once hypokalaemia has been excluded, treatment begins with an intravenous bolus of soluble regular insulin 0.1 units/kg, which is followed by infusion of 0.1 units/kg per hour. Alternatively, an infusion may be started (without a preceding bolus) at 0.14 units/kg per hour. The blood-glucose concentration should usually fall by about 2.5 to 4.0 mmol/litre per hour, but if it has not done so in the first hour then the intravenous infusion rate may be increased. (These intravenous insulin regimens may also be used in patients with **HHS**.) Treatment is continued until a blood-glucose concentration of about 11.0 mmol/-litre is reached (or about 17.0 mmol/litre for HHS), when the insulin infusion rate may be reduced to 0.02 to 0.05 units/kg per hour; alternatively, a rapid-acting subcutaneous insulin analogue may be given at 0.1 units/kg every 2 hours in mild to moderate diabetic ketoacidosis. An infusion of glucose 5% should also be started. The blood-glucose concentration should be maintained between 8.3 and 11.0 mmol/litre (or between 11.0 and 17.0 mmol/litre for HHS) until the metabolic disturbance has resolved. When the patient is able to eat, intravenous insulin should still be continued for 1 to 2 hours after a maintenance subcutaneous insulin regimen has begun.

Children in the *USA*[4] with diabetic ketoacidosis may be started on insulin treatment after initial fluid replacement (usually after about 1 to 2 hours), using an intravenous infusion of 0.1 units/kg per hour. An initial insulin bolus dose is considered unnecessary and may increase the risk of cerebral oedema. After a rapid decline in plasma glucose during the initial volume expansion, it usually decreases at a rate of about 3.0 to 5.0 mmol/litre per hour. The dose of insulin may be reduced to 0.05 units/kg per hour in patients who have a marked sensitivity to insulin. Glucose 5% infusion should be started when the blood-glucose concentration reaches about 17.0 mmol/litre, but may need to be started sooner if the concentration falls more rapidly than 5.0 mmol/litre per hour. Higher concentrations of 10 or 12.5% glucose may be needed to prevent hypoglycaemia while continuing the insulin infusion required to correct the metabolic acidosis. If intravenous administration is not possible, hourly or 2-hourly doses of a subcutaneous or intramuscular rapid-acting insulin analogue may be considered.

1. Savage MW *et al*. Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults. (issued March 2010). Available at: http://www.diabetes.nhs.uk/document.php?o=1336 (accessed 10/08/11)
2. Edge JA. British Society of Paediatric Endocrinology and Diabetes. Guidelines for the management of diabetic ketoacidosis (issued November 2009). Available at: http://www.bsped.org.uk/professional/guidelines/docs/DKAGuideline.pdf (accessed 17/03/11)
3. Kitabchi AE, *et al*. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32:** 1335–43.
4. Wolfsdorf J, *et al*. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; **29:** 1150–9. Also available at: http://care.diabetesjournals.org/content/29/5/1150.full.pdf (accessed 25/06/09)

TYPE 2 DIABETES MELLITUS. Traditionally the use of insulin in patients with type 2 diabetes has tended to be reserved for those who cannot be controlled by diet and oral antidiabetics alone.[1,2] Given the possible association between circulating insulin and atherosclerotic cardiovascular symptoms[3] there had been some concern about the use of exogenous insulin in insulin-resistant patients who are already hyperinsulinaemic, but evidence of harm is lacking.[4] Furthermore, patients switched to insulin tend to gain weight[2] which is undesirable in a frequently obese patient group.

Insulin is nonetheless being used more frequently in type 2 patients. This is largely because of a trend toward more intensive regimens designed to produce tighter glycaemic control, on the hypothesis that, as in patients with type 1 disease, this will reduce the development and progression of diabetic complications. Results from the UK Prospective Diabetes Study,[5-7] show that insulin is an effective option in type 2 diabetes, and confirm both the value of intensive therapy in retarding microvascular complications,[7,8] and that oral therapy should be used before insulin in patients with primary diet failure.[9]

Insulin is usually started when combination oral antidiabetic therapy does not achieve adequate glycaemic control. Some advocate the early initiation of insulin therapy to slow the rate of disease progression by minimising hyperglycaemia.[4,10] Which insulin regimen is most appropriate for a patient with type 2 diabetes will be influenced by baseline hyperglycaemia and other measures of glycaemic control, as well as lifestyle and patient preference. Suitable regimens might include a single injection of basal insulin at night, a premixed biphasic insulin, or a multiple injection basal-bolus regimen.[4,10-12] Insulin sensitisers, such as thiazolidinediones and in particular, metformin, are generally continued;[10,11] however, the combination of a thiazolidinedione with insulin is associated with an increased risk of fluid retention and heart failure.[4,11] The combination of insulin secretagogues, such as sulfonylureas, with insulin may reduce the required insulin dose. However, the effect may be transient because these drugs require some residual beta cell function, which diminishes as the disease progresses.[11] The combination of bedtime isophane insulin with oral antidiabetics provides similar glycaemic control to insulin monotherapy, and is associated with less weight gain if metformin is used.[13] See Insulin Analogues, p. 480.1, for further information on their use in type 2 diabetics.

Several studies[14-16] have investigated the use of short-term intensive insulin therapy in newly diagnosed type 2 diabetes. These studies suggest that early intensive insulin therapy for 2 to 3 weeks to correct hyperglycaemia may provide a foundation for good glycaemic control through diet.

For further discussion of the management of type 2 diabetes mellitus see p. 459.1.

1. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. *Postgrad Med J* 1987; **63:** 859–64.
2. Taylor R. Insulin for the non-insulin dependent? *BMJ* 1988; **296:** 1015–16.
3. Stern MP. Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? *Ann Intern Med* 1996; **124** (suppl): 110–16.
4. Wyne KL, Mora PF. Insulin therapy in type 2 diabetes. *Endocr Res* 2007; **32:** 71–107.
5. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. *BMJ* 1995; **310:** 83–8.
6. Turner R, *et al*. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; **124** (suppl): 136–45.
7. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid*. 1999; **354:** 602.
8. Holman RR, *et al*. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.
9. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med* 1998; **128:** 165–75.
10. Tibaldi J, Rakel RE. Why, when and how to initiate insulin therapy in patients with type 2 diabetes. *Int J Clin Pract* 2007; **61:** 633–44.
11. Raskin P. Why insulin sensitizers but not secretagogues should be retained when initiating insulin in type 2 diabetes. *Diabetes Metab Res Rev* 2008; **24:** 3–13.
12. Holman RR, *et al*. 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; **361:** 1736–47. Correction. *ibid*. 2010; **363:** 2078.
13. Goudswaard AN, *et al*. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 27/08/09).
14. Ryan EA, *et al*. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 2004; **27:** 1028–32.
15. Li Y, *et al*. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β-cell function. *Diabetes Care* 2004; **27:** 2597–2602.
16. Weng J, *et al*. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008; **371:** 1753–60.

Diagnosis and testing. *PITUITARY FUNCTION.* Insulin-induced hypoglycaemia has been used to provide a stressful stimulus in order to assess hypothalamic-pituitary function.[1] The insulin stress or insulin-tolerance test has been used as a standard test for assessment of growth hormone or corticotropin deficiency. However, it is unpleasant and not without risk, and is contra-indicated in patients with ischaemic heart disease or a history of seizures, and in the elderly. Testing should only be performed in specialist units under strict surveillance.[2-4]

1. Petersenn S, *et al*. The rational use of pituitary stimulation tests. *Dtsch Arztebl Int* 2010; **107:** 437–43.
2. Lange M, *et al*. An audit of the insulin-tolerance test in 255 patients with pituitary disease. *Eur J Endocrinol* 2002; **147:** 41–7.
3. Galloway PJ, *et al*. Safety of the insulin tolerance test. *Arch Dis Child* 2002; **87:** 354–6.
4. Wright D, *et al*. The insulin stress test performed by an experienced endocrine specialist nurse: a safe and reliable procedure. *Clin Endocrinol (Oxf)* 2007; **66:** 755–6.

Hyperkalaemia. Insulin promotes the intracellular uptake of potassium. It is therefore used in the management of moderate to severe hyperkalaemia, when it is given with glucose (see p. 1779.1).

Inpatient hyperglycaemia. Although few randomised controlled studies have been carried out to establish specific guidelines, recommendations have been made[1,2] for preventing hyperglycaemia in non-critically ill inpatients. These suggest that blood-glucose monitoring should be carried out and pre-meal blood-glucose targets should be less than 7.8 mmol/litre, with random blood-glucose values of less than 10.0 mmol/litre. To avoid hypoglycaemia, insulin regimens should be reassessed if blood-glucose falls below 5.6 mmol/litre and modified if blood-glucose falls below 3.9 mmol/litre (unless explained by factors such as a missed meal). Historically sliding scale insulin (SSI) has been the method of calculating the insulin dose required, based on urinary glucose measurement or blood-glucose concentrations. In SSI, subcutaneous insulin is given with no reference to the timing of meals consumed or to basal glucose production. SSI is not supported by evidence of improved glycaemic control or clinical outcome and its use is now discouraged.[3,4] Instead, the recommended method is to use a subcutaneous basal-bolus regimen. This method involves monitoring blood glucose and using basal, nutritional, and correction insulin doses to achieve and maintain glucose control. The basal insulin dose covers endogenous glucose production, the bolus (nutritional) dose covers carbohydrates consumed with a meal, and a corrective or supplemental dose can be added if blood glucose is above the target range.[1,2,5-7] The treatment of hyperglycaemia in critically ill patients is discussed p. 481.2.

1. Moghissi ES, *et al*. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; **32:** 1119–31. Also available at: http://care.diabetesjournals.org/content/32/6/1119.full.pdf (accessed 11/03/11) Also published in: *Endocr Pract* 2009; **15:** 353–69. Also available at: https://www.aace.com/sites/default/files/InpatientGlycemicControlConsensusStatement.pdf (accessed 10/08/11)
2. Umpierrez GE, *et al*. Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; **97:** 16–38.
3. Umpierrez GE, *et al*. Sliding scale insulin use: myth or insanity? *Am J Med* 2007; **120:** 563–7.
4. Hirsch IB. Sliding scale insulin—time to stop sliding. *JAMA* 2009; **301:** 213–14.
5. Umpierrez GE, *et al*. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 2007; **30:** 2181–6.
6. Juneja R, *et al*. The nuts and bolts of subcutaneous insulin therapy in non-critical care hospital settings. *Postgrad Med* 2010; **122:** 153–62.
7. Umpierrez GE, *et al*. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; **34:** 256–61.

Myocardial infarction. Discussions on the effects of insulin with glucose and potassium in the ischaemic heart, including its effect in reducing blood free fatty acids, have emphasised its potential benefits in left ventricular failure and cardiogenic shock.[1,2] A meta-analysis[3] of randomised controlled studies performed before the widespread use of thrombolytics found a reduction in mortality in recipients of glucose-insulin-potassium solutions. However, although a pilot study[4] that included patients undergoing reperfusion (thrombolysis or percutaneous coronary intervention) reported benefit, this was not confirmed in larger randomised studies using standard glucose-insulin-potassium infusions.[5,6] A further study[7] found that routine use of such infusions in patients undergoing reperfusion had no effect on myocardial salvage, although some improvement was reported in diabetics. Reviews have concluded that glucose-insulin-potassium infusions do not reduce mortality in patients with acute myocardial infarction,[8,9] and cannot be recommended as standard adjunctive treatment with reperfusion.[10]

Intensive glucose control, with insulin-glucose infusion followed by multiple daily subcutaneous insulin injections has been reported to reduce mortality in diabetics who suffered a myocardial infarction.[11,12] A similar study[13] of treatment after myocardial infarction included only patients with type 2 diabetes mellitus who were treated with routine care, or insulin-glucose infusion followed by either long-term subcutaneous insulin or standard glucose control. The study was stopped early due to slow patient recruitment, but results did suggest that although glucose concentration was a strong independent predictor of long-term mortality, the use of long-term insulin treatment did not improve survival compared with conventional treatment at similar levels of glucose control. Further analysis[14] of the results of this study found an increase in non-fatal re-infarction and stroke associated with ongoing insulin therapy, although the reason for this was not clear. An observational study[15] in non-diabetics with hyperglycaemia suggested that intensive glucose control also improved outcomes in this population,

but another study[16] found no benefit. However, the glucose control achieved in this study was similar in both the intensive and the conventional treatment groups and an analysis based on blood-glucose concentrations suggested that strict glucose control was beneficial.[16]

For the conventional management of myocardial infarction, see p. 1257.1.

1. Opie LH. Glucose and the metabolism of ischaemic myocardium. *Lancet* 1995; **345:** 1520–1.
2. Taegtmeyer H, *et al.* Metabolic support for the postischaemic heart. *Lancet* 1995; **345:** 1552–5.
3. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation* 1997; **96:** 1152–6.
4. Díaz R, *et al.* Metabolic modulation of acute myocardial infarction: the ECLA Glucose-Insulin-Potassium Pilot Trial. *Circulation* 1998; **98:** 2227–34.
5. Mehta SR, *et al.* Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 2005; **293:** 437–46.
6. Díaz R, *et al.* Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. *JAMA* 2007; **298:** 2399–2405.
7. Pache J, *et al.* A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 2004; **148:** e3.
8. Puskarich MA, *et al.* Effect of glucose-insulin-potassium infusion on mortality in critical care settings: a systematic review and meta-analysis. *J Clin Pharmacol* 2009; **49:** 758–67.
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10. Kloner RA, Nesto RW. Glucose-insulin-potassium for acute myocardial infarction: continuing controversy over cardioprotection. *Circulation* 2008; **117:** 2523–33.
11. Malmberg K, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; **26:** 57–65.
12. Malmberg K, *et al.* Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997; **314:** 1512–15.
13. Malmberg K, *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005; **26:** 650–61.
14. Mellbin LG, *et al.* DIGAMI 2 Investigators. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008; **29:** 166–76.
15. Weston C, *et al.* Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart* 2007; **93:** 1542–6.
16. Cheung NW, *et al.* The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care* 2006; **29:** 765–70.

Neonatal hyperglycaemia. Hyperglycaemia is common in very immature neonates because of delayed or reduced insulin production. It can be treated by glucose restriction until glucose tolerance improves. However, this may not provide enough glucose to meet basal metabolic needs, and the use of an insulin infusion can allow sufficient glucose to be given. It has been suggested that insulin is best given intravenously in a separate, easily titratable solution because of the frequent fluctuations of requirement in these infants.[1] However, evidence from large, randomised, controlled studies to weigh up the risks and benefits of treating hyperglycaemia is lacking.[2] In addition, a controlled study of preventive early insulin therapy, using a fixed-dose continuous insulin infusion with intravenous glucose adjusted to maintain euglycaemia, was stopped early.[3] Although glycaemic control was better compared with standard care, there were more episodes of hypoglycaemia in infants given early insulin therapy and mortality before 28 days after birth was increased.

1. Ditzenberger GR, *et al.* Continuous insulin intravenous infusion therapy for VLBW infants. *J Perinat Neonatal Nurs* 1999; **13:** 70–82.
2. Bottino M, *et al.* Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 07/04/09).
3. Beardsall K, *et al.* Early insulin therapy in very-low-birth-weight infants. *N Engl J Med* 2008; **359:** 1873–84.

Overdosage with calcium-channel blockers. High-dose insulin, with glucose and potassium as required to maintain normal plasma concentrations of these, has been reported to be of value in the treatment of overdosage with calcium-channel blockers[1] that has not been adequately managed with conventional therapy (which is described under Treatment of Adverse Effects under Nifedipine, p. 1452.3). A review[2] of 13 reported cases found that various dosage regimens had been tried. These included bolus doses of insulin 10 to 20 units, and continuous infusions of 0.1 to 1 unit/kg per hour. The authors of one report[3] proposed a regimen that includes an initial intravenous bolus dose of insulin 1 unit/kg, followed by a continuous infusion of 0.5 units/kg per hour; this may be increased to 1 unit/kg per hour if necessary. A prospective study[4] of 7 further cases permitted up to 2 units/kg per hour for the infusion dose. Others[5] have also suggested that because the onset of action may be delayed by about 30 to 45 minutes, the earlier use of a high-dose insulin regimen combined with supportive measures may be justified, and may reduce the need for more invasive circulatory support.

1. Engebretsen KM, *et al.* High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol* 2011; **49:** 277–83.
2. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923–30.
3. Boyer EW, *et al.* Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. *Pediatr Emerg Care* 2002; **18:** 36–7.
4. Greene SL, *et al.* Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med* 2007; **33:** 2019–24.
5. Lheureux PER, *et al.* Bench-to-bedside review: hyperinsulinaemia/euglycaemia therapy in the management of overdose of calcium-channel blockers. *Crit Care* 2006; **10:** 212. Available at: http://ccforum.com/content/pdf/cc4938.pdf (accessed 31/07/09)

Adverse Effects

The most frequent complication of insulin therapy is hypoglycaemia, the speed of onset and duration of which may vary according to the type of preparation and the route used. It is usually associated with an excessive dosage of insulin, the omission of a meal by the patient, or increased physical activity. Patients, especially the elderly or those with tightly controlled diabetes or diabetes of long standing, may not have the typical early warning symptoms of a hypoglycaemic attack. There have been reports of hypoglycaemia, sometimes with decreased warning symptoms, in patients changing from animal (especially bovine) to human insulin (see under Hypoglycaemia, p. 486.2). Symptoms of hypoglycaemia resulting from increased sympathetic activity include hunger, pallor, sweating, palpitations, anxiety, and tremulousness. Other symptoms include headache, visual disturbances such as blurred or double vision, slurred speech, paraesthesia of the mouth and fingers, alterations in behaviour, and impaired mental or intellectual ability. If untreated, hypoglycaemia may lead to convulsions and coma which should not be confused with hyperglycaemic coma. Excessive doses of insulin can also cause electrolyte disturbances. Insulin stimulates a shift of potassium to the intracellular space and hypokalaemia may be particularly associated with intravenous use in the management of diabetic ketoacidosis (see Diabetic Emergencies, p. 465.3).

Insulin, given subcutaneously, may cause either lipoatrophy or lipohypertrophy. Lipoatrophy appears to occur less frequently with purified insulins than with conventional insulins; if it has occurred, it may be reversed by the injection of a purer animal insulin or human insulin into and around the atrophied site. Lipohypertrophy is usually associated with repeated injections at the same site and may usually be overcome by rotating the site of injection, although absorption of insulin may vary from different anatomical areas. Weight gain is often associated with insulin treatment, particularly intensive therapy regimens. Transient blurred vision and peripheral oedema may occur in the first few weeks of therapy.

Insulin occasionally causes local or systemic hypersensitivity reactions. Local reactions, characterised by erythema and pruritus at the injection site, usually disappear with continued use. Generalised hypersensitivity may produce urticaria, angioedema, and very rarely anaphylactic reactions; if continued therapy with insulin is essential hyposensitisation may be needed. Again, hypersensitivity reactions occur less frequently with purified than with conventional insulins and porcine insulin is less immunogenic than bovine insulin; human insulins and insulin analogues are less immunogenic again, but reactions may still occur.

Many patients treated with insulin, either animal or human insulin, develop antibodies but the clinical significance of this is not entirely clear.

Of patients given intensive insulin therapy for type 1 diabetes as part of the Diabetes Control and Complications Trial, those who had the greatest weight gain also had increased blood concentrations of triglycerides and low-density-lipoprotein cholesterol, and lowered high-density-lipoprotein cholesterol.[1] These lipid changes, with higher blood pressure, increased waist-to-hip ratio, and greater insulin requirements, were held to be similar to the symptoms of insulin resistance and to indicate a possible increased risk of macrovascular disease. Results from the UK Prospective Diabetes Study indicated that type 2 diabetic patients treated with insulin had greater weight gain than those managed with other therapies,[2] but found no evidence of harmful cardiovascular effects.

For discussion of some of the specific problems associated with continuous infusion of insulin, see Intensive Administration Regimens under Uses, p. 480.3.

1. Purnell JQ, *et al.* Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. *JAMA* 1998; **280:** 140–6. Correction. *ibid.*; 1484.
2. UK Prospective Diabetics Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid.* 1999; **354:** 602.

Carcinogenicity. *Colorectal* cancer occurs more commonly in patients with type 2 diabetes mellitus than in the general population, and most studies estimate a 30 to 40% risk increase.[1] Results from a large retrospective cohort study with a nested case-control study, using data from the UK General Practice Research Database, suggested an increased risk of colorectal cancer associated with long-term insulin use in type 2 diabetics.[2] It has been hypothesised that hyperinsulinaemia is a risk factor, and that insulin therapy in patients with type 2 diabetes might increase the risk further.[1] Some have suggested colorectal cancer screening for patients with type 2 diabetes, particularly those treated with insulin,[1,2] but others have cautioned that further information would be needed before widespread screening is advocated.[3]

Primary *lung* malignancies have been found in a few patients receiving inhaled insulin; for further details, see Administration Routes, p. 479.2. A case-control study[4] of over 900 patients with *pancreatic* cancer also suggested an increase in risk in patients using insulin or insulin secretagogues.

There has been concern that insulin glargine, which has shown a greater affinity for the IGF-I receptor than human insulin, might also be linked with an increased risk of carcinogenicity.[5] Several cohort studies have reported differing results with a number of confounding factors affecting conclusions. An increase in malignancy was seen with increased human insulin dose[5] with a higher risk for the glargine analogue. An increase in the risk of breast cancer in users of insulin glargine alone in Sweden[6] was seen, but it was suggested that this might be due to random fluctuation. Furthermore a Scottish study[7] showed no overall increase in cancer risk; an increase in breast cancer with insulin glargine monotherapy was thought to be attributable to allocation bias. A retrospective cohort study of over 62 000 patients with type 2 diabetes[8] concluded that insulin glargine was not associated with an increased cancer risk compared with human insulin. A commentary on these cohort studies[9] concluded that the current epidemiological evidence was insufficient to confirm or refute a carcinogenic effect of specific insulins on specific cancers. Regulators in Europe and the USA[10,11] also concluded that study limitations did not allow a relationship between insulin glargine and cancer to be confirmed or excluded but continue to monitor the situation.

1. Berster JM, Göke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch Physiol Biochem* 2008; **114:** 84–98.
2. Yang Y-X, *et al.* Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004; **127:** 1044–50.
3. Renehan AG, Shalet SM. Diabetes, insulin therapy, and colorectal cancer. *BMJ* 2005; **330:** 551–2.
4. Li D, *et al.* Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; **137:** 482–8.
5. Hemkens LG, *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009; **52:** 1732–44.
6. Jonasson JM, *et al.* Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden. *Diabetologia* 2009; **52:** 1745–54.
7. Colhoun HM. SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009; **52:** 1755–65.
8. Currie CJ, *et al.* The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009; **52:** 1766–77.
9. Hernández-Díaz S, Adami H-O. Diabetes therapy and cancer risk: causal effects and other plausible explanations. *Diabetologia* 2010; **53:** 802–8.
10. EMEA. European Medicines Agency update on safety of insulin glargine (issued 23rd July, 2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010016.pdf (accessed 23/02/11)
11. FDA. FDA Drug Safety Communication: update to ongoing safety review of Lantus (insulin glargine) and possible risk of cancer (issued 12th January, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm239376.htm (accessed 23/02/11)

Effects on the liver. For a report of hepatomegaly occurring after insulin overdosage, see under Abuse, in Precautions, p. 487.2.

Effects on the skin. Skin reactions to insulin therapy include lipodystrophies and allergic skin reactions (see Hypersensitivity, p. 486.1). Although the incidence of some reactions have decreased considerably with the purification of conventional insulins and the development of recombinant human insulin, they continue to be reported with human insulin and have been associated with insulin analogues.

Lipohypertrophy is the most commonly reported cutaneous complication of insulin therapy. It usually presents as soft dermal nodules containing adipocytes, and is a consequence of repeated injection at the same site.[1,2] Patients have been found to preferentially inject into these sites because of their relative anaesthesia,[1] but insulin absorption from these nodules can be impaired,[1,3] resulting in poor glycaemic control.[4] Lipohypertrophy can be avoided or limited by rotation of injection sites, and avoidance of affected areas can bring about regression. The use of a rapidly absorbed short-acting insulin analogue might also have a less stimulatory effect on lipohypertrophy

development. Liposuction has been used when other measures have failed, but experience is limited.[1,2]

It is thought that *lipoatrophy*, a loss of fat at injection sites, might be caused by an immune reaction. The condition has become rare with the use of recombinant human insulin.[1,2] Insulin analogues, both short- and long-acting, have also been reported to cause lipoatrophy.[2,5-8] Patients are advised to avoid further injection into affected areas, but spontaneous resolution is rare.[1] The successful use of a corticosteroid injected into lipoatrophic areas has been described.[9]

The growth of *amyloid nodules* at insulin injection sites has been reported;[10] they may be mistaken for lipohypertrophy, but are usually harder.

1. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. *Am J Clin Dermatol* 2003; **4:** 661–7.
2. Radermecker RP, *et al*. Lipodystrophy reactions to insulin: effects of continuous insulin infusion and new insulin analogs. *Am J Clin Dermatol* 2007; **8:** 21–8.
3. Johansson U-B, *et al*. Impaired absorption of insulin aspart from lipohypertrophic injection sites. *Diabetes Care* 2005; **28:** 2025–7.
4. Chowdhury TA, Escudier V. Poor glycaemic control caused by insulin induced lipohypertrophy. *BMJ* 2003; **327:** 383–4.
5. Arranz A, *et al*. A case of lipoatrophy with lispro insulin without insulin pump therapy. *Diabetes Care* 2004; **27:** 625–6.
6. Ampudia-Blasco FJ, *et al*. A case of lipoatrophy with insulin glargine: long-acting insulin analogs are not exempt from this complication. *Diabetes Care* 2005; **28:** 2983.
7. Al-Khenaizan S, *et al*. Lispro insulin-induced lipoatrophy: a new case. *Pediatr Diabetes* 2007; **8:** 393–6.
8. del Olmo MI, *et al*. A case of lipoatrophy with insulin detemir. *Diabetes Res Clin Pract* 2008; **80:** e20–e21.
9. Ramos AJS, Farias MA. Human insulin-induced lipoatrophy: a successful treatment with glucocorticoid. *Diabetes Care* 2006; **29:** 926–7.
10. Nagase T, *et al*. The insulin ball. *Lancet* 2009; **373:** 184.

Hypersensitivity. The most common hypersensitivity reactions to subcutaneous insulin are localised urticarial reactions that start within 10 to 20 minutes of injection; late reactions of diffuse swelling and erythema may begin 2 to 3 hours after injection, peak at 6 to 12 hours, and resolve within 12 to 24 hours. Generalised reactions, including anaphylaxis, have also occurred.[1,2] Although the prevalence of insulin allergy decreased significantly with the introduction of highly purified and human insulins, such reactions may still occur.[1,3] Delayed pressure urticaria, in the form of large wheals occurring 4 to 6 hours after prolonged pressure, and lasting for up to 24 hours, was seen in a patient with type 1 diabetes within 6 months of changing from animal to human insulin.[4] The condition improved after a switch back to insulin of animal origin, and grew worse again after a second attempt to use human insulin. Intermittent urticaria simultaneously affecting previous injection sites was reported in a child receiving human insulin, who had never received animal insulin.[5] There are also reports of both local and generalised reactions to insulin analogues;[2,6-8] however, they have also been used successfully in patients with a history of hypersensitivity to human insulin.[9-11]

Substitution of a different insulin preparation or analogue may be tried in the management of allergy, and continuous subcutaneous insulin infusion using short-acting analogues has been successful. Treatment with an antihistamine and/or corticosteroid may be required for symptomatic relief, and a course of insulin desensitisation may be necessary in some cases.[1,2] Omalizumab was reported to improve symptoms in a case of severe, refractory insulin allergy; the patient first received a course of rituximab to reduce the total IgE level before omalizumab was given.[12]

The development of painful subcutaneous nodules at the injection site of insulin detemir has been reported.[13-16] The reactions generally started a few hours after injection and resolved spontaneously after a few days; in some cases the reaction started after the first injection of insulin detemir.

Hypersensitivity reactions to insulin preparations may be caused not only by the insulin itself, but also by other components of the formulation such as zinc,[17-19] protamine[2,20-25] (see also Hypersensitivity to Protamine under Precautions, p. 487.3), and *m*-cresol.[2]

1. Hoffman AG, *et al*. Type I allergy to insulin: case report and review of localized and systemic reactions to insulin. *Dermatitis* 2008; **19:** 52–8.
2. Ghazavi MK, Johnston GA. Insulin allergy. *Clin Dermatol* 2011; **29:** 300–5.
3. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993; **16** (suppl 3): 155–65.
4. Payne CMER, *et al*. True delayed pressure urticaria induced by human Monotard insulin. *Br J Dermatol* 1996; **134:** 184.
5. Sackey AH. Recurrent generalised urticaria at insulin injection sites. *BMJ* 2000; **321:** 1449.
6. Takata H, *et al*. The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care* 2003; **26:** 253–4.
7. Durand-Gonzalez K-N, *et al*. Glargine insulin is not an alternative in insulin allergy. *Diabetes Care* 2003; **26:** 2216.
8. JiXiong X, *et al*. The human insulin analog aspart can induce insulin allergy. *Diabetes Care* 2004; **27:** 2084–5.
9. Airaghi L, *et al*. The insulin analog aspart: a safe alternative in insulin allergy. *Diabetes Care* 2001; **24:** 2000.
10. Yasuda H, *et al*. Human insulin analog insulin aspart does not cause insulin allergy. *Diabetes Care* 2001; **24:** 2008–9.
11. Kara C, *et al*. Successful treatment of insulin allergy in a 1-year-old infant with neonatal diabetes by lispro and glargine insulin. *Diabetes Care* 2005; **28:** 983–4.
12. Yong PFK, *et al*. Rituximab and omalizumab in severe, refractory insulin allergy. *N Engl J Med* 2009; **360:** 1045–7.
13. Darmon P, *et al*. Type III allergy to insulin detemir. *Diabetes Care* 2005; **28:** 2980.
14. Blumer IR. Severe injection site reaction to insulin detemir. *Diabetes Care* 2006; **29:** 946.
15. Stechemesser L, *et al*. Type III allergy to insulin detemir: response to Darmon et al. *Diabetes Care* 2006; **29:** 2758.
16. Sola-Gazagnes A, *et al*. Type I and type IV allergy to the insulin analogue detemir. *Lancet* 2007; **369:** 637–8.
17. Feinglos MN, Jegasothy BV. "Insulin" allergy due to zinc. *Lancet* 1979; **i:** 122–4.
18. Bruni B, *et al*. Case of generalized allergy due to zinc and protamine in insulin preparation. *Diabetes Care* 1986; **9:** 552.
19. Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump. *Diabetes Care* 1987; **10:** 789–90.
20. Sánchez MB, *et al*. Protamine as a cause of generalised allergic reactions to NPH insulin. *Lancet* 1982; **i:** 1243.
21. Hulshof MM, *et al*. Granulomatous hypersensitivity to protamine as a complication of insulin therapy. *Br J Dermatol* 1992; **127:** 286–8.
22. Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. *Del Med J* 1993; **65:** 17–23.
23. Dykewicz MS, *et al*. Immunologic analysis of anaphylaxis to protamine component in neutral protamine Hagedorn human insulin. *J Allergy Clin Immunol* 1994; **93:** 117–25.
24. Blanco C, *et al*. Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy* 1996; **51:** 421–4.
25. Bollinger ME, *et al*. Protamine allergy as a complication of insulin hypersensitivity: a case report. *J Allergy Clin Immunol* 1999; **104:** 462–5.

HYPOSENSITISATION. After failure of standard hyposensitisation measures in a patient with cutaneous hypersensitivity to insulin, hyposensitisation was attempted by giving insulin orally.[1] Oral aspirin (1.3 g three times daily) was also given to antagonise vascular mediators of the reaction. After one week subsequent hyposensitisation using insulin by injection was successful. When the patient stopped taking aspirin after 6 months the original hypersensitivity reactions recurred; aspirin was then given permanently in a dose of 1.3 g twice daily.

1. Holdaway IM, Wilson JD. Cutaneous insulin allergy responsive to oral desensitisation and aspirin. *BMJ* 1984; **289:** 1565–6.

Hypoglycaemia. Hypoglycaemia is the major adverse effect of insulin treatment, with severe hypoglycaemic episodes occurring in up to a third of all insulin-treated patients at some point in their lives. Moves towards more intensive insulin therapy, in order to reduce the development of diabetic complications, increase the risk of hypoglycaemic episodes.[1,2] Patients maintaining strict glycaemic control are prone to 'hypoglycaemia unawareness' in which the normal adrenergic response to hypoglycaemia (characterised by symptoms such as pallor, sweating, and tremor) is reduced or lost.[3,4] The development of hypoglycaemic unawareness is linked to previous episodes of hypoglycaemia and increased duration of diabetes. In addition, the normal counter-regulatory hormonal response to hypoglycaemia becomes defective in diabetic patients. These factors predispose to the development of hypoglycaemia and neuroglycopenic symptoms (including irritability, blurred vision, lethargy, seizure, and coma) without warning. Nocturnal hypoglycaemia has also been implicated in the sudden nocturnal death of young, otherwise healthy, patients with type 1 diabetes;[4,5] this is a rare condition in which hypoglycaemia might contribute to cardiac arrhythmia.

Avoidance of hypoglycaemia for 2 to 3 weeks helps restore awareness. Patient education is an important strategy in avoiding hypoglycaemia, with particular attention paid to diet, exercise, and self-monitoring of blood-glucose concentrations. Adjustment of insulin regimens might include the use of rapid-acting insulin analogues at mealtimes to avoid hypoglycaemia between meals, long-acting (relatively peakless) analogues to reduce nocturnal hypoglycaemia, or use of a continuous subcutaneous insulin infusion (CSII).[3,4]

When recombinant human insulin became generally available in the late 1980s some patients complained of a loss of awareness of impending hypoglycaemia after transfer to human insulin,[6,7] and there were reports of severe or even fatal hypoglycaemia occurring in patients who had been well stabilised on animal insulins.[6-8]

This was, and remains, a somewhat controversial area. Despite some small studies suggesting a problem, others failed to find evidence of a difference between animal and human insulins, and a systematic review[9] concluded that the available evidence did not support the suggestion that human insulin increased the frequency or severity of hypoglycaemia, or affected the symptoms of hypoglycaemia, compared with animal insulins. However, most commentators appeared to consider that patients should continue to have access to animal insulins if desired, and that those well maintained on animal insulin should not be transferred to human insulin without appropriate clinical grounds,[8,10-13] and then only with careful monitoring.

There has also been concern about possible long-term sequelae of hypoglycaemic episodes on the CNS. However, a report on patients participating in the Diabetes Control and Complications Trial (DCCT) suggested that the increased risk of hypoglycaemia seen with intensive therapy was not associated with neuropsychological impairment.[14] Nevertheless, there is some evidence of an association between episodes of severe hypoglycaemia and cognitive impairment in young children (diagnosed before 5 or 6 years of age).[5]

For the treatment of insulin-induced hypoglycaemia, see p. 486.3.

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–86.
2. Egger M, *et al*. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; **14:** 919–28.
3. Dagogo-Jack S. Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. *Treat Endocrinol* 2004; **3:** 91–103.
4. de Galan BE, *et al*. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Neth J Med* 2006; **64:** 269–79.
5. Clarke W, *et al*. International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium: assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* 2009; **10** (suppl 12): 134–45. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Hypoglycemia.pdf (accessed 14/02/11)
6. Teuscher A, Berger WG. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet* 1987; **ii:** 382–5.
7. Pickup J. Human insulin: problems with hypoglycaemia in a few patients. *BMJ* 1989; **299:** 991–3.
8. Gale EAM. Hypoglycaemia and human insulin. *Lancet* 1989; **ii:** 1264–6.
9. Airey CM, *et al*. Hypoglycaemia induced by exogenous insulin - 'human' and animal insulin compared. *Diabet Med* 2000; **17:** 416–32.
10. Everett J, Kerr D. Changing from porcine to human insulin. *Drugs* 1994; **47:** 286–96.
11. Gerich JE. Unawareness of hypoglycaemia and human insulin. *BMJ* 1992; **305:** 324–5.
12. Williams G, Patrick AW. Human insulin and hypoglycaemia: burning issue or hot air? *BMJ* 1992; **305:** 355–7.
13. Teuscher A, Kiln MR. Patient-empowerment and free insulin market. *Lancet* 1994; **344:** 1299–1300.
14. The Diabetes Control and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 1996; **124:** 379–88.

Oedema. Severe, acute oedema is a rare adverse effect of insulin treatment, occurring most often when starting therapy.[1-7] It should be distinguished from chronic and subacute forms of oedema which may be complications of the diabetic disease process.[2,3] Possible mechanisms of acute oedema are sodium retention resulting from a direct action of insulin on the renal tubule or an effect of insulin on vascular permeability.[5] The oedema is usually self-limiting,[2,4] but does respond to a decrease in insulin dosage, or diuretic therapy.[1,3,5-7]

1. Bleach NR, *et al*. Insulin oedema. *BMJ* 1979; **2:** 177–8.
2. Lawrence JR, Dunnigan MG. Diabetic (insulin) oedema. *BMJ* 1979; **2:** 445.
3. Evans DJ, *et al*. Insulin oedema. *Postgrad Med J* 1986; **62:** 665–8.
4. Hirshberg B, *et al*. Natural course of insulin edema. *J Endocrinol Invest* 2000; **23:** 187–8.
5. Kalambokis GN, *et al*. The edematogenic properties of insulin. *Am J Kidney Dis* 2004; **44:** 575–90.
6. Mamoulakis D, *et al*. Insulin-induced oedema in children and adolescents. *J Paediatr Child Health* 2006; **42:** 655–7.
7. Kawashima S, *et al*. Acute progression of severe insulin edema accompanied by pericardial and pleural effusion in a patient with type 2 diabetes. *Diabetes Res Clin Pract* 2008; **81:** e18–e19.

Treatment of Insulin-induced Hypoglycaemia

In the conscious and cooperative patient hypoglycaemia is treated by eating a readily absorbable form of carbohydrate, such as sugar lumps or a glucose-based drink; all diabetics should always carry a suitable sugar source by way of precaution.

If the patient is drowsy or unconscious, then glucose must be given parenterally. Doses of 50 mL of a 20% solution of glucose or 25 to 50 mL of glucose 50% can be given intravenously; the higher concentration is more viscous and irritant to the veins. Lower concentrations are equally effective, and carry less risk of irritant effects, but larger volumes are required (e.g. up to 250 mL of 10%, titrated to patient response). Smaller quantities (e.g. 5 mL/kg of a 10% solution) are required in children. Bolus doses may need to be repeated, or a maintenance infusion started, to prevent persistent hypoglycaemia. If the patient has not regained consciousness within a few minutes after a bolus dose of glucose, the possibility of cerebral oedema should be considered.

In situations where giving intravenous glucose is impractical or not feasible, glucagon may be used to arouse the patient sufficiently to allow oral glucose to be given. Glucagon may be given intravenously, but is generally given by subcutaneous or intramuscular injection in a dose of 1 mg for adults and children weighing more than 25 kg, or 500 micrograms for children below 25 kg. The *BNFC* suggests that neonates requiring glucagon may be given 20 micrograms/kg. If the patient fails to respond to glucagon within about 10 to 15 minutes, then glucose has to be given intravenously despite any impracticalities. The effect of

glucagon relies upon the patient having adequate liver glycogen stores, which may not always be the case (as in starvation, adrenal insufficiency, alcohol-induced hypoglycaemia, or chronic hypoglycaemia).

After a return to consciousness, oral carbohydrates may need to be given until the action of insulin has ceased. For preparations with a relatively long duration of action such as isophane insulin, some insulin zinc suspensions, protamine zinc insulin, and long-acting insulin analogues, this may be several hours or possibly days.

Carbohydrate. A comparative study[1] of 7 different preparations of oral carbohydrate for the treatment of hypoglycaemia in the conscious patient found no significant difference in efficacy between glucose or sucrose in solution or tablet form; a hydrolysed polysaccharide solution containing glucose, maltose, and various more complex saccharides (*Glucidex 19*) was also roughly comparable. However, a glucose gel and orange juice were each less effective than the other formulations in treating hypoglycaemia.

1. Slama G, *et al*. The search for an optimized treatment of hypoglycemia: carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med* 1990: **150:** 589–93.

Glucagon. Although intravenous glucose is the treatment of choice in drowsy or unconscious patients with insulin-induced hypoglycaemia, parenteral glucagon is a suitable alternative when glucose is impractical or not feasible (see p. 484.3). Subcutaneous or intramuscular glucagon can be particularly useful in non-hospital settings when it may have to be given by a relative or friend.[1,2]

Low doses of subcutaneous glucagon (so-called 'mini-dose' glucagon) have been successfully used in the management of impending or mild hypoglycaemia in children and adolescents with type 1 diabetes mellitus and gastroenteritis or poor oral carbohydrate intake. Two studies have described a protocol based on a dose of 10 micrograms per year of age, ranging from 20 micrograms for children under 2 years of age up to 150 micrograms for those aged 15 years.[3,4]

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; **306:** 600–601.
2. Pearson T. Glucagon as a treatment of severe hypoglycemia: safe and efficacious but underutilized. *Diabetes Educ* 2008; **34:** 128–34.
3. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care* 2001; **24:** 643–5.
4. Hartley M, *et al*. Mini-dose glucagon rescue for mild hypoglycaemia in children with type 1 diabetes: the Brisbane experience. *J Paediatr Child Health* 2006; **42:** 108–11.

Overdose. The requirements for glucose are greater and more prolonged when hypoglycaemia is caused by insulin or insulin analogue overdosage rather than therapeutic doses.[1-4] Correction of insulin-induced hypokalaemia may also be required. Surgical excision of tissue at the site of injection has been used for massive overdose of a long-acting insulin.[5,6]

1. Roberge RJ, *et al*. Intentional massive insulin overdosage: recognition and management. *Ann Emerg Med* 1993; **22:** 228–34.
2. Brvar M, *et al*. Prolonged hypoglycaemia after insulin lispro overdose. *Eur J Emerg Med* 2005; **12:** 234–5.
3. Fromont I, *et al*. Prolonged glucose requirements after intentional glargine and aspart overdose. *Diabetes Metab* 2007; **33:** 390–2.
4. Ashawesh K, *et al*. Intentional overdose with insulin glargine. *Am J Health-Syst Pharm* 2009; **66:** 534.
5. Campbell IW, Ratcliffe JG. Suicidal insulin overdose managed by excision of insulin injection site. *BMJ* 1982; **285:** 408–9.
6. Levine DF, Bulstrode C. Managing suicidal insulin overdose. *BMJ* 1982; **285:** 974–5.

Precautions

Dosage requirements of insulin may be altered by many factors.

- Increased doses are usually necessary during infection, emotional stress, accidental or surgical trauma, puberty, and the last two trimesters of pregnancy.
- Decreased doses are usually necessary in patients with impaired renal or hepatic function or during the first trimester of pregnancy.

On first stabilising therapy in newly diagnosed diabetic patients, a temporary decrease in requirements may also occur (the so-called honeymoon period).

Because of the possibility of differing responses to insulins from different species, inadvertent change from insulin of one species to another should be avoided. Reduction in insulin dosage may be required on transfer from animal (especially bovine) to human insulin. Hypoglycaemic problems associated with a change to human insulin are discussed under Hypoglycaemia, p. 484.2. Care is also necessary during exercise, when insulin dosage and carbohydrate intake should be adjusted according to the intensity and duration of exercise. Insulin levels that are too low may not be sufficient to respond to the rising glucose concentrations stimulated by exercise, while insulin levels that are too high can attenuate the release of glucose and lead to hypoglycaemia; exercise might also increase insulin absorption.

The use of insulin requires monitoring of therapy, such as testing blood or urine for glucose concentrations and the urine for ketones, by the patient.

Drugs that have an effect on blood-glucose concentrations may alter glycaemic control with consequent need for a change in insulin dose (see Interactions, p. 488.3).

CAUTION. *Biphasic insulin, insulin zinc suspensions, isophane insulin, protamine zinc insulin, insulin detemir, and insulin glargine should never be given intravenously and they are not suitable for the emergency treatment of diabetic ketoacidosis.*

Abuse. Transient recurrent hepatomegaly associated with hypoglycaemia was associated with the surreptitious injection of additional insulin doses in an insulin-dependent diabetic. Increased storage of glycogen in the liver resulting from insulin excess was considered responsible for the hepatomegaly.[1]

Decreased plasma C-peptide concentrations or the presence of anti-insulin antibodies may be used to confirm insulin abuse as a cause of hypoglycaemia in patients who have never been treated with insulin medically.[2] Insulin has been abused by bodybuilders and other sportspersons;[3-5] severe brain damage after prolonged neuroglycopenia has resulted.[3] There are rare reports of the misuse of insulin to induce mind-altering effects of hypoglycaemia.[6]

1. Asherov J, *et al*. Hepatomegaly due to self-induced hyperinsulinism. *Arch Dis Child* 1979; **54:** 148–9.
2. Grunberger G, *et al*. Factitious hypoglycemia due to surreptitious administration of insulin: diagnosis, treatment, and long-term follow-up. *Ann Intern Med* 1988; **108:** 252–7.
3. Elkin SL, *et al*. Bodybuilders find it easy to obtain insulin to help them in training. *BMJ* 1997; **314:** 1280.
4. Honour JW. Misuse of natural hormones in sport. *Lancet* 1997; **349:** 1786.
5. Evans PJ, Lynch RM. Insulin as a drug of abuse in body building. *Br J Sports Med* 2003; **37:** 356–7.
6. Cassidy EM, *et al*. Insulin as a substance of misuse in a patient with insulin dependent diabetes mellitus. *BMJ* 1999; **319:** 1417–18.

Accelerated absorption. Factors such as a hot bath, sauna, or use of a sunbed have been reported to accelerate the absorption of subcutaneous injection, presumably by an increase in skin blood flow.[1-4] There may, therefore, be a risk of hypoglycaemia.[4]

1. Koivisto VA. Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *BMJ* 1980; **280:** 1411–13.
2. Clippers HJ, *et al*. Sauna-induced acceleration in insulin absorption? *BMJ* 1980; **281:** 307.
3. Koivisto VA. Sauna-induced acceleration in insulin absorption. *BMJ* 1980; **281:** 621–2.
4. Husband DJ, Gill GV. "Sunbed seizures": a hypoglycaemic hazard for insulin-dependent diabetics. *Lancet* 1984; **ii:** 1477.

Adrenocortical insufficiency. Recurrent severe hypoglycaemia, which occurred in 2 patients with type 1 diabetes, persisted despite a reduction in insulin doses and proved to be due to Addison's disease.[1] Insulin requirements rose again in both patients after replacement therapy with fludrocortisone and hydrocortisone.

1. Armstrong L, Bell PM. Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes. *BMJ* 1996; **312:** 1601–2.

Driving. In the UK, all patients with diabetes mellitus treated with insulin are required to notify their condition to the Driver and Vehicle Licensing Agency (DVLA), who then assess their fitness to drive. Those applying for an ordinary driving licence, who are treated with oral hypoglycaemics or non-insulin injectable medication, are only required to notify the DVLA if they have associated problems that may affect driving, such as impaired eyesight, impaired circulation or sensation in the legs or feet, episodes of disabling hypoglycaemia, or impaired hypoglycaemic awareness. Regardless of the type of diabetes or treatment, patients are required to notify the DVLA if such complications develop. Patients treated with oral hypoglycaemics or non-insulin injectable medication are generally allowed to retain ordinary driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years.[1] Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur.[2] Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (including field of vision of at least 120 degrees) for a licence to be valid.[1]

Patients treated with diet, oral hypoglycaemics, or non-insulin injectable medication are normally allowed to hold vocational driving licences for heavy goods or public service vehicles, unless they develop relevant disabilities. However, those treated with drugs that carry a risk of hypoglycaemia, such as sulfonylureas and glinides, must inform the DVLA and satisfy the criteria of well-controlled blood-glucose concentrations and full hypoglycaemic awareness; licences are issued for 1 to 3 years. Those treated with insulin may apply for a restricted 1 year licence provided they have not suffered from an episode of severe hypoglycaemia in the preceding 12 months and do not suffer from any other complication that may impair their ability to drive. Patients must undergo yearly medical assessments to satisfy the criteria of well-controlled blood-glucose concentrations and full hypoglycaemic awareness. Blood glucose must be monitored regularly and the risks of hypoglycaemia understood.[1]

Regulations in other countries differ widely.[3]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)
2. Diabetes UK. Information sheet: driving and diabetes: May 2012. Available at: https://shop.diabetes.org.uk/usr/downloads/Driving%20infosheet%202012.pdf (accessed 20/11/13)
3. DiaMond Project Group on Social Issues. Global regulations on diabetics treated with insulin and their operation of commercial motor vehicles. *BMJ* 1993; **307:** 250–3.

Exercise. Discussions[1-3] of the metabolic effects of exercise, and precautions to be taken by exercising diabetic patients using insulin.

1. Robertson K, *et al*. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. Exercise in children and adolescents with diabetes. *Pediatr Diabetes* 2009; **10** (suppl 12): 154–68. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Exercise.pdf (accessed 14/02/11)
2. Draznin MB. Managing the adolescent athlete with type 1 diabetes mellitus. *Pediatr Clin North Am* 2010; **57:** 829–37.
3. American College of Sports Medicine, American Diabetes Association. Joint position statement: exercise and type 2 diabetes. *Med Sci Sports Exerc* 2010; **42:** 2282–2303. Also available at: http://journals.lww.com/acsm-msse/Fulltext/2010/12000/Exercise_and_Type_2_Diabetes__American_College_of.18.aspx (accessed 10/08/11)

Fasting. Reduction in food intake or alteration in the pattern of meal times may affect insulin requirements and predispose to the development of hypoglycaemia (p. 484.2). Muslim patients who are receiving antidiabetic therapy and who fast during Ramadan have been shown to be at increased risk of severe hypoglycaemic episodes during this month.[1] Only a few small studies have reported on the adjustment of insulin regimens in patients with type 1 diabetes. Possible regimens[2] include once or twice daily injections of an intermediate- or long-acting insulin, given before the predawn and sunset meals, with a short-acting insulin at the meal itself. It has also been suggested that between 70 and 85% of the non-fasting daily insulin dose is used.[3] Most patients using insulin infusion pumps will need to reduce their basal infusion rate while increasing bolus doses to cover predawn and sunset meals.[2]

Patients with type 2 diabetes maintained on insulin may be managed similarly, by judicious use of intermediate or long-acting insulin plus a short-acting insulin given before meals, particularly at the sunset meal to cover the longer caloric load.[2] Studies have suggested that insulin lispro may produce good blood glucose control in fasting patients with type 2 diabetes during Ramadan.[4,5]

Care is also required in patients with type 2 diabetes being treated with oral antidiabetic drugs. Patients being treated with metformin or insulin sensitisers such as the glitazones have a low risk of hypoglycaemia, although it has been suggested that the timing of metformin doses be altered so that two-thirds of the daily dose is taken just before the sunset meal and the other third before the predawn meal. Short-acting secretagogues such as repaglinide or nateglinide can also be taken twice daily before the sunset and predawn meals. However, sulfonylureas should be used with caution, and the use of chlorpropamide may be contra-indicated because of the high risk of prolonged and unpredictable hypoglycaemia. Patients taking once-daily sulfonylureas may take the dose before the sunset meal, adjusting the dose based on glycaemic control and the risk of hypoglycaemia. Those taking a twice-daily dose of sulfonylurea may take half the normal morning dose with the predawn meal and the usual dose with the sunset meal.[2] For patients taking alpha-glucosidase inhibitors or incretin-based therapies it has been suggested that no dosage adjustments are required.[2]

1. Salti I, *et al*. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004; **27:** 2306–11.
2. Al-Arouj M, *et al*. Recommendations for management of diabetes during Ramadan: update 2010. *Diabetes Care* 2010; **33:** 1895–1902.
3. Kobeissy A, *et al*. Suggested insulin regimens for patients with type 1 diabetes mellitus who wish to fast during the month of Ramadan. *Clin Ther* 2008; **30:** 1408–15.
4. Akram J, De Verga V. Ramadan Study Group. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 1999; **16:** 861–6.
5. Mattoo V, *et al*. A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; **59:** 137–43.

Hypersensitivity to protamine. Retrospective surveys have indicated that patients receiving isophane insulin, which contains protamine, have an increased risk of severe anaphylactoid reactions when protamine is used to reverse

systemic heparinisation after cardiac catheterisation or cardiac surgery. The degree of increase in risk is unclear, however, as it has been reported as both large[1] and small.[2,3] A review of the literature suggested that surgical patients may be at greater risk because of a higher rate of prior sensitisation to protamine and the larger doses used.[3] A mechanism involving IgE and IgG antibodies to protamine has been proposed.[4]

See also Hypersensitivity under Adverse Effects, p. 484.1.

1. Stewart WJ, *et al.* Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; **70:** 788–92.
2. Levy JH, *et al.* Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; **98:** 200–204.
3. Vincent GM, *et al.* Protamine allergy reactions during cardiac catheterization and cardiac surgery: risk in patients taking protamine-insulin preparations. *Cathet Cardiovasc Diagn* 1991; **23:** 164–8.
4. Weiss ME, *et al.* Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. *N Engl J Med* 1989; **320:** 886–92.

Infections. Decreased requirements of insulin, added to the dialysate, occurred in 6 diabetic patients undergoing continuous ambulatory peritoneal dialysis for chronic renal failure during episodes of severe bacterial peritonitis.[1] This was contrary to the increased insulin requirements of most diabetic patients during severe infections and probably resulted from increased absorption of insulin due to mesothelial damage.

1. Henderson IS, *et al.* Decreased intraperitoneal insulin requirements during peritonitis on continuous ambulatory peritoneal dialysis. *BMJ* 1985; **290:** 1474.

Menstruation. Changes in glycaemic control associated with the menstrual cycle have been recorded in women with type 1 diabetes mellitus. In a retrospective review of 124 women,[1] 61% reported perimenstrual changes in glucose concentrations and 36% made adjustments to their insulin dose, usually a small increase in the premenstrual insulin dose followed by a small decrease at the onset of menstruation. Based on mean glycated haemoglobin measurements, there was no evidence of improved glycaemic control in women adjusting their insulin dose compared with those leaving it unchanged despite changes in capillary glucose measurements. Changes in appetite and food consumption associated with the menstrual cycle may affect variations in glucose concentrations and insulin requirements.

1. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; **13:** 525–30.

Morning hyperglycaemia. Patients with diabetes lack the normal circadian cycle of insulin release that occurs in response to the surge of glucose produced by the liver during the dawn hours. In insulin-treated diabetics, morning hyperglycaemia may therefore be the result of mere waning of insulin injected subcutaneously the evening before. Conversely, it may be rebound hyperglycaemia occurring after an episode of nocturnal hypoglycaemia, usually resulting from an excessive dose of insulin that peaks in the middle of the night (post-hypoglycaemic hyperglycaemia or the Somogyi phenomenon). However, morning hyperglycaemia commonly occurs without preceding hypoglycaemia and is referred to as the dawn phenomenon.[1,2] Clinically, it is important to distinguish between these 3 effects because their treatment differs.

Management of the dawn phenomenon and insulin waning is generally based on optimising basal insulin to provide adequate coverage between 4 a.m. and 8 a.m. Treatment must be individualised, but options include giving a long-acting insulin, or insulin analogue such as insulin glargine, or the use of a continuous subcutaneous insulin infusion. Overall improvement of glycaemic control can also reduce the dawn phenomenon.[2] The addition of a bedtime dose of basal insulin may also be considered for type 2 diabetics when adjustment of diet and oral therapy has not been sufficient to manage the dawn phenomenon.[1,2] Management of rebound hyperglycaemia is aimed at avoiding nocturnal hypoglycaemia, by improving basal insulin control with a peakless long-acting insulin such as insulin glargine, or providing additional late-evening carbohydrate. If an intermediate-acting insulin is being used, hypoglycaemia may be reduced by giving it at bedtime rather than before the evening meal, and injecting into the lower buttock to slow absorption.[1] Mistaking rebound hyperglycaemia for the dawn phenomenon or mere waning of injected insulin could result in more serious nocturnal hypoglycaemia, if evening doses of insulin were increased.

1. Sheehan JP. Fasting hyperglycemia: etiology, diagnosis, and treatment. *Diabetes Technol Ther* 2004; **6:** 525–33.
2. Carroll MF, Schade DS. The dawn phenomenon revisited: implications for diabetes therapy. *Endocr Pract* 2005; **11:** 55–64.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies human insulin and the analogues insulin aspart and insulin lispro as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1] Other forms of insulin have not yet been classified by NAPOS.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. For discussion of the precautions necessary in the management of diabetes mellitus during pregnancy, see p. 461.3.

There has been a report of 2 cases of fetal malformation in the offspring of well-controlled diabetic women who received *insulin lispro*.[1] However, the incidence of fetal malformation is increased in infants of women with diabetes. At that time the manufacturers were aware of 19 live births among women treated with insulin lispro, 1 of which had a congenital abnormality.[2] Since then, several retrospective studies[3-8] and a prospective observational study[9] have looked at the rates of fetal malformations in the offspring of women treated with insulin lispro, for either pre-existing diabetes mellitus or gestational diabetes. These have included groups ranging in size from 27 to 496 women, and none have found any evidence of an increase in the incidence of abnormalities with insulin lispro compared with rates for women treated with other insulins.

A single-dose study has reported[10] that *insulin aspart* was effective in reducing postprandial glucose concentration in gestational diabetes. Randomised studies in women with type 1 diabetes[11] or gestational diabetes[12] have also found no indication of an increase in congenital malformations with insulin aspart compared with human insulin.

The possible effects on the fetus of *insulin glargine* have also been examined in women with pre-existing or gestational diabetes. Several retrospective studies,[13-16] and a prospective observational study of 115 women with type 1 diabetes,[17] found no indication of an increased rate of fetal malformations in women given this long-acting insulin analogue at any stage during pregnancy. One retrospective case-control study[18] of women with type 1 diabetes did find a higher incidence of fetal femoral length < 50th centile associated with insulin glargine use in the second and third trimesters, compared with healthy controls, although the final neonatal length was not affected. This finding was the opposite of what might be expected because of insulin glargine's affinity for the insulin-like growth factor I (IGF-I) receptor, and the authors stated that further studies would be needed to confirm an effect. A subsequent meta-analysis,[19] which included the retrospective studies above, did not find any significant increase in adverse fetal outcomes with insulin glargine compared with standard insulin therapy.

1. Diamond T, Kormas N. Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337:** 1009.
2. Anderson JH, *et al.* Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337:** 1010.
3. Bhattacharyya A, *et al.* Insulin lispro and regular insulin in pregnancy. *Q J Med* 2001; **94:** 255–60.
4. Garg SK, *et al.* Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 2003; **9:** 187–93.
5. Masson EA, *et al.* Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 2003; **20:** 46–50.
6. Wyatt JW, *et al.* Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med* 2005; **22:** 803–7.
7. Lapolla A, *et al.* Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. *Acta Diabetol* 2008; **45:** 61–6.
8. Aydin Y, *et al.* Is insulin lispro safe in pregnant women: does it cause any adverse outcomes on infants or mothers? *Diabetes Res Clin Pract* 2008; **80:** 444–8.
9. Durnwald CP, Landon MB. A comparison of lispro and regular insulin for the management of type 1 and type 2 diabetes in pregnancy. *J Matern Fetal Neonatal Med* 2008; **21:** 309–13.
10. Pettitt DJ, *et al.* Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 2003; **26:** 183–6.
11. Hod M, *et al.* Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008; **198:** 186.e1–186.e7.
12. Pettitt DJ, *et al.* Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabet Med* 2007; **24:** 1129–35.
13. Price N, *et al.* Use of insulin glargine during pregnancy: a case-control pilot study. *BJOG* 2007; **114:** 453–7.
14. Di Cianni G, *et al.* Perinatal outcomes associated with the use of glargine during pregnancy. *Diabet Med* 2008; **25:** 993–6.
15. Smith JG, *et al.* Insulin glargine versus neutral protamine Hagedorn insulin for treatment of diabetes in pregnancy. *Am J Perinatol* 2009; **26:** 57–62.
16. Fang YMV, *et al.* Insulin glargine compared with neutral protamine Hagedorn insulin in the treatment of pregnant diabetics. *J Matern Fetal Neonatal Med* 2009; **22:** 249–53.
17. Gallen IW, *et al.* Survey of glargine use in 115 pregnant women with type 1 diabetes. *Diabet Med* 2008; **25:** 165–9.
18. Imbergamo MP, *et al.* Use of glargine in pregnant women with type 1 diabetes mellitus: a case-control study. *Clin Ther* 2008; **30:** 1476–84.
19. Pollex E, *et al.* Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. *Ann Pharmacother* 2011; **45:** 9–16.

Renal impairment. See under Infections, above.

Smoking. Smoking has been reported to decrease the absorption of insulin and dosage adjustment may be necessary, although glycaemic control does not seem to be significantly affected.[1]

1. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36:** 425–38.

Surgery. For a discussion of the management of diabetes mellitus during surgery, see p. 462.2. The use of insulin for the management of stress-induced hyperglycaemia is discussed under Critically Ill Patients, p. 481.2, and Inpatient Hyperglycaemia, p. 482.3.

Travelling. Advice for the diabetic patient when travelling, including adjustment of insulin dosage when crossing time zones, is available.[1-3] Since insulin solution or suspension must not be frozen, it should not be carried in the luggage hold of an aircraft.

1. Barry M, Bia F. Advice for the traveling diabetic. *JAMA* 1989; **261:** 1799.
2. Sane T, *et al.* Adjustment of insulin doses of diabetic patients during long distance flights. *BMJ* 1990; **301:** 421–2.
3. Dewey CM, Riley WJ. Have diabetes, will travel. *Postgrad Med* 1999; **105:** 111–13, 117–18, 124–6.

Interactions

Many drugs have an effect on blood-glucose concentrations and may alter insulin requirements. Drugs with hypoglycaemic activity or which may decrease insulin requirements include ACE inhibitors, alcohol, anabolic steroids, aspirin, beta blockers (which may also mask the warning signs of hypoglycaemia), disopyramide, fenfluramine, fluoxetine, guanethidine, some MAOIs, mebendazole, high-dose sulfonamide antibacterials, some tetracyclines, and the tricyclic antidepressant amitriptyline.

On the other hand, increased requirements of insulin may possibly be seen with atypical antipsychotics, chlordiazepoxide, chlorpromazine, some calcium-channel blockers such as diltiazem or nifedipine, corticosteroids, diazoxide, lithium, thiazide diuretics, and thyroid hormones.

Both increased and decreased requirements may occur with cyclophosphamide, isoniazid, and oral contraceptives. Octreotide may increase or decrease insulin requirements, but most patients with type 1 diabetes are likely to require a reduction in insulin dose. Lanreotide may similarly alter blood-glucose concentrations, which should be checked to determine whether antidiabetic treatment needs to be adjusted.

Mealtime doses of insulin need to be reduced when pramlintide is added to therapy, to avoid hypoglycaemia (see Adverse Effects and Precautions of Pramlintide, p. 497.1).

ACE inhibitors. Although ACE inhibitors are favoured for use in diabetic patients with hypertension or evidence of incipient nephropathy or both, they may increase insulin sensitivity and thus decrease insulin requirements.[1,2] A study[3] of hospital admissions found that ACE inhibitors increased the risk of severe hypoglycaemia in patients receiving insulin. However, an analysis of pharmacovigilance data[4] and a case-control study[5] have both found no such increase in risk.

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
2. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
3. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
4. Moore N, *et al.* Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; **44:** 513–8.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21:** 1387–1400.

Alcohol. Severe hypoglycaemic episodes have been reported in type 1 diabetics after heavy drinking episodes.[1,2] Alcohol inhibits gluconeogenesis, and its effects are therefore likely to be greatest if taken without food; however, it seems to be generally agreed that diabetics need not abstain from a moderate alcohol intake with meals.

1. Arky RA, *et al.* Irreversible hypoglycemia. *JAMA* 1968; **206:** 575–8.
2. Potter J, *et al.* Insulin-induced hypoglycaemia in an accident and emergency department: the tip of an iceberg. *BMJ* 1982; **285:** 1180–2.

Aspirin. Aspirin produces a modest decrease in blood-glucose concentrations but a significant interaction at conventional analgesic doses appears to be unlikely. A study in children with type 1 diabetes found an average 15% decrease in blood glucose values following treatment with aspirin 1.2 or 2.4 g daily for 3 days, but there were no significant changes in insulin requirements.[1] However, high doses of aspirin (3.5 to 7.5 g daily) can reduce or even replace the insulin dose required.[2] Other salicylates might be expected to have similar properties.

1. Kaye R, *et al.* Antipyretics in patients with juvenile diabetes mellitus. *Am J Dis Child* 1966; **112:** 52–5.
2. Reid J, Lightbody TD. The insulin equivalence of salicylate. *BMJ* 1959; **1:** 897.

Beta blockers. There are a few reports of severe hypoglycaemia in patients, including insulin-treated diabetics, who were given *propranolol* or *pindolol*;[1-3] there is also a report of an interaction with *timolol* given as eye drops.[4] Some evidence exists of an interaction with *metoprolol*,[5] but little evidence for some of the more selective beta blockers. Because of the effects of beta blockers on the sympathetic nervous system the usual premonitory signs of hypoglycaemia may not occur, allowing a severe episode to develop before the patient is aware and able to counter it.

1. Kotler MN, *et al.* Hypoglycaemia precipitated by propranolol. *Lancet* 1966; **ii:** 1389–90.
2. McMurtry RJ. Propranolol, hypoglycemia, and hypertensive crisis. *Ann InternMed* 1974; **80:** 669–70.
3. Samii K, *et al.* Severe hypoglycaemia due to beta-blocking drugs in haemodialysis patients. *Lancet* 1976; **i:** 545–6.
4. Angelo-Nielsen K. Timolol topically and diabetes mellitus. *JAMA* 1980; **244:** 2263.
5. Newman RJ. Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycaemia. *BMJ* 1976; **2:** 447–9.

Calcium-channel blockers. Diabetes worsened in an insulin-treated diabetic when given *diltiazem*.[1] The resultant intractable hyperglycaemia improved when the drug was withdrawn, and recurred, although at a more manageable level, when diltiazem was restarted at a lower dose. There are also reports of a diabetogenic effect of *nifedipine*.[2,3] However, reports of significant disturbances of metabolic control appear to be uncommon.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; **257:** 930–1.
2. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 19.
3. Heyman SN, *et al.* Diabetogenic effect of nifedipine. *DICP Ann Pharmacother* 1989; **23:** 236–7.

Interferons. Markedly increased insulin requirements developed in a previously well controlled diabetic after treatment with *interferon alfa 2a*.[1] Insulin requirements rapidly fell once interferon therapy was stopped.

1. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.

Oral contraceptives. Both increases and decreases (mainly the former) in insulin requirements have been reported in insulin-dependent diabetics given various oral contraceptives.[1] However, it appears that in most cases the effects of a hormonal contraceptive on diabetic control are modest or insignificant: limited data suggest that progestogen-only and combined oral contraceptives in general have little effect.[2,3]

1. Zeller WJ, *et al.* Verträglichkeit von hormonalen Ovulationskemmern bei Diabetikerinnen. *Arzneimittelforschung* 1974; **24:** 351–7.
2. Rådberg T, *et al.* Oral contraception in diabetic women: diabetes control, serum and high density lipoprotein lipids during low-dose progestogen, combined oestrogen/progestogen and non-hormonal contraception. *Acta Endocrinol (Copenh)* 1981; **98:** 246–51.
3. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; **13:** 525–30.

Pharmacokinetics

Insulin has no hypoglycaemic effect when given orally since it is inactivated in the gastrointestinal tract.

It is fairly rapidly absorbed from subcutaneous tissue on injection and although the half-life of unmodified insulin in blood is very short (being only a matter of minutes), the duration of action of most preparations is considerably longer because of their formulation (for further details see Uses and Administration, p. 476.3). The rate of absorption from different anatomical sites depends on local blood flow, with absorption from the abdomen being faster than that from the arm, and that from the arm faster than from buttock or thigh. Absorption may also be increased by exercise. The absorption of insulin after intramuscular injection is more rapid than that after subcutaneous doses. Human insulin may be absorbed slightly faster from subcutaneous tissue than porcine or bovine insulin.

Insulin is rapidly metabolised, mainly in the liver but also in the kidneys and muscle tissue. In the kidneys it is reabsorbed in the proximal tubule and either returned to venous blood or metabolised, with only a small amount excreted unchanged in the urine.

For discussion of factors which may affect the absorption of insulin, see under Precautions, Accelerated Absorption, p. 485.2, and Uses, Administration Routes, p. 479.2.

Resistance to Insulin

The term insulin resistance has traditionally been used to describe a state in which diabetic patients have considerably increased insulin requirements. It is now used in a much wider sense, and is for instance also applied to patients in whom a subnormal biological response to insulin can be shown, although many of these patients do not apparently present difficulties in their clinical management. Insulin resistance is found particularly in obese patients; resistance to endogenous insulin is thought to be linked to the development of type 2 diabetes in such patients. Insulin resistance is frequently associated with lipid disorders, hypertension, and ischaemic heart disease, a complex sometimes described as the metabolic syndrome. In women, it may also be linked to polycystic ovary syndrome.

Insulin resistance of the type manifested by greatly increased insulin requirements may be due to factors including antibody formation and inadequate absorption of insulin from subcutaneous sites. A few patients with severe insulin resistance have responded to insulin lispro (see Insulin Analogues under Uses, p. 480.1).

Mecasermin (insulin-like growth factor I) has been seen to improve insulin sensitivity in insulin resistance (see p. 1932.3).

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actrapid HM; Apidra; Betalin Lenta†; Betalin Mix; Betalin NPH†; Betalin; Betasint; Biohulin C; Biohulin N; Densulin; Humalog Mix 25 and 50; Humalog; Humulin 70/30; Humulin NPH; Humulin R; Insulatard HM; Insuman N; Insuman R; Lantus; Levemir; Mixtard 30 HM†; Novolin N; Novolin R; NovoMix 30; NovoRapid; ***Austral.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin 30/70; Humulin NPH; Humulin R; Hypurin Isophane; Hypurin Neutral; Lantus; Levemir; Mixtard 30/70, 50/50; NovoMix 30; NovoRapid; Protaphane; ***Austria***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Huminsulin Basal; Huminsulin Normal; Huminsulin Profil III; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 30 and 50; NovoMix 30 or 70; NovoRapid; ***Belg.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humuline 30/70; Humuline NPH; Humuline Regular; Insulatard; Insuman Basal; Insuman Rapid; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; ***Braz.***: Apidra; Biohulin NPH†; Biohulin Regular†; Exubera†; Humalog Mix 25; Humalog; Humulin 70/30; Humulin Lenta; Humulin NPH; Humulin Regular; Insuman Comb 85N/15R and 75N/25R; Insuman N; Insuman R; Insuneo N; Lantus; Levemir; Novolin 70/30; Novolin N; Novolin R; NovoMix; NovoRapid; ***Canad.***: Apidra; Humalog Mix 25 and 50; Humalog; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Hypurin NPH; Hypurin Regular; Iletin II Pork Lente†; Iletin II Pork NPH†; Iletin II Pork Regular†; Lantus; Levemir; Novolin 30/70, 40/60, 50/50; Novolin NPH; Novolin Toronto; NovoMix 30; NovoRapid; ***Chile***: Actrapid HM; Apidra; Bioinsugen-30/70; Bioinsugen-N; Bioinsugen-R; Humalog Mix 25; Humalog; Humulin 70/30; Humulin L; Humulin N; Humulin R; Insulatard HM; Insuman N; Insuman R; Lantus; Levemir; Mixtard 30 HM; NovoMix 30; NovoRapid; Wosulin 30/70†; Wosulin-N†; Wosulin-R†; ***China***: Apidra (艾倍得); Chang Xiu Lin (长秀霖); GanShuLin N (甘舒霖N); GanShuLin R (甘舒霖R); Humalog (优泌乐); Humalog Mix 25 and 50; Humulin 70/30 (优泌林 70/30); Humulin NPH (优泌林 NPH); Humulin R (优泌林 R); Lantus (来得时); Levemir (诺和平); Novolin 30R, 50R (诺和灵); Novolin N (诺和灵 N); Novolin R (诺和灵 R); NovoMix 30 (诺和锐30); NovoRapid (诺和锐); SciLin M30 (重和林M30); SciLin N (重和林N); SciLin R (重和林R); Su Bi Lin (苏泌啉); Su Mi Lin En (苏泌啉恩); Uslin (优思灵); Wan Bang Lin (万邦林); Wan Bang Lin N (万邦林N); Wan Bang Lin R (万邦林R); Wan Su Lin (万苏林); ***Cz.***: Actraphane 30, 40, 50; Actrapid; Apidra; Exubera†; Humalog Basal; Humalog Mix 25 and 50; Humalog NPL†; Humalog; Humulin M3; Humulin N; Humulin R; Insulatard; Insuman Basal; Insuman Comb 15, 25, 30, 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Basal; Liprolog Mix 25 and 50; Liprolog; Mixtard 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; Velosulin†; ***Denm.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal†; Insuman Rapid; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; Tresiba; ***Fin.***: Actrapid; Humalog Mix 25 and 50; Humalog; Humulin NPH; Humulin Regular; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; NovoMix 30; NovoRapid; Protaphane; ***Fr.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Insuplant†; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; Umuline NPH; Umuline Profil 30; Umuline Rapide; ***Ger.***: Actraphane 30, 50; Actrapid; Apidra; Berlinsulin H 30/70; Berlinsulin H Basal; Berlinsulin H Normal; Humalog Mix 25 and 50; Humalog; Huminsulin Basal; Huminsulin Normal; Huminsulin Profil III; Insulin Basal; Insulin Comb 30/70; Insulin Rapid; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Mix 25 and 50; Liprolog; NovoMix 30; NovoRapid; Protaphane; ***Gr.***: Actraphane 30; Actrapid; Apidra; Exubera; Humalog Basal; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin L; Humulin M1, M2, M3, M4, M5; Humulin NPH; Humulin Regular; Humulin UL; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; Protaphane; Ultratard; Velosulin; ***Hong Kong***: Actrapid HM; Humalog; Humulin 70/30; Humulin L†; Humulin N; Humulin R; Hypurin Isophane†; Hypurin Lente†; Hypurin Neutral†; Hypurin Protamine Zinc†; Lantus; Levemir; Mixtard 30 HM; Monotard HM†; NovoMix 30; NovoRapid; Protaphane HM; SciLin M30; SciLin N; SciLin R; Ultratard HM†; ***Hung.***: Actrapid; Apidra; Humalog Mix25 and Mix50; Humalog; Humulin M3; Humulin N; Humulin R; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; NovoMix 30; NovoRapid; ***India***: Actrapid HM; Actrapid†; Apidra; Bovine Fastact; Bovine Longact; Bovine-Mixact; FlexPen; Humalog Mix 25 and 50; Humalog; Human Fastact; Human Insunorm; Human Longact; Human Monotard; Human Prodica; Human Rapidica; Human Rapimix; Human Zinulin; Human-Mixact; Humanext N; Humapen; Huminsulin L; Huminsulin N; Huminsulin R; Huminsulin 30/70 and 50/50; Humstard; Iletin N; Iletin R; Insucare-N; Insugen-N; Insugen-R; Insugen 30/70 and 50/50; Insulatard HM; Insuman Basal; Insuman Rapid; Insuman 25/75 and 50/50; Lantus; Lentard; Lentisulin-CPI; Lentisulin-HPI-400; Lentisulin-HPI; Levemir; Lupisulin-N; Mixtard 30 and 50; Mixulin; NovoMix 30; NovoRapid; Rapidica; Rapimix; Wosulin N; Wosulin R; Wosulin 30/70 and 50/50; Zinulin; ***Indon.***: Actrapid; Apidra; Humalog Mix 25; Humalog; Humulin 30/70; Humulin N; Humulin R; Insulatard HM; Lantus; Levemir; Mixtard 30; Monotard HM; NovoMix 30; NovoRapid; Sansulin; ***Irl.***: Actraphane; Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin I; Humulin M3; Humulin S; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Mix 25 and 50; Liprolog; Mixtard 10, 20, 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; ***Israel***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin 70/30; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard HM 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; ***Ital.***: Actraphane 30, 50; Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin 30/70; Humulin I; Humulin R; Insuman Rapid; Lantus; Levemir; NovoMix 30, 50, 70; NovoRapid; Protaphane; ***Jpn***: Humacart 3/7†; InnoLet 10R, 20R, 30R, 40R, and 50R; InnoLet N; InnoLet R; Levemir; Novolin 30R, 40R, and 50R; Novolin N; Novolin R; NovoRapid 30 Mix; NovoRapid; Penfill N†; Penfill R†; Penfill 10R, 20R, 30R, 40R, 50R†; Tresiba; Velosulin†; ***Malaysia***: Actrapid HM; Humalog Mix 25; Humalog; Humulin 30/70; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 30 HM; NovoMix; NovoRapid; ***Mex.***: Bonglixan; Glinux 70/30; Glinux-N; Humalog Mix 25; Humalog; Humanilusin; Humulin 70/30; Humulin L†; Humulin N; Humulin R; Insulex 70/30; Insulex N; Insulex R; Insuman 100N; Insuman R; Insuman 15R/85N, 25R/75N, 50R/50N; Lantus; Levemir; Novolin 30/70; Novolin N; Novolin R; NovoMix 30; NovoRapid; Prodiabin-N; Shorant; ***Neth.***: Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Exubera†; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humuline 30/70; Humuline NPH; Humuline Regular; Insulatard; Insuman Basal; Insuman Comb 15, 25, 30, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Mix 25 and 50; Liprolog; Mixtard 10, 20, 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; Ryzodeg; Tresiba; Velosulin†; ***Norw.***: Actrapid; Apidra; Humalog Mix 25; Humalog; Humulin NPH; Insulatard; Insuman Basal; Insuman Comb 25†; Insuman Infusat†; Insuman Rapid; Lantus; Levemir; NovoMix 30; NovoRapid; ***NZ***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin 70/30; Humulin NPH; Humulin R; Insulatard MC; Lantus; Levemir; Mixtard 30; Monotard; NovoMix 30; NovoRapid; PenMix 10, 20, 30, 40, or 50; Protaphane; Ultratard; Velosulin HM; Velosulin MC; ***Philipp.***: Actrapid HM; Apidra; Biosulidd L; Humalog; Humulin 70/30; Humulin N (NPH); Humulin R (Regular); Insuget 70/30; Insuget-N; Insuget-R; Insulatard HM; Lantus; Levemir; Mixtard 30 HM; NovoMix 30; NovoRapid; Ransulin 70/30; Ransulin-N; Ransulin-R; SciLin M30; SciLin N; SciLin R; Wosulin 30/70; Wosulin-N; Wosulin-R; ***Pol.***: Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Gensulin N; Gensulin R; Gensulin M30, M40, or M50; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin M3 (30/70); Humulin N; Humulin R; Insulatard; Insulinum Lente; Insulinum Maxirapid; Insulinum Semilente†; Insulinum Ultralente†; Insuman Basal; Insuman Comb 15, 25, 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog; Mixtard 10, 20, 30, 40, and 50; NovoMix 30, 50, or 70; NovoRapid; Optisulin; Polhumin Mix -2, -3, -4, -5; Polhumin N; Polhumin R; Protaphane; Ultratard HM†; ***Port.***: Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Humalog Basal; Humalog Mix 25 and 50; Humalog; Humulin M3; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 15, 25, 30, 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Basal; Liprolog Mix 25 and 50; Liprolog; Mixtard 10, 20, 30, 40, and

50 HM; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; Velosulin†; ***Rus.***: Actrapid HM (Актрапид НМ); Actrapid MC (Актрапид МС)†; Apidra (Апидра); Biosulin N (Биосулин Н); Biosulin R (Биосулин Р); Humalog (Хумалог); Humalog Mix 25 (Хумалог Микс 25); Humodar B (Хумодар Б); Humodar K25-100 (Хумодар К25-100); Humulin M3 (Хумулин М3); Humulin NPH (Хумулин НПХ); Humulin Regular (Хумулин Регуляр); Insulidd L (Инсулидд Л)†; Insulin Lt (Инсулин Лт)†; Insulin Maxirapid (Инсулин Максирапид)†; Insuman Basal (Инсуман Базал); Insuman Comb 25 (Инсуман Комб 25); Insuman Rapid (Инсуман Рапид); Insuran NPH (Инсуран НПХ); Insuran R (Инсуран Р); Lantus (Лантус); Levemir (Левемир); Levulin L (Левулин Л)†; Mixtard 30 HM (Микстард 30 НМ); Monosuinsulin MK (Моносуинсулин МК); Monotard MC (Монотард МС)†; NovoMix 30, 50, 70 (НовоМикс 30); NovoRapid (Новорапид); Protaphane HM (Протафан НМ); Rinsulin NPH (Ринсулин НПХ); Rinsulin R (Ринсулин Р); Rosinsuline R (Росинсулин Р); Rosinsuline S (Росинсулин С); ***S.Afr.***: Actraphane HM; Actrapid HM; Apidra; Biosulin 30/70; Biosulin L; Biosulin N; Biosulin R; Humalog Mix 25 and 50; Humalog; Humulin 30/70; Humulin N; Humulin R; Insuman Comb; Lantus; Levemir; NovoMix 30; NovoRapid; Protaphane HM; ***Singapore***: Actrapid; Apidra; Humalog Mix 25; Humalog; Humulin 30/70; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 30 and 50; NovoMix 30; NovoRapid; Ultratard HM; ***Spain***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL†; Humalog; Humulina 30:70; Humulina NPH; Humulina Regular; Insulatard; Insuman Basal†; Insuman Comb 15, 25, 30, 50†; Insuman Infusat†; Insuman Rapid†; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; ***Swed.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin Mix 30/70†; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; NovoMix 30; NovoRapid; ***Switz.***: Actrapid HM; Apidra; Humalog; Huminsulin Basal (NPH); Huminsulin Normal†; Huminsulin Profil III†; Hypurin 30/70 Mix; Hypurin Isophane; Hypurin Neutral; Insulatard HM; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard HM 30; NovoMix 30; NovoRapid; Tresiba; ***Thai.***: Actrapid HM; Apidra; Basalin; Gensulin N; Gensulin R; Gensulin M30, M50; Humalog Mix 25; Humalog; Humulin 70/30; Humulin N; Humulin R; Insugen-30/70; Insugen-N; Insugen-R; Insulatard; Lantus; Levemir; Mixtard HM; NovoMix 30; NovoRapid; ***Turk.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin M 70/30 and 80/20; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 20, 30, and 40; NovoMix 30, 50, 70; NovoRapid; Orgasulin Mix 30/70†; Orgasulin NPH; ***UAE***: Jusline 30/70; Jusline N; Jusline R; ***UK***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin I; Humulin M3; Humulin S; Hypurin 30/70; Hypurin Isophane; Hypurin Lente; Hypurin Neutral; Hypurin Protamine Zinc; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 30†; NovoMix 30; NovoRapid; Tresiba; ***Ukr.***: Apidra (Эпайдра)†; Farmasulin H (Фармасулин Н); Farmasulin N 30/70 (Фармасулин Н 30/70); Farmasulin N NP (Фармасулин Н NP); Humodar B100 (Хумодар Б100Р); Humodar C25 100 (Хумодар К25 100Р); Humodar R100 (Хумодар Р100Р); Lantus (Лантус); Levemir (Левемир); NovoMix 30 (Новомикс 30); NovoRapid (Новорапид); Wosulin 30/70 (Восулин)†; Wosulin-N (Восулин-Н)†; Wosulin-R (Восулин-Н-Р)†; ***USA***: Apidra; Humalog Mix 75/25 and 50/50; Humalog; Humulin 70/30; Humulin N; Humulin R; Lantus; Lente Iletin II†; Lente; Levemir; Novolin 70/30; Novolin N; Novolin R; NovoLog; Regular Iletin II†; Ultralente; ***Venez.***: Humalog Mix 25; Humalog; Humulin 70/30; Humulin N; Humulin R; Insuman N; Insuman R; Lantus.

Pharmacopoeial Preparations

BP 2014: Insulin Aspart Injection; Insulin Lispro Injection; Protamine Zinc Insulin Injection;

Ph. Eur.: Biphasic Insulin Injection; Biphasic Isophane Insulin Injection; Insulin Zinc Injectable Suspension (Amorphous); Insulin Zinc Injectable Suspension (Crystalline); Insulin Zinc Injectable Suspension; Isophane Insulin Injection; Soluble Insulin Injection;

USP 36: Extended Insulin Human Zinc Suspension; Extended Insulin Zinc Suspension; Human Insulin Isophane Suspension and Human Insulin Injection; Insulin Human Injection; Insulin Human Zinc Suspension; Insulin Injection; Insulin Lispro Injection; Insulin Zinc Suspension; Isophane Insulin Human Suspension; Isophane Insulin Suspension; Prompt Insulin Zinc Suspension.

Linagliptin *(USAN, rINN)*

BI-1356; BI-1356-BS; Linagliptina; Linagliptine; Linagliptinum; Линаглиптин.

8-[(3*R*)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1*H*-purine-2,6-dione.

$C_{25}H_{28}N_8O_2$=472.6

CAS — 668270-12-0.

ATC — A10BH05.

ATC Vet — QA10BH05.

UNII — 3X29ZEJ4R2.

NOTE. The name Ondero has been used as a trade mark for linagliptin.

Uses and Administration

Like sitagliptin (p. 502.1), linagliptin is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1). The usual oral dose of linagliptin is 5 mg once daily, with or without food. When given with metformin, linagliptin may be given in 2 divided doses. The dose of sulfonylurea or insulin may need to be lowered when used with linagliptin.

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Adverse Effects, Treatment, and Precautions

As for Sitagliptin Phosphate, p. 502.1.

Interactions

The efficacy of linagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Linagliptin is a P-glycoprotein substrate; strong inducers of P-glycoprotein, such as rifampicin, may decrease plasma concentrations of linagliptin and reduce its efficacy.

Pharmacokinetics

Linagliptin has nonlinear pharmacokinetics because of high-affinity saturable binding to dipeptidylpeptidase-4 (DPP-4) in plasma and tissue. It is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations occur within about 1.5 hours. The absolute bioavailability of linagliptin is about 30%. The mean apparent volume of distribution after an intravenous dose is about 1110 litres indicating that linagliptin is extensively distributed to the tissues. Plasma protein binding of linagliptin is concentration-dependent; at low concentrations it is 99% bound, but at high concentrations when DPP-4 is fully saturated, 70 to 80% is bound to other plasma proteins and 20 to 30% is unbound.

After multiple oral doses, linagliptin has an accumulation half-life of about 12 hours. Linagliptin is not extensively metabolised. It undergoes biphasic (or possibly triphasic) elimination and at steady state has a terminal half-life of more than 100 hours. About 80% is eliminated in the faeces and 5% in the urine.

References.

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2. Graefe-Mody U, *et al.* Clinical pharmacokinetics and pharmacodynamics of linagliptin. *Clin Pharmacokinet* 2012; **51:** 411–27.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Trajenta; ***Belg.***: Trajenta; ***Canad.***: Trajenta; ***Denm.***: Trajenta; ***Fr.***: Trajenta; ***Irl.***: Trajenta; ***Jpn***: Trazenta; ***Neth.***: Trajenta; ***Norw.***: Trajenta; ***Singapore***: Trajenta; ***Spain***: Trajenta; ***UK***: Trajenta; ***USA***: Tradjenta.

Multi-ingredient Preparations. ***Denm.***: Jentadueto; ***Neth.***: Jentadueto; ***Spain***: Jentadueto; ***Switz.***: Jentadueto; ***UK***: Jentadueto; ***USA***: Jentadueto.

Liraglutide *(BAN, USAN, rINN)*

Liraglutida; Liraglutidum; NN-2211; NNC-901170; Лираглутид.

N^{26}-(Hexadecanoyl-L-γ-glutamyl)-(34-L-arginine)GLP-1-(7-37)-peptide.

$C_{172}H_{265}N_{43}O_{51}$=3751.3

CAS — 204656-20-2.

ATC — A10BX07.

ATC Vet — QA10BX07.

UNII — 839I73542A.

Uses and Administration

Liraglutide is an analogue of the incretin hormone, glucagon-like peptide 1 (GLP-1), and by acting as an agonist at the glucagon-like peptide 1 receptor has actions similar to those of exenatide (p. 471.1). Liraglutide is used as adjunctive therapy in type 2 diabetes mellitus (p. 459.1) in patients who do not have adequate glycaemic control with metformin, a sulfonylurea, or with dual therapy of metformin plus either a sulfonylurea or a thiazolidinedione. It is given once daily by subcutaneous injection, which may be independent of meal times but should preferably be at the same time each day. A low starting dose of 600 micrograms daily is used to reduce gastrointestinal adverse effects, and is not effective for glycaemic control. After at least 1 week, the dose is increased to 1.2 mg daily. Some patients may benefit from a further increase to 1.8 mg once daily, but the interval between dose increases should be at least 1 week.

References.

1. Croom KF, McCormack PL. Liraglutide: a review of its use in type 2 diabetes mellitus. *Drugs* 2009; **69:** 1985–2004.
2. Joffe D. Liraglutide: a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2010; **67:** 1326–36.
3. NICE. Liraglutide for the treatment of type 2 diabetes mellitus: Technology Appraisal 203 (issued October 2010). Available at: http://www.nice.org.uk/nicemedia/live/13248/51259/51259.pdf (accessed 12/09/11)
4. Shyangdan DS, *et al.* Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. *BMC Endocr Disord* 2010; **10:** 20. Available at: http://www.biomedcentral.com/1472-6823/10/20 (accessed 27/09/11)
5. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 2011; **34** (suppl 2): S279–S284.
6. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Pharmacother* 2011; **45:** 850–60.
7. Ryan GJ, *et al.* Review of the therapeutic uses of liraglutide. *Clin Ther* 2011; **33:** 793–811.

Administration in renal impairment. No dose adjustment is considered necessary for liraglutide in patients with mild renal impairment (creatinine clearance 60 to 90 mL/min); however, it should be used with caution, if at all, in those with moderate or severe impairment due to limited data.

Obesity. Liraglutide is under investigation in the management of obesity[1,2] (p. 2315.1).

1. Astrup A, *et al.* Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; **374:** 1606–16. Correction. *ibid.* 2010; **375:** 984.
2. Astrup A, *et al.* Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2011; doi: 10.1038/ijo.2011.158. Also available at: http://www.nature.com/ijo/journal/vaop/ncurrent/pdf/ijo2011158a.pdf (accessed 02/11/11)

Adverse Effects and Precautions

As for Exenatide, p. 471.2. Adverse thyroid effects have occurred with liraglutide treatment, particularly in patients with pre-existing thyroid disease; reports have included increased blood calcitonin, goitre, and thyroid neoplasms. Liraglutide is contra-indicated in patients with a history, or family history, of medullary thyroid cancer, and in patients with multiple endocrine neoplasia syndrome type 2.

Interactions

A reduction in the sulfonylurea dose may be required when liraglutide is added to therapy, because of an increased risk of hypoglycaemia with this combination. Doses of metformin and thiazolidinediones do not generally need adjustment when liraglutide is added. Liraglutide's effects on the gastrointestinal tract, such as a small delay in gastric emptying or diarrhoea, may affect the absorption of orally administered drugs.

Pharmacokinetics

Liraglutide is absorbed slowly after subcutaneous injection, reaching a maximum concentration after 8 to 12 hours. It has a bioavailability of about 55%, and is more than 98% bound to plasma proteins. Although a specific organ has not been identified as the major route for its removal, liraglutide is metabolised and has an elimination half-life of about 13 hours after a single subcutaneous dose.

References.

1. Meece J. Pharmacokinetics and pharmacodynamics of liraglutide, a long-acting, potent glucagon-like peptide-1 analog. *Pharmacotherapy* 2009; **29:** 33S–42S.
2. Watson E, *et al.* Population pharmacokinetics of liraglutide, a once-daily human glucagon-like peptide-1 analog, in healthy volunteers and subjects with type 2 diabetes, and comparison to twice-daily exenatide. *J Clin Pharmacol* 2010; **50:** 886–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Victoza; ***Austria***: Victoza; ***Belg.***: Victoza; ***Braz.***: Victoza; ***Canad.***: Victoza; ***China***: Victoza (诺和力); ***Cz.***: Victoza; ***Denm.***: Victoza; ***Fr.***: Victoza; ***Ger.***: Victoza; ***Gr.***: Victoza; ***Irl.***: Victoza; ***Israel***: Victoza; ***Jpn***: Victoza; ***Neth.***: Victoza; ***Norw.***: Victoza; ***Pol.***: Victoza; ***Port.***: Victoza; ***Rus.***: Victoza (Виктоза); ***Singapore***: Victoza; ***Spain***: Victoza; ***Swed.***: Victoza; ***Switz.***: Victoza; ***Thai.***: Victoza; ***UK***: Victoza; ***Ukr.***: Victoza (Виктоза); ***USA***: Victoza.

Lixisenatide *(rINN)*

AVE-0010; Lixisenatida; Lixisénatide; Lixisenatidum; ZP-10; Ликсисенатид.

Des-38-proline-exendine-4 (*Heloderma suspectum*)-(1-39)-peptidylpenta-Lysyl-L-lysinamide.

$C_{215}H_{347}N_{61}O_{65}S$=4858.6

CAS — 320367-13-3.

UNII — 74O62BB01U.

Uses and Administration

Lixisenatide is an analogue of the incretin hormone, glucagon-like peptide 1 (GLP-1), and by acting as an agonist at the GLP-1 receptor has actions similar to those of exenatide (p. 471.1). It is used as adjunctive therapy in type 2 diabetes mellitus (p. 459.1) in patients who do not have adequate glycaemic control with oral antidiabetics or basal insulin. It is given once daily by subcutaneous injection, within the hour before the first meal of the day or the evening meal. If a dose is missed it should be injected within the hour before the next meal. A starting dose of 10 micrograms daily is used for 14 days; the maintenance dose of 20 micrograms daily is started on day 15. If lixisenatide is added to either a sulfonylurea or basal insulin, the dose of sulfonylurea or insulin may need to be adjusted to reduce the risk of hypoglycaemia. Lixisenatide should not be given with a combination of sulfonylurea and basal insulin.

For administration in renal impairment, see p. 491.1.

References.
1. Christensen M, *et al.* Lixisenatide for type 2 diabetes mellitus. *Expert Opin Invest Drugs* 2011; **20:** 549–57.
2. Elkinson S, Keating GM. Lixisenatide: first global approval. *Drugs* 2013; **73:** 383–91.
3. Rosenstock J, *et al.* Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care* 2013;

Administration in renal impairment. No dose adjustment is considered necessary for lixisenatide in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min); however, it should be used with caution in those with moderate impairment and is not recommended in those with severe impairment or end-stage renal disease due to lack of data.

Adverse Effects and Precautions

As for Exenatide, p. 471.2.

Interactions

As for Exenatide, p. 471.3.

Pharmacokinetics

Lixisenatide is absorbed rapidly after subcutaneous injection reaching a maximum concentration after about 1 to 3.5 hours; it is about 55% bound to plasma proteins. Lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation into smaller peptides and amino acids. It has a mean terminal half-life of about 3 hours after multiple-dose subcutaneous administration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Lyxumia; ***UK***: Lyxumia.

Metformin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de metformina; LA-6023 (metformin or metformin hydrochloride); Metformiinihydrokloridi; Metformin Hidroklorür; Metformin hydrochlorid; Metformina, hidrocloruro de; Metformine, Chlorhydrate de; Metforminhidroklorid; Metforminhydrochlorid; Metforminhydroklorid; Metformini Hydrochloridum; Metformino hidrochloridas; Метформина Гидрохлорид.

1,1-Dimethylbiguanide hydrochloride.

$C_4H_{11}N_5$,HCl=165.6

CAS — 657-24-9 (metformin); 1115-70-4 (metformin hydrochloride).

ATC — A10BA02.

ATC Vet — QA10BA02.

UNII — 786Z46389E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8 (Metformin Hydrochloride). White or almost white crystals. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

USP 36: (Metformin Hydrochloride). A white crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

Uses and Administration

Metformin hydrochloride is a biguanide antidiabetic (p. 467.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 491.3), and is the drug of first choice in overweight patients. Initial dosage is 500 mg two or three times daily or 850 mg once or twice daily with or after meals, gradually increased if necessary, at intervals of at least 1 week, to 2 to 3 g daily; doses of 3 g daily are associated with an increased incidence of gastrointestinal adverse effects. Gastrointestinal effects are also common on beginning therapy, and the *BNF* recommends starting therapy more gradually with 500 mg at breakfast for at least 1 week, then increasing to 500 mg twice daily with the morning and evening meals for at least 1 week, then 500 mg three times daily; the usual maximum is 2 g daily in divided doses.

A modified-release preparation is also available, which is given in an initial dose of 500 mg once daily and may be increased in increments of 500 mg, at intervals of at least 1 week, to a maximum of 2 g once daily with the evening meal. If glycaemic control is not adequate the dose may be divided to give 1 g twice daily with meals. If doses above 2 g daily are required, they should be given as the standard preparation.

For doses used in children and adolescents, see p. 491.2.

Metformin is also used as the chlorophenoxyacetate and as the embonate.

General references.
1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; **49:** 721–49.
2. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997; **102:** 99–110.
3. Klepser TB, Kelly MW. Metformin hydrochloride: an antihyperglycemic agent. *Am J Health-Syst Pharm* 1997; **54:** 893–903. Correction. *ibid.*; 1335.
4. Kirpichnikov D, *et al.* Metformin: an update. *Ann Intern Med* 2002; **137:** 25–33.
5. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003; **63:** 1879–94.
6. Goodarzi MO, Bryer-Ash M. Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic agents. *Diabetes Obes Metab* 2005; **7:** 654–65.
7. Stumvoll M, *et al.* Metformin. *Endocr Res* 2007; **32:** 39–57.
8. Scarpello JHB, Howlett HCS. Metformin therapy and clinical uses. *Diab Vasc Dis Res* 2008; **5:** 157–67.

Action. The mechanisms by which metformin increases insulin sensitivity and glucose uptake into cells, and inhibits hepatic gluconeogenesis, are unclear. One reviewer[1] considered that metformin acts mainly at the level of the cell membrane. In insulin-resistant cells it is thought to correct defects in insulin signaling, which then normalises glucose transport and glycogen synthesis. In the presence of hyperglycaemia, metformin is also reported to improve the activity of membrane-inserted glucose transporters. There is also some evidence that metformin can inhibit the formation of advanced glycation end-products, which are associated with the development of diabetic complications.[2]

1. Wiernsperger NF. Membrane physiology as a basis for the cellular effects of metformin in insulin resistance and diabetes. *Diabetes Metab* 1999; **25:** 110–27.
2. Beisswenger P, Ruggiero-Lopez D. Metformin inhibition of glycation processes. *Diabetes Metab* 2003; **29:** 6S95–6S103.

Administration in children. In children aged 10 years and older with type 2 diabetes mellitus, oral metformin hydrochloride may be used in a starting dose of 500 mg or 850 mg once daily, or 500 mg twice daily, given with or after a meal. It may be gradually increased if needed, at intervals of at least 1 week, to a maximum of 2 g daily given in 2 or 3 divided doses. Gastrointestinal effects are common on starting therapy, and the *BNFC* suggests that the initial dose should be 500 mg once daily; it also suggests that children who are 8 to 10 years of age may be started on a dose of 200 mg once daily, although such use is unlicensed in the UK. Modified-release preparations are generally not licensed for use in children.

Although rare, the incidence of type 2 diabetes is increasing in children and adolescents, related in part to the increase in obesity occurring particularly in westernised countries. A small placebo-controlled study[1] of patients aged 10 to 17 years with type 2 diabetes found that metformin improved glycaemic control and that adverse effects were similar to those in adults. It was also found to be safe and effective in 131 children with a mean age of 13.8 years, in a comparison with glimepiride.[2] In obese children and adolescents with hyperinsulinaemia, who are at risk of developing type 2 diabetes, small studies[3-7] of metformin use have reported improvements in body composition and fasting insulin concentrations.

Insulin resistance and a deterioration in metabolic control can occur during puberty in adolescent type 1 diabetics. There has, therefore, been some interest in the use of metformin as an adjunct to insulin therapy in these patients, and small studies have reported improvements in glycaemic control[8-10] and reductions in insulin requirements.[8,10]

Metformin has also been studied in small groups of adolescents with polycystic ovary syndrome. There are reports of a reduction in testosterone and improvements in menstrual cycle regularity,[11-13] as well as improved insulin sensitivity in those with hyperinsulinism.[11] Some, but not all, studies have also reported beneficial effects on body-mass index[11,13] and hirsutism.[13]

1. Jones KL, *et al.* Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2002; **25:** 89–94.
2. Gottschalk M, *et al.* Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care* 2007; **30:** 790–4.
3. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Abstract: *Pediatrics* 2001; **107:** 763–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e55 (accessed 25/06/07)
4. Srinivasan S, *et al.* Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. *J Clin Endocrinol Metab* 2006; **91:** 2074–80.
5. Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. *J Pediatr Endocrinol Metab* 2008; **21:** 339–48.
6. Park MH, *et al.* Metformin for obesity in children and adolescents: a systematic review. *Diabetes Care* 2009; **32:** 1743–5.
7. Yanovski JA, *et al.* Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. *Diabetes* 2011; **60:** 477–85.
8. Hamilton J, *et al.* Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 2003; **26:** 138–43.
9. Särnblad S, *et al.* Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity. *Eur J Endocrinol* 2003; **149:** 323–9.
10. Urakami T, *et al.* Usefulness of the addition of metformin to insulin in pediatric patients with type 1 diabetes mellitus. *Pediatr Int* 2005; **47:** 430–3.
11. Allen HF, *et al.* Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. *J Pediatr Endocrinol Metab* 2005; **18:** 761–8.
12. Bridger T, *et al.* Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome. *Arch Pediatr Adolesc Med* 2006; **160:** 241–6.
13. De Leo V, *et al.* Metformin treatment is effective in obese teenage girls with PCOS. *Hum Reprod* 2006; **21:** 2252–6.

Diabetes mellitus. Results of the UK Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control with metformin reduces the risk of diabetic complications (p. 462.3) and death in overweight patients with **type 2 diabetes**.[1,2] The study also generated some concern regarding intensive therapy with metformin plus a sulfonylurea (see under Interactions, p. 503.3) but this was not borne out on further analysis and such combinations are widely used in the management of type 2 diabetes mellitus (p. 459.1). Metformin is also used with other antidiabetic drugs in patients requiring combined or more intensive therapy. A systematic review[3] found only a limited number of controlled studies comparing various combinations of metformin with another oral antidiabetic (acarbose, exenatide, meglitinides, sulfonylureas, and thiazolidinediones) or insulin, and concluded that no particular combination provided better glycaemic control.

Metformin has also been investigated for the *prevention* of type 2 diabetes in patients at high risk. Although metformin treatment for an average 2.8 years reduced the incidence of type 2 diabetes by 31% in a placebo-controlled study[4] of patients with impaired glucose tolerance, intensive lifestyle modification was actually more effective (58% reduction). Lifestyle modification was also more effective than metformin in reducing cardiovascular risk factors[5] and the development of the metabolic syndrome.[6] After completion of this study all patients were offered lifestyle interventions and, in addition, those previously in the metformin group were continued on the drug.[7] Follow up of these patients found that there was no significant difference in incidence of diabetes between the groups which was attributed to a fall in the number of new cases in the metformin and placebo groups to similar rates to those seen in the lifestyle group. Cardiovascular risk factors also improved in all 3 groups. The cumulative incidence of diabetes in the 10 years since initial randomisation was reduced by 34% in the lifestyle group and by 18% in the metformin group when compared with placebo. A meta-analysis[8] also found that metformin improved body-weight, lipid profiles, and insulin resistance, and reduced the onset of type 2 diabetes in patients at risk, but concluded that diet and exercise remained the basis of diabetes prevention.

Insulin is generally preferred for the treatment of **diabetes during pregnancy**. However, there is increasing evidence to suggest that metformin might be used safely in pregnant women with type 2 diabetes (see Pregnancy under Precautions, p. 493.1), and UK guidance[9] has suggested that it may be used either as an adjunct or alternative to insulin if the likely benefits from improved glycaemic control outweigh the potential for harm. Nevertheless, the use of oral hypoglycaemics during pregnancy remains controver-

sial; see Diabetes Mellitus, p. 459.1 for further details. Metformin has also been tried in women who develop gestational diabetes[10] and UK guidance[9] states that there is sufficient evidence of efficacy and safety to consider metformin as an adjunct or alternative to insulin. Following the birth, glucose tolerance returns to normal in most women; however, the risk of developing type 2 diabetes in the future is increased. Metformin use in women with a history of gestational diabetes has been shown to reduce the incidence of type 2 diabetes by about 50% when compared with placebo.[11] A similar reduction was seen in women managed through lifestyle interventions.

There is some interest in using oral metformin as an adjunct to insulin therapy in patients with **type 1 diabetes**,[12] particularly those who are overweight or have poor glycaemic control. Studies have consistently reported that total daily insulin requirements were reduced in patients given metformin.[13-17] Although results from small short-term studies have suggested that metformin may improve glycaemic control,[14-16] larger studies lasting 6 months[13] and 12 months[17] found no significant changes in glycated haemoglobin (HbA_{1c}). Reductions in body-weight[17] and body-mass index[16] were only significant in groups of patients given metformin for at least 1 year. Overall, the addition of metformin did not affect the frequency of hypoglycaemic events, but results from one study[17] suggested that major events were potentially more serious.

Metformin has also been studied in adolescents with type 1 diabetes and pubertal insulin resistance, and type 2 diabetes (see Administration in Children, p. 489.2).

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65.
2. Holman RR, *et al*. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.
3. Monami M, *et al*. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008; **79:** 196–203.
4. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.
5. Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. *Diabetes Care* 2005; **28:** 888–94.
6. Orchard TJ, *et al*. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005; **142:** 611–19.
7. Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374:** 1677–86.
8. Salpeter SR, *et al*. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med* 2008; **121:** 149–57.
9. National Collaborating Centre for Women's and Children's Health/NICE. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period (issued March 2008, reissued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG63NICEGuideline.pdf (accessed 21/02/11)
10. Wensel TM. Role of metformin in the treatment of gestational diabetes. *Ann Pharmacother* 2009; **43:** 939–43.
11. Ratner RE, *et al*. Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008; **93:** 4774–9.
12. Vella S, *et al*. The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia* 2010; **53:** 809–20.
13. Meyer L, *et al*. The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. *Diabetes Care* 2002; **25:** 2153–8.
14. Gunton JE, Twigg SM. Metformin use as an adjunct to insulin treatment in selected patients with type 1 diabetes mellitus. *Med J Aust* 2003; **178:** 591–2.
15. Khan ASA, *et al*. The effect of metformin on blood glucose control in overweight patients with type 1 diabetes. *Diabet Med* 2006; **23:** 1079–84.
16. Moon RJ, *et al*. The addition of metformin in type 1 diabetes improves insulin sensitivity, diabetic control, body composition and patient well-being. *Diabetes Obes Metab* 2007; **9:** 143–5.
17. Lund SS, *et al*. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control: a randomized study. *PLoS One* 2008; **3:** e3363. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0003363 (accessed 17/08/09)

Malignant neoplasms. There is some evidence to suggest that the incidence of, or mortality from, malignant neoplasms may be reduced in patients taking metformin,[1-4] and there has been considerable interest in the potential of metformin as a prophylactic agent or as an adjuvant in the management of malignant neoplasms.[5-13]

1. Libby G, *et al*. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 2009; **32:** 1620–5.
2. Landman GW, *et al*. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care* 2010; **33:** 322–6.
3. Bodmer M, *et al*. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* 2010; **33:** 1304–8.
4. Donadon V, *et al*. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int* 2010; **30:** 750–8.
5. Jiralerspong S, *et al*. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol* 2009; **27:** 3297–3302.
6. Martin-Castillo B, *et al*. Incorporating the antidiabetic drug metformin in HER2-positive breast cancer treated with neo-adjuvant chemotherapy and trastuzumab: an ongoing clinical-translational research experience at the Catalan Institute of Oncology. *Ann Oncol* 2010; **21:** 187–9.
7. Gonzalez-Angulo AM, Meric-Bernstam F. Metformin: a therapeutic opportunity in breast cancer. *Clin Cancer Res* 2010; **16:** 1695–1700.
8. Martin-Castillo B, *et al*. Metformin and cancer: doses, mechanisms and the dandelion and hormetic phenomena. *Cell Cycle* 2010; **9:** 1057–64.
9. Ben Sahra I, *et al*. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Mol Cancer Ther* 2010; **9:** 1092–9.
10. Wysocki PJ, Wierusz-Wysocka B. Obesity, hyperinsulinemia and breast cancer: novel targets and a novel role for metformin. *Expert Rev Mol Diagn* 2010; **10:** 509–19.
11. Papanas N, *et al*. Metformin and cancer: licence to heal? *Expert Opin Invest Drugs* 2010; **19:** 913–17.
12. Li D, *et al*. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; **137:** 482–8.
13. DeCensi A, *et al*. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 2010; **3:** 1451–61.

Nutritional and metabolic disorders. In addition to its use in diabetes mellitus (p. 489.3), metformin has also been tried in a diverse range of nutritional and metabolic disorders that may involve weight gain, hyperinsulinaemia and insulin resistance, glucose intolerance, and lipodystrophies. These include obesity in patients without diabetes,[1-3] obesity-related acanthosis nigricans,[4] antipsychotic-induced weight gain,[5,6] HIV-associated lipodystrophy,[7,8] and precocious puberty.[9]

1. Desilets AR, *et al*. Role of metformin for weight management in patients without type 2 diabetes. *Ann Pharmacother* 2008; **42:** 817–26.
2. Park MH, *et al*. Metformin for obesity in children and adolescents: a systematic review. *Diabetes Care* 2009; **32:** 1743–5.
3. Glaser Pediatric Research Network Obesity Study Group. Metformin extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. *Arch Pediatr Adolesc Med* 2010; **164:** 116–23.
4. Romo A, Benavides S. Treatment options in insulin resistance obesity-related acanthosis nigricans. *Ann Pharmacother* 2008; **42:** 1090–4.
5. Wu R-R, *et al*. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* 2008; **299:** 185–93.
6. Ehret M, *et al*. The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: a meta-analysis. *J Clin Psychiatry* 2010; **71:** 1286–92.
7. Driscoll SD, *et al*. Differential effects of metformin and exercise on muscle adiposity and metabolic indices in human immunodeficiency virus-infected patients. *J Clin Endocrinol Metab* 2004; **89:** 2171–8.
8. van Wijk JPH, *et al*. Comparison of rosiglitazone and metformin for treating HIV lipodystrophy: a randomized trial. *Ann Intern Med* 2005; **143:** 337–46.
9. Ibáñez L, *et al*. Pubertal metformin therapy to reduce total, visceral, and hepatic adiposity. *J Pediatr* 2010; **156:** 98–102.

Polycystic ovary syndrome. It has been suggested that hyperinsulinism may play a pathogenetic role in stimulating the abnormal androgen production from the ovary seen in women with polycystic ovary syndrome (PCOS, p. 2253.3). Most early studies of metformin in PCOS were small, observational, and of short duration, with mixed results. Although there were reports of reduced insulin levels, increased insulin sensitivity, and improved androgen concentrations, other studies failed to confirm these effects.[1] Later randomised studies were also small, but some were of longer duration. These reported weight reductions in obese patients,[2] reductions in insulin levels[2-4] and increased sensitivity,[5] improved androgen and other hormonal measures,[2,3,5] and improved menstrual patterns,[2,4,5] but again, not consistently. Metformin has also been reported to reduce hirsutism in women with PCOS, but it appears to have only a modest effect similar to that of hormonal contraceptives, and is less effective than anti-androgen therapy.[6,7]

The effect of metformin on infertility in PCOS has also been investigated. Early small studies suggested that it could improve ovulation when used alone or with clomifene citrate; pregnancy rates were also improved when metformin was used with clomifene.[8] However, 2 large, placebo-controlled studies later found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[9,10] A meta-analysis[11] that included these 2 large studies concluded that metformin did not improve live birth rates when given alone or with clomifene in clomifene therapy-naive women, but there was evidence of better rates when metformin was added to clomifene therapy in clomifene-resistant women. Based on limited data, it also appeared that there was no benefit from the addition of metformin to laparoscopic ovarian drilling or follicle-stimulating hormone. A systematic review[12] of studies using assisted reproduction (IVF or intra-cytoplasmic sperm injection) found that addition of metformin did not improve rates of live birth, clinical pregnancy, or miscarriage. Metformin was associated with a reduced risk of ovarian hyperstimulation syndrome, but the possible mechanism for this was unclear. It has also been suggested that pre-pregnancy metformin may decrease the rate of first-trimester miscarriage, which is common in women with PCOS; however, a meta-analysis[13] found no evidence of significant benefit with metformin use, when given alone or with other fertility drugs before pregnancy. Although it is usual to stop treatment with metformin after conception, some women have continued treatment throughout their pregnancies and there is growing evidence to suggest that this may have a beneficial effect on pregnancy outcome.[14,15]

Women with PCOS are at increased risk of developing impaired glucose tolerance, type 2 diabetes mellitus, and other features of the metabolic syndrome. In the USA, metformin has been recommended for consideration in most women with PCOS, particularly in those who are overweight or obese.[16] Although metformin may have beneficial effects on these risk factors for cardiovascular disease, prospective long-term studies are lacking.[7]

1. Norman RJ, *et al*. Metformin and intervention in polycystic ovary syndrome. *Med J Aust* 2001; **174:** 580–3.
2. Pasquali R, *et al*. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000; **85:** 2767–74.
3. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996; **335:** 617–23.
4. Morin-Papunen LC, *et al*. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 2000; **85:** 3161–8.
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6. Cosma M, *et al*. Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *J Clin Endocrinol Metab* 2008; **93:** 1135–42.
7. Mathur R, *et al*. Use of metformin in polycystic ovary syndrome. *Am J Obstet Gynecol* 2008; **199:** 596–609.
8. Lord JM, *et al*. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; **327:** 951–3.
9. Moll E, *et al*. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. Abridged version: *BMJ* 2006; **332:** 1485–8. Full version: http://www.bmj.com/cgi/reprint/332/7556/1485 (accessed 17/06/08) Correction available at: http://www.bmj.com/cgi/content/full/336/7643/0-b (accessed 17/06/08)
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11. Moll E, *et al*. The role of metformin in polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2007; **13:** 527–37.
12. Tso LO, *et al*. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 30/06/09).
13. Palomba S, *et al*. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2009; **92:** 1646–58.
14. Glueck CJ, *et al*. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; **17:** 2858–64.
15. Nawaz FH, *et al*. Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? *J Obstet Gynaecol Res* 2008; **34:** 832–7.
16. AACE Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. *Endocr Pract* 2005; **11:** 126–34. Also available at: http://www.aace.com/pub/pdf/guidelines/PCOSpositionstatement.pdf (accessed 30/06/09)

Adverse Effects, Treatment, and Precautions

As for biguanides in general, p. 468.1.

Breast feeding. Based on *animal* studies, UK and US licensed product information warns that metformin may be distributed into breast milk, and that the possible effects on the infant should be considered if women wish to breast feed while receiving the drug. However, a study in 7 breast-feeding women receiving metformin at a median dose of 1.5 g daily found the concentrations in milk to be about a third of those in maternal plasma, resulting in a mean calculated dose to the infants of 40 micrograms/kg daily. Blood samples were taken from 4 of the infants: metformin concentrations were undetectable in 2, and were very low (10 to 15% of maternal values) in the others. Given these results the authors considered that women receiving metformin need not be discouraged from breast feeding.[1] Similar results from 3 other studies[2,3] that included 13 women have provided further evidence that metformin is distributed into breast milk, that concentrations in milk are less than those in maternal plasma, and that breast-fed infants would be exposed to a very small percentage of the maternal dose. Six infants were breast-fed with no adverse effects that could be attributed to metformin. A prospective study[4] of weight, height, and motor-social development over 6 months, in infants of women taking metformin (1.5 to 2.55 g daily) for polycystic ovary syndrome, found no difference between 61 infants who were breast-fed and 50 who were formula-fed.

1. Hale TW, *et al*. Transfer of metformin into human milk. *Diabetologia* 2002; **45:** 1509–14.
2. Gardiner SJ, *et al*. Transfer of metformin into human milk. *Clin Pharmacol Ther* 2003; **73:** 71–7.
3. Briggs GG, *et al*. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol* 2005; **105:** 1437–41.
4. Glueck CJ, *et al*. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr* 2006; **148:** 628–32.

Fasting. For the view that metformin could be used with little risk of hypoglycaemia in fasting Muslim patients during Ramadan, and suggestions for modifying the timing of doses, see under Precautions of Insulin, p. 485.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metformin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/07/11)

Pregnancy. Insulin is generally preferred for treatment of diabetes during pregnancy. However, there are limited data to suggest that metformin does not increase the risk of congenital abnormalities[1,2] and does not adversely affect pregnancy outcome in diabetic women.[2] In gestational diabetes, a controlled study[3] in more than 700 women found that metformin, either alone or with insulin, did not increase adverse maternal or neonatal complications, compared with insulin therapy alone. Although the rate of preterm birth (before 37 weeks) was higher in the metformin group, this was not associated with a higher rate of other complications. For the use of metformin in the management of diabetes during pregnancy, see Diabetes Mellitus under Uses, p. 489.3.

The use of metformin to improve ovulation in polycystic ovary syndrome is increasing (see under Uses, p. 490.2) and there is evidence to suggest that metformin used before and during pregnancy in these women does not increase the risk of congenital abnormalities.[1,4-7]

1. Gilbert C, *et al*. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril* 2006; **86:** 658–63.
2. Hughes RCE, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? *Diabet Med* 2006; **23:** 318–22.
3. Rowan JA, *et al*. MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; **358:** 2003–15. Correction. *ibid.*; **359:** 106.
4. Glueck CJ, *et al*. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; **17:** 2858–64.
5. Glueck CJ, *et al*. Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. *Hum Reprod* 2004; **19:** 1323–30.
6. Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril* 2006; **85:** 1002–9.
7. Nawaz FH, *et al*. Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? *J Obstet Gynaecol Res* 2008; **34:** 832–7.

Renal impairment. Biguanides are generally avoided in patients with renal impairment because of the risk of lactic acidosis, and US licensed product information advises that metformin should not be given if serum-creatinine concentrations are above the upper limit of normal for age, or there is any other evidence of renal impairment. In the UK, licensed product information suggests that metformin should not be used when creatinine clearance is less than 60 mL/min. However, some authors consider that the risk of lactic acidosis with metformin in patients with renal impairment has been overstated.[1,2] Indeed, guidelines from NICE[3] advise that the dose of metformin should be reviewed if serum creatinine exceeds 130 micromoles/litre or the estimated glomerular filtration rate is below 45 mL/min per 1.73 m^2, and that the drug should be stopped if serum creatinine exceeds 150 micromoles/litre or the estimated glomerular filtration rate falls below 30 mL/min per 1.73 m^2.

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2. Pilmore HL. Review: metformin: potential benefits and use in chronic kidney disease. *Nephrology (Carlton)* 2010; **15:** 412–18.
3. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes (issued May 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 16/06/09)

Interactions

As for biguanides in general, p. 469.1.

Pharmacokinetics

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours. Metformin crosses the placenta and is distributed into breast milk in small amounts.

References.

1. Sambol NC, *et al*. Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *J Clin Pharmacol* 1996; **36:** 1012–21.
2. Charles B, *et al*. Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006; **28:** 67–72.
3. Zolk O. Current understanding of the pharmacogenomics of metformin. *Clin Pharmacol Ther* 2009; **86:** 595–8.
4. Eyal S, *et al*. Pharmacokinetics of metformin during pregnancy. *Drug Metab Dispos* 2010; **38:** 833–40.
5. Graham GG, *et al*. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 2011; **50:** 81–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Baligluc; DBI AP; Diab Dos; Diabesil; Duburina; Glucaminol; Glucogood; Glucophage; Islotin; Mectin; Medobis; Melgib; Metforal; Metglucon; MTF; Oxemet; Quexel; Reduglucˆ; ***Austral.***: Diabex; Diaformin; Formet; Glucohexal†; Glucomet; Glucophage; Metex; Novomet†; ***Austria***: Diabetex; Glucophage; Meglucon; ***Belg.***: Glucophage; Metformax; ***Braz.***: Diaformin; Dimefor; Formyn; Glicefor; Glifage; Gliformil; Glucoformin; Meguanin; Metform; Metformed; Metformix; Metta; Teutoformin; ***Canad.***: Glucophage; Glumetza; Glycon; ***Chile***: Diabetyl; Diaglitab; Fintaxim; Glafornil; Glicenex; Glidanil; Glifortex; Glucophage; Hipoglucin; Oxemet; ***China***: Bai Si Ping (佰思平); Bei Shun (倍顺); Bo Ke (卜可); De Ai Xin (德艾欣); Diaformin (迪化唐锭); Du Le Ning (都乐宁); Glucophage (格华止); Hong Fei Kang (弘飞康); Jiang Li Shu (降力舒); JinZhenXing (津真型); Jun Li Da (君力达); Jun Shi Da Xin (君士达新); Li Le Er (力乐尔); Ming Nuo (名诺); Pu Le Kang Ni (普乐康尼); Qi Ji (齐信); Qing Kuang (清旷); Ren Xin (仁欣); Rui Nuo Shu (瑞诺舒); Ruijiu (瑞久); San Xiao Ping (三肖平); Shan Mu Shi (山姆士); Sheng Bang Jie (圣邦杰); Tai Bai (泰白); Tang Bi Fu (唐必呋); Tang Ge (唐格); Tang Luo (唐落); Tang Tan (唐坦); Wei Er Tang (维尔唐); Xin Shu Shi Ning (欣舒施宁); Xin Tang Ping (欣唐屏); Yi Heng (亿恒); Yue Da Ning (悦达宁); Zhong Shi De (众氏得); ***Cz.***: Adimet; Diaphage†; Glucomerck†; Glucophage; Gluformin†; Glumetsan†; Langerin; Metfirex; Metfogamma; Metfogen; Normaglyc; Siofor; Stadamet; ***Denm.***: Glucophage†; Mitforgen; Orabet; ***Fin.***: Diformin; Glucophage; Metforem; Metgol†; Oramet; ***Fr.***: Diabamyl; Glucophage; Stagid; ***Ger.***: Biocos†; Diabesin†; Diabetase†; Glucobon†; Glucophage; Juformin†; Mediabet†; Meglucon†; Mescorit†; Met; Metfogamma; Metformdoc†; Siofor; ***Gr.***: Glucofree; Glucophage; Glucoplus; Metforil; Sukontrol; ***Hong Kong***: CP-Metform; Deson; Diabesafe†; Diabetmin; Diaformin; Glucodown; Glucomet; Glucomin†; Glucophage; Glumet; Guamet; Melbin; ***Hung.***: Adimet; Meforal; Meglucon; Merckformin; Metfogamma; Metrivin; Stadamet; ***India***: Alnamet; Atformin; Avimet; Bigan; Bigomet; Bigsens; Bimode-M; C-Mine; Cetapin; Conformin; D-Bay; D-Met; Daomet; Diafer; Diamet; Dibeta; Dibimet; Diform; Emfor; Emnorm; Etformin; Eumet; Exermet; Formet; Formin; Forminal; Frame; G Reg; G-Met; G-Reg; Glinate-MF; Gluconorm; Gluformin; Glumet; Glyciphage; Glycomet; Glycotan; Glyree M; Glyrep; Insumet; K-Met; M-Forlin; Matce; Medformin; Melmet; Mesite; Metadoze-IPR; Metafor; Metanorm; Metcalf; Metchek; Metco; Metfor; Metica; Metkap; Metkor; Metlife; Metlong; Metmin; Metneed; Metsafe; Metsar; Metswift; MF; Minimet; MR-Met; Obimet; Okamet; Omet; Oriphage; Walaphage; Xmet; ***Indon.***: Adecco; Benofomin; Diabex; Diafac; Efomet; Eraphage; Forbetes; Formell; Gliformin; Glikos; Glucofor; Glucophage; Glucotika; Gludepatic; Glufor; Glumin; Glunor; Gradiab; Methormyl; Methpica; Metphar; Nevox; Pionix-M; Reglus; Tudiab; Zendiab; Zumamet; ***Irl.***: Bellformin†; Gerformin; Glucophage; Metophage; ***Israel***: Glucomin; Glucophage; Glufor; ***Ital.***: Glucophage; Metbay; Metespina; Metfonorm; Metforal; Zuglimet; ***Jpn***: Glycoran; Melbin†; ***Malaysia***: Diabetmin; Glucomet; Glucon; Glucophage; Glumet; Riomet; Xmet; ***Mex.***: Aglumet; Anglucid; Apozemia; Dabex; Debeone; Dimefor; Dinamel; Ficonax; Forlucyl; Glucophage; Glucotec S; Glunovag; Harbamind; Ifor; Meglubet; Melbexa; Metbax†; Metixor; Mifelar; Minatozil; Minraam; Pharmafet; Pre-Dial; Sibet; ***Neth.***: Diabex†; Glucophage†; Metnova; Niformina†; ***Norw.***: Glucophage; ***NZ***: Glucomet; Metchek; Metomin†; ***Philipp.***: Ansures; Briform; Diafat; Diazen; Euform; Formet; Fornidd; Glucare†; Glucoform; Glucomed; Glucophage; Glucopres; Gludin; Glumet; Glyformin; Horsulin†; Humamet; I-Max; Insunex; Marphage; Mellinix; Metanorm; Neoform; Neomet; Nidcor; Panfor; Sucranorm†; Vimetrol†; Xmet; ***Pol.***: Avamina; Etform; Formetic; Glucophage; Gluformin; Metfogamma; Metformax; Metifor; Metral; Mylformet; Siofor; ***Port.***: Diabex; Glucophage; Mekoll; Risidon; Romac; Stagid; ***Rus.***: Bagomet (Багомет); Dianormet (Дианормет); Formetin (Форметин); Formin (Формин Плив); Gliformin (Глиформин); Gliminfor (Глиминфор); Glucophage (Глюкофаж); Lanagerin (Ланжерин); Metadien (Метадиен); Metfogamma (Метфогамма); Metospanin (Метоспанин); NovoFormin (НовоФормин); Siofor (Сиофор); ***S. Afr.***: Bigsens; Diabetmin; Diaformin; Forminal; Gluconorm; Glucophage; Mengen; Metforal; Metored; Metphage; ***Singapore***: Diabetmin; Diaformin; Formet; Glucomet; Glucophage; Glycomet; Glyformin; Metforal; SP-Glucomet; ***Spain***: Dianben; ***Swed.***: Glucophage; ***Switz.***: Glucophage; Metfin; ***Thai.***: Ammiformin; Buformin; Deglucos; Deson; Diamet; Diaslim; Formin; Glucino; Gluco; Glucoles; Glucolyte; Glucono; Glucophage; Gluformin†; Glugenmin; Glugon; Glustress; Glutabloc; Gluzolyte; Maformin; ME-F; Meformed; Metfor†; Metforex; Metfron; Metica; Miformin; Pocophage; Poli-Formin; Prophage; Serformin†; Siamformet; ***Turk.***: Diaformin; Glifor; Glucophage; Gluformin; Glukofen; Matofin; ***UAE***: Dialon; ***UK***: Bolamyn; Glucophage; Metabet; Metsol; ***Ukr.***: Diaformin (Диаформин); Dianormet (Дианормет); Glucophage (Глюкофаж); Glycomet (Глікомет); Metfogamma (Метфогамма); Panfor (Панфор)†; Siofor (Сиофор); Tefor (Тефор)†; ***USA***: Fortamet; Glucophage; Glumetza; Riomet; ***Venez.***: Diaformina; Glafornil; Glucaminol; Glucofage.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Metformin Oral Solution; Metformin Tablets;
USP 36: Glipizide and Metformin Hydrochloride Tablets; Glyburide and Metformin Hydrochloride Tablets; Metformin Hydrochloride Extended-Release Tablets; Metformin Hydrochloride Tablets; Pioglitazone and Metformin Hydrochloride Tablets.

Miglitol *(BAN, USAN, pINN)*

Bay-m-1099; Miglitoli; Miglitolum; Миглитол.
(2*R*,3*R*,4*R*,5*S*)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol.
$C_8H_{17}NO_5$=207.2
CAS — 72432-03-2.
ATC — A10BF02.
ATC Vet — QA10BF02.
UNII — 0V5436JAQW.

Uses and Administration

Miglitol is an alpha-glucosidase inhibitor similar in action to acarbose (p. 466.3). It is given orally in the management of type 2 diabetes mellitus (p. 459.1), alone or with a sulfonylurea. Usual initial doses are 25 mg three times daily with meals, although a lower dose may be used to minimise gastrointestinal disturbances, starting at 25 mg once daily and gradually increasing to three times daily. After 4 to 8 weeks of a regimen of 25 mg three times daily, the dose may be increased to 50 mg three times daily, then adjusted after a further 3 months, if necessary. The maximum recommended dose of miglitol is 100 mg three times daily.

References.

1. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs* 2000; **59:** 521–49.
2. Aoki K, *et al*. Comparison of pre- vs. postmeal administration of miglitol for 3 months in type 2 diabetic patients. *Diabetes Obes Metab* 2008; **10:** 970–2.
3. Nemoto M, *et al*. Efficacy of combined use of miglitol in type 2 diabetes patients receiving insulin therapy-placebo-controlled double-blind comparative study. *Acta Diabetol* 2011; **48:** 15–20.

Adverse Effects and Precautions

As for alpha-glucosidase inhibitors in general (see Acarbose, p. 466.3 and p. 467.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies miglitol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for alpha-glucosidase inhibitors in general (see Acarbose, p. 467.1). Miglitol may reduce the bioavailability of propranolol and ranitidine.

Pharmacokinetics

Miglitol is completely absorbed at a dose of 25 mg, but only 50 to 70% of a 100 mg-dose is absorbed. It is not metabolised, and is excreted unchanged in the urine with a plasma elimination half-life of about 2 hours. Increased plasma concentrations of miglitol have been found in patients with renal impairment (creatinine clearance less than 25 mL/min), but the clinical significance of this effect is unknown. A small amount of miglitol is distributed into breast milk, and the estimated exposure to a breastfed infant is about 0.4% of the maternal dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Diastabol; ***China***: Diastabol (德赛天); Laiping (来平); ***Cz.***: Diastabol†; ***Fin.***: Diastabol†; ***Fr.***: Diastabol; ***Ger.***: Diastabol†; ***Gr.***: Diastabol; ***Hung.***: Diastabol; ***India***: Diamig; Elitox; Euglitol; Miglit; Mignar; Migset; Migtor; Minerva; Misobit; ***Irl.***: Diastabol†; ***Mex.***: Diastabol; ***Neth.***: Diastabol; ***Pol.***: Diastabol†; ***Port.***: Diastabol; Limarcan; ***Spain***: Diastabol; Plumarol; ***Switz.***: Diastabol†; ***USA***: Glyset.

Mitiglinide *(rINN)*

Mitiglinida; Mitiglinidum; Митиглинид.
(-)-(2*S*,3a*R*,7a-*cis*)-α-Benzylhexahydro-γ-oxo-2-isoindolinebutyric acid.
$C_{19}H_{25}NO_3$=315.4
CAS — 145375-43-5.
ATC — A10BX08.
ATC Vet — QA10BX08.
UNII — D86I0XLB13.

Mitiglinide Calcium *(rINNM)*

Calcii Mitiglinidum; KAD-1229; Mitiglinida cálcica; Mitiglinide Calcique; Mitiglinide Calcium Hydrate; S-21403; Кальций Митиглинид.

$C_{38}H_{48}CaN_2O_6,2H_2O$=704.9

CAS — 145525-41-3 (anhydrous mitiglinide calcium); 207844-01-7 (mitiglinide calcium).

ATC — A10BX08.

ATC Vet — QA10BX08.

UNII — 9651C21W3Z.

Profile

Mitiglinide is a meglitinide antidiabetic (see Repaglinide, p. 497.2) that is used in the treatment of type 2 diabetes mellitus (p. 459.1). Mitiglinide calcium is given in usual oral doses of 10 mg three time daily, immediately before meals.

References.

1. Yoshihara T, *et al.* Therapeutic efficacy of mitiglinide combined with once daily insulin glargine after switching from multiple daily insulin regimen of aspart insulin and glargine in patients with type 2 diabetes mellitus. *Endocr J* 2006; **53:** 67–72.
2. Kumashiro N, *et al.* Long-term effect of combination therapy with mitiglinide and once daily insulin glargine in patients who were successfully switched from intensive insulin therapy in short-term study. *Endocr J* 2007; **54:** 163–6.
3. Yamada S, *et al.* Effect of combination therapy of a rapid-acting insulin secretagogue (glinide) with premixed insulin in type 2 diabetes mellitus. *Intern Med* 2007; **46:** 1893–7.
4. Malaisse WJ. Mitiglinide: a rapid- and short-acting non-sulfonylurea insulinotropic agent for the treatment of type 2 diabetic patients. *Expert Opin Pharmacother* 2008; **9:** 2691–8.
5. Kaku K, *et al.* Effect of mitiglinide on glycemic control over 52 weeks in Japanese type 2 diabetic patients insufficiently controlled with pioglitazone monotherapy. *Endocr J* 2009; **56:** 739–46.
6. Gao X. Multicentre, double-blind, randomized study of mitiglinide compared with nateglinide in type 2 diabetes mellitus patients in China. *J Int Med Res* 2009; **37:** 812–21.
7. Abe M, *et al.* Efficacy and safety of mitiglinide in diabetic patients on maintenance hemodialysis. *Endocr J* 2010; **57:** 579–86.
8. Phillippe HM, Wargo KA. Mitiglinide: a novel agent for the treatment of type 2 diabetes mellitus. *Ann Pharmacother* 2010; **44:** 1615–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fa Ai Si (法艾斯); Fadi (法迪); Glufast (快如妥); ***Jpn***: Glufast; ***Thai.***: Glufast.

Multi-ingredient Preparations. *Jpn*: Glubes.

Nateglinide *(USAN, rINN)*

A-4166; AY-4166; DJN-608; Nateglinid; Nateglinida; Natéglinide; Nateglinidi; Nateglinidum; SDZ-DJN-608; Senaglinide; YM-026; Натеглинид.

(-)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl]-D-phenylalanine.

$C_{19}H_{27}NO_3$=317.4

CAS — 105816-04-4.

ATC — A10BX03.

ATC Vet — QA10BX03.

UNII — 41X3PWK4O2.

Pharmacopoeias. In *Eur.* see (p. vii) and *US.*

Ph. Eur. 8: (Nateglinide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane.

USP 36: (Nateglinide). A white powder. Practically insoluble in water; freely soluble in alcohol and methyl alcohol; soluble in ether; sparingly soluble in acetonitrile and octanol. Store in airtight containers.

Uses and Administration

Nateglinide, like repaglinide (p. 497.2), is a meglitinide antidiabetic used in the treatment of type 2 diabetes mellitus (p. 459.1). It is given within the 30 minutes before meals in oral doses of 60 or 120 mg three times daily. This may be increased to 180 mg three times daily if necessary. Nateglinide is also given in similar doses with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by these drugs alone.

Although dose adjustment is not generally required in renal impairment, serious hypoglycaemia has occurred in patients with chronic renal failure (see p. 494.2).

References.

1. Dunn CJ, Faulds D. Nateglinide. *Drugs* 2000; **60:** 607–15.
2. Hanefeld M, *et al.* Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 2000; **23:** 202–7.
3. Levien TL, *et al.* Nateglinide therapy for type 2 diabetes mellitus. *Ann Pharmacother* 2001; **35:** 1426–34.
4. Black C, *et al.* Meglitinide analogues for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 03/04/09).
5. Holman RR, *et al.* NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362:** 1463–76. Correction. *ibid.*; 1748.
6. Grunberger G. Quo vadis nateglinide? Ten-year perspective. *Expert Opin Pharmacother* 2011; **12:** 2097–2106.

Adverse Effects and Precautions

As for Repaglinide, p. 497.2.

Incidence of adverse effects. A postmarketing cohort study collected adverse effect data for the first 6 months after starting nateglinide in 4557 patients.[1] Of these, 336 (7.4%) used nateglinide alone, but the majority (76%) were treated with nateglinide plus metformin. There were 80 adverse event reports attributed to nateglinide. Gastrointestinal disturbances were most common, particularly diarrhoea. There were 4 reports of hypersensitivity reactions, presenting as pruritus or rash. Of the 45 reports of hypoglycaemia involving nateglinide, 5 patients were on monotherapy, while the rest were also taking other antidiabetics. Isolated reports that were assessed as probably related to nateglinide included palpitations, Raynaud's phenomenon, and oedema and fluid retention.

1. Twaites B, *et al.* Safety of nateglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2007; **44:** 233–9.

Overdosage. A blood-glucose concentration of 2.0 mmol/litre was measured 1 hour after ingestion of nateglinide 3.42 g in a 30-year-old woman.[1] She was able to walk unaided, but seemed drowsy. The hypoglycaemic effect of nateglinide lasted for 6 hours and was treated with intravenous glucose (total dose 100 g).

1. Nakayama S, *et al.* Hypoglycemia following a nateglinide overdose in a suicide attempt. *Diabetes Care* 2005; **28:** 227–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nateglinide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Insulin is generally preferred to oral antidiabetics in the treatment of diabetes mellitus during pregnancy. An analysis of postmarketing data found 2 reports of nateglinide use during pregnancy.[1] In both cases the drug was given in the first trimester only, with metformin. One pregnancy resulted in a live birth with no reported congenital abnormalities. In the other, nateglinide was stopped 3 months after the last menstrual period and replaced with metformin for the rest of the pregnancy; the baby was reported to have polycystic kidneys.

1. Twaites B, *et al.* Safety of nateglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2007; **44:** 233–9.

Renal impairment. A single-dose pharmacokinetic study[1] found that moderate to severe renal impairment (creatinine clearance 15 to 50 mL/minute per 1.73 m^2) and haemodialysis did not significantly affect the pharmacokinetics of nateglinide. However, the metabolite M1 has been found to accumulate after repeated doses of nateglinide in patients with renal impairment requiring haemodialysis, although haemodialysis removes it.[2] M1 is a major metabolite that has modest hypoglycaemic activity compared with nateglinide. An analysis[3] of pooled study data found that efficacy and tolerability of nateglinide in elderly diabetic patients were not significantly affected by renal impairment (mean creatinine clearance 50.9 mL/minute per 1.73 m^2). Nevertheless, a 56-year-old diabetic woman whose renal failure was managed with haemodialysis developed severe hypoglycaemia with nateglinide; the reaction was attributed to the accumulation of M1.[4] Severe hypoglycaemia, attributed to therapeutic doses of nateglinide, also occurred in a 73-year-old diabetic woman with chronic renal failure managed with haemodialysis.[5] In this case, octreotide (100 micrograms subcutaneously) was given as well as parenteral glucose treatment. Licensed product information in the UK and USA suggest that no dosage adjustment is necessary in renal impairment, although UK information suggests that dose adjustment might be required in patients on haemodialysis.

1. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
2. Inoue T, *et al.* Pharmacokinetics of nateglinide and its metabolites in subjects with type 2 diabetes mellitus and renal failure. *Clin Nephrol* 2003; **60:** 90–5.
3. Del Prato S, *et al.* Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care* 2003; **26:** 2075–80.
4. Nagai T, *et al.* Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. *Diabetes Res Clin Pract* 2003; **59:** 191–4.
5. Sherk DK, Bryant SM. Octreotide therapy for nateglinide-induced hypoglycemia. *Ann Emerg Med* 2007; **50:** 745–6.

Interactions

The efficacy of nateglinide may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Reviews.

1. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. *Rifampicin* reduced the plasma concentrations and half-life of nateglinide in healthy subjects, probably by induction of the cytochrome P450 isoenzyme CYP2C9.[1] The glucose-lowering effect of nateglinide was not affected, but there was a marked interindividual variation in the pharmacokinetic changes, and the authors suggested that some diabetic patients could be affected.

1. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of nateglinide in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 427–32.

Antifungals. *Fluconazole* raised the plasma concentrations and prolonged the half-life of nateglinide in healthy subjects, probably by inhibition of its metabolism by the cytochrome P450 isoenzyme CYP2C9.[1] The glucose-lowering effect of nateglinide was not affected, but a low dose of nateglinide had been used and the authors suggested that in diabetic patients fluconazole may enhance and prolong the effects of nateglinide.

1. Niemi M, *et al.* Effect of fluconazole on the pharmacokinetics and pharmacodynamics of nateglinide. *Clin Pharmacol Ther* 2003; **74:** 25–31.

Lipid regulating drugs. A study[1] investigating the effects of the *gemfibrozil* and *itraconazole* combination on the pharmacokinetics of nateglinide showed only a limited interaction. Nateglinide plasma concentrations were raised moderately and the blood glucose response to nateglinide was not significantly changed. This is in contrast to the substantial interaction of gemfibrozil with repaglinide (p. 498.2).

1. Niemi M, *et al.* Coadministration of gemfibrozil and itraconazole has only a minor effect on the pharmacokinetics of the CYP2C9 and CYP3A4 substrate nateglinide. *Br J Clin Pharmacol* 2005; **60:** 208–17.

Pharmacokinetics

Nateglinide is rapidly absorbed after oral doses and peak plasma concentrations occur within one hour. It has an absolute bioavailability of 73% and is 98% bound to plasma proteins. Nateglinide is mainly metabolised by cytochrome P450 isoenzyme CYP2C9, and to a lesser extent by CYP3A4. The major metabolites are less potent than nateglinide. The parent drug and metabolites are mainly excreted in the urine but about 10% is eliminated in the faeces. The elimination half-life is about 1.5 hours.

References.

1. Choudhury S, *et al.* Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 2000; **40:** 634–40.
2. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
3. McLeod JF. Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. *Clin Pharmacokinet* 2004; **43:** 97–120.
4. Kirchheiner J, *et al.* Influence of CYP2C9 and CYP2D6 polymorphisms on the pharmacokinetics of nateglinide in genotyped healthy volunteers. *Clin Pharmacokinet* 2004; **43:** 267–78.
5. Zhang W, *et al.* Effect of SLCO1B1 genetic polymorphism on the pharmacokinetics of nateglinide. *Br J Clin Pharmacol* 2006; **62:** 567–72.
6. Kalliokoski A, *et al.* Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol* 2008; **48:** 311–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nateglin†; Starlix; ***Braz.***: Starlix; ***Canad.***: Starlix; ***Chile***: Gluconol; Starlix; ***China***: Antangping (安唐平); Bei Jia (贝加); Cankexin (参可欣); ChangTai (常泰); Danping (丹平); Di Fang (迪方); Fei Ge Na (菲戈纳); Fu Ge Qing (芙格清); Kai Shu (凯舒); Ke Bin (可宾); La Mu (拉姆); Luoyu (罗愉); Qi Fu (齐复); Starlix (唐力); Tang Ling (唐苓); Tang Na (唐那); Tang Rui (唐瑞); Tang Yi (唐易); Wan Su Xin (万苏欣); Xi Rui (锡瑞); Ya Li Ding (亚立订); Yi Ke Xian (逸可仙); Yi Ke Ya Xin (易克亚欣); Yi You Li An (易优利安); ***Cz.***: Starlix; Trazec†; ***Fin.***: Starlix†; ***Ger.***: Starlix; ***Gr.***: Starlix; ***Hung.***: Starlix; ***India***: Glinate-MF; Glinate; Natelide; ***Indon.***: Starlix; ***Irl.***: Starlix; ***Jpn***: Starsis; ***Malaysia***: Starlix; ***Mex.***: Starlix; ***Neth.***: Starlix; ***Norw.***: Starlix; ***Philipp.***: Starlix; ***Pol.***: Starlix; ***Port.***: Starlix; ***Rus.***: Starlix (Старликс); ***S.Afr.***: Starlix; ***Singapore***: Starlix; ***Spain***: Starlix; ***Swed.***: Starlix; ***Switz.***: Starlix; ***Turk.***: Incuria; Mecosyn; Starlix; Teglix; ***UK***: Starlix; ***USA***: Starlix; ***Venez.***: Starlix.

Multi-ingredient Preparations. ***Braz.***: Starform; ***Venez.***: Starform.

Pharmacopoeial Preparations

USP 36: Nateglinide Tablets.

All cross-references refer to entries in Volume A

Phenformin Hydrochloride *(BANM, pINNM)*

Fenformin-Hidroklorid; Fenformina Cloridrato; Fenformina, hidrocloruro de; Hidrocloruro de fenformina; Phenformine, Chlorhydrate de; Phenformini Hydrochloridum; Фенформина Гидрохлорид.

1-Phenethylbiguanide hydrochloride.

$C_{10}H_{15}N_5$,HCl=241.7

CAS — 114-86-3 (phenformin); 834-28-6 (phenformin hydrochloride).

ATC — A10BA01.

ATC Vet — QA10BA01.

UNII — 91XC93EU03.

Pharmacopoeias. In *Chin.*

Profile

Phenformin hydrochloride is a biguanide antidiabetic (p. 467.3). Although it is generally considered to be associated with an unacceptably high incidence of lactic acidosis, often fatal, it is still available in some countries for the treatment of type 2 diabetes mellitus.

Phenformin was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p. 503.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Informin; ***India***: DBI.

Multi-ingredient Preparations. ***Gr.***: Daopar; ***India***: Chlorformin; ***Ital.***: Bidiabe; Gliben F; ***Mex.***: Glinorboral.

Pioglitazone Hydrochloride

(BANM, USAN, rINNM)

AD-4833 (pioglitazone); Hidrocloruro de pioglitazona; Pioglitazona, hidrocloruro de; Pioglitazone, Chlorhydrate de; Pioglitazoni Hydrochloridum; U-72107A; U-72107E (pioglitazone); Пиоглитазона Гидрохлорид.

(±)-5-{*p*-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione hydrochloride.

$C_{19}H_{20}N_2O_3S$,HCl=392.9

CAS — 111025-46-8 (pioglitazone); 112529-15-4 (pioglitazone hydrochloride).

ATC — A10BG03.

ATC Vet — QA10BG03.

UNII — JQT35NPK6C.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pioglitazone Hydrochloride). White or almost white crystals or crystalline powder. Practically insoluble in water; slightly soluble to soluble in methyl alcohol; very slightly soluble in dichloromethane.

USP 36: (Pioglitazone Hydrochloride). White crystals or crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone and in acetonitrile; insoluble in ether; soluble in dimethylformamide.

Uses and Administration

Pioglitazone is a thiazolidinedione antidiabetic with actions similar to those of rosiglitazone (p. 498.3). It is used in the management of type 2 diabetes mellitus (p. 459.1). It is given as pioglitazone hydrochloride but doses are expressed in terms of the base; pioglitazone hydrochloride 1.1 mg is equivalent to about 1 mg of pioglitazone. It is given orally as monotherapy, particularly in patients who are overweight and for whom metformin is contra-indicated or not tolerated. Pioglitazone may also be added to metformin or a sulfonylurea or both, or to insulin, when such therapy is inadequate (but see Administration, p. 495.1). The usual dose is 15 or 30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary. Pioglitazone may be taken with or without food.

References.

1. Waugh J, *et al.* Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2006; **66:** 85–109. Correction. *ibid.*: 340–1.
2. Richter B, *et al.* Pioglitazone for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/03/07).
3. Deeks ED, Scott LJ. Pioglitazone/metformin. *Drugs* 2006; **66:** 1863–77.
4. Derosa G. Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus: comparison with other oral antihyperglycaemic agents. *Drugs* 2010; **70:** 1945–61.

Administration. Although pioglitazone is licensed for use with other antidiabetic drugs, the specifics of licensing and use may vary from country to country. In both the UK and USA, pioglitazone (*Actos; Takeda*) is licensed for monotherapy, and for use with metformin or a sulfonylurea when single agent therapy is inadequate. In the UK, pioglitazone may also be used with both if necessary. However, UK[1] and combined European/US guidelines[2] do not endorse the use of thiazolidinedione monotherapy. In the UK, NICE only recommends dual therapy that includes a thiazolidinedione in patients who cannot be given a combination of metformin plus a sulfonylurea (because of drug intolerance or contra-indication, or where the risk or consequences of hypoglycaemia would be unacceptable). NICE also suggests that a thiazolidinedione only be added to metformin plus a sulfonylurea if insulin is likely to be unacceptable or inappropriate.[1] The European/US guidelines suggest that pioglitazone may be considered for addition to metformin, or metformin plus a sulfonylurea, only when hypoglycaemia is particularly undesirable.[2]

The addition of pioglitazone to insulin is licensed for use in the USA, and in the UK when the addition of metformin is inappropriate. However, there is an associated increased risk of fluid retention and heart failure for which patients should be monitored (see also Effects on the Heart, under Rosiglitazone, p. 500.2). The European/US guidelines[2] do not include a combination of thiazolidinedione with insulin, and NICE[1] only recommends pioglitazone with insulin when a thiazolidinedione has previously had a marked glucose-lowering effect, or when blood glucose is not adequately controlled on high-dose insulin therapy.

1. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes: partial update (issued March 2010). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 11/10/11)
2. Nathan DM, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32:** 193–203.

Diabetic complications. It has been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications (p. 462.2). Studies[1,2] in patients with type 2 diabetes mellitus have shown that pioglitazone may slow the progression of carotid intima-media thickness, an indicator for cardiovascular risk. It may also slow the progression of coronary atherosclerosis in patients with coronary artery disease.[3] The PROactive study[4] of secondary prevention found that, compared with placebo (in addition to usual medications for glucose control), pioglitazone reduced the secondary composite endpoint of death from any cause, myocardial infarction, and stroke. There was also a reduced need to add insulin for glucose control. However, there was no significant difference between the groups for the broader primary endpoint that also included acute coronary syndrome, leg amputation, and coronary or leg revascularisation. Subgroup analysis[5] also found that pioglitazone reduced the risk of fatal and non-fatal myocardial infarction and acute coronary syndrome in patients with a history of myocardial infarction. There was also a suggestion that pioglitazone reduced the risk of recurrent stroke, but there was no effect on first strokes.[6] It was unclear, however, whether this apparent effect of pioglitazone was applicable to all types of stroke, as data on stroke pathology were not available. A meta-analysis[7] that included the results of PROactive with cardiovascular outcome data from studies of glycaemic control found that pioglitazone significantly reduced the risk of death, myocardial infarction, and stroke in a diverse population of patients with type 2 diabetes. However, the risk of serious heart failure was increased (see also Effects on the Heart, p. 500.2).

It is unclear whether other thiazolidinediones might have similar effects and whether patients at lower risk might benefit.[8] Rosiglitazone and pioglitazone are known to have different effects on lipids (p. 496.1) and there is evidence that rosiglitazone may have adverse cardiovascular effects (p. 499.3).

1. Langenfeld MR, *et al.* Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation* 2005; **111:** 2525–31.
2. Mazzone T, *et al.* Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296:** 2572–81.
3. Nissen SE, *et al.* PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008; **299:** 1561–73.
4. Dormandy JA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366:** 1279–89.
5. Erdmann E, *et al.* The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007; **49:** 1772–80.
6. Wilcox R, *et al.* PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007; **38:** 865–73.
7. Lincoff AM, *et al.* Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298:** 1180–8.
8. Rizza R, *et al.* Commentary on the results and clinical implications of the PROactive study. *Diabetes Care* 2005; **28:** 2965–7.

Liver disorders. Small studies using pioglitazone in patients with nonalcoholic steatohepatitis have reported improvements in insulin sensitivity, liver function, and histology.[1-4] However, weight gain was common[1-4] and benefits were not maintained after treatment was stopped.[4,5]

1. Promrat K, *et al.* A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 2004; **39:** 188–96.
2. Belfort R, *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; **355:** 2297–2307.
3. Aithal GP, *et al.* Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008; **135:** 1176–84.
4. Sanyal AJ, *et al.* Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362:** 1675–85.
5. Lutchman G, *et al.* The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. *Hepatology* 2007; **46:** 424–9.

Malignant neoplasms. For references to the experimental use of pioglitazone with rofecoxib and trofosfamide as anti-angiogenic therapy for malignant neoplasms see Trofosfamide, p. 878.1.

Psoriasis. It has been suggested that by binding to peroxisome proliferator-activated receptor gamma (PPARγ), pioglitazone may have an anti-inflammatory effect in conditions such as chronic plaque psoriasis (p. 1688.1) and psoriatic arthritis (see Spondyloarthropathies, p. 14.3). In a small open-label study,[1] oral doses of 30 mg daily were reported to improve moderate chronic plaque psoriasis in 4 of 5 patients, with definite improvement seen 1 to 3 months after starting therapy. Treatment was stopped in 1 other patient because of fluid retention. In a double-blind study,[2] 70 patients with moderate to severe disease were treated for 10 weeks with daily doses of pioglitazone 15 mg, 30 mg, or placebo. Greater improvements were reported with pioglitazone than with placebo, and the dose of 30 mg appeared to be slightly more effective than 15 mg. A 12-week randomised placebo-controlled study[3] in 41 patients also with moderate to severe disease found that those who were given pioglitazone 15 mg daily plus acitretin 25 mg daily showed more improvement than patients given acitretin plus placebo. There has also been a report[4] of improvements in tender and swollen joints in a small group of patients with psoriatic arthritis who were given a high dose of pioglitazone (30 mg twice daily) for 12 weeks. Fluid retention was reported.

The effect of rosiglitazone has also been studied in moderate to severe chronic plaque psoriasis. Two large studies that included more than 2500 patients found that rosiglitazone, in oral doses of 2 mg, 4 mg, or 8 mg daily, was no more effective than placebo over a treatment period of 12 months. Similar results were also found in patients who continued in 44-week blinded extension studies. Interestingly, improvement occurred in all groups, and there was evidence of a large placebo response.[5]

1. Robertshaw H, Friedmann PS. Pioglitazone: a promising therapy for psoriasis. *Br J Dermatol* 2005; **152:** 189–91.
2. Shafiq N, *et al.* Pilot trial: pioglitazone versus placebo in patients with plaque psoriasis (the P6). *Int J Dermatol* 2005; **44:** 328–33.
3. Mittal R, *et al.* Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *Arch Dermatol* 2009; **145:** 387–93.
4. Bongartz T, *et al.* Treatment of active psoriatic arthritis with the PPAR γ ligand pioglitazone: an open-label pilot study. *Rheumatology (Oxford)* 2005; **44:** 126–9.
5. Ellis CN, *et al.* Avandia Psoriasis Study Group. Placebo response in two long-term randomized psoriasis studies that were negative for rosiglitazone. *Am J Clin Dermatol* 2007; **8:** 93–102.

Reperfusion and revascularisation procedures. Thiazolidinediones are under investigation in the prevention of restenosis after percutaneous coronary revascularisation procedures—see under Rosiglitazone, p. 499.2.

Adverse Effects and Precautions

As for Rosiglitazone, p. 499.2. The effects of pioglitazone on serum lipid concentrations appear to differ from those of rosiglitazone, see p. 496.1. Other adverse effects reported include upper respiratory-tract infections, haematuria, and visual disturbances. For precautions and contra-indications to the use of thiazolidinediones in heart failure see Effects on the Heart, under Rosiglitazone, p. 500.2. Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see p. 496.2).

An increased risk of bladder cancer has been reported for pioglitazone (see p. 496.1).

Incidence of adverse effects. The placebo-controlled PROactive study[1] of pioglitazone for secondary prevention of cardiovascular events in patients with type 2 diabetes recorded oedema in 26.4% of 2605 patients given pioglitazone, compared with 15.1% in 2633 given placebo; heart failure occurred in 10.8% and 7.5%, respectively, but rates of death from heart failure were similar for the 2 groups. The study also found an increased rate of fracture

in women given pioglitazone. Average weight gain was 3.8 kg (after 30 months or at the final visit) compared with a loss of 0.6 kg for placebo. Hypoglycaemia occurred in 27.2% of patients treated with pioglitazone, compared with 18.8% in the placebo group, but was highly dependent on the use of other antidiabetic drugs, particularly insulin and sulfonylureas.

A study of postmarketing events used data from more than 12 000 patients started on pioglitazone treatment, almost all of whom were also taking at least one other oral antidiabetic.[2] The suspected adverse effects most commonly attributed to pioglitazone were malaise or lassitude, nausea or vomiting, dizziness, headache, diarrhoea, oedema, visual disturbances, joint pain, and weight gain.

1. Dormandy J, *et al*. PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Safety* 2009; **32:** 187–202.
2. Kasliwal R, *et al*. Monitoring the safety of pioglitazone: results of a prescription-event monitoring study of 12 772 patients in England. *Drug Safety* 2008; **31:** 839–50.

Carcinogenicity. An interim report of a longitudinal cohort study[1] concluded that pioglitazone use for more than 2 years was weakly associated with an increased risk of bladder cancer. This prompted the FDA to recommend that pioglitazone should not be used in patients with active bladder cancer, and used with caution in those with a history of the disease.[2] However, based on this and other epidemiological studies, the EMEA concluded that pioglitazone should be avoided in patients with either a history of bladder cancer or current disease.[3]

1. Lewis JD, *et al*. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011; **34:** 916–22.
2. FDA. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer (issued 15th June, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm (accessed 01/08/11)
3. EMEA. European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer: benefit-risk balance remains positive in a limited population of type 2 diabetics (issued 21st July, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf (accessed 01/08/11)

Effects on lipids. Thiazolidinediones are reported to affect serum concentrations of lipids. Compared with placebo in short-term studies,[1,2] pioglitazone has been found to reduce triglycerides, increase high-density lipoprotein (HDL)-cholesterol, and have little or no effect on low-density lipoprotein (LDL)- and total cholesterol. Pooled data from 4 studies of pioglitazone given for a year, used alone or with metformin or a sulfonylurea, also found that pioglitazone reduced triglycerides and increased HDL-cholesterol.[3] There were also reductions in free fatty acid concentrations and in the ratio of total to HDL-cholesterol.

In studies of patients transferred from troglitazone to another thiazolidinedione, lipid profiles have improved in those given pioglitazone,[4,5] but significant increases in total and LDL-cholesterol, and triglycerides, have occurred in some patients transferred to rosiglitazone.[4] A controlled study[6] in more than 800 patients with type 2 diabetes and dyslipidaemia has also directly compared the effects of two thiazolidinediones, finding again a more desirable response to pioglitazone than to rosiglitazone. Triglycerides significantly decreased with pioglitazone but increased with rosiglitazone, greater rises in HDL-cholesterol occurred with pioglitazone than rosiglitazone, and although both increased LDL-cholesterol the effect was less significant with pioglitazone.[6] The study also found that these drugs had different effects on lipoprotein particle concentrations and size.[6,7]

Whether these effects of pioglitazone reduce cardiovascular risk in patients with type 2 diabetes is yet to be fully established, but the large prospective PROactive study did suggest that it could reduce the risk of macrovascular events in patients with evidence of macrovascular disease, although the risk of heart failure appears to be *increased* (see Diabetic Complications, p. 493.2, and Effects on the Heart, under Rosiglitazone, p. 500.2).

1. Kipnes MS, *et al*. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med* 2001; **111:** 10–17.
2. Rosenblatt S, *et al*. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis* 2001; **12:** 413–23.
3. Khan M, *et al*. Effects of pioglitazone on the components of diabetic dyslipidaemia: results of double-blind, multicentre, randomised studies. *Int J Clin Pract* 2004; **58:** 907–12.
4. Gegick CG, Altheimer MD. Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 2001; **7:** 162–9.
5. Khan MA, *et al*. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 2002; **25:** 708–11.
6. Goldberg RB, *et al*. GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; **28:** 1547–54.
7. Deeg MA, *et al*. GLAI Study Investigators. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2007; **30:** 2458–64.

Effects on the liver. There have been isolated reports of hepatocellular injury including fatalities, in patients receiving pioglitazone.[1-6] However, retrospective analysis of a medical and pharmacy claims database found no evidence of an increased risk of liver failure or hepatitis for pioglitazone, compared with rosiglitazone, sulfonylureas, or metformin.[7] Additionally, a 3-year randomised study of liver safety in type 2 diabetics using pioglitazone[8] showed no serious drug-induced liver injury.

UK and US licensed product information recommends that liver enzymes should be checked before starting therapy with pioglitazone; patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given pioglitazone. ALT concentrations should then be monitored periodically during treatment. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with pioglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. *Ann Intern Med* 2001; **135:** 306.
2. May LD, *et al*. Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; **136:** 449–52.
3. Pinto AG, *et al*. Severe but reversible cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; **137:** 857.
4. Chase MP, Yarze JC. Pioglitazone-associated fulminant hepatic failure. *Am J Gastroenterol* 2002; **97:** 502–3.
5. Farley-Hills E, *et al*. Fatal liver failure associated with pioglitazone. *BMJ* 2004; **329:** 429.
6. Floyd JS, *et al*. Case series of liver failure associated with rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Safety* 2009; **18:** 1238–43.
7. Rajagopalan R, *et al*. Comparison of pioglitazone with other antidiabetic drugs for associated incidence of liver failure: no evidence of increased risk ofliver failure with pioglitazone. *Diabetes Obes Metab* 2005; **7:** 161–9.
8. Tolman KG, *et al*. Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. *Drug Safety* 2009; **32:** 787–800.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pioglitazone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Pioglitazone is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP2C8. When given with gemfibrozil, an inhibitor of CYP2C8, there may be a threefold increase in the AUC of pioglitazone; a decrease in pioglitazone dose may be needed if it is given with gemfibrozil or similar CYP2C8 inhibitors. Conversely, rifampicin, a potent inducer of cytochrome P450, halves the AUC of pioglitazone when both are given, and the pioglitazone dose may need to be increased.

Use of insulin with pioglitazone may increase the risk of oedema and heart failure (see also Effects on the Heart, under Rosiglitazone, p. 500.2, and Administration, p. 493.1).

Antibacterials. See under Rosiglitazone, p. 501.1, for a reference to the interaction between pioglitazone and *rifampicin*. For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving oral hypoglycaemics including pioglitazone, see p. 304.1.

Lipid regulating drugs. For references to the interaction between pioglitazone and *gemfibrozil*, see under Rosiglitazone, p. 501.1.

Pharmacokinetics

Pioglitazone is rapidly absorbed after oral doses. Peak plasma concentrations occur within 2 hours and bioavailability exceeds 80%. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP2C8 to both active and inactive metabolites. It is excreted in urine and faeces and has a plasma half-life of up to 7 hours. The active metabolites have a half-life of up to 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actos; Cereluc; Higlucem; Miglen; Pioglit; Piotamax; Zatium; ***Austral.***: Acpio; Actos; Vexazone; ***Austria***: Actos; ***Belg.***: Actos; ***Braz.***: Actos; Aglitil; Piotaz; ***Canad.***: Actos; ***Chile***: Actos; Tiazac; Zatium; ***China***: ActIns (艾汀); Actos (艾可拓); An Ke Tuo (安可妥); An Long Ping (安龙平); Beitangning (贝唐宁); Dun Ling (顿灵); Jia Pu Xi (佳普喜); Jiang Shuang (绛爽); Kai Bao Wei Yuan (凯宝维元); Kasiping (卡司平); Kecheng (可成); Lie Luo (列洛); Ou Di Bei (欧迪贝); Qian Er (倩尔); Rui Ge Lin (瑞格临); Rui Tong (瑞彤); Tai Luo Ping (泰洛平); Wan Su Min (万苏敏); Wei Yuan (维元); Yi You (夷友); ***Cz.***: Actos; Glustin; ***Denm.***: Actos; ***Fin.***: Actos; ***Fr.***: Actos†; ***Ger.***: Actos; ***Gr.***: Actos; ***Hong Kong***: Actos; ***Hung.***: Actos; ***India***: Betapride; Depel; Diaglit; Diavista; G-Tase; Glita; Glito; Glitter; Glizone; Glufit; K-Pio; Lita; Logit; Oglo; Opam; P-Glitz; Pepar; Piomed; Piosafe; Piozulin; ***Indon.***: Actos; Deculin; Pionix-M; Pionix; ***Irl.***: Actos; Glustin; ***Ital.***: Actos; ***Jpn***: Actos; ***Malaysia***: Actos; ***Mex.***: Zactos; ***Neth.***: Actos; Glustin; Paglitaz; Sepioglin†; Sympion; ***Norw.***: Actos; ***NZ***: Actos; Pizaccord; ***Philipp.***: Actos; Diabetone; Glitaz; Glitter; Glizone; Glucozone; Insulact; Piotaz; Piouno; Piozar; Piozone; Ppar; Prialta; Pyoglit; Zolid; Zypi; ***Pol.***: Actos; Glustin; ***Port.***: Actos; Glustin; ***Rus.***: Actos (Актос); Amalvia (Амальвия); Astrozone (Астрозон); Diab-Norm (Диаб-Норм); Diaglitazon (Диаглитазон); Pioglar (Пиоглар); Pioglit (Пиоглит); ***S.Afr.***: Actos; ***Singapore***: Actos; ***Spain***: Actos; Glustin; ***Swed.***: Actos; ***Switz.***: Actos; ***Thai.***: Actos; Gitazone; Glubosil; Piozone; Senzulin; Utmos; ***Turk.***: Actos; Dropia; Glifix; Pioforce; Piogtan; Piondia; ***UK***: Actos; Glidipion; ***Ukr.***: Nilgar (Нилгар)†; Pioglar (Пиоглар); Pioz (Пиоз); ***USA***: Actos; ***Venez.***: Actos.

Multi-ingredient Preparations. ***Austria***: Competact; Tandemact; ***Chile***: Actos Met; ***China***: Furuitong (复瑞彤); ***Cz.***: Competact; Glubrava; Tandemact; ***Fr.***: Competact†; Tandemact†; ***Ger.***: Competact; Tandemact; ***Gr.***: Competact; ***Hong Kong***: Actosmet; ***Hung.***: Competact; ***India***: Adride-P; Bigan-P; Cetapin P; Daoride-PM; Diamet PG; Dianosis-P3; Diavista-M; Diazero-PM; Dibiglim-P; Euglim-MP; Euglim-P; Euroglip Forte; Exermet P; G-Tase G; G-Tase M; Gemer P; Gimip-PM; Gitar; Glamor-P; Glamor-PM; Glimestar PM; Glimizide-PG; Glimsite-MP; Glimy-MP; Glimy-P; Glita-M; Glitafor; Glitter-M; Glizone-M; GLP-PM; Gluconorm-P; Glucut-GMP; Glyciphage PG; Glyciphage-P; GPM; Idapride-PM; Ioglime; Iscept-P; K-Pio-G; K-Pio-M; Lita-M; Matce-P; Matce-PG; Metanorm P; Metride Plus; Mopaday; One Dia; P&M; P-Glitz M; Piomed M; Piosafe MF; ***Irl.***: Competact; Glubrava; Tandemact; ***Ital.***: Competact; Tandemact; ***Jpn***: Liovel; Sonias; ***Mex.***: Competact; Diabamet; ***Neth.***: Competact; Glubrava; Tandemact; ***Norw.***: Competact; ***Philipp.***: Actosmet; Asenza Plus; Prialta-Met; ***Pol.***: Competact; Glubrava; Tandemact; ***Port.***: Competact; Glubrava; Tandemact; ***Spain***: Competact; Glubrava; Tandemact; ***Swed.***: Competact; ***Switz.***: Competact; ***Thai.***: Actosmet; ***Turk.***: Dropia-Met; Preko; ***UK***: Competact; ***Ukr.***: Tripride (Трипрайд); ***USA***: Actoplus Met; Duetact; Oseni.

Pharmacopoeial Preparations

USP 36: Pioglitazone and Glimepiride Tablets; Pioglitazone and Metformin Hydrochloride Tablets; Pioglitazone Tablets.

Pramlintide *(BAN, USAN, rINN)*

AC-0137 (pramlintide or pramlintide acetate); AC-137; Pramlintida; Pramlintidum; Pramlintyd; Tripro-amylin; Прамлинтид.

$C_{171}H_{267}N_{51}O_{53}S_2$=3949.4

CAS — 151126-32-8.

ATC — A10BX05.

ATC Vet — QA10BX05.

UNII — D3FM8FA78T.

Pramlintide Acetate *(BANM, USAN, rINNM)*

AC-0137 (pramlintide or pramlintide acetate); Acetato de pramlintida; Pramlintide, Acétate de; Pramlintidi Acetas; Прамлинтида Ацетат.

25-L-Proline-28-L-proline-29-L-prolineamylin (human) acetate hydrate.

$C_{171}H_{267}N_{51}O_{53}S_2$, $xC_2H_4O_2$, yH_2O

CAS — 196078-30-5.

ATC — A10BX05.

ATC Vet — QA10BX05.

UNII — 726I6TE06G.

Incompatibility. The possible effect of mixing pramlintide with insulin (regular or isophane) in the same syringe has been studied.[1] Patients with type 1 diabetes were given the study treatments, either separately or as a combination mixed within 5 minutes before injection, on single occasions in a crossover study. Although there were minor changes in the pharmacokinetics of pramlintide, they were considered to be clinically insignificant. However, the authors cautioned that the study did not cover the full range of insulin formulations available, the long-term use of such combinations, or the range of doses used in clinical practice. Licensed product information for pramlintide warns that it should not be mixed in the same syringe with insulin because of reported changes in the pharmacokinetic parameters of pramlintide.

1. Weyer C, *et al*. Properties of pramlintide and insulin upon mixing. *Am J Health-Syst Pharm* 2005; **62:** 816–22.

Uses and Administration

Pramlintide is a synthetic analogue of amylin, a pancreatic peptide hormone thought to play a role in the regulation of glucose homoeostasis. It differs from amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine). Pramlintide slows the rate of gastric emptying,

prevents the postprandial rise in glucagon concentrations, and reduces appetite. It is used in the management of diabetes mellitus (p. 459.1) that is not adequately controlled by mealtime insulin therapy. Pramlintide is given as the acetate, but doses are expressed in terms of the base.

In patients with type 1 diabetes mellitus, an initial dose of pramlintide 15 micrograms is given subcutaneously immediately before major meals. The dose of any rapid-acting or short-acting insulins, including premixed insulins, given before meals should be halved. The pramlintide dose may be increased in increments of 15 micrograms to a maintenance dose of 30 or 60 micrograms when no clinically significant nausea has occurred for at least 3 days. Once the maintenance dose of pramlintide has been achieved, the dose of insulin should be further adjusted for optimum glycaemic control.

In patients with type 2 diabetes mellitus who are using insulin, the initial dose of pramlintide is 60 micrograms, subcutaneously, immediately before major meals. The dose may be increased to 120 micrograms when no nausea has occurred for 3 to 7 days. The dose of insulin therapy should be adjusted as described for patients with type 1 diabetes mellitus (above).

References.

1. Hollander PA, *et al.* Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003; **26:** 784–90.
2. Kruger DF, Gloster MA. Pramlintide for the treatment of insulin-requiring diabetes mellitus: rationale and review of clinical data. *Drugs* 2004; **64:** 1419–32.
3. Ratner RE, *et al.* Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004; **21:** 1204–12.
4. Riddle M, *et al.* Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes Care* 2007; **30:** 2794–9.
5. Singh-Franco D, *et al.* Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther* 2007; **29:** 535–62.
6. Ryan G, *et al.* Review of pramlintide as adjunctive therapy in treatment of type 1 and type 2 diabetes. *Drug Des Devel Ther* 2009; **2:** 203–14.
7. Pencek R, *et al.* Safety of pramlintide added to mealtime insulin in patients with type 1 or type 2 diabetes: a large observational study. *Diabetes Obes Metab* 2010; **12:** 548–51.
8. Lee NJ, *et al.* Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. *Ann Fam Med* 2010; **8:** 542–9.
9. Singh-Franco D, *et al.* The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2011; **13:** 169–80.
10. Younk LM, *et al.* Pramlintide and the treatment of diabetes: a review of the data since its introduction. *Expert Opin Pharmacother* 2011; **12:** 1439–51.

Obesity. Pramlintide is under investigation in the management of obesity[1-4] (p. 2315.1).

1. Smith SR, *et al.* Pramlintide treatment reduces 24-h caloric intake and meal sizes and improves control of eating in obese subjects: a 6-wk translational research study. *Am J Physiol Endocrinol Metab* 2007; **293:** E620–E627.
2. Smith SR, *et al.* Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008; **31:** 1816–23.
3. Dunican KC, *et al.* The role of pramlintide for weight loss. *Ann Pharmacother* 2010; **44:** 538–45.
4. Singh-Franco D, *et al.* The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2011; **13:** 169–80.

Adverse Effects and Precautions

Pramlintide alone does not cause hypoglycaemia, but increases the risk associated with insulin use, particularly in type 1 diabetes mellitus; severe hypoglycaemia may occur within 3 hours of pramlintide injection. Blood-glucose concentrations must be closely monitored, both before and after meals, and the dose of insulin should be halved when pramlintide therapy is started (see Uses and Administration, p. 494.3).

Other adverse effects of pramlintide include nausea, vomiting, anorexia, headache, reactions at the injection site, and hypersensitivity. Nausea commonly occurs at the beginning of therapy and decreases with time; incidence and severity are reduced if pramlintide is gradually titrated to the maintenance dose. Pramlintide is contra-indicated in patients with gastroparesis.

Interactions

Pramlintide has the potential to delay the absorption of oral medication; in cases where the rapid onset of action from an oral drug is critical, it should be given at least 1 hour before or 2 hours after pramlintide. Also, pramlintide may interfere with drugs given to alter gastrointestinal motility or absorption.

Pramlintide increases the risk of insulin-induced hypoglycaemia (see Adverse Effects and Precautions, above).

Pharmacokinetics

The bioavailability of pramlintide is about 30 to 40% from a subcutaneous injection, and peak plasma concentrations are reached after about 20 minutes. It is metabolised by the kidneys and has a half-life of about 48 minutes in healthy subjects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Symlin.

Repaglinide *(BAN, USAN, rINN)*

AG-EE-6232W; AG-EE-623-ZW; Repaglinid; Repaglinida; Repaglinidas; Répaglinide; Repaglinidi; Repaglinidum; Репаглинид.

(+)-2-Ethoxy-α-{[(*S*)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl}-*p*-toluic acid; (*S*)-2-Ethoxy-4-{[1-(*o*-piperidinophenyl)-3-methylbutyl]carbamoylmethyl}benzoic acid.

$C_{27}H_{36}N_2O_4$=452.6

CAS — 135062-02-1.

ATC — A10BX02.

ATC Vet — QA10BX02.

UNII — 668Z8C33LU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8 (Repaglinide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 36: (Repaglinide). A white to off-white solid. Soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Repaglinide is a meglitinide antidiabetic used for the treatment of type 2 diabetes mellitus (p. 459.1). It has a chemical structure different from that of the sulfonylureas, but appears to have a similar mode of action and is also described as an insulin secretagogue.

Repaglinide is given up to 30 minutes before meals, and usually within 15 minutes, in initial oral doses of 500 micrograms; initial doses of 1 or 2 mg are given to patients who have had previous hypoglycaemic treatment. The dose may be adjusted, at intervals of 1 to 2 weeks, up to a maximum of 4 mg before meals; a total of 16 mg daily should not be exceeded. Repaglinide is also given with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by monotherapy. When given with metformin in a combination preparation, the maximum recommended daily dose of repaglinide is 10 mg.

References.

1. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; **24:** 11–15.
2. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; **61:** 1625–60.
3. Black C, *et al.* Meglitinide analogues for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 13/03/09).
4. Johansen OE, Birkeland KI. Defining the role of repaglinide in the management of type 2 diabetes mellitus: a review. *Am J Cardiovasc Drugs* 2007; **7:** 319–35.

Administration in renal impairment. Although repaglinide is cleared mainly by hepatic metabolism, small pharmacokinetic studies have reported that exposure to repaglinide may be increased in patients with renal impairment.[1,2] A larger open-label study[3] that included 151 patients with normal renal function and 130 patients with varying degrees of renal impairment found that the incidence of adverse effects was not influenced by renal function. However, at the end of the 3-month maintenance treatment period, there was a trend towards lower effective doses of repaglinide with increasing degree of renal impairment. US licensed product information suggests that the usual initial oral dose of repaglinide 500 micrograms before meals may be used in severe renal impairment, and adjusted with care.

1. Marbury TC, *et al.* Pharmacokinetics of repaglinide in subjects with renal impairment. *Clin Pharmacol Ther* 2000; **67:** 7–15.
2. Schumacher S, *et al.* Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *Eur J Clin Pharmacol* 2001; **57:** 147–52.
3. Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. *Diabetes Care* 2003; **26:** 886–91.

Adverse Effects and Precautions

Repaglinide may cause gastrointestinal adverse effects including abdominal pain, diarrhoea, constipation, nausea, and vomiting. Hypoglycaemia may be common, but is usually mild. Back and joint pain have also been reported. Rare effects have included hypersensitivity reactions, vasculitis, pruritus, rashes, urticaria, Stevens-Johnson syndrome, elevated liver enzyme values, severe hepatic dysfunction, pancreatitis, haemolytic anaemia, leucopenia, and thrombocytopenia. There have also been rare cases of transient visual disturbances attributed to changes in blood-glucose concentrations associated with starting repaglinide treatment. Myocardial ischaemia has been reported in patients who were treated with repaglinide and isophane insulin; the combination is not recommended.

Precautions are similar to those which apply with the shorter-acting sulfonylurea hypoglycaemics (p. 504.2). Repaglinide should be given with caution to patients with hepatic impairment (consideration should be given to extending the interval between dose adjustments), and possibly avoided in severe impairment.

Incidence of adverse effects. Diarrhoea, abdominal pain, and nausea were found to be the adverse effects most commonly reported during the first 6 months of repaglinide therapy in an analysis of postmarketing data relating to 5731 patients. The effects that occurred more often in the first month of treatment, compared with months 2 to 6, included diarrhoea, nausea or vomiting, abdominal pain or distension, malaise or lassitude, headache or migraine, dizziness, and hypoglycaemia. There were also reports of rash, visual disturbance, palpitations, and abnormal liver function values.[1]

1. Marshall V, *et al.* Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2006; **43:** 6–13.

Abuse. Several episodes of serious hypoglycaemia, once accompanied by seizures, occurred in a young man who covertly took repaglinide.[1]

1. Hirshberg B, *et al.* Repaglinide-induced factitious hypoglycemia. *J Clin Endocrinol Metab* 2001; **86:** 475–7.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Effects on the liver. Hepatotoxic reactions have been reported for repaglinide[1,2] including cholestatic hepatitis and jaundice with pruritus.

1. Nan DN, *et al.* Acute hepatotoxicity caused by repaglinide. *Ann Intern Med* 2004; **141:** 823.
2. López-García F, *et al.* Cholestatic hepatitis associated with repaglinide. *Diabetes Care* 2005; **28:** 752–3.

Fasting. For mention that nateglinide or repaglinide can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p. 485.3.

Hypoglycaemia. Mild hypoglycaemia has been reported in patients receiving repaglinide,[1] although in a study comparing flexible repaglinide dosing with fixed glibenclamide dosing, all hypoglycaemic events recorded were in the glibenclamide group.[2] Other studies have found rates of hypoglycaemia in patients receiving repaglinide to be less than, or similar to, sulfonylureas.[3] The risk of hypoglycaemia may be reduced as patients can omit a dose of repaglinide if a meal is missed. Serious hypoglycaemia resulting in a seizure has been reported[4] in a patient who took a missed dose of repaglinide 3 hours after his evening meal. The risk was probably further increased because of hepatic impairment. An observational study[5] based on prescription-event monitoring data in the UK suggested that hypoglycaemic events were most likely shortly after starting treatment with repaglinide. For a report of factitious hypoglycaemia, see Abuse, above.

1. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; **24:** 11–15.
2. Damsbo P, *et al.* A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 1999; **22:** 789–94.
3. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; **61:** 1625–60.
4. Flood TM. Serious hypoglycemia associated with misuse of repaglinide. *Endocr Pract* 1999; **5:** 137–8.
5. Vlckova V, *etal.* Hypoglycaemia with oral antidiabetic drugs: results from prescription-event monitoring cohorts of rosiglitazone, pioglitazone, nateglinide and repaglinide. *Drug Safety* 2009; **32:** 409–18.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies repaglinide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Insulin is generally preferred to oral antidiabetics in the treatment of diabetes mellitus during pregnancy. Repaglinide has been used in 3 women during the first 6 to 7 weeks of gestation;[1,2] treatment was then changed to insulin for the rest of the pregnancy. Their babies were delivered at term, with adequate weight for birth age and no congenital malformations. An analysis of postmarketing data found 5 reports of repaglinide use dur-

ing pregnancy.[3] Three babies were born with no abnormalities reported, the outcome of one pregnancy was unknown, and in one case Fraser syndrome was diagnosed and the baby stillborn at 26 weeks.

1. Napoli A, *et al*. Use of repaglinide during the first weeks of pregnancy in two type 2 diabetic women. *Diabetes Care* 2006; **29:** 2326–7.
2. Mollar-Puchades MA, *et al*. Use of repaglinide on a pregnant woman during embryogenesis. *Diabetes Obes Metab* 2007; **9:** 146–7.
3. Marshall V, *et al*. Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2006; **43:** 6–13.

Interactions

The efficacy of repaglinide may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Drugs that affect the cytochrome P450 isoenzymes CYP2C8 and CYP3A4 may alter the metabolism of repaglinide. Use of repaglinide with the CYP2C8 inhibitor gemfibrozil has resulted in marked reduction in repaglinide clearance, and severe hypoglycaemia; licensed product information contra-indicates concomitant use. Repaglinide also appears to be a substrate for active hepatic uptake by the organic anion transporting protein OATP1B1, and may be affected by drugs that have the potential for its inhibition.

References.

1. Hatorp V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J Clin Pharmacol* 2000; **40:** 184–92.
2. Hatorp V, *et al*. Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 2003; **43:** 649–60.
3. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. A study[1] in healthy subjects found that the plasma concentration of a single dose of repaglinide was reduced, and its half-life shortened, when it was given 12.5 hours after the last dose of a 5-day course of *rifampicin*. This effect was attributed to the induction of the cytochrome P450 isoenzyme CYP3A4 by rifampicin. In another study[2] repaglinide was given either with the last dose of a 7-day course of rifampicin or 24 hours later, and the effects on repaglinide were found to be greater on day 8 than day 7. The authors suggested that rifampicin acted as both an inducer and an inhibitor of CYP3A4 and possibly CYP2C8, and that after rifampicin was stopped its inductive effect lasted longer, thereby having a greater effect 24 hours later.

A study[3] in healthy subjects reported that *clarithromycin* can increase the plasma concentrations and prolong the elimination half-life of repaglinide, probably by inhibition of CYP3A4. An 80-year-old man stabilised on repaglinide therapy suffered severe hypoglycaemia about 48 hours after starting clarithromycin.[4] *Telithromycin*, another inhibitor of CYP3A4, also increased plasma concentrations of repaglinide in a study of healthy subjects, although the elimination half-life of repaglinide was not significantly affected.[5] *Trimethoprim*[6,7] can have a similar effect by the inhibition of CYP2C8.

For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving repaglinide, see p. 304.1.

1. Niemi M, *et al*. Rifampin decreases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2000; **68:** 495–500.
2. Bidstrup TB, *et al*. Rifampicin seems to act as both an inducer and an inhibitor of the metabolism of repaglinide. *Eur J Clin Pharmacol* 2004; **60:** 109–14.
3. Niemi M, *et al*. The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2001; **70:** 58–65.
4. Khamaisi M, Leitersdorf E. Severe hypoglycemia from clarithromycin-repaglinide drug interaction. *Pharmacotherapy* 2008; **28:** 682–4.
5. Kajosaari LI, *et al*. Telithromycin, but not montelukast, increases the plasma concentrations and effects of the cytochrome P450 3A4 and 2C8 substrate repaglinide. *Clin Pharmacol Ther* 2006; **79:** 231–42.
6. Niemi M, *et al*. The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 441–7.
7. Roustit M, *et al*. Symptomatic hypoglycemia associated with trimethoprim/sulfamethoxazole and repaglinide in a diabetic patient. *Ann Pharmacother* 2010; **44:** 764–7.

Ciclosporin. Ciclosporin markedly increased plasma concentrations of repaglinide in healthy subjects, probably by inhibiting both its metabolism by the cytochrome P450 isoenzyme CYP3A4 and hepatic uptake by the organic anion transporting polypeptide OATP1B1.[1] However, there was a large variation in the effect, which may have been partly related to genetic factors. Although there is, therefore, a possibility of increased risk of hypoglycaemia if these 2 drugs are taken together, repaglinide has been used successfully, in usual doses, for diabetes mellitus following renal transplantation in patients receiving immunosuppression regimens that included ciclosporin.[2] Hypoglycaemia was reported,[2] but it was mild and occurred at a similar rate in patients given repaglinide with either ciclosporin (1 of 7 patients) or with tacrolimus (2 of 14).[3] Nevertheless, the authors stated that in these patients, oral antidiabetics in general should be started at a low dose and adjusted gradually with close monitoring of blood-glucose concentrations.[3]

1. Kajosaari LI, *et al*. Cyclosporine markedly raises the plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2005; **78:** 388–99.
2. Türk T, *et al*. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant* 2006; **6:** 842–6.
3. Türk T, Witzke O. Pharmacological interaction between cyclosporine A and repaglinide. Is it clinically relevant? *Am J Transplant* 2006; **6:** 2223.

Deferasirox. In a single-dose study[1] in healthy subjects, deferasirox, an inhibitor of the cytochrome P450 isoenzyme CYP2C8, increased plasma-repaglinide concentrations about twofold but with little change in blood glucose. The authors recommended monitoring blood-glucose concentrations when these drugs are taken together.

1. Skerjanec A, *et al*. Investigation of the pharmacokinetic interactions of deferasirox, a once-daily oral iron chelator, with midazolam, rifampin, and repaglinide in healthy volunteers. *J Clin Pharmacol* 2010; **50:** 205–13.

Grapefruit juice. Grapefruit juice increased the bioavailability of repaglinide in a study of healthy subjects.[1] The half-life of repaglinide was not affected, suggesting that grapefruit juice inhibited its presystemic metabolism by the cytochrome P450 isoenzyme CYP3A4 in the gut wall. Blood-glucose concentrations were not affected.

1. Bidstrup TB, *et al*. The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol* 2006; **61:** 49–57.

Lipid regulating drugs. A study[1] in healthy subjects found that *gemfibrozil* significantly increased the plasma concentrations of repaglinide and enhanced and prolonged its glucose-lowering effect. This interaction can persist for at least 12 hours after a gemfibrozil dose; it might be caused by accumulation in the liver of the metabolite gemfibrozil glucuronide and subsequent prolonged inhibition of the cytochrome P450 isoenzyme CYP2C8.[2] To a lesser extent, gemfibrozil may inhibit the hepatic uptake of repaglinide by the organic anion transporting protein 1B1, and the extent of this effect might be influenced by OATP1B1-related genotype.[3] An *in-vitro* study[4] found that gemfibrozil inhibited uridine diphosphate glucuronosyltransferase (UGT) enzymes, particularly UGT1A1, and suggested that inhibition of repaglinide glucuronidation by gemfibrozil may also contribute to the mechanism of this interaction. In 2003, the EMEA stated that it had received 5 reports of serious hypoglycaemia in patients given repaglinide and gemfibrozil, and contra-indicated the combination.[5] Other studies in healthy subjects found, however, that repaglinide was not affected by *bezafibrate*,[6] *colesevelam*,[7] or *fenofibrate*.[6]

1. Niemi M, *et al*. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 2003; **46:** 347–51.
2. Tornio A, *et al*. The effect of gemfibrozil on repaglinide pharmacokinetics persists for at least 12h after the dose: evidence for mechanism-based inhibition of CYP2C8 in vivo. *Clin Pharmacol Ther* 2008; **84:** 403–11.
3. Kalliokoski A, *et al*. Effects of gemfibrozil and atorvastatin on the pharmacokinetics of repaglinide in relation to SLCO1B1 polymorphism. *Clin Pharmacol Ther* 2008; **84:** 488–96.
4. Gan J, *et al*. Repaglinide-gemfibrozil drug interaction: inhibition of repaglinide glucuronidation as a potential additional contributing mechanism. *Br J Clin Pharmacol* 2010; **70:** 870–80.
5. EMEA. EMEA public statement on repaglinide (NovoNorm/Prandin) contraindication of concomitant use of repaglinide and gemfibrozil (issued 21st May, 2003). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/08/WC500095476.pdf (accessed 24/08/10)
6. Kajosaari LI, *et al*. Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide. *Br J Clin Pharmacol* 2004; **58:** 390–6.
7. Brown KS, *et al*. Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *J Clin Pharmacol* 2010; **50:** 554–65.

Pharmacokinetics

Repaglinide is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 hour. The mean bioavailability is about 60%. Repaglinide is highly bound to plasma proteins, and has a plasma elimination half-life of about 1 hour. It appears to be a substrate for active hepatic uptake by the organic anion transporting protein OATP1B1, and undergoes almost complete hepatic metabolism involving the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. The glucuronidation of repaglinide is thought to involve uridine diphosphate glucuronosyltransferase (UGT) enzymes, particularly UGT1A1. The metabolites, which are inactive, are excreted in the bile. Higher plasma concentrations and prolonged half-life of repaglinide may occur in patients with renal impairment (creatinine clearance less than 40 mL/min) or chronic liver disease.

References.

1. Hatorp V, *et al*. Single-dose pharmacokinetics of repaglinide in subjects with chronic liver disease. *J Clin Pharmacol* 2000; **40:** 142–52.
2. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. *Clin Pharmacokinet* 2002; **41:** 471–83.
3. Bidstrup TB, *et al*. CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. *Br J Clin Pharmacol* 2003; **56:** 305–14.
4. Niemi M, *et al*. Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2003; **74:** 380–7.
5. Niemi M, *et al*. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. *Clin Pharmacol Ther* 2005; **77:** 468–78.
6. Kalliokoski A, *et al*. Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol* 2008; **48:** 311–21.
7. Kalliokoski A, *et al*. The effect of SLCO1B1 polymorphism on repaglinide pharmacokinetics persists over a wide dose range. *Br J Clin Pharmacol* 2008; **66:** 818–25.
8. Ruzilawati AB, Gan SH. CYP3A4 genetic polymorphism influences repaglinide's pharmacokinetics. *Pharmacology* 2010; **85:** 357–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cravenorm; Glukenil; NovoNorm; Sestrine; ***Austral.***: NovoNorm; ***Austria***: NovoNorm; ***Belg.***: NovoNorm; ***Braz.***: Gluconorm†; NovoNorm; Posprand; Prandin; ***Canad.***: Gluconorm; ***Chile***: Hipover; NovoNorm; ***China***: Fulaidi (孚来迪); NovoNorm (诺和龙); ***Cz.***: Enyglid; NovoNorm; Prandin; Reneos; ***Denm.***: NovoNorm; ***Fin.***: NovoNorm; ***Fr.***: NovoNorm; ***Ger.***: Enyglid; NovoNorm; ***Gr.***: NovoNorm; ***Hong Kong***: NovoNorm; ***Hung.***: NovoNorm; ***India***: Eurepa; NovoNorm; Page; Rapilin; ***Indon.***: Dexanorm; ***Irl.***: Enyglid; NovoNorm; Prandin; ***Israel***: NovoNorm; ***Ital.***: NovoNorm; ***Jpn***: Surepost; ***Malaysia***: NovoNorm; ***Mex.***: NovoNorm; Prandin; ***Neth.***: Enyglid; NovoNorm; Prandin; ***Norw.***: NovoNorm; ***NZ***: NovoNorm; ***Philipp.***: NovoNorm; ***Pol.***: Enyglid; Ilgaper; NovoNorm; Prandin; ***Port.***: Enyglid; NovoNorm; Prandin; ***Rus.***: NovoNorm (НовоНорм); ***S.Afr.***: NovoNorm; ***Singapore***: NovoNorm; ***Spain***: NovoNorm; Prandin; ***Swed.***: NovoNorm; ***Switz.***: NovoNorm; ***Thai.***: NovoNorm; ***Turk.***: Diafree; Novade; NovoNorm; ***UK***: Prandin; ***Ukr.***: NovoNorm (Новонорм); ***USA***: Prandin.

Multi-ingredient Preparations. ***Israel***: Novogard; ***USA***: Prandi-Met.

Pharmacopoeial Preparations

USP 36: Repaglinide Tablets.

Rosiglitazone *(BAN, rINN)*

Rosiglitatsoni; Rosiglitazon; Rosiglitazona; Rosiglitazonum; Rozyglitazon; Розиглитазон.

(±)-5-{*p*-[2-(Methyl-2-pyridylamino)ethoxy]benzyl}-2,4-thiazolidinedione.

$C_{18}H_{19}N_3O_3S$=357.4

CAS — 122320-73-4.

ATC — A10BG02.

ATC Vet — QA10BG02.

UNII — 05V02F2KDG.

Rosiglitazone Maleate *(BANM, USAN, rINNM)*

BRL-49653-C; Maleato de rosiglitazona; Rosiglitazona, maleato de; Rosiglitazone, Maléate de; Rosiglitazoni Maleas; Roziglitazon Maleat; Розиглитазона Малеат.

$C_{18}H_{19}N_3O_3S,C_4H_4O_4$=473.5

CAS — 155141-29-0.

ATC — A10BG02.

ATC Vet — QA10BG02.

UNII — KX2339DP44.

Pharmacopoeias. In *US*.

USP 36: (Rosiglitazone Maleate). A white to off-white solid. Practically insoluble to very slightly soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers.

Rosiglitazone Potassium *(BANM, rINNM)*

Kalii Rosiglitazonum; Rosiglitazona potásica; Rosiglitazone Potassique; Калия Розиглитазон.

$C_{18}H_{19}N_3O_3SK$=396.5

CAS — 316371-84-3.

ATC — A10BG02.

ATC Vet — QA10BG02.

Uses and Administration

Rosiglitazone is a thiazolidinedione antidiabetic that acts as a selective agonist at the peroxisome proliferator-activated receptor gamma (PPARγ). It improves insulin sensitivity in adipose tissue, skeletal muscle, and the liver, and is therefore used for the treatment of type 2 diabetes mellitus (p. 459.1), although its use is limited because of possible increased cardiovascular risks. It is usually given as rosiglitazone maleate, and the potassium salt is used in some countries, but doses are expressed in terms of the base; rosiglitazone maleate 1.32 mg and rosiglitazone potassium 1.11 mg are both equivalent to about 1 mg of rosiglitazone.

The hydrochloride has also been used. Rosiglitazone is given orally as monotherapy, particularly in patients who do not achieve adequate glycaemic control with other antidiabetics or in whom other antidiabetics are contra-indicated or not tolerated. It may also be added to metformin, a sulfonylurea, or a combination of the two. The combination of insulin and rosiglitazone is generally avoided (see Administration, p. 499.1). The usual initial dose is 4 mg daily, given in a single dose or two divided doses. The dose may be increased to a maximum of 8 mg daily if necessary after 8 to 12 weeks. Rosiglitazone may be taken with or without food.

References.
1. Czoski-Murray C, *et al.* Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. *Health Technol Assess* 2004; **8:** 1–91.
2. Wellington K. Rosiglitazone/metformin. *Drugs* 2005; **65:** 1581–92.
3. Deeks ED, Keam SJ. Rosiglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2007; **67:** 2747–79.
4. Richter B, *et al.* Rosiglitazone for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 06/07/09).
5. Anonymous. Glitazones in type 2 diabetes: an update. *Drug Ther Bull* 2008; **46:** 25–9.

Administration. Although rosiglitazone was licensed for use with other antidiabetic drugs the specifics of licensing and use have varied from country to country. In both the UK and USA, rosiglitazone (*Avandia; GSK*) was licensed for monotherapy, and for use with metformin or a sulfonylurea, or both if necessary, in patients in whom single or dual agent therapy is inadequate. However, UK[1] and combined European/US guidelines[2] do not endorse the use of thiazolidinedione monotherapy. In the UK, NICE only recommends dual therapy that includes a thiazolidinedione in patients who cannot be given a combination of metformin plus a sulfonylurea (because of drug intolerance or contra-indication, or where the risk or consequences of hypoglycaemia would be unacceptable). NICE also suggests that a thiazolidinedione only be added to metformin plus a sulfonylurea if insulin is likely to be unacceptable or ineffective.[1] The European/US guidelines discourage the use of rosiglitazone altogether, but do suggest a role for pioglitazone.[2] In September 2010 the EMEA suspended the marketing authorisation of rosiglitazone and the FDA restricted its use; in 2013 the FDA removed its restrictions (for details, see Effects on the Cardiovascular System, p. 499.3).

The combination of rosiglitazone with insulin is now generally avoided because of an increased risk of heart failure and other cardiac adverse events (see also Effects on the Heart, p. 500.2), and licensed product information recommends against such use. The European/US guidelines[2] do not include a combination of thiazolidinedione with insulin, and NICE[1] only recommends pioglitazone with insulin in particular circumstances.

1. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes: partial update (issued March 2010). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 10/10/11)
2. Nathan DM, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32:** 193–203.

Inflammatory bowel disease. There is some evidence[1] to suggest that drugs such as rosiglitazone that act as ligands to peroxisome proliferator-activated receptor gamma (PPARγ) may offer a novel therapeutic approach to management of inflammatory bowel disease (p. 1811.3).

1. Lewis JD, *et al.* Rosiglitazone for Ulcerative Colitis Study Group. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology* 2008; **134:** 688–95.

Liver disorders. Small studies using rosiglitazone in nonalcoholic steatohepatitis have reported improvements in insulin sensitivity, liver function, and histology.[1-4] However, weight gain was common[1-3] and benefits were not maintained after treatment was stopped.[1] Furthermore, no additional improvement in histology was shown beyond 1 year of treatment despite a maintained effect on insulin sensitivity and transaminase levels.[4]

1. Neuschwander-Tetri BA, *et al.* Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-γ ligand rosiglitazone. *Hepatology* 2003; **38:** 1008–17.
2. Wang C-H, *et al.* Safety and effectiveness of rosiglitazone in type 2 diabetes patients with nonalcoholic fatty liver disease. *J Formos Med Assoc* 2006; **105:** 743–52.
3. Ratziu V, *et al.* LIDO Study Group. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 2008; **135:** 100–10.
4. Ratziu V, *et al.* LIDO Study Group. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. *Hepatology* 2010; **51:** 445–53.

Polycystic ovary syndrome. Insulin resistance is a feature of polycystic ovary syndrome (PCOS; p. 2253.3) and the use of rosiglitazone has been investigated. Rosiglitazone has been reported to improve insulin resistance in women with PCOS, as well as reduce androgen concentrations and normalise sex-hormone binding globulin. There have been reports of reduced hirsutism, a return to regular menstrual cycles, and improved ovulation rates. Many women with PCOS are overweight or obese and there has been concern that thiazolidinediones might exacerbate this, but some studies have reported improvements in measures of PCOS without significant weight gain. Improvements in PCOS have also been found in lean women without insulin resistance. Overall, however, studies have been small and short-term, and further research is needed.[1]

1. Elkind-Hirsch KE. Thiazolidinediones for the therapeutic management of polycystic ovary syndrome: impact on metabolic and reproductive abnormalities. *Treat Endocrinol* 2006; **5:** 171–187.

Psoriasis. Rosiglitazone has been studied in the treatment of chronic plaque psoriasis (see under Pioglitazone, p. 493.3).

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Oral thiazolidinediones have been reported to reduce the risk of repeat revascularisation in patients with and without diabetes, but studies have been small and have not always documented the type of stent used.[1]

1. Riche DM, *et al.* Thiazolidinediones and risk of repeat target vessel revascularization following percutaneous coronary intervention: a meta-analysis. *Diabetes Care* 2007; **30:** 384–8.

Adverse Effects and Precautions

Hypoglycaemia is uncommon during rosiglitazone monotherapy, but it may be common when the drug is given with other oral antidiabetics, particularly a sulfonylurea, or insulin. Weight gain appears to be dose-related, and may be caused by a combination of fat accumulation and fluid retention. Other common adverse effects of rosiglitazone include increased appetite, gastrointestinal disturbances, and headache, Reductions in haemoglobin and haematocrit can occur and appear to be related to both rosiglitazone dose and increased plasma volume; patients with low haemoglobin concentrations before starting therapy may be at risk of developing anaemia. Changes in serum lipids may also occur, including hypertriglyceridaemia and mild to moderate hypercholesterolaemia. Other adverse effects that have been reported include dizziness, palpitations, muscle cramps, back pain, arthralgia, paraesthesia, and alopecia. There have also been very rare reports of anaphylactic reactions, angioedema, and skin reactions such as urticaria, pruritus, and rashes. Rosiglitazone can also increase the risk of bone fracture in women.

Rosiglitazone can cause fluid retention, which may worsen or precipitate heart failure; rapid weight gain and dyspnoea may be indicative of fluid retention. It should therefore be used with caution in patients with oedema, and should not be used in those with a history of heart failure (see also Effects on the Heart, p. 500.2). Renal impairment may increase the risk of fluid retention and heart failure. Rosiglitazone should also be avoided in patients having an acute coronary event because this condition has the potential to precipitate heart failure. There have been very rare reports of new onset and worsening diabetic macular oedema with decreased visual acuity (see also Effects on the Eyes, p. 500.1). There is evidence of a possible increased cardiovascular risk with the use of rosiglitazone, and it is not recommended in patients with ischaemic heart disease or peripheral arterial disease (see also Effects on the Cardiovascular System, p. 499.3). Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see Effects on the Liver, p. 500.3).

Rosiglitazone is not appropriate for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

In women who are anovulatory because of insulin resistance, rosiglitazone therapy may result in a resumption of ovulation.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Effects on the blood. Leucopenia and thrombocytopenia developed in a 50-year-old woman treated with rosiglitazone. The effect resolved after the drug was stopped, but recurred when pioglitazone was later given. The patient again recovered after pioglitazone treatment was withdrawn.[1] A case of rosiglitazone-induced immune thrombocytopenia, with recovery after drug withdrawal, has also been described.[2]

1. Digman C, *et al.* Leukopenia and thrombocytopenia caused by thiazolidinediones. *Ann Intern Med* 2005; **143:** 465–6.
2. Liu X, *et al.* Rosiglitazone-induced immune thrombocytopenia. *Platelets* 2006; **17:** 143–8.

Effects on the bones. Use of thiazolidinediones such as pioglitazone or rosiglitazone has been associated with decreases in bone mineral density and increased risk of fractures in female patients. Analysis of data from a comparative study (ADOPT)[1] of glycaemic control with rosiglitazone, metformin, or glibenclamide involving 4360 randomised patients found that the risk of fracture in female patients in these 3 groups was 9.3%, 5.1%, and 3.5% respectively;[2] the risk in male patients was not significantly different in the 3 groups at around 3.4 to 3.95%. Analysis of data from another large ongoing study was also consistent with an increased fracture risk with rosiglitazone,[2] and data from the manufacturer of pioglitazone involving over 8100 treated patients also revealed an increased risk of fracture in women given the drug;[3] the excess risk was calculated to be 0.8 per 100 patient years of use. Following on from these reports, a meta-analysis of fracture data from 10 studies of thiazolidinediones in diabetes was undertaken, although none were prospectively designed to measure fracture risk.[4] The analysis confirmed an increased risk of fracture overall with thiazolidinedione use. Based on the 5 studies providing data by sex, the risk of fracture was found to be doubled in women, but not significantly increased in men.

The pattern of fractures seemed to differ from that associated with postmenopausal osteoporosis, being mainly in the upper arm, hand, or foot, rather than hip or spine.[2] However, this may be because many affected patients were relatively younger (mean age 56 years),[1] and there is some evidence that hip and femur fractures in older women are significantly associated with thiazolidinediones.[4] An observational study has suggested that thiazolidinedione use is associated with ongoing loss of whole-body bone mineral density in women but not men.[5] Further analysis of the ADOPT results found that the increased risk of fracture only became apparent after 1 year of rosiglitazone treatment, but identified no particular risk factors in affected women.[6]

This adverse effect has been reviewed[7,8] and attributed to the selective agonist action of rosiglitazone at the peroxisome proliferator-activated receptor (PPAR)-γ; *animal* studies have shown that the activation of PPAR-γ decreases bone formation and increases bone resorption.

1. Kahn SE, *et al.* ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355:** 2427–43. Correction. *ibid.* 2007; **356:** 1387–8.
2. GSK, Canada. Increased incidence of fractures in female patients who received long-term treatment with Avandia (rosiglitazone maleate) tablets for type 2 diabetes mellitus (issued 23rd February, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2007/avandia_hpc-cps_3-eng.pdf (accessed 01/11/11)
3. Takeda, USA. Re observation of an increased incidence of fractures in female patients who received long-term treatment with Actos (pioglitazone HCl) tablets for type 2 diabetes mellitus (issued March 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153896.pdf (accessed 01/11/11)
4. Loke YK, *et al.* Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009; **180:** 32–9.
5. Schwartz AV, *et al.* Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 2006; **91:** 3349–54.
6. Kahn SE, *et al.* Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2008; **31:** 845–51.
7. Bodmer M, *et al.* Risk of fractures with glitazones: a critical review of the evidence to date. *Drug Safety* 2009; **32:** 539–47.
8. Lecka-Czernik B. Bone loss in diabetes: use of antidiabetic thiazolidinediones and secondary osteoporosis. *Curr Osteoporos Rep* 2010; **8:** 178–84.

Effects on the cardiovascular system. It had been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications, and there is some evidence that pioglitazone may improve some cardiovascular outcomes (see Diabetic Complications, p. 493.2). However, a meta-analysis[1] of 42 studies found that, compared with either placebo or other antidiabetic drugs, rosiglitazone was associated with a significant increase in the risk of myocardial infarction, and an increase of borderline significance in death from cardiovascular causes. There were limitations to this analysis as the studies were not primarily intended to examine cardiovascular outcomes, and many were small and short-term. Studies with no recorded cardiovascular events were excluded from the meta-analysis,[1] and this has been questioned. An alternative analysis[2] that accounted for these excluded studies, with appropriate analysis adjustment, found odds ratios for myocardial infarction and cardiovascular death that were not statistically significant, and concluded that neither increased nor decreased risk could be established.

In response to concerns raised by the initial meta-analysis, an unplanned interim analysis of an ongoing open-label study (RECORD) designed to assess cardiovascular outcomes was published (rosiglitazone added to either metformin or a sulfonylurea compared with metformin plus

a sulfonylurea).[3] The data, however, were insufficient to determine whether there was an increased risk of myocardial infarction, and the findings were inconclusive regarding any effect on overall risks of hospitalisation or death from cardiovascular causes. A subsequent meta-analysis[4] was restricted to 4 long-term studies (at least 12 months of treatment) that had specified an intention to evaluate cardiovascular adverse effects, including the interim RECORD results. It found an increased risk of myocardial infarction with rosiglitazone use, without a significant increase in the risk of cardiovascular mortality. The final results of RECORD[5] showed that after 5 to 7 years of follow-up, rosiglitazone did not increase overall cardiovascular morbidity or mortality, but the data could not rule out a small increased risk in myocardial infarction. The strength of these findings were weakened by a substantially lower than expected rate of cardiovascular events. A later meta-analysis considered that the risk-benefit ratio for rosiglitazone was unfavourable.[6] Concerns about the cardiovascular safety of rosiglitazone contributed to recommendations that its use should be limited, and in September 2010 the FDA restricted rosiglitazone to patients with diabetes that could not be controlled by other medications,[7] and the marketing of rosiglitazone was suspended in the EU.[8] The FDA also requested an independent review of the RECORD results because of questions about potential bias in the identification of cardiovascular events. Based on this, the FDA concluded that it was not clear whether the risk of death, heart attack, and stroke were truly different between rosiglitazone and metformin plus sulfonylurea, and in 2013 lifted restrictions on its prescription.[9] (See also Administration, p. 497.1.)

For the risks of heart failure associated with thiazolidinediones, see Effects on the Heart, p. 500.2.

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2. Diamond GA, *et al*. Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann Intern Med* 2007; **147:** 578–81.
3. Home PD, *et al*. RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007; **357:** 28–38.
4. Singh S, *et al*. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298:** 1189–95.
5. Home PD, *et al*. RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; **373:** 2125–35.
6. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; **170:** 1191–1201.
7. FDA. Avandia (rosiglitazone): REMS - risk of cardiovascular events (issued 23rd September, 2010). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226994.htm (accessed 24/09/10)
8. EMEA. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim: anti-diabetes medication to be taken off the market (issued 23rd September, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf (accessed 24/09/10)
9. FDA. FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines (issued 25th November, 2013). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm (accessed 26/11/13)

Effects on the eyes. The manufacturers in the USA and Canada (*GSK*) have received postmarketing reports of the development or worsening of **diabetic macular oedema** in patients treated with rosiglitazone-containing products; in most cases the patients also reported peripheral oedema or fluid retention.[1,2] In some cases visual impairment improved or resolved after stopping the drug. A later observational study[3] in 170 000 diabetic patients showed that treatment with a thiazolidinedione was modestly associated with an increased 1-year incidence of diabetic macular oedema after adjusting for age, glycaemic control, and insulin use. More recently, however, a cross-sectional analysis[4] of data from a substudy of a large multicentre randomised controlled study in diabetic patients did not find any association, although this study did not adjust for duration of exposure, past exposure, and type of thiazolidinedione used.

A retrospective review[5] of 30 patients with lower extremity oedema, and clinically significant diabetic macular oedema, assessed the changes that were recorded after rosiglitazone or pioglitazone had been stopped. Although weight loss and improvement in peripheral oedema were generally rapid (usually within 2 months), the resolution of macular oedema was often very slow. Most patients underwent macular laser treatment, and in some cases visual acuity remained poor because of macular scarring from chronic oedema.

The manufacturers advise that rosiglitazone should be used with caution in patients with pre-existing diabetic retinopathy or macular oedema, and should be stopped, and ophthalmological consultation sought, if visual impairment develops while using the drug.[2] This adverse effect has also been reviewed.[6]

There have been reports of the exacerbation of **thyroid eye disease**, particularly proptosis associated expansion of the orbital fat compartment, in euthyroid patients given thiazolidinediones.[7,8] Proptosis, with normal orbital fat and extra-ocular muscles, has also been reported with rosiglitazone in the absence of thyroid disease.[9] A small study in 36 patients measured eye protrusion before and after 6 months of pioglitazone therapy.[10] Overall there was a small increase, but none of the patients noted any changes in the appearance of their eyes. Previous or current thyroid disturbances, a low adiponectin level, and higher pioglitazone dose, were found more frequently in patients with the greatest increase in protrusion.

1. GSK, USA. Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin HCl): letter to healthcare professionals (issued December 2005). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153072.pdf (accessed 24/08/10)
2. GSK, Canada. Association of Avandia and Avandamet with new onset and/or worsening of macular edema (issued 19th December, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps-eng.pdf (accessed 02/11/11)
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4. Ambrosius WT, *et al*. ACCORD Study Group. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye study. *Arch Ophthalmol* 2010; **128:** 312–18.
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6. Merante D, *et al*. Diabetic macular edema: correlations with available diabetes therapies—evidence across a qualitative review of published literature from MEDLINE and EMBASE. *Drug Safety* 2010; **33:** 643–52.
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8. Lee S, *et al*. Thiazolidinedione induced thyroid associated orbitopathy. *BMC Ophthalmol* 2007; **7:** 8.
9. Levin F, *et al*. Rosiglitazone-induced proptosis. *Arch Ophthalmol* 2005; **123:** 119–21.
10. Dorkhan M, *et al*. Treatment with a thiazolidinedione increases eye protrusion in a subgroup of patients with type 2 diabetes. *Clin Endocrinol (Oxf)* 2006; **65:** 35–9.

Effects on the heart. Both pioglitazone and rosiglitazone can cause peripheral and pulmonary oedema, which can worsen or precipitate heart failure; several cases have been described.[1-6] A large retrospective cohort study[7] also found that the use of thiazolidinediones increased the risk of heart failure. The incidence of peripheral oedema with monotherapy has been reported[8] to range from 3 to 5%, and this increases slightly when a thiazolidinedione is used with another oral antidiabetic. The incidence is about 15% when a thiazolidinedione is used with insulin. The incidence of heart failure is generally lower, but has been reported to be 2 to 3% when a thiazolidinedione is used with insulin; however, a large prospective study,[9] which was intended to examine the cardiovascular benefits of pioglitazone in preventing secondary macrovascular events in diabetic patients with pre-existing macrovascular disease, reported a 6% incidence of heart failure, compared with 4% in the placebo group. Mortality rates from heart failure did not differ between groups. These figures were confirmed on re-analysis.[10,11] Subsequent reviews have also concluded that thiazolidinediones increase the risk of heart failure,[12,13] but without an associated increase in the risk of cardiovascular death.[13]

The American Heart Association and American Diabetes Association have recommended[8] that patients with risk factors for heart disease or a depressed ejection fraction but without symptoms, and patients with NYHA class I or II heart failure, should start with a low dose of a thiazolidinedione that is only increased gradually as necessary and with careful monitoring. Patients with more severe heart failure (class III and IV) should not receive these drugs. These recommendations are reflected in US licensed product information. Licensed product information in other countries may contra-indicate the use of pioglitazone or rosiglitazone in patients with heart failure or any history of heart failure, even of class I or II.

For restrictions on combination therapy see Administration, p. 497.1.

1. Page RL, *et al*. Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy* 2003; **23:** 945–54.
2. Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 2003; **78:** 1088–91.
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5. CSM/MHRA. Reminder: thiazolidinediones (glitazones) contraindications. *Current Problems* 2004; **30:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074486&RevisionSelectionMethod=LatestReleased (accessed 02/06/06)
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7. Delea TE, *et al*. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2003; **26:** 2983–9.
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10. Rydén L, *et al*. Adjudication of serious heart failure in patients from PROactive. *Lancet* 2007; **369:** 189–90.
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12. Singh S, *et al*. Thiazolidinediones and heart failure: a teleo-analysis. *Diabetes Care* 2007; **30:** 2148–53.
13. Lago RM, *et al*. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007; **370:** 1129–36.

Effects on lipids. Rosiglitazone and pioglitazone have different effects on serum lipids—see p. 494.1.

Effects on the liver. Several cases of hepatotoxicity, including fatalities, have been described in patients receiving rosiglitazone. Most of these occurred within a few weeks or months of starting rosiglitazone therapy,[1-5] but some patients had been taking the drug for about a year or more.[6-8] However, the causality of some of these cases has been debated[9,10] because of coexisting disease and concomitant medication.

Licensed product information recommends that liver enzymes should be checked before starting therapy with rosiglitazone. Patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given rosiglitazone, and it should be used with caution, if at all, in patients with milder elevations of liver enzyme values. ALT concentrations should be monitored periodically in all patients given rosiglitazone. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with rosiglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Forman LM, *et al*. Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med* 2000; **132:** 118–21.
2. Al-Salman J, *et al*. Hepatocellular injury in a patient receiving rosiglitazone: a case report. *Ann Intern Med* 2000; **132:** 121–4.
3. Ravinuthala RS, Nori U. Rosiglitazone toxicity. *Ann Intern Med* 2000; **133:** 658.
4. Hachey DM, *et al*. Isolated elevation of alkaline phosphatase level associated with rosiglitazone. *Ann Intern Med* 2000; **133:** 752.
5. Floyd JS, *et al*. Case series of liver failure associated with rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Safety* 2009; **18:** 1238–43.
6. Gouda HE, *et al*. Liver failure in a patient treated with long-term rosiglitazone therapy. *Am J Med* 2001; **111:** 584–5.
7. Su D-H, *et al*. Liver failure in a patient receiving rosiglitazone therapy. *Diabet Med* 2006; **23:** 105–6.
8. El-Naggar MHM, *et al*. Late-onset rosiglitazone-associated acute liver failure in a patient with Hodgkin's lymphoma. *Ann Pharmacother* 2008; **42:** 713–18.
9. Freid J, *et al*. Rosiglitazone and hepatic failure. *Ann Intern Med* 2000; **132:** 164.
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Fasting. For mention that glitazones can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p. 485.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rosiglitazone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Insulin is generally preferred for treatment of diabetes mellitus during pregnancy. Rosiglitazone crosses the placenta and is detectable in fetal tissue, but there is some evidence that the fetus may be able to metabolise the drug.[1] Data on the clinical use of rosiglitazone during pregnancy are limited. There was no evidence of congenital abnormalities or delayed development in the infants of a series of 8 women with polycystic ovary syndrome who had been given rosiglitazone for ovulation induction and during the first 12 weeks of gestation.[2] There has also been a report of rosiglitazone use during weeks 13 to 17 of gestation in a woman with diabetes mellitus, with no malformations detected in the baby.[3]

1. Chan LY-S, *et al*. Placental transfer of rosiglitazone in the first trimester of human pregnancy. *Fertil Steril* 2005; **83:** 955–8.
2. Haddad GF, *et al*. Case series of rosiglitazone used during the first trimester of pregnancy. *Reprod Toxicol* 2008; **26:** 183–4.
3. Kalyoncu NI, *et al*. A case of rosiglitazone exposure in the second trimester of pregnancy. *Reprod Toxicol* 2005; **19:** 563–4.

Interactions

Rosiglitazone is mainly metabolised by the cytochrome P450 isoenzyme CYP2C8. Use with CYP2C8 inhibitors such as gemfibrozil, ketoconazole, and trimethoprim, can increase plasma concentrations of rosiglitazone. Conversely, rifampicin, a potent inducer of cytochrome P450, can

reduce rosiglitazone concentrations. These drugs should be given with caution to patients taking rosiglitazone, and glycaemic control should be monitored.

Use of NSAIDs or insulin with rosiglitazone may increase the risk of oedema and heart failure (see also Effects on the Heart, p. 498.2, and Administration, p. 497.1).

Reviews.

1. Scheen AJ. Pharmacokinetic interactions with thiazolidinediones. *Clin Pharmacokinet* 2007; **46:** 1–12.

Antibacterials. *Rifampicin* significantly reduced the plasma concentration and elimination half-life of rosiglitazone[1,2] and pioglitazone[3] in studies of healthy subjects, probably by induction of the cytochrome P450 isoenzyme CYP2C8. Conversely, *trimethoprim* can inhibit CYP2C8, and was found to modestly increase the concentration and half-life of rosiglitazone.[2,4]

1. Park J-Y, *et al.* Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004; **75:** 157–62.
2. Niemi M, *et al.* Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. *Clin Pharmacol Ther* 2004; **76:** 239–49.
3. Jaakkola T, *et al.* Effect of rifampicin on the pharmacokinetics of pioglitazone. *Br J Clin Pharmacol* 2006; **61:** 70–8.
4. Hruska MW, *et al.* The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 70–9.

Antifungals. In healthy subjects,[1] *ketoconazole* increased the plasma concentration and elimination half-life of rosiglitazone, probably by inhibition of the cytochrome P450 isoenzyme CYP2C8 and to a lesser extent CYP2C9.

1. Park J-Y, *et al.* Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 397–402.

Lipid regulating drugs. *Gemfibrozil* significantly increased the plasma concentration and about doubled the half-life of rosiglitazone in healthy subjects,[1] probably by inhibiting its metabolism. The authors suggested that these drugs should not be used together, or that the dose of rosiglitazone should be at least halved if gemfibrozil treatment is started. Marked increases in the plasma concentration and half-life of pioglitazone have also been found in healthy subjects given gemfibrozil.[2,3]

For reports of a paradoxical decrease in plasma high-density-lipoprotein cholesterol in patients taking thiazolidinediones with fibrates, see p. 1325.2.

1. Niemi M, *et al.* Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. *Diabetologia* 2003; **46:** 1319–23.
2. Jaakkola T, *et al.* Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. *Clin Pharmacol Ther* 2005; **77:** 404–14.
3. Deng L-J, *et al.* Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol* 2005; **61:** 831–6.

Pharmacokinetics

Rosiglitazone is well absorbed from the gastrointestinal tract after oral dosing. Peak plasma concentrations occur about 1 hour after a dose and the bioavailability is 99%. It is 99.8% bound to plasma proteins. Rosiglitazone is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP2C8. It is excreted in the urine and faeces, and has a half-life of 3 to 4 hours. Rosiglitazone crosses the placenta and has been found in fetal tissue.

References.

1. Baldwin SJ, *et al.* Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. *Br J Clin Pharmacol* 1999; **48:** 424–32.
2. Chapelsky MC, *et al.* Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. *J Clin Pharmacol* 2003; **43:** 252–9.
3. Kirchheiner J, *et al.* Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. *Clin Pharmacol Ther* 2006; **80:** 657–67.
4. Aramwit P, *et al.* Pharmacokinetics of single-dose rosiglitazone in chronic ambulatory peritoneal dialysis patients. *J Clin Pharm Ther* 2008; **33:** 685–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avandia; Diaben; Gaudil; Glimide; Gliximina; Gludex; Rosiglit; ***Austral.***: Avandia; ***Austria***: Avandia†; ***Belg.***: Avandia†; ***Braz.***: Avandia†; ***Canad.***: Avandia; ***Chile***: Avandia; Rosivan; ***China***: Ai Neng (爱能); Ao Luo Hua (奥洛华); Avandia (文迪雅)†; Naidi (耐迪); Sheng Ao (圣奥); Sheng Min (圣敏); Weigeluo (维戈洛); Yi Li Xi (宜力喜); ***Cz.***: Avandia†; ***Denm.***: Avandia†; ***Fin.***: Avandia†; ***Fr.***: Avandia†; ***Ger.***: Avandia†; ***Gr.***: Avandia†; ***Hong Kong***: Avandia; ***Hung.***: Avandia†; ***India***: Rezult; Roglin; Rosicon; ***Indon.***: Avandia; ***Irl.***: Avandia†; ***Israel***: Avandia; Rosi; Rossini†; ***Ital.***: Avandia†; ***Malaysia***: Avandia; ***Mex.***: Avandia; ***Neth.***: Avandia†; ***Norw.***: Avandia†; ***NZ***: Avandia; ***Philipp.***: Avandia†; ***Pol.***: Avandia†; ***Port.***: Avandia†; ***Rus.***: Avandia (Авандия); Roglit (Роглит); ***S.Afr.***: Avandia†; ***Singapore***: Avandia; ***Spain***: Avandia†; ***Swed.***: Avandia†; ***Switz.***: Avandia†; ***Thai.***: Avandia†; ***Turk.***: Avandia; Rosenda; Rosette; Rositaz; Rosvel; ***UK***: Avandia†; ***Ukr.***: Diaglytason (Диаглитазон)†; Roglit (Роглит); ***USA***: Avandia; ***Venez.***: Avandia.

Multi-ingredient Preparations. ***Arg.***: Avandamet; Avandaryl; Gludex Plus; Rosiglit-Met; ***Austral.***: Avandamet; ***Austria***: Avaglim†; Avandamet†; ***Belg.***: Avandamet†; ***Braz.***: Avandamet†; ***Canad.***: Avandamet; Avandaryl†; ***Chile***: Avandamet; Avandaryl; ***China***: Avandamet (文达敏)†; ***Cz.***: Avaglim†; Avandamet†; ***Denm.***: Avaglim†; Avandamet†; ***Fin.***: Avandamet†; ***Fr.***: Avandamet†; ***Ger.***: Avaglim†; Avandamet†; ***Gr.***: Avaglim†; Avandamet†; ***Hong Kong***: Avandamet; ***Hung.***: Avaglim†; Avandamet†; ***India***: Diabetrol-3D; Glyroz; Roglin-M; Rosicon MF; ***Indon.***: Avandamet; Avandaryl; ***Irl.***: Avaglim†; Avandamet†; ***Israel***: Avandamet; ***Ital.***: Avaglim†; Avandamet†; ***Malaysia***: Avandamet; ***Mex.***: Avandamet; ***Neth.***: Avaglim†; Avandamet†; ***Norw.***: Avaglim†; Avandamet†; ***Philipp.***: Avandamet; Avandaryl†; ***Pol.***: Avandamet†; ***Port.***: Avaglim†; Avandamet†; ***Rus.***: Avandaglim (Авандаглим); Avandamet (Авандамет); ***Singapore***: Avandamet; ***Spain***: Avaglim†; Avandamet†; ***Swed.***: Avaglim†; Avandamet†; ***Switz.***: Avandamet†; ***Thai.***: Avandamet†; Avandaryl†; ***Turk.***: Avandamet; ***UK***: Avandamet†; ***Ukr.***: Avandamet (Авандамет)†; ***USA***: Avandamet; Avandaryl; ***Venez.***: Avandamet.

Ruboxistaurin *(rINN)*

LY-333531; LY-341684 (ruboxistaurin mesilate); Ruboxistaurina; Ruboxistaurine; Ruboxistaurinum; Рубоксистаурин.

(9*S*)-9-[(Dimethylamino)methyl]-6,7,10,11-tetrahydro-9*H*,19*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-18,20-dione.

$C_{28}H_{28}N_4O_3$=468.6

CAS — 169939-94-0 (ruboxistaurin); 169939-93-9 (ruboxistaurin hydrochloride); 202260-21-7 (ruboxistaurin mesilate).

UNII — 721809WQCP.

NOTE. The name Arxxant has been used as a trade mark for ruboxistaurin.

Profile

Ruboxistaurin is an oral inhibitor of the β-isoform of the enzyme protein kinase C, which is thought to play a role in the development of diabetic microvascular complications. It is under investigation as an adjunct in the treatment of diabetic retinopathy (p. 464.2).

References.

1. Joy SV, *et al.* Ruboxistaurin, a protein kinase C β inhibitor, as an emerging treatment for diabetes microvascular complications. *Ann Pharmacother* 2005; **39:** 1693–9.
2. Vinik A. The protein kinase C-β inhibitor, ruboxistaurin, for the treatment of diabetic microvascular complications. *Expert Opin Invest Drugs* 2005; **14:** 1547–59.
3. The PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: initial results of the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter randomized clinical trial. *Diabetes* 2005; **54:** 2188–97.
4. Vinik AI, *et al.* The MBBQ Study Group. Treatment of symptomatic diabetic peripheral neuropathy with the protein kinase C β -inhibitor ruboxistaurin mesylate during a 1-year, randomized, placebo-controlled, double-blind clinical trial. *Clin Ther* 2005; **27:** 1164–80.
5. Aiello LP, *et al.* PKC-DRS 2 Group. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. *Ophthalmology* 2006; **113:** 2221–30.
6. The PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007; **125:** 318–24.
7. Tuttle KR, *et al.* PKC-DRS, PKC-DMES, and PKC-DRS 2 Study Groups. Kidney outcomes in long-term studies of ruboxistaurin for diabetic eye disease. *Clin J Am Soc Nephrol* 2007; **2:** 631–6.
8. Danis RP, Sheetz MJ. Ruboxistaurin: PKC-beta inhibition for complications of diabetes. *Expert Opin Pharmacother* 2009; **10:** 2913–25.
9. Sheetz MJ, *et al.* The Mbdv Study Group. Effect of ruboxistaurin (RBX) on visual acuity decline over a 6-year period with cessation and reinstitution of therapy: results of an open-label extension of the Protein Kinase C Diabetic Retinopathy Study 2 (PKC-DRS2). *Retina* 2011; **31:** 1053–9.
10. Aiello LP, *et al.* The PKC-DRS and PKC-DRS2 Study Groups. Oral protein kinase C β inhibition using ruboxistaurin: efficacy, safety, and causes of vision loss among 813 patients (1,392 eyes) with diabetic retinopathy in the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study and the Protein kinase C β Inhibitor-Diabetic Retinopathy Study 2. *Retina* 2011; **31:** 2084–94.

Saxagliptin *(BAN, USAN, rINN)*

BMS-477118-11 (saxagliptin monohydrate); BMS-477118; Saksagliptyna; Saxagliptina; Saxagliptine; Saxagliptinum; Саксаглиптин.

(1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile.

$C_{18}H_{25}N_3O_2$=315.4

CAS — 361442-04-8 (saxagliptin); 945667-22-1 (saxagliptin monohydrate); 709031-78-7 (saxagliptin hydrochloride).

ATC — A10BH03.

ATC Vet — QA10BH03.

UNII — 8I7IO46IVQ (saxagliptin); 9GB927LAJW (saxagliptin monohydrate).

NOTE. Saxagliptin (*INN*) is anhydrous, while Saxagliptin (*USAN*) refers to the monohydrate.

Saxagliptin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de saxagliptina; Saxagliptine, Chlorhydrate de; Saxagliptini Hydrochloridum; Саксаглиптина Гидрохлорид.

$C_{18}H_{25}N_3O_2$,HCl=351.9

CAS — 709031-78-7.

ATC — A10BH03.

ATC Vet — QA10BH03.

UNII — Z8J84YIX6L.

Uses and Administration

Like sitagliptin (p. 502.1), saxagliptin is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1). Saxagliptin is given as the hydrochloride, but doses are expressed in terms of the anhydrous base; 2.79 mg of saxagliptin hydrochloride is equivalent to about 2.5 mg of saxagliptin. The usual oral dose is 2.5 or 5 mg once daily, given with or without food. When saxagliptin is given with strong inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, the dose of saxagliptin is usually 2.5 mg once daily.

For the dose of saxagliptin used in renal impairment, see p. 501.3.

References.

1. Neumiller JJ, Campbell RK. Saxagliptin: a dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2010; **67:** 1515–25.
2. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; **71:** 1441–67.
3. Scheen AJ. Metformin + saxagliptin for type 2 diabetes. *Expert Opin Pharmacother* 2012; **13:** 139–46.
4. Yang LP. Saxagliptin: a review of its use as combination therapy in the management of type 2 diabetes mellitus in the EU. *Drugs* 2012; **72:** 229–48.
5. Barnett AH, *et al.* Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin* 2012; **28:** 513–23.

Administration in renal impairment. UK and US licensed product information state that no dose adjustment for saxagliptin is needed in patients with mild renal impairment. A maximum oral dose of 2.5 mg once daily has been recommended for patients with moderate or severe impairment (creatinine clearance less than or equal to 50 mL/min), including those with end-stage renal disease requiring haemodialysis (although UK product information recommends against use altogether in the last patient group). Saxagliptin should be given after haemodialysis.

Adverse Effects and Precautions

As for Sitagliptin Phosphate, p. 502.1. Small decreases in lymphocyte counts have been seen in patients given saxagliptin, but clinically relevant adverse effects did not occur.

Interactions

The efficacy of saxagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3. Drugs that alter the activity of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 could affect the metabolism of saxagliptin. Although dosage adjustment of saxagliptin is not thought necessary with moderate inhibitors of these enzymes, such as diltiazem, low doses of saxagliptin should be used when strong inhibitors, such as ketoconazole, are given with saxagliptin (see above). The enzyme inducer rifampicin can significantly decrease exposure to saxagliptin, but exposure to its active metabolite (5-hydroxy saxagliptin) and plasma dipeptidylpeptidase-4 inhibition are not affected.

Pharmacokinetics

Saxagliptin is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations occur within about 2 hours. It is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and its major metabolite, 5-hydroxy saxagliptin, has half the potency of saxagliptin. Peak plasma concentrations of this metabolite occur within about 4 hours. The terminal plasma elimination half-lives of saxagliptin and its metabolite are about 2.5 and 3.1 hours, respectively. Both saxagliptin and 5-hydroxy saxagliptin are excreted in the urine; there may be some active renal excretion of unchanged saxagliptin. There is also some elimination of a dose in the faeces.

References.

1. Boulton DW, *et al.* Influence of renal or hepatic impairment on the pharmacokinetics of saxagliptin. *Clin Pharmacokinet* 2011; **50:** 253–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Onglyza; ***Austral.***: Onglyza; ***Austria***: Onglyza; ***Belg.***: Onglyza; ***Braz.***: Onglyza; ***Canad.***: Onglyza; ***Chile***: Onglyza; ***China***: Onglyza (安立泽); ***Cz.***: Onglyza; ***Denm.***: Onglyza; ***Fr.***: Onglyza; ***Ger.***: Onglyza; ***Gr.***: Onglyza; ***Hong Kong***: Onglyza; ***Hung.***: Onglyza; ***India***: Onglyza; ***Israel***: Onglyza; ***Ital.***: Onglyza; ***Jpn***: Onglyza; ***Malaysia***: Onglyza; ***Mex.***: Onglyza; ***Neth.***: Onglyza; ***Norw.***: Onglyza; ***NZ***: Onglyza; ***Philipp.***: Onglyza; ***Pol.***: Onglyza; ***Port.***: Onglyza; ***Rus.***: Onglyza (Онглиза); ***Singapore***: Onglyza; ***Spain***: Onglyza; ***Swed.***: Ongly-

za; ***Switz.***: Onglyza; ***Thai.***: Onglyza; ***Turk.***: Onglyza; ***UK***: Onglyza; ***Ukr.***: Ongliza (Онглиза); ***USA***: Onglyza.

Multi-ingredient Preparations. ***Belg.***: Kombiglyze; ***Neth.***: Komboglyze; ***Spain***: Komboglyze; ***Switz.***: Duoglyze; Kombiglyze; ***UK***: Komboglyze; ***USA***: Kombiglyze.

Sitagliptin Phosphate

(BANM, USAN, rINNM)

Fosfato de sitagliptina; MK-0431; MK-431; Ono-5435; Sitagliptine, Phosphate de; Sitagliptini Phosphas; Ситаглиптина Фосфат.

7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine monophosphate monohydrate.

$C_{16}H_{15}F_6N_5O.H_3O_4P.H_2O$=523.3

CAS — 486460-32-6 (sitagliptin); 654671-78-0 (sitagliptin phosphate); 654671-77-9 (sitagliptin phosphate monohydrate).

UNII — TS63EW8X6F.

Uses and Administration

Sitagliptin inhibits dipeptidylpeptidase-4, an enzyme responsible for degradation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (see Action, under Exenatide, p. 471.1, for more detail on the role of incretin hormones in glucose homoeostasis). Sitagliptin is used in the treatment of type 2 diabetes mellitus (p. 459.1).

Sitagliptin is given as the phosphate, but doses are in terms of the base; 128.5 mg of sitagliptin phosphate is equivalent to about 100 mg of sitagliptin. The usual oral dose is the equivalent of 100 mg of sitagliptin once daily. When given with metformin, sitagliptin may be given in 2 divided doses. The dose of sulfonylurea or insulin may need to be lowered when used with sitagliptin. Sitagliptin may be taken with or without food. Dosage should be adjusted in patients with renal impairment (see p. 502.1).

References.

1. Lyseng-Williamson KA. Sitagliptin. *Drugs* 2007; **67:** 587–97.
2. Florentin M, *et al.* Sitagliptin in clinical practice: a new approach in the treatment of type 2 diabetes. *Expert Opin Pharmacother* 2008; **9:** 1705–20.
3. Richter B, *et al.* Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 01/07/09).
4. Williams-Herman D, *et al.* Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. *Curr Med Res Opin* 2009; **25:** 569–83.
5. Dhillon S. Sitagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2010; **70:** 489–512.
6. Chwieduk CM. Sitagliptin/metformin fixed-dose combination: in patients with type 2 diabetes mellitus. *Drugs* 2011; **71:** 349–61.
7. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; **71:** 1441–67.

Administration in renal impairment. Sitagliptin has been studied in patients with type 2 diabetes mellitus and renal impairment.[1] Licensed product information suggests the following oral doses of sitagliptin in patients with renal impairment, based on creatinine clearance (CC):

- mild impairment (CC 50 mL/min or more): no adjustment necessary, 100 mg once daily
- moderate impairment (CC 30 to less than 50 mL/min): 50 mg once daily
- severe impairment (CC less than 30 mL/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis: 25 mg once daily. It may be given without regard to the timing of haemodialysis

1. Chan JC, *et al.* Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab* 2008; **10:** 545–55.

Adverse Effects, Treatment, and Precautions

Adverse effects reported with sitagliptin include headache, dizziness, and gastrointestinal disturbances. Peripheral oedema has occurred, particularly in patients also being treated with a thiazolidinedione. Upper respiratory-tract infections and nasopharyngitis have also occurred, but a causal relationship has not been established. Rashes and other hypersensitivity reactions including anaphylaxis, angioedema, urticaria, cutaneous vasculitis, and Stevens-Johnson syndrome have been reported. There have also been isolated cases of elevated liver enzyme values and pancreatitis, including haemorrhagic and necrotising pancreatitis. Impaired renal function, including acute renal failure (sometimes requiring dialysis), has also been reported. Hypoglycaemia is unlikely with sitagliptin given alone, but it may contribute to hypoglycaemia caused by other oral antidiabetics such as sulfonylureas.

Sitagliptin should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. The dose of sitagliptin should be reduced in moderate and severe renal impairment. It is recommended that renal function is assessed before starting treatment and periodically thereafter.

Incidence of adverse effects. A pooled analysis included data from 12 studies of sitagliptin given as monotherapy or with other oral antidiabetics, and compared with placebo or other oral antidiabetics, in 6139 patients treated for up to 2 years.[1] Overall, the incidence of adverse experiences did not significantly differ between patients exposed to sitagliptin and those who were not. About 13% of patients given sitagliptin had an adverse experience that was determined to be possibly, probably, or definitely drug-related; 0.2% had a serious adverse experience. As expected, hypoglycaemia occurred more often during co-treatment with a sulfonylurea. For those not given a sulfonylurea the incidence of hypoglycaemia was 2.6% in patients given sitagliptin, which was similar to 2.3% in those not exposed to sitagliptin.

1. Williams-Herman D, *et al.* Safety and tolerability of sitagliptin in patients with type 2 diabetes: a pooled analysis. *BMC Endocr Disord* 2008; **8:** 14. Available at: http://www.biomedcentral.com/content/pdf/1472-6823-8-14.pdf (accessed 14/09/09)

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Effects on the immune system. In addition to regulating glucose homoeostasis, dipeptidyl peptidase-4 (DPP-4) has many diverse functions such as modulating cell growth, differentiation, and transformation, and immune function. Long-term inhibition of this enzyme by drugs, such as sitagliptin, may cause immune suppression and increase the risk of cancer.[1-3] A case-control study has shown an increased incidence of reports of infections, especially upper respiratory-tract infections, in users of DPP-4 inhibitors compared with users of other antidiabetic drugs.[4]

1. Stulc T, Sedo A. Inhibition of multifunctional dipeptidyl peptidase-IV: is there a risk of oncological and immunological adverse effects? *Diabetes Res Clin Pract* 2010; **88:** 125–31.
2. Elashoff M, *et al.* Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; **141:** 150–6.
3. Spranger J, *et al.* GLP-1-based therapies: the dilemma of uncertainty. *Gastroenterology* 2011; **141:** 20–3.
4. Willemen MJ, *et al.* Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. *Diabetes Care* 2011; **34:** 369–74.

Effects on the pancreas. There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis, associated with sitagliptin use;[1,2] licensed product information states that if pancreatitis is suspected, sitagliptin should be stopped at once.

Patients with type 2 diabetes may have a greater incidence of pancreatitis when compared with non-diabetic subjects,[3] and some observational studies have not found a further increase in risk with sitagliptin itself.[3,4] However, a review of the FDA Adverse Event Reporting System (AERS) database from 2004 to 2009 showed that pancreatitis was six times more likely to be reported with sitagliptin (or exenatide) than other therapies in type 2 diabetes.[5]

1. FDA. Information for healthcare professionals: acute pancreatitis and sitagliptin (marketed as Januvia and Janumet) (issued 25th September, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm (accessed 26/09/11)
2. Anonymous. Sitagliptin: too many cases of pancreatitis. *Prescrire Int* 2010; **19:** 75.
3. Garg R, *et al.* Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010; **33:** 2349–54.
4. Dore DD, *et al.* Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 2009; **25:** 1019–27.
5. Elashoff M, *et al.* Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; **141:** 150–6.

Overdosage. In the UK, the *National Poisons Information Service* states that oral activated charcoal may be considered in adults and children who have ingested more than 15 mg/kg of sitagliptin and present within 1 hour, provided they are conscious and the airway can be protected. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p. 484.3).

Interactions

The efficacy of sitagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3. For reports of a possible interaction between sitagliptin and statins, see Antidiabetics under Simvastatin, p. 1495.1.

References.

1. Scheen AJ. Dipeptidylpeptidase-4 inhibitors (gliptins): focus on drug-drug interactions. *Clin Pharmacokinet* 2010; **49:** 573–88.

Pharmacokinetics

Sitagliptin is absorbed from the gastrointestinal tract, with a peak plasma concentration occurring about 1 to 4 hours after an oral dose, and a bioavailability of about 87%. It undergoes minimal metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2C8. About 79% of a dose is excreted unchanged in the urine. Renal excretion of sitagliptin involves active tubular secretion; it is a substrate for organic anion transporter-3 and P-glycoprotein. Its terminal half-life is about 12 hours.

References.

1. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* 2010; **12:** 648–58.
2. Golightly LK, *et al.* Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet* 2012; **51:** 501–14. Correction. *ibid.*; 831.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Januvia; ***Austral.***: Januvia; ***Austria***: Januvia; ***Belg.***: Januvia; ***Braz.***: Januvia; ***Canad.***: Januvia; ***Chile***: Januvia; ***China***: Januvia (捷诺维); ***Cz.***: Januvia; Ristaben; Tesavel; Xelevia; ***Denm.***: Januvia; ***Fr.***: Januvia; Xelevia; ***Ger.***: Januvia; Xelevia; ***Gr.***: Januvia; Xelevia; ***Hong Kong***: Januvia; ***Hung.***: Januvia; Xelevia; ***India***: Januvia; ***Indon.***: Januvia; ***Irl.***: Januvia; Ristaben; Tesavel; Xelevia; ***Israel***: Januvia; ***Ital.***: Januvia; Tesavel; Xelevia; ***Jpn***: Glactiv; Januvia; ***Malaysia***: Januvia; ***Mex.***: Januvia; ***Neth.***: Januvia; Ristaben; Tesavel; Xelevia; ***Norw.***: Januvia; ***NZ***: Januvia; ***Philipp.***: Januvia; ***Pol.***: Januvia; Ristaben; Tesavel; Xelevia; ***Port.***: Januvia; Ristaben; Tesavel; Xelevia; ***Rus.***: Januvia (Янувия); ***Singapore***: Januvia; ***Spain***: Januvia; Ristaben; Tesavel; Xelevia; ***Swed.***: Januvia; ***Switz.***: Januvia; Xelevia; ***Thai.***: Januvia; ***Turk.***: Januvia; ***UK***: Januvia; ***Ukr.***: Yanuvia (Янувия); ***USA***: Januvia.

Multi-ingredient Preparations. ***Arg.***: Janumet; ***Austral.***: Janumet; ***Austria***: Janumet; Velmetia; ***Belg.***: Janumet; ***Braz.***: Janumet; ***Canad.***: Janumet; ***Chile***: Janumet; ***Cz.***: Efficib; Janumet; Ristfor; Velmetia; ***Denm.***: Janumet; ***Fr.***: Janumet; Velmetia; ***Ger.***: Janumet; Velmetia; ***Gr.***: Janumet; ***Hong Kong***: Janumet; ***Hung.***: Janumet; Velmetia; ***India***: Janumet; ***Irl.***: Efficib; Janumet; Ristfor; Velmetia; ***Israel***: Janumet; ***Ital.***: Efficib; Janumet; Velmetia; ***Malaysia***: Janumet; ***Neth.***: Efficib; Janumet; Ristfor; Velmetia; ***Norw.***: Janumet; ***NZ***: Janumet; ***Philipp.***: Janumet; ***Pol.***: Efficib; Janumet; Ristfor; Velmetia; ***Port.***: Efficib; Janumet; Ristfor; Velmetia; ***Singapore***: Janumet; ***Spain***: Efficib; Janumet; Ristfor; Velmetia; ***Swed.***: Janumet; ***Switz.***: Janumet; Velmetia; ***Thai.***: Janumet; ***UK***: Janumet; ***Ukr.***: Janumet (Янумет); ***USA***: Janumet; Juvisync.

Sulfonylurea Antidiabetics

Antidiabéticos sulfonilureas; Sulphonylurea Antidiabetics.

Uses and Administration

The sulfonylurea antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p. 459.1). They are given to supplement treatment by diet modification and exercise when these have not proved effective on their own, although the biguanide metformin is preferred in patients who are obese.

Sulfonylureas, often described as insulin secretagogues, appear to have several modes of action, apparently mediated by inhibition of ATP-sensitive potassium channels. Initially, secretion of insulin by functioning islet beta cells is increased. However, insulin secretion subsequently falls again but the hypoglycaemic effect persists and may be due to inhibition of hepatic glucose production and increased sensitivity to any available insulin; this may explain the clinical improvement seen in glycaemic control. The duration of action of sulfonylureas is variable; drugs such as tolbutamide are relatively short-acting (about 6 to 12 hours) while chlorpropamide has a prolonged action (over 24 hours).

Sulfonylurea therapy may be combined with metformin or other oral hypoglycaemics in patients who fail to respond to a single type of drug; such combination therapy is usually tried (in the absence of contra-indications) before considering the addition of, or transfer to, insulin therapy.

Reviews.

1. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 2004; **64:** 1339–58.
2. Bell DS. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. *Clin Ther* 2004; **26:** 1714–27.

Administration in children. Although rare, the incidence of type 2 diabetes mellitus in children and adolescents is increasing, related in part to the increase in obesity occurring particularly in westernised countries. There is limited experience with the use of sulfonylureas in children, and the biguanide metformin is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision, and that initial doses for adolescents should be given at the lower end of the adult dose range before adjusting according to response. The *BNFC* also sug-

gests that longer-acting sulfonylureas such as chlorpropamide and glibenclamide should generally be avoided because of the risk of hypoglycaemia, and that shorter-acting alternatives such as tolbutamide may be preferred.

For details on the use of sulfonylureas in neonatal diabetes, see p. 503.1.

Diabetes mellitus. *Neonatal diabetes mellitus* (a diagnosis of diabetes within the first 6 months of life) in the absence of pancreatic islet autoantibodies is generally the result of mutation in the genes that regulate beta-cell function. Some forms of neonatal diabetes are transient, but the most common cause of permanent neonatal diabetes is mutation in the KCNJ11 gene, which encodes the Kir6.2 subunit of the beta cell ATP-sensitive potassium channel.[1] Insulin treatment is necessary, but there has been some interest in a possible role for sulfonylureas because of their action at this potassium channel.

The use of sulfonylureas has been described in 49 patients with Kir6.2 mutations ranging in age from 3 months to 36 years old.[2] Most were given glibenclamide, but a few were treated with gliclazide, glimepiride, glipizide, or tolbutamide. Patients managed in hospital were started on an oral glibenclamide dose of 100 micrograms/kg twice daily, which was increased daily by 200 micrograms/kg; those managed as outpatients started with 100 micrograms/kg daily and had the dose increased by 100 micrograms/kg once each week. Insulin therapy was gradually withdrawn during this dose escalation period, in which glibenclamide dosage was increased until insulin independence or a dose of at least 800 micrograms/kg daily was reached. Of the 49 patients, 44 were successfully transferred to a sulfonylurea at a median dose equivalent to glibenclamide 450 micrograms/kg daily (range 50 micrograms/kg to 1.5 mg/kg daily), with improved glycated haemoglobin and no change in the frequency of hypoglycaemic episodes. Over time, the dose of sulfonylurea could be reduced. Neurological features including developmental delay and epilepsy were much more prevalent in the patients who could not be transferred to a sulfonylurea. Similar success has also been described in a group of 10 children aged between 6 months and 10 years old, using either glibenclamide or glipizide.[3]

Mutations of the ABCC8 gene, which encodes the sulfonylurea receptor 1 subunit of the beta cell ATP-sensitive potassium channel, can cause transient or permanent neonatal diabetes. Patients with this condition have also been successfully transferred from insulin to sulfonylurea therapy, although the dosage requirement appears to be lower than that for patients with Kir6.2 mutations. In 23 of 27 patients aged from 2 months to 46 years, a median glibenclamide dose of 260 micrograms/kg daily (or the dose equivalent using gliclazide, glipizide, or tolbutamide) was found to be effective.[4]

1. Hattersley A, *et al*. ISPAD Clinical Practice Consensus Guidelines 2009 compendium: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2009; **10** (suppl 12): 33–42. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Monogenic%20diabetes.pdf (accessed 09/02/11)
2. Pearson ER, *et al*. Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; **355:** 467–77.
3. Tonini G, *et al*. Early-Onset Diabetes Study Group of the Italian Society of Paediatric Endocrinology and Diabetology. Sulfonylurea treatment outweighs insulin therapy in short-term metabolic control of patients with permanent neonatal diabetes mellitus due to activating mutations of the KCNJ11 (KIR6.2) gene. *Diabetologia* 2006; **49:** 2210–13.
4. Rafiq M, *et al*. Neonatal Diabetes International Collaborative Group. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. *Diabetes Care* 2008; **31:** 204–9.

Adverse Effects

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhoea, and a metallic taste may occur with sulfonylureas and are usually mild and dose-dependent; increased appetite and weight gain may occur. Rashes and pruritus may occur and photosensitivity has been reported. Rashes are usually hypersensitivity reactions and may progress to more serious disorders (see below). Facial flushing may develop in patients receiving sulfonylureas, particularly chlorpropamide, when alcohol is consumed (see under Interactions, p. 505.2).

Mild hypoglycaemia may occur; severe hypoglycaemia is usually an indication of overdosage and is relatively uncommon. Hypoglycaemia is more likely with long-acting sulfonylureas such as chlorpropamide and glibenclamide, which have been associated with severe, prolonged, and sometimes fatal hypoglycaemia.

Other severe effects may be manifestations of a hypersensitivity reaction. They include altered liver enzyme values, hepatitis and cholestatic jaundice, leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, erythema multiforme or the Stevens-Johnson syndrome, exfoliative dermatitis, and erythema nodosum.

The sulfonylureas, particularly chlorpropamide, occasionally induce a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) characterised by water retention, hyponatraemia, and CNS effects. However, some sulfonylureas, such as glibenclamide, glipizide, and tolazamide are also stated to have mild diuretic actions.

Work on tolbutamide has suggested that the sulfonylureas might be associated with an increase in cardiovascular mortality; this has been the subject of considerable debate (see Effects on the Cardiovascular System, p. 503.2).

Reviews.

1. Paice BJ, *et al*. Undesired effects of the sulphonylurea drugs. *Adverse Drug React Acute Poisoning Rev* 1985; **4:** 23–36.
2. Harrower ADB. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Safety* 2000; **22:** 313–20.
3. Salas M, Caro JJ. Are hypoglycaemia and other adverse effects similar among sulphonylureas? *Adverse Drug React Toxicol Rev* 2002; **21:** 205–17.

Effects on the blood. There have been isolated reports of thrombocytopenia in patients given sulfonylurea antidiabetics.[1,2] Cases of haemolytic anaemia have also been described,[3,4] some in patients found to have G6PD deficiency.[5,6]

1. Israeli A, *et al*. Glibenclamide causing thrombocytopenia and bleeding tendency: case reports and a review of the literature. *Klin Wochenschr* 1988; **66:** 223–4.
2. Cartron G, *et al*. Glimepiride-induced thrombocytopenic purpura. *Ann Pharmacother* 2000; **34:** 120.
3. Nataas OB, Nesthus I. Immune haemolytic anaemia induced by glibenclamide in selective IgA deficiency. *BMJ* 1987; **295:** 366–7.
4. Noto H, *et al*. Glyburide-induced hemolysis in myelodysplastic syndrome. *Diabetes Care* 2000; **23:** 129.
5. Meloni G, Meloni T. Glyburide-induced acute haemolysis in a G6PD-deficient patient with NIDDM. *Br J Haematol* 1996; **92:** 159–60.
6. Vinzio S, *et al*. Glibenclamide-induced acute haemolytic anaemia revealing a G6PD-deficiency. *Diabetes Res Clin Pract* 2004; **64:** 181–3.

Effects on the cardiovascular system. A multicentre study carried out under the University Group Diabetes Program (UGDP) reported an increased incidence in mortality from cardiovascular complications in diabetic patients given tolbutamide as compared with those treated with diet alone or insulin;[1] a similar increase was also noted in patients given phenformin.[2] The reports from the UGDP aroused prolonged controversy, which was not entirely settled by detailed reassessment of relevant studies.[3] Eventually in 1984 the FDA made it a requirement that sulfonylurea oral antidiabetics be labelled with a specific warning about the possibility of increased cardiovascular mortality associated with the use of these drugs.[4] Subsequently the cardiovascular effects of the sulfonylureas were reviewed.[5] It has been hypothesised that the action of the sulfonylureas in preventing the opening of ATP-sensitive potassium channels in the myocardium may abolish adaptive changes (ischaemic preconditioning) that protect the heart against ischaemic insult.[6]

There is still debate about the risk of death and cardiovascular events in patients taking sulfonylureas. The UK Prospective Diabetes Study did not find any adverse cardiovascular effects associated with sulfonylurea therapy.[7] However, other studies have suggested that there are increased risks associated with sulfonylurea use. A retrospective cohort study[8] found that among patients newly treated for type 2 diabetes, sulfonylurea monotherapy was associated with an increased risk of death, which also appeared to be dose related, compared with metformin therapy. Using data from the UK General Practice Research Database, another retrospective cohort study[9] also found an excess risk for all cause mortality associated with sulfonylureas when compared with metformin. An increased risk of myocardial infarction was no longer statistically significant in the fully adjusted model, but newer sulfonylureas were associated with an increased risk of congestive heart failure. The results of a case-control study[10] suggested that the risk of myocardial infarction was higher in users of older sulfonylureas (glibenclamide, glipizide, and tolbutamide) than of newer drugs (gliclazide and glimepiride) or non-sulfonylurea antidiabetics (mainly metformin). The risk was higher again in patients receiving insulin, and worst in those not receiving any drug treatment for their diabetes. A retrospective cohort study[11] also found a trend suggesting that, in terms of mortality risk, glimepiride might be preferred in patients with a history of coronary artery disease.

A few observational studies have looked at in-hospital events in diabetic patients admitted with acute myocardial infarction. One study[12] found that prior use of a sulfonylurea was not associated with an increased risk of death in hospital, and actually suggested that outcome was better in those who had been taking a sulfonylurea compared with those who had not (other treatments were generally metformin or insulin). Another[13] compared different sulfonylureas and found a lower risk of in-hospital arrhythmias, ischaemic complications, or death in patients who had been taking gliclazide or glimepiride before admission, compared with glibenclamide. Relating survival effects to pre-admission therapy, an epidemiological study[14] suggested that use of a sulfonylurea (glibenclamide, glimepiride, or glipizide) before the myocardial infarction did not adversely affect mortality rates up to 1 year later compared with insulin.

The effects of sulfonylureas given after discharge following myocardial infarction have also been studied. Follow-up[15] over about 2 years in patients who had taken part in the DIGAMI 2 study suggested a neutral effect on the risk of non-fatal myocardial infarction and stroke compared with a decreased risk from metformin and an increased risk from insulin. In a cohort study[16] of diabetic patients who were not treated with percutaneous coronary intervention within 48 hours of admission, follow-up for about 2 years found an increased risk of non-fatal myocardial infarction and cardiovascular mortality in patients taking sulfonylureas compared with metformin. Only gliclazide was not associated with an increased risk of cardiovascular events.

1. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes III: clinical implications of UGDP results. *JAMA* 1971; **218:** 1400–10.
2. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes IV: a preliminary report on phenformin results. *JAMA* 1971; **217:** 777–84.
3. Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. *JAMA* 1975; **231:** 583–600.
4. FDA. Class labeling for oral hypoglycemics. *FDA Drug Bull* 1984; **14:** 16–17.
5. Huupponen R. Adverse cardiovascular effects of sulphonylurea drugs: clinical significance. *Med Toxicol* 1987; **2:** 190–209.
6. Yellon DM, *et al*. Angina reassessed: pain or protector? *Lancet* 1996; **347:** 1159–62.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid*. 1999; **354:** 602.
8. Simpson SH, *et al*. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *Can Med Assoc J* 2006; **174:** 169–74.
9. Tzoulaki I, *et al*. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009; **339:** b4731.
10. Johnsen SP, *et al*. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther* 2006; **13:** 134–40.
11. Pantalone KM, *et al*. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care* 2010; **33:** 1224–9.
12. Danchin N, *et al*. Role of previous treatment with sulfonylureas in diabetic patients with acute myocardial infarction: results from a nationwide French registry. *Diabetes Metab Res Rev* 2005; **21:** 143–9.
13. Zeller M, *et al*. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *J Clin Endocrinol Metab* 2010; **95:** 4993–5002.
14. Arruda-Olson AM, *et al*. Effect of second-generation sulfonylureas on survival in patients with diabetes mellitus after myocardial infarction. *Mayo Clin Proc* 2009; **84:** 28–33.
15. Mellbin LG, *et al*. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008; **29:** 166–76.
16. Jørgensen CH, *et al*. Effects of oral glucose-lowering drugs on long term outcomes in patients with diabetes mellitus following myocardial infarction not treated with emergent percutaneous coronary intervention-a retrospective nationwide cohort study. *Cardiovasc Diabetol* 2010; **9:** 54. Available at: http://www.cardiab.com/content/pdf/1475-2840-9-54.pdf (accessed 14/03/11)

Effects on the eyes. When a diabetic patient who had had bilateral visual loss for several months and who had been taking chlorpropamide for a year stopped treatment, visual acuity improved and colour vision rapidly returned.[1] A 5-day challenge with chlorpropamide resulted in a mild decrease in acuity followed by return to baseline values when treatment was again stopped. Drug-induced optic neuropathy was considered to have occurred. There is also a report of a patient with type 2 diabetes mellitus who developed myopia 2 days after starting treatment with glibenclamide 10 mg daily.[2] Visual difficulties resolved a few days after stopping glibenclamide.

1. Wymore J, Carter JE. Chlorpropamide-induced optic neuropathy. *Arch Intern Med* 1982; **142:** 381.
2. Teller J, *et al*. Accommodation insufficiency induced by glybenclamide. *Ann Ophthalmol* 1989; **21:** 275–6.

Effects on the kidneys. The nephrotic syndrome has been reported in a patient treated with chlorpropamide.[1] Serological testing and renal biopsy showed that the glomerular lesions were of an immune-complex nature. Both the nephrotic syndrome and the glomerulonephritis resolved after treatment was stopped. The patient also developed a skin eruption, hepatitis, and eosinophilia.

1. Appel GB, *et al*. Nephrotic syndrome and immune complex glomerulonephritis associated with chlorpropamide therapy. *Am J Med* 1983; **74:** 337–42.

Effects on the liver. Chlorpropamide was implicated[1] in 8 of 53 cases of drug-induced acute liver disease admitted to a hospital in Jamaica over the years 1973 to 1988. Hepatocanalicular cholestasis occurred in 5 cases and diffuse necrosis in 3. One patient with massive hepatic necrosis died. Other hepatic reactions associated with sulfonylurea antidiabetics have included intrahepatic cholestasis with glibenclamide[2-4] and glimepiride,[5,6] and acute hepatitis-like reactions with glibenclamide,[7] glimepiride,[8] and gliclazide.[9,10] A case of mixed liver damage involving necrosis, intrahepatic cholestasis, and hepatitis with gliben-

clamide[11] has been described. Granulomatous hepatitis has also been reported with glibenclamide.[12]

1. Lee MG, *et al.* Drug-induced acute liver disease. *Postgrad Med J* 1989; **65:** 367–70.
2. Wongpaitoon V, *et al.* Intrahepatic cholestasis and cutaneous bullae associated with glibenclamide therapy. *Postgrad Med J* 1981; **57:** 244–6.
3. Krivoy N, *et al.* Fatal toxic intrahepatic cholestasis secondary to glibenclamide. *Diabetes Care* 1996; **19:** 385–6.
4. Tholakanahalli VN, *et al.* Glibenclamide-induced cholestasis. *West J Med* 1998; **168:** 274–7.
5. Sitruk V, *et al.* Hépatite aiguë cholestatique induite par le glimépiride. *Gastroenterol Clin Biol* 2000; **24:** 1233–4.
6. Chounta A, *et al.* Cholestatic liver injury after glimepiride therapy. *J Hepatol* 2005; **42:** 944–6.
7. Goodman RC, *et al.* Glyburide-induced hepatitis. *Ann Intern Med* 1987; **106:** 837–9.
8. Dusoleil A, *et al.* Hépatite aiguë induite par le glimépiride. *Gastroenterol Clin Biol* 1999; **23:** 1096–7.
9. Dourakis SP, *et al.* Gliclazide-induced acute hepatitis. *Eur J Gastroenterol Hepatol* 2000; **12:** 119–21.
10. Chitturi S, *et al.* Gliclazide-induced acute hepatitis with hypersensitivity features. *Dig Dis Sci* 2002; **47:** 1107–10.
11. Petrogiannopoulos C, Zacharof A. Glibenclamide and liver disease. *Diabetes Care* 1997; **20:** 1215.
12. Saw D, *et al.* Granulomatous hepatitis associated with glyburide. *Dig Dis Sci* 1996; **41:** 322–5.

Effects on the thyroid. See under Precautions, p. 504.3.

Hypoglycaemia. All sulfonylurea antidiabetics can cause hypoglycaemia. Those with a prolonged action, such as chlorpropamide and glibenclamide, appear to cause severe hypoglycaemia more often than shorter-acting drugs such as tolbutamide.[1] Newer short-acting sulfonylureas, such as glibornuride, gliclazide, glimepiride, and glipizide, also appear to be less often associated with severe hypoglycaemia.[1-3] The risk of hypoglycaemia in patients receiving sulfonylureas may be increased by missed or irregular meals, older age, hepatic or renal impairment, and drug interactions.[3] A small study[4] has also suggested that the presence of the rare cytochrome P450 isoenzyme genotypes CYP2C9*2/*3 or *3/*3, which are predictive of impaired metabolism of many sulfonylureas, might be considered an additional, but not major, risk factor for severe hypoglycaemia.

See also under Abuse, p. 504.2, and Overdosage, p. 504.1.

1. Shorr RI, *et al.* Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 1996; **44:** 751–5.
2. Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. *Diabet Med* 1999; **16:** 586–90.
3. Amiel SA, *et al.* Hypoglycaemia in type 2 diabetes. *Diabet Med* 2008; **25:** 245–54.
4. Holstein A, *et al.* Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol* 2005; **60:** 103–6.

Overdosage. An analysis[1] found that hypoglycaemia developed only in 56 of 185 children reported to 10 regional poison centres in the USA after ingesting sulfonylureas. A lack of hypoglycaemia during the first 8 hours after ingestion was predictive of a benign outcome, and it was recommended that suspected cases be observed for 8 hours with frequent blood glucose monitoring and free access to oral foods. Children who developed signs of hypoglycaemia, or in whom blood glucose fell below 3.3 mmol/litre could be given intravenous glucose if necessary. Others[2] have suggested that because multiple fingerstick blood sampling can be painful and stressful to young children, overnight monitoring for clinical signs of hypoglycaemia may be adequate for asymptomatic toddlers thought to have ingested a sulfonylurea. The use of prophylactic intravenous glucose (before clinical or laboratory evidence of hypoglycaemia) has also been discouraged,[2] because it may delay the onset and detection of hypoglycaemia, and confound the diagnosis of sulfonylurea poisoning.

1. Spiller HA, *et al.* Prospective multicenter study of sulfonylurea ingestion in children. *J Pediatr* 1997; **131:** 141–6.
2. Calello DP, *et al.* Case files of the Medical Toxicology Fellowship Training Program at the Children's Hospital of Philadelphia: a pediatric exploratory sulfonylurea ingestion. *J Med Toxicol* 2006; **2:** 19–24.

Treatment of Adverse Effects

Oral activated charcoal may be given in acute poisoning with sulfonylureas, if the patient presents within 1 hour of ingestion and is conscious, and the airway can be protected. Gastric lavage might be considered, particularly after a potentially life-threatening overdose, but it is generally of limited benefit and not necessary if activated charcoal can be given promptly. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p. 484.3). The patient should be observed over several days in case hypoglycaemia recurs. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia.

References.

1. Spiller HA. Management of antidiabetic medication in overdose. *Drug Safety* 1998; **19:** 411–24.

Octreotide. Octreotide inhibits the secretion of insulin and has, therefore, been tried in addition to the usual management of sulfonylurea overdosage (above). It has been used to manage prolonged or refractory hypoglycaemia, and to prevent rebound hypoglycaemia, in cases of poisoning and in sulfonylurea-treated patients with renal impairment. A review[1] of reported cases found that octreotide was usually given by subcutaneous injection, in doses ranging from 40 to 100 micrograms; the most commonly used regimen was 50 micrograms given 2 or 3 times daily. There have also been reports of using a continuous intravenous infusion of 1.8 micrograms/kg per hour. In most cases, octreotide treatment was continued for 12 to 72 hours, but it may be needed for several days after long-acting sulfonylureas or modified-release preparations. Patients should be observed for at least 12 to 24 hours after the last dose of octreotide, to monitor for rebound hypoglycaemia.

There have also been a few reports of the use of intravenous octreotide in children.[2,3] In a girl aged 2 years and 9 months, an initial dose of 2 micrograms/kg was followed by an infusion of 2 micrograms/kg per hour.[2] In another case,[2] a 12-month-old boy was given a single dose of 2.5 micrograms/kg. It has also been suggested[1] that a subcutaneous dose of 1 to 1.25 micrograms/kg might be suitable for children.

The use of octreotide has also been studied[4] in patients presenting with hypoglycaemia during sulfonylurea treatment (none were believed to have taken a large amount of drug as a suicide attempt). The small controlled study found that, compared with placebo, there were higher serum-glucose concentrations in the 8 hours after a single dose of subcutaneous octreotide 75 micrograms, and recurrent hypoglycaemic episodes were less frequent.

1. Lheureux PER, *et al.* Bench-to-bedside review: antidotal treatment of sulfonylurea-induced hypoglycaemia with octreotide. *Crit Care* 2005; **9:** 543–9.
2. Rath S, *et al.* Octreotide in children with hypoglycaemia due to sulfonylurea ingestion. *J Paediatr Child Health* 2008; **44:** 383–4.
3. Glatstein M, *et al.* Sulfonylurea intoxication at a tertiary care paediatric hospital. *Can J Clin Pharmacol* 2010; **17:** e51–6. Available at: http://www.cjcp.ca/cjcp_09023_koren3_e51_e56-pdf-r108986 (accessed 22/09/11)
4. Fasano CJ, *et al.* Comparison of octreotide and standard therapy versus standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2008; **51:** 400–406.

Precautions

Sulfonylureas should not be used in type 1 diabetes mellitus. Use in type 2 diabetes mellitus is contra-indicated in patients with ketoacidosis and in those with severe infection, trauma, or other severe conditions where the sulfonylurea is unlikely to control the hyperglycaemia; insulin should be used in such situations.

Insulin is also preferred for therapy during pregnancy although there is growing interest in the use of glibenclamide in the management of gestational diabetes (see Pregnancy, p. 504.3).

Sulfonylureas are associated with an increased risk of hypoglycaemia. They should therefore be used with caution or avoided in patients with impaired renal or hepatic function, and a similar precaution would tend to apply in other groups with an increased susceptibility to this effect, such as the elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency. Irregular mealtimes, missed meals, changes in diet, or prolonged exercise may also provoke hypoglycaemia. Sulfonylureas with a long half-life, such as chlorpropamide and glibenclamide, should be avoided in those at risk. Where a sulfonylurea needs to be used in at-risk patients, a short-acting drug such as tolbutamide or gliclazide may be preferred; these 2 sulfonylureas, being mainly inactivated in the liver, are perhaps particularly suitable in renal impairment, although careful monitoring of blood-glucose concentration is essential.

Sulfonylureas should be used with caution in patients with G6PD deficiency, because of a risk of haemolytic anaemia.

Abuse. Severe hypoglycaemia, at first thought to be due to insulinoma but later found to be due to nesidioblastosis [proliferation of the islet cells], was reported in a woman covertly taking chlorpropamide.[1] Other sulfonylureas have been detected in blood samples from patients with unexplained hypoglycaemia; some cases may have been related to factitious drug ingestion.[2,3]

The presence of glibenclamide, in illegal products promoted in Singapore for sexual enhancement, in levels up to 40 times those used in the management of diabetes mellitus had been responsible for cases of severe hypoglycaemia and several deaths.[4] The rationale for including glibenclamide in such products was unknown.

1. Rayman G, *et al.* Hyperinsulinaemic hypoglycaemia due to chlorpropamide-induced nesidioblastosis. *J Clin Pathol* 1984; **37:** 651–4.
2. Kwong PYP, Teale JD. Screening for sulphonylureas in the investigation of hypoglycaemia. *J R Soc Med* 2002; **95:** 381–5.
3. Trenque T, *et al.* Prevalence of factitious hypoglycaemia associated with sulphonylurea drugs in France in the year 2000. *Br J Clin Pharmacol* 2002; **54:** 548.
4. Low M-Y, *et al.* Safety and quality assessment of 175 illegal sexual enhancement products seized in red-light districts in Singapore. *Drug Safety* 2009; **32:** 1141–6.

Administration. It has been suggested that continuously high plasma concentrations of sulfonylureas may lead to the development of tolerance, and that therefore the maximum recommended doses should be reduced.[1] Also, the addition of an insulin sensitiser, to improve glucose transport into the tissues, has been advocated for patients with insulin resistance, instead of increasing the sulfonylurea dose.[2]

1. Melander A, *et al.* Is there a concentration-effect relationship for sulphonylureas? *Clin Pharmacokinet* 1998; **34:** 181–8.
2. Rambiritch V, *et al.* Dose-response relationships of sulfonylureas: will doubling the dose double the response? *South Med J* 2007; **100:** 1132–6.

Breast feeding. The sulfonylureas chlorpropamide (p. 470.2) and tolbutamide (p. 504.3) have been detected in breast milk, and this class of drug is generally avoided during breast feeding because of the risk of hypoglycaemia in the breast-fed infant. However, neither glibenclamide nor glipizide was detected in breast milk in a small study[1] of 5 women with type 2 diabetes, and normal blood-glucose concentrations were found in the 3 infants who were wholly breast fed.

1. Feig DS, *et al.* Transfer of glyburide and glipizide into breast milk. *Diabetes Care* 2005; **28:** 1851–5.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Fasting. For the suggestion that sulfonylureas should be used with caution in fasting Muslim patients during Ramadan, and that chlorpropamide is contra-indicated in this group, see under Precautions of Insulin, p. 485.3.

Pregnancy. Insulin is generally preferred for the management of diabetes mellitus during pregnancy, and sulfonylurea antidiabetics are avoided. Chlorpropamide and tolbutamide cross the placenta, and symptomatic hypoglycaemia has been reported in some exposed neonates. Pharmacokinetic data are lacking for other sulfonylureas, but some studies show only poor placental transfer of glibenclamide.[1] There is no strong evidence that sulfonylureas have teratogenic effects during the first trimester, but their safety has not been established.[2]

Sulfonylureas have also generally been avoided in the management of gestational diabetes, but there is increasing interest in their use. Studies have found glibenclamide to be safe and effective, but these have mostly been observational and non-randomised.[3,4] Although some reviewers have cautioned against the use of glibenclamide until further evidence is available,[5] some guidelines now suggest that it may be considered as an adjunct or alternative to insulin in gestational diabetes.[6]

1. Garcia-Bournissen F, *et al.* Maternal-fetal transport of hypoglycaemic drugs. *Clin Pharmacokinet* 2003; **42:** 303–13.
2. Feig DS, *et al.* Oral antidiabetic agents in pregnancy and lactation: a paradigm shift? *Ann Pharmacother* 2007; **41:** 1174–80.
3. Moore TR. Glyburide for the treatment of gestational diabetes: a critical appraisal. *Diabetes Care* 2007; **30** (suppl): S209–S213.
4. Moretti ME, *et al.* Safety of glyburide for gestational diabetes: a meta-analysis of pregnancy outcomes. *Ann Pharmacother* 2008; **42:** 483–90.
5. Kimber-Trojnar Ż. , *et al.* Glyburide for the treatment of gestational diabetes mellitus. *Pharmacol Rep* 2008; **60:** 308–18.
6. National Collaborating Centre for Women's and Children's Health/NICE. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (issued March 2008, reissued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/DiabetesFullGuidelineRevisedJULY2008.pdf (accessed 06/03/09)

Thyroid disorders. There are conflicting reports concerning the effects of sulfonylureas on thyroid function, with some studies suggesting an increased incidence of thyroid dysfunction in patients treated with tolbutamide or chlorpropamide,[1] while other suggest no antithyroid action.[2,3] Some licensed product information consequently recommends that chlorpropamide should be avoided in patients with impaired thyroid function. Changes in thyroid function may conversely affect glycaemic control—for mention of the possible effects of thyroid hormones on antidiabetic drug requirements see under Interactions, p. 504.1.

1. Hunton RB, *et al.* Hypothyroidism in diabetics treated with sulphonylurea. *Lancet* 1965; **ii:** 449–51.
2. Burke G, *et al.* Effect of long-term sulfonylurea therapy on thyroid function in man. *Metabolism* 1967; **16:** 651–7.
3. Feely J, *et al.* Antithyroid effect of chlorpropamide? *Hum Toxicol* 1983; **2:** 149–53.

Interactions

Many interactions have been reported with the sulfonylureas, largely representing either pharmacokinetic interactions (due to the displacement of the antidiabetic from plasma proteins or alteration in its metabolism or excretion) or pharmacological interactions with drugs having an independent effect on blood glucose. In the former class

most reports concern older sulfonylureas such as chlorpropamide and tolbutamide, although the possibility of such reactions with newer drugs should be borne in mind.

- A *reduced* hypoglycaemic effect, possibly requiring an increased dose of sulfonylurea, has been seen or might be expected on theoretical grounds with adrenaline, aminoglutethimide, chlorpromazine, corticosteroids, diazoxide, oral contraceptives, rifamycins, thiazide diuretics, and thyroid hormones.
- An *increased* hypoglycaemic effect has occurred or might be expected with ACE inhibitors, alcohol, allopurinol, some analgesics (notably azapropazone, phenylbutazone, and the salicylates), azole antifungals (fluconazole, ketoconazole, and miconazole), chloramphenicol, cimetidine, clarithromycin, clofibrate and related compounds, coumarin anticoagulants, disopyramide, fluoroquinolones, heparin, MAOIs, ranitidine, SSRIs, sulfinpyrazone, sulfonamides (including co-trimoxazole), tetracyclines, and tricyclic antidepressants.

Beta blockers may reduce the efficacy of sulfonylureas by impairing the release of insulin from the pancreas; cardioselective beta blockers may have less of an effect than non-selective ones. Beta blockers can also inhibit the normal physiological response to hypoglycaemia and mask the typical sympathetic warning signs. There are sporadic and conflicting reports of a possible interaction with calcium-channel blockers, but overall any effect seems to be of little clinical significance. Octreotide can inhibit sulfonylurea-induced release of insulin from the pancreas; this effect has been exploited in the management of sulfonylurea overdose (see under Treatment of Adverse Effects, p. 502.2).

In addition to producing hypoglycaemia alcohol can interact with chlorpropamide to produce an unpleasant flushing reaction. Such an effect is rare with other sulfonylureas and alcohol.

General references.

1. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part I). *Drugs* 1990; **40:** 6–18.
2. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; **40:** 203–19.
3. Girardin E, *et al*. Hypoglycémies induites par les sulfamides hypoglycémiants. *Ann Med Interne (Paris)* 1992; **143:** 11–17.
4. Tirkkonen T, *et al*. Potential CYP2C9-mediated drug-drug interactions in hospitalized type 2 diabetes mellitus patients treated with the sulphonylureas glibenclamide, glimepiride or glipizide. *J Intern Med* 2010; **268:** 359–66.

ACE inhibitors. There are sporadic reports of marked hypoglycaemia developing in patients taking a sulfonylurea who are given an ACE inhibitor (mainly *captopril* or *enalapril*),[1-3] and 2 case-control studies have indicated that the combination is associated with an increased risk of developing severe hypoglycaemia.[4,5] However, other studies have failed to find much evidence of a problem.[6-10]

1. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
2. Rett K, *et al*. Hypoglycemia in hypertensive diabetic patients treated with sulfonylureas, biguanides, and captopril. *N Engl J Med* 1988; **319:** 1609.
3. Arauz-Pacheco C, *et al*. Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. *Am J Med* 1990; **89:** 811–13.
4. Herings RMC, *et al*. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345:** 1195–8.
5. Morris AD, *et al*. ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
6. Ferriere M, *et al*. Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
7. PassaP, *et al*. Enalapril, captopril, and blood glucose. *Lancet* 1986; **i:** 1447.
8. Winocour P, *et al*. Captopril and blood glucose. *Lancet* 1986; **ii:** 461.
9. Shorr RI, *et al*. Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 1997; **278:** 40–3.
10. Moore N, *et al*. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; **44:** 513–18.

Alcohol. Sulfonylurea-induced alcohol intolerance is seen mainly but not exclusively with chlorpropamide;[1,2] this is similar to the disulfiram-alcohol interaction, although it is not clear whether the mechanism is the same. The main symptom of the reaction is facial flushing.

Alcohol has been reported both to increase and to decrease the half-life of tolbutamide depending on whether the alcohol administration was acute or chronic.[3] Alcohol may also have a variable effect of its own on blood-glucose concentrations; there is a general tendency to increased hypoglycaemia when alcohol and sulfonylureas are taken concurrently.[2,4]

1. Fui SNT, *et al*. Epidemiological study of prevalence of chlorpropamide alcohol flushing in insulin dependent diabetes, non-insulin dependent diabetics, and non-diabetics. *BMJ* 1983; **287:** 1509–12.
2. Lao B, *et al*. Alcohol tolerance in patients with non-insulin-dependent (type 2) diabetes treated with sulphonylurea derivatives. *Arzneimittelforschung* 1994; **44:** 727–34.
3. Sellers EM, Holloway MR. Drug kinetics and alcohol ingestion. *Clin Pharmacokinet* 1978; **3:** 440–52.
4. Burge MR, *et al*. Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. *Diabetes Care* 1999; **22:** 2037–43.

Analgesics. *Phenylbutazone*[1,2] and related drugs such as *azapropazone*[3] have been associated with acute hypoglycaemic episodes when given to patients receiving sulfonylureas (in most reports, tolbutamide). Other analgesics may enhance the hypoglycaemic effect of sulfonylureas, including *indobufen*,[4] *fenclofenac*,[5] and the *salicylates*.[6,7] Although a study in healthy subjects found no interaction,[7] there has been a report of hypoglycaemia with *ibuprofen* in a diabetic patient who had been stabilised on glibenclamide.[8]

1. Tannenbaum H, *et al*. Phenylbutazone-tolbutamide drug interaction. *N Engl J Med* 1974; **290:** 344.
2. Dent LA, Jue SG. Tolbutamide-phenylbutazone interaction. *Drug Intell Clin Pharm* 1976; **10:** 711.
3. Andreasen PB, *et al*. Hypoglycaemia induced by azapropazone-tolbutamide interaction. *Br J Clin Pharmacol* 1981; **12:** 581–3.
4. Elvander-Ståhl E, *et al*. Indobufen interacts with the sulphonylurea, glipizide, but not with the β-adrenergic receptor antagonists, propranolol and atenolol. *Br J Clin Pharmacol* 1984; **18:** 773–8.
5. Allen PA, Taylor RT. Fenclofenac and thyroid function tests. *BMJ* 1980; **281:** 1642.
6. Richardson T, *et al*. Enhancement by sodium salicylate of the blood glucose lowering effect of chlorpropamide—drug interaction or summation of similar effects? *Br J Clin Pharmacol* 1986; **22:** 43–8.
7. Kubacka RT, *et al*. Effects of aspirin and ibuprofen on the pharmacokinetics and pharmacodynamics of glyburide in healthy subjects. *Ann Pharmacother* 1996; **30:** 20–6.
8. Sone H, *et al*. Ibuprofen-related hypoglycemia in a patient receiving sulfonylurea. *Ann Intern Med* 2001; **134:** 344.

Antibacterials. *Chloramphenicol* markedly inhibits the metabolism of tolbutamide and increases its half-life,[1] which can result in hypoglycaemia. Sulfonamides,[2] including *co-trimoxazole*,[3-5] may also enhance the hypoglycaemic effects of the sulfonylureas. There have been rare reports of elevated glibenclamide concentrations[6] and hypoglycaemia[6,7] when *ciprofloxacin* was given to patients who were on stable glibenclamide therapy. Profound and prolonged hypoglycaemia after an intravenous dose of *levofloxacin* contributed to the death of an elderly patient also taking glibenclamide.[8] For reports of hypoglycaemia when *gatifloxacin* was given to patients already receiving a sulfonylurea (glimepiride in one case, and glibenclamide plus pioglitazone in another), see p. 304.1. *Clarithromycin* may increase the absorption of glibenclamide[9] and tolbutamide.[10] There have also been a few cases of severe hypoglycaemia when clarithromycin was given to patients taking glibenclamide[11,12] or glipizide;[11] renal impairment may have played a role in some of these cases.[11] A case controlled study[13] concluded that the infection itself or its sequelae may increase the risk of severe hypoglycaemia in patients on glipizide or glibenclamide; co-administration of clarithromycin, co-trimoxazole, ciprofloxacin, or levofloxacin appeared to increase the risk of hypoglycaemia even further.

Rifampicin (and probably other rifamycins) can enhance the metabolism and decrease the effect of tolbutamide, chlorpropamide,[14,15] and glibenclamide[16] and dosage of the hypoglycaemic drug may need to be increased. The effects on glipizide[16] and glimepiride[17] appear to be less pronounced, but gliclazide may be more severely affected.[18] In one case report, the established dose of gliclazide had to be eventually doubled in an attempt to maintain glycaemic control in a patient given rifampicin.[19]

1. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
2. Soeldner JS, Steinke J. Hypoglycemia in tolbutamide-treated diabetes: report of two cases with measurement of serum insulin. *JAMA* 1965; **193:** 148–9.
3. Wing LMH, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: effects of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985; **20:** 482–5.
4. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. *DICP Ann Pharmacother* 1990; **24:** 250–1.
5. Abad S, *et al*. Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52:** 456–7.
6. Roberge RJ, *et al*. Glyburide-ciprofloxacin interaction with resistant hypoglycemia. *Ann Emerg Med* 2000; **36:** 160–3.
7. Lin G, *et al*. Refractory hypoglycemia from ciprofloxacin and glyburide interaction. *J Toxicol Clin Toxicol* 2004; **42:** 295–7.
8. Friedrich LV, Dougherty R. Fatal hypoglycemia associated with levofloxacin. *Pharmacotherapy* 2004; **24:** 1807–12.
9. Lilja JJ, *et al*. Effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. *Br J Clin Pharmacol* 2007; **63:** 732–40.
10. Jayasagar G, *et al*. Effect of clarithromycin on the pharmacokinetics of tolbutamide. *Drug Metabol Drug Interact* 2000; **16:** 207–15.
11. Bussing R, Gende A. Severe hypoglycemia from clarithromycin-sulfonylurea drug interaction. *Diabetes Care* 2002; **25:** 1659–61.
12. Leiba A, *et al*. An unusual case of hypoglycemia in a diabetic patient. *Ann Emerg Med* 2004; **44:** 427–8.
13. Schelleman H, *et al*. Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010; **88:** 214–22.
14. Syvälahti EKG, *et al*. Rifampicin and drug metabolism. *Lancet* 1974; **ii:** 232–3.
15. Self TH, Morris T. Interaction of rifampin and chlorpropamide. *Chest* 1980; **77:** 800–801.
16. Niemi M, *et al*. Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. *Clin Pharmacol Ther* 2001; **69:** 400–406.
17. Niemi M, *et al*. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. *Br J Clin Pharmacol* 2000; **50:** 591–5.
18. Park J-Y, *et al*. Effect of rifampin on the pharmacokinetics and pharmacodynamics of gliclazide. *Clin Pharmacol Ther* 2003; **74:** 334–40.
19. Kihara Y, Otsuki M. Interaction of gliclazide and rifampicin. *Diabetes Care* 2000; **23:** 1204–5.

Anticoagulants. *Dicoumarol* increases serum concentrations and therefore the hypoglycaemic effects of tolbutamide, and possibly chlorpropamide. In addition, sulfonylureas may affect anticoagulant function (p. 1531.3).

Antiepileptics. For references to *phenytoin* toxicity when tolbutamide or tolazamide was given, see under Phenytoin p. 543.1.

Antifungals. Increased plasma concentrations of tolbutamide have been reported when *fluconazole* was given,[1] but there was no evidence of hypoglycaemia, and no hypoglycaemic symptoms were seen in 29 women receiving gliclazide or glibenclamide who were given fluconazole or *clotrimazole* for vulvovaginitis.[2] A study in healthy subjects found that fluconazole increased plasma concentrations of glimepiride, but again there was no significant effect on glucose concentrations.[3] However, there are reports of hypoglycaemia in a patient who took fluconazole with glipizide,[4] and another who took fluconazole and co-trimoxazole with gliclazide.[5] Additionally in a large study, from the United States, the risk of severe hypoglycaemia was increased when fluconazole was used with either glipizide or glibenclamide.[6] Similar interactions have been reported for *ketoconazole* (with tolbutamide, in healthy subjects),[7] *miconazole* (with tolbutamide, in a diabetic),[8] and *voriconazole* (with glimepiride, in a diabetic),[9] suggesting that such combinations should be regarded with caution.

1. Lazar JD, Wilner DK. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12** (suppl 3): S327–S333.
2. Rowe BR, *et al*. Safety of fluconazole in women taking oral hypoglycaemic agents. *Lancet* 1992; **339:** 255–6.
3. Niemi M, *et al*. Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. *Clin Pharmacol Ther* 2001; **69:** 194–200.
4. Fournier JP, *et al*. Coma hypoglycémique chez une patiente traitée par glipizide et fluconazole: une possible interaction? *Therapie* 1992; **47:** 446–7.
5. Abad S, *et al*. Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52:** 456–7.
6. Schelleman H, *et al*. Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010; **88:** 214–22.
7. Krishnaiah YSR, *et al*. Interaction between tolbutamide and ketoconazole in healthy subjects. *Br J Clin Pharmacol* 1994; **37:** 205–7.
8. Meurice JC, *et al*. Interaction miconazole et sulfamides hypoglycémiants. *Presse Med* 1983; **12:** 1670.
9. Shobha JC, Muppidi MR. Interaction between voriconazole and glimepiride. *J Postgrad Med* 2010; **56:** 44–5.

Ciclosporin. For the effect of glibenclamide on blood concentrations of ciclosporin see Hypoglycaemic Drugs, p. 1956.3.

Colesevelam. A study[1] has shown that co-administration of colesevelam reduced the absorption of glibenclamide. The authors concluded that glibenclamide should be given at least 4 hours before colesevelam to avoid this interaction.

1. Brown KS, *et al*. Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *J Clin Pharmacol* 2010; **50:** 554–65.

Endothelin receptor antagonists. The combination of glibenclamide and *bosentan* should be avoided. The plasma concentrations of both drugs may be reduced with concomitant use; however, this does not explain the elevated liver transaminase levels that have been reported when used together.[1]

1. van Giersbergen PLM, *et al*. In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide. *Clin Pharmacol Ther* 2002; **71:** 253–62.

Metformin. Results apparently suggesting increased mortality in patients who received intensive drug therapy with metformin and a sulfonylurea were reported by the UK Prospective Diabetes Study.[1] This was considered to be artefactual, since it was not confirmed by epidemiological analysis, and such combinations are widely used in practice, but some concern remained and further study thought necessary. A meta-analysis[2] of 9 observational studies found that the combination was associated with an increased risk of a composite end-point of fatal or non-fatal cardiovascular events, but in separate analyses of cardiovascular death or all-cause mortality there was no significant effect. The authors hypothesised that an increased risk may be related to the likely use of combination therapy in patients who have a more aggressive form of diabetes and therefore a more rapid deterioration in glycaemic control; also, weight gain induced by sulfonylureas could negate any weight loss or other beneficial effects on cardiovascular risk factors associated with metformin. They also felt that further studies were still needed.

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with

type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65. Correction. *ibid.*; 1558.
2. Rao AD, *et al.* Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality? A meta-analysis of observational studies. *Diabetes Care* 2008; **31:** 1672–8.

Thyroid hormones. It has been suggested that starting thyroid replacement therapy may increase the requirement for insulin or oral antidiabetic drugs in diabetic patients, which would not seem unreasonable given the stimulant effects of thyroid hormones on metabolic function. For a discussion of the mooted effects of sulfonylureas on thyroid function, see under Precautions, p. 502.3.

Pharmacokinetics

Reviews.
1. Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycaemic agents: an update. *Clin Pharmacokinet* 1989; **16:** 100–28.
2. Marchetti P, *et al.* Pharmacokinetic optimisation of oral hypoglycaemic therapy. *Clin Pharmacokinet* 1991; **21:** 308–17.
3. Harrower AD. Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. *Clin Pharmacokinet* 1996; **31:** 111–19.

Metabolism. The cytochrome P450 isoenzyme CYP2C9 is the main enzyme involved in the metabolism of many sulfonylureas, and its activity can be altered by genetic polymorphism. Sulfonylurea clearance has been found to be significantly reduced in healthy subjects with the homozygous CYP2C9*3/*3 genotype, compared with the most extensive metabolism in wild-type *1/*1 carriers; metabolism in homozygous *2/*2 carriers and heterozygous genotypes ranges between these two.[1] It has been suggested that genotyping might be a useful tool for dosage adjustment, to optimise efficacy and reduce adverse effects[1] (see also Hypoglycaemia, p. 502.1). While the relevance of genotype to serum-glucose and insulin levels in diabetic patients treated with sulfonylureas is still unclear,[1,2] a further study of over 1000 patients[3] found that carriers of the *2 or *3 variant were more likely to achieve a treatment target haemoglobin A_{1c} compared with wild-type *1 carriers. Additionally *2 and *3 carriers were less likely to have treatment failure.

1. Kirchheiner J, *et al.* Effect of genetic polymorphisms in cytochrome P450 (CYP) 2C9 and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance. *Clin Pharmacokinet* 2005; **44:** 1209–25.
2. Becker ML, *et al.* Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. *Clin Pharmacol Ther* 2008; **83:** 288–92.
3. Zhou K, *et al.* Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. *Clin Pharmacol Ther* 2010; **87:** 52–6.

Teneligliptin *(rINN)*

Teneligliptina; Téneligliptine; Teneligliptinum; Тенелиглептин.

{(2*S*,4*S*)-4-[4-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone.

$C_{22}H_{30}N_6OS$=426.6

CAS — 760937-92-6.

UNII — 28ZHI4CF9C.

Profile

Like sitagliptin (p. 500.1), teneligliptin is an inhibitor of dipeptidylpeptidase-4. Teneligliptin hydrobromide is used orally in the treatment of type 2 diabetes mellitus.

References.
1. Eto T, *et al.* Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: a 4-week, randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2012; **14:** 1040–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Tenelia.

Tolazamide *(BAN, USAN, rINN)*

NSC-70762; Tolatsamidi; Tolazamid; Tolazamida; Tolazamidum; U-17835; Толазамид.

1-(Perhydroazepin-1-yl)-3-tosylurea; 1-(Perhydroazepin-1-yl)-3-*p*-tolylsulphonylurea.

$C_{14}H_{21}N_3O_3S$=311.5

CAS — 1156-19-0.

ATC — A10BB05.

ATC Vet — QA10BB05.

UNII — 9LT1BRO48Q.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Tolazamide). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

USP 36: (Tolazamide). A white or off-white crystalline powder, odourless or having a slight odour. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

Uses and Administration

Tolazamide is a sulfonylurea antidiabetic (p. 500.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of at least 10 hours and sometimes up to 20 hours. The usual initial dose is 100 to 250 mg daily given as a single dose with breakfast. Dosage may be increased if necessary at weekly intervals by 100 to 250 mg to a usual maintenance dose of 250 to 500 mg daily, or a maximum of 1 g daily; no further benefit is likely to be gained with higher doses. Doses of more than 500 mg daily may be given in divided doses.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 501.1, p. 502.1, and p. 502.2.

Interactions

As for sulfonylureas in general, p. 502.3.

Pharmacokinetics

Tolazamide is slowly absorbed from the gastrointestinal tract, peak plasma concentrations occurring 4 to 8 hours after an oral dose, and is extensively bound to plasma proteins. It has a half-life of about 7 hours. It is metabolised in the liver to metabolites with some hypoglycaemic activity. About 85% of an oral dose is excreted in the urine, chiefly as metabolites.

Preparations

Pharmacopoeial Preparations

BP 2014: Tolazamide Tablets;
USP 36: Tolazamide Tablets.

Tolbutamide *(BAN, rINN)*

Butamidum; Tolbutamid; Tolbutamida; Tolbutamidas; Tolbutamidi; Tolbutamidum; Tolglybutamide; Тольбутамид.

1-Butyl-3-tosylurea; 1-Butyl-3-*p*-tolylsulphonylurea.

$C_{12}H_{18}N_2O_3S$=270.3

CAS — 64-77-7 (tolbutamide); 473-41-6 (tolbutamide sodium).

ATC — A10BB03; V04CA01.

ATC Vet — QA10BB03; QV04CA01.

UNII — 982XCM1FOI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Tolbutamide). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

USP 36: (Tolbutamide). A white or practically white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol and in chloroform.

Uses and Administration

Tolbutamide is a sulfonylurea antidiabetic (p. 500.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of about 10 hours.

The usual initial dose in type 2 diabetes mellitus may range from 1 to 2 g daily, given either as a single dose with breakfast or, more usually, in divided doses. Maintenance doses usually range from 0.25 to 2 g daily. Although it is unlikely that the response will be improved by increasing the dose further, daily doses of 3 g have been given. For doses used in adolescents, see p. 504.2.

Tolbutamide sodium ($C_{12}H_{17}N_2NaO_3S$ = 292.3) has sometimes been used in the diagnosis of insulinoma as well as other pancreatic disorders including diabetes mellitus. The equivalent of 1 g of tolbutamide is given by intravenous injection as a 5% solution usually over 2 to 3 minutes. Tolbutamide sodium 1.08 g is equivalent to about 1 g of tolbutamide.

Administration in children. There is limited experience with the use of sulfonylureas in children with type 2 diabetes mellitus, and the biguanide metformin is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision and that shorter-acting alternatives such as tolbutamide may be preferred to longer-acting sulfonylureas that have a greater risk of hypoglycaemia. Although not licensed for use in children in the UK, the *BNFC* suggests that tolbutamide may be given to adolescents aged 12 to 18 years in an oral dose of 0.5 to 1.5 g daily, to a maximum of 2 g daily. It may be given in divided doses, with or immediately after meals, or as a single dose at breakfast.

Diagnosis and testing. References.
1. McMahon MM, *et al.* Diagnostic interpretation of the intravenous tolbutamide test for insulinoma. *Mayo Clin Proc* 1989; **64:** 1481–8.
2. Marks V. Diagnosis and differential diagnosis of hypoglycemia. *Mayo Clin Proc* 1989; **64:** 1558–61.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 501.1, p. 502.1, and p. 502.2. Tolbutamide was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p. 501.2).

Thrombophlebitis with thrombosis has occurred after the intravenous injection of tolbutamide sodium, but this is usually painless and the vein gradually recovers. Rapid injection may cause a transient mild pain or sensation of heat in the vein.

The *BNF* has suggested that tolbutamide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential and that the smallest possible dose for adequate control should be used. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Breast feeding. Tolbutamide is distributed into breast milk in relatively low quantities.[1] The last available guidance from the American Academy of Pediatrics[2] stated that although usually compatible with breast feeding, use of tolbutamide by breast-feeding mothers may possibly result in jaundice in the infant.

1. Moiel RH, Ryan JR. Tolbutamide orinase in human breast milk. *Clin Pediatr (Phila)* 1967; **6:** 480.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/07/04)

Porphyria. UK licensed product information states that tolbutamide is contra-indicated in porphyria.

Interactions

As for sulfonylureas in general, p. 502.3.

Pharmacokinetics

Tolbutamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins; the half-life is generally within the range of 4 to 7 hours but may be considerably longer. Tolbutamide is metabolised in the liver by hydroxylation mediated by the cytochrome P450 isoenzyme CYP2C9. It is excreted in the urine chiefly as metabolites with little hypoglycaemic activity. Tolbutamide has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Rastinon†; ***Cz.***: Dirastan†; ***Denm.***: Arcosal; ***Gr.***: Rastinon; ***Hong Kong***: Diatol; ***Israel***: Orsinon†; ***Mex.***: Artosin; Dabetil; Diatelan; Diaval; Flusan; Rastinon; ***NZ***: Diatol†; ***Pol.***: Diabetol†; ***S.Afr.***: Tydadex†; ***Singapore***: Tobumide; Tolmide; ***USA***: Orinase Diagnostic†; Orinase†.

Pharmacopoeial Preparations

BP 2014: Tolbutamide Tablets;
USP 36: Tolbutamide for Injection; Tolbutamide Tablets.

Vildagliptin *(BAN, rINN)*

LAF-237; NVP-LAF-237; Vildagliptina; Vildagliptine; Vildagliptinum; Вильдаглиптин.

(2*S*)-{[(3-Hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile.

$C_{17}H_{25}N_3O_2$=303.4

CAS — 274901-16-5.

ATC — A10BH02.

ATC Vet — QA10BH02.

UNII — I6B4B2U96P.

Uses and Administration

Like sitagliptin (p. 500.1), vildagliptin is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1). It is given orally in a usual dose of 50 mg twice daily with or without food. A total daily dose of more than 100 mg of vildagliptin is not recommended. When given with metformin and a sulfonylurea, the usual dose of vildagliptin may be used; in dual therapy with a sulfonylurea, a dose of vildagliptin 50 mg once daily in the morning is recommended because higher doses were found to be no more effective. The dose of sulfonylurea may need to be lowered when used with vildagliptin. Dosage may need to be adjusted in patients with renal impairment (see p. 505.1).

References.
1. Pratley RE, *et al.* Management of type 2 diabetes in treatment-naive elderly patients: benefits and risks of vildagliptin monotherapy. *Diabetes Care* 2007; **30:** 3017–22.
2. Scherbaum WA, *et al.* Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycaemia. *Diabetes Obes Metab* 2008; **10:** 1114–24.
3. Croxtall JD, Keam SJ. Vildagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2008; **68:** 2387–2409.
4. Banerjee M, *et al.* Vildagliptin in clinical practice: a review of literature. *Expert Opin Pharmacother* 2009; **10:** 2745–57.
5. Matthews DR, *et al.* Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab* 2010; **12:** 780–9.
6. Keating GM. Vildagliptin: a review of its use in type 2 diabetes mellitus. *Drugs* 2010; **70:** 2089–2112.
7. Schweizer A, *et al.* Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ⩾ 75 years: a pooled analysis from a database of clinical trials. *Diabetes Obes Metab* 2011; **13:** 55–64.
8. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; **71:** 1441–67.

Administration in renal impairment. UK licensed product information says that no dose adjustment is required in patients with mild renal impairment (creatinine clearance 50 mL/min or more). In patients with more severe renal impairment or with end-stage renal disease (ESRD), the recommended oral dose of vildagliptin is 50 mg once daily.

Adverse Effects, Treatment, and Precautions

As for Sitagliptin Phosphate, p. 500.1. Arthralgia has also been reported for vildagliptin. Dosage should be reduced in patients with moderate or severe renal impairment or end-stage renal disease.

Rare cases of hepatic dysfunction, including hepatitis, have been reported. Vildagliptin should not be used in patients with hepatic impairment; liver function should be tested before starting the drug, and monitored during therapy (every 3 months in the first year and periodically thereafter). Vildagliptin should be stopped if there is a persistent increase of 3 or more times the upper limit of normal in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or if the patient develops jaundice or other signs of liver dysfunction; in such cases, it should not be restarted.

References.
1. Schweizer A, *et al.* Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large phase III type 2 diabetes population. *Diabetes Obes Metab* 2010; **12:** 485–94.
2. Ligueros-Saylan M, *et al.* An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of phase II and III clinical trials. *Diabetes Obes Metab* 2010; **12:** 495–509.
3. Banerji MA, *et al.* Safety and tolerability of vildagliptin vs. thiazolidinedione as add-on to metformin in type 2 diabetic patients with and without mild renal impairment: a retrospective analysis of the GALIANT study. *Diabetes Res Clin Pract* 2010; **90:** 182–90.
4. Schweizer A, *et al.* Assessing the general safety and tolerability of vildagliptin: value of pooled analyses from a large safety database versus evaluation of individual studies. *Vasc Health Risk Manag* 2011: **7:** 49–57.

Overdosage. In the UK, the *National Poisons Information Service* states that oral activated charcoal may be considered in adults and children who have ingested more than 15 mg/kg of vildagliptin and present within 1 hour, provided they are conscious and the airway can be protected. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p. 484.3).

Interactions

The efficacy of vildagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 502.3.

Pharmacokinetics

Vildagliptin is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1.7 hours after an oral dose. It has a bioavailability of 85%. About 69% of a dose is metabolised, mainly by hydrolysis in the kidney. About 85% of a dose is excreted in the urine (23% is unchanged drug), and 15% in the faeces. The elimination half-life of vildagliptin is about 2 hours after intravenous injection, and about 3 hours after an oral dose.

References.
1. He Y-L. Clinical pharmacokinetics and pharmacodynamics of vildagliptin. *Clin Pharmacokinet* 2012; **51:** 147–62.

Hepatic impairment. Although much of a dose of vildagliptin is hydrolysed by the kidney, the liver is also an important site for its metabolism. A small pharmacokinetic study[1] found that exposure to vildagliptin was decreased in subjects with mild (Child-Pugh score 5 or 6) or moderate (score 7 to 9) hepatic impairment, and increased in those with severe impairment (score 10 to 12), compared with healthy subjects. However, the differences were less than 30% and not consistent with the severity of hepatic impairment. The authors did not consider the differences to be clinically meaningful and concluded that initial dose adjustment of vildagliptin would not be necessary. Nevertheless, licensed product information cautions against its use in diabetic patients with hepatic impairment (see above).

1. He Y-L, *et al.* The influence of hepatic impairment on the pharmacokinetics of the dipeptidyl peptidase IV (DPP-4) inhibitor vildagliptin. *Eur J Clin Pharmacol* 2007; **63:** 677–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Galvus; Zomarist; ***Austral.***: Galvus; ***Austria***: Galvus; ***Belg.***: Galvus; ***Braz.***: Galvus; ***Chile***: Galvus; ***China***: Galvus (佳维乐); ***Cz.***: Galvus; Jalra; Xiliarx; ***Denm.***: Galvus; ***Fr.***: Galvus; ***Ger.***: Galvus; Jalra; ***Gr.***: Galvus; Jalra; Xiliarx; ***Hong Kong***: Galvus; ***Hung.***: Galvus; ***India***: Galvus; ***Indon.***: Galvus; ***Irl.***: Galvus; Jalra; Xiliarx; ***Israel***: Galvus; ***Ital.***: Galvus; ***Malaysia***: Galvus; ***Mex.***: Galvus; ***Neth.***: Galvus; Jalra; Xiliarx; ***Norw.***: Galvus; ***Philipp.***: Galvus; ***Pol.***: Galvus; Jalra; ***Port.***: Galvus; Jalra; Xiliarx; ***Rus.***: Galvus (Галвус); ***Singapore***: Galvus; ***Spain***: Galvus; Jalra; Xiliarx; ***Swed.***: Galvus; ***Switz.***: Galvus; ***Thai.***: Galvus; ***Turk.***: Galvus; ***UK***: Galvus; ***Ukr.***: Galvus (Гальвус).

Multi-ingredient Preparations. ***Arg.***: Galvus Met; Zomarist Met; ***Austral.***: Galvumet; ***Austria***: Eucreas; ***Belg.***: Eucreas; ***Braz.***: Galvus Met; ***Chile***: Galvus Met; ***Cz.***: Eucreas; Icandra; Zomarist; ***Denm.***: Eucreas; ***Fr.***: Eucreas; ***Ger.***: Eucreas; Icandra; ***Gr.***: Eucreas; Icandra; Zomarist; ***Hong Kong***: GalvusMet; ***Hung.***: Eucreas; ***India***: Galvusmet; ***Indon.***: Galvusmet; ***Irl.***: Eucreas; Icandra; Zomarist; ***Israel***: Eucreas; ***Ital.***: Eucreas; ***Malaysia***: Galvus Met; ***Mex.***: Galvus Met; ***Neth.***: Eucreas; Icandra; Zomarist; ***Norw.***: Eucreas; ***Philipp.***: Galvusmet; ***Pol.***: Eucreas; Zomarist; ***Port.***: Eucreas; Icandra; Zomarist; ***Rus.***: Galvus Met (Галвус Мет); ***Singapore***: Galvusmet; ***Spain***: Eucreas; Icandra; Zomarist; ***Swed.***: Eucreas; ***Switz.***: Galvumet; ***Thai.***: Galvus Met; ***Turk.***: Galvus Met; ***UK***: Eucreas; ***Ukr.***: Galvusmet (Гальвусмет).

Voglibose *(USAN, rINN)*

A-71100; AO-128; Voglibosa; Voglibosum; Воглибоза.

3,4-Dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-*C*-(hydroxymethyl)-*D*-epi-inositol

$C_{10}H_{21}NO_7$=267.3

CAS — 83480-29-9.

ATC — A10BF03.

ATC Vet — QA10BF03.

UNII — S77P977AG8.

Pharmacopoeias. In *Jpn*.

Profile

Voglibose is an alpha-glucosidase inhibitor with general properties similar to those of acarbose (p. 466.2). It is used in the treatment of diabetes mellitus (p. 459.1) in oral doses of 200 to 300 micrograms three times daily, immediately before meals. Voglibose is also under investigation for the prevention of type 2 diabetes in patients with impaired glucose tolerance.

References.
1. Kawamori R, *et al.* Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 2009; **373:** 1607–14.

Hepatic encephalopathy. Voglibose has been investigated[1] in the management of hepatic encephalopathy (p. 1811.2).

1. Uribe M, *et al.* Beneficial effect of carbohydrate maldigestion induced by a disaccharidase inhibitor (AO-128) in the treatment of chronic portal systemic encephalopathy: a double-blind, randomized controlled trial. *Scand J Gastroenterol* 1998; **33:** 1099–1106.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Basen (倍欣); ***Jpn***: Basen; ***Philipp.***: Basen; ***Thai.***: Basen.

Multi-ingredient Preparations. ***Jpn***: Glubes.

Antiepileptics

Epilepsy, p. 506
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Epilepsy, cognition, and mood, p. 508
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This chapter describes drugs whose main use is in the management of epilepsy, status epilepticus, and other convulsive disorders.

Epilepsy

Epilepsy is a common neurological disorder. An individual's lifetime risk of developing epilepsy is between 3 and 5%; neonates, children, and the elderly are at the highest risk of developing the disorder.

Definitions and classification. An epileptic seizure has been defined as a paroxysmal discharge of cerebral neurones accompanied by clinical phenomena apparent to the patient or to an observer. The phenomena can be motor, sensory, or autonomic and there may also be impairment or complete loss of consciousness. Motor disturbances may include convulsions—which are involuntary, violent, and spasmodic—or prolonged contraction of skeletal muscles. The word 'fit' is often used colloquially to describe an epileptic seizure. Epilepsy is defined as a condition characterised by a recurrence of such seizures. A patient should not be described as having epilepsy until a second non-febrile seizure occurs.

The following is a broad account of the classification of seizures, epilepsies, and epileptic syndromes based on the views of the International League Against Epilepsy (ILAE) in 1981[1] and 1989.[2] A later proposed revision of the classification[3] does not yet seem to have been widely adopted.

- **Partial seizures** or **focal seizures** (localisation-related seizures) are epileptic seizures in which the initial neuronal discharges are localised in one area of the brain. The phenomena associated with such a seizure depend on the site of origin of the discharge. If there is no loss of consciousness, the seizure has been known as a *simple partial seizure* and includes Jacksonian epilepsy, which may be associated with motor or sensory disturbances. If there is impaired consciousness the seizure has been referred to as a *complex partial seizure*. Partial seizures were formerly referred to as psychomotor epilepsy or temporal lobe epilepsy, but the terms are not synonymous and should be avoided. Partial seizures may become *secondarily generalised seizures* if the neuronal discharge spreads to involve the entire brain
- **Generalised seizures** are characterised by neuronal discharges involving both cerebral hemispheres simultaneously from the outset. Subclassifications are based on the presence or absence of different types of convulsions.
  Absences (petit mal) are generalised seizures, usually occurring in children, characterised by a sudden loss of consciousness lasting for a few seconds. There is usually accompanying motor activity which may vary in degree from eyelid blinking to more extensive clonic body movements. *Atypical absence seizures* are those with a slower onset and longer duration.
  Myoclonic seizures are epileptic seizures in which the motor manifestation is myoclonus (see p. 511.3).
  Clonic seizures are characterised by loss of consciousness, autonomic symptoms, and rhythmic clonic contractions of all muscles.
  Tonic seizures are also associated with loss of consciousness and autonomic symptoms accompanied by tonic contractions of the limbs. *Tonic-clonic seizures* (grand mal) are characterised by disordered contraction of muscles. During the tonic phase, all the muscles go into spasm followed up to a minute later by rhythmic clonic contractions. Finally, the patient enters a deep stupor followed by a period of confusion as consciousness is regained.
  Atonic seizures are characterised by loss of postural tone; the head sags or the patient falls down.

Within the categories of partial and generalised epilepsies, seizures have also been classified as **idiopathic, symptomatic** (in which the seizures are associated with diagnosable underlying disorders), or **cryptogenic** or **probably symptomatic** (in which the epilepsies are known or suspected to be symptomatic but the cause is not clear).

Partial **syndromes** include Rolandic and occipital epilepsies (both idiopathic), while generalised idiopathic syndromes include childhood absence epilepsies, juvenile myoclonic epilepsy, and the cryptogenic or symptomatic generalised syndromes include infantile spasms (as for example in West's syndrome), Lennox-Gastaut syndrome, and epilepsy with myoclonic absences. A third unclassified category covers undetermined epilepsies and epileptic syndromes. **Special syndromes** include conditions such as febrile convulsions (see p. 511.2) in which seizures are related to specific situations.

It has been suggested that classification based on seizure type is the most useful in choice of antiepileptic drug whereas the syndrome classification has more benefits in deciding an overall therapeutic strategy and assessing long-term prognosis.

Status epilepticus has previously been defined as a seizure lasting more than 30 minutes or several distinct episodes without restoration of consciousness in between (but see p. 510.2).

Other convulsive disorders include alcohol withdrawal syndrome p. 1735.1, eclampsia and pre-eclampsia p. 511.1, myoclonus p. 511.3, neonatal seizures p. 511.3, and porphyria p. 512.1.

Starting antiepileptic therapy. A single seizure does not constitute epilepsy and therefore does not necessarily warrant immediate treatment with antiepileptics. The decision to start antiepileptic therapy should be based on whether the risks of further seizures outweigh the risks of treatment.

- Starting antiepileptic therapy *too early* means that the patient may be unnecessarily exposed to the adverse effects of the drugs used, and may have social implications if erroneously diagnosed, such as the loss of a patient's driving licence
- However, the implications of *delaying* treatment must also be considered. Although there has long been concern that seizures may damage the brain and intellectual capabilities, or even cause death, there are insufficient data to support these claims. Status epilepticus, rather than individual or frequent seizures, may be the factor associated with brain injury or death, but the risks of a newly diagnosed epileptic patient developing status epilepticus are unknown. The most compelling reasons for treatment are risk of personal injury or causing injury to others during a seizure, and the psychosocial consequences of untreated epilepsy such as low self-esteem, anxiety, and domestic and employment difficulties

There has been a long-held belief that seizures beget seizures. This is not necessarily borne out by epidemiological studies,[4] and there is evidence in children[5] and adults[6] that the risk of recurrence after a first unprovoked seizure may be 50% or less. Furthermore, a decelerating disease process with successively longer intervals between seizures has been shown[7] in untreated children with newly diagnosed tonic-clonic seizures followed up for 2 years. Results from another study[8] suggested that seizure control or the prospects for and success of eventual withdrawal of therapy is little influenced by the number of pretreatment seizures up to 10 seizures; above this number there was a reduced chance of completely controlling seizures. Similarly, although patients treated immediately after a first seizure have a lower 2-year risk of recurrence than patients whose treatment is deferred, immediate treatment does not affect the probability of achieving longer-term seizure control.[6,9-11]

However, epilepsy is a heterogeneous disorder and there is some experimental evidence[12] that certain seizure types can have a detrimental effect on prognosis. Differences in reported risks in seizure recurrence may be attributable to differences in methodology as well as different important risk factors in the populations studied; also, few studies have followed up patients for more than 2 to 4 years.

Whether antiepileptic therapy should be started early to improve prognosis or delayed or avoided altogether therefore remains contentious.[13-15] Some neurologists do not advise treatment of a first seizure but prefer to wait for evidence of recurrence unless clinical features such as more than one seizure type or a neurological deficit predispose to poor seizure control. However, a first nonconvulsive seizure may go undetected.[15] Furthermore, as single partial seizures appear to occur less frequently than single generalised tonic-clonic seizures, many neurologists assume that the first detected attack of a nonconvulsive seizure is in fact one of multiple seizures and begin treatment. UK guidelines[16,17] suggest that antiepileptic therapy should be offered to patients after a first tonic-clonic seizure if a previous myoclonic, absence, or partial seizure has occurred, if the EEG shows unequivocal epileptic discharges, if congenital neurological deficits are present, or if the risk of recurrence is unacceptable to the patient.

Choice of antiepileptic. Once a decision to treat has been made, the choice of antiepileptic is determined mainly by its efficacy against the type of seizures experienced and its potential adverse effects.[16-30]

In recent years many newer drugs have been licensed and added to the classical treatments for epilepsy, and others continue to be developed.[31,32] The role of these drugs relative to the classical agents is only slowly becoming established, and evidence of relative efficacy on which to base a choice is limited. Many new drugs have been promoted on the basis of superior tolerance and quality of life for epileptic patients, but even this is not always well established, and will, in any case, vary from patient to patient, as individuals will differ in the symptoms they find intolerable. In consequence, guidelines have often reserved their use for situations in which the older drugs are less suitable.

Certain principles of management are, however, well established:

- monotherapy is preferable to a multiple-drug regimen and treatment is therefore begun with a single drug, increasing the dose gradually until seizures are brought under control or adverse effects become unacceptable
- if treatment with the first drug fails, it is preferable to try alternative single first-line antiepileptics before giving combinations of drugs. It has been suggested that for practical purposes a patient should be considered to have refractory epilepsy if seizure control is not obtained with consecutive trials of 2 well tolerated antiepileptics[27]
- the change-over from one antiepileptic to another should be made cautiously, withdrawing the first drug only when the new regimen has been largely established
- if combinations are necessary in intractable cases, regimens should avoid the inclusion, where possible, of sedating drugs such as the barbiturates or benzodiazepines
- drugs with different modes of action should be selected for combined therapy, to reduce the risk that adverse effects will be additive
- many antiepileptics interact with each other through complex mechanisms. Dosage adjustments may be necessary to maintain plasma concentrations within the therapeutic range during combination therapy; plasma monitoring may be advisable. (UK guidelines[17] recommend regular monitoring of antiepileptic drug concentrations only when clinically indicated, e.g. to manage pharmacokinetic interactions, or in cases of suspected toxicity or non-adherence)
- if trials of combination therapy do not produce worthwhile benefits, treatment should revert to the regimen (monotherapy or combination) that has provided the most acceptable balance of seizure control and adverse effects

Around 60% of patients with newly diagnosed epilepsy will respond to monotherapy with the first- or second-choice antiepileptic without developing intolerable adverse effects. The remaining 30 to 40% will have epilepsy that is difficult to control from the start, although some of these patients will respond to combination therapy.[27] Patients who fail to respond to adequate medical treatment may be considered for resective surgery; vagus nerve stimulation by means of an implanted device has also proved effective in those with severe intractable epilepsy who have an aura before the onset of a seizure.[18,19] UK guidelines recommend consideration of the adjunctive use of vagus nerve

stimulation in patients refractory to drug therapy but unsuitable for resective surgery.[16,17]

Partial seizures with or without **secondary generalisation** may be treated with *carbamazepine* or *valproate*, or with the newer drugs *lamotrigine* or *oxcarbazepine*.[16,17,33] *Topiramate* is also used, as monotherapy or as an adjunct to other treatments (in the UK, it is considered a first-line option in some circumstances[17,23]). Other second-line drugs are *phenytoin, clobazam*, or the newer antiepileptics *gabapentin, levetiracetam, pregabalin, tiagabine*, or *zonisamide*,[17,24,33] but whether these are recommended for monotherapy or adjunctive treatment may vary from country to country. Other drugs that have been used[17] include *acetazolamide, clonazepam*, and the barbiturates *phenobarbital* or *primidone*, although the latter in particular are little used now because of the problems of sedation. *Vigabatrin* is licensed in the UK for adjunctive use in patients in whom all other combinations have failed.

The response rate is somewhat lower for partial seizures than for tonic-clonic seizures associated with primary generalised epilepsy (see below). There is some evidence in favour of carbamazepine rather than valproate in the treatment of partial seizures.[34] More recently, some evidence was found in favour of lamotrigine rather than carbamazepine,[35,36] and of oxcarbazepine rather than phenytoin,[37] in terms of tolerability and time to treatment failure. However, there is no evidence of any significant difference between phenytoin and carbamazepine[38] or valproate[39] in partial seizures.

Calcium-channel blockers such as *flunarizine* have been studied with equivocal results in patients with refractory epilepsy, particularly those with partial seizures.[40]

The drugs used most often to treat **generalised** tonic-clonic seizures are *carbamazepine, lamotrigine*, or *valproate*. For tonic-clonic seizures as part of the syndrome of primary generalised epilepsy, valproate is the drug of choice, although systematic reviews were unable to establish evidence for this.[34,39] *Topiramate* is also considered a first choice in patients in whom the other older drugs are unsuitable or ineffective.[17,23] More recently, valproate was found to be better tolerated than topiramate and more effective than lamotrigine in generalised and unclassified epilepsy.[41] Second-line drugs in UK guidelines are *clobazam, levetiracetam*, and *oxcarbazepine*, while other drugs that may be considered include *acetazolamide, clonazepam, phenobarbital, phenytoin*, or *primidone*.[17] *Tiagabine* or *vigabatrin* should be avoided as they may worsen the seizures.[17]

The drugs of choice for **absence seizures** are *ethosuximide, valproate*, or, where these are unsuitable, *lamotrigine*,[17,24,42] although the evidence base to support this use is weak.[43] Second-choice drugs include *clobazam, clonazepam*, and *topiramate*, but *carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine*, and *vigabatrin* should be avoided as they may worsen seizures.[17,42] Since absence seizures occur mainly in children the precautions concerning valproate hepatotoxicity apply. However, where absence seizures are associated with tonic-clonic seizures valproate is the drug of choice since it is effective in both conditions; valproate is also preferred for atypical absence seizures. *Levetiracetam* may be used as an alternative for the syndrome of juvenile absence epilepsy.[17]

Valproate is normally the drug of choice for **myoclonic seizures**, including those associated with juvenile myoclonic epilepsy.[44,45] *Lamotrigine* may also be used in juvenile myoclonic epilepsy,[17,45] although some forms of myoclonus may be exacerbated;[17,44] *topiramate* may be considered, particularly for severe myoclonic epilepsy of infancy (in which *stiripentol* may also be effective), and second-line drugs also include *clobazam* and *clonazepam*, and adjunctive *levetiracetam* or *piracetam*.[17] *Zonisamide*[45] has also been used, as has *ethosuximide*.

The classical antiepileptics may not be particularly effective for **atonic** or **tonic** seizures, which are often associated with specific epileptic syndromes or with cerebral damage or mental retardation. UK guidelines suggest *valproate* or *lamotrigine* as first-line drugs; *clobazam, clonazepam, levetiracetam*, or *topiramate* are possible second-line drugs. Others that have been tried include *acetazolamide* and the barbiturates such as *phenobarbital*, while *phenytoin* may be considered for tonic seizures.[17] The *BNF* suggests *ethosuximide* may occasionally be helpful.

In **catamenial epilepsy** (epilepsy associated with menstruation) seizures can be predicted and intermittent therapy with *clobazam* may be useful. Hormonal manipulation has also been tried using *progestogens, gonadorelin analogues*, and *clomifene*.[46]

The **Lennox-Gastaut syndrome** begins in early childhood and is particularly difficult to treat because multiple seizure types co-exist; seizures rarely remit entirely. *Valproate* is most frequently used[47] because of its broad spectrum of activity; UK guidelines consider *lamotrigine* or *topiramate* as alternative first-line drugs if valproate is unsuitable; second-line choices include *clobazam, clonazepam, ethosuximide*, or *levetiracetam*.[17] *Rufinamide* is licensed in the UK for adjunctive use. *Felbamate* has also been used. The optimum treatment remains uncertain, but monotherapy with any drug has not been shown to be particularly effective.[48]

The classical antiepileptics are often ineffective in **infantile spasms** (as for example in **West's syndrome**).[49] UK guidelines recommend treatment with *corticotropin* or a *corticosteroid*, or else with *vigabatrin*;[17] in the USA, however, the American Academy of Neurology considers that the evidence does not support the use of corticosteroids, although corticotropin or vigabatrin appear to be of benefit.[50] *Vigabatrin* is effective either as adjunctive treatment or monotherapy. Many consider that, despite the risk of visual field defects,[51] it should replace corticotropin or corticosteroids as the treatment of choice,[52-58] although others disagree.[59,60] A systematic review[61] found that treatment with corticotropin or *tetracosactide*, or a corticosteroid such as *prednisone* resolved spasms in more infants than vigabatrin; a high dosage of prednisone or vigabatrin has been recommended but the optimum dose of corticotropin or tetracosactide is unknown. However, vigabatrin may offer the best first option in the treatment of infantile spasms due to tuberous sclerosis.[58,61,62] In some countries, *valproate*, alone or with *clonazepam* and/or *pyridoxine*, has been tried for initial management of infantile spasms.[63] Other second-line drugs include *clobazam* and *topiramate*;[17] *nitrazepam*,[17,57] *felbamate*,[49,64] and *lamotrigine*[49,64] have also been used. It is unclear to what extent treatment improves long-term outcome.[42,50,61]

Choice of antiepileptics in children. The use of antiepileptics in general in children has been reviewed.[42,64-71] Again, appropriate treatment depends on seizure type, but there is a lack of evidence to support many therapeutic choices,[66,71-73] in part because of the difficulties in undertaking studies in this population. In addition, children may be particularly susceptible to some adverse effects, including effects on behaviour, cognition, and development; behavioural problems have been associated particularly with phenobarbital.[71,74] Nonetheless the principles of pharmacological management are similar to those in adults (above) although UK guidelines recommend that treatment should only be begun by a specialist.[17] Dietary modification (the ketogenic diet) may also be tried.[71,75-78]

Withdrawal of antiepileptic therapy. Concern over the potential adverse effects of antiepileptic therapy clearly makes withdrawal attractive in patients who achieve prolonged seizure-free periods; however, the practical and social consequences of seizure recurrence may be considerable (for example, loss of driving licence and restricted employment prospects). The incidence of relapse after withdrawal has been variously estimated to range from 12% to over 60%.[79,80] Many studies have been carried out in children; data in adults is more scanty and given the differences between the populations, extrapolation of results in children to adults may be invalid.[79] A meta-analysis[81] that included 25 studies and 5354 patients (children and adults) found the overall rate of relapse in seizure-free patients after stopping antiepileptic therapy was 25% at 1 year and 29% at 2 years. There was a higher risk for relapse in adolescent- and adult-onset epilepsy compared with childhood-onset epilepsy. A more recent longitudinal population-based study[82] following 148 patients long-term from the onset of epilepsy in childhood found that of 90 patients in whom antiepileptic therapy was stopped, 33 relapsed and although in most cases relapse took place within 3 years, in one case it occurred 28 years after withdrawal.

Although these findings indicate that it is often possible to withdraw therapy successfully, it is more difficult to offer an individual *prognosis*.[11,83] It has been suggested that adult patients whose livelihood or lifestyle depends on being seizure-free would be generally ill advised to contemplate drug withdrawal.[84] Several strategies for predicting the likely outcome after withdrawal of antiepileptic therapy in individuals have been published.[85-87] Recognising that epilepsy is a heterogeneous disorder, scoring systems to allow for various risk factors have been devised.[85,86]

Prognostic risk factors (some of which are likely to be surrogate measures for the underlying condition) may include:

- the *aetiology* of the condition.[79,88] Patients classified as having symptomatic or cryptogenic epilepsy generally fare less well than those with idiopathic epilepsy with regard to seizure control, and withdrawal is less likely to be successful
- the *seizure type* and *syndrome*.[79,80,88] Studies have identified an increased risk of relapse in patients with particular seizure types; in particular, patients with partial, generalised tonic-clonic, and mixed seizure types seem to be at increased risk. However, it has been pointed out that increased risk has been associated with almost all seizure types other than generalised absence seizures, which seem to have a favourable prognosis; the context in which the seizure arises, such as the associated epilepsy syndrome and the aetiology, is more important than the type alone when considering withdrawal.[79] Examples of syndromes associated with a favourable outcome for withdrawal include benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions. However, withdrawal is inappropriate in juvenile myoclonic epilepsy, despite its good response to treatment, as relapse occurs in over 90% of patients
- the presence of accompanying *neurological* or *mental deficits*.[79] Some studies have suggested that mental retardation or other neurological deficits are associated with a poorer prognosis on withdrawal; these are probably surrogate markers for symptomatic epilepsy. However, mental retardation is not a contra-indication to withdrawal, and these patients may benefit from the elimination of any sedative effects if other risk factors are absent[79]
- the *age at onset*.[79,80,88] Several studies have identified a markedly increased risk of relapse on withdrawal in patients with seizure onset in adolescence or adulthood, whereas those with onset before 10 to 12 years of age have a generally more favourable prognosis. This is probably a surrogate marker for particular epileptic syndromes or aetiologies
- the *duration of remission*.[79,80,88,89] There is evidence in children that waiting for at least 2 seizure-free years before attempting withdrawal is associated with less risk of relapse than doing so earlier. However, the 2-year period was chosen arbitrarily, and the true optimum timing is unknown.[89] There is little evidence to guide the timing of withdrawal in adults.[89] However, in practice most support a requirement of at least 2 years free from seizures before drug withdrawal[79,80,88] and some suggest at least 4 years[83]
- the *response to therapy*.[79] Refractory epilepsy, as indicated by the occurrence of seizures once therapy has been begun, or the need for adjunctive or combination therapy to control seizures, is a poor prognostic sign for withdrawal. Patients with a history of multiple seizures before beginning therapy are also at increased risk on withdrawal

There is less agreement about the prognostic significance of some other factors:

- it is unclear whether the *type of drug* used to control seizures affects the risk of recurrence on withdrawal. It has been suggested that patients taking phenobarbital or benzodiazepines may be at increased risk of relapse, but there is little supportive evidence.[79] A poorer prognosis for patients taking valproate has also been reported;[90] a study in patients given combination therapy noted an increased risk when the carbamazepine component of the regimen was withdrawn.[91] It should be borne in mind that withdrawal of an enzyme-inducing antiepileptic may alter the serum concentrations of other drugs in the regimen[92]
- there is also controversy about the prognostic value of the *EEG* for the success of withdrawal.[79-81,88] Although an abnormal EEG before withdrawal was a negative prognostic factor in many studies, EEG abnormalities are not present in all epileptic patients, and some antiepileptic drugs suppress EEG abnormalities and can lead to false-negative results[79]

When a decision to withdraw is made, it is agreed that the *withdrawal regimen* should be gradual to reduce the risk of provoking withdrawal seizures. Drugs should be withdrawn one at a time but there is no agreement on the order or the optimum rate of withdrawal for individual drugs. It has been suggested that tapering therapy over less than 6 months increases the relapse rate.[79] However, one study in children indicated no significant difference in seizure recurrence rate when various antiepileptics, including barbiturates, were withdrawn over 6 weeks or 9 months.[93] Nonetheless, it has been pointed out that relapses tended to occur earlier in the group tapered more rapidly, and in practice it is rarely necessary to withdraw medication more rapidly than over a 6-month period.[79] It may be possible to withdraw phenytoin or valproate quickly (over a few days in hospital) if necessary.

If seizures recur on withdrawal it is almost always possible to restore good control by *re-instituting therapy*, and morbidity, mortality, and incidence of status epilepticus are reported to be low in the setting of prescribed antiepileptic drug withdrawal.[79] However, in a very small number of patients intractable seizures may develop.[83,94]

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Epilepsy and breast feeding. Antiepileptics are generally distributed into breast milk (although this information is not always known for the newer ones), but for most of the older established drugs, the concentrations are lower than in maternal plasma, and breast feeding is considered to be safe for these antiepileptics when given in usual doses.[1-7] The American Academy of Pediatrics[8] also considers that most of the older antiepileptics, specifically *carbamazepine*, *ethosuximide*, *phenytoin*, and *valproate*, are usually compatible with breast feeding; however, they also recommend that *phenobarbital* and *primidone* should be used with caution as significant adverse effects have occurred in nursing infants. Problems of neonatal sedation may occur with the *benzodiazepines* and *barbiturates* (including primidone). Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. There is little data for the new antiepileptics regarding breast feeding (the manufacturers and the UK Drugs in Lactation Advisory Service[9] generally recommend that breast feeding should be avoided). *Lamotrigine* may accumulate in breast-fed infants, as the metabolic pathway for lamotrigine may not be fully developed in newborns;[3,10] the American Academy of Pediatrics[8] considers that the use of lamotrigine during breast feeding may be of concern. *Gabapentin*,[11] *levetiracetam*,[12] and *topiramate*[13] are transferred into breast milk in significant amounts, but serum concentrations in breast-fed infants are very low. The American Academy of Neurology and American Epilepsy Society, while noting[14] that gabapentin, lamotrigine, levetiracetam, and topiramate were transferred into breast milk to a greater extent than carbamazepine, phenobarbital, phenytoin, and valproate (as was primidone), considered that the clinical effects of indirect exposure to antiepileptics via breast milk were not well enough explored.

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Epilepsy, cognition, and mood. Patients with epilepsy are at increased risk of **cognitive** and **behavioural** deficits. These are often multifactorial in origin: the disease itself and its underlying pathology, psychosocial and environmental factors, and the effects of antiepileptic treatment may all play a role.[1-8] Children are particularly vulnerable: recurrent seizures in the immature brain appear to have an adverse effect on the development of brain structure and function;[8] furthermore, behavioural and cognitive deficits may not be detected for a long time, while imposing detrimental effects on development and learning.[4,6] Because of the multifactorial nature of the problem, and the difficulties of assessing often subtle changes in cognition, it has proved difficult to study appropriately, and evidence is often scanty. Many studies have been small, and have had methodological flaws.[4,6] In addition, there is a need for studies in patient populations at greater risk, such as children.[5,6]

There is particular interest in assessing the risks associated with antiepileptic treatment, since it is perhaps the most readily modifiable factor. Strategies such as avoiding unnecessary polytherapy, using the lowest effective dose of an antiepileptic, keeping drug concentrations in therapeutic ranges, and slow titration when doses are increased, have been associated with fewer cognitive adverse effects. However, it should also be borne in mind that appropriate treatment and good seizure control may offset the negative cognitive effects.[4] (There is an interesting suggestion that suppression of interictal discharges in the EEG with lamotrigine may be associated with an improvement in behaviour in children with epilepsy and behavioural problems.[9])

The most common cognitive effects seem to be sedation, somnolence, distractibility, memory impairment, insomnia, and dizziness; adult patients often have depression (see below), whereas in children hyperactivity and aggression may occur.[5] (Aggression has also been reported in adults.[10]) More subtle effects on cognitive function and neuropsychological variables also occur. It has proved difficult, for the reasons mentioned above, to establish the comparative severity of cognitive effects between different antiepileptics. However, it seems to be generally agreed that barbiturate antiepileptics such as *phenobarbital*, and (particularly in the elderly) benzodiazepines such as *clobazam* and *clonazepam*, have the worst profiles, including decreased arousal and deterioration in most areas of cognitive performance;[4] in children, phenobarbital may decrease IQ and impair academic achievement.[5-7] Other standard antiepileptics such as *phenytoin*, *carbamazepine*, and *valproate* seem to have more modest, and broadly comparable, effects.[2,4-6] Most of the newer antiepileptics appear to be better tolerated; however, *topiramate*, and to some extent *zonisamide*, do produce impairment. There is also limited evidence that *gabapentin*, *lamotrigine*, and *vigabatrin* may enhance cognitive function. However, further data are required for the newer antiepileptics before a definitive assessment can be made.[1-7]

In view of the potential effect of antiepileptics on cognition, the recommendations of the Committee on Drugs of the American Academy of Pediatrics[11] include:

- the relative influence of each antiepileptic on cognitive and behavioural function should be considered along with all other potential adverse effects
- the child's behaviour and academic progress should be monitored through routine questioning of parents and teachers as well as by the physician's own observations of cognitive function, mood, and behaviour
- should behavioural or cognitive changes occur in relation to starting antiepileptic therapy, the need for medication and/or possible alteration of medication must be reassessed

For comment on the potential effects of maternal antiepileptic therapy on fetal neurodevelopment, see Epilepsy and Pregnancy, below.

Epilepsy is also associated with a greater prevalence of mood disorders, particularly **depression**, than is seen in the general population.[12-15] There have been concerns that antiepileptic drugs may play a significant role in exacerbating these. A review[16] has suggested that the commoner antiepileptics could be classified by the risk of associated depression as follows:

- highest risk (about 10% of patients):
  - barbiturate antiepileptics such as phenobarbital
  - topiramate
  - vigabatrin
  - zonisamide (associated with mood disorders in about 7% of those taking high doses)
- intermediate risk (4% or less):
  - felbamate
  - levetiracetam
  - tiagabine
- lower risk (less than 1%; some might actually have positive effects on mood):
  - carbamazepine
  - ethosuximide
  - gabapentin
  - lamotrigine
  - oxcarbazepine
  - phenytoin
  - pregabalin
  - valproate

In January 2008, the FDA issued an alert[17] after analysis of 199 placebo-controlled studies of antiepileptic drugs in the management of not only epilepsy but also psychiatric disorders (including bipolar disorder and depression) and other conditions such as migraine and neuropathic pain. This analysis, which involved 27 863 drug-treated patients and 16 029 controls, found that the risk of suicidal ideation or behaviour was about twice as great in the drug treatment groups (0.43%) as in those given placebo (0.22%). The relative risk was greater in patients with epilepsy than in those with other disorders. Drugs implicated by this analysis were carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. However, the FDA considered that the increased risk was a class effect that would be shared by *all* antiepileptics except those indicated only for short-term use. It was recommended that prescribers and patients and their families should be aware of the risk, and should be alert for behavioural changes and other warning signs that might signal suicidal ideation. Similar advice has been issued in the EU.[18] The risk factors (particularly antiepileptic drugs) for suicidal ideation in patients with epilepsy have been reviewed.[19]

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Epilepsy and driving. Driving by patients with epilepsy is generally regulated[1,2] and restricted to those whose seizures are adequately controlled. Also, antiepileptic drugs may produce CNS-related adverse effects, including dizziness and drowsiness, that could impair a patient's ability to drive a vehicle or operate machinery, particularly during the initial stages of therapy.

In the UK,[3,4] patients suffering from epilepsy may drive a motor vehicle (but not a heavy goods or public service vehicle) provided that:

- they have had a seizure-free period of 1 year *or*
- if subject to attacks while asleep and awake, have established a 3-year period without an awake attack *or*
- if subject only to attacks while asleep have an established pattern of attack for 1-year

It is recommended that patients should not drive during withdrawal of antiepileptic drugs, or for 6 months afterwards. Drivers of heavy goods and public service vehicles must have been seizure-free for 10 years without antiepileptic treatment.

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Epilepsy and pregnancy. The management of epilepsy during pregnancy may present problems for both the mother and the fetus.[1-10]

The outcome of pregnancy in women with epilepsy is generally recognised to be poorer than that in the general population. Still-births and neonatal loss are increased, and maternal deaths are more common;[3,6] there is also an increased incidence of preterm delivery and low birthweight at term.[4] In addition, there is a clearly increased risk of fetal malformation. The factors responsible for this poorer outcome are complex, and may include the disease itself, seizure frequency during pregnancy, and socio-economic factors, as well as the effects of antiepileptic drugs.[1,3,4,6,11-13]

A single generalised seizure does not usually pose clinical problems for the fetus, but both mother and fetus are at risk of serious trauma from maternal falls, and intra-uterine deaths have been reported. It is widely considered that status epilepticus is associated with significant mortality in mother and fetus.

The frequency of seizures may increase during pregnancy in some women; this might be related to hormonal or other factors such as lack of sleep, but one of the main reasons is likely to be decreased plasma-antiepileptic concentrations due to changes in drug clearance and binding as pregnancy progresses. Therapeutic drug monitoring has been recommended[14,15] in at-risk patients; the American Academy of Neurology and American Epilepsy Society (AAN/AES),[8] have particularly recommended monitoring the serum concentrations of carbamazepine, lamotrigine, and phenytoin, and possibly levetiracetam and oxcarbazepine. However, analysis[16] of 1956 pregnancies of 1882 epileptic women recorded in an international antiepileptic drugs and pregnancy registry (EURAP) found that 58.3% were seizure-free throughout pregnancy. Seizures occurred during delivery in 3.5%, most commonly in those who had seizures earlier during pregnancy, and status epilepticus occurred in 1.8%, with one case of still-birth and none of miscarriage or maternal mortality. The authors noted that publication bias favoured the reporting of adverse outcomes in pregnancy. An evidence-based review[9] suggested that freedom from seizures for at least 9 months before pregnancy is associated with a high likelihood (84 to 92%) of remaining seizure-free during pregnancy.

As with many other aspects of epilepsy, it is difficult to disentangle the potential adverse effects of therapy from those of the disease. However, although the risk of **major malformations** such as congenital heart defects, neural tube defects, urogenital defects, and orofacial clefts is somewhat increased in offspring of all women with epilepsy,[1,6] there is clear evidence that in children of women treated with antiepileptic drugs it is 2 to 3 times that in the general population, and the risk is higher in women taking multiple drugs or in those who take antiepileptics during the first trimester.[6]

Despite this, evidence linking specific drugs with particular patterns of malformation is limited and often unclear. There appears to be strong evidence for a dose-related increased risk of major malformation with *valproate*,[6,10-13,17-21] and increased risk has been reported for *carbamazepine*, *phenobarbital*, and *primidone*.[6,11,12] The rate of major abnormality with *phenytoin* does not seem to be higher than in the general population.[6] However, a well established **fetal antiepileptic syndrome** (FAS) has been reported with phenytoin, as with other antiepileptic drugs,[4] including some older drugs such as *trimethadione*. Although early reports associated syndromes with specific drugs, such as fetal hydantoin syndrome (phenytoin), or fetal valproate syndrome, there is considerable overlap in the reported effects and recent reviews consider these as manifestations of a single condition, FAS.[4,12] The dysmorphic facial changes characteristic of FAS can be quite subtle, and may become less apparent as the child grows.[6]

Evidence for any effect of the newer antiepileptics on the fetus is particularly scanty. It is unclear if *oxcarbazepine* is associated with an increased risk in major malformation,[6] and limited data have not so far suggested a significant increase in risk with *lamotrigine*[12,21,22] and *levetiracetam*.[23] There are reports suggestive of an increased risk with *topiramate*[6] and licensed product information for this drug, and also *pregabalin* and *zonisamide* advises against use in pregnancy on the basis of *animal* studies and lack of human data. Caution is also advised with *tiagabine* and *vigabatrin*. There appears to be little evidence of teratogenic potential for *felbamate* or *gabapentin* in *animal* studies to date, although cases of malformation have been seen in pregnancies exposed to gabapentin.[6]

In a study[20] of the UK Epilepsy and Pregnancy Register that examined the outcome of 3607 pregnancies in mothers with epilepsy, the overall rate of major congenital malformations was 3.5% in those untreated with antiepileptics and 4.2% in those given antiepileptics during pregnancy, with rates of 3.7% and 6.0% in those given monotherapy or polytherapy, respectively. For monotherapy, the malformation rates for individual drugs were topiramate (7.1%), valproate (6.2%), phenytoin (3.7%), gabapentin (3.2%), lamotrigine (3.2%), and carbamazepine (2.2%). For polytherapy, those regimens containing valproate had a significantly higher risk of major congenital malformations than valproate-free combinations. A relationship between malformations and dose was seen for lamotrigine monotherapy and although the trend with valproate dosage did not reach statistical significance, infants exposed to more than 1 g of valproate daily had the highest rate of malformations for any monotherapy. The authors also noted that for lamotrigine the risk with doses more than 200 mg daily was no different to that associated with 1 g or less of valproate daily.

There is evidence that antiepileptic therapy is associated with lower birth-weight at term, presumably due to drug-induced **intra-uterine growth retardation**; the effect may be seen largely in women taking multiple antiepileptic drugs.[6]

Additional problems that may occur in the immediate postpartum period include the potential for neonatal **sedation** and **dependence** with drugs such as phenobarbital or *benzodiazepines*, if given close to term. Evidence of withdrawal symptoms has also been reported in infants exposed to sodium valproate or phenytoin. Some antiepileptics induce hepatic enzymes and may also increase the risk of vitamin K deficiency and **neonatal bleeding**.[4,6]

There is also increasing concern about the possibility of long-term **impairment of neurodevelopment** in children exposed to antiepileptic drugs *in utero*.[3,6,11,12,24,25] A population-based cohort study[26] in young men with epileptic mothers found lower IQ scores and shorter adult heights than in those born to mothers without epilepsy, although information on fetal exposure to individual antiepileptic drugs was unavailable. Again, most evidence implicates valproate;[6,10-12,27,28] some consider that there is also evidence for phenytoin[6,10-12] and carbamazepine,[6,11,12] and perhaps phenobarbital,[10,11] although a systematic review could not find evidence to implicate any individual antiepileptic,[24] and a study involving 182 children exposed to carbamazepine monotherapy could not find evidence of a reduction in verbal and nonverbal IQ scores.[29]

Patients with epilepsy should be offered **pre-conception advice** and treatment should be individualised.[1,2,4,6] Women should be advised to plan their pregnancies, and informed of the potential risks of seizures to mother and baby as well as the risks of antiepileptics;[6] fatalities have been associated with the mother stopping her antiepileptic regimen inappropriately.[3] It should be borne in mind that some antiepileptics may reduce the efficacy of oral contraception and increase the risk of unplanned pregnancy.[4,12] Equally, there is some evidence that a degree of sexual dysfunction and impaired fertility may occur in both women[4,12] and men[30,31] with epilepsy.

In women with epilepsy who intend to become pregnant, certain guidelines and principles are widely followed.

- Withdrawal of antiepileptic therapy may be an option if the patient has been seizure-free for at least 2 years (for further details of drug withdrawal, see p. 506.1); resumption of therapy may be considered after the end of the first trimester.
- If antiepileptics are to be continued throughout pregnancy, monotherapy is preferred using the lowest possible effective dose, although doses may have to be increased in response to changes in drug disposition during pregnancy, with the necessary readjustments being made after delivery.
- High daily doses of valproate (more than 1 g daily) should be avoided if possible, and peak plasma concentrations may be reduced by dividing the daily dose into 3 or 4 parts or by giving a modified-release preparation.
- Since there is a risk of fetal malformations with all the established antiepileptics, and a lack of data for the newer ones, it is generally considered that as long as there is good seizure control there is little to be gained from changing a pregnant patient's antiepileptic.

For those patients who first present when **already pregnant** there is probably little to be gained in altering potentially teratogenic antiepileptics as the time for intervention has almost certainly passed.[1,2,6,10] If a patient becomes pregnant while taking carbamazepine, phenytoin, or valproate she should be counselled regarding the risk of neural tube and other defects and should be offered antenatal screening. Adequate supplementation of folic acid is advised before pregnancy and during the first trimester to counteract the risk of neural tube defects. It has been suggested that women taking antiepileptics should be given folic acid in similar doses to those used in women who have previously given birth to an infant with neural tube defects, i.e. 4 or 5 mg daily (for further details, see Neural Tube Defects under Folic Acid, p. 2064.3). However, the AAN/AES[8] only suggest supplementation with the standard female dose of at least 400 micrograms daily of folic acid, before and during pregnancy, as it is unknown whether higher doses offer greater benefit in these patients. Although folic acid can reduce serum-phenytoin concentrations this does not appear to be a problem in practice (see Vitamins, p. 545.2).

To counteract the risk of neonatal bleeding associated with enzyme-inducing antiepileptics it is particularly important that the neonate be given vitamin K after delivery[4-6] (for further details, see Vitamin K Deficiency Bleeding, p. 2123.2). Some have advocated oral doses for the mother in the last 4 weeks of pregnancy,[4] but the justification for prophylactic maternal dosage is unclear[8,32] given the available evidence.

Patients with epilepsy have also a higher risk of preterm delivery and antenatal corticosteroid therapy may, therefore, be warranted. High doses of corticosteroid may be required in those women receiving enzyme-inducing antiepileptics.[1]

Status epilepticus during pregnancy should be treated in the same way as for the general population (see below). First seizures occurring during the second half of pregnancy may be part of eclampsia (see p. 511.1) and should be differentiated from epilepsy.

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Status epilepticus

Although status epilepticus has been defined as continuous or repeated seizure activity lasting 30 minutes or more without any regaining of normal consciousness, current definitions generally consider it to be any continuous seizure of more than 5 minutes, or 2 or more seizures without regaining normal consciousness.[1-8] Although status may occur with any seizure type, generalised convulsive status is the most common clinical presentation,[4] with an estimated mortality rate of about 20%; it is most frequent in young children and the elderly.[1,3,9] It is a medical emergency, and the longer seizures continue, the more difficult they are to control and the higher the morbidity and mortality; permanent neuronal damage can occur after 30 minutes of seizure activity.[8]

Management of status epilepticus varies slightly between centres and countries, but the general principles seem to be fairly well established.[1-12]

- In **initial management**, it is important to secure the airway and give oxygen as required, assess cardiac and respiratory function, and establish intravenous access. Blood glucose should be assessed and any hypoglycaemia corrected with glucose; intravenous thiamine should be given if there is any suggestion of alcohol abuse or inadequate nutrition.[1,4-7,11]
- Initial antiepileptic treatment is usually with a benzodiazepine. Although *diazepam* has been widely used in the past, intravenous *lorazepam* is now preferred for first-line treatment in most protocols,[1-7,9-15] as it appears to be more effective and has a longer duration of antiepileptic action.[6,7,13] *Clonazepam*[16] or diazepam followed immediately by phenytoin or fosphenytoin[15] have been proposed as alternatives where intravenous lorazepam is not available. Rectal diazepam or buccal *midazolam* may be used in the home setting or where intravenous access is not available.[4,5,12,14,17] (Rectal diazepam may also have a role in this setting to treat acute repetitive seizures,[18] which may evolve into status epilepticus.) Both midazolam[19,20] and lorazepam[21] have also been given intranasally.
- For sustained control in patients with established epilepsy their usual antiepileptic regimen may be given orally or by nasogastric tube once immediate control is established, or if necessary, for those drugs with an intravenous formulation, parenterally.[4,5]
- In other patients, or in patients with **established status** not abolished by the benzodiazepine, additional treatment with one of several first-line antiepileptics is normally required. The choice is usually between intravenous *phenytoin, fosphenytoin,* or *phenobarbital*,[1,4,5,7,8] all of which are effective. Repeat doses may need to be given. Although there is some evidence that phenobarbital is more effective than phenytoin in abolishing seizures,[22] many favour the use of the barbiturate only in patients who do not respond to phenytoin or fosphenytoin,[1-3,9,10] because of the risk of severe respiratory depression. ECG monitoring is required in patients given intravenous phenytoin or fosphenytoin.[4]
- Other antiepileptics have been used for established status. Some have found intravenous *valproate* to be useful in this situation,[8,23-25] and have incorporated it into local protocols. Other alternatives have included *paraldehyde* rectally or by deep intramuscular injection, and intravenous *clomethiazole edisilate* was formerly available. Rectal paraldehyde has been noted to cause little respiratory depression and may therefore be useful where facilities for resuscitation are poor. Another option is to give *lidocaine* intravenously.[1] *Pyridoxine* may be tried in children under 3 years of age with established convulsive status epilepticus, in case the seizures are pyridoxine dependent or responsive.[2]
- Once seizures have continued for 60 to 90 minutes despite treatment with a benzodiazepine and one of the first-line antiepileptics, the patient is considered to have **refractory status epilepticus**.[1,5,26] At this point general anaesthesia should be instituted. The usual choice is between treatment with *propofol, midazolam,* or a short-acting barbiturate anaesthetic such as *pentobarbital* or *thiopental*.[1,4-10,15,26,27] Midazolam may be the preferred alternative in children.[16] The anaesthetic should be continued for 12 to 24 hours after the last clinical or electrographic seizure and the dose then gradually reduced.[5,26] Some consider that all patients unresponsive to first-line therapy with a benzodiazepine should be considered refractory and proceed to treatment with propofol or midazolam.[6]
- Other drugs tried in refractory status include the inhalational anaesthetics *desflurane* and *isoflurane*.[28] *Tiagabine* and *ketamine* have also been suggested,[6] as has *valproate*,[8,27] and there are a few reports of responses to *levetiracetam*[29] and *topiramate*.[30-32]

Evidence to support the management of **nonconvulsive** forms of status epilepticus (NCSE) is scanty. The *BNF* recommends that usual oral antiepileptics should initially be continued or restarted in patients with incomplete loss of awareness. Otherwise, it has been suggested that management should be as for convulsive status,[6] albeit less aggressive,[33] with intravenous benzodiazepines the first choice for initial management.[4-6,11,15,33] Subsequent man-

agement will probably be influenced by the drugs known to be effective in the given seizure type. The prognosis depends on the aetiology and level of consciousness: comatose patients with refractory NCSE have a poorer prognosis and general anaesthesia may be appropriate.[6] Conscious patients generally have a more favourable outcome and termination of status is considered less urgent; general anaesthetics should thus be used more cautiously.[11,33]

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Other convulsive disorders

Disorders that feature convulsions or epileptic seizures but are not considered to be forms of epilepsy are described below.

Alcohol withdrawal syndrome. For a discussion of the management of seizures associated with alcohol withdrawal syndrome, see p. 1735.1.

Eclampsia and pre-eclampsia. Pre-eclampsia is a hypertensive disorder occurring in pregnancy that entails increased blood pressure together with proteinuria, and sometimes abnormal coagulation, liver dysfunction, and oedema; rarely the disorder may progress to eclampsia, which is a convulsive phase. It is difficult to identify those patients who will have eclamptic seizures. The treatment of pre-eclampsia and eclampsia is mainly aimed at reducing hypertension (see Hypertension in Pregnancy, under Hypertension, p. 1251.1) and treating or preventing resultant seizures. However, the treatment of the hypertension alone may not be sufficient to prevent the progression of pre-eclampsia to eclampsia.

Eclampsia in the UK was traditionally **treated** with *diazepam, clomethiazole,* or *phenytoin. 'Lytic cocktails'* consisting of chlorpromazine, pethidine, and/or promethazine have also been used in some countries in the management of pre-eclampsia and imminent eclampsia but they result in heavy sedation and the use of phenothiazines is generally not recommended late in pregnancy. *Magnesium sulfate* is now the drug of choice for the treatment of eclampsia;[1-3] it has been the preferred treatment of eclampsia in the USA for many years, on the grounds that it is more effective and causes fewer adverse effects than other antiepileptics. A meta-analysis[4] of 9 randomised studies involving 2390 patients with pre-eclampsia and 1743 patients with eclampsia concluded that magnesium sulfate was more effective than phenytoin or no therapy in prevention of seizures in pre-eclamptic patients. In eclamptic patients, magnesium sulfate was superior to phenytoin, diazepam, or a lytic cocktail in terms of seizure recurrence, a result that was confirmed in subsequent systematic reviews.[5-7]

Until recently there has been insufficient evidence to establish the benefits and hazards of antiepileptics in the **prevention** of eclampsia in pre-eclamptic patients although it was considered that magnesium sulfate was the best choice if an antiepileptic was needed.[8-10] Some commentators suggested,[11] in the light of evidence of possible neonatal toxicity, that magnesium sulfate should be restricted to use in more severe pre-eclampsia or eclampsia. However, the significant benefits of magnesium sulfate in the prevention of eclampsia were confirmed in a large, international study,[12] and follow-up studies found that magnesium sulfate was not associated with an increased risk of death or disability in the children at 18 months[13] and in the mothers at 2 years.[14]

1. Gülmezoglu AM, Duley L. Use of anticonvulsants in eclampsia and pre-eclampsia: survey of obstetricians in the United Kingdom and Republic of Ireland. *BMJ* 1998; **316:** 975–6.
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14. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for women at 2 years. *BJOG* 2007; **114:** 300–9.

Febrile convulsions. Febrile convulsions have been defined[1] as epileptic seizures occurring between the ages of 6 months to 5 years and associated with a fever arising from an infectious illness outside the CNS. They usually occur during the rising phase of fever early in the course of the infection and are not considered to be a form of epilepsy.[2,3]

Febrile convulsions are considered to be benign if limited to a single tonic or tonic-clonic seizure lasting less than 15 minutes without any focal characteristics[2] (also known as simple febrile convulsions).[4] About one-third of children who have a benign febrile convulsion will have a recurrence.[1,2,5] Risk factors for recurrence include a young onset age, a history of epilepsy or febrile seizures in a first-degree relative, subsequent episodes of fever, and a first complex febrile seizure.[5] The risk of developing epilepsy is low, but nevertheless it is 2 to 3 times greater than the risk in the population as a whole.[2] Unless they are recurrent, benign febrile convulsions need only simple treatment to lower body temperature[1,2] such as that described under Fever and Hyperthermia, p. 11.3.

Prolonged febrile convulsions lasting longer than 15 minutes and associated with some focal characteristics are not considered to be benign (also known as complex febrile convulsions[4]) and further increase the risk of developing epilepsy.[2,3] When they are prolonged or recurrent they are treated with *diazepam* intravenously, or as a rectal solution, to prevent possible brain damage resulting from continued seizure activity, although any such effect appears to be rare.[6]

The prophylactic use of *antiepileptics* in children thought to be at risk of recurrence of febrile convulsions remains controversial. Many consider that even if recurrences can be prevented there is no evidence that the risk of developing epilepsy is reduced.[1,2,5] A working group of the Royal College of Physicians and the British Paediatric Association considered that pooled analyses of studies of the prophylactic use of *phenobarbital* or *sodium valproate* showed that long-term prophylaxis was rarely indicated.[1] Although some have found that intermittent prophylaxis with phenobarbital or diazepam[7] given at the onset of and during fever could prevent recurrence of febrile convulsions, the working group did not recommend their routine use in this way.[1] Other workers have found that giving paracetamol as an antipyretic and diazepam for intermittent prophylaxis failed to prevent recurrences of febrile convulsions.[8] A later meta-analysis[9] concluded that neither continuous nor intermittent prophylaxis could be recommended as the benefits did not outweigh the potential adverse effects, a view endorsed by the American Academy of Pediatrics.[4]

1. Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association. Guidelines for the management of convulsions with fever. *BMJ* 1991; **303:** 634–6. Also available at: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1671115&blobtype=pdf (accessed 09/06/08)
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8. Uhari M, *et al*. Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126:** 991–5.
9. Rantala H, *et al*. A meta-analytic review of the preventative treatment of recurrences of febrile seizures. *J Pediatr* 1997; **131:** 922–5.

Myoclonus. Myoclonus consists of brief, involuntary, jerky movements of sudden onset which may be focal, segmental, or generalised, and are caused by muscular contractions (positive myoclonus) or inhibitions/pauses (negative myoclonus). The term 'myoclonus' is non-specific and classification is important in order to decide on treatment:[1-6]

- physiological (in normal subjects)
- essential (no known cause)
- epileptic (seizures dominate)
- symptomatic (encephalopathy dominates—causes include storage diseases, neurodegenerative syndromes, toxic and drug-induced syndromes, and hypoxia)

In epileptic myoclonus, epileptic seizures (myoclonic seizures in which the motor manifestation is myoclonus) dominate. Their treatment is discussed under Epilepsy, p. 506.1. Essential myoclonus may benefit from *clonazepam. Botulinum toxin* has been used successfully for spasmodic movements in some forms of myoclonus.

Myoclonus may also be subdivided into cortical, reticular, or spinal forms. Cortical myoclonus is considered to be a subset of epilepsy and responds best to antiepileptics, usually *valproate* and/or clonazepam; *piracetam* or *levetiracetam* are also used, usually as adjunctive therapy. Reticular myoclonus is usually caused by anoxia or acute encephalopathy and may be treated with clonazepam; *serotonin* or serotonergic agonists have also been tried. Posthypoxic myoclonus occurring after hypoxic coma may respond to *oxitriptan* or serotonin combined with *carbidopa*; antiepileptics may help.

1. Caviness JN. Myoclonus. *Mayo Clin Proc*. 1996; **71:** 679–88.
2. Blindauer K. Myoclonus and its disorders. *Neurol Clin North Am* 2001; **19:** 723–34.
3. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol* 2003; **16:** 515–21.
4. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; **3:** 598–607.
5. Andrade DM, *et al*. Treatment options for epileptic myoclonus and epilepsy syndromes associated with myoclonus. *Expert Opin Pharmacother* 2009; **10:** 1549–60.
6. Caviness JN. Pathophysiology and treatment of myoclonus. *Neurol Clin* 2009; **27:** 757–77.

Neonatal seizures. Neonatal seizures differ from epilepsy, and the definitions in the 1989 international classification of epilepsy and epileptic syndromes (see p. 506.1) may be of little value; (a study[1] has suggested that the proposed 2001 classification may be more helpful). They are frequently subtle and difficult to recognise.[2] Causes include asphyxia, glucose or electrolyte imbalance, infection, CNS or cerebrovascular lesions, inborn errors of metabolism, and drug withdrawal or intoxication.[3-5]

Neonatal seizures represent a neurological emergency in the newborn and rapid diagnosis and treatment is essential.[3-7] Infusion of glucose or electrolytes may be of benefit.[4,5] Current practice involves giving antiepileptic

drugs to control seizures, although there is no consensus on, nor good evidence for, their use.[2,7] *Phenobarbital* and *phenytoin* are the most widely used.[3-6] Traditionally, phenobarbital has been considered to be the mainstay of treatment for all types of seizures in neonates; however response rates are variable.[6-8] If seizures persist, phenytoin may be added to therapy.[8] Other drugs that have been tried include *carbamazepine*, *levetiracetam*,[9] *benzodiazepines*,[3-5,8,10,11] *lidocaine*,[3,8,11] and *primidone*.[4,5] Pyridoxine-dependent seizures can be abolished by regular large doses of the vitamin[4,5] (see p. 2106.2).

1. Mastrangelo M, *et al.* Epileptic seizures, epilepsy and epileptic syndromes in newborns: a nosological approach to 94 new cases by the 2001 proposed diagnostic scheme for people with epileptic seizures and with epilepsy. *Seizure* 2005; **14:** 304–11.
2. Rennie J, Boylan G. Treatment of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F148–F150.
3. Evans D, Levene M. Neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F70–F75.
4. Hill A. Neonatal seizures. *Pediatr Rev* 2000; **21:** 117–21.
5. Painter MJ, Alvin J. Neonatal seizures. *Curr Treat Options Neurol* 2001; **3:** 237–48.
6. Painter MJ, *et al.* Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999; **341:** 485–9.
7. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 09/06/08).
8. Boylan GB, *et al.* Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004; **62:** 486–8.
9. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.
10. Castro Conde JR, *et al.* Midazolam in neonatal seizures with no response to phenobarbital. *Neurology* 2005; **64:** 876–9.
11. Shany E, *et al.* Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007; **22:** 255–9.

Porphyria. Convulsions may occur at the peak of an attack of acute porphyria (p. 1556.1) but usually disappear as the attack resolves and therapy should be aimed at the underlying disease. However, some patients continue to have convulsions while in remission and their management poses a major therapeutic problem as all the first-line antiepileptics have been associated with acute attacks.

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies and gives recommendations for drug use based on the risk of porphyrinogenicity; for details see the individual monographs in this chapter and also clomethiazole (p. 1054.3), diazepam (p. 1067.3), and magnesium sulfate (p. 1791.1).

Reflex anoxic seizures. For a discussion of the management of reflex anoxic seizures, see p. 1311.3.

4-Amino-3-hydroxybutyric Acid

Ácido 4-amino-3-hidroxibutírico; Buxamin; GABOB; Gamma-amino-beta-hydroxybutyric acid; γ-Amino-β-hydroxybutyric acid; 4-Амино-3-оксимасляная Кислота.

$C_4H_9NO_3$=119.1

CAS — 352-21-6.

UNII — 1ZHM019FLD.

Profile

Aminohydroxybutyric acid has been claimed to be of value in a variety of neurological disorders including use as an adjunct in the treatment of epilepsy. It has also been promoted as a dietary supplement for its supposed beneficial effects on the CNS and growth hormone. It should be distinguished from its isomer 3-amino-4-hydroxybutyric acid (GOBAB), which is reported to possess anti-inflammatory and antifungal activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gabimex; ***Braz.***: Gamibetal; ***Ital.***: Gamibetal; ***Mex.***: Gamibetal.

Multi-ingredient Preparations. ***Arg.***: Gabimex Plus; ***Chile***: Gamalate B6; Gamavit B6; ***Ital.***: Gamibetal Complex; Gamibetal Plus; Parvisedil; ***Mex.***: Gamibetal Complex†; ***Spain***: Dorken†; Gamalate B6; Redutona†; ***Ukr.***: Gamalate B6 (Гамалате В6).

Barbexaclone *(rINN)*

Barbeksaklon; Barbexaclona; Barbexaclonum; Барбексаклон.

Compound of (-)-*N*,α-Dimethylcyclohexaneethylamine with 5-ethyl-5-phenylbarbituric acid .

$C_{12}H_{12}N_2O_3,C_{10}H_{21}N$=387.5

CAS — 4388-82-3.

ATC — N03AA04.

ATC Vet — QN03AA04.

UNII — 291GX1YB65.

Profile

Barbexaclone is a compound of levopropylhexedrine (see under Propylhexedrine, p. 2330.1) with phenobarbital (p. 535.2). It is used in the treatment of various types of epilepsy (p. 506.1). Usual adult doses are 200 to 400 mg daily given orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Maliasin; ***Braz.***: Maliasin†; ***Gr.***: Maliasin; ***Ital.***: Maliasin; ***Switz.***: Maliasin†; ***Turk.***: Maliasin.

Benzobarbital *(rINN)*

Benzobarbitalum; Benzobarbitone; Benzonal; Benzonalum; Бензобарбитал.

1-Benzoyl-5-ethyl-5-phenylbarbituric acid.

$C_{19}H_{16}N_2O_4$=336.3

CAS — 744-80-9.

UNII — YNJ78BD0AH.

NOTE. The name benzonal has also been used as a proprietary name for benzonatate (p. 1656.2).

Pharmacopoeias. In *Int.*

Profile

Benzobarbital is a barbiturate that has been used in the treatment of epilepsy.

Brivaracetam *(USAN, rINN)*

Brivaracétam; Brivaracetamum; UCB-34714; Бриварацетам.

(2*S*)-2-[(4*R*)-2-Oxo-4-propylpyrrolidin-1-yl]butanamide.

$C_{11}H_{20}N_2O_2$=212.3

CAS — 357336-20-0.

UNII — U863JGG2IA.

Profile

Brivaracetam is under investigation for the treatment of various types of epilepsy including progressive myoclonic epilepsy and refractory partial seizures.

References.

1. Sargentini-Maier ML, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63:** 680–8.
2. Rolan P, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men. *Br J Clin Pharmacol* 2008; **66:** 71–5.
3. Malawska B, Kulig K. Brivaracetam: a new drug in development for epilepsy and neuropathic pain. *Expert Opin Invest Drugs* 2008; **17:** 361–9.

Carbamazepine *(BAN, USAN, rINN)*

Carbamazepin; Carbamazepina; Carbamazépine; Carbamazepinum; G-32883; Karbamatsepiini; Karbamazepin; Karbamazepinas; Karbamazepinum; Карбамазепин.

5*H*-Dibenz[*b*,*f*]azepine-5-carboxamide.

$C_{15}H_{12}N_2O$=236.3

CAS — 298-46-4.

ATC — N03AF01.

ATC Vet — QN03AF01.

UNII — 33CM23913M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Carbamazepine). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.

USP 36: (Carbamazepine). A white or off-white powder. Practically insoluble in water; soluble in alcohol and in acetone. Store in airtight containers.

Incompatibility. Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric use as undiluted suspension is adsorbed onto PVC nasogastric tubes.[1]

The FDA has received a report of a patient who passed an orange rubbery mass in his faeces the day after taking a carbamazepine suspension (*Tegretol; Novartis, USA*) followed immediately by chlorpromazine solution (*Thorazine; GSK, USA*). Subsequent testing showed that mixing the same carbamazepine suspension with a thioridazine hydrochloride solution (*Mellaril; Novartis, USA*) also resulted in the precipitation of a rubbery orange mass.

1. Clark-Schmidt AL, *et al.* Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm* 1990; **47:** 2034–7.

Stability. FDA studies indicate that carbamazepine tablets could lose up to one-third of their efficacy if stored in humid conditions.[1] This appears to be due to formation of a dihydrate form which leads to hardening of the tablet and poor dissolution and absorption.[2,3] As the dihydrate has also been detected after storage under ambient conditions some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets.[2]

1. Anonymous. Moisture hardens carbamazepine tablets, FDA finds. *Am J Hosp Pharm* 1990; **47:** 958.
2. Lowes MMJ. More information on hardening of carbamazepine tablets. *Am J Hosp Pharm* 1991; **48:** 2130–1.
3. Wang JT, *et al.* Effects of humidity and temperature on in vitro dissolution of carbamazepine tablets. *J Pharm Sci* 1993; **82:** 1002–5.

Uses and Administration

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalised tonic-clonic seizures and partial seizures, and in some primary generalised seizures. Carbamazepine is also used in the treatment of trigeminal neuralgia and has been tried with variable success in glossopharyngeal neuralgia and other severe pain syndromes associated with neurological disorders such as tabes dorsalis and multiple sclerosis. Another use of carbamazepine is in the management of bipolar disorder unresponsive to lithium.

In the treatment of **epilepsy** (p. 513.2), the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre). A low initial dose of carbamazepine is recommended to minimise adverse effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary.

For details of doses in children, see p. 513.1.

Oral carbamazepine is usually given in divided doses 2 to 4 times daily. A twice-daily regimen may sometimes be suitable for monotherapy, and be associated with improved compliance but can produce widely fluctuating plasma-carbamazepine concentrations that lead to intermittent adverse effects. Modified-release formulations can minimise fluctuations in plasma concentration and may also allow effective twice-daily use. The time and manner of taking carbamazepine should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations. Different preparations vary in bioavailability and it may be prudent to avoid changing the formulation.

Carbamazepine may be given by the rectal route in doses up to a maximum of 250 mg every 6 hours to patients for whom oral treatment is temporarily not possible. The dosage should be increased by about 25% when changing from an oral formulation to suppositories, and it is recommended that the rectal route should not be used for longer than 7 days.

As with other antiepileptics, withdrawal of carbamazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

The treatment of **trigeminal neuralgia** (p. 513.3) is typically begun with low oral doses, such as 100 mg of carbamazepine twice daily (although up to 200 mg twice daily has been suggested in the UK), and increased gradually as needed to maintain freedom from pain. This is usually at maintenance doses of 400 to 800 mg in divided doses; up to 1.2 g is the maximum daily dose recommended in the USA, while UK licensed product information considers that up to 1.6 g daily may be needed in some patients. When pain relief has been obtained attempts should be made to reduce, and if possible stop, therapy, until another attack occurs.

For the management of **bipolar disorder** (p. 513.1), carbamazepine is given in an initial oral dose of 400 mg daily in divided doses, increased gradually as necessary up to a maximum of 1.6 g daily; the usual maintenance dose range is 400 to 600 mg daily.

Administration. A modified-release formulation of carbamazepine can reduce fluctuations in carbamazepine concentrations,[1] and tolerability and seizure control in patients with epilepsy may be improved.[2,3] Such formulations should be considered in patients receiving high doses who suffer intermittent adverse effects, and might also permit a reduction to twice- or even, in some patients, once-daily dosage.[2,4] However, bioavailability appears to be slightly less than conventional preparations and dosage

adjustments may be required when changing between formulations.[1]

1. McKee PJW, *et al.* Monotherapy with conventional and controlled-release carbamazepine: a double-blind, double-dummy comparison in epileptic patients. *Br J Clin Pharmacol* 1991; **32:** 99–104.
2. Anonymous. Carbamazepine update. *Lancet* 1989; **ii:** 595–7.
3. Ryan SW, *et al.* Slow release carbamazepine in treatment of poorly controlled seizures. *Arch Dis Child* 1990; **65:** 930–5.
4. McKee PJW, *et al.* Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. *Br J Clin Pharmacol* 1993; **36:** 257–61.

Administration in children. In the UK, the usual recommended oral dose of carbamazepine for generalised tonic-clonic and partial seizures in children is 10 to 20 mg/kg daily in divided doses. Alternatively the daily dose may be given according to age as follows:

- up to 1 year: 100 to 200 mg
- 1 to 5 years: 200 to 400 mg
- 5 to 10 years: 400 to 600 mg
- 10 to 15 years: 0.6 to 1 g

As with adults, children should be started on a low initial dose of carbamazepine to minimise adverse effects; the *BNFC* suggests that those aged 1 month to 12 years may initially be given 5 mg/kg at night or 2.5 mg/kg twice daily, increasing by 2.5 to 5 mg/kg every 3 to 7 days as necessary to a usual maintenance dose of 5 mg/kg 2 or 3 times daily. Older children may be given the usual adult dose (see p. 512.3) although a maximum of 1.8 g daily has been suggested.

The *BNFC* also states that these doses may be used for the treatment of trigeminal neuralgia and prophylaxis of bipolar disorder.

Carbamazepine may be given rectally to children in whom oral treatment is temporarily not possible; the *BNFC* suggests this route may be used from 1 month of age. Doses should be about 25% greater than the corresponding oral dose, to a maximum of 250 mg, and given up to 4 times daily.

Bipolar disorder. Carbamazepine may be given as an alternative to lithium or valproate in patients with bipolar disorder (p. 397.2). Studies of its efficacy have been conflicting; although clearly effective in some patients, at least one early study suggested that short-term benefit was not sustained in the longer term.[1] More recent results[2,3] have suggested that lithium or valproate are generally more effective, but that carbamazepine may conceivably have a role in patients with nonclassical features. Carbamazepine has also been used with lithium, particularly in patients unresponsive to either drug alone; although there are suggestions that the combination may be more effective than monotherapy, particularly in patients with a history of rapid cycling,[4] it is associated with a potential risk of serious neurotoxicity—see Antidepressants, under Interactions, p. 516.2. While some commentators have suggested that carbamazepine is falling out of favour with specialists prescribing for bipolar disorder,[5] more recent reviews[6,7] have concluded that it may still be a feasible treatment option.

1. Frankenburg FR, *et al.* Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; **8:** 130–2.
2. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000; **42** (suppl 1): 2–10.
3. Vasudev K, *et al.* Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology (Berl)* 2000; **150:** 15–23.
4. Denicoff KD, *et al.* Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 1997; **58:** 470–8.
5. Ferrier IN. Developments in mood stabilisers. *Br Med Bull* 2001; **57:** 179–92.
6. Stoner SC, *et al.* Historical review of carbamazepine for the treatment of bipolar disorder. *Pharmacotherapy* 2007; **27:** 68–88.
7. Ceron-Litvoc D, *et al.* Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. *Hum Psychopharmacol* 2009; **24:** 19–28.

Depression. Carbamazepine has been tried[1-4] for the augmentation of antidepressant therapy in the treatment of resistant depression (p. 398.1). However, such combined therapy may lead to interactions—see also Antidepressants, under Interactions, p. 516.2.

1. De la Fuente JM, Mendlewicz J. Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. *Biol Psychiatry* 1992; **32:** 369–74.
2. Otani K, *et al.* Carbamazepine augmentation therapy in three patients with trazodone-resistant depression. *Int Clin Psychopharmacol* 1996; **11:** 55–7.
3. Ciusani E, *et al.* Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. *J Psychopharmacol* 2004; **18:** 559–66.
4. Zhang Z-J, *et al.* The effectiveness of carbamazepine in unipolar depression: a double-blind, randomized, placebo-controlled study. *J Affect Disord* 2008; **109:** 91–7.

Diabetes insipidus. Cranial diabetes insipidus (p. 2348.2) is usually treated by replacement therapy with antidiuretic hormone (ADH) in the form of desmopressin. Carbamazepine is one of a variety of other drugs that have been tried to promote ADH secretion, although some consider that it is usually ineffective and has unwanted effects.[1,2] Oral doses of 200 to 600 mg daily have been given. See also Effects on Electrolytes, under Adverse Effects, p. 514.2.

1. Seckl J, Dunger D. Postoperative diabetes insipidus. *BMJ* 1989; **298:** 2–3.
2. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; **157:** 1293–1301.

Epilepsy. Carbamazepine is one of the drugs of choice for partial seizures with or without secondary generalisation (p. 506.1). It has been used for generalised tonic-clonic seizures (although valproate is the drug of choice where these occur in primary generalised epilepsy), but it may exacerbate absence and myoclonic seizures.

Hemifacial spasm. Carbamazepine has been reported to have been of help in the treatment of hemifacial spasm (p. 2018.3).

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Carbamazepine may be of value for the treatment of neurogenic hiccups such as those that occur in multiple sclerosis.[1] Carbamazepine has also been reported to have been of benefit in 3 patients with diaphragmatic flutter,[2] a rare disorder associated with involuntary contractions of the diaphragm.

1. McFarling DA, Susac JO. Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* 1979; **29:** 797–801.
2. Vantrappen G, *et al.* High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. *Lancet* 1992; **339:** 265–7.

Hyperactivity. When drugs are indicated for attention deficit hyperactivity disorder (p. 2314.1) initial treatment is usually with a central stimulant but meta-analysis of a small number of studies has provided evidence that carbamazepine may be effective.[1]

1. Silva RR, *et al.* Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 352–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p. 1047.1) has been reported to improve in those given antiepileptics such as carbamazepine.[1]

1. Roach ES, *et al.* Carbamazepine trial for Lesch-Nyhan self-mutilation. *J Child Neurol* 1996; **11:** 476–8.

Movement disorders. Carbamazepine is one of many drugs that have been tried in the symptomatic treatment of *chorea* (p. 1029.3); there have been anecdotal reports of benefit in both non-hereditary[1,2] and hereditary choreas.[3] Carbamazepine is also among the drugs that have been tried in the treatment of *dystonias* (p. 903.3) that have not responded to levodopa or antimuscarinics. Although some patients may benefit from carbamazepine, it is not generally recommended because of a relatively low success rate and the possibility of adverse effects.[4] Carbamazepine therapy has also been associated with movement disorders—see Effects on the Nervous System: Extrapyramidal Effects, under Adverse Effects, p. 515.1.

Carbamazepine has also been used in resistant cases of *tardive dyskinesia* (see under Extrapyramidal Disorders, p. 1049.2).

1. Roig M, *et al.* Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. *Pediatrics* 1988; **82:** 492–5.
2. García González MM, *et al.* Corea de Sydenham: presentación de un caso tratado con carbamazepina con excelente respuesta clínica. *An Pediatr (Barc)* 2007; **66:** 80–3.
3. Roulet E, Deonna T. Successful treatment of hereditary dominant chorea with carbamazepine. *Pediatrics* 1989; **83:** 1077.
4. Anonymous. Dystonia: underdiagnosed and undertreated? *Drug Ther Bull* 1988; **26:** 33–6.

Neonatal seizures. Carbamazepine has been tried in the management of neonatal seizures (p. 511.3).

Neuropathic pain. As well as being used to ease the pain of trigeminal neuralgia (see below) carbamazepine may be of use in other neuropathic pain including that associated with diabetic neuropathy (p. 8.2). A systematic review[1] concluded that about two-fifths of patients who take carbamazepine for neuropathic pain will achieve moderate pain relief, but this was based on small studies. The authors found no evidence that carbamazepine was effective for acute pain.

Carbamazepine has also been tried in an attempt to prevent the painful sensory neuropathy associated with oxaliplatin treatment (see Effects on the Nervous System, p. 838.3); results of small studies have been conflicting.[2-4]

1. Wiffen PJ, *et al.* Carbamazepine for acute and chronic pain in adults. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Eckel F, *et al.* Prophylaxe der Oxaliplatin-induzierten Neuropathie mit Carbamazepin: eine Pilotstudie. *Dtsch Med Wochenschr* 2002; **127:** 78–82.
3. Wilson RH, *et al.* Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002; **20:** 1767–74.
4. von Delius S, *et al.* Carbamazepine for prevention of oxaliplatin-related neurotoxicity in patients with advanced colorectal cancer: final results of a randomised, controlled, multicenter phase II study. *Invest New Drugs* 2007; **25:** 173–80.

Nocturnal enuresis. Carbamazepine has been reported to be of benefit in the treatment of primary nocturnal enuresis; a dose of 200 mg at night for 15 nights markedly decreased the frequency of bed-wetting episodes in 8 children.[1]

For the conventional management of nocturnal enuresis see p. 2349.1.

1. Al-Waili NS, *et al.* Effect of carbamazepine on urinary volume and osmolality, water clearance, and serum osmolality in patients with primary enuresis. *Eur Urol* 2006; **50:** 844–9.

Psychiatric disorders. Carbamazepine has psychotropic properties and has been tried in the management of several psychiatric disorders, particularly in patients with *bipolar disorder* (see above). Carbamazepine has also been used with mixed results in various disorders for the control of symptoms such as agitation, aggression, and rage[1-4] (see Disturbed Behaviour, p. 1030.2). It may produce modest benefit when used as an adjunct to antipsychotics in the management of refractory *schizophrenia* (p. 1031.3) but any improvement appears to be related to its mood stabilising effect.[5] However, a more recent systematic review,[6] albeit based on small studies, found carbamazepine to have no significant benefit either as monotherapy or as an adjunct to antipsychotics; the authors considered that further randomised studies may be warranted. Carbamazepine also has the potential to reduce serum concentrations of antipsychotics, resulting in clinical deterioration (see under Interactions of Chlorpromazine, p. 1052.2). Carbamazepine has also been tried[7] in *post-traumatic stress disorder* (p. 1029.2).

1. Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatr Clin Neurosci* 1990; **2:** 159–64.
2. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; **51:** 115–18.
3. Tariot PN, *et al.* Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998; **155:** 54–61.
4. Cueva JE, *et al.* Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 480–90.
5. Okuma T. Use of antiepileptic drugs in schizophrenia: a review of efficacy and tolerability. *CNS Drugs* 1994; **1:** 269–84.
6. Leucht S, *et al.* Carbamazepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/06/08).
7. Wolf ME, *et al.* Posttraumatic stress disorder in Vietnam veterans: clinical and EEG findings; possible therapeutic effects of carbamazepine. *Biol Psychiatry* 1988; **23:** 642–4.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has been largely empirical. In a double-blind study involving 174 patients carbamazepine appeared to be more effective than placebo.[1] Oxcarbazepine has been reported[2] to be of benefit in restless legs syndrome induced by paroxetine.

1. Telstad W, *et al.* Treatment of the restless legs syndrome with carbamazepine: a double blind study. *BMJ* 1984; **288:** 444–6.
2. Öztürk Ö, *et al.* Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. *Gen Hosp Psychiatry* 2006; **28:** 264–5.

Tinnitus. Treatment of tinnitus (p. 1994.1) is difficult, and many drugs have been tried. Although carbamazepine has been reported to be effective in some patients, it is rarely used because of its adverse effects.

Trigeminal neuralgia. Carbamazepine is the drug of choice in the treatment of the acute stages of trigeminal neuralgia (p. 11.2). Satisfactory pain relief may be achieved in 70% or more of patients, although increasingly larger doses may be required and adverse effects can be troublesome.

Although not licensed in the UK for trigeminal neuralgia in children, the *BNFC* suggests that carbamazepine may be tried in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

Withdrawal syndromes. Carbamazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Reduction in *cocaine use* associated with carbamazepine treatment was found in one short-term controlled study,[1] although a systematic review[2] of data from later studies concluded that there was no evidence to support the use of antiepileptics, including carbamazepine, in the treatment of cocaine dependence (p. 1990.1). It has been reported[3,4] to be of benefit in some patients during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p. 1065.1). Carbamazepine has been shown[5,6] to be effective in the treatment of symptoms of the *alcohol withdrawal syndrome* (p. 1735.1) but as there are limited data on its efficacy in preventing associated delirium tremens and seizures it is usually recommended that it should only be used as an adjunct to benzodiazepine therapy. Carbamazepine has also been studied[7] as an aid in the treatment of alcohol dependence.

1. Halikas JA, *et al.* Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. *Clin Pharmacol Ther* 1991; **50:** 81–95.

2. Minozzi S, *et al.* Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 24/07/09).
3. Schweizer E, *et al.* Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 1991; **48:** 448–52.
4. Klein E, *et al.* Alprazolam withdrawal in patients with panic disorder and generalized anxiety disorder: vulnerability and effect of carbamazepine. *Am J Psychiatry* 1994; **151:** 1760–6.
5. Malcolm R, *et al.* Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *Am J Psychiatry* 1989; **146:** 617–21.
6. Stuppaeck CH, *et al.* Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. *Alcohol Alcohol* 1992; **27:** 153–8.
7. Mueller TI, *et al.* A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1997; **21:** 86–92.

Adverse Effects

Fairly common adverse effects of carbamazepine, particularly in the initial stages of therapy, include dizziness, drowsiness, and ataxia. Gastrointestinal disturbances, such as nausea and vomiting, and mild skin reactions are also common. These effects may be minimised by starting therapy with a low dose. Drowsiness and disturbances of cerebellar and oculo-motor function (with ataxia, nystagmus, and diplopia) are also symptoms of excessive plasma concentrations of carbamazepine, and may disappear spontaneously with continued treatment or at reduced or divided dosage.

Although rare, generalised erythematous rashes can be severe and treatment may have to be withdrawn. Photosensitivity reactions, urticaria, alopecia, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome, and SLE (but see p. 515.2) have also been reported.

Transient leucopenia is common and usually resolves with continued therapy; however, rarer blood disorders reported include agranulocytosis, aplastic anaemia, eosinophilia, persistent leucopenia, leucocytosis, thrombocytopenia, and purpura. Lymphadenopathy, splenomegaly, pneumonitis, abnormalities of liver and kidney function, hepatitis, and cholestatic jaundice have occurred. Some or all of these symptoms as well as fever and rashes may represent a generalised hypersensitivity reaction to carbamazepine.

Gastrointestinal symptoms reported to be less common include dry mouth, abdominal pain, anorexia, and diarrhoea or constipation. Hyponatraemia, and sometimes oedema, have occurred. Other adverse effects reported include paraesthesia, headache, arrhythmias and heart block, heart failure, impotence, male infertility, gynaecomastia, galactorrhoea, and dystonias and dyskinesias with asterixis. Rectal use has resulted in local irritation.

Overdosage may be manifested by many of the adverse effects listed above, especially those on the CNS, and may result in stupor, coma, convulsions, respiratory depression, and death.

In rare cases, carbamazepine has been reported to exacerbate seizures in patients suffering from mixed-type epilepsy—see Precautions, p. 515.3.

Congenital malformations have been reported in infants born to women given carbamazepine during pregnancy.

Effects on the blood. Occasional reports of fatal haematological reactions associated with carbamazepine led the manufacturers to recommend extensive blood monitoring during therapy. However, because of the rarity of such reactions these recommendations were questioned and the manufacturers subsequently modified their guidelines (see Precautions, p. 515.3).

Case reports and studies of carbamazepine's haematological effects have been reviewed.[1] The incidence of haematological reactions to carbamazepine has been estimated to range between 1:10 800 and 1:38 000 per year while one group reported the rate of bone marrow suppression to be between 1:10 000 and 1:50 000 cases. The incidence of aplastic anaemia has been calculated to be 1:200 000 per year. Another investigator indicated that 2.2 deaths per million exposures were associated with aplastic anaemia and agranulocytosis. However, of 27 reports of aplastic anaemia (16 fatal) associated with carbamazepine many were found to have had co-incidental disease or were receiving multiple-drug therapy. Benign or clinically insignificant leucopenia has occurred, usually during the first 3 months of treatment, in about 12% of children and 7% of adults but in most patients this resolved despite continuation of therapy. Mild transient thrombocytopenia has occurred in about 2% of patients; transient eosinophilia has also occurred.

The reviewers[1] suggested that all patients should have blood and platelet counts before treatment. Patients with low white cell and neutrophil counts were at risk of developing leucopenia and should be monitored every 2 weeks for the first 1 to 3 months. If counts fell further the dose should be reduced or treatment stopped. It should be noted that the *BNF* doubts the practical value of routine monitoring: in particular, aplastic anaemia, agranulocytosis, and thrombocytopenia have a rapid onset and are best monitored by instructing the patient to report warning symptoms (see Precautions, p. 515.3).

For a discussion of the effects of antiepileptics, including carbamazepine, on serum folate, see Folic Acid Deficiency, under Phenytoin, p. 540.2.

1. Sobotka JL, *et al.* A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP Ann Pharmacother* 1990; **24:** 1214–19.

Effects on bone. For the effects of antiepileptics including carbamazepine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on electrolytes. There have been reports of *hyponatraemia* or *water intoxication* in patients receiving carbamazepine.[1-7] One review[8] states that although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. However, care should be taken to distinguish the confusion, dizziness, nausea and headache of water intoxication from the central and gastrointestinal effects of the drug.[2] The mechanism is uncertain; although some studies suggest an increase in secretion of antidiuretic hormone in subjects given carbamazepine,[3,4,6] others indicate the reverse,[5,9] and the fact that the hyponatraemic effects of carbamazepine can be partly reversed by demeclocycline[5] is cited as evidence for an effect on the kidney, either directly upon the distal tubule or by increasing sensitivity to the effects of antidiuretic hormone. Risk factors for developing carbamazepine-induced hyponatraemia include age of over 40 years, use of sodium-depleting drugs, and low pre-treatment plasma-sodium concentrations; it is unclear whether this adverse effect is dose-related.[7]

1. Henry DA, *et al.* Hyponatraemia during carbamazepine treatment. *BMJ* 1977; **1:** 83–4.
2. Stephens WP, *et al.* Water intoxication due to carbamazepine. *BMJ* 1977; **1:** 754–5.
3. Ashton MG, *et al.* Water intoxication associated with carbamazepine treatment. *BMJ* 1977; **1:** 1134–5.
4. Smith NJ, *et al.* Raised plasma arginine vasopressin concentration in carbamazepine-induced water intoxication. *BMJ* 1977; **2:** 804.
5. Ballardie FW, Mucklow JC. Partial reversal of carbamazepine-induced water intolerance by demeclocycline. *Br J Clin Pharmacol* 1984; **17:** 763–5.
6. Sørensen PS, Hammer M. Effects of long-term carbamazepine treatment on water metabolism and plasma vasopressin concentration. *Eur J Clin Pharmacol* 1984; **26:** 719–22.
7. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother* 2005; **39:** 1943–6.
8. Mucklow J. Selected side-effects 2: carbamazepine and hyponatraemia. *Prescribers' J* 1991; **31:** 61–4.
9. Stephens WP, *et al.* Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. *BMJ* 1978; **1:** 1445–7.

Effects on the endocrine system. Carbamazepine may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p. 2341.3.

For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

Effects on the eyes. On rare occasions lenticular opacities have been associated with carbamazepine.[1] Retinotoxicity associated with long-term carbamazepine use has been reported[2] in 2 patients. After stopping the drug visual function and retinal morphological changes improved. A review[3] of the effect of antiepileptics on the eyes noted that despite reports of colour vision disturbances and impaired contrast sensitivity associated with carbamazepine therapy, studies in healthy subjects had shown conflicting results.

1. Anonymous. Adverse ocular effects of systemic drugs. *Med Lett Drugs Ther* 1976; **18:** 63–4.
2. Nielsen NV, Syversen K. Possible retinotoxic effect of carbamazepine. *Acta Ophthalmol (Copenh)* 1986; **64:** 287–90.
3. Hilton EJR, *et al.* The effect of antiepileptic drugs on visual performance. *Seizure* 2004; **13:** 113–28.

Effects on the heart. A review[1] of reports of cardiac effects associated with carbamazepine revealed that patients could be divided into 2 distinct groups based on their symptoms. One group consisted mainly of young patients with non life-threatening sinus tachycardia after carbamazepine overdosage while the other group was composed of older female patients with potentially life-threatening bradycardia or AV block associated with therapeutic or modestly raised blood concentrations of carbamazepine. However, there has been a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient.[2] Carbamazepine should be avoided in patients who develop conduction abnormalities, or who have conditions such as myotonic dystrophy in which conduction abnormalities are likely.[1]

Elevation of ventricular and atrial stimulation thresholds was reported in a 59-year-old man with a permanent dual-chamber pacemaker, 5 days after starting carbamazepine for mania.[3]

For a report of carbamazepine producing fatal eosinophilic myocarditis, see under Hypersensitivity, p. 515.1.

1. Kasarkis EJ, *et al.* Carbamazepine-induced cardiac dysfunction: characterization of two distinct clinical syndromes. *Arch Intern Med* 1992; **152:** 186–91.
2. Stone S, Lange LS. Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic. *J Neurol Neurosurg Psychiatry* 1986; **49:** 1460–1.
3. Ambrosi P, *et al.* Carbamazepine and pacing threshold. *Lancet* 1993; **342:** 365.

Effects on the immune system. There have been reports of hypogammaglobulinaemia associated with carbamazepine.[1-4] The authors of one report[2] stated that this was a recognised but rare adverse effect of carbamazepine and noted that the UK CSM had 9 reports on file of hypogammaglobulinaemia or gammaglobulin abnormalities related to the use of carbamazepine.

1. Moschione Castro APB, *et al.* Secondary hypogammaglobilinemia after use of carbamazepine: case report and review. *Rev Hosp Clin Fac Med Sao Paulo* 2001; **56:** 189–92.
2. Hayman G, Bansal A. Antibody deficiency associated with carbamazepine. *BMJ* 2002; **325:** 1213.
3. Rice CM, *et al.* Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1011–12.
4. Tamada T, *et al.* Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. *Thorax* 2007; **62:** 100.

Effects on the liver. A report in 1990 commented that of 499 reports of unwanted effects of carbamazepine on the liver about half comprised only abnormal results from liver function tests;[1] however, deaths have occurred from liver failure[1,2] or hepatic necrosis.[3] Reversible vanishing bile duct syndrome has been associated with long-term use of carbamazepine.[4]

Hepatotoxicity may form part of the antiepileptic hypersensitivity syndrome reported with carbamazepine (see p. 515.1).

1. Hadžić N, *et al.* Acute liver failure induced by carbamazepine. *Arch Dis Child* 1990; **65:** 315–17.
2. Zucker P, *et al.* Fatal carbamazepine hepatitis. *J Pediatr* 1977; **91:** 667–8.
3. Smith DW, *et al.* Fatal hepatic necrosis associated with multiple anticonvulsant therapy. *Aust N Z J Med* 1988; **18:** 575–81.
4. Ramos AMO, *et al.* Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002; **14:** 1019–22.

Effects on mental function. Carbamazepine therapy has been associated in a few patients with the development of acute psychotic and paranoid symptoms[1-3] and with phobias[2] and mood disturbances, including mania[4] and melancholia.[5] One case of acute paranoid psychosis was associated with the addition of carbamazepine to long-term sodium valproate therapy in a patient subsequently diagnosed as having a schizotypal personality.[3] For nonconvulsive status epilepticus associated with carbamazepine presenting as psychiatric disorders, see under Effects on the Nervous System, p. 515.1. The problems of antiepileptic therapy adversely affecting cognition and the risk of mood disorders, including suicidal ideation, are discussed on p. 508.3.

1. Berger H. An unusual manifestation of Tegretol(carbamazepine) toxicity. *Ann Intern Med* 1971; **74:** 449–50.
2. Mathew G. Psychiatric symptoms associated with carbamazepine. *BMJ* 1988; **296:** 1071.
3. McKee RJW, *et al.* Acute psychosis with carbamazepine and sodium valproate. *Lancet* 1989; **i:** 167.
4. Reiss AL, O'Donnell DJ. Carbamazepine-induced mania in two children: case report. *J Clin Psychiatry* 1984; **45:** 272–4.
5. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol* 1986; **6:** 236–9.

Effects on the nervous system. *ASEPTIC MENINGITIS.* Aseptic meningitis has developed in a patient with Sjögren's syndrome given carbamazepine. It abated when the drug was withdrawn and symptoms recurred on rechallenge.[1] Aseptic meningitis has also been associated with carbamazepine in patients without Sjögren's syndrome.[2-4]

1. Hilton E, Stroh EM. Aseptic meningitis associated with administration of carbamazepine. *J Infect Dis* 1989; **159:** 363–4.
2. Simon LT, *et al.* Carbamazepine-induced aseptic meningitis. *Ann Intern Med* 1990; **112:** 627–8.
3. Hemet C, *et al.* Aseptic meningitis secondary to carbamazepine treatment of manic-depressive illness. *Am J Psychiatry* 1994; **151:** 1393.
4. Dang CT, Riley DK. Aseptic meningitis secondary to carbamazepine therapy. *Clin Infect Dis* 1996; **22:** 729–30.

ENCEPHALOPATHY. Carbamazepine-induced encephalopathy with symptoms resembling Creutzfeldt-Jakob disease was reported in a 71-year-old man; the cognitive decline, bradykinesia, tremor, and abnormal EEG improved on stopping carbamazepine.[1] In another report,[2] carbamazepine use was associated with the development of hyperammonaemia and associated behavioural changes on 2 occasions.

1. Horvath J, *et al.* Carbamazepine encephalopathy masquerading as Creutzfeldt-Jakob disease. *Neurology* 2005; **65:** 650–1.
2. Adams EN, *et al.* Carbamazepine-induced hyperammonemia. *Am J Health-Syst Pharm* 2009; **66:** 1468–70.

EXTRAPYRAMIDAL EFFECTS. Although carbamazepine has been associated with extrapyramidal adverse effects,[1-4] it has also been tried in the treatment of movement disorders—see under Uses and Administration, p. 513.2.

1. Schwartzman MJ, Leppik IE. Carbamazepine-induced dyskinesia and ophthalmoplegia. *Cleve Clin J Med* 1990; **57:** 367–72.
2. Soman P, *et al.* Dystonia—a rare manifestation of carbamazepine toxicity. *Postgrad Med J* 1994; **70:** 54–5.
3. Lee JW. Persistent dystonia associated with carbamazepine therapy: a case report. *N Z Med J* 1994; **107:** 360–1.
4. Stryjer R, *et al.* Segmental dystonia as the sole manifestation of carbamazepine toxicity. *Gen Hosp Psychiatry* 2002; **24:** 114–15.

STATUS EPILEPTICUS. Nonconvulsive status epilepticus, misdiagnosed as behavioural and psychiatric disorders, was reported[1] to have been precipitated by carbamazepine in 2 patients; seizure control and behaviour improved when carbamazepine was stopped and replaced with valproate.

1. Marini C, *et al.* Nonconvulsive status epilepticus precipitated by carbamazepine presenting as dissociative and affective disorders in adolescents. *J Child Neurol* 2005; **20:** 693–6.

Effects on the skin. Rashes occurring with carbamazepine may form part of an antiepileptic hypersensitivity syndrome (see below). In a report,[1] erythema multiforme occurred when a generic formulation was given instead of a proprietary brand of carbamazepine. Skin lesions resolved when the patient stopped taking the generic formulation and did not recur when the proprietary brand was restarted. In another report, a 6-year-old boy developed Stevens-Johnson syndrome 5 weeks after carbamazepine was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.[2] Carbamazepine was stopped and the patient eventually made a full recovery; valproic acid was continued because it was not thought to be the causative agent (but see under Valproate, p. 556.1). Fatal toxic epidermal necrolysis has been seen when carbamazepine was given to a patient who had previously had Stevens-Johnson syndrome during carbamazepine treatment.[3] Pseudo mycosis fungoides with lymphoid cell infiltration of the dermis and raised liver enzymes has been reported[4] in a 54-year-old man who was taking carbamazepine for seizures; symptoms resolved within about 2 weeks of stopping therapy.

For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, p. 516.1. For the relative incidence of skin reactions to different antiepileptics, see under Phenytoin, p. 541.1.

1. Busch RL. Generic carbamazepine and erythema multiforme: generic-drug nonequivalency. *N Engl J Med* 1989; **321:** 692–3.
2. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. *Ann Pharmacother* 1995; **29:** 538–9.
3. Huang L-Y, *et al.* Fatal toxic epidermal necrolysis induced by carbamazepine treatment in a patient who previously had carbamazepine-induced Stevens-Johnson syndrome. *J Formos Med Assoc* 2007; **106:** 1032–7.
4. Gül Ü, *et al.* Carbamazepine-induced pseudo mycosis fungoides. *Ann Pharmacother* 2003; **37:** 1441–3.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly hepatosplenomegaly and eosinophilia, has been associated with some antiepileptic drugs including carbamazepine.[1-3] Although a literature search[1] was only able to find 20 published cases to 1986, 22 cases had been reported to the Australian Adverse Drug Reactions Advisory Committee between 1975 and 1990. Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[2,3] but the true incidence is uncertain due to variations in presentation and reporting. Most reactions occurred within 30 days of the start of carbamazepine treatment,[1] although symptoms may occur anywhere between 1 and 8 weeks after exposure.[2] In previously sensitised individuals the reactions may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2] Suspected cross-sensitivity between carbamazepine and lamotrigine has also been reported in a patient.[4]

Carbamazepine antibodies were detected in an 8-year-old child who developed symptoms of serum sickness including fever, skin rash, oedema, and lymphadenopathy during treatment with carbamazepine.[5] Hypersensitivity to carbamazepine with multisystem effects clinically resembling a mononucleosis syndrome was reported in a 15-year-old boy 2 weeks after starting monotherapy with carbamazepine;[6] all symptoms resolved on stopping carbamazepine and giving prednisone. There have been other cases[7-9] of an infectious mononucleosis syndrome associated with hypersensitivity to carbamazepine, leading the authors to suggest that reactivation of human herpesvirus 6 or 7 infection is a cofactor and an early manifestation of carbamazepine hypersensitivity syndrome; however, further studies are warranted.

A hypersensitivity reaction producing fatal eosinophilic myocarditis has been reported in a 13-year-old patient; initial symptoms mimicked scarlet fever.[10] A 21-year-old woman developed fatal fulminant hepatic failure after taking carbamazepine for about 2 months; she had presented with initial symptoms of fever, breathlessness, bloody diarrhoea, and a spreading rash.[11]

Generalised erythroderma with renal, hepatic, and bone-marrow failure (characterised by hypercellularity and dyserythropoiesis) has been reported[12] in an 81-year-old man 50 days after starting carbamazepine therapy. Symptoms recurred following an inadvertent rechallenge. The presence of underlying lymphoproliferative disease may have potentiated the severe drug-induced reaction.

If the antiepileptic hypersensitivity syndrome develops, immediate withdrawal of carbamazepine is recommended. In most cases this is all that is required and does not seem to precipitate an increase in seizures, compared with gradual withdrawal.[13]

Successful desensitisation to carbamazepine was reported[14] in a 12-year-old boy who was sensitive to carbamazepine, sodium valproate, and phenytoin. Starting with a low dose of carbamazepine 100 micrograms daily the dose was doubled, generally every 2 days, up to 100 mg daily. The dose was then gradually increased over 4 weeks to a maintenance dose of 200 mg twice daily. The same technique was used to desensitise 7 patients, all of whom developed dramatic skin rashes when first exposed to carbamazepine.[15] Carbamazepine therapy in full doses was achieved without problem in about 6 weeks. Some[2] consider that desensitisation is not to be recommended in patients with full-blown antiepileptic hypersensitivity syndrome.

1. Anonymous. Anticonvulsants and lymphadenopathy. *WHO Drug Inf* 1991; **5**: 11.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.
4. Aouam K, *et al.* Hypersensitivity syndrome induced by anticonvulsants: possible cross-reactivity between carbamazepine and lamotrigine. *J Clin Pharmacol* 2009; **49:** 1488–91.
5. Hosoda N, *et al.* Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness. *Arch Dis Child* 1991; **66:** 722–3.
6. Merino N, *et al.* Multisystem hypersensitivity reaction to carbamazepine. *Ann Pharmacother* 1994; **28:** 402–3.
7. Zeller A, *et al.* Drug hypersensitivity syndrome to carbamazepine and human herpes virus 6 infection: case report and literature review. *Infection* 2003; **31:** 254–6.
8. Aihara Y, *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; **149:** 165–9.
9. Oskay T, *et al.* Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6, 7. *Epilepsy Res* 2006; **70:** 27–40.
10. Salzman MB, *et al.* Carbamazepine and fatal eosinophilic myocarditis. *N Engl J Med* 1997; **336:** 878–9.
11. Syn W-K, *et al.* Carbamazepine-induced acute liver failure as part of the DRESS syndrome. *Int J Clin Pract* 2005; **59:** 988–91. Correction. *ibid.*; 1371.
12. Lombardi SM, *et al.* Severe multisystemic hypersensitivity reaction to carbamazepine including dyserythropoietic anemia. *Ann Pharmacother* 1999; **33:** 571–5.
13. Pirmohamed M, *et al.* Hypersensitivity to carbamazepine and lamotrigine: clinical considerations. *Br J Clin Pharmacol* 2000; **49:** 519P–520P.
14. Smith H, Newton R. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1985; **i:** 753.
15. Eames P. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1989; **i:** 509–10.

Sudden unexplained death in epilepsy. Sudden unexplained death in epilepsy (SUDEP), a common cause of seizure-related mortality in patients with chronic epilepsy, has been reviewed.[1,2] Risk factors may include early onset of epilepsy, frequent generalised tonic-clonic seizures, intractability, frequent medication changes, and polytherapy. *Carbamazepine* use has also been implicated but the evidence was considered to be tenuous although frequent dose change resulting in plasma-carbamazepine levels outside the therapeutic range was found to be an independent risk factor. Although the FDA in the USA had required data about the specific risk of SUDEP to be included in the prescribing information for the newer antiepileptic drugs *gabapentin, lamotrigine, tiagabine, topiramate,* and *zonisamide,* some commentators[3] consider that none of these antiepileptics have shown an associated change in the risk of SUDEP. It has been suggested[2,3] that the incidence of SUDEP is related to the disease rather than a specific drug effect.

1. Walczak T. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? *Drug Safety* 2003; **26:** 673–83.
2. Nashef L, *et al.* Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. *Epilepsia* 2007; **48:** 859–71.
3. Lathers CM, Schraeder PL. Clinical pharmacology: drugs as a benefit and/or risk in sudden unexpected death in epilepsy? *J Clin Pharmacol* 2002; **42:** 123–36.

Systemic lupus erythematosus. A review[1] of 80 cases of SLE-like syndromes associated with carbamazepine that had been reported to the manufacturer suggested that the frequency of reports (less than 0.001%) was below that for idiopathic lupus. There have been subsequent reports[2-4] of late-onset SLE occurring after up to 8 years of carbamazepine therapy without previous adverse effects. The symptoms due to carbamazepine usually resolved on stopping treatment.

1. Jain KK. Systemic lupus erythematosus (SLE)-like syndromes associated with carbamazepine therapy. *Drug Safety* 1991; **6:** 350–60.
2. Toepfer M, *et al.* Drug-induced systemic lupus erythematosus after 8 years of treatment with carbamazepine. *Eur J Clin Pharmacol* 1998; **54:** 193–4.
3. Pelizza L, *et al.* Drug-induced systemic lupus erythematosus after 7 years of treatment with carbamazepine. *Acta Biomed* 2006; **77:** 17–19.
4. Amerio P, *et al.* Drug-induced cutaneous lupus erythematosus after 5 years of treatment with carbamazepine. *Eur J Dermatol* 2006; **16:** 281–3.

Treatment of Adverse Effects

In the treatment of carbamazepine overdosage repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if undertaken within 1 hour of ingestion. Supportive and symptomatic therapy alone may then suffice, with particular attention to correcting hypoxia and hypotension; haemoperfusion has been suggested for severe poisoning. If there is doubt about the diagnosis, or if multiple-dose oral activated charcoal is being considered, then monitoring plasma-carbamazepine concentration can be useful; it may also help determine when carbamazepine therapy should be restarted. See also Overdosage, below.

Hypersensitivity reactions. For reference to successful desensitisation in patients sensitive to carbamazepine, see Hypersensitivity under Adverse Effects, above.

Overdosage. Carbamazepine poisoning and its management has been reviewed.[1] Management is mainly supportive, with prompt attention to airway management and seizure control. Activated charcoal should be given; although multiple-dose activated charcoal has been recommended for carbamazepine overdosage, care must be taken to protect the airway since carbamazepine inhibits intestinal motility and there is a significant risk of aspiration. In patients with seizures unresponsive to benzodiazepines phenobarbital should be used; phenytoin is not a drug of choice in this situation. Hypotension is rare, and should be managed with fluid and vasopressor support; hypotension with refractory seizures should be treated aggressively as it has led to permanent neurological disability and death.

Haemodialysis or haemoperfusion may be warranted in patients with unstable cardiac status or status epilepticus complicated by bowel hypomotility and unresponsive to more conventional therapy. However, a report[2] of the use of plasmapheresis in the treatment of an acute overdose of carbamazepine concluded that plasmapheresis removed a very small percentage of the total body load of carbamazepine and could not be recommended. As carbamazepine is highly protein-bound, albumin-enhanced continuous venovenous haemodialysis was tried and found to be effective in the treatment of a 10-year-old child after ingestion of 1.4 g of carbamazepine.[3]

1. Spiller HA. Management of carbamazepine overdose. *Pediatr Emerg Care* 2001; **17:** 452–6.
2. Kale PB, *et al.* Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother* 1993; **27:** 866–70.
3. Askenazi DJ, *et al.* Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. *Pediatrics* 2004; **113:** 406–9.

Precautions

Carbamazepine should be avoided in patients with AV conduction abnormalities. It should not be given to patients with a history of bone marrow depression. Carbamazepine should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or of cardiac, hepatic, or renal disease. Patients or their carers should be told how to recognise signs of blood, liver, and skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn, if necessary under cover of a suitable alternative antiepileptic, if severe, progressive, or symptomatic leucopenia develops, or if symptoms suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis occur. Licensed product information recommends blood counts and hepatic and renal-function tests before starting carbamazepine therapy and periodically during treatment, but the *BNF* considers the evidence of practical value unsatisfactory. Clinical monitoring is of primary importance throughout treatment. Some patients of Asian ancestry may be at increased risk of severe skin reactions; for recommendations that such patients' genotype should be tested before beginning carbamazepine, see Skin Reactions, p. 516.1.

Care is required in identifying patients with mixed seizure disorders that include generalised absence or atypical absence seizures, who may be at risk of an increase

in generalised seizures if given carbamazepine. Carbamazepine may also exacerbate absence and myoclonic seizures.

Care is required when withdrawing carbamazepine therapy—see also Uses and Administration, p. 512.3.

Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra-ocular pressure; scattered punctate lens opacities occur rarely with carbamazepine and it has been suggested that patients should be examined periodically for eye changes.

Abuse. Overdosage requiring hospital admission has been reported after abuse of carbamazepine.[1]

1. Crawford PJ, Fisher BM. Recreational overdosage of carbamazepine in Paisley drug abusers. *Scott Med J* 1997; **42:** 44–5.

Breast feeding. The American Academy of Pediatrics considers[1] that carbamazepine is usually compatible with breast feeding, although there have been reports[2] of transient cholestatic hepatitis in breast-fed infants.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Frey B, *et al*. Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 2002; **36:** 644–7.

Driving. For comment on antiepileptic drugs and driving, see p. 509.2.

Multiple sclerosis. Exacerbation of symptoms of multiple sclerosis has been reported[1] in 5 patients on starting carbamazepine therapy for paroxysmal neurological symptoms and pain. There was a close temporal association between starting carbamazepine and worsening of symptoms, followed by resolution when it was stopped. A 3-year follow-up observational study[2] found that out of 36 multiple sclerosis patients who received carbamazepine therapy, 12 developed neurological adverse effects that mimicked a relapse. The authors concluded that carbamazepine was associated with higher rates of adverse effects and stopping therapy than gabapentin or lamotrigine.

1. Ramsaransing G, *et al*. Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000; **320:** 1113.
2. Solaro C, *et al*. Antiepileptic medications in multiple sclerosis: adverse effects in a three-year follow-up study. *Neurol Sci* 2005; **25:** 307–10.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carbamazepine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including carbamazepine; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have also been described. Exposure to carbamazepine has been calculated to carry a 1% risk of spina bifida.[1] A 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation has been described;[2] such syndromes are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding.

1. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; **324:** 674–7.
2. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; **75:** 517–20.

Skin reactions. The FDA has issued a warning[1] that severe and potentially fatal skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are significantly more common in patients with the HLA allele HLA-B*1502, which occurs almost exclusively in persons of Asian ancestry. They recommend that patients with such ancestry should be screened for the presence of this allele before beginning therapy with carbamazepine, and if present the risks and benefits of therapy should be considered with particular care; those who have already taken carbamazepine for more than a few months without developing skin reactions are, however, at low risk of them ever developing, regardless of genotype. Similar recommendations have since been issued in the UK by the MHRA.[2] See also under Phenytoin, p. 542.1.

1. FDA. Information for healthcare professionals: dangerous or even fatal skin reactions–carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics) (issued 12th December, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm (accessed 25/08/10)
2. MHRA/CHM. Carbamazepine: genetic testing recommended in some Asian populations. *Drug Safety Update* 2008:**1** (9): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0145066&RevisionSelectionMethod=Latest (accessed 09/06/08)

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

The metabolism of carbamazepine is reported to be less susceptible to inhibition by other drugs than that of phenytoin but a few drugs are reported to inhibit its metabolism by the cytochrome P450 isoenzyme CYP3A4, resulting in raised plasma concentrations and associated toxicity. Conversely, drugs that induce CYP3A4 may increase the metabolism of carbamazepine, leading to reduced plasma concentrations and potentially a decrease in therapeutic effect. Licensed product information advises that, in such situations, the dose of carbamazepine should be adjusted accordingly and/or the plasma concentrations monitored.

Carbamazepine is itself a hepatic enzyme inducer, and induces its own metabolism as well as that of several other drugs including some antibacterials (notably, doxycycline), anticoagulants, and sex hormones (notably oral contraceptives). Carbamazepine and phenytoin may mutually enhance one another's metabolism. The metabolism of carbamazepine is similarly enhanced by enzyme inducers such as phenobarbital.

General references.

1. Spina E, *et al*. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996; **31:** 198–214.

Alcohol. Alcohol may exacerbate the CNS adverse effects of carbamazepine and vice versa.

Analgesics. *Dextropropoxyphene* has been reported to cause substantial elevation of serum-carbamazepine concentrations[1] and carbamazepine toxicity,[1,2] probably due to inhibition of carbamazepine metabolism.[1]

Use of enzyme-inducing antiepileptics such as carbamazepine affects the threshold for use of antidote in the treatment of *paracetamol* poisoning, see p. 118.3.

For the effect of carbamazepine on *methadone*, see p. 90.3, and on *tramadol*, see p. 140.3.

1. Dam M, Christiansen J. Interaction of propoxyphene with carbamazepine. *Lancet* 1977; **ii:** 509.
2. Yu YL, *et al*. Interaction between carbamazepine and dextropropoxyphene. *Postgrad Med J* 1986; **62:** 231–3.

Anthelmintics. For the effect of carbamazepine on *mebendazole* and *praziquantel*, see p. 160.1 and p. 165.2, respectively.

Antibacterials. The antimycobacterial *isoniazid*[1,2] and macrolides[3] such as *clarithromycin*, *erythromycin*, and *troleandomycin* have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity. Clarithromycin has also been reported to have caused hyponatraemia when added to carbamazepine therapy in a 30-year-old epileptic woman.[4] *Rifampicin* and isoniazid decreased the serum concentrations of carbamazepine in a 44-year-old woman being treated for bipolar disorder and suspected tuberculosis, resulting in hypomania.[5]

Use of carbamazepine with isoniazid may increase the risk of isoniazid-induced hepatotoxicity.

1. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. *BMJ* 1982; **285:** 261–2.
2. Wright JM, *et al*. Isoniazid-induced carbamazepine toxicity and vice versa. *N Engl J Med* 1982; **307:** 1325–7.
3. Pauwels O. Factors contributing to carbamazepine-macrolide interactions. *Pharmacol Res* 2002; **45:** 291–8.
4. Kanbay M, *et al*. Hyponatremia due to an additive effect of carbamazepine and clarithromycin. *South Med J* 2007; **100:** 222.
5. Zolezzi M. Antituberculosis agents and carbamazepine. *Am J Psychiatry* 2002; **159:** 874.

Anticoagulants. For the effect of carbamazepine on *warfarin*, see p. 1532.1.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antidepressants such as *desipramine*,[1] *fluoxetine*,[2] *fluvoxamine*,[3] *nefazodone*[4] (and perhaps *trazodone*[5]), and *viloxazine*[6] increase plasma concentrations of carbamazepine and may induce carbamazepine toxicity. A toxic serotonin syndrome (see p. 443.2) has been reported in a patient who received fluoxetine with carbamazepine.[7] Severe neurotoxicity reported during therapy with *lithium* and carbamazepine[8,9] may be due to a synergistic effect as reports indicate that either drug was tolerated when not given with the other and measured plasma concentrations did not indicate overdosage.[9] However, toxic serum concentrations of lithium have also been reported, due to carbamazepine-induced acute renal failure (see p. 431.3).

Because of the structural similarity to tricyclic antidepressants licensed product information suggests that carbamazepine should not be given to patients taking an *MAOI* or within 14 days of stopping such treatment.

St John's wort has been shown to induce several drug metabolising enzymes (see p. 449.3) and consequently it has been suggested that it might reduce the blood concentrations of carbamazepine leading to an increased risk of seizure.[10] However, a multiple-dose study[11] in healthy subjects reported that St John's wort had no significant effect on the pharmacokinetics of carbamazepine or its active epoxide metabolite.

For the effect of carbamazepine on antidepressants, see Bupropion (p. 410.2), Fluoxetine (p. 424.2), Mianserin (p. 435.2), Nefazodone (p. 439.2), and Amitriptyline (p. 406.2).

1. Lesser I. Carbamazepine and desipramine: a toxic reaction. *J Clin Psychiatry* 1984; **45:** 360.
2. Pearson HJ. Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 1990; **51:** 126.
3. Fritze J, *et al*. Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 1991; **84:** 583–4.
4. Ashton AK, Wolin RE. Nefazodone-induced carbamazepine toxicity. *Am J Psychiatry* 1996; **153:** 733.
5. Sánchez Romero A, *et al*. Interaction between trazodone and carbamazepine. *Ann Pharmacother* 1999; **33:** 1370.
6. Scarpello JHB, Cottrell N. Overuse of monitoring of blood concentrations of antiepileptic drugs. *BMJ* 1987; **294:** 1355.
7. Dursun SM, *et al*. Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342:** 442–3.
8. Andrus PF. Lithium and carbamazepine. *J Clin Psychiatry* 1984; **45:** 525.
9. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. *J Clin Psychiatry* 1983; **44:** 30–1.
10. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
11. Burstein AH, *et al*. Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2000; **68:** 605–12.

Antiepileptics. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics.

Serum concentrations of carbamazepine are reported to be reduced by *phenobarbital*, but without loss of seizure control;[1,2] this reduction is probably due to induction of carbamazepine metabolism.

The interaction with *phenytoin* is somewhat more complex and the consequences vary. There is evidence of a lowering of serum-carbamazepine concentrations, presumably due to induction of metabolism by phenytoin;[1-3] in return carbamazepine has been reported both to lower and increase serum phenytoin—see p. 543.2. Again, these reports do not indicate a loss of seizure control or toxicity resulting from the interaction, although the possibility presumably exists. Gradually withdrawing phenytoin from 2 patients who had been receiving carbamazepine and phenytoin resulted in a dramatic increase in plasma-carbamazepine concentrations;[4] one patient exhibited neurotoxic symptoms. The authors recommended that plasma-carbamazepine monitoring should be carried out whenever phenytoin is withdrawn in patients taking these two drugs together.

Valproic acid produces an increase in serum concentrations of the active epoxide metabolite of carbamazepine. This is usually attributed to inhibition of its hydrolysis by epoxide hydrolase, although an additional proposed mechanism[5] is inhibition of the glucuronidation of carbamazepine-10,11-trans-diol, the compound to which the epoxide is converted under normal circumstances. Adverse effects may be a problem if unusually high epoxide concentrations arise but, in general, this interaction is of limited clinical significance. However, *valpromide*, the amide derivative, is a much more powerful inhibitor of epoxide hydrolase than valproic acid,[6-8] and therefore produces greater increases in epoxide plasma concentrations with clinical signs of toxicity.[7] Switching from sodium valproate to valpromide has resulted in toxicity in patients also receiving carbamazepine.[7] Neither valproic acid nor valpromide have any significant effect on plasma concentrations of the parent drug, carbamazepine. *Valnoctamide*, an isomer of valpromide, appears to be at least as potent as valpromide in inhibiting the elimination of the epoxide metabolite of carbamazepine.[9] Valnoctamide has been used as an anxiolytic, although it does appear to possess some antiepileptic activity. For a report of acute psychosis associated with the combination of carbamazepine and sodium valproate, see Effects on Mental Function under Adverse Effects, p. 514.3. For the effects of carbamazepine on valproate, see p. 557.3.

Of the other antiepileptics *stiripentol*[10,11] has been reported to inhibit carbamazepine metabolism, while *felbamate* causes a significant fall in plasma-carbamazepine concentrations which may require an increase in the dose of carbamazepine.[12] However, another study[13] has shown a

significant increase in plasma-concentrations of the active epoxide metabolite, which may counteract the effect of the decrease in plasma concentrations of the parent compound. Neurotoxicity has been seen after use of carbamazepine with *lamotrigine*.[14] The suggestion that this was due to raised concentrations of carbamazepine epoxide was not confirmed in a controlled study in which the 2 drugs were used together safely and effectively.[15] Toxic epidermal necrolysis occurred[16] when lamotrigine was added to carbamazepine therapy in a patient who had been taking carbamazepine for 3 years; symptoms resolved progressively when both drugs were stopped. Symptoms of carbamazepine toxicity have been reported[17] when *levetiracetam* was added to carbamazepine therapy; this interaction appeared to be due to a pharmacodynamic mechanism as blood levels of carbamazepine and its epoxide metabolite were not altered. There have also been reports[18] of carbamazepine toxicity when *topiramate* was added to carbamazepine therapy; symptoms resolved when the dose of carbamazepine was reduced. Fulminant liver failure has been reported[19] after an increase in adjunctive topiramate dose in a patient maintained on carbamazepine for 2 years without any signs of hepatotoxicity. The GABA agonist *progabide* has increased plasma concentrations of the epoxide metabolite, probably due to inhibition of microsomal epoxide hydrolase.[20] *Vigabatrin* is reported[21] to increase the clearance of carbamazepine by about 35%.

For the effects of carbamazepine on *ethosuximide*, see p. 521.3, on *lamotrigine*, see p. 530.1, on *oxcarbazepine*, see p. 534.2, on *primidone*, see p. 547.3, on *tiagabine*, see p. 550.3, and on *topiramate*, see p. 552.3. For interactions with benzodiazepines, see below.

1. Cereghino JJ, *et al*. The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; **18:** 733–41.
2. Rane A, *et al*. Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* 1976; **19:** 276–83.
3. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* 1973; **49:** 543–6.
4. Chapron DJ, *et al*. Unmasking the significant enzyme-inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. *Ann Pharmacother* 1993; **27:** 708–11.
5. Bernus I, *et al*. The mechanism of the carbamazepine-valproate interaction in humans. *Br J Clin Pharmacol* 1997; **44:** 21–7.
6. Levy RH, *et al*. Inhibition of carbamazepine epoxide elimination by valpromide and valproic acid. *Epilepsia* 1986; **27:** 592.
7. Meijer JWA, *et al*. Possible hazard of valpromide-carbamazepine combination therapy in epilepsy. *Lancet* 1984; **i:** 802.
8. Pisani F, *et al*. Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br J Clin Pharmacol* 1988; **25:** 611–13.
9. Pisani F, *et al*. Impairment of carbamazepine-10,11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects. *Br J Clin Pharmacol* 1992; **34:** 85–7.
10. Levy RH, *et al*. Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* 1985; **26:** 544–5.
11. Cazali N, *et al*. Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *Br J Clin Pharmacol* 2003; **56:** 526–36.
12. Albani F, *et al*. Effect of felbamate on plasma levels of carbamazepine and its metabolites. *Epilepsia* 1991; **32:** 130–2.
13. Wagner ML, *et al*. Effect of felbamate on carbamazepine and its major metabolites. *Clin Pharmacol Ther* 1993; **53:** 536–43.
14. Warner T, *et al*. Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. *Epilepsy Res* 1992; **11:** 147–50.
15. Stolarek I, *et al*. Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 921–4.
16. Mansouri P, *et al*. Toxic epidermal necrolysis associated with concomitant use of lamotrigine and carbamazepine: a case report. *Arch Dermatol* 2005; **141:** 788–9.
17. Sisodiya SM, *et al*. Carbamazepine toxicity during combination therapy with levetiracetam: a pharmacodynamic interaction. *Epilepsy Res* 2002; **48:** 217–19.
18. Mack CJ, *et al*. Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience. *Seizure* 2002; **11:** 464–7.
19. Bjøro K, *et al*. Topiramate and fulminant liver failure. *Lancet* 1998; **352:** 1119.
20. Kroetz DL, *et al*. In vivo and in vitro correlation of microsomal epoxide hydrolase inhibition by progabide. *Clin Pharmacol Ther* 1993; **54:** 485–97.
21. Sánchez-Alcaraz A, *et al*. Effect of vigabatrin on the pharmacokinetics of carbamazepine. *J Clin Pharm Ther* 2002; **27:** 427–30.

Antifungals. Malaise, myoclonus, and trembling were reported[1] to have developed in a patient receiving carbamazepine after the addition of *miconazole* to therapy. *Ketoconazole* was associated with a significant increase in plasma-carbamazepine concentrations in 8 epileptic patients stabilised on carbamazepine;[2] plasma concentrations of the epoxide metabolite were unchanged. A threefold increase in serum-carbamazepine concentrations, reported[3] in a patient after addition of *fluconazole* to carbamazepine therapy, did not result in toxicity; however, the latter has been reported[4,5] in 2 patients stabilised on carbamazepine who were given fluconazole. *Terbinafine* has also been reported[6] to cause possible carbamazepine toxicity.

For the effect of carbamazepine on *itraconazole*, see p. 585.1.

1. Loupi E, *et al*. Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
2. Spina E, *et al*. Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. *Ther Drug Monit* 1997; **19:** 535–8.
3. Finch CK, *et al*. Fluconazole-carbamazepine interaction. *South Med J* 2002; **95:** 1099–1100.
4. Nair DR, Morris HH. Potential fluconazole-induced carbamazepine toxicity. *Ann Pharmacother* 1999; **33:** 790–2.
5. Ulivelli M, *et al*. Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* 2004; **251:** 622–3.
6. Baath NS, *et al*. Possible carbamazepine toxicity with terbinafine. *Can J Clin Pharmacol* 2006; **13:** e228–e231.

Antihistamines. *Terfenadine* and carbamazepine are both highly protein bound and therefore may compete for protein binding sites. An 18-year-old woman receiving carbamazepine as an antiepileptic had symptoms of neurotoxicity shortly after starting treatment with terfenadine for rhinitis.[1] The concentration of free carbamazepine in the plasma was higher than normal and returned to normal on stopping terfenadine.

1. Hirschfeld S, Jarosinski P. Drug interaction of terfenadine and carbamazepine. *Ann Intern Med* 1993; **118:** 907–8.

Antimalarials. *Chloroquine* and *mefloquine* may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antiprotozoals. A patient receiving carbamazepine for bipolar disorder developed dizziness, diplopia, and nausea 4 days after the addition of *metronidazole* for diverticulitis.[1]

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* 1994; **28:** 1303–4.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Increased plasma concentrations of carbamazepine epoxide have been reported to occur during therapy with carbamazepine and *loxapine*[1] or *quetiapine*,[2] possibly due to induction of carbamazepine metabolism or inhibition of metabolism of the epoxide. Raised serum concentrations of carbamazepine have also been reported in patients receiving *haloperidol*.[3]

For the effect of carbamazepine on antipsychotics, see under Chlorpromazine, p. 1052.2.

1. Collins DM, *et al*. Potential interaction between carbamazepine and loxapine: case report and retrospective review. *Ann Pharmacother* 1993; **27:** 1180–3.
2. Fitzgerald BJ, Okos AJ. Elevation of carbamazepine-10,11-epoxide by quetiapine. *Pharmacotherapy* 2002; **22:** 1500–3.
3. Iwahashi K, *et al*. The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* 1995; **18:** 233–6.

Antivirals. The HIV-protease inhibitor *ritonavir* inhibits several microsomal liver enzymes and therefore may potentially increase plasma concentrations of carbamazepine. Licensed product information for ritonavir advises that such combinations may require monitoring. Carbamazepine toxicity has been reported[1,2] after interaction with ritonavir. In one report,[2] the patient was also taking *nelfinavir* and *lopinavir*, both of which are substrates and inhibitors of cytochrome P450 isoenzymes.

For the effect of carbamazepine on HIV-protease inhibitors, see p. 987.3.

Concurrent use of carbamazepine and the NNRTI *efavirenz* reduces the levels of both drugs; for further information see under Efavirenz, p. 976.1.

1. Mateu-de Antonio J, Grau S. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* 2001; **35:** 125–6.
2. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. *Ann Pharmacother* 2006; **40:** 1190–5.

Anxiolytics. For a discussion of the potential interaction between carbamazepine and the anxiolytic *valnoctamide*, an isomer of the antiepileptic valpromide, see Antiepileptics, p. 516.3.

See also Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced by induction of hepatic drug-metabolising enzymes in patients who have received long-term therapy with carbamazepine; benzodiazepine plasma concentrations are reduced, half-life is shorter, and clearance is increased[1,2] (see also Antiepileptics, under Interactions of Diazepam, p. 1069.1).

Some benzodiazepines may also affect carbamazepine. One group of workers reported that after addition of *clobazam* to carbamazepine therapy a dose reduction for the latter was required due to increased blood concentrations.[3] In a later study[4] it appeared that clobazam could produce a moderate increase in the metabolism of carbamazepine. The plasma ratio of metabolites of carbamazepine, including carbamazepine-10,11-epoxide, to parent compound was increased in patients taking clobazam and carbamazepine.

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Lai AA, *et al*. Time-course of interaction between carbamazepine and clonazepam in normal man. *Clin Pharmacol Ther* 1978; **24:** 316–23.
3. Franceschi M, *et al*. Clobazam in drug-resistant and alcoholic withdrawal seizures. *Clin Trials J* 1983; **20:** 119–25.
4. Muñoz JJ, *et al*. The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; **29:** 763–5.

Calcium-channel blockers. Six patients with steady-state carbamazepine concentrations had symptoms of neurotoxicity consistent with carbamazepine intoxication within 36 to 96 hours of the first dose of *verapamil*.[1] In 5 patients, in whom plasma concentrations were measured, there was a mean increase of 46% in total carbamazepine and 33% in free carbamazepine; no effect on the plasma protein binding of carbamazepine was seen. The results suggested that verapamil inhibits the metabolism of carbamazepine to an extent likely to have important clinical repercussions. There has also been a report[2] of a patient in whom *diltiazem*, but not *nifedipine*, precipitated carbamazepine neurotoxicity.

For the effect of carbamazepine on dihydropyridine calcium-channel blockers, see under Nifedipine, p. 1453.3.

1. Macphee GJA, *et al*. Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; **i:** 700–703.
2. Brodie MJ, Macphee GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *BMJ* 1986; **292:** 1170–1.

Ciclosporin. For the effect of carbamazepine on ciclosporin, see p. 1956.3.

Corticosteroids. For the effect of carbamazepine on corticosteroids, see p. 1619.3.

Danazol. Use of danazol with carbamazepine has been reported to increase the half-life and decrease clearance of carbamazepine,[1] resulting in increases in plasma-carbamazepine concentrations of up to 100%[1,2] and resultant toxicity in several patients.[2]

1. Krämer G, *et al*. Carbamazepine-danazol drug interaction: its mechanism examined by a stable isotope technique. *Ther Drug Monit* 1986; **8:** 387–92.
2. Zielinski JJ, *et al*. Clinically significant danazol-carbamazepine interaction. *Ther Drug Monit* 1987; **9:** 24–7.

Dermatological drugs. Addition of *isotretinoin* to regular carbamazepine therapy appeared to reduce plasma concentrations of the latter and its active epoxide metabolite.[1] However, no adverse events were noted during a 6-week period of treatment with isotretinoin. Nonetheless, licensed product information for carbamazepine recommends that the levels of carbamazepine are monitored if both are used together.

1. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* 1988; **119:** 403–4.

Diuretics. There has been a report of symptomatic hyponatraemia associated with use of carbamazepine and a diuretic (*hydrochlorothiazide* or *furosemide*—see under Interactions of Furosemide, p. 1390.1). Carbamazepine serum concentrations are increased by *acetazolamide*.[1]

1. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* 1984; **16:** 393.

Gastrointestinal drugs. *Cimetidine* is reported to produce a transient increase in plasma-carbamazepine concentrations, with a return to pre-cimetidine values within about a week;[1] some increase in adverse effects was seen. *Ranitidine* does not appear to affect plasma-carbamazepine concentrations.[2] Neurotoxicity has been seen in a patient receiving carbamazepine and *metoclopramide*.[3]

1. Dalton MJ, *et al*. Cimetidine and carbamazepine: a complex drug interaction. *Epilepsia* 1986; **27:** 553–8.
2. Dalton MJ, *et al*. Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. *Drug Intell Clin Pharm* 1985; **19:** 941–4.
3. Sandyk R. Carbamazepine and metoclopramide interaction: possible neurotoxicity. *BMJ* 1984; **288:** 830.

Grapefruit juice. The bioavailability and plasma concentrations of carbamazepine have been reported[1] to be increased by grapefruit juice.

1. Garg SK, *et al*. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998; **64:** 286–8.

Levothyroxine. For the effect of carbamazepine on levothyroxine, see p. 2341.3.

Neuromuscular blockers. For the effect of carbamazepine on *suxamethonium*, see p. 2039.3 and on *competitive neuromuscular blockers*, see under Atracurium, p. 2032.1.

Sex hormones. For the effect of carbamazepine on *oral contraceptives*, see p. 2243.2 and for the possible effect on *tibolone*, see p. 2310.2.

See also Danazol, above

Theophylline. A decrease in serum-carbamazepine concentrations of about 50% was reported[1] in an epileptic patient given theophylline. The patient had seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine.

For the effect of carbamazepine on theophylline, see p. 1235.1.

1. Mitchell EA, *et al*. Interaction between carbamazepine and theophylline. *N Z Med J* 1986; **99:** 69–70.

Vitamins. The plasma concentration of carbamazepine was increased in 2 patients given *nicotinamide*.[1]

For the effect of antiepileptics, including carbamazepine, on *vitamin D* concentrations, see Effects on Bone under the Adverse Effects of Phenytoin, p. 540.2.

1. Bourgeois BFD, *et al.* Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* 1982; **32:** 1122–6.

Pharmacokinetics

Carbamazepine is slowly and irregularly absorbed from the gastrointestinal tract and has a bioavailability of 85 to 100%. It is extensively metabolised in the liver, notably by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8. One of its primary metabolites, carbamazepine-10,11-epoxide, is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some are also excreted in faeces. Elimination of carbamazepine is reported to be more rapid in children and accumulation of the active metabolite may often be higher than in adults.

Carbamazepine is widely distributed throughout the body and is about 70 to 80% bound to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated dosage. The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be considerably shorter in children than in adults. Moreover, the metabolism of carbamazepine is readily induced by drugs that induce hepatic microsomal enzymes (see Interactions, p. 516.2).

Monitoring of plasma concentrations may be performed when clinically indicated and the therapeutic range of total plasma-carbamazepine is usually quoted as being about 4 to 12 micrograms/mL (17 to 50 micromoles/litre), although this is subject to considerable variation. It has been suggested by some, but not all investigators, that measurement of free carbamazepine concentrations in plasma may prove more reliable, and concentrations in saliva or tears, which contain only free carbamazepine, have also been measured.

Carbamazepine crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of carbamazepine are affected by use with other antiepileptics (see under Interactions, p. 516.3).

References.

1. Schmidt D, Haenel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 1984; **34:** 1252–5.
2. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide: an update. *Clin Pharmacokinet* 1986; **11:** 177–98.
3. Gilman JT. Carbamazepine dosing for pediatric seizure disorders: the highs and lows. *DICP Ann Pharmacother* 1991; **25:** 1109–12.
4. Kodama Y, *et al.* In vivo binding characteristics of carbamazepine and carbamazepine-10,11-epoxide to serum proteins in paediatric patients with epilepsy. *Eur J Clin Pharmacol* 1993; **44:** 291–3.
5. Bernus I, *et al.* Early stage autoinduction of carbamazepine metabolism in humans. *Eur J Clin Pharmacol* 1994; **47:** 355–60.
6. Caraco Y, *et al.* Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* 1995; **29:** 843–7.
7. Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C_{max} of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol* 1998; **45:** 241–6.
8. Cohen H, *et al.* Feasibility and pharmacokinetics of carbamazepine oral loading doses. *Am J Health-Syst Pharm* 1998; **55:** 1134–40.
9. Bondareva IB, *et al.* Population pharmacokinetic modelling of carbamazepine in epileptic elderly patients: implications for dosage. *J Clin Pharm Ther* 2006; **31:** 211–21.
10. Vucićević K, *et al.* Population pharmacokinetic model of carbamazepine derived from routine therapeutic drug monitoring data. *Ther Drug Monit* 2007; **29:** 781–8.
11. Tothfalusi L, *et al.* Exposure-response analysis reveals that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. *Br J Clin Pharmacol* 2008; **65:** 110–22.
12. Makmor-Bakry M, *et al.* Genetic variants in microsomal epoxide hydrolase influence carbamazepine dosing. *Clin Neuropharmacol* 2009; **32:** 205–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actinerval; Carbagramon; Carbamat; Conformal; Elebe; Tegretol; ***Austral.***: Tegretol; Teril; ***Austria***: Deleptin; Neurotop; Tegretol; ***Belg.***: Tegretol; ***Braz.***: Carmazin; Convulsan; Tegretard; Tegretol; Tegrex; Tegrezin; Uni Carbamaz; ***Canad.***: Mazepine; Novo-Carbamaz†; Tegretol; ***Chile***: Eposal; Tegretal; ***China***: Li Zhen (粒珍); Tegretol (得理多); ***Cz.***: Biston; Neurotop; Tegretol; Timonil; ***Denm.***: Tegretol; Timonil; Trimonil; ***Fin.***: Neurotol; Tegretol; ***Fr.***: Tegretol; ***Ger.***: Carba†; Carbabeta; Carbaflux; Carbagamma†; Finlepsin; Tegretal; Timonil; ***Gr.***: Tegretol; ***Hong Kong***: Convulzine†; CP-Carba; Tegretol; Teril; ***Hung.***: Neurotop; Stazepine; Tegretol; Timonil; ***India***: Acetol; Antilep; Carbacontin†; Carbadac; Carbasure; Carbatol; Cariv; Carizine; Carmaz; Carmeg; Carzep; Carzine; Cincar; Cizetol; Corgone; Epinil; Epix; Maze; Mazetol; Mezapin; Mezaril; Tegrital; ***Indon.***: Bamgetol; Lepsitol; Tegretol; Teril†; ***Irl.***: Gericarb; Tegretol; ***Israel***: Tegretol; Teril; Timonil; ***Ital.***: Tegretol; ***Malaysia***: Taver; Tegretol; ***Mex.***: Bioneuril; Carbalan; Carbasal; Carbaval†; Carbazep; Carbazina; Carpin; Cinazel; Clostedal; Dateril†; Neugeron; Neurolep; Sepibest; Tegretol; Trencir; Trepina†; Ultrepyl; Volutol; Zepiken; ***Neth.***: Tegretol; ***Norw.***: Tegretol; Trimonil; ***NZ***: Tegretol; Teril†; ***Philipp.***: Carbapsy; Carbilepp†; Epazin; Epikor; Lestremor; Tegrepin; Tegretol; ***Pol.***: Amizepin; Finlepsin; Neurotop; Tegretol; Timonil; ***Port.***: Tegretol; ***Rus.***: Carbalepsin (Карбалепсин); Carbapin (Карбапин)†; Finlepsin (Финлепсин); Mazepine (Мазепин); Tegretol (Тегретол); Zeptol (Зептол); ***S.Afr.***: Degranol; Tegretol; ***Singapore***: Carbatol; Carzepin; Mazetol; Neurotop; Storilat; Tegretol; ***Spain***: Tegretol; ***Swed.***: Hermolepsin; Tegretol; Trimonil; ***Switz.***: Carsol; Neurotop†; Tegretol; Timonil; ***Thai.***: Antafit; Carbazene; Carmapine; Carpine; Carzepine; Mapezine; Panitol†; Pantol; Taver†; Tegretol; Zeptol; ***Turk.***: Karazepin; Karbalex; Karbasif; Karberol; Kazepin; Tegretol; Teril; ***UAE***: Fitzecalm; ***UK***: Arbil; Carbagen; Epimaz; Tegretol; ***Ukr.***: Carbapin (Карбапин); Finlepsin (Финлепсин); Tegretol (Тегретол); ***USA***: Carbatrol; Epitol; Equetro; Tegretol; Teril; ***Venez.***: Convulex; Tanfedin; Tegretol.

Pharmacopoeial Preparations

BP 2014: Carbamazepine Tablets;
USP 36: Carbamazepine Extended-Release Tablets; Carbamazepine Oral Suspension; Carbamazepine Tablets.

Carisbamate *(USAN, rINN)*

Carisbamato; Carisbamatum; JNJ-10234094; RWJ-333369; YKP-509; Карисбамат.

(+)-(2S)-2-(2-Chlorophenyl)-2-hydroxyethyl carbamate.

$C_9H_{10}ClNO_3$=215.6

CAS — 194085-75-1.

ATC — N03AX19.

ATC Vet — QN03AX19.

UNII — P7725I9V3Z.

Profile

Carisbamate is under investigation for the management of infantile spasms. It has also been investigated for adjunctive treatment of partial-onset seizures in adults.

References.

1. Novak GP, *et al.* Carisbamate (RWJ-333369). *Neurotherapeutics* 2007; **4:** 106–9.
2. Sperling MR, *et al.* Carisbamate as adjunctive treatment of partial onset seizures in adults in two randomized, placebo-controlled trials. *Epilepsia* 2010; **51:** 333–43.
3. Moore K, *et al.* Effect of mild and moderate hepatic impairment on the pharmacokinetics and safety of carisbamate. *J Clin Pharmacol* 2012; **52:** 738–46.

Clobazam *(BAN, USAN, rINN)*

Clobazamum; H-4723; HR-376; Klobatsaami; Klobazam; Klobazamas; LM-2717; Клобазам.

7-Chloro-1,5-dihydro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3*H*)-dione.

$C_{16}H_{13}ClN_2O_2$=300.7

CAS — 22316-47-8.

ATC — N05BA09.

ATC Vet — QN05BA09.

UNII — 2MRO291B4U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clobazam). A white or almost white crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

Uses and Administration

Clobazam is a long-acting 1,5-benzodiazepine with uses similar to those of diazepam (a 1,4-benzodiazepine; see p. 1063.3). It may be used as an adjunct with other antiepileptics in the treatment of epilepsy including seizures associated with the Lennox-Gastaut syndrome, although its use may be limited by the development of tolerance or sedation (but see below). It is also used in the short-term treatment of acute anxiety (p. 1028.1).

As an adjunct in **epilepsy** usual oral doses are 20 to 30 mg daily, increased if necessary to a maximum of 60 mg daily.

For doses in children, see below.

As with other antiepileptics, withdrawal of clobazam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1 and under Clonazepam, p. 520.1.

For the short-term management of acute **anxiety** usual oral doses of 10 to 30 mg daily may be taken in divided doses or as a single dose at night; up to 80 mg daily has been used in hospitalised patients with severe anxiety states. Low initial doses and cautious increments to a usual daily dose of 10 to 20 mg are recommended in elderly or debilitated patients.

Administration in children. In the UK, clobazam is licensed for use as an adjunct in epilepsy in children over 6 years of age; the recommended usual initial oral dose is 5 mg daily with a maintenance dose range of 0.3 to 1 mg/kg daily (up to a maximum of 60 mg daily). Doses of up to 30 mg daily may be given as a single dose at bedtime; higher doses should be divided. For younger children, the *BNFC* suggests the following oral doses according to age:

- 1 month to 6 years: initially 125 micrograms/kg twice daily, increased every 5 days to a usual maintenance dose of 250 micrograms/kg twice daily. The maximum dose is 500 micrograms/kg twice daily and should not exceed 15 mg twice daily

The *BNFC* also suggests that clobazam may be given for cluster seizures and as monotherapy under specialist supervision for catamenial seizures (usually for 7 to 10 days each month just before and during menstruation).

In the USA, clobazam is licensed specifically for the adjunctive treatment of seizures associated with the Lennox-Gastaut syndrome in patients aged 2 years or older. Doses are calculated according to body-weight:

- 30 kg or less, the initial oral dose is 5 mg daily, increased to 10 mg daily on day 7 then to 20 mg daily on day 14, according to response
- more than 30 kg, the initial dose is 10 mg daily, increased to 20 mg daily on day 7 then to 40 mg daily on day 14, according to response

Doses greater than 5 mg daily should be given in 2 divided doses.

Epilepsy. Benzodiazepines are sometimes used in the management of epilepsy (p. 506.1), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects.

Clobazam, a 1,5-benzodiazepine, is considered to be somewhat better tolerated than conventional benzodiazepines, and has been widely used for adjunctive oral therapy in patients with epilepsy.[1,2] Clobazam is active against partial and generalised seizures in epilepsy of widely differing aetiology in patients of all ages and has also been used for short-term cover in patients with intermittent seizures, including in women with catamenial epilepsy (seizures associated with menstruation) or patients whose epileptic attacks occur in clusters. Clobazam has also been tried with some success in children, including those with refractory epilepsy,[3-5] epileptic encephalopathy,[6] and Lennox-Gastaut syndrome.[7-9] However, a systematic review[10] concluded that although clobazam may reduce seizure frequency and may be most effective in partial onset seizures, it was not clear who would best benefit from its use and over what time-frame.

1. Trimble MR. On the use of tranquillisers in epilepsy. *Epilepsia* 2002; **43** (suppl 2): 25–7.
2. Ng Y-T, Collins SD. Clobazam. *Neurotherapeutics* 2007; **4:** 138–44.
3. Munn R, Farrell K. Open study of clobazam in refractory epilepsy. *Pediatr Neurol* 1993; **9:** 465–9.
4. Sheth RD, *et al.* Clobazam for intractable pediatric epilepsy. *J Child Neurol* 1995; **10:** 205–8.
5. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. *Epilepsia* 1998; **39:** 952–9.
6. Silva RC, *et al.* Clobazam as add-on therapy in children with epileptic encephalopathy. *Can J Neurol Sci* 2006; **33:** 209–13.
7. Conry JA, *et al.* Clobazam in the treatment of Lennox-Gastaut syndrome. *Epilepsia* 2009; **50:** 1158–66.
8. Ng YT, *et al.* OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011; **77:** 1473–81.
9. Leahy JT, *et al.* Clobazam as an adjunctive therapy in treating seizures associated with Lennox-Gastaut syndrome. *Neuropsychiatr Dis Treat* 2011; **7:** 673–81.
10. Michael B, Marson AG. Clobazam as an add-on in the management of refractory epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 16/06/08).

Neuropathic pain. There has been a mention[1] of the complete relief of *phantom limb pain* (p. 10.3) refractory to other therapy in an elderly patient given clobazam 10 mg three times daily.

1. Rice-Oxley CP. The limited list: clobazam for phantom limb pain. *BMJ* 1986; **293:** 1309.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 10 mg of clobazam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Breast feeding. Benzodiazepines, such as clobazam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on menstruation. Occasionally the use of clobazam before menstruation for catamenial epilepsy appeared to delay the period.[1]

1. Feely M. Prescribing anticonvulsant drugs 3: clonazepam and clobazam. *Prescribers' J* 1989; **29:** 111–15.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clobazam, on *cognition* and *mood*, including risk of suicidal ideation, see p. 508.3.

Effects on the skin. Report[1] of toxic epidermal necrolysis that developed in light-exposed areas in a patient being treated with clobazam.

1. Redondo P, *et al.* Photo-induced toxic epidermal necrolysis caused by clobazam. *Br J Dermatol* 1996; **135:** 999–1002.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

As for Diazepam, p. 1068.1.

Antiepileptics. For reference to the interactions of clobazam with *felbamate* and *stiripentol*, see under Diazepam, p. 1069.1.

Pharmacokinetics

Clobazam is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 4 hours after oral doses. It is about 85% bound to plasma proteins. Clobazam is highly lipophilic and rapidly crosses the blood-brain barrier. It is metabolised in the liver by demethylation and hydroxylation; the cytochrome P450 isoenzyme CYP2C19 plays a role in its metabolism. Unlike the 1,4-benzodiazepines such as diazepam, clobazam, a 1,5-benzodiazepine, is hydroxylated at the 4-position rather than the 3-position (see also Metabolism, under Diazepam, p. 1071.1). Clobazam is excreted unchanged and as metabolites mainly in the urine. Mean half-lives of 18 hours and 42 hours have been reported for clobazam and its main active metabolite *N*-desmethylclobazam, respectively.

References.

1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; **8:** 233–52.
2. Ochs HR, *et al.* Single and multiple dose kinetics of clobazam, and clinical effects during multiple dosage. *Eur J Clin Pharmacol* 1984; **26:** 499–503.
3. Kinoshita M, *et al.* Efficacy of low-dose, add-on therapy of clobazam (CLB) is produced by its major metabolite, N-desmethyl-CLB. *J Neurol Sci* 2007; **263:** 44–8.
4. Seo T, *et al.* Impact of CYP2C19 polymorphisms on the efficacy of clobazam therapy. *Pharmacogenomics* 2008; **9:** 527–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clozam; Karidium; ***Austral.***: Frisium; ***Austria***: Frisium; ***Belg.***: Frisium; ***Braz.***: Frisium; Urbanil; ***Canad.***: Frisium; ***Chile***: Grifoclobam; ***Cz.***: Frisium; ***Denm.***: Frisium; ***Fin.***: Frisium; ***Fr.***: Urbanyl; ***Ger.***: Frisium†; ***Gr.***: Etaco; Frisium; ***Hong Kong***: Frisium; ***Hung.***: Frisium; ***India***: Aedon; Bazzy; Cloba; Clobastar; Clobator; Clodus; Clozam; Czam; Frisium; Lobazam; ***Indon.***: Anxibloc; Asabium; Clobium; Clofritis; Frisium; Proclozam; ***Irl.***: Frisium; ***Israel***: Frisium; ***Ital.***: Frisium; ***Malaysia***: Frisium; ***Mex.***: Frisium; ***Neth.***: Frisium; ***NZ***: Frisium; ***Pol.***: Frisium; ***Port.***: Castilium; ***S.Afr.***: Urbanol; ***Singapore***: Frisium; ***Spain***: Noiafren; ***Switz.***: Urbanyl; ***Thai.***: Frisium; ***UK***: Frisium; Tapclob; ***USA***: Onfi; ***Venez.***: Frisium.

Pharmacopoeial Preparations

BP 2014: Clobazam Oral Suspension; Clobazam Tablets.

Clonazepam *(BAN, USAN, rINN)*

Clonazépam; Clonazepamum; Klonatsepaami; Klonazepam; Klonazepám; Klonazepamas; Ro-5-4023; Клоназепам.

5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one.

$C_{15}H_{10}ClN_3O_3$=315.7

CAS — 1622-61-3.

ATC — N03AE01.

ATC Vet — QN03AE01.

UNII — 5PE9FDE8GB.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of clonazepam:

K-Pins; Klondike Bars; Klonnies; Klons; La Roche; Pin; Pins; R2; R-2; Roaches; Roachies; Roche.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clonazepam). A slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Clonazepam). A light yellow powder having a faint odour. Insoluble in water; slightly soluble in alcohol and in ether; sparingly soluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Sorption. Significant loss of clonazepam (up to 50% over 24 hours) has been reported[1] from solutions infused through PVC tubing; the effect was concentration dependent. The authors recommended that non-PVC tubing should always be used.

1. Schneider JJ, *et al.* Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion. *J Pain Symptom Manage* 2006; **31:** 563–7.

Uses and Administration

Clonazepam is a benzodiazepine derivative similar to diazepam (p. 1063.3), with marked antiepileptic properties.

It may be used in the treatment of all types of epilepsy and seizures (p. 506.1), including status epilepticus (p. 510.2), but its usefulness in chronic treatment is sometimes limited by the development of tolerance and by sedation, and other antiepileptics are often preferred. It may also be used in myoclonus (p. 511.3) and associated abnormal movements, and for the treatment of panic disorder (see Psychiatric Disorders, below).

For **epilepsy** and **myoclonus**, treatment is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses may initially be taken in 3 or 4 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. In the UK the initial oral dose is 1 mg (500 micrograms in the elderly) at night for 4 nights gradually increased over 2 to 4 weeks to a usual maintenance dose of 4 to 8 mg daily; it is recommended that the total dose should not exceed 20 mg daily. Dosage recommendations in the USA are generally similar although initial doses of up to 1.5 mg daily are permitted and dosage increments of 0.5 to 1 mg every 3 days are recommended. There is little value in routinely monitoring plasma-clonazepam concentrations.

Clonazepam may be an alternative to other benzodiazepines in the emergency management of **status epilepticus**. The usual dose is 1 mg given by slow intravenous injection over at least 2 minutes or by intravenous infusion, repeated if necessary to a maximum total dose of 20 mg.

For doses in children, see below.

As with other antiepileptics, withdrawal of clonazepam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1 and p. 520.1.

In the treatment of **panic disorder**, clonazepam is given in an initial oral dose of 250 micrograms twice daily. This may be increased after 3 days to a total of 1 mg daily; a few patients may benefit from further increases, up to a maximum of 4 mg daily. In order to minimise drowsiness, clonazepam may be taken as a single dose at bedtime. Withdrawal should again be gradual.

Administration. Serum concentrations of clonazepam after buccal, intranasal, or intravenous dosage were measured in a crossover study[1] in 7 healthy males. The results showed that intranasal clonazepam may offer an alternative to buccal use in patients with serial seizures but the initial concentrations were too low to recommend its use as an alternative to intravenous clonazepam in the management of status epilepticus. The nasal formulation used in this study contained dimethyl-β-cyclodextrin as a solubiliser and absorption enhancer.

1. Schols-Hendriks MWG, *et al.* Absorption of clonazepam after intranasal and buccal administration. *Br J Clin Pharmacol* 1995; **39:** 449–51.

Administration in children. For **epilepsy** and **myoclonus** treatment with clonazepam is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses are taken in 3 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. Alternatively, the *BNFC* suggests giving the initial dose at night for 4 nights and gradually increasing it over 2 to 4 weeks. In the UK, the recommended initial oral daily dose is up to 250 micrograms for infants and children aged up to 5 years, or up to 500 micrograms for older children. The following usual maintenance doses are given according to age:

- neonate to 1 year (although the *BNFC* recommends a minimum age of 1 month): 0.5 to 1 mg daily
- 1 to 5 years: 1 to 3 mg daily
- 5 to 12 years: 3 to 6 mg daily

Older children may be given the usual adult dose (see above).

If control of childhood epilepsy ceases to be adequate with clonazepam, the dose may be increased, or treatment interrupted for 2 or 3 weeks. The *BNFC* states that the UK injection formulation (*Rivotril; Roche, UK*) can be given orally if necessary; this may not apply to other injection formulations available elsewhere.

In the USA, doses may be given according to bodyweight. Infants and children aged up to 10 years or weighing up to 30 kg may be given an initial daily dose of 10 to 30 micrograms/kg (maximum 50 micrograms/kg) in 2 or 3 divided doses. This may be increased by a total of 250 to 500 micrograms every 3 days to a maintenance dose of 100 to 200 micrograms/kg daily given in 3 divided doses.

In the emergency management of **status epilepticus**, clonazepam is used as an alternative to other benzodiazepines. The usual dose in children is 500 micrograms given by slow intravenous injection or by intravenous infusion. Alternatively, the *BNFC* suggests giving the following doses by slow intravenous injection over at least 2 minutes according to age:

- neonates: 100 micrograms/kg, repeated if necessary after 24 hours
- 1 month to 12 years: 50 micrograms/kg (maximum 1 mg), repeated if necessary

Older children may be given the usual adult dose (see Uses and Administration, above).

In children aged over 1 month, these doses by injection may be followed by an intravenous infusion of 10 micrograms/kg per hour, adjusted according to response to a maximum of 60 micrograms/kg per hour.

Extrapyramidal disorders. Clonazepam may be of benefit in some extrapyramidal disorders. It has been tried in the management of patients with *tic disorders* such as *Tourette's syndrome* (p. 1030.1) but evidence of efficacy from controlled studies is limited.[1] Some use clonazepam in preference to haloperidol[2] since it does not carry the risk of tardive dyskinesia associated with such antipsychotics and a case report[3] described the successful use of clonazepam for haloperidol-induced tardive Tourette's syndrome in an adult patient. There is also limited evidence of benefit with clonazepam in antipsychotic-induced *akathisia*[4,5] and *tardive dyskinesia*[6,7] (see under Extrapyramidal Disorders, p. 1049.2), and of improvement in *dysarthria* in a study in patients with parkinsonism.[8]

1. Goetz CG. Clonidine and clonazepam in Tourette syndrome. *Adv Neurol* 1992; **58:** 245–51.
2. Truong DD, *et al.* Clonazepam, haloperidol, and clonidine in tic disorders. *South Med J* 1988; **81:** 1103–5.
3. Reid SD. Neuroleptic-induced tardive Tourette treated with clonazepam: a case report and literature review. *Clin Neuropharmacol* 2004; **27:** 101–4.
4. Kutcher S, *et al.* Successful clonazepam treatment of neuroleptic-induced akathisia in older adolescents and young adults: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 1989; **9:** 403–6.
5. Pujalte D, *et al.* A double-blind comparison of clonazepam and placebo in the treatment of neuroleptic-induced akathisia. *Clin Neuropharmacol* 1994; **17:** 236–42.
6. Thaker GK, *et al.* Clonazepam treatment of tardive dyskinesia: a practical GABAmimetic strategy. *Am J Psychiatry* 1990;**147:** 445–51.
7. Shapleske J, *et al.* Successful treatment of tardive dystonia with clozapine and clonazepam. *Br J Psychiatry* 1996; **168:** 516–18.
8. Biary N, *et al.* A double-blind trial of clonazepam in the treatment of parkinsonian dysarthria. *Neurology* 1988; **38:** 255–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Clonazepam may also be of value, especially in neurogenic hiccups.

Neuropathic pain. The management of *phantom limb pain* (p. 10.3) can be difficult, and tricyclic antidepressants and antiepileptics are used for the neuropathic components of the pain. Rapid and marked pain relief was achieved in 2 patients with lancinating phantom limb pain after treatment with clonazepam with or without amitriptyline.[1]

Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p. 11.2), clonazepam may be used in carbamazepine-intolerant patients.

1. Bartusch SL, *et al.* Clonazepam for the treatment of lancinating phantom limb pain. *Clin J Pain* 1996; **12:** 59–62.

Psychiatric disorders. Although the risk of dependence with benzodiazepines may outweigh their benefits in panic disorder (p. 1029.1), clonazepam has been used for the treatment of panic disorder with or without agoraphobia, and reported benefit in such patients[1] suggests a similar action to alprazolam. A literature review[2] evaluated the use of clonazepam in a range of psychiatric disorders and found that it may also be effective in the treatment of social anxiety disorder (see Phobic Disorders, p. 1029.1) although further studies are warranted. There was evidence to suggest that clonazepam may be useful in acute mania (see Bipolar Disorder, p. 397.2) and for the augmentation of antidepressant therapy with SSRIs in depression (p. 398.1). A study[3] found that augmentation was significantly more effective with a daily dose of 3 mg of clonazepam than with lower doses; a later review[4] suggested that doses of between 2 and 6 mg daily were recommended, and that clonazepam should be withdrawn if no response was seen in 2 to 4 weeks.

1. Davidson JRT, Moroz G. Pivotal studies of clonazepam in panic disorder. *Psychopharmacol Bull* 1998; **34:** 169–74.
2. Nardi AE, Perna G. Clonazepam in the treatment of psychiatric disorders: an update. *Int Clin Psychopharmacol* 2006; **21:** 131–42.
3. Morishita S, Aoki S. Clonazepam in the treatment of prolonged depression. *J Affect Disord* 1999; **53:** 275–8.
4. Morishita S. Clonazepam as a therapeutic adjunct to improve the management of depression: a brief review. *Hum Psychopharmacol* 2009; **24:** 191–8.

Sleep-associated movement disorders. Treatment of sleep-associated movement disorders (p. 1034.2) including

sleep behaviour disorder, restless legs syndrome, and periodic limb movements in sleep is largely empirical, but benzodiazepines such as clonazepam are often used.[1] Small studies have provided some evidence of benefit with clonazepam therapy in these disorders,[2-4] including bruxism.[5]

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100:** 333–7.
2. Montagna P, *et al*. Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand* 1984; **69:** 428–30.
3. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *J Neurol Neurosurg Psychiatry* 1987; **50:** 1679–81.
4. Saletu M, *et al*. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol* 2001; **11:** 153–61.
5. Saletu A, *et al*. On the pharmacotherapy of sleep bruxism: placebo-controlled polysomnographic and psychometric studies with clonazepam. *Neuropsychobiology* 2005; **51:** 214–25.

Stiff-man syndrome. Clonazepam has been used as an alternative to diazepam in the management of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) and is reported[1] to be effective for familial startle disease, a rare congenital form of stiff-man syndrome.

1. Ryan SG, *et al*. Startle disease, or hyperekplexia: response to clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. *Ann Neurol* 1992; **31:** 663–8.

Tinnitus. Clonazepam is one of many drugs that have been tried in tinnitus (p. 1994.1), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

References.
1. Ganança MM, *et al*. Clonazepam in the pharmacological treatment of vertigo and tinnitus. *Int Tinnitus J* 2002; **8:** 50–3.
2. Albertino S, *et al*. Pulsatile tinnitus: treatment with clonazepam and propranolol. *Rev Bras Otorrinolaringol (Engl Ed)* 2005; **71:** 111–13.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 250 micrograms of clonazepam may be considered equivalent to about 5 mg of diazepam.

Abuse. The liability of clonazepam for abuse has been evaluated[1] from analysis of a drug prescription database.

1. Frauger E, *et al*. Estimation of clonazepam abuse liability: a new method using a reimbursed drug database. *Int Clin Psychopharmacol* 2009; **24:** 318–24.

Withdrawal. A study[1] of the withdrawal of clonazepam therapy in 40 epileptic children found that 19 had withdrawal symptoms of increased seizure frequency, either alone or with other symptoms, but that this effect was transient. Withdrawal seizures and status might become an obstacle to the removal of useless or even deleterious therapy with clonazepam because the transient nature of these effects was not always recognised. Clonazepam should not be used for more than 3 to 6 months and should be stopped if clear and lasting therapeutic benefit could not be shown.

See also Uses and Administration, p. 519.2.

1. Specht U, *et al*. Discontinuation of clonazepam after long-term treatment. *Epilepsia* 1989; **30:** 458–63.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

The principal adverse effect of clonazepam is drowsiness, which occurs in about 50% of all patients when starting therapy. Salivary or bronchial hypersecretion may cause respiratory problems in children. Thrombophlebitis has been associated with intravenous use and may be avoided by injection into a large vein at a rate not exceeding 500 micrograms/minute. Respiration and blood pressure should also be monitored.

Care is required when withdrawing clonazepam therapy—see above.

Breast feeding. Benzodiazepines, such as clonazepam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on the endocrine system. Precocious development of secondary sexual characteristics occurred in a 15-month-old girl 2 months after starting treatment with clonazepam 500 micrograms twice daily for convulsions.[1] Symptoms regressed upon withdrawal of clonazepam.

1. Choonara IA, *et al*. Clonazepam and sexual precocity. *N Engl J Med* 1985; **312:** 185.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clonazepam, on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Effects on the mouth. A 52-year-old woman developed burning mouth syndrome after starting clonazepam;[1] some improvement was noted when the dose was reduced but symptoms were still intolerable and clonazepam was withdrawn. Subsequently, symptoms resolved within 3 weeks.

1. Culhane NS, Hodle AD. Burning mouth syndrome after taking clonazepam. *Ann Pharmacother* 2001; **35:** 874–6.

Effects on sexual function. Sexual dysfunction was reported[1] in 18 of 42 male patients receiving clonazepam for the treatment of post-traumatic stress disorder; symptoms resolved when therapy was changed to diazepam in 17 patients and lorazepam in the remaining patient.

1. Fossey MD, Hamner MB. Clonazepam-related sexual dysfunction in male veterans with PTSD. *Anxiety* 1994-95; **1:** 233–6.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of benzodiazepines including clonazepam, see Effects on the Nervous System, under Diazepam, p. 1066.1. However, clonazepam is also used in the treatment of some extrapyramidal disorders as discussed under Uses and Administration, p. 519.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clonazepam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

As for Diazepam, p. 1068.1.

Antiepileptics. For reference to possible interactions between clonazepam and other antiepileptics, see under Diazepam, p. 1069.1 and Benzodiazepines, under Interactions of Phenytoin, p. 544.2.

Pharmacokinetics

Clonazepam is quickly absorbed after oral doses with a bioavailability of about 90%; peak plasma concentrations occur between 1 and 4 hours after ingestion. It is extensively metabolised in the liver, its principal metabolite being 7-aminoclonazepam, which has no antiepileptic activity; minor metabolites are the 7-acetamido- and 3-hydroxy-derivatives. It is excreted mainly in the urine almost entirely as its metabolites in free or conjugated form. It is about 85% bound to plasma proteins and estimations of its elimination half-life range from about 20 to 40 hours, and occasionally more.

A therapeutic range of plasma concentrations has not been established.

Clonazepam crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of clonazepam may be affected by use with other antiepileptics (see under Interactions, above).

A single-dose pharmacokinetic study[1] in healthy subjects found that absorption of clonazepam was slower and intersubject variability was greater after intramuscular injection than after an oral dose. The pharmacokinetics of a modified-release subcutaneous injection have also been studied in healthy subjects;[2] plasma-clonazepam concentrations were sustained and elimination occurred slowly over 13 days.

1. Crevoisier C, *et al*. Comparative single-dose pharmacokinetics of clonazepam following intravenous, intramuscular and oral administration to healthy volunteers. *Eur Neurol* 2003; **49:** 173–7.
2. Greenblatt DJ, *et al*. Clonazepam pharmacokinetics: comparison of subcutaneous microsphere injection with multiple-dose oral administration. *J Clin Pharmacol* 2005; **45:** 1288–93.

Bioavailability. It has been suggested, on the basis of anecdotal evidence,[1] that there may be differences in bioavailability, and hence in clinical effect, between formulations of clonazepam tablets.

1. Rapaport MH. Clinical differences between the generic and nongeneric forms of clonazepam. *J Clin Psychopharmacol* 1997; **17:** 424.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alerion†; Ciclox; Clonabay; Clonagin; Clonasedan; Clonax; Clonazen 2; Cloner; Diocam; Edictum; Felanor†; Flozepan; Induzepam; Leptic; Miozepam†; Neuryl; Olimer†; Paditex; Placidiax†; Ribocler; Riuclonaz; Rivocler; Rivotril; Sedovanon; Sensaton; Solfidin; Tecepin; ***Austral.***: Paxam; Rivotril; ***Austria***: Rivotril; ***Belg.***: Rivotril; ***Braz.***: Clonotril; Clopan†; Epileptil; Navotrax; Rivotril; Uni Clonazepax; ***Canad.***: Clonapam; Rivotril; ***Chile***: Acepran; Celaxin; Clonapam; Clonex; Clozanil; Crismol; Neuryl; Ravotril; Ropsil; Valpax; ***China***: Jing Kang (静康); ***Cz.***: Rivotril; ***Denm.***: Rivotril; ***Fin.***: Rivatril; ***Fr.***: Rivotril; ***Ger.***: Rivotril; ***Gr.***: Rivotril; ***Hong Kong***: Rivotril; ***Hung.***: Clonapam†; Rivotril; ***India***: Alcona; Anxrea; Clon; Clonafit; Clonapax; Clonapik; Clonatrac; Clonopam; Clonotril; Clopam; Closed; Clozep; Convaclon; Copam; Czap; Epcon; Epitril; Epizam; Incloz; Logen-MD; Lonazep; Lonin; Lonna; Lozep; Melzap; Norep; Onz; Ozepam; Panik; ***Indon.***: Riklona; Rivotril; ***Irl.***: Rivotril; ***Israel***: Clonex; Rivotril; ***Ital.***: Rivotril; ***Malaysia***: Rivopam; Rivotril; ***Mex.***: Clozer; Kenoket; Kriadex; Panazeclox; Rivotril; Zymanta; ***Neth.***: Rivotril; ***Norw.***: Rivotril; ***NZ***: Paxam; Rivotril; ***Philipp.***: Clonotril; Rivotril; ***Pol.***: Rivotril†; ***Port.***: Rivotril; ***Rus.***: Rivotril (Ривотрил); ***S.Afr.***: Rivotril; ***Singapore***: Clonotril; Rivotril; ***Spain***: Rivotril; ***Swed.***: Iktorivil; ***Switz.***: Rivotril; ***Thai.***: Clonaril; Convolsil; Povanil; Prenarpil; Rivotril; ***Turk.***: Rivotril; ***UK***: Rivotril; ***USA***: Klonopin; ***Venez.***: Rivotril.

Multi-ingredient Preparations. ***India***: C-Pram-S Plus; Cita-S Forte; Cita-S Plus; Ecitalop-C; Escin Plus; Escita Plus; Escitrac-CZ; Esfany-CZ; Esitor Forte; Esjoy Plus; Espar-CL; Estomine Zee; Estomine-SF; Feliz-S Plus; Nexito Forte; Nexito-Plus.

Pharmacopoeial Preparations

BP 2014: Clonazepam Injection; Clonazepam Oral Suspension; Clonazepam Tablets;

USP 36: Clonazepam Oral Suspension; Clonazepam Orally Disintegrating Tablets; Clonazepam Tablets.

Eslicarbazepine *(BAN, USAN, rINN)*

BIA-2-194; Eslicarbazepina; Eslicarbazépine; Eslicarbazepinum; Эсликарбазепин.

(10*S*)-10-Hydroxy-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-carboxamide.

$C_{15}H_{14}N_2O_2$=254.3

CAS — 104746-04-5.

ATC — N03AF04.

ATC Vet — QN03AF04.

UNII — S5VXA428R4.

Eslicarbazepine Acetate *(BANM, USAN, rINNM)*

Acetato de eslicarbazepina; BIA-2-093; Eslicarbazépine, Acétate d'; Eslicarbazepini Acetas; SEP-0002093; Эсликарбазепин Ацетат.

$C_{17}H_{16}N_2O_3$=296.3

CAS — 236395-14-5.

ATC — N03AF04.

ATC Vet — QN03AF04.

UNII — BEA68ZVB2K.

NOTE. The name Stedesa has been used as a trade mark for eslicarbazepine acetate.

Profile

Eslicarbazepine is the *S*-enantiomer of licarbazepine, the active monohydroxy metabolite of oxcarbazepine (p. 533.2). It is used as adjunctive therapy in partial seizures with or without secondary generalisation (p. 506.1) in patients aged 18 years and older. Eslicarbazepine is given orally as the acetate and doses are expressed in terms of this salt.

The initial dose is 400 mg once daily, increased to 800 mg daily after 1 or 2 weeks. This dose may be further increased to 1.2 g daily according to response.

Reduced doses are recommended in patients with renal impairment (see below).

References.
1. Almeida L, *et al*. Single-dose and steady-state pharmacokinetics of eslicarbazepine acetate (BIA 2-093) in healthy elderly and young subjects. *J Clin Pharmacol* 2005; **45:** 1062–6.
2. McCormack PL, Robinson DM. Eslicarbazepine acetate. *CNS Drugs* 2009; **23:** 71–9.
3. Elger C, *et al*. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. *Epilepsia* 2009; **50:** 454–63.
4. Rauchenzauner M, Luef G. Update on treatment of partial onset epilepsy: role of eslicarbazepine. *Neuropsychiatr Dis Treat* 2010; **6:** 723–30.
5. Chang XC, *et al*. Eslicarbazepine acetate add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2011 (accessed 16/11/12).
6. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. *Epilepsia* 2012; **53:** 935–46.

Administration in renal impairment. The initial oral dose of eslicarbazepine acetate for patients with a creatinine clearance (CC) of 30 to 60 mL/min is 400 mg every other day for 2 weeks followed by a once-daily dose of 400 mg; this dose may be further increased according to response. Use in severe impairment (CC less than 30 mL/min) is not recommended due to a lack of data.

Reference to the effect of renal impairment on the pharmacokinetics of eslicarbazepine acetate.[1]

1. Maia J, *et al*. Effect of renal impairment on the pharmacokinetics of eslicarbazepine acetate. *Int J Clin Pharmacol Ther* 2008; **46:** 119–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Zebinix; ***Cz.***: Exalief†; Zebinix; ***Denm.***: Zebinix; ***Fr.***: Zebinix; ***Ger.***: Zebinix; ***Gr.***: Zebinix; ***Irl.***: Exalief†; Zebinix; ***Neth.***: Exalief†; Zebinix; ***Norw.***: Zebinix; ***Pol.***: Exalief†; Zebinix; ***Port.***: Exalief†; Zebinix; ***Spain***: Zebinix; ***Swed.***: Zebinix; ***UK***: Zebinix; ***USA***: Aptiom.

Ethosuximide *(BAN, USAN, rINN)*

CI-366; CN-10395; Ethosuximid; Éthosuximide; Ethosuximidum; Etosüksimid; Etosuksimidas; Etosuksimidi; Etosuksymid; Etosuximid; Etosuximida; Etoszuximid; NSC-64013; PM-671; Этосуксимид.

2-Ethyl-2-methylsuccinimide.

$C_7H_{11}NO_2$=141.2

CAS — 77-67-8.

ATC — N03AD01.

ATC Vet — QN03AD01.

UNII — 5SEH9X1D1D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Ethosuximide). A white or almost white powder or waxy solid. It exhibits polymorphism. Freely soluble in water; very soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Ethosuximide). A white to off-white crystalline powder or waxy solid, having a characteristic odour. Freely soluble in water and in chloroform; very soluble in alcohol and in ether; very slightly soluble in petroleum spirit. Store in airtight containers.

Uses and Administration

Ethosuximide is a succinimide antiepileptic used in the treatment of absence seizures (below). It may also be used for myoclonic seizures. Ethosuximide is ineffective against tonic-clonic seizures and may unmask them if given alone in mixed seizure types. However, it is occasionally helpful for atonic and tonic seizures.

A plasma-ethosuximide concentration of 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre) appears to be generally necessary. The initial oral dose is 500 mg daily. The dosage is then adjusted in steps of 250 mg every 4 to 7 days, according to response. Control of seizures is usually produced with a daily dose of 1 to 1.5 g, although some patients may require doses of up to 2 g; strict supervision is necessary when the dose exceeds 1.5 g. Daily doses at the higher end of the range should be given in 2 divided doses.

For doses in children, see below.

As with other antiepileptics, withdrawal of ethosuximide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in children. Ethosuximide may be used in the treatment of absence (petit mal) seizures and for myoclonic seizures in infants and children. In the UK, the following recommended oral doses are given according to age:

- up to 6 years of age: an initial dose of 250 mg daily, increased gradually in small steps every few days to a usual dose of 20 mg/kg daily; licensed information for one product (*Emeside; Chemidex, UK*) recommends that the dose should not exceed 1 g. (Similar dosages are recommended in the USA for children aged between 3 to 6 years). The *BNFC* suggests giving the daily dose as 2, or if necessary 3, divided doses
- aged 6 years and above: usual adult doses (see above)

Epilepsy. Ethosuximide is a drug of choice in the treatment of absence seizures; it may also be used for myoclonic, atonic, and tonic seizures but is ineffective in other forms of epilepsy (p. 506.1). Ethosuximide may be given with other antiepileptics in the treatment of mixed-seizure syndromes that include absences. It has been suggested that ethosuximide may provoke tonic-clonic seizures, but there is not a great deal of evidence for this. One early report indicated that 22 of 85 patients receiving a regimen of ethosuximide, mesuximide, and trimethadione for absence seizures developed tonic-clonic seizures[1] and another of similar vintage reported exacerbation of mixed-seizure types in 7 patients receiving ethosuximide.[2] However, it is recognised that patients with absence seizures have a high incidence of generalised tonic-clonic seizures[3] and it would presumably be difficult to distinguish such attacks from any putative effect of ethosuximide. Furthermore, ethosuximide is not effective against tonic-clonic seizures, and in patients with mixed-seizure types it might be expected to unmask the non-absence components of the disease. A retrospective comparison[4] in patients with absence seizures found no evidence that ethosuximide was associated with a greater risk of generalised tonic-clonic seizures than valproate.

Ethosuximide has also been tried in the management of absence status epilepticus (p. 510.2).

1. Friedel B, Lempp R. Grand-mal-Provokation bei der Behandlung kindlicher petit-mal mit Oxazolidinen oder Succinimiden und ihre therapeutischen Konsequenzen. *Z Kinderheilk* 1962; **87:** 42–51.
2. de Haas AML, Kuilman M. Ethosuximide (α-ethyl-α-methylsuccinimide) and grand mal. *Epilepsia* 1964; **5:** 90–6.
3. Glauser TA. Succinimides: Adverse Effects. In: Levy RG, *et al.*, eds. *Antiepileptic drugs* 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 658–64.
4. Schmitt B, *et al.* Is ethosuximide a risk factor for generalised tonic-clonic seizures in absence epilepsy? *Neuropediatrics* 2007; **38:** 83–7.

Adverse Effects and Treatment

Gastrointestinal adverse effects including nausea, vomiting, diarrhoea, anorexia, gastric upset, and abdominal pain occur quite often with ethosuximide. Other effects that may occur include headache, fatigue, lethargy, drowsiness, dizziness, ataxia, hiccup, and mild euphoria.

More rarely dyskinesias, personality changes, depression, psychosis, sleep disturbances including night terrors, skin rashes, erythema multiforme or Stevens-Johnson syndrome, SLE, photophobia, gum hypertrophy, tongue swelling, myopia, increased libido, and vaginal bleeding have been reported. There are a few reports of blood disorders including eosinophilia, leucopenia, agranulocytosis, thrombocytopenia, pancytopenia, and aplastic anaemia; fatalities have occurred.

Abnormal renal and liver function values have been recorded.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Precautions

Ethosuximide should be used with caution in patients with impaired hepatic or renal function. Licensed product information recommends regular hepatic and renal-function tests (and some suggest blood counts) during treatment with ethosuximide, although the practical value of such monitoring has been questioned. Patients or their carers should be told how to recognise signs of blood toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Care is required when withdrawing ethosuximide therapy—see also Uses and Administration, above.

Breast feeding. Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. Although licensed product information recommends that breast feeding should be avoided, the American Academy of Pediatrics[1] considers that ethosuximide is usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ethosuximide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antibacterials. *Isoniazid* raises the plasma concentration of ethosuximide and increases the risk of toxicity. Psychotic behaviour has been reported[1] in a patient stabilised on ethosuximide and sodium valproate, after the introduction of isoniazid. Serum-ethosuximide concentrations rose substantially until both ethosuximide and isoniazid were stopped.

1. van Wieringen A, Vrijlandt CM. Ethosuximide intoxication caused by interaction with isoniazid. *Neurology* 1983; **33:** 1227–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Antiepileptics. Since ethosuximide has a limited spectrum of antiepileptic action, patients with mixed seizure syndromes may require addition of other antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* have all been shown[1] to increase the clearance of ethosuximide and thus reduce plasma concentrations. This interaction is likely to be clinically relevant and higher ethosuximide dosages may be necessary to achieve therapeutic drug levels. The effect of *valproic acid* on ethosuximide concentrations is unclear. One study[2] showed a marked increase in serum ethosuximide concentrations once valproate was added to combination therapies; increases in ethosuximide concentrations have also been noted in healthy subjects when taken with valproic acid.[3] Conversely, other studies have reported reductions[4] or no significant changes in serum ethosuximide concentrations[5,6] with valproic acid. For the effect of ethosuximide on valproic acid, see p. 557.3.

1. Giaccone M, *et al.* Effect of enzyme inducing anticonvulsants on ethosuximide pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1996; **41:** 575–9.
2. Mattson RH, Cramer JA. Valproic acid and ethosuximide interaction. *Ann Neurol* 1980; **7:** 583–4.
3. Pisani F, *et al.* Valproic acid-ethosuximide interaction: a pharmacokinetic study. *Epilepsia* 1984; **25:** 229–33.
4. Battino D, *et al.* Ethosuximide plasma concentrations: influence of age and associated concomitant therapy. *Clin Pharmacokinet* 1982; **7:** 176–80.
5. Fowler GW. Effect of dipropylacetate on serum levels of anticonvulsants in children. *Proc West Pharmacol Soc* 1978; **21:** 37–40.
6. Bauer LA, *et al.* Ethosuximide kinetics: possible interaction with valproic acid. *Clin Pharmacol Ther* 1982; **31:** 741–5.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Pharmacokinetics

Ethosuximide is readily absorbed from the gastrointestinal tract and extensively hydroxylated in the liver to its principal metabolite which is reported to be inactive. Ethosuximide is excreted in the urine mainly in the form of its metabolites, either free or conjugated, but about 12 to 20% is also excreted unchanged.

Ethosuximide is widely distributed throughout the body, but is not significantly bound to plasma proteins. A half-life of about 40 to 60 hours has been reported for adults with a shorter half-life of about 30 hours in children.

Monitoring of plasma concentrations has been suggested as an aid in assessing control and the therapeutic range of ethosuximide is usually quoted as being 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre); concentrations in saliva and tears have also been measured.

Ethosuximide crosses the placental barrier, and is distributed into breast milk.

The pharmacokinetics of ethosuximide are affected by use with other antiepileptics (see under Interactions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zarontin; ***Austral.***: Zarontin; ***Austria***: Petinimid; Suxinutin†; ***Belg.***: Zarontin; ***Braz.***: Etoxin; ***Canad.***: Zarontin; ***Chile***: Suxinutin†; ***Cz.***: Petinimid; ***Denm.***: Zarondan; ***Fr.***: Zarontin; ***Ger.***: Petnidan; Suxilep; ***Gr.***: Petinimid; Zarontin; ***Hung.***: Petnidan; ***Irl.***: Zarontin; ***Ital.***: Zarontin; ***Mex.***: Fluozoid; ***Neth.***: Ethymal; ***NZ***: Zarontin; ***Pol.***: Petinimid; ***Rus.***: Suxilep (Суксилеп); ***S.Afr.***: Zarontin; ***Swed.***: Suxinutin; ***Switz.***: Petinimid; ***Turk.***: Petimid; ***UK***: Emeside; Zarontin; ***USA***: Zarontin.

Pharmacopoeial Preparations

BP 2014: Ethosuximide Capsules; Ethosuximide Oral Solution;
USP 36: Ethosuximide Capsules; Ethosuximide Oral Solution.

Ethotoin *(BAN, rINN)*

Éthotoïne; Ethotoinum; Etotoiini; Etotoin; Etotoína; Этотоин.

3-Ethyl-5-phenylhydantoin.

$C_{11}H_{12}N_2O_2$=204.2

CAS — 86-35-1.

ATC — N03AB01.

ATC Vet — QN03AB01.

UNII — 46QG38NC4U.

Pharmacopoeias. In *US.*

USP 36: (Ethotoin). A white crystalline powder. Insoluble in water; freely soluble in dehydrated alcohol and in chloroform; soluble in ether. Store in airtight containers.

Profile

Ethotoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p. 538.2), but it is reported to be both less toxic and less effective and is not commonly used in epilepsy (p. 506.1).

Ethotoin is given orally for tonic-clonic and complex partial seizures in initial doses of up to 1 g daily, increased gradually at intervals of several days to 2 to 3 g daily, given in 4 to 6 divided doses after meals.

Administration. A study[1] of the pharmacokinetics of ethotoin given at more convenient intervals of every 8 hours.

1. Browne TR, Szabo GK. A pharmacokinetic rationale for three times daily administration of ethotoin (Peganone). *J Clin Pharmacol* 1989; **29:** 270–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Peganone.

Pharmacopoeial Preparations
USP 36: Ethotoin Tablets.

Felbamate *(USAN, rINN)*

AD-03055; Felbamato; Felbamatum; W-554; Фелбамат.
2-Phenyl-1,3-propanediol dicarbamate.
$C_{11}H_{14}N_2O_4$=238.2
CAS — 25451-15-4.
ATC — N03AX10.
ATC Vet — QN03AX10.
UNII — X72RBB02N8.

Pharmacopoeias. In *US*.

USP 36: (Felbamate). A white to off-white powder. Very slightly soluble in water; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; slightly soluble in acetonitrile.

Uses and Administration

Felbamate is a carbamate structurally related to meprobamate (p. 1083.3). It is used in the treatment of epilepsy (below); however, because of its toxicity, it should only be used in severe cases unresponsive to other drugs.

Felbamate is given orally as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation. It is used in children as adjunctive therapy in controlling the seizures associated with the Lennox-Gastaut syndrome (see below).

The initial dose of felbamate when given as *monotherapy* is 1.2 g daily in 3 or 4 divided doses. The daily dose should be increased gradually under close supervision; increments of 600 mg every 2 weeks are given according to response, up to 2.4 g daily. Thereafter doses may be further increased to a maximum of 3.6 g daily if necessary.

Similar initial doses are given as *adjunctive* therapy, but the doses of the other antiepileptics should be decreased as necessary. This adjunctive dose may be increased by 1.2 g at weekly intervals, up to a maximum of 3.6 g daily.

As with other antiepileptics, withdrawal of felbamate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

References.
1. Pellock JM, *et al.* Felbamate: consensus of current clinical experience. *Epilepsy Res* 2006; **71:** 89–101.

Administration in children. As an adjunct in Lennox-Gastaut syndrome, the initial oral dose of felbamate in children aged 2 to 14 years is 15 mg/kg daily in 3 or 4 divided doses. This may be increased gradually in increments of 15 mg/kg at weekly intervals to a maximum of 45 mg/kg daily; the doses of other antiepileptics should be decreased as necessary. The efficacy and tolerability of felbamate in children under 4 years of age have been discussed.[1]

Those aged 14 years and over may be given the usual adult dose (see above) as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation.

1. Grosso S, *et al.* Efficacy and safety of felbamate in children under 4 years of age: a retrospective chart review. *Eur J Neurol* 2008; **15:** 940–6.

Administration in the elderly. The elderly may require lower initial doses of felbamate and slower dose titration. After single doses of felbamate, plasma concentrations and half-lives were greater and mean clearance lower in elderly than in young subjects, whereas pharmacokinetic parameters after multiple dosing schedules were similar.[1]

1. Richens A, *et al.* Single and multiple dose pharmacokinetics of felbamate in the elderly. *Br J Clin Pharmacol* 1997; **44:** 129–34.

Administration in renal impairment. A single-dose pharmacokinetic study[1] indicated that in patients with renal impairment the initial dose of felbamate may need to be lower and increases made more cautiously than in patients with normal renal function (licensed product information suggests halving initial and maintenance doses).

1. Glue P, *et al.* Single-dose pharmacokinetics of felbamate in patients with renal dysfunction. *Br J Clin Pharmacol* 1997; **44:** 91–3.

Epilepsy. Although felbamate was well tolerated in clinical studies, rare but serious adverse effects were noted during early postmarketing use.[1,2] Aplastic anaemia and serious hepatotoxic reactions, sometimes with fatal outcomes, developed in some patients. Patients taking felbamate should have frequent blood counts and monitoring of liver enzymes. However there is no evidence that such monitoring will prevent adverse outcomes; in addition, the risk of aplastic anaemia is thought to decrease after the first year of therapy, and the need for ongoing blood counts is still less clear.[3] Successful long-term use has been described.[4] Even if detected early, aplastic anaemia and hepatic impairment may not be reversible.[1] Usage in the USA is restricted to patients with refractory partial seizures with or without secondary generalisation or for adjunctive therapy for children with Lennox-Gastaut syndrome. Guidelines on appropriate use have been issued.[3]

The overall management of epilepsy is discussed on p. 506.1.

1. Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med* 1996; **334:** 1583–90.
2. Appleton RE. The new antiepileptic drugs. *Arch Dis Child* 1996; **75:** 256–62.
3. French J, *et al.* The use of felbamate in the treatment of patients with intractable epilepsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 1999; **40:** 803–8. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/119061174/PDFSTART (accessed 01/09/08)
4. White JR, *et al.* Long-term use of felbamate: clinical outcomes and effect of age and concomitant antiepileptic drug use on its clearance. *Epilepsia* 2009; **50:** 2390–6.

Adverse Effects

The most frequently reported adverse effects with felbamate are anorexia, weight loss, nausea and vomiting, rash, insomnia, headache, dizziness, somnolence, and diplopia. Aplastic anaemia or acute liver failure, sometimes fatal, have occurred rarely, and there have been reports of Stevens-Johnson syndrome.

Effects on the kidneys. A 15-year-old boy given up to 3 g of felbamate daily developed urethral obstruction due to formation of urethral stones composed of felbamate.[1] Records revealed that 2 years earlier unidentified urinary crystals had been found in the patient's urine.

For reports of crystalluria associated with felbamate overdosage, see below.

1. Sparagana SP, *et al.* Felbamate urolithiasis. *Epilepsia* 2001; **42:** 682–5.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a patient 16 days after she started monotherapy with felbamate for partial complex seizures.

1. Travaglini MT, *et al.* Toxic epidermal necrolysis after initiation of felbamate therapy. *Pharmacotherapy* 1995; **15:** 260–4.

Overdosage. A 20-year-old woman presented with slurred speech and nausea 4 hours after ingesting 18 g of felbamate and 12 to 25 g of sodium valproate.[1] Over the next 4 to 5 hours she became combative, uncooperative, and progressively obtunded and eventually required endotracheal intubation and assisted ventilation. Peak plasma concentrations of 200 micrograms/mL for felbamate and 470 micrograms/mL for sodium valproate occurred 12 and 14 hours, respectively, after ingestion. Large quantities of macroscopic crystals, identified as containing felbamate, were noted in the urine 18 hours after ingestion and the patient developed renal failure. The crystalluria and renal failure responded to parenteral hydration. In another case report,[2] a 3-year-old child ingested 232 mg/kg of felbamate resulting in ataxia, vomiting, crystalluria, haematuria, and mild tachycardia. The plasma concentration of felbamate 15 hours after ingestion was 138 micrograms/mL. She was successfully treated with an infusion of sodium chloride 0.9% and intravenous metoclopramide; no renal impairment was seen.

1. Rengstorff DS, *et al.* Felbamate overdose complicated by massive crystalluria and acute renal failure. *J Toxicol Clin Toxicol* 2000; **38:** 667–9.
2. Meier KH, *et al.* Acute felbamate overdose with crystalluria. *Clin Toxicol* 2005; **43:** 189–92.

Precautions

Felbamate is contra-indicated in patients with a history of blood disorders or hepatic impairment. It should be used only in the treatment of severe epilepsy refractory to other antiepileptics because of the risk of fatal aplastic anaemia or acute liver failure. Patients or their carers should be advised of the symptoms of aplastic anaemia and be told to report immediately should any such symptoms develop. Complete blood counts should be carried out before the patient starts treatment and regularly during treatment (but see Epilepsy, under Uses and Administration, above). Aplastic anaemia may occur after felbamate has been stopped so patients should continue to be monitored for some time. Liver function tests are also recommended before starting and regularly (at 1- to 2-week intervals) during treatment. Felbamate should be stopped if there is any evidence of bone marrow depression or liver abnormalities.

Felbamate should be used with caution in patients with renal impairment. Felbamate may cause photosensitivity reactions and patients should be advised to take protective measures against exposure to UV radiation.

Care is required when withdrawing felbamate therapy—see also Uses and Administration, above.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

The elderly. Felbamate may need to be given with care in elderly patients (see Administration in the Elderly, above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies felbamate as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of felbamate is enhanced by enzyme inducers such as phenytoin, phenobarbital, or carbamazepine. In contrast, the half-life of felbamate may be prolonged by gabapentin. Felbamate inhibits or enhances the metabolism of several other antiepileptics and care is required when it is added to therapy.

Anticoagulants. For the effect of felbamate on *warfarin*, see p. 1532.1.

Antiepileptics. For some references to the effect of felbamate on other antiepileptics, see under *Carbamazepine*, p. 516.3, *Phenobarbital*, p. 537.2, *Phenytoin*, p. 543.2, and *Valproate* p. 557.3.

Sex hormones. For the effect of felbamate on *oral contraceptives*, see p. 2243.2 and also under Gestodene, p. 2279.3.

Pharmacokinetics

Felbamate is well absorbed from the gastrointestinal tract and peak plasma concentrations have occurred 1 to 6 hours after oral doses. Protein binding is reported to be about 22 to 25%. It is partly metabolised in the liver by hydroxylation and conjugation to inactive metabolites. Felbamate is excreted mainly in the urine as metabolites and unchanged drug (40 to 50%); less than 5% appears in the faeces. The terminal half-life is reported to be between 16 and 23 hours. Felbamate is distributed into breast milk.

The pharmacokinetics of felbamate are reported to be linear at clinical doses. Therapeutic plasma concentrations have been reported to be between 30 and 80 micrograms/mL.

The pharmacokinetics of felbamate are affected by use with other antiepileptics (see Interactions, above).

See under Uses and Administration (above) for mention of pharmacokinetic studies of felbamate in the elderly and in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Felbamyl; ***Austria***: Taloxa; ***Belg.***: Taloxa; ***Fr.***: Taloxa; ***Ger.***: Taloxa; ***Gr.***: Taloxa; ***Hung.***: Taloxa; ***Ital.***: Taloxa; ***Neth.***: Taloxa; ***Norw.***: Taloxa; ***Port.***: Taloxa; ***Swed.***: Taloxa; ***Switz.***: Taloxa; ***USA***: Felbatol.

Pharmacopoeial Preparations
USP 36: Felbamate Oral Suspension; Felbamate Tablets.

Fosphenytoin Sodium

(BANM, USAN, rINNM)

ACC-9653-010; ACC-9653; CI-982 (fosphenytoin or fosphenytoin sodium); Fosfenitoin Sodyum; Fosfenitoína sódica; Fosphénytoïne Sodique; Natrii Fosphenytoinum; PD-135711-15B; Натрий Фосфенитоин.

5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium; 3-(Hydroxymethyl)-5,5-diphenylhydantoin disodium phosphate; 2,5-Dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphate disodium.

$C_{16}H_{13}N_2Na_2O_6P$=406.2

CAS — 93390-81-9 (fosphenytoin); 92134-98-0 (fosphenytoin sodium).

ATC — N03AB05.

ATC Vet — QN03AB05.

UNII — 7VLR55452Z.

Pharmacopoeias. In *US.*

USP 36: (Fosphenytoin Sodium). A white to pale yellow solid. Freely soluble in water. pH of a 7.5% solution in water is between 8.5 and 9.5. Store in airtight containers.

Stability. References.
1. Fischer JH, *et al.* Stability of fosphenytoin sodium with intravenous solutions in glass bottles, polyvinyl chloride bags, and polypropylene syringes. *Ann Pharmacother* 1997; **31**: 553–9.

Uses and Administration

Fosphenytoin is a prodrug of phenytoin (p. 538.2) used similarly as part of the emergency treatment of status epilepticus (p. 510.2). It is also used for the prevention and treatment of post-traumatic seizures (p. 539.3) associated with neurosurgery or head trauma and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy (p. 506.1).

Fosphenytoin is given as the sodium salt and doses of fosphenytoin sodium are expressed as phenytoin sodium equivalents (PSE); therefore no adjustment in dosage is necessary when substituting fosphenytoin for phenytoin or vice versa. Fosphenytoin may be given by intramuscular injection or intravenous infusion; only the intravenous route is recommended in children.

The maximum rate of intravenous infusion in PSE is 150 mg/minute and should not be exceeded. Continuous monitoring of ECG, blood pressure, and respiratory function is recommended during intravenous infusion. Patients should also be observed for at least 30 minutes after the end of infusion.

In the treatment of tonic-clonic status epilepticus a benzodiazepine such as diazepam or lorazepam is usually given initially intravenously or rectally followed by fosphenytoin. In the UK, the loading dose in PSE is 15 mg/kg given as a single dose by intravenous infusion at a rate of 100 to 150 mg/minute. The intramuscular route is not appropriate for the management of status epilepticus because peak phenytoin concentrations will not be reached quickly enough. The loading dose for seizures other than in status epilepticus is 10 to 15 mg/kg given as a single dose by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Initial maintenance doses for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 or 2 divided doses by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given intramuscularly or by intravenous infusion at a rate of 50 to 100 mg/minute may be substituted for oral phenytoin at the same equivalent total daily dose for up to 5 days.

In the USA, loading doses in PSE of up to 20 mg/kg are permitted, and initial maintenance doses are 4 to 6 mg/kg daily.

For doses in children, see below.

A lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing may be necessary for elderly patients; UK licensed product information suggests a reduction in dose or rate of 10 to 25%. Similar reductions are suggested for patients with renal or hepatic impairment (see also below) or in those with hypoalbuminaemia, except in the treatment of status epilepticus.

References.
1. Wilder BJ, *et al.* Safety and tolerance of multiple doses of intramuscular fosphenytoin substituted for oral phenytoin in epilepsy or neurosurgery. *Arch Neurol* 1996; **53**: 764–8.
2. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. *Arch Intern Med* 1999; **159**: 2639–44.
3. Heafield MTE. Managing status epilepticus: new drug offers real advantages. *BMJ* 2000: **320**: 953–4.
4. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Safety* 2000; **22**: 459–66.
5. McCleane GJ. Intravenous infusion of fosphenytoin produces prolonged pain relief: a case report. *J Pain* 2002; **3**: 156–8.
6. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; **42**: 33–58.
7. Rudis MI, *et al.* Cost-effectiveness of oral phenytoin, intravenous phenytoin, and intravenous fosphenytoin in the emergency department. *Ann Emerg Med* 2004; **43**: 386–97.
8. Eriksson K, *et al.* Fosphenytoin. *Expert Opin Drug Metab Toxicol* 2009; **5**: 695–701.

Administration in children. In the UK, fosphenytoin sodium may be given to children over 5 years of age for the emergency treatment of status epilepticus, the prevention and treatment of post-traumatic seizures associated with neurosurgery or head trauma, and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy. It is given by intravenous infusion and doses are expressed as phenytoin sodium equivalents (PSE).

In the treatment of tonic-clonic status epilepticus, the loading dose in PSE is 15 mg/kg given as a single dose at a rate of 2 to 3 mg/kg per minute; however, the *BNFC* allows 20 mg/kg. In the treatment or prophylaxis of seizures other than in status epilepticus, the loading dose in PSE is 10 to 15 mg/kg given as a single dose at a rate of 1 to 2 mg/kg per minute. The maximum rate of infusion of loading doses is 3 mg/kg per minute or 150 mg/minute and should not be exceeded. Initial maintenance doses in PSE for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 to 4 divided doses at a rate of 1 to 2 mg/kg per minute, not exceeding 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given at a rate of 1 to 2 mg/kg per minute, not exceeding 50 to 100 mg/minute, may be substituted for oral phenytoin at equivalent total daily doses for up to 5 days.

Similar precautions to those in adults apply to the monitoring of clinical parameters and plasma-phenytoin concentrations in children (see above).

Administration in hepatic or renal impairment. The rate and extent of conversion of fosphenytoin to phenytoin in patients with hepatic cirrhosis or renal impairment requiring dialysis was not found to be significantly different from those for healthy controls.[1] However, there was a trend towards an increase in fosphenytoin clearance and a decrease in the time to peak phenytoin concentrations in those with hepatic or renal impairment. Consequently, the authors recommended that fosphenytoin may need to be given at lower doses or infused more slowly (see above for the licensed product recommendations).

1. Aweeka FT, *et al.* Pharmacokinetics of fosphenytoin in patients with hepatic or renal disease. *Epilepsia* 1999; **40**: 777–82.

Adverse Effects and Precautions

As for Phenytoin, p. 540.1.

Severe cardiovascular reactions, sometimes fatal, have been reported after intravenous doses of fosphenytoin. Therefore, continuous monitoring of ECG, blood pressure, and respiratory function is recommended during the infusion, and the patient should be kept under observation for at least 30 minutes after the end of the infusion. Hypotension may occur with recommended doses and rates of infusion; a reduction in the infusion rate or stopping therapy may be necessary. Fosphenytoin is contra-indicated in patients with sinus bradycardia, sino-atrial block, second- or third-degree AV block, or Stokes-Adams syndrome.

Burning, itching, and paraesthesia, particularly in the groin area, have also been reported after intravenous fosphenytoin; reducing the rate of, or temporarily stopping, the infusion may relieve the discomfort.

Caution should be exercised when giving fosphenytoin to patients in whom phosphate restriction is necessary. The rate of metabolism of fosphenytoin to phenytoin may be increased in patients with hepatic or renal disease, or in those with hypoalbuminaemia, and consequently there is an increased risk of adverse effects in such patients.

Effects on the cardiovascular system. The UK CSM[1] stated in May 2000 that worldwide there had been reports of 21 cases of asystole, ventricular fibrillation, or cardiac arrest associated with intravenous use of fosphenytoin. Of these, 5 cases had received doses or infusion rates greater than recommended. There had also been 34 reports of hypotension, 15 of bradycardia, and 10 of varying degrees of heart block. Most reactions had occurred within 30 minutes of the infusion. A review[2] of adverse events associated with fosphenytoin infusion received by the FDA Adverse Event Reporting System between 1997 and 2002 identified 29 of adverse cardiac events, including 10 fatalities. Of these reports, 5 were of sinus arrest, 4 of AV block, and 8 of asystole. The authors acknowledged that the majority of patients had serious confounders including renal failure, stroke, acute cardiac ischaemia or failure, overdose, or infection.

ECG changes consistent with hypocalcaemia have occurred in a patient who received 1500 mg-equivalents of phenytoin over 85 minutes as an intravenous infusion of fosphenytoin.[3] The patient had initially been normocalcaemic and it was suggested that the effect may have been due to acute inorganic phosphate toxicity.

1. CSM/MCA. Fosphenytoin sodium (Pro-Epanutin): serious arrhythmias and hypotension. *Current Problems* 2000; **26**: 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
2. Adams BD, *et al.* Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. *J Emerg Med* 2006; **30**: 75–9.
3. Keegan MT, *et al.* Hypocalcemia-like electrocardiographic changes after administration of intravenous fosphenytoin. *Mayo Clin Proc* 2002; **77**: 584–6.

Effects on the skin. For a possibly increased risk of severe skin reactions to fosphenytoin in patients with the HLA allele HLA-B*1502, see Skin Reactions, under Precautions of Phenytoin, p. 542.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fosphenytoin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Phenytoin, p. 542.1.

Pharmacokinetics

Plasma concentrations of fosphenytoin are maximal at the end of intravenous infusion and about 30 minutes after intramuscular injection. Protein binding of fosphenytoin is high (95 to 99%), mainly to albumin, and is saturable. Fosphenytoin displaces phenytoin from protein binding sites which increases the fraction of unbound phenytoin to up to 30% for about half to one hour post-infusion. Fosphenytoin is rapidly and completely hydrolysed to phenytoin with a conversion half-life of about 15 minutes; 1 mmol of fosphenytoin yields 1 mmol of phenytoin, and the same of phosphate and formate. Metabolites of phenytoin are excreted in the urine. For the pharmacokinetics of phenytoin, see p. 545.2.

References.
1. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; **42**: 33–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Cerebyx; ***Denm.***: Pro-Epanutin; ***Fin.***: Pro-Epanutin; ***Fr.***: Prodilantin; ***Gr.***: Pro-Epanutin; ***India***: Fosolin; Fosphen; ***Irl.***: Pro-Epanutin; ***Jpn***: Fostoin; ***Norw.***: Pro-Epanutin; ***Swed.***: Pro-Epanutin; ***Thai.***: Cereneu; ***UK***: Pro-Epanutin; ***USA***: Cerebyx.

Pharmacopoeial Preparations
USP 36: Fosphenytoin Sodium Injection.

Gabapentin *(BAN, USAN, rINN)*

CI-945; Gabapentiini; Gabapentina; Gabapentine; Gabapentinum; GOE-3450; Габапентин.

1-(Aminomethyl)cyclohexaneacetic acid.

$C_9H_{17}NO_2$=171.2

CAS — 60142-96-3.

ATC — N03AX12.

ATC Vet — QN03AX12.

UNII — 6CW7F3G59X.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Gabapentin). A white or almost white crystalline powder. It shows polymorphism. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

USP 36: (Gabapentin). A white to off-white, crystalline solid. Freely soluble in water and in alkaline and acidic solutions. A 2% solution in water has a pH of 6.5 to 8.0.

Gabapentin Enacarbil *(USAN, rINN)*

ASP-8825; Gabapentina Enacarbilo; Gabapentine Énacarbil; Gabapentinum Enacarbilum; GSK-1838262; XP-13512; Габапентин Энакарбил.

(1-{[{[(1*RS*)-1-{(2-Methylpropanoyl)oxy}ethoxy}carbonyl) amino]methyl}cyclohexyl)acetic acid.

$C_{16}H_{27}NO_6$=329.4

CAS — 478296-72-9.

UNII — 75OCL1SPBQ.

Uses and Administration

Gabapentin is an antiepileptic used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. It is not generally considered effective for absence seizures. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), it is neither a GABA agonist nor antagonist and its mechanism of action is unknown. Gabapentin is also used in the treatment of neuropathic pain and restless legs syndrome.

In the UK, the initial oral dose of *gabapentin* for the treatment of **epilepsy** (below) is 300 mg on the first day of treatment, 300 mg twice daily on the second day, and 300 mg three times daily on the third day; alternatively, gabapentin may be given as 300 mg three times daily on the first day of treatment. Thereafter the dose may be increased in increments of 300 mg every 2 to 3 days until effective antiepileptic control is achieved, which is usually within the range of 0.9 to 3.6 g daily. Higher doses up to a maximum of 4.8 g daily have been reported to be well tolerated. Similar doses are used in the USA. The total daily dose should be taken in three equally divided doses and the maximum dosage interval should not exceed 12 hours.

For details of doses in children, see below.

In the treatment of **neuropathic pain** (p. 525.1) in adults, doses of gabapentin should be titrated to a usual maximum of 1.8 g daily in three divided doses, in a similar manner to that recommended above for the treatment of epilepsy. Higher doses have sometimes been given. In some countries, a modified-release preparation of gabapentin is also available for once-daily dosing.

A prodrug of gabapentin, *gabapentin enacarbil*, is available as an oral modified-release preparation for use in adults. In the treatment of moderate to severe **restless legs syndrome**, 600 mg is given once daily with food at about 5 p.m. For the treatment of **postherpetic neuralgia**, an initial dose of 600 mg is given in the morning for 3 days, then increased to 600 mg twice daily. Gabapentin enacarbil is also being investigated for the treatment of painful diabetic neuropathy and for migraine prophylaxis.

As with other antiepileptics, withdrawal of gabapentin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information for gabapentin recommends reducing the dose gradually over at least 7 days regardless of indication; licensed information for gabapentin enacarbil states that doses over 600 mg daily should be tapered to 600 mg once daily before stopping. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Dosage of gabapentin and gabapentin enacarbil should be reduced in patients with renal impairment (see below).

Administration in children. In the UK, for the treatment of partial seizures with or without secondary generalisation, gabapentin is licensed for use as adjunctive therapy in children aged 6 years and over and as monotherapy in those aged 12 years and over. As *adjunctive therapy*, gabapentin may be given in an initial oral dose of 10 to 15 mg/kg daily, titrated over a period of about 3 days until effective antiepileptic control is achieved, which is usually within the range of 25 to 35 mg/kg daily given in 3 divided doses. Higher doses up to a maximum of 50 mg/kg daily have been reported to be well tolerated. Although not licensed for use in younger children, the *BNFC* suggests similar titration from an initial daily dose of 10 mg/kg in those aged 2 years and over, up to a usual maintenance dose of 30 to 70 mg/kg daily given in 3 divided doses; a maximum dose of 70 mg/kg daily has also been suggested in children aged 6 to 12 years. Older children may be given the usual adult dosage regimen (see above) titrated to a maximum of 3.6 g daily. When used as *monotherapy*, the usual adult dosage regimen is given.

In the USA, gabapentin is licensed for *adjunctive* use in children aged 3 years and over. Initial doses are as for the UK; the maintenance dose for children aged 3 to 4 years is 40 mg/kg daily, and for those aged 5 years and over is 25 to 35 mg/kg daily. Children aged 12 years and over may be given the usual adult dosage regimen (see above).

The total daily dose should be taken in 3 equally divided doses and the maximum dosage interval should not exceed 12 hours.

For a pharmacokinetic study suggesting that initial doses in younger children should be proportionately higher than in older ones, see Children, under Pharmacokinetics p. 526.2.

Administration in renal impairment. Reduced doses of *gabapentin* are recommended for patients with renal impairment or those undergoing haemodialysis. Licensed UK product information recommends the following maintenance doses based on creatinine clearance (CC) and given as 3 divided doses:

- CC 50 to 79 mL/minute: 600 to 1800 mg daily
- CC 30 to 49 mL/minute: 300 to 900 mg daily
- CC 15 to 29 mL/minute: 300 mg on alternate days to 600 mg daily
- CC less than 15 mL/minute: 300 mg on alternate days to 300 mg daily

For those undergoing haemodialysis who have never received gabapentin, the recommended loading dose is 300 to 400 mg followed by 200 to 300 mg after each 4 hours of haemodialysis. On dialysis-free days no doses of gabapentin should be given (see also Overdosage, p. 525.3).

Reduced doses are also recommended for the modified-release preparation *gabapentin enacarbil* based on indication and CC, as follows:

- **restless legs syndrome**
  - CC 30 to 59 mL/minute: 300 mg daily initially, increased to 600 mg daily, if necessary
  - CC 15 to 29 mL/minute: 300 mg daily
  - CC less than 15 mL/minute: 300 mg on alternate days
  - haemodialysis: not recommended
- **postherpetic neuralgia**
  - CC 30 to 59 mL/minute: 300 mg in the morning for the first 3 days followed by 300 mg twice daily; a further increase to 600 mg twice daily may be made
  - CC 15 to 29 mL/minute: 300 mg in the morning on days 1 and 3 followed by 300 mg daily in the morning; a further increase to 300 mg twice daily may be made
  - CC less than 15 mL/minute: 300 mg in the morning on alternate days; a further increase to 300 mg daily in the morning may be made
  - haemodialysis: 300 mg after each dialysis session, increased to 600 mg, if necessary

Ciguatera poisoning. Gabapentin has relieved some of the neurological symptoms associated with ciguatera poisoning (p. 1428.2).

Epilepsy. Gabapentin is used in epilepsy (p. 506.1) as adjunctive therapy for partial seizures with or without secondary generalisation in patients refractory to standard antiepileptics. In double-blind placebo-controlled studies[1-4] in such patients seizure frequency was reduced when gabapentin was added to treatment. Long-term efficacy has been encouraging,[5-7] and its lack of potential for interactions with other antiepileptics is considered to make it particularly suitable for adjunctive treatment. Dosage is adjusted against clinical response rather than by monitoring blood concentrations. Gabapentin is also used as monotherapy in partial epilepsy;[8-10] its efficacy as adjunctive treatment in generalised seizures remains to be determined.

Gabapentin has been found to be effective as adjunctive therapy in children with refractory partial seizures.[11]

1. UK Gabapentin Study Group. Gabapentin in partial epilepsy. *Lancet* 1990; **335:** 1114–17.
2. Sivenius J, *et al*. Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991; **32:** 539–42.
3. US Gabapentin Study Group. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993; **43:** 2292–8.
4. Anhut H, *et al*. International Gabapentin Study Group. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. *Epilepsia* 1994; **35:** 795–801.
5. US Gabapentin Study Group. The long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in drug-resistant partial epilepsy. *Epilepsy Res* 1994; **18:** 67–73.
6. Sivenius J, *et al*. Long-term study with gabapentin in patients with drug-resistant epileptic seizures. *Arch Neurol* 1994; **51:** 1047–50.
7. Anhut H, *et al*. Long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in patients with refractory partial seizures. *J Epilepsy* 1995; **8:** 44–50.
8. Ojemann LM, *et al*. Long-term treatment with gabapentin for partial epilepsy. *Epilepsy Res* 1992; **13:** 159–65.
9. Beydoun A, *et al*. Gabapentin monotherapy II: a 26-week, double-blind, dose-controlled multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily generalized seizures. *Neurology* 1997; **49:** 746–52.
10. Chadwick DW, *et al*. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. *Neurology* 1998; **51:** 1282–8.
11. Appleton R, *et al*. Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. *Epilepsia* 1999; **40:** 1147–54.

Headache. Benefit has been reported[1] from the use of gabapentin in the prophylaxis of *migraine* (p. 670.3). Gabapentin may also be effective[2,3] in the management of *cluster headache* (p. 670.1), and has been tried[4] in the prophylaxis of *chronic daily headache* and headache associated with *high-altitude disorders* (p. 1276.2).[5]

A prodrug of gabapentin, gabapentin enacarbil, is under investigation for migraine prophylaxis.

1. Mathew NT, *et al*. Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001; **41:** 119–128.
2. Leandri M, *et al*. Drug-resistant cluster headache responding to gabapentin: a pilot study. *Cephalalgia* 2001; **21:** 744–6.
3. Schuh-Hofer S, *et al*. The use of gabapentin in chronic cluster headache patients refractory to first-line therapy. *Eur J Neurol* 2007; **14:** 694–6.
4. Spira PJ, Beran RG. Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003; **61:** 1753–9.
5. Jafarian S, *et al*. Gabapentin for prevention of hypobaric hypoxia-induced headache: randomized double-blind clinical trial. *J Neurol Neurosurg Psychiatry* 2008; **79:** 321–3.

Hiccup. Gabapentin has been tried[1,2] in the treatment of hiccups. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

1. Hernández JL, *et al*. Gabapentin for intractable hiccup. *Am J Med* 2004; **117:** 279–81.
2. Alonso-Navarro H, *et al*. Refractory hiccup: successful treatment with gabapentin. *Clin Neuropharmacol* 2007; **30:** 186–7.

Hot flushes. Gabapentin appears to be of benefit in the management of hot flushes associated with treatment of breast cancer; a study involving 420 women with breast cancer experiencing hot flushes (excluding women on active chemotherapy, but most of whom were receiving adjuvant endocrine therapy), found that an oral dose of 900 mg daily in three divided doses for 8 weeks was effective, although a dose of 300 mg daily was not.[1]

There is also evidence of benefit[2,3] from gabapentin in the same dose (900 mg daily) in women who have hot flushes as a symptom of the menopause (p. 2245.1). Another randomised placebo-controlled study[4] found gabapentin 2.4 g daily to be as effective as conjugated oestrogens 625 micrograms daily in the treatment of hot flushes in postmenopausal women. A meta-analysis[5] concluded that gabapentin resulted in a 20 to 30% reduction in the frequency and severity of hot flushes in women with natural or chemotherapy-induced menopause, although this was at the price of adverse effects such as dizziness and somnolence which resulted in many women withdrawing from treatment. A later literature review[6] of randomised controlled studies found gabapentin to be safe and effective for short-term (12 weeks or less) therapy of menopausal hot flushes; an initial dose of 300 to 400 mg at night, increased as required every 3 to 7 days to a usual dose of 0.6 to 2.4 g daily in 2 or 3 divided doses was suggested for women with natural menopause who are having moderate to severe hot flushes.

1. Pandya KJ, *et al*. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005; **366:** 818–24.
2. Guttuso T, *et al*. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *ObstetGynecol* 2003; **101:** 337–45.
3. Loprinzi CL, *et al*. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. *J Clin Oncol* 2007; **25:** 308–12.
4. Reddy SY, *et al*. Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol* 2006; **108:** 41–8.
5. Toulis KA, *et al*. Gabapentin for the treatment of hot flashes in women with natural or tamoxifen-induced menopause: a systematic review and meta-analysis. *Clin Ther* 2009; **31:** 221–35.
6. Hayes LP, *et al*. Use of gabapentin for the management of natural or surgical menopausal hot flashes. *Ann Pharmacother* 2011; **45:** 388–94.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p. 1047.1) has been reported to improve in those given antiepileptics such as gabapentin.[1]

1. McManaman J, Tam DA. Gabapentin for self-injurious behavior in Lesch-Nyhan syndrome. *Pediatr Neurol* 1999; **20:** 381–2.

Motor neurone disease. Interest has been shown in gabapentin as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) because it may inhibit glutamate formation. Results from an early study[1] showed a trend towards a beneficial effect; however, a randomised study[2] failed to confirm any benefit from gabapentin on disease progression or symptoms.

1. Miller RG, *et al*. Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 1996; **47:** 1383–8.
2. Miller RG, *et al*. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001; **56:** 843–8.

Multiple sclerosis. Gabapentin has been found to control pain, spasm, and spasticity in patients with multiple sclerosis (p. 996.3).[1-6] It may also be of benefit in acquired nystagmus secondary to multiple sclerosis.[7]

1. Mueller ME, *et al*. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Arch Phys Med Rehabil* 1997; **78:** 521–4.
2. Samkoff LM, *et al*. Amelioration of refractory dysesthetic limb pain in multiple sclerosis by gabapentin. *Neurology* 1997; **49:** 304–5.
3. Solaro C, *et al*. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998; **51:** 609–11.
4. Dunevsky A, Perel AB. Gabapentin for relief of spasticity associated with multiple sclerosis. *Am J Phys Med Rehabil* 1998; **77:** 451–4.

5. Cutter NC, *et al.* Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. *Arch Phys Med Rehabil* 2000; **81:** 164–9.
6. Solaro C, *et al.* Gabapentin is effective in treating nocturnal painful spasms in multiple sclerosis. *Multiple Sclerosis* 2000; **6:** 192–3.
7. Shery T, *et al.* The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. *Br J Ophthalmol* 2006; **90:** 839–43.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p. 4.2). Gabapentin is used in the treatment of neuropathic pain,[1-5] including central pain[6] (p. 7.3), complex regional pain syndrome (p. 8.1), postherpetic neuralgia[7-9] (p. 10.3), trigeminal neuralgia (p. 11.2), and painful diabetic neuropathy[10,11] (p. 8.2). There is also interest in its use for postoperative pain (see below).

In a small study of patients with diabetic polyneuropathy or postherpetic neuralgia, gabapentin given with nortriptyline was more effective than use of either alone for control of neuropathic pain.[12]

A prodrug of gabapentin, gabapentin enacarbil, is used in the treatment of postherpetic neuralgia[13] and is under investigation for the treatment of painful diabetic neuropathy.

1. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002; **57:** 451–62.
2. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther* 2003; **25:** 81–104.
3. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. *Curr Opin Anaesthesiol* 2007; **20:** 456–72.
4. Tzellos TG, *et al.* Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. *Eur J Clin Pharmacol* 2008; **64:** 851–8.
5. Moore RA, *et al.* Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 11/07/12).
6. Schachter SC, Sauter MK. Treatment of central pain with gabapentin: case reports. *J Epilepsy* 1996; **9:** 223–5.
7. Rowbotham M, *et al.* Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998; **280:** 1837–42.
8. Rice ASC, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001; **94:** 215–24.
9. Singh D, Kennedy DH. The use of gabapentin for the treatment of postherpetic neuralgia. *Clin Ther* 2003; **25:** 852–89.
10. Backonja M, *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998; **280:** 1831–6.
11. Morello CM, *et al.* Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999; **159:** 1931–7.
12. Gilron I, *et al.* Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 2009; **374:** 1252–61.
13. Backonja MM, *et al.* Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin. *Pain Med* 2011; **12:** 1098–1108.

Parkinsonism. While some overall ratings of Parkinson's disease (p. 889.1) appeared to be improved by gabapentin in a double-blind study involving 19 patients with advanced parkinsonism, improvements in individual signs and symptoms were not significant.[1] It was also reported that 5 of 6 other patients with progressive supranuclear palsy had experienced worsening of their disease when given gabapentin. Another study[2] in 15 patients with motor complications failed to find any clinically significant benefit from gabapentin therapy.

1. Olson WL, *et al.* Gabapentin for parkinsonism: a double-blind, placebo-controlled, crossover trial. *Am J Med* 1997; **102:** 60–6.
2. Van Blercom N, *et al.* Effects of gabapentin on the motor response to levodopa: a double-blind, placebo-controlled, crossover study in patients with complicated Parkinson disease. *Clin Neuropharmacol* 2004; **27:** 124–8.

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as gabapentin to modulate opioid dosage and efficacy for postoperative pain (p. 6.1).[1,2] A systematic review of 4 unpublished studies found a single oral dose of gabapentin 250 mg to be statistically superior to placebo in the treatment of acute postoperative pain; however, it was considered to be of limited clinical value and inferior to other commonly used analgesics.[3] Nevertheless, another systematic review found that perioperative use of gabapentin effectively reduced opioid consumption and postoperative pain; further studies were considered warranted.[4] It has been suggested that perioperative use of gabapentin may have other benefits, including pre-operative anxiolysis, attenuation of the haemodynamic response to intubation, and reduction in postoperative nausea and vomiting.[5]

1. Dahl JB, *et al.* Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48:** 1130–6.
2. Dauri M, *et al.* Gabapentin and pregabalin for the acute post-operative pain management: a systematic-narrative review of the recent clinical evidences. *Curr Drug Targets* 2009; **10:** 716–33.
3. Straube S, *et al.* Single dose oral gabapentin for established acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 12/07/12).
4. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104:** 1545–56.
5. Kong VKF, Irwin MG. Gabapentin: a multimodal perioperative drug? *Br J Anaesth* 2007; **99:** 775–86.

Psychiatric disorders. Gabapentin has psychotropic properties and has been tried in the management of several psychiatric disorders, including as an adjunct in the treatment of resistant *depression*[1] (p. 398.1) and in the treatment of *post-traumatic stress disorder*[2] (p. 1029.2). Although early open studies[3] found that gabapentin may be of benefit in patients with *bipolar disorder* (p. 397.2) randomised controlled studies have so far failed to confirm this effect.[4-6] Gabapentin is under investigation for the treatment of *social anxiety disorder* (see Phobic Disorders, p. 1029.1).

1. Yasmin S, *et al.* Adjunctive gabapentin in treatment-resistant depression: a retrospective chart review. *J Affect Disord* 2001; **63:** 243–7.
2. Malek-Ahmadi P. Gabapentin and posttraumatic stress disorder. *Ann Pharmacother* 2003; **37:** 664–6.
3. Maidment ID. Gabapentin treatment for bipolar disorders. *Ann Pharmacother* 2001; **35:** 1264–9.
4. Pande AC, *et al.* Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord* 2000; **2:** 249–55.
5. Frye MA, *et al.* A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; **20:** 607–14.
6. Vieta E, *et al.* A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry* 2006; **67:** 473–7.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has been largely empirical. Two small randomised double-blind crossover studies[1,2] found 6 weeks of treatment with gabapentin to produce improvement in symptoms; in patients undergoing haemodialysis the effects were seen with a dose of 300 mg after each of the 3 dialysis sessions per week,[1] although in patients with idiopathic disease the mean effective dose was 1.855 g daily.[2]

A prodrug of gabapentin, gabapentin enacarbil, is licensed for the treatment of restless legs syndrome in adults.[3]

1. Thorp ML, *et al.* A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis* 2001; **38:** 104–8.
2. Garcia-Borreguero D, *et al.* Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* 2002; **59:** 1573–9.
3. Hayes WJ, *et al.* Gabapentin enacarbil for treatment of restless legs syndrome in adults. *Ann Pharmacother* 2012; **46:** 229–39.

Soft-tissue rheumatism. Gabapentin may be of benefit in some patients with fibromyalgia (p. 14.2). In a randomised controlled study treatment with oral gabapentin 1.2 to 2.4 g daily in 75 patients produced a greater improvement in mean pain score over 12 weeks than placebo in 75 controls.[1] Sleep problems were also improved, but there was no difference between the groups in a depression rating scale. The drug was generally well tolerated. A meta-analysis[2] of this and 4 further studies confirmed the apparent benefits of gabapentin in reducing pain and improving sleep, but again showed no effect on depression, or anxiety or fatigue.

1. Arnold LM, *et al.* Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007; **56:** 1336–44.
2. Häuser W, *et al.* Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain* 2009; **145:** 69–81.

Stiff-man syndrome. Gabapentin may improve the symptoms of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) in patients unable to tolerate benzodiazepine therapy.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p. 1318.3); however, gabapentin has also been tried with some success.[1-3]

1. Gironell A, *et al.* A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch Neurol* 1999; **56:** 475–80.
2. Ondo W, *et al.* Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. *Mov Disord* 2000; **15:** 678–82.
3. Faulkner MA, *et al.* Gabapentin for the treatment of tremor. *Ann Pharmacother* 2003; **37:** 282–6.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with gabapentin are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, rhinitis, dysarthria, nausea and vomiting, weight gain, oedema, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, myalgia, headache, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently. Rarely, pancreatitis, altered liver function tests, erythema multiforme, Stevens-Johnson syndrome, and blood glucose fluctuations in diabetics have been reported. Common psychiatric effects include confusion, depression, and nervousness, and, more rarely, hallucinations and psychoses. Other adverse effects include acute renal failure, allergic reactions, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, and tinnitus.

An antiepileptic hypersensitivity syndrome, comprising fever, rash, eosinophilia, and lymphadenopathy, along with other organ involvement such as hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis, has been associated with some antiepileptic drugs including gabapentin. Early manifestations, such as fever and/or lymphadenopathy, may be present without evident rash; patients with such signs or symptoms should be evaluated immediately and therapy stopped in the absence of a clear aetiology.

Overdosage of gabapentin, particularly in combination with other CNS depressants, may result in coma (see also below).

Gabapentin should be used with caution in patients with renal impairment and in those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin.

Care is required when withdrawing gabapentin therapy—see also Uses and Administration, p. 524.1.

Incidence of adverse effects. A postmarketing surveillance study[1] of 3100 patients taking gabapentin identified drowsiness or sedation as the most frequent adverse effect, occurring in about 6.7%. The incidences of other adverse effects were: headache, 3.6%; fatigue, 3.5%; nausea and vomiting, 2.6%; and dizziness, 2.4%. Less common adverse events included rash, visual defect, and ataxia. Overall, adverse effects were reported as the reason for stopping treatment in about 10% of patients. In the 136 children aged under 12 years whose data were included in the study, the most frequently reported treatment-related adverse events were eczema, rash, and vomiting. In this study, none of the 11 infants born to mothers taking gabapentin throughout pregnancy had congenital abnormalities.

1. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002; **43:** 983–92.

Breast feeding. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, p. 526.2.

For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Carcinogenicity. It had been reported[1] that studies on gabapentin had been temporarily stopped in 1990 when pancreatic tumours were seen in *rodent* studies. However, the tumours were benign, occurred only with large doses, and were not thought to relate to humans.

1. Ramsay RE. Clinical efficacy and safety of gabapentin. *Neurology* 1994; **44** (suppl 5): S23–S30.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on bone. For the effects of antiepileptics, including gabapentin, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the liver. A report[1] of a patient who developed cholestatic jaundice 2 weeks after starting therapy with gabapentin 300 mg three times daily for diabetic neuropathy. Clinical symptoms and liver function tests improved on withdrawal of gabapentin.

1. Richardson CE, *et al.* Gabapentin induced cholestasis. *BMJ* 2002; **325:** 635.

Effects on mental function. For a review of the effects of antiepileptic therapy including gabapentin on *cognition*, and on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on skeletal muscle. A report[1] of rhabdomyolysis with myoglobinuria and acute renal impairment associated with gabapentin use in a diabetic patient. Resolution gradually occurred on stopping the drug.

1. Bilgir O, *et al.* Gabapentin-induced rhabdomyolysis in a patient with diabetic neuropathy. *Intern Med* 2009; **48:** 1085–7.

Effects on the skin. For a suggestion that skin reactions are less common with gabapentin than with some other antiepileptics, see under Phenytoin, p. 541.1.

Overdosage. A 16-year-old girl complained of dizziness 6 hours after ingesting 48.9 g of gabapentin and was lethargic but arousable 2 hours later.[1] Her gabapentin plasma concentration was 62 micrograms/mL 8.5 hours after ingestion. By 18 hours she was alert and had no further complaints of lethargy or dizziness. In another report[2] a patient with renal failure inadvertently received inappro-

priately high doses of gabapentin for 3 weeks and had a serum gabapentin concentration of 85 micrograms/mL without serious adverse effects. However, a patient with end-stage renal disease who twice took extra doses of gabapentin between haemodialysis sessions developed marked somnolence and hypoxia severe enough to require intubation on both occasions; haemodialysis produced rapid improvement.[3] A prospective observational study[4] of gabapentin exposures reported to 3 poison centers has described a case series of 20 patients who took from 50 mg to 35 g of gabapentin alone. Of these, 12 had clinical symptoms including drowsiness, dizziness, gastrointestinal disturbance, hypotension, and mild tachycardia. These effects developed in under 5 hours and lasted for less than 24 hours; toxicity was generally mild and there were no fatalities.

1. Fischer JH, *et al.* Lack of serious toxicity following gabapentin overdose. *Neurology* 1994; **44:** 982–3.
2. Verma A, *et al.* A case of sustained massive gabapentin overdose without serious side effects. *Ther Drug Monit* 1999; **21:** 615–17.
3. Jones H, *et al.* Gabapentin toxicity requiring intubation in a patient receiving long-term hemodialysis. *Ann Intern Med* 2002; **137:** 74.
4. Klein-Schwartz W, *et al.* Characterization of gabapentin overdose using a poison center case series. *J Toxicol Clin Toxicol* 2003; **41:** 11–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gabapentin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

For comments on the management of epilepsy during pregnancy, see p. 509.2.

Withdrawal. Withdrawal symptoms, including akathisia, anxiety, confusion, diaphoresis, headache, and palpitations, have been reported[1-3] after abrupt withdrawal of gabapentin. A withdrawal syndrome with flu-like symptoms has also been reported[4] after gradual withdrawal over 1 week. A literature search[3] found 10 case reports with symptoms that occurred from 12 hours to 3 days after stopping gabapentin and generally resolved on restarting; patients had been taking doses that ranged from 0.4 to 8 g daily for durations of 3 weeks to 5 years.

1. Hellwig TR, *et al.* Withdrawal symptoms after gabapentin discontinuation. *Am J Health-Syst Pharm* 2010; **67:** 910–12.
2. Finch CK, *et al.* Gabapentin withdrawal syndrome in a post-liver transplant patient. *J Pain Palliat Care Pharmacother* 2010; **24:** 236–8.
3. See S, *et al.* Akathisia induced by gabapentin withdrawal. *Ann Pharmacother* 2011; **45:** e31.
4. Tran KT, *et al.* Gabapentin withdrawal syndrome in the presence of a taper. *Bipolar Disord* 2005; **7:** 302–4.

Interactions

The absorption of gabapentin from the gastrointestinal tract is reduced by antacids containing aluminium with magnesium; it is recommended that gabapentin is taken at least 2 hours after any such antacid. Morphine has been reported to reduce the clearance of gabapentin; patients receiving both drugs should be monitored for signs of CNS depression and doses should be reduced accordingly. Cimetidine has also been reported to reduce the renal clearance of gabapentin but licensed product information does not consider this to be of clinical importance. For references to possible interactions with other antiepileptics, see under Phenytoin, p. 543.2 and under Felbamate, p. 522.3.

Pharmacokinetics

Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. After multiple dosing peak plasma concentrations usually occur within 2 to 3 hours of a dose and a steady state within 1 to 2 days. When given as its prodrug, gabapentin enacarbil, peak plasma concentrations are reached in 5 hours in fasted subjects and 7.3 hours in fed subjects; the bioavailability of gabapentin from its prodrug is increased when given with food, particularly meals high in fat.

Gabapentin enacarbil undergoes extensive first-pass metabolism, mainly in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid; blood levels of the enacarbil are low and transient. Gabapentin itself is not appreciably metabolised and most of a dose is excreted unchanged in the urine with the remainder appearing in the faeces. Gabapentin is widely distributed throughout the body but binding to plasma proteins is minimal. The elimination half-life has been reported to be about 5 to 7 hours. Gabapentin is distributed into breast milk.

References.

1. Blum RA, *et al.* Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther* 1994; **56:** 154–9.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Berry DJ, *et al.* The absorption of gabapentin following high dose escalation. *Seizure* 2003; **12:** 28–36.
4. Cundy KC, *et al.* Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. *J Clin Pharmacol* 2008; **48:** 1378–88.
5. Chen C, *et al.* Pharmacokinetics of gabapentin in a novel gastric-retentive extended-release formulation: comparison with an immediate-release formulation and effect of dose escalation and food. *J Clin Pharmacol* 2011; **51:** 346–58.
6. Lal R, *et al.* Clinical pharmacokinetics of gabapentin after administration of gabapentin enacarbil extended-release tablets in patients with varying degrees of renal function using data from an open-label, single-dose pharmacokinetic study. *Clin Ther* 2012; **34:** 201–13.

Children. A study[1] of the pharmacokinetics of single doses of gabapentin in healthy children aged 1 month to 12 years found that peak plasma concentrations occurred 2 to 3 hours after the dose in all age groups but that the mean value was higher in those older than 5 years than in younger children, and the exposure was calculated to be about 30% less in the younger age group. As a result it was suggested that the initial dose of gabapentin in studies of safety and efficacy should be 40 mg/kg daily in children aged from 1 month up to 5 years, and 30 mg/kg daily in children aged 5 to 12 years. (For licensed doses, see Administration in Children, p. 524.1.) A pharmacokinetics study[2] in children with uncontrolled seizures (aged from 3 to about 15 years) also found a markedly higher mean oral clearance of gabapentin when compared with adults.

1. Haig GM, *et al.* Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. *J Clin Pharmacol* 2001; **41:** 507–14.
2. Tallian KB, *et al.* Pharmacokinetics of gabapentin in paediatric patients with uncontrolled seizures. *J Clin Pharm Ther* 2004; **29:** 511–15.

Pregnancy and breast feeding. The pharmacokinetics of gabapentin were studied[1] in 6 women, and in their offspring, during pregnancy, delivery, and breast feeding. Findings suggested that gabapentin is actively transported across the placenta and accumulates in the fetus although its effect was unclear. All the deliveries, including one preterm, were uneventful and all of the infants were healthy, apart from one who became cyanosed and mildly hypotonic 8 hours after birth.

The distribution of gabapentin into breast milk was extensive and neonates were found to have a lower capacity to eliminate gabapentin than adults, with an elimination half-life of about 14 hours. However, the plasma concentrations in the breast-fed infants appeared to be low and the relative infant dose was estimated to be 1.3 to 3.8% of the mothers' weight-adjusted dose at 0.2 to 1.3 mg/kg daily. No adverse effects were reported in the infants, and the authors considered that gabapentin was generally safe during breast feeding.

1. Öhman I, *et al.* Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia* 2005; **46:** 1621–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abaglin; Alidial; Elifer; Logistic; Neurontin; Ultraneural; ***Austral.***: Gabahexal†; Gabaran; Gabatine; Gantin; Neurontin; Nupentin; Pendine†; ***Austria***: Gabatal; Neurontin; ***Belg.***: Neurontin; ***Braz.***: Gabaneurin; Neurontin; Progresse; ***Canad.***: Neurontin; ***Chile***: Dineurin; Gabacross; Gabex; Gabictal; Neugabin†; Normatol; Ritmenal; ***China***: Die Li (迭力); Neurontin (纽诺汀); Pai Ting (派汀); Wei Nuo Ding (维诺定); ***Cz.***: Apo-Gab; Gabagamma; Gabalept†; Gabanox; Gabatem; Gabator; Gabenta†; Gordius; Grimodin; Neurontin; Nurabax†; ***Denm.***: Gabadoz; Gabalept; Gabalix; Gabamed; Gabanicht; Gabaratio; Gabatifin; Neuril; Neurontin; Pentagab; ***Fin.***: Gabrion; Neurontin; ***Fr.***: Neurontin; ***Ger.***: Gabagamma; GabaLich; Gabax; Neurontin; ***Gr.***: Belgabin; Brilian; Gabantin; Gabapen; Gabaront; Gabental; Gabiton; Gapenten; Medivapom; Neurontin; Neuros; Pentin; Peronten; Seni-Ven; ***Hong Kong***: Gabenil; Neurontin; ***Hung.***: Gabagamma; Gordius; Grimodin; Neuroba; Neurontin; ***India***: Encentin; Gaba; Gabacap; Gabacent; Gabalept; Gabantin; Gabapin; Gabata; Gabatin; Gabator; Gaby; Gentin; Goben; Mygaba; Neogaba; Neupent AF; Neurontin; ***Indon.***: Alpentin; Epiven; Gabexal; Galepsi; Ganin; Nepatic; Neurontin; Repligen; Sipentin; Tineuron; ***Irl.***: Gabin; Gabture; Neurontin; Neurostil; Rangabax; ***Israel***: Neurontin; ***Ital.***: Apentin; Gabexine; Neurontin; Semerial†; Yalipent†; ***Jpn***: Gabapen; Regnite; ***Malaysia***: Neurontin; ***Mex.***: Aconeuba; Bapex; Blugat; Clozepaxel; Compulxine†; Gabantin; Gapridol; Microleptin; Neurontin; Nopatic; Nyepzyl; Wermy; ***Neth.***: Neurontin; ***Norw.***: Neurontin; ***NZ***: Neurontin; Nupentin; ***Philipp.***: Calmpent; Gabalept; Gabatin; Gabatrex; Gabix; Gonnaz; Neurontin; Reinin; ***Pol.***: Gabagamma; Gabatem; Gabax†; Neuran; Neurontin; Symleptic; ***Port.***: Anabix†; Aneptir; Gabacalma; Gabamox; Mengaptrix†; Molnarux; Neurontin; ***Rus.***: Convalis (Конвалис); Gabagamma (Габагамма); Gapentek (Гапентек); Katena (Катэна); Lepsitin (Лепситин); Neurontin (Нейронтин); Tebantin (Тебантин); ***S.Afr.***: Epleptin; Neurexal; Neurontin; ***Singapore***: Neurontin; Nupentin; ***Spain***: Equipax†; Gabamerck†; Gabatur; Gabmylan†; Neurontin; ***Swed.***: Neurontin; ***Switz.***: Gabantine; Neurontin; ***Thai.***: Gabantin; Gabutin; Neurontin; Neverpentin; Rontin; Vultin; ***Turk.***: Gabaset; Gabateva; Gabtin; Nepitin; Neruda; Neurontin; ***UK***: Neurontin; ***Ukr.***: Gabagamma (Габагамма); Gabalept (Габалепт); Gabantin (Габантин); Gatonin (Гатонин)†; Meditan (Медитан); Tebantin (Тебантин); ***USA***: Gabarone; Gralise; Horizant; Neurontin; ***Venez.***: Neurontin.

Multi-ingredient Preparations. ***India***: Alcobal; Alnacob-G; Armet G; Bigvin Forte; Capin-G; Chiny-GP; Cobalvit-GT; Cobanerve-G; Cobaver-M; Cobsa-G; Doloneuron; Electa-GP; Encentin Plus; Encentin-AM; Encentin-M; G-Care; G-Neuro; Gaba-MC; Gabafact; Gabaneuron; Gabanez-M; Gabapentin Forte; Gabastar M; Gabator M; Gabaz; Gabil; Gabin-M; Gabion-M; Gabsoft-M; Game; Gamet; GBN-M; Gelina-M; Gentin-MC; Gibi Forte; Gic-M; Hyteron-M; Indcobal; Magic-M; Malzix-GB; Marinol-GB; Me-Gab; Mecobal-GB; Mecoday-G; Mecoriv-G; Melife-G; Mericobal-G; Methipas-GP; Mewin-GB; Miko G; Mokia-G; Motrin GB; Mycovit-GB; Nervic-G; Nervicin-G; Nervimax-G; Nervon-GM; Nervoptin; Nervuptin; Nervz-G; Nerwin-GT; Neuro-GM; Neuroage GF; Neurocap-G; Neurogab; Neuromas-G; Neuromed-GF; Neuropill; Neurotop-G; Nexcob-G; Novomine-GB; NTOmec-G; Nuroclad-GB; Nurokind-G; Nuthyl-GB; Orogab-M; ***Mex.***: Gavindo; Tremecox; Tremepen.

Pharmacopoeial Preparations

USP 36: Gabapentin Capsules; Gabapentin Tablets.

Lacosamide *(BAN, USAN, rINN)*

ADD-234037; Erlosamida; Erlosamide; Erlosamidum; Harkoseride; Lacosamida; Lacosamidum; SPM-927; Эрлозамид.

(*2R*)-2-(Acetylamino)-*N*-benzyl-3-methoxypropanamide.

$C_{13}H_{18}N_2O_3$=250.3

CAS — 175481-36-4.

ATC — N03AX18.

ATC Vet — QN03AX18.

UNII — 563KS2PQY5.

Uses and Administration

Lacosamide is an antiepileptic used as adjunctive therapy in partial seizures with or without secondary generalisation (below) in patients aged 16 years and older.

The initial oral dose of lacosamide is 100 mg daily, increased to 200 mg daily after 1 week. Further weekly increments of 100 mg may be given, according to response and tolerability, to a maximum daily dose of 400 mg. The total daily dose of lacosamide should be given in 2 equally divided doses.

When oral use is not feasible, lacosamide may be given by intravenous infusion over 15 to 60 minutes in the same doses as those used orally. Licensed product information states that there is experience with the use of intravenous lacosamide for up to 5 days.

Reduced doses are recommended by some authorities in patients with hepatic and severe renal impairment (see below).

As with other antiepileptics, withdrawal of lacosamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the dose of lacosamide by 200 mg each week. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Lacosamide is also being studied for use in fibromyalgia, osteoarthritis, and migraine prophylaxis.

Administration in hepatic impairment. Although UK licensed product information states that no dosage adjustment of lacosamide is needed for patients with mild to moderate hepatic impairment, US licensed information suggests a maximum dose of 300 mg daily orally or by intravenous infusion; use in severe impairment is not recommended due to lack of data.

Administration in renal impairment. In patients with severe renal impairment (creatinine clearance of 30 mL/min or less) and in those with end-stage renal disease, UK licensed product information recommends a maximum daily dose of lacosamide 250 mg orally or by intravenous infusion whereas US licensed information recommends a maximum dose of 300 mg daily.

In patients undergoing haemodialysis a supplemental dose of up to 50% of the morning dose should be given at the end of the procedure.

Epilepsy. Lacosamide is used in the treatment of epilepsy (p. 506.1) as adjunctive therapy for partial seizures with or without secondary generalisation. It has also been investigated as a second-line drug in status epilepticus.

References.

1. Doty P, *et al.* Lacosamide. *Neurotherapeutics* 2007; **4:** 145–8.
2. Ben-Menachem E, *et al.* Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; **48:** 1308–17.
3. Biton V, *et al.* Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. *Epilepsia* 2008; **49:** 418–24.
4. Cross SA, Curran MP. Lacosamide: in partial-onset seizures. *Drugs* 2009; **69:** 449–59.

5. Wehner T, *et al.* Six months of postmarketing experience with adjunctive lacosamide in patients with pharmacoresistant focal epilepsy at a tertiary epilepsy center in Germany. *Epilepsy Behav* 2009; **16:** 423–5.
6. Kellinghaus C. Lacosamide as treatment for partial epilepsy: mechanisms of action, pharmacology, effects, and safety. *Ther Clin Risk Manag* 2009; **5:** 757–66.
7. Kellinghaus C, *et al.* Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first-line therapy. *Epilepsy Behav* 2009; **14:** 429–31.

Neuropathic pain. Lacosamide is being studied in the management of neuropathic pain[1-3] but its role, if any, remains to be established.[4]

1. Wymer JP, *et al.* Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. *Clin J Pain* 2009; **25:** 376–85.
2. Shaibani A, *et al.* Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial. *J Pain* 2009; **10:** 818–28.
3. Ziegler D, *et al.* Efficacy and safety of lacosamide in painful diabetic neuropathy. *Diabetes Care* 2010; **33:** 839–41.
4. McCleane G. Lacosamide for pain. *Expert Opin Invest Drugs* 2010; **19:** 1129–34.

Adverse Effects and Precautions

The most frequently reported adverse effects with lacosamide are usually mild to moderate in severity, and include dizziness, headache, nausea, and diplopia. Other commonly reported adverse effects include depression, CNS disorders such as abnormal coordination, memory impairment, somnolence, tremor, and nystagmus, blurred vision, vertigo, gastrointestinal disorders such as vomiting, constipation, and flatulence, pruritus, gait disturbance, asthenia, and fatigue. The incidence and severity of CNS and gastrointestinal disorders usually decrease over time.

Lacosamide has been associated with a dose-related increase in the PR interval, and should be used with caution in patients with cardiac conduction disorders or severe cardiac disease such as a history of myocardial infarction or heart failure. It is contra-indicated in those with second- or third-degree AV block.

Doses of lacosamide should be titrated cautiously in patients with renal impairment.

Care is required when withdrawing lacosamide therapy—see also Uses and Administration, p. 526.3.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lacosamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Lacosamide plasma concentrations may be reduced by carbamazepine, phenytoin, and phenobarbital.

Systemic exposure to lacosamide may be reduced by strong inducers of cytochrome P450 isoenzymes such as rifampicin or St John's wort. Lacosamide should be used with caution in patients also receiving other drugs that prolong the PR interval, and with class I antiarrhythmics.

Pharmacokinetics

Lacosamide is quickly and completely absorbed after oral doses. The oral bioavailability is about 100% and peak plasma concentrations occur within 4 hours. Steady state is achieved after 3 days. About 95% of a dose is excreted in the urine, about 40% as unchanged drug and less than 30% as the inactive *O*-desmethyl metabolite. Less than 0.5% of a dose is excreted in the faeces. The elimination half-life of lacosamide is about 13 hours. Lacosamide is removed by haemodialysis.

The pharmacokinetics of lacosamide are affected by use with other antiepileptics (see Interactions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vimpat; ***Austral.***: Vimpat; ***Austria***: Vimpat; ***Belg.***: Vimpat; ***Canad.***: Vimpat; ***Cz.***: Vimpat; ***Denm.***: Vimpat; ***Fr.***: Vimpat; ***Ger.***: Vimpat; ***Gr.***: Vimpat; ***Irl.***: Vimpat; ***Israel***: Vimpat; ***Neth.***: Vimpat; ***Norw.***: Vimpat; ***NZ***: Vimpat; ***Pol.***: Vimpat; ***Port.***: Vimpat; ***Rus.***: Vimpat (Вимпат); ***Spain***: Vimpat; ***Swed.***: Vimpat; ***Switz.***: Vimpat; ***UK***: Vimpat; ***Ukr.***: Vimpat (Вимпат); ***USA***: Vimpat.

Lamotrigine *(BAN, USAN, rINN)*

BW-430C; Lamotrigiini; Lamotrigin; Lamotrigina; Lamotriginum; Lamotrijin; Ламотригин.

6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diyldiamine.

$C_9H_7Cl_2N_5$=256.1

CAS — 84057-84-1.

ATC — N03AX09.

ATC Vet — QN03AX09.

UNII — U3H27498KS.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lamotrigine). A white or almost white powder. Very slightly soluble in water; slightly soluble in dehydrated alcohol.

USP 36: (Lamotrigine). A white to pale cream-coloured powder. Slightly soluble in water, in methyl alcohol, in 0.1N hydrochloric acid, and in acetone. Store in airtight containers.

Uses and Administration

Lamotrigine, a phenyltriazine compound, is an antiepileptic used mainly for monotherapy or adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures. It may be used for seizures associated with the Lennox-Gastaut syndrome and for the maintenance treatment of bipolar disorder.

The doses given below for the use of lamotrigine in **epilepsy** (p. 528.1) are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- The initial oral dose for use as *monotherapy* is 25 mg once daily for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily.
- In those taking lamotrigine as an *adjunct* to therapy but *not taking valproate or enzyme-inducing or -inhibiting antiepileptics* the dosage regimen is as for monotherapy.
- The initial oral dose of lamotrigine for use as an adjunct to therapy *with enzyme-inducing antiepileptics* (but *not with valproate*) is 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks; thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily.
- In those *taking valproate* (and regardless of any other concomitant drugs) the initial oral dose of lamotrigine is 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses.

If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate. For comment on the need to modify maintenance doses when starting or stopping oral contraceptives, see Sex Hormones, under Interactions, p. 530.2.

For doses in children, see below.

In the management of **bipolar disorder** (below), the target dose of lamotrigine is 200 mg daily as *monotherapy*; for patients *taking valproate* the target dose is 100 mg daily and in those taking enzyme-inducing drugs (but *not with valproate*) the target dose is 400 mg daily. Lamotrigine should be started at a reduced dose and increased gradually to the target dose in a regimen similar to that used in the treatment of epilepsy (see above).

Doses should be reduced in patients with hepatic impairment regardless of indication (see below).

As with other antiepileptics, withdrawal of lamotrigine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1. In patients with epilepsy the withdrawal of lamotrigine should be tapered over at least 2 weeks. A step-wise reduction is also suggested when lamotrigine is stopped in patients with bipolar disorder although a more abrupt withdrawal may be considered if there are safety concerns.

Administration in children. Lamotrigine is used as an adjunct in the treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures in children aged 2 to 12 years; it is also used as monotherapy for typical absence seizures in children aged 2 to 12 years. Lamotrigine may also be used for seizures associated with the Lennox-Gastaut syndrome.

The doses given below are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- The initial oral dose of lamotrigine for use as *monotherapy* in typical absence seizures, given as a single dose or in 2 divided doses, is 300 micrograms/kg daily for 2 weeks, followed by 600 micrograms/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 600 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 10 mg/kg daily. Some patients have required up to 15 mg/kg daily.
- In those taking lamotrigine as an *adjunct* to therapy but *not taking valproate or enzyme-inducing or -inhibiting antiepileptics* the initial oral dose of lamotrigine, given as a single dose or in 2 divided doses, is 300 micrograms/kg daily for 2 weeks, followed by 600 micrograms/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 600 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 10 mg/kg daily. The maximum dose is 200 mg daily.
- In those *taking enzyme-inducing antiepileptics* (but *not with valproate*) the initial oral dose of lamotrigine is 600 micrograms/kg daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily, given as a single dose or in 2 divided doses. The maximum dose is 400 mg daily.
- In those *taking valproate* the initial oral dose of lamotrigine is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg daily, given as a single dose or in 2 divided doses. The maximum dose is 200 mg daily.
- In those taking lamotrigine as adjunctive therapy with drugs where it is not known if an interaction may occur, the doses as recommended for lamotrigine with concurrent valproate should be used.

If the calculated daily dose of lamotrigine lies between 1 and 2 mg, then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be given if the calculated daily dose is less than 1 mg.

The use and doses of lamotrigine in children over 12 years of age is as for adults (see above).

Administration in hepatic impairment. UK licensed product information for lamotrigine recommends that doses should be reduced by about 50% in patients with moderate hepatic impairment (Child-Pugh category B), and by about 75% in severe impairment (Child-Pugh category C). US licensed product information recommends that doses should be reduced by about 25% in patients with moderate to severe hepatic impairment without ascites, and by about 50% in those with severe hepatic impairment with ascites.

Anxiety disorders. Small studies have suggested that lamotrigine may relieve some of the symptoms of post-traumatic stress disorder (p. 1029.2).

References.
1. Hertzberg MA, *et al.* A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999; **45:** 1226–9.
2. Hageman I, *et al.* Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. *Acta Psychiatr Scand* 2001; **104:** 411–22.

Bipolar disorder. In a multicentre placebo-controlled study involving 195 patients, oral lamotrigine 50 or 200 mg daily produced dose-related improvement in patients with bipolar disorder (p. 397.2) experiencing a major depressive episode.[1] Further data from randomised controlled studies[2-8] and meta-analysis[9] have confirmed benefit for depressive symptoms (although not for mania), and reviews[10-14] have generally favoured its use, although some have queried the strength of the evidence.[15] Guidelines for the treatment of bipolar disorder now recommend lamotrigine as a first-line option for bipolar depression, and it is licensed for such use in some countries (see also Uses and Administration, above).

1. Calabrese JR, *et al.* A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry* 1999; **60:** 79–88.
2. Bowden CL, *et al.* Lamotrigine in the treatment of bipolar depression. *Eur Neuropsychopharmacol* 1999; **9** (suppl 4): S113–S117.

3. Calabrese JR, *et al*. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry* 2000; **61:** 841–50.
4. Ichim L, *et al*. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000; **12:** 5–10.
5. Obrocea GV, *et al*. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 2002; **51:** 253–60.
6. Bowden CL, *et al*. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; **60:** 392–400. Correction. *ibid*. 2004; **61:** 680.
7. Calabrese JR, *et al*. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; **64:** 1013–24.
8. Nierenberg AA, *et al*. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 2006; **163:** 210–16.
9. Geddes JR, *et al*. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009; **194:** 4–9.
10. Engle PM, Heck AM. Lamotrigine for the treatment of bipolar disorder. *Ann Pharmacother* 2000; **34:** 258–62.
11. Hurley SC. Lamotrigine update and its use in mood disorders. *Ann Pharmacother* 2002; **36:** 860–73.
12. Goldsmith DR, *et al*. Lamotrigine: a review of its use in bipolar disorder. *Drugs* 2003; **63:** 2029–50.
13. Muzina DJ, *et al*. Lamotrigine and antiepileptic drugs as mood stabilizers in bipolar disorder. *Acta Psychiatr Scand Suppl* 2005; 21–8.
14. Smith LA, *et al*. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 2007; **9:** 394–412.
15. van der Loos MLM, *et al*. Lamotrigine bij de behandeling van bipolaire stoornissen: een overzicht. *Tijdschr Psychiatr* 2007; **49:** 95–103.

Epilepsy. Lamotrigine is used in the treatment of epilepsy (p. 506.1). It is used in partial seizures with or without secondary generalisation, and in generalised tonic-clonic seizures, although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. It is also recommended in absence seizures, although the evidence base is not particularly strong, and may be used in juvenile myoclonic epilepsy and tried in tonic or atonic seizures.

As monotherapy for partial seizures with or without secondary generalisation, lamotrigine was found to be better than carbamazepine (the established first-line drug) in terms of time to treatment failure and tolerability.[1] In patients with newly-diagnosed partial seizures with or without secondary generalisation, lamotrigine had a similar efficacy to carbamazepine, but again was better tolerated.[2] A systematic review[3] of randomised, placebo-controlled studies concluded that lamotrigine is also effective in reducing the seizure frequency when added to current antiepileptic regimens in patients with refractory partial seizures.

As monotherapy for primary generalised and unclassifiable seizures lamotrigine was found[4] to be significantly inferior to valproate (the established first-line drug) in terms of seizure control, with almost twice the failure rate; valproate was also significantly more effective for achieving 12-month remission and prolonging the time to first seizure. Benefit was seen with adjunctive lamotrigine when compared with placebo in children[5] and adults[6] for treatment-resistant primary generalised seizures; it was also suggested[6] that lamotrigine therapy may be appropriate when determination of the type of epilepsy in these patients is not possible.

Lamotrigine appears to be an effective adjunctive treatment in children with the Lennox-Gastaut syndrome.[7,8]

It has also been found to be effective and well tolerated as adjunctive therapy in paediatric patients with refractory epilepsy including those with developmental impairment;[9] it was particularly effective in absence and atypical seizures in this open-label study. (Evidence for the use of lamotrigine to treat absence seizures, as for the other common alternatives ethosuximide and valproate, is, however, generally poor.[10])

1. Marson AG, *et al*. SANAD Study Group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1000–15.
2. Brodie MJ, *et al*. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995; **345:** 476–9.
3. Ramaratnam S, *et al*. Lamotrigine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).
4. Marson AG, *et al*. SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1016–26.
5. Trevathan E, *et al*. Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Abstract: *Pediatrics* 2006; **118:** 777–8. Full version: http://www.pediatrics.org/cgi/content/full/118/2/e371 (accessed 09/06/08)
6. Biton V, *et al*. Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. *Neurology* 2005; **65:** 1737–43.
7. Donaldson JA, *et al*. Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut Syndrome). *Epilepsia* 1997; **38:** 68–73.
8. Motte J, *et al*. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *N Engl J Med* 1997; **337:** 1807–12. Correction. *ibid*. 1998; **339:** 851–2.
9. Besag FMC, *et al*. Lamotrigine for the treatment of epilepsy in childhood. *J Pediatr* 1995; **127:** 991–7.
10. Posner EB, *et al*. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).

Migraine. Case reports[1] and open studies[2,3] have suggested that lamotrigine may be of benefit in the prophylaxis of migraine aura.

1. d'Onofrio F, *et al*. Basilar-type migraine responsive to lamotrigine: three case reports. *Neurol Sci* 2007; **28:** S239–S241.
2. Pascual J, *et al*. Preventing disturbing migraine aura with lamotrigine: an open study. *Headache* 2004; **44:** 1024–8.
3. Lampl C, *et al*. Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry* 2005; **76:** 1730–2.

Motor neurone disease. Lamotrigine has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) but with disappointing results.[1]

1. Ryberg H, *et al*. A double-blind randomized clinical trial in amyotrophic lateral sclerosis using lamotrigine: effects on CSF glutamate, aspartate, branched-chain amino acid levels and clinical parameters. *Acta Neurol Scand* 2003; **108:** 1–8.

Movement disorders. Symptomatic improvement and a trend towards decreased chorea was reported[1] with lamotrigine in a double-blind, placebo-controlled study of 64 patients with Huntington's chorea (p. 1029.3) with motor signs of less than 5 years' duration. There was, however, no clear evidence that lamotrigine retarded the progression of early Huntington disease over a period of 30 months.

1. Kremer B, *et al*. Influence of lamotrigine on progress of early Huntington disease: a randomized clinical trial. *Neurology* 1999; **53:** 1000–11.

Neuropathic pain. There is growing evidence that lamotrigine is of use in the management of neuropathic pain.[1] It was effective when used with carbamazepine or phenytoin in the treatment of refractory *trigeminal neuralgia*[2] (p. 11.2), and has also shown promise in the treatment of pain associated with *HIV-related distal sensory neuropathy*[3] (p. 958.3). Some benefit has been found[4] in the treatment of *diabetic neuropathy* (see p. 8.2). Case reports[5] and a placebo-controlled study[6] have also indicated that lamotrigine may be effective in *central post-stroke pain* (p. 7.3). More recently, the use of lamotrigine in neuropathic pain has been reviewed.[7,8] Based on the same studies, one review[7] concluded that lamotrigine is an effective treatment for various types of neuropathic pain and that further studies are warranted while another[8] concluded that it is unlikely to be of benefit and that further studies are probably not justified.

1. McCleane GJ. Lamotrigine in the management of neuropathic pain: a review of the literature. *Clin J Pain* 2000; **16:** 321–6.
2. Zakrewska JM, *et al*. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover study. *Pain* 1997; **73:** 223–30.
3. Simpson DM, *et al*. Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003; **60:** 1508–14.
4. Eisenberg E, *et al*. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* 2001; **57:** 505–9.
5. Canavero S, Bonicalzi V. Lamotrigine control of central pain. *Pain* 1996; **68:** 179–81.
6. Vestergaard K, *et al*. Lamotrigine for central post-stroke pain: a randomized controlled trial. *Neurology* 2001; **56:** 184–90.
7. Eisenberg E, *et al*. Lamotrigine for neuropathic pain. *Expert Rev Neurother* 2005; **5:** 729–35.
8. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/06/08).

Schizophrenia. Lamotrigine has been tried[1] as adjunctive therapy in treatment-resistant schizophrenia (p. 1031.3) and a benefit has been reported in few studies,[2-4] although patient numbers have been small. A systematic review[5] of the use of lamotrigine in schizophrenia concluded that the evidence for its use was poor, although it was suggestive of a positive effect on symptoms. However, a later meta-analysis[6] concluded that severely ill patients with treatment-refractory schizophrenia might get significant clinical benefit from augmentation with lamotrigine.

1. Large CH, *et al*. The potential role of lamotrigine in schizophrenia. *Psychopharmacology (Berl)* 2005; **181:** 415–36.
2. Tiihonen J, *et al*. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003; **54:** 1241–8.
3. Kremer I, *et al*. Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. *Biol Psychiatry* 2004; **56:** 441–6.
4. Zoccali R, *et al*. The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophr Res* 2007; **93:** 109–16.
5. Premkumar TS, Pick J. Lamotrigine for schizophrenia. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 09/06/08).
6. Tiihonen J, *et al*. The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2009; **109:** 10–14.

Adverse Effects and Treatment

Skin rashes may occur during therapy with lamotrigine; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting lamotrigine (see Effects on the Skin, p. 529.1). Symptoms such as fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, facial oedema and, rarely, hepatic dysfunction have been reported. Blood dyscrasias such as leucopenia, neutropenia, and thrombocytopenia have also been reported, sometimes with rashes as part of a hypersensitivity syndrome.

Movement disorders such as tics, ataxia, nystagmus, and tremor have occurred; lamotrigine may worsen symptoms in patients with pre-existing Parkinson's disease. Other adverse effects include angioedema, photosensitivity, diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, insomnia, headache, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion. Very rarely, lupus-like reactions and increases in seizure frequency have been reported.

Licensed product information states that there have been rare instances of death after a rapidly progressive illness involving status epilepticus, multi-organ dysfunction, and disseminated intravascular coagulation in patients taking multiple antiepileptics including lamotrigine, although the role of lamotrigine remains to be established. It has been suggested[1] that multi-organ failure and disseminated intravascular coagulation, with associated rhabdomyolysis, are complications of severe convulsive seizures rather than of lamotrigine therapy. However, there has been a report[2] of a patient with no history of generalised seizures who developed a syndrome of disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, and ataxia 14 days after lamotrigine was added to her antiepileptic regimen. Two cases of disseminated intravascular coagulation were found in a cohort of 11 316 patients involved in prescription-event monitoring of lamotrigine therapy in general practice.[3]

1. Yuen AWC, Bihari DJ. Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizures. *Lancet* 1992; **340:** 618.
2. Schaub JEM, *et al*. Multisystem adverse reaction to lamotrigine. *Lancet* 1994; **344:** 481.
3. Mackay FJ, *et al*. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38:** 881–6.

Effects on the blood. Septic shock secondary to leucopenia occurred in a patient when lamotrigine was added to therapy with sodium valproate.[1] There has also been a report of agranulocytosis in a child started on high-dose lamotrigine monotherapy.[2] The fall in the blood count was noted several days after lamotrigine had been stopped due to skin rash. The UK CSM subsequently reported[3] that 7 cases of aplastic anaemia, 12 of bone-marrow depression, and 20 of pancytopenia associated with lamotrigine had been received worldwide. Given the extensive usage of lamotrigine the CSM considered the risk of aplastic anaemia to be small and routine blood monitoring was not recommended. However, prescribers were warned to be alert for symptoms and signs suggestive of bone-marrow depression.

1. Nicholson RJ, *et al*. Leucopenia associated with lamotrigine. *BMJ* 1995; **310:** 504.
2. de Camargo OAK, Bode H. Agranulocytosis associated with lamotrigine. *BMJ* 1999; **318:** 1179.
3. CSM/MCA. Lamotrigine (Lamictal): rare blood dyscrasias. *Current Problems* 2000; **26:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Effects on bone. For the effects of antiepileptics including lamotrigine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the liver. Fatal fulminant hepatic failure has been reported[1] in a patient after addition of lamotrigine to antiepileptic therapy with sodium valproate and carbamazepine. Another fatal case was reported[2] in a patient who was given lamotrigine for bipolar disorder; she was also taking other drugs for pain and insomnia. Reversible eosinophilic hepatitis occurred[3] as part of a hypersensitivity syndrome in a patient given lamotrigine for seizures. Others[4] have also suggested that fulminant hepatitis is a manifestation of an antiepileptic hypersensitivity syndrome.

1. Makin AJ, *et al*. Fulminant hepatic failure induced by lamotrigine. *BMJ* 1995; **311:** 292.
2. Overstreet K, *et al*. Fatal progressive hepatic necrosis associated with lamotrigine treatment: a case report and literature review. *Dig Dis Sci* 2002; **47:** 1921–5.
3. Fix OK, *et al*. Eosinophilic hepatitis caused by lamotrigine. *Clin Gastroenterol Hepatol* 2006; **4:** xxvi.
4. Ouellet G, *et al*. Fulminant hepatitis induced by lamotrigine. *South Med J* 2009; **102:** 82–4.

Effects on the lungs. Interstitial pneumonitis with pulmonary infiltrates occurred when lamotrigine was added to

antiepileptic therapy in a 57-year-old woman; the condition resolved when lamotrigine was stopped.[1]

1. Saravanan N, *et al*. Interstitial pneumonitis during lamotrigine therapy. *Br J Clin Pharmacol* 2005; **60:** 666–7.

Effects on mental function. Acute *psychosis* was reported[1] in 6 out of about 1400 patients when lamotrigine was added to antiepileptic therapy and/or when the dose of lamotrigine was increased. Symptoms resolved when lamotrigine was stopped, and recurred in 1 case of rechallenge. Psychiatric symptoms associated with lamotrigine use have been reviewed.[2]

For a review of the effects of antiepileptic therapy including lamotrigine on *cognition*, and on *mood* (including the risk of suicidal ideation), see p. 508.3.

1. Brandt C, *et al*. Development of psychosis in patients with epilepsy treated with lamotrigine: report of six cases and review of the literature. *Epilepsy Behav* 2007; **11:** 133–9.
2. Villari V, *et al*. Psychiatric symptoms related to the use of lamotrigine: a review of the literature. *Funct Neurol* 2008; **23:** 133–6.

Effects on the nervous system. Of 93 patients with idiopathic generalised epilepsy who were treated with lamotrigine, 5 adults had *de novo* or exacerbated myoclonic jerks.[1] In each case, symptoms resolved when the dose of lamotrigine was reduced by 25 to 50% or stopped altogether. In another report, a 17-year-old girl with idiopathic Rolandic epilepsy had a sudden increase in seizure frequency when lamotrigine was added to therapy with sodium valproate; other adverse effects included emotional lability, headaches, and drowsiness.[2] Again symptoms resolved when lamotrigine was stopped.[2]

Overdose of lamotrigine has been known to cause seizures (see below).

Aseptic meningitis has been associated with lamotrigine use.[3] A total of 40 cases have been submitted to the FDA between December 1994 and November 2009; symptoms reported included headache, fever, nausea, vomiting, nuchal rigidity, photophobia, and myalgias and occurred within a mean of 16 days of starting therapy. Most patients recovered when lamotrigine was stopped although 15 patients reported a rapid return of symptoms when rechallenged.

1. Crespel A, *et al*. Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 2005; **65:** 762–4.
2. Cerminara C, *et al*. Lamotrigine-induced seizure aggravation and negative myoclonus in idiopathic rolandic epilepsy. *Neurology* 2004; **63:** 373–5.
3. FDA. News release: aseptic meningitis risk with use of seizure drug Lamictal (issued 12th August, 2010). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm222212.htm (accessed 24/08/10)

Effects on the skin. Rashes account for withdrawal from therapy in about 2% of those given lamotrigine,[1,2] and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur in about 1 in 1000 adult patients.[3,4] The majority of rashes resolve once lamotrigine has been stopped; however, some patients have developed permanent scarring and there have been rare reports of fatalities. The main risk factors appear to be use with valproate, exceeding the recommended initial dose of lamotrigine or the recommended rate of dose escalation, and a history of antiepileptic-induced rash. The risk appears to be greater in children[1,4-6] and has been estimated to be between 1 in 300 and 1 in 50. These skin reactions usually occur within 8 weeks of starting therapy with lamotrigine, but onset as early as the first day and as late as 2 years has been noted.[7] After continuing reports of serious skin reactions in children, UK recommended dosage regimens for children have been revised to further reduce the risk of such reactions.[8] For the relative incidence of rash with different antiepileptics see under Phenytoin, p. 541.1.

1. Mackay FJ, *et al*. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38:** 881–6.
2. Messenheimer J, *et al*. Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 1998; **18:** 281–96.
3. CSM/MCA. Lamotrigine (Lamictal) and serious skin reactions. *Current Problems* 1996; **22:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015622&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
4. CSM/MCA. Lamotrigine (Lamictal): increased risk of serious skin reactions in children. *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Mitchell P. Paediatric lamotrigine use hit by rash reports. *Lancet* 1997; **349:** 1080.
6. Hirsch LJ, *et al*. Predictors of lamotrigine-associated rash. *Epilepsia* 2006; **47:** 318–22.
7. Adverse Drug Reactions Advisory Committee (ADRAC). Lamotrigine and severe skin reactions. *Aust Adverse Drug React Bull* 1997; **16:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr9702.htm (accessed 09/06/08)
8. CSM/MCA. Lamotrigine (Lamictal): revised doses for children. *Current Problems* 2000; **26:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Hypersensitivity. For reference to a case of suspected cross-sensitivity between carbamazepine and lamotrigine, see p. 515.1.

Overdosage. An evaluation[1] of 493 cases of lamotrigine-only overdoses reported to the American Association of Poison Control Centers over a 2-year period found that 52.1% of patients had no toxic effects. The most commonly reported adverse effects were drowsiness, nausea, vomiting, and ataxia. Serious effects such as seizures, coma, and respiratory depression were reported in 0.6 to 1.2% of cases; no deaths were reported.

No serious toxicity was seen in a patient who deliberately took an overdose of 1.35 g of lamotrigine and was subsequently treated with gastric lavage and activated charcoal.[2] Symptoms at presentation one hour after ingestion had included nystagmus and muscle hypertonicity. ECG monitoring had revealed widening of the QRS interval. Low-grade fever, erythema, and periorbital oedema suggestive of a hypersensitivity syndrome developed in another patient who inadvertently received lamotrigine 2.7 g daily for 4 days.[3] The patient recovered after corticosteroid treatment and stopping lamotrigine. Generalised tonic-clonic seizures, tremor, muscle weakness, ataxia, and hypertonia were reported[4] in a 2-year-old child after ingestion of 800 mg of lamotrigine. Symptoms resolved within 24 hours after treatment with gastric lavage and activated charcoal, midazolam, and fluids. Plasma-lamotrigine concentrations were in the high adult therapeutic range (3.8 micrograms/mL) with a slow elimination rate. Generalised seizures also occurred[5] after an unknown quantity of lamotrigine was ingested by a 19-month-old child who had no history of seizures; other presenting symptoms included tachycardia and vomiting. The serum-lamotrigine concentration measured 1 hour post ingestion was 20.3 mg/L. Symptoms resolved within 24 hours after treatment with trimethobenzamide and activated charcoal.

1. Lofton AL, Klein-Schwartz W. Evaluation of lamotrigine toxicity reported to poison centers. *Ann Pharmacother* 2004; **38:** 1811–15.
2. Buckley NA, *et al*. Self-poisoning with lamotrigine. *Lancet* 1993; **342:** 1552–3.
3. Mylonakis E, *et al*. Lamotrigine overdose presenting as anticonvulsant hypersensitivity syndrome. *Ann Pharmacother* 1999; **33:** 557–9.
4. Briassoulis G, *et al*. Lamotrigine childhood overdose. *Pediatr Neurol* 1998; **19:** 239–42.
5. Thundiyil JG, *et al*. Lamotrigine-induced seizures in a child: case report and literature review. *Clin Toxicol* 2007; **45:** 169–72.

Precautions

Lamotrigine should be given with caution to patients with hepatic or renal impairment. All patients should be warned to see their doctor immediately if rashes or symptoms associated with hypersensitivity develop. To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. Particular care is needed in patients also receiving valproate—see under Interactions, p. 530.1.

Withdrawal of lamotrigine should be considered if rash, fever, flu-like symptoms, drowsiness, or worsening of seizure control occurs. Care is required when withdrawing lamotrigine therapy—see also Uses and Administration, p. 527.2. Abrupt withdrawal should be avoided unless serious skin reactions have occurred. Lamotrigine should not be restarted in patients with previous hypersensitivity.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of lamotrigine by mothers during breast feeding may be of concern, since there is the potential for therapeutic serum concentrations to occur in the infant. A report in 4 breast-fed infants whose mothers were taking lamotrigine found that although serum concentrations of the drug 10 days after birth were about 30% of maternal concentrations in 3 infants, no short-term adverse effects were seen; the drug was undetectable in the fourth.[2] A study[3] in 6 mothers taking lamotrigine found that the relative dose in their breast-fed infants was 7.6% (mean absolute dose: 450 micrograms/kg daily) and infant plasma concentrations were 18% of maternal concentrations; no adverse effects were reported. The authors also noted that no adverse effects were reported in 12 previous cases. However, there has been a report[4] of severe apnoea in a neonate exposed to lamotrigine via breast milk; drug concentrations in the infant were 4.87 micrograms/mL at admission, which was towards the upper end of the therapeutic range, and his calculated intake in breast milk was at least 1.15 mg/kg daily.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Liporace J, *et al*. Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav* 2004; **5:** 102–5.
3. Page-Sharp M, *et al*. Transfer of lamotrigine into breast milk. *Ann Pharmacother* 2006; **40:** 1470–1.
4. Nordmo E, *et al*. Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother* 2009; **43:** 1893–7.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Hepatic impairment. The pharmacokinetics of lamotrigine were not significantly altered in patients with moderate cirrhosis;[1] however, those with severe cirrhosis showed significantly lower oral clearance and longer elimination half-lives than those in healthy subjects.

The recommended licensed doses in patients with hepatic impairment are given under Uses and Administration, p. 527.3.

1. Marcellin P, *et al*. Influence of cirrhosis on lamotrigine pharmacokinetics. *Br J Clin Pharmacol* 2001; **51:** 410–14.

Intellectual impairment. Aggressive behaviour has been reported in intellectually impaired patients given lamotrigine.[1] Of 19 such patients given lamotrigine, aggressive behaviour developed in 9; the drug was stopped in 5, and stopped but reintroduced in a further 2, together with psychiatric management. One patient responded to a reduction in lamotrigine dosage.

1. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia* 1998; **39:** 280–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lamotrigine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2. For reference to alteration of lamotrigine pharmacokinetics in pregnancy, see under Pharmacokinetics, p. 530.3.

There is a theoretical risk of teratogenicity with lamotrigine because, like valproate, it is a folate antagonist. In 2002 the manufacturer of lamotrigine, *GlaxoSmithKline*, reported[1] that it had follow-up information on 395 outcomes of pregnancies exposed to lamotrigine between September 1992 and September 2001 from the International Lamotrigine Pregnancy Registry. Major birth defects were found in 13 infants but no distinctive pattern of abnormalities suggestive of a common cause could be identified. Of the 168 who had been exposed to lamotrigine monotherapy during the first trimester, birth defects were reported in 3 (1.8%). The frequency of major birth defects in pregnancies exposed to polytherapy containing lamotrigine with valproate was 10% compared with 4.3% in lamotrigine polytherapy without valproate. Although it was considered that the sample sizes were too small to rule out a small increase in the frequency of major birth defects, it was noted that the frequency of malformations after lamotrigine monotherapy did not differ from that reported in the literature for women with epilepsy receiving antiepileptic monotherapy. Updated results from 785 pregnancies up to March 2004 included 414 first-trimester exposures to lamotrigine monotherapy, of which 12 were associated with a major abnormality.[2] As of March 2006, the registry had recorded 802 first-trimester exposures to lamotrigine monotherapy with major abnormalities occurring in 22; there was no evidence to suggest a dose-response relationship with daily doses of up to 400 mg.[3]

In August 2006, the manufacturer[4] reported that data from the North American Antiepileptic Drug Pregnancy Registry suggested an association between lamotrigine and an increased risk of oral clefts. Of 564 first-trimester exposures to lamotrigine monotherapy, 5 cases of oral clefts were reported giving an incidence rate of 8.9 per 1000 compared with 0.37 per 1000 in the reference population. Again, however, no increase in the overall risk of major malformations was found. Analysis of data from other pregnancy registries found 4 additional cases of oral clefts in about 2200 first-trimester exposures to lamotrigine monotherapy.

1. Tennis P, Eldridge RR. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. *Epilepsia* 2002; **43:** 1161–7.
2. Cunnington M, Tennis P. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005; **64:** 955–60.
3. Cunnington M, *et al*. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007; **48:** 1207–10.
4. GlaxoSmithKline, Canada. Association of Lamictal (lamotrigine) with an increased risk of non-syndromic oral clefts (issued 1st August, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_2_hpc-cps-eng.pdf (accessed 01/09/08)

Renal impairment. Results from a pharmacokinetic study[1] indicated that impaired renal function was likely to have little effect on plasma concentrations of lamotrigine. The drug is mainly cleared by metabolism and although the

glucuronide metabolite accumulates it is inactive. Nevertheless, there is limited clinical experience with lamotrigine in such patients and caution was recommended.

1. Wootton R, *et al*. Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. *Br J Clin Pharmacol* 1997; **43:** 23–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of lamotrigine is enhanced by the enzyme inducers carbamazepine, phenytoin, phenobarbital, and primidone, and inhibited by valproate (see below).

Analgesics. *Paracetamol* affects the metabolic disposition of lamotrigine but the clinical significance of this interaction remains to be determined.[1] Paracetamol reduced the area under the plasma concentration-time curve for lamotrigine, reduced lamotrigine's half-life, and increased the percentage of lamotrigine recovered in the urine.

1. Depot M, *et al*. Kinetic effects of multiple oral doses of acetaminophen on a single oral dose of lamotrigine. *Clin Pharmacol Ther* 1990; **48:** 346–55.

Antibacterials. Use with *rifampicin* significantly increased the clearance of lamotrigine.[1] The total urinary excretion of lamotrigine and the amount excreted as glucuronide were significantly higher compared with placebo.

1. Ebert U, *et al*. Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol* 2000; **56:** 299–304.

Antidepressants. An epileptic patient maintained on lamotrigine 200 mg daily complained[1] of increasing confusion and cognitive impairment after starting *sertraline* 25 mg daily for post-traumatic disorder; after 6 weeks her lamotrigine blood concentrations had risen from 2.5 to 5.1 micrograms/mL during this period. The adverse effects cleared and blood concentrations of lamotrigine fell to 3.1 micrograms/mL within 3 weeks of changing the daily dosage to lamotrigine 100 mg and sertraline 50 mg. A patient, with poorly controlled epilepsy, who initially had been taking lamotrigine 450 mg and sertraline 75 mg together daily for 6 weeks without adverse effects had marked sedation, fatigue, and decreased cognition 6 weeks after the daily dosage of lamotrigine was increased to 600 mg. Her lamotrigine blood concentration was 19.3 micrograms/mL. The patient was subsequently stabilised on lamotrigine 800 mg and sertraline 50 mg daily and had less sedation and fatigue and clearer cognition; blood concentrations of lamotrigine fell to 9.8 micrograms/mL.

1. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. *Seizure* 1998; **7:** 163–5.

Antiepileptics. *Valproate* can inhibit the metabolism of lamotrigine resulting in increased concentrations of lamotrigine. This effect can be beneficial in the control of certain seizures, although careful monitoring is required as toxicity may occur. Disabling tremor that occurred in 3 patients taking such a combination resolved when the dose of lamotrigine or valproate was reduced.[1] Other reports of toxicity, resolving on reduction of the lamotrigine dose, were marked by sedation, ataxia, and fatigue,[2] or delirium.[3] Symptoms of neurotoxicity were reported in 3 patients on lamotrigine therapy who were given valproate, intravenously then orally, for absence status epilepticus. Serum concentrations of lamotrigine in these patients were raised about three- to sevenfold.[4] Reversible encephalopathy has been reported[5] when sodium valproate was substituted for phenytoin in a patient also taking lamotrigine, although her clinical condition had been satisfactory on this new regimen for several months. Symptoms improved when the doses of both valproate and lamotrigine were reduced. Pharmacokinetic studies[6,7] in healthy adults have attempted to elucidate the mechanism of the interaction between lamotrigine and valproate. The clearance of lamotrigine was found to be reduced, and exposure and elimination half-life increased when valproate was also given. Renal elimination was not affected and the investigators[6] suggested that there was hepatic competition for glucuronidation between valproate and lamotrigine. However, there was no substantial alteration in the linear kinetics of lamotrigine in the presence of therapeutic plasma concentrations of valproate.[7] Similar observations were made when lamotrigine was added to existing antiepileptic regimens in children,[8] although the clinical relevance of the influence of age on the pharmacokinetics remains to be determined. Both young age and use with valproate are risk factors for lamotrigine-induced dermatological toxicity—see Effects on the Skin, p. 529.1.

For details of dosage reductions required for lamotrigine used with valproate, see Uses and Administration, p. 527.2.

Other antiepileptics also affect plasma concentrations of lamotrigine. In contrast to valproate, *carbamazepine, phenytoin,* or *phenobarbital* all markedly induced the elimination of lamotrigine.[9] Others have confirmed a reduction in plasma-lamotrigine concentrations when given with phenytoin and other enzyme-inducing antiepileptics,[10] but analysis of results from another study[11] suggested that the increase in lamotrigine clearance by phenytoin and carbamazepine was of minimal clinical significance. For reports of an interaction between lamotrigine and carbamazepine, see p. 516.3. *Oxcarbazepine* has also been reported[12] to decrease serum-lamotrigine concentrations (although to a lesser extent than carbamazepine). However, a study[13] in healthy subjects found that oxcarbazepine did not affect the pharmacokinetics of lamotrigine, although adverse effects occurred more frequently when they were used together (for a report of severe toxicity associated with such use see p. 534.2). *Mesuximide* was found[12,14] to have a marked inducing effect on the metabolism of lamotrigine. In one study,[14] plasma-lamotrigine concentrations were significantly reduced when given together.

For the effect of lamotrigine on *clonazepam* concentrations, see p. 1069.1.

1. Reutens DC, *et al*. Disabling tremor after lamotrigine with sodium valproate. *Lancet* 1993; **342:** 185–6.
2. Pisani F, *et al*. Interaction of lamotrigine with sodium valproate. *Lancet* 1993; **341:** 1224.
3. Mueller TH, Beeber AR. Delirium from valproic acid with lamotrigine. *Am J Psychiatry* 2004; **161:** 1128–9.
4. Burneo JG, *et al*. Neurotoxicity following addition of intravenous valproate to lamotrigine therapy. *Neurology* 2003; **60:** 1991–2.
5. Hennessy MJ, Wiles CM. Lamotrigine encephalopathy. *Lancet* 1996; **347:** 974–5.
6. Yuen AWC, *et al*. Sodium valproate acutely inhibits lamotrigine metabolism. *Br J Clin Pharmacol* 1992; **33:** 511–13.
7. Anderson GD, *et al*. Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* 1996; **60:** 145–56.
8. Vauzelle-Kervroëdan F, *et al*. Influence of concurrent antiepileptic medication on the pharmacokinetics of lamotrigine as add-on therapy in epileptic children. *Br J Clin Pharmacol* 1996; **41:** 325–30.
9. May TW, *et al*. Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* 1996; **18:** 523–31.
10. Battino D, *et al*. Lamotrigine plasma concentrations in children and adults: influence of age and associated therapy. *Ther Drug Monit* 1997; **19:** 620–7.
11. Grasela TH, *et al*. Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. *J Clin Pharmacol* 1999; **39:** 373–84.
12. May TW, *et al*. Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. *Ther Drug Monit* 1999; **21:** 175–81.
13. Theis JGW, *et al*. Lack of pharmacokinetic interaction between oxcarbazepine and lamotrigine. *Neuropsychopharmacology* 2005; **30:** 2269–74.
14. Besag FM, *et al*. Methsuximide lowers lamotrigine blood levels: a pharmacokinetic antiepileptic drug interaction. *Epilepsia* 2000; **41:** 624–7.

Antipsychotics. An apparent interaction between lamotrigine and *aripiprazole*, resulting in Stevens-Johnson syndrome, has been reported[1] in 2 patients with schizophrenia after the introduction of lamotrigine; both patients recovered with supportive treatment.

1. Shen Y-C, *et al*. Concomitant use of lamotrigine and aripiprazole increases risk of Stevens-Johnson syndrome? *Int Clin Psychopharmacol* 2007; **22:** 247–8.

Antivirals. A study[1] in healthy subjects found that *ritonavir-boosted lopinavir* decreased the steady-state minimum plasma concentration of lamotrigine by about 55%; doubling the dose of lamotrigine achieved concentrations similar to those with lamotrigine alone.

1. van der Lee MJ, *et al*. Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2006; **80:** 159–68.

Sex hormones. Studies in patients taking lamotrigine have indicated that *combined oral contraceptives*[1,2] may halve plasma concentrations of the antiepileptic. Other studies[3,4] have also found a significant increase in lamotrigine-plasma concentrations within one week of stopping contraceptive therapy; however, wide interpatient variability was noted in one study.[3] Significant adjustments in maintenance doses of lamotrigine may be needed if combined contraceptives are started or stopped (see below), and patients should be warned not to make changes in their contraceptive therapy without consulting their physician.[5] However, in a study,[6] progestogen-only contraceptives did not appear to affect lamotrigine concentrations. Licensed product information recommends that, when starting treatment with combined oral contraceptives, the dose of lamotrigine may need to be increased by as much as twofold in those women not taking drugs known to induce cytochrome P450-mediated metabolism of lamotrigine; conversely, the dose of lamotrigine may need to be halved when stopping contraceptive therapy in women not taking enzyme inducers. Dosage adjustment may not be necessary when starting or stopping combined oral contraceptive therapy in women taking lamotrigine with known enzyme inducers.

Adjustments may also be needed if other hormonal preparations are taken with lamotrigine.

Some reduction in plasma concentrations of levonorgestrel, and to a lesser extent ethinylestradiol, may also occur with lamotrigine, and there have been reports of breakthrough bleeding and unexpected pregnancies.[5]

1. Sabers A, *et al*. Oral contraceptives reduce lamotrigine plasma levels. *Neurology* 2003; **61:** 570–1.
2. Sidhu J, *et al*. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006; **61:** 191–9.
3. Contin M, *et al*. Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia* 2006; **47:** 1573–5.
4. Christensen J, *et al*. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia* 2007; **48:** 484–9.
5. GlaxoSmithKline, Canada. Important new safety information concerning the antiepileptic, Lamictal (lamotrigine) (issued September 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_hpc-cps-eng.pdf (accessed 01/09/08)
6. Reimers A, *et al*. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 2005; **46:** 1414–17.

Pharmacokinetics

Lamotrigine is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of 98%. Peak plasma concentrations occur about 2.5 hours after oral doses. It is widely distributed in the body and is reported to be about 55% bound to plasma proteins. It is extensively metabolised in the liver and excreted almost entirely in urine, principally as an inactive glucuronide conjugate. It slightly induces its own metabolism and the mean elimination half-life is reported to be 24 to 35 hours. Clearance is reported to be higher in children aged up to 12 years than in adults, with the highest values occurring in those under 5 years of age. Lamotrigine is distributed into breast milk.

The pharmacokinetics of lamotrigine are affected by other antiepileptics (see Interactions, above).

General references.

1. Rambeck B, Wolf P. Lamotrigine clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 433–43.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Reimers A, *et al*. Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. *Eur J Clin Pharmacol* 2007; **63:** 687–92.
4. Punyawudho B, *et al*. Population pharmacokinetics of lamotrigine in elderly patients. *J Clin Pharmacol* 2008; **48:** 455–63.

Hepatic impairment. See under Precautions, p. 529.3.

Pregnancy. Decreased plasma-lamotrigine concentrations have occurred during pregnancy, with deterioration of seizure control and a need for dosage adjustment in some patients.

References

1. Pennell PB, *et al*. The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 2004; **62:** 292–5.
2. de Haan G-J, *et al*. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004; **63:** 571–3.
3. Petrenaite V, *et al*. Individual changes in lamotrigine plasma concentrations during pregnancy. *Epilepsy Res* 2005; **65:** 185–8.
4. Pennell PB, *et al*. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 2008; **70:** 2130–6.

Renal impairment. See under Precautions, p. 529.3.

Therapeutic drug monitoring. A literature review[1] concluded that a clear relationship between lamotrigine concentrations and toxicity or antiepileptic efficacy has not been shown. Routine therapeutic drug monitoring was therefore not recommended and clinical end-points rather than plasma concentrations remained the best guide for dosage adjustment of lamotrigine.

1. Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. *Ann Pharmacother* 2002; **36:** 917–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dafex; Epilepax; Lagotran; Lamictal; Lamirax; Lamocas; Lamotril†; Latrigin; ***Austral.***: Elmendos†; Lamictal; Lamidus; Lamitrin†; Lamogine; Seaze; ***Austria***: Gerolamic; Lamictal; ***Belg.***: Doclamotri†; Lambipol; Lamictal; ***Braz.***: Lamictal; Lamitor; Lamoctril; Lamotrix; Neural; Neurium; Nortrigin; ***Canad.***: Lamictal; ***Chile***: Daksol; Flamus; Lafigin; Lamictal; Lomarin; Meganox; Tradox; Trigilab; Trizol; ***China***: An Xian (安闲); Lamictal (利必通); ***Cz.***: Danoptin†; Epimil; Epiral†; Lameton†; Lamictal; Lamiger†; Lamogine†; Lamolep†; Lamotax; Lamotri†; Lamotrix; Latrigil†; Plexxo; Rubimar; Triginet†; ***Denm.***: Delitrig†; Ginalam†; Lamictal; Raklam†; ***Fin.***: Lamictal; ***Fr.***: Lamicstart†; Lamictal; ***Ger.***: Elmendos†; Lamictal; Lamo-Q†; Lamo†; Lamotrig†; ***Gr.***: Dezepil; Lamictal; Lamot; Lamotrix; ***Hong Kong***: Lamictal; Lamotrin; ***Hung.***: Epitrigine; Gerolamic; Lamictal; Lamitrin; Lamolep; Plexxo†; ***India***: Epitic; Favlam; Lamepil; Lamepril; Lametec; Lamidus; Lamitor; Lamogin; Lamorig; Lamosyn; Lemogen; ***Indon.***: Lamictal; ***Irl.***: Bymot†; Lameutral; Lamictal; Lamoro; Larig; ***Israel***: Lamictal; Lamodex; Lamogine; ***Ital.***: Lamictal; ***Jpn***: Lamictal; ***Malaysia***:

Lamictal; Lamotrix; ***Mex.***: Fenebra; Lamdra; Lamictal; Latrigin; Limatic; Motricord; Prilkenzide; Protalgine; Ramitrine; Trimolep; ***Neth.***: Lambipol; Lamictal; Lamopan†; Lamotrigal; Symla†; ***Norw.***: Lamictal; ***NZ***: Lamictal; Logem; Mogine; ***Philipp.***: Lamictal; Lamitor; ***Pol.***: Danoptin†; Epilactal†; Epitrigine; Lameptil; Lamexim; Lamia†; Lamilept; Lamitrin; LamoMerck; Lamotrihexal†; Lamotrix; Lamox†; Lamozor; Plexxo; Symla; Triginet†; Trogine; ***Port.***: Lamictal; Lamix; Motrigi; ***Rus.***: Convulsan (Конвульсан); Lameptil (Ламептил); Lamictal (Ламиктал); Lamitor (Ламитор); Lamolep (Ламолеп); Sazar (Сейзар); Triginet (Тригинет); ***S.Afr.***: Epitec; Lamictin; Lamidus; Lamitor; ***Singapore***: Lamictal; Lanotrix; ***Spain***: Crisomet; Labileno; Lamictal; Lamomylan; Lavinol†; Silam†; ***Swed.***: Lamictal; ***Switz.***: Lamictal; Lamotrine; ***Thai.***: Lamictal; ***Turk.***: Lamictal; Pinral; ***UK***: Lamictal; ***Ukr.***: Epileptal (Эпилептал); Epimil (Эпимил); Lameton (Ламетон)†; Lamictal (Ламиктал); Lamidum (Ламидум)†; Lamotrin (Ламотрин); Latrigil (Латригил); Latrigin (Латриджин); ***USA***: Epitrogine; Lamictal; ***Venez.***: Lamictal.

Pharmacopoeial Preparations

BP 2014: Dispersible Lamotrigine Tablets; Lamotrigine Tablets;
USP 36: Lamotrigine Tablets for Oral Suspension; Lamotrigine Tablets.

Levetiracetam *(BAN, USAN, rINN)*

S-Etiracetam; Lévétiracétam; Levetiracetamum; Levetiracetam; SIB-S1; UCB-22059; UCB-L059; Леветирацетам.

(*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide.

$C_8H_{14}N_2O_2$=170.2

CAS — 102767-28-2.

ATC — N03AX14.

ATC Vet — QN03AX14.

UNII — 44YRR34555.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Levetiracetam). A white or almost white powder. Very soluble in water; soluble in acetonitrile; practically insoluble in hexane.

USP 36: (Levetiracetam). A white to almost white powder. Very soluble in water; soluble in acetonitrile; practically insoluble in hexane.

Uses and Administration

Levetiracetam is an analogue of piracetam (p. 393.3) used in the treatment of epilepsy (below). Details of licensed indications, ages at which levetiracetam may be used, and the route employed, vary from country to country. The following indications and age limits apply to oral use. It is used as an adjunct in the treatment of partial seizures with or without secondary generalisations in adults and children from 1 month of age. In the UK, adults and adolescents aged 16 years and over may also be given levetiracetam as monotherapy in the treatment of partial seizures with or without secondary generalisation. In addition, levetiracetam is licensed in both the UK and the USA for adjunctive use in the treatment of myoclonic seizures in adults and children aged 12 years and over with juvenile myoclonic epilepsy. It is also licensed for use as an adjunct in the treatment of primary generalised tonic-clonic seizures in adults and children with idiopathic generalised epilepsy; for this indication, in the UK, licensed use is restricted to children aged 12 years and over, whereas in the USA, it is licensed from 6 years of age.

The daily oral dose of levetiracetam is given in two divided doses.

- The initial adult dose when used *as an adjunct* is 1 g on the first day of treatment; thereafter, the daily dose may be increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved, up to a maximum dose of 3 g daily.
  The initial dose in children aged from 1 month to less than 6 months is 14 mg/kg daily which may be increased in steps of 14 mg/kg every 2 weeks to a maximum of 42 mg/kg daily.
  The initial dose in children aged from 6 months and weighing less than 50 kg is 20 mg/kg daily which may be increased in steps of 20 mg/kg every 2 weeks to a maximum of 60 mg/kg daily.
  Children and adolescents weighing 50 kg or more should be given the usual adult dose (see above).
- When used as *monotherapy*, the initial dose of levetiracetam is 500 mg daily, increased after 2 weeks to 1 g daily. Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily.

A modified-release preparation is available for once-daily dosing *as an adjunct* in the treatment of partial seizures in patients aged 16 years and over.

When oral use is not feasible, levetiracetam may be given by intravenous infusion over 15 minutes in doses similar to those used orally. As with the oral formulation, details of licensed uses and ages may vary from country to country; in the UK, it is licensed in adults and children from 4 years of age, whereas in the USA, use is restricted to those aged 16 years and over. UK licensed product information states that there has been no experience with the use of intravenous levetiracetam for more than 4 days.

Reduced doses are recommended in renal and severe hepatic impairment (see below).

As with other antiepileptics, withdrawal of levetiracetam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose in patients weighing more than 50 kg by 1 g every 2 to 4 weeks, and in those weighing less than 50 kg, the dose reduction should not exceed 20 mg/kg every 2 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1).

References.
1. De Smedt T, *et al.* Levetiracetam: the profile of a novel anticonvulsant drug—part I: preclinical data. *CNS Drug Rev* 2007; **13:** 43–56.
2. De Smedt T, *et al.* Levetiracetam: part II, the clinical profile of a novel anticonvulsant drug. *CNS Drug Rev* 2007; **13:** 57–78.
3. Crepeau AZ, Treiman DM. Levetiracetam: a comprehensive review. *Expert Rev Neurother* 2010; **10:** 159–71.

Administration in children. Licensed indications and doses of levetiracetam in children vary from country to country, see Uses and Administration, above, and Administration in Renal Impairment, below.

Levetiracetam is mainly used for partial and myoclonic seizures, and in idiopathic generalised epilepsy, often as an adjunct. It has also been tried in children with status epilepticus (p. 532.1). A retrospective review[1] of 122 children aged from 1 month to 2 years given levetiracetam either as monotherapy (48 patients) or adjunctive therapy (74 patients) found that 70 achieved seizure remission. Of these, a longer duration of remission was seen in those receiving less than 30 mg/kg daily of levetiracetam. A case series[2] of 3 infants aged from 2 days to 3 months reported that levetiracetam 30 mg/kg daily was effective in the treatment of refractory neonatal seizures. A randomised multicentre study[3] of 116 children aged from 1 month to under 4 years with refractory partial seizures found that adjunctive levetiracetam significantly reduced the frequency of seizures and was generally well tolerated.

1. Perry MS, Benatar M. Efficacy and tolerability of levetiracetam in children younger than 4 years: a retrospective review. *Epilepsia* 2007; **48:** 1123–7.
2. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.
3. Piña-Garza JE, *et al.* Levetiracetam N01009 Study Group. Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. *Epilepsia* 2009; **50:** 1141–9.

Administration in hepatic impairment. No dose adjustment of levetiracetam is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, creatinine clearance (CC) may underestimate concomitant renal impairment, and UK licensed product information recommends that the usual adult maintenance dose (see above) should be reduced by 50% in those with a CC of less than 60 mL/minute per 1.73 m^2.

Administration in renal impairment. Reduced doses of levetiracetam are recommended for patients with renal impairment. Suitable daily doses for adults and adolescents weighing more than 50 kg according to UK and US licensed product information and based on creatinine clearance (CC) per 1.73 m^2, are:

- CC 50 to 79 mL/minute: 1 to 2 g
- CC 30 to 49 mL/minute: 0.5 to 1.5 g
- CC less than 30 mL/minute: 0.5 to 1 g
- Patients receiving dialysis may be given a loading dose of 750 mg when starting levetiracetam followed by doses of 0.5 to 1 g once daily; a supplemental dose of 250 to 500 mg is recommended after dialysis

UK licensed product information also gives suitable daily doses for children weighing less than 50 kg with renal impairment:

In children aged from 6 months:

- CC 50 to 79 mL/minute: 20 to 40 mg/kg
- CC 30 to 49 mL/minute: 10 to 30 mg/kg
- CC less than 30 mL/minute: 10 to 20 mg/kg
- Those receiving dialysis may be given a loading dose of 15 mg/kg when starting levetiracetam followed by doses of 10 to 20 mg/kg once daily; a supplemental dose of 5 to 10 mg/kg is recommended after dialysis

In children aged 1 month to less than 6 months:

- CC 50 to 79 mL/minute: 14 to 28 mg/kg
- CC 30 to 49 mL/minute: 7 to 21 mg/kg
- CC less than 30 mL/minute: 7 to 14 mg/kg
- Those receiving dialysis may be given a loading dose of 10.5 mg/kg when starting levetiracetam followed by doses of 7 to 14 mg/kg once daily; a supplemental dose of 3.5 to 7 mg/kg is recommended after dialysis

Doses may be given orally or intravenously, as necessary, in 2 divided doses.

See also above for dosage recommendations in those patients with severe hepatic impairment and concomitant renal impairment.

Epilepsy. Levetiracetam is used in epilepsy (p. 506.1) as an adjunct or monotherapy in the management of partial seizures with or without secondary generalisation.[1] It is also used as an adjunct in myoclonic seizures and for generalised tonic-clonic seizures,[1] although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. Levetiracetam may be considered as second-line drug for atonic or tonic seizures, and has been tried in Lennox-Gastaut syndrome and in juvenile absence epilepsy.[2] In children, levetiracetam has also been tried as adjunctive therapy for nonconvulsive status epilepticus,[3] in infantile spasms,[4] and in severe myoclonic epilepsy of infancy,[5] and as monotherapy in partial and generalised epilepsy.[6]

1. Lyseng-Williamson KA. Levetiracetam: a review of its use in epilepsy. *Drugs* 2011; **71:** 489–514.
2. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020fullguideline.pdf (accessed 09/06/08)
3. Trabacca A, *et al.* Levetiracetam in nonconvulsive status epilepticus in childhood: a case report. *J Child Neurol* 2007; **22:** 639–41.
4. Mikati MA, *et al.* Response of infantile spasms to levetiracetam. *Neurology* 2008; **70:** 574–5.
5. Striano P, *et al.* An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007; **69:** 250–4.
6. Khurana DS, *et al.* Levetiracetam monotherapy in children with epilepsy. *Pediatr Neurol* 2007; **36:** 227–30.

Movement disorders. Levetiracetam may be of benefit in some movement disorders. It has been tried in antipsychotic-induced *tardive dyskinesia*[1-3] and with equivocal benefit in levodopa-induced tardive dyskinesia[4,5] (see under Extrapyramidal Disorders on p. 1049.2). There is also limited evidence of benefit with levetiracetam for the treatment of *chorea* (p. 1029.3) in Huntington's disease[6,7] and in *paroxysmal kinesigenic choreoathetosis.*[8]

1. Konitsiotis S, *et al.* Levetiracetam in tardive dyskinesia: an open label study. *Mov Disord* 2006; **21:** 1219–21.
2. Meco G, *et al.* Levetiracetam in tardive dyskinesia. *Clin Neuropharmacol* 2006; **29:** 265–8.
3. Woods SW, *et al.* Effects of levetiracetam on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2008; **69:** 546–54.
4. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2005; **20:** 1205–9.
5. Lyons KE, Pahwa R. Efficacy and tolerability of levetiracetam in Parkinson disease patients with levodopa-induced dyskinesia. *Clin Neuropharmacol* 2006; **29:** 148–53.
6. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of chorea in Huntington's disease. *Mov Disord* 2006; **21:** 1998–2001.
7. de Tommaso M, *et al.* Efficacy of levetiracetam in Huntington disease. *Clin Neuropharmacol* 2005; **28:** 280–4.
8. Chatterjee A, *et al.* Levetiracetam in the treatment of paroxysmal kinesiogenic choreoathetosis. *Mov Disord* 2002; **17:** 614–15.

Muscle spasm. Levetiracetam has been tried with some success in *Meige's syndrome*,[1] and *hemifacial spasm.*[2] For use in *stiff-man syndrome* see p. 532.1.

1. Yardimci N, *et al.* Levetiracetam in Meige's syndrome. *Acta Neurol Scand* 2006; **114:** 63–6.
2. Deleu D. Levetiracetam in the treatment of idiopathic hemifacial spasm. *Neurology* 2004; **62:** 2134–5.

Psychiatric disorders. Levetiracetam has psychotropic properties and has been tried in the management of *anxiety disorders*[1,2] (p. 1028.1) including *social anxiety disorder*[2-4] (see Phobic Disorders, p. 1029.1), *post-traumatic stress disorder*[2,5] (p. 1029.2), and *panic disorder*[2,6] (p. 1029.1). There is also limited evidence[7] from case reports and small open-label studies that levetiracetam may be of benefit in the treatment of *bipolar disorder* (p. 397.2); however, a later randomised placebo-controlled study[8] found that adjunctive levetiracetam was not superior to placebo in the short-term treatment of depression in these patients.

1. Kinrys G, *et al.* Levetiracetam as adjunctive therapy for refractory anxiety disorders. *J Clin Psychiatry* 2007; **68:** 1010–13.
2. Farooq MU, *et al.* Levetiracetam for managing neurologic and psychiatric disorders. *Am J Health-Syst Pharm* 2009; **66:** 541–61.
3. Simon NM, *et al.* An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry* 2004; **65:** 1219–22.
4. Stein MB, *et al.* Levetiracetam in generalized social anxiety disorder: a double-blind, randomized controlled trial. *J Clin Psychiatry* 2010; **71:** 627–31.
5. Kinrys G, *et al.* Levetiracetam for treatment-refractory posttraumatic stress disorder. *J Clin Psychiatry* 2006; **67:** 211–14.
6. Papp LA. Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry* 2006; **67:** 1573–6.
7. Muralidharan A, Bhagwagar Z. Potential of levetiracetam in mood disorders: a preliminary review. *CNS Drugs* 2006; **20:** 969–79.
8. Saricicek A, *et al.* Levetiracetam in the management of bipolar depression: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2011; **72:** 744–50.

Restless legs syndrome. Levetiracetam has been reported to be of benefit in the treatment of refractory restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2).[1]

1. Della Marca G, *et al.* Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases. *J Neurol Neurosurg Psychiatry* 2006; **77:** 566–7.

Status epilepticus. Levetiracetam has been tried, with some success, in the management of nonconvulsive status epilepticus[1] and refractory status epilepticus,[2-7] including in children.[5-7] For the conventional management of status epilepticus see p. 510.2.

1. Rupprecht S, *et al*. Levetiracetam as a treatment option in non-convulsive status epilepticus. *Epilepsy Res* 2007; **73:** 238–44.
2. Patel NC, *et al*. The use of levetiracetam in refractory status epilepticus. *Seizure* 2006; **15:** 137–41.
3. Eue S, *et al*. Two years of experience in the treatment of status epilepticus with intravenous levetiracetam. *Epilepsy Behav* 2009; **15:** 467–9.
4. Möddel G, *et al*. Intravenous levetiracetam: a new treatment alternative for refractory status epilepticus. *J Neurol Neurosurg Psychiatry* 2009; **80:** 689–92.
5. Kirmani BF, *et al*. Role of intravenous levetiracetam in acute seizure management of children. *Pediatr Neurol* 2009; **41:** 37–9.
6. Abend NS, *et al*. Intravenous levetiracetam in critically ill children with status epilepticus or acute repetitive seizures. *Pediatr Crit Care Med* 2009; **10:** 505–10.
7. Gallentine WB, *et al*. Levetiracetam in children with refractory status epilepticus. *Epilepsy Behav* 2009; **14:** 215–8.

Stiff-man syndrome. In a report[1] of a patient with stiff-man syndrome (see under Muscle Spasm, p. 1064.3), substitution of levetiracetam for previous valproate therapy (because of suspected valproate-induced parkinsonism) resulted in complete suppression of paroxysmal spasms; benefit was sustained with continued therapy over 2 years of follow-up.

1. Rüegg SJ, *et al*. Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome. *Neurology* 2004; **62:** 338.

Tremor. A beta blocker is often the first drug used in patients with essential tremor (p. 1318.3) who require regular treatment. Levetiracetam has also been tried with some success;[1] however, an evidence-based guideline[2] found no benefit and recommended against such use. An open-label study reported[3] benefit with levetiracetam in the treatment of tremor secondary to multiple sclerosis but, again, a later randomised placebo-controlled study found[4] that it did not affect the severity of tremor or functionality in this patient group.

1. Bushara KO, *et al*. The effect of levetiracetam on essential tremor. *Neurology* 2005; **64:** 1078–80.
2. Zesiewicz TA, *et al*. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology* 2011; **77:** 1752–5. Also available at: http://www.neurology.org/content/77/19/1752.full.pdf+html (accessed 01/05/12)
3. Striano P, *et al*. Levetiracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. *J Neurol* 2006; **253:** 762–6.
4. Feys P, *et al*. The effect of levetiracetam on tremor severity and functionality in patients with multiple sclerosis. *Multiple Sclerosis* 2009; **15:** 371–8.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with levetiracetam are somnolence, weakness, and dizziness. Anorexia, diarrhoea, dyspepsia, nausea, weight gain or loss, myalgia, ataxia, headache, amnesia, depression, emotional lability, insomnia, nervousness, tremor, vertigo, diplopia, and rash (see below) may occur less frequently. Other adverse effects include paraesthesia, pancreatitis, hepatic failure, and hepatitis. A raised incidence of mild infections, such as the common cold and upper respiratory-tract infections, has been reported. Alopecia may also develop; in some cases, stopping levetiracetam has resulted in regrowth of hair.

Other adverse effects reported include abnormal behaviour, aggression, anger, anxiety, confusion, hallucinations, irritability, and psychotic disorders; these adverse effects may be more common in children than in adults. Blood dyscrasias such as neutropenia, pancytopenia, and thrombocytopenia may develop. Severe skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely.

Levetiracetam should be used with caution in patients with renal impairment, and/or severe hepatic impairment.

Care is required when withdrawing levetiracetam therapy—see also Uses and Administration, p. 531.1.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on the endocrine system. Hyponatraemia developed[1] in a patient given levetiracetam in whom carbamazepine had previously caused the syndrome of inappropriate antidiuretic hormone secretion; symptoms resolved on stopping levetiracetam and recurred on rechallenge.

For mention of the effects of antiepileptics on *sexual function*, including a lack of effect of levetiracetam, see under Phenytoin, p. 540.3.

1. Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. *Epilepsia* 2005; **46:** 972–3.

Effects on the liver. Fulminant hepatic failure requiring transplantation has been reported[1] in a patient 1 month after switching from oxcarbazepine to levetiracetam to improve seizure control. Levetiracetam was restarted after transplantation, resulting in rapid deterioration of liver function tests which subsequently normalised 4 weeks after the drug was stopped. In another case,[2] severe acute hepatitis occurred 3 weeks after levetiracetam was added to antiepileptic therapy with valproate; symptoms (such as fever, rash, eosinophilia, and interstitial pulmonary infiltrates) suggestive of an antiepileptic hypersensitivity syndrome were also reported. The patient made a full recovery after levetiracetam was stopped.

1. Tan TCH, *et al*. Levetiracetam as a possible cause of fulminant liver failure. *Neurology* 2008; **71:** 685–6.
2. Lens S, *et al*. Severe acute hepatitis in the dress [sic] syndrome: report of two cases. *Ann Hepatol* 2010; **9:** 198–201.

Effects on the lungs. Diffuse interstitial lung disease developed[1] after a dose increase of levetiracetam in a 9-year-old girl who had been taking the drug for 2 years. The condition resolved when levetiracetam was stopped and treatment with corticosteroids was given.

1. Newsome SD, *et al*. Levetiracetam-induced diffuse interstitial lung disease. *J Child Neurol* 2007; **22:** 628–30.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of levetiracetam on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the skin. For a suggestion that skin reactions are less common with levetiracetam than with some other antiepileptics, see under Phenytoin, p. 541.1.

Hypersensitivity. For mention of antiepileptic hypersensitivity syndrome possibly associated with levetiracetam, see Effects on the Liver, above.

Movement disorders. Levetiracetam has been associated with symptoms of parkinsonism including resting tremor, bradykinesia, and rigidity when used to treat Huntington's chorea in a 58-year-old man;[1] symptoms resolved within 7 days of stopping levetiracetam. The patient was also taking other drugs at the time and the authors suggested that these symptoms might have been caused by a drug interaction. However, levetiracetam has been tried in the treatment of some movement disorders as discussed under Uses and Administration, p. 531.3.

1. Zesiewicz TA, *et al*. Levetiracetam-induced parkinsonism in a Huntington disease patient. *Clin Neuropharmacol* 2005; **28:** 188–90.

Overdosage. A 38-year-old woman who ingested 30 g of levetiracetam vomited 4 hours later and presented with hypoxia, hypotension, and respiratory depression 6 hours after ingestion; peak plasma-levetiracetam concentration was 400 micrograms/mL.[1] The patient recovered without sequelae over 48 hours with symptomatic treatment.

1. Barrueto F, *et al*. A case of levetiracetam (Keppra) poisoning with clinical and toxicokinetic data. *J Toxicol Clin Toxicol* 2002; **40:** 881–4.

Porphyria. Levetiracetam has been successfully used in a few patients with porphyria[1,2] and the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levetiracetam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[3]

1. Paul F, Meencke HJ. Levetiracetam in focal epilepsy and hepatic porphyria: a case report. *Epilepsia* 2004; **45:** 559–60.
2. Bilo L, *et al*. Levetiracetam in idiopathic generalised epilepsy and porphyria cutanea tarda. *Clin Drug Investig* 2006; **26:** 357–9.
3. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

The UK Epilepsy and Pregnancy Register[1] provided data as of July 2005 from 117 first-trimester exposures to levetiracetam with 39 to monotherapy and 78 to adjunctive therapy. In the former group, 4 infants had a low birthweight and 4 were born at 37 weeks of gestation or less. In the latter, 10 had a low birth-weight, 18 were born at 37 weeks of gestation or less, and 3 had major congenital malformations. A subsequent review[2] commented that the risk of malformation with levetiracetam appeared low. Clearance of levetiracetam is increased during pregnancy, and monitoring of serum concentrations may be desirable, especially in the third trimester.

1. Hunt S, *et al*. Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006; **67:** 1876–9.
2. Longo B, *et al*. Levetiracetam use in pregnancy. *Ann Pharmacother* 2009; **43:** 1692–5.

Interactions

Evidence of significant interactions between levetiracetam and other antiepileptics is mostly lacking. However, for the effects of levetiracetam on carbamazepine, see p. 516.3.

Pharmacokinetics

Levetiracetam is readily absorbed from the gastrointestinal tract with a bioavailability of almost 100%; peak plasma concentrations usually occur within 1.3 hours of oral doses and steady state after 2 days. Plasma protein binding is minimal at less than 10%. Levetiracetam is not extensively metabolised; about 25% of a dose is metabolised by hydroxylation to inactive metabolites. Around 95% of a dose is excreted as unchanged drug and metabolites in the urine. The plasma elimination half-life has been reported to be about 7 hours in adults and children aged 12 years and over; the half-life may be shorter in younger children. Levetiracetam is distributed into breast milk.

References.

1. Radtke RA. Pharmacokinetics of levetiracetam. *Epilepsia* 2001; **42** (suppl 4): 24–7.
2. Pellock JM, *et al*. Pharmacokinetic study of levetiracetam in children. *Epilepsia* 2001; **42:** 1574–9.
3. Coupez R, *et al*. Levetiracetam: relative bioavailability and bioequivalence of a 10% oral solution (750 mg) and 750-mg tablets. *J Clin Pharmacol* 2003; **43:** 1370–6.
4. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet* 2004; **43:** 707 24.
5. Brockmöller J, *et al*. Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. *Clin Pharmacol Ther* 2005; **77:** 529–41.
6. Glauser TA, *et al*. Pharmacokinetics of levetiracetam in infants and young children with epilepsy. *Epilepsia* 2007; **48:** 1117–22.
7. Tomson T, *et al*. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007; **48:** 1111–16.
8. Hirsch LJ, *et al*. Effect of age and comedication on levetiracetam pharmacokinetics and tolerability. *Epilepsia* 2007; **48:** 1351–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Callexe; Keppra; Levron; Molival; Vecetam; ***Austral.***: Kepcet; Keppra; Kevtam; Levitam; ***Austria***: Keppra; ***Belg.***: Keppra; ***Canad.***: Keppra; ***Chile***: Ceumid; Keppra; Kopodex; Kredit; ***China***: Keppra (开浦兰); ***Cz.***: Keppra; ***Denm.***: Keppra; ***Fin.***: Keppra; ***Fr.***: Keppra; ***Ger.***: Keppra; ***Gr.***: Keppra; ***Hong Kong***: Keppra; ***Hung.***: Keppra; ***India***: Epictal; Keppra; Lenerve; Levecetam; Levera; Levesam; Levexx; Levipil; Levroxa; Levtam; ***Indon.***: Keppra; ***Irl.***: Keppra; Matever; ***Israel***: Keppra; Levetrim; ***Ital.***: Keppra; ***Jpn***: E Keppra; ***Malaysia***: Keppra; ***Mex.***: Keppra; ***Neth.***: Cezarius; Dretacen; Eliptus; Keppra; Latrea; Matever; Trund; Vetira; ***Norw.***: Keppra; ***NZ***: Keppra; ***Philipp.***: Ivetra; Keppra; ***Pol.***: Keppra; ***Port.***: Keppra; ***Rus.***: Keppra (Кеппра); ***S.Afr.***: Keppra; Redilev; ***Singapore***: Keppra; ***Spain***: Keppra; Laurak; Tirbas; ***Swed.***: Keppra; ***Switz.***: Keppra; Rivoleve; ***Thai.***: Keppra; ***Turk.***: Epileptal; Epitam; Epixx; Keppra; Lev-End; Netrolex; Vetria; ***UK***: Desitrend; Keppra; ***Ukr.***: Keppra (Кеппра); Levicitam (Левицитам); ***USA***: Keppra.

Pharmacopoeial Preparations

USP 36: Levetiracetam Extended-Release Tablets; Levetiracetam Oral Solution; Levetiracetam Tablets.

Mephenytoin *(BAN, USAN, rINN)*

Mefenitoína; Mefenytoiini; Mefenytoin; Mephenetoin; Méphénytoïne; Mephenytoinum; Methantoin; Methoin; NSC-34652; Phenantoin; Мефенитоин.

5-Ethyl-3-methyl-5-phenylhydantoin.

$C_{12}H_{14}N_2O_2$=218.3

CAS — 50-12-4.

ATC — N03AB04.

ATC Vet — QN03AB04.

UNII — R420KW629U.

Pharmacopoeias. In *US.*

USP 36: (Mephenytoin). Store in airtight containers.

Profile

Mephenytoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p. 538.2), but it is more toxic. Because of its potential toxicity it is not one of the main drugs used in the treatment of epilepsy (p. 506.1) and has been given orally only to patients unresponsive to other treatment. Some of the adverse effects of mephenytoin may be due to the metabolite, 5-ethyl-5-phenylhydantoin (also termed nirvanol). Like phenytoin the rate of metabolism of mephenytoin is subject to genetic polymorphism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Epilan†.

Pharmacopoeial Preparations
USP 36: Mephenytoin Tablets.

Mesuximide *(BAN, rINN)*

Mesuksimidi; Mesuximid; Mesuximida; Mésuximide; Mesuximidum; Methsuximide; PM-396; Мезуксимид.

N,2-Dimethyl-2-phenylsuccinimide.

$C_{12}H_{13}NO_2$=203.2

CAS — 77-41-8.

ATC — N03AD03.

ATC Vet — QN03AD03.

UNII — 0G76K8X6C0.

Pharmacopoeias. In *US.*

USP 36: (Methsuximide). A white to greyish-white crystalline powder. Is odourless or has a slight odour. Soluble 1 in 350 of water, 1 in 3 of alcohol, 1 in less than 1 of chloroform, and 1 in 2 of ether. Store in airtight containers.

Profile

Mesuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p. 521.1) that is used in the treatment of absence seizures; although it also has some activity in complex partial seizures it is reported to be less well tolerated than ethosuximide, and is usually only given to patients unresponsive to other antiepileptic treatment (below). It is thought to owe its activity to its major metabolite *N*-desmethylmesuximide.

The usual initial oral dosage is a single dose of 300 mg daily for the first week, and this is increased by 300 mg at weekly intervals to an optimum dosage, according to response. The suggested maximum daily dose is 1.2 g in divided doses.

Epilepsy. Mesuximide is used for absence seizures that are refractory to less toxic antiepileptics such as ethosuximide or valproate, which are the usual first-line drugs (see p. 506.1). Mesuximide has also been tried in complex partial seizures and myoclonic seizures.

References.
1. Tennison MB, *et al.* Methsuximide for intractable childhood seizures. *Pediatrics* 1991; **87:** 186–9.
2. Sigler M, *et al.* Effective and safe but forgotten: methsuximide in intractable epilepsies in childhood. *Seizure* 2001; **10:** 120–4.

Interactions. For the effect of mesuximide on lamotrigine and valproate, see p. 530.1 and p. 557.3, respectively.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Celontin; ***Ger.***: Petinutin; ***Switz.***: Petinutin; ***USA***: Celontin.

Pharmacopoeial Preparations
USP 36: Methsuximide Capsules.

Methylphenobarbital *(BAN, rINN)*

Enphenemalum; Mephobarbital; Methylfenobarbital; Méthylphénobarbital; Methylphenobarbitalum; Methylphenobarbitone; Metilfenobarbital; Metilfenobarbitál; Metilfenobarbitalis; Metylfenobarbital; Metyylifenobarbitaali; Phemitone; Метилфенобарбитал.

5-Ethyl-1-methyl-5-phenylbarbituric acid.

$C_{13}H_{14}N_2O_3$=246.3

CAS — 115-38-8.

ATC — N03AA01.

ATC Vet — QN03AA01.

UNII — 5NC67NU76B.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Methylphenobarbital). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; very slightly soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 36: (Mephobarbital). A white, odourless, crystalline powder. Slightly soluble in water, in alcohol, and in ether; soluble in chloroform and in solutions of fixed alkali hydroxides and carbonates. Its saturated solution in water is acid to litmus.

Profile

Methylphenobarbital is demethylated to phenobarbital (p. 535.2) and has been used similarly in the treatment of epilepsy; it has also been used as a sedative.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Mebaral†.

Multi-ingredient Preparations. ***Arg.***: Cumatil-L†; ***Ital.***: Dintoinale; Metinal-Idantoina L; Metinal-Idantoina.

Pharmacopoeial Preparations
BP 2014: Methylphenobarbital Tablets;
USP 36: Mephobarbital Tablets.

Oxcarbazepine *(BAN, USAN, rINN)*

GP-47680; KIN-493; Okskarbatsepiini; Okskarbazepin; Oxcarbazepin; Oxcarbazepina; Oxcarbazépine; Oxcarbazepinum; Окскарбазепин.

10,11-Dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide.

$C_{15}H_{12}N_2O_2$=252.3

CAS — 28721-07-5.

ATC — N03AF02.

ATC Vet — QN03AF02.

UNII — VZI5B1W380.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Oxcarbazepine). A white or faintly orange, crystalline powder. Practically insoluble in water and in alcohol; slightly soluble in dichloromethane.

USP 36: (Oxcarbazepine). Light orange to creamish white or off-white powder. Practically insoluble in water, sparingly soluble in chloroform; soluble in acetic acid. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Oxcarbazepine is a derivative of carbamazepine (p. 512.3) with similar actions. It is used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation (below). The initial oral dose for monotherapy and adjunctive therapy is 600 mg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 600 mg at about weekly intervals until the desired clinical response has been achieved. Maintenance doses are usually in the range of 600 mg to 1.2 g daily or up to 2.4 g daily if given as adjunctive therapy or in refractory patients switched from other antiepileptics.

For doses in children, see below.

Reduced initial doses are recommended in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of oxcarbazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in children. Oxcarbazepine is used in children as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. In the UK, the recommended initial oral dose for monotherapy and adjunctive therapy in those aged 6 years and over is 8 to 10 mg/kg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 10 mg/kg at about weekly intervals to a maximum dose of 46 mg/kg daily; usual maintenance doses in adjunctive therapy are around 30 mg/kg daily. In the USA, similar doses are recommended for adjunctive therapy in children aged 2 years and over (the initial dose may be doubled in those weighing under 20 kg), and for monotherapy in those aged 4 years and over; a maximum daily dose of 60 mg/kg is permitted for adjunctive therapy.

Administration in renal impairment. Initial doses of oxcarbazepine for adult patients with a creatinine clearance of less than 30 mL/minute should be 300 mg daily (half the usual starting dose, above), increased at weekly intervals or longer.

Bipolar disorder. Like the related drug carbamazepine (p. 513.1), oxcarbazepine has antimanic properties and has been tried in the management of patients with bipolar disorder (p. 397.2). Reviews[1,2] have suggested that it may be useful in treating acute mania and in patients with refractory disease; however, the evidence base is weak[3] and further studies are needed.

1. Pratoomsri W, *et al.* Oxcarbazepine in the treatment of bipolar disorder: a review. *Can J Psychiatry* 2006; **51:** 540–5.
2. Popova E, *et al.* Oxcarbazepine in the treatment of bipolar and schizoaffective disorders. *Expert Rev Neurother* 2007; **7:** 617–26.
3. Vasudev A, *et al.* Oxcarbazepine in the maintenance treatment of bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).

Epilepsy. Oxcarbazepine is used in the treatment of epilepsy (p. 506.1) and may be a useful alternative in patients unable to tolerate carbamazepine. A systematic review[1] found them to be of similar efficacy in partial seizures.

In a double-blind study[2] involving newly diagnosed adult patients, oxcarbazepine was of similar efficacy and tolerability to valproate for partial or generalised tonic-clonic seizures. Oxcarbazepine was of similar efficacy to phenytoin, but was better tolerated in adults and children with newly diagnosed partial or generalised tonic-clonic seizures.[3,4] Further randomised controlled studies and 2 small systematic reviews[5,6] have also confirmed the efficacy and tolerability of oxcarbazepine as adjunctive therapy[5,7] or monotherapy[6,8-10] in refractory partial seizures in children and adults.

1. Koch MW, Polman SKL. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 24/11/09).
2. Christe W, *et al.* A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997; **26:** 451–60.
3. Bill PA, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997; **27:** 195–204.
4. Guerreiro MM, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997; **27:** 205–13.
5. Castillo SM, *et al.* Oxcarbazepine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 09/06/08).
6. Muller M, *et al.* Oxcarbazepine versus phenytoin monotherapy for epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/06/08).
7. Glauser TA, *et al.* Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 2000; **54:** 2237–44.
8. Beydoun A, *et al.* Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology* 2000; **54:** 2245–51.
9. Sachdeo R, *et al.* Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 2001; **57:** 864–71.
10. Herranz Fernández JL, *et al.* Oxcarbacepina en monoterapia en 324 pacientes con crisis parciales (estudio TRINOVA). *Rev Neurol* 2004; **39:** 601–6.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p. 4.2). Oxcarbazepine has been tried in various neuropathic pain syndromes[1] including painful diabetic neuropathy[2-4] (see p. 8.2), postherpetic neuralgia[5,6] (p. 10.3), complex regional pain syndrome[7] (p. 8.1), glossopharyngeal neuralgia,[8] oxaliplatin-induced neuropathy[9] (see Effects on the Nervous System, p. 838.3), and trigeminal neuralgia (p. 11.2).

1. Magenta P, *et al.* Oxcarbazepine is effective and safe in the treatment of neuropathic pain: pooled analysis of seven clinical studies. *Neurol Sci* 2005; **26:** 218–26.
2. Dogra S, *et al.* Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. *Eur J Pain* 2005; **9:** 543–54.
3. Grosskopf J, *et al.* A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2006; **114:** 177–80.
4. Beydoun S, *et al.* Long-term safety and tolerability of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2007; **115:** 284–8.
5. Criscuolo S, *et al.* Oxcarbazepine (Trileptal) monotherapy dramatically improves quality of life in two patients with postherpetic neuralgia refractory to carbamazepine and gabapentin. *J Pain Symptom Manage* 2004; **28:** 535–6.
6. Criscuolo S, *et al.* Oxcarbazepine monotherapy in postherpetic neuralgia unresponsive to carbamazepine and gabapentin. *Acta Neurol Scand* 2005; **111:** 229–32.
7. Lalwani K, *et al.* Use of oxcarbazepine to treat a pediatric patient with resistant complex regional pain syndrome. *J Pain* 2005; **6:** 704–6.
8. Luef G, Poewe W. Oxcarbazepine in glossopharyngeal neuralgia: clinical response and effect on serum lipids. *Neurology* 2004; **63:** 2447–8.
9. Argyriou AA, *et al.* Efficacy of oxcarbazepine for prophylaxis against cumulative oxaliplatin-induced neuropathy. *Neurology* 2006; **67:** 2253–5.

Psychiatric disorders. Case reports[1,2] in children and adolescents and a randomised, placebo-controlled study[3] in adults have indicated some benefit from oxcarbazepine in the treatment of *aggression* and *disturbed behaviour* (p. 1030.2). A retrospective review[4] of 14 children and adolescents with various psychiatric and behavioural disorders found moderate symptomatic improvement in 50% after the addition of oxcarbazepine. Oxcarbazepine has also been tried in the treatment of *schizophrenia*[5] (p. 1031.3) and *post-traumatic stress disorder*[6] (p. 1029.2). For use in *bipolar disorder* see above.

1. Kapetanovic S. Oxcarbazepine in youths with autistic disorder and significant disruptive behaviors. *Am J Psychiatry* 2007; **164:** 832–3.
2. Gaudino MP, *et al.* Use of oxcarbazepine for treatment-resistant aggression. *Psychiatr Serv* 2003; **54:** 1166–7.
3. Mattes JA. Oxcarbazepine in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2005; **25:** 575–9.
4. Staller JA, *et al.* Oxcarbazepine in the treatment of child psychiatric disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2005; **15:** 964–9.
5. Leweke FM, *et al.* Oxcarbazepine as an adjunct for schizophrenia. *Am J Psychiatry* 2004; **161:** 1130–1.
6. Malek-Ahmadi P, Hanretta AT. Possible reduction in posttraumatic stress disorder symptoms with oxcarbazepine in a patient with bipolar disorder. *Ann Pharmacother* 2004; **38:** 1852–4.

Withdrawal syndromes and abstinence. Oxcarbazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Although it was not found[1] to be superior to placebo in the treatment of symptoms of the *alcohol withdrawal syndrome* (p. 1735.1), oxcarbazepine has been reported[2-4] to be of benefit in relapse prevention; further studies are considered warranted. It has been

given with tiapride.[5] It has also been tried[6,7] during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p. 1065.1).

1. Koethe D, *et al.* Oxcarbazepine—efficacy and tolerability during treatment of alcohol withdrawal: a double-blind, randomized, placebo-controlled multicenter pilot study. *Alcohol Clin Exp Res* 2007; **31:** 1188–94.
2. Croissant B, *et al.* Oxcarbazepine in alcohol relapse prevention: a case series. *Pharmacopsychiatry* 2004; **37:** 306–7.
3. Croissant B, *et al.* A pilot study of oxcarbazepine versus acamprosate in alcohol-dependent patients. *Alcohol Clin Exp Res* 2006; **30:** 630–5.
4. Martinotti G, *et al.* High and low dosage oxcarbazepine versus naltrexone for the prevention of relapse in alcohol-dependent patients. *Hum Psychopharmacol* 2007; **22:** 149–56.
5. Croissant B, *et al.* Oxcarbazepine in combination with Tiaprid in inpatient alcohol-withdrawal—a RCT. *Pharmacopsychiatry* 2009; **42:** 175–81.
6. Croissant B, *et al.* Scheme-based benzodiazepine detoxification with oxcarbazepine: a case report. *Pharmacopsychiatry* 2005; **38:** 222–3.
7. Croissant B, *et al.* Oxcarbazepine in rapid benzodiazepine detoxification. *Am J Drug Alcohol Abuse* 2008; **34:** 534–40.

Adverse Effects, Treatment, and Precautions

As for Carbamazepine, p. 514.1.

Hypersensitivity reactions occur less frequently with oxcarbazepine than with carbamazepine (see also under Carbamazepine, p. 515.1). However, cross-sensitivity does occur and about 25 to 30% of patients hypersensitive to carbamazepine may have such reactions with oxcarbazepine. Immediate (type I) hypersensitivity reactions including rash, pruritus, urticaria, angioedema, and anaphylaxis have occurred with oxcarbazepine therapy. Angioedema and anaphylaxis involving the larynx, glottis, lips, and eyelids have been reported in patients after the first or subsequent doses. Treatment should be stopped in those who develop hypersensitivity reactions to oxcarbazepine.

Reductions in plasma-sodium levels have also been seen with oxcarbazepine (see Hyponatraemia, below). Patients with cardiac insufficiency and secondary heart failure should be weighed regularly to detect fluid retention. Oxcarbazepine may, very rarely, impair cardiac conduction and patients with pre-existing conduction disorders should be carefully monitored. Very rarely, oxcarbazepine treatment has been associated with pancreatitis.

Dosage reductions are recommended in renal impairment.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on the blood. Although it would appear that oxcarbazepine is less likely than carbamazepine to cause blood dyscrasias such as leucopenia, individual cases have been reported. In one such case leucopenia and hyponatraemia developed in a 57-year-old woman while taking oxcarbazepine;[1] she recovered after treatment with filgrastim. It was noted that the patient had had a similar reaction when taking carbamazepine. Oxcarbazepine has also been associated with reversible pancytopenia[2] in a 40-year-old woman, and reversible thrombocytopenia[3] in a 63-year-old woman.

1. Ryan M, *et al.* Hyponatremia and leukopenia associated with oxcarbazepine following carbamazepine therapy. *Am J Health-Syst Pharm* 2001; **58:** 1637–9.
2. Calamaras MR, *et al.* Pancytopenia associated with the introduction of oxcarbazepine. *J Clin Psychopharmacol* 2007; **27:** 217–18.
3. Mahmud J, *et al.* Oxcarbazepine-induced thrombocytopenia. *Psychosomatics* 2006; **47:** 73–4.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of oxcarbazepine on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on sexual function. For mention of the effects of antiepileptics including oxcarbazepine on sexual function in male epileptic patients, see Effects on the Endocrine System, under Phenytoin, p. 540.3.

Hyponatraemia. Hyponatraemia appears to be more pronounced at clinical doses of oxcarbazepine than with carbamazepine. Hyponatraemia was reported[1] in 12 of 15 patients in whom oxcarbazepine was substituted for carbamazepine therapy. The fall in plasma-sodium concentrations appeared to be related to the dose of oxcarbazepine. In another report[2] hyponatraemia occurred in 23% of 350 patients whose serum-sodium concentrations were monitored. The manufacturers state that in 14 controlled studies sodium levels of less than 125 mmol/litre occurred in 2.5% of 1524 patients treated with oxcarbazepine compared with no such patients in the control groups. Most patients remain asymptomatic but some may experience drowsiness, increase in seizure frequency, and impaired consciousness.[3] In a later study[4] in 97 patients taking oxcarbazepine and 451 taking carbamazepine, hyponatraemia occurred in 29 (12 severe) of the former and in 61 (13 severe) of the latter. The authors failed to find a correlation between high doses of oxcarbazepine and the occurrence of hyponatraemia.

It has been suggested that serum-sodium concentrations should be measured before the start of therapy but routine monitoring, may be indicated only in elderly patients or if a high dosage is used.[5] Licensed product information recommends that monitoring be considered in those with pre-existing conditions associated with low sodium levels and in those taking other medications known to interfere with sodium levels, for example NSAIDs and diuretics.

Severe hyponatraemia has been reported[6] in a 12-year-old child during treatment with oxcarbazepine. A review of 48 other children who had received oxcarbazepine in the same centre, found that 9 had hyponatraemia, and the authors suggested that sodium levels should be monitored in paediatric patients. In another case,[7] a 7-year old boy developed a reversible coma caused by oxcarbazepine-induced hyponatraemia.

1. Pendlebury SC, *et al.* Hyponatraemia during oxcarbazepine therapy. *Hum Toxicol* 1989; **8:** 337–44.
2. Friis ML, *etal.* Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. *Acta Neurol Scand* 1993; **87:** 224–7.
3. Steinhoff BJ, *et al.* Hyponatraemic coma under oxcarbazepine therapy. *Epilepsy Res* 1992; **11;** 67–70.
4. Dong X, *et al.* Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005; **65:** 1976–8.
5. Kälviäinen R, *et al.* Place of newer antiepileptic drugs in the treatment of epilepsy. *Drugs* 1993; **46:** 1009–24.
6. Borusiak P, *et al.* Hyponatremia induced by oxcarbazepine in children. *Epilepsy Res* 1998; **30:** 241–6.
7. Paliwal V, *et al.* Oxcarbazepine induced hyponatremic coma. *NeurolIndia* 2006; **54:** 214–15.

Overdosage. A 36-year-old man[1] who ingested 30.6 g of oxcarbazepine showed no serious signs of toxicity. Serum concentrations of oxcarbazepine were 31.6 mg/litre 2 hours after ingestion; corresponding serum concentrations of the active monohydroxy metabolite were 37.2 mg/litre, which later peaked at 59.0 mg/litre 7 hours after ingestion. The patient remained conscious, though somnolent, and had fully recovered within 2 days.

1. van Opstal JM, *et al.* Severe overdosage with the antiepileptic drug oxcarbazepine. *Br J Clin Pharmacol* 2004; **58:** 329–31.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxcarbazepine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Plasma concentrations of the active monohydroxy metabolite of oxcarbazepine may be reduced by strong inducers of cytochrome P450 isoenzymes, such as carbamazepine, phenytoin, or phenobarbital. Oxcarbazepine appears to induce hepatic enzymes to a lesser extent than carbamazepine. However, oxcarbazepine and its active metabolite do inhibit the cytochrome P450 isoenzyme CYP2C19, and in high doses may raise plasma concentrations of phenobarbital or phenytoin. Oxcarbazepine and its metabolite also have the capacity to induce CYP3A4 and CYP3A5 with the possibility of reducing plasma concentrations of drugs such as carbamazepine (but see below), dihydropyridine calcium-channel blockers, and oral contraceptives.

References.
1. Sallas WM, *et al.* Pharmacokinetic drug interactions in children taking oxcarbazepine. *Clin Pharmacol Ther* 2003; **74:** 138–49.

Antiepileptics. In a study[1] of epileptic patients the area under the concentration-time curve (AUC) seen with monotherapy of *carbamazepine*, *phenytoin*, or *valproate* was unchanged when oxcarbazepine was added to treatment; only carbamazepine affected the pharmacokinetics of oxcarbazepine, producing a reduction in the AUC for the active metabolite hydroxycarbazepine. It was considered that there was unlikely to be any clinically relevant pharmacokinetic interaction if oxcarbazepine was used with any of these antiepileptics, including carbamazepine. However, increases in plasma-phenytoin concentration have been reported after use with oxcarbazepine (see p. 543.2).

There is a report of severe toxicity occurring when oxcarbazepine was used with *lamotrigine*.[2] For the effect of oxcarbazepine on lamotrigine concentrations, see p. 530.1.

1. McKee PJW, *et al.* A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. *Br J Clin Pharmacol* 1994; **37:** 27–32.
2. Alving J. Case of severe acute intoxication with oxcarbazepine combined with lamotrigine. *Epilepsia* 1994; **35** (suppl 7): 72.

Pharmacokinetics

Oxcarbazepine is completely absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver to the principal metabolite 10,11-dihydro-10-hydroxy-carbamazepine (licarbazepine, often referred to as MHD), which also possesses antiepileptic activity. The monohydroxy metabolite is widely distributed in the body and is about 40% bound to plasma proteins, mainly albumin. The plasma half-life has been reported to be about 2 hours for oxcarbazepine, and about 9 hours for the monohydroxy metabolite; consequently the latter provides most of the antiepileptic activity. Clearance of the monohydroxy metabolite is reported to be about 40% higher in children aged 4 to 12 years, and about 80% higher in those aged 2 to 4 years, than in adults. Oxcarbazepine is excreted in the urine mainly as metabolites; less than 1% is excreted as unchanged drug.

Oxcarbazepine and its monohydroxy metabolite cross the placental barrier and are distributed into breast milk.

The pharmacokinetics of oxcarbazepine and its monohydroxy metabolite are affected by use with other antiepileptics (see Interactions, above).

References.
1. Dickinson RG, *et al.* First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. *Eur J Clin Pharmacol* 1989; **37:** 69–74.
2. Patsalos PN, *et al.* Protein binding of oxcarbazepine and its primary active metabolite, 10-hydroxycarbazepine, in patients with trigeminal neuralgia. *Eur J Clin Pharmacol* 1990; **39:** 413–15.
3. Kumps A, Wurth C. Oxcarbazepine disposition: preliminary observations in patients. *Biopharm Drug Dispos* 1990; **11:** 365–70.
4. van Heiningen PNM, *et al.* The influence of age on the pharmacokinetics of the antiepileptic agent oxcarbazepine. *Clin Pharmacol Ther* 1991; **50:** 410–19.
5. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
6. May TW, *et al.* Clinical pharmacokinetics of oxcarbazepine. *Clin Pharmacokinet* 2003; **42:** 1023–42.
7. Rey E, *etal.* Oxcarbazepine pharmacokinetics and tolerability in children with inadequately controlled epilepsy. *J Clin Pharmacol* 2004; **44:** 1290–1300.
8. Flesch G. Overview of the clinical pharmacokinetics of oxcarbazepine. *Clin Drug Investig* 2004; **24:** 185–203.
9. Bring P, Ensom MH. Does oxcarbazepine warrant therapeutic drug monitoring? A critical review. *Clin Pharmacokinet* 2008; **47:** 767–78.

Pregnancy. Clearance of the active monohydroxy metabolite of oxcarbazepine was reported to increase[1,2] during pregnancy and to decrease[2] after delivery; one study[1] reported a reduction in plasma concentrations of about 36% during the third trimester. However, sample sizes in both studies were small.

1. Christensen J, *et al.* Oxcarbazepine concentrations during pregnancy: a retrospective study in patients with epilepsy. *Neurology* 2006; **67:** 1497–9.
2. Mazzucchelli I, *et al.* Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia* 2006; **47:** 504–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aurene; Oxca†; Rupox; Trileptal; ***Austral.***: Trileptal; ***Austria***: Trileptal; ***Belg.***: Trileptal; ***Braz.***: Alzepinol; Auram; Leptard; Oleptal; Oxcarb; Trileptal; Zyoxipina; ***Canad.***: Trileptal; ***Chile***: Oxicodal; Trileptal; Tussdra; ***China***: Ren Ao (仁澳); Trileptal (曲莱); Wan Yi (万仪); ***Cz.***: Trileptal†; ***Denm.***: Apydan; Trileptal; ***Fin.***: Apydan; Trileptal; ***Fr.***: Trileptal; ***Ger.***: Apydan; Timox; Trileptal; ***Gr.***: Trileptal; ***Hong Kong***: Trileptal; ***Hung.***: Apydan†; Trileptal; ***India***: Carbox; Mezalog; Oleptal; Oxana; Oxcarb; Oxcazo; Oxep; Oxeptal; Oxetol; Oxine; Oxmazetol; Oxrate; Oxzey; ***Indon.***: Barzepin; Prolepsi; Trileptal; ***Irl.***: Trileptal; ***Israel***: Trexapin; Trileptin; ***Ital.***: Tolep; ***Malaysia***: Trileptal; ***Mex.***: Actinium; Deprectal; Oxetol; Trileptal; ***Neth.***: Trileptal; ***Norw.***: Trileptal; ***NZ***: Trileptal; ***Philipp.***: Trileptal; ***Pol.***: Apydan†; Karbagen; Trileptal; ***Port.***: Epilfarmo; Proaxen; Trileptal; Zigabal; ***Rus.***: Trileptal (Трилептал); ***S.Afr.***: Trileptal; ***Spain***: Epilexter†; Oxcarmylan†; Trileptal; ***Swed.***: Trileptal; ***Switz.***: Apydan; Trileptal; ***Thai.***: Trileptal; ***Turk.***: Apilep; Epsile; Oxilepsi; Trileptal; ***UK***: Trileptal; ***USA***: Oxtellar; Trileptal; ***Venez.***: Trileptal.

Pharmacopoeial Preparations

USP 36: Oxcarbazepine Oral Suspension; Oxcarbazepine Tablets.

Perampanel *(USAN, rINN)*

E-2007; ER-155055-90; Pérampanel; Perampanelum; Перампанел.

5′-(2-Cyanophenyl)-1′-phenyl-2,3′-bipyridinyl-6′(1′*H*)-one.

$C_{23}H_{15}N_3O$=349.4

CAS — 380917-97-5.

ATC — N03AX22.

ATC Vet — QN03AX22.

UNII — H821664NPK.

Uses and Administration

Perampanel, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, is an antiepileptic used as adjunctive therapy in partial seizures with or without secondary generalisation (below) in patients aged 12 years and older. It is given orally as a single dose before bedtime. The initial dose is 2 mg daily, increased, according to response in steps of 2 mg at intervals of not less than 2 weeks, to a maximum of 12 mg daily. Maintenance doses are usually in the range of 4 to 8 mg daily. Patients who are also taking drugs that shorten the half-life of perampanel should be titrated at intervals of not less than 1 week (see also Interactions, below).

Reduced doses are recommended in patients with hepatic impairment (see below).

As with other antiepileptics, withdrawal of perampanel therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. However, due to its long half-life and slow decline in plasma concentrations, it can be stopped abruptly if absolutely necessary. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in hepatic impairment. Patients with mild or moderate hepatic impairment may be given the usual initial oral dose of perampanel (see Uses and Administration, above), increased according to response and tolerability to a maximum of 8 mg daily. Use in severe impairment is not recommended.

Epilepsy. Perampanel is one of the newer drugs used as adjunctive therapy in patients with partial seizures with or without secondary generalisation (p. 506.1). It appears to be reasonably well tolerated. Perampanel has also been investigated for the treatment of generalised epilepsy and epileptic syndromes such as Lennox-Gastaut syndrome.

References.
1. Krauss GL, *et al.* Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012; **78:** 1408–15.
2. French JA, *et al.* Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012; **79:** 589–96.
3. French JA, *et al.* Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2012. Available at: doi:10.1111/j.1528-1167.2012.03638.x
4. Krauss GL, *et al.* Perampanel, a selective, noncompetitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia* 2012. Available at: doi:10.1111/j.1528-1167.2012.03648.x
5. Rektor I, *et al.* Perampanel Study 207: long-term open-label evaluation in patients with epilepsy. *Acta Neurol Scand* 2012; **126:** 263–9.

Adverse Effects and Precautions

The most frequently reported adverse effects with perampanel are dizziness and somnolence. Other commonly reported adverse effects include ataxia, dysarthria, gait disturbance, balance disorders, vertigo, irritability, aggression, anger, anxiety, confusion, increased or decreased appetite, nausea, fatigue, back pain, diplopia, and blurred vision. An increased risk of falls has also been reported, particularly in the elderly.

Aggression appears to be dose-related; most cases were reported to be mild or moderate with recovery occurring spontaneously or after dosage adjustment, however, therapy had to be stopped in severe cases. Dosage reduction should be considered in patients who develop persistent symptoms of aggression.

Perampanel should be used with caution in those with a history of substance abuse.

Due to a lack of data, perampanel is not recommended in patients with severe hepatic impairment, or moderate or severe renal impairment, and in those undergoing haemodialysis. It should be used with caution in patients with mild or moderate hepatic impairment.

Care is required when withdrawing perampanel therapy—see also Uses and Administration, above.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The hepatic metabolism of perampanel is increased by antiepileptics that induce the cytochrome P450 isoenzyme CYP3A subfamily such as carbamazepine, oxcarbazepine, or phenytoin. Plasma concentrations of perampanel may be reduced up to threefold by use with these drugs and dosage adjustments may be necessary. Use with other drugs that induce or inhibit enzymes of the cytochrome P450 system may also alter plasma concentrations of perampanel and adjustments to the dosage of perampanel may be required. (For details, see Uses and Administration, above.)

Sex hormones. An oral dose of perampanel 12 mg daily for 21 days in healthy women also taking a combined *oral contraceptive* was found to decrease both the AUC and peak concentration of levonorgestrel by 40%; peak concentrations of ethinylestradiol were also reduced by 18%. No effects were noted in women receiving lower doses of perampanel.

A possible decrease in the efficacy of oral contraceptives, and a need for additional non-hormonal contraceptives, should be considered in women taking perampanel 12 mg daily.

Pharmacokinetics

Perampanel is readily absorbed after oral doses; food may delay absorption but does not affect the extent of absorption. It is about 95% bound to plasma proteins. Perampanel is extensively metabolised by oxidation, via the cytochrome P450 isoenzyme CYP3A subfamily, and glucuronidation. It is excreted in the urine and faeces mainly as oxidative and conjugated metabolites. The average half-life is about 105 hours, although this may be reduced to 25 hours by carbamazepine, a potent liver-enzyme inducer (see also Interactions, above).

Distribution into milk has been found in studies in *rats.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Fycompa; ***Norw.***: Fycompa; ***Switz.***: Fycompa; ***UK***: Fycompa; ***USA***: Fycompa.

Pheneturide *(BAN, rINN)*

Ethylphenacemide; Feneturida; Phénéturide; Pheneturidum; S-46; Фенетурид.

(2-Phenylbutyryl)urea.

$C_{11}H_{14}N_2O_2$=206.2

CAS — 90-49-3.

ATC — N03AX13.

ATC Vet — QN03AX13.

UNII — 878CEJ4HGX.

Profile

Pheneturide is an acetylurea antiepileptic that has been used orally in the treatment of complex partial seizures with or without secondary generalisation (p. 506.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Laburide.

Phenobarbital *(BAN, rINN)*

Ácido feniletilbarbitúrico; Fenobarbitaali; Fenobarbital; Fenobarbitál; Fenobarbitalis; Fenobarbitona; Phenemalum; Phénobarbital; Phenobarbitalum; Phenobarbitone; Phenylethylbarbituric Acid; Phenylethylmalonylurea; Фенобарбитал.

5-Ethyl-5-phenylbarbituric acid.

$C_{12}H_{12}N_2O_3$=232.2

CAS — 50-06-6.

ATC — N03AA02.

ATC Vet — QN03AA02.

UNII — YQE403BP4D.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phenobarbital:

Feenies; Phennies; Phenos.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Phenobarbital). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 36: (Phenobarbital). White, odourless, glistening, small crystals or a white crystalline powder. It may exhibit polymorphism. Soluble 1 in 1000 of water and 1 in 10 of alcohol; sparingly soluble in chloroform; soluble in ether and in solutions of fixed alkali hydroxides and carbonates. A saturated solution in water has a pH of about 5.

Phenobarbital Sodium *(BANM, rINN)*

Fenobarbitaalinatrium; Fenobarbital sódico; Fenobarbital sodná sůl; Fenobarbital sodowy; Fenobarbitalio natrio druska; Fenobarbitalnatrium; Fenobarbitál-nátrium; Natrii Phenobarbitalum; Phenemalnatrium; Phenobarbital-Natrium; Phénobarbital Sodique; Phenobarbitalum natricum; Phenobarbitone Sodium; Sodium Phenylethylbarbiturate; Soluble Phenobarbitone; Натрий Фенобарбитал.

Sodium 5-ethyl-5-phenylbarbiturate.

$C_{12}H_{11}N_2NaO_3$=254.2

CAS — 57-30-7.

ATC — N03AA02.

ATC Vet — QN03AA02.

UNII — SW9M9BB5K3.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.,* and *US.*

Ph. Eur. 8: (Phenobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in carbon dioxide-free water (a small amount may be insoluble); soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH not greater than 10.2. Store in airtight containers.

USP 36: (Phenobarbital Sodium). Flaky crystals, or white crystalline granules, or a white powder. It is odourless and hygroscopic. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 10% solution in water is between 9.2 and 10.2. Solutions decompose on standing. Store in airtight containers.

Incompatibility. Phenobarbital sodium is incompatible with many other drugs and phenobarbital may be precipitated from mixtures containing phenobarbital sodium. This precipitation is dependent upon the concentration and the pH, and also on the presence of other solvents.

Stability. Extemporaneous oral preparations of phenobarbital 10 mg/mL in a 1:1 mixture of *Ora-Plus* and either *Ora-Sweet* or *Ora-Sweet SF* (*Paddock, USA*) were found[1] to be stable for at least 115 days in amber plastic bottles stored at room temperature.

1. Cober MP, Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007; **64:** 644–6.

Uses and Administration

Phenobarbital is a barbiturate that may be used as an antiepileptic to control partial and generalised tonic-clonic seizures (p. 536.1). It is also used as part of the emergency management of acute seizures including status epilepticus (p. 536.2).

The dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires plasma concentrations of 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre. However, plasma-drug concentration monitoring is less useful than with other drugs because tolerance occurs. In the UK, the usual oral dose is 60 to 180 mg daily, taken at night. In the USA, total daily doses of up to 300 mg have been given.

Phenobarbital sodium may be given parenterally as part of the emergency management of acute seizures including status epilepticus. In the UK, for the control of status epilepticus, doses of 10 mg/kg to a maximum of 1 g may be given intravenously. The *BNF* recommends that intravenous injection solutions should be diluted 1 in 10 and given at a rate not exceeding 100 mg/minute. In some countries intramuscular doses of up to 320 mg have been used, repeated after 6 hours if necessary. However, doubts have been expressed about the efficacy of the intramuscular route owing to the delay in achieving adequate blood concentrations, and the subcutaneous route may cause tissue necrosis.

For doses in children, see p. 536.1.

As with other antiepileptics, withdrawal of phenobarbital therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Phenobarbital has also been used as a hypnotic and sedative but drugs such as the benzodiazepines are preferred.

Phenobarbital stimulates the enzymes in hepatic microsomes responsible for the metabolism of some drugs and normal body constituents including bilirubin, and for

this reason it has been used to reduce hyperbilirubinaemia in neonatal jaundice.

Phenobarbital magnesium and phenobarbital diethylamine have also been used.

Tetrabamate is a complex of phenobarbital, difebarbamate, and febarbamate but its use has been associated with the development of hepatitis.

Administration in children. Phenobarbital may be used in children as an antiepileptic to control all forms of epilepsy except absence seizures. It is also used as part of the emergency management of status epilepticus. The doses given below for all indications are those recommended by the *BNFC* in the UK.

For treatment of epilepsy, the following doses are given orally, unless stated otherwise, according to age:

- neonates: an initial dose of 20 mg/kg by slow intravenous injection, then 2.5 to 5 mg/kg once daily by slow intravenous injection or orally, adjusted according to response
- 1 month to 12 years: an initial dose of 1 to 1.5 mg/kg twice daily, increased by 2 mg/kg daily if necessary to a usual maintenance dose of 2.5 to 4 mg/kg once or twice daily
- 12 to 18 years: 60 to 180 mg once daily

For status epilepticus, the following doses are given intravenously, according to age:

- neonate to 12 years: an initial dose of 20 mg/kg, followed by 2.5 to 5 mg/kg once or twice daily
- 12 to 18 years: an initial dose of 20 mg/kg (to a maximum of 1 g), followed by 300 mg twice daily

Intravenous injection solutions should be diluted 1 in 10 and given at a rate not exceeding 1 mg/kg per minute.

Cerebral malaria. Various studies have investigated whether antiepileptics are beneficial in preventing seizures or long-term neurological disability that may be associated with cerebral malaria (p. 644.1). Single intramuscular doses of phenobarbital ranging from 3.5 mg/kg to 20 mg/kg have been reported to be effective anticonvulsants[1,2] but it was also found that the higher dose was associated with a doubling of mortality.[2] A systematic review,[3] that included these two studies as well as other data, concluded that phenobarbital should not be given routinely to patients with cerebral malaria as it might increase mortality. WHO[4] has also expressed the opinion that prophylactic anticonvulsants cannot be recommended.

If convulsions do occur, WHO[4] has noted that treatment should be similar to that for repeated seizures from any cause.

1. White NJ, *et al.* Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet* 1988; **ii:** 64–6.
2. Crawley J, *et al.* Effect of phenobarbitone on seizure frequency and mortality in childhood cerebral malaria: a randomized, controlled intervention study. *Lancet* 2000; **355:** 701–6.
3. Meremikwu MM, Marson AG. Routine anticonvulsants for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 09/06/08).
4. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: 2010. Also available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 08/06/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Epilepsy. Phenobarbital is used in the treatment of epilepsy (p. 506.1) for partial seizures with or without secondary generalisation and for primary generalised tonic-clonic seizures. It may also be tried for atypical absence, atonic, and tonic seizures but is not effective in absence seizures. However, the usefulness of phenobarbital is limited by problems of sedation in adults and paradoxical excitement in children. There is also concern about its effects on behaviour and cognition in children. Phenobarbital is therefore usually reserved for use in cases unresponsive to other antiepileptics, although some have suggested that its low cost and broad efficacy make it a suitable first-line drug in developing countries.

References.

1. Pal DK, *et al.* Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. *Lancet* 1998; **351:** 19–23.
2. Kwan P, Brodie MJ. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. *Epilepsia* 2004; **45:** 1141–9.
3. Wilmshurst JM, van Toorn R. Use of phenobarbitone for treating childhood epilepsy in resource-poor countries. *S Afr Med J* 2005; **95:** 392, 394, 396.
4. Wang WZ, *et al.* Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. *Lancet Neurol* 2006; **5:** 46–52.

Febrile convulsions. Phenobarbital has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p. 511.2), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63:** 1189–91.
2. Farwell JR, *et al.* Phenobarbital for febrile seizures: effects on intelligence and on seizure recurrence. *N Engl J Med* 1990; **322:** 364–9. Correction. *ibid.* 1992; **326:** 144.

Neonatal abstinence syndrome. For reference to the use of phenobarbital for the treatment of neonates with opioid abstinence syndrome, see p. 110.1.

Neonatal intraventricular haemorrhage. Phenobarbital is one of several drugs that has been tried to prevent the development of neonatal intraventricular haemorrhage (p. 1128.3). Initial studies[1-3] of antenatal use in the mother were promising, but a larger randomised study[4] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants that could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[5] A systematic review[6] of these and other studies concluded that giving phenobarbital before preterm birth cannot be recommended for routine clinical practice; strategies for future studies were suggested to improve methodology. Studies of use in neonates have also shown inconsistent results. A systematic review[7] of studies of phenobarbital for prophylaxis of intraventricular haemorrhage in preterm neonates concluded that postnatal use cannot be recommended either, and is associated with an increased need for mechanical ventilation.

1. Kaempf JW, *et al.* Antenatal phenobarbital for the prevention of periventricular and intraventricular hemorrhage: a double-blind, randomized, placebo-controlled, multihospital trial. *J Pediatr* 1990; **117:** 933–8.
2. Barnes ER, Thompson DF. Antenatal phenobarbital to prevent or minimize intraventricular hemorrhage in the low-birthweight neonate. *Ann Pharmacother* 1993; **27:** 49–52.
3. Thorp JA, *et al.* Antepartum vitamin K and phenobarbital for preventing intraventricular hemorrhage in the premature newborn: a randomized, double-blind, placebo-controlled trial. *Obstet Gynecol* 1994; **83:** 70–6.
4. Shankaran S, *et al.* The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. *N Engl J Med* 1997; **337:** 466–71.
5. Shankaran S, *et al.* Neurodevelopmental outcome of premature infants after antenatal phenobarbital exposure. *Am J Obstet Gynecol* 2002; **187:** 171–7.
6. Crowther CA, *et al.* Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 25/08/10).
7. Whitelaw A, Odd D. Postnatal phenobarbital for the prevention of intraventricular hemorrhage in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/06/08).

Neonatal seizures. Some consider phenobarbital to be the mainstay of treatment for all types of neonatal seizures (p. 511.3). In a study[1] in 120 neonates with clinical seizure activity of varying aetiology, 48 were controlled by an initial intravenous loading dose of phenobarbital 15 to 20 mg/kg over 10 to 15 minutes, and a further 37 were controlled by sequential bolus doses of phenobarbital 5 to 10 mg/kg every 20 to 30 minutes up to a serum concentration of 40 micrograms/mL. Of the remaining 35 neonates only 7 responded when the serum-phenobarbital concentration was increased to 100 micrograms/mL, 13 required addition of a second antiepileptic (phenytoin or lorazepam) and 4 were controlled by addition of a third drug. Phenobarbital alone can effectively control seizures in the majority of neonates with recurrent seizure activity.

Phenobarbital given prophylactically as a single dose of about 40 mg/kg intravenously over one hour has also been shown to be effective in reducing the incidence of seizures in 15 infants with severe perinatal asphyxia compared with a control group who only received phenobarbital if there was clinical evidence of seizures.[2] Subsequent follow-up over 3 years suggested that prophylactic phenobarbital might also improve later neurological outcome.[2] However, a later retrospective cohort study[3] found no significant difference in the rate of seizure recurrence and developmental outcome between infants who were discharged with prophylactic phenobarbital (33 patients) and those who were discharged without any antiepileptics (99).

1. Gilman JT, *et al.* Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics* 1989; **83:** 674–8.
2. Hall RT, *et al.* High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. *J Pediatr* 1998; **132:** 345–8.
3. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis. *J Child Neurol* 2007; **22:** 389–95.

Status epilepticus. Phenobarbital given intravenously is an alternative to intravenous phenytoin in the management of status epilepticus (p. 510.2). It should not be used in patients who have recently received oral phenobarbital or primidone.

Although one study[1] suggested that phenobarbital might be at least as effective, safe, and practical as diazepam with phenytoin for the initial treatment of convulsive status epilepticus, it tends to be reserved for patients who do not respond to benzodiazepines or phenytoin.

1. Shaner DM, *et al.* Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988; **38:** 202–7.

Withdrawal syndromes. Phenobarbital is used in some centres for the management of alcohol withdrawal syndrome (p. 1735.1), but has a lower safety profile than benzodiazepines (the treatment of choice) and creates the potential for multiple drug interactions. Additionally, a lack of well-defined studies make its role difficult to assess.[1] However, it has been reported of use in resistant cases.[2]

1. Rodgers JE, Crouch MA. Phenobarbital for alcohol withdrawal syndrome. *Am J Health-Syst Pharm* 1999; **56:** 175–8.
2. Hayner CE, *et al.* Phenobarbital treatment in a patient with resistant alcohol withdrawal syndrome. *Pharmacotherapy* 2009; **29:** 875–8.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects

The most frequent adverse effect associated with phenobarbital is sedation, but this often becomes less marked with continued use. Like some of the other antiepileptics, phenobarbital may produce subtle mood changes and impairment of cognition and memory that may not be apparent without testing. Depression may occur.

Prolonged use can occasionally result in folate deficiency; rarely, megaloblastic anaemia has been reported. There is some evidence that phenobarbital interferes with vitamin D metabolism.

At high doses nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage can prove fatal; toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock leading to renal failure. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) reportedly occur in about 6% of patients with barbiturate overdose.

Sodium salts of barbiturates have a very high pH in solution, and necrosis has followed subcutaneous injection or extravasation. Intravenous injections can be hazardous and cause hypotension, shock, laryngospasm, and apnoea, especially if given too rapidly.

Hypersensitivity reactions occur in a small proportion of patients; skin reactions are reported in 1 to 3% of patients taking phenobarbital, and are most commonly maculopapular, morbilliform, or scarlatiniform rashes. More severe reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are extremely rare. Hepatitis and disturbances of liver function have been reported.

Paradoxical excitement, restlessness, and confusion may sometimes occur in the elderly, and irritability and hyperactivity may occur in children.

Neonatal drug dependence and symptoms resembling vitamin K deficiency have been reported in infants born to mothers who received phenobarbital during pregnancy. Congenital malformations have been reported in children of women who received phenobarbital during pregnancy but the causal role of the drug is a matter of some debate.

Effects on the blood. For the effects of antiepileptics including phenobarbital on serum folate, see under Phenytoin, p. 540.2.

Effects on bone. For the effects of antiepileptics including phenobarbital on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on connective tissue. The use of phenobarbital and primidone has been associated with the development of Dupuytren's contracture, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, and general joint pain.[1]

1. Mattson RH, *et al.* Barbiturate-related connective tissue disorders. *Arch Intern Med* 1989; **149:** 911–14.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

Barbiturates may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p. 2341.3.

Effects on the liver. For mention of the effects of phenobarbital on the liver, see under Phenytoin, p. 541.1.

Effects on mental function. For a review of the effects of antiepileptics, including phenobarbital, on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

DEPRESSION. Follow-up of 28 patients aged 6 to 16 who had received phenobarbital or carbamazepine for epilepsy indi-

cated that the rate of major depression was significantly higher in those receiving phenobarbital.[1] It was recommended that treatment with phenobarbital should be avoided particularly in patients with a personal or family history of an affective disorder; patients who do receive it should be monitored for symptoms of depression.

1. Brent DA, *et al*. Phenobarbital treatment and major depressive disorder in children with epilepsy: a naturalistic follow-up. *Pediatrics* 1990; **85:** 1086–91.

DISTURBED BEHAVIOUR. Disturbed behaviour is a recognised adverse effect of phenobarbital, especially in children and the elderly; however, no excess in behavioural adverse effects was seen[1] on follow-up for up to 12 months in 40 children who took phenobarbital when compared with 45 who took carbamazepine.

1. Banu SH, *et al*. Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. Abridged version: *BMJ* 2007; **334:** 1207–10. Full version: http://www.bmj.com/cgi/reprint/334/7605/1207 (accessed 09/06/08)

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptics including phenobarbital.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[1,2] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[1]

1. Knowles SR, *et al*. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
2. Bessmertny O, *et al*. Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.

Treatment of Adverse Effects

As for the barbiturates (see Amobarbital, p. 1038.1).

Precautions

Phenobarbital and other barbiturates should be used with care in children and in elderly or debilitated patients, in those in acute pain, and in those with depressive disorders. Phenobarbital should be used with caution in patients with impaired hepatic, renal, or respiratory function; its use is contra-indicated in those with severe respiratory depression.

Breast feeding. The American Academy of Pediatrics[1] considers that phenobarbital should be given with caution to breast-feeding mothers, since there have been significant adverse effects including sedation and methaemoglobinaemia in nursing infants. The *BNF* also advises caution during breast feeding. Both authorities make similar recommendations for primidone.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Neonates. Care should be taken when giving phenobarbital orally as the elixir to neonates because regular dosing could result in alcohol toxicity [the BP 2014 formulation contains 38% v/v alcohol].[1] Aqueous preparations are more readily made using the sodium salt than the acid.[2]

1. Colquhoun-Flannery W, Wheeler R. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67:** 152.
2. Leach F. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67:** 152.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenobarbital as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Congenital craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described with antiepileptics including phenobarbital. *In utero* exposure to phenobarbital might result in neonatal sedation and drug dependence and also in neonatal bleeding due to vitamin K deficiency.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Valproate and phenytoin have been reported to cause rises in phenobarbital (and primidone) concentrations in plasma.

The effects of phenobarbital and other barbiturates are enhanced by other CNS depressants including alcohol.

Phenobarbital and other barbiturates may reduce the activity of many drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes.

Analgesics. *Dextropropoxyphene* 65 mg given three times daily to 4 epileptic patients stabilised on phenobarbital therapy increased serum-phenobarbital concentration by 8 to 29% but this was not considered of major importance in light of the normally accepted therapeutic range for phenobarbital.[1]

For the effect of phenobarbital on *fenoprofen*, *methadone*, and *pethidine*, see p. 59.3, p. 90.3, and p. 123.2, respectively. Enzyme-inducing antiepileptics such as phenobarbital also affect the threshold for the use of antidote in the treatment of *paracetamol* poisoning, see p. 118.3.

1. Hansen BS, *et al*. Influence of dextropropoxyphene on steady state serum levels and protein binding of three anti-epileptic drugs in man. *Acta Neurol Scand* 1980; **61:** 357–67.

Antiarrhythmics. For the effect of barbiturates such as phenobarbital on *disopyramide*, *lidocaine*, and *quinidine*, see p. 1365.2, p. 1995.1, and p. 1483.1, respectively.

Antibacterials. Serum concentrations of phenytoin and phenobarbital in a previously stabilised patient were increased when he took *chloramphenicol*.[1] Subsequent monitoring revealed a similar effect when chloramphenicol was taken with phenobarbital alone. In turn, phenobarbital may affect serum concentrations of chloramphenicol (see p. 259.1).

Barbiturates such as phenobarbital and primidone may enhance the metabolism of *doxycycline*.[2]

1. Koup JR, *et al*. Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24:** 571–5.
2. Neuvonen PJ, *et al*. Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9:** 147–54.

Anticoagulants. For the effect of barbiturates such as phenobarbital and primidone on *warfarin* and other coumarins, see p. 1532.1.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

St John's wort has been shown to induce several drug metabolising enzymes (see p. 449.3) and so might reduce the blood concentrations of phenobarbital, and increase the seizure risk.[1]

For the effect of phenobarbital on antidepressants, see under the monographs for *amitriptyline* (under Barbiturates, p. 406.3), *bupropion* (p. 410.2), *fluoxetine* (p. 424.2), *lithium* (p. 431.3), and *mianserin* (p. 435.2).

Inhibition of drug-metabolising enzymes by *MAOIs* may enhance the effects of barbiturates.

1. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antiepileptics. Interactions may occur if phenobarbital is given with other antiepileptics, of which probably the most significant is the interaction with *valproate*. Valproate increases plasma-phenobarbital concentration by a reported 17 to 48%,[1] and it may be necessary to reduce the dose of phenobarbital in some patients.[1,2] The mechanism for the increase appears to be inhibition of the metabolism of phenobarbital, resulting in reduced clearance;[2,3] valproate appears to inhibit both the direct *N*-glucosidation of phenobarbital and the *O*-glucuronidation of *p*-hydroxyphenobarbital.[4] However, phenobarbital reciprocally increases the clearance of valproate, and the valproate dose may also need to be adjusted.[5]

A similarly complex interaction exists between phenobarbital and *phenytoin*. Phenytoin can increase plasma concentrations of phenobarbital in some patients[6] since the two drugs compete for metabolism by the same enzyme system, but other evidence suggests that where this occurs it is rarely of significant magnitude.[7] Similarly, although phenobarbital induces the metabolism of phenytoin it is also, as stated, a competitive inhibitor and in practice the two effects appear to balance out, with rarely any need for dose adjustment.[7-9] However, dosage adjustment of phenobarbital may be crucial for some patients.[10] Measurement of serum concentrations of phenytoin and phenobarbital in one patient[10] showed that, in her case, large increases in serum-phenobarbital concentrations resulted from use with phenytoin; the increases were concentration-dependent.

The GABA-agonist, *progabide* has also been reported to cause a significant increase in phenobarbital concentrations when the two were given together to healthy subjects.[11]

Neurotoxicity, attributed to an increase in plasma concentrations of phenobarbital, has been seen[12] in one patient taking phenobarbital and sodium valproate when *felbamate* was added to treatment. The dosage of phenobarbital had already been reduced before treatment with felbamate was started. Data from a pharmacokinetic study[13] indicated that the interaction may result from the inhibition of phenobarbital hydroxylation by felbamate.

Vigabatrin has been reported to lower plasma concentrations of phenobarbital in some patients,[14] although dosage changes were not necessary in these patients.

High dose of *oxcarbazepine* may increase the plasma concentrations of phenobarbital but this was thought unlikely to be clinically significant;[15] conversely phenobarbital may reduce the plasma concentrations of the active metabolite of oxcarbazepine (p. 534.2).

For the effect of phenobarbital on the metabolism of other antiepileptics, see under *Carbamazepine*, p. 516.3, *Diazepam*, p. 1069.1, *Ethosuximide*, p. 521.3, *Lamotrigine*, p. 530.1, *Tiagabine*, p. 550.3, and *Zonisamide*, p. 561.3.

1. Richens A, Ahmad S. Controlled trial of sodium valproate in severe epilepsy. *BMJ* 1975; **4:** 255–6.
2. Patel IH, *et al*. Phenobarbital-valproic acid interaction. *Clin Pharmacol Ther* 1980; **27:** 515–21.
3. Kapetanović IM, *et al*. Mechanism of valproate-phenobarbital interaction in epileptic patients. *Clin Pharmacol Ther* 1981; **29:** 480–6.
4. Bernus I, *et al*. Inhibition of phenobarbitone N-glucosidation by valproate. *Br J Clin Pharmacol* 1994; **38:** 411–16.
5. Perucca E, *et al*. Disposition of sodium valproate in epileptic patients. *Br J Clin Pharmacol* 1978; **5:** 495–9.
6. Morselli PL, *et al*. Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179:** 88–107.
7. Eadie MJ, *et al*. Factors influencing plasma phenobarbitone levels in epileptic patients. *Br J Clin Pharmacol* 1977; **4:** 541–7.
8. Cucinell SA, *et al*. Drug interactions in man: lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6:** 420–9.
9. Booker HE, *et al*. Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21:** 383–5.
10. Kuranari M, *et al*. Effect of phenytoin on phenobarbital pharmacokinetics in a patient with epilepsy. *Ann Pharmacother* 1995; **29:** 83–4.
11. Bianchetti G, *et al*. Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28:** 68–73.
12. Gidal BE, Zupanc ML. Potential pharmacokinetic interaction between felbamate and phenobarbital. *Ann Pharmacother* 1994; **28:** 455–8.
13. Reidenberg P, *et al*. Effects of felbamate on the pharmacokinetics of phenobarbital. *Clin Pharmacol Ther* 1995; **58:** 279–87.
14. Browne TR, *et al*. A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl): 95S–100S.
15. Hossain M, *et al*. Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.

Antifungals. For the effect of phenobarbital on *griseofulvin*, see p. 583.1, and on *itraconazole*, see p. 585.1.

Antineoplastics. For the effect of phenobarbital on *teniposide*, see p. 867.2.

Antiprotozoals. For the effect of phenobarbital on *metronidazole*, see p. 939.2.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

For the effect of phenobarbital on antipsychotics, see under Chlorpromazine, p. 1052.2.

Antivirals. A patient stabilised on phenobarbital 100 mg daily had an episode of seizures 4 weeks after starting *HAART* therapy with abacavir, didanosine, ritonavir-boosted tipranavir, and enfuvirtide.[1] The patient's phenobarbital plasma concentrations had fallen from 16 to 8 micrograms/mL and an increase in the phenobarbital dosage to 150 mg daily was required to restore concentrations. The tipranavir/ritonavir component of HAART therapy was considered to be responsible.

For the possible effect of phenobarbital on *HIV-protease inhibitors*, see p. 987.3.

1. Bonora S, *et al*. Clinically significant drug interaction between tipranavir-ritonavir and phenobarbital in an HIV-infected subject. *Clin Infect Dis* 2007; **45:** 1654–5.

Beta blockers. For the effect of barbiturates on beta blockers, see Anxiolytics and Antipsychotics, under Interactions of Beta Blockers, p. 1322.1.

Calcium-channel blockers. For the effect of phenobarbital on *dihydropyridine calcium-channel blockers*, see under Nifedipine, p. 1453.3, and on *verapamil*, see p. 1525.2.

Cardiac glycosides. Phenobarbital may greatly accelerate the metabolism of *digitoxin* (p. 1353.2).

Ciclosporin. For the effect of phenobarbital on ciclosporin, see p. 1956.3.

Corticosteroids. For the effect of phenobarbital on corticosteroids, see p. 1619.3.

Diuretics. Serum-phenobarbital concentrations were raised in 8 of 10 epileptic patients taking phenobarbital and additional antiepileptics when given *furosemide* 40 mg three times daily for 4 weeks.[1] This might have been the cause of drowsiness in 5 of 14 patients, 3 of whom had to stop furosemide.

1. Ahmad S, *et al.* Controlled trial of frusemide as an antiepileptic drug in focal epilepsy. *Br J Clin Pharmacol* 1976; **3:** 621–5.

Levothyroxine. For the effects of barbiturates on levothyroxine, see p. 2341.3.

Montelukast. For the effect of phenobarbital on montelukast, see p. 1216.1.

Sex hormones. For the effect of phenobarbital on sex hormones in *oral contraceptives*, see p. 2243.2.

Theophylline. For the effect of phenobarbital on theophylline, see p. 1235.1.

Vaccines. *Influenza vaccination* can cause prolonged rises in serum-phenobarbital concentrations in some patients.[1]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; **5:** 817–20.

Vitamins. *Pyridoxine* reduced serum-phenobarbital concentrations in 5 patients.[1] Plasma concentrations of phenobarbital and primidone are possibly reduced by *folic acid* and *folinic acid*. For the effect of antiepileptics, including phenobarbital, on *vitamin D* concentrations, see Effects on Bone, under Adverse Effects of Phenytoin, p. 540.2.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; **i:** 256.

Pharmacokinetics

Like other barbiturates phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid-insoluble; peak concentrations occur about 2 hours after oral doses and within 4 hours of intramuscular doses.

Phenobarbital is about 45 to 60% bound to plasma proteins and is only partly metabolised in the liver. About 25% of a dose is excreted in the urine unchanged at normal urinary pH. The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. Phenobarbital kinetics show considerable interindividual variation.

Monitoring of plasma concentrations has been performed as an aid in assessing control and the therapeutic range of plasma-phenobarbital has been quoted as 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre.

Phenobarbital crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of phenobarbital are affected if given with other antiepileptics (see under Interactions, p. 537.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alepsal; Gardenal; Luminal; Luminaletas; Neurogabaf†; ***Belg.***: Gardenal; ***Braz.***: Barbitron; Carbital; Edhanol; Fenocris; Garbital; Gardenal; Unifenobarb; ***Cz.***: Luminal; Phenaemal; Phenaemaletten; ***Denm.***: Fenemal; ***Fr.***: Aparoxal; Gardenal; Kaneuron; ***Ger.***: Luminal; Luminaletten; ***Gr.***: Gardenal; Kaneuron; Lumidrops; ***Hong Kong***: Uni-Feno†; ***Hung.***: Sevenal; Sevenaletta; ***India***: Barbee; Emgard; Epitan; Fenobarb; Gardenal; Luminal; Phenetone; ***Indon.***: Sibital; ***Ital.***: Gardenale; Luminale; ***Mex.***: Alepsal; Fenabbott†; ***Norw.***: Fenemal; ***Philipp.***: Luminal; ***Pol.***: Luminalum; ***Port.***: Bialminal; Luminal; Luminaletas; ***Rus.***: Valocordin (Валокордин); ***S.Afr.***: Lethyl; Sedabarb; ***Spain***: Gardenal; Luminal; Luminaletas; ***Swed.***: Fenemal; ***Switz.***: Aphenylbarbit; Luminal†; ***Thai.***: Elixir Phenobarb; Gardenal; Menobarb†; Phenobarb; Phenoco†; Phenotal; ***Turk.***: Luminal; Luminaletten; ***USA***: Luminal; ***Venez.***: Gardenal.

Multi-ingredient Preparations. ***Arg.***: Cumatil-L†; Lotoquis; ***Belg.***: Vethoine; ***Braz.***: Vagostesyl; ***Canad.***: Bellergal; Diclophen†; ***Chile***: Abalgin; Baldmin; Bufacyl; Ergobelan; Sinpasmon; Valpin; ***China***: Xi Li Shu (希力舒); ***Cz.***: Alnagon†; Sanepil†; ***Fr.***: Alepsal; ***Gr.***: Diphenal; ***Hong Kong***: Sedral†; Uni-Theodal†; ***Hung.***: Germicid-C; Meristin; Radipon†; Troparinum; ***India***: Alergin; Asmapax; Barbitoin; Beetal; Cadiphylate; Cortasthma; Dilantin with Phenobarbital†; Epilan C; Epiphen; Episol Plus; Ergophen; Garoin; ***Indon.***: Bellapheen; Ditalin; Piptal; ***Israel***: Philinal†; Philinet†; ***Ital.***: Gamibetal Complex; Metinal-Idantoina L; ***Jpn***: Trancolon P; ***Mex.***: Alepsal Compuesto; Gamibetal Complex†; Paliatil; ***Pol.***: Bellergot; Milocardin; ***Port.***: Anti-Asmatico†; ***Rus.***: Andipal (Андипал); Barboval (Барбовал); Bellataminal (Беллатаминал); Pagluferal (Паглюферал); Pentabufen (Пентабуфен); Pentalgin Plus (Пенталгин Плюс); Pentalgin-N (Пенталгин-Н); Pyralgin (Пиралгин); Quintalgine (Квинталгин); Santoperalgin (Сантопералгин); Santotitralgin (Сантотитралгин); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); Tetralgin (Тетралгин); Theophedrinum-N (Теофедрин-Н); Valoserdin (Валосердин); ***S.Afr.***: Adco-Phenobarbitone Vitalet; Donnatal†; Millerspas†; Natrophylline Compound†; Propain Forte; ***Spain***: Redutona†; ***Thai.***: Benera†; Neuramizone; ***Turk.***: Bellergal; Para-Nox; Pedimat; ***Ukr.***: Barboval (Барбовал); Corvaldinum (Корвалдин); Corvaltab (Корвалтаб); Pentased (Пентасед); Sedal-M (Седал-М); Tetralgin (Тетралгин); ***USA***: Alkabel; Antispasmodic Elixir; Bel-Phen-Ergot S†; Bellacane; Bellamine†; Bellatal; Bellergal-S; Donnatal; Folergot-DF; Hyosophen; PB-Hyos; Phenerbel-S; Quadrapax; Quadrinal; Se-Donna PB HYOS; Servira; Susano; Tedrigen; Theodrine; ***Venez.***: Ervostal; Traveget.

Pharmacopoeial Preparations

BP 2014: Paediatric Phenobarbital Oral Solution; Phenobarbital Elixir; Phenobarbital Injection; Phenobarbital Sodium Tablets; Phenobarbital Tablets;

USP 36: Phenobarbital Elixir; Phenobarbital Oral Suspension; Phenobarbital Sodium for Injection; Phenobarbital Sodium Injection; Phenobarbital Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Phensuximide *(BAN, rINN)*

Fensuksimidi; Fensuximid; Fensuximida; Phensuximidum; Фенсуксимид.

N-Methyl-2-phenylsuccinimide.

$C_{11}H_{11}NO_2$=189.2

CAS — 86-34-0.

ATC — N03AD02.

ATC Vet — QN03AD02.

UNII — 6WVL9C355G.

Pharmacopoeias. In *US*.

USP 36: (Phensuximide). A white to off-white crystalline powder. Is odourless or has not more than a slight odour. Slightly soluble in water; soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Phensuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p. 521.1), but it is reported to be less effective.

Preparations

Pharmacopoeial Preparations

USP 36: Phensuximide Capsules.

Phenytoin *(BAN, USAN, rINN)*

Difenilhidantoína; Diphenylhydantoin; Fanantina; Fenantoína; Fenitoin; Fenitoína; Fenitoinas; Fenytoiini; Fenytoin; Fenytoina; Phenantoinum; Phénytoïne; Phenytoinum; Фенитоин.

5,5-Diphenylhydantoin; 5,5-Diphenylimidazolidine-2,4-dione.

$C_{15}H_{12}N_2O_2$=252.3

CAS — 57-41-0.

ATC — N03AB02.

ATC Vet — QN03AB02.

UNII — 6158TKW0C5.

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Phenytoin). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Phenytoin). A white, odourless powder. Practically insoluble in water; soluble in hot alcohol; slightly soluble in cold alcohol, in chloroform, and in ether. Store in airtight containers.

Phenytoin Sodium *(BANM, rINNM)*

Diphenin; Fenitoin Sodyum; Fenitoína sódica; Fenitoinátrium; Fenitoino natrio druska; Fenytoiininatrium; Fenytoin sodná sůl; Fenytoina sodowa; Fenytoinnatrium; Natrii Phenytoinum; Phenytoin-Natrium; Phénytoïne sodique; Phenytoinum natricum; Soluble Phenytoin; Натрий Фенитоин.

$C_{15}H_{11}N_2NaO_2$=274.3

CAS — 630-93-3.

ATC — N03AB02.

ATC Vet — QN03AB02.

UNII — 4182431BJH.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Phenytoin Sodium). A white or almost white, slightly hygroscopic, crystalline powder. Soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 36: (Phenytoin Sodium). A white, odourless powder. Is somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide. Freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Phenytoin sodium only remains in solution when the pH is considerably alkaline (about 10 to 12) and there have been reports of loss of clarity or precipitation of phenytoin crystals when solutions of phenytoin sodium for injection have been mixed with other drugs[1-6] or added to intravenous infusion fluids,[7-10] while binding has been reported after addition to enteral nutrition solutions.[11] A phenytoin precipitate has blocked implanted central venous access devices after the inadvertent admixture of phenytoin sodium with glucose 5% or glucose in sodium chloride (pH 4);[12,13] the blockage can be successfully cleared by the local instillation of sodium bicarbonate 8.4% to increase the pH of the medium.

1. Misgen R. Compatibilities and incompatibilities of some intravenous solution admixtures. *Am J Hosp Pharm* 1965; **22:** 92–4.
2. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
3. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
4. Hasegawa GR, Eder JF. Visual compatibility of dobutamine hydrochloride with other injectable drugs. *Am J Hosp Pharm* 1984; **41:** 949–51.
5. Gayed AA, *et al.* Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52:** 516–20.
6. Trissel LA, *et al.* Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1287–92.
7. Bauman JL, *et al.* Phenytoin crystallization in intravenous fluids. *Drug Intell Clin Pharm* 1977; **11:** 646–9.
8. Bauman JL, Siepler JK. Intravenous phenytoin (concluded). *N Engl J Med* 1977; **296:** 111.
9. Cloyd JC, *et al.* Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids. *Am J Hosp Pharm* 1978; **35:** 45–8.
10. Giacona N, *et al.* Crystallization of three phenytoin preparations in intravenous solutions. *Am J Hosp Pharm* 1982; **39:** 630–4.
11. Miller SW, Strom JG. Stability of phenytoin in three enteral nutrient formulas. *Am J Hosp Pharm* 1988; **45:** 2529–32.
12. Akinwande KI, Keehn DM. Dissolution of phenytoin precipitate with sodium bicarbonate in an occluded central various access device. *Ann Pharmacother* 1995; **29:** 707–9.
13. Tse CST, Abdullah R. Dissolving phenytoin precipitate in central venous access device. *Ann Intern Med* 1998; **128:** 1049.

Uses and Administration

Phenytoin is a hydantoin antiepileptic used to control partial and generalised tonic-clonic seizures (see Epilepsy, p. 539.2). It is also used as part of the emergency treatment of status epilepticus (p. 539.3) and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head (see Post-traumatic Seizures, p. 539.3). Phenytoin has also been used in the treatment of trigeminal neuralgia. It is a class Ib antiarrhythmic and has been used to treat cardiac arrhythmias.

Doses may be expressed in terms of phenytoin or phenytoin sodium; although phenytoin 92 mg is equivalent to about 100 mg of phenytoin sodium these molecular equivalents are not necessarily biologically equivalent. In the UK an oral suspension of phenytoin 90 mg in 15 mL may be considered about equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg. In the USA a suspension containing phenytoin 125 mg in 5 mL is available.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; in many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some have control at concentrations outside this range. A suggested initial oral dose of phenytoin or phenytoin sodium given as a single dose or in divided doses is 3 to 4 mg/kg daily or 150 to 300 mg daily progressively increased with care to 600 mg daily if necessary; the suggested minimum interval between increments has ranged from about 7 to 10 days. Particular care is needed at higher doses, where saturation of metabolism may mean that a small increment produces a large rise in plasma concentrations. A usual maintenance dose is 200 to 500 mg daily.

The practice of starting phenytoin therapy with initial small doses means that more than a week may be required before therapeutic plasma concentrations are attained; it has been reported that it may even be several weeks before a steady-state concentration is established. An initial loading

dose may therefore be given, with the usual maintenance dosage being instituted 24 hours after the loading dose. Once the patient is stabilised the long half-life of phenytoin may permit the total daily dose to be given in two daily divisions or as a single dose, usually at night.

Although clinical evidence is lacking, different brands of phenytoin, as well as different formulations from the same manufacturer, may vary in their bioavailability and patients may need to be restabilised in the event of a change.

In order to lessen gastric irritation, phenytoin should be taken with or after food. The time and manner of taking phenytoin should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

As with other antiepileptics, withdrawal of phenytoin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Treatment of tonic-clonic **status epilepticus** is usually begun with a benzodiazepine such as diazepam or lorazepam given intravenously or rectally, and followed by phenytoin sodium intravenously. A suggested dose of phenytoin sodium is 10 to 15 mg/kg given by slow intravenous injection or by intermittent infusion at a uniform rate of not more than 50 mg/minute. Thereafter maintenance doses of 100 mg orally or intravenously are given every 6 to 8 hours; the rate and dose should be reduced according to body-weight.

For doses in children, see below.

Deaths have been caused by the over-rapid intravenous injection of phenytoin sodium and continuous monitoring of the ECG and blood pressure is recommended whenever phenytoin sodium is given intravenously.

Phenytoin sodium is absorbed slowly and erratically from the intramuscular site and therefore intramuscular injections are not appropriate for the emergency arrest of status epilepticus. They may, however, be used in certain situations to maintain or establish therapeutic plasma concentrations of phenytoin in patients who are unconscious or otherwise unable to take phenytoin orally. Owing to the slower absorption of phenytoin from intramuscular sites, patients stabilised on the oral route require an increase in the intramuscular dose of about 50%; it is recommended that, if possible, intramuscular injections of phenytoin sodium should not be continued for longer than one week. On transfer back to the oral route the patient should receive 50% of the original oral dose for the same period of time as intramuscular injections were given, to allow for continued absorption of the residual phenytoin in the intramuscular sites. For the **prevention and treatment of seizures associated with neurosurgery** in patients who have not previously taken phenytoin sodium, a suggested intramuscular dose is 100 to 200 mg given at 4-hourly intervals during surgery and continued post-operatively for 48 to 72 hours. Thereafter, the dose should be reduced to a maintenance dose of 300 mg daily and adjusted according to plasma-phenytoin concentrations. If more than one week of intramuscular therapy is required, an alternative route such as gastric intubation should be used.

Administration in children. Phenytoin may be given to children for the control of all forms of epilepsy except absence seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; young children may require a higher dose per kg body-weight than adults due to more rapid metabolism. In many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range; the *BNFC* suggests concentrations of 6 to 15 micrograms/mL (25 to 60 micromoles/litre) in neonates and those aged up to 3 months. The recommended initial oral dose of phenytoin or phenytoin sodium for children is 5 mg/kg daily in 2 or 3 divided doses up to a maximum of 300 mg daily; the usual maintenance dose is 4 to 8 mg/kg daily in divided doses. Alternatively, the *BNFC* suggests the following doses given according to age:

- neonates: an initial loading dose of 18 mg/kg by slow intravenous injection, over 20 to 30 minutes, followed by oral doses of 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily
- 1 month to 12 years: an initial oral dose of 1.5 to 2.5 mg/kg twice daily followed by 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily or 300 mg daily
- 12 years and older: usual adult doses (see p. 538.3)

For **status epilepticus** and for the **prevention and treatment of seizures associated with neurosurgery or trauma** the *BNFC* suggests the following doses of phenytoin sodium given by slow intravenous injection or infusion according to age:

- neonates and children up to 12 years: a loading dose of 20 mg/kg followed by 2.5 to 5 mg/kg twice daily
- 12 to 18 years: a loading dose of 20 mg/kg followed by up to 100 mg 3 or 4 times daily

Intravenous injections and infusions of phenytoin sodium should be given at a rate not exceeding 1 mg/kg per minute (a maximum of 50 mg per minute).

A comparison of methods[1] for the prediction of required phenytoin dosage in paediatric patients indicated that all methods produced a sizeable number of predictions with an error of more than 10% and that close monitoring of serum concentrations and clinical status was recommended regardless of the method chosen to adjust dosage. Similar conclusions have been made regarding the need to monitor plasma concentrations of phenytoin in the newborn and young infants.[2]

1. Yuen GJ, *et al.* Phenytoin dosage predictions in paediatric patients. *Clin Pharmacokinet* 1989; **16:** 254–60.
2. Loughnan PM, *et al.* Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 1977; **52:** 302–9.

Administration in the elderly. Pharmacokinetic studies in elderly patients have shown reduced binding to plasma proteins which was not itself an indication for dosage change,[1] but a study showing a decreased metabolism[2] did indicate that elderly patients may need lower doses of phenytoin than younger adults to maintain similar serum concentrations.

1. Patterson M, *et al.* Plasma protein binding of phenytoin in the aged: in vivo studies. *Br J Clin Pharmacol* 1982; **13:** 423–5.
2. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. *Clin Pharmacol Ther* 1982; **31:** 301–4.

Cardiac arrhythmias. Phenytoin has been given intravenously in the treatment of ventricular arrhythmias (p. 1266.1), especially those caused by overdosage with cardiac glycosides. Although this use now appears to be obsolete, in the UK the licensed dose of phenytoin sodium is 3.5 to 5 mg/kg given by slow intravenous injection at a uniform rate of not more than 50 mg/minute, repeated once if necessary.

Eclampsia and pre-eclampsia. Phenytoin has been used for eclampsia but now treatment with magnesium sulfate is preferred, see p. 511.1.

Epidermolysis bullosa. There have been reports[1-3] of a favourable but variable clinical response to phenytoin in patients with some variants of epidermolysis bullosa (p. 1684.3), a condition for the severe forms of which there is no truly effective treatment. However, a double-blind placebo-controlled study[4] concluded that phenytoin was not an effective treatment for the recessive dystrophic variant, and offered no overall benefit when compared with placebo.

1. Bauer EA, *et al.* Phenytoin therapy of recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1980; **303:** 776–81.
2. Cooper TW, Bauer EA. Therapeutic efficacy of phenytoin in recessive dystrophic epidermolysis. *Arch Dermatol* 1984; **120:** 490–5.
3. Scheinfeld N. Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. *Dermatol Online J* 2003; **9:** 6.
4. Caldwell-Brown D, *et al.* Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1992; **327:** 163–7.

Epilepsy. Phenytoin has long been used in the treatment of partial seizures with or without secondary generalisation and in primarily generalised tonic-clonic seizures, although other drugs may be better tolerated and easier to use (see p. 506.1). It is also effective in other forms of epilepsy with the exception of absence and myoclonic seizures.

Hiccup. Phenytoin may be of value for the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups, see under Chlorpromazine, p. 1046.3.

1. Petroski D, Patel AN. Diphenylhydantoin for intractable hiccups. *Lancet* 1974; **i:** 739.

Myotonia. A review[1] of myotonia congenita, a hereditary muscular disorder characterised by symptoms of muscle stiffness especially after rest and on starting to move. Where treatment is necessary it is usually with phenytoin or procainamide, the former being preferred as being better tolerated.

1. Gutmann L, *et al.* Myotonia congenita. *Semin Neurol* 1991; **11:** 244–8.

Neonatal seizures. Phenytoin is one of the antiepileptics that may be used in the management of neonatal seizures (p. 511.3).

Neuropathic pain. Phenytoin is used alone or added to treatment in trigeminal neuralgia (p. 11.2) in patients unresponsive to or intolerant of carbamazepine. It has also been used in the treatment of painful diabetic neuropathy (p. 8.2).

Post-traumatic seizures. About 12% of patients with severe traumatic brain injury develop seizures and the rate may be more than 50% for those with penetrating missile injuries.[1] The use of antiepileptics to treat such seizures is standard but there has been some debate about prophylactic use. Evidence suggests that prophylaxis with phenytoin (and perhaps carbamazepine or levetiracetam) is effective in preventing early seizures (arbitrarily defined as those occurring up to 7 days after trauma), but prophylaxis with these or other antiepileptics such as phenobarbital valproate, has not been shown to be effective for preventing late seizures, disability, or death.[1-7] Guidelines and recommendations for such use have been issued.[1,8,9] Children with severe, acute neurotrauma were found to have markedly altered protein binding and phenytoin metabolism, and therefore may require increased doses.[10]

1. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; **60:** 10–16. Also available at: http://www.neurology.org/cgi/reprint/60/1/10.pdf (accessed 09/06/08)
2. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/06/08).
3. Chadwick D. Seizures and epilepsy after traumatic brain injury. *Lancet* 2000; **355:** 334–5.
4. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia* 2001; **42:** 515–24.
5. Agrawal A, *et al.* Post-traumatic epilepsy: an overview. *Clin Neurol Neurosurg* 2006; **108:** 433–9.
6. Beghi E. Overview of studies to prevent posttraumatic epilepsy. *Epilepsia* 2003; **44** (suppl 10): 21–6.
7. Jones KE, *et al.* Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus* 2008; **25:** E3. Also available at: http://thejns.org/doi/pdf/10.3171/FOC.2008.25.10.E3 (accessed 25/11/09)
8. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products. *Arch Intern Med* 1999; **159:** 2639–44.
9. Bratton SL, *et al.* Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, and Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury—XIII: antiseizure prophylaxis. *J Neurotrauma* 2007; **24** (suppl 1): S-83–S-86. Also available at: https://www.braintrauma.org/pdf/protected/Guidelines_Management_2007w_bookmarks.pdf (accessed 25/08/10)
10. Stowe CD, *et al.* Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. *J Clin Pharmacol* 2000; **40:** 1452–61.

Status epilepticus. A benzodiazepine is the usual choice to abort an attack of status epilepticus (p. 510.2). If this fails to control the seizures or the seizures recur, then intravenous phenytoin may be given.

Once seizures have been brought under control, maintenance antiepileptic therapy may be started.

Syndrome of inappropriate ADH secretion. Phenytoin has been used occasionally to inhibit pituitary antidiuretic hormone (ADH) secretion in patients with the syndrome of inappropriate ADH secretion (SIADH), the management of which is discussed on p. 2351.2.

Tinnitus. Phenytoin is one of many drugs that have been tried in tinnitus (p. 1994.1), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

Withdrawal syndromes. Phenytoin has little place in the management of seizures associated with the *alcohol withdrawal syndrome* (p. 1735.1). Prophylaxis with phenytoin has been shown[1,2] to be ineffective for prevention of recurrent alcohol-related seizures and therefore drugs such as the benzodiazepines or clomethiazole, which are effective both for the treatment and prophylaxis of such seizures, are preferred.

Results from a double-blind study[3] indicated that phenytoin was associated with a reduction in *cocaine abuse* compared with placebo. A later review,[4] which included this study, found insufficient evidence to support the use of antiepileptics (carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and valproate) for the treatment of cocaine dependence. The authors noted that although the methodological quality of the included studies was high, the sample sizes were small. The abuse of cocaine is discussed on p. 1988.3 and treatment of cocaine withdrawal on p. 1990.1.

1. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. *Ann Emerg Med* 1991; **20:** 520–2.
2. Rathlev NK, *et al.* The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Ann Emerg Med* 1994; **23:** 513–8.
3. Crosby RD, *et al.* Phenytoin in the treatment of cocaine abuse: a double-blind study. *Clin Pharmacol Ther* 1996; **59:** 458–68.
4. Minozzi S, *et al.* Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 31/07/09).

Wounds and ulcers. Phenytoin has been used to promote wound healing (p. 1690.1). Topical application of phenytoin has produced encouraging results in the healing of various types of ulcers[1-7] and large abscess cavities.[8] It has been suggested that phenytoin may reduce bacterial colonisation by changing the pH or by a direct antibacterial effect.[2] The enhanced wound healing may also be due to increased fibroblast proliferation and increased collagen content.[2] Limited absorption from the wound site may occur[9,10] and patients may need to be monitored for signs of toxicity. A systematic review,[11] which included some of these studies, found evidence to support the use of phenytoin in the treatment of leg ulcers, leprosy wounds, chronic wounds, and diabetic foot ulcers despite the poor methodological quality in the majority of studies.

1. Muthukumarasamy MG, *et al.* Topical phenytoin in diabetic foot ulcers. *Diabetes Care* 1991; **14:** 909–11.
2. Pendse AK, *et al.* Topical phenytoin in wound healing. *Int J Dermatol* 1993; **32:** 214–17.
3. Anstead GM, *et al.* Phenytoin in wound healing. *Ann Pharmacother* 1996; **30:** 768–75.
4. Adjei O, *et al.* Phenytoin in the treatment of Buruli ulcer. *Trans R Soc Trop Med Hyg* 1998; **92:** 108–9.
5. Rhodes RS, *et al.* Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother* 2001; **35:** 675–81.
6. Bhatia A, *et al.* Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized, double-blind, comparative study. *J Dermatolog Treat* 2004; **15:** 321–7.
7. Younes N, *et al.* Wound bed preparation with 10 percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J* 2006; **12:** 5. Available at: http://dermatology.cdlib.org/126/pearls/phenytoin/younes.html (accessed 09/06/08)
8. Lodha SC, *et al.* Role of phenytoin in healing of large abscess cavities. *Br J Surg* 1991; **78:** 105–8.
9. Gore R, *et al.* Topical phenytoin. *Pharm J* 1991; **247:** 620.
10. Lewis WG, Rhodes RS. Systemic absorption of topical phenytoin sodium. *Ann Pharmacother* 1994; **28:** 961.
11. Shaw J, *et al.* The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol* 2007; **157:** 997–1004.

Adverse Effects

Adverse effects are fairly frequent in patients receiving phenytoin, but some remit with dose reduction or continued use. Often reported are CNS-related effects (such as headache, dizziness, tremor, transient nervousness, and insomnia), and gastrointestinal disturbances including nausea, vomiting, and constipation. Tenderness and hyperplasia of the gums often occur, particularly in younger patients. Acne, hirsutism, and coarsening of the facial features may be associated with phenytoin therapy, and may be particularly undesirable in adolescents and women.

Phenytoin toxicity may be manifested as a syndrome of cerebellar, vestibular, and ocular effects, notably nystagmus, diplopia, slurred speech, and ataxia. Mental confusion, sometimes severe, may occur, and dyskinesias and exacerbations of seizure frequency have been noted. Hyperglycaemia has been associated with toxic concentrations.

Overdosage may result in hypotension, coma, and respiratory depression. Hypotension and CNS depression may also follow intravenous dosage, if too rapid, as may cardiac arrhythmias and impaired cardiac conduction. Solutions for injection are very alkaline and may result in irritation at the injection site or phlebitis. A syndrome of distal limb oedema, discoloration, and pain ('purple glove syndrome') has been reported occasionally.

Prolonged therapy may produce subtle effects on mental function and cognition, especially in children. In addition there is some evidence that phenytoin interferes with vitamin D and folate metabolism. Rickets and osteomalacia have occurred in a few patients not exposed to adequate sunlight. A proportion of patients develop peripheral neuropathies, usually mild, and occasional cases of megaloblastic anaemia have been seen.

Mild hypersensitivity reactions are common, with skin rashes, often morbilliform, sometimes accompanied by fever. Bullous, exfoliative, or purpuric rashes may be symptoms of rare but severe reactions such as lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Eosinophilia, lymphadenopathy, hepatitis, polyarteritis nodosa, and blood disorders such as aplastic anaemia, leucopenia, thrombocytopenia, and agranulocytosis, have occurred rarely; some of these conditions may also represent hypersensitivity reactions.

Hypoprothrombinaemia of the newborn after use of phenytoin during pregnancy has been reported. Congenital malformations have been seen in the offspring of mothers receiving phenytoin during pregnancy (see under Precautions, p. 542.1).

Effects on the blood. *AGRANULOCYTOSIS.* Fatal agranulocytosis has been reported[1] in a patient 17 years after starting therapy with phenytoin and primidone. Between 1963 and 1994 the UK CSM had received reports of 3 previous cases of fatal agranulocytosis associated with phenytoin and none associated with primidone. The most likely cause was considered to be a direct toxic effect of phenytoin although other possible mechanisms included the ability of both drugs to produce folate deficiency. For a discussion of the effect of antiepileptics on serum folate, see below.

1. Laurenson IF, *et al.* Delayed fatal agranulocytosis in an epileptic taking primidone and phenytoin. *Lancet* 1994; **344:** 332–3.

FOLIC ACID DEFICIENCY. Antiepileptic therapy has long been associated with folate deficiency: early studies suggested that more than half of all patients on long-term therapy with drugs such as phenytoin, phenobarbital, and primidone had subnormal serum-folate concentrations.[1,2] Megaloblastic haematopoiesis is often present,[3] but clinical megaloblastic anaemia appears to be rare.

The relative importance of individual antiepileptics in causing folate deficiency and macrocytosis has been difficult to establish, because of the tendency to use combination regimens; with greater emphasis on single drug therapy there is evidence that monotherapy may produce less significant changes.[4,5] Despite suggestions that carbamazepine has relatively little effect on folic acid concentrations, its effects have been found to be comparable with those of phenytoin;[5] however, valproate had little or no effect on red cell folate concentrations.

The mechanism by which phenytoin and similar antiepileptics reduce serum folate is uncertain; there is good evidence for a reduction in absorption of glutamate both *in vitro*[6] and *in vivo*,[7] but the drugs associated with subnormal serum folate are all enzyme inducers and it has been suggested that enzyme induction and enhanced folate metabolism may also play a role.[2,5,8] Adverse blood changes also result from hypersensitivity (see p. 541.2).

1. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i:** 563–5.
2. Maxwell JD, *et al.* Folate deficiency after anticonvulsant drugs: an effect of hepatic enzyme induction? *BMJ* 1972; **1:** 297–9.
3. Wickramasinghe SN, *et al.* Megaloblastic erythropoiesis and macrocytosis in patients on anticonvulsants. *BMJ* 1975; **4:** 136–7.
4. Dellaportas DI, *et al.* Chronic toxicity in epileptic patients receiving single-drug treatment. *BMJ* 1982; **285:** 409–10.
5. Goggin T, *et al.* A comparative study of the relative effects of anticonvulsant drugs and dietary folate on the red cell folate status of patients with epilepsy. *Q J Med* 1987; **NS65** (247): 911–9.
6. Hoffbrand AV, Necheles TF. Mechanism of folate deficiency in patients receiving phenytoin. *Lancet* 1968; **ii:** 528–30.
7. Rosenberg IH, *et al.* Impairment of intestinal deconjugation of dietary folate. *Lancet* 1968; **ii:** 530–2.
8. Kishi T, *et al.* Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. *J Neurol Sci* 1997; **145:** 109–12.

Effects on bone. There are many reports indicating effects of antiepileptics on bone and on calcium and vitamin D metabolism. Therapy with *carbamazepine*, *phenobarbital*, or *phenytoin* has been associated with reduction in serum-calcium concentration to hypocalcaemic values, significant reduction in 25-hydroxycholecalciferol concentrations, and elevated alkaline phosphatase.[1] In this study, involving 226 outpatients with epilepsy, the association was not seen with *valproate*. The effects were significantly greater in the group of patients receiving polytherapy, and there was limited evidence that these biochemical changes were exacerbated by reduced exposure to sunlight.

Measurements of bone mineral density (BMD) found that children treated for epilepsy have reduced BMD during the first 1 to 5 years of therapy and that this progressively deteriorates thereafter.[2] Studies[3-5] of children receiving antiepileptic monotherapy revealed a reduction in density in those taking *valproate*; no reduction was found with *carbamazepine*.[3,4] The authors of one study[5] concluded that longer duration of therapy and higher doses resulted in lower BMD, and that this effect appeared to be more prominent in children under 5 years of age. A study[6] in 54 male patients followed for 12 to 29 months revealed that treatment with antiepileptics was associated with bone loss at the hip in the absence of vitamin D deficiency. There was no evidence that any particular drug produced more bone loss than another. Risk factors appear to include treatment duration of more than 2 years, age of over 40 years, and use of enzyme-inducing antiepileptics; the greatest rate of bone loss occurred in those with a combination of risk factors.[7] In a large cohort study[8] of women aged 65 years and older, continuous use of antiepileptics, particularly *phenytoin*, almost doubled the rate of bone loss.

A review[9] stated that there have been no significant reports of altered bone metabolism associated with the newer antiepileptics (*gabapentin*, *lamotrigine*, *topiramate*, and *vigabatrin*). However, short stature, low BMD, and reduced bone formation have been reported with long-term *lamotrigine* treatment, particularly when used with *valproate*;[10] further study is needed. *Oxcarbazepine* was found to have[11] similar effects on bone and vitamin D metabolism to *carbamazepine*; both drugs were associated with a reduction in 25-hydroxycholecalciferol serum concentrations and an increased bone turnover.

A more recent literature review[12] considered that most studies to date have been limited by factors such as small sample size, possible selection bias, lack of appropriate controls, and not adjusting for potential confounders. Nevertheless, long-term antiepileptic therapy was found to have an adverse effect on BMD and to increase fracture risk in some patients; there was little information regarding the relative risk with different types of antiepileptics. The authors suggested monitoring indices of bone health, optimising lifestyle factors, maintaining vitamin D and calcium status, and preventing falls in patients on long-term therapy.

Despite these alterations in bone metabolism reports of clinical osteomalacia associated with antiepileptics are rare.[13] A study in 20 epileptic outpatients who had received antiepileptic therapy for a mean of 14½ years failed to show any clinical evidence of osteomalacia although there was some evidence of altered calcium metabolism.[14] Similarly osteomalacia was seen in only 1 of 19 elderly inpatients in another study,[15] a rate similar to that previously seen in elderly patients with acute illness not receiving antiepileptic therapy. There was evidence of femoral osteopenia in over half of a group of 30 patients on long-term phenytoin therapy,[16] which was higher than that in the general population, and one male patient had clinical osteoporosis.

After review of data from studies[7,17,18] and data submitted to its Yellow Card scheme, the UK MHRA[19] considered that long-term treatment with *carbamazepine*, *phenytoin*, *primidone*, and *valproate* is associated with decreased BMD resulting in an increased risk of osteopenia, osteoporosis, and fractures in patients who are immobilised for long periods, or have inadequate sun exposure, or inadequate dietary calcium intake. In addition, *carbamazepine*, *phenytoin*, and *primidone* therapy were found to be associated with an increased risk of osteomalacia. The MHRA advises that vitamin D supplementation should be considered in at-risk patients on long-term therapy with these antiepileptics.

1. Gough H, *et al.* A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. *Q J Med* 1986; **NS59** (230): 569–77.
2. Sheth RD, *et al.* Progressive bone deficit in epilepsy. *Neurology* 2008; **70:** 170–6.
3. Sheth RD, *et al.* Effect of carbamazepine and valproate on bone mineral density. *J Pediatr* 1995; **127:** 256–62.
4. Kafali G, *et al.* Effect of antiepileptic drugs on bone mineral density in children between ages 6 and 12 years. *Clin Pediatr (Phila)* 1999; **38:** 93–8.
5. Öner N, *et al.* Bone mineral metabolism changes in epileptic children receiving valproic acid. *J Paediatr Child Health* 2004; **40:** 470–3.
6. Andress DL, *et al.* Antiepileptic drug-induced bone loss in young male patients who have seizures. *Arch Neurol* 2002; **59:** 781–6.
7. Petty SJ, *et al.* Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005; **65:** 1358–63.
8. Ensrud KE, *et al.* Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 2004; **62:** 2051–7.
9. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic indications. *CNS Drugs* 2001; **15:** 633–42.
10. Guo C-Y, *et al.* Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. *Epilepsia* 2001; **42:** 1141–7.
11. Mintzer S, *et al.* Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. *Epilepsia* 2006; **47:** 510–15.
12. Petty SJ, *et al.* Anti-epileptic medication and bone health. *Osteoporos Int* 2007; **18:** 129–42.
13. Beghi E, *et al.* Adverse effects of anticonvulsant drugs: a critical review. *Adverse Drug React Acute Poisoning Rev* 1986; **2:** 63–86.
14. Fogelman I, *et al.* Do anticonvulsant drugs commonly induce osteomalacia? *Scott Med J* 1982; **27:** 136–42.
15. Harrington MG, Hodkinson HM. Anticonvulsant drugs and bone disease in the elderly. *J R Soc Med* 1987; **80:** 425–7.
16. Moro-Alvarez MJ, *et al.* Bone disease induced by phenytoin therapy: clinical and experimental study. *Eur Neurol* 2009; **62:** 219–30.
17. Pack AM, *et al.* Bone disease associated with antiepileptic drugs. *Cleve Clin J Med* 2004; **71** (suppl 2): S42–S48.
18. Vestergaard P. Epilepsy, osteoporosis and fracture risk: a meta-analysis. *Acta Neurol Scand* 2005; **112:** 277–86.
19. MHRA/CHM. Antiepileptics: adverse effects on bone. *Drug Safety Update* 2009; **2** (9): 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON043810&RevisionSelectionMethod=LatestReleased (accessed 25/08/10)

Effects on the endocrine system and metabolism. Although it may be difficult to separate from the effects of the disease itself, there is some evidence that antiepileptics can diminish *sexual potency* and *fertility* in male epileptics. Phenytoin is excreted in human semen in small quantities and might affect sperm morphology and motility. Reduced plasma concentrations of free testosterone have been detected in male epileptic patients receiving one or more of the following: carbamazepine, phenytoin, primidone, and sodium valproate.[1] There is, however, some evidence[2] that some of the changes in sex hormone concentrations induced by antiepileptics in men and women are reversible. A higher frequency of sperm abnormalities has been found[3] in men given carbamazepine, oxcarbazepine, or valproate monotherapy when compared with healthy controls; those on valproate also had reduced testicular volume. Women may also have altered reproductive function and impaired fertility associated with antiepileptic therapy, particularly with the enzyme-inducing antiepileptics and valproate.[4] There is less information about the newer antiepileptic drugs. However, a comparison[5] in men and women taking carbamazepine, lamotrigine, or levetiracetam found that lamotrigine and levetiracetam did not seem to affect sexual function in men, and improved it in women. There was some evidence of decreased androstenedione concentrations in both sexes with lamotrigine,

and in women prasterone (dehydroepiandrosterone) concentrations were increased by the drug. Levetiracetam had no significant hormonal effects in women but again was associated with decreased androstenedione in men (it was considered possible that this was an effect of the disease rather than the drugs).

Gynaecomastia has been reported[6] in 5 men receiving long-term antiepileptic treatment; one also complained of impotence but libido was stated to be normal in all 5. Phenytoin was a component of therapy in all patients and was the sole drug used in one.

Phenytoin may cause reversible *hyperglycaemia* at toxic doses but it does not appear to produce long-term effects on glucose tolerance when used in therapeutic doses.[7] Paradoxically, phenytoin has also been reported to improve insulin resistance in some patients. There has been a case report[8] of severe *hypoglycaemia* in a patient who was given intravenous phenytoin for the treatment of status epilepticus; symptoms resolved when glucose 5% was infused and no further episodes of hypoglycaemia occurred after phenytoin infusion was stopped.

Phenytoin may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p. 2341.3.

1. Dana-Haeri J, *et al.* Reduction of free testosterone by antiepileptic drugs. *BMJ* 1982; **284:** 85–6.
2. Lossius MI, *et al.* Reversible effects of antiepileptic drugs on reproductive endocrine function in men and women with epilepsy—a prospective randomized double-blind withdrawal study. *Epilepsia* 2007; **48:** 1875–82.
3. Isojärvi JI, *et al.* Effect of epilepsy and antiepileptic drugs on male reproductive health. *Neurology* 2004; **62:** 247–53.
4. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17:** 111–19.
5. Svalheim S, *et al.* Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. *Epilepsy Behav* 2009; **16:** 281–7.
6. Monson JP, Scott DF. Gynaecomastia induced by phenytoin in men with epilepsy. *BMJ* 1987; **294:** 612.
7. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; **174:** 659–62.
8. Di Gennaro G, *et al.* Hypoglycaemia induced by phenytoin treatment for partial status epilepticus. *J Neurol Neurosurg Psychiatry* 2002; **73:** 349–50.

Effects on the liver. There have been occasional reports of liver damage, probably due to hypersensitivity, associated with phenobarbital and phenytoin; the authors of an early study suggested that such drugs need not be withdrawn if there were merely transient elevations in transaminase values,[1] but care is needed to distinguish such effects from the early symptoms of the antiepileptic hypersensitivity syndrome (see below).

1. Aiges HW, *et al.* The effects of phenobarbital and diphenylhydantoin on liver function and morphology. *J Pediatr* 1980; **97:** 22–6.

Effects on the lungs. Pulmonary eosinophilia and acute respiratory failure requiring mechanical ventilation have been reported[1] in a patient receiving phenytoin; other pulmonary symptoms associated with phenytoin were reviewed.

1. Mahatma M, *et al.* Phenytoin-induced acute respiratory failure with pulmonary eosinophilia. *Am J Med* 1989; **87:** 93–4.

Effects on mental function. For a review of the effects of antiepileptic therapy including phenytoin on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the skin. A retrospective analysis involving 1890 outpatients taking antiepileptics found that rates of skin reactions associated with treatment varied with different drugs, the risk being greatest with carbamazepine, lamotrigine, and phenytoin, and lowest with gabapentin, levetiracetam, and valproate.[1] Overall, the rate of skin reactions in this study was 2.8%, but as also mentioned in Hypersensitivity, below (where more details on phenytoin-associated skin reactions are given), there appeared to be cross-sensitivity; risk in this study was increased to 8.8% in those who had previously had a rash with another antiepileptic drug.

Rare, but severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred. For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, p. 542.1.

For reference to cutaneous manifestations of zinc deficiency, possibly due to chelation with phenytoin, see under Valproate, p. 556.1.

1. Arif H, *et al.* Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007; **68:** 1701–9.

Gingival hyperplasia. Gingival hyperplasia, characterised by inflammation and a marked fibrotic response, may affect up to 50% of patients receiving phenytoin. It usually becomes apparent within the first few months of therapy and occurs more frequently in children; there is no increase in alveolar bone loss. The mechanism underlying its development is unknown, although the main metabolite of phenytoin, 5-(4-hydroxyphenyl)-5-phenylhydantoin, has been implicated.[1-3]

1. Ball DE, *et al.* Plasma and saliva concentrations of phenytoin and 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) in relation to gingival overgrowth in epileptic patients. *Br J Clin Pharmacol* 1995; **39:** 539P–588P.
2. Ieiri I, *et al.* Effect of 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) enantiomers, major metabolites of phenytoin, on the occurrence of chronic-gingival hyperplasia: in vivo and in vitro study. *Eur J Clin Pharmacol* 1995; **49:** 51–6.
3. Zhou LX, *et al.* Metabolism of phenytoin by the gingiva of normal humans: the possible role of reactive metabolites of phenytoin in the initiation of gingival hyperplasia. *Clin Pharmacol Ther* 1996; **60:** 191–8.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptic drugs including phenytoin.[1-3] Clinical manifestations may include interstitial nephritis, anaemia, interstitial pulmonary infiltrates, thrombocytopenia, eosinophilia, myopathy, and diffuse intravascular coagulation.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic antiepileptics,[2,3] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. The mean interval to onset is 17 to 21 days with phenytoin. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2] An early review[1] of the syndrome in patients taking phenytoin commented that it occurred mainly in black male patients and should not be confused with more common mild general hypersensitivity reactions. More recent evidence does not suggest that ethnic origin predicts differences in risk.[2]

Most cases resolve spontaneously on withdrawal of the drug and symptomatic management. The use of corticosteroids in the management of severe cases remains controversial in the absence of controlled studies of their efficacy.[1,2]

Phenytoin-induced pseudolymphoma mimicking cutaneous T-cell lymphoma has also been reported.[2,4] In most cases, symptoms resolve within 7 to 14 days of stopping the drug, and the condition is not considered premalignant.[2] However, in one report[4] the cutaneous eruption and lymphadenopathy persisted after withdrawal of phenytoin for one year when the patient eventually became asymptomatic.

In a prospective study[5] of 306 patients given phenytoin there was an overall incidence of 8.5% of morbilliform rash, but there was a marked seasonal incidence with most reactions occurring during the summer months. The results did not appear to be due to photosensitivity and might represent seasonal alterations in the immune system.

1. Flowers FP, *et al.* Phenytoin hypersensitivity syndrome. *J Emerg Med* 1987; **5:** 103–8.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.
4. Harris DWS, *et al.* Phenytoin-induced pseudolymphoma: a report of a case and review of the literature. *Br J Dermatol* 1992; **127:** 403–6.
5. Leppik IE, *et al.* Seasonal incidence of phenytoin allergy unrelated to plasma levels. *Arch Neurol* 1985; **42:** 120–2.

Peripheral neuropathies. Electrophysiological abnormalities after prolonged phenytoin treatment are common, but clinically significant peripheral neuropathy is rare.[1] The neuropathy usually involves sensory nerves and lesions are generally mild and asymptomatic.[2] Much of the reported clinical neuropathy has been associated with multiple drug therapy of epilepsy and with exposure to toxic concentrations of phenytoin.[1,3] Although an association with folate deficiency has been suggested, a study in 52 patients on long-term antiepileptic therapy failed to find any convincing evidence of a relationship between serum-folate concentration and peripheral neuropathy.[4]

1. Bruni J. Phenytoin and other hydantoins: adverse effects. In: Levy RH, *et al.*, eds. *Antiepileptic drugs.* 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 605–10.
2. Argov Z, Mastaglia FL. Drug-induced peripheral neuropathies. *BMJ* 1979; **1:** 663–6.
3. Toth C, Kotecha SA. Prolonged and excessive phenytoin therapy leading to a severe and partially reversible polyneuropathy. *J Peripher Nerv Syst* 2004; **9:** 198–9.
4. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **1:** 563–5.

Treatment of Adverse Effects

Treatment of poisoning with phenytoin tends to be supportive. Repeated doses of activated charcoal may be given orally to adults and children who present within 1 hour of ingesting more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if a very large amount has been taken within 1 hour.

Multiple oral doses of activated charcoal may reduce the absorption of phenytoin[1,2] but the degree of clinical benefit is unclear.[3] The value of charcoal haemoperfusion in the management of phenytoin overdosage is debatable. A review of haemoperfusion included data from 2 patients who ingested phenytoin[4] but, although it was suggested that haemoperfusion should contribute significantly to drug removal, results are difficult to evaluate in these patients who had also ingested phenobarbital. An evaluation in a patient who had also taken primidone[5] suggested that, although initial clearance of phenytoin was promising, the system rapidly became saturated and there was little overall benefit. A review[3] of the features and management of phenytoin poisoning concluded that supportive care is the mainstay of treatment. Gastric lavage and multiple-dose activated charcoal should not be used routinely, although they might be considered for life-threatening ingestion. They were most effective when used within 1 hour of ingestion; the airway should be secured first. Extracorporeal methods of elimination (e.g. haemodialysis, haemoperfusion, peritoneal dialysis, or plasmapheresis) had not been shown to be of benefit;[3] however, some such procedures may be beneficial in patients with renal failure[3] or hypoalbuminaemia[6] in whom free phenytoin concentrations are raised.

1. Weidle PJ, *et al.* Multiple-dose activated charcoal as adjunct therapy after chronic phenytoin intoxication. *Clin Pharm* 1991; **10:** 711–14.
2. Dolgin JG, *et al.* Pharmacokinetic simulation of the effect of multiple-dose activated charcoal in phenytoin poisoning—report of two pediatric cases. *DICP Ann Pharmacother* 1991; **25:** 646–9.
3. Craig S. Phenytoin poisoning. *Neurocrit Care* 2005; **3:** 161–70.
4. Pond S, *et al.* Pharmacokinetics of haemoperfusion for drug overdose. *Clin Pharmacokinet* 1979; **4:** 329–54.
5. Baehler RW, *et al.* Charcoal hemoperfusion in the therapy for methsuximide and phenytoin overdose. *Arch Intern Med* 1980; **140:** 1466–8.
6. De Schoenmakere G, *et al.* Phenytoin intoxication in critically ill patients. *Am J Kidney Dis* 2005; **45:** 189–92.

Precautions

Phenytoin is metabolised in the liver and should be given with care to patients with impaired liver function. Caution is also advocated in diabetic patients because of the potential effects of phenytoin on blood sugar.

Protein binding may be reduced in certain disease states such as uraemia, and in certain patient populations such as neonates, pregnant women, and the elderly. Although phenytoin is extensively protein bound this may be of little clinical significance in itself, provided that hepatic function is not impaired, because the concentration of free (pharmacologically active) drug in the plasma often remains more or less unchanged, due to distribution, metabolism, and excretion. Thus, an alteration in protein binding would not necessarily require a change in dosage of phenytoin to be made although, when plasma concentrations are being monitored, relatively lower total plasma-phenytoin concentrations will be found to be effective since there is less bound (pharmacologically inactive) phenytoin available for measurement.

Intravenous phenytoin must be given slowly and extravasation and intra-arterial injection must be avoided. Phenytoin should not be given intravenously to patients with sinus bradycardia, heart block, or Stokes-Adams syndrome, and should be used with caution in patients with hypotension, heart failure, or myocardial infarction; monitoring of blood pressure and the ECG is recommended during intravenous use.

Patients or their carers should be told how to recognise signs of blood or skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Phenytoin should be stopped, if necessary under cover of a suitable alternative antiepileptic, if leucopenia which is severe, progressive, or associated with clinical symptoms develops. It should also be stopped if a skin rash develops; in the case of mild rashes phenytoin may be reintroduced cautiously, but should be stopped immediately and permanently if the rash recurs.

Care is required when withdrawing phenytoin therapy—see also Uses and Administration, p. 538.3.

Phenytoin may interfere with some tests of thyroid function as it can reduce free and circulating concentrations of levothyroxine, mainly by enhanced conversion to triiodothyronine, and it may also produce lower than normal values for dexamethasone and metyrapone suppression tests.

Breast feeding. The American Academy of Pediatrics[1] considers that phenytoin is usually compatible with breast feeding, although there had been an early case report of methaemoglobinaemia in a breast-fed infant.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May

2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For comment on antiepileptic drugs and driving, see p. 509.2.

Infections. A 52-year-old woman previously well-controlled on phenytoin 400 mg daily suffered phenytoin toxicity after a viral infection;[1] her plasma-phenytoin concentration had increased from 16 to 51 micrograms/mL. Six weeks later she had recovered and was re-stabilised on phenytoin 400 mg daily.

1. Levine M, Jones MW. Toxic reaction to phenytoin following a viral infection. *Can Med Assoc J* 1983; **128:** 1270–1.

AIDS. Renal abnormalities or hypoalbuminaemia associated with AIDS may increase the risk of elevated free phenytoin concentrations and subsequent toxicity. Altered protein binding resulted in marked phenytoin toxicity, with lethargy and seizure-like activity, in an HIV-positive patient with profound hypoalbuminaemia and moderate renal insufficiency.[1] Therapeutic drug monitoring in 21 patients with AIDS indicated that although total serum concentrations of phenytoin were lower than in a reference population, the fraction of unbound drug was higher.[2] These changes might be attributed to hypoalbuminaemia and it was suggested that free rather than total phenytoin concentrations should be measured in HIV-infected patients with hypoalbuminaemia.

Phenytoin itself was associated with reversible hypogammaglobulinaemia in an HIV-positive patient who previously had borderline hypergammaglobulinaemia.[3]

1. Toler SM, *et al.* Severe phenytoin intoxication as a result of altered protein binding in AIDS. *DICP Ann Pharmacother* 1990; **24:** 698–700.
2. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; **16:** 616–20.
3. Britigan BE. Diphenylhydantoin-induced hypogammaglobulinemia in a patient infected with human immunodeficiency virus. *Am J Med* 1991; **90:** 524–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenytoin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including phenytoin; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described. Specific syndromes such as the 'fetal hydantoin syndrome' with phenytoin have been linked to individual antiepileptics. However, there is overlap between the effects seen with different antiepileptics and these are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding with phenytoin.

Skin reactions. In November 2008, the FDA[1] reported that it was analysing preliminary data[2,3] which suggested that patients of Asian ancestry with the HLA allele HLA-B*1502 may be at increased risk of severe skin reactions with phenytoin therapy; this increased risk also applies to fosphenytoin, a prodrug of phenytoin. There is currently insufficient evidence to recommend routine screening for the presence of HLA-B*1502 in this patient group before starting therapy with these 2 antiepileptics. However, phenytoin and fosphenytoin should be avoided in patients with such ancestry who are known to be positive for this allele. Similar recommendations have since been issued in the UK by the MHRA.[4] See also under Carbamazepine, p. 516.1.

1. FDA. Phenytoin (marketed as Dilantin, Phenytek and generics) and fosphenytoin sodium (marketed as Cerebyx and generics)—healthcare professional sheet text version (issued 24th November, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm (accessed 30/07/09)
2. Man CBL, *et al.* Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; **48:** 1015–18. Correction. *ibid.* 2008; **49:** 941.
3. Locharernkul C, *et al.* Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008; **49:** 2087–91. Correction. *ibid.* 2009; **50:** 971.
4. MHRA/CHM. Phenytoin: risk of Stevens-Johnson syndrome associated with HLA-B*1502 allele in patients of Thai or Han Chinese ethnic origin. *Drug Safety Update* 2010: 3(6): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0682986&RevisionSelectionMethod=LatestReleased (accessed 13/01/10)

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Since phenytoin is extensively bound to plasma proteins it can be displaced by drugs competing for protein-binding sites, thus liberating more free (pharmacologically active) phenytoin into the plasma. However, elevation of free phenytoin is reported to be of little clinical significance provided hepatic function is not impaired (see Precautions, p. 541.3). A potentially more serious type of interaction may occur because phenytoin metabolism is saturable: toxic concentrations of phenytoin can develop in patients given drugs that inhibit phenytoin metabolism even to quite a minor degree. Phenytoin itself is also a potent enzyme inducer, and induces the metabolism of many drugs, including some antibacterials, anticoagulants, corticosteroids, quinidine, and sex hormones (notably, oral contraceptives).

The hypotensive properties of dopamine and the cardiac depressant properties of drugs such as lidocaine may be dangerously enhanced by intravenous phenytoin.

General references.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part I). *Clin Pharmacokinet* 1990; **18:** 37–60.
2. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; **18:** 131–50.

Anaesthetics. A 10-year-old girl with epilepsy who had been treated with phenytoin 100 mg three times daily for 5 years and who had lateral nystagmus developed symptoms of phenytoin intoxication after anaesthesia with *halothane*.[1] The plasma concentration of phenytoin 72 hours after anaesthesia was 41 microgram/mL. It was suggested that temporary liver dysfunction was responsible for impaired metabolism of phenytoin.

1. Karlin JM, Kutt H. Acute diphenylhydantoin intoxication following halothane anesthesia. *J Pediatr* 1970; **76:** 941–4.

Analgesics. *Aspirin* is reported to displace phenytoin from plasma binding[1,2] but there is no evidence of any effect on metabolism and effects are unlikely to be clinically significant.[3,4] *Paracetamol* is reported to have no significant effect on serum-phenytoin concentrations.[4] (However, enzyme-inducing antiepileptics such as phenytoin affect the threshold for use of antidote in the treatment of paracetamol poisoning, see p. 118.3.) Alterations of the pharmacokinetics of phenytoin have been reported with *bromfenac*, but it was thought unlikely that a change in phenytoin dose would be necessary.[5]

Other analgesic and anti-inflammatory drugs may have clinically significant effects. *Phenylbutazone* has been reported to cause an initial decrease in serum phenytoin, followed by an increase;[4] in addition to effects on protein binding it inhibits phenytoin metabolism[6] and severe phenytoin toxicity may result.[7] *Azapropazone* appears to be a competitive inhibitor of phenytoin metabolism and has also been implicated in interactions resulting in toxicity.[8,9] Substantial increases in serum phenytoin have been found in healthy subjects given the analgesic and muscle relaxant *fenyramidol*,[10] indicating a potential for toxicity. There is a single report of toxicity in a patient receiving *ibuprofen* with phenytoin[11] but in a study in 9 healthy subjects, ibuprofen had no effect on the pharmacokinetics of phenytoin.[12] In another report, phenytoin toxicity developed[13] in a patient who was also taking *celecoxib*.

The opioid analgesic *dextropropoxyphene* has also been reported to affect phenytoin metabolism, with the resultant development of toxic blood-phenytoin concentrations;[14] however, the patient in this case was taking relatively high doses of dextropropoxyphene (650 mg daily). For the effect of phenytoin on *methadone* and *pethidine*, see p. 90.3 and p. 123.2, respectively.

1. Fraser DG, *et al.* Displacement of phenytoin from plasma binding sites by salicylate. *Clin Pharmacol Ther* 1980; **27:** 165–9.
2. Paxton JW. Effects of aspirin on salivary and serum phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1980; **27:** 170–8.
3. Leonard RF, *et al.* Phenytoin-salicylate interaction. *Clin Pharmacol Ther* 1981; **29:** 56–60.
4. Neuvonen PJ, *et al.* Antipyretic analgesics in patients on antiepileptic drug therapy. *Eur J Clin Pharmacol* 1979; **15:** 263–8.
5. Gumbhir-Shah K, *et al.* Evaluation of pharmacokinetic interaction between bromfenac and phenytoin in healthy males. *J Clin Pharmacol* 1997; **37:** 160–8.
6. Andreasen PB, *et al.* Diphenylhydantoin half-life in man and its inhibition by phenylbutazone: the role of genetic factors. *Acta Med Scand* 1973; **193:** 561–4.
7. Kristensen MB. Drug interactions and clinical pharmacokinetics. *Clin Pharmacokinet* 1976; **1:** 351–72.
8. Roberts CJC, *et al.* Anticonvulsant intoxication precipitated by azapropazone. *Postgrad Med J* 1981; **57:** 191–2.
9. Geaney DP, *et al.* Interaction of azapropazone with phenytoin. *BMJ* 1982; **284:** 1373.
10. Solomon HM, Schrogie JJ. The effect of phenyramidol on the metabolism of diphenylhydantoin. *Clin Pharmacol Ther* 1967; **8:** 554–6.
11. Sandyk R. Phenytoin toxicity induced by interaction with ibuprofen. *S Afr Med J* 1982; **62:** 592.
12. Townsend RJ, *et al.* The effects of ibuprofen on phenytoin pharmacokinetics. *Drug Intell Clin Pharm* 1985; **19:** 447–8.
13. Keeling KL, *et al.* Prolonged elimination half-life of phenytoin in an elderly patient also on celecoxib. *Clin Chem* 2002; **48** (suppl): A52–A53.
14. Kutt H. Interactions between anticonvulsants and other commonly prescribed drugs. *Epilepsia* 1984; **25** (suppl 2): S118–S131.

Anthelmintics. For report of an interaction between phenytoin and *levamisole* with fluorouracil, see Antineoplastics, p. 544.1. For the effect of phenytoin on *mebendazole* and *praziquantel*, see p. 160.1 and p. 165.2, respectively.

Antiarrhythmics. There have been reports of phenytoin toxicity associated with substantial rises in serum-phenytoin concentrations after addition of *amiodarone* to the therapeutic regimen.[1,2] For the effect of phenytoin on amiodarone, see p. 1303.2.

For the effect of phenytoin on other antiarrhythmics, see p. 1365.2 (*disopyramide*), p. 1437.2 (*mexiletine*), p. 1483.1 (*quinidine*), and p. 1995.1 (*lidocaine*).

1. Gore JM, *et al.* Interaction of amiodarone and diphenylhydantoin. *Am J Cardiol* 1984; **54:** 1145.
2. McGovern B, *et al.* Possible interaction between amiodarone and phenytoin. *Ann Intern Med* 1984; **101:** 650.

Antibacterials. Interactions, some clinically significant, may occur between phenytoin and various antibacterials. Giving *chloramphenicol* with phenytoin has resulted in moderate[1] to marked[2] elevation of serum-phenytoin concentrations due to inhibition of phenytoin metabolism;[2] toxicity has resulted.[3,4] In turn, phenytoin may affect serum concentrations of chloramphenicol (see p. 259.1).

Phenytoin may enhance the metabolism of *doxycycline*.[5]

There is limited evidence that *erythromycin* decreases phenytoin clearance[6] but this was subject to considerable interindividual variation and is of unknown clinical significance. Results from another study[7] suggested that *clarithromycin* might also raise phenytoin levels.

The interaction with *isoniazid* is well documented and potentially significant in slow acetylators of isoniazid who may develop raised phenytoin concentrations and signs of toxicity;[8,9] in at least one case, death has resulted.[10] Plasma-isoniazid concentrations may become sufficiently raised in slow acetylators of isoniazid to produce marked inhibition of the hepatic microsomal enzymes responsible for the metabolism of phenytoin.

There have been conflicting reports of the effect of *ciprofloxacin* on serum concentrations of phenytoin. While some report no effect[11] others have reported reduced[12-16] or increased[17,18] concentrations of phenytoin in patients given ciprofloxacin. A fall in serum-phenytoin concentrations, and resultant loss of seizure control has been reported in a patient in whom *nitrofurantoin* was added to therapy.[19] The mechanism of this interaction is unknown although a combination of impaired absorption and increased metabolism of the phenytoin was suggested. Something similar was reported in a patient given *oxacillin* in whom plasma-phenytoin concentrations dropped markedly and status epilepticus developed.[20] This effect was thought to be due to impaired phenytoin absorption.

Rifampicin can also reduce plasma-phenytoin concentrations and markedly increase its clearance;[21,22] this is in marked contrast to the effects of isoniazid, and when given together it overrides the effects of isoniazid on phenytoin, even in slow acetylators.[22]

Various sulfonamides are reported to interact with phenytoin, reducing clearance and prolonging half-life: *sulfaphenazole* is reportedly the strongest inhibitor of phenytoin metabolism but *sulfamethizole* also inhibits phenytoin metabolism and the latter has been implicated in producing phenytoin toxicity.[23] *Co-trimoxazole* reportedly inhibits phenytoin metabolism to a modest degree; a case of phenytoin toxicity in a child given co-trimoxazole has been reported[24] but the role of the co-trimoxazole is uncertain since the patient was also receiving sultiame. Fatal acute fulminant hepatic failure in a 60-year-old patient was suggested[25] to be due to phenytoin-induced hepatitis exacerbated by addition of co-trimoxazole to her drug regimen.

See also Antiprotozoals, p. 544.1.

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24:** 571–5.
2. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
3. Ballek RE, *et al.* Inhibition of diphenylhydantoin metabolism by chloramphenicol. *Lancet* 1973; **i:** 150.
4. Rose JQ, *et al.* Intoxication caused by interaction of chloramphenicol and phenytoin. *J AMA* 1977; **237:** 2630–1.
5. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9:** 147–54.
6. Bachmann K, *et al.* Single dose phenytoin clearance during erythromycin treatment. *Res Commun Chem Pathol Pharmacol* 1984; **46:** 207–17.
7. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; **16:** 616–20.
8. Brennan RW, *et al.* Diphenylhydantoin intoxication attendant to slow inactivation of isoniazid. *Neurology* 1970; **20:** 687–93.
9. Kutt H, *et al.* Diphenylhydantoin intoxication: a complication of isoniazid therapy. *Am Rev Respir Dis* 1970; **101:** 377–84.
10. Johnson J, Freeman HL. Death due to isoniazid (INH) and phenytoin. *Br J Psychiatry* 1976; **129:** 511.
11. Slavich IL, *et al.* Grand mal epileptic seizures during ciprofloxacin therapy. *J AMA* 1989; **261:** 558–9.
12. Dillard ML, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1992; **26:** 263.

13. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. *Ann Pharmacother* 1997; **31:** 61–4.
14. Brouwers PJ, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1997; **31:** 498.
15. McLeod R, Trinkle R. Unexpectedly low phenytoin concentration in a patient receiving ciprofloxacin. *Ann Pharmacother* 1998; **32:** 1110–11.
16. Otero M-J, *et al.* Interaction between phenytoin and ciprofloxacin. *Ann Pharmacother* 1999; **33:** 251–2.
17. Schroeder D, *et al.* Effect of ciprofloxacin on serum phenytoin concentrations in epileptic patients. *Pharmacotherapy* 1991; **11:** 276.
18. Hull RL. Possible phenytoin-ciprofloxacin interaction. *Ann Pharmacother* 1993; **27:** 1283.
19. Heipertz R, Pilz H. Interaction of nitrofurantoin with diphenylhydantoin. *J Neurol* 1978; **218:** 297–301.
20. Fincham RW, *et al.* Use of phenytoin serum levels in a case of status epilepticus. *Neurology* 1976; **26:** 879–81.
21. Wagner JC, Slama TG. Rifampin-phenytoin drug interaction. *Drug Intell Clin Pharm* 1984; **18:** 497.
22. Kay L, *et al.* Influence of rifampicin and isoniazid on the kinetics of phenytoin. *Br J Clin Pharmacol* 1985; **20:** 323–6.
23. Siersbaek-Nielsen K, *et al.* Sulfamethizole-induced inhibition of diphenylhydantoin and tolbutamide metabolism in man. *Clin Pharmacol Ther* 1973; **14:** 148.
24. Gillman MA, Sandyk R. Phenytoin toxicity and co-trimoxazole. *Ann Intern Med* 1985; **102:** 559.
25. Ilario MJ-M, *et al.* Acute fulminant hepatic failure in a woman treated with phenytoin and trimethoprim-sulfamethoxazole. *Arch Pathol Lab Med* 2000; **124:** 1800–3.

Anticoagulants. Serum-phenytoin concentrations have been reported to be markedly elevated by *dicoumarol*[1,2] and elevated to a lesser extent by *phenprocoumon*.[2] *Acenocoumarol* and *warfarin* have also been implicated in phenytoin toxicity,[3,4] although other evidence suggests that warfarin has no effect on serum-phenytoin concentrations in most patients.[2]

For the effect of phenytoin on anticoagulants such as dicoumarol and warfarin, see p. 1532.1.

1. Hansen JM, *et al.* Dicoumarol-induced diphenylhydantoin intoxication. *Lancet* 1966; **ii:** 265–6.
2. Skovsted L, *et al.* The effect of different oral anticoagulants on diphenylhydantoin and tolbutamide metabolism. *Acta Med Scand* 1976; **199:** 513–5.
3. Rothermich NO. Diphenylhydantoin intoxication. *Lancet* 1966; **ii:** 640.
4. Jose L, *et al.* Acenocoumarol and phenytoin toxicity in the presence of CYP2C9 mutation. *J Assoc Physicians India* 2008; **56:** 250–2.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Plasma-phenytoin concentrations rose in 2 epileptic patients also receiving *imipramine* 75 mg daily for about 3 months for depression.[1] In one patient the concentration gradually increased over several weeks to more than twice the pretreatment figure and he showed mild signs of phenytoin intoxication, which remitted after imipramine was stopped. Increased serum-phenytoin concentration and phenytoin toxicity possibly precipitated by addition of *trazodone* has been described;[2] licensed product information for trazodone recommends monitoring serum-phenytoin concentrations in patients receiving these two drugs. Elevated plasma-phenytoin concentrations, in some cases accompanied by signs and symptoms of phenytoin toxicity, have also been reported with *fluoxetine*,[3] *fluvoxamine*,[4,5] *sertraline*,[6] and *viloxazine*.[7] Product information for *mianserin* also recommends that plasma concentrations of phenytoin should be monitored carefully when both are given.

St John's wort has been shown to induce several drug metabolising enzymes (see p. 449.3) and consequently it might reduce the blood concentrations of phenytoin leading to an increased risk of seizure.[8] Some licensed product information for phenytoin in the UK therefore recommends that phenytoin should not be used with St John's wort and warns that the effects of St John's wort may persist for at least 2 weeks after it was last used.

For the effects of phenytoin on antidepressants, see under Amitriptyline (p. 406.2), Fluoxetine (p. 424.2), and Lithium (p. 431.3).

1. Perucca E, Richens A. Interaction between phenytoin and imipramine. *Br J Clin Pharmacol* 1977; **4:** 485–6.
2. Dorn JM. A case of phenytoin toxicity possibly precipitated by trazodone. *J Clin Psychiatry* 1986; **47:** 89–90.
3. Nightingale SL. Fluoxetine labeling revised to identify phenytoin interaction and to recommend against use in nursing mothers. *JAMA* 1994; **271:** 1067.
4. Feldman D, *et al.* Cas clinique d'interaction médicamenteuse entre phénytoïne et fluvoxamine. *J Pharm Clin* 1995; **14:** 296–7.
5. Mamiya K, *et al.* Phenytoin intoxication induced by fluvoxamine. *Ther Drug Monit* 2001; **23:** 75–7.
6. Haselberger MB, *et al.* Elevated serum phenytoin concentrations associated with coadministration of sertraline. *J Clin Psychopharmacol* 1997; **17:** 107–9.
7. Pisani F, *et al.* Elevation of plasma phenytoin by viloxazine in epileptic patients: a clinically significant interaction. *J Neurol Neurosurg Psychiatry* 1992; **55:** 126–7.
8. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antidiabetics. Transient rises in the amount of non-protein-bound phenytoin occurred in 17 patients when *tolbutamide* was given in addition to phenytoin, but none developed signs of intoxication.[1] Toxic symptoms were reported in another patient given phenytoin with tolbutamide, although she had tolerated this combination on a previous occasion.[2]

Symptoms of phenytoin toxicity are known to have occurred[1] in one patient receiving *tolazamide* and phenytoin.

1. Wesseling H, Mols-Thürkow I. Interaction of diphenylhydantoin (DPH) and tolbutamide in man. *Eur J Clin Pharmacol* 1975; **8:** 75–8.
2. Beech E, *et al.* Phenytoin toxicity produced by tolbutamide. *BMJ* 1988; **297:** 1613–14.

Antiepileptics. Interactions may occur when phenytoin is used with other antiepileptics, but these are often variable in their effect and difficult to predict.

For a discussion of the effect of *benzodiazepines* on plasma concentrations of phenytoin, see Benzodiazepines, p. 544.2.

Carbamazepine has been generally reported to lower serum-phenytoin concentrations,[1,2] although reports exist of elevated serum-phenytoin concentrations when the two were given concurrently.[3] It should be noted that phenytoin also reduces serum-carbamazepine values—see p. 516.3. These studies have not indicated any loss of seizure control due to this interaction.

For the effects of phenytoin on *ethosuximide*, see p. 521.3.

Felbamate has caused increases in serum-phenytoin concentrations, and in some cases toxicity requiring a reduction in phenytoin dose.[4,5]

Increased plasma concentrations of phenytoin with symptoms of toxicity have been reported in a patient receiving phenytoin, carbamazepine, and clobazam after *gabapentin* was added to treatment.[6]

Phenytoin reduces plasma concentrations of *lamotrigine* as described on p. 530.1.

Phenytoin plasma concentrations may be increased by high doses of *oxcarbazepine*;[7] licensed product information for oxcarbazepine suggests that doses of phenytoin may need to be reduced when high doses of oxcarbazepine are given.

Phenobarbital both induces the metabolism of phenytoin and competes with it for metabolism by the same enzyme system; in practice there is rarely sufficient alteration for a change in phenytoin dosage to be necessary.[8-10] For the effect of phenytoin on phenobarbital, see p. 537.2. Phenytoin has also been reported to enhance the metabolism of *primidone* to phenobarbital, see p. 547.3.

The GABA agonist *progabide* increased blood-phenytoin concentrations[11] and *stiripentol* appears to produce a dose-dependent reduction in phenytoin clearance.[12]

Sultiame causes substantial increases in plasma-phenytoin concentrations, in some cases resulting in phenytoin toxicity;[13] the dose of phenytoin may therefore require adjustment if these drugs are given together.

Modest increases in plasma-phenytoin concentrations have occurred in some patients when *topiramate* was added to therapy, but it was considered that dosage adjustments were unlikely to be necessary.[14] For the effect of phenytoin on topiramate, see p. 552.3.

The interaction between phenytoin and *valproate* is complex. Valproate displaces phenytoin from serum binding sites and may inhibit its metabolism;[15] the former effect increases the concentration of free drug but reduces total serum phenytoin.[16,17] Most studies seem to suggest that the dose of phenytoin need only rarely be adjusted, but the possibility of loss of seizure control, or phenytoin toxicity, does exist.[15] Interestingly there is some evidence that the interactions may be affected by circadian variations in valproate concentrations.[18] Total plasma-phenytoin concentrations rose significantly in 9 of 11 patients, 2 of whom developed toxic symptoms, when the formulation of sodium valproate that they were taking with phenytoin was changed from a standard tablet to a slow-release form.[19] The authors hypothesised that reduced diurnal fluctuations in plasma-valproate concentrations due to the use of slow-release tablets reduced the displacement interaction between phenytoin and valproate, thereby increasing total plasma-phenytoin concentrations. Phenytoin may also cause a fall in serum concentrations of valproate—see p. 557.3.

Gradual or delayed reductions in plasma-phenytoin concentrations have been seen in several studies in patients given *vigabatrin*;[20] a review[20] states that concentrations have been reduced by 20 to 30%. The manufacturer of vigabatrin considers that this is unlikely to be of clinical significance although in a study the reduction was considered to compromise seizure control.[21]

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12:** 539–43.
2. Windorfer A, Sauer W. Drug interactions during anticonvulsant therapy in childhood: diphenylhydantoin, primidone, phenobarbitone, clonazepam, nitrazepam, carbamazepin, and dipropylacetate. *Neuropadiatrie* 1977; **8:** 29–41.
3. Zielinski JJ, *et al.* Carbamazepine-phenytoin interaction: elevation of plasma phenytoin concentrations due to carbamazepine comedication. *Ther Drug Monit* 1985; **7:** 51–3.
4. Sheridan PH, *et al.* Open pilot study of felbamate (ADD03055) in partial seizures. *Epilepsia* 1986; **27:** 649.
5. Wilensky AJ, *et al.* Pharmacokinetics of W-554 (ADD 03055) in epileptic patients. *Epilepsia* 1985; **26:** 602–6.
6. Tyndel F. Interaction of gabapentin with other antiepileptics. *Lancet* 1994; **343:** 1363–4.
7. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.
8. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179:** 88–107.
9. Cucinell SA, *et al.* Drug interactions in man: 1. lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6:** 420–9.
10. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21:** 383–5.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28:** 68–73.
12. Levy RH, *et al.* Stiripentol kinetics in epileptic patients: nonlinearity and interactions. *Epilepsia* 1984; **25:** 657.
13. Hansen JM, *et al.* Sulthiame (Ospolot) as inhibitor of diphenylhydantoin metabolism. *Epilepsia* 1968; **9:** 17–22.
14. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37** (suppl 2): S14–S17.
15. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
16. Monks A, Richens A. Effect of single doses of sodium valproate on serum phenytoin levels and protein binding in epileptic patients. *Clin Pharmacol Ther* 1980; **27:** 89–95.
17. Perucca E, *et al.* Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. *Clin Pharmacol Ther* 1980; **28:** 779–89.
18. Riva R, *et al.* Time-dependent interaction between phenytoin and valproic acid. *Neurology* 1985; **35:** 510–15.
19. Suzuki Y, *et al.* Interaction between valproate formulation and phenytoin concentrations. *Eur J Clin Pharmacol* 1995; **48:** 61–3.
20. Grant SM, Heel RC. Vigabatrin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs* 1991; **41:** 889–926.
21. Browne TR, *et al.* Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. *Neurology* 1987; **37:** 184–9.

Antifungals. There have been several reports of interactions, sometimes resulting in phenytoin toxicity, between imidazole antifungals and phenytoin. The drug most frequently implicated is *miconazole*.[1-3] The related triazole antifungals *fluconazole*[4-6] and *voriconazole*[7] are also reported to interact with phenytoin,[4-6] possibly due to dose-related inhibition of cytochrome P450 isoenzymes by these antifungals.[4,7]

Phenytoin can decrease plasma concentrations of azole antifungals such as *ketoconazole*, voriconazole, and *itraconazole*.

1. Bourgoin B, *et al.* Interaction pharmacocinétique possible phénytoïne-miconazole. *Therapie* 1981; **36:** 347–9.
2. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
3. Rolan PE, *et al.* Phenytoin intoxication during treatment with parenteral miconazole. *BMJ* 1983; **287:** 1760.
4. Mitchell AS, Holland JT. Fluconazole and phenytoin: a predictable interaction. *BMJ* 1989; **298:** 1315.
5. Howitt KM, Oziemski MA. Phenytoin toxicity induced by fluconazole. *Med J Aust* 1989; **151:** 603–4.
6. Cadle RM, *et al.* Fluconazole-induced symptomatic phenytoin toxicity. *Ann Pharmacother* 1994; **28:** 191–5.
7. Purkins L, *et al.* Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 37–44.

Antigout drugs. Licensed product information for *sulfinpyrazone* states that it displaces phenytoin from its protein-binding sites, and also inhibits microsomal liver enzymes. The net result is an increase in plasma-phenytoin concentrations and a prolonged half-life, which is potentially hazardous.

Reduced doses of phenytoin were necessary to avoid toxicity when *allopurinol* was added to the therapy of a child with the Lesch-Nyhan syndrome.[1] Although the authors thought caution was advisable in using these two drugs together, they did emphasise that overgeneralisation may be dangerous since the child also received other antiepileptics and the role his disease may have played was unknown.

1. Yokochi K, *et al.* Phenytoin-allopurinol interaction: Michaelis-Menten kinetic parameters of phenytoin with and without allopurinol in a child with Lesch-Nyhan syndrome. *Ther Drug Monit* 1982; **4:** 353–7.

Antihistamines. A young woman developed drowsiness, ataxia, diplopia, tinnitus, and episodes of occipital headaches associated with vomiting after taking phenytoin sodium and *chlorphenamine*.[1] Chlorphenamine might have delayed the hepatic metabolism of phenytoin thereby increasing the plasma concentrations.

1. Pugh RNH, *et al.* Interaction of phenytoin with chlorpheniramine. *Br J Clin Pharmacol* 1975; **2:** 173–5.

Antihypertensives. In 2 patients with hypoglycaemia associated with hyperinsulinism, therapeutic serum-phenytoin concentrations could not be achieved while they were also receiving *diazoxide*.[1] It was suggested that an increased rate of metabolism, and possibly a decreased binding, of phenytoin induced by diazoxide might have been responsible.

1. Roe TF, *et al.* Drug interaction: diazoxide and diphenylhydantoin. *J Pediatr* 1975; **87:** 480–4.

Antimalarials. Antimalarials may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Antineoplastics. There have been reports of decreased plasma-phenytoin concentrations associated with cancer chemotherapy,[1-4] resulting in some cases in loss of seizure control.[2-4] The effect appears to be due to impaired absorption of phenytoin arising from antineoplastic damage to the gastrointestinal mucosa. In a patient a mean of 32% of an oral dose of phenytoin was absorbed after therapy with *cisplatin, vinblastine,* and *bleomycin*; this compared with a reported oral bioavailability of 80% or more.[3] *Trabectedin* may also reduce phenytoin absorption leading to an exacerbation of seizures.

Some licensed product information for *levamisole* reports that increased plasma-phenytoin concentrations have been seen in patients taking phenytoin with levamisole given as an adjuvant to *fluorouracil* therapy. Treatment with fluorouracil (alone or with folinic acid) has also led to phenytoin toxicity in patients on long-term antiepileptic therapy.[5-7] Similar interactions have occurred with *doxifluridine*[8] and *capecitabine*[7] (both prodrugs of fluorouracil), and a combination preparation containing *tegafur* (a prodrug of fluorouracil) with *uracil*. However, a decrease in phenytoin serum concentrations has been seen when such a preparation was given with folinic acid to a patient receiving the antiepileptic.[9] For the potential effect of phenytoin on *busulfan*, see Effects on the Nervous System, under Adverse Effects of Busulfan, p. 755.3. For the effect of phenytoin on the use of *streptozocin* and on *teniposide*, see p. 859.1 and p. 867.2, respectively.

1. Fincham RW, Schottelius DD. Decreased phenytoin levels in antineoplastic therapy. *Ther Drug Monit* 1979; **1:** 277–83.
2. Bollini P, *et al*. Decreased phenytoin level during antineoplastic therapy: a case report. *Epilepsia* 1983; **24:** 75–8.
3. Sylvester RK, *et al*. Impaired phenytoin bioavailability secondary to cisplatinum, vinblastine, and bleomycin. *Ther Drug Monit* 1984; **6:** 302–5.
4. Grossman SA, *et al*. Decreased phenytoin levels in patients receiving chemotherapy. *Am J Med* 1989; **87:** 505–10.
5. Gilbar PJ, Brodribb TR. Phenytoin and fluorouracil interaction. *Ann Pharmacother* 2001; **35:** 1367–70.
6. Rosemergy I, Findlay M. Phenytoin toxicity as a result of 5-fluorouracil administration. *N Z Med J* 2002; **115:** U124.
7. Brickell K, *et al*. Phenytoin toxicity due to fluoropyrimidines (5FU/capecitabine): three case reports. *Br J Cancer* 2003; **89:** 615–16.
8. Konishi H, *et al*. Probable metabolic interaction of doxifluridine with phenytoin. *Ann Pharmacother* 2002; **36:** 831–4.
9. Veldhorst-Janssen NML, *et al*. Oral tegafur/folinic acid chemotherapy decreases phenytoin efficacy. *Br J Cancer* 2004; **90:** 745.

Antiprotozoals. Conflicting results have been reported with *metronidazole*: while one study has suggested only minimal effects on phenytoin concentrations and metabolism,[1] another has indicated inhibition of the metabolism of phenytoin.[2] For the effect of phenytoin on metronidazole, see p. 939.2.

1. Jensen JC, Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* 1985; **37:** 407–10.
2. Blyden GT, *et al*. Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. *Clin Pharmacol Ther* 1986; **39:** 181.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold. Two cases of phenytoin toxicity and elevated plasma-phenytoin concentrations associated with the phenothiazine *thioridazine* have been reported;[1] but another study indicated that *thioridazine, chlorpromazine,* or *mesoridazine* reduced serum-phenytoin concentrations.[2]

The non-phenothiazine antipsychotic *loxapine* has also been implicated as producing a fall in serum-phenytoin concentration.[3]

For the effect of phenytoin on antipsychotics in general, see under Chlorpromazine, p. 1052.2. For the effect of phenytoin on *clozapine*, see p. 1061.3.

1. Vincent FM. Phenothiazine-induced phenytoin intoxication. *Ann Intern Med* 1980; **93:** 56–7.
2. Haidukewych D, Rodin EA. Effect of phenothiazines on serum antiepileptic drug concentrations in psychiatric patients with seizure disorder. *Ther Drug Monit* 1985; **7:** 401–4.
3. Ryan GM, Matthews PA. Phenytoin metabolism stimulated by loxapine. *Drug Intell Clin Pharm* 1977; **11:** 428–9.

Antivirals. *Zidovudine* may possibly reduce or increase plasma concentrations of phenytoin. There has been a report[1] of markedly decreased serum-phenytoin concentrations resulting in a recurrence of seizure activity in an epileptic patient after starting *nelfinavir* as part of antiretroviral therapy. Serum concentrations of phenytoin and valproate decreased[2,3] in 2 reports in children after the addition of *aciclovir*. *Ritonavir-boosted lopinavir* was reported[4] to increase the clearance of phenytoin in healthy subjects, probably due to hepatic enzyme induction; phenytoin similarly increased the clearance of the HIV-protease inhibitor. A case report[5] described the inhibition of phenytoin clearance by *efavirenz* resulting in elevated phenytoin plasma concentrations, and subtherapeutic levels of efavirenz resulting from hepatic enzyme induction by phenytoin.

For the possible effect of phenytoin on HIV-protease inhibitors, see p. 987.3.

1. Honda M, *et al*. A generalized seizure following initiation of nelfinavir in a patient with human immunodeficiency virus type 1 infection, suspected due to interaction between nelfinavir and phenytoin. *Intern Med* 1999; **38:** 302–3.
2. Parmeggiani A, *et al*. Possible interaction between acyclovir and antiepileptic treatment. *Ther Drug Monit* 1995; **17:** 312–15.
3. Iglesias Iglesias A-A, *et al*. Disminución de la concentración sérica de antiepilépticos durante el tratamiento con aciclovir. *Med Clin (Barc)* 2005; **124:** 355–6.
4. Lim ML, *et al*. Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. *J Acquir Immune Defic Syndr* 2004; **36:** 1034–40.
5. Robertson SM, *et al*. A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. *Clin Infect Dis* 2005; **41:** e15–e18.

Anxiolytics. See Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced as a result of induction of hepatic drug-metabolising enzymes after long-term use of phenytoin. In comparison with healthy subjects, half-lives have been shorter and clearance increased.[1,2]

There are sporadic reports of interactions between phenytoin and benzodiazepines, but the evidence is conflicting. Elevated plasma concentrations of phenytoin have been reported in patients given *diazepam*[3,4] or *chlordiazepoxide*[3] but, in contrast, another study suggested that these drugs produced a significant fall in serum-phenytoin concentrations.[5] It has been suggested that phenytoin intoxication could result from the impaired metabolism associated with the combination[3,4,6] but in practice this seems to be uncommon. There are similar conflicting reports for *clonazepam*.[7-9]

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Scott AK, *et al*. Oxazepam pharmacokinetics in patients with epilepsy treated long-term with phenytoin alone or in combination with phenobarbitone. *Br J Clin Pharmacol* 1983; **16:** 441–4.
3. Vajda FJE, *et al*. Interaction between phenytoin and the benzodiazepines. *BMJ* 1971; **1:** 346.
4. Murphy A, Wilbur K. Phenytoin-diazepam interaction. *Ann Pharmacother* 2003; **37:** 659–63.
5. Houghton GW, Richens A. The effect of benzodiazepines and pheneturide on phenytoin metabolism in man. *Br J Clin Pharmacol* 1974; **1:** 344P–345P.
6. Kutt H, McDowell F. Management of epilepsy with diphenylhydantoin sodium: dosage regulation for problem patients. *JAMA* 1968; **203:** 969–72.
7. Eeg-Oloffson O. Experiences with Rivotril in treatment of epilepsy—particularly minor motor epilepsy—in mentally retarded children. *Acta Neurol Scand* 1973; **49** (suppl 53): 29–31.
8. Johannessen SI, *et al*. Lack of effect of clonazepam on serum levels of diphenylhydantoin, phenobarbital and carbamazepine. *Acta Neurol Scand* 1977; **55:** 506–12.
9. Saavedra IN, *et al*. Phenytoin/clonazepam interaction. *Ther Drug Monit* 1985; **7:** 481–4.

Calcium-channel blockers. Raised serum-phenytoin concentration with phenytoin toxicity developed in a patient who had been taking *nifedipine* in addition to phenytoin for 3 weeks;[1] symptoms resolved completely after nifedipine withdrawal. The mechanism of interaction appeared to be complex. Similar effects have been reported with *diltiazem*[2] and *isradipine*.[3]

For the effect of phenytoin on dihydropyridine calcium-channel blockers, see under Nifedipine, p. 1453.3, and on verapamil, see p. 1525.2.

1. Ahmad S. Nifedipine-phenytoin interaction. *J Am Coll Cardiol* 1984; **3:** 1582.
2. Bahls FH, *et al*. Interactions between calcium channel blockers and the anticonvulsants carbamazepine and phenytoin. *Neurology* 1991; **41:** 740–2.
3. Cachat F, Tufro A. Phenytoin/isradipine interaction causing severe neurologic toxicity. *Ann Pharmacother* 2002; **36:** 1399–1402.

Cardiac glycosides. For the effect of phenytoin on cardiac glycosides, see under Digoxin, p. 1357.1.

Corticosteroids. Serum concentrations of phenytoin have been elevated[1] or reduced[2-4] by *dexamethasone* and adjustment of phenytoin dosage may be required.[2-4] For the effect of phenytoin on corticosteroids, see p. 1619.3.

1. Lawson LA, *et al*. Phenytoin-dexamethasone interaction: a previously unreported observation. *Surg Neurol* 1981; **16:** 23–4.
2. Wong DD, *et al*. Phenytoin-dexamethasone: a possible drug-drug interaction. *JAMA* 1985; **254:** 2062–3.
3. Recuenco I, *et al*. Effect of dexamethasone on the decrease of serum phenytoin concentrations. *Ann Pharmacother* 1995; **29:** 935.
4. Lackner TE. Interaction of dexamethasone with phenytoin. *Pharmacotherapy* 1991; **11:** 344–7.

Dermatological drugs. For the effect of phenytoin on *methoxsalen*, see p. 1713.3.

Disulfiram. A well-documented interaction exists between phenytoin and disulfiram, which may result in clinical phenytoin toxicity.[1,2] The effect appears to be due to non-competitive inhibition of the metabolism of phenytoin by disulfiram,[2] which results in a substantial increase in phenytoin half-life and a decrease in its clearance.[3]

1. Dry J, Pradalier A. Intoxication par la phénytoïne au cours d'une association thérapeutique avec le disulfirame. *Therapie* 1973; **28:** 799–802.
2. Taylor JW, *et al*. Mathematical analysis of a phenytoin-disulfiram interaction. *Am J Hosp Pharm* 1981; **38:** 93–5.
3. Svendsen TL, *et al*. The influence of disulfiram on the half-life and metabolic clearance rate of diphenylhydantoin and tolbutamide in man. *Eur J Clin Pharmacol* 1976; **9:** 439–41.

Diuretics. Severe osteomalacia in 2 previously active young women taking *acetazolamide* with phenytoin or primidone and phenobarbital has been reported.[1]

For the effect of antiepileptics such as phenytoin on *furosemide*, see p. 1390.1.

1. Mallette LE. Anticonvulsants, acetazolamide and osteomalacia. *N Engl J Med* 1975; **293:** 668.

Dopaminergics. For the effect of phenytoin on *levodopa*, see p. 907.2.

Enteral and parenteral nutrition. Therapeutic plasma concentrations of phenytoin may be difficult to achieve in patients receiving enteral or total parenteral nutrition.[1,2] Incompatibility studies indicate that phenytoin probably binds to components of the feed (see Incompatibility, p. 538.3), which might explain this interaction when both are given together nasogastrically, but the same effect has also been reported when they were given separately by the intravenous route.[2] A review[3] of case reports and studies concluded that the exact role of enteral feeding in this interaction still remained unclear because of a lack of prospective, randomised, controlled studies performed in patients, rather than in healthy subjects. However, because of the amount of literature describing such a phenomenon, it was considered unlikely to occur just by chance. Monitoring of serum-phenytoin concentrations to guide therapy was recommended, and measures such as staggering phenytoin and enteral feeding might be considered to minimise the occurrence of this reaction.

1. Summers VM, Grant R. Nasogastric feeding and phenytoin interaction. *Pharm J* 1989; **243:** 181.
2. Messahel FM, *et al*. Does total parenteral nutrition lower serum phenytoin levels? *Curr Ther Res* 1990; **47:** 1017–20.
3. Au Yeung SC, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother* 2000 **34:** 896–905.

Gastrointestinal drugs. Evidence for an interaction between phenytoin and *antacids* is conflicting. Some studies have shown a decrease in the bioavailability of phenytoin given with various antacid mixtures[1,2] but others have failed to find any evidence of reduced absorption.[3] Furthermore even those studies that recorded decreased absorption varied in their results with regard to particular drugs, suggesting for example that calcium carbonate both does[1] and does not[2] reduce phenytoin bioavailability. The clinical significance of these data is uncertain but it has been suggested that if antacids and phenytoin are both needed, doses should be spaced several hours apart.[4,5] *Sucralfate* is also reported to reduce phenytoin absorption.[6]

A well documented interaction exists between phenytoin and *cimetidine*, which produces a dose-dependent reduction in phenytoin clearance[7] and a significant elevation of serum-phenytoin concentration.[8] There are reports of phenytoin toxicity when cimetidine was given to epileptic patients[9,10] including a report of severe granulocytopenia.[11] Although some studies have found that neither *ranitidine*[12] nor *famotidine*[13] appear to affect the pharmacokinetics of phenytoin significantly, there have been isolated reports of raised plasma concentrations of phenytoin associated with use of ranitidine[14-16] or famotidine.[17]

Omeprazole 40 mg daily can decrease the plasma clearance of phenytoin[18] and increase the area under the serum-phenytoin concentration-time curve,[19] but one study[20] suggests that the dosage of 20 mg daily usually used for peptic ulcer disease is unlikely to produce a clinically significant effect on the steady-state plasma concentrations of phenytoin in patients with epilepsy.

1. Garnett WR, *et al*. Bioavailability of phenytoin administered with antacids. *Ther Drug Monit* 1979; **1:** 435–6.
2. Kulshrestha VK, *et al*. Interaction between phenytoin and antacids. *Br J Clin Pharmacol* 1978; **6:** 177–9.
3. O'Brien LS, *et al*. Failure of antacids to alter the pharmacokinetics of phenytoin. *Br J Clin Pharmacol* 1978; **6:** 176–7.
4. Cacek AT. Review of alterations in oral phenytoin bioavailability associated with formulation, antacids, and food. *Ther Drug Monit* 1986; **8:** 166–71.
5. D'Arcy PF, McElnay JC. Drug-antacid interactions: assessment of clinical importance. *Drug Intell Clin Pharm* 1987; **21:** 607–17.
6. Smart HL, *et al*. The effects of sucralfate upon phenytoin absorption in man. *Br J Clin Pharmacol* 1985; **20:** 238–40.
7. Bartle WR, *et al*. Dose-dependent effect of cimetidine on phenytoin kinetics. *Clin Pharmacol Ther* 1983; **33:** 649–55.
8. Iteogu MO, *et al*. Effect of cimetidine on single-dose phenytoin kinetics. *Clin Pharm* 1983; **2:** 302–4.
9. Phillips P, Hansky J. Phenytoin toxicity secondary to cimetidine administration. *Med J Aust* 1984; **141:** 602.
10. Hetzel DJ, *et al*. Cimetidine interaction with phenytoin. *BMJ* 1981; **282:** 1512.

11. Sazie E, Jaffe JP. Severe granulocytopenia with cimetidine and phenytoin. *Ann Intern Med* 1980; **93:** 151–2.
12. Watts RW, *et al.* Lack of interaction between ranitidine and phenytoin. *Br J Clin Pharmacol* 1983; **15:** 499–500.
13. Sambol NC, *et al.* A comparison of the influence of famotidine and cimetidine on phenytoin elimination and hepatic blood flow. *Br J Clin Pharmacol* 1989; **27:** 83–7.
14. Bramhall D, Levine M. Possible interaction of ranitidine with phenytoin. *Drug Intell Clin Pharm* 1988; **22:** 979–80.
15. Tse CST, *et al.* Phenytoin concentration elevation subsequent to ranitidine administration. *Ann Pharmacother* 1993; **27:** 1448–51.
16. Tse CST, Iagmin P. Phenytoin and ranitidine interaction. *Ann Intern Med* 1994; **120:** 892–3.
17. Shinn AF. Unrecognized drug interactions with famotidine and nizatidine. *Arch Intern Med* 1991; **151:** 814.
18. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism: studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. *Gastroenterology* 1985; **89:** 1235–41.
19. Prichard PJ, *et al.* Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987; **24:** 543–5.
20. Andersson T, *et al.* A study of the interaction between omeprazole and phenytoin in epileptic patients. *Ther Drug Monit* 1990; **12:** 329–33.

Ginkgo biloba. A fatal breakthrough seizure occurred[1] in a 55-year-old man who was taking phenytoin and valproate semisodium for a seizure disorder; he was also taking non-prescription supplements, such as vitamin preparations and herbal medicines including ginkgo biloba extract, without the knowledge of his physician. Autopsy revealed subtherapeutic plasma concentrations of both antiepileptics. Although the exact cause was unclear, the authors postulated that hepatic enzyme induction by ginkgo biloba might have increased the clearance of phenytoin and valproate semisodium.

1. Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with ginkgo biloba. *J Anal Toxicol* 2005; **29:** 755–8.

Immunosuppressants. Increased plasma-phenytoin concentrations were reported[1] in one patient when *tacrolimus* was added to existing therapy. Phenytoin was stopped until values were within the therapeutic range and then restarted at a lower dose, tacrolimus therapy continuing throughout; phenytoin levels remained stable thereafter.

For the effect of phenytoin on *ciclosporin*, see p. 1956.3.

1. Thompson PA, Mosley CA. Tacrolimus-phenytoin interaction. *Ann Pharmacother* 1996; **30:** 544.

Levothyroxine. For the effects of phenytoin on levothyroxine, see p. 2341.3.

Muscle relaxants. An increase in serum concentrations of phenytoin has been reported[1] in a patient when *tizanidine* was added to therapy.

1. Ueno K, *et al.* Phenytoin-tizanidine interaction. *DICP Ann Pharmacother* 1991; **25:** 1273.

Neuromuscular blockers. For the effect of phenytoin on *suxamethonium*, see p. 2039.3 and on *competitive neuromuscular blockers*, see under Atracurium, p. 2032.1.

Sex hormones. For the effect of phenytoin on *oral contraceptives*, see p. 2243.2. Similar effects may also be noted in patients receiving *HRT*, see p. 2251.1.

Stimulants and anorectics. Although there has been a report of elevated phenytoin and primidone serum concentrations in a 5-year-old after addition of *methylphenidate* to therapy[1] there was no similar elevation in 2 other children receiving phenobarbital and phenytoin in the same report, nor in 11 patients of varying ages given methylphenidate with antiepileptic therapy as part of a controlled study.[2] The likelihood of an interaction seems small in the majority of patients.

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate. *JAMA* 1969; **207:** 2053–6.
2. Kupferberg HJ, *et al.* Effect of methylphenidate on plasma anticonvulsant levels. *Clin Pharmacol Ther* 1972; **13:** 201–4.

Theophylline. Although most reports of an interaction between phenytoin and theophylline concern effects on theophylline concentrations, one study in 14 healthy subjects suggested that treatment with both could lower serum-phenytoin concentrations, with a subsequent rise in concentration on stopping theophylline.[1] The mechanism was suggested to be enzyme induction by the xanthine resulting in increased phenytoin metabolism.

For the effect of phenytoin on theophylline, see p. 1235.1.

1. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; **14:** 638.

Ticlopidine. Acute phenytoin toxicity has been reported in a well-stabilised 44-year-old patient on introduction of ticlopidine to prevent restenosis after placement of a coronary stent.[1] The patient also took metoprolol, aspirin, and for a short period lovastatin, but inhibition of the cytochrome P450 isoenzyme CYP2C19 by ticlopidine was considered the most likely cause of the patient's elevated serum phenytoin. A later report[2] by the same authors found that ticlopidine inhibited the clearance of phenytoin in 6 patients on phenytoin monotherapy; the involvement of CYP2C19 was also supported. The authors recommended that dosage adjustment of phenytoin should be considered if ticlopidine is also given.

A similar interaction occurred in a 72-year-old patient,[3] and the authors postulated that, since steady-state plasma concentrations of ticlopidine are almost twofold higher in elderly patients than those in younger patients, the higher ticlopidine concentrations may have played a role in this drug interaction.

1. Donahue SR, *et al.* Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* 1997; **62:** 572–7.
2. Donahue S,*et al.* Ticlopidine inhibits phenytoin clearance. *Clin Pharmacol Ther* 1999; **66:** 563–8.
3. Klaassen SL. Ticlopidine-induced phenytoin toxicity. *Ann Pharmacother* 1998; **32:** 1295–8.

Vaccines. Contradictory results have been reported for the effects of *influenza vaccine* on serum-phenytoin concentrations. A significant elevation in total phenytoin concentration has been reported[1] after vaccination, and was suggested to be due to interferon induction and inhibition of the cytochrome P450 enzyme system. In contrast, other reports have suggested that any increase in serum-phenytoin concentration was temporary and not significant overall[2] or even that there was a slight fall in serum-phenytoin concentration.[3] One study reported a significant increase in total phenytoin concentration two days after vaccination, followed by a return to previous values but this was accompanied by evidence of a gradual and prolonged fall in free phenytoin concentrations.[4] The possibility of either phenytoin toxicity or loss of seizure control may exist in some epileptic patients given influenza vaccine during phenytoin therapy.[5]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; **5:** 817–20.
2. Levine M, *et al.* Increased serum phenytoin concentration following influenza vaccination. *Clin Pharm* 1984; **3:** 505–9.
3. Sawchuk RJ, *et al.* Effect of influenza vaccination on plasma phenytoin concentrations. *Ther Drug Monit* 1979; **1:** 285–8.
4. Smith CD, *et al.* Effect of influenza vaccine on serum concentrations of total and free phenytoin. *Clin Pharm* 1988; **7:** 828–32.
5. Grabenstein JD. Drug interactions involving immunologic agents, part 1: vaccine-vaccine, vaccine-immunoglobulin, and vaccine-drug interactions. *DICP Ann Pharmacother* 1990; **24:** 67–81.

Vitamins. *Pyridoxine* given in large doses produced a reduction in serum-phenytoin concentrations in 7 patients,[1] perhaps reflecting increased activity by pyridoxal phosphate-dependent enzymes involved in phenytoin metabolism.

Correction of antiepileptic-associated folate deficiency with *folic acid* has been reported to result in a decrease in serum-phenytoin concentrations and an increase in seizure frequency.[2-4] The effect has been reported to be most marked in subjects with high initial serum-phenytoin concentrations[5] and is associated with an increased phenytoin metabolism.[4,6] However, in the majority of patients the effect is unlikely to assume clinical significance,[2,5] and there is some evidence that very low doses of folic acid may be used to maintain normal serum-folate values without an increase in seizure frequency.[3] Information regarding the dual and interdependent interaction between phenytoin and folic acid has been reviewed.[7] Although limited numbers of patients and healthy subjects were involved, evaluation of the data suggested that starting phenytoin and folic acid at the same time prevents decreased folate levels and steady-state concentrations of phenytoin are reached sooner. Plasma concentrations of phenytoin are also possibly reduced by *folinic acid* (see also Antineoplastics, p. 544.1).

For the effect of antiepileptics, including phenytoin, on *vitamin D* concentrations, see Effects on Bone, under Adverse Effects, p. 540.2.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; **i:** 256.
2. Baylis EM, *et al.* Influence of folic acid on blood-phenytoin levels. *Lancet* 1971; **i:** 62–4.
3. Inoue F. Clinical implications of anticonvulsant-induced folate deficiency. *Clin Pharm* 1982; **1:** 372–3.
4. Steinweg DL, Bentley ML. Seizures following reduction in phenytoin level after orally administered folic acid. *Neurology* 2005; **64:** 1982.
5. Furlanut M, *et al.* Effects of folic acid on phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1978; **24:** 294–7.
6. Berg MJ, *et al.* Phenytoin and folic acid interaction: a preliminary report. *Ther Drug Monit* 1983; **5:** 389–94.
7. Lewis DP, *et al.* Phenytoin-folic acid interaction. *Ann Pharmacother* 1995; **29:** 726–35.

Pharmacokinetics

Phenytoin is slowly but almost completely absorbed from the gastrointestinal tract. It is largely insoluble at the acid pH of the stomach, most being absorbed from the upper intestine; the rate of absorption is variable and is reported to be affected by the presence of food. Absorption after intramuscular injection is slower than that from the gastrointestinal tract.

Phenytoin is extensively metabolised in the liver to inactive metabolites, chiefly 5-(4-hydroxyphenyl)-5-phenylhydantoin. The rate of metabolism appears to be subject to genetic polymorphism and may also be influenced by racial characteristics; it is reported to be increased during pregnancy and menstruation and to decrease with age. Phenytoin hydroxylation is saturable and is therefore readily inhibited by drugs that compete for its metabolic pathways; this is also the reason why small increments in dose may produce large rises in plasma concentration. Phenytoin undergoes enterohepatic recycling and is excreted in the urine, mainly as its hydroxylated metabolite, in either free or conjugated form.

Phenytoin is widely distributed throughout the body. It is about 90% bound to plasma proteins, although this may be reduced in certain disease states and in certain patient populations (see Precautions, p. 541.3). It has a very variable, dose-dependent half-life, but the mean plasma half-life appears to be about 22 hours at steady state; because phenytoin inhibits its own metabolism it may sometimes be several weeks before a steady-state plasma-phenytoin concentration is attained.

Monitoring of plasma concentrations may be performed as an aid in assessing control, and the therapeutic range of total plasma-phenytoin concentrations is usually quoted as 10 to 20 micrograms/mL (40 to 80 micromoles/litre); some patients, however, achieve control at concentrations outside this range. It has been suggested that, because of differences in protein binding, measurement of free phenytoin concentrations in plasma may prove more reliable; measurement of concentrations in saliva, which contains only free phenytoin, has also been performed.

Phenytoin crosses the placental barrier and small amounts are distributed into breast milk.

The pharmacokinetics of phenytoin are affected by other antiepileptics (see Interactions, p. 542.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Epamin; Etoina; Fenigramon; Fenitenk; Lotoquis Simple; Opliphon; ***Austral.***: Dilantin; ***Austria***: Epanutin; Epilan-D; ***Belg.***: Diphantoine; Epanutin; ***Braz.***: Dantalin; Epelin; Fenital; Feniton; Hidantal; Unifenitoin; ***Canad.***: Dilantin; Tremytoine; ***Chile***: Epamin; ***Cz.***: Epanutin; Epilan D; ***Fin.***: Hydantin; ***Fr.***: Di-Hydan; Dilantin; ***Ger.***: Phenhydan; Zentropil†; ***Gr.***: Epanutin; ***Hong Kong***: Dilantin; Ditoin; ***Hung.***: Diphedan; Epanutin; ***India***: Dilantin; Epicent; Epileptin; Episol; Epitab; Epsolin; Eptoin; Fentoin; Gentoin; M-Toin; Neptoin; Nutoin; ***Indon.***: Dilantin; Ikaphen; Kutoin; Movileps; Phenilep†; ***Irl.***: Epanutin; ***Israel***: Dilantin; Epanutin; ***Ital.***: Aurantin; Dintoina; ***Jpn***: Aleviatin; ***Malaysia***: Dilantin; Ditoin; ***Mex.***: Biodan; Comvufen; Epamin; Fenidantoin S; Feniffler; Fenitron; Hidantoina; ***Neth.***: Diphantoine; Epanutin; ***Norw.***: Epinat; ***NZ***: Dilantin; ***Philipp.***: Dilantin; Epilantin†; Fenitin; Lantidin; ***Pol.***: Epanutin; ***Port.***: Fenitan; Hidantina; ***S.Afr.***: Epanutin; ***Singapore***: Dilantin; ***Spain***: Epanutin; Sinergina; ***Swed.***: Epanutin; Fenantoin; Lehydan; ***Switz.***: Phenhydan; ***Thai.***: Dantoin; Dilantin; Ditoin; Ditomed†; Pepsytoin; Utoin; ***Turk.***: Epanutin; Epdantoin; Hidantin; Phenhydan; ***UK***: Epanutin; ***USA***: Dilantin; Phenytek; ***Venez.***: Dantoinal; Dilantin; Epamin; Fentoinal.

Multi-ingredient Preparations. ***Arg.***: Cumatil-L†; Lotoquis; ***Belg.***: Vethoine; ***Braz.***: Dialudon; ***China***: Di Er Kang Xin (迪尔康欣); ***Cz.***: Sanepil†; ***Gr.***: Diphenal; ***India***: Barbitoin; Dilantin with Phenobarbital†; Epilan C; Epiphen; Episol Plus; Garoin; ***Indon.***: Ditalin; ***Ital.***: Dintoinale; Gamibetal Complex; Metinal-Idantoina L; Metinal-Idantoina; ***Mex.***: Alepsal Compuesto; Gamibetal Complex†; ***Spain***: Redutona†.

Pharmacopoeial Preparations

BP 2014: Phenytoin Capsules; Phenytoin Injection; Phenytoin Oral Suspension; Phenytoin Tablets;

USP 36: Extended Phenytoin Sodium Capsules; Phenytoin Oral Suspension; Phenytoin Sodium Injection; Phenytoin Tablets; Prompt Phenytoin Sodium Capsules.

Pregabalin *(BAN, USAN, rINN)*

CI-1008; PD-144723; Pregabalina; Prégabaline; Pregabalinum; Прегабалин.

(*S*)-3-(Aminomethyl)-5-methylhexanoic acid.

$C_8H_{17}NO_2$=159.2

CAS — 148553-50-8.

ATC — N03AX16.

ATC Vet — QN03AX16.

UNII — 55JG375S6M.

Uses and Administration

Pregabalin is an antiepileptic used as an adjunct in the treatment of partial seizures with or without secondary generalisation (p. 546.1). It is also used in the treatment of generalised anxiety disorder (p. 546.1), neuropathic pain (p. 546.1), and fibromyalgia (see Soft-tissue Rheumatism, p. 546.2).

Pregabalin is given orally in 2 or 3 divided doses daily.

The initial dose in the treatment of **epilepsy** is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 600 mg daily after another week.

In the treatment of **generalised anxiety disorder**, the initial dose is 150 mg daily; this may be increased at weekly intervals in steps of 150 mg, to a maximum of 600 mg daily.

For **neuropathic pain** the initial dose in the UK is 150 mg daily increased after 3 to 7 days according to response to 300 mg daily and then to 600 mg daily after another 7 days. Similar doses are licensed in the USA for the treatment of neuropathic pain in diabetic neuropathy, postherpetic neuralgia, and spinal cord injury, although a maximum daily dose of 300 mg is recommended in diabetic neuropathy.

For **fibromyalgia** the initial dose is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 450 mg daily if necessary.

Dosage of pregabalin should be reduced in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of pregabalin therapy in epilepsy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1. Licensed product information states that if pregabalin therapy has to be stopped, this should be done gradually over a minimum of 1 week, regardless of indication.

References.

1. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005; **39:** 2029–37.
2. Tassone DM, *et al.* Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007; **29:** 26–48.

Administration in renal impairment. The dose of pregabalin for patients with renal impairment should be reduced according to creatinine clearance (CC):

- CC 30 to less than 60 mL/minute: starting daily dose: 75 mg; maximum daily dose: 300 mg; daily dose given in 2 or 3 divided doses
- CC 15 to less than 30 mL/minute: starting daily dose: 25 to 50 mg; maximum daily dose: 150 mg; daily dose given in 2 divided doses or once daily
- CC less than 15 mL/minute: starting daily dose: 25 mg; maximum daily dose: 75 mg; daily dose given as one dose
- haemodialysis patients should receive in addition to the daily dose a supplementary dose of 25 to 100 mg immediately after each 4-hour haemodialysis session

Anxiety disorders. Pregabalin is used for the treatment of generalised anxiety disorder[1-5] (p. 1028.1); it has also been tried in social anxiety disorder[6-8] (see Phobic Disorders, p. 1029.1).

1. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. *Drugs Today* 2007; **43:** 601–10.
2. Montgomery S, *et al.* Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. *Br J Psychiatry* 2008; **193:** 389–94.
3. Anonymous. Pregabalin for generalised anxiety disorder. *Drug Ther Bull* 2010; **48:** 19–22.
4. Boschen MJ. A meta-analysis of the efficacy of pregabalin in the treatment of generalized anxiety disorder. *Can J Psychiatry* 2011; **56:** 558–66.
5. Wensel TM, *et al.* Pregabalin for the treatment of generalized anxiety disorder. *Ann Pharmacother* 2012; **46:** 424–9.
6. Pande AC, *et al.* Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2004; **24:** 141–9.
7. Feltner DE, *et al.* Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixed-dose study. *Int Clin Psychopharmacol* 2011; **26:** 213–20.
8. Greist JH, *et al.* Efficacy of pregabalin in preventing relapse in patients with generalized social anxiety disorder: results of a double-blind, placebo-controlled 26-week study. *Int Clin Psychopharmacol* 2011; **26:** 243–51.

Epilepsy. Pregabalin is one of the newer drugs used as adjunctive therapy in patients with partial seizures with or without secondary generalisation (p. 506.1). It appears to be reasonably well tolerated.

References.

1. Hamandi K, Sander JW. Pregabalin: a new antiepileptic drug for refractory epilepsy. *Seizure* 2006; **15:** 73–8.
2. Lozsadi D, *et al.* Pregabalin add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).
3. Beydoun A, *et al.* Efficacy and tolerability of pregabalin in partial epilepsy. *Expert Rev Neurother* 2008; **8:** 1013–24.
4. Arain AM. Pregabalin in the management of partial epilepsy. *Neuropsychiatr Dis Treat* 2009; **5:** 407–13.
5. Gil-Nagel A, *et al.* Add-on treatment with pregabalin for partial seizures with or without generalisation: pooled data analysis of four randomised placebo-controlled trials. *Seizure* 2009; **18:** 184–92.
6. Lee BI, *et al.* Pregabalin add-on therapy using a flexible, optimized dose schedule in refractory partial epilepsies: a double-blind, randomized, placebo-controlled, multicenter trial. *Epilepsia* 2009; **50:** 464–74.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p. 4.2). Pregabalin is used in the treatment of peripheral neuropathic pain[1] including postherpetic neuralgia[2-4] (p. 10.3) and painful diabetic neuropathy[5-7] (p. 8.2). It has been studied in the treatment of trigeminal neuralgia[8] (p. 11.2) and post-traumatic peripheral neuropathic pain.[9] Pregabalin may also be used in central neuropathic pain associated with spinal cord injury.[10,11] It has also been tried with some success in the management of central post-stroke pain[12] (p. 7.3). In the UK, NICE recommends pregabalin as first-line and second-line treatment for neuropathic pain in non-specialist settings.[13]

A systematic review[14] of the use of pregabalin in acute and chronic pain found that pregabalin in doses of 300 to 600 mg daily produced clear benefit in chronic neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia, and to a lesser extent central neuropathic pain), and in fibromyalgia (see Soft-tissue Rheumatism, below), but the benefit was high only in a minority of patients, and effective doses were also associated with increased frequency of adverse effects such as dizziness and somnolence. There was no clear evidence of any benefit in acute postoperative pain (see also below).

1. Blommel ML, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health-Syst Pharm* 2007; **64:** 1475–82.
2. Sabatowski R, *et al.* Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004; **109:** 26–35.
3. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs* 2005; **65:** 111–18.
4. McKeage K, Keam SJ. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs Aging* 2009; **26:** 883–92.
5. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. *Drugs* 2004; **64:** 2813–20.
6. Freeman R, *et al.* Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008; **31:** 1448–54.
7. Satoh J, *et al.* Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. *Diabet Med* 2011; **28:** 109–16.
8. Obermann M, *et al.* Efficacy of pregabalin in the treatment of trigeminal neuralgia. *Cephalalgia* 2008; **28:** 174–81.
9. van Seventer R, *et al.* Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. *Eur J Neurol* 2010; **17:** 1082–9.
10. Siddall PJ, *et al.* Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006; **67:** 1792–800.
11. Vranken JH, *et al.* Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008; **136:** 150–7.
12. Kim JS, *et al.* Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain* 2011; **152:** 1018–23.
13. NICE. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings (issued March 2010). Available at: http://www.nice.org.uk/nicemedia/live/12948/47949/47949.pdf (accessed 07/06/10)
14. Moore RA, *et al.* Pregabalin for acute and chronic pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 25/11/09).

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as pregabalin to modulate opioid dosage and efficacy for postoperative pain (p. 6.1). However, although pregabalin has been investigated for this purpose[1-3] a systematic review found no evidence to support such use (see Neuropathic Pain, above).

1. Dahl JB, *et al.* Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48:** 1130–6.
2. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104:** 1545–56.
3. Dauri M, *et al.* Gabapentin and pregabalin for the acute post-operative pain management: a systematic-narrative review of the recent clinical evidences. *Curr Drug Targets* 2009; **10:** 716–33.

Restless legs syndrome. Pregabalin has been reported[1,2] to be of benefit in the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2).

1. Garcia-Borreguero D, *et al.* Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. *Neurology* 2010; **74:** 1897–1904.
2. Allen R, *et al.* A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. *Sleep Med* 2010; **11:** 512–19.

Soft-tissue rheumatism. Three large, multicentre controlled studies[1-3] have shown that pregabalin in oral doses of between 300 and 600 mg daily is effective in reducing pain and other core symptoms of fibromyalgia (p. 14.2) such as sleep disturbance and fatigue. A small study[4] suggested that it may also be of benefit in refractory disease. The drug was reported to be generally well tolerated, dizziness and somnolence being the most common adverse effects. Pain relief appears to be largely independent of reduction in anxiety or depression scores.[5,6] The use of pregabalin in fibromyalgia has been reviewed.[7,8] For a systematic review that also found some degree of benefit from the use of pregabalin in fibromyalgia see Neuropathic Pain, above.

Although pregabalin is licensed in some countries including the USA for the treatment of fibromyalgia, the EMEA did not authorise such use in the EU; after having reviewed the submitted studies (some of which are cited above), it considered that there were no consistent or relevant reductions in pain in short-term studies, and that maintenance of pregabalin's effect was not shown in a longer study.

1. Crofford LJ, *et al.* Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 1264–73.
2. Mease PJ, *et al.* A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008; **35:** 502–14.
3. Crofford LJ, *et al.* Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008; **136:** 419–31.
4. Stacey BR, *et al.* Pregabalin in treatment-refractory fibromyalgia. *Open Rheumatol J* 2010; **4:** 35–8.
5. Arnold LM, *et al.* The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med* 2007; **8:** 633–8.
6. Häuser W, *et al.* Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain* 2009; **145:** 69–81.
7. Lyseng-Williamson KA, Siddiqui MAA. Pregabalin: a review of its use in fibromyalgia. *Drugs* 2008; **68:** 2205–23.
8. Boomershine CS. Pregabalin for the management of fibromyalgia syndrome. *J Pain Res* 2010; **3:** 81–8.

Adverse Effects and Precautions

The most common adverse effects reported during therapy with pregabalin are dizziness and somnolence. Other common adverse effects include blurred vision, diplopia, increased appetite and weight gain, dry mouth, constipation (occasionally severe), vomiting, flatulence, euphoria, confusion, reduced libido, erectile dysfunction, irritability, vertigo, ataxia, tremor, dysarthria, paraesthesia, fatigue, and oedema. Disturbances of attention, memory, coordination, and gait also occur frequently. Syncope and congestive heart failure have been reported less frequently. Reversible renal failure, raised liver enzymes, elevation of creatine kinase concentration, and rhabdomyolysis have been reported rarely. Breast enlargement and gynaecomastia have also been reported. Hypersensitivity reactions have occurred shortly after starting pregabalin therapy; symptoms include rash, blisters, urticaria, dyspnoea, and wheezing. Stevens-Johnson syndrome has also been reported. An increased incidence of haemangiosarcoma occurred in *mice* that had been given high doses of pregabalin.

Licensed product information states that care is required when withdrawing pregabalin therapy, regardless of the indication—see also Uses and Administration, p. 545.3.

References.

1. Zaccara G, *et al.* The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2011; **52:** 826–36.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of pregabalin on *mood* (including the risk of suicidal ideation), see p. 508.3.

Hypersensitivity reactions. The Australian Adverse Drug Reactions Advisory Committee[1] stated in December 2007 that 13% of all pregabalin adverse reaction reports in its database were hypersensitivity reactions. Presenting symptoms included anaphylaxis, skin rash, and angioedema. Of the 22 reports received, 6 women developed symptoms within hours of their first dose and pregabalin was the sole suspected drug in 14.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Reports of hypersensitivity reactions to pregabalin. *Aust Adverse Drug React Bull* 2007; **26:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0712.pdf (accessed 09/06/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pregabalin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Pharmacokinetics

Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations occur within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by haemodialysis.

Distribution into milk has been found in studies in *rats*.

References.
1. Randinitis EJ, *et al.* Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 2003; **43:** 277–83.
2. Bockbrader HN, *et al.* A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010; **49:** 661–9.
3. Bockbrader HN, *et al.* Population pharmacokinetics of pregabalin in healthy subjects and patients with chronic pain or partial seizures. *Epilepsia* 2011; **52:** 248–57.
4. Shoji S, *et al.* Population pharmacokinetics of pregabalin in healthy subjects and patients with post-herpetic neuralgia or diabetic peripheral neuropathy. *Br J Clin Pharmacol* 2011; **72:** 63–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Axual; Balfibro; Clasica; Gavin; Kabian; Linprel; Lyrica; Mystika; Neuristan; Plenica; Prebanal; ***Austral.***: Lyrica; ***Austria***: Lyrica; ***Belg.***: Lyrica; ***Braz.***: Lyrica; ***Canad.***: Lyrica; ***Chile***: Lyrica; Neurum; Prebictal; Prefaxil; Pregalex; Pregobin; ***China***: Lyrica (乐瑞卡); ***Cz.***: Lyrica; ***Denm.***: Lyrica; ***Fin.***: Lyrica; ***Fr.***: Lyrica; ***Ger.***: Lyrica; ***Gr.***: Lyrica; ***Hong Kong***: Lyrica; ***Hung.***: Lyrica; ***India***: Gabafit; Gabanext; Galinerve; Lyrica; Maxgalin; Mygalin; Neugaba; Neupreg; Nuramed; Pregab; ***Indon.***: Lyrica; ***Irl.***: Lyrica; ***Israel***: Lyrica; ***Ital.***: Lyrica; ***Jpn***: Lyrica; ***Malaysia***: Lyrica; ***Mex.***: Lyrica; ***Neth.***: Lyrica; ***Norw.***: Lyrica; ***NZ***: Lyrica; ***Philipp.***: Lyrica; ***Pol.***: Lyrica; ***Port.***: Lyrica; ***Rus.***: Lyrica (Лирика); ***S.Afr.***: Lyrica; ***Singapore***: Lyrica; ***Spain***: Lyrica; ***Swed.***: Lyrica; ***Switz.***: Lyrica; ***Thai.***: Lyrica; ***Turk.***: Lyrica; ***UK***: Lyrica; ***Ukr.***: Lyrica (Лирика); Pregamed (Прегамед); ***USA***: Lyrica; ***Venez.***: Lyrica.

Multi-ingredient Preparations. ***India***: Alnacob-P; Capin Plus; Cobal-PG; Doloneuron-PG; Ecogab; Gaba-PM; Gabafix M; Gabatop; Galinerve M; GB-29; Leogab-M; Macraberin-P; Mahagaba-M; Maxgalin-M; Mecap-P; Mecobil-P; Mecobion-P; Mecoday-PG; Mepik; MGTec-P; Miol-P; Nerjuwin-P; Nervelin-M; Nervijen-P; Nervim-P; Nervon-PM; Nervonic-P; Nervup-PG; Neupreg Forte; Neurica-M; Neutron-OD; Nurocare-PG; Nuromas-PG; Nuromax-PG; Nurovole-PG.

Primidone *(BAN, rINN)*

Desoxifenobarbitona; Hexamidinum; Primaclona; Primaclone; Primidon; Primidona; Primidonas; Primidoni; Primidonum; Prymidon; Примидон.

5-Ethyl-5-phenylperhydropyrimidine-4,6-dione.

$C_{12}H_{14}N_2O_2$=218.3

CAS — 125-33-7.

ATC — N03AA03.

ATC Vet — QN03AA03.

UNII — 13AFD7670Q.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Primidone). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in alkaline solutions.

USP 36: (Primidone). A white, odourless, crystalline powder. Soluble 1 in 2000 of water and 1 in 200 of alcohol; very slightly soluble in most organic solvents.

Uses and Administration

Primidone is an antiepileptic that is partially metabolised to phenobarbital (p. 535.3), but is also considered to have some antiepileptic activity in its own right. It may be given to control partial and generalised tonic-clonic seizures (below). Primidone is also used in the management of essential tremor (below).

In the treatment of **epilepsy** the dose of primidone should be adjusted according to response; a limited correlation with plasma concentrations has suggested that concentrations of 5 to 12 micrograms/mL (23 to 55 micromoles/litre) are usually necessary, but the *BNF* recommends monitoring of phenobarbital concentrations instead.

Recommended initial oral doses in the UK are 125 mg at bedtime increased, if necessary, by 125 mg every 3 days to a total of 500 mg daily given in 2 divided doses. If necessary, the daily dose may be increased further every 3 days by 250 mg up to a maximum of 1.5 g daily given in divided doses. Usual maintenance doses are 0.75 to 1.5 g daily; maintenance doses are usually given as 2 divided doses. Dosage recommendations in the USA are generally similar although a maximum daily dose of 2 g is permitted.

For doses in children, see below.

As with other antiepileptics, withdrawal of primidone or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

For **essential tremor** primidone is usually started at daily oral doses of 50 mg, increased gradually over 2 to 3 weeks if necessary, to a maximum of 750 mg daily.

Administration in children. Children may be given primidone to control partial and generalised tonic-clonic seizures. Recommended initial oral doses in the UK are 125 mg at bedtime, increased if necessary, by 125 mg every 3 days to the following usual maintenance daily doses (given in 2 divided doses) according to age:

- up to 2 years: 250 to 500 mg
- 2 to 5 years: 500 to 750 mg
- 6 to 9 years: 750 to 1000 mg

Older children may be given the usual adult dose (see above).

In the USA, a lower initial oral dose of 50 mg daily is recommended. This is doubled every 3 days, to reach a usual maintenance dose of 125 to 250 mg 3 times daily (10 to 25 mg/kg daily in divided doses) after 10 or more days. Children over 8 years of age may be given the usual adult dose (see above).

Epilepsy. Primidone, like its metabolite phenobarbital, is used in the treatment of epilepsy (p. 506.1) for partial seizures with or without secondary generalisation and for primary generalised tonic-clonic seizures. However, because of problems of sedation, it is usually reserved for use in cases unresponsive to other antiepileptics. It has been suggested that it may be suitable for use in patients with QT-interval prolongation.[1]

1. Christidis D, *et al.* Is primidone the drug of choice for epileptic patients with QT-prolongation? A comprehensive analysis of literature. *Seizure* 2006; **15:** 64–6.

Neonatal apnoea. Results from a preliminary study suggested that adjunctive treatment with primidone[1] might be of value in neonatal apnoea resistant to first-line therapy with xanthines alone, but subsequent confirmatory studies seem to be lacking.

1. Miller CA, *et al.* The use of primidone in neonates with theophylline-resistant apnea. *Am J Dis Child* 1993; **147:** 183–6.

Neonatal seizures. Primidone has been tried in the management of neonatal seizures (p. 511.3).

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p. 1318.3) but primidone[1] may also be tried. A high incidence of acute adverse reactions has been reported after initial doses (see Tremor, under Precautions, below). There has been concern that long-term use may produce tolerance to primidone's effects, although a small study has found a reduced response in only a few patients.[2] A later study[3] found a dose of 250 mg daily to be as or more effective than 750 mg daily without there being evidence of loss of efficacy during a 12-month follow-up.

1. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
2. Sasso E, *et al.* Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990; **13:** 67–76.
3. Serrano-Dueñas M. Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor: double-blind comparative study with one-year follow-up. *Parkinsonism Relat Disord* 2003; **10:** 29–33.

Adverse Effects, Treatment, and Precautions

As for Phenobarbital, p. 536.3.

Adverse effects may be more frequent than with phenobarbital. Most patients rapidly develop tolerance to the adverse effects of primidone, including ataxia, dizziness, drowsiness, headache, nausea and vomiting, nystagmus, skin rashes, and visual disturbances.

Care is required when withdrawing primidone therapy—see also Uses and Administration, above.

Effects on the blood. For a report of delayed agranulocytosis in a patient treated with phenytoin and primidone, see p. 540.1.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

Overdosage. Crystalluria has been reported[1] after acute overdosage of primidone and 7 other reported cases were also reviewed. Based on these few reports, crystalluria appears to be associated with serum-primidone concentrations in excess of 80 micrograms/mL. There is evidence from 2 reports of renal damage associated with crystal formation *in vivo*. Vigorous hydration is recommended in patients at risk, in order to lessen the potential for renal toxicity and improve elimination.

1. Lehmann DF. Primidone crystalluria following overdose: a report of a case and an analysis of the literature. *Med Toxicol* 1987; **2:** 383–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies primidone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Tremor. It was noted that patients receiving primidone for essential tremor have a high incidence of acute adverse reactions after small initial doses.[1] This could be due to the absence of induced hepatic enzymes in these patients previously not exposed to antiepileptics.

1. Findley LJ, *et al.* Primidone in essential tremor of the hands and head: a double blind controlled clinical study. *J Neurol Neurosurg Psychiatry* 1985; **48:** 911–15.

Interactions

Primidone is metabolised in the body in part to phenobarbital, and interactions recorded for phenobarbital (p. 537.2) might potentially occur in patients receiving primidone. In addition, enzyme-inducing drugs enhance this metabolism and have the potential to produce elevated phenobarbital concentrations.

Antiepileptics. Both *phenytoin*[1] and *carbamazepine*[2] have been reported to enhance the metabolism of primidone to phenobarbital and when primidone was combined with phenytoin there have been instances of phenobarbital toxicity.[3] *Vigabatrin* has been reported[4] to lower plasma concentrations of primidone in some patients, although it is unlikely that dosage changes would be necessary. *Valproate* may increase plasma concentrations of primidone and phenobarbital, but patient response seems to be inconsistent.[5-7]

1. Reynolds EH, *et al.* Interaction of phenytoin and primidone. *BMJ* 1975; **2:** 594–5.
2. Baciewicz AM. Carbamazepine drug interactions. *Ther Drug Monit* 1986; **8:** 305–17.
3. Galdames D, *et al.* Interacción fenitoína-primidona: intoxicación por fenobarbital, en un adulto tratado con ambas drogas. *Rev Med Chil* 1980; **108:** 716–20.
4. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl 1): 95S–100S.
5. Windorfer A, *et al.* Elevation of diphenylhydantoin and primidone serum concentration by addition of dipropylacetate, a new anticonvulsant drug. *Acta Paediatr Scand* 1975; **64:** 771–2.
6. Bruni J. Valproic acid and plasma levels of primidone and derived phenobarbital. *Can J Neurol Sci* 1981; **8:** 91–2.
7. Yukawa E, *et al.* The effect of concurrent administration of sodium valproate on serum levels of primidone and its metabolite phenobarbital. *J Clin Pharm Ther* 1989; **14:** 387–92.

Pharmacokinetics

Primidone is readily absorbed from the gastrointestinal tract and is reported to have a plasma half-life ranging from 10 to 15 hours, which is shorter than those of its principal metabolites phenylethylmalonamide and phenobarbital, both of which are active. Therapeutic plasma concentrations of primidone have been suggested to be between 5 and 12 micrograms/mL. It is excreted in urine as unchanged drug (40%) and metabolites.

Primidone is widely distributed but is only partially bound to plasma proteins; it has been suggested that it exhibits variable binding of up to about 20%. It crosses the placenta and is distributed into breast milk.

The pharmacokinetics of primidone may be affected by use with other antiepileptics (see under Interactions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mysoline; ***Austral.***: Mysoline; ***Austria***: Mysoline; ***Belg.***: Mysoline; ***Braz.***: Mysoline; Primid; ***Cz.***: Liskantin; ***Fr.***: Mysoline; ***Ger.***: Mylepsinum; Resimatil†; ***Gr.***: Mysoline; ***Hung.***: Sertan; ***India***: Mysoline; ***Irl.***: Mysoline; ***Israel***: Prysoline; ***Ital.***: Mysoline; ***Mex.***: Mysoline; ***Neth.***: Mysoline; ***Pol.***: Mizodin; ***Port.***: Mysoline; ***Rus.***: Hexamidin (Гексамидин); ***S.Afr.***: Mysoline; ***Singapore***: Mysoline; ***Spain***: Mysoline; ***Switz.***: Mysoline; ***Turk.***: Mysoline; ***UK***: Mysoline†; ***USA***: Mysoline.

Pharmacopoeial Preparations
BP 2014: Primidone Oral Suspension; Primidone Tablets;
USP 36: Primidone Oral Suspension; Primidone Tablets.

Retigabine *(rINN)*

AWD21-360; D-23129; Ezogabine (USAN); GKE-841; GW-582892X; Retigabina; Rétigabine; Retigabinum; WAY-143841; Ретигабин.

Ethyl 2-amino-4-[(*p*-fluorobenzyl)amino]carbanilate.

$C_{16}H_{18}FN_3O_2$=303.3

CAS — 150812-12-7.

ATC — N03AX21.

ATC Vet — QN03AX21.

UNII — 12G01I6BBU.

Uses and Administration

Retigabine is a neuronal potassium channel opener that is used for the adjunctive treatment of partial-onset seizures with or without secondary generalisation (see Epilepsy, p. 506.1) in patients aged 18 years and older. In the EU, its

The symbol † denotes a preparation no longer actively marketed

use is restricted to those who have had an inadequate response to, or are intolerant of, other antiepileptics (for details, see Abnormal Coloration, under Adverse Effects and Precautions, below).

The maximum initial oral dose is 300 mg daily for 1 week; thereafter, the total daily dose may be increased by a maximum of 150 mg weekly, according to response and tolerability, to a usual maintenance dose of between 600 mg to 1.2 g daily. Retigabine should be taken in 3 divided doses daily.

Reduced initial and maintenance doses are recommended in patients aged 65 years and older: 150 mg daily should be taken initially, followed by maximum weekly increments of 150 mg to a maximum maintenance dose of 900 mg daily.

Reduced doses are also recommended in patients with hepatic or renal impairment (see below).

As with other antiepileptics, withdrawal of retigabine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the dose over a period of 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

References.

1. Blackburn-Munro G, *et al*. Retigabine: chemical synthesis to clinical application. *CNS Drug Rev* 2005; **11:** 1–20.
2. Porter RJ, *et al*. Retigabine. *Neurotherapeutics* 2007; **4:** 149–54.
3. Brodie MJ, *et al*. RESTORE 2 Study Group. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010; **75:** 1817–24.
4. Owen RT. Ezogabine: a novel antiepileptic as adjunctive therapy for partial onset seizures. *Drugs Today* 2010; **46:** 815–22.
5. French JA, *et al*. RESTORE 1/Study 301 Investigators. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology* 2011; **76:** 1555–63.
6. Deeks ED. Retigabine (ezogabine): in partial-onset seizures in adults with epilepsy. *CNS Drugs* 2011; **25:** 887–900.
7. Gunthorpe MJ, *et al*. The mechanism of action of retigabine (ezogabine), a first-in-class K+ channel opener for the treatment of epilepsy. *Epilepsia* 2012; **53:** 412–24.
8. Martyn-St James M, *et al*. The efficacy and safety of retigabine and other adjunctive treatments for refractory partial epilepsy: a systematic review and indirect comparison. *Seizure* 2012; **21:** 665–78.
9. Yamada M, Welty TE. Ezogabine: an evaluation of its efficacy and safety as adjunctive therapy for partial-onset seizures in adults. *Ann Pharmacother* 2012; **46:** 1358–67.
10. Craig D, *et al*. Retigabine for the adjunctive treatment of adults with partial-onset seizures in epilepsy with and without secondary generalization: a NICE single technology appraisal. *Pharmacoeconomics* 2013; **31:** 101–10.
11. Amabile CM, Vasudevan A. Ezogabine: a novel antiepileptic for adjunctive treatment of partial-onset seizures. *Pharmacotherapy* 2013; **33:** 187–94.

Administration in hepatic or renal impairment. The usual initial dose of retigabine (see p. 547.3) should be reduced by 50% to 150 mg daily in patients with moderate or severe hepatic (Child-Pugh score 7 and over) or renal (creatinine clearance below 50 mL/min) impairment. Thereafter, UK licensed product information recommends weekly increments of 50 mg to a maximum of 600 mg daily; however, US product information permits the usual weekly increments of 150 mg in these patients, and recommends a higher maintenance dose of 750 mg daily in those with moderate hepatic impairment (Child-Pugh score of 7 to 9). No dose adjustment is necessary in mild impairment.

Adverse Effects and Precautions

The most commonly reported adverse effects with retigabine are usually mild to moderate in intensity, occur within the first 8 weeks of therapy, and show a dose-effect relationship; these include dizziness, somnolence, fatigue, confusional state, aphasia, abnormal coordination, tremor, balance disorder, memory impairment, gait disturbance, blurred vision, and constipation. Other commonly reported effects include anxiety, psychotic disorders, paraesthesia, weight increase, nausea, and dyspepsia. Urinary retention and hesitation, and dysuria have also been reported usually within the first 8 weeks to 6 months of therapy; retigabine should be used with caution in patients at risk of urinary retention.

Pigment changes of ocular tissues (including the retina), skin, lips, and nails have been commonly reported after long-term use; retigabine therapy should only be continued in affected patients after careful assessment of the balance of risks and benefits. As some reports of ocular discoloration have been associated with visual impairment, an ophthalmological examination should be performed in all patients at baseline and at least every 6 months thereafter.

Retigabine, at a dose of 1.2 g daily, has been associated with prolongation of the QT interval in healthy subjects; consequently, retigabine should be used with caution in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalaemia, or hypomagnesaemia, in those who are taking drugs known to prolong the QT interval, and in elderly patients. Such patients should have an ECG before starting therapy; those with a corrected QT of > 440 milliseconds at baseline should also have an ECG on reaching the maintenance dose.

Patients aged 65 years and older may be at increased risk of developing CNS effects, urinary retention, and atrial fibrillation; retigabine must be used with caution and reduced doses are recommended. Lower doses of retigabine are also recommended in patients with moderate to severe hepatic or renal impairment.

Care is required when withdrawing retigabine therapy—see also Uses and Administration, p. 547.3.

Abnormal coloration. Pigment changes or discoloration of ocular tissues, skin, lips, and nails have been reported in long-term studies of retigabine.[1-3] Up to May 2013, 55 patients have been examined and 21 were found to have pigment changes in ocular tissues; of these, 15 had retinal pigmentation (5 of whom also had impaired vision).[3] Almost all cases of retinal pigmentation occurred after at least 3 years of treatment and some have occurred in the absence of skin discoloration.[1] In addition, 51 cases of blue-grey pigmentation of the skin, lips, and nails have been reported;[3] the median time to onset was 4.4 years (range: 4 months to 6.7 years) and symptoms tended to occur at high doses (usually 900 mg or more daily) although they have also been reported with lower doses. The cause and long-term prognosis of pigmentation changes associated with retigabine therapy are unknown. Consequently, both the European Medicines Agency (EMEA)[2] and the FDA[1] have recommended that baseline and periodic ophthalmological examination should be performed in all patients; furthermore, the EMEA[2] has also restricted the use of retigabine to patients who have had an inadequate response to, or are intolerant of, other antiepileptics.

1. FDA. FDA drug safety communication: anti-seizure drug Potiga (ezogabine) linked to retinal abnormalities and blue skin discoloration (issued 26th April, 2013). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM349554.pdf (accessed 12/09/13)
2. EMEA. European Medicines Agency recommends restricting Trobalt to last-line therapy in partial epilepsy (issued 30th May, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/human/001245/WC500143799.pdf (accessed 12/09/13)
3. MHRA/CHM. Retigabine (Trobalt): indication restricted to last-line use, and new monitoring requirements after reports of pigment changes in ocular tissue, skin, lips, or nails. *Drug Safety Update* 2013; **6** (12): A2. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296401 (accessed 12/09/13)

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. *In-vitro* data indicated a low potential for interaction with other antiepileptics; however, *in-vivo* studies found that carbamazepine and phenytoin reduced the systemic exposure to retigabine by about 33% and 35%, respectively, and an increase in the dosage of retigabine should be considered when adding these drugs.

Alcohol can increase the systemic exposure to retigabine and potentially increase the incidence of adverse effects; such use has resulted in an increase in visual blurring in healthy subjects. Retigabine has been shown to interfere with serum and urine bilirubin assays, resulting in falsely elevated readings.

Pharmacokinetics

Retigabine is readily absorbed after oral doses; peak concentrations occur about half an hour to 2 hours later. The pharmacokinetics of retigabine are reported to be linear at clinical doses. It is well distributed in the body and about 80% bound to plasma proteins. Retigabine is extensively metabolised, mainly undergoing glucuronidation by the uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) to form inactive *N*-glucuronides, the major metabolites. Retigabine also undergoes acetylation by *N*-acetyltransferase 2 (NAT2) to form an active, but less potent, *N*-acetyl metabolite (NAMR) that is subsequently glucuronidated. About 85% of a dose is excreted in the urine: 36% as unchanged retigabine, 18% as NAMR, and 24% as *N*-glucuronides of retigabine and NAMR. About 14% of a dose is excreted in the faeces, with 3% as unchanged drug. Retigabine and NAMR have similar elimination half-lives of about 6 to 11 hours.

References.

1. Hermann R, *et al*. Effects of age and sex on the disposition of retigabine. *Clin Pharmacol Ther* 2003; **73:** 61–70.
2. Tompson DJ, Crean CS. Clinical pharmacokinetics of retigabine/ezogabine. *Curr Clin Pharmacol* 2013; **8:** 319–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Trobalt; ***Cz.***: Trobalt; ***Denm.***: Trobalt; ***Fr.***: Trobalt; ***Irl.***: Trobalt; ***Israel***: Trobalt; ***Neth.***: Trobalt; ***Norw.***: Trobalt; ***Spain***: Trobalt; ***Swed.***: Trobalt; ***Switz.***: Trobalt; ***UK***: Trobalt; ***USA***: Potiga.

Rufinamide *(BAN, USAN, rINN)*

60231/4; CGP-33101; E-2080; RUF-331; Rufinamida; Rufinamidum; Руфинамид.

1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.

$C_{10}H_8F_2N_4O$=238.2

CAS — 106308-44-5.

ATC — N03AF03.

ATC Vet — QN03AF03.

UNII — WFW942PR79.

Pharmacopoeias. In *US*.

USP 36: (Rufinamide). A white, crystalline neutral powder. Practically insoluble in water; very slightly soluble in alcohol and in acetonitrile; slightly soluble in methyl alcohol and in tetrahydrofuran. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Rufinamide is an antiepileptic used as an adjunct in the treatment of seizures associated with the Lennox-Gastaut syndrome (see Epilepsy, p. 506.1) in patients aged 4 years and over. Rufinamide is given orally in 2 divided doses daily with food.

In the UK, the recommended initial daily dose in patients weighing less than 30 kg is 200 mg, increased according to response in increments of 200 mg every 2 days to a usual maximum of 1 g daily; the recommended maximum dose in those taking *valproate* is 600 mg daily. In patients weighing more than 30 kg, the initial daily dose is 400 mg, increased according to response in increments of 400 mg every 2 days to a maximum daily dose of 1.8 g in those weighing up to 50 kg, 2.4 g in those weighing up to 70 kg, and 3.2 g in those over 70 kg.

In the USA, the initial daily dose is 400 to 800 mg, increased according to response in increments of 400 to 800 mg every 2 days to a maximum daily dose of 3.2 g. The recommended initial daily dose in children aged 4 years and over is about 10 mg/kg, increased according to response in increments of about 10 mg/kg every other day to a target dose of 45 mg/kg daily or 3.2 g daily, whichever is less.

As with other antiepileptics, withdrawal of rufinamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the daily dose by about 25% every 2 days. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Rufinamide has also been investigated as adjunctive therapy in the treatment of partial and primary generalised tonic-clonic seizures.

References.

1. Deeks ED, *et al*. Rufinamide. *CNS Drugs* 2006; **20:** 751–60.
2. Cheng-Hakimian A, *et al*. Rufinamide: pharmacology, clinical trials, and role in clinical practice. *Int J Clin Pract* 2006; **60:** 1497–501.
3. Glauser T, *et al*. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008; **70:** 1950–8.
4. Kluger G, *et al*. Effectiveness and tolerability of rufinamide in children and adults with refractory epilepsy: first European experience. *Epilepsy Behav* 2009; **14:** 491–5.
5. Brodie MJ, *et al*. Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: a randomized placebo-controlled trial. *Epilepsia* 2009; **50:** 1899–909.
6. Stafstrom CE. Update on the management of Lennox-Gastaut syndrome with a focus on rufinamide. *Neuropsychiatr Dis Treat* 2009; **5:** 547–51.
7. Verrotti A, *et al*. Efficacy of rufinamide in drug-resistant epilepsy: a meta-analysis. *Pediatr Neurol* 2011; **44:** 347–9.
8. Coppola G. Update on rufinamide in childhood epilepsy. *Neuropsychiatr Dis Treat* 2011; **7:** 399–407.

Administration in children. For doses of rufinamide in children, see above.

Adverse Effects and Precautions

The most common adverse effects with rufinamide include headache, dizziness, fatigue, somnolence, nausea, and vomiting. Other reported adverse effects include anorexia, weight loss, anxiety, insomnia, vertigo, nystagmus, tremor,

dyspepsia, constipation, and diarrhoea. Convulsions, including status epilepticus, have occurred. Lymphadenopathy, abnormal liver function tests, and haematuria, as well as fever and rash, have been reported as part of a hypersensitivity syndrome.

Rufinamide can reduce the QT interval and should be used with caution in those with a shortening of their QT interval or with a family history of congenital short QT syndrome.

Care is required when withdrawing rufinamide therapy—see Uses and Administration, p. 548.3.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Rufinamide plasma concentrations are reportedly decreased by carbamazepine, phenobarbital, phenytoin, vigabatrin, or primidone; however, these interactions are not considered to be clinically relevant. In contrast, significant increases in rufinamide plasma concentrations can occur with valproate and dosage adjustments may be necessary (see Uses and Administration, p. 548.3).

Rufinamide induces the cytochrome P450 isoenzyme CYP3A4 and may be expected to decrease plasma concentrations of drugs metabolised by this route, such as oral contraceptives. Rufinamide reportedly increases steady-state plasma concentrations of phenytoin.

Pharmacokinetics

Rufinamide is well absorbed after oral doses; peak plasma concentrations occur after about 6 hours. Food increases the bioavailability of rufinamide by about 34 to 40%. It is 34% bound to serum proteins, mainly to albumin.

Rufinamide is hydrolysed to an inactive metabolite and has a plasma elimination half-life of about 6 to 10 hours, although clearance in children is reported to be slower. It is mainly excreted in urine as the inactive metabolite.

References

1. Cardot JM, *et al.* The influence of food on the disposition of the antiepileptic rufinamide in healthy volunteers. *Biopharm Drug Dispos* 1998; **19:** 259–62.
2. Perucca E, *et al.* Rufinamide: clinical pharmacokinetics and concentration-response relationships in patients with epilepsy. *Epilepsia* 2008; **49:** 1123–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Inovelon; ***Belg.***: Inovelon; ***Canad.***: Banzel; ***Cz.***: Inovelon; ***Denm.***: Inovelon; ***Fr.***: Inovelon; ***Ger.***: Inovelon; ***Gr.***: Inovelon; ***Hung.***: Inovelon; ***Irl.***: Inovelon; ***Israel***: Inovelon; ***Ital.***: Inovelon; ***Jpn***: Inovelon; ***Neth.***: Inovelon; ***Norw.***: Inovelon; ***Pol.***: Inovelon; ***Port.***: Inovelon; ***Spain***: Inovelon; ***Swed.***: Inovelon; ***Switz.***: Inovelon; ***UK***: Inovelon; ***USA***: Banzel.

Pharmacopoeial Preparations
USP 36: Rufinamide Tablets.

Stiripentol *(USAN, rINN)*

BCX-2600; Estiripentol; Stiripentolum; Стирипентол.
4,4-Dimethyl-1-[(3,4-methylenedioxy)phenyl]-1-penten-3-ol.
$C_{14}H_{18}O_3$=234.3
CAS — 49763-96-4.
ATC — N03AX17.
ATC Vet — QN03AX17.
UNII — R02XOT8V8I.

Uses and Administration

Stiripentol is used with clobazam and valproate as adjunctive therapy in the treatment of refractory generalised tonic-clonic seizures in severe myoclonic epilepsy in infancy (below). It is thought to be less potent than some conventional antiepileptics, but may reduce their adverse effects when used adjunctively.

Stiripentol is given orally and should be started at a low dose, gradually increased over 3 days, to the recommended dose of 50 mg/kg daily given in 2 or 3 divided doses with food (but not with dairy products, carbonated drinks, fruit juice, or food and drinks that contain caffeine or theophylline). After starting adjunctive stiripentol therapy, the daily dose of clobazam may be reduced by 25% every week if there are signs of adverse effects or overdosage with clobazam. The daily dose of valproate is not usually adjusted, however, it may be reduced by 30% every week if there are signs of gastrointestinal adverse effects.

Epilepsy. A 24-week study[1] in 10 children found that stiripentol might be effective as adjunctive therapy for the treatment of atypical absence seizures (p. 506.1). Further studies suggested benefit from adjunctive use in children with partial epilepsy[2] and severe myoclonic epilepsy.[2-4]

1. Farwell JR, *et al.* Stiripentol in atypical absence seizures in children: an open trial. *Epilepsia* 1993; **34:** 305–11.
2. Perez J, *et al.* Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia* 1999; **40:** 1618–26.
3. Chiron C, *et al.* Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet* 2000; **356:** 1638–42.
4. Chiron C. Stiripentol. *Expert Opin Invest Drugs* 2005; **14:** 905–11.

Adverse Effects and Precautions

The most common adverse effects of stiripentol include anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia, and dystonia. Other common adverse effects include nausea, vomiting, and aggressiveness, and other mood or behavioural disorders. Neutropenia is also reported to be common; persistent severe neutropenia usually resolves spontaneously when stiripentol is stopped. Photosensitivity, rash, and urticaria have occurred. Patients may exhibit altered liver enzyme values.

Growth rates, blood counts, and hepatic function should be monitored periodically in patients given stiripentol.

Interactions

Stiripentol is a potent inhibitor of several cytochrome P450 isoenzymes, including CYP1A2, CYP2C19, and CYP3A4, and may markedly reduce clearance of drugs metabolised by these enzymes. The possibility of an effect on stiripentol metabolism by other inhibitors or inducers of these enzymes should also be borne in mind.

For interactions of stiripentol with other antiepileptics, see under Carbamazepine, p. 516.3, Diazepam, p. 1069.1, and Phenytoin, p. 543.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Diacomit; ***Cz.***: Diacomit; ***Denm.***: Diacomit; ***Fr.***: Diacomit; ***Irl.***: Diacomit; ***Jpn***: Diacomit; ***Neth.***: Diacomit; ***Norw.***: Diacomit; ***Pol.***: Diacomit; ***Port.***: Diacomit; ***Swed.***: Diacomit; ***UK***: Diacomit.

Sultiame *(BAN, rINN)*

Riker-594; Sulthiame (USAN); Sulthiame; Sultiaami; Sultiam; Sultiamo; Sultiamum; Сультиам.
4-(Tetrahydro-2*H*-1,2-thiazin-2-yl)benzenesulphonamide *S,S*-dioxide.
$C_{10}H_{14}N_2O_4S_2$=290.4
CAS — 61-56-3.
ATC — N03AX03.
ATC Vet — QN03AX03.
UNII — I00Q766CZ2.

Pharmacopoeias. In *Jpn.*

Profile

Sultiame is a carbonic anhydrase inhibitor that has been used as an antiepileptic in most forms of epilepsy (p. 506.1) except absence seizures. It has usually been given with other antiepileptics and it is believed that much of its activity is due to the inhibition of metabolism of the other drugs.

Sultiame has been given orally in initial doses of 100 mg twice daily or 50 mg three times daily gradually increased according to response to 200 mg three times daily. A dose of 5 to 10 mg/kg daily, adjusted according to response, has been recommended in Rolandic epilepsy.

Interactions. For the effect of sultiame on *phenytoin*, see p. 543.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ospolot; ***Austral.***: Ospolot; ***Austria***: Ospolot; ***Cz.***: Ospolot; ***Ger.***: Ospolot; ***Gr.***: Ospolot; ***Hung.***: Ospolot; ***Israel***: Ospolot; ***Switz.***: Ospolot.

Tiagabine Hydrochloride

(BANM, USAN, rINNM)

Abbott-70569.1; ABT-569; Hidrocloruro de tiagabina; NNC-05-0328; NO-05-0328; NO-328; Tiagabina, hidrocloruro de; Tiagabine, Chlorhydrate de; Tiagabini Hydrochloridum; Тиагабина Гидрохлорид.
(-)-(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride.
$C_{20}H_{25}NO_2S_2$,HCl=412.0
CAS — 115103-54-3 (tiagabine); 145821-59-6 (tiagabine hydrochloride).
ATC — N03AG06.
ATC Vet — QN03AG06.
UNII — DQH6T6D8OY.

Pharmacopoeias. In *US.*

USP 36: (Tiagabine Hydrochloride). A white to off-white powder. Sparingly soluble in water; freely soluble in alcohol and methyl alcohol; soluble in isopropyl alcohol; very slightly soluble in chloroform; practically insoluble in *n*-heptane. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Stability. An extemporaneously prepared suspension containing tiagabine hydrochloride 1 mg/mL in a mixture of simple syrup and 1% methylcellulose was found,[1] when stored in plastic amber bottles, to be stable for 6 weeks at 25 degrees or 13 weeks at 4 degrees. When prepared in a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (*Paddock, USA*), the suspension was stable for 10 weeks at 25 degrees or 13 weeks at 4 degrees.

1. Nahata MC, Morosco RS. Stability of tiagabine in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; **60:** 75–7.

Uses and Administration

Tiagabine is a nipecotic acid derivative used in the treatment of epilepsy (below) as adjunctive therapy for refractory partial seizures with or without secondary generalisation. It inhibits the uptake of GABA into neuronal and glial cells, and therefore increases the availability of GABA at receptor sites.

UK licensing information states that tiagabine hydrochloride is given as the monohydrate, but doses are described in terms of tiagabine; dose forms providing the equivalent of 5, 10, and 15 mg of tiagabine are available. In the USA, however, the licensed product is stated to contain anhydrous tiagabine hydrochloride, and doses are described in terms of this substance; dose forms providing 2, 4, 12, and 16 mg are available. As a result, the doses in the UK and US literature may not be directly comparable.

In the UK, the initial oral daily dose as adjunctive therapy is the equivalent of tiagabine 5 to 10 mg as a single dose or in 2 divided doses, increased weekly as necessary by increments of 5 to 10 mg. The usual maintenance dose is 30 to 45 mg daily, in 2 or 3 divided doses, in patients receiving enzyme-inducing antiepileptics; in patients *not* taking enzyme-inducing drugs an initial maintenance dosage of 15 to 30 mg daily is suggested. Lower initial doses of the hydrochloride are recommended in the USA. Doses should be taken with food to avoid rapid rises in plasma concentrations, thereby reducing the incidence of adverse effects. Reduced doses should be given in hepatic impairment—see below.

As with other antiepileptics, withdrawal of tiagabine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends gradual withdrawal over a period of 2 to 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in hepatic impairment. The dose of tiagabine should be reduced, or the dosage interval prolonged, in patients with mild to moderate hepatic impairment. Tiagabine should not be given to patients with severe impairment.

Bipolar disorder. Two systematic reviews[1,2] of the use of tiagabine to treat bipolar disorder (p. 397.2) found that the evidence was anecdotal and insufficiently rigorous to support such use.

1. Vasudev A, *et al.* Tiagabine in the treatment of acute affective episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/11/09).
2. Vasudev A, *et al.* Tiagabine in the maintenance treatment of bipolar disorders. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/11/09).

Epilepsy. Tiagabine is one of several drugs that may be used as adjunctive therapy in patients with partial seizures (with or without secondary generalisation) refractory to standard treatment (p. 506.1). It appears to be reasonably

well tolerated. For the suggestion that it might be tried in refractory status epilepticus, see p. 510.2.

References.
1. Leach JP, Brodie MJ. Tiagabine. *Lancet* 1998; **351:** 203–7.
2. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; **55:** 437–60.
3. Luer MS, Rhoney DH. Tiagabine: a novel antiepileptic drug. *Ann Pharmacother* 1998; **32:** 1173–80.
4. Loiseau P. Review of controlled trials of gabitril (tiagabine): a clinician's viewpoint. *Epilepsia* 1999; **40** (suppl 9): S14–S19.
5. Anonymous. Tiagabine: add-on treatment for partial seizures. *Drug Ther Bull* 2000; **38:** 47–8.
6. Dodrill CB, *et al.* Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000; **42:** 123–32.
7. Crawford P, *et al.* Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001; **42:** 531–8.
8. Biraben A, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001; **3:** 91–100.
9. Pereira J, *et al.* Tiagabine add-on for drug-resistant partial epilepsy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 09/06/08).
10. Arroyo S, *et al.* A randomised open-label study of tiagabine given two or three times daily in refractory epilepsy. *Seizure* 2005; **14:** 81–4.

Pain. Antiepileptics are among the drugs used to manage pain (see Choice of Analgesic, p. 4.2); tiagabine has been tried in chronic pain[1] and was found to be effective.

1. Todorov AA, *et al.* Tiagabine and gabapentin for the management of chronic pain. *Clin J Pain* 2005; **21:** 358–61.

Psychiatric disorders. Tiagabine has been tried for the treatment of *generalised anxiety disorder*[1-3] (p. 1028.1) and *major depressive disorder* with anxiety[4] (p. 398.1), with variable results. It has also been tried in *post-traumatic stress disorder* (p. 1029.2) with some success in a case series[5] and a small open-label study[6] although a later multicentre placebo-controlled study[7] found no significant difference between tiagabine and placebo; further studies are considered warranted. A preliminary study[8] suggested that tiagabine may be effective and generally well tolerated as augmentation therapy in patients with anxiety disorders.

1. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003; **64:** 1245–9.
2. Pollack MH, *et al.* The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 1401–8.
3. Pollack MH, *et al.* Tiagabine in adult patients with generalized anxiety disorder: results from 3 randomized, double-blind, placebo-controlled, parallel-group studies. *J Clin Psychopharmacol* 2008; **28:** 308–16.
4. Carpenter LL, *et al.* Open-label tiagabine monotherapy for major depressive disorder with anxiety. *J Clin Psychiatry* 2006; **67:** 66–71.
5. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. *J Clin Psychiatry* 2003; **64:** 1421–5.
6. Connor KM, *et al.* Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. *Psychopharmacology (Berl)* 2006; **184:** 21–5.
7. Davidson JRT, *et al.* The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol* 2007; **27:** 85–8.
8. Schwartz TL, *et al.* An open-label study of tiagabine as augmentation therapy for anxiety. *Ann Clin Psychiatry* 2005; **17:** 167–72.

Stiff-man syndrome. There have been anecdotal reports[1] of improvement of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) with tiagabine in patients unable to tolerate benzodiazepine therapy.

1. Murinson BB, Rizzo M. Improvement of stiff-person syndrome with tiagabine. *Neurology* 2001; **57:** 366.

Adverse Effects

The most common adverse effects include dizziness, nervousness, tiredness, somnolence, and tremor. Other reported adverse effects include irritability, confusion, depression, psychosis, difficulties in concentration, diarrhoea, abdominal pain, nausea, ataxia, emotional lability, and nystagmus. Bruising, rashes, speech difficulties, and a flu-like syndrome of chills, fever, myalgia, and headache have also been reported. Visual field defects have been reported rarely and decreased white blood cell counts have been noted at routine screenings.

Incidence of adverse effects. A systematic review[1] considered 5 double-blind studies involving about 1000 patients of whom 675 were receiving tiagabine as adjunctive therapy for refractory partial seizures. Withdrawal due to adverse effects was infrequent and occurred in 15% of patients receiving tiagabine compared with 5% receiving placebo. Adverse effects were usually associated with dose titration, and were generally mild to moderate in severity, and transient. Another review[2] by the same author on data from all clinical studies (52 studies involving nearly 3100 patients) reported that in 21% of patients receiving tiagabine had the drug stopped for adverse effects, mostly during the first 6 months of therapy. Sub-analysis showed that figures for placebo-controlled, adjunctive studies were similar to those of the earlier review.

1. Leppik IE. Tiagabine: the safety landscape. *Epilepsia* 1995; **36** (suppl 6): S10–S13.
2. Leppik IE, *et al.* Safety of tiagabine: summary of 53 trials. *Epilepsy Res* 1999; **33:** 235–46.

Effects on the eyes. Unlike vigabatrin, which is associated with visual field defects (see p. 559.2), studies of visual function in patients taking tiagabine, another GABAergic antiepileptic, have been generally reassuring. However, in a case report[1] a 39-year-old patient was noted to have visual field defects while receiving long-term tiagabine therapy for bipolar disorder. The defects reversed after tiagabine was withdrawn.

1. Kaufman KR, *et al.* Visual fields and tiagabine: a quandary. *Seizure* 2001; **10:** 525–9.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of tiagabine on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the nervous system. Acute dystonic reactions occurred in 3 patients when tiagabine was added to their existing carbamazepine treatment;[1] the reactions were associated with an increase in the dose of tiagabine to 20 mg daily or more. In all cases the dystonias disappeared despite continuing tiagabine therapy at the same dose, although in one patient carbamazepine was withdrawn.

There have been case reports of nonconvulsive status epilepticus,[2-4] associated with tiagabine. The authors of one such report[2] noted that, in placebo-controlled studies, the incidence of such an event was no higher in the tiagabine group than in the placebo group. However, a retrospective analysis[5] of inpatients with refractory localised epilepsy found that nonconvulsive status epilepticus occurred more frequently in patients treated with tiagabine (6.7%) than in those who were not (1.1%).

The FDA has warned of the risk of seizures with tiagabine when used in *non-epileptic patients* for unlicensed indications;[6] it had received over 30 reports of new-onset seizures or status epilepticus in such patients. Predisposing factors may include the use of other drugs known to lower the seizure threshold, and probably the dose. Although some cases were noted after doses as low as 4 mg daily, licensed doses in patients with epilepsy take into account the customary use of other enzyme-inducing antiepileptics which can roughly halve the plasma levels of tiagabine by inducing its metabolism. For reports of status epilepticus occurring in non-epileptic patients after tiagabine overdosage, see below.

1. Wolańczyk T, Grabowska-Grzyb A. Transient dystonias in three patients treated with tiagabine. *Epilepsia* 2001; **42:** 944–6.
2. Fitzek S, *et al.* Drug-induced nonconvulsive status epilepticus with low dose of tiagabine. *Epileptic Disord* 2001; **3:** 147–50.
3. Skardoutsou A, *et al.* Non-convulsive status epilepticus associated with tiagabine therapy in children. *Seizure* 2003; **12:** 599–601.
4. Vinton A, *et al.* Tiagabine-induced generalised non convulsive status epilepticus in patients with lesional focal epilepsy. *J Clin Neurosci* 2005; **12:** 128–33.
5. Koepp MJ, *et al.* Status epilepticus and tiagabine therapy revisited. *Epilepsia* 2005; **46:** 1625–32.
6. FDA. Tiagabine hydrochloride (marketed as Gabitril): seizures in patients without epilepsy (issued 18 February, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107285.htm (accessed 25/08/10)

Overdosage. A 30-year-old man who took 320 mg of tiagabine in overdose with 400 mg of phenytoin showed no serious signs of toxicity other than significantly depressed levels of consciousness from which he quickly recovered.[1] Plasma concentrations of tiagabine measured 4 hours after ingestion were 30 times higher than those seen with therapeutic doses; phenytoin concentrations just exceeded the therapeutic range. A 46-year-old woman[2] who ingested about 72 mg of tiagabine exhibited facial grimacing, rigid flexure posturing of the upper extremities, and dilated pupils. She was uncommunicative and unresponsive to commands. Treatment with benzodiazepines was given, and symptoms resolved within 12 hours of admission.

Seizures, including status epilepticus, are a recognised adverse effect of tiagabine (see above); there have been reports of status epilepticus occurring in non-epileptic patients after overdosage, including nonconvulsive status epilepticus[3] in a 14-year-old girl who took about 180 mg of tiagabine, and myoclonic status epilepticus[4] in an 18-year-old man who took 120 mg of tiagabine with 400 mg of lamotrigine. Generalised tonic-clonic seizures were reported[5] in a 2-year-old child who had taken 90 mg of tiagabine.

A retrospective review[6] of 57 overdoses with tiagabine reported to several poison centres in the USA found that the most common adverse effects were lethargy (in 56%), seizures (37%, including status epilepticus in 5%), agitation (32%), confusion (30%), and coma (28%). Other adverse effects included tachycardia, respiratory depression, tremor, and hallucinations; no deaths were reported. The mean onset and duration of symptoms were 1.3 and 9.1 hours, respectively. The lowest dose associated with seizures was 96 mg.

1. Leach JP, *et al.* Deliberate overdose with the novel anticonvulsant tiagabine. *Seizure* 1995; **4:** 155–7.
2. Cantrell FL, *et al.* Intentional overdose with tiagabine: an unusual clinical presentation. *J Emerg Med* 2004; **27:** 271–2.
3. Jette N, *et al.* Tiagabine-induced nonconvulsive status epilepticus in an adolescent without epilepsy. *Neurology* 2006; **67:** 1514–15.
4. Vollmar C, Noachtar S. Tiagabine-induced myoclonic status epilepticus in a nonepileptic patient. *Neurology* 2007; **68:** 310.
5. Kazzi ZN, *et al.* Seizures in a pediatric patient with a tiagabine overdose. *J Med Toxicol* 2006; **2:** 160–2.
6. Spiller HA, *et al.* Retrospective evaluation of tiagabine overdose. *Clin Toxicol* 2005; **43:** 855–9.

Precautions

Hepatic metabolism of tiagabine is reduced in patients with hepatic impairment, and dosage should therefore be reduced and/or the intervals between doses increased. It should not be used in patients with severely impaired hepatic function.

Use of tiagabine in non-epileptic patients may be associated with an increased risk of seizures— see Effects on the Nervous System, above.

Care is required when withdrawing tiagabine therapy— see Uses and Administration, p. 549.3.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. Tiagabine has been found to increase hepatic and urinary porphobilinogen concentrations.[1]

1. Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci* 2004; **11:** 356–61.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The hepatic metabolism of tiagabine is accelerated by antiepileptics that induce enzymes of the cytochrome P450 system such as carbamazepine, phenobarbital, phenytoin, or primidone. Plasma concentrations of tiagabine may be reduced up to threefold by use with these drugs.

Pharmacokinetics

Tiagabine is readily absorbed after oral doses, with a bioavailability of 89%. Food reduces the rate but not the extent of absorption. The absorption and elimination pharmacokinetics of tiagabine are linear within the therapeutic dosage range.

Tiagabine is widely distributed throughout the body and plasma protein binding is 96%.

Tiagabine is extensively metabolised in the liver and excreted as metabolites in the faeces or, to a lesser extent, in the urine; less than 2% of a dose is eliminated as unchanged drug. The plasma-elimination half-life is 7 to 9 hours, although this may be reduced to 2 to 3 hours by liver enzyme-inducing drugs (see also Interactions, above).

References.
1. Gustavson LE, Mengel HB. Pharmacokinetics of tiagabine, a γ-aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiples doses. *Epilepsia* 1995; **36:** 605–11.
2. Sole EL, *et al.* Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing antiepilepsy drugs. *Epilepsy Res* 1995; **22:** 221–6.
3. Snel S, *et al.* The pharmacokinetics of tiagabine in healthy elderly volunteers and elderly patients with epilepsy. *J Clin Pharmacol* 1997; **37:** 1015–20.
4. Cato A, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of tiagabine. *Epilepsia* 1998; **39:** 43–7.
5. Samara EE, *et al.* Population analysis of the pharmacokinetics of tiagabine in patients with epilepsy. *Epilepsia* 1998; **39:** 868–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gabitril; ***Austria***: Gabitril; ***Belg.***: Gabitril; ***Cz.***: Gabitril; ***Denm.***: Gabitril†; ***Fin.***: Gabitril†; ***Fr.***: Gabitril; ***Ger.***: Gabitril; ***Gr.***: Gabitril; ***Hung.***: Gabitril†; ***Irl.***: Gabitril; ***Ital.***: Gabitril; ***Pol.***: Gabitril; ***Port.***: Gabitril; ***Spain***: Gabitril; ***Switz.***: Gabitril; ***UK***: Gabitril; ***USA***: Gabitril.

Pharmacopoeial Preparations

USP 36: Tiagabine Hydrochloride Oral Suspension.

Topiramate *(BAN, USAN, rINN)*

KW-6485; McN-4853; RWJ-17021; Topiramaatti; Topiramat; Topiramato; Topiramatum; Топирамат.

2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulphamate.

$C_{12}H_{21}NO_8S$=339.4

CAS — 97240-79-4.

ATC — N03AX11.
ATC Vet — QN03AX11.
UNII — 0H73WJJ391.

Pharmacopoeias. In *US.*

USP 36: (Topiramate). A white to off-white powder. Freely soluble in dichloromethane. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Topiramate, a sulfamate-substituted monosaccharide, is an antiepileptic used as adjunctive therapy in refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures (below). It may also be used as monotherapy in patients who have generalised tonic-clonic seizures or partial seizures. Topiramate is also used for the prophylaxis of migraine (see Headache, below) and, as a modified-release combination preparation with phentermine hydrochloride, in the management of obesity (below; see under Phentermine, p. 2329.2, for details of doses).

For both adjunctive and monotherapy of **epilepsy**, the initial oral dose of topiramate is 25 to 50 mg at night for 1 week increased thereafter by increments of 25 or 50 mg at intervals of 1 to 2 weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses. The usual daily dose for *adjunctive therapy* is 200 to 400 mg. When used as *monotherapy*, usual doses range from 100 mg daily to a maximum of 500 mg daily.

For doses in children, see below.

As with other antiepileptics, withdrawal of topiramate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. The daily dose should generally be decreased by 50 to 100 mg at weekly intervals. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

In the prophylaxis of **migraine**, topiramate is given orally in initial doses of 25 mg at night for 1 week, increased by 25-mg increments every week, to a usual dose of 50 mg twice daily. If topiramate therapy is to be stopped the daily dose should usually be decreased by 25 to 50 mg at weekly intervals.

Smaller increments or longer intervals between increments may be necessary if patients cannot tolerate the above regimens; doses should be halved in patients with moderate to severe renal impairment regardless of indication (see also below).

Administration in children. Topiramate is used as adjunctive therapy in children for refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures. It may also be used as monotherapy in those with newly diagnosed **epilepsy** who have generalised tonic-clonic seizures or partial seizures.

In the UK, the initial oral dose for *adjunctive* therapy in children from 2 years of age is 25 mg. This is given as a single dose at night for 1 week, then increased by 1 to 3 mg/kg every 1 or 2 weeks until the effective dose is reached; these higher daily doses are divided and given twice daily. About 5 to 9 mg/kg daily is usually required, although up to 30 mg/kg daily has been given.

For *monotherapy*, in children from 6 years of age, the initial daily oral dose is 0.5 to 1 mg/kg at night for the first week, increased thereafter by 0.5 to 1 mg/kg every 1 or 2 weeks, to an initial target dose of 100 mg (about 2 mg/kg) daily in 2 divided doses.

The adult dose (above) is recommended in those over 18 years of age.

In the USA, licensed doses are similar to those in the UK; however, monotherapy is licensed for children as young as 2 years old.

Although unlicensed for the prophylaxis of **migraine** in children, the *BNFC* suggests that the usual adult dose (see above) for this indication may be given to those aged 16 years and older.

Administration in renal impairment. Patients with moderate to severe renal impairment take longer to reach steady-state plasma concentrations of topiramate than patients with normal renal function (see Pharmacokinetics, p. 552.3) and the dosage regimen may need adjusting; the usual adult doses (see above) should be halved in such patients.

In patients undergoing haemodialysis a supplemental dose equal to about one-half of the daily dose should be given in divided doses (at the start and finish of the procedure).

Alcohol withdrawal and abstinence. Topiramate may be of use as an adjunct in achieving and maintaining abstinence in patients with alcohol dependence[1-5] (p. 1735.1).

1. Johnson BA, *et al.* Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003; **361:** 1677–85.
2. Johnson BA, *et al.* Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007; **298:** 1641–51.
3. Johnson BA, *et al.* Improvement o f physical health and quality o f life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* 2008; **168:** 1188–99.
4. Olmsted CL, Kockler DR. Topiramate for alcohol dependence. *Ann Pharmacother* 2008; **42:** 1475–80.
5. Kenna GA, *et al.* Review of topiramate: an antiepileptic for the treatment of alcohol dependence. *Curr Drug Abuse Rev* 2009; **2:** 135–42.

Bipolar disorder. Mood-stabilising antiepileptics such as carbamazepine and valproate are alternatives to lithium in the management of bipolar disorder (p. 397.2). Topiramate has also been investigated after favourable case reports,[1,2] but randomised controlled studies[3,4] have produced disappointing results and a systematic review[5] found insufficient evidence for its use as monotherapy or adjunctive therapy.

1. Teter CJ, *et al.* Treatment of affective disorder and obesity with topiramate. *Ann Pharmacother* 2000; **34:** 1262–5.
2. Erfurth A, Kuhn G. Topiramate monotherapy in the maintenance treatment of bipolar I disorder: effects on mood, weight and serum lipids. *Neuropsychobiology* 2000; **42** (suppl 1): 50–1.
3. Kushner SF, *et al.* Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord* 2006; **8:** 15–27.
4. Chengappa KNR, *et al.* Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2006; **67:** 1698–1706.
5. Vasudev K, *et al.* Topiramate for acute affective episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 09/06/08).

Epilepsy. Topiramate is used[1-6] in epilepsy (p. 506.1) for refractory partial seizures, for primary generalised tonic-clonic seizures,[7] and in patients with the Lennox-Gastaut syndrome;[8] in the UK, it may be a first-line option in some circumstances. Starting topiramate therapy gradually improves tolerability without delaying therapeutic response.[9]

Topiramate has also been investigated in children with infantile spasms (as for example in West's syndrome),[10] severe myoclonic epilepsy,[11] and juvenile myoclonic epilepsy;[12] it has been tried as a second-line drug in absence seizures and for tonic or atonic seizures. A retrospective review[13] and later studies[14,15] of the use of topiramate in such drug-resistant childhood epilepsies have concluded that it is efficacious and well tolerated.

Topiramate has also been investigated as an alternative antiepileptic in the management of refractory status epilepticus (p. 510.2).[16,17]

1. Sachdeo RC, *et al.* Topiramate: clinical profile in epilepsy. *Clin Pharmacokinet* 1998; **34:** 335–46.
2. Garnett WR. Clinical pharmacology of topiramate: a review. *Epilepsia* 2000; **41** (suppl 1); S61–S65.
3. Glauser TA, *et al.* Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. *J Child Neurol* 2007; **22:** 693–9.
4. Lyseng-Williamson KA, Yang LPH. Topiramate: a review of its use in the treatment of epilepsy. *Drugs* 2007; **67:** 2231–56.
5. Jette N, *et al.* Topiramate add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 27/08/08).
6. Novotny E, *et al.* Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures. *Neurology* 2010; **74:** 714–20.
7. Biton V. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology* 1999; **52:** 1330–7.
8. Sachdeo RC, *et al.* A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology* 1999; **52:** 1882–7.
9. Biton V, *et al.* Topiramate titration and tolerability. *Ann Pharmacother* 2001; **35:** 173–9.
10. Glauser TA, *et al.* Long-term response to topiramate in patients with West syndrome. *Epilepsia* 2000; **41** (suppl 1): S91–S94.
11. Nieto-Barrera M, *et al.* Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 2000; **9:** 590–4.
12. Biton V, Bourgeois BFD. Topiramate in patients with juvenile myoclonic epilepsy. *Arch Neurol* 2005; **62:** 1705–8.
13. Yeung S, *et al.* Topiramate for drug-resistant epilepsies. *Eur J Paediatr Neurol* 2000; **4:** 31–3.
14. Al Ajlouni S, *et al.* The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multi-center clinical trial. *Seizure* 2005; **14:** 459–63.
15. Grosso S, *et al.* Efficacy and safety of topiramate in refractory epilepsy of childhood: long-term follow-up study. *J Child Neurol* 2005; **20:** 893–7.
16. Towne AR, *et al.* The use of topiramate in refractory status epilepticus. *Neurology* 2003; **60:** 332–4.
17. Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 2003; **4:** 757–60.

Headache. Topiramate is used for the prophylaxis of *migraine* (p. 670.3). Results from placebo-controlled studies[1-5] have shown a significant reduction in frequency of migraines in those patients receiving prophylactic topiramate.

Topiramate has been tried for prophylaxis of *cluster headache* attacks[6] (p. 670.1) and chronic *tension-type headache*[7] (p. 671.3). It has also been used to control headache due to *raised intracranial pressure* (see p. 1271.3).

1. Storey JR, *et al.* Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001; **41:** 968–75.
2. Brandes JL, *et al.* Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; **291:** 965–73.
3. Silberstein SD, *et al.* Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; **61:** 490–5.
4. Silberstein SD, *et al.* Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; **47:** 170–80.
5. Diener H-C, *et al.* Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; **27:** 814–23.
6. Láinez MJA, *et al.* Topiramate in the prophylactic treatment of cluster headache. *Headache* 2003; **43:** 784–9.
7. Lampl C, *et al.* A prospective, open-label, long-term study of the efficacy and tolerability of topiramate in the prophylaxis of chronic tension-type headache. *Cephalalgia* 2006; **26:** 1203–8.

Hyperhidrosis. Reduced sweating has been associated with topiramate therapy (see Effects on the Nervous System, under Adverse Effects, p. 552.2). There have been 2 case reports[1,2] of the use of topiramate in the treatment of hyperhidrosis.

1. Owen DB, Meffert JJ. The suppression of primary palmar-plantar hyperhidrosis by topiramate. *Br J Dermatol* 2003; **148:** 826–7.
2. Hoehn-Saric R. Facial hyperhidrosis-induced social fear alleviated with topiramate. *J Clin Psychiatry* 2006; **67:** 1157.

Motor neurone disease. Topiramate has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) but with disappointing results.[1]

1. Cudkowicz ME, *et al.* A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003; **61:** 456–64.

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p. 11.2), topiramate has also been tried successfully.[1] It has also been tried in the treatment of *diabetic neuropathy*[2,3] (p. 8.2), *postherpetic neuralgia*[4] (p. 10.3), and of *phantom limb pain*[5] (p. 10.3). Some benefit in poorly-controlled neuropathic *pain in cancer patients* (p. 7.1) has also been reported.[6]

1. Zvartau-Hind M, *et al.* Topiramate relieves refractory trigeminal neuralgia in MS patients. *Neurology* 2000; **55:** 1587–8.
2. Raskin P, *et al.* Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 2004; **63:** 865–73.
3. Donofrio PD, *et al.* Safety and effectiveness of topiramate for the management of painful diabetic peripheral neuropathy in an open-label extension study. *Clin Ther* 2005; **27:** 1420–31.
4. Fowler JA, *et al.* Successful use of topiramate in a patient with severe postherpetic neuralgia. *Ann Pharmacother* 2009; **43:** 139–42.
5. Harden RN, *et al.* Topiramate for phantom limb pain: a time-series analysis. *Pain Med* 2005; **6:** 375–8.
6. Bendaly EA, *et al.* Topiramate in the treatment of neuropathic pain in patients with cancer. *Support Cancer Ther* 2007; **4:** 241–6.

Obesity. Weight loss has been associated with topiramate therapy (see Adverse Effects, p. 552.1) and it has been tried as an adjunct in the treatment of overweight or obese patients (p. 2315.1); topiramate appears to be reasonably well tolerated and is available in some countries as a combination preparation with phentermine hydrochloride for the management of obesity. Topiramate has also been tried in binge eating (see below).

References.

1. Astrup A, Toubro S. Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* 2004; **12** (suppl): 167S–173S.
2. Kirov G, Tredget J. Add-on topiramate reduces weight in overweight patients with affective disorders: a clinical case series. *BMC Psychiatry* 2005; **5:** 19. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-5-19.pdf (accessed 09/06/08)
3. Khazaal Y, *et al.* Long-term topiramate treatment of psychotropic drug-induced weight gain: a retrospective chart review. *Gen Hosp Psychiatry* 2007; **29:** 446–9.
4. Eliasson B, *et al.* Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. *Int J Obes* 2007; **31:** 1140–7.
5. Rosenstock J, *et al.* A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care* 2007; **30:** 1480–6.
6. Cates ME, *et al.* Efficacy of add-on topiramate therapy in psychiatric patients with weight gain. *Ann Pharmacother* 2008; **42:** 505–10.
7. Kramer CK, *et al.* Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. *Obes Rev* 2011; **12:** e338–e347.
8. Cameron F, *et al.* Phentermine and topiramate extended release (Qsymia®): first global approval. *Drugs* 2012; **72:** 2033–42.
9. Smith SM, *et al.* Phentermine/topiramate for the treatment of obesity. *Ann Pharmacother* 2013; **47:** 340–9.
10. Cosentino G, *et al.* Phentermine and topiramate for the management of obesity: a review. *Drug Des Devel Ther* 2013; **7:** 267–78.
11. Shin JH, Gadde KM. Clinical utility of phentermine/topiramate (Qsymia®) combination for the treatment of obesity. *Diabetes Metab Syndr Obes* 2013; **6:** 131–9.

Psychiatric disorders. Topiramate has been tried in several psychiatric disorders, including *schizophrenia*[1] (p. 1031.3), *disturbed behaviour*[2] (p. 1030.2), *post-traumatic stress disorder*[3,4] (p. 1029.2), and *social anxiety disorder*[5] (see Phobic Disorders, p. 1029.1). It has also been tried in *binge eating*.[6-9] For its use in *bipolar disorder* see above.

1. Tiihonen J, *et al.* Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry* 2005; **66:** 1012–15.
2. Nickel MK, *et al.* Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2004; **65:** 1515–19.
3. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry* 2004; **4:** 24. Available at: http://www.

biomedcentral.com/content/pdf/1471-244X-4-24.pdf (accessed 09/06/08)
4. Alderman CP, *et al.* Topiramate in combat-related posttraumatic stress disorder. *Ann Pharmacother* 2009; **43:** 635–41.
5. Van Ameringen M, *et al.* An open trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry* 2004; **65:** 1674–8.
6. Nickel C, *et al.* Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 2005; **38:** 295–300.
7. Tata AL, Kockler DR. Topiramate for binge-eating disorder associated with obesity. *Ann Pharmacother* 2006; **40:** 1993–7.
8. Claudino AM, *et al.* Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry* 2007; **68:** 1324–32.
9. Leombruni P, *et al.* Treatment of obese patients with binge eating disorder using topiramate: a review. *Neuropsychiatr Dis Treat* 2009; **5:** 385–92.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p. 1318.3); however, topiramate[1,2] has also been tried.

1. Galvez-Jimenez N, Hargreave M. Topiramate and essential tremor. *Ann Neurol* 2000; **47:** 837–8.
2. Ondo WG, *et al.* Topiramate in essential tremor: a double-blind, placebo-controlled trial. *Neurology* 2006; **66:** 672–7.

Adverse Effects

Adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability, and mood disorders may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

Effects on bone. For the effects of antiepileptics, including topiramate, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on electrolytes. Metabolic acidosis has been associated with topiramate treatment. Data from clinical studies estimate that the incidence of persistently decreased serum bicarbonate concentrations ranges from 23 to 67% with topiramate compared with 1 to 10% with placebo;[1] children, in particular, may be at a greater risk than adults.[1,2] A retrospective cohort study also found that 48% of adult patients developed decreased serum bicarbonate concentrations while receiving topiramate.[3] Generally, the decreases in serum bicarbonate are mild to moderate and occur soon after starting topiramate. Clinical signs such as hyperventilation may develop. The mechanism involves inhibition of carbonic anhydrase, which results in impaired reabsorption of bicarbonate ions by the proximal renal tubule and reduced excretion of H^+ by the distal tubule (mixed renal tubular acidosis).[4] As well as the risk of acute symptoms, chronic acidosis may contribute to effects on bone and the development of renal calculi.

Some sources such as the US licensed product information recommend that baseline and periodic serum bicarbonate levels should be monitored during topiramate treatment. If metabolic acidosis develops or persists, it may be necessary to reduce the dose or stop topiramate although, in some cases, correcting the acidosis with alkali therapy may be more appropriate.

1. Janssen-Ortho Inc. Health Canada. Important drug safety information: Topamax (topiramate) use is associated with metabolic acidosis (issued 12 January, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/topamax_3_hpc-cps-eng.pdf (accessed 01/09/08)
2. Philippi H, *et al.* Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia* 2002; **43:** 744–7.
3. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. *Ann Pharmacother* 2005; **39:** 424–6.
4. Mirza N, *et al.* Effect of topiramate on acid-base balance: extent, mechanism and effects. *Br J Clin Pharmacol* 2009; **68:** 655–61.

Effects on the eyes. There have been rare reports of acute myopia with or without secondary angle-closure glaucoma in adults and children receiving topiramate:[1-3] as of April 2002 the UK CSM was aware of 23 cases worldwide occurring with secondary angle-closure glaucoma.[4] Symptoms include decreased visual acuity and ocular pain which generally appear within one month of starting treatment; hyperaemia and raised intra-ocular pressure may be present with or without mydriasis. Choroidal effusions resulting in anterior displacement of lens and iris have been reported. Appropriate measures to reduce intra-ocular pressure should be taken, and topiramate stopped as rapidly as is clinically feasible.[4] A later review[5] of 115 reports of ocular adverse effects associated with topiramate described 83 cases of bilateral and 3 cases of unilateral acute angle-closure glaucoma; of these, 7 sustained permanent loss of vision. Onset of glaucoma was between 1 and 49 days after starting topiramate therapy, with 85% of cases occurring within the first 2 weeks. Also reported were cases of acute bilateral myopia (17 patients), suprachoroidal effusions (9), scleritis (4), blepharospasm (2), oculogyric crisis (2), and myokymia (1). Diplopia and nystagmus were reported with daily doses of at least 200 to 400 mg topiramate.

1. Gubbay SS. The occurrence of drug-induced myopia as a transient side effect of topiramate. *Epilepsia* 1998; **39:** 451.
2. Sen HA, *et al.* Topiramate-induced acute myopia and retinal striae. *Arch Ophthalmol* 2001; **119:** 775–7.
3. Rhee DJ, *et al.* Bilateral angle-closure glaucoma and ciliary body swelling from topiramate. *Arch Ophthalmol* 2001; **119:** 1721–3.
4. CSM/MCA. Topiramate (Topamax): acute myopia and raised intraocular pressure. *Current Problems* 2002; **28:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=-CON007454&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Fraunfelder FW, *et al.* Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004; **111:** 109–11.

Effects on the liver. For reports of hepatotoxicity associated with the addition of topiramate to antiepileptic therapy with carbamazepine or valproate see Antiepileptics, under Interactions, on p. 516.3 and p. 557.3 respectively.

Effects on mental function. For a review of the effects of antiepileptic therapy including topiramate on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the nervous system. Hyperthermia was reported in 10.5% of patients taking topiramate compared with 0.15% of patients taking other antiepileptic drugs in one centre.[1] Children under the age of 6 years, patients on daily doses of 6 mg/kg or more, and those exposed to high ambient temperatures were most at risk. Licensed product information recommends that children should be monitored closely for decreased sweating and hyperthermia, especially during warm or hot weather. Caution is also advised when giving topiramate with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.

Hemiparesis that resolved on withdrawal of topiramate has been reported[2] in 2 patients, although both already had compromised neurological function.

1. Ziad EK, *et al.* Age, dose, and environmental temperature are risk factors for topiramate-related hyperthermia. *Neurology* 2005; **65:** 1139–40.
2. Stephen LJ, *et al.* Transient hemiparesis with topiramate. *BMJ* 1999; **318:** 845.

Effects on sexual function. Topiramate has been associated with sexual dysfunction[1-3] in male and female patients; in all cases symptoms resolved with dosage reduction or withdrawal of the drug.

1. Holtkamp M, *et al.* Erectile dysfunction with topiramate. *Epilepsia* 2005; **46:** 166–7.
2. Sun C, *et al.* Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. *Headache* 2006; **46:** 1450–3.
3. Calabrò RS, *et al.* Topiramate-induced erectile dysfunction. *Epilepsy Behav* 2009; **14:** 560–1.

Precautions

Topiramate should be used with caution in patients with renal or hepatic impairment. Adequate hydration is recommended to reduce the risk of developing renal calculi, especially in predisposed patients.

Care is required when withdrawing topiramate therapy—see also Uses and Administration, p. 551.1.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies topiramate as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

References.

1. Bialer M, *et al.* Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 2004; **43:** 763–80.

Antiepileptics. In pharmacokinetic studies hepatic enzyme inducers such as *carbamazepine*,[1-3] *phenobarbital*,[2] and *phenytoin*[1,2] were reported to decrease the plasma concentration of topiramate.

For the effect of topiramate on phenytoin and carbamazepine, see p. 543.2 and p. 516.3, respectively. For reports of an increased risk of hepatic impairment in patients taking topiramate with valproate, see p. 557.3.

1. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37:** (suppl 2): S14–S17.
2. Contin M, *et al.* Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2002; **24:** 332–7.
3. Mimrod D, *et al.* A comparative study of the effect of carbamazepine and valproic acid on the pharmacokinetics and metabolic profile of topiramate at steady state in patients with epilepsy. *Epilepsia* 2005; **46:** 1046–54.

Cardiac glycosides. For the effect of topiramate on *digoxin*, see p. 1357.1.

Corticosteroids. For the effect of topiramate on corticosteroids, see p. 1619.3.

Sex hormones. For the effects of antiepileptics including topiramate on *oral contraceptives*, see p. 2243.2.

Pharmacokinetics

Topiramate is readily absorbed after oral doses, with peak plasma concentrations occurring after about 2 hours. Bioavailability is not affected by the presence of food. Protein binding is about 9 to 17%. The volume of distribution in women is about half that in men. Topiramate crosses the placental barrier and is distributed into breast milk.

In healthy subjects topiramate is not extensively metabolised; however, up to 50% of a dose may undergo metabolism in the liver in patients also receiving enzyme-inducing drugs. It is eliminated chiefly in urine, as unchanged drug and metabolites; mean plasma elimination half-life is about 21 hours. Steady-state concentrations occur after about 4 to 8 days in patients with normal renal function. Clearance is decreased in patients with impaired renal or hepatic function, and steady-state plasma concentrations may not occur for 10 to 15 days in the former. Children exhibit a higher clearance and shorter elimination half-life than adults.

The pharmacokinetics of topiramate may be affected by use with other antiepileptics (see under Interactions, above).

References.

1. Perucca E, Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs: focus on topiramate, zonisamide, and tiagabine. *Clin Pharmacokinet* 1996; **31:** 29–46.
2. Glauser TA, *et al.* Topiramate pharmacokinetics in infants. *Epilepsia* 1999; **40:** 788–91.
3. Öhman I, *et al.* Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia* 2002; **43:** 1157–60.
4. Ferrari AR, *et al.* Influence of dosage, age, and co-medication on plasma topiramate concentrations in children and adults with severe epilepsy and preliminary observations on correlations with clinical response. *Ther Drug Monit* 2003; **25:** 700–8.
5. Battino D, *et al.* Topiramate pharmacokinetics in children and adults with epilepsy: a case-matched comparison based on therapeutic drug monitoring data. *Clin Pharmacokinet* 2005; **44:** 407–16.
6. Britzi M, *et al.* Pharmacokinetic and metabolic investigation of topiramate disposition in healthy subjects in the absence and in the presence of enzyme induction by carbamazepine. *Epilepsia* 2005; **46:** 378–84.
7. Zanotta N, *et al.* Clinical experience with topiramate dosing and serum levels in patients with epilepsy. *Seizure* 2006; **15:** 86–92.
8. Öhman I, *et al.* Pharmacokinetics of topiramate during pregnancy. *Epilepsy Res* 2009; **87:** 124–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Neutop; Topamac; Topictal; Topirex†; Zinalow; ***Austral.***: Epiramax; Epiramax; Tamate; Topamax; ***Austria***: Topamax; Topilex; ***Belg.***: Topamax; ***Braz.***: Amato; Sigmax; Topamax; Toptil; ***Canad.***: Topamax; ***Chile***: Piracross; Topamax; Topictal; Toprel; ***China***: Topamax (妥泰); ***Cz.***: Epimaxan; Erravia; Topafis; Topamax; Topilept; Topilex; Topimark; Topiragis†; Zidoxer; ***Denm.***: Epitomax†; Maritop; Monotop; Topaben; Topamax†; Topimatil†; Topimax; Topiratore; ***Fin.***: Topimax; ***Fr.***: Epitomax; ***Ger.***: Topamax; Topiragamma†; Topiramed†; ***Gr.***: Jadix; Letop; Pirantal; Topamac; Topepil; Topiref; Toramat; ***Hong Kong***: Topamax; ***Hung.***: Epilania; Etopro; Talopam; Topamax; Topepsil; Topilex; ***India***: Epimate; Epitome; Epitop; Nextop; Topamac; Topamate; ***Indon.***: Topamax; ***Irl.***: Topamax; Topirama; Topit; ***Israel***: Topamax; Topitrim; ***Ital.***: Topamax; ***Jpn***: Topina; ***Malaysia***: Topamax; ***Mex.***: Nabian-K†; Topamax; ***Neth.***: Epitomax†; Erudan†; Symtopiram†; Topamax; Topepsil; Topilept; Topitex†; ***Norw.***: Topimax; ***NZ***: Topamax; ***Philipp.***: Epimate; Epitop; Topamax; ***Pol.***: Epimaxan; Epiramat; Epitoram; Erudan; Etopro; Monotop; Symtopiram; Topamax; Topiegis; Topifar; Topigen; TopiLek; Topimatil; Topimerck; Topistad; Toramat; Zidoxer; ***Port.***: Amlix†; Arroserra; Bluantina†; Olandic; Pirepil; Tomix; Topamax; Toptrix†; Vermedis; ***Rus.***: Maxitopir (Макситопир); Topalepsin (Топалепсин); Topamax (Топамакс); Topiromax (Топиромакс); Topsaver (Топсавер); Toreal (Тореал); ***S.Afr.***: Epitoz; Piramax;

Topalex; Topamax; Toplep; ***Singapore***: Topamax; ***Spain***: Acomicil; Bipomax†; Epilmax; Fagodol; Topamax; Topibrain; Topimylan†; ***Swed.***: Topimax; ***Switz.***: Topamax; ***Thai.***: Topamax; ***Turk.***: Letop; Noromat; Topamax; ***UK***: Topamax; ***Ukr.***: Epiramat (Эпирамат); Rantopir (Рантопир)†; Topilepsin (Топилепсин); Topiromax (Топиромакс); ***USA***: Topamax; Topiragen; Trokendi; ***Venez.***: Topamax.

Multi-ingredient Preparations. ***USA***: Qsymia.

Pharmacopoeial Preparations
USP 36: Topiramate Tablets.

Trimethadione *(BAN, rINN)*

Trimetadion; Trimetadiona; Trimetadionas; Trimetadioni; Trimethadion; Triméthadione; Trimethadionum; Trimethinum; Troxidone; Триметадион.
3,5,5-Trimethyl-1,3-oxazolidine-2,4-dione.
$C_6H_9NO_3$=143.1
CAS — 127-48-0.
ATC — N03AC02.
ATC Vet — QN03AC02.
UNII — R7GV3H6FQ4.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.*

Ph. Eur. 8: (Trimethadione). Colourless or almost colourless crystals. Soluble in water; very soluble in alcohol. Protect from light.

Profile

Trimethadione is an oxazolidinedione antiepileptic that has been given in the treatment of absence seizures refractory to other antiepileptics. However, because of its potential toxicity, other antiepileptics are preferred (see Epilepsy, p. 506.1).

Pregnancy. Characteristic congenital malformations, termed the fetal trimethadione syndrome, have been associated with the use of trimethadione in pregnancy.

For comments on the management of epilepsy during pregnancy, see p. 509.2.

Valproate

Valproato; Вальпроат.

NOTE. Valproate is a generic term applied to valproic acid and its salts and esters.

Valproic Acid *(BAN, USAN, rINN)*

Abbott-44089; Acide valproïque; Ácido dipropilacético; Ácido valproico; Acidum Valproicum; Kyselina valproová; Valproico, ácido; Valproiinihappo; Valproik Asit; Valproinė rūgštis; Valproinsäure; Valproinsav; Valproinsyra; Вальпроевая Кислота.
2-Propylvaleric acid; 2-Propylpentanoic acid.
$C_8H_{16}O_2$=144.2
CAS — 99-66-1.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 614OI1Z5WI.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Valproic Acid). A colourless or very slightly yellow, slightly viscous, clear liquid. Very slightly soluble in water; miscible with alcohol and with dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

USP 36: (Valproic Acid). A colourless to pale yellow, slightly viscous, clear liquid having a characteristic odour. Slightly soluble in water; freely soluble in alcohol, in acetone, in chloroform, in ether, in methyl alcohol, in benzene, in *n*-heptane, and in 1N sodium hydroxide; slightly soluble in 0.1N hydrochloric acid. Store in airtight glass, stainless steel, or polyethylene containers.

Sodium Valproate *(BANM, rINNM)*

Abbott-44090; Natrii Valproas; Natrio valproatas; Natriumvalproaatti; Natriumvalproat; Natrium-valproát; Nátrium-valproát; NIK-240; Sodium, valproate de; Sodyum Valproat; Valproate de Sodium; Valproate Sodium (USAN); Valproato sódico; Натрий Вальпроат.
Sodium 2-propylvalerate; Sodium 2-propylpentanoate.
$C_8H_{15}NaO_2$=166.2
CAS — 1069-66-5.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 5VOM6GYJ0D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.*

Ph. Eur. 8: (Sodium Valproate). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

Valproate Pivoxil *(rINN)*

CHF-1504; Valproato de pivoxilo; Valproato pivoxilo; Valproatum Pivoxilum; Вальпроат Пивоксил.
Hydroxymethyl 2-propylvalerate pivalate.
$C_{14}H_{26}O_4$=258.4
CAS — 77372-61-3.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 9F5A05A29T.

Valproate Semisodium *(rINN)*

Abbott-50711; Divalproex Sodium (USAN); Semisodium Valproate (BAN); Valproate Semisodique; Valproato semisódico; Valproatum Seminatricum; Вальпроат Семинатрий.
2-Propylvaleric acid—Sodium 2-propylvalerate (1:1); Sodium hydrogen bis(2-propylvalerate) oligomer.
$(C_{16}H_{31}NaO_4)_n$=310.4
CAS — 76584-70-8.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 644VL95AO6.

Pharmacopoeias. In *US.*

USP 36: (Divalproex Sodium). A white to off-white powder. Soluble in acetone; practically insoluble in acetonitrile; very soluble in chloroform; freely soluble in ethyl ether and in methyl alcohol. Store in airtight containers.

Valpromide *(rINN)*

Dipropilacetamida; Dipropylacetamide; Valpromida; Valpromidum; Вальпромид.
2-Propylvaleramide.
$C_8H_{17}NO$=143.2
CAS — 2430-27-5.
ATC — N03AG02.
ATC Vet — QN03AG02.
UNII — RUA6CWU76G.

Uses and Administration

Valproate is an antiepileptic used particularly in the treatment of primary generalised seizures, has notable benefit in absence and myoclonic seizures, and is also used for partial seizures. Its actions are complex and its mode of action in epilepsy is not fully understood. Valproate is also used to treat the acute manic phase of bipolar disorder and for the prophylaxis of migraine.

Forms used include the sodium salts (valproate semisodium and sodium valproate), the amide derivative (valpromide), and valproic acid. Magnesium valproate has also been tried as has calcium valproate. Valproate should preferably be taken with or after food.

In the treatment of **epilepsy** (p. 554.1) the dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Plasma concentrations of valproate (see Pharmacokinetics, p. 558.1) are not considered to be a useful index of efficacy and thus their routine monitoring is generally not helpful.

- A suggested initial *oral* daily dose of ***sodium valproate*** is 600 mg given in 2 divided doses. The daily dose may be increased by 200 mg every 3 days to a usual range of 1 to 2 g daily (20 to 30 mg/kg daily); up to a maximum of 2.5 g daily may be necessary if adequate control has not been achieved. Modified-release formulations are available to minimise fluctuations in plasma concentration.
  When oral dosage is not possible, sodium valproate may be given *intravenously* to start therapy or to continue therapy previously given orally. A suggested dose to *begin* therapy is up to 10 mg/kg by intravenous injection over 3 to 5 minutes followed by intravenous infusion, as necessary, up to a maximum of 2.5 g daily. To *continue* therapy intravenously, doses are the same as the patient's previous oral dose. In the USA, intravenous sodium valproate is given in doses equivalent to those used orally for valproic acid (see below).
- A suggested initial oral dose of ***valproic acid*** is 10 to 15 mg/kg daily increased at one-week intervals by 5 to 10 mg/kg. The maximum recommended dose of valproic acid in the UK is 30 mg/kg daily whereas in the USA it is 60 mg/kg daily. Valproic acid may be given in 2 to 4 divided doses.
- ***Valproate semisodium*** is given orally in doses equivalent to those used for oral valproic acid (see above).
- The amide derivative of valproic acid, ***valpromide***, is also used in some countries. Usual oral doses have ranged from 600 mg to 1.8 g daily, in divided doses.

For details of valproate doses in children, see below.

As with other antiepileptics, withdrawal of valproate or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

In the treatment of acute manic episodes of **bipolar disorder** (p. 554.1), the initial oral dose of ***valproate semisodium*** is the equivalent of valproic acid 750 mg daily in 2 or 3 divided doses. Thereafter, the dose is increased as rapidly as possible to achieve the optimal response; the usual range is 1 to 2 g daily with a maximum of up to 60 mg/kg daily. Patients receiving doses higher than 45 mg/kg daily should be carefully monitored. ***Valpromide*** has also been used in some countries for bipolar disorder in doses similar to those for epilepsy (see above).

In the prophylaxis of **migraine** (see Headache, p. 554.2) valproate semisodium is given orally in a dose equivalent to valproic acid 250 mg twice daily; up to 1 g daily may be necessary in some patients.

Action. The actions of valproate are complex and not well understood. As well as enhancing central GABAergic neurotransmission and inhibiting neuronal sodium channels, it affects cellular signalling systems such as the Wnt/β-catenin and extracellular signal-regulated kinase (ERK) pathways, and has actions on inositol and arachidonate metabolism. In addition it has potent effects on transcription of several genes, mediated at least in part by its action as a direct histone deacetylase inhibitor. It is probable that its clinical effects in different disorders depend on a combination of such properties.[1]

1. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? *Cell Mol Life Sci* 2007; **64:** 2090–2103.

Administration in children. Valproate is used as an antiepileptic in children in the treatment of primary generalised seizures, notably for absence and myoclonic seizures, and also for partial seizures. Available forms include the sodium salts (valproate semisodium and sodium valproate) or as valproic acid. The *BNFC* suggests that sodium valproate may also be used for infantile spasms.

A suggested initial *oral* dose of ***sodium valproate*** for children weighing over 20 kg is 400 mg daily (irrespective of weight) in 2 divided doses. This may be gradually increased to a usual dose of 20 to 30 mg/kg daily; up to a maximum of 35 mg/kg daily may be necessary if adequate control has not been achieved. Children weighing under 20 kg may be given 20 mg/kg daily in 2 divided doses, which may be increased to 40 mg/kg daily or more if necessary (but see below). Modified-release formulations are available to minimise fluctuations in plasma concentration. Alternatively the *BNFC* suggests the following *oral* or *rectal* doses, given according to age:

- neonates: initially 20 mg/kg once daily followed by a usual maintenance dose of 10 mg/kg twice daily
- 1 month to 12 years: initially 5 to 7.5 mg/kg twice daily followed by a usual maintenance dose of 12.5 to 15 mg/kg twice daily; up to 30 mg/kg twice daily may be given for infantile spasms (but see below)
- over 12 years: usual adult doses (see above)

When used rectally, the *BNFC* recommends that sodium valproate oral solution may be used and retained for 15 minutes; dilution with water may be required, if necessary.

When oral dosage is not possible, sodium valproate is licensed for use *intravenously* to start therapy or to continue therapy previously given orally. The usual dose is in the range of 20 to 30 mg/kg daily by intravenous injection over 3 to 5 minutes or by infusion; up to 40 mg/kg daily or more may be necessary if adequate control is not achieved (but see below). When switching from oral to intravenous therapy, the intravenous dose should be the same as the established oral dose.

Alternatively, the *BNFC* suggests giving neonates 10 mg/kg twice daily by intravenous injection; those aged from 1 month to 12 years may be given 10 mg/kg initially by intravenous injection, followed by continuous or intermittent infusion, or intravenous injection in 2 to 4 divided doses, up to a usual range of 20 to 40 mg/kg daily, and older children may be given the usual adult doses (see above).

When a dose over 20 mg/kg daily is given, regardless of route, it is recommended that plasma-valproate concentrations should be monitored. If the dose exceeds 40 mg/kg daily, the patient's clinical chemistry and haematological parameters should also be monitored.

The *BNFC* states that children of all ages may be given ***valproic acid*** in doses as for sodium valproate (see above). In the USA, valproic acid is only licensed for children aged 10 years and older, who may be given the adult dose.

In the USA, ***valproate semisodium*** may also be given to children aged 10 years and over in the usual adult doses (see p. 553.2) for the treatment of epilepsy.

Bipolar disorder. Valproate, usually as valproate semisodium, is increasingly being used as an alternative to lithium in patients with bipolar disorder (p. 397.2).[1-9] Most guidelines consider it to be a first-line alternative to lithium particularly in those who have rapid cycling disease with 4 or more affective episodes a year or in those with mixed or dysphoric states. However, a study[9] failed to show particular benefit in rapid cycling disease, and a systematic review considered that any shift in prescribing practice in favour of valproate was not based on reliable evidence of efficacy,[10] although another concluded it was effective in acute mania.[8] A more recent systematic review[11] concluded that valproate was effective for the relief of depressive symptoms in acute bipolar disorder, and there was no evidence for an increased risk of mania. However, the studies on which this conclusion was based were relatively small, and a large controlled study was advocated.

1. Pope HG, *et al.* Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry* 1991; **48:** 62–8.
2. Joffe RT. Valproate in bipolar disorder: the Canadian perspective. *Can J Psychiatry* 1993; **38** (suppl 2): S46–S50.
3. Schaff MR, *et al.* Divalproex sodium in the treatment of refractory affective disorders. *J Clin Psychiatry* 1993; **54:** 380–4.
4. Bowden CL, *et al.* Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA* 1994; **271:** 918–24. Correction. *ibid.*; 1830.
5. Stoll AL, *et al.* Neurologic factors predict a favorable valproate response in bipolar and schizoaffective disorders. *J Clin Psychopharmacol* 1994; **14:** 311–13.
6. Swann AC, *et al.* Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry* 1997; **54:** 37–42.
7. Müller-Oerlinghausen B, *et al.* Valproate as adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2000; **20:** 195–203.
8. Macritchie K, *et al.* Valproate for acute mood episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 09/06/08).
9. Calabrese JR, *et al.* A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 2005; **162:** 2152–61.
10. Macritchie K, *et al.* Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Available in The Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).
11. Smith LA, *et al.* Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. *J Affect Disord* 2010; **122:** 1–9.

Cushing's syndrome. Sodium valproate has been used in the management of Cushing's syndrome (p. 2559.1).

Epilepsy. Valproate is one of the drugs of choice in partial seizures, primary generalised tonic-clonic seizures, absence seizures, and myoclonic seizures (p. 506.1), although evidence for some of these is lacking. It is also the drug of choice in epileptic syndromes such as the Lennox-Gastaut syndrome because of its wide therapeutic spectrum, and it may be useful in tonic or atonic seizures and infantile spasms.

References.

1. Mattson RH, *et al.* A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. *N Engl J Med* 1992; **327:** 765–71.
2. Richens A, *et al.* A multicentre trial of sodium valproate and carbamazepine in adult onset epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 682–7.
3. Verity CM, *et al.* A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. *Dev Med Child Neurol* 1995; **37:** 97–108.
4. Beydoun A, *et al.* and the Depakote Monotherapy for Partial Seizures Study Group. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. *Neurology* 1997; **48:** 182–8.
5. Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; **34:** 199–205.
6. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
7. Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. *Paediatr Drugs* 2006; **8:** 113–29.
8. Aldenkamp A, *et al.* Role of valproate across the ages: treatment of epilepsy in children. *Acta Neurol Scand* 2006; **184** (suppl): 1–13.
9. Ben-Menachem E, *et al.* Role of valproate across the ages: treatment of epilepsy in adults. *Acta Neurol Scand* 2006; **184** (suppl): 14–27.
10. Perucca E, *et al.* Role of valproate across the ages: treatment of epilepsy in the elderly. *Acta Neurol Scand* 2006; **184** (suppl): 28–37.
11. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1016–26.
12. Gerstner T, *et al.* Oral valproic acid for epilepsy—long-term experience in therapy and side effects. *Expert Opin Pharmacother* 2008; **9:** 285–92.

Extrapyramidal disorders. Valproate is one of several drugs with GABAergic action that has been tried in the management of tardive dyskinesia (see under Extrapyramidal Disorders, p. 1049.2).

Febrile convulsions. Sodium valproate has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p. 511.2), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63:** 1189–91.

Headache. Valproate, as valproate semisodium, may be used for the prophylaxis of *migraine* (p. 670.3) in patients refractory to drugs such as propranolol.[1-7] Valproate has also been shown to be effective and well-tolerated for the prophylaxis of migraine in children aged between 7 and 16 years.[8,9] Intravenous valproate has been tried in the treatment of acute migraine but a review[10] concluded that its use could not be recommended. To date, published studies had mostly been small, open-label, and uncontrolled and had used variable doses. Valproate had not been shown to be superior to other antimigraine drugs and had been inferior to prochlorperazine in one study.

Valproate has also been tried in the prophylaxis of persistent chronic daily headache including *tension-type headache* (p. 671.3) unresponsive to other drugs.[11]

It has also been tried for prevention of *cluster headache* (p. 670.1).

1. Sørensen KV. Valproate: a new drug in migraine prophylaxis. *Acta Neurol Scand* 1988; **78:** 346–8.
2. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992; **12:** 81–4.
3. Coria F, *et al.* Low-dose sodium valproate in the prophylaxis of migraine. *Clin Neuropharmacol* 1994; **17:** 569–73.
4. Mathew NT, *et al.* Migraine prophylaxis with divalproex. *Arch Neurol* 1995; **52:** 281–6.
5. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol* 1997; **54:** 1141–5.
6. Erdemoglu AK, Ozbakir S. Valproic acid in prophylaxis of refractory migraine. *Acta Neurol Scand* 2000; **102:** 354–8.
7. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacol Bull* 2003; **37** (suppl 2): 98–115.
8. Caruso JM, *et al.* The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. *Headache* 2000; **40:** 672–6.
9. Ashrafi MR, *et al.* Sodium valproate versus propranolol in paediatric migraine prophylaxis. *Eur J Paediatr Neurol* 2005; **9:** 333–8.
10. Frazee LA, Foraker KC. Use of intravenous valproic acid for acute migraine. *Ann Pharmacother* 2008; **42:** 403–7.
11. Mathew NT, Ali S. Valproate in the treatment of persistent chronic daily headache: an open label study. *Headache* 1991; **31:** 71–4.

Hiccup. Valproic acid may be of value in the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups, see under Chlorpromazine, p. 1046.3.

1. Jacobson PL, *et al.* Treatment of intractable hiccups with valproic acid. *Neurology* 1981; **31:** 1458–60.

HIV infection and AIDS. As mentioned under Precautions, p. 557.1, valproate appears to induce replication of HIV, and this effect has been used to reduce latent, and therefore treatment-resistant, HIV-infection in resting CD4+ T-cells. In a preliminary study,[1] 4 HIV-positive patients on HAART were started on the fusion inhibitor enfuvirtide to intensify their HIV treatment and prevent viral spread due to valproate; oral valproic acid (500 to 750 mg twice daily) was then introduced a few weeks later and continued for 3 months. In 3 of these patients, the frequency of latent infection in resting T-cells significantly declined after enfuvirtide and valproate treatment when compared with pre-treatment values. However, a later study[2] found the levels of latently infected T-cells in 9 HIV-positive patients receiving HAART and oral valproic acid for at least 3 months to be similar to those of patients receiving HAART alone. Other studies[3,4] also suggested the benefits were small or absent. A case report[5] described rapid rebound viraemia occurring in a 54-year-old man when HAART and sodium valproate were stopped after more than 2 years of therapy, suggesting little benefit in eradicating latent infection.

1. Lehrman G, *et al.* Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005; **366:** 549–55.
2. Siliciano JD, *et al.* Stability of the latent reservoir for HIV-1 in patients receiving valproic acid. *J Infect Dis* 2007; **195:** 833–6.
3. Sagot-Lerolle N, *et al.* ANRS EP39 study. Prolonged valproic acid treatment does not reduce the size of latent HIV reservoir. *AIDS* 2008; **22:** 1125–9.
4. Archin NM, *et al.* Valproic acid without intensified antiviral therapy has limited impact on persistent HIV infection of resting CD4+ T cells. *AIDS* 2008; **22:** 1131–5.
5. Steel A, *et al.* No change to HIV-1 latency with valproate therapy. *AIDS* 2006; **20:** 1681–2.

Malignant neoplasms. Valproate appears to have anti-tumour activity, thought to be mediated through the inhibition of cellular histone deacetylase. It has been tried[1-9] usually as an adjunct to other antineoplastics in the treatment of various malignancies, with some reported benefit.

1. Bug G, *et al.* Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia. *Cancer* 2005; **104:** 2717–25.
2. Raffoux E, *et al.* Treatment of elderly acute myeloid leukemia with valproic acid and all-trans retinoic acid. *Haematologica* 2005; **90:** 986–8.
3. Pilatrino C, *et al.* Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid. *Cancer* 2005; **104:** 101–9.
4. Chavez-Blanco A, *et al.* Histone acetylation and histone deacetylase activity of magnesium valproate in tumor and peripheral blood of patients with cervical cancer: a phase I study. *Mol Cancer* 2005; **4:** 22. Full version: http://www.molecular-cancer.com/content/pdf/1476-4598-4-22.pdf (accessed 09/06/08)
5. Münster P, *et al.* Phase I trial of histone deacetylase inhibition by valproic acid followed by the topoisomerase II inhibitor epirubicin in advanced solid tumors: a clinical and translational study. *J Clin Oncol* 2007; **25:** 1979–85.
6. Blum W, *et al.* Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J Clin Oncol* 2007; **25:** 3884–91.
7. Michaelis M, *et al.* Valproic acid as anti-cancer drug. *Curr Pharm Des* 2007; **13:** 3378–93.
8. Duenas-Gonzalez A, *et al.* Valproic acid as epigenetic cancer drug: preclinical, clinical and transcriptional effects on solid tumors. *Cancer Treat Rev* 2008; **34:** 206–22.
9. Bellos F, Mahlknecht U. Valproic acid and all-trans retinoic acid: meta-analysis of a palliative treatment regimen in AML and MDS patients. *Onkologie* 2008; **31:** 629–33.

Migraine. See under Headache, above.

Muscle spasm. The mainstay of management of *spasticity* is physiotherapy and an antispastic drug (see p. 2014.2). Valproate has been tried for its GABAergic activity and case reports[1] of 4 patients with spastic conditions of various aetiologies indicated that the addition of valproate to the existing regimen of antispastic drugs might produce improvements in spasticity and pain; further studies are warranted.

Valproate has also been tried[2] in the management of *stiff-man syndrome* (see under Muscle Spasm, p. 1064.3) unresponsive to diazepam.

1. Zachariah SB, *et al.* Positive response to oral divalproex sodium (Depakote) in patients with spasticity and pain. *Am J Med Sci* 1994; **308:** 38–40.
2. Spehlmann R, *et al.* Improvement of stiff-man syndrome with sodium valproate. *Neurology* 1981; **31:** 1162–3.

Myoclonus. Valproate is used alone or with clonazepam for cortical myoclonus (p. 511.3).

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p. 11.2), sodium valproate is an alternative antiepileptic that may be used in carbamazepine-intolerant patients. Valproate has also been tried, with some success, in painful *diabetic neuropathy*[1] (p. 8.2), *postherpetic neuralgia*[2] (p. 10.3), and neuropathic *cancer pain*[3] (p. 7.1). However, a placebo-controlled study[4] did not find any benefit with valproate therapy in the treatment of pain in diabetic and nondiabetic polyneuropathy.

1. Kochar DK, *et al.* Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. *Q J Med* 2004; **97:** 33–8.
2. Kochar DK, *et al.* Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. *Q J Med* 2005; **98:** 29–34.
3. Hardy JR, *et al.* A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2001; **21:** 204–9.
4. Otto M, *et al.* Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. *Neurology* 2004; **62:** 285–8.

Psychiatric disorders. Valproate has psychotropic properties and has been used in the management of bipolar disorder (see above) and in some countries as a mood stabiliser for augmentation of antidepressant therapy in the treatment of resistant depression (p. 398.1). Valproate has also been tried in various disorders for the control of symptoms such as agitation, aggression, and rage[1,2] (see Disturbed Behaviour, p. 1030.2). However, a systematic review of the use of valproate for agitation in dementia found no convincing evidence of efficacy at low doses, and adverse effects may be unacceptable at higher doses.[3] Valproate has also been reported[4,5] to be efficacious as adjunctive therapy to antipsychotics, but again, systematic review[6] has thrown doubt upon its efficacy. More recently, a systematic review[7] found no data to support or refute the use of valproate, either alone or as an adjunct to antipsychotics, in the treatment of schizophrenia (p. 1031.3). It has also been tried in anxiety disorders such as panic disorder[8-10] (p. 1029.1), and post-traumatic stress disorder[11,12] (p. 1029.2).

1. Geracioti TD. Valproic acid treatment of episodic explosiveness related to brain injury. *J Clin Psychiatry* 1994; **55:** 416–17.
2. Narayan M, *et al.* Treatment of dementia with behavioral disturbances using divalproex or a combination of divalproex and a neuroleptic. *J Clin Psychiatry* 1997; **58:** 351–4.
3. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 26/11/09).
4. Wassef AA, *et al.* Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* 2000; **20:** 357–61.
5. Grove VE, *et al.* Improvement of Huntington's disease with olanzapine and valproate. *N Engl J Med* 2000; **343:** 973–4.
6. Basan A, *et al.* Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res* 2004; **70:** 33–7.
7. Schwarz C, *et al.* Valproate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 06/08/09).

8. Primeau F, *et al.* Valproic acid and panic disorder. *Can J Psychiatry* 1990; **35:** 248–50.
9. Keck PE, *et al.* Valproate treatment of panic disorder and lactate-induced panic attacks. *Biol Psychiatry* 1993; **33:** 542–6.
10. Woodman CL, Noyes R. Panic disorder: treatment with valproate. *J Clin Psychiatry* 1994; **55:** 134–6.
11. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1991; **52:** 361–4.
12. Petty F, *et al.* Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 100–101.

Status epilepticus. Valproate has been used in *absence* status epilepticus once the initial attack has been brought under control with intravenous benzodiazepines[1] and has been considered to be the drug of choice to prevent its recurrence.[2] Its place in the management of *convulsive* status epilepticus (p. 510.2) is less clear, but it has been tried, mainly as a second- or third-line drug in benzodiazepine-refractory patients,[3-11] and some centres have included it in management protocols.[5]

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
2. Berkovic SF, *et al.* Valproate prevents the recurrence of absence status. *Neurology* 1989; **39:** 1294–7.
3. Giroud M, *et al.* Use of injectable valproic acid in status epilepticus: a pilot study. *Drug Invest* 1993; **5:** 154–9.
4. Hovinga CA, *et al.* Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. *Ann Pharmacother* 1999; **33:** 579–84.
5. Campistol J, *et al.* Estado de mal convulsivo en el niño: experiencia con valproato endovenoso, actualización del protocolo de tratamiento. *Rev Neurol* 1999; **29:** 359–65.
6. Peters CNA, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005; **14:** 164–9.
7. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
8. Misra UK, *et al.* Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006; **67:** 340–2.
9. Olsen KB, *et al.* Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. *Acta Neurol Scand* 2007; **187** (suppl): 51–4.
10. Agarwal P, *et al.* Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007; **16:** 527–32.
11. Mehta V, *et al.* Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol* 2007; **22:** 1191–7.

Adverse Effects

The most frequently reported adverse effects associated with valproate therapy are gastrointestinal disturbances, particularly at the start of therapy; enteric-coated formulations, taking doses with meals, and starting with low doses may minimise symptoms. There may be increased appetite, and weight gain is common.

Less common adverse effects include oedema, headache, reversible prolongation of bleeding time, and thrombocytopenia. Leucopenia and bone marrow depression have been reported. Neurological adverse effects including ataxia, tremor, sedation, lethargy, confusion, and more rarely encephalopathy and coma, have occasionally been reported, although these are often associated with too high a starting dose, increasing doses too rapidly, or use with other antiepileptics. Very rare cases of extrapyramidal symptoms or reversible dementia associated with cerebral atrophy have been reported. Increased alertness may occur, which is generally considered beneficial, but occasionally aggression, hyperactivity, and behavioural disturbances have been reported. Hearing loss has been noted. There may occasionally be rashes, and, rarely, hirsutism, acne, toxic epidermal necrolysis and Stevens-Johnson syndrome or erythema multiforme. Transient hair loss, sometimes with regrowth of curly hair, has occurred. Irregular periods, amenorrhoea, and gynaecomastia have been reported rarely.

Liver dysfunction including hepatic failure has occasionally been reported, usually in the first few months of treatment, and requires valproate withdrawal; there have been fatalities. Elevation of liver enzyme values is common but normally transient and dose-related. Hyperammonaemia has occurred, even in the absence of overt hepatic failure, and is sometimes associated with neurological symptoms; hyperglycinaemia has also been reported. Pancreatitis has also been reported rarely, and fatalities have occurred; plasma amylase should be measured if there is acute abdominal pain, although the value of serum amylase as a diagnostic tool has been questioned—see Effects on the Pancreas, p. 556.1. In a few patients there have been reports of reversible defects in renal tubular function (Fanconi's syndrome).

Congenital malformations have been reported in infants born to women who had received antiepileptics including valproate during pregnancy.

Inflammatory reactions and pain have been reported at the injection site after intravenous doses.

Incidence of adverse effects. Adverse effects were present in 71 of 88 children receiving sodium valproate monotherapy[1] and, although average doses in these patients were significantly higher than in the 17 with no adverse effects, no difference in the plasma concentrations was seen between the 2 groups.

- Behavioural alterations seen in 56 included irritability, longer and deeper sleep, superficial sleep, hyperactivity, being more alert, lassitude, drowsiness, being more sociable, calmness, being happier, absent mindedness, being sadder, aggressiveness, being more skillful, and docility; it was emphasised that stimulatory reactions were as frequent as depressant effects
- Digestive disorders occurred in 43 children with anorexia, abdominal pain, and nausea and vomiting being the most frequent; diarrhoea, constipation, an increase in appetite, and a gain in weight also occurred. With the exception of a temporary increase in plasma transaminase concentrations in 2 patients, hepatic or pancreatic dysfunction was not seen
- Neurological changes in the form of tremor, paraesthesia, or ataxia, occurring in only 4 patients, were less frequent than either behavioural or digestive reactions
- Miscellaneous reactions including polydipsia, polyuria, diaphoresis, enuresis, hair loss, change in hair colour or texture, and rash were seen in 23 children
- Of the 71 children having reactions, therapy continued unchanged in 56, was changed in 3 either by altering the pharmaceutical formulation (syrup, tablets, granules), by changing the frequency of dosing, or by reducing the dose in 6, and in the remaining 9 children valproate therapy was stopped

1. Herranz JL, *et al.* Side effects of sodium valproate in monotherapy controlled by plasma levels: a study in 88 pediatric patients. *Epilepsia* 1982; **23:** 203–14.

Carnitine deficiency. Carnitine deficiency may occasionally arise during long-term use of valproate; although it is unclear whether carnitine supplementation (p. 2053.3) is of value in children receiving valproate, some neurologists consider it justified in selected cases, including those with, or at risk of, severe acute toxicity such as valproate-induced hepatotoxicity.[1-4]

1. De Vivo DC, *et al.* L-Carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; **39:** 1216–25.
2. Lheureux PER, *et al.* Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005; **9:** 431–40.
3. Russell S. Carnitine as an antidote for acute valproate toxicity in children. *Curr Opin Pediatr* 2007; **19:** 206–10.
4. Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. *Clin Toxicol* 2009; **47:** 101–11.

Effects on the blood. Reports have implicated valproate as a cause of occasional neutropenia,[1-3] leucopenia,[4] and thrombocytopenia.[2] A 1-year prospective study involving 45 patients found that absolute neutropenia developed in 12 and thrombocytopenia in 15, but that the disorders were transient and self-limiting.[2] However, neutropenia has occasionally been sufficiently severe to warrant withdrawal of valproate.[5] A case of delayed-onset neutropenia associated with valproate semisodium has been reported[6] in a 45-year-old man after almost 8 years of therapy; symptoms resolved when the drug was stopped. Red cell aplasia has also been associated with valproate therapy.[7,8] A study[9] involving 30 children indicated that valproate might produce symptoms similar to those of von Willebrand's disease; 19 of the 30 had a history of minor haemorrhage during therapy, and 7 had abnormal bleeding times. Factor VIII therapy might need to be given in patients receiving valproate who underwent surgery or in whom bleeding was severe.

For a discussion of the effects of antiepileptics, including valproate, on serum folate, see under Phenytoin, p. 540.2.

1. Jaeken J, *et al.* Neutropenia during sodium valproate treatment. *Arch Dis Child* 1979; **54:** 986–7.
2. Barr RD, *et al.* Valproic acid and immune thrombocytopenia. *Arch Dis Child* 1982; **57:** 681–4.
3. Vesta KS, Medina PJ. Valproic acid-induced neutropenia. *Ann Pharmacother* 2003; **37:** 819–21.
4. Coulter DL, *et al.* Valproic acid therapy in childhood epilepsy. *JAMA* 1980; **244:** 785–8.
5. Symon DNK, Russell G. Sodium valproate and neutropenia. *Arch Dis Child* 1983; **58:** 235.
6. Stoner SC, *et al.* Delayed-onset neutropenia with divalproex sodium. *Ann Pharmacother* 2008; **42:** 1507–10.
7. MacDougall LG. Pure red cell aplasia associated with sodium valproate therapy. *JAMA* 1982; **247:** 53–4.
8. Watts RG, *et al.* Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. *J Pediatr* 1990; **117:** 495–9.
9. Kreuz W, *et al.* Induction of von Willebrand disease type I by valproic acid. *Lancet* 1990; **335:** 1350–1.

Effects on bone. For the effects of antiepileptics including valproate on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the endocrine system. An early study[1] reported that menstrual disturbances were associated more often with valproate than with other antiepileptics among 238 women with epilepsy; 80% of those treated with valproate before 20 years of age had polycystic ovaries or hyperandrogenism. A later study[2] found that the occurrence of polycystic ovaries in 105 epileptic women taking carbamazepine or valproate was no greater than that in the general population, although valproate appeared to increase glucose-stimulated pancreatic insulin secretion. Subsequent studies[3-5] and reviews[6-9] support the association between valproate therapy and reproductive endocrine disorders and metabolic disturbances in female patients with epilepsy. However, a causal link could not be established since epilepsy itself affects the endocrine system. Symptoms such as hyperandrogenism, menstrual disturbances, polycystic ovaries, weight gain, and insulin resistance have been attributed to the development of polycystic ovary syndrome (p. 2253.3) in some patients. Other adverse effects of valproate on the endocrine system include dyslipidaemia, hypocalcaemia, and hypothyroidism.

For mention of the effects of antiepileptics, including valproate, on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

1. Isojärvi JIT, *et al.* Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993; **329:** 1383–8.
2. Luef G, *et al.* Polycystic ovaries, obesity and insulin resistance in women with epilepsy: a comparative study of carbamazepine and valproic acid in 105 women. *J Neurol* 2002; **249:** 835–41.
3. Betts T, *et al.* A study of anticonvulsant medication on ovarian function in a group of women with epilepsy who have only ever taken one anticonvulsant compared with a group of women without epilepsy. *Seizure* 2003; **12:** 323–9.
4. Mikkonen K, *et al.* Long-term reproductive endocrine health in young women with epilepsy during puberty. *Neurology* 2004; **62:** 445–50.
5. Tan H, *et al.* Valproate-induced insulin resistance in prepubertal girls with epilepsy. *J Pediatr Endocrinol Metab* 2005; **18:** 985–9. Correction. *ibid.*; 1134.
6. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia* 2003; **44** (suppl 4): 11–20.
7. Rasgon N. The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol* 2004; **24:** 322–34.
8. Verrotti A, *et al.* Endocrine and metabolic changes in epileptic patients receiving valproic acid. *J Pediatr Endocrinol Metab* 2005; **18:** 423–30.
9. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17:** 111–19.

Effects on the liver. An early review[1] of the hepatotoxicity of valproate included an analysis of 42 cases with fatal hepatitis, 3 cases with a Reye's-like syndrome, and 22 instances of hyperammonaemia:

- In 19 studies the incidence of *abnormal serum aminotransferase* activity ranged from 0 to 44% with an overall incidence of 11% in the 1197 patients monitored; in the non-fatal cases activity was usually between one and three times the upper limit of normal and was not usually, except in the most severe cases, accompanied by rises in serum bilirubin or alkaline phosphatase
- In the 42 cases of *hepatitis* with a fatal outcome the age at presentation ranged from 2.5 months to 34 years with 69% aged 10 years or less. Below the age of 15 years the proportion of males was 62.5% but above this age it was 30%; the disproportionate vulnerability of young individuals, particularly boys, did not appear to be a reflection of prescribing habits in that age group. In more than two-thirds of these patients with a fatal outcome, prodromal symptoms comprised anorexia and vomiting, loss of epilepsy control, impaired consciousness, and ataxia; in about one-third there were signs of liver damage with fever, jaundice, ascites, peripheral oedema, and easy bruising. In all of the patients hepatic coma developed. In 36 patients on whom data were available the onset of hepatic illness in one-third occurred between 1 and 2 months and in only 2 patients did the onset occur after more than 5 months. Of these 42 patients with fatal hepatotoxicity 36 were also given other drugs, mostly antiepileptics
- The 3 children with a *Reye's-like syndrome* all died within 3 weeks of the first occurrence of symptoms as a result of cerebral oedema (2 patients) or aspiration pneumonia (1 patient)
- In the 22 patients with symptomatic *hyperammonaemia*, characterised usually by impaired consciousness and ataxia, but without overt liver disease, withdrawal of valproate resulted in all becoming asymptomatic and biochemical abnormalities returned to normal. Hyperammonaemia has also been reported in asymptomatic patients, and has been stated to occur in the great majority of valproate-treated patients;[2] it is not necessarily related to hepatotoxicity

Hyperammonaemia and encephalopathy may also be precipitated when valproate is used with certain drugs (see Antibacterials, p. 557.2 and Antiepileptics, p. 557.3, under Interactions).

Various hypotheses for the cause of valproate hepatotoxicity have been discussed in detail.[3]

Analysis of deaths in the USA attributed to valproate liver toxicity identified a decline in the incidence of fatalities as use in young children and use with other antiepileptics declined.[4] However, occasional reports still occur in some countries.[5] For the suggestion that carnitine might be useful in the management of valproate hepatotoxicity, see Carnitine Deficiency, above.

1. Powell-Jackson PR, *et al.* Hepatotoxicity to sodium valproate: a review. *Gut* 1984; **25:** 673–81.

2. Chicharro AV, *et al*. The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? *Epilepsy Behav* 2007; **11:** 361–6.
3. Eadie MJ, *et al*. Valproate-associated hepatotoxicity and its biochemical mechanisms. *Med Toxicol* 1988; **3:** 85–106.
4. Dreifuss FE, *et al*. Valproic acid hepatic fatalities: II US experience since 1984. *Neurology* 1989; **39:** 201–7.
5. Koenig SA, *et al*. Valproic acid-induced hepatopathy: nine new fatalities in Germany from 1994 to 2003. *Epilepsia* 2006; **47:** 2027–31.

Effects on mental function. For a review of the effects of antiepileptic therapy including valproate on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the nervous system. An *extrapyramidal* syndrome of tremor and rigidity, unresponsive to benzatropine or trihexyphenidyl, developed in a 52-year-old man with schizophrenia given a therapeutic trial of sodium valproate 1 to 2 g daily.[1] Giving sodium valproate to a man with dystonic movements of the neck and spine produced a severe subjective and objective deterioration in his symptoms, which returned to their previous severity on withdrawal of the drug.[2] There have also been reports[3,4] of *parkinsonism* associated with valproate antiepileptic therapy; onset was usually insidious and progressive, occurring after several years of good tolerability. A case series[4] also reported *cognitive impairment* in 6 of 10 patients who developed parkinsonism. In most cases symptoms improved on stopping valproate.

Spasmodic dysphonia associated with valproate has been reported;[5] symptoms resolved when the dose of valproate was reduced.

A *stuporous state* associated with EEG abnormalities has been described[6,7] during valproate therapy for complex partial or mixed seizure types and it was suggested that in certain forms of epilepsy valproate may exhibit a paradoxical epileptogenic effect. Other findings[8] have argued against an epileptic origin for valproate-induced stupor.

1. Lautin A, *et al*. Extrapyramidal syndrome with sodium valproate. *BMJ* 1979; **2:** 1035–6.
2. Dick DJ, Saunders M. Extrapyramidal syndrome with sodium valproate. *BMJ* 1980; **280:** 189.
3. Easterford K, *et al*. Reversible parkinsonism with normal β-CIT-SPECT in patients exposed to sodium valproate. *Neurology* 2004; **62:** 1435–7.
4. Masmoudi K, *et al*. Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. *Pharmacopsychiatry* 2006; **39:** 9–12.
5. Oh J, *et al*. Spasmodic dysphonia induced by valproic acid. *Epilepsia* 2004; **45:** 880–1.
6. Marescaux C, *et al*. Stuporous episodes during treatment with sodium valproate: report of seven cases. *Epilepsia* 1982; **23:** 297–305.
7. Stecker MM, Kita M. Paradoxical response to valproic acid in a patient with a hypothalamic hamartoma. *Ann Pharmacother* 1998; **32:** 1168–72.
8. Aguglia U, *et al*. Negative myoclonus during valproate-related stupor: neurophysiological evidence of a cortical non-epileptic origin. *Electroencephalogr Clin Neurophysiol* 1995; **94:** 103–8.

Effects on the pancreas. An early report of 4 cases of pancreatitis associated with valproic acid therapy also reviewed 10 previously published cases.[1] None of the 14 patients, 2 of whom died, suffered other symptoms of a toxic reaction to valproic acid. Pancreatitis was not dose-related and had developed as early as one week and as late as 4.5 years after the introduction of therapy. Symptoms recurred on rechallenge in 6 of 7 patients. However, routine monitoring of serum-amylase concentrations in asymptomatic patients did not seem necessary. In February 1994 the UK CSM commented[2] in a review of drug-induced pancreatitis that they had received 29 reports of pancreatitis, including 2 fatalities, associated with sodium valproate. A later review[3] of 22 children who developed pancreatitis while taking valproate (2 of whom died) found that duration of therapy, dose, serum concentrations, and polytherapy were not risk factors. The authors advised against rechallenge as the rate of relapse is high. Serum amylase concentrations were found to be nondiagnostic in 39% of these patients, and the authors considered that serum lipase concentrations were far more likely to be elevated.

1. Wyllie E, *et al*. Pancreatitis associated with valproic acid therapy. *Am J Dis Child* 1984; **138:** 912–14.
2. CSM/MCA. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 01/09/08)
3. Werlin SL, Fish DL. The spectrum of valproic acid-associated pancreatitis. *Pediatrics* 2006; **118:** 1660–3.

Effects on the skin, hair, and nails. Five of 250 patients developed curly hair during treatment with sodium valproate 1 g daily;[1] in 3 patients this effect followed temporary alopecia. Another report of hair curling in a patient who received sodium valproate in doses up to 3 g daily for 30 months commented that her hair started to revert to the former straight style 9 months after stopping the drug.[2]

Valproate-induced nicotinic-acid deficiency with an associated pellagra-like syndrome has been reported in a young boy;[3] the condition responded dramatically to treatment with nicotinamide.

Reduced serum-zinc concentrations and cutaneous manifestations of zinc deficiency were found in 2 patients receiving antiepileptic drugs.[4] It was thought that deficiency resulted from chelation by sodium valproate, and possibly phenytoin, together with malabsorption and that, in one case, malabsorption was triggered by valproate.

Cutaneous vasculitis has been reported[5] in 2 patients taking sodium valproate. The reaction recurred on rechallenge.

Very rarely, skin rashes occurring with valproate may form part of an antiepileptic hypersensitivity syndrome (see below). Valproate might share the same order of risk as other antiepileptics for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis,[6] although it had previously been regarded as safer in this respect. For a suggestion that skin reactions are less common with valproate than with some other antiepileptics see under Phenytoin, p. 541.1.

Reversible yellow nail pigmentation has been reported[7] in a woman who was taking valproate semisodium.

1. Jeavons PM, *et al*. Valproate and curly hair. *Lancet* 1977; **i:** 359.
2. Gupta AK. Perming' effects associated with chronic valproate therapy. *Br J Clin Pract* 1988; **42:** 75–7.
3. Gillman MA, Sandyk R. Nicotinic acid deficiency induced by sodium valproate. *S Afr Med J* 1984; **65:** 986.
4. Lewis-Jones MS, *et al*. Cutaneous manifestations of zinc deficiency during treatment with anticonvulsants. *BMJ* 1985; **290:** 603–4.
5. Kamper AM, *et al*. Cutaneous vasculitis induced by sodium valproate. *Lancet* 1991; **337:** 497–8.
6. Anonymous. Drugs as risk factors in severe cutaneous diseases. *WHO Drug Inf* 1996; **10:** 33–5.
7. Buka R, *et al*. Yellow nail pigmentation following Depakote therapy. *J Drugs Dermatol* 2003; **2:** 545–7.

Enuresis. Nocturnal enuresis associated with sodium valproate therapy has been reported[1] in 2 children. Remission of the enuresis was achieved either by reducing or redistributing the doses. Several studies have recorded enuresis as an adverse effect of valproate in children,[2] the frequency being between 1 and 7%. The most likely explanations are that either it is secondary to a central effect on the thirst centre resulting in polydipsia or it is a consequence of the increased depth of sleep associated with valproate.

1. Panayiotopoulos CP. Nocturnal enuresis associated with sodium valproate. *Lancet* 1985; **i:** 980–1.
2. Choonara IA. Sodium valproate and enuresis. *Lancet* 1985; **i:** 1276.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some aromatic antiepileptic drugs; however, there have also been case reports[1-3] associated with valproate, a non-aromatic compound. In one case[1] a patient developed these symptoms with carbamazepine but they resolved when the drug was stopped; however, when valproate was started 2 weeks later the symptoms reappeared. Another report[2] described a fatal case occurring in a 2-year-old girl who developed fulminant hepatitis.

1. Arévalo-Lorido JC, *et al*. Antiepileptic drug hypersensitivity syndrome in a patient treated with valproate. *Br J Clin Pharmacol* 2003; **55:** 415–16.
2. Huang Y-L, *et al*. Fatal sodium valproate-induced hypersensitivity syndrome with lichenoid dermatitis and fulminant hepatitis. *J Am Acad Dermatol* 2003; **49:** 316–19.
3. Roepke S, *et al*. Valproic acid and hypersensitivity syndrome. *Am J Psychiatry* 2004; **161:** 579.

Overdosage. A cohort study[1] of valproate poisonings reported to a regional toxicology centre between January 1991 and November 2001 reported 79 cases. Of these, valproate was the only drug taken in 15 cases with a median dose of 15 g; symptoms were mild and included drowsiness (2 patients), vomiting (4), and tachycardia (5). The authors concluded that overdoses of more than 400 mg/kg could cause severe, potentially life-threatening toxicity, but these were uncommon. Symptoms of severe toxicity include significant CNS depression, respiratory insufficiency, and multi-organ failure; fatalities have been reported.[2] Children younger than 2 years of age are considered to be at significant risk for developing fatal valproate-induced hepatotoxicity in overdose; there has been a report of a 26-day-old neonate who died 42 hours after receiving a dose of 75 mg/kg.[3]

1. Isbister GK, *et al*. Valproate overdose: a comparative cohort study of self poisonings. *Br J Clin Pharmacol* 2003; **55:** 398–404.
2. Eyer F, *et al*. Acute valproate poisoning: pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. *J Clin Psychopharmacol* 2005; **25:** 376–80.
3. Unal E, *et al*. Fatal valproate overdose in a newborn baby. *Hum Exp Toxicol* 2007; **26:** 453–6.

Treatment of Adverse Effects

The value of gastric decontamination for overdose is uncertain since valproic acid and its salts are rapidly absorbed. Activated charcoal may be given orally to adults and children who present within 1 hour of ingesting more than 100 mg/kg; alternatively gastric lavage may be considered in adults within 1 hour of a potentially life-threatening overdose, generally 400 mg/kg or more. Supportive therapy alone may then suffice although haemodialysis and/or haemoperfusion should be considered in very severe poisoning.

Overdosage. Active treatments including forced diuresis, whole bowel irrigation, naloxone, and haemodialysis or haemoperfusion have been advocated for valproate overdose;[1,2] however, supportive measures provided sufficient treatment for a patient who had taken 25 g of sodium valproate.[1] A consensus guideline on out-of-hospital management of valproate poisoning[3] considered that such management was appropriate in patients who had unintentionally ingested up to 50 mg/kg of the drug and were merely somnolent; activated charcoal or, for comatose patients, naloxone, might be given as prehospital management although good evidence to support their use was lacking.

1. Lakhani M, McMurdo MET. Survival after severe self poisoning with sodium valproate. *Postgrad Med J* 1986; **62:** 409–10.
2. Sztajnkrycer MD. Valproic acid toxicity: overview and management. *J Toxicol Clin Toxicol* 2002; **40:** 789–801. Correction. *ibid.* 2003; **41:**215.
3. Manoguerra AS, *et al*. American Association of Poison Control Centers. Valproic acid poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2008; **46:** 661–76.

Precautions

Valproate is contra-indicated in patients with pre-existing liver disease or a family history of severe hepatic dysfunction. Children under 3 years of age and those with congenital metabolic or degenerative disorders, organic brain disease, or severe seizure disorders associated with mental retardation may be at particular risk of hepatotoxicity and the drug should be used with particular caution in these groups. Use with other antiepileptics, which may also increase the risks of liver damage, should be avoided if possible. Liver function tests should be carried out, particularly in those most at risk, before and during the first 6 months of therapy. Raised liver enzymes are not uncommon during treatment and are usually transient or respond to reduction in dosage, but patients should be reassessed clinically and liver function, including prothrombin time, monitored until they return to normal. An abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities, requires treatment to be stopped. If given with salicylates, these should also be stopped. Treatment should also be stopped if pancreatitis is diagnosed.

Patients or their carers should be told how to recognise signs of blood and liver toxicity or pancreatitis, and they should be advised to seek immediate medical attention if symptoms develop.

Patients should be monitored for potential bleeding complications before major elective surgery; some licensed product information suggests regular monitoring before and during therapy.

Valproate should be used with caution if the patient is at risk of SLE.

Patients should be warned of the risk of weight gain and appropriate strategies adopted to minimise the effect.

Care is required when withdrawing valproate therapy—see also Uses and Administration, p. 553.2.

The protein binding of valproate is saturable and thus shows concentration dependency; significant increases in free drug occur at high total plasma concentrations.

Because valproate is partly excreted in the form of ketone bodies, it may cause false positives in urine tests for diabetes mellitus.

Dosage adjustments may be necessary in severe renal impairment in accordance with free serum valproate levels.

Breast feeding. Thrombocytopenic purpura and anaemia occurred in a breast-fed infant whose mother was being treated with valproic acid.[1] The baby recovered when breast feeding was stopped. Low serum-valproate levels were detected[2] in 6 breast-fed infants whose mothers had been taking valproate semisodium post partum; no adverse effects were seen in the infants. Similar results have previously been obtained for patients taking sodium valproate[3] or valproic acid.[4] The American Academy of Pediatrics considers[5] that valproate is, therefore, usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. Stahl MMS, *et al*. Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. *J Pediatr* 1997; **130:** 1001–3.
2. Piontek CM, *et al*. Serum valproate levels in 6 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2000; **61:** 170–2.
3. Alexander FW. Sodium valproate and pregnancy. *Arch Dis Child* 1979; **54:** 240.
4. von Unruh GE, *et al*. Valproic acid in breast milk: how much is really there? *Ther Drug Monit* 1984; **6:** 272–6.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

HIV infection and AIDS. Limited data from several small *in-vitro* studies have found that valproic acid may induce viral replication of HIV;[1] some clinicians have therefore suggested increased monitoring of viral load in HIV-positive patients treated with valproic acid. For the use of this effect to reduce latent viral load, see under Uses and Administration, p. 554.2.

1. Jennings HR, Romanelli F. The use of valproic acid in HIV-positive patients. *Ann Pharmacother* 1999; **33:** 1113–16.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valproate as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy see p. 509.2.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including valproate and craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described, which may form part of a fetal antiepileptic syndrome.[1,2] In an unselected series[3] of 17 infants whose epileptic mothers had received valproate during pregnancy, 9 had minor abnormalities and of these 5 also had major abnormalities, including congenital heart defect in 4. In another series,[4] involving 149 women whose offspring were exposed to valproate monotherapy in the first trimester, 16 infants with major malformations were identified (a relative risk calculated at about 7 times that in the population at large). The abnormalities reported included craniosynostosis, spina bifida, and pulmonary atresia. A population-based study[5] of 2350 births to epileptic women between 1991 and 2000 found that the offspring of mothers who were given valproate, as mono- or polytherapy, in the first trimester had a fourfold increase in risk for congenital malformations compared with untreated mothers; the risk was tenfold in those who were given daily doses of more than 1.5 g. The risk of malformations was not increased in the offspring of mothers taking carbamazepine, oxcarbazepine, or phenytoin as mono- or polytherapy without valproate.

The FDA more recently reported[6] that data from the North American Antiepileptic Drug Pregnancy Registry showed that the rate of major malformations in neonates born to women with epilepsy taking antiepileptic monotherapy was 10.7% in those whose mothers took an average of 1 g of valproic acid daily compared with 2.9% in those whose mothers took other antiepileptic drugs. Major malformations had occurred in 16 of the offspring of 149 women given valproate during pregnancy and included neural tube defects, craniofacial defects, and malformations of cardiovascular and other body systems.

Neonatal bleeding, attributed to fibrinogen depletion and sometimes fatal, has been reported after exposure *in utero* to valproate.[7,8] Hypoglycaemia was recorded[9] in 13 of 22 neonates whose mothers had taken valproate during pregnancy. Valproate-withdrawal symptoms, including irritability, jitteriness, hypertonia, seizures, and feeding problems were also noted.

1. Genton P, *et al*. Valproic acid in epilepsy: pregnancy-related issues. *Drug Safety* 2006; **29:** 1–21.
2. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? *Reprod Toxicol* 2009; **28:** 1–10.
3. Thisted E, Ebbesen F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 1993; **69:** 288–91.
4. Wyszynski DF, *et al*. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; **64:** 961–5.
5. Artama M, *et al*. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 2005; **64:** 1874–8.
6. FDA. Information for healthcare professionals: risk of neural tube birth defects following prenatal exposure to valproate (issued 3rd December, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm192649.htm (accessed 11/01/10)
7. Majer RV, Green PJ. Neonatal afibrinogenaemia due to sodium valproate. *Lancet* 1987; **ii:** 740–1.
8. Bavoux F, *et al*. Neonatal fibrinogen depletion caused by sodium valproate. *Ann Pharmacother* 1994; **28:** 1307.
9. Ebbesen F, *et al*. Neonatal hypoglycaemia and withdrawal symptoms after exposure in utero to valproate. *Arch Dis Child Fetal Neonatal Ed* 2000; **83:** F124–F129.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Caution is recommended when giving valproate with other drugs liable to interfere with blood coagulation, such as aspirin or warfarin. Use with other hepatotoxic drugs should be avoided. Use of highly protein bound drugs with valproate may increase free valproate plasma concentrations.

General references.

1. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.

Analgesics. The free fraction of valproate was increased eightfold in a 76-year-old man[1] who was also given *aspirin* 325 mg daily, resulting in signs of clinical toxicity. Aspirin displaces valproate from plasma protein binding sites, as well as inhibiting its metabolism by inhibition of beta-oxidation. Similarly, the valproic acid free fraction was reported to be increased, as was the half-life, when aspirin was given in a study in 6 epileptic children.[2] Furthermore, salicylates have been associated with an increased risk of Reye's syndrome (p. 25.3) in children, and combination with another hepatotoxic drug such as valproate is clearly undesirable. In addition, both aspirin and valproate affect blood coagulation and platelet function.

Naproxen has also been reported to produce a slight displacement of protein-bound valproic acid but the effect is probably not sufficiently marked for it to have a clinical effect.[3]

1. Sandson NB, *et al*. An interaction between aspirin and valproate: the relevance of plasma protein displacement drug-drug interactions. *Am J Psychiatry* 2006; **163:** 1891–6.
2. Orr JM, *et al*. Interaction between valproic acid and aspirin in epileptic children: serum protein binding and metabolic effects. *Clin Pharmacol Ther* 1982; **31:** 642–9.
3. Grimaldi R, *et al*. In vivo plasma protein binding interaction between valproic acid and naproxen. *Eur J Drug Metab Pharmacokinet* 1984; **9:** 359–63.

Antibacterials. Raised valproate blood concentrations and symptoms consistent with valproate toxicity have been reported in a patient also given *erythromycin*.[1]

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving *pivampicillin* and valproate. Hyperammonaemic encephalopathy developed in a 72-year-old woman who had been taking valproate for 10 months when she was given *pivmecillinam* for a urinary-tract infection. It was suggested that valproate's propensity to produce hyperammonaemia had been exacerbated by a secondary hyperammonaemia induced by both drugs reducing carnitine concentrations.[2]

Decreases in plasma concentrations of valproate to subtherapeutic levels (and sometimes with loss of seizure control) have been noted in patients during therapy with antibacterial treatment containing *ertapenem*,[3,4] *imipenem*,[5] or *meropenem*.[5-9] Marked reductions in valproate concentrations have also been reported in 3 children given *panipenem* (with betamipron).[10] There is potential for a similar interaction with *doripenem*.[11] The MHRA[12] advises that given the rapid and substantial decrease in valproate concentrations, neither monitoring of sodium valproate concentrations nor making dose adjustments is likely to be of benefit. Therefore, the use of carbapenems with valproic acid/sodium valproate is not recommended.

Increased serum-valproate concentrations resulting in signs of valproate toxicity occurred in a child after beginning therapy with *isoniazid*;[13] the child was a slow acetylator of isoniazid and valproate dosage had to be reduced by about 60% to maintain satisfactory concentrations. When isoniazid was subsequently stopped, valproate dosage had to be increased to its previous value in order to maintain a therapeutic effect.

1. Redington K, *et al*. Erythromycin and valproate interaction. *Ann Intern Med* 1992; **116:** 877–8.
2. Lokrantz C-M, *et al*. Hyperammonemic encephalopathy induced by a combination of valproate and pivmecillinam. *Acta Neurol Scand* 2004; **109:** 297–301.
3. Lunde JL, *et al*. Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. *Pharmacotherapy* 2007; **27:** 1202–5.
4. Liao F-F, *et al*. Decrease in serum valproic acid levels during treatment with ertapenem. *Am J Health-Syst Pharm* 2010; **67:** 1260–4.
5. Llinares Tello F, *et al*. Interacción farmacocinética entre ácido valproico y antibióticos carbapenémicos: descripción de tres casos. *Farm Hosp* 2003; **27:** 258–63.
6. De Turck BJG, *et al*. Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother* 1998; **42:** 563–4.
7. Coves-Orts FJ, *et al*. Acute seizures due to a probable interaction between valproic acid and meropenem. *Ann Pharmacother* 2005; **39:** 533–7.
8. Fudio S, *et al*. Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. *J Clin Pharm Ther* 2006; **31:** 393–6.
9. Spriet I, *et al*. Interaction between valproate and meropenem: a retrospective study. *Ann Pharmacother* 2007; **41:** 1130–6.
10. Nagai K, *et al*. Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J Antimicrob Chemother* 1997; **39:** 295–6.
11. Hellwig TR, *et al*. Potential interaction between valproic acid and doripenem. *Curr Drug Saf* 2011; **6:** 54–8.
12. MHRA/CHM. Carbapenems: concomitant use with valproic acid not recommended. *Drug Safety Update* 2010; **3**(10): 4–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON081863 (accessed 07/06/10)
13. Jonville AP, *et al*. Interaction between isoniazid and valproate: a case of valproate overdosage. *Eur J Clin Pharmacol* 1991; **40:** 197–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

There have been conflicting reports of the effect of *fluoxetine* on serum concentrations of valproate. While some reported an increase,[1-3] others have reported a decrease[4] in valproate-serum concentrations when the 2 drugs were used together.

For the effect of valproate on *amitriptyline*, see p. 406.2.

1. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid. *J Clin Psychopharmacol* 1991; **11:** 389.
2. Lucena MI, *et al*. Interaction of fluoxetine and valproic acid. *Am J Psychiatry* 1998; **155:** 575.
3. Cruz-Flores S, *et al*. Valproic toxicity with fluoxetine therapy. *Mo Med* 1995; **92:** 296–7.
4. Droulers A, *et al*. Decrease of valproic acid concentration in the blood when coprescribed with fluoxetine. *J Clin Psychopharmacol* 1997; **17:** 139–40.

Antiepileptics. The barbiturate antiepileptic *phenobarbital* is reported to decrease serum-valproate concentrations when given together,[1] apparently by induction of valproate metabolism.[2] This effect is overshadowed, however, by the marked increase in serum-phenobarbital concentrations caused by valproate inhibition of phenobarbital metabolism—see p. 537.2. It has been suggested that phenobarbital may also increase the risk of valproate-induced hyperammonaemic encephalopathy.[3]

Carbamazepine and *phenytoin* are also enzyme-inducing drugs and, as might be expected, are reported to increase the metabolism and decrease the serum concentration of valproate.[4-6] The effect may be clinically significant.[7] The reciprocal effects of valproate on both drugs are complex, with conflicting effects on metabolism and protein binding, and the clinical outcome is difficult to predict. For more details see under Carbamazepine, p. 516.3 and Phenytoin, p. 543.2. An interaction with *oxcarbazepine*, resulting in valproate toxicity, has also been reported.[8]

Serum concentrations of valproic acid were reduced, with considerable interpatient variability, when *ethosuximide*[9] or *mesuximide*[10] was added to the antiepileptic therapy of some patients.

Raised serum concentrations of valproic acid have been reported in patients given *felbamate*.[11]

Reversible hepatic impairment has been reported[12,13] when *topiramate* was added to valproate therapy in patients who had previously tolerated valproate well. Use of valproate with topiramate has also been associated with hyperammonaemia and encephalopathy.[14]

Valproate inhibits the metabolism of *lamotrigine* which may result in serious toxic reactions—see p. 530.1. There is limited evidence that valproic acid may affect the metabolism of *ethosuximide* in some patients—see p. 521.3. Valproate reduces the half-life of *zonisamide*—see p. 561.3.

For interactions with benzodiazepines, see under Diazepam, p. 1069.1.

1. Perucca E. Pharmacokinetic interactions with antiepileptic drugs. *Clin Pharmacokinet* 1982; **7:** 57–84.
2. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
3. Segura-Bruna N, *et al*. Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006; **114:** 1–7.
4. Panesar SK, *et al*. The effect of carbamazepine on valproic acid disposition in adult volunteers. *Br J Clin Pharmacol* 1989; **27:** 323–8.
5. Reunanen MI, *et al*. Low serum valproic acid concentrations in epileptic patients on combination therapy. *Curr Ther Res* 1980; **28:** 456–62.
6. Cramer JA, *et al*. Variable free and total valproic acid concentrations in sole- and multi-drug therapy. *Ther Drug Monit* 1986; **8:** 411–15.
7. Jann MW, *et al*. Increased valproate serum concentrations upon carbamazepine cessation. *Epilepsia* 1988; **29:** 578–81.
8. Xiong GL, *et al*. Toxic interaction between valproate and oxcarbazepine: a case detected by the free valproate level. *J Clin Psychopharmacol* 2008; **28:** 472–3.
9. Sälke-Kellermann RA, *et al*. Influence of ethosuximide on valproic acid serum concentrations. *Epilepsy Res* 1997; **26:** 345–9.
10. Besag FMC, *et al*. Methsuximide reduces valproic acid serum levels. *Ther Drug Monit* 2001; **23:** 694–7.
11. Wagner ML, *et al*. The effect of felbamate on valproic acid disposition. *Clin Pharmacol Ther* 1994; **56:** 494–502.
12. Longin E, *et al*. Topiramate enhances the risk of valproate-associated side effects in three children. *Epilepsia* 2002; **43:** 451–4.
13. Bumb A, *et al*. Adding topiramate to valproate therapy may cause reversible hepatic failure. *Epileptic Disord* 2003; **5:** 157–9.
14. Latour P, *et al*. Drug induced encephalopathy in six epileptic patients: topiramate? valproate? or both? *Hum Psychopharmacol* 2004; **19:** 193–203.

Antimalarials. Low serum concentrations of valproate have been reported[1] in patients taking *mefloquine*. Also, mefloquine and *chloroquine* may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Antineoplastics. A marked reduction in serum-valproate concentration occurred in a 6-year-old child after a high-dose 24-hour infusion of *methotrexate*.[1]

1. Schrøder H, Østergaard JR. Interference of high-dose methotrexate in the metabolism of valproate? *Pediatr Hematol Oncol* 1994; **11:** 445–9.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold. Although a study[1] found that *risperidone* had no significant effect on the pharmacokinetics of valproate, 2 earlier case reports

showed conflicting results; one[2] described increased serum-valproate concentrations, and the other[3] decreased concentrations, when risperidone was added to valproate therapy. For the effect of valproate on *clozapine*, see p. 1061.3.

1. Ravindran A, *et al.* Risperidone does not affect steady-state pharmacokinetics of divalproex sodium in patients with bipolar disorder. *Clin Pharmacokinet* 2004; **43:** 733–40.
2. van Wattum PJ. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 866–7.
3. Bertoldo M. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 632.

Antivirals. There have been 2 reports that describe a reduction in plasma-valproate concentrations in HIV-positive patients who were taking valproate for bipolar disorder and were given *efavirenz* in one case[1] and *ritonavir-boosted lopinavir* in another,[2] resulting in mania. However, an earlier study[3] in a small number of HIV-positive patients did not find any clinically significant interactions between these drugs and valproic acid. For the effect of *aciclovir* on valproate, see under Interactions of Phenytoin, p. 544.1.

For the effect of valproate on *zidovudine*, see p. 1026.3.

1. Saraga M, *et al.* Reduced valproate plasma levels possible after introduction of efavirenz in a bipolar patient. *Bipolar Disord* 2006; **8:** 415–17.
2. Sheehan NL, *et al.* Possible interaction between lopinavir/ritonavir and valproic acid exacerbates bipolar disorder. *Ann Pharmacother* 2006; **40:** 147–50.
3. DiCenzo R, *et al.* Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2004; **48:** 4328–31.

Anxiolytics. For interactions between valproate and *benzodiazepines*, see under Diazepam, p. 1069.1. For an interaction between valproate and *zolpidem*, see p. 1117.3.

Calcium-channel blockers. For the effect of sodium valproate on *nimodipine*, see under Nifedipine, p. 1453.3.

Colestyramine. Colestyramine may decrease the absorption of valproate.

Gastrointestinal drugs. Use with an *antacid* (aluminium and magnesium hydroxides) significantly increased the bioavailability of a valproic acid preparation in healthy subjects;[1] other antacids in this study (calcium carbonate and an aluminium magnesium trisilicate mixture) had a lesser, insignificant effect.

Cimetidine significantly increased the half-life and decreased the clearance of sodium valproate in another study;[2] *ranitidine* had no effect on valproate pharmacokinetics.[2]

These interactions have not been reported to be of clinical significance, although the possibility must exist, particularly in patients on high-dose therapy.

1. May CA, *et al.* Effects of three antacids on the bioavailability of valproic acid. *Clin Pharm* 1982; **1:** 244–7.
2. Webster LK, *et al.* Effect of cimetidine and ranitidine on carbamazepine and sodium valproate pharmacokinetics. *Eur J Clin Pharmacol* 1984; **27:** 341–3.

Ginkgo biloba. For a report of a fatal breakthrough seizure occurring when phenytoin and valproate semisodium were used with ginkgo biloba, see under Phenytoin, p. 545.1.

Sex hormones. A 26-year-old woman who was taking valproate for epilepsy and a combined *oral contraceptive* had lower serum-valproate concentrations and an increase in seizure frequency during the active pill phase when compared with the inactive pill phase.[1] A subsequent study[2] in 9 epileptic women who were taking valproate and a combined oral contraceptive found that the apparent oral clearance of total and unbound valproic acid increased during contraceptive intake compared with the pill-free interval; the authors suggested that this effect was due to the induction of glucuronidation of valproate by ethinylestradiol.

1. Herzog AG, *et al.* Serum valproate levels with oral contraceptive use. *Epilepsia* 2005; **46:** 970–1.
2. Galimberti CA, *et al.* Increased apparent oral clearance of valproic acid during intake of combined contraceptive steroids in women with epilepsy. *Epilepsia* 2006; **47:** 1569–72.

Pharmacokinetics

Valproic acid and its salts are rapidly and completely absorbed from the gastrointestinal tract; the rate, but not the extent, of absorption is delayed if given with or after food.

Valproic acid is extensively metabolised in the liver, a large part by glucuronidation and the rest by a variety of complex pathways. It does not appear to enhance its own metabolism, but metabolism may be enhanced by other drugs that induce hepatic microsomal enzymes. It is excreted in the urine almost entirely in the form of its metabolites; small amounts are excreted in faeces and expired air.

Valproic acid is extensively bound to plasma proteins. The extent of protein binding is concentration dependent and is stated to be about 90 to 95% at total concentrations of 50 micrograms/mL, falling to about 80 to 85% at 100 micrograms/mL. Reported half-lives for valproic acid have ranged from about 5 to 20 hours; the shorter half-lives have generally been recorded in epileptic patients receiving multiple drug therapy. Clearance is usually higher in children than in adults.

The 'target' range of total plasma-valproic acid is usually quoted as being 40 to 100 micrograms/mL (280 to 700 micromoles/litre) but routine monitoring of plasma concentrations is not generally considered to be of use as an aid to assessing control.

Valproic acid crosses the placental barrier and small amounts are distributed into breast milk.

Valpromide is an amide derivative of valproic acid and its absorption is slower and its bioavailability somewhat less than that of valproic acid. Valpromide is rapidly and almost completely metabolised in the liver to valproic acid.

The pharmacokinetics of valproate are affected by other antiepileptics (see under Interactions, p. 557.3).

References.

1. Zaccara G, *et al.* Clinical pharmacokinetics of valproic acid—1988. *Clin Pharmacokinet* 1988; **15:** 367–89.
2. Bialer M. Clinical pharmacology of valpromide. *Clin Pharmacokinet* 1991; **20:** 114–22.
3. Cloyd JC, *et al.* Valproic acid pharmacokinetics in children IV: effects of age and antiepileptic drugs on protein binding and intrinsic clearance. *Clin Pharmacol Ther* 1993; **53:** 22–9.
4. Yukawa E, *et al.* Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: influence of drug-drug interaction and patient characteristics. *J Clin Pharmacol* 1997; **37:** 1160–7.
5. Dutta S, *et al.* Absolute bioavailability and absorption characteristics of divalproex sodium extended-release tablets in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 737–42.
6. Dutta S, *et al.* Comparative absorption profiles of divalproex sodium delayed-release versus extended-release tablets: clinical implications. *Ann Pharmacother* 2006; **40:** 619–25.
7. Reed RC, *et al.* Every-12-hour administration of extended-release divalproex in patients with epilepsy: impact on plasma valproic acid concentrations. *Epilepsy Behav* 2006; **8:** 391–6.
8. Dutta S, *et al.* Valproate protein binding following rapid intravenous administration of high doses of valproic acid in patients with epilepsy. *J Clin Pharm Ther* 2007; **32:** 365–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Depakene; Exibral; Logical; Valcas; Valcote; Valnar; ***Austral.***: Epilim; Valprease; Valpro; ***Austria***: Convulex; Depakine Chrono; Depakine Chronosphere; Depakine; ***Belg.***: Convulex; Depakine Chrono; Depakine; ***Braz.***: Depacon; Depakene; Depakote; Epilenil; Torval; Valpakine; Valprene; Zyvalprex; ***Canad.***: Depakene; Epival; ***Chile***: Atemperator; Depakene; DI VP; Neuractin; Valcote; ***China***: Depakine (德巴金); Dian Tai (典泰); ***Cz.***: Absenor; Convulex; Depakine Chrono; Depakine Chronosphere; Depakine; Everiden†; Orfiril; ***Denm.***: Delepsine; Deprakine; Orfiril; ***Fin.***: Absenor; Deprakine Depot; Deprakine; Orfiril; ***Fr.***: Depakine Chrono; Depakine; Depakote; Depamide; Micropakine; ***Ger.***: Convulex; Convulsofin; Ergenyl Chrono; Ergenyl Chronosphere†; Ergenyl; Leptilan; Orfiril; Valpro Beta chrono; Valpro Beta; Valpro chrono†; Valpro†; ***Gr.***: Depakine Chrono; Depakine; Depamide; ***Hong Kong***: Epilim; Orlept†; Valpro; ***Hung.***: Convulex; Depakine Chrono; Depakine; Orfiril; ***India***: D-Val; Depakote; Desval; Dicorate; Dilex; Diproex; Disorate; Disoval; Divaa; Divalex-OD; Divalin; Divalprid-OD; Divalpro; Divalrate; Drvel; Elival; Encorate; Epilex Chrono; Epilex; Epival; Eprea; Epsoval; Genval-OD; Kayval; Macorate; Manoval; Navalin; Valcontin; Valparin; Valrate; Valtec; ***Indon.***: Depakene; Depakote; ***Irl.***: Epi-Chrono†; Epilim Chrono; Epilim Chronosphere; Epilim; ***Israel***: Depalept Chrono; Depalept; Orfiril; Valporal; ***Ital.***: Depakin Chrono; Depakin; Depamag; Depamide; ***Jpn***: Depakene; Selenica; ***Malaysia***: Epilim Chrono; Epilim; Orfiril; ***Mex.***: Atemperator; Criam; Depakene; Edorame; Epival; Leptilan; Pimiken; Trankitec; Vematina; ***Neth.***: Depakine Chrono; Depakine; Orfiril; Propymal; ***Norw.***: Deprakine†; Orfiril; ***NZ***: Epilim; ***Philipp.***: Aleptiz; Depacon; Depakene; Depakote; Epival; Valparin XR; ***Pol.***: Absenor; Convulex; Depakine Chrono; Depakine Chronosphere; Depakine; Depamide; Dipromal; Orfiril; Valpro-Ratiopharm Chrono; ValproLek; ***Port.***: Depakine Chrono; Depakine Chronosphere; Depakine; Diplexil-R; Diplexil; ***Rus.***: Apilepsin (Апилепсин)†; Convulex (Конвулекс); Convulsofin (Конвульсофин); Depakine (Депакин); Depakine Chrono (Депакин Хроно); Depakine Chronosphere (Депакин Хроносфера); Encorate (Энкорат); Encorate Chrono (Энкорат Хроно); Valparin XR (Вальпарин ХР); ***S.Afr.***: Convulex; Epilim; ***Singapore***: Convulex; Epilim; Orfiril; Valparin; ***Spain***: Depakine Crono; Depakine; Depamide; Milzone†; ***Swed.***: Absenor; Ergenyl Retard; Ergenyl; Orfiril; ***Switz.***: Convulex; Depakine Chrono; Depakine; Orfiril; ***Thai.***: Depakine; Desorate; Encorate; Epiate; Oltril; Valparin; Valrem; ***Turk.***: Convulex; Depakin Chrono; Depakin; ***UAE***: Valopin; ***UK***: Convulex; Depakote; Epilim Chrono; Epilim; Episenta; Orlept; ***Ukr.***: Convulsofin (Конвульсофин); Depakin Chrono; Depakine (Депакин); Valprocom Chrono (Вальпрокома Хроно); ***USA***: Depacon; Depakene; Depakote; Mendatrex; Stavzor; ***Venez.***: Depakine; Valcote; Valpron.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Sodium Valproate Tablets; Sodium Valproate Oral Solution; Sodium Valproate Tablets;

USP 36: Divalproex Sodium Delayed-Release Capsules; Divalproex Sodium Delayed-Release Tablets; Divalproex Sodium Extended-Release Tablets; Valproate Sodium Injection; Valproic Acid Capsules; Valproic Acid Syrup.

Vigabatrin *(BAN, USAN, rINN)*

4-Amino-5-hexenoic Acid; MDL-71754; RMI-71754; Vigabatriini; Vigabatrina; Vigabatrine; Vigabatrinum; γ-Vinyl Aminobutyric Acid; γ-Vinyl-GABA; Вигабатрин.

4-Aminohex-5-enoic acid.

$C_6H_{11}NO_2$=129.2

CAS — 60643-86-9.

ATC — N03AG04.

ATC Vet — QN03AG04.

UNII — GR120KRT6K.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Vigabatrin). A white or almost white powder. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in dichloromethane.

USP 36: (Vigabatrin). A white or almost white powder. Freely soluble in water; slightly soluble in methyl alcohol; very slightly soluble in alcohol and in chloroform; practically insoluble in dichloromethane; insoluble in hexane and in toluene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Vigabatrin is an analogue of gamma-aminobutyric acid (GABA) that acts as an irreversible inhibitor of GABA-transaminase, the enzyme responsible for the catabolism of GABA. It is used as an adjunctive antiepileptic in patients with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome). (See Epilepsy, p. 559.1.)

The recommended initial oral dose of vigabatrin as adjunctive therapy is 1 g daily, increased, according to response and tolerability, in increments of 500 mg at weekly intervals to a maximum of 3 g daily.

Doses may be divided and given twice daily or taken as a single daily dose. Dosage reductions may be required in the elderly and in patients with renal impairment, particularly those with a creatinine clearance of less than 60 mL/min. For further details of doses in renal impairment, see p. 559.1.

For details of doses in children, see below.

As with other antiepileptics, withdrawal of vigabatrin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1. Licensed product information recommends that the dose of vigabatrin should be gradually reduced over 2 to 4 weeks.

References.

1. Wheless JW, *et al.* Vigabatrin. *Neurotherapeutics* 2007; **4:** 163–72.

Administration in children. Vigabatrin is used as an adjunctive antiepileptic in children with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome).

The recommended initial oral dose of vigabatrin as *adjunctive therapy* is 40 mg/kg daily, as a single dose or in 2 divided doses. Maintenance doses are given according to body-weight as follows:

- 10 to 15 kg: 0.5 to 1 g daily
- 15 to 30 kg: 1 to 1.5 g daily
- 30 to 50 kg: 1.5 to 3 g daily
- over 50 kg: 2 to 3 g daily

Alternatively, the *BNFC* suggests giving the following oral doses according to age:

- neonates to 12 years: initially 15 to 20 mg/kg (maximum of 250 mg) twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 30 to 40 mg/kg twice daily; maximum of 75 mg/kg or 1.5 g twice daily, whichever is less
- 12 to 18 years: initially 250 mg twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 1 to 1.5 g twice daily

Vigabatrin has been given rectally; in the UK, the *BNFC* has suggested that children over 1 month old may be given the same rectal doses, calculated by age, as those used orally (see above). The commercially available oral powder should be dissolved in a small amount of water before use.

For *monotherapy* in infantile spasms, the recommended initial oral dose of vigabatrin is 50 mg/kg daily, adjusted

according to response. Up to 150 mg/kg daily has been used. The *BNFC* suggests starting with 15 to 25 mg/kg twice daily, adjusted according to response over 7 days; the usual maintenance dose is 40 to 50 mg/kg twice daily (maximum of 75 mg/kg twice daily) for neonates and children up to 2 years of age.

Administration in renal impairment. Reduced oral doses of vigabatrin are recommended for patients with renal impairment. US licensed product information recommends the following dose adjustments based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: 25% dose reduction
- CC 30 to 50 mL/minute: 50% dose reduction
- CC 10 to 30 mL/minute: 75% dose reduction

Epilepsy. Vigabatrin is used in the treatment of epilepsy (p. 506.1) as adjunctive therapy for refractory seizures. Reviews[1-4] of vigabatrin have considered it to be most effective in the treatment of complex partial seizures with or without secondary generalisation; it may, however, exacerbate myoclonic or absence seizures. Efficacy as adjunctive therapy in refractory partial seizures was shown by 2 multicentre studies[5,6] involving 228 patients (including 46 children) and a study[7] involving 52 patients being assessed for epilepsy surgery. However, in a follow-up study[8] of 120 patients who had participated in an open-label study of vigabatrin as adjunctive therapy for refractory epilepsy 6 to 8 years earlier, it was considered that vigabatrin had had only marginal benefit on the long-term prognosis of severe refractory epilepsy, despite favourable results from the original study. A later systematic review[9] concluded that although vigabatrin has proven efficacy in the short term for reducing seizure frequency in refractory partial epilepsy, associated adverse effects such as visual field defects are common and can be severe; further study is considered warranted.

Vigabatrin is also of value in infantile spasms (as for example in West's syndrome). In an assessment of vigabatrin as monotherapy in 192 infants with infantile spasms who were followed up for an average of 7.6 months,[10] there was complete cessation of spasms in 131 patients, a decrease in cluster frequency in 37, and no improvement in 24 (including deterioration in 1 infant). A crossover study comparing vigabatrin with corticotropin in 42 infants found that both drugs produced some benefit;[11] a larger multicentre comparison of treatment with prednisolone and tetracosactide versus vigabatrin found that the former produced better initial control, but that the treatments were equivalent after more prolonged follow-up to 12 to 14 months of age.[12] A review of the literature suggested that vigabatrin was particularly effective in infantile spasms associated with tuberous sclerosis;[13] the authors considered that its efficacy might be less in other forms of infantile spasm.[13] A later guideline[14] also tentatively concluded that vigabatrin was effective in the short-term treatment of infantile spasms including those associated with tuberous sclerosis.

1. French JA. Vigabatrin. *Epilepsia* 1999; **40** (suppl 5): S11–S16.
2. Gidal BE, *et al*. Vigabatrin: a novel therapy for seizure disorders. *Ann Pharmacother* 1999; **33:** 1277–86.
3. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001 **43:** 833–5.
4. Willmore LJ, *et al*. Vigabatrin: 2008 update. *Epilepsia* 2009; **50:** 163–73.
5. Dalla Bernadina B, *et al*. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995; **36:** 687–91.
6. French JA, *et al*. A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996; **46:** 54–61.
7. Malmgren K, *et al*. Cost analysis of epilepsy surgery and of vigabatrin treatment in patients with refractory partial epilepsy. *Epilepsy Res* 1996; **25:** 199–207.
8. Walker MC, *et al*. Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ* 1996; **313:** 1184–5.
9. Hemming K, *et al*. Vigabatrin for refractory partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 12/08/09).
10. Aicardi J, *et al*. Sabril IS Investigator and Peer Review Groups. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. *Epilepsia* 1996; **37:** 638–42.
11. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997; **38:** 1270–4.
12. Lux AL, *et al*. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005; **4:** 712–17.
13. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis. *J Child Neurol* 1999; **14:** 71–4.
14. Mackay MT, *et al*. Practice parameter: medical treatment of infantile spasms—report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; **62:** 1668–81.

Metabolic disorders. Vigabatrin, an irreversible inhibitor of GABA-transaminase, has been tried in GABA metabolic disorders, with or without concurrent epilepsy,[1-5] with ambivalent results. Data from 23 case reports of patients with succinic semialdehyde dehydrogenase deficiency indicated that vigabatrin was clinically beneficial in only about one-third of patients.[4]

1. Jaeken J, *et al*. Vigabatrin in GABA metabolism disorders. *Lancet* 1989; **i:** 1074.
2. Gibson KM, *et al*. Vigabatrin therapy in patient with succinic semialdehyde dehydrogenase deficiency. *Lancet* 1989; **ii:** 1105–6.
3. Stephenson JBP. Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. *Lancet* 1992; **340:** 430–1.
4. Gibson KM, *et al*. The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. *Pediatrics* 1997; **99:** 567–74.
5. Leuzzi V, *et al*. Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2007; **68:** 1320–1.

Stiff-man syndrome. There have been anecdotal reports[1-3] of improvement of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) with vigabatrin in patients unable to tolerate benzodiazepine therapy.

1. Vermeij FH, *et al*. Improvement of stiff-man syndrome with vigabatrin. *Lancet* 1996; **348:** 612.
2. Prevett MC, *et al*. Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1997; **48:** 1133–4.
3. Sharoqi IA. Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1998; **50:** 833–4.

Withdrawal syndromes. Vigabatrin has been investigated[1,2] with some benefit as an adjunct in the management of *cocaine* and *metamfetamine* dependence; with short-term use no ocular effects were evident.[1]

1. Fechtner RD, *et al*. Short-term treatment of cocaine and/or methamphetamine abuse with vigabatrin: ocular safety pilot results. *Arch Ophthalmol* 2006; **124:** 1257–62.
2. Brodie JD, *et al*. Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in Mexican parolees. *Am J Psychiatry* 2009; **166:** 1269–77.

Adverse Effects, Treatment, and Precautions

About half of all patients have adverse effects with vigabatrin. The most common are drowsiness and fatigue, although in children excitation and agitation occur more frequently. The incidence of these effects is generally higher at the start of therapy and decreases over time. Other CNS-related adverse effects include dizziness, headache, ataxia, paraesthesia, tremor, impaired concentration, confusion, and memory disturbances. Other reported adverse effects include weight gain, gastrointestinal disturbances, oedema, alopecia, angioedema, urticaria, and skin rash. Haemoglobin and liver enzyme values may be decreased. Rarely, marked sedation, stupor and confusion, with other symptoms suggestive of encephalopathy, have occurred.

About one-third of all patients receiving vigabatrin have developed irreversible visual field defects, ranging from mild to severe and usually occurring after months or years of therapy. Blurred vision, diplopia, or nystagmus are somewhat less common. Retinal disorders such as peripheral retinal atrophy, or very rarely optic neuritis or atrophy have also been reported (see also below). Visual field function should be assessed before beginning treatment and during routine follow-up (ideally at 6-month intervals), and patients should be warned to report any new visual symptoms that develop during therapy. Vigabatrin should not be used in patients with pre-existing visual field defects.

Psychiatric reactions such as agitation, aggression, irritability, nervousness, depression, and paranoid reactions have occurred in patients with or without a psychiatric history; psychosis, hypomania, or mania have been reported rarely. Patients receiving vigabatrin should be observed carefully for any signs of adverse effects on neurological function. Caution is warranted in patients with a history of psychosis, depression, or behavioural problems.

Vigabatrin may exacerbate myoclonic or absence seizures.

Vigabatrin should be given with caution to the elderly and patients with renal impairment.

Care is required when withdrawing vigabatrin therapy—see also Uses and Administration, p. 558.3.

Breast feeding. Licensed product information states that breast feeding is not recommended in women receiving vigabatrin. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Particular care should be taken in view of the possible effects of vigabatrin on visual acuity.

Effects on bone. For the effects of antiepileptics, including vigabatrin, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the eyes. A report of 3 patients who developed bilateral severely constricted visual fields 2 to 3 years after vigabatrin was added to their antiepileptic regimens[1] prompted publication of similar anecdotal reports.[2-5] Peripheral retinal atrophy rather than optic nerve damage appeared to be the cause. Symptoms showed no improvement on stopping the drug, although there was no further deterioration. At that time (1997) the manufacturers replied[6] stating that it was a rare occurrence (less than 0.1%) and was being monitored in further clinical studies. The UK CSM subsequently stated[7] (in March 1998) that it had received 41 reports of visual field defects since December 1989, which persisted in most cases despite stopping treatment. The evidence suggested that the onset of symptoms varied from 1 month to several years after starting vigabatrin. In most cases, visual field defects have persisted despite stopping vigabatrin.[8,9] Interim results of a Prescription Event Monitoring Study[10] in the UK stated that vigabatrin was considered to be probably or possibly associated with objective evidence of a visual field defect in 0.2% of patients. However, subsequent evidence appears to have confirmed that the incidence of visual field defects is much higher;[11-14] revised product literature issued in late 1999 indicated that visual field defects occurred in about one-third of all patients receiving vigabatrin. Male patients appear to be at an increased risk of developing defects.[15,16] Whether cumulative dose may be considered a risk factor remains unclear:[16] some have failed to find a correlation[17] whereas a later open-label study noted an increased risk with increasing duration of treatment.[18]

The CSM considered[14] that vigabatrin should only be prescribed by a specialist, and only where all other combination therapies have failed. Ophthalmological consultation and visual field assessment should be undertaken before starting vigabatrin and visual field screening repeated at 6-monthly intervals during treatment. Conventional perimetry is unsuitable in patients under 9 years of age, in whom alternative methods should be employed. Opinion amongst some paediatricians[19] was that the risk of developing visual field defects had to be weighed against the potential benefit of seizure control. In very young patients, in whom monitoring of vision was impossible, the benefits of vigabatrin in the treatment of infantile spasms were felt by some to outweigh this risk.[20]

Vigabatrin should not be used in patients with pre-existing visual field defects.[14,19]

There is some evidence, mainly from studies in *animals* that retinal toxicity may be associated with an induced deficiency of taurine.[21]

1. Eke T, *et al*. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 180–1.
2. Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1693.
3. Wong ICK, *et al*. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1693–4.
4. Blackwell N, *et al*. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694.
5. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694.
6. Backstrom JT, *et al*. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694–5.
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8. Hardus P, *et al*. Long term changes in the visual fields of patients with temporal lobe epilepsy using vigabatrin. *Br J Ophthalmol* 2000; **84:** 788–90.
9. Johnson MA, *et al*. Visual function loss from vigabatrin: effect of stopping the drug. *Neurology* 2000; **55:** 40–5.
10. Wilton LV, *et al*. Interim report on the incidence of visual field defects in patients on long term vigabatrin therapy. *Pharmacoepidemiol Drug Safety* 1999; **8** (suppl): S9–S14.
11. Wilton LV, *et al*. Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999; **319:** 1165–6.
12. Kälviäinen R, *et al*. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual defects. *Neurology* 1999; **53:** 922–6.
13. Lawden MC, *et al*. Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999; **67:** 716–22.
14. CSM/MCA. Vigabatrin (Sabril): visual field defects. *Current Problems* 1999; **25:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
15. Kälviäinen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. *CNS Drugs* 2001; **15:** 217–30.
16. Wild JM, *et al*. Vigabatrin and epilepsy: lessons learned. *Epilepsia* 2007; **48:** 1318–27.
17. Kinirons P, *et al*. Vigabatrin retinopathy in an Irish cohort: lack of correlation with dose. *Epilepsia* 2006; **47:** 311–17.
18. Wild JM, *et al*. Visual field loss in patients with refractory partial epilepsy treated with vigabatrin: final results from an open-label, observational, multicentre study. *CNS Drugs* 2009; **23:** 965–82.
19. Appleton RE. Guideline may help in prescribing vigabatrin. *BMJ* 1998; **317:** 1322.
20. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1998; **316:** 232–3.
21. Jammoul F, *et al*. Taurine deficiency is a cause of vigabatrin-induced retinal phototoxicity. *Ann Neurol* 2009; **65:** 98–107.

Effects on the liver. Vigabatrin has shown *in-vivo* and *in-vitro* inhibition of plasma-alanine transaminase activity, which may mask signs of early underlying hepatic disease if only transaminase levels are evaluated.[1]

1. Richens A, *et al*. Evidence for both in vivo and in vitro interaction between vigabatrin and alanine transaminase. *Br J Clin Pharmacol* 1997; **43:** 163–8.

Effects on mental function. *Behavioural disturbances* ranging from irritability and confusion to psychotic reactions have been reported in patients receiving vigabatrin.[1-7] An analysis[8] of adverse effect reports from double-blind controlled studies found that the incidence of psychotic reactions was about 2.5% in vigabatrin-treated patients; however, the most common psychiatric reaction was depression, which occurred in 8 to 12% of patients. Symptoms of psychiatric

disturbance were often relatively mild. Psychiatric reactions are generally reversible when doses are reduced or gradually stopped. In 2 patients[9,10] psychosis developed after sudden withdrawal of vigabatrin; mental state improved when the drug was reinstated. It is not clear whether patients with a history of previous psychiatric disturbances are at greater risk when given vigabatrin.[8,11] Also, using low doses of vigabatrin to start therapy did not reduce the incidence of disturbances.[11]

The problems of antiepileptic therapy adversely affecting *cognition* and *mood* (including the risk of suicidal ideation) are discussed on p. 508.3.

1. Sander JWAS, Hart YM. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 57.
2. Dam M. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 605.
3. Betts T, Thomas L. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 605–6.
4. Johnston SJ. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 606.
5. Robinson MK, *et al*. Vigabatrin and behaviour disturbances. *Lancet* 1990; **336:** 504.
6. Naumann M, *et al*. Bipolar affective psychosis after vigabatrin. *Lancet* 1994; **343:** 606–7.
7. Martínez AC, *et al*. Vigabatrin-associated reversible acute psychosis in a child. *Ann Pharmacother* 1995; **29:** 1115–17.
8. Levinson DF, Devinsky O. Psychiatric adverse events during vigabatrin therapy. *Neurology* 1999; **53:** 1503–11.
9. Ring HA, Reynolds EH. Vigabatrin and behaviour disturbance. *Lancet* 1990; **335:** 970.
10. Brodie MJ, McKee PJW. Vigabatrin and psychosis. *Lancet* 1990; **335:** 1279.
11. Wong ICK. Retrospective study of vigabatrin and psychiatric behavioural disturbances. *Epilepsy Res* 1995; **21:** 227–30.

Effects on the nervous system. Two patients developed disturbances of motor behaviour associated with the addition of vigabatrin to therapy for intractable seizures.[1] Abnormal brain magnetic resonance imaging (MRI) findings have been reported in infants treated with vigabatrin for infantile spasms,[2,3] particularly in young infants given doses of 125 mg/kg daily or more. Although the abnormalities appeared to be transient, resolving in most patients despite continued treatment, their clinical significance is unknown. Movement disorders such as dystonia, dyskinesia, and hypertonia have been associated with the use of vigabatrin for infantile spasms and the MHRA[3] has warned that if any new movement disorders appear during its use, consideration should be given to a dose reduction or a gradual withdrawal of vigabatrin in consultation with specialist advice.

Acute encephalopathy was reported[4] in two patients after starting vigabatrin in addition to carbamazepine; symptoms of stupor, dysphoria, and irritability were present in both and their EEG background activity was slowed. Clinical symptoms could not be related to intoxication with carbamazepine or its epoxide but it was not known whether an interaction between carbamazepine and vigabatrin had caused the acute encephalopathy. Acute encephalopathy was also reported[5] when vigabatrin was given to a 6-month-old girl who was also receiving phenobarbital. Symptoms resolved when vigabatrin was stopped. In another report[6] vigabatrin was associated with the development of encephalopathy in 3 patients already receiving a variety of antiepileptic drugs other than carbamazepine; withdrawal of vigabatrin led to full recovery. The authors suggested that acute encephalopathy after vigabatrin may be related to a pre-existing cerebral abnormality. Other predisposing factors suggested by licensed product information include higher than recommended initial doses, faster dose increases at greater increments than those recommended, and renal failure.

1. Jongsma MJ, *et al*. Reversible motor disturbances induced by vigabatrin. *Lancet* 1991; **338:** 893.
2. Wheless JW, *et al*. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. *Epilepsia* 2009; **50:** 195–205.
3. MHRA/CHM. Vigabatrin for infantile spasms: risk of movement disorders and MRI abnormalities. *Drug Safety Update* 2009; **3** (4): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON062549&RevisionSelectionMethod=LatestReleased (accessed 13/01/10)
4. Sälke-Kellermann A, Baier H. Acute encephalopathy with vigabatrin. *Lancet* 1993; **342:** 185.
5. Haas-Lude K, *et al*. Acute encephalopathy associated with vigabatrin in a six-month-old girl. *Epilepsia* 2000; **41:** 628–30.
6. Sharief MK, *et al*. Acute encephalopathy with vigabatrin. *Lancet* 1993; **342:** 619.

Interference with diagnostic tests. Vigabatrin can cause changes in the urinary excretion of amino acids which could be potentially misleading in patients undergoing investigation for metabolic disorders.[1,2]

1. Bonham JR, *et al*. Pyroglutamicaciduria from vigabatrin. *Lancet* 1989; **i:** 1452–3.
2. Shih VE, Tenanbaum A. Aminoaciduria due to vinyl-gaba administration. *N Engl J Med* 1990; **323:** 1353.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vigabatrin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] There has, however, been a report of a bullous skin eruption in a patient with porphyria cutanea tarda given vigabatrin.[2]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)
2. Hommel L, *et al*. Acute bullous skin eruption after treatment with vigabatrine. *Dermatology* 1995; **191:** 181.

Pregnancy. For comments on the management of epilepsy in pregnancy, see p. 509.2.

Little is known of the effects of newer antiepileptics such as vigabatrin on the fetus, although congenital anomalies have been reported in the offspring of some mothers using vigabatrin during pregnancy.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antiepileptics. For the effect of vigabatrin on plasma concentrations of other antiepileptics, see under *Carbamazepine*, p. 516.3; *Phenobarbital*, p. 537.2; *Phenytoin*, p. 543.2; and *Primidone*, p. 547.3.

Pharmacokinetics

Vigabatrin is well absorbed after oral doses of the racemate; the inactive *R* (-)-enantiomer is reported to be present at much higher plasma concentrations than the active *S*(+)-enantiomer, perhaps indicating a difference in bioavailability. About 60 to 80% of an oral dose is excreted in urine as unchanged drug. The elimination half-life is reported to be 5 to 8 hours. Vigabatrin is not significantly bound to plasma proteins.

There does not appear to be any correlation between plasma concentrations of vigabatrin and its efficacy or toxicity. Children exhibit a lower area under the concentration-time curve than adults and may need higher doses to achieve therapeutic plasma concentrations.

Vigabatrin crosses the placenta and is distributed into breast milk.

References.

1. Rey E, *et al*. Vigabatrin: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **23:** 267–78.
2. Hoke JF, *et al*. Pharmacokinetics of vigabatrin following single and multiple oral doses in normal volunteers. *J Clin Pharmacol* 1993; **33:** 458–62.
3. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
4. Vauzelle-Kervroëdan F, *et al*. Pharmacokinetics of the individual enantiomers of vigabatrin in neonates with uncontrolled seizures. *Br J Clin Pharmacol* 1996; **42:** 779–81.
5. Jacqz-Aigrain E, *et al*. Pharmacokinetics of the S(+) and R(-) enantiomers of vigabatrin during chronic dosing in a patient with renal failure. *Br J Clin Pharmacol* 1997; **44:** 183–5.
6. Armijo JA, *et al*. Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. *Ther Drug Monit* 1997; **19:** 491–8.
7. Tran A, *et al*. Vigabatrin: placental transfer in vivo and excretion into breast milk of the enantiomers. *Br J Clin Pharmacol* 1998; **45:** 409–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sabril; ***Austral.***: Sabril; ***Austria***: Sabril; ***Belg.***: Sabril; ***Braz.***: Sabril; ***Canad.***: Sabril; ***Chile***: Sabril; ***Cz.***: Sabril; ***Denm.***: Sabrilex; ***Fin.***: Sabrilex; ***Fr.***: Sabril; ***Ger.***: Sabril; ***Gr.***: Sabril; ***Hong Kong***: Sabril; ***Hung.***: Sabril; ***Irl.***: Sabril; ***Israel***: Sabrilan; ***Ital.***: Sabril; ***Mex.***: Sabril; ***Neth.***: Sabril; Sabrilex†; ***Norw.***: Sabrilex; ***NZ***: Sabril; ***Pol.***: Sabril; ***Port.***: Sabril; ***S.Afr.***: Sabril; ***Singapore***: Sabril; ***Spain***: Sabrilex; ***Swed.***: Sabrilex; ***Switz.***: Sabril; ***Turk.***: Sabril; ***UK***: Sabril; ***USA***: Sabril.

Pharmacopoeial Preparations
BP 2014: Vigabatrin Oral Powder; Vigabatrin Tablets.

Zonisamide *(BAN, USAN, rINN)*

AD-810; CI-912; PD-110843; Zonisamida; Zonisamidum; Зонизамид.

1-(1,2-Benzoxazol-3-yl)methanesulphonamide.

$C_8H_8N_2O_3S$=212.2

CAS — 68291-97-4.

ATC — N03AX15.

ATC Vet — QN03AX15.

UNII — 459384H98V.

Pharmacopoeias. In *US.*

USP 36: (Zonisamide). A white to off-white powder. Soluble in methyl alcohol; freely soluble in dimethylformamide.

Stability. An extemporaneously prepared suspension containing zonisamide 10 mg/mL in a mixture of simple syrup was found[1] to be stable for 28 days in plastic amber bottles when stored at room temperature or under refrigeration; when prepared in 0.5% methylcellulose, the suspension was stable for 28 days under refrigeration and for 7 days at room temperature.

1. Abobo CV, *et al*. Stability of zonisamide in extemporaneously compounded oral suspensions. *Am J Health-Syst Pharm* 2009; **66:** 1105–9.

Uses and Administration

Zonisamide, a benzisoxazole derivative, is used as an adjunctive antiepileptic in the treatment of partial seizures, with or without secondary generalisation (below); it may also be used as monotherapy in newly diagnosed patients. In some countries, it is also used as an adjunct to levodopa in the management of Parkinson's disease (p. 561.1) when response to standard therapy is inadequate.

For the *adjunctive* treatment of **epilepsy**:

- in the UK, the usual initial oral dose in adults over 18 years of age is 50 mg daily in 2 divided doses, increased after 1 week to 100 mg daily. Thereafter, the dose may be further increased at weekly intervals by increments of up to 100 mg, to a usual dose of 300 to 500 mg daily, although some patients may respond to lower doses. Dose increments at intervals of 2 weeks should be considered in patients with hepatic or renal impairment and in patients who are not receiving CYP3A4 inducers (see also Interactions, p. 561.3). Zonisamide may be given as a single dose or in 2 divided doses after the titration phase
- in the USA, the usual initial oral dose in patients over 16 years of age is 100 mg daily, increased after at least 2 weeks to 200 mg daily, given as a single dose or in 2 divided doses. Thereafter, if necessary, the dose may be further increased at intervals of at least 2 weeks by increments of 100 mg, to a dose of 400 mg daily. Doses of up to 600 mg daily have been used, but there is no current evidence of an increase in response above 400 mg daily; many of the adverse effects of zonisamide are reported to be more frequent at doses of 300 mg daily and above

For *monotherapy*, in the UK, the usual initial oral dose in patients over 18 years of age is 100 mg daily, increased after 2 weeks to 200 mg daily, given as a single dose. Thereafter, the dose may be further increased at intervals of at least 2 weeks by increments of 100 mg, to a usual dose of 300 mg daily, although some patients may require higher doses of up to 500 mg daily.

For details of doses in children, see below.

As with other antiepileptics, withdrawal of zonisamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures; UK licensed product information has suggested that the dose may be decreased in steps of 100 mg at weekly intervals. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

In the management of **Parkinson's disease**, the usual oral dose is 25 mg once daily.

Administration in children. In the UK, zonisamide is licensed as an adjunct in the treatment of partial seizures with or without secondary generalisation in children aged 6 years and over; it is given as a single daily dose. The usual initial oral dose is 1 mg/kg daily for 1 week. Thereafter, the dose may be increased at weekly intervals by increments of 1 mg/kg, to a usual dose of 6 to 8 mg/kg daily in those weighing 20 to 55 kg and 300 to 500 mg daily in heavier children, although some may respond to lower doses. Dose increments at intervals of 2 weeks should be considered in those who are not receiving CYP3A4 inducers (see also Interactions, p. 561.3). Withdrawal of zonisamide therapy should be done gradually: the daily dose should generally be decreased by about 2 mg/kg at weekly intervals.

Bipolar disorder. Zonisamide may have psychotropic properties, and has been tried in the management of bipolar disorder[1-5] (p. 397.2). However, a randomised controlled study[6] did not find statistically significant differences between patients treated with adjunctive zonisamide and those with placebo.

1. Baldassano CF, *et al*. Acute treatment of bipolar depression with adjunctive zonisamide: a retrospective chart review. *Bipolar Disord* 2004; **6:** 432–4.
2. Anand A, *et al*. A preliminary open-label study of zonisamide treatment for bipolar depression in 10 patients. *J Clin Psychiatry* 2005; **66:** 195–8.
3. McElroy SL, *et al*. Open-label adjunctive zonisamide in the treatment of bipolar disorders: a prospective trial. *J Clin Psychiatry* 2005; **66:** 617–24.
4. Ghaemi SN, *et al*. An open prospective study of zonisamide in acute bipolar depression. *J Clin Psychopharmacol* 2006; **26:** 385–8.
5. Wilson MS, Findling RL. Zonisamide for bipolar depression. *Expert Opin Pharmacother* 2007; **8:** 111–13.
6. Dauphinais D, *et al*. Zonisamide for bipolar disorder, mania or mixed states: a randomized, double blind, placebo-controlled adjunctive trial. *Psychopharmacol Bull* 2011; **44:** 5–17.

Epilepsy. Zonisamide is used in the treatment of refractory epilepsy (p. 506.1). Studies in Japan and elsewhere have showed its efficacy mainly as an adjunct in the treatment

of partial seizures with or without secondary generalisation.[1-5] It is also effective as monotherapy.[3,5-10] Efficacy in primary generalised and mixed-seizure epilepsies appears to be more variable, although it may be of value in refractory myoclonic seizures[11,12] and absence seizures.[13] Zonisamide might also be of use in the treatment of epileptic syndromes such as Lennox-Gastaut syndrome,[14] and infantile spasms (as for example in West's syndrome), although only a small number of patients with the latter condition have been studied.[15-17]

1. Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Brodie MJ, *et al*. Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 2005; **46:** 31–41.
3. Zaccara G, Specchio LM. Long-term safety and effectiveness of zonisamide in the treatment of epilepsy: a review of the literature. *Neuropsychiatr Dis Treat* 2009; **5:** 249–59.
4. Lu Y, *et al*. Efficacy and safety of adjunctive zonisamide in adult patients with refractory partial-onset epilepsy: a randomized, double-blind, placebo-controlled trial. *Clin Drug Investig* 2011; **31:** 221–9.
5. Hoy SM. Zonisamide: a review of its use in the management of adults with partial seizures. *Drugs* 2013; **73:** 1321–38.
6. Tosches WA, Tisdell J. Long-term efficacy and safety of monotherapy and adjunctive therapy with zonisamide. *Epilepsy Behav* 2006; **8:** 522–6.
7. Kothare SV, *et al*. Efficacy and safety of zonisamide monotherapy in a cohort of children with epilepsy. *Pediatr Neurol* 2006; **34:** 351–4.
8. Park SP, *et al*. Long-term efficacy and safety of zonisamide monotherapy in epilepsy patients. *J Clin Neurol* 2007; **3:** 175–80.
9. Eun S-H, *et al*. Comparative trial of low- and high-dose zonisamide as monotherapy for childhood epilepsy. *Seizure* 2011; **20:** 558–63.
10. Baulac M, *et al*. Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurol* 2012; **11:** 579–88.
11. Kyllerman M, Ben-Menachen E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. *Epilepsy Res* 1998; **29:** 109–14.
12. Vossler DG, *et al*. Zonisamide for the treatment of myoclonic seizures in progressive myoclonic epilepsy: an open-label study. *Epileptic Disord* 2008; **10:** 31–4.
13. Wilfong A, Schultz R. Zonisamide for absence seizures. *Epilepsy Res* 2005; **64:** 31–4.
14. You SJ, *et al*. Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. *Brain Dev* 2008; **30:** 287–90.
15. Yanai S, *et al*. Treatment of infantile spasms with zonisamide. *Brain Dev* 1999; **21:** 157–61.
16. Lotze TE, Wilfong AA. Zonisamide treatment for symptomatic infantile spasms. *Neurology* 2004; **62:** 296–8.
17. Yum M-S, Ko T-S. Zonisamide in West syndrome: an open label study. *Epileptic Disord* 2009; **11:** 339–44.

Migraine. Zonisamide has been tried with some success in the prophylaxis of migraine (p. 670.3) in patients refractory to, or intolerant of, topiramate.[1-3]

1. Bermejo PE, Dorado R. Zonisamide for migraine prophylaxis in patients refractory to topiramate. *Clin Neuropharmacol* 2009; **32:** 103–6.
2. Villani V, *et al*. Zonisamide for migraine prophylaxis in topiramate-intolerant patients: an observational study. *Headache* 2011; **51:** 287–91.
3. Mohammadianinejad SE, *et al*. Zonisamide versus topiramate in migraine prophylaxis: a double-blind randomized clinical trial. *Clin Neuropharmacol* 2011; **34:** 174–7.

Obesity. Anorexia and weight loss have been associated with zonisamide therapy (see Adverse Effects, below) and it has been tried, with some success, as an adjunct in the treatment of obesity[1-3] (p. 2315.1); it has also been tried in binge-eating disorder associated with obesity.[4,5] Combination with bupropion (p. 408.2) is under investigation.[2]

1. Gadde KM, *et al*. Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA* 2003; **289:** 1820–5.
2. Gadde KM, *et al*. Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatry* 2007; **68:** 1226–9.
3. Gadde KM, *et al*. Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med* 2012; **172:** 1557–64.
4. McElroy SL, *et al*. Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry* 2006; **67:** 1897–1906. Correction. *ibid*. 2007; **68:** 172.
5. Ricca V, *et al*. Zonisamide combined with cognitive behavioral therapy in binge eating disorder: a one-year follow-up study. *Psychiatry (Edgmont)* 2009; **6:** 23–8.

Parkinsonism. The use of zonisamide in the management of Parkinson's disease (p. 889.1) has been reviewed.[1] Preliminary studies have shown that, when used as an adjunct to levodopa, zonisamide improved motor function and was generally well tolerated.

1. Yang LPH, Perry CM. Zonisamide: in Parkinson's disease. *CNS Drugs* 2009; **23:** 703–11.

Withdrawal syndromes and abstinence. Zonisamide has been tried with some success in the management of alcohol withdrawal syndrome[1] and dependence[2-4] (p. 1735.1).

1. Rubio G, *et al*. Zonisamide versus diazepam in the treatment of alcohol withdrawal syndrome. *Pharmacopsychiatry* 2010; **43:** 257–62.
2. Knapp CM, *et al*. Open label trial of the tolerability and efficacy of zonisamide in the treatment of alcohol dependence. *Am J Drug Alcohol Abuse* 2010; **36:** 102–5.
3. Arias AJ, *et al*. Placebo-controlled trial of zonisamide for the treatment of alcohol dependence. *J Clin Psychopharmacol* 2010; **30:** 318–22.
4. Rubio G, *et al*. Effects of zonisamide in the treatment of alcohol dependence. *Clin Neuropharmacol* 2010; **33:** 250–3.

Adverse Effects

The most common adverse effects reported with adjunctive zonisamide therapy are somnolence, dizziness, and anorexia; decreased serum-bicarbonate concentrations, decreased appetite, and weight loss are most commonly reported with monotherapy. Other common adverse effects have included gastrointestinal disturbances such as abdominal pain, constipation, diarrhoea, dyspepsia, and nausea, ecchymosis, headache, pruritus, peripheral oedema, ataxia, paraesthesia, diplopia, fatigue, insomnia, anxiety, depression, and agitation or irritability.

Zonisamide is a sulfonamide derivative; potentially fatal hypersensitivity reactions and blood dyscrasias associated with sulfonamides (see Sulfamethoxazole, p. 365.3) have also been reported with zonisamide. Severe, sometimes fatal, skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Other hypersensitivity reactions have been reported, including drug rash with eosinophilia and systemic symptoms (DRESS). The incidence of peripheral oedema, pruritus, Stevens-Johnson syndrome, and drug-induced hypersensitivity syndrome appears to be higher in elderly patients. There have been isolated reports of aplastic anaemia, agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, and leucocytosis.

Decreased serum-bicarbonate concentrations resulting in metabolic acidosis have been associated with zonisamide therapy and usually occurs early in treatment although it can develop at any time; it appears to be dose-dependent but can occur with doses as low as 25 mg daily. The incidence and severity appear to be greater in younger patients.

Other rare adverse effects have included renal calculi (see below), renal impairment, pancreatitis, rhabdomyolysis, abnormal liver function tests, psychosis, psychomotor slowing, reduced concentration, speech or language difficulties, and nystagmus. Reduced sweating with hyperthermia has occurred mainly in children (see below).

Effects on mental function. For a review of the effects of antiepileptic therapy including zonisamide on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Hyperthermia. Decreased sweating and hyperthermia have been reported in patients given zonisamide. By the end of December 2001 the manufacturers in the USA were aware of 40 such cases; of these, 38 had occurred in the first 11 years of marketing in Japan and 2 in the first year of marketing in the USA. Many cases were reported after exposure to high ambient temperatures and some progressed to heat stroke, but none had led to death.

The manufacturer noted that children appeared to be at an increased risk of developing these adverse reactions and should be monitored closely for such effects especially during warm or hot weather. Caution was also advised when zonisamide was given with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.[1]

1. O'Brien C [Elan Pharmaceuticals]. Important drug warning. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM171098.pdf (accessed 25/08/10)

Overdosage. A 20-year-old woman who ingested up to 8.7 g of zonisamide in a suicide attempt vomited twice about 3 hours later and presented with nausea, diffuse chest pain, blurred vision, dizziness, and mild headache 5 hours after ingestion;[1] she also had a 5-minute episode of seizure-like activity that recovered spontaneously. Plasma concentrations 5.5 and 48 hours after ingestion were 110 mg/L and 38 mg/L, respectively (the usual therapeutic concentration is 10 to 30 mg/L); half-life was calculated to be 30 hours. Previous case reports,[2,3] one fatal, of zonisamide overdosage were associated with more severe symptoms, however, other drugs had also been ingested.

1. Wightman RS, *et al*. Zonisamide toxicity in a patient with an intentional overdose. *Ann Pharmacother* 2011; **45:** 547.
2. Naito H, *et al*. Monitoring plasma concentrations of zonisamide and clonazepam in an epileptic attempting suicide by an overdose of the drugs. *Curr Ther Res* 1988; **43:** 463–7.
3. Sztajnkrycer MD, *et al*. Acute zonisamide overdose: a death revisited. *Vet Hum Toxicol* 2003; **45:** 154–6.

Renal calculi. Patients treated with zonisamide in the USA and Europe may have had a higher incidence of renal calculi than those treated in Japan. In one US study,[1] 4 of 113 patients (3.5%) receiving long-term treatment with zonisamide developed renal calculi, but a familial relationship was found for 2. In pooled data[2] from earlier studies, renal calculi had been reported in 13 of 700 patients (1.9%) treated in the USA and Europe compared with 2 of 1008 patients (0.2%) in Japan. Another review,[3] involving information from more than 750 patients, considered the risk of renal calculi in zonisamide-treated patients to be 5 to 9 times greater than that in the general population. However, a later study[4] that evaluated all safety data available at the time (from the US and European clinical trial programme and the manufacturer's postmarketing surveillance database) found the prevalence of symptomatic renal calculi to be low. There has been a report[5] of 3 patients who developed renal calculi associated with zonisamide but were able to continue therapy with hydration and/or citrate supplementation.

1. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; **11:** 37–67.
2. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; **45:** 760–87.
3. Bennett WM. Risk of kidney stones in patients treated with zonisamide. *Neurology* 2002; **58** (suppl 3): A298–A299.
4. Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? *Curr Med Res Opin* 2007; **23:** 1765–73.
5. Richards KC, *et al*. Continued use of zonisamide following development of renal calculi. *Neurology* 2005; **64:** 763–4.

Precautions

Zonisamide is a sulfonamide derivative and is therefore contra-indicated in patients with a history of hypersensitivity to sulfonamides. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

It should be used with care in patients with renal impairment; there is no data on safety in those with hepatic impairment. Zonisamide should be used with caution in patients who have risk factors for nephrolithiasis; adequate hydration is recommended to increase urine output, to try to reduce the risk of developing renal calculi, especially in predisposed patients.

Baseline and periodic measurements of serum-bicarbonate concentrations have been recommended during zonisamide treatment. If metabolic acidosis develops or persists, reducing the dose or stopping the drug should be considered. If treatment is continued, alkali therapy should be considered in patients with persistent acidosis. Zonisamide should be used with caution in those who are also taking carbonic anhydrase inhibitors.

Pancreatic lipase and amylase levels should be monitored in patients who develop pancreatitis and consideration should be given to withdrawing zonisamide. Patients who develop severe muscle pain or weakness, with or without fever, should have their serum creatine phosphokinase and aldolase levels assessed; if these are elevated, zonisamide may need to be withdrawn. A dietary supplement or increased food intake may be appropriate in patients who are losing weight or are underweight with zonisamide; withdrawing zonisamide may be warranted in those with substantial undesirable weight loss. Consideration should be given to withdrawing zonisamide in patients who develop unexplained rash.

Care is required when withdrawing zonisamide therapy—see also Uses and Administration p. 560.3.

Breast feeding. Zonisamide is distributed into breast milk;[1] in view of the potential for serious adverse effects in infants from zonisamide, licensed product information recommends that it should only be used in nursing mothers if the benefits outweigh the risks. It is also recommended that breast feeding must not be resumed until 1 month after stopping zonisamide therapy. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. Kawada K, *et al*. Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zonisamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. Zonisamide crosses the placenta.[1] For comments on the management of epilepsy during pregnancy, see p. 509.2.

1. Kawada K, *et al*. Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Use with drugs that induce or inhibit the cytochrome P450 isoenzyme CYP3A4 may alter plasma concentrations of zonisamide. Carbamazepine, phenytoin, or phenobarbital reduce the half-life of zonisamide; reductions have also been noted with valproate but to a lesser degree.

The use of zonisamide with other drugs that cause nephrolithiasis should be avoided because of the increased risk of developing renal calculi (see under Adverse Effects, p. 561.2). Caution is advised when zonisamide is used with other drugs known to cause heat-related disorders because of the increased risk of developing hyperthermia (see under Adverse Effects, p. 561.2), and with carbonic anhydrase inhibitors because of the increased risk of developing metabolic acidosis (see Precautions, p. 561.3).

References.
1. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48:** 435–41.

Pharmacokinetics

Zonisamide is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur within 2 to 6 hours of oral doses. Bioavailability is essentially complete; the presence of food does not affect the bioavailability of zonisamide but the time to reach peak plasma concentrations is delayed. Steady-state concentrations are achieved within 14 days. It is widely distributed into body tissues. Plasma protein binding is low (40 to 50%) but zonisamide is extensively bound to erythrocytes. The plasma elimination half-life is about 63 hours.

Zonisamide undergoes acetylation to *N*-acetylzonisamide and reduction mediated by the cytochrome P450 isoenzyme CYP3A4 to 2-sulfamoylacetylphenol (SMAP); both metabolites are inactive. Excretion is mainly in the urine; about 15 to 30% appearing as unchanged drug, 15% as *N*-acetylzonisamide, and 50% as the glucuronide of SMAP.

Zonisamide crosses the placenta and is distributed into breast milk.

The pharmacokinetics of zonisamide are affected by use with other antiepileptics (see Interactions, p. 561.3).

References.
1. Kochak GM, *et al.* Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. *J Clin Pharmacol* 1998; **38:** 166–71.
2. Mimaki T. Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Ther Drug Monit* 1998; **20:** 593–7.
3. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure* 2004; **13** (suppl 1): S5–S9.
4. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48:** 435–41.
5. Okada Y, *et al.* Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance. *Ther Drug Monit* 2008; **30:** 540–3.
6. Oles KS, Bell WL. Zonisamide concentrations during pregnancy. *Ann Pharmacother* 2008; **42:** 1139–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kinaplase; ***Austria***: Zonegran; ***Cz.***: Zonegran; ***Denm.***: Zonegran; ***Fr.***: Zonegran; ***Ger.***: Zonegran; ***Gr.***: Zonegran; ***Hung.***: Zonegran; ***Indon.***: Zonegran; ***Irl.***: Zonegran; ***Ital.***: Zonegran; ***Jpn***: Excegran; Trerief; ***Malaysia***: Zonegran; ***Neth.***: Zonegran; ***Norw.***: Zonegran; ***Philipp.***: Zonegran; ***Pol.***: Zonegran; ***Port.***: Zonegran; ***Spain***: Zonegran; ***Swed.***: Zonegran; ***Switz.***: Zonegran; ***Thai.***: Zonegran; ***Turk.***: Excegran; ***UK***: Zonegran; ***USA***: Zonegran.

Pharmacopoeial Preparations
USP 36: Zonisamide Tablets.

Antifungals

Aspergillosis, p. 563
Blastomycosis, p. 564
Candidiasis, p. 564
Chromoblastomycosis, p. 564
Coccidioidomycosis, p. 565
Cryptococcosis, p. 565
Dermatophytoses, p. 565
Endocarditis, p. 565
Eye infections, p. 565
Histoplasmosis, p. 566
Infections in immunocompromised patients, p. 566
Meningitis, p. 566
Mucormycosis, p. 566
Mycetoma, p. 567
Nail infections, p. 567
Paracoccidioidomycosis, p. 567
Peritonitis, p. 567
Pityriasis versicolor, p. 567
Pneumocystis pneumonia, p. 567
Protothecosis, p. 567
Respiratory-tract infections, p. 568
Skin infections, p. 568
Sporotrichosis, p. 568
Tinea, p. 569

This chapter describes the drugs that are used mainly in the treatment and prophylaxis of fungal infections (mycoses). They include:

- the azole derivatives, including:
  - imidazoles (such as ketoconazole)
  - triazoles (such as fluconazole, itraconazole, posaconazole, and voriconazole)
- the allylamines (naftifine and terbinafine)
- the echinocandins (such as anidulafungin, caspofungin and micafungin)
- several polyene antibiotics (including amphotericin B and nystatin)
- other antifungal antibiotics (for example griseofulvin)
- other compounds such as amorolfine, ciclopirox olamine, flucytosine, haloprogin, tolnaftate, and undecenoic acid and its salts.

Choice of Antifungal

Fungi may be classified as yeasts or moulds according to their appearance and means of growth. Examples of yeasts are *Candida* and *Cryptococcus* spp., while moulds include *Aspergillus* spp., the dermatophytes, and the Mucorales fungi. Some fungi are termed dimorphic as they appear to be yeast-like in the host, but grow as moulds *in vitro*. Blastomycosis, chromoblastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis are examples of diseases caused by dimorphic fungi.

Most fungi that are pathogenic in humans are saprophytic in nature, but cause infection when airborne spores reach the lungs or paranasal sinuses or are inoculated accidentally into the skin or cornea. Most fungal infections are therefore not transmissible between patients, with the exception of ringworm of the scalp. Endemic mycoses such as blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis are true pathogens and can cause disease in otherwise healthy persons. Other fungi, such as *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis jirovecii* are of low pathogenicity and require an alteration in the normal defence mechanisms for disease to occur; such disease is called opportunistic. Fungal diseases are classified into 3 groups: the superficial, subcutaneous, and deep or systemic mycoses. **Superficial** infections are confined to the skin, hair, nails, or mucous membranes. **Subcutaneous** infections are largely limited to the subcutaneous tissue but may spread to surrounding bone and skin. **Deep or systemic** infections may involve organs such as the lung, spleen, or brain, or may affect the body as a whole, and tend to occur more frequently in immunocompromised patients. Fungal infections may also be described as **local** when they are restricted to one body area, as **invasive** when there is spread into the tissues, or as **disseminated** when the infection has spread from the primary site to other organs throughout the body.

Ideally antifungal treatment should be chosen after the infecting organism has been identified, but it is often necessary to start empirical treatment before the pathogen can be cultured and identified, especially in immunocompromised patients in whom infections are often rapidly progressive.

The choice of treatment for the important fungal diseases is described below.

Aspergillosis

Aspergillosis[1] is an infection caused by fungi of the genus *Aspergillus*, usually *A. fumigatus*, although *A. flavus*, *A. nidulans*, *A. niger*, and *A. terreus* may occasionally be encountered. Aspergillosis is usually acquired by inhalation and most often causes non-invasive disease of the respiratory tract. Other sites of infection include the eye after trauma or cataract surgery. Tissue invasion adjacent to the site of infection and dissemination to distant organs may occur, mainly in immunocompromised patients. In severely immunocompromised patients aspergillosis usually presents as a severe acute rapidly progressive lung disease. Other organs affected may include the heart (particularly damaged or prosthetic valves), kidneys, bone, brain, liver, and skin.

In general the response of **invasive** aspergillosis to *treatment* is poor and early treatment is essential. Surgical excision may be necessary. High intravenous doses of amphotericin B have traditionally been the antifungal of choice.[2] However, the overall response rate to conventional amphotericin B is reported to be only 30 to 35%; this may be improved by the use of liposomal amphotericin B.[3,4] Studies have shown voriconazole to be better[5-7] than amphotericin B for the treatment of invasive aspergillosis and comparable[8] as empirical therapy for patients with persistent fever and neutropenia. Intravenous or oral voriconazole is now the recommended treatment for invasive pulmonary aspergillosis;[2,9-11] liposomal amphotericin B may be an acceptable first-line alternative for some patients.[9] Favourable responses with caspofungin have been reported in those with invasive disease[12] as well as in patients with persistent fever and neutropenia.[13] In neutropenic patients with prolonged fever despite broad-spectrum antibacterial therapy, empirical treatment with amphotericin B or its lipid formulations, itraconazole, voriconazole, or caspofungin is recommended.[9]

Drugs that may be used for salvage therapy include itraconazole, posaconazole, caspofungin, micafungin, and conventional or (preferably) lipid formulations of amphotericin B.[9] Salvage therapy may also include combination therapy with the initial antifungal drug or combination therapy with antifungal drugs from classes other than that used in the initial treatment regimen.[9] A retrospective review of patients given salvage therapy with voriconazole plus caspofungin or voriconazole alone reported that 3-month survival was greater for the combination than for voriconazole alone.[14] Successful treatment for invasive aspergillosis was also described in 2 patients given caspofungin with itraconazole.[15]

Treatment for invasive pulmonary aspergillosis should be given for a minimum of 6 to 12 weeks; in immunosuppressed patients, it should be continued throughout the period of immunosuppression and until the lesions have cleared.[9] In HIV-infected adults, therapy should continue at least until the CD4+ T lymphocyte count has risen above 200 cells/microlitre, and there is evidence of clinical response.[10]

Antifungal *prophylaxis* with posaconazole is recommended for haematopoietic stem cell transplant recipients with graft-versus-host disease and in patients with acute myeloid leukaemia or myelodysplastic syndromes who are at high risk for invasive aspergillosis. Itraconazole may be useful, but it is not well tolerated.[2,9,16]

Non-invasive forms of aspergillosis include allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to *Aspergillus* usually occurring in asthmatic patients, and aspergilloma, a fungal mass or ball developing within a pre-existing pulmonary cavity or paranasal sinus.

Allergic bronchopulmonary aspergillosis is usually treated with corticosteroids and oral itraconazole.[9,17] A systematic review[18] has concluded that itraconazole modifies the immunological activation associated with allergic bronchopulmonary aspergillosis in asthmatic patients and improves clinical outcome in the first 4 months of treatment.

The treatment of **aspergilloma** depends on the severity of symptoms, and includes conservative management, antifungal therapy, or surgical resection. Treatment with itraconazole, voriconazole, and possibly also posaconazole are considered to have some benefit. Surgical resection and direct intracavitary instillation of antifungals may also be useful in selected patients with a single aspergilloma.[9]

Chronic necrotising pulmonary aspergillosis (CNPA or subacute invasive pulmonary aspergillosis)[19] is a subacute infection seen in patients with an underlying lung disease or systemic risk factors for immunosuppression. Case reports have shown amphotericin B to be successful in about 50% of patients and clinical benefit has also been achieved with intracavitary amphotericin B. Flucytosine has been used with or without amphotericin B. Itraconazole has a reported success rate of 70 to 90%. Voriconazole was also reported to be effective in non-immunocompromised patients with chronic pulmonary aspergillosis,[20] including some with necrotising disease. Evidence therefore supports the use of itraconazole, with voriconazole and possibly also posaconazole as alternatives, for the treatment of CNPA.[9] Treatment needs to be prolonged, so oral antifungals are preferred to parenteral antifungal therapy.

Aspergillosis of the **eye**, like other fungal eye infections, is difficult to treat; antifungals are generally not well absorbed after topical application and infections extending into the vitreous or anterior chamber require subconjunctival, intra-ocular, and/or systemic treatment. Systemic treatment is necessary for ocular manifestations of disseminated disease. Intravenous and intravitreal amphotericin B are recommended for the treatment of *Aspergillus* endophthalmitis; intravitreal or systemic voriconazole may be given as an alternative. For the management of *Aspergillus* keratitis topical antifungal therapy plus systemic antifungal therapy with either amphotericin B, voriconazole, or itraconazole is recommended.[9] For superficial eye infections several drugs including natamycin, amphotericin B, azoles, and sulfadiazine silver have been applied topically alone or as an adjunct to systemic therapy. Surgical excision of infected tissue may be necessary in severe infections.

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7. Steinbach WJ, *et al.* Infections due to Aspergillus terreus: a multicenter retrospective analysis of 83 cases. *Clin Infect Dis* 2004; **39:** 192–8.
8. Walsh TJ, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346:** 225–34.
9. Walsh TJ, *et al.* Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 327–60.
10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 17/09/13)
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20. Camuset J, *et al*. Treatment of chronic pulmonary aspergillosis by voriconazole in nonimmunocompromised patients. *Chest* 2007; **131:** 1435–41.

Blastomycosis

Blastomycosis (not to be confused with South American blastomycosis, see Paracoccidioidomycosis, p. 567.1) is an infection caused by the fungus *Blastomyces dermatitidis*, which is endemic to much of North America. Inhalation of spores results in pulmonary infection which may be followed in 25 to 40% of patients by dissemination; the skin, skeleton, and genito-urinary system may become infected. While blastomycosis may affect anyone living in an endemic area, disseminated disease (including CNS involvement) is more common in immunocompromised patients.

Acute pulmonary infection may be mild and self-limiting in immunocompetent patients, but treatment should be considered in patients presenting with clinical symptoms. All patients with moderate to severe pneumonia or disseminated disease, and all immunocompromised patients require treatment.[1]

In immunocompetent patients, mild to moderate disease is treated with oral itraconazole; the duration of treatment is at least 6 months for pulmonary disease and 12 months for bone disease. Ketoconazole or fluconazole are less effective alternatives (and ketoconazole is more toxic); the role of voriconazole or posaconazole is not clear,[1] although they may be effective. Patients unable to tolerate azoles or in whom disease progresses should be switched to amphotericin B.[1] Life-threatening disease (either pulmonary or extrapulmonary) should be treated intravenously with a lipid or conventional formulation of amphotericin B; patients are usually switched to oral itraconazole once stabilised.[1] All patients with CNS disease should be given a lipid formulation of amphotericin B intravenously for 4 to 6 weeks, followed by an oral azole; the options for the latter include fluconazole, itraconazole, or voriconazole but some favour the use of voriconazole.[2] Oral treatment should be continued for at least 12 months and until resolution of abnormalities in the CSF.[1]

In patients who are immunosuppressed, the recommended initial treatment is a lipid formulation of amphotericin B given intravenously for 1 to 2 weeks, or until improvement is noted. Once the patient has responded to this initial treatment they may be switched to oral itraconazole, which is continued until at least 12 months of therapy has been given. Life-long itraconazole treatment may be needed in patients in whom immunosuppression cannot be reversed, or in those who relapse despite appropriate therapy (a well-documented phenomenon in immunosuppressed patients).

In pregnant patients presenting with blastomycosis a lipid formulation of amphotericin B is recommended; azoles should be avoided because of possible teratogenicity. If the neonate shows signs of infection, treatment with a conventional (deoxycholate) formulation of amphotericin B is recommended. Children may be treated with amphotericin B or oral itraconazole, depending on the severity of infection; in general, they tolerate conventional amphotericin B better than adults, and lipid formulations may not be needed.

1. Chapman SW, *et al*. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 1801–12. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/588300 (accessed 03/07/08)
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Candidiasis

Candida spp. are commensal fungi commonly found in the gastrointestinal tract, mouth, and vagina; they may become pathogenic when natural defence mechanisms are impaired. *C. albicans* is the species most commonly associated with infection although infections with other *Candida* spp., notably *C. glabrata* (*Torulopsis glabrata*), *C. krusei*, *C. lusitaniae*, *C. parapsilosis*, and *C. tropicalis*, also occur and together are commonly referred to as non-*albicans* species. Predisposing factors for candidiasis include antibacterial therapy, skin or mucosal breach, abdominal surgery, debility, diabetes mellitus, pregnancy, and neutropenia and T-cell immunodeficiency; candidiasis often occurs in patients with HIV infection.

Candidiasis (or candidosis) may be classified as mucocutaneous (or superficial), invasive (deep-organ), or disseminated.

Mucocutaneous candidiasis includes infections of the oropharynx, genital organs, and skin. Oropharyngeal and vulvovaginal candidiasis are commonly termed thrush. Most superficial infections may be effectively treated with topical antifungals, although the rare chronic mucocutaneous candidiasis syndrome usually requires systemic treatment. The choice of antifungal should be guided by the availability of an appropriate formulation for the site of infection, toxicity, and the duration of treatment.

Oropharyngeal candidiasis may be treated with topical clotrimazole, miconazole, or nystatin, or oral fluconazole. Topical therapy may not be adequate in severely immunocompromised patients or in those with moderate to severe infection, and oral fluconazole generally is preferred in these patients.[1-3] Oral posaconazole or itraconazole solution are suitable alternatives, particularly for fluconazole-refractory infection.[1-3] Oral posaconazole was found to be as effective as oral fluconazole in the treatment of oropharyngeal candidiasis in HIV-infected persons, but more effective than fluconazole in sustaining clinical benefit after treatment was stopped;[4] it is generally better tolerated than itraconazole.[2,3] Oral amphotericin B suspension may also be considered for fluconazole-refractory infection.[1-3] Intravenous amphotericin B, voriconazole, and the echinocandins are usually effective for oropharyngeal candidiasis, but generally are reserved for use when other agents fail or are not tolerated.[1,3]

Oesophageal infections are not normally accessible to topical therapy and oral or intravenous fluconazole[1-3] or oral itraconazole[2,3] are considered to be the drugs of choice. Severe or refractory disease may be treated with oral posaconazole, oral or intravenous voriconazole, an intravenous echinocandin, or intravenous amphotericin B.[1-3]

Vulvovaginal candidiasis responds well to topical antifungal treatment with creams or pessaries. Uncomplicated vaginitis responds to short-course topical therapy with azoles such as butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, terconazole, or tioconazole, to topical nystatin, or to oral therapy with fluconazole or itraconazole.[1,5,6] Complicated vulvovaginal candidiasis may occur in up to 10% of cases, and includes disease that is severe, recurrent, caused by non-*albicans* candida, or that occurs in a compromised patient (such as those who are pregnant or have an underlying debilitating medical condition).[1,5,6]

- *Severe* disease will generally require at least 7 to 14 days of treatment with a topical azole[1,5] or high-dose oral fluconazole given twice[5,6] or 3 times[1] at 72 hour intervals. Alternatively, use of a single dose vaginal pessary with a second dose given after 72 hours can be considered.[6]
- For *recurrent* disease (at least 4 symptomatic episodes in a 1-year period) therapy consists of induction, followed by a 6-month maintenance regimen. For induction, 3 doses of high-dose oral fluconazole (given at 72 hour intervals) are recommended; alternatively, 7 to 14 days of topical azole therapy, or 10 to 14 days of oral azole therapy can be used.[1,5,6] Recommended maintenance regimens include high-dose oral fluconazole given once weekly,[1,5,6] oral fluconazole, itraconazole, or ketoconazole given daily,[6] or intermittent topical azoles,[1,5] such as weekly use of a clotrimazole vaginal pessary.[1,6]
- Vulvovaginal candidiasis with non-*albicans* species may not respond to azoles, in which case topical use of nystatin,[6] boric acid,[1,5,6] or flucytosine (alone, or with amphotericin B)[1,6] are often effective; longer treatment courses may be necessary, and 7 to 14 days has been recommended.
- Among *compromised patients* with vulvovaginal candidiasis, a more prolonged (7 to 14 days) conventional antimycotic regimen is again recommended.[5] Treatment regimens for HIV-infected women generally should not differ from those of HIV-uninfected women.[1,5] In pregnancy, topical azoles are recommended[5,6] and appear to be more effective than nystatin;[7] treatment is given for 7 days.

Yogurt preparations containing *Lactobacillus* spp. have been used in the treatment and prevention of vaginal candidiasis in an attempt to restore the natural vaginal flora but evidence to support their use is limited.

Candidal balanitis in men usually responds well to treatment with topical antifungals,[5] generally for 10 to 14 days. Alternatively, a single oral dose of high-dose fluconazole can be considered.

Primary ***prophylaxis*** against mucocutaneous candidiasis is generally not recommended for patients with advanced HIV infection since this may select for resistant *Candida* spp.[2,3] Due to similar concerns, secondary prophylaxis in other patients with mucocutaneous candidiasis is largely restricted to those with frequent or severe recurrences, or those at risk of developing invasive disease, in which case oral fluconazole or itraconazole may be considered.[1,3]

Invasive and **disseminated** candidiasis require systemic antifungal treatment. Intravenous amphotericin B, with or without flucytosine, has traditionally been regarded as the standard initial treatment in most infections but flucytosine is now infrequently used, except in combination treatment of more serious, invasive infections such as meningitis or endocarditis, because of concerns over its bone-marrow toxicity in AIDS patients. Fluconazole, voriconazole, amphotericin B, and the echinocandins have all been shown to be effective and now offer alternatives for initial antifungal therapy. Either fluconazole or an echinocandin have been suggested for first-line treatment of candidaemia, although the echinocandins may be preferred for more severe infection, those with recent azole exposure, or when infection with *C. glabrata* or *C. krusei* is suspected. Conventional or lipid formulations of amphotericin B are considered appropriate for refractory infections, or where intolerance or resistance limits the use of the more preferred antifungals; it should also be considered for patients suspected to have concomitant candidal meningitis.[1] Neonates with disseminated candidiasis are usually best treated with amphotericin B, although lipid formulations should only be considered where urinary-tract involvement is ruled out. Fluconazole may also be effective.[1,8]

Empirical antifungal therapy may be necessary for persistently febrile neutropenic patients and for non-neutropenic, critically ill patients with unexplained fever and risk factors for invasive candidiasis. Drugs that may be considered for neutropenic patients include caspofungin, amphotericin B (preferably a lipid formulation), or voriconazole. Itraconazole and fluconazole are alternatives, but the latter is considered less suitable due to its restricted antifungal spectrum; azoles should not be used for empirical therapy in patients who have used them for prior prophylaxis.[1] Treatment should generally be continued until signs and symptoms have resolved and the patient is no longer neutropenic. For empirical antifungal treatment in non-neutropenic patients, treatment with fluconazole or an echinocandin has been suggested;[1] echinocandins are preferred where the patient is more seriously ill, recently azole-exposed, or at risk of infection caused by fluconazole-resistant *Candida*. When first-line antifungals are unavailable or ineffective, amphotericin B is a suitable alternative.[1]

Although antifungal ***prophylaxis*** is generally not routinely recommended for non-neutropenic patients, some would consider it appropriate in patients who are at high risk of infection such as patients who are critically ill, neutropenic, or receiving solid organ or bone marrow transplants.[1,9] There is also limited evidence to suggest that prophylactic fluconazole, generally for the first 4 to 6 weeks of life, may reduce the risk of invasive fungal infections (including candidiasis) in very low birth-weight neonates;[10] routine prophylaxis has therefore been recommended by some experts for premature and extremely low birth-weight (less than 1000 g) neonates born in nurseries with a high incidence of invasive candidiasis.[1]

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Chromoblastomycosis

Chromoblastomycosis (chromomycosis) is a chronic fungal infection that affects skin and subcutaneous tissue. It occurs worldwide but is more common in tropical and subtropical climates. Chromoblastomycosis may result from traumatic inoculation of several fungal species including *Fonsecaea compacta* (*Phialophora compacta*), *F. pedrosoi* (*P. pedrosoi*), *Exophiala spinifera*, *E. jeanselmei*, *Phialophora verrucosa*, *Cladosporium carrionii*, and *Rhinocladiella aquaspersa*. In its early stages, when lesions are small, surgical excision or cryotherapy are the treatments of choice, although there is some risk of dissemination during surgery. Many antifungals have been tried but itraconazole and terbinafine, often in high doses and for prolonged periods, have been the most successful. However, recurrence and drug resistance has

been a problem with monotherapy. Itraconazole and terbinafine (given daily on alternate weeks or daily concomitantly for up to 9 months) have been shown to be effective in selected cases of chromoblastomycosis that were unresponsive to monotherapy. Local heat treatment aids healing and may be a useful adjunct.

Coccidioidomycosis

Coccidioidomycosis is an infection caused by inhalation of the spores of *Coccidioides immitis* or *C. posadassi*, fungi found in the soil in arid and semi-desert areas mainly of North, Central, and South America. Common names for the infection include valley fever, desert fever, and desert rheumatism. In endemic areas, coccidioidomycosis is a common opportunistic infection in immunocompromised patients.

Patients with coccidioidomycosis may have acute or chronic lung infections, meningitis, and disseminated disease although many infections are subclinical. In immunocompetent individuals, acute pulmonary disease is usually mild and self-limiting and in 60% of cases resolves without specific chemotherapy. In some patients the infection progresses to chronic pulmonary coccidioidomycosis with granulomatous lesions, fibrosis, and cavitation. Less than 1% of patients develop acute progressive pneumonia (which is commonly fatal if untreated) or disseminated disease (usually involving the skin, bone, meninges, and joints). Severe pulmonary and disseminated infections are more likely in pregnant women, males, certain ethnic groups, diabetics, and immunocompromised patients.

Because the spectrum of disease varies widely, the decision to treat coccidioidomycosis must be individualised, taking into account the severity of infections and risk factors for more serious disease (particularly immunosuppression).[1] If antifungal therapy is given, it is preferably with an oral azole as initial therapy or with intravenous amphotericin B;[1-4] of the azoles, itraconazole and fluconazole are generally preferred,[2,4] while voriconazole[5,6] and posaconazole[6-9] have been reported to be effective in some patients who have not responded to conventional therapy. Amphotericin B is generally used as initial therapy for rapidly progressive non-meningeal disease while azoles are generally preferred for chronic or subacute disease.[1,2] Although combination therapy with a n azole and amphotericin B has been used,[1,2] there is no evidence that it is superior to a single antifungal drug.[1] Fluconazole is effective in meningeal infections and is the most frequently recommended antifungal for this indication,[1-3,5] although itraconazole has also produced beneficial responses; intrathecal amphotericin B may also be used, especially in aggressive infections.[1-3] Due to the high incidence of relapse, indefinite suppressive therapy with fluconazole or itraconazole is recommended for patients with coccidioidal meningitis or diffuse pulmonary coccidioidomycosis.[1-3]

Patients with **HIV** infection and **solid organ transplant** recipients who have completed induction therapy should subsequently receive lifelong suppressive fluconazole or itraconazole.[2,10] It may, however, be possible to stop after 12 months total therapy in HIV-infected patients on antiretroviral therapy with sustained CD4+ T lymphocyte counts above 250 cells/microlitre (except in those with meningitis or diffuse pulmonary disease) if there is clinical evidence that the coccidioidal infection is controlled.[2] Primary prophylaxis for HIV-infected adult patients living in coccidioidomycosis-endemic areas is generally only recommended for those with positive IgM or IgG serology and CD4+ T lymphocyte counts below 250 cells/microlitre.[1,2] If prophylaxis is given, it is usually with oral fluconazole.[2] It may also be considered for solid organ transplant recipients who are at risk of coccidioidal infection.[1,10]

The management of **pregnant** women is complicated by the fact that azole antifungals are considered to be teratogenic when given at high doses early in pregnancy (see Pregnancy, under Precautions of Fluconazole, p. 579.3). Recommendations have therefore been published for the management of coccidioidomycosis during pregnancy.[11] Broadly, these are as follows:

- for recent or active non-meningeal infections, amphotericin B based treatment should be given to those in the first trimester; for those in the second or third trimester, azole antifungals or amphotericin B based treatment may be given
- for meningeal infections, intrathecal amphotericin B should be given in the first trimester with azole antifungals being an alternative; for those in the second or third trimester, azole antifungals or intrathecal amphotericin B may be given

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Cryptococcosis

Cryptococcosis is an infection caused by inhalation of the fungi *Cryptococcus neoformans*. or *C. gattii*; it is an important opportunistic infection affecting immunocompromised patients, including those infected with HIV or receiving immunosuppressive drugs, but may rarely afflict apparently immunocompetent individuals. The presentation and severity of cryptococcal disease is often determined by the immune status of the patient and can vary widely, from asymptomatic pulmonary infection to severe CNS or disseminated disease; among HIV-infected individuals, meningitis is the most common presentation.

In immunocompetent and most immunocompromised patients, mild, non-meningeal infections involving a single site such as the lung or skin can generally be ***treated*** with oral fluconazole; for pulmonary infection in immunocompetent patients, itraconazole, voriconazole, and posaconazole are suitable alternatives. Treatment should be continued for 6 to 12 months. In severely immunocompromised individuals, however, mild infections are much more likely to lead to disseminated disease, and therefore should always be treated as severe (see below).[1]

In all patients, severe or disseminated infection and cryptococcal meningitis require a step-wise approach to management that includes induction therapy, followed by consolidation, and then maintenance treatment.

- **Induction therapy** is usually based on amphotericin B and flucytosine.
  - *HIV-infected individuals*[1-3] should generally receive intravenous amphotericin B plus oral or intravenous flucytosine for at least 2 weeks; a lipid formulation is preferred, especially if renal toxicity is a concern.[2] Conventional and lipid formulations of amphotericin B may also be given alone (for 4 to 6 weeks), or with fluconazole (for at least 2 weeks) in patients unable to tolerate flucytosine. Similarly, high-dose fluconazole (see p. 578.3) with flucytosine (for 4 to 6 weeks) may be considered for patients intolerant or refractory to amphotericin B,[1-3] but carries a high risk of toxicity. In some cases fluconazole monotherapy can be considered, but success rates are generally low unless high doses are used.[1]
  - In *solid organ transplant recipients*, lipid formulations of amphotericin B with flucytosine are preferred[1,4,5] due to the high incidence of pre-existing renal dysfunction and frequent use of nephrotoxic medications among such patients.[1,4] Alternatively amphotericin B (lipid or conventional formulation) may be used alone but should be given for at least 4 to 6 weeks.[1]
  - There is less evidence available to guide the choice of induction therapy in *non-HIV infected, non-transplant patients* (including those who are apparently immunocompetent), however, a lipid or conventional formulation of amphotericin B given with flucytosine for at least 4 weeks is usually sufficient;[1] if amphotericin B is given alone, a minimum of two further weeks of therapy should be considered.
- **Consolidation** therapy is required after successful induction therapy in all patients with severe or disseminated cryptococcosis or cryptococcal meningitis, and 8 weeks of oral or intravenous fluconazole is generally recommended.[1-4] Alternatively, oral itraconazole might be considered for HIV-infected patients, but potential drug interactions with antiretrovirals are a concern.[2,3]
- The regimen for **maintenance** therapy in severe disease again depends on the patient's underlying immune status.
  - *Immunocompetent*, and *immunocompromised, non-HIV infected* patients should receive 6 to 12 months of maintenance therapy with oral fluconazole.[1,4]
  - For *HIV-infected patients*, maintenance therapy (secondary prophylaxis) is generally life-long;[1-3] oral fluconazole is preferred but alternatives include oral itraconazole[1,3] or weekly, intravenous amphotericin B.[1] It may be possible to stop maintenance therapy in patients who have received antifungal therapy for at least 12 months,[1] who have shown a sustained response to HAART for more than 6 months,[3] and who remain asymptomatic with regard to cryptococcosis. US guidelines[1-3] recommend restarting secondary prophylaxis if the CD4+ T lymphocyte count falls below 100 to 200 cells/microlitre.

Primary prophylaxis in patients with HIV infection[1-3] or after solid organ transplantation[1,4] is not generally recommended since it has not been shown to be more beneficial than treating cryptococcal infections when they occur and may increase the risk of resistance.

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Dermatophytoses

See under Skin Infections, p. 568.1.

Endocarditis

Infective endocarditis caused by fungi such as *Aspergillus* or *Candida* is much less common than that caused by bacteria (p. 179.2); it most frequently occurs among intravenous drug users, the immunosuppressed,[1,2] or those with a prosthetic heart valve.[1,3]

Mortality due to fungal endocarditis is high. Patients should be treated with antifungal therapy and in most cases surgical removal of the infected heart valve.[1-3] Amphotericin B has commonly been used, usually alone but in some cases combined with flucytosine[1,4-6] or an azole.[2] Alternatives for endocarditis caused by *Candida* spp. are fluconazole or caspofungin. Voriconazole may now be the drug of choice for endocarditis caused by *Aspergillus* spp.[1] Initial treatment regimens should continue for at least 6 weeks, but in many cases considerably longer is needed.[1,3] Since relapse rates of up to 40% have been reported after stopping therapy, secondary prophylaxis is recommended with fluconazole, itraconazole, posaconazole, or voriconazole (depending on the susceptibilities of the infecting organism) for a minimum of 2 years and in some cases for life. Lifelong suppressive therapy is also given to patients who are not suitable candidates for valve replacement.[3-7]

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Eye infections

Fungal infections of the eye are less common than infections with bacteria or viruses, but are usually severe and may lead to loss of vision. Diagnosis may be delayed due to a gradual onset of symptoms and empirical treatment with antibacterials. Patients with impaired host resistance such as diabetics or immunocompromised patients are particularly

at risk. The most common fungi causing eye infections are *Aspergillus, Candida,* and *Fusarium;* others include *Blastomyces, Cryptococcus,* and *Sporothrix*. Corneal infection (keratitis) occurs most frequently, but the orbit, eyelids, lachrymal sacs, conjunctiva, sclera, and intra-ocular structures may also become infected. Infections of the orbit rarely occur spontaneously but are more common with systemic fungal infection or may spread from the adjacent paranasal sinus tissue, as seen in mucormycosis or aspergillosis.[1,2]

Ocular fungal infections are difficult to treat. Diagnosis may be delayed due to a gradual onset of symptoms and empirical treatment with topical antibacterials or corticosteroids. Topical natamycin is generally considered the drug of choice for fungal keratitis due to filamentous fungi, while topical amphotericin B is an alternative. Topical amphotericin B with or without topical flucytosine, is preferred for yeast infections. Azoles have a wide spectrum of activity and clotrimazole, fluconazole, itraconazole, ketoconazole, and miconazole are all used topically; topical posaconazole and voriconazole have also been used in some case reports.

Topical antifungals are not well absorbed and infections extending into the eye require subconjunctival, intraocular, or systemic therapy. Systemic treatment may also be indicated when there is a poor response to topical agents, for fungal endophthalmitis, or for ocular manifestations of disseminated fungal disease. When systemic treatment is indicated intravenous amphotericin B is usually given. Azoles may be given for less severe infections or as adjunctive therapy in severe infections. Oral fluconazole and ketoconazole have better penetration into the cornea, aqueous humour, and vitreous humour than itraconazole. Intravitreal injections may be required in infections unresponsive to systemic antifungals.[3,4] For refractory infections, oral posaconazole, systemic voriconazole, and combinations of these with various topical or intravitreal drugs have been effective in some case reports; combination intravenous therapy with voriconazole and caspofungin has also been successfully used.[5]

Surgical debridement or excision may be necessary if the infection progresses despite appropriate antifungal therapy.[1,2]

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Histoplasmosis

Histoplasmosis is a systemic infection caused by *Histoplasma capsulatum,* a fungus found in the soil in endemic areas, particularly at sites with heavy accumulations of bird or bat excrement. Infection is by inhalation of spores. Two types of histoplasmosis occur:

- American histoplasmosis, due to infection with *H. capsulatum* var. *capsulatum*
- African histoplasmosis, due to infection with *H. capsulatum* var. *duboisii*

H. capsulatum var. *capsulatum* is endemic in the central USA where 50 to 90% of the population is infected. Mild infections are generally asymptomatic. However, acute pulmonary infection can occur. Massive infection can be fatal. Chronic pulmonary histoplasmosis can result in lung fibrosis and cavitation. Acute or chronic disseminated infection involving widespread infiltration of the reticuloendothelial system, is mainly seen in immunodeficient or immunocompromised patients.

Histoplasma capsulatum var. *duboisii* is found in Africa and may cause a chronic disseminated form of histoplasmosis with focal lesions mainly in skin and bone.

Antifungal **therapy** for histoplasmosis is necessary in patients with severe acute pulmonary infections, chronic pulmonary disease, or disseminated infection.

Infections which are not life-threatening but not resolving spontaneously may be treated with an oral azole in both immunocompetent and immunocompromised patients.[1,2] Itraconazole is the preferred drug.[1-3] Ketoconazole is moderately effective but more toxic. Fluconazole is less effective than either itraconazole or ketoconazole.[2-4] Posaconazole[3] and voriconazole[2,3] have shown benefit in some cases. Patients with chronic cavitary pulmonary histoplasmosis should be treated with oral itraconazole for a minimum of 1 year.[1]

Patients with moderately severe to severe acute pulmonary histoplasmosis may be treated with intravenous liposomal amphotericin B for 1 to 2 weeks followed by oral itraconazole for a total of 12 weeks. Conventional intravenous amphotericin B may be given as an alternative. The same treatment regimen is recommended for those with progressive disseminated disease; oral itraconazole in these patients should be continued for 12 months.[1-3] Patients with CNS histoplasmosis should be given intravenous liposomal amphotericin B for 4 to 6 weeks, followed by oral itraconazole for a minimum of 1 year.[1-3] Immunocompromised patients with disseminated disease, including those with HIV infection, may need to continue maintenance therapy indefinitely, generally with daily oral itraconazole,[1-3] if immunosuppression cannot be reversed;[1] similar lifelong suppressive therapy should be considered for HIV-infected patients with CNS histoplasmosis,[3] and for patients with disease relapse despite appropriate treatment.[1-3] Intravenous amphotericin B given once weekly has also been suggested for chronic maintenance therapy.[5]

Primary prophylaxis with itraconazole is not recommended routinely but may be considered for adults and adolescents with advanced AIDS at especially high risk of infection due to occupational exposure or residence in a hyperendemic area.[2,3]

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Infections in immunocompromised patients

Immunocompromised patients are at increased risk of infections, including those caused by fungi. Fungi most commonly affecting AIDS patients include *Cryptococcus neoformans, Pneumocystis jirovecii* and *Candida albicans* while those associated with immunosuppressive therapy and cancer are mainly *Aspergillus* and *Candida* spp. Immunocompromised patients are also at increased risk of endemic mycoses, such as coccidioidomycosis, histoplasmosis, and *Penicillium marneffei* as well as a growing number of uncommon fungi reported to cause invasive infections, including *Fusarium, Scedosporium,* and *Trichosporon* species.

Fungal infections in immunocompromised patients are often invasive or disseminated and treatment should start as early as possible. A fungal cause of infection should be considered in patients with persistent febrile neutropenia who have not responded to broad spectrum antibacterials. If the infection has not been identified, **empirical treatment** should be started. Conventional intravenous amphotericin B has been considered first-line empirical therapy and is no less effective than lipid formulations. Fluconazole, itraconazole, voriconazole, and caspofungin appear at least as effective as amphotericin B. For patients with renal impairment lipid formulation of amphotericin B or voriconazole may be given. For patients not responding to an amphotericin B formulation voriconazole, itraconazole, or caspofungin are alternatives. Fluconazole may be considered for low risk patients infected with susceptible *Candida* species.

The benefit and role of **primary prophylaxis** in the management of fungal infections associated with HIV, cancer, and organ transplants is controversial as this may select for resistant isolates and species not susceptible to the antifungals used. This is of particular concern with fluconazole (see Resistance, p. 580.2), one of the drugs most widely used for this purpose. Fluconazole has been shown to be effective as primary prophylaxis against invasive candidiasis but not aspergillosis. Itraconazole, posaconazole, or voriconazole may be preferred for patients at risk of invasive aspergillosis, such as patients being treated for graft-versus-host disease or CMV disease.

Long term suppressive therapy has been recommended for immunocompromised patients with proven or probable invasive aspergillosis or candidiasis. **Secondary prophylaxis** may be stopped when patients are no longer profoundly neutropenic.

Antifungals are also used in selective digestive tract decontamination (see Intensive Care, p. 187.3).

Treatment and prophylaxis of specific fungal infections in immunocompromised patients is discussed under the appropriate headings—see Aspergillosis (p. 563.1), Candidiasis (p. 564.1), Coccidioidomycosis (p. 565.1), Cryptococcosis (p. 565.2), and Histoplasmosis (above), and Pneumocystis Pneumonia (p. 567.2).

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Meningitis

Fungal diseases associated with meningitis include aspergillosis (see p. 563.1), candidiasis (see p. 564.1), coccidioidomycosis (see p. 565.1), cryptococcosis (see p. 565.2), and histoplasmosis (see above), although many disseminated fungal infections can involve the CNS, especially in immunocompromised patients. The treatment of each infection is discussed under the appropriate heading, but in general the initial drug of choice in fungal meningitis is intravenous amphotericin B, sometimes with flucytosine.

Mucormycosis

Mucormycosis,[1-6] a rare but invasive and rapidly progressive infection caused by Mucorales fungi, is a form of zygomycosis, a term that is sometimes used synonymously. Mucormycosis usually acquired by inhalation of spores, although trauma and ingestion may also be routes of infection. It usually occurs in immunocompromised patients, or in patients at risk of metabolic acidosis (including those with poorly-controlled diabetes or renal failure). Patients given desferrioxamine may also be at increased risk of infection (see Infection Susceptibility, p. 1547.2). Infections of the mucosa of the respiratory tract or gastrointestinal tract, or of abraded skin, usually with *Rhizopus* or *Rhizomucor* spp., can result in local invasion of deeper tissues including bone and the CNS, with extensive tissue destruction. Disseminated disease may also occur.

The **treatment** of mucormycosis includes a combination of antifungal therapy, surgical debridement when possible, and management of the underlying disease. Invasive or disseminated disease is difficult to treat and is usually fatal. The standard antifungal therapy is relatively high doses of intravenous amphotericin B in standard, or (preferably) lipid formulations; as well as having lower toxicity, the latter may produce better response rates.[6] Fluconazole, itraconazole, ketoconazole, or voriconazole are not considered to have a role in the treatment of mucormycosis, although the newer triazoles, posaconazole and ravuconazole, have reported *in-vitro* activity against zygomycetes and posaconazole has been tried in patients with refractory disease. Although the echinocandins appear to have no *in-vitro* activity against mucorales fungi, concomitant use of caspofungin was found to improve the response to lipid formulations of amphotericin B in a small study of patients with rhino-orbital-cerebral mucormycosis.[7]

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Mycetoma

Mycetoma[1-4] is a localised infection found worldwide, but most commonly in the tropics and subtropics. Infection mainly results from trauma to the skin, and may spread locally through the lymphatic system to surrounding tissues, progressively destroying connective tissue (fascia) and bone. It is characterised by painless soft-tissue swelling, draining sinus tracts, and discharge of grains composed of large aggregates of filaments (fungal or actinomycete). The foot is most often affected (70 to 80% of cases), less often hand (12%), legs, and knee joints. The term Madura foot is used for mycetoma affecting the foot. Mycetomas may be caused by various organisms; those caused by fungi such as *Madurella mycetomatis, M. grisea,* or *Pseudallescheria boydii* are called eumycetomas. Those caused by the filamentous bacteria, actinomycetes, are called actinomycetomas and are discussed on p. 193.1.

Eumycetomas do not heal spontaneously and are poorly responsive to treatment. They often require both surgical excision and antifungal therapy. Itraconazole or ketoconazole are recommended as first-line antifungals for eumycetomas and the duration of treatment depends on the severity of the infection and ranges from a few months to years. Itraconazole has resulted in good clinical responses and low recurrence rates. Use of oral voriconazole for up to 16 months has also been successful in some case reports.[5-7] Treatment with antifungals before surgery results in lesions that are localised and encapsulated and easier to excise during surgery.[1,2]

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Nail infections

See under Skin Infections, p. 568.1.

Paracoccidioidomycosis

Paracoccidioidomycosis (South American blastomycosis) is caused by an infection with the fungus *Paracoccidioides brasiliensis.* The disease occurs mainly in inhabitants of Central and South America. Infection is thought to be by inhalation and may remain dormant for long periods. While most primary infections are subclinical, some may be progressive and severe, particularly in immunocompromised patients. Paracoccidioidomycosis usually presents as a chronic infection affecting the lungs. Disseminated disease may affect the skin, mucous membranes, gastrointestinal tract, reticuloendothelial system, and adrenals, and may be acute or chronic. Relatively mild cases may be treated with oral itraconazole, or alternatively ketoconazole, for 6 to 12 months or longer.[1] Itraconazole allows shorter treatment courses and lower doses than ketoconazole; relapse rates are also lower. A small open-label study reported that oral voriconazole was as effective as oral itraconazole for long-term treatment of paracoccidioidomycosis.[2] More severe infections or those not responding to azoles are treated with intravenous amphotericin B followed by maintenance azole therapy.[1] Sulfonamides are now used less often since more effective drugs are available. Terbinafine has been used successfully when access to azoles was not possible.[3]

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Peritonitis

Fungal peritonitis may be a complication of peritoneal dialysis, abdominal surgery, or trauma. It is usually caused by yeasts such as *Candida* and rarely moulds such as *Aspergillus.* Fungal peritonitis is associated with considerable mortality and morbidity (including the development of adhesions and other complications that preclude further peritoneal dialysis). Diagnosis and treatment can be difficult.

Amphotericin B is often used to **treat** fungal peritonitis;[1-4] intravenous dosage has been preferred to intraperitoneal use since the latter route is painful,[4] but intravenous use may lead to poor penetration into the peritoneum.[3] Fluconazole, posaconazole, voriconazole, caspofungin, or flucytosine may also be effective.[3-5] Amphotericin B is often given with flucytosine, particularly for initial empirical therapy,[3] although some prefer to begin treatment with fluconazole alone or with flucytosine, reserving amphotericin B for patients who are immunosuppressed or have significant previous exposure to azoles.[4] Early removal of the peritoneal catheter may reduce the risk of death,[3] and should be rapid if fungal peritonitis is confirmed, although it has been suggested that removal be delayed long enough to allow for vigorous peritoneal lavage with antifungals.[4] Oral continuation therapy with flucytosine and fluconazole has been given after removal of the catheter.[3]

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Pityriasis versicolor

See under Skin Infections, p. 568.1.

Pneumocystis pneumonia

Pneumocystis pneumonia (PCP) is caused by the organism *Pneumocystis jirovecii* (previously named *Pneumocystis carinii* f. sp. *hominis* and at one time considered to be a protozoan). It is an opportunistic pathogen and infection is acquired by inhalation. In persons with normally functioning immune systems infection rarely produces disease, but in immunocompromised patients it may produce interstitial pneumonia which, if untreated, is almost always fatal. In patients with AIDS (p. 957.2) PCP was once a common occurrence, but widespread use of HAART and PCP prophylaxis in many parts of the world has now caused a substantial decline in its incidence; most infections occur in those who have advanced immunosuppression, or who are not receiving appropriate HIV care.

The **treatment** of choice for PCP is:

- intravenous or oral co-trimoxazole[1-4]

Alternative regimens are:[1-4]

- intravenous pentamidine (usually the drug of second choice in severe disease)
- oral or intravenous clindamycin plus oral primaquine
- oral atovaquone
- oral trimethoprim and dapsone
- nebulised pentamidine has occasionally been suggested for mild to moderate infection but is now generally reserved for prophylaxis due to limited treatment efficacy and higher rate of relapse

The recommended duration of treatment is generally 21 days.[1-4]

Intravenous trimetrexate with oral or intravenous folinic acid has been suggested as a possible treatment option for patients who fail to respond to standard first-line drugs.[5]

Adjunctive folinic acid with co-trimoxazole has been associated with an increased risk of therapeutic failure and death in AIDS patients.[3] Combination therapy with co-trimoxazole and pentamidine is not more effective and is potentially more toxic than either drug alone.[6]

Adjunctive treatment with glucocorticosteroids should be given to patients with severe infection[1-4] if they are hypoxic, and treatment should be started as soon as antimicrobial treatment is begun.

Primary **prophylaxis** is indicated for all HIV-positive adolescents and adults (including pregnant women and patients on HAART) with CD4+ T lymphocyte counts lower than 200 cells/microlitre, or a history of oropharyngeal candidiasis.[2,4] It should also be considered for those with a CD4+ T lymphocyte count percentage below 14%, a history of other AIDS-defining illnesses, or in patients with a CD4+ T lymphocyte count less than 250 cells/microlitre for whom routine follow-up counts are not possible.[3] Infants are at increased risk to PCP during their first year of life and, in infants and young children, PCP may occur at higher CD4+ T lymphocyte counts compared with adults. WHO/UNICEF[7] and US guidelines[4] recommend that all infants born to HIV-positive mothers should be given prophylaxis beginning at 4 to 6 weeks of age. Therapy should continue until breast feeding is stopped and the infant is confirmed to be HIV-negative, or for at least 1 year initially. Infants subsequently confirmed to be HIV-positive may need to remain on prophylactic therapy depending on age and CD4+ T lymphocyte cell counts[4,7] or clinical status.[7] In Europe, some clinicians have tended to have a less aggressive approach and only offer prophylaxis once HIV infection is confirmed or opportunistic infections occur.[8] Some recommendations for primary prophylaxis in patients without HIV infection suggest that prophylaxis should be considered for patients with primary immune deficiency, severe protein malnutrition, organ or stem cell transplants, persistent CD4+ T lymphocyte counts lower than 200 cells/microlitre, or patients receiving cytotoxic or immunosuppressive therapy.[2,9,10] In particular, it has been suggested that prophylaxis be considered in adults when the risk of developing PCP exceeds about 3%, as in solid organ transplantation (for the first 6 months after transplantation), allogeneic bone marrow transplantation (for at least the first 6 months, and for the duration of immunosuppression), Wegeners granulomatosis, and acute lymphoblastic leukemia.[11]

Secondary prophylaxis is given to all patients after successful treatment of PCP.[2]

For both primary and secondary prophylaxis[1,3,4] the drug of choice is:

- oral co-trimoxazole; this has the added advantage of also protecting against bacterial infections and toxoplasmosis, a common opportunistic infection in AIDS patients[3,4,7]

Alternative prophylactic regimens[1,2,4] for patients not able to receive co-trimoxazole are:

- oral dapsone (alone, or with oral pyrimethamine if prophylaxis for toxoplasmosis is also required)
- aerosolised pentamidine
- oral atovaquone (alone, or with oral pyrimethamine if prophylaxis for toxoplasmosis is also required)

Other prophylactic regimens include intermittent parenteral administration of pentamidine, pyrimethamine with sulfadoxine, and clindamycin with primaquine, but these are not recommended unless the more usual drugs cannot be used.[4]

In HIV-infected adults, primary and secondary prophylaxis may be discontinued in those who attain a CD4+ T lymphocyte count above 200 cells/microlitre for longer than 3 months on antiretroviral therapy. Primary and secondary prophylaxis should be restarted in adults whose CD4+ T lymphocyte count falls to below 200 cells/microlitre, and in those in whom PCP recurs at a count of greater than 200 cells/microlitre;[4,12] in children, criteria for stopping or restarting prophylaxis vary according to patient age.[4] A study of solid organ transplant recipients[13] suggested that lung transplant recipients are at continued risk of developing PCP and prophylaxis should be continued indefinitely in this group.

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Protothecosis

Protothecosis is an infection with algae of the *Prototheca* spp., usually *P. wickerhamii.* Infection occurs rarely in humans but may follow minor trauma or surgery, leading to a chronic skin lesion and occasionally dissemination. Amphotericin B appears to be the most effective antifungal,[1,2] and has been combined with an oral tetracycline.[2] There are also case reports of itraconazole[3,4] being used successfully and fluconazole has been of benefit in a case unresponsive to itraconazole,[5] but azole therapy has also been associated with treatment failure in some cases.[2] Azole antifungals and

surgery may be considered for patients with more localised disease.[1]

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Respiratory-tract infections

Pathogenic fungi may enter the body by inhalation and colonise the respiratory tract. Fungal infections of the respiratory tract include aspergillosis (see p. 563.1), blastomycosis (see p. 564.1), coccidioidomycosis (see p. 565.1), cryptococcosis (see p. 565.2), histoplasmosis (see p. 566.1), and paracoccidioidomycosis (see p. 567.1). *Pneumocystis jirovecii* is an important cause of pneumonia in HIV-infected patients (see p. 567.2). Other fungi reported to produce respiratory-tract infections mainly in immunocompromised patients include *Candida* spp. (see p. 564.1), *Fusarium* spp., *Penicillium marneffei*, *Pseudoallescheria boydii*, and Zygomycetes such as *Rhizopus arrhizus*. Acute pulmonary fungal infections in immunocompetent individuals are mostly self-limiting conditions that resolve without treatment. Severe, persistent, or progressive infections, or infections in immunocompromised patients, require treatment. Intravenous amphotericin B is usually the drug of choice but mild to moderate infection can be treated with an oral azole such as fluconazole, itraconazole, or ketoconazole. Pulmonary granulomas may require surgical removal. Chronic suppressive treatment is recommended for patients with ongoing immunosuppression due to HIV infection.

Skin infections

The most common fungal skin infections are the dermatophytoses, pityriasis versicolor, and candidiasis. The first two are described here; for candidiasis, see p. 564.1. Other fungal skin infections are discussed under the appropriate headings: blastomycosis (p. 564.1), chromoblastomycosis (p. 564.3), mycetoma (p. 567.1), mucormycosis (p. 566.3), protothecosis (p. 567.3), and sporotrichosis (below). Fungal infections that may involve the skin by dissemination include aspergillosis (p. 563.1), coccidioidomycosis (p. 565.1), cryptococcosis (p. 565.2), histoplasmosis (p. 566.1), and paracoccidioidomycosis (p. 567.1). Less common fungi causing skin infections include *Penicillium marneffei*. Sometimes a fungal infection may affect mucous membranes, nails, or subcutaneous tissue, and there can be spread to deeper tissue and dissemination especially in immunosuppressed patients. The term superficial fungal infections includes those involving the skin, nails, and mucous membranes. Antifungal treatment may be topical or systemic.[1,2]

Dermatophytoses (ringworm, tinea) are infections by dermatophytes, a group of fungi which includes soil-dwelling organisms and human and animal pathogens from 3 genera — *Epidermophyton, Microsporum*, and *Trichophyton*. Dermatophytoses are encouraged by hot and humid conditions and poor hygiene and occur throughout tropical and temperate regions of the world.

Dermatophytoses are classified according to the body site affected. They include

- tinea barbae (beard)
- tinea capitis (scalp)
- tinea corporis (body)
- tinea cruris (groin)
- tinea manuum (hand)
- tinea pedis (athlete's foot)
- tinea unguium (nail)

A chronic infection most commonly seen in the tropics is known as favus (tinea favosa) and a variant of tinea corporis known as tinea imbricata (tokelau) is caused by *T. concentricum* and is endemic in parts of the Far East and Central and South America. A severe form of dermatophytosis caused by animal pathogens with deep, suppurant, inflammatory lesions is known as kerion.

Deep infections may occur rarely in immunocompromised patients; they can spread to involve lymph nodes, liver, and brain, and may be fatal.

Mild localised superficial dermatophytoses of hairless skin sites will often respond to ***topical*** therapy.[3-5] Non-specific agents with a long history of topical use include benzoic acid, methylrosanilinium chloride, selenium sulfide, and salicylic acid. Many of these agents are effective, and while some older preparations such as Compound Benzoic Acid Ointment may be less cosmetically acceptable than modern products, they still have a role in the treatment of minor infections, particularly in the tropics.[6] However, the use of methylrosanilinium chloride is restricted due to fears over possible carcinogenicity (see p. 1762.2). There are many topical antifungals that are active against dermatophytes. The azoles used topically include clotrimazole, econazole, ketoconazole, and miconazole. Ciclopirox olamine[7] and the allylamine antifungals naftifine and terbinafine[5] are also active, and a systematic review[5] considered that allylamines such as terbinafine were slightly more effective than azoles in the treatment of fungal infections of the foot. Chlorphenesin, tolnaftate, and undecenoic acid salts are all effective in uncomplicated dermatophytoses, but there are few comparative studies of their relative efficacy. Amorolfine has also been shown to be effective in skin infections, although its major application is in nail infections (see below).

Infections of some body sites respond poorly to topical therapy, as do extensive infections or those in heavily keratinised areas.[4,8] ***Systemic*** therapy may be appropriate in these cases as well as in disseminated disease. Griseofulvin, ketoconazole, and itraconazole have been the drugs most widely used, although terbinafine has been reported to be more effective than itraconazole in some forms of tinea[9,10] and also requires only short-duration therapy.[11,12] However, efficacy of terbinafine is reported to depend on the infecting organism.[13] Griseofulvin has proved to have few major toxic effects during long-term therapy and is useful for tinea capitis, extensive or disseminated infections, and nail infections in selected patients. However, since it has a narrow spectrum of activity largely confined to the dermatophytes, accurate diagnosis is essential, particularly before embarking on a prolonged treatment course when no immediate response is anticipated. Ketoconazole has a broader spectrum of activity, but severe adverse effects can occur on prolonged use. Itraconazole appears to produce a rapid response and thus requires shorter treatment periods.[4] Other azoles such as fluconazole may also be effective.[14] Selenium sulfide and povidone-iodine shampoos may be useful adjuncts to oral therapy for tinea capitis to improve efficacy and limit the spread of infection.[15,16] A suitable topical antifungal is used in individuals suspected of carrying infection.[17]

Infections of the **nails (onychomycoses)** are notoriously difficult to treat.[18] Infections of the fingernails take up to 6 months to respond to oral griseofulvin and those of the toenails, a year or longer, but about 60% of nail infections fail to respond or relapse after the initial treatment course. The ***oral*** antifungals terbinafine, itraconazole, and fluconazole produce persistent antifungal concentrations in the nail more rapidly than griseofulvin.[18,19] Terbinafine and itraconazole have been most widely studied. Both are reported to produce clinical and mycological cures in a high proportion of patients more quickly than griseofulvin, generally after 12 weeks of treatment or less. Long-term follow-up has shown that the response to terbinafine is maintained.[20-22] Terbinafine has been reported to be more effective than itraconazole,[23-26] although neither is effective in all patients. Although ***topical*** treatments have generally been ineffective in nail infections, ciclopirox nail lacquer has been reported to be effective,[27] but a systematic review[5] noted that cure rates were poor. Amorolfine as a 5% lacquer has also shown benefit,[28] and may be more effective than ciclopirox although evidence is scanty.[5] It has also been used with oral itraconazole[29] or terbinafine[30] with some success. Topical butenafine may also be of benefit.[5] Another approach has been the dissolution of the nail plate with 40% urea paste, usually in combination with topical bifonazole.[31] Guidelines for the treatment of onychomycosis have been published in the UK.[32]

Pityriasis versicolor (tinea versicolor) is a superficial infection caused by the commensal yeast *Malassezia furfur (Pityrosporum orbiculare)*. It is more common in tropical than in temperate latitudes and sun exposure may trigger the infection. Pityriasis versicolor will often respond to topical treatment with an azole antifungal or with selenium sulfide. Topical terbinafine (but not oral) or ciclopirox are alternatives.[33] Immunocompromised patients, including those receiving corticosteroids, may develop extensive infections. In addition, these fungi have caused septicaemia in patients receiving parenteral nutrition.[34] Severe infections require oral treatment with an azole.[35] Griseofulvin is not effective.

Other infections in which *Malassezia* yeasts are implicated include seborrhoeic dermatitis (p. 1689.1) and pityrosporum folliculitis, both of which may present in a more severe form in patients with AIDS. Topical or systemic azole antifungals are effective in these conditions and are the main drugs used. However, relapses are common.[36]

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Sporotrichosis

Sporotrichosis is a disease caused by *Sporothrix schenckii*, a fungus found in soil and vegetation. The infection occurs in the Americas and Africa, and may give rise to cutaneous or extracutaneous disease. The cutaneous form is the more common. It probably follows entry of the organism through skin abrasions and usually presents as a single skin lesion, although infection may spread along lymphatic channels causing a series of skin lesions. Extracutaneous sporotrichosis usually presents as osteoarticular infection. Pulmonary infections are occasionally seen and, rarely, CNS and ocular infections.

Infections rarely heal spontaneously and most patients require **treatment**. Oral potassium iodide has traditionally been used for cutaneous and lymphocutaneous infections although the mode of action is unclear since potassium iodide does not show antifungal activity *in vitro*. Oral itraconazole 200 mg daily for 3 to 6 months is also effective[1-3] and is regarded by some[3,4] as the treatment of choice. The dose of itraconazole may be increased to 200 mg twice daily in non responders; alternatively patients may be given oral terbinafine or a saturated potassium iodide

solution taken orally. Oral fluconazole should only be used in patients who cannot tolerate any of the preferred drugs.[4]

For patients with osteoarticular infections, oral itraconazole 200 mg twice daily for at least 12 months is recommended, with either liposomal or conventional amphotericin B given intravenously as alternatives. Oral itraconazole 200 mg twice daily may be given as maintenance therapy once the patient has responded to the amphotericin B treatment.[4]

Patients with life-threatening pulmonary, disseminated, or meningeal disease should receive treatment for at least 12 months. The drug of choice is intravenous liposomal amphotericin B with conventional amphotericin B given intravenously as an alternative. Oral itraconazole 200 mg twice daily may be given as maintenance therapy. Oral itraconazole may be given in non-life-threatening pulmonary infections and for patients who cannot tolerate amphotericin B.[4]

Lifelong *maintenance* therapy with oral itraconazole 200 mg daily may be beneficial after initial treatment for meningeal or disseminated sporotrichosis in immunocompromised patients, including those with AIDS, if immunosuppression cannot be reversed.[4]

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3. Anonymous. Antifungal drugs. *Treat Guidel Med Lett* 2005; **3:** 7–14.
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Tinea

See under Skin Infections, p. 568.1.

Amorolfine *(BAN, USAN, rINN)*

Amorolfiini; Amorolfin; Amorolfina; Amorolfinum; Ro-14-4767/000; Аморольфин.

(±)-*cis*-2,6-Dimethyl-4-[2-methyl-3-(*p*-*tert*-pentylphenyl)propyl]morpholine.

$C_{21}H_{35}NO$=317.5

CAS — 78613-35-1.

ATC — D01AE16.

ATC Vet — QD01AE16.

UNII — AB0BHP2FH0.

Amorolfine Hydrochloride *(BANM, rINNM)*

Amorolfina, hidrocloruro de; Amorolfine, Chlorhydrate d'; Amorolfini Hydrochloridum; Hidrocloruro de amorolfina; Ro-14-4767/002; Аморольфина Гидрохлорид.

$C_{21}H_{35}NO,HCl$=354.0

CAS — 78613-38-4.

ATC — D01AE16.

ATC Vet — QD01AE16.

UNII — 741YH7379H.

Uses and Administration

Amorolfine is a morpholine derivative applied topically as the hydrochloride in the treatment of fungal nail and skin infections (p. 568.1). After topical application, systemic absorption of amorolfine is negligible.

For the treatment of nail infections caused by dermatophytes, yeasts, and moulds a lacquer containing the equivalent of 5% amorolfine is painted onto the affected nail once or sometimes twice weekly until the nail has regenerated. Treatment generally needs to be continued for 6 to 12 months.

For skin infections, including dermatophyte infections, a cream containing the equivalent of 0.25% amorolfine is applied once daily for at least 2 to 3 weeks (up to 6 weeks for foot infections) and continued for 3 to 5 days after clinical cure is achieved.

Reviews.

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2. Flagothier C, *et al.* New insights into the effect of amorolfine nail lacquer. *Mycoses* 2005; **48:** 91–4.

Adverse Effects and Precautions

Skin irritation, presenting as erythema, pruritus, or a burning sensation, and, rarely, more severe skin reactions have been reported after topical application of amorolfine.

Hypersensitivity. A report[1] of allergic contact dermatitis to amorolfine nail lacquer.

1. Pérez-Varela L, *et al.* Dermatitis alérgica de contacto por amorolfina en laca de uñas. *Actas Dermosifiliogr* 2010; **101:** 281–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amorolfine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Antimicrobial Action

Amorolfine is a morpholine derivative with antifungal activity. It appears to act by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes.

Amorolfine is active *in vitro* against many pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis*, *Candida* spp., *Histoplasma capsulatum*, and *Sporothrix schenckii*. It also has variable activity against *Aspergillus* spp. However, despite its *in vitro* activity, amorolfine is inactive when given systemically and this limits its use to topical application for superficial infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Laquifun; Loceryl; Micobutina; Micocide A; ***Austral.***: Loceryl; ***Austria***: Loceryl; ***Belg.***: Loceryl; ***Braz.***: Loceryl; ***Chile***: Loceryl; ***China***: Loceryl (罗每乐); ***Cz.***: Loceryl; ***Denm.***: Loceryl; ***Fin.***: Loceryl; ***Fr.***: Curanail; Loceryl; ***Ger.***: Amofin; Loceryl; ***Gr.***: Loceryl; ***Hong Kong***: Loceryl; ***Hung.***: Loceryl; ***India***: Am-Laqer; Loceryl; ***Irl.***: Loceryl; ***Israel***: Loceryl; ***Ital.***: Locetar; ***Jpn***: Pekiron; ***Malaysia***: Loceryl; ***Mex.***: Loceryl; Onylaq; ***Norw.***: Loceryl; ***NZ***: Loceryl; ***Philipp.***: Locetar; ***Pol.***: Loceryl; ***Port.***: Locetar; ***Rus.***: Loceryl (Лоцерил); ***S.Afr.***: Loceryl; ***Singapore***: Loceryl; ***Spain***: Locetar; Odenil; ***Swed.***: Finail; Loceryl; ***Switz.***: Curanel; Loceryl; ***Thai.***: Loceryl; ***UK***: Curanail; Loceryl; Omicur; ***Venez.***: Loceryl.

Amphotericin B *(BANM, rINN)*

Amfotericin; Amfotericin B; Amfotericina B; Amfotericinas B; Amfoterisiini; Amfoterisiini B; Amfoterisin; Amfoterisin B; Amfoterycyna b; Amphotericin; Amphotericin B Cholesteryl Sulfate Complex; Amphotericin B Lipid Complex; Amphotericin B Liposome; Amphotericin B Phospholipid Complex; Amphotericin B-Sodium Cholesteryl Sulfate Complex; Amphotéricine B; Amphotericinum; Amphotericinum B; Anfotericina B; Liposomal Amphotericin B; Амфотерицин В.

$C_{47}H_{73}NO_{17}$=924.1

CAS — 1397-89-3.

ATC — A01AB04; A07AA07; G01AA03; J02AA01.

ATC Vet — QA01AB04; QA07AA07; QG01AA03; QJ02AA01.

UNII — 7XU7A7DROE.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Amphotericin B; Amphotericin BP 2014). A mixture of antifungal polyenes produced by the growth of certain strains of *Streptomyces nodosus* or by any other means. It consists largely of amphotericin B. It occurs as a yellow or orange, hygroscopic powder. The potency is not less than 750 units per mg with reference to the dried substance. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide and in propylene glycol; slightly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Amphotericin B). A yellow to orange, odourless or practically odourless, powder. It contains not less than 750 micrograms of $C_{47}H_{73}NO_{17}$ per mg, and, for material intended for oral or topical use, not more than 15% of amphotericin A, both calculated on the dried substance. Insoluble in water, in dehydrated alcohol, in ether, in benzene, and in toluene; soluble in dimethylformamide, in dimethyl sulfoxide, and in propylene glycol; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8 degrees in airtight containers. Protect from light.

References.

1. Kintzel PE, Smith GH. Practical guidelines for preparing and administering amphotericin B. *Am J Hosp Pharm* 1992; **49:** 1156–64.

Formulation. Conventional formulations of amphotericin B injection are typically a complex of amphotericin B and deoxycholate with suitable buffers which form a colloidal dispersion when reconstituted. Nonconventional **'lipid'** formulations of amphotericin B for injection include liposomal amphotericin B, a colloidal dispersion of an amphotericin B and sodium cholesteryl sulfate complex, and a phospholipid complex.

Incompatibility. Because of the wide range of incompatibilities reported with conventional and lipid formulations of amphotericin B, it is generally advisable not to mix them with any other drug. Most incompatibilities are caused by precipitation of amphotericin B due to a change in pH or by the disruption of the colloidal suspension. Precipitation can occur if amphotericin B is added to sodium chloride 0.9% or to electrolyte solutions.

Although heparin is generally reported to be compatible with conventional amphotericin B injection, care should be taken if heparin flush solutions, which are diluted with sodium chloride solution, are used to maintain the patency of intravenous lines in patients receiving amphotericin B. Flushing the intravenous line with 5% glucose solution has been suggested.

Mixtures of conventional amphotericin B in commercial lipid emulsions have been reported to be unstable,[1-3] although others have reported satisfactory stability.[4-6] In one study,[6] vigorous agitation of the mixtures enhanced their stability when compared with gentle mixing.

1. Ericsson O, *et al.* Amphotericin B is incompatible with lipid emulsions. *Ann Pharmacother* 1996; **30:** 298.
2. Ranchère JY, *et al.* Amphotericin B intralipid formulation: stability and particle size. *J Antimicrob Chemother* 1996; **37:** 1165–9.
3. Heide PE. Precipitation of amphotericin B from iv fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 1449.
4. Lopez RM, *et al.* Stability of amphotericin B in an extemporaneously prepared iv fat emulsion. *Am J Health-Syst Pharm* 1996; **53:** 2724–7.
5. Owens D, *et al.* Stability of amphotericin B 0.05 and 0.5 mg/mL in 20% fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 683–6.
6. Shadkhan Y, *et al.* The use of commercially available lipid emulsions for the preparation of amphotericin B-lipid admixtures. *J Antimicrob Chemother* 1997; **39:** 655–8. Correction. *ibid.* 1998; **42:** 413.

Preparation of solutions for injection. Recommendations from the manufacturers for preparation of amphotericin solutions are:

- *conventional amphotericin B* formulations for injection are prepared by reconstitution of amphotericin B with sterile water for injection without preservatives, then dilution with glucose injection 5% with a pH above 4.2 to the desired final concentration.
- *liposomal amphotericin B*: injections are prepared by reconstitution with sterile water for injection without a preservative; the required reconstituted amount is then withdrawn and injected via a sterile filter into the desired volume of glucose 5%.
- *amphotericin B-sodium cholesteryl sulfate complex*: injections are prepared by rapidly adding the required amount of water for injection, then further diluting with glucose 5% until the desired final concentration is reached.
- *amphotericin B-phospholipid complex*: before infusion the suspension concentrate must be diluted to the required final concentration with glucose 5%. The required amount of concentrate is injected via a sterile filter into the glucose 5%.

CAUTION: Mixture with sodium chloride injection 0.9% would precipitate amphotericin B.

Stability of oral suspensions. An oral suspension of amphotericin B 100 mg/mL, prepared from a powder of Amphotericin B (USP) and a cherry-flavoured vehicle and maintained at pH 5.3, was found to be stable at 22 to 25 degrees for 93 days.[1]

1. Dentinger PJ, *et al.* Stability of amphotericin B in an extemporaneously compounded oral suspension. *Am J Health-Syst Pharm* 2001; **58:** 1021–4.

Uses and Administration

Amphotericin B is a polyene antifungal antibiotic. It is reported to be fungistatic at concentrations achieved clinically. Amphotericin B is given by intravenous infusion in the treatment of severe *systemic* fungal infections including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, paracoccidioidomycosis, and sporotrichosis, and is the usual treatment of choice in fungal endocarditis, meningitis, peritonitis, or severe respiratory-tract infections. Many of these infections are most likely to occur in immunocompromised patients. Amphotericin may be given with flucytosine (p. 581.1) in severe infections.

Amphotericin B is also used for the *local* treatment of superficial candidiasis. It is taken orally for intestinal candidiasis, sometimes as part of regimens for selective decontamination of the digestive tract in patients at special risk of infection, such as those in intensive care (see p. 187.3).

The role of amphotericin B in the treatment of the above systemic and local infections is discussed under Choice of Antifungal, p. 563.1.

Amphotericin B also has antiprotozoal activity. It is used for primary amoebic meningoencephalitis caused by *Naegleria* spp. p. 571.1 and for the treatment of visceral, cutaneous, and mucocutaneous leishmaniasis (see p. 570.3).

Administration and dosage. Amphotericin B is given by *intravenous* infusion conventionally as a colloidal complex with sodium deoxycholate. There is also a liposomal form and other complexes of amphotericin B available for use by infusion when conventional amphotericin B is contra-indicated because of toxicity, especially nephrotoxicity. Before starting therapy with any form of intravenous amphotericin B a test dose is usually advised and the patient observed carefully for about 30 minutes.

Details of intravenous administration and dosage vary according to the formulation being used and it is important not to confuse their dosage regimens; indicative doses for some UK formulations are given below. Therapy has sometimes continued for several months depending on the infection. Doses are expressed in terms of amphotericin B.

- ***Conventional amphotericin B*** (*Fungizone, UK*). After an initial test dose (1 mg infused over 20 to 30 minutes) treatment usually starts with a daily dose of 250 micrograms/kg, increased gradually to a maximum of 1 mg/kg daily; in seriously ill patients up to 1.5 mg/kg daily or on alternate days may be necessary. If treatment is stopped for longer than 7 days, it should be resumed at a dose of 250 micrograms/kg daily and increased gradually. The daily dose is infused over 2 to 4 hours at a concentration of 100 micrograms/mL in glucose 5%. Slower infusion, over up to 6 hours, may be necessary to reduce the incidence of acute toxic effects.
- ***Liposomal amphotericin B*** (*AmBisome, UK*). After an initial test dose (1 mg infused over 10 minutes), the usual dose is 1 mg/kg daily, increased gradually to 3 mg/kg if necessary; the *BNF* advises that up to 5 mg/kg daily may be used if required.. The daily dose is infused over 30 to 60 minutes at a concentration of 0.2 to 2 mg/mL in glucose injection.
- ***Amphotericin B-sodium cholesteryl sulfate complex*** (*Amphocil, UK*). After an initial test dose (2 mg infused over 10 minutes) the usual dose is 1 mg/kg daily, increased gradually to 3 to 4 mg/kg daily if necessary; doses of up to 6 mg/kg daily have been given. The daily dose is infused at a rate of 1 to 2 mg/kg per hour at a concentration of 625 micrograms/mL in glucose 5%.
- ***Amphotericin B-phospholipid complex*** (*Abelcet, UK*). After an initial test dose (1 mg infused over 15 minutes) the usual dose is 5 mg/kg daily. The daily dose is infused at a rate of 2.5 mg/kg per hour as a diluted suspension containing 1 mg/mL in glucose 5%.

For details of dosing in children, see below.

Conventional amphotericin B may be given by *intrathecal* injection to patients with severe meningitis especially when intravenous therapy has been ineffective. Starting with 25 micrograms, the dose is gradually increased to the maximum that can be tolerated without excessive discomfort. The usual dosage is 0.25 to 1 mg given two to four times each week.

Conventional amphotericin B is also used *orally* as 10-mg lozenges or as a suspension containing 100 mg/mL for oral or perioral candidiasis. The suspension is given in a dose of 1 mL four times daily; it should be retained in the mouth for as long as possible before swallowing. The lozenges are intended to be dissolved in the mouth and are given four times daily, increased to 8 lozenges daily if necessary. Doses of 100 to 200 mg are given four times daily as tablets or suspension to suppress intestinal *Candida*.

Conventional amphotericin B has been given for candiduria as a *continuous bladder irrigation* daily at a suggested concentration of 50 mg in 1000 mL of sterile water. Intermittent irrigation has also been tried.

Conventional amphotericin B has also been given into the lung by nebulised solution, into the eye topically or by subconjunctival or intravitreal injection, to the skin by topical application, into body cavities by instillation, and into joint spaces by intra-articular injection. Liposomal amphotericin B has also been used via inhalation for the prevention of pulmonary aspergillosis (see below).

Administration. *LIPID FORMULATIONS.* Lipid formulations of amphotericin B have been developed in an attempt to minimise renal toxicity and acute toxic reactions. Three lipid-based formulations of amphotericin B available commercially in some countries are:

- liposomes (e.g. *AmBisome*)[1]
- a lipid complex with L-α-dimyristoylphosphatidylcholine and L-α-dimyristoylphosphatidylglycerol (e.g. *Abelcet*)
- a colloidal dispersion with sodium cholesteryl sulfate (e.g. *Amphocil*)

The aim of reducing renal toxicity has largely been achieved, and in some cases patients unable to tolerate conventional amphotericin B have subsequently been successfully treated with one of the lipid-based formulations. Experience with these formulations suggests that they also produce fewer acute toxic reactions. Review articles[2-11] on lipid formulations of amphotericin B generally indicate that clinical studies have been encouraging, and that although they differ in their pharmacodynamics, pharmacokinetics, and dosage, they appear to be clinically at least as effective as amphotericin B.[5,6,11]

1. Barnes RA, *et al.*, eds. AmBisome: an international workshop. *J Antimicrob Chemother* 2002; **49** (suppl S1): 1–86.
2. Coukell AJ, Brogden RN. Liposomal amphotericin B: therapeutic use in the management of fungal infections and visceral leishmaniasis. *Drugs* 1998; **55:** 585–612.
3. Brogden RN, *et al.* Amphotericin-B colloidal dispersion: a review of its use against systemic fungal infections and visceral leishmaniasis. *Drugs* 1998; **56:** 365–83.
4. Johansen HK, Gøtzsche PC. Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 21/06/05).
5. Dupont B. Overview of the lipid formulations of amphotericin B. *J Antimicrob Chemother* 2002; **49** (Suppl 1): 31–6.
6. Barrett JP, *et al.* A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. *Clin Ther* 2003; **25:** 1295–320.
7. Herbrecht R, *et al.* The lipid formulations of amphotericin B. *Expert Opin Pharmacother* 2003; **4:** 1277–87.
8. Fohrer C, *et al.* Apports des derives lipidiques de l'amphotéricine B dans la prise en charge des infections fongiques. *Therapie* 2006; **61:** 235–42.
9. Adler-Moore JP, Proffitt RT. Amphotericin B lipid preparations: what are the differences? *Clin Microbiol Infect* 2008; **14** (suppl 4): 25–36.
10. Bellmann R, *et al.* Clinical roundtable monograph: safety and efficacy of lipid-based amphotericin B. *Clin Adv Hematol Oncol* 2009; **7:** 1–8.
11. Moen MD, *et al.* Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections. *Drugs* 2009; **69:** 361–92.

INFUSION RATE. Conventional amphotericin B is licensed for use by intravenous infusion over at least 2 hours. A long infusion time is inconvenient for outpatients and often impractical in patients receiving other intravenous medications. This may be overcome by using one of the lipid formulations that can be infused over 30 to 120 minutes. Shorter infusion times have been tried with conventional amphotericin B but although 2 studies[1,2] in small numbers of patients without pre-existing renal impairment found rapid infusion over 1 hour was generally no more toxic than infusion over 4 hours, another[3] found infusion over 45 minutes to be more toxic than a 4-hour infusion during the first 5 to 7 days of treatment. Cardiotoxicity reported in patients receiving rapid infusions includes atrial fibrillation in a patient with pre-existing cardiac disease,[2] ventricular fibrillation associated with hyperkalaemia in a patient with severe renal impairment,[4] and bradycardia[5] and dilated cardiomyopathy[6] in patients without apparent risk factors. Ventricular dysrhythmias were not seen in 27 patients with adequate renal function.[7]

Conversely, continuous infusion of amphotericin B over 24 hours has resulted in fewer adverse effects and a significant reduction in nephrotoxicity compared with infusion over 4 hours.[8] Furthermore, an observational study of 33 patients concluded that a continuous infusion of amphotericin B deoxycholate, started at 1 mg/kg daily and gradually escalated to 2 mg/kg daily was safe and well tolerated by most patients.[9]

1. Oldfield EC, *et al.* Randomized, double-blind trial of 1- versus 4-hour amphotericin B infusion durations. *Antimicrob Agents Chemother* 1990; **34:** 1402–6.
2. Cruz JM, *et al.* Rapid intravenous infusion of amphotericin B: a pilot study. *Am J Med* 1992; **93:** 123–30.
3. Ellis ME, *et al.* Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. *Antimicrob Agents Chemother* 1992; **36:** 172–9.
4. Craven PC, Gremillion DH. Risk factors of ventricular fibrillation during rapid amphotericin B infusion. *Antimicrob Agents Chemother* 1985; **27:** 868–71.
5. Soler JA, *et al.* Bradycardia after rapid intravenous infusion of amphotericin B. *Lancet* 1993; **341:** 372–3.
6. Arswa EL, *et al.* Amphotericin B-induced dilated cardiomyopathy. *Am J Med* 1994; **97:** 560–2.
7. Bowler WA, *et al.* Risk of ventricular dysrhythmias during 1-hour infusions of amphotericin B in patients with preserved renal function. *Antimicrob Agents Chemother* 1992; **36:** 2542–3.
8. Eriksson U, *et al.* Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ* 2001; **322:** 579–82.
9. Imhof A, *et al.* Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. *Clin Infect Dis* 2003; **36:** 943–51.

Administration in children. Conventional and lipid formulations of amphotericin B may be used in children for the treatment of severe systemic fungal infections, and intravenous doses similar to those in adults (see p. 569.3) have been found to be safe and effective. The *BNFC* advises that conventional and liposomal amphotericin B may also be used in neonates; the conventional form may be used in a dose of 1 mg/kg once daily; after a week, the dosing frequency may be reduced to every other day. Daily doses up to 1.5 mg/kg have been tolerated in some studies. The liposomal form may be used in similar doses to adults (see above). Although the most appropriate dose of lipid formulations of amphotericin B for low-birth-weight preterm infants has yet to be firmly established reports suggest that they may be safe and effective at doses similar to those used in adults, relative to body-weight.[1-3]

For all children and neonates, the *BNFC* also advises the use of a weight-based test dose. A dose of 100 micrograms/kg is recommended, to a maximum of 1 mg. For the conventional preparation, the test dose is included as part of the first therapeutic dose. In some countries amphotericin B-sodium cholesteryl sulfate complex is available and it has been suggested that a maximum test dose of 2 mg may be used for this product.

For prophylaxis of neonatal intestinal candidiasis conventional amphotericin B solution 100 mg is given orally once daily.

For information on the pharmacokinetics and doses in children and neonates, see, p. 573.1.

1. Scarcella A, *et al.* Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J* 1998; **17:** 146–8.
2. Weitkamp J-H, *et al.* Candida infection in very low birth-weight infants: outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome). *Infection* 1998; **26:** 11–15.
3. Walsh TJ, *et al.* Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J* 1999; **18:** 702–8.

Aspergillosis. While intravenous amphotericin B preparations have a role in the treatment of aspergillosis infections (see p. 563.1), nebulisation may be of value in the prevention of pulmonary disease. In a randomised, placebo-controlled study[1] involving patients with haematological disease where at least 10 days of neutropenia was expected, 12.5 mg liposomal amphotericin B nebulised on 2 consecutive days each week (until neutrophil recovery or a maximum of 12 doses) significantly reduced the incidence of invasive pulmonary aspergillosis.

1. Rijnders BJ, *et al.* Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis* 2008; **46:** 1401–8.

Leishmaniasis. The treatment of visceral and mucocutaneous leishmaniasis including the use of amphotericin B is described on p. 923.1 and p. 923.1, respectively.

VISCERAL LEISHMANIASIS. Evidence of declining responsiveness to pentavalent antimonials has led to the evaluation of intravenous amphotericin B as an alternative for first-line therapy. WHO has included liposomal amphotericin B 3 mg/kg daily on each of 5 consecutive days and a sixth dose 6 days later among the regimens suggested for first-line therapy of Mediterranean visceral leishmaniasis in immunocompetent patients,[1] and the drug has been widely adopted as first-line treatment in Europe.[2] Similar doses are recommended by US licensed product information for liposomal amphotericin B (*AmBisome; Gilead, USA*), which recommends 3 mg/kg daily for 5 days with further doses on days 14 and 21. Experience with a short course of 10 mg/kg daily for 2 days was also shown to be effective in 41 immunocompetent children under 14 years, although 1 subsequently relapsed after 5 weeks.[3]

Responses to liposomal amphotericin B have been reported to be slower in immunocompromised patients; relapses occurred in 8 of 11 patients despite treatment with liposomal amphotericin B 1.38 to 1.85 mg/kg daily for 21 days.[4] Increasing the dose to 4 mg/kg daily given on 10 days over a 38-day period did not improve the long-term outcome, although initial responses were good[5] and this regimen is now that recommended by the licensed product information above.

Due to frequent relapse in these patients secondary prophylaxis with intermittent amphotericin B has been considered. An open-label, multicentre study with amphotericin B lipid complex in doses of 3 mg/kg every 21 days for 12 months[6] was effective in 50% of HIV-infected patients. Another cohort study[7] reported that 80% of HIV-infected patients were relapse free at 12 months after receiving an initial treatment course of liposomal amphotericin B in doses of 4 mg/kg daily for 5 consecutive days and then once weekly for 5 weeks, followed by secondary prophylaxis in doses of 5 mg/kg every 3 weeks. However, at 24 months about 45% of the patients had experienced relapses.

Amphotericin B is also being evaluated in other parts of the world. In India, conventional amphotericin B in modest doses (500 micrograms/kg on alternate days) produced good responses both in patients unresponsive to antimonials[8,9] and as first-line therapy.[10] Experience with a higher dose of 1 mg/kg daily for 20 days achieved a 99% cure rate in 938 patients[11] and a dose of 1 mg/kg on alternate days for 30 days is also highly effective.[12] In addition a lower dose regimen of 750 micrograms/kg daily for 15 days was also found to be effective.[13] Liposomal amphotericin B 2 mg/kg daily on 3, 5 or 7 days over a 10-day period all produced clinical cures and minimal toxicity,[14] as did single infusions of 10 mg/kg, 7.5 mg/kg, or 5 mg/kg, or once-daily infusion of 0.75 to 1 mg/kg for 5 days.[15-18] Amphotericin B lipid complex 1, 2, or 3 mg/kg daily for 5 days,[19] or 5 mg/kg given once or twice (5 days apart),[20] has been used successfully although relapses occurred in some patients taking the lower doses in these latter studies. In Brazil, colloidal amphotericin B with sodium cholesteryl sulfate in a dose of 2 mg/kg daily for 5 days produced cures in 10 patients although 1 subsequently relapsed.[21] A study by WHO[22] suggested that more intensive courses of treatment may be needed in Brazil compared with India and Kenya.

MUCOCUTANEOUS LEISHMANIASIS. Amphotericin B is used in mucocutaneous leishmaniasis unresponsive to antimonials. Successful treatment with liposomal amphotericin B has been reported in immunocompetent[23] and immunocompromised[24] patients.

1. Gradoni L, *et al.* Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; **73:** 191–7.

2. Rosenthal E, *et al*. Le traitement de la leishmaniose viscérale en Europe en 2009: place de l'amphotéricine B liposomale. *Med Mal Infect* 2009; **39:** 741–4.
3. Syriopoulou V, *et al*. Two doses of a lipid formulation of amphotericin B for the treatment of Mediterranean visceral leishmaniasis. *Clin Infect Dis* 2003; **36:** 560–6.
4. Davidson RN, *et al*. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med* 1994; **87:** 75–81.
5. Russo R, *et al*. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect* 1996; **32:** 133–7.
6. López-Vélez R, *et al*. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother* 2004; **53:** 540–3.
7. Molina I, *et al*. Efficacy of liposomal amphotericin B for secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother* 2007; **60:** 837–42.
8. Giri OP. Amphotericin B therapy in kala-azar. *J Indian Med Assoc* 1993; **91:** 91–3.
9. Mishra M, *et al*. Amphotericin versus pentamidine in antimony-unresponsive kala-azar. *Lancet* 1992; **340:** 1256–7.
10. Mishra M, *et al*. Amphotericin versus sodium stibogluconate in first-line treatment of Indian kala-azar. *Lancet* 1994; **344:** 1599–1600.
11. Thakur CP, *et al*. Amphotericin B deoxycholate treatment of visceral leishmaniasis with newer modes of administration and precautions: a study of 938 cases. *Trans R Soc Trop Med Hyg* 1999; **93:** 319–23.
12. Sundar S, *et al*. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis* 2004; **38:** 377–83.
13. Sundar S, *et al*. Amphotericin B treatment for Indian visceral leishmaniasis: response to 15 daily versus alternate-day infusions. *Clin Infect Dis* 2007; **45:** 556–61.
14. Thakur CP, *et al*. Comparison of three treatment regimens with liposomal amphotericin B (AmBisome) for visceral leishmaniasis in India: a randomized dose-finding study. *Trans R Soc Trop Med Hyg* 1996; **90:** 319–22.
15. Sundar S, *et al*. Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial. *BMJ* 2001; **323:** 419–22.
16. Sundar S, *et al*. Single-dose liposomal amphotericin B in the treatment of visceral leishmaniasis in India: a multicenter study. *Clin Infect Dis* 2003; **37:** 800–4.
17. Sundar S, *et al*. Low-dose liposomal amphotericin B in refractory Indian visceral leishmaniasis: a multicenter study. *Am J Trop Med Hyg* 2002; **66:** 143–6.
18. Sundar S, *et al*. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N Engl J Med* 2010; **362:** 504–12.
19. Sundar S, *et al*. Short-course, low-dose amphotericin B lipid complex therapy for visceral leishmaniasis unresponsive to antimony. *Ann Intern Med* 1997; **127:** 133–7.
20. Sundar S, *et al*. Treatment of antimony-unresponsive Indian visceral leishmaniasis with ultra-short courses of amphotericin-B-lipid complex. *Ann Trop Med Parasitol* 1998; **92:** 755–64.
21. Dietze R, *et al*. Treatment of kala-azar in Brazil with Amphocil (amphotericin B cholesterol dispersion) for 5 days. *Trans R Soc Trop Med Hyg* 1995; **89:** 309–11.
22. Berman JD, *et al*. Efficacy and safety of liposomal amphotericin B (AmBisome) for visceral leishmaniasis in endemic developing countries. *Bull WHO* 1998; **76:** 25–32.
23. Sampaio RNR, Marsden PD. Mucosal leishmaniasis unresponsive to glucantime therapy successfully treated with AmBisome. *Trans R Soc Trop Med Hyg* 1997; **91:** 77.
24. Amato VS, *et al*. Mucocutaneous leishmaniasis associated with HIV infection treated successfully with liposomal amphotericin B (AmBisome). *J Antimicrob Chemother* 2000; **46:** 341–2.

Primary amoebic meningoencephalitis. Amphotericin B is active *in vitro* against *Naegleria fowleri* and has been recommended for the treatment of primary amoebic meningoencephalitis (p. 920.2) caused by this amoeba. There have been some case reports[1-8] of survival after the use of intravenous and intrathecal amphotericin B. In all cases amphotericin B was combined with other antimicrobials, notably oral rifampicin.

1. Anderson K, Jamieson A. Primary amoebic meningoencephalitis. *Lancet* 1972; **i:** 902–3.
2. Seidel JS, *et al*. Successful treatment of primary amebic meningoencephalitis. *N Engl J Med* 1982; **306:** 346–8.
3. Brown RL. Successful treatment of primary amebic meningoencephalitis. *Arch Intern Med* 1991; **151:** 1201–2.
4. Poungvarin N, Jariya P. The fifth nonlethal case of primary amoebic meningoencephalitis. *J Med Assoc Thai* 1991; **74:** 112–15.
5. Loschiavo F, *et al*. Acute primary meningoencephalitis from entamoeba Naegleria fowleri: report of a clinical case with a favourable outcome. *Acta Neurol (Napoli)* 1993; **15:** 333–40.
6. Wang A, *et al*. Successful treatment of amoebic meningoencephalitis in a Chinese living in Hong Kong. *Clin Neurol Neurosurg* 1993; **95:** 249–52.
7. Jain R, *et al*. Naegleria meningitis: a rare survival. *Neurol India* 2002; **50:** 470–2.
8. Vargas-Zepeda J, *et al*. Successful treatment of Naegleria fowleri meningoencephalitis by using intravenous amphotericin B, fluconazole and rifampicin. *Arch Med Res* 2005; **36:** 83–6.

Adverse Effects

Amphotericin B for intravenous use was originally only available in a conventional colloidal form; lipid formulations have been developed to reduce toxicity. The following adverse effects apply to the **conventional** form. Common adverse effects which occur during or after intravenous infusion of amphotericin B include headache, nausea, vomiting, chills, fever, malaise, muscle and joint pains, anorexia, diarrhoea, and gastrointestinal cramp. Hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation and cardiac arrest, skin rashes, flushing, anaphylactoid reactions including bronchospasm and dyspnoea, blurred vision, tinnitus, hearing loss, vertigo, gastrointestinal bleeding, liver disorders, peripheral neuropathy, and convulsions have been reported occasionally.

Some degree of nephrotoxicity occurs in almost all patients given amphotericin B intravenously. Both tubular and glomerular damage occur; there may be improvement on cessation of therapy, but there is a risk of permanent renal impairment, particularly in patients given large cumulative doses (over 5 g). Renal tubular acidosis without systemic acidosis may develop. Use of amphotericin B is associated with increased urinary excretion of potassium and magnesium resulting in hypokalaemia and hypomagnesaemia respectively. Uric acid excretion is increased and nephrocalcinosis can occur. Limited data indicate that renal toxicity may be associated with sodium depletion; for strategies to improve sodium load see Nephrotoxicity, under Treatment of Adverse Effects, p. 572.1.

A reversible, normocytic, normochromic anaemia develops in most patients given amphotericin B, possibly due to a direct suppressive effect on erythropoietin production. There are rare reports of thrombocytopenia, leucopenia, agranulocytosis, eosinophilia, and coagulation defects.

Leukoencephalopathy has been reported rarely in patients also receiving total body irradiation.

Amphotericin B solutions irritate the venous endothelium and may cause pain and thrombophlebitis at the injection site. Extravasation may cause tissue damage.

After intrathecal injection amphotericin B may also cause irritation of the meninges, neuropathy with pain, impaired vision, and retention of urine.

In general, adverse effects of **lipid** formulations have been similar to those of conventional amphotericin B, but are less frequent and less severe. Brief reversible episodes of renal impairment have occurred but these formulations have been considered to be safe enough to use in patients with renal impairment who could not be given conventional amphotericin B. Anaphylaxis has been reported rarely.

Amphotericin applied **topically** may produce local irritation, pruritus, and skin rash.

Effects on the cardiovascular system. Ventricular arrhythmias in 2 patients, resulting in fatal sudden cardiac arrest in 1, were associated with both conventional and liposomal formulations of amphotericin B at conventional doses and infusion rates,[1] but cardiotoxicity is more common with high doses or rapid infusion rates (see Infusion Rate, under Administration, p. 570.2). Cardiac arrests in 5 infants and children, fatal in 4 cases, were associated[2] with overdoses of conventional amphotericin B of between 3.8 and 40.8 mg/kg. Fatal cardiotoxicity has also been reported in an adult who inadvertently received an overdose (5 mg/kg) of conventional amphotericin B on 2 consecutive days.[3] A case of reversible dilated cardiomyopathy and congestive heart failure has been reported in a 20-year-old male patient after about 2 months of treatment, initially with conventional amphotericin B for 30 days and then with amphotericin B phospholipid complex. Symptoms resolved within 6 weeks of stopping treatment.[4] An increased risk of arrhythmia and cardiac arrest has been reported in patients with evidence of antimony-induced myocardial damage who were switched to amphotericin B treatment for visceral leishmaniasis.[5] A rest period of at least 10 days was advised before beginning amphotericin B in such patients.

Severe hypertension was associated with infusion of phospholipid-amphotericin B complex in 1 patient.[6]

1. Aguado JM, *et al*. Ventricular arrhythmias with conventional and liposomal amphotericin. *Lancet* 1993; **342:** 1239.
2. Cleary JD, *et al*. Amphotericin B overdose in pediatric patients with associated cardiac arrest. *Ann Pharmacother* 1993; **27:** 715–19.
3. Burke D, *et al*. Acute amphotericin B overdose. *Ann Pharmacother* 2006; **40:** 2254–9.
4. Danaher PJ, *et al*. Reversible dilated cardiomyopathy related to amphotericin B therapy. *J Antimicrob Chemother* 2004; **53:** 115–17.
5. Thakur CP. Sodium antimony gluconate, amphotericin, and myocardial damage. *Lancet* 1998; **351:** 1928–9.
6. Rowles DM, Fraser SL. Amphotericin B lipid complex (ABLC)-associated hypertension: case report and review. *Clin Infect Dis* 1999; **29:** 1564–5.

Effects on the eyes. Rapid loss of vision resulting in permanent bilateral blindness occurred in a patient with lupus erythematosus and cryptococcal meningitis after a 1-mg test dose of amphotericin B.[1] Amphotericin B was considered to be the cause as visual disturbances associated with cryptococcal meningitis are usually progressive in nature and acute blindness with normal funduscopic appearance had not previously been reported.

1. Li PKT, Lai KN. Amphotericin B induced ocular toxicity in cryptococcal meningitis. *Br J Ophthalmol* 1989; **73:** 397–8.

Effects on the liver. Amphotericin B has only rarely been associated with adverse effects on the liver. Fatal hepatic failure was reported in a patient after a total dose of 4.82 g given intermittently over 1 year.[1] The patient had been given a potentially incompatible intravenous admixture of amphotericin B and diphenhydramine.

There have been a few reports of abnormal liver-function tests during amphotericin B therapy;[2,3] in such cases amphotericin B should be stopped. Hyperbilirubinaemia associated with amphotericin B has also been reported.[4] An episode of reversible hepatic and renal toxicity has been reported in a child with cystic fibrosis after a cumulative dose of 84 mg of conventional amphotericin B and 168 mg of liposomal amphotericin B.[5]

1. Carnecchia BM, Kurtzke JF. Fatal toxic reaction to amphotericin B in cryptococcal meningo-encephalitis. *Ann Intern Med* 1960; **53:** 1027–36.
2. Miller MA. Reversible hepatotoxicity related to amphotericin B. *Can Med Assoc J* 1984; **131:** 1245–7.
3. Abajo FJ, Carcas AJ. Amphotericin B hepatotoxicity. *BMJ* 1986; **293:** 1243.
4. Olin JL, Spooner LM. Amphotericin B-associated hyperbilirubinemia: case report and review of the literature. *Pharmacotherapy* 2006; **26:** 1011–7.
5. Mohan UR, Bush A. Amphotericin B-induced hepatorenal failure in cystic fibrosis. *Pediatr Pulmonol* 2002; **33:** 497–500.

Effects on the lungs. Reports implicating use of leucocytes[1] or other blood products[2] in the development of pulmonary reactions in patients receiving amphotericin B have been refuted,[3,4] and a report has indicated that amphotericin B can produce pulmonary toxicity in the absence of blood products.[5] An increased incidence of pulmonary symptoms was noted in patients given amphotericin B in lipid emulsion,[6] including acute respiratory distress after starting the infusion. Chest discomfort, including tightness, pain, dyspnoea, and acute hypoxia, has been reported in 3 patients during one-hour infusions of liposomal amphotericin B. The reactions occurred within 5 to 10 minutes of starting the infusion and resolved on stopping the infusion. A slower rate of infusion was subsequently tolerated in 2 patients.[7]

1. Wright DG, *et al*. Lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **304:** 1185–9.
2. Haber RH, *et al*. Acute pulmonary decompensation due to amphotericin B in the absence of granulocyte transfusions. *N Engl J Med* 1986; **315:** 836.
3. Forman SJ, *et al*. Pulmonary reactions associated with amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **305:** 584–5.
4. Bow EJ, *et al*. Pulmonary complications in patients receiving granulocyte transfusions and amphotericin B. *Can Med Assoc J* 1984; **130:** 593–7.
5. Roncoroni AJ, *et al*. Bronchiolis obliterans possibly associated with amphotericin B. *J Infect Dis* 1990; **161:** 589.
6. Schöffski P, *et al*. Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study. *BMJ* 1998; **317:** 379–84.
7. Johnson MD, *et al*. Chest discomfort associated with liposomal amphotericin B: report of three cases and review of the literature. *Pharmacotherapy* 1998; **18:** 1053–61.

Effects on potassium homoeostasis. In addition to the hypokalaemia known to be associated with amphotericin B and due to increased urinary excretion of potassium, hyperkalaemia has been reported in a patient with severe renal impairment who received a rapid infusion of amphotericin B (see Infusion Rate, under Administration, p. 570.2). Hyperkalaemia also occurred in a 2-year-old child with chronic renal failure after a two-hour infusion of conventional amphotericin B. Hyperkalaemia and fatal cardiac arrest were also reported in a 4-year-old child after 3 infusions of amphotericin B lipid complex.[1]

1. Barcia JP. Hyperkalemia associated with rapid infusion of conventional and lipid complex formulations of amphotericin B. *Pharmacotherapy* 1998; **18:** 874–6.

Hypersensitivity. Anaphylactoid reactions have occurred with conventional amphotericin B, but have also been associated with liposomal amphotericin B,[1-3] including reports of patients who subsequently tolerated conventional formulations.[1,3]

1. Laing RBS, *et al*. Anaphylactic reactions to liposomal amphotericin. *Lancet* 1994; **344:** 682.
2. Torre I, *et al*. Anaphylactic reaction to liposomal amphotericin B in children. *Ann Pharmacother* 1996; **30:** 1036–7.
3. Vaidya SJ, *et al*. Anaphylactic reaction to liposomal amphotericin B. *Ann Pharmacother* 2002; **36:** 1480–1.

Red man syndrome. Red man syndrome (see Vancomycin, p. 386.1) occurred in a patient on 2 occasions after a 1-mg test dose of amphotericin B.[1]

1. Ellis ME, Tharpe W. Red man syndrome associated with amphotericin B. *BMJ* 1990; **300:** 1468.

Treatment of Adverse Effects

To reduce febrile reactions antipyretics and antihistamines may be given before the intravenous infusion of conventional amphotericin B. Hydrocortisone given intravenously before or during amphotericin B infusion may also reduce febrile reactions. However, corticosteroids should not be given indiscriminately to patients given amphotericin B (see Interactions, p. 572.2) and dosage should be kept to a minimum. In the UK the advice is to give antipyretics or hydrocortisone prophylactically, but only to patients who have previously had acute adverse reactions and in whom continued treatment with intravenous amphotericin B is essential (see Prophylaxis, p. 572.1). Pethidine has been given intravenously to treat amphotericin B-induced shaking chills. Antiemetics may also be required. Amphotericin B is not removed by haemodialysis. Hypokalaemia and hypomagnesaemia should be corrected, and adequate hydration and sodium supplements may

reduce the severity of renal impairment. Lipid formulations of amphotericin B can be substituted for conventional amphotericin B if the latter cannot be tolerated.

Heparin has been added to conventional amphotericin B infusions to reduce the incidence of thrombophlebitis.

Reference to the management of adverse effects with *lipid* formulations.

1. Craddock C, *et al.* Best practice guidelines for the management of adverse events associated with amphotericin B lipid complex. *Expert Opin Drug Safety* 2010; **9:** 139–47.

Anaemia. Amphotericin B appears to produce a normochromic, normocytic anaemia by suppression of erythropoietin production.[1,2] Stopping amphotericin B reverses the suppression but if the anaemia is severe, or treatment with amphotericin B cannot be stopped, blood transfusions may be required. Recombinant erythropoietin may prove an alternative to blood transfusions in patients who need to continue treatment with amphotericin B.

1. MacGregor RR, *et al.* Erythropoietin concentrations in amphotericin B-induced anemia. *Antimicrob Agents Chemother* 1978; **14:** 270–3.
2. Lin AC, *et al.* Amphotericin B blunts erythropoietin response to anemia. *J Infect Dis* 1990; **161:** 348–51.

Electrolyte disturbances. It has been suggested[1] that amiloride could ameliorate the hypokalaemia and hypomagnesaemia associated with amphotericin B. However, since amiloride may produce sodium depletion and its own associated renal toxicity this strategy is potentially hazardous. Another report[2] has suggested that spironolactone may be a safe and effective method of preventing hypokalaemia.

1. Wazny LD, Brophy DF. Amiloride for the prevention of amphotericin B-induced hypokalemia and hypomagnesemia. *Ann Pharmacother* 2000; **34:** 94–7.
2. Ural AU. Comment: spironolactone prevents amphotericin B-induced hypokalemia in neutropenic patients. *Ann Pharmacother* 2000; **34:** 1488.

Nephrotoxicity. A review of strategies for limiting the toxicity of amphotericin B concluded that sodium balance should be monitored and sodium replacement implemented if necessary and that, where possible, salt restriction and drugs that potentiate sodium loss or nephrotoxicity should be avoided.[1] Correction of sodium depletion may reverse amphotericin B-induced nephrotoxicity.[2] However, assessment of sodium status and correction of deficiency should precede use of amphotericin B.[3,4] While supplementation with 150 mmol sodium has been recommended for suitable patients,[4] routine prophylactic use of sodium is not advised.[5] However, a randomised study in a small number of patients has suggested that prophylactic sodium supplementation could be beneficial, but that it enhances potassium loss.[6] Diuretics in general should be avoided[7] although there have been suggestions that potassium-sparing diuretics such as amiloride or spironolactone may be useful in preventing hypokalaemia (see Electrolyte Disturbances, above). Use of mannitol as a protective agent is controversial and is not recommended.[3,4,8] Amphotericin B is often given on alternate days although this has never been proven to reduce nephrotoxicity.[3,4]

More recently, lipid formulations have been reported to overcome most problems of chronic nephrotoxicity, even in patients with renal impairment after previous treatment with conventional amphotericin B (see Lipid Formulations, under Administration, p. 570.1).

1. Khoo SH, *et al.* Administering amphotericin B—a practical approach. *J Antimicrob Chemother* 1994; **33:** 203–13.
2. Heidemann HT, *et al.* Amphotericin B nephrotoxicity in humans decreased by salt repletion. *Am J Med* 1983; **75:** 476–81.
3. Warda J, Barriere SL. Amphotericin B nephrotoxicity. *Drug Intell Clin Pharm* 1985; **19:** 25–6.
4. Sabra R, Branch RA. Amphotericin B nephrotoxicity. *Drug Safety* 1990; **5:** 94–108.
5. Gardner ML, *et al.* Sodium loading treatment for amphotericin B-induced nephrotoxicity. *DICP Ann Pharmacother* 1990; **24:** 940–6.
6. Llanos A, *et al.* Effect of salt supplementation on amphotericin B nephrotoxicity. *Kidney Int* 1991; **40:** 302–8.
7. Fisher MA, *et al.* Risk factors for amphotericin B-associated nephrotoxicity. *Am J Med* 1989; **87:** 547–52.
8. Bullock WE, *et al.* Can mannitol reduce amphotericin B nephrotoxicity? Double-blind study and description of a new vascular lesion in kidneys. *Antimicrob Agents Chemother* 1976; **10:** 555–63.

Prophylaxis. The value of prophylaxis against generalised reactions to amphotericin B infusion was questioned after a retrospective study in 397 patients.[1] The most commonly used drugs were diphenhydramine, corticosteroids, paracetamol, and heparin. It was concluded that patients who had had an adverse reaction after amphotericin B should be given appropriate premedication before subsequent amphotericin B infusions, but that routine premedication was not justified.

1. Goodwin SD, *et al.* Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis* 1995; **20:** 755–61.

Precautions

Although anaphylaxis is rare after intravenous amphotericin B, it is advisable to give a test dose and then to observe the patient carefully for about 30 minutes before starting treatment. Patients with acute toxic reactions in whom treatment is essential may be given prophylactic treatment, as mentioned in Treatment of Adverse Effects, p. 571.3, to ameliorate the reactions. To reduce the risk of vein irritation and infusion-related adverse effects, the rate of intravenous infusion of conventional amphotericin B should be slow (see Infusion Rate, under Administration, p. 570.2). Patients given any parenteral form of amphotericin B should be monitored for changes in renal function, liver function, serum electrolytes, and haematological status. If the BUN or creatinine concentrations increase to clinically significant levels amphotericin B therapy should be interrupted or the dose reduced until renal function improves. Alternatively, a lipid amphotericin B preparation may be substituted. Treatment should be stopped if liver function tests are abnormal. Acute pulmonary reactions have been noted in patients given amphotericin B during or shortly after leucocyte transfusions. Although the association is contested (see Effects on the Lungs, p. 571.3), manufacturers of some amphotericin B products consider it advisable to separate the two and to monitor pulmonary function in these patients.

Care should be taken not to confuse the dosage regimens for individual preparations, and in particular those of conventional and lipid formulations; fatal overdoses have occurred after confusion between the various injectable formulations.

Interference with laboratory tests. Liposomal amphotericin B has been reported to interfere with a specific serum-phosphorus concentration assay;[1,2] when using the Synchron-LX-20 assay (*Beckman Coulter*), falsely elevated readings (as high as 2.5 mg/dL above the normal value) might be expected after around 7 days of therapy with liposomal amphotericin B, until around 5 or 6 days after treatment is stopped.[2]

1. Lane JW, *et al.* Pseudohyperphosphatemia associated with high-dose liposomal amphotericin B therapy. *Clin Chim Acta* 2008; **387:** 145–9.
2. Mendoza D, *et al.* Liposomal amphotericin B as a cause of pseudohyperphosphatemia. *Clin Infect Dis* 2008; **46:** 645–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amphotericin B (for systemic use) as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Stomatological preparations are classified as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. There are case reports of conventional amphotericin B having been used successfully to treat fungal infections in pregnant women without any adverse effects on the infant.[1-3] A review[4] of the use of antifungal drugs in pregnancy concluded that parenteral amphotericin B was the drug of first choice in the treatment of serious fungal infections in pregnancy. The safety of the lipid amphotericin formulations in pregnancy is not yet clear, although there are reports of pregnant women with visceral leishmaniasis who were treated in the first or second trimester with a short course of liposomal amphotericin B without adverse effects on the infant.[5,6]

1. Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman. *Am Rev Respir Dis* 1982; **126:** 350–3.
2. Peterson CM, *et al.* Coccidiodal meningitis and pregnancy: a case report. *Obstet Gynecol* 1989; **73:** 835–6.
3. Dean JL, *et al.* Use of amphotericin B during pregnancy: case report and review. *Clin Infect Dis* 1994; **18:** 364–8.
4. Sobel JD. Use of antifungal drugs in pregnancy: a focus on safety. *Drug Safety* 2000; **23:** 77–85.
5. Pagliano P, *et al.* Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother* 2005; **55:** 229–33.
6. Mueller M, *et al.* A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother* 2006; **58:** 811–5.

Interactions

Most interactions involving amphotericin B have been seen during treatment with conventional formulations. Since lipid formulations appear to be less toxic, it may be anticipated that they will produce fewer serious interactions.

Use of nephrotoxic antibacterials, ciclosporin or other nephrotoxic immunosuppressants, or parenteral pentamidine may lead to an increased risk of nephrotoxicity. If possible, amphotericin B should not be given to patients receiving antineoplastics. Diuretics should generally be avoided in patients taking amphotericin B. If a diuretic has to be given then volume and electrolyte depletion should be monitored carefully. The potassium-depleting effect of amphotericin B may enhance the effects of neuromuscular blocking drugs and may increase the toxicity of digitalis glycosides; corticosteroids may enhance the depletion of potassium and their immunosuppressive effects may be detrimental in patients with severe fungal infections.

Amphotericin B may increase the toxicity of flucytosine, but the combination is nonetheless used in severe infections for its synergistic activity. For information on synergistic and antagonistic effects with other antimicrobials, see under Antimicrobial Action, below. Renal excretion of zalcitabine may be reduced by amphotericin B.

For an increased risk of cardiac arrhythmias and arrest when amphotericin B was given to patients with myocardial damage induced by an antimony compound, see Effects on the Cardiovascular System, under Adverse Effects, p. 571.2.

Antimicrobial Action

Amphotericin B is a polyene antifungal antibiotic that appears to act mainly by interfering with the permeability of the cell membrane of sensitive fungi by binding to sterols, chiefly ergosterol. It is reported to be fungistatic at concentrations achieved clinically. It is active against *Absidia* spp., *Aspergillus* spp., *Basidiobolus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Conidiobolus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Mucor* spp., *Paracoccidioides brasiliensis*, *Rhizopus* spp., *Rhodotorula* spp., and *Sporothrix schenckii*. Other organisms that have been reported to be sensitive to amphotericin B include the algal *Prototheca* spp. and the protozoa *Leishmania* and *Naegleria* spp. It is inactive against bacteria (including rickettsia) and viruses.

Some resistant strains of *Candida* have been isolated from immunocompromised patients given prolonged treatment with amphotericin B.

Microbiological interactions. *Azoles.* Although there have been occasional reports of synergy between amphotericin B and the azole antifungals, greater emphasis has been placed on possible antagonism. Studies *in vitro* have supported theoretical concerns that the action of amphotericin B (which depends on binding to ergosterol in the fungal cell membrane) would be antagonised by azoles (which inhibit ergosterol synthesis).[1,2] *Animal* studies appear to have confirmed antagonism between amphotericin B and the imidazole ketoconazole, but not between amphotericin B and the triazoles fluconazole or itraconazole. Available clinical evidence seems to indicate that azoles given with, or as continuation therapy after, induction therapy with amphotericin B, are effective in severe infections, although reduced plasma concentrations of itraconazole have been reported in some patients while being given amphotericin B.[3] However, strains of *Candida albicans* resistant to both amphotericin B and fluconazole have emerged in patients who have received repeated or prolonged courses of fluconazole.[4,5]

1. Martin E, *et al.* Antagonistic effects of fluconazole and 5-fluorocytosine on candidacidal action of amphotericin B in human serum. *Antimicrob Agents Chemother* 1994; **38:** 1331–8.
2. Sud IJ, Feingold DS. Effect of ketoconazole on the fungicidal action of amphotericin B in Candida albicans. *Antimicrob Agents Chemother* 1983; **23:** 185–7.
3. Pennick GJ, *et al.* Concomitant therapy with amphotericin B and itraconazole: does this combination affect the serum concentration of itraconazole? *Intersci Conf Antimicrob Agents Chemother* 1994; **34:** 39 (A34).
4. Kelly SL, *et al.* Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; **348:** 1523–4.
5. Nolte FS, *et al.* Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; **44:** 196–9.

Pharmacokinetics

There is little or no absorption of amphotericin B from the gastrointestinal tract. When given intravenously in the *conventional colloidal form* and in the usual increasing dosage regimens, peak plasma concentrations of 0.5 to 4 micrograms/mL have been reported; the average plasma concentration with maintenance doses of 400 to 600 micrograms/kg daily tends to be 500 nanograms/mL. Amphotericin B is highly bound to plasma proteins and is widely distributed, but passes into the CSF only in small quantities. The plasma half-life is about 24 hours; with long-term use the terminal half-life increases to 15 days.

Unchanged amphotericin B is excreted in small amounts slowly in the urine. Traces are present in the serum and urine several weeks after completion of treatment. Amphotericin B is not removed by haemodialysis.

The pharmacokinetics of the lipid formulations differ considerably from the conventional formulation and from each other:

- at clinical doses of 1 to 7.5 mg/kg, *liposomal amphotericin B* produces peak plasma concentrations of around 8 to 80 micrograms/mL, around 20 times those with conventional formulations
- after doses of 0.5 to 8 mg/kg, *amphotericin B-sodium cholesteryl sulfate complex* produces peak plasma concentrations of about 0.7 to 6.2 micrograms/mL
- at a dose of 5 mg/kg daily, *amphotericin B phospholipid complex* produces peak plasma concentrations of about 1.7 micrograms/mL

Studies in *animals* have shown that concentrations in the kidney are several times lower after lipid formulations than with conventional ones.

Children and neonates. There was an inverse relationship between age and total clearance in 12 children aged 4 months to 14 years after the intravenous infusion of *conventional amphotericin B* 0.25 to 1.5 mg/kg daily, suggesting that children older than 9 years may require lower doses.[1] Peak serum concentrations ranged from 0.78 to about 10 micrograms/mL and did not correlate with dose. The elimination half-life was 18.1 ± 6.65 hours. A study in a group of 13 neonates with systemic fungal infections[2] considered that an initial dose of 500 micrograms/kg over 4 to 6 hours was well tolerated and could produce therapeutic serum concentrations more quickly than a regimen which consisted of 100 micrograms/kg on day one increased over 4 to 6 days to 500 micrograms/kg daily. After 5 days of treatment peak serum-amphotericin B concentrations ranged from 0.5 to 4.0 micrograms/mL and this was considered to be the range that could be achieved with the daily maintenance dose of 500 micrograms/kg. The elimination half-life was 14.8 hours. Drug elimination between doses was not detected in 4 of the infants; one was in oliguric renal failure and the other 3 had developed increases in serum-creatinine concentrations. Drug concentrations in CSF of 5 of the neonates were between 40 and 90% of simultaneous serum concentrations.

A comparative study[3] of plasma concentrations of *liposomal amphotericin B* in adults, children, and neonates after a dose of 1 mg/kg daily for 28 days, reported peak concentrations in children and neonates that were significantly lower than in adults. Increases in the mean peak plasma concentrations over days 1 to 28 were: adults, 1.02 to 1.66 micrograms/mL; children aged 1 to 12 years, 0.63 to 1.10 micrograms/mL; and neonates, 0.54 to 0.73 micrograms/mL. This was thought to be due to the greater volume of distribution in the neonates and greater clearance in older children.

The pharmacokinetics of *amphotericin B lipid complex* was studied in a cohort of 6 paediatric cancer patients with hepatosplenic candidiasis receiving a dose of 2.5 mg/kg daily for 6 weeks, to a total dosage of 105 mg/kg.[4] It was noted that the mean plasma concentrations over the dosing interval and area under the curve increased between the first and seventh doses but were similar between doses 7 and 42, suggesting that a steady state was achieved within 1 week of therapy. After the final dose of amphotericin B lipid complex, the mean plasma-amphotericin concentration was noted to be 0.50 micrograms/mL and the maximum concentration in whole blood was 1.69 micrograms/mL.

1. Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. *Antimicrob Agents Chemother* 1989; **33:** 1989–93.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116:** 791–7.
3. Kotwani RN, *et al.* A comparative study of plasma concentrations of liposomal amphotericin B (L-AMP-LRC-1) in adults, children and neonates. *Int J Pharm* 2002; **238:** 11–15.
4. Walsh TJ, *et al.* Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. *Antimicrob Agents Chemother* 1997; **41:** 1944–8.

Distribution. Amphotericin B concentrations in various organs and tissues were determined in 13 cancer patients who had received conventional amphotericin B before death.[1] Concentrations were determined by high-pressure liquid chromatography (HPLC) and bioassay. Mean recovery by HPLC reported as a percentage of total dose given was liver 27.5%, spleen 5.2%, lungs 3.2%, kidney 1.5%, heart 0.4%, brain 0.3%, and pancreas 0.2%; each organ had a specific accumulation pattern. The mean total recovery was 38.8%. Reported median bile concentration was 7.3 micrograms/mL. The drug concentrations obtained by bioassay were much lower than those measured by HPLC. As the HPLC-determined concentrations of amphotericin B were higher than the MICs for the pathogens in patients with candidiasis or aspergillosis, the poor clinical outcome in these patients suggested that amphotericin B in the tissue lacked antifungal activity.

In another study,[2] amphotericin B was not detected in the CSF of 4 AIDS patients with cryptococcal meningitis on intravenous maintenance doses of 350 to 1890 micrograms/kg of the conventional formulation given 1 to 7 times weekly. The clinical success of amphotericin B for this indication could not be explained by measurable CSF drug concentrations.

Concentrations of amphotericin B have been measured in fetal-cord serum in an infant and were 37.5% of maternal serum concentration.[3]

1. Collette N, *et al.* Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. *Antimicrob Agents Chemother* 1989; **33:** 362–8.
2. Dugoni BM, *et al.* Amphotericin B concentrations in cerebrospinal fluid of patients with AIDS and cryptococcal meningitis. *Clin Pharm* 1989; **8:** 220–1.
3. Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman. *Am Rev Respir Dis* 1982; **126:** 350–3.

Half-life. The terminal half-life for amphotericin B was 15 days in 2 patients on completion of conventional amphotericin B infusion therapy for disseminated histoplasmosis.[1] In another study,[2] the half-life was 21.5 hours (based on the exponential phase of disappearance from the blood) in a 65-year-old patient on a maintenance dose of 500 micrograms/kg of conventional amphotericin B infused over 1 hour every other day. Serum concentrations appeared to plateau at about 600 nanograms/mL 36 to 48 hours after each dose. This suggested that alternate-day dosage might be effective.

1. Atkinson AJ, Bennett JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother* 1978; **13:** 271–6.
2. Hoeprich PD. Elimination half-life of amphotericin B. *J Infect* 1990; **20:** 173–5.

Lipid formulations. References.

1. Janknegt R, *et al.* Liposomal and lipid formulations of amphotericin B: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **23:** 279–91.
2. Adedoyin A, *et al.* Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. *Antimicrob Agents Chemother* 1997; **41:** 2201–8.
3. Adedoyin A, *et al.* A pharmacokinetic study of amphotericin B lipid complex injection (Abelcet) in patients with definite or probable systemic fungal infections. *Antimicrob Agents Chemother* 2000; **44:** 2900–2.
4. Bekersky I, *et al.* Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. *Antimicrob Agents Chemother* 2002; **46:** 828–33.
5. Gubbins PO, *et al.* Pharmacokinetics and buccal mucosal concentrations of a 15 milligram per kilogram of body weight total dose of liposomal amphotericin B administered as a single dose (15 mg/kg), weekly dose (7.5 mg/kg), or daily dose (1 mg/kg) in peripheral stem cell transplant patients. *Antimicrob Agents Chemother* 2009; **53:** 3664–74.
6. Lestner JM, *et al.* Pharmacokinetics and pharmacodynamics of amphotericin B deoxycholate, liposomal amphotericin B, and amphotericin B lipid complex in an in vitro model of invasive pulmonary aspergillosis. *Antimicrob Agents Chemother* 2010; **54:** 3432–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abelcet; AmBisome; Amphotec; Anfogen†; ***Austral.***: Abelcet; AmBisome; Amphocil†; Fungilin; Fungizone†; ***Austria***: Abelcet; AmBisome; Ampho-Moronal; Amphocil; ***Belg.***: Abelcet; AmBisome; Fungizone†; ***Braz.***: Abelcet; AmBisome; Amphocil; Anforicin B; Fungi B; Fungizon; Funtex B; Unianf; ***Canad.***: Abelcet; AmBisome; Amphotec; Fungizone; ***Chile***: Fungizon; ***China***: Amphotec (安浮特克); Fengkesong (锋克松); ***Cz.***: Abelcet; Amphocil; ***Denm.***: Abelcet; AmBisome; Amphocil; Fungizone; ***Fin.***: Abelcet; AmBisome; Fungizone; ***Fr.***: Abelcet; AmBisome; Fungizone; ***Ger.***: Abelcet†; AmBisome; Ampho-Moronal; ***Gr.***: Abelcet; Aglutin; AmBisome; Amphiprol; Amphocil; Fungizone; ***Hong Kong***: AmBisome; Fungizone; ***Hung.***: Abelcet; AmBisome; Amphocil; Fungizone; ***India***: AmBisome; Amfocan; Amfotex; Ampholip; Amphotin-Lip; Amphotin; Amphotret; Fungisome; Fungizone; Mycol; ***Indon.***: Fungizone†; ***Irl.***: Abelcet; AmBisome; Amphocil†; Fungizone; ***Israel***: AmBisome; Amphocil†; Amphotec†; ***Ital.***: Abelcet; AmBisome; Amphocil; Fungilin; Fungizone; ***Jpn***: AmBisome; ***Malaysia***: Amphocil; Fungizone; ***Mex.***: Abelcet; Amfostat; Amphocil; Candipres; Terix; ***Neth.***: Abelcet; AmBisome; Amphocil; Fungizone; ***Norw.***: Abelcet; AmBisome; Fungizone†; ***NZ***: Abelcet; AmBisome; Fungilin; Fungizone†; ***Philipp.***: Ampholip; Amphotret; Fungizone†; ***Pol.***: Abelcet; AmBisome; Amphocil; ***Port.***: Abelcet; AmBisome; Amphocil; Fungizone†; ***Rus.***: AmBisome (АмБизом)†; Amphoglucamin (Амфоглюкамин)†; Fungizone (Фунгизон); ***S.Afr.***: AmBisome; Fungizone; ***Singapore***: Abelcet; AmBisome; Amphocil; Fungizone; ***Spain***: Abelcet; AmBisome; Amphocil; Fungizona†; ***Swed.***: Abelcet; AmBisome; Amphocil†; Fungizone; ***Switz.***: AmBisome; Ampho-Moronal; Fungizone; ***Thai.***: ADPHO†; AmBisome; Amphocil†; Ampholin; Amphotret; Fungizone†; ***Turk.***: Abelcet; AmBisome; Amphocil; Amphotec; Fungizone; ***UK***: Abelcet; AmBisome; Amphocil†; Fungilin†; Fungizone; ***USA***: Abelcet; AmBisome; Amphotec; ***Venez.***: Amphotec; Fungizone.

Multi-ingredient Preparations. ***Austria***: Mysteclin; ***Braz.***: Anfoterin; Gino-Teracin; Novasutin; Talsutin; Tericin AT; Tricocilin B; Vagiklin†; ***Ger.***: Mysteclin; ***Hong Kong***: Talsutin†; ***Indon.***: Talsutin†; ***Philipp.***: Vagimycin†; ***S.Afr.***: Vagmycin†.

Pharmacopoeial Preparations

BP 2014: Amphotericin for Infusion; Amphotericin Lozenges; Amphotericin Oral Suspension;
USP 36: Amphotericin B Cream; Amphotericin B for Injection; Amphotericin B Lotion; Amphotericin B Ointment.

Anidulafungin *(BAN, USAN, rINN)*

Anidulafungina; Anidulafungine; Anidulafunginum; LY-303366; V-Echinocandin; Анидулафунгин.

(4*R*,5*R*)-4,5-Dihydroxy-N^2-{[4″-(pentyloxy)-*p*-terphenyl-4-yl]carbonyl}-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-L-threonyl-L-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide; 1-((4*R*,5*R*)-4,5-Dihydroxy-N^2-{[4″-(pentyloxy)(1,1′:4′,1″-terphenyl)-4-yl]carbonyl}-L-ornithine)-echinocandin B.

$C_{58}H_{73}N_7O_{17}$=1140.3

CAS — 166663-25-8.

ATC — J02AX06.

ATC Vet — QJ02AX06.

UNII — 9HLM53094I.

Uses and Administration

Anidulafungin is an echinocandin antifungal active against *Aspergillus* and *Candida* spp. It is used in the treatment of candidaemia, oesophageal candidiasis, and other forms of invasive candidiasis.

Anidulafungin is given by intravenous infusion, the rate of which should not exceed 1.1 mg/minute. For candidaemia and other invasive candidiasis a loading dose of 200 mg is given on the first day followed by 100 mg daily thereafter. For oesophageal candidiasis the loading dose is 100 mg followed by 50 mg daily.

For details of doses in children, see below.

Reviews.

1. Murdoch D, Plosker GL. Anidulafungin. *Drugs* 2004; **64:** 2249–58.
2. Vazquez JA, Sobel JD. Anidulafungin: a novel echinocandin. *Clin Infect Dis* 2006; **43:** 215–22.
3. Menichetti F. Anidulafungin, a new echinocandin: effectiveness and tolerability. *Drugs* 2009; **69** (suppl 1): 95–7.

Administration in children. Although anidulafungin is not licensed for use in children, a small study[1] found that neonates and infants given an intravenous loading dose of 3 mg/kg followed by 1.5 mg/kg daily thereafter had overall drug exposures similar to older children receiving the same weight-adjusted dosage and adult patients receiving 100 mg daily; no serious drug-related adverse effects were reported in this study. The American Academy of Pediatrics[2] suggests that an intravenous loading dose of 1.5 to 3 mg/kg may be given on the first day followed by 0.75 to 1.5 mg/kg daily thereafter for susceptible *Candida* infections.

1. Cohen-Wolkowiez M, *et al.* Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. *Clin Pharmacol Ther* 2011; **89:** 702–7.
2. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Precautions

As for Caspofungin, see p. 575.1.

Dose adjustments are not required in patients with hepatic or renal impairment.

Interactions

Few drug interactions are expected with anidulafungin, as it is not metabolised by the hepatic cytochrome P450 system and almost no renal clearance occurs.

Antimicrobial Action

As for Caspofungin, see p. 575.2.

References.

1. Morace G, *et al.* Anidulafungin, a new echinocandin: in vitro activity. *Drugs* 2009; **69** (suppl 1): 91–4.

Pharmacokinetics

Steady state plasma concentrations of anidulafungin occur after the first loading dose; systemic clearance is about 1 litre/hour and the terminal elimination half-life is 40 to 50 hours. Anidulafungin is 84% bound to plasma proteins and the volume of distribution is 30 to 50 litres. It is not metabolised, but undergoes slow chemical degradation to inactive peptide degradants. Less than 10% of the intact drug is eliminated in the faeces and less than 1% is excreted in the urine.

References.

1. Dowell JA, *et al.* Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; **44:** 590–8.
2. Benjamin DK, *et al.* Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006; **50:** 632–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ecalta; ***Austral.***: Eraxis; ***Austria***: Ecalta; ***Belg.***: Ecalta; ***Braz.***: Ecalta; ***Canad.***: Eraxis; ***Chile***: Ecalta; ***Cz.***: Ecalta; ***Denm.***: Ecalta; ***Fr.***: Ecalta; ***Ger.***: Ecalta; ***Gr.***: Ecalta; ***Hong Kong***: Eraxis; ***Hung.***: Ecalta; ***Irl.***: Ecalta; ***Israel***: Eraxis; ***Ital.***: Ecalta; ***Malaysia***: Eraxis; ***Neth.***: Ecalta; ***Norw.***: Ecalta; ***Philipp.***: Eraxis; ***Pol.***: Ecalta; ***Port.***: Ecalta; ***Singapore***: Eraxis; ***Spain***: Ecalta; ***Swed.***: Ecalta; ***Switz.***: Ecalta; ***Thai.***: Eraxis; ***Turk.***: Eraxis; ***UK***: Ecalta; ***Ukr.***: Eraxis (Эраксис); ***USA***: Eraxis.

Bifonazole *(BAN, USAN, rINN)*

Bay-h-4502; Bifonatsoli; Bifonazol; Bifonazolas; Bifonazolum; Бифоназол.

1-(α-Biphenyl-4-ylbenzyl)imidazole.

The symbol † denotes a preparation no longer actively marketed

$C_{22}H_{18}N_2$=310.5
CAS — 60628-96-8.
ATC — D01AC10.
ATC Vet — QD01AC10.
UNII — QYJ305Z91O.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Bifonazole). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol.

Profile

Bifonazole is an imidazole antifungal with a broad spectrum of activity; sensitive fungi include dermatophytes, *Malassezia furfur*, and *Candida* spp. It also has some antibacterial activity.

Bifonazole is mainly used by topical application in the treatment of fungal skin and nail infections (p. 568.1). It is applied once daily as a 1% cream, powder, solution, or gel. Treatment is usually continued for 2 to 4 weeks. More prolonged treatment is necessary for nail infections and bifonazole may be applied initially with a 40% urea paste to soften the nail.

Local reactions including burning and itching have been reported.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

References.
1. Lackner TE, Clissold SP. Bifonazole: a review of its antimicrobial activity and therapeutic use in superficial mycoses. *Drugs* 1989; **38:** 204–25.
2. Bonifaz A, Ibarra G. Onychomycosis in children: treatment with bifonazole-urea. *Pediatr Dermatol* 2000; **17:** 310–314.
3. Watanabe S, *et al.* A comparative clinical study between 2 weeks of luliconazole 1% cream treatment and 4 weeks of bifonazole 1% cream treatment for tinea pedis. *Mycoses* 2006; **49:** 236–41. Correction. *ibid.*; 441.
4. Linder N, *et al.* Association of high-dose bifonazole administration during early pregnancy and severe limb reduction defects in the newborn. *Birth Defects Res A Clin Mol Teratol* 2010; **88:** 201–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bifonazole as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bimicot; Micosol; Sinamida Atleta; Sinamida Plus; ***Austral.***: Canesten Once Daily; Mycospor; ***Austria***: Canesten Bifonazol; ***Belg.***: Canestene Derm Bifonazole; ***Braz.***: Mycospor; ***Chile***: Multifung; Mycosporan; ***China***: Bayclear Plus (金美克); Bi Fu (必伏); Fu Kang (孚康); Fu Ning (孚宁); Fu Qi (孚琪); FuKang (孚康); Hui Fu De (惠复得); Lie He Suo (列合素); Mycospor (美克); ***Cz.***: Canespor; Mycospor; ***Fr.***: Amycor; ***Ger.***: Antifungol Extra†; Bifomyk; Bifon; Canesten Extra; Mycospor; ***Gr.***: Aeroderma; Bifized; Bifon; Compaser; Fungiderm; Gloryskin; Helpovion; Kavaderm; Myco-flusemidon; Mycospor; Neltolon; Ofniforte; Poulmycin; Rye; ***Hong Kong***: Canesten Extra; Mycospor†; ***Hung.***: Canesten Plus; Mycospor†; ***India***: Mycospor; ***Indon.***: Mycospor; ***Israel***: Agispor; ***Ital.***: Azolmen; Bifazol†; Canesten Unidie; ***Mex.***: Mycospor; ***Neth.***: Mycospor; ***Pol.***: Mycospor; ***Port.***: Mycospor; Topical; ***Rus.***: Bifosin (Бифосин); Mycospor (Микоспор); ***S.Afr.***: Mycospor; ***Singapore***: Mycospor; ***Spain***: Bifokey; Canespie Bifonazol; Levelina; Mycospor; ***Swed.***: Mycosporan†; ***Turk.***: Mycospor; ***Ukr.***: Bifonal (Бифонал); Canespor (Канеспор); Mycospor (Микоспор); ***Venez.***: Mycospor.

Multi-ingredient Preparations. ***Arg.***: Empecid Pie; Piecidex NF; ***Austria***: Canesten Bifonazol comp; ***Cz.***: Mycospor Sada na Nehty; ***Fr.***: Amycor Onychoset; ***Ger.***: Canesten Extra Nagelset; ***Hung.***: Canespro; ***Israel***: Agispor Onychoset; Comagis; Keratospor; ***Mex.***: Mycospor Onicoset; ***Pol.***: Mycospor Onychoset; ***Rus.***: Mycospor (Микоспор); ***S.Afr.***: Mycospor Onycho-set†; ***Spain***: Mycospor Onicoset; ***Turk.***: Mycospor; ***Ukr.***: Canespor Set (Канеспор Набор); Mycospor Kit (Микоспор Набор)†; ***Venez.***: Mycospor Onicoset.

Bromochlorosalicylanilide

Bromchlorsalicylanilidum; Bromisalisyylikloorianilidi; Bromoclorosalicilanilida; Bromsalicylkloranilid; Бромохлоросалициланилин.
5-Bromo-4′-chlorosalicylanilide; 5-Bromo-*N*-(4-chlorophenyl)-2-hydroxybenzamide.
$C_{13}H_9BrClNO_2$=326.6
CAS — 3679-64-9.
ATC — D01AE01.
ATC Vet — QD01AE01.

Profile

Bromochlorosalicylanilide is a bromsalan antifungal that has been applied topically. Photosensitivity may occur. See also Bromsalans, p. 1741.2.

Butenafine Hydrochloride *(BANM, USAN, rINNM)*

Butenafiinihydrokloridi; Butenafina, hidrocloruro de; Buténafine, Chlorhydrate de; Butenafinhydroklorid; Butenafini Hydrochloridum; Hidrocloruro de butenafina; KP-363; Бутенафина Гидрохлорид.
N-(*p*-*tert*-Butylbenzyl)-*N*-methyl-1-naphthalenemethylamine hydrochloride; 4-*tert*-Butylbenzyl(methyl)(1-naphthalenemethyl)amine hydrochloride.
$C_{23}H_{27}N,HCl$=353.9
CAS — 101828-21-1 (butenafine); 101827-46-7 (butenafine hydrochloride).
ATC — D01AE23.
ATC Vet — QD01AE23.
UNII — R8XA2029ZI.

Profile

Butenafine is a benzylamine antifungal with actions similar to those of the allylamine antifungal terbinafine (p. 593.3). The hydrochloride is used topically as a 1% cream for the treatment of superficial dermatophyte infections (see Skin Infections, p. 568.1).

Reviews.
1. McNeely W, Spencer CM. Butenafine. *Drugs* 1998; **55:** 405–12.
2. Singal A. Butenafine and superficial mycoses: current status. *Expert Opin Drug Metab Toxicol* 2008; **4:** 999–1005.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ingebut†; ***Braz.***: Tefin; ***Chile***: Dermacom; ***China***: Fu Da Jing (孚答静); Jia Rui (嘉瑞); Te Li Da (特利达); ***India***: Butop; Fintop; ***Israel***: Mentax; ***Jpn***: Mentax; ***Mex.***: Derfina; Lexoderil; ***Philipp.***: Funcid†; ***USA***: Lotrimin Ultra; Mentax.

Butoconazole Nitrate *(BANM, USAN, rINNM)*

Butoconazol, nitrato de; Butoconazole, Nitrate de; Butoconazoli Nitras; Nitrato de butoconazol; RS-35887-00-10-3; RS-35887; Бутоконазола Нитрат.
1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)butyl]imidazole mononitrate.
$C_{19}H_{17}Cl_3N_2S,HNO_3$=474.8
CAS — 64872-76-0 (butoconazole); 64872-77-1 (butoconazole nitrate).
ATC — G01AF15.
ATC Vet — QG01AF15.
UNII — 4805237NP5.

Pharmacopoeias. In *US.*

USP 36: (Butoconazole Nitrate). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in acetone, in acetonitrile, in dichloromethane, and in tetrahydrofuran; very slightly soluble in ethyl acetate; sparingly soluble in methyl alcohol. Protect from light.

Uses and Administration

Butoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vulvovaginal candidiasis (p. 564.1). It is given intravaginally as a 100-mg pessary or as 5g of a 2% cream for 3 consecutive nights; a single application of the cream has also been used.

Adverse Effects and Precautions

Local reactions including burning and irritation and pelvic or abdominal pain or cramping may occur when butoconazole is applied vaginally.

Intravaginal preparations of butoconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Effects on the blood. Severe reversible thrombocytopenia was associated with treatment with intravaginal butoconazole.[1] The patient had previously had a drop in white cell count after treatment with intravaginal clotrimazole, suggestive of an idiosyncratic reaction to imidazoles.

1. Maloley PA, *et al.* Severe reversible thrombocytopenia resulting from butoconazole cream. *DICP Ann Pharmacother* 1990; **24:** 143–4.

Antimicrobial Action

Butoconazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p. 587.2) including activity against *Candida* spp.

Pharmacokinetics

About 5% of a dose of butoconazole is absorbed after vaginal use. The plasma half-life is 21 to 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gynazole; ***Belg.***: Gynomyk; ***Braz.***: Gynazole; ***Canad.***: Gynazole; ***China***: Gynazole (洁娜宁); ***Fr.***: Gynomyk†; ***Hung.***: Gynazol; ***Indon.***: Gynofort; ***Malaysia***: Gynofort; ***Mex.***: Gynafem†; ***Neth.***: Gynomyk; ***Pol.***: Gynazol; ***Rus.***: Gynofort (Гинофорт); ***Singapore***: Gynofort†; ***Switz.***: Gynazole†; ***Ukr.***: Gynofort (Гинофорт); ***USA***: Gynazole†; Mycelex-3†.

Pharmacopoeial Preparations
USP 36: Butoconazole Nitrate Vaginal Cream.

Caspofungin Acetate

(BANM, USAN, rINNM)

Acetato de caspofungina; Caspofungina, acetato de; Caspofungine, Acétate de; Caspofungini Acetas; Kaspofungiiniasetaatti; Kaspofunginacetat; L-743873; MK-0991; Каспофунгина Ацетат.
(4*R*,5*S*)-5-[(2-Aminoethyl)amino]-N^2-(10,12-dimethyltetradecanoyl)-4-hydroxy-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-L-threonyl-*threo*-3-hydroxy-L-ornithyl-*trans*-3-hydroxy-L-proline cyclic (6→1)-peptide diacetate.
$C_{52}H_{88}N_{10}O_{15},2C_2H_4O_2$=1213.4
CAS — 179463-17-3.
ATC — J02AX04.
ATC Vet — QJ02AX04.
UNII — VUW370O5QE.

Uses and Administration

Caspofungin is an echinocandin antifungal used in the treatment of invasive aspergillosis (p. 563.1) in patients who are refractory to, or intolerant of, other therapy. It is also used in the treatment of invasive candidiasis (and in some countries for oesophageal candidiasis) and as empirical therapy for presumed fungal infections in febrile, neutropenic patients.

Caspofungin is used as the acetate but doses are expressed in terms of the base; caspofungin acetate 77.7 mg is equivalent to about 70 mg of caspofungin. It is given by slow intravenous infusion over about 1 hour. A loading dose of 70 mg is given on the first day and is followed by 50 mg daily; a loading dose is not used in those being treated for oesophageal candidiasis. In adult patients weighing more than 80 kg, and in patients taking hepatic enzyme-inducing drugs who fail to respond, a daily dose of 70 mg is recommended. Doses may need to be reduced in patients with hepatic impairment (see p. 575.1).

Extemporaneously prepared 0.5% caspofungin acetate eye drops have been used to treat fungal eye infections (see p. 575.1).

Reviews.
1. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. *J Antimicrob Chemother* 2003; **51:** 513–21.
2. Deresinski SC, Stevens DA. Caspofungin. *Clin Infect Dis* 2003; **36:** 1445–57.
3. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 1. *Am J Health-Syst Pharm* 2006; **63:** 1693–1703.
4. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 2. *Am J Health-Syst Pharm* 2006; **63:** 1813–20.
5. Falagas ME, *et al.* Caspofungin for the treatment of fungal infections: a systematic review of randomized controlled trials. *Int J Antimicrob Agents* 2007; **29:** 136–43.
6. Hope WW, *et al.* The pharmacology and clinical use of caspofungin. *Expert Opin Drug Metab Toxicol* 2007; **3:** 263–74.
7. Waters L, Nelson M. The use of caspofungin in HIV-infected individuals. *Expert Opin Invest Drugs* 2007; **16:** 899–908.
8. Lichtenstern C, *et al.* Efficacy of caspofungin in invasive candidiasis and candidemia—de-escalation strategy. *Mycoses* 2008; **51** (suppl 1): 35–46.
9. Heinz WJ, Einsele H. Caspofungin for treatment of invasive aspergillus infections. *Mycoses* 2008; **51** (suppl 1): 47–57.
10. Mu XD, *et al.* Caspofungin in salvage treatment of severe pneumocystis pneumonia: case report and literature review. *Chin Med J (Engl)* 2009; **122:** 996–9.
11. Colombo AL, *et al.* Caspofungin use in patients with invasive candidiasis caused by common non-albicans Candida species: review of the caspofungin database. *Antimicrob Agents Chemother* 2010; **54:** 1864–71.
12. Holt SL, Drew RH. Echinocandins: addressing outstanding questions surrounding treatment of invasive fungal infections. *Am J Health-Syst Pharm* 2011; **68:** 1207–20.
13. Chen SC-A, *et al.* Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs* 2011; **71:** 11–41.

Administration in children. Use of caspofungin appears to be effective and well tolerated in paediatric patients.[1-6] In

the UK, it is licensed for use in children from 12 months of age for the treatment of invasive aspergillosis in those who are refractory to, or intolerant of other therapy. It is also licensed for treatment of invasive candidiasis, and for empirical therapy of presumed fungal infection in those with febrile neutropenia. In the USA, caspofungin is licensed for use in similar indications in children as young as 3 months; it is also licensed for use in oesophageal candidiasis. (The *BNFC* also suggests that children 3 months to 1 year of age may receive caspofungin treatment.)

Doses are based on body-surface and given by intravenous infusion over about 1 hour. For all indications, a 70 mg/m^2 loading dose is given on the first day, followed by 50 mg/m^2 once daily thereafter; the maintenance dose may be increased to 70 mg/m^2 where the standard dose has been well tolerated, but led to inadequate clinical response. Single doses for infants and children should not exceed 70 mg.

Although unlicensed, the use of caspofungin in neonates has been studied. A case series[4] of 10 neonates (9 preterm) with invasive candidiasis not responsive to amphotericin B and/or fluconazole reported that *Candida* spp. were cleared from the blood in all patients in a mean of 4.3 days after starting caspofungin therapy. Nine neonates were given an initial dose of 1 mg/kg daily for the first 2 days followed by 2 mg/kg daily for 15 to 21 days; the other was given a lower dose. UK licensed product information and the *BNFC* both suggest that neonates and infants less than 3 months of age may be given a dose of 25 mg/m^2 once daily.

1. Lehrnbecher T, Groll AH. Experiences with the use of caspofungin in paediatric patients. *Mycoses* 2008; **51** (suppl 1): 58–64.
2. Franklin JA, *et al*. Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J* 2003; **22:** 747–9.
3. Groll AH, *et al*. Treatment with caspofungin in immunocompromised paediatric patients: a multicentre survey. *J Antimicrob Chemother* 2006; **57:** 527–35.
4. Odio CM, *et al*. Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004; **23:** 1093–7.
5. Zaoutis TE, *et al*. A prospective, multicenter study of caspofungin for the treatment of documented Candida or Aspergillus infections in pediatric patients. *Pediatrics* 2009; **123:** 877–84.
6. Garnock-Jones KP, Keam SJ. Caspofungin: in pediatric patients with fungal infections. *Paediatr Drugs* 2009; **11:** 259–69.

Administration in hepatic impairment. Patients with mild hepatic impairment do not require dosage adjustment. In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9), a daily dose of caspofungin 35 mg should be used after the initial dose of 70 mg; appropriate doses for patients with severe hepatic impairment have not been established.

Fungal eye infections. Fungal keratitis caused by *Candida albicans* was successfully treated with extemporaneously prepared 0.5% caspofungin acetate eye drops after the patient failed to respond to one-months' treatment with topical and oral voriconazole. The eye drops were initially applied hourly for one week followed by a progressive decrease in the dose over a further 3 weeks.[1] Caspofungin acetate 0.5% eye drops have also been used with intrastromal caspofungin acetate 0.5% plus topical, oral, and intrastromal voriconazole for the treatment of a patient with atypical *Alternaria* keratitis.[2]

Caspofungin acetate 0.5% eye drops are prepared aseptically by reconstituting a 50-mg vial of caspofungin acetate with 10.5 mL of normal saline[1] or water for injection.[2,3] A stability study[3] found that the solution was stable under refrigerated conditions (at about 4 degreesC) for 4 weeks and at room temperature (about 25 degreesC) for 3 days.

1. Hurtado-Sarrió M, *et al*. Successful topical application of caspofungin in the treatment of fungal keratitis refractory to voriconazole. *Arch Ophthalmol* 2010; **128:** 941–2.
2. Neoh CF, *et al*. Treatment of Alternaria keratitis with intrastromal and topical caspofungin in combination with intrastromal, topical, and oral voriconazole. *Ann Pharmacother* 2011; **45:** e24.
3. Neoh CF, *et al*. Stability of extemporaneously prepared 0.5-percent caspofungin eye drops: a potential cost-savings exercise. *Antimicrob Agents Chemother* 2012; **56:** 3435–7.

Adverse Effects and Precautions

Adverse effects reported with caspofungin have included diarrhoea, nausea and vomiting, flushing, headache, fever, tachycardia, and venous complications around the infusion site. Possible histamine-mediated symptoms have been rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Hypokalaemia and decreased red and white blood cell counts are common. Anaphylaxis has occurred.

Raised liver enzyme values are common and there have been isolated cases of hepatotoxicity; patients who develop abnormal liver function tests should be monitored for deterioration in hepatic function. Caspofungin may need to be given in reduced doses to patients with hepatic impairment (see above).

Breast feeding. Caspofungin is excreted in the breast milk of lactating *animals* but the risk to breast-fed infants is suggested to be low. Recommendations in licensed product information vary: in the UK it recommends against use in women who are breast feeding, while in the USA caution is advised.

Effects on the skin. Severe toxic epidermal necrolysis, which progressed and was eventually fatal despite systemic hydrocortisone and diphenhydramine, developed in an elderly man given a dose of caspofungin for disseminated candidal infection.[1] The patient had developed transient rash, responsive to corticosteroid and antihistamine treatment, after a previous dose.

1. Lee M-C, *et al*. Caspofungin-induced severe toxic epidermal necrolysis. *Ann Pharmacother* 2010; **44:** 1116–18.

Hypersensitivity. Cross-sensitivity to caspofungin has been reported[1] in a patient hypersensitive to micafungin.

1. Patel S, *et al*. Immediate cross-hypersensitivity between micafungin and caspofungin: a case report. *J Oncol Pharm Pract* 2009; **15:** 187–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies caspofungin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Caspofungin has been shown to cross the placenta in *animal* studies and was shown to be embryotoxic in *rats* and *rabbits*; it was noted that there were no adequate and well-controlled studies in human pregnancy. Caspofungin is generally only recommended in pregnancy if the benefits to the mother are considered to outweigh the risks to the fetus.

Interactions

Although caspofungin is not appreciably metabolised by the hepatic cytochrome P450 system, drugs that induce hepatic enzymes may increase its clearance. Such effects have been noted with carbamazepine, dexamethasone, efavirenz, nevirapine, phenytoin, and rifampicin, and an increase in the dose of caspofungin should be considered in patients who are also taking these drugs and who are not clinically responding (see Uses and Administration, p. 574.3).

When caspofungin has been given with ciclosporin, an increase in the area under the concentration-time curve for caspofungin, as well as increases in hepatic enzymes, were seen and use of the two drugs together should be avoided unless the potential benefit outweighs the risk.

Caspofungin has resulted in decreased blood concentrations of tacrolimus and therapeutic drug monitoring and appropriate dosage adjustments to tacrolimus are recommended.

Antimicrobial Action

Caspofungin inhibits the synthesis of β-1,3-D-glucan, an essential component of the cell wall of many fungi. Caspofungin shows *in-vitro* activity against many *Aspergillus* spp. and is fungicidal against *Candida* spp. including non-albicans strains.

Pharmacokinetics

Plasma concentrations of caspofungin decline in a polyphasic manner after intravenous infusion. The initial short α-phase occurs immediately post-infusion and is followed by a β-phase with a half-life of 9 to 11 hours; an additional longer γ-phase also occurs with a half-life of 40 to 50 hours. Plasma clearance is dependent on distribution rather than on biotransformation or excretion. Caspofungin is highly bound to plasma protein. There is slow metabolism of caspofungin by hydrolysis and *N*-acetylation and excretion in faeces and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cancidas; ***Austral.***: Cancidas; ***Austria***: Cancidas; ***Belg.***: Cancidas; ***Braz.***: Cancidas; ***Canad.***: Cancidas; ***Chile***: Cancidas; ***China***: Cancidas (科赛斯); ***Cz.***: Cancidas; ***Denm.***: Cancidas; ***Fin.***: Cancidas; ***Fr.***: Cancidas; ***Ger.***: Cancidas; ***Gr.***: Cancidas; ***Hong Kong***: Cancidas; ***Hung.***: Cancidas; ***India***: Cancidas; ***Irl.***: Cancidas; ***Israel***: Cancidas; ***Ital.***: Cancidas; ***Jpn***: Cancidas; ***Malaysia***: Cancidas; ***Neth.***: Cancidas; ***Norw.***: Cancidas; ***NZ***: Cancidas; ***Philipp.***: Cancidas; ***Pol.***: Cancidas; ***Port.***: Cancidas; ***Rus.***: Cancidas (Кансидас); ***S.Afr.***: Cancidas; ***Singapore***: Cancidas; ***Spain***: Cancidas; ***Swed.***: Cancidas; ***Switz.***: Cancidas; ***Thai.***: Cancidas; ***Turk.***: Cancidas; ***UK***: Cancidas; ***Ukr.***: Cancidas (Кансидаз); ***USA***: Cancidas; ***Venez.***: Cancidas.

Chlormidazole Hydrochloride *(BANM, rINNM)*

Chlormidazole, Chlorhydrate de; Chlormidazoli Hydrochloridum; Clomidazole Hydrochloride; Clormidazol, hidrocloruro de; Hidrocloruro de clormidazol; Хлормидазола Гидрохлорид.

1-(4-Chlorobenzyl)-2-methylbenzimidazole hydrochloride.

$C_{15}H_{13}ClN_2,HCl$=293.2

CAS — 3689-76-7 (chlormidazole); 54118-67-1 (chlormidazole hydrochloride).

ATC — D01AC04.

ATC Vet — QD01AC04.

UNII — 0RH29TB951.

Profile

Chlormidazole hydrochloride is an imidazole antifungal used topically as the hydrochloride in the treatment of fungal infections of the skin.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Unifungicid†.

Multi-ingredient Preparations. ***Pol.***: Polfungicid.

Chlorphenesin *(BAN, pINN)*

Chlorphénésine; Chlorphenesinum; Clorfenesina; Kloorifenesiini; Klorfenesin; Хлорфенезин.

3-(4-Chlorophenoxy)propane-1,2-diol.

$C_9H_{11}ClO_3$=202.6

CAS — 104-29-0.

ATC — D01AE07.

ATC Vet — QD01AE07.

UNII — I670DAL4SZ.

Profile

Chlorphenesin has antifungal and antibacterial properties. It has been applied locally in mild uncomplicated dermatophyte and other cutaneous infections and in vaginal infections.

Chlorphenesin carbamate (p. 2022.2) is used as a skeletal muscle relaxant.

Adverse effects. References.

1. Brown VL, Orton DI. Two cases of facial dermatitis due to chlorphenesin in cosmetics. *Contact Dermatitis* 2005; **52:** 48–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Dermicil.

Multi-ingredient Preparations. ***Austral.***: ZSC; ***Braz.***: Oto-Betnovate; ***India***: Derby Cool; Exomega.

Ciclopirox *(BAN, USAN, rINN)*

Ciclopiroxum; Ciklopiroksas; Ciklopirox; Hoe-296b; Siklopiroksi; Циклопирокс.

6-Cyclohexyl-1-hydroxy-4-methyl-2-pyridone.

$C_{12}H_{17}NO_2$=207.3

CAS — 29342-05-0.

ATC — D01AE14; G01AX12.

ATC Vet — QD01AE14; QG01AX12.

UNII — 19W019ZDRJ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ciclopirox). A white or yellowish-white, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Ciclopirox). A white to slightly yellowish white, crystalline powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane; soluble in ether. Store at a temperature of 15 degrees to 30 degrees. Protect from light.

Ciclopirox Olamine *(BANM, USAN, rINNM)*

Ciclopirox-Olamin; Ciclopirox olamina; Ciclopirox olaminum; Ciclopiroxi Olaminum; Ciclopiroxolamine; Ciclopiroxum Olaminum; Ciklopiroksas olaminas; Ciklopirox olamin; Ciklopiroxolamin; Ciklopirox-olamin; Hoe-296; Siklopiroksiolamiini; Sikloproks Olamin; Циклопирокс Оламин.

The 2-aminoethanol salt of 6-Cyclohexyl-1-hydroxy-4-methyl-2-pyridone.

$C_{12}H_{17}NO_2,C_2H_7NO$=268.4

CAS — 41621-49-2.

ATC — D01AE14; G01AX12.
ATC Vet — QD01AE14; QG01AX12.
UNII — 50MD4SB4AP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Ciclopirox Olamine). A white or pale yellow crystalline powder. It exhibits polymorphism. Slightly soluble in water; very soluble in alcohol and in dichloromethane; slightly soluble in ethyl acetate; practically insoluble in cyclohexane. A 1% solution in water has a pH of 8.0 to 9.0. Protect from light.

USP 36: (Ciclopirox Olamine). A white to slightly yellowish-white, crystalline powder. Slightly soluble in water; very soluble in alcohol and in dichloromethane; practically insoluble in cyclohexane. pH of a 1% solution in water is between 8.0 and 9.0. Store in airtight containers at a temperature of 5 degrees to 25 degrees. Protect from light.

Uses and Administration

Ciclopirox is an antifungal that is applied topically in the treatment of fungal skin and nail infections, including cutaneous candidiasis (p. 564.1), dermatophytosis, pityriasis versicolor (see Skin Infections, p. 568.1), and seborrhoeic dermatitis (p. 1689.1). It has also been used in the treatment of vaginal candidiasis.

It is applied twice daily for skin infections, as a cream, gel, suspension, solution, or powder; both the base and the olamine salt have been used, with products containing the equivalent of 0.77% ciclopirox base.

A lacquer containing 8% ciclopirox base is applied once daily for nail infections.

A shampoo containing 1% ciclopirox base is used twice weekly for the treatment of seborrhoeic dermatitis.

References.
1. Gupta AK, Skinner AR. Ciclopirox for the treatment of superficial fungal infections: a review. *Int J Dermatol* 2003; **42** (suppl 1): 3–9.
2. Gupta AK, Nicol KA. Ciclopirox 1% shampoo for the treatment of seborrheic dermatitis. *Int J Dermatol* 2006; **45:** 66–9.

Adverse Effects

Irritation and pruritus have been reported after topical application of ciclopirox.

Antimicrobial Action

Ciclopirox has a wide spectrum of antifungal activity. It inhibits most *Candida, Epidermophyton, Microsporum,* and *Trichophyton* spp. and is also active against *Malassezia furfur.* It has some antibacterial activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Loprox; Micopirox; Mycosten†; Stieprox; ***Austral.***: Stieprox; ***Austria***: Batrafen; Kitonail; Stieprox; ***Belg.***: Mycosten; ***Braz.***: Celamina; Derm Prox; Fungirox; Gino-Loprox; Loprox; Micolamina; Mupirox; Stiprox; ***Canad.***: Loprox; Penlac; Stieprox; ***Chile***: Batrafen; Fungopirox; Micopirox; Stiprox; ***China***: Batrafen (巴特芬); Dafnegin (得凡尼金); Huanli (环利); Sai Jie (赛洁); ***Cz.***: Batrafen; Dafnegin; Polinail; Stieprox; ***Denm.***: Mycofen; Sebiprox; ***Fin.***: Sebiprox†; ***Fr.***: Mycosquam†; Mycoster; Onytec; Sebiprox; Stiprox; ***Ger.***: Batrafen; Ciclocutan; Ciclopoli; Inimur Myko†; Nagel Batrafen; Sebiprox; ***Gr.***: Batrafen; Candimyc; Dafnegin; Kitonail; Myclopir; Mycolacil; Mycomycen; Neo-botacreme; Neo-mycodermol; Rozolam; Stieprox; ***Hong Kong***: Batrafen; Stieprox; ***Hung.***: Batrafen; ***India***: Batrafan; Olamin; Onylac; ***Indon.***: Batrafen; Loprox; ***Irl.***: Batrafen†; Oilatum Scalp Treatment†; Stieprox; ***Israel***: Batrafen; Cicloderm; Ciclopoli; Funginail; Mycoster; ***Ital.***: Batrafen; Bioginal; Brumixol; Ciclopoli; Dafnegin; Miclast; Micomicen; Micoxolamina; Roxolac; Sebiprox; Stiprox; ***Malaysia***: Stieprox; ***Mex.***: Funamix; Loprox; Stiprox; ***Neth.***: Batrafen; Loprox; Sebiprox†; ***Norw.***: Sebiprox; Stieprox†; ***NZ***: Batrafen; Stieprox; ***Philipp.***: Stieprox; ***Pol.***: Batrafen; Dafnegin; Hascofungin; Mycosten; Pirolam; Polinail; Stieprox; ***Port.***: Batrafen†; Mycoster; Sebiprox; ***Rus.***: Batrafen (Батрафен); Dafnegin (Дафнеджин); ***Singapore***: Stieprox; ***Spain***: Ciclochem; Fungowas; Miclast; Ony-Tec; Sebiprox; ***Swed.***: Sebiprox; ***Switz.***: Batrafen†; Ciclocutan; Ciclopoli; Dafnegil Neo†; Dafnegil; Mycoster; Sebiprox; ***Thai.***: Loprox; Stieprox; ***Turk.***: Canolen; Nibulen; ***UK***: Oilatum Scalp Treatment; ***USA***: Ciclodan; Loprox; Pedipirox; Penlac; ***Venez.***: Batrafen.

Multi-ingredient Preparations. ***Arg.***: Derm's; Piroctol; Pityrum; Stieproxal; ***Fr.***: Kelual DS; Stiproxal; Trigopax; ***India***: Flucort-C; Fluticare-C; Olamin-F; ***Israel***: Cicloderm-C; ***UK***: Oilatum Scalp Intensive; ***USA***: CNL Nail Kit.

Pharmacopoeial Preparations
USP 36: Ciclopirox Olamine Cream; Ciclopirox Olamine Topical Suspension; Ciclopirox Topical Solution.

Climbazole *(BAN, rINN)*

Bay-e-6975; Climbazol; Climbazolum; MEB-6401; Климбазол.
1-(*p*-Chlorophenoxy)-1-imidazol-1-yl-3,3-dimethyl-2-butanone.
$C_{15}H_{17}ClN_2O_2$=292.8
CAS — 38083-17-9.
UNII — 9N42CW7154.

NOTE. The name Crinipan AD has been used as a trade mark for climbazole.

Profile

Climbazole is an azole antifungal included in preparations for the topical treatment of seborrhoeic dermatitis.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Mencogrin; Micocert; Micodual; ***Chile***: Eucerin Shampoo Anticaspa†; Eucerin Shampoo para el Tratamiento de la Caspa; Micodual; Node DS†; Shampoo Anticaspa†; ***Fr.***: Node DS; Node P†; Sebosquam†; Squaphane E; Squaphane P; Squaphane S; Squaphane; Squaphane; ***Ital.***: Cue Soluzione Otologica; Pitiren; ***Port.***: Efluvium Anticaspa†; ***Venez.***: Node DS; Sensibio DS.

Clotrimazole *(BAN, USAN, rINN)*

Bay-5097; Clotrimazol; Clotrimazolum; FB-5097; Klotrimatsoli; Klotrimazol; Klotrimazolas; Klotrymazol; Клотримазол.
1-(α-2-Chlorotrityl)imidazole.
$C_{22}H_{17}ClN_2$=344.8
CAS — 23593-75-1.
ATC — A01AB18; D01AC01; G01AF02.
ATC Vet — QA01AB18; QD01AC01; QG01AF02; QJ02AB90.
UNII — G07GZ97H65.

NOTE. Compounded preparations of clotrimazole may be represented by the following names:
- Co-climasone (*PEN*)—clotrimazole and betamethasone dipropionate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Clotrimazole). A white or pale yellow crystalline powder. Practically insoluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Clotrimazole). A white to pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, in chloroform, and in methyl alcohol. Store in airtight containers.

Uses and Administration

Clotrimazole is an imidazole antifungal used topically in superficial candidiasis (p. 564.1), and in the skin infections pityriasis versicolor and dermatophytosis (see Skin Infections, p. 568.1).

Clotrimazole i s applied topically two or three times daily for 2 to 4 weeks as a 1% cream, lotion, spray, or solution in the treatment of fungal skin infections; a 1% powder may be used with the cream or solution and has been applied to prevent re-infection. The 1% solution is also used topically for fungal otitis externa. Clotrimazole is given as pessaries in dosage regimens of 100 mg for 6 days, 200 mg for 3 days, or a single dose of 500 mg in the treatment of vulvovaginal candidiasis; similar doses are given as a 1, 2, or 10% vaginal cream. It may be necessary to treat balanitis in male partners concurrently.

For the treatment of oropharyngeal candidiasis one 10-mg lozenge of clotrimazole is dissolved in the mouth five times daily for 14 days. For the prophylaxis of oropharyngeal candidiasis in patients receiving immunosuppressant therapy the dose is one 10-mg lozenge three times daily for the duration of the immunosuppressant treatment. Clotrimazole has also been given orally but has now been largely superseded by other azole drugs.

Sickle-cell disease. Oral clotrimazole has been investigated for the treatment of sickle-cell disease (p. 1123.2).

1. Brugnara C, *et al.* Therapy with oral clotrimazole induces inhibition of the Gardos channel and reduction of erythrocyte dehydration in patients with sickle cell disease. *J Clin Invest* 1996; **97:** 1227–34.

Adverse Effects and Precautions

Nausea, vomiting, unpleasant mouth sensations, and pruritus have been reported after the use of oral clotrimazole lozenges. Raised liver enzyme values have also occurred. Local reactions including irritation and a burning sensation may occur in patients treated topically; contact allergic dermatitis has been reported.

Intravaginal preparations of clotrimazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

Gastrointestinal disturbance, elevation of liver enzymes, dysuria, and mental depression have been reported after oral clotrimazole (although this route is no longer used). For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clotrimazole (for gynaecological use) as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. Dermatological preparations are classified as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Antimicrobial Action

Clotrimazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p. 587.2).

Pharmacokinetics

When applied topically clotrimazole penetrates the epidermis but there is little if any systemic absorption. Absorption of 3 to 10% of a dose has been reported after vaginal use. Clotrimazole is metabolised in the liver to inactive compounds and excreted in the faeces and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aflorix; Clotri-Q; Clotrix; Dr Scholl's; Empecid; Eximius; Fiasole; Fungocop Premium; Ikolan; Klomazole; Livomonil; Medifungol; Micoclin; Micomax†; Micomazol Deo; Micomazol; Micosep B; Micosep; Micotrim; Mycanden; Otrix; Panmicol; Permykot; Sinamida Gyno; Sinfung; Trimazol; ***Austral.***: Canesten; Chemists Own Clozole; Clofeme†; Clonea; Femizol†; Tinaderm Extra†; Topizol†; ***Austria***: Candibene; Canesten; Imazol; Myko Cordes†; Pedikurol; ***Belg.***: Canestene; ***Braz.***: ABC; Antimicotico Martel†; Canesten; Clomazen; Clomazol; Clotigen†; Clotren; Clotriderm; Clotrigel; Clotrizan†; CTL; Dermo-Trimazen; Dermobene; Dermotrizol; Gino-Canesten; Gino-Clotrimix†; Gino-Trimazen; Kinasten†; Miclonazol; Micotrat†; Neo Clotrimazyl; Trimazen; ***Canad.***: Canesten; Clotrimaderm; ***Chile***: Arnela; Axasol; Canesten; Clotrimin; Cotrisan; Creminem; Dermicin; Fungos; Funzal; Gynocanesten; Konifungil; Novacetol; Telugren; ***China***: Gyno Canesten (凯妮汀); Lin Guan (林冠); Noah Smearing Film (诺亚涂膜); Zhengmeiting (正美汀); ***Cz.***: Aknecolor; Baycuten†; Candibene; Candimax; Canesten; Canifug; Clotricyd; Imazol; Jenamazol; ***Denm.***: Canesten; Canvag; ***Fin.***: Canesten; ***Fr.***: MycoHydralin; ***Ger.***: Antifungol†; Canesten; Canifug; Cloderm; Clotri OPT; Clotrigalen; cutistad; Fungiderm†; Fungizid; Gilt; KadeFungin; Mycofug; Myko Cordes; Mykofungin; Mykohaug; SD-Hermal; Uromykol; ***Gr.***: Canesten; Factodin; ***Hong Kong***: Aristen; Can Vag†; Canasderm†; Candinox†; Canesten; Clocreme; Clotri-Denk; Clozole; Cotren; Fungesten†; Gyne-Lotremin; Gyne-Zole†; Kamicin; Lotremin; Mycoril; Synesten†; Tricloderm†; ***Hung.***: Candibene; Canesten; Canifug†; ***India***: Antican; Calcrem; Canazole; Cancap-VT; Candasia; Candiclo; Candid; Candinil; Canesten; Canfem VG; Canison; Cansoft; Cazol; Clenorush Torche; Cloben; Clocip; Clogen; Clomax; Clotrin-V; Clozol; CTM; CTZole; Decand; Demazole; Endid; Fungimac; Gynostatum; Imidil; Intramol-V6; Kundo-V; Leozole; Lotril; Lotrim; Mycocid; Mycoclear; Mycoderm-C; Nifugal; Nuforce Dust Powder; Nuforce Mouth Paint; Nuforce V6; Oraloz; Ortho Applicator; Surfaz; ***Indon.***: Bernesten; Canesten; Clonitia†; Fungiderm†; Gyne-Lotremin†; Kranos; Lotremin; Medisten†; Trimadan†; ***Irl.***: Canazole Clotrimazole†; Canesten; ***Israel***: Agisten; Clothree; Clotrimaderm; Fungicare; Myco-Hermal; Oralten; ***Ital.***: Antimicotico; Canesten; Cangil; Gyno-Canesten; ***Malaysia***: Candazole; Candid; Canesten; Clomazole†; Fungicip; Gyne-Lotremin; Lotremin; Taraten; ***Mex.***: Altenal†; Candimon; Candiphen; Canesten; Clocan; Clomacin; Dermasten; Euroderm; Liferzol; Lodirtrem; Lomecan V†; Lotrimin; Rangyn†; Tenescan; Toczol; Traxelan; ***Neth.***: Canesten; Imazol; Parvemaxol†; ***Norw.***: Canesten; ***NZ***: Canesten; Clocreme†; Clomazol; Clotrihexal†; Clotrimaderm; ***Philipp.***: Candid V6; Candiva; Canesten; Canison; Clorifort; Cloxy; Gixaderm; Gynesol; Vaff; Vagizol; Yeastazol; ***Pol.***: Canesten†; Imazol; ***Port.***: Canesten; Diomicete; Gino-Canesten; Gino-Lotremine†; Lotremine; Micolysin; Nalbix; Pan-Fungex; ***Rus.***: Amyclon (Амиклон); Antifungol (Антифунгол)†; Candibene (Кандибене); Candid (Кандид); Candid V6 (Кандид В6); Candizole (Кандизол); Canesten (Канестен); Canison (Канизон); Imidil (Имидил); ***S.Afr.***: A-Por; Canalba; Candaspor; Candizole; Canesten; Canex; Clomaderm; Closcript; Covospor; Dynaspor; Fungispor; Gynezol; Gyno-Trimaze; Innospore; Medaspor; Micomisan; Mycoban; Mycohexal†; Normospor; Pinaspor; Stiemazol†; Trimaze; Xeraspor†; ***Singapore***: Candazole; Candid; Canesten; Cotren; Cristan; Myco-Hermal; Mycoril; Sastid Anti-Fungal; ***Spain***: Canesmed; Canespie Clotrimazol; Canesten; Fungidermo; Gine Canesten; ***Swed.***: Canesten; ***Switz.***: Acneco-

lor; Aknecolor; Canestene; Corisol; Fungotox; Gromazol; Gyno-Canestene; Imazol; Undex au clotrimazole; ***Thai.***: Caginal; Canasone; Canazol; Candazole; Candex; Candid; Candinox; Canesten; Cenecon; Chingazol; Clomaz; Clotri; Clotricin; Clotrimed; Comat†; Comazol; Cotren; CST†; Defungo; Dermaten; Dermizole; Fadae†; Fango Cream; Fungi; Fungicon; Fungiderm; Gynebo; Gynestin 200; Gyno-Clotrin; Gynosten; Hofra B; Hofra; Kanezin†; Kenet; Klamacin; Lamazone; Lyma; Manomazole; Mycoda; Mycoderm-C; Mycoril; Mycotopic; Mycozole; Myda; Nestic; P-Gyzole; RanoTroc†; Taraten; Vagizole; Vamazole; Vanesten; Zema; ***Turk.***: Canesten; Clozol; Fungosten†; Gyno-Canesten; ***UK***: Canesten Combi; Canesten; Fungederm; ***Ukr.***: Candibene (Кандибене); Candid (Кандид); Imazol (Имазол); ***USA***: Fungi Cure Intensive; Gyne-Lotrimin; Lotrimin AF; Lotrimin; Mycelex-7; Mycelex; ***Venez.***: Canesten; Clortilen; Clotrizol; Fugolin; Ginolotricomb; Gyno Canesten; Imazol; Ipalat; Micozol; Polik.

Multi-ingredient Preparations. ***Arg.***: Becortin; Calmurid; Cortispec; Dicasone Complex; Empecid Cort; Gentacort Plus; Hongal; Lotricomb; Micomazol B; Quadriderm; Quiacort G Plus; Vagisan Compuesto; Vitacortil; ***Austral.***: Canesoral Duo; Femazole Duo; Hydrozole; VagiClear Duo; ***Austria***: Imazol Duo; Myko Cordes†; ***Belg.***: Lotriderm; ***Braz.***: Baycuten; ***Canad.***: Canesoral Combi-Pak; Lotriderm; ***Chile***: B-Laboterol; Baycuten; Clotrimin-B; Creminem-B; Cutanil; Dermicin B; Donomix; Locrim; Lotriderm; Novadrel; Novarnela; Telugren Plus; Tribesona; ***China***: Clotrasone (荷洛松); Shan Qing (山庆); Shuang Zuo Tai (双唑泰); ***Cz.***: Imacort; Imazol Plus; ***Denm.***: Clotrason; ***Ger.***: Antifungol†; Baycuten HC; Fungidexan; Imazol comp; Imazol Plus; Imazol; Lotricomb; Myko Cordes Plus; ***Gr.***: Lotriderm; ***Hong Kong***: Candacort; Canesten HC; Clobert-G†; Clobeta-G; Clotrim-B†; Clotrinolon; Cobetsol†; Dermacloft†; Derzid-C; Lozopin†; Synco-CFN†; Triderm; Tridewel†; Uni-Quaderm†; ***India***: Adcort; Advin-NC; Aliderma; Alvi; Arima; Atasol; Baclasia-CG; Baclasia-CN; BC-Zole; BC-Zole; Beclasone-C; Beclocid-G; Beclocid; Beclocin-O; Beclolab-CG; Beclolab-NC; Beclotis-C; Beclotis-CG; Becmet-CG; Becmet-CG; Bectop; Benda; Bestec; Bestonim C; Bestopic-N; Bugderm; Caltec; Candasia-B; Candibiotic; Candid B; Candid Ear Drops; Candid-CL; Candid-TV; Candiderma +; Candiderma; Candigen-BG; Candikit-N; Candivate; Canesten-S; Canison-B; Canison-BN; Canison-C; Canoderma; Cazol-B; CBL; Ceflox-CF; Cezel-PT; Ciprolar-FC; CLCD; Clenorush; Clevyx; Clima-V; Clingen Plus; Clingen; Cloat-V; Cloben-G; Cloben; Clobiotic; Clocain; Clocip B; Clocip NB; Clodaz-V6; Clofung GM; Clofung-G; Clofung-N; Clofung; Clomax BN; Clomax-B; Clomax-BG; Clomycin†; Clorid-B; Clovar-V; Clozed; CNB; Convoy; Corge-C; Cuticare; Cutigard; Dandruff Plus; Decand B; Decand BG; Dermaspan; Derminol; Diprogen; Drep; Drocort; Eligao; Epicort-GC; Everbate; Evergum; Excan; Flucocip; Fourderm AF; Fubac; Fungi-BC; Fungidrops; GCB; Gentacort-MF; Gentalene Plus; Gentalene-C; Ginal-V; Ginal-V; Ginlac-V; Hill-V; Hydrozole; IFB; Ifyclo-G; Imidil B; Imidil Plus; Imidil-CV; Infabact; Itchasia; Itchicos; Itchicure; Itchipol; Lamonte-BG; LBC; Leobet-NC; Leozole-B; Lotriderm; Lotril-B; Lotril-BG; Lotril-LB; Mycoderm; Myconip-C; Myconorm; Mycotic; Naderm RF; NC Derm; Neobate; Neocip FC; Nifugal-B; Nivate-NC; Nuforce-CD; Nuforce-GM; Olotic; Onderm; Otek-AC Plus; Otichek; Otiden; Otiderm; Otiflox; Otocin-O; Otocin; Otocos; Otosym; Sigmaderm; Sofradex-F; Surfaz-SN; Surfaz; Translipo-Triple; ***Indon.***: Baycuten-N; Heltiskin†; Lotriderm; ***Irl.***: Canesten HC; Lotriderm; ***Israel***: Agisten 1; Agisten with Aloe Vera; Clotrisone; Hydroagisten; Polycutan; Tevacutan; Triderm; ***Ital.***: Desamix Effe; Meclon; ***Malaysia***: Baycuten N†; Betamethasone Clo; Candacort; Candid B; Triderm-C; ***Mex.***: Barmicil Compuesto; Baycuten N; Baycuten; Beclogen; Beclotrin; Betrigen; Clotricina; Gelmicin; Miclobet; Prubagen; Quadriderm NF; Qudermin; Triderm; Xyloderm; ***Neth.***: Imazol Duo; ***NZ***: Canesten Duo; ***Philipp.***: Baycuten; Candacort; Candibec; Clotrasone; Combiderm; Triderm; ***Pol.***: Imazol Plus; Lotriderm; Triderm; ***Port.***: Baycuten; Beta-Micoter; Flotiran; Quadriderme; ***Rus.***: Akriderm GK (Акридерм ГК); Candibiotic (Кандибиотик); Candid B (Кандид Б); Candiderm (Кандидерм); Canison Plus (Канизон Плюс); Metrogyl Plus (Метрогил Плюс); Triderm (Тридерм); ***S.Afr.***: Lotriderm; ***Singapore***: Candacort; Canesten HC; Combiderm; Gentriderm; Gentrisone; Modaderm; Neoderm; Saerogenta-A; Triderm; ***Spain***: Beta Micoter; Clotrasone; ***Switz.***: Imacort; Imazol; Triderm; ***Thai.***: Bacda-B; Canasone CB; Canazol-BE; Candacort; Candex Plus; Chingazone; Derzid-C; Fada-B; Fango-B; Fungicon; Fungiderm-B; Gynesten-B†; Gynestin; Mycosone-B; Mycozole-B; Myda-B; Myrazole-B; Sema-X; Twina; Zema B†; ***Turk.***: Imazol; ***UK***: Canesten HC; ***Ukr.***: Candibiotic (Кандибиотик); Candid B (Кандид-Б); Candiderm (Кандидерм); Clotrex (Клотрекс); Clotrisal (Клотрисал); Imacort (Имакорт); Triacutan (Триакутан); Triderm (Тридерм); Vagiklin (Вагиклин); ***USA***: Lotrisone; ***Venez.***: Baycuten N; Lotricomb; Lotrisone; Triderm.

Pharmacopoeial Preparations
BP 2014: Clotrimazole Cream; Clotrimazole Pessaries;
USP 36: Clotrimazole and Betamethasone Dipropionate Cream; Clotrimazole Cream; Clotrimazole Lotion; Clotrimazole Lozenges; Clotrimazole Topical Solution; Clotrimazole Vaginal Tablets.

Cloxiquine *(rINN)*

5-Chloro-8-hydroxyquinoline; Cloxiquina; Cloxiquinum; Cloxyquin; Cloxyquin (USAN); Клоксихин.
5-Chloroquinolin-8-ol.
C_9H_6ClNO=179.6
CAS — 130-16-5.
UNII — BPF36H1G6S.

Profile

Cloxiquine has been included in preparations used topically for the treatment of fungal and bacterial skin infections. It is a component of halquinol, p. 309.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Decoderm trivalent†; ***Indon.***: Decoderm 3.

Croconazole Hydrochloride *(rINNM)*

Cloconazole Hydrochloride; Croconazol, Chlorhydrate de; Croconazol, hidrocloruro de; Croconazoli Hydrochloridum; Hidrocloruro de croconazol; 710674-S (croconazole); Кроконазола Гидрохлорид.
1-(1-[*o*-[(*m*-Chlorobenzyl)oxy]phenyl}vinyl)imidazole hydrochloride.
$C_{18}H_{15}ClN_2O,HCl$=347.2
CAS — 77175-51-0 (croconazole).
UNII — I0WFH323HZ.

Pharmacopoeias. In *Jpn*.

Profile

Croconazole is an imidazole antifungal used topically in the treatment of superficial cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. It is applied as a 1% cream or gel containing the hydrochloride.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Pilzcin†.

Eberconazole Nitrate *(rINNM)*

Éberconazole, Nitrate de; Eberconazoli Nitras; Nitrato de eberconazol; Эберконазола Нитрат.
(±)-1-(2,4-Dichloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)imidazole nitrate.
$C_{18}H_{14}Cl_2N_2,NO_3$=391.2
CAS — 128326-82-9 (eberconazole).
ATC — D01AC17.
ATC Vet — QD01AC17.

Profile

Eberconazole nitrate is an imidazole antifungal used topically as a 1% cream in the treatment of superficial fungal infections of the skin.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

References.
1. del Palacio A, *et al.* A double-blind randomized comparative trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in Candida and dermatophyte skin infections. *Mycoses* 2001; **44:** 173–80.
2. Repiso Montero T, *et al.* Eberconazole 1% cream is an effective and safe alternative for dermatophytosis treatment: multicenter, randomized, double-blind, comparative trial with miconazole 2% cream. *Int J Dermatol* 2006; **45:** 600–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Ebernet; ***Spain***: Ebermac; Ebernet; Ebertop; ***Turk.***: Ebernet.

Econazole *(BAN, USAN, rINN)*

Econazol; Éconazole; Econazolum; Ekonatsoli; Ekonazol; Ekonazolas; Эконазол.
1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole.
$C_{18}H_{15}Cl_3N_2O$=381.7
CAS — 27220-47-9.
ATC — D01AC03; G01AF05.
ATC Vet — QD01AC03; QG01AF05.
UNII — 6Z1Y2V4A7M.

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Econazole). A white or almost white powder. M.p. 88 degrees to 92 degrees. Practically insoluble in water; very soluble in alcohol and in dichloromethane. Protect from light.

Econazole Nitrate *(BANM, USAN, rINNM)*

C-C2470; Econazol, nitrato de; Éconazole, nitrate d'; Econazoli Nitras; Econazolnitrat; Ekonatsolinitraatti; Ekonazolnitrat; Ekonazol-nitrát; Ekonazolo nitratas; Nitrato de econazol; R-14827; SQ-13050; Эконазола Нитрат.
(±)-1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole nitrate.
$C_{18}H_{15}Cl_3N_2O,HNO_3$=444.7
CAS — 24169-02-6 (econazole nitrate); 68797-31-9 ((±)-econazole nitrate).
ATC — D01AC03; G01AF05.
ATC Vet — QD01AC03; QG01AF05.
UNII — H438WYN10E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Econazole Nitrate). A white or almost white crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 36: (Econazole Nitrate). A white or practically white, crystalline powder, with not more than a slight odour. Very slightly soluble in water and in ether; slightly soluble in alcohol; sparingly soluble in chloroform; soluble in methyl alcohol. Protect from light.

Uses and Administration

Econazole is an imidazole antifungal used topically in the treatment of superficial candidiasis (see p. 564.1) and in dermatophytosis and pityriasis versicolor (see Skin Infections, p. 568.1).

Econazole nitrate is applied topically up to 3 times daily as a 1% cream, lotion, powder, or solution in the treatment of fungal skin infections. Treatment is continued for 2 to 4 weeks. It is also used in the treatment of vaginal candidiasis as pessaries of 150 mg once daily at bedtime for 3 consecutive nights; a single dose of 150 mg in a long-acting formulation has also been used. Intravaginal use of 5 g of a 1% cream once daily at night has been given for 2 weeks. A 1% cream may be used concurrently for the treatment of vulval infections or for the treatment of balanitis in a male partner.

In the treatment of fungal infections of the nails, a 1% cream or lotion is applied once daily and covered with an occlusive dressing.

Econazole nitrate has also been used as eye or ear drops.

Econazole sulfosalicylate has also been used.

Adverse Effects and Precautions

Local reactions including burning and irritation may occur when econazole nitrate is applied topically. Contact dermatitis has been reported rarely.

Intravaginal preparations of econazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies econazole (for gynaecological use) as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients. Dermatological preparations are classified as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Antimicrobial Action

Econazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p. 587.2).

Pharmacokinetics

Absorption is not significant when econazole nitrate is applied to the skin or vagina.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermocitran; Excelentia Antimicotico; Micocide; Micolis; Micotex; Nomicon; Novo Paramicon; Sinamida Econazol; ***Austral.***: Dermazole†; Pevaryl; ***Austria***: Gyno-Pevaryl; Pevaryl; ***Belg.***: Pevaryl†; ***Braz.***: Dermazol; Micostyl; ***Chile***: Micolis; ***China***: Confort (康妇特); ***Cz.***: Gyno-Pevaryl; Pevaryl; ***Denm.***: Pevaryl†; ***Fin.***: Pevaryl†; ***Fr.***: Dermazol; Fongeryl†; Fongileine; Gyno-Pevaryl; Mycoapaisyl; Mycosedermyl; Myleugyn; Pevaryl; ***Ger.***: Epi-Pevaryl Pv; Epi-Pevaryl; Gyno-Pevaryl; ***Gr.***: Bismultin; Fungistat; Mycobacter; Nectarmicin; Penicomb; Pevaryl; Unifungin; ***Hong Kong***:

Ecomi; Econite†; Ecosone†; Ecozol; Heads Shampoo†; ***Hung.***: Gyno-Pevaryl; Pevaryl; ***India***: Ecanol; ***Irl.***: Ecostatin†; Gyno-Pevaryl; ***Israel***: Gyno-Pevaryl; Pevaryl†; ***Ital.***: Dermazol†; Ecodergin; Ecomesol; Ecomi; Ecorex; Ecosteril; Ganazolo; Ifenec; Micos; Pevaryl; Polinazolo; ***Malaysia***: Gyno-Pevaryl; ***Mex.***: Arecolex; Micostyl; Pevaryl; ***Neth.***: Pevaryl; ***Norw.***: Pevaryl; ***NZ***: Ecreme†; Pevaryl; ***Philipp.***: Pevaryl; ***Pol.***: Gyno-Pevaryl; Pevaryl; Pevazol; ***Port.***: Gyno-Pevaryl; Pevaryl; ***Rus.***: Ecalin (Экалин)†; Ecodax (Экодакс); Gyno-Pevaryl (Гино-Певарил); Ifenec (Ифенек); ***S.Afr.***: Ecoderm†; Econal-C†; Gyno-Pevaryl; Pevaryl; ***Singapore***: Gyno-Pevaryl; Pevaryl; ***Spain***: Ecotam; Micoespec†; ***Swed.***: Pevaryl; ***Switz.***: Gyno-Pevaryl; Pevaryl; ***Thai.***: Econ; ***UK***: Ecostatin†; Gyno-Pevaryl; Pevaryl; ***Ukr.***: Ecodax (Екодакс); ***USA***: Ecoza; Spectazole; ***Venez.***: Gyno-Pevaryl; Miconax; Pevaryl.

Multi-ingredient Preparations. ***Arg.***: Diflunazol; Filoderma Plus; Griseocrem; Griseoplus; ***Austria***: Pevisone; ***Belg.***: Pevisone†; ***China***: Fu Yan Ning (扶严宁); Ji Bai Fu (吉佰芙); Pevisone (派瑞松); YiFuQing (益富清); Zhaohuile (朝晖乐); ***Denm.***: Pevison; Pevisone†; ***Fin.***: Pevisone; ***Fr.***: Pevisone; ***Ger.***: Epipevisone; ***Gr.***: Pevison; ***Hong Kong***: Ecocort; Pevisone; Triamecon; Triconazole; ***India***: Bestopic; Cobederm-H†; Ecodax-G; Halog-E; Mediron; ***Israel***: Pevisone†; ***Ital.***: Pevisone; ***Malaysia***: Aecoras; Ecocort; Econazine; Endix; Kifugan; ***Norw.***: Pevisone; ***Philipp.***: Nizolex; Pevaryl HP†; Pevisone; ***Pol.***: Pevisone; ***Port.***: Pevisone; ***S.Afr.***: Pevisone; ***Singapore***: Ecocort; Econazine; Epiderm; Pevisone; ***Swed.***: Pevisone; ***Switz.***: Pevisone; ***Thai.***: Ecocort; Ecoderm; Econazine; Tricozole; ***UK***: Econacort†.

Pharmacopoeial Preparations
BP 2014: Econazole Cream; Econazole Pessaries.

Enilconazole *(BAN, USAN, rINN)*

Enilconazol; Énilconazole; Enilconazolum; Enilkonatsoli; Enilkonazol; R-23979; Энилконазол.
(±)-1-(β-Allyloxy-2,4-dichlorophenethyl)imidazole.
$C_{14}H_{14}Cl_2N_2O$=297.2
CAS — 35554-44-0.
ATC Vet — QD01AC90.
UNII — 6K0NOF3XQ6.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Enilconazole for Veterinary Use; Enilconazole BP(Vet) 2014). A clear, yellowish, oily liquid or solid mass. Very slightly soluble in water; freely soluble in alcohol, in methyl alcohol, and in toluene. Store in airtight containers. Protect from light.

Profile

Enilconazole is an imidazole antifungal used topically in veterinary medicine for the treatment of fungal skin infections in cattle, horses, and dogs. It is also used by inhalation for the treatment of aspergillosis in ostriches.

Fenticonazole Nitrate

(BANM, USAN, rINNM)

Fenticonazol, nitrato de; Fenticonazole, Nitrate de; Fenticonazoli Nitras; Fenticonazolnitrat; Fentikonatsolinitraatti; Fentikonazolnitrat; Fentikonazol-nitrát; Fentikonazolo nitratas; Nitrato de fenticonazol; Rec-15/1476; Фентиконазола Нитрат.
(±)-1-[2,4-Dichloro-β-{[*p*-(phenylthio)benzyl]oxy}phenethyl] imidazole mononitrate.
$C_{24}H_{20}Cl_2N_2OS,HNO_3$=518.4
CAS — 72479-26-6 (fenticonazole); 73151-29-8 (fenticonazole nitrate).
ATC — D01AC12; G01AF12.
ATC Vet — QD01AC12; QG01AF12.
UNII — 8V4JGC8YRF.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fenticonazole Nitrate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dimethylformamide and in methyl alcohol. Protect from light.

Uses and Administration

Fenticonazole is an imidazole antifungal used locally as the nitrate in the treatment of vulvovaginal candidiasis (p. 564.1). A 200-mg pessary is inserted into the vagina at bedtime for 3 nights or a 600-mg pessary is inserted once only at bedtime. It is also available as a 2% vaginal cream; 5 g is inserted into the vagina twice daily for 3 days. Fenticonazole nitrate is also applied topically as a 2% cream or solution for the treatment of fungal skin infections.

Reviews.

1. Veraldi S, Milani R. Topical fenticonazole in dermatology and gynaecology: current role in therapy. *Drugs* 2008; **68:** 2183–94.

Adverse Effects and Precautions

Burning and itching have been reported after the application of fenticonazole nitrate.

Intravaginal preparations of fenticonazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Fenticonazole is an imidazole antifungal active against a range of organisms including dermatophyte pathogens, *Malassezia furfur*, and *Candida albicans*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lomexin; ***Belg.***: Gynoxin; ***Braz.***: Fentizol; Lomexin; ***Cz.***: Lomexin; ***Fr.***: Lomexin; Terlomexin; ***Ger.***: Fenizolan; Lomexin†; ***Gr.***: Lomexin; ***Hung.***: Gynoxin; Lomexin; ***Irl.***: Gynoxin; Lomexin; ***Ital.***: Falvin; Lomexin; Lorenil; ***Mex.***: Lomexin; ***Neth.***: Gynoxin; ***Pol.***: Gynoxin; ***Port.***: Lomexin; ***Rus.***: Lomexin (Ломексин); ***S.Afr.***: Lomexin; ***Spain***: Laurimic; Lomexin; ***Turk.***: Gyno-Lomexin; ***UK***: Gynoxin; ***Ukr.***: Lomexin (Ломексин); ***Venez.***: Mycofentin.

Fluconazole *(BAN, USAN, rINN)*

Fluconazol; Fluconazolum; Flukonatsoli; Flukonazol; UK-49858; Флуконазол.
2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.
$C_{13}H_{12}F_2N_6O$=306.3
CAS — 86386-73-4.
ATC — D01AC15; J02AC01.
ATC Vet — QD01AC15; QJ02AC01.
UNII — 8VZV102JFY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Fluconazole). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in methyl alcohol; soluble in acetone. Store in airtight containers.

USP 36: (Fluconazole). A white or almost white, crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone; sparingly soluble in chloroform and in isopropyl alcohol; freely soluble in methyl alcohol; very slightly soluble in toluene. Store in airtight containers at a temperature below 30 degrees.

Incompatibility and stability. References.

1. Lor E, *et al.* Visual compatibility of fluconazole with commonly used injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1991; **48:** 744–6.
2. Couch P, *et al.* Stability of fluconazole and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1992; **49:** 1459–62.
3. Hunt-Fugate AK, *et al.* Stability of fluconazole in injectable solutions. *Am J Hosp Pharm* 1993; **50:** 1186–7.
4. Ishisaka DY. Visual compatibility of fluconazole with drugs given by continuous infusion. *Am J Hosp Pharm* 1994; **51:** 2290 and 2292.
5. Dotson B, Churchwell MD. Physical compatibility of 4% sodium citrate with 23.4% sodium chloride, fluconazole, and micafungin. *Am J Health-Syst Pharm* 2011; **68:** 377–8.

Uses and Administration

Fluconazole is a triazole antifungal used for superficial mucosal (oropharyngeal, oesophageal, or vaginal) candidiasis and for fungal skin infections. It is also given for systemic infections including systemic candidiasis, coccidioidomycosis, and cryptococcosis, and has been tried in blastomycosis, histoplasmosis, and sporotrichosis. The place of fluconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p. 563.1. Fluconazole has also been used for the treatment of cutaneous leishmaniasis, for details see p. 579.2.

Fluconazole is given orally or by intravenous infusion in similar doses. For intravenous infusion it is given as a solution containing 2 mg/mL at a rate of 5 to 10 mL/minute (300 to 600 mL/hour). In the USA, a maximum infusion rate of 100 mL/hour is recommended.

For **superficial mucosal candidiasis** (other than genital candidiasis), the usual oral dose of fluconazole in the UK is 50 mg daily, although 100 mg daily may be given if necessary. Treatment usually continues for 7 to 14 days in *oropharyngeal* candidiasis (except in severely immunocompromised patients), for 14 days in *atrophic oral candidiasis* associated with dentures, and for 14 to 30 days in other mucosal candidal infections including *oesophagitis*.

Higher doses are recommended in the USA where an initial dose of fluconazole 200 mg is followed by 100 mg once daily and where the minimum treatment period is 14 days for oropharyngeal infection, or a minimum of 21 days and at least 14 days after resolution of symptoms for oesophageal infections; doses of up to 400 mg daily may be used for oesophageal candidiasis if necessary.

Fluconazole 150 mg as a single oral dose may be used for **genital candidiasis** (vaginal candidiasis or candidal balanitis).

Dermatophytosis, pityriasis versicolor, and *Candida* **infections of the skin** may be treated with fluconazole 50 mg orally once daily for up to 6 weeks.

Systemic candidiasis, **cryptococcal meningitis**, and other **cryptococcal infections** may be treated with fluconazole orally or by intravenous infusion; the initial dose is 400 mg followed by a maintenance dose of 200 to 400 mg once daily. Duration of therapy is based on clinical and mycological response, but is usually at least 6 to 8 weeks in cryptococcal meningitis; in the USA, treatment for 10 to 12 weeks after the CSF cultures become negative is recommended. Fluconazole may also be used in daily doses of 100 to 200 mg orally or intravenously to prevent relapse after a primary course of antifungal treatment for acute cryptococcal meningitis in patients with AIDS.

In *immunocompromised patients* at risk of fungal infections, fluconazole may be given **prophylactically** in a dose of 50 to 400 mg daily orally or by intravenous infusion, although long-term prophylaxis has been associated with the emergence of resistant organisms (see under Intermittent Doses, below).

For details of doses used in children and in those with renal impairment, see p. 579.1.

Reviews.

1. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990; **39:** 877–916. Correction. *ibid.* **40:** 862.
2. Kowalsky SF, Dixon DM. Fluconazole: a new antifungal agent. *Clin Pharm* 1991; **10:** 179–94.
3. Goa KL, Barradell LB. Fluconazole: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. *Drugs* 1995; **50:** 658–90.
4. Charlier C, *et al.* Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? *J Antimicrob Chemother* 2006; **57:** 384–410.

Administration. *HIGH DOSES.* Doses higher than those in licensed product information for fluconazole have been tried, and in some cases are routinely recommended, for patients with some life-threatening fungal infections. For **cryptococcal meningitis** in *HIV-infected* patients, oral fluconazole doses of 800 mg to 2 g daily have been used in some second-line induction regimens. In the USA, some experts[1] have suggested:

- 800 mg daily when used with amphotericin B
- at least 800 mg, and preferably 1.2 g daily when used with flucytosine
- 800 mg to 2 g daily, preferably 1.2 g daily or more, when fluconazole is used alone

Daily oral doses of up to 800 mg have also been used in consolidation treatment of *non-HIV infected* patients with cryptococcal meningitis,[1] and 800 mg daily has been suggested for **CNS blastomycosis**.[2] For the treatment of **CNS coccidioidomycosis**, some experts[3] suggest initial oral doses of 800 mg to 1 g fluconazole daily; for disseminated disease, up to 2 g daily has been used. Intravenous doses of 10 mg/kg daily have been tried in **disseminated candidiasis**,[4] and US guidelines[5] suggest up to 12 mg/kg daily if fluconazole is to be used for CNS infection. When used for treatment of disseminated neonatal candidiasis, a dose of 12 mg/kg daily has also been suggested.[5]

1. Perfect JR, *et al.* Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010; **50:** 291–322. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/649858 (accessed 16/08/10)
2. Chapman SW, *et al.* Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 1801–12. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/588300 (accessed 16/08/10)
3. Galgiani JN, *et al.* Infectious Diseases Society of America. Coccidioidomycosis. *Clin Infect Dis* 2005; **41:** 1217–23. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/496991 (accessed 16/08/10)
4. Graninger W, *et al.* Treatment of Candida albicans fungaemia with fluconazole. *J Infect* 1993; **26:** 133–46.
5. Pappas PG, *et al.* Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48:** 503–35. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/596757 (accessed 16/08/10)

INTERMITTENT DOSES. Concern has been expressed about the increasingly widespread use of fluconazole[1] and, in particular, about the impact of continuous fluconazole therapy in immunocompromised patients on the development of resistance (see under Antimicrobial Action, p. 580.2). Nevertheless, fluconazole remains popular for primary and secondary prophylaxis. Some investigators have suggested the use of intermittent doses[2,3] although this could further increase the risk of infections with resistant organisms.

Once-weekly treatment with fluconazole has been tried in onychomycosis[4] and tinea capitis.[5] In HIV-infected patients with oropharyngeal candidiasis, a single 750-mg oral dose of fluconazole has been reported to be as effective

and well tolerated as a standard, 2 week course of fluconazole 150 mg orally once daily.[6]

1. Mangino JE, *et al*. When to use fluconazole. *Lancet* 1995; **345:** 6–7.
2. Singh N, *et al*. Low-dose fluconazole as primary prophylaxis for cryptococcal infection in AIDS patients with CD4 cell counts of ≤ 100/mm³: demonstration of efficacy in a prospective, multicenter trial. *Clin Infect Dis* 1996; **23:** 1282–6.
3. Schuman P, *et al*. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 689–96.
4. Scher RK, *et al*. Once-weekly fluconazole (150 mg, 300 mg, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38:** S77–S86.
5. Gupta AK, *et al*. Once weekly fluconazole is effective in children in the treatment of tinea capitis: a prospective, multicentre study. *Br J Dermatol* 2000; **142:** 965–8.
6. Hamza OJ, *et al*. Single-dose fluconazole versus standard 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, double-blind, double-dummy trial. *Clin Infect Dis* 2008; **47:** 1270–6.

Administration in children. Fluconazole may be used in neonates and children for the treatment of candidiasis and cryptococcal infections (including meningitis), as well as for prevention of fungal infection in those who are immunocompromised; in children, it may also be used for the treatment of fungal skin infections. Fluconazole may be given orally, or by intravenous infusion at a rate not exceeding 5 to 10 mL/min.

For children from 4 weeks of age, the following licensed doses have been recommended, to a maximum of 400 mg daily; the duration of treatment is generally as for adults (see Uses and Administration, p. 578.2):

- **mucosal candidiasis**: 3 to 6 mg/kg initially, followed by 3 mg/kg once daily
- **systemic candidiasis** and **cryptococcal infections**: 6 to 12 mg/kg once daily
- **prevention of fungal infections** if immunocompromised: 3 to 12 mg/kg once daily

Neonates may be given the same doses as older children, but the dosing interval must be extended due to slower excretion of fluconazole. For neonates less than 2 weeks of age, UK licensed product information suggests doses should be given every 72 hours, for those between 2 and 4 weeks of age doses should be given every 48 hours.

Additionally, the *BNFC* makes the following unlicensed recommendations for children from 1 month of age:

- treatment of **tinea corporis, cruris, and pedis infections, pityriasis versicolor, and dermal candidiasis**: 3 mg/kg orally (maximum 50 mg) once daily for up to 6 weeks
- treatment of **tinea capitis** infection: 6 mg/kg orally (maximum 300 mg) once daily for 2 to 4 weeks
- **prevention of relapse of cryptococcal meningitis in AIDS patients** after completion of primary therapy: 6 mg/kg (maximum 200 mg) orally or intravenously once daily

The use of fluconazole for prophylaxis in neonatal intensive care has been reviewed.[1-7] There is some evidence to suggest that prophylactic systemic fluconazole, generally for the first 4 to 6 weeks of life, may reduce the risk of invasive fungal infections in **very low birth-weight** (less than 1500 g) neonates.[8] Doses that have been tried in some studies are:

- 3 mg/kg every third day for the first two weeks, then every second day during the third and fourth weeks, then daily during the fifth and sixth weeks
- 3 or 6 mg/kg every second day until 30 days after birth or until 45 days in infants of birth-weight less than 1000 g
- 6 mg/kg every third day for the first week, then every day until 4 weeks
- 3 mg/kg twice weekly for six weeks

1. Isaacs D. Fungal prophylaxis in very low birth weight neonates: nystatin, fluconazole or nothing? *Curr Opin Infect Dis* 2008; **21:** 246–50.
2. Kaufman DA. Fluconazole prophylaxis: can we eliminate invasive Candida infections in the neonatal ICU? *Curr Opin Pediatr* 2008; **20:** 332–40.
3. Healy CM, Baker CJ. Fluconazole prophylaxis in the neonatal intensive care unit. *Pediatr Infect Dis J* 2009; **28:** 49–52.
4. Manzoni P, *et al*. The use of fluconazole in neonatal intensive care units. *Arch Dis Child* 2009; **94:** 983–7.
5. McGuire W, Clerihew L. The effect of fluconazole prophylaxis in very low birthweight infants is overestimated by before-after studies. *Arch Dis Child Fetal Neonatal Ed* 2010; **95:** F182–F187.
6. Reed BN, *et al*. Fluconazole prophylaxis in high-risk neonates. *Ann Pharmacother* 2010; **44:** 178–84.
7. Kaufman DA. Epidemiology and prevention of neonatal candidiasis: fluconazole for all neonates? *Adv Exp Med Biol* 2010; **659:** 99–119.
8. Clerihew L, *et al*. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/01/12).

Administration in renal impairment. Patients with renal impairment may require dosage reduction. Normal loading or initial doses of oral and parenteral formulations of fluconazole should be given on the first day of treatment and subsequent doses should be adjusted according to creatinine clearance (CC):

- CC more than 50 mL/minute: 100% of the standard recommended dose
- CC less than 50 mL/minute and not receiving dialysis: 50% of the standard recommended dose
- patients on regular haemodialysis: 100% of the standard recommended dose after each dialysis session

No dosage adjustment is needed in patients with renal impairment given single-dose therapy.

A review[1] of antimicrobial dosing in renal replacement therapy has recommended that critically ill patients undergoing intermittent haemodialysis should receive a dose of 200 to 400 mg every 48 to 72 hours, or 100 to 200 mg every 24 hours (after dialysis on dialysis days). The authors also recommend that those undergoing continuous renal replacement therapy (CRRT) receive a loading dose of 400 to 800 mg, with the following maintenance doses depending on the type of CRRT:

- continuous venovenous haemofiltration (CVVH): 200 to 400 mg every 24 hours
- continuous venovenous haemodialysis (CVVHD): 400 to 800 mg every 24 hours
- continuous venovenous haemodiafiltration (CVVHDF): 800 mg every 24 hours

1. Heintz BH, *et al*. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Leishmaniasis. Fluconazole has been tried in the treatment of cutaneous leishmaniasis (p. 922.1) caused by *Leishmania major*. In a randomised, double-blind, placebo-controlled study,[1] 80 patients received a six-week course of oral fluconazole 200 mg daily, of whom 63 had complete healing of lesions after 3 months, compared with 22 of 65 patients who received placebo. However, others[2] have reported a response rate not significantly different from placebo. High-dose oral fluconazole has also been tried for the treatment of cutaneous leishmaniasis due to *L. braziliensis*. A small study[3] of 28 patients reported a cure rate of 75% for those patients who took a daily dose of 5 mg/kg for 4 to 12 weeks (mean 7.6 weeks) and a cure rate of 100% for those who took a daily dose of 8 mg/kg for 4 to 5 weeks (mean 4.2 weeks).

1. Alrajhi AA, *et al*. Fluconazole for the treatment of cutaneous leishmaniasis caused by Leishmania major. *N Engl J Med* 2002; **346:** 891–5.
2. Morizot G, *et al*. Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? *Am J Trop Med Hyg* 2007; **76:** 48–52. Correction. *ibid.*; 791.
3. Sousa AQ, *et al*. High-dose oral fluconazole therapy effective for cutaneous leishmaniasis due to Leishmania (Vianna) braziliensis. *Clin Infect Dis* 2011; **53:** 693–5.

Adverse Effects

Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhoea, flatulence, nausea and vomiting, and taste disturbance. Other adverse effects include headache, dizziness, leucopenia, thrombocytopenia, hyperlipidaemias, and raised liver enzyme values. Serious hepatotoxicity has been reported in patients with severe underlying disease such as AIDS or malignancy. Anaphylaxis and angioedema have been reported rarely.

Skin reactions are rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred, more commonly in patients with AIDS.

Alopecia. Alopecia has occasionally been reported in patients receiving fluconazole, especially during prolonged use.[1,2]

1. Weinroth SE, Tuazon CU. Alopecia associated with fluconazole treatment. *Ann Intern Med* 1993; **119:** 637.
2. Pappas PG, *et al*. Alopecia associated with fluconazole therapy. *Ann Intern Med* 1995; **123:** 354–7.

Effect on electrolyte balance. Hypokalaemia was associated with fluconazole in 3 patients with acute myeloid leukaemia.[1]

1. Kidd D, *et al*. Hypokalaemia in patients with acute myeloid leukaemia after treatment with fluconazole. *Lancet* 1989; **i:** 1017.

Effects on the heart. Prolonged QT interval and torsade de pointes have been reported rarely in patients receiving fluconazole.[1-5]

1. Wassmann S, *et al*. Long QT syndrome and torsade de pointes in a patient receiving fluconazole. *Ann Intern Med* 1999; **131:** 797.
2. Tholakanahalli VN, *et al*. Fluconazole-induced torsade de pointes. *Ann Pharmacother* 2001; **35:** 432–4.
3. Khazan M, Mathis AS. Probable case of torsades de pointes induced by fluconazole. *Pharmacotherapy* 2002; **22:** 1632–7.
4. Pham CP, *et al*. Long QTc interval and torsade de pointes caused by fluconazole. *Ann Pharmacother* 2006; **40:** 1456–61.
5. McMahon JH, Grayson ML. Torsades de pointes in a patient receiving fluconazole for cerebral cryptococcosis. *Am J Health-Syst Pharm* 2008; **65:** 619–23.

Effects on the liver. Although severe hepatic reactions to fluconazole are rare they have been reported, especially in patients with severe underlying diseases or hepatic dysfunction.[1,2] Elevated liver enzymes are commonly found and there have been reports of jaundice.[3,4] Hepatic necrosis has been seen rarely post mortem in patients with severe underlying disease who had received fluconazole. In one such patient, hepatotoxicity was concluded to be dose-dependent.[5]

1. Wells C, Lever AML. Dose-dependent fluconazole hepatotoxicity proven on biopsy and rechallenge. *J Infect* 1992; **24:** 111–12.
2. Jacobson MA, *et al*. Fatal acute hepatic necrosis due to fluconazole. *Am J Med* 1994; **96:** 188–90.
3. Holmes J, Clements D. Jaundice in HIV positive haemophiliac. *Lancet* 1989; **i:** 1027.
4. Franklin IM, *et al*. Fluconazole-induced jaundice. *Lancet* 1990; **336:** 565.
5. Bronstein J-A, *et al*. Fatal acute hepatic necrosis due to dose-dependent fluconazole hepatotoxicity. *Clin Infect Dis* 1997; **25:** 1266–7.

Hypersensitivity. Desensitisation has been successfully carried out in a patient with AIDS who had hypersensitivity to both fluconazole and itraconazole.[1] Gradually increasing oral doses of fluconazole (starting at 5 mg daily) were given over 7 days; thereafter dosage was maintained at 400 mg daily. No adverse reactions were seen during desensitisation or in the 3 months up to the publication of the report.

1. Takahashi T, *et al*. Desensitization to fluconazole in an AIDS patient. *Ann Pharmacother* 2001; **35:** 642–3.

Precautions

Fluconazole should be used with caution in patients with impaired hepatic or renal function. Abnormalities in haematological, hepatic, and renal-function tests have been noted in patients with serious underlying diseases such as AIDS or malignancy. Cases of torsade de pointes and QT prolongation have been reported rarely and caution is advised when giving fluconazole to patients with proarrhythmic conditions.

Teratogenicity has occurred in *animals* given high doses of fluconazole and its use is not recommended in pregnancy (see Pregnancy, below).

Breast feeding. Fluconazole is distributed into breast milk, achieving concentrations similar to those found in maternal plasma,[1] and its use in women who are breast feeding is not recommended by licensed product information.

In one report,[2] no untoward effects, other than a slight increase in lactase dehydrogenase level, were seen in an infant who was exposed to fluconazole in breast milk for 6 weeks.

The American Academy of Pediatrics considers that the use of fluconazole is usually compatible with breast feeding.[3]

1. Force RW. Fluconazole concentrations in breast milk. *Pediatr Infect Dis J* 1995; **14:** 235–6.
2. Bodley V, Powers D. Long-term treatment of a breastfeeding mother with fluconazole-resolved nipple pain caused by yeast: a case study. *J Hum Lact* 1997; **13:** 307–11.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 21/06/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluconazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. High (toxic) doses of *fluconazole*, *itraconazole*, and *ketoconazole* have been reported to be teratogenic in *rodents*. Although there is little information about the use of these drugs in human pregnancy, there is a report of a woman who took fluconazole 400 mg daily throughout pregnancy and who gave birth to an infant with severe craniofacial and limb abnormalities.[1] The abnormalities resembled those associated with the Antley-Bixler syndrome, a genetic disorder, but a teratogenic effect could not be excluded. Although prescription-event-monitoring studies of fluconazole did not reveal adverse effects on the fetus,[2-5] congenital abnormalities have occurred in infants whose mothers were given high doses of fluconazole for 3 months or more. In August 2011 the FDA issued a drug safety communication to draw attention to the fact that use of long-term, high-dose fluconazole (400 to 800 mg daily) during most or all of the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants. These features include brachycephaly, abnormal facial features and calvarial development, cleft palate, femoral bowing, thin ribs and long bones, muscle weaknesses, joint deformities, and congenital heart disease.[6] However, they also stated that a single dose of fluconazole (150 mg) used to treat vaginal candidiasis during pregnancy does not appear to be associated with the birth defects.[6] Data collected by the manufacturer,[7] relating to 198 women exposed to itraconazole during the first trimester of pregnancy, indicated that the malformation rate for both exposed women and matched controls was within the expected baseline risk for the general population; a prospective cohort study[8] involving 206

women with first-trimester exposure to itraconazole also found no difference in the rate of congenital abnormalities between exposed and unexposed infants, although a possible increased rate of spontaneous abortion was suggested. Nevertheless, the manufacturers recommend that fluconazole, itraconazole, and ketoconazole should be avoided during pregnancy.

Licensed product information states that doses of *voriconazole* equivalent to those used therapeutically have been shown to be teratogenic and embryotoxic in *rodents*. It therefore recommends that voriconazole should be avoided during pregnancy and that women of child-bearing potential should use effective contraception during treatment. Similar recommendations have been made for *posaconazole*.

Other azole antifungals including butoconazole, clotrimazole, econazole, miconazole, sulconazole, terconazole, and tioconazole are reported to be embryotoxic but not teratogenic in *rodents* given high doses. Many of these drugs are used topically or intravaginally and the systemic absorption from these routes of administration varies. While these drugs may not necessarily be contra-indicated in pregnancy, consideration should be given to these potential risks when choosing antifungal therapy for such patients.

1. Lee BE, *et al*. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992; **11:** 1062–4.
2. Rubin PC, *et al*. Fluconazole and pregnancy: results of a prescription event-monitoring study. *Int J Gynecol Obstet* 1992; **37** (suppl): 25–7.
3. Inman W, *et al*. Safety of fluconazole in the treatment of vaginal candidiasis: a prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994; **46:** 115–18.
4. Sørensen HT, *et al*. Risk of malformations and other outcomes in children exposed to fluconazole in utero. *Br J Clin Pharmacol* 1999; **48:** 234–8.
5. Nørgaard M, *et al*. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother* 2008; **62:** 172–6.
6. FDA. FDA drug safety communication: use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants (issued 3rd August, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm (accessed 17/01/12)
7. Bar-Oz B, *et al*. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 2000; **183:** 617–20.
8. De Santis M, *et al*. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Safety* 2009; **32:** 239–44.

Renal impairment. For dose adjustments in renal impairment, see Administration in Renal Impairment, under Uses and Administration, p. 579.1.

Interactions

In general, fewer interactions are considered to occur with fluconazole than with either itraconazole or ketoconazole.

Use of rifampicin with fluconazole results in reduced plasma concentrations of fluconazole. Use of hydrochlorothiazide and fluconazole has resulted in clinically insignificant increases in plasma-fluconazole concentrations.

Fluconazole may interfere with the metabolism of some other drugs, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. This may account for the reported increases in plasma concentrations of bosentan, ciclosporin, midazolam, nevirapine, amitriptyline, nortriptyline, phenytoin, rifabutin, sulfonylurea hypoglycaemics and nateglinide, selective cyclo-oxygenase-2-inhibitors such as celecoxib and parecoxib, tacrolimus, triazolam, warfarin, and zidovudine; fluconazole may inhibit the formation of a toxic metabolite of sulfamethoxazole.

Increases in terfenadine concentrations after high doses of fluconazole have been associated with ECG abnormalities. A similar effect may be anticipated with astemizole. Use of fluconazole with cisapride could result in increased cisapride concentrations and associated toxicity. The use of fluconazole with astemizole, cisapride, or terfenadine should therefore be avoided because of the risk of cardiac arrhythmias. Syncope attributed to increased amitriptyline concentrations has occurred when amitriptyline was given with fluconazole.

Fluconazole may also reduce the clearance of theophylline. The concentration of contraceptive steroids has been reported to be both increased and decreased in patients receiving fluconazole and the efficacy of oral contraceptives may be affected.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p. 585.1.

Antineoplastics. For the effect of azole antifungals on *cyclophosphamide* metabolism, see p. 773.3.

Fluoroquinolones. Both *levofloxacin* and fluconazole can cause a prolonged QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al*. Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; **60:** 2479–83.

Nitrofurans. For a report of pulmonary and hepatic toxicity due to a possible interaction between *nitrofurantoin* and fluconazole, see p. 332.3.

Antimicrobial Action

Fluconazole is a triazole antifungal drug that in sensitive fungi inhibits cytochrome P450-dependent enzymes, resulting in impairment of ergosterol synthesis in fungal cell membranes. It is active against *Blastomyces dermatitidis, Candida* spp., *Coccidioides immitis, Cryptococcus neoformans, Epidermophyton* spp., *Histoplasma capsulatum, Microsporum* spp., and *Trichophyton* spp.

Resistance has developed in some *Candida* spp. following long-term prophylaxis with fluconazole, and cross-resistance with other azoles has been reported.

Microbiological interactions. A synergistic antifungal effect was seen *in vitro* with terbinafine and fluconazole against strains of *Candida albicans*.[1] For effects on the antifungal activity of fluconazole when given with amphotericin B, see p. 572.3.

1. Barchiesi F, *et al*. In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.

Resistance. The emergence of strains of *Candida* spp. resistant to fluconazole has become increasingly important, particularly in immunocompromised patients receiving long-term prophylaxis with fluconazole.[1,2] In addition to resistance in *C. albicans*,[3-5] infections caused by *C. dubliniensis*,[5] *C. glabrata*, and *C. krusei*, all of which may be less sensitive to fluconazole than *C. albicans*, have been noted in these patients,[6,7] and more recently the non-albicans species have emerged as a prominent cause of candidiasis in immunocompromised patients.[8] Secondary resistance of *C. glabrata* has also been reported during fluconazole therapy.[9,10] Resistance to fluconazole has been reported to occur more frequently than resistance to either ketoconazole or itraconazole and may be related to the widespread use of this drug.[4,7] Cross-resistance with other azoles[11,12] and with amphotericin B[13,14] has been reported.

Fluconazole resistance has also been reported in *Cryptococcus neoformans*[15] and *Histoplasma capsulatum*.[16] Histoplasmosis developed during treatment with fluconazole in a patient with HIV infection.[17] Fluconazole-resistant *C. neoformans* has been isolated from an immunocompetent patient who had not been exposed to azole antifungals previously.[18]

1. Rex JH, *et al*. Resistance of Candida species to fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 1–8.
2. Brion LP, *et al*. Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007; **54:** 521–9.
3. Sandven P, *et al*. Susceptibilities of Norwegian Candida albicans strains to fluconazole: emergence of resistance. *Antimicrob Agents Chemother* 1993; **37:** 2443–8.
4. Johnson EM, *et al*. Emergence of azole drug resistance in Candida species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. *J Antimicrob Chemother* 1995; **35:** 103–14.
5. Ruhnke M, *et al*. Development of simultaneous resistance to fluconazole in Candida albicans and Candida dubliniensis in a patient with AIDS. *J Antimicrob Chemother* 2000; **46:** 291–5.
6. Price MF, *et al*. Fluconazole susceptibilities of Candida species and distribution of species recovered from blood cultures over a 5-year period. *Antimicrob Agents Chemother* 1994; **38:** 1422–4.
7. Odds FC. Resistance of yeasts to azole-derivative antifungals. *J Antimicrob Chemother* 1993; **31:** 463–71.
8. Kanafani ZA, Perfect JR. Resistance to antifungal agents: mechanisms and clinical impact. *Clin Infect Dis* 2008; **46:** 120–8.
9. Hitchcock CA, *et al*. Fluconazole resistance in Candida glabrata. *Antimicrob Agents Chemother* 1993; **37:** 1962–5.
10. Miyazaki H, *et al*. Fluconazole resistance associated with drug efflux and increased transcription of a drug transporter gene, PDH1, in Candida glabrata. *Antimicrob Agents Chemother* 1998; **42:** 1695–1701.
11. Martinez-Suarez JV, Rodriguez-Tudela JL. Patterns of in vitro activity of itraconazole and imidazole antifungal agents against Candida albicans with decreased susceptibility to fluconazole from Spain. *Antimicrob Agents Chemother* 1995; **39:** 1512–16.
12. Goldman M, *et al*. Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; **44:** 1585–7.
13. Kelly SL, *et al*. Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; **348:** 1523–4.
14. Nolte FS, *et al*. Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; **41:** 196–9.
15. Venkateswarlu K, *et al*. Fluconazole tolerance in clinical isolates of Cryptococcus neoformans. *Antimicrob Agents Chemother* 1997; **41:** 748–51.
16. Wheat J, *et al*. Hypothesis on the mechanism of resistance to fluconazole in Histoplasma capsulatum. *Antimicrob Agents Chemother* 1997; **41:** 410–14.
17. Pottage JC, Sha BE. Development of histoplasmosis via human immunodeficiency virus infected patient receiving fluconazole. *J Infect Dis* 1991; **164:** 622–3.
18. Omi-Wasserlauf R, *et al*. Fluconazole-resistant Cryptococcus neoformans isolated from an immunocompetent patient without prior exposure to fluconazole. *Clin Infect Dis* 1999; **29:** 1592–3.

Pharmacokinetics

Fluconazole is well absorbed after oral doses, bioavailability from the oral route being 90% or more of that from the intravenous route. Mean peak plasma concentrations of 6.72 micrograms/mL have occurred in healthy subjects after a 400-mg oral dose. Peak concentrations occur within 1 to 2 hours of oral doses. Plasma concentrations are proportional to the dose over a range of 50 to 400 mg. Multiple dosing leads to increases in peak plasma concentrations; steady-state concentrations are reached in 5 to 10 days but may be attained on day 2 if a loading dose is given.

Fluconazole is widely distributed and the apparent volume of distribution is close to that of total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluid are similar to those achieved in plasma. Concentrations in the CSF range from 50 to 90% of plasma concentrations, even in the absence of meningeal inflammation. Protein binding is only about 12%.

About 80% of a dose is excreted unchanged in the urine and about 11% as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with renal impairment. Fluconazole is removed by dialysis.

Reviews.

1. Debruyne D, Ryckelynek J-P. Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet* 1993; **24:** 10–27.
2. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. *Clin Pharmacokinet* 1997; **33:** 52–77.
3. Pittrow L, Penk A. Special pharmacokinetics of fluconazole in septic, obese and burn patients. *Mycoses* 1999; **42** (suppl 2): 87–90.
4. Silling G. Fluconazole: optimized antifungal therapy based on pharmacokinetics. *Mycoses* 2002; **45** (suppl 3): 39–41.

Burns. The mean half-life of fluconazole was decreased to 24.4 hours in 9 patients with burns.[1] Fluconazole clearance was 27.5 mL/minute, which was 30% higher than that reported in healthy subjects.

1. Boucher BA, *et al*. Fluconazole pharmacokinetics in burn patients. *Antimicrob Agents Chemother* 1998; **42:** 930–3.

Children and neonates. References.

1. Saxén H, *et al*. Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993; **54:** 269–77.
2. Nahata MC, Brady MT. Pharmacokinetics of fluconazole after oral administration in children with human immunodeficiency virus infection. *Eur J Clin Pharmacol* 1995; **48:** 291–3.

Distribution. Salivary concentrations of fluconazole after oral doses should be adequate for the treatment of oropharyngeal and oesophageal candidiasis[1,2] even in patients with AIDS who may have decreased salivation.[3] Treatment failures are more likely to be due to inadequate dosage or resistant organisms than to decreased salivary secretion.[3]

Pharmacologically active concentrations of fluconazole have been detected in scalp hair[4] and nails[5] after oral treatment with conventional daily doses and with once-weekly dosage.

1. Force RW, Nahata MC. Salivary concentrations of ketoconazole and fluconazole: implications for drug efficacy in oropharyngeal and esophageal candidiasis. *Ann Pharmacother* 1995; **29:** 10–15.
2. Koks CHW, *et al*. Pharmacokinetics of fluconazole in saliva and plasma after administration of an oral suspension and capsules. *Antimicrob Agents Chemother* 1996; **40:** 1935–7.
3. Garcia-Hermoso D, *et al*. Fluconazole concentrations in saliva from AIDS patients with oropharyngeal candidosis refractory to treatment with fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 656–60.
4. Yeates R, *et al*. Accumulation of fluconazole in scalp hair. *J Clin Pharmacol* 1998; **38:** 138–43.
5. Faergemann J. Pharmacokinetics of fluconazole in skin and nails. *J Am Acad Dermatol* 1999; **40** (suppl): S14–S20.

HIV-infected patients. Plasma clearance of fluconazole may be lower in patients with HIV infection than in immunocompetent patients, and the half-life may be prolonged.[1,2]

1. Tett S, *et al*. Pharmacokinetics and bioavailability of fluconazole in two groups of males with human immunodeficiency virus (HIV) infection compared with those in a group of males without HIV infection. *Antimicrob Agents Chemother* 1995; **39:** 1835–41.
2. McLachlan AJ, Tett SE. Pharmacokinetics of fluconazole in people with HIV infection: a population analysis. *Br J Clin Pharmacol* 1996; **41:** 291–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antimicon; Candimicol; Damicol; Femixol; Flucoginkan; Flucolaf; Fluconovag; Fluzol; Fungicil; Fungocina; Fungototal; Honguil Plus; Klonarizol; Klonazol†; Micolis Novo; Micoral Fluco; Mutum; Naxo C; Nifurtox; Nimic; Niofen; Periplum; Ponaris; Proseda F; Triflucan; ***Austral.***: Canesoral; Di-Con One; Diflucan; Dizole; Flufeme; Fluzole; Ozole; ***Austria***: Diflucan; Difluzol; Flucosept; Fungata; ***Belg.***: Candizole; Diflucan; Fungimed; ***Braz.***: Candix†; Candizol; Floltec; Flucanil; Flucazol; Flucocin; Flucodan; Flucol; Flucomed; Fluconal; Fluconeo; Fluconid; Flucoton; Flucozen; Flusan; Fluxilase; Fungnon; Glyflucan; Helmicin; Pantec; Riconazol; Triazol; Unizol; Zelix; Zolanix†; Zolmic; Zoltec; Zoltren; ***Canad.***: Diflucan; ***Chile***: Diflucan; Felcar; Felsol; Flucoxan; Fluctin; Fungimax; Ibarin; Microvaccin; Plusgin; Tavor; ***China***: Bin Li (滨力); Conquer (静达); Diflucan (大扶康); Fu Da (扶达);

Fu Kang (扶亢); Fupengxing (芙芃星); Hao Kang (昊康); Hong Xu Guang (弘旭光); Hu Qi (护齐); Hua Shi Xin (华士欣); Jin Zhou (金周); Kai Xing (凯兴); Kang Li Yin (康立因); Ke Da Kang (科达康); Lai Kang (莱抗); Li Xing (力星); Luo Rui (罗瑞); Medoflucon (麦道氟康); Mei Di Ke (美狄克); Qian De (仟德); QianYi (乾意); Qu Er Man Duo (曲尔曼多); Ru Ning (汝宁); Sai Ke Lu Ding (赛可路丁); Shuai Ke Feng (帅克风); Shuang Wei Du Qing (双威独青); Sunvecon (三维康); Tai Ning (泰宁); Wei Ke Hen (维可衡); Wen Qing (文清); Xinlizuo (信利唑); Yi Li Kang (依利康); Yi Qi Fu (易启扶); Yi Zhen Shi (益真施); You Ni An (尤尼安); **Cz.**: Diflazon†; Diflucan; Fluco†; Forcan; Mycomax; Mycosyst; Mykohexal; ***Denm.***: Diflucan; Fluconastad; Generazole†; Lozanoc; Stadanazol; ***Fin.***: Canesoral; Diflucan; ***Fr.***: Beagyne; Triflucan; ***Ger.***: Canifug Fluco†; Diflucan; Flucobeta; Flucoderm; FlucoLich; Flunazul; Fungata; ***Gr.***: Azoflu; Azzol-S; Dalrich; Diflucan; Falipan; Farviron; Figalol; Flucalit; Flucanid; Flucocaps; Flucodrug; Flucofin; Fluconapen; Flucoran; Flucovein; Flucozol; Flukatril; Flusenil; Fluzomic; Fumecal; Funadel; Fungo; Fungram; Fungustatin; Fungusteril; Fuxilidin; Gynosant; Hadlinol; Medoflucon; Mycazole; Neomycol†; Novoflon; Opumyk; Rifagen; Stabilanol; Tierlite; Varmec; Zidonil; ***Hong Kong***: Diflazon; Diflucan; Flucoric; Flucozal; Fludicon; Forcan†; Lucon; Nofung; Stalene; Vick-Flucan; ***Hung.***: Dermyc; Diflucan; Flucohexal; Fluconer; Flucoric†; Mycosyst; Nofung; ***India***: Adcon; Adecon; AF; Aglocon; Alfa Tab; Alfucoz; Alicon; Alsflu; Antican-O; Aviflu; Cancap; Candicon; Cinflu; Clozole; Concize; Conflu; Cyflu; E-Flu; Endida; Excan; F-Con; F-Zole; Fabizol; Fantizole; Fasicon; FCN; Fiscon; Fixit; Flecon; Flori; Flozol; Fluact; Flubit; Fluc; Flucalup; Flucan; Flucare; Flucoat; Flucolab; Flucomet; Flucoric; Flucos; Flucoside; Flucovar; Flucozed; Fludia; Flufact; Flufung; Fluka; Flukamep; Flumed; Flumicon; Flunaz; Flunec; Flunif; Flunova; Fluol; Flusta; Flustate; Flusyst; Flutaur; Flutel; Flutrox; Fluzart; Fluzeet; Fluzide; Fluzole; Fluzon; Foflu; Forcan; Ful; Fumac; Fumycin; Funcan; Funesta; Fungal-F; Fungard; Fungazol; Fungdor; Fungiban; Fungicon; Fungid; Fungina; Fungisan-F; Fungo; Funspor; Fusys; Futiza; GFlu; Glenflu; Gocan; Gusnil; Hif; Indcon; Kairflu; Kit; Kon; Koni; Kozole; Leecon; Lido; Logican; Lozic; Lucoz; M-Fluk; Myconorm-F; Mycorest; Mycosure; Myzole; NBOzole; Neocon; Nipcan; Nuforce; Odicon; One Can; Optican; Ozus; Syscan; ***Indon.***: Cancid†; Candipar; Candizol†; Cryptal; Diflucan; Flucess†; Flucoral; Fludis; Funzela; Govazol; Kifluzol; Zemyc; ***Irl.***: ByFluc; CanOral; Diflazole; Diflucan; Flucandid†; Flucol; ***Israel***: Diflucan; Flucanol; Stabilanol; Trican; Triflucan; ***Ital.***: Alozof; Aviflucox; Canazol; Diflucan; Dizolo; Elazor; Flukimex; Flumicon; Flumos; Fluores; Fungus; Klaider; Lefunzol; Miconix; Riflax; Trimikos; Winch; Zerfun; Zoloder; ***Jpn***: Diflucan; ***Malaysia***: Avezol; Biozole; Diflucan; Difluvid; Flucess; Flucon; Fluconol; Flucoric; Flugal; Fukole; Medoflucon; Odaft; Stalene; Zolstan; ***Mex.***: Afungil; Bioxel; Candizol; Diflucan; Difusel; Fectrin; Fharder; Fleridux; Flucoxan; Fludisol; Fluhexal†; Flukezol; Fluxes; Fluxicap; Fluzor†; Fucandyl; Funser; Lanfluzol; Menifar; Neofomiral; Ongicil; Oxifungol; Ranflu†; Solarisol†; Terplex; Trifuncan; Zilrin; Zoldicam; ***Neth.***: Diflucan; Flucoderm†; ***Norw.***: Diflucan; ***NZ***: Canesten Fluconazole; Diflucan; Flucasten; Flucazole; ***Philipp.***: Diflucan; Dyzolor; Exomax; Flucandia; Flucon; Flucoral; Fluzocan; Fukole; Funzela; Odaft; Reflucan; Syscan; ***Pol.***: Diflucan; Flucofast; FlucoLEK†; Fluconazin; Flucorta; Flumycon; Mycomax; Mycosyst; ***Port.***: Azoflune†; Diflucan; Fludocel; Maxflin†; Reforce; Supremase; ***Rus.***: Diflazon (Дифлазон); Diflucan (Дифлюкан); Flucomabol (Флукомабол); Flucostat (Флюкостат); Flucozan (Флукозан); Flucozyd (Флукозид); Flukonorm (Флуконорм); Flumicon (Флюмикон)†; Forcan (Форкан); Fungolon (Фунголон)†; Funzole (Фунзол); Medoflucon (Медофлюкон); Mycoflucan (Микофлюкан); Mycomax (Микомакс); Mycosyst (Микосист); Nofung (Нофунг); Procanazol (Проканазол); Syscan (Цискан); ***S.Afr.***: Diflucan; Difluzole; Exomax; Flucoric; Fluzol; Mycorest; ***Singapore***: Diflucan; Medoflucon; Mycorest; Omastin; Stalene†; ***Spain***: Acandix; Candifix; Citiges; Diflucan; Lavisa; Loitin; ***Swed.***: Diflucan; ***Switz.***: Diflucan; Flucazol; Flucoderm; Fluconax; Flunizol†; ***Thai.***: Biozole; Diflucan; Flucozole; Fludizol; Flunco; Fluzoral; Funa; Kyrin; Stalene; ***Turk.***: Biocanol†; Candidin; Flucan; Flurit; Fluzole; Fulurit; Fungan; Funolteva; Kandizol; Lumen; Triflucan; Trizol; Zolax; ***UAE***: Oramax; ***UK***: Canesten Oral; Diflucan; ***Ukr.***: Diflazon (Дифлазон); Diflucan (Дифлюкан); Difluzol (Дифлюзол); Flucoric (Флюкорик); Flunol (Флунол)†; Fluzamed (Флузамед); Mycomax (Микомакс); Mycosyst (Микосист); ***USA***: Diflucan; ***Venez.***: Aflumicort; Albesin; Diflucan; Flucess; Flucon; Flunal; Fluval; Fugin; Fungomax; Funizol; Micoflux; Mutum.

Multi-ingredient Preparations. ***Arg.***: Gynerium UD; ***Austral.***: Canesoral Duo; Femazole Duo; VagiClear Duo; ***Canad.***: Canesoral Combi-Pak; ***India***: AF-Kit; Azintra-3; Azithral XP; Azostat; Cancap-Kit; Eradikit; Eve Kit; Fas-3 Kit; FC-Kit; Fiscon Tab; Flucos-TZ; Flucoti; Flunec Combikit; Flutini Kit; Fluzon-T; Forcan TZ; Fulkit; Fungid-OR; Fusys-TZ; Fygek-AS; Gyn-3; Gynotrim Kit; Hif-AS; Kit-3D; Myconor-4; Nuforce Kit; Nuforce-3 Kit; Od-Kit; Orflaz Kit; Saf Kit; ***Mex.***: Afumix; ***NZ***: Canesten Duo; ***Rus.***: Safocid (Сафоцид); ***Ukr.***: Ginekit (Гинекит).

Pharmacopoeial Preparations

USP 36: Fluconazole for Oral Suspension; Fluconazole Injection; Fluconazole Tablets.

Flucytosine *(BAN, USAN, rINN)*

5-FC; Flucitosina; Flucitozin; Flucitozinas; Flucytosin; Flucytosinum; Flucytozyna; Flusitozin; Flusytosiini; Ro-2-9915; Флуцитозин.

5-Fluorocytosine; 4-Amino-5-fluoropyrimidin-2(1*H*)-one.

$C_4H_4FN_3O$=129.1

CAS — 2022-85-7.

ATC — D01AE21; J02AX01.

ATC Vet — QD01AE21; QJ02AX01.

UNII — D83282DT06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Flucytosine). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in dehydrated alcohol. Protect from light.

USP 36: (Flucytosine). A white to off-white crystalline powder, odourless or with a slight odour. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. A solution of flucytosine for intravenous infusion should be stored between 18 degrees and 25 degrees. Precipitation may occur at lower temperatures and decomposition, with the formation of fluorouracil, at higher temperatures.

Uses and Administration

Flucytosine is a fluorinated pyrimidine antifungal used in the treatment of systemic fungal infections, the treatments for which are discussed under Choice of Antifungal, p. 563.1. It is mainly used with amphotericin B or fluconazole in the treatment of severe systemic candidiasis and cryptococcal meningitis. It has also been tried in other infections due to susceptible fungi including chromoblastomycosis.

Flucytosine is given by *intravenous infusion* as a 1% solution over 20 to 40 minutes. The usual dose is 200 mg/kg daily in 4 divided doses; a dose of 100 to 150 mg/kg daily may be sufficient in some patients. Dosage should be adjusted to produce trough plasma concentrations of 25 to 50 micrograms/mL. This is particularly important in patients with AIDS who are at increased risk of bone marrow toxicity. Parenteral treatment is rarely given for more than 7 days, except for cryptococcal meningitis when it is continued for at least 4 months. For intravenous doses to be used in patients with renal impairment, see below.

Flucytosine is given *orally* in usual doses of 50 to 150 mg/kg daily in 4 divided doses. Again, blood concentrations should be monitored and dosage adjusted in patients with renal impairment to avoid accumulation of the drug.

For details of doses in children, see below.

Flucytosine has been used *topically* for azole-refractory vaginitis caused by *Candida* spp., but such use may increase problems of resistance.

Reviews.

1. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
2. Summers KK, *et al.* Therapeutic drug monitoring of systemic antifungal therapy. *J Antimicrob Chemother* 1997; **40:** 753–64.
3. Vermes A, *et al.* Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46:** 171–9.

Administration in children. Flucytosine may be given to neonates and children for the treatment of systemic fungal infections, including as an adjunct to amphotericin B in the management of severe infections, including cryptococcal meningitis or severe systemic candidiasis. The following doses, given orally or by intravenous infusion over 20 to 40 minutes, are recommended by the *BNFC*:

- neonates: 50 mg/kg every 12 hours
- children from 1 month of age: 50 mg/kg every 6 hours: 25 to 37.5 mg/kg every 6 hours may be sufficient for infections caused by very susceptible fungi. As an adjunct in cryptococcal meningitis, 25 mg/kg every 6 hours is recommended.

Administration in renal impairment. Flucytosine is mainly excreted by the kidneys and the dose must be adjusted in patients with renal impairment.

Dose intervals for intravenous flucytosine should be adjusted according to creatinine clearance (CC):

For intravenous use,

- CC 20 to 40 mL/minute: 50 mg/kg every 12 hours
- CC 10 to 20 mL/minute: 50 mg/kg every 24 hours
- CC less than 10 mL/minute: 50 mg/kg then further doses should be based on plasma concentrations which should not exceed 80 micrograms/mL

Initial oral doses should be at the lower end of the recommended range (see above) and dosage should be adjusted subsequently to avoid accumulation.

Adverse Effects

Adverse effects of flucytosine include nausea, vomiting, diarrhoea, and skin rashes. Less frequently reported adverse effects include confusion, hallucinations, convulsions, headache, sedation, and vertigo, and also allergic reactions, toxic epidermal necrolysis, and cardiotoxicity. Alterations in liver function tests are generally dose-related and reversible; hepatotoxicity may also occur. Hypokalaemia may occur. There have been a few reports of peripheral neuropathy.

Bone-marrow depression, especially leucopenia and thrombocytopenia, is associated with blood concentrations of flucytosine greater than 100 micrograms/mL, with concurrent use of amphotericin B, and with renal impairment. Fatal agranulocytosis and aplastic anaemia have been reported.

Effects on the blood. Bone marrow toxicity associated with flucytosine has been attributed to its conversion to fluorouracil, possibly by intestinal flora.[1] A pilot study[2] of 6 patients given intravenous flucytosine found that the amounts of fluorouracil in serum samples were undetectable, whereas flucytosine could be detected in the samples. This might be because intravenous dosage did not allow the conversion of flucytosine to fluorouracil by intestinal microflora. However, one patient still developed thrombocytopenia and another leucocytopenia and the authors hypothesised that toxicity might be due to flucytosine and not the metabolite.

1. Pirmohamed M, *et al.* The role of active metabolites in drug toxicity. *Drug Safety* 1994; **11:** 114–44.
2. Vermes A, *et al.* 5-fluorocytosine-related bone-marrow depression and conversion to fluorouracil: a pilot study. *Fundam Clin Pharmacol* 2002; **16:** 39–47.

Precautions

Flucytosine should be given with great care to patients with renal impairment, or with blood disorders or bone marrow depression. Renal and hepatic function and blood counts should be monitored during therapy (at least weekly in patients with renal impairment or blood disorders). In patients with renal impairment, doses should be reduced and trough blood concentrations of flucytosine should be checked regularly from blood samples taken just before an injection of flucytosine (see under Uses, above). Care should be taken in patients given radiation therapy or other drugs which depress bone marrow.

Flucytosine is teratogenic in *rats*.

AIDS. Frequent bone marrow toxicity has been reported in patients with AIDS during flucytosine therapy.[1] However, in a study in 381 patients, no additional haematotoxicity was reported in patients given amphotericin B plus flucytosine compared with those given amphotericin B alone.[2] The toxicity could be minimised by monitoring serum concentrations[3] and the British Society for Antimicrobial Chemotherapy has suggested that these should be maintained within 25 to 50 micrograms/mL in patients with AIDS.[4]

1. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **321:** 794–9.
2. van der Horst CM, *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* 1997; **337:** 15–21.
3. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
4. British Society for Antimicrobial Chemotherapy Working Party. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. *Lancet* 1992; **340:** 648–51.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flucytosine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Teratogenicity has been reported in some *animal* models and licensed product information recommends that flucytosine should only be used if the benefit justifies that possible risk to the fetus. The congenital defects are thought to be as a result of the conversion of flucytosine to fluorouracil by the intestinal microflora. However, there are some case reports of pregnant patients receiving flucytosine (with or without amphotericin B) in the second[1-4] and third[5] trimesters with no reports of abnormalities in the infants.

1. Philpot CR, Lo D. Cryptococcal meningitis in pregnancy. *Med J Aust* 1972; **2:** 1005–7.
2. Schönebeck J, Segerbrand E. Candida albicans septicaemia during first half of pregnancy successfully treated with 5-fluorocytosine. *BMJ* 1973; **4:** 337–8.
3. Curole DN. Cryptococcal meningitis in pregnancy. *J Reprod Med* 1981; **26:** 317–19.
4. Chotmongkol V, Siricharoensang S. Cryptococcal meningitis in pregnancy: a case report. *J Med Assoc Thai* 1991; **74:** 421–2.
5. Chen C-P, Wang K-G. Cryptococcal meningitis in pregnancy. *Am J Perinatol* 1996; **13:** 35–6.

Interactions

Flucytosine is commonly used with amphotericin B. Amphotericin B can cause a deterioration in renal function,

which can result in raised flucytosine blood concentrations and increased toxicity. However, the two drugs are generally regarded as having synergistic antifungal activity. Cytarabine has been claimed to reduce blood concentrations of flucytosine and to antagonise its antifungal activity, although the evidence is limited.

Antimicrobial Action

Flucytosine is a fluorinated pyrimidine antifungal. In susceptible fungi it is converted by cytosine deaminase to fluorouracil which is then incorporated in place of uracil into fungal RNA and disrupts protein synthesis. The activity of thymidilate synthetase is also inhibited and this effect interferes with fungal DNA synthesis.

Flucytosine is active against *Candida* spp., *Cryptococcus neoformans*, *Cladosporium* spp., and *Fonsecaea* spp. Some *Aspergillus* spp. have also been reported to be sensitive. There is synergy between flucytosine and amphotericin B against *Candida* spp. and *Cryptococcus neoformans*.

There is a high incidence of primary resistance to flucytosine among isolates of *Candida* spp. and *Cryptococcus neoformans*. Resistance also develops during treatment with flucytosine and has been reported rarely from combination therapy with flucytosine and amphotericin B.

Pharmacokinetics

Flucytosine is absorbed rapidly and almost completely from the gastrointestinal tract. Bioavailability is 78 to 89%. After oral doses of 37.5 mg/kg every 6 hours, peak plasma concentrations of 70 to 80 micrograms/mL occur within 2 hours; similar concentrations occur, but more rapidly, after an intravenous dose. The plasma-flucytosine concentration for optimum response is 25 to 50 micrograms/mL. Flucytosine is widely distributed through the body tissues and fluids; concentrations in the CSF are 65 to 90% of those in serum. About 2 to 4% of flucytosine is protein bound.

About 90% of a dose is excreted unchanged by glomerular filtration; a small amount of flucytosine may be metabolised to fluorouracil. The small amount of an oral dose of flucytosine not absorbed from the gastrointestinal tract is eliminated unchanged in the faeces. The elimination half-life is 2.5 to 6 hours in patients with normal renal function but increases with decreasing renal function. Flucytosine is removed by haemodialysis or peritoneal dialysis.

References[1-3] to the pharmacokinetics of flucytosine. A study[3] reviewing flucytosine concentrations in serum, blood, or plasma from 233 patients, including 33 neonates, found that they were within the therapeutic range in only about 20% of cases; of the remainder, 40% were low (5% undetectable) and 40% were excessive (potentially toxic in about 10% of the samples). The results emphasised the importance of therapeutic drug monitoring.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal agents. *Clin Pharmacokinet* 1983; **8:** 17–42.
2. Baley JE, *et al*. Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116:** 791–7.
3. Pasqualotto AC, *et al*. Flucytosine therapeutic monitoring: 15 years experience from the UK. *J Antimicrob Chemother* 2007; **59:** 791–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ancotil†; ***Austral.***: Ancotil; ***Austria***: Ancotil; ***Denm.***: Ancotil; ***Fr.***: Ancotil; ***Ger.***: Ancotil; ***Gr.***: Ancotil; ***Hong Kong***: Ancobon; Ancotil†; ***Irl.***: Ancotil; ***Ital.***: Ancotil; ***Neth.***: Ancotil; ***NZ***: Ancotil†; ***Pol.***: Ancotil; ***Rus.***: Ancotyl (Анкотил); ***Singapore***: Ancotil†; ***Swed.***: Ancotil; ***Switz.***: Ancotil; ***UK***: Ancotil; ***USA***: Ancobon.

Pharmacopoeial Preparations
BP 2014: Flucytosine Tablets;
USP 36: Flucytosine Capsules; Flucytosine Oral Suspension.

Flutrimazole *(BAN, rINN)*

Flutrimatsoli; Flutrimazol; Flutrimazolas; Flutrimazolum; UR-4056; Флутримазол.
1-[*o*-Fluoro-α-(*p*-fluorophenyl)-α-phenylbenzyl]imidazole; (*RS*)-1-(2,4′-Difluorotrityl)imidazole.
$C_{22}H_{16}F_2N_2$=346.4
CAS — 119006-77-8.
ATC — D01AC16; G01AF18.
ATC Vet — QD01AC16; QG01AF18.
UNII — 776S0UP252.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flutrimazole). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in tetrahydrofuran. Protect from light.

Profile

Flutrimazole is an imidazole antifungal used topically as a 1% cream, gel, powder, or solution in the treatment of superficial fungal infections.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

References.

1. Rigopoulos D, *et al*. Flutrimazole shampoo 1% versus ketoconazole shampoo 2% in the treatment of pityriasis versicolor. A randomised double-blind comparative trial. *Mycoses* 2007; **50:** 193–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Micetal; ***Braz.***: Micetal; ***Chile***: Micetal; ***Cz.***: Micetal; ***Gr.***: Topiderm; ***Hung.***: Micetal; ***Ital.***: Micetal; ***Mex.***: Micetal; ***Pol.***: Micetal; ***Port.***: Flutrim†; ***Spain***: Flusporan; Gine Micetal†; Micetal.

Fosfluconazole *(BAN, rINN)*

Fosfluconazol; Fosfluconazolum; UK-292663; Фосфлуконазол.
1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-[(1*H*-1,2,4-triazol-1-yl)methyl]ethyl dihydrogen phosphate.
$C_{13}H_{13}F_2N_6O_4P$=386.3
CAS — 194798-83-9.
UNII — 3JIJ299EWH.

Profile

Fosfluconazole is a phosphate prodrug of fluconazole that is used for the treatment of systemic fungal infections, including oral candidiasis and recurrent cryptococcal meningitis in AIDS patients.

References.

1. Takahashi D, *et al*. Fosfluconazole for antifungal prophylaxis in very low birth weight infants. *Int J Pediatr* 2009; **2009:** 274768.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Prodif.

Griseofulvin *(BAN, rINN)*

Curling Factor; Griseofulviini; Griseofulvina; Griséofulvine; Griseofulvinum; Grizeofulvin; Grizeofulvinas; Gryzeofulwina; Гризеофульвин.
(2*S*,4′*R*)-7-Chloro-2′,4,6-trimethoxy-4′-methylspiro[benzofuran-2(3*H*),3′-cyclohexene]-3,6′-dione.
$C_{17}H_{17}ClO_6$=352.8
CAS — 126-07-8.
ATC — D01AA08; D01BA01.
ATC Vet — QD01AA08; QD01BA01.
UNII — 32HRV3E3D5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Griseofulvin). An antifungal substance produced by the growth of certain strains of *Penicillium griseofulvum*, or by any other means. It is a white or yellowish-white powder. The particles of the powder are generally up to 5 micrometres in maximum dimension, though larger particles, which may occasionally exceed 30 micrometres, may be present. It contains 97 to 102% of $C_{17}H_{17}ClO_6$, calculated on the dried substance.

Practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in dimethylformamide and in tetrachloroethane.

USP 36: (Griseofulvin). A white to creamy-white, odourless powder, in which particles of the order of 4 micrometres in diameter predominate. It has a potency of not less than 900 micrograms of $C_{17}H_{17}ClO_6$ per mg. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, and in dimethylformamide. Store in airtight containers.

Uses and Administration

Griseofulvin is an antifungal used orally in the treatment of dermatophyte infections. It is generally given when such infections involve the scalp, hair, nails, and skin and do not respond to topical treatment (see Skin Infections, p. 568.1); infections of the soles of the feet, the palms of the hands, and the nails respond slowly.

The usual dose of griseofulvin has been 0.5 to 1 g daily in single or divided doses; these doses are for preparations of griseofulvin of reduced particle size, sometimes known as microcrystalline or microsize griseofulvin. Doses have been reduced by about one-quarter when preparations, available in some countries, containing ultramicrocrystalline or ultramicrosize griseofulvin are used. Griseofulvin should be given with or after meals.

For details of doses in children, see below.

The duration of treatment depends on the thickness of the keratin layer: 2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toenails.

Griseofulvin has also been used as a 1% topical spray in tinea pedis.

Reviews.

1. Fleece D, *et al*. Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; **114:** 1312–15.
2. Gupta AK, *et al*. Meta-analysis: griseofulvin efficacy in the treatment of tinea capitis. *J Drugs Dermatol* 2008; **7:** 369–72.

Administration in children. Griseofulvin may be given orally to children for the treatment of dermatophyte infections where topical therapy has failed or is inappropriate. For children from 1 month of age, 10 to 20 mg/kg daily (to a maximum of 1 g) of the microcrystalline preparation, given once daily or in divided doses, has been recommended by the *BNFC* and the American Academy of Pediatrics (AAP);[1] for ultramicrocrystalline preparations, the AAP recommends a dose of 5 to 15 mg/kg once daily (to a maximum of 750 mg). For tinea capitis caused by *Trichophyton tonsurans*, the *BNFC* suggests microcrystalline griseofulvin 15 to 20 mg/kg daily (to a maximum of 1 g) once daily or in divided doses.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Non-infective skin disorders. Lichen planus is usually treated with corticosteroids or retinoids (see p. 1685.2) but griseofulvin has been suggested as an alternative to topical corticosteroids in erosive disease.[1] However, some researchers have found it to be of no value.[2]

Dramatic responses of pigmented purpuric dermatoses to griseofulvin 500 to 750 mg daily have been reported in 5 patients.[3]

1. Lamey P-J, Lewis MAO. Oral medicine in practice: white patches. *Br Dent J* 1990; **168:** 147–52.
2. Bagan JV, *et al*. Treatment of lichen planus with griseofulvin. *Oral Surg Oral Med Oral Pathol* 1985; **60:** 608–10.
3. Tamaki K, *et al*. Successful treatment of pigmented purpuric dermatosis with griseofulvin. *Br J Dermatol* 1995; **132:** 159–60.

Adverse Effects

Adverse effects are usually mild and transient and consist of headache, skin rashes and urticaria, dry mouth, an altered sensation of taste, and gastrointestinal disturbances. Angioedema, erythema multiforme, toxic epidermal necrolysis, proteinuria, leucopenia and other blood dyscrasias, oral candidiasis, peripheral neuropathy, photosensitisation, and severe headache have been reported occasionally. Depression, confusion, dizziness, impaired coordination, insomnia, and fatigue have also been reported. Griseofulvin may precipitate or aggravate SLE.

There have been a few reports of hepatotoxicity attributed to griseofulvin.

Effects on the skin. Fatal toxic epidermal necrolysis in a 19-year-old woman[1] was attributed to griseofulvin that she had taken for 6 days; she had also taken metronidazole for 1 day. There are also reports[2,3] of erythema multiforme in 4 patients occurring within 10 days of starting griseofulvin. The precipitation or aggravation of SLE is a known complication of griseofulvin. Most cases are said to be characterised by prominent skin manifestations and absence of renal disease although the nephrotic syndrome has been described[4] in a 16-year-old male after 2 single doses of griseofulvin taken 3 weeks apart.

1. Mion G, *et al*. Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **ii:** 1331.
2. Rustin MHA, *et al*. Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120:** 455–8.
3. Thami GP, *et al*. Erythema multiforme due to griseofulvin with positive re-exposure test. *Dermatology* 2001; **203:** 84–5.
4. Bonilla-Felix M, *et al*. Nephrotic syndrome related to systemic lupus erythematosus after griseofulvin therapy. *Pediatr Nephrol* 1995; **9:** 478–9.

Hypersensitivity. A serum sickness-like reaction has been reported in a 5-year-old child being treated for tinea capitis with griseofulvin.[1] About 3 weeks after starting treatment the child developed fever, rash on his legs and back, swelling of his toes and fingers, and leg pain. Symptoms resolved after griseofulvin was stopped.

1. Colton RL, *et al*. Serum sickness-like reaction associated with griseofulvin. *Ann Pharmacother* 2004; **38:** 609–11.

Precautions

Griseofulvin is contra-indicated in patients with severe liver disease or SLE.

Griseofulvin is embryotoxic and teratogenic in *rats* and there have been isolated cases of conjoined twins after its use during the first trimester of pregnancy. It is therefore

contra-indicated in pregnancy and women should not become pregnant during, or within 1 month of stopping therapy. Griseofulvin may reduce the efficacy of oral contraceptives and additional contraceptive precautions should be used during treatment. Data from *in-vitro* and *in-vivo* studies using mammalian cells, which showed aneuploidy, have led to the warning that men taking griseofulvin should not father children within 6 months of treatment.

Griseofulvin may impair the ability to drive or operate machinery, and has been reported to enhance the effects of alcohol.

Porphyria. Although griseofulvin has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] both Porphyria South Africa[2] and the European Porphyria Network[3] classify griseofulvin as unsafe and it should be avoided in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 2/11/11)
2. Porphyria South Africa. Available at: http://web.uct.ac.za/depts/porphyria/ (accessed 2/11/11)
3. European Porphyria Network. Available at: http://www.porphyria-europe.com (accessed 2/11/11)

Interactions

Phenobarbital has been reported to decrease the gastrointestinal absorption of griseofulvin. Plasma concentrations of griseofulvin have also been reported to be reduced by drugs that induce metabolising enzymes.

Griseofulvin may increase the rate of metabolism and diminish the effects of some drugs such as coumarin anticoagulants and oral contraceptives.

Griseofulvin may enhance the effects of alcohol.

Alcohol. In addition to reports of griseofulvin enhancing the effects of alcohol, a severe disulfiram-like reaction to alcohol has been reported in a patient taking griseofulvin.[1]

1. Fett DL, Vukov LF. An unusual case of severe griseofulvin-alcohol interaction. *Ann Emerg Med* 1994; **24:** 95–7.

Bromocriptine. For a report that griseofulvin can block the response to bromocriptine, see p. 899.1.

Salicylates. Griseofulvin has been reported to reduce plasma concentrations of salicylate in a patient taking aspirin, see p. 26.3.

Antimicrobial Action

Griseofulvin is a fungistatic antibiotic that inhibits fungal cell division by disruption of the mitotic spindle structure. It may also interfere with DNA production. It is active against the common dermatophytes, including some species of *Epidermophyton, Microsporum,* or *Trichophyton.*

Pharmacokinetics

Absorption of griseofulvin from the gastrointestinal tract is variable and incomplete, but is enhanced by reducing the particle size or when given with a fatty meal. Peak plasma concentrations occur within 4 hours and are maintained for 10 to 20 hours.

Griseofulvin is about 84% bound to plasma proteins. It is deposited in keratin precursor cells and is concentrated in the stratum corneum of the skin and in the nails and hair, thus preventing fungal invasion of newly formed cells. Concentrations of 12 to 25 micrograms/g are maintained in skin during long-term use, while plasma concentrations remain at about 1 to 2 micrograms/mL. Griseofulvin has an elimination half-life of 9 to 24 hours, and is metabolised by the liver mainly to 6-demethylgriseofulvin and its glucuronide conjugate which are excreted in the urine. A large amount of a dose of griseofulvin of reduced particle size appears unchanged in the faeces; less than 1% is excreted unchanged in the urine; some is excreted in the sweat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Grisovin; ***Austral.***: Grisovin; ***Braz.***: Fulcin; Sporostatin; ***Fr.***: Grisefuline; ***Ger.***: Griseo; Likuden M†; ***Gr.***: Grisenova; ***Hong Kong***: CP-Griseo†; Grisuvin; ***India***: Dermonorm; Fluvin; Fungal; Fungivin; Geovin; Griderm; Gris-OD; Grisactin; Grisomed; Grisonorm; Grisoral; Grisovin; Idifulvin; Microfulvin; Myconorm; Nufulvin; Walavin; ***Indon.***: Fulcin; Fungistop; Griseofort; Grivin; Mycostop†; Rexavin; ***Irl.***: Grisol; ***Israel***: Grifulin†; ***Ital.***: Fulcin; Grisovina FP; ***Malaysia***: Grisuvin; Grivin; Krisovin; ***Mex.***: Fulcin; Fulsivin†; Grisovin; ***Philipp.***: Grisovin; ***Port.***: Grisovin†; ***S.Afr.***: Microcidal; ***Singapore***: Hexene; Krisovin; SP-Grevin; ***Spain***: Fulcin; ***Thai.***: Aofen; Fulvin; Fungivin; Fusovin; Grifulvin; Griseo-Med; Grisflavin; Grisin; Grisovex; Grivin; KB Vinecin; Mycovin; Mycoxyl; Neofulvin; Trivanex; ***Turk.***: Gefulvin; Grisovin; ***UK***: Fulsovin†; Grisol; ***USA***: Grifulvin V; Gris-PEG; ***Venez.***: Grisovin.

Multi-ingredient Preparations. ***Arg.***: Griseoplus.

Pharmacopoeial Preparations
BP 2014: Griseofulvin Tablets;
USP 36: Griseofulvin Capsules; Griseofulvin Oral Suspension; Griseofulvin Tablets; Ultramicrosize Griseofulvin Tablets.

Isoconazole *(BAN, USAN, rINN)*

Isoconazol; Isoconazolum; Isokonatsoli; Isokonazol; Izokonazol; Izokonazolas; Изоконазол.
1-[2,4-Dichloro-β-(2,6-dichlorobenzyloxy)phenethyl]imidazole.
$C_{18}H_{14}Cl_4N_2O$=416.1
CAS — 27523-40-6.
ATC — D01AC05; G01AF07.
ATC Vet — QD01AC05; QG01AF07.
UNII — GRI7WFR424.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Isoconazole). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Protect from light.

Isoconazole Nitrate *(BANM, rINNM)*

Isoconazol, nitrato de; Isoconazole, bitrate d'; Isoconazole, Nitrate d'; Isoconazoli Nitras; Isoconazolnitrat; Isokonatsolinitraatti; Isokonazolnitrat; Isokonazol-nitrát; Izokonazol Nitrat; Izokonazol-nitrát; Izokonazolo nitratas; Nitrato de isoconazol; R-15454; Изоконазола Нитрат.
$C_{18}H_{14}Cl_4N_2O,HNO_3$=479.1
CAS — 24168-96-5 (isoconazole mononitrate); 40036-10-0 (isoconazole nitrate).
ATC — D01AC05; G01AF07.
ATC Vet — QD01AC05; QG01AF07.
UNII — 5AS8P3N30X.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Isoconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. Protect from light.

Uses and Administration

Isoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vaginal mycoses, particularly due to *Candida* spp. (p. 564.1) and in fungal skin infections (p. 568.1). For vaginal infections it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days, or as a 1% vaginal cream daily for 7 days. For skin infections a 1% or 2% cream or other topical formulation has been used.

Adverse Effects and Precautions

Local reactions including burning or itching may occur after application of isoconazole.

Intravaginal preparations of azole antifungals may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Isoconazole is an imidazole antifungal active against a wide spectrum of fungi including *Candida* spp., dermatophytes, and *Malassezia furfur*. It is also active against some Gram-positive bacteria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Isomicot; Mupaten; ***Austria***: Gyno-Travogen; Travogen; ***Belg.***: Travogen; ***Braz.***: Gino-Isomax†; Ginotrax; Gyno-Icaden; Icaden; Isomax†; Micaden; Mycel Gyno†; Neo Isocaden; ***Chile***: Ufarin; ***Fr.***: Fazol G; Fazol; ***Gr.***: Travogen; ***Hong Kong***: Travogen; ***Israel***: Isogen; ***Ital.***: Abimono; Isogyn; Travogen; ***Malaysia***: Travogen; ***Mex.***: Icaden; Nocazin; ***Philipp.***: Travogen; ***Pol.***: Gyno-Travogen†; Travogen; ***Port.***: Gino-Travogen; ***Rus.***: Gyno-Travogen (Гино-травоген); Travogen (Травоген); ***Singapore***: Gyno-Travogen; Travogen; ***Switz.***: Gyno-Travogen; Travogen; ***Thai.***: Travogen; ***Turk.***: Gyno-Travogen; Travogen; ***Ukr.***: Gyno-Travogen (Гино-Травоген); Travogen (Травоген); ***Venez.***: Icaden; Noginox.

Multi-ingredient Preparations. ***Arg.***: Scheriderm; ***Austria***: Travocort; ***Belg.***: Travocort; ***Ger.***: Travocort; ***Gr.***: Travocort; ***Hong Kong***: Travocort; ***Indon.***: Travocort; ***Irl.***: Travocort; ***Israel***: Isocort; Tevaderm; ***Ital.***: Travocort; ***Malaysia***: Isoradin; Travocort; ***Mex.***: Scheriderm; ***Philipp.***: Travocort; ***Pol.***: Travocort; ***Port.***: Travocort; ***Rus.***: Travocort (Травокорт); ***S.Afr.***: Maxaderm; Travocort; ***Singapore***: Travocort; ***Switz.***: Travocort; ***Thai.***: Travocort; ***Turk.***: Travazol; Travocort; ***Ukr.***: Travocort (Травокорт).

Pharmacopoeial Preparations
BP 2014: Isoconazole Pessaries.

Itraconazole *(BAN, USAN, rINN)*

Itraconazol; Itraconazolum; Itrakonatsoli; Itrakonazol; Itrakonazolas; Oriconazole; R-51211; Итраконазол.
(±)-2-*sec*-Butyl-4-[4-(4-[4-[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl)-piperazin-1-yl)phenyl]-2,4-dihydro-1,2,4-triazol-3-one.
$C_{35}H_{38}Cl_2N_8O_4$=705.6
CAS — 84625-61-6.
ATC — J02AC02.
ATC Vet — QJ02AC02.
UNII — 304NUG5GF4.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Itraconazole). A white or almost white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Itraconazole). A white or almost white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane; sparingly soluble in tetrahydrofuran. Store in airtight containers. Protect from light.

Uses and Administration

Itraconazole is a triazole antifungal given orally for the treatment of oropharyngeal and vulvovaginal candidiasis, for pityriasis versicolor, for dermatophytoses unresponsive to topical treatment, for onychomycosis, and for systemic infections including aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis. It is also given for the prophylaxis of fungal infections in immunocompromised patients. The place of itraconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p. 563.1. Itraconazole has also been used in the management of some protozoal infections including acanthamoeba keratitis (p. 584.2), leishmaniasis (p. 584.2), and trypanosomiasis (p. 584.2).

Doses of itraconazole oral liquid and capsules are not equivalent and may not be used interchangeably.

In the UK, itraconazole ***oral liquid*** is licensed for use in *oral* and *oesophageal candidiasis* in a dose of 200 mg daily for 1 week; it may be taken as a single daily dose, or, preferably, in 2 divided doses, the liquid being retained in the mouth for 20 seconds before swallowing. If there is no response after a week, treatment may be continued for a further week. In the USA, a similar regimen is licensed for *oropharyngeal candidiasis,* but in oesophageal candidiasis an alternative regimen of 100 mg daily for at least 3 weeks is preferred, although the dose may be increased to 200 mg daily if necessary.

For patients with *fluconazole-resistant infections* the dose in the UK is 100 to 200 mg twice daily for 2 weeks; if there is no response, treatment may be given for a further 2 weeks. In the USA the recommended dose is 100 mg twice daily.

Itraconazole oral liquid is also licensed in the UK for prophylaxis of susceptible fungal *infections in immunocompromised patients,* in doses of 5 mg/kg daily, in 2 divided doses.

The following oral doses all apply to itraconazole ***capsules.***

- the dose in *oropharyngeal candidiasis* is 100 mg (or 200 mg in patients with AIDS or neutropenia) daily for 15 days
- *vulvovaginal candidiasis* may be treated with itraconazole 200 mg twice daily for 1 day
- *pityriasis versicolor* may be treated with itraconazole 200 mg daily for 7 days
- for dermatophytoses the dose is 100 mg daily for 15 days or 200 mg daily for 7 days in *tinea corporis* or *tinea cruris*; doses are 100 mg daily for 30 days or 200 mg twice daily for 7 days in *tinea pedis* or *tinea manuum*
- for *nail infections* the dose is 200 mg daily for 3 months or pulse therapy with 200 mg twice daily for 7 days repeated once (for fingernails) or twice (for toenails) after drug-free intervals of 21 days
- For *systemic infections,* itraconazole capsules are given in usual doses of 100 to 200 mg once daily, increased to 200 mg twice daily for invasive or disseminated infections, including cryptococcal meningitis.
  In life-threatening infections a loading dose of 200 mg three times daily for 3 days has been given. A dose of 200 mg daily is used for primary or secondary prophylaxis in neutropenic patients or those with AIDS. Absorption may be impaired in these patients and monitoring of plasma concentrations is advised with an increase in dose to 200 mg twice daily if necessary. This

higher dose is recommended routinely by some authorities in the USA such as the CDC.

Itraconazole may also be given by **intravenous infusion** in a dose of 200 mg given twice daily over 1 hour for two days, then 200 mg daily thereafter.

It has been suggested that a daily dose of 200 mg should not be exceeded when itraconazole is to be **co-administered** with ritonavir-boosted HIV-protease inhibitors.

For details of doses in children, see below.

Reviews.

1. Haria M, *et al*. Itraconazole: a reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. *Drugs* 1996; **51:** 585–620.
2. Pierard GE, *et al*. Itraconazole. *Expert Opin Pharmacother* 2000; **1:** 287–304.
3. Stevens DA (ed). Managing fungal infections in the 21st century: focus on itraconazole. *Drugs* 2001; **61** (suppl 1): 1–56.
4. Slain D, *et al*. Intravenous itraconazole. *Ann Pharmacother* 2001; **35:** 720–9.
5. Boogaerts M, Maertens J. Clinical experience with itraconazole in systemic fungal infections. *Drugs* 2001; **61** (suppl 1): 39–47.
6. Maertens J, Boogaerts M. The place for itraconazole in treatment. *J Antimicrob Chemother* 2005; **56** (suppl 1): i33–i38.
7. Potter M. Strategies for managing systemic fungal infection and the place of itraconazole. *J Antimicrob Chemother* 2005; **56** (suppl 1): i49–i54.
8. Korting HC, Schöllmann C. The significance of itraconazole for treatment of fungal infections of skin, nails and mucous membranes. *J Dtsch Dermatol Ges* 2009; **7:** 11–20.

Administration. *HIGH DOSES.* Doses of itraconazole 600 mg daily in two divided doses for 3 to 16 months were used in 8 patients with systemic mycoses resistant to conventional therapy.[1] Two patients with AIDS and cryptococcal meningitis failed to respond and 2 who responded initially later relapsed or developed progressive disease when the dose was reduced. The main adverse effects were hypokalaemia, hypertension, and oedema possibly associated with adrenal suppression.

In a patient with cerebral aspergillosis, itraconazole 800 mg daily for 5 months then 400 mg daily for a further 4½ months produced complete resolution of cerebral lesions.[2]

1. Sharkey PK, *et al*. High-dose itraconazole in the treatment of severe mycoses. *Antimicrob Agents Chemother* 1991; **35:** 707–13.
2. Sánchez C, *et al*. Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? *Clin Infect Dis* 1995; **21:** 1485–7.

Administration in children. A review of the use of itraconazole in children[1] considered oral itraconazole to be safe and effective against most fungal organisms causing superficial infections.

Itraconazole was given to 2 premature infants with disseminated candidiasis in a dose of 10 mg/kg daily in two divided doses for 3 or 4 weeks without adverse effects.[2] Treatment was successful in both infants.

Although itraconazole oral liquid is not licensed for use in children in the UK, and the capsules are only licensed from 12 years of age, the *BNFC* suggests the following daily ***oral*** doses; unlike in adults (p. 583.3) it makes no distinction between doses of the oral liquid and the capsules. Doses are given as a single dose (unless otherwise specified):

for **oropharyngeal candidiasis**:

- 1 month to 12 years of age, 3 to 5 mg/kg (to a maximum of 100 mg) daily for 15 days; up to 200 mg daily may be given to patients with neutropenia or AIDS
- 12 to 18 years of age, 100 mg (200 mg in those with neutropenia or AIDS) daily for 15 days

for **dermatophyte infections**:

- 1 month to 12 years of age, 3 to 5 mg/kg daily; this is given to a maximum of 200 mg daily for 7 days (pityriasis versicolor), to a maximum of 100 mg daily for 15 days (tinea corporis and tinea cruris), to a maximum of 100 mg daily for 30 days (tinea pedis and tinea manuum), or to a maximum of 200 mg daily for 2 to 6 weeks (tinea capitis)
- 12 to 18 years of age, 200 mg daily for 7 days (pityriasis versicolor); 100 mg daily for 15 days or as in pityriasis (tinea corporis and tinea cruris); or 100 mg daily for 30 days or 200 mg *twice* daily for 7 days (tinea pedis and tinea manuum); or up to a maximum of 200 mg daily for 2 to 6 weeks (tinea capitis)

for **onychomycosis**, from 1 year of age:

- 1 to 12 years, courses of 5 mg/kg (to a maximum of 200 mg) daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections
- 12 to 18 years, either 200 mg daily for 3 months, or courses of 200 mg *twice* daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections

for **histoplasmosis** or for **systemic fungal infections** such as aspergillosis, candidiasis, and cryptococcosis (including cryptococcal meningitis) where other antifungal drugs are inappropriate or ineffective:

- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) once or twice daily; the *twice* daily dose should be used in invasive or disseminated disease or cryptococcal meningitis. For intravenous doses, see below

for **maintenance in AIDS patients** to prevent relapse of underlying fungal infection, or for **prophylaxis in neutropenia** when standard therapy is inappropriate:

- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) daily, increased to *twice* daily if plasma-itraconazole concentrations are low

for **prophylaxis in haematological malignancy or bone marrow transplantation** (in patients expected to become neutropenic), where standard therapy is inappropriate the *oral liquid* may be given as follows:

- from 1 month of age to 18 years, 2.5 mg/kg *twice* daily, starting before transplantation or chemotherapy and continued until the neutrophil count recovers

As for the oral liquid, the intravenous product is not licensed in children in the UK; the *BNFC* suggests the following ***intravenous*** doses by infusion in children with **systemic fungal infections**:

- from 1 month of age to 18 years, 2.5 mg/kg (to a maximum of 200 mg) every 12 hours for 2 days, then the same dose once daily for a maximum of 12 days. Doses should be given by diluting 250 mg as the intravenous concentrate in 50 mL of sodium chloride 0.9% and infusing over 60 minutes

1. Gupta AK, *et al*. Efficacy and safety of itraconazole use in children. *Dermatol Clin* 2003; **21:** 521–35.
2. Bhandari V, Narang A. Oral itraconazole therapy for disseminated candidiasis in low birth weight infants. *J Pediatr* 1992; **120:** 330.

Amoebic infections. Topical and oral itraconazole has been tried for *Acanthamoeba* keratitis (p. 919.3).

Leishmaniasis. When systemic therapy is required for the treatment of leishmaniasis (p. 922.1), pentavalent antimonials are generally most commonly used. The successful use of itraconazole has been reported in some patients[1-5] with **cutaneous** disease (p. 922.1) and a systematic review[6] reported that for *L. tropica* infections there was reasonable evidence that itraconazole (200 mg daily) for 6 weeks was more effective than placebo. Infections with *Leishmania aethiopica* may not respond.[7] In a study of patients in Kuwait with cutaneous leishmaniasis, combination therapy with oral itraconazole (100 mg twice daily) and topical imiquimod 5% cream (applied 3 times a week) was found to produce better cure rates than treatment with itraconazole alone.[8]

Although a pilot study[9] in patients with **mucocutaneous** leishmaniasis (p. 923.1) reported benefit with itraconazole this was not confirmed in another study[10] where the response was only transient in the majority of patients. Similarly, itraconazole with terbinafine has been found to be ineffective in post kala-azar dermal leishmaniasis.[11]

1. Albanese G, *et al*. Cutaneous leishmaniasis: treatment with itraconazole. *Arch Dermatol* 1989; **125:** 1540–2.
2. Pialoux G, *et al*. Cutaneous leishmaniasis in an AIDS patient: cure with itraconazole. *J Infect Dis* 1990; **162:** 1221–2.
3. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *Int J Parasitol* 1996; **26:** 1413–15.
4. Consigli J, *et al*. Cutaneous leishmaniasis: successful treatment with itraconazole. *Int J Dermatol* 2006; **45:** 46–9.
5. Baroni A, *et al*. Cutaneous leishmaniasis treated with itraconazole. *Dermatol Ther* 2009; **22** (suppl 1): S27–S29.
6. González U, *et al*. Interventions for Old World cutaneous leishmaniasis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 31/03/09).
7. Akuffo H, *et al*. The use of itraconazole in the treatment of leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1990; **84:** 532–4.
8. Al-Mutairi N, *et al*. Treatment of Old World cutaneous leishmaniasis with dapsone, itraconazole, cryotherapy, and imiquimod, alone and in combination. *Int J Dermatol* 2009; **48:** 862–9.
9. Amato VS, *et al*. Use of itraconazole in the treatment of mucocutaneous leishmaniasis: a pilot study. *Int J Infect Dis* 2000; **4:** 153–7.
10. Calvopina M, *et al*. Itraconazole in the treatment of New World mucocutaneous leishmaniasis. *Int J Dermatol* 2004; **43:** 659–63.
11. Khalil EAG, *et al*. Failure of a combination of two antifungal drugs, terbinafine plus itraconazole, in Sudanese post kala-azar dermal leishmaniasis. *Trans R Soc Trop Med Hyg* 1996; **90:** 187–8.

Trypanosomiasis. Itraconazole, alone or with allopurinol, may produce beneficial responses in American trypanosomiasis (p. 925.3).

Adverse Effects

The most common adverse effects associated with itraconazole include dyspepsia, abdominal pain, nausea, vomiting, constipation, diarrhoea, headache, and dizziness. Others include allergic reactions such as pruritus, rash, urticaria, angioedema, and photosensitivity. Isolated cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and leucocytoclastic vasculitis have also been associated with itraconazole.

An increase in liver enzyme values has occurred in some patients and cases of hepatitis and cholestatic jaundice have been seen, especially in those treated for more than one month. There have been rare cases of liver failure and death.

Heart failure and pulmonary oedema have been reported rarely and serious cardiovascular events including arrhythmias and sudden death have been attributed to drug interactions in patients receiving itraconazole (see Interactions, p. 585.1). Blood disorders including leucopenia, neutropenia, and thrombocytopenia have also occurred.

Alopecia, oedema, and hypokalaemia have also been associated with prolonged use. Menstrual disorders and peripheral neuropathy, as well as visual disorders, tinnitus, and transient or permanent hearing loss, have been reported in a few patients.

Incidence of adverse effects. Itraconazole 50 to 400 mg daily for a median of 5 months was considered to be well tolerated in 189 patients with systemic fungal infections.[1] Of 86 patients with underlying disease, including 49 with AIDS, 16 with diabetes, and 23 with malignancy, nausea and vomiting occurred in 19 patients, hypertriglyceridaemia in 16, hypokalaemia in 11, and elevated liver enzyme values in 13. The role of itraconazole in hypertriglyceridaemia could not be assessed because all the samples were not drawn in the fasting state and hypertriglyceridaemia is a complication of HIV infection. Gynaecomastia occurred in 2 patients, 1 of whom also took spironolactone. Rash occurred in 4 patients.

Of 49 patients taking itraconazole 100 to 400 mg daily for up to 39 months, 23 had no adverse effects during treatment,[2] while 6 had nausea and vomiting, 5 developed oedema, and 2 developed hypertension; 3 of the patients who developed oedema and 1 who became hypertensive were diabetic. Three patients stopped itraconazole, 1 due to vomiting, 1 to leucopenia, and 1 to nephrotic syndrome. The patient with nephrotic syndrome had pre-existing oedema and hypertension; the syndrome cleared when itraconazole was stopped.

1. Tucker RM, *et al*. Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother* 1990; **26:** 561–6.
2. Graybill JR, *et al*. Itraconazole treatment of coccidioidomycosis. *Am J Med* 1990; **89:** 282–90.

Effects on the heart. Between September 1992, when itraconazole was approved in the USA, and April 2001, the FDA had received 58 reports of potential cases of heart failure associated with itraconazole.[1] There had been 28 patients admitted to hospital, and 13 had died. However, a causal relationship was difficult to prove. Overall, 43 patients had risk factors or diseases which might confound an association between the use of itraconazole and development of heart failure. Unpublished studies in *dogs* and humans had suggested a negative inotropic effect with intravenous itraconazole.

In August 2001, the UK CSM published a similar alert.[2] By this time, about 67 million patients worldwide had received itraconazole and there had been 75 spontaneously reported cases of suspected heart failure and an additional 63 reports of oedema suggestive of heart failure associated with oral formulations; there had been only 1 report of suspected heart failure in the UK. The CSM considered that the risk of heart failure with itraconazole was low, especially in young healthy patients receiving short courses of treatment (e.g. for vulvovaginal candidiasis). However, the risks appeared to be higher for older patients, patients with pre-existing heart disease or risk factors for heart failure, and for those receiving high doses and longer treatment courses (e.g. for onychomycosis).

The CSM[2] therefore advised caution when prescribing itraconazole to patients at risk of heart failure, whereas the FDA[1] contra-indicated it for the treatment of onychomycosis in patients with evidence of ventricular dysfunction.

1. Ahmad SR, *et al*. Congestive heart failure associated with itraconazole. *Lancet* 2001; **357:** 1766–7.
2. CSM. Cardiodepressant effect of itraconazole (Sporanox). *Current Problems* 2001; **27:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 04/06/06)

Precautions

Itraconazole has caused abnormalities in fetal development in *rodents* and is therefore contra-indicated in pregnancy. For further information, see Pregnancy, under Precautions of Fluconazole, p. 579.3.

Itraconazole is not recommended in patients with raised liver enzyme values, active liver disease, or a history of drug-induced hepatotoxicity; liver function should be monitored in patients with pre-existing liver function abnormalities and testing should be considered for all patients using itraconazole. Treatment should be stopped if signs or symptoms of hepatitis occur.

Dose adjustments may also be required in some patients with renal impairment. Licensed product information warns that the use of intravenous preparations of itraconazole formulated with hydroxypropylbetadex is contra-indicated in patients with a creatinine clearance of less than 30 mL/minute.

Itraconazole should be stopped if neuropathy develops.

Itraconazole should not be used for the treatment of less severe fungal infections such as onychomycosis in patients with evidence of, or a history of, ventricular dysfunction such as heart failure.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of itraconazole. In this case absorption may be improved by giving itraconazole with an acidic drink, such as a cola beverage.

Breast feeding. Licensed product information does not recommend breast feeding while receiving itraconazole although only small amounts of itraconazole are distributed into breast milk.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies itraconazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Enzyme-inducing drugs such as carbamazepine, isoniazid, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, or St John's wort may *decrease* plasma concentrations of itraconazole sufficiently to reduce its efficacy. Conversely, enzyme inhibitors such as clarithromycin, erythromycin, HIV-protease inhibitors, including ritonavir-boosted HIV-protease inhibitors, may *increase* plasma concentrations of itraconazole. Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, proton pump inhibitors, and histamine H_2-receptor antagonists, may reduce the absorption of itraconazole.

Like other triazole antifungals, itraconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, and may increase plasma concentrations of other drugs reliant upon it for their metabolism. This increases the risk of adverse effects and such combinations should be given with caution and careful monitoring, if at all. Drugs so affected may include:

- *antiarrhythmics* such as disopyramide, dofetilide and quinidine
- *antidepressants* such as reboxetine
- *antiepileptics* such as carbamazepine (which in turn decreases the concentration of the antifungal, see above)
- *antihistamines* such as astemizole, mizolastine, and terfenadine
- *antimalarials* such as halofantrine
- *antimigraine drugs* such as dihydroergotamine, ergometrine, ergotamine, methylergometrine, and eletriptan
- the *antimycobacterial* rifabutin (which again also decreases antifungal concentrations)
- *antineoplastics* such as busulfan, docetaxel, trimetrexate, and the vinca alkaloids
- *antipsychotics* such as pimozide and sertindole
- *anxiolytics and sedatives* such as buspirone
- *benzodiazepines* such as alprazolam, brotizolam, diazepam, midazolam, and triazolam
- *calcium-channel blockers* such as bepridil, verapamil, and the dihydropyridines felodipine, nifedipine, and nisoldipine (see also below)
- some *corticosteroids* such as budesonide, dexamethasone, fluticasone and methylprednisolone
- the *coumarin anticoagulant* warfarin
- the *gastrointestinal prokinetic* cisapride
- *HIV-protease inhibitors* such as indinavir, ritonavir, and saquinavir (concentrations of the antifungal may be increased in turn by indinavir, ritonavir, or co-formulated lopinavir-ritonavir, but not by saquinavir)
- *immunosuppressants* such as ciclosporin, sirolimus, and tacrolimus
- *opioids* such as alfentanil, fentanyl, and levacetylmethadol
- some *oral hypoglycaemics* such as repaglinide
- the *phosphodiesterase type-5 inhibitors* sildenafil and vardenafil and the *phosphodiesterase type-3 inhibitor* cilostazol
- *statins* (HMG Co-A reductase inhibitors) such as atorvastatin, lovastatin, and simvastatin
- *vasopressin receptor antagonists* such as conivaptan and tolvaptan

Itraconazole is also an inhibitor of p-glycoprotein, and may increase plasma concentrations of substrates such as digoxin.

Where drugs metabolised via CYP3A4 also prolong the QT interval, the risk of serious cardiovascular effects such as torsade de pointes means that the combination should be avoided; this includes astemizole, bepridil, cisapride, dofetilide, levacetylmethadol, mizolastine, pimozide, quinidine, sertindole, and terfenadine. Other drugs that should not be used with itraconazole due to the risk of unacceptable toxicity include eletriptan, the ergotamine derivatives, and the benzodiazepines midazolam and triazolam; additionally, UK licensed product information advises that halofantrine and disopyramide be avoided when oral pulse regimens of itraconazole are used. Care is also required with calcium-channel blockers, which may increase the risk of congestive heart failure if given together, and nisoldipine in particular is considered contra-indicated. Use with the statins is also best avoided because of the risk of muscle damage.

Reviews of drug interactions with azole antifungals.

1. Baciewicz AM, Baciewicz FA. Ketoconazole and fluconazole drug interactions. *Arch Intern Med* 1993; **153:** 1970–6.
2. Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. *Ann Pharmacother* 1998; **32:** 915–28.
3. Venkatakrishnan K, *et al.* Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; **38:** 111–80.

Immunosuppressants. Fatal hepatitis occurred in a 68-year-old woman[1] after 2 months of use of itraconazole and *leflunomide*. The authors suggested that the combined hepatotoxicity of both drugs might have accounted for this.

1. Legras A, *et al.* Fatal hepatitis with leflunomide and itraconazole. *Am J Med* 2002; **113:** 352–3.

Metal ions. Didanosine in a formulation containing aluminium and magnesium ion buffering agents could reduce the absorption of itraconazole due to the resultant increase in gastric pH.[1]

1. Moreno F, *et al.* Itraconazole-didanosine excipient interaction. *JAMA* 1993; **269:** 1508.

Antimicrobial Action

Itraconazole is a triazole antifungal drug that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes. It has a slightly wider spectrum of activity than ketoconazole. It is active against *Aspergillus* spp., *Blastomyces dermatitidis, Candida*spp., *Coccidioides immitis, Cryptococcus neoformans, Epidermophyton*spp., *Histoplasma capsulatum, Malassezia furfur, Microsporum* spp., *Paracoccidioides brasiliensis, Sporothrix schenckii,* and *Trichophyton* spp. Itraconazole also has some antiprotozoal activity against *Leishmania* spp.

Acquired resistance to itraconazole is rare but ketoconazole-resistant strains of *Candida albicans* have been found to be cross resistant to itraconazole.

Microbiological interactions. Synergistic antifungal effects were seen *in vitro* with terbinafine and itraconazole against strains of *Candida albicans*[1] and *Scedosporium prolificans*.[2] For effects on the antifungal activity of azoles when given with amphotericin B, see p. 572.3.

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.
2. Meletiadis J, *et al.* In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; **44:** 470–2.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles, see under Antimicrobial Action of Fluconazole, p. 580.2. Decreased susceptibility to itraconazole and cross-resistance to fluconazole has been reported in *C. albicans* isolated from patients with AIDS given long-term prophylaxis with itraconazole.[1] *Aspergillus fumigatus* resistant to itraconazole has also been seen.[2,3]

1. Goldman M, *et al.* Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; **44:** 1585–7.
2. Denning DW, *et al.* Itraconazole resistance in Aspergillus fumigatus. *Antimicrob Agents Chemother* 1997; **41:** 1364–8.
3. Dannaoui E, *et al.* Acquired itraconazole resistance in Aspergillus fumigatus. *J Antimicrob Chemother* 2001; **47:** 333–340.

Pharmacokinetics

Itraconazole is absorbed from the gastrointestinal tract when given orally either as capsules containing itraconazole coated onto sugar spheres or as an oral liquid formulated with hydroxypropylbetadex. Absorption from the capsule formulation is enhanced by an acidic gastric environment and is greatest when doses are taken with food; absorption from the oral liquid is not dependent on an acid environment, and absorption is greatest in the fasting state. Peak plasma concentrations occur between 1.5 and 5 hours after a dose of either formulation, and steady state is reached within 15 days during daily dosing. Peak plasma concentrations at steady state of about 2 micrograms/mL have been reported after daily doses of 200 mg.

Bioavailability increases with doses of 100 to 400 mg in such a manner as to suggest that itraconazole undergoes saturable metabolism. Itraconazole is highly protein bound; only 0.2% circulates as free drug. Itraconazole is widely distributed but only small amounts diffuse into the CSF. Concentrations attained in the skin, sebum, pus, and many organs and tissues are several times higher than simultaneous plasma concentrations. Therapeutic concentrations of itraconazole remain in the skin and mucous membranes for 1 to 4 weeks after the drug is stopped. Small amounts are distributed into breast milk.

Itraconazole is metabolised in the liver mainly by cytochrome P450 isoenzyme CYP3A4. The major metabolite, hydroxyitraconazole, has antifungal activity comparable with that of itraconazole. Itraconazole is also excreted as inactive metabolites in the bile or urine; 3 to 18% is excreted in the faeces as unchanged drug. Small amounts are eliminated in the stratum corneum and hair. Itraconazole is not removed by dialysis.

The elimination half-life after a single 100-mg dose has been reported as 20 hours, increasing to 30 to 40 hours with continued use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Itrac; Micotenk; Nitridazol; Panastat; Salimidin; Sporanox; ***Austral.***: Sporanox; ***Austria***: Itrabene; Sporanox; ***Belg.***: Sporanox; ***Braz.***: Estiranox; Fungonax; Itraconol†; Itracotan; Itrahexal; Itralex; Itraspor; Itrazol; Neo Itrax; Sporanox; Spozol; Traconal; Tracozon†; Tratzol; Traxonol; ***Canad.***: Sporanox; ***Chile***: Itodal; Sporanox; Teramic; ***China***: Mei Fu (美扶); Sporanox (斯皮仁诺); Yi Qi Kang (易启康); ***Cz.***: Cladostad; Prokanazol; Sporanox; ***Denm.***: Itrastad; Niddazol; Sporanox; ***Fin.***: Sporanox; ***Fr.***: Sporanox; ***Ger.***: Itracol†; Itraconbeta; Itraderm; Sempera; Siros; ***Gr.***: Assosept-S; Bevonazole; Brovicton; Deratil; Etrel; Fansidol; Flunol; Fungonazol; Fungospor; Idranox; Inrozol; Isoflon; Itrabest; Itracon; Itraconal; Itralfa; Itraproton; Itraspor; Itraviron; Itrazol; Laverio; Lorenzol; Mesmor; Micronazol; Mycodrox; Neo-Candimyk; Prominox; Soprazon; Sporanox; Sporizole; Stas; Sterginox; Zetilox; ***Hong Kong***: Aranox; Inox; Itracon; Itranstad; Quali-itrazole; Sporacid†; Sporanox; ***Hung.***: Cladostad; Itraconep; Itragen; Omicral; Orungal; ***India***: Biospore; Candistat; Canditral; Fulcover; Fungicap; Itaspor; Itra; Itracan; Itrazen; Itrole; ***Indon.***: Forcanox; Fungitrazol; Furolnok†; Itzol; Mycotrazol; Nufatrac; Petrazole; Sporacid; Sporanox; Sporax; Spyrocon; Trachon; Tracor; Unitrac; Zitrazol†; ***Irl.***: Sporanox; ***Israel***: Itranol; Sporanox; ***Ital.***: Sporanox; Tranizolo; Trazer; Triasporin; ***Jpn***: Itrizole; ***Malaysia***: Canditral; Inox; Itracon; Sporanox; Unitrac; ***Mex.***: Carexan†; Conamed; Congox; Derusil; Ergospharma†; Fitocyd; Fuzoltec; Imazol†; Iqcona; Isoporum; Isox; Itracosid; Itranax; Lozartil; Rixtal; Seritral; Silicsan; Sinozol; Solmavin; Sporanox; Steitraz; Trax; Z-Fin; Zitriasol; Zolken; Zotril; ***Neth.***: Trisporal; ***Norw.***: Sporanox; ***NZ***: Itcozol; Itrazole; Sporanox; ***Philipp.***: Inox; Sporanox; ***Pol.***: ItraGen; ItraMerck; Orungal; Trioxal; ***Port.***: Fungizol; Itracic; Sporanox; Unisens; ***Rus.***: Canditral (Кандитрал); Irunine (Ирунин); Itramicol (Итрамикол); Itrazol (Итразол); Miconihol (Миконихол); Orungal (Орунгал); Orungamin (Орунгамин); Orunit (Орунит); Rumycoz (Румикоз); Teknazol (Текназол); ***S.Afr.***: Adco-Sporozole; Sporanox; Trisporal; ***Singapore***: Canditral; Hitrazole; Sporanox; Unitrac; ***Spain***: Canadiol; Hongoseril; Oromic†; Sporanox; ***Swed.***: Sporanox; ***Switz.***: Gosegyne G; Itraderm; Sporanox; ***Thai.***: Canditral†; Icona†; Itra; Itracon; Itrasix; Itrazole; Norspor; Spazol; Sporal; Sporlab†; Spornar; ***Turk.***: Funit; Itraspor; Sporanox; Sporex; ***UK***: Sporanox; ***Ukr.***: Funit (Фунит); Itracon (Итракон); Itral (Итрал); Orunzol (Орунзол)†; Sporagal (Спорагал); Trioxal (Триоксал)†; ***USA***: Onmel; Sporanox; ***Venez.***: Fungosin; Sporanox.

Multi-ingredient Preparations. ***Mex.***: Gitrasek; Sepia; Sporasec; ***Venez.***: Sporasec.

Ketoconazole *(BAN, USAN, rINN)*

Ketoconazol; Kétoconazole; Ketoconazolum; Ketokonatsoli; Ketokonazol; Ketokonazolas; R-41400; Кетоконазол.

(±)-*cis*-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl}piperazine.

$C_{26}H_{28}Cl_2N_4O_4$=531.4

CAS — 65277-42-1.

ATC — D01AC08; G01AF11; J02AB02.

ATC Vet — QD01AC08; QG01AF11; QJ02AB02.

UNII — R9400W927I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Ketoconazole). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Uses and Administration

Ketoconazole is an imidazole antifungal used topically or orally. However, the risk of liver damage and adrenal gland problems (see Effects on the Liver p. 587.1 and Effects on Endocrine Function, p. 586.3, respectively) with *oral* use is considered by some licensing authorities to outweigh any benefits: the EMEA states that oral ketoconazole should not be used to treat fungal infections, while the FDA states it should not be given as first-line treatment but may be considered for the treatment of life-threatening infections when other effective antifungal drugs are not available or tolerated. It has been given for the prophylaxis of fungal infections in immunocompromised patients, although

fluconazole or itraconazole are usually preferred. It has been recommended that, because of its erratic absorption and slow therapeutic response, ketoconazole should not be used for the treatment of life-threatening fungal infections, including fungal meningitis, or for severe infections in immunocompromised patients.

The place of ketoconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p. 563.1. Ketoconazole has also been used in the treatment of some protozoal infections, including acanthamoeba infections and leishmaniasis. It has also been used in the management of acute respiratory distress syndrome, hypercalcaemia, and certain endocrine disorders and malignancies. For further information see below.

The usual oral dose for treatment and prophylaxis of fungal infections is 200 mg once daily taken with food. This may be increased to 400 mg daily if an adequate response is not obtained; in some infections even higher doses have been used. Treatment should usually be continued until symptoms have cleared and cultures have become negative. Some infections may require several months of treatment and giving ketoconazole for such prolonged periods may increase the risk of hepatotoxicity.

It has been suggested that daily doses of 200 mg should not be exceeded when ketoconazole is given with ritonavir-boosted HIV-protease inhibitors.

For details of doses in children, see below.

Ketoconazole is applied topically as a 2% cream in the treatment of candidal or dermatophyte infections of the skin, or in the treatment of pityriasis versicolor. It is used once or twice daily and continued for at least a few days after the disappearance of symptoms. A foam containing 2% ketoconazole applied twice daily for 4 weeks may be used in the treatment of seborrhoeic dermatitis. A shampoo containing 1 or 2% ketoconazole is also used; it is applied twice weekly for 2 to 4 weeks (or occasionally longer) in the treatment of dandruff or seborrhoeic dermatitis. The 2% shampoo is used once daily for up to 5 days in pityriasis versicolor. For prophylaxis of seborrhoeic dermatitis the 2% shampoo is used once every 1 to 2 weeks; for prophylaxis of pityriasis versicolor it may be used once daily for a maximum of 3 days before exposure to sunshine.

Administration in children. In infants and children, ketoconazole may be used topically for the treatment of fungal skin infections similarly to in adults. Oral use should be restricted to situations where other antifungals cannot be used due to resistance or intolerance.

In the UK, an oral dose of 100 mg once daily is recommended for children weighing from 15 to 30 kg; children weighing more than 30 kg may be dosed as for adults (see p. 585.3). Alternatively, in the USA, the American Academy of Pediatrics[1] has recommended an oral dose of 3.3 to 6.6 mg/kg once daily for children from 2 years of age.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Acanthamoeba infections. Although there is currently no established treatment for granulomatous amoebic encephalitis, ketoconazole may have some activity against the *Acanthamoeba* spp. responsible for this infection and has been applied topically to skin lesions. Ketoconazole has also been suggested for *Acanthamoeba* keratitis (p. 919.3), when it has been given orally with topical miconazole.

Acute respiratory distress syndrome. In two small double-blind, controlled studies,[1,2] the development of acute respiratory distress syndrome (ARDS—p. 1599.3) and mortality rates were lower in high-risk patients given ketoconazole than in those given placebo. An accompanying editorial[3] commented that adequate blood concentrations appeared to be essential. The mode of action could be associated with inhibition of leukotriene and thromboxane synthesis.[2,3] Nevertheless, in a study in 234 patients,[4] ketoconazole failed to reduce mortality or improve clinical outcomes when given early in the course of ARDS. Some centres have developed guidelines for ketoconazole prophylaxis in patients at risk of ARDS.[5]

1. Slotman GJ, *et al.* Ketoconazole prevents acute respiratory failure in critically ill surgical patients. *J Trauma* 1988; **28:** 648–54.
2. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; **21:** 1635–42.
3. Slotman GJ. Ketoconazole: maybe it isn't the magic potion, but... *Crit Care Med* 1993; **21:** 1642–4.
4. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; **283:** 1995–2002.
5. Sinuff T, *et al.* Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; **14:** 1–6.

Blastomycosis. Ketoconazole has largely been replaced by itraconazole as the azole of choice in the treatment of blastomycosis (p. 564.1) because of its higher incidence of adverse effects, and lower efficacy. If used as an alternative it is given in doses of 400 to 800 mg daily.[1]

1. Chapman SW, *et al.* Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 1801–12. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/588300 (accessed 03/07/08)

Endocrine disorders and malignant neoplasms. Ketoconazole has been reported to impair steroid hormone synthesis[1] and to blunt the response of cortisone to adrenocorticotrophic hormone (ACTH)[2] and has been tried in the management of some endocrine disorders.

In **Cushing's syndrome** (p. 2559.1), ketoconazole in doses of up to 1200 mg daily has been used successfully as an alternative or adjuvant to definitive therapies such as surgery or radiotherapy.[3-6]

Treatment of **hirsutism** is usually with an anti-androgen (see under Cyproterone, p. 2262.1), but ketoconazole has been tried in small numbers of women at a dose of 300 mg daily[7] or 400 mg daily,[8,9] with variable results.

Ketoconazole has been reported to produce a beneficial response in some forms of **precocious puberty** (p. 2254.1) that do not generally respond to gonadorelin analogues; cessation of menstruation and regression of pubertal signs in girls[10] and reduced testosterone secretion and increase in adult height in boys[11-13] has been noted in small numbers of patients studied.

The anti-androgenic effects of ketoconazole have also been found useful in the management of **prostatic cancer** (p. 712.3) in selected patients,[14-18] although there have been some concerns about its tolerability,[17] and it is not generally used as a first-line treatment.

Ketoconazole was ineffective in suppressing **postoperative erection** in patients undergoing penile reconstructive surgery;[19] it has been tried with prednisone for the management of recurrent ischaemic **priapism.**[20]

1. Pont A, *et al.* Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; **97:** 370–2.
2. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i:** 44–5.
3. Winquist EW, *et al.* Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. *J Clin Oncol* 1995; **13:** 157–64.
4. Estrada J, *et al.* The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med* 1997; **336:** 172–7.
5. Berwaerts JJ, *et al.* Corticotropin-dependent Cushing's syndrome in older people: presentation of five cases and therapeutical use of ketoconazole. *J Am Geriatr Soc* 1998; **46:** 880–4.
6. Chou SC, Lin JD. Long-term effects of ketoconazole in the treatment of residual or recurrent Cushing's disease. *Endocr J* 2000; **47:** 401–6.
7. Venturoli S, *et al.* A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *J Clin Endocrinol Metab* 1999; **84:** 1304–10.
8. Sonino N, *et al.* Low-dose ketoconazole treatment in hirsute women. *J Endocrinol Invest* 1990; **13:** 35–40.
9. Venturoli S, *et al.* Ketoconazole therapy for women with acne and/or hirsutism. *J Clin Endocrinol Metab* 1990; **71:** 335–9.
10. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; **12:** 81–3.
11. Bertelloni S, *et al.* Long-term outcome of male-limited gonadotropin-independent precocious puberty. *Horm Res* 1997; **48:** 235–9.
12. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90:** 147–51.
13. Almeida MQ, *et al.* Long-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. *Clin Endocrinol (Oxf)* 2008; **69:** 93–98.
14. Lowe FC, Bamberger MH. Indications for use of ketoconazole in management of metastatic prostate cancer. *Urology* 1990; **36:** 541–5.
15. Mahler C, *et al.* Ketoconazole and liarozole in the treatment of advanced prostatic cancer. *Cancer* 1993; **71:** 1068–73.
16. Small EJ, *et al.* Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. *J Urol (Baltimore)* 1997; **157:** 1204–7.
17. Bok RA, Small EJ. The treatment of advanced prostate cancer with ketoconazole: safety issues. *Drug Safety* 1999; **20:** 451–8.
18. Pettaway CA, *et al.* Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol* 2000; **18:** 1050–7.
19. DeCastro BJ, *et al.* Oral ketoconazole for prevention of postoperative penile erection: a placebo controlled, randomized, double-blind trial. *J Urol (Baltimore)* 2008; **179:** 1930–2.
20. Abern MR, Levine LA. Ketoconazole and prednisone to prevent recurrent ischemic priapism. *J Urol (Baltimore)* 2009; **182:** 1401–6.

Hypercalcaemia. Ketoconazole has been used[1-3] in the treatment of hypercalcaemia (p. 1778.1). It acts to reduce 1,25-dihydroxycholecalciferol concentrations by inhibiting cytochrome P450-dependent 1α-hydroxylation of vitamin D. For the treatment of infantile hypercalcaemia initial doses have ranged from 3 to 9 mg/kg daily, depending on the severity of the disease; the dose has then been progressively decreased, and finally stopped when the urinary calcium/creatinine ratio decreased below the upper limits of normal.[3]

1. Yavuz H. Familiar drugs for the treatment of hypercalcemia. *J Pediatr* 1998; **133:** 311.
2. Young C, *et al.* Hypercalcaemia in sarcoidosis. *Lancet* 1999; **353:** 374.
3. Nguyen M, *et al.* Infantile hypercalcemia and hypercalciuria: new insights into a vitamin D-dependent mechanism and response to ketoconazole treatment. *J Pediatr* 2010; **157:** 296–302.

Leishmaniasis. Ketoconazole has been tried as an alternative to conventional first- and second-line therapy for **visceral** leishmaniasis (p. 923.1),[1,2] although reports of treatment have not all been favourable.[3,4]

It has also been tried in **cutaneous** leishmaniasis (p. 922.1). A cure rate of 70% was reported in over 100 patients with *Leishmania major* infections treated with oral ketoconazole 200 to 400 mg daily for 4 to 6 weeks. Ketoconazole was not considered to be effective in infections due to *L. tropica, L. aethiopica,*[5] or *L. guyanensis.*[6] Ketoconazole 600 mg daily for 28 days has produced similar results to sodium stibogluconate intramuscularly for 20 days in patients with cutaneous leishmaniasis due to *L. panamensis.*[7] A further comparative study[8] of 96 patients being treated for cutaneous leishmaniasis, caused mainly by *L. major* or *L. tropica,* found ketoconazole given in doses of 600 mg in adults or 10 mg/kg in children for 30 days to be more effective than 6 to 8 bi-weekly intralesional injections of meglumine antimonate. In another study,[9] ketoconazole was less effective than sodium stibogluconate when cutaneous leishmaniasis was due to *L. braziliensis,* but more effective when *L. mexicana* was the cause.

1. Wali JP, *et al.* Ketoconazole in treatment of visceral leishmaniasis. *Lancet* 1990; **330:** 810–11.
2. Wali JP, *et al.* Ketoconazole in the treatment of antimony- and pentamidine-resistant Kala-azar. *J Infect Dis* 1992; **166:** 215–16.
3. Sundar S, *et al.* Ketoconazole in visceral leishmaniasis. *Lancet* 1990; **336:** 1582–3.
4. Rashid JR, *et al.* The efficacy and safety of ketoconazole in visceral leishmaniasis. *East Afr Med J* 1994; **71:** 392–5.
5. Weinrauch L, *et al.* Ketoconazole in cutaneous leishmaniasis. *Br J Dermatol* 1987; **117:** 666–7.
6. Dedet J-P, *et al.* Failure to cure Leishmania braziliensis guyanensis cutaneous leishmaniasis with oral ketoconazole. *Trans R Soc Trop Med Hyg* 1986; **80:** 176.
7. Saenz RE, *et al.* Efficacy of ketoconazole against Leishmania braziliensis panamensis cutaneous leishmaniasis. *Am J Med* 1990; **89:** 147–55.
8. Salmanpour R, *et al.* Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimoniate (Glucantime) for the treatment of cutaneous leishmaniasis. *J Dermatol Treat* 2001; **12:** 159–62.
9. Navin TR, *et al.* Placebo-controlled clinical trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis* 1992; **165:** 528–34.

Adverse Effects

Gastrointestinal disturbances are the most frequently reported adverse effect after the oral use of ketoconazole. Nausea and vomiting have been reported in about 3% of patients, and abdominal pain in about 1%. These adverse effects are dose-related and may be minimised by giving ketoconazole with food. Asymptomatic, transient elevations in serum concentrations of liver enzymes may occur in about 10% of patients. Hepatitis has been reported and the risk appears to increase if treatment with ketoconazole is continued for longer than 2 weeks; it is usually reversible on stopping ketoconazole but fatalities have occurred. Ketoconazole interferes with steroid biosynthesis and adverse endocrine effects include gynaecomastia, oligospermia, menstrual irregularities, and adrenal cortex suppression, especially at high doses.

Other adverse effects include allergic reactions such as urticaria and angioedema, and rare cases of anaphylaxis after the first dose have been reported. Pruritus, rash, alopecia, headache, dizziness, impotence, and somnolence may also occur. Thrombocytopenia, paraesthesia, raised intracranial pressure, photophobia, and photosensitivity have been reported rarely.

After topical use of ketoconazole, irritation, dermatitis, or a burning sensation has occurred.

Effects on the blood. A case of fatal aplastic anaemia was reported[1] in a 23-year-old woman who had taken oral ketoconazole for 4 days for the treatment of vaginal discharge.

1. Duman D, *et al.* Fatal aplastic anemia during treatment with ketoconazole. *Am J Med* 2001; **111:** 737.

Effects on endocrine function. Oral ketoconazole blocks testosterone synthesis and adrenal response to corticotropin, resulting in azospermia and oligospermia, gynaecomastia, impotence and decreased libido, and adrenal insufficiency.[1-8] As an inhibitor of steroid production, ketoconazole is valuable in controlling hypercortisolism and is used therapeutically in some endocrine disorders and prostatic cancer. For further discussion see under Uses and Administration, above.

1. DeFelice R, *et al.* Gynecomastia with ketoconazole. *Antimicrob Agents Chemother* 1981; **19:** 1073–4.
2. Pont A, *et al.* High-dose ketoconazole therapy and adrenal and testicular function in humans. *Arch Intern Med* 1984; **144:** 2150–3.
3. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i:** 44–5.
4. Dandona P, *et al.* Non-suppression of cortisol secretion by long term treatment with ketoconazole in patients with acute leukaemia. *J Clin Pathol* 1985; **38:** 677–8.

5. Pillans PI, *et al*. Hyponatraemia and confusion in a patient taking ketoconazole. *Lancet* 1985; **i:** 821–2.
6. McCance DR, *et al*. Acute hypoadrenalism and hepatotoxicity after treatment with ketoconazole. *Lancet* 1987; **i:** 573.
7. Best TR, *et al*. Persistent adrenal insufficiency secondary to low-dose ketoconazole therapy. *Am J Med* 1987; **82:** 676–80.
8. Khosla S, *et al*. Adrenal crisis in the setting of high-dose ketoconazole therapy. *Arch Intern Med* 1989; **149:** 802–4.

Effects on the liver. Hepatic adverse reactions to oral ketoconazole are well known.[1-4] Transient minor elevations of liver enzymes without clinical signs or symptoms of hepatic disease occur in about 10% of patients and may occur at any stage of treatment. Although this reaction is not usually clinically important it may signal the onset of more serious hepatic injury and indicates the need for close monitoring of liver function. Symptomatic hepatic reactions are much rarer (less than 0.1% of patients) but are potentially fatal. There is usually a hepatocellular pattern of damage and sometimes cholestasis. Patients at increased risk of hepatic injury include those with a history of liver disease, those aged over 50, especially women, and those requiring prolonged treatment. It is important to monitor liver function during treatment as well as to limit the length of treatment. If liver enzyme values continue to rise or jaundice or hepatitis occur, ketoconazole should be withdrawn immediately since fatalities have occurred in patients who continued treatment after signs of hepatic injury developed.

1. Janssen PA, Symoens JE. Hepatic reactions during ketoconazole treatment. *Am J Med* 1983; **74:** 80–5.
2. Lewis JH, *et al*. Hepatic injury associated with ketoconazole therapy. *Gastroenterology* 1984; **86:** 503–13.
3. Lake-Bakaar G, *et al*. Hepatic reactions associated with ketoconazole in the United Kingdom. *BMJ* 1987; **294:** 419–21.
4. García Rodríguez LA, *et al*. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999; **48:** 847–52.

Precautions

Since ketoconazole has been reported to cause hepatotoxicity it should not be given to patients with pre-existing liver disease. Patients given ketoconazole should be monitored for symptoms of hepatitis; also, liver function tests should be performed before starting oral treatment with ketoconazole lasting for more than 14 days and then at least monthly throughout therapy. Adrenal function should be monitored in patients with actual or borderline adrenal insufficiency, those under prolonged periods of physiological stress, or those on prolonged therapy showing signs or symptoms suggestive of adrenal insufficiency.

Ketoconazole has been shown to be teratogenic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of ketoconazole. In this case absorption may be improved by giving ketoconazole with an acidic drink, such as a cola beverage.

Breast feeding. Ketoconazole is excreted in breast milk and licensed product information states that oral use should be avoided during breast feeding. However, no adverse effects were seen in a breast-fed infant whose mother was receiving ketoconazole;[1] it was calculated that the infant was exposed to about 0.4% of the usual therapeutic dose of ketoconazole for this age group. The American Academy of Pediatrics considers[2] that use of ketoconazole is therefore usually compatible with breast feeding.

1. Moretti ME, *et al*. Disposition of maternal ketoconazole in breast milk. *Am J Obstet Gynecol* 1995; **173:** 1625–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/06/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketoconazole for systemic use as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients. Dermatological preparations are classified as possibly porphyrinogenic; they should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, histamine H_2-antagonists, and proton pump inhibitors, may reduce the absorption of ketoconazole. Absorption of ketoconazole may also be reduced by sucralfate. Enzyme-inducing drugs such as rifampicin, isoniazid, efavirenz, nevirapine, or phenytoin may reduce plasma-ketoconazole concentrations. Concentrations of isoniazid and rifampicin may also be reduced by ketoconazole.

Ketoconazole inhibits certain hepatic oxidase enzymes, especially the cytochrome P450 isoenzyme CYP3A4, in a similar way to itraconazole (p. 585.1) and similar care should be taken to avoid adverse effects due to increased plasma concentrations of the interacting drugs.

A disulfiram-like reaction may occur in patients taking ketoconazole after drinking alcohol. The efficacy of oral contraceptives may be reduced.

For reviews of drug interactions with azole antifungals, see Itraconazole, p. 585.2.

Antimicrobial Action

Ketoconazole is an imidazole antifungal that interferes with ergosterol synthesis and therefore alters the permeability of the cell membrane of sensitive fungi. It is reported to be fungistatic at concentrations achieved clinically. Ketoconazole has a wide spectrum of antimicrobial activity including activity against *Blastomyces dermatitidis, Candida* spp., *Coccidioides immitis, Epidermophyton floccosum, Histoplasma capsulatum, Malassezia* spp., *Microsporum canis, Paracoccidioides brasiliensis, Trichophyton mentagrophytes,* and *T. rubrum.* Some strains of *Aspergillus* spp., *Cryptococcus neoformans,* and *Sporothrix schenckii* are sensitive.

Ketoconazole has activity against some Gram-positive bacteria and some antiprotozoal activity against *Leishmania* spp.

There are rare reports of *Candida albicans* acquiring resistance to ketoconazole.

Microbiological interactions. For the effect of imidazoles and amphotericin B on each other's antimicrobial activity, see Amphotericin B, p. 572.3.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles see Fluconazole, Antimicrobial Action, p. 580.2.

Pharmacokinetics

The absorption of ketoconazole from the gastrointestinal tract is variable and increases with decreasing stomach pH. Mean peak plasma concentrations of about 3.5 micrograms/mL occur about 2 hours after an oral dose of 200 mg. Systemic absorption after topical or vaginal application in healthy subjects is minimal. Ketoconazole is more than 90% bound to plasma proteins, mainly albumin. It is widely distributed and appears in breast milk. Penetration into the CSF is poor. The elimination of ketoconazole is reported to be biphasic, with an initial half-life of 2 hours and a terminal half-life of about 8 hours.

Ketoconazole is metabolised in the liver to inactive metabolites. It is excreted as metabolites and unchanged drug chiefly in the faeces; some is excreted in the urine.

References.
1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. *Clin Pharmacokinet* 1988; **14:** 13–34.
2. Lelawongs P, *et al*. Effect of food and gastric acidity on absorption of orally administered ketoconazole. *Clin Pharm* 1988; **7:** 228–35.
3. Lake-Bakaar G, *et al*. Gastropathy and ketoconazole malabsorption in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988; **109:** 471–3.
4. Daneshmend TK. Diseases and drugs but not food decrease ketoconazole 'bioavailability'. *Br J Clin Pharmacol* 1990; **29:** 783–4.
5. Hurwitz A, *et al*. Gastric function in the elderly: effects on absorption of ketoconazole. *J Clin Pharmacol* 2003; **43:** 996–1002.
6. Fitch WL, *et al*. Revisiting the metabolism of ketoconazole using accurate mass. *Drug Metab Lett* 2009; **3:** 191–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: C-86; Cetonil; Eumicel; Faction; Fangan; Fitonal; Grenfung; Keduo; Ketogeno; Ketolef; Ketonazol; Micoespec; Micoral; Orifungal; Perative; Pitylis; Quadion; Sinamida Accion Caspa; Socosep; Tikl; Triatop; ***Austral.***: Hexal Konazol Shampoo†; Nizoral; Sebizole; ***Austria***: Fungoral; Nizoral; ***Belg.***: Docketoral†; Nizoral; Pelikair†; ***Braz.***: Aciderm†; Arcolan; Candiderm; Candoral; Cetoconalab; Cetoderm; Cetohexal; Cetomed; Cetomizol; Cetonax; Cetoneo; Cetonil; Cetonin; Cetozan; Cetozol; Cleartop; Conazol; Dermitrat; Ketonazol; Lozan; Miconan; Micoral; Nizonazol; Nizoral; Nizoretic†; Noriderm; Noronal; Zanoc; Zolmicol; ***Canad.***: Ketoderm; Nizoral; Nu-Ketocon†; ***Chile***: Arcolane; Biogel; Fungarest; Fungium; Soridermal; TKC; ***China***: 999 Xuanling (999 选灵); Gold Daktarin (金达克宁); Jing Yu (敬宇); Kexin (可欣); Nizoral (里素劳); Pikangwang (皮康王); Triatop (采乐); Xian Ke Xin (显克欣); Zhuolixin (卓立欣); ***Cz.***: Asquam†; Nizoral; ***Denm.***: Nizoral; Samkol; ***Fin.***: Konact; Nizoral; ***Fr.***: Ketoderm; Ketolium†; Nizoral†; ***Ger.***: Nizoral; Terzolin; ***Gr.***: Abba; Adenosan; Aquarius; Botaderm; Cezolin; Ebersept; Flidaphen; Fungoral; Ilgem; Libroman; Lovegin; Mycofebrin; Neo-egmol; Nyoxep; Reprol; Scalpin; Sostatin; Tonsil; Vafluson; Zemidral; ***Hong Kong***: CP-Keto†; Dezor; Diazon; Fluzoral†; Fungazol†; Funginox†; Ketocon; Ketovid; Ketozol; Ketozole; Larry; Nizoral; Pristine; Pristinex; Stada K†; Synizoral†; Ziconal†; ***Hung.***: Ketospor; Nizoral; ***India***: Arclone; Arcolane; Dandoff; Dandrex; Danfree; Danruf; Denfast; Derm-Keta; Emcon; Finazole; Fulkit; Funazole†; Fungicide; Funginoc; Fungizole; Hyphoral; Jacanzole; Jcanzole; K to Z; Ke-Toza; Kenazol; Ketafung; Keto; Ketocare; Ketoco; Ketocure; Ketonex; Ketopil; Ketovate; Ketoz; Ketozoe; Ketozole; Kezole; Kiton; Koiz; KZ; KZL; Nizol; Nizral; Novale; Ocona; ***Indon.***: Anfuhex†; Dermaral; Dexazol; Dysfungal†; Fexazol; Formyco; Funet; Fungasol; Fungoral; Grazol; Interzol; Ketomed; Lusanoc; Micoticum†; Muzoral; Mycoderm; Mycoral; Mycozid; Nizol; Nizoral; Nofung; Picamic; Profungal; Solinfec; Sporex; Thicazol; Wizol; Zoloral; Zoralin; Zumazol†; ***Irl.***: Ketopine; Ketozol; Nizoral; ***Israel***: Ketozol; Nizoral; ***Ital.***: Asquam; Nizoral; Triatop; ***Malaysia***: Dezor; Diazon; Fungazol; Funginox; Ketozotan; Kezoral; Larry; Nizoral; Pristine; Pristinex; Yucomy; ***Mex.***: Akorazol†; Biozoral; Conazol; Cremosan; Ergomicon; Eurolat; Fomiral; Fungipar; Fungoral; Fungosine†; Hispazzon†; Honzil; Ketofar; Ketomed; Ketomizol; Ketoril; Konaderm; Konaturil; Lizovag; Messelzol; Mi-Ke-Sons; Micoser; Micozol; Mycocil; Mycodib; Nastil; Nazolfarm; Nazoltec; Nizoral; Onofin-K; Prenalon; Remecon; Strizole†; Termizol; Tiniasil; Tiniazol; Toconal; Tolcrem; Tomiko; Triatop; ***Neth.***: Nizoral; ***Norw.***: Fungoral; Konazal†; ***NZ***: Daktagold; Ketopine; Nizoral; Sebizole; ***Philipp.***: Conatab†; Dezor; Donaxene; Fungizol; Ketovid; Konazole; Kozec; Nizoral; Reduff; ***Pol.***: Fungores†; Nizoral; Noell; Zoxinat; ***Port.***: Farmorol; Nizale; Nizoral; Tedol; ***Rus.***: Fungistab (Фунгистаб); Livarole (Ливарол); Mycoket (Микокет); Mycosoral (Микозорал); Nizoral (Низорал); Oronazol (Ороназол); Perkhotal (Перхотал); Sebozole (Себозол); ***S.Afr.***: Adco-Dermed; Ketazol; Kez; Nizcreme; Nizoral; Nizorelle†; Nizovules†; Nizshampoo; ***Singapore***: Antanazol; Beatoconazole; Dezor; Diazon; Formyco; Ketozole†; Kezoral†; Mycoral; Nicozone; Ninazol; Nitozol; Nizoral; Phytoral; Pristine; Pristinex; Sebizole; Sunazol; Yucomy; ***Spain***: Fungarest; Fungo Farmasierra†; Fungo Zeus; Keto-Cure; Ketoisdin; Medezol; Micoticum†; Panfungol; ***Swed.***: Fundan†; Fungoral; Ketoson†; Kezol†; ***Switz.***: Keto-med; Ketozol; Lur; Nizoral; Terzolin; ***Thai.***: AC-FA; Chintaral; Chintoral; Dandril; Dezor; Diazon; Fungazol; Fungiderm-K; Funginox; Fungizin; Kandex; Kara; Katsin; Kazinal; Kenalyn†; Kenazol; Kenoral; Ketazon; Ketocine; Ketolan; Ketomed; Ketonazole; Ketopac; Ketoral; Ketosil†; Ketozal; Kezole; Kezon; Konaz; Konazol; Lama†; Larry; Liquimed; Manoketo; Masarol; Mizoco; Mizoron; Mycella; Myco-shampoo; Myco; Mycoral; Nazole; Ninazol; Nizoral; Nora; Pasalen; SP-Keto; Sporaxyl; Sporoxyl; ***Turk.***: Fungoral; Keto; Ketoderm; Ketoral; Konazol; Nizoral; ***UK***: Daktarin Gold; Dandrazol; Dandrid; Nizoral; ***Ukr.***: Kenazole (Кеназол); Ketodin (Кетодин); Ketozoral (Кетозорал); Livarol (Ливарол); Nizoral (Низорал); ***USA***: Extina; Ketodan; Nizoral; Xolegel; ***Venez.***: Arcolane; Freetop; Kenazol; Ketazol; Ketomed; Nizoral.

Multi-ingredient Preparations. ***Arg.***: Bactisona†; Butimerin Complex; Ciprocort; Colposan; Dercotex; Dermoperative; Gentacler; Gynerium; Linfol Dermico; Magicrem; Microsona C; Ovogin; Torgyn Duo; Tricur; Tridermal; ***Braz.***: Betacortazol; Betazol Cort†; Betricort; Candicort; Capel; Celocort; Cetobeta; Cetocort; Cetocorten; Cimecort; Conacort; Cortifungin; Dermocorte; Emscort; Naderm; Novacort; Trok-N; Trok; ***China***: Baolongkang (保龙慷); Bi Liang (必亮); Compound Ketoconazole (复方酮康唑); ***India***: Apodruff; Clinhair; Cotar-K; Danclear; Dancure; Emvate; Everzple; Flakefree; Fungicide; Hyphoral; Kekona; Ketosis; Ketotar; Ketz; Koiz; Konaz; KTC; Nazcare; Nazz; Nuforce Shampoo; Ocona-CT; Ocona-Z; Scalpe; ***Ital.***: Keto Z; Ketomousse; ***Malaysia***: Ketoplus; ***Mex.***: Femisan; Loffymix†; Trexen Duo; ***Philipp.***: Scalpex; ***Rus.***: Keto Plus (Кето Плюс); ***Thai.***: Nizoral Cool; ***Ukr.***: Keto Plus (Кето Плюс); ***USA***: Xolegel CorePak; Xolegel Duo.

Pharmacopoeial Preparations
USP 36: Ketoconazole Oral Suspension; Ketoconazole Tablets.

Lanoconazole *(rINN)*

Lanoconazol; Lanoconazolum; Latoconazole; NND-318; TJN-318; Ланоконазол.

(±)-α-[(*E*)-4-(*o*-Chlorophenyl)-1,3-dithiolan-2-ylidene]imidazole-1-acetonitrile.

$C_{14}H_{10}ClN_3S_2$=319.8

CAS — 101530-10-3.

UNII — 4E7858311F.

Profile

Lanoconazole is an imidazole antifungal used topically in the treatment of fungal skin infections as a 1% cream, ointment, or solution, applied once daily. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Hypersensitivity. For reports of cross-sensitivity between lanoconazole and luliconazole, see p. 588.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Astat.

Liranaftate *(rINN)*

Liranaftato; Liranaftatum; M-732; Piritetrate; Лиранафтат.
O-5,6,7,8-Tetrahydro-2-naphthyl 6-methoxy-*N*-methylthio-2-pyridinecarbamate.
$C_{18}H_{20}N_2O_2S$=328.4
CAS — 88678-31-3.
UNII — 5253IGO5X3.

Profile

Liranaftate is an antifungal related to tolnaftate (p. 596.1) and is applied once daily as a 2% cream or solution in the treatment of superficial dermatophyte infections (p. 568.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Shu Zhi (澳舒旨); Dang Zhi (当止); Fu An (扶安); Jia Yi (嘉益); Li Wei Kang (利维康); Liang Qi (良奇); Sheng Fu Shuang (圣夫爽); Sifulin (斯芙林); Yi Fu Ping (一孚平); Yi Shen (易神); ***Jpn***: Zefnart.

Luliconazole *(USAN, rINN)*

Luliconazol; Luliconazolum; NND-502; PR-2699; Луликоназол.
(-)-(*E*)-[(4*R*)-4-(2,4-Dichlorophenyl)-1,3-dithiolan-2-ylidene](1*H*-imidazol-1-yl)acetonitrile.
$C_{14}H_9Cl_2N_3S_2$=354.3
CAS — 187164-19-8.
UNII — RE91AN4S8G.

Profile

Luliconazole is an imidazole antifungal that is applied topically, as a 1% solution or cream, in the treatment of fungal skin infections.

Hypersensitivity. Two patients who had allergic contact dermatitis to luliconazole were found on patch testing to be cross-sensitive to lanoconazole but not to several other imidazole antifungals.[1,2]

1. Shono M. Allergic contact dermatitis from luliconazole. *Contact Dermatitis* 2007; **56:** 296–7.
2. Tanaka T, *et al.* Allergic contact dermatitis from luliconazole: implication of the dithioacetal structure. *Acta Derm Venereol* 2007; **87:** 271–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Lulicon.

Mepartricin *(BAN, USAN, rINN)*

Mepartricina; Mépartricine; Mepartricinum; Methylpartricin; SN-654; SPA-S-160; Менартрицин.
CAS — 11121-32-7.
ATC — A01AB16; D01AA06; G01AA09; G04CX03.
ATC Vet — QA01AB16; QD01AA06; QG01AA09; QG04CX03.
UNII — B7FBW3Y74G.

Profile

Mepartricin is a mixture of the methyl esters of 2 related polyene antibiotics that may be obtained from a strain of *Streptomyces aureofaciens*. It has antifungal and antiprotozoal activity and has been used in vaginal candidiasis and trichomoniasis as pessaries or as a vaginal cream. A cream is also available for the treatment of superficial candidiasis. An oral form of mepartricin sodium laurilsulfate is also used. Oral mepartricin 40 mg daily is used in the treatment of some prostate disorders.

Prostate disorders. Studies[1,2] have shown that mepartricin given orally is effective in the treatment of *benign prostatic hyperplasia* (see p. 2347.1 for the more usual treatments); a dose of 40 mg daily is commonly used.[2] Mepartricin is thought to reduce cholesterol, oestrogen, and androgen binding to the prostate. Similarly, another study[3] has shown that the same dose of mepartricin provides symptomatic improvement in the management of *chronic prostatitis/chronic pelvic pain syndrome* (see Prostatitis, p. 2350.2).

1. Tosto A, *et al.* A double-blind study of the effects of mepartricin in the treatment of obstruction due to benign prostatic hyperplasia. *Curr Ther Res* 1995; **56:** 1270–75.
2. Denis L, *et al.* Double-blind, placebo-controlled trial to assess the efficacy and tolerability of mepartricin in the treatment of BPH. *Prostate* 1998; **37:** 246–52.
3. De Rose AF, *et al.* Role of mepartricin in category III chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. *Urology* 2004; **63:** 13–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Iperplasin†; ***Cz.***: Ipertrofan; ***Ital.***: Ipertrofan; Tricandil; ***Philipp.***: Ipertrofan†; ***Pol.***: Ipertrofan; ***Port.***: Iperplasin; Ipertrofan; Tricandil; ***Rus.***: Ipertrofan (Ипертрофан).

Multi-ingredient Preparations. ***Braz.***: Tricangine.

Micafungin Sodium *(BANM, USAN, rINNM)*

FK-463; Micafungina sódica; Micafungine Sodique; Natrii Micafunginum; Натрий Микафунгин.
5-((1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(1*R*)-3-Amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(1*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-[(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzoyl)amino]tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2′,1′-*l*][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl)-1,2-dihydroxyethyl)-2-hydroxyphenyl sodium sulfate.
$C_{56}H_{70}N_9NaO_{23}S$=1292.3
CAS — 235114-32-6 (micafungin); 208538-73-2 (micafungin sodium).
ATC — J02AX05.
ATC Vet — QJ02AX05.
UNII — IS1UP79R56.

Uses and Administration

Micafungin is an echinocandin antifungal with general properties similar to those of caspofungin (p. 575.1). It is used for the treatment and prophylaxis of candidiasis and, in some countries, for the treatment of aspergillosis. It is given as the sodium salt by intravenous infusion in doses of 50 mg once daily for candidiasis. For the treatment of oesophageal candidiasis the recommended dose is 150 mg daily. For invasive candidiasis, including candidaemia or disseminated infection, a dose of 100 mg once daily is recommended; if clinical response is inadequate, the dose may be increased to 200 mg once daily. For aspergillosis 50 to 150 mg is given once daily. Doses up to 300 mg daily have been used in severe or refractory disease. A dose of 50 mg daily is used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation, or in those expected to have neutropenia for 10 days or more.

For details of doses in children, see below. UK licensed product information advises that adults weighing 40 kg or less should also be dosed as for children.

Reviews.

1. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; **362:** 1142–51.
2. Jarvis B, *et al.* Micafungin. *Drugs* 2004; **64:** 969–84.
3. Carver PL. Micafungin. *Ann Pharmacother* 2004; **38:** 1707–21.
4. van Burik JA, *et al.* Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; **39:** 1407–16.
5. Chandrasekar PH, Sobel JD. Micafungin: a new echinocandin. *Clin Infect Dis* 2006; **42:** 1171–8.
6. Fritz JM, *et al.* Micafungin for the prophylaxis and treatment of Candida infections. *Expert Rev Anti Infect Ther* 2008; **6:** 153–62.
7. Cross SA, Scott LJ. Micafungin: a review of its use in adults for the treatment of invasive and oesophageal candidiasis, and as prophylaxis against Candida infections. *Drugs* 2008; **68:** 2225–55.
8. Horn DL, *et al.* Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. *Eur J Clin Microbiol Infect Dis* 2010; **29:** 223–9.
9. Bormann AM, Morrison VA. Review of the pharmacology and clinical studies of micafungin. *Drug Des Devel Ther* 2009; **3:** 295–302.

Administration in children. In the UK, micafungin is licensed for use in neonates and children for the treatment of invasive candidiasis, and the prophylaxis of candida infection in patients undergoing haematopoietic stem cell transplantation or those expected to have neutropenia for 10 days or more. In those 16 years of age and older, it may also be used for treatment of oesophageal candidiasis. The following doses are recommended based on body weight, and given by intravenous infusion over 1 hour:

- for treatment of invasive candidiasis: 2 mg/kg once daily; if adequate clinical response does not occur, the dose may be doubled
- for oesophageal candidiasis: 3 mg/kg once daily
- for prophylaxis of candidiasis: 1 mg/kg once daily

For children weighing more than 40 kg, adult doses (see above) should be used.

References.

1. Carter NJ, Keating GM. Micafungin: a review of its use in the prophylaxis and treatment of invasive Candida infections in pediatric patients. *Paediatr Drugs* 2009; **11:** 271–91.
2. Lehrnbecher T, Groll AH. Micafungin: a brief review of pharmacology, safety, and antifungal efficacy in pediatric patients. *Pediatr Blood Cancer* 2010; **55:** 229–32.

Adverse Effects

As for Caspofungin, p. 575.1. Rare cases of haemolysis, including acute intravascular haemolysis and haemolytic anaemia have been reported in patients given micafungin. Serious hepatic dysfunction has occurred after micafungin use, including fatalities. Children less than 1 year old may be more prone to liver injury. Isolated cases of renal dysfunction or acute renal failure have also occurred in patients taking micafungin.

Hypersensitivity. For reference to cross-sensitivity to caspofungin in a patient hypersensitive to micafungin see p. 575.2.

Precautions

Patients who develop abnormal liver- or renal-function tests while taking micafungin should be monitored for deterioration in hepatic or renal function respectively. Liver tumours have occurred in *rats* given micafungin for 3 months or more. Although the risk to humans is unknown, micafungin should be used with caution in patients with pre-existing risk of malignancy due to severe liver function impairment or chronic liver disease, or in those also using hepatotoxic or genotoxic medications.

Interactions

Micafungin may increase the area under the concentration-time curve for conventional amphotericin B, itraconazole, nifedipine, and sirolimus.

Antimicrobial Action

As for Caspofungin, p. 575.2.

Pharmacokinetics

Micafungin is absorbed from the gastrointestinal tract after oral doses. It is more than 99% bound to plasma proteins, mainly albumin.

Micafungin is metabolised by arylsulfatase to its catechol form and further metabolised to the methoxy form by catechol-*O*-methyltransferase. Some hydroxylation to micafungin via cytochrome P450 isoenzymes also occurs.

After 28 days about 71% of a dose is recovered in the faeces and 12% in the urine. Mean half-lives of 14.0 to 17.2 hours have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Mycamine; ***Braz.***: Mycamine; ***Canad.***: Mycamine; ***China***: Mycamine (米开民); ***Cz.***: Mycamine; ***Denm.***: Mycamine; ***Fr.***: Mycamine; ***Ger.***: Mycamine; ***Gr.***: Mycamine; ***Hong Kong***: Mycamine; ***Hung.***: Mycamine; ***Indon.***: Mycamine; ***Irl.***: Mycamine; ***Ital.***: Mycamine; ***Jpn***: Funguard; ***Neth.***: Mycamine; ***Norw.***: Mycamine; ***Philipp.***: Mycamine; ***Pol.***: Mycamine; ***Port.***: Mycamine; ***Rus.***: Micamin (Микамин); ***Spain***: Mycamine; ***Swed.***: Mycamine; ***Switz.***: Mycamine; ***Thai.***: Mycamine; ***UK***: Mycamine; ***Ukr.***: Micamin (Микамин); ***USA***: Mycamine.

Miconazole *(BAN, rINN)*

Miconazol; Miconazolum; Mikonatsoli; Mikonazol; Mikonazolas; R-18134; Миконазол.
1-[2,4-Dichloro-β-(2,4-dichlorobenzyloxy)phenethyl]imidazole.
$C_{18}H_{14}Cl_4N_2O$=416.1
CAS — 22916-47-8.
ATC — A01AB09; A07AC01; D01AC02; G01AF04; J02AB01; S02AA13.
ATC Vet — QA01AB09; QA07AC01; QD01AC02; QG01AF04; QJ02AB01; QS02AA13.
UNII — 7NNO0D7S5M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Miconazole). A white or almost white powder. It exhibits polymorphism. M.p. 83 degrees to 87 degrees. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Miconazole). A white to pale cream powder. It may exhibit polymorphism. M.p. 78 degrees to 88 degrees. Insoluble in water; soluble 1 in 9.5 of alcohol, 1 in 2 of chloroform, 1 in 15 of ether, 1 in 4 of isopropyl alcohol, 1 in 5.3 of methyl alcohol, and 1 in 9 of propylene glycol; freely soluble in acetone and in dimethylformamide. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Miconazole Nitrate *(BANM, USAN, rINNM)*

Miconazol, nitrato de; Miconazole, Nitrate de; Miconazoli Nitras; Miconazolnitrat; Mikonatsolinitraatti; Mikonazol Nitrat; Mikonazolnitrat; Mikonazol-nitrát; Mikonazolo nitratas; Mikonazolu azotan; Nitrato de miconazol; R-14889; Миконазола Нитрат.

$C_{18}H_{14}Cl_4N_2O,HNO_3$=479.1

CAS — 22832-87-7.

ATC — A01AB09; A07AC01; D01AC02; G01AF04; J02AB01; S02AA13.

ATC Vet — QA01AB09; QA07AC01; QD01AC02; QG01AF04; QJ02AB01; QS02AA13.

UNII — VW4H1CYW1K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Miconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Miconazole Nitrate). A white or practically white, crystalline powder, with not more than a slight odour. Soluble 1 in 6250 of water, 1 in 312 of alcohol, 1 in 75 of methyl alcohol, 1 in 525 of chloroform, 1 in 1408 of isopropyl alcohol, 1 in 119 of propylene glycol; freely soluble in dimethyl sulfoxide; soluble in dimethylformamide; insoluble in ether. Protect from light.

Uses and Administration

Miconazole is an imidazole antifungal used as miconazole base or nitrate in the treatment of superficial candidiasis (p. 564.1), and of the skin infections dermatophytosis and pityriasis versicolor (p. 568.1). It has also been given intravenously by infusion in the treatment of disseminated fungal infections, but other azoles are now more commonly used.

Miconazole may be given orally as a gel containing 20 mg/g (24 mg/mL) for the treatment and prevention of oropharyngeal and intestinal candidiasis. The usual adult dose is 5 to 10 mL four times daily (equivalent to a total of about 15 mg/kg daily). For the treatment of oral lesions the oral gel is applied directly. Miconazole may also be given once daily as a muco-adhesive buccal tablet (containing 50 mg miconazole) for the treatment of oropharyngeal candidiasis in immunocompromised patients.

Miconazole nitrate is usually applied twice daily as a 2% cream, lotion, or powder in the treatment of fungal infections of the skin including candidiasis, dermatophytosis, and pityriasis versicolor; it may be applied once or twice daily to treat fungal nail infections. In the treatment of vaginal candidiasis, 5 g of a 2% intravaginal cream is inserted into the vagina once daily for 10 to 14 days or twice daily for 7 days. Miconazole nitrate pessaries may be inserted in dosage regimens of 100 mg once daily for 7 or 14 days, 100 mg twice daily for 7 days, 200 or 400 mg daily for 3 days, or in a single dose of 1200 mg.

For details of miconazole use in children, see below.

Administration in children. Miconazole may be used in children for the treatment and prevention of oropharyngeal and intestinal candidiasis. In the UK, the oral gel (containing miconazole 20 mg/g) may be given to children from 4 months of age for **oral infections** in the following licensed doses:

- 4 months to 2 years of age: 1.25 mL 4 times daily
- from 2 years of age: 2.5 mL 4 times daily

Although unlicensed for use in younger children, the *BNFC* suggests that a dose of 1.25 mL 4 times daily may also be used in children as young as 1 month; for neonates, a dose of 1 mL 2 to 4 times daily is recommended.

For **intestinal infections** in children from 4 months of age miconazole oral gel is given in a daily dose of 20 mg/kg (to a maximum of 1 g) in 4 divided doses.

Miconazole nitrate may be used topically to treat fungal skin and nail infections in neonates and children similarly to adults (see above).

Acanthamoeba keratitis. Miconazole has been applied topically in *Acanthamoeba* keratitis (p. 919.3).

Skin disorders. Topical preparations containing an imidazole such as ketoconazole or miconazole, usually with hydrocortisone, are used in the management of *seborrhoeic dermatitis* (p. 1689.1). A cream containing miconazole nitrate 2% and benzoyl peroxide 5% has been used topically in the treatment of *acne* (p. 1682.2).

Adverse Effects

After oral use of miconazole, nausea and vomiting have been reported, and also diarrhoea (usually on long-term treatment). There have been allergic reactions, rarely, and isolated reports of hepatitis.

Local irritation and sensitivity reactions may occur when miconazole nitrate is used topically; contact dermatitis has been reported.

After the intravenous infusion of miconazole, phlebitis, nausea, vomiting, diarrhoea, anorexia, pruritus, rash, febrile reactions, flushes, drowsiness, and hyponatraemia have been reported. Other effects include hyperlipidaemia, aggregation of erythrocytes, anaemia, and thrombocytosis. Transient tachycardia and other cardiac arrhythmias have followed the rapid intravenous injection of miconazole (but see also Effects on the Heart, below). Rare adverse effects include acute psychosis, arthralgia, and anaphylaxis. Many of these adverse effects have been associated with the injection vehicle, which contains polyoxyl castor oil (p. 2202.3).

Effects on the heart. Bradycardia, progressing to fatal ventricular fibrillation and cardiac arrest, occurred in a heart transplant patient during intravenous infusion of miconazole for an invasive fungal infection.[1]

1. Coley KC, Crain JL. Miconazole-induced fatal dysrhythmia. *Pharmacotherapy* 1997; **17:** 379–82.

Overdosage. A report[1] of a generalised tonic-clonic convulsion that occurred in an infant 10 to 15 minutes after the inadvertent infusion of miconazole 500 mg instead of 50 mg.

1. Coulthard K, *et al.* Convulsions after miconazole overdose. *Med J Aust* 1987; **146:** 57–8.

Precautions

Systemic use of miconazole should be avoided in patients with hepatic impairment;

Intravaginal preparations of miconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

Miconazole has been fetotoxic at high doses in *animals* and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies miconazole (for dermatological use) as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Stomatological preparations are classified as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Miconazole can inhibit the metabolism of drugs metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and may thus have effects similar to those of fluconazole (p. 580.1). Miconazole may enhance the activity or serum concentrations of oral anticoagulants, sulfonylurea hypoglycaemics, or phenytoin. Adverse effects have been reported when miconazole was given with carbamazepine.

There is a risk of cardiac arrhythmias if oral miconazole is used with substrates of CYP3A4 that may prolong the QT interval, such as, astemizole, cisapride, dofetilide, halofantrine, mizolastine, pimozide, quinidine, sertindole, or terfenadine and such combinations should be avoided.

Anticoagulants. The anticoagulant activity of coumarin anticoagulants can be potentiated by miconazole given orally,[1] intravaginally,[2] or topically.[3] As of December 2002 the Australian Adverse Drug Reactions Advisory Committee had received 18 reports of significant increases in the INR of patients previously stabilised on warfarin within 1 to 2 weeks of starting treatment with miconazole oral gel.[4]

1. Ortín M, *et al.* Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; **33:** 175–7.
2. Lansdorp D, *et al.* Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; **47:** 225–26.
3. Devaraj A, *et al.* Interaction between warfarin and topical miconazole cream. *BMJ* 2002; **325:** 77.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Miconazole oral gel elevates INR—a reminder. *Aust Adverse Drug React Bull* 2002; **21:** 14. Available at: http://www.tga.gov.au/adr/aadrb/aadr0212.pdf (accessed 28/06/05)

Antimicrobial Action

Miconazole is an imidazole antifungal with similar antimicrobial activity to that of ketoconazole (p. 587.2). It also has some activity against *Aspergillus* spp., *Cryptococcus neoformans*, *Pseudallescheria boydii*, and some Gram-positive bacteria including staphylococci and streptococci.

References.

1. Barasch A, Griffin AV. Miconazole revisited: new evidence of antifungal efficacy from laboratory and clinical trials. *Future Microbiol* 2008; **3:** 265–9.

Microbiological interactions. A study *in vitro* indicating antimicrobial synergism of miconazole and benzoyl peroxide against *Staphylococcus* spp. and *Propionibacterium acnes*.[1]

For the effect on antifungal activity of giving azoles and amphotericin B together, see p. 572.3.

1. Vanden Bossche H, *et al.* Synergism of the antimicrobial agents miconazole and benzoyl peroxide. *Br J Dermatol* 1982; **107:** 343–8.

Pharmacokinetics

Miconazole is incompletely absorbed from the gastrointestinal tract. Peak plasma concentrations of 1 microgram/mL occur about 4 hours after a dose of 1 g daily. Over 90% is reported to be bound to plasma proteins.

Miconazole is metabolised in the liver to inactive metabolites. From 10 to 20% of an oral dose is excreted in the urine, mainly as metabolites, within 6 days. About 50% of an oral dose may be excreted unchanged in the faeces. The elimination pharmacokinetics of miconazole have been described as triphasic, with a biological half-life of about 24 hours.

Very little miconazole is removed by haemodialysis.

There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.

Reviews.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. *Clin Pharmacokinet* 1983; **8:** 17–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daktarin; Deralbine; Gynotran; Miconol; Micopul; Micotgez; Micotral; Micotrim P; Monizol; Nedis; ***Austral.***: Daktarin; Hairscience Anti-Dandruff; Resolve Thrush; Resolve Tinea; Resolve; ***Austria***: Daktarin; ***Belg.***: Daktarin; Gyno-Daktarin; Tibozole; ***Braz.***: Amicozol; Anfugitarin; Ciconazol; Colpadak; Dakgran†; Daktarin; Daktazol; Dermalina; Ginedak†; Gino Mizonol; Gino-Daczol; Ginotarin; Gyno Daknax; Gyno-Daktarin; Micofim; Micogyn; Micotarin†; Micotrin†; Micozen; Mizonol; Mycosin†; Vodol; ***Canad.***: Micatin; Micozole; Monistat Derm; Monistat; ***Chile***: Daktarin; ZeaSorb AF†; ***China***: Ao Xian Ning (澳先宁); Bai Ni Duo (拜尼多); Beikang (倍康); Daktarin (达克宁); Le Wei (乐蔚); Qingkun (清坤); Wu Mei (吾玫); ***Cz.***: Loramyc; ***Denm.***: Brentan; ***Fin.***: Daktarin; Gyno-Daktarin; Loramyc†; ***Fr.***: Daktarin; Gyno-Daktarin; Loramyc; ***Ger.***: Castellani mit Miconazol; Daktar; Derma-Mykotral†; Fungur M†; Gyno-Daktar; Gyno-Mykotral; InfectoSoor; Loramyc; Micobeta†; Micotar; Mykoderm Mund-Gel; Mykoderm; Mykotin; Vobamyk; ***Gr.***: Crimak; Daktarin; Fantersol; Gnostoderm; Gyno-Daktarin; Iristop; Medacter; Mezolitan; Untano; ***Hong Kong***: BF-Micozo†; Daktarin; Dermon; Funga†; Microtin†; Tinazol†; Uni-Mizole†; Zarin†; ***India***: Candistat; Candizole; Canticid; Daktarin; Decanazole; Emiconazole; Fungitop; Gyno-Daktarin; Micogel; Miconit; Micoptic; Micoson; Mizole; Zole; ***Indon.***: Daktarin; Daktazol; Fungares; Funtas; Micoskin; Micrem; Moladerm; Mycorine; Sporend; Zolagel; ***Irl.***: Daktarin; Gyno-Daktarin; ***Israel***: Daktarin; Fungiderm; Gyno-Daktarin; Pitrion; Zimycan†; ***Ital.***: Daktarin; Miconal; Micotef; Miderm†; Nizacol; Prilagin; ***Jpn***: Florid; ***Malaysia***: Antifungal; Becarin; Daktarin; Decozol; Dermon; Resolve; Zarin; ***Mex.***: Aloid; Biodantyl-C; Daktarin; Dermifun; Falernol; Fucoderm; Fungicrem†; Fungiquim; Ginazol†; Gyno-Daktarin; Hipo Femme; K-Mizol; Lotrimin AF; Micoffen; Nacomic; Neomicol; Nimicon; Niscamil; Oz Crema; Vigasil; ***Neth.***: Daktarin; Dermacure; Gyno-Daktarin; Kruidvat Antischimmelcreme; Kruidvat Antischimmelpoeder; Loramyc; Zimycan†; ***Norw.***: Daktar; ***NZ***: Daktarin; Fungo†; Micozole; Micreme; Monistat; ***Philipp.***: Daktarin; De-Ol; Defungin†; Emizole; Fungtopic; Micoson; Micotran; Monistat; ***Pol.***: Daktarin; Gyno-Femidazol; Loramyc; Miconal; ***Port.***: Daktarin; Gyno-Daktarin; Zimycan†; ***Rus.***: Daktarin (Дактарин)†; Gynezol (Гинезол); Micoson (Микозон); ***S.Afr.***: Covarex; Daktarin; Dermazole; Gyno-Daktarin; Gynospor†; Micmat; ***Singapore***: Antifungal; Candiplas; Daktarin; Decozol; Guardian Antifungal; Liconar; Micon; Minazol; Mycoban; Resolve; SP-Micozol; Tinazol; Zarin; ***Spain***: Daktarin; Fungisdin; Pasedon†; ***Swed.***: Daktar; ***Switz.***: Daktarin; Monistat; Sebolox; ***Thai.***: Daktarin; Dermon†; Funcort; Funga; Fungi-M; Fungisil; Mic†; Micazin; Mysocort; Nikarin; Noxraxin; Podakrin; Ranozol; Skindure; Tara; ***Turk.***: Fungucit; Lotrimin; Miko-Penetran; ***UAE***: Gyno-Mikozal; Mikozal; ***UK***: Daktarin; Gyno-Daktarin; Loramyc; ***Ukr.***: Micogel (Микогель); ***USA***: Aloe Vesta; Azolen; Baza Antifungal; Critic-Aid Clear AF; Cruex; Desenex Liquid Spray†; Desenex Powder; Femizol-M†; Fungoid; Lotrimin AF; M-Zole†; Micatin; Micro-Guard†; Miranel AF; Monistat; Neosporin AF†; Oravig; Podactin; Prescription Strength Desenex†; Ting; Triple Paste AF; Vagistat-3; ZeaSorb AF†; ***Venez.***: Daktarin; Gyno-Daktarin.

Multi-ingredient Preparations. ***Arg.***: Adenil; Betacort Plus; Blamy; Ciprocort; Colpofilin Max; Cuta Crema; Daktozin; Delisan; Denvercrem; Dermizol Trio; Dermosona; Factor Dermico; Fangan Plus; Genamic†; Gentasol; Ginal Cent; Ginkan; Gynormal; Hifamonil Crema; Ladylen; Lazar-Cort Complex; Lichensa; Linfol Cicatrizante; Macril; Mailen; Miklogen; Monizol Cort Crema; Monizol Cort; Neo Pelvicillin; Ovufem; Ovumix; Pentol; Protiderm; Septigyn; Tribiocort; Tricifa; Triliver; Triplex; Vagicural Plus; ***Austral.***: Daktozin; Resolve Nappy Rash; Resolve Plus; Resolve Tinea; Resolve; ***Austria***: Acne Plus; Vobaderm; ***Belg.***: Acneplus; Daktacort; Daktozin; ***Braz.***: Amplium-G; Anfu-

gine; Daktozin†; Facyl M; Gino-Colon; Gino-Pletil; Ginosutin-M†; Limpele Ginecologico; Trinizol M; ***Chile***: Doxifen; Exomicol; Famidal; Ginecopast Dual; Ginecopast; Ginedazol Dual; Ginedazol; Medidos; Mizonase; Tinidazol Compuesto; ***China***: Dapule (达普乐); ***Cz.***: Klion-D; ***Denm.***: Brentacort; ***Fin.***: Daktacort; ***Fr.***: Squaphane E; Squaphane P; Squaphane S; Squaphane; Squaphane; ***Ger.***: Acne Plus; Decoderm tri; Infecto-Soor; Micotar ZP; Vobaderm; ***Gr.***: Antimycotic; Catrigel; Combi; Conazol; Daktodor; Decoderm Trivalente-N; Domycotin; Edmudo; Expectein; Feminella; Finicort; Flenazole; Flumicomplex; Fluniprol; Flunovon; Fosemyk; Fumicon; Iflerit; Micoflup; Micogen; Mifler†; Milfer; Oxigon; Panderm; Panmyk; Sarmel; Verdal; ***Hong Kong***: Axcel Fungicort†; Conazole; Daktacort; Fungo Soothing Balm†; Hydro-Funga†; Micosone; Uni-Mizole-HC†; Zaricort†; ***Hung.***: Klion-D; Mycosolon; ***India***: Alclos-GM; Atderm; Beclasone-GM; Beclex-GM; Beclomin; Beclomin; Beclozen; Becmet-GM; Betamil-GM; Betamil-M; Betanate GM; Betanate M; Betaspi-GM; Betnederm GM; Betnovate-GM; Betnovate-M; Betzee-GM; Betzee-M; Candifem; Candizole-T†; CGM; Clobact-GM; Clobaderm-GM; Clobasia-GM; Clobecos-GM; Clobequad; Cloberis-GM; Clobesym-GM; Clobeta-CF; Clobquad; Cloby; Cloderm-GM; Clodip-GM; Clofung GM; Clogem; Clomic-M; Clomic-ZM; Clonate-GM; Clop-M; Clop-MG; Clos-GM; Clotof-GM; Clotof-M; Cortiderm-GM; Cosvate-GM; Cutasol-GM; Daktacort; Daktarin-T; Dandrid; Dermocrat Plus; Dermonit; Dermotel; Dermotriad; Dermotyl-M; Dermowin-GM; Drez-V; E-Derm; Eclospan; Ecziclo-GM; Elderm; Enderm-GM; Etan-GM; Eumosone-M; Excel-M; Flual-M; Flucort-MZ; Flucreme-NM; Flunec; Fungifite; Fungitop-F; Gemiderm; Gentacort-FC; GMF; Halostrol-M; Hyton; Kloryl-M; Labosol-GM; Leobet-GM; Leta-GM; Lobate-GM; Lobate-M; Losweat; Lozee-GM; Lozee-M; Lupiderm-GM; Lupiderm-M; Metazole; Miclogenta; Micocort-G; Micogel F; Micogram; Micolon; Mictop-F; Nazo-F; Stecort-NM†; Tenovate M; Valbet; Zole-F; ***Indon.***: Benoson M; Brentan; Daktarin Diaper; Thecort; Zolacort; Zolagel Diaper; ***Irl.***: Daktacort; ***Israel***: Daktacort; ***Ital.***: Acnidazil; Decoder Micoflu; ***Malaysia***: Daktacort; Decocort; Neo-Penotran; Zaricort; ***Mex.***: Bebektin; Daktacort; Gynotran; ***Neth.***: Acnecare; Daktacort; ***Norw.***: Cortimyk†; Daktacort; ***NZ***: Daktacort; Micreme H; Resolve Plus; ***Philipp.***: Acne Plus†; Daktacort; Neo-Penotran; ***Pol.***: Mycosolon; ***Port.***: Daktacort; Zaспе†; ***Rus.***: Klion-D (Клион-Д); Mycosolon (Микозолон); Neo-Penotran (Нео-Пенотран); ***S.Afr.***: Acneclear†; Acnidazil†; Daktacort; Elozart; Trialone†; ***Singapore***: Axcel Fungicort; Conazole; Daktacort; Decocort; Micon-H; Neo-Penotran; Tri-Micon; Zaricort; ***Spain***: Bexicortil†; Blastoestimulina; Brentan; Nutracel; ***Swed.***: Cortimyk; Daktacort; ***Switz.***: Acne Creme Plus; Daktacort; Decoderm bivalent; ***Thai.***: Daktacort; Decocort†; Fungisil-T; Kelaplus; Ladocort; Lymarin; Tara-Plus; Timi; Trimicon; ***Turk.***: Ekze-Mant; Gynotran; Neo-Penotran; Nidazol-M; Pers-Mant; ***UK***: Acorvio Plus; Daktacort HC; Daktacort; ***Ukr.***: Klion-D (Клион-Д); Mycosolon (Микозолон)†; Neo-Penotran (Нео-Пенотран); Neotrizol (Неотризол); ***USA***: Fungoid HC; Vusion; ***Venez.***: Daktozin.

Pharmacopoeial Preparations
BP 2014: Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment; Miconazole Cream; Miconazole Oromucosal Gel;
USP 36: Miconazole Injection; Miconazole Nitrate Cream; Miconazole Nitrate Topical Powder; Miconazole Nitrate Vaginal Suppositories.

Naftifine Hydrochloride *(BANM, USAN, rINNM)*

AW-105-843; Hidrocloruro de naftifina; Naftifin Hidroklorür; Naftifina, hidrocloruro de; Naftifine, Chlorhydrate de; Naftifini Hydrochloridum; Naftifungin Hydrochloride; SN-105-843 (naftifine); Нафтифина Гидрохлорид.
(*E*)-*N*-Cinnamyl-*N*-methyl(1-naphthylmethyl)amine hydrochloride.
$C_{21}H_{21}N,HCl$=323.9
CAS — 65472-88-0 (naftifine); 65473-14-5 (naftifine hydrochloride).
ATC — D01AE22.
ATC Vet — QD01AE22.
UNII — 25UR9N9041.

Pharmacopoeias. In *US*.

USP 36: (Naftifine Hydrochloride). Store in airtight containers.

Profile

Naftifine hydrochloride is an allylamine derivative (see Terbinafine, p. 593.3) which is fungicidal against dermatophytes, but only fungistatic against *Candida* spp.

Naftifine hydrochloride 1 or 2% is applied topically for fungal nail and skin infections, particularly dermatophytosis (see Skin Infections, p. 568.1).

Local reactions such as burning or stinging may occur.

Reviews.
1. Gupta AK, *et al.* Naftifine: a review. *J Cutan Med Surg* 2008; **12:** 51–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Exoderil; ***Canad.***: Naftin†; ***China***: Fang Di (芳迪); Xin Xin (欣欣); ***Cz.***: Exoderil; ***Ger.***: Exoderil†; ***Gr.***: Exoderil; ***Hong Kong***: Exoderil; ***Hung.***: Exoderil; ***Indon.***: Exoderil; ***Israel***: Exoderil; ***Ital.***: Suadian; ***Malaysia***: Exoderil; ***Pol.***: Exoderil; ***Rus.***: Exoderil (Экзодерил); ***Spain***: Micosona†; ***Turk.***: Exoderil; ***Ukr.***: Exoderil (Экзодерил); ***USA***: Naftin.

Multi-ingredient Preparations. ***China***: Bi Liang (必亮).

Pharmacopoeial Preparations
USP 36: Naftifine Hydrochloride Cream; Naftifine Hydrochloride Gel.

Natamycin *(BAN, USAN, pINN)*

Antibiotic A-5283; CL-12625; E235; Natamicina; Natamycine; Natamycinum; Natamycyna; Natamysiini; Pimaricin; Pimarisin; Натамицин.
$C_{33}H_{47}NO_{13}$=665.7
CAS — 7681-93-8.
ATC — A01AB10; A07AA03; D01AA02; G01AA02; S01AA10.
ATC Vet — QA01AB10; QA07AA03; QD01AA02; QG01AA02; QS01AA10.
UNII — 8O0C852CPO.

Pharmacopoeias. In *Jpn*, *Pol.*, and *US*.

USP 36: (Natamycin). An off-white to cream-coloured powder. It may contain up to 3 moles of water. Practically insoluble in water; soluble in glacial acetic acid and in dimethylformamide; slightly soluble in methyl alcohol. A 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

Uses and Administration

Natamycin is a polyene antifungal antibiotic produced by the growth of *Streptomyces natalensis*. It is used for the local treatment of candidiasis (p. 564.1) and fungal keratitis (see Eye Infections, p. 565.3). It has also been used in vaginal trichomoniasis (p. 925.1).

A 5% ophthalmic suspension or a 1% ointment of natamycin is used in the treatment of blepharitis, conjunctivitis, or keratitis due to susceptible fungi, including *Fusarium solani*.

Natamycin lozenges are used for the treatment of oral candidiasis in a dose of 10 mg every 4 to 6 hours. Tablets have been given orally for the treatment of intestinal candidiasis. Natamycin has also been used topically for fungal skin infections and for candidal and trichomonal infections of the vagina.

Adverse Effects and Precautions

Gastrointestinal disturbances have occurred after oral use of natamycin. Local application has sometimes produced irritation.

Antimicrobial Action

Natamycin is a polyene antifungal active against *Candida* and *Fusarium* spp. In addition it is active against the protozoan *Trichomonas vaginalis*.

Pharmacokinetics

Natamycin is poorly absorbed from the gastrointestinal tract. It is not absorbed through the skin or mucous membranes when applied topically. After ocular use, natamycin is present in therapeutic concentrations in corneal stroma but not in intra-ocular fluid; systemic absorption does not usually occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Natacyn; ***China***: Natezhen (那特真); ***Cz.***: Pimafucin; ***Fin.***: Pimafucin; ***Ger.***: Infectomyk; Pima Biciron N†; Pimafucin†; ***Hong Kong***: Natacyn†; ***Hung.***: Pimafucin; ***India***: Elmycin; Natadrops; Natam; Natamet; Natoptic; ***Indon.***: Fukricin; ***Malaysia***: Natacyn; ***Mex.***: Miconacina; ***Neth.***: Pimafucin; ***Pol.***: Pimafucin; ***Rus.***: Pimafucin (Пимафуцин); ***S.Afr.***: Natacyn; ***Singapore***: Natacyn; ***Thai.***: Natacyn; ***Turk.***: Pimafucin; ***Ukr.***: Pimafucin (Пимафуцин); ***USA***: Natacyn.

Multi-ingredient Preparations. ***Cz.***: Pimafucort; ***Fin.***: Pimafucort; ***Hung.***: Pimafucort; ***Neth.***: Pimafucort; ***NZ***: Pimafucort; ***Pol.***: Pimafucort; ***Port.***: Pimafucort; ***Rus.***: Pimafucort (Пимафукорт); ***Ukr.***: Pimafucort (Пимафукорт).

Pharmacopoeial Preparations
USP 36: Natamycin Ophthalmic Suspension.

Neticonazole Hydrochloride *(rINNM)*

Hidrocloruro de neticonazol; Neticonazol, hidrocloruro de; Néticonazole, Chlorhydrate de; Neticonazoli Hydrochloridum; SS-717; Нетиконазола Гидрохлорид.
(*E*)-1-[2-(Methylthio)-1-[*o*-(pentyloxy)phenyl]vinyl]imidazole hydrochloride.
$C_{17}H_{22}N_2OS,HCl$=338.9
CAS — 130726-68-0 (neticonazole); 130773-02-3 (neticonazole hydrochloride).
UNII — PKF582ZH6P.

Profile

Neticonazole is an imidazole antifungal that has been used topically in preparations containing 1% of the hydrochloride in the treatment of superficial fungal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Atolant.

Nifuroxime *(rINN)*

CCRIS-1180; NF-6; Nifuroxima; Nifuroximum; Nitrofuroxime; Нифуроксим.
5-Nitro-2-furaldehyde oxime.
$C_5H_4N_2O_4$=156.1
CAS — 6236-05-1.
UNII — 465N7PSU85.

NOTE. The names carbilquinone and carbazylquinone have been (possibly erroneously) applied to nifuroxime; however, carbazilquinone is a synonym for the antineoplastic carboquone, and care should be taken to avoid confusion.

Profile

Nifuroxime is a nitrofuran antimicrobial that has been used with furazolidone to treat vaginal candidiasis and trichomoniasis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Mex.***: Reuginal.

Nystatin *(BAN, USAN, rINN)*

Fungicidin; Nistatin; Nistatina; Nistatinas; Nisztatin; Nystatiini; Nystatine; Nystatinum; Nystatyna; Нистатин.
CAS — 1400-61-9.
ATC — A07AA02; D01AA01; G01AA01.
ATC Vet — QA07AA02; QD01AA01; QG01AA01.
UNII — BDF1O1C72E (nystatin); W1LX4T91WI (nystatin A_1).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Nystatin). An antifungal substance obtained by fermentation using certain strains of *Streptomyces noursei*. It contains mainly tetraenes, the principal component being nystatin A_1. The potency is not less than 4400 units/mg and not less than 5000 units/mg if intended for oral use, calculated with reference to the dried substance. It is a yellow or slightly brownish hygroscopic powder. Practically insoluble in water and in alcohol; freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Nystatin). A substance, or a mixture of two or more substances, produced by the growth of *Streptomyces noursei* (Streptomycetaceae). It has a potency of not less than 4400 units/mg, or, where intended for use in extemporaneous preparation of oral suspensions, not less than 5000 units/mg. A yellow to light tan, hygroscopic powder, with an odour suggestive of cereals; it is affected by long exposure to light, heat, and air. Practically insoluble in water and in alcohol; insoluble in chloroform and in ether; freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly to sparingly soluble in methyl alcohol, in *n*-butyl alcohol, and in *n*-propyl alcohol. A 3% suspension in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

Uses and Administration

Nystatin is a polyene antifungal antibiotic used for the prophylaxis and treatment of candidiasis of the skin and mucous membranes (see p. 564.1). It has been used with antibacterials in various regimens to suppress the overgrowth of gastrointestinal flora and as part of selective decontamination regimens (see Intensive Care, p. 187.3).

For the treatment of intestinal or oesophageal candidiasis, nystatin is given in oral doses of 500 000 or 1 000 000 units, as a tablet or capsule, 3 or 4 times daily.

For the treatment of lesions of the mouth, pastilles or a suspension may be given in a dosage of 100 000 units 4 times daily. The formulation should be kept in contact with the affected area for as long as possible, and patients should avoid taking food or drink for one hour after a dose. In the USA, doses of 400 000 to 600 000 units 4 times daily of the suspension, or 200 000 to 400 000 units 4 or 5 times daily as lozenges, are used.

For prophylaxis of intestinal candidiasis in patients given broad-spectrum antibacterials, tablets to a total dose of 1 000 000 units daily may be given.

For details of doses in children, see below.

For the treatment of vaginal infections, nystatin is given in a dosage of 100 000 to 200 000 units daily for 14 days or longer as pessaries or vaginal cream. For cutaneous lesions, ointment, gel, cream, or dusting powder containing 100 000 units/g may be applied 2 to 4 times daily.

A liposomal formulation of nystatin for *parenteral* use is under investigation.

Administration in children. Nystatin may be used orally in infants and children for the prevention and treatment of candida infections of the mucous membranes. It may also be used topically for candidiasis of the skin.

For the treatment of intestinal candidiasis, an oral dose of 100 000 units 4 times daily is recommended. Nystatin oral suspension is used locally for the treatment of oral lesions: UK licensed product information recommends a dose of 100 000 units be applied 4 times daily for infants and children; in the USA, 200 000 units for infants, or 400 000 to 600 000 units for older children, may be given 4 times daily. The formulation should be kept in contact with the affected areas for as long as possible.

For prophylaxis of oral infection in infants born to mothers with vaginal candidiasis, nystatin 100 000 units once daily is recommended. Oral nystatin has also been studied for the prevention of invasive fungal infections, such as candidiasis, in very premature or very low birthweight infants;[1] typically doses of 100 000 units 3 times daily have been used.

1. Austin N, *et al.* Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue **4**. Chichester: John Wiley; 2009 (accessed 01/12/09).

Candidiasis. A systematic review[1] of 14 studies (12 of prophylaxis, 2 of treatment) considered that nystatin could not be recommended for prophylaxis or treatment of *Candida* infections in patients with immunosuppression. In practice, fluconazole is usually preferred in such patients (see p. 564.1). Despite this, it has been suggested that nystatin may be a better choice for prophylaxis in very low birth-weight infants[2] (those weighing below 1.5 kg at birth).

1. Gøtzsche PC, Johansen HK. Nystatin prophylaxis and treatment in severely immunodepressed patients. Available in The Cochrane Database of Systematic Reviews; Issue **4**. Chichester: John Wiley; 2002 (accessed 28/06/05).
2. Isaacs D. Fungal prophylaxis in very low birth weight neonates: nystatin, fluconazole or nothing? *Curr Opin Infect Dis* 2008; **21:** 246–50.

Adverse Effects

Nausea, vomiting, and diarrhoea have occasionally been reported after oral use of nystatin. Oral irritation or sensitisation may occur. Rashes, including urticaria, have occurred and Stevens-Johnson syndrome has been reported rarely. Irritation may occur rarely after the topical use of nystatin.

Effects on the skin. Generalised pustular eruptions were reported in 3 patients after oral nystatin.[1] Subsequent sensitivity testing revealed delayed (type IV) hypersensitivity to nystatin.

1. Küchler A, *et al.* Acute generalized exanthematous pustulosis following oral nystatin therapy: a report of three cases. *Br J Dermatol* 1997; **137:** 808–11.

Precautions

Some intravaginal preparations of nystatin may damage latex contraceptives and additional contraceptive precautions may be necessary during treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nystatin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Antimicrobial Action

Nystatin is a polyene antifungal antibiotic that interferes with the permeability of the cell membrane of sensitive fungi by binding to sterols, chiefly ergosterol. Its main action is against *Candida* spp.

Pharmacokinetics

Nystatin is poorly absorbed from the gastrointestinal tract. It is not absorbed through the skin or mucous membranes when applied topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Candermil; Candidias; Dipni; Micostatin; Neostatin; Nistagrand; Nistamed; Nistat; ***Austral.***: Mycostatin; Nilstat; ***Austria***: Candio; Mycostatin; Nystaderm†; ***Belg.***: Nilstat; ***Braz.***: Albistin; Bebex N; Canditrat; Inofungin; Kandistat†; Micostal†; Micostalab; Micostatin; Neo Mistatin; Neostatin; Nicostat; Nidazolin; Nistagyn†; Nistatec; Nistatin†; Nistaval; Nistomic; Nistrazin; Tricocet; Vagistatina; ***Canad.***: Mycostatin†; Nyaderm; ***Chile***: Micostatin; Nistoral; ***China***: Fukangning (馥康宁); Mycostatin (米可定); ***Cz.***: Fungicidin; ***Denm.***: Mycostatin; ***Fin.***: Mycostatin; ***Fr.***: Mycostatine; ***Ger.***: Adiclair; Biofanal; Candio-Hermal; Lederlind; Moronal; Mykoderm Heilsalbe; Mykundex mono; Mykundex; Nystaderm; ***Gr.***: Mycostatin; Nystamysyn; ***Hong Kong***: Christatin†; Lystin; Mycostatin†; ***India***: Mycostatin; ***Indon.***: Candistin; Cazetin; Enystin; Fungatin; Fustin; Kandistatin; Mycostatin; Nymiko; Nystin; ***Irl.***: Mycostatin; ***Ital.***: Mycostatin; ***Malaysia***: Mikostat; Mycostatin; Uphastatin; ***Mex.***: Aponistan; Bistatin; Mibesan-S; Micostatin; Nistan; Nistaquim; Nizin-V; ***Norw.***: Mycostatin; ***NZ***: Mycostatin; Nilstat; ***Philipp.***: Afunginal; Maicostat; Mycostatin†; Mycosyl; Orastin; Stanys; ***Port.***: Micostatin; ***S.Afr.***: Candacide; Canstat; Mycostatin; Nystacid; ***Singapore***: Candistatin; Mycostatin; ***Spain***: Mycostatin; ***Swed.***: Mycostatin; ***Switz.***: Multilind; Mycostatine; ***Thai.***: Mycostatin†; Tystatin; ***Turk.***: Fungostatin; Mikostatin; ***UAE***: Mikostat; ***UK***: Nystan; ***USA***: Mycostatin; Nilstat; Nystop; Pedi-Dri; pediaderm AF; ***Venez.***: Micostatin.

Multi-ingredient Preparations. ***Arg.***: Bacticort Complex; Bexon; Biotaer Nebulizable; Dermadex NN; Farm-X Duo; Fasigyn Nistatina; Flagystatin; Kenacomb; Linfol; Linfol; Metanis; Mini O; Naxo TV; Nistinol†; O-Biol P†; O-Biol; Pelvicillin NF; Polygynax; Tratomax; Tratomax; Vagilen; ***Austral.***: Kenacomb; Otocomb Otic; ***Austria***: Mycostatin-Zinkoxid; ***Belg.***: Mycolog; ***Braz.***: Alivbaby; Babyneo; Benzevit; Bio-Vagin; Colpagex-N†; Colpatrin; Colpist; Colpistar; Colpistatin; Colpolase†; Dermodex; Dermokin†; Dermostatin; Donnagel; Flagyl Nistatina; Fungimax; Ginec; Ginestatin†; Gynax-N; Kolpitrat; Londerm-N†; Mud; Naxogin Composto; Neolon D; Omcilon-A M; Oncibel; Oncileg; Onciplus†; Oxyderme; Poliginax; Pratiderm; Tricolpex; Tricomax; Trinodazol Nistatina; Trinodazol; Trivagel N; Vagi Biotic; Vagimax†; Vagitrin-N; ***Canad.***: Flagystatin; ratio-Triacomb; Viaderm-KC; ***Chile***: Multilind; Naxogin Compositum†; Nistaglos; ***China***: Kenacomb (复方康纳乐霜); Lang Yi (朗依); Shui Qing (水青); ***Cz.***: Macmiror Complex; Polygynax; ***Denm.***: Kenalog Comp med Mycostatin†; ***Fin.***: Flagyl Comp; ***Fr.***: Auricularum; Polygynax Virgo; Polygynax; Tergynan; ***Ger.***: Candio-Hermal Plus; Lokalison-antimikrobiell Creme N†; Moronal V†; Multilind; Mykoproct sine†; Mykundex Heilsalbe; Nystaderm comp; Nystalocal; Nystatin Softpaste; Volonimat Plus N†; ***Gr.***: Auricularum; Beclomycin; Bioderm; Dermochrom; Kenacomb; ***Hong Kong***: Anlina†; Centacomb; Clonetin†; Dermawell†; Inquadeicren; Kenacomb†; Macmiror Complex; Neoclobet†; Polygynax; Triacomb†; Uni-Quaderm†; ***India***: Kenacomb; ***Indon.***: Fasigyn-Nystatin†; Fladystin; Flagystatin; Gynoxa; Myco-Z; Naxogin Complex; Neo Gynoxa; New Kenacomb†; Provagin; Trichostatic; Vagistin; ***Irl.***: Kenacomb†; Nystaform†; Timodine; Tinaderm-M†; ***Israel***: Dermacombin; ***Ital.***: Assocort†; Fasigin N; Inimur Complex; Macmiror Complex; ***Malaysia***: Kenacomb; ***Mex.***: Acenil; Bidrozil†; Decadron con Nistatina; Dermalog-C; Flagystatin V; Kenacomb; Macmiror Complex V; Metrofur†; Micostatin Baby; Novageon; Nysmosons-V; Promibasol-Plus†; Vagitrol-V; ***Neth.***: Mycolog†; ***NZ***: Kenacomb; Viaderm-KC; ***Philipp.***: Dermovate-NN; Flagystatin; Kenacomb†; Lidex NGN; Oticom; ***Pol.***: Macmiror Complex; Triacomb; ***Port.***: Dafnegil; ***Rus.***: Gyterna (Гитерна); Macmiror Complex (Макмирор Комплекс); Polygynax (Полижинакс); Tergynan (Тержинан); ***S.Afr.***: Hiconcil-NS†; Kenacomb†; Riostatin†; Tetrex-F†; ***Singapore***: Flagystatin; Polygynax; ***Spain***: Interderm; Positon; ***Swed.***: Kenacombin Novum†; ***Switz.***: Multilind; Mycolog N; Nystalocal; Topsym polyvalent; ***Thai.***: Dermacombin; Gynecon-T; Gynecon; Gynoco†; Gynova†; Gyonep; Gyracon; Kenacomb†; Nystin; Quinradon-N†; Vagicin; VG Med; ***Turk.***: Macmiror Complex; ***UAE***: Mikostat Baby Ointment; Panderm; ***UK***: Dermovate-NN†; Nystaform-HC; Nystaform; Timodine; Tinaderm-M†; Trimovate; ***Ukr.***: Macmiror Complex (Макмирор Комплекс); Micogynax (Микожинакс); Polygynax (Полижинакс); Tergynan (Тержинан); ***USA***: First Duke's Mouthwash; First Mary's Mouthwash; Myco-Biotic II; Myco-Triacet II; Mycogen II; Mycolog-II; Myconel; NGT; Tri-Statin II; ***Venez.***: Halcicomb; Kenacomb.

Pharmacopoeial Preparations

BP 2014: Nystatin Ointment; Nystatin Oral Suspension; Nystatin Pastilles; Nystatin Pessaries; Nystatin Tablets;

USP 36: Nystatin and Triamcinolone Acetonide Cream; Nystatin and Triamcinolone Acetonide Ointment; Nystatin Cream; Nystatin for Oral Suspension; Nystatin Lotion; Nystatin Lozenges; Nystatin Ointment; Nystatin Oral Suspension; Nystatin Tablets; Nystatin Topical Powder; Nystatin Vaginal Suppositories; Nystatin Vaginal Tablets; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment; Oxytetracycline and Nystatin Capsules; Oxytetracycline and Nystatin for Oral Suspension; Tetracycline Hydrochloride and Nystatin Capsules.

Omoconazole Nitrate *(USAN, rINNM)*

10-80-07; Nitrato de omoconazol; Omoconazol, nitrato de; Omoconazole, Nitrate d'; Omoconazoli Nitras; Омоконазола Нитрат.

(*Z*)-1-[2,4-Dichloro-β-[2-(*p*-chlorophenoxy)ethoxy]-α-methylstyryl]imidazole nitrate.

$C_{20}H_{17}Cl_3N_2O_2.HNO_3$=486.7

CAS — 74512-12-2 (omoconazole); 83621-06-1 (omoconazole nitrate).

ATC — D01AC13; G01AF16.

ATC Vet — QD01AC13; QG01AF16.

UNII — 15LTY5STY6.

Profile

Omoconazole is an imidazole antifungal used locally for fungal skin infections (p. 568.1) and for vaginal candidiasis (p. 564.1). It is applied topically as the nitrate as a 1% cream, powder, or solution in the treatment of cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. For vaginal candidiasis, omoconazole nitrate is given as pessaries in doses of 150 mg daily for 6 days, 300 mg daily for 3 days, or 900 mg as a single dose.

Intravaginal preparations of azoles may damage latex contraceptives.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Fongamil; Fongarex; ***Gr.***: Afongan; Fongamil; ***Hung.***: Mikogal; ***Mex.***: Afongan†; ***Port.***: Fongamil; ***Rus.***: Mikogal (Микогал); ***Ukr.***: Micogal (Микогал).

Oxiconazole Nitrate *(BANM, USAN, rINNM)*

Nitrato de oxiconazol; Oxiconazol, nitrato de; Oxiconazole, Nitrate d'; Oxiconazoli Nitras; Ro-13-8996; Ro-13-8996/000 (oxiconazole); Ro-13-8996/001; SGD-301-76; ST-813; Оксиконазола Нитрат.

2′,4′-Dichloro-2-imidazol-1-ylacetophenone (*Z*)-*O*-(2,4-dichlorobenzyl)oxime mononitrate.

$C_{18}H_{13}Cl_4N_3O.HNO_3$=492.1

CAS — 64211-45-6 (oxiconazole); 64211-46-7 (oxiconazole nitrate).

ATC — D01AC11; G01AF17.

ATC Vet — QD01AC11; QG01AF17.

UNII — RQ8UL4C17S.

Profile

Oxiconazole is an imidazole antifungal applied topically as the nitrate as a cream, solution, or powder equivalent to oxiconazole 1% in the treatment of fungal infections of the skin (p. 568.1). It is also given as a pessary in a single dose equivalent to 600 mg of oxiconazole in the treatment of vaginal candidiasis (p. 564.1).

Local reactions including burning and itching have been reported. Intravaginal preparations of azoles may damage latex contraceptives.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Reviews.

1. Jegasothy BV, Pakes GE. Oxiconazole nitrate: pharmacology, efficacy, and safety of a new imidazole antifungal agent. *Clin Ther* 1991; **13:** 126–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Oxistat†; ***Austria***: Lidermant†; ***Braz.***: Micotin; Oceral; Oxipelle; ***Cz.***: Myfungar; ***Fr.***: Fonx; ***Ger.***: Myfungar†; ***Mex.***: Myfungar; Oxistat; ***Rus.***: Myfungar (Мифунгар); ***Spain***: Salongo; ***Switz.***: Oceral; ***Turk.***: Oceral; ***Ukr.***: Myfungar (Мифунгар)†; ***USA***: Oxistat.

Multi-ingredient Preparations. ***India***: Zoderm.

Parconazole Hydrochloride *(USAN, rINNM)*

Hidrocloruro de parconazol; Parconazol, hidrocloruro de; Parconazole, Chlorhydrate de; Parconazoli Hydrochloridum; R-39500; Парконазола Гидрохлорид.

cis-1-{[2-(2,4-Dichlorophenyl)-4-[(2-propynyloxy)methyl]-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride.

$C_{17}H_{16}Cl_2N_2O_3$. HCl=403.7

CAS — 61400-59-7 (parconazole); 68685-54-1 (parconazole); 62973-77-7 (parconazole hydrochloride).

UNII — 8IF7HES548.

Profile

Parconazole is an antifungal that has been used as the hydrochloride in the treatment of gastrointestinal candidiasis in veterinary medicine.

Pentamycin

Fungichromin; Lagosin; Pentamicina; Пентамицин.

$C_{35}H_{58}O_{12}$=670.8

CAS — 6834-98-6.

ATC — G01AA11.

ATC Vet — QG01AA11.

UNII — 1JB340D58S.

NOTE. The name FemiFect has been used as a trade mark for pentamycin.

Profile

Pentamycin is a polyene antifungal antibiotic obtained from *Streptomyces pentaticus*. It has been used in the treatment of vaginal candidiasis and for the protozoal infection trichomoniasis.

References.

1. Frey Tirri B, *et al.* Safety, tolerability and pharmacokinetics of intravaginal pentamycin. *Chemotherapy* 2010; **56:** 190–6.

Posaconazole *(BAN, USAN, rINN)*

Posaconazol; Posaconazolum; Sch-56592; Позаконазол.

4-[*p*-[4-(*p*-[[(3*R*,5*R*)-5-(2,4-Difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furyl]methoxy]phenyl)-1-piperazinyl]phenyl]-1-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-Δ^2-1,2,4-triazolin-5-one.

$C_{37}H_{42}F_2N_8O_4$=700.8

CAS — 171228-49-2.

ATC — J02AC04.

ATC Vet — QJ02AC04.

UNII — 6TK1G07BHZ.

Uses and Administration

Posaconazole is an oral triazole antifungal used in the treatment of oropharyngeal candidiasis. It is also indicated in the treatment of invasive aspergillosis, chromoblastomycosis, coccidioidomycosis, fusariosis, or mycetoma infections in patients who are resistant to, or intolerant of, other antifungals. Posaconazole is also given for the prophylaxis of fungal infections in patients who are at high risk for invasive fungal disease due to prolonged neutropenia.

Posaconazole is given orally as a suspension; doses should be given with a meal, or a nutritional supplement in those who cannot tolerate food, in order to enhance oral absorption and ensure adequate exposure.

For the treatment of **oropharyngeal candidiasis** posaconazole is given in a loading dose of 200 mg on the first day, followed by 100 mg daily for 13 days. In patients with oropharyngeal candidiasis refractory to itraconazole and/or fluconazole, posaconazole is given at a dose of 400 mg twice daily.

In patients with refractory **invasive systemic fungal infections**, it is given at a dose of 400 mg twice daily. Patients not tolerating food or nutritional supplements should take 200 mg four times daily.

In the **prophylaxis** of invasive fungal infections, the recommended dose is 200 mg three times daily. Treatment is continued until recovery from neutropenia or immunosuppression. In patients undergoing cytotoxic chemotherapy for haematological malignancies, or haematopoietic stem-cell transplantation, treatment should begin several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells/mm^3.

References.

1. Herbrecht R. Posaconazole: a potent, extended-spectrum triazole anti-fungal for the treatment of serious fungal infections. *Int J Clin Pract* 2004; **58:** 612–24.
2. Segal BH, *et al.* Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis* 2005; **40:** 1684–8.
3. Keating GM. Posaconazole. *Drugs* 2005; **65:** 1553–67.
4. Raad II, *et al.* Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis* 2006; **42:** 1726–34.
5. Nagappan V, Deresinski S. Posaconazole: a broad-spectrum triazole antifungal agent. *Clin Infect Dis* 2007; **45:** 1610–7.
6. Frampton JE, Scott LJ. Posaconazole: a review of its use in the prophylaxis of invasive fungal infections. *Drugs* 2008; **68:** 993–1016.
7. Rachwalski EJ, *et al.* Posaconazole: an oral triazole with an extended spectrum of activity. *Ann Pharmacother* 2008; **42:** 1429–38.
8. Morris MI. Posaconazole: a new oral antifungal agent with an expanded spectrum of activity. *Am J Health-Syst Pharm* 2009; **66:** 225–36.
9. Cornely OA, *et al.* Current experience in treating invasive zygomycosis with posaconazole. *Clin Microbiol Infect* 2009; **15** (suppl 5): 77–81.
10. Bhattacharya M, *et al.* Posaconazole. *J Postgrad Med* 2010; **56:** 163–7.

Trypanosomiasis. For mention of posaconazole being tried in American trypanosomiasis see p. 925.3

Adverse Effects

The most commonly reported adverse effects with posaconazole are headache and nausea. Other common adverse effects include abdominal pain, anorexia, asthenia, back pain, diarrhoea, dyspepsia, dizziness, dry mouth, dry skin, fatigue, fever, flatulence, hot flushes, insomnia, neutropenia, paraesthesia, pruritus, rash, somnolence, and vomiting. Increased liver enzyme values, and rarely more severe hepatotoxicity (including fatal cases), have occurred in some patients, especially in those with serious underlying disease. Hypersensitivity and allergic reactions, including Stevens-Johnson syndrome, have occurred rarely.

Precautions

Some azoles have been associated with QT interval prolongation and licensed product information therefore advises that posaconazole should be used with caution in patients with potentially proarrhythmic conditions. Patients who develop abnormal liver function tests while being treated with posaconazole should be routinely monitored for the development of more serious liver injury.

Breast feeding. Breast feeding while taking posaconazole is not recommended by UK licensed product information.

Pregnancy. Posaconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3. UK licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with posaconazole.

Interactions

Posaconazole is metabolised by the uridine diphosphate glucuronosyltransferase UGT1A4, and is a substrate for p-glycoprotein. The use of drugs that either inhibit (for example, clarithromycin, erythromycin, ciclosporin, and verapamil) or induce (see below) enzymes in this pathway may increase or decrease plasma-posaconazole concentrations, respectively. Rifabutin and phenytoin have been shown to decrease plasma-posaconazole concentrations and a similar effect may be expected with rifampicin, carbamazepine, primidone, and phenobarbital. Concentrations of posaconazole are reduced by cimetidine possibly due to reduced absorption of posaconazole as a result of decreased acid production and reduced posaconazole concentrations may also be expected with other H_2-antagonists and proton pump inhibitors.

Posaconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and concentrations of other drugs that are metabolised by this enzyme pathway may be increased by posaconazole. Increased plasma concentrations of astemizole, cisapride, halofantrine, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. In the UK, HMG-CoA reductase inhibitors such as atorvastatin, lovastatin, and simvastatin are contra-indicated as concomitant use has been associated with rhabdomyolysis; US licensed product information, however, suggests that use may be possible if consideration is given to lowering the statin dose. Increased plasma concentrations of ciclosporin, sirolimus, and tacrolimus have been noted. Doses of ciclosporin and tacrolimus may need to be reduced and concentrations monitored, although use of sirolimus with posaconazole should generally be avoided. Close monitoring of blood glucose is necessary if posaconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for calcium-channel blockers, digoxin, vinca alkaloids, and some benzodiazepines (such as alprazolam, midazolam, and triazolam). It is expected that posaconazole will increase the concentrations of HIV-protease inhibitors and NNRTIs.

Interactions may occur where both posaconazole and the other drug are affected. Examples are ciclosporin (where concentrations of both posaconazole and ciclosporin are increased) and rifabutin (where concentrations of posaconazole are reduced but those of rifabutin are increased).

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A4 and azoles, see under Itraconazole, p. 585.1.

For reviews of drug interactions with azole antifungals, see Itraconazole, p. 585.2.

Antimicrobial Action

Posaconazole is a triazole antifungal drug that in sensitive fungi inhibits the enzyme lanosterol 14α-demethylase (CYP51) resulting in the impairment of ergosterol synthesis in fungal cell membranes. Posaconazole has activity against *Candida* spp., *Aspergillus* spp., *Coccidioides immitis*, *Fonsecaea pedrosoi*, and some species of *Fusarium* and zygomycetes.

Reports of breakthrough fungal infections in patients treated empirically or prophylactically with posaconazole.[1-3]

1. Rieger C, *et al.* Breakthrough infection of Trichosporon asahii during posaconazole treatment in a patient with acute myeloid leukaemia. *Eur J Clin Microbiol Infect Dis* 2007; **26:** 843–5.
2. Kishel JJ, Sivik J. Breakthrough invasive fungal infection in an immunocompromised host while on posaconazole prophylaxis: an omission in patient counseling and follow-up. *J Oncol Pharm Pract* 2008; **14:** 189–93.
3. Lekakis LJ, *et al.* Fatal rhizopus pneumonia in allogeneic stem cell transplant patients despite posaconazole prophylaxis: two cases and review of the literature. *Biol Blood Marrow Transplant* 2009; **15:** 991–5.

Pharmacokinetics

Posaconazole has linear pharmacokinetics after single and multiple doses with a high fat meal. No further increases in plasma concentration are seen with doses above 800 mg daily. It is slowly absorbed from the gastrointestinal tract and has a large volume of distribution. Peak plasma concentrations occur about 5 hours after an oral dose. Steady state plasma-posaconazole concentrations occur after 7 to 10 days of multiple dosage. Plasma protein binding is over 98%.

Metabolism plays only a minor role in the elimination of posaconazole; most circulating metabolites are glucuronide conjugates with only small amounts of oxidative metabolites. Posaconazole is slowly eliminated with a mean elimination half-life of 35 hours. The main elimination route of posaconazole is via the faeces (77%) where 66% of a dose is excreted unchanged. About 14% of a dose is excreted in the urine with only trace amounts excreted unchanged.

Reviews.

1. Courtney R, *et al.* Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother* 2003; **47:** 2788–95.
2. Krishna G, *et al.* Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. *Antimicrob Agents Chemother* 2007; **51:** 812–8.
3. Dodds Ashley ES, *et al.* Pharmacokinetics of posaconazole administered orally or by nasogastric tube in healthy volunteers. *Antimicrob Agents Chemother* 2009; **53:** 2960–4.
4. Moton A, *et al.* Pharmacokinetics of a single dose of the antifungal posaconazole as oral suspension in subjects with hepatic impairment. *Curr Med Res Opin* 2010; **26:** 1–7.
5. Li Y, *et al.* Pharmacokinetic/pharmacodynamic profile of posaconazole. *Clin Pharmacokinet* 2010; **49:** 379–96.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Noxafil; ***Austral.***: Noxafil; ***Austria***: Noxafil; ***Belg.***: Noxafil; ***Canad.***: Posanol; ***Chile***: Noxafil; ***Cz.***: Noxafil; ***Denm.***: Noxafil; ***Fr.***: Noxafil; ***Ger.***: Noxafil; ***Gr.***: Noxafil; ***Hung.***: Noxafil; ***Irl.***: Noxafil; ***Israel***: Noxafil; ***Ital.***: Noxafil; ***Malaysia***: Noxafil; ***Mex.***: Spriafil; ***Neth.***: Noxafil; ***Norw.***: Noxafil; ***NZ***: Noxafil; ***Pol.***: Noxafil; ***Port.***: Noxafil; ***Rus.***: Noxafil (Ноксафил); ***Singapore***: Noxafil; ***Spain***: Noxafil; ***Swed.***: Noxafil; ***Switz.***: Noxafil; ***Thai.***: Noxafil; ***Turk.***: Noxafil; ***UK***: Noxafil; ***Ukr.***: Noxafil (Ноксафил); ***USA***: Noxafil.

Propionic Acid

Ácido propiónico; E280; E283 (potassium propionate); Kwas propionowy; Propanoico, ácido; Пропионовая Кислота.

Propanoic acid.

$C_2H_5CO_2H$=74.08

CAS — 79-09-4.

UNII — JHU490RVYR.

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 31: (Propionic Acid). An oily liquid having a slight pungent, rancid odour. Miscible with water, with alcohol, and with various other organic solvents. Store in airtight containers.

Calcium Propionate

E282; Пропионат Кальция.

Calcium propanoate.

$(C_3H_5O_2)_2Ca$=186.2
CAS — 4075-81-4 (anhydrous calcium propionate); 56744-45-7 (calcium propionate monohydrate).
UNII — 8AI80040KW.

Pharmacopoeias. In *USNF.*

USNF 31: (Calcium Propionate). A white, crystalline solid. Soluble 1 in 3 of water. A 10% solution in water has a pH of 7.5 to 10.5. Store in airtight containers.

Sodium Propionate

E281; Natrii propionas; Natrio propionatas; Natriumpropionaatti; Natriumpropionat; Nátrium-propionát; Propionan sodný; Propionato de sodio; Sodium, propionate de; Пропионат Натрия.
Sodium propanoate.
$C_3H_5NaO_2$=96.06
CAS — 137-40-6 (anhydrous sodium propionate); 6700-17-0 (sodium propionate hydrate).
ATC — S01AX10.
ATC Vet — QA16QA02; QS01AX10.
UNII — DK6Y9P42IN.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Sodium Propionate). Slightly hygroscopic colourless crystals or white or almost white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 7.8 to 9.2. Store in airtight containers.

USNF 31: (Sodium Propionate). Colourless transparent crystals or a granular crystalline powder; odourless or with a faint acetic-butyric odour. Deliquescent in moist air. Soluble 1 in 1 of water, 1 in 0.65 of boiling water, and 1 in 24 of alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Profile

Propionic acid and its salts are antifungals. Calcium and sodium propionate have been used topically, usually with other antimicrobials for the treatment of dermatophyte infections. Eye drops containing sodium propionate have also been used.

Propionic acid and its calcium, sodium, and potassium salts are used in the baking industry as inhibitors of moulds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Propionat.

Multi-ingredient Preparations. ***Arg.***: Cicatrol; Farm-X; Fungicida; Hipoglos Cicatrizante; Novo Miconol†; ***Austral.***: Mycoderm; ***Austria***: Dermowund†; ***Braz.***: Andriodermol; Andriodermol; Colpagex-N†; Gynax-N; Vagitrin-N; ***Chile***: Fittig Antimicotico; ***Fr.***: Angispray; Dermacide; ***Gr.***: Buccasept†; Dermacide; ***Indon.***: Decyline; Decyline; ***Israel***: Otomycin; ***Malaysia***: Mycoderm†; ***S.Afr.***: Neopan; ***USA***: Amino-Cerv; Prophyllin.

Pyrrolnitrin *(USAN, rINN)*

52230; NSC-107654; Pirrolnitrina; Pyrrolnitrine; Pyrrolnitrinum; Пирролнитрин.
3-Chloro-4-(3-chloro-2-nitrophenyl)pyrrole.
$C_{10}H_6Cl_2N_2O_2$=257.1
CAS — 1018-71-9.
ATC — D01AA07.
ATC Vet — QD01AA07.
UNII — N0P24B6EDQ.

Pharmacopoeias. In *Jpn.*

Profile

Pyrrolnitrin is an antifungal antibiotic isolated from *Pseudomonas pyrrocinia* and has been applied topically in the treatment of superficial fungal infections.

Ravuconazole *(pINN)*

BMS-207147; ER-30346; Ravuconazol; Ravuconazolum; Равуконазол.
4-{2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-thiazolyl}-benzonitrile.
$C_{22}H_{17}F_2N_5OS$=437.5
CAS — 182760-06-1.
UNII — 95YH599JWV.

Profile

Ravuconazole is a triazole antifungal said to possess a broader spectrum of activity than fluconazole or itraconazole. It is under investigation for the treatment of systemic fungal infections. A prodrug of ravuconazole, E-1224, is also being studied for the treatment of American trypanosomiasis.

References.

1. Urbina JA, *et al.* In vitro and in vivo activities of ravuconazole on Trypanosoma cruzi, the causative agent of Chagas disease. *Int J Antimicrob Agents* 2003; **21:** 27–38.
2. Gupta AK, *et al.* A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. *J Eur Acad Dermatol Venereol* 2005; **19:** 437–43.
3. Pasqualotto AC, *et al.* Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole. *Curr Opin Investig Drugs* 2010; **11:** 165–74.

Sertaconazole Nitrate *(BANM, rINNM)*

Nitrato de sertaconazol; Sertaconazol, nitrato de; Sertaconazole, Nitrate de; Sertaconazoli Nitras; Sertaconazolnitrat; Sertakonatsolinitraatti; Sertakonazol Nitrat; Sertakonazolnitrat; Sertakonazol-nitrát; Sertakonazolo nitratas; Szertakonazol-nitrát; Сертаконазола Нитрат.
(±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[*b*]thien-3-yl)methoxy]phenethyl]imidazole nitrate.
$C_{20}H_{15}Cl_3N_2OS,HNO_3$=500.8
CAS — 99592-32-2 (sertaconazole); 99592-39-9 (sertaconazole nitrate).
ATC — D01AC14.
ATC Vet — QD01AC14.
UNII — 1DV05410M5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sertaconazole Nitrate). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol and in dichloromethane; soluble in methyl alcohol. Protect from light.

Profile

Sertaconazole is an imidazole antifungal used topically as the nitrate as a 2% cream, gel, solution, or powder in the treatment of superficial candidiasis, dermatophytosis, seborrhoeic dermatitis, and pityriasis versicolor. In the treatment of vaginal candidiasis it is used as a 2% vaginal cream daily for 7 or 8 days or as a single dose of a 300-mg or 500-mg pessary.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3. Intravaginal preparations of azole antifungals may damage latex contraceptives.

References.

1. Croxtall JD, Plosker GL. Sertaconazole: a review of its use in the management of superficial mycoses in dermatology and gynaecology. *Drugs* 2009; **69:** 339–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zalain; ***Braz.***: Gyno Zalain; Zalain†; ***Chile***: Tromderm; Zalain; ***China***: Li Ling Qi (立灵奇); Zalain (卓兰); ***Ger.***: Mykosert; Zalain; ***Gr.***: Fuganol; ***Hong Kong***: Zalain; ***Hung.***: Zalain; ***India***: Onabet; ***Indon.***: Dermofix†; ***Ital.***: Sertacream; Sertaderm; Sertadie; Sertagyn; ***Mex.***: Ertaczo; ***Mon.***: Monazol; ***Philipp.***: Zalain; ***Port.***: Dermofix; Sertopic; ***Rus.***: Zalain (Залаин); ***Singapore***: Zalain; ***Spain***: Dermofix; Dermoseptic; Gine Zalain†; Ginedermofix; Zalain; ***Thai.***: Zalain; ***Turk.***: Zalain; ***Ukr.***: Zalain (Залаин); ***USA***: Ertaczo; ***Venez.***: Zalain.

Siccanin *(rINN)*

Sicanina; Siccanine; Siccaninum; Сикканин.
(13a*S*)-1,2,3,4,4aβ,5,6,6a,11bβ,13bβ-Decahydro-4-4-6aβ,9-tetramethyl-13*H*-benzo[*a*]furo[2,3,4-*mn*]xanthen-11-ol.
$C_{22}H_{30}O_3$=342.5
CAS — 22733-60-4.
UNII — L702S858Z6.

Pharmacopoeias. In *Jpn.*

Profile

Siccanin is obtained from *Helminthosporium siccans,* a parasitic organism of rye grass It has antifungal activity and has been used topically as a 1% ointment for dermatophyte infections.

Sodium Parachlorobenzoate

Sodium *p*-Chlorobenzoate; Натрий Парахлорбензоат.
$C_7H_4ClNaO_2$=178.5
CAS — 3686-66-6.

Profile

Sodium parachlorobenzoate has antifungal activity and is used as a 4% powder in the treatment of fungal skin infections (p. 568.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Mycosid.

Sulconazole Nitrate *(BANM, USAN, rINNM)*

Nitrato de sulconazol; RS-44872-00-10-3; RS-44872; Sulconazol, nitrato de; Sulconazole, Nitrate de; Sulconazoli Nitras; Sulkonazol Nitrat; Сульконазола Нитрат.
1-[2,4-Dichloro-β-(4-chlorobenzyl)thiophenethyl]imidazole nitrate.
$C_{18}H_{15}Cl_3N_2S,HNO_3$=460.8
CAS — 61318-90-9 (sulconazole); 61318-91-0 (sulconazole nitrate).
ATC — D01AC09.
ATC Vet — QD01AC09.
UNII — 1T89100D5U.

Pharmacopoeias. In *Fr.* and *US.*

USP 36: (Sulconazole Nitrate). A white to off-white crystalline powder. Soluble 1 in 3333 of water, 1 in 100 of alcohol, 1 in 130 of acetone, 1 in 333 of chloroform, 1 in 286 of dichloromethane, 1 in 2000 of dioxan, 1 in 71 of methyl alcohol, 1 in 10 of pyridine, and 1 in 2000 of toluene. Protect from light.

Uses and Administration

Sulconazole is an imidazole antifungal used topically as the nitrate once or twice daily as a 1% cream or solution in the treatment of fungal skin infections including dermatophyte infections and pityriasis versicolor (see Skin Infections, p. 568.1), and candidiasis (p. 564.1).

Adverse Effects and Precautions

Local reactions including blistering, burning, itching, and erythema have been reported after sulconazole use.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Sulconazole is an imidazole antifungal with activity against dermatophytes, *Candida* spp., and *Malassezia furfur.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antifungal; ***Belg.***: Myk-1; ***China***: Ge Xuan (革选); ***Fr.***: Myk†; ***Gr.***: Suldisyn; ***Neth.***: Myk-1; ***Turk.***: Exelderm; ***UK***: Exelderm†; ***USA***: Exelderm.

Terbinafine *(BAN, USAN, rINN)*

SF-86-327; SF-86327; Terbinafiini; Terbinafin; Terbinafina; Terbinafinum; Тербинафин.
(*E*)-6,6-Dimethylhept-2-en-4-ynl(methyl)-(1-naphthylmethyl) amine.
$C_{21}H_{25}N$=291.4
CAS — 91161-71-6.
ATC — D01AE15; D01BA02.
ATC Vet — QD01AE15; QD01BA02.
UNII — G7RIW8S0XP.

Terbinafine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de terbinafina; Terbinafiinihydrokloridi; Terbinafin Hidroklorür; Terbinafina, hidrocloruro de; Terbinafine, Chlorhydrate de; Terbinafinhydrochlorid; Terbinafin-hydrochlorid; Terbinafinhydrokloríd; Terbinafini Hydrochloridum; Terbinafiny chlorowodorek; Тербинафина Гидрохлорид.
$C_{21}H_{26}ClN$=327.9
CAS — 78628-80-5.
ATC — D01AE15; D01BA02.
ATC Vet — QD01AE15; QD01BA02.
UNII — 012C11ZU6G.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Terbinafine Hydrochloride). A white or almost white powder. Very slightly or slightly soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in acetone. Protect from light.

USP 36: (Terbinafine Hydrochloride). A white or off-white powder. Very slightly or slightly soluble in water; freely

soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in acetone; Protect from light.

Uses and Administration

Terbinafine is an allylamine antifungal given orally as the hydrochloride in the treatment of dermatophyte infections of the skin and nails (p. 568.1). Oral doses are stated in terms of the base. Terbinafine hydrochloride 1.13 g is equivalent to about 1 g of terbinafine. It is also applied, as the hydrochloride, to the skin in dermatophytoses, in pityriasis versicolor (see Skin Infections, p. 568.1), and in cutaneous candidiasis (p. 564.1).

An oral dose of 250 mg is given once daily for 2 to 4 weeks for tinea cruris; treatment may be continued for up to 6 weeks for tinea pedis infections; a 4-week course is used in tinea corporis infections. A cream, gel, or solution containing 1% terbinafine hydrochloride is applied once or twice daily for 1 to 2 weeks to treat tinea corporis and tinea cruris; a 1-week course is recommended for tinea pedis. A 2-week course of treatment is used in cutaneous candidiasis and pityriasis versicolor.

Dermatophyte infections of the nails are treated with the equivalent of terbinafine 250 mg orally once daily for 6 to 12 weeks although longer treatment may be necessary in toe-nail infections.

Dosage should be reduced in patients with renal impairment (see below).

References.

1. Balfour JA, Faulds D. Terbinafine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. *Drugs* 1992; **43:** 259–84.
2. Abdel-Rahman SM, Nahata MC. Oral terbinafine: a new antifungal agent. *Ann Pharmacother* 1997; **31:** 445–56.
3. McClellan KJ, *et al.* Terbinafine: an update of its use in superficial mycoses. *Drugs* 1999; **58:** 179–202.
4. Darkes MJ, *et al.* Terbinafine: a review of its use in onychomycosis in adults. *Am J Clin Dermatol* 2003; **4:** 39–65.
5. Fleece D, *et al.* Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; **114:** 1312–15.
6. Gupta AK, *et al.* The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence. *J Drugs Dermatol* 2005; **4:** 302–8.
7. Revankar SG, *et al.* Use of terbinafine in rare and refractory mycoses. *Future Microbiol* 2008; **3:** 9–17.
8. Krishnan-Natesan S. Terbinafine: a pharmacological and clinical review. *Expert Opin Pharmacother* 2009; **10:** 2723–33.

Administration in children. Although terbinafine is not currently licensed in the UK for use in children, the *BNFC* suggests the following oral doses for the treatment of dermatophyte infections of the skin and nails in children over 1 year of age:

- in those weighing 10 to 20 kg: the equivalent of terbinafine 62.5 mg once daily
- in those weighing 20 to 40 kg: 125 mg once daily
- in those weighing over 40 kg: 250 mg once daily

Treatment is usually given for 4 weeks for tinea capitis, 2 to 4 weeks for tinea cruris, 4 weeks for tinea corporis, and may be continued for up to 6 weeks in tinea pedis. Infections of the nails are treated for 6 weeks to 3 months, although longer treatment may occasionally be required for toe-nail infections.

Similar regimens have been suggested by the American Academy of Pediatrics[1] and also reported in the literature.[2,3] A review on the use of terbinafine in children considered it both safe and effective in the management of tinea capitis and onychomycosis.[4]

Children with renal impairment may need lower doses (see below).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Jones TC. Overview of the use of terbinafine (Lamisil) in children. *Br J Dermatol* 1995; **132:** 683–9.
3. Fuller LC, *et al.* A randomized comparison of 4 weeks of terbinafine vs 8 weeks of griseofulvin for the treatment of tinea capitis. *Br J Dermatol* 2001; **144:** 321–7.
4. Gupta AK, *et al.* The efficacy and safety of terbinafine in children. *J Eur Acad Dermatol Venereol* 2003; **17:** 627–40.

Administration in renal impairment. Although UK licensed product information does not recommend the use of oral terbinafine in patients with renal impairment, the *BNF* and *BNFC* suggest that the usual recommended oral doses for adults (see above) and children (see above) should be reduced by half if the estimated glomerular filtration rate is less than 50 mL/min per 1.73 m^2.

Leishmaniasis. An inadvertent beneficial response has been reported[1] in an HIV-positive patient with cutaneous leishmaniasis (p. 922.1) who was taking terbinafine 250 mg daily for tinea corporis and onychomycosis. Beneficial results were also reported in a pilot study[2] in which patients with cutaneous leishmaniasis took either terbinafine 125 mg twice daily (those aged 5 to 15 years), or terbinafine 250 mg twice daily (those over 15 years), for 4 weeks.

1. González-Rupérez J, *et al.* Remission of localized cutaneous leishmaniasis in a HIV-positive patient using systemic terbinafine. *Dermatology* 1997; **194:** 85–6.
2. Bahamdan KA, *et al.* Terbinafine in the treatment of cutaneous leishmaniasis: a pilot study. *Int J Dermatol* 1997; **36:** 59–60.

Non-dermatophyte fungal infections. Beneficial responses to oral terbinafine have been reported in candidal infections of the nails and mouth,[1-3] aspergillosis, chromoblastomycosis, paracoccidioidomycosis, and sporotrichosis.[3,4]

1. Nolting S, *et al.* Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. *Br J Dermatol* 1994; **130** (suppl 43): 16–21.
2. Segal R, *et al.* Treatment of Candida nail infection with terbinafine. *J Am Acad Dermatol* 1996; **35:** 958–61.
3. Pérez A. Terbinafine: broad new spectrum of indications in several subcutaneous and systemic and parasitic diseases. *Mycoses* 1999; **42** (suppl 2): 111–4.
4. Francesconi G, *et al.* Terbinafine (250 mg/day): an effective and safe treatment of cutaneous sporotrichosis. *J Eur Acad Dermatol Venereol* 2009; **23:** 1273–6.

Seborrhoeic dermatitis. Terbinafine has been tried in the treatment of seborrhoeic dermatitis (p. 1689.1). In one study, 60 patients were randomised to receive oral terbinafine 250 mg daily or a placebo cream applied twice daily for 4 weeks.[1] Clinical improvement, maintained 8 weeks after completing treatment, in the terbinafine group led the investigators to conclude that oral terbinafine is an effective treatment for seborrhoeic dermatitis, and to suggest that this might be due to its activity against *Malassezia ovalis* (*Pityrosporum ovale*) as well as to some anti-inflammatory action. However, the methodology of this study has been questioned[2] and further investigation is needed. A further, uncontrolled, study[3] of 661 patients who received oral terbinafine 250 mg daily for 12 days each month for 3 months concluded that intermittent oral terbinafine could be effective for seborrhoeic dermatitis, at least in severe or recalcitrant forms. It has also been tried topically as a 1% cream.[4]

1. Scaparro E, *et al.* Evaluation of the efficacy and tolerability of oral terbinafine (Daskil) in patients with seborrhoeic dermatitis: a multicentre, randomized, investigator-blinded, placebo-controlled trial. *Br J Dermatol* 2001; **144:** 854–7.
2. Faergemann J. Treatment of seborrhoeic dermatitis with oral terbinafine? *Lancet* 2001; **358:** 170.
3. Cassano N, *et al.* Oral terbinafine for the treatment of seborrheic dermatitis in adults. *Int J Dermatol* 2002; **41:** 821–2.
4. Gündüz K, *et al.* Efficacy of terbinafine 1% cream on seborrhoeic dermatitis. *J Dermatol* 2005; **32:** 22–5.

Adverse Effects

The most frequent adverse effects after oral use of terbinafine hydrochloride are gastrointestinal disturbances such as nausea, diarrhoea, and mild abdominal pain. Loss or disturbance of taste may occur and occasionally may be severe enough to lead to anorexia and weight loss. Other frequent adverse effects include headache and skin reactions, including rash or urticaria, sometimes with arthralgia or myalgia. Severe skin reactions including angioedema, photosensitivity, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Allergic reactions, including anaphylaxis, have been reported. Liver dysfunction with isolated reports of cholestasis, hepatitis, and jaundice, has occurred and there have also been rare cases of hepatic failure, sometimes leading to death or needing liver transplantation, in patients both with and without pre-existing liver disease. Other rare adverse effects include paraesthesia, hypoaesthesia, dizziness, malaise, fatigue, alopecia, impaired hearing, tinnitus, rhabdomyolysis, and vasculitis. Smell disturbances, including loss of smell, have also been reported; these may resolve when treatment is stopped but may also be prolonged or permanent. Haematological disorders including neutropenia, thrombocytopenia, agranulocytosis, and pancytopenia have occurred. Psychiatric disturbances such as depression and anxiety, and precipitation or exacerbation of cutaneous and systemic lupus erythematosus, and psoriasis have been reported very rarely.

There may be local reactions after topical use of terbinafine.

Incidence of adverse effects. Postmarketing surveillance of about 10 000 patients[1] suggested the following incidences of adverse effects to oral terbinafine: gastrointestinal symptoms, 4.7%; dermatological effects, 3.3%; CNS symptoms (commonly headache), 1.8%; taste disturbances, 0.6%; and transient disturbances in liver function, 0.1%. Serious adverse effects possibly or probably related to terbinafine included angioedema, bronchospasm, erythema multiforme, extended stroke, and unilateral leg oedema. Combined data from 25 884 patients from this and 3 further studies[2] generally confirmed these results. Overall, adverse effects were reported in 10.5% of patients and caused treatment to be stopped in 5.3%. Serious adverse effects probably or possibly related to terbinafine occurred in 12 patients (0.046%).

1. O'Sullivan DP, *et al.* Postmarketing surveillance of oral terbinafine in the UK: report of a large cohort study. *Br J Clin Pharmacol* 1996; **42:** 559–65.
2. O'Sullivan DP. Terbinafine: tolerability in general medical practice. *Br J Dermatol* 1999; **141** (suppl 56): 21–5.

Effects on the blood. Up to August 2006, the Australian Adverse Drug Reactions Advisory Committee had received 16 reports of blood dyscrasias attributed to oral terbinafine including agranulocytosis (7 reports), neutropenia (7 reports), and pancytopenia (2 reports).[1] The reactions generally occurred within 4 to 6 weeks of starting therapy. Eleven patients recovered, 4 within one week of stopping treatment. However, a 79-year-old patient who developed agranulocytosis about 2 months after starting terbinafine died from septic shock.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Life threatening blood dyscrasias with oral terbinafine. *Aust Adverse Drug React Bull* 2006; **25:** 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 02/05/08)

Effects on the eyes. The US manufacturer has noted that changes in the lens and retina of the eye have sometimes been associated with oral terbinafine, although the significance of these changes is unknown.

Effects on the salivary glands. Bilateral parotid swelling was associated with terbinafine in a 38-year-old man.[1] Information from the manufacturer and the UK CSM indicated that this effect had occurred in other patients but was very rare. More recently, severe sialadenitis as a complication of drug reaction with eosinophilia and systemic complications (DRESS—a type of hypersensitivity reaction) was reported in an 80-year-old woman treated with terbinafine.[2] She also had severe xerostomia, lachrymal gland swelling, dry eyes, and keratitis.

1. Torrens JK, McWhinney PH. Parotid swelling and terbinafine. *BMJ* 1998; **316:** 440–1.
2. Abecassis S, *et al.* Severe sialadenitis: a new complication of drug reaction with eosinophilia and systemic symptoms. *J Am Acad Dermatol* 2004; **51:** 827–30.

Effects on the skin. Serious skin reactions are occasionally reported in patients receiving terbinafine and have included erythema multiforme,[1,2] erythroderma,[1] severe urticaria,[1] pityriasis rosea,[1] worsening of pre-existing psoriasis,[1,3] acrodermatitis continua of Hallopeau,[4] bullous pemphigoid,[5] acute generalised exanthematous pustulosis,[6,7] and lupus erythematosus.[8-11] Several of these patients had a history of auto-immune disease[2,10] and it has been suggested that this could be a risk factor for developing severe reactions.[2] Photo-allergic reactions have also been reported.[12]

1. Gupta AK, *et al.* Cutaneous adverse effects associated with terbinafine therapy: 10 case reports and a review of the literature. *Br J Dermatol* 1998; **138:** 529–32.
2. Goeteyn V, *et al.* Is systemic autoimmune disease a risk factor for terbinafine-induced erythema multiforme? *Br J Dermatol* 2000; **142:** 578–9.
3. Wilson NJE, Evans S. Severe pustular psoriasis provoked by oral terbinafine. *Br J Dermatol* 1998; **139:** 168.
4. Nishiwaki F, *et al.* Acrodermatitis continua of Hallopeau due to oral terbinafine. *Br J Dermatol* 2007; **157:** 1073–4.
5. Aksakal BA, *et al.* Oral terbinafine-induced bullous pemphigoid. *Ann Pharmacother* 2003; **37:** 1625–7.
6. Beltraminelli HS, *et al.* Acute generalized exanthematous pustulosis induced by the antifungal terbinafine: case report and review of the literature. *Br J Dermatol* 2005; **152:** 780–3.
7. Ibrahimi OA, *et al.* Terbinafine-induced acute generalized exanthematous pustulosis (AGEP) responsive to high dose intravenous corticosteroid. *Dermatol Online J* 2009; **15** (9): 8.
8. Murphy M, Barnes L. Terbinafine-induced lupus erythematosus. *Br J Dermatol* 1998; **138:** 708–9.
9. Brooke R, *et al.* Terbinafine-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 1998; **139:** 1132–3.
10. Holmes S, Kemmett D. Exacerbation of systemic lupus erythematosus induced by terbinafine. *Br J Dermatol* 1998; **139:** 1133.
11. Hill VA, *et al.* Subacute lupus erythematosus-like eruption due to terbinafine: report of three cases. *Br J Dermatol* 2003; **148:** 1056.
12. Spiewak R. Systemic photoallergy to terbinafine. *Allergy* 2010; **65:** 1071–2.

Effects on taste. Disturbance and loss of taste have been reported in about 0.6% of patients taking terbinafine. While this usually resolves gradually once the drug is withdrawn, persistent impairment of taste has been reported.[1,2]

1. Bong JL, *et al.* Persistent impairment of taste resulting from terbinafine. *Br J Dermatol* 1998; **139:** 747–8.
2. Duxbury AJ, *et al.* Persistent impairment of taste associated with terbinafine. *Br Dent J* 2000; **188:** 295–6.

Precautions

Terbinafine should not be used in patients with existing liver disease and liver function tests should be performed in all patients before starting oral therapy. Terbinafine should be stopped if clinical or biochemical evidence of hepatotoxicity develops. It should also be stopped if any progressive skin rash occurs and should be used with caution in patients with psoriasis.

Licensed product information advises that the use of terbinafine in patients with renal impairment is not recommended, however, dosing guidance has been issued by some authorities (see Administration in Renal Impairment, under Uses and Administration, p. 594.1).

Breast feeding. Terbinafine is excreted in breast milk and licensed product information states that it should be avoided during breast feeding.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terbinafine (for systemic use) as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients. Topical preparations for dermatological use are classified as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Plasma concentrations of terbinafine may be increased by drugs that inhibit its metabolism by cytochrome P450, such as cimetidine, and decreased by drugs that induce cytochrome P450 enzymes, such as rifampicin. Menstrual disturbances including breakthrough bleeding have been reported in patients taking oral contraceptives and terbinafine.

Terbinafine has been shown to inhibit metabolism mediated by the cytochrome P450 isoenzyme CYP2D6. Hence it may affect the plasma concentrations of drugs mainly metabolised by this enzyme such as tricyclic antidepressants, antiarrhythmics (such as flecainide and propafenone), beta blockers, SSRIs, and type B MAOIs.

For the effects of terbinafine on some other drugs, see caffeine (p. 1206.2), carbamazepine (p. 517.1), ciclosporin (p. 1956.3), tricyclic antidepressants (p. 406.3), theophylline (p. 1235.1), and warfarin (p. 1532.1).

Antimicrobial Action

Terbinafine is an allylamine derivative reported to have a broad spectrum of antifungal activity. It is considered to act through inhibition of fungal sterol synthesis. Terbinafine is fungicidal against dermatophytes, moulds, and certain dimorphic fungi and some yeasts.

Microbiological interactions. Additive and synergistic activity was reported with terbinafine plus fluconazole or itraconazole against strains of *Candida albicans* that had reduced susceptibility to azoles *in vitro*.[1] Terbinafine was also reported to enhance the activity of azoles against *Scedosporium prolificans*[2] and against the protozoan *Leishmania braziliensis*.[3]

1. Barchiesi F, *et al*. In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.
2. Meletiadis J, *et al*. In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; **44:** 470–2.
3. Rangel H, *et al*. Naturally azole-resistant Leishmania braziliensis promastigotes are rendered susceptible in the presence of terbinafine: comparative study with azole-susceptible Leishmania mexicana promastigotes. *Antimicrob Agents Chemother* 1996; **40:** 2785–91. Correction. *ibid*. 1997; **41:** 496.

Pharmacokinetics

Terbinafine hydrochloride is well absorbed from the gastrointestinal tract. The bioavailability is about 40% because of first-pass hepatic metabolism. Mean peak plasma concentrations of about 1 microgram/mL occur within 2 hours of a single oral dose of 250 mg. Steady state concentrations are about 25% higher than those seen after a single dose and occur in 10 to 14 days. Terbinafine is extensively bound to plasma proteins. Terbinafine is distributed into the stratum corneum of the skin, the nail plate, and hair where it reaches concentrations considerably higher than those found in plasma. It appears in breast milk.

Terbinafine is metabolised in the liver to inactive metabolites which are excreted mainly in the urine. A plasma elimination half-life varying from 17 to 36 hours has been reported and a terminal elimination half-life of up to 400 hours in patients given prolonged therapy, probably representing elimination from skin and adipose tissue. Fungicidal concentrations in nails are maintained for several weeks after therapy is stopped. The elimination rate may be altered in patients with liver or kidney disease. Less than 5% of a topical dose of terbinafine hydrochloride is absorbed.

References.

1. Kovarik JM, *et al*. Multiple-dose pharmacokinetics and distribution in tissue of terbinafine and metabolites. *Antimicrob Agents Chemother* 1995; **39:** 2738–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fungueal; Lamisil; Maditez; Piecidex NF; Replioderm; Sinamida Terbinafina; Tacna; Terbi-Derm; Terekol; Terfin; ***Austral.***: Lamisil; SolvEasy; Tamsil; Terbihexal; Tinasil; Zabel; ***Austria***: Amisan; Amykal; Daskil†; Lamisil; Myconafin†; Myconormin; Pedibene; Terbiderm; Terbinac†; ***Belg.***: Fungster; Lamisil; ***Braz.***: Funtyl; Lamisil; Lamisilate; Lorentil; Micosil; Terbinacol; ***Canad.***: Lamisil; ***Chile***: Dermoxyl; Dicil; Donter; Elater; Farbicil; Finex; Lamisil; Micoset; Mucivil; Terfex; Terfin; ***China***: Dingke (丁克); Fusu (扶苏); Futeshu (芙特抒); Kang Ning (康宁); Lamisil (兰美抒); Mujonal (采特); Pi Fu Te (彼孚特); ***Cz.***: Atifan†; Lamisil; Mycodekan†; Onychon†; Tefine†; Terbihexal†; Terbisil†; Terbistad; Terfimed; Verbinaf†; Zonesis†; ***Denm.***: Finigen; Funginix†; Lamisil; Tefin; Terbisil; Terbistad; Terimed†; ***Fin.***: Fungis; Fungorin; Lamisil; Terbistada; ***Fr.***: Fungster; Lamisil; Lamisilate; LamisilDermgel; ***Ger.***: Amiada; Dermatin; Fungizid Extra; Lamisil; Myconormin; Octosan†; Onymax†; Terbiderm; Terbigalen; Terbina-Q†; ***Gr.***: Anaplas; Chemiderm; Demsil; Drogenil; Ealk; Flixid; Frezylin; Funger; Fungitherapy; Fungster; Lamiderm; Lamigen; Lamisil; Mycutol; Optimus; Pavlinox; Pro-Misil; Romiver; Seralon; Soluterb; Teranfis; Terbafin; Terbigram; Terbin; Terbiprol; Terbiskin; Terbisol; Terfinil; Terfinor; Termisil; Ternafinol; Thateron; Vifaderm; Zakofin; ***Hong Kong***: Interbi; Lamisil; Orlasil; Tebinisil; Terbifin; ***Hung.***: Lamigard; Lamisil; Myconafine; Terbigen; Terbiner; Terbisil; Terfin; Tineal; ***India***: Daskil; Dermafine; Exifine; Fin; Fungotek; Lamisil; Mycofem; Terbifin†; ***Indon.***: Interbi; Lamisil; Termisil; ***Irl.***: Fungafine; Fungasil; Lamater; Lamisil; Lanafine; Nailderm; Terbasil; Ternaf; ***Israel***: Dermasil; Lamisil; Patir; ***Ital.***: Daskil; Lamisil; Onymax; ***Malaysia***: Camisan; Dermafin; Exifine; Lamisil; Lisim†; ***Mex.***: Binafex; Erbitrax; Fyterdin; Lamisil; Losil; Mycelvan; Sebifin†; Unasal; Xilatril; ***Neth.***: Atifan; Binanidda; Finanidda†; Lamisil; Niddafin; Niddavita†; Terbiderm; Terbinavita†; Vitabin; ***Norw.***: Lamisil; ***NZ***: Lamisil; Terbafin†; ***Philipp.***: Lamifen; Lamisil; ***Pol.***: Afugin†; Dermogen; Erfin; Lamisil; Lamisilatt; Myconafine; Onymax; Tenasil; Terbiderm; TerbiGen; Terbisil; Undofen Max; Verbinaf; Zelefion; ***Port.***: Arrolina; Daskyl; Fungil; Fungster; Lamisil; Termycol; ***Rus.***: Atifin (Атифин); Binafin (Бинафин); Cidocan (Цидокан); Exifine (Экзифин); Fungoterbine (Фунготербин); Lamican (Ламикан); Lamisil (Ламизил); Lamitel (Ламитель); Medofloran (Медофлоран); Miconorm (Миконорм); Onychon (Онихон); Terbifin (Тербифин); Terbinox (Тербинокс); Terbised (Тербизед); Terbisil (Тербизил); Terbix (Тербикс); Termicon (Термикон); ***S.Afr.***: Dermax; Finderm; Lamisil; Lamispor; Nafin; Terbane; Terbicil; Terbiclear; ***Singapore***: Lamisil; ***Spain***: Fungicare†; Isis; Lamicosil; Lamisil; Talixane†; Tighum†; ***Swed.***: Funginix; Lamisil; Terbisil; ***Switz.***: Fungster†; Helvepedin; Lamisil; Myconormin; Onymax†; Terbifil; Terbinax; Tineafine; ***Thai.***: EU 2000; Lamisil; ***Turk.***: Corbinal; Laminox; Lamisil; Mikonafin; Mycocur; Myconaf; Tekfin; Terafin; Terbin; Terbisil; Terbonile; Terinateva; Terminus; Tigal; ***UAE***: Negafen; ***UK***: Boots Athlete's Foot Cream; Lamisil; ***Ukr.***: Exifine (Экзифин); Fungoterbine (Фунготербин); Lamicon (Ламикон); Lamifen (Ламифен); Lamisil (Ламизил); Mycofin (Микофин); Myconorm (Миконорм)†; Terbisil (Тербизил); ***USA***: DesenexMax; Lamisil; Terbinex; ***Venez.***: Lamisil; Nafina; Terfex.

Multi-ingredient Preparations. ***India***: Cutivate-GT; Cutizone-T; Mecloma-T; Mezo-T; Momoz-T.

Pharmacopoeial Preparations

USP 36: Terbinafine Oral Suspension; Terbinafine Tablets.

Terconazole *(BAN, USAN, rINN)*

R-42470; Terconazol; Terconazolum; Terkonatsoli; Terkonazol; Terkonazolas; Triaconazole; Терконазол.

1-{4-[[2-(2,4-Dichlorophenyl)-*r*-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-*c*-4-yl]methoxy]phenyl}-4-isopropylpiperazine.

$C_{26}H_{31}Cl_2N_5O_3$=532.5

CAS — 67915-31-5.

ATC — G01AG02.

ATC Vet — QG01AG02.

UNII — 0KJ2VE664U.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Terconazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Terconazole). A white to off-white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in acetone. Protect from light.

Uses and Administration

Terconazole is a triazole antifungal used in the local treatment of vulvovaginal candidiasis (p. 564.1). Intravaginal dosage regimens are terconazole 40 mg (as 0.8% vaginal cream) or 80 mg (as a pessary) at bedtime for 3 nights or 20 mg (as 0.4% cream) at bedtime for 7 nights.

Adverse Effects

Local reactions including burning and itching have been reported with vaginal use of terconazole. Other adverse effects have included dysmenorrhoea and genital, body, and abdominal pain. A flu-like syndrome with headache, fever, chills, and hypotension has been reported in some patients and may be more prevalent with vaginal pessaries providing doses larger than 80 mg.

Flu-like syndrome. References.

1. Moebius UM. Influenza-like syndrome after terconazole. *Lancet* 1988; **ii:** 966–7.

Precautions

Intravaginal preparations of terconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Terconazole is a triazole derivative that is thought to disrupt normal fungal cell membrane permeability. Terconazole is active *in vitro* against *Candida* spp. and other fungi. It has some antibacterial activity *in vitro* but not against usual vaginal flora such as lactobacilli.

Pharmacokinetics

After intravaginal use, 5 to 16% of terconazole is absorbed. Systemically absorbed drug is metabolised by the liver and excreted in urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Gyno-Fungix; Tecomax; Terconan; ***Canad.***: Terazol; ***India***: Gyno-Terazol; ***Mex.***: Fungistat; ***S.Afr.***: Terazol†; ***USA***: Terazol; Zazole†; ***Venez.***: Fungistat.

Multi-ingredient Preparations. ***Mex.***: Gynoclin-V.

Tioconazole *(BAN, USAN, rINN)*

Tioconazol; Tioconazolum; Tiokonatsoli; Tiokonazol; Tiokonazolas; UK-20349; Тиоконазол.

1-[2,4-Dichloro-β-(2-chloro-3-thenyloxy)phenethyl]imidazole.

$C_{16}H_{13}Cl_3N_2OS$=387.7

CAS — 65899-73-2.

ATC — D01AC07; G01AF08.

ATC Vet — QD01AC07; QG01AF08.

UNII — S57Y5X1117.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tioconazole). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Tioconazole). Store in airtight containers.

Uses and Administration

Tioconazole is an imidazole antifungal used in the treatment of superficial candidiasis (p. 564.1), and dermatophytoses and pityriasis versicolor (see Skin Infections, p. 568.1).

For vaginal candidiasis it is used as pessaries or vaginal ointment usually as a single 300-mg dose.

It has been used topically as a 1% cream, lotion, or powder in the treatment of superficial fungal infections. Tioconazole has also been used for nail infections as a 28% w/w topical solution, although systemic treatment is generally preferred.

Adverse Effects and Precautions

Local reactions to tioconazole including burning, itching, and erythema have been reported.

Intravaginal preparations of tioconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Hypersensitivity. Tioconazole, an imidazole antifungal widely used in Finland, appeared to be an important cause of contact allergy in that country, since an incidence of more than 1% was reported in patients undergoing routine patch testing.[1] There may be cross-reactivity with other commonly used imidazole derivatives.

1. Heikkilä H, *et al*. A study of 72 patients with contact allergy to tioconazole. *Br J Dermatol* 1996; **134:** 678–80.

Antimicrobial Action

Tioconazole is an imidazole antifungal with a broad spectrum of activity including action against dermatophytes, *Malassezia furfur*, and *Candida albicans*. Tioconazole is active *in vitro* against some Gram-positive bacteria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Honguil; Niofen; Tiomicol; Trosyd; ***Austria***: Trosyd; ***Braz.***: Gino Conazol†; Gino Tralen†; Neo Tionazol; Tioconax; Tionazen; Tralen; ***Chile***: Telset; ***Fin.***: Gyno-Trosyd; Trosyd; ***Fr.***: Gyno-Trosyd; Trosyd; ***Ger.***: Mykontral; ***Gr.***: Cotinazin; Infester; Lakafin; ***Hong Kong***: Gyno-Trosyd; Trosyd; ***Indon.***: Prodermal; Trosyd; ***Irl.***: Trosyl; ***Ital.***: Trosyd; ***Malaysia***: Gyno-Trosyd; Trosyd; ***Philipp.***: Trosyd; ***Port.***: Gino-Trosyd; Trosyd; ***S.Afr.***: Gyno-Trosyd†; Trosyd; ***Singapore***: Gyno-Trosyd; Trosyd; ***Spain***: Onicozol†; Sernax; Trosderm; Trosid; ***Switz.***: Trosyd†; ***Thai.***: Trosyd; ***Turk.***: Dermo-Rest; Dermo-Trosyd; Gyno-Trosyd; Tiocan; Tiocell; Tioderma; ***UK***: Trosyl; ***USA***: Vagistat-1; ***Venez.***: Gino-Tralen; Tralen.

Multi-ingredient Preparations. ***Braz.***: Cartrax; Duozol; Gynben; Gynomax; Gynopac; Seczol; Takil; Tinin; Tiotrax; Travogyn; Vulnagen; ***Fin.***: Trosycort; ***Mex.***: Fasigyn VT; ***Turk.***: Gynomax.

Pharmacopoeial Preparations

BP 2014: Tioconazole Cream; Tioconazole Nail Solution.

Tolciclate *(USAN, rINN)*

K-9147; KC-9147; Tolciclato; Tolciclatum; Тольциклат.

O-(1,2,3,4-Tetrahydro-1,4-methano-6-naphthyl) *m,N*-dimethylthiocarbanilate.

$C_{20}H_{21}NOS$=323.5

CAS — 50838-36-3.

ATC — D01AE19.

ATC Vet — QD01AE19.

UNII — T3TZ02X2AZ.

Profile

Tolciclate is an antifungal with activity against *Epidermophyton, Microsporum,* and *Trichophyton* spp. It is used topically as a 1% cream or lotion, or as a 0.5% powder in the treatment of various dermatophyte infections and in pityriasis versicolor.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Tolmicil; ***NZ***: Tolmicen†; ***Rus.***: Tolmicen (Толмицен).

Tolnaftate *(BAN, USAN, rINN)*

Sch-10144; Tolnaftaatti; Tolnaftat; Tolnaftát; Tolnaftatas; Tolnaftato; Tolnaftatum; Тольнафтат.

O-2-Naphthyl *m,N*-dimethylthiocarbanilate; *O*-Naphthalen-2-yl methyl(3-methylphenyl)carbamothioate.

$C_{19}H_{17}NOS$=307.4

CAS — 2398-96-1.

ATC — D01AE18.

ATC Vet — QD01AE18.

UNII — 06KB629TKV.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tolnaftate). A white or yellowish-white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Tolnaftate). A white to creamy-white, fine powder, with a slight odour. Practically insoluble in water; slightly soluble in alcohol; freely soluble in acetone and in chloroform; sparingly soluble in ether. Store in airtight containers.

Uses and Administration

Tolnaftate is an antifungal used topically as a 1% gel, solution, powder, ointment, or cream in the treatment or prophylaxis of superficial dermatophyte infections and of pityriasis versicolor (see Skin Infections, p. 568.1). Tolnaftate is applied twice daily for 2 to 6 weeks. Repeat treatment may be required.

Adverse Effects

Skin reactions occur rarely with tolnaftate and include irritation and contact dermatitis.

Antimicrobial Action

Tolnaftate inhibits the growth of the dermatophytes *Epidermophyton, Microsporum, Trichophyton* spp., and *Malassezia furfur*, but is not active against *Candida* spp. or bacteria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Curatin†; Ringworm Ointment; Tinaderm; Tineafax; ***Canad.***: Absorbine Jr Antifungal; Athlete's Foot; Avon Footworks; Dr Scholl's Athlete's Foot; Fungicure; Pitrex; Proclearz; Tinactin; ZeaSorb AF†; ***Chile***: Tinaderm†; ***Fr.***: Sporiline; ***Ger.***: Tinatox; ***Gr.***: Tinaderm; ***Hung.***: Chinofungin; Digifungin; ***India***: Tinaderm; Tolnaderm†; ***Indon.***: Naftate†; ***Irl.***: Mycil; Scholl Athlete's Foot; Tinaderm; ***Israel***: Athletes Foot; Pitrex; Tinasol†; ***Malaysia***: Dermoplex Antifungal; Myco-Aid; Tolnaderm; ***Mex.***: Excelsior; Tinaderm; Tinoxal; ***Philipp.***: Tinactin; Tolnaderm; ***Port.***: Tinaderme; ***S. Afr.***: Tinaderm; ***Singapore***: Creobic; Naftate; Scholl Athlete's Foot; Tolnaderm; ***Thai.***: Ezon-T; Tonaf; Tono†; ***Turk.***: Mikoderm†; Tinactin; ***UK***: Mycil; Scholl Athlete's Foot; Tinaderm; ***USA***: Aftate†; Blis-To-Sol; Dr Scholl's Athlete's Foot; Genasport†; Lamisil AF Defense; Mycocide NS; Podactin; Quinsana Plus†; Tinactin; Ting; ***Venez.***: Tinaderm; Tolnaftan.

Multi-ingredient Preparations. ***Arg.***: Bacticort Complex; Cevaderm; ***Austral.***: Mycil Healthy Feet; Mycil Healthy Feet; ***Braz.***: Cremederme; Permut; Poliderms; Quadribeta; Quadriderm; Quadrihexal; Quadrikin†; Quadrilon; Quadriplus†; Qualiderm; Tetraderm; ***Gr.***: Helpogen; ***Hong Kong***: Alox†; Alphate†; Aselan†; Dermafacte†; Ezon-T; Mycil†; Mycostop†; Quadriderm; Triditol-G; ***India***: ABC Derm; Alcoderm; Darederm; Dermitop; Esgiderm; Fourderm; Quiss; Surfaz-SN; ***Irl.***: Mycil; Mycil; Tinaderm-M†; ***Israel***: Phytoderm Compositum; ***Malaysia***: Elan-Forte; ***Philipp.***: Quadriderm; Quadrotopic; ***S.Afr.***: Quadriderm; ***Spain***: Cuatroderm; ***Switz.***: Undex; ***Thai.***: Alber T; Dermaheu; Dertec; Ezon-T; Quadriderm; Spectroderm; ***UK***: Mycil; Mycil; Tinaderm-M†; ***USA***: Dermasept Antifungal.

Pharmacopoeial Preparations

USP 36: Tolnaftate Cream; Tolnaftate Gel; Tolnaftate Topical Aerosol; Tolnaftate Topical Powder; Tolnaftate Topical Solution.

Triacetin *(rINN)*

E1518; Glicerin-triacetát; Glycerol Triacetate; Glycerolum Triacetas; Glyceryl Triacetate; Triacetato de glicerilo; Triacetina; Triacetinas; Triacétine; Triacetinum; Triacetyna; Triasetiini; Триацетин.

1,2,3-Propanetriol triacetate.

$C_9H_{14}O_6$=218.2

CAS — 102-76-1.

UNII — XHX3C3X673.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Triacetin). A clear, colourless, slightly viscous, oily liquid. Soluble in water; miscible with dehydrated alcohol and with toluene. Store in well-filled containers.

USP 36: (Triacetin). A colourless, somewhat oily liquid with a slight, fatty odour. Soluble in water; slightly soluble in carbon disulfide; miscible with alcohol, with chloroform, and with ether. Store in airtight containers.

Profile

Triacetin is reported to possess fungistatic properties based on the liberation of acetic acid. It has been applied topically in the treatment of superficial dermatophyte infections. It has also been used as a plasticiser in oral preparations.

Triacetin may destroy rayon fabric. It should not come into contact with metals.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Ezon-T; ***Thai.***: Alber T; Ezon-T.

Trimetrexate Glucuronate *(BANM, USAN, rINNM)*

CI-898 (trimetrexate); Glucuronato de trimetrexato; JB-11 (trimetrexate); NSC-249008 (trimetrexate); NSC-328564 (trimetrexate); NSC-352122; Trimétrexate, Glucuronate de; Trimetrexati Glucuronatum; Trimetrexato, glucuronato de; Триметрексата Глюкуронат.

5-Methyl-6-(3,4,5-trimethoxyanilinomethyl)quinazolin-2,4-diyldiamine mono-D-glucuronate.

$C_{19}H_{23}N_5O_3.C_6H_{10}O_7$=563.6

CAS — 52128-35-5 (trimetrexate); 82952-64-5 (trimetrexate glucuronate).

ATC — P01AX07.

UNII — L137U4A79K.

Profile

Trimetrexate is a dihydrofolate reductase inhibitor with general properties similar to those of methotrexate (p. 822.2). It has been used in a regimen with folinic acid in the management of moderate to severe pneumocystis pneumonia in immunocompromised patients, notably patients with AIDS, where other therapy has proved ineffective (see also p. 567.2). At therapeutic doses the selective transport of trimetrexate, but not folinic acid, into *Pneumocystis jirovecii* allows folinic acid to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting its antifungal activity. It has also been tried as an antineoplastic in the management of various solid tumours.

Trimetrexate has been given as the glucuronate but doses are stated in terms of trimetrexate. Trimetrexate glucuronate 1.53 mg is equivalent to about 1 mg of trimetrexate. It is given by intravenous infusion, over 60 to 90 minutes. The schedule in pneumocystis pneumonia is 45 mg/m^2 daily for 21 days, with folinic acid rescue for 24 days; for details of the folinic acid dose regimen, see Uses and Administration of Folinic Acid, p. 2067.1. The dosage of trimetrexate and folinic acid should be adjusted according to the results of blood tests, which should be performed at least twice a week during therapy. Renal and hepatic function and haemoglobin values should also be monitored. Treatment with zidovudine and other myelosuppressive drugs should be interrupted to allow full doses of trimetrexate to be given.

References.

1. Fulton B, *et al.* Trimetrexate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of Pneumocystis carinii pneumonia. *Drugs* 1995; **49:** 563–76.
2. Short CE, *et al.* Trimetrexate and folinic acid: a valuable salvage option for Pneumocystis jirovecii pneumonia. *AIDS* 2009; **23:** 1287–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Neutrexin; ***Thai.***: Neutrexin.

Undecenoic Acid

Acide Undécylénique; Ácido undecenoico; Acidum undecylenicum; 10-Hendecenoic Acid; Kyselina undecylenová; Undecilénico, ácido; Undecileno rūgštis; Undecilénsav; Undecylenic Acid; Undecylensäure; Undecylensyra; Undesenoatlar; Undesilenatlar; Undesyleenihappo; Ундеценовая Кислота.

Undec-10-enoic acid.

$C_{11}H_{20}O_2$=184.3

CAS — 112-38-9.

ATC — D01AE04.

ATC Vet — QD01AE04.

UNII — K3D86KJ24N.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Undecylenic Acid; Undecenoic Acid BP 2014). A colourless or pale yellow liquid or a white or very pale yellow crystalline mass. Practically insoluble in water; freely soluble in alcohol and in fatty and essential oils. Store in nonmetallic containers. Protect from light.

USP 36: (Undecylenic Acid). A clear, colourless to pale yellow liquid with a characteristic odour. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils. Store in airtight containers. Protect from light.

Calcium Undecenoate

Calcium Undecylenate (USAN); Undecenoato de calcio; Undecilenato de calcio; Ундециленат Кальция.

Calcium di(undec-10-enoate).

$(C_{11}H_{19}O_2)_2Ca$=406.6

ATC — D01AE04.

ATC Vet — QD01AE04.

UNII — 77YW1RTU8V.

Pharmacopoeias. In *US*.

USP 36: (Calcium Undecylenate). A fine white powder with a characteristic odour and no grit. Practically insoluble in water, in cold alcohol, in acetone, in chloroform, and in ether; slightly soluble in hot alcohol.

Zinc Undecenoate

Cinko undecilenatas; Çinko Undesilenat; Cink-undecilenát; Sinkkiundesylenaatti; Undecenoato de zinc; Undecilenato de zinc; Undecilinato de Zinco; Undecylenan zinečnatý; Zinc Undecylenate; Zinc, undécylénate de; Zinci undecylenas; Zinkundecylenat; Ундециленат Цинка.

Zinc di(undec-10-enoate).

$(C_{11}H_{19}O_2)_2Zn$=431.9

CAS — 557-08-4.

ATC — D01AE04.
ATC Vet — QD01AE04.
UNII — 388VZ25DUR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Zinc Undecylenate; Zinc Undecenoate BP 2014). A fine white or almost white powder. Practically insoluble in water and in alcohol. Protect from light.

USP 36: (Zinc Undecylenate). A fine, white powder. Practically insoluble in water and in alcohol.

Uses and Administration

Undecenoic acid and its zinc salt are applied topically in the prophylaxis and treatment of superficial dermatophytoses, particularly tinea pedis (see Skin Infections, p. 568.1). Typical concentrations are undecenoic acid 2 to 5% and zinc undecenoate 20%. They are used in creams, ointments, solutions, or powders, often with each other. Calcium undecenoate is used as a 10 or 15% powder.

Several other salts and derivatives of undecenoic acid including methyl, phenyl, and propyl undecenoate, disodium sulfosuccinated undecenoic acid monoethanolamide, and undecenoic acid monoethanolamide and diethanolamide have been used similarly.

A systematic review[1] of topical treatments for fungal skin or nail infections considered undecenoates to be effective, although comparative studies with other classes of topical antifungal were largely lacking.

1. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/07/08).

Adverse Effects

Irritation may rarely occur after the topical application of undecenoic acid or its salts.

Antimicrobial Action

Undecenoic acid and its derivatives are active against some pathogenic fungi, including the dermatophytes *Epidermophyton*, *Trichophyton*, and *Microsporum* spp.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bentophyto; Sinamida Pies; Umasam; ***Austria***: Crino Cordes; Pelsana Med; ***Canad.***: Desenex†; ***Cz.***: Mykoseptin; ***Fr.***: Mycodecyl; Mycodecyl; Mycodecyl; ***Hung.***: Lubex; ***Indon.***: Decyline; Topix†; Undecyl; ***Irl.***: Caldesene; Desenex; ***Israel***: Undecyl; ***Mex.***: Derman; ***Pol.***: Mykodermina; Mykodermina; Unguentum Undecylenicum; ***Rus.***: Mykoseptin (Микосептин); ***S.Afr.***: Mycota; ***Switz.***: Lubex; Turexan Creme†; Turexan Douche†; ***Turk.***: Undo-Pate; Utalk†; ***UK***: Mycota; ***Ukr.***: Mykoseptin (Микосептин); ***USA***: Blis-To-Sol; Cruex; Cruex; Decylenes; Desenex; DiabetiDerm; Elon Dual Defense; Fungi Cure; Protectol; Undelenic.

Multi-ingredient Preparations. ***Arg.***: Bentophyto; Bifena; Champuacid; Cicatrol; Dettonjab; Farm-X; Fungicida; Fungocop; Hipoglos Cicatrizante; Laurinol Plus; Novo Miconol†; Zinc-S Plus; ***Austral.***: Pedoz; Sebitar; ***Austria***: Mycopol; Pelsana Med; ***Braz.***: Andriodermol; Andriodermol; ***Canad.***: Feet Athletes Foot and Antifungal†; ***Chile***: Fittig Antimicotico; NP-27; NP-27; ***Fr.***: Paps†; ***Ger.***: Skinman Soft; ***Gr.***: Ekzegamma; Hemorrocort; Undex; ***Hong Kong***: Sebitar; ***Hung.***: Pedimed; Pelsano Med; Squa-med; ***Indon.***: Decyline; Decyline; Mikorex†; Skintex†; ***Irl.***: Pedamed; ***Israel***: Acti Talc; Fungimon; Pedisol†; Pitrisan†; ***Ital.***: Foot Zeta; Genisol; Micofoot; Propast; Sideck Shampoo Antiforfora; ***Malaysia***: Sebitar; ***Mex.***: Micotex; ***NZ***: Grans Remedy; Sebitar; ***Pol.***: Undofen; ***Port.***: Micaveen†; ***S.Afr.***: AF; ***Singapore***: Sebitar; Vetic; ***Switz.***: Crimanex; Ederphyt†; Pelsano; Pruri-med; Undex†; Undex; ***Turk.***: Fungecyl; Undo-Talk; ***UK***: Ceanel; Healthy Feet; Mycota; ***USA***: Breezee Mist Foot Powder; Dermasept Antifungal; Gordochom; Phicon-F.

Pharmacopoeial Preparations

USP 36: Compound Undecylenic Acid Ointment.

Voriconazole *(BAN, USAN, rINN)*

UK-109496; Voriconazol; Voriconazolum; Vorikonazol; Вориконазол.

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

$C_{16}H_{14}N_5F_3O$=349.3

CAS — 137234-62-9.
ATC — J02AC03.
ATC Vet — QJ02AC03.
UNII — JFU09I87TR.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Voriconazole). A white or almost white powder. Very slightly soluble in water; freely soluble in acetone and in dichloromethane. If the substance is sterile, store in airtight containers.

USP 36: (Voriconazole). A white to almost white powder. Very slightly soluble in water; freely soluble in acetone and in dichloromethane.

Uses and Administration

Voriconazole is a triazole antifungal used mainly in immunocompromised patients for the treatment of invasive aspergillosis (p. 563.1), candidaemia (p. 564.1) in non-neutropenic patients, fluconazole-resistant serious invasive candidiasis, oesophageal candidiasis, and serious fungal infections due to *Scedosporium* and *Fusarium* spp.

Voriconazole may be given orally or intravenously. It has also been used topically, usually as a 1% eye drop, in the treatment of certain fungal and protozoal eye infections (see below).

Oral doses as film-coated tablets should be taken at least 1 hour before, or 1 hour after a meal; oral suspensions should be taken at least 1 hour before, or 1 to 2 hours after a meal.

The following ***oral loading doses*** of voriconazole are given every 12 hours for the first 24 hours:

- adults and adolescents weighing more than 40 kg: 400 mg
- under 40 kg: 200 mg

Subsequent ***oral maintenance doses*** are:

- adults and adolescents over 40 kg: 200 mg twice daily, increased to 300 mg twice daily if the response is inadequate
- under 40 kg: 100 mg twice daily, increased to 150 mg twice daily if the response is inadequate

Intravenous loading doses of voriconazole are:

- adults and adolescents: 6 mg/kg every 12 hours for the first 24 hours

Intravenous maintenance doses are:

- adults and adolescents: 4 mg/kg twice daily; a lower dose of 3 mg/kg twice daily may be suitable for candidaemia in non-neutropenic patients or for deep tissue *Candida* infections, or for patients unable to tolerate the higher dose

Intravenous infusions should be given at a maximum rate of 3 mg/kg per hour over 1 to 2 hours. UK licensed product information recommends that intravenous therapy should not be given for longer than 6 months.

Doses of voriconazole may need to be modified in patients with hepatic or renal impairment (see below).

The dose of voriconazole may also need to be adjusted for the management of significant drug interactions. Increased oral maintenance doses of 400 mg, and 350 mg twice daily have been suggested when voriconazole must be used with phenytoin or rifabutin respectively; for patients weighing less than 40 kg, a dose of 200 mg twice daily is recommended. For intravenous voriconazole, the maintenance dose should be increased to 5 mg/kg twice daily. When given with efavirenz, the maintenance dose of voriconazole should be increased to 400 mg twice daily; the dose of efavirenz must also be adjusted, for details, see Uses and Administration of Efavirenz, p. 975.1.

For details of doses in children, see below.

Reviews.

1. Muijsers RBR, *et al.* Voriconazole: in the treatment of invasive aspergillosis. *Drugs* 2002; **62:** 2655–64.
2. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis* 2003; **36:** 630–7.
3. Pearson MM, *et al.* Voriconazole: a new triazole antifungal agent. *Ann Pharmacother* 2003; **37:** 420–32.
4. Gothard P, Rogers TR. Voriconazole for serious fungal infections. *Int J Clin Pract* 2004; **58:** 74–80.
5. Donnelly JP, De Pauw BE. Voriconazole—a new therapeutic agent with an extended spectrum of antifungal activity. *Clin Microbiol Infect* 2004; **10** (suppl 1): 107–17.
6. Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs* 2007; **67:** 269–98.
7. Ta M, *et al.* The role of voriconazole in the treatment of central nervous system blastomycosis. *Ann Pharmacother* 2009; **43:** 1696–700.
8. Thompson GR, Lewis JS. Pharmacology and clinical use of voriconazole. *Expert Opin Drug Metab Toxicol* 2010; **6:** 83–94.

Administration in children. In the UK, voriconazole is licensed for use in children for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, serious fluconazole-resistant invasive candidiasis, and serious infections caused by *Scedosporium* or *Fusarium* spp. Children from 2 years of age, and young adolescents (12 to 14 years of age) weighing less than 50 kg should be treated with intravenous voriconazole initially and then switched to oral treatment only if clinically appropriate. The following doses are suggested:

- for **intravenous** use: a loading dose of 9 mg/kg twice daily for the first 24 hours, followed by a maintenance dose of 8 mg/kg twice daily; the infusion rate should not exceed 3 mg/kg per hour
- for **oral** use: 9 mg/kg (to a maximum of 350 mg) twice daily of the oral suspension; doses should be taken at least one hour before, or two hours after a meal

Adult doses are suggested for young adolescents (12 to 14 years of age) weighing 50 kg or more, and for adolescents aged 15 to 17 years (see above).

In the USA, voriconazole is not licensed for use in children; however, the American Academy of Pediatrics[1] suggests it may be given orally or intravenously from 2 years of age; recommended doses are similar to those for the UK.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in hepatic impairment. No dosage adjustment is necessary when voriconazole is given to patients with acute hepatic impairment but doses should be modified in patients with chronic disease. Patients with mild to moderate hepatic cirrhosis (Child-Pugh category A and B) should receive the standard loading doses of oral or intravenous voriconazole (see Uses and Administration, above) but maintenance doses should be halved. Doses for patients with severe hepatic cirrhosis (Child-Pugh category C) have not been established.

Administration in obese patients. Although the ideal voriconazole dose regimen in obese patients has not been determined, it has been suggested that an intravenous dose regimen based on the adjusted body-weight will give a voriconazole area under the curve similar to a non-obese patient.[1] On the other hand, a study that evaluated the steady-state plasma pharmacokinetics of oral voriconazole in a small number of healthy subjects with class II obesity or greater concluded that adjustment of oral doses does not appear to be necessary on the basis of body weight.[2]

1. Dickmeyer NJ, Kiel PJ. Dosing voriconazole in an obese patient. *Clin Infect Dis* 2011; **53:** 745.
2. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. *Antimicrob Agents Chemother* 2011; **55:** 2601–5.

Administration in renal impairment. No dose adjustment is needed for oral voriconazole in patients with renal impairment. Patients with a creatinine clearance less than 50 mL/minute should receive oral voriconazole instead of intravenous voriconazole, as accumulation of the intravenous vehicle, sulfobutyl ether beta-cyclodextrin sodium (SBECD), may occur. When intravenous voriconazole is considered justified in such patients, serum creatinine should be closely monitored and consideration given to changing to the oral route if increases occur. A retrospective, observational study[1] in a small number of patients treated with either oral or intravenous voriconazole for a minimum of 3 consecutive days and with a creatinine clearance of less than 50 mL/minute, found that the route of administration and/or baseline renal function were not predictors of worsening renal dysfunction after 3 to 7 days of consecutive treatment. The strongest predictors for renal dysfunction were reported to be underlying disease, baseline liver impairment, and the concomitant use of other drugs such as penicillins, fluoroquinolones, and immunosuppressants; treatment with fluconazole within 30 days of starting voriconazole treatment was also identified as a major risk factor for renal dysfunction by day 3.

Although voriconazole is haemodialysed, no dose adjustment is required for patients on haemodialysis.

1. Neofytos D, *et al.* Administration of voriconazole in patients with renal dysfunction. *Clin Infect Dis* 2012; **54:** 913–21.

Eye infections. Topical voriconazole, either alone or combined with other therapy, has been investigated for the treatment of various types of fungal eye infection.[1] Voriconazole 1% eye drops were found to be successful as first-line treatment in a patient with keratitis caused by *Candida albicans*.[2] Effective salvage treatment of *Scedosporium apiospermum* keratitis has also been reported with topical voriconazole in a patient who relapsed after treatment with topical natamycin.[3] Additionally, the use of topical plus oral voriconazole has been effective for *Aspergillus fumigatus* keratitis refractory to treatment with topical natamycin, topical amphotericin B, and systemic ketoconazole.[4]

Topical voriconazole has also been tried as an adjunctive treatment for *Acanthamoeba* keratitis unresponsive to standard treatment with chlorhexidine and hexamidine.[5] Of three eyes additionally treated with voriconazole 1% eye drops, 2 had clinical resolution of disease. Recurrent disease in one eye was successfully treated with voriconazole by intrastromal injection.

1. Hariprasad SM, *et al.* Voriconazole in the treatment of fungal eye infections: a review of current literature. *Br J Ophthalmol* 2008; **92:** 871–8.
2. Al-Badriyeh D, *et al.* Successful use of topical voriconazole 1% alone as first-line antifungal therapy against Candida albicans keratitis. *Ann Pharmacother* 2009; **43:** 2103–7.
3. Al-Badriyeh D, *et al.* Successful salvage treatment of Scedosporium apiospermum keratitis with topical voriconazole after failure of natamycin. *Ann Pharmacother* 2009; **43:** 1139–42.
4. Mehta H, *et al.* Voriconazole for the treatment of refractory Aspergillus fumigatus keratitis. *Indian J Ophthalmol* 2008; **56:** 243–5.
5. Bang S, *et al.* Treatment with voriconazole in 3 eyes with resistant Acanthamoeba keratitis. *Am J Ophthalmol* 2010; **149:** 66–9.

Fusariosis. The results of a retrospective study[1] suggest that voriconazole may have a role in the treatment of disseminated *Fusarium* infection in severely immunocompromised patients; in the study of 73 immunocompromised patients with invasive fusariosis, 47% had complete or partial response to voriconazole therapy after a median of 57 days of therapy. Most patients had failed prior antifungal therapy.

1. Lortholary O, *et al.* International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010; **54:** 4446–50.

Adverse Effects

The most commonly reported adverse effects with voriconazole are visual disturbances, fever, rashes, nausea, vomiting, diarrhoea, abdominal pain, headache, sepsis, respiratory disorders, and peripheral oedema. There have been some serious hepatic reactions including fatalities. Skin reactions have included rare cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions may occur and are more likely during long-term treatment; some patients with phototoxic skin reactions while on long-term voriconazole treatment have gone on to develop melanoma or squamous cell carcinoma of the skin (risk factors include skin phototype, cumulative exposure to sunlight, and immunosuppression, particularly of a chronic nature).

Other adverse effects reported as being common during treatment with voriconazole include: chills, flu-like syndrome, asthenia, back pain, chest pain, injection site reactions, facial oedema, hypotension, sinusitis, altered liver function tests, jaundice, cheilitis, blood disorders, hypokalaemia, hypoglycaemia, dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia, pruritus, alopecia, exfoliative dermatitis, acute renal failure, and haematuria. Hypersensitivity reactions, including anaphylaxis, have occurred rarely.

Effects on the blood. Fever and leucocytosis with eosinophilia in one patient has been attributed to voriconazole treatment.[1]

1. Vishnubhotla P, *et al.* Fever and eosinophilia associated with voriconazole. *Ann Pharmacother* 2004; **38:** 900–901.

Effects on plasma-fluoride concentration. Voriconazole contains 16.3% fluorine by weight and cases of elevated plasma fluoride concentrations have been reported in transplant patients taking normal doses of oral voriconazole for longer than 6 months. Long-term use of oral voriconazole has also been associated with painful periostitis and exostoses; plasma fluoride levels decreased and symptoms improved on stopping voriconazole.[1]

1. Wermers RA, *et al.* Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. *Clin Infect Dis* 2011; **52:** 604–11.

Effects on the heart. Bradycardia with a prolonged QT interval and asymptomatic episodes of torsade de pointes occurred in a 15-year-old patient, after 3 weeks of voriconazole therapy at usual doses.[1] All drug treatment was stopped but the effects recurred on rechallenge with a small dose of voriconazole.

Arrhythmia also occurred in an elderly patient after 40 days of treatment with oral voriconazole at usual doses.[2] Voriconazole treatment was stopped and the patient's QTc returned to baseline with supportive treatment (see p. 1537.1). However, 2 days later oral voriconazole was re-started at the same dose and the patient developed episodes of torsade de pointes. Voriconazole was again stopped but the next day the patient developed a fatal polymorphic ventricular tachycardia despite serum-voriconazole concentrations being below the lower limit of detection. The authors considered that repeat doses of voriconazole may have led to the accumulation of active compounds that predisposed to arrhythmia or that a drug interaction with the proton pump inhibitor lansoprazole could have inhibited the metabolism of voriconazole (see also under Interaction, below).

1. Alkan Y, *et al.* Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis* 2004; **39:** e49–e52.
2. Tsubokura M, *et al.* Fatal dysrhythmia following initiation of lansoprazole during a long-term course of voriconazole. *J Clin Pharmacol* 2011; **51:** 1488–90.

Effects on the liver. A patient who developed hepatotoxicity (liver enzyme values > 10 times the upper limit of normal) and a severe cutaneous reaction during high-dose oral treatment with voriconazole for aspergillosis was subsequently treated with high-dose intravenous voriconazole without recurrence of toxicity.[1] The authors considered that oral use might have led to higher concentrations of potentially toxic metabolites, due to a first-pass effect, although alternative explanations were possible.

1. Alffenaar JW, *et al.* Intravenous voriconazole after toxic oral administration. *Antimicrob Agents Chemother* 2010; **54:** 2741–2.

Effects on the lungs. Cases of interstitial pneumonia have been reported in a few elderly patients after the use of intravenous voriconazole. The condition resolved after voriconazole treatment was stopped; some patients were also treated with corticosteroids.[1]

1. Japanese Pharmaceuticals and Medical Devices Safety Information no. 284 (issued October 2011). Available at: http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-284.pdf (accessed 23/04/12)

Effects on mental function. There have been reports[1,2] of patients having hallucinations (auditory or visual) during treatment with voriconazole. In one study 18 of 415 patients (4.3%) given voriconazole had visual hallucinations compared with 2 of 422 (0.5%) given amphotericin B.[1]

1. Walsh TJ, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346:** 225–34.
2. Agrawal AK, Sherman LK. Voriconazole-induced musical hallucinations. *Infection* 2004; **32:** 293–5.

Precautions

Acute renal failure may occur with voriconazole and renal function should be monitored during treatment. Liver function should also be monitored before and during treatment with voriconazole. It should be used with caution in patients with hepatic impairment and doses may need to be adjusted (see under Uses and Administration, p. 597.3). Visual disturbances may occur and patients affected should not drive or operate hazardous machinery. In addition, all patients, whether affected by visual disturbances or not, should not drive at night, and should have their visual function monitored if they are receiving voriconazole for more than 28 days. Voriconazole has been associated with QT interval prolongation and should therefore be given with caution to patients with potentially pro-arrhythmic conditions. Any electrolyte disturbances should be corrected, if necessary before starting treatment with voriconazole; the intravenous form must not be given simultaneously with concentrated electrolyte infusions or blood products, even by separate lines. To minimise the risk of phototoxicity, direct sun exposure should be avoided and suitable clothing and sunscreen worn. Treatment periods should be as short as possible, and long-term treatment (> 6 months) should be considered only where the benefits clearly outweigh the risks.

Voriconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3. Licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with voriconazole.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies voriconazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Voriconazole is metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. Use of drugs that either inhibit or induce these isoenzymes may increase or decrease plasma concentrations of voriconazole, respectively. Rifampicin has been shown to decrease voriconazole plasma concentrations and a similar effect may be expected with carbamazepine, phenobarbital, or St John's wort; use of voriconazole with these drugs is therefore contra-indicated.

Concentrations of other drugs that are metabolised by CYP2C19, CYP2C9, or CYP3A4 may be increased by voriconazole. Increased plasma concentrations of astemizole, cisapride, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. Increased plasma concentrations of ciclosporin, sirolimus, and tacrolimus have been noted; use with sirolimus is contra-indicated, although ciclosporin or tacrolimus may be used providing doses are reduced and concentrations monitored. Likewise, monitoring and possible dose reductions of some opioid analgesics (such as alfentanil, fentanyl, hydrocodone, methadone, oxycodone, and sufentanil) may be needed during concomitant use. Concentrations of oral anticoagulants may be affected and increased prothrombin time has occurred with warfarin; monitoring should therefore be carried out. Close monitoring of blood glucose is necessary if voriconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for some statins, calcium-channel blockers, NSAIDs, vinca alkaloids, and some benzodiazepines (such as alprazolam, midazolam, and triazolam) if their plasma concentrations are increased.

Interactions may occur where both voriconazole and the other drug are affected. Examples are phenytoin and rifabutin (where concentrations of voriconazole are reduced but those of phenytoin or rifabutin are increased). If it is essential to give either drug with voriconazole, then an increase in the dose of voriconazole is recommended (see Uses and Administration, p. 597.2). With omeprazole, the plasma concentration of both drugs may be increased and a reduced dose of omeprazole is recommended (see under Interactions of Omeprazole, p. 1874.1). Similar effects may be noted between other proton pump inhibitors and voriconazole.

Voriconazole may inhibit metabolism of non-nucleoside reverse transcriptase inhibitors and they in turn may either inhibit the metabolism of voriconazole (e.g. delavirdine) or induce the metabolism of voriconazole (e.g. efavirenz and nevirapine); if co-administration of voriconazole and efavirenz cannot be avoided, an increase in the dose of voriconazole and a decrease in the dose of efavirenz is recommended. Similarly, voriconazole may inhibit metabolism of HIV-protease inhibitors (e.g. saquinavir, amprenavir, and nelfinavir) while they may in turn inhibit the metabolism of voriconazole. High doses of ritonavir (400 mg twice daily) significantly decrease plasma concentrations of voriconazole and co-administration is contra-indicated. Similar effects have been seen with low doses of ritonavir (100 mg twice daily) and use with voriconazole should be avoided where possible. Indinavir, however, does not appear to interact with voriconazole.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A4 and azoles, see under Itraconazole, p. 585.1.

For reviews of drug interactions with azole antifungals, see Itraconazole, p. 585.2.

Antimicrobial Action

Voriconazole is a triazole antifungal that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in the impairment of ergosterol synthesis in fungal cell membranes. Voriconazole has a broad spectrum of activity against all *Candida* species, including fluconazole-resistant strains, as well as *Aspergillus* spp., *Scedosporium* spp., and *Fusarium* spp.

Reports of breakthrough zygomycosis and other fungal infections in immunocompromised patients treated empirically or prophylactically with voriconazole.[1-6]

1. Marty FM, *et al.* Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004; **350:** 950–2.
2. Siwek GT, *et al.* Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. *Clin Infect Dis* 2004; **39:** 584–7.
3. Imhof A, *et al.* Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis* 2004; **39:** 743–6.
4. Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. *Clin Infect Dis* 2005; **40:** 770–1.
5. Vigouroux S, *et al.* Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. *Clin Infect Dis* 2005; **40:** e35-e37.
6. Trifilio S, *et al.* Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant* 2007; **40:** 451–6.

Pharmacokinetics

Voriconazole has non-linear pharmacokinetics due to saturable metabolism. It is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma protein binding of voriconazole is about 58%. Voriconazole diffuses into CSF.

Voriconazole is metabolised by hepatic cytochrome P450 isoenzyme CYP2C19; the major metabolite is the inactive *N*-oxide. Metabolism via isoenzymes CYP2C9 and CYP3A4 has also been shown *in vitro*. About 80% of voriconazole is excreted in the urine.

References.
1. Purkins L, *et al.* Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; **46:** 2546–53.
2. Johnston A. The pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 1.
3. Walsh TJ, *et al.* Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother* 2004; **48:** 2166–72.
4. Theuretzbacher U, *et al.* Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; **45:** 649–63.
5. Brüggemann RJ, *et al.* Therapeutic drug monitoring of voriconazole. *Ther Drug Monit* 2008; **30:** 403–11.
6. Berge M, *et al.* Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients. *Transpl Infect Dis* 2009; **11:** 211–9.
7. Scholz I, *et al.* Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. *Br J Clin Pharmacol* 2009; **68:** 906–15.
8. Johnson HJ, *et al.* Voriconazole pharmacokinetics in liver transplant recipients. *Antimicrob Agents Chemother* 2010; **54:** 852–9.

9. Neely M, *et al*. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis* 2010; **50:** 27–36.
10. Pasqualotto AC, *et al*. Voriconazole therapeutic drug monitoring: focus on safety. *Expert Opin Drug Safety* 2010; **9:** 125–37.
11. Walsh TJ, *et al*. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrob Agents Chemother* 2010; **54:** 4116–23.
12. Han K, *et al*. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. *Antimicrob Agents Chemother* 2010; **54:** 4424–31.
13. Michael C, *et al*. Voriconazole pharmacokinetics and safety in immunocompromised children compared to adult patients. *Antimicrob Agents Chemother* 2010; **54:** 3225–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vfend; ***Austral.***: Vfend; ***Austria***: Vfend; ***Belg.***: Vfend; ***Braz.***: Vfend; ***Canad.***: Vfend; ***Chile***: Vfend; ***China***: Pinup (匹纳普); Vfend (威凡); ***Cz.***: Vfend; ***Denm.***: Vfend; ***Fin.***: Vfend; ***Fr.***: Vfend; ***Ger.***: Vfend; ***Gr.***: Vfend; ***Hong Kong***: Vfend; ***Hung.***: Vfend; ***Indon.***: Vfend; ***Irl.***: Vfend; ***Israel***: Vfend; ***Ital.***: Vfend; ***Malaysia***: Vfend; ***Mex.***: Vfend; ***Neth.***: Vfend; ***Norw.***: Vfend; ***NZ***: Vfend; ***Philipp.***: Vfend; ***Pol.***: Vfend; ***Port.***: Vfend; ***Rus.***: Vfend (Вифенд); ***S.Afr.***: Vfend; ***Singapore***: Vfend; ***Spain***: Vfend; ***Swed.***: Vfend; ***Switz.***: Vfend; ***Thai.***: Vfend; ***Turk.***: Vfend; ***UK***: Vfend; ***Ukr.***: Vfend (Вифенд); ***USA***: Vfend; ***Venez.***: Vorcum.

Antigout Drugs

This chapter deals with the treatment of gout and hyperuricaemia and the drugs used mainly for these disorders.

Gout and hyperuricaemia

Uric acid is the final product of the metabolism of endogenous and exogenous purine in man. An excess of uric acid, measured in the plasma as sodium urate, constitutes **hyperuricaemia**. A patient is usually considered to be hyperuricaemic when plasma-urate concentrations exceed

- 0.42 mmol/litre (7 mg per 100 mL) in men and postmenopausal women
- 0.36 mmol/litre (6 mg per 100 mL) in premenopausal women.

Hyperuricaemia may be caused by an overproduction of urate (e.g. due to excessive dietary purine intake, certain cancers or their treatment, or, more rarely, enzyme defects of purine metabolism), or reduced urate excretion due to renal disease, hypertension, or the intake of certain drugs such as thiazide diuretics and some immunosuppressants (such as ciclosporin and tacrolimus). Other factors contributing to hyperuricaemia include hyperlipidaemia, obesity, alcohol consumption, and lead exposure.

At hyperuricaemic concentrations there is a risk of crystals of monosodium urate monohydrate being formed and deposited in synovial fluid and various tissues. The presence of urate crystals in the synovial fluid leads to an inflammatory response in the affected joint, commonly at the base of the big toe (podagra). The ensuing exquisite pain, tenderness, erythema, and swelling constitute the clinical manifestations of **acute inflammatory gouty arthritis**. Repeated acute attacks may be associated with a visible or palpable build up of crystal deposits (**tophi**) at various sites including in and around the affected joint. Tophi release urate crystals into the synovial fluid after various stimuli and so cause further acute attacks, leading to **chronic tophaceous gout**. Intra-articular and peri-articular tophi may cause gradual joint erosion, which, without treatment, results in disabling **chronic gouty arthritis**. Rarely, the kidney can be affected by urate deposits producing a gouty nephropathy or by uric acid calculi or stones (uric acid nephrolithiasis or urolithiasis).

Treatment aims to:

- alleviate the acute attack
- prevent future attacks
- lower plasma-urate concentration.

Plasma-urate concentrations may be reduced by control of obesity and modification of diet and alcohol intake. Drug treatment can relieve the pain of acute attacks but more prolonged therapy for hyperuricaemia is generally only considered if there are recurrent attacks of gout or there is renal involvement (see under Chronic Gout, below).

Acute gout. An attack of acute inflammatory gouty arthritis is best treated as soon as possible with an NSAID. Aspirin or other salicylates are not suitable since they may increase plasma-urate concentrations. Treatment is started with high doses of an NSAID, the doses being reduced as the patient responds. Usually treatment can be withdrawn within 1 to 2 weeks. Colchicine is an effective alternative; it may be used alone, or with an NSAID. Another alternative to NSAIDs or colchicine, for example in those for whom these drugs are contra-indicated, is an oral or intramuscular corticosteroid. Intra-articular corticosteroids are effective in acute monoarticular gout, or when used adjunctively in patients with polyarticular gout; infection of joints should be excluded before injection. Canakinumab, a recombinant human monoclonal interleukin-1β antibody, may be used for the treatment of frequent attacks when NSAIDs, colchicine, and repeated courses of corticosteroids are inappropriate or ineffective. Intravenous, intramuscular, or subcutaneous corticotropin has also been used, alone or adjunctively. Other therapies for acute gout include adjunctive analgesics and topical ice. Drugs used for chronic gout (allopurinol or the uricosurics) should not be started during an acute attack since they can exacerbate and prolong it (see below).

Chronic gout. If the patient suffers frequent acute attacks or develops tophaceous gout, or has renal complications as a result of urate overproduction, then long-term treatment of hyperuricaemia may be needed. Such **urate-lowering therapy** should not be started during an acute attack, or for 2 to 3 weeks thereafter, as fluctuations in urate concentration may prolong the existing attack or trigger a new one. Treatment involves inhibiting the production of uric acid or enhancing its urinary excretion, in order to maintain a serum urate concentration at or below 0.3 or 0.36 mmol/litre. Hyperuricaemia due to *overproduction* of urate is treated with allopurinol, which inhibits the enzyme xanthine oxidase, involved in purine metabolism. Hyperuricaemia associated with *underexcretion* of uric acid can be treated with either allopurinol or a uricosuric such as probenecid or sulfinpyrazone.

Allopurinol is most commonly given as first-line therapy, but may be combined with or replaced by uricosurics if treatment fails. Allopurinol should also be used for patients with renal urate deposits or with uric acid renal calculi as it reduces urolithiasis. Febuxostat is an alternative xanthine oxidase inhibitor for those patients who cannot take allopurinol.

With either treatment there is mobilisation of urate crystals from established tophi, as the plasma-urate concentration falls, which can trigger further acute attacks of gout. Patients are thus also given **prophylaxis** with an NSAID or colchicine from the start of urate-lowering treatment until at least a month after the plasma-urate has been reduced to an acceptable concentration; up to 6 months of prophylactic cover has been recommended.

Once the hyperuricaemia is corrected, the patient continues to receive therapy with allopurinol or uricosurics indefinitely. If an acute attack occurs during such maintenance therapy, this therapy should be continued to avoid fluctuations in urate concentration, and the acute attack treated in its own right. For chronic gout that is refractory to conventional urate-lowering therapy, peglotícase, a recombinant form of urate oxidase, may be tried.

Surgery may have to be considered for patients severely affected by chronic tophaceous gout.

References to gout and its management are given below.[1-14]

1. Anonymous. Gout in primary care. *Drug Ther Bull* 2004; **42:** 37–40.
2. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 2004; **64:** 2399–2416.
3. Wortmann RL. Recent advances in the management of gout and hyperuricemia. *Curr Opin Rheumatol* 2005; **17:** 319–24.
4. Underwood M. Gout. *Clin Evid* 2005; **13:** 1435–44.
5. Suresh E. Diagnosis and management of gout: a rational approach. *Postgrad Med J* 2005; **81:** 572–9.
6. Teng GG, *et al.* Pathophysiology, clinical presentation and treatment of gout. *Drugs* 2006; **66:** 1547–63.
7. Underwood M. Diagnosis and management of gout. *BMJ* 2006; **332:** 1315–19.
8. Zhang W, *et al.* EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; **65:** 1312–24.
9. Jordan KM, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007; **46:** 1372–4. Also available at: http://rheumatology.oxfordjournals.org/cgi/reprint/46/8/1372 (accessed 22/04/08)
10. Tausche A-K, *et al.* Gout—current diagnosis and treatment. *Dtsch Arztebl Int* 2009; **106:** 549–55.
11. Underwood M, Adebajo A. Gout, hyperuricaemia and crystal arthritis. In: Adebajo A, ed. *ABC of rheumatology.* 4th ed. Chichester: Wiley-Blackwell, 2010: 59–64.
12. Richette P, Bardin T. Gout. *Lancet* 2010; **375:** 318–28.
13. Wilson JF. In the clinic. Gout. *Ann Intern Med* 2010; **152:** ITC2-2–ITC2-14. Correction. *ibid.*; 479–80.
14. Bhansing KJ, *et al.* Gout: a clinical syndrome illustrated and discussed. *Neth J Med* 2010; **68:** 352–9.

Allopurinol *(BAN, USAN, rINN)*

Allopürinol; Allopurinoli; Allopurinolo; Allopurinolum; Allopurynol; Alopurinol; Alopurinolis; BW-56-158; HPP; NSC-1390; Аллопуринол.

$C_5H_4N_4O$=136.1

CAS — 315-30-0 (allopurinol); 17795-21-0 (allopurinol sodium).

ATC — M04AA01.

ATC Vet — QM04AA01.

UNII — 63CZ7GJN5I.

Description. Allopurinol is a tautomeric mixture of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol and 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Allopurinol). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides.

USP 36: (Allopurinol). A fluffy white to off-white powder having only a slight odour. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of potassium and sodium hydroxides.

Incompatibility. Allopurinol sodium as a 3 mg/mL solution in 0.9% sodium chloride was visually incompatible with amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlormethine hydrochloride, chlorpromazine hydrochloride, cimetidine hydrochloride, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin hydrochloride, diphenhydramine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine hydrochloride, idarubicin hydrochloride, imipenem with cilastatin sodium, methylprednisolone sodium succinate, metoclopramide hydrochloride, minocycline hydrochloride, nalbuphine hydrochloride, netilmicin sulfate, ondansetron hydrochloride, pethidine hydrochloride, prochlorperazine edisilate, promethazine hydrochloride, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.[1]

1. Trissel LA, Martinez JF. Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51:** 1792–9.

Uses and Administration

Allopurinol is used to treat hyperuricaemia (above) associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme disorders, or cancer and its treatment (see Tumour Lysis Syndrome, p. 730.2). It is not used for asymptomatic hyperuricaemia. Allopurinol is also used in the management of renal calculi caused by the deposition of calcium oxalate (in the presence of hyperuricosuria) and of 2,8-dihydroxyadenine (see Renal Calculi, p. 602.1). It may have the potential to reduce oxidative stress by blocking the production of free radicals and is an ingredient of kidney preservation solutions. In addition allopurinol has antiprotozoal activity and has been used in leishmaniasis and American trypanosomiasis.

Allopurinol is used in **gout and hyperuricaemia** to inhibit the enzyme xanthine oxidase, thus preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. The urinary purine load, normally almost entirely uric acid, is thereby divided between hypoxanthine, xanthine, and uric acid, each with its independent solubility. This results in the reduction of urate and uric acid concentrations in plasma and urine, ideally to such an extent that deposits of monosodium urate monohydrate or uric acid are dissolved or prevented from forming. At low concentrations allopurinol acts as a competitive inhibitor of xanthine oxidase and at higher concentrations as a non-competitive inhibitor. However, most of its activity is due to the metabolite oxipurinol which is a non-competitive inhibitor of xanthine oxidase.

Allopurinol is used in *chronic gout* to correct hyperuricaemia, reduce the likelihood of acute attacks, and prevent the sequelae of chronic gout. Initially, it may increase plasma-concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, so allopurinol should not be started until an acute attack has completely subsided, and treatment should be started with a low dose and increased gradually; an NSAID (but not aspirin or salicylates) or colchicine should also be given for at least 1 month after hyperuricaemia is corrected. It may take several months to deplete the uric acid level sufficiently to control acute attacks.

A suggested oral starting dose of allopurinol is 100 mg daily, gradually increased by 100 mg for example at weekly intervals until the concentration of urate in plasma is reduced to 0.36 mmol/litre (6 mg per 100 mL) or less. A daily dose range of 100 to 300 mg may be adequate for those with mild gout and up to 600 mg for those with moderately severe tophaceous gout. The maximum recommended daily dose is 800 mg in the USA and 900 mg in the UK. Up to 300 mg may be taken as a single daily dose; larger amounts should be taken in divided doses to reduce the risk of gastric irritation. Taking allopurinol after food will also minimise gastric irritation. Patients should maintain an adequate fluid intake to prevent renal xanthine deposition.

Doses of allopurinol should be reduced in patients with renal impairment (see p. 601.1)

When used for the *prevention of uric acid nephropathy associated with cancer therapy* 600 to 800 mg may be given daily, generally for 2 or 3 days before starting the cancer treatment. A high fluid intake is essential. Maintenance doses of allopurinol in patients with hyperuricaemia secondary to cancer or cancer chemotherapy are similar to those used in gout and are given according to the response.

Allopurinol sodium has been given by intravenous infusion in sodium chloride 0.9% or glucose 5% to patients (usually cancer patients) unable to take allopurinol orally. The recommended dose in adults is the equivalent of allopurinol 200 to 400 mg/m^2 daily up to a maximum of 600 mg daily. Allopurinol sodium 116.2 mg is equivalent to about 100 mg of allopurinol.

The oral dose of allopurinol recommended for the management of recurrent calcium oxalate **renal calculi** in patients with hyperuricosuria is 200 to 300 mg daily, adjusted on the basis of subsequent 24-hour urinary urate excretion.

For doses in children, see Administration in Children, below.

Administration in children. The main use of allopurinol in children is for hyperuricaemia associated with cancer or cancer chemotherapy or with enzyme disorders. The dosage used may vary: in the UK an oral dose of 10 to 20 mg/kg daily, up to a maximum of 400 mg daily, is recommended for children under 15 years of age, while in the USA the dose is 150 mg daily for children under 6 years of age and 300 mg daily for those aged 6 to 10 years, adjusted if necessary after 48 hours.

Administration in hepatic impairment. UK licensed product information recommends that reduced oral doses of allopurinol be used in patients with hepatic impairment, and that liver function should be periodically monitored in the early stages of therapy.

Administration in renal impairment. Excretion of allopurinol and its active metabolite oxipurinol is mainly via the kidneys and therefore the dosage should be reduced in renal impairment according to creatinine clearance (CC).

In the USA the following doses are suggested for oral and intravenous use:

- CC 10 to 20 mL/minute: 200 mg daily
- CC less than 10 mL/minute: no more than 100 mg daily
- CC less than 3 mL/minute: consider also a longer dosage interval

In the UK a maximum initial oral daily dosage of 100 mg is recommended for those with renal impairment, increased only if the response is inadequate. Doses less than 100 mg daily or 100 mg at intervals longer than 1 day are recommended for those with severe renal insufficiency. Because of the imprecision of low creatinine clearance values, it is suggested that, if facilities are available for monitoring, the allopurinol dose should be adjusted to maintain plasma-oxipurinol concentrations below 100 micromoles/litre (15.2 micrograms/mL). A suggested alternative dose for patients requiring dialysis two or three times weekly is 300 to 400 mg allopurinol immediately after dialysis only.

The difficulties of maintaining an appropriate dose in such patients were illustrated by a study[1] in New Zealand involving 227 allopurinol-treated patients. The guidelines used suggested maintenance doses based on CC as follows:

- less than 10 mL/minute: 100 mg every 3 days
- 10 mL/minute: 100 mg every 2 days
- 20 mL/minute: 100 mg daily
- 40 mL/minute: 150 mg daily
- 60 mL/minute: 200 mg daily

The recommended dose or less was used in the majority of cases (183 of 227). However, of 214 patients for whom serum-uric acid concentrations were available, only 48 achieved values of 0.36 mmol/litre or less. The proportion of patients achieving acceptable serum-uric acid concentrations was higher (38%) in patients given higher than recommended doses than in those on doses recommended by the guidelines (19%). Although guidelines might be useful for initial dosing, longer term use could lead to inadequate control of hyperuricaemia.

1. Dalbeth N, *et al.* Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; **33:** 1646–50.

Angina pectoris. Allopurinol has been investigated for its apparent anti-ischaemic effects in angina (p. 1254.3). A randomised study[1] in 60 subjects with chronic stable angina found that high-dose allopurinol significantly improved exercise tolerance compared with placebo. A proposed mechanism was enhanced myocardial oxygen and ATP balance, possibly supplemented by improved coronary blood flow and reduced left ventricular afterload.

1. Noman A, *et al.* Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010; **375:** 2161–7.

Bipolar disorder. A double-blind study was conducted in 141 adults with bipolar disorder (p. 397.2), diagnosed as being acutely manic with or without psychotic features. Patients received lithium and were randomised to either oral allopurinol 600 mg daily, oral dipyridamole, or placebo. Improvements in mania were significant for those randomised to allopurinol, and were associated with decreasing uric acid concentrations, suggesting a role for purinergic system dysfunction in mania.[1]

1. Machado-Vieira R, *et al.* A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. *J Clin Psychiatry* 2008; **69:** 1237–45.

Diagnosis and testing. Deficiency of the enzyme ornithine carbamoyltransferase can result in severe CNS dysfunction or even in death, and identification of women at risk of being carriers of this genetic enzyme deficiency has been described.[1] The enzyme deficiency causes carbamoyl phosphate to accumulate, which stimulates the synthesis of orotidine. The test relies on giving a single dose of allopurinol, which will, in carriers, greatly increase the urinary excretion of orotidine. However, mutation analysis is now more usually used to establish the diagnosis.

1. Hauser ER, *et al.* Allopurinol-induced orotidinuria. *N Engl J Med* 1990; **322:** 1641–5. Correction. *ibid.* 1997; **336:** 1335.

Epilepsy. Reduction in the frequency of seizures has been described in some patients with severe or intractable epilepsy (p. 506.1) when allopurinol was added to their existing antiepileptic therapy.[1-4] Although the mode of action was unknown it was noted that the patients were not hyperuricaemic and that allopurinol did not affect plasma concentrations of existing antiepileptics.[1] However, others[5] have seen no benefit.

1. DeMarco P, Zagnoni P. Allopurinol and severe epilepsy. *Neurology* 1986; **36:** 1538–9.
2. Tada H, *et al.* Clinical effects of allopurinol on intractable epilepsy. *Epilepsia* 1991; **32:** 279–83.
3. Zagnoni PG, *et al.* Allopurinol as an add-on therapy in refractory epilepsy—a double-blind placebo-controlled randomised study. *Epilepsia* 1994; **35:** 107–12.
4. Togha M, *et al.* Allopurinol as adjunctive therapy in intractable epilepsy: a double-blind and placebo-controlled trial. *Arch Med Res* 2007; **38:** 313–16.
5. Coppola G, Pascotto A. Double-blind, placebo-controlled, cross-over trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* 1996; **18:** 50–2.

Hypertension. Hypertension (p. 1251.1) may be associated with hyperuricaemia. Thirty adolescents with mild hypertension and a serum uric acid concentration of 6 mg per 100 mL or more, and not on any antihypertensive therapy, were randomised to oral allopurinol 200 mg twice daily or placebo for 4 weeks in a double-blind, crossover study. Allopurinol treatment was associated with a significant decrease in systolic and diastolic blood pressure.[1]

1. Feig DI, *et al.* Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 2008; **300:** 924–32.

Organ and tissue transplantation. Allopurinol 25 mg on alternate days has been added to the immunosuppressive treatment for renal transplantation,[1] and is reported to reduce the frequency of acute rejection. One possible explanation for this effect is allopurinol's ability to suppress the production of free radicals (see Oxidative Stress, below). Organ and tissue transplantation, and the more usual drugs used in immunosuppressive regimens are discussed on p. 1936.2. It should be noted that allopurinol interacts with azathioprine (see Immunosuppressants, under Interactions, p. 603.2) and ciclosporin (p. 1957.1).

1. Chocair P, *et al.* Low-dose allopurinol plus azathioprine/cyclosporin/prednisolone, a novel immunosuppressive regimen. *Lancet* 1993; **342:** 83–4.

Oxidative stress. Allopurinol, through its inhibition of xanthine oxidase, can block the development of superoxide free radicals during reperfusion after an ischaemic episode. Consequently, the ability of allopurinol to reduce oxidative stress has been investigated in a number of clinical situations.

In a small study[1] of patients with idiopathic dilated cardiomyopathy, short-term intracoronary allopurinol improved myocardial efficiency by decreasing the oxygen demand of left ventricular contraction.

In patients undergoing coronary artery bypass graft surgery, perioperative allopurinol reduced hospital mortality, the incidence of arrhythmias, the number of ischaemic events, and the need for inotropic support, although the findings were not consistent in all studies.[2]

Improved endothelial dysfunction has been found in patients with chronic heart failure given allopurinol.[3,4]

A large study[5] in neonates undergoing cardiac surgery found that allopurinol caused a reduction in seizures and cardiac events in those with hypoplastic left heart syndrome. No benefit was found in neonates with less severe forms of congenital heart disease, considered to be at lower risk of adverse surgical outcome or reperfusion injury. Allopurinol also failed to reduce the incidence of periventricular leucomalacia (thought to represent ischaemic infarction of the developing brain) in preterm infants compared with placebo in a large study.[6] Similarly, allopurinol did not reduce the incidence of infarct extension in patients with acute myocardial infarction,[7] nor did it improve cerebrovascular reactivity in a small study in patients who had recently had subcortical stroke,[8] despite earlier results suggesting improvements in inflammatory indices.[9]

A pilot study using allopurinol showed a beneficial effect on free radical formation, cerebral blood volume, and electrical brain activity in severely asphyxiated newborns.[10] However, a systematic review[11] of this and 2 other studies in such infants was unable to determine whether allopurinol produced clinically important benefits.

Women in labour with signs of fetal distress were given intravenous allopurinol in a study to determine whether treatment would reduce free radical formation in the fetus, leading to a reduction of the neurodevelopmental consequences of fetal hypoxia.[12] Allopurinol was found to cross the placenta, although concentrations of allopurinol and its metabolite oxipurinol were lower in the umbilical cord compared with concentrations measured after an equivalent dose of oral allopurinol to mothers in uncomplicated labour. Newborns with therapeutic allopurinol and/or oxipurinol concentrations in cord blood had lower concentrations of the brain injury marker S-100B.

The possibility that allopurinol limits the production of free radicals has also led to allopurinol sodium being included as an ingredient of the University of Wisconsin solution [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)], which is used for the preservation of organs for transplantation.[13]

For evidence that allopurinol may be of value in angina pectoris see above.

1. Cappola TP, *et al.* Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 2001; **104:** 2407–11.
2. Weimert NA, *et al.* Allopurinol as a cardioprotectant during coronary artery bypass graft surgery. *Ann Pharmacother* 2003; **37:** 1708–11.
3. Doehner W, *et al.* Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricaemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; **105:** 2619–24.
4. Farquharson CAJ, *et al.* Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; **106:** 221–6.
5. Clancy RR, *et al.* Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. *Pediatrics* 2001; **108:** 61–70.
6. Russell GAB, Cooke RWI. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **73:** F27–F31.
7. Parmley LF, *et al.* Allopurinol therapy of ischemic heart disease with infarct extension. *Can J Cardiol* 1992; **8:** 280–6.
8. Dawson J, *et al.* The effect of allopurinol on the cerebral vasculature of patients with subcortical stroke; a randomized trial. *Br J Clin Pharmacol* 2009; **68:** 662–8.
9. Muir SW, *et al.* Allopurinol use yields potentially beneficial effects on inflammatory indices in those with recent ischemic stroke: a randomized, double-blind, placebo-controlled trial. *Stroke* 2008; **39:** 3303–7.
10. Van Bel F, *et al.* Effect of allopurinol on postasphyxial free radical formation, cerebral haemodynamics, and electrical brain activity. *Pediatrics* 1998; **101:** 185–93.
11. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 14/07/08).
12. Torrance HL, *et al.* Maternal allopurinol during fetal hypoxia lowers cord blood levels of the brain injury marker S-100B. *Pediatrics* 2009; **124:** 350–7. Also available at: http://pediatrics.aappublications.org/cgi/reprint/124/1/350 (accessed 05/01/11)
13. Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995; **46:** 235–47.

Prostatitis. Although allopurinol has been reported to be of benefit[1] in a small study in patients with chronic prostatitis (p. 2350.2), a systematic review[2] found no other satisfactory evidence of benefit, and considered that the clinical relevance of the original study results was unclear.

1. Persson BE, *et al.* Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. *J Urol (Baltimore)* 1996; **155:** 961–4.
2. McNaughton Collins M, Wilt T. Allopurinol for chronic prostatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 18/05/06).

Protozoal infections. Allopurinol has been widely used as an adjunct to pentavalent antimonials in the treatment[1,2] of Old World *visceral leishmaniasis* (p. 923.1), particularly where resistance to antimony alone is likely, although the degree of benefit has been called into question.[3] It has also been used with other drugs such as pentamidine[4] or azole antifungals,[5-8] including in transplant patients[7] or those with AIDS,[5] or in whom antimonials were otherwise poorly tolerated.[8] Allopurinol has also been tried alone[9,10] or with other drugs in both Old World[11-13] and New World[14-16] *cutaneous* (p. 922.1) or *mucocutaneous leishmaniasis*; (p. 923.1) results, particularly in the latter, have been variable. Allopurinol is usually given in oral doses of 15 to 20 mg/kg daily in 3 divided doses for leishmaniasis, and treatment lasts about 30 days.[3,4,11,12]

Beneficial results have been noted in some[17-20] but not all[21] studies using allopurinol in indeterminate and chronic Chagas' disease (*American trypanosomiasis*, p. 925.3). It may be less effective and have more adverse effects than itraconazole. Allopurinol 8.5 mg/kg daily is typically given orally for about 60 days;[17,19,20] higher doses (900 mg daily) were ineffective for chronic disease.[21]

The selective antiparasitic action of allopurinol is believed to be due to its incorporation into the protozoal, but not the mammalian, purine salvage pathway. This leads to the formation of 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analogue of adenosine triphosphate, that is incorporated into ribonucleic acid. This action of allopurinol is shared by allopurinol riboside, one of the minor metabolites in man, but not by oxipurinol, the major human metabolite. Thus, some studies have been conducted with allopurinol riboside, rather than allo-

purinol, in an attempt to enhance activity by avoiding host-mediated inactivation.[22]

1. di Martino L, *et al*. Low dosage combination of meglumine antimoniate plus allopurinol as first choice treatment of infantile visceral leishmaniasis in Italy. *Trans R Soc Trop Med Hyg* 1990; **84:** 534–5.
2. Gradoni L, *et al*. Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; **73:** 191–7.
3. Singh NKP, *et al*. Combination therapy in kala-azar. *J Assoc Physicians India* 1995; **43:** 319–20.
4. Das VNR, *et al*. A randomized clinical trial of low dosage combination of pentamidine and allopurinol in the treatment of antimony unresponsive cases of visceral leishmaniasis. *J Assoc Physicians India* 2001; **49:** 609–13.
5. Raffi F, *et al*. Use of an itraconazole/allopurinol combination for the treatment of visceral leishmaniasis in a patient with AIDS. *Clin Infect Dis* 1995; **21:** 1338–9.
6. Torrus D, *et al*. Fluconazole plus allopurinol in treatment of visceral leishmaniasis. *J Antimicrob Chemother* 1996; **37:** 1042–3.
7. Hueso M, *et al*. The renal transplant patient with visceral leishmaniasis who could not tolerate meglumine antimoniate-cure with ketoconazole and allopurinol. *Nephrol Dial Transplant* 1999; **14:** 2941–3.
8. Kuyucu N, *et al*. Successful treatment of visceral leishmaniasis with allopurinol plus ketoconazole in an infant who developed pancreatitis caused by meglumine antimoniate. *Pediatr Infect Dis J* 2001; **20:** 455–7.
9. Halbert AR, *et al*. Allopurinol for Old World cutaneous leishmaniasis. *Pediatr Dermatol* 1995; **12:** 287–8.
10. D'Oliveira A, *et al*. Evaluating the efficacy of allopurinol for the treatment of cutaneous leishmaniasis. *Int J Dermatol* 1997; **36:** 938–40.
11. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2002; **41:** 521–4.
12. Momeni AZ, Aminjavaheri M. Successful treatment of non-healing cases of cutaneous leishmaniasis, using a combination of meglumine antimoniate plus allopurinol. *Eur J Dermatol* 2003; **13:** 40–3.
13. Esfandiarpour I, Dabiri SH. Treatment of cutaneous leishmaniasis recidivans with a combination of allopurinol and meglumine antimoniate: a clinical and histologic study. *Int J Dermatol* 2007; **46:** 848–52.
14. Velez I, *et al*. Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 232–6.
15. Martinez S, *et al*. Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis* 1997; **24:** 165–9.
16. Llanos-Cuentas A, *et al*. Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. *Clin Infect Dis* 1997; **25:** 677–84.
17. Apt W, *et al*. Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; **59:** 133–8.
18. Amato Neto V. Etiological treatment for infection by Trypanosoma cruzi. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 211–3.
19. Apt W, *et al*. Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; **97:** 23–9.
20. Apt W, *et al*. Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the results of clinical and parasitological examinations 11 years post-treatment. *Ann Trop Med Parasitol* 2005; **99:** 733–41.
21. Rassi A, *et al*. Specific treatment for Trypanosoma cruzi: lack of efficacy of allopurinol in the human chronic phase of Chagas disease. *Am J Trop Med Hyg* 2007; **76:** 58–61.
22. Shapiro TA, *et al*. Pharmacokinetics and metabolism of allopurinol riboside. *Clin Pharmacol Ther* 1991; **49:** 506–14.

Renal calculi. In conjunction with a reduced dietary purine intake, high fluid intake, and potassium citrate, allopurinol may be used to prevent the recurrence of calcium oxalate renal calculi (p. 2350.3) in patients with hyperuricosuria.[1,2] Allopurinol is also advocated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with deficient activity of the enzyme adenine phosphoribosyltransferase.

1. Ettinger B, *et al*. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986; **315:** 1386–9.
2. Sorensen CM, Chandhoke PS. Hyperuricosuric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002; **31:** 915–25.

Sarcoidosis. Although corticosteroids remain the mainstay of drug therapy for sarcoidosis (p. 1612.2), and other drugs are very much second line, there are reports[1-3] of benefit in cutaneous disease from the use of allopurinol.

1. Brechtel B, *et al*. Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol* 1996; **135:** 307–9.
2. Antony F, Layton AM. A case of cutaneous acral sarcoidosis with response to allopurinol. *Br J Dermatol* 2000; **142:** 1052–3.
3. Bregnhoej A, Jemec GB. Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. *J Dermatol Treat* 2005; **16:** 125–7.

Schizophrenia. Involvement of purinergic neurotransmission has been hypothesised to play some role in schizophrenia (p. 1031.3), and allopurinol has been investigated as a possible adjunctive treatment, with some evidence of benefit, especially in patients with refractory positive symptoms.[1]

1. Buie LW, *et al*. Allopurinol as adjuvant therapy in poorly responsive or treatment refractory schizophrenia. *Ann Pharmacother* 2006; **40:** 2200–4.

Skin disorders. Reactive perforating collagenosis (RPC) is a condition in which altered collagen is eliminated through the epidermis; it may be inherited or acquired. In 3 of 4 patients with RPC refractory to antibacterials and oral and topical corticosteroids, significant improvement was seen with allopurinol, in terms of reduction of new lesions, improvement of existing lesions, and reduction of pruritus. The fourth patient died from unrelated causes before review.[1]

1. Hoque SR, *et al*. Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. *Br J Dermatol* 2006; **154:** 759–62.

Adverse Effects

The most common adverse effect of allopurinol is rash. Rashes are generally maculopapular or pruritic, sometimes purpuric, but more serious hypersensitivity reactions may occur and include exfoliative rashes, the Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is therefore recommended that allopurinol be withdrawn immediately if a rash occurs (see Precautions, below). Further symptoms of hypersensitivity include fever and chills, lymphadenopathy, leucopenia or leucocytosis, eosinophilia, arthralgia, and vasculitis leading to renal and hepatic damage and, very rarely, seizures. These hypersensitivity reactions may be severe, even fatal, and patients with hepatic or renal impairment are at special risk.

Hepatotoxicity and signs of altered liver function may also be found in patients who are not hypersensitive. Haematological effects include thrombocytopenia, aplastic anaemia, agranulocytosis, and haemolytic anaemia.

Many other adverse effects have been noted rarely and include paraesthesia, peripheral neuropathy, alopecia, gynaecomastia, hypertension, taste disturbances, nausea, vomiting, abdominal pain, diarrhoea, headache, malaise, drowsiness, vertigo, and visual disturbances.

Patients with gout may have an increase in acute attacks on beginning treatment with allopurinol, although attacks usually subside after several months.

Incidence of adverse effects. A Boston Collaborative Drug Surveillance Program involving 29 524 hospitalised patients found that, with the exception of skin reactions, 33 of 1835 patients treated with allopurinol (1.8%) had adverse effects. These effects were dose-related and the most frequent were haematological (11 patients, 0.6%), diarrhoea (5 patients, 0.3%), and drug fever (5 patients, 0.3%). Hepatotoxicity was reported in 3 patients (0.2%). Two patients developed possible hypersensitivity reactions to allopurinol.[1]

A further analysis involving 1748 outpatients indicated no instances of acute blood disorders, skin diseases, or hypersensitivity that warranted hospital treatment. Liver disease, although found, was not considered to be associated with allopurinol. There were only 2 patients in whom renal disease could possibly have been caused by allopurinol.[2]

1. McInnes GT, *et al*. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40:** 245–9.
2. Jick H, Perera DR. Reactions to allopurinol. *JAMA* 1984; **252:** 1411.

Effects on the blood. In addition to the haematological abnormalities of leucopenia, thrombocytopenia, haemolytic anaemia, and clotting abnormalities noted in the Boston Collaborative Drug Surveillance Program,[1] aplastic anaemia has also been reported, sometimes in patients with renal impairment.[2] Pure red cell aplasia has also been reported.[3,4]

1. McInnes GT, *et al*. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40:** 245–9.
2. Anonymous. Allopurinol and aplastic anaemia. *WHO Drug Inf* 1989; **3:** 26.
3. Lin Y-W *et al*. Acute pure red cell aplasia associated with allopurinol therapy. *Am J Hematol* 1999; **61:** 209–11.
4. Chao S-C, *et al*. Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. *Ann Pharmacother* 2005; **39:** 1552–6.

Effects on the eyes. Some case reports have suggested an association between allopurinol use and the development of cataracts,[1] but a detailed ophthalmological survey involving 51 patients who had taken allopurinol failed to confirm this.[2] However, a large retrospective case-control study in elderly patients concluded that long-term, or high-dose, allopurinol therapy did increase the risk of cataract extraction.[3]

1. Fraunfelder FT, *et al*. Cataracts associated with allopurinol therapy. *Am J Ophthalmol* 1982; **94:** 137–40.
2. Clair WK, *et al*. Allopurinol use and the risk of cataract formation. *Br J Ophthalmol* 1989; **73:** 173–6.
3. Garbe E, *et al*. Exposure to allopurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 1998; **116:** 1652–6.

Effects on the skin. Skin reactions are the most common adverse effects of allopurinol.

One report calculated that of 215 adverse effects noted over a 16-year period 188 (87.4%) were related to the skin or mucous membranes.[1] An analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 6 allergic skin reactions attributed to allopurinol among 784 recipients of the drug.[2] Desensitisation protocols[3] and alternative drugs[4] have been used after cutaneous reactions to allopurinol.

Serious skin reactions to allopurinol may occur as part of a generalised hypersensitivity reaction (see also Hypersensitivity, below). A review of the literature between 1970 and the end of 1990 revealed 101 cases of allopurinol hypersensitivity syndrome, 94 of which involved the skin.[5] Skin reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or a diffuse maculopapular or exfoliative dermatitis; 27 of the 101 patients died. The relative risk of toxic epidermal necrolysis or Stevens-Johnson syndrome occurring with allopurinol was high (calculated to be 5.5) in a case-control study including 13 patients with these cutaneous reactions who had received allopurinol.[6] This risk was not constant over time, being higher during the first 2 months of treatment. During these 2 months the estimated excess risk was 1.5 cases per million users per week. Another case-control study,[7] involving 379 patients with Stevens-Johnson syndrome or toxic epidermal necrolysis, found that allopurinol was the drug most frequently associated with these reactions. The risk again appeared to be restricted to short-term use (less than 8 weeks) and was greater in patients taking 200 mg or more daily.

1. Vinciullo C. Allopurinol hypersensitivity. *Med J Aust* 1984; **141:** 449–50.
2. Bigby M, *et al*. Drug-induced cutaneous reactions. *JAMA* 1986; **256:** 3358–63.
3. Fam AG, *et al*. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001; **44:** 231–8.
4. Fam AG. Difficult gout and new approaches for control of hyperuricemia in the allopurinol-allergic patient. *Curr Rheumatol Rep* 2001; **3:** 29–35.
5. Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; **27:** 337–43.
6. Roujeau J-C, *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–1607.
7. Halevy S, *et al*. EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008; **58:** 25–32.

Hypersensitivity. Skin reactions to allopurinol are common (see Effects on the Skin, above), and may occur as part of a hypersensitivity reaction. A DRESS syndrome (drug rash with eosinophilia and systemic symptoms) characterised by exfoliative dermatitis with eosinophilia, complicated by symptoms such as hepatitis and interstitial nephritis, has been described.[1-5] Pathogenesis of the syndrome is not entirely clear, but may relate to the accumulation of the metabolite oxipurinol. Risk factors include renal impairment and use with thiazide diuretics.[1,2] Patients who developed this syndrome have been successfully treated by immediate withdrawal of allopurinol and use of corticosteroids.[1,2]

1. Tausche A-K, *et al*. The Janus faces of allopurinol—allopurinol hypersensitivity syndrome. *Am J Med* 2008; **121:** e3–e4.
2. Markel A. Allopurinol hypersensitivity and DRESS syndrome. *Am J Med* 2008; **121:** e25.
3. Calogiuri GF, *et al*. Therapeutic alternatives in a patient with DRESS syndrome induced by allopurinol. *J Investig Allergol Clin Immunol* 2009; **19:** 333–4.
4. Dewan AK, Quinonez RA. Allopurinol-induced DRESS syndrome in an adolescent patient. *Pediatr Dermatol* 2010; **27:** 270–3.
5. Yang DC, Chang CM. Allopurinol-induced drug reaction with eosinophilia and systemic symptoms syndrome with recurrence. *J Am Geriatr Soc* 2010; **58:** 2043–4.

Precautions

Allopurinol should not be used for the treatment of an acute attack of gout; additionally, allopurinol therapy should not be begun for any purpose during an acute attack. However, allopurinol is continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately.

Treatment should be stopped immediately if any skin reactions or other signs of hypersensitivity develop:

- cautious reintroduction at a low dose may be attempted after resolution of *mild skin reactions* (see Effects on the Skin, above)
- allopurinol should not be reintroduced in those patients who have had *other forms of hypersensitivity* reaction

Dosage should be reduced in renal or hepatic impairment. Care is advised in patients being treated for hypertension or cardiac insufficiency, who may also have renal impairment.

To reduce the risk of renal xanthine deposition an adequate fluid intake (2 to 3 litres daily) is required. In addition, a neutral or slightly alkaline urine may be desirable.

Breast feeding. Allopurinol and its metabolite, oxipurinol, are distributed into breast milk, and licensed product information recommends that allopurinol should be used with caution in breast-feeding women. Although oxipurinol was detected in the plasma of a breast-fed infant, no adverse effects were noted in the infant during 6 weeks of maternal treatment with allopurinol.[1] The last available guidance from the American Academy of Pediatrics noted that there had been no documented problems with allopurinol and its use was considered to be usually compatible with breast feeding.[2]

1. Kamilli I, Gresser U. Allopurinol and oxypurinol in human breast milk. *Clin Investig* 1993; **71:** 161–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies allopurinol as

probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

Drugs that can increase uric acid concentrations may decrease the efficacy of allopurinol. Aspirin and the salicylates possess this activity and should generally be avoided in hyperuricaemia and gout. An increase in hypersensitivity reactions, and possibly also other adverse effects, has been reported in patients taking allopurinol with ACE inhibitors or thiazide diuretics, particularly in patients with renal impairment.

The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and their doses should be markedly reduced when either of them is given with allopurinol to avoid potentially life-threatening toxicity. There have also been reports of allopurinol enhancing the activity of, and possibly increasing the toxicity of, several other drugs including some antibacterials, some anticoagulants, some other antineoplastics, ciclosporin, some sulfonylurea antidiabetics, theophylline, and vidarabine.

ACE inhibitors. An apparent interaction between allopurinol and *captopril* has been reported in patients with chronic renal failure. Development of fatal Stevens-Johnson syndrome after the introduction of allopurinol in 1 case was thought to be due to potentiation by captopril.[1] In another patient hypersensitivity, characterised by fever, arthralgia, and myalgia, occurred and was believed to be due to captopril, or one of its metabolites, potentiated by the addition of allopurinol.[2] Care is advised if allopurinol is used with captopril, especially in patients with chronic renal failure.

1. Pennell DJ, *et al*. Fatal Stevens-Johnson syndrome in a patient on captopril and allopurinol. *Lancet* 1984; **i:** 463.
2. Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet* 1984; **i:** 679.

Antacids. Allopurinol failed to reduce blood-uric-acid concentrations when given at the same time as *aluminium hydroxide* in 3 patients on chronic haemodialysis. However, if allopurinol was given 3 hours before aluminium hydroxide the expected decrease in uric acid concentration did occur.[1]

1. Weissman I, Krivoy N. Interaction of aluminium hydroxide and allopurinol in patients on chronic hemodialysis. *Ann Intern Med* 1987; **107:** 787.

Antibacterials. There may be an increased incidence of rash when allopurinol is used with *ampicillin* or *amoxicillin*. For further details, see Ampicillin, p. 219.2.

Anticoagulants. For the effect of allopurinol on *dicoumarol*, *phenprocoumon*, or *warfarin*, see Warfarin, p. 1532.2.

Antiepileptics. For a report of allopurinol possibly inhibiting the metabolism of *phenytoin*, see under Antigout Drugs, p. 543.3.

Antigout drugs. Uricosuric drugs are likely to increase the renal elimination of oxipurinol (the major active metabolite of allopurinol). For example, *benzbromarone* lowered plasma concentrations of oxipurinol by about 40% when used with allopurinol, although plasma concentrations of allopurinol itself were not affected.[1] The interaction was not of concern, since the combination was more effective than allopurinol alone in lowering serum concentrations of uric acid. Licensed product information recommends reassessing the dosage of allopurinol on an individual basis when a uricosuric drug is added.

Probenecid has been reported to decrease the clearance of oral allopurinol riboside.[2] In a pharmacokinetic study in healthy subjects,[3] giving allopurinol and probenecid together significantly reduced oxipurinol concentrations; again, however, this combination had a greater hypouricaemic effect than either drug given alone.

1. Müller FO, *et al*. The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. *Eur J Clin Pharmacol* 1993; **44:** 69–72.
2. Were JBO, Shapiro TA. Effects of probenecid on the pharmacokinetics of allopurinol riboside. *Antimicrob Agents Chemother* 1993; **37:** 1193–6.
3. Stocker SL, *et al*. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects. *Clin Pharmacokinet* 2008; **47:** 111–18.

Antineoplastics. Allopurinol inhibits the metabolism of *mercaptopurine* and marked dosage reduction of this drug to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Deliberate use of the effects of allopurinol on mercaptopurine metabolism has been investigated (see p. 821.3).

There are also reports of interactions between allopurinol and other antineoplastics. Mild chronic allopurinol-induced hepatotoxicity has been reported in a male patient to have been exacerbated by *tamoxifen*.[1] Hypersensitivity vasculitis resulting in the death of a patient receiving allopurinol and *pentostatin* has been described. Although it could not be ascertained whether this effect was due to one of the drugs alone or to an interaction it was believed that this combination should not be used.[2]

For a report of an increased incidence of bone-marrow toxicity in patients given allopurinol with *cyclophosphamide*, see p. 773.2.

1. Shah KA, *et al*. Allopurinol hepatotoxicity potentiated by tamoxifen. *N Y State J Med* 1982; **82;** 1745–6.
2. Steinmetz JC, *et al*. Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; **86:** 499.

Antivirals. For the effect of allopurinol on *didanosine*, see p. 973.3.

Immunosuppressants. Allopurinol inhibits the metabolism of mercaptopurine, the metabolite of *azathioprine*, and marked dosage reduction of azathioprine to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Similar caution is also required with mercaptopurine itself (see Antineoplastics, above). The effects of allopurinol on *ciclosporin* concentrations (a marked increase) are reported on p. 1957.1.

Xanthines. For the effect of allopurinol on the pharmacokinetics of *caffeine* and *theophylline*, see p. 1206.2 and p. 1235.2 respectively.

Pharmacokinetics

Up to 90% of an oral dose of allopurinol is rapidly absorbed from the gastrointestinal tract; its plasma half-life is about 1 to 2 hours. Allopurinol's major metabolite is oxipurinol (alloxanthine), which is also an inhibitor of xanthine oxidase with a plasma half-life of about 15 or more hours in patients with normal renal function, although this is greatly prolonged by renal impairment. Both allopurinol and oxipurinol are conjugated to form their respective ribonucleosides. Allopurinol and oxipurinol are not bound to plasma proteins.

Excretion is mainly through the kidney, but it is slow since oxipurinol undergoes tubular reabsorption. About 70% of a daily dose may be excreted in the urine as oxipurinol and about 10% as allopurinol. The remainder of the dose is excreted in the faeces. Allopurinol and oxipurinol have also been detected in breast milk. Allopurinol has been found to cross the placenta.

References.

1. Murrell GAC, Rapeport WG. Clinical pharmacokinetics of allopurinol. *Clin Pharmacokinet* 1986; **11:** 343–53.
2. Turnheim K, *et al*. Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects. *Br J Clin Pharmacol* 1999; **48:** 501–9.
3. Day RO, *et al*. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin Pharmacokinet* 2007; **46:** 623–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfadiman; Colpuril A; Puritenk; ***Austral.***: Allohexal†; Allosig; Progout; Zyloprim; ***Austria***: Allostad; Gewapurol†; Gichtex; Purinol; Urosin; Zyloric; ***Belg.***: Alpuric†; Docallopu†; Zyloric; ***Braz.***: Lopurax; Zilopur†; Zyloric; ***Canad.***: Alloprin; Novo-Purol; Zyloprim; ***Chile***: Talol; Urogotan A; Zyloric; ***China***: Ao Mai Bi Li (奥迈必利); Lu Bi Li (路必利); Valeric (维洛林); Yi Da Tong (易达通); ***Cz.***: Milurit; Purinol; ***Denm.***: Hexanurat; ***Fin.***: Allonol; Apurin; Zyloric; ***Fr.***: Zyloric; ***Ger.***: Allo†; Allobeta; Bleminol†; Cellidrin†; Epidropal; Foligan†; Remid; Uribenz†; Zyloric; ***Gr.***: Arsol; Gealgica; Petrazyc; Purigan; Soluric; Stradumel; Zylapour; Zyloric; ***Hong Kong***: Allopin†; Arnol†; Marinol†; Milurit; Progout; Purinol†; Synpurinol†; Zyloric†; ***Hung.***: Milurit; ***India***: Aligout; Allgoric; Aloric; Aloriv; Alur; Alurid; Ciploric; Edorin; Gurik; Lodiric; Logout; Orlu; Zyloric; ***Indon.***: Algut†; Alluric; Benoxuric; Hycemia†; Isoric; Licoric; Llanol†; Nilapur; Ponuric; Pritanol; Puricemia; Reucid; Rinolic; Sinoric; Tylonic; Urica; Uricnol; Xanturic; Zyloric; ***Irl.***: Alopur; Purinol; Tipuric; Zyloric; ***Israel***: Alloril; ***Ital.***: Allurit; Zyloric; ***Malaysia***: Zyloric; ***Mex.***: Acyprin†; Alzoprim; Atisuril; Bionol; Darzune; Etindrax; Unizuric; Zyloprim; ***Neth.***: Acepurin; Zyloric; ***Norw.***: Allopur; Zyloric; ***NZ***: Allohexal†; Allorin; Progout†; ***Philipp.***: AL; Allocor; Allurase; Alpurase; Elavil; Llanol; Lopric; Loricid; Prinol; Purinase; Purispec; Puristen†; Synol; Trianol; Urinol; Xanurace; Zyloprim; ***Pol.***: Allupol; Milurit; Zyloric; ***Port.***: Alosfar†; Uriprim; Zurim; Zyloric; ***Rus.***: Purinol (Пуринол); ***S.Afr.***: Lonol; Puricos; Redurate; Urinol†; Zyloprim; ***Singapore***: Progout; Zyloric; ***Spain***: Zyloric; ***Swed.***: Zyloric; ***Switz.***: Allopur; Cellidrine†; Mephanol; Uriconorm; Zyloric; ***Thai.***: Alinol; Allo; Allonol; Allopin; Alloric; Apnol; Apronol; Apurol†; Chinnol; Loporic; Medoric†; Puride; Uricad; Valeric; Xandase; Xanol; Zylic; Zyloric; ***Turk.***: Allo-Urik; Allogut; Urikoliz†; ***UK***: Caplenal; Cosuric; Rimapurinol; Zyloric; ***Ukr.***: Allohexal (Аллогексал)†; ***USA***: Aloprim; Zyloprim; ***Venez.***: Aluron; Zyloric.

Multi-ingredient Preparations. ***Arg.***: Artrex; Colpuril; Xuric-A; ***Austria***: Allobenz; Gichtex plus; ***China***: Allo Comp (通益风宁); ***Ger.***: Allo.comp.†; ***India***: Aluno-A; ***Malaysia***: Lanolone; ***Philipp.***: Allomaron; ***Thai.***: Allomaron.

Pharmacopoeial Preparations

BP 2014: Allopurinol Oral Suspension; Allopurinol Tablets;
USP 36: Allopurinol Oral Suspension; Allopurinol Tablets.

Benzbromarone *(BAN, USAN, rINN)*

Bensbromaron; Bentsbromaroni; Benzbromaron; Benzbromarona; Benzbromaronas; Benzbromaronum; L-2214; MJ-10061; Бензбромарон.

3,5-Dibromo-4-hydroxyphenyl 2-ethylbenzofuran-3-yl ketone.

$C_{17}H_{12}Br_2O_3$=424.1

CAS — 3562-84-3.

ATC — M04AB03.

ATC Vet — QM04AB03.

UNII — 4POG0RL69O.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Benzbromarone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Uses and Administration

Benzbromarone is a uricosuric drug that reduces plasma concentrations of uric acid by blocking renal tubular reabsorption. It has been suggested that benzbromarone may also increase the intestinal elimination of uric acid. It has been used to treat hyperuricaemia including that associated with chronic gout (p. 600.1) although it has been withdrawn in many countries due to reports of hepatotoxicity. Some countries restrict its use to those patients in whom allopurinol is contra-indicated.

Benzbromarone is not used to treat acute attacks of gout and may exacerbate and prolong them if given during an attack; treatment should not start therefore until an acute attack has subsided.

The usual oral dose has been 50 to 200 mg daily. An NSAID or colchicine should be given initially to reduce the risk of precipitating acute gout. An adequate fluid intake should be maintained. Lower doses of benzbromarone (20 mg) have also been used in the form of a combination product with allopurinol.

References.

1. Hanvivadhanakul P, *et al*. Efficacy of benzbromarone compared to allopurinol in lowering serum uric acid level in hyperuricemic patients. *J Med Assoc Thai* 2002; **85** (suppl 1): S40–S47.
2. Kumar S, *et al*. Benzbromarone therapy in management of refractory gout. *N Z Med J* 2005; **118:** U1528.
3. Lee M-HH, *et al*. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? *Drug Safety* 2008; **31:** 643–65.
4. Reinders MK, *et al*. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis* 2009; **68:** 51–6.

Adverse Effects

Benzbromarone may cause gastrointestinal adverse effects, especially diarrhoea. It may precipitate an acute attack of gout and cause uric acid renal calculi and renal colic. Hepatotoxicity, sometimes fatal, has occurred and monitoring of liver function has been recommended.

Effects on the liver. Benzbromarone-induced liver damage, sometimes fatal, has been reported.[1-4]

1. Van Der Klauw MM, *et al*. Hepatic injury caused by benzbromarone. *J Hepatol* 1994; **20:** 376–9.
2. Anonymous. Benzbromarone and hepatitis. *WHO Drug Inf* 2000; **14:** 29.
3. Wagayama H, *et al*. Fatal fulminant hepatic failure associated with benzbromarone. *J Hepatol* 2000; **32:** 874.
4. Arai M, *et al*. Fulminant hepatic failure associated with benzbromarone treatment: a case report. *J Gastroenterol Hepatol* 2002; **17:** 625–6.

Effects on the lungs. Benzbromarone has been associated with the development of drug-induced eosinophilic pneumonia and pulmonary alveolar haemorrhage.[1] Symptoms resolved on stopping the drug and treatment with corticosteroids.

1. Hara A, *et al*. Drug-induced eosinophilic pneumonia with pulmonary alveolar hemorrhage caused by benzbromarone. *Intern Med* 2010; **49:** 435–8.

Precautions

Benzbromarone should be avoided in patients with liver impairment, severe renal impairment, in those with uric acid renal calculi, and in those with urinary uric acid excretion rates of greater than 700 mg per 24 hours. Like other uricosurics, treatment with benzbromarone should not be started during an acute attack of gout. Similarly, an adequate fluid intake should be maintained to reduce the risk of uric acid renal calculi; additionally, alkalinisation of the urine may be considered.

Interactions

Aspirin and other salicylates antagonise the effect of benzbromarone. Pyrazinamide, sulfinpyrazone, and thiazide diuretics can also inhibit the uricosuric effect of benzbromarone. Benzbromarone may increase the anticoagulant activity of coumarin oral anticoagulants (see under Interactions of Warfarin, p. 1532.2).

Antigout drugs. For mention of the effects of benzbromarone on the clearance of oxipurinol, the major active metabolite of *allopurinol*, and the view that this was not clinically significant, see under Interactions of Allopurinol, p. 603.1.

Pharmacokinetics

Benzbromarone is only partially absorbed from the gastrointestinal tract, reaching peak plasma concentrations about 2 to 4 hours after an oral dose. Benzbromarone is extensively bound to plasma proteins. It is metabolised in the liver, and is excreted mainly in the faeces; a small amount appears in the urine.

References.
1. Maurer H, Wollenberg P. Urinary metabolites of benzbromarone in man. *Arzneimittelforschung* 1990; **40:** 460–2.
2. Walter-Sack I, *et al*. Variation of benzbromarone elimination in man—a population study. *Eur J Clin Pharmacol* 1990; **39:** 173–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Narcaricina; ***China***: Er Tong Shu (尔同舒); Narcaricin (立加利仙/步利仙); You Nuo (尤诺); ***Jpn***: Urinorm; ***Neth.***: Desuric; ***Spain***: Urinorm; ***Thai.***: Benarone.

Multi-ingredient Preparations. ***Austria***: Allobenz; Gichtex plus; ***China***: Allo Comp (通益风宁); ***Ger.***: Allo.comp.†; ***Malaysia***: Lanolone; ***Philipp.***: Allomaron; ***Thai.***: Allomaron.

Colchicine

Colchicin; Colchicina; Colchicinum; Kolchicin; Kolchicinas; Kolşisin; Kolkicin; Kolkisiini; Колхицин.

(*S*)-*N*-(5,6,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)acetamide.

$C_{22}H_{25}NO_6$=399.4

CAS — 64-86-8.

ATC — M04AC01.

ATC Vet — QM04AC01.

UNII — SML2Y3J35T.

Description. Colchicine is an alkaloid obtained from various *Colchicum* spp.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*. *Chin.* also has a monograph for colchicine amide.

Ph. Eur. 8: (Colchicine). A yellowish-white amorphous or crystalline powder. Very soluble in water, rapidly recrystallising from concentrated solutions as the sesquihydrate; freely soluble in alcohol and in chloroform. Protect from light.

USP 36: (Colchicine). An alkaloid obtained from various *Colchicum* spp. and other genera. Pale yellow to pale greenish-yellow amorphous scales, or powder or crystalline powder. Is odourless or nearly so, and darkens on exposure to light. Soluble 1 in 25 of water and 1 in 220 of ether; freely soluble in alcohol and in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Colchicine is used for the relief of acute gout (p. 600.1) and for the prophylaxis of acute attacks, particularly during the first few months of treatment with allopurinol or uricosurics. Colchicine produces a dramatic response in acute gout, probably by reducing the inflammatory reaction to urate crystals; this effect might be due to several actions including decreased lactic acid production by leucocytes. It is not an analgesic and has no effect on blood concentrations of uric acid, or on the excretion of uric acid. Colchicine also appears to inhibit β-tubulin polymerisation, inhibiting the activation, degranulation and migration of neutrophils, which may mediate some gout symptoms.

Colchicine is used for the treatment of familial Mediterranean fever and has also been used in several other conditions including amyloidosis, Behçet's syndrome, pericarditis, primary biliary cirrhosis, and pyoderma gangrenosum.

If colchicine is used for *acute attacks* of **gout**, then treatment should be started as soon as possible and an effect may be expected within 12 hours. The recommended oral dose in the UK is 1 mg initially, then 500 micrograms every 2 to 3 hours until pain relief is obtained or gastrointestinal adverse effects occur (but see also Administration, below). The total dose should not exceed 6 mg. At least 3 days should elapse before another course is given. In the USA the oral dose is 1.2 mg initially followed by 600 micrograms one hour later. The maximum total dose for an acute attack is 1.8 mg over 1 hour. This dose may also be used (in the USA) for treatment of a gout flare while the patient is taking colchicine for prophylaxis (see below); the prophylactic dose may be resumed 12 hours after treatment.

Colchicine is also used for the *prophylaxis* of gout; oral doses are 500 micrograms two or three times daily in the UK whereas in the USA 600 micrograms may be given once or twice daily, to a maximum of 1.2 mg daily.

Although no longer licensed in many countries, colchicine was formerly given intravenously for *acute attacks* of gout in a usual treatment dose of 2 mg over 2 to 5 minutes with additional doses of 500 micrograms every 6 hours as required to a total dose of not more than 4 mg in 24 hours; once this amount of colchicine has been given further doses should not then be given by any route for at least 7 days. Colchicine has also been given intravenously for *prophylaxis*, usually in doses of 500 micrograms to 1 mg once or twice daily; however, the oral route is preferable. For the view that the intravenous route should be avoided, see Administration, below.

For **familial Mediterranean fever**, US licensed product information for colchicine recommends an oral dose of 1.2 to 2.4 mg daily (which can be given in 2 divided doses); doses can be increased or decreased as needed within this range in increments of 300 micrograms daily.

Although colchicine is not licensed in the UK for familial Mediterranean fever, the *BNF* suggests an oral dose of 500 micrograms to 2 mg once daily as prophylaxis.

For dose recommendations in children, patients with hepatic or renal impairment, or when colchicine is used with other drugs, see below.

References.
1. Lange U, *et al*. Current aspects of colchicine therapy: classical indications and new therapeutic uses. *Eur J Med Res* 2001; **6:** 150–60.
2. Schlesinger N, *et al*. Colchicine for acute gout. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/04/08).
3. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. *Curr Rheumatol Rep* 2008; **10:** 218–27.
4. Yang LPH. Oral colchicine (Colcrys): in the treatment and prophylaxis of gout. *Drugs* 2010; **70:** 1603–13.
5. Richette P, Bardin T. Colchicine for the treatment of gout. *Expert Opin Pharmacother* 2010; **11:** 2933–8.

Administration. Although colchicine 1 mg **orally**, followed by 500 micrograms every 2 to 3 hours, is recommended in the UK for the treatment of acute gout, many rheumatologists consider this excessive; a low-dose regimen of 500 micrograms no more than 3 times daily has been advocated in preference.[1] In the USA, a total oral dose of 1.8 mg is recommended, as studies found low-dose (1.2 mg followed by a single dose of 600 micrograms) and high-dose (1.2 mg followed by 600 micrograms every hour for 6 hours) colchicine regimens to have similar efficacy, but considerably fewer adverse effects were seen with the low-dose schedule.[2,3]

The safety of **intravenous** colchicine has been questioned, and it has been suggested that, although undoubtedly effective, it should not be used because of the risk of severe or fatal adverse effects.[4,5] For reports of fatalities with intravenous colchicine during unlicensed use, see Inappropriate Administration, p. 606.1.

1. Morris I, *et al*. Colchicine in acute gout. *BMJ* 2003; **327:** 1275–6.
2. FDA. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys) (issued 30th July, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm (accessed 10/09/09)
3. Terkeltaub RA, *et al*. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010; **62:** 1060–8.
4. Morris I, *et al*. Colchicine in acute gout. *BMJ* 2004; **328:** 289.
5. Schlesinger N. Reassessing the safety of intravenous and compounded injectable colchicine in acute gout treatment. *Expert Opin Drug Safety* 2007; **6:** 625–9.

Administration in children. In the USA, colchicine is licensed for use in children for the treatment of familial Mediterranean fever. It is given orally in the following daily doses according to age:

- 4 to 6 years: 300 micrograms to 1.8 mg
- 6 to 12 years: 900 micrograms to 1.8 mg
- over 12 years: adult doses are given, see above

Administration in hepatic impairment. The clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment, compared with healthy subjects.

When colchicine is used for the *treatment* of acute **gout**, licensed product information in the USA considers dose reduction is not necessary for patients with hepatic impairment, but suggests that they should be monitored closely for adverse effects. Treatment courses should not be repeated more often than once every 2 weeks in patients with severe impairment, and alternative therapy considered in those patients who require repeated courses.

When used for *prophylaxis* of gout flares, US licensed product information states that no dose adjustment is recommended for patients with mild to moderate hepatic impairment, although patients should be monitored closely for adverse effects. Dose reduction should be considered in patients with severe hepatic impairment.

Patients with hepatic impairment who are given colchicine prophylaxis should not be treated with colchicine for acute gout flares.

In **familial Mediterranean fever**, US licensed product information suggests that patients with mild to moderate hepatic impairment are monitored closely for adverse effects. Dose reduction may be considered for patients with severe hepatic impairment.

Colchicine should not be used in patients with hepatic impairment who are taking P-glycoprotein inhibitors, strong cytochrome P450 isoenzyme CYP3A4 inhibitors, or HIV-protease inhibitors.

Administration in renal impairment. When oral colchicine is used for the *treatment* of acute **gout**, licensed product information in the UK suggests a dose reduction or an increased interval between doses in patients with a creatinine clearance (CC) of 10 to 50 mL/min, and contra-indicates its use in patients with severe renal impairment (CC less than 10 mL/min), or those on dialysis. In the USA, no dose reduction is considered necessary in patients with mild to moderate renal impairment (CC 30 to 80 mL/min), although patients should be monitored closely for adverse effects. Patients with severe renal impairment (CC less than 30 mL/min) also do not require a dose reduction, but treatment courses should not be repeated more than once every 2 weeks; alternative therapy should be considered in those patients who require repeated courses. In dialysis patients, the total recommended dose for acute gout should be reduced to a single oral dose of 600 micrograms, not repeated more than once every 2 weeks.

When used for *prophylaxis* of gout flares, US licensed product information states that dose reduction is not considered necessary in those patients with mild to moderate renal impairment (CC 30 to 80 mL/min), although patients should be monitored closely for adverse effects. For patients with severe renal impairment (CC less than 30 mL/min), however, the initial dose should be 300 micrograms daily and any increase done with close monitoring. In patients on dialysis, 300 micrograms can be given twice weekly, with close monitoring.

Patients with renal impairment who are given colchicine prophylaxis should not be treated with colchicine for acute gout flares.

In **familial Mediterranean fever**, US licensed product information suggests that patients with mild to moderate renal impairment (30 to 80 mL/min) should be monitored closely; a reduction in colchicine dose may be necessary. For patients with severe renal impairment (CC less than 30 mL/min) or dialysis patients, an initial oral dose of colchicine 300 micrograms daily is recommended, with close monitoring after any dose increases.

Colchicine should **not** be used in patients with renal impairment who are taking P-glycoprotein inhibitors, strong cytochrome P450 isoenzyme CYP3A4 inhibitors, or HIV-protease inhibitors.

Administration with other drugs. Use of colchicine with drugs that inhibit cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein increases the risk of colchicine toxicity. In the USA, if no alternative is available, licensed product information recommends adjustment of the colchicine dose when it is used with these drugs, or if these drugs have been taken within 14 days of colchicine. Patients with renal or hepatic impairment should not be given colchicine with these drugs. Patients receiving colchicine prophylactically who are given CYP3A4 inhibitors should not be treated with colchicine for gout flares.

When used for the **treatment of gout flares**, oral colchicine doses are reduced from the usual dose (see Uses and Administration, above) as follows:

- with strong CYP3A4 inhibitors: a single dose of colchicine 600 micrograms, followed by 300 micrograms 1 hour later
- with moderate CYP3A4 inhibitors: a single dose of colchicine 1.2 mg
- with P-glycoprotein inhibitors: a single dose of 600 micrograms
- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): a single dose of colchicine 600 micrograms, followed by 300 micrograms 1 hour later
- with fosamprenavir (when given alone and not with ritonavir): a single dose of colchicine 1.2 mg

Treatment courses should not be repeated within 3 days.

When used for the **prophylaxis of gout flares**, if the original *intended* oral dose of colchicine would have been 600 micrograms *twice* daily (see Uses and Administration, above), the following colchicine doses are recommended:

- with strong CYP3A4 inhibitors: 300 micrograms once daily
- with moderate CYP3A4 inhibitors: 300 micrograms twice daily, or 600 micrograms once daily
- with P-glycoprotein inhibitors: 300 micrograms once daily

- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): 300 micrograms once daily
- with fosamprenavir (when given alone and not with ritonavir): 300 micrograms twice daily, or 600 micrograms once daily

When used for the prophylaxis of gout flares, if the original *intended* oral dose of colchicine would have been 600 micrograms *once* daily (see Uses and Administration, p. 604.1), the following colchicine doses are recommended:

- with strong CYP3A4 inhibitors: 300 micrograms once every other day
- with moderate CYP3A4 inhibitors: 300 micrograms once daily
- with P-glycoprotein inhibitors: 300 micrograms once every other day
- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): 300 micrograms once every other day
- with fosamprenavir (when given alone and not with ritonavir): 300 micrograms once daily

When used in the management of **familial Mediterranean fever**, the maximum daily dose of oral colchicine (given as a single dose or in 2 divided doses) is as follows:

- with strong CYP3A4 inhibitors: 600 micrograms
- with moderate CYP3A4 inhibitors: 1.2 mg
- with P-glycoprotein inhibitors: 600 micrograms
- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): 600 micrograms
- with fosamprenavir (when given alone and not with ritonavir): 1.2 mg

Amyloidosis. Colchicine is well known to have a useful role in amyloidosis (p. 819.3) secondary to familial Mediterranean fever, where results have suggested the possibility of reversing nephropathic changes due to renal amyloid deposition (see below). However, combination therapy with melphalan and prednisone was found to be more effective than colchicine alone in primary amyloidosis,[1] and a later study[2] found no benefit in adding colchicine to the standard therapy. The mechanism of the anti-amyloid effect of colchicine is not clear.

1. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomised trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100:** 290–8.
2. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; **336:** 1202–7.

Behçet's syndrome. Behçet's syndrome (p. 1601.1) has been treated with many drugs. Where possible, topical treatment of local lesions should be tried before starting systemic therapy. Corticosteroids are favoured for systemic treatment in many countries, but colchicine has also been widely used. Beneficial responses have been described for most of the symptoms including the arthritic, ocular, and cutaneous manifestations, although a systematic review has questioned colchicine's efficacy.[1] The mechanism of action in this condition is believed to be based on the effect on polymorphonuclear leucocytes and other cellular effects.[2] Colchicine has also been used with corticosteroids for acute exacerbations, followed by colchicine maintenance;[3] colchicine with aspirin has also been recommended in acute disease,[4] and colchicine with benzathine benzylpenicillin has been tried.[5]

1. Saenz A, *et al.* Pharmacotherapy for Behcet's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 27/04/05).
2. Schattner A. Colchicine—expanding horizons. *Postgrad Med J* 1991; **67:** 223–6.
3. Rakover Y, *et al.* Behcet disease: long-term follow-up of three children and review of the literature. *Pediatrics* 1989; **83:** 986–92.
4. Wechsler B, Piette JC. Behçet's disease. *BMJ* 1992; **304:** 1199–1200.
5. Çalgüneri M, *et al.* Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. *Dermatology* 1996; **192:** 125–8.

Familial Mediterranean fever. Familial Mediterranean fever (recurrent or paroxysmal polyserositis; periodic disease) is an inherited disorder that mainly affects Sephardic Jews or persons of Arab, Armenian, or Turkish ancestry.[1,2] It is characterised by attacks of acute abdominal pain, fever, and signs of peritonitis, which resolve spontaneously, usually in 24 to 48 hours. Pleuritic chest pain, arthritis, rash, pericarditis, and headache may occur. The most dangerous complication, however, is type AA amyloidosis (see also p. 819.3), which can lead to nephrotic syndrome, renal failure, and death.

Familial Mediterranean fever is managed with colchicine.[1-3] Colchicine cannot stop an established attack, but, given prophylactically, it reduces the frequency of attacks, prevents amyloidosis and reverses proteinuria. Attacks are usually treated with NSAIDs[1,3] or, in severe cases, opioids.[3] Anecdotal evidence has suggested that prazosin may also be of benefit,[4] but initial reports of improvement with interferon alfa have not been borne out.[1] Anakinra has also been investigated.[5]

1. Drenth JPH, van der Meer JWM. Hereditary periodic fever. *N Engl J Med* 2001; **345:** 1748–57.
2. Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. *Arthritis Rheum* 2009; **61:** 1447–53.
3. Kallinich T, *et al.* Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; **119:** e474–e483. Also available at: http://pediatrics.aappublications.org/cgi/reprint/119/2/e474 (accessed 21/04/08)
4. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129:** 424–5.
5. Roldan R, *et al.* Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine* 2008; **75:** 504–5.

Interstitial lung disease. Colchicine has been used in patients with idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1607.1). However, studies have generally shown no evidence of survival benefit, and it is not recommended.

Pericarditis. Mild cases of recurrent pericarditis may be treated with colchicine, as an adjunct to NSAID therapy.[1-3] It may also provide effective prophylaxis, allowing the tapering of corticosteroids, which are usually reserved for the treatment of severe acute attacks.[2,3] The drug has also been used successfully in children.[4] In an open-label study, colchicine added to conventional therapy with aspirin or prednisone significantly decreased the recurrence rate in patients with a first episode of recurrent pericarditis, compared with conventional therapy alone.[5] Another open-label study had similar results using adjunctive colchicine for the first episode of acute pericarditis.[6] In patients with two or more relapses of acute pericarditis, colchicine was found to be highly effective in preventing recurrence.[7] The proportion of patients with relapses during or after colchicine therapy was significantly higher, and the duration of colchicine therapy significantly longer, in those who had pretreatment with corticosteroids.

Colchicine has also been investigated in the prevention of post-pericardiotomy syndrome, a complication of cardiac surgery characterised by fever, pleuritic chest pain, and evidence of pleural effusion and new or worsening pericardial effusion. A multicentre double-blind study[8] found that oral colchicine 1 mg twice daily on the first day and then 500 micrograms twice daily for one month (or half these doses in patients weighing under 70 kg or intolerant to the higher dose) markedly reduced incidence of the syndrome at 12 months compared with placebo; the condition was diagnosed in 16 of 180 patients given colchicine versus 38 of 180 in the placebo group. Secondary end-points of disease-related hospitalisation, cardiac tamponade, constrictive pericarditis, or recurrent pericarditis occurred in 9 of the placebo group versus 1 patient given colchicine. No serious adverse effects occurred, although about 10% of patients taking colchicine developed diarrhoea.

1. Millaire A, *et al.* Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994; **15:** 120–4.
2. Adler Y, *et al.* Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998; **97:** 2183–5.
3. Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000; **84:** 449–54.
4. Yazigi A, *et al.* Colchicine for recurrent pericarditis in children. *Acta Paediatr Scand* 1998; **87:** 603–4.
5. Imazio M, *et al.* Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005; **165:** 1987–91.
6. Imazio M, *et al.* Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation* 2005; **112:** 2012–16.
7. Artom G, *et al.* Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-centre all-case analysis. *Eur Heart J* 2005; **26:** 723–7.
8. Imazio M, *et al.* COPPS Investigators. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. *Eur Heart J* 2010; **31:** 2749–54.

Peyronie's disease. Beneficial effects have been reported with colchicine in men with Peyronie's disease. Small studies show colchicine to be most effective in reducing pain during penile erection.[1] A combination of vitamin E and colchicine has also been suggested as an alternative in early disease.[2]

1. Kadioğlu A, *et al.* Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res* 2000; **12:** 169–75.
2. Prieto Castro RM, *et al.* Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int* 2003; **91:** 522–4.

Primary biliary cirrhosis. Primary biliary cirrhosis (p. 2638.3) is a chronic progressive liver disease with no specific treatment, and in general drug therapy has been poor or largely ineffective. Reviewers have noted[1-3] that several studies have been conducted with colchicine, and, although biochemical parameters were improved, a beneficial effect on clinical symptoms or liver histology was not found. A comparative study of colchicine and methotrexate showed that while both drugs improved biochemical test results and symptoms, the response to methotrexate was greater.[4] Some consider that combination therapy with colchicine, methotrexate, and ursodeoxycholic acid may be more promising than monotherapy.[2]

1. Heathcote EJ. Evidence-based therapy of primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999; **11:** 607–15.
2. Holtmeier J, Leuschner U. Medical treatment of primary biliary cirrhosis and primary sclerosing cholangitis. *Digestion* 2001; **64:** 137–50.
3. Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 27/04/05).
4. Kaplan MM, *et al.* A prospective trial of colchicine and methotrexate in the treatment of primary biliary cirrhosis. *Gastroenterology* 1999; **117:** 1173–80.

Pyoderma gangrenosum. Pyoderma gangrenosum (p. 1688.3) associated with inflammatory bowel disease has been successfully treated with colchicine in 2 patients.[1,2] Colchicine was also of benefit in 3 patients with pyoderma associated with familial Mediterranean fever.[3] Other isolated reports include the use of low-dose colchicine in idiopathic pyoderma gangrenosum.[4]

1. Paolini O, *et al.* Treatment of pyoderma gangrenosum with colchicine. *Lancet* 1995; **345:** 1057–8.
2. Rampal P, *et al.* Colchicine in pyoderma gangrenosum. *Lancet* 1998; **351:** 1134–5.
3. Lugassy G, Ronnen M. Severe pyoderma associated with familial Mediterranean fever: favourable response to colchicine in three patients. *Am J Med Sci* 1992; **304:** 29–31.
4. Kontochristopoulos GJ, *et al.* Treatment of pyoderma gangrenosum with low-dose colchicine. *Dermatology* 2004; **209:** 233–6.

Retroperitoneal fibrosis. There are reports[1-3] of success with colchicine, with or without corticosteroids, in the treatment of retroperitoneal fibrosis (p. 1612.1).

1. Vega J, *et al.* Treatment of idiopathic retroperitoneal fibrosis with colchicine and steroids: a case series. *Am J Kidney Dis* 2009; **53:** 628–37.
2. de Socio G, *et al.* Association between familial Mediterranean fever and retroperitoneal fibrosis: retroperitoneal fibrosis regression after colchicine therapy. *Int J Immunopathol Pharmacol* 2009; **22:** 521–4.
3. de Socio G, *et al.* Effectiveness of colchicine therapy in 4 cases of retroperitoneal fibrosis associated with autoinflammatory diseases. *J Rheumatol* 2010; **37:** 1971–2.

Adverse Effects and Treatment

Colchicine has a narrow therapeutic margin, and overdosage may be serious (see p. 606.1). The most frequent adverse effects of oral colchicine are those involving the gastrointestinal tract and may be associated with its antimitotic action. Diarrhoea, nausea, vomiting, and abdominal pain are often the first signs of toxicity and are usually an indication that colchicine therapy should be stopped or the dose reduced. Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, rashes, and renal and hepatic damage.

Rarely, bone marrow depression with agranulocytosis, thrombocytopenia, and aplastic anaemia have occurred on prolonged treatment as have peripheral neuropathy, myopathy, rashes, disseminated intravascular coagulation, and alopecia. Fatal pancytopenia has been reported.

Adverse effects after intravenous use include cardiac arrhythmias and local reactions such as thrombophlebitis and neuritis. Extravasation may cause tissue necrosis.

Effects on the neuromuscular system. Colchicine-induced myoneuropathy may be a common but unrecognised condition in patients with *reduced* renal function who receive usual doses of colchicine.[1] Although both skeletal muscles and peripheral nerves are affected, myopathy is most prominent and associated axonal neuropathy is mild. The condition usually presents with proximal muscle weakness and is always accompanied by elevations in serum creatine kinase concentrations. Withdrawal of colchicine leads to spontaneous remission of these symptoms within a few weeks but resolution of the polyneuropathy is slow. Examination of proximal muscles shows marked abnormal spontaneous activity and, because of the features of the condition, it is often initially misdiagnosed as probable polymyositis or uraemic myopathy. A literature review[2] identified renal impairment as the primary risk factor for the development of colchicine-induced myopathy; dosage adjustment is advised in these patients.

There have been reports suggesting colchicine-induced myopathy may develop in patients who have *normal* renal function.

A patient with normal renal function but chronic alcohol-induced liver disease developed an unusual form of myoneuropathy after receiving only a short course of colchicine. This patient was also taking tolbutamide, the microsomal enzyme-inhibiting activity of which may have exacerbated the toxicity of colchicine.[3] A teenager with familial Mediterranean fever who had normal renal and hepatic function developed toxic myopathy due to colchicine use. Myopathy improved after colchicine was stopped and recurred when it was restarted at a lower dose.[4]

Rhabdomyolysis has also been reported.[5,6]

1. Kuncl RW, *et al.* Colchicine myopathy and neuropathy. *N Engl J Med* 1987; **316:** 1562–8.
2. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy* 2004; **24:** 1784–92.
3. Besana C, *et al.* Colchicine myoneuropathy. *Lancet* 1987; **ii:** 1271–2.

4. Sayarlioglu M, *et al*. Colchicine-induced myopathy in a teenager with familial Mediterranean fever. *Ann Pharmacother* 2003; **37:** 1821–4.
5. Chattopadhyay I, *et al*. Colchicine induced rhabdomyolysis. *Postgrad Med J* 2001; **77:** 191–2.
6. Boomershine KH. Colchicine induced rhabdomyolysis. *Ann Pharmacother* 2002; **36:** 824–6.

Effects on the reproductive system. UK licensed product information states that colchicine may adversely affect spermatogenesis under certain conditions of therapy. *Animal* data have shown that colchicine in high doses may arrest spermatogenesis and lead to azoospermia. However, in clinical practice male infertility does not seem to be common in patients given colchicine, and may be related in some cases to the underlying disease rather than the drug.[1] Similarly, although colchicine is not recommended in the first trimester of pregnancy, it may improve fertility in women with familial Mediterranean fever, and results in women who have been taking colchicine at conception and during pregnancy have been relatively reassuring[1] (see also under Pregnancy, below).

1. Mijatovic V, *et al*. Familial Mediterranean fever and its implications for fertility and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2003; **108:** 171–6.

Inappropriate administration. Intravenous use of colchicine is associated with a risk of severe or fatal adverse effects (see Administration, p. 604.2). Although unlicensed either orally or parenterally for use in back pain, intravenous colchicine has apparently been used in alternative medicine for this indication. As of February 2008, the FDA had received reports of 50 adverse events, including 23 deaths, associated with the unapproved use of intravenous colchicine. Three of the reported deaths were associated with compounded colchicine that, due to preparation errors, was 8 times more potent than the amount stated on the label. Potentially fatal effects include neutropenia, thrombocytopenia, pancytopenia, acute renal failure, and congestive heart failure.[1,2]

1. FDA. FDA takes action to stop the marketing of unapproved injectable drugs containing colchicine (issued 6th February 2008). Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01791.html (accessed 21/04/08)
2. FDA. Questions and answers about FDA's enforcement action against unapproved injectable colchicine products (issued 6th February 2008). Available at: http://www.fda.gov/cder/drug/unapproved_drugs/colchicine_qa.htm (accessed 21/04/08)

Overdosage. Colchicine has a narrow therapeutic index and is extremely toxic in overdose;[1] it has been associated with serious and fatal toxicity.[1-7] Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and the very young or very old.[1]

There is often a delay of up to 6 hours before toxicity is apparent; some features may be delayed up to 1 week or longer. Early features (which occur up to 1 day after ingestion) include nausea, vomiting, abdominal pain, and diarrhoea. Diarrhoea may be profuse and bloody, causing electrolyte disturbances and hypovolaemic shock. Features occurring after 1 to 7 days include confusion, decreased cardiac output, cardiac arrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone marrow depression. These can progress in severe cases to multiple organ damage with bone marrow aplasia, convulsions, coma, rhabdomyolysis, and disseminated intravascular coagulation.[1] Alopecia and rebound leucocytosis can occur.[3,8] A toxic epidermal necrolysis-like reaction has also been reported.[6]

The lethal dose varies: 7 mg has caused death,[8] yet recovery has occurred after much larger doses.[9-11]

In acute overdosage, the UK National Poisons Information Service (NPIS) states that the value of gut decontamination is uncertain. Oral activated charcoal 50 g can be considered for adults who have ingested more than 100 micrograms/kg within 1 hour; children who have ingested any amount of colchicine within 1 hour may be given activated charcoal 1 g/kg. Doses may be repeated every 4 hours in both adults and children, for those who have ingested more than 300 micrograms/kg, provided they are not vomiting. Gastric lavage may be an alternative in adults who present within 1 hour of a potentially life-threatening overdose. Management is mainly symptomatic and supportive, with attention given to pulse, blood pressure, and cardiac rhythm; fluid and electrolyte imbalances should be corrected. Patients are monitored for at least 6 hours after ingestion, or 12 hours if they have taken more than 300 micrograms/kg. Asymptomatic patients may then be discharged, with advice to return if gastrointestinal symptoms appear. Haemodialysis and haemoperfusion are of no benefit as they do not enhance colchicine elimination; blood and urine concentrations are of no use diagnostically.

1. MHRA/CHM. Colchicine: reminder on risk of serious and fatal toxicity in overdose. *Drug Safety Update* 2009; **3** (issue 4): 5. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con062549.pdf (accessed 05/01/11)
2. McIntyre IM, *et al*. Death following colchicine poisoning. *J Forensic Sci* 1994; **39:** 280–6.
3. Milne ST, Meek PD. Fatal colchicine overdose: report of a case and review of the literature. *Am J Emerg Med* 1998; **16:** 603–8.
4. Kubler PA. Fatal colchicine toxicity. *Med J Aust* 2000; **172:** 498–9.
5. Mullins ME, *et al*. Fatal cardiovascular collapse following acute colchicine ingestion. *J Toxicol Clin Toxicol* 2000; **38:** 51–4.
6. Arroyo MP, *et al*. Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol* 2004; **150:** 581–8.
7. Miller MA, *et al*. Colchicine-related death presenting as an unknown case of multiple organ failure. *J Emerg Med* 2005; **28:** 445–8.
8. Hood RL. Colchicine poisoning. *J Emerg Med* 1994; **12:** 171–7.
9. Baud FJ, *et al*. Brief report: treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Engl J Med* 1995; **332:** 642–5.
10. Critchley JAJH, *et al*. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol* 1997; **16:** 229–32.
11. Harris R, *et al*. Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *J Emerg Med* 2000; **18:** 435–40.

Precautions

Colchicine should be given with great care to elderly or debilitated patients who may be particularly susceptible to cumulative toxicity. It should also be used with caution in patients with cardiac, hepatic, renal, or gastrointestinal disease. Colchicine should be avoided in patients with blood disorders. It should also generally be avoided in pregnancy since it is known to be teratogenic in *animals* and there have also been some suggestions of a risk of fetal chromosome damage in humans.

Colchicine should not be given by subcutaneous or intramuscular injection as it causes severe local irritation.

Breast feeding. Colchicine is distributed into breast milk,[1-3] and some have recommended waiting for 8 hours[2] or 12 hours[3] after a dose before breast feeding to minimise exposure of the infant. However, since no adverse effects on the infant have been noted in these reports, the last available guidance from the American Academy of Pediatrics considered its use to be usually compatible with breast feeding.[4]

1. Milunsky JM, Milunsky A. Breast-feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr* 1991; **119:** 164.
2. Guillonneau M, *et al*. Colchicine is excreted at high concentrations in human breast milk. *Eur J Obstet Gynecol Reprod Biol* 1995; **61:** 177–8.
3. Ben-Chetrit E, *et al*. Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; **39:** 1213–17.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Pregnancy. Colchicine is contra-indicated in pregnancy because of *animal* teratogenicity. However, it has been used during pregnancy in women with familial Mediterranean fever (see under Uses, p. 605.1). There was no increase in abnormality rate of the newborns and no problems were detected in 130 offspring.[1]

1. Rabinovitch O, *et al*. Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. *Am J Reprod Immunol* 1992; **28:** 245–6.

Interactions

Colchicine is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these may increase colchicine blood concentrations and the potential for toxicity; life-threatening or fatal drug interactions have been reported when colchicine was given with clarithromycin, erythromycin, ciclosporin, or calcium channel antagonists such as verapamil and diltiazem. If treatment with a P-glycoprotein inhibitor, CYP3A4 inhibitors, or HIV-protease inhibitors is required in patients with normal renal and hepatic function, the colchicine dose may need to be adjusted (see Administration with Other Drugs, p. 604.3). Such combinations should be avoided in patients with renal or hepatic impairment.

Cases of myopathy and rhabdomyolysis have been reported in patients taking colchicine with statins, fibrates, ciclosporin, or digoxin.

Thiazide diuretics may increase serum uric acid and interfere with the activity of colchicine. Colchicine may impair the absorption of vitamin B_{12}.

Cardiovascular drugs. Muscle toxicity is a known adverse effect of both colchicine and statins, and there may be an increased risk if they are given together, particularly if renal function is impaired. Acute myopathy has been reported in patients with chronic renal impairment given colchicine with *fluvastatin*,[1] *pravastatin*,[2] or *simvastatin*,[3,4] while a patient[5] with nephrotic syndrome but normal renal function developed rhabdomyolysis when *atorvastatin* was added to long-standing colchicine therapy. Another patient with normal renal function developed myopathy when *lovastatin* was added to colchicine.[6] Since many statins are metabolised by the cytochrome P450 isoenzyme CYP3A4, as is colchicine, this has been proposed as one possible mechanism.[1,2,6] However, fluvastatin and pravastatin are cleared through different isoenzymes. Alternative proposed mechanisms are synergistic myopathy[1,4] or interference with transport mediated by P-glycoprotein.[2,5]

Tetraparesis developed in a patient who took colchicine with *verapamil*; this was considered to be due to a pharmacokinetic interaction which increased serum and CSF concentrations of colchicine.[7]

1. Atasoyu EM, *et al*. Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005; **39:** 1368–9.
2. Alayli G, *et al*. Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005; **39:** 1358–61.
3. Hsu W-C, *et al*. Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002; **25:** 266–8.
4. Baker SK, *et al*. Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004; **30:** 799–802.
5. Tufan A, *et al*. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. *Ann Pharmacother* 2006; **40:** 1466–9.
6. Torgovnick J, *et al*. Colchicine and HMG Co-A reductase inhibitors induced myopathy—a case report. *Neurotoxicology* 2006; **27:** 1126–7.
7. Tröger U, *et al*. Tetraparesis associated with colchicine is probably due to inhibition by verapamil of the P-glycoprotein efflux pump in the blood-brain barrier. *BMJ* 2005; **331:** 613. Correction. *ibid*. 2006; **332:** 882.

Ciclosporin. There is a need for caution if colchicine is used with ciclosporin. Myopathies or rhabdomyolysis[1] may be a problem, especially in transplant patients[2] or those with renal impairment.[3] In addition, increased blood-ciclosporin concentrations and nephrotoxicity developed in a renal transplant patient after the introduction of colchicine therapy.[4]

1. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; **337:** 915.
2. Simkin PA, Gardner GC. Colchicine use in cyclosporine treated transplant recipients: how little is too much? *J Rheumatol* 2000; **27:** 1334–7.
3. Rumpf KW, Henning HV. Is myopathy in renal transplant patients induced by cyclosporin or colchicine? *Lancet* 1990; **335:** 800–1.
4. Menta R, *et al*. Reversible acute cyclosporin nephrotoxicity induced by colchicine administration. *Nephrol Dial Transplant* 1987; **2:** 380–1.

Grapefruit juice. Near-fatal colchicine toxicity occurred in an 8-year-old girl with familial Mediterranean fever who was also drinking large quantities of grapefruit juice daily.[1]

1. Goldbart A, *et al*. Near fatal acute colchicine intoxication in a child: a case report. *Eur J Pediatr* 2000; **159:** 895–7.

Macrolides. Life-threatening or fatal colchicine toxicity has been reported with use of colchicine and clarithromycin[1,2] or erythromycin.[3] A FDA analysis of safety data found that about half of the reported deaths associated with therapeutic oral doses of colchicine involved patients who were also taking clarithromycin.[4] A retrospective study in 116 patients given both drugs concluded that clarithromycin increased the risk of colchicine toxicity, especially in those patients with renal impairment, and that the two drugs should not be used together.[5]

1. Dogukan A, *et al*. Acute fatal colchicine intoxication in a patient on continuous ambulatory peritoneal dialysis (CAPD): possible role of clarithromycin administration. *Clin Nephrol* 2001; **55:** 181–2.
2. Rollot F, *et al*. Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004; **38:** 2074–7.
3. Caraco Y, *et al*. Acute colchicine intoxication—possible role of erythromycin administration. *J Rheumatol* 1992; **19:** 494–6.
4. FDA. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys) (issued 30th July, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm (accessed 10/09/09)
5. Hung IFN, *et al*. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005; **41:** 291–300.

Tolbutamide. For a suggestion that tolbutamide may have exacerbated the toxicity of colchicine in a patient with liver disease, see under Effects on the Neuromuscular System, p. 605.3.

Pharmacokinetics

Peak plasma concentrations of colchicine occur within 2 hours of oral use. Absolute bioavailability is reported to be about 45%. The absorption of colchicine from the gastrointestinal tract is thought to be limited by its expulsion by P-glycoprotein, for which colchicine is a substrate. Absorbed colchicine is found in high concentrations in the kidney, liver, and spleen. It is demethylated in the liver via the cytochrome P450 isoenzyme CYP3A4 to 2 primary metabolites, 2-*O*-demethylcolchicine and 3-*O*-demethylcolchicine (2-DMC and 3-DMC, respectively), and 1 minor metabolite, 10-*O*-demethylcolchicine (also known as colchiceine). Plasma concentrations of metabolites are minimal. Enterohepatic recycling occurs. The main route of elimination is hepatobiliary excretion in the faeces. Renal excretion accounts for 10 to 20% of colchicine elimination in patients with normal renal function. The mean elimination half-life is about 28 hours. Colchicine crosses the placenta and is distributed into breast milk.

References.

1. Rochdi M, *et al*. Pharmacokinetics and absolute bioavailability of colchicine after iv and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol* 1994; **46:** 351–4.
2. Ferron GM, *et al*. Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol* 1996; **36:** 874–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Xuric; ***Austral.***: Colgout; Lengout; ***Braz.***: Cixin; Cocichimil; Colchin; Colchis; Colcitrat; Colzuric; ***Hong Kong***: Colcina; Colgout; CP-Colchi; ***Hung.***: Colchicum-Dispert; ***India***: Colchicindon; Coljoy; Goutnil; ***Indon.***: Recolfar; ***Mex.***: Colchiquim; Sixol; Ticolcin; ***NZ***: Colgout; ***Philipp.***: Goutnil; ***Thai.***: Cochic; Colchily; Colcine; Colcitex; Gouticine; Koji; Prochic; Tolchicine; Zoric; ***Turk.***: Colchicum-Dispert; Kolsin; ***USA***: Colcrys.

Multi-ingredient Preparations. ***Arg.***: Artrex; Colchimax; Colpuril; Xuric-A; ***Fr.***: Colchimax; ***Mex.***: Butayonacol; ***Spain***: Colchimax; ***USA***: ColBenemid.

Homoeopathic Preparations. ***Ger.***: Anore rheumat; Cefarheumin S†.

Pharmacopoeial Preparations
BP 2014: Colchicine Tablets;
USP 36: Colchicine Injection; Colchicine Tablets; Probenecid and Colchicine Tablets.

Colchicum

Colchico; Colchique; Безвременник.
UNII — 7SUW9D360K.

Profile

Colchicum, the dried ripe seeds or dried corm of the meadow saffron, *Colchicum autumnale*, contains colchicine (p. 604.1) and has been used similarly for the prophylaxis and relief of acute gout.

It is also included in several herbal preparations.

Homoeopathy

Colchicum has been used in homoeopathic medicines under the following names: Colchicinum; Colchicum autumnale; Colchicum, tuber; Colch. at.

Poisoning. *Colchicum autumnale* is quite similar to a species of garlic *Allium ursinum*, especially in leaf appearance, and both plants grow in the same areas at the same time of year. There are reports of colchicine poisoning, some of them fatal, after accidental ingestion of *C. autumnale*.[1-6] Colchicine poisoning should be considered in patients with gastroenterocolitis after a wild plant meal.

1. Brnčić N, *et al.* Accidental plant poisoning with Colchicum autumnale: report of two cases. *Croat Med J* 2001; **42:** 673–5.
2. Sannohe S, *et al.* Colchicine poisoning resulting from accidental ingestion of meadow saffron (Colchicum autumnale). *J Forensic Sci* 2002; **47:** 1391–6.
3. Gabrscek L, *et al.* Accidental poisoning with autumn crocus. *J Toxicol Clin Toxicol* 2004; **42:** 85–8.
4. Brvar M, *et al.* Case report: fatal poisoning with Colchicum autumnale. *Crit Care* 2004; **8:** R56–R59.
5. Brvar M, *et al.* Acute poisoning with autumn crocus (Colchicum autumnale L.). *Wien Klin Wochenschr* 2004; **116:** 205–8.
6. Sundov Z, *et al.* Fatal colchicine poisoning by accidental ingestion of meadow saffron-case report. *Forensic Sci Int* 2005; **149:** 253–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Colchysat.

Multi-ingredient Preparations. ***Chile***: Uroknop; ***Ger.***: Unguentum lymphaticum†; ***Neth.***: Diarrheel S; ***Venez.***: Linfoderm.

Homoeopathic Preparations. ***Austria***: Colchicum Med Complex; Daram; Pulsatilla Med Complex; ***Canad.***: Arnica-Heel Comp†; Arthflex; Homeo-Form AR†; Hyalgesic LBP†; Indigestion†; Renelix; ***Chile***: Arnica Compuesta; Artroplex; ***Fr.***: Basilicum Complexe No 96; Berberis Complexe No 83; L 8; Ledum Complexe No 81; Momordica Complexe No 109†; Rhus Toxicodendron Complexe No 80; Urarthone; ***Ger.***: Alho-Arthrosan N; Arthrorell N; Berberis N Oligoplex; Colchicum Complex; Doloject; G1-Injektopas; Gelenk Albin; Girheulit НМ†; Girheulit HOM; Harnsauretropfen F; Hewerheum N†; Lymphdiaral; Poly-Arthrisan M; Rheucostan R; rheuma-loges; Rheuma-Pasc; Rheuma-Pasc; Rheumodoron 2; Uro Albin; ***Neth.***: Apo-Rheum†; Apo-STOM; Reudol; ***Rus.***: Rhus-Plus (Рус-Плюс); ***Ukr.***: Homvio-Reuman (Хомвио-Ревман).

Febuxostat *(BAN, USAN, rINN)*

Febuxostatum; TMX-67; Фебуксостат.
2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.
$C_{16}H_{16}N_2O_3S$=316.4
CAS — 144060-53-7.
ATC — M04AA03.
ATC Vet — QM04AA03.
UNII — 101V0R1N2E.

Uses and Administration

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase. It is used for the treatment of hyperuricaemia in patients with chronic gout. In the EU, the recommended oral dose is 80 mg once daily. If the serum uric acid is above 6 mg per 100 mL after 2 to 4 weeks, the dose may be increased to 120 mg once daily. In the USA, febuxostat 40 mg once daily is given initially; if the serum uric acid is 6 mg per 100 mL or above after 2 weeks, the dose may be increased to 80 mg once daily.

Initially, febuxostat may increase plasma concentrations of urate and uric acid, and treatment should not be started until an acute attack of gout has completely subsided; an NSAID or colchicine should be given for at least 6 months after starting febuxostat.

For dosage recommendations in hepatic and renal impairment, see below.

Administration in hepatic impairment. Exposure to febuxostat did not change significantly in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment compared with subjects with normal hepatic function.[1] EU licensed product information states that the recommended oral dose of febuxostat in patients with mild hepatic impairment is 80 mg daily. No dose recommendations are given for moderate impairment; efficacy and safety of febuxostat has not been studied in those with severe (Child-Pugh class C) hepatic impairment. In the USA, no dosage adjustment is considered necessary for mild or moderate hepatic impairment; caution is advised in severe impairment due to a lack of data.

1. Khosravan R, *et al.* The effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2006; **46:** 88–102.

Administration in renal impairment. In patients with mild, moderate, or severe renal impairment, peak plasma concentrations of febuxostat did not alter, relative to those with normal renal function; however, the mean area under the concentration-time curve was increased in those with severe renal impairment. EU and US licensed product information state that no dosage adjustments are considered necessary in those with mild or moderate renal impairment, but that efficacy and safety have not been evaluated in those with severe renal impairment (creatinine clearance of less than 30 mL/min).

A study[1] found that although exposure to febuxostat and its metabolites was generally higher in subjects with increasing degrees of renal impairment, decreases in uric acid were comparable regardless of renal function.

1. Mayer MD, *et al.* Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther* 2005; **12:** 22–34.

Gout. The use of febuxostat in gout has been reviewed.[1-4] Studies have shown febuxostat to be more effective than allopurinol at lowering the serum uric acid concentration; however, the dose of allopurinol was fixed and not titrated, so the efficacy of febuxostat compared with optimal use of allopurinol is unknown.[5] While febuxostat has generally been well tolerated,[6] it has been associated with more gout flares when compared with allopurinol, despite prophylaxis, leading to more withdrawals from treatment.[5] Concerns have also been raised about elevations in liver enzyme concentrations and a trend towards a higher rate of death and cardiovascular events compared with allopurinol therapy.[6] An international position paper[6] and NICE[7] both recommend that the use of febuxostat be restricted to those patients who are intolerant of allopurinol or for whom allopurinol is either contra-indicated or ineffective.

1. Bruce SP. Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. *Ann Pharmacother* 2006; **40:** 2187–94.
2. Hair PI, *et al.* Febuxostat. *Drugs* 2008; **68:** 1865–74.
3. Ernst ME, Fravel MA. Febuxostat: a selective xanthine-oxidase/xanthine-dehydrogenase inhibitor for the management of hyperuricemia in adults with gout. *Clin Ther* 2009; **31:** 2503–18.
4. Schlesinger N. New agents for the treatment of gout and hyperuricemia: febuxostat, puricase, and beyond. *Curr Rheumatol Rep* 2010; **12:** 130–4.
5. Anonymous. Febuxostat for gout. *Drug Ther Bull* 2010; **48:** 78–82.
6. Jansen TL, *et al.* International position paper on febuxostat. *Clin Rheumatol* 2010; **29:** 835–40.
7. NICE. Febuxostat for the management of hyperuricaemia in people with gout (TA164, issued December 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA164Guidance.pdf (accessed 07/01/09)

Adverse Effects

The most common adverse effects of febuxostat are liver function abnormalities, diarrhoea, headache, nausea, and rashes. Liver function should be monitored periodically; hepatitis and gallstones have also been reported. Less commonly reported effects include gastrointestinal adverse effects such as abdominal pain and constipation, fatigue, oedema, thirst, hemiparesis, Guillain-Barré syndrome, agitation, depression, flushing, dizziness, paraesthesia, somnolence, insomnia, altered taste, tinnitus, vertigo, hearing loss, blurred vision, hypersensitivity, herpes zoster infection, electrolyte disturbances, hyperglycaemia, hyperlipidaemia, diabetes mellitus, renal failure, nephrolithiasis, haematuria, urinary frequency, dermatitis, urticaria, pruritus, altered skin pigmentation, photosensitivity, and musculoskeletal effects such as arthralgia and myalgia. Blood disorders include anaemia, leucopenia, and thrombocytopenia. Abnormal coagulation tests have occurred. Thromboembolic events such as myocardial infarction and stroke have been reported, as have arrhythmias, angina, hypotension, hypertension, and palpitations. Respiratory adverse effects include cough, bronchitis, dyspnoea, and upper respiratory-tract infections. Erectile dysfunction, breast pain, and gynaecomastia have occurred. Alterations in hair colour and growth pattern have been reported, as has alopecia.

Precautions

Febuxostat therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Febuxostat is not recommended for the control of hyperuricaemia secondary to malignant disease or cancer chemotherapy. Treatment in patients with ischaemic heart disease or congestive heart failure is not recommended.

Interactions

Inhibition of xanthine oxidase is known to increase concentrations of mercaptopurine or azathioprine, so use of febuxostat with these drugs is not recommended. Similarly, caution is advised when febuxostat is given with theophylline, and theophylline concentrations should be monitored.

Febuxostat is metabolised via the uridine diphosphate glucuronosyltransferase enzyme system, and inhibitors or inducers of this system might affect exposure to febuxostat. Serum uric acid should be monitored 1 to 2 weeks after starting treatment with a potent inducer of glucuronidation.

Pharmacokinetics

Febuxostat is rapidly and well absorbed after oral doses. Although dosage with a high-fat meal decreases peak plasma concentration and exposure, this is not thought clinically significant, and febuxostat may be taken with or without food. Plasma protein binding is about 99%. Febuxostat is extensively metabolised by conjugation via the uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system, and by oxidation via the cytochrome P450 isoenzyme system; active metabolites are formed mainly by UGT1A1, UGT1A8, UGT1A9, and by CYP1A1, CYP1A2, CYP2C8, or CYP2C9. Febuxostat has a mean terminal half-life of about 5 to 8 hours. About half of a dose is excreted via the urine, and the other half via the faeces.

References.

1. Khosravan R, *et al.* Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin Pharmacokinet* 2006; **45:** 821–41.
2. Khosravan R, *et al.* The effect of age and gender on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2008; **48:** 1014–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Adenuric; ***Canad.***: Uloric; ***Cz.***: Adenuric; ***Fr.***: Adenuric; ***Ger.***: Adenuric; ***Gr.***: Adenuric; ***Irl.***: Adenuric; ***Ital.***: Adenuric; ***Jpn***: Feburic; Uloric†; ***Neth.***: Adenuric; ***Port.***: Adenuric; ***Spain***: Adenuric; ***UK***: Adenuric; ***USA***: Uloric.

Probenecid *(BAN, rINN)* ⊗

Probenecidas; Probénécide; Probenecidum; Probenesid; Probenesidi; Пробенецид.
4-(Dipropylsulphamoyl)benzoic acid.
$C_{13}H_{19}NO_4S$=285.4
CAS — 57-66-9.
ATC — M04AB01.
ATC Vet — QM04AB01.
UNII — PO572Z7917.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Probenecid). A white or almost white crystalline powder or small crystals. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone.

USP 36: (Probenecid). A white or practically white, fine, practically odourless, crystalline powder. Practically insoluble in water and in dilute acids; soluble in alcohol, in acetone, in chloroform, and in dilute alkali.

Uses and Administration

Probenecid is a uricosuric drug used to treat hyperuricaemia (p. 600.1) associated with chronic gout; it has also been used to treat hyperuricaemia caused by diuretic therapy. It is also used as an adjunct to some antibacterials to reduce their renal tubular excretion and is given with the antiviral cidofovir to reduce nephrotoxicity.

Probenecid is used in **chronic gout and hyperuricaemia** to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. Probenecid is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production, and is not used for hyperuricaemia associated with cancer or cancer therapy.

Probenecid has no analgesic or anti-inflammatory action and is of no value in acute gout. Initially it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence probenecid should not be started until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

It is usual to start treatment for gout with oral doses of 250 mg twice daily increased after a week to 500 mg twice daily and later, if the therapeutic effects are inadequate, by increments of 500 mg every 4 weeks, up to 2 g daily. Probenecid may not be effective in chronic renal impairment particularly when the glomerular filtration rate is less than 30 mL/minute. An adequate fluid intake is required to reduce the risk of uric acid renal calculi.

When the patient has been free from acute attacks for at least 6 months, and provided that the plasma-urate concentration is within acceptable limits, the daily dose may be gradually reduced, by 500 mg every 6 months, to the lowest effective maintenance dose which is then given indefinitely.

Probenecid may also be used as an **adjunct to antibacterial therapy** particularly when treating severe or resistant infections. It reduces the tubular excretion of penicillins and most cephalosporins and may increase their plasma concentrations up to fourfold. The usual dosage for reducing tubular excretion of penicillins and cephalosporins is 500 mg four times daily, or less in elderly patients with suspected renal impairment. When renal impairment is sufficient to retard the excretion of antibacterials, probenecid should not be given.

For doses in children, see Administration in Children, below.

Single oral doses of probenecid 1 g are given with a suitable oral antibacterial, or at least 30 minutes before an injected antibacterial, in the single-dose treatment of gonorrhoea (p. 204.2).

Doses of probenecid to be used with cidofovir are given on p. 970.1.

Administration in children. For children aged 2 years of age or older and weighing 50 kg or less, the recommended oral dose of probenecid is 25 mg/kg (or 700 mg/m^2) initially, followed by 40 mg/kg (or 1.2 g/m^2) daily, given in 4 divided doses. For children weighing more than 50 kg, the usual adult dose is recommended (see Uses and Administration, above).

Adverse Effects and Treatment

Probenecid may cause nausea, vomiting, anorexia, headache, sore gums, flushing, alopecia, dizziness, anaemia, and urinary frequency. Hypersensitivity reactions, with fever, dermatitis, pruritus, urticaria, and, rarely, anaphylaxis, and Stevens-Johnson syndrome have occurred. There have been reports of leucopenia, hepatic necrosis, nephrotic syndrome, and aplastic anaemia. Haemolytic anaemia has also occurred, and may be associated with G6PD deficiency.

When used in chronic gout, and particularly during the first few months of therapy, probenecid may precipitate acute attacks. Uric acid renal calculi, with or without haematuria, costovertebral pain and renal colic may occur.

In massive overdosage probenecid causes stimulation of the CNS, with convulsions and death from respiratory failure. Severe overdosage should be managed by lavage and symptomatic treatment.

Precautions

Probenecid therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Probenecid is also unsuitable for the control of hyperuricaemia secondary to cancer or cancer chemotherapy. Probenecid should not be given to patients with a history of uric acid renal calculi or blood disorders. It should be used with caution in patients with a history of peptic ulceration. Probenecid should not be used as an antibacterial adjunct in patients with known renal impairment, and it is ineffective in gout in patients with severe renal impairment.

To reduce the risk of uric acid renal calculi in patients with gout an adequate fluid intake (2 to 3 litres daily) is required, and, if necessary, especially during the first few months of treatment, sodium bicarbonate or potassium citrate may be given to render the urine alkaline.

A reducing substance has been found in the urine of some patients taking probenecid, and may give false positive results with some tests for glucose in the urine. Probenecid reduces the excretion of some iodinated contrast media and may interfere with laboratory tests by decreasing the excretion of aminohippuric acid, phenolsulfonphthalein, and sulfobromophthalein.

Abuse. It has been alleged that some athletes using banned anabolic steroids have taken probenecid in an attempt to inhibit the urinary excretion of steroid metabolites in order to avoid detection by urine screening tests.[1] The World Anti-Doping Agency includes probenecid among substances prohibited for use by athletes in and out of competition.

1. Anonymous. Does probenecid mask steroid use? *Pharm J* 1987; **239**: 299.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies probenecid as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

The dose of probenecid may need to be increased if patients are also given drugs, such as diuretics or pyrazinamide, that increase the blood concentration of uric acid. Salicylates, including aspirin, and probenecid are mutually antagonistic and should not be given together.

Probenecid may also affect many other drugs. By inhibiting renal tubular secretion, it has the potential to increase the toxicity and/or to enhance the therapeutic efficacy of drugs excreted by that route. In some instances a reduction in dose is essential to counteract an increase in toxicity, as is the case with methotrexate. Some combinations, such as that with ketorolac, should be avoided. Conversely, probenecid may be given with some antibacterials such as the penicillins and cephalosporins to increase their effects.

Altered excretion may also increase serum concentrations of other antibacterials (aminosalicylic acid, conjugated sulfonamides, dapsone, meropenem, some quinolones, rifampicin), some antivirals (aciclovir, ganciclovir, zalcitabine, zidovudine, and possibly famciclovir), some benzodiazepines (adinazolam, lorazepam, and nitrazepam), some ACE inhibitors (captopril and enalapril), some NSAIDs (diflunisal, indometacin, ketoprofen, meclofenamate, naproxen), paracetamol, and sulfonylurea hypoglycaemic drugs. The clinical significance of such interactions is not entirely clear although the possibility of the need for a reduction in dosage of these drugs should be borne in mind.

It has been reported that patients receiving probenecid require lower doses of thiopental for induction of anaesthesia. Probenecid may increase the speed of induction of anaesthesia with midazolam.

Reducing the urinary concentration of some drugs could diminish their activity in certain diseases as might happen with nitrofurantoin or some quinolones in urinary-tract infections and penicillamine in cystinuria.

Allopurinol. Probenecid may increase the clearance of allopurinol despite an increased hypouricaemic effect when these 2 drugs are given together (see Antigout Drugs, under Allopurinol, p. 603.1).

Pharmacokinetics

Probenecid is completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after a dose. It is extensively bound to plasma proteins (85 to 95%). The plasma half-life is dose-dependent and ranges from less than 5 to more than 8 hours. Probenecid crosses the placenta. It is metabolised by the liver, and excreted in the urine mainly as metabolites. Excretion of unchanged probenecid is increased in alkaline urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Pro-Cid; ***Canad.***: Benuryl; ***Fr.***: Benemide; ***Gr.***: Benemid†; ***India***: Bencid; ***Mex.***: Benecid; ***Norw.***: Probecid; ***S.Afr.***: Proben; ***Swed.***: Probecid; ***Switz.***: Santuril; ***Thai.***: Benacid; Bencid; Benecid; Benemid; ***USA***: Benemid†.

Multi-ingredient Preparations. ***China***: Zhuo Tong (卓彤); ***India***: Alcephin-LA; Ampilong; Cefalong-DS; Ceff-LA; Dax-LA; Himox Plus; ***USA***: ColBenemid.

Used as an adjunct in:. *Braz.*: Emicilin; Gonol; ***China***: Ai Luo Di (艾罗迪); En Pu Luo (恩普洛); ***India***: Moxylong; Mydrox.

Pharmacopoeial Preparations

BP 2014: Probenecid Tablets;

USP 36: Ampicillin and Probenecid for Oral Suspension; Probenecid and Colchicine Tablets; Probenecid Tablets.

Sulfinpyrazone *(BAN, rINN)*

G-28315; Sulfinpirazona; Sulfinpirazonas; Sulfinpyratsoni; Sulfinpyrazon; Sulfinpyrazonum; Sulphinpyrazone; Sulphoxyphenylpyrazolidine; Szulfinpirazon; Сульфинпиразон.

1,2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3,5-dione.

$C_{23}H_{20}N_2O_3S$=404.5

CAS — 57-96-5.

ATC — M04AB02.

ATC Vet — QM04AB02.

UNII — V6OFU47K3W.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulfinpyrazone). A white or almost white powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Sulfinpyrazone). A white to off-white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol and in acetone; sparingly soluble in dilute alkali.

Uses and Administration

Sulfinpyrazone is a uricosuric drug used to treat hyperuricaemia associated with chronic gout (p. 600.1). It also has some antiplatelet activity and has been used in thromboembolic disorders.

Sulfinpyrazone inhibits the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. It is therefore used in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production and is not suitable for hyperuricaemia associated with cancer or cancer therapy.

Sulfinpyrazone has little analgesic or anti-inflammatory action and is of no value in acute gout. Initially, it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence sulfinpyrazone should not be given until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

The initial oral dose of sulfinpyrazone in the UK is 100 to 200 mg daily, taken with meals or milk. This may be gradually increased over 2 to 3 weeks until a daily dosage of 600 mg is reached; up to 800 mg daily may be given if necessary. After the plasma-urate concentration has been controlled, the daily maintenance dose may be reduced to as low as 200 mg. An adequate fluid intake is required to prevent formation of uric acid renal calculi.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of sulfinpyrazone involve the gastrointestinal tract, and include nausea, vomiting, diarrhoea and abdominal pain. It may cause gastric bleeding or aggravate existing peptic ulcers. Rashes have been reported, and may be associated with a hypersensitivity reaction. Aplastic anaemia, agranulocytosis, leucopenia, and thrombocytopenia have been reported rarely as have raised liver enzyme values, jaundice, and hepatitis, renal impairment, salt and water retention, and acute renal failure.

Sulfinpyrazone should not be started during an acute attack of gout; however, treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. When used in chronic gout, particularly during the first few months of treatment, sulfinpyrazone may precipitate acute attacks and there is a risk of uric acid renal calculi developing. To reduce the risk of uric acid renal calculi an adequate fluid intake (2 to 3 litres daily) is required; alkalinising the urine with sodium bicarbonate or potassium citrate may also be considered.

Sulfinpyrazone should be given with care to patients with renal impairment or heart failure and is contra-indicated in those with severe renal or hepatic impairment. It is also contra-indicated in patients with blood dyscrasias or blood coagulation disorders, and in patients with uric acid renal calculi or peptic ulcer disease or a history of such disorders. It is recommended that patients

have periodic full blood counts to detect any haematological abnormalities.

Sulfinpyrazone should not be given to patients hypersensitive to it or to other pyrazole derivatives such as phenylbutazone; nor should it be given to patients in whom hypersensitivity reactions (including bronchospastic reactions in asthmatics) have been provoked by aspirin or by other drugs with prostaglandin-synthetase inhibiting activity.

Renal-function tests involving aminohippuric acid or phenolsulfonphthalein may be invalidated.

Interactions

Doses of sulfinpyrazone may need to be increased if it is given with other drugs, such as diuretics or pyrazinamide, that increase uric acid concentrations. Sulfinpyrazone and salicylates including aspirin are mutually antagonistic and should not be used together. There may also be an increased risk of bleeding when sulfinpyrazone is used with other drugs such as aspirin that inhibit platelet function.

Sulfinpyrazone's renal tubular secretion is inhibited by probenecid although with little clinical effect. Since sulfinpyrazone, like probenecid, inhibits the tubular secretion of weak organic acids, interactions can be expected with penicillins although the effect is not considered to be clinically useful.

Sulfinpyrazone can potentiate the action of some drugs. The most significant interaction of this type involves warfarin, acenocoumarol, and possibly other coumarin anticoagulants (p. 1532.2). Patients receiving sulfinpyrazone and such an anticoagulant should have their prothrombin times monitored and the anticoagulant dosage reduced as appropriate. Similarly, sulfinpyrazone may potentiate the effects of phenytoin (see Antigout Drugs, p. 543.3), and possibly some sulfonamides and sulfonylureas.

In contrast, sulfinpyrazone may increase the metabolism of theophylline (p. 1235.2) and diminish its activity.

Pharmacokinetics

Sulfinpyrazone is readily absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins and has a plasma half-life of about 2 to 4 hours. Sulfinpyrazone is partly metabolised in the liver and some of the metabolites are active. On long-term therapy, sulfinpyrazone induces its own metabolism. Unchanged drug and metabolites are mainly excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Eryfrace; ***Ital.***: Enturen; ***Philipp.***: Sulfin; ***Thai.***: Sulfin; ***UK***: Anturan†; ***USA***: Anturane†.

Pharmacopoeial Preparations
BP 2014: Sulfinpyrazone Tablets;
USP 36: Sulfinpyrazone Capsules; Sulfinpyrazone Tablets.

Tisopurine *(rINN)*

MPP; Thioallopurinol; Thiopurinol; Tisopurina; Tisopurinum; Тизопурин.

1*H*-Pyrazolo[3,4-*d*]pyrimidine-4-thiol.

$C_5H_4N_4S$=152.2

CAS — 5334-23-6.
ATC — M04AA02.
ATC Vet — QM04AA02.
UNII — 79F9I2R16M.

Profile

Tisopurine, an analogue of allopurinol, is an inhibitor of uric acid synthesis. It is used orally in the treatment of disorders associated with hyperuricaemia (p. 600.1), including gout, in doses of 100 to 400 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Exuracid.

Urate Oxidase

CB-8129; Urato oxidasa; Uricasa; Uricase; Уратоксидаза.

CAS — 9002-12-4.
ATC — M04AX01.
ATC Vet — QM04AX01.

Pegloticase *(USAN, rINN)*

Pegloticasa; Pègloticase; Pegloticasum; Пэглотиказа.

CAS — 885051-90-1.
ATC — M04AX02.
ATC Vet — QM04AX02.
UNII — R581OT55EA.

Rasburicase *(BAN, USAN, rINN)*

Rasburicasa; Rasburicasum; Rasburikaasi; Rasburikas; Rasburikaz; SR-29142; Разбуриказа.

CAS — 134774-45-1.
ATC — V03AF07.
ATC Vet — QV03AF07.
UNII — 08GY9K1EUO.

Description. Rasburicase is a recombinant form of the enzyme urate oxidase.

Uses and Administration

Rasburicase is a recombinant form of the enzyme urate oxidase, which oxidises uric acid to allantoin. It is used in the treatment and prophylaxis of severe hyperuricaemia (p. 600.1) associated with the treatment of malignancy. Rasburicase is diluted to a final volume of 50 mL with sodium chloride 0.9%, and given by intravenous infusion over 30 minutes. The recommended dose is 200 micrograms/kg as a single daily dose. Duration of treatment may vary from 5 to 7 days.

For doses in children, see Administration in Children, below.

Pegloticase is a recombinant, pegylated form of the enzyme urate oxidase. It is used for the treatment of chronic gout that is refractory to conventional urate-lowering therapy. Pegloticase is diluted in 250 mL of sodium chloride (0.45 or 0.9%) and given by intravenous infusion over not less than 2 hours. The recommended dose is 8 mg every 2 weeks.

The native form of urate oxidase has also been used.

Administration in children. Rasburicase is used in children for the treatment and prophylaxis of severe hyperuricaemia associated with treatment of malignancy in the same dose as for adults (see Uses and Administration, above). For further discussion of its use in children with tumour lysis syndrome, see below.

Gout. Rasburicase has been used successfully to treat gout in patients allergic to allopurinol.[1,2] Pegloticase has also successfully reduced plasma-urate concentrations in patients with treatment-resistant disease,[3,4] although more evidence is needed to assess its risks and benefits.[5]

1. Vogt B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol Dial Transplant* 2005; **20:** 431–3.
2. Richette P, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol* 2006; **2:** 338–42.
3. Sundy JS, *et al.* Pegloticase Phase 2 Study Investigators. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. *Arthritis Rheum* 2008; **58:** 2882–91.
4. Reinders MK, Jansen TL. New advances in the treatment of gout: review of pegloticase. *Ther Clin Risk Manag* 2010; **6:** 543–50.
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Tumour lysis syndrome. The tumour lysis syndrome (p. 730.2) represents a biochemical disturbance after massive release of cellular breakdown products from tumour cells sensitive to therapy; hyperuricaemia is a cardinal feature. Rasburicase was effective in the prophylaxis or treatment of hyperuricaemia in children and young adults with leukaemia or lymphoma who either presented with abnormally high plasma concentrations of uric acid or had large tumour cell burdens.[1] Treatment was mostly well tolerated; one patient developed nausea and vomiting and one experienced bronchospasm and hypoxaemia 3 hours after infusion. Antibodies to rasburicase were seen in 17 of 121 assessable patients. Safety and efficacy were confirmed in further studies of children[2] and adults[2,3] considered to be at particularly high risk of tumour lysis syndrome. In children[4] with haematologic malignancies at high risk for tumour lysis, rasburicase given intravenously achieved more rapid control and lower levels of plasma uric acid than oral allopurinol. No antibodies to rasburicase were detected at day 14. In 3 children with acute lymphoblastic leukaemia, hyperuricaemia was reportedly controlled with oral allopurinol and a single dose of rasburicase, although subclinical tumour lysis was apparent.[5] Rasburicase has also been used for tumour lysis syndrome in neonates. One infant was given a single dose of rasburicase after 2 days of induction chemotherapy for neuroblastoma, started on day 21 of life; serum urate normalised and chemotherapy was completed without further incident. A second infant, with acute lymphoblastic leukaemia and renal dysfunction, presented with tumour lysis syndrome, and had 6 doses of intravenous rasburicase plus aggressive supportive therapy, but died of complications on day 7 of life.[6] Reviews[7,8] have concluded that rasburicase is highly effective at decreasing uric acid concentrations rapidly and thoroughly; there is some suggestion that shorter durations of treatment (between 1 and 3 days as opposed to 5 days) may be sufficient even in high-risk patients.

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Adverse Effects and Treatment

The most serious adverse effects of rasburicase involve hypersensitivity reactions, including anaphylaxis, rashes, bronchospasm, rhinitis, urticaria, hypotension, dyspnoea, arthralgia, peripheral oedema, and chest pain and tightness. Haemolysis and methaemoglobinaemia have also been reported. Rasburicase can interfere with uric acid measurements. Other adverse effects are nausea, vomiting, abdominal pain, constipation, diarrhoea, headache, fever, respiratory distress, sepsis, and mucositis. Pulmonary haemorrhage, arrhythmias, and coronary artery disorders have also been reported.

Hypersensitivity reactions including anaphylaxis due to pegloticase can be serious. Infusion reactions, despite pretreatment with corticosteroids and antihistamines, are common. Gout flares can occur, especially upon starting therapy, and prophylaxis with an NSAID or colchicine is recommended, starting 1 week before pegloticase and continuing for at least 6 months, unless contra-indicated or not tolerated. Exacerbation of congestive cardiac failure has been reported. Other adverse effects include gastrointestinal disturbances, and chest pain.

Precautions

Treatment with rasburicase should be immediately and permanently stopped if hypersensitivity reactions, methaemoglobinaemia, or haemolysis develop. Rasburicase is contra-indicated in patients with G6PD deficiency or other cellular metabolic disorders known to cause haemolytic anaemia; hydrogen peroxide, which is produced during oxidation of uric acid to allantoin, can induce haemolytic anaemia in these patients. Patients at higher risk of having G6PD deficiency should be screened before receiving rasburicase.

The risk for anaphylaxis and infusion reactions in patients given pegloticase is higher in those whose uric acid concentration increases to above 6 mg per 100 mL, especially if two consecutive readings above this concentration are seen; serum uric acid should be monitored and treatment possibly stopped if increases above this level occur. Patients should be pretreated with antihistamines and corticosteroids, and pegloticase infused slowly over no less than 2 hours. Caution is recommended when treating patients with congestive cardiac failure.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rasburicase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fasturtec; ***Austria***: Fasturtec; ***Belg.***: Fasturtec; ***Braz.***: Fasturtec; ***Canad.***: Fasturtec; ***Cz.***: Fasturtec; ***Denm.***: Fasturtec; ***Fin.***: Fasturtec; ***Fr.***: Fasturtec; ***Ger.***: Fasturtec; ***Gr.***: Fasturtec; ***Hong Kong***: Fasturtec; ***Hung.***: Fasturtec; ***Irl.***: Fasturtec; ***Ital.***: Fasturtec; ***Neth.***: Fasturtec; ***Norw.***: Fasturtec; ***NZ***: Fasturtec; ***Pol.***: Fasturtec; ***Port.***: Fasturtec; ***Singapore***: Fasturtec; ***Spain***: Fasturtec; ***Swed.***: Fasturtec; ***Switz.***: Fasturtec; ***Turk.***: Fasturtec; ***UK***: Fasturtec; ***USA***: Elitek; Krystexxa; ***Venez.***: Fasturtec.

Antihistamines

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The peripheral effects of histamine are chiefly mediated by 2 sets of receptors termed H_1 and H_2. Effects mediated by the H_1 receptors include the contraction of smooth muscle and the dilatation and increased permeability of the capillaries. The effects of histamine on vascular smooth muscle are mediated by H_2 as well as H_1 receptors. Other effects that are mediated by H_2 receptors include cardiac accelerating effects and, in particular, the stimulating action of histamine on the secretion of gastric acid. An H_3 receptor has also been identified in several systems including the CNS and peripheral nerves. It is thought that H_3 receptors are involved in the autoregulation of the release of histamine and other neurotransmitters from neurones. More recently, a H_4-receptor has been discovered.

The term 'antihistamines' is normally reserved for histamine H_1-antagonists and this is the convention used in *Martindale*. H_2-antagonists, typified by cimetidine (p. 1830.1), are described in the chapter on Gastrointestinal Drugs. H_3-antagonists are under investigation.

The older antihistamines are associated with troublesome sedative and antimuscarinic effects, and are often termed 'sedating antihistamines'. The newer antihistamines, which are essentially devoid of these effects, are correspondingly termed 'non-sedating antihistamines' and include acrivastine, cetirizine, and loratadine.

On the basis of their chemical structure most antihistamines can be classified into one of 6 groups:

- *Alkylamines:* drugs within this group typically possess significant sedative actions, although paradoxical stimulation can occur, especially in children. They are highly potent H_1-antagonists. Brompheniramine and chlorphenamine are typical alkylamines; acrivastine is a non-sedating alkylamine antihistamine.
- *Monoethanolamines:* monoethanolamine derivatives have pronounced sedative and antimuscarinic actions but a low incidence of gastrointestinal effects. Examples include clemastine and diphenhydramine.
- *Ethylenediamines:* these antihistamines are selective H_1-antagonists. They cause moderate sedation (despite having weak CNS effects), gastric disturbances, and skin sensitisation. Antazoline and mepyramine are examples.
- *Phenothiazines:* phenothiazine antihistamines have significant sedative, and pronounced antiemetic and antimuscarinic effects. Photosensitivity reactions have occurred. Promethazine is a typical phenothiazine.
- *Piperazines:* this group of antihistamines possesses moderate sedative and significant antiemetic actions. Piperazine derivatives include cetirizine, cyclizine, and hydroxyzine. Cetirizine causes less sedation than other members of this group.
- *Piperidines:* piperidines cause moderate or low sedation and are highly selective for H_1 receptors. Examples include azatadine, cyproheptadine, and the non-sedating antihistamine loratadine.

Although characteristic pharmacological properties have been described for members of each group it should be noted that many of the effects of antihistamines vary as much with each patient as with each drug and that, in particular, some of the newer non-sedating antihistamines may share the chemical structure of a group in which the other members have sedative effects.

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3. Huang JF, Thurmond RL. The new biology of histamine receptors. *Curr Allergy Asthma Rep* 2008; **8:** 21–7.
4. Thurmond RL, *et al.* The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* 2008; **7:** 41–53.

Hypersensitivity. Hypersensitivity may be defined as an exaggerated or inappropriate immune response causing tissue damage. Hypersensitivity reactions are generally classified into 4 types (types I to IV) although this may be considered an over simplification and more than one type can often be postulated for a patient's hypersensitivity. In each of the 4 types, prior sensitisation of the patient to the specific antigen is required. The term *'allergy'* by definition originally covered all types of hypersensitivity reactions as well as the induction of immunity in an individual. Nowadays, the term is more commonly applied to type I hypersensitivity reactions.

Type I, immediate hypersensitivity reactions occur after exposure to an antigen (the allergen) in a sensitised subject; that is, one in whom the initial exposure to the antigen has caused the production of specific antibodies, mainly IgE (immunoglobulin E), which are bound to the surface of mast cells and basophils. At subsequent exposure, antigen binds to antibody resulting in degranulation of mast cells and basophils with release of mediators. These include preformed mediators such as histamine and chemotactic factors, and newly synthesised mediators such as leukotrienes, platelet-activating factor, and prostaglandins. Although type I reactions are usually described as being acute and short-lived, clinically there may often also be a late-phase and more prolonged reaction affecting the skin and bronchi. Examples of type I hypersensitivity reactions include allergic conjunctivitis (p. 611.1), allergic rhinitis (p. 612.1), urticaria and angioedema (p. 612.3), and anaphylactic shock (p. 611.1).

Type II, cell-surface hypersensitivity reactions are caused by the interaction of circulating antibodies, mainly IgG (immunoglobulin G) and IgM (immunoglobulin M), with antigens that are on the surface of specific cells or tissues. This interaction results in activation of complement and of phagocytic and killer cells leading to cell damage or lysis. Type II reactions are responsible for blood transfusion reactions, some drug-induced blood disorders, and many auto-immune disorders.

Type III, immune complex hypersensitivity reactions, are caused by the interaction of fixed or circulating antigens with circulating antibodies, mainly IgG and IgM (either soluble or particulate), resulting in formation of immune complexes. The immune complexes trigger a variety of inflammatory processes including complement activation, mediator release from mast cells and basophils, and platelet aggregation. Examples of type III reactions include serum sickness, some auto-immune and neoplastic disorders, type 2 lepra reactions (see Leprosy, p. 188.3), and reactions, particularly in the lung, to some particulate antigens such as micro-organisms.

Type IV, cell-mediated or delayed hypersensitivity reactions, are caused by interaction of an antigen with sensitised T-lymphocytes; lymphokines are released by T-lymphocytes and inflammation ensues. Type IV reactions usually occur at least 24 hours after contact with the antigen. A type IV reaction is responsible for tuberculin reactions used for sensitivity testing, contact dermatitis, and some reactions to chronic infectious disease for example type 1 lepra reactions (p. 188.3).

An **anaphylactoid** (pseudoallergic) reaction produces similar symptoms to those of anaphylaxis (see p. 611.1), but is caused by direct release of histamine provoked by an unclear, non-immune mechanism. There is thus no requirement for prior exposure to the triggering factor, commonly a drug.

Uses of Antihistamines

The activation of histamine H_1 receptors by histamine results in vasodilatation, increased capillary permeability, flare and itch reactions in the skin, and, to some extent, contraction of smooth muscle in the bronchi and gastrointestinal tract. Histamine H_1-antagonists (termed 'antihistamines' in *Martindale*) reduce or abolish the major actions of histamine in the body by competitive, reversible blockade of histamine H_1-receptor sites on tissues; they do not inactivate histamine or prevent its synthesis, nor, in most cases, its release (although some are claimed to have mast-cell stabilising properties).

Many *sedating antihistamines may* also possess antimuscarinic, adrenaline-antagonising, serotonin-antagonising, and local anaesthetic effects. Some have calcium-channel blocking activity.

Antihistamines are used mainly for the alleviation of conditions such as urticarial **rashes** and **nasal allergy** that are characterised by type I hypersensitivity (see above), but by virtue of their associated pharmacological actions they are also used to alleviate the symptoms of many other conditions (such as pruritus and nausea and vomiting).

The antihistamines can improve or relieve the symptoms of **seasonal allergic rhinitis** ('hay fever') in many patients. They alleviate rhinorrhoea and sneezing (and ocular symptoms such as conjunctivitis) but may be less effective for nasal congestion. The relief obtained is dependent on the severity and nature of the symptoms, being greater in the milder stages. The *non-sedating antihistamines* are preferred for daytime control, but a *sedating antihistamine* may be preferred at night. Antihistamines may also be of value in **vasomotor rhinitis**, despite the fact that this is not mainly an allergic condition. *Sedating antihistamines* are widely marketed, often with a decongestant, in compound preparations for the symptomatic treatment of coughs and **colds** although there is little evidence of value.

Antihistamines are of value in preventing **urticaria** and are used to treat urticarial rashes and mild **angioedema**. They are also used as adjuncts to adrenaline in the emergency treatment of **anaphylaxis** and severe angioedema. However, the use of an antihistamine is not appropriate for the control of blood transfusion reactions caused by ABO incompatibility.

The *sedating antihistamines* are of value in the alleviation of **pruritus** both of allergic and of non-allergic origin; they have a major role in pruritus associated with atopic eczema. The *non-sedating antihistamines* do not alleviate pruritus of non-allergic origin owing to their poor penetration of the blood-brain barrier.

Sedating antihistamines have marked antiemetic activity and are used to control **nausea and vomiting** caused by a variety of vestibular disorders. In the case of motion sickness a sedating antihistamine, such as dimenhydrinate or promethazine, is used if severe drowsiness (or even sleep) is not considered undesirable, but generally a less sedative antihistamine, such as cyclizine, cinnarizine, or meclozine may be preferred. Sedating antihistamines are similarly used to control the vertigo and nausea associated with **Ménière's disease** and related conditions, with cinnarizine promoted as a specific treatment. Sedating antihistamines also have an important role in the alleviation of the nausea and vomiting of **migraine**, and buclizine or cyclizine are marketed in some countries in a combination preparation for this purpose; cyproheptadine, which has serotonin antagonist and calcium-channel blocking activity, may be of value in the prophylaxis of migraine. Sedating antihistamines have a very limited role in the short-term management of vomiting of pregnancy but are no longer considered appropriate for nausea alone. *Sedating antihistamines* have also been used in anaesthetic practice for **premedication** and the prevention of postoperative nausea and vomiting.

Some of the antihistamines with very pronounced sedative effects, such as diphenhydramine and promethazine, have been marketed for treatment of occasional **insomnia** but their long duration of action can cause hangover effects. Some antihistamines are also available as preparations for topical application for the alleviation of **insect bites**, but there is little evidence of any real value and such use may be associated with sensitisation.

General references.
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2. Slater JW, *et al.* Second-generation antihistamines: a comparative review. *Drugs* 1999; **57:** 31–47.
3. Simons FER. Advances in H_1-antihistamines. *N Engl J Med* 2004; **351:** 2203–17.
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Anaesthesia

Phenothiazine antihistamines have been used for anaesthetic premedication (p. 1899.1) and to relieve anxiety

during surgical and obstetric procedures, but benzodiazepines are now used more routinely. However, sedating antihistamines such as promethazine and cyclizine do have a role in the control of postoperative vomiting (below). Alimemazine is licensed for premedication in children, although when given alone it may cause postoperative restlessness if pain is present.

Anaphylaxis

Anaphylaxis is commonly a type I (immediate) hypersensitivity reaction (see p. 610.1) to various allergens such as drugs, foods, and insect venoms. A clinically identical reaction can, however, be provoked by some other immune mechanisms, or by non-immune mechanisms (previously termed anaphylactoid reactions). Symptoms include erythema, pruritus, urticaria, and angioedema; respiratory obstruction may result from oedema of the larynx or epiglottis. Gastrointestinal disturbances, bronchospasm, hypotension, and coma can occur in severe reactions.

Anaphylaxis is a medical emergency and requires prompt treatment with adrenaline. (see Anaphylaxis and Anaphylactic Shock, p. 1293.2). The use of antihistamines in the management of anaphylaxis has been a matter of some debate. During acute treatment they are unlikely to be life-saving, and should never be used alone. However, an intramuscular or slow intravenous injection of an H_1-antagonist such as chlorphenamine or diphenhydramine may be given after adrenaline and repeated over the next 24 to 48 hours to counter histamine-mediated vasodilatation and bronchoconstriction. The use of antihistamines in treating the symptoms of milder forms of hypersensitivity is discussed under individual symptoms such as Pruritus (p. 612.1) and Urticaria and Angioedema (p. 612.3).

Angioedema

See under Urticaria and Angioedema, p. 612.3.

Asthma

Antihistamines appear to have no place in the treatment of asthma (p. 1195.2). A meta-analysis[1] of double-blind randomised placebo-controlled studies published since 1980 did not support the use of antihistamines in the treatment of asthma, although the quality of the studies was generally considered to be poor.

1. Van Ganse E, *et al.* Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J* 1997; **10:** 2216–24.

Conjunctivitis

Allergic conjunctivitis is a type I hypersensitivity reaction (p. 610.1). It is usually seasonal but perennial attacks due to allergens such as house dust mites can occur. Itching, tears, and burning are common symptoms and frequently rhinitis (p. 612.1) will co-exist. Conjunctivitis can also be caused by pathogenic micro-organisms (see Eye Infections, p. 182.1).

Avoidance of unnecessary exposure to aeroallergens is of prime importance in the management of allergic conjunctivitis. Since a large number of inflammatory mediators are involved in its pathogenesis no single drug will be completely effective. Systemic sedating and non-sedating antihistamines are effective in reducing allergic symptoms and preventing attacks; the choice of drug depends on the degree of sedation required. Ophthalmic antihistamine preparations such as antazoline, azelastine, emedastine, levocabastine, and olopatadine may also be used for acute attacks. Ophthalmic corticosteroids may reduce inflammation, but should be restricted to severe cases only and limited to 5 to 7 days of use because of the risk of local adverse effects such as cataract or raised intra-ocular pressure. Mast-cell stabilisers including ketotifen, lodoxamide, nedocromil, and sodium cromoglicate have been widely used for prophylaxis; some antihistamines also have mast-cell stabilising properties. Diclofenac and ketorolac eye drops are available for the treatment of allergic conjunctivitis. Combined preparations of astringents such as zinc sulfate and sympathomimetics or other conjunctival decongestants such as naphazoline may also be used for symptomatic relief.

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Coughs and colds

Sedating antihistamines are frequently used in combination preparations for the treatment of coughs and colds (p. 1651.2 and p. 951.1 respectively). The mechanism of their antitussive action may involve reduction in cholinergic nerve transmission or may simply result from their sedative effects; reduction of nasal secretions may be of value in treating cough caused by postnasal drip. Antihistamines should not be used to treat productive coughs because reduction in bronchial secretions may cause formation of viscid mucus plugs. The sedative effects of antihistamines may prove troublesome for daytime use but may be a short-term advantage for night coughs.

Cough and cold preparations containing antihistamines should be used with caution in children, and generally avoided in young children (for details see p. 614.1). However, antihistamines may be useful in the management of children with an acute allergic cough in the pollen season. They may also be used, with allergen avoidance and intranasal corticosteroids, in children with a chronic throat clearing type of cough and signs of allergic rhinitis.[1]

1. Shields MD, *et al.* British Thoracic Society Cough Guideline Group. Recommendations for the assessment and management of cough in children. *Thorax* 2008; **63** (suppl III): iii1–iii15. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/cough_in_children.pdf (accessed 01/08/08)

Food allergy

The term food allergy (food hypersensitivity) should be reserved for instances in which an immune mechanism for the reaction is proven, as may occur, for example, with nuts; food intolerance is used to describe a non-immune reaction. Food allergy may be the result of a type I (immediate), or possibly a type III (immune complex), hypersensitivity reaction (see p. 610.1). Management revolves around the identification of the provoking food allergen and its subsequent avoidance. Individualised diets are designed and patients are educated about possible hidden sources of the allergen. Drug therapy has a very limited role in the prevention of food allergy; oral sodium cromoglicate has been used but efficacy has not been unequivocally established.

Inadvertent exposure to an allergen resulting in anaphylaxis (p. 1293.2) requires immediate treatment with adrenaline. Milder symptoms may be controlled by antihistamines and corticosteroids. Allergen immunotherapy (p. 2435.1) plays no role in the routine management of food allergy.

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Hay fever

Hay fever is a seasonal form of allergic rhinitis in which symptoms of conjunctivitis are also present. Management is symptomatic and therapies used are discussed under Conjunctivitis, above and Rhinitis, p. 612.1.

Insomnia

Some of the older sedating antihistamines including diphenhydramine and promethazine, have been promoted to the public for occasional insomnia (p. 1033.2), although their long duration of action may cause hangover effects. Promethazine was formerly popular for children but the use of hypnotics in this age group is not usually justified. Moreover a possible association between phenothiazines and sudden infant death syndrome (see under the Adverse Effects of Promethazine, p. 639.1) contributed to the recommendation that such antihistamines should not be used in young children.

Ménière's disease

Ménière's disease is a disorder of the labyrinth (the inner ear) characterised by recurrent attacks of vertigo, progressive hearing loss, and worsening tinnitus (p. 1994.1). It usually presents in middle age and may equally affect men and women. The main pathological feature is an excess of endolymph fluid producing an increase in pressure in the membranous labyrinth (endolymphatic hydrops). Attacks occur in clusters over a few weeks with periods of remission lasting weeks or months.

The aims of treatment are to alleviate symptoms and preserve hearing if possible. It is therefore important to assess how far the disease has progressed, particularly in terms of hearing loss. In addition to conventional hearing tests, cochlear dysfunction may be assessed pharmacologically. Hypertonic glycerol has been given orally to reduce the endolymphatic fluid volume by osmotic diuresis, any temporary improvement in hearing indicating reversible impairment. However, this test is associated with adverse effects that some consider unacceptable. Urea has been used as an alternative to glycerol. Intravenous acetazolamide has been used diagnostically to increase endolymphatic pressure temporarily in order to produce transient hearing loss in patients in the reversible stages of the disease.

Acute attacks of vertigo in the early stages may be treated with the same drugs used for vertigo of any cause (see p. 612.3).

Vasodilators have been advocated for maintenance treatment because ischaemia of the labyrinth has been postulated as a factor in the aetiology. Betahistine, a histamine analogue, is used. Restriction of dietary sodium and administration of diuretics, such as chlortalidone, furosemide, and hydrochlorothiazide, has also been used traditionally to reduce the amount of fluid in the endolymphatic spaces.

As the disease progresses, vestibular ablation with aminoglycosides may be indicated. Systemic streptomycin has been used but the risk of further hearing loss and other serious adverse effects has limited its use. Intratympanic use of gentamicin is now preferred, and can improve vertigo in up to 90% of patients, although exacerbation of hearing loss is still a risk, albeit at a lower incidence than that with systemic streptomycin.

Surgical treatment remains an option for patients with Ménière's disease refractory to medical interventions.

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Migraine

Antihistamines have several uses in the management of migraine (p. 670.3). Those with antiemetic activity such as buclizine and cyclizine are used to alleviate the nausea and vomiting associated with migraine; they are common ingredients of compound analgesic preparations given for the initial treatment of migraine.

Those antihistamines with antiserotonin actions, including cyproheptadine and flunarizine, have been used for the prophylaxis of migraine.

Nausea and vomiting

The management of various types of nausea and vomiting is discussed in detail on p. 1814.3.

The older antihistamines such as cinnarizine, cyclizine, dimenhydrinate, meclozine, and promethazine are among the principal drugs used for **motion sickness**. They are all of similar efficacy but may differ in onset and duration of action and in the extent of adverse effects such as drowsiness. If a sedative effect is desired dimenhydrinate and promethazine are useful, otherwise a slightly less sedating antihistamine such as cinnarizine, cyclizine, or meclozine may be preferred. The aim is prevention of motion sickness since antiemetics are more effective for prophylaxis than for treatment; intramuscular promethazine may be effective as a treatment if injection is feasible. Antihistamines may be slightly less effective against motion sickness than the antimuscarinic hyoscine (p. 1848.3), but are often better tolerated. Non-sedating antihistamines, which penetrate poorly into the CNS, do not appear to be effective against motion sickness.

Diphenhydramine has been included in antiemetic regimens for the control of nausea and vomiting associated with **cancer chemotherapy** to reduce the extrapyramidal reactions associated with metoclopramide; it may also improve overall antiemetic control. Cyclizine is used as an antiemetic in **palliative care**.

Cyclizine is given as a supplement to opioids for premedication and has been effective prophylactically as well as in established **postoperative nausea and vomiting**. Promethazine has also been used for the

prevention and treatment of postoperative nausea and vomiting, but has marked sedative effects. Dimenhydrinate is also effective for prophylaxis.

Nausea in the first trimester of **pregnancy** does not usually require drug therapy, but on rare occasions if vomiting is severe an antihistamine such as promethazine may be required pending specialist advice. A combination preparation containing doxylamine and pyridoxine is also available for use during early pregnancy in women who have not responded to conservative management. See under Precautions for Antihistamines, p. 614.2, for a discussion of the risks of antiemetic therapy during pregnancy.

Otitis media

Acute otitis media (p. 195.2) and otitis media with effusion may resolve without treatment although antibacterials are often given. Antihistamines and decongestants, alone or in combination, have been widely given to children for symptomatic management of acute otitis media and associated respiratory symptoms, but studies have failed to show benefit and their use is not recommended.[1] Indeed in one study,[2] adjunctive treatment with chlorphenamine was found to prolong the duration of middle ear effusion.

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Pruritus

The sedating antihistamines are commonly used to relieve pruritus (itching) (p. 1687.3) from a variety of causes. They are effective in relieving pruritus associated with urticaria (below) but are also used for itching associated with dermatoses such as atopic eczema (p. 1684.1), where the degree of benefit is less certain. They are given in the latter to control nocturnal itching and for severe pruritus associated with relapse.

The exact pathophysiology of itching remains unclear.[1-3] Although histamine release is associated with itching in atopic eczema different inflammatory mediators are involved in other dermatoses. The CNS is also thought to play a part in the perception of itch. Hence, the relative roles of CNS sedation and peripheral histamine-receptor blockade in the mode of action of antihistamines in these conditions is a matter of debate. Although sedation has generally been considered the more important, the benefits of sedating antihistamines appear to be less in eczema than in urticaria. In addition, clemastine has been reported to provide no antipruritic benefit, yet it induces significant sedation. Studies with non-sedating antihistamines have been inconclusive; most found no benefit in pruritus associated with atopic eczema, although one early study has shown a slight benefit from the addition of acrivastine or terfenadine to treatment with a topical corticosteroid and an emollient.[4] Some have questioned whether any antihistamine offers much benefit in pruritus.[5]

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Rhinitis

Rhinitis may be allergic or non-allergic in origin. Allergic rhinitis is a type I hypersensitivity reaction (see p. 610.1); both early (sneezing, rhinorrhoea, and nasal congestion) and late (nasal congestion) reactions may be provoked. It may be seasonal (as in hay fever) or perennial and, in some patients, will frequently co-exist with conjunctivitis (p. 611.1). Non-allergic rhinitis may be divided into eosinophilic non-allergic rhinitis or non-eosinophilic non-allergic rhinitis. The term vasomotor rhinitis has been used to describe the latter although its use is best avoided since no vasomotor dysfunction has been clearly identified.

In the management of **allergic rhinitis**, avoidance of unnecessary exposure to aeroallergens is of prime importance. However, in most sufferers this is not possible and some form of drug therapy will be necessary. A large number of inflammatory mediators are involved in the pathogenesis of rhinitis and no single drug is completely effective in the alleviation of symptoms.

- Some antihistamines may nonetheless be useful in reducing secretions, nasal itching, sneezing, and ocular symptoms such as conjunctivitis, but are less effective for relief of nasal congestion. Non-sedating oral antihistamines such as acrivastine, cetirizine, ebastine, fexofenadine, loratadine, and mizolastine are now considered the first-choice treatment for mild and/or intermittent allergic rhinitis. They are also used for the management of breakthrough symptoms in those sufferers using prophylactic intranasal corticosteroids or sodium cromoglicate (see below). Since the maximum effect of antihistamines occurs several hours after peak serum concentrations have been obtained, they should be given in anticipation of a reaction to achieve the maximum response. Most antihistamines are unsuitable for topical use in the nose or eye since they are generally ineffective at the concentrations suitable for local therapy; also there is the potential for sensitisation. However, the antazoline salts, azelastine and levocabastine have been used topically in the nose for control of symptoms and are an alternative to oral antihistamines. Such preparations are considered less effective than intra-nasal corticosteroids but probably more effective than cromoglicate.
- The actions of topical corticosteroids in allergic rhinitis include relief of inflammation, a decrease in capillary permeability and in mucus production, and vasoconstriction; they inhibit both the early and late response to allergen exposure. Corticosteroids are first-line treatment for the prophylaxis of moderate to severe and/or persistent allergic rhinitis. In seasonal allergic rhinitis, they should be started at least 2 weeks before the pollen season and taken regularly throughout the season. Those applied intranasally include beclometasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone. At recommended dosage, local adverse effects are mild and transient, and systemic effects are not a risk; aqueous sprays may cause less local effects than pressurised aerosols. Treatment of allergic rhinitis with oral or parenteral corticosteroids has been reserved for short-term treatment in special circumstances only, although some have contested even this practice.
- Mast-cell stabilisers such as ketotifen, nedocromil, and sodium cromoglicate are thought to act mainly by preventing release of inflammatory mediators from sensitised mast cells through stabilisation of mast-cell membranes. They are an alternative to corticosteroids in the prophylactic treatment of allergic rhinitis and may be preferred for therapy in children. They may also be useful in controlling mild to moderate symptoms.
- The leukotriene receptor antagonist montelukast has produced benefits comparable to those seen with antihistamines, and is licensed in some countries for management of seasonal allergic rhinitis.
- Intranasal sympathomimetics such as phenylephrine, naphazoline, oxymetazoline, and xylometazoline may be useful for short-term treatment of allergic rhinitis to relieve severe nasal congestion which can be painful and may impede delivery of sodium cromoglicate or a corticosteroid to the mucosal surfaces. Oral sympathomimetic decongestants such as pseudoephedrine and phenylpropanolamine are less effective than topical sympathomimetics and adverse effects may be troublesome.
- Ipratropium bromide given intranasally may be useful as adjunctive therapy in patients with rhinorrhoea as it has a localised parasympathetic blocking action which reduces watery hypersecretion from nasal mucosa.

Allergen immunotherapy (p. 2435.1) is generally only indicated in severe allergic rhinitis when sensitivity testing shows sensitivity to one allergen and when exposure to the allergen is unavoidable or symptomatic treatment has failed.

The management of **non-allergic rhinitis** is similar to that of allergic rhinitis despite different mechanisms being involved in its aetiology. Topical corticosteroids are often first-line therapy especially if nasal congestion is a dominant feature. The role of antihistamines is more limited; sedating antihistamines are useful in reducing nasal secretions because of their antimuscarinic actions; however, non-sedating antihistamines are relatively ineffective. In patients in whom rhinorrhoea is a particular problem, intranasal ipratropium is of value. Although intranasal sympathomimetics have also been used they should generally be avoided because of the risk of rebound congestion. Oral sympathomimetics are largely ineffective.

Other therapies tried include topical capsaicin, to induce local desensitisation, and nasal douching with a saline and sodium bicarbonate solution.

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Urticaria and angioedema

Most patients with urticaria or angioedema (p. 1689.2) derive some benefit from oral antihistamines, especially in relief of pruritus. However, patients who are severely affected, particularly those with laryngeal oedema, are allergic emergencies and require immediate treatment with adrenaline (see Anaphylaxis and Anaphylactic Shock, p. 1293.2). Also, large doses of antihistamines are sometimes required and urticarias with a type I immunological origin and iatrogenic urticarias respond better than physical urticarias. If attacks of urticaria are frequent, antihistamines may be given prophylactically. Sedating antihistamines such as chlorphenamine and diphenhydramine have been widely used in the treatment of urticaria but non-sedating antihistamines are now generally preferred. Hydroxyzine has been used particularly in dermographism and cholinergic urticaria. Cyproheptadine has generally been considered the drug of choice for cold urticaria, although appetite stimulation may be a problem.

Some drugs with both H_1-antagonist and mast-cell stabilising actions, such as ketotifen, oxatomide, and azatadine have shown efficacy in the treatment of urticaria; the role of mast-cell stabilisation is unknown.

Topical treatment is rarely effective except for cases of mild urticaria; topical antihistamines carry a risk of sensitisation.

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Vertigo

Vertigo is a symptom of vestibular disorders. It is characterised by a sensation of rotation of the surroundings or of movement of static objects. Dizziness is considered to be a wider term, although sometimes it is used as a synonym for vertigo.

A variety of disorders may affect the vestibular system and produce vertigo, including cerebrovascular disorders, epilepsy, head injury, malignant neoplasms, Ménière's disease, migraine, multiple sclerosis, and infections. Motion sickness can induce vertigo. Ototoxic drugs may also cause vestibular damage and precipitate vertigo.

Patients suffering from vertigo should undergo thorough investigations to identify any underlying cause. Simple measures to improve the integration of sensory input from visual, proprioceptive, and vestibular receptors may prove effective, especially in the elderly, in whom the inappropriate prescribing of drugs for postural instability needs to be avoided. Such measures include improving visual acuity, balance exercises, and the use of walking aids.

The most widely used drugs for acute vertigo are the antihistamines. They may have a direct action on the inner ear besides acting centrally. Antimuscarinic actions may contribute to their activity; antimuscarinics, especially hyoscine, have a long history of use in vertigo. Antihistamines used in the treatment of vertigo include buclizine, cyclizine, dimenhydrinate, diphenhydramine, meclozine, and promethazine. Cinnarizine and flunarizine are also used for vertigo although they are devoid of any significant antimuscarinic actions; their activity may be due to calcium-channel blockade. Phenothiazines such as prochlorperazine are also used to control any associated vomiting. Benzodiazepines including diazepam have been given in acute

severe attacks. However, their prolonged use in those with chronic symptoms is of questionable value.

Vasodilators may be of benefit in the treatment of vertigo of vascular aetiology. Parenteral or sublingual histamine was formerly widely used, and betahistine is still advocated especially for vertigo associated with Ménière's disease. Nicotinyl alcohol has also been used.

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Adverse Effects of Antihistamines

The most common adverse effect of the *sedating antihistamines* is CNS depression, with effects varying from slight drowsiness to deep sleep, and including lassitude, dizziness, and incoordination (although paradoxical stimulation may occasionally occur, especially at high doses and in children or the elderly). These sedative effects, when they occur, may diminish after a few days of treatment. *Non-sedating antihistamines* generally cause little or no drowsiness (but see Sedation, below).

Other adverse effects that are more common with the *sedating antihistamines* include headache, psychomotor impairment, and antimuscarinic effects, such as dry mouth, thickened respiratory-tract secretions, blurred vision, urinary difficulty or retention, constipation, and increased gastric reflux. Most *non-sedating antihistamines* have little or no antimuscarinic effect.

Occasional gastrointestinal adverse effects of antihistamines include nausea, vomiting, diarrhoea, or epigastric pain. Those with antiserotonin actions, such as cyproheptadine, may cause an increase in appetite with resultant weight gain, whereas anorexia has been reported with some other antihistamines.

Palpitations and arrhythmias have been reported occasionally with most antihistamines, but a particular disadvantage of the *non-sedating antihistamines* astemizole and terfenadine was the rare occurrence of hazardous ventricular arrhythmias which led to important restrictions on their use (see Precautions, below).

Antihistamines sometimes cause rashes and hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis) and cross-sensitivity to related drugs may occur. Photosensitivity can be a problem, particularly with the phenothiazine antihistamines.

Blood disorders, including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia, although rare, have been reported. Jaundice has also been seen, particularly with the phenothiazine antihistamines.

Other adverse effects that have been reported with the antihistamines include convulsions, sweating, myalgia, paraesthesias, extrapyramidal effects, tremor, sleep disturbances, depression, confusion, tinnitus, hypotension, and hair loss.

Despite reports suggesting a possibility of human fetal abnormalities resulting from the use of some antihistamines, especially the piperazine derivatives, a causal relationship has largely been rejected; for details see Pregnancy, under Precautions, p. 614.2.

Some antihistamines have been abused for their CNS effects.

Antihistamines available as preparations for application to the skin may occasionally cause skin sensitisation; systemic adverse effects have been reported after topical application to large areas of the skin.

Overdosage with *sedating antihistamines* is associated with antimuscarinic, extrapyramidal, and CNS effects. When CNS stimulation predominates over CNS depression, which is more likely in children or the elderly, it causes ataxia, excitement, tremors, psychoses, hallucinations, and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, CNS depression is more common with drowsiness, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse. In the case of the *non-sedating antihistamines*, antimuscarinic effects are less marked, but hazardous ventricular arrhythmias (below) have been a particular problem with astemizole and terfenadine, even in modest overdoses, and led to restrictions on their use.

Reviews.
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Arrhythmias. Ventricular arrhythmias have been reported rarely with astemizole and terfenadine particularly in association with increased blood concentrations. For full details and specific warnings see under Astemizole, p. 616.2, and Terfenadine, p. 640.3.

The suspicion that such life-threatening arrhythmias may be a class effect of the non-sedating antihistamines has so far proven unfounded. Data[1] from the WHO adverse drug reaction database showed that cardiac events had been reported with the 5 most widely prescribed non-sedating antihistamines at that time (acrivastine, astemizole, cetirizine, loratadine, and terfenadine), and an attempt to quantify the risk[2] suggested that use of these drugs was associated overall with a fourfold increase in likelihood of developing ventricular arrhythmias, although the absolute risk remained low. However, other centres[3] have argued that definitive causality has only been proven for astemizole and terfenadine. In addition, a possible mechanism for drug-induced cardiac toxicity has only been found with astemizole and terfenadine;[4] both drugs have been shown to block cardiac potassium channels *in vitro*, a phenomenon that results in prolongation of the QT interval, which is a risk factor for developing ventricular arrhythmias. Studies[5] with loratadine and cetirizine have found that neither drug blocked potassium channels *in vitro*, and a similar lack of activity might be expected with desloratadine and levocetirizine; however, there is some evidence that mizolastine can block potassium channels at high concentrations *in vitro*[6] (although a small study in healthy subjects noted no adverse effects on cardiac conduction at doses up to 4 times those normally given).[7] A case report[8] of arrhythmias in a patient with pre-existing QT-prolongation given fexofenadine, did not appear to be associated with blocking of potassium channels.[9]

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Reye's syndrome. For criticism of a suggested link in children between antihistamines and Reye's syndrome, see p. 25.3.

Sedation. CNS depression is a common adverse effect of the *sedating antihistamines* and sedative effects can range from slight drowsiness to deep sleep. Daytime sedation can be a problem especially for those who have to drive or operate machinery. When sedative effects do occur they are most apparent at the start of treatment and often diminish after a few days despite continued use. Sedation caused by alcohol or other CNS depressants is enhanced. Many studies have attempted to quantify and compare the sedative effects of the older antihistamines, but results vary widely and classifications are difficult to make. Theoretically, the onset, degree, and persistence of sedation depend on factors such as penetration of the blood-brain barrier and on the relative affinity for central and peripheral histamine H_1 receptors. In general, antihistamines of the monoethanolamine and phenothiazine classes cause the most sedation.

In view of these problems, *non-sedating antihistamines* have been developed. These compounds have poor penetration into the CNS and/or higher affinity for peripheral rather than central histamine H_1 receptors. Studies with acrivastine,[1] astemizole,[2] fexofenadine,[3] loratadine,[4] and terfenadine[5] have generally indicated a lower incidence of sedation and related CNS effects than that seen with older antihistamines and comparable with that of placebo; prescription-event monitoring suggested that sedation was lower with fexofenadine and loratadine than with acrivastine or cetirizine, although the risk was low with all 4 drugs.[6] In a study[7] to compare the effects of acrivastine, terfenadine, and diphenhydramine on driving performance, terfenadine had no significant effect on driving performance. Acrivastine's effects were dose-related, but with little effect at the normal therapeutic dose, whereas diphenhydramine profoundly impaired all the measures of driving performance. In another study,[8] the effects of fexofenadine on driving performance were comparable with placebo. Studies with terfenadine[5] suggest that the incidence of sedation does not increase significantly with increased dose or duration of administration. Cetirizine appears to be more sedating than loratadine or terfenadine but less sedating than older antihistamines; the effect appears to be dose dependent.[9] Limited data with azelastine[10] indicate a similar incidence of drowsiness to that with terfenadine. An incidence of sedation comparable with that caused by terfenadine has also been seen for mequitazine when given in the recommended dosage of 5 mg twice daily.[5] Sedation has, however, occurred after doses of 10 mg twice daily.[11] Other newer antihistamines claimed to produce no troublesome sedation include ebastine, epinastine, mizolastine, and setastine.

A review[12] of studies in drivers divided antihistamines into:

- first-generation (such as clemastine, diphenhydramine, and triprolidine), which produced significant impairment of driving ability
- second-generation (acrivastine, cetirizine, ebastine, emedastine, loratadine, mizolastine, and terfenadine), which produced more modest degrees of impairment; higher doses than normal produced significant impairment
- third-generation (levocetirizine, fexofenadine), which seemed to produce little or no impairment

Several studies have indicated that the non-sedating antihistamines do not seem to enhance the effects of alcohol and other CNS depressants.

A few patients treated with non-sedating antihistamines have experienced drowsiness. Therefore it is prudent to exercise caution before driving or operating machinery; the effect of a drug on a particular patient can be ascertained after the first few doses.

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Precautions for Antihistamines

Drowsiness is a major problem with the *sedating antihistamines* and those affected should not drive or operate machinery; alcohol should be avoided. In the case of *non-sedating antihistamines*, although drowsiness is rare, it can occur and may affect the performance of skilled tasks.

Because of their antimuscarinic actions the *sedating antihistamines* should be used with care in conditions such as angle-closure glaucoma, urinary retention, prostatic hyperplasia, or pyloroduodenal obstruction; antimuscarinic adverse effects are not a significant problem with the *non-sedating antihistamines*.

Occasional reports of convulsions in patients taking antihistamines suggest a need for caution in patients with epilepsy.

Many antihistamines are excreted in the urine in the form of active metabolites so that dosage reduction may be necessary in renal impairment (see individual monographs for specific advice). Caution is also needed in hepatic impairment, notably with phenothiazine antihistamines (for further details, see Effects on the Liver, under Chlorpromazine, p. 1049.1) and, above all, with the *non-sedating antihistamines*, astemizole and terfenadine (hazardous ventricular arrhythmias may occur in the presence of excessive blood concentrations). Other important cautions for astemizole and terfenadine include avoidance of use with drugs liable to interfere with their hepatic metabolism or otherwise increase the risk of arrhythmias, and contra-indication in patients with cardiac disease, known or suspected prolongation of the QT interval, or hypokalaemia or other electrolyte imbalances. For full details see under Astemizole, p. 616.2, and Terfenadine, p. 640.3.

Antihistamines should not be given to neonates because the latter are more susceptible to antimuscarinic effects. It has also been recommended that antihistamines should be

avoided in young children (see Children, below, and under Promethazine, p. 639.2, and Alimemazine, p. 615.2). Elderly patients are also more susceptible to many of the adverse effects of antihistamines and, in particular, their inappropriate use for postural giddiness should be avoided (see Vertigo, p. 612.3).

Topical preparations containing antihistamines should not be used on broken or eczematous skin.

Several large studies have failed to find any strong associations between fetal abnormalities and antihistamines taken during pregnancy (see under Pregnancy, below).

Asthma. Antihistamines are not considered effective in the management of asthma[1] and their use has often been contra-indicated in patients with asthma because of fears that they may cause airway obstruction. However, antihistamine-induced airway obstruction has rarely been noted clinically and many patients with asthma tolerate concurrent treatment with antihistamines without obvious adverse effects. Therefore the American Academy of Allergy and Immunology has recommended that antihistamines are not contra-indicated in patients with asthma, unless an adverse reaction has previously occurred, and the FDA no longer warns against the use of over-the-counter antihistamines by people with asthma.[2]

1. Meltzer EO. To use or not to use antihistamines in patients with asthma. *Ann Allergy* 1990; **64:** 183–6.
2. FDA. Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use: final monograph for OTC antihistamine drug products: final rule. *Fed Regist* 1992; **57:** 58369–70.

Children. In 2004, the FDA[1] reviewed all reports that it had received, between 1969 and 2003, of serious adverse events in children (aged from birth to 16 years) given promethazine. Of 125 reports there were 38 cases of respiratory depression, apnoea, or cardiac arrest; 29 cases of extrapyramidal dystonic reactions; 24 cases of other CNS reactions; 15 cases of seizures or seizure-like activity; 12 cases of dermatological reactions; and 5 cases of neuroleptic malignant syndrome. These reports included 22 cases of respiratory depression in patients aged 1.5 months to 2 years, 7 of which were fatal. Doses received in these 22 cases ranged from 0.45 to 6.4 mg/kg. Serious outcomes occurred with all routes of use (oral, rectal, and parenteral). US licensed product information for promethazine hydrochloride now contra-indicates its use in children under 2 years of age because of the potential for fatal respiratory depression; a strengthened warning regarding use in children aged 2 years and older advises use of the lowest effective dose and to avoid concomitant use of other drugs with respiratory depressant effects. UK licensed product information for phenothiazine antihistamines, such as promethazine and alimemazine, also warns that these should not be given to children under 2 years of age, and the *BNFC* advises that sedating antihistamines such as these should not be given to children under 2 years of age, except on specialist advice, because safety has not been established.

Concern has also been expressed about the safety in children of cough and cold preparations that contain antihistamines, cough suppressants, expectorants, and sympathomimetic decongestants, either alone or in combination. A systematic review[2] has also found no good evidence for or against the efficacy of over-the-counter (OTC) preparations in acute cough. In early 2008, the FDA[3] and MHRA[4] both advised that over-the-counter cough and cold preparations should not be given to children under 2 years of age. They warned of the potential for serious and potentially life-threatening adverse effects and that such preparations provided only symptomatic relief, at best. They also advised that if these products were to be used in children older than 2 years of age, the recommended dose should be followed carefully and measured accurately, and that only one preparation should be used to avoid overdosage of the same drug or similar drugs. A review by the FDA of the use of such preparations in older children (2 to 11 years of age) is ongoing. However, in October 2008, most US manufacturers voluntarily revised the labelling of OTC cough and cold preparations to state not for use in children aged under 4 years.[5] In early 2009, after further review, the MHRA[6] advised that OTC cough and cold preparations should not be given to children under 6 years of age as there was no robust evidence of their efficacy and because they can cause adverse effects such as allergic reactions, sleep disturbances, and hallucinations. In those aged from 6 to 12 years, such preparations should only be used as second-line therapy and for no more than 5 days; the MHRA also considers that further research is warranted in this age group. For the MHRA's suggested management of the symptoms of coughs and colds, see Cough, p. 1651.2.

An association between phenothiazine antihistamines and sudden infant death syndrome has also been investigated—see p. 639.1.

1. Starke PR, *et al.* Boxed warning added to promethazine labeling for pediatric use. *N Engl J Med* 2005; **352:** 2653.
2. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
3. FDA. FDA releases recommendations regarding use of over-the-counter cough and cold products (issued 17th January, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116839.htm (accessed 17/08/10)
4. MHRA/CHM. Updated advice—over-the-counter cough and cold medicines for children. *Drug Safety Update* 2008; **1** (9): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 15/04/08)
5. FDA. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children (issued 8th October, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm (accessed 17/08/10)
6. MHRA. Press release: better medicines for children's coughs and colds (issued 28th February, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON038902 (accessed 06/04/09)

Pregnancy. Antihistamines have been used for antiemetic therapy during pregnancy, but considerable anxiety has surrounded such use and its potential for risk to the fetus. The most widely studied preparation was *Debendox* which contained doxylamine, dicycloverine, and pyridoxine, and was known as *Bendectin* in some countries. Dicycloverine was removed from the preparation in 1976 in the USA and subsequently in other countries, and the product was withdrawn from the market in 1983 because of threatened litigation.[1] By that time *Debendox* had been used for over 27 years and in over 33 million pregnancies worldwide.[1]

Initial concern came from anecdotal reports of malformations in infants whose mothers had taken *Debendox* during pregnancy.[2,3] Evidence was found[4] of an association between prenatal exposure to the 3-component formulation of *Bendectin* and an increased risk of pyloric stenosis and possibly also defective heart valves in a study of 1369 malformed infants and 2968 healthy control cases. Other studies have suggested an increased incidence of oral clefts,[5] gastrointestinal atresia,[6] and genital tract disorders,[7] but generally such increases have been small. No overall pattern of malformations appears to have emerged, and many large studies have failed to confirm an association between doxylamine use and congenital malformations.[8-13]

A prospective study of 11 481 pregnancies found no increased incidence of either severe congenital abnormalities or perinatal mortality rates in women who had been prescribed prochlorperazine, meclozine, cyclizine, or *Bendectin* during pregnancy, although there was some evidence of an excess number of congenital abnormalities in patients taking trimethobenzamide.[14]

The Collaborative Perinatal Project[15] monitored the mothers of 50 282 children between 1958 and 1965. Of these, 5401 used antihistamines and 1309 phenothiazines during the first 4 months of pregnancy. There was no evidence to suggest that exposure to these drugs was related to malformations, although there were slight suggestions of associations between respiratory malformations and pheniramine, inguinal hernia and meclozine, inguinal hernia or genito-urinary malformations and diphenhydramine, and cardiovascular deformities and phenothiazines. A report[16] on the same study found no effects of phenothiazines on perinatal mortality, birth-weight, or IQ scores at the age of 4 years. The Collaborative Perinatal Project also noted a relationship between cardiovascular defects and inguinal hernia and dimenhydrinate exposure.[15]

Both the UK CSM[17] and the FDA in the USA[18] reviewed the literature in 1981 and concluded that while the scientific evidence did not show an increase in birth defects with *Debendox*, the risk of teratogenicity could not be completely excluded. A further review[19] by the FDA in 1999 into the reasons for withdrawal stated that the evidence supported the conclusion that the combination had not been withdrawn from the market for reasons of safety or efficacy. In some countries, such as Canada, a combination preparation of doxylamine and pyridoxine remained available for the treatment of nausea and vomiting in pregnancy; subsequently, in April 2013, the FDA approved the return of such a combination preparation onto the market. There has been a study indicating that vomiting itself is not teratogenic.[20]

Several other studies have been carried out on meclozine prompted by reports of fetal abnormalities in 10 patients associated with a preparation of meclozine and pyridoxine;[21] these studies have not supported the original reports.[22-24]

1. Merrell Pharmaceuticals. Production of Debendox to stop. *Lancet* 1983; **i:** 1395.
2. Paterson DC. Congenital deformities associated with Bendectin. *Can Med Assoc J* 1977; **116:** 1348.
3. Donnai D, Harris R. Unusual fetal malformations after antiemetics in early pregnancy. *BMJ* 1978; **1:** 691–2.
4. Eskenazi B, Bracken MB. Bendectin (Debendox) as a risk factor for pyloric stenosis. *Am J Obstet Gynecol* 1982; **144:** 919–24.
5. Golding J, *et al.* Maternal anti-nauseants and clefts of lip and palate. *Hum Toxicol* 1983; **2:** 63–73.
6. Jick H, *et al.* First-trimester drug use and congenital disorders. *JAMA* 1981; **246:** 343–6.
7. Gibson GT, *et al.* Congenital anomalies in relation to the use of doxylamine/dicyclomine and other antenatal factors: an ongoing prospective study. *Med J Aust* 1981; **i:** 410–4.
8. Shapiro S, *et al.* Antenatal exposure to doxylamine succinate and dicyclomine hydrochloride (Bendectin) in relation to congenital malformations: perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 1977; **128:** 480–5.
9. Harron DWG, *et al.* Debendox and congenital malformations in Northern Ireland. *BMJ* 1980; **281:** 1379–81.
10. Fleming DM, *et al.* Debendox in early pregnancy and fetal malformation. *BMJ* 1981; **283:** 99–101. Correction. *ibid.* 2010; **340:** 1196.
11. Mitchell AA, *et al.* Birth defects related to Bendectin use in pregnancy 1: Oral clefts and cardiac defects. *JAMA* 1981; **245:** 2311–14.
12. Mitchell AA, *et al.* Birth defects in relation to Bendectin use in pregnancy. *Am J Obstet Gynecol* 1983; **147:** 737–42.
13. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–9.
14. Milkovich L, van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. *Am J Obstet Gynecol* 1976; **125:** 244–8.
15. Heinonen OP, *et al. Birth defects and drugs in pregnancy.* Massachusetts: Publishing Sciences Group, 1977.
16. Slone D, *et al.* Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 1977; **128:** 486–8.
17. CSM. Data sheet change—Debendox. *Current Problems 6* 1981. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024413&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
18. FDA. Indications for Bendectin narrowed. *FDA Drug Bull* 1981; **11**(1).
19. FDA. Determination that Bendectin was not withdrawn from sale for reasons of safety or effectiveness. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/080999e.pdf (accessed 08/04/04)
20. Klebanoff MA, Mills JL. Is vomiting during pregnancy teratogenic? *BMJ* 1986; **292:** 724–6.
21. Watson GI. Meclozine ("Ancoloxin") and foetal abnormalities: preliminary report by the epidemic observation unit of the College of General Practitioners. *BMJ* 1962; **ii:** 1446.
22. Lenz W. How can the teratogenic action of a factor be established in man? *South Med J* 1971; **64** (suppl 1): 41–7.
23. Greenberg G, *et al.* Maternal drug histories and congenital abnormalities. *BMJ* 1977; **2:** 853–6.
24. Shapiro S, *et al.* Meclizine in pregnancy in relation to congenital malformations. *BMJ* 1978; **i:** 483.

Interactions of Antihistamines

Sedating antihistamines may enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and antipsychotics. Sedative interactions apply to a lesser extent with the *non-sedating antihistamines*; they do not appear to potentiate the effects of alcohol, but it should be avoided in excess.

Sedating antihistamines have an additive antimuscarinic action with other antimuscarinic drugs, such as atropine and some antidepressants (both tricyclics and MAOIs).

Potentially hazardous ventricular arrhythmias have occurred when the *non-sedating antihistamines* astemizole and terfenadine have been given with drugs liable to interfere with their hepatic metabolism, with other potentially arrhythmogenic drugs including those that prolong the QT interval, or with those likely to cause electrolyte imbalance. For full details see under Astemizole, p. 616.2, and Terfenadine, p. 641.1.

It has been suggested that some *sedating antihistamines* could mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibacterials.

Antihistamines may suppress the cutaneous histamine response to allergen extracts (p. 2434.3) and should be stopped several days before skin testing. For the effect of antihistamines on histamine given exogenously, see p. 2525.3.

Acrivastine *(BAN, USAN, rINN)*

Acrivastin; Acrivastina; Acrivastinum; Akrivastiini; Akrivastin; BW-825C; Акривастин.

(*E*)-3-{6-[(*E*)-3-Pyrrolidin-1-yl-1-*p*-tolylprop-1-enyl]-2-pyridyl} acrylic acid.

$C_{22}H_{24}N_2O_2$=348.4

CAS — 87848-99-5.

ATC — R06AX18.

ATC Vet — QR06AX18.

UNII — A20F9XAI7W.

Uses and Administration

Acrivastine is a non-sedating antihistamine structurally related to triprolidine. It does not have any significant sedative or antimuscarinic actions. It is used for the symptomatic relief of allergic conditions such as rhinitis (p. 612.1) and various types of urticaria (p. 612.3) when it is given in oral doses of 8 mg up to three times daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Acrivastine should be given with care in renal impairment; UK licensed product information recommends that it should not be given to patients with significant renal impairment, while product information in other countries, such as Switzerland for example, contra-indicates its use in those with a creatinine clearance of less than 50 mL/minute. Acrivastine should not be used in patients hypersensitive to triprolidine.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acrivastine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Sedation. For a discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Acrivastine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur in about 1.5 hours after oral use. The plasma half-life of acrivastine is about 1.5 hours and the drug does not appear to cross the blood-brain barrier to a significant extent. Acrivastine along with an active metabolite is excreted principally in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Semprex (欣民立); ***Denm.***: Benadryl; ***Fin.***: Benadryl; ***Hong Kong***: Semprex†; ***Ital.***: Semprex†; ***Malaysia***: Semprex†; ***Neth.***: Semprex; ***Philipp.***: Semprex; ***Rus.***: Semprex (Семпрекс); ***S.Afr.***: Semprex; ***Singapore***: Semprex; ***Swed.***: Semprex†; ***Switz.***: Semprex†; ***Turk.***: Semprex; ***UK***: Benadryl Allergy Relief.

Multi-ingredient Preparations. ***Denm.***: Duact; ***Fin.***: Duact; ***Turk.***: Duact; ***UK***: Benadryl Plus; ***USA***: Semprex-D.

Alcaftadine *(USAN, rINN)*

Alcaftadina; Alcaftadinum; R-89674; Алкафтадин.

11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-imidazo[2,1-*b*][3]benzazepine-3-carbaldehyde.

$C_{19}H_{21}N_3O$=307.4

CAS — 147084-10-4.

ATC — S01GX11.

ATC Vet — QS01GX11.

UNII — 7Z8O94ECSX.

Profile

Alcaftadine is an antihistamine (p. 610.1) that also inhibits the release of histamine from mast cells. It is used once daily, as an eye drop containing 0.25% of alcaftadine to prevent itching associated with allergic conjunctivitis in adults and children aged 2 years and over.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Lastacaft.

Alimemazine Tartrate *(BANM, rINNM)*

Alimemazina, tartrato de; Alimémazine, Tartrate d'; Alimemazini Tartras; Tartrato de alimemazina; Trimeprazine Tartrate; Алимемазина Тартрат.

NN-Dimethyl-2-methyl-3-(phenothiazin-10-yl)propylamine tartrate.

$(C_{18}H_{22}N_2S)_2,C_4H_6O_6$=747.0

CAS — 84-96-8 (alimemazine); 4330-99-8 (alimemazine tartrate).

ATC — R06AD01.

ATC Vet — QR06AD01.

UNII — 362NW1LD6Z.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Alimemazine Hemitartrate). A white or very slightly yellowish powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in toluene. It deteriorates when exposed to air and light. A 2% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Trimeprazine Tartrate). A white to off-white, odourless, crystalline powder. Soluble 1 in 2 of water, 1 in 20 of alcohol, 1 in 5 of chloroform, and 1 in 1800 of ether; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Alimemazine, a phenothiazine derivative, is a sedating antihistamine with antiemetic activity and pronounced sedative effects. It also has some antimuscarinic actions. It is used mainly for the relief of urticaria (p. 612.3) and pruritus (p. 612.1); in the UK it is also licensed for pre-operative medication in children. Alimemazine may also be used in compound preparations for the symptomatic treatment of coughs (p. 611.2).

Alimemazine tartrate is given orally; doses in the UK are given as the amount of alimemazine tartrate, while those in some other countries are expressed in terms of the equivalent amount of alimemazine. Alimemazine tartrate 25 mg is equivalent to about 20 mg of alimemazine.

- The dose of alimemazine tartrate used for the relief of **urticaria** and **pruritus** in the *UK* is 10 mg two or three times daily; up to 100 mg daily has been given in refractory cases. Elderly patients are given 10 mg once or twice daily.
- Doses used in the *USA* have been lower, even allowing for them being expressed in terms of alimemazine. The usual dose was the equivalent of alimemazine 2.5 mg four times daily. However, it appears that proprietary preparations are no longer available in the USA.

For dosage in children, see below.

Administration in children. Alimemazine tartrate may be given to children to relieve **urticaria** and **pruritus**. In the UK, those over 2 years of age may be given 2.5 to 5 mg, orally, three or four times daily. Despite the view that alimemazine should not be given to younger children (see below), and although not licensed in the UK in this age group, the *BNFC* suggests that 250 micrograms/kg (maximum of 2.5 mg) three or four times daily may be given to children aged 6 months to 2 years, but only under specialist care.

The usual recommended dose in the UK for **premedication** in children aged 2 to 7 years is up to 2 mg/kg given orally about one to two hours before the procedure.

Anaesthesia. Alimemazine tartrate may be used for anaesthetic premedication (see p. 610.3) in children if the oral route is preferred to the more usual parenteral route of other phenothiazine antihistamines. Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, below), and in the UK alimemazine tartrate is not licensed for use in infants less than 2 years of age.

Insomnia. Antihistamines such as alimemazine tartrate have been used as alternatives to benzodiazepines for the short-term treatment of insomnia (p. 611.2), particularly for children. However, their antimuscarinic adverse effects may prove troublesome.

Regimens involving a short course of alimemazine tartrate in high dosage were tried in order to alter the sleep pattern of children with sleeping difficulties.[1,2] Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, below). The UK product is no longer indicated for short-term sedation in children and should not be used in infants less than 2 years of age.

1. Valman HB. ABC of 1 to 7 (revised): sleep problems. *BMJ* 1987; **294:** 828–30.
2. Anonymous. What can be done for night waking in children? *Lancet* 1987; **ii:** 948–9.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Children. There have been reports of adverse effects in children given alimemazine tartrate orally. Fatal malignant hyperthermia[1] and severe cardiovascular depression[2] have occurred after its use for premedication, and severe respiratory and CNS depression[3] after use as a postoperative sedative. Doses in these 3 reports ranged from 2.4 to 4.4 mg/kg. Although unconfirmed, a possible association between phenothiazine sedatives and sudden infant death syndrome has also been suggested (see Promethazine Hydrochloride, p. 639.1). Alimemazine tartrate is no longer licensed in the UK for short-term sedation in children and it is recommended that it should not be used in infants less than 2 years of age (but see Administration in children, above). The maximum recommended oral dose for premedication of children aged 2 to 7 years is 2 mg/kg. There has been a warning[4] that the use of alimemazine for deep sedation in diagnostic and therapeutic procedures in children is associated with prolonged drowsiness and that standards of monitoring, starvation, and postprocedural care should be similar to those with general anaesthesia.

1. Moyes DG. Malignant hyperpyrexia caused by trimeprazine. *Br J Anaesth* 1973; **45:** 1163–4.
2. Loan WB, Cuthbert D. Adverse cardiovascular response to oral trimeprazine in children. *BMJ* 1985; **290:** 1548–9.
3. Mann NP. Trimeprazine and respiratory depression. *Arch Dis Child* 1981; **56:** 481–2.
4. Cray SH, Hinton W. Sedation for investigations: prolonged effect of chloral and trimeprazine. *Arch Dis Child* 1994; **71:** 179.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alimemazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For a discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vallergan; ***Belg.***: Theralene; ***Canad.***: Panectyl; ***Fr.***: Theralene; ***Irl.***: Vallergan; ***Neth.***: Nedeltran; ***Norw.***: Vallergan; ***NZ***: Vallergan; ***Rus.***: Teraligen (Тералиджен); ***S.Afr.***: Vallergan; ***Spain***: Variargil; ***Swed.***: Theralen; ***UK***: Vallergan.

Multi-ingredient Preparations. ***Fr.***: Sirop Teyssedre†.

Pharmacopoeial Preparations

BP 2014: Alimemazine Tablets; Paediatric Alimemazine Oral Solution; Strong Paediatric Alimemazine Oral Solution;

USP 36: Trimeprazine Tartrate Syrup; Trimeprazine Tartrate Tablets.

Antazoline *(BAN, rINN)*

Antatsoliini; Antazolin; Antazolina; Antazolinum; Антазолин.

N-Benzyl-*N*-(2-imidazolin-2-ylmethyl)aniline.

$C_{17}H_{19}N_3$=265.4

CAS — 91-75-8.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — DHA8014S51.

Antazoline Hydrochloride *(BANM, rINNM)*

Antatsoliinihydrokloridi; Antazolin hydrochlorid; Antazolina, hidrocloruro de; Antazoline, Chlorhydrate d'; Antazolinhidroklorid; Antazolinhydrochlorid; Antazolinhydroklorid; Antazolini Hydrochloricum; Antazolini Hydrochloridum; Antazolinium Chloride; Antazolino hidrochloridas; Antazoliny chlorowodorek; Hidrocloruro de antazolina; Imidamine Hydrochloride; Phenazolinum; Антазолина Гидрохлорид.

$C_{17}H_{19}N_3$,HCl=301.8

CAS — 2508-72-7.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — FP8Q8F72JH.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Antazoline Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in dichloromethane.

Antazoline Mesilate *(BANM, rINNM)*

Antazolina, mesilato de; Antazoline, Mésilate d'; Antazoline Mesylate; Antazoline Methanesulphonate; Antazolini Mesilas; Antazoliny mezylan; Imidamine Mesylate; Mesilato de antazolina; Антазолина Мезилат.

$C_{17}H_{19}N_3$,CH_3SO_3H=361.5

CAS — 3131-32-6.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — KU470J7TY6.

Pharmacopoeias. In *Pol.*

Antazoline Phosphate *(BANM, rINNM)*

Antazolin Fosfat; Antazolina, fosfato de; Antazoline, Phosphate d'; Antazolini Phosphas; Fosfato de antazolina; Imidamine Phosphate; Антазолина Фосфат.

$C_{17}H_{19}N_3$,H_3PO_4=363.4

CAS — 154-68-7.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — VPR5FPH326.

Pharmacopoeias. In *US.*

USP 36: (Antazoline Phosphate). A white to off-white crystalline powder. Soluble in water; practically insoluble in ether and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 4.0 and 5.0. Store in airtight containers.

Antazoline Sulfate *(BANM, rINNM)*

Antazolina, sulfato de; Antazoline, Sulfate d'; Antazoline Sulphate; Antazolini Sulfas; Imidamine Sulphate; Sulfato de antazolina; Антазолина Сульфат.

$(C_{17}H_{19}N_3)_2H_2SO_4,2H_2O$=664.8

CAS — 24359-81-7 (anhydrous antazoline sulfate).

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — 6T74I07212.

NOTE. The above molecular formula is that provided in the *It. P.* Other sources give a molecular formula of $C_{17}H_{19}N_3$, H_2SO_4.

Pharmacopoeias. In *It.*

Uses and Administration

Antazoline, an ethylenediamine derivative, is an antihistamine used topically for the treatment of allergic conjunctivitis (p. 611.1). It is used as the hydrochloride, phosphate, or sulfate in eye drops, most commonly in a concentration of 0.5%; the mesilate has also been used. Antazoline salts are often used with a vasoconstrictor such as naphazoline hydrochloride or nitrate or xylometazoline hydrochloride.

The hydrochloride and sulfate salts of antazoline have been used topically for the treatment of minor skin irritations, but as with other antihistamines there is a risk of sensitisation. The hydrochloride has also been given orally.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively.

Hypersensitivity. Reports of acute interstitial pneumonitis (with fever, rash, and dyspnoea)[1] and of immune thrombocytopenic purpura[2] were attributed to hypersensitivity reactions after the oral use of antazoline.

1. Pahissa A, *et al.* Antazoline-induced allergic pneumonitis. *BMJ* 1979; **2:** 1328.
2. Nielsen JL, *et al.* Immune thrombocytopenia due to antazoline (Antistina). *Allergy* 1981; **36:** 517–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Albalon-A; Antistine-Privine; Murine Allergy; ***Canad.***: Albalon-A; Refresh Eye Allergy Relief; Zincfrin-A†; ***Chile***: Bacitopic Compuesto†; Nasomin; Oftalirio; Red Off Plus; Rinobanedif; Spersallerg; ***Cz.***: Sanorin-Analergin; Spersallerg; ***Denm.***: Ansal†; Antistina-Privin; Sesal; ***Ger.***: Allergopos N†; Antistin-Privin†; Spersallerg†; ***Gr.***: Spersallerg; Zincfrin-A; ***Hong Kong***: Spersallerg; Vista-Tone†; ***Hung.***: Spersallerg; ***Indon.***: Indofrin-A†; ***Irl.***: Otrivine-Antistin; RBC†; ***Ital.***: Antistin-Privina; ***Malaysia***: Alergoftal†; Napha A; Spersallerg; ***Mex.***: Midazol Ofteno; Zincfrin-A; ***Norw.***: Spersallerg; ***NZ***: Otrivine-Antistin†; ***Philipp.***: Spersallerg; ***Pol.***: Dermophenazol; Oftophenazol; Rhinophenazol; Spersallerg; ***Port.***: Alergiftalmina; ***Rus.***: Sanorin-Analergin (Санорин-аналергин); Spersallerg (Спесаллерг); ***S.Afr.***: Antistin-Privin; Covosan†; Gemini; Oculerge; Spersallerg; Zincfrin-A†; ***Singapore***: Antistin-Privin; Spersallerg; ***Spain***: Alergoftal; ***Swed.***: Antasten-Privin†; ***Switz.***: Antistin-Privin†; Spersallerg; ***Thai.***: Allergis; Antazallerge; Histaoph; Opsil-A; Spersallerg; ***Turk.***: Alergoftal; Sulfarhin; ***UK***: Otrivine-Antistin; ***Ukr.***: Sanorin-Analergin (Санорин-Аналергин); ***USA***: Antazoline-V; Geneye AC Allergy†; Vasocon-A.

Astemizole *(BAN, USAN, rINN)*

Astemitsoli; Astemizol; Astemizolas; Astémizole; Astemizolum; Asztemizol; MJD-30; Астемизол.

1-(4-Fluorobenzyl)-2-{[1-(4-methoxyphenethyl)-4-piperidyl]amino}benzimidazole.

$C_{28}H_{31}FN_4O$=458.6

CAS — 68844-77-9.

ATC — R06AX11.

ATC Vet — QR06AX11.

UNII — 7HU6337315.

NOTE. The code R-43512 has been used to describe both astemizole and its metabolite tecastemizole (norastemizole).

Pharmacopoeias. In *US.*

USP 36: (Astemizole). Store in airtight containers.

Uses and Administration

Astemizole, a piperidine derivative, is a non-sedating antihistamine with a very long duration of action. It does not have significant sedative or antimuscarinic actions. Astemizole has been used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and skin disorders such as urticaria (p. 612.3). Preparations of astemizole have now been withdrawn from the market in most countries because of the risk of adverse effects.

Astemizole has been given in an oral dose of 10 mg once daily. This dose must not be exceeded because of the risk of cardiac arrhythmias with higher doses.

The active metabolite of astemizole, tecastemizole (norastemizole) has been investigated for the treatment of allergic rhinitis.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Increased appetite and weight gain have been reported with astemizole.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with astemizole, particularly with raised blood concentrations (see Arrhythmias below) and as a result the drug has been withdrawn from the market in most countries. To reduce the risk of developing such arrhythmias recommendations were that licensed doses should **not** be exceeded, and that it should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of astemizole, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance, is **contra-indicated** (see Interactions below).

Arrhythmias. Although severe life-threatening cardiovascular effects including torsade de pointes and other ventricular arrhythmias were initially reported mainly after substantial overdoses of astemizole, such reactions have also occurred rarely with doses as low as 20 to 30 mg daily and even as low as 10 mg daily in those with possible predisposing factors. There has been a report[1] of astemizole-induced torsade de pointes in a 15-year-old girl who claimed to have taken 10 mg daily for 10 weeks but pharmacokinetic data were more consistent with acute ingestion of higher doses. There have also been several reports of cardiotoxicity after accidental overdosage with astemizole in children.[2-4]

Recommendations were made by the UK CSM to reduce the risk of developing serious arrhythmias[5-7] (see Adverse Effects above for details); however, the drug has since been withdrawn in the UK and many other countries. It was considered that astemizole should be stopped immediately in patients who have syncope, and appropriate clinical evaluation including ECG monitoring instituted, because syncope has preceded or accompanied severe arrhythmias in some cases. Convulsions in patients taking astemizole may also be related to cardiovascular effects.[8]

Studies have suggested that astemizole induces ventricular arrhythmias by inhibiting cardiac potassium channels which results in prolongation of the QT interval, a risk factor for developing arrhythmias.[9] For further discussion, see p. 613.2.

1. Simons FER, *et al.* Astemizole-induced torsade de pointes. *Lancet* 1988; **ii:** 624.
2. Hoppu K, *et al.* Accidental astemizole overdose in young children. *Lancet* 1991; **338:** 538–40.
3. Tobin JR, *et al.* Astemizole-induced cardiac conduction disturbances in a child. *JAMA* 1991; **266:** 2737–40.
4. Wiley JF, *et al.* Cardiotoxic effects of astemizole overdose in children. *J Pediatr* 1992; **120:** 799–802.
5. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
6. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
7. CSM/MCA. Astemizole (Hismanal): only available on prescription. *Current Problems* 1999; **25:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 19/05/06)
8. Clark A, Love H. Astemizole-induced ventricular arrhythmias: an unexpected cause of convulsions. *Int J Cardiol* 1991; **33:** 165–7.
9. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

Overdosage. Severe cardiac events have been associated with astemizole overdosage (see Arrhythmias, above); management is mainly supportive. The absorption of astemizole from the gastrointestinal tract can be prevented by giving activated charcoal[1] but because astemizole is rapidly absorbed it would need to be given as soon as possible after poisoning. Haemodialysis does not appear to increase the clearance of astemizole.

1. Laine K, *et al.* The effect of activated charcoal on the absorption and elimination of astemizole. *Hum Exp Toxicol* 1994; **13:** 502–5.

Sedation. For discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Astemizole should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the imidazole and triazole antifungals such as ketoconazole and itraconazole, and the macrolide antibacterials clarithromycin, erythromycin, troleandomycin, and possibly other macrolides. Others, similarly to terfenadine (p. 641.1), may include serotonin reuptake inhibitors, HIV-protease inhibitors, NNRTIs, and zileuton. The metabolism of astemizole may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, and the beta blocker sotalol should be avoided, as should diuretics that cause electrolyte imbalances such as hypokalaemia. The use of terfenadine and astemizole together is not recommended.

Pharmacokinetics

Absorption of astemizole from the gastrointestinal tract is rapid and is reduced by food. First-pass metabolism is extensive, therefore plasma concentrations of unchanged drug are very low. The plasma concentration of astemizole plus metabolites takes about 4 to 8 weeks to reach steady state. The metabolism of astemizole is mediated through the cytochrome P450 enzyme system by the isoenzymes CYP3A4, CYP2D6, and CYP2A6. The elimination half-life of astemizole and its metabolites at steady state is about 19 days. Unchanged astemizole is highly bound to plasma proteins and does not appear to cross the blood-brain barrier to a significant extent. Desmethylastemizole, the major metabolite of astemizole, has histamine H_1-receptor-blocking activity; tecastemizole (norastemizole) is another active metabolite. The metabolites of astemizole are excreted slowly in the urine and faeces, and undergo enterohepatic recycling. Virtually none of an oral dose is excreted as unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Leanimol; Maxirgot; Mibiron; Tulipe-R; Tyrenol; Varivenot; Waruzol; ***India***: Acemiz; Acipax; Alerzole; Astelong; Astizole†; Stemiz; ***Mex.***: Alerfur†; Alerken; Alermi; Aleztem†; Anerzol†; Antagon 1†; Astemina†; Astesen; Aztemin†; Aztil†; Aztrolen; Biostan; Dexodin†; Emdar†; Emizol†; Farmidal S; Fustermizol†; Histalino; Histaser; Novasten; Practizol†; Urtigen†.

Pharmacopoeial Preparations

USP 36: Astemizole Tablets.

Azatadine Maleate *(BANM, USAN, rINNM)*

Atsatadiinimaleaatti; Azatadina, maleato de; Azatadine, Maléate d'; Azatadini Maleas; Azatadinmaleat; Maleato de azatadina; Sch-10649; Азатадина Малеат.

6,11-Dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine dimaleate.

$C_{20}H_{22}N_2,2C_4H_4O_4$=522.6

CAS — 3964-81-6 (azatadine); 3978-86-7 (azatadine maleate).

ATC — R06AX09.

ATC Vet — QR06AX09.

UNII — F3Q391WTX7.

Pharmacopoeias. In *US.*

USP 36: (Azatadine Maleate). A white to light cream-coloured, odourless powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; practically insoluble in ether and in benzene.

Profile

Azatadine maleate is a piperidine derivative closely related to cyproheptadine. It is a sedating antihistamine (p. 610.1) with a long duration of action; it also has antimuscarinic and antiserotonin properties.

Azatadine maleate has been used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and urticaria (p. 612.3); it was also used for other pruritic skin disorders as well as reactions to insect bites and stings. It has been given in usual oral doses of 1 mg twice daily; if necessary 2 mg twice daily has been used. For children's doses, see below. Azatadine has also been used with a decongestant such as pseudoephedrine sulfate.

Administration in children. Children aged 6 to 12 years have been given 0.5 to 1 mg azatadine maleate, orally, twice daily for the symptomatic relief of allergic conditions including rhinitis and urticaria.

Extrapyramidal effects. An acute dystonic reaction was reported in a patient who had taken azatadine maleate

20 to 30 mg orally over a 24-hour period.[1] The condition was reversed by intravenous injection of benzatropine 2 mg.

1. Joske DJL. Dystonic reaction to azatadine. *Med J Aust* 1984; **141:** 449.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zadine†; ***Canad.***: Optimine†; ***Gr.***: Nalomet.

Multi-ingredient Preparations. ***Braz.***: Cedrin; ***Gr.***: Nalomet-D.

Pharmacopoeial Preparations
USP 36: Azatadine Maleate Tablets.

Azelastine Hydrochloride

(BANM, USAN, rINNM)

A-5610 (azelastine or azelastine hydrochloride); Atselastiini-hydrokloridi; Azelastin Hidroklorür; Azelastina, hidrocloruro de; Azélastine, chlorhydrate d'; Azelastinhydrochlorid; Azelastin-hydrochlorid; Azelastinhydroklorid; Azelastini hydrochloridum; Azelastino hidrochloridas; E-0659 (azelastine or azelastine hydrochloride); Hidrocloruro de azelastina; W-2979M (azelastine or azelastine hydrochloride); Азеластина Гидрохлорид.

4-(*p*-Chlorobenzyl)-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone monohydrochloride.

$C_{22}H_{24}ClN_3O,HCl$=418.4

CAS — 58581-89-8 (azelastine); 79307-93-0 (azelastine hydrochloride).

ATC — R01AC03; R06AX19; S01GX07.

ATC Vet — QR01AC03; QR06AX19; QS01GX07.

UNII — 0L591QR10I.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Azelastine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in dehydrated alcohol and in dichloromethane.

Uses and Administration

Azelastine hydrochloride is an antihistamine that, in addition to its histamine H_1-receptor-blocking activity, appears to inhibit the release of inflammatory mediators from mast cells. It is used topically in the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and conjunctivitis (p. 611.1). It is also used in the treatment of non-allergic rhinitis.

In the treatment of allergic **rhinitis** in adults and children aged 5 years and over, the usual dose in the UK is 140 micrograms of azelastine hydrochloride by nasal spray into each nostril twice daily. In the USA, however, 1 or 2 sprays of a similar preparation (supplying 137 micrograms per spray) may be given into each nostril twice daily in adults; children aged 5 to 12 years may be given 1 spray into each nostril twice daily. In the USA, azelastine is also licensed for the treatment of non-allergic rhinitis in adults and children aged 12 years and over. The dose is 2 sprays (274 micrograms) into each nostril twice daily. Also available in the USA is a nasal preparation supplying 205.5 micrograms of azelastine hydrochloride per spray. It may be given in a dose of 1 or 2 sprays per nostril twice daily or 2 sprays once daily for the treatment of allergic rhinitis in adults and children aged 12 years and over.

In the management of **conjunctivitis**, azelastine is licensed in the UK for the treatment and prophylaxis of seasonal allergic conjunctivitis in adults and children aged 4 years and over and for the treatment of perennial allergic conjunctivitis in adults and children aged 12 years and over. In the USA, it is licensed for the treatment of allergic conjunctivitis in adults and children aged 3 years and over. Regardless of the age and indication, a 0.05% solution is instilled into each eye twice daily; this may be increased to four times daily in severe conditions.

Azelastine hydrochloride has also been given orally.

References.

1. Lenhard G, *et al*. Double-blind, randomised, placebo-controlled study of two concentrations of azelastine eye drops in seasonal allergic conjunctivitis or rhinoconjunctivitis. *Curr Med Res Opin* 1997; **14:** 21–8.
2. Sabbah A, Marzetto M. Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children. *Curr Med Res Opin* 1998; **14:** 161–70.
3. Duarte C, *et al*. Treatment of severe seasonal rhinoconjunctivitis by a combination of azelastine nasal spray and eye drops: a double-blind, double-placebo study. *J Investig Allergol Clin Immunol* 2001; **11:** 34–40.
4. Canonica GW, *et al*. Topical azelastine in perennial allergic conjunctivitis. *Curr Med Res Opin* 2003; **19:** 321–9.
5. Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. *Pharmacotherapy* 2007; **27:** 852–9.
6. Bernstein JA. Azelastine hydrochloride: a review of pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Curr Med Res Opin* 2007; **23:** 2441–52.
7. Lee C, Corren J. Review of azelastine nasal spray in the treatment of allergic and non-allergic rhinitis. *Expert Opin Pharmacother* 2007; **8:** 701–9.
8. Anonymous. Azelastine (Astepro) nasal spray for allergic rhinitis. *Med Lett Drugs Ther* 2009; **51:** 29–30.

Administration in children. Doses of azelastine hydrochloride in children are similar to those used in adults (see above).

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively.

When given intranasally, irritation of the nasal mucosa and taste disturbances have been reported; somnolence, headache, and dry mouth have also been noted in some patients. Taste disturbance can occur after use in the eye.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azelastine as possibly porphyrinogenic when given intranasally; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. It is considered non-porphyrinogenic when used in eye preparations.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

About 40% of an intranasal dose of azelastine reaches the systemic circulation. Elimination is via hepatic metabolism with excretion mainly in the faeces.

Azelastine is rapidly and almost completely absorbed when given *orally* and peak plasma concentrations occur in 4 to 5 hours. Azelastine undergoes hepatic metabolism; the major metabolite, demethylazelastine, has antihistamine activity. The elimination half-life of azelastine is about 25 hours, increasing to 35.5 hours after multiple oral doses, possibly as a result of accumulation of the demethyl metabolite. Azelastine and its metabolites are excreted mainly in the faeces and also in urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alager; Allergodil; Brixia; Xanaes; ***Austral.***: Azep; Eyezep; ***Austria***: Allergodil; Allergospray; ***Belg.***: Allergodil; Otrivine Anti-Allergie; ***Braz.***: Rino-Lastin; ***Chile***: AZ Ofteno; Brixia; ***China***: Azep (爱赛平); Fu Di (芙迪); Min Qi (敏奇); Xin Bai Ke (新百克); ***Cz.***: Allergodil; ***Denm.***: Allergodil; ***Fin.***: Lastin; Oculastin; ***Fr.***: Allergodil; Proallergodil; Prorhinite†; ***Ger.***: Allergodil; Vividrin akut Azelastin; ***Gr.***: Afluon; ***Hong Kong***: Azep; ***Hung.***: Allergodil; ***India***: Arzep; Azelast; Azep; Oculast; ***Irl.***: Optilast; Rhinolast; ***Israel***: Optilast; Rhinolast; ***Ital.***: Allergodil; Lasticom; ***Jpn***: Azeptin; ***Mex.***: Amsler; Astelin; AZ Ofteno; ***Neth.***: Allergodil; Oculastin; Otrivin neusallergie azelastine; ***Norw.***: Azelvin†; Lastin; ***NZ***: Eyezep; ***Philipp.***: Azela; Azelone; Azep; ***Pol.***: Allergodil; ***Port.***: Allergodil; Azep; Oculastin; ***Rus.***: Allergodil (Аллергодил); ***S.Afr.***: Optilast; Rhinolast; ***Singapore***: Azep; ***Spain***: Afluon; Corifina; ***Swed.***: Azelvin†; Lastin; ***Switz.***: Allergodil; Otrivin rhume des foins; ***Turk.***: Allergodil; ***UK***: Aller-Eze; Optilast; Rhinolast; ***Ukr.***: Allergodil (Аллергодил); ***USA***: Astelin; Astepro; Optivar; ***Venez.***: Alergot; Allergodil; AZ; Brixia.

Multi-ingredient Preparations. ***Fin.***: Dymista; ***India***: Azeflo; Duonase; Nezalast; ***UK***: Dymista; ***USA***: Dymista.

Bamipine *(BAN, rINN)*

Bamipiini; Bamipin; Bamipina; Bamipinum; Бамипин.

N-Benzyl-*N*-(1-methyl-4-piperidyl)aniline.

$C_{19}H_{24}N_2$=280.4

CAS — 4945-47-5.

ATC — D04AA15; R06AX01.

ATC Vet — QD04AA15; QR06AX01.

UNII — Y6BHZ28O92.

Profile

Bamipine is a sedating antihistamine (p. 610.1) with pronounced sedative effects.

Bamipine and its salts have been used mainly for the symptomatic relief of allergic conditions such as urticaria (p. 612.3) and in pruritic skin disorders. Bamipine hydrochloride has been given orally; bamipine, bamipine lactate, and bamipine salicylate have all been applied topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Soventol; ***Ger.***: Soventol; ***Gr.***: Soventol; ***Neth.***: Soventol; ***Pol.***: Soventol.

Multi-ingredient Preparations. ***India***: Multifungin H.

Bepotastine *(USAN, rINN)*

Bepotastina; Bépotastine; Bepotastinum; Betotastine; Бепотастин.

(+)-4-{[(*S*)-*p*-Chloro-α-2-pyridylbenzyl]oxy}-1-piperidinebutyric acid.

$C_{21}H_{25}ClN_2O_3$=388.9

CAS — 125602-71-3; 190786-43-7.

UNII — HYD2U48IAS.

Bepotastine Besilate *(rINNM)*

BB; Bépotastine, Bésilate de; Bepotastine Besylate (USAN); Bepotastini Besilas; Besilato de bepotastina; Betotastine Besilate; TAU-284; Бепотастина Безилат.

$C_{21}H_{25}ClN_2O_3$, $C_6H_6O_3S$=547.1

CAS — 190786-44-8.

UNII — 6W18MO1QR3.

Profile

Bepotastine is an antihistamine (p. 610.1) used as the besilate in the treatment of allergic rhinitis and for the symptomatic relief of urticaria and pruritic skin disorders. The usual oral dose is 10 mg of bepotastine besilate twice daily.

Bepotastine besilate is also used in the treatment of allergic conjunctivitis in adults and children aged 2 years and over; a 1.5% solution is instilled into each affected eye twice daily.

Reviews.

1. Lyseng-Williamson KA. Oral bepotastine: in allergic disorders. *Drugs* 2010; **70:** 1579–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Talion (坦亮); ***Jpn***: Talion; ***USA***: Bepreve.

Bilastine *(rINN)*

Bilastina; Bilastinum; Биластин.

p-(2-{4-[1-(2-Ethoxyethyl)-2-benzimidazolyl]piperidino}ethyl)-α-methylhydratropic acid.

$C_{28}H_{37}N_3O_3$=463.6

CAS — 202189-78-4.

ATC — R06AX29.

ATC Vet — QR06AX29.

UNII — PA1123N395.

Profile

Bilastine is a long-acting non-sedating antihistamine (p. 610.1). It is used in the symptomatic treatment of allergic rhinitis, conjunctivitis, and urticaria. An oral dose of 20 mg is given once daily, at least 1 hour before or 2 hours after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Bellozal; ***Cz.***: Xados; ***Fin.***: Revitelle; ***Fr.***: Bilaska; Inorial; ***Irl.***: Drynol; ***Ital.***: Olisir; Robilas; ***Port.***: Bilaxten; ***Spain***: Bilaxten; Ibis; Obalix; ***Switz.***: Bilaxten; ***UK***: Ilaxten.

Bisulepin

Бисулепин.

4-[3-(Dimethylamino)propylidene]-4,9-dihydrothienol[2,3-*b*]benzo[*e*]thiepin.

$C_{17}H_{19}NS_2$=301.5

CAS — 5802-61-9 (bisulepin); 1154-12-7 (bisulepin hydrochloride).

UNII — 595726R32U.

Profile

Bisulepin is given orally as an antihistamine; the hydrochloride salt is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Dithiaden.

Bromazine Hydrochloride *(BANM, rINNM)*

Bromazina, hidrocloruro de; Bromazine, Chlorhydrate de; Bromazini Hydrochloridum; Bromodiphenhydramine Hydro-

chloride; Hidrocloruro de bromazina; Бромазина Гидрохлорид.
2-(4-Bromobenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.
$C_{17}H_{20}BrNO,HCl$=370.7
CAS — 118-23-0 (bromazine); 1808-12-4 (bromazine hydrochloride).
ATC — R06AA01.
ATC Vet — QR06AA01.
UNII — 202J683U97.

Pharmacopoeias. In *US.*

USP 36: (Bromodiphenhydramine Hydrochloride). A white to pale buff-coloured, crystalline powder having no more than a faint odour. Soluble 1 in less than 1 of water, 1 in 2 of alcohol and of chloroform, 1 in 3500 of ether, and 1 in 31 of isopropyl alcohol; insoluble in petroleum spirit. Store in airtight containers.

Profile

Bromazine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and marked sedative actions. It has been used in combination preparations for the symptomatic treatment of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Ambenyl Cough Syrup†; Amgenal Cough†; Bromotuss with Codeine†.

Pharmacopoeial Preparations
USP 36: Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Bromodiphenhydramine Hydrochloride Elixir.

Brompheniramine Maleate

(BANM, rINNM)

Bromfeniramin Maleat; Bromfeniramina, maleato de; Brómfeniramin-maleát; Bromfeniraminmaleat; Bromfeniramin-maleinát; Bromfeniramino maleatas; Bromifeniramiini-maleaatti; Bromphéniramine, Maléate de; Brompheniramini Maleas; Brompheniraminmaleat; Maleato de bromfeniramina; Parabromdylamine Maleate; Бромфенирамина Малеат.
(±)-3-(4-Bromophenyl)-*NN*-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.
$C_{16}H_{19}BrN_2.C_4H_4O_4$=435.3
CAS — 86-22-6 (brompheniramine); 980-71-2 (brompheniramine maleate).
ATC — R06AB01.
ATC Vet — QR06AB01.
UNII — IXA7C9ZN03.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Brompheniramine Maleate). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Brompheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 5 of water, 1 in 15 of alcohol and of chloroform; slightly soluble in ether and in benzene. pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Incompatibility. Brompheniramine maleate has been reported to be incompatible with some amidotrizoate, adipiodone, and iotalamate salts.

Dexbrompheniramine Maleate

(BANM, rINNM)

Dexbromfeniramina, maleato de; Dexbromphéniramine, Maléate de; Dexbrompheniramini Maleas; Maleato de dexbromfeniramina; Дексбромфенирамина Малеат.
CAS — 2391-03-9.
ATC — R06AB06.
ATC Vet — QR06AB06.
UNII — BPA9UT29BS.

Pharmacopoeias. In *US.*

USP 36: (Dexbrompheniramine Maleate). A white, odourless, crystalline powder. It exists in two polymorphic forms, one melting between 106 degrees and 107 degrees, and the other between 112 degrees and 113 degrees; a mixture of the two forms may melt between 105 degrees and 113 degrees. Soluble 1 in 1.2 of water, 1 in 2.5 of alcohol, 1 in 2 of chloroform, and 1 in 3000 of ether. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Uses and Administration

Brompheniramine maleate, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative actions.

Brompheniramine is a racemic mixture; dexbrompheniramine, the dextrorotatory isomer, has about twice the activity of brompheniramine by weight. Brompheniramine maleate and dexbrompheniramine maleate are used for the symptomatic relief of allergic conditions, mainly rhinitis (p. 612.1) and conjunctivitis (p. 611.1). They are common ingredients of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2). Brompheniramine tannate has been used similarly.

Brompheniramine maleate is given in usual oral doses of 4 mg every four to six hours. It has also been given by subcutaneous, intramuscular, or slow intravenous injection.

Dexbrompheniramine maleate is normally given as an ingredient of decongestant preparations containing pseudoephedrine. The dose of dexbrompheniramine maleate in these oral combinations is 6 mg no more than twice daily.

Modified-release oral preparations of brompheniramine maleate or dexbrompheniramine maleate are available in some countries; dosage is specific to a particular formulation.

For dosage in children, see below.

Administration in children. Brompheniramine maleate may be given orally to children, for the symptomatic relief of allergic conditions such as rhinitis and conjunctivitis; doses are as follows:

- children aged 2 to 6 years: 1 mg every four to six hours
- those aged 6 to 12 years: 2 mg every four to six hours
- those aged over 12 years: 4 mg every four to six hours

Brompheniramine maleate is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold. However, such preparations should be used with caution in children, and generally avoided in young children, for details see p. 614.1.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers which contain dexbrompheniramine maleate with pseudoephedrine have resulted in crying, irritability, and poor sleep patterns in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Effects on the blood. Agranulocytosis in a 34-year-old alcoholic man was possibly associated with brompheniramine therapy.[1]

1. Hardin AS, Padilla F. Agranulocytosis during therapy with a brompheniramine-medication. *J Arkansas Med Soc* 1978; **75:** 206–8.

Extrapyramidal disorders. Facial dyskinesias have been reported[1,2] after use of antihistamines including brompheniramine or dexbrompheniramine maleate.

1. Thach BT, *et al.* Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. *N Engl J Med* 1975; **293:** 486–7 (brompheniramine maleate, chlorpheniramine maleate, and phenindamine tartrate).
2. Barone DA, Raniolo J. Facial dyskinesia from overdose of an antihistamine. *N Engl J Med* 1980; **303:** 107 (dexbrompheniramine maleate).

Withdrawal. Withdrawal symptoms have been reported[1] after stopping long-term therapy with brompheniramine maleate. A patient had been taking 48 mg almost every day for 20 years and developed tremor, nausea, depression, and apyrexial sweating within 48 hours of stopping treatment; symptoms resolved over the following weeks.

1. Kavanagh GM, *et al.* Withdrawal symptoms after discontinuation of long-actingbrompheniramine maleate. *Br J Dermatol* 1994; **131:** 913–14.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Brompheniramine maleate appears to be well absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about 5 hours. An elimination half-life of about 25 hours has been reported. Unchanged drug and metabolites are excreted mainly in the urine.

References.

1. Simons FER, *et al.* The pharmacokinetics and antihistaminic effects of brompheniramine. *J Allergy Clin Immunol* 1982; **70:** 458–64.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Dimegan; ***Gr.***: Dimetane; ***Hong Kong***: Bromiton†; ***Malaysia***: Bomex; ***Singapore***: Bomex; ***Thai.***: Babycold†; Bomine; Bromma; Bromphen; Bromsin; Dimetane†; Probrom; ***USA***: Alahist IR; Bidhist†; J-Tan; Lodrane 12†; Lodrane 24†; Oraminic II; P-Tex†.

Multi-ingredient Preparations. ***Arg.***: Factus; ***Austral.***: Dimetapp DM; Dimetapp; ***Braz.***: Bialerge; Decongex Plus; Dimetapp; Winter AP; ***Canad.***: Cold And Allergy Liquid†; Cold Syrup; Dimetane Expectorant C; Dimetane Expectorant DC; Dimetapp Chewables for Kids; Dimetapp Cold†; Dimetapp DM Cough & Cold; Dimetapp-C; Dimetapp; DM Cough and Cold; Drixoral Day/Night†; Drixoral; Drixtab†; Extra Strength Cold Syrup; Extra Strength DM Cough and Cold; Oral Infant Cold Drops†; ***China***: Cofetol (奥亭); Neosed (尔可适); Rhinobol (尔可安); ***Cz.***: Disophrol; ***Gr.***: Dimetapp New; Dimetapp; Disofrin; ***Hong Kong***: America†; B.P.P.†; BPP Cough Syrup†; Brom-PP; Brom-Ramine Compound; Bromphenex†; DF Multi-Symptom†; Dimeta-2; Dimetapp; Drixoral†; Eascold; Eurotapp; Fastolin†; Fludane†; Futalin†; Futara†; Mecostop†; Unihist; Vidatapp Forte†; Vidatapp†; ***Indon.***: Alco Plus DMP; Alco Plus; Drixoral; ***Irl.***: Dimotane Co†; Ilvico; ***Malaysia***: Rinafort; Unihist; ***Mex.***: Afrinex†; Cripofen; Dimetapp; Sedalmerck Flu; ***NZ***: Dimetapp DM Cold & Cough; Dimetapp; ***Philipp.***: Bromitapp; Dimerrin; Dimetapp; DMT; Hisdec; Nasatapp; Nostero†; Pediatapp; Penbrosol; PPB; Remedril; Rhinodec; Rhinotapp; Snizee; Solvamin; Zeditapp; ***Pol.***: Disophrol†; NeoAfrin; ***Port.***: Constipal†; Ilvico N; ***S.Afr.***: Dimetapp†; Ilvico†; ***Singapore***: Dimetapp; Rinafort; ***Spain***: Disofrol; Ilvico; ***Swed.***: Disofrol†; ***Switz.***: Disofrol†; ***Thai.***: Aorinyl; Asiatapp; Bepeno-G; Bepeno; Bluco; Bromavon†; Bromceryl; Bromesep Elixir; Bromesep Expectorant; Bromesep Syrup; Bromiphed; Bromlamine; Bromped; Bromsuno; Bromtussia DC†; Bromtussia; Brontus; Centapp; Chintacold; Cold-tab; Coldate; Cotapp Expectorant; Cotapp; Daminate; Decon; Dimetapp; Ditap; Leffrin; Meditapp Expectorant†; Meditapp; MEXY; Minra; Nartap; Nased; Nasorest Expectorant; Nasorest; Nasotane; Nasotapp; Pharcold; Pharfed; Phemine; Polamine; Polydine; Polydrop; Postap Expectorant†; Postap†; Rhinadine†; Sinufen; St Luke's Cold; Topamine; Unihist; ***Turk.***: Disophrol; ***UK***: Dimotane Co; Dimotane Expectorant; ***USA***: 12 Hour Antihistamine Nasal Decongestant; 12 Hour Cold; Accuhist DM Pediatric; Accuhist PDX†; Alacol DM†; Alahist DM; Allent; Anaplex DM; Anaplex HD†; B-Vex PD; Balacall DM; BP New Allergy DM†; BPM PE DM; Brofed; Brohist D; Brom/PE/DM; Bromadine-DM; Bromaline DM†; Bromaline†; Bromarest DX; Bromatan-DM†; Bromatane DX; Bromdex D; Bromfed-DM; Bromfed-PD; Bromfed; Bromhist PDX†; Bromhist PDX; Bromhist-DM†; Bromhist-NR†; Bromhist†; Bromphen DX Cough; Brompheniramine Cough; Brompheniramine/Pseudoephedrine DM; Brotapp DM; Brotapp; Brovex ADT†; BroveX CB†; BroveX CBX†; BroveX PB C†; BroveX PB CX†; BroveX PB DM†; Brovex PB†; Brovex PD†; Brovex PEB DM; BroveX PEB; BroveX PSB DM; BroveX PSB; BroveX PSE DM; BroveX PSE; C-Tan D†; Carbodex DM; Cenhist; Childrens Dimaphen DM Cold & Cough; Coldec DM; Comtrex Acute Head Cold; Conex Cold & Allergy†; CPB WC; Cytuss-HC NR†; Dallergy DM†; DEKA; Dexaphen-SA; Dicel CD; Dimetane DX†; Dimetapp Childrens Cough & Cold; Dimetapp Cold & Fever; Dimetapp DM; Dimetapp Nighttime Flu; Dimetapp; Disobrom; Disophrol; DM/PSE/BPM; Dristan Allergy; Dristan Cold Maximum Strength Multi-symptom Formula; Drixoral Cold & Allergy; Drixoral Cold & Flu; Drixoral Plus; Drixoral; Drocon-CS; Enda-Cof-AC; EndaCof-DH†; Endafed; Histacol DM†; Histussin HC; Iofed; J-COF DHC; J-Tan D HC†; J-Tan D†; Lodrane 12D; Lodrane D; Lodrane†; LoHist PEB DM; LoHist PEB; LoHist PSB; LoHist-DM; M-End Max D; M-End PE; M-END WC; Mar-Cof BP; Maximum Strength Dristan Cold; Mesehist WC; Myphetane DX†; Nalex AC; Neo DM; P-Hist DM; Panatuss DXP; PBM Allergy†; Pediahist DM†; Pediahist DM; Phenylephrine Complex; Poly-Tussin AC; Poly-Tussin DHC; Q-Tapp DM; Relhist; Respahist-II†; Respahist†; Resperal-DM†; Rondamine-DM; Rondec†; Rynex PE; Seradex-LA†; Sildec-DM; Sinadrin PE; Sinadrin Plus; Sinuhist†; SymPak II; Tanabid†; TG PSE/BRM/DM; TGQ PEH/BRM/DM; TGQ PSE/BRM/DM; TL-Hist DM; Touro A & H; Touro Allergy†; Trexbrom; Tusdec-DM†; Tusnel-HC†; Tussall; ULTRAbrom†; V-Cof; Vazobid PD; VaZol-D†; Vazotab†; Vazotan; Vazotuss HC†; Zotex-PE†; ***Venez.***: Dimetapp; Ilvico; Ilvico; Metorfedrin.

Pharmacopoeial Preparations
BP 2014: Brompheniramine Tablets;
USP 36: Brompheniramine Maleate Elixir; Brompheniramine Maleate Injection; Brompheniramine Maleate Tablets; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution.

Buclizine Hydrochloride *(BANM, USAN, rINNM)*

Buclizina, hidrocloruro de; Buclizine, Chlorhydrate de; Buclizini Hydrochloridum; Buklizin Hidroklorür; Hidrocloruro de buclizina; NSC-25141; UCB-4445; Буклизина Гидрохлорид.
(*RS*)1-(4-*tert*-Butylbenzyl)-4-(4-chlorobenzhydryl)piperazine dihydrochloride.

$C_{28}H_{33}ClN_2,2HCl$=506.0
CAS — 82-95-1 (buclizine); 129-74-8 (buclizine hydrochloride).
ATC — R06AE01.
ATC Vet — QR06AE01.
UNII — 58FQD093NU.

Pharmacopoeias. In *Br.*

BP 2014: (Buclizine Hydrochloride). A white or slightly yellowish, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; sparingly soluble in chloroform and in propylene glycol.

Uses and Administration

Buclizine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative actions. It is used mainly for its antiemetic action, particularly in the prevention of motion sickness (p. 611.3) and with analgesics in the treatment of migraine (p. 670.3). In some countries it is given in the management of allergic conditions and in pruritic skin disorders (p. 612.1). Buclizine has also been used in the treatment of vertigo (p. 612.3) associated with disorders of the vestibular system, although its value in these conditions is unproven.

For most indications, the usual dose is 25 or 50 mg daily; in severe cases up to 100 mg daily has been given.

In the treatment of migraine, buclizine hydrochloride is given in usual doses of 12.5 mg at the start of an attack or when one is known to be imminent.

For children's doses, see below.

Administration in children. An oral dose of 12.5 to 30 mg daily of buclizine hydrochloride has been given to children aged 5 to 10 years in the management of allergic conditions and as an antiemetic in, for example, the treatment of motion sickness.

Buclizine hydrochloride is also used with analgesics in the management of migraine; children aged 10 to 14 years may be given 6.25 mg at the start of an attack, or when one is known to be imminent.

Older children can be given the usual adult dose (see above).

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Longifene; ***Braz.***: Buclina; Postafen; ***India***: Longifene; ***S.Afr.***: Longifene†; ***Turk.***: Longifene.

Multi-ingredient Preparations. ***Braz.***: Apetil; Buclimax†; Carnabol; Complevit†; Klizin; Nutrimaiz SM; Pondusvitam; Profol; Propan; ***Irl.***: Migraleve; ***Israel***: Migraleve; ***Phil.ipp.***: Appebon with Iron; Appebon with Iron; Appebon; Appebon; Appetason; Appetite Plus; Appetite with Iron; Biotermin AS; Ferlette; Medifortan-AS; Pediafortan-AS; Propan with Iron; Propan; Regeron-E Plus; ***Port.***: Migraleve; ***S.Afr.***: Vomifene; ***Spain***: Migraleve; ***Switz.***: Migraleve†; ***UK***: Migraleve; ***Venez.***: Dexapostafen.

Carbinoxamine Maleate *(BANM, rINNM)*

Carbinoxamina, maleato de; Carbinoxamine, Maléate de; Carbinoxamini Maleas; Karbinoksamin Maleat; Maleato de carbinoxamina; Карбиноксамина Малеат.

2-[4-Chloro-α-(2-pyridyl)benzyloxy]-*NN*-dimethylethylamine hydrogen maleate.

$C_{16}H_{19}ClN_2O,C_4H_4O_4$=406.9
CAS — 486-16-8 (carbinoxamine); 3505-38-2 (carbinoxamine maleate).
ATC — R06AA08.
ATC Vet — QR06AA08.
UNII — 02O55696WH.

Pharmacopoeias. In *US.*

USP 36: (Carbinoxamine Maleate). A white, odourless, crystalline powder. Soluble 1 in less than 1 of water, 1 in 1.5 of alcohol and of chloroform, and 1 in 8300 of ether. pH of a 1% solution in water is between 4.6 and 5.1. Store in airtight containers. Protect from light.

Uses and Administration

Carbinoxamine maleate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and serotonin antagonist effects. Carbinoxamine maleate is used for the relief of allergic conditions such as rhinitis (p. 612.1), and is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2).

Dose recommendations for carbinoxamine maleate may vary between preparations. Licensed US product information suggests a usual oral dose of carbinoxamine maleate of 4 to 8 mg given 3 or 4 times daily. Lower doses, sometimes less than half these licensed in the US, may be used in other countries.

For children's doses, see below. Carbinoxamine polistirex has also been given orally.

Administration in children. In children, carbinoxamine maleate may be used for the symptomatic treatment of allergic conditions including rhinitis and urticaria. The oral doses below are suggested by licensed US product information; lower doses, sometimes less than half, may be used in other countries.

- children aged 2 to 3 years: 2 mg three or four times daily
- those aged 3 to 6 years: 2 to 4 mg three or four times daily
- those aged over 6 years: 4 to 6 mg three or four times daily

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Omega 100; ***Mon.***: Allergefon†; ***Rus.***: Rhinopront (Ринопронт); ***Thai.***: Histin; ***USA***: Arbinoxa; Histex CT; Histex I/E; Histex PD; Karbinal; Palgic; Pediatex.

Multi-ingredient Preparations. ***Arg.***: Aseptobron C; Omega 100 Expectorante; ***Austria***: Rhinopront†; ***Braz.***: Naldecon Bebe†; Naldecon Noite; Naldecon; Naldecon; Nasaliv; Nasaliv; Neolefrin Baby; Neolefrin; Neolefrin; Resprin; ***Chile***: Matinor; ***Gr.***: Rhinopront-S; Rhinopront; Rondec; ***Hong Kong***: Became; Coritussal†; Metoplex; Rhinopront†; ***India***: Clistin; ***Indon.***: Kenantist†; ***Malaysia***: Became; ***Mex.***: Lentostamin†; Prindex†; ***Singapore***: Became; ***Spain***: Rinomax†; ***Thai.***: Rhinar; Rhinohist; ***Turk.***: Rhinopront; Rhinopront; Rhinotussal; Rhinotussal; ***USA***: Aridex; Carbiset; Carbodec DM; Carbodec; Carbodex DM; Carboxine-PSE; Coldec D; Cordron-D†; Cordron-DM; Dacex-A; DMax; Histex HC†; Nacon; Norel LA†; Palgic DS; Palgic-D; Pediatex-D; Pediatex-DM; Pseudo-Car DM; Rondec†; Sildec-DM; Trituss-A; XiraHist DM; ***Venez.***: Resprin.

Pharmacopoeial Preparations
USP 36: Carbinoxamine Maleate Tablets; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Cetirizine Hydrochloride

(BANM, USAN, rINNM)

Cetirizina, hidrocloruro de; Cetirizin-dihidroklorid; Cetirizin-dihydrochlorid; Cetirizindihydroklorid; Cétirizine, Chlorhydrate de; Cétirizine, dichlorhydrate de; Cetirizini dihydrochloridum; Cetirizini Hydrochloridum; Cetirizino dihidrocloridas; Cetyryzyny dichlorowodorek; Hidrocloruro de cetirizina; P-071; Setiritsiinidihydrokloridi; Setirizin Hidroklorür; UCB-P071; Цетиризина Гидрохлорид.

The dihydrochloride of 2-[4-(4-chlorobenzhydryl)piperazin-1-yl]ethoxyacetic acid.

$C_{21}H_{25}ClN_2O_3,2HCl$=461.8
CAS — 83881-51-0 (cetirizine); 83881-52-1 (cetirizine hydrochloride).
ATC — R06AE07.
ATC Vet — QR06AE07.
UNII — 64O047KTOA.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Cetirizine Dihydrochloride; Cetirizine Hydrochloride BP 2014). A white or almost white powder. Freely soluble in water; practically insoluble in acetone and in dichloromethane. A 5% solution in water has a pH of 1.2 to 1.8. Protect from light.

USP 36: (Cetirizine Hydrochloride). White to almost white powder. Freely soluble in water; practically insoluble in acetone and in dichloromethane. pH of a 5% solution in water is between 1.2 to 1.8. Store in airtight containers. Protect from light and moisture.

Uses and Administration

Cetirizine hydrochloride, a piperazine derivative and metabolite of hydroxyzine (p. 630.3), is described as a long-acting non-sedating antihistamine with some mast-cell stabilising activity. It appears to have a low potential for drowsiness in usual doses and to be virtually free of antimuscarinic activity.

Cetirizine hydrochloride is used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and chronic urticaria (p. 612.3). It is given in a usual oral dose of 10 mg once daily or 5 mg twice daily although, in the USA, initial doses of 5 mg daily have also been used.

It is also used with a decongestant such as pseudoephedrine hydrochloride.

For doses in children, see below. Dosage of cetirizine should be reduced in patients with hepatic or renal impairment, see below.

References.

1. Curran MP, *et al.* Cetirizine: a review of its use in allergic disorders. *Drugs* 2004; **64:** 523–61.

Administration in children. In the UK, cetirizine is licensed for use in children aged 2 years and over in the treatment of allergic rhinitis and urticaria; in the USA, it may be given to those aged 6 months and over for perennial allergic rhinitis and urticaria and to those aged 2 years and over for seasonal allergic rhinitis.

Regardless of indication, licensed oral doses of cetirizine hydrochloride are as follows:

- children aged 6 to 23 months: 2.5 mg once daily increased to a maximum of 2.5 mg twice daily in those aged 12 months and over
- children aged 2 to 5 years: 5 mg daily as a single dose or in 2 divided doses
- those aged 6 years and above: 10 mg daily as a single dose or in 2 divided doses

US licensed product information also suggests an initial dose of half the above doses, given once daily, in children aged 2 years and over and increasing as necessary.

Cetirizine is not licensed in the UK for children under 2 years of age; however, the *BNFC* suggests a dose of 250 micrograms/kg twice daily may be given to children aged 1 to 2 years.

For dose adjustment in hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. In adults with hepatic or renal impairment, US licensed product information recommends that the oral dose of cetirizine hydrochloride should be 5 mg once daily. In children aged between 6 to 11 years, US product information advises the lower recommended dose of cetirizine be used. In the UK, half the normal recommended dose is advised in adults and children with renal impairment.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Cetirizine should be used with caution in patients with hepatic or renal impairment.

Arrhythmias. The ECG effects of cetirizine were studied[1] in normal subjects; doses of up to 6 times the usual recommended dose did not prolong the QT interval. Additionally, the FDA[2] in the USA and representatives of the manufacturers[3] in Belgium did not find any association between cetirizine and the development of ventricular arrhythmias. However, there has been a subsequent report[4] of torsade de pointes after overdosage with cetirizine in a hypokalaemic patient undergoing haemodialysis for chronic renal failure. See also p. 613.2.

1. Sale ME, *et al.* The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther* 1994; **56:** 295–301.
2. Himmel MH, *et al.* Dangers of non-sedating antihistamines. *Lancet* 1997; **350:** 69.
3. Coulie P, *et al.* Non-sedating antihistamines and cardiac arrhythmias. *Lancet* 1998; **351:** 451.
4. Renard S, *et al.* Torsades de pointes induites par surdosage en cétirizine. *Arch Mal Coeur Vaiss* 2005; **98:** 157–61.

Effects on the liver. Life-threatening hepatitis developed in a 23-year-old man who had been taking cetirizine long-term for atopic dermatitis.[1] He recovered after treatment with prednisolone.

Recurrent acute hepatitis associated with the short-term use of cetirizine for seasonal allergic rhinitis has also been reported in a 26-year-old man.[2]

1. Watanabe M, *et al.* Severe hepatitis in a patient taking cetirizine. *Ann Intern Med* 2001; **135:** 142–3.
2. Pompili M, *et al.* Recurrent acute hepatitis associated with use of cetirizine. *Ann Pharmacother* 2004; **38:** 1844–7.

Hypersensitivity. Hypersensitivity reactions manifesting as urticaria[1,2] and fixed drug eruptions[3] have been reported with cetirizine.

1. Karamfilov T, *et al.* Cetirizine-induced urticarial reaction. *Br J Dermatol* 1999; **140:** 979–80.
2. Calista D, *et al.* Urticaria induced by cetirizine. *Br J Dermatol* 2001; **144:** 196.
3. Inamadar AC, *et al.* Multiple fixed drug eruptions due to cetirizine. *Br J Dermatol* 2002; **147:** 1025–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cetirizine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Sedation. For discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3. However, some interactions are less likely with cetirizine than with non-sedating antihistamines such as astemizole and terfenadine, since cetirizine appears to have low hepatic metabolism and little arrhythmogenic potential (see Arrhythmias, p. 619.3).

Anticoagulants. For a report of an interaction between cetirizine and *acenocoumarol*, see under Interactions in Warfarin, p. 1532.2.

Pharmacokinetics

Cetirizine is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about an hour. Food delays the time to peak plasma concentrations but does not decrease the amount of drug absorbed. Cetirizine is highly bound to plasma proteins and has an elimination half-life of about 10 hours. It has been detected in breast milk. Cetirizine is excreted primarily in the urine mainly as unchanged drug. It does not appear to cross the blood-brain barrier to a significant extent.

References.
1. Awni WM, *et al.* Effect of haemodialysis on the pharmacokinetics of cetirizine. *Eur J Clin Pharmacol* 1990; **38:** 67–9.
2. Desager JP, *et al.* A pharmacokinetic evaluation of the second-generation H_1-receptor antagonist cetirizine in very young children. *Clin Pharmacol Ther* 1993; **53:** 431–5.
3. Pitsiu M, *et al.* Retrospective population pharmacokinetic analysis of cetirizine in children aged 6 months to 12 years. *Br J Clin Pharmacol* 2004; **57:** 402–11.
4. Hussein Z, *et al.* Retrospective population pharmacokinetics of levocetirizine in atopic children receiving cetirizine: the ETAC study. *Br J Clin Pharmacol* 2005; **59:** 28–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alernix; Atopix; Cabal; Cetidac; Cetizine; Cetriler; Salvalerg; Stopaler; Zyrtec; ***Austral.***: Alzene; Zilarex; Zodac; Zyrtec; ***Austria***: Cetirhexal; Cetiristad; ratioAllerg; Tirizin; Zyrtec; ***Belg.***: Histimed; Hyperpoll; Reactine; Zyrtec; ***Braz.***: Aletir; Cetihexal; Cetirtec; Cetrizin; Zetalerg; Zetir; Zinetrin†; Zyrtec; ***Canad.***: Allergy Relief; Reactine; ***Chile***: Alertop; Coolips; Findaler; Histalen; Histax; Nonaler; Remitex; Rigotax; Sanaler; Sixacina; Zyrtec; ***China***: An Di Pian (安迪片); An Di Xi Si (安迪西司); BeiFen (贝分); Bi Te Li (比特力); Cetrine (斯特林); Cetrizet (赛特赞); Da Nei (达内); Li Min (立泯); Lian Shuang (联双); Lucheng (路成); Min Da (敏达); Shengminqing (圣敏清); Shi Di (适迪); Shuang Te (爽特); Wei Di Min (威狄敏); Xi Li (昔利); Xi Ning (喜宁); Xi Te Rui (希特瑞); Xi Wa Ding (希瓦丁); Xian Da An (仙达安); Xikewei (西可韦); Xue Ting (雪町); Yi Meng (怡蒙); Yi Wei Tuo (伊维妥); Yingxin MeiShu (盈信美舒); Zinit (仙利特); Zyrtec (仙特明); ***Cz.***: Alerid; Analergin; Cerex; Cetixin; Letizen; Parlazin; Reactine; Zodac; Zyrtec; ***Denm.***: Alnok; Benaday; Histapharm; Tiracetin; Vialerg; Zyrtec; ***Fin.***: Alzyr; Cetimax; Gardex; Heinix; Histanova†; Histec; Lomfast; Senirex†; Zanlan; Zyrtec; ***Fr.***: Actifed Allergie; Alairgix; Aldirek; Humex Allergie Cetirizine; Reactine†; Virlix; Zyrtec; ZyrtecSet; ***Ger.***: Ceterifug†; Ceti-Puren†; Cetiderm; CetiLich†; Cetirigamma†; Reactine; Zyrtec; ***Gr.***: Agelmin; Alenstran; Alergoxal; Arzedyn; Auroxizine; Bebexin; Blezamont; Cetialfa; Cetiram; Cetirgen; Cetril; Cezirin; Cirizine; Dermizin; Enahimine; Gentiran; Habitek; Hamiltosin; Histafren; Kilsol; Lambeta; Ralizon; Remezine; Rezerc; Spatanil; Tasker; Telarix; Vitinelin; Zeda; Zepholin; Ziptek†; Znupril; ***Hong Kong***: Adezio; Cerotec†; Cetihis; Cetirin; Histacet; Histasin; Histazine†; Marizine†; Parlazin; Rhinil; Ricam; Ryvel†; Sancotec†; Simtec; Sunizine; Tirizine; Vick-Tec†; Vick-Zyrt†; Zertine; Zicet†; Zyrtec; ***Hung.***: Alerid†; Cetigen; Cetrin; Cetripharm†; Parlazin; Revicet; Zyrtec; ***India***: A-Cet; Acit; Aglocet; Airtis; Alcare; Alcet; Alerbloc; Alerid; Alervin; Allercet; Allerzine; Alquit; Asicet; Atcet-MD; Avcet; Avizin; Bio Act; Biozin; C-Triz; Cefid; Cerizine-FT; Cetariv; Cetcip; Cetgel; Ceticad; Cetin; Cetiriz; Cetjust; Cetlong; Cetmac; Cetmet; Cetnaz; Cetos; Cetract; Cetrezol; Cetricare; Cetrid; Cetriken; Cetrilin; Cetrina-MD; Cetrine; Cetrisan; Cetritop; Cetriwal; Cetrizet; Cetrizine; Cettop; Cetven-DT; Cetzine; Cetzy; Cez; Cistin; Claritec; Cope; Coszin; CTZ; Cucet-DT; CZ-3; CZN; E-Cet-MD; Ekon-DT; Elgnil; Etric-DT; Eze; Flamoset; Floramin; Fomicet; Forzin; Hicet; Hisnofil; Hispokyn; Ifycet-DT; Incez; Incid-L; Intazin; Kidcet; Lancizin; Lezine; LGNil; M-Cet; M-Cit; Morazin; Noalzy; Odacet; Okacet; Oncet; Pancet; Rinitrin; Zyrtec; ***Indon.***: Betarhin; Cerini; Cetinal; Cetrixal; Cetryn†; Cetymin†; Estin; Falergi; Histrine; Incidal-OD; Intrizin; Lerzin; Nichorizin; Ozen; Risina; Rydian; Ryvel; Ryzen; Ryzicor; Ryzo; Tiriz; Zenriz; ***Irl.***: Cetirelief Allergy; Cetricure; Cetrine; Cetriz; Histek; Reactine; Tiritek Allergy; Zirpine; Zirtek Plus; Zirtek; Zirtene; Zynor†; ***Israel***: Allergone; Allergy-Care; Histazine; Zyllergy; ***Ital.***: Cerchio; Ceteris; Formistin; Generit; Kruzin; Reactidiem; Rinalgit; Sotrizol†; Stamidix; Suspiria; Tezastin; Zirtec; ***Jpn***: Zyrtec; ***Malaysia***: Adezio; Alatrol; Ceritec; Cetihis; Hismazine; Ricam; Simtec; Zicet†; Zyrtec; ***Mex.***: Apoliz; Cethexal; Cetitev; Dercetina; Kenicet; Miseda; Namitace; Raamcinet; Reactine; Trizinet; Virlix; Visertral; Zyrtec; ***Neth.***: Prevalin Allerstop; Reactine; Revalintabs†; Zyrtec; ***Norw.***: Alzyr; Reactine†; Zyrtec; ***NZ***: Razene; Zetop; Zyrtec; ***Philipp.***: Aforvir; Aletor; Allerkid; Allermed; Alnix; Antrazine; Askey; Azurex; Brellercet†; Cerotec; Cet-10; Ceti-Med; Cetimin; Cetriz; Cetyrol; Ezaller; H-One; Histamed; Medan; Prixlae; Recozin; Rhinitrin; Ricam; Sigrel; Texzine; Unizef; Virlix; Virtec; Virtex; Zerlex; Zetir; Zetrix; Zinex; Zyrrigin; Zyrtec; ***Pol.***: Acer†; Alermed; Alero; Alerton; Alerzina; Allertec; Amertil; Ceratio; CetAlergin; Cetigran; Cetiozone†; Cetrivax†; Cetrizen†; Cetyryzyna†; Letizen; Virlix; Zyrtec; ***Port.***: Cetix; Cinaz; Rinair†; Rinoliber; Virlix†; Zyrtec; ***Rus.***: Alerza (Алерза); Allertec (Аллертек); Analergin (Аналергин)†; Cetirinax (Цетиринак); Cetrine (Цетрин); Letizen (Летизен); Parlazin (Парлазин); Zetrinal (Зетринал); Zodac (Зодак); Zyncet (Зинцет); Zyrtec (Зиртек); ***S.Afr.***: Acuzyrt; Allecet; Allermine; Betek; Sinutab Sinus Allergy; Texa; Zetop; Zyncet; Zyrtec; ***Singapore***: Adezio; Agelmin; Allercet; Alzytec; Ceritec; Cetihis; Cetrine; Cetrizin; Rhinil; Sancotec; Simtec; Sunizine; Terizin; Zyrtec; ***Spain***: Alercina; Alerlisin; Cetimerck†; Coulergin; Ratioalerg†; Reactine Plus†; Reactine†; Virlix; Zyrtec; ***Swed.***: Acura; Cetimax; Cidron†; Zyrlex; ***Switz.***: Cerzine; Cet-Mepha Allergie; Cetallerg; Ceteco; Cetrine; Helvecin; Hista-X; Histatec†; Triofan Allergie; Zyrtec; ***Thai.***: Alerest; Aller-Go; Allercet†; Cetihis; Cetinac; Cetizin; Cetrimed; Cetrine†; Cetrizet; Cetrizin; Cettec; Ceza; Cintar; Cistamine; Cyzine; Fatec; Histec; Histica; Incidal-OD; Mantab; One-Trex; Ormist; Rentex; Rhitecin; Rizetec; Setin; Sutac; Sytrex; Terzine†; Tizine; Triz; Unicet†; Zensil; Zermed; Zertine; Zetecine; Zetrix; Zittec; Zymed; Zyrac; Zyral; Zyrazine; Zyrcon; Zyrex; Zyril; Zyrlergic; Zyrtec; Zytizine; ***Turk.***: Allerset; Cetiteva; Cetityrol; Cetryn; Hitrizin; Ressital; Rynset; Setiral; Virlix†; Yenizin; Zyrtec; ***UAE***: Cetralon; ***UK***: AllerTek; Benadryl Allergy; Benadryl One A Day; Hayfever & Allergy Relief; Hayfever Relief; Piriteze; Pollenshield; Zirtek; ***Ukr.***: Allertek (Аллертек); Analergin (Аналергин); Cetrine (Цетрин)†; Zetrynal (Цетринал); Zodac (Зодак); Zyrtec (Зиртек); ***USA***: All Day Allergy; Zyrtec; ***Venez.***: Celay; Cetirex; Cetirivax; Cetral; Talzic; Zyrtec.

Multi-ingredient Preparations. ***Arg.***: Cabal-D; Cetriler D; Zyrtec-D; ***Belg.***: Cirrus; Reactine Pseudoephedrine; Rhinosinutab; ***Braz.***: Zyrtec-D; ***Canad.***: Reactine Allergy & Sinus; ***Chile***: Alertop-D†; Findaler-D; Histalen D†; Remitex D; Rigotax-D; Sanaler-D; ***China***: Si Te Meng (斯特蒙); Xin Gan Ning; ***Fin.***: Cirrus; ***Fr.***: Actifed Rhinite Allergique; Humex Rhinite Allergique; ***Ger.***: Reactine duo; ***Hong Kong***: Cirrus†; Zyrtec-D; ***Hung.***: Zyrtec-D; ***India***: A'Cold; Aceper; Agrus-NS; Airtis Plus; Alcold; Alerid Cold; Alerid D; Allercet-DC; Allset; Ambcet; Ambrol-C; Ambrolite-D; Amcold; Amven-C; Arid Plus; Arid-D; Arid; Asicold; Belrin-D; Belrin-D; Bio-Cold; Brick; Broncodil; Calscot; Car-OD; Carcet; CCFS; Cetcip Cold; Cetcip-D; Cetin Cold; Cetin Kid; Cetin Plus; Cetiriz-D; Cetmet TCF; Cetra; Cetrifed-D; Cetrizet-D; Cetzine-A; Cez-A; Cez-D; Cezcold; Chescare; Cheston Cold; Cheston Cold; Codylex-CC; Cofstop-Z; Cofsym; Coftex-DMR; Cold-Relief; Coldec; Coldfree; Coldrest; Coldrest; Coldwar; Coldwar; Combit; Cope-D; Cor-4; Cozine; Cozymin-AF; Cozymin; CPP; CTZ Plus; CZ-Cold; Decet-BD; Decet-OD; Dextur; Elcold; Elgnil Cold; Esnopil; Etric Plus; Evercold; Fincof; Flu-4-XN; Fricold; Hicet-AX; Hicet-DC; Ifycet; Ika; Incold; Incold; Indikof-A; Kazicold; Kidcet-Cold; Kofrid Plus; Kofrid-D; Kofrid; Kol-DC; Kold Time; Koldy; Kolq; Kolq; Kozifed; Kuffdac-C; Lemohist-C; Lezine-P; Mastifen-C; Moncet; Mucoresp-CZ; Nam Cold-Z; Nam Cold; Nam Cold; Natcold Plus; Nimucold; Noalzy Plus; Nozee; Nozik-P; Nozik; Pamagin C; Pamagin C; ***Indon.***: Cirrus; ***Ital.***: Naristar; Reactine; ***Malaysia***: Cirrus†; Zyrtec-D; ***Mex.***: Virlix-D; Zyrtec-D†; ***NZ***: Zyrtec Decongestant†; ***Pol.***: Cirrus; Zyrtec D; ***Port.***: Cirrus†; ***Singapore***: Zyrtec-D; ***Spain***: Stopcold; Virlix Plus; ***Thai.***: Zyrtec-D†; ***Turk.***: Cirrus; ***Ukr.***: Helpex Hot Cap (Хелпекс Хот Кап); Milistan Multisymptomic (Мілістан Мультисимптомный); ***USA***: All Day Allergy-D; Zyrtec-D; ***Venez.***: Cetirivax D; Zyrtec-D.

Pharmacopoeial Preparations
BP 2014: Cetirizine Oral Solution; Cetirizine Tablets;
USP 36: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Capsules; Cetirizine Hydrochloride Oral Solution; Cetirizine Hydrochloride Tablets.

Chlorcyclizine Hydrochloride *(BANM, rINNM)*

Chlorciklizino hidrochloridas; Chlorcyclizine, Chlorhydrate de; Chlorcyclizinhydrochlorid; Chlorcyclizini Hydrochloridum; Chlorcyclizinium Chloride; Chlorcyklizin-hydrochlorid; Clorciclizina, hidrocloruro de; Hidrocloruro de clorciclizina; Kloorisyklitsiinihydrokloridi; Klórciklizin-hidroklorid; Klorcyklizinhydroklorid; Хлорциклизина Гидрохлорид.

1-(4-Chlorobenzhydryl)-4-methylpiperazine hydrochloride.

$C_{18}H_{21}ClN_2HCl$=337.3

CAS — 82-93-9 (chlorcyclizine); 1620-21-9 (chlorcyclizine hydrochloride); 14362-31-3 (chlorcyclizine hydrochloride).

ATC — R06AE04.

ATC Vet — QR06AE04.

UNII — NPB7A7874U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Chlorcyclizine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.0. Protect from light.

Profile

Chlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p. 610.1). It has been given orally for the symptomatic relief of hypersensitivity reactions; it has also been used as an antiemetic. It has been used in topical preparations, although as with other antihistamines, there is a risk of sensitisation.

Chlorcyclizine dibunate (naftoclizine) has been used as a cough suppressant similarly to sodium dibunate (p. 1677.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Ahist.

Multi-ingredient Preparations. ***Fin.***: Anervan†; ***Israel***: Temigran†; ***Neth.***: Primatour; ***Norw.***: Anervan†; ***Spain***: Dominex Antitusigeno; ***Swed.***: Anervan; Exolyt†; ***USA***: Biclora-D; Biclora; Dallergy; Dallergy; NasOpen; Nasotuss; Notuss-NX†; Notuss-NXD†; Poly-Tussin D; Poly-Tussin; Stahist AD.

Chloropyramine Hydrochloride

(BANM, rINNM)

Chloropyramine, Chlorhydrate de; Chloropyramini Hydrochloridum; Cloropiramina, hidrocloruro de; Halopyramine Hydrochloride; Hidrocloruro de cloropiramina; Хлоропирамина Гидрохлорид.

N-(4-Chlorobenzyl)-*N*′*N*′-dimethyl-*N*-(2-pyridyl)ethylenediamine hydrochloride.

$C_{16}H_{20}ClN_3HCl$=326.3

CAS — 59-32-5 (chloropyramine); 6170-42-9 (chloropyramine hydrochloride).

ATC — D04AA09; R06AC03.

ATC Vet — QD04AA09; QR06AC03.

UNII — FWA92Z14NN.

Profile

Chloropyramine hydrochloride, an ethylenediamine derivative, is an antihistamine (p. 610.1). It has been given orally in a dose of 25 mg three or four times daily or as an intramuscular injection of 20 to 40 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Suprastin; ***Mex.***: Avapena; ***Rus.***: Subrestine (Субрестин); Suprastin (Супрастин); ***Ukr.***: Suprastin (Супрастин).

Chlorphenamine Maleate

(BANM, rINNM)

Chlorfenamin-maleinát; Chlorfenamino maleatas; Chlorofenaminy maleinian; Chlorphénamine, Maléate de; Chlorphenamini maleas; Chlorphenaminmaleat; Chlorpheniramine Maleate; Chlorprophenpyridamine Maleate; Clorfenamina, maleato de; Kloorifenamiinimaleaatti; Klorfenaminmaleat; Klórfenamin-maleát; Maleato de clorfenamina; Хлорфенамина Малеат.

(±)-3-(4-Chlorophenyl)-*NN*-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.

$C_{16}H_{19}ClN_2C_4H_4O_4$=390.9

CAS — 132-22-9 (chlorphenamine); 113-92-8 (chlorphenamine maleate).

ATC — R06AB04.

ATC Vet — QR06AB04.

UNII — V1Q0O9OJ9Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chlorphenamine Maleate). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. Protect from light.

USP 36: (Chlorpheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 4 of water and 1 in 10 of alcohol and of chloroform; slightly soluble in ether and in benzene. Its solutions in water have a pH between 4 and 5. Store in airtight containers. Protect from light.

Incompatibility. Chlorphenamine maleate has been reported to be incompatible with calcium chloride, kanamycin sulfate, noradrenaline acid tartrate, pentobarbital sodium, and meglumine adipiodone.

Dexchlorpheniramine Maleate (BANM, rINNM)

Dekschlorfeniramino maleatas; Dekskloorifeniramiinimaleaatti; Dexchlorfeniramin-maleinát; Dexchlorphenamine Maleate; Dexchlorphéniramine, Maléate de; Dexchlorpheniramini Maleas; Dexchlorpheniraminmaleat; Dexclorfeniramina, maleato de; Dexklorfeniraminmaleat; Dexklórfeniraminmaleát; Maleato de dexclorfeniramina; Дексхлорфенирамина Малеат.

CAS — 25523-97-1 (dexchlorpheniramine); 2438-32-6 (dexchlorpheniramine maleate).

ATC — R06AB02.

ATC Vet — QR06AB02.

UNII — B10YD955QW.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. & (Dexchlorpheniramine Maleate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

USP 36: (Dexchlorpheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 1.1 of water, 1 in 2 of alcohol, 1 in 1.7 of chloroform, and 1 in 2500 of ether; slightly soluble in benzene. pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Uses and Administration

Chlorphenamine maleate, an alkylamine derivative, is a sedating antihistamine that causes a moderate degree of sedation; it also has antimuscarinic activity.

Chlorphenamine is a racemic mixture; the dextrorotatory isomer, dexchlorpheniramine, has about twice the activity of chlorphenamine by weight.

Chlorphenamine maleate and dexchlorpheniramine maleate are used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1), and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). They are common ingredients of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2). Chlorphenamine may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p. 611.1).

Chlorphenamine maleate is given in oral doses of 4 mg every 4 to 6 hours up to a maximum of 24 mg daily. It may also be given by intramuscular, by subcutaneous, or by slow intravenous injection over a period of 1 minute. The usual dose is 10 to 20 mg and the total dose given by these routes in 24 hours should not normally exceed 40 mg.

Dexchlorpheniramine maleate is given in oral doses of 2 mg every 4 to 6 hours up to a maximum of 12 mg daily.

For dosage in children, see below.

Modified-release oral preparations of chlorphenamine maleate or dexchlorpheniramine maleate are available in some countries; dosage is specific to a particular formulation.

Dexchlorpheniramine maleate has been applied topically in some countries, although as with other antihistamines there is a risk of sensitisation. Chlorphenamine polistirex (a sulfonated diethenylbenzene-ethenylbenzene copolymer complex), chlorphenamine tannate, and dexchlorpheniramine tannate are given orally and are used similarly to the maleate.

Administration in children. In children, *chlorphenamine maleate* may be given orally for the symptomatic relief of allergic conditions such as rhinitis and urticaria; doses are as follows:

- children aged 1 to 2 years: 1 mg twice daily
- those aged 2 to 6 years: 1 mg every 4 to 6 hours
- those aged 6 to 12 years: 2 mg every 4 to 6 hours

In the UK, chlorphenamine maleate is not licensed in children younger than 1 year. However, the *BNFC* suggests that children aged 1 month to 2 years of age may be given 1 mg twice daily.

Chlorphenamine maleate may be given by slow intravenous injection over a period of 1 minute, as an adjunct in the emergency treatment of anaphylactic shock. It may also be given by intramuscular, by subcutaneous, or by slow intravenous injection, for the symptomatic management of allergy. The following parenteral doses may be used:

- children aged 1 month to 1 year: 250 micrograms/kg
- those aged 1 to 5 years: 2.5 to 5 mg
- those aged 6 to 12 years: 5 to 10 mg

Alternatively, children and adolescents aged 1 to 18 years may be given a dose of 200 micrograms/kg. If necessary, intramuscular or intravenous injections may be repeated up to a total of 4 doses in 24 hours.

Dexchlorpheniramine maleate is usually used to manage allergic rhinitis in the following oral doses:

- children aged 2 to 6 years: 500 micrograms every 4 to 6 hours
- those aged 6 to 12 years: 1 mg every 4 to 6 hours

Chlorphenamine maleate and dexchlorpheniramine maleate are common ingredients of compound preparations for the symptomatic treatment of coughs and the common cold. However, such preparations should be used with caution in children, and generally avoided in young children, for details see p. 614.1.

Malaria. Chlorphenamine may be tried in patients with malaria who have chloroquine-induced pruritus (see Effects on the Skin, p. 652.2), but additionally it has been shown to have some promise as an adjunct in the treatment of chloroquine-resistant malaria itself. Early studies indicated that chlorphenamine was only one of several drugs that reversed chloroquine resistance *in vitro* in isolates of *Plasmodium falciparum*. Later clinical studies in children in Nigeria showed enhanced efficacy when chlorphenamine was given with chloroquine[1-6] or with amodiaquine.[7] The overall management of malaria is discussed on p. 644.1.

1. Sowunmi A, *et al.* Enhanced efficacy of chloroquine-chlorpheniramine combination in acute uncomplicated falciparum malaria in children. *Trans R Soc Trop Med Hyg* 1997; **91:** 63–7.
2. Sowunmi A, Oduola AMJ. Comparative efficacy of chloroquine/chlorpheniramine combination and mefloquine for the treatment of chloroquine-resistant Plasmodium falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1997; **91:** 689–93.
3. Sowunmi A, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine and pyrimethamine/sulfadoxine in acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1998; **92:** 77–81.
4. Sowunmi A, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine and halofantrine in acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1998; **92:** 441–5.
5. Okonkwo CA, *et al.* Effect of chlorpheniramine on the pharmacokinetics of and response to chloroquine of Nigerian children with falciparum malaria. *Trans R Soc Trop Med Hyg* 1999; **93:** 306–11.
6. Ogungbamigbe TO, *et al.* Chloroquine resistant Plasmodium falciparum malaria in Osogbo Nigeria: efficacy of amodiaquine + sulfadoxine-pyrimethamine and chloroquine + chlorpheniramine for treatment. *Mem Inst Oswaldo Cruz* 2008; **103:** 79–84.
7. Falade CO, *et al.* Enhanced efficacy of amodiaquine and chlorpheniramine combination over amodiaquine alone in the treatment of acute uncomplicated Plasmodium falciparum malaria in children. *Med Princ Pract* 2008; **17:** 197–201.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Exfoliative dermatitis may develop. Injections may be irritant and cause transient hypotension or stimulation of the CNS.

Effects on the blood. There are several old and isolated reports of blood dyscrasias after use of chlorphenamine maleate; these include agranulocytosis,[1,2] thrombocytopenia,[3] pancytopenia,[4] and aplastic anaemia.[5] Haemolytic anaemia has occurred after use of dexchlorpheniramine maleate.[6] The association with antihistamine use has been questioned in some of these cases.[7]

1. Shenfield G, Spry CJF. Unusual cause of agranulocytosis. *BMJ* 1968; **ii:** 52–3.
2. Hardin AS. Chlorpheniramine and agranulocytosis. *Ann Intern Med* 1988; **108:** 770.
3. EisnerEV, *et al.* Chlorpheniramine-dependent thrombocytopenia. *JAMA* 1975; **231:** 735–6.
4. Deringer PM, Maniatis A. Chlorpheniramine-induced bone-marrow suppression. *Lancet* 1976; **i:** 432.
5. Kanoh T, *et al.* Aplastic anaemia after prolonged treatment with chlorpheniramine. *Lancet* 1977; **i:** 546–7.
6. Duran-Suarez JR, *et al.* The I antigen as an immune complex receptor in a case of haemolytic anaemia induced by an antihistaminic agent. *Br J Haematol* 1981; **49:** 153–4.
7. Spry CJF. Chlorpheniramine-induced bone-marrow suppression. *Lancet* 1976; **i:** 545.

Effects on the senses. Chlorphenamine has been reported to affect the senses of smell and taste.[1]

1. Schiffman SS. Taste and smell in disease. *N Engl J Med* 1983; **308:** 1275–9.

Extrapyramidal disorders. Facial dyskinesias have been reported[1,2] after oral doses of chlorphenamine maleate.

1. Thach BT, *et al.* Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. *N Engl J Med* 1975; **293:** 486–7.
2. Davis WA. Dyskinesia associated with chronic antihistamine use. *N Engl J Med* 1976; **294:** 113.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexchlorpheniramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Antiepileptics. For a report of the effect of chlorphenamine on *phenytoin*, see p. 543.3.

Pharmacokinetics

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract and peak plasma concentrations occur about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide interindividual variation in the pharmacokinetics of chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS.

Chlorphenamine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine. Unchanged drug and metabolites are excreted mainly in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

References.

1. Rumore MM. Clinical pharmacokinetics of chlorpheniramine. *Drug Intell Clin Pharm* 1984; **18:** 701–7.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
3. Yasuda SU, *et al.* The roles of CYP2D6 and stereoselectivity in the clinical pharmacokinetics of chlorpheniramine. *Br J Clin Pharmacol* 2002; **53:** 519–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Afeme; Alergidryl; Alergitrat; Qura Plus; ***Austral.***: Polaramine; ***Austria***: Polaramin†; ***Belg.***: Kelargine; Polaramine; ***Braz.***: Alergonil; Alergyo; Alermine; Dexlerg; Expectamin F; Fenirax; Histamin; Hystin; Polaramine; Polaratin; Polaren; Polaryn; ***Canad.***: Chlor-Tripolon; Novo-Pheniram; ***Chile***: Clorprimeton; Nipolen; Prodel; Scadan; ***China***: Hui Ji (惠济); Kang Yu Deng Tong (康裕登通); Runjie (润洁); ***Denm.***: Polaramin†; ***Fr.***: Polaramine; ***Ger.***: Polaronil†; ***Gr.***: Istamex; Istaminol; Losmanin; Polaramine; ***Hong Kong***: Antamin†; Antihist†; Chloramine†; Chlorminol†; Chlorpyrimine; Coriton†; Dapriton†; Dex Antihist; Flentist†; Horamine†; Kenyamine†; Marpeniramine†; Pirimat†; Polaramine; Rhiniramine; Synchloramin†; Tromine; Uni-Dexmine†; Uni-Ramine; ***India***: Cadistin; Cepiam TR; Cesiran; Chloram; Cocorex; Cofton; Dexcpm; Dexodil; DPM-2; ***Indon.***: Chlorphenon†; Cohistan; CTM; Dehista; Orphen; Pehachlor; Polamec†; Polaramine; Polarist†; Polofar†; ***Irl.***: Piriton; ***Israel***: Ahiston; ***Ital.***: Polaramin; Trimeton; ***Malaysia***: Chloramine; Chlormine; Chlorpyrimine; Dexatamin; Dexchloramine; Kotamin; Pirimat; Polaramine; Somin; Zoramine; ***Mex.***: Alerdil; Antadex-H; Blendox†; Cloro-Trimeton; Cronal; Docsi; Hierbal; Histadryl; ***Neth.***: Polaramine; ***Norw.***: Phenamin†; Polaramin; ***NZ***: Histafen; Polaramine; ***Philipp.***: Antamin; Baromonic; Chlor-Trimeton; Chlormin; Clornamin; Metromine; Valemine; Virgomine†; ***Port.***: Trenelone; ***S.Afr.***: Allergex; Allerhist†; Rhineton; ***Singapore***: Allermin; Allersin; Alleryl; Antamin; Chloramine; Chlormine; Chlorpyrimine; Dexatamin; Dexchloramine; Dextramine; Horamine; Pirimat; Piriton; Polaramine; Polarax; Rhiniramine; Somin; SP-Arnamin; Synchloramin; ***Spain***: Antihistaminico; Polaramine; ***Swed.***: Polaramin†; ***Switz.***: Arbid N; Polaramine†; ***Thai.***: Allergen; Allergin; Aly; Arc-Chlor; Chlophe; Chlophen; Chlorahist; Chloramine-S; Chloramine; Chlordon; Chlorleate; Chlorphencap; Chlorpheno; Chlorpyrimine; Cohistan†; Hisdaron; Histatab; Histatapp; Icolid Plus; Ilcid; KB Ramine; Kloramin; Patarphen; Pophen; Sinchlormine; Suramine; ***UAE***: Chlorohistol; ***UK***: Allercalm; Allergy Relief; Allerief; Calimal; Hayleve; Piriton; Pollenase Antihistamine; ***Ukr.***: Glycodin (Глікодин)†; ***USA***: Aller-Chlor; Allergy Relief; Allergy-Time; Allergy; Chlo-Amine†; Chlor-Pro; Chlor-Trimeton Allergy 4 Hour; Chlor-Trimeton; ChlorTan; ED Chlorped Jr; Ed-Chlor-Tan; Ed-Chlortan; Efidac 24 Chlorpheniramine; PediaCare Allergy Formula; Pediatan†; Pediox-S†; Pharbechlor; QDALL AR†; TanaHist PD†; Teldrin; ***Venez.***: Clorotrimeton; Liramin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Chlorphenamine Injection; Chlorphenamine Oral Solution; Chlorphenamine Tablets;

USP 36: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Tablets; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution; Chlorpheniramine Maleate Extended-release Capsules; Chlorpheniramine Maleate Injection; Chlorpheniramine Maleate Syrup; Chlor-

pheniramine Maleate Tablets; Dexchlorpheniramine Maleate Syrup; Dexchlorpheniramine Maleate Tablets.

Chlorphenoxamine Hydrochloride

(BANM, rINNM)

Chlorphénoxamine, Chlorhydrate de; Chlorphenoxamini Hydrochloridum; Clorfenoxamina, hidrocloruro de; Hidrocloruro de clorfenoxamina; Klorfenoksamin Hidroklorür; Хлорфеноксамина Гидрохлорид.

2-(4-Chloro-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{18}H_{22}ClNO,HCl$=340.3

CAS — 77-38-3 (chlorphenoxamine); 562-09-4 (chlorphenoxamine hydrochloride).

ATC — D04AA34; R06AA06.

ATC Vet — QD04AA34; QR06AA06.

UNII — 5I159322PY.

Profile

Chlorphenoxamine, a congener of diphenhydramine (p. 626.1), has antimuscarinic and antihistaminic properties. It has been used in nausea, vomiting, and vertigo, and was formerly used in the symptomatic treatment of parkinsonism. Chlorphenoxamine has also been used in hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Systral†; ***Gr.***: Systral; ***Indon.***: Systral†; ***Philipp.***: Systral; ***Port.***: Systral; ***Thai.***: Systral; ***Turk.***: Sistral†; Systral.

Multi-ingredient Preparations. ***Austria***: Spirbon†.

Cinnarizine *(BAN, USAN, rINN)*

Cinarizin; Cinarizina; Cinarizinas; Cinnarizin; Cinnarizinum; Cynaryzyna; 516-MD; R-516; R-1575; Sinarizin; Sinnaritsiini; Циннаризин.

1-Benzhydryl-4-cinnamylpiperazine; (*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine.

$C_{26}H_{28}N_2$=368.5

CAS — 298-57-7.

ATC — N07CA02.

ATC Vet — QN07CA02.

UNII — 3DI2E1X18L.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Cinnarizine). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

Uses and Administration

Cinnarizine is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p. 612.3) and for the prevention and treatment of motion sickness (p. 611.3). It is also used in the management of various peripheral and cerebral vascular disorders.

In the UK, the usual oral dose for vertigo and vestibular disorders is 30 mg three times daily. For motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. In other European countries, a dose of 75 mg once or twice daily may be given for vertigo and vestibular disorders. Doses of 75 mg may also be given once daily for cerebrovascular disorders and 2 or 3 times daily for peripheral vascular disorders

For doses in children, see below.

References.

1. Shupak A, *et al.* Cinnarizine in the prophylaxis of seasickness: laboratory vestibular evaluation and sea study. *Clin Pharmacol Ther* 1994; **55:** 670–80.

Administration in children. Cinnarizine may be used orally in children aged 5 to 12 years. A dose of 15 mg is given three times a day for the control of vestibular disorders. For motion sickness, 15 mg is taken 2 hours before the start of the journey followed by 7.5 mg every 8 hours during the journey if necessary.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

There have been rare reports of extrapyramidal symptoms after taking cinnarizine, sometimes associated with depressive feelings.

High doses of cinnarizine should be used with caution in patients with hypotension because of the possibility of decreasing blood pressure further.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of cinnarizine, see Flunarizine, p. 630.1.

Hypersensitivity. Immunologically-defined lichen planus pemphigoides has been reported[1] in a 72-year-old woman taking cinnarizine. Lesions began to clear when treatment was stopped but challenge with cinnarizine provoked severe itching and reactivation of pigmented lesions. Another case[2] has also been described.

1. Miyagawa S, *et al.* Lichen planus pemphigoides-like lesions induced by cinnarizine. *Br J Dermatol* 1985; **112:** 607–13.
2. Ramallal M, *et al.* Lichenoid eruption associated with cinnarizine use. *Pharm World Sci* 2002; **24:** 215–16.

Tinnitus. The Spanish System of Pharmacovigilance had received reports[1] of tinnitus associated with calcium-channel blockers; some of the reports, including the one relating to cinnarizine, were in patients also receiving other ototoxic drugs. WHO was said to have additional reports of tinnitus associated with calcium-channel blockers including cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Weight gain. There has been a report[1] of weight gain in 4 patients who had taken cinnarizine for 1 to 2 years; in all cases the weight gain was associated with increased appetite.

1. Navarro-Badenes J, *et al.* Weight-gain associated with cinnarizine. *Ann Pharmacother* 1992; **26:** 928–30.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Cinnarizine is absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral doses. It undergoes metabolism and has a half-life of 3 to 6 hours. Cinnarizine is excreted in the faeces mainly as unchanged drug, and in the urine predominantly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dismaren; Fabracin; Folcodal; Natropas; Stugeron; ***Austria***: Cinnabene†; Pericephal; Stutgeron†; ***Belg.***: Stugeron; ***Braz.***: Antigeron; Cinaran; Cinarite; Cinarix; Cinazon; Civertim; Cronogeron; Ductogeron; Fluxon; Labigeron; Stugerina; Stugeron; Vertigeron; Verzum; ***Chile***: Cinergil; Siridone; Stugeron; ***China***: Bo Rui Te (博瑞特); ***Cz.***: Cinnabene†; Stugeron; ***Denm.***: Sepan; ***Gr.***: Derozin; Geronik; Libotasin; Stugeron; ***Hong Kong***: Medozine†; Mosion-6†; Stugeron; Urizine; ***Hung.***: Stugeron; ***India***: Avidazine†; Cinact; Cinadil; Cinaz; Cingeron; Cini; Cinnasia; Cintac; Cintigo; Cinvert; Cinzan; Diziron; Diznil; Dizzigo; Emzine; Stugeron; Vertiron; ***Indon.***: Merron; Nariz; Perifas; Stugeron; Vertizine; ***Irl.***: Stugeron; ***Israel***: Stunarone; ***Ital.***: Cinazyn; Stugeron; Toliman; ***Malaysia***: Celenid; Cinna; Cinnaron; Nazin; Stugeron; Uphageron; ***Mex.***: Bulasan; Ceretec†; Cisaken; Cyslev; Dilateron-F; Dilper-INA; Karilex; Oblant; Reynaven; Stugeron; Venoxil; Winpar; ***Philipp.***: Cinamin; Cinarin; Cinnabloc; Dizzinon; Nizirar; Stugeron; Vertisin; ***Port.***: Cinon; Stugeron; ***Rus.***: Phezam (Фезам); Stugeron (Структум); Stugesin (Стугезин); ***S.Afr.***: Purazine†; Stugeron; ***Singapore***: Celenid; Cinna; Cinnar; Cinnaron; Nazin; Stugeron; Vertigon; ***Spain***: Stugeron; ***Switz.***: Cerepar†; Cinnageron; Stugeron; ***Thai.***: Bugeron; C-Pela; C-Ricin; Celenid†; Cenai; Cerebroad; Ceremin; Cinerine; Cinna; Cinnar; Cinnarin; Cinnarine; Cinnatab; Cinnaza; Cinrizine; Fageron†; KB Gyding; Linazine; Manoron; Medozine; Naricin; Narizine; Nazine; Siarizine; Silicin; Sorebral; Stugeron; Stugin; Stuno†; Sturon; Urizine†; Vernarin; ***Turk.***: Sefal; ***UK***: Stugeron; ***Ukr.***: Stugeron (Стугерон); ***Venez.***: Cinaren; Cinarin; Sinver; Stugeron; Vericin.

Multi-ingredient Preparations. ***Arg.***: Cadencial Plus; Cinacris; Difusil; Ribex; ***Belg.***: Arlevertan; Touristil; ***Braz.***: Coldrin; Exit; Sureptil; ***China***: Limai (利脉); Xin Naolilong (新瑙力隆); ***Cz.***: Arlevert; ***Fin.***: Arlevert; Rinomar; ***Ger.***: Arlevert; ***Hong Kong***: Cinnasin†; SE-25†; ***Hung.***: Arlevert; ***India***: Aridom-C; Azinorm C; Cimdom; Cinact-D; Cinadil-D; Cingeron-D; Cinnasia-D; Cintac-D; Dompon CZ; Dompro-C; Domstal-CZ; Donriz; Kandor CZ; Mosic; Neurozine; Pacidom-C; Vertigil; ***Irl.***: Arlevert; ***Ital.***: Arlevertan; ***Neth.***: Arlevert; Primatour; ***Philipp.***: Stugil; ***Rus.***: Combitropil (Комбитропил); NooCam (НооКам); Omaron (Омарон); Piracezine (Пирацезин); ***Spain***: Clinadil; Diclamina†; ***Swed.***: Arlevert; Rinomar; ***Switz.***: Arlevert; ***Thai.***: Cinnapac; ***UK***: Arlevert; ***Ukr.***: Cinatropil (Цинатропил)†; Evrisam (Эвризам); Memosam (Мемозам); Neuro-Norm (Нейро-Норм); Omaron (Омарон); Phezam (Фезам).

Clemastine Fumarate

(BANM, USAN, rINNM)

Clemastina, fumarato de; Clémastine, Fumarate de; Clemastine Hydrogen Fumarate; Clemastini Fumaras; Fumarato de clemastina; HS-592 (clemastine); Klemastiinifumaraatti; Klemastin fumarát; Klemastin Hidrojen Fumarat; Klemastinfumarat; Klemastino fumaratas; Klemastyny fumaran; Klemasztin-fumarát; Meclastine Fumarate; Mecloprodine Fumarate; Клемастина Фумарат.

(+)-(2*R*)-2-[2-[(*R*)-4-Chloro-α-methylbenzhydryloxy]ethyl]-1-methylpyrrolidine hydrogen fumarate.

$C_{21}H_{26}ClNO,C_4H_4O_4$=460.0

CAS — 15686-51-8 (clemastine); 14976-57-9 (clemastine fumarate).

ATC — D04AA14; R06AA04.

ATC Vet — QD04AA14; QR06AA04.

UNII — 19259EGQ3D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clemastine Fumarate). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol (70%); slightly soluble in alcohol (50%) and in methyl alcohol. A 10% suspension in water has a pH of 3.2 to 4.2.

USP 36: (Clemastine Fumarate). A colourless to faintly yellow, odourless, crystalline powder. Very slightly soluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. pH of a 10% suspension in water is between 3.2 to 4.2. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Clemastine fumarate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It has been reported to have a duration of action of about 10 to 12 hours. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1).

Clemastine is given as the fumarate although doses are expressed in terms of the base. Clemastine fumarate 1.34 mg is equivalent to about 1 mg of clemastine base. The usual oral dose is 1 mg twice daily. Up to 6 mg daily has been given, particularly for urticaria and angioedema.

Clemastine fumarate may be given by intramuscular or slow intravenous injection in a total daily dose equivalent to 4 mg of clemastine for acute allergic reactions; for prophylaxis 2 mg is given by intravenous injection.

For doses in children, see below.

Clemastine fumarate has also been used topically, although as with other antihistamines, there is a risk of sensitisation.

Administration in children. Clemastine fumarate may be given to children for the symptomatic relief of allergic conditions including rhinitis, angioedema, and pruritic skin disorders. Oral doses, expressed in terms of clemastine, are as follows:

- children aged 1 to 3 years, 250 to 500 micrograms twice daily
- those aged 3 to 6 years, 500 micrograms twice daily
- those aged 6 to 12 years, 0.5 to 1 mg twice daily

Children aged 1 year and over, can be given an intramuscular dose equivalent to 25 micrograms/kg of clemastine daily, in two divided doses.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Breast feeding. The American Academy of Pediatrics[1] considers that clemastine should be given with caution to breast-feeding mothers, since it has been associated with adverse effects in the infant. Drowsiness, irritability, a high-pitched cry, neck stiffness, and refusal to feed in a 10-week-old breast-fed baby occurred 12 hours after her mother started treatment with clemastine.[2] Clemastine was detected in the mother's breast milk. The baby recovered and was feeding normally on the day after the drug was stopped.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Kok THHG, *et al.* Drowsiness due to clemastine transmitted in breast milk. *Lancet* 1982; **i:** 914–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clemastine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Clemastine fumarate is rapidly and almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral use. Unchanged drug and metabolites are excreted principally in the urine. An elimination half-life of about 21 hours has been reported. Clemastine is distributed into breast milk.

References.

1. Schran HF, *et al*. The pharmacokinetics and bioavailability of clemastine and phenylpropanolamine in single-component and combination formulations. *J Clin Pharmacol* 1996; **36:** 911–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Agasten; ***Canad.***: Tavist; ***China***: Langjing (浪静); Si Nuo Ping (斯诺平); Tai Wei (泰威); ***Cz.***: Tavegyl†; ***Denm.***: Tavegil; Tavegyl; ***Ger.***: Tavegil; ***India***: Clamist; ***Indon.***: Tavegyl; ***Malaysia***: Tavetine; ***Mex.***: Tavist; ***Neth.***: Tavegil; Tavegyl; ***Philipp.***: Marsthine; Tavegyl; Tavist; ***Port.***: Tavegyl; Tavist; ***Rus.***: Tavegyl (Тавегил); ***S.Afr.***: Tavegyl†; ***Spain***: Tavegil; ***Swed.***: Tavegyl; ***Switz.***: Tavegyl; ***Turk.***: Tavegyl; ***UK***: Tavegil; ***USA***: Contac 12 Hour Allergy; Dayhist-1; Tavist Allergy.

Multi-ingredient Preparations. ***Braz.***: Emistin; ***China***: Feng Lai (丰莱); ***Spain***: Dexa Tavegil.

Pharmacopoeial Preparations
BP 2014: Clemastine Oral Solution; Clemastine Tablets;
USP 36: Clemastine Fumarate Tablets.

Clemizole Hydrochloride *(BANM, rINNM)*

AL-20; Clemizol, hidrocloruro de; Clémizole, Chlorhydrate de; Clemizoli Hydrochloridum; Hidrocloruro de clemizol; Клемизола Гидрохлорид.
1-(4-Chlorobenzyl)-2-(pyrrolidin-1-ylmethyl)benzimidazole hydrochloride.
$C_{19}H_{20}ClN_3,HCl$=362.3
CAS — 442-52-4 (clemizole); 1163-36-6 (clemizole hydrochloride).
UNII — 85W6I13D8M.

Profile

Clemizole hydrochloride is a sedating antihistamine (p. 610.1). It has been used for the symptomatic relief of allergic conditions, in pruritic skin disorders, and in combination preparations for the treatment of symptoms of the common cold. Clemizole has also been applied topically as the hexachlorophene, the sodium sulfate, and the undecylate derivatives in topical and rectal preparations combined with corticosteroids and local anaesthetics, although as with other antihistamines, there is a risk of sensitisation.

See p. 269.2 for the use of clemizole penicillin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Apracur; ***Braz.***: Ultraproct; ***Indon.***: Ultraproct†; ***Thai.***: Apracur.

Clocinizine Hydrochloride *(rINNM)*

Chlorcinnazine Dihydrochloride; Clocinizina, hidrocloruro de; Clocinizine, Chlorhydrate de; Clocinizini Hydrochloridum; Hidrocloruro de clonizina; Клоцинизина Гидрохлорид.
1-(4-Chlorobenzhydryl)-4-cinnamylpiperazine dihydrochloride.
$C_{26}H_{27}ClN_2,2HCl$=475.9
CAS — 298-55-5 (clocinizine).
UNII — AE8KM1QU3Q.

Profile

Clocinizine hydrochloride, a piperazine derivative, is an antihistamine (p. 610.1) given orally in combination preparations for the symptomatic treatment of upper respiratory-tract disorders, often with a decongestant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Senioral.

Cyclizine *(BAN, rINN)*

Ciclizina; Cyclizinum; Cyklizin; Siklizin; Syklitsiini; Циклизин.
1-Benzhydryl-4-methylpiperazine.
$C_{18}H_{22}N_2$=266.4
CAS — 82-92-8.
ATC — R06AE03.
ATC Vet — QR06AE03.
UNII — QRW9FCR9P2.

Pharmacopoeias. In *Br.*

BP 2014: (Cyclizine). A white or creamy white, crystalline powder. Practically insoluble in water. It dissolves in most organic solvents and in dilute acids. M.p. about 107 degrees. A saturated solution in water has a pH of 7.6 to 8.6.

Cyclizine Hydrochloride *(BANM, rINNM)*

Ciclizina, hidrocloruro de; Ciklizin-hidroklorid; Ciklizino hidrochloridas; Cyclizine, Chlorhydrate de; Cyclizinhydrochlorid; Cyclizini Hydrochloridum; Cyklizin hydrochlorid; Cyklizinhydroklorid; Hidrocloruro de ciclizina; Syklitsiinihydrokloridi; Циклизина Гидрохлорид.
$C_{18}H_{22}N_2,HCl$=302.8
CAS — 303-25-3.
ATC — R06AE03.
ATC Vet — QR06AE03.
UNII — W0O1NHP4WE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cyclizine Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol. A 2% solution in alcohol 2 vol. and water 3 vol. has a pH of 4.5 to 5.5. Protect from light.

USP 36: (Cyclizine Hydrochloride). A white, odourless, crystalline powder or small colourless crystals. Soluble 1 in 115 of water and of alcohol and 1 in 75 of chloroform; insoluble in ether. pH of a 2% solution in alcohol 2 vol. and water 3 vol. is between 4.5 and 5.5. Store in airtight containers. Protect from light.

Cyclizine Lactate *(BANM, rINNM)*

Ciclizina, lactato de; Cyclizine, Lactate de; Cyclizini Lactas; Lactato de ciclizina; Циклизина Лактат.
$C_{18}H_{22}N_2,C_3H_6O_3$=356.5
CAS — 5897-19-8.
ATC — R06AE03.
ATC Vet — QR06AE03.
UNII — 861R00J986.

Pharmacopoeias. *Br.* includes an injection of cyclizine lactate.

Incompatibility. Cyclizine lactate is reported to be incompatible with oxytetracycline hydrochloride, chlortetracycline hydrochloride, benzylpenicillin, and solutions with a pH of 6.8 or more.

Cyclizine Tartrate *(BANM, rINNM)*

Ciclizina, tartrato de; Cyclizine, Tartrate de; Cyclizini Tartras; Tartrato de ciclizina; Циклизина Тартрат.
$C_{18}H_{22}N_2,C_4H_6O_6$=416.5
ATC — R06AE03.
ATC Vet — QR06AE03.

Uses and Administration

Cyclizine, a piperazine derivative, is a sedating antihistamine with antimuscarinic activity, although the sedative effects are not marked.

It is used as an antiemetic in the management of nausea and vomiting (p. 611.3) including motion sickness, postoperative nausea and vomiting, after radiotherapy, and in drug-induced nausea and vomiting. It is included as an antiemetic with some opioids, and in combination preparations for the treatment of migraine attacks (p. 670.3). Cyclizine is also used for the symptomatic treatment of vertigo (p. 612.3) caused by Ménière's disease and other vestibular disturbances.

In the management of nausea and vomiting, cyclizine hydrochloride is given in a usual oral dose of 50 mg up to three times daily, although up to 200 mg may be given in 24 hours if necessary. For the prevention of motion sickness, the first dose should be given about 30 minutes before travelling.

Cyclizine is given intramuscularly or intravenously as the lactate. Doses of cyclizine lactate are similar to those of cyclizine hydrochloride given orally. For the prevention of postoperative nausea and vomiting the first dose of cyclizine lactate should be given about 20 minutes before the anticipated end of surgery.

Although not licensed in the UK, cyclizine is also available as suppositories on a named-patient basis.

For dosage in children, see below.

Cyclizine salts are used as antiemetics in combination with morphine or dipipanone; the use of such fixed-combination opioid preparations is considered to be unsuitable for the prolonged treatment that may be required in palliative care. See also under Interactions, p. 624.1.

Administration in children. In the management of nausea and vomiting children aged 6 to 12 years can be given 25 mg of cyclizine hydrochloride, orally, up to three times daily; older children may be given the usual adult dose (see above). Although not licensed in the UK, the *BNFC* suggests that those aged 1 month to 6 years may be given 0.5 to 1 mg/kg (maximum of 25 mg) up to three times daily.

Cyclizine lactate injection is not licensed for use in children in the UK. However, the *BNFC* suggests the following doses may be given by continuous intravenous or subcutaneous infusion over 24 hours:

- children aged 1 month to 2 years: 3 mg/kg
- those aged 2 to 5 years: 50 mg
- those aged 6 to 12 years: 75 mg
- those aged 12 to 18 years: 150 mg

Cyclizine is also available as suppositories from specialist manufacturers, but again, is not licensed for this route in the UK. The *BNFC* suggests the following rectal doses may be given, up to three times daily:

- children aged 2 to 6 years: 12.5 mg
- those aged 6 to 12 years: 25 mg
- those aged 12 to 18 years, 50 mg

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Cyclizine may aggravate severe heart failure. Hypotension may occur on injection.

Abuse. Cyclizine tablets have been abused either alone or with opioids for their euphoric effects.[1-7] They have been taken orally or used to make injections. It has been suggested that cyclizine dependence may occur when it is used with opioids in the treatment of chronic pain.[8] Abuse of cyclizine has been reported in cancer patients receiving it by injection to control chemotherapy- or disease-related nausea.[9]

1. Gott PH. Cyclizine toxicity—intentional drug abuse of a proprietary antihistamine. *N Engl J Med* 1968; **279:** 596.
2. Kahn A, Harvey GJ. Increasing misuse of cyclizine. *Pharm J* 1985; **235:** 706.
3. Atkinson MK. Misuse of cyclizine. *Pharm J* 1985; **235:** 773.
4. Halpin D. Misuse of cyclizine. *Pharm J* 1985; **235:** 773.
5. Council of the Pharmaceutical Society of Great Britain. Sales of preparations containing cyclizine. *Pharm J* 1985; **235:** 797.
6. Ruben SM, *et al*. Cyclizine abuse among a group of opiate dependents receiving methadone. *Br J Addict* 1989; **84:** 929–34.
7. Bassett KE, *et al*. Cyclizine abuse by teenagers in Utah. *Am J Emerg Med* 1996; **14:** 472–4.
8. Hughes AM, Coote J. Cyclizine dependence. *Pharm J* 1986; **236:** 130.
9. Bailey F, Davies A. The misuse/abuse of antihistamine antiemetic medication (cyclizine) by cancer patients. *Palliat Med* 2008; **22:** 869–71.

Effects on the blood. Agranulocytosis occurred in a patient after 6 weeks of treatment with cyclizine 50 mg three times daily.[1] The blood count returned to normal once cyclizine was withdrawn.

1. Collier PM. Agranulocytosis associated with oral cyclizine. *BMJ* 1986; **292:** 174.

Effects on the heart. In a study[1] of 11 patients with severe heart failure, cyclizine produced detrimental haemodynamic effects including increased systemic and pulmonary artery pressures and ventricular filling pressures, and negated the vasodilator effects of diamorphine. It was suggested that the use of cyclizine should be avoided in patients with acute myocardial infarction or severe heart failure.

1. Tan LB, *et al*. Detrimental haemodynamic effects of cyclizine in heart failure. *Lancet* 1988; **i:** 560–1.

Effects on the liver. An 8-year-old girl developed jaundice on 2 occasions after taking oral cyclizine hydrochloride 25 mg daily. 'Hypersensitivity hepatitis' was considered responsible.[1]

1. Kew MC, *et al*. "Hypersensitivity hepatitis" associated with administration of cyclizine. *BMJ* 1973; **2:** 307.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclizine as probably porphyrinogenic; it should be prescribed only for

compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving cyclizine, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3. Cyclizine may counteract the haemodynamic benefits of opioids (see Effects on the Heart, p. 623.3) and this should be considered before using preparations that contain a combination of cyclizine and an opioid analgesic.

General anaesthetics. For a possible interaction between cyclizine premedication and *barbiturate anaesthetics* see under Thiopental, p. 1919.3.

Pharmacokinetics

Cyclizine is absorbed from the gastrointestinal tract and has an onset of action within 2 hours. The duration of action is reported to be about 4 hours. Cyclizine is metabolised in the liver to the relatively inactive metabolite, norcyclizine. Both cyclizine and norcyclizine have plasma elimination half-lives of 20 hours. Less than 1% of the total oral dose is eliminated in the urine in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Echnatol; ***Denm.***: Marzine; ***Fin.***: Marzine; ***India***: Medazine; ***Irl.***: Valoid; ***Neth.***: Kruidvat Reistabletten†; ***Norw.***: Marzine; ***NZ***: Marzine†; Nausicalm; Valoid; ***S.Afr.***: Aculoid; Covamet; Emitex; Medazine; Nauzine; Pinaloid; Triazine; Valoid; ***Singapore***: Marzine; ***Switz.***: Marzine†; ***UK***: Valoid; ***USA***: Bonine for Kids; Cyclivert; Marezine.

Multi-ingredient Preparations. ***Austria***: Echnatol B_6; ***Fin.***: Vertipam†; ***India***: Migril; ***Irl.***: Cyclimorph; ***S.Afr.***: Cyclimorph; Migril; Wellconal; ***UK***: Cyclimorph; Diconal†; Migril.

Pharmacopoeial Preparations
BP 2014: Cyclizine Injection; Cyclizine Tablets; Dipipanone and Cyclizine Tablets;
USP 36: Cyclizine Hydrochloride Tablets.

Cyproheptadine Hydrochloride

(BANM, rINNM)

Ciproheptadina, hidrocloruro de; Ciproheptadin-hidroklorid; Ciproheptadino hidrocloridas; Cyproheptadine, chlorhydrate de; Cyproheptadinhydrochlorid; Cyproheptadin-hydrochlorid seskvihydrát; Cyproheptadinhydroklorid; Cyproheptadini hydrochloridum; Cyproheptadini Hydrochloridum Sesquihydricum; Hidrocloruro de ciproheptadina; Siproheptadin Hidroklorür; Syproheptadiinihydrokloridi; Ципрогептадина Гидрохлорид.

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sesquihydrate.

$C_{21}H_{21}N,HCl,1½H_2O=350.9$

CAS — 129-03-3 (cyproheptadine); 969-33-5 (anhydrous cyproheptadine hydrochloride); 41354-29-4 (cyproheptadine hydrochloride sesquihydrate).

ATC — R06AX02.

ATC Vet — QR06AX02.

UNII — NJ82J0F8QC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8 (Cyproheptadine Hydrochloride). A white or slightly yellow, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Cyproheptadine Hydrochloride). A white to slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 275 of water, 1 in 35 of alcohol, 1 in 26 of chloroform, and 1 in 1.5 of methyl alcohol; practically insoluble in ether.

Uses and Administration

Cyproheptadine, a piperidine derivative, is a sedating antihistamine with antimuscarinic, serotonin-antagonist, and calcium-channel blocking actions. It is used as the hydrochloride for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). Other uses include the management of migraine (p. 611.3). Cyproheptadine hydrochloride is given as the sesquihydrate although doses are expressed in terms of the anhydrous substance. Anhydrous cyproheptadine hydrochloride 10 mg is equivalent to about 11 mg of cyproheptadine hydrochloride sesquihydrate.

For allergic conditions and pruritus the oral dose is initially 4 mg three times daily, adjusted as necessary. The average dose requirement is 12 to 16 mg daily in three or four divided doses, but up to 32 mg daily may occasionally be necessary. Cyproheptadine is not recommended in debilitated elderly patients. For dosage in children, see below.

A dose of 4 mg is used for both prophylaxis and treatment of migraine and other vascular headaches and may be repeated after 30 minutes; patients who respond usually obtain relief with 8 mg, and this dose should not be exceeded within a 4- to 6-hour period. A maintenance dose of 4 mg may be given every 4 to 6 hours.

Other cyproheptadine salts that have been given orally include the acetylaspartate, aspartate, cyclamate, orotate, acefyllinate (7-theophyllineacetate), and the pyridoxal phosphate salt (dihexazine).

Administration in children. For allergic conditions and pruritus, the oral dose of cyproheptadine hydrochloride for children aged 2 to 6 years is 2 mg two or three times daily. This may be increased to a maximum of 12 mg daily if necessary. For children aged 7 to 14 years, 4 mg two or three times daily may be given, increased up to a maximum of 16 mg daily.

Abdominal migraine. Cyproheptadine has been tried in the prophylactic treatment of children with abdominal migraine (see Pizotifen, p. 678.2).

Angina pectoris. Cyproheptadine was used successfully to treat 2 patients with Prinzmetal's angina (p. 1254.3) refractory to standard treatment with calcium-channel blockers and nitrates.[1] Serotonin is an important endocrine mediator of coronary vasospasm and the beneficial effects of cyproheptadine were attributed to its activity as a serotonin antagonist.

1. Schecter AD, *et al.* Refractory Prinzmetal angina treated with cyproheptadine. *Ann Intern Med* 1994; **121:** 113–14.

Appetite disorders. Cyproheptadine has been widely used as an appetite stimulant, including for anorexia nervosa and cachexia (see under Megestrol, p. 2289.3), but in the long-term appears to have little value in producing weight gain and such use is no longer generally recommended. There has been concern that cyproheptadine was being promoted and used inappropriately as an appetite stimulant in some developing countries.[1]

1. Anonymous. Cyproheptadine: no longer promoted as an appetite stimulant. *WHO Drug Inf* 1994; **8:** 66.

Carcinoid syndrome. The management of neuroendocrine tumours (p. 716.3) is largely symptomatic. Cyproheptadine hydrochloride, a serotonin antagonist, has had limited success in relieving symptoms such as diarrhoea but somatostatin analogues may now be preferred.[1] It has been used successfully with fenclonine, aprotinin, methylprednisolone, and antibacterials to prevent complications arising from release of tumour metabolites during hepatic embolisation, a procedure sometimes used to relieve the symptoms of carcinoid syndrome.[2] There have been a few reports of tumour regression, in addition to symptomatic control, after treatment of carcinoid tumours with cyproheptadine.[3,4]

1. Caplin ME, *et al.* Carcinoid tumour. *Lancet* 1998; **352:** 799–805.
2. Maton PN, *et al.* Role of hepatic arterial embolisation in the carcinoid syndrome. *BMJ* 1983; **287:** 932–5. Correction to dosage. ibid.; 1664.
3. Harris AL, Smith IE. Regression of carcinoid tumour with cyproheptadine. *BMJ* 1982; **285:** 475.
4. Leitner SP, *et al.* Partial remission of carcinoid tumor in response to cyproheptadine. *Ann Intern Med* 1989; **111:** 760–1.

Serotonin syndrome. Cyproheptadine has been successfully used to treat the serotonin syndrome (p. 443.2) in patients who have developed the syndrome after overdoses involving serotonergic drugs or who have had their antidepressant therapy changed without an adequate wash-out period.[1,2]

1. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med* 1994; **331:** 1021–2.
2. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother* 2001; **35:** 870–3.

Sexual dysfunction. Cyproheptadine has been tried in the management of sexual dysfunction induced by SSRIs (see Effects on Sexual Function under Fluoxetine, p. 421.1) but may possibly reduce the efficacy of the SSRI.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Increased appetite and weight gain may occur with cyproheptadine.

Abuse. Dependence developed in a patient who took about 180 mg of oral cyproheptadine daily for 5 years.[1]

1. Craven JL, Rodin GM. Cyproheptadine dependence associated with an atypical somatoform disorder. *Can J Psychiatry* 1987; **32:** 143–5.

Effects on the nervous system. Antimuscarinic toxicity manifest by hallucinations and agitation developed in a 9-year-old child taking cyproheptadine 4 mg twice daily for migraine prophylaxis.[1]

1. Watemberg NM, *et al.* Central anticholinergic syndrome on therapeutic doses of cyproheptadine. *Pediatrics* 1999; **103:** 158–60.

Interference with diagnostic tests. Cyproheptadine reduced hypoglycaemia-induced growth hormone secretion by between 5 and 97% in 8 healthy subjects.[1] It was suggested that cyproheptadine therapy should be stopped before giving a pituitary function test that used growth hormone response to insulin-induced hypoglycaemia.

UK licensed product information states that cyproheptadine may cause a false positive test result for tricyclic antidepressants in urine or serum.

1. Bivens CH, *et al.* Inhibition of hypoglycaemia-induced growth hormone secretion by the serotonin antagonists cyproheptadine and methysergide. *N Engl J Med* 1973; **289:** 236–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyproheptadine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Antidepressants. For reports suggesting that cyproheptadine can reduce the efficacy of *SSRIs*, see under Fluoxetine, p. 424.2. Cyproheptadine may interfere with diagnostic tests for tricyclic antidepressants, see above.

Pharmacokinetics

After absorption from the gastrointestinal tract, cyproheptadine hydrochloride undergoes almost complete metabolism. Metabolites are excreted principally in the urine as conjugates, and also in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Periactin; ***Austria***: Periactin; ***Belg.***: Periactin; ***Braz.***: Periatin; ***Chile***: Viternum; ***Cz.***: Peritol; ***Fr.***: Periactine; ***Ger.***: Peritol; ***Gr.***: Adekin; Istam-Far; Kulinet; Periactin†; ***Hong Kong***: Appetin†; CH Syrup†; Cyprodine†; Cyprogin; Uni-Heptadine†; ***Hung.***: Peritol; ***India***: Add App; Anabol; Apedin; Apel; Apenorm; Apeplus; Apetamin; App-Up; Appetidin; Aptaur; Bal-Riactin; Cedel; Ciplactin; Cyp-L; Cypgo; Cyphoden; Cyproden; Hito-EN; Hungree; Indocyp; Peritol; Practin; ***Indon.***: Alphahist†; Apeton; Cydifar†; Cylat†; Ennamax; Esprocy; Glocyp; Heptasan; Lexahist; Poncohist; Profut†; Prohessen; Pronicy; Sinapdin†; ***Irl.***: Periactin†; ***Ital.***: Periactin; ***Mex.***: Viternum; ***Neth.***: Periactin; ***NZ***: Periactin; ***Pol.***: Peritol; ***Port.***: Viternum; ***Rus.***: Peritol (Перитол); ***S.Afr.***: Cipla-Actin; Periactin; ***Singapore***: Cyprotin; Periactin†; Pilian; ***Spain***: Periactin; Viternum; ***Swed.***: Periactin†; ***Thai.***: Anpro; Cycodine; Cyheptine; Cyprocap; Cyprodine; Cyprogin; Cypronam; Cyprono; Cypropicco; Cyprosian; Cyprotec; Hepdine†; Periactin; Polytab; ***Turk.***: Prakten; Sipraktin; ***UK***: Periactin; ***Ukr.***: Peritol (Перитол); ***Venez.***: Cyprodin.

Multi-ingredient Preparations. ***Arg.***: Apeplus; Apetitol Forte; Ciprocort; Ciprovit Calcio; Ciprovit Energizante; Ciprovit Magnesico; Mikesan; Potencil; Sudevil Vita; ***Braz.***: Apetivit BC; Apetiviton BC; Apevinat BC; Apevitin BC; Apmed; Cobactin; Cobaglobal; Cobavit; Cobavital; Petivit BC; Trimetabol†; ***Chile***: Apetrol; Orodina; Peracon; Revil; Rodepan; Viternum Vitaminado; ***Hong Kong***: Calbolex†; Calibo Chewable†; Lysinevita†; Petina Compound; Tres Orix Forte†; Tricavita†; Vigueur†; ***India***: Anorexin Plus; Apel-G; Apenic; Apirich; Apitus-TC; App-Up; Appe-Care; Appet; Appetidin; Asi-Liv; Atric Plus; Auz; Bio Cyp; Chocy; Cipliv; Clydin; Cyaptin With Calcium; Cyaptin-SF; Cyaptin; Cydine; Cyp-L; Cypee; Cypine-TS; Cypolin; Cypon DPS; Cypon-I; Cypon; Cyprea-T; Cypro-L; Cypro; Cyprobit; Cyprowal; Cyproz; Decyp-P; Devlup; Forliv; Fortil; Growise; Hapeast; Hapeast; Hepsandinn; Hypetin; In-OZ; Karnatakaiv; Lecyp; Livpron; LSky; Lycyp; M-Cyp; NBTone; O-AP; Oraxin; Orliv; ***Mex.***: Ciprolisina; Pangavit Pediatrico; Rocavit; ***Spain***: Anti-Anorex Triple; Covitasa B12; Desarrol; Medenorex†; Novogumil; Pantobamin; Pranzo; Stolina; Tonico Juventus; Trimetabol; Troforex Pepsico†; Vita Menal; ***Ukr.***: Trimetabol (Триметабол); ***Venez.***: Cyprodex.

Pharmacopoeial Preparations
BP 2014: Cyproheptadine Tablets;
USP 36: Cyproheptadine Hydrochloride Syrup; Cyproheptadine Hydrochloride Tablets.

Deptropine Citrate *(BANM, rINNM)*

Citrato de deptropina; Deptropiinisitraatti; Deptropina, citrato de; Deptropincitrat; Deptropin-citrát; Deptropine, Citrate de; Deptropini Citras; Deptropino citratas; Dibenzheptropine Citrate; Дептропина Цитрат.

(1*R*,3*r*,5*S*)-3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yloxy)tropane dihydrogen citrate.

$C_{23}H_{27}NO_7C_6H_8O_7$=525.6

CAS — 604-51-3 (deptropine); 2169-75-7 (deptropine citrate).

ATC — R06AX16.

ATC Vet — QR06AX16.

UNII — 05LW13XKKR.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Deptropine Citrate). A white or almost white, microcrystalline powder. Very slightly soluble in water and in dehydrated alcohol; practically insoluble in dichloromethane. A saturated solution in water has a pH of 3.7 to 4.5. Protect from light.

Profile

Deptropine citrate is a sedating antihistamine (p. 610.1) with a marked antimuscarinic action. It was given by mouth mainly in the treatment of respiratory-tract disorders.

Desloratadine *(BAN, USAN, rINN)*

Descarboethoxyloratadine; Descarboetoxiloratadina; Desloratadin; Desloratadina; Desloratadinum; Sch-34117; Дезлоратадин.

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

$C_{19}H_{19}ClN_2$=310.8

CAS — 100643-71-8.

ATC — R06AX27.

ATC Vet — QR06AX27.

UNII — FVF865388R.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Desloratadine). A white or almost white powder. Very slightly soluble or practically insoluble in water; freely soluble in alcohol; slightly soluble or very slightly soluble in heptane. It shows polymorphism.

Profile

Desloratadine, the major, active metabolite of loratadine (p. 633.2), is a non-sedating antihistamine. Desloratadine is used in the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and urticaria (p. 612.3).

Desloratadine is given in an oral dose of 5 mg once daily.

It is also used with a decongestant such as pseudoephedrine sulfate.

For dosage in children, and in hepatic or renal impairment, see below.

References.

1. McClellan K, Jarvis B. Desloratadine. *Drugs* 2001; **61:** 789–96.
2. Simons FER, ed. Desloratadine: clinical pharmacokinetics of a novel H_1 receptor antagonist. *Clin Pharmacokinet* 2002; **41** (suppl 1): 1–44.
3. Limon L, Kockler DR. Desloratadine: a nonsedating antihistamine. *Ann Pharmacother* 2003; **37:** 237–46. Correction. *ibid.*; 454.
4. Murdoch D, *et al*. Desloratadine: an update of its efficacy in the management of allergic disorders. *Drugs* 2003; **63:** 2051–77.
5. Berger WE. The safety and efficacy of desloratadine for the management of allergic disease. *Drug Safety* 2005; **28:** 1101–18.
6. Canonica GW, *et al*. Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy* 2007; **62:** 359–66.
7. Layton D, *et al*. Examining the tolerability of the non-sedating antihistamine desloratadine: a prescription-event monitoring study in England. *Drug Safety* 2009; **32:** 169–79.

Administration in children. In the UK, desloratadine is licensed for use in children aged 1 year and over in the treatment of allergic rhinitis and urticaria; in the USA, it may be given to those aged 6 months and over for perennial allergic rhinitis and urticaria and to those aged 2 years and over for seasonal allergic rhinitis.

Regardless of indication, oral doses of desloratadine are as follows:

- children aged 6 to 11 months: 1 mg once daily
- those aged 1 to 5 years: 1.25 mg once daily
- those aged 6 to 11 years: 2.5 mg once daily.

References.

1. Gupta S, *et al*. Pharmacokinetics of desloratadine in children between 2 and 11 years of age. *Br J Clin Pharmacol* 2007; **63:** 534–40.
2. Gupta SK, *et al*. Desloratadine dose selection in children aged 6 months to 2 years: comparison of population pharmacokinetics between children and adults. *Br J Clin Pharmacol* 2007; **64:** 174–84.

Administration in hepatic or renal impairment. US licensed product information recommends that patients with hepatic or renal impairment should be given desloratadine 5 mg orally on alternate days initially.

Breast feeding. Desloratadine is distributed into breast milk and consequently UK and US licensed product information does not recommend its use during breast feeding. For a discussion of the use of *loratadine* in breast feeding, see under Adverse Effects and Precautions, p. 633.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desloratadine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Desloratadine was not teratogenic in *animal* studies; however, product information recommends it should be used with caution, if at all, in pregnant women.

For a discussion of the use of loratadine in pregnancy, see under Adverse Effects and Precautions, p. 633.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerius; Delorat; Desaler; Deslo; Frenaler; Hexaler; Novo Alerpriv; Predualergin; ***Austral.***: Aerius; Claramax†; ***Austria***: Aerius; ***Belg.***: Aerius; ***Braz.***: Aleradina; Desalex; Deslorana; Destadin; ***Canad.***: Aerius; ***Chile***: Aerius; D-Histaplus; Deslocross; Despeval; Despex; Mailen; Neo Larmax; Neo-Alledryl; Neoclaritine; Neohysticlar; Rinaid; Rinofilax; ***China***: Aerius (恩理思); Dihengsai (地恒赛); Fu Bi Ding (芙必叮); Xin Ming Ting (信敏汀); ***Cz.***: Aerius; Azomyr; Neoclarityn; ***Denm.***: Aerius; Dasselta; ***Fin.***: Aerius; ***Fr.***: Aerius; ***Ger.***: Aerius; ***Gr.***: Aerius; Azomyr; Neoclarityn; ***Hong Kong***: Aerius; ***Hung.***: Aerius; ***India***: Alerdain; Allerede; Allergesic; D-Loratin; D-Lordex; Dazit; Delorta; Delotid; Des-OD; Desent; Deslor; Desloriv; Desnova; Dexly; Dilora; DYL; Lorday; Loreta; Neoloridin; Nucope; Otrivin-Alert; ***Indon.***: Aerius; ***Irl.***: Aerius; Azomyr; Dasselta; Neoclarityn; ***Israel***: Aerius; ***Ital.***: Aerius; Azomyr; Efestad; Neokatall; ***Malaysia***: Aerius; ***Mex.***: Aviant; Azomyr; Lirudine; ***Neth.***: Aerius; Azomyr; Dasselta; Desloratsam; Lodesdineta; Neoclarityn; ***Norw.***: Aerius; ***NZ***: Aerius; Claramax; ***Philipp.***: Aerius; ***Pol.***: Aerius; Azomyr; Neoclarityn; ***Port.***: Aerius; Azomyr; Neoclarityn; ***Rus.***: Aerius (Эриус); Lordestin (Лордестин); ***S.Afr.***: Dazit; Desaway; Deselex; Desodene; ***Singapore***: Aerius; ***Spain***: Aerius; Azomyr; Dasselta; ***Swed.***: Aerius; Dasselta; ***Switz.***: Aerius; ***Thai.***: Aerius; ***Turk.***: Aerius; Doxafin; Lordes; ***UK***: Neoclaritvn; ***Ukr.***: Aerius (Эриус); Allergostop (Аллергостоп); Desorus (Дезорус)†; Edem (Эдем); Eridez (Эридез); Loratek (Лоратек); ***USA***: Clarinex; ***Venez.***: Aerius; Desalex; Deslorat; Esparflin; Mailen.

Multi-ingredient Preparations. ***Arg.***: Desaler Cort; Frenaler Cort; Hexaler Cort; Hexaler Plus; ***Belg.***: Aerinaze; ***Canad.***: Aerius Dual Action 12 Hour; ***Cz.***: Aerinaze; ***Gr.***: Aerinaze; ***India***: DM; DYL-AX; DYL-D; Mondeslor; Neoloridin-D; Nucope-AD; ***Irl.***: Aerinaze; ***Israel***: Aerinaze; ***Neth.***: Aerinaze; ***Pol.***: Aerinaze; ***Port.***: Aerinaze; ***Singapore***: Aerius D-12; ***USA***: Clarinex-D.

Dimenhydrinate *(BAN, rINN)*

Chloranautine; Dimenhidrinat; Dimenhidrinát; Dimenhidrinatas; Dimenhidrinato; Dimenhydramina; Dimenhydrinaatti; Dimenhydrinat; Dimenhydrinát; Diménhydrinate; Dimenhydrinatum; Diphenhydramine Teoclate; Diphenhydramine Theoclate; Дименгидринат.

The diphenhydramine salt of 8-chlorotheophylline.

$C_{17}H_{21}NO,C_7H_7ClN_4O_2$=470.0

CAS — 523-87-5.

ATC — R06AA02.

ATC Vet — QR06AA02.

UNII — JB937PER5C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dimenhydrinate). A white or almost white, crystalline powder or colourless crystals. M.p. 102 degrees to 106 degrees. Slightly soluble in water; freely soluble in alcohol. A saturated solution in water has a pH of 7.1 to 7.6.

USP 36: (Dimenhydrinate). A white, odourless, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether.

Incompatibility. Dimenhydrinate has been reported to be incompatible in solution with many compounds; those most likely to be encountered include: aminophylline, glycopyrronium bromide, hydrocortisone sodium succinate, hydroxyzine hydrochloride, meglumine adipiodone, some phenothiazines, and some soluble barbiturates.

Uses and Administration

Dimenhydrinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and significant sedative effects. It is used mainly as an antiemetic in the prevention and treatment of motion sickness (p. 611.3). It is also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disturbances (see Vertigo, p. 612.3).

The usual oral dose of dimenhydrinate is 50 to 100 mg, given 3 or 4 times daily. For the prevention of motion sickness, the first dose should be given at least 30 minutes before travelling.

Dimenhydrinate may be given parenterally in usual doses of 50 mg, a concentration of 5% being used for intramuscular injection and 0.5% for slow intravenous injection (usually over 2 minutes).

For doses in children, see below.

Dimenhydrinate has also been given by the rectal route.

Administration in children. Dimenhydrinate can be given to children for the symptomatic treatment of nausea and vomiting associated with various conditions. The following doses may be given orally, depending on age:

- children aged 2 to 6 years: 12.5 to 25 mg every 6 to 8 hours to a maximum of 75 mg daily
- those aged 6 to 12 years: 25 to 50 mg every 6 to 8 hours to a maximum of 150 mg daily

For the prevention of motion sickness, the first dose should be given at least 30 minutes before travelling.

Alternatively, children have been given dimenhydrinate intramuscularly, in a dose of 1.25 mg/kg four times daily to a maximum of 300 mg daily.

Children and adolescents aged 12 years and over may be given usual adult doses, see above.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Effects on the eyes. Dimenhydrinate 100 mg, given at 4-hourly intervals for 3 doses, was found to affect colour discrimination, night vision, reaction time, and stereopsis.[1]

1. Luria SM, *et al*. Effects of aspirin and dimenhydrinate (Dramamine) on visual processes. *Br J Clin Pharmacol* 1979; **7:** 585–93.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between cardiovascular defects or inguinal hernia and dimenhydrinate exposure, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agirax; Dr Amin; Dramamine; Vertigmine; ***Austral.***: Dramamine†; ***Austria***: Emedyl; Travel-Gum; Vertirosan; ***Belg.***: Paranausine†; ***Braz.***: Dramamine†; Dramin; Neodrin; ***Canad.***: Anti-Nauseant; Anti-Nausee†; Childrens Motion Sickness Liquid; Dinate; Gravol; Motion Sickness†; Nauseatol; Novo-Dimenate; Travel Tabs; ***Chile***: Mareamin; ***China***: Yi Han Ning (贻晗柠); ***Cz.***: Travel-Gum; ***Fr.***: Nausicalm; ***Ger.***: Reisefit; Reisetabletten†; Superpep; Vertigo-Vomex; Vomacur†; Vomex A; ***Gr.***: Baderol; Dravom; Drimen; Retager; Travelgum; Vertirosan; Vomex A; ***Hong Kong***: Dimate†; Dimenate; Garcol; Gravol; Gravolvick†; Neo-Diphenamine†; Novomin; Setmenate; Synavol†; Uni-Hydrin†; ***Hung.***: Daedalon; Daedalonetta; ***India***: Dramamine; Draminate; Gravol; ***Indon.***: Dramamine; Stopmun†; ***Israel***: Travamin; ***Ital.***: Lomarin; Motozina†; Travelgum; Valontan; Xamamina; ***Malaysia***: Dimenate; Dramamine†; Driminate; Hydrinate; Novomin; Votmine; Zoranate; ***Mex.***: Apo-Mina; Dimicaps; Dramamine; Dramit-GB; Vomisin; ***NZ***: Dramamine†; ***Philipp.***: Emes; Gravol; ***Pol.***: Aviomarin; ***Port.***: Draminal; Enjomin; Viabom; Vomidrine; ***Rus.***: Dramina (Драмина); Siel (Сиэль); ***Singapore***: Dimenate; Dramamine†; Medrinate; Novomin; Votmine; ***Spain***: Biodramina; Cinfamar; Travel Well; ***Swed.***: Amosyt; Calma; ***Switz.***: Antemine†; Trawell; ***Thai.***: Denim; Dimenine; Dimeno; Dimesian; Dimin; Dimonate; Divomit; Dramamine†; Dramine; Gravol†; KB Dramine; Motivan; Nausamine†; Navamin; Phrachedi†; Vomen; ***Turk.***: Anti-Em; Dramamine; Xamamina; ***UAE***: Dizinil; ***Ukr.***: Dramina (Драмина); ***USA***: Dimetabs; Dinate†; Dramamine†; Dramanate; Dymenate; Triptone; ***Venez.***: Viajesan.

Multi-ingredient Preparations. ***Austral.***: Travacalm; ***Austria***: Neo-Emedyl; Synkapton; Vertirosan Vitamin B_6; ***Belg.***: Arlevertan; ***Braz.***: Dramin B6 DL; Dramin B6; Nausicalm; Nausilon B6; ***Canad.***: Gravergol†; ***Cz.***: Arlevert; Migraeflux†; ***Fin.***: Arlevert; ***Fr.***: Mercalm; ***Ger.***: Arlevert; ***Gr.***: Vertigo-Vomex; ***Hong Kong***: Rhinocap†; ***Hung.***: Arlevert; ***Indon.***: Dramasine; ***Irl.***: Arlevert; ***Ital.***: Arlevertan; ***Mex.***: Bomine; ***Neth.***: Arlevert; ***Rus.***: Synkapton (Синкаптон); ***Spain***: Acetuber; Biodramina Cafeina; Cinfamar Cafeina; Saldeva; Salvarina; ***Swed.***: Arlevert; ***Switz.***: Antemin compositum; Arlevert; Coop Vitality†; Dragees contre les maux de voyage†; Gem Voyage Dragees contre les maux de voyage; Rhin-X; Rhinocap; Rotpunkt Apotheke dragees contre les maux de voyage; Tesero Voyage; ***Thai.***: Roxine; ***UK***: Arlevert.

Pharmacopoeial Preparations

BP 2014: Dimenhydrinate Tablets;
USP 36: Dimenhydrinate Injection; Dimenhydrinate Syrup; Dimenhydrinate Tablets.

Dimetindene Maleate *(BANM, rINNM)*

Dimethindene Maleate (USAN); Dimethindene Maleate; Dimethpyrindene Maleate; Dimethylpyrindene Maleate; Dimetindeenimaleaatti; Dimetinden Maleat; Dimétindène, Maléate de; Dimetindeni Maleas; Dimetindenmaleat; Dimetindén-maleát; Dimetinden-maleinát; Dimetindeno maleatas; Dimetindeno, maleato de; Maleato de dimetindeno; NSC-107677; Su-6518; Диметиндена Малеат.

NN-Dimethyl-2-{3-[1-(2-pyridyl)ethyl]-1*H*-inden-2-yl}ethylamine hydrogen maleate.

$C_{20}H_{24}N_2.C_4H_4O_4$=408.5

CAS — 5636-83-9 (dimetindene); 3614-69-5 (dimetindene maleate).

ATC — D04AA13; R06AB03.

ATC Vet — QD04AA13; QR06AB03.

UNII — 6LL60J9E0O.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dimetindene Maleate). A white to almost white, crystalline powder. Slightly soluble in water; soluble in methyl alcohol. Protect from light.

Profile

Dimetindene maleate, an alkylamine derivative, is a sedating antihistamine (p. 610.1); it is mildly sedative and is reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3) and rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It is also used in compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

Dimetindene maleate is given in an oral dose of 1 to 2 mg three times daily; modified-release preparations are also available. It may also be given by the intravenous route. Dimetindene maleate is applied topically as a 0.1% gel or lotion although, as with other antihistamines, there is a risk of sensitisation. It is used in a strength of 0.025% in compound nasal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Fenistil; ***Belg.***: Fenistil; ***Cz.***: Fenistil; ***Ger.***: Fenistil; ***Gr.***: Fenistil; Specisun; ***Hung.***: Fenistil; ***India***: Foristal; ***Indon.***: Fenistil; ***Israel***: Fenistil; ***Ital.***: Fenistil; ***Neth.***: Fenistil; ***Philipp.***: Fenistil; ***Pol.***: Fenistil; ***Port.***: Fenistil; Neostil†; ***Rus.***: Fenistil (Фенистил); ***Spain***: Fenistil; ***Switz.***: Feniallerg; Fenistil; ***Thai.***: Fenistil; ***Turk.***: Fenistil; ***Ukr.***: Fenistil (Фенистил).

Multi-ingredient Preparations. ***Arg.***: Vibragel; ***Austria***: Trimedil compositum†; Vibrocil; ***Belg.***: Vibrocil; ***Braz.***: Gripen; Trimedal; ***Cz.***: Vibrocil; ***Gr.***: Vibrocil-S; ***Hung.***: Otrivin Allergia; Vibrocil; ***Israel***: Vibrocil; ***Pol.***: Otrivin Allergy; ***Port.***: Vibrocil; ***Rus.***: Vibrocil (Виброцил); ***S.Afr.***: Vibrocil-S; Vibrocil; ***Switz.***: Otriduo Rhume; Vibrocil; ***Ukr.***: Vibrocil (Виброцил).

Dimetotiazine Mesilate *(BANM, rINNM)*

Dimethothiazine Mesylate; Dimetotiazina, mesilato de; Dimétotiazine, Mésilate de; Dimetotiazini Mesilas; Fonazine Mesylate (USAN); IL-6302 (dimetotiazine); Mesilato de dimetotiazina; 8599-RP (dimetotiazine); Диметотиазина Мезилат.

10-(2-Dimethylaminopropyl)-*NN*-dimethylphenothiazine-2-sulphonamide methanesulphonate.

$C_{19}H_{25}N_3O_2S_2.CH_3SO_3H$=487.6

CAS — 7456-24-8 (dimetotiazine); 7455-39-2 (dimetotiazine mesilate).

ATC — N02CX05.

ATC Vet — QN02CX05.

UNII — B28V86NGNK.

Profile

Dimetotiazine mesilate, a phenothiazine derivative, is a sedating antihistamine (p. 610.1). It has been used for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders, and in the management of headaches including migraine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Migristene†; ***Mex.***: Migristene†.

Diphenhydramine *(BAN, rINN)*

Benzhydramine; Difenhidramina; Difenhydramiini; Difenhydramin; Diphénhydramine; Diphenhydraminum; Дифенгидрамин.

2-Benzhydryloxy-*NN*-dimethylethylamine.

$C_{17}H_{21}NO$=255.4

CAS — 58-73-1.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — 8GTS82S83M.

Pharmacopoeias. In *Jpn.*

Jpn also includes Diphenhydramine Tannate.

Diphenhydramine Citrate *(BANM, rINNM)*

Benzhydramine Citrate; Citrato de difenhidramina; Difenhidramina, citrato de; Diphénhydramine, Citrate de; Diphenhydramini Citras; Дифенгидрамина Цитрат.

$C_{17}H_{21}NO.C_6H_8O_7$=447.5

CAS — 88637-37-0.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — 4OD433S209.

Pharmacopoeias. In *US.*

USP 36: (Diphenhydramine Citrate). Store in airtight containers. Protect from light.

Diphenhydramine Di(acefyllinate) *(rINNM)*

Benzhydramine Di(acefyllinate); Bietanautine; Di(acefilinato) de difenhidramina; Difenhidramina, di(acefilinato) de; Diphénhydramine Diacéfylline; Diphenhydramine Di(acephyllinate); Diphenhydramini Diacefyllinas; Дифенгидрамина Диацефиллинат.

Diphenhydramine bis(theophyllin-7-ylacetate).

$C_{17}H_{21}NO.2C_9H_{10}N_4O_4$=731.8

CAS — 6888-11-5.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — F3D8G86A29.

NOTE. The name Etanautine has been applied both to diphenhydramine monoacefyllinate and to ethylbenzhydramine, an antimuscarinic formerly used in the symptomatic treatment of parkinsonism.

Diphenhydramine Hydrochloride

(BANM, rINNM)

Benzhydramine Hydrochloride; Difenhidramin Hidroklorür; Difenhidramina, hidrocloruro de; Difenhidramin-hidroklorid; Difenhidramino hidrochloridas; Difenhydramiinihydrokloridi; Difenhydramin-hydrochlorid; Difenhydraminhydroklorid; Difenhydraminy chlorowodorek; Dimedrolum; Diphénhydramine, Chlorhydrate de; Diphenhydraminhydrochlorid; Diphenhydramini Hydrochloridum; Diphenhydraminium Chloride; Hidrocloruro de difenhidramina; Дифенгидрамина Гидрохлорид.

$C_{17}H_{21}NO.HCl$=291.8

CAS — 147-24-0.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — TC2D6JAD40.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Jpn also includes Diphenhydramine Tannate.

Ph. Eur. 8: (Diphenhydramine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Diphenhydramine Hydrochloride). A white, odourless, crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 50 of acetone; very slightly soluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Incompatibility. Diphenhydramine hydrochloride has been reported to be incompatible with amphotericin B, cefmetazole sodium, cefalotin sodium, hydrocortisone sodium succinate, some soluble barbiturates, some contrast media, and solutions of alkalis or strong acids.

Uses and Administration

Diphenhydramine, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It is also used for its antiemetic properties in the treatment of nausea and vomiting (p. 611.3), particularly in the prevention and treatment of motion sickness (when it should be given at least 30 minutes before travelling), and in the treatment of vertigo of various causes (p. 612.3). Diphenhydramine is used for its antimuscarinic properties in the control of parkinsonism (p. 889.1) and drug-induced extrapyramidal disorders (p. 1049.2) (although the possibility that diphenhydramine itself may cause extrapyramidal symptoms should be remembered). Diphenhydramine has pronounced central sedative properties and may be used as a hypnotic in the short-term management of insomnia (p. 611.2). It is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2), or preparations containing analgesics, particularly paracetamol. Diphenhydramine may be used parenterally as an adjunct in the emergency treatment of anaphylactic shock (p. 611.1) or when oral therapy is not feasible.

For most indications, *diphenhydramine hydrochloride* is given in usual oral doses of 25 to 50 mg three or four times daily; the maximum dose is about 300 mg daily. A dose of 50 mg may be used as a hypnotic.

When oral therapy is not feasible, diphenhydramine hydrochloride may be given by deep intramuscular injection or by intravenous injection using concentrations of 1% or 5%. Usual doses are 10 to 50 mg, although doses of 100 mg have been given. No more than 400 mg should be given in 24 hours.

For dosage in children, see below.

Diphenhydramine hydrochloride is applied topically, usually in preparations containing 1 to 2% although, as with other antihistamines, there is a risk of sensitisation.

Diphenhydramine citrate is given orally in a dose of 76 mg at night in combination preparations for its hypnotic action. *Diphenhydramine di(acefyllinate)* is given as an antiemetic for the prevention and treatment of motion sickness. The usual oral dose is 90 to 135 mg, which may be repeated if necessary at intervals of at least 6 hours, to a maximum of 540 mg daily.

Other diphenhydramine salts that have been used include the polistirex, the salicylate, and the tannate orally, the methylbromide rectally, and the laurilsulfate and the metilsulfate applied topically.

Dimenhydrinate (p. 625.2) is diphenhydramine teoclate and mefenidramium metilsulfate is diphenhydramine methylsulfomethylate.

Administration in children. Diphenhydramine hydrochloride may be used in children for the symptomatic relief of allergic conditions such as rhinitis. It is also used in the prevention and treatment of motion sickness (when it should be given at least 30 minutes before travelling). Diphenhydramine may also be given in combination preparations containing analgesics, particularly paracetamol. It may be used parenterally as an adjunct in the emergency treatment of anaphylactic shock or when oral therapy is not feasible.

The oral dose of diphenhydramine hydrochloride for most indications is as follows:

- children aged 2 to 6 years: 6.25 mg every four to six hours
- those aged 6 to 12 years: 12.5 to 25 mg every four to six hours

When oral therapy is not feasible, diphenhydramine hydrochloride may be given by deep intramuscular injection or by intravenous injection. Children may be given 5 mg/kg daily in four divided doses, to a maximum of 300 mg in 24 hours.

Diphenhydramine is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold. However, such preparations should be used with caution in children, and generally avoided in young children, for details see p. 614.1.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Abuse. Reports of the abuse of diphenhydramine hydrochloride.

1. Anonymous. Is there any evidence that Benylin syrup is addictive? *BMJ* 1979; **1:** 459.
2. Smith SG, Davis WM. Nonmedical use of butorphanol and diphenhydramine. *JAMA* 1984; **252:** 1010.
3. Feldman MD, Behar M. A case of massive diphenhydramine abuse and withdrawal from use of the drug. *JAMA* 1986; **255:** 3119–20.
4. de Nesnera AP. Diphenhydramine dependence: a need for awareness. *J Clin Psychiatry* 1996; **57:** 136–7.
5. Dinndorf PA, *et al.* Risk of abuse of diphenhydramine in children and adolescents with chronic illnesses. *J Pediatr* 1998; **133:** 293–5.

Extrapyramidal disorders. Reports of dystonic extrapyramidal reactions to diphenhydramine.

1. Lavenstein BL, Cantor FK. Acute dystonia: an unusual reaction to diphenhydramine. *JAMA* 1976; **236:** 291.
2. Santora J, Rozek S. Diphenhydramine-induced dystonia. *Clin Pharm* 1989; **8:** 471.
3. Roila F, *et al.* Diphenhydramine and acute dystonia. *Ann Intern Med* 1989; **111:** 92–3.

Overdosage. In an evaluation of 136 cases, one fatal, of intoxication with diphenhydramine, the plasma concen-

tration was correlated with frequency or extent of symptoms.[1] The most common symptom was impaired consciousness; psychosis, seizures, antimuscarinic symptoms such as mydriasis, tachycardia, and tachyarrhythmias, and respiratory failure were also seen. The positive association between dose and frequency and severity of symptoms was confirmed in a more recent study;[2] it was also found that severe symptoms were more likely to occur when 1 g or more of diphenhydramine had been taken.

There have been reports[3,4] of rhabdomyolysis as an effect of oral diphenhydramine overdosage. The liberal application of a lotion containing diphenhydramine produced acute delirium with visual and auditory hallucinations in a 9-year-old boy[5] and similar effects were seen in 3 children with varicella-zoster infection after the topical application of diphenhydramine (2 of these children also received oral diphenhydramine).[6]

1. Köppel C, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. *Clin Toxicol* 1987; **25:** 53–70.
2. Radovanovic D, *et al.* Dose-dependent toxicity of diphenhydramine overdose. *Hum Exp Toxicol* 2000; **19:** 489–95.
3. Hampel G, *et al.* Myoglobinuric renal failure due to drug-induced rhabdomyolysis. *Hum Toxicol* 1983; **2:** 197–203.
4. Haas CE, *et al.* Rhabdomyolysis and acute renal failure following an ethanol and diphenhydramine overdose. *Ann Pharmacother* 2003; **37:** 538–42.
5. Filloux F. Toxic encephalopathy caused by topically applied diphenhydramine. *J Pediatr* 1986; **108:** 1018–20.
6. Chan CYJ, Wallander KA. Diphenhydramine toxicity in three children with varicella-zoster infection. *DICP Ann Pharmacother* 1991; **25:** 130–2.

Pregnancy. A pregnant woman who was receiving diphenhydramine hydrochloride 150 mg daily for a pruritic rash gave birth to an infant who developed diarrhoea and generalised tremulousness 5 days later.[1] The delay in appearance of withdrawal symptoms was considered to be due to reduced activity of glucuronyl conjugating enzymes in the first few days of life.

For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between inguinal hernia or genito-urinary malformations and diphenhydramine exposure, see p. 614.2. See also under Interactions, below, for a report of perinatal death possibly associated with temazepam and diphenhydramine.

1. Parkin DE. Probable Benadryl withdrawal manifestations in a new-born infant. *J Pediatr* 1974; **85:** 580.

Interactions

As for the sedating antihistamines in general, p. 614.3. Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 that is partly responsible for the metabolism of some beta blockers including metoprolol and the antidepressant venlafaxine.

Benzodiazepines. There has been a report[1] suggesting that a reduction in *temazepam* metabolism caused by diphenhydramine may have contributed to perinatal death after ingestion of these drugs by the mother.

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; **313:** 1417–18.

Pharmacokinetics

Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations occur about 1 to 4 hours after oral doses. Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly bound to plasma proteins. Metabolism is extensive. Diphenhydramine is excreted mainly in the urine as metabolites; little is excreted as unchanged drug. The elimination half-life has been reported to range from 2.4 to 9.3 hours.

References.

1. Glazko AJ, *et al.* Metabolic disposition of diphenhydramine. *Clin Pharmacol Ther* 1974; **16:** 1066–76.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97. (includes studies indicating a correlation between plasma concentrations and both antihistaminic and sedative effects).
3. Simons KJ, *et al.* Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol* 1990; **30:** 665–71.
4. Scavone JM, *et al.* Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. *J Clin Pharmacol* 1998; **38:** 603–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alermina†; Amodormin; Benadryl; Caladryl D†; Fabolergic; Fadalex; Histaler; Klonadryl Antialergico; Nelfigen†; TheraFlu Alergia†; ***Austral.***: Snuzaid; Unisom; ***Austria***: Calmaben; Dermodrin; Dibondrin; Histaxin; Noctor; ***Belg.***: Azaron; Diphamine; Nustasium; R Calm; ***Braz.***: Difenidrin; ***Canad.***: Aller-Aide; Allerdryl; Allergy Elixir; Allergy Formula; Allergy Tablets; Allergy; Allernix; Anti-Itch; Benadryl; Benylin Night Cough†; Calmex; Children's Allergy Formula; Childrens Cough, Cold & Allergy†; Childrens Liquid Allergy; Diphenist; Dormax; Dormex; Dormiphen; Extra Stength Sleep Aid; Insomnal; Jack & Jill Bedtime; Jack & Jill Thin Strips Cough & Cold†; Nadryl; Neocitran Nighttime Cough; Night Cough; Nytol; Simply Sleep; Sleep Aid; Sleep-Eze D; Sominex†; Triaminic Thin Strips Nighttime Cough & Runny Nose; Unisom; ***Chile***: Jaquedryl; Somol; ***Cz.***: Psilo-Balsam; ***Denm.***: Benylan; ***Fr.***: Butix; Nautamine; ***Ger.***: Betadorm D; Dolestan; Hevert-Dorm; Moradorm; nervo OPT N; Sediat; Sedopretten; Vivinox Sleep; ***Gr.***: Benadryl; ***Hong Kong***: Bendol; Bendrol†; Calmitch†; Diphenamine†; Histergan†; Unisom†; ***Hung.***: Psilo-Balsam; ***India***: Benacof; Benadryl; Cofryl; Kuffdryl; Novadryl; ***Indon.***: Arcodryl; Benadryl†; Otede; Paradryl; Recodryl; Sidiadryl†; Valdres; ***Israel***: Nytol; ***Ital.***: Aliserin; Allergan; ***Jpn***: Venapasta; ***Mex.***: Benadryl; Bionaryl; Bonanoti; Drafen; Glicodril; Histadryl; Indumir; Lurispan; Nytol; Ulcoid; ***NZ***: Unisom; ***Philipp.***: Alerace; Allerin AH; Benadryl Antihistamine; Benaxil; Dramelin; Tussicon; ***Port.***: Benaderma; Benergina; Codilergi†; ***Rus.***: Psilo-Balsam (Псило-Бальзам); ***S.Afr.***: Betasleep; Sleepeze-PM; ***Singapore***: Benadryl; Bendrol; Paxidorm; ***Spain***: Benadryl†; Neosayomol; Sonodor; ***Swed.***: Desentol; ***Switz.***: Benocten; Bonox; Nardyl Sommeil; ***Thai.***: Benadryl; Cabana; Codiphen; Dibendryl; Sedatab; Sedi; Tussodryl; ***Turk.***: Allenik; Allerjin†; Benadryl; Benison; Difedrin; Fenotral; ***UAE***: Amydramine II; ***UK***: Adult Chesty Cough; Boots Skin Allergy Relief; Child Chesty Cough; Dreemon; Histergan; Mandalyn Paediatric; Nightcalm; Nytol; Paxidorm; Sleep Aid; Sleepeaze; ***Ukr.***: Dermodrin (Дермадрин); Psilo-Balsam (Псило-Бальзам); ***USA***: 40 Winks; Aler-Dryl; AllerMax; Altaryl Childrens Allergy; Banophen Allergy; Ben-Tann†; Benadryl Allergy; Benadryl Childrens Allergy; Benadryl Itch; Benadryl; Childrens PediaCare Nighttime Cough; Compoz Night-time Sleep Aid; Derma-Pax; Dermamycin; Diphen AF; Diphenhist; Dormin; Dytan†; Dytuss; Genahist; Maximum Strength Sleepinal; Maximum Strength Unisom SleepGels; Miles Nervine; Nytol; Q-dryl; Scot-Tussin Allergy; Siladryl; Silphen; Simply Sleep; Sleep-Ettes D; Sleepettes Nighttime Sleep Aid; Sleepwell 2-nite; Snooze Fast; Sominex; Triaminic Children's Allergy†; Triaminic Cough & Runny Nose†; Tusstat; Twilite; Unisom SleepMelts; ZzzQuil; ***Venez.***: Benadryl.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Diphenhydramine Oral Solution; Diphenhydramine Tablets;

USP 36: Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Diphenhydramine and Pseudoephedrine Capsules; Diphenhydramine Citrate and Ibuprofen Tablets; Diphenhydramine Hydrochloride Capsules; Diphenhydramine Hydrochloride Elixir; Diphenhydramine Hydrochloride Injection.

Diphenylpyraline Hydrochloride

(BANM, rINNM)

Difenilpiralina, hidrocloruro de; Diphénylpyraline, Chlorhydrate de; Diphenylpyralini Hydrochloridum; Hidrocloruro de difenilpiralina; Дифенилпиралина Гидрохлорид.

4-Benzhydryloxy-1-methylpiperidine hydrochloride.

$C_{18}H_{23}NO,HCl$=317.9

CAS — 147-20-6 (diphenylpyraline); 132-18-3 (diphenylpyraline hydrochloride).

ATC — R06AA07.

ATC Vet — QR06AA07.

UNII — G9FU7F1E87.

Pharmacopoeias. In *Br.*

BP 2014: (Diphenylpyraline Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether.

Profile

Diphenylpyraline hydrochloride, a piperidine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and significant sedative properties.

It has been given for the symptomatic relief of allergic conditions including rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It has also been used in compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2). Diphenylpyraline and diphenylpyraline hydrochloride have been applied topically although, as with other antihistamines, there is a risk of sensitisation.

Diphenylpyraline teoclate is piprinhydrinate (p. 638.1).

References.

1. Graham G, Bolt AG. Half-life of diphenylpyraline in man. *J Pharmacokinet Biopharm* 1974; **2:** 191–5 (ranged from 24 to 40 hours).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Arbid-S†.

Multi-ingredient Preparations. ***Austria***: Eucillin; Prurimix; ***Belg.***: Rhini-San; ***Canad.***: Creo-Rectal; ***Ger.***: Tempil N†; ***Hong Kong***: Phenahist; ***India***: Cinaryl; Eskold Expectorant; Eskold; ***Mex.***: Flumil; ***S.Afr.***: Actophlem; Eskornade†; Solphyllex; Theophen Comp; ***Switz.***: Arbid†.

Doxylamine Succinate *(BANM, rINNM)*

Doksilamin Süksinat; Doksilamino-vandenilio sukcinatas; Doksylamiinivetysuksinaatti; Doxilamina, succinato de; Doxilamin-hidrogén-szukcinát; Doxylamine Hydrogen Succinate; Doxylamine, hydrogénosuccinate de; Doxylamine, Succinate de; Doxylaminhydrogensuccinat; Doxylamin-hydrogen-sukcinát; Doxylamini Hydrogenosuccinas; Doxylamini Succinas; Doxylaminium Succinate; Doxylamin-vätesuccinat; Histadoxylamine Succinate; Succinato de doxilamina; Доксиламина Суксинат.

NN-Dimethyl-2-[α-methyl-α-(2-pyridyl)benzyloxy]ethylamine hydrogen succinate.

$C_{17}H_{22}N_2O,C_4H_6O_4$=388.5

CAS — 469-21-6 (doxylamine); 562-10-7 (doxylamine succinate).

ATC — R06AA09.

ATC Vet — QR06AA09.

UNII — V9BI9B5YI2.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Doxylamine Hydrogen Succinate; Doxylamine Succinate BP 2014). A white or almost white powder. Very soluble in water; freely soluble in alcohol. It shows polymorphism.

USP 36: (Doxylamine Succinate). A white or creamy-white powder having a characteristic odour. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 370 of ether; very slightly soluble in benzene. Protect from light.

Uses and Administration

Doxylamine succinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative effects.

Doxylamine succinate is given for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders (p. 612.1), as a hypnotic in the short-term treatment of insomnia (p. 611.2), and as an ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2). Oral doses of up to 25 mg of doxylamine succinate have been given every 4 to 6 hours to a maximum of 150 mg daily. The usual hypnotic dose is 25 mg orally, up to half an hour before bedtime, although this may be increased to 50 mg if necessary.

It is also used in the management of nausea and vomiting of early pregnancy (p. 1814.3) in women who have not responded to conservative management such as dietary and lifestyle modifications. (See p. 614.2 for the controversy that has surrounded the use in pregnancy of combination products of doxylamine.) It is given orally as a modified-release combination preparation with pyridoxine hydrochloride (see Vitamin B_6 Substances, p. 2105.3); each tablet contains doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg. The recommended initial dose is 2 tablets at bedtime, taken on an empty stomach; if symptoms are not adequately controlled, the dose may be gradually increased, according to response, to a maximum of 4 tablets daily (1 in the morning and at mid-afternoon, and 2 at bedtime). This preparation should be taken regularly and not on an as-required basis; the need for continued treatment should be reassessed as the pregnancy progresses and the dose gradually tapered when stopping treatment.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. The controversy surrounding the use in pregnancy of combination products of doxylamine is discussed on p. 614.2.

Overdosage. In an evaluation of 109 cases of intoxication with doxylamine,[1] no correlation was found between the amount ingested or plasma concentration and the frequency or extent of symptoms. The most common symptom was impaired consciousness. Psychotic behaviour, seizures, and antimuscarinic symptoms such as tachycardia and mydriasis were also seen. Rhabdomyolysis occurred in one patient and was accompanied by transient impairment of renal function. The same group commented[2] that rhabdomyolysis had been noted in 7 of 442 cases of doxylamine overdosage, with an associated rise in plasma creatine kinase and myoglobinuria, and suggested that doxylamine has a direct toxic effect on striated muscle.

1. Köppel C, *et al.* Poisoning with over-the-counter doxylamine preparations: an evaluation of 109 cases. *Hum Toxicol* 1987; **6:** 355–9.
2. Köppel C, *et al.* Rhabdomyolysis in doxylamine overdose. *Lancet* 1987; **i:** 442–3.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Peak plasma concentrations of doxylamine succinate occur 2 to 3 hours after oral doses. An elimination half-life of about 10 hours has been reported.

References.

1. Friedman H, *et al.* Clearance of the antihistamine doxylamine: reduced in elderly men but not in elderly women. *Clin Pharmacokinet* 1989; **16:** 312–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dozile; Restavit; ***Canad.***: Unisom-2; ***Chile***: Calmex; Dorminoctil; Nocpaz†; Zarcop; ***Fr.***: Donormyl; Lidene; Noctyl; ***Ger.***: Gittalun; Hoggar Night; Mereprine†; SchlafTabs; Sedaplus; Valocordin-Doxylamin; ***Hong Kong***: Sominar†; ***Israel***: Sleep Aid; Tonight; ***NZ***: Dozile; ***Philipp.***: Unisom; ***Port.***: Dormidina; ***Rus.***: Donormyl (Донормил); ***S.Afr.***: Restwel; Somnil; ***Spain***: Dormidina; Dormirel; ***Switz.***: Sanalepsi N; ***Thai.***: Hoggar N; Sominar; ***Turk.***: Unisom; ***Ukr.***: Donormyl (Донормил); Sonmil (Сонмил); ***USA***: Aldex AN; Doxytex; Unisom SleepTabs.

Multi-ingredient Preparations. ***Arg.***: Epidac; ***Austral.***: Analgesic/Calmative†; Chemists Own Dolased Day/Night Pain Relief†; Codagesic; Codalgin Plus; Dimetapp Cold & Flu Night Relief†; Dimetapp Cough, Cold & Flu; Dolased Analgesic-Calmative; Fiorinal; Maxydol; Mersyndol; Panadeine Plus†; Panalgesic; Tensodeine; ***Austria***: Wick Erkaltungs-Saft fur die Nacht†; Wick Erkaltungssirup fur die Nacht; Wick Hustensaft†; ***Belg.***: Pholco-Mereprine; ***Braz.***: EMS Expectorante; Hytos Plus; Revenil Dospan; Revenil Expectorante; Revenil; Silencium; Xpe Expectorante; ***Canad.***: Buckley's Nighttime Cold and Sinus; Cold & Flu Nighttime; Cold Flu Relief; Cold/Flu Medicine; Dalmacol; Diclectin; Medicament Sinus pour La Nuit†; Mersyndol with Codeine; Night Relief Cold & Flu†; Nighttime Cold & Flu Relief; Nighttime Cold & Flu; Nighttime; Nitetime Cold Medicine; ratio-Calmydone; Regular Strength Sinus Medication†; Sinus Medication Night; Sinus Medication; Tylenol Cold and Flu Nighttime†; Tylenol Sinus (Nighttime Relief)†; Vicks Nyquil Cold & Flu; Vicks NyQuil Cough; Vicks Nyquil Sinus; Zicam Multi-Symptom Cold & Flu Nighttime†; ***Chile***: Pluriamin; ***Fr.***: DolirhumePro; ***Ger.***: Wick Medinait fur die Nacht; Wick Medinait mit Honig und Kamillenaroma; ***India***: Bedoxin; Bookey Plus; Bookey; DBSix; Dixip; Dolibird; Domi-6; Dopyx; Doria-F; Doris-F; Dosix-F; Doxilan; Doximon; Doxinate Plus; Doxinate; Doxyfem-B6; Doxyfol; Doxyla B6 Plus; Doxyla B6; Doxylic; DPF-OD; DPF; Dymin-P; E-Preg; Emestat; Env; Erywell; Evadox; Feel Good-HR; Feel Good; Floridox; Folifact; Foxydol; Freshta Plus; Freshta-DS; Fullday; Genis; Good Day; Gooday; Goodmorn Plus; Goodmorn; Ibeln; Indaxin-B6; Kan-Fresh; Kindvom; Lupinate; MFresh; Morsi; Morsik-R; Nausik; Nomit; Noms; Nona; Norvomin; Nosic; Novoter; NVDP; Onat; Optidox; Oxidox; Rest-Aid; Vominate; ***Indon.***: Dexmolex; Siladex†; ***Irl.***: Syndol; ***Ital.***: Vicks Medinait; ***NZ***: Mersyndol; Pharmacist's Own Pain Relief Plus; ***Pol.***: Tabcin Impakt; ***Port.***: Nausefe; ***S. Afr.***: Abflex; Acurate; Adco-Dol; Asic; B-Dol; Betapyn; Cepacol Cough; Codoxol; Doxsyn†; Lenapain; Nethaprin Dospan†; Nethaprin Expectorant†; Nomopain†; Paxidal†; Pynstop; Sedapain†; Sedinol†; Syndol; Tensopyn; Vicks Medinite†; ***Spain***: Cariban; Medinait; ***Switz.***: Vicks Medinait; ***Turk.***: Vicks Medi-Nait; ***UK***: Painex; Propain Plus; Syndol; Vicks Medinite; ***USA***: Alka-Seltzer Plus Day & Night Cold; Alka-Seltzer Plus Day & Night Cold; Alka-Seltzer Plus Night Cold; Alka-Seltzer Plus Night-Time Cold; Alka-Seltzer Plus Severe Sinus Congestion Allergy & Cough; All-Nite Cold Formula; Diclegis; Genite; Lortuss DM; Lortuss DM; Lortuss LQ; Night Time Cold/Flu Relief; Nite Time Cold Formula; NyQuil Hot Therapy; NyQuil Nighttime Cold/Flu; Nytcold Medicine; Vicks NyQuil LiquiCaps; Vicks NyQuil Multi-Symptom Cold Flu Relief; Vicks NyQuil Sinex; ***Venez.***: Mercindol.

Pharmacopoeial Preparations

USP 36: Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Doxylamine Succinate Syrup; Doxylamine Succinate Tablets.

Ebastine *(BAN, USAN, rINN)*

Ebastiini; Ebastin; Ebastina; Ebastinas; Ébastine; Ebastinum; LAS-W-090; W-090; Эбастин.

4′-*tert*-Butyl-4-[4-(diphenylmethoxy)piperidino]butyrophenone.

$C_{32}H_{39}NO_2$=469.7

CAS — 90729-43-4.

ATC — R06AX22.

ATC Vet — QR06AX22.

UNII — TQD7Q784P1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ebastine). A white or almost white crystalline powder. M.p. about 86 degrees. Practically insoluble in water; very soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

Profile

Ebastine, a piperidine derivative, is a non-sedating antihistamine (p. 610.1) with a long duration of action. It does not have significant sedative or antimuscarinic actions.

Ebastine is given for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and in pruritic skin disorders (p. 612.1). The usual oral dose is 10 to 20 mg daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

References.

1. Luria X. Comparative clinical studies with ebastine: efficacy and tolerability. *Drug Safety* 1999; **21** (suppl 1): 63–7.
2. Hurst M, Spencer CM. Ebastine: an update of its use in allergic disorders. *Drugs* 2000; **59:** 981–1006.
3. Lasseter KC, *et al.* Pharmacokinetics and safety of ebastine in patients with impaired hepatic function compared with healthy volunteers: a phase I open-label study. *Clin Pharmacokinet* 2004; **43:** 121–9.
4. Noveck RJ, *et al.* Pharmacokinetics and safety of ebastine in healthy subjects and patients with renal impairment. *Clin Pharmacokinet* 2007; **46:** 525–34.
5. Sastre J. Ebastine in allergic rhinitis and chronic idiopathic urticaria. *Allergy* 2008; **63** (suppl 89): 1–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ebastine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ebastel; ***Belg.***: Estivan; ***Braz.***: Ebastel; ***China***: Kestine (开思亭); Si Jin (思金); Su Di (苏迪); ***Denm.***: Durfin†; Kestine; ***Fin.***: Kestine; Kestox; ***Fr.***: Kestin; Kestinlyo; ***Ger.***: Ebastel; ***Gr.***: Kestine; ***Hong Kong***: Kestine†; ***India***: Ebast; Erostin; ***Irl.***: Kestine†; ***Ital.***: Clever; Kestine; ***Jpn***: Ebastel; ***Mex.***: Evastel; Pinaval-T; ***Neth.***: Kestine; Netan; ***Norw.***: Kestine; ***Philipp.***: Aleva; ***Port.***: Ebastion; Estivan†; Kestine; Ribastex†; ***Rus.***: Kestine (Кестин); ***S.Afr.***: Kestine; ***Singapore***: Kestine; ***Spain***: Alastina; Bactil; Ebastel; ***Swed.***: Kestine; ***Turk.***: Kestine; ***Venez.***: Ebastel.

Multi-ingredient Preparations. ***Braz.***: Ebastel D; ***India***: EBA-P; Ebast-DC; Erostin-DC; ***Mex.***: Evastel-D; ***Philipp.***: Co-Aleva; ***Spain***: Rino Ebastel; Rinobactil.

Embramine Hydrochloride *(BANM, rINNM)*

Embramina, hidrocloruro de; Embramine, Chlorhydrate d'; Embramini Hydrochloridum; Embraminium Chloratum; Hidrocloruro de embramina; Mebrophenhydramine Hydrochloride; Mebrophenhydraminium Chloratum; Эмбрамина Гидрохлорид.

2-(4-Bromo-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{18}H_{22}BrNO,HCl$=384.7

CAS — 3565-72-8 (embramine); 13977-28-1 (embramine hydrochloride); 21661-63-2 (embramine teoclate).

UNII — 7BJ3V657VC.

Profile

Embramine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p. 610.1). Embramine hydrochloride and embramine teoclate have been given orally for their antihistamine and antiemetic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Medrin†; ***India***: Mebryl.

Emedastine Fumarate *(BANM, rINNM)*

AL-3432A; Emedastiinidifumaraatti; Emedastin difumarát; Emedastin Fumarat; Emedastina, fumarato de; Emedastindifumarat; Emedastine Difumarate (USAN); Émédastine, difumarate d'; Émédastine, Fumarate d'; Emedastini Difumaras; Emedastini Fumaras; Emedastyny difumaran; Fumarato de emedastina; KB-2413; KG-2413; LY-188695; Эмедастина Фумарат.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)benzimidazole fumarate (1:2).

$C_{17}H_{26}N_4O,2C_4H_4O_4$=534.6

CAS — 87233-61-2 (emedastine); 87233-62-3 (emedastine fumarate).

ATC — S01GX06.

ATC Vet — QS01GX06.

UNII — 42MB94QOSM.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Emedastine Difumarate). A white or yellowish powder. It exhibits polymorphism. Soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 0.2% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 36: (Emedastine Difumarate). A white to faintly yellow crystalline powder. Soluble in water. pH of a 0.2% solution in water is between 3.0 and 4.5. Store in airtight containers. Protect from light.

Uses and Administration

Emedastine is an antihistamine. It is instilled twice daily as the fumarate as eye drops containing the equivalent of 0.05% of emedastine for the symptomatic relief of allergic conjunctivitis (p. 611.1). It is also given orally in usual doses of 2 to 4 mg of the fumarate daily in two divided doses for allergic rhinitis (p. 612.1), urticaria (p. 612.3), and pruritic skin disorders (p. 612.1).

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively.

Ocular corneal infiltrates, local irritation, photophobia, rhinitis, and headaches have been reported after use of emedastine eye drops. Treatment should be stopped if corneal infiltrates develop.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies emedastine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Emedastine is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 3 hours after an oral dose. Small amounts of emedastine are absorbed after application to the eye. It is mainly metabolised in the liver to two primary metabolites 5- and 6-hydroxyemedastine which are excreted in the urine along with a small amount of unchanged drug. The elimination half-life is reported to be 7 hours after an oral dose and 10 hours after topical use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Emadine; ***Belg.***: Emadine; ***Braz.***: Emadine; ***Canad.***: Emadine; ***China***: Emadine (埃美丁); ***Cz.***: Emadine; ***Denm.***: Emadine; ***Fin.***: Emadine; ***Fr.***: Emadine†; ***Ger.***: Emadine; ***Gr.***: Emadine; ***Hong Kong***: Emadine; ***Hung.***: Emadine; ***Irl.***: Emadine; ***Israel***: Emadine; ***Ital.***: Emadine; ***Jpn***: Daren; Remicut; ***Malaysia***: Emadine; ***Neth.***: Emadine; ***Norw.***: Emadine; ***Pol.***: Emadine; ***Port.***: Emadine; ***S.Afr.***: Emadine; ***Spain***: Emadine; ***Swed.***: Emadine; ***Switz.***: Emadine; ***Thai.***: Emadine†; ***Turk.***: Emadine; ***UK***: Emadine; ***USA***: Emadine.

Pharmacopoeial Preparations

USP 36: Emedastine Ophthalmic Solution.

Epinastine Hydrochloride *(BANM, rINNM)*

Epinastina, hidrocloruro de; Epinastine, chlorhydrate d'; Épinastine, Chlorhydrate d'; Epinastinhydrochlorid; Epinastini hydrochloridum; Hidrocloruro de epinastina; WAL-801-Cl; Эпинастина Гидрохлорид.

3-Amino-9,13b-dihydro-1*H*-dibenz[*c*,*f*]imidazo[1,5-*a*]azepine hydrochloride.

$C_{16}H_{15}N_3,HCl$=285.8

CAS — 80012-43-7 (epinastine).

ATC — R06AX24; S01GX10.

ATC Vet — QR06AX24; QS01GX10.

UNII — GFM41555XL.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Epinastine Hydrochloride). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in acetonitrile; sparingly soluble in dichloromethane. Store in airtight containers.

Profile

Epinastine hydrochloride is an antihistamine (p. 610.1) reported t o have n o significant sedative activity. It has been given orally in the management of allergic rhinitis and pruritic skin disorders. It is also used twice daily as eye

drops, usually in a concentration of 0.05%, in the symptomatic relief of allergic conjunctivitis.

References.
1. Sarashina A, *et al.* Population pharmacokinetics of epinastine, a histamine H_1 receptor antagonist, in adults and children. *Br J Clin Pharmacol* 2005; **59:** 43–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alket; Epioftal; Flurinol; Relestat; ***Austria***: Relestat; ***Belg.***: Relestat; ***Braz.***: Relestat; Talerc; ***Chile***: Flurinol; Relestat; ***China***: Alesion (爱理胜); Kai Lai Zhi (凯莱止); ***Cz.***: Purivist; ***Denm.***: Relestat; ***Fin.***: Relestat†; ***Fr.***: Purivist; ***Ger.***: Relestat; ***Gr.***: Relestat; ***Hong Kong***: Relestat; ***Hung.***: Relestat; ***Irl.***: Relestat; ***Israel***: Relestat; ***Ital.***: Relestat; ***Jpn***: Alesion; ***Mex.***: Elestat; Flurinol; ***Neth.***: Relestat; ***Pol.***: Relestat; ***Port.***: Relestat; ***S.Afr.***: Relestat; ***Singapore***: Relestat; ***Spain***: Relestat; ***Swed.***: Relestat†; ***Switz.***: Relestat; ***Thai.***: Relestat; ***Turk.***: Relestat; ***UK***: Relestat; ***USA***: Elestat; ***Venez.***: Flurinol.

Multi-ingredient Preparations. ***Arg.***: Flurinol D; ***Braz.***: Talerc D; ***Mex.***: Flurinol D.

Fexofenadine Hydrochloride

(BANM, USAN, rINNM)

Feksofenadiinihydrokloridi; Feksofenadin Hidroklorür; Fexofenadina, hidrocloruro de; Fexofénadine, Chlorhydrate de; Fexofenadinhydrochlorid; Fexofenadinhydroklorid; Fexofenadini Hydrochloridum; Hidrocloruro de fexofenadina; MDL-16455A; Terfenadine Carboxylate Hydrochloride; Фексофенадина Гидрохлорид.

(±)-*p*-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-piperidino] butyl]-α-methylhydratropic acid hydrochloride.

$C_{32}H_{39}NO_4$,HCl=538.1

CAS — 138452-21-8.

ATC — R06AX26.

ATC Vet — QR06AX26.

UNII — 2S068B75ZU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fexofenadine Hydrochloride). A white or almost white powder. Slightly soluble in water; freely soluble in methyl alcohol; very slightly soluble in acetone. It exhibits polymorphism.

USP 36: (Fexofenadine Hydrochloride). A white to off-white powder. Slightly soluble in water; freely soluble in methyl alcohol; very slightly soluble in acetone. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Fexofenadine, an active metabolite of terfenadine (p. 640.3), is a non-sedating antihistamine. It does not possess significant sedative or antimuscarinic actions. Fexofenadine is used as the hydrochloride in the symptomatic relief of allergic conditions including seasonal allergic rhinitis (p. 612.1) and chronic urticaria (p. 612.3).

In the UK a dose of fexofenadine hydrochloride 120 mg once daily is given orally in the treatment of seasonal allergic rhinitis; the recommended dose in chronic idiopathic urticaria is 180 mg once daily. US licensed product information suggests a dose of 60 mg twice daily or 180 mg once daily for both indications.

Fexofenadine is also used with a decongestant such as pseudoephedrine hydrochloride.

For doses in children or in patients with renal impairment, see below.

References.
1. Markham A, Wagstaff AJ. Fexofenadine. *Drugs* 1998; **55:** 269–74.
2. Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 2000; **59:** 301–21.
3. Kawashima M, *et al.* Review of fexofenadine in the treatment of chronic idiopathic urticaria. *Int J Dermatol* 2002; **41:** 701–6.
4. Meeves SG, Appajosyula S. Aventis, USA]. Efficacy and safety profile of fexofenadine HCl: a unique therapeutic option in H1-receptor antagonist treatment. *J Allergy Clin Immunol* 2003; **112** (suppl): S69–S77.
5. Mansfield LE. Once-daily immediate-release fexofenadine and sustained-release pseudoephedrine combination: a new treatment option for allergic rhinitis. *Expert Opin Pharmacother* 2006; **7:** 941–51.

Administration in children. Fexofenadine hydrochloride is used in children for the treatment of seasonal allergic rhinitis in an oral dose of 30 mg twice daily; in the UK it is licensed for use in children aged 6 to 11 years whereas in the USA it may be used in children as young as 2 years.

In the USA, fexofenadine is also licensed for use in paediatric chronic idiopathic urticaria. The dose in children aged 6 months to less than 2 years is 15 mg twice daily; older children may be given 30 mg twice daily.

For suggested doses in children with renal impairment see below.

Administration in renal impairment. US licensed product information recommends that initial oral doses of fexofenadine hydrochloride in adults with renal impairment should be reduced to 60 mg once daily. In children with renal impairment, the initial dose should be reduced to 30 mg once daily in patients aged 2 to 11 years, and to 15 mg once daily in children aged 6 months to less than 2 years.

UK product information advises that fexofenadine should be given with caution to patients with renal impairment; however, it also states that dose adjustment is not considered to be necessary in such patients.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Arrhythmias. A 67-year-old man suffered syncope after taking fexofenadine 180 mg daily for 2 months.[1] His ECG showed an abnormally prolonged QT interval which shortened once fexofenadine was stopped, although the interval tended to be long even without drug therapy. Nonetheless rechallenge was positive. The manufacturers of fexofenadine have commented[2] that the patient was at risk of developing arrhythmias before taking the drug.

The ECG effects of fexofenadine have been studied[3] in normal subjects and doses of up to 480 mg daily [4 times the recommended dose for seasonal allergic rhinitis] did not prolong the QT interval. See also p. 613.2.

1. Pinto YM, *et al.* QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 1999; **353:** 980.
2. Giraud T. QT lengthening and arrhythmias associated with fexofenadine. *Lancet* 1999; **353:** 2072.
3. Pratt CM, *et al.* Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999; **83:** 1451–4.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving fexofenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

See also under Adverse Effects and Precautions, in Terfenadine, p. 641.1.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fexofenadine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Psoriasis. Exacerbation of psoriasis has been reported[1] with fexofenadine use.

1. Saraswat A, Saraswat M. Pustular exacerbation of psoriasis due to fexofenadine. *Clin Exp Dermatol* 2006; **31:** 477–8.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Plasma concentrations of fexofenadine have been increased when given with erythromycin or ketoconazole, but, unlike terfenadine, licensed product information states that this was not associated with adverse effects on the QT interval.

Antacids containing aluminium and magnesium hydroxide have reduced the absorption of fexofenadine. Fruit juices including grapefruit may reduce the bioavailability of fexofenadine and use together should be avoided.

Grapefruit juice. References.

1. Dresser GK, *et al.* Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* 2005; **77:** 170–7.

Pharmacokinetics

Fexofenadine is rapidly absorbed after oral doses and peak plasma concentrations occur in 2 to 3 hours. It is about 60 to 70% bound to plasma proteins. Fexofenadine undergoes negligible metabolism: about 5% of the total dose is metabolised, mostly by the intestinal mucosa, with 0.5 to 1.5% of the dose undergoing hepatic biotransformation by the cytochrome P450 system. Elimination half-life of about 14 hours has been reported although this may be prolonged in patients with renal impairment. Excretion is mainly in the faeces with only 10% being present in the urine. Fexofenadine does not appear to cross the blood-brain barrier.

Fexofenadine is a metabolite of terfenadine and as such has been detected in breast milk after the use of terfenadine.

References.
1. Russell T, *et al.* Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. *Clin Pharmacol Ther* 1998; **64:** 612–21.
2. Devillier P, *et al.* Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clin Pharmacokinet* 2008; **47:** 217–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alercas; Alerfedine; Allegra; ***Austral.***: Allerfexo; Fexal; Fexotabs; Telfast; Xergic; ***Austria***: Telfast; ***Belg.***: Allergo Rhinathiol; Telfast; ***Braz.***: Allegra; Allexofedrin; Altiva; Fexodane; Rafex; ***Canad.***: Allegra; ***Chile***: Aerodan†; Alexia; Allegra; Fenax; ***China***: BiXin (毕馨); Lai Duo Fei (莱多菲); Min Jie (敏杰); Raltiva (阿特拉); Rui Fei (瑞菲); Sailexi (赛乐西); ***Cz.***: Afexil†; Ewofex; Fexigra; Telfast†; ***Denm.***: Alterfast; Altifex; Histafast; Nefoxef; Telfast; ***Fin.***: Alterfast†; Nefoxef; Telfast; ***Fr.***: Telfast; ***Ger.***: Fexofenaderm; Telfast; ***Hong Kong***: Bosnum; Fexodine; Telfast; Zafil†; ***Hung.***: Allegra; Altiva; Fexgen; Fexofep; Telfast; ***India***: Afexdine; Alernex; Alert; Alfexo; Allefast; Allegix; Allegra; Allofex; Altiva; Fegra; Fenadin; Fexamed; Fexidine; Fexigra; Fexo; Fexodex; Fexodin; Fexofast; Fexofen; Fexona; Fexoquit; Fexot; Fexotrol; Fexova; Histagra; Histaloc; Infexo; Odifex; Oregra; ***Indon.***: Telfast; ***Irl.***: Telfast; ***Israel***: Telfast; ***Ital.***: Telfast; ***Malaysia***: Fexofin; Telfast; ***Mex.***: Aldifex; Allegra; Apertum-Ox; Fexoff-R; Gebenir†; Ranfast; ***Neth.***: Allegra; STP-free†; Telfast; ***Norw.***: Altifex; Telfast; ***NZ***: Fexofast; Telfast; Xergic; ***Philipp.***: Fenafex; Fexet; Fexoral; Histofen†; Neofex; Rhinogan; Sensitin; Telfast; ***Pol.***: Fexofast; FexoGen; Telfast; Telfexo; ***Port.***: Fexocare; Telfast; ***Rus.***: Allerfex (Аллерфекс); Dinox (Динокс); Fexadin (Фексадин); Fexofast (Фексофаст); Rapido (Рапидо); Telfast (Телфаст); ***S.Afr.***: Fastway; Fenofex; Fexaway; Fexo; Fexofast†; Telfast; Tellerge; ***Singapore***: Telfast; ***Spain***: Telfast; ***Swed.***: Allegra; Nefoxef; Telfast; ***Switz.***: Telfast; Telfastin Allergo; ***Thai.***: Bosnum; Fenafex; Fexofast; Fexotine; Telfast; Tofexo; Vifas; ***Turk.***: Feksine; Fexadyne; Fexavil; Fexizin; Fexofen; Mayfex; Telfast; Vivafeks; ***UK***: Telfast; ***Ukr.***: Altiva (Алтива); Fexofast (Фексофаст); Telfast (Телфаст); ***USA***: Allegra; ***Venez.***: Allegra; Fexidine; Fexoril; Rinolast.

Multi-ingredient Preparations. ***Arg.***: Alercas D; Alerfedine D; Allegra-D; ***Austral.***: Telfast Decongestant; ***Braz.***: Allegra-D; Fexo-D†; ***Canad.***: Allegra-D; ***Chile***: Alexia D; Allegra-D; ***Hong Kong***: Telfast-D; ***India***: Altiva-D; ***Indon.***: Fexofed; Telfast Plus; ***Jpn***: Dellegra; ***Malaysia***: Altiva-D; Telfast-D; ***Mex.***: Allegra-D; ***Singapore***: Telfast-D; ***Thai.***: Telfast D†; ***USA***: Allegra-D; ***Venez.***: Allegra-D; Rinolast D.

Pharmacopoeial Preparations

BP 2014: Fexofenadine Tablets;

USP 36: Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Fexofenadine Hydrochloride Capsules; Fexofenadine Hydrochloride Tablets.

Flunarizine Hydrochloride *(BANM, USAN, rINNM)*

Flunaritsiinidihydrokloridi; Flunarizina, hidrocloruro de; Flunarizin-dihydrochlorid; Flunarizindihydroklorid; Flunarizine, Chlorhydrate de; Flunarizine, dichlorhydrate de; Flunarizini dihydrochloridum; Flunarizini Hydrochloridum; Flunarizino dihidrochloridas; Hidrocloruro de flunarizina; R-14950; Флунаризина Гидрохлорид.

trans-1-Cinnamyl-4-(4,4′-difluorobenzhydryl)piperazine dihydrochloride.

$C_{26}H_{26}F_2N_2$,2HCl=477.4

CAS — 52468-60-7 (flunarizine); 30484-77-6 (flunarizine hydrochloride).

ATC — N07CA03.

ATC Vet — QN07CA03.

UNII — C11102TO53.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Flunarizine Dihydrochloride). A white or almost white hygroscopic powder. Slightly soluble in water, in alcohol, and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Flunarizine is the difluorinated derivative of cinnarizine. It has antihistamine, sedative, and calcium-channel blocking activity. Flunarizine hydrochloride is used for migraine prophylaxis, for vertigo and vestibular disorders, and for peripheral and cerebral vascular disorders. It has also been used as adjunctive antiepileptic therapy in patients refractory to standard regimens.

Flunarizine is given orally as the hydrochloride although doses are expressed in terms of the base. Flunarizine hydrochloride 11.8 mg is equivalent to about 10 mg of flunarizine. The usual dose is 5 to 10 mg daily, usually given at night to minimise the effects of drowsiness.

Flunarizine betadex (flunarizine betacyclodextrin) has been used similarly.

Epilepsy. Several drugs with calcium-channel blocking activity have been investigated as adjuncts in epilepsy (p. 506.1), including flunarizine. Some individual studies have reported benefit, but a systematic review[1] concluded that although flunarizine might have a weak effect on seizure frequency the evidence was not convincing, and the withdrawal rate was significant, probably because of poor tolerability; it should therefore not be recommended as adjunctive antiepileptic therapy. The pharmacokinetic profile of flunarizine may in any case be too complex for clinical use as an antiepileptic.[2]

1. Chaisewikul R, *et al.* Calcium antagonists as an add-on therapy for drug-resistant epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/05).
2. Hoppu K, *et al.* Flunarizine of limited value in children with intractable epilepsy. *Pediatr Neurol* 1995; **13:** 143–7.

Migraine. Flunarizine reduces the frequency of migraine attacks in both adult and paediatric patients and is used for the prophylaxis of migraine (p. 670.3) in some countries. Its effects are comparable with several other prophylactic antimigraine drugs, including the generally preferred propranolol,[1-4] but it is more likely to be reserved for use when first-line drugs have proved to be ineffective or unsuitable. Its mode of action in migraine is unclear; possible mechanisms are inhibition of vasospasm induced by mediators such as serotonin and prostaglandins, inhibition of cellular hypoxia, and improved blood viscosity and erythrocyte deformability. Calcium-channel blocking activity might have a role, but evidence for the efficacy of other calcium-channel blockers in migraine prophylaxis (see Nifedipine, p. 1449.1) is less convincing than for flunarizine.

Case reports have indicated benefit with flunarizine in the prophylaxis of the rare disorder of alternating hemiplegia in childhood[5,6] but a subsequent study[7] in 12 children did not produce conclusive findings. A later long-term study[8] reported that 7 of 9 children given flunarizine for up to 5 years for hemiplegia showed a reduction in the duration of attacks, and 3 had a reduction in frequency, but only 1 of these obtained a complete cessation of episodes.

The role of antihistamines in general in the management of migraine is discussed briefly on p. 611.3.

1. Todd PA, Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; **38:** 481–99.
2. Andersson K-E, Vinge E. β-Adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. *Drugs* 1990; **3:** 355–73.
3. Soelberg Sørensen P, *et al.* Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; **31:** 650–7.
4. Gawel MJ, *et al.* Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992; **19:** 340–5.
5. Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; **ii:** 579.
6. Curatolo P, Cusmai R. Drugs for alternating hemiplegic migraine. *Lancet* 1984; **ii:** 980.
7. Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics* 1987; **18:** 191–5.
8. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. *Neurology* 1993; **43:** 36–41.

Tourette's syndrome. A small unblinded study[1] involving 7 patients has suggested that flunarizine is more effective than placebo in the treatment of Tourette's syndrome (see Tics, p. 1030.1).

1. Micheli F, *et al.* Treatment of Tourette's syndrome with calcium antagonists. *Clin Neuropharmacol* 1990; **13:** 77–83.

Vertigo. Antihistamines are the mainstay of the treatment of vertigo (p. 612.3). However, their antimuscarinic adverse effects may prove troublesome, particularly in the elderly, and they produce central sedation. Flunarizine is devoid of antimuscarinic properties, although it may produce central sedation.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Adverse effects also seen with flunarizine include weight gain, extrapyramidal symptoms (sometimes associated with depression), and, rarely, galactorrhoea.

Extrapyramidal disorders. Extrapyramidal motor signs (including parkinsonism, orofacial tardive dyskinesia, and akathisia) have been reported in 12 patients given flunarizine 10 to 40 mg daily for between 3 weeks and 15 months; 11 also had depression.[1] Partial or complete improvement of symptoms occurred after withdrawal of flunarizine. There have been other reports of similar effects,[2-5] but the association with flunarizine has not always been certain. Some workers have commented that flunarizine is often used in patients at increased risk of depression (migraine and geriatric patients) or extrapyramidal symptoms (geriatric patients)[2,6] or that flunarizine may unmask subclinical idiopathic Parkinson's disease.[6,7]

Extrapyramidal signs, including parkinsonism, have also been associated with the related drug, cinnarizine.[3-5] It has been suggested that such effects may be less likely to occur with cinnarizine than with flunarizine because of its shorter half-life and lower lipophilicity.[3]

1. Chouza C, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; **i:** 1303–4.
2. Meyboom RHB, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; **ii:** 292.
3. Laporte J-R, Capella D. Useless drugs are not placebos: lessons from flunarizine and cinnarizine. *Lancet* 1986; **ii:** 853–4.
4. Laporte J-R, Capella D. Useless drugs are not placebos. *Lancet* 1987; **i:** 1324.
5. Teive HAG, *et al.* Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord* 2004; **10:** 243–5.
6. Amery W. Side-effects of flunarizine. *Lancet* 1986; **i:** 1497.
7. Benvenuti F, *et al.* Side-effects of flunarizine. *Lancet* 1986; **ii:** 464.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Hepatic enzyme inducers such as carbamazepine, phenytoin, and valproate may interact with flunarizine by increasing its metabolism; an increase in dosage of flunarizine may be required.

Pharmacokinetics

Flunarizine hydrochloride is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. Flunarizine hydrochloride is very lipophilic and is more than 90% bound to plasma proteins. It appears to undergo extensive metabolism; metabolites are excreted principally in the bile. Flunarizine hydrochloride has an elimination half-life of about 18 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bercetina; Coromert; Flufenal; Mondus; Niflucan; Sibelium; ***Austria***: Sibelium; ***Belg.***: Flunarimed†; Flunatop; Sibelium; ***Braz.***: Flunarin; Fluvert; Fluzix; Sibelium; Vertigium; Vertix; ***Canad.***: Sibelium†; ***Chile***: Flerox†; Fluxus; Irrigor; Sibelium; Zentralin; ***China***: Ao Li Bao Ke (奥力保克); Fu Rui Er (孚瑞尔); Fu Rui Lin (弗瑞林); Hua Xin (花欣); Sibelium (西比灵); ***Cz.***: Sibelium; ***Denm.***: Sibelium; ***Fr.***: Sibelium; ***Ger.***: Flunavert; Natil-N; ***Gr.***: Sibelium; ***Hong Kong***: Fludan; ***Hung.***: Sibelium; ***India***: Cinzin; Efigraine; Fine; Flubery; Flugraine; Flunarin; Flunaris; Flunatrac; Fluriz; Flury; Flutom; Fluvert; Fluz; Fzin; Graton; Grenate; Grenil-F; MGR; Migarid; Migazin; Migon; Migrecure; Migrid; Nariz; Narizine; Narzine; Nomigrain; Nubelium; ***Indon.***: Bartolium; Cevadil; Degrium; Dizilium†; Dizine; Frego; Seremig; Sibelium; Siberid; Silum; Sinral; Unalium; Xepalium; ***Irl.***: Sibelium; ***Ital.***: Flugeral; Flunagen; Fluxarten; Gradient; Issium; Sibelium; ***Malaysia***: Fludan; Forknow; Migarid; Sibelium; ***Mex.***: Axilin†; Fasolan; Naflurył; Sibelium; ***Neth.***: Sibelium; ***Philipp.***: Flumig; Flunariz; Migralin; Sibelium; ***Port.***: Sibelium; Vasilium; Zinasen; ***S.Afr.***: Sibelium; ***Singapore***: Forknow; Narizine; Sibelium; ***Spain***: Flerudin; Flurpax; Sibelium; ***Switz.***: Sibelium; ***Thai.***: Cebrium; Cedelate; Fabelium; Finelium; Floxin; Flubelin; Flucilium; Fludan; Flulium†; Flunamed; Flunaric; Flunarium; Fluricin; Flurin; Furin; Hexilium; Liberal; Medilium†; Poli-Flunarin; Sibelium; Simoyiam; Sobelin; Sovelium; Vanid; Vertilium; Zelium; ***Turk.***: Sibelium; ***Venez.***: Fludil; Sibelium.

Multi-ingredient Preparations. ***Arg.***: Sibelium Plus; ***Braz.***: Vertizine D; ***India***: Egrin; Fluner; Mygran; Oxokool Plus.

Homochlorcyclizine Hydrochloride

(BANM, rINNM)

Hidrocloruro de homoclorciclizina; Homochlorcyclizine, Chlorhydrate d'; Homochlorcyclizini Hydrochloridum; Homoclorciclizina, hidrocloruro de; Гомохлорциклизина Гидрохлорид.

1-(4-Chlorobenzhydryl)perhydro-4-methyl-1,4-diazepine dihydrochloride.

$C_{19}H_{23}ClN_2,2HCl$=387.8

CAS — 848-53-3 (homochlorcyclizine); 1982-36-1 (homochlorcyclizine hydrochloride).

Pharmacopoeias. In *Jpn*.

Profile

Homochlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and moderate sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3) and rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It is given in oral doses of 10 to 20 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Homoclomin; ***Indon.***: Homoclomin; ***Jpn***: Homoclomin; ***Thai.***: Homoclomin†.

Hydroxyzine *(BAN, rINN)*

Hidroxizina; Hydroksitsiini; Hydroxizin; Hydroxyzinum; Гидроксизин.

(*RS*)-2-{2-[4-(*p*-Chloro-α-phenylbenzyl)piperazin-1-yl]ethoxy}ethanol.

$C_{21}H_{27}ClN_2O_2$=374.9

CAS — 68-88-2.

ATC — N05BB01.

ATC Vet — QN05BB01.

UNII — 30S50YM8OG.

Hydroxyzine Embonate *(BANM, rINNM)*

Embonato de hidroxizina; Hidroxizina, embonato de; Hydroxyzine, Embonate d'; Hydroxyzine Pamoate; Hydroxyzini Embonas; Pamoato de hidroxizina; Гидроксизина Эмбонат.

2-{2-[4-(4-Chlorobenzhydryl)piperazin-1-yl]ethoxy}ethanol 4,4'-methylenebis(3-hydroxy-2-naphthoate).

$C_{21}H_{27}ClN_2O_2,C_{23}H_{16}O_6$=763.3

CAS — 10246-75-0.

ATC — N05BB01.

ATC Vet — QN05BB01.

UNII — M20215MUFR.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Hydroxyzine Pamoate). A light yellow, practically odourless powder. Soluble 1 in more than 1000 of water, of chloroform, and of ether, 1 in 700 of alcohol, 1 in 10 of dimethylformamide, and 1 in 3.5 of 10M sodium hydroxide solution; practically insoluble in methyl alcohol. Store in airtight containers.

Hydroxyzine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidroxizina; Hidroksizin Hidroklorür; Hidroksizino hidrochloridas; Hidroxizina, hidrocloruro de; Hidroxizin-hidroklorid; Hydroksitsiinihydrokloridi; Hydroxizinhydroklorid; Hydroxyzin dihydrochlorid; Hydroxyzindihydrochlorid; Hydroxyzine, chlorhydrate d'; Hydroxyzini Dihydrochloridum; Hydroxyzini Hydrochloridum; Гидроксизина Гидрохлорид.

$C_{21}H_{27}ClN_2O_2,2HCl$=447.8

CAS — 2192-20-3.

ATC — N05BB01.

ATC Vet — QN05BB01.

UNII — 76755771U3.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Hydroxyzine Hydrochloride). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Hydroxyzine Hydrochloride). A white, odourless, powder. Soluble 1 in 1 of water, 1 in 4.5 of alcohol, and 1 in 13 of chloroform; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Incompatibility. Hydroxyzine hydrochloride has been reported to be incompatible with aminophylline, benzylpenicillin salts, chloramphenicol sodium succinate, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), thioridazine, and some soluble barbiturates.

Stability. A mixture of hydroxyzine hydrochloride, chlorpromazine hydrochloride, and pethidine hydrochloride stored in glass or plastic syringes was found[1] to be stable for 366 days at 4 degrees and 25 degrees.

1. Conklin CA, *et al.* Stability of an analgesic-sedative combination in glass and plastic single-dose syringes. *Am J Hosp Pharm* 1985; **42:** 339–42.

Uses and Administration

Hydroxyzine, a piperazine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an antiemetic. Its main use is as an anxiolytic (p. 1028.1) but see Anxiety Disorders p. 631.1. It is also used as an adjunct to pre- and postoperative medication (see Anaesthesia, p. 610.3) and in the management of pruritus (p. 612.1) and urticaria (p. 612.3) and has been used as an adjunct to opioid analgesia in the management of cancer pain (p. 7.1).

Hydroxyzine may be given orally as the hydrochloride or the embonate; doses are expressed in terms of the hydrochloride. Hydroxyzine embonate 170 mg is equivalent to about 100 mg of hydroxyzine hydrochloride.

Usual oral doses are: 50 to 100 mg four times daily for the short-term management of anxiety; for pruritus an initial dose of 25 mg given at night, increased if necessary to 25 mg three or four times daily; and 50 to 100 mg for pre- or postoperative sedation.

Hydroxyzine hydrochloride may also be given by deep intramuscular injection. For prompt control of anxiety or

agitation 50 to 100 mg is injected intramuscularly initially, and the dose may be repeated every four to six hours as required. For other indications when oral dosage is not practical, the intramuscular dose is 25 to 100 mg. Hydroxyzine should not be given by intravenous injection since haemolysis may result.

For doses in children, see below. Dosage should be reduced in patients with hepatic or renal impairment, see below.

Administration in children. Hydroxyzine may be given to children to treat pruritus in the following oral doses expressed as the hydrochloride:

- children aged 6 months to 6 years: initially 5 to 15 mg daily increased if necessary to 50 mg daily in divided doses
- those 6 to 12 years of age: initially 15 to 25 mg daily increased if necessary to 50 to 100 mg daily in divided doses

Alternatively, 1 mg/kg daily may be given in divided doses, to a maximum of 2.5 mg/kg daily in children aged 1 to 6 years or to a maximum of 2 mg/kg daily in those aged over 6 years.

The pre- or postoperative sedative dose in children is 600 micrograms/kg orally; alternatively, a dose of 1.1 mg/kg has been given by intramuscular injection.

Children and adolescents aged 12 years and over may be given usual adult doses, see p. 630.3.

Administration in hepatic or renal impairment. In patients with hepatic impairment, UK licensed product information recommends a 33% reduction in the total oral daily dose of hydroxyzine. In patients with moderate or severe renal impairment, a dose reduction of 50% is recommended.

Anxiety disorders. Although hydroxyzine is used in the management of anxiety, there is little evidence to support its efficacy in anxious patients,[1] and the *BNF* considers that use of antihistamines solely for their sedative effect in anxiety is not appropriate.

1. Ballenger JC, *et al.* Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2001; **62** (suppl 11): 53–8. Available at: http://www.psychiatrist.com/private/supplenet/v62s11/v62s1108.pdf (accessed 15/08/08)

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Intramuscular injection of hydroxyzine has been reported to cause marked local discomfort. Intravenous use has been associated with haemolysis.

Arrhythmias. ECG abnormalities, particularly alterations in T-waves, were associated with anxiolytic doses of hydroxyzine hydrochloride and were similar to those produced by thioridazine and tricyclic antidepressants.[1]

1. Hollister LE. Hydroxyzine hydrochloride: possible adverse cardiac interactions. *Psychopharmacol Comm* 1975; **1:** 61–5.

Effects on sexual function. A 32-year-old man had prolonged penile erections (priapism) after taking two separate doses of hydroxyzine for a skin rash.[1] It was suggested that the effect might be due to a hydroxyzine metabolite that was found to be structurally similar to a metabolite of trazodone, a drug known to induce penile erections.

1. Thavundayil JX. *et al.* Prolonged penile erections induced by hydroxyzine: possible mechanism of action. *Neuropsychobiology* 1994; **30:** 4–6.

Effects on the skin. Four children given hydroxyzine hydrochloride for restlessness developed a fixed drug eruption of the penis.[1] All recovered on drug withdrawal and subsequently had positive rechallenges.

1. Cohen HA, *et al.* Fixed drug eruption of the penis due to hydroxyzine hydrochloride. *Ann Pharmacother* 1997; **31:** 327–9.

Intra-arterial injection. Accidental intra-arterial injection of hydroxyzine has led to necrosis of the extremity requiring amputation of the digits of the affected limb.[1]

1. Hardesty WH. Inadvertent intra-arterial injection. *JAMA* 1970; **213:** 872.

Liver disorders. It has been suggested[1] that hydroxyzine should only be given once daily for the relief of pruritus in patients with primary biliary cirrhosis. The mean serum elimination half-lives of hydroxyzine and its metabolite cetirizine in 8 patients with primary biliary cirrhosis were prolonged at 36.6 and 25.0 hours, respectively.

1. Simons FER, *et al.* The pharmacokinetics and pharmacodynamics of hydroxyzine in patients with primary biliary cirrhosis. *J Clin Pharmacol* 1989; **29:** 809–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxyzine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Cimetidine. A pharmacokinetic study in 16 patients noted that *cimetidine* increased the serum concentration of hydroxyzine.[1] The combination generally produced a greater suppression of the cutaneous response to histamine than hydroxyzine alone, but the difference was not significant.

1. Simons FER, *et al.* Effect of the H_2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H_1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *J Allergy Clin Immunol* 1995; **95:** 685–93.

Pharmacokinetics

Hydroxyzine is rapidly absorbed from the gastrointestinal tract and is metabolised. Metabolites include cetirizine (p. 619.2), which has antihistaminic activity. An elimination half-life of about 20 hours has been reported.

References.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.

Liver disorders. For reference to a prolonged half-life of hydroxyzine in patients with primary biliary cirrhosis, see under Adverse Effects and Precautions, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ataraxone; Hyderax; ***Austria***: Atarax; ***Belg.***: Atarax; ***Braz.***: Drotizin; Hidroxine; Hixilerg; Hixizine; Pruri-Gran; Prurizin; ***Canad.***: Atarax; ***Chile***: Dalun; Fasarax; ***Cz.***: Atarax; ***Denm.***: Atarax; ***Fin.***: Atarax; ***Fr.***: Atarax; ***Ger.***: AH 3 N; Atarax; ***Gr.***: Atarax; Ictinal; Iremofar; ***Hong Kong***: Atarax; Qualidrozine; Vatarax†; ***Hung.***: Atarax; ***India***: Atarax; H-Rax; Hozen; Hydil; Hydroze; Krust; Nizod; ***Indon.***: Bestalin; Iterax; ***Irl.***: Ucerax; ***Israel***: Otarex; ***Ital.***: Atarax; ***Malaysia***: Atarax; ***Mex.***: Atarax; ***Neth.***: Atarax†; ***Norw.***: Atarax; ***NZ***: Serecid; ***Philipp.***: Iterax; ***Pol.***: Atarax; ***Port.***: Atarax; Corapheneț; ***Rus.***: Atarax (Атаракс); ***S.Afr.***: Aterax; Neuraxț; ***Singapore***: Atarax; Hizin; Phymorax; ***Spain***: Atarax; ***Swed.***: Atarax; ***Switz.***: Atarax; ***Thai.***: Abacus; Actadon; Allerax; Antipru; Antizine; Atalog; Atano; Atarax; Cerax; Dormirax; Drazine; Hadarax; Histan; Hiszine; Hizin; Honsa; Hydrox; Hyzine; Katrax; Polizine; R-Rax; Taraxin; Trandrozine; Unamineț; Xyzine; ***Turk.***: Atarax; Validol; Vistaril; ***UK***: Atarax; Ucerax; ***Ukr.***: Atarax (Атаракс); ***USA***: Vistaril.

Multi-ingredient Preparations. ***Braz.***: Marax; ***India***: Marax; ***S. Afr.***: Geratarț; ***Spain***: Calmoplexț; Dolodensț; ***Ukr.***: Distonin (Дистонин)†; ***USA***: Hydrophed; Marax; Theomax DF.

Pharmacopoeial Preparations

BP 2014: Hydroxyzine Oral Solution; Hydroxyzine Tablets;
USP 36: Hydroxyzine Hydrochloride Injection; Hydroxyzine Hydrochloride Syrup; Hydroxyzine Hydrochloride Tablets; Hydroxyzine Pamoate Capsules; Hydroxyzine Pamoate Oral Suspension.

Isothipendyl Hydrochloride *(BANM, rINNM)*

Hidrocloruro de isotipendil; Isothipendyl, Chlorhydrate d'; Isothipendyli Hydrochloridum; Isotipendil, hidrocloruro de; Изотипендила Гидрохлорид.

NN-Dimethyl-1-(pyrido[3,2-*b*][1,4]benzothiazin-10-ylmethyl) ethylamine hydrochloride.

$C_{16}H_{19}N_3S,HCl$=321.9

CAS — 482-15-5 (isothipendyl); 1225-60-1 (isothipendyl hydrochloride).

ATC — D04AA22; R06AD09.

ATC Vet — QD04AA22; QR06AD09.

UNII — 953AP1LBV8.

Profile

Isothipendyl hydrochloride, an azaphenothiazine derivative, is an antihistamine (p. 610.1) that has been applied topically for hypersensitivity and pruritic skin disorders although as with any antihistamine there is a risk of sensitisation. It has also been given orally and by the rectal route.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actapront; ***Braz.***: Andantol; ***Fr.***: Apaisylț; Apaisylgel; Histapaisyl; Sedermyl; ***Indon.***: Andantol; ***Israel***: Thiodantol; ***Ital.***: Calmogel; ***Mex.***: Andantol.

Multi-ingredient Preparations. ***Indon.***: Nipe; Transpulmin.

Ketotifen Fumarate *(BANM, USAN, rINNM)*

Fumarato de ketotifeno; HC-20511 (ketotifen); Ketotifeenivetyfumaraatti; Ketotifen Hydrogen Fumarate; Kétotifène, Fumarate de; Kétotifène, hydrogénofumarate de; Ketotifenfumarát; Ketotifén-hidrogén-fumarát; Ketotifenhydrogenfumarat; Ketotifeni Fumaras; Ketotifeni hydrogenofumaras; Ketotifeno, fumarato de; Ketotifeno-vandenilio fumaratas; Ketotifenvätefumarat; Кетотифена Фумарат.

4-(1-Methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophen-10(9*H*)-one hydrogen fumarate.

$C_{19}H_{19}NOS,C_4H_4O_4$=425.5

CAS — 34580-13-7 (ketotifen); 34580-14-8 (ketotifen fumarate).

ATC — R06AX17; S01GX08.

ATC Vet — QR06AX17; QS01GX08.

UNII — HBD503WORO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Ketotifen Hydrogen Fumarate; Ketotifen Fumarate BP 2014). A white to brownish-yellow, fine crystalline powder. Sparingly soluble in water; very slightly soluble in acetonitrile; slightly soluble in methyl alcohol.

Uses and Administration

Ketotifen is a sedating antihistamine (p. 610.2) that also has a stabilising action on mast cells analogous to that of sodium cromoglicate (p. 1226.1). It is used in the treatment of allergic conditions such as rhinitis (p. 612.1) and conjunctivitis (p. 611.1). Ketotifen has also been used in the prophylactic management of asthma, when it may take several weeks to exert its full effect; it should not be used to treat acute asthma attacks.

Ketotifen is given as the fumarate, but doses are expressed in terms of the base; ketotifen fumarate 1.38 mg is equivalent to about 1 mg of ketotifen.

Ketotifen fumarate is taken in oral doses equivalent to 1 mg of ketotifen twice daily with food, increased if necessary to 2 mg twice daily; 0.5 to 1 mg at night may be preferable for the first few days of treatment if drowsiness is likely to be a problem.

Ketotifen fumarate has also been applied topically, as eye drops equivalent to 0.025% ketotifen, used twice daily.

For children's doses, see below.

Action. It has been suggested that the anti-allergic action of ketotifen was independent of its antihistaminic properties.[1] This might be due to its effect on responses to platelet-activating factor (PAF).[2] However, the significance of PAF in the pathogenesis of asthma has been questioned.

1. Greenwood C. The pharmacology of ketotifen. *Chest* 1982; **82** (suppl): 45S–8S.
2. Morley J, *et al.* Effects of ketotifen upon responses to platelet activating factor: a basis for asthma prophylaxis. *Ann Allergy* 1986; **56:** 335–40.

Administration in children. Ketotifen fumarate can be given to children for the treatment of allergic conditions such as rhinitis (p. 612.1) or conjunctivitis (p. 611.1), and has been used in the prophylactic management of asthma. Oral doses equivalent to 1 mg of ketotifen twice daily with food may be used from 3 years of age. A dose equivalent to 500 micrograms ketotifen twice daily has been given to children aged between 6 months and 3 years.

Ketotifen fumarate has also been applied topically twice daily, as eye drops equivalent to 0.025% ketotifen, in children from 3 years of age.

Asthma. Results of studies on the efficacy of ketotifen in the treatment of asthma (p. 1195.2) have been conflicting; although some have found it effective in reducing symptoms[1-4] and in enabling a reduction in use of other anti-asthmatic drugs,[2,4] others have reported no significant benefits,[5,6] and UK guidelines on the management of asthma consider ketotifen to be ineffective.[7] A systematic review[8] found that it was of benefit in improving control of asthma and wheezing in children with mild to moderate disease, but noted that the high prevalence of atopy in several of the studies reviewed meant that the results might not be generalisable to children with asthma in general. A study in children described as 'preasthmatic' (that is, being at high risk of developing asthma) suggested that long-term therapy with ketotifen decreased the risk of asthma onset.[9]

1. Paterson JW, *et al.* Evaluation of ketotifen (HC20-511) in bronchial asthma. *Eur J Clin Pharmacol* 1983; **25:** 187–93.
2. Tinkelman DG, *et al.* A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma. *J Allergy Clin Immunol* 1985; **76:** 487–97.
3. Miraglia Del Giudice M, *et al.* Study of the efficacy of ketotifen treatment in asthmatic children under 3 years of age. *Curr Ther Res* 1986; **40:** 685–93.
4. Rackham A, *et al.* A Canadian multicenter study with Zaditen (ketotifen) in the treatment of bronchial asthma in children aged 5 to 17 years. *J Allergy Clin Immunol* 1989; **84:** 286–96.
5. White MP, *et al.* Ketotifen in the young asthmatic—a double-blind placebo-controlled trial. *J Int Med Res* 1988; **16:** 107–13.
6. Volovitz B, *et al.* Efficacy and safety of ketotifen in young children with asthma. *J Allergy Clin Immunol* 1988; **81:** 526–30.

7. Scottish Intercollegiate Guidelines Network/British Thoracic Society. British guideline on the management of asthma: a national clinical guideline (issued May 2008, revised June 2009). Available at: http://www.sign.ac.uk/pdf/sign101.pdf (accessed 06/08/09)
8. Bassler D, *et al*. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).
9. Bustos GJ, *et al*. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995; **25:** 568–73.

Conjunctivitis. References.

1. Martín AP, *et al*. The effect of ketotifen on inflammatory markers in allergic conjunctivitis: an open, uncontrolled study. *BMC Ophthalmol* 2003; **3:** 2. Available at: http://www.biomedcentral.com/content/pdf/1471-2415-3-2.pdf (accessed 17/08/10)
2. Kidd M, *et al*. Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *Br J Ophthalmol* 2003; **87:** 1206–11.
3. Ganz M, *et al*. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Therapy* 2003; **20:** 79–91.
4. Abelson MB, *et al*. Efficacy and safety of single-and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population. *Pediatr Allergy Immunol* 2004; **15:** 551–7.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively; drowsiness may be a problem, and dry mouth and dizziness may occur at the beginning of treatment but usually resolve with continued use. Weight gain and CNS stimulation have been reported. Isolated cases of severe skin reactions, cystitis, and hepatitis have been reported. Irritation, pain, and punctate keratitis are commonly reported after topical application to the eye.

Similar precautions to those for sodium cromoglicate (p. 1227.2) should be observed in asthmatic patients. Ketotifen may take several weeks to exert its full effect; existing anti-asthma treatment should not be abruptly withdrawn after starting ketotifen therapy. It should not be used for the treatment of acute asthma attacks.

Overdosage. Overdoses of ketotifen ranging from 10 to 120 mg were reported in 8 patients.[1] Symptoms included drowsiness, confusion, dyspnoea, bradycardia or tachycardia, disorientation, and convulsions. Gastric lavage was performed in 6 patients, and all 8 recovered within 12 hours after supportive treatment.

In an overview of 21 cases of overdosage (including those reported above) the manufacturers stated that no serious signs or symptoms had been reported with doses below 20 mg, and there had been no fatalities.[2] The most serious effects reported had included unconsciousness, convulsions, bradycardia and tachycardia, and a severe hypotensive reaction. Management is essentially supportive and symptomatic.

1. Jefferys DB, Volans GN. Ketotifen overdose: surveillance of the toxicity of a new drug. *BMJ* 1981; **282:** 1755–6.
2. Le Blaye I, *et al*. Acute ketotifen overdosage: a review of present clinical experience. *Drug Safety* 1992; **7:** 387–92.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketotifen as not porphyrinogenic when given by the ophthalmic route; it may be used as a drug of first choice and no precautions are needed. The safety of systemic formulations has not yet been classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

A reversible fall in the platelet count has been seen in a few patients receiving ketotifen with oral antidiabetics and it has been suggested that this combination should therefore be avoided.

Pharmacokinetics

Ketotifen fumarate is almost completely absorbed from the gastrointestinal tract after oral doses, but bioavailability is reported to be only about 50% due to hepatic first-pass metabolism. Peak plasma concentrations occur 2 to 4 hours after an oral dose. It is mainly excreted in the urine as inactive metabolites with a small amount of unchanged drug; the terminal elimination half-life is about 21 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antilerg; Bilozen; Biomira†; Farmoftal; Ketocev; Respimex; Zaditen; ***Austral.***: Zaditen; ***Austria***: Ketotisan; Zaditen; ***Belg.***: Altriabak; Zaditen; ***Braz.***: Asdron; Asmalergin; Asmanon; Asmax; Asmen; Asmifen; Asmofen; Biatos; Octifen; Prurifen; Zaditen; Zetitec; ***Canad.***: Zaditen; Zaditor; ***Chile***: Farmoftal; Ketotisin; Oftaler; Zaditen; ***China***: Bei Ka Ming (贝卡明); Rui Na Ti (瑞那替); Tong Fen (同芬); ***Cz.***: Ketof; Zabak; Zaditen; ***Denm.***: Zaditen; Zalerg; ***Fin.***: Zaditen; ***Fr.***: Zaditen; Zalerg; ***Ger.***: Ketof†; Padiatifen†; Zaditen; ***Gr.***: Cleroptic; Demetofrin; Dovidin; Ecradin; Eucycline; Fental; Firmapol; Frenasma; Isocaren; K-Drops; Kathricol; Klevistamin; Labelphen; Lavoptik; Meni-drops; Nostimex; Noxtor; Orpidix; Pellexeme; Sudaved; Urpem; Zaditen; Zeoklamin; Zethrinal; Zidofen; ***Hong Kong***: Amitone; Asmafen; Astifen; Dhatifen; Ketifen†; Vidatifen†; Zaditen; ***Hung.***: Zaditen; ***India***: Airyfen; Albalon; Asthafen; Azofen; Ketasma; Ketorid; Ketotif; Mastifen; ***Indon.***: Astifen†; Intifen; Nortifen; Prevas†; Profilas; Scanditen; Zaditen; ***Irl.***: Zaditen; ***Israel***: Profiten; Zaditen; ***Ital.***: Alleal†; Allerket; Bentifen; Chetofen; Chetotifene; Ketoftil; Sosefen; Stamifen†; Zaditen; ***Jpn***: Zaditen; ***Malaysia***: Asmafen; Asmaten; Asumalife; Denerel; Dhatifen; Ketifen; Licoften; Zaditen; ***Mex.***: Asmaral-K; Biotifen; Cantel†; Kasmal; Kedrop; Keraffler; Nemodine; Nomotec; Osaten; Pretifen; Saluket-H1; Ventisol; Zaditen; ***Neth.***: Altriabak; Bentifen†; Zaditen; ***Norw.***: Zaditen; ***NZ***: Asmafen†; Zaditen; ***Philipp.***: Azimef; Zadec; Zaditen; ***Pol.***: Zaditen; ***Port.***: Bentifen; Cipanfeno; Zabak; Zaditen; ***Rus.***: Zaditen (Задитен); Zetifen (Зетифен)†; ***S.Afr.***: Adco-Zetofen; Ketohexal†; Zaditen; ***Singapore***: Amitone; Asmafen; Asmaten; Asumalife; Beatifen; Denerel; Dhatifen; Erliten; Licoften; SP-Totifen; Suntotifen; Tofen; Zaditen; ***Spain***: Bentifen; Okeye; Zaditen; Zasten; ***Swed.***: Zaditen; ***Switz.***: Zabak; Zaditen; ***Thai.***: Ibis; Katifen; Kenefen; Keten; Ketifen†; Keto; Ketofen; Medkofen†; Politifen; Sukafen; Sykofen; TM Fen; Zadino; Zaditen; Zetofen; Zytofen; ***Turk.***: Astafen; Fumast; Mitofen; Zaditen; ***UAE***: Asmafort; ***UK***: Zaditen; ***Ukr.***: Zaditen (Задитен); ***USA***: Alaway; Claritin Eye; Itchy Eye Drops†; Visine All Day Eye Itch Relief; Zaditor; Zyrtec Itchy Eye Drops; ***Venez.***: Cosolve; Ketoptic; Ketotisin; Zaditen.

Multi-ingredient Preparations. ***Arg.***: Hyalcrom NF; ***China***: Xu Hong (旭宏); ***India***: Azofen-T; Mastifen-C; Mastifen-S; ***Mex.***: Hyalcrom NF.

Latrepirdine *(USAN, rINN)*

BRN-0622478; Dimebol; Dimebolin; Dimeboline; Dimebon; Dimebone; Latrepirdina; Latrépirdine; Latrepirdinum; PF-1913539; Латрепиридин; Димеболин.

2,3,4,5-Tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl) ethyl]-1*H*-pyrido[4,3-*b*]indole.

$C_{21}H_{25}N_3$=319.5

CAS — 3613-73-8 (latrepirdine); 97657-92-6 (latrepirdine dihydrochloride); 14292-23-0 (latrepirdine x-hydrochloride).

UNII — OD9237K1Z6.

Profile

Latrepirdine is an antihistamine that is reported to also have neuroprotective effects. It is under investigation as the dihydrochloride in the treatment of Alzheimer's disease (see Dementia, p. 388.1) and Huntington's disease.

References.

1. Doody RS, *et al*. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet* 2008; **372:** 207–15.
2. Kieburtz K, *et al*. A randomized, placebo-controlled trial of latrepirdine in Huntington disease. *Arch Neurol* 2010; **67:** 154–60.

Levocabastine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levocabastina; Levocabastina, hidrocloruro de; Lévocabastine, chlorhydrate de; Levocabastinhydrochlorid; Levocabastini Hydrochloridum; Levokabastiinihydrokloridi; Levokabastin-hydrochlorid; Levokabastinhydroklorid; Levokabastino hidrochloridas; Levokabasztinhidroklorid; R-50547; Левокабастина Гидрохлорид.

(-)-*trans*-1-[*cis*-4-Cyano-4-(*p*-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid hydrochloride.

$C_{26}H_{29}FN_2O_2$,HCl=457.0

CAS — 79516-68-0 (levocabastine); 79547-78-7 (levocabastine hydrochloride); 79449-98-2 (cabastine).

ATC — R01AC02; S01GX02.

ATC Vet — QR01AC02; QS01GX02.

UNII — 124XMA6YEI.

NOTE. Cabastine *(rINN)* is the racemate of levocabastine.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Levocabastine Hydrochloride). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in a 0.2% solution of sodium hydroxide; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Levocabastine Hydrochloride). Protect from light.

Uses and Administration

Levocabastine, a piperidine derivative, is a long-acting and potent antihistamine with a rapid onset of action. Levocabastine hydrochloride equivalent to 0.05% levocabastine is used topically twice daily as eye drops or as a nasal spray in the treatment of allergic conjunctivitis (p. 611.1) and rhinitis (p. 612.1), respectively, in adults and children aged 9 years and over. The frequency of the dose in both conditions may be increased to 3 or 4 times daily if necessary. It is recommended that treatment should be stopped if there is no improvement within 3 days.

References.

1. Noble S, McTavish D. Levocabastine: an update of its pharmacology, clinically efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. *Drugs* 1995; **50:** 1032–49.
2. Doughty MJ. Levocabastine, a topical ocular antihistamine available as a pharmacy medicine – a literature review. *Pharm J* 2002; **268:** 367–70.

Administration in children. For dosage in children, see above.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively. The most common adverse effects reported with levocabastine eye drops are transient stinging and burning of the eyes, urticaria, dyspnoea, drowsiness, and headache. With nasal use headache, nasal irritation, somnolence, and fatigue have been noted. The use of levocabastine nasal spray is not recommended in those with significant renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levocabastine as probably not porphyrinogenic when given intra-nasally; it may be used as a drug of first choice and no precautions are needed. When given ophthalmically it has been classified as not porphyrinogenic.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Levocabastine is absorbed after both nasal and ocular use. Systemic availability has been estimated at 60 to 80% after nasal doses and 30 to 60% after ocular use. However absolute peak plasma concentrations are low. Plasma protein binding is about 55%. An elimination half-life of 35 to 40 hours has been reported for all routes of delivery. Elimination of levocabastine is mainly renal with 70% excreted as unchanged drug and 10% as an inactive acetylglucuronide metabolite; the remaining 20% is excreted unchanged in the faeces.

Trace amounts of levocabastine have been found in breast milk after ocular and nasal use.

References.

1. Heykants J, *et al*. The pharmacokinetic properties of topical levocabastine: a review. *Clin Pharmacokinet* 1995; **29:** 221–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Histimet; ***Austral.***: Livostin; ***Austria***: Livostin; ***Belg.***: Livostin; ***Braz.***: Livostin; ***Canad.***: Livostin; ***Chile***: Livostin†; ***China***: Livostin (立复汀); ***Cz.***: Livostin; ***Denm.***: Benaliv; Livostin†; ***Fin.***: Livostin; ***Fr.***: Allergiflash; Levofree; Levophta; ***Ger.***: Livocab; ***Gr.***: Livostin; ***Israel***: Livostin; ***Ital.***: Levoreact; Levostab; Livocab†; Livostin; ***Jpn***: Livostin; ***Mex.***: Livostin; ***Neth.***: Livocab; ***Norw.***: Livostin; ***NZ***: Livostin; ***Port.***: Livostin; ***S.Afr.***: Livostin; Sinumax Allergy; ***Spain***: Bilina; Livocab†; Reactine Levocabastina; ***Swed.***: Livostin; ***Switz.***: Livostin; ***Turk.***: Livostin†; ***Venez.***: Livostin.

Levocetirizine *(BAN, USAN, rINN)*

Levocetirizina; Lévocétirizine; Levocetirizinum; Левоцетиризин.

(2-{4-[(*R*)-*p*-Chloro-α-phenylbenzyl]-1-piperazinyl}ethoxy) acetic acid.

$C_{21}H_{25}ClN_2O_3$=388.9

CAS — 130018-77-8.

ATC — R06AE09.

ATC Vet — QR06AE09.

UNII — 6U5EA9RT2O.

Levocetirizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocetirizina; Lévocétirizine, Chlorhydrate de; Levocetirizine Dihydrochloride (USAN); Levocetirizini Hydrochloridum; UCB-28556; Левоцетиризина Гидрохлорид.

$C_{21}H_{25}ClN_2O_3$,2HCl=461.8

CAS — 130018-87-0 (levocetirizine dihydrochloride); 823178-28-5 (levocetirizine hydrochloride).

ATC — R06AE09.

ATC Vet — QR06AE09.

UNII — SOD6A38AGA (levocetirizine dihydrochloride); W69HSF2416 (levocetirizine hydrochloride).

Profile

Levocetirizine is the *R*-enantiomer of cetirizine (p. 619.2) and is used similarly, as the hydrochloride, for the symptomatic relief of allergic conditions including rhinitis

(p. 612.1) and chronic urticaria (p. 612.3). The usual oral dose of levocetirizine hydrochloride is 5 mg once daily. US licensed product information suggests that the dose should be given in the evening, and that a dose of 2.5 mg may be adequate in some patients.

For doses in children or in patients with renal impairment, see below.

References.
1. Scheinfeld N. The new antihistamines—desloratadine and levocetirizine: a review. *J Drugs Dermatol* 2002; **1:** 311–16.
2. Tillement JP, *et al.* Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H1-receptor antagonists. *Biochem Pharmacol* 2003; **66:** 1123–6.
3. Horak F, *et al.* Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. *Br J Clin Pharmacol* 2005; **60:** 24–31.
4. Nettis E, *et al.* Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **154:** 533–8.
5. Hair PI, Scott LJ. Levocetirizine: a review of its use in the management of allergic rhinitis and skin allergies. *Drugs* 2006; **66:** 973–96.
6. Devillier P, *et al.* Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clin Pharmacokinet* 2008; **47:** 217–30.

Administration in children. Levocetirizine hydrochloride may be given orally to children for the symptomatic relief of allergic rhinitis and chronic idiopathic urticaria, although licensed doses may vary between countries.

In the UK, children aged 2 to 6 years may be given a dose of 2.5 mg daily in 2 divided doses, and those older than 6 years may be given the adult dose of 5 mg once daily.

In the USA, levocetirizine hydrochloride is licensed for the symptomatic treatment of seasonal allergic rhinitis in children aged 2 years and older, and for perennial allergic rhinitis and chronic idiopathic urticaria in children aged 6 months and older. Doses are lower than those used in the UK, at 1.25 mg given once daily in the evening to children aged from 6 months to 5 years, 2.5 mg in the evening for those aged 6 to 11 years, and the adult dose of 5 mg daily only given to children aged 12 years and older.

For doses in children with renal impairment, see below.

Administration in renal impairment. The dose of levocetirizine hydrochloride should be reduced in patients with renal impairment according to creatinine clearance (CC), although recommendations can vary between countries. The following oral doses have been suggested for adults in the UK and for adults and adolescents aged 12 years and over in the USA:

- CC 50 to 79 mL/minute: 5 mg once daily in the UK; 2.5 mg once daily in the USA
- CC 30 to 49 mL/minute: 5 mg every other day in the UK; 2.5 mg every other day in the USA
- CC 10 to 29 mL/minute: 5 mg once every 3 days in the UK; 2.5 mg once every 3 or 4 days in the USA
- CC less than 10 mL/minute and patients undergoing dialysis: contra-indicated in both the UK and USA

Data are lacking for the use of levocetirizine in children with renal impairment. UK licensed product information suggests that the dose should be adjusted on an individual basis, taking into account the patient's renal clearance and body-weight.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Analerg; Cetimer L; Levomine; Supraler; ***Austral.***: Xyzal; ***Austria***: Xyzall; ***Belg.***: Xyzall; ***Braz.***: Zyxem; ***Chile***: Alerfix; Degraler; Dofitex; Levorigotax; Neo Alertop; Xuzal; ***China***: Chang Ran (畅然); Di Min (迪皿); Nuo Si Da (诺思达); Qi Ping (齐平); Qiang Yi (强溢); Xikexin (西可新); Xyzal (优泽); ***Cz.***: Cezera; Lavaz; Lecivriens; Levozine; Silardex; Sintir; Volnostin; Xyzal; Zenaro; ***Denm.***: Levazyr; Xyzal; ***Fin.***: Levazyr; Nocedan; Xyzal; ***Fr.***: Xyzall; ***Ger.***: Xusal; ***Gr.***: Xozal; ***Hong Kong***: Xyzal; ***Hung.***: Histisynt; Lertazin; Levocep; Novocetrin; Sefaller; Xyzal; ***India***: Adicure; Airitis; Alcare-L; Alcetra; Alci; Aldine; Alertriz; Alervo; Aleva; Alexfix; Alidil; Allcet-DC; Allrite; Alnacet; Alquit-L; Altase; Altin-LE; Alvicet; Alzero; Arcet; Arizin-L; Atcet-LV; Belrin-LZ; Bencet-L; Bincet-L; Biolev; Biozine; Borox; Cefid-L; Cetjust L; Cetliv; Cetlong-L; Cetom-L; Cetril; Cetrina-LV; Cetrite; Cetsafe; Ciz-L; Ciz-LE; Covil; CTLevo; Deall; Dilevocet; Eelax; Ekon-XL; Elcet; Elcy; Elnacin; Elriz; Enocet-LV; Fitin; Fitzine-MD; Flamoset; Folcet; Genuhist; Glencet; Hatric; Hicet-L; His; Histachek; Idalez; Incet-L; Incet; Kind; Kurecet; L-5; L-Asicet; L-CBit; L-Cet; L-Cetridoc; L-Cetrizet; L-Cetron; L-Cit; L-CZN; L-Siacet; L-Triz; Labocet; Largy; Laveta; Lavoriz; Lazine; LCN; LCRal; LCZ; LDZin; Le Zyncet; Lecetzy; Lecope; Lecy; Leczine-MD; Leday; Leeviz; Leez; Lehist; Lentocit; Leoriv; Lepit; Lerid; Lerzin; Leset; Lesie; Lest; Lestal; Let; Leverest; Levoace; Levoc; Levocet; Levocetriwal; Levocets; Levodil; Levogo; Levohext; Levokair; Levonitrin; Levorid; Levoril; Levoriz; Levosiz; Levosoz; Levostar; Levotin; Levotra; Levotrin; Levoz; Levozin; Levzed; Lexzin; Lezer; Lezo; LFast; LG; Livit; Livot-MD; Lizine; Loviroc; Luzei; Luzer; Lycet; Lycit; Macliz; Medicet-L; NBLcet; Nislevo; Nizla; Noal-LC; Notril; Novolev; Nucet; Nucez; Okacet-L; Oriel; Ostril; Oxycet; Teczine; ***Indon.***: Xyzal; ***Irl.***: Muntel; Rinozal; Xyzal; ***Ital.***: Xyzal; ***Jpn***: Xyzal; ***Malaysia***: Xyzal; ***Mex.***: Xuzal; Zyxem; ***Neth.***: Cetirmar; Levocetira; Virdos†; Xyzal; ***Norw.***: Xyzal; ***Philipp.***: L-zet; Lisinex; Xyzal; Zocet; ***Pol.***: Cezera; Lirra; Xyzal; Zenaro; Zyx; ***Port.***: Levrix; Xyzal; ***Rus.***: Suprastinex (Супрастинекс); Xyzal (Ксизал); ***S.Afr.***: Xyzal; ***Singapore***: Xyzal; ***Spain***: Aralevo; Muntel; Xazal; ***Switz.***: Xyzal; ***Thai.***: Xyzal; ***Turk.***: Crebros; Xyzal; ***UK***: Xyzal; ***Ukr.***: Aleron (Алерон); Alerzin (Алерзин); Cetrilev (Цетрилев); Xyzal (Ксизал); Zenaro (Зенаро); Zilola (Зилола); ***USA***: Xyzal.

Multi-ingredient Preparations. ***India***: Abcet; Acolate Plus; Acolate; Airitis Plus; Airway-L; Alcare-CC; Alcetra Plus; Aldine-D; Allrite-D; Alnacet-AL; Alnacet-M; Ambicet; Amlee-P; Arokast; Borox-L; Breathezy-L; Carlev; Cetliv A; Cetry Plus; Ciz Cold; Ciz-LE-D; Cold Calm; Cold-CZ; Coldastat-LX; Covil-A; CZ-L; Dilevocet-M; Dilevocet-Plus; Elcet-P; Elcy-A; Festa; Fitin-CF; Folcet-MT; Hatric-2; Hatric-3; His-P; Hiskast; Idalez Plus; Kurecet-M; L-Cit Plus; L-Montus; L-Triz Plus; L-Triz-A; Largy-M; Laveta-A; Laveta-D; Lazine Plus; Lazine-D; Lazine-M; LCBit-P; LCN-Plus; LCRal Plus; LCZ-Plus; LCZ-XP; Le Zyncet-A; Le Zyncet-D; Le-Zyncet-M; Lecope-AD; Lecope-DX; Leczine-A; Leday-CC; Lemont-LC; Lenex; Lenomol; Lepit-A; Lepit-AM; Lepit-MK; Leverest Plus; Leverest-AM; Leverest-MK; Levocet Plus; Levocet-D; Levocet-M; Levoclic-M; Levogo Plus; Levorid D; Levoriz Plus; Levoriz-AM; Levoriz-MK; Levostar Plus Exp; Levostar Plus; Levostar-AM; Levostar-D; Levotan; Levotin Plus; Levotra-A; Levotra-M; Levotrin-M; Levotrin-P; Levoz-M; Levzed-A; Levzed-MK; Lexzin-P; Lezo-AM; LFast-AM; LG Plus; LG-Plus; Luka; Luzei-M; Luzer-A; Luzer-M; Lycit-M; M-Kast-L; Molly-Plus; Mondeo-LC; Montair-LC; Montasma Plus; Montbre; Montegen-L; Montek-LC; Montilife; Montlu-L; Montral; Monty; Mosha-L; Mucopen; Mucoresp-CT; Nam Cold-L; NBLcet Plus; Nislevo-MK; Nizla Plus; Noal-LM; Nucez Plus; Nukast; Okasma; Ontelio-L; Oox-LC; ***Philipp.***: Co-Altria; Zykast.

Loratadine *(BAN, USAN, rINN)*

Loratadiini; Loratadin; Loratadina; Loratadinum; Loratadyna; Sch-29851; Лоратадин.

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate.

$C_{22}H_{23}ClN_2O_2$=382.9

CAS — 79794-75-5.

ATC — R06AX13.

ATC Vet — QR06AX13.

UNII — 7AJO3BO7QN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Loratadine). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in acetone and in methyl alcohol.

USP 36: (Loratadine). A white to off-white powder. Insoluble in water; freely soluble in acetone, in chloroform, in methyl alcohol, and in toluene.

Uses and Administration

Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine with no significant antimuscarinic activity. It is used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and chronic urticaria (p. 612.3). It is also used with a decongestant such as pseudoephedrine sulfate.

Loratadine is given in an oral dose of 10 mg once daily; alternatively, 5 mg every 12 hours may be given. For dosage in children or in patients with hepatic or renal impairment, see below.

References.
1. Haria M, *et al.* Loratadine: a reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994; **48:** 617–37.

Administration in children. Loratadine is used orally for the symptomatic relief of seasonal allergic rhinitis and chronic idiopathic urticaria in children. Doses, according to age, are:

- 2 to 5 years, 5 mg once daily
- 6 years and over, usual adult doses, see above

For doses in children with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. US product information recommends that adults and children aged 6 years and over with hepatic failure or renal impairment (glomerular filtration rate less than 30 mL/minute) should be given an initial oral dose of loratadine 10 mg on alternate days; in younger children aged 2 years and over, the dose is 5 mg on alternate days.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving loratadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding. However, UK licensed product information recommends that loratadine should not be used in breast-feeding mothers.

A study[2] in 6 women reported that about 0.03% of a single 40-mg oral dose of loratadine was distributed into breast milk over 48 hours as loratadine and its active metabolite, desloratadine.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Hilbert J, *et al.* Excretion of loratadine in human breast milk. *J Clin Pharmacol* 1988; **28:** 234–9.

Effects on the liver. Two patients[1] developed severe necroinflammatory liver injury after receiving loratadine 10 mg daily for allergic rhinitis. Although both recovered after drug withdrawal, one patient required a liver transplantation and recovery was prolonged.

The product information notes that abnormal hepatic function including jaundice, hepatitis, and hepatic necrosis has been reported rarely.

1. Schiano TD, *et al.* Subfulminant liver failure and severe hepatotoxicity caused by loratadine use. *Ann Intern Med* 1996; **125:** 738–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies loratadine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. UK product information does not recommend the use of loratadine in pregnancy.

Analysis of data collected by the Swedish Medical Birth Registry between 1994 and 2001 revealed 15 cases of hypospadias among a cohort of 2780 newborns exposed to loratadine during the first trimester of pregnancy.[1] The authors noted that the individual risk for having an infant with hypospadias after loratadine use is small (less than 1%) and the attributive risk of extra cases in the population is low. The US CDC has also analysed data from the National Birth Defects Prevention study;[2] they found no increase in the risk of second- or third-degree hypospadias in the infants of women who used loratadine in early pregnancy. In addition, an earlier prospective multicentre study[3] in 161 women taking a median dose of loratadine 10 mg daily in the first trimester of pregnancy suggested that its use was not associated with a significant risk of major congenital malformations.

1. Källén B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? *Int J Risk Safety Med* 2001; **14:** 115–19.
2. CDC. Evaluation of an association between loratadine and hypospadias — United States, 1997-2001. *MMWR* 2004; **53:** 219–21. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5310.pdf (accessed 11/05/04)
3. Moretti ME, *et al.* Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol* 2003; **111:** 479–83.

Sedation. For discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Loratadine is metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Drugs known to inhibit one or other of these enzymes include cimetidine, erythromycin, ketoconazole, quinidine, fluconazole, and fluoxetine.

Antibacterials. Data held on file by the manufacturer show that *erythromycin* can inhibit the metabolism of loratadine. However, even when given in large doses loratadine does not appear to cause the cardiac conduction disorders associated with the non-sedating antihistamines astemizole (see p. 616.2) and terfenadine (see p. 640.3).[1] Similarly, *clarithromycin* seemed to inhibit the metabolism of loratadine and its active metabolite desloratadine.[2]

1. Affrime MB, *et al.* Three month evaluation of electrocardiographic effects of loratadine in humans. *J Allergy Clin Immunol* 1993; **91:** 259.
2. Carr RA, *et al.* Steady-state pharmacokinetics and electrocardiographic pharmacodynamics of clarithromycin and loratadine after individual or concomitant administration. *Antimicrob Agents Chemother* 1998; **42:** 1176–80.

Antifungals. *Ketoconazole* appears to be able to inhibit the metabolism of loratadine and at therapeutic doses, is about 3 times more inhibitory than erythromycin (Antibacterials, above).[1] However, the concentrations of ketoconazole required are reported to be much higher than those required to inhibit the metabolism of astemi-

zole or terfenadine. Clearance of the active metabolite desloratadine is also reduced.

1. Brannan MD, *et al.* Effects of various cytochrome P450 inhibitors on the metabolism of loratadine. *Clin Pharmacol Ther* 1995; **57:** 193.

Gastrointestinal drugs. *Cimetidine* appears to have an inhibitory effect on the metabolism of loratadine and also attenuates the clearance of its active metabolite desloratadine although no clinically significant consequences have been seen.[1]

1. Brannan MD, *et al.* Effects o f various cytochrome P450 inhibitors on the metabolism of loratadine. *Clin Pharmacol Ther* 1995; **57:** 193.

Pharmacokinetics

Loratadine is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur in about 1 hour. Bioavailability is increased and time to peak plasma concentrations is delayed when taken with food. Loratadine undergoes extensive metabolism. The major metabolite, desloratadine (p. 625.1), has potent antihistaminic activity. Reported mean elimination half-lives for loratadine and desloratadine are 8.4 and 28 hours, respectively. Loratadine is about 98% bound to plasma proteins; desloratadine is less extensively bound. Loratadine and its metabolites have been detected in breast milk, but do not appear to cross the blood-brain barrier to a significant extent. Most of a dose is excreted equally in the urine and faeces, mainly in the form of metabolites.

Renal impairment. The disposition of loratadine does not appear to be significantly altered in patients with severe renal impairment and haemodialysis does not appear to be an effective means of removing loratadine or its metabolite desloratadine from the body.[1]

1. Matzke GR, *et al.* Pharmacokinetics of loratadine in patients with renal insufficiency. *J Clin Pharmacol* 1990; **30:** 364–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerotina; Alergiano; Alergipan; Alergitrat L; Alermuc; Alerpriv; Algistop†; Aseptobron Descongestivo; Bedix; Benadryl 24; Biloina; Clarityne; Devedryl; Dexitis; Excelentia Antialergico; Hisplex; Lisaler; Loisan; Loralivio; Loratine†; Loremex Antialergico; Megalorat; Mudantil L; Niltro; Nularef; Omega 100 L; Pulmosan Aller; Sinaler; Tabcin Alergia; Vagran; Vixidone L; ***Austral.***: Alledine; Aller-Eze; Claratyne; Lorano; Lorastyne; ***Austria***: Allernon; Clarityn; Lictyn†; Lorano; ***Belg.***: Claritine; Rupton; Sanelor; ***Braz.***: Alergaliv; Clarilerg; Claritin; Clistin; Cloratadd; Histadin; Loradine; Loradrina D; Loralerg; Loranil; Lorasliv; Loratamed; Loremix; Loritil; Neo Loratadin; ***Canad.***: Claritin; ***Chile***: Alergan; Alledryl; Clarityne; Frenaler; Hysticlar; Lontadex†; Loptame; Primorix; ***China***: Ao Hui Feng (奥慧丰); Ao Mi Xin (奥米新); Ao Shu (奥纾); Bai Wei Le (百为乐); Bang Nuo (邦诺); Bi Sai Ning (彼赛宁); Bi Yan Tong (毕研通); Chang Ke (常克); Clarityne (开瑞坦); Da Sheng Rui Li (大生瑞丽); Fei Ge Man (菲格曼); Fu Lai Xi (福莱西); Hua Chang (华畅); Jin Su Rui (金苏瑞); Jing Wei (精威); Ke Mi (可米); Kui Yin (奎因); Lei Ning (雷宁); Min Li Ke (敏立可); Profadine (百为坦); Rui Fu (瑞孚); Run Lai (润来); She Tai (舍泰); Shi Nuo Min (施诺敏); Shi Tai Shu (史泰舒); Shu Rui (抒瑞); Shun Ta Xin (顺他欣); Tai Ming Ke (泰明可); Xian Ning (先宁); Xin Da Yue (信达悦); Xing Yuan Jia (星元佳); Xue Fei (雪菲); Yi Fei (亿菲); Yi Li Xin (伊利欣); Yi Shu Chang (逸舒长); Yibang (怡邦); ZhengShu (天晴正舒); Zhi Min (芷敏); ***Cz.***: Claritine; Erolin; Flonidan; Loranol†; Roletra†; ***Denm.***: Claritynj; Loradis; Lorapharm; Mildin; ***Fin.***: Claritynj; Histadin; Loraxin; Tuulix; ***Fr.***: Clarityne; Doliallergie; Humex Allergie Loratadine; Zaprilis; ***Ger.***: Lisino†; Lobeta†; Lora-Lich; Lora-Puren†; Loraderm; Lorano†; ***Gr.***: Allerdrug; Allergofact; Biliranin; Bollinol; Claritynе; Difmedol; Helporigin; Hobatadine; Horestyl; Igir; Latoren; Lora; Loratab; Novacloxab; Ralinet; Ristotadin; Tirlor; Utel; Zelmar; ***Hong Kong***: Allertyn; Carin; Clarinet†; Claritynе; CP-Loradine; Erolin; Ezede; Loradin; Loranox†; Loraton; Loratyn†; Lorita†; Lotadine; Lotin; Marlora†; Rinityn; Rotifar†; Sunadine; Voratadine†; ***Hung.***: Claritine; Erolin; Flonidan; Lorano; Roletra; ***India***: Alaspan; Algyfree; Allerban; Aura; Claridin; Cozy; Eldin-MD; Intralor; Japlor; Latar; Lonlor; Lor; Lora; Lorange; Lorariv; Loratia; Loratin; Lorfast; Lorid; Loridin; Lorin; Lorinol; Lorispa; Lorkind; Lorly; Lormeg; Loronet; LR; LTD; Nexx; ***Indon.***: Alernitis; Allohex; Alloris; Anhissen†; Anlos; Clarihis; Claritin; Clatatin; Cronitin; Dayhist; Folerin; Hislorex†; Histaritin†; Imunex†; Inclarin; Klinset; Lergia†; Lesidas; Logista; Lolergi; Loran; Lorapharm†; Lorihis; Nosedin; Nufalora; Prohistin; Pylor; Rahistin; Rihest; Safetin†; Sohotin; Tinnic; Urtilar; Winatin; Xepalodin; ***Irl.***: Clareeze Allergy; Claritynj; Histaclar; Lorat; ***Israel***: Allergyx; Lorastine; Loratrim; ***Ital.***: Claritynj; Fristamin; ***Jpn***: Claritin; ***Malaysia***: Carin; Clarityne; Ezede; Loradine; Ridamin; Roletra; Rotifar; Tirlor; ***Mex.***: Alerfin; Aludix; Antilergal; Biodin; Biolorat; Claritynе; Curyken; Dimegan; Dissen; Ditana; Doralan; Dotagil; Dymaten; Efectine; Fartadin; Grimeral; Histina†; Histox; HL-ysta; Inigrin; Laritol; Lertamine; Lictyn; Liferamin; Lotan; Lotinex; Lotos; Lovarin†; Neoalexil; Nidatar; Quimtadine; Rodakin†; Roletra†; Sensibit; Serralsina; Sitinir; Urtisin; Vincidal; ***Neth.***: Allerfre; Claritine; Kruidvat Hooikoortstabletten; Lorastad; Otrivin neusallergie loratadine†; ***Norw.***: Claritynj; ***NZ***: Claratyne; Lora-Tabs; Loraclear; ***Philipp.***: Allerta; Clarihist; Claritin; Flamitin; Folerin; Immunix; Lergicyl†; Loradex†; Loradine; Lorahist; Lorange; Lorano; Loratyne; Lordam; Lordane; Loren; Lorfast; Lorid; Onemin; Prevahist; Rinityn; Toral; Zylohist; ***Pol.***: Alerfan†; Aleric; Claritine; Flonidan; Lorafast†; Lorahexal†; Loram; Loratan; Loratine; Nalergine; Rotadin†; ***Port.***: Alerdaune; Alertrin; Claritine; Crizin; Evertine; Histadin; Loraxine†; Profenox; Zolargene; ***Rus.***: Alerpriv (Алерприв); Clargotil (Кларготил); Clarisens (Кларисенс); Claritine (Кларитин); Clarotadine (Кларотадин); Erolin (Эролин); Klallergine (Клаллергин); Klarfast (Кларфаст); Klaridol (Кларидол); Klarifer (Кларифер); Lomilan (Ломилан); Lorahexal (Лорагексал); Lorid (Лорид); Loridin (Лоридин); Lotaren (Лотарен); ***S.Afr.***: Clarinese; Claritynе; Laura; Lorahist; Lorano; Lorfast; Lormeg; Pollentyme; Rhinigine; Rohist; ***Singapore***: Allertyn; Alloris; Ardin; Carin; Claritynе; Ezede; Halodin; Histalor; Loracin; Lorfast; Loridin; Lotadine; Ridamin†; Rinityn; Roletra; Tirlor†; ***Spain***: Civeran; Claritynе; Velodan†; ***Swed.***: Claritynj; Versal†; ***Switz.***: Claritine; Lora Allergie; Lorado; Loratine; ***Thai.***: Alertyne; Aller-Tab; Allerdine; Allersil; Aridine; Botidine; Caradine†; Carinose; Clalodine; Clarid; Claridine; Clarigy; Claritex; Claritino; Claritynе; Fatynе†; Halodin; Hisracon; Histadine; Kalidin; Klaryne; Lindine; Logadine; Lolergy; Loracine; Loradine; Loragis; Loranox; Lorapac; Lordin; Loridin; Lorin†; Lorita; Lorsedin; Lortadine; Lotidyne; Ridamin†; Rityne; Roletra; Sanotyne; Tiradine; Tirlor; ***Turk.***: Alarin; Claritine; Histadin; Klodin; Loradif; Lorantis; Lorateva; Loritine; Ritin; ***UAE***: Loratin; ***UK***: Claritynj; ***Ukr.***: Agistam (Агистам)†; Aleric (Алерик); Claritin (Кларитин); Lorano (Лорано); Lorizan (Лоризан); ***USA***: Alavert; Claritin; Non-Drowsy Allergy; ***Venez.***: Alerdina; Biolorat; Claritynе; Lorat; Loraval; Lorex; Loriden; Lotal; Polaramine Reformulado; Tirlor.

Multi-ingredient Preparations. ***Arg.***: Alerpriv D; Aliviatos; Antitusivo L; Bedix-D; Benadryl 24 D; Celestamine-L; Ciprocort D; Ciprocort L; Clarifriol; Claritynе Cort; Claritynе D; Corticas L; Cortistamin L; Decidex Plus; Dexaprof D; Histamino Corteroid L; Ideobron; Ideogrip; Labsalerg-B; Lisaler Beta; Loisan-D; Lorabrox; Loremex Antigripal†; Loremex Descongestivo; Nastizol-L; Nularef Cort; Nularef-D; Paracetamol Grip NF; Pulmonix Grip; Pulmonix Plus; Sinaler B; Sinaler D; Toraxan; Vagran D; Vixidone LB; ***Austral.***: Clarinase†; ***Austria***: Clarinase; ***Belg.***: Clarinase; ***Braz.***: Alergaliv D; Claritin-D; Cloratadd D; Histadin D; Histamix D; Loralerg-D; Loranil D; Loremix D; Loritil D; Neofedrin; ***Canad.***: Chlor-Tripolon ND†; Claritin Allergy & Sinus; Liberator†; ***Chile***: Alledryl D; Clarinase; Frenaler-D; Larmax D†; Lertamine Extra†; Lertamine; Rinomex; ***China***: Bai Wei Qing (百为晴); Clarinase (开瑞能); Hui Fei Shun (惠菲顺); Jin De Fei (金得菲); Ke Shuai (可帅); QiKe (琦克); Wei Kuai (维快); Zhuang Qi (壮奇); ***Cz.***: Clarinase; ***Denm.***: Clarinase; ***Fin.***: Clarinase†; ***Gr.***: Claritynе D; ***Hong Kong***: Clariflu; Clarinase; Rhinos; ***Hung.***: Clarinase; ***India***: Amy; Claridin-D; Colbid; Cozy-AM; Cozy-AM; Loran-D; Loratin D; Lorfast-AM; Lorfast-AM; Lorfast-D; Loridin-D; Lormeg-D; Nam Cold-SR; ***Indon.***: Aldisa; Clarinase; Cronase; Glanos†; Rhinos; ***Israel***: Clarinase; ***Malaysia***: Allerpid; Carinox; Clarinase; ***Mex.***: Alerfin Ex; Bisincof; Bramin†; Bronar; Broquixol; Celestamine NS; Clariflu; Clarifriol; Claritynе D; Coricidin Expec; Dimegan D; Doralan-Ax; Efectine D; Farmalor; Fluxibit; Gralddep†; Laritol D; Laritol Ex; Laritol G; Lertamine D; Linfarden; Lyrsedin†; Quimtadine DSQ†; Quimtafriol†; Sensibit D-NF; Sensibit D; Sensibit XP; Sibilex; Tadinar-C; Tamex; Tavexyl; TheraFlu 24; TheraFlu N 12; TheraFlu TD; ***Philipp.***: Claricort; Clarinase; Loraped; Rhinase†; Rhinos†; ***Pol.***: Clarinase†; Claritine Active; ***Port.***: Claridon; ***Rus.***: Antigrippin-Maximum (Антигриппин-Максимум); Antigrippin-Maximum (Антигриппин-Максимум); ***S.Afr.***: Claritynе D†; Demazin NS; ***Singapore***: Clarinase; De-cold; ***Spain***: Claritynе Plus; Narine; ***Thai.***: Clarinase; ***Turk.***: Clarinase; ***Ukr.***: Pulmolor (Пульмолор); ***USA***: Alavert Allergy & Sinus D; Allergy Relief & Nasal Decongestant; Claritin-D; Loratadine D; ***Venez.***: Ambroclar; Celestamincort; Claricort; Claridex; Claridexultra; Clariflu; Clarigrip; Fedyclar; Lokarin; Loracert.

Pharmacopoeial Preparations

BP 2014: Loratadine Tablets;

USP 36: Loratadine Oral Solution; Loratadine Orally Disintegrating Tablets; Loratadine Tablets.

Mebhydrolin *(BAN, rINN)*

Mebhidrolina; Mebhydroline; Mebhydrolinum; Мебгидролин.

5-Benzyl-1,2,3,4-tetrahydro-2-methyl-γ-carboline.

$C_{19}H_{20}N_2$=276.4

CAS — 524-81-2.

ATC — R06AX15.

ATC Vet — QR06AX15.

UNII — 9SUK9B7XVY.

Mebhydrolin Napadisilate *(BANM, rINNM)*

Diazolinum; Mebhidrolina, napadisilato de; Mebhydrolin Napadisylate; Mebhydrolin Naphthalenedisulphonate; Mebhydroline, Napadisilate de; Mebhydrolini Napadisilas; Napadisilato de mebhidrolina; Мебгидролина Нападизилат.

Mebhydrolin naphthalene-1,5-disulphonate.

$(C_{19}H_{20}N_2)_2C_{10}H_8O_6S_2$=841.1

CAS — 6153-33-9.

ATC — R06AX15.

ATC Vet — QR06AX15.

UNII — O5G04RB25M.

Profile

Mebhydrolin, an ethylenediamine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and sedative properties. It has been given orally as the base or as the napadisilate salt for the symptomatic relief of allergic conditions including urticaria and rhinitis, and in pruritic skin disorders. Granulocytopenia and agranulocytosis have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Biolergy†; Gabiten; Histapan; Incitin†; Interhistin; Tralgi; Zoline; ***Israel***: Cidalin†; ***Rus.***: Diazolin (Диазолин); ***S.Afr.***: Fabahistin†; ***Thai.***: Dalhist†; Dayhist; Hydrolate; Manocidal; Manoeidai†; Medal; Posidol.

Multi-ingredient Preparations. ***Rus.***: Diacine (Диацин).

Meclozine Hydrochloride

(BANM, pINNM)

Hidrocloruro de meclozina; Meclizine Hydrochloride; Meclizinium Chloride; Meclozina, hidrocloruro de; Méclozine, Chlorhydrate de; Meclozini Dihydrochloridum; Meclozini hydrochloridum; Meklotsiinihydrokloridi; Meklozin Hidroklorür; Meklozin-dihydrochlorid; Meklozin-hidroklorid; Meklozinhydroklorid; Meklozino hidrochloridas; Meklozyny chlorowodorek; Parachloramine Hydrochloride; Меклозина Гидрохлорид.

1-(4-Chlorobenzhydryl)-4-(3-methylbenzyl)piperazine dihydrochloride.

$C_{25}H_{27}ClN_2$,2HCl=463.9

CAS — 569-65-3 (meclozine); 1104-22-9 (anhydrous meclozine hydrochloride); 31884-77-2 (meclozine hydrochloride monohydrate).

ATC — R06AE05.

ATC Vet — QR06AE05.

UNII — L997QXC9J1 (anhydrous meclizine hydrochloride); HDP7W44ClO (meclizine hydrochloride monohydrate).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

US specifies the monohydrate.

Ph. Eur. 8: (Meclozine Dihydrochloride). A white or yellowish-white, slightly hygroscopic, crystalline powder. Slightly soluble in water; soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Meclizine Hydrochloride). The monohydrate is white or slightly yellowish crystalline powder that has a slight odour. Practically insoluble in water and in ether; freely soluble in chloroform, in pyridine, and in acid-alcohol-water mixtures; slightly soluble in dilute acids and in alcohol. Store in airtight containers.

Uses and Administration

Meclozine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It is mainly used for its antiemetic action, which may last for up to 24 hours. Meclozine hydrochloride is used in the prevention and treatment of nausea and vomiting associated with a variety of conditions including motion sickness (p. 611.3) and for the symptomatic treatment of vertigo (p. 612.3) caused by Ménière's disease and other vestibular disorders. Meclozine hydrochloride has also been used for the symptomatic relief of hypersensitivity reactions and pruritic skin disorders (p. 612.1).

The usual oral dose of meclozine hydrochloride for motion sickness is 25 to 50 mg taken either the night before or about one hour before travelling and repeated every 24 hours if necessary; up to 100 mg daily in divided doses has been given for the treatment of vertigo and vestibular disorders. For doses in children, see below.

Both meclozine hydrochloride and meclozine base have been given by the rectal route; doses are similar to those given orally.

Administration in children. Meclozine hydrochloride may be given orally for the prevention and treatment of motion sickness in children. The following doses should be given either the night before or about one hour before travelling and repeated every 24 hours if necessary:

- children aged 2 to 6 years: 6.25 mg once daily
- those aged 6 to 12 years: 12.5 mg once daily

Older children and adolescents may be given usual adult doses, see above.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. For reports of the use of antihistamines, including meclozine, in pregnancy, see p. 614.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies meclozine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Agyrax; Postafene; ***Braz.***: Meclin; ***Canad.***: Bonamine†; ***Chile***: Bonamina†; ***Denm.***: Postafen; ***Fin.***: Postafen; ***Fr.***: Agyrax; ***Gr.***: Emetostop; Postafene; ***Hong Kong***: Postafene†; Sea Far†; ***Irl.***: Sea-Legs; ***Mex.***: Chiclida; Marenin; ***Neth.***: Suprimal; ***Norw.***: Postafen; ***NZ***: Sea-Legs; ***Philipp.***: Bonamine; Dizitab; Nodiz; Postadoxine; ***Port.***: Navicalm†; ***Rus.***: Bonine (Бонин)†; ***Spain***: Chiclida; Dramine†; Navicalm; ***Swed.***: Postafen; ***Turk.***: Postadoxine; ***UK***: Sea-Legs; Traveleeze; ***USA***: Antivert; Antrizine; Bonine; Dizmiss; Dramamine Less Drowsy Formula; Meni-D†.

Multi-ingredient Preparations. ***Austria***: Contravert B_6†; ***Hong Kong***: Navidoxine†; ***India***: Diligan; Pregnidoxin; ***Malaysia***: Veloxin; ***Mex.***: Bonadoxina; Bonalen; Bonazin†; Emediba†; Liatriz; Meclifar; Meclison; Pidoxina; Vo-Remi; ***Neth.***: Emesafene; ***S.Afr.***: Geratar†; ***Switz.***: Itinerol B_6; ***Venez.***: Bonadoxina.

Pharmacopoeial Preparations
USP 36: Meclizine Hydrochloride Tablets.

Mepyramine *(BAN, rINN)*

Mepiramina; Mepyramiini; Mepyramin; Mépyramine; Mepyraminum; Pyranisamine; Pyrilamine; Мепирамин.

2-(*N*-*p*-Anisyl-*N*-2-pyridylamino)ethyldimethylamine.

$C_{17}H_{23}N_3O$=285.4

CAS — 91-84-9.

ATC — D04AA02; R06AC01.

ATC Vet — QD04AA02; QR06AC01.

UNII — HPE317O9TL.

Mepyramine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mepiramina; Mepiramina, hidrocloruro de; Mépyramine, Chlorhydrate de; Mepyramini Hydrochloridum; Pyranisamine Hydrochloride; Pyrilamine Hydrochloride; Мепирамина Гидрохлорид.

$C_{17}H_{23}N_3O$,HCl=321.8

CAS — 6036-95-9.

ATC — D04AA02; R06AC01.

ATC Vet — QD04AA02; QR06AC01.

UNII — 5T3R4P0114.

Mepyramine Maleate *(BANM, rINNM)*

Maleato de mepiramina; Mepiramin Maleat; Mepiramina, maleato de; Mepiramin-maleát; Mepiramino maleatas; Mepyramiinimaleaatti; Mepyramin maleinát; Mépyramine, Maléate de; Mepyramini maleas; Mepyraminmaleat; Pyranisamine Maleate; Pyrilamine Maleate; Мепирамина Малеат.

Mepyramine hydrogen maleate.

$C_{17}H_{23}N_3O$,$C_4H_4O_4$=401.5

CAS — 59-33-6.

ATC — D04AA02; R06AC01.

ATC Vet — QD04AA02; QR06AC01.

UNII — R35D29L3ZA.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mepyramine Maleate). A white or slightly yellowish, crystalline powder. Very soluble in water; freely soluble in alcohol. M.p. 99 degrees to 103 degrees. A 2% solution in water has a pH of 4.9 to 5.2. Protect from light.

USP 36: (Pyrilamine Maleate). A white crystalline powder usually having a faint odour. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, 1 in 15 of dehydrated alcohol, and 1 in 2 of chloroform; slightly soluble in ether and in benzene. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Mepyramine, an ethylenediamine derivative, is a sedating antihistamine with antimuscarinic and sedative properties. Mepyramine maleate is used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders (p. 612.1). Mepyramine maleate is also a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

A cream containing 2% mepyramine maleate is used topically for insect bites or stings, and for hypersensitivity and pruritic skin conditions but, as with any antihistamine, there is a risk of sensitisation. It has also been used in eye drops.

Mepyramine maleate has been given orally at night as a hypnotic in the short-term management of insomnia (p. 611.2).

In some countries mepyramine maleate is available for parenteral use. Mepyramine hydrochloride has also been given parenterally or by the rectal route. Mepyramine tannate and mepyramine acefyllinate have been used orally.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Relaxa-Tabs†; ***Braz.***: Alergitanil†; ***Hong Kong***: Anthisan; Antihist†; ***Irl.***: Anthisan; Boots Bite & Sting Relief Antihistamine; ***NZ***: Anthisan; ***S.Afr.***: Alsan; Anthisan; Antihist†; Mepyraderm; Mepyrimal; ***Spain***: Fluidasa; ***UK***: Anthisan; ***USA***: Pyrlex†.

Multi-ingredient Preparations. ***Arg.***: Drynisan; Everfem; Fadanasal; Piracalamina; ***Belg.***: Nortussine; ***Braz.***: Beclase†; Conidrin; Engov; Enjoy; Gripsay; Naridrin; Nariflux; Nasogrip; Posdrink†; ***Canad.***: Extra Strength Multi-Symptom PMS Relief; Hycomine†; Jack & Jill; Menstrual Midol; Midol PMS; Midol Teen; Multi-Symptom PMS Relief; Pamprin; Prefrin A†; ratio-Theo-Bronc; Relievol PMS; Tylenol Menstrual; ***Chile***: Alerzona†; Dolo-Esan Periodo Menstrual; Kitadol Periodo Menstrual; Minfaden; Panagesic Periodo Menstrual; Predual; Rinolergan; Sentual Periodo; Tapsin Periodo Menstrual; ***Fr.***: Nortussine†; ***Gr.***: Prefrin A; ***Hong Kong***: Alox†; Alphate†; Aselan†; ***India***: Anthical; ***Irl.***: Wasp-Eze; ***Israel***: Alnase; Phenyphrine-Azol†; ***Ital.***: Balsamina Kroner; Vasofen; ***Mex.***: Femsedin Kutz; Lentostamin†; ***Pol.***: Kato-Nasal; Pro-Miss; ***Port.***: Antigrippine; ***Rus.***: Femizol (Фемизол); ***S.Afr.***: Adco-Metaxol; Codef†; Colcaps†; Coughcod†; Docsed†; Flucol†; Histodor†; Histodor; ***Switz.***: Fenipic; Parapic; Stilex; Stilex; ***Thai.***: Antergan; ***Turk.***: Peditus; Stilex; ***UAE***: Profinal FM†; ***UK***: Anthisan Plus; Wasp-Eze; ***USA***: 4-Way Fast Acting; Albatussin; C-Tanna 12D; Calamycin; Codal-DH†; Codal-DM†; Codimal DM†; Codimal PH†; Conal†; Corzall Plus; De-Chlor MR†; Deconsal CT†; Duonate; Gelhist; HC Derma-Pax; Midol Maximum Strength Multi-Symptom Menstrual; Midol Pre-Menstrual Syndrome; Myci-Spray; MyHist-DM; MyHist-PD†; Nalex-A 12†; Nalfrx†; ND-Gesic; P-Hist; P-Tanna; Pamprin; Poly Hist DHC; Poly Hist DM; Premsyn PMS; Pro-Red AC; Pro-Red†; Pyrichlor PE; Pyril D; Pyril DM; Pyrlex CB; R-Tanna†; R-Tannamine; R-Tannate; Rectagene Medicated Rectal Balm; Resperal; Rhinatate; Robitussin Night Relief; Ryna-12†; Rynesa 12S†; Soothaderm; Tanoral; Tri-Tannate; Tricodene Cough & Cold; Triotann†; Triplex AD†; Tritan; Tussi-12 D; Tussi-12D S; Tussplex; Vanacof-8; Viravan-DM; Viravan-P†; Viravan-PDM; Viravan; Z-Xtra; Zotex-C; ***Venez.***: Pi-Fedrin; Pinazo.

Pharmacopoeial Preparations
BP 2014: Mepyramine Tablets;
USP 36: Pyrilamine Maleate Tablets.

Mequitazine *(BAN, rINN)*

LM-209; Mekitatsiini; Mekitazin; Mequitazina; Méquitazine; Mequitazinum; Мехитазин.

10-(Quinuclidin-3-ylmethyl)phenothiazine.

$C_{20}H_{22}N_2S$=322.5

CAS — 29216-28-2.

ATC — R06AD07.

ATC Vet — QR06AD07.

UNII — Y463242LY2.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Mequitazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic and mild sedative properties.

Mequitazine is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It has been given in usual oral doses of 5 mg twice daily.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Mequitazine is used as a racemic mixture, and there is some evidence that a risk of significant prolongation of the QT interval may be associated with the *l*-mequitazine enantiomer. It should be avoided in patients with long QT syndrome, electrolyte disturbances such as hypokalaemia, or significant bradycardia. It should also be avoided in patients known to be slow cytochrome isoenzyme P450 CYP2D6 metabolisers because of the potential for accumulation of *l*-mequitazine.

Sedation. For discussion of the sedative effects of antihistamines, see p. 613.2. When mequitazine is given in the recommended dosage of 5 mg twice daily the incidence of sedation appears comparable with that of terfenadine. Sedation has, however, occurred after doses of 10 mg twice daily.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Mequitazine should be avoided in patients taking inhibitors of the cytochrome P450 isoenzyme CYP2D6 and potentially arrhythmogenic drugs including those that prolong the QT interval.

Antibacterials. For a report of torsade de pointes in a patient taking *spiramycin* and mequitazine, see Cytochrome P450 Isoenzymes under Interactions of Spiramycin, p. 358.3.

Pharmacokinetics

After absorption from the gastrointestinal tract, mequitazine is metabolised. Unchanged drug and metabolites are excreted principally in the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Primalan; ***Chile***: Mircol; ***Fr.***: Primalan; Quitadrill†; ***Ger.***: Metaplexan†; ***Gr.***: Istalar; ***Mex.***: Primalan; ***Philipp.***: Primalan; ***Port.***: Primalan; ***Rus.***: Primalan (Прималан); ***Spain***: Mircol.

Methdilazine *(BAN, rINN)*

Metdilatsiini; Metdilazin; Metdilazina; Methdilazinum; Metodilazina; Метдилазин.

10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine.

$C_{18}H_{20}N_2S$=296.4

CAS — 1982-37-2.

ATC — R06AD04.

ATC Vet — QR06AD04.

UNII — 4Q13LY9Z8X.

Methdilazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metodilazina; Methdilazine, Chlorhydrate de; Methdilazini Hydrochloridum; Metodilazina, hidrocloruro de; Метдилазина Гидрохлорид.

$C_{18}H_{20}N_2S$,HCl=332.9

CAS — 1229-35-2.

ATC — R06AD04.

ATC Vet — QR06AD04.

UNII — T0GSO02UEZ.

Pharmacopoeias. In *US.*

USP 36: (Methdilazine Hydrochloride). A light tan crystalline powder having a slight characteristic odour. Soluble 1 in 2 of water and of alcohol, 1 in 6 of chloroform, and 1 in 1 of 0.1N hydrochloric acid and of 0.1N sodium hydroxide solution; practically insoluble in ether. pH of a 1% solution in water is between 4.8 and 6.0. Store in airtight containers. Protect from light.

Profile

Methdilazine, a phenothiazine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and sedative activity. Methdilazine is also reported to have serotonin-antagonist properties. It has been used for the symptomatic relief of hypersensitivity reactions and particularly for the control of pruritic skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Dilosyn.

Multi-ingredient Preparations. ***India***: Dilosyn Expectorant.

Pharmacopoeial Preparations
USP 36: Methdilazine Hydrochloride Syrup; Methdilazine Hydrochloride Tablets.

Mizolastine *(BAN, rINN)*

Mitsolastiini; Mizolastin; Mizolastina; Mizolastinum; SL-85.0324-00; Мизоластин.
2-{1-[1-(4-Fluorobenzyl)-1*H*-benzimidazol-2-yl]-4-piperidyl (methyl)amino}pyrimidin-4(1*H*)-one.
$C_{24}H_{25}FN_6O$=432.5
CAS — 108612-45-9.
ATC — R06AX25.
ATC Vet — QR06AX25.
UNII — 244O1F90NA.

Uses and Administration

Mizolastine is a non-sedating antihistamine with a long duration of action. It does not have significant antimuscarinic actions; it is reported to have mast-cell stabilising properties. Mizolastine is used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1), conjunctivitis (p. 611.1), and skin disorders such as urticaria (p. 612.3). The oral dose is 10 mg once daily.

References.

1. Leynadier F, *et al.* Efficacy and safety of mizolastine in seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1996; **76:** 163–8.
2. Brostoff J, *et al.* Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria. *Allergy* 1996; **51:** 320–5.
3. Stern MA, *et al.* Can an antihistamine delay appearance of hayfever symptoms when given prior to pollen season? *Allergy* 1997; **52:** 440–4.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Mizolastine has only a weak potential to prolong the QT interval (see also Arrhythmias, p. 613.2) and has not been associated with arrhythmias. However, the manufacturers have warned against the use of mizolastine in patients with significant cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected QT prolongation. Use with drugs liable to interfere with the hepatic metabolism of mizolastine or with other potentially arrhythmogenic drugs should also be avoided (see under Interactions, below).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mizolastine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the non-sedating antihistamines in general, p. 614.3. Moderate increases in plasma concentrations of mizolastine have been reported with erythromycin and ketoconazole; use with macrolide antibacterials or systemic imidazole antifungals is contra-indicated by the manufacturer. They also advise against use of mizolastine with drugs known to prolong the QT interval, such as class I and III antiarrhythmics.

Other potent inhibitors of or substrates for the hepatic metabolism of mizolastine include cimetidine, ciclosporin, and nifedipine; caution is advised if given together.

Pharmacokinetics

Mizolastine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 1.5 hours. Plasma protein binding is about 98%. The mean elimination half-life is about 13 hours. Mizolastine is mainly metabolised by glucuronidation although other metabolic pathways are involved, including metabolism by the cytochrome P450 isoenzyme CYP3A4, with the formation of inactive hydroxylated metabolites.

References.

1. Rosenzweig P, *et al.* Pharmacodynamics and pharmacokinetics of mizolastine (SL 85.0324), a new nonsedative H_1 antihistamine. *Ann Allergy* 1992; **69:** 135–9.
2. Lebrun-Vignes B, *et al.* Clinical pharmacokinetics of mizolastine. *Clin Pharmacokinet* 2001; **40:** 501–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Mizollen; ***China***: Ao Ni Jie (奥尼捷); Mizollen (皿治林); Nile (尼乐); ***Fr.***: Mizollen; ***Ger.***: Mizollen; Zolim; ***Gr.***: Mizollen; Oriens; ***India***: Elina; ***Israel***: Mizollen; ***Ital.***: Mizollen; Zolistam; ***Mex.***: Mistamine; ***Neth.***: Mizollen; ***Pol.***: Mizollen†; ***Port.***: Mizollen; Zolistam†; ***S.Afr.***: Mizollen; ***Spain***: Mizolen; Zolistan; ***Swed.***: Mizollen†; ***Switz.***: Mizollen†; ***UK***: Mizollen.

Moxastine Teoclate *(rINNM)*

Mephenhydramine Theoclate; Mephenhydrinate; Moxastine, Téoclate de; Moxastine Theoclate; Moxastini Teoclas; Teoclato de moxastina; Моксастина Теоклат.
2-(1,1-Diphenylethoxy)-*N*,*N*-dimethylethylamine 8-chlortheophyllinate.
$C_{18}H_{23}NO,C_8H_7ClN_4O_2$=472.0
CAS — 3572-74-5 (moxastine); 21661-62-1 (moxastine teoclate).
UNII — J566J1RZ9J.

Profile

Moxastine teoclate is an antihistamine with antiemetic properties. It is used to treat nausea and vertigo associated with Ménière's disease and other vestibular disorders, and for the prevention and treatment of motion sickness.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Kinedryl.

Multi-ingredient Preparations. ***Rus.***: Kinedril (Кинедрил).

Niaprazine *(rINN)*

1709-CERM; Niaprazina; Niaprazinum; Ниапразин.
N-[3-(4-*p*-Fluorophenylpiperazin-1-yl)-1-methylpropyl]nicotinamide.
$C_{20}H_{25}FN_4O$=356.4
CAS — 27367-90-4.
ATC — N05CM16.
ATC Vet — QN05CM16.
UNII — R2H3YN6E3L.

Profile

Niaprazine, a piperazine derivative, is an antihistamine (p. 610.1) used in children for its sedative and hypnotic properties. The usual oral dose is 1 mg/kg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Nopron†; ***Ital.***: Nopron.

Olopatadine Hydrochloride *(BANM, USAN, pINNM)*

ALO-4943A; Hidrocloruro de olopatadina; KW-4679; Olopatadin Hidroklorür; Olopatadina, hidrocloruro de; Olopatadine, Chlorhydrate d'; Olopatadini Hydrochloridum; Олопатадина Гидрохлорид.
11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid hydrochloride.
$C_{21}H_{23}NO_3$,HCl=373.9
CAS — 113806-05-6 (olopatadine); 140462-76-6 (olopatadine hydrochloride).
ATC — R01AC08; S01GX09.
ATC Vet — QS01GX09.
UNII — 2XG66W44KF.

Pharmacopoeias. In *US*.

USP 36: (Olopatadine Hydrochloride). A white, crystalline powder. Sparingly soluble in water; very slightly soluble in anhydrous alcohol; very soluble in formic acid. pH of a 1% solution in water is between 2.0 and 4.0. Store in airtight containers. Protect from light.

Uses and Administration

Olopatadine hydrochloride is an antihistamine with mast-cell stabilising properties. It is used twice daily as eye drops containing the equivalent of 0.1% of olopatadine base in the treatment of allergic conjunctivitis (p. 611.1); alternatively, 0.2% eye drops are available for once-daily use. In the treatment of seasonal allergic rhinitis (p. 612.1) the usual dose is 1.33 mg of olopatadine hydrochloride by nasal spray into each nostril twice daily. For doses used in children, see below.

References.

1. Abelson MB. A review of olopatadine for the treatment of ocular allergy. *Expert Opin Pharmacother* 2004; **5:** 1979–94.
2. McGill JI. A review of the use of olopatadine in allergic conjunctivitis. *Int Ophthalmol* 2004; **25:** 171–9.
3. Abelson MB, *et al.* Efficacy of olopatadine ophthalmic solution 0.2% in reducing signs and symptoms of allergic conjunctivitis. *Allergy Asthma Proc* 2007; **28:** 427–33.
4. Abelson MB, *et al.* Efficacy of once-daily olopatadine 0.2% ophthalmic solution compared to twice-daily olopatadine 0.1% ophthalmic solution for the treatment of ocular itching induced by conjunctival allergen challenge. *Curr Eye Res* 2007; **32:** 1017–22.
5. Shah SR, *et al.* Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. *Clin Ther* 2009; **31:** 99–107.

Administration in children. Olopatadine eye drops may be used for allergic conjunctivitis in children aged 3 years and over in the same doses as those used in adults (see above). In seasonal allergic rhinitis, children aged 6 to 11 years may be given a dose of 665 micrograms of olopatadine hydrochloride by nasal spray into each nostril twice daily.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively. Headache and stinging or burning of the eye are common after ocular use. When given intranasally, common adverse effects include bitter taste, headache and epistaxis. Somnolence has been reported with both routes.

Pharmacokinetics

Olopatadine is absorbed after nasal use; the average systemic bioavailability is 57%. Absorption after ocular use is said to be minimal. Plasma protein binding is about 55%. Based on oral pharmacokinetics studies, the elimination half-life is reported to be 8 to 12 hours. Elimination is primarily renal with 60 to 70% excreted as unchanged drug; about 17% is excreted in the faeces.

Olopatadine has been detected in breast milk after oral use in *animals*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Olopat; Patanol; Zoloatlas; ***Austral.***: Patanol; ***Belg.***: Opatanol; ***Braz.***: Patanol; ***Canad.***: Pataday; Patanol; ***Chile***: Patanol; ***China***: Allelock (阿洛刻); Patanol (帕坦洛); ***Cz.***: Opatanol; ***Denm.***: Opatanol; ***Fin.***: Opatanol; ***Fr.***: Opatanol; ***Ger.***: Opatanol; ***Gr.***: Opatanol; ***Hong Kong***: Pataday; Patanol; ***Hung.***: Opatanol; ***India***: Alerchek; Dynolap; O-Din; Olgeria; Olo; Oloblu; Olodin; Opat; ***Indon.***: Patanol; ***Irl.***: Opatanol; ***Israel***: Pataday; Patanol; ***Ital.***: Opatanol; ***Jpn***: Allelock; Patanol; ***Malaysia***: Pataday; Patanol; ***Mex.***: Patanol; ***Neth.***: Opatanol; ***Norw.***: Opatanol; ***NZ***: Patanol; ***Philipp.***: Pataday; Patanol; ***Pol.***: Opatanol; ***Port.***: Opatanol; ***Rus.***: Opatanol (Опатанол); ***S.Afr.***: Patanol; ***Singapore***: Patanol; ***Spain***: Opatanol; ***Swed.***: Opatanol; ***Switz.***: Opatanol; ***Thai.***: Patanol; ***Turk.***: Hexos; Patanol; ***UK***: Opatanol; ***Ukr.***: Opatanol (Опатанол); ***USA***: Pataday; Patanase; Patanol; ***Venez.***: Patanol.

Pharmacopoeial Preparations
USP 36: Olopatadine Hydrochloride Ophthalmic Solution.

Oxatomide *(BAN, USAN, rINN)*

Oksatomidi; Oxatomid; Oxatomida; Oxatomidum; R-35443; Оксатомид.
1-[3-(4-Benzhydrylpiperazin-1-yl)propyl]benzimidazolin-2-one.
$C_{27}H_{30}N_4O$=426.6
CAS — 60607-34-3.
ATC — R06AE06.
ATC Vet — QR06AE06.
UNII — J31IL9Z2EE.

Profile

Oxatomide, a piperazine derivative, is a sedating antihistamine (p. 610.1) that has also been reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3), rhinitis (p. 612.1), and conjunctivitis (p. 611.1). Oxatomide is given as the anhydrous substance or as the monohydrate; doses are expressed as the anhydrous substance. Oxatomide monohydrate 1.04 mg is equivalent to about 1 mg of anhydrous oxatomide. The usual oral dose is 30 mg twice daily. The hydrate has also been applied topically but, as with other antihistamines, there is a risk of sensitisation.

Effects on the nervous system. Acute dystonic reactions and long-lasting impaired consciousness were associated with oxatomide therapy in 6 children.[1] Impaired consciousness varied from lethargy and somnolence to a clinical picture resembling encephalitis and persisted for 2 days or more in 3 patients. Plasma-oxatomide concentrations

were measured in 3 patients and found to be high, although 2 of these had been given the recommended dose.

1. Casteels-Van Daele M, *et al.* Acute dystonic reactions and long-lasting impaired consciousness associated with oxatomide in children. *Lancet* 1986; **i:** 1204–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fensedyl; Tinset; ***Austria***: Tinset†; ***Chile***: Tinset†; ***Fr.***: Tinset†; ***Gr.***: Tinset; ***Indon.***: Oxtin; Tinset; ***Ital.***: Tinset; ***Jpn***: Celtect; ***Mex.***: Tinset; ***Neth.***: Tinset; ***Port.***: Tinset; ***S.Afr.***: Tinset; ***Spain***: Cobiona†; Oxatokey†; ***Thai.***: Tinset.

Multi-ingredient Preparations. ***Arg.***: Causalon Bronquial; Causalon Grip; Letondal.

Oxomemazine *(rINN)*

Oxomemazina; Oxométazine; Oxomemazinum; RP-6847; Trimeprazine *SS*-Dioxide; Оксомемазин.

10-(3-Dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide.

$C_{18}H_{22}N_2O_2S$=330.4

CAS — 3689-50-7.

ATC — R06AD08.

ATC Vet — QR06AD08.

UNII — 305MB3BV1C.

Oxomemazine Hydrochloride *(rINNM)*

Hidrocloruro de oxomemazina; Oxométazine, Chlorhydrate d'; Oxomemazini Hydrochloridum; Оксомемазина Гидрохлорид.

$C_{18}H_{22}N_2O_2S$,HCl=366.9

CAS — 4784-40-1.

ATC — R06AD08.

ATC Vet — QR06AD08.

Pharmacopoeias. In *Fr.*

Profile

Oxomemazine, a phenothiazine derivative, is a sedating antihistamine (p. 610.1) used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders (p. 612.1). It is also an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

Oxomemazine has been given orally in doses ranging from about 5 to 13 mg daily in divided doses. It has also been given by the rectal route. Oxomemazine hydrochloride has been used similarly by mouth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Toplexil; ***Neth.***: Toplexil; ***Switz.***: Toplexil N.

Multi-ingredient Preparations. ***Belg.***: Toplexil; ***Braz.***: Expec; Iodesin; KI-Expectorante; Toplexil; ***Gr.***: Toplexil; ***Indon.***: Comtusi; Oroxin; Oxopect; Toplexil; ***Israel***: Oxacatin.

Parathiazine Teoclate *(plNNM)*

Parathiazine, Téoclate de; Parathiazini Teoclas; Parathiazone Theoclate; Pyrathiazine Theoclate; Teoclato de paratiazina; Паратиазина Теоклат.

10-(2-Pyrrolidin-1-ylethyl)phenothiazine 8-chlorotheophyllinate.

$C_{18}H_{20}N_2S$,$C_7H_7ClN_4O_2$=511.0

CAS — 84-08-2 (parathiazine); 14006-99-6 (parathiazine teoclate); 522-25-8 (parathiazine monohydrochloride).

Profile

Parathiazine is a phenothiazine derivative with the properties of the antihistamines (p. 610.1). It has been given as the teoclate as an antiemetic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Anvomer B6; Emegrav B6; Mediamer B6; Pregvomit; Provomer; Pyramer; Voldiamer B6.

Phenindamine Tartrate *(BANM, USAN, rINNM)*

Fenindamina, tartrato de; Phenindamine Acid Tartrate; Phénindamine, Tartrate de; Phenindamini Tartras; Phenindaminium Tartrate; Tartrato de fenindamina; Фениндамина Тартрат.

1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine hydrogen tartrate.

$C_{19}H_{19}N$,$C_4H_6O_6$=411.5

CAS — 82-88-2 (phenindamine); 569-59-5 (phenindamine tartrate).

ATC — R06AX04.

ATC Vet — QR06AX04.

UNII — 28725X3PV8.

Pharmacopoeias. In *Br.*

BP 2014: (Phenindamine Tartrate). A white or almost white, odourless or almost odourless, voluminous powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 1% solution in water has a pH of 3.4 to 3.9. Protect from light.

Profile

Phenindamine, a piperidine derivative, is a sedating antihistamine (p. 610.1); however, it may be mildly stimulating in certain individuals. It has been used as the tartrate for the symptomatic relief of allergic conditions including urticaria and rhinitis, and as an ingredient of compound preparations for coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Nolahist†.

Multi-ingredient Preparations. ***USA***: P-V-Tussin†.

Pheniramine *(BAN, rINN)*

Feniramiini; Feniramin; Feniramina; Phéniramine; Pheniraminum; Prophenpyridamine; Фенирамин.

NN-Dimethyl-3-phenyl-3-(2-pyridyl)propylamine.

$C_{16}H_{20}N_2$=240.4

CAS — 86-21-5.

ATC — R06AB05.

ATC Vet — QR06AB05.

UNII — 134FM9ZZ6M.

Pheniramine Aminosalicylate *(BANM, rINNM)*

Aminosalicilato de feniramina; Feniramina, aminosalicilato de; Pheniramine 4-Aminosalicylate; Pheniramine *p*-Aminosalicylate; Phéniramine, Aminosalicylate de; Pheniramine Para-aminosalicylate; Pheniramini Aminosalicylas; Фенирамина Аминосалицилат.

Pheniramine 4-amino-2-hydroxybenzoate.

$C_{16}H_{20}N_2$,$C_7H_7NO_3$=393.5

CAS — 3269-83-8.

ATC — R06AB05.

ATC Vet — QR06AB05.

Pheniramine Maleate *(BANM, USAN, rINNM)*

Feniramiinimaleaatti; Feniramin Hidrojen Maleat; Feniramin Maleat; Feniramin maleinát; Feniramina, maleato de; Feniraminmaleat; Feniramin-maleát; Feniramino maleatas; Maleato de feniramina; Phéniramine, maléate de; Pheniramini Maleas; Pheniraminium Maleate; Pheniraminmaleat; Prophenpyridamine Maleate; Фенирамина Малеат.

Pheniramine hydrogen maleate.

$C_{16}H_{20}N_2$,$C_4H_4O_4$=356.4

CAS — 132-20-7.

ATC — R06AB05.

ATC Vet — QR06AB05.

UNII — NYW9056558.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pheniramine Maleate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. M.p. 106 degrees to 109 degrees. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

USP 36: (Pheniramine Maleate). A white crystalline powder having a faint amine-like odour. Soluble in water and in alcohol. pH of a 1% solution in water is between 4.5 and 5.5.

Uses and Administration

Pheniramine, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties.

It is used as the maleate for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1), and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It has also been used for its antiemetic properties in the prevention and control of motion sickness (p. 611.3). Pheniramine maleate is used as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2). It is also used with a decongestant in eye and nasal preparations.

Pheniramine maleate is given orally in doses up to about 45 mg three times daily. In some countries pheniramine maleate has been given parenterally.

The aminosalicylate, the hydrochloride, and the tannate have also been used.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Abuse. References to the abuse of oral pheniramine.

1. Jones IH, *et al.* Pheniramine as an hallucinogen. *Med J Aust* 1973; **1:** 382–6.
2. Csillag ER, Landauer AA. Alleged hallucinogenic effect of a toxic overdose of an antihistamine preparation. *Med J Aust* 1973; **1:** 653–4.
3. Buckley NA, *et al.* Pheniramine—a much abused drug. *Med J Aust* 1994; **160:** 188–92.

Pregnancy. For discussion of the use of antihistamines, including pheniramine, in pregnancy, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

The pharmacokinetics of pheniramine and its metabolites, *N*-desmethylpheniramine and *N*-didesmethylpheniramine, were investigated in 6 healthy subjects.[1] After oral doses of pheniramine aminosalicylate, peak-plasma pheniramine concentrations were reached in 1 to 2.5 hours. The terminal half-life ranged between 8 and 17 hours after intravenous doses (pheniramine maleate) and 16 and 19 hours after oral doses. The total recovery of pheniramine as unchanged drug and metabolites from the urine was 68 to 94% of the intravenous dose and 70 to 83% of the oral dose.

1. Witte PU, *et al.* Pharmacokinetics of pheniramine (Avil) and metabolites in healthy subjects after oral and intravenous administration. *Int J Clin Pharmacol Ther Toxicol* 1985; **23:** 59–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Avil; ***India***: Avil; ***Indon.***: Avil; ***Turk.***: Avil; ***UAE***: Histol.

Multi-ingredient Preparations. ***Arg.***: Mira Klonal; Mirus; Refenax Colirio; Visuclar; ***Austral.***: Avil Decongestant†; Naphcon-A; Visine Allergy; ***Austria***: Neo Citran; ***Belg.***: Naphcon-A; ***Braz.***: Clanistil; Claril; Cristalin; ***Canad.***: Ak Vernacon; Calmylin Ace; Citron Chaud DM†; Cold & Flu; Diopticon A; Diorouge; Dristan; Hot Lemon Cough and Colds Relief DM; Hot Lemon Relief for Symptoms of Cold and Flu; Hot Lemon Relief for Symptoms of Cough and Cold; Hot Lemon Relief; Hot Lemon†; Naphcon-A; Neo Citran Colds & Flu; Neo Citran DM; Neocitran Extra Strength Cold and Flu†; Opcon-A; Pulmorphan Pediatrique; Pulmorphan; Rhume et de la Grippe†; Rhume et de la Toux†; Rhume et Grippe; Robitussin AC; TheraFlu Cold & Flu; Visine Advance Allergy; ***Chile***: Clarimir F; Dessolets; Miral; Naphcon-A; ***China***: Naphcon-A (那素达); ***Cz.***: Fervex†; ***Fr.***: Fervex; ***Hong Kong***: Dristan Nasal Spray†; Fortolin Nite†; Konjunktival; Naphcon-A; Opcon-A; ***Hung.***: Fervex†; Neo Citran; ***India***: Avil Expectorant; Cof Q; Cosavil†; Dristan Nasal Drops†; ***Indon.***: Flamergi; Isotic Azora; Naphcon-A; ***Israel***: TheraFlu Colds & Flu†; TheraFlu Cough & Colds†; Tussosedan†; ***Ital.***: Stillergy; Tetramil; Triaminic Flu; ***Malaysia***: Naphcon-A; ***Mex.***: Eyrasil; Istasol; Mirus; Opcon-A; Solutina; ***NZ***: Naphcon-A; Visine Allergy; ***Philipp.***: Decocon A; Irazol; Naphcon-A; Optaphen; Vistallerg; ***Pol.***: Fervex; Theraflu ExtraGRIP; ***Rus.***: Febricet (Фебрицет); Fervex (Фервекс); Flucoldin (Флуколдин); Grippoflu Extra Cold and Flu (Гриппофлю От Простуды И Гриппа); Influnorm (Инфлюнорм); Pentalgin (Пенталгин); Rinicold Hot-Mix (Риниколд ХотМикс); Rinzasip (Ринзасип); Rinzasip with Vitamin C (Ринзасип с Витамином С); Stopgripan (Стопгрипан); Theraflu (Терафлю); TheraFlu Flu and Cold (ТераФлю от Гриппа и Простуды Экстра); ***S.Afr.***: Calasthetic; Coff-Up†; Dristan Decongestant Nasal Mist†; ***Singapore***: Naphcon-A; ***Switz.***: Neo Citran Grippe/refroidissement; ***Thai.***: Naphcon-A; ***Turk.***: Antibeksin; ***UAE***: Histol Exp†; ***Ukr.***: Grippocitron (Гриппоцитрон); Milistan Hot Tea for Children Orange (Мілістан Гарячий Чай Для Дітей Зі Смаком Апельсина); Milistan Hot Tea Lemon (Мілістан Гарячий Чай Зі Смаком Лимона); Rinza Hotsip (Ринза Хотсип); Rinza Hotsip with Vitamin C (Ринза Хотсип с Витамином С); Stopgripan (Стопгрипан)†; Theraflu (Терафлю); Theraflu Extra (Терафлю Экстра); TheraFlu Flu and Cold (Терафлю Від Грипу Та Застуди); ***USA***: Dristan Nasal Spray; Naphazoline Plus†; Naphcon-A; Naphoptic-A; Ocuhist; Opcon-A; Scot-Tussin Original 5-Action; TheraFlu Cold & Cough; Tussirex; Visine-A; ***Venez.***: Soluclear; Tempragrip.

Pharmacopoeial Preparations
USP 36: Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution.

Phenyltoloxamine Citrate *(BANM, rINNM)*

C-5581H (phenyltoloxamine); Citrato de feniltoloxamina; Feniltoloxamina, citrato de; Phényltoloxamine, Citrate de; Phenyltoloxamini Citras; Phenyltolyloxamine Citrate; PRN (phenyltoloxamine); Фенилтолоксамина Цитрат.
2-(2-Benzylphenoxy)-*NN*-dimethylethylamine dihydrogen citrate.
$C_{17}H_{21}NO,C_6H_8O_7$=447.5
CAS — 92-12-6 (phenyltoloxamine); 1176-08-5 (phenyltoloxamine citrate).
UNII — 8UE48MJH8M.

Pharmacopoeias. In *US*.

USP 36: (Phenyltoloxamine Citrate). A white crystalline powder. Very soluble in boiling water; slightly soluble in cold water and in alcohol; practically insoluble in cold acetone, in solvent ether, and in toluene. pH of a 1% solution in water is between 3.2 and 4.2.

Profile

Phenyltoloxamine citrate, a monoethanolamine derivative, is a sedating antihistamine (p. 610.1). It is usually given orally in combination preparations with a decongestant or analgesic. Phenyltoloxamine citrate has been used in nasal preparations. Phenyltoloxamine polistirex has also been given orally.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Codipront†; ***Braz.***: Setux Expectorante; Setux; ***Canad.***: Tussionex; ***Chile***: Matinor; Sinutab; ***Fr.***: Biocidan; ***Hong Kong***: Codipront; ***Indon.***: Codipront cum Expectorant; Codipront cum Expectorant; Codipront; ***Israel***: Codivis; ***Philipp.***: Sinutab PE; ***Port.***: Codipront; ***Rus.***: Orinol Plus (Оринол Плюс); ***S.Afr.***: Adco-Sinal Co; Dequa-Flu†; Pholtex Linctus; Sinustop with Codeine†; Sinustop†; Sinutab with Codeine; Sinutab†; Suncodin; ***Switz.***: Codipront†; ***Thai.***: Codipront; ***Turk.***: Benzoleks†; ***USA***: Anabar†; Be-Flex Plus†; Biphenox; BP Poly-650; By-Ache†; Cafgesic Forte†; Chlorex-A†; Combiflex ES†; Combiflex†; Comhist LA; Digex NF; Digex†; Durabac Forte; Durabac; Duraxin†; Flextra; Hyflex†; Lagesic; Levacet; Lobac†; Major-gesic; Momentum; Nalex-A†; Norel SR; Pain-gesic; Phenylgesic; Relagesic; Staflex; Tetra-Mag†; ZFlex; Zgesic; ***Venez.***: Codipront.

Pimethixene *(rINN)*

BP-400; Piméthixène; Pimethixenum; Pimetixene; Pimetixeno; Пиметиксен.
9-(1-Methyl-4-piperidylidene)thioxanthene.
$C_{19}H_{19}NS$=293.4
CAS — 314-03-4.
ATC — R06AX23.
ATC Vet — QR06AX23.
UNII — T46J20J26F.

Profile

Pimethixene is reported to be a sedating antihistamine (p. 610.1) and an inhibitor of serotonin. It is given to children in usual oral doses of about 1.8 to 5.5 mg daily for coughs. It has been used as a sedative and for the treatment of respiratory disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Ansiotex; Muricalm; ***Fr.***: Calmixene.

Multi-ingredient Preparations. ***Braz.***: Santussal.

Piprinhydrinate *(BAN, rINN)*

Diphenylpyraline Teoclate; Diphenylpyraline Theoclate; Piprinhidrinato; Piprinhydrinatum; Пипрингидринат.
The diphenylpyraline salt of 8-chlorotheophylline; 4-Benzhydryloxy-1-methylpiperidine salt of 8-chlorotheophylline.
$C_{19}H_{23}NO,C_7H_7ClN_4O_2$=496.0
CAS — 606-90-6.
UNII — SI78RFJ7XI.

Profile

Piprinhydrinate, a piperidine derivative, is an antihistamine (p. 610.1) that has been given orally as an ingredient of compound preparations for the symptomatic relief of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Plokon†.

Promethazine *(BAN, rINN)*

Prometatsiini; Prometazin; Prometazina; Prométhazine; Promethazinum; Прометазин.
Dimethyl (1-methyl-2-phenothiazin-10-ylethyl)amine.
$C_{17}H_{20}N_2S$=284.4
CAS — 60-87-7.
ATC — D04AA10; R06AD02.
ATC Vet — QD04AA10; QR06AD02.
UNII — FF28EJQ494.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of promethazine:
Finegan; Finnagan.

Promethazine Hydrochloride *(BANM, rINNM)*

Diprazinum; Hidrocloruro de prometazina; Proazamine Chloride; Prometatsiinihydrokloridi; Prometazin Hidroklorür; Prometazina, hidrocloruro de; Prometazin-hidroklorid; Prometazinhydroklorid; Prometazino hidrochloridas; Prometazyny chlorowodorek; Prométhazine, chlorhydrate de; Promethazin-hydrochlorid; Promethazinhydrochlorid; Promethazini Hydrochloridum; Promethazinium Chloride; Прометазина Гидрохлорид.
$C_{17}H_{20}N_2S,HCl$=320.9
CAS — 58-33-3.
ATC — D04AA10; R06AD02.
ATC Vet — QD04AA10; QR06AD02.
UNII — R61ZEH7I1I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Promethazine Hydrochloride). A white or faintly yellowish, crystalline powder. Very soluble in water; freely soluble in alcohol and in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Promethazine Hydrochloride). A white to faint yellow, practically odourless, crystalline powder. Slowly oxidises and acquires a blue colour on prolonged exposure to air. Freely soluble in water, in hot dehydrated alcohol, and in chloroform; practically insoluble in acetone, in ether, and in ethyl acetate. pH of a 5% solution in water is between 4.0 to 5.0. Store in airtight containers. Protect from light.

Adsorption. The adsorption of promethazine hydrochloride onto various glass and plastic containers and infusion systems has been studied.[1-4] Factors affecting the degree of adsorption included the particular material tested and the pH of the solution.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
3. Rhodes RS, *et al.* Stability of meperidine hydrochloride, promethazine hydrochloride, and atropine sulfate in plastic syringes. *Am J Hosp Pharm* 1985; **42:** 112–5.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Incompatibility. Solutions of promethazine hydrochloride are incompatible with alkaline substances, which precipitate the insoluble promethazine base. Compounds reported to be incompatible with promethazine hydrochloride include aminophylline, barbiturates, benzylpenicillin salts, carbenicillin sodium, chloramphenicol sodium succinate, chlorothiazide sodium, cefmetazole sodium, cefoperazone sodium, cefotetan disodium, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), furosemide, heparin sodium, hydrocortisone sodium succinate, meticillin sodium, morphine sulfate, nalbuphine hydrochloride, and some contrast media and parenteral nutrient solutions.

Promethazine Teoclate *(BAN, rINN)*

Prometazina, teoclato de; Prométhazine, Téoclate de; Promethazine Theoclate; Promethazini Teoclas; Teoclato de prometazina; Прометазина Теоклат.
The promethazine salt of 8-chlorotheophylline .
$C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$=499.0
CAS — 17693-51-5.
ATC — D04AA10; R06AD02.
ATC Vet — QD04AA10; QR06AD02.
UNII — S5PUP23U26.

Pharmacopoeias. In *Br.*

BP 2014: (Promethazine Teoclate). A white or almost white, odourless or almost odourless powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. Protect from light.

Uses and Administration

Promethazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and some serotonin-antagonist properties. It is usually given as the hydrochloride or teoclate. Promethazine embonate and promethazine maleate have also been given orally. Promethazine dioxide (dioxopromethazine) has been used as the hydrochloride in eye and nasal drops. The antihistamine action has been reported to last for between 4 and 12 hours.

Promethazine hydrochloride is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p. 611.1).

Promethazine hydrochloride and promethazine teoclate are used for their antiemetic action in the prevention and treatment of nausea and vomiting in conditions such as motion sickness, drug-induced vomiting, and postoperative vomiting (p. 611.3). They are also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p. 612.3). Promethazine hydrochloride is also employed pre- and postoperatively in surgery and obstetrics for its sedative effects and for the relief of apprehension (see Anaesthesia, p. 610.3); it is often given with pethidine hydrochloride. Promethazine hydrochloride may be used for night-time sedation (see Insomnia, p. 611.2).

Promethazine hydrochloride is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

The following doses have been given **orally**.

- For the treatment of *allergic conditions* promethazine hydrochloride is usually given in a dose of 25 mg at night increased to 25 mg twice daily if necessary; owing to its pronounced sedative effect it is preferably given at night but an alternative dose is 10 to 20 mg two or three times daily.
- Promethazine hydrochloride is given in doses of 20 to 50 mg at night for the short-term management of *insomnia* although its prolonged duration of action can lead to considerable drowsiness the following day.
- For the prevention of *motion sickness* promethazine hydrochloride can be given in a dose of 20 or 25 mg the night before travelling followed by a similar dose the following morning if necessary. The teoclate is used similarly. For the prevention of motion sickness the dose of promethazine teoclate is 25 mg given either on the night, or one to two hours, before travelling. For the treatment of motion sickness, a dose of promethazine teoclate 25 mg may be given as soon as possible and repeated in the evening, followed by a third dose the next evening.
- For nausea and vomiting arising from causes such as *labyrinthitis* a dose of promethazine teoclate 25 mg at night is usually adequate; this may be increased to 50 or 75 mg at night or to 25 mg two or three times daily if necessary to a maximum of 100 mg daily.
- For *severe vomiting in pregnancy* the *BNF* recommends a dose of promethazine teoclate 25 mg at night, increased if necessary to a maximum of 100 mg.

Promethazine hydrochloride is also given by the **rectal** route as suppositories. Doses are similar to those given orally.

Promethazine hydrochloride is given **parenterally** by deep intramuscular injection as a solution of 25 or 50 mg/mL. It may also be given by slow intravenous injection or injected into the tubing of a freely running infusion in a concentration of not more than 25 mg/mL, although it is usually diluted to 2.5 mg/mL. The rate of infusion should not exceed 25 mg/minute. The usual parenteral dose for all indications apart from nausea and vomiting is 25 to 50 mg; a dose of 100 mg should not be exceeded. Doses of 12.5 to 25 mg, repeated at intervals of not less than 4 hours, may be given for the treatment of nausea and vomiting, although not more than 100 mg is usually given in 24 hours.

For doses in children, see p. 639.1.

Promethazine has been used **topically** to provide relief in hypersensitivity disorders of the skin and for burns but, as with other antihistamines, it may produce skin sensitisation.

Administration in children. Promethazine may be given to children **orally**, dosage being dependent on age, indication, and the salt used.

For *allergic conditions*, promethazine hydrochloride can be given as follows:

- children aged 2 to 5 years: 5 to 15 mg daily in one or two divided doses
- those aged 5 to 10 years: 10 to 25 mg daily in one or two divided doses

For *night sedation or premedication*, promethazine hydrochloride can be given as follows:

- children aged 2 to 5 years: 15 to 20 mg
- those aged 5 to 10 years: 20 to 25 mg

For the prevention of *motion sickness*, the following doses of promethazine hydrochloride may be given the night before the journey and repeated on the following morning (6 to 8 hours later) if necessary:

- children aged 2 to 5 years: 5 mg
- those aged 5 to 10 years: 10 mg

Promethazine teoclate may also be given orally to children aged 5 to 10 years for the prevention of motion sickness in a dose of 12.5 mg given either on the night, or one to two hours, before travelling. For the treatment of motion sickness, a dose of promethazine teoclate 12.5 mg may be given as soon as possible and repeated in the evening, followed by a third dose the next evening.

Children aged 5 to 10 years may also receive promethazine teoclate for nausea and vomiting from causes such as *labyrinthitis* in a dose of 12.5 to 37.5 mg daily.

Children aged over 10 years may be given oral promethazine in doses similar to those used in adults (see p. 638.3).

Children aged 5 to 10 years may be given 6.25 to 12.5 mg of promethazine hydrochloride by deep **intramuscular** injection, for *allergic conditions* or *sedation*. Older children may be given the usual adult dose (see above).

Although not licensed in the UK for children aged under 2 years, the *BNFC* suggests those aged 1 month to 12 years may be given promethazine hydrochloride for *sedation in intensive care*. A dose of 0.5 to 1 mg/kg (to a maximum of 25 mg), four times daily, **orally**, or by deep **intramuscular** or **slow intravenous** injection has been suggested, adjusted according to response. Adolescents aged 12 to 18 years may be given 25 to 50 mg four times daily.

Sedation. For reference to the use of lytic cocktails of chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see under Pethidine, p. 122.2.

Adverse Effects

As for the sedating antihistamines in general, p. 613.1.

Cardiovascular adverse effects are more commonly seen after injection, and bradycardia, tachycardia, transient minor increases in blood pressure, and occasional hypotension have all been reported with promethazine hydrochloride. Jaundice and blood dyscrasias have been reported, and extrapyramidal effects may occur at high doses.

Parenteral administration of promethazine may cause various problems, ranging from pain and burning, to paralysis, thrombophlebitis, severe spasm of distal vessels, necrosis, and gangrene; such adverse effects are particularly seen after inadvertent intra-articular injection.

Overdosage. A toxic neurological syndrome, which included CNS depression, acute excitomotor manifestations, ataxia and visual hallucinations, plus peripheral antimuscarinic effects developed in 2 children aged 44 months and 16 months after topical application of a 2% promethazine cream providing between 12.9 and 26 mg/kg.[1] The older child had also received hydroxyzine 10 mg orally 1 hour earlier.

1. Shawn DH, McGuigan MA. Poisoning from dermal absorption of promethazine. *Can Med Assoc J* 1984; **130:** 1460–1.

Sudden infant death syndrome. Although some early reports raised the possibility of an association between the use of phenothiazine antihistamines and the sudden infant death syndrome (SIDS) this has not been confirmed. Following an initial report that 4 of 7 infants with SIDS had been given alimemazine before death and that a series of severe apnoeic crises had been seen in the twin of a SIDS victim given promethazine,[1] the same workers studied 52 SIDS victims, 36 near-miss infants (those who had had severe unexplained episodes of cyanosis or pallor during sleep), and 175 control subjects to investigate the role of nasopharyngitis and phenothiazines in this syndrome.[2] They found that there was no difference in the incidence of nasopharyngitis between the 3 groups, but the proportion of infants given phenothiazines was higher in both the SIDS group (23%) and the near-miss group (22%) than in the control group (2%). In a subsequent study,[3] they found that the incidence of central and obstructive sleep apnoeas was increased in 4 healthy infants given promethazine for 3 days, although the duration of the attacks was unaltered and generally short, with a range of 3 to 10 seconds. A report on behalf of the European Commission,[4] stated that no link between sudden deaths in infants and drug use had been confirmed by national drug monitoring centres. It was likely that the risk of apnoea was associated with all sedative drugs, especially in overdose.[4] Previously, phenothiazine-induced hyperthermia had been proposed as a contributory factor in SIDS.[5]

For general precautions regarding the use of antihistamines in children, see p. 614.1.

1. Kahn A, Blum D. Possible role of phenothiazines in sudden infant death. *Lancet* 1979; **ii:** 364–5.
2. Kahn A, Blum D. Phenothiazines and sudden infant death syndrome. *Pediatrics* 1982; **70:** 75–8.
3. Kahn A, *et al*. Phenothiazine-induced sleep apneas in normal infants. *Pediatrics* 1985; **75:** 844–7.
4. Cockfield. Phenergan, Theralene, Algotropyl—drugs responsible for the death of new-born babies. *Off J EC* 1986; **29:** C130/25–6.
5. Stanton AN. Sudden infant death syndrome and phenothiazines. *Pediatrics* 1983; **71:** 986–7.

Precautions

As for the sedating antihistamines in general, p. 613.3.

Intravenous injections of promethazine hydrochloride must be given slowly and extreme care must be taken to avoid extravasation or inadvertent intra-arterial injection, because of the risk of severe irritation and tissue damage. Deep intramuscular injection is preferred but may be painful; promethazine should not be given by subcutaneous injection.

False negative and positive results have been reported with some pregnancy tests.

Anaesthesia. In 8 healthy subjects promethazine 25 mg intravenously decreased lower oesophageal sphincter pressure and increased the incidence of gastro-oesophageal reflux.[1] It might, therefore, increase the risk of regurgitation and aspiration of gastric contents during induction of and recovery from anaesthesia. The effect was attributed to the antimuscarinic properties of promethazine.

1. Brock-Utne JG, *et al*. The action of commonly used antiemetics on the lower oesophageal sphincter. *Br J Anaesth* 1978; **50:** 295–8.

Children. A possible association between phenothiazine sedatives and sudden infant death syndrome has been suggested, but has not been confirmed (see under Adverse Effects, above). The current view in the UK and USA is that promethazine should not be given to children under 2 years of age.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies promethazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p. 614.2.

Renal impairment. Phenothiazine-induced toxic psychosis occurred in a patient with chronic renal failure who had been given promethazine.[1]

1. McAllister CJ, *et al*. Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; **10:** 191–5.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Promethazine is well absorbed after oral or intramuscular doses and peak plasma concentrations occur 2 to 3 hours after a dose by these routes, although there is low systemic bioavailability after oral doses, due to high first-pass metabolism in the liver. Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Values ranging from 76 to 93% have been reported for plasma-protein binding. Promethazine undergoes extensive metabolism, mainly to promethazine sulfoxide, and also to *N*-desmethylpromethazine. It is excreted slowly via the urine and bile, chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported.

References.

1. Taylor G, *et al*. Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man. *Br J Clin Pharmacol* 1983; **15:** 287–93.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
3. Stavchansky S, *et al*. Bioequivalence and pharmacokinetic profile of promethazine hydrochloride suppositories in humans. *J Pharm Sci* 1987; **76:** 441–5.
4. Strenkoski-Nix LC, *et al*. Pharmacokinetics of promethazine hydrochloride after administration of rectal suppositories and oral syrup to healthy subjects. *Am J Health-Syst Pharm* 2000; **57:** 1499–1505.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fenergan; ***Austral.***: Avomine; Fenezal; Phenergan; ***Belg.***: Phenergan; ***Braz.***: Alergiderm†; Cremefenergan; Fenergan; Pamergan; Profergan; Promergan; Prometazol; ***Canad.***: Histantil; ***Cz.***: Prothazin; ***Denm.***: Phenergan; ***Fr.***: Phenergan; ***Ger.***: Atosil; Closin; Proneurin†; Prothanon†; ***Gr.***: Phenergan; Titanox; ***Hong Kong***: Anvomin; Fenamin†; Fenazin†; Promin†; Synvomin†; Uni-Prozine†; Xepagan; ***Hung.***: Pipolphen; ***India***: Avomine; Ceedokid; Emin; Emispan; Histazine; Normagan; Phenergan; ***Indon.***: Nufapreg; Phenergan†; ***Irl.***: Phenergan; ***Israel***: Prothiazine; ***Ital.***: Fargan; Farganesse; Fenazil; ***Malaysia***: Votazine; Zoralix; ***Norw.***: Phenergan; ***NZ***: Allersoothe; Avomine; Phenergan; ***Philipp.***: Metagon; Phenerzin; Promet; Promezin; Zinmet; ***Pol.***: Diphergan; Polfergan; ***Port.***: Fenergan; ***Rus.***: Pipolphen (Пипольфен); Pipolzine (Пипользин); ***S.Afr.***: Avomine; Brunazine; Daralix†; Lenazine; Phenergan; Prohist; Receptozine; ***Singapore***: Fenazin; Phenergan; Promagen; Prozine; Synvomin; Votazine; Xepagan; ***Spain***: Fenergan Topico; Frinova†; ***Swed.***: Lergigan; ***Thai.***: Meta†; Phenergan; Procodyl; ***UAE***: Histaloc; ***UK***: Avomine; Phenergan; Sominex; Vertigon; Ziz; ***Ukr.***: Pipolphen (Пиполфен); ***USA***: Phenadoz; Phenergan; Promethegan.

Multi-ingredient Preparations. ***Austral.***: Painstop Night-Time Pain Reliever; Panquil†; Tixylix Night†; ***Braz.***: Dorilen; Doriless; Fenergan Expectorante; Lisador; Lisantil; Sedador; ***China***: Fufang Dan An Pian (复方胆氨片); Fufang Lixueping (复方利血平); Ke Li An (克立安); Kefei (可非); ***Cz.***: Coldrex Nite; ***Fr.***: Algotropyl; Fluisedal; Rhinathiol Promethazine; Transmer†; Tussisedal; ***Ger.***: Prothazin; ***Hong Kong***: Against Cough†; Coughlin†; Dhasedyl; Double 'P' Syrup†; Ephedyl-DM†; Ephedyl†; Ephendyln†; Fendil†; Fendyl; Marsedyl II†; Marsedyl†; Methorsedyl; Mucoprom; Nosazine†; P.E.D.†; PEC; Pecolin†; Phensedyn; Pholix†; Promethazine Compound Linctus†; Prosedyl†; Rhinathiol Promethazine; Sedylin†; Tripe P; Wel-Coplex†; ***India***: Ceedokid Plus; Childryl; Crophen; Emispan Plus; Emispan-H; Febrinil-P; Fevomax; Fevril; Ficlo-P; Kelvin Plus; Kelvin-P; Lincotuss-P; Nimkair-F; Paral-P; Paratel Plus; Tixylix; ***Indon.***: Berlifed; Halmezin; Neo Davenol†; Phenadex; Prome; Promedex; Promethazine Ikapharmindo; ***Irl.***: Night Nurse; ***Israel***: Promethazine Expectorants; Prothiazine Expectorant; ***Ital.***: Nuleron; Tachinotte; ***Malaysia***: Axcel Dextrozine; CP Cough Syrup; Dextrodyl; Dextromethorphan Compound; Dhasedyl DM; Hosedyl DM; Mucoease Plus; Mucoprom; Phensedyl Dry Cough; Rhinathiol Promethazine; Russedyl Plus; Sedilix DM; Sinovid; ***Neth.***: Promethazine comp†; ***NZ***: Tixylix; ***Rus.***: Coldrex Nite (Колдрекс Найт); Prothiazine Expectorant (Протиазин Экспекторант); ***S.Afr.***: Acustop†; Adco-Kiddipayne; Adco-Salterpyn; Ban Pain; Brunacod†; Colcaps; Dequa-Coff; Fevapar†; Go-Pain; Goldgesic; Histodor†; Infacet†; Infapain Forte; Kid-Eeze; Lenazine Forte; Lentogesic; Medipyn; Megapyn†; Mepromol†; Painagon; Pedpain†; Phensedyl; Pynmed; Stilpane; Stopayne; Tenston; Tixylix†; Vacudol†; ***Singapore***: Beacodyl; Cophadyl-E; Cophadyl; Dhasedyl DM; Dhasedyl; Ephedyl DM; Ephedyl; Phensedyl; Procodin; Promedyl; Promelix; Rhinathiol Promethazine; Sedilix DM; Sedilix; SP-Codrine; SP-Cosedyl; Sunsedyl; ***Spain***: Actithiol Antihist; Fenergan Expectorante; Psicosoma; ***Swed.***: Lergigan comp; ***Switz.***: Rhinathiol Promethazine†; ***Thai.***: Codyl; Cofcodyl; Comodine Cough; Decos†; Nordyl†; Nortuss†; Phencodin†; Phensedyl; Poly-Cof†; Teradyl†; Tussidyl; ***Turk.***: Artu; ***UAE***: Flukit; ***UK***: Day & Night Nurse; Night Nurse; Pamergan P100; Tixylix Night-Time†; ***USA***: Meprozine†; Pentazine VC with Codeine; Phenameth DM; Pherazine DM; Pherazine VC with Codeine; Pherazine VC; Pherazine with Codeine; Prometh VC Plain†; Prometh with Dextromethorphan; Promethazine VC with Codeine; ***Venez.***: Preveral con Codeina; Preveral con Dextrometorfano.

Pharmacopoeial Preparations

BP 2014: Promethazine Hydrochloride Tablets; Promethazine Injection; Promethazine Oral Solution; Promethazine Teoclate Tablets;

USP 36: Promethazine Hydrochloride Injection; Promethazine Hydrochloride Suppositories; Promethazine Hydrochloride Syrup; Promethazine Hydrochloride Tablets.

Propiomazine *(BAN, USAN, rINN)*

CB-1678 (propiomazine or propiomazine maleate); Propiomatsiini; Propiomazin; Propiomazina; Propiomazinum; Wy-1359 (propiomazine or propiomazine maleate); Пропиомазин.

1-[10-(2-Dimethylaminopropyl)phenothiazin-2-yl]propan-1-one.

$C_{20}H_{24}N_2OS$=340.5

CAS — 362-29-8.

ATC — N05CM06.

ATC Vet — QN05CM06.

UNII — 242Z0PM79Y.

Propiomazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propiomazina; Propiomazine, Chlorhydrate de; Propiomazini Hydrochloridum; Пропиомазина Гидрохлорид.

$C_{20}H_{24}N_2OS,HCl$=376.9

CAS — 1240-15-9.

ATC — N05CM06.

ATC Vet — QN05CM06.

UNII — 70BO17YR03.

Propiomazine Maleate *(BANM, rINNM)*

CB-1678 (propiomazine or propiomazine maleate); Maleato de propiomazina; Propiomazina, maleato de; Propiomazine Hydrogen Maleate; Propiomazine, Maléate de; Propiomazini Maleas; Wy-1359 (propiomazine or propiomazine maleate); Пропиомазина Малеат.

$C_{20}H_{24}N_2OS,C_4H_4O_4$=456.6

CAS — 3568-23-8.

ATC — N05CM06.

ATC Vet — QN05CM06.

Profile

Propiomazine, a phenothiazine derivative, is a sedating antihistamine (p. 610.1) that has been used for its sedative and antiemetic properties in insomnia (p. 611.2) and nausea and vomiting (p. 611.3).

Propiomazine is given as the maleate but doses are expressed in terms of the base; propiomazine maleate 1.3 mg is equivalent to about 1 mg of propiomazine. Doses equivalent to 25 to 50 mg orally at night have been given as a hypnotic.

Propiomazine hydrochloride has been given parenterally.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propiomazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Swed.***: Propavan.

Quifenadine Hydrochloride *(rINNM)*

Hidrocloruro de quifenadina; Quifénadine, Chlorhydrate de; Quifenadini Hydrochloridum; Хифенадина Гидрохлорид.

α,α-Diphenyl-3-quinuclidinemethanol hydrochloride.

$C_{20}H_{23}NO,HCl$=329.9

CAS — 10447-39-9 (quifenadine); 10447-38-8 (quifenadine hydrochloride).

ATC — R06AX31.

ATC Vet — QR06AX31.

Profile

Quifenadine is an antihistamine given orally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Phencarol (Фенкарол); ***Ukr.***: Phencarol (Фенкарол).

Rupatadine *(rINN)*

Rupatadina; Rupatadinum; Рупатадин.

8-Chloro-6,11-dihydro-11-{1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene}-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

$C_{26}H_{26}ClN_3$=416.0

CAS — 158876-82-5.

ATC — R06AX28.

ATC Vet — QR06AX28.

UNII — 2AE8M83G3E.

Rupatadine Fumarate *(rINNM)*

Fumarato de rupatadina; Rupatadine, Fumarate de; Rupatadini Fumaras; UR-12592 Fumarate; Рупатадина Фумарат.

8-Chloro-6,11-dihydro-11-{1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene}-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (*E*)-2-butenedioate.

$C_{26}H_{26}ClN_3,C_4H_4O_4$=532.0

CAS — 182349-12-8.

ATC — R06AX28.

ATC Vet — QR06AX28.

Profile

Rupatadine is an antihistamine with platelet-activating factor (PAF) antagonist activity that is used for the treatment of allergic rhinitis (p. 612.1) and chronic idiopathic urticaria (p. 612.3). It is given as the fumarate although doses are expressed in terms of the base; rupatadine fumarate 12.8 mg is equivalent to about 10 mg of rupatadine. The usual oral dose is the equivalent of 10 mg once daily of rupatadine.

References.

1. Izquierdo I, *et al.* Rupatadine: a new selective histamine H1 receptor and platelet-activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today* 2003; **39:** 451–68.
2. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007; **67:** 457–74.
3. Fantin S, *et al.* International Rupatadine study group. A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008; **63:** 924–31.
4. Valero A, *et al.* Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain. *Drug Safety* 2009; **32:** 33–42.

Effects on the cardiovascular system. Licensed product information states that the cardiac safety of rupatadine has been assessed; no adverse ECG effects were noted when rupatadine was given in doses of up to 10 times the normal dose. Nevertheless, it is recommended that rupatadine is used with caution in patients with known prolongation of the QT interval, uncorrected hypokalaemia, or conditions such as bradycardia or acute myocardial ischaemia.

A review of Spanish and Portuguese spontaneous reporting scheme data found 5 cases of heart rhythm disturbances in patients taking rupatadine.[1] Such effects included palpitations and tachycardia and 1 case of torsade de pointes in an elderly man.

1. Carvajal A, *et al.* Heart rhythm disturbances associated with rupatadine: a case series from the Spanish and Portuguese pharmacovigilance systems. *Clin Pharmacol Ther* 2009; **85:** 481–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rupafin; ***Austria***: Rupafin; ***Belg.***: Rupatall; ***Braz.***: Rupafin; ***Cz.***: Tamalis; ***Fr.***: Wystamm; ***Ger.***: Rupafin†; Urtimed; ***Gr.***: Rupafin; ***India***: Levostar-R; ***Irl.***: Rupafin; ***Ital.***: Pafinur; Rupafin; ***Neth.***: Rupafin; ***Pol.***: Rupafin; ***Port.***: Rinialer; ***Spain***: Alergoliber; Riniáler; Rupafin; ***Thai.***: Rupafin; ***Turk.***: Rupafin; ***UK***: Rupafin.

Sequifenadine *(rINN)*

Bicarphene (sequifenadine or sequifenadine hydrochloride); Bikarfen (sequifenadine or sequifenadine hydrochloride); Sequifenadina; Séquifénadine; Sequifenadinum; Сехифенадин.

α,α-Di-*o*-tolyl-3-quinuclidinemethanol.

$C_{22}H_{27}NO$=321.5

CAS — 57734-69-7.

UNII — C7Q3TBR3FP.

Profile

Sequifenadine is an antihistamine used in a wide range of allergic conditions. A usual dose is 50 to 100 mg given orally 2 or 3 times daily. Sequifenadine is reported also to have antiserotonin properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Histafen (Гистафен); ***Ukr.***: Gistaphen (Гистафен).

Setastine Hydrochloride *(rINNM)*

EGIS-2062; EGYT-2062; Hidrocloruro de setastina; Setastina, hidrocloruro de; Sétastine, Chlorhydrate de; Setastini Hydrochloridum; Сетастина Гидрохлорид.

1-{2-[(*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]ethyl}hexahydro-1*H*-azepine hydrochloride.

$C_{22}H_{28}ClNO,HCl$=394.4

CAS — 64294-95-7 (setastine).

Profile

Setastine hydrochloride, a derivative of clemastine, is an antihistamine that has been claimed to have no sedative activity. It is given for the symptomatic relief of hypersensitivity disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Qi Qi (齐齐); ***Hung.***: Loderix†.

Terfenadine *(BAN, USAN, rINN)*

MDL-9918; RMI-9918; Terfenadiini; Terfenadin; Terfenadina; Terfenadinas; Terfénadine; Terfenadinum; Терфенадин.

1-(4-*tert*-Butylphenyl)-4-[4-(α-hydroxybenzhydryl)piperidino] butan-1-ol.

$C_{32}H_{41}NO_2$=471.7

CAS — 50679-08-8.

ATC — R06AX12.

ATC Vet — QR06AX12.

UNII — 7BA5G9Y06Q.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Terfenadine). A white or almost white, crystalline powder. It shows polymorphism. Very slightly soluble in water and in dilute hydrochloric acid; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Uses and Administration

Terfenadine, a piperidine derivative, is a non-sedating antihistamine. It does not have significant antimuscarinic actions. It has been used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and conjunctivitis (p. 611.1) and skin disorders such as urticaria (p. 612.3).

The maximum oral dose of terfenadine is 120 mg daily given either as 60 mg twice daily or 120 mg in the morning; a starting dose of 60 mg daily in a single dose or in two divided doses is recommended for rhinitis and conjunctivitis.

For dosage in renal impairment see below.

Administration in renal impairment. Half the usual oral daily dose of terfenadine (see above) has been suggested for patients with creatinine clearance less than 40 mL/minute.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1. Erythema multiforme and galactorrhoea have also been reported.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with terfenadine, particularly in association with raised blood concentrations (see Arrhythmias, below). To *reduce the risk* of developing such arrhythmias the recommended dose should **not** be exceeded and terfenadine should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of terfenadine, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance is **contra-indicated** (see Interactions, p. 641.1). If palpitations, dizziness, syncope, or convulsions occur terfenadine should be withdrawn and the patient investigated for potential arrhythmias.

Alopecia. Hair loss was associated with use of terfenadine in a 24-year-old patient.[1] Regrowth occurred when treatment was stopped.

1. Jones SK, Morley WN. Terfenadine causing hair loss. *BMJ* 1985; **291:** 940.

Arrhythmias. Ventricular arrhythmias including torsade de pointes have occurred with terfenadine at doses greater than those recommended[1] and also at normal doses in patients whose metabolism of terfenadine is impaired by drugs or by liver disease. Generalised convulsions and a quinine-like effect on the ECG have also been reported after a presumed overdose of terfenadine.[2] Consequently recommendations have been made to *reduce the risk* of developing serious arrhythmias (see Adverse Effects and Precautions, above, for details), including those from the UK CSM.[3,4] Terfenadine should be stopped immediately, and the patient evaluated for potential arrhythmias, in those who have syncope, palpitations, dizziness, or convulsions after taking terfenadine.

Studies[5] have suggested that the ventricular arrhythmias are due to terfenadine itself rather than its active metabolite fexofenadine (p. 629.1). Terfenadine has been shown to inhibit cardiac potassium channels, which results in prolongation of the QT interval, a risk factor for developing arrhythmias, while the non-sedating antihistamines cetir-

izine, fexofenadine, and loratadine have had no demonstrable effect[5,6] (see also p. 613.2).

1. MacConnell TJ, Stanners AJ. Torsades de pointes complicating treatment with terfenadine. *BMJ* 1991; **302:** 1469.
2. Davies AJ, *et al.* Cardiotoxic effect with convulsions in terfenadine overdose. *BMJ* 1989; **298:** 325.
3. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
4. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
5. Woolsey RL, *et al.* Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993; **269:** 1532–6.
6. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving terfenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] of 4 healthy lactating women given 60 mg of terfenadine every 12 hours for 48 hours, terfenadine was undetected in breast milk; its active metabolite, fexofenadine, was excreted in limited amounts.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Lucas BD, *et al.* Terfenadine pharmacokinetics in breast milk in lactating women. *Clin Pharmacol Ther* 1995; **57:** 398–402.

Effects on the liver. Three episodes of acute hepatitis with jaundice occurred in a patient taking terfenadine intermittently over a period of 17 months.[1] Liver function tests returned to normal after the drug was stopped. Two further cases[2] of cholestatic hepatitis associated with terfenadine have been reported. Again, liver function tests returned to normal after drug withdrawal. A study[3] by the Boston Collaborative Drug Surveillance Program of 210 683 patients who had received prescriptions for terfenadine concluded that the use of terfenadine was rarely associated with important idiopathic liver disease. The investigators found only 3 cases of acute liver disease where a causal connection to terfenadine could not be ruled out; all these patients had also received a hepatotoxic drug and had made a full recovery.

1. Larrey D, *et al.* Terfenadine and hepatitis. *Ann Intern Med* 1985; **103:** 634.
2. Sahai A, Villeneuve JP. Terfenadine-induced cholestatic hepatitis. *Lancet* 1996; **348:** 552–3.
3. Myers MW, Jick H. Terfenadine and risk of acute liver disease. *Br J Clin Pharmacol* 1998; **46:** 251–3.

Effects on the nervous system. Non-sedating effects on the CNS have been reported after a single dose of terfenadine;[1] these have included anxiety, palpitations, and insomnia. The UK manufacturers commented that clinical studies suggest that the incidence of such effects is similar to that seen after placebo.[2]

Workers who had described a generalised tonic-clonic seizure in a patient taking terfenadine[3] later reported that the patient had subsequently had a second unprovoked seizure[4] and now considered that terfenadine may not have been the cause of his original seizure. Convulsions have been reported after overdosage with terfenadine (see under Arrhythmias, p. 640.3).

The sedative effects of the older antihistamines and the lower incidence of such effects with the non-sedating antihistamines including terfenadine are discussed under Sedation on p. 613.2.

1. Napke E, Biron P. Nervous reactions after first dose of terfenadine in adults. *Lancet* 1989; **ii:** 615–16.
2. Masheter HC. Nervous reactions to terfenadine. *Lancet* 1989; **ii:** 1034.
3. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 241.
4. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 736.

Hypersensitivity. Terfenadine use was associated with 108 reports of skin reactions, including rashes, urticaria, angioedema, photosensitivity reactions and peeling of the skin of the hands or feet.[1]

1. Stricker BHCh, *et al.* Skin reactions to terfenadine. *BMJ* 1986; **293:** 536.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terfenadine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Terfenadine should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the triazole and imidazole antifungals such as itraconazole and ketoconazole, the macrolide antibacterials including clarithromycin, erythromycin, josamycin, and troleandomycin, the streptogramin antibacterial quinupristin/dalfopristin, the serotonin reuptake inhibitors citalopram, fluoxetine, fluvoxamine, nefazodone, and paroxetine, the HIV-protease inhibitors, the NNRTIs delavirdine and efavirenz, and zileuton. The metabolism of terfenadine may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, probucol, pentamidine isetionate, and the beta blocker sotalol should be avoided as should diuretics that cause electrolyte imbalances especially hypokalaemia. The use of terfenadine and astemizole together is not recommended.

General references.

1. Kivistö KT, *et al.* Inhibition of terfenadine metabolism: pharmacokinetic and pharmacodynamic consequences. *Clin Pharmacokinet* 1994; **27:** 1–5.

Antibacterials. Pharmacokinetic studies have shown that the macrolide antibacterials *erythromycin*[1] and *clarithromycin*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with erythromycin[3] or *troleandomycin*.[4]

1. Honig PK, *et al.* Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; **52:** 231–8.
2. Honig P, *et al.* Effect of erythromycin, clarithromycin and azithromycin on the pharmacokinetics of terfenadine. *Clin Pharmacol Ther* 1993; **53:** 161.
3. Biglin KE, *et al.* Drug-induced torsades de pointes: a possible interaction of terfenadine and erythromycin. *Ann Pharmacother* 1994; **28:** 282.
4. Fournier P, *et al.* Une nouvelle cause de torsades de pointes: association terfenadine et troleandomycine. *Ann Cardiol Angeiol (Paris)* 1993; **42:** 249–52.

Antidepressants. Cardiac abnormalities have been reported in 2 patients taking *fluoxetine* with terfenadine.[1,2] Similarly, the use of *nefazodone* with terfenadine has resulted in prolongation of the QT interval.[3]

1. Swims MP. Potential terfenadine-fluoxetine interaction. *Ann Pharmacother* 1993; **27:** 1404–5.
2. Marchiando RJ, Cook MD. Probable terfenadine-fluoxetine-associated cardiac toxicity. *Ann Pharmacother* 1995; **29:** 937–8.
3. Abernethy DR, *et al.* Loratadine and terfenadine interaction with nefazodone: both antihistamines are associated with QTc prolongation. *Clin Pharmacol Ther* 2001; **69:** 96–103.

Antiepileptics. For reference to an interaction between terfenadine and *carbamazepine*, see p. 517.2.

Antifungals. Pharmacokinetic studies have shown that *itraconazole*[1] and *ketoconazole*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with ketoconazole[3] or itraconazole.[1,4] While there has been a pharmacokinetic study[5] that suggested that the interaction between terfenadine and *fluconazole* might not be clinically significant, as the mechanism of the interaction appeared to involve the metabolite of terfenadine and did not lead to accumulation of the cardiotoxic parent compound, this may not always be the case. Studies in a small group of patients who had abnormal patterns of terfenadine metabolism found increases in terfenadine concentrations associated with ECG abnormalities when terfenadine was given with high doses of fluconazole.[6]

1. Pohjola-Sintonen S, *et al.* Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. *Eur J Clin Pharmacol* 1993; **45:** 191–3.
2. Honig PK, *et al.* Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. *JAMA* 1993; **269:** 1513–18.
3. Monahan BP, *et al.* Torsades de pointes occurring in association with terfenadine use. *JAMA* 1990; **264:** 2788–90.
4. Crane JK, *et al.* Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. *Am J Med* 1993; **95:** 445–6.
5. Honig PK, *et al.* The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin Pharmacol Ther* 1993; **53:** 630–6.
6. Cantilena LR, *et al.* Fluconazole alters terfenadine pharmacokinetics and electrocardiographic pharmacodynamics. *Clin Pharmacol Ther* 1995; **57:** 185.

Calcium-channel blockers. For reference to an interaction between terfenadine and *nifedipine*, see p. 1453.3.

Grapefruit juice. A study[1] in healthy subjects given terfenadine and grapefruit juice for 7 days found raised plasma-terfenadine concentrations and prolongation of the QT interval. These effects were less pronounced when terfenadine was given 2 hours before grapefruit juice, but were nevertheless quantifiable in some subjects. In another study QT interval changes were not found in healthy subjects given single doses of terfenadine and grapefruit juice.[2] However, the highly variable pharmacokinetics between individuals led the authors to conclude that prolongation of the QT interval was possible following single doses. The probable mechanism of the interaction is inhibition of the metabolism of terfenadine by the cytochrome P450 isoenzyme CYP3A4.

1. Benton RE, *et al.* Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. *Clin Pharmacol Ther* 1996; **59:** 383–8.
2. Rau SE, *et al.* Grapefruit juice-terfenadine single-dose interaction: magnitude, mechanism, and relevance. *Clin Pharmacol Ther* 1997; **61:** 401–9.

Pharmacokinetics

Terfenadine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 2 hours. It is a prodrug and undergoes extensive first-pass metabolism in the liver to its active metabolite the carboxylic acid derivative fexofenadine (p. 629.1). The other main metabolite is an inactive piperidine-carbinol derivative. About 97% of terfenadine is bound to plasma proteins; fexofenadine is reported to be less extensively bound. Terfenadine does not appear to cross the blood-brain barrier to a significant extent; limited amounts of fexofenadine, but not the parent drug, have been detected in breast milk. An elimination half-life of 16 to 23 hours has been reported for terfenadine. The metabolites, and traces of unchanged drug, are excreted in the urine and the faeces.

References.

1. Eller MG, *et al.* Pharmacokinetics of terfenadine in healthy elderly subjects. *J Clin Pharmacol* 1992; **32:** 267–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Min An Fen (敏安芬); ***Gr.***: Sminosan; Syneptine; Terfedin; Tricosal; Voromin; ***Hong Kong***: Histafen†; Tamagon†; ***India***: Daylert; Histafen; Trexyl; ***Indon.***: Alpenaso†; Histastop†; Terfin; ***S.Afr.***: Fendin†; ***Spain***: Ternadin; ***Turk.***: Teradin†.

Multi-ingredient Preparations. ***China***: Livzon Ganle (丽珠感乐); ***India***: Tusant; ***Indon.***: Rhinofed.

Pharmacopoeial Preparations

BP 2014: Terfenadine Oral Suspension; Terfenadine Tablets.

Thenyldiamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tenildiamina; Tenildiamina, hidrocloruro de; Thényldiamine, Chlorhydrate de; Thenyldiamini Hydrochloridum; Thenyldiaminium Chloride; Тенилдиамина Гидрохлорид.

NN-Dimethyl-*N'*-(2-pyridyl)-*N'*-(3-thenyl)ethylenediamine hydrochloride.

$C_{14}H_{19}N_3S$,HCl=297.8

CAS — 91-79-2 (thenyldiamine); 958-93-0 (thenyldiamine hydrochloride).

UNII — 7ZQC1892H9.

Profile

Thenyldiamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p. 610.1). It is given orally as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: NTR.

Thiethylperazine *(BAN, USAN, rINN)*

Thiéthylpérazine; Thiethylperazinum; Tietilperazina; Tietylperazin; Tietyyliperatsiini; Тиэтилперазин.

2-Ethylthio-10-[3-(4-methylpiperazin-1-yl)-propyl]phenothiazine.

$C_{22}H_{29}N_3S_2$=399.6

CAS — 1420-55-9.

ATC — R06AD03.

ATC Vet — QR06AD03.

UNII — 8ETK1WAF6R.

Thiethylperazine Malate *(BANM, rINNM)*

Malato de tietilperazina; Thiéthylpérazine, Malate de; Thiethylperazini Malas; Tietilperazina, malato de; Тиэтилперазина Малат.

$C_{22}H_{29}N_3S_2.2C_4H_6O_5$=667.8

CAS — 52239-63-1.

ATC — R06AD03.

ATC Vet — *QR06AD03.*
UNII — *HP46XK89XB.*

Thiethylperazine Maleate *(BANM, USAN, rINNM)*

GS-95; Maleato de tietilperazina; NSC-130044; Thiethylperazine Dimaleate; Thiéthylpérazine, Maléate de; Thiethylperazini Maleas; Tietilperazina, maleato de; Тиэтилперазина Малеат.

$C_{22}H_{29}N_3S_2.2C_4H_4O_4$=631.8

CAS — *1179-69-7.*
ATC — *R06AD03.*
ATC Vet — *QR06AD03.*
UNII — *RUK64CF26E.*

Pharmacopoeias. In *Swiss* and *US.*

USP 36: (Thiethylperazine Maleate). A yellowish granular powder, odourless or has not more than a slight odour. Soluble 1 in 1700 of water and 1 in 530 of alcohol; practically insoluble in chloroform and in ether; slightly soluble in methyl alcohol. pH of a 0.1% solution in water is between 2.8 and 3.8. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between injections of thiethylperazine maleate and nalbuphine hydrochloride.[1]

1. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; **39:** 841–3.

Profile

Thiethylperazine, a phenothiazine derivative with a piperazine side-chain, is a sedating antihistamine (p. 610.1) used as an antiemetic for the control of nausea and vomiting (p. 611.3) associated with surgical procedures and cancer therapy. It has also been used for the management of vertigo (p. 612.3) and motion sickness although there is some doubt over its efficacy for these indications.

Thiethylperazine is given as the maleate or malate and doses are expressed in terms of the appropriate salt. Thiethylperazine maleate 10 mg is equivalent to about 10.53 mg of thiethylperazine malate.

Thiethylperazine *maleate* is given in usual oral doses of 6.5 mg up to three times daily; the maleate has also been given rectally. Where oral dosage is impractical similar doses of the *malate* may be given by deep intramuscular injection.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiethylperazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Torecan; ***Cz.***: Torecan; ***Hung.***: Torecan; ***Ital.***: Torecan; ***Mex.***: Torecan; ***Pol.***: Torecan; ***Rus.***: Torecan (Торекан); ***Spain***: Torecan; ***Swed.***: Torecan†; ***Switz.***: Torecan.

Pharmacopoeial Preparations
USP 36: Thiethylperazine Maleate Suppositories; Thiethylperazine Maleate Tablets.

Thonzylamine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tonzilamina; Thonzylamine, Chlorhydrate de; Thonzylamini Hydrochloridum; Tonzilamina, hidrocloruro de; Тонзиламина Гидрохлорид.

N-p-Anisyl-*N'N'*-dimethyl-*N*-(pyrimidin-2-yl)ethylenediamine hydrochloride.

$C_{16}H_{22}N_4O$,HCl=322.8

CAS — *91-85-0 (thonzylamine); 63-56-9 (thonzylamine hydrochloride).*
ATC — *D04AA01; R01AC06; R06AC06.*
ATC Vet — *QD04AA01; QR01AC06; QR06AC06.*
UNII — *6K9YKD48Y4.*

Profile

Thonzylamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p. 610.1) that has been used for the symptomatic relief of hypersensitivity disorders. It has been given orally and applied topically as an ointment, but as with other antihistamines, there is a risk of skin sensitisation with the ointment. It is also used in nasal preparations for congestion, and in eye drops with a vasoconstrictor such as naphazoline nitrate for allergic conjunctivitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Tonamil.

Multi-ingredient Preparations. ***Ital.***: Ascotodin; Collirio Alfa Antistaminico; Imidazyl Antistaminico; Iristamina; Narlisim; Pupilla Antistaminico; ***Port.***: Narizima; ***USA***: NasOpen PE; Vanacof APE.

Trimethobenzamide Hydrochloride *(rINNM)*

Hidrocloruro de trimetobenzamida; Triméthobenzamide, Chlorhydrate de; Trimethobenzamidi Hydrochloridum; Trimetobenzamid Hidroklorür; Trimetobenzamida, hidrocloruro de; Триметобензамида Гидрохлорид.

N-[4-(2-Dimethylaminoethoxy)benzyl]-3,4,5-trimethoxybenzamide hydrochloride.

$C_{21}H_{28}N_2O_5$,HCl=424.9

CAS — *138-56-7 (trimethobenzamide); 554-92-7 (trimethobenzamide hydrochloride).*
UNII — *WDQ5P1SX7Q.*

Pharmacopoeias. In *US.*

USP 36: (Trimethobenzamide Hydrochloride). A white crystalline powder having a slight phenolic odour. Soluble 1 in 2 of water, 1 in 59 of alcohol, 1 in 67 of chloroform, and 1 in 720 of ether; insoluble in benzene.

Uses and Administration

Trimethobenzamide hydrochloride, a monoethanolamine derivative, is a sedating antihistamine used as an antiemetic in the control of nausea and vomiting (p. 611.3) including postoperative nausea and vomiting.

The usual dose is 300 mg orally or 200 mg by deep intramuscular injection three or four times daily. In 2007, the FDA ordered a stop to the marketing and distribution of rectal trimethobenzamide products, because they lack evidence of efficacy.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Dose adjustment should be considered for patients with any renal impairment.

Pain at the site of intramuscular injection and local irritation after rectal use have been noted.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including some evidence of an excess number of congenital abnormalities in infants born to mothers exposed to trimethobenzamide, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Maximum plasma concentrations may occur after about 30 minutes of giving trimethobenzamide intramuscularly, and about 45 minutes after oral use. Relative bioavailability between an oral dose of 300 mg and an intramuscular dose of 200 mg is believed to be similar. Between 30 to 50% of a single dose is excreted unchanged in the urine within 48 to 72 hours. The mean elimination half-life is about 7 to 9 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Ametik; Anti-Vomit; Emedur; Vomet; Vomitin; ***USA***: Ticon; Tigan.

Multi-ingredient Preparations. ***Turk.***: Emedur; ***USA***: Emergent-Ez.

Pharmacopoeial Preparations
USP 36: Trimethobenzamide Hydrochloride Capsules; Trimethobenzamide Hydrochloride Injection.

Tripelennamine Citrate *(BANM, rINNM)*

Citrato de tripelenamina; Tripelenamina, citrato de; Tripélennamine, Citrate de; Tripelennamini Citras; Tripelennaminium Citrate; Трипеленнамина Цитрат.

N-Benzyl-*N'N'*-dimethyl-*N*-(2-pyridyl)ethylenediamine dihydrogen citrate.

$C_{16}H_{21}N_3.C_6H_8O_7$=447.5

CAS — *91-81-6 (tripelennamine); 6138-56-3 (tripelennamine citrate).*
ATC — *D04AA04; R06AC04.*
ATC Vet — *QD04AA04; QR06AC04.*
UNII — *30OC46A3J9.*

Tripelennamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tripelenamina; Tripelenamina, hidrocloruro de; Tripélennamine, Chlorhydrate de; Tripelennamini Hydrochloridum; Tripelennaminium Chloride; Трипеленнамина Гидрохлорид.

$C_{16}H_{21}N_3$,HCl=291.8

CAS — *154-69-8.*
ATC — *D04AA04; R06AC04.*
ATC Vet — *QD04AA04; QR06AC04.*
UNII — *FWV8GJ56ZN.*

Pharmacopoeias. In *US.*

USP 36: (Tripelennamine Hydrochloride). A white crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 6 of alcohol and of chloroform, and 1 in 350 of acetone; insoluble in ether, in ethyl acetate, and in benzene. Its solutions are practically neutral to litmus. Protect from light.

Profile

Tripelennamine, an ethylenediamine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and moderate sedative properties. It has been used for the symptomatic relief of hypersensitivity reactions. It may also be used in compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

Tripelennamine has been given orally as the citrate or the hydrochloride. Tripelennamine hydrochloride has also been applied topically to the skin, although, as with other antihistamines, there is a risk of sensitisation.

Abuse. References to the intravenous abuse of tripelennamine alone[1] or with pentazocine in the combination known as T's and blues.[2-4]

1. Addington J, el-Guebaly N. Intravenous tripelennamine abuse in schizophrenia. *Can J Psychiatry* 1996; **41:** 63.
2. Showalter CV. T's and blues: abuse of pentazocine and tripelennamine. *JAMA* 1980; **244:** 1224–5.
3. von Almen WF, Miller JM. "Ts and Blues" in pregnancy. *J Reprod Med* 1986; **31:** 236–9.
4. McGwier BW, *et al.* Acute myocardial infarction associated with intravenous injection of pentazocine and tripelennamine. *Chest* 1992; **101:** 1730–2.

Overdosage. A severe toxic reaction, including agitation, hallucinations, and myoclonic jerks occurred in an 8-year-old child who was sprayed over the trunk and extremities with tripelennamine hydrochloride 2.1375 g in the treatment of severe poison ivy poisoning.[1] It was likely that inhalation of the fine mist of the aerosol spray contributed to the reaction but in this patient the initial reaction began 3 hours after exposure suggesting that percutaneous absorption through the multiple skin lesions probably contributed significantly. The original reaction was inadvertently prolonged by subsequent treatment with diphenhydramine hydrochloride and promethazine hydrochloride.

1. Schipior PG. An unusual case of antihistamine intoxication. *J Pediatr* 1967; **71:** 589–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Azaron; ***Austria***: Azaron; ***Canad.***: Vagin-X; ***Fin.***: Etono; ***Ger.***: Azaron; ***Indon.***: Tripel; ***Neth.***: Azaron; ***Spain***: Azaron.

Multi-ingredient Preparations. ***Arg.***: Quemicetina Nasal Compuesta; ***India***: Bradex-Vioform; ***Pol.***: Viosept†; ***Ukr.***: Viosept (Виосепт)†; ***USA***: Di-Delamine.

Pharmacopoeial Preparations
USP 36: Tripelennamine Hydrochloride Tablets.

Triprolidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de triprolidina; Triprolidina, hidrocloruro de; Triprolidine, Chlorhydrate de; Triprolidini Hydrochloridum; Трипролидина Гидрохлорид.

(*E*)-2-[3-(Pyrrolidin-1-yl)-1-*p*-tolylprop-1-enyl]pyridine hydrochloride monohydrate.

$C_{19}H_{22}N_2$,HCl,H_2O=332.9

CAS — *486-12-4 (triprolidine); 550-70-9 (anhydrous triprolidine hydrochloride); 6138-79-0 (triprolidine hydrochloride monohydrate).*
ATC — *R06AX07.*
ATC Vet — *QR06AX07.*
UNII — *YAN7R5L890.*

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Triprolidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Freely soluble in water and in alcohol; very soluble in chloroform; practically insoluble in ether.

USP 36: (Triprolidine Hydrochloride). A white crystalline powder, having no more than a slight, but unpleasant, odour. Soluble 1 in 2.1 of water, 1 in 1.8 of alcohol, 1 in 1 of chloroform, and 1 in 2000 of ether. Its solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Triprolidine hydrochloride, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and mild sedative effects. It is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3) and rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It is often used in compound preparations with pseudoephedrine hydrochloride for rhinitis and in other preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

It is given orally, the usual dose being 2.5 mg up to four times daily.

Triprolidine tannate has been used similarly.

Triprolidine hydrochloride has also been applied topically to the skin although, as with other antihistamines, there is a risk of sensitisation.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. UK product information for acrivastine has warned that acrivastine should not be used in patients hypersensitive to triprolidine.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving triprolidine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] in 3 women of the excretion of triprolidine and pseudoephedrine, taken orally in a combined preparation, triprolidine was found to reach concentrations in breast milk similar to those found in plasma in one subject, and slightly lower than in plasma in the others. It was calculated that 0.06 to 0.2% of the ingested dose was distributed into breast milk over 24 hours. Concentrations of pseudoephedrine in breast milk exceeded those in plasma in all 3 women.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/01/04)
2. Findlay JWA, *et al.* Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; **18:** 901–6.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

After absorption from the gastrointestinal tract, triprolidine is metabolised; a carboxylated derivative accounts for about half the dose excreted in the urine. Reported half-lives vary from 3 to 5 hours or more. Triprolidine is distributed into breast milk.

General references.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
2. Miles MV, *et al.* Pharmacokinetics of oral and transdermal triprolidine. *J Clin Pharmacol* 1990; **30:** 572–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kemian (刻兔); ***UAE***: Sedofan T; ***USA***: Vanahist PD; Zymine†.

Multi-ingredient Preparations. ***Arg.***: Actifedrin; ***Austral.***: Actifed CC Junior†; Actifed†; Codral Original Day & Night Cold & Flu; Sudafed Sinus Day & Night Relief†; Sudafed Sinus Pain & Allergy Relief†; ***Belg.***: Actifed†; ***Braz.***: Actifedrin; Trifedrin; ***Canad.***: Actifed Plus; Actifed; CoActifed; CoActifed; Covan; ratio-Cotridin Expectorant; ratio-Cotridin; ***Chile***: Actifedrin Antitusivo; Actifedrin; ***China***: Feidile (菲迪乐); Photifed-M (澳特斯); Xin Tai Luo Qi (新泰洛其); ***Fr.***: Actifed; ***Ger.***: Rhinopront Kombi; ***Gr.***: Actifedon; ***Hong Kong***: Actifed Compound; Antifort; Decofed†; Fedac Compound; Fedac; Prolifed; Syncofit Compound†; Syncofit†; Uni-Fedra Compound; Uni-Fedra DM†; Uni-Fedra†; Vidalidine†; ***India***: Actifed DM; Actifed Plus; Actifed; Actiflu Plus; Actiflu; Ascoril-D; Brodil-D; Corex-T; Deletus D; Deletus; Isofed; Megatuss-D; Nocold Plus; Oox-DM; Teguphen; ***Indon.***: Actifed Plus Cough Suppressant; Actifed Plus Expectorant; Actifed; Actigesic†; Alerfed; Crofed; Eflin; Flutrop; Gifed; Grafed; Lapifed DM; Lapifed Expectorant; Lapifed; Librofed; Nasafed Plus†; Nasafed†; Nichofed; Nostel; Protifed†; Quantidex; Stop Cold; Tremenza; Trifed; Trifedrin Plus; Trifedrin; Valved DM; Valved; Zentra; ***Irl.***: Actifed; Benylin Childrens Cough and Cold; Benylin Dual Action Dry; ***Israel***: Cold-Care; Histafed Comp; Histafed Expectorant; Histafed; Histamine-Care; ***Ital.***: Actifed Composto; Actifed; Actigrip; ***Malaysia***: Actifed DM; Actifed Expectorant; Actifed; Actihist Expectorant†; Actihist-Co†; Actihist†; Actimin; Axcel Tridine; Beatafed; Cough-EN; Deco Expectorant; Deco Syrup; Decol†; Fedac; Pabron Cold & Flu†; Pabron Cough & Sinus; Pabron Cough-D; Peace; Pseudoephedrine T; Rhynacol†; ***Mex.***: Actifed DM†; Actifed†; Giparlix; ***NZ***: Actifed†; Codral Daytime/Nightime†; Sudafed Day/Nightime Relief†; Sudafed Sinus Pain & Allergy Relief†; ***Pol.***: Acatar Acti-Tabs; Actifed; Actitrin; ***Port.***: Actifed; Dinaxil; ***Rus.***: Fastoric Plus (Фасторик Плюс); ***S. Afr.***: Actifed Cold & Fever†; Actifed Dry Cough Regular; Actifed Dry Cough Sugar Free†; Actifed; Acuflu P; Acugest Co†; Acugest DM†; Acugest Expect†; Acugest†; Acutussive†; Adco-Flupain; Adco-Muco Expect†; Adco-Neofed; Adco-Tussend; Betafed; Coryx†; Fludactil Co†; Flusin Sinus; Linctifed; Medifed; Merck-Cough Linctus†; Merck-Expectorant†; Merck-Fed; Sinuclear; Tixylix Flu†; Trifen; ***Singapore***: Actifed Compound; Actifed DM; Actifed Expectorant; Actifed; Actihist; Afidil; Beactafed Co; Beactafed; Cough-EN; Decondine; Fedac Compound; Fedac DM; Fedac; Peacef; SP-Rhinodyl; Syncofit; Trisedyl; ***Spain***: Cinfatos Descongestivo; Iniston Antitusivo y Descongestivo; Iniston Descongestivo†; Iniston Expectorante y Descongestivo; ***Thai.***: A-fed; Actifed DM†; Actifed†; Actil; Actiplex†; Adulfed; Clinikold†; Cofed; Coldifed; Colidin; Colidine; Consudine; Decolfed; Fafed; Feddic; Hiscifed; KB Pophedin; Medifed; Medofed; Milafed; Nasifed; Nasolin; Nostrilet; Pabron SN; Pacifed; Policol; Policold; Polyfed†; Pondactil; Profed; Prophedin; Sidan†; Sinofed; Sinusaid; SP-Fed; Sudophrine; Sufed†; Suphedrine; Trifed; Triofed; Tripo; Triprodrine; Trisodine; Vefed; Vesprolid-HCl; ***Turk.***: A-ferin; Actidem; Actifed; ***UAE***: Sedofan DM; Sedofan; ***UK***: Benylin Childrens Coughs & Colds; Multi-Action Actifed Chesty Coughs Expectorant; Multi-Action Actifed Dry Coughs; Multi-Action Actifed; Sudafed Plus; ***Ukr.***: Actifed (Актифед)†; Actifed Expectorant (Актифед Экспекторант)†; Trifed (Трайфед)†; Trifed-Expectorant (Трайфед-Экспекторант)†; ***USA***: Actagen-C Cough; Actagen; Actifed Cold & Allergy; Actifed Cold & Sinus; Actifed Plus; Actifed; Allercon; Allerfrim with Codeine†; Allerfrim†; Allerphed; Altafed; Aprodine with Codeine†; Aprodine†; Bayer Select Night Time Cold; Cenafed Plus†; Ed A-Hist PSE; Entre-Hist PSE; Genac; Hist-PSE; Poly Hist NC; Prohist CF; Silafed; Trifed-C Cough; Triofed; Tripohist D†; Triposed; Zymine HC†; Zymine-D.

Pharmacopoeial Preparations

BP 2014: Triprolidine Tablets;

USP 36: Triprolidine and Pseudoephedrine Hydrochlorides Syrup; Triprolidine and Pseudoephedrine Hydrochlorides Tablets; Triprolidine Hydrochloride Syrup; Triprolidine Hydrochloride Tablets.

Tritoqualine *(rINN)*

L-554; Tritocualina; Tritoqualinum; Тритоквалин.

7-Amino-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl)phthalide.

$C_{26}H_{32}N_2O_8$=500.5

CAS — 14504-73-5.

ATC — R06AX21.

ATC Vet — QR06AX21.

UNII — F4MW5166YH.

Profile

Tritoqualine is stated to inhibit histidine decarboxylase which catalyses the conversion of histidine to histamine. It has no action on histamine H_1-receptors and at therapeutic doses has no sedative or antimuscarinic effects. It has the uses of antihistamines (p. 610.2) and has been given orally in usual doses of 200 to 600 mg daily in 2 or 3 divided doses for the symptomatic relief of hypersensitivity reactions including allergic rhinitis and urticaria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hypostamine†.

Antimalarials

This chapter describes the main drugs used in the treatment and prophylaxis of malaria, one of the most serious protozoal infections in man. An estimated 40% of the world's population may be at risk of malaria; more than 500 million develop clinical infection, which is often very severe, and 1 to 3 million die each year. WHO produces guidelines for its strategic control and the management of malaria is under constant review. Measures to control malaria include *protection* from mosquito bites, *prophylaxis* with antimalarial drugs, and prompt *treatment* of any infection that develops. They also involve *vector control*; it is now recognised that for many countries vector eradication is an unrealistic aim.

Malaria

Malaria is a serious and potentially fatal disease, particularly in the case of falciparum malaria (see below) and especially in non-immune individuals (patients are classified as *non-immune* if they have recently or not previously been exposed to *Plasmodium* infection and as *semi-immune* or *immune* if they have a history of prolonged exposure). It is such a problem in many parts of the world that a global partnership named Roll Back Malaria[1] has been founded by WHO, United Nations Development Programme, UNICEF, and the World Bank with the aim of significantly reducing the world's malaria burden and virtually eliminating preventable deaths due to malaria by 2015. Prompt diagnosis and effective treatment of malaria are crucial.[2,3]

Malaria is traditionally caused by infection with any of 4 species of *Plasmodium* protozoa. *P. falciparum* causes falciparum (malignant tertian or subtertian) malaria, which is the most serious form and can be rapidly fatal in non-immune individuals if not treated promptly. The other 3 species cause what are often termed non-falciparum or 'benign' malarias: *P. vivax* causes vivax (benign tertian) malaria, which is widespread but rarely fatal, although symptoms during the primary attack can be severe; *P. malariae* causes quartan malaria, which is generally mild, but can cause fatal nephrosis; and *P. ovale* causes ovale (ovale tertian) malaria, which is the least common type of non-falciparum malaria and produces clinical features similar to *P. vivax*.[4] A fifth species that normally occurs in monkeys, *P. knowlesi*, has more recently emerged as a cause of malaria (termed monkey malaria) in travellers returning from forested areas in South-East Asia.[2] The organism closely resembles *P. malariae* on microscopy, but causes a wide spectrum of disease.[5] Although most cases are uncomplicated and respond promptly to treatment, about 10% of patients develop potentially fatal complications.[5]

The **life cycle** of *Plasmodium* is complex, comprising a sexual phase (sporogony) in the mosquito (vector) and an asexual phase (schizogony) in man (see Figure 1, below).

- Infection in man is usually caused by *sporozoites* from the bite of an infected female anopheline mosquito. It may rarely be acquired in other ways, congenitally via the placenta, or through blood transfusion, needlestick injuries, or organ transplantation.
- After an infected mosquito bite, sporozoites rapidly enter liver parenchymal cells, where they undergo *exoerythrocytic* or *pre-erythrocytic schizogony* forming *tissue schizonts* which mature and release thousands of *merozoites* into the blood on rupture of the cell.
- Merozoites enter erythrocytes where they transform into *trophozoites*. These produce *blood schizonts* which, as they mature, rupture and release merozoites into the circulation, which can infect other erythrocytes.
  This is termed the *erythrocytic cycle* and it is this periodic release of merozoites that is responsible for the characteristic periodicity of the fever in malaria.
- After several erythrocytic cycles, depending on the type of malaria, some erythrocytic forms develop into sexual *gametocytes*. Ingestion of infected blood containing gametocytes by a biting female mosquito allows the life cycle to be completed with the sexual phase in the mosquito.
- In *P. vivax* and *P. ovale* infections, some of the sporozoites entering the liver cells enter a latent tissue stage in the form of *hypnozoites*, which are responsible for recurrence of malaria caused by these organisms.

Recurrences resulting from the persistence of latent tissue forms are often referred to as *relapses* while renewed attacks caused by persistent residual erythrocytic forms are termed *recrudescences*. True relapses do not occur with falciparum or quartan malarias.

Clinical manifestations of malaria

The clinical symptoms of malaria are varied and non-specific; they usually include fever, fatigue, malaise, headache, myalgia, and sweating. Vomiting occurs in about 20% of patients, and mild diarrhoea in less than 5%. As the infection progresses, the spleen enlarges and the patient may develop anaemia and thrombocytopenia. The prognosis worsens with increasing parasite counts, more mature parasites, and more neutrophils containing malaria pigment.[6] Severe falciparum malaria may be complicated by acute renal failure, pulmonary oedema, and cerebral dysfunction. None of the clinical features of malaria are diagnostic and WHO recommends[3] that all patients should have a confirmed parasitological diagnosis, using either microscopy or the rapid diagnostic tests (based on parasite specific antigens or enzymes) that are now widely available, before antimalarial drug treatment is started. However, treatment should not be withheld if tests are unavailable and there is clinical suspicion of malaria. Any patient who has been in a malarial area in the previous two months should be considered to have malaria until proved otherwise.

Antimalarial drugs

Antimalarial drugs can be classified by the stage of the parasitic life cycle they affect. Thus:

Blood schizontocides act on the erythrocytic stages of the parasite that are directly responsible for the clinical symptoms of the disease. They can produce a clinical cure or suppression of infection by susceptible strains of all 4 species of malaria parasite but, since they have no effect on exoerythrocytic forms, do not produce a radical cure of ovale or vivax malarias.

Tissue schizontocides act on the exoerythrocytic stages of the parasite and are used for causal prophylaxis to prevent invasion of the blood cells, or as anti-relapse drugs to produce radical cures of vivax and ovale malarias.

Gametocytocides destroy the sexual forms of the parasite to interrupt transmission of the infection to the mosquito vector.

Sporontocides have no direct effect on the gametocytes in the human host but prevent sporogony in the mosquito.

Antimalarial drugs can also be classified by the chemical group to which they belong, which in turn determines the stage of the life cycle they affect. The principal antimalarial drugs, classified according to *drug group* and *activity*, are listed in Table 1 p. 645.

The quinolone antibacterials have been studied for their antimalarial activity. The 9-aminoacridines, such as mepacrine, are no longer used in the treatment of malaria.

The differing mechanisms of action of antimalarial drugs sometimes allow the use of combinations of antimalarials to improve efficacy. Such combinations are usually designed to potentiate each other, for instance by acting at sequential steps in the parasite's folic acid pathway (e.g. pyrimethamine with sulfadoxine or dapsone). Alternatively, a combination may be complementary, when the drugs involved act against different stages in the life cycle of the parasite (e.g. the use of chloroquine with primaquine to produce radical cure of *P. vivax* or *P. ovale* infections). The rationale behind the use of such combinations may be to enhance efficacy, particularly when drug resistance is a problem (see below), or it may be an attempt to delay the development of resistance to one or more of the drugs used.

Resistance.

Resistance to antimalarials has been documented for *P. falciparum*, *P. vivax*, and *P. malariae* and is seen with all classes of antimalarials, including artemisinin and its derivatives, for which resistance has been reported in some parts of South-East Asia (particularly the Cambodia–Thailand border).[3,7-9] Chloroquine resistance in *P. falciparum* now occurs virtually everywhere that *P. falciparum* malaria is transmitted, with the exception of certain parts of Central America and the Caribbean.[3,10] Resistance in *P. falciparum* to proguanil and pyrimethamine is apparent in many endemic areas. Cross-resistance between proguanil and pyrimethamine may also occur. Resistance in *P. falciparum* to the combination pyrimethamine-sulfadoxine (*Fansidar*) has spread rapidly in South-East Asia, but also occurs in other parts of the world including parts of South America, southern China, and Africa.[3,10] Mefloquine resistance is frequent in some areas of South-East Asia and migrant workers are thought to have spread mefloquine resistance to India and Bangladesh. Resistance has also occurred in the Amazon region of South America and, sporadically, in Africa, but generally, clinical mefloquine resistance outside South-East Asia is rare.[3,10] Resistance to quinine and halofantrine has also been noted. Cross-resistance between halofantrine and mefloquine may occur, as evidenced by reduced responses to halofantrine in some patients who have had treatment failure with mefloquine.[10] The emergence of multidrug resistance in *P. falciparum* makes the selection of effective prophylaxis and treatment difficult.

Multidrug resistance is defined as resistance to three or more antimalarial compounds from different chemical classes, of which two of the classes are the 4-aminoquinolines (e.g. chloroquine) and diaminopyrimidines (e.g. pyrimethamine-sulfadoxine (*Fansidar*)). Multidrug resistance occurs in South-East Asia (particularly along the borders of Thailand with Burma and Cambodia) and in the Amazon basin.[2,3]

P. vivax has developed resistance rapidly to pyrimethamine-sulfadoxine (*Fansidar*) in many areas and resistance to chloroquine and primaquine has also been reported in several parts of the world.[3,10] However, it remains sensitive to chloroquine in South-East Asia, the Indian subcontinent, the Korean peninsula, the Middle East, north-east Africa, and most of South and Central America.[3] Resistance of *P. malariae* to chloroquine has been seen in Indonesia.[3]

A knowledge of the geographical distribution and degree of resistance is important for the selection of appropriate control measures and for the development of policies for the rational use of antimalarial drugs. Resistance can be prevented, or slowed considerably, by selecting effective drugs and drug combinations according to local patterns of resistance, combining antimalarials with different mechan-

Figure 1. Life cycle of the malaria parasite *Plasmodium*.

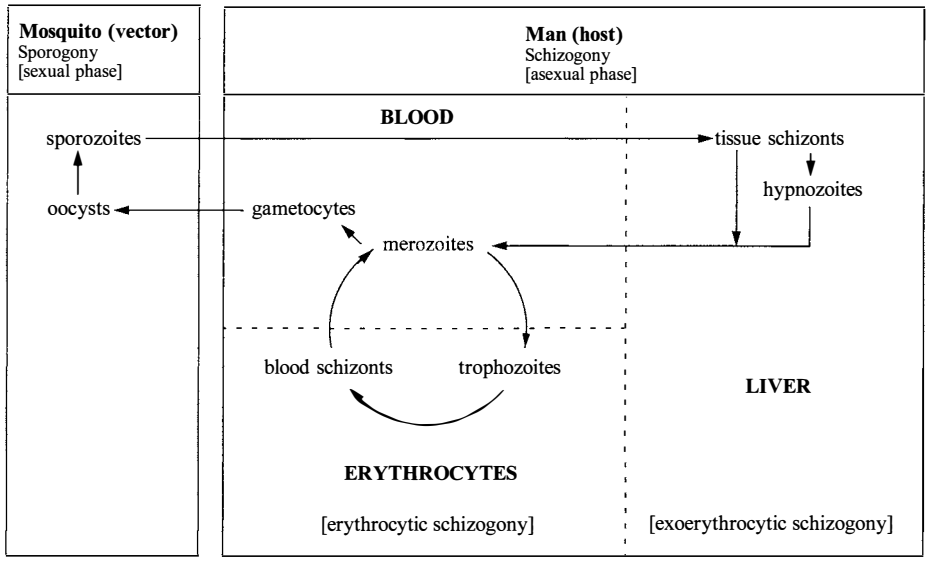

Table 1. Principal antimalarial drugs.

Antimalarial groups	Principal drugs	Activity
4-Aminoquinolines	Chloroquine Hydroxychloroquine Amodiaquine	Rapid-acting blood schizontocides. Some gametocytocidal activity.
8-Aminoquinolines	Primaquine Tafenoquine	Tissue schizontocide. Also gametocytocidal activity and some activity at other stages of the parasite's life-cycle.
Artemisinin and its derivatives (Sesquiterpene lactones)	Artemether Artenimol Artesunate	Blood schizontocide.
Biguanides	Proguanil Chlorproguanil	Tissue schizontocides and slow-acting blood schizontocides. Some sporontocidal activity. Dihydrofolate reductase inhibitors.
Diaminopyrimidines	Pyrimethamine	Tissue schizontocide and slow-acting blood schizontocide. Some sporontocidal activity. Dihydrofolate reductase inhibitor. Usually used with antimalarials that inhibit different stages of folate synthesis (sulfonamides or sulfones) to form synergistic combinations.
Dichlorobenzylidines	Lumefantrine	Blood schizontocide.
Hydroxynaphthoquinones	Atovaquone	Blood schizontocide. Usually given in combination with proguanil.
Lincosamides	Clindamycin	Blood schizontocides. Some tissue schizontocidal activity.
4-Methanolquinolines	Cinchona alkaloids Quinine Quinidine	Rapid-acting blood schizontocides. Some gametocytocidal activity.
	Mefloquine	Blood schizontocide.
Naphthyridines (Acridines)	Pyronaridine	Blood schizontocide. Usually given in combination with artesunate.
9-Phenanthrenemethanols	Halofantrine	Blood schizontocide.
4-Piperazinoquinolines	Piperaquine	Blood schizontocide. Usually given in combination with artenimol. Hydroxypiperaquine has also been studied.
Sulfonamides	Sulfadoxine Sulfametopyrazine	Blood schizontocides. Dihydropteroate and folate synthesis inhibitors. Usually given in combination with pyrimethamine.
Sulfones	Dapsone	Blood schizontocide. Folate synthesis inhibitor. Usually given in combination with pyrimethamine.
Tetracyclines	Doxycycline Tetracycline	Blood schizontocides. Some tissue schizontocidal activity.

isms of action, preventing indiscriminate and uncontrolled use, and ensuring very high cure rates through full compliance with the correct antimalarial dose regimens. Malaria control strategies also need to involve other measures such as vector control and health education.[3,11]

TREATMENT OF MALARIA

Malaria is treated with a *blood schizontocide*, selected with due regard to the prevalence of specific patterns of drug resistance in the area of infection. In the case of vivax and ovale malarias (see below) subsequent treatment with a *tissue schizontocide* is needed where it is considered appropriate to prevent relapse.

Antimalarials are generally given orally, although in order to obtain a rapid response in patients with severe or complicated falciparum malaria (see below) it may be necessary to start with parenteral therapy, the patient being transferred to oral therapy when feasible.[3] Where there are only minimal healthcare facilities and parenteral therapy is not possible or may be delayed, artemisinin or artesunate suppositories may be given.

Treatment of falciparum malaria.

In most parts of the world *P. falciparum* is now resistant to chloroquine and therefore, apart from the rare circumstance of exposure in one of the few remaining areas of chloroquine sensitivity, chloroquine is **not** suitable for treatment. Resistance to pyrimethamine-sulfadoxine (*Fansidar*) has also occurred in most countries where it was used in place of chloroquine.[4]

In **uncomplicated falciparum malaria** (symptomatic malaria without signs of severity or evidence of vital organ dysfunction) artemisinin-based combination drug therapy (ACT) is recommended by WHO[3] for treatment in all *malaria endemic areas*. Such combinations include either artemisinin or one of its derivatives paired with a long-acting partner drug; it is the level of resistance to the partner drug that determines the specific choice of ***first-line*** ACT used in a country or region. A course of at least 3 days is required for optimal efficacy. Recommended ACTs are:

- artemether-lumefantrine (*Riamet*)
- artesunate and amodiaquine (in areas where resistance to amodiaquine is low)
- artesunate and pyrimethamine-sulfadoxine (*Fansidar*) (in areas where pyrimethamine-sulfadoxine efficacy is still high)
- artesunate and mefloquine
- artenimol and piperaquine

Due to the continued spread of resistance to component drugs such as chloroquine, amodiaquine, and pyrimethamine-sulfadoxine (Fansidar), use of non-artemisinin-based combinations is no longer recommended by WHO for first-line treatment of malaria. Recommended ***second-line*** regimens used in the management of treatment failure (within 14 days of initial treatment) are:

- an alternative ACT known to be effective in the region
- artesunate with either tetracycline, doxycycline, or clindamycin (given for 7 days)
- quinine with either tetracycline, doxycycline, or clindamycin (given for 7 days)

In *non-endemic areas* the British Infection Society[12] and the Health Protection Agency Advisory Committee on Malaria Prevention in UK Travellers[13] recommend treating uncomplicated falciparum malaria or mixed infections with one of the following:

- oral quinine sulfate plus follow-on treatment with either doxycycline or clindamycin
- atovaquone-proguanil (*Malarone*)
- artemether-lumefantrine (*Riamet*)

In the USA, the CDC[14] recommends that uncomplicated falciparum malaria acquired in a chloroquine-sensitive area may be treated with oral chloroquine. Hydroxychloroquine may be used as an alternative. Malaria acquired in chloroquine-resistant areas is treated with one of the following:

- atovaquone-proguanil (*Malarone*)
- artemether-lumefantrine (*Coartem*)
- quinine sulfate plus doxycycline, tetracycline, or clindamycin (doxycycline or tetracycline are generally preferred as more data on efficacy are available)
- mefloquine (although when used in treatment doses it is associated with a higher rate of severe neuropsychiatric events and should only be given when one of the other 3 options cannot be used)

In **severe or complicated falciparum malaria** including cerebral malaria, parenteral treatment is required to produce adequate blood concentrations as quickly as possible.[3] Patients need to be closely monitored while undergoing parenteral therapy and treatment is changed to an oral antimalarial as soon as the patient's condition permits.

In *malaria endemic areas*, intravenous or intramuscular artesunate is the recommended first-line treatment, although quinine, given by slow, rate-controlled, intravenous infusion or intramuscular injection is an acceptable alternative if parenteral artesunate is not available; intravenous quinidine is considered more toxic than quinine and should only be used if no other effective parenteral drugs are available.

Where referral to an appropriate healthcare facility delays intravenous therapy, pre-referral treatment with intramuscular artesunate, artemether, or quinine, or rectal artesunate is recommended. Where referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication.[3]

Parenteral therapy should continue for at least 24 hours; after this, when the patient can tolerate oral therapy, it is necessary to continue and complete treatment with an effective oral follow-on regimen, and suitable alternatives are:[3]

- artesunate with amodiaquine
- artemether with lumefantrine
- artenimol with piperaquine
- artesunate with sulfadoxine-pyrimethamine
- artesunate with either clindamycin or doxycycline
- quinine with either clindamycin or doxycycline

In *non-endemic areas* intravenous quinine plus either oral doxycycline or oral clindamycin are recommended by authorities in the UK;[12,13] intravenous artesunate may be available on a named patient basis for the most severe cases if they are not responding to quinine therapy, are possibly infected with quinine-resistant falciparum, or quinine is contra-indicated. In the USA,[15] intravenous quinidine gluconate is used, in place of intravenous quinine, with doxycycline, tetracycline, or clindamycin; if required, intravenous artesunate is also available on an emergency basis from the CDC.

Supportive therapy in patients with severe or complicated malaria needs to be directed at reducing hyperpyrexia, controlling convulsions, maintaining fluid balance, and correcting hypoglycaemia. Severe malaria is associated with rapid development of anaemia, and blood transfusions are recommended for children with a haemoglobin concentration of less than 5 g per 100 mL (haematocrit less than 15%) living in areas of high transmission or for those with a haemoglobin level of 7 g per 100 mL (haematocrit threshold of 20%) living in an area of low transmission.[3] Although the benefit of exchange transfusion has not been proven in comparative studies, UK and US guidelines recommend that it be considered for patients with a parasite density of more than 10% or if the patient has cerebral malaria, renal complications, or acute respiratory distress syndrome.[13,14] Prophylactic use of anticonvulsants is not recommended and the use of intravenous or intramuscular phenobarbital resulted in increased mortality due to respiratory arrest.[3] Since iron might be involved in the pathogenesis of cerebral malaria, the iron chelator desferrioxamine has been tried in addition to standard antimalarial therapy, but any benefit is yet to be established and WHO advises against its use.[3] Anecdotal reports of the value of corticosteroids in cerebral malaria have not been substantiated by controlled studies and they have no place in the management of this condition.[3,16] There is insufficient data to recommend the use of osmotic diuretics such as mannitol to reduce intracranial pressure in patients with cerebral malaria.[17] Other approaches such as the use of hyperimmune serum or monoclonal antibody to tumour necrosis factor have also been unsuccessful.

Treatment of non-falciparum or benign malarias.

Non-falciparum malarias, which are usually caused by *P. vivax* or, less commonly, by *P. ovale* or *P. malariae*, can be debilitating but are usually less severe than falciparum malaria. Treatment for *P. vivax* and *P. ovale* includes a *radical cure*: that is, cure of both the blood and liver stage infections in order to prevent relapse and recrudescence. Treatment of *P. malariae* does not include radical cure as no hypnozoites are formed during infection. Chloroquine is still generally the drug of choice (but chloroquine-resistant vivax infection has been reported from some areas—notably Papua New Guinea, Indonesia, Burma, and Vanuatu). Either chloroquine or hydroxychloroquine alone are adequate for *P. malariae* and *P. knowlesi* infections; for those caused by *P. vivax* or *P. ovale* a tissue schizontocide, usually primaquine, is added for radical cure.[3,12-14] In areas where ACTs are being used as first-line treatment for *P. falciparum* malaria, they may be given with primaquine for *P. vivax* infection as an alternative to chloroquine, with the exception of artesunate and pyrimethamine-sulfadoxine (*Fansidar*) as *P. vivax* resistance to pyrimethamine-sulfadoxine (*Fansidar*) is rapidly developing.[3] WHO[3] recommends that chloroquine-resistant *P. vivax* may be treated with an ACT (based on amodiaquine, mefloquine, or piperaquine) followed by primaquine for radical cure, while the CDC[14] recommends that patients not responding to chloroquine monotherapy or those with chloroquine-resistant infections should be given either quinine sulfate plus doxycycline (or tetracycline), or atovaquone-proguanil (*Malarone*), followed by primaquine; an alternative is mefloquine followed by primaquine. UK[13] guidelines recommend that resistant vivax malaria be treated with one of the 3 regimens used for the treatment of uncomplicated falciparum malaria (see above). Radical cure is inappropriate for patients living within an endemic area since re-infection is likely and therefore WHO[3] recommends that it should be limited to patients resident in areas where transmission is *very low* or *absent*, and it may be attempted in *epidemic situations*, but should be postponed

until the post-epidemic period when the risk of re-infection is lower. Other patients should simply be treated with a further course of chloroquine in the event of relapse or re-infection. Severe vivax malaria should be treated the same way as severe and complicated falciparum malaria (see above).[3]

Treatment of malaria during pregnancy. Malaria is especially dangerous during pregnancy and the seriousness of the disease usually outweighs any potential risk from treatment. Malaria infection during pregnancy can result in maternal anaemia, miscarriage, premature birth, congenital malaria infection, low birth-weight, and neonatal death.[2,14,18] Pregnant women living in areas where malaria transmission is low or unstable have little or no acquired immunity and are 2 to 3 times more likely to develop severe disease than non-pregnant women living in the same area;[3,14] however, those living in endemic areas where malaria transmission is high have often acquired partial immunity.

For pregnant women living in *endemic areas* quinine plus follow-on treatment with clindamycin (or quinine monotherapy where clindamycin is not available) may be given for first-line treatment of uncomplicated falciparum malaria in the first trimester. Data regarding the use of artemisinin derivatives in the first trimester are at present limited; however, artesunate with clindamycin can be given if first-line treatment fails, or is unavailable. In the second or third trimester an ACT (excluding artenimol with piperaquine) known to be effective in the region, or either artesunate or quinine may be given, plus follow-on treatment with clindamycin.[3] For the treatment of severe malaria in the first trimester quinine or artesunate may be used;[2,3] however, care should be taken that patients given quinine do not become hypoglycaemic. Artemisinin derivatives (particularly artesunate but alternatively, artemether) are the drugs of choice for treatment of severe malaria in the second and third trimesters.[2,3]

In *non-endemic areas* it is recommended that uncomplicated falciparum malaria in pregnancy be treated with quinine plus follow-on treatment with clindamycin.[12-14,19] Atovaquone-proguanil (*Malarone*), artemether-lumefantrine (Coartem), or mefloquine may be given as alternatives where first-line treatment is not tolerated or no other treatment options are available.[14,19] Although fetal abnormalities have been associated with the use of high doses of chloroquine, extensive clinical experience suggests it is safe; its value is limited, however, due to resistance. The CDC recommends oral chloroquine for pregnant women with malaria infections acquired in chloroquine-sensitive areas and with non-falciparum malaria; hydroxychloroquine may be used as an alternative. Chloroquine-resistant *P. vivax* should be treated with quinine.[14] Radical cure for patients with vivax or ovale malaria during pregnancy should be postponed until after delivery due to the risk of intravascular haemolysis in the mother and fetus;[14,18] weekly chloroquine should be given during the remaining weeks of pregnancy.[3,14] WHO recommends chloroquine or amodiaquine for pregnant women with *P. vivax* malaria.[2] For treatment of severe malaria, recommendations[19] are similar to those for women living in endemic areas (see above).

There may be difficulty if other drugs are required as opinion varies over their suitability. The tetracyclines are contra-indicated due to adverse effects on bone growth and teeth.

Treatment of splenomegaly syndrome. A few individuals infected with *Plasmodium* develop chronic hyperreactive malarial splenomegaly syndrome, an aberrant immunological response formerly known as the tropical splenomegaly syndrome. Traditionally, patients have first received a full course of antimalarial chemotherapy appropriate to the causative species followed by lengthy and probably lifelong chemoprophylaxis; however, a study in 312 patients suggested that pyrimethamine given with folinic acid for 30 days could produce a rapid reduction of splenomegaly which persisted for at least 3 months.[20]

PROPHYLAXIS OF MALARIA

Chemoprophylaxis of malaria may refer to absolute prevention of infection (*causal prophylaxis*) or to suppression of parasitaemia and its symptoms (*clinical prophylaxis*). Causal prophylaxis is provided by tissue schizontocides which destroy the exoerythrocytic forms of the parasite. Clinical prophylaxis is provided by blood schizontocides which, if continued until all exoerythrocytic forms of the parasite are destroyed, will ultimately produce a *suppressive cure*. In *P. falciparum* infections this would be achieved by about a month after the last infected bite, but relapses with *P. vivax* and *P. ovale* may still occur after standard clinical prophylactic regimens due to the presence of latent exoerythrocytic forms (hypnozoites).

The continuing increase in the prevalence of strains of *P. falciparum* resistant to chloroquine and other antimalarials, along with growing evidence of toxicity of some regimens, make recommendations for malaria prophylaxis increasingly difficult. Absolute protection cannot be guaranteed by any chemoprophylactic regimen currently in use and the importance and efficacy of methods of avoiding bites from infected mosquitoes, such as the use of *protective clothing, bed netting, insect repellents,* and *insecticides* must be stressed.[2,11] WHO recommends the following measures to protect against mosquito bites:

- application of an effective insect repellent to exposed skin, especially between dusk and dawn when mosquitoes commonly bite
- accommodation in buildings with screens over doors and windows
- use of mosquito nets at night, preferably impregnated with pyrethroid insecticides such as permethrin or deltamethrin
- and use of anti-mosquito sprays or insecticide dispensers, or mosquito coils in bedrooms at night

Studies have shown that insecticide-impregnated mosquito nets can reduce mortality substantially.[21] In addition to these measures, travellers should be advised, even if chemoprophylaxis has been taken regularly, to regard **any** fever *after the first week* and for *up to 1 year after possible exposure*, especially within the first 3 months, as being caused by malaria and to seek medical advice **immediately**. Some authorities advise that travellers should also have antimalarial drugs ready for emergency self-treatment (*standby treatment*) when prompt medical attention is not available (see below).

Chemoprophylaxis should be reserved for those at high **risk**, notably *non-immune visitors*; widespread chemoprophylaxis in *immune or semi-immune* populations is no longer recommended except for women who are *pregnant*. For the elderly, pregnant women, and children, careful consideration should be given as to whether travel to areas where falciparum malaria occurs is absolutely necessary. WHO specifically advises pregnant women not to travel to areas where transmission of malaria occurs and also advises against taking babies and young children to areas with risk of falciparum malaria.[2] Advice on chemoprophylaxis must be based on a knowledge of the occurrence and susceptibility of *Plasmodium* strains in specific geographical areas. Local variations due to altitude, seasonal variations in temperature and rainfall, the degree of urbanisation, and many other factors further complicate the issue. WHO collates information provided by national health administrations and regularly publishes this information to assist in advising international travellers on the current situation; similar information is provided at national level by local institutes specialising in tropical diseases. However, the situation is so complex that advice differs. Recommendations issued by various authorities are usually for short-term stays and expert advice should be sought if long-term cover is required.

It is generally recommended that chemoprophylaxis should start about 1 week (or longer for mefloquine) before exposure to malaria, or if this is not possible at the earliest opportunity up to 1 or 2 days before exposure; this is partly to ensure that the patient is able to tolerate the drug. Chemoprophylaxis should continue throughout exposure and for at least 4 weeks after leaving the malarious area, with the exception of atovaquone-proguanil (*Malarone*) which may be stopped one week after leaving.

Prophylactic regimens.

Depending upon the risk of infection and the availability and standard of local medical care, WHO[2] has made recommendations on chemoprophylaxis and/or standby treatment for non-immune travellers:

- in areas where there is limited risk of any malaria transmission no chemoprophylaxis is needed; measures to protect against mosquito bites should be used
- in areas where *P. falciparum* is *absent* or still *sensitive to chloroquine*, or there is a risk of *P. vivax*, travellers can take chloroquine for prophylaxis
- in areas with a risk of *P. vivax* and *P. falciparum*, as well as *emerging resistance* to chloroquine, travellers can take chloroquine plus proguanil
- in areas of high risk of *P. falciparum* and where there is *multidrug resistance*, or in areas of low to moderate risk of *P. falciparum* but high levels of multidrug resistance, mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*) is recommended. These recommendations are subject to the local patterns of drug resistance

WHO[2] also recommends that for the small number of travellers who would be unable to obtain prompt medical attention when malaria is suspected (within 24 hours of the onset of symptoms), it may be necessary to provide for a course of self-treatment (**standby treatment**). Clear instructions must be given and persons taking standby medication must seek medical advice as soon as possible and resume any prophylaxis on completing the course. The basis upon which the choice of prophylaxis is made (as detailed above) in turn broadly determines the appropriate choice of standby treatment. Thus one of the following treatment regimens can be used:

- artemether-lumefantrine
- atovaquone-proguanil
- quinine plus doxycycline or clindamycin

In each instance, prophylaxis should be resumed 1 week after the *first* standby treatment dose, except for mefloquine prophylaxis which should be resumed at least 12 hours after the *last* treatment dose of quinine.

In the USA, recommendations for prophylaxis are provided by the CDC.[22] For chloroquine-sensitive malaria, recommended alternatives include chloroquine (or hydroxychloroquine) alone, atovaquone-proguanil (*Malarone*), doxycycline, or mefloquine. Primaquine may also be considered for short-term travellers to areas with mainly *P. vivax* transmission, providing they are not G6PD-deficient. For all areas with chloroquine-resistant malaria, 3 alternatives are available, mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*). Atovaquone-proguanil (*Malarone*) is recommended for emergency standby treatment. Presumptive antirelapse therapy (or terminal prophylaxis) with primaquine is also advocated during the last 2 weeks of prophylaxis to prevent relapses due to *P. vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic.

UK experts[23] have also published guidelines for the prophylaxis of malaria. In areas where *P. falciparum* is sensitive to chloroquine, travellers can either take chloroquine or proguanil for prophylaxis. In areas of little chloroquine resistance travellers can take chloroquine plus proguanil, while travellers to areas of high infection risk or where there is chloroquine resistance may take mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*) as prophylaxis. Standby treatment with chloroquine is recommended for travellers to chloroquine-sensitive areas who do not take any prophylaxis or who take proguanil as prophylaxis. Atovaquone-proguanil (*Malarone*), artemether-lumefantrine (*Riamet*), or quinine plus doxycycline or clindamycin are recommended in areas with chloroquine resistance.

Malaria vaccines are under development and several are currently undergoing clinical evaluation (see p. 2398.1).

Prophylaxis during pregnancy. The choice of drugs for prophylaxis during pregnancy is limited and whenever possible, women who are pregnant or likely to become so should avoid travelling to malarious areas (see also above). In pregnant women who cannot avoid travelling to endemic areas, chloroquine may be given alone for prophylaxis in the few areas where *P. falciparum* is sensitive to chloroquine, or with proguanil in areas where resistance is emerging.[2] Folate supplements (folic acid 5 mg daily) need to be taken with proguanil. Mefloquine is normally avoided during the first trimester but may be given during the second and third trimesters and CDC[22] and UK[23,24] guidelines consider that it may be used *with caution* in the first trimester, especially in areas where there is a high risk of acquiring falciparum malaria. Doxycycline, atovaquone-proguanil (*Malarone*), or primaquine are contra-indicated in pregnant women by most experts; the *BNF* considers that atovaquone-proguanil (*Malarone*) should be avoided during pregnancy unless there is no suitable alternative. In non-pregnant women of child-bearing potential, pregnancy needs to be avoided for 3 months after completing mefloquine prophylaxis and for one week after doxycycline prophylaxis.

For pregnant women living in endemic areas, routine antimalarial drugs have been shown to reduce antenatal parasitaemia; during first and second pregnancies, severe antenatal anaemia and perinatal deaths may also be reduced and birth-weight may be improved.[25] WHO[11] recommends that, in areas of stable transmission of *P. falciparum* malaria, pregnant women should be given **intermittent preventative treatment (IPT)** with an antimalarial drug, usually pyrimethamine-sulfadoxine (*Fansidar*). The first dose should be given after quickening in the second trimester and further doses should be given at intervals at least one month apart. For maximum benefit 2 or 3 doses of IPT should be given. For further information on the use of pyrimethamine in pregnancy, see under Precautions for Pyrimethamine, p. 664.1. Pregnant women and their newborn should also sleep under insecticide-treated nets.[11] In areas of low or unstable malaria transmission, where pregnant women have low immunity to malaria, use of insecticide-treated nets and prompt case management of pregnant women with fever and malarial illness is recommended. In addition, all pregnant women should take iron and folate supplements.

Prophylaxis during breast feeding. It is generally accepted for most antimalarials that the amounts distributed into breast milk and consumed by nursing infants are too small to be harmful, although they are also too small to provide protection.[2,22] However, doxycycline is contra-indicated during breast feeding, and advice regarding atovaquone-proguanil (*Malarone*) varies: in the UK it is contra-indicated,[23] but in the USA it may be given once the infant weighs over 5 kg;[22] both permit use if no suitable alternative is available. Mefloquine is probably safe to use in breast-feeding mothers.[23]

Prophylaxis in children. Chloroquine and proguanil may be given in scaled down doses to children of all ages but

the choice of alternative drugs may be restricted, especially in very young children, and consideration should be given to whether their travel to malarious areas is absolutely necessary (see also above). Mefloquine is an option for use in children and infants weighing 5 kg or more[2] if travelling to areas with chloroquine-resistant *P. falciparum* and atovaquone-proguanil (*Malarone*) may be given to children weighing 11 kg or more; the CDC considers that it may be used in infants weighing at least 5 kg. Doxycycline is contra-indicated in children less than 8 years of age, and higher age limits may apply in some countries such as the UK.[2,22,23] As in pregnant women (above), IPT is being explored as a means of reducing malaria in infants in areas of sustained high transmission;[26] the strategy for infants (IPTi) involves giving 2 or 3 doses of antimalarials during the first year of life, timed to coincide with routine vaccinations. A meta-analysis[27] of 6 studies involving infants in Africa reported that IPTi with sulfadoxine-pyrimethamine (*Fansidar*) led to a 30% reduction in the incidence of clinical malaria. For sub-Saharan Africa, the WHO technical expert group on preventative chemotherapy[28] has recommended that implementation of IPTi with sulfadoxine-pyrimethamine be considered in specific areas, such as those where there is moderate-to-high malaria transmission without high levels of resistance to sulfadoxine-pyrimethamine (the efficacy of sulfadoxine-pyrimethamine is decreasing in many areas,[28] and its use as IPTi has been shown to be of no benefit in areas of very high sulfadoxine-pyrimethamine resistance[29]).

Prophylaxis in epilepsy. In subjects with a history of epilepsy, the UK guidelines[23] advise that both chloroquine and mefloquine are unsuitable for prophylaxis. In areas without chloroquine resistance, proguanil alone is recommended. In areas with a high risk of chloroquine resistance, atovaquone-proguanil (*Malarone*) or doxycycline may be considered, but the metabolism of doxycycline may be influenced by antiepileptics. Dapsone with pyrimethamine (*Maloprim*) was considered to have been of particular value in travellers with epilepsy, especially children, but is no longer available in the UK.

Prophylaxis in HIV-infected travellers. HIV-infected travellers may take chloroquine routinely for antimalarial prophylaxis but its potential immunosuppressive effects should be recognised; proguanil, mefloquine, or doxycycline can also be used. Although patients with AIDS may be at increased risk of adverse effects to sulfonamides, a combination such as pyrimethamine-sulfadoxine (*Fansidar*) can be used for standby treatment if an alternative is not available.

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Amodiaquine *(BAN, rINN)*

Amodiactin; Amodiaquin; Amodiaquina; Amodiaquinum; Амодиахин.

4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol.

$C_{20}H_{22}ClN_3O$=355.9

CAS — 86-42-0.

ATC — P01BA06.

UNII — 220236ED28.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Amodiaquine). Very pale yellow to light tan-yellow, odourless, powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in 1.0N hydrochloric acid. Store in airtight containers.

Amodiaquine Hydrochloride *(BANM, rINNM)*

Amodiaquina, hidrocloruro de; Amodiaquine, Chlorhydrate d'; Amodiaquini Hydrochloridum; Hidrocloruro de amodiaquina; Амодиахина Гидрохлорид.

4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol dihydrochloride dihydrate.

$C_{20}H_{22}ClN_3O,2HCl,2H_2O$=464.8

CAS — 69-44-3 (anhydrous amodiaquine hydrochloride); 6398-98-7 (amodiaquine hydrochloride dihydrate).

ATC — P01BA06.

UNII — K6PW2S574L.

Pharmacopoeias. In *Fr., Int.,* and *US.*

USP 36: (Amodiaquine Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 78 of alcohol; very slightly soluble in chloroform, in ether, and in benzene. Store in airtight containers.

Sorption. For reference to loss of amodiaquine hydrochloride from solutions during membrane filtration, see Chloroquine, p. 650.2.

Uses and Administration

Amodiaquine is a 4-aminoquinoline antimalarial with an action similar to that of chloroquine (p. 650.2). It is as effective as chloroquine against chloroquine-sensitive strains of *Plasmodium falciparum* and is also effective against some chloroquine-resistant strains, although resistance to amodiaquine has developed and there may be partial cross-resistance between amodiaquine and chloroquine. To prevent the emergence and spread of drug resistant parasites WHO recommends that amodiaquine be given with an artemisinin derivative, such as artesunate, for the treatment of uncomplicated falciparum malaria or chloroquine-resistant vivax malaria. Amodiaquine is not recommended for the prophylaxis of malaria because of resistance and the risk of major toxicity.

Amodiaquine is given orally as the hydrochloride, but doses are expressed in terms of amodiaquine base; amodiaquine hydrochloride 260 mg is equivalent to about 200 mg of amodiaquine base. For the treatment of falciparum malaria and uncomplicated chloroquine-resistant vivax malaria in adults and children 5 months of age and older, a total dose of 30 mg/kg is given over 3 days (10 mg/kg daily for 3 days). Treatment of vivax malaria must be followed by radical cure with primaquine.

A fixed-dose combination product of amodiaquine and artesunate (ASAQ) has been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance, and is available in some countries.

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Administration in children. Amodiaquine may be used in children from 5 months of age for the treatment of uncomplicated falciparum malaria, or uncomplicated, chloroquine-resistant vivax malaria; doses are the same as for adults (see above).

References to the use of amodiaquine-containing therapy in children.

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Adverse Effects and Precautions

As for Chloroquine, p. 651.2, although amodiaquine was associated with hepatitis and a much higher incidence of agranulocytosis when it was used for the prophylaxis of malaria.

Incidence of adverse effects. Early isolated reports of severe neutropenia with amodiaquine usually concerned use in anti-inflammatory doses for rheumatoid arthritis, but there was a cluster of cases in 1986 associated with its use in malaria prophylaxis.[1] In all, 23 cases of agranulocytosis, 7 of which were fatal, were reported in the UK, USA, and Switzerland during a 12-month period ending March 1986. Nearly all of these patients had used the drug at a dosage of 400 mg weekly and the periods of exposure ranged from 3 to 24 weeks.[1] Some of these patients also had evidence of liver damage[1] and there have been other reports of hepatotoxicity associated with the prophylactic use of amodiaquine.[2] Examination of data submitted to the UK CSM[3] suggested that the frequency of adverse reactions to amodiaquine was about 1 in 1700 for serious reactions, 1 in 2200 for blood disorders, 1 in 15 650 for serious hepatic disorders, and 1 in 15 650 for fatal reactions. In contrast the frequency of agranulocytosis in users in France[4] has been estimated to be 1 in 25 000. Worldwide[4] the risk of severe reactions appears to be between 1 in 1000 and 1 in 5000. The manufacturers reportedly had 42 cases of serious adverse effects during amodiaquine prophylaxis, between 1985 and 1991; there were 28 cases of agranulocytosis (9 deaths) and 14 of hepatitis (3 deaths).[5]

In contrast, the risk of adverse events when amodiaquine is used for treatment, rather than prophylaxis of malaria appears to be substantially lower, likely because the relatively shorter courses used for treatment are associated with lower cumulative drug exposure than with prophylaxis.[6] Certain populations may be at higher risk however, and in a cohort study[7] of children being treated for malaria in Uganda, treatment with amodiaquine plus artesunate led to a significantly higher risk of neutropenia in HIV-infected children compared with HIV-uninfected children (44% and 6% respectively); risk was highest among children also receiving antiretroviral therapy (particularly regimens containing zidovudine).

It has been suggested that an immunological reaction to amodiaquine quinone imine, which can be produced by autoxidation among other processes, may partially account for amodiaquine's greater tendency to induce agranulocytosis compared with chloroquine.[8,9]

The acute toxicity of amodiaquine appears to differ from that of chloroquine in that there have been no reports of cardiovascular symptoms after overdosage with amodiaquine[10] but intoxication with amodiaquine is also far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions, and involuntary movements.[10]

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Pregnancy. A study[1] to assess the safety and efficacy of amodiaquine or amodiaquine plus sulfadoxine-pyrimethamine in 900 pregnant women (in their second or third trimester) reported that PCR-corrected parasitological failure by day 28 was 14%, 11%, 3%, and 0% in those given chloroquine, sulfadoxine-pyrimethamine, amodiaquine alone, and amodiaquine plus sulfadoxine-pyrimethamine, respectively. No serious adverse effects were reported.

WHO considers that amodiaquine may be an alternative to chloroquine for treatment of malaria due to *P. vivax* during pregnancy (see Treatment of Malaria during Pregnancy, under Malaria, p. 644.1).

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Pharmacokinetics

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract. Amodiaquine is rapidly converted in the liver, via the cytochrome P450 isoenzyme CYP2C8, to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more. Amodiaquine and desethylamodiaquine have been detected in the urine several months after use.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Flavoquine†; ***India***: Basoquin†; Camoquin†.

Multi-ingredient Preparations. ***Belg.***: Amonate†; ***China***: Artemodi; ***Gr.***: Arsuamoon.

Pharmacopoeial Preparations
USP 36: Amodiaquine Hydrochloride Tablets.

Artemisinin Derivatives

Artemisinina, derivados.

Artemether *(BAN, USAN, rINN)*

Artemeetteri; Artemeter; Artéméter; Artemetero; Artéméther; Artemetherum; Dihydroartemisinin Methyl Ether; Dihydroqinghaosu Methyl Ether; *o*-Methyldihydroartemisinin; SM-224; Артеметер.

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.

$C_{16}H_{26}O_5$=298.4

CAS — 71963-77-4.

ATC — P01BE02.

UNII — C7D6T3H22J.

Pharmacopoeias. In *Chin.* and *Int.*

Artemisinin *(rINN)*

Arteannuin; Artemisiini; Artemisinina; Artemisinine; Artémisinine; Artemisininum; Huanghuahaosu; Qinghaosu; Артемизинин.

(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one.

$C_{15}H_{22}O_5$=282.3

CAS — 63968-64-9.

ATC — P01BE01.

UNII — 9RMU91N5K2.

Pharmacopoeias. In *Chin.*, *Int.*, and *Viet.*

Artemotil *(rINN)*

Artémotil; Artemotilo; Artemotilum; Beta-arteether; Dihydroartemisinin Ethyl Ether; Dihydroqinghaosu Ethyl Ether; SM-227; Артемотил.

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-ethoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.

$C_{17}H_{28}O_5$=312.4

CAS — 75887-54-6.

ATC — P01BE04.

UNII — XGL7GFB9YI.

Pharmacopoeias. In *Int.*

Artenimol *(USAN, rINN)*

Arténimol; Artenimolum; Dihydroartemisinin; Dihydroqinghaosu; Артенимол.

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol.

$C_{15}H_{24}O_5$=284.4

CAS — 81496-81-3.

ATC — P01BE05.

UNII — 6A9O50735X.

Pharmacopoeias. In *Chin.* and *Int.*

Artesunate *(BAN, USAN, rINN)*

Artesunat; Artésunate; Artesunato; Artesunatum; Артезунат.

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate.

$C_{19}H_{28}O_8$=384.4

CAS — 83507-69-1; 88495-63-0; 182824-33-5.

ATC — P01BE03.

UNII — 60W3249T9M.

Pharmacopoeias. In *Int.* and *Viet.*

Sodium Artesunate *(BANM, rINNM)*

Artésunate de Sodium; Artesunato sódico; Dihydroartemisinin Hemisuccinate Sodium; Dihydroqinghaosu Hemisuccinate Sodium; Natrii Artesunatum; SM-804; Натрий Артезунат.

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate sodium.

$C_{19}H_{27}O_8Na$=406.4

CAS — 82864-68-4.

UNII — CN5E49Z611.

Uses and Administration

Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua*, a herb that has traditionally been used in China for the treatment of malaria. It is a potent and rapidly acting blood schizontocide active against *Plasmodium vivax* and against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*.

Artemisinin has been given orally or rectally in the treatment of malaria (see p. 649.1); regimens were often empirical with typical rectal doses ranging from 10 to 40 mg/kg daily over a variable number of days. However, it has largely been replaced in practice by its derivatives such as artemether and artesunate.

The following *oral* doses are recommended by WHO for the treatment of uncomplicated falciparum malaria.

Artesunate, when used with other antimalarials such as amodiaquine, mefloquine, or pyrimethamine-sulfadoxine, is given orally to provide a target dose of 4 mg/kg once daily, for 3 days.

Artenimol is given with piperaquine orally to provide a target dose of 4 mg/kg once daily, for 3 days.

Artemether is given orally with lumefantrine to provide a target dose of 1.7 mg/kg twice daily, for 3 days.

Fixed-dose combination products containing an artemisinin derivative and another antimalarial have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance; these formulations are recommended over co-packaged or loose tablets combinations. The following fixed-dose combinations have been licensed for use in some countries:

- artemether with lumefantrine (for further dosing information, see under Lumefantrine, p. 656.3)
- artenimol with piperaquine (for further dosing information, see under Piperaquine, p. 659.3)
- artesunate with amodiaquine
- artesunate with pyronaridine phosphate (for further dosing information, see under Pyronaridine Phosphate, p. 664.3)

For *parenteral* use in severe malaria, WHO recommends **artesunate** 2.4 mg/kg intravenously or intramuscularly, repeated after 12 and 24 hours and then once daily thereafter. The patient should then be transferred to an appropriate oral regimen (see p. 644.1) after at least 24 hours of parenteral therapy and complete a full course of oral treatment. Alternatively, in the USA a 5-dose regimen of 2.4 mg/kg intravenously at 0, 12, 24, 48, and 72 hours has been recommended, with oral follow-on treatment using atovaquone-proguanil (*Malarone*), doxycycline, clindamycin, or mefloquine.

If artesunate is not available, intramuscular **artemether** may be substituted in a dose of 3.2 mg/kg on day 1, followed by 1.6 mg/kg daily thereafter. **Artemotil** may also be used intramuscularly for the treatment of severe falciparum malaria; the suggested regimen is an initial dose of 4.8 mg/kg, evenly divided over both anterior thighs, followed by doses of 1.6 mg/kg given after 6, 24, 48, and 72 hours (injected into alternating thighs).

Where *rectal* **artesunate** is required for pre-referral treatment of severe malaria, a single dose of 10 mg/kg has been recommended.

For details of doses in children, see below.

Other derivatives of artemisinin are under investigation or commercial development (see Administration of Artemisinin Derivatives, below).

Reviews.

1. McIntosh H, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 17/05/05).
2. McIntosh H, Olliaro P. Artemisinin derivatives for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 17/05/05).
3. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: a review. *J Postgrad Med* 2004; **50:** 40–4.
4. Afolabi BB, Okoromah CAN. Intramuscular arteether for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 14/06/11).
5. Ashley EA, White NJ. Artemisinin-based combinations. *Curr Opin Infect Dis* 2005; **18:** 531–6.
6. Davis TME, *et al.* Artemisinin-based combination therapies for uncomplicated malaria. *Med J Aust* 2005; **182:** 181–5.
7. Bukirwa H, Critchley JA. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).
8. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. *Clin Pharmacokinet* 2008; **47:** 91–102.
9. Rosenthal PJ. Artesunate for the treatment of severe falciparum malaria. *N Engl J Med* 2008; **358:** 1829–36.
10. Sinclair D, *et al.* Artemisinin-based combination therapy for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 01/09/09).
11. Douglas NM, *et al.* Artemisinin combination therapy for vivax malaria. *Lancet Infect Dis* 2010; **10:** 405–16.

Administration of artemisinin derivatives. To overcome the poor solubility of *artemisinin* in water several dosage forms and routes have been tried. More potent derivatives with more suitable pharmaceutical properties have also been developed, notably the methyl ether derivative, *artemether*, and the ethyl ether derivative, *artemotil*, which are more lipid soluble; the sodium salt of the hemisuccinate ester, *sodium artesunate*, which is soluble in water but appears to have poor stability in aqueous solutions; and *sodium artelinate*, which is both soluble and stable in water. The active metabolite of these derivatives, *artenimol*, has also been developed as a pharmaceutical preparation. Other derivatives that have been studied include *arteflene* and *alpha-beta arteether*.

Several preparations of artemisinin derivatives are available either commercially or for studies organised by bodies such as WHO. These include oral formulations of artemether, artesunate, artemisinin itself, and artenimol; intramuscular formulations of artemotil, artemether, and artesunate; intravenous formulations of *artelinic acid* and artesunate; and suppositories of artemether, artemisinin, artesunate, and artenimol.

Administration in children. The artemisinin derivatives may be used in infants and children for the treatment of both uncomplicated falciparum malaria and severe malaria; the main derivatives currently in use are artesunate and artemether. For uncomplicated falciparum malaria WHO[1] recommends that combinations based on the same artemisinin derivatives as in adults be used, in equivalent

doses per kg body-weight (see p. 648.2); the specific combination chosen will be influenced by the safety and tolerability of the partner drug.

For treatment of severe malaria, WHO[1] recommends initial parenteral therapy (preferably with artesunate) followed by a complete course of an appropriate oral regimen (see p. 644.1) once the patient has completed at least 24 hours of parenteral therapy, and can tolerate oral medication. The following parenteral doses are recommended:

- **artesunate** 2.4 mg/kg *intravenously* or *intramuscularly*, repeated after 12 and 24 hours and given once daily thereafter
- **artemether** 3.2 mg/kg *intramuscularly*, followed by 1.6 mg/kg daily thereafter

Rectal artesunate may be used for pre-referral treatment of severe malaria in children in the same doses as for adults (see p. 648.2).[1]

Alternatively, in the USA[2] a 5-dose regimen of **artesunate** 2.4 mg/kg *intravenously* at 0, 12, 24, 48, and 72 hours (followed by treatment with atovaquone-proguanil (*Malarone*), clindamycin, or mefloquine) has been recommended for treatment of severe malaria.

A systematic review[3] has shown that oral formulations (granules, oral suspensions, or dispersible tablets) of artemisinin combinations that were designed specifically for paediatric dosage resulted in improved tolerance of therapy, with no loss of efficacy.

1. WHO. *Guidelines for the treatment of malaria* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
2. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
3. Kurth F, *et al.* Do paediatric drug formulations of artemisinin combination therapies improve the treatment of children with malaria? A systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 125–32.

Malaria. A systematic review[1] has suggested that intravenous artesunate should be the treatment of choice for adults and children with severe malaria (p. 644.1) in all geographical regions of the world. WHO[2] similarly recommends artesunate, given intravenously or intramuscularly, as the preferred treatment for severe malaria in both adults and children; intramuscular artemether or parenteral quinine can be considered where parenteral artesunate is not available. Rectal artesunate has been successful and is recommended by WHO[2] if parenteral therapy is not possible. In acute uncomplicated malaria artemisinin derivatives are usually given orally. Those used have been artemisinin, artemether, artenimol, or artesunate.

Although the increasing first-line use of artemisinin derivatives has been driven by the development of resistance to conventional treatment, resistance to this class of drugs has begun to develop in its turn, and no new group of drugs is yet in a position to replace them; treatment of artemisinin-resistant malaria will require optimisation of combinations of existing drugs.[3]

1. Sinclair D, *et al.* Artesunate versus quinine for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 08/07/11).
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update issued (April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Dondorp AM, *et al.* Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol* 2010; **8:** 272–80.

Schistosomiasis. Findings of a reduced intensity of *Schistosoma mansoni* infection in patients treated with sodium artesunate for malaria[1] prompted further investigation into the use of artemisinin derivatives for the control of schistosomiasis (p. 148.1). A double-blind placebo-controlled study[2] in children negative for *S. mansoni* found a significantly lower incidence of infection in those given artemether orally. There was also a significant reduction in the prevalence of *Plasmodium falciparum* infection. Some studies in China have confirmed the benefits of artemether or artesunate, often with praziquantel, against *S. japonicum*.[3] Another, open-label study appeared to suggest that a combination of mefloquine with artesunate was effective against *S. haematobium* and *S. mansoni*, see p. 657.3. However, in a randomised, double-blind, placebo-controlled study,[4] combination therapy with artemether plus praziquantel was no more effective in the treatment of acute *S. japonicum* infection than praziquantel alone.

1. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; **94:** 90–1.
2. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; **355:** 1320–5.
3. Xiao S-H. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Trop* 2005; **96:** 153–67.
4. Hou XY, *et al.* A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute schistosomiasis japonica in China. *Bull WHO* 2008; **86:** 788–95.

Adverse Effects and Precautions

Artemisinin and its derivatives appear to be generally well tolerated, although there have been reports of mild gastrointestinal disturbance (including nausea, vomiting, diarrhoea, and abdominal pain), pruritus and rash, dizziness, headache, tinnitus, neutropenia, elevated liver enzyme values, and ECG abnormalities including prolongation of the QT interval. Some parenteral artemisinin derivatives are formulated in sesame oil, which may rarely cause severe allergic reaction.

Evidence of severe neurotoxicity has been seen in *animals* given high doses.

General references to adverse effects associated with artemisinin derivatives.

1. Price R, *et al.* Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg* 1999; **60:** 547–55.
2. Medhi B, *et al.* Pharmacokinetic and toxicological profile of artemisinin compounds: an update. *Pharmacology* 2009; **84:** 323–32.
3. Efferth T, Kaina B. Toxicity of the antimalarial artemisinin and its dervatives [sic]. *Crit Rev Toxicol* 2010; **40:** 405–21.

Effects on the blood. For a report of severe haemolytic anaemia occurring in patient after taking artemether-lumefantrine and mention of neutropenia in HIV-infected patients treated with amodiaquine-artesunate, see p. 656.3 and p. 647.3 respectively.

Effects on the heart. Bradycardia was reported in 10 of 34 patients who received artemether orally for 4 days.[1] Other ECG abnormalities, such as QT-interval prolongation, have also been reported, although most studies have found no such effects.[2]

1. Karbwang J, *et al.* Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; **340:** 1245–8.
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 25/05/11)

Effects on the liver. Acute hepatitis was reported in a patient who took a herbal supplement supplying artemisinin 7.5 mg/kg daily for 10 days;[1] when the supplement was stopped, the patient's symptoms and liver function tests returned to normal over a 2 week period. Analysis of the supplement confirmed the presence and quantity of artemisinin and the absence of other contaminants or pharmaceutically active ingredients.

1. CDC. Hepatitis temporally associated with an herbal supplement containing artemisinin – Washington, 2008. *MMWR* 2009; **58:** 854–6.

Effects on the nervous system. Neurotoxicity has been reported in *animals* given artemotil or artemether; toxicity appears to relate to the sustained blood concentrations that occur after intramuscular administration, and is much less frequent when similar doses are given by the oral route or when similar doses of water-soluble artemisinin derivatives (such as artesunate) are used.[1] Clinical studies in humans have so far failed to show similar findings. However, there has been a report[2] of acute cerebellar dysfunction manifesting as ataxia and slurred speech in a patient who took a 5-day course of oral artesunate. Tremor, lack of coordination, restlessness, anxiety, hyperreflexia, and spasticity were also reported[3] in a patient misdiagnosed with malaria and treated with five 10-day courses of artesunate, and one 10-day course of chloroquine (p. 650.1). Symptoms improved markedly once the drugs were stopped, and neurotoxicity was felt to be a cumulative result of multiple artesunate courses, although chloroquine use may have also contributed.

1. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 25/05/11)
2. Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. *N Engl J Med* 1997; **336:** 1328.
3. Franco-Paredes C, *et al.* Neurotoxicity due to antimalarial therapy associated with misdiagnosis of malaria. *Clin Infect Dis* 2005; **40:** 1710–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the combination of artemether plus lumefantrine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Pregnancy. Artesunate or artemether was used to treat multidrug-resistant falciparum malaria in 83 pregnant women in Thailand; of 73 pregnancies resulting in live births none showed evidence of any congenital abnormality.[1] Sixteen of the women were given artesunate during the first trimester; of these, 12 had normal deliveries, 1 was lost to study, and 3 had spontaneous abortions.

No undue adverse effects on the neonates occurred in a study[2] involving 45 women treated for multidrug-resistant malaria during their second or third trimester of pregnancy with either artemether or artemether plus mefloquine. Intramuscular artemether was also used to treat chloroquine/quinine-resistant falciparum malaria in 28 pregnant women in eastern Sudan. Artemether was given to 1 woman during the first trimester, to 12 during the second trimester, and to 15 during the third trimester. One baby was delivered at 32 weeks but died 6 hours later; all the other babies were delivered at full term and there were no reports of congenital abnormalities.[3]

WHO[4] recommends that, where available, artesunate is the first option, and artemether is the second, for the parenteral treatment of severe falciparum malaria during the second and third trimesters. In the first trimester, until more evidence becomes available, artesunate may be considered as an option.

1. McGready R, *et al.* Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 1998; **92:** 430–3.
2. Sowunmi A, *et al.* Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine[sic]-pyrimethamine-resistant falciparum malaria during pregnancy. *J Obstet Gynaecol* 1998; **18:** 322–7.
3. Adam I, *et al.* Artemether in the treatment of falciparum malaria during pregnancy in eastern Sudan. *Trans R Soc Trop Med Hyg* 2004; **98:** 509–13.
4. WHO. *International travel and health.* 2011 ed. Available at: http://www.who.int/ith/en (accessed 25/05/11)

Interactions

Use of artemisinin derivatives with drugs that prolong the QT interval should be avoided if possible; caution is advised when artemisinin derivatives are given with other antimalarials that have this propensity.

Artemisinin has been reported to be a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2,[1] and might interact with drugs metabolised via this enzyme (such as theophylline). In contrast it is said to be an inducer of CYP2A6,[2] although the clinical implications of this are unclear.

1. Bapiro TE, *et al.* Artemisinin and thiabendazole are potent inhibitors of cytochrome P450 1A2 (CYP1A2) activity in humans. *Eur J Clin Pharmacol* 2005; **61:** 755–61.
2. Asimus S, *et al.* Artemisinin and CYP2A6 activity in healthy subjects. *Eur J Clin Pharmacol* 2008; **64:** 283–92.

Grapefruit juice. The oral bioavailability of artemether may be increased if taken with grapefruit juice.[1]

1. van Agtmael MA, *et al.* The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. *Clin Pharmacol Ther* 1999; **66:** 408–14.

Pharmacokinetics

Peak plasma concentrations of *artemisinin* occur about 3 hours after an oral dose, and 11 hours after a rectal dose. It undergoes hepatic metabolism, mainly via the cytochrome P450 isoenzyme CYP2B6, and is a potent inducer of its own metabolism; very little artemisinin is recovered in the urine, and inactive metabolites are excreted in the bile. The elimination half-life of artemisinin is about 2 to 3 hours.

Artemisinin derivatives are rapidly absorbed after an oral dose, with peak-plasma concentrations occurring after less than an hour for artesunate, and after 2 to 3 hours for artemether. Peak-plasma concentrations occur later (at 4 to 7 hours) when artesunate is given rectally. Absorption of intramuscular artemether is highly variable, with peak-serum concentrations occurring anywhere from 2 to 10 hour after a dose. For intramuscular artemotil, absorption is even slower and more erratic, with some patients having undetectable plasma concentrations until more than 24 hours after a dose.

After absorption, artemisinin derivatives (but not artemisinin itself) are rapidly biotransformed to the active metabolite artenimol (dihydroartemisinin). Biotransformation of artesunate by hydrolysis is almost immediate, such that artesunate is often regarded as a prodrug. In contrast, biotransformation of artemether and artemotil occurs more slowly, via CYP3A4-mediated demethylation. Artenimol is ultimately converted to inactive metabolites via cytochrome P450 and other enzyme systems, which are then excreted in the bile. The elimination half-life of artemether can range from 2 to 12 hours in patients with malaria. There are very few published data on the pharmacokinetics of artemotil, but its elimination half-life appears to be longer than that of artemether.

Reviews.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37:** 105–25.
2. Svensson US, Ashton M. Identification of the human cytochrome P450 enzymes involved in the in vitro metabolism of artemisinin. *Br J Clin Pharmacol* 1999; **48:** 528–35.
3. Navaratnam V, *et al.* Pharmacokinetics of artemisinin-type compounds. *Clin Pharmacokinet* 2000; **39:** 255–70.
4. Gautam A, *et al.* Pharmacokinetics and pharmacodynamics of endoperoxide antimalarials. *Curr Drug Metab* 2009; **10:** 289–306.

5. Mercer AE, Sarr Sallah M. The pharmacokinetic evaluation of artemisinin drugs for the treatment of malaria in paediatric populations. *Expert Opin Drug Metab Toxicol* 2011; **7:** 427–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Arinate†; Artesiane; ***Braz.***: Paluther; Plasmotrim; ***China***: Cotecxin; ***Gr.***: Artemax†; ***India***: Aartee; AB-AT; Ab-Ther; ABA-AT; ABA; ABC-9; Abkwik; Abter; Acter; Adthec; Alfabet; Alither; Alnather; Altinate; Amther; Arh Plus; Arh; Arh; Arial; Arither; Armer; Arnet; Artem E; Artemotial; Artesa; Artestar; Artfin; Arth; Artimal; Artisin; Artiz; Asunate; Ate; Avbet; Beta Plus; Betamotil; Bioart; Cadither; Chingasu; Crush; Cumal; DMel; Dunate; Duther; E Mal; E-Dalther; Elther; Emsunate; Endomal-AT; Endomal-O; Endomal; Eralpha; Erod-M; Falciat; Falcicare; Falcicure; Falcide; Falcidium-AB; Falcidium; Falcifast; Falcigo; Falcimax; Falcinez; Falcinil; Falciquin; Falcither; Falcized; Falcy; Falcydol; Falcyguard; Falcynate; Falno; Falpar; Falrap; Falz; Flamether; Foal-BR; Fydomal; Geether; Gether; Gleether; Gofalcy; Hosither; Karat; Keether; L-Ther; Laboether; Larinate; Larither; LB Ether; Lemal; Leother; Lether; M-Quit; Malater; Malatrit-E; Malatrit-S; Malexit; Maligon-Art; Malijet; Malisoz; Malither; Malnate-R; Malnate; Malona; Malther; Martis; Match; Mate; Maver; Maxinate; MDTher; Melat; Melbet-A; Melovar; Methicap; Mononate; Mosether; Myquine; Naya-AB; Nisunate; Orinate; Oxynate-AR; Palther; Paluther; Rapither-AB; ***Indon.***: Artem; ***Neth.***: Artecef.

Multi-ingredient Preparations. ***Austral.***: Riamet; ***Austria***: Riamet; ***Belg.***: Amonate†; Co-Arinate; Co-Artesiane; Riamet; ***China***: An Li Kang (安立康); Artemodi; Duo-Cotecxin; Ke Tai Fu (科泰复); ***Cz.***: Riamet†; ***Fr.***: Riamet; ***Ger.***: Riamet; ***Gr.***: Arsuamoon; Riamet; ***India***: Alither; Alphabetas; Arh-L; Arlufe; Arsumet-L; Arte Plus; Coartrin; Combither; Falcigo Plus; Falcimax Plus; Falcirid; Larinate Kit; Larinate-MF; Lumeart; Lumecap-A; Lumerax; Lumether; Malatrit-EL; Masunate; ***Indon.***: Coartem; ***Irl.***: Eurartesim; ***Kor.***: Pyramax; ***Neth.***: Eurartesim; Riamet; ***Philipp.***: Coartem; ***Port.***: Falcitrim; Riamet; ***S.Afr.***: Coartem; ***Singapore***: Riamet; ***Swed.***: Riamet; ***Switz.***: Riamet; ***Thai.***: Coartem; ***UK***: Eurartesim; Riamet; ***USA***: Coartem.

Chloroquine *(BAN, rINN)*

Chlorochin; Chlorochina; Chloroquin; Chloroquinum; Clorochina; Cloroquina; Klorokiini; Klorokin; Хлорохин.

4-(7-Chloro-4-quinolylamino)pentyldiethylamine; 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

$C_{18}H_{26}ClN_3$=319.9

CAS — 54-05-7.

ATC — P01BA01.

UNII — 886U3H6UFF.

Pharmacopoeias. In *US*.

USP 36: (Chloroquine). A white or slightly yellow, odourless, crystalline powder. M.p. 87 degrees to 92 degrees. Very slightly soluble in water; soluble in chloroform, in ether, and in dilute acids. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Chloroquine Hydrochloride *(BANM, rINNM)*

Chloroquine, Chlorhydrate de; Chloroquini Hydrochloridum; Cloroquina, hidrocloruro de; Hidrocloruro de cloroquina; Хлорохина Гидрохлорид.

$C_{18}H_{26}ClN_3,2HCl$=392.8

CAS — 3545-67-3.

ATC — P01BA01.

UNII — NT0J0815S5.

Pharmacopoeias. *US* includes an injection.

Chloroquine Phosphate *(BANM, rINNM)*

Chingaminum; Chlorochin-difosfát; Chlorochinium Phosphoricum; Chlorochinum Diphosphoricum; Chlorochiny fosforan; Chlorokvino fosfatas; Chloroquine, Phosphate de; Chloroquini Diphosphas; Chloroquini Phosphas; Chloroquinphosphat; Cloroquina, fosfato de; Fosfato de cloroquina; Khingamin; Klorokiinifosfaatti; Klorokinfosfat; Klorokin-foszfát; Quingamine; SN-7618; Хлорохина Фосфат.

$C_{18}H_{26}ClN_3,2H_3PO_4$=515.9

CAS — 50-63-5.

ATC — P01BA01.

UNII — 6E17K3343P.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Chloroquine Phosphate). A white or almost white, hygroscopic, crystalline powder. It exists in two forms, one melting at about 195 degrees and the other at about 218 degrees. Freely soluble in water; very slightly soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 3.8 to 4.3. Store in airtight containers. Protect from light.

USP 36: (Chloroquine Phosphate). A white, odourless, crystalline powder, which slowly discolours on exposure to light. It exists in two polymorphic forms, one melting between 193 degrees and 195 degrees and the other between 210 degrees and 215 degrees; mixture of the two forms melts between 193 degrees and 215 degrees. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions have a pH of about 4.5.

Chloroquine Sulfate *(BANM, rINNM)*

Chlorochin-sulfát monohydrát; Chlorochiny siarczan; Chlorokvino sulfatas; Chloroquine, Sulfate de; Chloroquine Sulphate; Chloroquini Sulfas; Chloroquini Sulfas Monohydricus; Chloroquini Sulphas; Chloroquinsulfat; Cloroquina, sulfato de; Klorokiinisulfaatti; Klorokinsulfat; Klorokin-szulfát; RP-3377; Sulfato de cloroquina; Хлорохина Сульфат.

$C_{18}H_{26}ClN_3,H_2SO_4,H_2O$=436.0

CAS — 132-73-0 (anhydrous chloroquine sulfate).

ATC — P01BA01.

UNII — OE48649K6N.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Ph. Eur. 8: (Chloroquine Sulfate). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in alcohol. An 8% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

Sorption. Studies using low concentrations of chloroquine phosphate or chloroquine sulfate indicate that chloroquine shows pH-dependent binding to several materials used in medical equipment and membrane filters, including soda glass and various plastics such as cellulose acetate, cellulose propionate, methacrylate butadiene styrene, polypropylene, PVC, ethylvinyl acetate, and polyethylene.[1-3] Although this effect may not be of relevance at doses used clinically,[4] laboratory workers undertaking assays and sensitivity testing must recognise that significant reductions in concentrations can occur when chloroquine is prepared or stored in equipment made from these materials.[2,3] As the effect of borosilicate glass or polystyrene appears to be minimal, it has been suggested that they may be suitable for use in such procedures.[2,3]

Similar sorption has also been reported during membrane filtration of solutions of amodiaquine hydrochloride, mefloquine hydrochloride, or quinine sulfate.[1]

1. Baird JK, Lambros C. Effect o f membrane filtration o f antimalarial drug solutions on in vitro activity against Plasmodium falciparum. *Bull WHO* 1984; **62:** 439–44.
2. Yahya AM, *et al.* Binding of chloroquine to glass. *Int J Pharmaceutics* 1985; **25:** 217–23.
3. Yahya AM, *et al.* Investigation of chloroquine binding to plastic materials. *Int J Pharmaceutics* 1986; **34:** 137–43.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Uses and Administration

Chloroquine is a 4-aminoquinoline antimalarial used in the treatment and prophylaxis of malaria (p. 644.1), as well as the treatment of hepatic amoebiasis (p. 919.1). It may also be used in the management of inflammatory disorders such as rheumatoid arthritis and SLE (below), as well as in sarcoidosis (p. 651.1), various skin disorders (p. 651.2) and porphyria cutanea tarda (p. 651.1). It has also been used as an adjunct to standard treatment for malignant neoplasms of the brain (p. 651.1).

Chloroquine is used for the prophylaxis and treatment of malaria due to susceptible strains of *Plasmodium ovale*, *P. vivax*, and *P. malariae*. It has also been used for susceptible strains of *P. falciparum* but in most of the world *P. falciparum* is now resistant to chloroquine, which should *not* therefore be given for treatment. Chloroquine is a rapid-acting blood schizontocide with some gametocytocidal activity against *P. ovale*, *P. vivax*, *P. malariae*, and immature gametocytes of *P. falciparum*. Since it has no activity against exoerythrocytic forms, it does not produce a radical cure of vivax or ovale malarias. The mechanism of action of chloroquine against blood schizonts remains unclear, but it may influence haemoglobin digestion by raising intravesicular pH in malaria parasite cells. It also interferes with synthesis of nucleoproteins by the parasite.

Chloroquine may be given as the phosphate, sulfate, or hydrochloride. Doses are normally expressed in terms of chloroquine base, and as a general guide:

- chloroquine base 300 mg is equivalent to about chloroquine phosphate 500 mg or chloroquine sulfate 400 mg
- chloroquine base 40 mg is equivalent to about chloroquine hydrochloride 50 mg

Oral bioavailability is increased when chloroquine is taken with food.

For the **treatment of malaria** caused by chloroquine-sensitive strains of *P. vivax*, *P. ovale*, and *P. malariae*, the usual total oral dose is the equivalent of about 25 mg/kg of chloroquine base given over 3 days. This total dose has been given in a variety of ways. One way is to give 10 mg/kg, followed after 6 to 8 hours by 5 mg/kg, then 5 mg/kg daily for the next 2 days; alternatively, 10 mg/kg may be given daily for the first 2 days and 5 mg/kg on the third day. Sometimes doses are not expressed in terms of body-weight but as 600 mg followed after 6 to 8 hours by 300 mg, then 300 mg daily for the next 2 days.

Chloroquine has been given by injection for patients who are unable to take oral medication; the intravenous route is preferred and a slow rate of infusion is essential, the required dose of 25 mg/kg being given in several infusions over 30 to 32 hours. Should the patient recover sufficiently to be able to take chloroquine orally then the intravenous regimen should be halted and oral therapy started.

For **prophylaxis of malaria** in areas where *P. falciparum* is absent or in one of the few remaining areas where it is still sensitive to chloroquine, a dose equivalent to about 300 mg of chloroquine base is given once each week, beginning about one week before exposure and continuing throughout, and for at least 4 weeks after, exposure. In areas of chloroquine-resistant malaria, but with a low risk of infection, chloroquine is given with proguanil; where there is a high risk of infection alternative antimalarial regimens are recommended.

In the treatment of **hepatic amoebiasis**, chloroquine is used with an intestinal amoebicide. The usual dose is the equivalent of 600 mg of chloroquine base daily for 2 days then 300 mg daily for 2 or 3 weeks.

When chloroquine is used for *long-term therapy* in conditions such as rheumatoid arthritis or lupus erythematosus, the dosage in obese patients should be calculated on the basis of lean body-weight in order to avoid excessive dosage.

In **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months, but if there is no improvement by then treatment should be stopped. The usual dose is the equivalent of chloroquine base 150 mg daily (maximum 2.5 mg/kg daily). For precautions and guidelines concerning use by rheumatologists see under Effects on the Eyes, p. 651.2.

In discoid and systemic **lupus erythematosus** chloroquine is used in a dose equivalent to 150 mg (maximum 2.5 mg/kg) of base daily.

In the management of **light-sensitive skin eruptions**, adults may be given the equivalent of 150 to 300 mg of chloroquine base daily during periods of intense light exposure.

For details of doses in children, see below.

Administration in children. In children, chloroquine may be used orally in the treatment and prophylaxis of malaria. It may be given as the phosphate, sulfate, or hydrochloride salt, but doses are normally expressed in terms of chloroquine base.

For the **treatment of malaria** caused by chloroquine-sensitive strains of *P. vivax*, *P. ovale*, and *P. malariae*, children may be given a total dose of 25 mg/kg chloroquine base distributed over 3 days in one of the following regimens:

- 10 mg/kg initially, 5 mg/kg 6 to 8 hours later, then 5 mg/kg once daily for the next 2 days
- 10 mg/kg once daily for 2 days, then 5 mg/kg on the third day

For **prophylaxis of malaria** in areas where *P. falciparum* is absent or still sensitive to chloroquine, children may be given a weekly dose of 5 mg/kg (to a maximum of 310 mg per dose); prophylaxis should begin about 1 week before the period of malaria exposure and continue until 4 weeks after. Alternatively, UK malaria experts[1] suggest the following weekly doses based on fractions of the adult dose (see above), noting that body-weight is a better guide to dosage than age for children over 6 months of age:

- under 6 kg (up to 12 weeks of age): one-eighth the adult dose
- 6 to 9.9 kg (3 to 11 months): one-quarter the adult dose
- 10 to 15.9 kg (1 year to 3 years 11 months): three-eighths the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months): half the adult dose
- 25 to 44.9 kg (8 year to 12 years 11 months): three-quarters the adult dose
- 45 kg and over (13 years and over): the adult dose (see above)

1. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Inflammatory disorders. Chloroquine and hydroxychloroquine possess anti-inflammatory properties and they have been tried or used with some benefit in a range of inflammatory conditions which often have an immunological basis, although they rarely constitute first-line therapy in these disorders. Such conditions include rheumatoid arthritis and SLE (see under Hydroxychloroquine,

p. 655.3 and p. 656.1 respectively), ulcerative colitis,[1] infantile interstitial pneumonitis,[2,3] asthma,[4] giant cell arteritis,[5] and various skin disorders (see below). The mode of action in these conditions is unclear. Results of studies have been conflicting but it does appear that chloroquine and hydroxychloroquine might have some immunosuppressive effects.[6,7]

1. Mayer L, Sachar DB. Efficacy of chloroquine in the treatment of inflammatory bowel disease. *Gastroenterology* 1988; **94:** A293.
2. Springer C, *et al.* Chloroquine treatment in desquamative interstitial pneumonia. *Arch Dis Child* 1987; **62:** 76–7.
3. Kerem E, *et al.* Sequential pulmonary function measurements during treatment of infantile chronic interstitial pneumonitis. *J Pediatr* 1990; **116:** 61–7.
4. Dewey A, *et al.* Chloroquine as a steroid sparing agent for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 08/10/09).
5. Le Guennec P, *et al.* Management of giant cell arteritis: value of synthetic antimalarial agents: a retrospective study of thirty six patients. *Rev Rhum* 1994; **61:** 423–8.
6. Bygbjerg IC, Flachs H. Effect of chloroquine on human lymphocyte proliferation. *Trans R Soc Trop Med Hyg* 1986; **80:** 231–5.
7. Prasad RN, *et al.* Immunopharmacology of chloroquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 168–9.

Malignant neoplasms of the brain. Chloroquine is a strong DNA-intercalating agent and inhibitor of lysosomic enzymes.[1] As a result, there has been interest in its ability to sensitise cancer cells to the cytotoxic effects of radio- and chemotherapy, particularly in patients with glioblastoma multiforme (GBM), the treatment of which is described under Malignant Neoplasms of the Brain, p. 701.2.

In a randomised, double-blind, placebo-controlled study[2] involving 30 patients with GBM, addition of long-term chloroquine therapy to the standard treatment regimen of surgery, radiotherapy, and chemotherapy (with carmustine) resulted in a median survival of 24 months, compared with only 11 months for those not treated with chloroquine. A subsequent retrospective study[3] observing 41 patients given chloroquine as an optional adjunct to conventional treatment noted similar improvement in survival compared with controls.

1. Munshi A. Chloroquine in glioblastoma–new horizons for an old drug. *Cancer* 2009; **115:** 2380–3.
2. Sotelo J, *et al.* Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; **144:** 337–43.
3. Briceño E, *et al.* Institutional experience with chloroquine as an adjuvant to the therapy for glioblastoma multiforme. *Surg Neurol* 2007; **67:** 388–91.

Porphyria cutanea tarda. Chloroquine and hydroxychloroquine have been used with some benefit in the treatment of porphyria cutanea tarda (p. 1556.1) and low doses (such as chloroquine phosphate 125 mg or hydroxychloroquine sulfate 200 mg given twice weekly) have been considered by some to be useful in patients unsuitable for phlebotomy.[1-4] However, the acute increase in urinary porphyrins and fall in hepatic porphyrin content produced by these drugs have been associated with a variable degree of hepatotoxicity[5,6] and others prefer to use desferrioxamine.[7]

1. Grossman ME, *et al.* Porphyria cutanea tarda. *Am J Med* 1979; **67:** 277–86.
2. Cainelli T, *et al.* Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1983; **108:** 593–600.
3. Ashton RE, *et al.* Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1984; **111:** 609–13.
4. Stölzel U, *et al.* Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. *Arch Dermatol* 2003; **139:** 309–13.
5. Scholnick PL, *et al.* The molecular basis of the action of chloroquine in porphyria cutanea tarda. *J Invest Dermatol* 1973; **61:** 226–32.
6. Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda: effects and risk factors for hepatotoxicity from high-dose chloroquine treatment. *Acta Derm Venereol* 2007; **87:** 401–5.
7. Rocchi E. Treatment of porphyria cutanea tarda. *Br J Dermatol* 1987; **116:** 139–40.

Rheumatoid arthritis. For reference to the use of chloroquine in the treatment of rheumatoid arthritis, see under Hydroxychloroquine, p. 655.3.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p. 1612.2) as alternatives or adjuncts to corticosteroid therapy.

References.

1. O'Leary TJ, *et al.* The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; **315:** 727–30.
2. Adams JS, *et al.* Effective reduction in the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia with short-course chloroquine therapy. *Ann Intern Med* 1989; **111:** 437–8.
3. DeSimone DP, *et al.* Granulomatous infiltration of the talus and abnormal vitamin D and calcium metabolism in a patient with sarcoidosis: successful treatment with hydroxychloroquine. *Am J Med* 1989; **87:** 694–6.
4. Jones E, Callen JP. Hydroxychloroquine is effective therapy for control of cutaneous sarcoidal granulomas. *J Am Acad Dermatol* 1990; **23:** 487–9.
5. Zic JA, *et al.* Treatment of cutaneous sarcoidosis with chloroquine: review of the literature. *Arch Dermatol* 1991; **127:** 1034–40.
6. Baltzan M, *et al.* Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999; **160:** 192–7.

Scorpion stings. Local infiltration of 2.5 mL (161 mg) of a parenteral chloroquine formulation has been used to relieve pain from scorpion stings (p. 2418.1) in Ghana.[1]

1. Yenli EM, *et al.* Managing scorpion stings in the tropics: chloroquine as an effective drug. *Trop Doct* 2010; **40:** 119–20.

Skin disorders. In addition to their use in lupus erythematosus hydroxychloroquine and chloroquine have been tried in some other skin disorders including polymorphic light eruptions[1] (see Photosensitivity Disorders, p. 1686.2), lichen planus[2,3] (p. 1685.2), cutaneous symptoms of dermatomyositis (p. 1611.1), erythema nodosum,[4,5] and recurrent erythema multiforme (p. 1684.3). It has also been tried in mild type 2 lepra reactions (erythema nodosum leprosum, see Leprosy, p. 188.3). Hydroxychloroquine, in particular, has been successfully used to treat idiopathic follicular mucinosis.[6]

1. Murphy GM, *et al.* Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. *Br J Dermatol* 1987; **116:** 379–86.
2. Mostafa WZ. Lichen planus of the nail: treatment with antimalarials. *J Am Acad Dermatol* 1989; **20:** 289–90.
3. De Argila D, *et al.* Isolated lichen planus of the lip successfully treated with chloroquine phosphate. *Dermatology* 1997; **195:** 284–5.
4. Alloway JA, Franks LK. Hydroxychloroquine in the treatment of chronic erythema nodosum. *Br J Dermatol* 1995; **132:** 661–2.
5. Jarrett P, Goodfield MJD. Hydroxychloroquine and chronic erythema nodosum. *Br J Dermatol* 1996; **134:** 373.
6. Schneider SW, *et al.* Treatment of so-called idiopathic follicular mucinosis with hydroxychloroquine. *Br J Dermatol* 2010; **163:** 420–3.

Systemic lupus erythematosus. For reference to the use of chloroquine in cutaneous lupus erythematosus and SLE, see Hydroxychloroquine, p. 656.1.

Adverse Effects

Adverse effects from dosage regimens of chloroquine used in the treatment and prophylaxis of malaria are generally less common and less severe than those associated with the higher doses used for prolonged periods in rheumatoid arthritis.

Frequent adverse effects of chloroquine include headache, various skin eruptions, pruritus, and gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. More rarely, mental changes including psychotic episodes and hallucinations, delirium, anxiety, and agitation, insomnia, depression, and personality changes may occur. Polyneuritis and convulsions have also been reported.

Visual disturbances such as blurred vision and difficulties in focusing have occurred but these are more common with higher doses, when they may be associated with keratopathy or retinopathy, as discussed under Effects on the Eyes, below. Keratopathy usually occurs in the form of corneal opacities and is normally reversible when chloroquine is withdrawn. Retinopathy is the most serious adverse effect of chloroquine on the eyes and it can result in severe visual impairment. Changes may be irreversible and can even progress after chloroquine is stopped. Those taking high doses of chloroquine for prolonged periods appear to be at greatest risk of developing retinopathy.

Other uncommon adverse effects from prolonged use include loss of hair, bleaching of hair pigment, bluish-black pigmentation of the mucous membranes and skin, photosensitivity, tinnitus, reduced hearing, nerve deafness, neuromyopathy, and myopathy, including cardiomyopathy.

Blood disorders have been reported rarely. They include pancytopenia, aplastic anaemia, reversible agranulocytosis, thrombocytopenia, and neutropenia.

There have also been rare reports of changes in liver function, including hepatitis and abnormal liver function tests.

Parenteral therapy with chloroquine can be hazardous and rapid intravenous dosage or the use of high doses can result in cardiovascular toxicity and other symptoms of acute overdosage.

Acute overdosage with chloroquine is extremely dangerous and death can occur within a few hours. Initial effects include headache, gastrointestinal disturbances, drowsiness, and dizziness. Hypokalaemia may occur within a few hours of ingestion of chloroquine. Visual disturbances may be dramatic with a sudden loss of vision. However, the main effect of overdosage with chloroquine is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, coma, and death.

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy.

Keratopathy, characterised by corneal deposits, may occur within a few weeks of starting treatment. However, patients are often asymptomatic and fewer than 50% of affected patients complain of visual symptoms such as photophobia, haloes around lights, or blurred vision. Keratopathy is completely reversible on withdrawal of treatment and is not usually considered to be a contra-indication to continued treatment.[1]

Retinopathy is potentially more serious. The outcome on stopping treatment is unpredictable and changes may be irreversible or may even progress.[2,3] Delayed-onset retinopathy has also been reported in patients many years after cessation of treatment.[4] The reported incidence of retinopathy varies according to the methodology and criteria used.[1,5,6] From studies in patients on long-term antimalarial treatment, it was reported[1] that an accumulation of 100 g of chloroquine [phosphate] (250 mg daily for 1 year) might cause retinopathy; the risk was significantly increased as the total dosage exceeded 300 g. Experience in rheumatology also indicates that the incidence of retinal toxicity is dose-related. While the total cumulative dose, the duration of treatment, and the age of the patient might all affect the incidence of retinal toxicity,[7,8] the daily dose might be the most important factor.[9] It has been suggested that the risk of retinal damage is small with daily doses of up to 4 mg/kg of chloroquine phosphate (= about 2.5 mg/kg of chloroquine base daily) or up to 6.5 mg/kg of hydroxychloroquine sulfate.[9] In obese patients, excessive dosage should be avoided by calculating dosage on the basis of lean body-weight. It appears that retinopathy is rarely, if ever, associated with the weekly dosages of chloroquine recommended for the prophylaxis of malaria.[10,11]

In the UK, a review group[12] convened by the Royal College of Ophthalmologists made **recommendations** regarding use by rheumatologists and dermatologists. Chloroquine should only be used if other drugs have failed as there are inadequate data to advise on a safe daily or cumulative dose; thus the following recommendations relate only to *hydroxychloroquine* as no guidelines have been published for chloroquine.

- Baseline assessment before treatment with hydroxychloroquine is commenced (maximum daily dosage 6.5 mg/kg lean body-weight) should consist of checking renal and hepatic function, questioning the patient about visual impairment not corrected by glasses, and recording near visual acuity.
- Thereafter, patients should be monitored annually with enquiry about visual symptomatology, rechecking of acuity, and assessment for impaired vision.
- Patients should be referred to an ophthalmologist if problems are detected either before or during treatment.
- Those taking long-term hydroxychloroquine should be subject to occasional ophthalmological review after 5 years of continuous treatment.

UK licensed product information for *chloroquine* recommends ophthalmic examination at 3 to 6 monthly intervals in patients receiving continuous high doses for more than a year, or weekly treatment for more than 3 years, or for those in whom total intake exceeds 100 g or 1.6 g/kg.

Similar guidelines on screening have been issued in the USA.[13]

1. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; **75** (suppl 1A): 25–34.
2. Ogawa S, *et al.* Progression of retinopathy long after cessation of chloroquine therapy. *Lancet* 1979; **i:** 1408.
3. Easterbrook M. Ocular effects and safety of antimalarial agents. *Am J Med* 1988; **85** (suppl 4A): 23–9.
4. Ehrenfeld M, *et al.* Delayed-onset chloroquine retinopathy. *Br J Ophthalmol* 1986; **70:** 281–3.
5. Finbloom DS, *et al.* Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; **12:** 692–4.
6. Morsman CDG, *et al.* Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye* 1990; **4:** 572–6.
7. Elman A, *et al.* Chloroquine retinopathy in patients with rheumatoid arthritis. *Scand J Rheumatol* 1976; **5:** 161–6.
8. Marks JS, Power BJ. Is chloroquine obsolete in treatment of rheumatic disease? *Lancet* 1979; **i:** 371–3.
9. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; **75** (suppl 1A): 40–5.
10. Breckenridge A. Risks and benefits of prophylactic antimalarial drugs. *BMJ* 1989; **299:** 1057–8.
11. Lange WR, *et al.* No evidence for chloroquine-associated retinopathy among missionaries on long-term malaria chemoprophylaxis. *Am J Trop Med Hyg* 1994; **51:** 389–92.
12. Bourke B *et al.* Royal College of Ophthalmologists, British Association of Dermatologists, and British Society for Rheumatology. Hydroxychloroquine and ocular toxicity: recommendations on screening (October 2009). Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Hydroxychloroquine_and_Ocular_Toxicity_final%20Oct%202009.pdf (accessed 04/08/10)
13. Marmor MF, *et al.* American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 2011; **118:** 415–22.

Effects on glucose metabolism. While hypoglycaemia has occurred with quinine (see p. 667.1), it was not generally thought to be associated with *chloroquine*; however, there has been a report of its occurrence in a patient with reactive hypoglycaemia who was using chloroquine for the management of psoriatic arthritis.[1]

Recurrent hypoglycaemia was also reported in a non-diabetic patient given *hydroxychloroquine* for the treatment of rheumatoid arthritis.[2]

1. Abu-Shakra M, Lee P. Hypoglycemia: an unusual adverse reaction to chloroquine. *Clin Exp Rheumatol* 1994; **12:** 95.

2. Cansu DÜ, Korkmaz C. Hypoglycaemia induced b y hydroxychloroquine in a non-diabetic patient treated for RA. *Rheumatology (Oxford)* 2008; **47:** 378–9.

Effects on the hair. Hair depigmentation is a rare, but reversible adverse effect of chloroquine.[1,2] Most cases have occurred after 3 consecutive months of treatment with daily oral doses of 500 mg or more, although rapid onset is also possible;[1] hypopigmentation seldom occurs with daily doses of less than 300 mg.[2] These effects are entirely reversible, with normal pigmentation returning once the dose of chloroquine is stopped or reduced.[2] Although hydroxychloroquine has also very rarely been reported to cause hypopigmentation,[2,3] chloroquine-induced hypopigmentation has resolved after chloroquine was replaced with hydroxychloroquine.[2]

1. Donovan JC, Price VH. Images in clinical medicine. Chloroquine-induced hair hypopigmentation. *N Engl J Med* 2010; **363:** 372.
2. Di Giacomo TB, *et al.* Chloroquine -induced hair depigmentation. *Lupus* 2009; **18:** 264–6.
3. Meller S, *et al.* Clinical image: blonde by prescription. *Arthritis Rheum* 2008; **58:** 2286.

Effects on the heart. Studies in patients with malaria[1] and in healthy subjects[2] indicate that the acute cardiovascular toxicity that may be associated with parenteral use of chloroquine is related to transiently high plasma concentrations produced during the early part of the distribution phase; these findings appear to confirm that the dosage rate is a major determinant of this toxicity. Cardiac conduction abnormalities, including heart block and sudden cardiac arrest, have also occurred in patients receiving long-term oral therapy with chloroquine,[3,4] including use in lupus erythematosus,[5,6] as well as after chloroquine overdosage or abuse.[7,8] Histological changes in endomyocardial biopsy specimens from 2 patients with cardiomyopathy associated with chloroquine or hydroxychloroquine therapy were found to be virtually identical to those seen in the skeletal muscle of patients with chloroquine-induced myopathy[9] (see also Effects on the Muscles, below).

1. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; **155:** 192–201.
2. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; **22:** 31–6.
3. Ogola ESN, *et al.* Chloroquine related complete heart block with blindness: case report. *East Afr Med J* 1992; **69:** 50–2.
4. Aslanger E, Altun I. Sudden cardiac arrest in a patient taking chloroquine. *Resuscitation* 2009; **80:** 285–6.
5. Piette J-C, *et al.* Chloroquine cardiotoxicity. *N Engl J Med* 1987; **317:** 710–11.
6. Baguet J-P, *et al.* Chloroquine cardiomyopathy with conduction disorders. *Heart* 1999; **81:** 221–3.
7. Ihenacho HNC, Magulike E. Chloroquine abuse and heart block in Africans. *Aust N Z J Med* 1989; **19:** 17–21.
8. Phipps C, *et al.* Fatal chloroquine poisoning: a rare cause of sudden cardiac arrest. *Ann Acad Med Singapore* 2011; **40:** 296–2.
9. Ratliff NB, *et al.* Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. *N Engl J Med* 1987; **316:** 191–3.

Effects on mental function. Serious psychotic effects (depersonalisation and anxiety) developed in a healthy subject who took a standard 3-day course of oral chloroquine for the treatment of *Plasmodium falciparum* malaria, as part of a clinical study. Three weeks after completing the course she still had serious concentration problems and her symptoms gradually resolved over the next 4 months.[1]

1. Telgt DS, *et al.* Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. *Ann Pharmacother* 2005; **39:** 551–4.

Effects on the muscles. The myopathy induced by chloroquine is characterised by progressive weakness and atrophy of proximal muscles and can develop insidiously after periods of therapy ranging from a few weeks to a few years.[1] There are often mild sensory changes, depression of tendon reflexes, and abnormal nerve conduction studies suggestive of an associated peripheral neuropathy. The myopathy is reversible on withdrawal of treatment but recovery may take several months. Cardiomyopathy may also occur (see under Effects on the Heart, above). Similar effects have been reported with hydroxychloroquine.[2] In a retrospective review of 4405 patients with rheumatic disorders, 214 had received chloroquine or hydroxychloroquine and, of these, 3 developed myopathy.[3]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; **24:** 304–21.
2. Estes ML, *et al.* Chloroquine neuromyotoxicity. *Am J Med* 1987; **82:** 447–55.
3. Avina-Zubieta JA, *et al.* Incidence of myopathy in patients treated with antimalarials: a report of three cases and a review of the literature. *Br J Rheumatol* 1995; **34:** 166–70.

Effects on the nervous system. Apart from neuropathies (see Effects on the Muscles, above) other adverse effects of chloroquine on the nervous system have included isolated reports of extrapyramidal symptoms and other involuntary movements[1,2] (in patients being treated for malaria), nystagmus[3] (in a patient on prolonged treatment for rheumatoid arthritis), and convulsions[4,5] and nonconvulsive status epilepticus[6] (in patients on malaria prophylaxis).

1. Umez-Eronini EM, Eronini EA. Chloroquine induced involuntary movements. *BMJ* 1977; **1:** 945–6.
2. Singhi S, *et al.* Chloroquine-induced involuntary movements. *BMJ* 1977; **2:** 520.
3. Marks JS. Motor polyneuropathy and nystagmus associated with chloroquine phosphate. *Postgrad Med J* 1979; **55:** 569.
4. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; **297:** 526–7.
5. Fish DR, Espri MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
6. Mülhauser P, *et al.* Chloroquine and nonconvulsive status epilepticus. *Ann Intern Med* 1995; **123:** 76–7.

Effects on the skin. *Pruritus* is common in patients given chloroquine for the treatment of malaria and it may become so severe as to compromise treatment. Itching starts a few hours after use but usually remits spontaneously within 72 hours. Although antihistamines are generally thought ineffective,[1,2] a few patients may obtain some relief.[3] The incidence of pruritus is purported to be higher in black patients, but this may only reflect the greater number of black patients surveyed. The aetiology of this reaction is unknown, but this apparent higher incidence has prompted suggestions that it may have a genetic basis[4] or be related to the affinity of chloroquine for melanin.[2] Chloroquine's main metabolite, monodesethylchloroquine, has been implicated,[5] although there is also some evidence suggesting that patients with pruritus metabolise chloroquine more slowly.[6] A survey[1] in Nigeria found that, of 1100 patients, 74% had pruritus during antimalarial therapy; 61% of these reacted to chloroquine, 30% reacted to amodiaquine, 2.5% to Fansidar (pyrimethamine-sulfadoxine), and, 6.5% reacted to all three. In another study in Nigeria,[4] the incidence of pruritus was reported to be 14% (8 of 56 patients) for chloroquine, 27% (14 of 52) for amodiaquine, and 13% (7 of 53) for halofantrine; none of 58 patients receiving quinine or 82 patients receiving mefloquine had pruritus. In contrast, in a study in Thailand only 1.9% of 1189 chloroquine-treated patients reported pruritus.[7]

There have been rare reports of more severe cutaneous reactions associated with chloroquine, including *toxic epidermal necrolysis*,[8,9] *erythema multiforme*,[10] and *Stevens-Johnson syndrome*,[11] although the causal role of chloroquine is not always clear as some of these patients also received other antimalarials, sometimes at an inappropriate dosage. In a more recent case of toxic epidermal necrolysis,[12] chloroquine given alone for malaria prophylaxis was the probable cause. A young patient receiving radiotherapy developed a localised bullous eruption and rapid progressive moist desquamation on the third day of treatment with oral chloroquine for malaria.[13] For a discussion including the possible effect of chloroquine on the incidence of erythema multiforme in patients taking pyrimethamine with sulfadoxine, see Adverse Effects with Sulfonamides, under Pyrimethamine, p. 663.3.

1. Ajayi AA, *et al.* Epidemiology of antimalarial-induced pruritus in Africans. *Eur J Clin Pharmacol* 1989; **37:** 539–40.
2. Osifo NG. Chloroquine-induced pruritus among patients with malaria. *Arch Dermatol* 1984; **120:** 80–2.
3. Okor RS. Responsiveness of chloroquine-induced pruritus to antihistamine therapy—clinical survey. *J Clin Pharm Ther* 1990; **15:** 147–50.
4. Sowunmi A, *et al.* Pruritus and antimalarial drugs in Africans. *Lancet* 1989; **ii:** 213.
5. Essien EE, *et al.* Chloroquine disposition in hypersensitive and non-hypersensitive subjects and its significance in chloroquine-induced pruritus. *Eur J Drug Metab Pharmacokinet* 1989; **14:** 71–7.
6. Ademowo OG, *et al.* The disposition of chloroquine and its main metabolite desethylchloroquine in volunteers with and without chloroquine-induced pruritus: evidence for decreased chloroquine metabolism in volunteers with pruritus. *Clin Pharmacol Ther* 2000; **67:** 237–41.
7. Bussaratid V, *et al.* Frequency of pruritus in Plasmodium vivax malaria patients treated with chloroquine in Thailand. *Trop Doct* 2000; **30:** 211–14.
8. Kanwar AJ, Singh OP. Toxic epidermal necrolysis—drug induced. *Indian J Dermatol* 1976; **21:** 73–7.
9. Phillips-Howard PA, Warwick Buckler J. Idiosyncratic reaction resembling toxic epidermal necrolysis caused by chloroquine and Maloprim. *BMJ* 1988; **296:** 1605.
10. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine-pyrimethamine in Switzerland. *Lancet* 1986; **i:** 610.
11. Bamber MG, *et al.* Fatal Stevens-Johnson syndrome associated with Fansidar and chloroquine. *J Infect* 1986; **13:** 31–3.
12. Boffa MJ, Chalmers RJG. Toxic epidermal necrolysis due to chloroquine phosphate. *Br J Dermatol* 1994; **131:** 444–5.
13. Rustogi A, *et al.* Unexpected skin reaction induced by radiotherapy after chloroquine use. *Lancet Oncol* 2006; **7:** 608–9.

Overdosage. For adverse effects associated with chloroquine overdosage, see Treatment of Adverse Effects, below.

Treatment of Adverse Effects

Acute overdosage with chloroquine can be rapidly lethal and intensive symptomatic supportive treatment should be started immediately (see Acute Poisoning, p. 1537.1). The first steps should be to maintain adequate respiration and to correct any cardiovascular disturbances. Early use of adrenaline with diazepam (see below) may minimise the cardiotoxicity of chloroquine and control arrhythmias. The benefit of gastric decontamination is uncertain, but the UK *National Poisons Information Service* advises that the use of oral activated charcoal can be considered for adults or children who present within 1 hour of ingesting more than the equivalent of 20 mg/kg of chloroquine base; alternatively, for adults, gastric lavage can be considered within 1 hour of a potentially life-threatening overdose (but see below). Intravenous sodium bicarbonate should be given to correct metabolic acidosis. Other methods to increase the elimination of chloroquine, such as dialysis, are probably of little use.

Overdosage. Chloroquine overdosage is the most severe and frequent cause of intoxication with antimalarial drugs and chloroquine is often used for suicide attempts. Severe toxic manifestations may occur within 1 to 3 hours and fatal outcomes usually occur within 2 to 3 hours of drug ingestion. The major clinical symptoms are of neurological, respiratory, and cardiovascular toxicity;[1] death is usually due to cardiac arrest related to the direct effect of chloroquine on the myocardium.[2] Chloroquine has a low safety margin: doses of 20 mg/kg are considered toxic and 30 mg/kg may be lethal. The mortality rate in some published studies has ranged from 10 to 30%.[1]

Gastric lavage is not generally recommended by the UK *National Poisons Information Service* but they suggest it may be considered in adults if seen within 1 hour of a potentially life-threatening overdose of chloroquine. However, it has been noted that if it were attempted it should be preceded by correction of severe cardiovascular disturbances and institution of artificial ventilation because insertion of the stomach tube may induce sudden cardiac arrest or convulsions; induction of emesis is contra-indicated because of the risk of lung aspiration.[1]

Activated charcoal has been recommended to limit absorption of chloroquine that may be left in the gut.[3] There is no evidence to indicate that attempts to increase chloroquine elimination such as acidification of the urine, haemodialysis, peritoneal dialysis, or exchange transfusion, are effective in overdosage. Elimination in the urine is more dependent on haemodynamic status than on infusion of osmotic solutions or acidification. Any clearance achieved by haemoperfusion or haemodialysis is low in comparison with the normal total body clearance.[1]

It is not clear if correction of hypokalaemia is essential, but giving potassium should be avoided in the initial phases of intoxication when conduction disturbances still exist. The degree of hypokalaemia may be correlated with the severity of chloroquine intoxication and might be useful diagnostically.[4] However, chloroquine-induced hypokalaemia may be due to a transport-dependent mechanism rather than to true potassium depletion and overzealous correction could result in hyperkalaemia.[4]

Since there had been no effective treatment for severe chloroquine poisoning, one group of workers tried using early mechanical ventilation, with adrenaline and high doses of diazepam, both given intravenously, to counteract cardiotoxicity, with encouraging results.[2] Diazepam had earlier been shown to decrease the cardiotoxicity of chloroquine in *animal* studies and there had been several clinical reports of beneficial responses. It was considered that routine use of adrenaline before the onset of cardiac arrhythmia might be beneficial in the treatment of severe chloroquine poisoning.[2] UK licensed product information for chloroquine suggests giving adrenaline by intravenous infusion in a dose of 250 nanograms/kg per minute initially, with increments of 250 nanograms/kg per minute until adequate systolic blood pressure is restored, and diazepam by intravenous infusion in a dose of 2 mg/kg over 30 minutes as a loading dose, followed by 1 to 2 mg/kg per day for up to 2 to 4 days.

Overdosage with hydroxychloroquine has responded to measures similar to those used in the management of chloroquine overdosage.[5]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
2. Riou B, *et al.* Treatment of severe chloroquine poisoning. *N Engl J Med* 1988; **318:** 1–6.
3. Neuvonen PJ, *et al.* Prevention of chloroquine absorption by activated charcoal. *Hum Exp Toxicol* 1992; **11:** 117–20.
4. Clemessy J-L, *et al.* Hypokalaemia related to acute chloroquine ingestion. *Lancet* 1995; **346:** 877–80.
5. Jordan P, *et al.* Hydroxychloroquine overdose: toxicokinetics and management. *J Toxicol Clin Toxicol* 1999; **37:** 861–4.

Precautions

Excessive doses of chloroquine and hydroxychloroquine are associated with retinal or visual field changes and the precautions to be taken in order to minimise such toxicity are discussed under Effects on the Eyes in Adverse Effects, p. 651.2. There may be a temporary effect on visual accommodation.

Care is necessary when giving chloroquine to patients with hepatic or renal impairment, or to those with severe gastrointestinal disorders, a history of psoriasis, or

neurological disorders, especially a history of epilepsy (see below for advice not to use for malaria prophylaxis). Chloroquine should be used with caution in patients with myasthenia gravis as it may aggravate the condition. Patients with G6PD deficiency should be observed for haemolytic anaemia during chloroquine treatment (but see below). Full blood counts should be performed at regular intervals during extended treatment with chloroquine. Although there have been reports of fetal abnormalities associated with the use of chloroquine during pregnancy, the risks of malaria are considered to be greater and there appears to be no justification for withholding chloroquine for the treatment or prophylaxis of malaria.

It is important that if chloroquine is given intravenously it should be by slow infusion (typically around 0.8 to 1.25 mg/kg per hour) otherwise severe cardiotoxicity may develop.

Breast feeding. Chloroquine is distributed into breast milk, but not in an amount adequate to provide chemoprophylaxis against malaria for the infant (see under Pharmacokinetics, p. 654.2). Furthermore, no adverse effects have been seen in breast-feeding infants whose mothers were receiving chloroquine, and the most recent guidance from the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/04/04)

Epilepsy. After reports[1,2] of convulsions associated with the use of chloroquine for malaria prophylaxis in 4 previously healthy patients and in 2 patients with a history of seizures, it has been suggested that prospective travellers who have a history of epilepsy should be warned of the risk. Although it was initially considered[3] that this should not restrict the use of chloroquine, UK malaria experts have recommended that it should be avoided for malaria prophylaxis in patients with epilepsy.[4]

1. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; **297:** 526–7.
2. Fish DR, Espir MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
3. Hellgren U, Rombo L. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
4. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

G6PD deficiency. Licensed product information for chloroquine advises that the drug be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as there may be a risk of haemolysis. However, a review[1] noted that reports of haemolysis in G6PD-deficient patients given chloroquine involved its use with other agents known to cause haemolysis and that there were no reports showing an association between chloroquine monotherapy and haemolysis in G6PD-deficient patients. It concluded that, while it was prudent to use caution in G6PD-deficient patients when combining chloroquine with drugs that may cause haemolysis, there was no basis upon which to contravene chloroquine monotherapy.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies *chloroquine* as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1] Other drugs used for the prophylaxis and/or treatment of malaria such as *doxycycline*, *hydroxychloroquine*, *mefloquine*, *proguanil* (alone or with *atovaquone*), and *quinine* are also classified as possibly porphyrinogenic.

Tetracycline and the combination of *artemether plus lumefantrine* are classified as probably porphyrinogenic, while *clindamycin* is classified as porphyrinogenic; they should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

Atovaquone is classified as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

Pyrimethamine is not classified.

Chloroquine has been tried in the treatment of porphyria cutanea tarda, but this may be associated with hepatotoxicity (see under Uses, p. 651.1).

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/10/11)

Pregnancy. There has been concern about the potential teratogenic effects of chloroquine because of a few case reports including defects in hearing and vision.[1] Two of 169 infants, born to women given chloroquine 300 mg weekly throughout pregnancy, had birth defects compared with 4 of 454 control infants whose mothers had not received antimalarials; the difference was not significant. Similarly, a randomised, placebo-controlled study[2] in 951 pregnant Thai women found that the use of prophylactic chloroquine (dosed as above) during pregnancy had no impact on maternal anaemia, infant birth-weight, gestational age, or development, or on their growth, neurological development, or visual acuity at 1 year of age. The data suggested that chloroquine in the recommended *prophylactic* doses is not a strong teratogen and that its proved antimalarial benefits outweigh any possible risk of low-grade teratogenicity. The UK *National Teratology Information Service*[3] notes that, despite isolated case reports suggesting an increased risk of ototoxicity, the majority of studies have similarly failed to find any increased risk to the fetus from *high* maternal doses of chloroquine during pregnancy; based on the available data, they consider that chloroquine does not lead to an increased teratogenic risk and the drug may therefore be used at any stage of pregnancy if indicated and anticipated to be effective.[3]

1. Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. *BMJ* 1985; **290:** 1466–7.
2. Villegas L, *et al.* Chloroquine prophylaxis against vivax malaria in pregnancy: a randomized, double-blind, placebo-controlled trial. *Trop Med Int Health* 2007; **12:** 209–18.
3. National Teratology Information Service. Use of chloroquine in pregnancy (issued September 2008). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Chloroquine%202008.pdf (accessed 08/06/11)

Psoriatic arthritis. It is recommended that chloroquine and hydroxychloroquine should not be used in the treatment of psoriatic arthritis as exacerbations of skin lesions can occur. Some patients may go on to develop generalised erythroderma with subsequent exfoliative dermatitis.[1] However, there has been controversy over the reported incidence of this adverse effect.[2,3]

1. Slagel GA, James WD. Plaquenil-induced erythroderma. *J Am Acad Dermatol* 1985; **12:** 857–62.
2. Luzar MJ. Hydroxychloroquine in psoriatic arthropathy: exacerbations of psoriatic skin lesions. *J Rheumatol* 1982; **9:** 462–4.
3. Sayers ME, Mazanec DJ. Use of antimalarial drugs for the treatment of psoriatic arthritis. *Am J Med* 1992; **93:** 474–5.

Renal impairment. Although the elimination of chloroquine is prolonged in renal impairment no dosage adjustment is required in the treatment of malaria. Similarly, dosage reduction is not required for chloroquine prophylaxis except in those with severe renal impairment. Doses tend to be reduced when it is given for longer periods to patients with renal impairment.

Interactions

There is an increased risk of inducing ventricular arrhythmias if chloroquine is used with halofantrine (see p. 655.1) or other arrhythmogenic drugs such as amiodarone and moxifloxacin. There is an increased risk of convulsions when chloroquine is given with mefloquine. The absorption of chloroquine can be reduced by antacids or kaolin; when any of these drugs are used with chloroquine dosing should be separated by at least 4 hours. The metabolism of chloroquine may be inhibited by cimetidine.

Agalsidase. For a warning that chloroquine should not be used with *agalsidase alfa* or *beta*, see p. 2438.1.

Antiepileptics. Chloroquine may lower the convulsive threshold and thus antagonise the actions of antiepileptics such as *carbamazepine* and *valproate*.

Antimalarials. Chloroquine should not be used with *halofantrine* since the latter prolongs the QT interval and therefore there is an increased potential to induce arrhythmias (see p. 655.1). Use of chloroquine with *mefloquine* increases the risk of convulsions. Also use of chloroquine with *proguanil* may increase the incidence of proguanil-associated mouth ulceration.[1] The activity of chloroquine may be affected when it is given with other *antimalarials*. *Quinine* and chloroquine when used together may be antagonistic.[2] Mixtures of chloroquine with *quinine*, *mefloquine*, *amodiaquine*, *artemisinin*, or *pyrimethamine-sulfadoxine* were antagonistic *in vitro* against *Plasmodium falciparum*.[3]

1. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; **335:** 164.
2. Hall AP. Quinine and chloroquine antagonism in falciparum malaria. *Trans R Soc Trop Med Hyg* 1973; **67:** 425.
3. Stahel E, *et al.* Antagonism of chloroquine with other antimalarials. *Trans R Soc Trop Med Hyg* 1988; **82:** 221.

Antimicrobials. A woman who had previously tolerated chloroquine alone had acute dystonic reactions when also given *metronidazole*.[1] Chloroquine may also reduce the gastrointestinal absorption of *ampicillin* (see p. 219.3).

1. Achumba JI, *et al.* Chloroquine-induced acute dystonic reactions in the presence of metronidazole. *Drug Intell Clin Pharm* 1988; **22:** 308–10.

Ciclosporin. Chloroquine has been reported to increase plasma concentrations of ciclosporin (see p. 1957.1).

Digoxin. Hydroxychloroquine has been reported to increase plasma concentrations of digoxin (see p. 1357.1).

Gastrointestinal drugs. Patients often wish to take chloroquine with food, antacids, or other gastrointestinal drugs to alleviate gastrointestinal irritation. Dosage with *food* may be beneficial as it appears to improve the absorption of chloroquine.[1,2] However, *antacids* or *kaolin* can reduce the absorption of chloroquine and it is therefore recommended that they should be given at least 4 hours apart.[3,4]

Cimetidine and chloroquine should be used with caution as *cimetidine* can significantly reduce the metabolism and elimination of chloroquine and increase its volume of distribution;[5] *ranitidine*, however, appears to have little effect on the pharmacokinetics of chloroquine.[6]

1. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; **23:** 271–3.
2. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; **79:** 559.
3. McElnay JC, *et al.* In vitro experiments on chloroquine and pyrimethamine absorption in the presence of antacid constituents or kaolin. *J Trop Med Hyg* 1982; **85:** 153–8.
4. McElnay JC, *et al.* The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. *J Trop Med Hyg* 1982; **85:** 159–63.
5. Ette EI, *et al.* Chloroquine elimination in humans: effect of low-dose cimetidine. *J Clin Pharmacol* 1987; **27:** 813–16.
6. Ette EI, *et al.* Effect of ranitidine on chloroquine disposition. *Drug Intell Clin Pharm* 1987; **21:** 732–4.

Levothyroxine. For a report of a possible interaction of chloroquine with levothyroxine, see p. 2341.3.

Praziquantel. For a report of reduced bioavailability of praziquantel when given with chloroquine, see p. 165.2.

Vaccines. Although chloroquine has been reported to reduce the antibody response to *human diploid rabies vaccine* (see p. 2415.1), the immune response to other vaccines used in routine immunisation schedules (tetanus, diphtheria, measles, poliomyelitis, typhoid, and BCG) has not been found to be altered by chloroquine prophylaxis.[1,2]

1. Greenwood BM. Chloroquine prophylaxis and antibody response to immunisation. *Lancet* 1984; **ii:** 402–3.
2. Wolfe MS. Precautions with oral live typhoid (Ty 21a) vaccine. *Lancet* 1990; **336:** 631–2.

Pharmacokinetics

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when given orally. Absorption is also rapid after intramuscular or subcutaneous use. It is widely distributed into body tissues and has a large apparent volume of distribution. It accumulates in high concentrations in some tissues, such as the kidneys, liver, lungs, and spleen and is strongly bound in melanin-containing cells such as those in the eyes and the skin. It also crosses the placenta. Chloroquine is eliminated very slowly from the body and it may persist in tissues for months or even years after stopping therapy.

Chloroquine is extensively metabolised in the liver, mainly to monodesethylchloroquine with smaller amounts of bisdesethylchloroquine (didesethylchloroquinine) and other metabolites being formed. Monodesethylchloroquine has been reported to have some activity against *Plasmodium falciparum*. Chloroquine and its metabolites are excreted in the urine, with about half of a dose appearing as unchanged drug and about 10% as the monodesethyl metabolite. Chloroquine and its monodesethyl metabolite are both distributed into breast milk.

General references.

1. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine; clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.
2. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine: focus on recent advancements. *Clin Pharmacokinet* 1996; **31:** 257–74.
3. Obua C, *et al.* Population pharmacokinetics of chloroquine and sulfadoxine and treatment response in children with malaria: suggestions for an improved dose regimen. *Br J Clin Pharmacol* 2008; **65:** 493–501.
4. Lee SJ, *et al.* Chloroquine pharmacokinetics in pregnant and nonpregnant women with vivax malaria. *Eur J Clin Pharmacol* 2008; **64:** 987–92.
5. Karunajeewa HA, *et al.* Pharmacokinetics of chloroquine and monodesethylchloroquine in pregnancy. *Antimicrob Agents Chemother* 2010; **54:** 1186–92.

Chloroquine is rapidly **absorbed** from the gastrointestinal tract but peak plasma concentrations after *oral* doses can vary considerably.[1] A mean peak plasma concentration of 76 nanograms/mL has been obtained in healthy adults a mean of 3.6 hours after giving the equivalent of 300 mg of chloroquine base orally as tablets.[2] In children with uncomplicated malaria given the equivalent of 10 mg/kg peak plasma concentrations of 250 nanograms/mL have been reached after 2 hours;[3] a mean peak of 134 nanograms/mL has been obtained after 5 hours in healthy children given a similar dose.[4] *Nasogastric* use has also

produced therapeutic concentrations in children with severe falciparum malaria.[5]

Oral bioavailability is increased if chloroquine is taken with food[6,7] and some beverages[8] and may also be affected by the state of health of the patient; mean values have ranged from about 70% in patients with malaria[9] to 78 or 89% in healthy adults.[2] Although oral bioavailability appears to be unaltered in moderately undernourished adults[10] it has been reported that it may be significantly reduced in children with kwashiorkor.[4]

Preliminary studies with chloroquine suppositories indicated that, although *rectal* bioavailability is less than half of that of oral chloroquine, sustained therapeutic concentrations may be achieved.[11]

Absorption is also rapid after *subcutaneous* or *intramuscular* injection and mean peak plasma concentrations of chloroquine have been obtained within about 30 minutes.[5,9,12]

Chloroquine has a large apparent volume of **distribution**. A multicompartmental model appears to be necessary to describe the distribution kinetics of chloroquine.[2,13] After intravenous dosage there is a multi-exponential decline in plasma concentrations as chloroquine distributes out of a central compartment that has been estimated to be several orders of magnitude smaller than the total volume of distribution.[5,14] This slow distribution out of the central compartment produces transiently high cardiotoxic concentrations of chloroquine if the overall rate of parenteral delivery is not carefully controlled.

Reported mean values for **protein binding** have ranged from about 58 to 64%.[15,16] Chloroquine is also bound to platelets and granulocytes so that the plasma concentration is only 10 to 15% of that in whole blood.[17] If these cells are not removed by gentle centrifugation during analysis, erroneously high plasma concentrations will be reported. Furthermore, as chloroquine concentrations determined in serum are higher than those in plasma, probably due to release of chloroquine from platelets during coagulation, it is crucial to state whether analysis has been done on whole blood, serum, or properly separated plasma.

About 50% of a dose of chloroquine is **metabolised** in the liver, mainly to the *N*-dealkylated metabolite monodesethylchloroquine; smaller amounts of bisdesethylchloroquine, 7-chloro-4-aminoquinoline, and *N*-oxidation products are formed. Some of these metabolites may contribute to the cardiotoxicity associated with chloroquine. In one study, peak plasma concentrations of 7-chloro-4-aminoquinoline were found to be twice those of unchanged chloroquine despite the fact that only relatively small amounts are formed; this appears to be due to its fast rate of formation and long elimination half-life.[18]

A mean of 42 to 47% of a dose has been reported to be **excreted** in the urine as unchanged chloroquine and 7 to 12% as monodesethylchloroquine.[2] Various estimates of the terminal elimination half-life of chloroquine range from several days to up to 2 months, but its slow release from tissues ensures that small amounts may still be detected after a year.[18,19]

1. Hellgren U, *et al.* On the question of interindividual variations in chloroquine concentrations. *Eur J Clin Pharmacol* 1993; **45:** 383–5.
2. Gustafsson LL, *et al.* Disposition of chloroquine in man after single intravenous and oral doses. *Br J Clin Pharmacol* 1983; **15:** 471–9.
3. Adelusi SA, *et al.* Kinetics of the uptake and elimination of chloroquine in children with malaria. *Br J Clin Pharmacol* 1982; **14:** 483–7.
4. Walker O, *et al.* Single dose disposition of chloroquine in kwashiorkor and normal children—evidence for decreased absorption in kwashiorkor. *Br J Clin Pharmacol* 1987; **23:** 467–72.
5. White NJ, *et al.* Chloroquine treatment of severe malaria in children: pharmacokinetics, toxicity, and new dosage recommendations. *N Engl J Med* 1988; **319:** 1493–1500.
6. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; **23:** 271–3.
7. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; **79:** 559.
8. Mahmoud BM, *et al.* Significant reduction in chloroquine bioavailability following coadministration with the Sudanese beverages aradaib, karkadi and lemon. *J Antimicrob Chemother* 1994; **33:** 1005–9.
9. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; **155:** 192–201.
10. Tulpule A, Krishnaswamy K. Chloroquine kinetics in the undernourished. *Eur J Clin Pharmacol* 1983; **24:** 273–6.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Phillips RE, *et al.* Divided dose intramuscular regimen and single dose subcutaneous regimen for chloroquine: plasma concentrations and toxicity in patients with malaria. *BMJ* 1986; **293:** 13–16.
13. Frisk-Holmberg M, *et al.* The single dose kinetics of chloroquine and its major metabolite desethylchloroquine in healthy subjects. *Eur J Clin Pharmacol* 1984; **26:** 521–30.
14. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; **22:** 31–6.
15. Walker O, *et al.* Characterization of chloroquine plasma protein binding in man. *Br J Clin Pharmacol* 1983; **15:** 375–7.
16. Ofori-Adjei D, *et al.* Protein binding of chloroquine enantiomers and desethylchloroquine. *Br J Clin Pharmacol* 1986; **22:** 356–8.
17. Gustafsson LL, *et al.* Pitfalls in the measurement of chloroquine concentrations. *Lancet* 1983; **i:** 126.
18. Ette EI, *et al.* Pharmacokinetics of chloroquine and some of its metabolites in healthy volunteers: a single dose study. *J Clin Pharmacol* 1989; **29:** 457–62.
19. Gustafsson LL, *et al.* Chloroquine excretion following malaria prophylaxis. *Br J Clin Pharmacol* 1987; **24:** 221–4.

Distribution into breast milk. Studies[1,2] have suggested that it is safe for mothers to breast feed when they are receiving chloroquine for treatment of malaria. Although chloroquine and its monodesethyl metabolite are distributed into breast milk, it has been estimated that the amount that would be consumed by an infant is well below the therapeutic range and separate chemoprophylaxis for the infant is required.

There appear to be no data on the excretion of hydroxychloroquine in milk after doses appropriate for the prevention or treatment of malaria, but hydroxychloroquine has been detected in breast milk from 2 mothers receiving doses of 400 mg daily for SLE or rheumatoid arthritis.[3,4] One group of workers estimated that, calculated on a body-weight basis, a 9-month-old infant could receive about 2% of a maternal dose via breast feeding.[3]

1. Ogunbona FA, *et al.* Excretion of chloroquine and desethylchloroquine in human milk. *Br J Clin Pharmacol* 1987; **23:** 473–6.
2. Akintonwa A, *et al.* Placental and milk transfer of chloroquine in humans. *Ther Drug Monit* 1988; **10:** 147–9.
3. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; **17:** 368–9.
4. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; **28:** 357.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nivaquine; ***Austral.***: Chlorquin†; ***Austria***: Resochin; ***Belg.***: Nivaquine; ***Braz.***: Diclokin†; Quinacris; ***Cz.***: Delagil; ***Denm.***: Malarex; ***Fin.***: Heliopar; ***Fr.***: Nivaquine; ***Ger.***: Resochin; Weimerquin†; ***Gr.***: Demoquine; ***Hong Kong***: Chlorocin†; Syncoquin†; ***Hung.***: Delagil; ***India***: Bitaquine; C-Quin; Cadiquin; Chlorolex; Clokit; Cloquin; E-Vivax; Emquin; Idiquin; Ingaquine; Jagquin; La-Quin; Lariago; Larover; Malaquin; Maliago; Maligon; Malswift; Melubrin; Neoquine; Nivaquine-P; Paraquin; Resochin; ***Indon.***: Avloclor†; Malarex; Mexaquin†; Resochin; Riboquin; ***Irl.***: Avloclor†; ***Mex.***: Aralen; Maclorex†; ***Neth.***: Nivaquine; ***NZ***: Chlorquin†; Nivaquine†; ***Philipp.***: Aralen†; Chlorofoz; Chloromax; Clorkin; ***Pol.***: Arechin; ***Port.***: Resochina; ***Rus.***: Delagil (Делагил); ***S.Afr.***: Daramal; Mirquin; Nivaquine; Plasmoquine; ***Singapore***: Malarex; ***Spain***: Resochin; ***Switz.***: Chlorochin; Nivaquine; ***Thai.***: Chewoquine; Diroquine; Genocin; Malacin; Maliaquine†; Nitaquin; P-Roquine; Sinmoquin; ***UK***: Avloclor; Malarivon; Malaviron; Nivaquine; ***Ukr.***: Delagil (Делагил); ***USA***: Aralen.

Multi-ingredient Preparations. ***Fr.***: Nopalu; Savarine; ***Gr.***: Savarine; ***Rus.***: Insanovin (Инсановин); ***Thai.***: Chewoquine SC.

Pharmacopoeial Preparations

BP 2014: Chloroquine Phosphate Tablets; Chloroquine Sulphate Injection; Chloroquine Sulphate Tablets;

USP 36: Chloroquine Hydrochloride Injection; Chloroquine Phosphate Oral Suspension; Chloroquine Phosphate Tablets.

Chlorproguanil Hydrochloride *(BANM, rINNM)*

Chlorproguanil, Chlorhydrate de; Chlorproguanili Hydrochloridum; Clorproguanil, hidrocloruro de; Hidrocloruro de clorproguanil; M-5943; Хлорпрогуанила Гидрохлорид.

1-(3,4-Dichlorophenyl)-5-isopropylbiguanide hydrochloride.

$C_{11}H_{15}Cl_2N_5,HCl$=324.6

CAS — 537-21-3 (chlorproguanil); 15537-76-5 (chlorproguanil hydrochloride).

UNII — 6T04V14CU9.

NOTE. The names Lapdap and Dacart have been used as trade names for fixed-dose combinations of chlorproguanil with dapsone, and chlorproguanil with dapsone and artesunate, respectively.

Profile

Chlorproguanil is a biguanide antimalarial used for malaria prophylaxis similarly to proguanil (p. 661.3). It has sometimes been given as a fixed-dose combination with dapsone. Combination with both dapsone and artesunate has also been investigated for malaria treatment. However, combination products have been associated with decreases in haemoglobin concentrations in patients with G6PD deficiency.

Reviews.

1. Bukirwa H, *et al.* Chlorproguanil-dapsone for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 17/05/05).
2. Fanello CI, *et al.* A randomised trial to assess the efficacy and safety of chlorproguanil/dapsone + artesunate for the treatment of uncomplicated Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 2008; **102:** 412–20.
3. Owusu-Agyei S, *et al.* An open label, randomised trial of artesunate +amodiaquine, artesunate+chlorproguanil-dapsone and artemether-lumefantrine for the treatment of uncomplicated malaria. *PLoS One* 2008; **3:** e2530.
4. Fanello CI, *et al.* High risk of severe anaemia after chlorproguanil-dapsone+artesunate antimalarial treatment in patients with G6PD (A-) deficiency. *PLoS One* 2008; **3:** e4031.
5. Premji Z, *et al.* Chlorproguanil-dapsone-artesunate versus artemether-lumefantrine: a randomized, double-blind phase III trial in African children and adolescents with uncomplicated Plasmodium falciparum malaria. *PLoS One* 2009; **4:** e6682.
6. Tiono AB, *et al.* Chlorproguanil-dapsone-artesunate versus chlorproguanil-dapsone: a randomized, double-blind, phase III trial in African children, adolescents, and adults with uncomplicated *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 2009; **81:** 969–78.

Halofantrine Hydrochloride

(BANM, USAN, rINNM)

Alofantrina Cloridrato; drug entry is base); Halofantriinihydrokloridi; Halofantrin hydrochlorid; Halofantrina, hidrocloruro de; Halofantrine, Chlorhydrate d'; Halofantrine, chlorhydrate de; Halofantrin-hidroklorid; Halofantrinhydrochlorid; Halofantrinhydroklorid; Halofantrini Hydrochloridum; Halofantrino hidrochloridas; Hidrocloruro de halofantrina; WR-171669; Галофантрина Гидрохлорид.

(*RS*)-3-Dibutylamino-1-(1,3-dichloro-6-trifluoromethyl-9-phenanthryl)propan-1-ol hydrochloride; 1,3-Dichloro-α-[2-(dibutylamino)ethyl]-6-trifluoromethyl-9-phenanthrenemethanol hydrochloride.

$C_{26}H_{30}Cl_2F_3NO,HCl$=536.9

CAS — 69756-53-2 (halofantrine); 36167-63-2 (halofantrine hydrochloride); 66051-63-6 (±-halofantrine).

ATC — P01BX01.

UNII — H77DL0Y630.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Halofantrine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

Uses and Administration

Halofantrine is a 9-phenanthrenemethanol antimalarial that has been used in the *treatment* of uncomplicated chloroquine-resistant falciparum and of chloroquine-resistant vivax malaria (see p. 644.1). Halofantrine is a blood schizontocide but has no activity against exoerythrocytic forms. Its value is limited by its unpredictable bioavailability and by cardiotoxicity. It should *not* be used where mefloquine has been used for prophylaxis (for cardiac hazard, see Effects on the Heart, below). Halofantrine should also *not* be used for malaria prophylaxis and is no longer recommended for standby treatment.

In the treatment of malaria, halofantrine hydrochloride has been given orally as 3 doses of 500 mg at intervals of 6 hours, on an empty stomach. A second course should be given after a week to patients with little or no previous exposure to malaria.

For details of doses in children, see below.

Administration in children. Halofantrine has been used in children from 1 year of age for the treatment of uncomplicated chloroquine-resistant falciparum or chloroquine-resistant vivax malaria. A total oral dose of about 24 mg/kg, divided into 3 doses given at 6-hour intervals, has been recommended; children weighing more than 40 kg may be dosed as for adults (see above).

Adverse Effects and Precautions

Adverse effects associated with halofantrine include diarrhoea, abdominal pain, nausea, vomiting, pruritus, and rash. Transient elevation of serum transaminases, intravascular haemolysis, and hypersensitivity reactions have also been reported.

Halofantrine can adversely affect the heart particularly by prolonging QT interval. Serious ventricular arrhythmias have been reported and fatalities have occurred. As a result it is contra-indicated in patients known to have a prolonged QT interval or those with cardiac disease or a family history of congenital QT prolongation, and also in those with unexplained syncopal attacks, thiamine deficiency, or electrolyte disturbances, or taking other arrhythmogenic drugs (see also Effects on the Heart, below, and Interactions, p. 655.1).

Halofantrine is not recommended during pregnancy or breast feeding. It should not be taken on a full stomach since this increases its bioavailability and thus the risk of toxicity; after taking halofantrine, fatty food should be avoided for 24 hours.

Effects on the blood. Halofantrine has been associated with acute intravascular haemolysis.[1,2]

1. Vachon F, *et al.* Halofantrine and acute intravascular haemolysis. *Lancet* 1992; **340:** 909–10.
2. Mojon M, *et al.* Intravascular haemolysis following halofantrine intake. *Trans R Soc Trop Med Hyg* 1994; **88:** 91.

Effects on the heart. Prolonged PR[1,2] and QT[1-5] intervals have been reported in patients given halofantrine and there are individual reports of fatal cardiac arrest[1,5] and of torsade de pointes.[4] In 1994, the UK CSM[6] noted that QT interval prolongation occurred at recommended doses of halofantrine in the majority of patients and that worldwide there had been 14 reports of cardiac arrhythmias associated with halofantrine; 8 patients were known to

have died. To reduce the risk of arrhythmias they stressed that halofantrine should *not* be taken with meals, with other drugs that may induce arrhythmias (e.g. quinine, chloroquine, and mefloquine; tricyclic antidepressants; antipsychotics; certain antiarrhythmics; and the antihistamines terfenadine and astemizole), or with drugs causing electrolyte disturbances. They also stated that it should *not* be given to patients known to have prolongation of the QT interval or with any form of cardiac disease associated with QT interval prolongation or ventricular arrhythmia (e.g. coronary heart disease, cardiomyopathy, or congenital heart disease). Some workers[2] have suggested ECG screening of all patients before starting treatment with halofantrine. Others[7] found pretreatment ECGs to be poorly predictive of QT lengthening during treatment. Children may have serious cardiac effects at standard doses.[8] A later review,[9] which included data from the manufacturer's database, analysed 35 deaths thought to be due to halofantrine-associated cardiotoxicity, including 5 children, occurring between 1988 and 2005. In the great majority of cases there were predisposing factors such as underlying heart disease, higher than recommended dosage, or use with another drug that prolonged QT intervals. The authors re-iterated the need to check for contra-indications (particularly in women) before prescribing, in those countries where halofantrine was still in use.

1. Nosten F, *et al*. Cardiac effects of antimalarial treatment with halofantrine. *Lancet* 1993; **341:** 1054–6.
2. Monlun E, *et al*. Cardiac complications of halofantrine: a prospective study of 20 patients. *Trans R Soc Trop Med Hyg* 1995; **89:** 430–3.
3. Castot A, *et al*. Prolonged QT interval with halofantrine. *Lancet* 1993; **341:** 1541.
4. Monlun E, *et al*. Prolonged QT interval with halofantrine. *Lancet* 1993; **341:** 1541–2.
5. Anonymous. Halofantrine: revised data sheet. *WHO Drug Inf* 1993; **7:** 66–7.
6. CSM/MCA. Cardiac arrhythmias with halofantrine (Halfan). *Current Problems* 1994; **20:** 6. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con2023215.pdf (accessed 04/08/10)
7. Matson PA, *et al*. Cardiac effects of standard-dose halofantrine therapy. *Am J Trop Med Hyg* 1996; **54:** 229–31.
8. Sowunmi A, *et al*. Cardiac effects of halofantrine in children suffering from acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 446–8.
9. Bouchaud O, *et al*. Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. *Malar J* 2009; **8:** 289.

Effects on the skin. For a comparison of the incidence of pruritus associated with halofantrine and other antimalarials, see Effects on the Skin under Adverse Effects of Chloroquine, p. 652.2.

Interactions

Halofantrine prolongs the QT interval and should not be used with other drugs that have the potential to induce cardiac arrhythmias, in particular the antimalarials mefloquine, chloroquine, and quinine, and also tricyclic antidepressants, phenothiazine antipsychotics, some antiarrhythmics (including amiodarone, disopyramide, flecainide, procainamide, quinidine, and the beta blocker sotalol), cisapride, and the antihistamines astemizole and terfenadine. Also, halofantrine should not be given with drugs that cause electrolyte disturbances (such as diuretics) or with HIV-protease inhibitors.

Grapefruit juice. In a study in 12 healthy patients, the bioavailability of halofantrine was reported to be increased when taken with grapefruit juice and this was found to accentuate halofantrine-associated QT prolongation.[1] It was suggested that grapefruit juice should be contra-indicated during use of halofantrine.

1. Charbit B, *et al*. Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. *Clin Pharmacol Ther* 2002; **72:** 514–23.

Tetracycline. Plasma concentrations of halofantrine were increased in 8 healthy subjects who were also given tetracycline.[1]

1. Bassi PU, *et al*. Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers. *Br J Clin Pharmacol* 2004; **58:** 52–5.

Pharmacokinetics

Halofantrine is slowly and erratically absorbed after oral dosage. Although it appears in the circulation within about 1 hour, peak concentrations occur in 3 to 7 hours. Bioavailability of halofantrine is increased when given with or after food, particularly food high in fat content, and it must therefore be taken on an empty stomach because of the risk of cardiotoxicity. The elimination half-life of halofantrine varies considerably between individuals, but is generally about 1 to 2 days. Halofantrine is metabolised in the liver, its major metabolite being desbutylhalofantrine, which appears to be as active as the parent compound. Excretion of halofantrine is mainly via the faeces.

References.
1. Karbwang J, Na Bangchang K. Clinical pharmacokinetics of halofantrine. *Clin Pharmacokinet* 1994; **27:** 104–19.
2. Watkins WM, *et al*. Halofantrine pharmacokinetics in Kenyan children with non-severe and severe malaria. *Br J Clin Pharmacol* 1995; **39:** 283–7.
3. Ohrt C, *et al*. Pharmacokinetics of an extended-dose halofantrine regimen in patients with malaria and in healthy volunteers. *Clin Pharmacol Ther* 1995; **57:** 525–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Halfan; ***Port.***: Halfan; ***S.Afr.***: Halfan.

Hydroxychloroquine Sulfate

(BANM, rINNM)

Hidroxicloroquina, sulfato de; Hydroxychloroquine, Sulfate d'; Hydroxychloroquine Sulphate; Hydroxychloroquini Sulfas; Oxichlorochin Sulphate; Sulfato de Hidroxicloroquina; Win-1258-2; Гидроксихлорохина Сульфат.

2-{*N*-[4-(7-Chloro-4-quinolylamino)pentyl]-*N*-ethylamino} ethanol sulphate.

$C_{18}H_{26}ClN_3O,H_2SO_4$=433.9

CAS — 118-42-3 (hydroxychloroquine); 747-36-4 (hydroxychloroquine sulfate).

ATC — P01BA02.

UNII — 8Q2869CNVH.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Hydroxychloroquine Sulfate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. A 1% solution in water has a pH of 3.5 to 5.5. Protect from light.

USP 36: (Hydroxychloroquine Sulfate). A white or practically white, odourless, crystalline powder. It exists in two forms, the usual form melting at about 240 degrees and the other form at about 198 degrees. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions in water have a pH of about 4.5. Protect from light.

Uses and Administration

Hydroxychloroquine sulfate is a 4-aminoquinoline antimalarial with actions similar to those of chloroquine (p. 650.2). Although used in the treatment and prophylaxis of malaria (see p. 644.1), its main roles are in the management of systemic and discoid lupus erythematosus (p. 656.1) and rheumatoid arthritis (below). It has also been tried for prophylaxis of venous thromboembolism (p. 656.1). Additionally, hydroxychloroquine has been used similarly to chloroquine in the management of porphyria cutanea tarda (p. 651.1), sarcoidosis (p. 651.1), and various skin disorders (p. 651.2).

Hydroxychloroquine sulfate is given orally.

In **lupus erythematosus** and **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months but if there is no improvement by then, treatment should be stopped. In the UK, treatment is usually started with 400 mg daily in divided doses with meals. In the USA, recommended initial doses are 400 to 600 mg daily for rheumatoid arthritis and 400 mg once or twice daily for lupus erythematosus. Doses are reduced to the minimum effective dose for maintenance; this is usually 200 to 400 mg daily but should not exceed 6.5 mg/kg daily (or 400 mg daily whichever is the smaller). To avoid excessive dosage in obese patients, special care is needed to calculate the dosage on the basis of lean body-weight. For further details, see under Effects on the Eyes in Chloroquine, p. 651.2.

Hydroxychloroquine sulfate is also used in similar doses for the treatment of **light-sensitive skin eruptions**, but treatment should only be given during periods of maximum exposure to light.

Hydroxychloroquine sulfate may be used in **malaria** both for treatment and prophylaxis, when chloroquine is not available, with the same limitations as for chloroquine. In the USA, a licensed dose for *prophylaxis* of malaria is 400 mg every 7 days. Prophylaxis should be started 2 weeks before the period of malaria exposure and continue until 8 weeks after exposure has ended; if a two-week lead-in period is not possible, an initial loading dose of 800 mg can be used, given in 2 divided doses 6 hours apart. In *treating* an acute malarial attack, a dose of 800 mg has been used, followed after 6 to 8 hours by 400 mg and a further 400 mg on each of the 2 following days; alternatively, a single dose of 800 mg has been given.

For details of doses in children, see below.

Administration in children. Hydroxychloroquine sulfate may be used orally in infants and children for the management of certain inflammatory conditions, and also for the prophylaxis and treatment of malaria, where it is subject to the same limitations as chloroquine (see Uses and Administration of Chloroquine, p. 650.2).

For the treatment of **rheumatoid arthritis** (juvenile idiopathic arthritis), discoid or systemic **lupus erythematosus**, and **light-sensitive skin eruptions**; UK licensed product information suggests that infants and children may be given an oral dose of up to 6.5 mg/kg daily, based on ideal body-weight (or 400 mg daily, whichever is the smaller).

For **treatment of malaria**, US licensed product information recommends that infants and children may be given an initial oral dose of 13 mg/kg (to a maximum of 800 mg), followed by 6.5 mg/kg (to a maximum of 400 mg) after 6, 24, and 48 hours. For **prophylaxis**, 6.5 mg/kg (to a maximum of 400 mg) given once every 7 days is recommended. Prophylaxis should be started 2 weeks before the period of malaria exposure and continue until 8 weeks after exposure has ended; if a two-week lead-in period is not possible, an initial loading dose of 13 mg/kg (to a maximum of 800 mg) can be used, given in 2 divided doses 6 hours apart.

Diabetes. As a result of reported hypoglycaemic effects with chloroquine and hydroxychloroquine (see Effects on Glucose Metabolism, under Chloroquine, p. 651.3), there has been interest in whether such drugs might improve glucose tolerance or prevent diabetes in patients at risk.

In a prospective, multicentre, 21-year observational study[1] involving 4905 patients with rheumatoid arthritis, incident diabetes occurred at a significantly lower rate among patients who had ever taken hydroxychloroquine, versus those who had not (5.2 cases, versus 8.9 cases per 1000 patient years of observation respectively). The relative risk of developing diabetes also progressively declined with increased duration of hydroxychloroquine use. Others[2] have also reported a reduction in risk based on retrospective data.

1. Wasko MCM, *et al*. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 2007; **298:** 187–93.
2. Bili A, *et al*. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. *J Clin Rheumatol* 2011; **17:** 115–20.

Inflammatory disorders. For the use of hydroxychloroquine and chloroquine in a range of inflammatory conditions, see under Chloroquine, p. 650.3 and under Rheumatoid Arthritis, below.

Porphyria cutanea tarda. For reference to the use of hydroxychloroquine in the treatment of porphyria cutanea tarda, see under the Uses and Administration of Chloroquine, p. 651.1.

Rheumatoid arthritis. Hydroxychloroquine and chloroquine are used orally as disease-modifying antirheumatic drugs (DMARDs) in the management of **rheumatoid arthritis** (p. 13.2) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease.[1] They are considered to be less effective than the other DMARDs but they are usually better tolerated and so may be preferred in patients with milder forms of the disease.[2] Additional benefit has been obtained using antimalarials with other DMARDs especially methotrexate and sulfasalazine,[3-5] although adverse effects may be more common. For reference to precautions to reduce the incidence of retinopathy, see under Effects on the Eyes in Adverse Effects of Chloroquine, p. 651.2.

Generally the lowest effective dose should be used for maintenance to minimise toxicity; for hydroxychloroquine sulfate this should not exceed 6.5 mg/kg lean body-weight daily. Daily doses of 200 or 400 mg are commonly used but one study indicates that there is little advantage in using the higher dose.[6]

Experience with antimalarials to treat **juvenile idiopathic arthritis** (p. 12.1) is limited and the results have been variable.[7,8]

Chloroquine and hydroxychloroquine have also been reported to be of use in **palindromic rheumatism**.[9-11]

1. Suarez-Almazor ME, *et al*. Antimalarials for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 17/05/05).
2. HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995; **98:** 156–68.
3. Clegg DO, *et al*. Safety and efficacy of hydroxychloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with methotrexate and hydroxychloroquine. *J Rheumatol* 1997; **24:** 1896–1902.
4. O'Dell JR. Triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine in patients with rheumatoid arthritis. *Rheum Dis Clin North Am* 1998; **24:** 465–77.
5. O'Dell JR, *et al*. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1164–70.
6. Pavelka K, *et al*. Hydroxychloroquine sulphate in the treatment of rheumatoid arthritis: a double blind comparison of two dose regimens. *Ann Rheum Dis* 1989; **48:** 542–6.
7. Brewer EJ, *et al*. Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. *N Engl J Med* 1986; **314:** 1269–76.

8. Grondin C, *et al*. Slow-acting antirheumatic drugs in chronic arthritis of childhood. *Semin Arthritis Rheum* 1988; **18:** 38–47.
9. Richardson MR, Zalin AM. Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; **294:** 741.
10. Hanonen P, *et al*. Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; **294:** 1289.
11. Youssef W, *et al*. Palindromic rheumatism: a response to chloroquine. *J Rheumatol* 1991; **18:** 35–7.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p. 1612.2) as alternatives or adjuncts to corticosteroid therapy. For references to the use of hydroxychloroquine, see under Chloroquine, p. 651.1.

Skin disorders. For reference to the use of hydroxychloroquine in a variety of skin disorders, see under Chloroquine, p. 651.2.

Systemic lupus erythematosus. Antimalarials have been widely used in the treatment of lupus erythematosus (p. 1613.3), particularly its cutaneous manifestations, although much of the evidence is based on case series and reports.[1] Hydroxychloroquine is most widely used,[1,2] as it is thought to have fewer adverse effects than chloroquine, although any benefit with chloroquine generally starts to become evident within several weeks of starting treatment, whereas it may take up to 2 months for any effect of hydroxychloroquine to be seen. For extracutaneous disease, antimalarials are often combined with other drugs; treatment may be continued for many years. For reference to precautions to reduce the risk of retinopathy see Effects on the Eyes, under Adverse Effects of Chloroquine, p. 651.2. There is evidence from a case-control study[3] that long-term hydroxychloroquine treatment is associated with improved survival in patients with SLE, and some consider it to be underused.[2] It has been suggested that hydroxychloroquine may also have a role in reducing the thrombotic symptoms of SLE, including in patients with antiphospholipid syndrome.[4]

1. Wozniacka A, McCauliffe DP. Optimal use of antimalarials in treating cutaneous lupus erythematosus. *Am J Clin Dermatol* 2005; **6:** 1–11.
2. Costedoat-Chalumeau N, *et al*. Hydroxychloroquine dans le traitement du lupus: le renouveau. *Rev Med Interne* 2008; **29:** 735–7.
3. Alarcón GS, *et al*. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis* 2007; **66:** 1168–72.
4. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep* 2011; **13:** 77–80.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p. 1274.1) is usually with an anticoagulant. Hydroxychloroquine has been described by some as an antiplatelet agent[1] and although its mechanism of action is uncertain the incidence of fatal pulmonary embolism has been reduced in patients given hydroxychloroquine prophylactically after total hip replacement;[2] the usual daily divided oral dose was about 800 mg from the day before surgery until discharge; larger doses had been used.

See also Systemic Lupus Erythematosus, above.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; **308:** 235–46.
2. Loudon JR. Hydroxychloroquine and postoperative thromboembolism after total hip replacement. *Am J Med* 1988; **85:** (suppl 4A): 57–61.

Adverse Effects, Treatment, and Precautions

As for Chloroquine, p. 651.2.

Breast feeding. Hydroxychloroquine has been detected in human breast milk[1,2] but no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Nation RL, *et al*. Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; **17:** 368–9.
2. Østensen M, *et al*. Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; **28:** 357.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy. With respect to retinopathy, precautions should be taken in patients undergoing long-term treatment, as described under Chloroquine on p. 651.2.

Further references.

1. Jones SK. Ocular toxicity and hydroxychloroquine: guidelines for screening. *Br J Dermatol* 1999; **140:** 3–7.
2. Tripp JM, Maibach HI. Hydroxychloroquine-induced retinopathy: a dermatologic perspective. *Am J Clin Dermatol* 2006; **7:** 171–5.
3. Tehrani R, *et al*. Ocular toxicity of hydroxychloroquine. *Semin Ophthalmol* 2008; **23:** 201–9.
4. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010; **62:** 775–84.
5. Bergholz R, *et al*. Evaluation of risk factors for retinal damage due to chloroquine and hydroxychloroquine. *Br J Ophthalmol* 2010; **94:** 1637–42.
6. Payne JF, *et al*. Clinical characteristics of hydroxychloroquine retinopathy. *Br J Ophthalmol* 2011; **95:** 245–50.
7. Michaelides M, *et al*. Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. *Arch Ophthalmol* 2011; **129:** 30–9.

Effects on glucose metabolism. For the effects of hydroxychloroquine on glucose metabolism, see under Chloroquine, p. 651.3.

Overdosage. References[1-4] to the management of hydroxychloroquine overdose. Management has largely been based on that used for overdoses of chloroquine (p. 652.2).

1. Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. *Am J Emerg Med* 2001; **19:** 420–4.
2. Ling Ngan Wong A, *et al*. Hydroxychloroquine overdose: case report and recommendations for management. *Eur J Emerg Med* 2008; **15:** 16–8.
3. Olgers TJ, *et al*. Ernstige intoxicatie met hydroxychloroquine, met hemodynamische instabiliteit: casuistische ondersteuning voor behandeling met diazepam. *Ned Tijdschr Geneeskd* 2008; **152:** 509–12.
4. Gunja N, *et al*. Survival after massive hydroxychloroquine overdose. *Anaesth Intensive Care* 2009; **37:** 130–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxychloroquine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/10/11)

Pregnancy. In a study[1] of 133 pregnancies in 90 women treated with hydroxychloroquine, no statistical difference in pregnancy outcome was found compared with a control group consisting of 70 pregnancies in 53 women. It was concluded that the findings supported preliminary evidence for the safety of hydroxychloroquine treatment in pregnancy, and that treatment should probably therefore be maintained during pregnancy in patients with SLE. A later systematic review[2] also concluded that there was no increased risk of congenital defects, spontaneous abortion, fetal death or prematurity associated with use of hydroxychloroquine for auto-immune diseases during pregnancy.

1. Costedoat-Chalumeau N, *et al*. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. *Arthritis Rheum* 2003; **48:** 3207–11.
2. Sperber K, *et al*. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. *Pediatr Rheumatol Online J* 2009; **7:** 9.

Interactions

As for Chloroquine, p. 653.2.

Pharmacokinetics

The pharmacokinetics of hydroxychloroquine are similar to those of chloroquine (see p. 653.3).

References.

1. Tett SE, *et al*. Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; **27:** 771–9.
2. Miller DR, *et al*. Steady-state pharmacokinetics of hydroxychloroquine in rheumatoid arthritis. *DICP Ann Pharmacother* 1991; **25:** 1302–5.
3. Ducharme J, *et al*. Enantioselective disposition of hydroxychloroquine after a single oral dose of the racemate to healthy subjects. *Br J Clin Pharmacol* 1995; **40:** 127–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Axokine; Evoquin; Metirel; Narbon; Plaquenil; Polirreumin; ***Austral.***: Plaquenil; ***Belg.***: Plaquenil; ***Braz.***: Plaquinol; Reuquinol; ***Canad.***: Apo-Hydroxyquine; Plaquenil; Pro-Hydroxyquine; ***Chile***: Ilinol; Plaquinol; ***China***: Fen Le (纷乐); Plaquenil (赛能); ***Cz.***: Plaquenil; ***Denm.***: Ercoquin; Plaquenil; ***Fin.***: Oxiklorin; ***Fr.***: Plaquenil; ***Ger.***: Quensyl; ***Gr.***: Plaquenil; ***Hong Kong***: Plaquenil; ***India***: HCQS; HQTor; Hydrocad; Hydroquin; Oxcq; Oxy-Q; ***Irl.***: Plaquenil; ***Israel***: Plaquenil; ***Ital.***: Plaquenil; ***Malaysia***: Plaquenil; ***Mex.***: Plaquenil; ***Neth.***: Plaquenil; ***Norw.***: Plaquenil; ***NZ***: Plaquenil; ***Philipp.***: Plaquenil; ***Port.***: Plaquinol; ***Rus.***: Immard (Иммард); Plaquenil (Плаквенил); ***Singapore***: Plaquenil; ***Spain***: Dolquine; ***Swed.***: Plaquenil; ***Switz.***: Plaquenil; ***Thai.***: HCQS; Hydroquin; Plaquenil; ***Turk.***: Plaquenil; ***UK***: Plaquenil; ***Ukr.***: Immard (Иммард); Plaquenil (Плаквенил); ***USA***: Plaquenil; ***Venez.***: Plaquinol.

Pharmacopoeial Preparations

BP 2014: Hydroxychloroquine Tablets;
USP 36: Hydroxychloroquine Sulfate Tablets.

Lumefantrine *(BAN, USAN, rINN)*

Benflumelol; Benflumetol; Lumefantrin; Lumefantrina; Luméfantrine; Lumefantrinum; Lumefantryna; Лумефантрин.

2,7-Dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9*H*-fluorene-4-methanol.

$C_{30}H_{32}Cl_3NO$=528.9

CAS — 82186-77-4.

UNII — F38R0JR742.

Pharmacopoeias. In *Chin.*

Uses and Administration

Lumefantrine is a dichlorobenzylidine derivative given orally with artemether (p. 648.1) for the treatment of uncomplicated falciparum malaria (p. 644.1). In some countries, the combination is also used for the treatment of chloroquine-resistant non-falciparum malaria. Lumefantrine is a blood schizontocide with a relatively slow onset of action but it has a longer duration of action than artemether. The combination is given as a six-dose regimen, with each dose containing lumefantrine 480 mg and artemether 80 mg. The first dose is given at initial diagnosis, with subsequent doses given after 8, 24, 36, 48, and 60 hours; it has been suggested that doses be given after a milky drink or fat-containing food to ensure adequate absorption.

For details of dosing in children, see below.

References.

1. Omari AAA, *et al*. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 19/07/06).
2. Omari AAA, *et al*. Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/07/06).
3. Kokwaro G, *et al*. Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. *Expert Opin Pharmacother* 2007; **8:** 75–94.
4. Adjei GO, *et al*. Artemether-lumefantrine: an oral antimalarial for uncomplicated malaria in children. *Expert Rev Anti Infect Ther* 2009; **7:** 669–81.
5. Ngasala BE, *et al*. Efficacy and effectiveness of artemether-lumefantrine after initial and repeated treatment in children < 5 years of age with acute uncomplicated *Plasmodium falciparum* malaria in rural Tanzania: a randomized trial. *Clin Infect Dis* 2011; **52:** 873–82.

Administration in children. Lumefantrine may be given orally to infants and children, with artemether, for the treatment of **uncomplicated falciparum malaria**. In some countries, the combination is also used for the treatment of **chloroquine-resistant non-falciparum malaria**. A total of 6 doses are given, starting at diagnosis and repeated after 8, 24, 36, 48, and 60 hours; recommended doses according to body-weight are as follows:

- 5 to 14 kg: lumefantrine 120 mg with artemether 20 mg
- 15 to 24 kg: lumefantrine 240 mg with artemether 40 mg
- 25 to 34 kg: lumefantrine 360 mg with artemether 60 mg
- over 35 kg: as for adults (see above)

It has been suggested that doses be given after a milky drink or fat-containing food to ensure adequate absorption.

Adverse Effects and Precautions

Adverse effects associated with the combination of lumefantrine with artemether commonly include headache, dizziness, sleep disturbance, palpitations, gastrointestinal disturbances, anorexia, pruritus, rash, cough, arthralgia, myalgia, and fatigue.

Lumefantrine-artemether may cause prolongation of the QT interval, and therefore should be avoided in patients with serum-potassium or magnesium disturbances, any clinical condition known to prolong the QT interval (such as congenital long QT syndrome, symptomatic cardiac arrhythmia, or severe heart failure), or a family history of sudden cardiac death.

Lumefantrine-artemether should be given with caution in severe hepatic or renal impairment and ECG and blood potassium monitored.

Effects on the blood. Severe haemolytic anaemia necessitating corticosteroid treatment, blood transfusion, and haemodialysis occurred in a patient after taking 8 lumefantrine-artemether tablets after a malarial attack.[1] It was considered that, given its molecular similarity to other antimalarials known to cause haemolysis, the causative drug was probably lumefantrine.

1. Mérat S, *et al*. Case report: combination artemether-lumefantrine and haemolytic anaemia following a malarial attack. *Trans R Soc Trop Med Hyg* 2003; **97:** 433–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the combination of lumefantrine plus artemether as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Interactions

Use of lumefantrine-artemether should be avoided in patients who are using other drugs known to prolong the QT interval (such as halofantrine, quinine, and mefloquine). For patients previously treated with halofantrine, licensed product information recommends that at least a month should pass before starting lumefantrine-artemether. The combination is also considered contra-indicated in patients taking any drugs that are metabolised by the cytochrome enzyme CYP2D6, particularly those with cardiac effects (including amitriptyline, clomipramine, flecainide, imipramine, and metoprolol). Given the long elimination half-life of lumefantrine (see Pharmacokinetics, below), care must also be taken when starting potentially interacting medications soon after lumefantrine has been stopped.

Pharmacokinetics

The bioavailability of lumefantrine after oral doses is variable; absorption begins after a lag-time of up to 2 hours and bioavailability is substantially increased when given with food, particularly meals high in fat. Peak plasma concentrations occur after about 6 to 8 hours. Lumefantrine is almost completely protein bound. It is considered to be metabolised mainly in the liver and is excited in the faeces. The elimination half-life is reported to be between 4 to 6 days in patients with malaria.

References.

1. White NJ, *et al*. Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37:** 105–25.
2. Ezzet F, *et al*. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* 2000; **44:** 697–704.
3. Tarning J, *et al*. Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria. *Antimicrob Agents Chemother* 2009; **53:** 3837–46.
4. Djimdé A, Lefèvre G. Understanding the pharmacokinetics of Coartem. *Malar J* 2009; **8** (suppl 1): S4.
5. Hietala SF, *et al*. Population pharmacokinetics and pharmacodynamics of artemether and lumefantrine during combination treatment in children with uncomplicated falciparum malaria in Tanzania. *Antimicrob Agents Chemother* 2010; **54:** 4780–8.
6. Mwesigwa J, *et al*. Pharmacokinetics of artemether-lumefantrine and artesunate-amodiaquine in children in Kampala, Uganda. *Antimicrob Agents Chemother* 2010; **54:** 52–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Riamet; ***Austria***: Riamet; ***Belg.***: Co-Artesiane; Riamet; ***Cz.***: Riamet†; ***Fr.***: Riamet; ***Ger.***: Riamet; ***Gr.***: Riamet; ***India***: Alither; Arh-L; Arlufe; Arsumet-L; Arte Plus; Coartrin; Combither; Falcimax Plus; Falcirid; Lumeart; Lumecap-A; Lumerax; Lumether; Malatrit-EL; ***Indon.***: Coartem; ***Neth.***: Riamet; ***Philipp.***: Coartem; ***Port.***: Riamet; ***S.Afr.***: Coartem; ***Singapore***: Riamet; ***Swed.***: Riamet; ***Switz.***: Riamet; ***Thai.***: Coartem; ***UK***: Riamet; ***USA***: Coartem.

Mefloquine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mefloquina; Meflochina Cloridrato; Meflochin-hydrochlorid; Meflokiinihydrokloridi; Meflokin-hidroklorid; Meflokinhydroklorid; Meflokvino hidrochloridas; Mefloquina, hidrocloruro de; Méfloquine, Chlorhydrate de; Mefloquinhydrochlorid; Mefloquini Hydrochloridum; Ro-21-5998 (mefloquine); Ro-21-5998/001 (mefloquine hydrochloride); WR-142490 (mefloquine); Мефлохина Гидрохлорид.

(*RS*)-[2,8-Bis(trifluoromethyl)-4-quinolyl]-(*SR*)-(2-piperidyl) methanol hydrochloride.

$C_{17}H_{16}F_6N_2O,HCl$=414.8

CAS — 53230-10-7 (mefloquine); 51773-92-3 (mefloquine hydrochloride).

ATC — P01BC02.

UNII — 5Y9L3636O3.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Sorption. For reference to loss of mefloquine hydrochloride from solutions during membrane filtration, see Chloroquine, p. 650.2.

Stability. A report of the photolytic degradation of mefloquine hydrochloride in water.[1]

1. Tønnesen HH, Grislingaas A-L. Photochemical stability of biologically active compounds II: photochemical decomposition of mefloquine in water. *Int J Pharmaceutics* 1990; **60:** 157–62.

Uses and Administration

Mefloquine is a 4-methanolquinoline antimalarial related to quinine. It is a blood schizontocide effective against all forms of malaria including chloroquine- or multidrug-resistant strains of *Plasmodium falciparum*, although some strains are naturally resistant to mefloquine. It is used for the treatment of uncomplicated falciparum malaria and chloroquine-resistant vivax malaria, and also for malaria prophylaxis (see below). Mefloquine is also used after treatment with an artemisinin derivative for acute uncomplicated malaria, to reduce the risk of recrudescence.

Mefloquine is given orally as the hydrochloride but variation in the way doses are expressed could lead to confusion. In the UK and elsewhere, doses are expressed in terms of the base and a dose of 250 mg base is equivalent to about 274 mg of mefloquine hydrochloride. In the USA, doses are expressed in terms of the hydrochloride and a dose of 250 mg is therefore equivalent to only about 228 mg of mefloquine base. Doses in the USA could therefore be about 10% less than elsewhere.

For the *treatment of uncomplicated malaria in non-immune travellers*, WHO recommends 25 mg/kg of mefloquine base given in a split-dose regimen of 15 mg/kg initially, followed by 10 mg/kg 6 to 24 hours later. However, the *BNF* notes that mefloquine is rarely used for treatment of falciparum malaria or chloroquine-resistant non-falciparum malarias due to concern about resistance and, in the case of the non-falciparum malarias, the availability of better tolerated treatments.

For the *treatment of uncomplicated falciparum malaria in endemic areas*, WHO recommends that mefloquine 25 mg/kg be given with a 3-day course of artesunate (see p. 648.2); the mefloquine dose may be given as the split-dose regimen above, or as 8.3 mg/kg once daily for 3 days.

For the *prophylaxis* of malaria, a once-weekly dose of 250 mg mefloquine base has been recommended; prophylaxis should start at least 1 week, but preferably 2 to 3 weeks before entering the malarious area and continue for 4 weeks after leaving.

For further information, and for details of dosing in children, see below.

Administration in children. Mefloquine may be given orally to infants and children for malaria prophylaxis, as well as for the treatment of uncomplicated falciparum malaria and chloroquine-resistant vivax malaria, although it is not licensed for use in children under 3 months of age or weighing less than 5 kg.

For the **treatment of uncomplicated malaria in non-immune travellers**, WHO[1] recommends 25 mg/kg of mefloquine base given in a split-dose regimen of 15 mg/kg initially, followed by 10 mg/kg 6 to 24 hours later.

For the **treatment of uncomplicated falciparum malaria in endemic areas**, WHO[2] recommends that mefloquine 25 mg/kg be given with a 3-day course of artesunate (see p. 648.2); the mefloquine dose may be given as the split-dose regimen above, or as 8.3 mg/kg once daily for 3 days.

Recommended doses for **prophylaxis** are generally based on 5 mg/kg of mefloquine base as a single weekly dose in children weighing over 5 kg.[1] Typical once-weekly doses used in the UK[3] for infants and children from 5 kg bodyweight and over 3 months of age are as follows:

- 5 to 15.9 kg (3 months to 3 years 11 months): 62.5 mg
- 16 to 24.9 kg (4 years to 7 years 11 months): 125 mg
- 25 to 44.9 kg (8 years to 12 years 11 months): 187.5 mg
- 45 kg and over: the adult dose (see above)

1. WHO. *International travel and health.* 2011 ed. Available at: http://www.who.int/ith/en/ (accessed 17/06/11)
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Malaria. The overall treatment and prophylaxis of malaria and the place of mefloquine in current recommendations are discussed on p. 644.1.

TREATMENT. Clinical studies have shown mefloquine to be effective in the treatment of chloroquine- or multidrug-resistant falciparum malaria. It is also effective in non-falciparum malarias, but is not normally required since they usually respond to chloroquine.

Mefloquine has been widely used as an alternative to regimens using quinine for the treatment of chloroquine-resistant or multidrug-resistant strains of *Plasmodium falciparum*. It is now also used with an artemisinin derivative in multidrug resistance (see p. 649.1).

As there is no parenteral formulation of mefloquine currently available it can only be used in patients who can take oral medication and is therefore unsuitable for sole treatment in severe infections. Mefloquine has produced adequate blood concentrations by the nasogastric route, but this route cannot be relied upon in seriously ill patients.[1] If mefloquine is given to patients after parenteral doses of quinine, it is recommended that a period of 12 hours should be allowed after the last dose of quinine to avoid toxicity.

WHO[2] considers that drugs used for the treatment of uncomplicated falciparum malaria may in principle be carried as a *standby* for use in similar doses for the emergency self-treatment of malaria, although mefloquine is not recommended by WHO as a first-line regimen.

PROPHYLAXIS. It had been hoped that mefloquine could be reserved for the treatment of malaria, but increasing drug resistance to chemoprophylactic regimens has led to it being widely used for malaria prophylaxis.[3] WHO recommends[2] that mefloquine should be used where there is a high risk of falciparum malaria and drug resistance or a moderate to low risk but with high drug resistance. The equivalent of 250 mg of mefloquine base is given every week, starting 1 to 3 weeks before departure, and continuing throughout the period of exposure and for 4 weeks after leaving the malarious area. Starting mefloquine prophylaxis 2 to 3 weeks before exposure allows for detection of possible adverse effects before travelling (see Effects on the Nervous System, p. 658.1, for concerns about neurotoxicity). It is now considered that mefloquine prophylaxis can be given for periods of up to one year instead of the previous limit of 3 months.

In the event of breakthrough malaria during malaria prophylaxis there may be a delay of up to several months before the onset of symptoms in contrast to that seen with other forms of prophylaxis.[4] Mefloquine should not be used for treatment if it has been used for prophylaxis.

1. Chanthavanich P, *et al*. Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34:** 1028–36.
2. WHO. *International travel and health.* 2012 ed. Available at: http://www.who.int/ith/en (accessed 29/10/12)
3. Schlagenhauf P, *et al*. The position of mefloquine as a 21st century malaria chemoprophylaxis. *Malar J* 2010; **9:** 357.
4. Day JH, Behrens RH. Delay in onset of malaria with mefloquine prophylaxis. *Lancet* 1995; **345:** 398.

Schistosomiasis. A combination of mefloquine plus artesunate (p. 648.2) has been investigated for use in the treatment of schistosomiasis (p. 148.1). In a randomised, open-label study,[1] mefloquine 250 mg plus artesunate 100 mg both given orally once daily for 3 days resulted in a cure rate of 61% among schoolchildren infected with *Schistosoma haematobium*; high cure rates and egg reduction rates were also seen in children coinfected with *S. mansoni*.

1. Keiser J, *et al*. Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium*: randomized, exploratory open-label trial. *Clin Infect Dis* 2010; **50:** 1205–13.

Adverse Effects

Since mefloquine has a long elimination half-life, adverse effects may occur or persist up to several weeks after the last dose.

The most frequent adverse effects of mefloquine are nausea, diarrhoea, vomiting, abdominal pain, anorexia, headache, somnolence, and sleep disorders, notably insomnia and abnormal dreams. Dizziness, vertigo, and loss of balance may also occur, and in rare cases have continued for months after the drug was stopped.

Neurological or psychiatric disturbances have also been reported with mefloquine and include sensory and motor neuropathies, tremor, ataxia, visual disturbances, tinnitus and hearing impairment, convulsions, anxiety, depression, confusion, hallucinations, panic attacks, emotional instability, aggression and agitation, and acute psychosis. There have been rare reports of suicidal ideation.

Other adverse effects include rashes, pruritus and urticaria, hair loss, muscle weakness, myalgia, liver function disturbances, and very rarely thrombocytopenia and leucopenia. There have been rare occurrences of erythema multiforme and Stevens-Johnson syndrome. Anaphylaxis has occurred rarely. Cardiovascular effects have included hypotension, hypertension, tachycardia or palpitations, bradycardia, QT prolongation, and other minor ECG changes. There have been isolated cases of atrioventricular block.

Incidence of adverse effects. The frequencies of adverse effects reported[1] in 134 soldiers given mefloquine hydrochloride 250 mg weekly for malaria chemoprophylaxis were: diarrhoea (48%), nausea (13%), vomiting (2%), headache (13%), and dizziness (7%). All of 7 healthy sub-

jects who received a dose of mefloquine hydrochloride 15 mg/kg had symptoms that included vertigo, nausea, dizziness, and lightheadedness.[2] The manufacturers reported that dizziness occurred in 24% of patients with malaria treated with 750 mg of mefloquine, in 38% treated with 1 g, and in 96% treated with 1.5 g; splitting a dose into two doses given 8 hours apart can reduce the incidence of dizziness.[3] A prospective study involving 3673 patients found that anorexia, nausea, vomiting, dizziness, and sleep disorders were 1.1 to 1.4 times more frequent in patients receiving mefloquine 25 mg/kg for treatment of malaria than in those receiving 15 mg/kg, and that vomiting could be reduced by 40% if the higher dose was split and given as 15 mg/kg followed by a further 10 mg/kg after 16 to 24 hours.[4] The frequency of adverse effects is reported to be higher in subjects who become dehydrated.[5]

There has been concern that the adverse effects of mefloquine, especially neuropsychiatric reactions, might limit its use for the prophylaxis of malaria but, as discussed under Effects on the Nervous System, below, the incidence of adverse effects does not appear to be greater than with other prophylactic schedules.

1. Arthur JD, *et al*. Mefloquine prophylaxis. *Lancet* 1990; **335:** 972.
2. Patchen LC, *et al*. Neurologic reactions after a therapeutic dose of mefloquine. *N Engl J Med* 1989; **321:** 1415.
3. Stürchler D, *et al*. Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; **322:** 1752–3.
4. ter Kuile FO, *et al*. Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bull WHO* 1995; **73:** 631–42.
5. Perry IC. Malaria prophylaxis. *BMJ* 1995; **310:** 1673.

Effects on the blood. Agranulocytosis was reported[1] in a patient with malaria 48 hours after treatment with a 1250-mg course of mefloquine. The patient had previously taken 250 mg of mefloquine weekly for 7 weeks without adverse effects. Thrombotic thrombocytopenic purpura has been reported[2] in a patient after taking two standard weekly doses of mefloquine for malaria prophylaxis. Symptoms improved after plasmapheresis.

1. Hennequin C, *et al*. Agranulocytosis during treatment with mefloquine. *Lancet* 1991; **337:** 984.
2. Fiaccadori E, *et al*. Thrombotic-thrombocytopenic purpura following malaria prophylaxis with mefloquine. *J Antimicrob Chemother* 2006; **57:** 160–1.

Effects on the liver. Acute fatty liver was reported[1] in a patient who had recently received mefloquine 250 mg weekly for 5 weeks for malaria prophylaxis. Symptoms resolved with fluid, electrolyte, and albumin replacement, after stopping mefloquine. In another report,[2] acute elevation of liver transaminases, associated with severe acute hepatitis, occurred in a patient with pre-existing mild hepatic impairment after a 6-week course of mefloquine 250 mg weekly.

1. Grieco A, *et al*. Acute fatty liver after malaria prophylaxis with mefloquine. *Lancet* 1999; **353:** 295–6.
2. Gotsman I, *et al*. Mefloquine-induced acute hepatitis. *Pharmacotherapy* 2000; **20:** 1517–19.

Effects on the lungs. Acute pneumonitis requiring hospitalisation[1] was reported in a patient after a single dose of oral mefloquine 250 mg for malaria prophylaxis. The condition slowly resolved after the drug was stopped but recurred with mefloquine rechallenge 4 months later, leading to intensive care unit admission. A subsequent case of eosinophilic pneumonia associated with mefloquine prophylaxis has also been reported.[2]

Between May 1989 and January 2008, the US FDA received 13 reports of pneumonitis associated with mefloquine use at either treatment or prophylactic doses.[3] Although most of these patients recovered fully after the drug was stopped, one death, in a 4-year old, occurred. Antibacterial treatment was not of benefit in many cases, although one-third of patients improved after treatment with corticosteroids, suggesting a possible allergic aetiology.

1. Soentjens P, *et al*. Mefloquine-induced pneumonitis. *J Travel Med* 2006; **13:** 172–4.
2. Katsenos S, *et al*. Mefloquine-induced eosinophilic pneumonia. *Pharmacotherapy* 2007; **27:** 1767–71.
3. FDA. Mefloquine Hydrochloride (marketed as Lariam and generics): pneumonitis. *FDA Drug Safety Newsletter* 2008; **1:** 41–3. Available at: http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm120613.htm#mefloquine_hydrochloride (accessed 08/09/09)

Effects on the nervous system. Neuropsychiatric reactions have been associated with the use of mefloquine[1] although various figures have been reported for their frequency. The UK CSM has quoted[2] figures of 1 in 10 000 to 1 in 20 000 for severe reactions to *prophylactic* doses and similarly the manufacturers report that 1 in 10 000 patients given mefloquine prophylaxis will have serious problems. Others consider that the incidence of serious reactions is extremely low,[3] with a frequency of about 1 in 80 000. The manufacturers have also reported that most reactions in patients taking mefloquine for prophylaxis appear to occur after the first dose and have suggested that monitoring after the first dose could identify 40% of those at risk of neuropsychiatric effects.[4] Some authorities consider that over 75% of such reactions to mefloquine are apparent by the third dose.[5] This may allow for tolerability problems with mefloquine prophylaxis to be identified before travel. There has been much discussion on the comparative tolerability of antimalarials used for chemoprophylaxis. The incidence of adverse events, including neuropsychiatric events, was comparable for mefloquine and chloroquine in 2 uncontrolled questionnaire studies, one in tourists[6] and one in US Peace Corps volunteers.[7] However, in a more recent questionnaire in travellers,[8] although the incidence of reported adverse events was similar for mefloquine and chloroquine plus proguanil, neuropsychiatric adverse events were significantly more common in mefloquine recipients. In two randomised controlled studies,[9,10] both in military personnel, there was no difference between CNS symptoms in those given weekly mefloquine and those receiving chloroquine (with or without proguanil). In one of these studies,[10] a subgroup receiving a loading dose of mefloquine daily for 3 days initially had a higher incidence of CNS events. A review[11] of 10 controlled studies found no significant difference in the rates of withdrawal and overall incidence of adverse effects for mefloquine and alternative prophylactic regimens, but mefloquine was more likely than other drugs to cause insomnia and fatigue. Women (particularly first-time users of mefloquine, or those with a low BMI)[12] may be at greater risk of adverse effects than men, and WHO has commented that the occurrence of such adverse effects may mean that only highly motivated occupational subgroups or individuals at high risk of infection with chloroquine-resistant malaria will be willing to continue with mefloquine prophylaxis.[13]

Neuropsychiatric reactions are more frequent after the higher doses of mefloquine used for *treatment* than those used for prophylaxis. Some workers have estimated that overall 1 in 8000 mefloquine users have such reactions, with the incidence 60 times higher after treatment than after prophylaxis.[14] Other workers who have used mefloquine in nearly 14 000 treatments calculated that the overall frequency of serious neuropsychiatric reactions was 1 per 1754 treatments; it therefore appeared that serious neuropsychiatric reactions were 10 times more probable after treatment than with prophylactic use of mefloquine.[15]

A severe neurological syndrome associated with mefloquine treatment, with agitation, delirium, stupor, hyperpyrexia, mydriasis, and generalised rigors responded rapidly to treatment with physostigmine, suggesting a central anticholinergic aetiology.[16]

A discrete post-malaria neurological syndrome (including an acute confusional state or acute psychosis, convulsions, and tremor) has been seen on recovery from falciparum malaria and there appeared to be a strong association with mefloquine although it was not the only risk factor.[17] Nevertheless the risk was considered unacceptable and the recommendation made[17] that, where there was an effective alternative drug, mefloquine should not be used after initial treatment of severe malaria.

Emergence delirium during recovery from general anaesthesia after mefloquine prophylaxis has been reported in 3 cases.[18]

There is evidence from a small study[19] in healthy subjects, and from similar results in *animals*, that mefloquine may induce deficits in motor learning skills.

1. Toovey S. Mefloquine neurotoxicity: a literature review. *Travel Med Infect Dis* 2009; **7:** 2–6.
2. CSM. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems* 1996; **22:** 6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023214 (accessed 18/06/08)
3. Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996; **347:** 326.
4. Stürchler D, *et al*. Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; **322:** 1752–3.
5. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. *Commun Dis Public Health* 2003; **6:** 180–99. Also available at: http://www.hpa.org.uk/cdph/issues/CDPHvol6/No3/6(3)p180-99.pdf (accessed 06/07/06)
6. Steffen R, *et al*. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; **341:** 1299–1303.
7. Lobel HO, *et al*. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341:** 848–51.
8. Barrett PJ, *et al*. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996; **313:** 525–8. Correspondence. *ibid.;* 1552–4.
9. Croft AMJ, *et al*. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. *Trans R Soc Trop Med Hyg* 1997; **91:** 199–203.
10. Boudreau E, *et al*. Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol* 1993; **44:** 257–65.
11. Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *BMJ* 1997; **315:** 1412–16. Correspondence. *ibid.* 1998; **316:** 1980–1.
12. van Riemsdijk MM, *et al*. Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine. *Br J Clin Pharmacol* 2004; **57:** 506–12.
13. Anonymous. Mefloquine effectiveness impaired by high withdrawal rates. *WHO Drug Inf* 1998; **12:** 7–8.
14. Weinke T, *et al*. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991; **45:** 86–91.
15. Luxemburger C, *et al*. Mefloquine for multidrug-resistant malaria. *Lancet* 1991; **338:** 1268.
16. Speich R, Haller A. Central anticholinergic syndrome with the antimalarial drug mefloquine. *N Engl J Med* 1994; **331:** 57–8.
17. Mai NTH, *et al*. Post-malaria neurological syndrome. *Lancet* 1996; **348:** 917–21.
18. Gullaho rn GM, *et al*. Anaesthesia emergence delirium after mefloquine prophylaxis. *Lancet* 1993; **341:** 632.
19. van Essen TA, *et al*. Anti-malaria drug mefloquine induces motor learning deficits in humans. *Front Neurosci* 2010; **4:** 191.

Effects on the oesophagus. Oesophageal ulceration in one patient and discomfort in another 4 was attributed to swallowing mefloquine tablets with insufficient fluid.[1]

1. Phillips M. Antimalarial mefloquine. *Med J Aust* 1994; **161:** 227–8.

Effects on the skin. Isolated cases of Stevens-Johnson syndrome,[1] severe facial lesions,[2,3] exfoliative dermatitis,[4] toxic epidermal necrolysis,[5] psoriasis exacerbation,[6] and cutaneous vasculitis[7] have been associated with use of mefloquine for malaria prophylaxis.

For a comparison of the incidence of pruritus induced by various antimalarials, including mefloquine, see under Chloroquine, p. 652.2.

1. Van den Enden E, *et al*. Mefloquine-induced Stevens-Johnson syndrome. *Lancet* 1991; **337:** 683.
2. Shlim DR. Severe facial rash associated with mefloquine. *JAMA* 1991; **266:** 2560.
3. Descloux E, *et al*. Mefloquine adverse effects with atypical facial lesions in an overweight patient. *Travel Med Infect Dis* 2010; **8:** 318–21.
4. Martin GJ, *et al*. Exfoliative dermatitis during malarial prophylaxis with mefloquine. *Clin Infect Dis* 1993; **16:** 341–2.
5. McBride SR, *et al*. Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis. *Lancet* 1997; **349:** 101.
6. Pace JL. Psoriasis triggered by mefloquine. *Skinmed* 2010; **8:** 301–2.
7. White AC, *et al*. Cutaneous vasculitis associated with mefloquine. *Ann Intern Med* 1995; **123:** 894.

Overdosage. Cardiac, hepatic, and neurological symptoms have been reported in a patient who inadvertently received 5.25 g of mefloquine over 6 days.[1] All symptoms disappeared rapidly when mefloquine was stopped.

1. Bourgeade A, *et al*. Intoxication accidentelle à la méfloquine. *Presse Med* 1990; **19:** 1903.

Precautions

Tasks requiring fine coordination such as driving should not be undertaken during treatment with mefloquine or for at least 3 weeks afterwards; in the case of prophylactic use, care should be exercised while taking mefloquine and for at least 3 weeks after stopping it. The use of mefloquine for malaria prophylaxis is contra-indicated in patients with a history of psychiatric (including depression) or convulsive disorders. Increased plasma concentrations may occur in patients with hepatic impairment. Mefloquine should be stopped should symptoms suggestive of psychiatric disturbance occur during prophylaxis, and an alternative antimalarial substituted.

Mefloquine is teratogenic in *animals* and its use during pregnancy is best avoided; however, in areas of chloroquine-resistant *Plasmodium falciparum*, WHO states that mefloquine may normally be taken for malaria prophylaxis during the second and third trimesters of pregnancy. It is recommended that women should also avoid becoming pregnant during, and for 3 months after, mefloquine use and that mothers should not breast feed while taking mefloquine.

Mefloquine should be used with caution in patients with renal impairment and in those with cardiac conduction disorders.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mefloquine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/10/11)

Pregnancy. Licensed product information for mefloquine reports that it is teratogenic in *rodents*. There is limited information on its effects in humans. One study in Thailand cited by WHO[1] found no difference between mefloquine and quinine in pregnancy outcome, but the numbers of treated patients who were in their first trimester were very small and its use should be kept to a minimum in that stage of pregnancy. Further spontaneous reports of exposure to mefloquine during the first trimester of pregnancy collected by the manufacturer revealed 24 fetal abnormalities and 17 spontaneous or missed abortions in 358 pregnancies, although a causal relationship was not established,[2] and a later study by the manufacturer involving 1627 reports of exposure during pregnancy appeared to show a similar incidence of congenital malformation to

that in offspring of unexposed women.[3] In 53 army service women who inadvertently used mefloquine in pregnancy, and for whom pregnancy outcome was known, there were 17 elective abortions, 12 spontaneous abortions, one molar pregnancy, and 23 healthy live births, with no major congenital malformations.[4] The rate of spontaneous abortions was considered high.[4] A prospective cohort study involving 236 pregnant women who received an antimalarial in the first trimester did not find an increased risk of spontaneous abortion or anomaly in women who took mefloquine compared with other antimalarials, and the rate of spontaneous abortion was comparable with background rates.[5]

Confidence in the safety of mefloquine has increased, and WHO now considers mefloquine suitable for malaria prophylaxis in the second and third trimesters;[6] WHO has stated its use is not recommended in the first trimester because of limited information on its safety. Authorities in the UK consider that use may sometimes be justified in the first trimester in areas of high risk of acquiring falciparum malaria; inadvertent use is not an indication to terminate pregnancy.[7]

Pregnancy should be avoided during and for 3 months after prophylactic use.

1. WHO. Practical chemotherapy of malaria: report of a WHO scientific group. *WHO Tech Rep Ser 805* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_805.pdf (accessed 18/06/05)
2. Palmer KJ, *et al*. Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.
3. Vanhauwere B, *et al*. Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. *Am J Trop Med Hyg* 1998; **58:** 17–21.
4. Smoak BL, *et al*. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army service women. *J Infect Dis* 1997; **176:** 831–3.
5. Phillips-Howard PA, *et al*. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *J Travel Med* 1998; **5:** 121–6.
6. WHO. *International travel and health*. 2011 ed. Available at: http://www.who.int/ith/en/ (accessed 16/06/11)
7. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Interactions

Halofantrine should not be given with, or within 15 weeks of the last dose of, mefloquine because of the increased potential to induce hazardous and potentially fatal cardiac arrhythmias, as discussed under Effects on the Heart on p. 654.3. Similarly, ketoconazole given with or after mefloquine may increase serum concentrations and the elimination half-life of mefloquine, potentially increasing the risk of QT-interval prolongation and arrhythmia. There is an increased risk of convulsions when mefloquine is used with chloroquine, quinidine, or quinine.

Alcohol. There has been a case report[1] of a patient who had neuropsychiatric disturbances after consuming a large quantity of alcohol with mefloquine; subsequent abstinence from alcohol led to complete reversal of the reactions.

1. Wittes RC, Saginur R. Adverse reaction to mefloquine associated with ethanol ingestion. *Can Med Assoc J* 1995; **152:** 515–17.

Antibacterials. Studies in healthy subjects have indicated that *ampicillin*[1] or *tetracycline*[2] could increase blood concentrations of mefloquine. Alternatively, concurrent use with *rifampicin* may decrease blood concentrations and reduce the elimination half-life of mefloquine.[3] Convulsions have been precipitated in 3 non-epileptic patients who were given mefloquine and the quinolone antibacterials *ciprofloxacin, ofloxacin,* or *sparfloxacin*.[4]

1. Karbwang J, *et al*. Effect of ampicillin on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1991; **40:** 631–3.
2. Karbwang J, *et al*. Effect of tetracycline on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1992; **43:** 567–9.
3. Ridtitid W, *et al*. Effect of rifampin on plasma concentrations of mefloquine in healthy volunteers. *J Pharm Pharmacol* 2000; **52:** 1265–9.
4. Mangalvedhekar SS, *et al*. Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration. *Natl Med J India* 2000; **13:** 47.

Antidepressants. Licensed product information for mefloquine states that in patients taking tricyclic antidepressants use of mefloquine may theoretically contribute to prolongation of the QT interval.

Antiepileptics. Licensed product information states that mefloquine may reduce seizure control by lowering the plasma concentration of antiepileptics, including carbamazepine, phenobarbital, and phenytoin. For the effect of mefloquine on *valproate*, see p. 557.3. For its effect on *carbamazepine*, see p. 517.2.

Antihistamines. Giving mefloquine with antihistamines may theoretically contribute to the prolongation of QT intervals; however, this is not considered to be an absolute contra-indication.

Antimalarials. It is well established that the use of *halofantrine* with or after mefloquine is contra-indicated because of the risk of hazardous cardiac arrhythmias. Mefloquine and other related compounds such as *quinine, quinidine,* and *chloroquine* may be given together only under close medical supervision because of possible additive cardiotoxicity; there is also an increased risk of convulsions.

A study in healthy subjects indicated that use of *primaquine* could increase blood concentrations of mefloquine and might increase the incidence of adverse effects due to mefloquine,[1] but others reported no such interaction.[2]

1. MacLeod CM, *et al*. Interaction of primaquine with mefloquine in healthy males. *J Clin Pharmacol* 1990; **30:** 841.
2. Karbwang J, *et al*. Pharmacokinetics of mefloquine in the presence of primaquine. *Eur J Clin Pharmacol* 1992; **42:** 559–60.

Antipsychotics. The use of mefloquine with *phenothiazines* or *pimozide* may theoretically contribute to prolonged QT intervals, although this is not considered to be an absolute contra-indication.

Cardiovascular drugs. It has been recommended that mefloquine should be used with extreme caution in patients also taking *antiarrhythmics, beta blockers, calcium-channel blockers,* or *digitalis,* until more was known about the risks of cardiotoxicity, since theoretically these drugs might contribute to prolongation of the QT interval. An increased risk of ventricular arrhythmias has been reported when mefloquine is given with *amiodarone*.

Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient who was taking *propranolol*.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Gastrointestinal drugs. Use with *metoclopramide* may increase plasma concentrations of mefloquine.[1]

1. Na Bangchang K, *et al*. The effect of metoclopramide on mefloquine pharmacokinetics. *Br J Clin Pharmacol* 1991; **32:** 640–1.

Vaccines. Unfortunately, conflicting advice has been issued concerning the use of mefloquine after typhoid vaccination, for details see p. 2423.1.

Pharmacokinetics

The pharmacokinetics of mefloquine may be altered by malaria infection in a manner similar to those of quinine, the main effects being reductions in both its volume of distribution and its overall clearance.

Mefloquine is well absorbed from the gastrointestinal tract but there is marked interindividual variation in the time required to achieve peak plasma concentrations. Mefloquine is about 98% bound to plasma proteins and high concentrations have been reported in red blood cells. It is widely distributed throughout the body. Mefloquine has a long elimination half-life; mean values of about 21 days have been reported for some patients, although like other pharmacokinetic data on mefloquine there is considerable variation in reported figures. Subtherapeutic concentrations of mefloquine may persist in the blood for several months. Mefloquine is metabolised in the liver. Little of a dose is excreted in the urine and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.

Mefloquine is distributed into breast milk in small amounts.

Reviews of pharmacokinetic studies of mefloquine reveal considerable interindividual variation for several pharmacokinetic parameters and some evidence that there might be pharmacokinetic differences between ethnic groups.[1,2] Mefloquine is well absorbed by healthy subjects and by patients with uncomplicated malaria after oral doses.[3,4] In patients with complicated malaria adequate blood concentrations have been obtained by the nasogastric route but this route cannot be relied upon for seriously ill patients[5] as absorption may be incomplete.[1] Mefloquine has a large apparent volume of distribution but this is reduced in the presence of malaria.[6,7] In children given mefloquine with sulfadoxine and pyrimethamine as tablets crushed and mixed with a glucose syrup, maximum blood-mefloquine concentrations were higher and reached in a shorter time compared with equivalent doses in adults.[8] In pregnant women with uncomplicated malaria, blood concentrations were lower than in non-pregnant women and the apparent volume of distribution was larger.[9] Once-weekly prophylactic doses of mefloquine resulted in steady-state conditions at about 10 doses with no evidence of subsequent accumulation.[10]

Mefloquine is metabolised in the liver[11] largely into 2,8-bis(trifluoromethyl)-4-quinoline carboxylic acid [Ro-21-5104][12] but this metabolite appears to be inactive against *Plasmodium falciparum*.[13] Only a small percentage of a dose is excreted in the urine[14] and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.[1] Mefloquine has an extremely long plasma elimination half-life; again there is considerable interindividual variation and mean values ranging from 13.9 to 27.5 days have been quoted, the lower end of the range referring to a formulation that was less well absorbed than the preparation now in use.[1]

Mefloquine is distributed into breast milk, but a single dose study in 2 women[15] indicated that the concentration of mefloquine in milk was only a small proportion of that seen in plasma.

1. Karbwang J, White NJ. Clinical pharmacokinetics of mefloquine. *Clin Pharmacokinet* 1990; **19:** 264–79.
2. Palmer KJ, *et al*. Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.
3. Karbwang J, *et al*. The pharmacokinetics of mefloquine when given alone or in combination with sulphadoxine and pyrimethamine in Thai male and female subjects. *Eur J Clin Pharmacol* 1987; **32:** 173–7.
4. Looareesuwan S, *et al*. Studies of mefloquine bioavailability and kinetics using a stable isotope technique: a comparison of Thai patients with falciparummalaria and healthy caucasian volunteers. *Br J Clin Pharmacol* 1987; **24:** 37–42.
5. Chanthavanich P, *et al*. Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34:** 1028–36.
6. Juma FD, Ogeto JO. Mefloquine disposition in normals and in patients with severe Plasmodium falciparum malaria. *Eur J Drug Metab Pharmacokinet* 1989; **14:** 15–17.
7. Karbwang J, *et al*. A comparison of the pharmacokinetics of mefloquine in healthy Thai volunteers and in Thai patients with falciparum malaria. *Eur J Clin Pharmacol* 1988; **35:** 677–80.
8. Singhasivanon V, *et al*. Pharmacokinetic study of mefloquine in Thai children aged 5-12 years suffering from uncomplicated falciparum malaria treated with MSP or MSP plus primaquine. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 27–32.
9. Na Bangchang K, *et al*. Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 321–3.
10. Pennie RA, *et al*. Steady state pharmacokinetics of mefloquine in long-term travellers. *Trans R Soc Trop Med Hyg* 1993; **87:** 459–62.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.
13. Håkanson A, *et al*. Comparison of the activity in vitro of mefloquine and two metabolites against Plasmodium falciparum. *Trans R Soc Trop Med Hyg* 1990; **84:** 503–4.
14. Schwartz DE, *et al*. Urinary excretion of mefloquine and some of its metabolites in African volunteers at steady state. *Chemotherapy* 1987; **33:** 305–8.
15. Edstein MD, *et al*. Excretion of mefloquine in human breast milk. *Chemotherapy* 1988; **34:** 165–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tropicur; ***Austral.***: Lariam; ***Austria***: Lariam; ***Belg.***: Lariam; ***Braz.***: Mephaquin; ***Canad.***: Lariam; ***Chile***: Lariam; ***Cz.***: Lariam; ***Denm.***: Lariam; ***Fin.***: Lariam; ***Fr.***: Lariam; ***Ger.***: Lariam; ***Gr.***: Lariam; Mephaquin; ***Hong Kong***: Lariam; Mephaquin; ***Hung.***: Lariam; ***India***: Confal; Facital; Falcital; Larimef; Mefact; Mefax; Mefcy; Mefliam; Mefloc; Meflotas; Mefque; Mepalex; MQF; ***Irl.***: Lariam; ***Israel***: Lariam; Mephaquin†; ***Ital.***: Lariam; ***Malaysia***: Lariam; Mephaquin; ***Neth.***: Lariam; ***Norw.***: Lariam; ***NZ***: Lariam; ***Philipp.***: Lariam; ***Port.***: Meflomax†; Mephaquin; ***Rus.***: Lariam (Лариам); ***S.Afr.***: Lariam; Mefliam; ***Singapore***: Lariam; Mephaquin; ***Swed.***: Lariam; ***Switz.***: Lariam; Mephaquine; ***Thai.***: Mequin; ***UAE***: Melophar; ***UK***: Lariam; ***Ukr.***: Lariam (Ларіам); Mephaquin (Мефахин)†; ***USA***: Lariam†.

Multi-ingredient Preparations. ***India***: Falcigo Plus; Larinate-MF; ***Port.***: Falcitrim.

Pharmacopoeial Preparations

USP 36: Mefloquine Hydrochloride Tablets.

Piperaquine Phosphate

Piperaquina, fosfato de; Piperaquini Phosphas; 13228-RP; Пиперахина Фосфат.

1,3-Bis[1-(7-chloro-4-quinolyl)-4′-piperazinyl]propane.

$C_{29}H_{32}Cl_2N_6.4H_3PO_4.4H_2O$=999.6

CAS — 85547-56-4.

UNII — 854D7K8LXB.

Pharmacopoeias. In *Chin.*

Uses and Administration

Piperaquine phosphate is a bisquinoline antimalarial that has traditionally been used in China for the treatment and prophylaxis of falciparum malaria (p. 644.1). It is a structural analogue of chloroquine (p. 650.2) and is thought to have a similar mechanism of action.

A fixed-dose combination product of piperaquine phosphate and artenimol (see Artemisinin Derivatives, p. 648.1) has been developed to improve patient adherence and avoid monotherapy, and thereby decrease the risk of acquired drug resistance. This combination product is used for the treatment of acute uncomplicated malaria caused by *Plasmodium falciparum*; it should not be used to treat severe malaria. The ratio of piperaquine phosphate to artenimol of 8 to 1 has been selected to provide a target daily dose of 18 mg/kg for piperaquine. The combination may be given to patients from 6 months of age and weighing 5 kg or more. It

is given orally once daily for 3 days; no food should be taken within 3 hours of each dose. For those who have difficulties swallowing, the tablets may be crushed and mixed with water. Recommended doses according to body-weight are as follows:

- 5 to less than 7 kg: 80 mg piperaquine phosphate with 10 mg artenimol
- 7 to less than 13 kg: 160 mg piperaquine phosphate with 20 mg artenimol
- 13 to less than 24 kg: 320 mg piperaquine phosphate with 40 mg artenimol
- 24 to less than 36 kg: 640 mg piperaquine phosphate with 80 mg artenimol
- 36 to less than 75 kg: 960 mg piperaquine phosphate with 120 mg artenimol
- 75 to 100 kg: 1280 mg piperaquine phosphate with 160 mg artenimol
- 100 kg or more: no data available on which to make a dose recommendation

Due to the long elimination half-life of piperaquine phosphate a second, 3-day course should not be given within 2 months of the first course; no more than 2 courses should be given within a 12 month period.

Combinations of piperaquine, artenimol, and trimethoprim (*Artecom*) and piperaquine with artemisinin and primaquine (*Artequick*) are available in some countries. Piperaquine is also under investigation for use with a synthetic artemisinin derivative artelolane maleate.

References.

1. Davis TME, *et al.* Piperaquine: a resurgent antimalarial drug. *Drugs* 2005; **65:** 75–87.
2. Ahmed T, *et al.* Safety, tolerability, and single-and multiple-dose pharmacokinetics of piperaquine phosphate in healthy subjects. *J Clin Pharmacol* 2008; **48:** 166–75.
3. Karunajeewa HA, *et al.* A trial of combination antimalarial therapies in children from Papua New Guinea. *N Engl J Med* 2008; **359:** 2545–57.
4. Tangpukdee N, *et al.* Efficacy of Artequick versus artesunate-mefloquine in the treatment of acute uncomplicated falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2008; **39:** 1–8.
5. Chinh NT, *et al.* Pharmacokinetics and bioequivalence evaluation of two fixed-dose tablet formulations of dihydroartemisinin and piperaquine in Vietnamese subjects. *Antimicrob Agents Chemother* 2009; **53:** 828–31.
6. Zwang J, *et al.* Safety and efficacy of dihydroartemisinin-piperaquine in falciparum malaria: a prospective multi-centre individual patient data analysis. *PLoS One* 2009; **4:** e6358.
7. Song J, *et al.* Rapid and effective malaria control in Cambodia through mass administration of artemisinin-piperaquine. *Malar J* 2010; **9:** 57.
8. Mayxay M, *et al.* A phase III, randomized, non-inferiority trial to assess the efficacy and safety of dihydroartemisinin-piperaquine in comparison with artesunate-mefloquine in patients with uncomplicated *Plasmodium falciparum* malaria in southern Laos. *Am J Trop Med Hyg* 2010; **83:** 1221–9.
9. Creek D, *et al.* Increased risk of early vomiting among infants and young children treated with dihydroartemisinin-piperaquine compared with artemether-lumefantrine for uncomplicated malaria. *Am J Trop Med Hyg* 2010; **83:** 873–5.
10. Nambozi M, *et al.* Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Zambian children. *Malar J* 2011; **10:** 50.
11. Menan H, *et al.* Comparative study of the efficacy and tolerability of dihydroartemisinin-piperaquine-trimethoprim versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Cameroon, Ivory Coast and Senegal. *Malar J* 2011; **10:** 185.
12. Yavo W, *et al.* Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in sub-Saharan Africa. *Malar J* 2011; **10:** 198.
13. Keating GM. Dihydroartemisinin/Piperaquine: a review of its use in the treatment of uncomplicated *Plasmodium falciparum* malaria. *Drugs* 2012; **72:** 937–61.
14. Valecha N, *et al.* Arterolane maleate plus piperaquine phosphate for treatment of uncomplicated *Plasmodium falciparum* malaria: a comparative, multicenter, randomized clinical trial. *Clin Infect Dis* 2012; **55:** 663–71.

Administration in children. The fixed-dose combination product of piperaquine phosphate and artenimol may be given to children from 6 months of age and weighing 5 kg or more for the treatment of acute uncomplicated infections caused by *Plasmodium falciparum*. For dose recommendations in these children, see p. 659.3.

Adverse Effects and Precautions

Piperaquine phosphate given as monotherapy or with artenimol is generally well tolerated. The most commonly reported adverse effects with piperaquine phosphate alone are dizziness, headache, and gastrointestinal effects such as nausea, vomiting, and abdominal pain.

Commonly reported adverse effects reported with the use of the fixed-dose combination product of piperaquine phosphate and artenimol are anaemia, asthenia, headache, and pyrexia. Prolongation of the QTc interval and tachycardia are also frequent and the combination is contra-indicated in those with a family history of sudden death or cardiovascular disorders such as congenital prolongation of the QTc interval, symptomatic cardiac arrhythmias, severe hypertension, left ventricular hypertrophy, congestive heart failure, and in those with electrolyte disturbances. It is also contra-indicated in those who have recently taken or are taking other drugs known to prolong the QTc interval. ECG and blood potassium monitoring are recommended. Caution is advised when giving the combination product to those with jaundice, and/or moderate or severe renal or hepatic impairment.

Interactions

Piperaquine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP2C19 and CYP2C9. It is an inhibitor of the CYP3A4 and CYP2C19 isoenzymes and may inhibit the metabolism of other drugs that are metabolised by this route; it also has the potential to increase the rate of metabolism for CYP2E1 substrates such as paracetamol and theophylline. Drugs that inhibit CYP3A4 may increase plasma concentrations of piperaquine and exacerbate the effect of QTc prolongation. Enzyme inducers may decrease plasma concentrations of piperaquine. Piperaquine should be avoided in patients taking potentially arrhythmogenic drugs including those that prolong the QT interval.

Pharmacokinetics

Piperaquine is slowly absorbed and peak plasma concentrations are generally reached 5 hours after an oral dose. It has a large volume of distribution and is more than 99% bound to plasma protein. *In vitro* studies show that piperaquine is mainly metabolised by the cytochrome P450 isoenzymes CYP3A4. It is eliminated slowly with an elimination half-life of about 22 days in adults and 20 days in children.

References.

1. Tarning J, *et al.* Population pharmacokinetics and pharmacodynamics of piperaquine in children with uncomplicated falciparum malaria. *Clin Pharmacol Ther* 2012; **91:** 497–505.
2. Tarning J, *et al.* Population pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and nonpregnant women with uncomplicated malaria. *Antimicrob Agents Chemother* 2012; **56:** 1997–2007.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***China***: An Li Kang (安立康); Duo-Cotecxin; Ke Tai Fu (科泰复); ***Irl.***: Eurartesim; ***Neth.***: Eurartesim; ***UK***: Eurartesim.

Primaquine Phosphate *(BANM, rINNM)*

Difosfato de Primaquina; Fosfato de primaquina; Primachin difosfát; Primachina Fosfato; Primachini Phosphas; Primakiinidifosfaatti; Primakindifosfat; Primakin-difoszfát; Primakvino difosfatas; Primaquina, fosfato de; Primaquinbisdihydrogenphosphat; Primaquine Diphosphate; Primaquine, diphosphate de; Primaquine, Phosphate de; Primaquini diphosphas; Primaquini Phosphas; Primaquinum Phosphoricum; SN-13,272; Примахина Фосфат.

(*RS*)-8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline diphosphate.

$C_{15}H_{21}N_3O,2H_3PO_4$=455.3

CAS — 90-34-6 (primaquine); 63-45-6 (primaquine phosphate).

ATC — P01BA03.

UNII — H0982HF78B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Primaquine Diphosphate). An orange crystalline powder. Soluble in water; practically insoluble in alcohol. Protect from light.

USP 36: (Primaquine Phosphate). An orange-red, odourless, crystalline powder. Soluble 1 in 15 of water; insoluble in chloroform and in ether. Its solutions are acid to litmus. Protect from light.

Uses and Administration

Primaquine is an 8-aminoquinoline antimalarial that is effective as a tissue schizontocide against intrahepatic forms of all types of *Plasmodium*. It is mainly used to produce radical cure of vivax and ovale malarias, but may also be given to reduce transmission of falciparum malaria. It also has some action against *Pneumocystis* and is used with clindamycin in the management of pneumocystis pneumonia. For further information, see below and p. 661.1.

Primaquine phosphate is given orally and doses may be expressed in terms of the base; primaquine phosphate 26.4 mg is equivalent to about 15 mg of primaquine base.

When used for *radical cure* of vivax or ovale malaria, a course of treatment with a blood schizontocide must be given first to kill any erythrocytic parasites. Primaquine phosphate is then given orally, usually in a dose equivalent to 15 mg (or 250 micrograms/kg) of the base daily for 14 days but higher doses or longer courses may be required to overcome resistance in some strains of *P. vivax* (see below); WHO has advised that for uncomplicated malaria acquired in South-East Asia (particularly Indonesia) and Oceania, the dose should be increased to 500 micrograms/kg daily. In the UK, the *BNF* suggests that while 15 mg (or 250 micrograms/kg) daily is appropriate for use in *P. ovale* malaria, 30 mg (or 500 micrograms/kg) daily is necessary for infections caused by *P. vivax*.

For patients with G6PD deficiency the use of up to 45 mg (or 750 micrograms/kg) once every 7 days for 8 weeks has been suggested to minimise haemolysis (but see under Adverse Effects, p. 661.2).

For details of doses in children, see below.

General reviews.

1. Vale N, *et al.* Primaquine revisited six decades after its discovery. *Eur J Med Chem* 2009; **44:** 937–53.
2. Fernando D, *et al.* Primaquine in vivax malaria: an update and review on management issues. *Malar J* 2011; **10:** 351–62.

Administration in children. Primaquine may be used orally in children for **radical cure** of **malaria** caused by *P. ovale* or *P. vivax*. Doses are expressed in terms of primaquine base, and WHO[1,2] has suggested a dose of 250 micrograms/kg (to a maximum of 15 mg) once daily for 14 days; in South-East Asia and Oceania, the dose should be increased to 500 micrograms/kg (maximum 30 mg) daily. In the UK, the *BNFC* has recommended that, although the lower dose is appropriate for treatment of *P. ovale* malaria, the higher dose regimen should be used for all infections caused by *P. vivax*.

Although a lower age limit for the use of primaquine has not been formally established,[2] the *BNFC* suggests that it may be used in children over 6 months of age, but that specialist advice should be sought for younger children. Primaquine should be avoided in patients with severe G6PD deficiency, however in milder deficiency, a dose of 500 to 750 micrograms/kg once every 7 days for 8 weeks has been found to be without harmful effects.[3] (The *BNFC* also comments that this regimen is safe but suggests that the total daily dose should not exceed 45 mg.)

For a discussion on the use of primaquine to reduce transmission of falciparum malaria, see below.

1. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 27/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
2. WHO. *International travel and health.* 2011 ed. Available at: http://www.who.int/ith/en (accessed 17/06/11)
3. WHO. *WHO model formulary for children: based on the second model list of essential medicines for children 2009.* Geneva: WHO, 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 27/07/10)

Malaria. The overall treatment and prophylaxis of malaria and the place of primaquine in current recommendations are described on p. 644.1.

Despite the generally successful use of oral primaquine for **radical cure** of benign (non-falciparum) malarias, resistance of vivax (but not ovale) malaria is a known problem in some areas of the world,[1,2] and failures have occurred. The suggestion has been made that higher doses of primaquine (15 mg twice daily for 14 days, to give a total dose of 6 mg/kg assuming a body-weight of 70 kg) should be considered wherever the vivax malaria was acquired,[1-4] and this is the standard recommendation in the UK (see above). A systematic review[5] concluded that when used with chloroquine, a 14-day course of primaquine 15 mg daily was more effective than a 5-day course in preventing relapses of vivax malaria. The 5-day course of primaquine plus chloroquine appeared to be no better than chloroquine alone.

Variable responses to primaquine in the Amazonian region were attributed to considerable variation in the content of primaquine both between and within batches of tablets; primaquine content ranged from 19 to 168% of the labelled content.[6]

In the USA, the CDC[7] have suggested presumptive antirelapse therapy (or terminal prophylaxis) with primaquine at the end of prophylaxis to prevent relapses due to *Plasmodium vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic. In those who have taken chloroquine, doxycycline, or mefloquine as prophylaxis, primaquine is usually given during the last 2 weeks of prophylaxis, but, when necessary, may also be taken immediately after prophylaxis is completed. When atovaquone plus proguanil is taken as prophylaxis, primaquine is preferably given during the last 7 days and then for an additional 7 days, but may also be given for 14 days after atovaquone plus proguanil prophylaxis is completed. The recommended daily oral dose of primaquine for terminal prophylaxis is 30 mg for adults and 500 micrograms/kg for children.

Primaquine has also been tried for **prophylaxis** of falciparum and vivax malaria; use for a year produced effective cover and was well tolerated by Javanese men without G6PD deficiency.[8] It was also effective for prophylaxis in Colombian military personnel; it was noted that primaquine prophylaxis could be stopped 1 week after departing the endemic area.[9]

The use of primaquine as a gametocytocide has the potential to **reduce the transmission** of falciparum malaria in low transmission areas and to help contain the

spread of artemisinin-resistant falciparum malaria.[10,11] WHO therefore initially suggested that primaquine be given as a single dose of 750 micrograms/kg (to a maximum of 45 mg) with an artemisinin derivative-based combination regimen for the treatment of uncomplicated *P. falciparum* malaria, provided the risk for G6PD deficiency was considered low or testing for deficiency was available.[10] However, testing for G6PD is not widely available in malaria endemic areas and concerns over primaquine's potential for haemolysis have limited its use. Following a review of safety and efficacy data, WHO has subsequently suggested that a lower dose of 250 micrograms/kg would be safer and equally effective and should be given on the first day of treatment (except in pregnant women and infants less than 1 year of age) without the need for G6PD testing.[10,12]

1. Ajdukiewicz KM, Ong EL. Management of vivax malaria with low sensitivity to primaquine. *J Infect* 2007; **54:** 209–11.
2. Beeching NJ, *et al.* Management of vivax malaria with primaquine. *J Infect* 2007; **55:** 282.
3. Doherty JF, *et al.* Treatment of Plasmodium vivax malaria—time for a change? *Trans R Soc Trop Med Hyg* 1997; **91:** 76.
4. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004; **39:** 1336–45.
5. Galappaththy GNL, *et al.* Primaquine for preventing relapses in people with Plasmodium vivax malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/03/08).
6. Petralanda I. Quality of antimalarial drugs and resistance to Plasmodium vivax in Amazonian region. *Lancet* 1995; **345:** 1433.
7. CDC. Malaria. In: *The Yellow Book: CDC Health Information for International Travel*; 2012. Also available at: http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm (accessed 12/09/11)
8. Fryauff DJ, *et al.* Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet* 1995; **346:** 1190–3.
9. Soto J, *et al.* Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Ann InternMed* 1998; **129:** 241–4.
10. White NJ, *et al.* Rationale for recommending a lower dose of primaquine as a *Plasmodium falciparum* gametocytocide in populations where G6PD deficiency is common. *Malar J* 2012; **11:** 418.
11. Sutanto I, *et al.* The effect of primaquine on gametocyte development and clearance in the treatment of uncomplicated falciparum malaria with dihydroartemisinin-piperaquine in South Sumatra, Western Indonesia: an open-label, randomized, controlled trial. *Clin Infect Dis* 2013; **56:** 685–93.
12. WHO. Single dose Primaquine as a gametocytocide in *Plasmodium falciparum* malaria: updated WHO policy recommendation (issued October 2012). Available at: http://www.who.int/malaria/pq_updated_policy_recommendation_en_102012.pdf (accessed 06/06/13)

Pneumocystis pneumonia. Primaquine with clindamycin is used in the treatment of pneumocystis pneumonia as an alternative to co-trimoxazole[1] (see p. 567.2). Treatment has usually lasted 3 weeks, and US experts suggest primaquine be given orally in daily doses equivalent to 15 to 30 mg of the base, and clindamycin be given in doses of 600 to 900 mg intravenously or 300 to 450 mg orally every 6 to 8 hours.[2,3] In the UK, the *BNF* suggests clindamycin 600 mg orally every 8 hours with oral primaquine 30 mg daily for mild to moderate disease, but notes that the combination may cause considerable toxicity.

A randomised multicentre study[4] compared this latter regimen (primaquine 30 mg daily and clindamycin 600 mg three times daily) with co-trimoxazole and with a combination of dapsone and trimethoprim in 181 AIDS patients who had confirmed mild to moderate pneumocystis pneumonia. Primaquine-clindamycin was as effective as the other two regimens, although the authors suggested that the combination might be best avoided in patients with severe myelosuppression.

Primaquine with clindamycin is not normally recommended for prophylaxis although there are reports of it being tried.[5] A retrospective examination[6] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Benfield T, *et al.* Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr* 2008; **48:** 63–7.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 2nd ed. New Rochelle NY: The Medical Letter 2010.
3. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 09/09/09)
4. Safrin S, *et al.* Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS: a double-blind, randomized trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. *Ann Intern Med* 1996; **124:** 792–802.
5. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
6. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Adverse Effects

Adverse effects with therapeutic doses of primaquine are usually minimal but abdominal pain and gastric distress are more common if taken on an empty stomach. Larger doses may cause nausea and vomiting. Methaemoglobinaemia may occur occasionally. Haemolytic anaemia can occur in persons with G6PD deficiency (see below). Other uncommon effects include mild anaemia and leucocytosis. Hypertension and cardiac arrhythmias have been reported on rare occasions. Primaquine may rarely produce leucopenia or agranulocytosis, usually after overdosage. Other effects associated with overdosage include gastrointestinal symptoms, haemolytic anaemia, and methaemoglobinaemia with cyanosis.

Many adverse effects have been reported after use of primaquine[1] but some, including pruritus and disturbances of visual accommodation, are considered to be inadequately documented or doubtfully attributed to the drug.

Acute intravascular haemolysis is the most serious toxic hazard of primaquine, especially in people with G6PD deficiency, other defects of the erythrocytic pentose phosphate pathway of glucose metabolism, or some types of haemoglobinopathy. In individuals with G6PD deficiency the severity of haemolysis is directly related to the degree of deficiency and to the quantity of primaquine given. In patients with the African variant the standard course of primaquine generally produces a moderate and self-limiting anaemia, while in those with the Mediterranean and related Asian variants, haemolysis can result in progressive haemoglobinaemia and haemoglobinuria which can be fatal. Whenever possible, therapy with primaquine should be delayed until the acute stage of malaria has been brought under control by a blood schizontocide because of the risk of inducing haemolysis and compromising the gastrointestinal tolerance of therapy.

1. Clyde DF. Clinical problems associated with the use of primaquine as a tissue schizontocidal and gametocytocidal drug. *Bull WHO* 1981; **59:** 391–5.

Precautions

Primaquine should be used cautiously in acutely ill patients with any serious systemic disease characterised by a tendency to granulocytopenia such as rheumatoid arthritis or lupus erythematosus. It should also be used with care in patients with G6PD deficiency. Primaquine should be withdrawn if signs of haemolysis or methaemoglobinaemia occur and the blood count should be monitored periodically.

Breast feeding. Primaquine should not be used in nursing women, unless the breast-fed infant has been determined not to be G6PD-deficient.

Pregnancy. Primaquine should not be given during pregnancy; radical cure of vivax or ovale malarias with primaquine should be delayed in pregnant women until after delivery.[1]

1. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.

Interactions

Primaquine should not be used with drugs liable to induce haemolysis or bone marrow depression. Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Antimalarials. The pharmacokinetics of primaquine were not altered by *mefloquine* in healthy subjects,[1] although the effect of primaquine on mefloquine pharmacokinetics is uncertain (see under Mefloquine, p. 659.2). In a study in patients with malaria, *quinine* reduced the plasma concentrations of primaquine, although the clinical importance of the interaction was unclear.[1]

1. Edwards G, *et al.* Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. *Br J Clin Pharmacol* 1993; **35:** 193–8.

Pharmacokinetics

Primaquine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after a dose and then rapidly diminish with a reported elimination half-life of 3 to 6 hours. It is widely distributed into body tissues.

Primaquine is rapidly metabolised in the liver. Its major metabolite carboxyprimaquine accumulates in the plasma on repeated dosage. Little unchanged drug is excreted in the urine.

References.

1. Fletcher KA, *et al.* Studies on the pharmacokinetics of primaquine. *Bull WHO* 1981; **59:** 407–12.
2. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
3. Mihaly GW, *et al.* Pharmacokinetics of primaquine in man, I: studies of the absolute bioavailability and effects of dose size. *Br J Clin Pharmacol* 1985; **19:** 745–50.
4. Ward SA, *et al.* Pharmacokinetics of primaquine in man, II: comparison of acute vs chronic dosage in Thai subjects. *Br J Clin Pharmacol* 1985; **19:** 751–5.
5. Bhatia SC, *et al.* Pharmacokinetics of primaquine in patients with P. vivax malaria. *Eur J Clin Pharmacol* 1986; **31:** 205–10.
6. Rønn A, Bygbjerg I. Unexpected high primaquine concentrations in acutely ill malaria patients. *Lancet* 1993; **341:** 305.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Primacin; ***Braz.***: Primakinder†; ***India:*** Malirid; Malquine; PMQ-INGA; Primacip.

Pharmacopoeial Preparations

USP 36: Primaquine Phosphate Tablets.

Proguanil Hydrochloride

(BANM, rINNM)

Bigumalum; Chloriguane Hydrochloride; Chloroguanide Hydrochloride; Chlorowodorek Prokwanilu; Hidrocloruro de proguanil; Proguanide Hydrochloride; Proguaniilihydrokloridi; Proguanil, chlorhydrate de; Proguanil, hidrocloruro de; Proguanil hydrochlorid; Proguanil-hidroklorid; Proguanilhydrochlorid; Proguanilhydroklorid; Proguanili hydrochloridum; Proguaniło hidrochloridas; RP-3359; SN-12,837; Прогуанила Гидрохлорид.

1-(4-Chlorophenyl)-5-isopropylbiguanide hydrochloride.

$C_{11}H_{16}ClN_5.HCl$=290.2

CAS — 500-92-5 (proguanil); 637-32-1 (proguanil hydrochloride).

ATC — P01BB01.

UNII — R71Y86M0WT.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Proguanil Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Proguanil Hydrochloride). A white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Stability. Although the Ph. Eur. 8 directs that proguanil hydrochloride should be protected from light, stability studies[1,2] suggest that it is a very stable compound with only small amounts of its major decomposition product 4-chloroaniline being formed during thermal and photochemical stress.

1. Owoyale JA, Elmarakby ZS. Effect of sunlight, ultraviolet irradiation and heat on proguanil. *Int J Pharmaceutics* 1989; **50:** 219–21.
2. Taylor RB, *et al.* A chemical stability study of proguanil hydrochloride. *Int J Pharmaceutics* 1990; **60:** 185–90.

Uses and Administration

Proguanil is a biguanide compound that has little antimalarial activity until metabolised in the body to the active antimalarial drug cycloguanil. Cycloguanil, like pyrimethamine, inhibits plasmodial dihydrofolate reductase and thus disrupts synthesis of nucleic acids in the parasite. Cycloguanil is active against pre-erythrocytic forms and is a slow-acting blood schizontocide. It also has some sporontocidal activity, rendering the gametocytes non-infective to the mosquito vector.

The value of proguanil is limited by the rapid development of resistance.

Proguanil is used orally as the hydrochloride for the chemoprophylaxis of malaria, with chloroquine or atovaquone. The schizontocidal activity of cycloguanil on erythrocytic forms is too slow for cycloguanil or proguanil to be used alone for the treatment of malaria, but proguanil hydrochloride is given with atovaquone for the treatment of uncomplicated falciparum malaria (p. 644.1).

For *prophylaxis* of malaria in combination with chloroquine, the usual adult daily dose of proguanil hydrochloride is 200 mg taken after food. For prophylaxis in combination with atovaquone 250 mg, the daily dose of proguanil hydrochloride is 100 mg. It is generally recommended that chemoprophylaxis for travellers should start 1 week before exposure to malaria, but if this is not possible it can be started 1 to 2 days before travel. Use should continue throughout exposure and for at least 4 weeks (1 week when proguanil is given with atovaquone) after leaving a malarious area.

In the *treatment* of uncomplicated falciparum malaria, adult doses are proguanil hydrochloride 400 mg with atovaquone 1 g, each orally as a single dose for 3 consecutive days.

For children's doses in the prophylaxis and treatment of malaria, see p. 662.1.

Cycloguanil was also formerly given by intramuscular injection as an oily suspension of the embonate.

Reviews.

1. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
2. Marra F, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.

3. Nakato H, *et al.* A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* 2007; **60:** 929–36.

Administration in children. Dosage recommendations for proguanil with **chloroquine** for **malaria prophylaxis** in children have varied. UK malaria experts[1] have suggested the following prophylactic oral doses of proguanil hydrochloride for children based on fractions of the adult dose of 200 mg daily:

- under 6.0 kg (up to 12 weeks of age): one-eighth the adult dose
- 6 to 9.9 kg (3 to 11 months): one-quarter the adult dose
- 10 to 15.9 kg (1 year to 3 years 11 months): three-eighths the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months): half the adult dose
- 25 to 44.9 kg (8 years to 12 years 11 months): three-quarters the adult dose
- 45 kg and over (13 years or more): the adult dose

They noted that body-weight was a better guide to dosage than age for children over 6 months.

Children may be given proguanil with **atovaquone** for the **prophylaxis** of malaria.[1] A daily dose based on either a paediatric tablet containing 25 mg of proguanil hydrochloride plus 62.5 mg of atovaquone *or* an adult tablet containing 100 mg of proguanil hydrochloride plus 250 mg of atovaquone is as follows:

- children weighing 5 to 8 kg: half of a paediatric tablet
- > 8 to 10 kg: three-quarters of a paediatric tablet
- > 10 to 20 kg: one paediatric tablet or one-quarter of the adult tablet
- > 20 to 30 kg: two paediatric tablets or half of the adult tablet
- > 30 to 40 kg: three paediatric tablets or three-quarters of the adult tablet
- > 40 kg: four paediatric tablets or one adult tablet

Doses of proguanil with atovaquone for the **treatment** of malaria, based on the adult dose of 400 mg of proguanil hydrochloride daily, are:

- children weighing 5 to 8 kg: one-eighth the adult dose
- 9 to 10 kg: three-sixteenths the adult dose
- 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- 40 kg and over: the adult dose

1. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Administration in renal impairment. Proguanil is excreted by the kidneys and should be given in reduced dosage or avoided in patients with renal impairment. The following oral doses have been recommended based on creatinine clearance (CC):

- CC 20 to 59 mL/minute: 100 mg daily
- CC 10 to 19 mL/minute: 50 mg every other day
- CC less than 10 mL/minute: 50 mg once weekly

Adverse Effects and Precautions

Apart from mild gastric intolerance, diarrhoea, and some reports of aphthous ulceration there appear to be few adverse effects associated with usual doses of proguanil hydrochloride. There have been rare reports of hypersensitivity reactions including urticaria and angioedema. Rare cases of seizures and psychotic events have also been reported. Haematological changes have been reported in patients with severe renal impairment. Overdosage may produce epigastric discomfort, vomiting, and renal irritation leading to haematuria.

Proguanil should be used with caution in patients with renal impairment; dosage should be reduced accordingly (see under Uses and Administration, above).

Proguanil may be taken during pregnancy, but UK guidelines recommend that folate supplements (folic acid 5 mg daily) should also be given; however, the combination of proguanil with atovaquone should be avoided as data regarding the safety of atovaquone are lacking.

For information on the adverse effects and precautions associated with the use of proguanil with atovaquone, see under p. 929.1.

Until 1985 proguanil was generally taken in a dose of 100 mg daily for malaria prophylaxis with few adverse effects. Although there was no increase in serious adverse effects when the dose was increased to 200 mg daily, and it began to be used with chloroquine, there were an increasing number of reports of reversible aphthous ulceration.[1] Chloroquine may exacerbate this effect.[2] There has also been a report of reversible alopecia in women and scaling of the skin in both men and women using proguanil.[3] More severe skin reactions have been coupled with symptoms such as acute eosinophilic pneumonia as part of a hypersensitivity reaction.[4]

Megaloblastic anaemia and pancytopenia have been associated with proguanil accumulation in patients with renal impairment.[5,6]

1. PetoTEA. Toxicity of antimalarial drugs. *J R Soc Med* 1989; **82** (suppl 17): 30–4.
2. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; **335:** 164.
3. Hanson SN, *et al.* Hairloss and scaling with proguanil. *Lancet* 1989; **i:** 225.
4. Just N, *et al.* Severe hypersensitivity reaction as acute eosinophilic pneumonia and skin eruption induced by proguanil. *Eur Respir J* 2011; **37:** 1526–8.
5. Boots M, *et al.* Megaloblastic anemia and pancytopenia due to proguanil in patients with chronic renal failure. *Clin Nephrol* 1982; **18:** 106–8.
6. Jolink H, *et al.* Pancytopenia due to proguanil toxicity in a returning traveller with fever. *Eur J Clin Pharmacol* 2010; **66:** 811–12.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pyrimethamine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Interactions

Antidepressants. *Fluvoxamine* can virtually abolish[1] the metabolism of proguanil to its active metabolite cycloguanil via an inhibitory effect on the cytochrome P450 isoenzyme CYP2C19.

1. Jeppesen U, *et al.* The CYP2C19 catalyzed bioactivation of proguanil is abolished during fluvoxamine intake. *Eur J Clin Pharmacol* 1997; **52** (suppl): A134.

Warfarin. For a report of haematuria and high prothrombin ratio in a patient stabilised on warfarin who took proguanil for malaria prophylaxis, see p. 1532.2.

Pharmacokinetics

Proguanil is readily absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about 4 hours. It is about 75% bound to plasma proteins. Proguanil is metabolised in the liver to the active metabolite cycloguanil. Peak plasma concentrations of cycloguanil occur about 1 hour after those of the parent drug. The elimination half-lives of both proguanil and cycloguanil are about 20 hours. About 40 to 60% of proguanil is eliminated in the urine, of which 60% is unchanged and 30% cycloguanil. There is also some elimination via the faeces. Proguanil is distributed into breast milk in small amounts (which are not adequate to provide chemoprophylaxis for the infant).

Early studies found proguanil to be well absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 4 hours.[1] In more recent studies, peak plasma concentrations of proguanil have been achieved within 2 to 4 hours.[2-4] Plasma protein binding for proguanil is 75%.[5] Proguanil is metabolised in the liver[3] to the active metabolite cycloguanil and to *p*-chlorophenylbiguanide which is inactive. Peak plasma concentrations of cycloguanil occur about 5.3 hours after doses of proguanil.[4] Unlike proguanil and *p*-chlorophenylbiguanide, cycloguanil is not concentrated in erythrocytes and thus concentrations of cycloguanil in plasma and whole blood are similar.[4] The elimination half-lives for proguanil and cycloguanil are about 20 hours.[3,4] A review of early studies states that 40 to 60% of a dose of proguanil is excreted in the urine, 60% of this as the unchanged drug, 30% as cycloguanil, and 8% as *p*-chlorophenylbiguanide.[1] About 10% of a dose is excreted in the faeces.[1] However, these values can vary greatly and wide interindividual variations in the ability to metabolise proguanil to cycloguanil have been reported.[3,6,7] Malaria prophylaxis with proguanil might be less effective in poor metabolisers although this has not been proved conclusively[8] and, anyway, other factors such as lack of protection against mosquitoes and sensitivity of the malaria parasite might be more important.[9]

Plasma concentrations of cycloguanil may be reduced in the third trimester of pregnancy.[10]

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Kelly JA, *et al.* The kinetics of proguanil during prophylaxis. *Trans R Soc Trop Med Hyg* 1986; **80:** 338.
3. Watkins WM, *et al.* Variability in the metabolism of proguanil to the active metabolite cycloguanil in healthy Kenyan adults. *Trans R Soc Trop Med Hyg* 1990; **84:** 492–5.
4. Wattanagoon Y, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in healthy subjects. *Br J Clin Pharmacol* 1987; **24:** 775–80.
5. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
6. Ward SA, *et al.* Inter-subject variability in the metabolism of proguanil to the active metabolite cycloguanil in man. *Br J Clin Pharmacol* 1989; **27:** 781–7.
7. Helsby NA, *et al.* The multiple dose pharmacokinetics of proguanil. *Br J Clin Pharmacol* 1993; **35:** 653–6.
8. Mberu EK, *et al.* Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough. *Trans R Soc Trop Med Hyg* 1995; **89:** 658–9.
9. Skjelbo E, *et al.* Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clin Pharmacol Ther* 1996; **59:** 304–11.
10. Wangboonskul J, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. *Eur J Clin Pharmacol* 1993; **44:** 247–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Paludrine†; ***Austria***: Paludrine†; ***Belg.***: Paludrine; ***Fr.***: Paludrine; ***Ger.***: Paludrine; ***Gr.***: Paludrine; ***India***: Laveran; ***Irl.***: Paludrine†; ***Ital.***: Paludrine†; ***Neth.***: Paludrine; ***Singapore***: Paludrine; ***Swed.***: Paludrine†; ***UK***: Paludrine.

Multi-ingredient Preparations. ***Austral.***: Malarone; ***Austria***: Malarone; ***Belg.***: Malarone; ***Canad.***: Malarone; ***Chile***: Malarone; ***Cz.***: Malarone; ***Denm.***: Malarone; ***Fin.***: Malarone; ***Fr.***: Malarone; Nopalu; Savarine; ***Ger.***: Malarone; ***Gr.***: Malarone; Savarine; ***Hong Kong***: Malarone; ***Hung.***: Malarone; ***Irl.***: Malarone; ***Israel***: Malarone; ***Ital.***: Malarone; ***Jpn***: Malarone; ***Malaysia***: Malarone; ***Neth.***: Malarone; ***Norw.***: Malarone; ***NZ***: Malarone; ***Pol.***: Malarone; ***Port.***: Malarone; ***S.Afr.***: Malanil; ***Singapore***: Malarone; ***Spain***: Malarone; ***Swed.***: Malarone; ***Switz.***: Malarone; ***Thai.***: Malanil; ***UK***: Malarone; Reprapog; ***USA***: Malarone.

Pharmacopoeial Preparations
BP 2014: Proguanil Tablets.

Pyrimethamine *(BAN, rINN)*

BW-50-63; Pirimetamin; Pirimetamina; Pirimetaminas; Pirymetamina; Pyrimetamiini; Pyrimetamin; Pyrimethamin; Pyriméthamine; Pyrimethaminum; RP-4753; Пириметамин.

5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diyldiamine.

$C_{12}H_{13}ClN_4$=248.7

CAS — 58-14-0.

ATC — P01BD01.

UNII — Z3614QOX8W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Pyrimethamine). An almost white crystalline powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Pyrimethamine). A white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 125 of chloroform; slightly soluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Pyrimethamine is a diaminopyrimidine antimalarial used with a sulfonamide in the treatment of malaria (see p. 644.1) and toxoplasmosis (see p. 663.1). Pyrimethamine with sulfadoxine has also been used in the treatment of actinomycetoma (p. 663.1), for prophylaxis of pneumocystis pneumonia (p. 663.1), and in the treatment of isosporiasis (p. 663.1).

Pyrimethamine exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase, thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is active against pre-erythrocytic forms and is also a slow-acting blood schizontocide. It also has some sporontocidal activity; it does not prevent the formation of gametocytes but renders them non-infective to the mosquito vector. It is mainly effective against *Plasmodium falciparum* but has some activity against *P. vivax*.

The development of plasmodial resistance has rendered obsolete the use of pyrimethamine on its own in malaria. Combinations of pyrimethamine with long-acting sulfonamides, such as sulfadoxine or sulfametopyrazine, are now used, although resistance has also developed to them.

For the *treatment* of uncomplicated falciparum **malaria**, pyrimethamine is given orally with sulfadoxine in a fixed dose ratio of 1 to 20 (*Fansidar*). WHO recommends that a single dose of pyrimethamine 1.25 mg/kg plus sulfadoxine 25 mg/kg be used with a 3-day course of artesunate.

For details of doses in children, see below.

A combination of pyrimethamine with sulfametopyrazine has also been used in the treatment of malaria.

Pyrimethamine and pyrimethamine combinations are no longer recommended for *prophylaxis* of malaria. Combined preparations of pyrimethamine with sulfadoxine (*Fansidar*), and with dapsone in a fixed ratio of 1 to 8 (*Maloprim*), have been used in areas of chloroquine or multidrug resistance, although other antimalarials are now preferred.

Pyrimethamine given with a sulfonamide such as sulfadiazine is used in the treatment of **toxoplasmosis**. Alternatively, pyrimethamine may be given with clindamycin in AIDS patients with toxoplasmosis unable to tolerate a sulfonamide. For details of dosage regimens used, see p. 663.1.

Administration in children. Pyrimethamine may be used orally with sulfadoxine (as the fixed-dose combination

product *Fansidar*) in infants and children 2 months of age and older for the treatment of **uncomplicated falciparum malaria**. WHO[1] recommends a single oral dose of pyrimethamine 1.25 mg/kg (with sulfadoxine 25 mg/kg) be given with a 3-day regimen of artesunate.

Alternatively, US licensed product information provides the following dosing recommendations based on bodyweight for children 2 months of age and older:

- 5 to 10 kg: 12.5 mg with sulfadoxine 250 mg
- 11 to 20 kg: 25 mg with sulfadoxine 500 mg
- 21 to 30 kg: 37.5 mg with sulfadoxine 750 mg
- 31 to 45 kg: 50 mg with sulfadoxine 1 g
- over 45 kg: as for adults

In infants and children, pyrimethamine may also be used with sulfadiazine for the management of toxoplasmosis. For further details and doses, see under Uses and Administration of Sulfadiazine, p. 362.1.

1. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Isosporiasis. Isosporiasis (p. 921.3) usually responds well to treatment with co-trimoxazole, but there is a high incidence of recurrence in immunocompromised patients, such as those with AIDS, and some form of maintenance therapy is generally required. Oral therapy with co-trimoxazole 960 mg given three times weekly or pyrimethamine 25 mg with sulfadoxine 500 mg given weekly were found to be equally effective maintenance regimens.[1] Pyrimethamine given alone in daily doses of 50 to 75 mg with folate therapy may be of use in the treatment of patients sensitive to sulfonamides.[2]

1. Pape JW, *et al.* Treatment and prophylaxis of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **320:** 1044–7.
2. Weiss LM, *et al.* Isospora belli infection: treatment with pyrimethamine. *Ann Intern Med* 1988; **109:** 474–5.

Malaria. The overall treatment and prophylaxis of malaria and the place of pyrimethamine-sulfadoxine (Fansidar) in current recommendations are discussed on p. 644.1.

Mycetoma. For reference to the use of pyrimethamine as part of the treatment of actinomycetoma, see under Mycetoma, p. 193.1.

Pneumocystis pneumonia. For a mention of pyrimethamine with either dapsone or sulfadoxine for the prophylaxis of pneumocystis pneumonia, and a discussion of conventional prophylaxis and treatment, see p. 567.2. For details of doses used, see under Uses and Administration of Dapsone, p. 282.1.

Toxoplasmosis. Pyrimethamine is given, usually with sulfadiazine or another appropriate sulphonamide, in the treatment of toxoplasmosis (p. 924.2), including the management of congenital toxoplasmosis in neonates (see Administration in Children, under Sulfadiazine, p. 362.1, for doses), although the management of maternal and fetal infection may vary considerably from country to country. Folinic acid is also given to counteract the megaloblastic anaemia associated with these regimens.

In the US, guidelines for the treatment of opportunistic infections in HIV-infected adults and adolescents[1] consider pyrimethamine plus sulfadiazine to be the initial therapy of choice for *Toxoplasma gondii* encephalitis and recommend the following doses, based on body-weight, be given for at least 6 weeks:

- less than 60 kg: pyrimethamine 200 mg orally, followed by 50 mg daily plus sulfadiazine 1 g orally every 6 hours
- 60 kg or more: pyrimethamine 200 mg orally, followed by 75 mg daily plus sulfadiazine 1.5 g orally every 6 hours

Pyrimethamine with clindamycin is an alternative in patients unable to tolerate a sulfonamide, for further information see under Clindamycin, p. 271.1.

Other drugs that have been tried with pyrimethamine include azithromycin,[2] clarithromycin,[3] and doxycycline.[4,5]

For *long-term maintenance* therapy, US guidelines[1] recommend that pyrimethamine 25 to 50 mg be given orally once daily with sulfadiazine 2 to 4 g daily divided in 2 or 4 oral doses; clindamycin may be used as an alternative to sulfadiazine if necessary. Alternatively, pyrimethamine 25 mg daily has been used with atovaquone 750 mg orally every 6 to 12 hours.

Although not typically considered first-line therapy, pyrimethamine may also be used for *primary prevention* of toxoplasmosis with either atovaquone or dapsone in the following regimens:[1]

- 25 mg daily with atovaquone 1.5 g daily
- 50 mg once weekly with dapsone 50 mg daily
- 75 mg once weekly with dapsone 200 mg once weekly (although this regimen may be poorly tolerated[6])

Pyrimethamine with sulfadoxine, also given once weekly, was of benefit in bone marrow transplant recipients.[7]

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58:** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 15/09/09)
2. Saba J, *et al.* Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis* 1993; **12:** 853–6.
3. Fernandez-Martin J, *et al.* Pyrimethamine-clarithromycin combination therapy of acute Toxoplasma encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1991; **35:** 2049–52.
4. Morris JT, Kelly JW. Effective treatment of cerebral toxoplasmosis with doxycycline. *Am J Med* 1992; **93:** 107–8.
5. Hagberg L, *et al.* Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis* 1993; **25:** 157–60.
6. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; **20:** 531–41.
7. Foot ABM, *et al.* Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. *Bone Marrow Transplant* 1994; **14:** 241–5.

Adverse Effects and Treatment

Use of pyrimethamine for prolonged periods, as used to be the case when it was **given alone** for the prophylaxis of malaria, can cause depression of haematopoiesis due to interference with folic acid metabolism. Rashes and hypersensitivity reactions also occurred.

Larger doses, such as those used in the treatment of toxoplasmosis, may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain, and vomiting; haematological effects such as megaloblastic anaemia, leucopenia, thrombocytopenia, and pancytopenia are also more likely to occur. CNS effects including headache, dizziness, and insomnia have also been reported.

Pulmonary eosinophilia has been reported in patients taking pyrimethamine **with other antimalarials**. Severe and sometimes fatal reactions have occurred when pyrimethamine has been used with sulfadoxine (*Fansidar*), including erythema multiforme and the Stevens-Johnson syndrome, and toxic epidermal necrolysis; there have also been isolated reports of hepatotoxicity. Agranulocytosis occurs more frequently when pyrimethamine is used with dapsone (*Maloprim*) and fatalities have been reported.

Acute overdosage with pyrimethamine can cause gastrointestinal effects and CNS stimulation with vomiting, excitability, and convulsions. Tachycardia, respiratory depression, circulatory collapse, and death may follow. Treatment of overdosage is symptomatic.

Adverse effects with dapsone. Between 1972 and 1988, the UK CSM received 76 reports of reactions that were attributed to the use of pyrimethamine with dapsone (*Maloprim*), of which 40 (53%) were considered to be serious, including 6 deaths.[1] The incidence was estimated to be 1 in 9100 for serious reactions and 1 in 60 200 for fatalities. Serious blood disorders including agranulocytosis, granulocytopenia, or leucopenia occurred in 15 patients (estimated incidence of 1 in 20 000), five of whom died. The other death was in a patient with myocarditis. Three patients had cyanosis due to methaemoglobinaemia. Respiratory disorders such as pulmonary eosinophilia, flu-like syndrome, and dyspnoea occurred in 6 patients. In 4 patients skin disorders were the principal effect and included epidermal necrolysis, angioedema, and bullous eruptions. Hepatic disorders were also reported in 4 patients. Three women using pyrimethamine-dapsone during pregnancy delivered malformed babies, one of them being stillborn. Other effects in 4 patients included convulsions, exacerbated epilepsy, pancreatitis, or a generalised allergic reaction.

A review[2] of 21 cases of agranulocytosis associated with pyrimethamine-dapsone concluded that, although agranulocytosis can occur very rarely in patients taking pyrimethamine or dapsone alone, agranulocytosis due to the combination appears to be caused by an idiosyncratic reaction to dapsone exacerbated by pyrimethamine. Of the 18 individuals for whom dosage was certain, 12 had been taking one tablet of pyrimethamine-dapsone twice weekly, twice the recommended dose of one tablet once weekly. Of the 9 patients who died, 6 had been taking one tablet twice weekly and one patient had taken one tablet once weekly; the dosage was uncertain in the remaining patients. The time of onset of symptoms had been 7 to 9 weeks after starting therapy in 16 of 19 of the patients.

Some consider that pyrimethamine with dapsone may produce some degree of immunosuppression and render users more susceptible to common infections. A higher incidence of non-specific upper respiratory-tract infections occurred in military recruits taking the combination than in those not given antimalarial prophylaxis.[3]

Pulmonary eosinophilia has also occurred in patients taking pyrimethamine with dapsone but, as there have also been similar reports of pulmonary toxicity in patients taking pyrimethamine with sulfadoxine (see below) or pyrimethamine with chloroquine, it has been suggested that pyrimethamine is probably the causative agent.[4]

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–5.
2. Hutchinson DBA, *et al.* Agranulocytosis associated with Maloprim: review of cases. *Hum Toxicol* 1986; **5:** 221–7.
3. Lee PS, Lau EYL. Risk of acute non-specific upper respiratory tract infections in healthy men taking dapsone–pyrimethamine for prophylaxis against malaria. *BMJ* 1988; **296:** 893–5.
4. Davidson AC, *et al.* Pulmonary toxicity of malaria prophylaxis. *BMJ* 1988; **297:** 1240–1.

Adverse effects with sulfonamides. Severe and potentially fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been associated with the combined use of pyrimethamine with sulfadoxine (*Fansidar*) for malaria prophylaxis. The reported incidence of these reactions has varied with surveys in the UK,[1] USA,[2] and Sweden[3] yielding similar results and a survey from Switzerland[4] finding a much lower incidence. The overall rate of serious reactions to pyrimethamine-sulfadoxine in the UK has been estimated to be 1 in 2100. The estimates for severe cutaneous reactions were 1 in 4900 in the UK, 1 in 5000 to 1 in 8000 in the USA, 1 in 10 000 in Sweden, and 1 in 150 000 in Switzerland, and the death rates were 1 in 11 100 in the UK, 1 in 11 000 to 1 in 25 000 in the USA, and 1 in 35 000 in Sweden; no fatalities were reported in Switzerland. Workers on the Swiss survey had suggested that the high incidence of cutaneous reactions reported in the USA might have been due to concurrent therapy with chloroquine but this has been disputed.[5] The authors of the UK survey[1] suggested that the lower incidence reported in Switzerland may have been due to the different methods used to estimate the amount of drug usage. Whether this toxicity is due to the combined use of pyrimethamine and sulfadoxine is unclear as the estimated frequency of fatal reactions associated with the use of sulfadoxine alone in Mozambique[6] was 1 in 50 000.

There have been isolated reports of other severe or life-threatening reactions associated with the use of pyrimethamine-sulfadoxine when used alone or with chloroquine, including hepatotoxicity[7-9] (estimated incidence of 1 in 11 100 in the UK[1]), fatal multisystem toxicity,[10] drug fever and photodermatitis,[11] agranulocytosis,[11] and erythroderma resembling Sézary syndrome.[12] Severe pulmonary reactions have also occurred[3,13] but, as similar reactions have also been reported when pyrimethamine has been used with other antimalarials, including dapsone, it has been suggested that pyrimethamine is the causative agent (see Adverse Effects with Dapsone, above). Hyperammonaemia and carnitine deficiency with deterioration in mental status has been reported in a patient given pyrimethamine and sulfadiazine for the treatment of toxoplasmosis.[14]

Severe megaloblastic anaemia in a patient taking pyrimethamine and sulfadiazine for toxoplasmosis of the CNS[15] was treated by withdrawing pyrimethamine and giving folinic acid orally with a single platelet infusion.

For a comparison of the incidence of pruritus induced by various antimalarials including pyrimethamine with sulfadoxine, see Effects on the Skin under Chloroquine, p. 652.2.

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R SocMed* 1990; **83:** 82–5.
2. Miller KD, *et al.* Severe cutaneous reactions among American travelers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35:** 451–8.
3. Hellgren U, *et al.* Adverse reactions to sulphadoxine–pyrimethamine in Swedish travellers: implications for prophylaxis. *BMJ* 1987; **295:** 365–6.
4. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine–pyrimethamine in Switzerland. *Lancet* 1986; **i:** 610.
5. Rombo L, *et al.* Does chloroquine contribute to the risk of serious adverse reactions to Fansidar? *Lancet* 1985; **ii:** 1298–9.
6. Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet* 1985; **ii:** 1072–3.
7. Lazar HP, *et al.* Fansidar and hepatic granulomas. *Ann Intern Med* 1985; **102:** 722.
8. Wejstal R, *et al.* Liver damage associated with Fansidar. *Lancet* 1986; **i:** 854–5.
9. Zitelli BJ, *et al.* Fatal hepatic necrosis due to pyrimethamine–sulfadoxine (Fansidar). *Ann Intern Med* 1987; **106:** 393–5.
10. Selby CD, *et al.* Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine (Fansidar). *BMJ* 1985; **290:** 113–14.
11. Olsen VV, *et al.* Serious reactions during malaria prophylaxis with pyrimethamine–sulfadoxine. *Lancet* 1982; **ii:** 994.
12. Langtry JAA, *et al.* Erythroderma resembling Sézary syndrome after treatment with Fansidar and chloroquine. *BMJ* 1986; **292:** 1107–8.
13. Svanbom M, *et al.* Unusual pulmonary reaction during short term prophylaxis with pyrimethamine–sulfadoxine (Fansidar). *BMJ* 1984; **288:** 1876.
14. Sekas G, Harbhajan PS. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95:** 112–13.
15. Chute JP, *et al.* Severe megaloblastic anemia complicating pyrimethamine therapy. *Ann Intern Med* 1995; **122:** 884–5.

Overdosage. Reports of overdosage with pyrimethamine in infants.

1. Akinyanju O, *et al.* Pyrimethamine poisoning. *BMJ* 1973; **4:** 147–8.

2. Elmalem J, *et al.* Les accidents graves lors de la prescription de pyriméthamine chez les nourrissons traités pour une toxoplasmose. *Therapie* 1985; **40:** 357–9.
3. Duveau E, *et al.* Convulsion liée à un surdosage en pyriméthamine. *Arch Pediatr* 1996; **3:** 286–7.

Precautions

Pyrimethamine may aggravate subclinical folic acid deficiency and it should not be given to patients with conditions associated with folate deficiency such as megaloblastic anaemia. Blood counts are required with prolonged treatment, and when large doses of pyrimethamine are used, as in the treatment of toxoplasmosis, blood counts should be checked twice weekly. Folinic acid, which does not interfere with the action of pyrimethamine against malaria or toxoplasmosis, has been given to prevent haematological toxicity due to pyrimethamine and its use is especially recommended if pyrimethamine is given during pregnancy. (Folic acid may be used as an alternative to folinic acid in malaria, but it interferes with the action of pyrimethamine against toxoplasmosis). For further information concerning use during pregnancy, see below.

Pyrimethamine should be given with caution to patients with renal or hepatic impairment. When patients with convulsive disorders need to receive large doses, as in the treatment of toxoplasmosis, it is recommended that small starting doses should be used.

When pyrimethamine is used with sulfonamides or dapsone, the general precautions applicable to those drugs should also be taken (see under Sulfamethoxazole, p. 366.1 and under Dapsone, p. 283.2) and treatment should be stopped immediately if any skin reactions, sore throat, or shortness of breath occurs.

Breast feeding. Pyrimethamine is distributed into breast milk[1] but as no adverse effects have been reported in breast-fed infants, the most recent guidance from the American Academy of Pediatrics considered breast feeding to be compatible with the use of pyrimethamine for malaria prophylaxis.[2] However, exposure of the infant to other folate antagonists should be avoided. The large doses of pyrimethamine used for treating toxoplasmosis may distribute into breast milk in sufficient quantities to interfere with folic acid metabolism in nursing infants.

1. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22:** 733–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Porphyria. For a discussion of the use of antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

Pregnancy. There have been concerns over the use of pyrimethamine during pregnancy as it has been shown to be teratogenic in *animal* studies.[1] In one report, severe congenital defects in a stillborn infant were attributed to the use of pyrimethamine in early pregnancy,[2] but the association was considered to be questionable.[3] Other instances of congenital malformations with pyrimethamine and dapsone are given under Adverse Effects with Dapsone, p. 663.2.

Others[4] suggest that intermittent preventive therapy for malaria with pyrimethamine-sulfadoxine has a favourable safety profile in pregnancy. WHO considers that pyrimethamine combinations may be used after the first trimester of pregnancy in the treatment of toxoplasmosis,[5] but that pyrimethamine-sulfadoxine although considered safe for malaria treatment in the second or third trimesters, is likely to be ineffective because of increasing resistance.[6]

1. Anonymous. Pyrimethamine combinations in pregnancy. *Lancet* 1983; **ii:** 1005–7. Correction. *ibid.;* 1378.
2. Harpey J-P, *et al.* Teratogenicity of pyrimethamine. *Lancet* 1983; **ii:** 399.
3. Smithells RW, Sheppard S. Teratogenicity of Debendox and pyrimethamine. *Lancet* 1983; **ii:** 623–4.
4. Peters PJ, *et al.* Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety* 2007; **30:** 481–501.
5. WHO. *WHO model formulary.* Geneva: WHO,2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 19/10/09)
6. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update issued April 2011 available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Interactions

Use of pyrimethamine with other folate antagonists such as co-trimoxazole, trimethoprim, methotrexate, proguanil, phenytoin, or zidovudine may exacerbate bone marrow depression. The absorption of pyrimethamine may be reduced by use with antacid salts or kaolin.

Pyrimethamine may displace other drugs from protein-binding sites, causing elevated concentrations of unbound drug; this may be of particular clinical concern for drugs (such as quinine and warfarin) that are both highly protein bound and have a narrow therapeutic index.

Lorazepam. Signs of mild liver toxicity in 2 of 5 subjects who received lorazepam and pyrimethamine appeared to confirm earlier suspicions that giving these drugs together could cause hepatotoxicity. Both patients tolerated each drug when given separately.[1]

1. Briggs M, Briggs M. Pyrimethamine toxicity. *BMJ* 1974; **1:** 40.

Zidovudine. Studies *in vitro* and in *animals* suggest that zidovudine could reduce the efficacy of pyrimethamine in the treatment of toxoplasmic encephalitis.[1] Furthermore, the dose of zidovudine may need to be altered if these drugs are used together as there has been a report that pyrimethamine with sulfadoxine (*Fansidar*) prolonged the serum half-life of zidovudine.[2]

1. Israelski DM, *et al.* Zidovudine antagonizes the action of pyrimethamine in experimental infection with Toxoplasma gondii. *Antimicrob Agents Chemother* 1989; **33:** 30–4.
2. Klein RS. Prophylaxis of opportunistic infections in individuals infected with HIV. *AIDS* 1989; **3** (suppl 1): S161–S173.

Pharmacokinetics

Pyrimethamine is almost completely absorbed from the gastrointestinal tract. Peak-plasma concentrations generally occur 2 to 4 hours after a dose and can vary widely between individuals; concentrations ranging from 260 to 1411 nanograms/mL may occur after daily oral doses of 25 mg. It is mainly concentrated in the kidneys, lungs, liver, and spleen; in AIDS patients given daily dose of pyrimethamine, concentrations of about one-fifth of those in the serum occur in the CSF. About 80 to 90% is bound to plasma proteins.

It is metabolised in the liver and slowly excreted via the kidney, the average half-life in plasma being about 4 days. Several metabolites have been detected in the urine. Pyrimethamine crosses the placenta. It is distributed into breast milk (see under Breast Feeding in Precautions, above).

References.
1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Cook IF, *et al.* Race-linked differences in serum concentrations of dapsone, monoacetyldapsone and pyrimethamine during malaria prophylaxis. *Trans R Soc Trop Med Hyg* 1986; **80:** 897–901.
3. Weiss LM, *et al.* Pyrimethamine concentrations in serum and cerebrospinal fluid during treatment of acute toxoplasma encephalitis in patients with AIDS. *J Infect Dis* 1988; **157:** 580–3.
4. Hellgren U, *et al.* Plasma concentrations of sulfadoxine-pyrimethamine, mefloquine and its main metabolite after regular malaria prophylaxis for two years. *Trans R Soc Trop Med Hyg* 1991; **85:** 356–7.
5. Winstanley PA, *et al.* The disposition of oral and intramuscular pyrimethamine/sulphadoxine in Kenyan children with high parasitaemia but clinically non-severe falciparum malaria. *Br J Clin Pharmacol* 1992; **33:** 143–8.
6. Newton CRJC, *et al.* A single dose of intramuscular sulfadoxine-pyrimethamine as an adjunct to quinine in the treatment of severe malaria: pharmacokinetics and efficacy. *Trans R Soc Trop Med Hyg* 1993; **87:** 207–10.
7. Jacobson JM, *et al.* Pyrimethamine pharmacokinetics in human immunodeficiency virus-positive patients seropositive for Toxoplasma gondii. *Antimicrob Agents Chemother* 1996; **40:** 1360–5.
8. Klinker H, *et al.* Plasma pyrimethamine concentrations during long-term treatment for cerebral toxoplasmosis in patients with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 1623–7.
9. Trenque T, *et al.* Human maternofoetal distribution of pyrimethamine-sulphadoxine. *Br J Clin Pharmacol* 1998; **45:** 179–80.
10. Trenque T, *et al.* Population pharmacokinetics of pyrimethamine and sulfadoxine in children with congenital toxoplasmosis. *Br J Clin Pharmacol* 2004; **57:** 735–41.
11. Barnes KI, *et al.* Sulfadoxine-pyrimethamine pharmacokinetics in malaria: pediatric dosing implications. *Clin Pharmacol Ther* 2006; **80:** 582–96.
12. Karunajeewa HA, *et al.* Pharmacokinetic properties of sulfadoxine-pyrimethamine in pregnant women. *Antimicrob Agents Chemother* 2009; **53:** 4368–76.
13. Nyunt MM, *et al.* Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. *Clin Pharmacol Ther* 2010; **87:** 226–34.
14. Salman S, *et al.* Pharmacokinetic properties of conventional and double-dose sulfadoxine-pyrimethamine given as intermittent preventive treatment in infancy. *Antimicrob Agents Chemother* 2011; **55:** 1693–1700.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daraprim; ***Austral.***: Daraprim; ***Belg.***: Daraprim; ***Braz.***: Daraprim; ***Canad.***: Daraprim; ***Chile***: Daraprim; ***Fr.***: Malocide; ***Ger.***: Daraprim; ***Gr.***: Daraprim; ***Hong Kong***: Daraprim†; ***Malaysia***: Fansidar; ***Mex.***: Daraprim; ***Neth.***: Daraprim; ***Pol.***: Daraprim; ***S.Afr.***: Daraprim; ***Spain***: Daraprim; ***Switz.***: Daraprim; ***UK***: Daraprim; ***USA***: Daraprim.

Multi-ingredient Preparations. ***Austral.***: Fansidar†; Maloprim†; ***Belg.***: Co-Arinate; Dafrafin†; ***Braz.***: Fansidar; ***Fr.***: Fansidar; ***Gr.***: Fansidar; ***India***: Amalar; Croydoxin-FM; Domine; Laridox; Larinate Kit; Malarwin; Malasulf; Malcidal; Malocide; Masunate; Metakelfin; Metasulfin; Onli-2; Pyralfin; Pyramet; Rimodar; ***Indon.***: Fansidar; Plasmodin; Suldox; ***Irl.***: Fansidar†; ***Israel***: Fansidar†; ***Ital.***: Metakelfin; ***Malaysia***: Madomine; Malafon; ***Philipp.***: Fansidar; ***Rus.***: Fansidar (Фансидар); ***S.Afr.***: Fansidar; ***Singapore***: Pyrisone; ***Switz.***: Fansidar†; ***Thai.***: Vinsilar; ***UK***: Fansidar; ***Ukr.***: Fansidar (Фансидар)†; ***USA***: Fansidar†.

Pharmacopoeial Preparations
BP 2014: Pyrimethamine Tablets;
USP 36: Pyrimethamine Oral Suspension; Pyrimethamine Tablets; Sulfadoxine and Pyrimethamine Tablets.

Pyronaridine Phosphate *(rINNM)*

Fosfato de pironaridina; Malaridine Phosphate; Pironaridina, fosfato de; Pyronaridine, Phosphate de; Pyronaridini Phosphas; Пиронаридина Фосфат.

4-[(7-Chloro-2-methoxybenzo[*b*]-1,5-naphthyridin-10-yl) amino]-2,6,-bis[(pyrrolidin-1-yl)methyl]phenol phosphate.

$C_{29}H_{32}ClN_5O_2.4H_3PO_4$=910.0

CAS — 74847-35-1 (pyronaridine); 76748-86-2 (pyronaridine phosphate).

UNII — 2T289F9ACO.

Pharmacopoeias. In *Chin.*

Uses and Administration

Pyronaridine is a naphthyridine derivative that has traditionally been used in China in the treatment of malaria (p. 644.1). Its use has also been investigated in Africa and in Thailand. It is a blood schizontocide active against *Plasmodium vivax* and against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum.* The drug produced in China has been given as the phosphate orally or by intramuscular or intravenous injection.

A fixed-dose combination product of pyronaridine phosphate and artesunate has been developed to improve patient adherence and avoid monotherapy, and thereby decrease the risk of acquired drug resistance. This combination product is used for the treatment of acute uncomplicated infections caused by *P. vivax* and *P. falciparum* in areas of low transmission with evidence of artemisinin resistance; it should not be used to treat severe malaria. The ratio of pyronaridine phosphate to artesunate of 3 to 1 has been selected to provide the current dose recommendations for each of the individual drugs when given as monotherapy. The combination is given orally, as a single, 3-day treatment course, to children and adults weighing 20 kg or more. Recommended doses are given once daily for 3 days according to body-weight as follows:

- 20 to less than 24 kg: 180 mg pyronaridine phosphate with 60 mg artesunate
- 24 to less than 45 kg: 360 mg pyronaridine phosphate with 120 mg artesunate
- 45 to less than 65 kg: 540 mg pyronaridine phosphate with 180 mg artesunate
- 65 kg or more: 720 mg pyronaridine phosphate with 240 mg artesunate

References.
1. Anonymous. Pyronaridine: yet another promising antimalarial substance from China. *WHO Drug Inf* 1996; **10:** 9–10.
2. Looareesuwan S, *et al.* Clinical study of pyronaridine for the treatment of acute uncomplicated falciparum malaria in Thailand. *Am J Trop Med Hyg* 1996; **54:** 205–9.
3. Ringwald P, *et al.* Efficacy of oral pyronaridine for the treatment of acute uncomplicated falciparum malaria in African children. *Clin Infect Dis* 1998; **26:** 946–53.
4. Vivas L, *et al.* Anti-malarial efficacy of pyronaridine and artesunate in combination in vitro and in vivo. *Acta Trop* 2008; **105:** 222–8.
5. Ramharter M, *et al.* Fixed-dose pyronaridine-artesunate combination for treatment of uncomplicated falciparum malaria in pediatric patients in Gabon. *J Infect Dis* 2008; **198:** 911–9.
6. Tshefu AK, *et al.* Pyronaridine-artesunate Study Team. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated Plasmodium falciparum malaria: a randomised non-inferiority trial. *Lancet* 2010; **375:** 1457–67.
7. Poravuth Y, *et al.* Pyronaridine-artesunate versus chloroquine in patients with acute *Plasmodium vivax* malaria: a randomized, double-blind, non-inferiority trial. *PLoS One* 2011; **6:** e14501.
8. Kurth F, *et al.* Pyronaridine: a new 'old' drug on the verge of entering the antimalarial armamentarium. *Expert Rev Anti Infect Ther* 2011; **9:** 393–6.
9. Rueangweerayut R, *et al.* Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. *N Engl J Med* 2012; **366:** 1298–1309.
10. Croft SL, *et al.* Review of pyronaridine anti-malarial properties and product characteristics. *Malar J* 2012; **11:** 270.

Administration in children. The fixed-dose combination product of pyronaridine phosphate and artesunate may be given to children weighing 20 kg or more for the treatment of acute uncomplicated infections caused by *Plasmodium vivax* and *P. falciparum* in areas of low transmission with evidence of artemisinin resistance. For dose recommendations in these children, see above.

Adverse Effects and Precautions

Adverse effects of pyronaridine are usually mild and resolve within 2 days of starting treatment. The most commonly reported adverse effects are dizziness, headache, pruritus, and gastrointestinal effects such as diarrhoea, nausea, vomiting, and abdominal pain. There have also been some reports of allergic skin reactions, palpitations, and transient ECG changes with the use of higher doses.

The most common adverse effects associated with the use of a fixed-dose combination product of pyronaridine

phosphate and artesunate are abdominal pain, bradycardia, headache, hypoglycaemia, vomiting, and haematological changes such as eosinophilia, neutropenia, anaemia, and an increased platelet count; abnormal laboratory test results include transient raises of serum transaminases (mostly ALT). Syncope, isolated prolongation of the QTc interval, and hypersensitivity reactions occur rarely.

Pyronaridine phosphate-artesunate should not be used for malaria prophylaxis. It is also contra-indicated in those with underlying hepatic injury or significant hepatic abnormalities; liver function tests should be carried out before and after a treatment course. The combination should be used with caution in those with cardiovascular disorders such as congenital prolongation of QTc interval, cardiac arrhythmia, and heart failure. Caution is also advised in patients with hypokalaemia, in those being treated with other drugs that block potassium channels, and in those who have recently taken medicines known to prolong the QTc interval.

Pregnancy. Data on the use of pyronaridine phosphate in pregnant women are not available, although *animal* studies have not reported any teratogenic effects. The safety of pyronaridine phosphate-artesunate in pregnancy has also not been established and the potential risk is unknown. For further information on the use of artesunate in pregnancy see under Artemisinin Derivatives, p. 649.2.

Interactions

In vitro studies have shown that pyronaridine phosphate is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and of P-glycoprotein. It should therefore be used with caution in patients taking drugs that are metabolised by the cytochrome P450 isoenzyme CYP2D6 and that are substrates for P-glycoprotein.

Pharmacokinetics

Peak plasma concentrations for pyronaridine are generally reached between 2 and 8 hours after an oral dose. Pyronaridine and its metabolites are extensively distributed into tissues. It is about 92 to 95% bound to plasma protein and may also bind to melanin in the eye. *In vitro* studies show that the cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4 could be involved in the metabolism of pyronaridine and that it inhibits the activity of CYP2D6. Pyronaridine is eliminated slowly with an elimination half-life of between 14 and 18 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Kor.*: Pyramax.

Quinine *(BAN)*

Chinin; Chinina; Chininum; Kiniini; Kinin; Kinine; Kuinina; Quinina; Хинин.

(8*S*,9*R*)-6′-Methoxycinchonan-9-ol; (α*R*)-α-(6-Methoxy-4-quinolyl)-α-[(2*S*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2$=324.4

CAS — 130-95-0 (anhydrous quinine).

ATC — P01BC01.

UNII — A7V27PHC7A.

Description. Quinine is the chief alkaloid of various species of *Cinchona* (Rubiaceae). It is an optical isomer of quinidine.

Quinine Bisulfate *(BANM)*

Chininum Bisulfuricum; Neutral Quinine Sulphate; Quinina, bisulfato de; Quinine Acid Sulphate; Quinine Bisulphate; Quinini Bisulfas; Двусернокислый Хинин; Хинина Бисульфат.

$C_{20}H_{24}N_2O_2.H_2SO_4.7H_2O$=548.6

CAS — 549-56-4 (anhydrous quinine bisulfate).

ATC — P01BC01.

UNII — M201HC068W (anhydrous quinine bisulfate); GNS01V2R3N (quinine bisulfate heptahydrate).

Pharmacopoeias. In *Br., Int.*, and *Viet.*

BP 2014: (Quinine Bisulphate). Colourless crystals or a white crystalline powder. It effloresces in dry air. Freely soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 2.8 to 3.4. Protect from light.

Quinine Dihydrochloride *(BANM)*

Chinini Dihydrochloridum; Neutral Quinine Hydrochloride; Quinina, dihidrocloruro de; Quinine Acid Hydrochloride; Quinini Dihydrochloridum; Двухлористоводородный Хинин; Хинина Дигидрохлорид.

$C_{20}H_{24}N_2O_2.2HCl$=397.3

CAS — 60-93-5.

ATC — P01BC01.

UNII — 8C3EMH7D9X.

Pharmacopoeias. In *Br., Chin.*, and *Int.*

Viet. includes the injection.

BP 2014: (Quinine Dihydrochloride). A white or almost white powder. Very soluble in water; soluble in alcohol. A 3% solution in water has a pH of 2.0 to 3.0. Protect from light.

Quinine Etabonate

Euquinina; Euquinine; Quinina, etilcarbonato de; Quinine Ethyl Carbonate; Хинина Этабонат.

$C_{23}H_{28}N_2O_4$=396.5

CAS — 83-75-0.

ATC — P01BC01.

UNII — L2V8911157.

Pharmacopoeias. In *Jpn.*

Quinine Hydrobromide *(BANM)*

Basic Quinine Hydrobromide; Chinini Bromidum; Quinina, hidrobromuro de; Quinine Monohydrobromide; Хинина Гидробромид.

$C_{20}H_{24}N_2O_2.HBr.H_2O$=423.4

CAS — 549-49-5 (anhydrous quinine hydrobromide).

ATC — P01BC01.

UNII — VWF36Q4G6V.

Pharmacopoeias. In *Fr.*

Quinine Hydrochloride *(BANM)*

Basic Quinine Hydrochloride; Chinin hydrochlorid dihydrát; Chininhydrochlorid; Chinini Hydrochloridum; Chininii Chloridum; Chininium Chloratum; Chinino hidrochloridas; Chininum Hydrochloricum; Chininy chlorowodorek; Kiniini-hydrokloridi; Kinin-hidroklorid; Kininhydroklorid; Quinina, hidrocloruro de; Quinine, chlorhydrate de; Quinine Monohydrochloride; Quinini Hydrochloridum; Quinini Hydrochloridum Dihydricum; Хинина Гидрохлорид.

$C_{20}H_{24}N_2O_2.HCl.2H_2O$=396.9

CAS — 130-89-2 (anhydrous quinine hydrochloride); 6119-47-7 (quinine hydrochloride dihydrate).

ATC — P01BC01.

UNII — 711S8Y0T33 (quinine hydrochloride dihydrate); 7CS0WNO31M (anhydrous quinine hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn*, and *Viet.*

Ph. Eur. 8: (Quinine Hydrochloride). White or almost white, or colourless, fine, silky needles, often grouped in clusters. Soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

Quinine Sulfate *(BANM)*

Basic Quinine Sulphate; Chinin sulfát dihydrát; Chinini sulfas; Chinino sulfatas; Chininsulfat; Chininum Sulfuricum; Chininy siarczan; Kiniinisulfaatti; Kininsulfat; Kinin-szulfát; Quinina, sulfato de; Quinine, sulfate de; Quinine Sulphate; Quinini Sulfas; Quinini Sulfas Dihydricus; Хинина Сульфат.

$(C_{20}H_{24}N_2O_2)_2.H_2SO_4.2H_2O$=783.0

CAS — 804-63-7 (anhydrous quinine sulfate); 6119-70-6 (quinine sulfate dihydrate).

ATC — P01BC01.

UNII — KF7Z0E0Q2B.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US*, and *Viet.*

Ph. Eur. 8: (Quinine Sulfate). A white or almost white, crystalline powder or fine, colourless needles. Slightly soluble in water; sparingly soluble in boiling water and in alcohol. A 1% suspension in water has a pH of 5.7 to 6.6. Protect from light.

USP 36: (Quinine Sulfate). It is the sulfate of an alkaloid obtained from the bark of species of *Cinchona*. White, odourless, fine needle-like crystals, usually lusterless, making a light and readily compressible mass. It darkens on exposure to light. Soluble 1 in 500 of water and 1 in 120 of alcohol; sparingly soluble in water at 100 degrees; slightly soluble in chloroform; freely soluble in alcohol at 80 degrees and in a mixture of 2 parts of chloroform and one part of dehydrated alcohol; very slightly soluble in ether; Its saturated solution in water is neutral or alkaline to litmus. Protect from light.

Sorption. For reference to loss of quinine sulfate from solutions during membrane filtration, see Chloroquine, p. 650.2.

Uses and Administration

Quinine is a cinchona alkaloid and a 4-methanolquinoline antimalarial that is a rapid-acting blood schizontocide with activity against *Plasmodium falciparum, P. vivax, P. ovale*, and *P. malariae*. It is active against the gametocytes of *P. malariae* and *P. vivax*, but not against mature gametocytes of *P. falciparum*. The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias. The increasing spread of resistance to chloroquine has been responsible for the re-emergence of quinine as an important drug in the treatment of falciparum malaria (p. 666.1). Quinine is not generally used for malaria prophylaxis.

Quinine is also used to treat the protozoal infection babesiosis (p. 666.1) and for the relief of nocturnal leg cramps (p. 666.2).

Quinine has mild analgesic and antipyretic properties and is sometimes included in preparations used for the symptomatic relief of the common cold and influenza; additional salts that have been used for this purpose include the camsilate and the gluconate.

Quinine is also used as a bitter and a flavour (p. 666.1).

Quinine is used as several salts and 100 mg of anhydrous quinine is equivalent to about:

- 169 mg of quinine bisulfate
- 122 mg of quinine dihydrochloride
- 122 mg of quinine etabonate
- 130 mg of quinine hydrobromide
- 122 mg of quinine hydrochloride
- 121 mg of quinine sulfate

For the treatment of **malaria** quinine is given orally, usually as the sulfate, hydrochloride, or dihydrochloride, or parenterally as the dihydrochloride; quinine etabonate is sometimes used orally because unlike other quinine salts, which are intensely bitter, it is tasteless. They all contain about the same amount of quinine and any of them can be used when the dose is cited in terms of "quinine salt"; this is not the case for the bisulfate, which contains a correspondingly smaller amount of quinine. Quinine formate is sometimes given parenterally.

A course of treatment with quinine for falciparum malaria usually lasts 7 days and is accompanied by follow-on treatment with clindamycin, tetracycline, or doxycycline; in uncomplicated infections treatment should preferably be given by the oral route. The usual *oral* dose is 600 mg of quinine salt given every 8 hours for 7 days.

In severe or complicated falciparum malaria, or when the patient is unable to take oral medication, quinine should be given parenterally by slow intravenous infusion, but this can be hazardous and patients generally need monitoring, particularly for signs of cardiotoxicity. Therapy should be changed to the oral route as soon as possible to complete the course. To obtain therapeutic concentrations rapidly with parenteral therapy, quinine is often given in an initial loading dose followed by maintenance doses. A recommended *intravenous* dosage regimen suggested by WHO is an initial loading dose of 20 mg/kg of quinine dihydrochloride (up to a maximum of 1.4 g) given over 4 hours with maintenance infusions being started 8 hours later, calculated from the start of the previous infusion. Alternatively, in intensive care units, an initial loading dose of 7 mg/kg may be given over 30 minutes followed immediately by the first of the maintenance infusions. Maintenance infusions consist of 10 mg/kg (up to a maximum of 700 mg) given over 4 hours every 8 hours. A loading dose should not be given if the patient has received quinine, quinidine, mefloquine, or halofantrine, during the previous 12 hours. If parenteral therapy is required for more than 48 hours the maintenance dose of quinine dihydrochloride should be reduced to 5 to 7 mg/kg.

If intravenous infusion is not possible, quinine dihydrochloride has been given *intramuscularly*. Doses, including the loading dose, are the same as those used intravenously; the drug should be diluted in sodium chloride 0.9% to a concentration of 60 to 100 mg of the dihydrochloride per mL and the loading dose should be divided between two injection sites, preferably each anterior thigh (not the buttock). However, intramuscular injection can be irritant and there have been concerns regarding its safety and efficacy (see under Malaria, p. 666.1).

For details of doses in children and advice on dosing in renal or hepatic failure, see below and p. 666.1, respectively.

When used for the relief of nocturnal **leg cramps**, quinine is given at night in an oral dose of 200 to 300 mg of the sulfate or bisulfate. Quinine benzoate has also been used.

Administration in children. Quinine may be used orally in children for the treatment of **uncomplicated falciparum malaria**, or parenterally when malaria is severe or oral

therapy is not possible. Doses are expressed in terms of quinine salt.

For treatment of uncomplicated malaria a dose of 10 mg/kg orally every 8 hours[1] for 7 days may be used, along with clindamycin for follow-on treatment.[2] When parenteral therapy is required, quinine may be given by slow intravenous infusion at a rate not exceeding 5 mg/kg per hour, but if this is not possible the intramuscular route may be considered.[2] Parenteral doses and administration are as for adults (see p. 665.3).

1. WHO. *WHO model formulary for children: based on the second model list of essential medicines for children 2009*. Geneva: WHO, 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 19/07/10)
2. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 19/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Administration in hepatic impairment. Quinine may accumulate in patients with hepatic impairment, and WHO[1] has therefore suggested that quinine doses for severe malaria be reduced by one-third after the first 48 hours of treatment in patients with severe hepatic impairment. Similarly, in the UK the *BNF* suggests that when *intravenous* quinine is used in patients with severe hepatic impairment, the maintenance dose should be reduced to 5 to 7 mg/kg of quinine salt every 8 hours.

1. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 07/07/11) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 07/07/11)

Administration in renal impairment. Quinine may accumulate in severe renal impairment, and WHO[1] has suggested that quinine doses for severe malaria should be reduced by one-third in such patients if severe renal failure persists after 48 hours of treatment. Some licensed product information also gives recommendations: when *oral* quinine is required for malaria treatment in patients with chronic, severe renal impairment, the usual dose may be given as an initial loading dose, followed at 12-hour intervals by half the usual dose. In the UK, the *BNF* suggests that when *intravenous* quinine is used in severe renal failure, the maintenance dose should be reduced to 5 to 7 mg/kg of quinine salt every 8 hours.

No dose adjustment is required for patients undergoing haemodialysis or haemofiltration.

1. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Babesiosis. Although there is no established specific treatment for babesiosis (p. 920.2), a combination of quinine and clindamycin has been used.[1,2] For suggested doses see under Clindamycin, p. 270.3. Quinine with azithromycin was reported to be effective in a patient who had not responded to quinine with clindamycin.[3]

1. Abramowicz M., ed. *Drugs for parasitic infections*. 2nd ed. New Rochelle NY: The Medical Letter. 2010.
2. Wormser GP, *et al*. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 17/06/08)
3. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; **91:** 214–15.

Flavouring. The Joint FAO/WHO Expert Committee on Food Additives concluded that quinine levels in soft drinks of up to 100 mg/litre (as quinine base) were not of toxicological concern.[1] However, because of the possibility of hypersensitivity reactions in some individuals, the committee recommended that consumers be informed of the presence of quinine in food or beverages.

1. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993. Also available at: http://libdoc.who.int/trs/WHO_TRS_837.pdf (accessed 12/09/11)

Malaria. Quinine has had an important role in the treatment of falciparum malaria (see p. 644.1). Quinine salts are normally given orally (any quinine lost through vomiting within one hour of an oral dose should be replaced by additional doses)[1] or in severe infection by slow intravenous infusion of the dihydrochloride.[2] If intravenous formulations of quinine are unavailable quinidine may be used as an alternative; for further details, see under the Uses and Administration of Quinidine, p. 1481.3.

If facilities for intravenous infusion, including monitoring, are not available quinine may be given by deep intramuscular injection.[2] The use of the intramuscular route has been controversial because of concerns over safety and efficacy but there is some evidence of benefit.[3-6] Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; fatal tetanus has developed in some patients.[7] It has been suggested that some such reactions may be related to the use of preparations formulated in urethane or other irritant substances. Diluted solutions of quinine dihydrochloride 60 mg/mL adjusted to neutral pH appear to be less painful than the usual undiluted preparation of 300 mg/mL.

If facilities do not exist to give quinine parenterally then patients with severe malaria should receive quinine by mouth or nasogastric tube.

Quinine as formerly standardised used to contain a higher concentration of cinchona alkaloids and there might be synergy between mixtures of these alkaloids.[8] In practice no advantage has been shown by such mixtures over quinine alone in the treatment of chloroquine-resistant falciparum malaria.[9]

1. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 07/04/09)
2. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Wattanagoon Y, *et al*. Intramuscular loading dose of quinine for falciparum malaria: pharmacokinetics and toxicity. *BMJ* 1986; **293:** 11–13. Correction. *ibid.*; 362.
4. Mansor SM, *et al*. The safety and kinetics of intramuscular quinine in Malawian children with moderately severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 482–7.
5. Waller D, *et al*. The pharmacokinetic properties of intramuscular quinine in Gambian children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 488–91.
6. Schapira A, *et al*. Comparison of intramuscular and intravenous quinine for the treatment of severe and complicated malaria in children. *Trans R Soc Trop Med Hyg* 1993; **87:** 299–302.
7. Yen LM, *et al*. Role of quinine in the high mortality of intramuscular injection tetanus. *Lancet* 1994; **344:** 786–7.
8. Druilhe P, *et al*. Activity of a combination of three cinchona bark alkaloids against Plasmodium falciparum in vitro. *Antimicrob Agents Chemother* 1988; **32:** 250–4.
9. Bunnag D, *et al*. A combination of quinine, quinidine and cinchonine (LA 40221) in the treatment of chloroquine resistant falciparum malaria in Thailand: two double-blind trials. *Trans R Soc Trop Med Hyg* 1989; **83:** 66.

Muscle spasm. Quinine (usually as quinine sulfate or bisulfate) has traditionally been used for nocturnal cramps (p. 2014.1) but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. In the USA, for example, the FDA ruled that quinine products should no longer be used for the management of nocturnal cramps.[1,2] A similar ban has been imposed in Australia.[3] Meta-analyses[4,5] concluded that although quinine was effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind. It was recommended that patients should be closely monitored while the efficacy of quinine is assessed over a period of at least 4 weeks. In contrast, a later Cochrane review[6] found moderate quality evidence to suggest that when quinine was used to treat muscle cramps for up to 60 days, the incidence of serious adverse effects was not significantly different than with placebo. Some[7] have recommended that treatment be stopped every 3 months to see whether it is still needed.

Haemodialysis-induced cramp (p. 1781.3) has been reported to respond to treatment with quinine[8,9] but similar concerns apply.

1. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
2. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; **123:** 86.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; **23:** 20. Also available at: http://www.tga.gov.au/hp/aadrb-0410.htm (accessed 12/09/11)
4. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
5. Man-Son-Hing M, *et al*. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
6. El-Tawil S, *et al*. Quinine for muscle cramps. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 08/07/11).
7. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; **34:** 7–8.
8. Kaji DM, *et al*. Prevention of muscle cramps in haemodialysis patients by quinine sulphate. *Lancet* 1976; **ii:** 66–7.
9. Roca AO, *et al*. Dialysis leg cramps; efficacy of quinine versus vitamin E. *ASAIO J* 1992; **38:** M481–M485.

Adverse Effects

Quinine or its salts given in usual therapeutic doses may give rise to a train of symptoms known as cinchonism, characterised in its mild form by tinnitus, impaired hearing, headache, nausea, and disturbed vision, with, in its more severe manifestations, vomiting, abdominal pain, diarrhoea, and vertigo.

Cinchonism may also occur after small doses in patients hypersensitive to quinine, but urticaria and flushing of the skin with intense pruritus are the most frequent reactions seen in these patients. Other effects include fever, rashes, and dyspnoea. Angioedema may also occur and asthma can be precipitated. Thrombocytopenia and other blood disorders have been reported. Thrombocytopenic purpura has been associated with quinine hypersensitivity. Haemoglobinuria occurs rarely.

Other adverse effects of quinine include hypoglycaemia, hypoprothrombinaemia, and renal failure.

The main symptoms of overdosage, which can be fatal, include gastrointestinal effects, oculotoxicity, CNS disturbances, and cardiotoxicity. Visual disturbances including sudden blindness are usually slowly reversible but there may be residual damage. Overdosage is discussed in detail p. 667.2. Quinine can produce cardiovascular toxicity similar to that seen with quinidine, including conduction disturbances, arrhythmias, anginal symptoms, and hypotension leading to cardiac arrest and circulatory failure. Severe or even fatal cardiovascular toxicity can result from rapid intravenous dosage of quinine.

Large amounts of quinine can induce abortion; congenital malformations, particularly of the optic and auditory nerves, have been reported after failure to induce abortion with quinine. However, quinine should not be withheld from pregnant women with life-threatening malaria (see also under Pregnancy in Precautions, p. 668.1).

Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; tetanus has developed in some patients (see under Malaria in Uses and Administration, above).

Effects on the blood. Between 1966 and 1975 the Swedish Adverse Drug Reaction Committee received 43 reports of *thrombocytopenia* attributable to quinine or quinidine[1] and the Boston Collaborative Drug Surveillance Program had 11 similar reports in patients studied between 1972 and 1981.[2] Up to October 2004, there had also been 228 cases of thrombocytopenia reported to the Australian Adverse Drug Reactions Advisory Committee, including 6 fatalities.[3] In the USA, the FDA has continued to receive reports of serious adverse events, including fatalities, despite efforts to restrict the use of quinine in response to existing toxicity concerns. Between April 2005 and October 2008, 24 domestic reports of serious haematological adverse events were received, of which 87.5% were thrombocytopenia requiring hospitalisation. The median time to onset of toxicity, and median reported quinine dose were 13.5 days and 325 mg daily respectively.[4] A similar analysis by Health Canada[5] of 71 reports of serious adverse effects suspected of being associated with quinine sulfate up to September 2010 included 43 cases where the indication had been leg cramps, for which the drug was not licensed; in 20 of these the adverse effect had been thrombocytopenia, often severe, while other adverse effects had included Stevens-Johnson syndrome, vasculitis, and arrhythmias. Quinine-induced thrombocytopenia appears to be a hypersensitivity reaction and beverages containing quinine as a bitter in concentrations as low as 20 micrograms/mL have precipitated thrombocytopenic purpura in previously sensitised individuals.[6]

Although quinine can cause *haemolysis*, there is some doubt over the traditional view that irregular dosage with quinine predisposes patients with malaria to *blackwater fever*, a syndrome of severe haemolytic anaemia, haemoglobinuria, oliguria, and renal failure.[7] Some of the patients affected may have had G6PD deficiency.[7] Haemolytic-uraemic syndrome[8-10] and pancytopenia with coagulopathy and renal impairment[11,12] have also been associated with the use of quinine.

There have also been reports of *disseminated intravascular coagulation*, including one fatality, after use of quinine by patients with quinine hypersensitivity.[13-15] In one case[15] the hypersensitivity reaction closely mimicked septic shock.

There have been isolated reports of *agranulocytosis* due to quinine.[16]

1. Böttiger LE, *et al*. Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205:** 457–61.
2. Danielson DA, *et al*. Drug-induced blood disorders. *JAMA* 1984; **252:** 3257–60.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; **23:** 20. Also available at: http://www.tga.gov.au/hp/aadrb-0410.htm (accessed 12/09/11)
4. FDA. Quinine sulfate (marketed as Qualaquin): off-label (not approved by FDA) use of quinine. *FDA Drug Safety Newsletter* 2009; **2:** 11–13. Also available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/UCM168579.pdf (accessed 10/09/09)
5. Health Canada. Quinine sulfate and serious adverse reactions. *Can Adverse React News* 2011; **21** (2): 5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v21n2-eng.pdf (accessed 02/08/11)
6. Murray JA, *et al*. Bitter lemon purpura. *BMJ* 1979; **2:** 1551–2.
7. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
8. Hagley MT, *et al*. Hemolytic-uremic syndrome associated with ingestion of quinine. *Am J Nephrol* 1992; **12:** 192–5.
9. Gottschall JL, *et al*. Quinine-induced immune thrombocytopenia with hemolytic uremic syndrome: clinical and serological findings in nine patients and review of literature. *Am J Hematol* 1994; **47:** 283–9.
10. McDonald SP, *et al*. Quinine-induced hemolytic uremic syndrome. *Clin Nephrol* 1997; **47:** 397–400.
11. Maguire RB, *et al*. Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. *Ann Intern Med* 1993; **119:** 215–17.

12. Schmitt SK, Tomford JW. Quinine-induced pancytopenia and coagulopathy. *Ann Intern Med* 1994; **120:** 90–1.
13. Spearing RL, *et al*. Quinine-induced disseminated intravascular coagulation. *Lancet* 1990; **336:** 1535–7.
14. Barr E, *et al*. Recurrent acute hypersensitivity to quinine. *BMJ* 1990; **301:** 323.
15. Schattner A. Quinine hypersensitivity simulating sepsis. *Am J Med* 1998; **104:** 488–90.
16. Sutherland R, *et al*. Quinine-induced agranulocytosis: toxic effect of quinine bisulphate on bone marrow cultures in vitro. *BMJ* 1977; **1:** 605–7.

Effects on the ears. Although ototoxicity such as tinnitus or deafness is known to be a possible adverse effect of quinine, reversible hearing loss may also occur. While one group of workers[1] found the reduction in auditory acuity to be greatest at higher frequencies, another group[2] have found that hearing loss was generally equal across the range of frequencies tested and appeared to be related to the plasma concentration of quinine.

1. Roche RJ, *et al*. Quinine induces reversible high-tone hearing loss. *Br J Clin Pharmacol* 1990; **29:** 780–2.
2. Karlsson KK, *et al*. Audiometry as a possible indicator of quinine plasma concentration during treatment of malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 765–7.

Effects on the eyes. Oculotoxicity after overdosage with quinine is well recognised (see below), but there has also been a report of blindness in two patients occurring during supposedly routine therapy.[1]

1. Waddell K. Blindness from quinine a s an antimalarial. *Trans R Soc Trop Med Hyg* 1996; **90:** 331–2.

Effects on glucose metabolism. Hypoglycaemia is now recognised to be a frequent complication of falciparum malaria and it is often associated with a poor prognosis. Children, pregnant women, and patients with severe disease appear to be particularly at risk. It is important to recognise that hypoglycaemia rather than cerebral malaria may be the cause of coma. Hypoglycaemia may also be induced by antimalarial therapy; first episodes of hypoglycaemia have been detected after patients received quinine[1-3] or quinidine[4] intravenously, although others have not found that quinine led to the development of hypoglycaemia.[5,6]

Quinine has also been reported to induce hypoglycaemia during treatment for leg cramps.[7]

1. White NJ, *et al*. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983; **309:** 61–6.
2. Okitolonda W, *et al*. High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. *BMJ* 1987; **295:** 716–18.
3. Looareesuwan S, *et al*. Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; **ii:** 4–8.
4. Phillips RE, *et al*. Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; **292:** 1319–21.
5. Taylor TE, *et al*. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N Engl J Med* 1988; **319:** 1040–7.
6. Kawo NG, *et al*. The metabolic effects of quinine in children with severe and complicated Plasmodium falciparum malaria in Dar es Salaam. *Trans R Soc Trop Med Hyg* 1991; **85:** 711–13.
7. Limburg PJ, *et al*. Quinine-induced hypoglycemia. *Ann Intern Med* 1993; **119:** 218–19.

Effects on the heart. Cardiotoxicity after overdosage with quinine is well recognised, and prolongation of the QT interval has been noted with therapeutic doses. There has also been a report[1] of fatal ventricular fibrillation with QT prolongation in an elderly patient who received standard doses of quinine by slow intravenous infusion for falciparum malaria. It was noted that the patient had some prolongation of the QT interval before starting quinine and also that her free quinine concentrations were unusually high despite total quinine concentrations considered to be within the therapeutic range.

1. Bonington A, *et al*. Fatal quinine cardiotoxicity in the treatment of falciparum malaria. *Trans R Soc Trop Med Hyg* 1996; **90:** 305–7.

Effects on the kidneys. See Effects on the Blood, p. 666.3.

Effects on the liver. Although hepatitis has been associated with quinidine therapy (see p. 1482.2), there appear to be few reports of hepatotoxicity due to quinine usage. Granulomatous hepatitis has been reported in 2 patients taking quinine,[1,2] but the diagnosis in the first of these cases was challenged as the histological findings were considered to be more indicative of non-specific reactive hepatitis.[3] Hepatotoxicity due to quinine hypersensitivity has been reported in another patient.[4] Symptoms of hepatotoxicity occurred within 24 hours in a further patient taking quinine for nocturnal leg cramps.[5]

1. Katz B, *et al*. Quinine-induced granulomatous hepatitis. *BMJ* 1983; **286:** 264–5.
2. Mathur S, *et al*. Quinine induced granulomatous hepatitis and vasculitis. *BMJ* 1990; **300:** 613.
3. Nirodi NS. Quinine induced granulomatous hepatitis. *BMJ* 1983; **286:** 647.
4. Punukollu RC, *et al*. Quinine hepatotoxicity: an underrecognized or rare phenomenon? *Arch Intern Med* 1990; **150:** 1112–13.
5. Farver DK, Lavin MN. Quinine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33:** 32–4.

Effects on the skin. Urticaria, cutaneous flushing, various rashes, and pruritus are the commonest symptoms of hypersensitivity reactions to quinine.

Topical contact with quinine may cause contact as well as photocontact allergy, but quinine can also induce photosensitivity reactions after systemic dosage.[1-3] Photosensitivity associated with quinine intake from excessive consumption of tonic water has been reported;[4] fixed drug eruptions due to quinine in tonic water have also occurred.[5] There have also been reports of eczematous dermatitis,[1] oedema and erythema,[6] hyperpigmentation,[7] and lichen planus.[6] Both phototoxic[6] and photoallergic[1] mechanisms have been suggested. Fatal cutaneous vasculitis related to quinine treatment for nocturnal cramps has been reported.[8]

For a comparison of the incidence of pruritus induced by various antimalarials, see under Chloroquine, p. 652.2.

1. Ljunggren B, Sjövall P. Systemic quinine photosensitivity. *Arch Dermatol* 1986; **122:** 909–11.
2. Ljunggren B, *et al*. Systemic quinine photosensitivity with photoepicutaneous cross-reactivity to quinidine. *Contact Dermatitis* 1992; **26:** 1–4.
3. Hickey JR, *et al*. Photoallergic reaction to systemic quinine sulphate. *Contact Dermatitis* 2007; **57:** 384–6.
4. Wagner GH, *et al*. 'I'll have mine with a twist of lemon': quinine photosensitivity from excessive intake of tonic water. *Br J Dermatol* 1994; **131:** 734–5.
5. Bel B, *et al*. Fixed eruption due to quinine contained in tonic water: positive patch-testing. *Contact Dermatitis* 2009; **61:** 242–4.
6. Ferguson J, *et al*. Quinine induced photosensitivity: clinical and experimental studies. *Br J Dermatol* 1987; **117:** 631–40.
7. Rosen T, Aponte C. Cutaneous hyperpigmentation due to chronic quinine ingestion. *Cutis* 2005; **75:** 114–6.
8. Price EJ, *et al*. Quinine-induced cutaneous vasculitis. *Br J Clin Pract* 1992; **46:** 138–9.

Hypersensitivity. For reference to hypersensitivity reactions associated with quinine, see Effects on the Blood (p. 666.3), Effects on the Liver (above), and Effects on the Skin (above).

Overdosage. Cinchonism may occur with therapeutic doses of quinine and symptoms include nausea, vomiting, tinnitus, deafness, headache, vasodilatation, and slightly disturbed vision. These symptoms may also occur in acute overdosage, but the visual disorders may be severe and there may be CNS disturbances and cardiotoxicity. A lethal dose or lethal plasma-quinine concentration has not been established but fatalities have been reported[1] in adults after doses of 2 to 8 g and in children after 1 g.

An analysis[2] of 165 cases of acute quinine poisoning revealed that: 21% had no symptoms, nausea with or without vomiting occurred in 47%, visual disturbances in 42%, tinnitus in 38%, other auditory disturbances in 23%, sinus tachycardia in 23%, and other ECG abnormalities in 8%. Mild impairment of consciousness was reported in 14% of the patients while 7 (4%) patients had deeper grades of coma. Of the 5 patients who died, 4 developed intractable ventricular arrhythmias and the fifth had a Jacksonian seizure followed by cardiac arrest. Another analysis,[3] of 96 cases of quinine intoxication reported in Scotland between 1997 and 2002, noted that there had been no changes in the pattern of poisoning from that in older studies; 6 cases involved moderate to serious toxicity after ingestion of 10 g or more. Intentional overdose was most common in patients aged between 11 and 30; children aged 10 or less were at greatest risk of accidental ingestion but toxicity was often not severe because the quantities were smaller. Both auditory and ocular toxicity appeared to be dose-related.

The effects of oculotoxicity may include blurred vision, defective colour perception, visual field constriction, and total blindness.[2,4] The onset of symptoms may vary from a few hours to a day or more after ingestion.[2,4] Suggested mechanisms for the oculotoxicity of quinine include an action on the retinal vasculature to produce ischaemia or a direct toxic effect on the retina.[1] Visual loss in one group of patients[4] was associated with plasma-quinine concentrations in excess of 10 micrograms/mL. However, in another group plasma-quinine concentrations were considered to be an imprecise guide to predicting visual disturbances.[2] The speed and degree of visual recovery varies. Of 70 patients with visual disturbances after quinine poisoning, 39 subsequently had a period of total blindness.[2] Permanent visual deficits remained in 19 of these but no patient had permanent bilateral blindness. All of the 31 patients who had blurred vision recovered full visual acuity.

It is considered that the actions of quinine on the myocardium are similar to those of quinidine but that it is less potent.[1] Sinus tachycardia and minor ECG changes are the most common cardiovascular effects. Conduction abnormalities and ventricular dysrhythmias may occur with severe poisoning. Ventricular tachycardia is mostly associated with cardiogenic shock or circulatory collapse. Hypokalaemia may also occur.[1]

1. Jaeger A, *et al*. Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
2. Boland ME, *et al*. Complications of quinine poisoning. *Lancet* 1985; **i:** 384–5.
3. Langford NJ, *et al*. Quinine intoxications reported to the Scottish Poisons Information Bureau 1997-2002: a continuing problem. *Br J Clin Pharmacol* 2003; **56:** 576–8.
4. Dyson EH, *et al*. Death and blindness due to overdose of quinine. *BMJ* 1985; **291:** 31–3.

Treatment of Adverse Effects

In acute overdosage with quinine or its salts multiple doses of activated charcoal (p. 1537.3) may be given to adults or children who present within one hour of ingesting more than the equivalent of 30 mg/kg of quinine base or any amount in a child under 5 years of age; gastric lavage may also be considered for use in adults. Other measures aimed at enhancing the elimination of quinine are largely ineffective. Treatment is mostly symptomatic with attention being given to maintaining blood pressure, respiration, and renal function, and to treating arrhythmias (for further information, see Acute Poisoning, p. 1537.1).

Vasodilators and stellate ganglion block have been used to prevent or reverse visual impairment but there is little evidence to support their use.

It has been suggested that, as quinine has antimuscarinic effects, gastric emptying may be delayed and considerable amounts of drug might be removed from the stomach beyond the usual 4 hours.[1] Others consider that gastric lavage is of doubtful value as quinine is rapidly absorbed and vomiting has often occurred before admission.[2] However, studies in healthy subjects and poisoned patients suggest that oral activated charcoal may increase the elimination of quinine.[3,4] Other methods of increasing elimination are probably ineffective. In a study involving 16 patients with quinine poisoning forced acid diuresis, haemodialysis, haemoperfusion, or plasma exchange were all found to be ineffective in increasing quinine elimination.[5]

Stellate ganglion block has been recommended to prevent or reverse retinal damage, the rationale being that quinine-induced oculotoxicity might arise from retinal arteriolar constriction. However, clinical studies have failed to find sufficient improvement to justify its use.[6,7] Intravenous nitrates produced beneficial responses in 2 patients.[8]

1. Boland M, Volans G. ABC of poisoning: miscellaneous drugs. *BMJ* 1984; **289:** 1361–5.
2. Jaeger A, *et al*. Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
3. Lockey D, Bateman DN. Effect of oral activated charcoal on quinine elimination. *Br J Clin Pharmacol* 1989; **27:** 92–4.
4. Prescott LF, *et al*. Treatment of quinine overdosage with repeated oral charcoal. *Br J Clin Pharmacol* 1989; **27:** 95–7.
5. Bateman DN, *et al*. Pharmacokinetics and clinical toxicity of quinine overdosage: lack of efficacy of techniques intended to enhance elimination. *Q J Med* 1985; **54:** 125–31.
6. Boland ME, *et al*. Complications of quinine poisoning. *Lancet* 1985; **i:** 384–5.
7. Dyson EH, *et al*. Quinine amblyopia: is current management appropriate? *J Toxicol Clin Toxicol* 1985–6; **23:** 571–8.
8. Moore D, *et al*. Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Precautions

Quinine and its salts are contra-indicated in patients with a history of hypersensitivity to quinine or quinidine and in patients with tinnitus or optic neuritis. They should not be used in the presence of haemolysis. They should be used with caution in patients with atrial fibrillation, cardiac conduction defects, or heart block. Quinine should be avoided in patients with myasthenia gravis as it may aggravate their condition.

Pregnancy in a patient with malaria is not generally regarded as a contra-indication to the use of quinine.

As quinine has been implicated in precipitating blackwater fever it is generally contra-indicated in patients who have already suffered an attack. Quinine may also cause haemolysis in some types of G6PD deficiency and should be used with care (but see also below).

It is important that when quinine is given intravenously it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity. Blood-glucose concentrations should also be monitored. Problems that have been associated with intramuscular use are discussed under Malaria in Uses and Administration, p. 666.1.

Breast feeding. Although quinine is distributed into breast milk in small amounts,[1] the most recent guidance from the American Academy of Pediatrics considered that the use of quinine was probably compatible with breast feeding.[2]

1. Phillips RE, *et al*. Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. *Br J Clin Pharmacol* 1986; **21:** 677–83.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Glucose-6-phosphate deficiency. Although licensed product information has noted that quinine may cause hae-

molysis in G6PD deficient patients (and in some countries, contra-indicates its use by such patients), a review[1] noted that haemolysis has not been seen in published studies, and re-affirmed an earlier conclusion[2] that full therapeutic doses may be safely administered to G6PD-deficient patients.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.
2. Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med* 1991; **324:** 169–74.

Liver disease. See under Pharmacokinetics, below.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Pregnancy. The use of quinine in large doses as an abortifacient in the past has led to concern over its use during pregnancy, but no evidence of an oxytocic effect was found when it was used to treat severe falciparum malaria in women in the third trimester of pregnancy.[1]

Congenital abnormalities including damage to the auditory and optic nerves have been seen, usually after attempted abortions, but WHO[2] considers quinine to be safe when used in normal therapeutic doses during pregnancy (although the problem of hypoglycaemia in the second and third trimesters may mean that artemisinin derivatives are preferred). Jitteriness attributed to quinine withdrawal has been reported in an infant whose mother had drunk large quantities of tonic water containing quinine during the last 17 weeks of pregnancy.[3]

As malaria is potentially serious during pregnancy and poses a threat to the mother and fetus, there appears to be little justification for withholding treatment in the absence of a suitable alternative. However, pregnant patients treated for malaria are at special risk from hypoglycaemia exacerbated or caused by quinine-induced hyperinsulinaemia (see under Effects on Glucose Metabolism in Adverse Effects, p. 667.1) and should be managed appropriately.

1. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; **ii:** 4–8.
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.

Renal impairment. See under Pharmacokinetics, below.

Interactions

As quinine shares many of the actions of quinidine, interactions seen between quinidine and other drugs (see p. 1483.1) might also occur with quinine. Both have actions on skeletal muscle and may potentiate the effects of drugs with neuromuscular-blocking activity (see under Antiarrhythmics on p. 2031.3). There is an increased risk of inducing ventricular arrhythmias if quinine is given with halofantrine (see p. 655.1) or other drugs that prolong the QT-interval such as amiodarone, the antihistamines astemizole and terfenadine, cisapride, moxifloxacin, and the antipsychotics pimozide and thioridazine. There may be an increased risk of convulsions when quinine is given with mefloquine. Quinine may also potentiate the effects of hypoglycaemic drugs.

Antibacterials. Elimination of quinine has been reported to increase in patients also receiving *rifampicin*.[1]

1. Wanwimolruk S, *et al.* Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* 1995; **40:** 87–91.

Amantadine. For a report of quinine reducing renal clearance of amantadine, see Antiarrhythmics, p. 892.2.

Anticoagulants. Quinine can cause hypoprothrombinaemia and thereby enhance the effect of anticoagulants. In one report, reductions in *warfarin* dosage were necessary after ingestion of large amounts of tonic water containing quinine (see p. 1532.2).

Antimalarials. Quinine and *chloroquine* may be antagonistic when used for falciparum malaria (see p. 653.2). For a report of quinine reducing plasma concentrations of *primaquine*, see p. 661.2.

Antivirals. In a pharmacokinetic study,[1] co-administration with *ritonavir* (in an oral dose of 200 mg twice daily) led to increases of about fourfold in the AUC and peak-plasma concentration of quinine; a modest, but significant increase in plasma concentrations of ritonavir was also noted. The authors of the study suggest that a downward dose adjustment of quinine may be necessary, given the magnitude of the plasma-concentration increase possible for the drug, and the seriousness of its adverse effects.

Although there appears to be no evidence regarding potential interaction with other HIV-protease inhibitors, they all have the potential to affect cytochrome P450 isoenzyme CYP3A4 (although to a lesser extent than ritonavir) and therefore might be expected to raise serum-concentrations of quinine (a substrate of CYP3A4); therefore, such combinations should be used with caution. UK licensed product information for *saquinavir* suggests its use (ritonavir-boosted) with quinine is contra-indicated, due to a potential risk for cardiac arrhythmia.

1. Soyinka JO, *et al.* Pharmacokinetic interactions between ritonavir and quinine in healthy volunteers following concurrent administration. *Br J Clin Pharmacol* 2010; **69:** 262–70.

Cardiovascular drugs. Quinidine has been reported to increase serum-digoxin concentrations (see Quinidine under Antiarrhythmics, p. 1356.2) and quinine has reduced total body clearance of digoxin (see Antimalarials, p. 1357.1).

For a report of quinine inhibiting the metabolism of *flecainide*, see p. 1384.3.

Histamine H_2-antagonists. *Cimetidine* has been reported to reduce the clearance of quinine and prolong its elimination half-life in a study in healthy subjects; no significant effect was seen with *ranitidine*.[1]

1. Wanwimolruk S, *et al.* Effects of cimetidine and ranitidine on the pharmacokinetics of quinine. *Br J Clin Pharmacol* 1986; **22:** 346–50.

Immunosuppressants. For a report of quinine decreasing plasma concentrations of *ciclosporin*, see p. 1957.1.

Tobacco smoking. A single-dose study in healthy subjects has suggested that blood concentrations of quinine are lower in heavy smokers than in non-smokers, potentially impairing efficacy.[1]

1. Wanwimolruk S, *et al.* Cigarette smoking enhances the elimination of quinine. *Br J Clin Pharmacol* 1993; **36:** 610–14.

Pharmacokinetics

The pharmacokinetics of quinine are altered significantly by malaria infection, the major effects being reductions in both its apparent volume of distribution and its clearance.

Quinine is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation occur about 1 to 3 hours after oral doses of the sulfate or bisulfate. Plasma protein binding is about 70% in healthy subjects and rises to 90% or more in patients with malaria. Quinine is widely distributed throughout the body. Concentrations attained in the CSF of patients with cerebral malaria have been reported to be about 2 to 7% of those in the plasma.

Quinine is extensively metabolised in the liver and rapidly excreted mainly in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5 to 20%. Excretion is increased in acid urine. The elimination half-life is about 11 hours in healthy subjects but may be prolonged in patients with malaria. Small amounts of quinine also appear in the bile and saliva.

Quinine crosses the placenta and is distributed into breast milk (see Breast Feeding, p. 667.3).

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1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Supanaranond W, *et al.* Disposition of oral quinine in acute falciparum malaria. *Eur J Clin Pharmacol* 1991; **40:** 49–52.
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5. Sowunmi A, Salako LA. Effect of dose size on the pharmacokinetics of orally administered quinine. *Eur J Clin Pharmacol* 1996; **49:** 383–6.
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7. Boele van Hensbroek M, *et al.* Quinine pharmacokinetics in young children with severe malaria. *Am J Trop Med Hyg* 1996; **54:** 237–42.
8. Zhang H, *et al.* Evidence for involvement of human CYP3A in the 3-hydroxylation of quinine. *Br J Clin Pharmacol* 1997; **43:** 245–52.
9. Viriyayudhakorn S, *et al.* Pharmacokinetics of quinine in obesity. *Trans R Soc Trop Med Hyg* 2000; **94:** 425–8.
10. Pukrittayakamee S, *et al.* Quinine pharmacokinetic-pharmacodynamic relationships in uncomplicated falciparum malaria. *Antimicrob Agents Chemother* 2003; **47:** 3458–63.
11. Abdelrahim II, *et al.* Pharmacokinetics of quinine and its metabolites in pregnant Sudanese women with uncomplicated Plasmodium falciparum malaria. *J Clin Pharm Ther* 2007; **32:** 15–9.
12. Mirghani RA, *et al.* Effects of *Plasmodium falciparum* infection on the pharmacokinetics of quinine and its metabolites in pregnant and non-pregnant Sudanese women. *Eur J Clin Pharmacol* 2010; **66:** 1229–34.

Administration in liver disease. Reduced clearance of quinine and prolonged elimination half-life have been reported in patients with acute hepatitis B given a single intravenous dose.[1] The results suggested that quinine accumulation after multiple doses could be greater in patients with hepatitis, even once hepatic function had returned to normal. In another study[2] patients with moderate chronic liver disease were given quinine orally; the half-life was prolonged but total clearance was not affected.

1. Karbwang J, *et al.* The pharmacokinetics of quinine in patients with hepatitis. *Br J Clin Pharmacol* 1993; **35:** 444–6.
2. Auprayoon P, *et al.* Pharmacokinetics of quinine in chronic liver disease. *Br J Clin Pharmacol* 1995; **40:** 494–7.

Administration in renal impairment. As urinary clearance comprises only 20% of total clearance of quinine, it appears that high plasma concentrations reported in patients with severe falciparum malaria and acute renal failure may be related more to the severity of the malaria, and associated pharmacokinetic changes, rather than to any reduction in the glomerular filtration rate.[1]

Continuous veno-venous high-volume haemofiltration appeared to have little effect on the pharmacokinetics of quinine,[2] suggesting that no dose supplementation would be needed in anuric patients undergoing this procedure. There were significant changes in the pharmacokinetics of quinine in 6 patients with chronic renal failure after a single oral dose.[3] The changes included a prolonged half-life, but there was no clear relationship between severity of renal failure and the degree of impairment of quinine clearance.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Liotier J, *et al.* Quinine clearance during continuous veno-venous high-volume hemofiltration. *Intensive Care Med* 2008; **34:** 1925–6.
3. Rimchala P, *et al.* Pharmacokinetics of quinine in patients with chronic renal failure. *Eur J Clin Pharmacol* 1996; **49:** 497–501.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Circonyl; ***Austral.***: Biquinate†; Quinate; Quinbisul; Quinsul†; ***Braz.***: Palukin†; ***Denm.***: Kinin; ***Fr.***: Quinoforme†; Surquina; ***Ger.***: Limptar N; ***Gr.***: Kinin; ***Hong Kong***: Q200†; Q300†; Quinbisul†; ***India***: Cinkona; Falcimax-Q; Foquin; Kwinil; Malgo; Mosgard; Nine; Quinarsol; Quininga; ***Indon.***: Euchinin; ***Malaysia***: Malakin; ***NZ***: Q200; Q300; ***Philipp.***: Malarin; ***Swed.***: Kinin; ***Thai.***: Alquinn; Genin; ***USA***: Qualaquin.

Multi-ingredient Preparations. ***Austria***: Iromin-Chinin-C†; Seltoc†; ***Braz.***: Monotrean B6; Monotrean; ***Fin.***: Crampiton; Relapamil†; ***Fr.***: Hexaquine; Okimus; Quinimax; ***Ger.***: Togal Classic†; ***Hung.***: Nicobrevin; ***Irl.***: Anadin; Nicobrevin†; ***Neth.***: Aflukin C†; ***NZ***: Nicobrevin; ***Rus.***: Analgin-Chinin (Анальгин-Хинин); ***S.Afr.***: Ilvico†; ***Spain***: Brota Rectal Balsamico†; ***UK***: Nicobrevin.

Homoeopathic Preparations. ***Canad.***: Pertudoron 1†; ***Fr.***: Selenium Complexe No 99; ***Ger.***: Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex.

Pharmacopoeial Preparations
BP 2014: Quinine Bisulphate Tablets; Quinine Dihydrochloride Infusion; Quinine Sulphate Tablets;
USP 36: Quinine Sulfate Capsules; Quinine Sulfate Tablets.

Tafenoquine *(BAN, rINN)*

SB-252263; Tafenoquin; Tafenoquina; Tafénoquine; Tafenoquinum; WR-238605; Тафенохин.

(±)-8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[(α,α,α-trifluoro-*m*-tolyl)oxy]quinoline; (*RS*)-N^4-[2,6-Dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-yl]pentane-1,4-diamine.

$C_{24}H_{28}F_3N_3O_3$=463.5

CAS — 106635-80-7.

UNII — 262P8GS9L9.

Profile

Tafenoquine is an 8-aminoquinoline antimalarial and more lipophilic derivative of primaquine. It acts as a tissue schizontocide and is under investigation as the succinate for the radical cure and prevention of relapse in vivax malaria. It may also have a role in the prophylaxis of falciparum malaria. Although it has been suggested to be better tolerated than primaquine, tafenoquine still carries a risk of haemolysis in G6PD-deficient patients.

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1. Walsh DS, *et al.* Randomized dose-ranging study of the safety and efficacy of WR 238605 (tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand. *J Infect Dis* 1999; **180:** 1282–7.
2. Lell B, *et al.* Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* 2000; **355:** 2041–5.
3. Shanks GD, *et al.* A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. *Clin Infect Dis* 2001; **33:** 1968–74.
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5. Hale BR, *et al*. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum. *Clin Infect Dis* 2003; **36:** 541–9.
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8. Charles BG, *et al*. Population pharmacokinetics of tafenoquine during malaria prophylaxis in healthy subjects. *Antimicrob Agents Chemother* 2007; **51:** 2709–15.
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Antimigraine Drugs

Cluster headache, p. 670
Medication-overuse headache, p. 670
Migraine, p. 670
Post-dural puncture headache, p. 671
Tension-type headache, p. 671

This chapter reviews the management of headache, in particular migraine and cluster headache, and the drugs used mainly for their treatment. The mechanisms of head pain or headache are not fully understood but may involve neurovascular changes (as in migraine and cluster headache), muscle contraction (tension headache), nerve lesions (neuralgias), direct head injury, infection (meningitis), or referred pain (sinusitis, toothache, eye disorders). Headache is also an adverse effect of many drugs including, paradoxically, those used to treat it. The International Headache Society has published guidelines to aid the diagnosis of the various headache types. Patients may have more than one headache disorder simultaneously and require separate treatment for each.

References.

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://ihs-classification.org/en/01_einleitung/ (accessed 14/06/11)

Cluster headache

Cluster headache (migrainous neuralgia, histaminic cephalalgia, Horton's syndrome) is of unknown aetiology but may be neurovascular in origin.[1-5] Patients have one or more short-lived attacks of intense unilateral head pain, usually at the same time of day (often at night). These are associated with autonomic symptoms such as conjunctival injection or lachrymation, miosis or ptosis, nasal congestion or rhinorrhoea, forehead or facial sweating, and eyelid oedema. Restlessness during the attacks is characteristic. The period during which attacks occur is called a cluster period; it may last several weeks or months. In the typical episodic form of cluster headache, cluster periods are followed by periods of remission lasting for months or years but in the more rare chronic form, patients may have cluster periods lasting for more than a year, or with short periods of remission in between. Substances such as alcohol, histamine, or glyceryl trinitrate can precipitate headache attacks during cluster periods, but not during periods of remission. There is speculation that sleep-disordered breathing[6] and increased body heat[7] may also trigger cluster headaches.

The **treatment** of individual acute attacks during a cluster period is difficult because the headache is short-lived and oral analgesics are unlikely to be absorbed fast enough to produce much benefit.[1,3,4] Inhalation of 100% oxygen should be considered in all patients.[8-11] It is rapid and effective in aborting attacks, but has practical difficulties. Some consider subcutaneous sumatriptan to be the acute therapy of choice in cluster attacks;[4,5,8-13] intranasal sumatriptan or zolmitriptan are possible alternatives, although less effective.[1,4,8,12] Oral zolmitriptan may be considered for patients who cannot tolerate subcutaneous or intranasal triptans and oxygen, or who prefer oral medication.[4] Intranasal instillation of lidocaine may be considered in patients who have still not responded.[8-11] It has been reported to be of some benefit but most patients do not obtain complete pain relief.[1,3,4,9] Intranasal dihydroergotamine[1,4] and inhaled ergotamine have also been used to treat acute attacks; injectable dihydroergotamine has usually been reserved for emergency settings.[4]

Since individual attacks are difficult to treat it is probably more effective to manage cluster headache by **prophylaxis** once a cluster period has started. The changing or combining of prophylactic treatment has also been advised by some,[12] if patients do not respond to the maximum possible dose of a drug within a week. Verapamil is usually considered the preventive therapy of choice,[1,4,8-13] particularly in patients with chronic long-lasting cluster periods.[5] Lithium may also be useful for the episodic or chronic form of the disorder.[9-13] Despite a lack of studies, oral corticosteroids are considered by some to be effective in the prophylaxis of cluster headache,[8,10,12] including those with short-lasting cluster periods (less than 2 months).[5] Methysergide, pizotifen, and valproate have also been tried.[1,3,5,9-11] Ergotamine may be used rectally in the short-term management of episodic cluster headache, if attacks are predictable;[10,12] it should not be used for prolonged periods. Other drugs under investigation include gabapentin, melatonin, and topiramate.[4,9-11,13]

Paroxysmal hemicrania is a rare variant of cluster headache and differs mainly in the high frequency and shorter duration of individual attacks. One of its features, which may be diagnostic, is its invariable response to indometacin.[10]

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Medication-overuse headache

Overuse of drugs such as ergotamine, triptans, and analgesics (including opioids and combination preparations containing caffeine or butalbital) to treat headache or migraine can lead to dependence and paradoxical chronic daily headache in headache-prone patients.[1-5] Such headaches do not appear to occur with regular use of analgesics to treat other disorders except occasionally in patients with a history of migraine.[1] Medication-overuse headaches, also referred to as rebound, analgesic abuse, or analgesic-induced headaches, can be difficult to treat and are relieved by withdrawal of the offending drug, but the primary headache may still persist and revert to its previous pattern of occurrence. Furthermore, stopping abruptly can exacerbate headache and produce other symptoms of withdrawal. This may then lead the patient to resume treatment to relieve the headache thereby setting up a vicious circle.

Options for outpatient **treatment** include either abrupt or gradual withdrawal of the overused drug. Abrupt withdrawal has been suggested if the headache has been caused by the use of simple analgesics, ergot derivatives, or triptans, and gradual withdrawal if it is due to opioids.[6,7] Aggravation of symptoms may be managed by the use of naproxen, prednisolone, or amitriptyline.[6,7] Substitution with long-acting NSAID or intramuscular dihydroergotamine has been tried in withdrawal from ergotamine or analgesics;[8,9] However, withdrawal symptoms may persist for up to 2 weeks and detoxification from ergotamine or analgesics may require hospitalisation; intravenous metoclopramide and repetitive intravenous dihydroergotamine may be required to control nausea and vomiting and intractable headache, respectively.[8] Withdrawal from triptans has been reported to be of shorter duration with no intensive withdrawal symptoms; however, triptan overuse produces headaches at a faster rate and at lower dosages compared with ergotamine and analgesics, and is associated with an increase in migraine attack frequency.[1]

General advice on the **prevention** of medication-overuse headache has included limiting the frequency of use of such drugs,[1,3,4,8] and starting prophylactic therapy in migraine patients having more than 2 headache days a week.[3]

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Migraine

Migraine is characterised by recurrent attacks of headache that typically last 4 to 72 hours. Attacks persisting for longer than 72 hours are referred to as status migrainosus. The headache is usually a unilateral pulsating pain that is aggravated by movement and is usually of sufficient severity to disturb or prevent daily activities. It is frequently accompanied by nausea, vomiting, or other gastrointestinal disturbances and there may be photophobia and phonophobia. Migraine with aura (classic migraine) is characterised by an aura consisting of visual or sensory symptoms that lasts less than an hour. The headache usually follows the aura directly, or within 1 hour, but may begin simultaneously with the aura. In addition, aura can occur without headache. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients with migraine. Premonitory symptoms may occur before a migraine attack (with or without aura). Familial hemiplegic migraine is a rare syndrome in which migraine with aura may be preceded or accompanied by dysphasia, confusion, and hemiparesis. Basilar-type migraine is another rare form of migraine with aura in which there may be disturbances of the brain stem or occipital lobes accompanied by symptoms such as decreased level of consciousness, vertigo, ataxia, dysarthria, and diplopia.

Migraine is described as a neurovascular headache. Traditionally, intracranial vasoconstriction was considered responsible for the aura and extracranial vasodilatation for the headache. However, it appears that vascular events may be secondary to neuropathic changes and the liberation of vasoactive substances including serotonin (5-HT), catecholamines, histamine, kinins, neuropeptides such as calcitonin gene-related peptide (CGRP), and prostaglandins.

There are several factors that may precipitate migraine attacks. These include anxiety, physical and emotional stress, a change in sleep pattern, bright lights, fasting, some foods, and menstruation. Menstrual migraine is characterised by attacks without aura which are most likely to occur within 2 days of the start of menstruation. Migraine may also be precipitated by drugs including combined oral contraceptives and oestrogens, and glyceryl trinitrate. The frequency of migraine attacks can be reduced if such precipitating factors can be identified and avoided. Quiet, darkness, and sleep can ease an attack, with sleep heralding recovery.

The drug **treatment** of migraine may be tailored to the severity of individual disease from the outset (stratified care) or may begin with simple analgesics and be subsequently adjusted according to response (step strategy); in the UK, stepped care seems to be increasingly preferred. Acute treatment of menstrual migraine is the same as for migraine; however, as menstrual migraine may be of longer duration, treatment may need to be repeated over several consecutive days.

Simple **analgesics** (paracetamol or NSAIDs including aspirin) are effective if taken at the earliest signs of an attack; weak opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations. However, the frequent use of analgesics is best avoided to decrease the risk of medication-overuse headaches. Other drugs used with analgesics in antimigraine preparations have included caffeine and the sympathomimetic vasoconstrictor isometheptene. Dispersible and effervescent analgesic preparations are preferable because of their more rapid absorption.

If the initial treatment of migraine is delayed, absorption of oral drugs may be compromised by development of gastric stasis and nausea and vomiting. The addition of **antiemetics** such as buclizine and cyclizine, and the **prokinetic** drugs metoclopramide and domperidone is recommended if needed; they are often included in compound antimigraine preparations. Prokinetic drugs also

have the advantage of promoting gastric emptying and normal peristalsis. If nausea and vomiting are prominent rectal administration may be necessary.

Attacks not responding to simple analgesics such as NSAIDs may be treated with specific antimigraine drugs such as the selective serotonin (5-HT_1) agonists (e.g. sumatriptan) or the ergot derivatives ergotamine and dihydroergotamine; poor absorption and adverse effects limit the use of ergot derivatives and selective serotonin (5-HT_1) agonists are preferred.

Serotonin (5-HT_1) agonists are highly effective in relieving the pain and nausea of a migraine attack. There are a number of **triptans** available; patient characteristics and preferences vary in response to use and can sometimes be unpredictable. Some patients experience recurrence of the headache within 24 to 48 hours and often respond to a second dose. Finding the best triptan to suit the individual patient may involve trial and error; a change in formulation should also be considered. Triptans should not be used in patients with major risk factors for, or suffering from, cardiovascular disease. The main concern with all triptans is their potential for coronary vasoconstriction and no triptan appears to be safer than the others. Medication-overuse headaches have also been noted with triptan use.

Ergot derivatives are rarely needed now in the treatment of migraine. If **ergotamine** is used it should be given at the first warning of an attack; the earlier it is given, the more effective the treatment. Since its oral bioavailability is poor and may be reduced further during a migraine attack, ergotamine has sometimes been given in sublingual or rectal preparations. Ergotamine can also exacerbate nausea and vomiting; metoclopramide or domperidone, or in severe cases the phenothiazines chlorpromazine or prochlorperazine, may be given. Dihydroergotamine may be of use if parenteral treatment is required; it can also be given intranasally but there is less experience with this route. Patients who fail to respond to monotherapy may find combination treatment, such as a simple analgesic with a triptan, helpful particularly in prolonged attacks.

Patients who rapidly develop severe migraine may be given **parenteral** dihydroergotamine or sumatriptan. Some consider parenteral metoclopramide to be suitable first-line treatment. Intramuscular diclofenac has also been recommended. If there is no response to these drugs, dopamine antagonists, such as chlorpromazine or prochlorperazine, given parenterally may be effective in relieving the pain of acute migraine attacks. Prolonged attacks (status migrainosus) may require intravenous administration of dihydroergotamine with metoclopramide. The NSAIDs naproxen or diclofenac are better than specific antimigraine drugs for long duration attacks that are really migraine with a superseding tension-type headache.

Other drugs that may be given alone or in combination include corticosteroids or pethidine. Lidocaine has been given intravenously for the emergency treatment of migraine; intranasal lidocaine has also been tried. The opioid agonist-antagonist butorphanol, given by nasal spray, has been advocated, but its place in therapy, if any, remains to be established. Other drugs that have been investigated include CGRP antagonists; intravenous valproic acid has also shown promise in aborting acute attacks.

Guidelines have been issued for the treatment of migraine in **children and adolescents**. For acute treatment, ibuprofen and paracetamol were found to be effective in children aged 6 years and over; sumatriptan nasal spray should be considered in those aged 12 years and over.

Prophylactic treatment should be considered for patients in whom abortive measures are ineffective or migraine attacks occur frequently, or for those with less frequent but severe or prolonged attacks. Some recommend prophylaxis if attacks occur more often than once or twice a month. Prophylaxis can reduce the severity and/or frequency of attacks but does not eliminate them completely and patients still need additional abortive or symptomatic treatment. Drugs suggested for prophylaxis have a range of actions which reflects uncertainty over the pathogenesis of migraine. It is important to give prophylactic drugs for an adequate period before assessing their efficacy; a general guide of 6 to 8 weeks is advisable. Once an optimum effect has been achieved the need for continuing prophylaxis should be reviewed at intervals of about 3 to 6 months. Treatment is best withdrawn gradually, over 2 to 3 weeks.

The main prophylactic drugs are **beta blockers**, tricyclic **antidepressants**, and the **antiepileptics**, topiramate and valproate. Propranolol is considered by many to be the prophylactic drug of choice. Lethargy appears to be the most common adverse effect. Other beta blockers reported to be effective are those that, like propranolol, possess no intrinsic sympathomimetic activity; these include atenolol, metoprolol, nadolol, and timolol. The potential for beta blockers to interact with some serotonin (5-HT_1) agonists and ergotamine should be borne in mind. Tricyclic antidepressants, particularly amitriptyline, given in gradually increasing doses at night are useful for preventing migraine, especially in patients who also have depression or tension-type headache, although antimuscarinic adverse effects may occur. Valproate is also used for preventing migraine. Nausea appears to be the most common adverse effect. Topiramate is the main alternative to valproate. Weight loss and paraesthesia are commonly reported adverse effects. Topiramate or valproate are particularly useful in patients who also have epilepsy or bipolar disorder. Gabapentin may also be used for the prophylaxis of migraine.

Other drugs have been used for the prophylaxis of migraine. Of the drugs with calcium-channel blocking activity, flunarizine appears to be effective, and has been suggested for use in children, and verapamil may be useful, but evidence for the efficacy of other calcium-channel blockers such as diltiazem, nifedipine, or nimodipine is less convincing; NSAIDs may be worth trying. Pizotifen, an antihistamine and serotonin antagonist, has been widely used but evidence for its efficacy is limited; it may be tried in children. The use of methysergide, a potent serotonin antagonist, has declined because of serious adverse effects, in particular retroperitoneal fibrosis. MAOIs such as phenelzine have been used occasionally but are best reserved for severe cases refractory to other forms of prophylactic treatment. Cyproheptadine, an antihistamine and serotonin antagonist, has been used for migraine prophylaxis, particularly in children. Botulinum A toxin is used for the prophylaxis of headaches in adults with chronic migraine. Other drugs used for the prophylaxis of migraine have included butterbur, clonidine, cyclandelate, indoramin, feverfew, and the ergot derivative metergoline. Positive results have been seen with magnesium and riboflavin. Investigated drugs which have shown potential for prevention of migraine attacks include: baclofen, candesartan, lisinopril, montelukast, and venlafaxine. Despite promising initial results, there is limited evidence to support the use of SSRIs.

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Post-dural puncture headache

For the management of headache associated with lumbar puncture or spinal anaesthesia, see Post-dural Puncture Headache under Local Anaesthetics, p. 1983.1.

Tension-type headache

Tension-type headaches, also referred to as muscle-contraction headaches, are probably the commonest form of headache. They are characterised by bilateral pain, which unlike migraine is continuous and non-pulsatile. The pain is often described by the patient as feeling like a tight band pressed around the head. Headaches of this type may be precipitated by many factors including psychosocial stress or muscular stress. Many patients also have associated symptoms of anxiety or depression. Tension-type headaches and migraine often co-exist and may then be referred to as combination or mixed headaches. Some patients only experience isolated acute attacks of tension-type headache (episodic tension-type headache), but others may develop chronic tension-type headache which is difficult to treat.

Treatment is aimed at removing the underlying causes where these can be identified. Simple massage may help if muscle contraction is a prominent component of the pain. Non-opioid analgesics, such as aspirin or other NSAIDs and paracetamol, may be tried for individual acute attacks of headache, but analgesic overuse must be avoided as this can lead to chronic headache resistant to other measures (see Medication-overuse Headache, p. 670.2). Opioids alone or in combination preparations with other analgesics should also be avoided. Hypnotics or sedatives have sometimes been used in combination preparations with analgesics in the management of tension-type headache that disrupts sleep but, because of the potential for abuse, they should be avoided in chronic headaches. Muscle relaxants appear to have little place in the management of tension-type headache; although some patients may respond, results are generally disappointing. Other drugs that have been tried include valproate and botulinum A toxin. **Prophylaxis** is preferable to regular short-term use of analgesics in controlling chronic tension-type headache. Tricyclic antidepressants, particularly amitriptyline, are generally considered as first choice, although benefit is rarely complete. The mode of action is unclear and appears to be independent of any antidepressant action. In most cases, improvement is seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression. Addition of a beta blocker such as propranolol may sometimes be of benefit for patients with some migraine features. The antiepileptic topiramate has also been tried with some success.

References.

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Almotriptan Malate *(BANM, USAN, rINNM)*

Almotriptan, Malate d'; Almotriptán, malato de; Almotriptani Malas; LAS-31416 (almotriptan); Malato de almotriptán; PNU-180638E; Альмотриптана Малат.

1-[{[3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl}sulfonyl] pyrrolidine malate (1:1).

$C_{17}H_{25}N_3O_2S,C_4H_6O_5$=469.6

CAS — 154323-57-6 (almotriptan); 181183-52-8 (almotriptan malate).

ATC — N02CC05.

ATC Vet — QN02CC05.

UNII — PJP312605E.

Uses and Administration

Almotriptan malate is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Almotriptan is given orally as the malate, and doses are expressed in terms of the base; almotriptan malate 8.75 mg is equivalent to about 6.25 mg of almotriptan.

The recommended dose of almotriptan is 12.5 mg in the UK and 6.25 or 12.5 mg in the USA. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. No more than 2 doses should be taken in a 24-hour period. For doses in hepatic and renal impairment see below.

References.
1. Holm KJ, Spencer CM. Almotriptan. *CNS Drugs* 1999; **11:** 159–64.
2. Keam SJ, *et al.* Almotriptan: a review of its use in migraine. *Drugs* 2002; **62:** 387–414.

Administration in hepatic or renal impairment. In patients with hepatic or severe renal impairment, no more than 12.5 mg of oral almotriptan should be taken in 24 hours; a starting dose of 6.25 mg may be used. No dose adjustment is needed in patients with mild to moderate renal impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

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Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Almotriptan should be given with caution to patients with hepatic impairment or severe renal impairment.

Patients with hypersensitivity to sulfonamides may theoretically show a similar reaction to almotriptan. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

Incidence of adverse effects. Results from studies involving more than 2500 patients with migraine suggested that adverse effects of almotriptan were infrequent.[1] The commonest adverse effects reported were dizziness, nausea and vomiting, headache, paraesthesia, fatigue, and drowsiness, all of which occurred in less than 3% of patients. The incidence of chest symptoms was 0.2% in 2 large phase III studies.

1. Dodick DW. Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 2001; **41:** 449–55.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies almotriptan as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Pharmacokinetics

After oral doses, peak plasma-almotriptan concentrations occur in about 1 to 3 hours, with a bioavailability of about 70%. Protein binding is about 35%. Almotriptan is metabolised mainly by monoamine oxidase type A to the inactive indole acetic acid derivative, and to a lesser extent by cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to the inactive gamma-aminobutyric acid derivative. More than 75% of an oral dose is excreted in the urine and the remainder in faeces. About 40% of the dose in the urine is excreted as unchanged drug. The plasma elimination half-life is about 3.5 hours in healthy subjects, increasing to about 7 hours in patients with severe renal impairment.

Distribution into milk has been found in studies in *rats*.

References.
1. Jansat JM, *et al.* Absolute bioavailability, pharmacokinetics, and urinary excretion of the novel antimigraine agent almotriptan in healthy male volunteers. *J Clin Pharmacol* 2002; **42:** 1303–10.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Almogran†; ***Belg.***: Almogran; ***Canad.***: Axert; ***Denm.***: Almogran; ***Fin.***: Almogran; ***Fr.***: Almogran; ***Ger.***: Almogran; ***Gr.***: Almogran; Amignul†; ***Irl.***: Almogran; ***Ital.***: Almogran; Almotrex; ***Neth.***: Almogran; ***Norw.***: Almogran; ***Port.***: Almogran; Amignul†; ***Spain***: Almogran; Amignul; ***Swed.***: Almogran; ***Switz.***: Almogran; ***UK***: Almogran; ***USA***: Axert.

Dihydroergotamine *(BAN, rINN)*

Dihidroergotamina; Dihydroergotamiini; Dihydroergotamin; Dihydroergotamina; Dihydroergotaminum; Diidroergotamina; Дигидроэрготамин.

(5′*S*,8*R*)-5′-Benzyl-9,10-dihydro-12′-hydroxy-2′-methyl-3′,6′,18-trioxoergotaman.

$C_{33}H_{37}N_5O_5$=583.7

CAS — 511-12-6.

ATC — N02CA01.

ATC Vet — QN02CA01.

UNII — 436O5HM03C.

Dihydroergotamine Mesilate *(BANM, rINNM)*

Dihidroergotamina, mesilato de; Dihidroergotamin-mezilát; Dihidroergotamino mesilatas; Dihydroergotamiinimesilaatti; Dihydroergotamine, mésilate de; Dihydroergotamine Mesylate (USAN); Dihydroergotamine Methanesulphonate; Dihydroergotamini Mesilas; Dihydroergotaminmesilat; Dihydroergotamin-mesylát; Dihydroergotaminy mezylan; Mesilato de dihidroergotamina; Дигидроэрготамина Мезилат.

$C_{33}H_{37}N_5O_5,CH_4O_3S$=679.8

CAS — 6190-39-2.

ATC — N02CA01.

ATC Vet — QN02CA01.

UNII — 81AXN7R2QT.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dihydroergotamine Mesilate). Colourless crystals or a white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 4.4 to 5.4. Protect from light.

USP 36: (Dihydroergotamine Mesylate). A white to slightly yellowish powder, or off-white to faintly red powder, having a faint odour. Soluble 1 in 125 of water, 1 in 90 of alcohol, 1 in 175 of chloroform, and 1 in 2600 of ether. pH of a 0.1% solution in water is between 4.4 and 5.4. Protect from light.

Dihydroergotamine Tartrate *(BANM, rINNM)*

Dihidroergotamina, tartrato de; Dihidroergotamino tartratas; Dihidroergotamin-tartarát; Dihydroergotamiinitartraatti; Dihydroergotamine, Tartrate de; Dihydroergotamini Tartras; Dihydroergotamin-tartarát; Dihydroergotamintartrat; Tartrato de dihidroergotamina; Дигидроэрготамина Тартрат.

$(C_{33}H_{37}N_5O_5)_2,C_4H_6O_6$=1317.5

CAS — 5989-77-5.

ATC — N02CA01.

ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dihydroergotamine Tartrate). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. A 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Dihydroergotamine is a semisynthetic ergot alkaloid that has weaker oxytocic and vasoconstrictor effects than ergotamine (p. 674.1). Its activity as a 5-HT_1 agonist is believed to contribute to its antimigraine action. It is used in the treatment of migraine and cluster headache, and in the treatment of orthostatic hypotension. It has also been used for the prophylaxis of venous thromboembolism (see p. 673.1).

Dihydroergotamine is commonly used as the mesilate by subcutaneous, intramuscular, or intravenous injection, although it may also be given as a nasal spray or orally.

For the treatment of **migraine** and to terminate an acute attack of **cluster headache**, dihydroergotamine mesilate is usually given by subcutaneous or intramuscular injection in doses of 1 mg repeated, if necessary, after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg up to a maximum daily dose of 2 mg. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 500 micrograms sprayed into each nostril as a 0.4% solution followed after 15 minutes by an additional 500 micrograms in each nostril. A total intranasal dose of 2 mg per attack should not be exceeded. In the USA, the maximum licensed intranasal dose in 24 hours is 3 mg and in a 7-day period is 4 mg, while maximum daily doses of up to 4 mg with a maximum dose of 12 mg in a 7-day period have been given in other countries. Dihydroergotamine may also be given orally; up to 10 mg daily has been given for the treatment of acute attacks of migraine while lower oral doses are recommended for migraine prophylaxis.

Dihydroergotamine mesilate has also been used alone or with etilefrine hydrochloride (p. 1379.1) in the treatment of **orthostatic hypotension**, in usual oral doses of up to 10 mg daily in divided doses. Doses of up to 40 to 60 mg have been used in some patients.

Dihydroergotamine tartrate has been used for indications similar to those of the mesilate.

Medication-overuse headache. Dihydroergotamine may be used in the treatment of medication-overuse headache (p. 670.2), including symptoms of ergotamine withdrawal.

Migraine and cluster headache. Although sumatriptan is often the treatment of choice to abort acute attacks of migraine that do not respond to simple analgesic preparations, parenteral dihydroergotamine, especially with an antiemetic, is an alternative for patients who develop severe or refractory migraine (p. 670.3).[1-3] Preparations for intranasal[4] and oral use are also available and one for inhalation[5] is under development. In a comparative study, relief of migraine was slower after subcutaneous dihydroergotamine than after subcutaneous sumatriptan, but headache recurred less often.[6] In other studies, intranasal dihydroergotamine was not as effective as subcutaneous[7] or intranasal[8] sumatriptan.

Dihydroergotamine is also used in the treatment of cluster headache (p. 670.1), usually in emergency settings, where it is given to abort individual headache attacks.

1. Scott AK. Dihydroergotamine: a review of its use in the treatment of migraine and other headaches. *Clin Neuropharmacol* 1992; **15:** 289–96.
2. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45:** 577–84.
3. Colman I, *et al.* Parenteral dihydroergotamine for acute migraine headache: a systematic review of the literature. *Ann Emerg Med* 2005; **45:** 393–401.
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5. Aurora SK, *et al.* MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. *Headache* 2011; **51:** 507–17.
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7. Touchon J, *et al.* A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology* 1996; **47:** 361–5.
8. Boureau F, *et al.* A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *Int J Clin Pract* 2000; **54:** 281–6.

Orthostatic hypotension. Dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p. 1634.3). It is sometimes used in preparations with sympathomimetics such as etilefrine. After parenteral dihydroergotamine, standing blood pressure is increased, but total peripheral resistance and supine blood pressure are also increased.[1] It does not prevent postprandial hypotension, presumably because it does not constrict the splanchnic veins, although use with caffeine may overcome this problem. The main disadvantage of dihydroergotamine, however, is that it is ineffective, or at best weakly effective, when given orally, although there has been some evidence that oral ergotamine tartrate may be of value.

Dihydroergotamine has been suggested for use in the prevention of hypotension associated with epidural[2] or spinal anaesthesia,[3] the usual management of which is discussed in Treatment of Adverse Effects of Local Anaesthetics, p. 1983.1. It has also been tried in the management of hypotension associated with haemodialysis.[4]

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Mattila M, *et al.* Dihydroergotamine in the prevention of hypotension associated with extradural anaesthesia. *Br J Anaesth* 1985; **57:** 976–82.
3. Critchley LAH, Woodward DK. Haemodynamic effects of three doses of dihydroergotamine during spinal anaesthesia. *Br J Anaesth* 2001; **87:** 499–501.
4. Milutinovic S. Dihydroergotamin i n der Behandlung von Patienten mit symptomatischer Hypotonie während Dauerhärnodialyse. *Arzneimittelforschung* 1987; **37:** 554–6.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p. 1274.1) is usually with anticoagulants, with unfractioned or low-molecular-weight heparin being the most widely used. Dihydroergotamine can reduce venous stasis by vasoconstriction of capacitance vessels and has enhanced postoperative prophylaxis when used with heparin.[1] The use of dihydroergotamine with low-molecular-weight heparin has been shown to be of similar efficacy to dihydroergotamine with heparin.[2,3] However, although dihydroergotamine might enhance the effect of heparin, a US National Institutes of Health consensus conference warned of the potential risk associated with its vasoconstrictive effects, and the contra-indications to its use[4] (see also Effects on the Cardiovascular System, under Adverse Effects, below).

1. Lindblad B. Prophylaxis of postoperative thromboembolism with low dose heparin alone or in combination with dihydroergotamine: a review. *Acta Chir Scand* 1988; (suppl 543): 31–42.
2. Sasahara AA, *et al.* Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *Br J Surg* 1986; **73:** 697–700.
3. Haas S, *et al.* Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. *Arzneimittelforschung* 1987; **37:** 839–43.
4. NIH Consensus Development. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986; **256:** 744–9.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p. 674.2, although vasoconstriction may be less pronounced and the frequency of nausea and vomiting lower with dihydroergotamine mesilate than with ergotamine tartrate. Dihydroergotamine does not appear to produce physical dependence.

Effects on the cardiovascular system. There have been conflicting reports on the risk of vasospasm in patients given dihydroergotamine with heparin for thromboembolism prophylaxis. Vasospastic or necrotic reactions have been reported on several occasions during such therapy.[1-4] In an Austrian study of 147 290 patients given drug prophylaxis for thromboembolism, complications attributable to ergotism were seen in 142 of 61 092 (0.23%) who received dihydroergotamine and heparin.[5] Others,[6] however, saw only 1 case of vasospasm in 5100 trauma patients (0.02%) given the combination. In 1989 the Swedish Adverse Drug Reactions Advisory Committee reported[7] that up to the end of September 1987 the manufacturer had received 201 reports of vasospastic reactions associated with the use of *Orstanorm* (dihydroergotamine + lidocaine) with heparin. Permanent damage occurred in 59% of these patients. Vasospastic reactions had occurred more frequently in patients who had undergone surgery for trauma and the prognosis for such patients was generally poorer than for others. Since the risk of permanent damage appeared to be related to treatment length the Committee recommended that this preparation should not be given for more than 7 days.

1. van den Berg E, *et al.* Ergotism leading to threatened limb amputation or to death in two patients given heparin-dihydroergotamine prophylaxis. *Lancet* 1982; **i:** 955–6.
2. van den Berg E, *et al.* Vascular spasm during thromboembolism prophylaxis with heparin-dihydroergotamine. *Lancet* 1982; **ii:** 268–9.
3. Monreal M, *et al.* Skin and muscle necrosis during heparin-dihydroergotamine prophylaxis. *Lancet* 1984; **ii:** 820.
4. Kilroy RA, *et al.* Vascular spasm during heparin-dihydroergotamine prophylaxis. *Clin Pharm* 1987; **6:** 575–7.
5. Gatterer R. Ergotism as complication of thromboembolic prophylaxis with heparin and dihydroergotamine. *Lancet* 1986; **ii:** 638–9.
6. Schlag G, *et al.* Risk/benefit of heparin-dihydroergotamine thromboembolic prophylaxis. *Lancet* 1986; **ii:** 1465.
7. Swedish Adverse Drug Reaction Advisory Committee. Dihydroergotamine + lidocaine – vasospasm. *Bull Swed Adverse Drug React Advisory Committee* 1989; (54): 1.

Fibrosis. For reference to fibrosis associated with the administration of dihydroergotamine, see Methysergide Maleate, p. 677.2.

Precautions

As for Ergotamine Tartrate, p. 675.1.

Cardiovascular disorders. For specific contra-indications and precautions in cardiovascular disorders, see under Ergotamine, p. 675.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dihydroergotamine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Interactions

As for Ergotamine (p. 675.2).

Use with other vasoconstrictive drugs, including supplementary antimigraine treatment with ergotamine or sumatriptan, should be avoided.

Pharmacokinetics

Peak plasma-dihydroergotamine concentrations occur within about 1 to 2 hours after oral doses, about 30 minutes after intramuscular injection, about 15 to 45 minutes after subcutaneous injection, and about 45 to 55 minutes after intranasal doses. However, the bioavailability of dihydroergotamine after oral doses is very low; values ranging from less than 0.1 to 1.5% have been reported. Although dihydroergotamine is incompletely absorbed from the gastrointestinal tract, the low bioavailability is considered to be determined primarily by extensive first-pass hepatic metabolism. Bioavailability after intranasal doses is 43%. Dihydroergotamine is 90 to 95% bound to plasma proteins.

Dihydroergotamine undergoes extensive metabolism, the major metabolite, 8′-β-hydroxydihydroergotamine, being active. Plasma concentrations of this metabolite are greater than those of dihydroergotamine. A further oxidation step produces 8′,10′-dihydroxydihydroergotamine, which is also active. Other metabolites are also formed. Most of a dose is excreted as metabolites, mainly in the bile; 5 to 10% is excreted in the urine of which only trace amounts are of unchanged drug. The elimination of dihydroergotamine is biphasic; half-lives of about 1 to 2 hours and 22 to 32 hours have been reported for the 2 phases, respectively.

References.
1. Little PJ, *et al.* Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol* 1982; **13:** 785–90.
2. Müller-Schweinitzer E. Pharmacological actions of the main metabolites of dihydroergotamine. *Eur J Clin Pharmacol* 1984; **26:** 699–705.
3. de Marées H, *et al.* Relationship between the venoconstrictor activity of dihydroergotamine and its pharmacokinetics during acute and chronic oral dosing. *Eur J Clin Pharmacol* 1986; **30:** 685–9.
4. Humbert H, *et al.* Human pharmacokinetics of dihydroergotamine administered by nasal spray. *Clin Pharmacol Ther* 1996; **60:** 265–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dihydergot; ***Austria***: Detemes; DHE; Dihydergot; Ergont; Ergovasan; Migranal; ***Belg.***: Diergo; Dihydergot; Dystonal; ***Canad.***: Migranal; ***China***: Seglor (赛格乐); ***Cz.***: Dihydergot†; ***Fin.***: Orstanorm; ***Fr.***: Ikaran; Seglor; Tamik; ***Ger.***: Agit†; Angionorm†; DET MS; DHE†; Ergotam; Verladyn; ***Gr.***: Bobinum; Cozetamin; Dihydergot; Hemocinol; Pervone; Tusedon; Verteblan; Yugovasin; ***India***: DHE; Migranil; ***Indon.***: Dihydergot†; ***Ital.***: Diidergot; Seglor; ***Mex.***: Dihydergot; ***Neth.***: Migranal†; ***Port.***: Seglor; ***Spain***: Dihydergot†; ***Swed.***: Orstanorm; ***Switz.***: Dihydergot; Ergotonine†; ***Thai.***: Poligot; ***USA***: DHE; Migranal; ***Venez.***: Dihydergot.

Multi-ingredient Preparations. ***Arg.***: Polper Vascular; ***Austria***: Agilan; Effortil comp; Hypodyn†; Tonopan; Venotop†; ***Braz.***: Cefalium; Cefaliv; Enxak; Migraliv; Parcel; Tonopan; ***Chile***: Emagrim; Migratapsin†; Migrax; ***Fr.***: Diergospray; ***Ger.***: Dihydergot plus; Effortil plus†; ***Mex.***: Parsel; Tonopan; ***Spain***: Tonopan; ***Switz.***: Dihydergot plus†; Dihydergot; Effortil plus†; ***Venez.***: Brudol; Difen; Dol; Ivagan; Letydol; Parsel.

Pharmacopoeial Preparations

USP 36: Dihydroergotamine Mesylate Injection.

Eletriptan Hydrobromide

(BANM, USAN, rINNM)

Eletriptaanihydrobromidi; Élétriptan, Bromhydrate d'; Eletriptán, hidrobromuro de; Eletriptanhydrobromid; Eletriptani Hydrobromidum; Hidrobromuro de eletriptán; UK-116044-04; Элетриптана Гидробромид.

3-[[(*R*)-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl) ethyl]indole hydrobromide.

$C_{22}H_{26}N_2O_2S,HBr$=463.4

CAS — 143322-58-1 (eletriptan); 177834-92-3 (eletriptan hydrobromide).

ATC — N02CC06.

ATC Vet — QN02CC06.

UNII — M41W832TA3.

Uses and Administration

Eletriptan hydrobromide is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Eletriptan is given orally as the hydrobromide, but doses are expressed in terms of the base; eletriptan hydrobromide 24.2 mg is equivalent to about 20 mg of eletriptan.

UK licensed product information recommends a usual dose of 40 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. Doses of 80 mg may be used in subsequent attacks, but should not be repeated within a 24-hour period. US licensed product information allows a lower dose of 20 mg with a maximum single dose of 40 mg and a maximum daily dose of 80 mg. For doses in renal impairment, see below.

Administration in renal impairment. UK licensed product information for eletriptan recommends an oral dose of 20 mg in patients with mild to moderate renal impairment; the maximum daily dose should not exceed 40 mg. Eletriptan should not be used in severe impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Mathew NT, *et al.* Tolerability and safety of eletriptan in the treatment of migraine: a comprehensive review. *Headache* 2003; **43:** 962–74.
2. Takiya L, *et al.* Safety and efficacy of eletriptan in the treatment of acute migraine. *Pharmacotherapy* 2006; **26:** 115–28.
3. McCormack PL, Keating GM. Eletriptan: a review of its use in the acute treatment of migraine. *Drugs* 2006; **66:** 1129–49.
4. Sandrini G, *et al.* Eletriptan: a review and new perspectives. *Expert Rev Neurother* 2006; **6:** 1413–21.
5. Sandrini G, *et al.* Eletriptan. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1587–98.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Eletriptan should not be used in patients with severe hepatic impairment; however, this is due to a lack of data. No dosage adjustment is needed in mild or moderate hepatic impairment. Blood pressure effects of eletriptan are increased in renal impairment and therefore UK licensed product information recommends that it should be used with caution in patients with mild to moderate renal impairment; its use in those with severe renal impairment is contra-indicated.

Breast feeding. Eletriptan is distributed into breast milk. The licensed product information states that in a study of 8 women given a single, 80-mg dose of eletriptan, the mean total amount excreted into breast milk over 24 hours was 0.02% of the dose. Nonetheless, caution is advised when eletriptan is used in breast-feeding women; infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eletriptan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Eletriptan should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as erythromycin and ketoconazole; increased plasma levels of eletriptan have been noted after such combinations. It is recommended that eletriptan should not be taken within at least 72 hours of treatment with such drugs.

Pharmacokinetics

After oral doses eletriptan is rapidly and well absorbed (at least 81%) and has a bioavailability of about 50%. Peak plasma concentrations occur within 1.5 hours. Eletriptan is about 85% protein bound. It is mainly metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4. Non-renal clearance accounts for about 90% of the elimination of eletriptan and the plasma elimination half-life is about 4 hours. A small amount is distributed into breast milk.

References.
1. Shah AK, *et al.* Pharmacokinetics and safety of oral eletriptan during different phases of the menstrual cycle in healthy volunteers. *J Clin Pharmacol* 2001; **41:** 1339–44.
2. Shah AK, *et al.* The pharmacokinetics and safety of single escalating oral doses of eletriptan. *J Clin Pharmacol* 2002; **42:** 520–7.
3. Milton KA, *et al.* Pharmacokinetics, pharmacodynamics, and safety of the 5-$HT_{1B/1D}$ agonist eletriptan following intravenous and oral administration. *J Clin Pharmacol* 2002; **42:** 528–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Relpax; ***Austria***: Relpax; ***Belg.***: Relert; ***Canad.***: Relpax; ***Chile***: Relpax; ***Cz.***: Relpax; ***Denm.***: Relert; Relpax; ***Fin.***: Relert; ***Fr.***: Relpax; ***Ger.***: Relpax; ***Gr.***: Relpax; ***Hung.***: Relpax; ***Irl.***: Relpax; ***Israel***: Relert; ***Ital.***: Relpax; ***Mex.***: Relpax; ***Neth.***: Relpax; ***Norw.***: Relpax; ***Pol.***: Relpax; ***Port.***: Relert; ***Rus.***: Relpax (Релпакс); ***S.Afr.***: Relpax; ***Singapore***: Relpax; ***Spain***: Relert; Relpax; ***Swed.***: Relpax; ***Switz.***: Relpax; ***Thai.***: Relpax; ***Turk.***: Relpax; ***UK***: Relpax; ***USA***: Relpax.

Ergotamine Tartrate *(BANM, rINNM)*

Ergotamiinitartraatti; Ergotamin Tartarat; Ergotamin Tartrat; Ergotamina, tartrato de; Ergotamine, tartrate d'; Ergotamini Tartras; Ergotamino tartratas; Ergotamin-tartarát; Ergotamin-tartrat; Ergotaminy winian; Tartrato de ergotamina; Эрготамина Тартрат.

(5′*S*)-12′-Hydroxy-2′-methyl-5′-benzylergotaman-3′,6′,18-trione tartrate; (5′*S*)-12′-Hydroxy-2′-methyl-3′,6′,18-trioxo-5-benzylergotaman (+)-tartrate.

$(C_{33}H_{35}N_5O_5)_2,C_4H_6O_6$=1313.4

CAS — 113-15-5 (ergotamine); 379-79-3 (ergotamine tartrate).

ATC — N02CA02.

ATC Vet — QN02CA02.

UNII — MRU5XH3B48.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ergotamine Tartrate). Slightly hygroscopic, colourless crystals or a white or almost white crystalline powder. It may contain 2 molecules of methanol of crystallisation. Slightly soluble in alcohol. Aqueous solutions slowly become cloudy owing to hydrolysis; this may be prevented by the addition of tartaric acid. A 0.25% suspension in water has a pH of 4.0 to 5.5. Store in airtight glass containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Ergotamine Tartrate). Colourless odourless crystals or a white or yellowish-white crystalline powder. Soluble 1 in about 3200 of water, but soluble 1 in about 500 of water in the presence of a slight excess of tartaric acid; soluble 1 in 500 of alcohol. Store at a temperature not exceeding 8 degrees. Protect from light.

Stability in solution. References.
1. Kreilgård B, Kisbye J. Stability of ergotamine tartrate in aqueous solution. *Arch Pharm Chemi (Sci)* 1974; **2:** 1–13 and 38–49.

Uses and Administration

Ergotamine is an alkaloid derived from ergot (p. 2137.1). It has marked vasoconstrictor effects, and a partial agonist action at serotonin (5-HT) receptors; it also has a powerful oxytocic action on the uterus, although less so than ergometrine (p. 2136.2). It is used in migraine and cluster headache, and has been tried in orthostatic hypotension.

Ergotamine is commonly used as the tartrate. It is usually given orally, but has also been given sublingually, rectally, and by oral inhalation. It was formerly given by subcutaneous or intramuscular injection. Caffeine is sometimes given with ergotamine tartrate with the intention of improving the latter's absorption, although whether it does so is not clear. Antiemetics such as cyclizine hydrochloride are sometimes included in combination preparations with ergotamine tartrate.

Ergotamine is used in **migraine** unresponsive to non-opioid analgesics. However, its adverse effects limit its use and prevent use for prophylaxis. It is most effective when given as early as possible in a migraine attack, preferably during the prodromal phase.

The usual oral dose is 2 mg of ergotamine tartrate; if necessary, doses of 1 to 2 mg may be given at half-hourly intervals thereafter. Usually not more than 6 mg should be given in 24 hours; some licensed product information recommends not more than 8 mg for each attack. The recommended minimum interval between successive 24-hour courses is 4 days, and the total weekly dose is limited to a maximum of 12 mg, although some recommend a lower weekly limit of 10 mg. It is also recommended that patients should receive no more than 2 courses in each month. Similar doses may be given sublingually.

Ergotamine tartrate may also be given rectally as suppositories, especially if the oral route is not effective or not practicable. The rectal dose of ergotamine tartrate is 2 mg repeated, if necessary, one hour later. Usually, not more than 4 mg should be given for each attack and not more than 10 mg in one week with an interval of at least 4 days between successive 24-hour courses.

Ergotamine is used in patients with **cluster headache** to treat individual attacks of headache. Doses used are similar to those given to treat migraine. It has also been used to prevent headache attacks during cluster periods, when it is usually given daily in low doses for up to 2 weeks, either orally or rectally (see below).

Migraine and cluster headache. Ergotamine was formerly one of the main drugs used to treat acute attacks of migraine (p. 670.3) unresponsive to non-opioid analgesics, but triptan serotonin (5-HT_1) agonists such as sumatriptan are now preferred. Since ergotamine may exacerbate the nausea and vomiting that commonly develops as a migraine attack progresses it is often necessary to give an antiemetic as well. Poor oral bioavailability may be reduced further during a migraine attack and ergotamine has sometimes been given sublingually, rectally, or by oral inhalation. Adverse effects limit the dose that can be used for an individual attack and prevent the long-term use that would be required for migraine prophylaxis.

Ergotamine may be used similarly in cluster headache (p. 670.1) to treat individual headaches during a cluster period. Ergotamine is also used in low doses given orally or rectally for limited periods of up to 2 weeks in the prophylaxis of headache attacks during a cluster period. Regimens that have been tried for such prophylaxis include 1 to 2 mg of ergotamine tartrate given 1 to 2 hours before an expected attack or 1 to 2 hours before bedtime for nocturnal attacks. The total maximum dose of ergotamine tartrate that may be given weekly for the prevention of cluster headache is less well established than for the treatment of migraine. Ergotamine is often given for only 5 to 6 days in each week, which allows the patient to assess whether the cluster period has ended.

References.
1. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45:** 577–84.
2. Tfelt-Hansen P, *et al.* Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 2000; **123:** 9–18.
3. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache* 2003; **43:** 144–66.
4. Tfelt-Hansen PC, Koehler PJ. History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward. *Cephalalgia* 2008; **28:** 877–86.

Orthostatic hypotension. Ergotamine and dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p. 1634.3). Ergotamine is believed[1] to be less selective than dihydroergotamine (p. 672.3) in its actions and affects both venous capacitance and peripheral resistance.[2,3] However, the oral bioavailability of ergotamine is greater[2] than that of dihydroergotamine and there have also been some reports of successful treatment with inhaled[3,4] or rectal[5] ergotamine.

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39:** 74–85.
3. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153:** 474–85.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51:** 648–60.
5. Toh V, *et al.* Ergotamine use in severe diabetic autonomic neuropathy. *Diabet Med* 2006; **23:** 574–6.

Adverse Effects

The adverse effects of ergotamine may be attributed either to its effects on the CNS, or to vasoconstriction of blood vessels and possible thrombus formation.

After therapeutic doses nausea and vomiting commonly occur as a result of the direct emetogenic effect of ergotamine; some patients may also have abdominal pain. Weakness and muscle pains in the extremities and numbness and tingling of the fingers and toes may occur. There may occasionally be localised oedema and itching in hypersensitive patients. Treatment should be stopped if symptoms of vasoconstriction develop. Susceptible patients, especially those with sepsis, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine.

Symptoms of acute overdosage include nausea, vomiting, diarrhoea, extreme thirst, coldness, tingling, and itching of the skin, a rapid and weak pulse, hypertension or hypotension, shock, confusion, convulsions, and unconsciousness; fatalities have been reported. Further symptoms of peripheral vasoconstriction or of cardiovascular disturbances, as seen in chronic ergotamine poisoning, may also occur but may be delayed.

In chronic poisoning or ergotism, resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, severe circulatory disturbances may develop. The extremities, especially the feet and legs, become numb, cold, tingling, and pale or cyanotic, with muscle pain; there may be no pulse in the affected limb. Eventually gangrene develops in the toes and sometimes the fingers. Anginal pain, tachycardia or bradycardia, and hypertension or hypotension have been reported. Myocardial infarction has occurred rarely. Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Chronic, intractable headache (rebound headache) may occur and is also a major withdrawal symptom following the development of ergotamine dependence (see under Precautions, p. 675.1). Other adverse effects include confusion and convulsions. On rare occasions symptoms of vasoconstriction of blood vessels in the brain, eye, intestines, and kidneys occur. Anorectal ulceration, sometimes leading to rectal necrosis and stenosis or rectovaginal fistula, has been reported after excessive use of suppositories containing ergotamine.

Effects on the cardiovascular system. Reports[1-9] of adverse cardiovascular effects associated with ergotamine, including mention of fatalities.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.
2. Corrocher R, *et al.* Multiple arterial stenoses in chronic ergot toxicity. *N Engl J Med* 1984; **310:** 261.
3. Fisher PE, *et al.* Ergotamine abuse and extra-hepatic portal hypertension. *Postgrad Med J* 1985; **61:** 461–3.
4. Deviere J, *et al.* Ischemic pancreatitis and hepatitis secondary to ergotamine poisoning. *J Clin Gastroenterol* 1987; **9:** 350–2.
5. Galer BS, *et al.* Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache* 1991; **31:** 446–50.
6. Redfield MM, *et al.* Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* 1992; **117:** 50–2.
7. Lazarides MK, *et al.* Severe facial ischaemia caused by ergotism. *J Cardiovasc Surg* 1992; **33:** 383–5.
8. Hillis W, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341:** 1564–5. Correction. *ibid.*; **342:** 1310.
9. Zavaleta EG, *et al.* St. Anthony's fire (ergotamine induced leg ischemia)—a case report and review of the literature. *Angiology* 2001; **52:** 349–56.

Fibrosis. For reference to fibrosis associated with the use of ergotamine tartrate, see Methysergide Maleate, p. 677.2.

Treatment of Adverse Effects

Treatment of acute poisoning with ergotamine is symptomatic (see also p. 1537.1). Although the benefit of gastric decontamination is uncertain, activated charcoal may be given to patients who present within 1 hour of ingesting a toxic dose (more than 125 micrograms/kg in adults) or any amount in a child or in adults with peripheral vascular disease, ischaemic heart disease, severe infection, or hepatic or renal impairment. Alternatively, gastric lavage may be considered in adults within 1 hour of ingesting a potentially life-threatening overdose. In chronic poisoning, withdrawal of ergotamine may be all that is required in some patients.

In both acute and chronic poisoning, attempts must be made to maintain an adequate circulation to the affected parts of the body in order to prevent the onset of gangrene. In severe arterial vasospasm vasodilators such as sodium nitroprusside by intravenous infusion have been given; heparin and dextran 40 have also been advocated to minimise the risk of thrombosis. Analgesics may be required for severe ischaemic pain.

Cardiovascular effects. Sodium nitroprusside has been used in severe ergotamine poisoning for its vasodilating and hypotensive actions; it should, however, be used with care if hypotension is a symptom of poisoning. It is usually given by intravenous infusion[1-4] although there have also been reports of intra-arterial infusion for ergotamine-induced ischaemia;[5,6] for details of precautions, see p. 1498.1.

Many other drugs have been used in the treatment of circulatory disturbances induced by ergotamine. These include oral captopril,[7] alprostadil by intra-arterial infusion,[8,9] and glyceryl trinitrate by intravenous infusion.[10,11]

1. Carliner NH, *et al.* Sodium nitroprusside treatment of ergotamine-induced peripheral ischemia. *JAMA* 1974; **277:** 308–9.
2. Andersen PK, *et al.* Sodium nitroprusside and epidural blockade in the treatment of ergotism. *N Engl J Med* 1977; **296:** 1271–3.
3. Eurin B, *et al.* Ergot and sodium nitroprusside. *N Engl J Med* 1978; **298:** 632–3.
4. Carr P. Self-induced myocardial infarction. *Postgrad Med J* 1981; **57:** 654–5.
5. O'Dell CW, *et al.* Sodium nitroprusside in the treatment of ergotism. *Radiology* 1977; **124:** 73–4.
6. Whitsett TL, *et al.* Nitroprusside reversal of ergotamine-induced ischemia. *Am Heart J* 1978; **96:** 700.
7. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288:** 364.
8. Levy JM, *et al.* Prostaglandin E_1 for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Intervent Radiol* 1984; **7:** 28–30.
9. Horstmann R, *et al.* Kritische Extremitätenischämie durch Ergotismus: Behandlung mit intraarterieller Prostaglandin-E_1-Infusion. *Dtsch Med Wochenschr* 1993; **118:** 1067–71.
10. Husum B, *et al.* Nitroglycerin infusion for ergotism. *Lancet* 1979; **ii:** 794–5.

11. Tfelt-Hansen P, *et al.* Nitroglycerin for ergotism: experimental studies in vitro and in migraine patients and treatment of an overt case. *Eur J Clin Pharmacol* 1982; **22:** 105–9.

Precautions

Ergotamine tartrate is contra-indicated in patients with severe or uncontrolled hypertension, shock, severe or persistent sepsis, peripheral vascular disease, ischaemic heart disease, temporal arteritis, hyperthyroidism, or hepatic or renal impairment. It is also contra-indicated in those with basilar or hemiplegic migraine. Ergotamine tartrate should be used with care in patients with anaemia. It is contra-indicated in pregnancy because of its oxytocic effect (see also below).

Patients should be warned to keep within the recommended dosage. Some symptoms of overdosage may mimic those of migraine. Numbness or tingling of the extremities generally indicates that ergotamine should be stopped. Although ergotamine is used for limited periods in the prevention of episodic cluster headache, it should not be given prophylactically in other circumstances, as prolonged use may give rise to gangrene. Dependence has occurred with regular use of ergotamine tartrate even if dosage recommendations are adhered to (see below).

Dizziness and feelings of anxiety have been reported; if affected, patients should avoid driving or operating machinery.

Breast feeding. Although the last available guidance from the American Academy of Pediatrics included ergotamine among those drugs that may be given with caution to breast-feeding mothers,[1] it notes that maternal use in doses equivalent to those given for the treatment of migraine has been associated with vomiting, diarrhoea, and convulsions in nursing infants. UK licensed product information recommends that ergotamine tartrate should be avoided during breast feeding; the distribution of unchanged drug and metabolites into breast milk presents a risk of ergotism in the infant and repeated doses of ergotamine may impair lactation.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/01/09)

Cardiovascular disorders. US licensed product information contra-indicates the use of dihydroergotamine in patients with ischaemic heart disease and other cardiovascular disorders such as uncontrolled hypertension, peripheral arterial disease, or coronary artery vasospasm; it is also recommended that dihydroergotamine should not be given to those with a family history of ischaemic heart disease, to postmenopausal women, men aged over 40, or to those with other ischaemic risk factors such as hypertension, hypercholesterolaemia, smoking, diabetes, or obesity, unless cardiovascular evaluation to exclude such disease has been carried out. Similar precautions and contra-indications, which resemble those that apply to serotonin (5-HT_1) agonists such as sumatriptan (p. 681.2), may be applicable to other ergot derivatives used in migraine such as ergotamine.

In other countries, warnings concerning the use of ergot derivatives in patients with risk factors for myocardial ischaemia appear to be less stringent, although caution is clearly advisable.

Dependence. Dependence can develop insidiously when ergotamine tartrate is used for more than 2 days each week, even if total daily or weekly dosage recommendations are observed.[1] Individual reports indicate a state of addiction characterised by a predictable and irresistible pattern of drug usage, the development of tolerance to adverse effects, and a syndrome of withdrawal on stopping the drug. Ergotamine-dependent patients suffer from daily, or almost daily, migraine headaches, often referred to as medication-overuse headaches or 'rebound headaches', which are only alleviated by ergotamine. Intensifying headache with autonomic disturbances occurs within 24 to 48 hours of withdrawal of ergotamine and may continue for 72 hours or longer. As with other medication-overuse headaches (p. 670.2), supportive and symptomatic measures should be taken to treat the withdrawal syndrome.

1. Saper JR. Ergotamine dependency—a review. *Headache* 1987; **27:** 435–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, does not classify the porphyrinogenic risk for single-ingredient preparations containing ergotamine although combinations containing the drug are classified as porphyrinogenic; such products should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Pregnancy. Ergotamine is contra-indicated in pregnancy because of its oxytocic effect. Accidental dosage of ergotamine in the form of a *Cafergot* suppository (ergotamine tartrate 2 mg and caffeine 100 mg) to a patient at 39 weeks of pregnancy caused uterine contractions and fetal tachycardia.[1] An emergency caesarean section was undertaken because of suspected placental abruption but no clear signs of retroplacental haemorrhage were found. The neonate recovered quickly after delivery and had developed normally during the next 10 years.

Jejunal atresia has been reported[2] in an infant born prematurely to a woman who had taken ergotamine tartrate 6 to 8 mg daily, as *Cafergot* tablets, throughout her pregnancy. Two cases of Möbius syndrome (a condition characterised by facial paralysis as a result of hypoplasia of cranial nerve nuclei) have been associated with exposure to ergotamine during the first trimester of pregnancy.[3,4] In the first report[3] the mother had inadvertently been given three *Cafergot* suppositories within a period of 1 to 2 hours and at the time had uterine cramping and a bloody vaginal discharge. The second mother[4] had used 2-mg ergotamine suppositories on a regular basis during the first 8 weeks of pregnancy.

1. de Groot ANJA, *et al.* Ergotamine-induced fetal stress: review of side effects of ergot alkaloids during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **51:** 73–7.
2. Graham JM, *et al.* Jejunal atresia associated with Cafergot ingestion during pregnancy. *Clin Pediatr (Phila)* 1983; **22:** 226–8.
3. Graf WD, Shepard TH. Uterine contraction in the development of Möbius syndrome. *J Child Neurol* 1997; **12:** 225–7.
4. Smets K, *et al.* Ergotamine as a possible cause of Möbius sequence: additional clinical observation. *J Child Neurol* 2004; **19:** 398.

Interactions

The vasoconstrictor effects of ergotamine are enhanced by sympathomimetics such as adrenaline. There is also an increased risk of peripheral vasoconstriction during use of ergotamine with beta blockers.

Ergotamine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and consequently it should not be given with potent inhibitors of this isoenzyme; elevated ergotamine concentrations sufficient to cause ergotism may occur with azole antifungals, macrolide antibacterials such as erythromycin and clarithromycin, and HIV-protease inhibitors including indinavir and ritonavir. Use of tetracycline with ergotamine may also increase the risk of ergotism and should be avoided.

Ergotamine should not be used with or given until several hours *after stopping* a serotonin (5-HT_1) agonist, since there is an additional risk of prolonged vasospastic reactions; at least 6 hours is advised for almotriptan, rizatriptan, sumatriptan, and zolmitriptan, and at least 24 hours for eletriptan, frovatriptan, and naratriptan. Conversely, a delay is advised *before starting* a serotonin agonist in patients who have been receiving ergotamine: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of preparations containing ergotamine.

Antibacterials. Acute reactions ranging from minor ergotism[1] to severe vasospasm[2] have been reported in patients given *erythromycin* in addition to ergotamine. There are also reports of acute ergotism in patients given ergotamine tartrate with *clarithromycin*[3,4] or *troleandomycin*.[5] The theoretical possibility exists that there may be a similar interaction with *azithromycin*. Ergotism has also been reported in patients given erythromycin[6] or troleandomycin[7] with dihydroergotamine.

1. Lagier G, *et al.* Un cas d'ergotisme mineur semblant en rapport avec une potentialisation de l'ergotamine par l'éthylsuccinate d'érythromycine. *Therapie* 1979; **34:** 515–21.
2. Ghali R, *et al.* Erythromycin-associated ergotamine intoxication: arteriographic and electrophysiologic analysis of a rare cause of severe ischemia of the lower extremities and associated ischemic neuropathy. *Ann Vasc Surg* 1993; **7:** 291–6.
3. Horowitz RS, *et al.* Clinical ergotism with lingual ischemia induced by clarithromycin-ergotamine interaction. *Arch Intern Med* 1996; **156:** 456–8.
4. Ausband SC, Goodman PE. An unusual case of clarithromycin associated ergotism. *J Emerg Med* 2001; **21:** 411–13.
5. Matthews NT, Havill JH. Ergotism with therapeutic doses of ergotamine tartrate. *N Z Med J* 1979; **89:** 476–7.
6. Leroy F, *et al.* Dihydroergotamine-erythromycin-induced ergotism. *Ann Intern Med* 1988; **109:** 249.
7. Franco A, *et al.* Ergotisme aigu par association dihydroergotamine-triacétyloléandomycine. *Nouv Presse Med* 1978; **7:** 205.

Antidepressants. There have been isolated case reports[1] of the serotonin syndrome (p. 443.2) in patients given dihydroergotamine with *amitriptyline*, *imipramine*, *paroxetine*, or *sertraline*.

1. Mathew NT, *et al.* Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* 1996; **16:** 323–7.

Antimigraine drugs. Arterial occlusion has been reported[1] in 2 patients given *methysergide* with a high parenteral dosage of ergotamine for cluster headache; the combination should be avoided. Use of ergotamine as supplementary antimigraine medication in patients receiving *dihydroergotamine* is not recommended.

For reports of arterial vasoconstriction in patients taking *beta blockers* and antimigraine drugs, see below. See also Interactions, above for a comment on the risk of vasospastic reactions with serotonin (5-HT_1) agonists such as *sumatriptan*.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.

Antivirals. There have been reports of ergotism in patients given ergotamine with combination antiviral treatment for HIV infection. It was suggested that the ergotism might have been caused by inhibition of ergotamine metabolism by *ritonavir* in 4 cases,[1-4] *indinavir* in one,[5] and *nelfinavir*[6] in another. One of the patients given ritonavir,[4] who had taken three 1-mg tablets of ergotamine tartrate over the 4 days before presentation, also developed signs of cerebrovascular involvement and eventually went into an irreversible coma.

The metabolism of ergot alkaloids may be inhibited by *delavirdine* or *efavirenz*.

1. Caballero-Granado FJ, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and ritonavir in an AIDS patient. *Antimicrob Agents Chemother* 1997; **41:** 1207.
2. Montero A, *et al.* Leg ischemia in a patient receiving ritonavir and ergotamine. *Ann Intern Med* 1999; **130:** 329–30.
3. Liaudet L, *et al.* Severe ergotism associated with interaction between ritonavir and ergotamine. *BMJ* 1999; **318:** 771.
4. Pardo Rey C, *et al.* Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* 2003; **37:** e72–e73.
5. Rosenthal E, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and indinavir. *JAMA* 1999; **281:** 987.
6. Mortier E, *et al.* Ergotism related to interaction between nelfinavir and ergotamine. *Am J Med* 2001; **110:** 594.

Beta blockers. Peripheral vasoconstriction was reported in a patient with migraine after addition of *propranolol* to regular use of *Cafergot* (ergotamine and caffeine) suppositories twice daily.[1] This combination has been used without complication by others, who suggested that excessive dosage of ergotamine tartrate, rather than an interaction between ergotamine and propranolol, was responsible.[2] However, arterial vasoconstriction has been reported after use of methysergide with propranolol and *oxprenolol* with ergotamine.[3] Such combinations should therefore be used with caution.

1. Baumrucker JF. Drug interaction—propranolol and Cafergot. *N Engl J Med* 1973; **288:** 916–17.
2. Diamond S. Propranolol and ergotamine tartrate. *N Engl J Med* 1973; **289:** 159.
3. Venter CP, *et al.* Severe peripheral ischaemia during concomitant use of beta blockers and ergot alkaloids. *BMJ* 1984; **289:** 288–9.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to increase the oral bioavailability and plasma concentrations of dihydroergotamine in patients with orthostatic hypotension.[1]

1. Bobik A, *et al.* Low oral bioavailability of dihydroergotamine and first-pass extraction in patients with orthostatic hypotension. *Clin Pharmacol Ther* 1981; **30:** 673–9.

Tacrolimus. Ergotamine may inhibit the metabolism of tacrolimus by cytochrome P450 isoenzymes (see p. 1977.3).

Pharmacokinetics

Absorption of ergotamine from the gastrointestinal tract is poor and may be further decreased by the occurrence of gastric stasis during migraine attacks. Bioavailability is also reduced by a high first-pass hepatic metabolism. Ergotamine has been given rectally or by inhalation in an attempt to overcome these effects, with some improvement in absorption, but bioavailability is still about 5% or less. Absorption of sublingual ergotamine is very poor. There is considerable interindividual variation in the bioavailability of ergotamine, regardless of the route. Caffeine is sometimes included in oral and rectal preparations of ergotamine to improve the latter's absorption, although whether it does so is not clear. Drugs such as metoclopramide are sometimes given with the aim of alleviating gastric stasis and thus improve the absorption of ergotamine.

Plasma protein binding is about 93 to 98%. Ergotamine is metabolised extensively in the liver via the cytochrome P450 isoenzyme CYP3A4; the majority of metabolites are excreted in the bile. About 4% of a dose is excreted in the urine. Some of the metabolites are pharmacologically active. The elimination of ergotamine is biphasic; half-lives of about 2 and 21 hours have been reported for the 2 phases, respectively. Ergotamine or its metabolites have been detected in breast milk.

References.

1. Schmidt R, Panchamps A. Effect of caffeine on intestinal absorption of ergotamine in man. *Eur J Clin Pharmacol* 1974; **7:** 213–16.
2. Eadie MJ. Ergotamine pharmacokinetics in man: an editorial. *Cephalalgia* 1983; **3:** 135–8.
3. Perrin VL. Clinical pharmacokinetics of ergotamine in migraine and cluster headache. *Clin Pharmacokinet* 1985; **10:** 334–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ergokapton†; ***Chile***: Jaquedryl; ***Ger.***: Ergo-Kranit Migrane; ***Hung.***: Ergam; ***Ital.***: Ergotan; ***Philipp.***: Avamigran; ***Thai.***: Ergosia; Gynaemine; ***USA***: Ergomar.

Multi-ingredient Preparations. ***Arg.***: Cafergot; Cefalex Plus; Ibu-Tetralgin; Ibupirac Migra; Integrobe Plus; Migra Dioxadol; Migra Dorixina; Migral Compositum; Migral II; Migral; Mikesan; Solacil; Tetralgin Novo; Tetralgin; ***Austral.***: Cafergot; ***Austria***: Avamigran; Secokapton; Synkapton; ***Belg.***: Cafergot; ***Braz.***: Migrane; Neogrein; Ormigrein; ***Canad.***: Bellergal; Cafergot; Ergodryl; Gravergol†; ***Chile***: Cefadol; Cefalmin; Cinabel; Clonalgin Compuesto; Ergobelan; Ergonef; Esamigran; Fredol; Migra-Nefersil; Migragesic; Migranol; Migratam; Ultrimin; ***Denm.***: Ergokoffin; ***Fin.***: Anervan†; ***Fr.***: Gynergene Cafeine; ***Ger.***: Cafergot N†; ***Gr.***: Cafergot; Medalidon; ***Hong Kong***: Cafergot; ***Hung.***: Kefalgin; ***India***: Ergophen; Migranil; Migril; Mizeco; ***Indon.***: Bellapheen; Cafergot; Ericaf; ***Irl.***: Migranat†; ***Israel***: Cafergot†; Temigran†; ***Ital.***: Cafergot; Virdex; ***Malaysia***: Cafergot†; ***Mex.***: Cafergot; Caftar; Ergocaf; Optium; Sydolil; Trinergot; ***Neth.***: Cafergot; ***Norw.***: Anervan†; ***NZ***: Cafergot; ***Pol.***: Bellergot; Coffecorn; ***Port.***: Migretil; ***Rus.***: Bellataminal (Беллатаминал); Coffetamin (Кофетамин); Synkapton (Синкаптон); ***S.Afr.***: Cafergot; Migril; ***Singapore***: Cafergot; Caffox; ***Spain***: Cafergot; Hemicraneal; ***Swed.***: Anervan; ***Switz.***: Cafergot-PB†; Cafergot; ***Thai.***: Avamigran; Benera†; Cafergot; Degran; Hofergot; Migana; Neuramizone; Poligot-CF; Polygot; Tofago; ***Turk.***: Avmigran; Bellergal; Cafergot; Ergafein; ***UK***: Cafergot†; Migril; ***Ukr.***: Nomigren (Номигрен); ***USA***: Bel-Phen-Ergot S†; Bellamine†; Bellergal-S; Cafatine-PB; Cafatine; Cafergot; Ercaf; Folergot-DF; Migergot; Phenerbel-S; ***Venez.***: Ervostal; Migradorixina; Traveget.

Pharmacopoeial Preparations

BP 2014: Ergotamine Sublingual Tablets;

USP 36: Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Ergotamine Tartrate Inhalation Aerosol; Ergotamine Tartrate Injection; Ergotamine Tartrate Tablets.

Feverfew

Camomille, grande; Matrem; Matricaria; Mattram; Mutterkraut; Nať kopretiny řimbaby; Partenio; Reunuspäivänkakkara; Rimbaba Obyčajná; Spilcuţă; Tanaceti Parthenii Herba; Tanaceto; Vaistinių skaistenių žolė; Wermod Wen; Пиретрум Девичий; Őszi margitvirág; Девичья Трава.

ATC Herb — HN02CW5005 (Tanacetum parthenium: *leaf*).

UNII — 6GE7Z0761K (Tanacetum parthenium); *Z64FK7P217* (Tanacetum parthenium *leaf*).

Pharmacopoeias. In *Eur.* (see p. vii) and in *US*. *US* also describes Powdered Feverfew.

Ph. Eur. 8: (Feverfew). The dried, whole or fragmented aerial parts of *Tanacetum parthenium*. It contains not less than 0.2% of parthenolide ($C_{15}H_{20}O_3$ = 248.3), calculated with reference to the dried drug. It has a camphoraceous odour. Protect from light.

USP 36: (Feverfew). It consists of the dried leaves of *Tanacetum parthenium* (Asteraceae), collected when the plant is in flower. Store in a dry place. Protect from light.

Uses and Administration

Feverfew consists of the dried leaves of the plant *Tanacetum parthenium* (Asteraceae). It is a traditional herbal remedy used in the prophylaxis of migraine. Its effects have been attributed to the plant's content of sesquiterpene lactones, notably parthenolide. A preparation of the dried leaf powder, which has been standardised to provide a minimum of 0.2% parthenolide, is available in some countries. A suggested oral dose is 250 mg daily; a lower dose of 100 mg daily has also been given.

Extracts of feverfew, particularly parthenolide-free extracts which have been promoted as less sensitising, have been used for their supposed anti-inflammatory benefits in cosmetics and topical products.

Parthenolide has also been investigated for its antineoplastic potential.

Migraine. Feverfew is a traditional herbal remedy used in the prophylaxis of migraine (p. 670.3). Studies of standardised preparations of the freeze-dried powdered leaf have produced variable results in preventing or ameliorating migraine attacks, and a systematic review[1] has concluded that its efficacy in preventing migraine is unproven.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Rheumatoid arthritis. Feverfew has anti-inflammatory activity *in vitro* and has been tried in the treatment of rheumatic diseases. However, an evidence-based report by the Arthritis Research Campaign[1] in the UK considered that it was ineffective in rheumatoid arthritis (p. 13.2), although adverse effects were minor with short-term use.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 25/11/10)

Adverse Effects and Precautions

Most adverse effects noted with feverfew are mild and reversible. Mouth ulceration and soreness have been reported, and may be due to sensitisation; if they occur feverfew should be withdrawn. Contact dermatitis has also been reported. Gastrointestinal effects such as nausea, constipation or diarrhoea, and heartburn occur rarely and there have been spontaneous reports of eosinophilia, abnormal liver function tests, renal failure, Raynaud's phenomenon, and hypertension. Withdrawal symptoms such as rebound headache, anxiety, and insomnia have been seen in long-term users of feverfew who stop treatment suddenly.

Feverfew is reputed to have abortifacient properties and it is recommended that preparations should not be used in pregnancy.

Effects on the blood. There have been suggestions that feverfew may increase the risk of bleeding during surgery or in patients taking anticoagulants. However, although inhibition of platelet aggregation has been reported *in vitro* or in *animals* a review[1] of clinical studies noted that feverfew did not appear to affect haematological safety parameters.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Interactions

It has been suggested that feverfew may enhance the effects of anticoagulants (but see Effects on the Blood, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Migraine Aid; ***Braz.***: Enxamed†; Tanaceto†; Tenliv; ***Canad.***: Tanacet†; ***Pol.***: Mariomigran†; ***UK***: DiaFeverfew; DiaMigraine; Migraherb; Tanacet.

Multi-ingredient Preparations. ***Austral.***: Albizia Complex; Extralife Arthri-Care†; Extralife Migrai-Care†; Rehmannia Complex; ***Ital.***: Neuralta Migren.

Homoeopathic Preparations. ***Fr.***: Poconeol no 43.

Frovatriptan *(BAN, rINN)*

Frovatriptaani; Frovatriptán; Frovatriptanum; SB-209509AX (frovatriptan or frovatriptan succinate); VML-251 (frovatriptan or frovatriptan succinate); Фроватриптан.

(6*R*)-5,6,7,8-Tetrahydro-6-methylaminocarbazole-3-carboxamide.

$C_{14}H_{17}N_3O$=243.3

CAS — 158747-02-5.

ATC — N02CC07.

ATC Vet — QN02CC07.

UNII — H82Q2D5WA7.

Frovatriptan Succinate *(BANM, USAN, rINNM)*

Frovatriptan, Succinate de; Frovatriptán, succinato de; Frovatriptani Succinas; SB-209509AX (frovatriptan or frovatriptan succinate); Succinato de frovatriptán; VML-251 (frovatriptan or frovatriptan succinate); Фроватриптана Сукцинат.

$C_{14}H_{17}N_3O,C_4H_6O_4,H_2O$=379.4

CAS — 158930-17-7.

ATC — N02CC07.

ATC Vet — QN02CC07.

UNII — D28J6W18HY.

Uses and Administration

Frovatriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Frovatriptan is given orally as the succinate although doses are expressed in terms of the base; frovatriptan succinate 3.9 mg is equivalent to about 2.5 mg of frovatriptan.

The recommended dose is 2.5 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of at least 2 hours. The maximum dose of frovatriptan in 24 hours is 5 mg in the UK although, in the USA, a maximum daily dose of 7.5 mg is allowed.

Reviews.

1. Markus F, Mikko K. Frovatriptan review. *Expert Opin Pharmacother* 2007; **8:** 3029–33.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Poolsup N, *et al.* Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005; **30:** 521–32.
2. Markus F, Mikko K. Frovatriptan review. *Expert Opin Pharmacother* 2007; **8:** 3029–33.
3. Elkind AH, MacGregor EA. Frovatriptan for the acute treatment of migraine and prevention of predictable menstrual migraine. *Expert Rev Neurother* 2008; **8:** 723–36.
4. Guidotti M, Ravasio R. Clinical and economic comparison of frovatriptan versus other oral triptans in the treatment of acute migraine in the real-world setting. *Clin Drug Investig* 2009; **29:** 693–702.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

UK licensed product information recommends that frovatriptan should not be used in patients with severe hepatic impairment (Child-Pugh class C); however, this is due to a lack of data and no dosage adjustment is needed in mild or moderate hepatic impairment.

Interactions

As for Sumatriptan, p. 681.3.

Frovatriptan is metabolised by the cytochrome P450 isoenzyme CYP1A2; fluvoxamine, a potent inhibitor of this isoenzyme, has been shown to increase the blood concentrations of frovatriptan by 27 to 49%.

Pharmacokinetics

After oral doses, peak plasma-frovatriptan concentrations occur in 2 to 4 hours, and bioavailability is about 20% in men and 30% in women. Food may delay the time to peak plasma concentrations by about 1 hour. Frovatriptan is 15% protein bound. It is mainly metabolised by the hepatic cytochrome P450 isoenzyme CYP1A2. About 32% of an oral dose is excreted in the urine and 62% in faeces. The plasma elimination half-life of frovatriptan is about 26 hours.

Distribution into milk has been found in studies in *rats*.

References.

1. Buchan P, *et al.* Clinical pharmacokinetics of frovatriptan. *Headache* 2002; **42** (suppl 2): S54–S62.
2. Elkind AH, *et al.* Pharmacokinetics of frovatriptan in adolescent migraineurs. *J Clin Pharmacol* 2004; **44:** 1158–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Eumitan; Frovamig; ***Belg.***: Provatex; Migard; ***Canad.***: Frova; ***Cz.***: Fromen; Recur; ***Denm.***: Migard; ***Fin.***: Migard; Tigreat†; ***Fr.***: Isimig; Tigreat; ***Ger.***: Allegro; ***Gr.***: Migard; Migralin; Pitunal; ***Irl.***: Frovex; ***Ital.***: Auradol; Rilamig; ***Neth.***: Fromirex; Migard; ***Port.***: Dorlise; Migard; ***Spain***: Forvey; Perlic; ***Swed.***: Migard; ***Switz.***: Menamig; ***Turk.***: Newart; ***UK***: Migard; ***USA***: Frova.

Iprazochrome *(rINN)*

Ipratsokromi; Iprazochromum; Iprazocromo; Iprazokrom; Ипразохром.

3-Hydroxy-1-isopropyl-5,6-indolinedione 5-semicarbazone.

$C_{12}H_{16}N_4O_3$=264.3

CAS — 7248-21-7.

ATC — N02CX03.

ATC Vet — QN02CX03.

UNII — 903A9K181P.

Profile

Iprazochrome is a serotonin antagonist used in the prophylaxis of migraine (p. 670.3) and in the management of diabetic retinopathy. It has been given in usual oral doses of 2.5 to 5 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Divascan; ***Pol.***: Divascan.

Lomerizine Hydrochloride *(rINNM)*

Flometizine Hydrochloride; Hidrocloruro de lomerizina; KB-2796; Lomérizine, Chlorhydrate de; Lomerizine Dihydrochloride; Lomerizini Hydrochloridum; Ломеризина Гидрохлорид.

1-[Bis(*p*-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl) piperazine dihydrochloride.

$C_{27}H_{30}F_2N_2O_3$,2HCl=541.5

CAS — 101477-55-8 (lomerizine); 101477-54-7 (lomerizine hydrochloride).
UNII — 3W473D5LIY.

Profile

Lomerizine is a calcium-channel blocker that is used orally as the hydrochloride in the treatment of migraine. It is also under investigation for its potential value in glaucoma.

References.

1. Hara H, *et al.* Clinical potential of lomerizine, a Ca_{2+} channel blocker as an anti-glaucoma drug: effects on ocular circulation and retinal neuronal damage. *Cardiovasc Drug Rev* 2004; **22:** 199–214.
2. Iwasaki S, *et al.* Migraine-associated vertigo: clinical characteristics of Japanese patients and effect of lomerizine, a calcium channel antagonist. *Acta Otolaryngol* 2007; (suppl 559): 45–9.
3. Imai N, *et al.* Do the effects of long-term lomerizine administration differ with age? *Intern Med* 2007; **46:** 683–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Hou Pu (后普); Luo Mei Er (罗美达); Qing Tian (清天); Shao Rong (绍容); Tesuxin (特苏欣); Xi Rui Li (西瑞利); XiJing (希静); Ya Yi Jia (亚伊加); ***Jpn***: Migsis; Terranas.

Methysergide *(BAN, USAN, rINN)*

1-Methyl-D-lysergic Acid Butanolamide; Methysergid; Méthysergide; Methysergidum; Metisergida; Metysergid; Metysergidi; Метизергид.
N-[1-(Hydroxymethyl)propyl]-1-methyl-D-lysergamide; 9,10-Didehydro-*N*-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8β-carboxamide.
$C_{21}H_{27}N_3O_2$=353.5
CAS — 361-37-5.
ATC — N02CA04.
ATC Vet — QN02CA04.
UNII — XZA9HY6Z98.

Methysergide Maleate *(BANM, rINNM)*

Maleato de metisergida; Méthysergide, Maléate de; Methysergidi Maleas; Metisergida, maleato de; Метизергида Малеат.
$C_{21}H_{27}N_3O_2.C_4H_4O_4$=469.5
CAS — 129-49-7.
ATC — N02CA04.
ATC Vet — QN02CA04.
UNII — 2U7H1466GH.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Methysergide Maleate). A white or almost white crystalline powder which may have a yellow or pink tinge; odourless or almost odourless. Slightly soluble in water and in methyl alcohol; practically insoluble in chloroform and in ether. A 0.2% solution in water has a pH of 3.7 to 4.7. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Methysergide Maleate). A white to yellowish-white or reddish-white, crystalline powder. Is odourless or has not more than a slight odour. Soluble 1 in 200 of water and 1 in 165 of alcohol; soluble 1 in 3400 of chloroform; practically insoluble in ether. pH of a 1 in 500 solution is between 3.7 and 4.7. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Methysergide maleate is a semisynthetic ergot alkaloid. It is a potent serotonin antagonist and, compared with ergotamine, has only weak vasoconstrictor and oxytocic effects. It may be used to prevent severe recurrent migraine (p. 670.3) and headache attacks during cluster periods (p. 670.1), although its use has declined because of adverse effects. It is ineffective in the treatment of acute attacks.

Methysergide is given orally as the maleate but doses are often expressed in terms of the base; 1.33 mg of methysergide maleate is equivalent to about 1 mg of methysergide. A usual dosage is 2 to 6 mg daily given in divided doses with meals. It is suggested that treatment should be started with 1 mg at bedtime and doses increased gradually over about 2 weeks; the minimum effective dose should be used. Careful and regular observation of the patient is essential because of the high incidence of adverse effects and it is recommended that treatment should only be carried out under hospital supervision. If treatment still proves to be ineffective after 3 weeks, further use is unlikely to be of benefit. Treatment should not be continued for more than 6 months, after which it should be gradually withdrawn over 2 or 3 weeks and then stopped for at least a month for reassessment. Some have considered that treatment courses should not exceed 3 months without a break.

Methysergide maleate has also been used to control diarrhoea associated with carcinoid syndrome (see under Neuroendocrine Tumours, p. 716.3) in high doses equivalent to 12 to 20 mg of methysergide daily.

As a serotonin antagonist, methysergide might be expected to help reverse the serotonin syndrome (p. 443.2).

Reviews.

1. Koehler PJ, Tfelt-Hansen PC. History of methysergide in migraine. *Cephalalgia* 2008; **28:** 1126–35.

Adverse Effects

Gastrointestinal effects such as nausea, vomiting, heartburn, and abdominal pain are common on initial treatment with methysergide maleate, as are dizziness and drowsiness. Other CNS effects reported include ataxia, insomnia, weakness, restlessness, lightheadedness, euphoria, and hallucinations. Peripheral or localised oedema, leg cramps, and weight gain have occurred and there have been occasional reports of rashes, loss of hair, joint and muscle pain, neutropenia, and eosinophilia. Orthostatic hypotension and tachycardia have been noted. There have been isolated reports of myocardial infarction particularly in patients with ischaemic heart disease or when given with other vasoconstrictive drugs, both of which are contra-indications for methysergide therapy.

Arterial spasm has occurred in some patients, and may present as paraesthesia of the extremities or anginal pain, as with ergotamine (p. 674.2); if such symptoms occur methysergide should be withdrawn, although rebound headaches may occur if it is withdrawn suddenly. Vascular insufficiency of the lower limbs may represent arterial spasm or fibrotic changes. Treatment should be stopped at the first signs of impaired peripheral circulation. Retroperitoneal fibrosis, with obstruction of abdominal blood vessels and ureters, pleuropulmonary fibrosis, and fibrotic changes in heart valves have occurred in patients on long-term treatment. Methysergide must be withdrawn immediately if fibrosis occurs. Retroperitoneal fibrosis is usually reversible, but other fibrotic changes are less readily reversed.

Effects on the skin. Scleroderma-like changes to the legs, in addition to aortic fibrosis in the absence of retroperitoneal fibrosis, was associated with long-term methysergide therapy in a 63-year old woman.[1] The patient presented with a 2-month history of inflammatory oedema of the legs and feet.

1. Kluger N, *et al.* Methysergide-induced scleroderma-like changes of the legs. *Br J Dermatol* 2005; **153:** 224–5.

Fibrosis. Fibrosis has been associated with the long-term use of methysergide maleate. In one early report[1] in 27 patients retroperitoneal fibrosis was attributed to use of methysergide for periods of 9 to 54 months in doses ranging from 2 to 28 mg daily. There was partial or complete regression of fibrosis in 13 of the patients whose treatment was withdrawn. Improvement usually began within a few days, in some cases with the aid of prednisone. The other 14 patients were treated by surgery; those few who continued taking methysergide had difficult postoperative courses. Cardiac murmurs occurred in 7 patients, and regressed wholly or partially in 3 after therapy was stopped. Fibrotic changes affecting the aorta, heart valves, and pulmonary tissues occurred in a few of the patients. Others have reported the development of endocardial fibrosis indicated by cardiac murmurs in 48 patients receiving methysergide.[2] The murmurs gradually regressed in 27 when methysergide was stopped. Retroperitoneal fibrosis was present in 9 patients and pleuropulmonary fibrosis in 2. A patient with fibrosis of the iliac vein has been described.[3]

A few cases of retroperitoneal fibrosis associated with ergotamine tartrate or dihydroergotamine have also been noted.[1] These 2 drugs have also been implicated in a few other cases of retroperitoneal fibrosis or other fibrotic disorders in patients taking high doses for long periods.[4-7]

1. Graham JR, *et al.* Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med* 1966; **274:** 359–68.
2. Bana DS, *et al.* Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *Am Heart J* 1974; **88:** 640–55.
3. Bucci JA, Manoharan A. Methysergide-induced retroperitoneal fibrosis: successful outcome and two new laboratory features. *Mayo Clin Proc* 1997; **72:** 1148–50.
4. Lepage-Savary D, Vallières A. Ergotamine as a possible cause of retroperitoneal fibrosis. *Clin Pharm* 1982; **1:** 179–80.
5. Robert M, *et al.* Fibrotic processes associated with long-term ergotamine therapy. *N Engl J Med* 1984; **311:** 601 and 602.
6. Damstrup L, Jensen TT. Retroperitoneal fibrosis after long-term daily use of ergotamine. *Int Urol Nephrol* 1986; **18:** 299–301.
7. Malaquin F, *et al.* Pleural and retroperitoneal fibrosis from dihydroergotamine. *N Engl J Med* 1989; **321:** 1760.

Treatment of Adverse Effects

As for Ergotamine Tartrate, p. 674.3.

Methysergide maleate should be withdrawn immediately if fibrosis develops. Corticosteroids have been used to treat fibrosis, although surgery may be required.

Precautions

As for Ergotamine Tartrate, p. 675.1.

In addition, methysergide maleate is contra-indicated in valvular heart disease, pulmonary and collagen diseases, diseases of the urinary tract, phlebitis and cellulitis of the lower extremities, and debilitated states. It should be used with caution in patients with peptic ulcer disease because it may increase gastric acidity. Patients should be closely supervised. Methysergide should not be given continuously for more than 6 months and should normally be withdrawn gradually (see Uses and Administration, above). However, it should be withdrawn immediately if symptoms of fibrosis or arterial spasm develop.

Interactions

Interactions involving those ergot alkaloids used mainly in the management of migraine are discussed under ergotamine (p. 675.2). References specific to methysergide may be found there under the headings Antimigraine Drugs (p. 675.2) and Beta Blockers (p. 675.3).

Pharmacokinetics

Methysergide maleate is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about one hour of ingestion. It is 66% bound to plasma proteins. Methysergide undergoes extensive first-pass hepatic metabolism to methylergometrine (p. 2137.3). About 50% of an oral dose is excreted in the urine as unchanged drug and metabolites. The elimination of methysergide is biphasic; half-lives of about 2.7 hours and 10 hours have been reported for the 2 phases respectively.

References.

1. Bredberg U, *et al.* Pharmacokinetics of methysergide and its metabolite methylergometrine in man. *Eur J Clin Pharmacol* 1986; **30:** 75–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Deseril; ***Belg.***: Deseril; ***Braz.***: Deserila; ***Canad.***: Sansert†; ***Fr.***: Desernil; ***Neth.***: Deseril; ***UK***: Deseril†.

Pharmacopoeial Preparations
BP 2014: Methysergide Tablets;
USP 36: Methysergide Maleate Tablets.

Naratriptan Hydrochloride

(BANM, USAN, rINNM)

GR-85548A; GR-85548X (naratriptan); Hidrocloruro de naratriptán; Naratriptan, Chlorhydrate de; Naratriptán, hidrocloruro de; Naratriptani Hydrochloridum; Наратриптана Гидрохлорид.
N-Methyl-3-(1-methyl-4-piperidyl)indole-5-ethanesulfonamide hydrochloride.
$C_{17}H_{25}N_3O_2S,HCl$=371.9
CAS — 121679-13-8 (naratriptan); 121679-19-4 (naratriptan hydrochloride); 143388-64-1 (naratriptan hydrochloride).
ATC — N02CC02.
ATC Vet — QN02CC02.
UNII — 10X8X4P12Z.

Pharmacopoeias. In *US.*

USP 36: (Naratriptan Hydrochloride). A white to pale yellow solid. Soluble in water. Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Naratriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. It is given orally as the hydrochloride, and doses are expressed in terms of the base; naratriptan hydrochloride 1.11 mg is equivalent to about 1 mg of naratriptan.

The recommended dose of naratriptan in the UK is 2.5 mg; in the USA a dose of 1 or 2.5 mg is allowed. If no response is obtained with the initial dose, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of 4 hours, to a maximum of 5 mg in any 24-hour period. For doses in hepatic or renal impairment see below.

Administration in hepatic or renal impairment. Naratriptan is contra-indicated in patients with severe hepatic (Child-Pugh class C) or severe renal impairment (creatinine clearance less than 15 mL/minute). In patients with mild to moderate hepatic or renal impairment, the recommended maximum oral dose in 24 hours is 2.5 mg and a lower starting dose should be considered.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Safety* 2004; **13:** 73–82.
2. Tfelt-Hansen PC. Published and not fully published double-blind, randomised, controlled trials with oral naratriptan in the treatment of migraine: a review based on the GSK Trial Register. *J Headache Pain* 2011; **12:** 399–403.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Naratriptan should not be used in patients with severe hepatic (Child-Pugh class C) or renal (creatinine clearance less than 15 mL/minute) impairment. Naratriptan should be used with caution in mild or moderate renal or hepatic impairment. Patients with hypersensitivity to sulfonamides may theoretically show a similar reaction to naratriptan. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

Medication-overuse headache. For a report of an association between naratriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p. 681.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naratriptan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Pharmacokinetics

After oral doses, peak plasma-naratriptan concentrations occur at 2 to 3 hours, and bioavailability is reported to be 63% in men and 74% in women. Plasma protein binding is about 29%. Naratriptan undergoes some hepatic metabolism via a wide range of cytochrome P450 isoenzymes. It is mainly excreted in the urine with 50% of a dose being recovered as unchanged drug and 30% as inactive metabolites. The elimination half-life is 6 hours, and is significantly prolonged in patients with renal or hepatic impairment.

Distribution into milk has been found in studies in *rats.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Naramig; ***Austral.***: Naramig; ***Austria***: Antimigrin†; Naramig; ***Belg.***: Naramig; ***Braz.***: Naramig; Naratrin; ***Canad.***: Amerge; ***Chile***: Bagomigral; Migtal; Miragran; Naramig; ***Cz.***: Naramig; ***Denm.***: Naragran; Naramig; ***Fin.***: Naramig; ***Fr.***: Naramig; ***Ger.***: Formigran; Naramig; ***Gr.***: Naramig; ***India***: Naratrex; ***Irl.***: Naramerg†; Naramig; Naraverg; ***Israel***: Naramig; ***Mex.***: Naramig†; ***Neth.***: Migatane; Naramig; ***Norw.***: Naramig; ***NZ***: Naramig; ***Port.***: Naramig; ***Rus.***: Naramig (Нарамиг); ***S.Afr.***: Naramig; ***Singapore***: Naramig; ***Spain***: Naramig; ***Swed.***: Naramig; ***Switz.***: Naramig; ***Turk.***: Naramig; ***UK***: Naramig; ***USA***: Amerge.

Pharmacopoeial Preparations
USP 36: Naratriptan Hydrochloride Oral Suspension; Naratriptan Tablets.

Oxetorone Fumarate *(USAN, rINNM)*

Fumarato de oxetorona; L-6257; Oxetorona, fumarato de; Oxétorone, Fumarate d'; Oxetoroni Fumaras; Оксеторона Фумарат.

3-(6,12-Dihydrobenzofuro[3,2-*c*][1]benzoxepin-6-ylidene)-*NN*-dimethylpropylamine hydrogen fumarate.

$C_{21}H_{21}NO_2.C_4H_4O_4$=435.5

CAS — 26020-55-3 (oxetorone); 34522-46-8 (oxetorone fumarate).

ATC — N02CX06.

ATC Vet — QN02CX06.

UNII — 5SYZ8I05SH.

Profile

Oxetorone fumarate is an antihistamine and serotonin antagonist used orally in the treatment of migraine (p. 670.3) and cluster headache (p. 670.1) in doses of up to 180 mg daily. Oxetorone was reported to have induced hyperplastic changes in breast tissue and the uterine endometrium of *rodents.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Nocertone†; ***Fr.***: Nocertone; ***Gr.***: Nocertone.

Pizotifen *(BAN, rINN)*

BC-105; Pitsotifeeni; Pizotifène; Pizotifeno; Pizotifenum; Pizotyfen; Pizotyline (USAN); Пизотифен.

9,10-Dihydro-4-(1-methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene.

$C_{19}H_{21}NS$=295.4

CAS — 15574-96-6.

ATC — N02CX01.

ATC Vet — QN02CX01.

UNII — 0BY8440V3N.

Pharmacopoeias. In *Chin.*

Pizotifen Malate *(BANM, rINNM)*

Malato de pizotifeno; Pizotifen Hydrogen Malate; Pizotifène, Malate de; Pizotifeni Malas; Pizotifeno, malato de; Pizotyline Malate; Пизотифена Малат.

$C_{19}H_{21}NS,C_4H_6O_5$=429.5

CAS — 5189-11-7.

ATC — N02CX01.

ATC Vet — QN02CX01.

Pharmacopoeias. In *Br.*

BP 2014: (Pizotifen Malate). A white or slightly yellowish-white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Protect from light.

Uses and Administration

Pizotifen is a sedating antihistamine (p. 610.1) that has strong serotonin antagonist and weak antimuscarinic properties. It also antagonises the action of tryptamine. Pizotifen is used, usually as the malate, for the prophylaxis of migraine and for the prevention of headache attacks during cluster periods. It is not effective in treating an acute attack. Doses of pizotifen malate are expressed in terms of the base; pizotifen malate 1.45 mg is equivalent to about 1 mg of pizotifen. Pizotifen hydrochloride has also been used in the management of migraine.

The usual oral dose is the equivalent of 1.5 mg of pizotifen daily either in three divided doses or as a single dose at night. Gradual increase from an initial dose of 500 micrograms may help to avoid undue drowsiness. Doses may vary from 500 micrograms up to a maximum of 4.5 mg daily; not more than 3 mg should be given as a single dose.

For details of doses in children, see below.

Administration in children. For the prophylaxis of migraine and for the prevention of headache attacks during cluster periods, children aged over 2 years may be given up to 1.5 mg daily of pizotifen orally, although the maximum single dose (at night) should not exceed 1 mg. Gradual increase from an initial dose of 500 micrograms may help to avoid undue drowsiness.

Abdominal migraine. Abdominal migraine is a recurrent disorder seen mainly in children and characterised by episodic midline abdominal pain lasting for up to 72 hours. The pain is severe enough to disrupt normal activities and may be associated with pallor, anorexia, nausea, and vomiting.[1,2] Sleep, and sometimes vomiting, terminate the attack.

In one small study pizotifen was found to be effective for the prophylaxis of abdominal pain in children with abdominal migraine;[3] however, a systematic review concluded that there was only weak evidence in favour of such use in recurrent abdominal pain and suggested that pizotifen should only be used in the context of clinical trials or in children with severe problems refractory to conventional management.[4] Prophylactic treatment with propranolol or cyproheptadine may also be of benefit.[5]

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/cha.2004.24.issue-s1/issuetoc (accessed 12/08/10)
2. Russell G, *et al.* The child with recurrent abdominal pain: is it abdominal migraine? *Br J Hosp Med* 2007; **68:** M110–M113.
3. Symon DNK, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995; **72:** 48–50.
4. Huertas-Ceballos A, *et al.* Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 14/12/10).
5. Worawattanakul M, *et al.* Abdominal migraine: prophylactic treatment and follow-up. *J Pediatr Gastroenterol Nutr* 1999; **28:** 37–40.

Migraine and cluster headache. Pizotifen has been widely used for the prophylaxis of migraine (p. 670.3) but evidence for its efficacy is limited. It has also been tried in the management of cluster headache (p. 670.1) to prevent headache attacks during a cluster period.

References.

1. Cleland PG, *et al.* Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997; **38:** 31–8.
2. Barnes N, Millman G. Do pizotifen or propranolol reduce the frequency of migraine headache? *Arch Dis Child* 2004; **89:** 684–5.

Adverse Effects and Precautions

As for the sedating antihistamines in general, see p. 613.1 and p. 613.3.

Increased appetite and weight gain may occur with pizotifen. Drowsiness may be troublesome.

Incidence of adverse effects. Adverse effects were noted in 22 of 47 patients with severe migraine given pizotifen 1 to 2 mg daily.[1] These reactions included weight increase (15 patients), muscle pain or cramps (3 patients), heavy or restless legs (3 patients), fluid retention (3 patients), drowsiness (2 patients), more frequent milder headaches (2 patients), facial flushing (1 patient), reduced libido (1 patient), exacerbation of epilepsy (1 patient), and dreaming (2 patients). Adverse effects necessitating withdrawal occurred in 11 patients.

1. Peet KMS. Use of pizotifen in severe migraine: a long-term study. *Curr Med Res Opin* 1977; **5:** 192–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pizotifen as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Interactions

As for the sedating antihistamines in general, see p. 614.3.

Antihypertensives. After a report[1] of loss of blood pressure control when treatment with pizotifen was started in a patient receiving *debrisoquine* the manufacturer suggested that since pizotifen had a similar chemical structure to the tricyclic antidepressants it might antagonise the actions of adrenergic neurone blockers in a similar manner.

1. Bailey RR. Antagonism of debrisoquine sulphate by pizotifen (Sandomigran). *N Z Med J* 1976; **1:** 449.

Pharmacokinetics

Pizotifen is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 5 hours after a single oral dose. Over 90% is bound to plasma proteins. Pizotifen undergoes extensive metabolism. Over half of a dose is excreted in the urine, mainly as metabolites; a significant proportion is excreted in the faeces. The primary metabolite of pizotifen (*N*-glucuronide conjugate) has a long elimination half-life of about 23 hours.

Distribution into milk has been found in *animal* studies.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sandomigran; ***Austral.***: Sandomigran; ***Belg.***: Sandomigran; ***Braz.***: Sandomigran; ***Canad.***: Sandomigran; ***Cz.***: Sandomigran; ***Denm.***: Sandomigrin; ***Fr.***: Sanmigran; ***Gr.***: Mosegor; ***Hong Kong***: Sandomigran; ***Indon.***: Lysagor; ***Irl.***: Sanomigran; ***Ital.***: Sandomigran; ***Malaysia***: Sandomigran; ***Neth.***: Sandomigran; ***NZ***: Sandomigran; ***Philipp.***: Litec; Mor-Vita; Mosegor; ***Pol.***: Polomigran; ***S.Afr.***: Sandomigran; ***Spain***: Mosegor; Sandomigran; ***Swed.***: Sandomigrin; ***Switz.***: Mosegor†; ***Thai.***: Anorsia; Bozo; Manzofen; Migrin; Mosegor; Moselar; Mozifen-EF; Pizomed; Zofen; ***Turk.***: Sandomigran; ***UK***: Sanomigran.

Multi-ingredient Preparations. ***Philipp.***: Appetens; Mosegor Vita.

Pharmacopoeial Preparations
BP 2014: Pizotifen Tablets.

Rizatriptan Benzoate

(BANM, USAN, pINNM)

Benzoato de rizatriptán; MK-0462; MK-462; Ritsatriptaanibentsoaatti; Rizatriptan, Benzoate de; Rizatriptán, benzoato de; Rizatriptani Benzoas; Ризатриптана Бензоат.

3-[2-(Dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl) indole monobenzoate; Dimethyl{2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)indol-3-yl]ethyl}amine monobenzoate.

$C_{15}H_{19}N_5.C_7H_6O_2$=391.5

CAS — 144034-80-0 (rizatriptan); 145202-66-0 (rizatriptan benzoate).
ATC — N02CC04.
ATC Vet — QN02CC04.
UNII — WR978S7QHH.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Rizatriptan Benzoate). A white or almost white powder or crystals. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. It shows polymorphism.

USP 36: (Rizatriptan Benzoate). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane.

Uses and Administration

Rizatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (below). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Rizatriptan is given as the benzoate, and doses are expressed in terms of the base; rizatriptan benzoate 14.5 mg is equivalent to about 10 mg of rizatriptan.

The licensed dose in the UK of rizatriptan is the equivalent of 10 mg orally. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, a further dose of 10 mg may be taken after an interval of at least 2 hours. In the USA licensed doses of 5 or 10 mg are used. The recommended maximum dose in 24 hours is 20 mg in the UK and 30 mg in the USA. A reduced dose of 5 mg is recommended in patients also receiving propranolol (see Interactions, below), with the maximum dose in 24 hours reduced to 10 mg in the UK and 15 mg in the USA. It is also recommended that doses of the 2 drugs should be separated by at least 2 hours.

For doses in children and in hepatic or renal impairment, see below.

Administration in children. In the USA, rizatriptan is licensed for the treatment of acute migraine in children and adolescents aged 6 to 17 years. A single oral dose of 5 mg may be given to children weighing less than 40 kg and 10 mg to those weighing 40 kg or more. In children also receiving propranolol (see Interactions, below), a single dose of rizatriptan 5 mg is recommended in those who weigh 40 kg or more; however, it should not be given to those who weigh less than 40 kg. The safety and efficacy of a second dose have not been established.

Administration in hepatic or renal impairment. UK licensed product information recommends that in patients with mild to moderate hepatic or renal impairment, the oral dose of rizatriptan should be reduced to 5 mg. If the headache recurs after an initial response, a further dose of 5 mg may be taken after an interval of at least 2 hours. The recommended maximum dose in 24 hours in these patients is 10 mg. It is also recommended that rizatriptan should not be used in patients with severe hepatic or renal impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

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Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2. Toxic epidermal necrolysis has also been reported with rizatriptan.

Rizatriptan should be given with caution to patients with mild or moderate hepatic or renal impairment; UK licensed product information contra-indicates its use in more severe impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rizatriptan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Propranolol increases plasma-rizatriptan concentrations and it is recommended that lower doses of rizatriptan should be used in patients receiving both drugs (see Uses and Administration, above).

Pharmacokinetics

After oral doses, peak plasma-rizatriptan concentrations occur in about 1 to 2.5 hours depending on the formulation. Bioavailability is about 40 to 45%. Food may delay the time to peak plasma concentrations of the tablet formulation by about 1 hour. Plasma protein binding is low (14%).

Rizatriptan is metabolised mainly by monoamine oxidase type A to the inactive indole acetic acid derivative. The active metabolite *N*-monodesmethyl-rizatriptan is formed to a minor degree; other minor metabolites are also produced. About 14% of an oral dose is excreted in the urine as unchanged rizatriptan, 51% as the indole acetic acid metabolite, and no more than 1% as *N*-monodesmethyl-rizatriptan. The plasma half-life is about 2 to 3 hours.

Distribution into milk has been found in studies in *rats.*

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4. Swan SK, *et al.* Pharmacokinetic profile of rizatriptan 10-mg tablet and 10-mg orally disintegrating tablet administered with or without water in healthy subjects: an open-label, randomized, single-dose, 3-period crossover study. *J Clin Pharmacol* 2006; **46:** 172–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Maxalt; ***Austria***: Maxalt; ***Belg.***: Maxalt; ***Braz.***: Maxalt; ***Canad.***: Maxalt; ***Chile***: Maxalt; ***China***: Ouliting (欧立停); ShanQing (善清); Xin Qu (欣渠); ***Denm.***: Maxalt; ***Fin.***: Maxalt; ***Fr.***: Maxalt; Maxaltlyo; ***Ger.***: Maxalt; ***Gr.***: Maxalt; Modinol; ***India***: Rizact; ***Israel***: Rizalt; ***Ital.***: Maxalt; Rizaliv; Trizadol; ***Mex.***: Maxalt†; ***Neth.***: Latariz; Maxalt; Rizatan; Triptosig; ***Norw.***: Maxalt; ***NZ***: Maxalt; ***Pol.***: Maxalt; ***Port.***: Maxalt; Migrof†; ***S.Afr.***: Maxalt; ***Spain***: Maxalt; ***Swed.***: Maxalt; ***Switz.***: Maxalt; ***Turk.***: Maxalt; ***UK***: Maxalt; ***USA***: Maxalt; ***Venez.***: Maxalt.

Sumatriptan *(BAN, rINN)*

GR-43175X; Sumatriptaani; Sumatriptán; Sumatriptanum; Sumatryptan; Суматриптан.

3-(2-Dimethylaminoethyl)indol-5-yl-*N*-methylmethanesulfonamide.

$C_{14}H_{21}N_3O_2S$=295.4

CAS — 103628-46-2.
ATC — N02CC01.
ATC Vet — QN02CC01.
UNII — 8R78F6L9VO.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Protect from light.

USP 36: (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Store in airtight containers at below 30 degrees. Do not allow to freeze. Protect from light.

Sumatriptan Succinate *(BANM, USAN, rINNM)*

GR-43175C; SN-308; Succinato de sumatriptán; Sumatriptaanisuksinaatti; Sumatriptan, succinate de; Sumatriptán, succinato de; Sumatriptani Succcinas; Sumatriptani succinas; Sumatriptano sukcinatas; Sumatriptansuccinat; Sumatriptansukcinát; Sumatriptanum Succinas; Sumatryptanu bursztynian; Szumatriptánszukcinát; Суматриптана Суксинат.

$C_{14}H_{21}N_3O_2S,C_4H_6O_4$=413.5

CAS — 103628-47-3 (sumatriptan hemisuccinate); 103628-48-4 (sumatriptan succinate).
ATC — N02CC01.
ATC Vet — QN02CC01.
UNII — J8BDZ68989.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.3. Protect from light.

USP 36: (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store in airtight containers at a temperature not exceeding 30 degrees. Do not allow to freeze. Protect from light.

Stability. Oral liquid preparations of sumatriptan 5 mg/mL prepared from crushed sumatriptan succinate tablets in 3 different syrups were stable for at least 21 days when stored at 4 degrees and protected from light.[1]

1. Fish DN, *et al.* Stability of sumatriptan succinate in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54:** 1619–22.

Uses and Administration

Sumatriptan is a selective serotonin agonist that acts at 5-HT_1 receptors and produces vasoconstriction of cranial arteries. Drugs such as sumatriptan, which are commonly known as triptans, are believed to act mainly at 5-HT_{1B} and 5-HT_{1D} subtype receptors and are therefore sometimes referred to as $5HT_{1B/1D}$-receptor agonists.

Sumatriptan is used for the acute treatment of migraine attacks and of cluster headache. It should not be used for prophylaxis. It may be given orally, subcutaneously, or transdermally as the succinate and intranasally as the base. Doses are expressed in terms of the base; sumatriptan succinate 70 mg is equivalent to about 50 mg of sumatriptan.

For the acute treatment of **migraine** sumatriptan should be used as soon as possible after the onset of the headache phase, but efficacy is independent of the duration of the attack before starting treatment. If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

- It is given *orally* to adults aged 18 years and over; the recommended dose in the UK is 50 mg, although some patients may require 100 mg. A clinical response can be expected after about 30 minutes. If symptoms recur after an initial response, further doses may be given provided that there is a minimum interval of 2 hours between doses and that not more than 300 mg is taken in any 24-hour period. US licensed product information recommends that a lower dose of 25 mg may be used, although some patients require 50 or 100 mg. This may be followed by a second dose of up to 100 mg if the headache returns or the patient has a partial response provided that the total daily dose does not exceed the recommended maximum of 200 mg. A minimum interval of 2 hours is recommended between doses. A tablet supplying a dose equivalent to 85 mg of sumatriptan, as a fixed-dose combination with 500 mg of naproxen sodium, is also available in the USA; a single dose may be taken, repeated once within 24 hours if necessary, with a minimum interval of 2 hours.
- When used *intranasally* a clinical response can be expected in 15 minutes. UK licensed product information recommends that patients aged 18 years and over may be given a single dose of 20 mg into one nostril, although 10 mg may be effective in some patients. US licensed product information recommends that a dose of 5, 10, or 20 mg may be used. If symptoms recur, a second dose may be given at least 2 hours after the first dose. Not more than 40 mg should be used in a 24-hour period.
- In patients aged 18 years and over sumatriptan may be self-administered by *subcutaneous injection* in a single dose of 6 mg; a clinical response may be expected after 10 to 15 minutes. If symptoms recur, a second dose of 6 mg may be injected at least one hour after the first dose; not more than 12 mg should be given in a 24-hour period. US licensed product information recommends that it may also be used in single doses of 1 to 5 mg if adverse effects are dose-limiting. A *needle-free subcutaneous delivery system* is also available for the delivery of 6-mg doses.
- An *iontophoretic transdermal* delivery system, supplying 6.5 mg of sumatriptan over 4 hours, may also be used by patients aged 18 years and over. It should be applied to dry, intact, and non-irritated skin on the upper arm or thigh; it should not be applied to a previous application site until the skin remains erythema free for at least 3 days. If symptoms recur, a second system may be applied to a different site at least 2 hours after activation of the first system; not more than 2 systems should be used in a 24-hour period.

For the acute treatment of **cluster headache,** sumatriptan succinate is given by subcutaneous injection in similar doses to those used for migraine.

For doses in children and in hepatic impairment, see below and p. 680.1, respectively.

Administration in children. Sumatriptan may be given for the treatment of acute **migraine** in children and adolescents. Although not licensed for oral paediatric use in the UK, the *BNFC* suggests that a single *oral* dose of 25 mg may be given to children aged 6 to 10 years, 50 mg to those aged 10 to 12 years, and 50 to 100 mg to those aged

12 to 18 years. The dose may be repeated once after at least 2 hours if symptoms recur after an initial response. Children aged 10 to 18 years may also be given the usual adult *subcutaneous* dose (see p. 679.3).

In the UK, *intranasal* sumatriptan is licensed for use in adolescents aged 12 to 17 years in a dose of 10 mg into one nostril; the dose may be repeated after at least 2 hours if symptoms recur within 24 hours although not more than 20 mg should be used within a 24-hour period. Alternatively, the *BNFC* suggests that the usual adult dose of 10 to 20 mg (see p. 679.3) may be used in those aged 12 years and over.

If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

Sumatriptan has also been tried in the treatment of acute **cluster headache**. The *BNFC* suggests that children aged 10 to 18 years may be given *subcutaneous* doses similar to those suggested in adults (see p. 679.3); alternatively, sumatriptan may be given *intranasally* to children aged 12 to 18 years in doses similar to those suggested for use in adolescents with migraine.

Administration in hepatic impairment. Sumatriptan should be used with caution in patients with hepatic impairment. An oral dose of up to 50 mg is considered suitable. It should not be given to patients with severe impairment.

High-altitude disorders. Sumatriptan has been tried with some success in a small study[1] for the prevention of symptoms of acute mountain sickness (p. 1276.2).

1. Jafarian S, *et al.* Sumatriptan for prevention of acute mountain sickness: randomized clinical trial. *Ann Neurol* 2007; **62:** 273–7.

Migraine and cluster headache. The use of sumatriptan and other triptans in the treatment of cluster headache (p. 670.1) and migraine (p. 670.3) has been reviewed.[1-7]

In **migraine** serotonin (5-HT_1) agonists are preferred to ergotamine for the treatment of acute attacks unresponsive to simple analgesics.

There are several *different triptans* clinically available. In a meta-analysis of 53 studies (involving 24 089 patients) and a separate analysis of all direct comparative studies of 5 other triptans with sumatriptan, all were found to be more effective than placebo.[2] At the marketed doses, all oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) were effective and well tolerated. Almotriptan, eletriptan, or rizatriptan were considered to provide the highest likelihood of consistent success. A review of the efficacy of the 5 triptans available in the USA also showed pain relief at 2 hours was comparable for all.[3] Almotriptan 12.5 mg offered high tolerability and good efficacy; eletriptan 80 mg provided high efficacy and low recurrence; and rizatriptan 10 mg was associated with consistent and rapid freedom from pain.[2] Frovatriptan was not included in the analyses, but publicly available data suggested lower efficacy. Only sumatriptan, though, has parenteral and transdermal formulations;[8] the 6-mg subcutaneous formulation is considered to be the fastest and most effective acute treatment[2] but there is a lack of comparative data with the newer iontophoretic transdermal delivery preparation.[8]

About 21 to 57% of patients who initially respond to sumatriptan have a *recurrence* of their headache within 24 to 48 hours; this may be related in part to its short half-life. Such recurrences usually respond to a second dose[9,10] but if a first dose is ineffective subsequent doses for the same attack are of no benefit and should not be given. Sumatriptan is considered[11] to be effective when given at any time once the headache phase of migraine has started but giving it during migraine aura appears to be of little benefit since it does not affect the aura or prevent or delay the development of headache.[12] Repeated or long-term use does not appear to be associated with reduced efficacy.[13,14] For reports of an association between sumatriptan and medication-overuse headache, see under Adverse Effects, p. 681.2. Oral sumatriptan may also be combined with naproxen sodium;[15-17] the combination is reported to be slightly more effective than either drug alone.[18]

Sumatriptan's efficacy appears to be maintained in *menstrual migraine*, a condition which is considered to be less responsive to treatment than nonmenstrual migraine;[19] it has also been given in a fixed-dose oral combination with naproxen sodium.[20,21] Frovatriptan,[22] rizatriptan,[23] and zolmitriptan[24] have also been found to be effective in menstrual migraine.

Experience of subcutaneous use in *children* has been reported.[25] Results of a randomised, placebo-controlled study[26] of intranasal sumatriptan in adolescents aged 12 to 17 years showed evidence of efficacy, tolerability, and safety in this age group; it was felt that the nasal spray might be particularly well suited for adolescent use. Intranasal sumatriptan has also been tried in younger children (aged 8 years and over) with some success.[27] For doses in children, see p. 679.3. The use of other triptans in children with migraine has also been reviewed.[28]

Subcutaneous sumatriptan has also been shown to be effective in relieving acute attacks of headache in patients with **cluster headache**. In studies about 75% of patients have obtained relief within 15 minutes of a 6-mg subcutaneous injection;[29,30] the use of higher doses was found to be of no advantage. Long term efficacy appears to be maintained[31] but the significance of the transient increase in the frequency of attacks seen in some patients remains to be determined.[32] It does not appear to be effective for the prevention of headache during cluster periods.[33] Another triptan found to be effective in the treatment of episodic cluster headache is zolmitriptan.[34]

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34. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54:** 1832–39.

Adverse Effects

The most commonly reported adverse effects of serotonin (5-HT_1) agonists such as sumatriptan include dizziness, flushing, weakness, drowsiness, and fatigue. Nausea and vomiting may occur. Dyspnoea and sensory disturbance including paraesthesia and hypoaesthesia have been reported. Pain or sensations of heaviness, heat or cold, pressure, or tightness have also been commonly reported, can affect any part of the body including the throat and chest, and may be intense. These symptoms may be due to vasospasm, which on rare occasions has resulted in severe cardiovascular events including cardiac arrhythmias, myocardial ischaemia, or myocardial infarction. There have been isolated reports of associated cerebrovascular events in patients receiving sumatriptan. Transient increases in blood pressure may occur soon after treatment. Rarely, significant increases in blood pressure, including hypertensive crisis with acute impairment of organ systems, have occurred even in patients without a history of hypertension. Hypotension, bradycardia or tachycardia, palpitations, peripheral vascular disorders such as Raynaud's syndrome, and ischaemic colitis have been reported. Visual disturbances have also occurred.

Medication-overuse headache has been reported with sumatriptan and may necessitate withdrawal of the drug. Sumatriptan has occasionally been associated with minor disturbances in hepatic function. There have also been rare reports of seizures with sumatriptan. Hypersensitivity reactions ranging from rashes to, more rarely, anaphylaxis have occurred.

Transient pain at the injection site is common after subcutaneous sumatriptan injections; stinging, burning, erythema, bruising, and bleeding have also been reported. Irritation of the nasal mucosa and throat and epistaxis have been reported after intranasal use. Application site reactions such as pain, paraesthesia, pruritus, warmth, and discomfort have been commonly reported after use of the iontophoretic transdermal delivery preparation.

Incidence of adverse effects. In a Dutch postmarketing survey[1] completed by 1187 patients the most common adverse reactions attributed to sumatriptan were paraesthesia (reported by 11.7% of patients), dizziness (8.1%), feeling of heaviness (8.0%), chest pain (7.9%), nausea and/or vomiting (7.3%), drowsiness/sedation (7.0%), flushing (5.1%), fatigue (4.6%), pressure in throat (3.3%), headache (3.1%), injection site reaction (3.0%), palpitations (2.8%), abdominal pain (2.6%), muscle pain (2.4%), and dyspnoea (2.2%).

The safety and tolerability of the triptans have been reviewed.[2,3]

1. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; **47:** 305–9.
2. Nappi G, *et al.* Tolerability of the triptans: clinical implications. *Drug Safety* 2003; **26:** 93–107.
3. Tfelt-Hansen P. Optimal balance of efficacy and tolerability of oral triptans and telcagepant: a review and a clinical comment. *J Headache Pain* 2011; **12:** 275–80.

Effects on the cardiovascular system. About 10 months after sumatriptan injection had been made available commercially, the UK CSM noted that it had received 34 reports of pain or tightness in the chest and 2 reports of myocardial ischaemia.[1] The Netherlands Centre for Monitoring of Adverse Reactions to Drugs declared about the same time that it had received 12 reports of chest or anginal pain mostly associated with oral sumatriptan.[2] A later postmarketing survey based on data from Dutch general practitioners identified chest pain in 1.3% of 1727 patients,[3] a figure considered to be lower than that seen in earlier studies, but in a subsequent questionnaire completed by 1187 of these patients 7.9% reported chest pain.[4] The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[5] stated in December 1994 that it had received 114 reports of chest pain since sumatriptan had been marketed in mid 1992. Most patients had recovered quickly but 2 had died. The first developed a fatal myocardial infarction after coronary artery dissection but the causal relation with sumatriptan was unclear. The second patient, who had hypertrophic obstructive cardiomyopathy, developed ventricular fibrillation a few hours after the onset of chest pain and this led to fatal cardiac arrest.

One group of workers[6] who studied the effect of sumatriptan 16 mg given subcutaneously suggested that the symptoms of chest pain might be due to an effect of sumatriptan on oesophageal function, but others have argued against this suggestion.[7] ADRAC[5] considered that the reaction in the 28 reports of throat tightness they had received by December 1994 was a different reaction to that of chest pain, and probably resulted from changes in oesophageal motility.

Several reports have provided details of individual cases of the adverse cardiovascular effects of sumatriptan including arrhythmias (ventricular tachycardia,[8] ventricular fibrillation,[8,9] or atrial fibrillation[10,11]), acute myocardial infarction,[12-19] and unstable angina.[20] Most of these reports concerned subcutaneous sumatriptan, but myocardial infarction[14,17-19] and cardiac arrhythmias[9,11] (sometimes fatal) may occur after oral use. These adverse effects have also been reported in patients with no predisposing factors.[9,12,17-19]

A review[21] of published reports on chest pain as well as relevant data held by the UK manufacturer considered that the risk of myocardial ischaemia after vasoconstriction induced by sumatriptan was small. However, the contra-indications and cautions given under Precautions,

p. 681.2, should be observed. A study[22] published in 2004 of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of cardiovascular death in those patients treated with serotonin agonists.

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12. Ottervanger JP, *et al*. Transmural myocardial infarction with sumatriptan. *Lancet* 1993; **341:** 861–2.
13. Kelly KM. Cardiac arrest following use of sumatriptan. *Neurology* 1995; **45:** 1211–13.
14. O'Connor P, Gladstone P. Oral sumatriptan-associated transmural myocardial infarction. *Neurology* 1995; **45:** 2274–6.
15. Mueller L, *et al*. Vasospasm-induced myocardial infarction with sumatriptan. *Headache* 1996; **36:** 329–31.
16. Main ML, *et al*. Cardiac arrest and myocardial infarction immediately after sumatriptan injection. *Ann Intern Med* 1998; **128:** 874.
17. Hack JB. Oral sumatriptan-induced myocardial infarction. *J Toxicol Clin Toxicol* 2004; **42:** 309–11.
18. Anghileri E, *et al*. Acute myocardial infarction after sumatriptan administration for cluster headache. *Neurol Sci* 2006; **26:** 456–9.
19. Weir RA, *et al*. Myocardial infarction after oral sumatriptan use in a woman with normal coronary arteries. *Am J Med* 2007; **120:** A13. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-9343/PIIS0002934307004743.pdf (accessed 17/03/09)
20. Walton-Shirley M, *et al*. Unstable angina pectoris associated with Imitrex therapy. *Cathet Cardiovasc Diagn* 1995; **34:** 188.
21. Hillis WS, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341:** 1564–5. Correction. *ibid.*; **342:** 1310.
22. Hall GC, *et al*. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–8.

Effects on the cerebrovascular system. Adverse cerebrovascular effects have been reported after the use of subcutaneous sumatriptan including hemiparesis,[1] stroke,[2,3] and intracerebral haemorrhage.[4] Cerebral vasospasm has also been reported[5] with the use of oral sumatriptan. However, a study[6] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of stroke in those patients treated with serotonin agonists.

1. Luman W, Gray RS. Adverse reactions associated with sumatriptan. *Lancet* 1993; **341:** 1091–2.
2. Cavazos J, *et al*. Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; **343:** 1105–6.
3. Meschia JF, *et al*. Reversible segmental cerebral arterial vasospasm and cerebral infarction: possible association with excessive use of sumatriptan and Midrin. *Arch Neurol* 1998; **55:** 712–14.
4. Edwards KR, *et al*. Intracerebral hemorrhage associated with sumatriptan. *Headache* 1995; **35:** 309.
5. Dash S, *et al*. Cerebral vasospasm from sumatriptan. *Neurology* 2004; **63:** 2128.
6. Hall GC, *et al*. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–8.

Effects on the gastrointestinal tract. Ischaemic colitis and mesenteric ischaemia have been reported in a few patients receiving sumatriptan,[1-3] including repeated episodes in 2 patients,[2] each within hours of a dose; some of these episodes were associated with doses above the recommended daily maximum.[2]

Oesophageal constriction or throat tightness has been reported in some patients using sumatriptan and may be due to a direct effect on the oesophagus (see Effects on the Cardiovascular System, p. 680.3).

1. Knudsen JF, *et al*. Ischemic colitis and sumatriptan use. *Arch Intern Med* 1998; **158:** 1946–8.
2. Liu JJ, Ardolf JC. Sumatriptan-associated mesenteric ischemia. *Ann Intern Med* 2000; **132:** 597.
3. Naik M, *et al*. Sumatriptan-associated ischemic colitis. *Dig Dis Sci* 2002; **47:** 2015–16.

Effects on the respiratory system. See Asthma under Precautions, below.

Hypersensitivity. Reactions to sumatriptan such as rashes and, more rarely, anaphylaxis have been noted by the manufacturer. Published reports include angioedema occurring in a patient 5 minutes after subcutaneous sumatriptan,[1] and urticaria occurring 20 to 24 hours after oral or subcutaneous sumatriptan in another patient.[2]

1. Dachs R, Vitillo J. Angioedema associated with sumatriptan administration. *Am J Med* 1995; **99:** 684–5.
2. Pradalier A, *et al*. Delayed urticaria with sumatriptan. *Cephalalgia* 1996; **16:** 280–1.

Medication-overuse headache. Sumatriptan and other triptans may have a similar risk of misuse to that associated with analgesics and ergotamine compounds in patients with medication-overuse headache (p. 670.2). There have been reports[1-3] of patients using one or more daily doses of sumatriptan to control migraine. Many of the patients had a history of abuse of other antimigraine drugs and were using sumatriptan to prevent recurrence of headache. Whether misuse of sumatriptan was due to addiction or rebound headache, as seen with ergotamine, is unknown. A postmarketing study in 952 patients receiving sumatriptan found that 36 of the patients (4%) used sumatriptan daily or more than 10 times each week. This overuse was related to poor efficacy and not to rebound headache.[4] One study[5] and an anecdotal report[6] suggest that, rather than producing euphoria or other effects associated with drugs of abuse such as morphine, sumatriptan is more likely to be associated with dysphoria and apathetic sedation.

The development of medication-overuse headache has also been reported with other serotonin (5-HT_1) agonists including naratriptan and zolmitriptan.[7] Indeed, US licensed product information for the triptans states that the safety of treating an average of more than 3 or 4 migraine attacks in a 30-day period has not been established.

1. Osborne MJ, *et al*. Is there a problem with long term use of sumatriptan in acute migraine? *BMJ* 1994; **308:** 113.
2. Kaube H, *et al*. Sumatriptan. *BMJ* 1994; **308:** 1573–4.
3. Gaist D, *et al*. Misuse of sumatriptan. *Lancet* 1994; **344:** 1090.
4. Ottervanger JP, *et al*. Pattern of sumatriptan use and overuse in general practice. *Eur J Clin Pharmacol* 1996; **50:** 353–5.
5. Sullivan JT, *et al*. Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992; **52:** 635–42.
6. Bakshi R, Yan-Go FL. Prolonged marijuana-like dysphoria after subcutaneous sumatriptan. *Ann Pharmacother* 1996; **30:** 683.
7. Limmroth V, *et al*. Headache after frequent use of serotonin agonists zolmitriptan and naratriptan. *Lancet* 1999; **353:** 378.

Precautions

Sumatriptan and other serotonin (5-HT_1) agonists should only be used where there is a clear diagnosis of migraine or cluster headache and care should be taken to exclude other potentially serious neurological conditions. They should not be used for prophylaxis and should not be given to patients with basilar, hemiplegic, or ophthalmoplegic migraine.

Serotonin (5-HT_1) agonists are contra-indicated in patients with uncontrolled hypertension, ischaemic heart disease (coronary artery disease), a history of myocardial infarction, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease, or a previous cerebrovascular accident or transient ischaemic attack. Unrecognised cardiovascular disease should be excluded before the use of serotonin (5-HT_1) agonists in postmenopausal women, men over 40 years of age, and those with risk factors for ischaemic heart disease. If chest pain and tightness occur during use, appropriate investigations should be performed. Sumatriptan should not be used intravenously because of the increased risk of producing coronary vasospasm.

Drowsiness may occur after treatment with serotonin (5-HT_1) agonists and patients thus affected should not drive or operate machinery.

Sumatriptan should be used with caution in patients with hepatic or renal impairment, and should generally be avoided if hepatic impairment is severe.

There have been rare reports of seizures after use of sumatriptan and it should therefore be used with caution in patients with a history of epilepsy or other conditions predisposing to seizures. Patients with hypersensitivity to sulfonamides may have a similar reaction to sumatriptan. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

Asthma. The manufacturers reviewed data from more than 75 clinical studies of sumatriptan involving 12 701 patients and reported[1] that the incidence of adverse events related to asthma did not differ between patients with or without the condition. Earlier there had been concern over the safety of sumatriptan in patients with asthma after 2 reports of bronchospasm and a report of a patient with asthma who died during a study of sumatriptan although the patient had not received sumatriptan in the month before her death.

1. Lloyd DK, Pilgrim AJ. The safety of sumatriptan in asthmatic migraineurs. *Cephalalgia* 1993; **13:** 201–4.

Breast feeding. No adverse effects have been seen in breast-fed infants of mothers given sumatriptan, and the last available guidance from the American Academy of Pediatrics considered that it is therefore usually compatible with breast feeding.[1] However, licensed product information suggests that infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment. Product information for other triptans suggests avoiding breast feeding for 24 hours.

The distribution of sumatriptan into breast milk after a 6-mg subcutaneous dose has been studied in 5 mothers.[2] The mean total recovery of sumatriptan in breast milk was estimated to be 14.4 micrograms or 0.24% of the dose. It was calculated that on a weight-adjusted basis an infant could receive a maximum of 3.5% of the maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)
2. Wojnar-Horton RE, *et al*. Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; **41:** 217–21.

Cerebrovascular disorders. A patient with a superior sagittal sinus thrombosis who presented with headache and was misdiagnosed as having migraine variant developed a cortical stroke within minutes of a second 6-mg subcutaneous injection of sumatriptan.[1] The importance of establishing a diagnosis of typical migraine or cluster headache before using sumatriptan was emphasised and caution given against its use in any patient who may have unstable cerebrovascular disease or raised intracranial pressure. Additionally, there was no clinical evidence that a second injection would relieve a headache when the initial injection had been ineffective.

1. Cavazos J, *et al*. Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; **343:** 1105–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sumatriptan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Pregnancy. Sumatriptan crosses the placenta; however, only a very small quantity reaches the fetus. A literature review concluded that exposure to sumatriptan in pregnancy posed no additional risk of birth defects compared with that in the general population,[1] but as for other drugs sumatriptan should only be used in pregnancy when the benefit justifies the potential risk to the fetus.

1. Hilaire ML, *et al*. Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004; **38:** 1726–30.

Interactions

Sumatriptan and other serotonin (5-HT_1) agonists should not be given with ergotamine or related compounds (including methysergide) since there is an increased risk of vasospastic reactions. In addition, a delay is advised *before starting* a serotonin (5-HT_1) agonist in patients who have been receiving ergotamine or related compounds: sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of ergotamine preparations. Conversely, ergotamine should not be given until 6 hours *after stopping* these drugs or at least 24 hours in the case of eletriptan, frovatriptan, and naratriptan. Serotonin (5-HT_1) agonists should not be given together.

Sumatriptan or rizatriptan should not be used with, and for 2 weeks after stopping, an MAOI. Use with the selective monoamine oxidase type B inhibitor selegiline is thought unlikely to provoke an interaction, but see p. 916.1. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A whereas in the USA it contra-indicates such combinations. There have been rare reports of serotonin syndrome associated with the use of triptan serotonin (5-HT_1) agonists with SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), but see also under Antidepressants, below.

Oral sumatriptan appeared to delay gastric emptying and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients.[1]

1. Rani PU, *et al*. Sumatriptan delays paracetamol absorption in migraine patients. *Clin Drug Invest* 1996; **11:** 300–304.

Antidepressants. Sumatriptan and rizatriptan are metabolised mainly by monoamine oxidase type A and licensed product information advises that patients taking *MAOIs*, including reversible selective type A inhibitors such as moclobemide, should not be given these triptan serotonin (5-HT_1) agonists. Clearance of zolmitriptan was decreased after moclobemide and UK licensed product information recommends a reduced dose of zolmitriptan if the drug is used with an inhibitor of monoamine oxidase type A; in the USA, the use of these drugs together is contra-indicated.

SSRIs such as fluoxetine may also interact with serotonin (5-HT_1) agonists with an increased risk of serotonin

syndrome (p. 443.2), and it has been suggested that *lithium* and sumatriptan may interact similarly. However, a review of the use of sumatriptan with MAOIs, SSRIs, or lithium found little evidence of an increased risk of serotonin syndrome.[1] It was concluded that most patients tolerate the combination of sumatriptan and an SSRI or lithium without incident. However, it was suggested that the use of sumatriptan with an MAOI should continue to be avoided until further data supporting safety become available. As there have since been rare reports of serotonin syndrome associated with the use of triptans with SSRIs or *serotonin and noradrenaline reuptake inhibitors (SNRIs)*, licensed product information for the triptans states that when such use is clinically warranted, appropriate observation of the patient is advised, particularly when starting treatment, with dose increases, or with addition of another serotonergic drug. Product information for zolmitriptan also advises a reduction in dosage if it is given with fluvoxamine as the latter may inhibit zolmitriptan metabolism through its effects on the cytochrome P450 isoenzyme CYP1A2. The American Headache Society has stated[2] that caution is certainly warranted but that official FDA advice should be reviewed as it is not clear what role triptans might play in contributing to serotonin syndrome with or without SSRIs or SNRIs.

Increased serotonergic effects with increased incidence of adverse effects have been reported following the use of *St John's wort* with triptans.[3] Patients should be advised to stop taking St John's wort if treatment with a serotonin ($5\text{-}HT_1$) agonist is necessary.

1. Gardner DM, Lynd LD. Sumatriptan contraindications and the serotonin syndrome. *Ann Pharmacother* 1998; **32:** 33–8.
2. Evans RW, *et al.* The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. *Headache* 2010; **50:** 1089–99.
3. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Antimigraine drugs. Although the efficacy and tolerability of subcutaneous sumatriptan in the acute treatment of migraine did not appear to be affected in patients already taking *dihydroergotamine* orally for migraine prophylaxis,[1] the bioavailability of oral dihydroergotamine is low and it could not be assumed that it was safe to use parenteral dihydroergotamine with sumatriptan.[2] Licensed product information for sumatriptan contra-indicates its use with *ergotamine* or other related compounds and also recommend that it should not be given until at least 24 hours after stopping ergotamine or related compounds (see Interactions, p. 681.3).

Acute myocardial infarction has been reported[3] in a premenopausal woman with controlled hypertension and no known coronary artery disease after subcutaneous use of sumatriptan within a few hours of taking *methysergide* orally.

1. Henry P, *et al.* Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache* 1993; **33:** 432–5.
2. Campbell JK. Editor's comment]. *Headache* 1993; **33:** 435.
3. Liston H, *et al.* The association of the combination of sumatriptan and methysergide in myocardial infarction in a premenopausal woman. *Arch Intern Med* 1999; **159:** 511–13.

Antipsychotics. For reference to a potential interaction between sumatriptan and *loxapine*, see Chlorpromazine, p. 1052.3.

Pharmacokinetics

Sumatriptan is rapidly but incompletely absorbed when given orally and undergoes first-pass metabolism, resulting in a low absolute bioavailability of about 14%. Peak plasma concentrations after oral doses occur in about 2 hours. Bioavailability is much higher (96%) after subcutaneous doses with peak concentrations occurring within 25 minutes. Bioavailability after intranasal doses is 16% of that achieved subcutaneously, with peak concentrations occurring in about 1.5 hours. Peak concentrations after iontophoretic transdermal delivery occur in about 1.1 hours; bioavailability is lower than that achieved after oral doses. Plasma protein binding is low at about 14 to 21%.

The elimination half-life of sumatriptan is about 2 hours. Sumatriptan is extensively metabolised in the liver mainly by monoamine oxidase type A and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Sumatriptan and its metabolites also appear in the faeces. Small amounts of sumatriptan are distributed into breast milk (see Breast Feeding, p. 681.2).

Reviews.

1. Scott AK. Sumatriptan clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **27:** 337–44.
2. Lacey LF, *et al.* Single dose pharmacokinetics of sumatriptan in healthy volunteers. *Eur J Clin Pharmacol* 1995; **47:** 543–8.
3. Fuseau E, *et al.* Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet* 2002; **41:** 801–11.
4. Moen MD, Keating GM. Sumatriptan fast-disintegrating/rapid-release tablets. *Drugs* 2006; **66:** 883–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Imigran; Micranil; Migraneitor; ***Austral.***: Imigran; Sumagran; Sumatab; Suvalan; ***Austria***: Imigran; ***Belg.***: Finigraine†; Imitrex; ***Braz.***: Imigran; Sumax; Sutriptan; ***Canad.***: Imitrex; ***Chile***: Imigran; Somatran; ***China***: Dan Tong Jing (丹同静); Na Chuan (纳川); Youshu (尤舒); ***Cz.***: Cinie; Dolorstad†; Imigran; Rosemig; Sumamigren; Sumigra; Wispra; ***Denm.***: Imigran; Imigrane; Oriptan; Sumavel; ***Fin.***: Cinie†; Imigran; Oriptan; Sumaratio; ***Fr.***: Imigrane; Imiject; ***Ger.***: Imigran; Sumavel; ***Gr.***: Altaxa; Forcet; Imigran; Precipitan; Sutriptan; ***Hong Kong***: Imigran; ***Hung.***: Cinie; Illument†; Imigran; Triptagram; ***India***: Migratan; Suminat; ***Indon.***: Cetatrex†; Imitrex†; Triptagic; ***Irl.***: Imigran; Imitag†; Migrastat; Sumagran; Sumatran; Suvalan; ***Israel***: Imitrex; Sumatridex; ***Ital.***: Imigran; ***Malaysia***: Imigran; Sumitran; ***Mex.***: Fermig; Gesigran; Imigran; Sumitrex; Tebegran; ***Neth.***: Imigran; Sumalin; Sumarix; ***Norw.***: Imigran; ***NZ***: Imigran; MyGran; Sumagran†; ***Philipp.***: Imigran; Sumigran; ***Pol.***: Amigrenex; Cinie; Frimig; Imigran; Sumamigren; Sumigra; Triptagram; ***Port.***: Imigran; Imigranradis; ***Rus.***: Amigrenin (Амигренин); Imigran (Имиграп); Mygrepam (Мигрепам); Sumamigren (Сумамигрен); Sumig (Сумиг); Sumitran (Сумитран); Trimigren (Тримигрен); ***S.Afr.***: Imigen; Imigran; Migrex; Triptam; ***Singapore***: Imigran; Sumatran; Sumitran; ***Spain***: Imigran; Sumamylan†; ***Swed.***: Imigran; Oriptan; Zumo†; ***Switz.***: Imigran; ***Thai.***: Imigran; ***Turk.***: Imigran; Sumatran; ***UK***: Imigran; ***Ukr.***: Algomax (Альгомакс); Antimigren (Антимигрен); Sumamigren (Сумамигрен); ***USA***: Imitrex; Sumavel; Zecuity; ***Venez.***: Imigran; Migraval.

Multi-ingredient Preparations. ***USA***: Treximet.

Pharmacopoeial Preparations

BP 2014: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Tablets;
USP 36: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Succinate Oral Suspension; Sumatriptan Tablets.

Zolmitriptan *(BAN, USAN, rINN)*

311C90; Tsolmitriptaani; Zolmitriptán; Zolmitriptano; Zolmitriptanum; Zolmitryptan; Золмитриптан.

(*S*)-4-{3-[2-(Dimethylamino)ethyl]indol-5-ylmethyl}-1,3-oxazolidin-2-one.

$C_{16}H_{21}N_3O_2$=287.4

CAS — 139264-17-8.

ATC — N02CC03.

ATC Vet — QN02CC03.

UNII — 2FS66TH3YW.

Uses and Administration

Zolmitriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of migraine attacks. Zolmitriptan should not be used for prophylaxis.

The licensed dose in the UK is 2.5 mg orally. A clinical response can be expected within 1 hour. If symptoms persist or return within 24 hours, a second dose may be taken not less than 2 hours after the first dose. If a patient does not achieve satisfactory relief with a dose of 2.5 mg, subsequent attacks may be treated with doses of 5 mg. The maximum dose of zolmitriptan in 24 hours is 10 mg. Licensed doses in the USA are somewhat lower; the dose is 1.25 or 2.5 mg with a maximum dose of 10 mg in 24 hours.

When used intranasally a clinical response can be expected in 15 minutes. The usual dose is 5 mg as a single dose into one nostril. If symptoms persist or return within 24 hours, a second dose may be given after at least 2 hours, up to a maximum of 10 mg daily.

Dose reductions are recommended in patients taking certain other drugs (see also Interactions, below). The maximum dose of zolmitriptan in 24 hours should be 5 mg in those receiving cimetidine or an inhibitor of monoamine oxidase type A (although use with inhibitors of monoamine oxidase type A is contra-indicated in US licensed product information). A similar reduction is also recommended in those taking drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2.

For dosage in children and in hepatic impairment, see below.

Administration in children. Although unlicensed for use in children in the UK, the *BNFC* suggests that zolmitriptan may be used in those aged 12 to 18 years for the treatment of acute cluster headache (intranasal route only) or migraine. Doses are similar to those used in adults (see above).

Administration in hepatic impairment. A study[1] has indicated that while there is no need to reduce the size of the initial dose of zolmitriptan in patients with moderate or severe hepatic impairment, accumulation may occur with repeated doses in patients with severe impairment and their total daily dosage should be reduced.

UK licensed product information recommends a maximum oral dose of 5 mg in 24 hours in patients with moderate to severe impairment. In the USA, a dose of 1.25 mg is recommended in those with moderate to severe impairment, with a maximum total daily dose of 5 mg in severe impairment.

1. Dixon R, *et al.* Effect of hepatic impairment on the pharmacokinetics of zolmitriptan. *J Clin Pharmacol* 1998; **38:** 694–701.

Migraine and cluster headache. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Spencer CM, *et al.* Zolmitriptan: a review of its use in migraine. *Drugs* 1999; **58:** 347–74.
2. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54:** 1832–9.
3. Dowson AJ, Charlesworth B. Review of zolmitriptan and its clinical applications in migraine. *Expert Opin Pharmacother* 2002; **3:** 993–1005.
4. Charlesworth BR, *et al.* Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003; **17:** 653–67.
5. Dowson AJ, *et al.* Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *CNS Drugs* 2003; **17:** 839–51.
6. Lewis DW, *et al.* Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics* 2007; **120:** 390–6.
7. Rapoport AM, *et al.* Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007; **69:** 821–6. Correction. *ibid.*; 2029.
8. Hedlund C, *et al.* Zolmitriptan nasal spray in the acute treatment of cluster headache: a meta-analysis of two studies. *Headache* 2009; **49:** 1315–23.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Zolmitriptan should also be avoided in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways. It should be given with caution in patients with moderate to severe hepatic impairment.

Ischaemia. A spinal cord lesion related to the use of zolmitriptan has been reported in a 50-year-old woman;[1] clinical features suggested that the lesion was an ischaemic infarct.

1. Vijayan N, Peacock JH. Spinal cord infarction during use of zolmitriptan: a case report. *Headache* 2000; **40:** 57–60.

Medication-overuse headache. For a report of an association between zolmitriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p. 681.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zolmitriptan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/04/11)

Renal impairment. Although renal clearance of zolmitriptan and its metabolites was reduced in patients with moderate to severe impairment,[1] the resulting effect was unlikely to be of clinical importance and adjustment of zolmitriptan dosage in patients with renal impairment was considered unnecessary.

1. Gillotin C, *et al.* No need to adjust the dose of 311C90 (zolmitriptan), a novel anti-migraine treatment in patients with renal failure not requiring dialysis. *Int J Clin Pharmacol Ther* 1997; **35:** 522–6.

Interactions

As for Sumatriptan, p. 681.3.

Zolmitriptan undergoes hepatic metabolism, mainly mediated by the cytochrome P450 isoenzyme CYP1A2 and also involving monoamine oxidase type A. It is recommended that the maximum dose of zolmitriptan in 24 hours should be reduced in patients receiving cimetidine, a general P450 inhibitor (see Uses and Administration, above). A similar reduction in zolmitriptan dosage is anticipated if it is given with drugs, such as fluvoxamine and ciprofloxacin, that inhibit the isoenzyme CYP1A2. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A (see Uses and Administration, above), whereas US licensed product information states that such combinations are contra-indicated.

References.

1. Dixon R, *et al.* The metabolism of zolmitriptan: effects of an inducer and an inhibitor of cytochrome P450 on its pharmacokinetics in healthy volunteers. *Clin Drug Invest* 1998; **15:** 515–22.

Beta blockers. *Propranolol* increased plasma-zolmitriptan concentrations in a study in 12 healthy subjects, but the changes were not thought to be clinically important enough to warrant dosage adjustment during concomitant use.[1]

1. Peck RW, *et al*. The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **44:** 595–9.

Pharmacokinetics

The absolute bioavailability of zolmitriptan after oral and intranasal doses is about 40%, and peak plasma concentrations occur about 1.5 to 3 hours after oral doses, depending on the formulation, and in about 3 hours with the intranasal spray. Plasma protein binding is about 25%. Zolmitriptan undergoes hepatic metabolism, mainly to the indole acetic acid, and also the *N*-oxide and *N*-desmethyl analogues. The *N*-desmethyl metabolite (183C91) was more active than the parent compound in *animal* studies, and would be expected to contribute to the therapeutic effect of zolmitriptan. The primary metabolism of zolmitriptan is mediated mainly by the cytochrome P450 isoenzyme CYP1A2 while monoamine oxidase type A is responsible for further metabolism of the *N*-desmethyl metabolite. Over 60% of a dose is excreted in the urine, mainly as the indole acetic acid, and about 30% appears in the faeces, mainly as unchanged drug. The elimination half-life is 2.5 to 3 hours, and is prolonged in patients with liver disease.

Distribution into milk has been found in studies in *rats*.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zomigon; ***Austral.***: Zomig; ***Austria***: Zomig; ***Belg.***: Zomig; ***Braz.***: Zomig; ***Canad.***: Zomig; ***China***: Dining (帝宁); Heng Li An (恒力安); Ka Qu (卡曲); Lin Ke Shu (林可舒); Nao Rui An (瑙瑞安); Shu Fu Lai (枢复来); Tian Shu (天疏); Tuo Fu Ning (托肤宁); Zomig (佐米格); ***Cz.***: Zolmiles; Zomig; ***Denm.***: Zolmiles; Zomig; ***Fin.***: Zolmistad; Zomig; ***Fr.***: Zomig; Zomigoro; ***Ger.***: AscoTop; ***Gr.***: Zomigon; ***Hong Kong***: Zomig; ***Hung.***: Zomig; ***Irl.***: Magrezol; Zolmiles†; Zomig; ***Israel***: Zomig; ***Ital.***: Headzol; Ponesta; Zomig; ***Mex.***: Zomig; ***Neth.***: Zalsterim; Zomig; ***Norw.***: Zomig; ***NZ***: Zomig; ***Philipp.***: Zomig; ***Pol.***: Zolmiles; Zomig; ***Port.***: Zomig; ***Rus.***: Zomig (Зомиг); ***S.Afr.***: Zomig; ***Singapore***: Zomig; ***Spain***: Zomig; ***Swed.***: Zomig; ***Switz.***: Zomig; ***Thai.***: Zomig; ***Turk.***: Gravis; Zomig; ***UK***: Zomig; ***Ukr.***: Rapimig (Рапимиг); Zolmigren (Золмигрен); ***USA***: Zomig; ***Venez.***: Zomig.

Antimyasthenics

This chapter includes those drugs used for their anticholinesterase action in the treatment of myasthenia gravis and related neuromuscular disorders. Other groups of drugs playing an important role in the management of myasthenia are the corticosteroids (p. 1597.1) and some drugs with immunosuppressant actions discussed in the chapters on Antineoplastics (p. 691.1) and Immunosuppressants (p. 1936.1).

Eaton-Lambert myasthenic syndrome

Eaton-Lambert myasthenic syndrome is a rare autoimmune disease of the neuromuscular junction. Unlike myasthenia gravis (below), in which autoantibodies affect acetylcholine receptors, antibodies in Eaton-Lambert syndrome act presynaptically to reduce release of acetylcholine. Weakness mostly affects the proximal muscles, particularly those of the limbs; respiratory and ocular muscles are usually spared. Autonomic symptoms including dry mouth, constipation, and impotence are common. Over half of patients also have underlying small cell carcinoma of the lung. Successful treatment of the tumour often leads to some improvement in symptoms.

The symptomatic treatment of Eaton-Lambert syndrome involves the use of drugs that increase the availability of acetylcholine at the neuromuscular junction.[1-8] Response to treatment with *anticholinesterases* alone is poor and treatment with *amifampridine*, which increases acetylcholine release, appears to be more effective, particularly when given with an anticholinesterase such as *pyridostigmine*. The use of drugs with a similar action such as *guanidine* and *fampridine* has been limited by severe adverse effects. Low-dose guanidine has been tried with pyridostigmine where amifampridine is not readily available;[9] although there has been some improvement with the combination, the incidence of adverse effects, especially gastrointestinal reactions, was still high. Immunosuppressants including *azathioprine* and *corticosteroids* are also used in patients who have an inadequate response to symptomatic treatment, and unlike in treatment for myasthenia gravis, corticosteroids do not appear to induce an initial exacerbation of symptoms. Plasma exchange or high-dose intravenous *normal immunoglobulin* have been tried in patients with severe weakness.

1. Seneviratne U, de Silva R. Lambert-Eaton myasthenic syndrome. *Postgrad Med J* 1999; **75:** 516–20.
2. Pascuzzi RM. Myasthenia gravis and Lambert-Eaton syndrome. *Ther Apher* 2002; **6:** 57–68.
3. Sanders DB. Lambert-Eaton myasthenic syndrome: diagnosis and treatment. *Ann N Y Acad Sci* 2003; **998:** 500–8.
4. Newsom-Davis J. Lambert-Eaton myasthenic syndrome. *Rev Neurol (Paris)* 2004; **160:** 177–80.
5. Verschuuren JJ, *et al.* Available treatment options for the management of Lambert-Eaton myasthenic syndrome. *Expert Opin Pharmacother* 2006; **7:** 1323–36.
6. Pourmand R. Lambert-Eaton myasthenic syndrome. *Front Neurol Neurosci* 2009; **26:** 120–5.
7. Skeie GO. *et al.* European Federation of Neurological Societies. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* 2010; **17:** 893–902.
8. Keogh M, *et al.* Treatment for Lambert-Eaton myasthenic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 05/04/11).
9. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; **20:** 1146–52.

Myasthenia gravis

Myasthenia gravis is an auto-immune disorder characterised by defective neuromuscular transmission and consequent muscular weakness. It is caused by the formation of autoantibodies to elements of the neuromuscular junction. In most patients, antibodies to the postsynaptic nicotinic acetylcholine receptor are present (described as 'seropositive myasthenia'). However, about 10 to 15% of patients have so-called 'seronegative myasthenia', in whom antibodies to other elements such as muscle-specific tyrosine kinase (MuSK) may be present instead; the proportion of such patients is much higher among those with ocular myasthenia (where the disease is initially confined to the extra-ocular muscles but may progress to generalised myasthenia). The thymus appears to be involved in many patients and some have a thymoma. Classifications of the disease may be based on the distribution and severity of symptoms, on the age of onset, and on the presence or absence of thymoma. Other types of myasthenia include transient neonatal myasthenia due to transplacental passage of receptor antibodies, which may persist for 1 to 6 weeks in the infants of myasthenic mothers, penicillamine-induced myasthenia, and congenital myasthenia (see under Amifampridine, p. 685.1).

Diagnosis of myasthenia gravis.[1-7]

Antibody testing remains the gold standard for diagnosis of myasthenia gravis. Patients may often be tested first for their reaction to an anticholinesterase. Intravenous edrophonium preceded by atropine (Tensilon test) is the most commonly used anticholinesterase test because of its rapid onset and short duration of action. Severe adverse effects can occasionally occur so testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available. A positive result is considered to be a rapid but temporary increase in muscle strength. Repetitive nerve stimulation and/or single-fibre electromyography are also used as a diagnostic test but, like the anticholinesterase test, are not specific for myasthenia gravis. Computed tomography or magnetic resonance imaging may be used to detect thymoma.

Treatment of myasthenia gravis.[1-17]

- Symptomatic treatment is with an *anticholinesterase*; pyridostigmine and neostigmine are those most commonly used. Most patients prefer pyridostigmine as it produces less muscarinic adverse effects and has a longer duration of action, although the quicker onset of action of neostigmine may offer an advantage at the beginning of the day. The dose must be adjusted to give the optimum therapeutic response but muscle strength may not be restored to normal and some patients must live with a degree of disability. The effect may vary for different muscles and the dosage should be adjusted so that the bulbar and respiratory muscles receive optimum treatment. Generally, anticholinesterases only provide partial remission and their effects tend to diminish with continued treatment. Overdosage may lead to a 'cholinergic crisis' (see Adverse Effects of Neostigmine, p. 688.2). Edrophonium may be used to establish whether the patient is underdosed or overdosed.
- *Corticosteroids* are the main immunosuppressive drugs used for treatment. They are also useful in patients with ocular myasthenia, who as a group respond poorly to anticholinesterases and to thymectomy, provided that their disability is severe enough to warrant long-term corticosteroid treatment with its attendant adverse effects. Many start with low doses such as 5 to 20 mg of prednisolone daily or on alternate days, to reduce the risk of steroid-induced exacerbations of weakness, and increase the dose slowly thereafter according to response; an improvement is usually seen after a few weeks. Others use more aggressive regimens to obtain a more rapid response and start with large doses such as 60 to 80 mg of prednisolone daily. Whichever method is used, once clinical benefit has been obtained the regimen should be modified to alternate-day dosage, with the dose being slowly tapered when the patient is in remission. Patients taking corticosteroids require less anticholinesterase therapy and, if the dosage of the anticholinesterase is not reduced, an initial deterioration in the myasthenia may occur in the first few weeks of treatment (see also under Interactions of Neostigmine, p. 689.1). It is rarely possible to withdraw corticosteroids completely but some patients may be maintained satisfactorily on as little as 10 mg on alternate days. If remission cannot be maintained on low-dose prednisolone, addition of azathioprine at a dosage of 2 to 3 mg/kg daily may be considered.
- Addition of *azathioprine* to treatment may allow a reduction in the dose of both corticosteroids and anticholinesterases. Azathioprine may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient, but it has a much slower onset of action than corticosteroids and is not usually used alone. *Ciclosporin* is effective in some patients unresponsive to standard combinations but serious adverse effects including nephrotoxicity may limit its use; the time to response is similar to that with corticosteroids. Other drugs such as *cyclophosphamide*, *mycophenolate mofetil*, and *methotrexate* have also been tried and benefit has been reported with *tacrolimus*. However, a systematic review[14] has found that only a small number of randomised controlled studies have been conducted on the use of immunosuppressive drugs for myasthenia gravis and most have been short-term. The review of this limited evidence concluded that, apart from cyclophosphamide used alone or ciclosporin used alone or with corticosteroids, there was no clear evidence of benefit from use of other immunosuppressants.
- Plasma exchange provides a dramatic but short-lived improvement and is useful as a short-term measure in myasthenic crisis to improve ill patients while other therapies take effect, but there is no evidence that repeated plasma exchange combined with immunosuppression is superior to immunosuppression alone. A similar short-term benefit has been seen from the use of high-dose intravenous *normal immunoglobulins*; however, a systematic review[15] considered further study to be warranted.
- Thymectomy may be offered to all patients sufficiently fit to undergo surgery unless they have minimal symptoms, purely ocular disease, or late onset or seronegative disease. Thymectomy is usually avoided in prepubertal children because of concern over the effect on growth and the developing immune system; it has been suggested that symptomatic treatment with anticholinesterases should be continued until adolescence, when the disease often improves spontaneously. After thymectomy, remission or improvement may be expected in about 80% of patients without thymomas, although this may take some years; the response is poorer in those with thymomas.

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2. Pascuzzi RM. Myasthenia gravis and Lambert-Eaton syndrome. *Ther Apher* 2002; **6:** 57–68.
3. Vincent A, Drachman DB. Myasthenia gravis. *Adv Neurol* 2002; **88:** 159–88.
4. Thanvi BR, Lo TCN. Update on myasthenia gravis. *Postgrad Med J* 2004; **80:** 690–700.
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6. Romi F, *et al.* Myasthenia gravis: clinical, immunological, and therapeutic advances. *Acta Neurol Scand* 2005; **111:** 134–41.
7. Juel VC, Massey JM. Myasthenia gravis. *Orphanet J Rare Dis* 2007; **2:** 44. Available at: http://www.ojrd.com/content/pdf/1750-1172-2-44.pdf (accessed 21/12/10)
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11. Schwendimann RN, *et al.* Management of myasthenia gravis. *Am J Ther* 2005; **12:** 262–8.
12. Schneider-Gold C, *et al.* Corticosteroids for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/02/06).
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14. Hart IK, *et al.* Immunosuppressive agents for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
15. Gajdos P, *et al.* Intravenous immunoglobulin for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 28/05/08).
16. Skeie GO, *et al.* European Federation of Neurological Societies. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* 2010; **17:** 893–902.
17. Mehndiratta MM, *et al.* Acetylcholinesterase inhibitor treatment for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 05/04/11).

Ambenonium Chloride *(BAN, rINN)*

Ambenonii Chloridum; Ambenonio, cloruro de; Ambenonium Chlorid; Ambénonium, Chlorure d'; Ambenoniumklorid; Ambenoniumkloridi; Ambestigmini Chloridum; Chlorure d'Ambénonium; Cloruro de ambenonio; Win-8077; Амбеноний Хлорид.

N,N'-Oxalylbis(*N*-2-aminoethyl-*N*-2-chlorobenzyldiethylammonium) dichloride.

$C_{28}H_{42}Cl_4N_4O_2$=608.5

CAS — 7648-98-8 (ambenonium); 115-79-7 (anhydrous ambenonium chloride); 52022-31-8 (ambenonium chloride tetrahydrate).

ATC — N07AA30.

ATC Vet — QN07AA30.

UNII — 51FOB87G3I (ambenonium chloride); 9T1OT01KW1 (ambenonium chloride tetrahydrate).

Pharmacopoeias. In *Jpn*.

Uses and Administration

Ambenonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2), but of longer duration. Ambenonium chloride is given orally in the treatment of myasthenia gravis (above) in usual doses of 5 to 25 mg three or four times daily, adjusted according to response. It may be of value in patients who cannot tolerate neostigmine or pyridostigmine.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2.

Ambenonium produces fewer muscarinic adverse effects than neostigmine. As there is only slight warning of overdosage, routine use of atropine with ambenonium is contra-indicated because the muscarinic symptoms of overdosage may be suppressed leaving only the more

serious nicotinic effects (fasciculation and paralysis of voluntary muscle).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ambenonium as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/07/11)

Pharmacokinetics

Ambenonium chloride is poorly absorbed from the gastrointestinal tract. It does not appear to be hydrolysed by cholinesterases.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Mytelase; ***Fr.***: Mytelase; ***Gr.***: Mytelase; ***Hung.***: Mytelase; ***Pol.***: Mytelase; ***Swed.***: Mytelase; ***USA***: Mytelase.

Amifampridine *(BAN, rINN)*

Amifampridin; Amifampridina; Amifampridinum; 3,4-Diaminopiridina; 3,4-Diaminopyridine; Амифампридин.

Pyridine-3,4-diamine.

$C_5H_7N_3$=109.1

CAS — 54-96-6.

ATC — N07XX05.

ATC Vet — QN07XX05.

UNII — RU4S6E2G0J.

Amifampridine Phosphate *(rINNM)*

Amifampridine, Phosphate de; Amifampridini Phosphas; Fosfato de amifampridina; Амифампридина Фосфат.

$C_5H_7N_3,H_3PO_4$=207.1

ATC — N07XX05.

ATC Vet — QN07XX05.

Uses and Administration

Amifampridine enhances the release of acetylcholine from nerve terminals; its actions and uses are similar to those of fampridine (p. 686.2) but it is reported to be more potent. It is used in the Eaton-Lambert myasthenic syndrome (below) and other myasthenic conditions. It has been tried in multiple sclerosis and in botulism. Amifampridine is given as the phosphate but doses are expressed as the base; 18.98 mg of amifampridine phosphate is equivalent to about 10 mg of amifampridine. The recommended oral starting dose in adults with Eaton-Lambert myasthenic syndrome is the equivalent of 15 mg daily given in 3 or 4 divided doses; the dose may be increased in steps of 5 mg every 4 or 5 days to a maximum of 60 mg daily. For doses in patients with hepatic or renal impairment see below.

Administration in hepatic or renal impairment. An oral starting dose the equivalent of amifampridine 5 mg daily is recommended in patients with moderate to severe hepatic or renal impairment; those with mild impairment may be given a starting dose of 10 mg daily. The dose may be increased in steps of 5 mg every 7 days.

Congenital myasthenia. Congenital or hereditary myasthenia[1-3] is a heterogeneous group of rare disorders associated with various defects in neuromuscular transmission including presynaptic impairment of acetylcholinesterase release, postsynaptic abnormality of acetylcholine receptors, or a deficiency of acetylcholinesterase. Consequently, for any given congenital myasthenic syndrome, the synaptic response to acetylcholine is either increased or decreased. Symptoms may be similar to those of myasthenia gravis (p. 684.1) but there are no immunological abnormalities. Treatment[2,3] is symptomatic and depends on both the structural defect of the neuromuscular junction and the underlying genetic defect. Drugs that are beneficial for one type of congenital myasthenia can be harmful for another; hence, a precise diagnosis including genetic testing is recommended for rational therapy. Anticholinesterases and amifampridine may be used when there is a decreased synaptic response to acetylcholine; up to 1 mg/kg daily of amifampridine has been given in divided doses. Quinidine sulfate and fluoxetine, both open-channel blockers of acetylcholine receptors, have been used when the synaptic response is increased, such as in the slow-channel syndromes. Initially, quinidine sulfate 200 mg may be given 3 times daily for a week, adjusted according to serum levels thereafter; when quinidine is not tolerated, fluoxetine may be given in gradual increments until a total daily dose of 80 to 100 mg is reached. Ephedrine, given in doses of 25 to 50 mg 2 or 3 times daily, has also been shown to be of benefit in certain types of congenital myasthenia although its mode of action is unclear.

1. Engel AG. Congenital myasthenic syndromes. *Neurol Clin North Am* 1994; **12:** 401–37.
2. Engel AG. The therapy of congenital myasthenic syndromes. *Neurotherapeutics* 2007; **4:** 252–7.
3. Schara U, Lochmüller H. Therapeutic strategies in congenital myasthenic syndromes. *Neurotherapeutics* 2008; **5:** 542–7.

Eaton-Lambert myasthenic syndrome. Oral daily doses of up to 100 mg of amifampridine have been found[1,2] to be effective in the treatment of both the motor and autonomic deficits of patients with Eaton-Lambert syndrome (p. 684.1). However, some workers have recommended limiting the dose to 80 mg daily because of the increased risk of seizures with higher doses.[3,4] (UK licensed product information recommends a maximum daily dose of 60 mg.) Amifampridine can produce mild excitatory effects and some patients may have difficulty in sleeping.

1. McEvoy KM, *et al.* 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989; **321:** 1567–71.
2. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; **33:** 205–212.
3. Sanders DB, *et al.* A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000; **54:** 603–7.
4. Oh SJ, *et al.* 3,4-Diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. *Muscle Nerve* 2009; **40:** 795–800.

Multiple sclerosis. Amifampridine has been tried in the management of multiple sclerosis (p. 996.3). In a crossover study[1] involving 36 patients with multiple sclerosis, amifampridine given in a dosage of up to 100 mg daily improved symptoms of leg weakness to a greater extent than placebo but paraesthesia and abdominal pain, which occurred in most patients, were dose-limiting in some. A systematic review[2] of the use of aminopyridines for symptomatic management of multiple sclerosis was unable to come to any conclusion, and commented on the problem of publication bias in this area.

1. Bever CT, *et al.* Treatment with oral 3,4-diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. *Neurology* 1996; **47:** 1457–62.
2. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).

Adverse Effects and Precautions

The most common adverse effects with amifampridine are paraesthesias and gastrointestinal disturbances such as epigastralgia, diarrhoea, nausea, and abdominal pain. Sleep disorders, anxiety, weakness, fatigue, headache, chorea, myoclonus, Raynaud's syndrome, cough, bronchial hypersecretion, and elevated liver enzyme values have also been reported. The severity and incidence of most adverse effects are dose-dependent.

Arrhythmias have been reported with amifampridine and ECG monitoring should be performed at the start of treatment and yearly thereafter; amifampridine should not be used in patients with congenital QT interval prolongation. There have also been isolated reports of seizures and amifampridine is therefore contra-indicated in patients with epilepsy. Asthma attacks have occurred in patients with asthma or a history of the disease; amifampridine should not be used in those with uncontrolled asthma.

Blurred vision, drowsiness, and dizziness have been reported with amifampridine and may affect the ability of a patient to drive or operate machinery.

References.

1. Flet L, *et al.* 3,4-Diaminopyridine safety in clinical practice: an observational, retrospective cohort study. *J Neurol* 2010; **257:** 937–46.

Overdosage. A 65-year-old woman with Eaton-Lambert myasthenic syndrome suffered a cardiac arrest 11 days after her dose of amifampridine had been mistakenly altered to 60 mg 6 times daily instead of her usual dose of 10 mg 6 times daily;[1] she had also complained of paraesthesia, nausea, vomiting, and palpitations and had suffered generalised convulsions in the days preceding the cardiac arrest. She recovered completely after amifampridine was stopped.

1. Boerma CE, *et al.* Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. *J Toxicol Clin Toxicol* 1995; **33:** 249–51.

Pregnancy. Licensed product information states that there are no adequate clinical data on the use of amifampridine during pregnancy; it is recommended that men and women of child-bearing potential use effective contraception during amifampridine treatment.

A healthy infant was born to a woman with congenital myasthenia who took pyridostigmine and amifampridine throughout her pregnancy.[1] Her dose of pyridostigmine was maintained at her pre-conception dose of 180 mg daily while her amifampridine dose was progressively reduced to about 20 mg daily which allowed an acceptable level of fatigue. The infant's weight and height were within normal limits when seen aged 5 months.

1. Pelufo-Pellicer A, *et al.* Fetal exposure to 3,4-diaminopyridine in a pregnant woman with congenital myasthenia syndrome. *Ann Pharmacother* 2006; **40:** 762–6.

Interactions

Use of amifampridine with sultopride is contra-indicated due to the increased risk of ventricular tachycardia, particularly torsade de pointes. The risk of seizures is increased if amifampridine is used with other drugs that are known to lower the seizure threshold.

Pharmacokinetics

Amifampridine is rapidly absorbed after oral use and peak plasma concentrations occur after 20 to 60 minutes. Its elimination half-life is about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Firdapse; ***Denm.***: Firdapse; ***Fr.***: Firdapse; ***Ger.***: Firdapse; ***Irl.***: Firdapse; ***Israel***: Firdapse; ***Neth.***: Firdapse; ***Pol.***: Firdapse; ***Port.***: Firdapse; ***Swed.***: Firdapse; ***Switz.***: Firdapse; ***UK***: Firdapse.

Distigmine Bromide *(BAN, rINN)*

BC-51; Bispyridostigmine Bromide; Bromure de Distigmine; Bromuro de distigmina; Distigmiinibromidi; Distigmin Bromid; Distigmina, bromuro de; Distiginbromid; Distigmine, Bromure de; Distigmini Bromidum; Hexamarium Bromide; Дистигмина Бромид.

3,3′-[*N*,*N*′-Hexamethylenebis(methylcarbamoyloxy)]bis(1-methylpyridinium bromide).

$C_{22}H_{32}Br_2N_4O_4$=576.3

CAS — 15876-67-2.

ATC — N07AA03.

ATC Vet — QN07AA03.

UNII — 750F36OP6J.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Distigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

Although it is rarely used, distigmine bromide may be given orally with other short-acting parasympathomimetics for the treatment of **myasthenia gravis** (p. 684.1); patients being treated with parasympathomimetics tend to prefer pyridostigmine. The initial dose is 5 mg daily 30 minutes before breakfast, increased at intervals of 3 to 4 days if necessary to a maximum of 20 mg daily. For details of doses in children, see below.

Distigmine is one of several drugs that have been used in the prevention and treatment of **postoperative gastrointestinal atony** (see Decreased Gastrointestinal Motility, p. 1808.2). It has also been used in **postoperative urinary retention** (p. 2349.2), although it has been superseded by catheterisation. An oral dose of 5 mg daily 30 minutes before breakfast may be given. A similar oral dose, given daily or on alternate days, has been used in the management of **neurogenic bladder**.

Distigmine has been given by intramuscular injection.

Administration in children. Although it is rarely used, distigmine bromide may be given to children for the treatment of myasthenia gravis in oral doses of up to 10 mg daily according to age.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2. The anticholinesterase action of distigmine, and hence its adverse effects, may be prolonged, and if treatment with atropine is required it should be maintained for at least 24 hours. Distigmine may stimulate uterine contractions and licensed product information advises that it should be avoided in pregnancy.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Distigmine is poorly absorbed from the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Ubretid; ***Ger.***: Ubretid; ***Gr.***: Ubretid; ***Hong Kong***: Ubretid; ***Neth.***: Ubretid; ***Pol.***: Ubretid; ***Rus.***: Ubretid (Убретид); ***Singapore***: Ubretid; ***Switz.***: Ubretid; ***UK***: Ubretid†.

Edrophonium Chloride *(BAN, rINN)*

Cloruro de edrofonio; Edrofonio chloridas; Edrofonio, cloruro de; Edrofonium-chlorid; Edrofoniumklorid; Edrofoniumkloridi; Edrofonyum Klorür; Edrophonii Chloridum; Edrophonium Chlorid; Édrophonium, chlorure d'; Edrophoniumchlorid; Эдрофония Хлорид.

Ethyl(3-hydroxyphenyl)dimethylammonium chloride.

$C_{10}H_{16}ClNO$=201.7

CAS — 312-48-1 (edrophonium); 116-38-1 (edrophonium chloride).

UNII — QO611KSM5P.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Edrophonium Chloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Edrophonium Chloride). A white odourless crystalline powder. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; insoluble in chloroform and in ether. A 10% solution in water is practically colourless and the pH is between 4.0 and 5.0.

Uses and Administration

Edrophonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity. It has actions similar to those of neostigmine (p. 687.2) but its effect on skeletal muscle is claimed to be particularly prominent. It has a rapid onset but short duration of action. In patients with myasthenia gravis, there is immediate subjective improvement and muscle strength increases. This effect usually lasts only for about 5 to 15 minutes, after which time the typical signs and symptoms return; because of its brief action the drug is not suitable for the routine treatment of myasthenia gravis.

Edrophonium chloride is used in **myasthenia gravis** (p. 684.1) both diagnostically and to distinguish between under- and over-treatment with other anticholinesterases.

- The usual *diagnostic procedure* is to inject 2 mg intravenously and, if no adverse reaction occurs within 30 to 45 seconds, to continue with the injection of a further 8 mg; the test may be repeated after 30 minutes if necessary.
  When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection in a usual dose of 10 mg. Atropine should always be available when the test is carried out in order to treat any severe muscarinic reactions that may occur.
- To *detect under- or over-treatment*, test doses of 1 to 2 mg of edrophonium chloride are given intravenously to distinguish severe symptoms of myasthenia gravis due to inadequate therapy from the effects of overdosage with anticholinesterase drugs. If treatment has been inadequate, edrophonium chloride will produce an immediate amelioration of symptoms, whereas in cholinergic crises due to over-treatment the symptoms will be temporarily aggravated. Licensed product information suggests testing one hour after the last dose of treatment but the *BNF* recommends testing just before the next dose is due. Testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available.

Edrophonium chloride was originally introduced for the **reversal of neuromuscular blockade** in anaesthesia. In the UK, the recommended dose for the reversal of the effects of competitive neuromuscular blockers is 500 to 700 micrograms/kg given by intravenous injection over several minutes either with or after atropine sulfate 7 micrograms/kg. It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before edrophonium. In the USA, a dose of 10 mg of edrophonium chloride is given over 30 to 45 seconds and repeated as required up to a maximum of 40 mg. The brevity of its action limits its value. Prolonged apnoea may occur in patients treated with a depolarising neuromuscular blocker, such as suxamethonium; to determine if this is caused by a phase II block (see p. 2037.2), edrophonium chloride 10 mg may be given intravenously with atropine.

For details of doses in children, see below.

Edrophonium bromide has been used similarly to edrophonium chloride.

Administration in children. The use of edrophonium chloride in children with **myasthenia gravis** is similar to that in adults (see Uses and Administration, above).

- The usual *diagnostic procedure* in the UK is to inject 20 micrograms/kg intravenously and, if no adverse reaction occurs within 30 seconds, to continue with the injection of a further 80 micrograms/kg. The *BNFC* suggests that this dose may be given to those aged from 1 month to 12 years. Older children may be given the usual adult dose. In the USA a total intravenous dose of 5 mg for children weighing less than 34 kg and 10 mg for heavier children is recommended, with one-fifth of the dose being given initially followed by increments of 1 mg every 30 to 45 seconds. Alternatively, a total of 200 micrograms/kg may be given, with one-fifth of the dose being given initially over 1 minute followed by the remainder if no adverse reactions occur within 45 seconds. The recommended total dose for infants is 500 micrograms. When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection; children weighing under 34 kg may be given 2 mg and heavier children 5 mg. The recommended dose for infants is 0.5 to 1 mg given intramuscularly or subcutaneously.
- To *detect under- or over-treatment*, the *BNFC* recommends that children aged from 1 month to 12 years be given a dose of 20 micrograms/kg by intravenous injection just before the next dose of anticholinesterase. Older children may be given the usual adult dose.

For the **reversal of neuromuscular blockade** in anaesthesia, usual doses in the UK for children are as for adults; the *BNFC* suggests that these doses may be given to children as young as 1 month of age.

Reversal of neuromuscular blockade. For a discussion of whether edrophonium might be more suitable than neostigmine for reversal of residual block after the use of the shorter-acting competitive neuromuscular blockers, see under Uses and Administration of Neostigmine, p. 688.1.

Snake bite. For the use of anticholinesterases in the treatment of snake bite, see under Uses and Administration of Neostigmine, p. 688.1.

Tetrodotoxin poisoning. Management of poisoning due to tetrodotoxin, a heat stable neuromuscular blocking toxin found in various marine animals, such as puffer fish, is mainly symptomatic and supportive. Reports[1-4] on the efficacy of intravenous anticholinesterases such as edrophonium or neostigmine in reversing muscle weakness in tetrodotoxin poisoning have been conflicting. Although it appears that anticholinesterases may only be effective during partial block produced by tetrodotoxin, some consider[5] that, as there is no specific antidote, any measure that brings about improvement may be tried.

For a discussion of the general principles of the management of acute poisoning, see p. 1537.1.

1. Chew SK, *et al.* Anticholinesterase drugs in the treatment of tetrodotoxin poisoning. *Lancet* 1984; **ii:** 108.
2. Tibballs J. Severe tetrodotoxic fish poisoning. *Anaesth Intensive Care* 1988; **16:** 215–17.
3. Isbister GK, Kiernan MC. Neurotoxic marine poisoning. *Lancet Neurol* 2005; **4:** 219–28.
4. Hwang D-F, Noguchi T. Tetrodotoxin poisoning. *Adv Food Nutr Res* 2007; **52:** 141–236.
5. Karalliedde L. Management of puffer fish poisoning. *Br J Anaesth* 1995; **75:** 500.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2.

Interactions

As for Neostigmine, p. 688.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Tensilon; ***Gr.***: Anticude; ***Singapore***: Tensilon; ***Spain***: Anticude; ***USA***: Enlon-Plus; Enlon; Reversol†; Tensilon.

Pharmacopoeial Preparations

BP 2014: Edrophonium Injection;
USP 36: Edrophonium Chloride Injection.

Fampridine *(rINN)*

Dalfampridine (USAN); EL-970; Fampridin; Fampridina; Fampridinum; Фампридин.

4-Aminopyridine; 4-Pyridinamine.

$C_5H_6N_2$=94.12

CAS — 504-24-5.

ATC — N07XX07.

ATC Vet — QN07XX07.

UNII — BH3B64OKL9.

Uses and Administration

Fampridine is an aminopyridine that, like its derivative amifampridine (p. 685.1), enhances the release of acetylcholine from nerve terminals. It is used to improve walking in patients with multiple sclerosis (below); the licensed dose is 10 mg twice daily as an oral modified-release preparation. Fampridine has also been tried in the management of Guillain-Barré syndrome (p. 2406.1) and spinal cord injury; oral doses used in patients with spinal cord injuries have ranged from 30 to 50 mg daily. Other uses of fampridine that have been investigated include the neurological disorders Eaton-Lambert myasthenic syndrome (p. 684.1) and Alzheimer's disease (see Dementia, p. 388.1), and the reversal of neuromuscular blockade in patients with botulism (p. 2380.2) or after the use of competitive neuromuscular blockers.

Fampridine has also been considered as a specific antidote in poisoning with calcium-channel blockers (see Overdosage under Treatment of Adverse Effects of Nifedipine, p. 1452.3).

References.

1. Soni N, Kam P. 4-Aminopyridine: a review. *Anaesth Intensive Care* 1982; **10:** 120–6.
2. Ter Wee PM, *et al.* 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum Toxicol* 1985; **4:** 327–9.
3. Davidson M, *et al.* 4-Aminopyridine in the treatment of Alzheimer's disease. *Biol Psychiatry* 1988; **23:** 485–90.
4. Hansebout RR, *et al.* 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. *J Neurotrauma* 1993; **10:** 1–18.
5. Halter JA, *et al.* Intrathecal administration of 4-aminopyridine in chronic spinal injured patients. *Spinal Cord* 2000; **38:** 728–32.
6. DeForge D, *et al.* Effect of 4-aminopyridine on gait in ambulatory spinal cord injuries: a double-blind, placebo-controlled, crossover trial. *Spinal Cord* 2004; **42:** 674–85.
7. Cardenas DD, *et al.* Phase 2 trial of sustained-release fampridine in chronic spinal cord injury. *Spinal Cord* 2007; **45:** 158–68.

Multiple sclerosis. Fampridine has potassium-channel blocking activity and has been tried in the treatment of multiple sclerosis (p. 996.3) to improve conduction in demyelinated fibres. Improvements have been reported in walking, dexterity, and vision, but only small numbers of patients have been studied. An early systematic review[1] was unable to come to a conclusion about its safety and efficacy, noting that publication bias posed a problem in this area. However, further multicentre randomised controlled studies,[2-4] and reviews[5-7] of these studies, suggested that fampridine improved walking ability in some patients. Any benefit is generally noted within 2 weeks of starting treatment.

1. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).
2. Goodman AD, *et al.* Fampridine MS-F202 Study Group. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology* 2008; **71:** 1134–41.
3. Goodman AD, *et al.* Fampridine MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 2009; **373:** 732–8.
4. Goodman AD, *et al.* MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010; **68:** 494–502.
5. Korenke AR, *et al.* Sustained-release fampridine for symptomatic treatment of multiple sclerosis. *Ann Pharmacother* 2008; **42:** 1458–65.
6. Blight AR. Treatment of walking impairment in multiple sclerosis with dalfampridine. *Ther Adv Neurol Dis* 2011; **4:** 99–109.
7. McDonald S, Clements JN. Dalfampridine: a new agent for symptomatic management of multiple sclerosis. *Am J Health-Syst Pharm* 2011; **68:** 2335–40.

Adverse Effects and Precautions

The most common adverse effect with fampridine is urinary-tract infection. Other adverse effects include insomnia, dizziness, headache, gastrointestinal disturbances such as constipation, dyspepsia, and nausea, asthenia, back pain, paraesthesia, and nasopharyngitis.

A dose-dependent increase in the incidence of seizures has been noted with fampridine treatment and therefore its use is contra-indicated in patients with a history of seizures.

Fampridine is mainly eliminated unchanged by the kidneys and patients with renal impairment therefore have an increased risk of adverse effects, particularly neurological reactions. Consequently, its use is contra-indicated in patients with moderate to severe renal impairment (creatinine clearance of 50 mL/min or less). In patients with mild renal impairment (creatinine clearance of 80 mL/min or less), the risk of seizures is unknown although plasma levels of fampridine may approach those associated with an increased risk; UK licensed product information also contra-indicates fampridine use in this patient group.

Overdosage. An 8-month-old boy had dramatic opisthotonic posturing and vermiform tongue fasciculations after ingestion of up to 20 mg of fampridine;[1] the child was also noted to be tachycardic and tachypnoeic. His symptoms resolved after treatment with benzodiazepines. Choreoathetoid movements in all limbs were also reported in a 45-year-old woman with multiple sclerosis who accidentally overdosed with fampridine;[2] when rechallenged,

symptoms including confusion, opisthotonus, risus sardonicus, motor distress, and head tremor were noted instantly.

Three adult patients[3] with multiple sclerosis developed status epilepticus within minutes to hours of taking incorrectly-compounded tablets that contained between 90.1 and 125.6 mg of fampridine per tablet instead of the prescribed 10 mg. Although acute recovery was seen in all 3 patients after treatment with benzodiazepines and phenytoin, chronic neurological disabilities remained.

In another case, a 56-year-old man developed altered mental status, hypothermia, and atrial fibrillation after taking an unknown quantity of fampridine for toothache.[4] He had rubbed a large 'rock' of fampridine against his tooth in an attempt to relieve the pain, inadvertently swallowing some flakes of drug, which resulted in the overdose.

1. Velez L, *et al.* Opisthotonic posturing with neuromuscular irritability attributable to 4-aminopyridine ingestion by a healthy pediatric patient. Abstract: *Pediatrics* 2003; **111:** 192–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/1/e82 (accessed 15/02/06)
2. De Cauwer H, *et al.* An unusual case of 4-aminopyridine toxicity in a multiple sclerosis patient: epileptic disorder or toxic encephalopathy? *Acta Neurol Belg* 2009; **109:** 40–1.
3. Burton JM, *et al.* 4-Aminopyridine toxicity with unintentional overdose in four patients with multiple sclerosis. *Neurology* 2008; **71:** 1833–4.
4. Johnson NC, Morgan MW. An unusual case of 4-aminopyridine toxicity. *J Emerg Med* 2006; **30:** 175–7.

Pharmacokinetics

Fampridine is rapidly and extensively absorbed from the gastrointestinal tract after oral use. Plasma protein binding is minimal (1 to 3%). Fampridine is eliminated mostly unchanged in the urine; less than 10% of the drug is metabolised, some via the cytochrome P450 isoenzyme CYP2E1. Two major metabolites have been identified: 3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulfate.

References.

1. Hayes KC, *et al.* Pharmacokinetics of an immediate-release oral formulation of fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. *J Clin Pharmacol* 2003; **43:** 379–85.
2. Smith W, *et al.* Single-dose pharmacokinetics of sustained-release fampridine (fampridine-SR) in healthy volunteers and adults with renal impairment. *J Clin Pharmacol* 2010; **50:** 151–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Fampyra; ***Denm.***: Fampyra; ***Fr.***: Fampyra; ***Ger.***: Fampyra; ***Israel***: Fampyra; ***Neth.***: Fampyra; ***Norw.***: Fampyra; ***Swed.***: Fampyra; ***UK***: Fampyra; ***USA***: Ampyra.

Ipidacrine *(rINN)*

Amiridin (base or hydrochloride); Ipidacrina; Ipidacrinum; NIK-247 (hydrochloride); Ипидакрин.

9-Amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]quinoline.

$C_{12}H_{16}N_2$=188.3

CAS — 62732-44-9 (ipidacrine); 90043-86-0 (ipidacrine hydrochloride); 118499-70-0 (ipidacrine hydrochloride monohydrate).

UNII — CV71VTP0VN.

Profile

Ipidacrine, an analogue of tacrine (p. 396.1), is a cholinesterase inhibitor. It is used in the management of various neurological disorders including CNS and peripheral nervous system disorders, demyelinating disease, myasthenia gravis (p. 684.1) and other myasthenic syndromes, Alzheimer's disease (see Dementia, p. 388.1), and gastrointestinal atony. For myasthenic syndromes an oral dose of 20 to 40 mg has been given up to 5 times daily. A usual dosage in Alzheimer's disease is 10 to 20 mg given 2 or 3 times daily but this may be increased gradually up to 200 mg daily given in divided doses.

Ipidacrine has also been given by injection as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Amiridine (Амиридин); Axamon (Аксамон); Neiromidin (Нейромидин); ***Ukr.***: Neiromidinum (Нейромидин).

Neostigmine *(BAN)*

Neostigmiini; Neostigmin; Neostigmina; Neostigminum; Neostygmina; Neosztigmin.

3-(Dimethylcarbamoyloxy)trimethylanilinium ion.

$C_{12}H_{19}N_2O_2$=223.3

CAS — 59-99-4.

ATC — N07AA01; S01EB06.

ATC Vet — QA03AB93; QN07AA01; QS01EB06.

UNII — 3982TWQ96G.

Neostigmine Bromide *(BANM, pINN)*

Bromuro de neostigmina; Bromuro de Sinstigmina; Neostig. Brom.; Neostigmiinibromidi; Neostigmina, bromuro de; Neostigminbromid; Néostigmine, Bromure de; Neostigmini Bromidum; Neostigminii Bromidum; Neostigminium-bromid; Neostigmino bromidas; Neostigminum Bromatum; Neosztigmin-bromid; Synstigminium Bromatum; Неостигмина Бромид.

$C_{12}H_{19}BrN_2O_2$=303.3

CAS — 114-80-7.

ATC — N07AA01; S01EB06.

ATC Vet — QN07AA01; QS01EB06.

UNII — 005SYP50G5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Neostigmine Bromide). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Neostigmine Bromide). Store in airtight containers.

Stability. References.

1. Porst H, Kny L. Kinetics of the degradation of neostigmine bromide in aqueous solution. *Pharmazie* 1985; **40:** 713–17.

Neostigmine Metilsulfate *(BANM)*

Neostig. Methylsulph.; Neostigmiinimetilsulfaatti; Neostigmina, metilsulfato de; Neostigmine Methylsulfate; Neostigmine Methylsulphate; Néostigmine, métilsulfate de; Neostigmini metilsulfas; Neostigminii Metilsulfas; Neostigminium-methylsulfát; Neostigminmetilsulfat; Neostigmin-metylsulfat; Neostigmino metilsulfatas; Neostygminy metylosiarczan; Neosztigmin-metilszulfát; Proserinum.

$C_{13}H_{22}N_2O_6S$=334.4

CAS — 51-60-5.

ATC — N07AA01; S01EB06.

ATC Vet — QN07AA01; QS01EB06.

UNII — 98IMH7M386.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Neostigmine Metilsulfate). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Neostigmine Methylsulfate). Store in airtight containers.

Uses and Administration

Neostigmine is a quaternary ammonium compound that inhibits cholinesterase activity and thus prolongs and intensifies the physiological actions of acetylcholine (p. 2003.2). It probably also has direct effects on skeletal muscle fibres. The anticholinesterase actions of neostigmine are reversible.

Neostigmine is used in the treatment of myasthenia gravis, and has been used as an alternative to edrophonium in the diagnosis of myasthenia gravis (p. 684.1). It is used in anaesthesia to reverse the neuromuscular blockade produced by competitive neuromuscular blockers (see p. 688.1). It is also used in the management of paralytic ileus. Neostigmine has been used in the management of postoperative urinary retention (p. 2349.2) but has generally been superseded by catheterisation. It has also been used to lower intra-ocular pressure in the management of glaucoma and to reduce rises in intra-ocular pressure associated with ophthalmic surgery, although other parasympathomimetics are usually used when such miotics are required.

Neostigmine is given as the bromide and as the metilsulfate. Neostigmine bromide is given orally and has been used topically as eye drops; the metilsulfate is given by intramuscular, intravenous, or subcutaneous injection.

Licensed product information states that 500 micrograms of neostigmine metilsulfate by intravenous injection is equivalent in effect to about 1 to 1.5 mg of neostigmine metilsulfate by intramuscular or subcutaneous injection, or 15 mg of neostigmine bromide orally.

In the treatment of **myasthenia gravis**, neostigmine bromide is given orally in a total daily dose that ranges from 75 to 300 mg, divided throughout the day, and if necessary the night, according to response; larger portions of the total dose may be given at times of greater fatigue. The *BNF* states that the maximum daily dose that most patients can tolerate is 180 mg. In patients in whom oral therapy is impractical neostigmine metilsulfate may be given in doses of 0.5 to 2.5 mg by intramuscular or subcutaneous injection at intervals, giving a total daily dose usually in the range 5 to 20 mg.

To **reverse neuromuscular blockade** produced by competitive neuromuscular blockers, the usual licensed dose in the UK is 50 to 70 micrograms/kg given by intravenous injection over a period of 60 seconds; the *BNF* suggests giving a dose of 2.5 mg. In the USA licensed doses of 0.5 to 2 mg are recommended. Additional neostigmine may be given until the muscle power is normal but a total of 5 mg should not be exceeded. The patient should be ventilated until complete recovery of normal respiration is assured. To counteract any muscarinic effects 0.6 to 1.2 mg (20 to 30 micrograms/kg) of atropine sulfate is given by intravenous injection with or before the dose of neostigmine. It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before neostigmine. Glycopyrronium bromide has been used as an alternative to atropine sulfate.

In the treatment of paralytic **ileus** and postoperative **urinary retention**, oral doses of 15 to 30 mg of the bromide, or more usually 0.5 to 2.5 mg of the metilsulfate by subcutaneous or intramuscular injection, have been used.

For details of doses in children, see below.

Administration in children. The use of neostigmine in children is similar to that in adults (see Uses and Administration above).

For the treatment of **myasthenia gravis** UK licensed product information states that neostigmine bromide may be given orally in an initial dose of 7.5 mg to children aged under 6 years, or 15 mg to those aged 6 to 12 years. This is adjusted according to response to a usual total daily dose of 15 to 90 mg, divided throughout the day.

When oral therapy is impractical, children aged under 12 years may be given intramuscular or subcutaneous injections of neostigmine metilsulfate in doses of 200 to 500 micrograms, repeated at suitable intervals throughout the day.

For all routes of administration, children aged over 12 years may be given the usual adult dose.

In the treatment of neonatal myasthenia gravis, UK licensed product information states that neostigmine metilsulfate may be given in an initial intramuscular dose of 100 micrograms followed by a usual dose of 50 to 250 micrograms, or 30 micrograms/kg, every 2 to 4 hours. The *BNFC* recommends higher doses: an initial intramuscular or subcutaneous dose of 150 micrograms/kg every 6 to 8 hours, increased to a maximum of 300 micrograms/kg every 4 hours if necessary. Alternatively, the *BNFC* suggests that neostigmine bromide may be given in an initial oral dose of 1 to 2 mg followed by 1 to 5 mg every 4 hours. For all routes of administration, doses should be given 30 minutes before feeding. Treatment is rarely needed beyond 8 weeks of age.

To **reverse neuromuscular blockade** produced by competitive neuromuscular blockers, children may be given doses similar to those used in adults; the *BNFC* recommends an intravenous dose of 50 micrograms/kg (to a maximum of 2.5 mg) in neonates and those aged up to 18 years; a further dose of 25 micrograms/kg may be given if required. To counteract any muscarinic effects, neonates and children may be given atropine sulfate 20 micrograms/kg (to a maximum of 1.2 mg) by intravenous injection with or before the dose of neostigmine. Glycopyrronium may be used as an alternative to atropine.

For the treatment of paralytic **ileus** or postoperative **urinary retention** in children, oral doses of 2.5 to 15 mg of the bromide, or more usually 0.125 to 1 mg of the metilsulfate by subcutaneous or intramuscular injection, have been used.

Decreased gastrointestinal motility. Parasympathomimetics enhance gastric contractions and increase intestinal motility and have been used in conditions associated with decreased gastrointestinal motility (p. 1808.2). Good results have been reported with intravenous neostigmine in the treatment of acute colonic pseudo-obstruction,[1,2] a condition that appears to be due to parasympathomimetic dysfunction. These results have been confirmed in a randomised double-blind study.[3] It has therefore been suggested that parasympathomimetics should be tried before colonic decompression or surgery when conservative management has failed or a rapid resolution is required.[3] Neostigmine has also been used in the treatment of severe constipation due to disrupted intestinal motility.[4-6]

1. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. *Ann R Coll Surg Engl* 1992; **74:** 364–7.
2. Stephenson BM, *et al.* Parasympathomimetic decompression of acute colonic pseudo-obstruction. *Lancet* 1993; **342:** 1181–2.
3. Ponec RJ, *et al.* Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341:** 137–41.
4. Miller LS. Neostigmine for severe constipation with spinal cord lesions. *Ann Intern Med* 1984; **101:** 279.
5. Thurtle OA, *et al.* Intractable constipation in malignant phaeochromocytoma: combined treatment with adrenergic blockade and cholinergic drugs. *J R Soc Med* 1984; **77:** 327–8.
6. Rosman AS, *et al.* Intramuscular neostigmine and glycopyrrolate safely accelerated bowel evacuation in patients with spinal cord injury and defecatory disorders. *Dig Dis Sci* 2008; **53:** 2710–13.

Local anaesthesia. Intrathecal neostigmine has been added to spinal local anaesthetics or opioids as an adjunct to prolong regional analgesia and improve haemodynamic stability. A systematic review[1] of studies of such use found that although neostigmine in doses up to 500 micrograms produced a very modest increase in analgesia in the perioperative and peripartum setting, it did not appear to improve haemodynamic stability and the incidence of adverse effects was greatly increased, even at low doses. The disadvantages were felt to outweigh whatever benefits such therapy might have.

Neostigmine has also been given by the epidural route as an adjunct to analgesia;[2] some adverse effects such as nausea may be less with this route.

1. Ho KM, *et al.* Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* 2005; **33:** 41–53.
2. Ross VH, *et al.* Neostigmine decreases bupivacaine use by patient-controlled epidural analgesia during labor: a randomized controlled study. *Anesth Analg* 2009; **109:** 524–31.

Reversal of neuromuscular blockade. Anticholinesterases have often been used after surgery to antagonise residual neuromuscular block induced by long-acting competitive neuromuscular blockers. However, there has been continuing debate[1-3] on whether anticholinesterases can be used in reduced doses or even omitted for intermediate-acting blockers such as atracurium and vecuronium and shorter-acting blockers such as mivacurium.

Decreasing the anticholinesterase dose may reduce adverse effects. Although it is not clear whether omitting neostigmine reversal reduces nausea and vomiting,[3,4] it avoids any adverse effects neostigmine may have on gut anastomoses. One commentator[1] considered that the wide variation in recovery time with aminosteroid blockers such as rocuronium was an indication for always using at least a small dose of anticholinesterase when these drugs were used. However, it was suggested that, if the block was being carefully monitored and recovery was established, a reduced dose of 1.25 mg of neostigmine might be preferable after a benzylisoquinolinium blocker such as atracurium or mivacurium. In children, smaller doses of an anticholinesterase could be used, even after an aminosteroid blocker, and after a blocker such as mivacurium, they might not be needed at all.

Others have preferred to reserve neostigmine reversal for cases where it was deemed clinically necessary: in a study[4] using such a protocol, 68% of those receiving rocuronium were given neostigmine, against 10% of those receiving mivacurium.

It has been suggested that because of its shorter duration of action edrophonium might be more suitable than neostigmine to antagonise residual block for neuromuscular blockers with shorter actions and in particular, that edrophonium might be more appropriate than neostigmine for use with mivacurium. Neostigmine inhibits the plasma cholinesterase responsible for the metabolism of mivacurium and its use can in theory delay rather than speed recovery, although in practice there is considered to be little evidence for such an effect.[1] Edrophonium also has lesser effects on the vagus, a more rapid onset of action, and may be associated with a lower incidence of nausea and vomiting than neostigmine.[5] Neostigmine can cause clinically significant neuromuscular blockade if it is given to a patient who has already recovered a large degree of neuromuscular function[6,7] but edrophonium appears not to have this effect.[8] However, the antagonism produced by edrophonium is not adequately and reliably sustained especially after profound block.[9,10]

1. Hunter JM. Is it always necessary to antagonize residual neuromuscular block? Do children differ from adults? *Br J Anaesth* 1996; **77:** 707–9.
2. Fawcett WJ. Neuromuscular block in children. *Br J Anaesth* 1997; **78:** 627.
3. Fuchs-Buder T, Mencke T. Use of reversal agents in day care procedures (with special reference to postoperative nausea and vomiting). *Eur J Anaesthesiol* 2001; **18** (suppl 23): 53–9.
4. Joshi GP, *et al.* The effects of antagonizing residual neuromuscular blockade by neostigmine and glycopyrrolate on nausea and vomiting after ambulatory surgery. *Anesth Analg* 1999; **89:** 628–31.
5. Watcha MF, *et al.* Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. *Anesth Analg* 1995; **80:** 713–17.
6. Hughes R, *et al.* Neuromuscular blockade by neostigmine. *Br J Anaesth* 1979; **51:** 568P.
7. Payne JP, *et al.* Neuromuscular blockade by neostigmine in anaesthetized man. *Br J Anaesth* 1980; **52:** 69–75.
8. Astley BA, *et al.* Electrical and mechanical responses after neuromuscular blockade with vecuronium, and subsequent antagonism with neostigmine or edrophonium. *Br J Anaesth* 1987; **59:** 983–8.
9. Caldwell JE, *et al.* Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine with edrophonium. *Br J Anaesth* 1986; **58:** 1285–9.
10. Mirakhur RK, *et al.* Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. *Br J Anaesth* 1987; **59:** 473–7.

Snake bite. The general management of snake bites is discussed on p. 2419.2. Many reports from India have claimed benefit for anticholinesterases in the treatment of neurotoxic snake bites but failure to distinguish between cobra and krait bites, lack of controls, and inadequate information about other therapy weaken the claims.[1] However, edrophonium has been shown in 2 double-blind studies to be more effective than placebo[2] and antivenom[3] in the treatment of snake bite due to the Philippine cobra (*Naja naja philippinensis*). Neostigmine has also been reported[4] to have been effective in reversing paralysis in 2 patients bitten by *Micrurus frontalis* (a coral snake). Similarly, another patient made a remarkable recovery when treated with neostigmine after being bitten by an Asiatic cobra (*Naja naja kaouthia*).[5] Anticholinesterases would be expected to be of little value for bites from snakes whose venom contains neurotoxins which act presynaptically, including the Asian krait, the Australian tiger snake, and the taipan[6] and, although beneficial results have been reported in individual patients,[7] overall results are considered to be inconsistent.[2,8] However, it is recommended that a test dose of edrophonium preceded by atropine should be given to patients with neurological signs after a snake bite by any species and if improvement occurs, a longer acting anticholinesterase such as neostigmine can be given.[2,3]

1. Reid HA. Venoms and antivenoms. *Trop Dis Bull* 1983; **80:** 23.
2. Watt G, *et al.* Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja naja philippinensis). *N Engl J Med* 1986; **315:** 1444–8.
3. Watt G, *et al.* Comparison of Tensilon and antivenom for the treatment of cobra-bite paralysis. *Trans R Soc Trop Med Hyg* 1989; **83:** 570–3.
4. Vital Brazil O, Vieira RJ. Neostigmine in the treatment of snake accidents caused by Micrurus frontalis: report of two cases. *Rev Inst Med Trop Sao Paulo* 1996; **38:** 61–7.
5. Gold BS. Neostigmine for the treatment of neurotoxicity following envenomation by the Asiatic cobra. *Ann Emerg Med* 1996; **28:** 87–9.
6. Brophy T, Sutherland SK. Use of neostigmine after snake bite. *Br J Anaesth* 1979; **51:** 264–5.
7. Warrell DA, *et al.* Severe neurotoxic envenoming by the Malayan krait Bungarus candidus (Linnaeus): response to antivenom and anticholinesterase. *BMJ* 1983; **286:** 678–80.
8. Trevett AJ, *et al.* Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (Oxyuranus scutellatus carini). *Trans R Soc Trop Med Hyg* 1995; **89:** 444–6.

Tetrodotoxin poisoning. For reference to the use of neostigmine in the treatment of tetrodotoxin poisoning caused by eating puffer fish, see under Uses and Administration of Edrophonium Chloride, p. 686.2.

Adverse Effects

The adverse effects of neostigmine are chiefly due to excessive cholinergic stimulation and most commonly include increased salivation, nausea and vomiting, abdominal cramps, and diarrhoea. Allergic reactions have been reported; rashes have been associated with the use of the bromide salt. Neostigmine penetrates the blood-brain barrier poorly and CNS effects are usually only seen with high doses.

Overdosage may lead to a 'cholinergic crisis', characterised by both muscarinic and nicotinic effects. These effects may include excessive sweating, lachrymation, increased peristalsis, involuntary defaecation and urination or desire to urinate, miosis, ciliary spasm, nystagmus, bradycardia and other arrhythmias, hypotension, muscle cramps, fasciculations, weakness and paralysis, tight chest, wheezing, and increased bronchial secretion combined with bronchoconstriction. CNS effects include ataxia, convulsions, coma, slurred speech, restlessness, agitation, and fear. Death may result from respiratory failure, due to a combination of the muscarinic, nicotinic, and central effects, or cardiac arrest.

It has been reported that a paradoxical increase in blood pressure and heart rate may result from nicotinic stimulation of sympathetic ganglia, especially where atropine has been given to reverse the muscarinic effects (see Treatment of Adverse Effects, below).

In patients with myasthenia gravis, in whom other symptoms of overdosage may be mild or absent, the major symptom of cholinergic crisis is increased muscular weakness, which must be differentiated from the muscular weakness caused by an exacerbation of the disease itself (myasthenic crisis).

The adverse effects of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p. 2011.2.

Treatment of Adverse Effects

If a life-threatening amount of neostigmine has been taken orally and the patient presents within 1 hour, the stomach may be emptied by lavage; giving activated charcoal to decrease absorption should also be considered. When necessary maintenance of respiration should take priority. Atropine sulfate should be given in usual doses of 1 to 2 mg, preferably intravenously, or else intramuscularly and repeated as necessary to control the muscarinic effects; single doses of up to 4 mg have also been suggested. Nicotinic effects, including muscle weakness and paralysis, are not antagonised by atropine; small doses of a competitive neuromuscular blocker have been suggested for the control of muscle twitching. Use of the cholinesterase reactivator pralidoxime as an adjunct to atropine has also been suggested (see p. 1571.2). Further supportive treatment should be given as required.

For a discussion of the general principles of the management of acute poisoning, see p. 1537.1.

Precautions

The precautions and contra-indications to be observed with neostigmine use relate mainly to its cholinergic effects.

Neostigmine is contra-indicated in patients with mechanical gastrointestinal or urinary-tract obstruction, or peritonitis. It should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma. It should be used with caution in patients with cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction, and hypotension, as well as in patients with vagotonia, epilepsy, hyperthyroidism, parkinsonism, renal impairment, or peptic ulcer disease. When neostigmine is given by injection, atropine should always be available to counteract any excessive muscarinic reactions; atropine may also be given before, or with, neostigmine to prevent or minimise muscarinic adverse effects but this may mask the initial symptoms of overdosage and lead to cholinergic crisis.

UK licensed product information states that as the severity of myasthenia gravis often fluctuates considerably during pregnancy, particular care is needed to avoid cholinergic crisis caused by overdosage; it has also been reported that neonatal myasthenia may follow large doses during pregnancy. The amount of neostigmine distributed into breast milk is very small but breast-fed infants need to be monitored.

Large oral doses of neostigmine should be avoided in conditions where there may be increased absorption from the gastrointestinal tract. It should be avoided in patients known to be hypersensitive to neostigmine; the bromide ion from neostigmine bromide may contribute to any allergic reaction.

The precautions of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p. 2011.2.

Neuromuscular disorders. Residual non-depolarising neuromuscular block in a patient with dystrophia myotonica was only partly reversed by neostigmine and atropine, and following a second dose of both drugs complete neuromuscular block developed.[1] In a second patient, with a history of progressive muscle dystrophy, the use of neostigmine to reverse residual non-depolarising blockade gave rise to a tonic response in the indirectly stimulated muscle. The type and degree of the response to neostigmine, and probably other anticholinesterases, cannot be predicted in patients with neuromuscular disease.

A patient with sero-negative ocular myasthenia gravis had exaggerated responses to both vecuronium and neostigmine.[2] The dose of neuromuscular blockers and their antagonists used in patients with myasthenia gravis should be titrated carefully regardless of the severity of the condition.

1. Buzello W, *et al.* Hazards of neostigmine in patients with neuromuscular disorders: report of two cases. *Br J Anaesth* 1982; **54:** 529–34.
2. Kim J-M, Mangold J. Sensitivity to both vecuronium and neostigmine in a sero-negative myasthenic patient. *Br J Anaesth* 1989; **63:** 497–500.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies neostigmine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/07/11)

Renal impairment. The dosage of neostigmine may need to be adjusted in patients with renal impairment. The mean serum elimination half-life of 79.8 minutes obtained in patients with normal renal function was found to be prolonged to 181.1 minutes in anephric patients.[1]

1. Cronnelly R, *et al.* Renal function and the pharmacokinetics of neostigmine in anesthetized man. *Anesthesiology* 1979; **51:** 222–6.

Interactions

Drugs with neuromuscular blocking activity, such as the aminoglycosides, clindamycin, colistin, cyclopropane, and the halogenated inhalational anaesthetics, may antagonise the effects of neostigmine. Those such as quinine, chloroquine, hydroxychloroquine, quinidine, procainamide, propafenone, lithium, and the beta blockers, that have the potential to aggravate myasthenia gravis, can reduce the efficacy of treatment with parasympathomimetics. Prolonged bradycardia has also occurred in patients receiving beta blockers when given neostigmine. Anticholinesterases, such as neostigmine, can inhibit the metabolism of suxamethonium, a depolarising neuro-

muscular blocker, and enhance and prolong its action; combined use is not recommended.

Ophthalmic use of anticholinesterases, such as ecothiopate, should be undertaken with care in patients receiving neostigmine systemically for myasthenia gravis, because of possible additive toxicity.

Antimuscarinics such as atropine antagonise the muscarinic effects of neostigmine.

Beta blockers. There have been several reports of bradycardia and hypotension when neostigmine or physostigmine were given to patients receiving beta blockers[1-4] but no significant changes in heart rate were noted in a study of pyridostigmine given to 8 patients taking beta blockers.[5] Beta blockers have the potential to aggravate the symptoms of myasthenia gravis and may therefore reduce the efficacy of parasympathomimetic treatment.

1. Sprague DH. Severe bradycardia after neostigmine in a patient taking propranolol to control paroxysmal atrial tachycardia. *Anesthesiology* 1975; **42:** 208–10.
2. Seidl DC, Martin DE. Prolonged bradycardia after neostigmine administration in a patient taking nadolol. *Anesth Analg* 1984; **63:** 365–7.
3. Baraka A, Dajani A. Severe bradycardia following physostigmine in the presence of beta-adrenergic blockade: a case report. *Middle East J Anesthesiol* 1984; **7:** 291–3.
4. Eldor J, *et al*. Prolonged bradycardia and hypotension after neostigmine administration in a patient receiving atenolol. *Anaesthesia* 1987; **42:** 1294–7.
5. Arad M, *et al*. Safety of pyridostigmine in hypertensive patients receiving beta blockers. *Am J Cardiol* 1992; **69:** 518–22.

Calcium-channel blockers. Use of calcium-channel blockers such as *verapamil* with neuromuscular blockers may produce an enhanced muscle block which is resistant to reversal with neostigmine[1] but which can be reversed by edrophonium.[2]

1. van Poorten JF, *et al*. Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; **63:** 155–7.
2. Jones RM, *et al*. Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; **64:** 1021–5.

Corticosteroids. Although use of glucocorticoids alone may improve strength in myasthenic patients, use of *methylprednisolone* in patients receiving neostigmine or pyridostigmine has exacerbated symptoms and produced profound weakness needing assisted ventilation.[1] Since the adverse effects of combined therapy usually occur before any expected benefits it has been suggested that the glucocorticoid should be given on alternate days in small doses which are increased gradually until the optimal effect is achieved.[2]

1. Brunner NG, *et al*. Corticosteroids in management of severe, generalized myasthenia gravis: effectiveness and comparison with corticotrophin therapy. *Neurology* 1972; **22:** 603–10.
2. Jubiz W, Meikle AW. Alterations of glucocorticoid actions by other drugs and disease states. *Drugs* 1979; **18:** 113–21.

Pharmacokinetics

Neostigmine is a quaternary ammonium compound and, as the bromide, is poorly absorbed from the gastrointestinal tract. After parenteral doses as the metilsulfate, neostigmine is rapidly eliminated and is excreted in the urine both as unchanged drug and metabolites. Neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Protein binding to human serum albumin is reported to range from 15 to 25%. Penetration into the CNS is poor. Neostigmine crosses the placenta and very small amounts are distributed into breast milk.

Neostigmine appears to be poorly and variably absorbed when given orally. In 3 myasthenic patients peak plasma concentrations were obtained 1 to 2 hours after a single 30-mg oral dose and the mean plasma half-life was 0.87 hours; bioavailability was estimated to be 1 to 2%.[1] Mean plasma half-lives of 0.89 and 1.20 hours have been obtained after intravenous[1] and intramuscular[2] injections of neostigmine metilsulfate, respectively, although again only a few patients were studied. Metabolism and biliary excretion may play significant roles in the elimination of neostigmine.[2] About 80% of a dose may be excreted in the urine within 24 hours: about 50% of a dose as unchanged drug and 15% as 3-hydroxyphenyltrimethylammonium.[2] Mean plasma elimination half-lives for neostigmine have been found to be shorter in infants (0.65 hours) and children (0.80 hours) compared with adults (1.12 hours) but this does not appear to be related to its duration of effect in antagonising neuromuscular blockade.[3] For the half-life in anephric patients, see Renal Impairment, p. 688.3.

1. Aquilonius S-M, *et al*. A pharmacokinetic study of neostigmine in man using gas chromatography–mass spectrometry. *Eur J Clin Pharmacol* 1979; **15:** 367–71.
2. Somani SM, *et al*. Kinetics and metabolism of intramuscular neostigmine in myasthenia gravis. *Clin Pharmacol Ther* 1980; **28:** 64–8.
3. Fisher DM, *et al*. The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983; **59:** 220–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fadastigmina; Prostigmin; ***Austral.***: Prostigmin†; ***Austria***: Normastigmin; Prostigmin†; ***Belg.***: Prostigmine; Robinul-Neostigmine; ***Braz.***: Normastig; Prostigmine; ***Canad.***: Prostigmin; ***China***: Yi Ding (依定); ***Cz.***: Syntostigmin; ***Denm.***: Robinul-Neostigmin; ***Fin.***: Glycostigmin; Robinul-Neostigmin; ***Fr.***: Prostigmine; ***Ger.***: Neostig; ***Gr.***: Normastigmin; Prostigmine; ***Hung.***: Stigmosan; ***India***: Beemine; Myostigmin; Tilstigmin; ***Indon.***: Prostigmin; ***Ital.***: Intrastigmina; Prostigmina; ***Malaysia***: Setisin; ***Mex.***: Prostigmine; ***Neth.***: Prostigmin; ***Norw.***: Robinul-Neostigmin; ***Philipp.***: Prostig; Prostigmin; ***Pol.***: Polstigminum; ***Port.***: Intrastigmina; ***Singapore***: Prostigmin; Setisin; ***Spain***: Prostigmine†; ***Swed.***: Robinul-Neostigmin; ***Switz.***: Prostigmin; Robinul-Neostigmine; ***Thai.***: Prostigmin; ***Turk.***: Plantigmin; ***UK***: Robinul-Neostigmine†; ***USA***: Bloxiverz; Neostigmine Min-I-Mix; Prostigmin.

Multi-ingredient Preparations. ***Austria***: Normastigmin mit Pilocarpin; ***China***: Xin Le Dun (新乐敦); ***India***: Myo-Pyrolate.

Pharmacopoeial Preparations

BP 2014: Neostigmine Injection; Neostigmine Tablets;
USP 36: Neostigmine Bromide Tablets; Neostigmine Methylsulfate Injection.

Pyridostigmine Bromide *(BAN, rINN)*

Bromure de Pyridostigmine; Bromuro de piridostigmina; Piridostigmin Bromür; Piridostigmina, bromuro de; Piridostigmino bromidas; Piridosztigmin-bromid; Pyridostig. Brom.; Pyridostigmiinibromidi; Pyridostigmin Bromid; Pyridostigminbromid; Pyridostigmine, Bromure de; Pyridostigmini bromidum; Pyridostigminii Bromidum; Pyridostigminium-bromid; Пиридостигмина Бромид.

3-Dimethylcarbamoyloxy-1-methylpyridinium bromide.

$C_9H_{13}BrN_2O_2$=261.1

CAS — 155-97-5 (pyridostigmine); 101-26-8 (pyridostigmine bromide).

ATC — N07AA02.

ATC Vet — QN07AA02.

UNII — KVI301NA53.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Pyridostigmine Bromide). A white or almost white deliquescent crystalline powder. Very soluble in water and in alcohol. Store in airtight containers. Protect from light.

USP 36: (Pyridostigmine Bromide). A white or practically white, hygroscopic, crystalline powder, having an agreeable characteristic odour. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether; slightly soluble in petroleum spirit. Store in airtight containers.

Uses and Administration

Pyridostigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2), but is slower in onset and of longer duration. It is given as the bromide.

Pyridostigmine is mainly used in the treatment of myasthenia gravis (p. 684.1) although its use in neonatal myasthenia has declined in favour of neostigmine. It has also been used in the treatment of paralytic ileus. Pyridostigmine is sometimes used to reverse the neuromuscular blockade produced by competitive neuromuscular blockers but is generally considered less satisfactory than neostigmine. It has also been used as prophylaxis against the neuromuscular effects of nerve gas poisoning (below). Pyridostigmine has been used in the management of postoperative urinary retention (p. 2349.2) but has generally been superseded by catheterisation.

For **myasthenia gravis**, UK licensed product information states that total daily oral doses may range from 300 mg to 1.2 g; however, the *BNF* states that daily doses of 450 mg should not be exceeded in order to avoid receptor downregulation. It also noted that patients receiving pyridostigmine in doses over 360 mg daily may need more aggressive therapy. In the USA, licensed doses are somewhat higher, ranging up to 1.5 g daily.

The dose should be divided throughout the day and, if necessary, the night, according to response; larger portions of the total daily dose may be given at times of greater fatigue.

Pyridostigmine has also been given as modified-release tablets, usually once or twice daily but these offer less flexibility of dosage. If necessary it has also been given by intramuscular injection or in severe cases by very slow intravenous injection. However, the intravenous route is hazardous and, if used, atropine must be available to counteract any severe muscarinic reactions. Parenteral doses are about one-thirtieth of the usual oral dose.

To **reverse neuromuscular blockade** produced by *competitive neuromuscular blockers*, doses of 100 to 250 micrograms/kg (about 10 to 20 mg) have been given intravenously, with or preceded by intravenous atropine sulfate 0.6 to 1.2 mg to counteract any muscarinic effects. Glycopyrronium bromide has been used as an alternative to atropine.

Pyridostigmine is also used for prophylaxis against the neuromuscular effects of nerve gas poisoning, including *soman*, in military combat use only; the recommended oral dose is 30 mg every 8 hours started at least several hours before exposure. If nerve gas poisoning occurs, pyridostigmine should be stopped and the patient should be treated with atropine and pralidoxime immediately.

In the treatment of paralytic **ileus** and postoperative **urinary retention** pyridostigmine bromide has been given in oral doses of 60 to 240 mg.

For details of doses in children, see below.

Administration in children. The use of pyridostigmine in children is similar to that in adults (see Uses and Administration, above).

UK licensed product information states that children may be given pyridostigmine, as the bromide, for the treatment of **myasthenia gravis** in an initial oral dose of 30 mg for those aged under 6 years or 60 mg for those aged 6 to 12 years, repeated throughout the day. This is increased gradually by increments of 15 to 30 mg daily until a satisfactory response is obtained, which is usually within the dosage range of 30 to 360 mg daily. Alternatively, the *BNFC* suggests that children aged 1 month to 12 years may be given an initial oral dose of 1 to 1.5 mg/kg daily, increased gradually to 7 mg/kg daily in 6 divided doses, to a usual total dose of 30 to 360 mg daily. Older children may be given the usual adult dose. In the USA, an oral dose of 7 mg/kg daily in 5 or 6 divided doses has also been suggested. Those patients who require parenteral therapy have been given an intramuscular or intravenous dose of 50 to 150 micrograms/kg (up to a maximum of 10 mg) every 4 to 6 hours.

In the treatment of neonatal myasthenia doses in the range of 50 to 150 micrograms/kg by intramuscular injection or 5 mg orally have been given every 4 to 6 hours. Alternatively, the *BNFC* recommends an oral dose based on neonatal weight: initially 1 to 1.5 mg/kg, increased gradually to a maximum of 10 mg, repeated throughout the day, and given 30 to 60 minutes before feeds. Treatment is rarely needed beyond 8 weeks of age.

For the treatment of paralytic **ileus** and postoperative **urinary retention**, children have been given oral doses of 15 to 60 mg.

Decreased gastrointestinal motility. Parasympathomimetics such as pyridostigmine enhance gastric contractions and increase intestinal motility; they have been used in conditions associated with decreased gastrointestinal motility (p. 1808.2).

Pyridostigmine, generally in doses of 60 mg up to 3 times daily, has been used to relieve severe constipation in patients with impaired intestinal motility due to Parkinson's disease.[1] It has also been tried in patients with constipation due to autonomic neuropathy;[2] however, results have been equivocal.

1. Sadjadpour K. Pyridostigmine bromide and constipation in Parkinson's disease. *JAMA* 1983; **249:** 1148.
2. Bharucha AE, *et al*. Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. *Clin Auton Res* 2008; **18:** 194–202.

Growth hormone deficiency. Although the value of stimulated growth hormone secretion tests in children has been questioned (see Growth Retardation, p. 1921.3), pyridostigmine with somatorelin has been found to be a potent and reproducible test for distinguishing adults with severe growth hormone deficiency from normal subjects.[1] However, the combination is not effective in patients over 55 years of age,[2] and somatorelin with arginine is generally preferred where an alternative to the gold standard of the insulin-tolerance test is required.[1]

1. Ghigo E, *et al*. Diagnostic and therapeutic uses of growth hormone-releasing substances in adult and elderly subjects. *Baillieres Clin Endocrinol Metab* 1998; **12:** 341–58.
2. Vierhapper H, *et al*. The use of the pyridostigmine growth hormone-releasing hormone stimulation test to detect growth hormone deficiency in patients with pituitary adenomas. *Metabolism* 2002; **51:** 34–7.

Nerve gas poisoning. Pyridostigmine has been used prophylactically to protect soldiers in the event of an attack with nerve gas agents (p. 2568.3) that inhibit acetylcholinesterase.[1] Pyridostigmine binds reversibly to acetylcholinesterase and provides a protected store from which acetylcholinesterase is later released.[1-3] Prophylaxis with pyridostigmine greatly enhances the efficacy of treatment with atropine and pralidoxime against exposure to *soman* but it is not effective alone and may not be uniformly effective against other nerve agents.[1] Giving 30 mg of pyridostigmine every 8 hours provides the optimum level of protection[2] and, although adverse effects are common at this dosage, the performance of military duties is not impaired.[4] However, neurological symptoms in veterans suffering the so-called Gulf War Syndrome appear to be

more common in those who reported exposure to a range of potentially toxic substances which include pyridostigmine.[5] It has been suggested that these symptoms may be evidence of organophosphate-induced polyneuropathy resulting from exposure to a combination of organophosphorus compounds and other cholinesterase inhibitors such as pyridostigmine.[6] A study in *hens*[7] (a species susceptible to anticholinesterases) has also found symptoms of enhanced neurotoxicity when pyridostigmine, the insect repellent diethyltoluamide, and the pyrethroid insecticide permethrin were used together.

1. United States Army, *Medical management of chemical casualties handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense;1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/Red-Handbook/001TitlePage.htm (accessed 15/02/06)
2. Ministry of Defence. *Medical manual of defence against chemical agents.* London: HMSO, 1987. (JSP312).
3. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; **44:** 1–4.
4. Keeler JR, *et al.* Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA* 1991; **266:** 693–5.
5. The Iowa Persian Gulf Study Group. Self-reported illness and health status among gulf war veterans: a population-based study. *JAMA* 1997; **277:** 238–45.
6. Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the gulf war: a cross-sectional epidemiologic study. *JAMA* 1997; **277:** 231–7.
7. Abou-Donia MB, *et al.* Neurotoxicity resulting from coexposure to pyridostigmine bromide, DEET, and permethrin: implications of gulf war chemical exposure. *J Toxicol Environ Health* 1996; **48:** 35–56.

Orthostatic hypotension. Pyridostigmine has been investigated in the treatment of orthostatic hypotension (p. 1634.3). A review[1] of 4 single-dose studies and a follow-up survey (involving a total of 106 patients and generally reporting an improvement in haemodynamic measurements) concluded that there was insufficient long-term data to support the routine use of pyridostigmine in the treatment of orthostatic hypotension.

1. Gales BJ, Gales MA. Pyridostigmine in the treatment of orthostatic intolerance. *Ann Pharmacother* 2007; **41:** 314–18.

Post-poliomyelitis syndrome. Although pyridostigmine has been reported[1] in some patients to reduce fatigue associated with post-poliomyelitis syndrome, a systematic review failed to find any benefit.[2] Doses used[3] have included 30 mg daily increased gradually to about 60 mg three times daily but adverse effects are common.

1. Trojan DA, Cashman NR. Anticholinesterases in post-poliomyelitis syndrome. *Ann N Y Acad Sci* 1995; **753:** 285–95.
2. Koopman FS, *et al.* Treatment for postpolio syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 12/04/11).
3. Thorsteinsson G. Management of postpolio syndrome. *Mayo Clin Proc* 1997; **72:** 627–38.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2. It has been stated that muscarinic adverse effects occur less frequently with pyridostigmine treatment than with neostigmine.

Breast feeding. Pyridostigmine was present in the breast milk of 2 nursing mothers, receiving maintenance therapy for myasthenia gravis, in a concentration between 36 and 113% of that in maternal plasma,[1] but in both cases the dose ingested per kg body-weight by the nursing infant was 0.1% or less of that ingested by the mother. Maternal medication with pyridostigmine should be no obstacle to breast feeding, at least with doses in the range of 180 to 300 mg daily.

On the basis of this study, the last available guidance from the American Academy of Pediatrics considered[2] that pyridostigmine is usually compatible with breast feeding.

1. Hardell L-I, *et al.* Pyridostigmine in human breast milk. *Br J Clin Pharmacol* 1982; **14:** 565–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/02/06)

Effects on the joints. Several years after starting oral pyridostigmine bromide 60 mg five times daily, a middle-aged woman had episodes of bilateral arthralgia and hyperalgesia of her hips, knees, toes, and shoulders.[1] Symptoms resolved when pyridostigmine was stopped and rechallenge was positive on several occasions.

1. Rostedt A, Stålberg E. Joint pain and hyperalgesia due to pyridostigmine bromide in a patient with myasthenia gravis. *Neurology* 2004; **62:** 835–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pyridostigmine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/07/11)

Psychosis. Postoperative psychosis in a patient with myasthenia gravis who received large doses of pyridostigmine bromide was attributed to bromide intoxication,[1] but this diagnosis has been challenged.[2]

1. Rothenberg DM, *et al.* Bromide intoxication secondary to pyridostigmine bromide therapy. *JAMA* 1990; **263:** 1121–2.
2. Senecal P-E, Osterloh J. Confusion from pyridostigmine bromide: was there bromide intoxication? *JAMA* 1990; **264:** 454–5.

Renal impairment. During use of pyridostigmine for the reversal of neuromuscular blockade produced by competitive neuromuscular blockers, pyridostigmine kinetics were not significantly different after renal transplantation in 5 patients compared with those in 5 patients with normal renal function. However, in 4 anephric patients the elimination half-life was significantly increased and the plasma clearance significantly decreased.[1] It appeared that about 75% of the plasma clearance of pyridostigmine depended on renal function.

1. Cronnelly R, *et al.* Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980; **28:** 78–81.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Pyridostigmine bromide is poorly absorbed from the gastrointestinal tract. It undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Pyridostigmine is excreted mainly in the urine as unchanged drug and metabolites. Pyridostigmine crosses the placenta and is distributed into breast milk (see Breast Feeding, above). Penetration into the CNS is poor.

It has been suggested[1] that data from pharmacokinetic studies of pyridostigmine might have varied because of the analytical methods used or inappropriate storage conditions of plasma samples; it was recommended that samples should be acidified and stored at -75 degrees. Mean terminal elimination half-life was 200 minutes in 11 healthy subjects given 60 mg of pyridostigmine orally; peak plasma concentrations were obtained 1 to 5 hours after dosing. The mean terminal elimination half-life after a 4-mg intravenous infusion in 10 of these subjects was 97 minutes.[1] Oral bioavailability was calculated to vary from 11.5 to 18.9%. In an earlier study food did not appear to affect bioavailability but did delay the time taken to achieve peak plasma concentrations.[2] It appears that 75% of the plasma clearance of pyridostigmine depends on renal function.[3] 3-Hydroxy-*N*-methylpyridinium has been identified as one of the 3 metabolites isolated from the urine of patients taking pyridostigmine.[4]

1. Breyer-Pfaff U, *et al.* Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther* 1985; **37:** 495–501.
2. Aquilonius S-M, *et al.* Pharmacokinetics and oral bioavailability of pyridostigmine in man. *Eur J Clin Pharmacol* 1980; **18:** 423–8.
3. Cronnelly R, *et al.* Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980; **28:** 78–81.
4. Somani SM, *et al.* Pyridostigmine in man. *Clin Pharmacol Ther* 1972; **13:** 393–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mestinon; Piridos†; ***Austral.***: Mestinon; ***Austria***: Mestinon; ***Belg.***: Mestinon; ***Braz.***: Mestinon; ***Canad.***: Mestinon; ***Chile***: Mestinon; ***Cz.***: Mestinon; ***Denm.***: Mestinon; ***Fin.***: Mestinon; ***Fr.***: Mestinon; ***Ger.***: Kalymin; Mestinon; ***Gr.***: Mestinon; ***Hong Kong***: Mestinon; ***Hung.***: Mestinon; ***India***: Distinon; Gravitor; Mesilon; Mustone; Myestin; ***Indon.***: Mestinon; ***Irl.***: Mestinon; ***Israel***: Mestinon; ***Ital.***: Mestinon; ***Malaysia***: Mestinon; ***Mex.***: Mestinon; ***Neth.***: Mestinon; ***Norw.***: Mestinon; ***NZ***: Mestinon; ***Philipp.***: Astinon; Mestinon; Pyrinon; ***Pol.***: Mestinon; ***Port.***: Mestinon; ***Rus.***: Kalymin (Калимин); ***S.Afr.***: Mestinon†; ***Singapore***: Mestinon; ***Spain***: Mestinon; ***Swed.***: Mestinon; ***Switz.***: Mestinon; ***Thai.***: Mestinon; Pyrimine; ***Turk.***: Mestinon; ***UK***: Mestinon; Nerve Agent Pre-Treatment Tablet Set L1A1; ***USA***: Mestinon; ***Venez.***: Mestinon.

Pharmacopoeial Preparations

BP 2014: Pyridostigmine Tablets;

USP 36: Pyridostigmine Bromide Injection; Pyridostigmine Bromide Syrup; Pyridostigmine Bromide Tablets.

Antineoplastics

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Antineoplastic drugs are used in the treatment of malignant neoplasms
- as the primary treatment in responsive neoplasms
- when surgery or radiotherapy is not possible or has proved ineffective
- combined in different ways with surgery or radiotherapy such as concurrently, sequentially, neoadjuvant (pre-operative), or adjuvant (postoperative)

Therapy with antineoplastics is notably successful in a few malignant conditions and may be used to palliate symptoms and prolong life in others.

Factors that are taken into account when prescribing chemotherapy include the type of cancer and its primary location, the general health of the patient (patient status), and the extent, or stage, of the disease. There are different staging systems; one commonly used system, the TNM staging system, describes the extent of solid cancers by numbers:
- T (tumour) refers to the size of the cancer: from 1 (small) to 4 (large)
- N (node) refers to whether the cancer has spread to the lymph nodes: from 0 (no positive nodes) to 3 (many positive nodes)
- M (metastases) refers to whether the cancer has metastasised: 0 (no metastases) or 1 (metastases)

Haematological cancers are classified differently and depend on the particular malignancy, but the extent of the disease is often described by the number and spread of affected lymph nodes and the symptoms of the patient.

The two main groups of classical cytotoxic drugs used in the treatment of malignant disease are the alkylating agents and the antimetabolites. Nitrogen mustards, ethyleneimine compounds, and alkyl sulfonates are the main **alkylating agents**. Other compounds with an alkylating action are the various nitrosoureas. Dacarbazine and the **platinum-containing complex** cisplatin appear to act similarly.

The **antimetabolites** may be subdivided into folic acid, purine, or pyrimidine antagonists.

Several natural products, or their derivatives, are used for their actions as **mitotic inhibitors**; they include the vinca alkaloids and the taxanes. Other drugs act as **topoisomerase inhibitors**, interfering with the coiling and uncoiling of DNA during replication. Drugs thought to act in this way include the podophyllotoxin derivatives such as etoposide, and camptothecin derivatives such as irinotecan and topotecan.

Some **antibiotics** such as the anthracyclines, bleomycin, and mitomycin C, also interfere with nucleic acids and are effective as antineoplastics.

Further described in this section are **other drugs** that act by various routes to affect the growth and proliferation of malignant cells. Better understanding of the biology of tumour cells has led to the development of new classes of these, including **tyrosine kinase inhibitors** such as imatinib and related drugs. Some neoplasms express receptors to endogenous sex hormones, and various **hormone antagonists**, including, notably, the **aromatase inhibitors** are used in their management. **Photosensitisers** such as porfimer sodium are used in photodynamic therapy.

In recent years considerable interest has focused on immunological approaches to the treatment of malignant disease and many **monoclonal antibodies** have been, or are being, developed. The use of **biological response modifiers** such as interleukins continues to be the subject of investigation and attempts to develop vaccines against individual neoplasms also continue.

Glucocorticoids (see Corticosteroids, p. 1597.3) are used with antineoplastics in the treatment of malignant disease, especially in acute leukaemias and lymphomas. Other agents used in antineoplastic therapy include sex hormones (p. 2231.1) and radiopharmaceuticals (p. 2222.1). Haematopoietic stem cell transplantation (p. 1937.1) is used for haematological malignancies.

Choice of Antineoplastic

The following section describes the treatment of some of the major malignant neoplasms, and in particular the role of combination chemotherapy with antineoplastics.

Table 1 (p. 719) lists published initial doses for some well-known combination chemotherapy regimens. Doses may be modified (particularly in subsequent cycles) to allow for patient status and toxic effects, although in some cases this may be at the expense of efficacy. Regimens can also vary slightly between institutions, or may be modified as part of the ongoing evolution of cancer chemotherapy; such therapy should preferably take place only in expert centres. The same acronym has sometimes been used for regimens containing different drugs, or using the same drugs in different doses or in different ways, and the reader should consult the literature for further details.

Management of malignant disease

Gestational trophoblastic tumours. The gestational trophoblastic diseases arise from the trophoblast, the first tissue to differentiate in the early embryo: they are associated with conception and pregnancy and affect women of reproductive age. They may be divided into premalignant forms such as molar pregnancy (complete or partial hydatidiform mole) and malignant forms (gestational trophoblastic tumours) which include invasive mole (chorioadenoma destruens), choriocarcinoma, and placental site trophoblastic tumour.[1-6] Hydatidiform moles are abnormal conceptions with excessive placental and some or no fetal development. Complete and partial hydatidiform moles have distinctive histological and genetic features, but both overexpress paternal genes.[1,2,7] Gestational trophoblastic neoplasia can develop after any type of pregnancy,[1,2,6] although the incidence is greater after premalignant complete or partial molar pregnancies;[3] the risk of malignancy after a complete or partial hydatidiform mole is about 15% and 0.5%, respectively.[3,5,7]

All these tumours secrete human chorionic gonadotrophin (hCG), and measurement of the urinary or serum concentrations is important in diagnosis of disease and monitoring of treatment.[1,4,5,7]

The trophoblastic tumours vary in aggressiveness but some, such as choriocarcinoma, are highly invasive; however, appropriate **treatment**, based on the perceived risk category, can result in an excellent prognosis. Prognostic factors for increased risk include high titres of hCG, liver or brain metastases, and failure of previous single-agent chemotherapy as well as greater age.[3-5,8] With current treatment, including local irradiation for metastases, virtually 100% of patients with localised disease should be cured, as are over 80% of patients with more advanced stages.

Prophylactic chemotherapy has been used in women considered at particular risk of persistent gestational trophoblastic tumour after evacuation of a complete molar pregnancy, but the practice is controversial, with anecdotal reports of fatalities; most consider the risk to be too high, especially given the low morbidity and mortality achieved with monitoring.[1,4]

In patients with ***low-risk disease***, the treatment of choice is single-agent therapy with methotrexate or dactinomycin.[1-3,5,6,9] The choice of regimen usually depends on geographical location and local experience,[9,10] as comparative data are lacking.[3] Intramuscular methotrexate is often given on alternate days, or weekly, with or without folinic acid rescue.[3-6,9,10] Several intravenous dactinomycin schedules have been used; there is some suggestion that a daily regimen may be more effective than pulsed treatment.[3,5] A systematic review that included 4 randomised studies concluded that pulsed dactinomycin was superior to weekly methotrexate.[10] However, while dactinomycin may provide slightly higher remission rates, toxicity may be greater,[4] and since methotrexate is easier to give some favour methotrexate with folinic acid as first-line treatment.[5] Alternating cycles or sequential use of both drugs have also been tried.[4,9]

Irrespective of which drug is used first-line, a switch to the alternate drug is considered appropriate in cases of resistance.[3,5] If this also fails, then combination chemotherapy is indicated; regimens are similar to those used in high-risk disease.[4]

The combination EMA-CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine) is the preferred treatment in ***high-risk*** patients.[2-6,8,11] Methotrexate, dactinomycin, and etoposide is also used.[2,3,5] Triple therapy with methotrexate, dactinomycin, and either cyclophosphamide or chlorambucil was the standard regimen for many years in the USA,[1,4] but was associated with toxicity and poor survival.[2,4] However, comparative data are lacking, and the superiority of any individual combination regimen remains to be established.[1,4,8] In

refractory disease, the salvage regimen EMA-EP uses etoposide and cisplatin in place of cyclophosphamide and vincristine in EMA-CO.[3,5,11,12] Other regimens have used etoposide and cisplatin with either bleomycin (BEP) or ifosfamide (VIP).[3,11,12]

Brain ***metastases*** are generally treated by local irradiation, given with systemic chemotherapy. Modified EMA-CO, using a higher dose of systemic methotrexate and adding intrathecal methotrexate, is also used.[1,2,4,5,11] Liver metastases have been treated with irradiation, local chemoembolisation, or surgical resection.[2,4,11]

Patients with placental site trophoblastic tumour, which is relatively insensitive to chemotherapy, may be best treated by hysterectomy in the early stages.[2,5] In patients with metastatic or recurrent disease, EMA-EP may be more effective than EMA-CO.[13] For further information on these and other common chemotherapy regimens, see Table 1, p. 719.

1. Soper JT, *et al*. American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. *Gynecol Oncol* 2004; **93:** 575–85.
2. El-Helw LM, Hancock BW. Treatment of metastatic gestational trophoblastic neoplasia. *Lancet Oncol* 2007; **8:** 715–24.
3. Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. *Curr Opin Oncol* 2007; **19:** 486–91.
4. Soper JT. Gestational trophoblastic disease. *Obstet Gynecol* 2006; **108:** 176–87.
5. Sarwar N, *et al*. Gestational trophoblastic neoplasia: the management of relapsing patients and other recent advances. *Curr Oncol Rep* 2004; **6:** 476–82.
6. Royal College of Obstetricians and Gynaecologists. Guideline no. 38: the management of gestational trophoblastic disease (issued February 2010). Available at: http://www.rcog.org.uk/files/rcog-corp/GT38ManagementGestational0210.pdf (accessed 12/07/10)
7. Sebire NJ, Seckl MJ. Gestational trophoblastic disease: current management of hydatidiform mole. Abridged version: *BMJ* 2008; **337:** a1193. Full version: http://www.bmj.com/cgi/content/full/337/aug15_1/a1193 (accessed 18/03/09) Correction. *ibid.;* a1473.
8. Deng L, *et al*. Combination chemotherapy for high-risk gestational trophoblastic tumour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 13/07/09).
9. Osborne R, Gerulath A. What is the best regimen for low-risk gestational trophoblastic neoplasia? A review. *J Reprod Med* 2004; **49:** 602–16.
10. Alazzam M, *et al*. First line chemotherapy in low risk gestational trophoblastic neoplasia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 18/03/09).
11. Lurain JR. Advances in management of high-risk gestational trophoblastic tumors. *J Reprod Med* 2002; **47:** 451–9.
12. Lurain JR, Nejad B. Secondary chemotherapy for high-risk gestational trophoblastic neoplasia. *Gynecol Oncol* 2005; **97:** 618–23.
13. Behtash N, Karimi Zarchi M. Placental site trophoblastic tumor. *J Cancer Res Clin Oncol* 2008; **134:** 1–6.

Histiocytic syndromes. Histiocytic syndromes cover a broad range of proliferative disorders of histiocytes (such as macrophages and dendritic cells).[1] Langerhans-cell histiocytosis is one such disorder characterised by proliferation of CD1a-positive Langerhans cells (a form of dendritic cell).[2] Terms that were formerly used for different clinical manifestations of Langerhans-cell histiocytosis include histiocytosis X, type II histiocytosis, eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe disease, but these are considered obsolete.[3] Langerhans-cell histiocytosis mainly presents in childhood, and is of uncertain aetiology: it is not clear whether it should be considered a malignancy.[2,4,5]

The clinical presentation of Langerhans-cell histiocytosis is highly variable and can include bone pain, weight loss, fever, skin rash, dyspnoea or tachypnoea, polydipsia and polyuria, lymphadenopathy, gingival hypertrophy, ataxia, and memory problems.[2,5] Depending on the organs involved, it has been categorised into localised or single-system disease, and disseminated or multisystem disease.[1,4,5] Single-system disease can be further categorised based on the number of sites involved (unifocal or multifocal).[1] Multisystem disease may be further subdivided into low-risk and high-risk groups depending upon which organs are involved; risk organs include the haematopoietic system, lungs, liver, and spleen.[1,5,6] Sequelae to the disease include diabetes insipidus, growth retardation, cognitive dysfunction, and orthopaedic handicap.[1,2,4] The morbidity and prognosis depends upon the number of organ systems involved, and whether normal function of these organs is affected.[1] Patients with **single-system disease** have a generally benign course, and single lesions often regress spontaneously. However, if a bone lesion does not resolve, or risks causing fracture or deformity before it resolves, or is causing disabling symptoms, it may be treated with curettage, intralesional corticosteroids, or radiotherapy.[1,4,5] Systemic chemotherapy may be suitable in some patients with multifocal bone disease; vinblastine with prednisone or prednisolone is a suggested regimen,[2,4,6] and may also be used for high-risk single lesions.[6] Similarly, single skin lesions may be allowed to resolve without treatment or treated with surgery, topical corticosteroids, methoxsalen plus UV light (PUVA), or topical chlormethine.[1,4,5,7]

Treatment for **multisystem disease** is controversial. Some advocate high-dose prednisone or single-agent chemotherapy as first-line options. Combination chemotherapy regimens may give greater response rates with fewer recurrences.[1] Corticosteroids and vinblastine for about 6 to 12 months are the most commonly used drugs; mercaptopurine and methotrexate have also been used with reports of efficacy.[4] A comparative study in children with multisystem disease found treatment with vinblastine or etoposide for 6 months to be equally effective.[8] Subsequent study showed that vinblastine with etoposide was not superior to vinblastine alone (when combined with corticosteroids and mercaptopurine).[2,4,6] Systemic corticosteroids have also been used for recalcitrant skin disease or multisystem disease in children[7] and for pulmonary Langerhans-cell histiocytosis in adults.[9] In patients who have not responded to combination chemotherapy, a number of treatments may be considered including ciclosporin,[4,7] thalidomide,[7] and high-dose chemotherapy with haematopoietic stem cell transplantation.[2,4,5] Cladribine has been used for multisystem disease with varying results;[5,7] an intensive regimen of cladribine and high-dose cytarabine may be effective for recurrent or refractory disease.[2] Anti-CD1 monoclonal antibodies[1,5] may offer improved therapeutic or diagnostic options in the future.

1. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008; **25:** 291–5.
2. Gasent Blesa JM, *et al*. Langerhans cell histiocytosis. *Clin Transl Oncol* 2008; **10:** 688–96.
3. Favara BE, *et al*. Contemporary classification of histiocytic disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations and Reclassification Working Group of the Histiocyte Society. *Med Pediatr Oncol* 1997; **29:** 157–66.
4. Henter JI, *et al*. Histiocyte disorders. *Crit Rev Oncol Hematol* 2004; **50:** 157–74.
5. Stockschlaeder M, Sucker C. Adult Langerhans cell histiocytosis. *Eur J Haematol* 2006; **76:** 363–8.
6. Windebank K, Nanduri V. Langerhans cell histiocytosis. *Arch Dis Child* 2009; **94:** 904–8.
7. Chu T. Langerhans cell histiocytosis. *Australas J Dermatol* 2001; **42:** 237–42.
8. Gadner H, *et al*. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; **138:** 728–34. Correction. *ibid.;* **139:** 170.
9. Vassallo R, *et al*. Pulmonary Langerhans'-cell histiocytosis. *N Engl J Med* 2000; **342:** 1969–78.

Leukaemias, acute. The acute leukaemias are malignancies affecting haematopoietic precursor cells. They are relatively rare (about 1 to 3 cases per 100 000 of population), and of uncertain cause in the majority of cases, although radiation, carcinogenic substances, or oncogenic retroviruses have been implicated in some types, and certain individuals appear to have a genetic predisposition to these diseases.

After the initiating event or events the progeny of the affected cell do not differentiate normally but proliferate in an uncontrolled fashion. The result is the accumulation in the blood and bone marrow of immature cell types (blasts) at the expense of normal functional blood cells.

The acute leukaemias may be broadly divided into **acute lymphoblastic leukaemia** (ALL), in which the neoplastic proliferation affects lymphoid cell lines, and the **acute myeloid leukaemias** (AML), variously known as acute myelogenous leukaemias or acute non-lymphoblastic leukaemias, which affect myeloid cell lines. These broad groups can be divided in various ways. ALL is subdivided by an immunophenotypic classification that distinguishes disease of B- and T-cell lineage; it was formerly divided morphologically into L1, L2, and L3 subtypes. For AML the French-American-British (FAB) classification has been widely used. This distinguishes, by lineage and estimated degree of differentiation:

- M0, undifferentiated AML
- M1, AML with minimal maturation
- M2, AML with maturation
- M3, acute promyelocytic leukaemia
- M4, acute myelomonocytic leukaemia
- M5, acute monocytic leukaemia
- M6, erythroid leukaemia
- M7, megakaryocytic leukaemia.

However, knowledge of the genotype, via cytogenetic or molecular analysis, is becoming increasingly important in the treatment of leukaemia. Consequently, a revised classification system has been proposed under the auspices of WHO, which uses a combination of morphology, immunophenotype, genetic, biological, and clinical features. In this classification,[1,2] AML is divided into 4 main groups:

- AML with recurrent cytogenic translocations
- AML with myelodysplasia-related features
- AML, therapy-related
- AML not otherwise specified.

The terms *de novo* and secondary AML are widely used but are without standardised definitions. It has been proposed that *de novo* AML should refer to AML in patients with no clinical history of myelodysplastic syndrome, myeloproliferative disorder, or exposure to potentially leukaemogenic agents; secondary AML should refer to patients with AML secondary to these disorders or proven leukaemogenic exposure.[3]

In the WHO classification of lymphoid neoplasms, the Revised European-American Lymphoma (REAL) classification has been adopted, in which acute lymphoblastic leukaemias and lymphoblastic lymphomas are considered to be a single disease with different presentations.[1]

Acute leukaemia usually presents with fatigue, anaemia, infection (due to granulocytopenia), and easy bruisability or bleeding (mainly due to thrombocytopenia). Onset is usually rapid with ALL, although AML may be preceded by myelodysplasia lasting months or years. Bone pain, and enlargement of liver, spleen and lymph nodes due to infiltration of leukaemic cells may occur. Other organs may also be affected, and various metabolic disturbances, including hyperuricaemia, hyponatraemia, and hypokalaemia may be present.

If untreated the acute leukaemias are normally fatal, usually within months. However, these malignancies are among those in which medical treatment can make a substantial difference to life expectancy, and in some cases a permanent remission may be effected.

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ACUTE LYMPHOBLASTIC LEUKAEMIA. Treatment of acute lymphoblastic leukaemia (ALL) is usually stratified according to risk, with the intensity of therapy tailored to the predicted risk of relapse. Factors associated with a poor prognosis or high risk include age (infant or age greater than 10 years), high white cell count at diagnosis, poor response to induction therapy, and some genetic abnormalities such as the Philadelphia chromosome.[1-5]

Standard chemotherapy treatment regimens for T-cell and precursor B-cell ALL generally consist of 2 to 3 years of therapy divided into several phases:

- **Remission induction**
  Induction regimens are typically based around a regimen that includes vincristine, a corticosteroid (dexamethasone, prednisolone, or prednisone), an anthracycline (doxorubicin or daunorubicin), with or without asparaginase or pegaspargase, and/or cyclophosphamide.
- **Consolidation (intensification)**
  Although the importance of this phase is rarely disputed, consensus is lacking on the best regimens and duration of treatment. Drugs used include high-dose cytarabine, high-dose methotrexate, mercaptopurine, vincristine, and other antineoplastics used in induction regimens; often 4- to 5-drug combinations are used. Re-induction can further improve outcomes.
- **Maintenance (continuation)**
  Maintenance therapy is generally given for some 2 to 3 years after remission. The standard combination of drugs consists of daily mercaptopurine and weekly methotrexate.

In order to clear leukaemic cells from harbour sites, **CNS-directed therapy** is given throughout the course of ALL treatment, and may include:

- intrathecal chemotherapy (methotrexate either alone or as part of triple therapy with cytarabine and corticosteroids)
- systemic chemotherapy (high-dose methotrexate)
- cranial irradiation (usually reserved for high-risk adult patients)

Targeted drug therapy may be used in patients with specific genetic abnormalities in addition to chemotherapy regimens and CNS prophylaxis. In patients with Philadelphia chromosome-positive ALL, the addition of a tyrosine kinase inhibitor, such as imatinib or dasatinib, to standard chemotherapy regimens has greatly enhanced remission-induction rates and duration of disease-free survival. In Philadelphia chromosome-negative disease that is CD20-positive, the monoclonal antibody rituximab can be included in the treatment regimen.

In **relapsed/refractory** Philadelphia chromosome-negative ALL, second-line therapy with an induction regimen not previously used, or salvage regimens containing clofarabine or cytarabine, alkylator combinations, or liposomal vincristine may be considered; nelarabine may be used in T-cell ALL. In Philadelphia chromosome-positive disease, targeted therapy with dasatinib, nilotinib, or ponatinib can be considered, with or without chemotherapy or a corticosteroid.

Allogeneic **haematopoietic stem cell transplantation** may be a treatment option in adults who are in remission after initial induction therapy, or for relapsed or refractory disease.

Treatments that are **under investigation** include novel monoclonal antibodies, the proteasome inhibitor bortezomib, and inhibitors of the mammalian target of rapamycin, such as sirolimus and temsirolimus.

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ACUTE MYELOID LEUKAEMIAS. Treatment of acute myeloid leukaemias (AML) is problematic because normal stem-cell precursors are sensitive to the drugs used, and therapy aimed at myeloid leukaemic clones results in destruction of part of the normal stem-cell pool. Wherever possible, treatment of AML should be in the context of clinical studies.[1-3] Treatment consists of induction and consolidation chemotherapy. Candidates for haematopoietic stem cell transplantation should be identified as early as possible.[3]

Induction of remission is usually possible with intensive chemotherapy. Complete remission has been stated to be achievable in up to 80% of younger patients and about 50% of older patients (who form the majority of those with AML), but patients suffer severe neutropenia during induction and remission rate is to some extent dependent upon the standard of supportive care. Remission rates are lower in those with adverse prognostic factors such as poor performance status, AML secondary to myelodysplasia or antineoplastics, high white cell count, features of multidrug resistance, and unfavourable cytogenetics.[4,5] Established regimens are based on cytarabine with an anthracycline, usually daunorubicin.[1-4,6-9] Although idarubicin may be preferred to daunorubicin,[10] especially in younger adult patients,[8] in children it is no more effective but may be associated with more toxicity.[11,12] Mitoxantrone is another alternative to daunorubicin,[8,10] and there is little evidence[1,4,10,12] that one anthracycline is better than another for induction protocols. Addition of etoposide or tioguanine to induction protocols of cytarabine and daunorubicin appears to be equally effective in younger adults and children,[13,14] but in older patients an induction regimen which added tioguanine was found to be more effective than one with etoposide.[15]

As in acute lymphoblastic leukaemia (see p. 692.3) there is a trend towards the use of more intensive induction regimens.[6,14] Use of high-dose cytarabine compared with standard doses potentially improves survival in younger patients with favourable cytogenetics, but in the elderly neurotoxicity outweighs any benefit;[10] a combination of cytarabine with fludarabine may be an alternative in these patients.[5] Some guidelines include low-intensity (with subcutaneous cytarabine, azacitidine, or decitabine) or intermediate-intensity induction therapy (with clofarabine) as treatment options for patients older than 60 years.[8] The use of haematopoietic growth factors is controversial; some allow for their use as an optional adjunct to intensive chemotherapy,[3,8] while others recommend against their routine use in AML.[1]

Once remission is induced, consolidation or **postremission therapy** is essential in preventing relapse.[1,6,10] Options include further chemotherapy, or allogeneic or autologous bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1937.1).[1,3,7-9] There is no consensus on the best postremission therapy.[3,7,8] Some advocate the use of high-dose cytarabine in those with favourable or intermediate risk; others are candidates for allogeneic stem cell transplantation.[3,7,8] Non-myeloablative chemotherapy with allogeneic transplantation may be an alternative in older patients.[3,5,7-9,16]

Patients who relapse or who fail to achieve complete remission will require **salvage** therapy. Standard salvage regimens can include high-dose cytarabine or fludarabine plus cytarabine.[7,8] Allogeneic stem cell transplantation can also be used for salvage therapy or for those in second or subsequent remission.[3,7,8] Decitabine may be an alternative for elderly patients who are not candidates for standard remission induction chemotherapy.[17]Investigational therapy is also an option.[7,8] Gemtuzumab ozogamicin has been used in elderly patients,[1,9] but is now withdrawn from the US market. Low-dose **maintenance** chemotherapy (with cytarabine and tioguanine) may improve disease-free survival but not overall survival,[4] and prolonged maintenance therapy is generally considered unnecessary in patients with AML.[1,6,12,14] Where debility or other medical conditions make standard or investigational therapy impossible in the elderly, **palliative** treatment with oral hydroxycarbamide is often given; low-dose cytarabine may also be of benefit.[1,2,7-9] Good results have been reported with a combination of idarubicin and etoposide in elderly patients.[5]

Other experimental therapies under investigation for AML include clofarabine, azacitidine, and imatinib.[2,7-9,12,14] The ciclosporin analogue valspodar, an inhibitor of multidrug resistance, has been investigated, but was associated with excessive early mortality.[18]

Acute promyelocytic leukaemia (APL) is a subtype of AML accounting for 10% of AML cases in adults.[19] It is important to distinguish APL from other forms since appropriate treatment is curative in most patients.[10] Most patients with APL can achieve complete remission after treatment with tretinoin alone, but remission durations are short and most patients relapse.[20] *Induction* therapy with tretinoin and chemotherapy (an anthracycline and cytarabine) improved event-free survival compared with chemotherapy alone.[19,21] It was also shown that cytarabine could be omitted for most patients,[20,22] and standard induction for low- and intermediate risk disease consists of concomitant tretinoin and an anthracycline.[8,10,23] There are few data to suggest that one anthracycline is vastly superior to another.[20,23] The addition of cytarabine can still be considered for high-risk patients.[8]

Consolidation therapy is given after complete remission,[8,20,21] and is usually anthracycline-based. Again, although most studies have included cytarabine, its role has been questioned,[19,20,22] and standard consolidation consists of concomitant tretinoin and an anthracycline.[8] As with induction, cytarabine may be added for high-risk disease.[8,23] Arsenic trioxide has been successfully combined with tretinoin for induction and consolidation,[8,10] and this combination is an alternative for those who cannot tolerate anthracyclines.[8,23] Arsenic trioxide has also been used alone as first-line therapy, but such use tends to be restricted to patients for whom chemotherapy is contra-indicated.[21]

For those in molecular remission after consolidation therapy, *maintenance* therapy with up to 2 years of tretinoin, with or without continuous low-dose chemotherapy (mercaptopurine plus methotrexate), is recommended.[8,21,22] Maintenance therapy is particularly beneficial for those at high risk of recurrence, such as those with a high leucocyte count and older adults.[20,22] Arsenic trioxide is recommended for those who remain molecularly positive at the end of consolidation.[8,21] It is also the treatment of choice for patients who relapse,[8,19-23] particularly those treated with tretinoin within the previous year. Patients who then achieve a second remission may be considered for autologous or allogeneic haematopoietic stem cell transplantation.[8,19,20,22,24] Gemtuzumab ozogamicin may also be an option for relapsed patients, although its precise role has not been determined,[21,24] and it should be used with caution in potential transplant candidates.[8] The synthetic retinoid, tamibarotene (AM-80), has been used to induce remission in patients who relapsed after successful remission induction with tretinoin.[25]

The efficacy of tretinoin appears to be achievable only because the characteristic chromosomal abnormalities in APL result in an abnormal retinoic acid receptor. The development of drugs that can effect differentiation in other forms of AML, and indeed in other neoplasms, seems likely to be a long and difficult task.

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Leukaemias, chronic. The chronic leukaemias may be broadly divided into those in which the neoplastic proliferation affects lymphoid cell lines, and those affecting the myeloid cell lines.

Chronic leukaemias affecting the *lymphoid cell lines* include chronic lymphocytic leukaemia (CLL), which is B-cell in about 95% of cases and T-cell in about 5%, and hairy-cell leukaemia, which affects B-cells. The revised European-American lymphoma classification,[1] and a proposed WHO classification of haematologic malignancies,[2] consider lymphoid leukaemias and lymphomas of the same cell type to be one disease with different clinical presentations. Thus B-cell CLL is the same disease as B-cell small lymphocytic lymphoma.

Chronic neoplasms affecting the *myeloid cell lines* include the myeloproliferative disorders chronic myeloid leukaemia (CML), polycythaemia vera, and primary (essential) thrombocythaemia, and the myelodysplastic syndromes. All of these may undergo transformation to acute myeloid leukaemia.

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CHRONIC LYMPHOCYTIC LEUKAEMIA. Chronic lymphocytic leukaemia (CLL) typically occurs in people over 60 years of age, and accounts for about 30% of leukaemias in the West although it is rarer in the Far East. CLL and small lymphocytic lymphoma (SLL) have been described as the same disease manifesting in different ways.[1] Stages of CLL are defined according to the American Rai system or the European Binet system, with both having prognostic value.[1-8] The clinical course is variable: low-risk patients (Rai stage O; Binet stage A) have a median survival of about 10 years, while high-risk patients (Rai stage III/IV; Binet stage C) have a median survival of about 1.5 years; median survival in the intermediate stages is about 6 years.[2,3,9] The mutational status of the immunoglobulin IGHV gene also affects prognosis; attempts to use surrogate markers of this status included CD38 and ZAP-70, and these have assisted in further risk stratification.[7,10-13]

In patients at low risk and those at intermediate risk with indolent disease cytotoxic chemotherapy is usually deferred until signs and symptoms of disease progression occur.[2,3,5-10,13] In these patient groups, studies of immediate versus deferred chemotherapy for early-stage CLL have shown no significant advantage, or disadvantage, for immediate chemotherapy in terms of 10-year survival.[14] Patients with high-risk or progressive disease are usually treated with immediate chemotherapy.

When **treatment** is required, several options exist. For many years, chlorambucil, given either continuously or intermittently, and with or without prednisone, was the mainstay of chemotherapy for CLL, with response rates ranging from about 40 to 70%.[10,12,15] Alkylator-based combination regimens such as COP or CVP (cyclophosphamide, vincristine, and prednisone or prednisolone), CAP (cyclophosphamide, doxorubicin, and prednisone or prednisolone), or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) were found to have no advantage over chlorambucil alone.[4,6,15]

Subsequent study with fludarabine found response rates to be higher than with alkylator-based therapy, although no overall survival advantage was shown.[6-8,10-12,15] Fludarabine has been studied in combination with other agents. Use with chlorambucil showed excessive toxicity.[1,7,15] Fludarabine plus cyclophosphamide was found to have higher remission rates and longer progression-free survival than either chlorambucil or fludarabine monotherapy,[8,11,13,15] and as such this combination is often recommended as the initial treatment of choice,[10] especially in fitter patients. Chlorambucil or fludarabine monotherapy are still considered appropriate first-line options[1,9,12,13] in those with comorbidities or poorer performance status, and CVP

or CHOP regimens are still alternatives for those unable to tolerate fludarabine-based therapy.[1]

Bendamustine, an alkylating agent, produced better response rates and progression-free survival compared with chlorambucil, and is approved in some countries as initial monotherapy; efficacy compared with other first-line therapies has not been established.[1] Other purine analogues have been investigated for CLL. Cladribine, with or without corticosteroids, achieved comparable results to those with fludarabine monotherapy.[11] Cladribine plus cyclophosphamide was found to have similar results to cladribine alone.[11] However, some do not recommend cladribine as a routine alternative to fludarabine for initial therapy.[6]

The monoclonal antibodies alemtuzumab and rituximab have been studied with other drugs for the treatment of CLL.[5,6,10,11,16] The use of rituximab with fludarabine (FR regimen) especially has shown marked clinical efficacy,[7,10,12,15] and the FCR regimen (fludarabine, cyclophosphamide, and rituximab) has shown high overall response rates;[1,11,17] some consider FCR to be a suitable first-line option.[1,9,12,13] However, others have stated that the use of rituximab with fludarabine (with or without cyclophosphamide) requires further evaluation.[6] The use of the purine analogue pentostatin with cyclophosphamide and rituximab (PCR regimen) has also been shown to have high response rates and is also an option for initial therapy for CLL.[1,8,9,12,13] Although some consider rituximab monotherapy to be suitable initial therapy for older patients or for those with comorbidities,[1,12] others do not recommend it for untreated CLL.[6] Similarly, alemtuzumab may be used as first-line therapy in patients with certain cytogenetic abnormalities associated with a poor prognosis,[1,7,10] or as consolidation therapy after fludarabine-based induction therapy.[10,11,17] However, some do not recommend alemtuzumab for untreated CLL[6] and others advise against its use in the consolidative setting given the risks of infectious complications and possible CMV reactivation.[15]

There is no definitive evidence that consolidation or maintenance therapy is better than treatment at the time of relapse, although investigation is ongoing and participation in clinical studies is encouraged.[8] Treatment of relapses depends upon response to initial therapy.[6,7,11] After long remissions, patients will usually respond again to induction treatment.[7,9] Alternative agents, or combination chemotherapy with or without monoclonal antibodies may then be tried.[1,7,9,11] Monoclonal antibody monotherapy is an option,[1,9] especially in patients refractory to chemotherapy; alemtuzumab, ofatumumab, or dose-dense rituximab may be used. Alemtuzumab with rituximab is also an option.[1] For further information on common chemotherapy regimens, see Table 1, p. 719.

Haematopoietic stem cell transplantation (HSCT) has been investigated for CLL.[7] Autologous HSCT is unlikely to provide a cure[11,13,15] and relapse is inevitable.[10] The principles of allogeneic HSCT, which is potentially curative,[6,13] include the graft-versus-leukaemia effect and the absence of stem cell contamination.[11] However, transplant-related mortality has been high. Non-myeloablative conditioning protocols are under investigation.[6,7,10,11,15] Allogeneic HSCT is suggested for younger patients with non-response or early relapse after purine analogues, or those who relapse within 2 years of an initial response with purine-analogue based therapy or autologous HSCT, or in patients with certain cytogenetic abnormalities with a poor prognosis.[10]

Other drugs that have been investigated for CLL include bortezomib,[10] denileukin diftitox,[10] lenalidomide,[7,10,18] lumiliximab,[7,10] oblimersen sodium,[10] and thalidomide.[18]

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CHRONIC MYELOID LEUKAEMIA. Chronic myeloid (myelogenous) or chronic granulocytic leukaemia (CML) is a rare disease, occurring usually in older patients, and representing about 15% of all adult leukaemias. It is associated in over 90% of cases with the presence in blood cells of an abnormal chromosome, the Philadelphia chromosome (Ph), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22, with the fusion of the BCR gene and the ABL gene. The product of this gene, the protein BCR-ABL, is leukaemogenic. Ph-negative disease (atypical CML) carries a worse prognosis, and some classification systems consider it to be a separate disease.

CML occurs in 3 different phases. It is usually diagnosed in the chronic phase, which may last for several years, which when untreated, progresses to an advanced phase; this consists of an often rapidly fatal blastic phase (blast crisis), which is often preceded by a transition period, the accelerated phase.

The development of imatinib, an inhibitor of the BCR-ABL protein tyrosine kinase, constituted a revolutionary change in the management of CML.[1-7] The International Randomized Study of Interferon and STI571 (IRIS), found imatinib to be better than interferon alfa with low-dose cytarabine for newly diagnosed CML in **chronic phase**.[8,9] Follow-up study found responses to be durable in a high proportion of patients,[10] and a tyrosine kinase inhibitor such as imatinib has become established as standard initial therapy for chronic phase CML.[1,5,11] Since relapse is common after stopping imatinib, therapy should be continued indefinitely in responsive patients.[1,5,7] Resistance may also be a problem.[2-6,12-15] For patients who do not respond to first-line therapy or who relapse, the preferred second-line treatment is an alternative tyrosine kinase inhibitor such as dasatinib, nilotinib, bosutinib, or ponatinib. Omacetaxine mepesuccinate, allogeneic haematopoietic stem cell transplantation (HSCT), or investigational therapies (see below) are further options in patients who are resistant to or have failed treatment with tyrosine kinase inhibitors. These therapies or an alfa interferon such as peginterferon alfa may also be tried in patients who are unable to tolerate tyrosine kinase inhibitors.For patients who only partially respond or who relapse after first-line imatinib and who are not able to take an alternative tyrosine kinase inhibitor or omacetaxine mepesuccinate, high-dose imatinib may be considered.[1]

Early allogeneic HSCT (p. 1937.1) has the potential to cure CML due to a graft-versus-leukaemia effect, but it is still associated with appreciable morbidity and mortality, including graft-versus-host disease,[6] and results with imatinib have challenged the role of HSCT as first-line therapy for chronic phase CML.[1,11] While HSCT is still an option in suitable patients such as younger patients with HLA-identical sibling donors,[4,7] or those with high-risk disease and low transplantation risk,[2] most recommend an initial period of therapy with imatinib since the response can either reinforce or weaken the indication for HSCT.[5-7,16] Ongoing advances in alternative donor sources (such as the use of HLA-matched unrelated donors and cord blood), improved HLA typing techniques, and less toxic non-myeloablative regimens are broadening the use of HSCT.[1,4] Options in patients who relapse after HSCT include the use of donor lymphocyte infusions, tyrosine kinase inhibitors, or interferon alfa.[1,2,7]

Tyrosine kinase inhibitors induce favourable response rates in those with **advanced phase** CML. In those whose disease has progressed after initial tyrosine kinase inhibitor therapy, an alternative tyrosine kinase inhibitor is used, and then allogeneic HSCT can be considered. Post-transplant tyrosine kinase treatment is continued for at least 1 year. Omacetaxine mepesuccinate is an option for patients whose disease has progressed to advanced phase due to resistance and/or intolerance to 2 or more tyrosine kinase inhibitors. For those whose disease has progressed to blast-phase, treatment includes a tyrosine kinase inhibitor, either alone or with chemotherapy, followed by allogeneic HSCT.[1]

Novel therapies for CML include farnesyl transferase inhibitors such as lonafarnib and tipifarnib, hypomethylating agents such as azacitidine and decitabine, histone deacetylase inhibitors, and vaccines.[4,15,17] Combinations of imatinib with other drugs are also under investigation.[2]

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HAIRY-CELL LEUKAEMIA. Hairy-cell leukaemia is a rare, chronic, B-cell lymphoproliferative disorder marked by the presence of white blood cells with prominent cytoplasmic villi, pancytopenia, and splenomegaly. Many patients are asymptomatic and there is no clear advantage to early treatment before symptoms appear.[1,2] Splenectomy was formerly used as initial therapy, but response duration tended to be short. Interferon alfa-2a or -2b given for one year produced at least a partial response in most cases but patients had a tendency to relapse once therapy was stopped.[1,3,4]

Better results were obtained with the purine analogues cladribine and pentostatin, and these are now considered first-line treatments for this disease.[1,3-8] Durable complete remission rates of 50% or more are seen after relatively short courses of therapy.[3,4,7-10] Toxicity is generally acceptable.[3] These drugs do not appear to show cross-resistance; cladribine has been used successfully in patients resistant to, or intolerant of, pentostatin,[1,3] and others[6] have used pentostatin in patients who do not respond to cladribine. Despite long disease-free survival rates associated with purine analogue therapy, they are not curative, and relapses occur in many patients, which suggests the presence of residual disease.[7,10] For patients who relapse, re-treatment with initial therapy is advocated.[1,7] Interferon alfa is an option in those patients relapsing after, or refractory to, treatment with a purine analogue.[1,4] There are reports of remission after use of rituximab in patients with relapsed or refractory disease,[1,3,4,7,8,10,11] or for residual disease,[10] and it has been suggested for use in those who fail cladribine and pentostatin.[6,7] Other immunotherapy under investigation for hairy-cell leukaemia includes alemtuzumab, and the recombinant immunotoxins LMB-2 and BL22.[4,7,8,10]

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MYELODYSPLASTIC SYNDROMES. Myelodysplastic syndromes are low-grade neoplasms of haematopoietic stem cells characterised by ineffective haematopoiesis that results in anaemia, neutropenia, or thrombocytopenia in various combinations. They have been described as smouldering leukaemia or preleukaemia, and transformation to acute myeloid leukaemia (AML) occurs in some patients.

The clinical course of myelodysplastic syndromes is variable, and a precise individual determination of prognostic score is important in planning **treatment**.[1,2] In the few younger patients with suitable HLA-matched

donors, allogeneic haematopoietic stem cell transplantation (HSCT) has curative potential.[1,3-8] As most patients are older, with medical conditions precluding the use of standard conditioning regimens, novel transplant conditioning regimens of reduced intensity are being investigated.[5,7-9] Autologous HSCT may be an option for those without a suitable donor.[7]

Patients who are likely to have an ***indolent*** course are best treated conservatively with observation and supportive care (transfusions, antibacterials, or epoetins plus colony-stimulating factors).[1-4,7-9] Iron chelation therapy may be needed in patients who develop iron overload (p. 1545.2) from blood transfusions.[2,7,9] Azacitidine, decitabine, or lenalidomide may be considered where a low serum-erythropoietin concentration does not respond to epoetins (with or without colony-stimulating factors). Lenalidomide is effective for patients with chromosome 5q deletions,[6,8,10-13] and is recommended as first-line therapy in these patients.[2,9] Patients with serum-erythropoietin above 500 milliunits/mL and a good probability of response to immunosuppressive therapy should be given antilymphocyte immunoglobulins with or without ciclosporin, or possibly ciclosporin alone.[2,9] Those likely to have a poor response to immunosuppressants should be given treatment with azacitidine, decitabine, lenalidomide, investigational agents, or considered for allogeneic HSCT.[2] Azacitidine or decitabine are also treatment options for patients with serious cytopenias; if not responsive, immunosuppressive therapy, investigational agents, or allogeneic HSCT can be tried.[2]

The treatment of ***progressive*** or advanced myelodysplastic syndromes or those that have transformed to AML may involve intensive chemotherapy similar to that for AML (see p. 693.1), but remission rates are lower,[1,3,4] and relapse common.[9] However, many patients are elderly with poor performance status, and are unable to tolerate intensive chemotherapy. They may be treated with supportive care and haematopoietic growth factors alone.[9] Low-intensity chemotherapy such as azacitidine or decitabine may be tried in such patients,[2] but has had limited success.[1,3] Other antineoplastics and immunomodulating agents investigated for use in myelodysplastic syndromes include histone deacetylase inhibitors such as valproic acid and vorinostat, farnesyl transferase inhibitors, amifostine, arsenic trioxide, thalidomide, and topotecan.[1,3-5,7,9,14,15] Attempts to induce cellular differentiation have generally been disappointing.[3]

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MYELOFIBROSIS. Myelofibrosis is a chronic Philadelphia-negative myeloproliferative disorder, associated with a mutation in the Janus kinase 2 (JAK2) gene in over 50% of patients. Bone marrow is replaced by collagen fibrosis. The disease may present as idiopathic or primary, or as transformation of an antecedent polycythaemia vera (below) or essential thrombocythaemia (below). Median survival after diagnosis is about 5 years, although this may be longer in younger patients with good prognostic features. Older age, anaemia, leucocytosis, peripheral blasts, and the presence of constitutional symptoms are the major risk factors. Symptoms include fatigue, night sweats, pruritus, bone pain, weight loss, and fever; patients typically develop cytopenia and splenomegaly.[1-4]

Allogeneic stem cell transplantation is the only potentially curative **treatment** approach. However, many patients are ineligible.[1,2,5] Hydroxycarbamide is used to treat splenomegaly; splenectomy may be performed for painful splenomegaly in those with good performance status.[5] Anti-angiogenic therapy with thalidomide or lenalidomide, usually given with corticosteroids, has shown response rates of between 20 and 30%.[1,4,5] Pomalidomide is under investigation.[2,4] JAK2-inhibitors such as ruxolitinib are under development.[1-3]

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POLYCYTHAEMIA VERA. Polycythaemia vera (polycythaemia rubra vera) is a Philadelphia-negative chronic myeloproliferative disorder,[1] associated in about 95% of patients with a mutation in the Janus kinase 2 (JAK2) gene.[1-3] It is characterised by an increased red cell mass and packed cell volume, and is often associated with increases in white cell and platelet counts and splenomegaly.[1,4] It is a disease of later life, with a median age at presentation of about 60 years.[4] The symptoms are related to hyperviscosity due to the increased number of cells in the blood; patients often present with either arterial or venous thrombosis (cerebrovascular accident, myocardial infarction, pulmonary embolism) or occasionally, with haemorrhage, particularly involving the skin and gastrointestinal tract.[1,4]

Untreated, the disease is associated with a high risk of morbidity and mortality, and patients can undergo myelofibrotic transformation into blast crisis and acute myeloid leukaemia.[1,4] The aims of **treatment** are therefore to reduce the risk of thrombosis and haemorrhage, minimise transformation risk, and manage complications, or pregnancy.[4]

The mainstay of treatment is periodic phlebotomy to maintain the haematocrit within normal values,[5,6] along with aspirin in low doses (40 to 100 mg daily)[1,7] sufficient to reduce thrombosis without increasing the risk of major bleeding.[8] This may be all that is required in younger patients at low risk of thrombosis. In patients at high risk of thrombosis, including those who have a high phlebotomy requirement, some form of myelosuppressive therapy may also be considered. Chlorambucil, which was formerly used for this purpose, has largely been stopped because of a high incidence of leukaemia in patients so treated.[4-6] In patients with a life expectancy of less than 10 years, radioactive phosphorus-32 is probably appropriate, and produces good results with few immediate adverse effects.[5] However, like the alkylating agents it is associated with an increased risk of secondary malignancies.[6] In younger patients hydroxycarbamide,[1,4,6] busulfan,[5,6] or in some countries pipobroman,[5] have been preferred because they were considered to have lower risk of inducing leukaemia. However, there is some evidence[9] that they too may have leukaemogenic potential, especially when used in combination,[7,10] and some recommend that busulfan and pipobroman be reserved for elderly patients.[1,4] Non-cytotoxic therapies that have been shown to be effective include interferon alfa.[1,4-7,9] This may be preferred in younger patients requiring treatment.[4,5] Anagrelide, another antiplatelet drug, has also been tried in polycythaemia vera. It is effective in controlling the platelet count, but does not control progression of polycythaemia vera, and its adverse effects may make it difficult for some patients to tolerate.[4]

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PRIMARY THROMBOCYTHAEMIA. Primary thrombocythaemia (essential thrombocythaemia) is a rare Philadelphia-negative myeloproliferative disorder in which abnormal platelet production results in elevated platelet counts.[1] The Janus kinase 2 (JAK2) genetic mutation occurs in about 50 to 60% of patients.[2] The disorder occurs mainly during later life[3] and unlike other myeloproliferative disorders, is associated with generally near-normal life expectancy.[3,4] However, microvascular occlusion marked by conditions such as erythromelalgia (burning pain and erythema of the hands and feet), paraesthesia, or migraine, and arterial or venous thrombosis (e.g. cerebrovascular accident, myocardial infarction, pulmonary embolism) may occur. The risk for thrombosis is highest in patients with a history of thrombosis and in those aged over 60 years. In less than 10% of patients the disease eventually enters a spent phase marked by fibrosis and marrow hypoplasia, or transforms to acute leukaemia.

Asymptomatic patients and those at low risk of thrombosis are generally not treated,[5] but when to begin **treatment** is controversial.[6] Some consider that primary antithrombotic prophylaxis seems rational even in asymptomatic patients if there are no contra-indications to this therapy. Low-dose aspirin (40 to 100 mg daily) is considered to be effective, without increasing the risk of major bleeding. Acute microvascular symptoms may be managed with higher doses of aspirin (100 to 300 mg daily).[1] In patients at risk of thrombosis, drugs that lower platelet counts are used, including cytotoxics.[1,6,7] Phosphorus-32 and alkylating agents such as busulfan or pipobroman are little used now because of their known potential to induce leukaemia.[1,3,7] Hydroxycarbamide can reduce thrombotic events,[5,7,8] and has tended to be preferred because it was thought to have lower risk of inducing leukaemia, but it too appears to have leukaemogenic potential.[3,4,6-9] The increased risk of leukaemia from therapy is particularly relevant in younger patients, for whom non-cytotoxic drugs may be preferred. Some non-cytotoxic therapies have also been shown to reduce platelet counts. Anagrelide[3,4] is often substituted for hydroxycarbamide,[1,5-8] but its value has been questioned by a comparison[10] of 2 regimens using aspirin with either anagrelide or hydroxycarbamide. Although the reductions in platelet count were similar for both groups, patients taking anagrelide were found to be at greater risk of arterial thrombosis, serious haemorrhage, and transformation to myelofibrosis (but the rate of venous thromboembolism was lower). Interferon alfa can also effectively reduce platelet counts;[4-7] it is a good alternative for younger patients who face lifelong treatment,[1] and is the treatment of choice in pregnant women.[1,3,5,6,8] Haematopoietic stem cell transplantation may be considered in younger patients who have advanced, complicated disease.[6]

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Lymphomas. The malignant lymphomas are neoplastic disorders of the lymphoreticular cells. These cells are primarily located in the lymph nodes, but because of their wide distribution in the body lymphomas may arise in extranodal and extralymphatic tissues such as lung, gastrointestinal tract, and skin.

The term covers a heterogeneous group of diseases, comprising two main subgroups: Hodgkin's disease, and the non-Hodgkin's lymphomas (NHL). The cellular origin of Hodgkin's disease is uncertain; the NHL are monoclonal malignancies arising from B cells in about 80% of cases, with the remainder from cells of T lineage and from undifferentiated cells.

Management of patients with malignant lymphoma is largely determined by interpretation of histological features, and, especially for NHL, by an allocation of subtype and grade. Various classification systems have been proposed for NHL of which the National Cancer Institute Working Formulation has been widely used.[1] Under the Working Formulation, NHL are divided into:

- *low grade*, including small lymphocytic, follicular small cleaved cell, and follicular mixed small cleaved and large cell lymphoma
- *intermediate grade*, including follicular large cell, diffuse large cell, diffuse small cleaved cell, and diffuse mixed types

- *high grade*, including large cell immunoblastic, lymphoblastic, and small non-cleaved cell (including Burkitt's) lymphomas

The International Lymphoma Study Group has proposed a revised European-American lymphoma (REAL) classification,[2] and this has subsequently also been published under the auspices of WHO.[3] It is based on a division into B-cell, T-cell and natural killer cell, and Hodgkin's neoplasms. In this classification, B-cell lymphomas include B-cell small lymphocytic lymphoma, MALT lymphoma, follicular lymphoma (35% of adult NHL, rare in children), diffuse large B-cell lymphoma (30% of adult NHL, 5% of NHL in children), and Burkitt's lymphoma (rare in adults; 30% of NHL in children) and Waldenström's macroglobulinaemia (lymphoplasmacytic lymphoma). Plasma-cell myeloma (multiple myeloma) is also a B-cell neoplasm. T-cell lymphomas include precursor T-cell lymphoblastic lymphoma (rare in adults; 45% of NHL in children) and mycosis fungoides; and Hodgkin's lymphoma is subdivided into nodular lymphocyte-predominant and classical (nodular sclerosis and mixed cellularity) forms.

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HODGKIN'S DISEASE. Hodgkin's disease (Hodgkin's lymphoma) is characterised histologically in most cases by the presence of a particular type of giant cell, the Reed-Sternberg cell. It is more common in males than in females, and in the West is seen particularly in young adults and in the elderly, although the age distribution differs elsewhere.

It usually presents as painless enlargement of one or more lymph nodes, particularly in the neck or axillae. About a third of all patients also have constitutional symptoms of fever, weight loss, and night sweats, which indicate poorer prognosis. In advanced disease, signs of organ infiltration may occur, as may infectious complications. The mass of the tumour may result in compression of vital organs.

Hodgkin's disease can be treated by radiotherapy or chemotherapy or both, and the choice of treatment depends on the volume and histological subtype of the tumour, the age of the patient, and, particularly, the stage of the disease.[1] The Ann Arbor classification (with Cotswold modifications) recognises 4 stages:

- Stage I, with involvement of a single lymph node region or extralymphatic site
- Stage II, in which spread is restricted to lymph nodes and sites on one side of the diaphragm only
- Stage III, involving spread on both sides of the diaphragm with possible splenic and extralymphatic involvement
- Stage IV, where the patient has diffuse or disseminated disease in one or more extralymphatic organs or tissues.

Stages are subclassified A or B according to the absence or presence respectively of the aforementioned constitutional symptoms.[1-3] X indicates bulky disease and E the involvement of single extranodal sites.[2,3] Survival rates after treatment for Hodgkin's disease are generally excellent, and there is increasing emphasis on tailoring therapy to decrease early and late treatment-related morbidity while not compromising survival.[1] For prognostic and therapeutic considerations, patients are grouped into early-stage favourable (limited) disease (IA or IIA, no bulky disease); early-stage unfavourable (intermediate) disease (IB or IIB, bulky disease); and advanced disease (stages III and IV).

In the treatment of stages I, II, and IIIA disease, **radiotherapy** alone was standard therapy for adult patients with limited disease, especially in those with good prognosis. However, there have been concerns about relapse rates and an increased risk of secondary malignancy after radiotherapy. Adding chemotherapy to radiotherapy was found to reduce recurrence rates, although this does not translate to an increase in overall survival.[4] Nonetheless, **combined modality** treatment is now the preferred treatment for favourable early stage disease.[1-3,5-10] Although the optimal chemotherapy regimen and radiation dose have yet to be determined, the ABVD or Stanford V regimens (see below) are commonly used.[1,7] Chemotherapy with ABVD alone is also used[1,8,11] and radiotherapy alone is still an option for highly selected patients unable to tolerate chemotherapy due to comorbidities.[1] Combined modality treatment is also generally accepted as the treatment of choice in those with unfavourable early stage disease, again using the ABVD[1,2,5-10] or Stanford V regimens.[1]

Chemotherapy alone is generally considered to be the treatment of choice in advanced disease although radiotherapy may be added for consolidation with some regimens.[1,7] Meta-analyses or systematic reviews of combined modality therapy in advanced disease have found no survival benefit from additional radiotherapy, although it may have a role in initial bulky or residual disease.[4,7,12]

There are several 4-drug standard **regimens** available and the choice lies between one of these, alternating cycles of 2 different regimens, or a hybrid cycle that involves giving 7 or 8 drugs in the same course of treatment. However, the single most important factor governing the outcome of chemotherapy is thought to be dose intensity of the drugs given.

The earliest of the successful 4-drug regimens was MOPP combination chemotherapy (chlormethine, vincristine, procarbazine, and prednisone or prednisolone). There are several MOPP-variant regimens that may be as effective and less toxic; these include substitution of chlorambucil or cyclophosphamide for chlormethine (LOPP or COPP, respectively), vinblastine for vincristine (MVPP), and both chlorambucil and vinblastine substituted in one regimen (ChlVPP). However, an alternative to the MOPP-based regimens, a non-cross resistant combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was found to be as effective as MOPP with a reduced risk of inducing sterility or secondary leukaemia. Better results were later reported with ABVD alone, or with MOPP/ABVD, than with MOPP alone, and ABVD has become the basis of standard treatment for advanced stage Hodgkin's disease.[1,3,7-11,13,14] The Stanford V regimen (doxorubicin, vinblastine, chlormethine, vincristine, bleomycin, etoposide and prednisone, with consolidative radiotherapy) is also used as primary treatment for advanced disease.[1]

Attempts to improve the results of ABVD or MOPP have centred on dose intensified hybrid regimens. The German Hodgkin's Lymphoma study group found improved results with a hybrid regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) compared with COPP/ABVD; overall survival was highest with an increased dose of BEACOPP, although toxicity was increased.[15] Escalated-dose BEACOPP may be considered for patients with high-risk disease.[1,7,11]

Salvage treatment options for patients who relapse depend on the initial treatment and the interval between treatment and relapse. Patients who are candidates for salvage therapy can be divided into 4 groups:

- those initially treated with radiotherapy who have a recurrence, in whom standard chemotherapy regimens are effective
- those who never achieve complete remission with standard chemotherapy, in whom prognosis is very poor, and who are candidates for an intensive salvage chemotherapy regimen with autologous haematopoietic stem cell transplantation (HSCT)
- those whose original remission lasted for over a year, of whom some will respond to re-treatment with standard therapy, but in whom intensive salvage chemotherapy regimens with HSCT may be considered
- and those whose remission is short, less than one year, in whom standard chemotherapy may be used to reduce tumour volume before intensive salvage chemotherapy and HSCT.[2,16]

Common salvage regimens include BEAM or mini-BEAM (carmustine, etoposide, cytarabine, and melphalan), DHAP (dexamethasone, high-dose cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, and etoposide), or gemcitabine-based regimens.[1,7,11,17] For further information on common chemotherapy regimens, see Table 1, p. 719. Although intensive chemotherapy and autologous HSCT is considered by some[2,7,11,14,17] to be the treatment of choice in relapsed patients, others[4] note that benefit on overall survival remains to be established.

Immunotherapy with brentuximab vedotin (a antibody-drug conjugate consisting of a CD30-specific monoclonal antibody and a microtubule disrupting agent) may be an option when autologous haematopoietic stem cell transplantation has failed, or when other therapies have failed in those deemed unsuitable for transplantation. Other immunotherapies under investigation for Hodgkin's disease include the anti-CD20 monoclonal antibody rituximab, and other monoclonal antibodies, some radiolabelled, to CD25 and CD30.[3,5,7,11,17]

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NON-HODGKIN'S LYMPHOMAS. The non-Hodgkin's lymphomas are a heterogeneous group of malignancies that vary considerably in their behaviour, prognosis, and management. Classifications have grouped them by grade (low, intermediate, or high) or cellular origin (B-cell, T-cell, or NK-cell), and histology (see Lymphomas, p. 695.3). The most recent WHO classification, while still considering cell of origin, does not group the non-Hodgkin's lymphomas into a distinct clinical framework.[1] The non-Hodgkin's lymphomas include Burkitt's lymphoma, MALT lymphoma, and mycosis fungoides, all of which are discussed separately.

The usual presentation of lymphomas is lymphadenopathy, which in low-grade lymphoma may develop insidiously over a long period. There may be constitutional symptoms of fever, night sweats, and weight loss. Extranodal involvement may occur, as may symptoms due to organ compression by the tumour mass. Lymphomas of T-cell origin have a worse prognosis than B-cell lymphomas of the same type, and excess tumour bulk, involvement of bone marrow or gastrointestinal tract, and elevated serum-lactic dehydrogenase concentrations are also adverse prognostic factors. Staging is of somewhat less importance as a determinant of treatment and prognosis than in Hodgkin's disease.

Follicular lymphoma is the commonest form of *indolent* non-Hodgkin's lymphoma.[2,3] Follicular lymphomas may be subclassified histologically into 3 grades according to the number of centroblasts, and grade 3, which is more aggressive, should be treated as for diffuse large B-cell lymphoma[1,4,5] (see below). The approach to therapy of other follicular lymphoma differs dramatically in patients with localised or disseminated (advanced) disease.[1]

In the few patients with limited disease at presentation, radiotherapy is potentially curative,[2,5-10] with most patients achieving long-term freedom from disease, and low rates of relapse.[2] The addition of chemotherapy to radiotherapy has not thus far convincingly prolonged remission or improved overall survival.[1,7] Patients who do not respond after therapy should be treated as those with more disseminated disease.[1] Even in more advanced disease, which is rarely curable,[2,6,8,10] follicular lymphoma may follow a fairly chronic course, with a median survival of 8 or more years[4,6,9] although transformation to more aggressive forms may occur.[2]

Treatment in advanced disease has not been shown to affect survival, and a conservative approach of withholding treatment until symptoms require it is considered viable.[1,3,6,7,9,11] The addition of rituximab to combination chemotherapy has increased overall response rate, response duration, and progression-free survival and hence some[1,10] recommend rituximab with chemotherapy (chemoimmunotherapy) for first-line treatment; caution is advised in patients with hepatitis B.[1]

Rituximab may be combined with either bendamustine or fludarabine.[1] Established regimens to which rituximab may be added include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or fludarabine-based regimens such as FCM (fludarabine, cyclophosphamide, and mitoxantrone) or FND (fludarabine, mitoxantrone, and dexamethasone).[1,3,5,10] Rituximab monotherapy is also an option for patients with a low-risk profile or who cannot tolerate more intensive chemoimmunotherapy or for the elderly and infirm.[1,10] Single-agent alkylators such as chlorambucil or cyclophosphamide are an option for these patients.[1] Rituximab maintenance therapy is under investigation; although benefits have been reported, the optimal dose and duration have not been established.[12]

The use of interferon alfa with chemotherapy for first-line treatment has produced conflicting results. However, when interferon alfa was used with anthracycline-containing regimens, improvements in response rate and prolonged remission were reported;[6,11] prolonged survival has not

been proven.[7] Interferon alfa as maintenance therapy appears to improve disease-free survival, but only if complete remission has been obtained with initial chemotherapy.[2,6] Overall, a meta-analysis[13] of 10 studies found that the ability of interferon alfa to prolong remission duration and survival may depend on it being used with relatively intensive chemotherapy and given in unit doses of at least 5 million units (at least 36 million units/month).

Radioimmunotherapy with radiolabelled monoclonal antibodies such as tositumomab and ibritumomab may also be considered first-line,[1,5] although myelosuppression may be a problem[9,14] and there may be practical difficulties associated with their use. Some consider radioimmunotherapy as an initial option for the elderly or infirm.[1]

Relapse of indolent lymphomas is generally inevitable. Selection of salvage therapy depends on the efficacy of initial regimens.[10] Options include chemoimmunotherapy with a different chemotherapy option to that used first-line, radioimmunotherapy (as discussed above), rituximab alone, or alkylator monotherapy.[1,3,5,10] High-dose chemotherapy followed by autologous or allogeneic haematopoietic stem cell transplantation (HSCT) may be an appropriate option for relapsed patients.[1,3,4,7,10] In the case of allogeneic HSCT, nonmyeloablative approaches may be considered.[1,3,10]

Intermediate- to high-grade lymphomas, of which **diffuse large B-cell lymphoma** (DLCL) is the most common form,[1] are *aggressive*. About one third of patients with DLCL have localised disease at presentation,[15] and treatment with CHOP (see above) and rituximab with or without radiotherapy is the treatment of choice.[1,4,16,17] Many also consider CHOP plus rituximab (R-CHOP) to be the standard of care in advanced disease,[1,4,16] although other, generally anthracycline-based, regimens are also considered acceptable, such as dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).[1] High-dose chemotherapy with autologous HSCT has been tried for initial therapy in patients with diffuse aggressive non-Hodgkin's lymphoma, but remains investigational.[1,11,15,18]

On relapse, patients are treated with salvage chemotherapy regimens such as DHAP (dexamethasone, cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, etoposide), ESHP or ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GemOx (gemcitabine and oxaliplatin), or MINE (mitoxantrone, ifosfamide, mesna, etoposide); all these regimens may be given with or without rituximab.[1] Monotherapy with pixantrone may also be considered in patients with B-cell lymphomas. Patients are then evaluated for high-dose chemotherapy and autologous HSCT, which is considered the treatment of choice in suitable patients who respond to the salvage regimens.[1,2,17,19] However, in disease resistant to salvage chemotherapy, its role has not been established,[19] and patients whose disease progresses are considered not likely to benefit from currently available standard therapy.[1] In an effort to improve outcomes after autologous HSCT, the addition of radioimmunotherapy (as above) to conditioning regimens is being investigated. Allogeneic HSCT is also under investigation.

There is no standard approach for those patients ineligible for transplant;[19] options include rituximab monotherapy, second-line chemotherapy regimens such as R-EPOCH or EPOCH, CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) with or without rituximab, lenalidomide, palliative radiotherapy, or investigational treatment.[1]

For further information on common chemotherapy regimens, see Table 1, p. 719.

High-grade lymphomas such as **precursor T-lymphoblastic lymphoma** (T-LBL) and Burkitt's lymphoma (see below) are *highly aggressive* and untreated patients survive only weeks. They occur mainly in children and young adults, and are often widely disseminated with bone marrow, peripheral blood, and CNS involvement. Lymphoblastic lymphoma is generally treated with protocols based on those used for acute lymphoblastic leukaemia (see p. 692.3), including the use of CNS prophylaxis.[1]

Vaccines for B-cell lymphomas are under investigation.

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AIDS-related lymphomas. Non-Hodgkin's lymphoma is often a late complication of AIDS and its incidence in HIV-infected individuals is about 60 times greater than in the general population.[1] Histologically, it is usually diffuse large cell lymphoma (see Non-Hodgkin's Lymphomas, p. 696.3) or small non-cleaved lymphoma (Burkitt's lymphoma—see below).[1-3] About 50% of these are associated with the presence of Epstein-Barr virus.[4] The other common HIV-associated lymphoma is primary CNS lymphoma (p. 698.1), which is invariably associated with Epstein-Barr virus.[1,2] More recently, primary effusion lymphoma or body cavity-based lymphoma has been identified,[1,2] which is associated with human herpes virus 8. Although Hodgkin's disease (see p. 696.1) is not considered an AIDS-defining illness, epidemiological studies have shown it to be associated with HIV infection.[2]

It was unclear if the introduction of HAART for HIV infection (p. 957.2) would reduce the risk of lymphomas by improving immune function,[5] or, conversely, increase the incidence by allowing patients to survive long enough for lymphoma to develop.[1] However, it has become apparent that the incidence of AIDS-related lymphoma has decreased with the advent of HAART.[1,3,5] There is some evidence of tumour response when antiretroviral therapy is started in a patient who already has a lymphoma.[4]

Most patients with AIDS-related non-Hodgkin's lymphomas have disseminated disease, often extranodal, at presentation.[1,2] Optimal management is not established.[3] Combination chemotherapy regimens used include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CDE (cyclophosphamide, doxorubicin, and etoposide) and a dose-adjusted EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).[1,3,5,6] M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) has also been used;[1] a low-dose modification of this regimen produced responses comparable to the standard-dose regimen.[7] There is some controversy about whether HAART should be given with or after chemotherapy,[2,6] although most seem to recommend concomitant treatment[2,6] as it results in a more modest decrease in immune function than when chemotherapy is given alone.[5] The addition of rituximab has been investigated, but results have been disappointing and an increased risk of neutropenic sepsis and death has been reported.[3,5] However, some consider the use of rituximab with chemotherapy to be more effective than chemotherapy alone, and safe in these patients provided appropriate antibacterial prophylaxis is used.[6] The use of colony-stimulating factors with chemotherapy has reduced neutropenia and febrile episodes, but there has been no effect on remission rates or overall survival.[1] Most studies used granulocyte-macrophage colony-stimulating factor, but this may increase HIV-1 replication.[1]

Patients with relapsed AIDS-related lymphoma who are responsive to salvage chemotherapy may be treated successfully with high-dose chemotherapy and autologous haematopoietic stem cell transplantation.[6]

HIV-positive patients with Hodgkin's disease are more likely to present with constitutional symptoms, at an advanced stage, with extranodal disease, and concomitant Epstein-Barr virus infection than HIV-negative individuals. Bone marrow involvement may be found in more than 50% of patients. Before HAART, patients with Hodgkin's disease and infected with HIV had a median survival of 1 to 2 years. Outcomes in the HAART era may be improving, although optimal treatment is undecided. Regimens that have been tried include the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and Stanford V regimens.[2]

For further information on common chemotherapy regimens, see Table 1, p. 719.

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Burkitt's lymphoma. Burkitt's lymphoma is a small non-cleaved cell lymphoma (SNCL) of B-cell origin, which is highly aggressive and with a characteristic chromosomal translocation involving the *c-myc* oncogene. The disease accounts for up to 50% of childhood non-Hodgkin's lymphoma in non-endemic areas. Three clinical variants have been described. The endemic form occurs most commonly in equatorial Africa and Papua New Guinea, in young children, and is almost always associated with Epstein-Barr virus (EBV) infection. It frequently involves the jaws and other facial bones; bone marrow and CNS involvement can occur. In contrast, the sporadic form, seen most commonly in developed countries, arises in the lymphoid tissues of the gut and upper respiratory tract. The immunodeficiency subtype is seen in the setting of HIV infection, and to a lesser extent post-transplantation. Adult patients with the latter 2 subtypes typically present with extranodal disease, and the abdomen is the most common site of involvement. Symptoms include abdominal pain, gastrointestinal bleeding, nausea, and vomiting, and may mimic appendicitis. Bone marrow and CNS involvement can occur. Jaw involvement is rare, and only about a third of patients are EBV-positive.

The main **treatment** for Burkitt's lymphoma is chemotherapy. Shorter duration, dose-intensive chemotherapy regimens have resulted in improved survival and in children complete remission is common and prognosis good: probability of long-term disease-free survival is usually greater than 80%.[1] Prognosis has been less good in adults, but with the increasing use of more intensive regimens similar to those used in children, is improving. About half of all adult cases are reported to be curable with intensive chemotherapy regimens.[2,3]

Commonly used regimens include CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate) for low-risk patients; it is given in an alternating regimen with IVAC (ifosfamide, etoposide, and high-dose cytarabine) in high-risk patients.[2-5] Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate plus cytarabine) is also given to adult patients.[2-6] A dose-adjusted EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) is also recommended for use in low-risk patients or in high-risk patients unable to tolerate more aggressive treatment.[4] Rituximab has been added to these regimens in an attempt to improve response and long-term survival;[2-7] initial results have been promising. Cytarabine and methotrexate are also given intrathecally for CNS prophylaxis.[2-4]

Relapsed or ***refractory*** Burkitt's lymphoma has not been well-studied and the optimal treatment regimen is unknown.[2,3] Drugs used for salvage chemotherapy include high-dose methotrexate and high-dose cytarabine or etoposide plus cisplatin;[2] combination regimens incorporating cisplatin, cytarabine, or ifosfamide may be of benefit, particularly if these were not used first-line.[3] Autologous or allogeneic haematopoietic stem cell transplantation may be considered for relapsed or refractory disease,[2-4] although its role in Burkitt's lymphoma remains controversial.[5,7] There are reports of improved survival with high-dose chemotherapy followed by autologous stem cell transplantation, compared with chemotherapy alone. Allogeneic transplantation has been reported to lower relapse rates when compared with autologous transplantation, but transplant-related mortality is higher.[7]

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Primary CNS lymphoma. Primary CNS lymphoma is an aggressive form of non-Hodgkin's lymphoma that develops in the brain, spinal cord, leptomeninges, or the eye.[1,2] It accounts for some 0.5 to 5% of all primary brain tumours (see also Malignant Neoplasms of the Brain, p. 701.2). There is a strong association with HIV infection (see AIDS-related Lymphomas, p. 697.2). Patients usually present with neurological symptoms such as hemiparesis or dysphasia, mental status changes, symptoms of increased intracranial pressure, and behavioural changes.[1,2] The ocular manifestation is termed primary intra-ocular lymphoma; it is often misdiagnosed as uveitis, and should be distinguished from systemic lymphoma with orbital involvement.[1,3,4]

Treatment options for primary CNS lymphoma include corticosteroids, radiotherapy, and chemotherapy. Corticosteroids such as dexamethasone, although the treatment of choice for short-term palliation, should be avoided before tissue biopsy since they can interfere with the histopathology.[1,2] These tumours are radiosensitive, but the timing of radiotherapy is controversial. Most recommend some form of radiation after chemotherapy; drug delivery may be optimal before radiation, when the blood-brain barrier is maximally disrupted by the tumour.[2] Others advise against first-line radiotherapy, based on limited efficacy and potential delayed neurotoxicity; consolidation radiotherapy may be beneficial in younger patients who achieve a complete response after methotrexate-based chemotherapy.[1,5]

While the optimum chemotherapy combination remains unclear,[1,5] chemotherapy has significantly improved disease-free and overall survival.[2] High-dose methotrexate appears to be the most effective drug and is recommended first-line, with or without other drugs such as cytarabine.[1,2,5] Regimens based on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) have been associated with increased neurotoxicity and found ineffective, probably due to poor penetration across the intact blood-brain barrier;[1,2] as a consequence, CHOP-like chemotherapy is considered to have no role in the treatment of primary CNS lymphoma.[1]

In patients who relapse after a relatively long-term response (longer than 1 year), then re-treatment with a methotrexate-based regimen is considered reasonable. For those who do not respond to initial chemotherapy or who relapse quickly, recommendations include radiotherapy with or without chemotherapy,[2] Alternative agents include rituximab, temozolomide, topotecan, and the combination regimen of cisplatin, cytarabine, and dexamethasone.[2] High-dose chemotherapy followed by autologous haematopoietic stem cell transplantation (HSCT) has been investigated, but evidence to support its use first-line is considered to be lacking.[1] However, it has been reported as being an effective treatment for relapsed and refractory disease.[6]

Optimal treatment for primary intra-ocular lymphoma is not known,[3] and recommendations for therapy remain controversial.[1] Options include ocular radiotherapy, intravitreal methotrexate, combined modality treatment, and systemic methotrexate-based chemotherapy.[1,3,4] High-dose chemotherapy with autologous HSCT has been tried,[1,4] and agents under investigation include rituximab and trofosfamide.[1]

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MALT lymphoma. Marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) occur most commonly in the stomach, but may also occur in the salivary gland, breast, thyroid, eye, or lung. They tend to be indolent and remain localised for long periods of time, but can transform to a more aggressive type. Clinical symptoms of gastric MALT lymphoma are vague and varied and include abdominal pain, dyspepsia, vomiting, and gastric bleeding.

Most gastric MALT lymphomas are associated with *Helicobacter pylori* infection.[1-4] The bacterium stimulates the formation of MALT in the stomach, which normally lacks organised lymphoid tissue, and there is evidence that it indirectly stimulates tumour growth. Eradication of *H. pylori* infection using antibacterial and antisecretory therapy, as described in Peptic Ulcer Disease, p. 1816.2, has been shown to result in regression of gastric MALT lymphoma in most patients.[1,2,4,5] Tumour response may be slow,[2] and lymphoma regression after *H.pylori* eradication is not always complete; eradication suppresses but does not necessarily eradicate the neoplastic clone. Only lymphomas limited to the mucosa or submucosa regress after eradication and lymphoma can recur.[1] Thus, patients who are *H. pylori*-positive with early stage primary gastric MALT lymphomas may be treated solely with *H. pylori* eradication regimens and long-term endoscopic follow-up.[2-4,6,7] The best treatment for patients without *H. pylori* infection, those whose tumours do not respond to eradication, and those with more advanced tumour stage at presentation remains to be established.

Radiation therapy is the treatment of choice for localised disease.[2,4,6,7] Rituximab monotherapy may be considered for early stage disease if radiation therapy is contra-indicated.[2] Surgical resection is generally limited to specific clinical situations,[2] such as the management of complications or for cases of locally persistent disease.[3,4] Single-agent or combination chemotherapy is recommended in advanced disease.[2,7] No standard chemotherapy regimen has been established.[4] Regimens that may be tried include alkylating agents such as cyclophosphamide or chlorambucil, purine analogues such as cladribine or fludarabine,[3,4,7] and occasionally anthracycline-based chemotherapy for younger patients with more aggressive disease.[3] Rituximab is also an option, given either alone or with chemotherapy.[2-4,7]

It has been suggested that screening for and eradication of *H. pylori* is worth investigating as a means of preventing gastric cancer.[8]

Non-gastrointestinal low-grade MALT lymphomas have been treated with surgery or radiation therapy if localised, and with single-agent or combination chemotherapy (similar to that used for other low-grade non-Hodgkin's lymphomas—see p. 696.3) if advanced.[2-4,6]

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Mantle cell lymphoma. Mantle cell lymphoma is a rare, aggressive lymphoma of B-cell origin, characterised in most cases by a chromosomal t(11;14) translocation. Patients are often elderly and more often male. Most patients present with advanced stage disease. Clinical features include fever, weight loss, drenching night sweats, and gastrointestinal symptoms.[1,2]

There is no established standard **treatment** for mantle cell lymphoma.[3,4] For the few patients presenting with *localised* disease, radiotherapy significantly improves progression-free survival, and is recommended first-line, with or without chemotherapy.[1,3]

Systemic combination chemotherapy, although non-curative, is recommended in *advanced* disease.[1,3] Rituximab plus chemotherapy is recommended first-line.[1,3,5] Chemotherapy options include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), HyperCVAD/MA (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin).[1-3,5] For further information on these and other common chemotherapy regimens, see Table 1, p. 719. An alternative treatment in younger patients, without significant comorbidities, is high-dose radiochemotherapy consolidated by autologous haematopoietic stem cell transplantation (HSCT).[1,3,5,6] Allogeneic HSCT may be curative, but only a few patients are suitable and it is associated with considerable morbidity and mortality.[1,2,6] For patients who cannot tolerate more intensive therapy, some recommend CHOP with or without rituximab[3] or anthracycline- or fludarabine-containing regimens.[1]

Patients who *relapse* after initial therapy or with progressive disease may be treated with bendamustine (with or without rituximab), bortezomib, lenalidomide, purine analogue-containing regimens (with or without rituximab), temsirolimus, thalidomide (alone or with rituximab),[1,3,5,6] or ibrutinib. Radioimmunotherapy, with radiolabelled monoclonal antibodies ibritumomab and tositumomab, has also been investigated for relapsed or refractory disease.[1,2,5,6] Allogeneic HSCT may be considered in suitable patients with relapsed disease after first-line therapy.[1,2,6]

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Mycosis fungoides. Mycosis fungoides is the most common of the cutaneous T-cell lymphomas. It is considered to have 3 stages which may overlap or occur simultaneously:

- a premycotic erythematous or patch phase, characterised by a pruritic rash resembling psoriasis, which may persist for years or even decades
- an infiltrative or plaque phase, in which some patches become thickened, darker plaques with marked T-cell infiltration
- a tumour phase where lesions enlarge and ulcerate. Ultimately there may be visceral involvement or potentially fatal sepsis secondary to skin breakdown

A leukaemic variant of mycosis fungoides presents as widespread pruritic erythroderma, accompanied by abnormal T-cells in the blood, and is known as the Sézary syndrome.

There are many therapeutic options for mycosis fungoides, but few have been evaluated in controlled studies. **Treatment** depends on disease stage and spread.[1-9] Patients with limited and slowly progressive *patch phase disease* have a good prognosis (median survival similar to age-matched controls) and may be managed with topical and local therapies. Topical therapies include emollients, corticosteroids, chlormethine, carmustine, the retinoids bexarotene or tazarotene, and imiquimod.[1,2,6-10] Phototherapy, using UV B light, or a psoralen plus UV A light (PUVA), is a useful alternative when topical treatments are ineffective or not tolerated.[1,2,8] Mycosis fungoides is very radiosensitive, and for clearly localised patches, or isolated patches that have failed to respond to other treatments, local x-ray or electron beam radiotherapy may be used.[2,3,6-8]

The initial therapy for patients with widespread *patch/plaque phase disease* is also topical, using chlormethine or PUVA.[1,6] Topical retinoids are not recommended for generalised skin involvement, as they can cause irritation.[6] Patients who fail to respond to a single drug may be treated with combinations such as chlormethine with phototherapy,[1] PUVA with interferon alfa,[1,3,7] or PUVA with retinoids.[7] Total skin electron beam therapy may be used, but it may not be widely available and is usually only given once;[3] it is generally used for thickened plaques or for disease that has not responded to other local therapies.[1-3]

In the *tumour phase*, combination therapy as described above is often used initially.[1,4,7] Alternatively, systemic retinoids (such as acitretin, bexarotene, isotretinoin, or tretinoin), interferons, vorinostat, romidepsin, denileukin diftitox, or low-dose methotrexate may be tried.[6] Systemic chemotherapy may be used for palliation in recalcitrant disease and advanced disease with extracutaneous involvement, but responses are often of short duration.[1,2,6] Options include single-agent liposomal doxorubicin, gemcitabine, chlorambucil, pentostatin, etoposide, cyclophosphamide, and temozolomide.[6] Combination regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (CHOP without doxorubicin), CAVE (cyclophosphamide, doxorubicin, vincristine, etoposide),[1] or EPOCH (etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide).[8] For further information on common chemotherapy regimens, see Table 1, p. 719.

Mycosis fungoides with erythrodermic features is treated similarly except that skin irradiation tends to be avoided or used in very low doses as it causes severe desquamation.[1] Extracorporeal photopheresis may be useful for disease with erythrodermic features.[1,3,5,6,10]

Therapies for *persistent or recurrent* mycosis fungoides include denileukin diftitox, bexarotene, and vorinostat.[2,4,5] Experience with autologous haematopoietic stem cell transplantation (HSCT) is limited, but allogeneic HSCT may be considered for patients with advanced disease that is progressive or refractory to multiple treatment options.[6,7] Alemtuzumab has been used in patients with advanced or refractory mycosis fungoides or Sézary syndrome.[4,6,8]

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Waldenström's macroglobulinaemia. Waldenström's macroglobulinaemia (primary macroglobulinaemia) is an uncommon B-cell lymphoproliferative disorder characterised by lymphoplasmacytic cells that infiltrate the bone marrow and by hypersecretion of immunoglobulin M (IgM). Patients are mainly elderly, and more often male. Although often asymptomatic, patients can present with weakness and fatigue, peripheral neuropathy, anaemia, hepatosplenomegaly, and lymphadenopathy. Some develop the hyperviscosity syndrome (characterised by oronasal bleeding, visual disturbances and retinal haemorrhage, neurological disturbances such as headache, vertigo, and hearing loss, and, rarely, heart failure).

Asymptomatic patients require no treatment and may remain stable for some years. Where **treatment** is required, first-line options include the use of alkylating agents, nucleoside analogues (such as cladribine or fludarabine), or the monoclonal antibody rituximab, as well as combinations of these.[1-9] Combination regimens include nucleoside analogues with either rituximab or cyclophosphamide, or a combination of all three drugs. Cyclophosphamide-based therapy with rituxumab may also be an option, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or DRC (dexamethasone, rituximab, and cyclophosphamide). Rituximab may also be used with thalidomide, and this combination or the DRC regimen may be useful for those whose main indication for treatment is cytopenias.

Rituximab-based therapies may be the preferred ***initial therapy*** for most patients; cyclophosphamide-based regimens are appropriate if rapid disease control is needed.[7] Rituximab monotherapy is discouraged in those patients with higher IgM concentrations and at risk of hyperviscosity,[2,3,5] although it is an appropriate choice for those patients with low-risk disease and associated comorbidities.[7] The use of chlorambucil has decreased in Waldenström's macroglobulinaemia,[8] but it may also be considered as monotherapy in low-risk disease and in older patients with comorbidities.[7]

High-dose therapy followed by autologous haematopoietic stem cell transplantation (HSCT) has a role in the management of selected patients,[2,5] and non-myeloablative allogeneic HSCT has also been investigated.[2,7,9,10] Although many patients are too old to tolerate the high-dose therapy,[5,10] candidacy for autologous HSCT is a factor in the choice of initial therapy;[7] it is recommended that exposure to alkylating agents and nucleoside analogues be limited if HSCT is to be considered.[2,3,6,7,9] Alternatively, stem cells may be collected before treatment with these drugs.[2] A retrospective study[11] found that use of nucleoside analogues was associated with an increased risk of disease transformation to high-grade lymphoma.

When disease stabilises, treatment may be stopped and begun again on ***relapse***.[3] The choice of therapy depends on the first-line treatment used, the quality and duration of response, and other variables such as patient age, tolerance of therapy, and candidacy for HSCT.[7] Initial treatments that produce relatively long responses (6 to 12 months) may be repeated; alternate first-line agents or combination regimens are recommended for earlier progressions.[3,7] Appropriate second- or third-line choices include bortezomib, thalidomide (with or without dexamethasone), HSCT, or alemtuzumab,[3,7] although some consider the use of the latter unacceptable in this context because of high treatment-related mortality.[8] Lenalidomide is under investigation for Waldenström's macroglobulinaemia[3,8,9] and small studies have reported benefit with interferon alfa.[2,6,10]

Plasmapheresis is indicated for the treatment of symptomatic hyperviscosity,[1,3-6,10] and high-dose corticosteroids may be used to treat systemic vasculitis arising from deposition of paraproteins.[6] Splenectomy, although rarely indicated, may be used to manage painful splenomegaly and hypersplenic syndromes.[1,6]

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PLASMA CELL NEOPLASMS. Multiple myeloma. Multiple myeloma (myelomatosis) is a lymphoproliferative disorder of B-cell origin, involving the development of an abnormal plasma-cell precursor. It occurs mainly in the elderly, and accounts for about 1% of all malignancies. It is more common in black than in white patients and in men than in women.

The proliferation of the abnormal clone tends to suppress normal haematopoiesis, resulting in anaemia and immunosuppression, with an increased risk of serious infection. Perhaps the most characteristic complication, however, is skeletal destruction, apparently due to release of an osteoclast stimulating factor, resulting in osteoporosis, lytic lesions and fractures, and bone pain, as well as consequent hypercalcaemia. In addition, the plasma cells release large quantities of monoclonal immunoglobulins, known as paraproteins, which can produce a hyperviscosity syndrome and in some cases may interfere with platelet function. Renal failure of various causes and neurological problems due to compression are also common.

Multiple myeloma is not curable with presently-available treatment, and **therapy** is concerned with prolongation of survival and alleviation of symptoms.[1,2] Those patients with stable, indolent or smouldering myeloma, or benign monoclonal gammopathy, are followed carefully but not treated until overt progressive disease occurs.[1-3] Early treatment may inhibit disease progression, but overall survival and response rates are not affected.[4]

The treatment of overt disease depends on eligibility for haematopoietic stem cell transplantation (HSCT) and risk assessment.[5] High-dose chemotherapy combined with autologous HSCT improves response rate, event-free survival, and overall survival compared with standard chemotherapy.[6] Evidence for these benefits is strongest for patients younger than 55 years old.[7] Although some[8] consider standard-dose chemotherapy to be the preferred initial treatment in patients older than 70 years, other reviews[6,9] have concluded that autologous HSCT is safe for the majority of patients older than 65 years, and guidelines have suggested its consideration in this group[2] if they have good functional status and limited comorbidity. With tandem transplantation, patients receive a second planned autologous HSCT,[1,10] since it was shown that patients who did not enter remission after one transplant could achieve remission after another.[11] Some recommend tandem transplants in those who do not have at least a very good partial response after the first,[12] and as such, some centres routinely collect enough stem cells for two transplants.[1,10,13,14] However, the benefit of a second transplantation has been challenged by the high efficacy of novel induction agents followed by one autologous HSCT, with these agents then used as consolidation therapy.[15] Allogeneic HSCT has been used for multiple myeloma, sometimes after autologous HSCT, but few patients are suitable, and transplant-related morbidity and mortality are high with conventional myeloablative chemotherapy regimens; non-myeloablative regimens (miniallogeneic HSCT) are under investigation.[5,10-13]

Although the VAD regimen (vincristine, doxorubicin, and dexamethasone) was used for many years as induction therapy, newer regimens are now recommended in preference.[3,5,10,15,16] Dexamethasone, which may be used alone, forms part of most recommended regimens.[1,16] Options include thalidomide plus dexamethasone, lenalidomide plus dexamethasone, and bortezomib-based regimens.[1,3,5,10,12,15,16] Although considered by some to be less favourable than the newer regimens,[16] the DVD regimen uses liposomal doxorubicin instead of doxorubicin in the VAD regimen.[1,16]

Peripheral stem cells are collected after giving high-dose cyclophosphamide and granulocyte colony-stimulating factor.[6,8] Although some suggest the use of alkylating agents and interferon alfa after stem cell collection,[8] earlier alkylator or nitrosurea therapy interferes with stem cell mobilisation,[1,10,12,13] and can result in poor engraftment.[7,9] The standard conditioning regimen before transplantation is considered to be high-dose melphalan.[2,3,6,8-10,13] Total body irradiation is no longer recommended, as combined with lower dose melphalan, it resulted in higher toxicity and no significant survival benefit compared with high-dose melphalan alone.[6,7,9] Similarly, stem cells are not purged of contaminating myeloma cells as a randomised study[17] showed no benefit.

Where transplantation is infeasible or inappropriate, ***chemotherapy*** may be given to induce remission and prolong survival. The standard first-line regimen has long been a combination of oral melphalan and corticosteroids, usually prednisolone or prednisone.[1-3,9,10,13-16] This MP regimen produces an objective response in about half of all patients, and prolongs median survival to between 2 and 3 years.[9] The contribution of corticosteroids to the regimen has been controversial although a trend towards increased survival was noted[6] compared with melphalan alone, and high-dose dexamethasone given alone has been reported to be effective in producing remissions.[9] Cyclophosphamide is active,[6] and has been substituted for melphalan.[2] The addition of thalidomide to melphalan and prednisone (the MPT regimen) has led to better response rates and progression-free survival, and it is recommended as standard induction for elderly patients ineligible for HSCT;[3,5] however, toxicity is higher than with the MP regimen.[12,16,18] Similarly, the MPV or MPB regimen (bortezomib added to melphalan and prednisone) was found to have improved response rates and overall survival compared with MP alone,[1,5,16] and it is also a recommended induction regimen. Lenalidomide added to melphalan plus prednisone is another option.[1] Other induction regimens include bortezomib plus dexamethasone, thalidomide plus dexamethasone, lenalidomide plus dexamethasone, the VAD or DVD regimens,[1] or bendamustine plus prednisone.

Maintenance chemotherapy with thalidomide has been used after autologous HSCT,[1,19] and may be offered to patients not achieving a complete response after tandem HSCT,[15,18] although optimal duration of maintenance therapy is not known.[3,19] Bortezomib and lenalidomide can also be used for maintenance,[1,12] although there may be an increased risk of secondary cancer with the latter. Other options include thalidomide plus prednisone.[1] Corticosteroids or interferon do not appear to provide significant clinical benefit,[5,10,15,19] although some guidelines suggest second-line use.[1]

In patients who fail to respond to initial treatment, or who subsequently ***relapse***, various regimens may be tried.[1] If relapse occurs more than 6 months after initial induction therapy, re-use of the initial regimen is recommended. However, a different regimen should be considered if disease recurs within 6 months of completing induction therapy.[1,16] Good responses have been achieved with bortezomib,[1,2] and it is recommended either as monotherapy, or with dexamethasone, or liposomal doxorubicin.[1,16] Other regimens include:[1,16]

- monotherapy with either bendamustine, thalidomide, lenalidomide, pomalidomide, high-dose cyclophosphamide, or carfilzomib
- dexamethasone plus either thalidomide, lenalidomide, or pomalidomide
- dexamethasone plus bortezomib and either thalidomide or lenalidomide
- dexamethasone plus cyclophosphamide and either bortezomib or lenalidomide
- dexamethasone plus lenalidomide and bendamustine
- bortezomib plus vorinostat
- cyclophosphamide-VAD
- DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin)
- DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide)

For further information on common chemotherapy regimens, see Table 1, p. 719.

Although chemotherapy aimed at the myelomatous clone will produce symptomatic relief as disease is brought under control, ***supportive and symptomatic care*** is also important. Bisphosphonates such as clodronate, pamidronate, and zoledronate have been found to be effective in reducing skeletal complications,[20,21] and are recommended in those patients with bone disease.[1,2,14,22] Some recommend that bisphosphonate therapy be stopped after 2 years in patients with responsive or stable disease.[22,23] (For further discussion, see Malignant Neoplasms of the Bone, under Bisphosphonates, p. 1174.1.) Radiotherapy is used for impending fracture or impending spinal cord compression, and is often effective in relieving uncontrolled bone pain.[1,9]

Erythropoietin therapy can improve anaemia and reduce the need for transfusion.[1,6,8,9] A high fluid intake is essential in patients with renal dysfunction or hypercalcaemia (for the appropriate management of the latter, see p. 1778.1). Vigorous antibacterial treatment may be needed if infection occurs (see Infections in Immunocompromised Patients, p. 186.3) and plasma exchange may alleviate the hyperviscosity syndrome.[1,8,10]

Drugs under investigation for the treatment of multiple myeloma include oblimersen, vorinostat, and arsenic trioxide.[13,14]

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Malignant effusions. The amount of interstitial fluid is normally regulated by a complex equilibrium between capillary filtration, osmotic pressure, and physical hydrostatic or hydraulic forces. Malignant neoplasms can disturb this equilibrium by obstruction of capillary or lymphatic drainage as well as causing active exudation of additional fluid after metastatic implantation. Malignant effusions are associated most often with lung, breast, and ovarian malignancies and lymphomas. Symptoms vary, and the fluid build-up may be asymptomatic; both pleural and pericardial effusions can produce cough, pleuritic chest pain, and dyspnoea and pericardial effusions may progress to cardiac tamponade. Peritoneal effusions may lead to malignant ascites.

The main aim of **treatment** for malignant effusions is effective palliation of symptoms, and depends in part on the tumour type, patient performance status, and prognosis.[1-4] If the tumour is chemosensitive, systemic chemotherapy may resolve the effusion.[1,4,5] Similarly, radiotherapy can be effective for pericardial effusions associated with radiosensitive tumours.[3] Simple fluid drainage (thoracentesis, paracentesis, or pericardiocentesis) will relieve symptoms until fluid build-up recurs,[2,3] and in patients with very poor prognosis and a limited life expectancy, may suffice for palliation.[4] Use of an indwelling pleural catheter allows convenient and minimally invasive fluid drainage in patients with pleural effusions, and may result in spontaneous pleurodesis.[4] In malignant ascites, paracentesis is usually effective temporarily; evidence for the value of diuretics is weak, but spironolactone may be of benefit in some patients, either alone or with a loop diuretic.[6] In other patients with refractory tumours, fluid drainage followed by sclerotherapy is likely to be preferred.

The principle of *sclerotherapy* is the instillation of an irritant agent into the pleural or pericardial cavity to promote inflammatory and fibrotic changes which result in the membranes adhering together and abolition of the space between the membranes in which fluid accumulates. When this is done to treat pleural effusions (pleurodesis) success is dependent on adequate fluid drainage beforehand and full re-expansion of the lung to bring the pleural surfaces together. Intrapleural thrombolytics such as streptokinase have been used to improve fluid drainage in cases of loculation of the effusion.[1,7]

Many drugs have been used for sclerotherapy, and the most common are a tetracycline (doxycycline or tetracycline), bleomycin, or talc. The choice between these three remains controversial, and opinions on the preferred option differ.[1,2,4,7,8] However, a systematic review[9] found talc to be the sclerosant of choice for malignant pleural effusions. Other sclerosants that have been used, with varying reported rates of success, include interferon alfa, mepacrine, mitoxantrone, picibanil, povidone-iodine, silver nitrate, *Corynebacterium parvum*, and *Staphylococcus aureus* superantigen.[8] After drainage of the effusions the sclerosant is instilled in a small volume (50 to 100 mL) of liquid through the drainage tube.[5] Talc may also be given as a powder insufflation (rather than slurry), but this involves a surgical procedure under general anaesthesia. Sclerotherapy results in painful inflammation, and local anaesthetics or analgesics should be given.[2,7] For patients who fail sclerotherapy, or for whom this is not considered suitable, there are various surgical options to manage effusions.[1,3,6]

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Malignant neoplasms of the bladder. Cancer of the bladder is the fourth or fifth most common cancer in Europe and the USA, where over 90% of bladder cancers are transitional cell in type. About two-thirds of all cases occur in men, and the median age at diagnosis is 65 years. Known risk factors include tobacco smoking, exposure to chemicals such as aniline dyes, and previous radiotherapy; in countries where it is endemic, schistosomiasis is also an important cause of squamous cell bladder cancer. Most patients present with haematuria; there may also be urinary frequency or dysuria.

Urothelial tumours fall into 3 major groups, non-invasive, invasive, and metastatic, which differ in prognosis and management.[1] About 70% of cases are non-muscle-invasive (superficial), 25% are muscle-invasive, and 5% are metastatic.[2]

The **non-muscle invasive** tumours are divided into low-grade carcinomas or papillomas confined to the mucosa (Ta), those that have invaded the submucosa (T1), and high-grade carcinoma *in situ* (CIS).[1,2] The standard initial treatment for primary or recurrent disease is surgery, in the form of transurethral resection (TUR). In an attempt to prolong remission and reduce the recurrence rate antineoplastics are instilled into the bladder soon after TUR (prophylactic or adjuvant intravesical therapy).[1-3] Effective agents include mitomycin, doxorubicin, epirubicin, and thiotepa; efficacy is similar in terms of outcome and choice depends on adverse effects.[2,4] The immunomodulator BCG is also used intravesically, with good results.[2] A single dose of intravesical chemotherapy is usually given within 24 hours of TUR, which may be sufficient for low-grade Ta tumours.[1,3,4] The need for further adjuvant intravesical therapy depends on the patient's prognosis and risk of tumour recurrence.[3,4] The ideal duration and intensity of the schedule remains undefined.[4]

Chemotherapy reduces recurrence, but not progression,[2,4] and BCG is considered by some to be the preferred option for high-grade tumours or those at high risk of progression.[1,3] Mitomycin is an alternative.[1] BCG is also generally preferred to antineoplastics for CIS,[1,5] and may be considered as maintenance therapy in those showing a complete response.[1,5] Those with recurrent or persistent disease can be given a second course of BCG or mitomycin.

If residual disease is still present, cystectomy should be considered; intravesical therapy with a different agent (mitomycin, valrubicin, or BCG plus interferon alfa) is an alternative to cystectomy. Radical cystectomy is recommended if disease progresses.[1] Photodynamic therapy using porfimer sodium or 5-aminolevulinic acid has also been investigated.[6]

Management of **muscle-invasive** bladder cancer that has not yet metastasised is a matter of some controversy, but conventional therapy has revolved around radical surgery.[1,2,7] Patients are usually also given systemic chemotherapy before (neoadjuvant) or after (adjuvant) complete cystectomy, in an attempt to prolong survival.[1,5,7] Neoadjuvant chemotherapy apparently favours survival;[3] there is insufficient evidence for routine use of adjuvant chemotherapy,[3,5] and use of the latter usually depends on prognosis, and whether or not neoadjuvant chemotherapy was given.[1] Some recommend considering the use of adjuvant chemotherapy in node-positive patients.[3] Selected patients may be considered for bladder-sparing approaches such as partial cystectomy followed by radiotherapy, chemotherapy, or both.[1,7]

The optimal chemotherapy regimen remains to be defined but regimens incorporating cisplatin, gemcitabine, or methotrexate are usually preferred. Typical regimens include gemcitabine plus cisplatin, CMV (cisplatin, methotrexate, and vinblastine), or MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin).[1,5] For further information on common chemotherapy regimens, see Table 1, p. 719.

Patients with unresectable or **metastatic** disease, or who subsequently develop metastatic disease, are usually treated with systemic chemotherapy with or without radiotherapy.[1,3] For patients with good prognosis, a combination regimen such as MVAC or CMV may be used. Various combinations of gemcitabine, taxanes, and cisplatin have shown clinical benefit,[1,7] and gemcitabine plus cisplatin has been shown to provide similar survival advantage to MVAC with better tolerability: some now consider that it should be the preferred regimen in advanced disease.[1,8] Taxane-based regimens may be considered in patients unable to receive cisplatin.[1] No standard second-line therapy exists and participation in clinical studies is encouraged; depending on first-line therapy, palliative options include monotherapy with bleomycin, fluorouracil, cisplatin, carboplatin, docetaxel, doxorubicin, gemcitabine, ifosfamide, methotrexate, paclitaxel, pemetrexed, or vinblastine.[1] Vinflunine is an option for those who progress on first-line platinum-based therapy.[3] Newer drugs under investigation include epidermal growth factor receptor inhibitors such as cetuximab and inhibitors of angiogenesis such as bevacizumab and sunitinib.[9]

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Malignant neoplasms of the bone. Skeletal complications may result from primary cancers or from bone metastases secondary to other cancers. Primary bone malignancies are rare, and are usually sarcomas (see Bone Sarcoma, p. 717.3). Multiple myeloma (p. 699.2) also produces bone involvement. Metastatic bone disease is a common problem with cancers of the breast, prostate, and lung.

Skeletal malignancies cause considerable morbidity, including cancer pain (the general management of which is discussed on p. 7.1) and also result in immobility, bone fractures, bone-marrow infiltration, spinal cord or nerve root compression, and hypercalcaemia.[1-3] The most common sites of metastasis are the axial skeleton including the spine and ribs, and the proximal ends of the long bones.

The goals of management of **bone metastases** are essentially palliative: to relieve pain, preserve and restore function, and to reduce the risk of fracture and stabilise the

skeleton. Treatment often requires a multi-disciplinary approach that includes radiation, surgery, and systemic therapy.[2,4-6]

Radiotherapy provides excellent palliation of localised metastatic bone pain,[2,3] with responses occurring in over 70% of patients treated with external beam irradiation. Radiation can also be used to prevent or treat fractures, or to prevent spinal cord compression.[2] Bone-seeking radiopharmaceuticals such as rhenium-186, phosphorus-32, samarium-153, or strontium-89 may be used as an alternative for pain palliation, or as an adjunct to external beam radiotherapy.[2,4,5,7] Radiofrequency ablation has also been reported to be effective for pain, but is contra-indicated in the spine owing to proximity of the spinal cord and nerve roots.[3]

Structural weakness due to extensive bone loss may require ***structural support***; external fixation with cast or brace immobilisation is an option. Internal surgical fixation or stabilisation can treat or prevent fractures.[2] Surgical excision and reconstruction with methylmethacrylate bone cement may also be required. Postoperative radiotherapy is used to prevent fractures[2] and improve mobility.[3]

Bone metastases cause local osteolysis and various bone-modifying agents (such as the bisphosphonates and denosumab) that ***inhibit bone resorption*** have been tried, not only to correct hypercalcaemia of malignancy (p. 1167.2), but also to relieve bone pain and reduce the risk of fractures. Bisphosphonates are of benefit in patients with severe bone pain that is too widespread for local use of radiotherapy and does not respond to other analgesics.[8] Reviews[9,10] concluded that bisphosphonates significantly decrease skeletal morbidity, except for spinal cord compression. Benefits in terms of skeletal events are only seen after about 6 months of treatment.[9] Despite the integration of bisphosphonate use into clinical practice for bone metastases, the optimal timing, schedule, or duration of treatment remains to be determined.[3,6,9,11,12] It has been suggested that bone-modifying treatment should start when bone metastases are diagnosed and continue until no longer clinically relevant; they do not affect survival.[10,13] While some continue bisphosphonate treatment despite disease progression, others advocate changing to a more potent bisphosphonate, or stopping treatment altogether.[9] There are no data about the consequences of stopping bone-modifying treatment after one or more skeletal-related events. Starting bone-modifying agents in women with breast cancer without evidence of bone metastases is not recommended.[13] There is little evidence supporting the efficacy of one bone-modifying agent over another;[13] denosumab and the bisphosphonates clodronate, ibandronate, pamidronate, and zoledronate have all been used.[1,2,6,9,12,13] Of the bisphosphonates, those given intravenously have shown a more significant reduction in skeletal-related events than those given orally.[3,10] Denosumab has shown some benefit over zoledronate at delaying or preventing skeletal events in advanced breast cancer,[14] and was noninferior to zoledronate in other cancers or multiple myeloma.[15]

There is much interest in the use of bisphosphonates to *prevent* the development of bone metastases.[11,12] However, preliminary evidence of their efficacy was conflicting.

Systemic ***antineoplastic therapy*** should also be given if the primary tumour is chemosensitive. Endocrine treatment is usually preferred for patients with breast and prostatic cancers,[2] and can produce useful control of symptoms from bone metastases.

Atrasentan is a new drug under investigation.[1,6]

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Malignant neoplasms of the brain. Metastatic brain cancer is the most common cause of intracranial tumours in adults, being up to ten times more common than primary brain tumours.[1] The cancers that most often metastasise to the brain are lung cancer, breast cancer, and melanoma,[1] as well as colorectal cancer, renal cell carcinoma, and adenocarcinoma.[2,3] CNS involvement in patients with acute leukaemia (see Acute Lymphoblastic Leukaemia, p. 692.3) or lymphoma (see CNS Lymphomas, p. 698.1) is also quite common. The frequency and natural history of *primary* brain tumours differ between children and adults. In adults, they are usually gliomas,[4] which are classified histologically into astrocytomas, oligodendrogliomas, and oligo-astrocytomas.[5] Astrocytomas are defined by grades: I (pilocytic), II (diffuse), III (anaplastic astrocytoma), and IV (glioblastoma multiforme), the latter two of which are the most common and are considered malignant.[4,6] Low-grade astrocytomas[7] and malignant medulloblastomas are the commonest primary brain tumours in children.[8]

The symptoms of primary and metastatic cranial neoplasms are those of local pressure and damage to the brain (such as focal seizures and neurological defects), of displacement of brain structures (like oculomotor paresis with tentorial herniation), and of raised intracranial pressure (such as impaired consciousness and papilloedema). Memory loss and personality changes may occur, and headache, nausea and vomiting are common symptoms.

The standard therapy for **primary brain tumours** involves surgery and radiotherapy.[4,5,8,9] General medical management includes control of seizures with antiepileptics, the use of corticosteroids such as dexamethasone to control peritumoral oedema, anticoagulation to manage venous thromboembolism, and treatment for fatigue.[4,6]

Surgery is generally used to relieve compression and cerebral oedema, establish diagnosis, decrease the need for corticosteroids, and where feasible resect as much of the tumour as possible.[1,4,6,10] Progress in image-guided resection has improved safety, and although some consider it to have increased the extent of resection,[4,8] others note it has not been as beneficial as expected for gliomas.[10] The value of surgery in prolonging survival is controversial;[4,10] there is some evidence that extensive resection prolongs survival,[1,4] but this may be biased[10] by the selection of younger fitter patients for surgery.

Adjuvant *radiotherapy* is widely used after surgical resection for malignant tumours in adults and children.[1,4-6,8,10] There is no consensus on the timing of the start of radiotherapy.[10] Strategies to increase the dose of radiation delivered to the tumour by using brachytherapy (radioactive implants) or stereotactic radiosurgery (a technique using highly focused beams of radiation) have failed to improve survival.[4]

Local chemotherapy using biodegradable polymers impregnated with carmustine, placed intraoperatively into the surgical cavity, has been shown to improve survival in patients with either newly diagnosed or recurrent malignant glioma.[1,9,10] While some recommend this after maximal resection in high-grade disease,[1] others consider it to have only marginal benefit over adjuvant radiotherapy alone.[6]

The role of adjuvant *systemic chemotherapy* for primary brain malignancies has been unclear, in part because of the difficulty in finding drugs that can cross the blood-brain barrier; until the advent of temozolomide, treatment was usually based on nitrosoureas such as carmustine and lomustine.[1,5,11] The PCV regimen (procarbazine, lomustine, and vincristine) has been widely used in the treatment of gliomas after surgical resection and radiation therapy.[5,10] The value of this regimen was called into question by a large randomised study of adjuvant PCV plus radiotherapy versus radiotherapy alone in high-grade astrocytoma, in which PCV provided no additional survival benefit.[12] However, a meta-analysis including this and 11 smaller studies found that giving some form of adjuvant chemotherapy (usually based on nitrosoureas) modestly improved survival in adults with high-grade glioma.[13] Temozolomide, an oral alkylating agent, was initially used for the treatment of recurrent gliomas.[5] Its use during and after radiotherapy in newly diagnosed glioblastoma, usually after debulking surgery, has improved survival,[14] and this regimen has largely replaced the nitrosoureas in the management of glioma.[1,4,6,9-11,15,16] For patients who progress after chemotherapy, there is no established second-line regimen.[6] Second-line agents include irinotecan, cisplatin or carboplatin, and platinum-based regimens.[1,5] Bevacizumab plus irinotecan may be tried for recurrent disease.[1,16]

In ***children***, the extent of resection correlates with survival and maximal safe resection is a major therapeutic goal.[17,18] The biology of brain tumours in very young children appears to differ from that seen in older children.[17,19] Chemotherapy is used to delay radiotherapy, reduce its dose or frequency, or even eliminate the need for it altogether, as it can cause neurodevelopmental damage.[7,17-21] Generally, in children older than 3 years, surgery can be followed by a reduced dose of craniospinal irradiation, while although those younger than 3 years are considered high-risk, radiotherapy is avoided if at all possible in this group.[18]

Common combination chemotherapy regimens used in children have included cisplatin or carboplatin, cyclophosphamide, etoposide, ifosfamide, lomustine, methotrexate, procarbazine, topotecan, vincristine, or vinblastine.[17,19,20] Temozolomide and oxaliplatin warrant further investigation.[19] Different tumour types vary in their sensitivity to chemotherapy.

Autologous haematopoietic stem cell transplantation (p. 1937.1) is also used for various paediatric brain tumours to limit the adverse effects of chemotherapy, and to maximise the dose of chemotherapy that can be used;[17-21] results have been conflicting and appear to depend on the type of tumour. Preparative regimens used have been based on thiotepa, busulfan, or melphalan, as well as high-dose combination chemotherapy regimens.[17,20,21] Intrathecal chemotherapy with drugs such as methotrexate, is also used.[19]

Since present regimens for primary brain tumours are far from optimal, alternatives continue to be tried.[1] Strategies include optimising current regimens, investigating different combinations of drugs, as well as methods to improve delivery across the blood-brain barrier.[5] Other treatments investigated include single or multitargeted kinase inhibitors, ligand-toxin conjugates, antisense oligonucleotides, and gene therapy.

Whole-brain radiation therapy (WBRT) is the common choice for most patients with **brain metastases**.[1,2,22] Surgery plus WBRT may be suitable for those with a single brain metastasis, especially if prognosis is favourable and systemic disease controlled.[1,2] Stereotactic radiosurgery (with or without WBRT) may be an alternative for patients with isolated metastases and for whom surgery is not an option.[1,2,22,23]

Chemotherapy has traditionally had a limited role in the treatment of brain metastases.[2,23] The blood-brain barrier was thought to limit delivery of drugs to the site of disease, especially those drugs that are large and less lipid-soluble. However, the blood-brain barrier appears to be partially dysfunctional in cerebral metastatic disease, and systemic therapy has led to responses in patients, especially in those who are chemotherapy-naive or who have not been heavily pre-treated.[2,3,22,23] It has been noted that the use of corticosteroids should be limited as they may restore an otherwise disrupted blood-brain barrier.[3] The chemosensitivity of the primary tumour may also be an important factor in determining response,[2,3,22,23] although many tumours that metastasise to the brain are not very chemosensitive.[1] In addition, metastases may progress and be resistant to further therapy simply due to prior exposure to the drugs used.[3,22] Thus the choice of drug needs to take previous treatment regimens into consideration.[3] Aside from common chemotherapy regimens used to treat the primary tumour (see Table 1, p. 719), other agents used for brain metastases include temozolomide (with or without radiotherapy), capecitabine, high-dose methotrexate, gefitinib, irinotecan, and topotecan. Radiosensitisers used include the platinum analogues and motexafin gadolinium.[1-3,22,23]

A brain cancer vaccine (DCVax-Brain) is also being investigated.

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Malignant neoplasms of the breast. Cancer of the breast is the most common malignant neoplasm in women. The disease is rare under the age of 25, and increases in incidence with age, although the rate of increase slows after the menopause. Risk factors include a family history (women with inherited BRCA1 or BRCA2 mutations are at higher risk), and reproductive hormonal factors such as early menarche, late menopause, nulliparity, and older age at birth of first child. Oral contraceptives and postmenopausal HRT are also associated with a small excess risk (see Carcinogenicity, Breast, on p. 2234.2 and p. 2246.3 respectively).

Ductal carcinoma in situ (DCIS) is a tumour localised to the breast ducts with no evidence of invasion. Invasive breast cancer can be divided into three main groups:

- early breast cancer (operable, primary, stage I/II)
- locally advanced disease (inoperable local, stage III)
- advanced disease (metastatic; stage IV)

Breast cancer is an extremely heterogeneous disorder, and the clinical course is consequently very variable; such factors as patient age and menopausal status, tumour size and grade, involvement of axillary lymph nodes or skin, and presence of hormone receptors within the tumour may be a guide to the extent and aggressiveness of disease, and hence have prognostic significance for treatment.[1] Early determination of oestrogen-receptor (ER) status and for overexpression of HER2 (human epidermal growth factor receptor-2) is recommended, since they are of value in determining response to certain treatments.[1-3] Progesterone-receptor (PR) status may also be measured, although UK guidelines recommend against routine assessment in patients with early breast cancer.[2]

About 20% of all cancers of the breast detected by mammographic screening are **ductal carcinoma in situ** (DCIS),[4-7] the management of which still has some areas of controversy. Most patients with DCIS will be offered breast-conserving surgery,[1,8,9] although mastectomy, which was historically preferred, is still the treatment of choice in high-risk patients.[1,4-6] Radiotherapy is usually recommended after successful breast-conserving surgery,[1,7-9] as it reduces the rate of recurrence and the risk of developing invasive disease (although it does not affect survival); there may be a subgroup of women in whom it is unnecessary, but there is controversy as to how to define the group. Studies examining the use of adjuvant tamoxifen have produced conflicting reports of benefit on recurrence,[5,6] and again, there is no proven effect on survival. UK guidelines recommend against use of adjuvant tamoxifen in patients with DCIS,[2] but some recommend it in selected patients such as those with ER-positive DCIS,[1,9] in young patients, and in those without risk factors for potential adverse effects.[7] Adjuvant use of newer oestrogen modulators such as anastrozole is also under investigation.[5-7]

In patients with **early disease** (stage I or II; a relatively small tumour with no or limited nodal involvement) the prognosis is fairly good. ***Primary treatment*** is surgical,[1,2,9,10] using breast-conserving surgery or mastectomy.[1,9,11] Neoadjuvant chemotherapy should be considered for those women with large tumours who are otherwise suitable for breast-conserving surgery, in order to downstage the tumour; there is no evidence of a survival benefit.[1,11,12] Chemotherapy regimens are the same as those recommended for adjuvant treatment (see below).[1] Adjuvant radiotherapy is recommended after breast-conserving surgery, as it reduces local recurrence rates. Radiotherapy is generally recommended after mastectomy in women with four or more positive lymph nodes, considered to be at high risk of recurrence.[1,9,11]

Further adjuvant therapy with cytotoxic chemotherapy or hormonal therapy as well as ovarian ablation or suppression has been tried in order to eradicate the micrometastases which cause relapses. Studies by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have confirmed the benefits of adjuvant therapy and attempted to determine which women derive most benefit and which regimens are most effective. Analyses from these[13] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 studies[14] permitting up to 15 years of follow-up have shown that:

- all women with early-stage breast cancer benefit from adjuvant therapy (although the size of the benefit varies)
- the benefit continues to increase with time, suggesting that adjuvant therapy is curative in a proportion of women who would otherwise relapse
- about 6 months of anthracycline-based chemotherapy reduces the annual death rate due to breast cancer by about 38% in women under 50 years of age at diagnosis, and about 20% in those aged 50 to 69 at diagnosis (too few women over 70 were given chemotherapy to estimate benefit in this group)
- this survival advantage occurs largely independent of oestrogen receptor (ER) status, nodal status, or other tumour characteristics
- adjuvant regimens including an anthracycline are more effective than those without a drug of this class
- in women with ER-positive disease, about 5 years of treatment with adjuvant tamoxifen reduces the annual death rate due to breast cancer by around 31%, largely independent of age, other tumour characteristics, or the use of chemotherapy
- combined chemotherapy and tamoxifen therefore increases the survival benefit further: for middle-aged women with ER-positive disease the breast-cancer mortality rate over 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen
- ovarian ablation (by surgery or irradiation) or ovarian suppression with a gonadorelin analogue also appear to reduce the mortality due to breast cancer, but that the advantage only applies where other adjuvant therapies are not given

Although these data help in making therapeutic decisions, the size of the benefit will always be less in patients with good prognosis; in the most favourable cases (small tumours with no involved nodes) the incremental benefit may be too small to warrant adjuvant treatment.[1] Tailoring systemic adjuvant therapy to the patient is important, and age and clinical characteristics alone are not adequate grounds to make the judgement: appropriate prognostic markers should be considered.[14,15] Patients with tumours considered hormone-responsive (ER-positive or PR-positive) may receive hormonal therapy alone, or with chemotherapy. Patients with hormone non-responsive tumours (ER-negative or PR-negative) derive greater benefit from chemotherapy and should not receive hormonal therapy.[1,9] In addition, most patients with HER2 overexpression should receive adjuvant trastuzumab as well,[1,9] as studies have shown improvements in both disease-free and overall survival,[16,17] and the benefits are independent of ER status.[1] However, there are concerns about cardiotoxicity.[18,19]

Anthracycline-based regimens are widely used for adjuvant ***chemotherapy***, replacing earlier historical regimens such as CMF (cyclophosphamide, methotrexate, and fluorouracil) with those such as FAC or CAF (cyclophosphamide, doxorubicin, fluorouracil), AC (doxorubicin plus cyclophosphamide), and their many variants. Anthracycline-containing regimens appear to be superior to non-anthracycline-containing regimens for those with HER2-positive tumours.[1,19] The EBCTCG analysis could not show any difference in efficacy between anthracycline regimens,[13] but regimens based on epirubicin have gained in popularity in many centres, since its lower cardiotoxicity compared with doxorubicin means that higher doses can be given.[10] Addition of a taxane (docetaxel or paclitaxel) to an anthracycline-based regimen appears to improve disease-free and overall survival.[19-21] (UK guidelines recommend the use of docetaxel rather than paclitaxel.[2])

Reducing dose intensity of chemotherapy results in poorer survival, and this has led to the hypothesis that higher doses may offer more benefit, particularly in patients at high risk of recurrence. However, despite some positive reports of high-dose chemotherapy with stem-cell support, randomised studies have largely failed to show any benefit of high-dose over standard-dose therapy.[22,23]

Hormonal therapy is only effective in hormone-responsive disease and results of the analyses above established 5 years of tamoxifen as the standard of care in ER-positive disease.[1,10] However, in postmenopausal women, there is evidence that 5 years of anastrozole is an effective alternative to tamoxifen,[24] and treatment with letrozole was found to further reduce the risk of recurrence compared with tamoxifen after 2 years of follow-up.[25] Studies in which 2 to 3 years of tamoxifen were followed by an aromatase inhibitor (anastrozole, exemestane, or letrozole) compared with continued tamoxifen found that disease-free survival was improved with sequential therapy; overall survival was improved in some studies but unaffected in others.[1,26] In addition, although extending tamoxifen beyond 5 years is not generally advocated, there may be significant benefits to following a full course of tamoxifen with extended therapy with an aromatase inhibitor.[27] Thus, aromatase inhibitors can be recommended either as initial, sequential, or extended therapy in postmenopausal women,[1,2,9,26,28] and UK guidelines[2] suggest that tamoxifen should only be used for initial therapy in those with contra-indications to an aromatase inhibitor, although others have questioned the evidence for their routine initial use.[29]

The optimum length of extended or sequential therapy has yet to be determined, but US guidelines allow for 5 years of an aromatase inhibitor after a full course of tamoxifen.[1] Prolonged use of tamoxifen alone is considered an acceptable option by some in those women who cannot tolerate an aromatase inhibitor,[30] and there is some preliminary evidence that 10 years of tamoxifen may be superior to 5 years,[19] although women should be closely monitored for endometrial cancer development.[30] Aside from some suggestion that breast cancer may be sensitive to steroidal aromatase inhibitors (such as exemestane) even after failure of a nonsteroidal inhibitor (such as anastrozole or letrozole),[27] there is no compelling evidence for meaningful efficacy or toxicity differences between the aromatase inhibitors.[1]

Aromatase inhibitors are not effective for hormonal therapy in premenopausal women with ER-positive disease;[1,9,19] tamoxifen is either given alone or it may be combined with ovarian suppression (using a gonadorelin analogue) or ovarian ablation (via oophorectomy or irradiation).[1,2,9,31]

The optimum sequencing of surgery, radiotherapy, and chemotherapy/hormonal therapy has been investigated. Concurrent chemoradiotherapy (chemotherapy given with radiotherapy) is generally considered too toxic, although some allow for its use with the CMF regimen. Otherwise sequential therapy is preferred, with adjuvant chemotherapy given before radiotherapy.[1] Whether tamoxifen should be given concurrently or sequentially with radiotherapy remains unclear, despite several studies addressing the question;[32] US guidelines allow for either option.[1] Where both chemotherapy and hormonal therapy are given, it is recommended that chemotherapy should precede hormonal therapy.[1]

In **locally advanced** breast cancer (stage III) the few patients for whom initial surgery is feasible may be treated as those with high-risk early breast cancer (see above). However, for inoperable disease, anthracycline-based neoadjuvant chemotherapy is standard, which usually results in sufficient tumour shrinkage to allow surgical management, as well as allowing assessment of the responsiveness of the tumour to subsequent treatment.[1,8] Radiotherapy and adjuvant chemotherapy are used after surgery, followed by hormonal therapy if the disease is ER-positive. Adjuvant trastuzumab is also given for those patients with overexpression of HER2. Adjuvant chemotherapy regimens should take into account what was given neoadjuvantly. For disease that does not respond to neoadjuvant chemotherapy, thus remaining inoperable, additional systemic chemotherapy and/or radiotherapy may be tried.[1,2]

The aims of therapy in **advanced or metastatic disease** (stage IV) are palliation and prolongation of life; cure is generally not possible with current regimens,[1,33] and it is often appropriate to select therapy on the basis of previous therapy and patient factors.[19] In women with ER-positive, limited, or asymptomatic disease, ***hormonal therapy*** is preferred: US guidelines advocate an aromatase inhibitor (anastrozole, letrozole, or exemestane), or an anti-oestrogen (usually tamoxifen) for first-line hormonal therapy in postmenopausal patients; second-line therapy options include fulvestrant, toremifene, progestogens such as megestrol, androgens such as fluoxymesterone, or oestrogens such as ethinylestradiol.[1,28] Premenopausal women should undergo ovarian ablation (by surgery or irradiation) or suppression with a gonadorelin analogue, and then be treated as for postmenopausal women. Initial hormonal therapy is continued until disease progression or unacceptable adverse effects occur at which point up to 2 further hormonal regimens may be tried. If these fail, or symptomatic visceral disease develops, the patient is a candidate for chemotherapy. UK guidelines suggest similar management, with the use of an aromatase inhibitor in postmenopausal women, and tamoxifen and ovarian suppression in premenopausal women who have not previously had tamoxifen, or ovarian suppression alone in those who have.[3]

Patients with ER-negative disease, or tumours that are not localised, or who have symptomatic visceral metastasis, or women who have ER-positive tumours refractory to hormonal therapy, should receive ***chemotherapy***.[1,3,33] The taxanes, and in particular docetaxel (which is considered the reference drug in metastatic breast cancer[34]) are acknowledged to be effective,[35] and anthracyclines (doxorubicin, epirubicin, and the related drug mitoxantrone) are also widely used,[1] although a systematic review suggested that their benefits in terms of tumour response did not

extend to improved survival.[36] The benefits of platinum-based therapy have not been established.[37] Capecitabine, gemcitabine, and vinorelbine are also active single agents.[1,3,33]

There is considerable uncertainty as to whether combination regimens offer any substantial benefit over sequential use of single drugs. Although a systematic review of older regimens suggested benefit from combination chemotherapy,[38] and this is the usual standard of care where therapy has curative intent,[34] some do not consider the evidence of benefit from combination therapy persuasive, since toxicity is likely to be increased.[1,33] Nonetheless, established combination regimens, including CMF and various anthracycline- and taxane-based regimens are in use,[1,8] along with newer combinations, such as gemcitabine plus paclitaxel, vinorelbine plus epirubicin, or paclitaxel plus bevacizumab.[1,33] However, while time to progression is improved by paclitaxel plus bevacizumab,[1] no significant effect on overall survival has been shown with bevacizumab combinations, and which patients may benefit is as yet unclear.[33] Ixabepilone with or without capecitabine, is another option.[1,39] In patients with HER2-overexpressing tumours, trastuzumab may be added to chemotherapy:[1,33] the combination is markedly more effective in this group than chemotherapy alone,[34] although use with anthracyclines may be problematic because of the increased risk of cardiotoxicity.[1] Trastuzumab or lapatinib may also be added to hormonal therapy in those with hormone-receptor positive disease.[1,33] UK guidelines recommend stopping trastuzumab once disease progresses outside the CNS, although it should be continued if progression is confined to the CNS alone.[3] Capecitabine plus lapatinib is an option for those refractory to trastuzumab therapy.[1,33]

For further information on common chemotherapy regimens, see Table 1, p. 719.

Higher response rates have been achieved by intensive regimens, combined with autologous bone marrow transplants or stem cells in some studies. However, the results of randomised studies have been disappointing, and a systematic review found no improvement in overall survival with the use of stem-cell supported high-dose therapy in metastatic breast cancer.[40]

The use of bisphosphonates in women with bone metastases reduces bone pain and skeletal complications such as fracture, spinal cord compression, and hypercalcaemia (see Malignant Neoplasms of the Bone, p. 700.3). Radiotherapy is also used for bone pain, and for the treatment of brain metastases (see Malignant Neoplasms of the Brain, p. 701.2).

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PROPHYLAXIS OF BREAST CANCER. The recognition of factors increasing the risk of breast cancer (p. 702.1), and particularly the identification of specific genes that confer a high risk, has spurred the search for effective ways of preventing the disease. Current options, other than regular screening to detect the cancer at early stages, include surgery, drug therapy (below), and possibly some life-style modifications.[1-7]

Prophylactic bilateral mastectomy and prophylactic salpingo-oophorectomy have both been shown to substantially decrease the incidence of breast cancer in moderate- and high-risk women and in known BRCA1/2 mutation carriers.[2,4-7] Mastectomy is recommended for women at high risk, such as those with genetic factors, or for women with a history of lobular carcinoma *in situ*, or thoracic radiation.[2] Bilateral salpingo-oophorectomy is generally limited to women with a known or strongly suspected BRCA1/2 mutation.[2,4,7]

The association between lifestyle modifications and breast cancer risk is not clear-cut,[2] and there is no evidence that specific dietary components can effectively reduce breast cancer risk.[7] Nevertheless, women judged to be at moderate or high risk may be advised to avoid alcohol or to decrease alcohol consumption, and postmenopausal women may benefit from weight loss.[2,7]

Treatment with tamoxifen as part of the adjuvant management of early breast cancer is associated with a reduced risk of developing cancer in the other breast. This led to the suggestion that prophylactic tamoxifen might prevent the development of breast cancer in women at risk, and to studies to test this hypothesis. These studies were not without controversy, since the risk/benefit for tamoxifen use in healthy women differed from that in women with breast cancer. The first study to be reported was the US National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study,[8] which randomised 13 388 women to 5 years of treatment with tamoxifen or placebo. Participants were either aged 60 years or older, had a history of lobular carcinoma in situ, or had a 5-year predicted risk of developing breast cancer of greater than 1.66% (as assessed by number of first-degree relatives with breast cancer, number of previous breast biopsies, presence of atypical hyperplasia, and reproductive factors). In this study there was a highly significant 49% reduction in the occurrence of invasive breast cancer in women given tamoxifen (21.4 cancers prevented per 1000 women treated). The incidence of non-invasive breast cancer was reduced to a similar extent. Tamoxifen reduced the incidence of oestrogen-receptor (ER) positive, but not ER-negative, tumours. Adverse effects of tamoxifen included a modest increase in the risk of endometrial cancer and vascular events (stroke and pulmonary embolism). Although this study was prematurely unblinded, and all women were offered a 5-year course of tamoxifen, follow-up continued for 7 years and the incidence of breast cancer remained relatively constant for the 2 years after tamoxifen therapy was stopped.[9] Preliminary results from 2 smaller randomised European studies did not confirm the benefit of tamoxifen in breast cancer prevention. The Italian study[10] was in hysterectomised women with no particular risk for breast cancer, and because of its size may not have been sufficiently powered to detect an effect of tamoxifen. The full follow-up[11] of 5 years of treatment in this study found no difference in breast cancer incidence between tamoxifen and placebo groups. A subgroup analysis of women at high risk of ER-positive breast cancer did find a protective effect from tamoxifen, and there was an apparent protective effect for women in this group who used HRT. However, this group was not identified at randomisation of the study and these results need to be confirmed. The British study[12] of 8 years of tamoxifen or placebo was in women with a first-degree family history of breast cancer, and their median age was younger than in the US study. Although preliminary results showed no benefit from tamoxifen, follow-up for a median of about 13 years did find a reduction in the risk of ER-positive tumours.[13] This reduced risk also appeared to improve with longer follow-up. Initial results of a further placebo-controlled study (IBIS-I)[14] of women at increased risk of breast cancer found that during 5 years of tamoxifen use, the risk of all breast cancers was reduced by 32%. As in other studies, the reduction occurred in ER-positive tumours. Similar adverse effects were found with tamoxifen use, but there was also an unexpected increase in deaths from all causes in tamoxifen users. This may be associated with the excess in thromboembolic events reported, although statistical variability could not be ruled out. Extended follow-up[15] for a further median of 8 years found that the beneficial effect of tamoxifen was maintained, and that reduction in the risk of ER-positive tumours increased with longer follow-up. However, the rate of adverse effects of tamoxifen reduced after treatment stopped. A retrospective analysis[16] of the NSABP P-1 data for women who had developed invasive breast cancer found that in carriers of the oncogene BRCA2, but not BRCA1 carriers, there was a reduction in breast cancer similar to the reduction in ER-positive cancer among all women in the study. The numbers available, however, were too small to be statistically significant, and it is therefore still not known if tamoxifen can reduce the risk of breast cancer in patients with these mutations.

Another anti-oestrogen, raloxifene, has reportedly shown a reduction in breast cancer risk while its effects on osteoporosis were being studied.[17] A further large placebo-controlled study[18] that included the incidence of breast cancer as a primary outcome also found a reduction with about 5 years of raloxifene use. There was a 55% lower risk of invasive ER-positive cancer (absolute risk reduction of 1.2 cancers per 1000 women treated for 1 year), but there was no effect on ER-negative disease. The effect of raloxifene has also been directly compared with tamoxifen in women with a predicted increased risk of breast cancer (STAR study).[19] After up to 5 years of use, the incidence of invasive disease was similar in both groups, suggesting that raloxifene is as effective as tamoxifen in reducing the risk of developing invasive breast cancer in this group of women. The aromatase inhibitors, anastrozole and exemestane, are also under investigation.[2,4,6,20]

From these studies, tamoxifen prophylaxis has been shown to reduce the incidence of ER-positive breast cancer in women at increased risk,[21] although there are limited data for women with BRCA1 and 2 mutations.[2] Tamoxifen remains the drug of choice for premenopausal women at increased risk of breast cancer;[2,5,6,22] raloxifene is not recommended for use in this population. In postmenopausal women, treatment is influenced by age, presence of uterus, and comorbidities.[2] Either tamoxifen or raloxifene is recommended for use in women at high risk;[2] some[5,6] recommend raloxifene over tamoxifen due to its more favourable adverse effect profile.

Other candidates for the prevention of breast cancer include plant oestrogens (phytoestrogens) such as those in soya.[6] Epidemiological evidence suggests that diets high in these compounds may be protective, but there are many confounding factors and inconsistencies in the data available.[23] It was thought that retinoids might also be protective, but a secondary prevention study of fenretinide failed to show any benefit.[24] Regular use of aspirin and other NSAIDs has been reported to decrease breast cancer risk, but this has not been supported in other studies.[4,6,7] Similarly, inconsistent associations have been reported with the use of statins; some suggest that additional study of lipophilic

statins is warranted.[6] Use of luteinising hormone releasing hormone (LHRH) agonists is also under investigation, although adverse effects may pose a problem.[6]

For the suggestion that bisphosphonates may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

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MALIGNANT NEOPLASMS OF THE MALE BREAST. Breast cancer can occur in men, although it has a much lower incidence than in women. Risk factors are not well understood, but it may sometimes be associated with abnormalities of sex hormone metabolism, including those acquired through liver disease or testicular trauma. In addition, the inherited mutation BRCA2, which is associated with an increased risk of breast cancer in women, also increases the risk of breast cancer in men; occasionally BRCA1 mutations are seen. Men with Klinefelter's syndrome, a sex chromosome anomaly, may be predisposed to development of breast cancer. Possible environmental risk factors include industrial exposure to chronic heat. Other risk factors include smoking, obesity, and alcohol consumption.

A painless mass is the most common presentation; nipple discharge may occur. Other less common symptoms include breast tenderness, swelling, or nipple itching. Diagnosis is often at a late stage. Breast cancer in men occurs at a slightly older median age than in women (60 to 70 years), and is more likely to be oestrogen-receptor (ER) positive. Survival by stage appears to be similar to that in women, with an overall 5-year survival about 40 to 65%.

Treatment is similar to that for women (see p. 702.1).[1-4] Primary management for ***early*** or ***localised*** disease is surgical and usually involves simple or radical mastectomy with axillary lymph node dissection, although breast-conserving surgery is also used. Because of the rarity of the disease large controlled studies are lacking but studies in limited numbers of men and extrapolation from results in women suggest that neoadjuvant and adjuvant therapy should be considered on the same basis as for women. Radiotherapy may be used to reduce the rate of local recurrence in those considered at high risk. As most male breast cancers are ER-positive, adjuvant hormonal therapy with tamoxifen is commonly used.[1-4] Use of aromatase inhibitors such as anastrozole or letrozole is considered controversial, since inhibition of oestrogen may be incomplete unless orchidectomy is also performed;[3,4] use with a gonadorelin analogue has been suggested.[4] Males with ER-negative disease should be offered chemotherapy. Regimens are usually anthracycline- or taxane-based; common combination regimens include CMF (cyclophosphamide, methotrexate, and fluorouracil) and FAC (fluorouracil, doxorubicin, and cyclophosphamide).[2-4] Adjuvant trastuzumab should be considered for men with high-risk HER2-positive disease.[2-4]

In ***advanced*** metastatic disease tamoxifen is generally the first choice treatment for ER-positive disease, although there is evidence of benefit from aromatase inhibitors such as anastrozole or letrozole. Again, combination with gonadorelin analogues has been suggested because of the risk of incomplete oestrogen inhibition.[3] Chemotherapy is used for patients with ER-negative disease, or for those who progress on hormonal therapy.[2-4] Regimens are usually doxorubicin-based, such as FAC.[2,4] For further information on common chemotherapy regimens, see Table 1, p. 719. There are reports of response to trastuzumab in males with metastatic HER2-positive disease,[2,4] and some consider its use justified in this instance.[3] Hormonal ablation by adrenalectomy or orchidectomy is also effective, but has become less popular since the advent of tamoxifen.

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Malignant neoplasms of the cervix. Cancer of the uterine cervix is one of the most common cancers in women, accounting for about 12% of all female malignancies. It is associated with early sexual activity and a high number of sexual partners, and the presence of human papillomavirus (HPV); high-risk types of the virus (HPV-16 and 18) that produce proteins E6 and E7 inactivate host tumour suppressor proteins and thus encourage malignant transformation. Smoking and long-term use of oral contraceptives (p. 2235.1) may also be risk factors. Widespread screening has meant that in many women the disease has been detected in the preinvasive or early stages, when the prognosis is excellent to good. An HPV vaccine is available in some countries for the primary prevention of cervical cancer.

Preinvasive cervical lesions (cervical intraepithelial neoplasia; CIN) may resolve spontaneously if low-grade (CIN1), and may be monitored by repeat screening or HPV testing.[1,2] High-grade CIN (CIN2; cervical dysplasia) and cervical carcinoma *in situ* (CIN3) may progress to invasive carcinoma and are usually treated by ablation or excision.[1,2] Conisation of the cervix (cone biopsy) may be used to rule out the presence of invasive disease.[3,4]

Invasive cervical cancers are mostly squamous cell in origin (about 80%), with about 20% being adenocarcinoma.[3,5] Invasive cervical cancers may be divided into early-stage, locally advanced, and metastatic. The earliest stage (IA1) may be treated by conisation of the cervix (which maintains fertility) or simple hysterectomy. Other ***early-stage*** cancers may be treated by surgery (radical hysterectomy) or by radiotherapy (usually brachytherapy with pelvic irradiation).[3-7] For patients at this stage who wish to preserve fertility, radical trachelectomy (removal of the cervix) with pelvic lymphadenectomy may be an option.[4-8] However, those with bulky tumours, poor prognostic factors, or high-risk features after surgery should be given postoperative pelvic radiotherapy with concurrent chemotherapy (chemoradiotherapy), which has been shown to improve survival.[3-6,9,10] Most regimens use cisplatin, either alone or with fluorouracil.[3,5,6,8-10] Hydroxycarbamide has also been used by some centres, but is less effective than cisplatin.[5]

Patients with ***locally advanced*** cervical cancer are also usually treated with primary chemoradiotherapy using cisplatin-based regimens,[3-5,7-9] as it improves overall and progression-free survival.[11] A meta-analysis of 13 studies (including patients at various stages, from early through to metastatic) confirmed the survival benefit of chemoradiotherapy in cervical cancer; there was no significant difference between platinum- and non-platinum-based chemoradiotherapy.[12] Neoadjuvant chemotherapy has been tried and although there is some indication that its use before surgery might be of benefit in bulky early-stage or locally advanced disease, no survival advantage has been shown and this approach remains controversial; it does not appear to be beneficial before radiotherapy.[10,13]

For local recurrence of disease, treatment options include radiotherapy if it has not already been used, more extensive surgery, or cisplatin-based chemoradiotherapy.[3-5,14] Patients with recurrence who are not candidates for surgery or radiotherapy may be offered palliative chemotherapy or best supportive care; chemotherapy regimens are the same as those used for metastatic disease.[5]

Treatment of ***metastases*** is palliative; radiotherapy, chemotherapy, or chemoradiotherapy can be used.[3,5,7,14] Cisplatin, carboplatin, or paclitaxel may all be considered for first-line monotherapy; if cisplatin has previously been used as a radiosensitiser a combination regimen of cisplatin with either paclitaxel, topotecan, or gemcitabine is preferred; carboplatin plus paclitaxel is also an option.[5] Drugs that have been tried for second-line treatment include bevacizumab, docetaxel, epirubicin, fluorouracil, gemcitabine, ifosfamide, irinotecan, liposomal doxorubicin, mitomycin, pemetrexed, topotecan, and vinorelbine.[5,14] Many combination regimens have shown higher response rates and improvements in progression-free survival but not overall survival compared with monotherapy; however, the CT regimen (cisplatin plus topotecan) has shown an improvement in overall survival.[5,15] UK guidelines[8] recommend treatment with cisplatin plus topotecan (for cisplatin-naïve patients), or cisplatin plus paclitaxel, for all women with stage IVB or recurrent disease. For further information on common chemotherapy regimens, see Table 1, p. 719.

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Malignant neoplasms of the endometrium. Cancer of the endometrium is a disease primarily of postmenopausal women, and is more common in developed than developing countries. Based on aetiology and pathology, endometrial cancer is generally classified into 2 subtypes:

- type I are the most common, with an endometrioid histology, and are mostly low-grade, with a background of endometrial hyperplasia. They are usually oestrogen-receptor positive, and associated with increased oestrogen exposure. Factors resulting in increased endogenous exposure include obesity, anovulatory infertility, early menarche, and late menopause. Exogenous factors include use of oestrogens without progestogens for hormone replacement therapy (p. 2247.3), and tamoxifen therapy (see Carcinogenicity, p. 861.3). Other associated findings include nulliparity, diabetes mellitus, and hypertension
- poorly differentiated or non-endometrioid type II cancers appear, in contrast, to be unrelated to high oestrogen concentrations, are often associated with endometrial atrophy, and often develop in non-obese women. They include serous or clear-cell carcinomas which are highly aggressive with a poorer prognosis; endometrial intraepithelial carcinoma is believed to be a precursor

Abnormal uterine bleeding is the most common sign of endometrial cancer, and all postmenopausal women with vaginal bleeding and other risk factors should be evaluated for the disease. In menopausal or premenopausal women, diagnosis may be delayed because abnormal bleeding patterns may not be so obvious. Type I endometrioid carcinomas are surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO) system; type II are classed as high-grade by definition.

Surgery is the primary **therapy** for operable endometrial cancer;[1-7] total hysterectomy and bilateral salpingo-oophorectomy is usually performed, with lymph node dissection in selected cases. No further treatment is required in women with FIGO stage I disease who are at low risk of recurrence. In those with stage I disease and a higher risk of recurrence, adjuvant vaginal brachytherapy or pelvic irradiation are used. In all other women, adjuvant radiotherapy is given, the field being tailored depending on the disease stage.[2-6] Adjuvant hormonal therapy with a progestogen has not been shown to be effective.[8] However, progesterone therapy has been used for young women with endometrial hyperplasia who wish to preserve their fertility, as well as for women who are poor surgical candidates.[3] There are a few studies of adjuvant chemotherapy in women with early-stage disease at high risk of recurrence, but no significant survival benefit has been seen.[1,2,4,6,9,10]

For women with advanced, recurrent, or metastatic disease, adjuvant chemotherapy or hormonal therapy may be considered as treatment options,[2-6,10,11] although response rates are only up to about 30%, and evidence for a survival benefit is questionable.[12] Progestogens such as medroxyprogesterone acetate are likely to be preferred because of their better tolerability.[2,4,5,11] Tamoxifen also produces minor benefit;[3] alternation with progestogens may prolong the response to hormonal therapy.[2] Well-differentiated tumours, long disease-free interval, and positive hormone receptor status are factors that suggest increased response to progestogens.[3,7] When progestogens are ineffective, chemotherapy may be tried. Single-agent drugs of choice include cisplatin or carboplatin, doxorubicin, and paclitaxel.[2-4,6,9,11] Response rates are slightly higher with combination regimens;[9,13] these include cisplatin plus doxorubicin, sometimes with paclitaxel (the TAP regimen), or carboplatin plus paclitaxel.[2-6,10,11,13] TAP has been found to be more effective, but also more toxic than cisplatin plus doxorubicin.[3,6,10,11,13] The combination of carboplatin and paclitaxel has become standard in many centres in the management of advanced or recurrent endometrial cancer.[2,9,10] For further information on common chemotherapy regimens, see Table 1, p. 719. Drugs that are being investigated for endometrial cancer include bevacizumab, erlotinib, everolimus, sorafenib, temsirolimus, and trastuzumab.[9]

For those with medically inoperable disease, radiotherapy is well-tolerated and can provide long-term progression-free survival.[1-3]

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Malignant neoplasms of the eye. Tumours of the orbit of the eye in adults are most commonly metastases from primary lesions elsewhere in the body, usually in the breast or lung. Radiotherapy using external beam radiation or brachytherapy with iodine-125 is given for control of visual symptoms unresponsive to chemotherapeutic treatment of primary disease.[1]

Primary eye tumours are rare. In children, the most common intra-ocular tumour is retinoblastoma (see p. 717.2), and the most common orbital tumour is rhabdomyosarcoma (see Soft-tissue Sarcomas, p. 718.2). In adults, primary CNS lymphoma (see p. 698.1) can originate in the eye. However, the most common primary intra-ocular cancer in adults is **uveal melanoma**, which accounts for 80% of all primary ocular cancers.[2] The incidence is greater in Caucasians, and less common in brown-eyed individuals; average age at presentation is in the sixth or seventh decade.[2,3] About 40% of patients are asymptomatic, while others present with blurred or distorted vision, visual field loss, or seeing flashing lights.[3] Untreated, uveal melanomas result in loss of vision.[3] If metastasis occurs it is usually to the liver, and survival is poor;[2-4] factors associated with metastatic spread include large tumour size, ciliary body involvement, local tumour recurrence after conservative treatment, and rapid tumour regression after radiotherapy.[3]

The main objective of ***treatment*** is to prevent metastatic spread.[3] Treatment options for uveal melanomas include observation of indeterminate pigmented lesions, or eye-conserving therapies, which include brachytherapy (with iodine-125 or ruthenium-106), radiotherapy, local resection, or phototherapy such as photocoagulation or laser-induced hyperthermia (transpupillary thermotherapy).[2,3] Enucleation (removal of the eye) does not offer any survival advantage over conservative treatment, and is indicated only when eye-conserving therapy fails or for large tumours with extensive involvement of all uveal structures, diffuse growth, extensive retinal invasion or perforation, or bulky extra-ocular extension.[3]

Various treatments have been tried for patients with *metastatic* uveal melanoma. Surgical resection of isolated hepatic metastasis offers a survival advantage, but while there is continued interest in adjuvant therapy, metastatic disease is highly resistant to traditional systemic chemotherapy.[3,4] Most regimens have included dacarbazine, but these are considered to be ineffective.[4] Hepatic intra-arterial chemotherapy using fotemustine, or melphalan has been reported to be of benefit; carboplatin has also been used. Responses have been seen using hepatic artery chemoembolisation with cisplatin or carmustine; while local control was achieved with the latter drug, progression occurred at extra-hepatic sites. Embolisation with granulocyte-macrophage colony-stimulating factor (immunoembolisation) has also been reported to be effective, although data from large-scale studies are lacking. Targeted therapy is under investigation, using various drugs such as lenalidomide, sorafenib, sunitinib, and temozolomide, either alone or in combination chemotherapy regimens. Implantation of yttrium-90 microspheres is also under investigation.[4]

Ocular surface neoplasms (lesions of the conjunctival or corneal epithelium) may be benign or precancerous. They occur more commonly in sub-Saharan Africa, Australia, and regions where exposure to sunlight is more frequent. Exposure to solar UV radiation is a major aetiological factor, although human papillomavirus (HPV) and HIV infection may also have a role in the development of these tumours. Ocular surface neoplasms are usually treated with local excision. Because of a high recurrence rate, cryotherapy or brachytherapy is usually combined with surgery. Chemotherapy can be used where surgery is not feasible, or it may be used intra-operatively or as adjuvant treatment; some centres use chemotherapy initially for treating intra-epithelial ocular surface tumours. The most commonly used drugs are mitomycin C, applied topically in the form of eye drops (0.02% or 0.04%), fluorouracil (1%) eye drops, and interferon alfa-2b, which is used topically, subconjunctivally, or by intralesional injection. Patients who fail treatment with one drug may respond to another, and combination regimens have also led to tumour regression. Other drugs that have been reported to be effective when used topically include dinitrochlorobenzene, urea, tretinoin, and cidofovir.[5,6]

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Malignant neoplasms of the gastrointestinal tract. Considered as a whole (and excluding skin cancers, which are often poorly registered) the gastrointestinal tract is the most frequent site of malignancies worldwide, although the frequencies of the various types of gastrointestinal cancer vary greatly from country to country. Genetic, environmental, and dietary factors may play a role in the aetiology of these cancers. Treatment may include surgery, radiotherapy, and chemotherapy, but the prognosis in most forms of gastrointestinal cancer is generally not encouraging.

Gastrointestinal cancers vary in their management depending on the site. Discussed in more detail below are:

- oesophageal cancer (below)
- stomach cancer (p. 706.1)
- colorectal cancer (p. 706.3) and its prophylaxis (p. 707.2)
- anal cancer (p. 708.1)

Cancers of the oral cavity are discussed under Malignant Neoplasms of the Head and Neck, p. 708.1.

Other cancers may sometimes manifest in the gastrointestinal tract, including the various endocrine neoplasms responsible for carcinoid syndrome (see Neuroendocrine Tumours, p. 716.3), and MALT lymphomas (p. 698.1). Gastrointestinal stromal tumours (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel (see Soft-tissue Sarcoma, p. 718.2).

MALIGNANT NEOPLASMS OF THE OESOPHAGUS. Oesophageal cancer has perhaps the greatest variation in incidence between different geographical regions of any cancer, and is endemic in many parts of the world. The two major histological types are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is strongly associated with tobacco and alcohol use, and may occur as a second primary tumour in patients with tumours of the upper aerodigestive tract (see Malignant Neoplasms of the Head and Neck, p. 708.1). Adenocarcinoma is more common in non-endemic regions, including many developed countries, and is associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p. 1810.2). Oesophageal cancer usually develops as a growth or ulcerative lesion of the oesophagus with extensive infiltration of the mucosa and invasion of neighbouring structures. Lymphatic and blood-borne metastasis occurs at a relatively early stage. Symptoms of pain and dysphagia due to obstruction occur late, and overall, more than half of all patients have unresectable or metastatic disease at initial presentation. Metastatic disease is associated with a median survival of less than 1 year.[1] The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and human epidermal growth factor receptor-2 (HER2) has been associated with a poor prognosis in patients with oesophageal and gastric cancers.

Patients with **locoregional disease** are treated with surgery if possible, or definitive chemoradiotherapy if they are not surgical candidates.[2-8] Chemoradiotherapy regimens usually include cisplatin, with a fluoropyrimidine (fluorouracil or capecitabine), or irinotecan, or a taxane. Alternatively, a fluoropyrimidine (such as fluorouracil or capecitabine) may be combined with either oxaliplatin or a taxane.[2] However, given the high rate of failure after surgery, in an attempt to improve survival rates, there has been great interest in neoadjuvant (pre-operative) or adjuvant (postoperative) therapies, incorporating radiotherapy or chemotherapy or both.[3,4,6]

There is no evidence that ***neoadjuvant*** radiotherapy alone improves survival.[1,3,6,9,10] The evidence for use of neoadjuvant chemotherapy is more conflicting.[1,3,6,11] A systematic review[12] found that it may offer a survival advantage compared with surgery alone, although the evidence was considered to be inconclusive. Meta-analysis[13] also suggested some survival benefit in those with adenocarcinoma, but not for those with squamous cell disease. Thus, some guidelines[2,8,9] consider neoadjuvant chemotherapy as a standard treatment option for localised adenocarcinoma. The ECF regimen (epirubicin, cisplatin, and fluorouracil), or one of its variants, is commonly used.[2]

Initial studies of neoadjuvant chemoradiotherapy also conflicted or were inconclusive due to small samples or inadequate dosage.[3,4,9,13,14] A systematic review[14] found that neoadjuvant chemoradiotherapy significantly improved the 3-year mortality rate compared with surgery alone, and a later meta-analysis[13] found a significant survival benefit, versus surgery alone, in patients with local operable oesophageal carcinoma, regardless of histological tumour type. However, the risk for postoperative mortality (within 90 days of surgery) was also increased by neoadjuvant chemoradiotherapy.[14] Despite this, many centres incorporate neoadjuvant chemoradiotherapy regimens for localised, resectable disease.[1,2,4,7,11] Regimens are largely cisplatin- or fluoropyrimidine-based.[2]

Studies of ***adjuvant*** radiotherapy have failed to show a survival advantage,[2] and, aside from possible benefit in certain subgroups, may actually increase mortality compared with surgery alone.[6] Adjuvant chemotherapy is generally not recommended,[5,9] except in those patients with adenocarcinoma who also received neoadjuvant chemotherapy;[2] treatment is usually with ECF. Adjuvant chemoradiotherapy has shown improved survival rates compared with surgery alone, in patients with adenocarcinoma.[2,6] However, it is not recommended,[5] except in selected high-risk adenocarcinoma patients who have not received neoadjuvant chemoradiotherapy.[2,6] Fluoropyrimidine-based regimens are preferred.[2]

Photodynamic therapy is under investigation for early-stage disease.[15]

In half to two-thirds of patients the disease is too advanced at presentation for anything but palliation. Chemotherapy, chemoradiotherapy, or best supportive care are all options for patients with **unresectable, advanced, or metastatic disease**. Chemoradiotherapy is an option in recurrent disease in those who have not had prior chemotherapy or radiotherapy; more extensive surgery is also an option.[2] Those with poor performance status should be offered supportive care.[2] This may include brachytherapy, laser therapy, stent placement, or photodynamic therapy with photosensitisers (such as porfimer sodium) to relieve obstruction.[2,3,5,9,16] Brachytherapy may be a better

primary therapy for obstruction than a stent.[8,17] In those patients with good performance status, chemotherapy or chemoradiotherapy may also offer some palliation of the disease. Standard options include cisplatin-based, fluoropyrimidine-based, irinotecan-based, oxaliplatin-based or taxane-based combinations.[2,9] In patients with advanced disease that is HER2-positive, trastuzumab may be added to systemic chemotherapy if chemoradiotherapy is not recommended.[2] For further information on common chemotherapy regimens, see Table 1, p. 719.

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MALIGNANT NEOPLASMS OF THE STOMACH. Cancer of the stomach is one of the most common cancers worldwide. Geographical distribution varies greatly, with particularly high incidence in the Far East, eastern Europe, and parts of Latin America, although the incidence is declining almost everywhere. (In contrast the incidence of cancers at the gastro-oesophageal junction appears to be increasing.) Over 90% of malignant gastric neoplasms are adenocarcinomas. Less frequent gastric neoplasms include lymphomas (see MALT lymphoma, p. 698.1) and carcinoid tumours (see Neuroendocrine Tumours, p. 716.3). Histologically, tumours are divided into intestinal and diffuse forms; the latter type may have a genetic basis.

Dietary factors, such as high consumption of salted or smoked foods, are thought to play a role in the development of gastric cancer. Smoking is also considered to be an independent risk factor. *Helicobacter pylori* infection, and resultant gastritis, plays a role in gastric lymphomas, and appears to almost double the risk for the development of gastric cancer.[1-5] However, it is not yet clear if elimination of *Helicobacter pylori* infection can help prevent the development of gastric cancer.[6] It is possible that some patients will have developed irreversible mucosal changes, and that *H. pylori* eradication will be ineffective.[5,7]

Early disease is relatively asymptomatic or produces non-specific gastrointestinal symptoms such as dyspepsia. There is concern that the use of antisecretory drugs for these symptoms may delay the diagnosis of gastric cancer (see Gastric Carcinoma, under Omeprazole Precautions, p. 1873.2). Gastric epithelial dysplasia is a premalignant condition, and warrants follow-up and possible surgical intervention. Similarly, persistent gastric ulcers may be malignant. More advanced disease, which is the norm at presentation in most western countries, may produce abdominal discomfort or pain, anaemia, weight loss, and anorexia; obstruction, haemorrhage, and perforation may develop. Extension to the liver and pancreas, and lymphatic and blood-borne (portal) metastases may occur. The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and human epidermal growth factor receptor-2 (HER2) has been associated with a poor prognosis in patients with gastric and oesophageal cancers.

Surgery is the mainstay of treatment for **locoregional disease**.[2-4,8-10] There is some uncertainty, however, about the appropriate extent of surgery and associated lymph-node dissection.[1-4,11] Typical 5-year survival rates in western patients have ranged from about 50 to 80% in those with stage I disease to 13% in those with stage III;[11,12] although much higher survival rates (over 96% in stage I disease and nearly 45% in stage III) have been reported in Japan,[11] Japanese and western patients may not be equivalent, a fact that has made comparisons difficult.[13]

Because of the poorer survival rates in patients with more advanced locoregional disease, postoperative (adjuvant) and pre-operative (neoadjuvant) treatments have been tried.[1,4,8,11,12] Postoperative radiotherapy has not been shown to produce a survival benefit, and the value of pre-operative radiotherapy is uncertain.[11,12] However, there has been considerable interest in the possible value of chemotherapy, alone or with radiotherapy (chemoradiotherapy).[1,11,12] Postoperative chemotherapy has failed to show a significant survival benefit, except for results with tegafur (plus gimeracil and oteracil potassium) in a Japanese population; it has not become standard practice in western countries.[3,8,10,12] Postoperative intraperitoneal chemotherapy (using mitomycin, cisplatin, or fluorouracil) is under investigation.[2,4,9] Preliminary studies of pre-operative chemotherapy suggested improved survival compared with historical controls, but randomised evidence is lacking.[2] However, perioperative chemotherapy, with cycles of ECF (epirubicin, cisplatin, and fluorouracil) given pre- and postoperatively, was found to improve progression-free and overall survival in patients with operable adenocarcinomas.[14] This strategy is recommended for centres with a multi-disciplinary approach, where there is an opportunity for patients to be considered for perioperative treatment.[8] Perioperative chemotherapy with ECF, or modifications thereof, has become standard practice in the UK and Europe,[4,8,10,15] and is considered an option for patients in the USA.[3] A large US study[16] found that median survival was improved from 27 to 36 months in patients given postoperative chemoradiotherapy (using a fluorouracil and folinic acid regimen). This strategy is recommended for centres where surgery is used as the primary therapy, or where referral is made postoperatively.[8] Using a regimen based on a fluoropyrimidine (such as fluorouracil or capecitabine), postoperative chemoradiotherapy has become the standard of care in the USA.[3,4,10,11] The value of pre-operative chemoradiotherapy, in contrast, remains to be determined,[3,4,11] although it may be a potential option in medically fit patients whose disease is resectable. The recommended regimen includes a taxane (paclitaxel or docetaxel) with a fluoropyrimidine (fluorouracil or capecitabine).[3] For patients with inoperable locoregional disease, radiotherapy with concurrent fluorouracil-based radiosensitisation is used. Palliative chemotherapy with any of the regimens used for metastatic disease is also an option in these patients.[3]

Treatment for **advanced disease** is purely palliative, and options include supportive care with or without chemotherapy.[3] Supportive care includes the relief of luminal obstruction with, for example, stent placement, laser surgery, or photodynamic therapy. Chemotherapy may have substantial palliative effect and modest survival gains, and may be considered in those with good performance status.[2,3] There is no gold standard regimen, although combination therapy is preferred to single-agent therapy for palliation.[17] A systematic review[18] found that combination regimens including a fluoropyrimidine, anthracyclines, and cisplatin produced significant survival benefits; ECF was considered the regimen of choice since it was best tolerated, and it is considered standard therapy in some countries.[17] Fluorouracil, doxorubicin, and mitomycin (FAM) has been widely used;[3] other combinations include the substitution of methotrexate for mitomycin, or cisplatin for doxorubicin, in the FAM regimen (FAMTX, and MFC, respectively),[3,17] and the use of docetaxel instead of epirubicin in ECF (DCF).[3,15] However, ECF has shown better response and median survival than FAMTX.[3,8,15,17] In turn, the use of EOX (epirubicin, oxaliplatin, and capecitabine) was found to be as effective as ECF, but with a more favourable toxicity profile.[4,8,17] ECF, DCF, or their modifications are usually preferred as first-line therapy.[3,9,10] Other combinations used in advanced or metastatic disease include irinotecan plus cisplatin or a fluoropyrimidine (such as fluorouracil or capecitabine), oxaliplatin plus a fluoropyrimidine, and paclitaxel-based regimens.[3,10] In those patients with advanced gastric cancer or gastro-oesophageal adenocarcinoma that is HER2-positive, trastuzumab may be added to systemic chemotherapy if chemoradiotherapy is not recommended.[3] Combination therapy using newer agents such as bevacizumab, cetuximab, and gefitinib are being investigated.[4,8,10,15,17] For further information on common chemotherapy regimens, see Table 1, p. 719.

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MALIGNANT NEOPLASMS OF THE COLON AND RECTUM. Colorectal cancers are very common in developed areas such as the USA and western Europe, but rare among African and Asian populations. Genetic, environmental, lifestyle, and dietary factors are thought to contribute to development of the disease. Inherited predisposition syndromes include familial adenomatous polyposis and hereditary non-polyposis colorectal cancer. Most large bowel cancers arise within pre-existing intestinal polyps. Over 50% occur in the rectum and about 20% in the sigmoid colon. There may be direct invasion of neighbouring structures and metastatic spread to the lymph nodes, and to lungs, bone, and in particular, liver. Over 50% of patients will develop metastases, and up to 25% present with metastatic disease. Signs and symptoms are non-specific and include blood in the stools, altered bowel habit, anaemia, abdominal pain, and weight loss; there may be local obstruction (depending on location) or perforation. Screening is effective in reducing mortality, although the ideal method to be used is controversial.

Pathological stage is an important prognostic factor. The Dukes classification and its modifications and in particular the tumour-node-metastasis (TNM) staging system have been widely used. The latter is based on depth of bowel wall invasion, extent of lymph node involvement, and presence of metastases. These are roughly grouped into stages; stages I and II have no lymph node involvement, stage III is lymph-node positive, and stage IV is metastatic.[1-3] About 40% of colorectal cancers are characterised by mutations in the KRAS gene, and about 5 to 8% show a specific mutation in the BRAF gene. KRAS mutations have been shown to predict for lack of response to cetuximab and panitumumab; mutated BRAF may be a marker of resistance to therapies that target the epidermal growth factor receptor, although data remain inconclusive.[1]

The first-line treatment for **early-stage** and **locally-advanced** disease (stages I to III; Dukes A to C) is surgery.[1,2] Survival in early-stage disease is good: published 5-year overall survival rates are 80 to 95% in patients with stage I disease, but fall to 25 to 60% (depending on prognostic factors such as nodal involvement and degree of tumour invasiveness) in those with stage III disease.[4] Adjuvant or neoadjuvant therapies have thus been widely investigated and incorporated into treatment.[1,2]

Adjuvant therapy for stage I ***colon cancer*** is considered to be unnecessary.[1,5] For stage III disease, fluoropyrimidine-based chemotherapy has been shown to have an overall survival benefit, and adjuvant therapy has become standard practice for these patients.[1,3,5-10] The evidence in favour of adjuvant therapy in stage II disease is weaker and its use has been controversial.[3,7,11] While it is not routinely recommended for all patients,[12] most consider that its use in high-risk patients with poor prognostic features is justified.[1,3,6,9,10,12,13] The FOLFOX regimen (infusional fluoro-

uracil, folinic acid, and oxaliplatin), compared with fluorouracil plus folinic acid, has been found to improve disease-free and overall survival in stage III patients.[1,10] The FLOX regimen (bolus fluorouracil, folinic acid, and oxaliplatin) also improves disease-free survival in patients with stage II and stage III colon cancer compared with fluorouracil and folinic acid.[1] Oral fluoropyrimidines have also been shown to improve survival after resection,[14] and oral capecitabine appears to be as effective as bolus fluorouracil plus folinic acid.[10] All the above are therefore options for adjuvant treatment.[1,10] Results with the IFL regimen (irinotecan, bolus fluorouracil, and folinic acid) have not proved satisfactory because of its toxicity,[4,7,9] and FOLFIRI (infusional fluorouracil, folinic acid, and irinotecan) has not been shown to be superior to fluorouracil plus folinic acid in the adjuvant setting.[1]

Neoadjuvant chemotherapy and adjuvant radiotherapy seem to play little role in the management of early colon cancer, and the latter is not generally recommended.[4] In contrast, in the management of early stage ***rectal cancer*** radiotherapy or chemoradiotherapy plays an important role, to decrease the size of the tumour pre-operatively, and to decrease the risk of recurrence.[6] Surgery alone may be sufficient for patients with early, favourable disease.[2,15] A meta-analysis[16] found that both neoadjuvant and adjuvant radiotherapy reduced the risk of recurrence compared with surgery alone, and that fewer patients who had neoadjuvant radiotherapy died from rectal cancer, although early deaths from other causes increased, and there was little impact on overall survival. Some still recommend neoadjuvant radiotherapy as a convenient, simple treatment with low toxicity for more locally advanced disease.[15] However, adjuvant chemoradiotherapy was shown to improve overall survival compared with surgery alone, and it was considered the standard of care for patients with stage II or stage III rectal cancer.[3,4,8,16] A large randomised study[17] subsequently found that neoadjuvant chemoradiotherapy significantly improved local control and was associated with less toxicity than adjuvant chemoradiotherapy, although there was no improvement in overall survival. As a result, neoadjuvant treatment has been advocated on the basis of better tumour control, lower morbidity,[3,4] and enhanced sphincter preservation.[6] Regimens are fluoropyrimidine-based, typically using infusional fluorouracil alone, or bolus fluorouracil plus folinic acid, or oral capecitabine. After surgery, adjuvant chemotherapy with a fluorouracil plus folinic acid regimen, FOLFOX, or capecitabine is recommended; the latter 2 options are extrapolations from results in colon cancer.[2] Adjuvant chemoradiotherapy is still used for patients if neoadjuvant radiotherapy or chemoradiotherapy has not been given.[2,15]

Palliative treatments for **advanced** colorectal cancer (stage IV; metastatic disease) include surgery, radiotherapy, chemotherapy, and chemoradiotherapy.[1,2,4,5,7,18] Genetic profiling may allow individualisation of therapy to improve efficacy and reduce toxicity.[19,20] Metastasis usually occurs first to the liver; for cases that are localised and resectable, surgery offers a chance of prolonged survival.[4,5] Systemic neoadjuvant chemotherapy can reduce tumour volume and render some previously unresectable metastases suitable candidates for surgery.[1,4,21] Another potential approach is the adjuvant use of hepatic arterial (intraportal) chemotherapy directed at the liver. However, it is unclear who should be offered such treatment, and what the survival benefits are; given the potential for biliary toxicity and the technical expertise required, hepatic arterial therapy is generally reserved for use at specialist centres.[1,2]

Conventional palliative chemotherapy is based on the use of fluorouracil, and has been shown to produce modest survival benefits.[22] Adding folinic acid improves the efficacy,[19,23] and the combination has long been regarded as standard. Although it has been suggested that regimens based on continuous infusion of fluorouracil are more effective than those using bolus dosage,[4,24] others consider that although response rates are improved, median survival is similar, and that differences in toxicity and convenience of administration are more significant in making the choice.[18] Oral fluorouracil prodrugs such as capecitabine, or tegafur with uracil, are considered valid alternatives to intravenous fluorouracil.[6,19,21,25]

Several newer drugs have now been shown to improve response rates and survival when used for chemotherapy in these patients. In particular, regimens including irinotecan or oxaliplatin, such as FOLFIRI or FOLFOX, are now considered options for first-line management of metastatic colorectal cancer.[1,2,6,8,18-21] There is also evidence for both improved response and survival when bevacizumab (an antagonist of vascular endothelial growth factor) is added to chemotherapy.[18,19] Similarly, cetuximab, a blocker of the epidermal growth factor receptor, appears to improve response rate and decrease the rate of progression if given with irinotecan,[8] and preliminary results suggest that it is effective when combined with a FOLFOX regimen.[20] As a result, currently recommended regimens combine bevacizumab with one of the first-line regimens—FOLFOX, FOLFIRI, a fluorouracil plus folinic acid regimen, or CapeOX (capecitabine plus oxaliplatin)—in patients with metastatic disease who are able to tolerate intensive therapy,[1,2,19-21] although the data to support some of these combinations are not yet available. Cetuximab or panitumumab may also be combined with FOLFIRI or FOLFOX (in those with the KRAS-wild type gene).[1,2,19] In those who fail to respond, an alternative first-line regimen may be tried (without bevacizumab). Other options include cetuximab plus irinotecan, or monotherapy with a drug not included in the original regimen (such as irinotecan, cetuximab, or panitumumab). In those in whom intensive therapy is not appropriate, options include capecitabine or fluorouracil plus folinic acid; either of these regimens may be combined with bevacizumab.[1,2,8,21] In those with the KRAS-wild type gene, the epidermal growth factor inhibitors cetuximab or panitumumab are alternatives.[1,2] The tyrosine kinase inhibitor regorafenib is an option when other treatments have failed.

For further information on common chemotherapy regimens, see Table 1, p. 719.

Other drugs and regimens continue to be investigated.

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Prophylaxis of cancer of the colon and rectum. Various drugs and dietary factors have been shown in epidemiological studies to be associated with a reduced risk of colorectal cancer, and some of these have been investigated in prospective randomised studies.[1-3]

- Aspirin and NSAIDs are the most widely studied.[1-10] In short-term randomised studies, both sulindac and celecoxib have reduced the size and number of colonic polyps in patients with familial adenomatous polyposis.[4] However, prophylactic surgical removal of the colon is still considered the standard of care for these patients.[1,11] Furthermore, despite significant reductions in adenoma formation in high-risk patients, cyclo-oxygenase-2 (COX-2) inhibitors have also been associated with cardiovascular toxicity.[12] There is some evidence of a dose-response effect, since the greatest prophylactic effect of aspirin in average-risk populations appears to be associated with doses substantially greater than those required for prevention of cardiovascular disease.[5,6,8,13] The effect of aspirin may depend on COX-2 expression: it appears only to reduce the risk of colorectal cancers that overexpress COX-2.[14]
- Calcium supplementation has shown a moderate reduction in the formation of new adenomas in patients with a history of colorectal adenomas,[15] and is well tolerated, but the evidence is not strong enough to recommend general supplementation to prevent colorectal cancer.
- Despite the epidemiological evidence for dietary fibre, several large randomised studies of fibre supplements or high-fibre diets have not found any reduction in the formation of new adenomas in patients with a history of colorectal adenomas.[1,2,16]
- Antoxidant vitamins have also been investigated, but evidence for their benefit is conflicting (see Prophylaxis of Malignant Neoplasms, p. 2047.3).
- Ursodeoxycholic acid has been shown to reduce the risk of colorectal cancer in patients with ulcerative colitis and primary sclerosing cholangitis, see Inflammatory Bowel Disease, p. 1811.3.
- Epidemiological evidence[17] suggests that long-term use of statins is associated with a marked reduction in the risk of colorectal cancer. Prospective studies are required to confirm these results. A meta-analysis[18] did not support this hypothesis, although a modest reduction in risk or an effect with higher doses of statins could not be ruled out.
- Other potential chemopreventive agents on the basis of epidemiological evidence include folic acid, selenium, and menopausal HRT.[1-3] For the suggestion that folate may have dual modulatory effects on carcinogenesis, see Carcinogenicity, under Folic Acid, p. 2065.3.

An important component of the care of patients with inherited predisposition or other risk factors for colon cancer is regular screening.[2,11,19,20] Various screening methods have also been investigated for use in normal-risk individuals. US guidelines[21] recommend screening for colorectal cancer using faecal occult blood testing, sigmoidoscopy, or colonoscopy in average-risk adults, starting at 50 years of age and continuing until age 75; routine screening is not recommended for those older than this.

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MALIGNANT NEOPLASMS OF THE ANUS. Anal cancer is a relatively uncommon malignancy. Tumours arising within the anal canal are most often squamous cell carcinomas.[1-5] Other types of cancer arising in the anal region include adenocarcinomas, which are managed similarly to rectal cancer (see Malignant Neoplasms of the Colon and Rectum, p. 706.3).[1,2,4] Anal intraepithelial neoplasia (AIN) is considered to be a precursor of squamous cell anal carcinoma.[5,6] Risk factors associated with anal carcinoma include immunosuppression, anal or genital human papillomavirus (HPV) infection (especially HPV-16), a history of receptive anal intercourse or sexually transmitted disease, multiple sexual partners, and a history of cervical, vulvar, or vaginal cancer. HIV infection, long-term corticosteroid use, and smoking may also be associated risk factors.[1-4,6,7] Clinical manifestations of anal carcinoma include anal bleeding, pain, or the sensation of a rectal mass; diagnosis may be delayed as bleeding is often attributed to haemorrhoids.[1,4,6]

Treatment of anal intraepithelial neoplasia includes excision for clinically definable lesions. Topical creams containing fluorouracil or imiquimod have also been used, and there is anecdotal evidence for the use of photodynamic therapy.[6] A vaccine for HPV-related AIN is under development.[5]

The primary treatment for anal canal carcinoma is combined modality treatment using chemotherapy and radiotherapy. Chemoradiotherapy with fluorouracil plus mitomycin is the regimen of choice, having been found to be superior to radiation alone.[1-8] Fluorouracil with cisplatin is also used. This regimen, when compared with fluorouracil plus mitomycin, had comparable survival and less haematological toxicity, but higher colostomy rates.[2,4,6] For persistent or locally recurrent disease, surgical resection with the formation of a colostomy is preferred.[1-6] Salvage chemoradiotherapy with a cisplatin-based regimen has also been reported to be successful in the treatment of persistent or relapsed disease.[1,4] About 12% of patients develop metastases, most commonly to the liver and lung.[8] There is no standard therapy for metastatic disease.[1,6,8] Treatment recommendations include platinum-based chemotherapy or enrolment in clinical studies.[2,4,6,8] Local chemotherapy for liver metastases using intra-arterial chemotherapy has been reported to be successful.[8]

The management of anal cancer in HIV-positive patients has improved with the advent of HAART; before this, standard chemoradiotherapy was associated with severe acute haematological toxicity.[5] HIV-positive patients should receive standard chemoradiotherapy treatment for anal squamous cell carcinoma, unless they are severely immunosuppressed (usually defined as CD4 cell count < 200 cells/mm^3), in which case monitoring and individualisation of therapy is advised.[4,6]

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Malignant neoplasms of the head and neck. Cancers of the head and neck are classically defined as those of the mucosal surfaces of the upper aerodigestive tract and include neoplasms of the lip, oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands. Most are squamous cell carcinomas, and the highest incidence is in men aged over 50 years. Overall, cancers of the head and neck account for about 6% of all malignant neoplasms worldwide. The major risk factor for these cancers is the use of tobacco (whether chewed, inhaled, or smoked) and alcohol. Human papillomavirus (HPV) infection appears to be a risk factor for some squamous cancers of the oropharynx. HPV-positive tumours have a better prognosis than HPV-negative disease, being more responsive to therapy. Vaccination against HPV is of potential use for primary prevention. Nasopharyngeal carcinoma is a unique type of head and neck cancer. It is endemic in Alaska, China, and North Africa and is associated with Epstein-Barr virus and the consumption of salt-cured fish. It tends to metastasise early.

Clinical manifestations of head and neck cancer vary according to the location of the primary tumour, and can be non-specific. Symptoms include mouth ulceration, tongue pain, epistaxis, hoarseness, sore throat, otalgia, dysphagia, chronic cough, haemoptysis, and stridor.

Premalignant lesions include **leucoplakia** and **erythroplakia**, and these can progress to invasive cancer. About one-third of cancers are diagnosed at early stages (I and II), and the rest are usually locally advanced (stage III and IVA). Although early-stage disease can be successfully treated, there is a high incidence of second primary cancers in the head and neck, lung, or oesophagus. Therefore, there is interest in the development of chemopreventive drugs to reduce this risk. Fewer than 30% of patients with locally advanced disease are cured. The treatment of head and neck cancer is complex, and is affected by the site and extent of disease, pathological findings, lymph node involvement, the patient's functional status, and comorbidities; the experience and skill of the team carrying out surgery and radiotherapy will also influence treatment recommendations.

Patients with early-stage **nasopharyngeal** disease are treated with radiotherapy alone. Those with locally advanced disease are treated with cisplatin-based chemotherapy given concurrently with radiotherapy (chemoradiotherapy) followed by adjuvant chemotherapy with cisplatin plus fluorouracil.[1-3] For metastatic disease, palliative chemotherapy can be considered; platinum-based combination regimens are used first-line. Other active drugs, used as monotherapy or in combination, include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, and oxaliplatin. Treatment is based on previous treatment and toxicity.[3]

Patients with early-stage resectable **squamous cell carcinoma** of the head and neck (excluding nasopharyngeal carcinoma) are treated with surgery or radiotherapy, with curative intent.[2,4-7] The two methods have comparable efficacy, and choice depends on the specific tumour site, resectability, and functional outcome after therapy.[2,5] For those with adverse prognostic factors such as nodal involvement, positive margins, or extracapsular spread, postoperative radiotherapy or postoperative chemoradiotherapy may be used.[4,8]

Locally advanced disease needs combined modality therapy,[2,4-6] individualised according to resectability, tumour site, the need for organ preservation, and functional outcome.[2] Historically, surgery plus radiotherapy was used for resectable disease, and radiotherapy alone for unresectable disease,[9] but combined chemoradiotherapy has proved a major advance in treatment.[5] It is superior to radiotherapy alone,[2,5-10] although toxicity is increased, and to the use of chemotherapy either before or after radiotherapy.[2,5] Resectable disease is therefore usually managed with surgery followed by adjuvant treatment with radiotherapy alone or chemoradiotherapy to reduce locoregional recurrence.[2,4,5,7,8] In resectable disease where organ preservation is important, and in unresectable disease, definitive chemoradiotherapy is the standard treatment,[2,4,5,7] unless the use of chemotherapy is contra-indicated due to poor performance status or comorbidities.[4,5] Platinum-based regimens are standard.[2,4,5,8] Use of cetuximab with radiotherapy may be considered as an alternative to chemoradiotherapy in those patients unable to tolerate chemotherapy.[2,4,5,8] While chemoradiotherapy improves locoregional control, its effect on distant recurrence or metastases is inconsistent, and induction or neoadjuvant chemotherapy has been studied in the hope of reducing metastasis. Interpretation of initial studies of induction chemotherapy (used before surgery or radiotherapy) was difficult given their heterogeneity, although a survival benefit was shown in those studies using cisplatin plus fluorouracil. The addition of docetaxel further improved survival and organ preservation in studies of induction chemotherapy (used before radiotherapy or chemoradiotherapy).[2,5,6] Induction chemotherapy is not regarded as standard treatment for locally advanced disease,[5] but its use before chemoradiotherapy (compared with chemoradiotherapy alone) is under investigation.[2,5]

Palliative chemotherapy is used in *metastatic* or *recurrent* disease.[4,5,9] Salvage surgery or a repeat course of radiotherapy are other options, depending on previous treatment. Drugs used for single-agent treatment include cisplatin, carboplatin, paclitaxel, docetaxel, fluorouracil, methotrexate, ifosfamide, bleomycin, cetuximab, and gemcitabine (for nasopharyngeal cancer). Common combination regimens such as cisplatin and fluorouracil produce more responses, but no clear improvement in survival.[4,5,9] Addition of cetuximab to this standard platinum plus fluorouracil regimen has been found to improve survival.[11] Other common combinations include cisplatin or carboplatin plus a taxane.[4] Gefitinib and erlotinib have shown modest benefit when used as monotherapy, and are under investigation in combination regimens.[2,5] The choice of best supportive care or single-agent or combination chemotherapy should be dictated by the patient's performance status, as the benefits of chemotherapy are limited.[4]

A local injection of cisplatin in a gel formulation containing adrenaline has been investigated in recurrent and refractory head and neck cancer.[12] Photodynamic therapy (see under Porfimer Sodium, p. 849.1) using temoporfin is a more recent development for palliative management. Head and neck cancers have high levels of p53 gene mutations, and gene therapy is under investigation.[13] Chemoprevention by treatment of premalignant disease is also under investigation (see Leucoplakia, p. 750.3).

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Malignant neoplasms of the kidney. Cancer of the kidney is relatively uncommon, accounting for about 2% of all cancers worldwide. About 90% of renal tumours are renal cell carcinoma, of which the majority are clear cell tumours. The disease is about twice as common in men as in women. Several hereditary types of renal cell carcinoma exist, the most common being von Hippel-Lindau (VHL) disease, caused by a mutation in the VHL-gene, which predisposes to clear cell carcinoma. Aside from genetic predisposition, risk factors include smoking, obesity, hypertension, use of analgesics such as phenacetin, and acquired cystic kidney disease associated with end-stage renal disease. Disease is often clinically silent; there may however be haematuria, flank and back pain, and a palpable mass in the flank or abdomen. Fatigue, anaemia, and weight loss can also occur. About one quarter of patients present with advanced disease. The most common sites for metastases are the lung, liver, and bone, although unusual sites for metastases are a known feature of renal cancer.

Radical nephrectomy is the main **treatment** for *early-stage* (stages I and II) disease although nephron-sparing partial nephrectomy may be considered in some patients.[1-4] Results achieved with nephron-sparing surgery are similar to radical nephrectomy, but recurrence rates are higher.[3] Minimally invasive procedures such as radiofrequency ablation and cryotherapy are options for treatment of small tumours, although comparisons with surgery are lacking.[2] Radical nephrectomy is also used in selected patients with *locally advanced* (stage III) disease. After surgery 20 to 30% of patients with localised tumours will relapse, usually at distant sites.[2] However, adjuvant therapy has no established role.[2] Radiotherapy is not beneficial, and no systemic therapy has been shown to reduce relapse; interferon alfa or interleukin-2 are not effective.[2,3] Standard care therefore remains close observation.[2]

Patients with *invasive* or *metastatic* (stage IV) disease are also candidates for surgery.[2,5,6] Palliative nephrectomy can be considered for alleviation of symptoms.[7] Nephrectomy and surgical removal of isolated metastases may be appropriate in some patients,[2,7] and cytoreductive nephrectomy before systemic therapy is recommended for patients with potentially resectable disease and multiple metastases,[2,8] since a small survival benefit has been shown with nephrectomy before cytokine therapy compared with cytokine therapy alone.[9,10]

Renal cell carcinoma has been largely resistant to conventional antineoplastic chemotherapy,[1,3,7,11] and cytokine therapy with either interleukin-2 or interferon alfa became a standard treatment,[2,8] despite toxicity problems and generally poor overall response rates.[5] It has usually been reserved for patients with good prognostic factors and good performance status.[8] A systematic review[12] found a modest survival benefit for interferon alfa. Higher response rates were reported with high-dose interleukin-2 than low-dose therapy,[2,13] but overall survival was not improved.[12] Attempts to improve the tolerability of interleukin-2 have

included the use of continuous infusion, lower doses given subcutaneously,[1,11,14] and inhalational use.[11,14] Attempts were made to improve the response rates to interleukin-2 and interferon alfa by combining them, or by addition of antineoplastics or retinoids. However, response was still generally poor and toxicity significant.[11,15]

The majority of patients with clear-cell renal cell carcinoma have overexpression of vascular endothelial growth factor (VEGF) in tumour tissues, and newer molecular therapies aimed at VEGF or its receptors have been developed.[5,16-18] The tyrosine kinase inhibitors sunitinib and sorafenib have respectively produced better and equivalent survival to interferon alfa treatment, and are both recommended as first-line options in stage IV disease, whether of clear cell or non-clear cell histology.[2] Some consider first-line use is appropriate only in favourable- or intermediate-risk patients, but that they are suitable in any patient who has failed cytokine immunotherapy.[6] Temsirolimus has also shown a significant overall survival benefit compared with interferon alfa; combination treatment using these 2 drugs did not, however, show any benefit over interferon alfa monotherapy.[2,5] Temsirolimus is recommended as a first-line option in patients with poor prognosis.[2,4,6] Bevacizumab, a monoclonal antibody directed against VEGF, has also shown activity in metastatic disease; addition of bevacizumab to interferon alfa significantly increased progression-free survival compared with interferon alfa, and this combination is also a first-line option for patients with mainly clear-cell histology.[2,4] Pazopanib is an alternative first-line agent in those with mainly clear-cell histology, and high-dose interleukin-2 also remains an option for selected patients with good performance status.[2] Sunitinib, sorafenib, pazopanib, and temsirolimus are all options in non-clear cell disease, as is chemotherapy with gemcitabine, capecitabine, floxuridine, fluorouracil, or doxorubicin.[2]

For *progressive* clear-cell disease, an alternative first-line may be given; supportive care remains a mainstay of therapy for all patients with metastatic renal cell carcinoma.[2] Treatment with everolimus has been found to prolong progression-free survival in patients who had disease after treatment with sunitinib, sorafenib, or both.[19] Interferon alfa may be used for progressive disease in clear cell carcinoma;[2] some consider its use in metastatic renal carcinoma to be inappropriate.[6]

Evolving therapies include vaccination therapy with autologous or allogeneic dendritic cell vaccines, or peptides, and allogeneic haematopoietic stem cell transplantation.[3,13,20,21]

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WILMS' TUMOUR. In children most cases of renal tumours are due to Wilms' tumour (nephroblastoma). This is one of the most frequent solid tumours in childhood with a peak incidence between 1 and 5 years of age and accounts for about 6% of all childhood malignancies. The usual presentation is an asymptomatic abdominal mass; abdominal pain, haematuria, fever, and hypertension can occur. Metastasis in advanced disease is usually to the lungs and liver. Most primary tumours occur in one kidney, but some 5% involve both kidneys.

Unlike other forms of renal cancer Wilms' tumour responds well to chemotherapy. The basis of **treatment** is surgery, combined with chemotherapy, and if necessary radiotherapy. Management varies with disease stage and also varies between different study groups.[1-7] The US National Wilms' Tumour Study Group (NWTSG), its successor the Children's Oncology Group (COG), and some other groups recommend initial surgery (nephrectomy) to confirm diagnosis and perform precise staging. Adjuvant chemotherapy and radiotherapy are based on stage and histology obtained at the time of surgery, which allows for accurate assessment. However, tumour spillage at the time of surgery can increase the risk of local abdominal relapse and subsequent poor outcome. In contrast, the European Société Internationale d'Oncologie Pédiatrique (SIOP) and some other groups use neoadjuvant chemotherapy to reduce the tumour size and make surgery easier. Staging is done after surgery, and adjuvant chemotherapy is given if needed. With this method, patients without a confirmed diagnosis may receive unnecessary neoadjuvant treatment, and more intensive chemotherapy regimens are needed to ensure any occult disease is treated. Although there continues to be controversy about the relative merits of the two approaches, overall survival for patients treated by either approach is very similar, being more than 90% for patients with favourable histology. The aim of the various study protocols has been to identify low-risk children who require less intensive therapy, and those with poor prognosis who require more intensive therapy or alternative investigative regimens.[1-7] It has been noted that the groups have borrowed freely from each other, with SIOP protocols advocating early surgery for infants, and COG protocols using neoadjuvant therapy for very large tumours. Neoadjuvant chemotherapy may also allow for treatment of children in developing countries in cases where surgery is not immediately feasible due to the general health status of the patient. The protocol selected should therefore be suited to the individual child and the particular patient population.[7]

SIOP *neoadjuvant* chemotherapy usually consists of dactinomycin and vincristine for clinically localised disease, with doxorubicin or epirubicin added for metastatic disease.[2,5-7] *Adjuvant* chemotherapy regimens for disease with favourable or standard histology are broadly similar between NWTS and SIOP. In early disease, chemotherapy consists of vincristine combined with dactinomycin; in more advanced disease radiotherapy, and an anthracycline (doxorubicin or epirubicin) are added.[2,5,6] The duration of adjuvant chemotherapy is dependent on the disease stage and whether or not neoadjuvant treatment was given.[2] The UK Children's Cancer Study Group found that adjuvant vincristine alone was as effective as vincristine plus dactinomycin for patients with stage I favourable histology, although this did not apply to children aged 4 years or older.[1,4,6] Various regimens have been investigated, and the NWTSG found that pulse-intensive dactinomycin courses were as effective as standard courses, but had less haematological toxicity.[1,4,5] Adjuvant radiotherapy is given for lung metastases in both protocols, with NWTSG giving whole-lung irradiation in all cases, and SIOP not irradiating those patients whose metastases respond to chemotherapy (which may be related to the higher dose of anthracycline used in SIOP regimens).[1,2,4,7]

For patients with ***unfavourable histologies*** and a poorer prognosis such as anaplastic Wilms' tumour or clear-cell sarcoma, treatment usually consists of three-or four-agent chemotherapy with combinations of vincristine, dactinomycin, doxorubicin, and cyclophosphamide,[4,6] or vincristine, doxorubicin, cyclophosphamide, and etoposide.[1] Radiotherapy is also used.[1]

For ***relapsed disease***, the use of combination chemotherapy regimens has improved survival; drugs such as cyclophosphamide, ifosfamide, cisplatin, carboplatin, and etoposide have shown substantial activity.[1,2,4] The ICE regimen (ifosfamide, carboplatin, and etoposide) or ICED regimen (with the addition of doxorubicin) are commonly used.[2,5] For other common combination regimens used in cancer chemotherapy, see Table 1, p. 719. A small study found that a protracted schedule of topotecan was effective for recurrent disease with favourable histology.[8] Treatment with high-dose chemotherapy and autologous haematopoietic stem-cell rescue has shown promising results in relapsed disease,[1] although intensive chemotherapy alone has been shown to be equally effective.[5]

Bilateral Wilms' tumour is not usually treated with primary bilateral nephrectomy because of the need to retain renal function. It may be biopsied to assess histology and stage and then treated with neoadjuvant chemotherapy.[1,2,4-6] Surgery is then performed, preserving as much of the kidneys as is possible. Survival has been reported to be comparable with that in other patients.[2] Because of these results, some have suggested the use of partial nephrectomy in patients with small unilateral tumours. However, most tumours are too large or too centrally located for partial nephrectomy to be routinely indicated.[1]

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Malignant neoplasms of the liver. Hepatocellular carcinoma (hepatoma) accounts for more than 90% of primary liver cancers. It is relatively uncommon in northern Europe and America but is the most common cancer among men in large parts of sub-Saharan Africa and Asia. The incidence in men ranges from 2 to 8 times that in women. Chronic infection with hepatitis B or hepatitis C virus is by far the most important factor associated with development of liver cancer. Other risk factors include ingestion of foodstuffs contaminated with aflatoxins (see p. 2432.2), alcoholic or non-alcoholic liver disease, haemochromatosis, and the long-term use of anabolic steroids (see Effects on the Liver, under Testosterone, p. 2308.1) and, rarely, combined oral contraceptives, (see p. 2235.3). Over 70% of patients with hepatocellular carcinoma have cirrhosis of the liver.

Clinical manifestations of liver cancer include increasing obstructive jaundice, upper abdominal pain, malaise, weight loss, and the presence of an epigastric mass; there may be metastasis to the lungs, kidney, bones, brain or other sites, or invasion of local structures. Multiple staging systems are used and there is no universally accepted method although most base liver function assessment on the Child-Pugh classification of disease severity. It has been noted that since the cause of hepatocellular carcinoma may vary geographically, different scoring systems may apply to different populations.[1,2]

Screening at-risk groups for hepatocellular carcinoma is feasible, although still controversial in terms of cost-effectiveness; the recommended surveillance interval is 6 months,[2-5] although 1 year may be equally effective.[6] Screening has led to increased detection of ***early disease***, and more than half of these cases will be suitable for potentially curative treatments such as resection, liver transplantation, or ablation.[5-7] Selection of which patients are best suited to which method is based on tumour factors such as resectability, liver function, patient comorbidities, candidacy for transplantation, and organ availability.[4,6,8,9] **Liver transplantation** (p. 1940.3) may be considered in those patients with small tumours and who have advanced cirrhosis and are therefore not suitable for surgical resection.[3-5,7,9,10] **Surgical resection** is suitable for patients without cirrhosis, or in cirrhotic patients with well-preserved liver function who are not candidates for transplantation and whose tumours are considered resectable.[3-5,7,9,10] However, recurrence rates after resection are high,[2,4,5,7,11] and 5-year survival is about 40%.[3,5,12]

As a result, **adjuvant** or **neoadjuvant chemotherapy** has been investigated in early-stage disease. Neoadjuvant chemotherapy has been used to reduce tumour burden before transplantation[7,12] or to permit resection.[13] A meta-analysis[14] of 7 studies concluded that adjuvant transcatheter arterial chemotherapy (drugs injected into the hepatic artery after curative resection, usually with embolisation which temporarily occludes the artery) significantly improved survival and decreased recurrence. However, a systematic review[11] found no clear evidence that either neoadjuvant or adjuvant regimens prolonged overall or disease-free survival; some evidence for benefit on disease-free survival was seen with adjuvant immunotherapy or iodine-131 with iodised oil. In patients who have small tumours and are not candidates for surgery or transplantation, percutaneous intratumoral alcohol injection is an option. Other ablative therapies include radiofrequency ablation and cryosurgery.[3-10,12,15,16]

For disease defined as ***intermediate*** or ***advanced***,[5,6] where tumours are large or unresectable and not amenable to local ablative therapies, transcatheter arterial chemoembolisation (TACE) is also used.[2-4,6,8,17] TACE uses substances such as gelatin foam or iodised oil to temporarily occlude the artery (the sole supply of blood to the tumour). This prolongs the duration of contact between drug and tumour and also attempts to induce tumour necrosis by ischaemia.[2,4,6,12] TACE compared with arterial embolisation

without chemotherapy was found to improve survival in one study.[18] Systematic review[19] confirmed a survival benefit with chemoembolisation, using doxorubicin or cisplatin, and suggested this method as standard therapy for selected patients with small unresectable tumours, and well-preserved liver function. Patients with severe hepatic impairment and portal vein thrombosis should not be treated with TACE as there is a risk of precipitating acute liver failure.[4,5,8,17] Other strategies to improve tumour response include the use of drug-eluting beads containing doxorubicin,[5,16] or transarterial radioembolisation (TARE), which injects radioactive isotopes such as iodine-131 or yttrium-90 into the hepatic artery, using the same principles as TACE.[2,4-6,17]

Systemic chemotherapy has been tried for the treatment of ***advanced or metastatic*** hepatocellular carcinoma, but has had no impact on survival.[1,3,8,10] The most active drug is doxorubicin, which has been associated with partial responses in about 10% of cases,[1,4,5] and has been widely used as the standard of care in disease not amenable or refractory to TACE.[17] Combination chemotherapy using a regimen of cisplatin, interferon, doxorubicin, and fluorouracil (PIAF) doubled the response rates compared with doxorubicin monotherapy, but toxicity was higher, and overall survival unaffected.[1,4,5,17] More recently, however, a survival benefit has been shown with the use of sorafenib when compared with placebo,[5,6,16] and some now consider it to be the new standard of care for patients with advanced disease,[5,10] although others consider it standard only in those who are not candidates for curative or locoregional therapies such as TACE, and have noted that it has only been studied in those with good liver function.[17] Other drugs under investigation for hepatocellular carcinoma include bevacizumab, sunitinib, and erlotinib.[1,3,5,6,10,16]

In contrast to the poor response of hepatocellular carcinoma to therapy, better progress has been made in strategies for its **prevention**. Neonatal vaccination against hepatitis B has dramatically decreased the incidence of chronic infection in children in Taiwan, and reduced the incidence of hepatocellular carcinoma[20] although some have noted that more time is needed to show the real impact of this measure.[2] Treatment of chronic hepatitis (p. 952.1) can prevent progression to liver cirrhosis and subsequent hepatocellular carcinoma.[20] There is also some suggestion of a possible inverse relation between coffee consumption and liver cancer risk.[16] Chemoprevention may also be a useful approach after surgical resection: use of a synthetic retinoid, peretinoin, was found to reduce the development of second primary tumours after resection.[21,22]

The liver is the most common site of ***metastatic disease***.[23] For most malignancies the presence of liver metastases is indicative of generalised dissemination, but isolated metastatic liver disease is common in colorectal cancer (p. 706.3) and rarer cancers such as some neuroendocrine tumours (p. 716.3).

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Malignant neoplasms of the lung. Lung cancer is the most common non-skin cancer in the developed countries and the second most common overall worldwide. About 20 to 25% of all lung cancers are small cell lung cancers (SCLC) derived from endocrine cells in the bronchial mucosa; the remainder, comprising chiefly squamous cell carcinomas (40 to 45% of cases), adenocarcinoma (25 to 30%), and large-cell carcinoma (about 10%), are known collectively as non-small cell lung cancer (NSCLC). More than 80% of all lung cancers are associated with tobacco smoking, and there is also evidence that exposure to the cigarette smoke of others can increase the risk in non-smokers. Other risk factors may include occupational exposure to substances such as asbestos, and the effects of environmental toxins such as air pollutants.

Symptoms due to a lesion in a main bronchus (the most common site) include persistent cough, dyspnoea, haemoptysis, weight loss and sometimes chest pain. Metastatic spread is common, and may affect sites such as brain, liver, and bone. It occurs early with adenocarcinoma and SCLC, but late with squamous cell carcinoma.

Disease staging plays an important role in determining treatment. The management of SCLC differs significantly from that of NSCLC (see below and p. 711.1, respectively).

Given the poor prognosis of lung cancers, and the high incidence of second primaries in patients curatively treated for early-stage disease, there has been great interest in **prophylaxis.** The most important factor in primary and secondary prevention is cessation of tobacco smoking, for which a number of interventions may be tried (see Smoking Cessation, p. 2570.2). Diets rich in fruit and vegetables have been associated with a lower incidence of malignant disease, and have prompted the investigation of antoxidant vitamins. However, primary prevention studies in those at risk of lung cancer have failed to show any benefit for vitamin supplements, and in the case of betacarotene, an increase in lung cancer was seen in those most at risk (see Prophylaxis of Malignant Neoplasms, p. 2047.3). Other drugs under investigation are retinoids and NSAIDs.[1]

While a meta-analysis[2] concluded that screening of patients with chest radiography or sputum cytology was ineffective, the Early Lung Cancer Action Project found that computed tomography improves the likelihood of detection of nodules suggestive of lung cancer in high-risk patients.[3] Since most of those cancers detected were at an early stage, resection was possible, and it is theorised that this technique may reduce mortality,[4] although it remains investigational.

Metastatic lung disease. The lung is the second most frequent site for metastatic disease, occurring in about 30% of cancer patients. Surgical resection may be used to treat pulmonary metastases when there are no effective systemic therapies, no extrapulmonary metastases, the pulmonary metastasis is completely resectable, and the patient is able to undergo surgery.[5] Specific cancers for which surgical resection of pulmonary metastases is considered include soft-tissue sarcoma, osteosarcoma, and sometimes breast cancer.

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SMALL CELL LUNG CANCER. The mainstay of treatment for small cell lung cancer (SCLC) is chemotherapy.[1-5] In ***limited disease*** (disease limited to one hemithorax with hilar and mediastinal lymph node involvement that can be encompassed within one tolerable radiotherapy field) the combination of chemotherapy and chest radiotherapy has been shown to improve survival[6,7] and is recommended therapy.[2-5] The most common chemotherapy regimen is 4 to 6 cycles of etoposide and cisplatin (EP or PE),[1,3-5,7,8] which offers a survival advantage over the previously used regimen of cyclophosphamide, doxorubicin, and vincristine (CAV). The optimum scheduling of chemotherapy and radiotherapy has been investigated and concurrent therapy found to be superior to sequential radiotherapy.[3] In comparing early and late concurrent therapy, a meta-analysis[9] of 7 studies found that a small improvement in overall survival at 2 years was associated with early radiotherapy (begun within 9 weeks of starting chemotherapy, or before the third cycle of chemotherapy) compared with late radiotherapy. There was also evidence that the use of hyperfractionated radiotherapy (given twice daily) and platinum-based regimens contributed to this benefit. In general, for limited disease it is recommended[2,3,5,7] that concurrent chest radiotherapy should be started with the first or second chemotherapy cycle. Response rates of 70 to 90% are reported, but median survival rates are only 14 to 20 months and the 2-year survival rate is about 40%.[5]

Only a few patients present with resectable early stage disease. Careful pre-operative staging is essential to rule out nodal involvement, and all patients should receive adjuvant chemotherapy. If nodal metastases are found, the addition of postoperative chest radiotherapy should be considered. Patients with later disease stages do not benefit from surgery.[3,5]

In ***extensive*** SCLC (spread beyond one hemithorax and thus beyond the boundaries of a single radiotherapy field; may include malignant pleural or pericardial effusion or haematogenous spread) chemotherapy alone is used to palliate symptoms and prolong survival. The combination of etoposide and cisplatin (or carboplatin) is also used in these patients[3-5,7] but response is poorer than that for limited disease, with response rates of 60 to 70% and a 2-year survival rate of less than 5%.[5] Alternative first-line regimens include irinotecan with cisplatin (or carboplatin), or the CAV regimen.[5] Other strategies that have been tried, but with little consistent evidence of improved results, include the addition of further drugs to EP (such as ifosfamide, paclitaxel, or cyclophosphamide plus an anthracycline), and the use of dose-intense or dose-dense regimens.[1,5,8]

The use of **consolidation or maintenance** chemotherapy has been studied in both limited and extensive disease. Most studies have found no improvement in progression-free or overall survival, and the general recommendation is that such extra therapy, with its associated toxicity, should not be used.[1-5,8] This view has been challenged by a meta-analysis[10] of 14 studies suggesting that there is evidence for benefit from maintenance therapy, although it is unclear which patients might benefit and which regimen would be most effective.

Patients who have responded to initial treatment still have a more than 50% risk of developing brain ***metastases***. Prophylactic cranial irradiation reduces this risk and improves survival in patients in complete remission.[4,5,11] It is generally recommended for all patients with limited disease who achieve remission, and for those with extensive disease who achieve remission and have good prognostic factors and performance status.[2-5,7,8]

The value of chemotherapy in ***relapsed*** SCLC depends in part on the duration of remission before relapse, with greater responses the longer the remission.[3,5,7,8] In the UK, NICE guidelines recommend second-line chemotherapy only in patients whose disease responded to first-line treatment.[2] Patients who relapse within 3 months of achieving remission are considered to have refractory disease; second-line drugs include ifosfamide, paclitaxel, docetaxel, irinotecan, topotecan, and gemcitabine, although response is likely to be poor. Response rates are better if relapse occurs between 3 and 6 months after remission, and topotecan has been suggested as the best option. Other drugs that may be considered include irinotecan, gemcitabine, a taxane, oral etoposide, vinorelbine, or the CAV regimen.[5,7,8] Drugs under investigation for SCLC include amrubicin, pemetrexed, and picoplatin.[7,8] Patients may be given a repeat of initial therapy if they have relapsed after more than 6 months. Second-line chemotherapy should be given until the patient receives maximal benefit, becomes refractory, or develops unacceptable toxicity. Radiotherapy may also be given for localised symptomatic palliation.[5]

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NON-SMALL CELL LUNG CANCER. Non-small cell lung cancer (NSCLC), like many malignancies, is treated according to the stage of the disease, for more information see p. 691.1.

For resectable NSCLC and locally-advanced unresectable disease, chemotherapy can be used with surgery or radiotherapy but, for advanced or metastatic disease, chemotherapy is the main treatment.[1-8] Platinum-based regimens prolong survival; cisplatin or carboplatin are effective when combined with docetaxel, etoposide, gemcitabine, irinotecan, conventional or albumin-bound paclitaxel, pemetrexed, vinblastine, or vinorelbine. Two-drug regimens are preferred although single-agent treatment is an option for those with poor performance status and the elderly; a third cytotoxic increases response but not survival. Targeted therapy may be added to chemotherapy for those whose tumours are a particular histology or have a specific genetic abnormality.

First-line options for advanced or metastatic NSCLC include:

- chemotherapy preferably with platinum-based regimens ± bevacizumab
- afatinib, erlotinib, or gefitinib in those with epidermal growth factor receptor (EGFR) mutations
- cetuximab plus cisplatin and vinorelbine in those with EGFR mutations
- crizotinib in those who are anaplastic lymphoma kinase (ALK) positive
- cisplatin plus pemetrexed for those with non-squamous histology
- cisplatin plus gemcitabine for those with squamous histology

First-line, platinum-based chemotherapy regimens are usually given for 4 to 6 cycles. For those who respond, or those with stable disease, the following options may be considered, although their relative benefits are still uncertain:

- continue first-line regimen
- continue treatment with a drug that was included in the first-line regimen (continuation maintenance). Often, targeted drug treatment or gemcitabine is continued after the initial 4 to 6 cycles of platinum-based chemotherapy
- change to a different drug that was not included first-line (switch maintenance). Second-line options (see below) are often used
- drug holiday

When disease progresses, a different regimen is started. Second-line options include:

- single-agent docetaxel
- single-agent afatinib, erlotinib, or gefitinib
- single-agent pemetrexed in those with non-squamous histology
- single-agent crizotinib in those who are ALK positive

Erlotinib may also be considered as a third-line option.

Emerging treatment options and alternative approaches for NSCLC include:[9,10]

- individualising treatment based on genetics or tumour characteristics
- drugs targeting the EGFR pathway
- vascular endothelial growth factor (VEGF) receptor kinase inhibitors
- cancer vaccines and immunotherapies
- histone deacetylase inhibitors

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MALIGNANT PLEURAL MESOTHELIOMA. Malignant pleural mesothelioma is a relatively rare tumour of the lining of the lung, yet its incidence is increasing. Occupational exposure to asbestos is the causative factor in most cases, with a mean latent interval of about 40 years between first exposure and death. Typical clinical manifestations include chest pain or dyspnoea or both. Neurological entrapment and pericardial involvement may occur. The disease is progressive, and median survival is poor. Histologically, disease may be epithelioid, sarcomatoid, or a mixture of the two. The epithelioid type is the most common, and may be confused with adenocarcinoma (see Malignant Neoplasms of the Lung, p. 710.2).

In patients with potentially resectable disease, surgery may be considered. Radical surgery (extrapleural pneumonectomy, EPP) is suitable only for a few patients, such as those with epithelioid tumours, and mortality and morbidity are high, despite the use of adjuvant chemotherapy and radiotherapy.[1-5] If EPP is planned, platinum-based neoadjuvant or adjuvant chemotherapy should be considered.[6] Pleurectomy is a cytoreductive procedure used for limited disease, or as palliation. Talc pleurodesis is usually the treatment of choice in the management of pleural effusions associated with mesothelioma. Palliative radiotherapy may be effective for pain relief,[1,6,7] but is generally of limited value.[2,8]

Numerous drugs have been tried in mesothelioma, but responses to monotherapy have been in the region of 10 to 20%, with cisplatin, carboplatin and doxorubicin being the most active agents.[3,9,10] Combination chemotherapy regimens, mostly cisplatin- or doxorubicin-based, have shown higher response,[5] but with little effect on overall survival.[9,10] However, the combination of pemetrexed and cisplatin was shown to improve survival,[1-4,6,8] and it is generally considered to be standard first-line therapy in patients with good performance status and unresectable disease.[2,3,5,7] The regimen is associated with high toxicity, however, and prophylactic use of vitamin B_{12} and folate is recommended.[2,4,10] Carboplatin has been substituted for cisplatin in attempts to reduce toxicity; comparable survival has been reported[4] and some recommend carboplatin with pemetrexed as an alternative first-line treatment.[6,7] The use of raltitrexed with cisplatin has also improved response rates and overall survival, with comparatively little toxicity, and this combination is considered to be an alternative first-line regimen.[4,6,10] Gemcitabine plus cisplatin is also active;[2,4,5] some consider it suitable first-line,[7] while others recommend it for second-line use.[3] Other combinations have been investigated; early use of the MVP regimen (mitomycin, vinblastine, and cisplatin) has shown a trend towards improved survival compared with delayed use.[4] No standard second-line therapy has been defined.[10] Vinorelbine, alone or with gemcitabine, has also been tried as a salvage regimen.[5] Multimodality approaches are increasingly used; neoadjuvant therapy has shown promising results.[4,10] Gene therapy, immunomodulation, angiogenesis inhibitors, ribonuclease inhibitors, and proteasome inhibitors are also being tried.[1,2,4,5,8,10]

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Malignant neoplasms of the ovary. Ovarian cancers account for about 5% of all malignancies in women. The most common form (90% of cases) is **epithelial ovarian cancer**, which ranks as fourth in the leading causes of cancer deaths in women. The lethality of this disease is related to the absence of symptoms in most women during its early stages: in about three-quarters of all patients disease is advanced at diagnosis and has spread to the peritoneum or beyond. It is mainly a disease of older women, the median age at diagnosis being 63 years. The risk of epithelial ovarian cancer appears to be related to the number of ovulatory cycles a women has in her lifetime, thus nulliparity increases the risk, whereas multiparity, breast feeding, and combined oral contraceptives (p. 2236.1) decrease the risk. Other risk factors are a family history (particularly when associated with the BRCA1 and BRCA2 genes), and possibly fertility drugs (see Clomifene, p. 2259.2), perineal talc use (p. 1722.3), and menopausal HRT (p. 2248.1).

The main ***treatment*** for epithelial ovarian cancer in most patients is surgical removal of womb, ovaries and fallopian tubes, and omentum, with debulking of any remaining gross disease.[1,2] For younger patients with favourable histology and disease confined to one ovary, and who wish to conserve fertility, unilateral salpingo-oophorectomy is possible.[1-4] The use of adjuvant chemotherapy depends on disease stage. Optimal surgical staging of early disease identifies those who have little or nothing to gain from adjuvant chemotherapy.[5]

For patients with *early stage* (stages IA/IB), well-differentiated (grade 1) disease, surgery alone is adequate;[1,2] more than 90% of women will have long-term (> 10 years) disease-free survival without further treatment.[4] In patients with poorly differentiated (high-grade) disease, or more extensive disease (stages IC and IIA), adjuvant chemotherapy should be considered.[1,2] Generally, 3 to 6 cycles of intravenous chemotherapy with carboplatin plus a taxane are recommended;[2,4] some recommend 6 cycles of carboplatin monotherapy.[1]

For patients with *advanced* disease (stages IIB to IV), intravenous adjuvant chemotherapy is also recommended, usually with a platinum and a taxane[1,2,4] for 6 to 8 cycles.[1,2] No difference in efficacy has been shown between cisplatin or carboplatin,[6] although carboplatin is usually preferred.[7] The amount of residual disease is an important prognostic factor[8,9] and secondary surgery (interval debulking surgery) can be considered for patients with suboptimal debulking at primary surgery who respond to chemotherapy.[1,3,8] However, a systematic review[9] found similar survival rates in patients who did and did not receive interval debulking surgery. Some recommend that this interval debulking surgery be performed after 3 cycles of chemotherapy, followed by a further 3 cycles of chemotherapy.[1] For patients who are considered initially not optimally resectable (for patient- or tumour-related factors), neoadjuvant chemotherapy followed by debulking surgery may be an option.[4,8-10] Some recommend this approach as standard for stage IV patients.[10]

Intraperitoneal chemotherapy is an option for those with *minimal residual disease* after surgery,[2,11,12] and may improve progression-free and overall survival compared with intravenous use.[4,7,13] However, it is not universally advocated,[3,4] because of adverse effects and complications, and the need for technical expertise;[4,11] some recommend it for stage III, optimally debulked patients.[1] The recommended regimen consists of intraperitoneal cisplatin and intraperitoneal paclitaxel, after an initial intravenous paclitaxel infusion.[2]

In patients with *recurrent* disease, the choice of therapy depends on the time since initial therapy and the drugs used.[1,2,14] Patients with long treatment-free intervals (more than 2 years) may be considered for secondary surgical resection of recurrent disease.[1] Relapse occurring more than 6 months after initial therapy is potentially platinum-sensitive and may be re-treated with platinum-based combination therapy.[1,2,4,15] Carboplatin or cisplatin monotherapy is used if combination therapy cannot be tolerated; oxaliplatin is also an option.[2] Those whose disease recurs in less than 6 months are considered to be platinum-resistant or platinum-refractory.[1,2,15] While re-treatment with a platinum compound is not generally recommended, some data suggest that altering the paclitaxel schedule may produce a secondary response.[2] Other drugs with activity include topotecan, liposomal doxorubicin, altretamine, capecitabine, cyclophosphamide, docetaxel, epirubicin, oral etoposide, gemcitabine, ifosfamide, irinotecan, pemetrexed, and vinorelbine.[1,2,7,8,12,14,15] Hormonal therapy is also an option; drugs include tamoxifen, anastrozole, letrozole, leuprorelin acetate, or megestrol acetate.[2] However, response rates are relatively low, and enrollment in clinical studies should be encouraged.[1,8] There has been considerable interest in the potential use of targeted therapy, but results in ovarian cancer with these drugs have generally not been favourable, except for bevacizumab.[4,12,15,16] Bevacizumab is active in both platinum-sensitive and platinum-resistant disease, and may be used in combination therapy in relapsed disease.[2] The monoclonal antibody oregovomab and ovarian cancer vaccines are under investigation.[16,17] Some success has been reported using high-dose chemotherapy followed by autologous stem cell transplantation,[18] although an improvement in survival has not been shown.[2,8]

Prophylaxis. The identification of genes conferring an inherited predisposition to ovarian cancer, and the difficulty

in identifying the disease and its poor prognosis has led to increased interest in prevention. Oral contraceptives are known to be protective in the general population, and there is growing evidence that women with mutation of the BRCA1 or BRCA2 gene might benefit similarly (see Ovary, under Carcinogenicity in Hormonal Contraceptives, p. 2236.1). Prophylactic oophorectomy may be considered in women with BRCA1 mutations after child-bearing or at age 35 years.[19,20] The risk/benefit ratio of this procedure is unknown, and a few women who undergo this procedure subsequently develop a primary peritoneal cancer.

Ovarian germ-cell cancers account for less than 3% of ovarian cancers and typically occur in women aged 20 to 30 years. Unlike epithelial ovarian cancer, most patients present with early disease, and have an excellent prognosis. Surgery is the main therapy (fertility-sparing if appropriate). Adjuvant chemotherapy is used except in those with stage I disease able to undergo frequent follow-up. Common regimens are similar to those used in male germ-cell tumours, such as bleomycin, etoposide, and cisplatin (BEP) or vinblastine, bleomycin, and cisplatin (VBP).[2,21-24]

Ovarian stromal tumours account for about 7% of ovarian cancers[25] and are mainly treated with surgery (fertility-sparing if appropriate).[2] For those with high-risk stage I tumours, recommendations include observation, radiotherapy, or platinum-based chemotherapy. For those with tumour stages II to IV, options include radiotherapy for limited disease, or platinum-based regimens such as BEP or paclitaxel plus carboplatin.[2,21,24]

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Malignant neoplasms of the pancreas. Pancreatic adenocarcinoma (cancer of the exocrine pancreas) accounts for about 95% of pancreatic tumours. A very small percentage of pancreatic tumours arise in the endocrine pancreas, and have different clinical features and treatment (see under Neuroendocrine Tumours, p. 716.3). Worldwide, pancreatic adenocarcinoma accounts for about 2% of all cancers, but is the eighth leading cause of cancer deaths. Its incidence is higher in developed countries. The risk for pancreatic carcinoma increases with age, and mean onset is in the seventh or eighth decade. Pancreatic adenocarcinoma is ductal in origin and metastasises early to the lymph nodes, and about 40% of patients present with metastatic disease. The 5-year survival rate is about 5%, and most patients die within the first 2 years. The most frequent symptom at presentation in patients with cancer of the pancreatic head is jaundice, often with other symptoms indicative of obstruction of the bile duct. In lesions of the body and tail of the pancreas severe and relentless pain may develop. Other symptoms include weight loss, steatorrhoea, dyspepsia, nausea, and depression. Diabetes mellitus is a manifestation of the disease, but there is also some evidence that it may be a predisposing factor. About 30% of pancreatic cancers are probably due to tobacco smoking.

Pancreatic adenocarcinoma has a very poor prognosis because of its usually advanced stage at diagnosis and lack of effective therapies.[1,2] The only curative **therapy** is resection of the tumour and the surrounding pancreatic tissue.[3] In the few patients who present with ***early-stage*** disease (tumour confined to the pancreas), radical surgery results in a 5-year survival of about 20% in optimally staged patients.[1] *Adjuvant treatment* has been shown to increase disease-free and overall survival and should be offered to all curatively resected patients.[4] The choice of the most effective adjuvant regimen has been the subject of much controversy and no definitive standard exists. Adjuvant chemotherapy with either fluorouracil or gemcitabine improves survival[5] and European guidelines[6] recommend 6 cycles of either drug; US guidelines state that where chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over fluorouracil or capecitabine for most patients.[3] Results with adjuvant chemoradiotherapy have been conflicting.[4,5] Early evidence showed that adjuvant fluorouracil-based chemoradiotherapy improved survival.[4] However, the results of a large European randomised study[7,8] suggested that there was no benefit from adjuvant fluorouracil-based chemoradiotherapy. A subsequent review[9] that included this study concluded that chemoradiotherapy should not yet be dismissed from further study because studies to date had used radiotherapy regimens that were now considered to be suboptimal, and the possibility of benefit could not be ruled out. European guidelines[6] state that fluorouracil-based chemoradiotherapy may be suitable for some patients after resection and gemcitabine chemotherapy, and US guidelines[3] state that, where chemoradiotherapy is the adjuvant treatment of choice, systemic gemcitabine followed by fluorouracil-based chemoradiotherapy should be used. However, with the emergence of newer drugs, patient enrolment into adjuvant clinical studies is encouraged in the USA.[3] Pre-operative (*neoadjuvant*) chemoradiotherapy is also under investigation, but a survival benefit has not been proven, and toxicity can be severe.[1,10,11] However, US guidelines state that, while data are lacking, it has not been shown to be clearly disadvantageous, and that some patients may benefit: prolonged recovery after resection may delay the use of adjuvant therapy; neoadjuvant treatment may also allow for selection of patients responsive to therapy, and could convert unresectable disease to resectable status.[3] For these reasons, patients with borderline resectable disease should be considered for neoadjuvant chemoradiotherapy; regimens are usually fluorouracil-based, and patients are still candidates for adjuvant therapy after surgery.[3,6]

In patients with symptomatic localised ***unresectable disease***, chemoradiotherapy may be used.[3] Most studies have reported a modest survival benefit from the combination of radiotherapy and fluorouracil.[1-3,11] Evidence suggests that radiotherapy with gemcitabine can yield similar outcomes.[3] A period of chemotherapy followed by chemoradiotherapy may be preferable to first-line chemoradiotherapy. Chemotherapy alone is also an option in these patients;[3,6] European regimens are similar to those for resectable disease, whereas gemcitabine monotherapy or gemcitabine-based combination therapy is advocated in the USA. Studies of neoadjuvant chemoradiotherapy to improve resectability rates in locally advanced disease should be encouraged.[6]

For patients with ***advanced*** (metastatic) disease, gemcitabine is recommended as the standard of care.[3,6,11,12] There is also some evidence that its effectiveness may be improved if it is given at a fixed dose rate of 10 mg/m^2 per minute, rather than by conventional infusion.[3,13] Other options in metastatic disease include gemcitabine-based combination therapy for those with good performance status, or best supportive care.[3] A meta-analysis[14] found a survival benefit for gemcitabine-based combination therapy compared with gemcitabine alone. Combinations showing benefit in terms of progression-free survival or overall survival include gemcitabine with capecitabine (GEMCAP), cisplatin (GEMCIS), oxaliplatin (GEMOX), erlotinib, or albumin-bound paclitaxel.[3,5,13,15-17] The combination of cisplatin, epirubicin, fluorouracil, and gemcitabine (PEFG) has also shown impressive results.[13]

There is no consensus on second-line therapy for patients with ***refractory*** disease. Gemcitabine may offer palliation if patients have not previously been treated with this drug; there is some suggestion that fixed-dose gemcitabine plus oxaliplatin may be useful in those patients refractory to standard gemcitabine therapy. For those patients who have had gemcitabine, enrolment in clinical studies is encouraged. If investigational therapy is not possible, treatment options include capecitabine or fluorouracil, both with or without oxaliplatin.[3]

Pancreatic cancer vaccines are under investigation for pancreatic cancer.[5,18]

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Malignant neoplasms of the prostate. Prostatic cancer is the most commonly diagnosed non-skin malignancy in men in the western world, and the second most common cause of cancer deaths in men in the UK and USA: about one in 6 white men can be expected to develop clinically evident carcinoma of the prostate during his lifetime. Black men are at higher risk for the disease. The incidence rises steadily with age. There is also a familial component to the disease. More than 95% of all prostate cancer is adenocarcinoma, which begins as a hard mass in the peripheral portion of the gland and infiltrates surrounding tissues slowly. Metastasis may occur in advanced disease, notably to bone. Presenting symptoms of advanced disease are usually those of urinary outflow obstruction, or pelvic or back pain due to bone metastases. However, most men are asymptomatic, and may be diagnosed as a result of screening.

Controversy exists regarding all aspects of the management of prostate cancer, from screening to the best treatment for each stage of the disease. Much of this is because of the lack of clear data to guide treatment decisions. Factors that guide treatment decisions include the extent (stage) of the tumour, tumour grade (Gleason score), baseline prostate specific antigen (PSA) levels, the patient's life expectancy (based on age and comorbid conditions), treatment morbidity, and patient preference.[1-3]

There is great controversy over the value of **screening** for early disease by detection of PSA. Screening increases the incidence, but may not decrease mortality, and can result in unnecessary treatment. PSA screening in the USA did not result in significant differences in mortality compared with the UK, where PSA screening was not widely adopted.[4] A large European study found that PSA screening reduced the rate of mortality from prostate cancer by 20% but was associated with a high risk of overdiagnosis.[5] European guidelines state that decisions on population screening await longer follow-up.[3] US expert groups vary in their recommendations. A large US study found that screening provided no reduction in death rates after 7 to 10 years of follow-up.[6] The US Preventive Services Task Force deemed the evidence insufficient to assess the balance of benefit and harm of screening in men younger than 75 years; men aged 75 years or older should not be

screened.[7] Others favour screening, subject to patient preference after discussing risks and benefits; the time at which they consider screening should start is based on the patient's perceived risk, and has varied from 40 to 50 years of age.[2,8,9]

In patients with **localised disease**, detected incidentally or by screening, the choices are radical prostatectomy, radical external beam radiotherapy, brachytherapy, or deferred treatment (active surveillance or watchful waiting).[1-3,10,11] There is no general consensus as to what constitutes best treatment.[3] Men may be stratified as low-, intermediate-, or high-risk, depending on stage, grade, and PSA level.[2,3] Treatment morbidity and patient preferences are particularly important. Adverse effects of surgery include impotence and incontinence, and for radiotherapy, radiation proctitis, impotence, urinary retention, or incontinence.[2,10,11] In medically fit patients with a life expectancy of 10 years or more or those with poorly differentiated tumours, many clinicians would consider radical prostatectomy or radiotherapy with curative intent.[1,2,12] In men with a life expectancy of less than 10 years and with low-grade tumours, there is a definite role for deferring treatment.[2,10,12] Use of continuous or intermittent androgen deprivation therapy (ADT) as primary treatment has increased,[11] although it does not improve survival, and some guidelines do not recommend it.[2] However, its use with other therapies may be considered. (For further discussion of ADT, see below.) A systematic review[13] concluded that neoadjuvant (given for 3 to 6 months before the primary curative therapy) or adjuvant hormonal therapies, used with prostatectomy or radiotherapy, were associated with clinical benefit in terms of local control. Use of either with prostatectomy did not affect survival, but neoadjuvant hormonal therapy before radiotherapy significantly improved disease-free survival, and adjuvant hormonal therapy after radiotherapy significantly improved disease-free and overall survival. Some US guidelines[2] recommend that where radiotherapy is used for intermediate-risk localised disease, short-term (4 to 6 months) of neoadjuvant, concomitant, or adjuvant ADT can be considered; for high-risk disease, long-term use (2 to 3 years) is recommended.

For patients with **locally advanced disease**, options include radiotherapy with neoadjuvant, concomitant, or adjuvant ADT, ADT alone, or radical prostatectomy.[2,3] There is evidence that the use of hormonal therapy before or after radiotherapy improves disease-free and overall survival.[13-15] Studies of ADT have found that treatment for 3 years[16] and 5 years[17] after radiotherapy have improved survival when compared with treatment of shorter duration. US guidelines recommend 2 to 3 years of ADT when radiotherapy is used for locally advanced disease.[2]

PSA may be used to monitor the efficacy of therapy and detect biochemical relapse.[1,2] For those thought at low risk of metastases, salvage options after surgery include radiotherapy with or without ADT, while after primary radiotherapy options include observation, salvage prostatectomy in selected cases, cryotherapy, or brachytherapy.[2]

For patients with **metastatic disease** cure is not possible and therapy is aimed at prolonging survival and palliating symptoms. The basis of therapy is hormonal manipulation: about 80% of patients will respond to such therapy, but resistance eventually develops.[1,18] Historically, oestrogens such as diethylstilbestrol were used, but these are no longer recommended due to cardiotoxicity.[1,19] Standard first-line therapy is now ADT, using a gonadorelin analogue (such as goserelin, leuprorelin, or triptorelin) to produce medical castration, or opting for surgical castration (orchidectomy);[1-3,18,19] these have been shown to be equally effective.[2] However, medical castration with a gonadorelin analogue causes an immediate increase in testosterone (flare reaction), and a short course of an anti-androgen (such as bicalutamide, flutamide, or nilutamide) is given (either before or with the LHRH agonist) to prevent this surge.[2,3,18]

Some consider that anti-androgen monotherapy (with nonsteroidal drugs) may be discussed as an alternative to medical or surgical castration,[19] but others[2] do not recommend it. There is some evidence that survival rates may be lower, and treatment withdrawals (due to gastrointestinal adverse effects) higher.[20] Steroidal anti-androgen monotherapy should not be offered.[19] The gonadorelin antagonist abarelix can also be used for ADT. It has a more rapid onset of effect than the gonadorelin analogue leuprorelin and does not stimulate tumour flare.[21,22] Abarelix may be an alternative for men who are not suitable candidates for orchidectomy or gonadorelin analogue therapy.

Combined androgen blockade (longer use of an anti-androgen with medical or surgical castration) is also an acceptable first-line option;[2,19] this blocks the action of adrenal androgens as well (total androgen blockade).[1] Early studies suggested a small survival advantage with this approach, but adverse effects are increased,[1,19] and some guidelines[2] state that combined androgen blockade provides no proven benefit over castration alone.

The timing of ADT is controversial; there is some suggestion that early ADT may be better than delayed ADT, but data are limited,[18,19] and treatment should be individualised.[2] However, in the presence of symptomatic or overt metastases, treatment should be started immediately.[2] Intermittent ADT may potentially offer improved disease control and quality of life; however, data are limited and this approach, while feasible, remains investigational.[1,18,19]

In patients who relapse after or during hormonal therapy, second-line hormonal therapy may be tried, although responses are variable. Anti-androgens may be used sequentially, particularly in men who wish to defer more aggressive approaches such as chemotherapy;[18] drugs used include bicalutamide, flutamide, ketoconazole, oestrogens, and corticosteroids.[2,3,18,23]

Patients with **hormone-refractory (castration-refractory)** disease should be offered chemotherapy as an option.[2,3,18,24] Personalised immunotherapy with sipuleucel-T is also an option in some countries; it is recommended for patients with good performance status, life expectancy of more than 6 months, and no visceral disease.[2] In those given chemotherapy, docetaxel-based regimens are considered the standard of care.[25] A schedule in which docetaxel is given every 3 weeks is advocated first-line,[2,3,24] since this has shown a survival benefit.[2] Docetaxel is used with prednisone or estramustine, although use with the latter increases adverse effects and is generally not recommended. Alternative regimens include weekly docetaxel plus prednisone, or mitoxantrone every 3 weeks plus prednisone.[2] No consensus exists for second-line chemotherapy after failure of docetaxel and enrolment into clinical studies is encouraged.[2] Combinations of docetaxel are under investigation, including with vinorelbine, capecitabine, or high-dose calcitriol.[25] Estramustine with etoposide, vinblastine, or vinorelbine has also shown favourable results.[26] Other drugs that might be used after treatment with docetaxel-based therapy include oral cyclophosphamide, alone or with vincristine and dexamethasone;[23,25] intravenous cabazitaxel with a corticosteroid or oral enzalutamide may be options in those with metastatic disease. Abiraterone acetate, an inhibitor of androgen synthesis, may be given to patients with disease progression after docetaxel-based therapy,[27] or where ADT has failed but chemotherapy is not yet indicated.[28] Drugs under investigation include satraplatin and ixabepilone.[23,25]

A herbal combination preparation, PC-SPES, had some beneficial results in androgen-dependent and androgen-independent disease and has been used widely as a complementary medicine, but there have been reports of adverse cardiovascular effects and contamination with diethylstilbestrol and warfarin, resulting in the withdrawal of this product from most markets.[29,30] Bone metastases are usually treated with palliative radiotherapy (see p. 700.3). Bone-targeted therapy with strontium-89 or samarium-153 may be beneficial;[2,3] radium-223 is also used. Combinations of radiopharmaceuticals with docetaxel are under investigation.[31] Intravenous bisphosphonates such as zoledronic acid are recommended for bone pain and to prevent skeletal complications.[2,3] Prostate cancer growth is thought to be stimulated by endothelin-1, a small peptide that acts at endothelin-A receptors; atrasentan is an endothelin-A receptor antagonist under investigation, and early studies have shown improvements in time to disease progression and markers of bone metastases.[25,26]

Prophylaxis.

Because of the difficulties involved in managing prostate cancer there has been interest in the concept of disease prophylaxis. In healthy men, a large controlled study[32] found that seven years of finasteride prophylaxis reduced the incidence of prostate cancer by about 25% compared with placebo, but this benefit was offset by an increased risk of high-grade tumours associated with finasteride. However, later studies found that finasteride increased the accuracy of PSA testing,[33] and decreased prostate gland volume,[34] which could have contributed to the greater detection of all grades of cancer with finasteride. Guidelines issued by the American Society of Clinical Oncology and the American Urological Association[35] concluded that while the higher incidence of high-grade cancer seen in the finasteride group was likely due to these confounding factors, an increased incidence of high-grade cancer could not be excluded with certainty. However, some men may benefit from 5-α-reductase inhibitor therapy. A systematic review[36] concluded that reduction of prostate cancer with 5-α-reductase inhibitors was limited to men who had a baseline PSA value of less than 4 nanograms/mL. Dutasteride is also under investigation.[35,37]

Results from a case-control study have suggested an association between warfarin use and a decreased risk of prostate cancer.[38] Suggestions that selenium (see p. 2087.2) or vitamin E (see p. 2047.3) supplementation, alone or in combination, might reduce the risk of prostate cancer have not been borne out.[39] However, interest in compounds such as vitamin D (see p. 2116.1) and soya isoflavones[40] continues.

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Malignant neoplasms of the skin. Basal cell carcinoma is the most common form of skin cancer, accounting for about 80% of cases. The second most common skin cancer is squamous cell carcinoma. These 2 types of carcinoma (collectively referred to as nonmelanoma skin cancers) are the most common malignancies among white populations, but because many are not recorded the exact incidence is uncertain and they are often omitted from calculations of the relative frequency of malignancy. A small but increasing proportion of all skin cancers are melanomas, arising from melanocytes (pigment cells). Other cancers that manifest in the skin include cutaneous T-cell lymphomas (see Mycosis Fungoides, p. 698.3) and Kaposi's sarcoma (see p. 718.1).

Nonmelanoma and melanoma skin cancers are related to solar radiation, and the incidence is greatest in those regions where light-skinned populations live closest to the equator. Individuals at particular risk include those with fair skin, blue eyes, red hair, a tendency to freckle, and to burn rather than tan. Use of methoxsalen with ultraviolet light (PUVA) has also been associated with an increased incidence of skin cancers (see Effects on the Skin, under Methoxsalen, p. 1713.1). Other risk factors for nonmelanoma skin cancers include various inherited disorders such as xeroderma pigmentosum (see Photosensitivity Disorders, p. 1686.2) and albinism (see Pigmentation Disorders, p. 1687.2). Immunosuppressive therapy, as used after solid organ transplantation (see p. 1936.2 *et seq*.), is associated with a very large increase in risk of squamous cell carcinoma.

Prophylaxis. Although nonmelanoma and melanoma skin cancers are related to solar radiation, and measures to reduce sun exposure are therefore advocated for prophylaxis, the relationship appears to differ between the types.

- Squamous cell carcinoma and its precursor lesions are clearly linked to cumulative chronic sun exposure.[1,2] These lesions are more common on frequently exposed skin (head, neck, and back of hands), and are more common in individuals with outdoor occupations. In addition, there is evidence that regular sunscreen use can reduce the incidence of new actinic keratoses and increase remission of existing lesions,[3] and reduce incident squamous cell carcinomas.[4,5]
- Although basal cell carcinomas are also common on sun-exposed skin (head and neck), it appears that they may be more related to a history of severe sunburns, particularly in childhood and adolescence, rather than to cumulative sun exposure.[1] In one study,[4] there was no difference in incidence of basal cell carcinomas between sunscreen users and non-users. Long-term follow-up of another study[5] found no clear benefit of regular sunscreen use in reducing basal cell carcinomas.
- Cutaneous melanoma is more common on skin exposed to the sun occasionally (particularly the legs in women, and the back in men), and appears to be more common in indoor than outdoor workers.[1,2] Cumulative occupational exposure seems to be protective in some white populations.[6] This suggests that intermittent sun exposure may be more risky than regular exposure for this cancer.[1,2] Short, sharp bursts of acute exposure in childhood and severe sunburn are also strongly associated with melanoma risk.[6] Although the use of sunscreens is advocated for protection against melanoma, some reports have suggested that sunscreen use may actually increase the risk.[7] However, systematic reviews[8,9] have found no good evidence for an association between sunscreens and the increasing incidence of melanoma, but did find that studies varied in accounting for confounding factors such as patient complexion and recall bias. Also, people at higher risk of sunburn and melanoma may also be more likely to use sunscreens, and some people may use sunscreens to allow for prolonged sun exposure, thus receiving a higher cumulative amount of UV radiation. Sunscreen formulation (see p. 1681.3), sun protection factor (SPF) rating, and protection against UVA (see Light-induced Skin Reactions, p. 1685.3), have also changed considerably over the last few decades, making it difficult to compare study results. Sunscreens are therefore recommended as an adjunct to other measures (such as protective clothing) to prevent over exposure, especially in young children.[7]

Chemoprevention has also been investigated as a means of reducing the incidence of squamous and basal cell cancers, particularly in those most at risk. Retinoids such as acitretin, etretinate, and isotretinoin have been shown to reduce the incidence of new squamous cell carcinomas in individuals with xeroderma pigmentosum, and in renal transplant recipients.[10] Conversely, neither betacarotene (p. 2047.3) nor selenium (p. 2087.2) has reduced the incidence of squamous or basal cell carcinomas in patients previously treated for these disorders. There is some evidence that a low-fat diet may reduce the incidence of actinic keratosis in patients with a history of nonmelanoma skin cancer.[11] Certain substances such as flavonoids, curcumin, grape seeds, resveratrol, silymarin, and green tea have been proposed as having antiphotocarcinogenic properties.[12]

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BASAL CELL AND SQUAMOUS CELL CARCINOMA. The great majority of skin cancers are basal cell carcinomas, which are completely curable if diagnosed early and treated appropriately. Although they rarely metastasise, they have a tendency to be locally destructive. The remainder are mainly squamous cell carcinomas, which, although curable when treated early, have a greater risk of metastatic spread. Common precursor lesions for squamous cell carcinoma are actinic keratosis (solar keratosis) and Bowen's disease (squamous cell carcinoma in situ).

- Treatments for **actinic keratosis** and **Bowen's disease** include cryosurgery, curettage, excision, radiotherapy, laser treatment, photodynamic therapy (see Porfimer Sodium, p. 849.1) using 5-aminolevulinic acid or methyl aminolevulinate, and topical fluorouracil or topical imiquimod.[1-5] Topical diclofenac or topical salicylic acid may be used for actinic keratosis.[2-4] The choice of treatment depends on the site and size of the lesion, evidence for efficacy, ease of application, and availability.[1]
- Treatment options for superficial low-risk **basal cell carcinomas** include curettage and electrodesiccation or cryosurgery.[6-9] Topical fluorouracil may be used for superficial lesions in some instances, as are topical imiquimod or photodynamic therapy using 5-aminolevulinic acid, methyl aminolevulinate, or porfimer.
- For superficial tumours at high-risk sites, and for most **squamous cell carcinomas**, excision with postoperatively determined margins or Mohs' micrographic surgery (tumour margins examined during the procedure) is more appropriate.[6-11] Radiotherapy is an alternative in patients at risk of surgical complications or where surgery would be difficult or extensive.

The prognosis with appropriate treatment is good, with 5-year disease free survival of over 90%. However, about 50% of patients will subsequently develop another skin cancer, and regular monitoring to detect this as early as possible is desirable.[7] In addition, patients should be educated about sun protection measures, and chemoprevention with retinoids may be appropriate for some high-risk patients (see Prophylaxis, in Malignant Neoplasms of the Skin, above).

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MELANOMA. Although cutaneous melanoma is rare it is the most aggressive skin cancer, accounting for the majority of all skin cancer deaths. Melanoma may arise in apparently normal skin or from an existing naevus. Early signs of a naevus that may indicate development of a melanoma are change in size, shape, or colour. Other signs include itching, ulceration, and bleeding. The most common site in women is the legs, and in men the back. For a discussion of sun protection measures in the prevention of melanoma, see Prophylaxis, in Malignant Neoplasms of the Skin, above.

Surgical resection is the mainstay of **curative treatment** for primary melanomas, and the margins of excision are determined by tumour depth (Breslow thickness).[1-7] Patients with thin tumours (less than 1 mm) can be treated with wide local excision only; patients with intermediate (1 to 4 mm) or thick (more than 4 mm) melanoma are at high risk for nodal disease, and lymph node dissection may also be performed if node biopsy is positive.[1,3,8] Because of the high risk of recurrence after surgery in the latter group, there is great interest in adjuvant therapies. There is no accepted standard adjuvant therapy in the UK,[2,7] and it is not recommended for stage II and III disease other than in the context of a clinical study.[8] In the USA, the FDA has approved high-dose interferon alfa, which has shown benefit in terms of relapse-free survival, although the effects on overall survival are less apparent.[1,5,6] As toxicity is a significant problem with high-dose therapy, both low-dose and intermediate dosage regimens have been studied, but neither have shown a clear benefit in terms of overall survival.[1,5,6] Some recommend pegylated interferon, if tolerated, in patients with low tumour burden.[9] Isolated limb perfusion (ILP) with melphalan has been used as adjuvant therapy, but a review of four randomised studies failed to show any survival benefit for this compared with surgery alone[10] and it is considered to have no role in the adjuvant setting.[8] Similarly, systemic chemotherapy has not proved useful in the adjuvant setting.[11] Various melanoma vaccines (e.g. GM2 ganglioside, autologous melanoma-associated antigens) have been investigated for adjuvant use, but high-dose interferon alfa was shown to produce greater clinical benefit than vaccination with GM2.[5,6,8,12,13] Other drugs such as bevacizumab,[7] cytokines such as interleukin-2,[5,6] and newer immunotherapeutic approaches[13] are under investigation in the adjuvant setting.

Local **recurrences** and in-transit metastases are treated by surgical excision where possible.[1-3,6,7] Other options include cryotherapy, carbon dioxide laser ablation, intralesional injection with BCG or interferon alfa, or topical imiquimod.[1-3,8] Radiotherapy is also included as a treatment option in some centres,[3] although others do not recommend its use in the first instance.[2] Adjuvant radiotherapy may be considered for positive margins unsuitable for re-excision.[1] ILP with melphalan is considered the standard treatment option for patients with limb involvement,[1,2,8] and those with disease that progresses despite surgery or laser therapy,[2] and is an option for those with unresectable in-transit metastases or recurrence.[3] ILP with melphalan plus tissue necrosis factor-α may also be used[2,8] although this does not significantly improve response rate. However, there is some evidence that a second ILP using this combination may be of value after an initial ILP with a poor response.[1] The ILP procedure is complex[1,6] and should only be performed in specialist centres.[8] Isolated limb infusion (ILI) is a simpler alternative that may produce equivalent results.[1,3,6] ILI usually uses melphalan with or without dactinomycin. However, it may be less effective than ILP, and some consider it more suitable for patients with low volume disease or for those with comorbidities that prevent ILP.[2]

For patients who present with **metastatic melanoma** the 5-year survival rate is poor.[11] Median survival in disseminated disease is only 6 to 9 months.[1,7,8] There is no evidence to show that any systemic treatments are better than best supportive care in these patients.[14] Chemotherapy has been tried in disseminated disease,[4-6,15] and dacarbazine, with response rates of about 5 to 20%, is the most commonly used single agent. However, the response duration is short, and complete responses are rare.[1] The orally active analogue temozolomide produces similar responses,[1] and is an alternative first-line agent.[3] Ipilimumab may also be considered for initial therapy, although extreme caution is advised in those with serious underlying auto-immune disorders because of the possibility of immune-mediated reactions.[3] Nitrosoureas (such as carmustine and lomustine) have response rates of

around 15% as single agents.[15] Fotemustine appears to be more active, particularly in the treatment of brain metastases.[15] It has been reported to have a higher response rate compared with dacarbazine, but with only a trend towards increased overall survival.[1,16] Other drugs with a response rate of about 15% include cisplatin, vinblastine, vindesine, docetaxel, and paclitaxel;[15] response duration has generally been poor. Vemurafenib has improved overall and progression-free survival compared with dacarbazine in those with metastatic melanoma with the $BRAF^{V600E}$ mutation,[17] although its place in therapy is not yet established. Dabrafenib and trametinib are other options for those with BRAF mutations.

Combination regimens have been used, such as CVD (cisplatin, a vinca alkaloid, and dacarbazine),[15] but they do not improve survival compared with monotherapy.[1] Tamoxifen has also been added to regimens, on the hypothesis that melanoma is oestrogen-dependent; an example was the CDBT or Dartmouth regimen (cisplatin, dacarbazine, carmustine, and tamoxifen; see Table 1, p. 719).[15] However, this regimen was no more effective than dacarbazine alone,[1] and the addition of tamoxifen to chemotherapy is ineffective.[1,8]

Cytokines such as interferon alfa and interleukin-2 have similar activity to chemotherapy in metastatic melanoma;[15] high-dose intravenous interleukin-2 is used in the USA,[6] but not for patients with untreated or active brain metastases.[3] Cytotoxic chemotherapy has been given with these cytokines and there have been some reports of improved response rates, but overall survival has not been improved.[1,2,5-7] Second-line therapy may be offered to patients (with good performance status) who progress or are unresponsive to, or intolerant of, first-line therapy. Options include clinical studies, or treatment with a different first-line agent.[3] Surgical resection or radiotherapy may be used palliatively or for symptomatic control.[1-3,6,9] Melanoma vaccines are also being used or investigated in metastatic or recurrent disease,[12,13] as are gene therapy,[5] antiangiogenic agents such as thalidomide,[15,16] and the antisense oligonucleotide oblimersen.[6,16] Sorafenib monotherapy is minimally active, but results of its use with carboplatin plus paclitaxel were encouraging and combination studies continue.[6,7,16]

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Malignant neoplasms of the testis. Testicular cancer only accounts for about 1% of all male malignancies but it is the most common cancer in young men. Patients with a history of cryptorchidism are at increased risk. Other risk factors include family history, infertility, and white race. About 95% of testicular tumours arise in germ cells, and 40% or so of these are pure seminomas. The remainder are collectively known as nonseminomatous germ cell tumours (NSGCT) in the WHO classification, and are commonly of mixed cell types with or without a seminoma component. Nonseminomatous tumours have been referred to as teratomas in the British classification system, but this term has a more specific meaning in the WHO classification.

Metastasis first occurs to the lymph nodes, then, in advanced disease, to distant sites such as lung, liver, brain, and bones. The leading symptom is a hard, painless swelling of the testis, but once metastasis occurs the patient may present with back pain (due to enlargement of retroperitoneal lymph nodes), cough, dyspnoea, gynaecomastia due to chorionic gonadotrophin production, or weight loss.

Surgical removal of the testis (orchidectomy) when diagnosis is confirmed is fundamental to the treatment of all types of testicular cancer, but further therapy depends upon the disease type and stage.[1-4]

In patients with **nonseminomatous** disease with the ***tumour confined to the testis*** (stage I), options after orchidectomy include surveillance, adjuvant chemotherapy, or retroperitoneal lymph-node dissection (RPLND). Overall survival rates are good, with a cure rate close to 100%.[4-6] With surveillance, about 20 to 30% of patients will relapse and it is not appropriate for patients who are unable to undergo regular follow-up.[1,4] Treatment options vary slightly between countries. In the USA, RPLND may be carried out to further stage the disease before making a decision regarding surveillance or adjuvant chemotherapy.[1] If resected nodes are clear, patients undergo surveillance, but if they involve tumour the decision to give adjuvant chemotherapy is based on the degree of nodal involvement and the ability of the patient to undergo regular follow-up.[1] In the UK and Europe, stage I patients are classified as low-risk or high-risk, based on the absence or presence, respectively, of vascular (venous or lymphatic) invasion.[3-6] The standard option for low-risk patients is surveillance, with treatment on relapse.[3,5,6] High-risk patients can also be surveyed, but relapse rates are higher, and about 50% of patients will require chemotherapy.[3,5] The usual regimen used for stage I patients is 2 cycles of BEP (bleomycin, etoposide, and cisplatin).[1,3] However, there is some suggestion that one cycle of BEP may be sufficient.[3] RPLND is considered only if surveillance or chemotherapy is declined by the patient for specific or personal reasons, as it has the highest treatment burden.[3,5]

Where ***metastasis to the lymph nodes*** (stage IIA/B) has occurred, options for management are 3 cycles of BEP, 4 cycles of EP (etoposide and cisplatin), or primary RPLND (followed by either surveillance or chemotherapy).[1,3,4] Patients with ***advanced*** nonseminoma (stage IIC and III) are treated with primary chemotherapy regimens based on risk status; extent of disease and serum tumour markers are prognostic, and patients are accordingly classified into good-, intermediate-, and poor-risk groups.[1,3] For patients with good prognosis, standard treatment regimens are 3 cycles of BEP or 4 cycles of EP.[1,3,4] Standard management for patients with intermediate- or poor-risk disease is 4 cycles of BEP.[1,3,4] For patients who may not tolerate bleomycin, ifosfamide can be substituted (VIP regimen).[1,3,4] Less than 50% of poor-prognosis patients achieve a durable response, and enrolment into clinical studies is encouraged.[1] Any residual tumour is resected after chemotherapy; further management depends on the results of the primary treatment and secondary surgery; consolidation chemotherapy with 2 cycles of EP, VIP, VeIP (vinblastine, ifosfamide, and cisplatin) or TIP (paclitaxel, ifosfamide, and cisplatin) may be given.[1,3]

Patients who fail, or who relapse after, standard chemotherapy, or who have unresectable disease, are treated with *salvage therapy*.[1] Common salvage regimens include cisplatin and ifosfamide with either vinblastine (VeIP regimen), paclitaxel (TIP regimen), or etoposide (VIP regimen).[1,3,5,7] High-dose chemotherapy with stem cell support may also be considered.[1,5,6,8,9] Drugs with activity as single agents in relapsed disease include paclitaxel, oxaliplatin, and gemcitabine.[5-7] Combinations of these have been tried as second-line salvage chemotherapy regimens for patients with cisplatin-resistant or refractory disease;[7,9,10] gemcitabine with either oxaliplatin (GEMOX regimen)[1] or paclitaxel[3] may be tried.

About 75% of patients with **seminoma** have stage I disease at diagnosis, with a cure rate close to 100%.[2,5,6] Treatment options after orchidectomy include surveillance (with treatment only in the case of relapse), adjuvant radiotherapy or adjuvant carboplatin monotherapy.[1,2,4-6] Surveillance offers the lowest burden of treatment,[2] and is an option for selected patients who are committed to long-term follow-up.[1,6] The optimum surveillance schedule is still uncertain,[4] but should include measurement of serum tumour markers, clinical examination, and imaging of the abdomen, pelvis, and thorax.[1,4] Seminomas are extremely sensitive to radiation,[4] and adjuvant radiotherapy is the treatment of choice after orchidectomy in stages IIA and IIB.[1,5,6] For those with relative contra-indications to radiotherapy, chemotherapy is recommended;[1,5] 3 cycles of BEP, or 4 cycles of EP are used. There is an increasing role for chemotherapy in stage IIB[5] and some[2] distinguish slightly between stages in terms of treatment, and advocate radiotherapy and chemotherapy as standard for stages IIA and IIB, respectively; non-candidates for either therapy may be offered the alternative. Patients with stages IIC to III seminoma have a relapse rate of 20 to 30% after adjuvant radiotherapy, and adjuvant chemotherapy is preferred.[5] Standard regimens are 3 cycles of BEP or 4 cycles of EP for good-risk patients, and 4 cycles of BEP for intermediate-risk patients;[1,2] using ifosfamide instead of bleomycin can also be an option in those at intermediate-risk.[2] About 90% of patients with advanced seminoma are cured with cisplatin-containing chemotherapy.[1] Salvage regimens for relapsed or unresponsive seminoma are similar to those used for nonseminomatous disease.[1,2]

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Malignant neoplasms of the thymus. Thymomas are tumours of the mediastinum, arising from thymic tissue. They are rare, and most commonly present in patients between 40 and 60 years of age. Thymoma originates from the epithelium of the thymus but may also contain a lymphocyte component, which is probably not neoplastic. Up to 50% of patients are asymptomatic, and others have local symptoms such as cough, chest pain, dyspnoea, and obstruction of the vena cava; associated systemic disorders include myasthenia gravis, red cell aplasia, and hypogammaglobulinaemia.

Thymomas may be classified based on cell type; they are also staged as non-invasive (encapsulated, stage I), invasive (localised, stage II; extensive, stage III; and disseminated, IVa), and metastatic (IVb).

The **treatment** of thymoma may involve surgery, radiation, and chemotherapy; these may be combined, with the combination determined by the stage of the tumour.[1] Non-invasive stage I disease can be treated solely by surgical resection[1-4] with low recurrence rates and long-term survival approaching 100%.[5] Use of adjuvant radiation therapy for stage II thymoma has been controversial,[2] with studies showing conflicting results.[3] Generally, however, routine adjuvant radiotherapy is not recommended for stage II disease;[1,4] it may be considered in those patients at high risk for local recurrence,[1] or in patients with incomplete resection;[4] late complications of radiation therapy may occur.[1,2] Patients with stage I or II disease who are medically unfit for surgery may be offered chemoradiotherapy or radiotherapy alone.[1]

For patients with potentially resectable invasive disease (stages III and IVa), surgery is considered either initially or after neoadjuvant therapy. Chemoradiotherapy is often used before surgery, although the optimal regimen or sequencing has not yet been established.[1] Cisplatin-based combination regimens are recommended.[1,4] Concurrent chemoradiotherapy is recommended, but if the tumour is bulky, sequential therapy, with chemotherapy given before radiation, is an option.[1] Adjuvant radiotherapy is also often used in stage III,[1] and is recommended to maximise local control.[4] Adjuvant chemotherapy may be considered, but is not routinely recommended.[1] For stage IVa, adjuvant chemoradiotherapy is an option.[1] Patients with unresectable invasive disease may be treated with chemotherapy alone,[1] radiotherapy alone,[4] or concurrent or sequential chemoradiotherapy.[1,4] Cisplatin plus anthracycline-containing regimens similar to those in metastatic disease (below) are used first-line, and single agents second-line.[1]

Therapy for recurrent or metastatic disease is not well established because of the rarity of the condition.[1,5] Radiotherapy may be appropriate in stage IVB, especially for life-threatening situations,[1] but chemotherapy is often used.[1,4] Cisplatin and anthracycline-containing regimens are used first-line.[1,4] These include cisplatin, doxorubicin, and cyclophosphamide (CAP or PAC regimen), and the same drugs with vincristine (ADOC regimen). Cisplatin plus

etoposide (PE regimen) or these 2 drugs with ifosfamide (VIP regimen) are also options.[2,4,5] For these and other commonly used chemotherapy regimens, see Table 1, p. 719. Carboplatin and paclitaxel can also be used first-line.[4] Second-line single agents with activity include etoposide, ifosfamide, pemetrexed, fluorouracil, gemcitabine, and paclitaxel.[4] There is some evidence that thymomas possess somatostatin receptors, and octreotide, alone or with a corticosteroid, is also a second-line option.[1,4]

Surgery is considered for localised recurrence after apparently successful initial therapy. For some patients with stage IV disease, resection of isolated pleural metastases is appropriate. Radiotherapy, alone or with cisplatin-based chemotherapy, may be used. Octreotide with or without a corticosteroid is also a reasonable option for recurrent disease.[1]

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Malignant neoplasms of the thyroid. Thyroid cancer accounts for only about 1% of all malignancies. The incidence is reportedly higher in women than men, in patients who received irradiation of the thyroid during childhood, and in populations where goitre is endemic. The natural history varies with the cell type and degree of differentiation. Well-differentiated papillary or follicular tumours (which constitute over 80% and about 10% of cases, respectively) are very slow to grow and metastasise, sometimes persisting for years with little change in size and extent, although they may prove more aggressive in children. In contrast medullary carcinomas (5 to 10% of cases), which develop from the cells responsible for calcitonin secretion, and undifferentiated (anaplastic) tumours (1%) metastasise early and follow a much more rapid and aggressive course. About 25% of medullary cancers are hereditary, including those due to multiple endocrine neoplasia type 2.

The well-differentiated types usually present as a thyroid nodule, although most nodules are not malignant, while with anaplastic tumours there is usually invasion into the trachea, larynx, or recurrent laryngeal nerve which leads to obstructive symptoms, haemoptysis, dysphagia, and hoarseness.

In patients with **well-differentiated tumours** total or partial thyroidectomy is the treatment of choice.[1-7] This may be followed by a course of iodine-131 to destroy any residual tumour (thyroid ablation), although in patients who have small tumours with no other high-risk features (such as extension beyond the thyroid capsule or lymph node metastases) there are no benefits to such ablation and iodine-131 is not usually recommended.[1-7] External radiation therapy may be considered in patients with evidence of extrathyroid extension at the time of surgery.[3,4] There is no role for routine adjunctive chemotherapy in the management of differentiated thyroid cancer.[4] Levothyroxine treatment is given to all patients to prevent hypothyroidism and to minimise stimulation of tumour growth by thyroid stimulating hormone (TSH).[2,5,6] Measurement of serum thyroglobulin concentrations aids the detection of residual, recurrent, or metastatic disease. After surgery and thyroid ablation, this should be undetectable after about 3 months, although occasionally it may take up to 2 years; raised concentrations imply the presence of functional thyroid tissue or tumour. Sensitivity of thyroglobulin measurements is enhanced by an increase in TSH. TSH stimulation can be achieved either by levothyroxine withdrawal or by injections of human recombinant thyrotropin alfa.[1-4,6]

Disease recurrence or metastases are commonly treated with further surgery, ablative iodine-131 therapy or external radiation therapy.[1-6] Chemotherapy for metastatic disease has been inadequately studied.[2,5] It may have a role in refractory disease.[1,3,6] Doxorubicin is often used,[5] with a response rate of up to 40%;[2] cisplatin is also used.[1] Durable responses are rare.[1,2] Combination chemotherapy is not clearly superior to doxorubicin monotherapy.[3] Some[7] recommend against chemotherapy due to a lack of efficacy and recommend enrolment into clinical studies. Novel agents are under investigation;[1,3,5,7,8] preliminary results with tyrosine kinase inhibitors have been promising.[7]

In patients with **medullary cancers** total thyroidectomy and central neck compartment dissection are indicated,[1-3,7] with levothyroxine treatment if needed.[2,3] Serum calcitonin should be measured to detect residual disease.[2,3] Adjuvant external beam radiotherapy may be used in patients at high risk of regional recurrence[2,3] but routine use has not shown any survival benefit.[1] There is no role for radioactive iodine in medullary disease,[2,3] and chemotherapy is generally ineffective.[1,3] Further surgery with or without adjuvant radiotherapy is recommended for recurrent disease. Palliative resection or radiofrequency ablation can be tried for distant metastases; chemotherapy is usually dacarbazine-based.[3] Novel agents such as tyrosine kinase inhibitors have been investigated, with promising initial results;[7] cabozantinib is used for metastatic disease, and vandetanib for unresectable locally advanced or metastatic disease. Prophylactic thyroidectomy may be considered in patients with a hereditary predisposition to medullary cancer.[1,2] In patients with **anaplastic tumours**, cure is impossible and treatment is purely palliative, with survival measured in months.[2,3,7] Treatment options include surgery, radiotherapy, and chemotherapy. Multimodality therapy should be considered.[2,3,9] Use of hyperfractionated radiotherapy with doxorubicin can increase response, with median survival of 1 year. Paclitaxel has also been tried.[2,3,7] Novel agents are under investigation,[7,8,10] including the vascular targeting agent fosbretabulin.[3]

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Neuroblastoma. Neuroblastoma accounts for about 7% of all childhood malignancies overall but is the most common extra-cranial solid tumour in children. The majority of cases present before the age of 5 years. The tumour is derived from cells of the neural crest, and may occur anywhere within the sympathetic nervous system, notably the sympathetic ganglia and the adrenal medulla. Clinical behaviour ranges from spontaneous remission to rapid metastatic progression and death. Sites of metastasis include lymph nodes, bone marrow, liver, and skin. Symptoms depend on the site of the primary tumour and extent of disease. About 50% of children present with metastatic disease. Adverse prognostic factors include age over 1 year at diagnosis, advanced or metastatic disease, and amplification of the oncogene MYCN. The International Neuroblastoma Staging System (INSS) divides localised tumours into stages 1 and 2, based on regional lymph node status; unresectable tumours are classified as stage 3, and stage 4 refers to all patients aged 1 year or older with distant disease. Stage 4S (4 special) refers to infants less than 1 year of age with small localised primary tumour and limited dissemination (confined to liver, skin, or bone marrow).[1,2] However, the INSS is based on the extent of surgical excision, and a new staging system has also been developed by the International Neuroblastoma Risk Group, which is based on tumour imaging and risk factors. Locoregional tumours are staged as L1 or L2 based on the absence or presence of one or more image-defined risk factors, respectively. Metastatic tumours are classified as stage M, except for stage MS, in which metastases are confined to the liver, skin, and/or bone marrow in children younger than 18 months of age.[3,4]

Treatment protocols are designed according to the risk stratification:[1,3,6]

- the *low-risk* group consists of stage 1, stage 2, and stage 4S non-amplified hyperploid tumours with favourable histology
- the *intermediate-risk* group includes stage 3, 4, and 4S MYCN non-amplified tumours
- the *high-risk* group consists of stage 2 to 4 MYCN amplified tumours, including stage 3 tumours with unfavourable histology in children older than 18 months

Surgical resection alone is appropriate for those with **low-risk** tumours; these patients have a good prognosis.[1,2,6] Patients with local recurrence after surgery can be salvaged with chemotherapy and local radiotherapy. Neoadjuvant chemotherapy is also an option for those with paraspinal tumours and spinal cord compression, in order to avoid the morbidity of laminectomy and radiation. Patients with symptomatic stage 4S disease may also require chemotherapy.[2]

In those classified as **intermediate-risk**, surgery is usually followed by a short course of standard-dose combination chemotherapy.[1,2,6] Regimens used include cisplatin (or carboplatin), etoposide, cyclophosphamide, and doxorubicin.[2]

High-risk tumours can be treated with surgery, combination chemotherapy, myeloablative chemotherapy with haematopoietic stem cell transplantation, and local radiation.[1,2,6] Most remission induction regimens incorporate some or all of the most active drugs available for neuroblastoma, including the platinum derivatives, cyclophosphamide, ifosfamide, doxorubicin, etoposide, and topotecan.[1,2] One such dose-intensive regimen that was reported to have good response rates in a small study consisted of cyclophosphamide, vincristine, plus doxorubicin, alternating with cisplatin and etoposide.

Consolidation with myeloablative chemotherapy is used to eradicate any residual cancer cells. The addition of isotretinoin improved event-free survival and some consider high-dose myeloablation followed by isotretinoin to be the standard of care for children with high-risk disease who are older than 1 year at diagnosis.[2] Stem cell transplantation may be autologous or allogeneic,[2] although autologous peripheral blood stem cells appear to be the preferred source; tandem transplants are under investigation.[2,7]

Neuroblastoma is radiosensitive and if complete surgical resection is not possible, adjuvant radiation is indicated.[2] It may also be used after chemotherapy, and occasionally as palliation for metastases.[1] However, the role of total body irradiation (TBI) in the treatment of high-risk neuroblastoma has not been established, and most protocols do not include TBI.[2]

Metaiodobenzylguanidine (*m*-iodobenzylguanidine; iobenguane; MIBG) is a guanethidine derivative and norepinephrine analogue that concentrates in neural crest tissues. When radiolabelled with isotopes of iodine, MIBG has been shown to be useful for both imaging and treatment of neuroblastoma. MIBG uptake can be seen at the site of primary disease as well as metastatic tumour sites.[6] Iodine-123-labelled MIBG is the radioisotope of choice for imaging, whereas Iodine-131-labelled MIBG is used for therapeutic purposes.[5,6] It has been used as monotherapy or with combination chemotherapy in advanced, relapsed, or refractory disease, and has been investigated for use in newly diagnosed patients.[6,8] MIBG with radiosensitisers is also under investigation.[6] Multiple infusions of MIBG have also been used.[6,8]

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Neuroendocrine tumours. Neuroendocrine tumours are rare and constitute a heterogeneous group of neoplasms that share certain biological features. They originate from cells that produce and secrete regulatory hormones, and frequently present as hypersecretory syndromes. Common sites of origin include the endocrine pancreas, gastroenteric tissue in the gut, and neuroendocrine cells in the respiratory epithelium, as well as the thyroid, parathyroid, adrenal, or pituitary glands. Examples of syndromes associated with such secretory neoplasms include acromegaly (p. 1921.1), Cushing's syndrome (p. 2559.1), hyperprolactinaemia (p. 2252.2), and phaeochromocytoma (p. 1278.1). Multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2) are inherited conditions in which many tumours occur in often more than one endocrine organ; tumours in this disorder are often secretory.

Gastroenteropancreatic neuroendocrine tumours include carcinoid tumours and pancreatic endocrine tumours.

Carcinoid syndrome. Carcinoid tumours have traditionally been classified according to their embryological origin, namely fore-gut (bronchi, stomach, duodenum), mid-gut (jejunum, ileum, appendix, proximal colon), and hind-gut (distal colon and rectum).[1-4] Carcinoid tumours can secrete various hormones. The carcinoid syndrome describes symptoms related to the secretion of serotonin, histamine, or tachykinins. However, symptomatic carcinoid syndrome

is rare, both because the tumours vary in their behaviour depending on their embryological origin and because the liver is capable of metabolising those tumour products which are secreted into the portal circulation; only if the carcinoid tumour secretes into the systemic circulation, notably after metastasis to the liver, do symptoms occur. Carcinoid syndrome is therefore most often associated with tumours of the mid-gut, since they are commonest, and frequently metastasise.[2,5]

The characteristic **symptoms** of carcinoid syndrome include episodic flushing of the face and upper trunk (which may be provoked by alcohol, food, or stress), secretory diarrhoea, wheezing and dyspnoea, weight loss, pellagra, painful hepatomegaly, and right-sided valvular heart disease, which sometimes progresses to right heart failure and death.[2,4,5]

The **management** of carcinoid tumours usually involves surgical resection.[2-5] For localised disease, surgery may be curative.[1,6] Although many patients present with metastatic disease,[1] cytoreductive surgery is a mainstay of management.[4,6] Other cytoreductive procedures can also be used, such as radiofrequency ablation, laser therapy, and hepatic regional therapy (arterial embolisation, or trans-arterial chemoembolisation).[1,2,4-6] Drugs used for chemoembolisation include doxorubicin, streptozocin,[5] or a combination regimen of cisplatin, doxorubicin, and mitomycin.[4] Systemic antineoplastic chemotherapy has been used, but is considered to be of limited benefit for carcinoid tumours.[5-7] However, combination regimens may be used first-line for malignant, highly proliferative carcinoid tumours.[4] A common combination includes streptozocin, fluorouracil, plus doxorubicin;[4] cisplatin plus etoposide has also been used.[7] Despite some initial reports of response to interferon alfa, its value has not been borne out in practice.[5] It has, however, been considered to be of value for symptomatic control.[7]

For **symptomatic relief** of carcinoid syndrome somatostatin analogues such as octreotide or lanreotide are highly effective[4,5,8] and are the treatment of choice.[1,2] The availability of depot intramuscular preparations has simplified treatment, removing the need for multiple daily subcutaneous injections.[1,7,9] However, with prolonged use a few patients develop resistance even to the highest doses; the mechanism behind this tachyphylaxis is not yet known, although down-regulation of receptors has been suggested.[3,4,7] Octreotide is also used in the perioperative management of these patients to treat or prevent carcinoid crisis, when it may be given intravenously.[1] Use of somatostatin analogues with interferon alfa does not appear to be superior to monotherapy with either drug, and most do not recommend combination therapy as a standard treatment option.[7,9,10] While some consider the sequential use of these drugs, or the use of the combination after progression on monotherapy, to be justified,[10] others rarely add interferon when somatostatin analogues are no longer effective.[3] There is growing interest in the use of radiolabelled somatostatin analogues for the management of tumours that express high levels of somatostatin receptors;[2,4,5,9] promising results have been reported with palliative use in inoperable or metastatic disease.[1,11] Newer therapies such as gefitinib, everolimus, sunitinib, and bevacizumab are also being tried.[2,5,6] Other drugs that reduce the effects of serotonin have been tried, including cyproheptadine.[5] Patients with histamine-producing tumours should avoid histaminic drugs; treatment is with somatostatin analogues, blockade of histamine receptors, and possibly corticosteroids.[3]

Apart from such specific pharmacological therapies, antidiarrhoeals such as loperamide are sometimes helpful in controlling diarrhoea. Supplementation with vitamin B substances is advisable to prevent pellagra. It is also important to avoid provocative factors such as stress, alcohol, and particular foods.[3]

Pancreatic endocrine tumours. Neoplasms of the pancreatic islet cells (pancreatic endocrine tumours) are uncommon compared with those of the exocrine pancreas (see Malignant Neoplasms of the Pancreas, p. 712.1). Pancreatic endocrine tumours, whether benign or malignant, often secrete clinically significant amounts of hormone; the hormone secreted, and hence the resultant clinical syndrome, depends on which of the several types of hormone-secreting islet cells is the origin of the tumour.[2] Primary **therapy** for solitary pancreatic endocrine tumours is surgical resection;[2] metastatic tumours may require a combination of symptomatic drug therapy, chemotherapy, radiotherapy, and surgical debulking. As for carcinoid tumours, somatostatin analogues such as octreotide or lanreotide are used to control symptomatic disease.[1,2] For those who present with significant tumour burden, or with disease progression, options include everolimus or sunitinib, which have been found to improve progression-free survival, or cytotoxic chemotherapy.[2] The most frequently used regimens involve combinations of streptozocin, doxorubicin, fluorouracil, and dacarbazine.[1,2,7] Capecitabine and temozolomide have also been used.[2] Hepatic regional therapy, including arterial embolisation or chemoembolisation, is used for patients who are not surgical candidates.[2]

Symptoms of hormonal excess should be treated, before surgery and/or after resection if needed; therapies depend on the tumour type,[2] and are used in cases refractory to somatostatin analogues, or in combination with them.[3]

- Up to 90% of **insulinomas** are benign[2,6] and do not metastasise. Only about half of these tumours have somatostatin type II receptors and are thus less sensitive to treatment with somatostatin analogues.[1,3] Excessive insulin secretion results in hypoglycaemia; glucose concentrations can be stabilised by diet and/or diazoxide.[1-3] Glucose infusions may be needed.[1]
- Most **glucagonomas**, which secrete glucagon, are malignant, and over 80% have metastases at presentation.[2,3] Common symptoms include a characteristic rash (necrolytic migratory erythema), diabetes mellitus, weight loss, and diarrhoea. Patients should be stabilised with intravenous fluids, octreotide, and zinc.[2,3]
- Another well-characterised syndrome results from tumours which release vasoactive intestinal polypeptide (VIP). Such **VIPomas** result in profound secretory diarrhoea, with consequent hypokalaemia and acidosis;[2,3] the syndrome is sometimes known as pancreatic cholera. Metabolic imbalances should be corrected by fluid and electrolyte supplementation.[1,2] Somatostatin analogues such as octreotide are used for chronic control of the diarrhoea;[1-3] other antidiarrhoeals are seldom effective, although glucocorticosteroids can be used for acute exacerbations.[3]
- Of the other pancreatic endocrine tumours **gastrinoma** is the commonest: it results in Zollinger-Ellison syndrome, for which proton pump inhibitors are the treatment of choice. For further information on the treatment of Zollinger-Ellison syndrome see p. 1817.3. Rarer malignant tumours include **somatostatinoma** (which secretes somatostatin) and **PPoma** (which secretes pancreatic polypeptide).[2,3]

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Retinoblastoma. Retinoblastoma is the most common eye tumour in children and accounts for about 3% of all childhood malignancies in the UK (for other malignant neoplasms of the eye, see p. 705.1). In about 60% of cases the tumour is sporadic and non-hereditary, producing a unilateral, unifocal lesion. In other cases there is an inherited abnormal tumour suppressor gene (RB1 gene mutation): these tumours are typically bilateral and are sometimes associated with an intracranial neuroblastic tumour or pinealoblastoma (trilateral retinoblastoma). In addition, patients with the hereditary form are at very high risk of secondary primary malignancies, particularly osteosarcoma and soft tissue sarcomas. Onset after age 5 is rare, but retinoblastomas are occasionally reported in adults. The most common manifestations of retinoblastoma are leukocoria (white pupil) and strabismus (squint). In intra-ocular disease, the tumour is confined to the eye; the majority of patients with unilateral disease present with advanced intra-ocular disease. Nevertheless, 5-year disease-free survival after treatment in these patients is over 90% in developed countries. Extra-ocular retinoblastoma is an advanced stage of the disease where the tumour has spread into the tissues around the eye (orbital invasion) or beyond the optic nerve with metastatic spread to the CNS and beyond. Extra-ocular disease is more prevalent in developing countries due to delayed diagnosis. The 5-year survival rate is less than 10% despite treatment. Management of retinoblastoma is individualised with consideration of the size and location of the tumour, laterality of the disease, age, risk of metastases, and stage.

The aim of treatment for **intra-ocular** retinoblastoma is to cure the disease, and to preserve as much vision as possible.[1,2] In patients with unilateral tumours, enucleation (removal of the eye) is the standard primary treatment when there is no expectation of useful vision (e.g. extensive disease within the eye).[3] The role of *adjuvant* treatment is controversial; adjuvant chemotherapy regimens include carboplatin plus etoposide, or vincristine, cyclophosphamide, and doxorubicin. Radiotherapy has also been used in cases of incomplete resection.[4] In bilateral retinoblastoma, standard treatment was enucleation of the advanced eye and external beam radiation therapy in the less advanced eye. However, there is increasing use of therapies to preserve the eye and to reduce the use of external beam radiotherapy which further increases the risk of secondary malignancies.[1,4,5] These include local treatments such as laser therapy, cryotherapy, thermotherapy, and plaque radiotherapy (brachytherapy).[1,3,4] Intravenous *neoadjuvant* chemotherapy may be given before local treatment to reduce tumour size (chemoreduction); regimens usually include carboplatin, etoposide (or teniposide), and vincristine.[1,3-5] Ciclosporin has also been included to overcome multidrug resistance due to P-glycoprotein.[3,5]

Chemothermotherapy (chemotherapy and thermotherapy used within hours of each other) may be useful for larger tumours, or for small tumours adjacent to the fovea or optic nerve.[3] *Local delivery* of chemotherapy directly into the periorbital tissues (focal chemotherapy) has also been investigated;[1,4,5] subconjunctival carboplatin may be useful in cases of vitreous seeding,[4] but local toxicity may be a problem and some reserve periocular injection for advanced intra-ocular disease that has not responded to multiple cycles of systemic chemotherapy.[5]

There is no standard treatment for **extra-ocular** retinoblastoma.[1,6] Patients with regional disease without overt metastases (micrometastatic retinoblastoma) may benefit from conventional systemic chemotherapy and external beam radiotherapy.[3,6] Patients with orbital extension may be treated with enucleation, radiotherapy, and intensive chemotherapy.[1] Regimens typically include cyclophosphamide, doxorubicin, and vincristine, and may include carboplatin and etoposide.[3,6] Intrathecal methotrexate and cranial irradiation may be added for CNS involvement or trilateral retinoblastoma.[6] Metastatic disease may be treated similarly,[6] but although conventional combination chemotherapy may produce a response it is rarely curative in such advanced disease.[1,3] High-dose chemotherapy with autologous stem cell rescue may be beneficial in metastatic disease, but it has not been effective for disease involving the CNS.[1,3]

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Sarcomas. The sarcomas are tumours arising from mesodermal cells, which form the bone and connective tissue (as opposed to carcinomas, which arise from ectodermal and endodermal cells, and leukaemias and lymphomas, which arise from the bone marrow and immune system).

Sarcomas are uncommon, and vary considerably in their sites, presentation, and prognosis. The primary malignancies of bone include osteosarcoma and Ewing's sarcoma, which most often occur in older children and adolescents, and chondrosarcoma which is most common in later life. Soft tissue sarcomas include those of fibrous tissue (fibrosarcoma), skeletal muscle (rhabdomyosarcoma), smooth muscle (leiomyosarcoma), adipose tissue (liposarcoma), and blood vessels (a group which includes Kaposi's sarcoma).

BONE SARCOMA. The commonest primary malignant tumour of bone is **osteosarcoma** (osteogenic sarcoma). It is composed of malignant osteoblasts, which form an osteoid matrix within which new bone formation may occur. Most osteosarcomas are aggressive high-grade malignancies that destroy overlying cortical bone and invade adjacent soft tissue, as well as spreading along the medulla. Metastasis, almost exclusively via the vascular system to the lungs and other distant sites, is usual and occurs early. Most patients present between 15 and 25 years of age.

Therapy is multimodal. Complete surgical resection is primarily used, with an increasing trend to more conservative, limb-sparing operations rather than amputation. Adjuvant chemotherapy is an important component of therapy, as metastasis of the tumour is common.[1-3] Neoadjuvant chemotherapy is also often given before surgery to attack micrometastases, shrink the primary tumour and enable evaluation of the tumour response.[2,4,5] Combinations of cisplatin, doxorubicin (or epirubicin),

ifosfamide, and high-dose methotrexate are recommended.[1-6] Aggressive treatment regimens can result in long-term relapse-free survival rates of 70%, although patients with overt metastatic disease at presentation have a poorer prognosis.[1,7] Osteosarcomas are relatively resistant to radiation therapy;[1,3] however, for unresectable high-grade osteosarcoma, radiotherapy followed by adjuvant chemotherapy is recommended.[4] Recurrent disease is treated surgically where possible. The role of second-line chemotherapy remains to be defined.[3,6,8] Regimens may include combinations of cyclophosphamide or ifosfamide, carboplatin, and etoposide. Gemcitabine, alone or with docetaxel, may also be tried. Progressive disease after second-line therapy can be treated with resection, palliative radiotherapy, or best supportive care.[4] Osteoclast-targeted therapy (such as bisphosphonates)[7] and the addition of mifamurtide to conventional chemotherapy[2,6] are under investigation.

Like osteosarcoma, **Ewing's sarcoma** is seen mainly in adolescents and older children. It is a round cell tumour that most often arises in the pelvis or the long bones of the limbs. There may be diffuse erosion of the bone and marked periosteal reaction. It spreads through the medullary cavity, and metastases to lung and other bones are common. Treatment is also multimodal.[9,10]

Initial treatment is neoadjuvant chemotherapy for several months.[1,4,6] Combinations of cyclophosphamide, ifosfamide, etoposide, doxorubicin, dactinomycin, and vincristine are recommended,[1,2,4,6,9] although the use of dactinomycin for localised disease is controversial.[1] Typically, patients are then given local therapy (surgery, radiation, or both), with additional adjuvant chemotherapy.[1,4,9,10] Ewing's sarcoma is relatively radiosensitive,[1] and unresponsive or progressive disease is best managed with radiation therapy with or without surgery, followed by chemotherapy or best supportive care.[4] The prognosis of recurrent Ewing's sarcoma is poor.[4,6,9] Salvage chemotherapy regimens are not standardised.[6,9] Combinations include ifosfamide plus etoposide with or without carboplatin, cyclophosphamide plus topotecan, temozolomide plus irinotecan, and gemcitabine plus docetaxel.[4] High-dose chemotherapy with stem cell rescue has been investigated[2,5,6] but its role has yet to be determined.[4] Targeted therapy with anti-angiogenic agents may represent a future therapeutic approach.[9]

Chemotherapy appears to have little place in the treatment of other bone sarcomas such as **chondrosarcoma**[1,4] (despite some reports of efficacy[4]) or **osteoclastoma** (giant cell tumours of bone);[1] it has been used in high-grade **fibrosarcomas** and in **histiocytoma** but its value is uncertain.

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KAPOSI'S SARCOMA. Kaposi's sarcoma is a tumour of endothelial or spindle cell origin. In its classical form it manifests as red or violet cutaneous lesions of the limbs in elderly men, usually of Jewish or Mediterranean ancestry. An endemic form is also seen in certain areas of Africa.[1,2] Lesions may eventually affect the whole of the skin, upper airways, gastrointestinal tract, lungs, and lymph nodes, but in general disease is only very slowly progressive, and may require no treatment. Patients given immunosuppressive therapy may be at greater risk of developing Kaposi's sarcoma, particularly if they are from ethnic groups that are susceptible to the classic or endemic forms of the disease.[1] In recent years an epidemic form of the disease has appeared in patients with disease due to HIV infection (p. 957.2).[2] HIV-associated Kaposi's sarcoma is more aggressive, with a greater tendency to disseminated and metastatic disease.

A novel herpesvirus (human herpesvirus 8, HHV8) has been implicated in the pathogenesis of Kaposi's sarcoma. HHV8 induces changes in endothelial cells that make them more susceptible to inflammatory cytokines and angiogenesis.[3] Some antivirals, such as cidofovir and to a lesser extent foscarnet and ganciclovir, have shown activity against HHV8 *in vitro*, but they have not been equally successful in treating Kaposi's sarcoma *in vivo*. Treatment with HAART has greatly reduced the occurrence of Kaposi's sarcoma in AIDS patients, and may cause regression of milder forms of the disease, but this is thought to be due to improvements in immune function rather than a direct effect on Kaposi's sarcoma.[4] The development of Kaposi's sarcoma is likely to be multifactorial, and as infection with HHV8 alone does not produce disease, and the replication of HHV8 in sarcoma cells is low, antiviral therapy alone is unlikely to be sufficient to control symptoms.[4]

Patients with classic or **endemic** Kaposi's sarcoma are often treated with surgery or radiotherapy of individual lesions.[1] Extensive or recurrent disease may be treated with vinca alkaloids, bleomycin, doxorubicin, and dacarbazine, alone or in combination.[1] Etoposide and interferon alfa have also been tried.[1] Patients with immunosuppression-associated Kaposi's sarcoma may be treated similarly to those with the classic form, or preferably by alteration of the immunosuppressive regimen if this can be done without graft loss.[1] Clinical and histological regression of cutaneous Kaposi's sarcoma has been described in a small number of renal transplant recipients when ciclosporin and mycophenolate mofetil were replaced with sirolimus.[5]

The **epidemic** form of Kaposi's sarcoma is associated with HIV infection, and seen particularly in homosexual patients. HAART may control Kaposi's sarcoma, and is considered first-line therapy,[6-8] but the response is unpredictable, so specific therapy is often needed.[1] ***Localised*** disease may be managed with cryotherapy or radiotherapy, but intralesional vinblastine, interferon alfa, and topical alitretinoin are also used.[2,3,6-9] Photodynamic therapy is also used.[2,7,8]

Systemic chemotherapy is generally reserved for patients with more ***extensive*** disease or mucosal or visceral involvement.[6,8] In patients with a CD4 cell count of 200 cells/mm^3 or above, treatment with interferon alfa plus zidovudine, has been advocated by some, but systemic chemotherapy is the treatment of choice.[1,3,4,6,7] The main combination regimens use a vinca alkaloid and bleomycin, with or without doxorubicin.[3,4] Liposomal formulations of doxorubicin and daunorubicin have produced response rates of 40 to 85%, and may be less toxic than conventional chemotherapy;[3,4,9] it has been suggested that a liposomal anthracycline is the drug of choice in extensive disease.[1,3,6-8] Paclitaxel is also used as a single agent in advanced disease.[3,4,8,9] However, although highly effective, doses may need to be reduced if given to patients taking HAART because of the risk of drug interactions.[6,8] Although data are limited, docetaxel may be a reasonable alternative.[8] Some response has also been reported for oral etoposide.[1]

Control of Kaposi's sarcoma has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but tumour regression ceased and regrowth occurred when dosage was reduced or withdrawn.[10] Further reports of intralesional or systemic use have included partial remissions and disease stabilisation, as well as no effect or disease progression. The reasons for these contradictory results are unclear, but they may be due to variability in chorionic gonadotrophin preparations, which contain a mixture of biological contaminants. A cytotoxic ribonuclease and the degradation product of the β-hCG subunit have been proposed as active contaminants against Kaposi's sarcoma, but other contaminants may stimulate the tumour.[11] Other lines of investigation include the use of sulfated polysaccharide peptidoglycans, imatinib, the tyrosine kinase inhibitors sorafenib and sunitinib, other inhibitors of angiogenesis including thalidomide, and the retinoids.[1,2,6-9]

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SOFT-TISSUE SARCOMA. Soft-tissue sarcomas are a varied group of malignant tumours that originate from mesenchymal stem cells residing in muscle, fat, or connective tissue,[1,2] and whose subtypes vary in terms of prognosis and response to different treatments.[3] The majority of soft-tissue sarcomas occur in the limb or limb girdle; some occur within the abdomen (retroperitoneal), in the head or neck, or in the gastrointestinal tract.[4,5] Patients have a 5-year survival rate of about 50 to 60%;[4] survival in those with extremity sarcomas is better than that in patients with retroperitoneal sarcomas.[2] Tumours often metastasise to the lung; those arising in the abdomen metastasise to the liver and peritoneum.[4]

Rhabdomyosarcoma is the commonest soft-tissue sarcoma in childhood, and is thought to arise from progenitor cells for skeletal muscle. The most frequent sites are the head and neck, genito-urinary tract, and extremities. Some genetic disorders are associated with rhabdomyosarcoma.[6,7] All patients are presumed to have micrometastatic disease at diagnosis; histologically the most common types are embryonal, which occurs at an earlier age, and alveolar, which is more common in adolescents.[7]

Surgery is the primary ***therapy*** for soft-tissue sarcomas,[1,2,4,8,9] and may be curative for *localised disease*.[5,10,11] Radiotherapy, as external-beam therapy or brachytherapy, may be given with surgery, or alone if surgery is inappropriate or declined by the patient.[5] Radiation may be given pre-operatively, during surgery, or postoperatively;[1,9] optimal timing is unclear.[5,8] Similar rates of local control and progression-free survival have been reported for pre- and postoperative radiotherapy, although preoperative treatment has been associated with a greater incidence of wound complications, especially in lower extremity tumours.[4] Postoperative radiation can cause acute and delayed bowel toxicity in those with retroperitoneal tumours, and significant toxicity has occurred with the use of brachytherapy, especially when used in the upper abdomen.[2]

Surgery and/or radiotherapy may be combined with chemotherapy. Pre-operative chemotherapy may allow for more efficient resection of the tumour.[1,8] The use of postoperative chemotherapy is controversial,[5,8,9] except for some tumours such as extraosseous Ewing's sarcoma or rhabdomyosarcoma. For these tumours, combinations of vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, or etoposide form the basis of most regimens.[5-8,11]

For those with *unresectable* or *metastatic* disease, chemotherapy may be used; ifosfamide and doxorubicin are routinely used in this setting.[5,9] These may be used as single agents or in combination; other acceptable single agent choices are dacarbazine, epirubicin, gemcitabine, temozolomide, or liposomal doxorubicin.[4] Data support the use of adjuvant doxorubicin-based chemotherapy to improve disease-free survival;[12] however, overall survival is not improved. For palliative treatment in advanced soft-tissue sarcoma, a systematic review[13] concluded that combination chemotherapy did not significantly increase survival rates compared with single-agent doxorubicin. A retrospective analysis[14] found that, in patients with high-risk disease, clinical benefits of doxorubicin-based chemotherapy were not sustained beyond 1 year. There is no consensus on the best second-line chemotherapy regimen for patients with metastatic disease refractory to doxorubicin-or ifosfamide-based regimens.[2,3] Dose-intensified combination regimens, with colony-stimulating factor support, have been investigated as adjuvant therapy[15] and in advanced disease;[16] although both these studies found a delay in disease progression, a beneficial effect on overall survival was only found in the former. Intensive combination chemotherapy benefited a subgroup of children with metastatic rhabdomyosarcoma and fewer than 2 unfavourable risk factors, in terms of event-free survival and overall survival. However, most patients have more than 2 risk factors; these patients should be considered for novel first-line therapies. No evidence was found for improved outcome after consolidation therapy with high-dose melphalan and autologous bone marrow or peripheral-blood stem cell rescue.[17] Response to topotecan has been reported in a study of metastatic rhabdomyosarcoma,[18] and trabectedin has shown some activity in advanced soft-tissue sarcomas.[3,5] Tasonermin and melphalan can be used together for isolated limb perfusion of unresectable soft-tissue sarcomas, but severe toxicity may limit use of this regimen. Potential salvage therapy options after failure of first-line therapy include paclitaxel, docetaxel, gemcitabine, trofosfamide, temozolomide, and various combinations thereof.[3]

The **gastrointestinal stromal tumours** (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel.[4,8,19] Symptoms may include abdominal pain, anorexia, weight loss, haemorrhage, changes in bowel movements, bowel obstruction, or perforation. Patients with liver metastases may have oedema of the lower extremity, ascites, or jaundice.[20] Spread to the lungs and other locations is seen only in advanced cases.[4]

Continued on p. 726.

Table 1. Common chemotherapy regimens for malignant disease.

Regimen	Drugs and Administration	Cycle	Typically used for	References
ABCM	Doxorubicin 30 mg/m^2 iv day 1; carmustine 30 mg/m^2 iv day 1; cyclophosphamide 100 mg/m^2 oral days 22–25; and melphalan 6 mg/m^2 oral days 22–25.	42 days	Multiple myeloma	1
ABVD	Doxorubicin 25 mg/m^2 iv days 1, 15; bleomycin 10 000 IU/m^2 iv[(b)] days 1, 15; vinblastine 6 mg/m^2 iv days 1, 15; and dacarbazine 375 mg/m^2 iv days 1, 15.	28 days	Lymphomas	2, 3
AC	Doxorubicin 60 mg/m^2 iv day 1 and cyclophosphamide 600 mg/m^2 iv day 1.	21 days (for 4 cycles; some studies used up to 8 cycles)	Breast cancer	4–6
AC + paclitaxel	As above, then followed by paclitaxel 175 mg/m^2 iv day 1.	21 days (further 4 cycles)	Breast cancer	7
AC + trastuzumab	Doxorubicin 60 mg/m^2 iv day 1; cyclophosphamide 600 mg/m^2 iv day 1; and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	21 days (for 6 cycles)	Breast cancer (HER2 overexpressing)	8
ACE	Doxorubicin 45 mg/m^2 iv day 1; cyclophosphamide 1 g/m^2 iv day 1; and etoposide 50 mg/m^2 iv days 1–5.	21 days	Small cell lung cancer	9
AT	Doxorubicin 60 mg/m^2 iv day 1 and paclitaxel 200 mg/m^2 iv day 1.	21 days (for 4 cycles)	Breast cancer	4
AT	Doxorubicin 50 mg/m^2 iv day 1 and docetaxel 75 mg/m^2 iv day 1.	21 days (for up to 8 cycles)	Breast cancer (metastatic)	5
BEAM (Mini-BEAM)	Carmustine 60 mg/m^2 iv day 1; etoposide 75 mg/m^2 iv days 2–5; cytarabine 100 mg/m^2 twice daily iv days 2–5; and melphalan 30 mg/m^2 iv day 6.	usually 28 to 42 days	Lymphomas (salvage)	10
BEP	Bleomycin 30 000 IU iv[(b)] days 2, 9, 16; etoposide 100 mg/m^2 iv days 1–5; and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Testicular cancer	11
CAF	Cyclophosphamide 500 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and fluorouracil 500 mg/m^2 iv day 1.	21 days	Breast cancer	12
CAP	Cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and prednisone 40 mg/m^2 oral days 1–5.	28 days	Chronic lymphocytic leukaemia	13
CAP	Cyclophosphamide 500 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and cisplatin 50 mg/m^2 iv day 1 (these doses are optimised from the original 600 mg/m^2, 45 mg/m^2, and 50 mg/m^2 respectively).	21 days (for 6 cycles)	Ovarian cancer	14, 15
CAV	Cyclophosphamide 900 mg/m^2 iv day 1; doxorubicin 45 mg/m^2 iv day 1; and vincristine 2 mg iv day 1.	21 days (for 6 cycles)	Small cell lung cancer	16
CHOP	Cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 (max. 2 mg) iv day 1; and prednisone 100 mg oral days 1–5.	21 days (for 6 to 8 cycles)	Lymphomas, chronic lymphocytic leukaemia	17, 18
CMF	Cyclophosphamide 100 mg/m^2 oral days 1–14; methotrexate 40 mg/m^2 iv days 1, 8; and fluorouracil 600 mg/m^2 iv days 1, 8.	28 days	Breast cancer	6, 19

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
CMF	Cyclophosphamide 600 mg/m^2 iv day 1; methotrexate 40 mg/m^2 iv day 1; and fluorouracil 600 mg/m^2 iv day 1.	21 days	Breast cancer	20
CMF	Cyclophosphamide 750 mg/m^2 iv day 1; methotrexate 40 mg/m^2 iv days 1, 8; and fluorouracil 600 mg/m^2 iv days 1, 8.	28 days	Breast cancer	6
CMV	Cisplatin 100 mg/m^2 iv day 2; methotrexate 30 mg/m^2 iv days 1, 8; and vinblastine 4 mg/m^2 iv days 1, 8.	21 days	Bladder cancer	21
COP (CVP)	Cyclophosphamide 800 mg/m^2 iv day 1; vincristine 2 mg iv day 1; and prednisone 60 mg/m^2 oral days 1–5, then tapered over days 6–8.	21 days (for 6 cycles)	Lymphomas (the original report of this regimen used a 14-day cycle)	22
CP	Cisplatin 100 mg/m^2 iv day 1 and cyclophosphamide 600 mg/m^2 iv day 1 *or* carboplatin 300 mg/m^2 iv day1 and cyclophosphamide 600 mg/m^2 iv day 1.	28 days (for 6 cycles)	Ovarian cancer	23
CT	Cisplatin 50 mg/m^2 iv day 1; topotecan 750 micrograms/m^2 iv days 1–3.	21 days	Cervical cancer	72
CYVADIC	Cyclophosphamide 500 mg/m^2 iv day 1; vincristine 1.5 mg/m^2 iv[(a)] days 1, 5; doxorubicin 50 mg/m^2 iv day 1; and dacarbazine 250 mg/m^2 iv days 1–5.	21 days	Sarcoma (alternative versions of this regimen using vincristine on day 1 only have also been reported)	24
Dartmouth regimen	Dacarbazine 220 mg/m^2 iv days 1–3, 22–24; cisplatin 25 mg/m^2 iv days 1–3, 22–24; carmustine 150 mg/m^2 iv day 1; and tamoxifen 10 mg oral twice daily.	42 days	Melanoma (metastatic)	25, 26
DCF	Docetaxel 75 mg/m^2 iv day 1; cisplatin 75 mg/m^2 iv day 1; fluorouracil 750 mg/m^2 continuous iv days 1–5.	21 days	Gastric cancer	75
DHAP	Dexamethasone 40 mg oral or iv days 1–4; cytarabine 2 g/m^2 iv over 3 hrs, repeated after 12 hrs, day 2; and cisplatin 100 mg/m^2 iv over 24 hrs, day 1.	21–28 days	Lymphomas (salvage)	27
EAP	Etoposide 120 mg/m^2 iv days 4–6; doxorubicin 20 mg/m^2 iv days 1, 7; and cisplatin 40 mg/m^2 iv days 2, 8.	21–28 days	Stomach cancer	28, 29
EC	Etoposide 100 mg/m^2 iv days 1–3 and carboplatin 450 mg/m^2 iv day 1.	28 days	Small cell lung cancer	30
EC	Etoposide 100 mg/m^2 iv days 1–3 and carboplatin 325 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	31
ECF	Epirubicin 50 mg/m^2 iv day 1; cisplatin 60 mg/m^2 iv day 1; and fluorouracil 200 mg/m^2 daily continuous iv.	21 days (for up to 8 cycles)	Stomach cancer	32
EDAP	Etoposide 100–200 mg/m^2 continuous iv, days 1–4; dexamethasone 40 mg oral or iv days 1–5; cytarabine 1 g/m^2 iv day 5; and cisplatin 20 mg/m^2 continuous iv, days 1–4.	21–28 days	Multiple myeloma (salvage), lymphomas	33

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
EMA-CO (or EMA-EP)	Etoposide 100 mg/m^2 iv days 1, 2; methotrexate 300 mg/m^2 iv over 12 hrs, day 1; folinic acid 15 mg oral or im, twice daily for 4 doses, starting day 2; and dactinomycin 500 micrograms iv days 1, 2. *with* cyclophosphamide 600 mg/m^2 iv day 8 and vincristine 1 mg/m^2 iv[(a)] day 8. *or* etoposide 150 mg/m^2 iv day 8 and cisplatin 75 mg/m^2 iv day 8.	14 days	Gestational trophoblastic tumours	34
EOX	Epirubicin 50 mg/m^2 iv day 1; oxaliplatin 130 mg/m^2 iv day 1; capecitabine 1.25 g/m^2 oral days 1–21.	21 days	Oesophagogastric cancer	74
E P (PE)	Etoposide 80 mg/m^2 iv days 1–3 and cisplatin 80 mg/m^2 iv day 1.	21 days	Small cell lung cancer (standard dose – other versions exist)	35
EP (PE)	Etoposide 80 mg/m^2 iv days 1–5 and cisplatin 27 mg/m^2 iv days 1–5.	21 days	Small cell lung cancer (high dose)	35
E P (PE)	Etoposide 100 mg/m^2 iv day 1, *then* 200 mg/m^2 oral days 2–4 and cisplatin 75 mg/m^2 iv day 1.	21 days	Small cell lung cancer	36
EPOCH	Etoposide 50 mg/m^2 continuous iv days 1–4; vincristine 400 micrograms/m^2 continuous iv[(a)] days 1–4; doxorubicin 10 mg/m^2 continuous iv days 1–4; cyclophosphamide 750 mg/m^2 iv day 5; and prednisone 60 mg/m^2 oral days 1–5.	21 days	Lymphomas (salvage)	37
ESHAP	Etoposide 40 mg/m^2 iv days 1–4; methylprednisolone 250–500 mg iv days 1–5; cisplatin 25 mg/m^2 continuous iv days 1–4; and cytarabine 2 g/m^2 iv day 5.	21–28 days (for up to 8 cycles)	Lymphomas (salvage)	38
FAM	Fluorouracil 600 mg/m^2 iv days 1, 8, 29, 36; doxorubicin 30 mg/m^2 iv days 1, 29; and mitomycin 10 mg/m^2 iv day 1.	56 days	Stomach cancer, pancreatic cancer	39–41
FAMTX	Fluorouracil 1.5 g/m^2 iv day 1; doxorubicin 30 mg/m^2 iv day 15; methotrexate 1.5 g/m^2 iv day 1, 1 hour before fluorouracil; and folinic acid 15 mg/m^2 oral every 6 hrs for 3 days, starting 24 hrs after methotrexate.	28 days	Stomach cancer	29, 32
FOLFIRI	Irinotecan 180 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv day 1; fluorouracil 400 mg/m^2 iv bolus day 1, then 2.4 g/m^2 continuous iv infusion (increased to 3 g/m^2 from cycle 3 if tolerated) over 46 hours.	14 days	Colorectal cancer	69
FOLFOX4	Oxaliplatin 85 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv days 1, 2; fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2.	14 days	Colorectal cancer (in addition to FOLFOX6, below, other variants of the FOLFOX regimen exist; combination with bevacizumab or cetuximab is also being tried)	70
FOLFOX6	Oxaliplatin 100 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv day 1; fluorouracil 400 mg/m^2 iv bolus day 1, then 2.4 g/m^2 continuous iv infusion (increased to 3 g/m^2 from cycle 3 if tolerated) over 46 hours.	14 days	Colorectal cancer	69
5FU/Folinic acid	Fluorouracil 370 mg/m^2 iv days 1–5 and folinic acid 200 mg/m^2 iv days 1–5.	28–35 days	Colorectal cancer	42

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
5FU/Folinic acid (Mayo regimen, Poon regimen)	Fluorouracil 425 mg/m^2 iv days 1–5 and folinic acid 20 mg/m^2 iv day 1–5.	28–35 days	Stomach cancer, colorectal cancer	42, 43
5FU/Folinic acid (de Gramont regimen)	Fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2 and folinic acid 200 mg/m^2 iv days 1, 2.	14 days	Colorectal cancer	44
Gemcitabine + cisplatin	Gemcitabine 1 g/m^2 iv days 1, 8, 15 and cisplatin 70 mg/m^2 iv day 2.	28 days	Bladder cancer (metastatic)	45
Hyper-CVAD	*Course A:* Cyclophosphamide 300 mg/m^2 iv every 12 hrs, days 1–3; doxorubicin 50 mg/m^2 iv day 4; vincristine 2 mg iv days 4, 11; and dexamethasone 40 mg iv or oral, days 1–4, 11–14. *CNS prophylaxis* Methotrexate 12 mg intrathecal, day 2 and cytarabine 100 mg intrathecal, day 8. *Course B:* Methotrexate 200 mg/m^2 iv over 2 hrs, then 800 mg/m^2 iv over 24 hrs, day 1; folinic acid 15 mg iv every 6 hrs for 8 doses, from 24 hrs after methotrexate (increased to 50 mg iv every 6 hrs if methotrexate levels are high); methylprednisolone 50 mg iv every 12 hrs, days 1–3; and cytarabine 3 g/m^2 every 12 hrs, days 2, 3.	4 cycles of A alternated with 4 cycles of B, given over as short a period as possible; the number of A cycles in which CNS prophylaxis is given varies with expected risk of CNS disease	Lymphomas, adult acute lymphoblastic leukaemia (some variants of this regimen exist, including the substitution of daunorubicin 60 mg/m^2 for doxorubicin in course A, the omission of methylprednisolone and addition of oral bicarbonate in course B, and simplification of methotrexate and folinic acid dosing; mesna, which was given in course A of the original regimen, is usually omitted)	48
ICE (ICbE)	Ifosfamide 5 g/m^2 iv over 24 hrs, day 1 (with mesna); carboplatin 400 mg/m^2 iv day 1; and etoposide 100 mg/m^2 iv days 1–3.	28 days (for 6 cycles)	Small cell lung cancer	46
IFL (Douillard 1-week regimen)	Irinotecan 80 mg/m^2 iv, day 1; fluorouracil 2.3 g/m^2 continuous iv infusion, day 1; folinic acid 500 mg/m^2 iv, day 1.	7 days	Colorectal cancer	71
IFL (Douillard 2-week regimen)	Irinotecan 180 mg/m^2 iv, day 1; fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2; folinic acid 200 mg/m^2 iv, days 1, 2.	14 days	Colorectal cancer	71
IFL (Saltz regimen)	Irinotecan 125 mg/m^2 iv; fluorouracil 500 mg/m^2 iv; and folinic acid 20 mg/m^2 iv all once a week for 4 weeks.	42 days	Colorectal cancer	47
M2	Vincristine 30 micrograms/kg iv[(a)] day 1; carmustine 500 micrograms/kg iv day 1; cyclophosphamide 10 mg/kg iv day 1; melphalan 250 micrograms/kg oral days 1–4 *or* 100 micrograms/kg oral days 1–7 *or* 1–10; and prednisone 1 mg/kg oral, days 1–7, then taper and discontinue by day 21 unless hypercalcaemia or bone disease persist.	35 days	Multiple myeloma	49
MACOP-B	Methotrexate 400 mg/m^2 iv days 8, 36, 64 (as 100 mg/m^2 iv bolus, then 300 mg/m^2 iv over 4 hrs); folinic acid 15 mg oral every 6 hrs for 6 doses, from 24 hrs after methotrexate; doxorubicin 50 mg/m^2 iv days 1, 15, 29, 43, 57, 71; cyclophosphamide 350 mg/m^2 iv days 1, 15, 29, 43, 57, 71; vincristine 1.4 mg/m^2 iv[(a)] days 8, 22, 36, 50, 64, 78; bleomycin 10 000 IU/m^2 iv[(b)] days 22, 50, 78; and prednisone 75 mg oral, daily for 10 weeks then tapered over 15 days.	12 weeks	Lymphomas	50
MCF	Mitomycin 7 mg/m^2 (max 14 mg) iv day 1; cisplatin 60 mg/m^2 iv days 1, 22; fluorouracil 300 mg/m^2 daily continuous iv.	42 days	Oesophagogastric cancer	76

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Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
MIC	Mitomycin 6 mg/m^2 iv day 2; ifosfamide 3 g/m^2 iv day 2; and cisplatin 120 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	51
MIC	Mitomycin 6 mg/m^2 i v day 1; ifosfamide 3 g/m^2 iv day 1; and cisplatin 50 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	52
MOPP	Chlormethine 6 mg/m^2 iv days 1, 8; vincristine 1.4 mg/m^2 (max. 2 mg), days 1, 8; procarbazine 100 mg/m^2 oral days 1–14; and prednisone 40 mg/m^2 oral days 1–14, cycles 1, 4.	28 days (for 6 cycles)	Lymphomas, Hodgkin's disease	3, 53
M-VAC	Methotrexate 30 mg/m^2 iv days 1, 15, 22; vinblastine 3 mg/m^2 iv days 2, 15, 22; doxorubicin 30 mg/m^2 iv day 2; and cisplatin 70 mg/m^2 iv day 2.	usually 28 days	Bladder cancer	45, 54, 55
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vinblastine 4 mg/m^2 iv day 1, cycle 1 2 mg/m^2 iv day 8, cycle 1 4.5 mg/m^2 iv days 15, 22, cycle 1 4.5 mg/m^2 iv days 1, 15, cycle 2 and later; and cisplatin 120 mg/m^2 iv day 1	28 days	Non-small cell lung cancer (neoadjuvant)	56
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vindesine 3 mg/m^2 iv days 1, 8, 15, 22, day 1 of cycle 2, then every 2 weeks until the 15th week; and cisplatin 120 mg/m^2 iv day 1, for 3 cycles.	28 days	Non-small cell lung cancer (neoadjuvant)	56, 57
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vinorelbine 25 mg/m^2 iv once a week for 16 weeks; and cisplatin 120 mg/m^2 iv day 1, for 3 cycles.	28 days	Non-small cell lung cancer (neoadjuvant)	57
PAC	Cisplatin 50 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and cyclophosphamide 500 mg/m^2 iv day 1.	21 days (for up to 8 cycles)	Thymoma	58
Paclitaxel and carboplatin	Paclitaxel 175 mg/m^2 iv day 1 and carboplatin – adjust dose to AUC of 7.5 mg/mL/minute by Calvert formula, iv day 1.	21 days (for 6 cycles)	Ovarian cancer	59
Paclitaxel and cisplatin	Paclitaxel 135 mg/m^2 continuous iv over 24 hrs, day 1 and cisplatin 75 mg/m^2 iv day 1.	21 days (for 6 cycles)	Ovarian cancer	60
Paclitaxel (standard) and trastuzumab	Paclitaxel 175 mg/m^2 iv on day 1 and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	21 days	Breast cancer (HER2 overexpressing)	8
Paclitaxel (weekly) and trastuzumab	Paclitaxel 90 mg/m^2 iv on day 1 and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	7 days	Breast cancer (HER2 overexpressing)	61
PCV	Procarbazine 60 mg/m^2 oral days 8–21; lomustine 110 mg/m^2 oral day 1; and vincristine 1.4 mg/m^2 iv$^{(a)}$ days 8, 29.	42–56 days	Gliomas (adjuvant)	62
PE	*See* EP			

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Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
ProMACE-CytaBOM	Prednisone 60 mg/m^2 oral days 1–14; doxorubicin 25 mg/m^2 iv day 1; cyclophosphamide 650 mg/m^2 iv day 1; etoposide 120 mg/m^2 iv day 1; cytarabine 300 mg/m^2 iv day 8; bleomycin 5000 IU/m^2 iv[(b)] day 8; vincristine 1.4 mg/m^2 iv[(a)] day 8; methotrexate 120 mg/m^2 iv day 8; and folinic acid 25 mg/m^2 oral every 6 hrs for 4 doses, from 24 hrs after methotrexate.	21 days	Lymphomas	63
PVB	See VBP			
SMF	Streptozocin 1 g/m^2 iv days 1, 8, 29, 36; mitomycin 10 mg/m^2 iv day 1; and fluorouracil 600 mg/m^2 iv days 1, 8, 29, 36.	56 days	Pancreatic cancer	41
Stanford V regimen	Doxorubicin 25 mg/m^2 iv days 1, 15; vinblastine 6 mg/m^2 iv days 1, 15; chlormethine 6 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 iv (max 2mg) days 8, 22; bleomycin 5000 IU/m^2 iv[(b)] days 8, 22; etoposide 60 mg/m^2 iv days 15, 16; prednisone 40 mg/m^2 oral on alternate days for 10 weeks then tapered by 10 mg on alternate days.	28 days (for 3 cycles)	Hodgkin's disease	64
TAP	Doxorubicin 45 mg/m^2 iv day 1; cisplatin 50 mg/m^2 iv day 1; paclitaxel 160 mg/m^2 iv day 2.	21 days[(c)] (up to 7 cycles)	Endometrial cancer	73
VAD	Vincristine 400 micrograms iv days 1–4; doxorubicin 9 mg/m^2 iv days 1–4; and dexamethasone 40 mg oral days 1–4, 9–12, 17–20.	28 days (usually for 4 cycles)	Multiple myeloma	65
VBAP	Vincristine 1 mg iv day 1; carmustine 30 mg/m^2 iv day 1; doxorubicin 30 mg/m^2 iv day 1; and prednisone 60 mg/m^2 oral or parenteral (may be rounded to 100 mg oral) days 1–4.	21 or 28 days	Multiple myeloma	66, 67
VBP	Vinblastine 150 micrograms/kg iv days 1, 2; bleomycin 30 000 IU iv[(b)] days 2, 9, 16; and cisplatin 20 mg/m^2 iv days 1–5.	21 days	Germ-cell (ovarian, testicular) cancer	11
VCMP	Vincristine 1 mg iv day 1; melphalan 9 mg/m^2 oral days 1–4; cyclophosphamide 500 mg/m^2 iv day 1; and prednisone 60 mg/m^2 oral or parenteral, days 1–4.	28 days	Multiple myeloma	67
VeIP	Vinblastine 110 micrograms/kg iv days 1, 2; ifosfamide 1.2 g/m^2 iv days 1–5 (with mesna); and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Germ-cell (especially testicular) cancer	68
VIP	Etoposide 75mg/m^2 iv days 1–5; ifosfamide 1.2 g/m^2 iv days 1–5 (with mesna); and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Germ-cell (especially testicular) cancer	68

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(a) Although not always reflected in the original papers it is now generally accepted that the total dose of vincristine should not exceed 2 mg, in order to minimise neurotoxicity

(b) Doses of bleomycin have been given in international units (IU) in this table, but doses in the original papers may be quoted in mg-potency or USP units. One mg-potency or one USP unit is equivalent to 1000 international units

(c) This regimen is invariably given with haematological support using subcutaneous filgrastim on days 3–12

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Surgery is used for localised, resectable disease arising in the gastrointestinal tract, although this does not routinely cure GISTs; median time to recurrence after resection is about 2 years. Imatinib produces durable clinical benefit and objective responses in most patients with GISTS, including those with metastatic or unresectable disease. If the tumour responds to imatinib, surgical resection may be indicated. In patients with imatinib-resistant GIST, or who experience life-threatening adverse effects such as hepatotoxicity and fluid retention with imatinib, sunitinib may be considered.[4,8,11,19,21,22] Regorafenib is an option when both imatinib and sunitinib have failed.

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Adverse Effects

The acute effects of antineoplastic drugs often include nausea and vomiting, sometimes extremely severe. In addition, many of these compounds are irritant or vesicant, and produce local pain, irritation, and inflammation at the administration site; extravasation may lead to ulceration and necrosis. Hypersensitivity reactions may also occur.

Many of the adverse effects of antineoplastics are an extension of their therapeutic action, which is generally not selective for malignant cells but affects all rapidly-dividing cells: antineoplastic therapy is then made possible only by increased sensitivity or less effective recovery of malignant cells compared with normal cells, and dosage is carefully controlled and timed, and, where possible, localised, to maximise the differences.

In consequence, adverse effects may be expected from most antineoplastics in tissues where normal cell division is fairly rapid, e.g. the bone marrow, lymphoreticular tissue, gastrointestinal mucosa, skin, and gonads, as well as in the fetus. The effects may not manifest for days or weeks, depending both on the drugs used and the rate of division in the tissue concerned, and may sometimes be cumulative. Perhaps the most common serious effect, and one which has often limited the doses that can be given, is bone-marrow depression. Because of their effects on the various types of white blood cell many antineoplastics also cause profound suppression of normal immunity, and patients may be at greatly increased risk of severe and disseminated infection.

The rapid destruction of large numbers of cells during antineoplastic therapy of certain highly sensitive tumours, and the consequent release of breakdown products, may also lead to problems with hyperuricaemia and acute renal failure due to uric acid nephropathy (the 'tumour lysis syndrome').

Additionally, some drugs may have specific toxicities that are not necessarily related to their therapeutic action, such as cardiotoxicity due to anthracycline antibiotics, nephrotoxicity with cisplatin, or the effects of bleomycin on the lung. Again these can be cumulative, and may limit the total lifetime dose that can be given.

In the very long term, patients who have undergone successful antineoplastic chemotherapy may develop secondary malignancies, suggesting that antineoplastics may themselves be carcinogenic. In addition, most are potentially mutagenic and teratogenic, and use in pregnancy, particularly in the first trimester, may lead to fetal abortion, stunting, or malformation.

Carcinogenicity. There is clear evidence that some antineoplastic drugs may themselves be carcinogenic, although it is difficult to control for the possible effects of primary disease, combination chemotherapy, and combined treatment with radiotherapy.[1]

Most convincingly associated with secondary malignancies are the various **alkylating agents**[2-5] including the nitrosoureas, the topoisomerase II inhibitor **podophyllotoxin derivatives** such as etoposide and teniposide,[2,3,5,6] and the **anthracyclines**.[7] Leukaemias, particularly acute myeloid leukaemia, are the most common forms of secondary disease.[1-3] Leukaemia associated with alkylating agents usually occurs about 5 to 7 years after treatment, and is often preceded by a preleukaemic myelodysplasia.[2,3] The nitrosoureas are associated with a relatively high frequency of secondary leukaemia, and busulfan and melphalan are considered to be more leukaemogenic than cyclophosphamide.[3] Another drug that has been associated with the development of secondary leukaemia is procarbazine.[3,4,8,9] Leukaemia associated with the podophyllotoxin derivatives has a shorter latency period of 2 to 3 years, with sudden onset and no myelodysplastic phase.[2,3] There is little evidence of carcinogenicity associated with **antimetabolites** such as methotrexate, although it has been suggested that they may act as co-carcinogens.[10] Fludarabine therapy has been reported to be associated with the development of myelodysplasia and acute myeloid leukaemias,[11] although a review of the purine nucleoside analogues, cladribine and fludarabine, concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-term follow-up of patients was needed.[12] Immunosuppression caused by antimetabolites including methotrexate, cladribine, and fludarabine, may also allow the development of Epstein-Barr virus-related lymphoma.[12,13]

Solid tumours can also occur as secondary malignancies and include bladder cancer associated with cyclophosphamide used to treat non-Hodgkin's lymphoma,[4,14] and bone sarcomas, and breast and lung cancers after the use of various alkylating agents.[4,7,15] Higher doses of anthracyclines also increase the risk of sarcoma. Podophyllotoxin derivatives are associated with a greater risk of lung carcinoma, while the risk of subsequent colorectal and kidney cancer increases with **platinum** therapy.[7] Platinum derivatives such as carboplatin and cisplatin have also been found in large cohort studies[16,17] to have a dose-response relationship with the development of secondary leukaemia. **Combinations** that may also be associated with leukaemias include cisplatin with doxorubicin,[18] and other anthracycline-based regimens.[19]

Estimates of **risk** have varied very widely between studies, and have been calculated in various ways, making direct comparison impossible. Factors influencing the incidence of secondary malignancy include the use of combination chemotherapy regimens, combined treatment modalities, exposure to environmental carcinogens, predisposing genetic risk factors, ethnicity, age at time of diagnosis and treatment, gender, and spontaneous occurrence.[2,3,20]

The risk of secondary acute myeloid leukaemia appears to be associated mainly with the **cumulative dose** of antineoplastics.[2] Of patients at risk for secondary leukaemias, those with Hodgkin's disease have been most extensively studied. The cumulative 10-year incidence of secondary myeloid leukaemia has been reported to range from less than 1% up to 10%.[2,3] The highest risk is associated with the use of MOPP (chlormethine, vincristine, procarbazine, prednisone) and relative risk increases with cumulative dose of chlormethine.[2,3] Splenectomy or radiation of the spleen doubles the risk of leukaemia, as does an age of more than 45 years at the time of treatment.[2] Secondary solid tumours, such as lung cancer, in patients with Hodgkin's disease have also been attributed to the use of regimens such as MOPP.[4] The risk of secondary acute myeloid leukaemia, in patients treated with adjuvant chemotherapy for breast cancer, increases with cumulative doses of melphalan and cyclophosphamide, and high-dose regimens of doxorubicin with cyclophosphamide.[2,3] In patients treated for multiple myeloma, the increased risk of secondary leukaemia has been attributed to the prolonged use of melphalan.[2,3] Patients treated for testicular cancer appear to be at increased risk of secondary leukaemia associated with cumulative doses of podophyllotoxin derivatives (more than 2 g/m^2 etoposide), and the addition of high cisplatin doses may increase this risk.[2,3] Another review[21] of studies using etoposide or teniposide for various cancers found no relationship between the cumulative dose of these and secondary leukaemia, and suggested that other drugs used in treatment regimens had a greater effect on the development of secondary malignancy. There is growing evidence that the use of high-dose therapy with alkylating agents and/or anthracyclines, followed by autologous stem cell transplantation, is associated with an increased risk of secondary myelodysplasias and leukaemias, and a cumulative incidence of about 9% at 5 years.[2] However, it is unclear whether this is due to the high-dose therapy or to previous chemotherapy that has caused bone-marrow damage.[2,3]

Radiotherapy is an established cause of secondary malignancy. It remains unclear, however, to what extent the use of chemotherapy combined **with radiotherapy** could have an additive effect on the risk of secondary leukaemias, and how dose and treatment regimen influence this effect.[3] Similarly, the role of combined modality treatment in the development of secondary solid tumours has not been defined, even though the radiation-enhancing effect of some antineoplastics is known and used in chemoradiation regimens for this reason.[4]

In many cases the risk of secondary malignancy is far less than that of undertreating, or of failing to treat, the primary disease.[2,4] However, secondary malignancies may be more resistant to treatment and more aggressive than primary disease,[3,22] and the risk of inducing malignant neoplasia is certainly a consideration in the use of alkylating agents and podophyllotoxin derivatives to treat non-malignant disease,[3] and is an increasing challenge in the design of suitable treatment regimens for primary neoplastic disease.

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EFFECTS ON CHROMOSOMES. Visible chromosome gaps, breaks, and structural rearrangements are found in blood lymphocytes from patients who have received substantial doses of combination chemotherapy, and the changes persist for years after the end of treatment. A more sensitive, if transient, measure of genetic damage is the increased rate of sister chromatid exchange (SCE) that occurs with even quite small doses of cytotoxic drugs.[1] Evidence from

All cross-references refer to entries in Volume A

a study[2] in patients given chlorambucil suggests that as the dose increases so the capacity of the cells to cope with induced genetic damage is progressively exceeded, and thus SCE frequency reflects cumulative toxicity throughout the course of treatment.

In patients who develop acute myeloid leukaemia after alkylating agent therapy, the most common chromosomal losses involve deletions of chromosome 13, loss of the entire chromosomes 5 and 7, or deletions of part or the whole long arm of chromosomes 5 and 7. Molecular alterations of the suppressor gene p53 have also been found.[3] Balanced translocations, usually involving chromosomes 11 and 21, are associated with treatment using topoisomerase II inhibitors.[3,4]

See also under Effects on Reproductive Potential, p. 729.2.

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Effects on the bladder. Cyclophosphamide (p. 772.3) and ifosfamide (p. 806.2) are the antineoplastics most frequently associated with adverse effects on the bladder, but see also Busulfan, p. 755.2, Chlorambucil, p. 764.3, Dacarbazine, p. 776.2, and Mitomycin, p. 831.3.

Effects on the blood. *BONE-MARROW DEPRESSION.* Bone-marrow depression, or myelosuppression, is common to the majority of cytotoxic antineoplastics, and is probably the single most important dose-limiting adverse effect, although its significance has been somewhat reduced in recent years by improvements in supportive care, including the availability of colony-stimulating factors and the development of techniques such as peripheral blood stem cell transfusion.

All the cellular elements of blood (see Haematopoiesis, p. 1121.1) may be affected by antineoplastic therapy, resulting in pancytopenia, but in many cases the toxicity appears to be greater for particular cell types. In addition, white blood cells and platelets tend to have shorter half-lives in circulation than erythrocytes. Hence the most usual manifestation of bone-marrow depression is leucopenia, leading to an increased risk of infection; thrombocytopenia is also fairly common. Anaemia is somewhat less frequent, and may be associated with megaloblastic changes in the bone marrow.

The onset, duration, and severity of bone-marrow depression vary considerably with different antineoplastics. For details, see under the individual monographs. For the management of bone-marrow depression, including discussion of the appropriate thresholds for treatment, see under Treatment of Adverse Effects, p. 730.3.

See also Effects on Immune Response, p. 728.3.

Effects on body-weight. The effects of antineoplastics on the gastrointestinal tract (p. 728.1) may lead to anorexia, malabsorption, and malnutrition, and hence to weight loss. A large cohort study[1] in survivors of childhood cancer found that treatment with total body irradiation, alkylating agents, or anthracyclines was associated with being underweight in females; in males, being underweight was associated with abdominal radiotherapy, younger age at treatment, and treatment with alkylating agents or anthracyclines. Antineoplastic therapy for breast cancer has however also been associated with weight gain, sometimes dramatic.[2] Weight gain appeared to be more likely in premenopausal women, in those receiving multidrug regimens, and in those treated for longer periods of time. A study of premenopausal women found that reduced physical activity may be a contributing factor to the development of this form of weight gain.[3] A subsequent small study has suggested that adjuvant regimens based on doxorubicin and cyclophosphamide, with or without a taxane, may not be associated with significant weight gain, although patients may undergo unfavourable changes in body-mass composition.[4] Weight gain has also been noted after long-term follow-up of paediatric leukaemia patients.[1,5,6] Causes include cranial irradiation[1,7] and corticosteroid therapy,[7] although some have suggested that weight gain depends more on inherent characteristics of the patients than the treatment given.[8]

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Effects on bones and joints. Osteoporosis occurs as both an acute[1] and late[2] complication of chemotherapy, but as multicomponent regimens are used and because the pathogenesis of osteoporosis is likely to be multifactorial, it is difficult to assess the impact of individual drugs.[3] A main cause of bone loss is hypogonadism induced by irradiation, surgical gonadal ablation, hormonal therapy, or chemotherapy.[2] These form part of treatment regimens for a variety of neoplasms, including breast, prostate and testicular cancers, lymphomas, and haematological malignancies. In particular, regimens containing cyclophosphamide, chlormethine, chlorambucil, busulfan, mitomycin, or procarbazine may cause ovarian insufficiency and therefore have the potential to lead to osteoporosis in females.[2,3] Males may be somewhat protected from the effects of chemotherapy-induced hypogonadism, as the cells that produce testosterone only replicate slowly.[3] Endocrine therapies for breast cancer such as selective oestrogen-receptor modulators and aromatase inhibitors, and androgen deprivation therapy for prostate cancer can also cause bone loss.[2,4,5]

In addition, several drugs may exert direct effects on the bone. Methotrexate has been found to increase bone resorption and inhibit bone formation to produce a massive uncoupling of bone turnover.[2,3] Repeated doses of methotrexate, given as monotherapy to children with acute lymphoblastic leukaemia in remission, have been associated with pain, osteoporosis, and fractures.[6] Other drugs, including doxorubicin, have been shown to be toxic to bone in *animals*.[3] High-dose conditioning regimens used for bone marrow transplantation may have a direct dose-dependent toxicity on bone marrow osteoprogenitor cells, contributing to osteopenia.[7]

Corticosteroids are believed to cause bone loss by decreasing osteoblast activity, an effect which may be alleviated by chlorambucil. Surprisingly, corticosteroids have not been implicated in bone loss for most chemotherapy regimens, perhaps because the duration of treatment is short.[3] Nevertheless, osteoporosis and fractures have occurred in young patients with acute lymphoblastic leukaemia, treated with regimens containing high total doses of corticosteroids.[6,8,9] However, the disease itself, other chemotherapy, and radiotherapy are also likely to be contributory factors in the development of osteopenia in these patients. Osteonecrosis has also been reported with high doses of corticosteroids used in the treatment of leukaemias and solid tumours in adults and children.[8,10-12] Adolescent patients may be at increased risk because their bones are in the process of maturation.[8,10]

Indirect effects of cancer therapies may also affect bone health. These effects include hyperparathyroidism, hypovitaminosis D, hypophosphataemia, gastrointestinal complications, and hyperprolactinaemia.[2] A study in children with leukaemia has suggested that the effects of chemotherapy on gastrointestinal and renal handling of nutrients may lead to alterations in calcium and magnesium homoeostasis and hence to abnormal turnover of bone mineral.[13] Renal phosphate loss following damage to the renal tubule caused by ifosfamide can lead to osteomalacia.[2,3] Hypophosphataemia, with associated changes in bone and mineral metabolism, has been seen with tyrosine kinase inhibitors such as imatinib, sorafenib, and sunitinib.[2]

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12. Diller L, *et al*. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol* 2009; **27:** 2339–55.
13. Atkinson SA, *et al*. Mineral homeostasis and bone mass in children treated for acute lymphoblastic leukemia. *J Pediatr* 1989; **114:** 793–800.

Effects on the cardiovascular system. *THROMBOEMBOLISM.* Patients with cancer are at increased risk of thromboembolic disease, and thrombosis can be the earliest clinical sign of malignancy.[1,2] Clinical risk factors for cancer-associated venous thromboembolism include type of cancer, stage of disease, presence of comorbidities, and treatment-related factors such as hospitalisation, and use of systemic chemotherapy.[3] Deep-vein thrombosis and pulmonary embolism have been reported with a variety of chemotherapeutic regimens. Studies in patients with breast cancer have found that adjuvant chemotherapy can significantly increase the risk of venous thromboembolism.[4] An increase in venous thromboembolism, including CNS thromboses, has also been found with the use of asparaginase in the treatment of acute lymphoblastic leukaemia[4] (see also Effects on the Blood, under Asparaginase, p. 744.2). Regimens that include bevacizumab, lenalidomide, or thalidomide have also reported high rates of venous thromboembolism.[3,5] Arterial thrombosis, including acute myocardial infarction, angina, stroke, and peripheral artery thrombosis, has also been reported with various regimens.[4,5] Mechanisms proposed for the possible role of antineoplastics in these effects include activation of coagulation, suppression of anticoagulant proteins and fibrinolysis, and a direct toxic effect on vascular endothelium.[1,4]

Several reports of arterial and venous thromboembolism have implicated combinations of bleomycin with cisplatin and another drug such as a vinca alkaloid or etoposide.[6-8] Such combinations, widely used for testicular cancer, have also been implicated in producing vasospastic reactions including angina[9] and Raynaud's syndrome,[10,11] although there is no evidence of a relationship between thromboembolism and vasospasm.[6]

In men with germ cell cancer there is some evidence that those with liver metastases, or receiving high-dose dexamethasone as antiemetic therapy, are at increased risk of thromboembolic complications.[12]

Various organisations have addressed the problems of prevention and treatment of cancer-associated venous thromboembolism. Generally, unless contra-indicated, most recommend prophylactic anticoagulation for hospitalised or surgical cancer patients; low-molecular-weight or unfractionated heparin or fondaparinux may be used. Prophylaxis is not recommended for the ambulatory cancer patient, with the exception of patients with multiple myeloma given thalidomide- or lenalidomide-based regimens.[13] Treatment of venous thrombosis usually consists of low-molecular-weight or unfractionated heparin therapy and long-term secondary prophylaxis with warfarin,[14] but a multicentre, randomised study found that a low-molecular-weight heparin was more effective than an oral anticoagulant in reducing the risk of recurrent venous thromboembolism without increasing the risk of bleeding,[15] and many now recommend low-molecular-weight heparin therapy for both initial and continuing treatment of cancer patients with venous thromboembolism.[13,14] Patients with arterial thrombosis may require heparin and warfarin, or anti-platelet therapy.[16]

Thromboembolic complications may also be associated with the indwelling catheters used to provide vascular access for antineoplastic therapy.[17,18] Prophylaxis with low-dose warfarin or a low-molecular-weight heparin may reduce the risk.[18]

1. Falanga A, Donati MB. Pathogenesis of thrombosis in patients with malignancy. *Int J Hematol* 2001; **73:** 137–44.
2. Lyman GH, Khorana AA. Cancer, clots and consensus: new understanding of an old problem. *J Clin Oncol* 2009; **27:** 4821–6.
3. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol* 2009; **27:** 4839–47.
4. Lee AYY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. *Semin Thromb Hemost* 1999; **25:** 137–45.
5. Zangari M, *et al*. Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol* 2009; **27:** 4865–73.
6. Cantwell BMJ, *et al*. Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; **ii:** 1086–7.
7. Hall MR, *et al*. Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; **ii:** 1259.
8. Garstin IWH, *et al*. Arterial thrombosis after treatment with bleomycin and cisplatin. *BMJ* 1990; **300:** 1018.
9. Rodriguez J, *et al*. Angina pectoris following cisplatin, etoposide, and bleomycin in a patient with advanced testicular cancer. *Ann Pharmacother* 1995; **29:** 138–9.
10. Vogelzang NJ, *et al*. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med* 1981; **95:** 288–92.
11. Pechère M, *et al*. Fingertip necrosis during chemotherapy with bleomycin, vincristine and methotrexate for HIV-related Kaposi's sarcoma. *Br J Dermatol* 1996; **134:** 378–9.
12. Weijl NI, *et al*. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. *J Clin Oncol* 2000; **18:** 2169–78.
13. Khorana AA, *et al*. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. *J Clin Oncol* 2009; **27:** 4919–26.
14. Lee A, Levine M. Treatment of venous thromboembolism in cancer patients. *Cancer Control* 2005; **12** (suppl 1): 17–21.
15. Lee AYY, *et al*. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349:** 146–53.
16. Sutherland DE, *et al*. Thromboembolic complications of cancer: epidemiology, pathogenesis, diagnosis, and treatment. *Am J Hematol* 2003; **72:** 43–52.

17. Monreal M, Davant E. Thrombotic complications of central venous catheters in cancer patients. *Acta Haematol (Basel)* 2001; **106:** 69–72.
18. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol* 2003; **21:** 3665–75.

Effects on electrolytes. Fluid and electrolyte disturbances are common in patients with cancer.[1-4] These can be caused by the disease process, or adverse effects of treatment such as surgery, chemotherapy, antibacterials and diuretics. Mechanisms of chemotherapy-induced electrolyte disturbances include loss of appetite, gastrointestinal electrolyte loss due to vomiting and diarrhoea, impaired intestinal absorption due to mucosal damage, direct nephrotoxicity causing renal electrolyte loss, and a syndrome of inappropriate antidiuretic hormone secretion or a condition resembling it. Hypoparathyroidism, which may be a complication of neck surgery, also affects electrolyte balance and is associated with hyperphosphataemia and hypocalcaemia. As well as the acute signs and symptoms of electrolyte disturbances, changes in electrolyte homoeostasis may result in abnormal bone turnover (see Effects on Bones and Joints, p. 727.2). Release of the contents of cells destroyed by chemotherapy is well-known to be associated with hyperuricaemia, hyperphosphataemia, hyperkalaemia, and hypocalcaemia (see Tumour Lysis Syndrome, p. 730.2).

Disturbances of electrolyte homoeostasis have been reported particularly with cisplatin (p. 767.2), cyclophosphamide (p. 772.3), and ifosfamide (see Effects on the Kidneys, p. 806.3). Hypomagnesaemia has been seen with cetuximab (p. 763.3).

1. Kapoor M, Chan GZ. Fluid and electrolyte abnormalities. *Crit Care Clin* 2001; **17:** 503–29.
2. Filippatos TD, *et al*. Alterations in electrolyte equilibrium in patients with acute leukemia. *Eur J Haematol* 2005; **75:** 449–60.
3. Miltiadous G, *et al*. Causes and mechanisms of acid-base and electrolyte abnormalities in cancer patients. *Eur J Intern Med* 2008; **19:** 1–7.
4. Lameire N, *et al*. Acute renal problems in the critically ill cancer patient. *Curr Opin Crit Care* 2008; **14:** 635–46.

Effects on the gastrointestinal tract. Apart from anorexia, and nausea and vomiting (see below), many antineoplastics produce gastrointestinal disturbances, sometimes severe. Mucosal inflammation (mucositis), notably as stomatitis and sometimes proctitis, is quite common, as are mucosal cellular changes, xerostomia, impaired absorption, and diarrhoea. In some cases gastrointestinal damage may progress to ulceration, haemorrhage, and perforation. Constipation may be a problem with the vinca alkaloids.

Use with radiotherapy may increase the toxicity of some drugs on the gastrointestinal tract. The neutropenia induced by many antineoplastic regimens can also lead to secondary gastrointestinal effects, such as stomatitis and gastrointestinal inflammation, associated with infection.

References.
1. Gibson RJ, Keefe DMK. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. *Support Care Cancer* 2006; **14:** 890–900.
2. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract* 2007; **13:** 181–98.
3. Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008; **36:** 413–23.
4. Sonis ST. Regimen-related gastrointestinal toxicities in cancer patients. *Curr Opin Support Palliat Care* 2010; **4:** 26–30.

CLOSTRIDIUM DIFFICILE INFECTION. Antineoplastic therapy has occasionally been associated with the development of *Clostridium difficile*-induced gastrointestinal disease, even in the absence of concomitant antibacterial therapy.[1] Most patients had received multiple drug regimens. Methotrexate, fluorouracil, cyclophosphamide, and doxorubicin have all been associated with a number of cases but this may simply reflect the frequency of their use. A retrospective analysis[2] of a group of patients treated for acute leukaemia or receiving bone marrow transplantation found that predictive variables for *C. difficile* diarrhoea included the use of low intensity chemotherapy, but speculated that patients receiving high intensity chemotherapy may be subjected to more strict isolation and infection control procedures, thereby reducing the risk of nosocomial transmission. Another review[3] of 875 courses of myelosuppressive chemotherapy found 61 episodes of *C. difficile* diarrhoea, and that in 36% of those episodes the patients had received high-dose cytarabine. In 35 of the 61 episodes, patients had also received prior intravenous antibacterials.

For discussion of the treatment of such disease, see Antibiotic-associated Colitis, p. 183.1

1. Anand A, Glatt AE. Clostridium difficile infection associated with antineoplastic chemotherapy: a review. *Clin Infect Dis* 1993; **17:** 109–13.
2. Hornbuckle K, *et al*. Determination and validation of a predictive model for Clostridium difficile diarrhea in hospitalized oncology patients. *Ann Oncol* 1998; **9:** 307–11.
3. Gorschlüter M, *et al*. Clostridium difficile infection in patients with neutropenia. *Clin Infect Dis* 2001; **33:** 786–91.

MUCOSITIS. The suffering associated with oral mucositis is by far the worst part of treatment for many patients undergoing curative chemotherapy or bone marrow transplantation, and for those undergoing oral radiotherapy.[1-3] Apart from pain and dysphagia the ulcerated mucosa provides a portal of entry for infection; loss of weight and malnutrition can further impair immune function, and if symptoms are severe enough the treatment cycle may have to be interrupted. Before the patient starts any intensive chemotherapy or local or systemic radiotherapy the oral cavity must be assessed with a view to eliminating sources of infection and chronic irritation. Established risk factors for mucotoxicity include smoking, poor oral hygiene, age, female gender, and previous antineoplastic therapy. However, the most significant risk factor is the treatment itself. Drugs such as fluorouracil, methotrexate, and etoposide are associated with an increased risk for mucositis, as are the more aggressive, dose-intense regimens such as TAC (docetaxel, doxorubicin, and cyclophosphamide). Infusional fluorouracil-based regimens appear to have less risk than standard-dose CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or bolus fluorouracil regimens. Drug dosing and scheduling are important in modulating the risk for mucositis.[4] For further comment on the prophylaxis and treatment of mucositis, see under Treatment of Adverse Effects, p. 732.1.

1. Calman FMB, Langdon J. Oral complications of cancer. *BMJ* 1991; **302:** 485–6.
2. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998; **34:** 39–43.
3. Sonis ST, *et al*. The Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004; **100** (suppl): 1995–2025.
4. Jones JA, *et al*. Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. *Support Care Cancer* 2006; **14:** 505–15.

NAUSEA AND VOMITING. Nausea and vomiting are common adverse effects of antineoplastic therapy, and for many patients, represent a major drawback to treatment. Once experienced, anticipatory vomiting may occur at the sight of medical staff, or a needle. The problem may be severe enough in some cases to hinder or completely prevent further treatment.

Antineoplastic or cytotoxic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone and a peripheral action on the gastrointestinal tract. Several neurotransmitters have been implicated over the years including acetylcholine, histamine, enkephalins, dopamine, and serotonin or 5-hydroxytryptamine (5-HT). The cerebral cortex is probably responsible for anticipatory vomiting. Antineoplastics may not all induce emesis by a common pathway, but 5-HT_3-receptor mechanisms are clearly important in the pathogenesis of *acute* cisplatin-associated vomiting. This was suspected when the antiemetic metoclopramide, a dopamine antagonist, was found to have serotonin (5-HT) antagonist activity at the high doses used against cisplatin emesis and confirmed when specific 5-HT_3 antagonists such as ondansetron proved to be effective. Different mechanisms are probably involved in *delayed* emesis since 5-HT_3 antagonists are less effective.

Some patients are more susceptible to emesis than others. The emetic potential of antineoplastics also varies in terms of severity and incidence, and may depend to some extent on the dose, route, and schedule of administration. Some combination therapy has resulted in a higher incidence of vomiting than would be expected from the constituents.

- Vomiting may be *very severe* with cisplatin, dacarbazine, dactinomycin, chlormethine, high-dose cyclophosphamide, and streptozocin, and occurs in most patients.
- *Moderate* vomiting is likely with the taxanes, doxorubicin, more modest doses of cyclophosphamide, and high-dose methotrexate.
- Vinca alkaloids, fluorouracil, lower doses of methotrexate, chlorambucil, bleomycin, and etoposide have *low* emetogenic potential.

The *onset and duration* of vomiting also varies from drug to drug. With cisplatin the onset may be between 4 and 8 hours after a dose, while the duration may be up to 48 hours or occasionally even longer; a persistent feeling of nausea, and sometimes vomiting, lasting for several days may also occur. After chlormethine, vomiting may begin within a half to 2 hours, whereas after cyclophosphamide there may be a latent interval of 9 to 18 hours, but in both cases vomiting is generally less prolonged than with cisplatin. Acute emesis (that occurring within 24 hours) has generally been easier to control than delayed emesis (that occurring more than 24 hours after chemotherapy) or anticipatory emesis.

The management of chemotherapy-induced nausea and vomiting is discussed on p. 1814.3.

Effects on the heart. The cardiotoxicity of antineoplastics has been reviewed.[1-6] Common cardiovascular complications include left ventricular dysfunction, heart failure, myocardial ischaemia or infarction, QT interval prolongation, arrhythmias, or bradycardia; thromboembolism (see Effects on the Cardiovascular System, p. 727.2) and hypertension are also common. Cardiotoxicity is the major dose-limiting toxicity with anthracyclines such as doxorubicin and daunorubicin (see Effects on the Heart, under Doxorubicin, p. 784.1). Cardiotoxicity has also been associated with other antineoplastics, such as the alkylating agents cyclophosphamide and ifosfamide, antimetabolites such as capecitabine and fluorouracil, taxanes, tyrosine kinase inhibitors, and the monoclonal antibodies bevacizumab and trastuzumab. Amsacrine has been associated with arrhythmias, sometimes fatal. As well as cardiac effects associated with a capillary leak syndrome, arrhythmias can occur with interleukin-2. Occasional reports of cardiotoxicity associated with busulfan, carmustine, cisplatin, cytarabine, etoposide, mitomycin, pentostatin, and vincristine also exist.

1. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Safety* 2000; **22:** 263–302.
2. Floyd JD, *et al*. Cardiotoxicity of cancer therapy. *J Clin Oncol* 2005; **23:** 7685–96.
3. Simbre VC, *et al*. Cardiotoxicity of cancer chemotherapy: implications for children. *Paediatr Drugs* 2005; **7:** 187–202.
4. Sereno M, *et al*. Cardiac toxicity: old and new issues in anti-cancer drugs. *Clin Transl Oncol* 2008; **10:** 35–46.
5. Anderson B, Sawyer DB. Predicting and preventing the cardiotoxicity of cancer therapy. *Expert Rev Cardiovasc Ther* 2008; **6:** 1023–33.
6. Yeh ETH, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009; **53:** 2231–47.

Effects on immune response. Lymphocytes are produced by stem cells in the bone marrow and at other sites, including the thymus, and are involved in humoral and cell-mediated immunity. Most antineoplastics have a depressant effect on bone marrow (see Effects on the Blood, p. 727.1) and many have immunosuppressant properties although the degree of suppression varies considerably and may depend on the dose and schedule used. Immunosuppression decreases the patient's resistance to infection and has been implicated in the development of malignancies. Response to vaccines may also be reduced, and there is a possibility of generalised infections with live viral vaccines (see Interactions, p. 2375.3).

For a discussion on the effects of immunosuppressant therapy on the immune response and the infections associated with it, see Corticosteroids, p. 1617.2.

Effects on the kidneys. Nephrotoxicity is well-recognised as an adverse effect of cisplatin (p. 767.2), ifosfamide (p. 806.3), and methotrexate (p. 825.2), but renal toxicity may occur with other antineoplastics including the nitrosoureas (such as carmustine and streptozocin), mitomycin (due to haemolytic-uraemic syndrome, see p. 831.3), azacitidine, gemcitabine, and pentostatin.[1] See also under individual monographs—other antineoplastics with which nephrotoxicity has been reported include aldesleukin (p. 811.3), bevacizumab (p. 748.2), and imatinib (p. 808.3).

1. Kintzel PE. Anticancer drug-induced kidney disorders: incidence, prevention and management. *Drug Safety* 2001; **24:** 19–38.

Effects on the liver. The range of hepatotoxic reactions that can occur with antineoplastics is wide. Toxic hepatitis (hepatocellular injury) can range from asymptomatic elevations of aminotransferases to signs of overt liver failure with hepatocellular necrosis. Other manifestations of hepatotoxicity include cholestatic injury, steatosis, hepatic veno-occlusive disease (VOD), and hepatic tumours. The important indicator of toxicity is liver biopsy rather than liver function tests as the latter may be normal in this setting.[1] The hepatotoxicity of various chemotherapy drugs has been reviewed.[1-4] Occasional reports of hepatotoxicity exist for many antineoplastics including anastrozole (p. 743.1), aminoglutethimide (p. 739.3), bicalutamide (p. 749.2), busulfan (p. 755.2), dacarbazine (p. 776.2), dactinomycin (p. 777.2), doxorubicin (p. 784.3), erlotinib (p. 789.2), floxuridine (p. 793.3), flutamide (p. 798.3), gemtuzumab, (p. 802.3), hydroxycarbamide (p. 804.2), imatinib (p. 808.2), methotrexate (p. 825.3), mitomycin (p. 832.1), mitoxantrone (p. 833.3), oxaliplatin (p. 838.3), tamoxifen (p. 862.3), tioguanine (p. 872.1), and trastuzumab (p. 877.1). However, the relationship of the drug to the adverse effect is not always easy to establish. The temporal relationship between drug use and the appearance of symptoms is important; rechallenge in most cases is not recommended as liver toxicity may be more severe on re-exposure.[1] Use with radiotherapy may increase the risk of hepatotoxicity.[4,5] Liver toxicity may not be confined to patients: one report described 3 cases of liver damage in nurses working on an oncology ward.[6]

VOD has occurred after the use of high doses of chemotherapy for conditioning regimens before haematopoietic stem cell transplantation.[3-5] Other antineoplastic drugs involved in the development of VOD include the alkylating agents, antimetabolites, and combination chemotherapy, typically with drugs that undergo hepatic metabolism.[4]

1. Rodriguez-Frias EA, Lee WM. Cancer chemotherapy I: hepatocellular injury. *Clin Liver Dis* 2007; **11:** 641–62.
2. Ménard DB, *et al*. Antineoplastic agents and the liver. *Gastroenterology* 1980; **78:** 142–64.

3. Field KM, *et al.* Part I: Liver function in oncology: biochemistry and beyond. *Lancet Oncol* 2008; **9:** 1092–1101.
4. Floyd J, *et al.* Hepatotoxicity of chemotherapy. *Semin Oncol* 2006; **33:** 50–67.
5. King PD, Perry MC. Hepatotoxicity of chemotherapy. *Oncologist* 2001; **6:** 162–76.
6. Sotaniemi EA, *et al.* Liver damage in nurses handling cytostatic agents. *Acta Med Scand* 1983; **214:** 181–9.

Effects on the lungs. Lung injury leading to pulmonary fibrosis occurs in about 10% of all patients who receive bleomycin, being fatal in 1 to 2%. Clinically, the reaction usually presents several months after completion of therapy as non-productive cough and dyspnoea. The reaction is dose-related, being more likely at total doses over 400 000 internationalunits (400 USP units), although it has occurred at much lower doses, and is more common in elderly patients. Injury may be exacerbated by the use of combination chemotherapy regimens and radiotherapy, and supplemental oxygen given even years after the use of bleomycin may precipitate pulmonary oedema.[1] Hypersensitivity pneumonitis, which is more amenable to treatment, has also been reported.[2]

Pulmonary damage has also been reported with an increasing number of antineoplastics apart from bleomycin.[1,3,4] Among the alkylating agents cyclophosphamide has been reported to produce lung injury in less than 1% of cases, although this may be increased where it is a component of combination regimens or given with radiotherapy. Busulfan may produce lung toxicity including insidious pulmonary fibrosis in as many as 4% of patients, usually developing several years after initiation of therapy, and with increased risk the longer that therapy lasts. A few reports exist of interstitial pneumonitis and fibrosis associated with chlorambucil and melphalan, but these appear to be extremely rare. The prognosis in patients with alkylating-agent-induced fibrosis is often poor, with mortality rates of 50% or more.

The antimetabolite methotrexate can produce symptoms similar to hypersensitivity pneumonitis in up to 7% of patients, sometimes with pleuritis and acute respiratory failure due to pulmonary oedema, but it is not clear whether a true hypersensitivity mechanism is involved, and symptoms are usually reversible even without stopping therapy. High-dose cytarabine has also been associated with pulmonary oedema. Gemcitabine (p. 801.3) has been associated with interstitial pneumonitis and potentially life-threatening symptoms have occurred when given with thoracic radiotherapy.

Other antineoplastics known to be associated with pulmonary toxicity include mitomycin (usually in less than 10% of patients though the incidence may be much higher in combination regimens); the vinca alkaloids (generally in combination, and usually producing acute respiratory failure); chlorozotocin; procarbazine; and possibly teniposide. The nitrosoureas, and particularly carmustine, have also emerged as pulmonary toxins. Carmustine has been associated with an insidious chronic pulmonary fibrosis, which in some early studies occurred in as many as 30% of patients and had a high mortality. Symptoms are associated particularly with cumulative doses in excess of about 1.4 g/m^2, although toxicity has occurred at cumulative doses as low as 240 mg/m^2. The onset of symptoms may be very delayed: some workers reported fibrosis occurring up to 17 years after treatment in patients who received carmustine as children.[5] Pneumonia and fibrosis have also been reported in patients receiving rituximab (p. 854.2), and fatal lung disease has occurred in patients given erlotinib (p. 789.2).

1. Abid SH, *et al.* Radiation-induced and chemotherapy-induced pulmonary injury. *Curr Opin Oncol* 2001; **13:** 242–8.
2. Holoye PY, *et al.* Bleomycin hypersensitivity pneumonitis. *Ann Intern Med* 1978; **88:** 47–9.
3. Twohig KJ, Matthay RA. Pulmonary effects of cytotoxic agents other than bleomycin. *Clin Chest Med* 1990; **11:** 31–54.
4. Fennell DA, Rudd RM. Pulmonary toxicity and cancer treatment. *Hosp Med* 2004; **65:** 462–5.
5. O'Driscoll BR, *et al.* Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med* 1990; **323:** 378–82.

Effects on mental function. Combination chemotherapy has been associated with psychiatric morbidity (anxiety, depression, behavioural changes) in both adults[1] and children.[2] It has been pointed out that patients receiving cancer chemotherapy inevitably suffer emotional distress, associated in part with the adverse effects of treatment. Patients should be fully informed of aims and likely outcomes of treatment, and adverse effects minimised, in order to keep emotional distress to a minimum.[3] Chemotherapy can also cause cognitive impairment,[4-7] affecting functions such as memory, reasoning, concentration, and language skills. Drugs may have direct central neurological toxic effects, or may indirectly affect brain function through adverse effects such as anaemia. Most studies have examined cognitive impairment in women being treated with chemotherapy for breast cancer, but many other cancer patients develop cognitive impairment, which has been described as 'chemo-brain' or 'chemo-fog'.

Some antineoplastics have been associated with mental symptoms, including methotrexate (p. 826.2), mitotane (p. 832.3), and the vinca alkaloids (see Vinblastine, p. 882.1). In many cases such symptoms can be attributed to direct central neurotoxicity (see also under Effects on the Nervous System, below).

1. Maguire GP, *et al.* Psychiatric morbidity and physical toxicity associated with adjuvant chemotherapy after mastectomy. *BMJ* 1980; **281:** 1179–80.
2. Dolgin MJ, *et al.* Behavioral distress in pediatric patients with cancer receiving chemotherapy. *Pediatrics* 1989; **84:** 103–10.
3. Brinkley D. Emotional distress during cancer chemotherapy. *BMJ* 1983; **286:** 663–4.
4. Tannock IF, *et al.* Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol* 2004; **22:** 2233–9.
5. Minisini A, *et al.* What is the effect of systemic anticancer treatment on cognitive function? *Lancet Oncol* 2004; **5:** 273–82.
6. Cavaliere R, Schiff D. Neurologic toxicities of cancer therapies. *Curr Neurol Neurosci Rep* 2006; **6:** 218–26.
7. Weiss B. Chemobrain: a translational challenge for neurotoxicology. *Neurotoxicology* 2008; **29:** 891–8.

Effects on the nervous system. The neurotoxicity of various antineoplastic drugs has been reviewed.[1-5] Effects can be central or peripheral, and can be dose-limiting.[3,5] For further details see under the individual monographs.

CNS toxicity is usually manifested as encephalopathy of various severities.[5,6] Drugs that can cause CNS toxicity include methotrexate, vincristine, ifosfamide, cytarabine, fludarabine, fluorouracil, cisplatin, and the taxanes.[5] Some drugs cause mental status changes, see Effects on Mental Function, above. Drugs that commonly cause peripheral neuropathy include the platinum compounds, the vinca alkaloids, taxanes, and other agents such as bortezomib.[3,4,7] Peripheral neuropathy can manifest as sensory, motor, or sensorimotor (combination) neuropathies.[8] Two patterns are common; a painful sensory neuropathy (seen with platinum compounds) and a mixed sensorimotor neuropathy with or without autonomic involvement (such as that seen with vincristine and taxanes).[5,8]

In some cases these effects may be associated with particular routes such as the intrathecal.[4] Radiotherapy can also cause damage to the nervous system so its use with chemotherapy may lead to additive effects.[6]

For discussion on management, see Neurotoxicity, p. 732.2.

1. Verstappen CCP, *et al.* Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs* 2003; **63:** 1549–63.
2. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006; **24:** 1633–42.
3. Cavaliere R, Schiff D. Neurologic toxicities of cancer therapies. *Curr Neurol Neurosci Rep* 2006; **6:** 218–26.
4. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 2008; **13:** 27–46.
5. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol* 2009; **63:** 761–7.
6. Perry A, Schmidt RE. Cancer therapy-associated CNS neuropathology: an update and review of the literature. *Acta Neuropathol* 2006; **111:** 197–212.
7. Visovsky C, *et al.* Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs* 2007; **11:** 901–13.
8. Walker M, Ni O. Neuroprotection during chemotherapy: a systematic review. *Am J Clin Oncol* 2007; **30:** 82–92.

EFFECTS ON THE EARS. Several antineoplastics have been associated with ototoxicity,[1] including vincristine and vinblastine, but cisplatin in particular is associated with high-frequency hearing loss and tinnitus. In addition, agents such as the nitrogen mustards and bleomycin are potentially ototoxic.

1. Seligmann H, *et al.* Drug-induced tinnitus and other hearing disorders. *Drug Safety* 1996; **14:** 198–212.

Effects on reproductive potential. *CHROMOSOMES.* If patients are fertile after treatment with antineoplastics, no significant increase has been seen in fetal chromosome damage, fetal abnormality, or the miscarriage rate. A review[1] of reports of survivors of *childhood cancers* found that adverse pregnancy outcomes were limited to particular groups of survivors. Female survivors of Wilms' tumours who had been treated with abdominal radiation, with or without chemotherapy, appeared to be at increased risk of complications including miscarriage, low birth-weight neonates, and neonatal death. After treatment of childhood Hodgkin's disease using both radiotherapy and chemotherapy, female survivors and partners of male survivors might be at increased risk of miscarriage; however, treatment with radiotherapy or chemotherapy alone did not increase this risk. For other cancers, data were more limited, but suggested that the risk of adverse pregnancy outcomes was not increased in survivors. The Childhood Cancer Survivor study[2] found that the offspring of women whose treatment included pelvic irradiation were more likely to be premature, to be of low birthweight, and small for gestational age. Treatment with doxorubicin or daunorubicin increased the risk of low birth-weight independently of radiotherapy. The risk of miscarriage was increased in those women treated with high-dose cranial or craniospinal radiotherapy. In general, the pregnancy outcome of the partners of male survivors was unaffected by the men's previous treatment; however, non-alkylating agent chemotherapy increased the risk of low birth-weight neonates.

Regarding the risk of congenital abnormalities in the offspring of survivors of childhood cancers, most studies have shown no excess of major or minor malformations.[1-3] There was also no evidence that the risk of cancer is increased in the offspring. However, because of the small numbers in many studies and heterogeneity regarding treatments used, it is possible that effects of individual drugs could have been masked. Long-term follow-up is needed as increasing numbers of children survive to adulthood after successful chemotherapy.

For *adult patients*, there is also a lack of evidence of adverse pregnancy outcomes and congenital abnormalities in offspring after chemotherapy. In a large series[4] of women treated with methotrexate, alone or in combination, for gestational trophoblastic tumours, there was no evidence of an increase in adverse outcomes or abnormalities, although women who had received three or more drugs in combination were less likely to have a live birth. A large case-control study carried out in Canada, and involving over 85 000 parents of children with congenital anomalies, also failed to confirm a higher incidence of congenital abnormality in the offspring of patients treated with radiotherapy or alkylating agents.[5] However, despite these generally reassuring results, it has been suggested that women should delay conception for a year after cessation of chemotherapy to allow mature ova that might have been damaged to be eliminated,[6] and that monitoring outcomes in patients who become pregnant shortly after exposure to cytotoxic drugs is desirable.[3]

See also Effects on Chromosomes under Carcinogenicity, p. 726.3.

1. Blatt J. Pregnancy outcome in long-term survivors of childhood cancer. *Med Pediatr Oncol* 1999; **33:** 29–33.
2. Green DM, *et al.* Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009; **27:** 2374–81.
3. Meirow D, Schiff E. Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data. *J Natl Cancer Inst Monogr* 2005; **34:** 21–5.
4. Rustin GJS, *et al.* Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours. *BMJ* 1984; **288:** 103–6.
5. Dodds L, *et al.* Case-control study of congenital anomalies in children of cancer patients. *BMJ* 1993; **307:** 164–8.
6. Walden PAM, Bagshawe KD. Pregnancies after chemotherapy for gestational trophoblastic tumours. *Lancet* 1979; **ii:** 1241.

GONADS. The effects of cytotoxic drugs on the gonads have been reviewed.[1-7] In male patients, antineoplastic drugs may damage the seminiferous tubules, resulting in testicular atrophy with decreased sperm count and motility. Testosterone secretion may also be reduced after damage to Leydig cells. In women, cytotoxic drugs act on the ovary to produce loss of primordial follicles with failure of ovulation, oligomenorrhoea or amenorrhoea, and failure of endocrine function resulting in loss of libido and menopausal symptoms. The degree of damage and its reversibility depend on the drug and its dose and the age and sex of the patient. Age is particularly important for women at the time of treatment, with older women (35 to 40 or over) being more sensitive, probably a reflection of the decrease in oocyte numbers with age.

Although dose also plays a role, estimates of the toxicity of various antineoplastics (as single agents) have been published.[4-6] The risk of gonadal dysfunction is high with alkylating agents (busulfan, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan), nitrosoureas (carmustine, lomustine), and procarbazine. Medium risk drugs include carboplatin, cisplatin, and doxorubicin. Low risk drugs include bleomycin, dactinomycin, fluorouracil, mercaptopurine, methotrexate, vinblastine, and vincristine.

Severe gonadal dysfunction in both men and women has been associated with combination chemotherapy regimens for Hodgkin's disease. Chlormethine and procarbazine are thought to be mainly responsible for the infertility produced. There is some evidence that currently favoured regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) result in less damage to gonadal cells than the earlier MOPP regimen (chlormethine, vincristine, procarbazine, and prednisone). Prolonged gonadal dysfunction has also been seen in patients given combination chemotherapy for acute lymphoblastic leukaemia; girls appear to be at less risk than boys, especially if treated in the prepubertal period.

Techniques for fertility preservation have been reviewed.[3-6,8] Established methods with the highest likelihood of success are sperm cryopreservation (sperm banking) for men and IVF with embryo cryopreservation for women. Other methods for women, for which there is less experience and investigation is underway, include oocyte cryopreservation for future IVF, gonadal tissue cryopreservation for autologous transplantation, and ovarian suppression using oral contraceptives or gonadotrophin-releasing hormone analogues. Such techniques are of little

benefit for the preservation of fertility in patients treated as young children, however, because of gonadal immaturity.

1. Goldman S, Johnson FL. Effects of chemotherapy and irradiation on the gonads. *Endocrinol Metab Clin North Am* 1993; **22:** 617–29.
2. Kovacs GT, Stern K. Reproductive aspects of cancer treatment: an update. *Med J Aust* 1999; **170:** 495–7.
3. Thomson AB, *et al.* Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. *Best Pract Res Clin Endocrinol Metab* 2002; **16:** 311–34.
4. Wallace WHB, *et al.* Fertility preservation for young patients with cancer: who is at risk and what can be offered? *Lancet Oncol* 2005; **6:** 209–18. Correction. *ibid.;* 922.
5. Magelssen H, *et al.* The effects of cancer and cancer treatments on male reproductive function. *Nat Clin Pract Urol* 2006; **3:** 312–22.
6. Lee SJ, *et al.* American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; **24:** 2917–31. Correction. *ibid.;* 5790.
7. Walshe JM, *et al.* Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006; **24:** 5769–79.
8. Fallat ME, Hutter J. American Academy of Pediatrics Committee on Bioethics. American Academy of Pediatrics Section on Hematology/Oncology. American Academy of Pediatrics Section on Surgery. Preservation of fertility in pediatric and adolescent patients with cancer. *Pediatrics* 2008; **121:** e1461–e1469. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/e1461 (accessed 23/02/10)

SEXUAL FUNCTION. Loss of libido and decline in sexual performance seem to be relatively common in men receiving combination chemotherapy,[1,2] and may persist after chemotherapy has ended.[1] However, it may sometimes be difficult to distinguish the effects of chemotherapy from those of the disease and the patient's reaction to it: at least one study has shown that gonadal function is disturbed in patients with Hodgkin's disease before treatment.[2] Erectile dysfunction can also result from local damage caused by pelvic surgery or irradiation.[3] Evidence for decreased libido in women is harder to find, but failure of endocrine function after chemotherapy may lead to loss of libido and menopausal symptoms.[4]

1. Chapman RM, *et al.* Cyclical combination chemotherapy and gonadal function: retrospective study in males. *Lancet* 1979; **i:** 285–9.
2. Chapman RM, *et al.* Male gonadal dysfunction in Hodgkin's disease: a prospective study. *JAMA* 1981; **245:** 1323–8.
3. Costabile RA. Cancer and male sexual dysfunction. *Oncology (Huntingt)* 2000; **14:** 195–205.
4. Shalet SM. Effects of cancer chemotherapy on gonadal function of patients. *Cancer Treat Rev* 1980; **7:** 141–52.

Effects on the skin, hair, and nails. Alopecia occurs with many antineoplastics, and may be severe with doxorubicin and other anthracyclines, cyclophosphamide, ifosfamide, etoposide, or teniposide, the taxanes docetaxel and paclitaxel, and topotecan. The alkylating agents and some antibiotic antineoplastics are often associated with hyperpigmentation, most commonly of skin, although pigmentation of nails, hair, and teeth has occurred. Some drugs, such as the taxanes, cause dystrophic changes in the nails. Certain drugs may interact with UV light or x-ray radiation to enhance its effects on the skin and may cause radiation recall, photosensitivity, or, in the case of methotrexate, reactivation of UV light burns. Hypersensitivity to antineoplastics may produce cutaneous reactions including allergic rashes, angioedema, and pruritus. In addition to the above there may be local reactions to irritant and vesicant drugs after extravasation. Finally, certain drugs are associated with specific dermatological reactions: acneform follicular rashes have been reported with cetuximab, bleomycin may produce hyperkeratotic and sclerotic lesions, dactinomycin is associated with an erythematous papular or pustular rash mimicking septic emboli, fluorouracil may produce inflammation of solar keratoses, and plicamycin is associated with a distinctive flushing phenomenon. A palmar-plantar erythrodysesthesia syndrome has been seen with some antineoplastics (see below).

See also Local Toxicity, below. References may also be found under individual monographs.

PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME. Palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome) associated with chemotherapy[1,2] usually presents as a tingling sensation in the palms and soles, which progresses in a few days to burning pain and well-defined swelling and erythema. In severe cases there is desquamation, ulceration, blistering, and severe pain. The reaction appears to be caused by a direct toxic effect and seems to be dose-dependent, affected by both peak drug concentration and total cumulative dose. The drugs most often associated with PPE or similar syndromes are capecitabine (p. 758.3), cytarabine (p. 775.2), docetaxel (p. 782.1), doxorubicin—particularly liposomal doxorubicin (p. 785.1), and fluorouracil (p. 797.2). PPE also occurs with the tyrosine kinase inhibitors, such as lapatinib (p. 815.2), sorafenib (p. 858.1), and sunitinib (p. 859.2). It has also been reported for bevacizumab (p. 747.3), cisplatin (see under Hypersensitivity, p. 768.1), cyclophosphamide (p. 773.1), ixabepilone (p. 815.1), and methotrexate (p. 826.2). PPE is usually managed by reducing the drug dose, increasing the dosage interval, or withdrawing the drug, along with symptomatic treatment and wound care. Systemic corticosteroids and pyridoxine have been used in prophylaxis and treatment. Topical dimethyl sulfoxide has been used for PPE caused by liposomal doxorubicin.

1. Nagore E, *et al.* Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. *Am J Clin Dermatol* 2000; **1:** 225–34.
2. Webster-Gandy JD, *et al.* Palmar-plantar erythrodysesthesia (PPE): a literature review with commentary on experience in a cancer centre. *Eur J Oncol Nurs* 2007; **11:** 238–46.

Hyperuricaemia. Overproduction of purines is a known complication of antineoplastic therapy and may result in hyperuricaemia (p. 600.1). Hyperuricaemia is also an important part of the tumour lysis syndrome—see below.

Local toxicity. Local toxicity due to intravenous cancer chemotherapy may include local irritation, extravasation necrosis, and hypersensitivity. **Venous irritation**, presenting as vasospasm and pain or endothelial chemical burn of the vessel, resulting in a painful, streaky, long-lasting sterile phlebitis, may be due to the drug, or, as with carmustine, due to the diluent (alcohol). Irritation and phlebitis have been reported particularly with fluorouracil, carmustine, vinorelbine, and chlormethine.

Some patients treated with peripheral intravenous chemotherapy experience **extravasation** (see p. 731.3), usually with pain, erythema, and swelling at the site of injection. Severe necrosis requiring surgical intervention can develop, particularly with antibiotic antineoplastics such as doxorubicin.

Local **hypersensitivity** reactions, usually self-limiting, must be distinguished from extravasation. In hypersensitivity reactions there is no swelling at the injection site, and pain is felt as a dull ache along the course of the vein, as opposed to the stinging commonly noted after extravasation.

Tumour lysis syndrome. The tumour lysis syndrome represents a biochemical disturbance due to massive release of cellular breakdown products from tumour cells sensitive to therapy. The amount of breakdown products is sufficient to overwhelm normal excretory and metabolic mechanisms for their clearance, and the cardinal features of the syndrome are hyperkalaemia, hyperuricaemia, and hyperphosphataemia accompanied by hypocalcaemia. Clinical symptoms may include urate nephropathy or nephrocalcinosis leading to renal impairment, and cardiac arrhythmias associated with the potassium abnormalities. The syndrome is seen particularly when bulky chemosensitive disease is present, and may be more likely in patients with pre-existing renal impairment or hyperuricaemia. It is most frequent in patients with Burkitt's or lymphoblastic lymphoma, or an acute leukaemia. Of patients with solid tumours, reports have implicated those with germ-cell tumours, small-cell lung cancer, or neuroblastoma although, surprisingly, the syndrome has also been reported in patients with breast cancer, which is normally less rapidly responsive to chemotherapy. For comment on prevention and treatment, see under Treatment of Adverse Effects, p. 732.2.

References.
1. Kalemkerian GP, *et al.* Tumor lysis syndrome in small cell carcinoma and other solid tumors. *Am J Med* 1997; **103:** 363–7.
2. Jeha S. Tumor lysis syndrome. *Semin Hematol* 2001; **38** (suppl 10): 4–8.
3. BaeksgaardL, Sørensen JB. Acute tumor lysis syndrome in solid tumors–a case report and review of the literature. *Cancer Chemother Pharmacol* 2003; **51:** 187–92.

Treatment of Adverse Effects

Intensive supportive care may be necessary to prevent or control the adverse effects of antineoplastic therapy. Antiemetic therapy should be given to reduce, and if possible prevent, nausea and vomiting, since once experienced it may become a conditioned response, and may not respond to antiemetics. Intensive oral care is desirable to minimise the effects of stomatitis (see also Mucositis, p. 732.1), while corticosteroids, and if necessary nutritional supplements, may be of some help in patients with anorexia. Chemotherapy-induced diarrhoea may also require treatment (see p. 731.3).

Techniques attempting to prevent the occurrence of alopecia have met with varying success (see below). Scalp tourniquets and local hypothermia have been used to minimise concentrations of antineoplastics in the scalp after intravenous injection. However, such methods may allow the development of a cancer-cell sanctuary and should not be used in patients with leukaemia or other conditions with circulating malignant cells.

Of particular importance is the management of bone-marrow depression. Colony-stimulating factors and epoetins can be used to promote the formation of replacement blood elements (see Anaemia, p. 731.1). Active measures may be necessary to combat infection and bleeding. Transfusions of blood products may be required; granulocyte transfusions have been given for infections unresponsive to antibiotics, although their value is a matter of debate, while transfusion of blood platelets or use of growth factors such as oprelvekin (interleukin-11) may be of value in preventing thrombocytopenia-induced bleeding.

Extravasation of antineoplastics can pose serious problems. Infusion should be stopped immediately once extravasation is noticed and any drug remaining at the site aspirated if possible but the details of treatment are controversial (see p. 731.3). If ulceration occurs plastic surgery may be required.

Hyperuricaemia secondary to tumour lysis in patients with leukaemias or lymphomas can be prevented by the addition of allopurinol or rasburicase to treatment schedules, and by adequate hydration and, if necessary, alkalinisation of the urine (see Tumour Lysis Syndrome, p. 732.2). Good hydration is also important to minimise the nephrotoxic effects of drugs such as cisplatin and methotrexate.

Specific treatments exist for the toxicity of certain antineoplastics (for example the use of calcium folinate to reduce methotrexate toxicity, or mesna to control the bladder toxicity of cyclophosphamide or ifosfamide). For further details of the treatment of specific adverse effects see under the individual monographs.

Alopecia. Attempts to prevent or reduce chemotherapy-induced alopecia have relied on either restriction of scalp blood flow with a tourniquet or the use of local hypothermia.[1] Both of these techniques have been based on the rationale that a temporary decrease in blood flow to the scalp will decrease the exposure of hair follicles to the antineoplastic. Therefore, most benefit would be expected for alopecia caused by drugs with a short half-life and for which both active drug and metabolites are rapidly cleared from the circulation.

Studies of scalp tourniquets carried out in the 1970s found head discomfort to be the main adverse effect. They used different chemotherapy regimens, definitions for success, and tourniquet techniques, making conclusions difficult, and tourniquets were largely replaced by local hypothermia techniques.

Regimens vary in their propensity to cause alopecia: drugs that normally produce hair loss include the anthracyclines, cyclophosphamide and ifosfamide, etoposide and topotecan, irinotecan, the taxanes, and vindesine or vinorelbine.[2] Most studies of local hypothermia have attempted to prevent doxorubicin-induced alopecia.[1] Again, chemotherapy regimens, devices used, and exposure times have varied between studies. Varying degrees of efficacy have been reported, but hypothermia has generally been of benefit, particularly with single-agent chemotherapy. The dose of chemotherapy may be relevant, with hypothermia being less effective at doxorubicin doses above 50 mg.[1] Better results have also been reported when cooling is continued for 90 minutes or more; theoretically, cooling time should be related to the half-life of the drugs used and any active metabolites.[2] Headache and cold intolerance may occur, but scalp hypothermia is generally well tolerated.

Despite the successes there is concern that this technique may provide a sanctuary for circulating malignant cells, with the potential risk of metastasis, and there are reports of scalp metastases after the use of hypothermia.[1-3] The technique is considered contra-indicated in patients with haematological malignancies and use is controversial where curative chemotherapy can be given.[2] It has been suggested that the use of scalp hypothermia might therefore be restricted to patients receiving single-agent chemotherapy with a palliative intent, or those with solid tumours that rarely metastasise to the scalp.[1]

In the USA commercial distribution of cooling caps designed to produce localised scalp hypothermia was halted by the FDA in 1990 because of concerns about their efficacy and their potential to create sanctuary sites and interfere with drug distribution elsewhere in the head. However, they continue to be available in many countries.

There has been limited investigation of pharmacological management.[2] For reference to the use of minoxidil to decrease the duration of alopecia after doxorubicin-containing chemotherapy, see p. 1439.1.

1. Dorr VJ. A practitioner's guide to cancer-related alopecia. *Semin Oncol* 1998; **25:** 562–70.
2. Trüeb RM. Chemotherapy-induced alopecia. *Semin Cutan Med Surg* 2009; **28:** 11–14.
3. Forsberg SA. Scalp cooling therapy and cytotoxic treatment. *Lancet* 2001; **357:** 1134.

Bone-marrow depression. Bone-marrow depression in patients receiving chemotherapy may require a modification of the dose regimen in subsequent cycles, either by delaying or reducing doses, although it is recognised that this may sometimes reduce efficacy.

Licensed product information for several myelosuppressive antineoplastics recommends that if neutropenia or thrombocytopenia occurs subsequent doses should be withheld until white cell counts have returned to 3000 to 3500 cells/mm^3 or more, and blood platelets to about 100 000 cells/mm^3. In practice, however, improved supportive care means that many expert centres routinely give treatment at lower blood counts than these. The values at which it is acceptable to treat will be influenced by whether the regimen is likely to result in further significant falls, and

whether the intent is curative (in which case maintaining treatment intensity is particularly important) or palliative (when avoiding toxicity becomes a prime consideration); local protocols may contain further guidance and should be consulted where available. However, it has been suggested[1] that with appropriate management treatment is usually possible at neutrophil counts of 1500 cells/mm^3 and platelet counts above 100 000 cells/mm^3.

For guidelines on the use of haematopoietic growth factors in the management of anaemia, neutropenia, and thrombocytopenia, see below.

1. Summerhayes M, Daniels S. *Practical chemotherapy: a multidisciplinary guide*. Oxford: Radcliffe Medical Press, 2003.

ANAEMIA. Chemotherapy-induced anaemia can be managed with transfusion of red cells (p. 1162.1), or treatment with epoetin (p. 1141.1) or darbepoetin (p. 1137.1).[1-4] Iron supplementation may be of benefit in anaemic cancer patients receiving erythropoietic therapy, even in those who are iron-replete.[3]

Guidelines for the use of epoetins and darbepoetin have been issued jointly by the American Society of Clinical Oncology and the American Society of Hematology,[5] and guidelines have also been issued by the US National Comprehensive Cancer Network.[4] In the treatment of chemotherapy-induced anaemia, the use of epoetins or darbepoetin can improve haemoglobin concentration and reduce the need for transfusion of red cells, but whether this improves symptoms and quality of life requires further study. The use of epoetins or darbepoetin is recommended as an option when haemoglobin has fallen to less than 10 g per 100 mL. For patients with a concentration between 10 and 12 g per 100 mL, the decision to use epoetins depends on clinical circumstances and patient preference.[5] In the UK, the use of epoetins or their analogues is not generally recommended[3] for chemotherapy-related anaemia except, in combination with intravenous iron, in patients in whom anaemia is profound and likely to affect survival, and who cannot be given blood transfusions, or in women given platinum-based chemotherapy for ovarian cancer in whom haemoglobin has fallen to 8 g per 100 mL or less.

1. Littlewood TJ. Management options for cancer therapy-related anaemia. *Drug Safety* 2002; **25:** 525–35.
2. Bohlius J, *et al*. Erythropoietin or darbepoetin for patients with cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/01/10).
3. NICE. Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia (TA 142, issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA142Guidance.pdf (accessed 26/01/10)
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: cancer- and chemotherapy-induced anemia (version 1.2011). Available at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf (accessed 12/07/10)
5. Rizzo JD, *et al*. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood* 2010; **116:** 4045–59. Also published in *J Clin Oncol* 2010; **28:** 4996–5010. Also available at: http://bloodjournal.hematologylibrary.org/cgi/reprint/116/20/4045 (accessed 16/12/10)

NEUTROPENIA. Use of granulocyte or granulocyte-macrophage colony-stimulating factors (G-CSF or GM-CSF), alone or with autologous bone marrow transplants or peripheral blood stem-cells, can markedly reduce the period of neutropenia after high-dose chemotherapy regimens (see Filgrastim, p. 1152.1, and Molgramostim, p. 1156.2). The use of filgrastim and pegfilgrastim has been reviewed;[1,2] it was considered that prophylactic use of these agents has enabled the use of more aggressive chemotherapy regimens, including dose-dense regimens (but see below), and treatment of a broader range of patients.

The American Society of Clinical Oncology has issued detailed guidelines for the use of colony-stimulating factors (CSFs) in patients receiving chemotherapy.[3] These point out that in current practice infectious mortality resulting from febrile neutropenia is rare, and that the incidence with common chemotherapy regimens seldom exceeds 20% in previously untreated patients; however, episodes of febrile neutropenia prolong hospital stay, expose the patient to further interventions, and may result in delay or dose-reduction of further chemotherapy cycles. Unfortunately, although CSFs can markedly reduce the incidence of febrile neutropenia, there was little evidence of improved clinical outcomes from the use of CSFs in most situations.

- Use of CSFs for **primary prophylaxis** in previously untreated patients should not normally be considered except where the risk of febrile neutropenia was 20% or more, or where the risk was less than 20% but bone-marrow compromise or comorbidity indicated a patient at high risk (and even here the evidence for improved clinical outcome was modest).
- There was no evidence of clinical benefit from the use of CSFs in **secondary prophylaxis**. In patients with a previous episode of febrile neutropenia the usual option (except where it would compromise the chances of cure) was dose reduction of the chemotherapy regimen.
- For adjunctive **treatment** of episodes of neutropenia, it was recommended that CSFs should not be routinely used for patients who were *afebrile*; there was also strong and consistent evidence against routine use for uncomplicated fever and neutropenia in *febrile* patients. Use might be considered in high-risk patients with febrile neutropenia.
- Although CSFs could permit **increased dose-density or dose-intensity** of chemotherapy, this was considered only justified within the context of a clinical study, since the limited data suggest survival benefit from dose-dense regimens with CSF support in only a few specific settings. Use in patients receiving combined **chemoradiotherapy** was not recommended.
- In patients with **haematological malignancies**, CSFs should be considered after induction chemotherapy in patients with acute myeloid leukaemias (patients aged over 55 may be most likely to benefit), after consolidation chemotherapy, and after initial induction or postremission chemotherapy in patients with acute lymphoblastic leukaemia; a subset of patients with myelodysplastic syndrome, severe neutropenia, and recurrent infection, might also benefit, but use in patients with refractory or relapsed myeloid leukaemia was not thought to be of benefit.
- CSFs were recommended as adjuncts to **progenitor cell transplantation** to help mobilise peripheral blood stem cells and to speed autologous engraftment.
- As **older patients** treated with curative chemotherapy for diffuse aggressive lymphoma are at increased risk of febrile neutropenia and infections, and dose reduction strategies have been associated with a reduced response rate and survival, prophylactic CSF was recommended for such patients aged 65 and older.
- Although the guidelines in adults were held to be generally applicable to **children**, it was noted that the potential for secondary myeloid leukaemia or myelodysplastic syndrome associated with CSFs was of concern in children with acute lymphoblastic leukaemia.

Guidelines issued by the US National Comprehensive Cancer Network[4] adopt a similar attitude to the use of CSFs, and suggest that they should be used for prophylaxis in all patients with a more than 20% risk of febrile neutropenia or neutropenia sufficient to compromise treatment, and may be considered in patients in whom this risk is judged to be between 10 and 20%. Factors that contribute to risk categorisation include the type of chemotherapy regimen and patient risk factors such as age, type of disease, disease stage, previous chemotherapy or irradiation, general health, and performance status.

For details on the management of infections in neutropenic patients, see Infections in Immunocompromised Patients, p. 186.3.

1. Marangolo M, *et al*. Dose and outcome: the hurdle of neutropenia (Review). *Oncol Rep* 2006; **16:** 233–48.
2. Renwick W, *et al*. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs* 2009; **23:** 175–86.
3. Smith TJ, *et al*. American Society of Clinical Oncology. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://www.jco.org/cgi/reprint/24/19/3187 (accessed 18/01/10)
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: myeloid growth factors (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf (accessed 18/01/10)

THROMBOCYTOPENIA. Chemotherapy-induced thrombocytopenia can be managed by chemotherapy dose reductions or delaying the next cycle of chemotherapy; treatment modifications depend on the drug used and the severity of the thrombocytopenia.[1] Severe thrombocytopenia can be rapidly treated with transfusion of platelets (p. 1159.3). Recombinant thrombopoietin[2] (p. 1164.1), interleukin-3 (p. 1155.2), and interleukin-6 have been evaluated for their ability to increase platelet numbers *in vivo*. Interleukin-11 has also been studied and is now available as oprelvekin (p. 1157.2), which can reduce chemotherapy-induced thrombocytopenia.[1,3,4] Interleukin-1 (p. 2533.3) has also been investigated in the prevention or treatment of thrombocytopenia. Eltrombopag (p. 1140.1) and romiplostim (p. 1162.2) are also under investigation.[1]

The American Society of Clinical Oncology has issued guidelines for the use of platelet transfusion.[5] They recommend that prophylactic platelet transfusion be given for thrombocytopenia resulting from impaired bone-marrow function to reduce the risk of haemorrhage when the platelet count falls below a predefined threshold. This threshold will vary depending on the patient's diagnosis, clinical condition, and treatment modality. A threshold of 10 000 cells/mm^3 has been recommended for patients being treated for acute leukaemia, with haematopoietic stem cell transplantation, or for solid tumours. A higher threshold of 20 000 cells/mm^3 may need to be considered for patients with signs of haemorrhage, high fever, rapid fall of platelet count, coagulation abnormalities, patients receiving aggressive therapy for bladder tumours, or those with necrotic solid tumours who are at increased risk of bleeding from these sites.

1. Vadhan-Raj S. Management of chemotherapy-induced thrombocytopenia: current status of thrombopoietic agents. *Semin Hematol* 2009; **46** (suppl 2): S26–S32.
2. Vadhan-Raj S, *et al*. Recombinant human thrombopoietin attenuates carboplatin-induced severe thrombocytopenia and the need for platelet transfusions in patients with gynecologic cancer. *Ann Intern Med* 2000; **132:** 364–8.
3. Gordon MS, *et al*. A phase I trial of recombinant human interleukin-11 (Neumega rhIL-11 growth factor) in women with breast cancer receiving chemotherapy. *Blood* 1996; **87:** 3615–24.
4. Isaacs C, *et al*. Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *J Clin Oncol* 1997; **15:** 3368–77.
5. Schiffer CA, *et al*. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1519–38. Also available at: http://www.jco.org/cgi/reprint/19/5/1519.pdf (accessed 18/01/10)

Diarrhoea. Patients receiving chemotherapy should be monitored for onset, duration, and severity of diarrhoea. Uncomplicated mild to moderate diarrhoea may be managed conservatively with dietary modification and loperamide. Severe diarrhoea, and mild to moderate cases that are complicated by moderate to severe cramping, nausea and vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration, may require more aggressive management including intravenous fluids, octreotide, and antibacterials.[1-3]

1. Benson AB, *et al*. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004; **22:** 2918–26.
2. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract* 2007; **13:** 181–98.
3. Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008; **36:** 413–23.

Extravasation. Extravasation is the leakage of a drug into subcutaneous tissue during parenteral dosage. Extravasation injuries can range from mild erythema to ulceration, and severe necrosis in some cases if not dealt with promptly. Antineoplastics vary in their propensity to cause extravasation injury:[1]

- *vesicant antineoplastics* cause pain, inflammation and blistering of the local skin, tissue death and necrosis; they include amsacrine, the anthracyclines (doxorubicin and its derivatives), carmustine, dacarbazine, dactinomycin, mitomycin, chlormethine, paclitaxel, plicamycin, streptozocin, and the vinca alkaloids
- *exfoliants* can cause inflammation and exfoliation, but are less likely to cause tissue death, and include cisplatin, docetaxel, mitoxantrone, oxaliplatin, and topotecan
- carboplatin, irinotecan, and the podophyllotoxin derivatives (etoposide and teniposide) are examples of *irritant* drugs which may cause inflammation and irritation, but rarely cause breakdown of tissue. Fluorouracil, methotrexate, and raltitrexed can cause mild to moderate inflammation of local tissue.

Measures to prevent the occurrence of extravasation include giving vesicant or irritant drugs via a central line, or peripherally via a recently sited cannula; vesicants are generally given by intravenous injection into a fast-running infusion. Glyceryl trinitrate patches applied distally to the cannula may be used to dilate veins where venous access is a problem. The site of administration should be regularly checked, and the patient asked to report any untoward sensations.

If extravasation should occur the infusion should be stopped immediately and as much as possible of the infiltrating drug removed by aspiration. Beyond this, however, the management of extravasation is not well standardised and there has been disagreement as to the most appropriate course; there is little data from controlled studies and much practice is based on anecdotal reports and individual experience. Intravenous and subcutaneous injection of a corticosteroid (usually hydrocortisone) has been suggested, although some consider it ineffective or possibly even disadvantageous. Topical application of a 1% hydrocortisone cream to inflamed skin has also been suggested, and antihistamines and, if necessary, analgesics, may be given orally. In most cases application of a cold dressing or ice pack is appropriate. However, after extravasation of the taxanes, vinca alkaloids, or cisplatin, the use of warm packs with hyaluronidase to enhance uptake from the skin has been recommended; a similar procedure has been suggested for large volume extravasations of the podophyllotoxin derivatives.

The use of specific antidotes is a particularly contentious area, since few are clinically validated and some (such as the use of sodium bicarbonate 8.4% for anthracycline extravasations) may do more harm than good. Brief infiltration of a less concentrated (2.1%) sodium bicarbonate solution, followed after a few minutes by aspiration, is still, however, advocated by some in the management of extravasations of the anthracyclines, carmustine, and plicamycin. Better accepted in the management of anthracycline and mitomycin extravasation is the topical application of dimethyl sulfoxide about every 6 hours,

sometimes alternated with hydrocortisone 1% cream. Dexrazoxane is also used for the management of anthracycline extravasation. Sodium thiosulfate 3 or 4% has been used to infiltrate the site of extravasations of cisplatin, dactinomycin, or chlormethine.

The role of surgery is also important. It is unequivocally necessary in cases where other methods have failed to prevent evolving tissue damage, but there is some dispute as to the role of early surgery to remove drug-laden tissue and prevent the development of more serious ulceration and necrosis. Techniques of saline flushout and liposuction have been developed for removing drug and non-viable tissue while preserving overlying skin.

Some references to the management of extravasation are given below.[1-6]

1. Stanley A. Managing complications of chemotherapy administration. In: Allwood M, *et al.*, eds. *The Cytotoxics Handbook*. 4th ed. Oxford: Radcliffe Medical Press, 2002: 119–93.
2. Dorr RT. Antidotes to vesicant chemotherapy extravasations. *Blood Rev* 1990; **4:** 41–60.
3. Gault DT. Extravasation injuries. *Br J Plast Surg* 1993; **46:** 91–6.
4. Bertelli G. Prevention and management of extravasation of cytotoxic drugs. *Drug Safety* 1995; **12:** 245–55.
5. Kassner E. Evaluation and treatment of chemotherapy extravasation injuries. *J Pediatr Oncol Nurs* 2000; **17:** 135–48.
6. Ener RA, *et al.* Extravasation of systemic hemato-oncological therapies. *Ann Oncol* 2004; **15:** 858–62.

Hypersensitivity. Desensitisation protocols have been described for cancer patients with hypersensitivity reactions to chemotherapy, including taxanes, platinum agents, and monoclonal antibodies.[1]

1. Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol* 2006; **6:** 271–7.

Mucositis. Many drugs have been tried for the *prophylaxis* of mucositis caused by antineoplastic therapy, by modifying exposure of the oral mucosa to chemotherapy, modifying epithelial proliferation, or reducing the potential for infection and inflammatory complications of mucositis.[1] Some drugs showed limited evidence of benefit in small studies, including benzydamine, betacarotene, granulocyte-macrophage colony-stimulating factor, povidone-iodine, propantheline bromide, vitamin E, and tretinoin. There are conflicting reports of benefit from studies of sucralfate and chlorhexidine. Other options that have been tried with less success include aciclovir, allopurinol, dinoprostone, glutamine, misoprostol, pentoxifylline, and bacterial and fungal decontamination.

A large systematic review[2] considered many of these and found that some drugs showed evidence of benefit, albeit weak, including amifostine, benzydamine, calcium phosphate, honey, hydrolytic enzymes, iseganan, and zinc sulfate; local cooling with ice chips and Chinese medicinal herb mixtures also showed some benefit. Practice guidelines[3] also suggested that local cooling may prevent oral mucositis associated with bolus fluorouracil or edatrexate and that ranitidine or omeprazole may prevent epigastric pain after treatment with cyclophosphamide, methotrexate, and fluorouracil, or after fluorouracil with or without folinic acid. Palifermin may prevent oral mucositis in patients with haematological neoplasms given high-dose chemotherapy and total body irradiation before autologous stem cell transplantation. Local cooling may be used in patients given high-dose melphalan. Amifostine may prevent radiation proctitis in those receiving standard-dose radiotherapy for rectal cancer, and although it has been suggested that it may reduce oesophagitis associated with chemoradiotherapy for non-small cell lung cancer,[3] others feel that data are insufficient to recommend routine use in such patients.[4]

There will be some overlap between measures for prophylaxis and treatment of mucositis, and another systematic review[5] of *treatment* strategies found that there was some evidence that topical allopurinol or granulocyte-macrophage colony-stimulating factor might improve chemotherapy-induced oral mucositis, but the evidence was weak and unreliable. Given the number of variables involved in the development of mucositis it is unlikely that any one prophylactic or treatment regimen will prove suitable for all patients.

1. Knox JJ, *et al.* Chemotherapy-induced oral mucositis: prevention and management. *Drugs Aging* 2000; **17:** 257–67.
2. Worthington HV, *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 16/07/08).
3. Keefe DM, *et al.* The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; **109:** 820–31. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/114078093/PDFSTART (accessed 16/07/08)
4. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; **27:** 127–45.
5. Clarkson JE, *et al.* Interventions for treating oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 26/01/10).

Nausea and vomiting. For a detailed discussion of the management of chemotherapy-induced nausea and vomiting, see p. 1814.3.

Neurotoxicity. Overall management of neurotoxicity comprises prevention, restoration of function, and symptomatic treatment.[1] Many agents have been tried for neuroprotection, including amifostine, carnitine, erythropoietin, glutamine, glutathione, and vitamin E.[1-4] Drug regimes have also been modified in an attempt to prevent neurotoxicity.[1] Treatment is supportive and symptomatic; pain management is similar to the management of other types of neuropathic pain.[1] Non-pharmacological interventions have also been investigated.[2]

1. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 2008; **13:** 27–46.
2. Visovsky C, *et al.* Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs* 2007; **11:** 901–13.
3. Walker M, Ni O. Neuroprotection during chemotherapy: a systematic review. *Am J Clin Oncol* 2007; **30:** 82–92.
4. Cavaletti G, Marmiroli P. The role of growth factors in the prevention and treatment of chemotherapy-induced peripheral neurotoxicity. *Curr Drug Saf* 2006; **1:** 35–42.

Osteoporosis. Bone loss that occurs with cancer therapy is generally more rapid and severe than postmenopausal bone loss in women or normal age-related osteoporosis in men. However, treatment principles are generally the same. For a detailed discussion on the management of osteoporosis, see p. 1168.1.

Further references.

1. Michaud LB, Goodin S. Cancer-treatment-induced bone loss, part 1. *Am J Health-Syst Pharm* 2006; **63:** 419–30.
2. Michaud LB, Goodin S. Cancer-treatment-induced bone loss, part 2. *Am J Health-Syst Pharm* 2006; **63:** 534–46.
3. Guise TA. Bone loss and fracture risk associated with cancer therapy. *Oncologist* 2006; **11:** 1121–31.

Thromboembolism. For discussion on the management of venous or arterial thrombosis, see Effects on the Cardiovascular System, p. 727.2.

Tumour lysis syndrome. Management of tumour lysis syndrome is based on hydration, correction of metabolic abnormalities, and supportive treatment of renal failure.[1-3] Aggressive hydration with isotonic sodium chloride reduces concentrations of uric acid, phosphate, and potassium, and should be considered in all patients at risk of the syndrome, except those at risk of volume overload. Management of acute hyperkalaemia may include cardiac membrane stabilisation with calcium gluconate, intracellular shift of potassium using insulin (with glucose) or inhaled beta$_2$ agonists, and increased excretion of potassium by diuretics or dialysis. In the management of hyperuricaemia[1,3,4] allopurinol may be given prophylactically to reduce the formation of uric acid, and rasburicase may be used for both prophylaxis and treatment by increasing uric acid oxidation. Adequate hydration, sometimes with urinary alkalinisation using sodium bicarbonate, also improves the solubility and hence renal excretion of uric acid.

1. Davidson MB, *et al.* Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med* 2004; **116:** 546–54.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; **127:** 3–11.
3. Coiffier B, *et al.* Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; **26:** 2767–78.
4. Holdsworth MT, Nguyen P. Role of i.v. allopurinol and rasburicase in tumor lysis syndrome. *Am J Health-Syst Pharm* 2003; **60:** 2213–24.

Precautions

In view of their severe toxicity and possible carcinogenicity these drugs should generally be reserved for severe or life-threatening disease, and it is widely suggested that their use should be confined to experienced staff in specialised centres.

Immunosuppression and bone-marrow depression are features of many of these drugs and their use is associated with an increased risk of infections caused by pathogenic or opportunistic micro-organisms, and a reduced capacity to cope with them. Where possible, immunosuppressant drugs should not be given to patients with acute infections, and dosage reduction or withdrawal should be considered if infection develops, until the infection has been controlled. For cautions regarding the use of vaccines in patients receiving these drugs see Interactions, p. 733.3. For discussion of the treatment of infections in immunosuppressed patients, see p. 186.3. Special care is necessary in debilitated patients.

Blood counts and measurement of haemoglobin concentrations should be carried out routinely to help predict the onset of bone-marrow depression. Great caution is needed when the marrow is already depressed from radiotherapy or therapy with other antineoplastics, and modification of dosage regimens may be required. The blood counts below which treatment is contra-indicated will vary depending on the regimen to be used and the therapeutic intent of that treatment (see Bone-Marrow Depression, p. 730.3); local protocols, including those for the use of colony-stimulating factors, should always be consulted.

Although positive evidence of teratogenicity in humans is not available for all antineoplastics, pregnancy should be avoided in women receiving them: in particular they should not be given, if possible, during the first trimester. Mothers receiving antineoplastic therapy should not breast feed. Because some regimens may result in permanent infertility, the storage of semen samples for male patients, and embryos for females before such therapy may be desirable.

Many antineoplastics are vesicant or irritant. Care must be taken to avoid extravasation since severe pain and tissue damage may ensue. They must be handled with great care and contact with skin and eyes avoided; they should not be inhaled. In many countries official or professional guidelines on precautions for the safe handling of cytotoxic drugs have been issued.

For precautions specific to particular drugs, see under the individual monographs.

Administration. Oral antineoplastic drugs have the same potential for treatment-related toxicity and serious medication errors as intravenous antineoplastic drugs.[1] The National Patient Safety Agency (NPSA) in the UK received 3 reports of fatalities and 400 safety incidents with *oral* antineoplastic drugs between November 2003 and July 2007. Errors included the incorrect dose, frequency, quantity, or duration of medication.[2] The NPSA has recommended that the prescribing, dispensing, and use of oral antineoplastics (excluding hormonal therapy) should be carried out and monitored to the same standard as that of parenteral therapy, requiring the inclusion of some of the following procedures:

- treatment should be started by a cancer specialist
- prescription in the context of a written protocol and treatment plan, including guidance on monitoring and treatment of toxicity
- access to the written protocol and treatment plan, and access to advice from an experienced cancer pharmacist, for non-specialist prescribers and dispensers
- patients should be provided with written information, including details of the original regimen and treatment plan and arrangements for monitoring

Recommendations for the dispensing and supply of oral chemotherapy in the primary care setting have been made by specialist organisations.[1]

Doses of antineoplastics are determined using different methods, including body-surface area or body-weight; alternatively, doses may be fixed. Doses are further adjusted after consideration of a patient's individual health status. Dose regimens may be complex and may differ depending on its indication, or on whether a drug is used as monotherapy or as part of a combination regimen. The *BNF* omits some dose statements of antineoplastic drugs for this reason, while stating that, even where dose statements are given, specialist literature, chemotherapy protocols, or local cancer networks should be consulted before prescribing, dispensing, and giving these drugs; furthermore, they advocate that prescriptions for these drugs should not be repeated without specialist instruction.

1. Williamson S. British Oncology Pharmacy Association, Royal Pharmaceutical Society, National Pharmacy Association. A report on the dispensing and supply of oral chemotherapy and systemic anticancer medicines in primary care (issued January 2011). Available at: http://www.rpharms.com/support-pdfs/providing-oral-chemotherapy-in-the-community.pdf (accessed 07/07/11)
2. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR001 (issued 22nd January, 2008): risks of incorrect dosing of oral anti-cancer medicines. Available at: www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60278&type=full&servicetype=Attachment (accessed 07/07/11)

Administration in the elderly. The use of antineoplastics in the elderly should take into consideration age-related physiological changes including decline in renal and hepatic function, reduced haematopoietic reserve, and reduced gastrointestinal and cardiac function. Other factors to consider are comorbid conditions and potential drug interactions with associated medications.[1-9] Neoplastic disorders in the elderly have been undertreated because of an impression that these diseases are less aggressive,[10] and the effects of chemotherapy more likely to be severe.[1,2,10,11] Elderly patients have often been excluded from clinical studies for reasons that included physician bias, protocol eligibility criteria with restrictions on comorbidities, and poor patient functional status.[12] There is evidence, however, that healthy older patients can tolerate chemotherapy as well as younger patients.[1,2] However, there have been few studies of chemotherapy specifically in elderly patients,[4,10] and selection of a suitable dosage regimen is more difficult as a consequence, although there is increasing effort to address this lack of data.[2,10,11] Old people vary as much as any other group in their response to drugs, and the consensus is that they should not be excluded from any form of treatment on the grounds of age alone.

1. Kimmick GG, *et al.* Cancer chemotherapy in older adults: a tolerability perspective. *Drugs Aging* 1997; **10:** 34–49.
2. Lichtman SM, Skirvin JA. Pharmacology of antineoplastic agents in older cancer patients. *Oncology (Huntingt)* 2000; **14:** 1743–55.
3. Wildiers H, *et al.* Pharmacology of anticancer drugs in the elderly population. *Clin Pharmacokinet* 2003; **42:** 1213–42.

4. Lichtman SM, *et al*. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.
5. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. *Cancer Control* 2007; **14:** 32–43.
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7. Balducci L. Pharmacology of antineoplastic medications in older cancer patients. *Oncology (Williston Park)* 2009; **23:** 78–85.
8. Balducci L. Supportive care in elderly cancer patients. *Curr Opin Oncol* 2009; **21:** 310–17.
9. Gillison TL, Chatta GS. Cancer chemotherapy in the elderly patient. *Oncology (Williston Park)* 2010; **24:** 76–85.
10. Balducci L, Beghe' C. Cancer and age in the USA. *Crit Rev Oncol Hematol* 2001; **37:** 137–45.
11. Muss HB. Older age—not a barrier to cancer treatment. *N Engl J Med* 2001; **345:** 1128–9.
12. Townsley CA, *et al*. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; **23:** 3112–24.

Administration at home. Outpatients taking oral antineoplastic therapy (such as capecitabine or tegafur with uracil) at home do not receive the same level of monitoring as inpatients, and should be cautioned to report any adverse effects, since such treatments may still produce severe toxicity. Problems with home administration include non-compliance, interactions with other drugs and food, and medication errors. However, many patients prefer oral therapy to intravenous administration, and such problems can be managed with better communication and patient education. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Bleyer WA, Danielson MG. Oral cancer chemotherapy in paediatric patients: obstacles and potential for development and utilisation. *Drugs* 1999; **58** (suppl 3): 133–40.
2. Hollywood E, *et al*. Nursing strategies for patients on oral chemotherapy. *Oncology (Williston Park)* 2001; **15** (1 suppl 2): 37–9.
3. Borner M, *et al*. Answering patients' needs: oral alternatives to intravenous therapy. *Oncologist* 2001; **6** (suppl 4): 12–16.
4. Gerbrecht B-M. Current Canadian experience with capecitabine: partnering with patients to optimize therapy. *Cancer Nurs* 2003; **26:** 161–7.
5. Gerbrecht B-M, Kangas T. Implications of capecitabine (Xeloda) for cancer nursing practice. *Eur J Oncol Nurs* 2004; **8** (suppl 1): S63–S71.
6. Bartel SB. Safe practices and financial considerations in using oral chemotherapeutic agents. *Am J Health-Syst Pharm* 2007; **64** (9 suppl 5): S8–S14.
7. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. *Am J Health-Syst Pharm* 2007; **64** (9 suppl 5): S4–S7.

Contraception. The *BNF* recommends that intra-uterine devices for contraception be used with caution in patients with drug- or disease-induced immunosuppression, because of the risk of infection; such devices are contra-indicated in marked immunosuppression.

Handling and disposal. Antineoplastics are usually potent and potentially highly toxic drugs that must be handled with due care. In many countries official or professional guidelines are available for the handling, reconstitution, and disposal of antineoplastics, and most centres or institutions in which these drugs are used will have individual handling policies based on these.[1]

Recommendations generally include:

- that these drugs be reconstituted by trained personnel;
- that reconstitution take place in designated areas, designed to protect personnel and the environment—for example, the use of safety cabinets;
- that protective clothing be worn, including gloves, eye protection, and masks if necessary (it should be noted that gloves may vary in their resistance to penetration, depending upon their thickness, the material of which they are made, and the drug in question[1,2]);
- that waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (it should be noted that the patient's body fluids and excreta may contain appreciable amounts of antineoplastic agents and it has been suggested that they and materials such as bed linen contaminated with them should also be treated as hazardous waste[3,4]);
- that adequate procedures should be in place for accidental contamination due to spillages;
- that staff exposure to antineoplastic agents be recorded and monitored;
- that pregnant staff should avoid handling these drugs if possible.

1. Allwood M, *et al*. eds. *The Cytotoxics Handbook*. 4th ed. Oxford: Radcliffe Medical Press,2002.
2. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. *Am J Health-Syst Pharm* 1999; **56:** 2450–3.
3. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.
4. Cass Y, Musgrave CF. Guidelines for the safe handling of excreta contaminated by cytotoxic agents. *Am J Hosp Pharm* 1992; **49:** 1957–8.

Pregnancy. Antineoplastics may be used during pregnancy for their immunosuppressant properties in auto-immune disease, and for the treatment of cancer, which can complicate 1 in 1000 pregnancies.[1-3] Although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus.[1]

The highest incidence of adverse effects appears to occur after exposure during the first trimester:[1-4] about 10 to 20% of fetuses exposed to cytotoxics during this period have major malformations, compared with 3% in the general population.[1] Malformations reflect the gestational age at exposure. The fetus is particularly vulnerable when exposed during organogenesis (weeks 2 to 8 after conception), and the heart, neural tube, and limbs are affected earlier than the palate and ear; after organogenesis, the eyes, genitalia, haematopoietic system, and CNS remain vulnerable to continued exposure.[3]

The risk of fetal malformations after exposure during the second and third trimesters is probably no higher than the background rate, but there may still be an increased risk of still-birth, fetal growth restriction, premature birth, and maternal or fetal myelosuppression.[1-3]

The delayed effects of antineoplastics on development have not been well-documented. Despite concerns that premature birth and low birth-weight could contribute to retardation of growth, development, and intellect,[5] long-term follow-up of a limited number of children has not shown any evidence of abnormalities.[3-5] Similarly, although maternal antineoplastic therapy has been implicated in a case of childhood neuroblastoma and papillary thyroid cancer, the child's fraternal twin, exposed to the same drugs *in utero*, was healthy.[3] There have been no reports of secondary leukaemias in exposed offspring, but the longer term risk is unknown.[3]

The teratogenicity of any drug depends on the timing of exposure, the dose, and the characteristics affecting placental transfer,[3] as well as the actions of the drug. Of the antineoplastics, the greatest risk seems to be associated with alkylating agents and antimetabolites, in particular aminopterin, fluorouracil, and methotrexate.[1,2,6] The vinca alkaloids and doxorubicin (but not epirubicin or idarubicin) may entail less risk,[2,3] although the former have produced malformations in *animals*.[1] Other drugs reported to be teratogenic or potentially teratogenic include busulfan,[1] chlorambucil,[1,6] chlormethine,[1] cyclophosphamide,[1,6] cytarabine,[1] and the podophyllotoxin derivatives.[1] The problems with thalidomide and its congeners are well known.

There are no specific dosage recommendations for the use of antineoplastics during pregnancy, but physiological changes occurring in the mother can alter the pharmacokinetics of drugs.[1-3] This could potentially increase the toxicity of the antineoplastic, or decrease its efficacy.[2] Anecdotal evidence suggests that adverse effects may be less marked during pregnancy, perhaps reflecting reduced peak or free-drug concentrations in the blood.[3] Myelosuppressive chemotherapy should be avoided 3 weeks before the anticipated delivery so that the mother is neither neutropenic nor thrombocytopenic.[1-3] For the same reason, chemotherapy should be avoided after 35 weeks of gestation, when spontaneous delivery is more likely to occur.[3] The timing of delivery is also critical for the neonate, as chemotherapy given shortly before delivery may not be eliminated through the placenta, prolonging exposure in the newborn.[1,3]

There has also been concern that long-term *occupational exposure* to antineoplastics might have an adverse effect on the fetus of pregnant healthcare workers: a study in 650 Finnish nurses found that women who experienced fetal loss were more than twice as likely to have had first trimester exposure to antineoplastic drugs as women who successfully gave birth.[7] These results have been criticised on the grounds that such results are not generally seen in cancer patients,[8,9] who presumably are exposed to much higher doses of antineoplastics. However, similar results were seen in a cross-sectional analysis of 7094 pregnancies involving 2815 nursing and pharmacy staff.[10] Another study[11] has suggested that the rate of ectopic pregnancy may be increased in nurses occupationally exposed to antineoplastics, but the small number of ectopic pregnancies involved (15 in 734 pregnancies) means that the association with antineoplastics may be due to chance. A further, larger, case-control study[12] by the same investigators found no evidence of an increased rate of ectopic pregnancy, and suggested that occupational exposure to higher levels of antineoplastics in the past possibly explained the earlier findings. Again, such an effect does not appear to have been reported in women treated with antineoplastics.

See also Effects on Reproductive Potential, p. 729.2.

1. Buekers TE, Lallas TA. Chemotherapy in pregnancy. *Obstet Gynecol Clin North Am* 1998; **25:** 323–9.
2. Falkenberry SS. Cancer in pregnancy. *Surg Oncol Clin N Am* 1998; **7:** 375–97.
3. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; **5:** 283–91.
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6. Østensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? *Drug Safety* 1998; **19:** 389–410.
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10. Valanis B, *et al*. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med* 1999; **41:** 632–8.
11. Saurel-Cubizolles MJ, *et al*. Ectopic pregnancy and occupational exposure to antineoplastic drugs. *Lancet* 1993; **341:** 1169–71.
12. Bouyer J, *et al*. Ectopic pregnancy and occupational exposure of hospital personnel. *Scand J Work Environ Health* 1998; **24:** 98–103.

Interactions

Because of their effects on the gastrointestinal mucosa antineoplastics have the potential to interfere with the absorption of drugs given orally. Antineoplastics that have an immunosuppressant effect may reduce the response to vaccines, and there is a possibility of generalised infection with live vaccines. Use with live vaccines should generally be avoided.

Many antineoplastics are inhibitors of certain isoenzymes of cytochrome P450 and some antineoplastics are also metabolised by these enzymes, and in consequence the possibility of interactions between antineoplastics, or between antineoplastics and other medication, cannot be discounted.

Interactions affecting specific drugs are covered under the individual monographs.

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1. Le Blanc GA, Waxman DJ. Interaction of anticancer drugs with hepatic monooxygenase enzymes. *Drug Metab Rev* 1989; **20:** 395–439.
2. Loadman PM, Bibby MC. Pharmacokinetic drug interactions with anticancer drugs. *Clin Pharmacokinet* 1994; **26:** 486–500.
3. Kivistö KT, *et al*. The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. *Br J Clin Pharmacol* 1995; **40:** 523–30.
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5. Beijnen JH, Schellens JHM. Drug interactions in oncology. *Lancet Oncol* 2004; **5:** 489–96.
6. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents: underlying mechanisms and implications for oral chemotherapy. *Clin Pharmacokinet* 2004; **43:** 1127–56.
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8. Harmsen S, *et al*. The role of nuclear receptors in pharmacokinetic drug-drug interactions in oncology. *Cancer Treat Rev* 2007; **33:** 369–80.
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Antiepileptics. Retrospective review of outcomes in children treated for acute lymphoblastic leukaemia indicated that long-term antiepileptic therapy increased the clearance of several antileukaemic drugs and reduced the efficacy of therapy.[1] Management of patients with brain tumours or metastases, which may predispose patients to convulsions, thus poses particular problems in the choice of antiepileptic treatment if interactions are to be avoided; the topic has been reviewed.[2,3]

1. Relling MV, *et al*. Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* 2000; **356:** 285–90.
2. Vecht CJ, *et al*. Treating seizures in patients with brain tumors: drug interactions between antiepileptic and chemotherapeutic agents. *Semin Oncol* 2003; **30** (suppl 19): 49–52.
3. Ruggiero A, *et al*. Interactions between antiepileptic and chemotherapeutic drugs in children with brain tumors: is it time to change treatment? *Pediatr Blood Cancer* 2010; **54:** 193–8.

Antivirals. The potential for interaction between antiretrovirals and antineoplastics has been reviewed.[1] Although clinical evidence of interactions is scanty, various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and thus have the potential to interact with some antineoplastics including taxanes, vinca alkaloids, and cyclophosphamide.

1. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet* 2005; **44:** 111–45.

Antoxidants. The potential for interactions between antoxidants and antineoplastics has been reviewed.[1] Theoretically, antoxidants might reduce the efficacy of antineoplastic chemotherapy. The authors raised three concerns regarding this effect:

- *acetylcysteine* should not be used with *cisplatin* or *doxorubicin*;
- *tangeretin*, a flavonoid, should not be used with *tamoxifen*; and
- *betacarotene* should not be used with *fluorouracil*.

Aside from these possible interactions, no *in-vivo* evidence was found to suggest that natural antoxidants interfere with conventional cancer chemotherapy.

1. Lamson DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Altern Med Rev* 1999; **4:** 304–29.

Effects on other drugs. Antineoplastics have been reported to affect several drugs including:

- digoxin (reduced absorption, see p. 1357.1)

- oral anticoagulants (increased or decreased effect, see Warfarin, p. 1532.2)
- phenytoin (increased or decreased effect, see p. 544.1)
- suxamethonium (prolonged effect, see p. 2039.3)
- vaccines (decreased response, see p. 2375.3).

Herbal medicines. The potential for interactions between antineoplastics and herbal medicines has been reviewed.[1,2] There is a general lack of information and reports, and warnings are largely based on theory and extrapolation from herbal interactions with other drugs.

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2. Yeung KS, Gubili J. Clinical guide to herb-drug interactions in oncology. *J Soc Integr Oncol* 2007; **5:** 113–17.

Pharmacokinetics

Many antineoplastics have intra- and interindividual pharmacokinetic variability that can be influenced by various factors. Patient age, disease state, and drug interactions can affect drug absorption, distribution, metabolism, and excretion. Genetic polymorphisms also affect drug disposition and are under investigation, but the clinical use of such information is currently limited. Various methods have been tried or are being investigated as ways of tailoring initial drug dosage and therapeutic drug monitoring for individual patients in order to improve treatment efficacy and minimise toxicity. Such methods include population pharmacokinetic modelling and individual pharmacogenetic typing; examples include carboplatin dosing based on glomerular filtration rate (see Administration, p. 759.2) and genotyping of patients thought to be at increased risk of irinotecan toxicity (see Genetic Factors, p. 813.3).

Reviews.

1. Schrijvers D. Role of red blood cells in pharmacokinetics of chemotherapeutic agents. *Clin Pharmacokinet* 2003; **42:** 779–91.
2. Tomita M, *et al*. Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs. *Clin Pharmacokinet* 2004; **43:** 515–27.
3. Fleischhack G, *et al*. Pharmacokinetics following intraventricular administration of chemotherapy in patients with neoplastic meningitis. *Clin Pharmacokinet* 2005; **44:** 1–31.
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8. Yong WP, *et al*. The role of pharmacogenetics in cancer therapeutics. *Br J Clin Pharmacol* 2006; **62:** 35–46.
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Action

Much of the development of cancer chemotherapy has been based on an understanding of the way in which tumour cells grow, and the way in which the drugs affect this growth.

After cell division the daughter cells enter a period of growth, G_1, which lasts for different lengths of time in different tissues. This is followed by a period of DNA synthesis, **S**, in which the amount of chromosomal material is doubled, then a postsynthetic, or premitotic, phase, G_2, then finally by mitotic cell division, **M**. As an alternative to re-entering the cycle, the products of cell division may enter a kinetically-dormant, nonproliferative stage, G_0, although it is not exactly clear what recruits such 'resting' cells back into the cell cycle.

The rate of cell division varies for different tumours; the doubling time for Burkitt's lymphoma and acute lymphoblastic leukaemia is less than 5 days, whereas the mean doubling time for seminoma is about 20 days, that for small-cell lung cancer about 50 days, and those for colon cancer and advanced breast cancer about 100 and 150 days respectively. The range of reported doubling times may also vary widely for a particular tumour type. Most common cancers increase very slowly in size in comparison with sensitive normal tissues, including those from which they derive, and the rate may decrease further in large tumours. This difference allows normal cells to recover more quickly than malignant ones from chemotherapy, and is the rationale behind cyclic dosage schedules. The lethal body tumour burden is reached when the tumour cell mass approaches or exceeds 1×10^{12} cells, equivalent to about 1 kg of tissue, and representing about 40 doublings.

Cell killing by cytotoxic agents is generally a first order process, so a given dose or course of antineoplastic kills a fixed percentage of tumour cells rather than a fixed number. Thus a drug that killed 99% of tumour cells would leave behind 10^{10} cells from a tumour containing 10^{12} cells, but only 10^2 cells from one containing 10^4, reinforcing the importance of treating malignant neoplasms as early as possible.

Cytotoxic drugs act to damage the reproductive integrity of cells. Some are active at a particular stage of the cell cycle. The antimetabolites interfere with DNA synthesis, as does hydroxycarbamide, and are thus active against cells in S phase, while the vinca alkaloids inhibit microtubular function and act on cells in phase M. Other drugs such as the alkylating agents, the anthracyclines, and cisplatin are not phase-specific, but since their actions are dependent at least in part on damaging DNA they are more effective against proliferating cells, particularly in S phase. It is now thought that many antineoplastics exert their ultimate effect by inducing cellular apoptosis (programmed cell death). Some drugs, such as bleomycin or vinblastine also have the property of arresting the cycle in a particular phase, and attempts have been made to synchronise tumour cell division in this way, to maximise the number of cells in a sensitive phase when a particular drug is used. However, in practice this approach has been less successful than early experimental results suggested.

Some drugs used in the treatment of neoplasms do not attack the tumour cells directly but are given in order to increase cell vulnerability to other modalities: these include radiosensitisers (which have proved of only limited benefit to date), and photosensitisers such as porfimer sodium, used in photodynamic therapy (PDT).

Apart from attacking cell division, increased understanding of the molecular biology of tumour cells has begun to open the possibility of other approaches to the treatment of malignant neoplasms. Some monoclonal antibodies are designed to bind to specific cell-surface proteins or receptors, enabling the immune system to recognise and attack tumour cells (targeted therapy); anti-tumour vaccines have also been developed. Control of tumour growth through inhibition of angiogenesis is also being used. Other areas of investigation include inducing tumour cells to differentiate into non-malignant forms, manipulation of cellular apoptosis and signal transduction, inhibiting the expression of abnormal growth factors, telomerases and other oncogene products (including the use of ribozymes or of 'antisense' compounds which inhibit oncogenic messenger RNA), and prevention or inhibition of metastasis. Gene therapy (p. 2511.2) is another form of treatment under consideration.

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5. Pirollo KF, *et al*. Antisense therapeutics: from theory to clinical practice. *Pharmacol Ther* 2003; **99:** 55–77.
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Resistance

Resistance to antineoplastics is one of the greatest limitations to the use of chemotherapy in malignant disease. Resistance may be intrinsic to the tumour or may be acquired during chemotherapy, which effectively acts to select resistant cells from a heterogeneous population; the latter is one reason that relapses, or malignancies in heavily-pretreated patients, may be particularly difficult to treat.

The mechanisms of resistance in cancer cells are complex and imperfectly understood, but appear to include:

- hypoxia and imperfect drug penetration in the centre of large, solid tumours
- the small proportion of cells actively dividing and thus vulnerable to antineoplastics (particularly in slow-growing tumours)
- decreased cellular uptake or increased efflux of antineoplastic
- increased metabolic breakdown or decreased activation of antineoplastic
- increased expression of target enzymes
- metabolism via alternative biochemical pathways to those blocked by the antineoplastic
- more efficient repair of damaged DNA
- possibly the expression of genes which inhibit drug-induced apoptosis.

Several of these mechanisms may be in operation at one time. Much interest has been expressed in the potential use of drugs which can modulate or inhibit mechanisms of resistance, and in particular in compounds such as valspodar, verapamil, quinidine, and ciclosporin, which have the ability to block the action of P-glycoprotein, a membrane glycoprotein which acts as an efflux pump for a range of cytotoxic substances and which is one of a group of so-called ATP-binding cassette (ABC) drug transporters responsible for the multidrug resistant (MDR) phenotype. However, for sustained benefit it seems likely that several drugs would be required, each to overcome a different mechanism of resistance, and it would be necessary to ensure that toxicity of antineoplastics to normal cells was not also enhanced.

If the emergence of heritable resistant phenotypes is a natural part of tumour-cell biology (the Goldie-Coldman hypothesis) it implies that the larger and older the tumour, the more likely is resistance to occur. This would confirm the benefits of surgery and radiotherapy to shrink the primary tumour, and of starting chemotherapy as soon as possible after (a preferably early) diagnosis.

Antiresistance agents. Some drugs have been reported to partially abolish multidrug resistance to antineoplastics *in vitro*.[1,2] These include:

- verapamil, its enantiomers and analogues such as Ro-11-2933
- other calcium-channel blockers including prenylamine, diltiazem, nifedipine analogues such as nicardipine and bepridil
- various phenothiazines and thioxanthenes including trifluoperazine and the *trans*-isomer of flupentixol
- structural analogues of the anthracyclines and vinca alkaloids
- progesterone and other steroid hormones, as well as, to some extent, anti-oestrogens such as tamoxifen
- ciclosporin and various of its nonimmunosuppressive analogues (such as valspodar)
- miscellaneous drugs including amiodarone, quinidine, propranolol, reserpine, yohimbine, dipyridamole, erythromycin, cefoperazone, and ceftriaxone

However, despite reported effects on resistance *in vitro* clinical results may be less impressive: studies in which verapamil was added to therapy for small cell lung cancer[3] or multiple myeloma[4] failed to show any benefit, and second-generation P-glycoprotein inhibitors such as valspodar have unpredictable pharmacokinetic interactions with cytotoxics.[5] Nevertheless, there is ongoing development of inhibitors of P-glycoprotein and other ATP-binding cassette drug transporters,[6] and drugs such as tariquidar are undergoing clinical studies.[5] It has been suggested that tumour growth may rely on a malignant equivalent of stem cells, with innate multidrug resistance, and that this may make overcoming resistance without damaging normal stem cells particularly difficult.[7]

1. Ford JM, Hait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 1990; **42:** 155–99.
2. Krishna R, Mayer LD. Multidrug resistance (MDR) in cancer: mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. *Eur J Pharm Sci* 2000; **11:** 265–83.
3. Milroy R, *et al*. A randomised clinical study of verapamil in addition to combination chemotherapy in small cell lung cancer. *Br J Cancer* 1993; **68:** 813–18.
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Abiraterone Acetate (BANM, USAN, rINNM)

Abirateron-azetat; Abiratérone, Acétate d'; Abirateroni Acetas; Acetato de abiraterona; CB-7630; Абиратерона Ацетат.

17-(Pyridin-3-yl)androsta-5,16-dien-3β-yl acetate.

$C_{26}H_{33}NO_2$=391.6

CAS — 154229-19-3 (abiraterone); 154229-18-2 (abiraterone acetate).

UNII — EM5OCB9YJ6.

Uses and Administration

Abiraterone acetate suppresses testosterone production by inhibiting the enzyme CYP17, which plays a key role in sex hormone synthesis, and is given orally with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer (p. 712.3). It is used in patients given previous docetaxel-based chemotherapy, and in those where androgen deprivation therapy has failed but chemotherapy is not yet indicated. Medical castration therapy with a gonadorelin (LHRH) analogue should be continued. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The recommended dose is 1 g daily as a single dose, plus prednisone or prednisolone 5 mg twice daily (or 10 mg daily). Abiraterone should be taken on an empty stomach, at least 2 hours after and one hour before any food. For doses in patients who develop hepatotoxicity or with pre-existing hepatic impairment, see below.

References.

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2. de Bono JS, *et al.* COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; **364:** 1995–2005.
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5. Ryan CJ, *et al.* COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; **368:** 138–48. Correction. *ibid.;* 584.

Administration in hepatic impairment. No dose adjustment of abiraterone is necessary for patients with pre-existing mild hepatic impairment (Child-Pugh class A). In patients with baseline moderate hepatic impairment (Child-Pugh class B), US licensed product information recommends that the oral dose of abiraterone acetate be reduced to 250 mg daily. Use in patients with severe hepatic impairment (Child-Pugh class C) should be avoided since data are lacking.

For patients who develop increases in liver enzymes above 5 times the upper limit of normal (ULN) or total bilirubin >3 times ULN during treatment, US licensed product information states that therapy should be interrupted, and only restarted (at a reduced dose of 750 mg daily) once these values have fallen to acceptable levels (baseline or no more than half the increased values above). If hepatotoxicity recurs at the lower dose, a dose of 500 mg daily is recommended once values have fallen to acceptable levels, but if it recurs again, treatment should be stopped.

UK licensed product information states that, for patients who develop increases in liver enzymes above 5 times the ULN, therapy should be stopped, and advocates restarting at 500 mg daily once values return to baseline levels; if hepatotoxicity recurs at this reduced dose, treatment should be stopped. If patients develop increases in enzymes 20 times the ULN at any time while on therapy, abiraterone should be stopped permanently and patients should not be re-treated.

Adverse Effects, Treatment, and Precautions

Abiraterone acetate inhibits the enzyme CYP17, which can result in mineralocorticoid excess, very often leading to hypertension, hypokalaemia, and fluid retention or oedema; patients should be monitored at least monthly for these effects, and treated appropriately. Use with a glucocorticoid can reduce the incidence and severity of these adverse effects. However, adrenocortical insufficiency has been reported in those treated with abiraterone acetate plus prednisone or prednisolone, and patients should be monitored for manifestations of this, particularly after withdrawal from the corticosteroid.

Caution is needed when treating patients with heart failure, recent myocardial infarction, ventricular arrhythmia, or any underlying medical condition likely to be adversely affected by mineralocorticoid effects. Cardiac disorders are common with abiraterone acetate, and include cardiac failure, chest pain, angina pectoris, arrhythmias, atrial fibrillation, and tachycardia.

Hepatotoxicity can occur, and treatment may need to be stopped, or the dose adjusted (see Administration in Hepatic Impairment, above). Serum transaminases and bilirubin levels should be measured before starting treatment, then every two weeks for the first three months, and monthly thereafter.

Joint swelling or discomfort, muscle discomfort, hot flushes, dyspepsia, diarrhoea, cough, urinary-tract infection, urinary frequency, nocturia, and upper respiratory-tract infection are common, as is hypertriglyceridaemia.

Interactions

Abiraterone inhibits the cytochrome P450 isoenzyme CYP2D6; caution is advised when abiraterone acetate is used with drugs activated or metabolised by CYP2D6, especially those with a narrow therapeutic index. *In-vitro* studies have shown that abiraterone is also an inhibitor of CYP2C8.

Abiraterone is metabolised by the cytochrome P450 isoenzyme CYP3A4. Strong inhibitors or inducers of CYP3A4 should be avoided, or used with caution, during treatment with abiraterone acetate.

Pharmacokinetics

Abiraterone acetate is hydrolysed to abiraterone, which is active. Peak plasma concentrations of abiraterone occur about 2 hours after an oral dose of abiraterone acetate. Systemic exposure to abiraterone is increased when abiraterone acetate is given with food. Abiraterone is over 99% bound to plasma proteins. Abiraterone is metabolised via sulfation, hydroxylation, and oxidation, mainly in the liver. The two main metabolites are abiraterone sulfate and *N*-oxide abiraterone sulfate, which are inactive; these are formed by the enzymes SULT2A1, and cytochrome P450 isoenzyme CYP3A4 and SULT2A1, respectively. The mean terminal plasma half-life of abiraterone is reported to be about 15 hours in healthy subjects, and about 12 hours in patients with metastatic castration-resistant prostate cancer. About 88% of a dose is excreted in the faeces, of which about 55% is unchanged abiraterone acetate and about 22% is abiraterone; about 5% of a dose is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Zytiga; ***Canad.***: Zytiga; ***Denm.***: Zytiga; ***Fr.***: Zytiga; ***Ger.***: Zytiga; ***Irl.***: Zytiga; ***Israel***: Zytiga; ***Neth.***: Zytiga; ***Norw.***: Zytiga; ***Spain***: Zytiga; ***Swed.***: Zytiga; ***Switz.***: Zytiga; ***UK***: Zytiga; ***USA***: Zytiga.

Aceglatone (rINN)

Aceglatona; Acéglatone; Aceglatonum; Ацеглатон.

D-Glucaric acid 1,4:6,3-dilactone diacetate.

$C_{10}H_{10}O_8$=258.2

CAS — 642-83-1.

UNII — 347Q3OOJ13.

Profile

Aceglatone inhibits the activity of β-glucuronidase and has an anti-inflammatory action. It has been given orally to prevent relapse after surgery for carcinoma of the bladder. Adverse effects have included anorexia, gastric discomfort, and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Glucaron.

Aclarubicin (BAN, USAN, rINN)

Aclacinomycin A; Aclarubicina; Aclarubicine; Aclarubicinum; Aklarubicin; Aklarubisiini; Aklarubisin; NSC-208734; Акларубицин.

Methyl (1*R*,2*R*,4*S*)-4-(*O*-[2,6-dideoxy-4-*O*-[(2*R*,6*S*)-tetrahydro-6-methyl-5-oxopyran-2-yl]-α-L-*lyxo*-hexopyranosyl]-(1→4)-2,3,6-trideoxy-3-dimethylamino-L-*lyxo*-hexopyranosyloxy)-2-ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxonaphthacene-1-carboxylate.

$C_{42}H_{53}NO_{15}$=811.9

CAS — 57576-44-0.

ATC — L01DB04.

ATC Vet — QL01DB04.

UNII — 74KXF8I502.

Description. Aclarubicin is an anthracycline antineoplastic antibiotic isolated from *Streptomyces galilaeus.*

Aclarubicin Hydrochloride (BANM, rINNM)

Aclarubicina, hidrocloruro de; Aclarubicine, Chlorhydrate d'; Aclarubicini Hydrochloridum; Hidrocloruro de aclarubicina; Акларубицина Гидрохлорид.

$C_{42}H_{53}NO_{15}$,HCl=848.3

CAS — 75443-99-1.

ATC — L01DB04.

ATC Vet — QL01DB04.

UNII — 501948RI66.

Pharmacopoeias. In *Jpn.*

Profile

Aclarubicin is an anthracycline antibiotic with actions similar to those of other anthracyclines such as doxorubicin (p. 782.3), although it inhibits RNA synthesis more strongly than DNA synthesis. It has been given by intravenous infusion as the hydrochloride in the treatment of malignant blood disorders, such as acute myeloid leukaemia. Alopecia and cardiotoxicity may be less pronounced than with doxorubicin, and extravasation of aclarubicin causes less local tissue inflammation.

Stability. In a study of the stability of anthracycline antineoplastic agents in 4 infusion fluids—glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid—stability appeared to be partly related to pH; aclarubicin was most stable in sodium chloride injection, with a pH of 6.2, and any increase or decrease in pH appeared to affect stability adversely.[1]

1. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.

Adverse effects. An early review[1] noted that a strikingly high incidence of ECG changes had been seen with aclarubicin, but that although acute cardiotoxicity occurred, the chronic cardiomyopathy classically associated with the anthracyclines (see p. 784.1) appeared to be rare. Alopecia was also rare, although gastrointestinal disturbances and mucositis were as common or more common than with doxorubicin.

1. Warrell RP. Aclacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; **12:** 275–82.

Uses. An early review of studies in patients with relapsed acute myeloid leukaemia confirmed the activity of aclarubicin, with reported complete remission rates of the order of 12 to 24%.[1] Doses varied from 10 to 30 mg/m² daily to higher doses of 75 to 120 mg/m² for 2 to 4 days; in general a total dose of about 300 mg/m² appeared to be necessary to induce remission. Less information was available concerning activity in acute lymphoblastic leukaemia, but response rates were lower than those in acute myeloid leukaemia. Results in the malignant lymphomas were generally disappointing.

Longer-term follow-up has confirmed that remission rates and survival are similar for induction regimens in acute myeloid leukaemia using either aclarubicin or daunorubicin.[2,3] A regimen of aclarubicin with low-dose cytarabine and granulocyte colony-stimulating factor (CAG) has been used, including in elderly patients and those with refractory disease.[4-6]

1. Warrell RP. Aclacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; **12:** 275–82.
2. de Nully Brown P, *et al.* Long-term survival and development of secondary malignancies in patients with acute myeloid leukemia treated with aclarubicin or daunorubicin plus cytosine arabinoside followed by intensive consolidation chemotherapy in a Danish national phase III trial. *Leukemia* 1997; **11:** 37–41.
3. Öberg G, *et al.* Long-term follow-up of patients ⩾60 yr old with acute myeloid leukaemia treated with intensive chemotherapy. *Eur J Haematol* 2002; **68:** 376–81.
4. Li JM, *et al.* Aclarubicin and low-dose cytosine arabinoside in combination with granulocyte colony-stimulating factor in treating acute myeloid leukemia patients with relapsed or refractory disease and myelodysplastic syndrome: a multicenter study of 112 Chinese patients. *Int J Hematol* 2005; **82:** 48–54.
5. Qian SX, *et al.* Effect of low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor priming (CAG regimen) on the outcome of elderly patients with acute myeloid leukemia. *Leuk Res* 2007; **31:** 1383–8.
6. Xue SL, *et al.* CAG regimen enables relapsed or refractory T-cell acute lymphocytic leukemia patients to achieve complete remission: a report of six cases. *Am J Hematol* 2008; **83:** 167–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Klasinomycin; ***Jpn***: Aclacinon.

AE-941

CAS — 305838-77-1.

NOTE. The name Neovastat has been used as a trade mark for AE-941.

Profile

AE-941 is an angiogenesis inhibitor derived from shark cartilage extract. It has been investigated for the treatment of renal cell carcinoma, non-small cell lung cancer, and some other neoplasms.

References.
1. Sauder DN, *et al.* Neovastat (AE-941), an inhibitor of angiogenesis: randomized phase I/II clinical trial results in patients with plaque psoriasis. *J Am Acad Dermatol* 2002; **47:** 535–41.
2. Gingras D, *et al.* Neovastat—a novel antiangiogenic drug for cancer therapy. *Anticancer Drugs* 2003; **14:** 91–6.
3. Lu C, *et al.* Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. *J Natl Cancer Inst* 2010; **102:** 859–65.

Afatinib *(USAN, rINN)*

Afatinibum; BIBW-2992; Афатиниб.

(2*E*)-*N*-[4-(3-Chloro-4-fluoroanilino)-7-{[(3*S*)-oxolan-3-yl]oxy}quinazolin-6-yl]-4-(dimethylamino)but-2-enamide.

$C_{24}H_{25}ClFN_5O_3$=485.9

CAS — 850140-72-6.

ATC — L01XE13.

ATC Vet — QL01XE13.

UNII — 41UD74L59M.

NOTE. The name Tomtovok has been used as a trade mark for afatinib.

Afatinib Maleate *(rINNM)*

Afatinib Dimaleate (USAN); Afatinib, Maléate de; Afatinibi Maleas; BIBW-2992 MA2; Maleato de afatinib; Афатиниба Малеат.

$C_{24}H_{25}ClFN_5O_3.2C_4H_4O_4$=718.1

CAS — 850140-73-7.

UNII — V1T5K7RZ0B.

Uses and Administration

Afatinib is a tyrosine kinase inhibitor directed against the epidermal growth factor receptor (EGFR) family; it is used in the treatment of metastatic non-small cell lung cancer (p. 711.1) that has EGFR exon 19 deletions or exon 21 (L858R) substitutions. It is given as the maleate but doses are expressed in terms of the base; 59.12 mg of afatinib maleate is equivalent to about 40 mg of afatinib. A usual oral dose of 40 mg once daily is taken on an empty stomach. A missed dose should not be taken within 12 hours of the next dose. Treatment may need to be modified if toxicity occurs, see Administration in Subsequent Cycles, below. Afatinib therapy is continued until disease progression or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

If afatinib is poorly tolerated when given with a P-glycoprotein inhibitor, the daily dose of afatinib should be reduced by 10 mg; afatinib may be increased back to the previous dose on stopping treatment with the inhibitor. If chronic treatment with a P-glycoprotein inducer is required, the daily dose of afatinib should be increased by 10 mg as tolerated; afatinib should be decreased back to the previous dose 2 to 3 days after stopping the inducer.

Afatinib is also under investigation in various other malignancies.

References.
1. Chen X, *et al.* Clinical perspective of afatinib in non-small cell lung cancer. *Lung Cancer* 2013; **81:** 155–61.
2. Nelson V, *et al.* Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. *Onco Targets Ther* 2013; **6:** 135–43.

Administration in subsequent cycles. Treatment with afatinib may need to be modified for toxicity. Doses should be withheld if any of the following adverse effects occur:
- grade 3 or worse adverse effects
- grade 2 or worse diarrhoea that persists for more than 2 consecutive days despite anti-diarrhoeal medication
- grade 2 cutaneous reactions that are intolerable or prolonged (lasting more than 7 days)
- grade 2 or worse renal dysfunction

When the adverse effect has resolved, returned to baseline, or improved to grade 1, afatinib can be restarted at a reduced oral dose of 10 mg less than that at which the effect occurred. Afatinib should be permanently stopped if severe adverse effects occur at a dose of 20 mg daily, or if any of the following reactions occur:
- life-threatening bullous, blistering, or exfoliative skin lesions
- interstitial lung disease
- severe drug-induced hepatic impairment
- persistent ulcerative keratitis
- symptomatic left ventricular dysfunction

Adverse Effects and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Commonly reported adverse effects with afatinib are diarrhoea, stomatitis, cheilitis, rash, pruritus, dry skin, conjunctivitis, epistaxis, rhinorrhoea, paronychia, cystitis, decreased appetite and body weight, and pyrexia. Skin reactions can be severe and include bullous, blistering, or exfoliating lesions. Pulmonary toxicity has been reported including interstitial lung disease. Hepatotoxicity with increased liver enzyme values, hypokalaemia, and ventricular dysfunction have also occurred. Treatment may need to be stopped or modified for severe toxicity, see Administration in Subsequent Cycles, above.

Based on its mechanism of action and data from *animal* studies, afatinib is not recommended during pregnancy. Women of reproductive potential should use effective contraception during and for at least 2 weeks after treatment.

References.
1. Lacouture ME, *et al.* Dermatologic adverse events associated with afatinib: an oral ErbB family blocker. *Expert Rev Anticancer Ther* 2013; **13:** 721–8.

Interactions

Afatinib is a substrate of P-glycoprotein and use with P-glycoprotein inhibitors or inducers could affect exposure to afatinib; dose adjustments may be required, see Uses and Administration, above. *In vitro* data suggest that afatinib is also an inhibitor of P-glycoprotein, and a substrate and an inhibitor of the breast cancer resistance protein (BCRP) transporter.

Pharmacokinetics

Peak concentrations of afatinib occur 2 to 5 hours after oral dosing. Exposure is reduced when afatinib is taken with a high-fat meal. It is 95% bound to plasma proteins. Afatinib is excreted, mainly as unchanged drug, in the faeces (85%) with a small amount in the urine (4%). The elimination half-life is 37 hours after repeated dosing, and steady state concentrations occur within 8 days.

Exposure to afatinib is increased in patients with renal impairment.

References.
1. Wind S, *et al.* Pharmacokinetics of afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours. *Clin Pharmacokinet* 2013;.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Gilotrif.

Aflibercept *(USAN, rINN)*

Afliberceptum; AVE-0005; VEGF Trap; VEGF Trap-Eye; VEGF $Trap_{R1R2}$; Афлиберцепт.

Des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211′:214-214′)-bisdisulfide dimer.

CAS — 862111-32-8.

ATC — S01LA05.

ATC Vet — QS01LA05.

UNII — 15C2VL427D.

NOTE. There are significant differences in the processing and formulation of preparations containing the active ingredient aflibercept and consequently they are not therapeutically interchangeable.

To emphasise this in the USA, preparations are available as:
- *Eylea* (*Regeneron, USA*): described as containing aflibercept
- *Zaltrap* (*Regeneron, USA*): described as containing ziv-aflibercept

However, in Europe and other countries the preparations *Eylea* and *Zaltrap* are both described as containing aflibercept, and the name ziv-aflibercept is not used.

Uses and Administration

Aflibercept is a recombinant human fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factor-A (VEGF-A), factor-B (VEGF-B), and placental growth factor (PlGF); this inhibits the activation of receptor tyrosine kinases, VEGFR-1 and VEGFR-2. The inhibition of these growth factors reduces neovascularisation and angiogenesis.

Aflibercept (*Eylea*) is used to treat neovascular (wet) age-related macular degeneration (p. 880.2). The initial recommended dose is 2 mg by intravitreal injection once each month for 3 doses, followed by 2 mg every 2 months. After 12 months of treatment, doses may be given less frequently, according to response. Aflibercept is also used for the treatment of macular oedema following central retinal vein occlusion, in a dose of 2 mg by intravitreal injection once every month. When visual and anatomical measures are stable for 3 monthly assessments, the interval between doses may be gradually increased and treatment stopped. Monitoring should continue and therapy may be restarted if necessary. However, if there is no improvement from the first 3 doses, treatment should be stopped.

Aflibercept, or as ziv-aflibercept in the USA, (*Zaltrap*) is used with fluorouracil, folinic acid, and irinotecan in the treatment of metastatic colorectal cancer (p. 706.3) that is resistant to or has progressed after an oxaliplatin-containing regimen. A dose of aflibercept 4 mg/kg is given by intravenous infusion over 1 hour every 2 weeks, and should be given before any other component of the regimen on that day of treatment. The dose should be diluted to a final concentration of 0.6 to 8 mg/mL in sodium chloride 0.9% or glucose 5% and infused through a 0.2 micrometre polyethersulfone filter; other filters made of polyvinylidene fluoride or nylon should not be used. Doses may need to be reduced or withheld if severe hypertension, proteinuria, or neutropenia develop (see Administration in Subsequent Cycles, below). Therapy should continue until there is disease progression or unacceptable toxicity.

References.
1. Boyer D, *et al.* Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology* 2012; **119:** 1024–32.
2. Van Cutsem E, *et al.* Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; **30:** 3499–3506.
3. Frampton JE. Aflibercept for intravitreal injection: in neovascular age-related macular degeneration. *Drugs Aging* 2012; **29:** 839–46.
4. Heier JS, *et al.* VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012; **119:** 2537–48. Correction. *ibid.* 2013; **120:** 209–10.
5. Brown DM, *et al.* Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. *Am J Ophthalmol* 2013; **155:** 429–37.
6. Holz FG, *et al.* VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol* 2013; **97:** 278–84.
7. Thomas M, *et al.* Comparative effectiveness of aflibercept for the treatment of patients with neovascular age-related macular degeneration. *Clin Ophthalmol* 2013; **7:** 495–501.
8. Evoy KE, Abel SR. Aflibercept: newly approved for the treatment of macular edema following central retinal vein occlusion. *Ann Pharmacother* 2013; **47:** 819–27.

Administration in subsequent cycles. In the treatment of metastatic colorectal cancer, aflibercept, or as ziv-aflibercept in the USA, (*Zaltrap*) should be withheld in patients who develop recurrent or severe hypertension. Treatment may be restarted when the blood pressure is under control, at a permanently reduced dose of 2 mg/kg by intravenous infusion every 2 weeks. Aflibercept should be withheld in patients who develop proteinuria, until it is less than 2 g per 24 hours. If the proteinuria is recurrent, treatment should be restarted at a permanently lower dose of 2 mg/kg by intravenous infusion every 2 weeks. Dose of aflibercept should also be delayed in patients who have a neutrophil count below 1500 cells/mm^3.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of aflibercept **intravitreal injection** are conjunctival haemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intra-ocular pressure. Other adverse effects include endophthalmitis, retinal detachment, and retinal tear. Hypersensitivity reactions have been reported. There is a potential risk of thromboembolic events such as stroke, myocardial infarction, or vascular death following intravitreal use of vascular endothelial growth factor (VEGF) inhibitors.

Common adverse effects that occur in patients given **intravenous** aflibercept, or as ziv-aflibercept in the USA, include bleeding, hypertension, proteinuria, leucopenia, neutropenia, thrombocytopenia, decreases in body-weight and appetite, diarrhoea, abdominal pain, stomatitis, dysphonia, increases in liver function tests and serum-creatinine, fatigue, and headache. Arterial and venous thromboembolic events and severe hypersensitivity reactions have occurred. Reversible posterior leukoencephalopathy syndrome has been reported in patients given aflibercept.

Severe and sometimes fatal haemorrhage and gastrointestinal perforation have been associated with the use of intravenous aflibercept. Fistula formation can occur and wound healing may be compromised. Aflibercept should be stopped at least 4 weeks before elective surgery. After major surgery it should not be restarted for at least 4 weeks and not

until the surgical wound is fully healed; after minor surgery it may be restarted when the wound is fully healed.

Severe hypertension, including cases of hypertensive crisis, has been reported. Blood pressure should be monitored every 2 weeks and antihypertensive therapy started when necessary. Aflibercept may need to be withheld and the dose reduced after severe or recurrent hypertension is under control; it should be stopped in patients with hypertensive crisis or hypertensive encephalopathy. Patients should also be monitored for proteinuria during aflibercept therapy, which may need to be withheld or the dose reduced; it should be stopped in those who develop nephrotic syndrome or thrombotic microangiopathy.

A complete blood count with differential count should be made before each dose of intravenous aflibercept; treatment should be delayed if the neutrophil count is below 1500 cells/mm^3.

Pharmacokinetics

Systemic absorption occurs after intravitreal administration of aflibercept; peak plasma concentrations are low and occur within 3 days, and free plasma-aflibercept concentrations are undetectable 2 weeks following administration. The terminal half-life of free aflibercept in plasma is about 6 days following intravenous administration of doses of 2 to 4 mg/kg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Eylea; ***Jpn***: Eylea; ***Neth.***: Zaltrap; ***Switz.***: Eylea; Zaltrap; ***UK***: Eylea; Zaltrap; ***USA***: Eylea; Zaltrap.

Alemtuzumab *(BAN, rINN)*

Alemtutsumabi; Alemtuzumabum; Campath-1; Campath-1H; Алемтузумаб.

Immunoglobulin G 1 (human-rat monoclonal CAMPATH-1H γ1-chain antihuman antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer.

CAS — 216503-57-0.

ATC — L01XC04.

ATC Vet — QL01XC04.

UNII — 3A189DH42V.

NOTE. The name FluCam has been used for a regimen of alemtuzumab with fludarabine. Distinguish from Flucam, which is a proprietary name for ampiroxicam (p. 21.1).

Uses and Administration

Alemtuzumab is a humanised derivative of campath-1G, a rat monoclonal antibody to the CD52 antigen found on lymphocytes. It is used in the treatment of B-cell chronic lymphocytic leukaemia (p. 693.3) and is also licensed in the EU (under the trade name of *Lemtrada*) for use in relapsing-remitting multiple sclerosis (below).

For the treatment of **chronic lymphocytic leukaemia** the dose of alemtuzumab must be increased gradually to avoid infusion-related reactions (see Adverse Effects, below). Alemtuzumab should be diluted in 100 mL sodium chloride 0.9% or glucose 5%. The initial dose is 3 mg daily, given as an intravenous infusion over 2 hours (it may be increased up to 8 hours in some patients, see Adverse Effects, below). This dose should be repeated daily until it is tolerated; the dose should then be increased to 10 mg daily. When this dose is tolerated, the maintenance dose of 30 mg can be started; this dose escalation usually takes 3 to 7 days. The maintenance dose of 30 mg is given three times weekly on alternate days. The total duration of therapy, including dose escalation, is 12 weeks. Doses should be modified according to haematological toxicity (see Administration in Subsequent Cycles, below).

For the treatment of **multiple sclerosis** alemtuzumab has been given by intravenous infusion over 4 hours for 2 treatment courses, as follows:

- initial treatment course: 12 mg daily for 5 consecutive days, to a total dose of 60 mg
- second treatment course given 12 months after the initial course: 12 mg daily for 3 consecutive days, to a total dose of 36 mg

Missed doses within a treatment course should not be given on the same day as a scheduled dose. Patients should be pre-treated with a corticosteroid on each of the first 3 days of any course. Oral prophylaxis with 200 mg twice daily of aciclovir (or similar) for herpes infection should also be started on the first day of each course and continued for a minimum of 1 month following treatment.

Alemtuzumab is under investigation for induction therapy in transplantation (see Organ and Tissue Transplantation, p. 1936.2, *et seq*).

References.

1. Hale G, *et al.* Alemtuzumab (Campath-1H) for treatment of lymphoid malignancies in the age of nonmyeloablative conditioning? *Bone Marrow Transplant* 2002; **30:** 797–804.
2. Frampton JE, Wagstaff AJ. Alemtuzumab. *Drugs* 2003; **63:** 1229–43.
3. Keating M, *et al.* Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. *Clin Lymphoma* 2004; **4:** 220–7.
4. Faderl S, *et al.* The evolving role of alemtuzumab in management of patients with CLL. *Leukemia* 2005; **19:** 2147–52.
5. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. *Transplantation* 2006; **81:** 1361–7.
6. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int* 2006; **19:** 705–14.
7. Ravandi F, O'Brien S. Alemtuzumab in CLL and other lymphoid neoplasms. *Cancer Invest* 2006; **24:** 718–25.
8. Boyd K, Dearden CE. Alemtuzumab in the treatment of chronic lymphocytic lymphoma. *Expert Rev Anticancer Ther* 2008; **8:** 525–33.
9. Robak T. Alemtuzumab for B-cell chronic lymphocytic leukemia. *Expert Rev Anticancer Ther* 2008; **8:** 1033–51.
10. Ciancio G, Burke GW. Alemtuzumab (Campath-1H) in kidney transplantation. *Am J Transplant* 2008; **8:** 15–20.
11. Dhesi S, *et al.* Alemtuzumab and liver transplantation: a review. *Curr Opin Organ Transplant* 2009; **14:** 245–9.
12. Gribben JG, Hallek M. Rediscovering alemtuzumab: current and emerging therapeutic roles. *Br J Haematol* 2009; **144:** 818–31.
13. Österborg A, *et al.* Management guidelines for the use of alemtuzumab in chronic lymphocytic leukemia. *Leukemia* 2009; **23:** 1980–8.

Administration. Subcutaneous use of alemtuzumab has been investigated as a means of reducing adverse infusion reactions associated with intravenous dosage. Studies have found it to be safe and effective.[1,2] Similar blood concentrations are achieved to those after intravenous use, although accumulation in the blood took longer to achieve with subcutaneous use, and higher cumulative doses were required.[3] A dose of 30 mg subcutaneously three times weekly has been widely used; given for 4 to 12 weeks it has been shown to be as effective and safe as intravenous alemtuzumab in patients with fludarabine-refractory disease, and it has been suggested that the convenience of subcutaneous injection, which can be given on an outpatient basis, makes it the preferred route for this indication.[4] Although treatment has normally been started with lower doses and gradually increased (e.g. 3 mg on day 1, 10 mg on day 2, 30 mg on day 3, and then 30 mg three times weekly), use with the higher dose from the outset has been investigated.[5] Prolonged treatment with subcutaneous low-dose alemtuzumab (10 mg three times weekly for 18 weeks) has also been tried and was reported to be as effective as intravenous infusion in patients with chronic lymphocytic leukaemia and a poor prognosis.[6]

1. Montillo M, *et al.* Safety and efficacy of subcutaneous Campath-1H for treating residual disease with chronic lymphocytic leukemia responding to fludarabine. *Haematologica* 2002; **87:** 695–700.
2. Lundin J, *et al.* Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). *Blood* 2002; **100:** 768–73.
3. Hale G, *et al.* Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration. *Blood* 2004; **104:** 948–55.
4. Stilgenbauer S, *et al.* Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2009; **27:** 3994–4001.
5. Karlsson C, *et al.* Phase II study of subcutaneous alemtuzumab without dose escalation in patients with advanced-stage, relapsed chronic lymphocytic leukaemia. *Br J Haematol* 2009; **144:** 78–85.
6. Cortelezzi A, *et al.* A pilot study of low-dose subcutaneous alemtuzumab therapy for patients with hemotherapy-refractory [sic] chronic lymphocytic leukemia. *Haematologica* 2005; **90:** 410–12.

Administration in subsequent cycles. The dose of alemtuzumab may be modified from the usual intravenous maintenance dose (see Uses and Administration, above) for neutropenia and thrombocytopenia in those being treated for chronic lymphocytic leukaemia as follows:

In patients with higher baseline values whose absolute neutrophil count (ANC) falls to < 250 cells/mm^3 and/or whose platelet count falls to ≤25 000 cells/mm^3:

- for first occurrence: withhold alemtuzumab. Resume at 30 mg when ANC ⩾ 500 cells/mm^3 and platelet count ⩾ 50 000 cells/mm^3
- for second occurrence: withhold alemtuzumab. Resume at 10 mg when ANC ⩾ 500 cells/mm^3 and platelet count ⩾ 50 000 cells/mm^3
- for third occurrence: stop alemtuzumab

In patients who are started on alemtuzumab with a baseline ANC already ≤250 cells/mm^3 and/or a baseline platelet count ≤25 000 cells/mm^3, and who have a ≥50% decrease from baseline:

- for first occurrence: withhold alemtuzumab. Resume at 30 mg upon return to baseline value
- for second occurrence: withhold alemtuzumab. Resume at 10 mg upon return to baseline value
- for third occurrence: stop alemtuzumab

If alemtuzumab is withheld, and the time to recovery is ≥7 days, then alemtuzumab should be restarted at the usual initial dose and increased gradually (see Uses and Administration, above).

Multiple sclerosis. Alemtuzumab has been licensed in the EU for the treatment of multiple sclerosis (p. 996.3). However, an FDA committee has raised concerns about its adverse effects such as auto-immune cytopenias and autoimmune thyroid disease which can be fatal and may outweigh its benefits. For further information on the adverse effects of alemtuzumab, see under Adverse Effects, Treatment, and Precautions, below.

It has been proposed that the secondary progressive phase of the disease might be due to post-inflammatory neurodegeneration and that immunotherapy would influence long-term disability only if given early in the disease course. A phase 2 randomised study assigned treatment-naive patients with early, relapsing-remitting multiple sclerosis to either alemtuzumab or interferon beta. Alemtuzumab (at a dose of either 12 mg daily or 24 mg daily) was given by intravenous infusion on 5 consecutive days during the first month, and on 3 consecutive days at months 12 and 24; interferon beta-1a at a dose of 44 micrograms was given subcutaneously 3 times weekly after dose escalation. All patients received intravenous methylprednisolone at the time of infusion. There were no significant differences between the groups receiving either dose of alemtuzumab on any outcome measure or adverse event. However, 6 cases of immune thrombocytopenic purpura occurred with alemtuzumab treatment, including one fatality, prompting suspension of therapy with alemtuzumab. Nonetheless, compared with interferon beta, alemtuzumab significantly improved mean disability scores and reduced the rate of relapse; efficacy was maintained over 36 months, even though some 70% of alemtuzumab-treated patients were not given the planned third cycle due to safety concerns. Alemtuzumab also increased brain volume on magnetic resonance imaging, whereas brain atrophy advanced among patients receiving interferon beta. The authors of the study noted that, while alemtuzumab appears to be more effective than interferon beta when given in the earliest stages of multiple sclerosis, there is a dilemma as to whether to expose young adults with little disability to the potentially serious adverse effects of alemtuzumab.[1]

Extended follow-up of patients in this study group, for up to 5 years from the start of therapy, found that alemtuzumab remained significantly more effective than interferon beta-1a.[2] The superiority of alemtuzumab compared with interferon beta-1a was further confirmed in a phase 3 study of previously untreated patients with early, relapsing-remitting multiple sclerosis[3] and also in those with at least one relapse after disease-modifying therapy with either interferon beta or glatiramer.[4]

1. Coles AJ, *et al.* CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; **359:** 1786–1801.
2. Coles AJ, *et al.* Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012; **78:** 1069–78.
3. Cohen JA, *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1819–28.
4. Coles AJ, *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1829–39.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Alemtuzumab commonly causes bone marrow depression, which may be severe and prolonged; fatalities have occurred. Auto-immune anaemia and auto-immune thrombocytopenia and haemolytic anaemia have been reported less commonly; however, fatalities have been reported. Single doses greater than 30 mg, or cumulative weekly doses greater than 90 mg should not be used, because of the increased incidence of pancytopenia. Complete blood and platelet counts should be measured weekly during alemtuzumab therapy, and more frequently if anaemia, neutropenia, or thrombocytopenia occur. Treatment should be interrupted if severe myelosuppression or evidence of haematological toxicity are seen and stopped permanently if auto-immune anaemia or auto-immune thrombocytopenia develops. Lymphopenia may be profound with alemtuzumab therapy, and opportunistic infections are common, and occasionally life-threatening. Antimicrobial prophylaxis is recommended from the start of therapy until after completion; if serious infection occurs, treatment should be interrupted. Recovery of lymphocyte counts may take 6 months or longer after stopping treatment.

Alemtuzumab commonly causes an acute cytokine release syndrome. The reaction usually includes rigors, fever, nausea and vomiting, hypotension, rash, urticaria, pruritus, shortness of breath, headache, and diarrhoea. Rarer, more serious reactions may include bronchospasm, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, and cardiac arrest. Cardiac adverse effects have been fatal in

some instances. These infusion-related reactions are most common at the start of therapy: the dose must be increased gradually when beginning treatment, or if it is interrupted for 7 days or more. Pre-medication with an oral or intravenous corticosteroid, oral antihistamine, and analgesic should also be used, particularly before the first dose, and with dose increases. If acute infusion reactions persist, the infusion time may be extended to 8 hours from the time of reconstitution.

Other adverse effects include fatigue, anorexia, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, chest pain, hypertension, cyanosis, and bradycardia or tachycardia. Localised oedema, stomatitis, mucositis, and abdominal pain have been reported, as have dizziness, paraesthesia, tremor, and taste loss. Confusion, insomnia or somnolence, depression, or anxiety may occur. Electrolyte disturbances include hyponatraemia and hypocalcaemia. Coughing, haemoptysis, sinusitis, bronchitis, and pharyngitis have been reported.

Alemtuzumab is contra-indicated for patients with active systemic infection, or underlying immunodeficiency.

Auto-immune disorders. Aside from auto-immune cytopenias, alemtuzumab has been associated with the development of auto-immune thyroid disease in 20 to 30% of patients, occurring months to years after treatment.[1] Anti-glomerular basement membrane disease has also been reported after alemtuzumab,[2] as has Guillain-Barré syndrome.[3] It has been commented[2] that B-cell recovery tends to precede T-cell recovery after alemtuzumab treatment, and that the auto-immune diseases seen after therapy are mainly antibody-mediated, and respond to B-cell depletion.

1. Jones JL, *et al*. IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). *J Clin Invest* 2009; **119:** 2052–61.
2. Clatworthy MR, *et al*. Anti-glomerular basement membrane disease after alemtuzumab. *N Engl J Med* 2008; **359:** 768–9.
3. Abbi KKS, *et al*. Guillain-Barré syndrome after use of alemtuzumab (Campath) in a patient with T-cell prolymphocytic leukemia: a case report and review of the literature. *Leuk Res* 2010; **34:** e154–e156.

Effects on the lungs. Diffuse alveolar haemorrhage has been reported after a single dose of alemtuzumab was used during renal transplantation in a patient with X-linked Alport syndrome (an inherited disorder involving damage to the kidneys, haematuria, and hearing loss).[1]

1. Sachdeva A, Matuschak GM. Diffuse alveolar hemorrhage following alemtuzumab. *Chest* 2008; **133:** 1476–8.

Infection. Reactivation of hepatitis B,[1] hepatitis C,[2] and CMV[3] has been reported with the use of alemtuzumab. Patients who have been pretreated with purine analogues or those with advanced disease and not responding to alemtuzumab therapy appear to be at highest risk for infectious complications. Recommendations for screening and prophylaxis[4] and guidelines[5] and reviews[6] concerning management have been published. Six infection-related deaths have been reported[7] after previously untreated patients with B-cell chronic lymphocytic leukaemia were treated with fludarabine and rituximab, followed by alemtuzumab. These deaths may have resulted from a prolonged period of immunosuppression due to the sequencing of these drugs without sufficient recovery time. In the EU, alemtuzumab is licensed for use in patients for whom fludarabine combination chemotherapy is not appropriate.

1. Iannitto E, *et al*. Hepatitis B virus reactivation and alemtuzumab therapy. *Eur J Haematol* 2005; **74:** 254–8.
2. Anoop P, *et al*. Severe liver dysfunction from hepatitis C virus reactivation following alemtuzumab treatment for chronic lymphocytic leukaemia. *Br J Haematol* 2010; **148:** 484–6.
3. Laurenti L, *et al*. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. *Haematologica* 2004; **89:** 1248–52.
4. Thursky KA, *et al*. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol* 2006; **132:** 3–12.
5. O'Brien SM, *et al*. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Clin Lymphoma Myeloma* 2006; **7:** 125–30.
6. Elter T, *et al*. Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Ann Hematol* 2009; **88:** 121–32.
7. Bayer, UK; Genzyme, UK. Important safety information: six infection-related deaths reported after treatment with MabCampath(alemtuzumab) following Fludarabine+Rituximab induction in patients with B-Cell Chronic Lymphocytic Leukemia (CLL) (issued 11th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014104&RevisionSelectionMethod=Latest (accessed 12/05/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alemtuzumab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

There are no formal interaction studies with alemtuzumab; however, it is recommended that it should not be given within 3 weeks of other chemotherapy drugs, and that patients should not receive live viral vaccines for at least 12 months after receiving alemtuzumab.

Pharmacokinetics

In patients with B-cell chronic lymphocytic leukaemia, distribution of alemtuzumab is mainly to the extracellular fluid and plasma. Over 12 weeks, clearance has been found to decrease with repeated dosing, with consequent accumulation in plasma, and the rate of elimination to approach zero-order kinetics. The half-life is reported to be 8 hours after a first dose of 30 mg, and 6 days after the last 30 mg dose. Steady-state concentrations are reached after about 6 weeks of therapy.

References.

1. Rebello P, *et al*. Pharmacokinetics of CAMPATH-1H in BMT patients. *Cytotherapy* 2001; **3:** 261–7.
2. Mould DR, *et al*. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath^{RTM}) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007; **64:** 278–91.
3. Elter T, *et al*. Pharmacokinetics of alemtuzumab and the relevance in clinical practice. *Leuk Lymphoma* 2008; **49:** 2256–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Campath; ***Austral.***: MabCampath; ***Austria***: MabCampath†; ***Belg.***: MabCampath†; ***Braz.***: Campath†; ***Canad.***: MabCampath; ***Cz.***: MabCampath†; ***Denm.***: MabCampath†; ***Fr.***: MabCampath†; ***Ger.***: MabCampath†; ***Gr.***: MabCampath†; ***Hong Kong***: MabCampath; ***Hung.***: MabCampath†; ***Indon.***: MabCampath; ***Irl.***: MabCampath†; ***Israel***: MabCampath†; ***Ital.***: MabCampath†; ***Malaysia***: MabCampath; ***Mex.***: MabCampath; ***Neth.***: MabCampath†; ***Norw.***: MabCampath†; ***NZ***: MabCampath; ***Pol.***: MabCampath†; ***Port.***: MabCampath†; ***Rus.***: Campath (Кэмпас); ***S.Afr.***: MabCampath; ***Singapore***: MabCampath; ***Spain***: MabCampath†; ***Swed.***: MabCampath†; ***Switz.***: MabCampath†; ***Thai.***: MabCampath; ***Turk.***: MabCampath; ***UK***: MabCampath†; ***Ukr.***: MabKampat (МабКампат); ***USA***: Campath.

Alitretinoin *(BAN, USAN, rINN)*

Ácido 9-*cis*-retinoico; AGN-192013; Alitretinoiini; Alitretinoína; Alitrétinoïne; Alitretinoinum; ALRT-1057; BAL-4079; 9-*cis*-Retinoic Acid; LG-100057; LGD-1057; NSC-659772; Алитретиноин.

(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

$C_{20}H_{28}O_2$=300.4

CAS — 5300-03-8.

ATC — D11AH04; L01XX22.

ATC Vet — QD11AH04; QL01XX22.

UNII — 1UA8E65KDZ.

Uses and Administration

Alitretinoin is a retinoid related to isotretinoin (p. 1706.2). It is given orally for severe chronic hand eczema (p. 1684.1) that is unresponsive to treatment with potent topical corticosteroids. Patients with mainly hyperkeratotic eczema are more likely to respond to treatment with alitretinoin. It is also used topically, in the management of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (p. 718.1).

The recommended starting dose of oral alitretinoin in adults is 30 mg once daily, with reduction to 10 mg once daily if adverse effects occur. The usual dose range is from 10 to 30 mg once daily, taken with meals. Treatment may be continued for 12 to 24 weeks depending on response. In the event of relapse, further treatment courses may be considered.

Topical treatment with a 0.1% alitretinoin gel is applied directly to the lesions twice daily, increasing to up to 4 times daily if tolerated. Doses should be increased at intervals of at least 2 weeks. If local toxicity occurs, application frequency should be reduced, or treatment temporarily stopped, until the symptoms subside. EU licensed product information states that if no response is seen after 12 weeks, therapy should be stopped; however, US licensed product information states that some patients have required over 14 weeks to respond. Treatment may be continued as long as the patient responds.

References.

1. Cheer SM, Foster RH. Alitretinoin. *Am J Clin Dermatol* 2000; **1:** 307–14.
2. Bodsworth NJ, *et al*. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. *Am J Clin Dermatol* 2001; **2:** 77–87.
3. Miles SA, *et al*. Antitumor activity of oral 9-cis-retinoic acid in HIV-associated Kaposi's sarcoma. *AIDS* 2002; **16:** 421–9.
4. Kurie JM, *et al*. Treatment of former smokers with 9-cis-retinoic acid reverses loss of retinoic acid receptor-beta expression in the bronchial epithelium: results from a randomized placebo-controlled trial. *J Natl Cancer Inst* 2003; **95:** 206–14.
5. Aboulafia DM, *et al*. 9-cis-Retinoic acid capsules in the treatment of AIDS-related Kaposi sarcoma: results of a phase 2 multicenter clinical trial. *Arch Dermatol* 2003; **139:** 178–86.
6. Ruzicka T, *et al*. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol* 2004; **140:** 1453–9.
7. Ruzicka T, *et al*. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158:** 808–17.
8. Garnock-Jones KP, Perry CM. Alitretinoin: in severe chronic hand eczema. *Drugs* 2009; **69:** 1625–34.
9. NICE. Alitretinoin for the treatment of severe chronic hand eczema (technology appraisal guidance 177, issued August 2009). Available at: http://www.nice.org.uk/nicemedia/live/12219/45225/45225.pdf (accessed 28/06/10)

Adverse Effects

Oral doses of alitretinoin may produce similar adverse effects to those of isotretinoin (see p. 1707.2). Decreases in concentrations of thyroid stimulating hormone and free T_4 are also often reported with alitretinoin, as are increases in platelets and increases in blood concentrations of creatine phosphokinase. Ankylosing spondylitis is uncommon.

Local skin toxicity may occur on topical application of alitretinoin, in particular erythema and oedema, and in some patients this may be dose-limiting. Pain, paraesthesia, rashes, pruritus, exfoliative dermatitis, and other skin disorders may also occur locally. Lymphadenopathy, phlebitis, cellulitis, and bacterial infections have been reported. Alitretinoin may have a weak photosensitising effect, and patients should minimise exposure of treated areas to sunlight or other ultraviolet light during therapy.

Precautions

When alitretinoin is given orally, the precautions described under isotretinoin (see p. 1709.2) including contra-indication of use in pregnancy and during breast feeding, should be adopted. Although absorption does not seem to occur to any great extent with topical use licensed product information also contra-indicates such use in pregnancy and in breast-feeding mothers. Oral alitretinoin is further contra-indicated in patients with severe renal impairment and uncontrolled hypothyroidism. Topical treatment with alitretinoin should not be used on lesions in close proximity to other skin disorders.

Interactions

The interactions described under isotretinoin (see p. 1710.1) also apply to oral alitretinoin. Alitretinoin is metabolised by the hepatic cytochrome P450 isoenzyme system, particularly CYP3A4. Use with CYP3A4 inhibitors such as ketoconazole increases the plasma concentration of alitretinoin and dose reduction may be required. Use of products containing diethyltoluamide is not recommended during topical alitretinoin therapy, as *animal* studies indicate an increase in diethyltoluamide toxicity with concurrent use.

Pharmacokinetics

After oral doses alitretinoin is variably absorbed from the gastrointestinal tract. When alitretinoin is taken with food, absorption becomes less variable and the systemic exposure is enhanced by a factor of 4. Alitretinoin is highly bound to plasma proteins. It undergoes metabolism by oxidation in the liver by the cytochrome P450 isoenzyme system into the major metabolite 4-oxo-alitretinoin. Alitretinoin and its metabolites are excreted mainly in the urine, with about 30% excreted in the faeces. The elimination half-life of unchanged alitretinoin is about 2 to 10 hours. Alitretinoin and 4-oxo-alitretinoin do not accumulate in the body.

Systemic absorption of topical alitretinoin is not considered to be extensive.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Panretin; ***Austria***: Panretin; Toctino; ***Canad.***: Toctino; ***Cz.***: Panretin; ***Denm.***: Toctino; ***Fin.***: Toctino; ***Fr.***: Panretin; Toctino; ***Ger.***: Panretin; Toctino; ***Gr.***: Panretin; ***Irl.***: Panretin; ***Israel***: Toctino; ***Neth.***: Panretin; Toctino; ***Norw.***: Toctino; ***Pol.***: Panretin; ***Port.***: Panretin; ***Spain***: Panretin; ***Switz.***: Toctino; ***UK***: Toctino; ***USA***: Panretin.

Altretamine *(BAN, USAN, rINN)*

Altretamiini; Altretamin; Altretamina; Altrétamine; Altretaminum; Hexamethylmelamine; HMM; NSC-13875; WR-95704; Альтретамин.

2,4,6-Tris(dimethylamino)-1,3,5-triazine; N^2,N^2,N^4,N^4,N^6,N^6-Hexamethyl-1,3,5-triazine-2,4,6-triamine.

$C_9H_{18}N_5$=210.3
CAS — 645-05-6.
ATC — L01XX03.
ATC Vet — QL01XX03.
UNII — Q8BIH59O7H.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Altretamine). A white crystalline powder. Insoluble in water; soluble in chloroform. Store in airtight containers.

Uses and Administration

Altretamine is an antineoplastic agent structurally similar to the alkylating agent tretamine (triethylenemelamine) although its mode of action may be different. It is given orally and is licensed for use as a single agent in the palliative treatment of ovarian carcinoma (p. 711.2). Altretamine has also been tried in lung cancer. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The usual dose as a single agent in ovarian cancer is 260 mg/m² daily in four divided doses, for 14 or 21 consecutive days out of a 28-day cycle. Up to 12 cycles may be given. Therapy should be interrupted for at least 14 days, and subsequently restarted at a lower dose of 200 mg/m² daily, if the white cell count falls below 2000 cells/mm³ or the platelet count below 75 000 cells/mm³ or if neurotoxic or intolerable gastrointestinal symptoms occur. Lower doses are also used in combination regimens.

Reviews.
1. Lee CR, Faulds D. Altretamine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cancer chemotherapy. *Drugs* 1995; **49:** 932–53.
2. Manetta A, *et al.* Hexamethylmelamine as a single second-line agent in ovarian cancer: follow-up report and review of the literature. *Gynecol Oncol* 1997; **66:** 20–6.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression is usually moderate, manifesting as leucopenia, thrombocytopenia, and anaemia, and may require dosage reduction; blood counts should be monitored regularly. Nausea and vomiting are common and usually moderate although they may be dose-limiting. Prolonged or high-dose therapy may be associated with neurotoxicity, both peripheral (neuropathies) and central (ataxia, depression, confusion, drowsiness, and hallucinations); neurological examination should be performed regularly and treatment interrupted or the dose reduced as appropriate. Renal toxicity may also be dose-limiting. Other rare adverse effects include rashes, alopecia, and hepatotoxicity.

Handling. Altretamine is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies altretamine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Pyridoxine appears to reduce the activity of altretamine.

Antidepressants. Severe and potentially life-threatening orthostatic hypotension developed in 3 patients who took *amitriptyline* or *imipramine* with altretamine and in a fourth patient who took *phenelzine* and altretamine.[1] One patient was able to tolerate the antineoplastic with *nortriptyline.*

1. Bruckner HW, Schleifer SJ. Orthostatic hypotension as a complication of hexamethylmelamine antidepressant interaction. *Cancer Treat Rep* 1983; **67:** 516.

Pharmacokinetics

Altretamine is well absorbed from the gastrointestinal tract after oral doses, but is rapidly demethylated in the liver producing variation in plasma-altretamine concentrations. The principal metabolites are pentamethylmelamine and tetramethylmelamine, which are excreted in urine. The elimination half-life has been reported to be 4 to 10 hours.

References.
1. Damia G, D'Incalci M. Clinical pharmacokinetics of altretamine. *Clin Pharmacokinet* 1995; **28:** 439–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hexalen†; ***Canad.***: Hexalen; ***Fr.***: Hexastat; ***India***: Cantret; ***Neth.***: Hexalen†; ***Rus.***: Hexalen (Гексален); ***Thai.***: Hexalen†; ***USA***: Hexalen.

Pharmacopoeial Preparations
USP 36: Altretamine Capsules.

Alvocidib *(BAN, USAN, rINN)*

Alvocidibum; Avodenib; Flavopiridol; HL-275; HMR-1275; L86-8275; MDL-107826A; NSC-649890; Альвоцидиб.
(-)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one.
$C_{21}H_{20}ClNO_5$=401.8
CAS — 146426-40-6.
UNII — 45AD6X575G.

Alvocidib Hydrochloride *(BANM, USAN, rINNM)*

Alvocidib, Chlorhydrate d'; Alvocidibi Hydrochloridum; Hidrocloruro de alvocidib; HL-275; HMR-1275; L-868275; MDL-107826A; NSC-649890; Альвоцидиба Гидрохлорид.
(-)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one hydrochloride.
$C_{21}H_{20}ClNO_5$,HCl=438.3
CAS — 131740-09-5.
UNII — D48MS3A6N9.

Profile

Alvocidib is an inhibitor of cyclin-dependent kinase that is under investigation as an antineoplastic for the treatment of chronic lymphocytic leukaemia.

Amatuximab *(USAN, rINN)*

Amatuximabum; MORAb-009; Аматуксимаб.
Immunoglobulin G1, anti-(mesothelin) (human-mouse monoclonal MORAb-009 heavy chain), disulfide with human-mouse monoclonal MORAb-009 κ-chain, dimer.
CAS — 931402-35-6.

Profile

Amatuximab is a humanised immunoglobulin G1 monoclonal antibody that targets the cell surface glycoprotein mesothelin which is overexpressed in several malignancies. It is under investigation in the treatment of mesothelioma.

Aminoglutethimide *(BAN, rINN)* ⊗

Aminoglutethimid; Aminoglutéthimide; Aminoglutethimidum; Aminoglutetimid; Aminoglutetimida; Aminoglutetimidas; Aminoglutetimidi; Aminoglutetymid; Aminoglutethetimide; Amminoglutetimide; Ba-16038; Аминоглутетимид.
2-(4-Aminophenyl)-2-ethylglutarimide; 3-(4-Aminophenyl)-3-ethylpiperidine-2,6-dione.
$C_{13}H_{16}N_2O_2$=232.3
CAS — 125-84-8.
ATC — L02BG01.
ATC Vet — QL02BG01.
UNII — 0O54ZQ14I9.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Aminoglutethimide). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol.

USP 36: (Aminoglutethimide). A white or creamy-white, fine, crystalline powder. Very slightly soluble in water; readily soluble in most organic solvents. It forms water-soluble salts with strong acids. The pH of a 0.1% solution in dilute methyl alcohol (1 in 20) is between 6.2 and 7.3.

Uses and Administration

Aminoglutethimide is an analogue of glutethimide and was formerly used for its weak anticonvulsant properties. Aminoglutethimide blocks the production of adrenal steroids and acts as an aromatase inhibitor to block the conversion of androgens to oestrogens (the major source of oestrogens in women without ovarian function). It was used in the treatment of metastatic breast cancer (p. 702.1) in postmenopausal or oophorectomised women and as palliative treatment in men with advanced prostatic cancer (p. 712.3) but has largely been superseded by other drugs.

Aminoglutethimide has also been used in the treatment of Cushing's syndrome (p. 2559.1). Usual oral doses range from 1 to 2 g daily, in divided doses.

The *dextro*-isomer of aminoglutethimide, dexaminoglutethimide has been investigated.

Adverse Effects

The most frequent adverse effects reported with aminoglutethimide include drowsiness, lethargy, and rash (sometimes with fever); these generally diminish after the first 6 weeks of therapy. Dizziness and nausea occasionally occur. Leucopenia, thrombocytopenia, agranulocytosis, or severe pancytopenia have occurred rarely. Adrenal insufficiency may rarely occur, and there have been reports of other endocrine disturbances including hypothyroidism, and virilisation. Other rare effects include ataxia, headache, depression, gastrointestinal disturbances, hypercholesterolaemia, and orthostatic hypotension.

Overdosage may lead to CNS depression and impairment of consciousness, electrolyte disturbances, and respiratory depression.

Effects on the liver. Aminoglutethimide has been associated with reports of cholestatic jaundice, accompanied by rash[1,2] and fever,[2] and probably due to an idiosyncratic hypersensitivity reaction.[1] It has been suggested that liver function tests should be carried out in patients receiving aminoglutethimide who develop fever and eruptions.[2]

1. Gerber SB, Miller KB. Cholestatic jaundice and aminoglutethimide. *Ann Intern Med* 1982; **97:** 138.
2. Perrault DJ, Domovitch E. Aminoglutethimide and cholestasis. *Ann Intern Med* 1984; **100:** 160.

Effects on the lungs. Pulmonary infiltrates in a patient who developed progressive dyspnoea on starting therapy with aminoglutethimide were found to be due to diffuse alveolar damage and haemorrhage; thrombocytopenia was present but prothrombin and bleeding times were normal. The patient's gas exchange and chest radiographs improved on stopping aminoglutethimide and giving corticosteroids.[1] Blood and pulmonary eosinophilia, which resolved on stopping aminoglutethimide therapy, has also been reported.[2]

1. Rodman DM, *et al.* Aminoglutethimide, alveolar damage, and hemorrhage. *Ann Intern Med* 1986; **105:** 633.
2. Bell SC, Anderson EG. Pulmonary eosinophilia associated with aminoglutethimide. *Aust N Z J Med* 1998; **28:** 670–1.

Lupus. SLE occurred in a patient who received aminoglutethimide, and resolved when the drug was withdrawn.[1] In another report, however, a patient with a lupus-like syndrome had a reduction in disease activity when tamoxifen therapy was changed to aminoglutethimide.[2]

1. McCraken M, *et al.* Systemic lupus erythematosus induced by aminoglutethimide. *BMJ* 1980; **281:** 1254.
2. Etherington J, *et al.* Effect of aminoglutethimide on the activity of a case of a connective tissue disorder with features of systemic lupus erythematosus. *Lupus* 1993; **2:** 387.

Precautions

Aminoglutethimide inhibits adrenal steroid production so supplementary glucocorticoid therapy with hydrocortisone must normally be given, although supplementation may not be necessary in patients with Cushing's syndrome. Some patients also require a mineralocorticoid. It has been suggested that aminoglutethimide should be temporarily withdrawn in patients who undergo shock or trauma, or develop intercurrent infection.

Blood pressure, blood counts, and serum electrolytes should be regularly monitored during aminoglutethimide therapy and periodic monitoring of liver and thyroid function is recommended.

Aminoglutethimide should not be given during pregnancy as pseudohermaphroditism may occur in the fetus.

Aminoglutethimide frequently causes drowsiness: patients so affected should not drive or operate machinery.

Interactions

The rate of metabolism of some drugs is increased by aminoglutethimide; patients also taking warfarin or other coumarin anticoagulants, theophylline, tamoxifen, medroxyprogesterone, or oral hypoglycaemics, may require increased dosages of these drugs. The metabolism of dexamethasone is also accelerated, which limits its value for corticosteroid supplementation in patients receiving aminoglutethimide. Use with diuretics may lead to hyponatraemia, while alcohol may potentiate the central effects of aminoglutethimide.

For reference to aminoglutethimide's interactions with *digitoxin* (see p. 1353.2), *theophylline* (see p. 1235.2), *progestogens* (see p. 2302.2), *tamoxifen* (see Antineoplastics, p. 863.3), and *anticoagulants* (under Warfarin, p. 1532.2).

Pharmacokinetics

Aminoglutethimide is well absorbed after oral doses and peak plasma concentrations occur after 1 to 4 hours. It is metabolised in the liver, mainly to *N*-hydroxylaminoglutethimide and *N*-acetylaminoglutethimide, and appears to induce its own metabolism. The half-life, which is reported to be about 13 hours after a single dose, is decreased to around 9 hours after about 2 weeks of continuous therapy. Aminoglutethimide is excreted in urine, about half a dose being excreted unchanged and the remainder as metabolites. Only about 20 to 25% of a dose is bound to plasma protein.

Half-life. A study in 17 patients showed that the plasma half-life of aminoglutethimide had a mean value of 15.5 hours after single doses but fell to 8.9 hours during multiple-dose therapy.[1] This marked reduction could largely be attributed to a decrease in the volume of distribution; auto-induction of metabolism might be of less importance in decreasing half-life than had been previously suggested.

1. Lønning PE, *et al.* Single-dose and steady-state pharmacokinetics of aminoglutethimide. *Clin Pharmacokinet* 1985; **10:** 353–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cytadren†; ***Gr.***: Orimetene; ***Hong Kong***: Orimetene†; ***Rus.***: Mamomit (Мамомит).

Pharmacopoeial Preparations
BP 2014: Aminoglutethimide Tablets;
USP 36: Aminoglutethimide Tablets.

5-Aminolevulinic Acid

5-ALA; ALA; 5-Aminolaevulinic Acid; 5-Aminolevulínico, ácido; 5-Amino-4-oxovaleric Acid; δ-Aminolaevulinic Acid. 5-Amino-4-oxopentanoic acid.
$C_5H_9NO_3$=131.1
CAS — 106-60-5.
ATC — L01XD04.
ATC Vet — QL01XD04.
UNII — 88755TAZ87.

Aminolevulinic Acid Hydrochloride *(USAN)*

Aminolaevulinic Acid Hydrochloride; Aminolevulínico, hidrocloruro ácido.
5-Aminolevulinic acid hydrochloride.
$C_5H_9NO_3$, HCl=167.6
CAS — 5451-09-2.
ATC — L01XD04.
ATC Vet — QL01XD04.
UNII — V35KBM8JGR.

Hexaminolevulinate Hydrochloride *(USAN)*

P-1026.
Hexyl 5-amino-4-oxopentanoate hydrochloride.
$C_{11}H_{21}NO_3$,HCl=251.8
CAS — 140898-91-5.
UNII — D4F329SL1O.

Methyl Aminolevulinate Hydrochloride *(USAN)*

Methyl Aminolaevulinate Hydrochloride; Metilaminolevulinato, hidrocloruro de; P-1202.
Methyl 5-amino-4-oxopentanoate hydrochloride.
$C_6H_{11}NO_3$,HCl=181.6
CAS — 79416-27-6.
ATC — L01XD03.
ATC Vet — QL01XD03.
UNII — 7S73606O1A.

Uses and Administration

5-Aminolevulinic acid is a naturally occurring haem precursor that is metabolised in the body to protoporphyrin IX, a photosensitiser that accumulates in malignant cells, and then to haem. 5-Aminolevulinic acid and its derivatives are used in photodynamic diagnosis and therapy (see under Porfimer Sodium, p. 849.1). They may be used to treat actinic keratoses, Bowen's disease, and basal cell carcinoma. Some are used in the diagnosis of bladder cancer or for visualisation of malignant tissue during surgery for glioma (see Malignant Neoplasms, below).

Aminolevulinic acid hydrochloride is used to treat actinic keratoses. It is applied topically as a 20% solution in the treatment of mild to moderate non-hyperkeratotic actinic keratoses of the face or scalp. The solution is applied to the surface of the lesions, allowed to dry, and then applied again. This is followed, 14 to 18 hours later, by illumination with blue wavelength light sufficient to supply a dose of 10 J/cm². Treatment may be repeated once after 8 weeks if necessary. Alternatively, a gel containing aminolevulinic acid hydrochloride equivalent to aminolevulinic acid 7.8% may be used. It is applied to the roughened surface of the lesions and about 5 mm of the surrounding skin, allowed to dry, then covered with an occlusive light-tight dressing for 3 hours. After removal of the dressing and any gel, the area is illuminated with red light, from either a narrow spectrum source supplying a dose of 37 J/cm² or a broader and continuous spectrum supplying a dose of 75 to 200 J/cm². Residual lesions may be re-treated after 3 months.

Aminolevulinic acid hydrochloride is given orally for the visualisation of malignant tissue during surgery for glioma. A dose of 20 mg/kg is given 3 hours before anaesthesia, and blue light illumination is used during surgery.

Methyl aminolevulinate hydrochloride is a derivative of 5-aminolevulinic acid that is applied topically for the treatment of non-hyperkeratotic, non-pigmented actinic keratoses of the face or scalp when other therapies are considered inappropriate. In some countries, it is also used for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other therapies or for the treatment of Bowen's disease (squamous cell carcinoma *in situ*) when surgical excision is inappropriate. A cream containing the equivalent of 16% methyl aminolevulinate is applied to the lesions and covered with an occlusive dressing. After 3 hours the cream is removed and the lesions are exposed to red wavelength light; in the UK a dose of 75 J/cm² is used, whereas 37 J/cm² has been used in the USA. Exposure to the cream for more than 4 hours should be avoided. In the USA, two sessions of photodynamic therapy are given for actinic keratoses, a week apart. In the UK, one session is given for actinic keratoses, repeated after 3 months if necessary; for basal cell carcinoma or Bowen's disease two sessions are given a week apart.

Patients should avoid sunlight or bright light sources for about 2 days after topical application, and for 24 hours after oral administration.

Hexaminolevulinate hydrochloride is used for the detection of bladder cancer. A 50 mL solution containing hexaminolevulinate hydrochloride 100 mg (equivalent to about 85 mg of hexaminolevulinate) is instilled into the bladder and retained for 1 hour. After subsequent evacuation of the bladder, fluorescence cystoscopy using blue light should be started within 30 to 60 minutes.

Malignant neoplasms. The use of *topical* aminolevulinic acid or methyl aminolevulinate in the photodynamic therapy (PDT) of **actinic keratosis** and **basal cell carcinoma** (p. 714.2) has been reviewed.[1-6] Both aminolevulinic acid and methyl aminolevulinate are considered to be effective in clearing non-hyperkeratotic actinic keratoses of the face and scalp, with superior response rates and cosmetic outcome compared with cryotherapy.[7] More than 80% of lesions cleared completely after 2 treatments with aminolevulinic acid PDT; a recurrence rate of 19% was reported over 12 months.[8] Single treatment with methyl aminolevulinate is effective for thin lesions but thicker, non-responsive lesions may benefit from repeated treatment.[9] No significant differences in efficacy were seen between PDT with aminolevulinic acid or methyl aminolevulinate in the treatment of scalp actinic keratosis.[10] Topical PDT is less effective for acral lesions, although some consider that it may still offer therapeutic benefit.[7] Topical PDT with aminolevulinic acid was also found to prevent the development of new malignant lesions in patients with recurrent non-melanoma skin cancer.[11] A self-adhesive patch containing aminolevulinic acid (PD P 506 A) has been developed for easier application before therapy;[12] the patch also provides light protection. In one study, the majority of actinic keratosis lesions remained clear 12 months after a single patch-PDT treatment, and recurrence rates were superior to those of cryosurgery.[13] *Topical* PDT is considered effective for superficial basal cell carcinoma; it is less effective for nodular disease.[7] *Intralesional* use has been investigated to improve penetration of the photosensitiser, with good preliminary results.[14] Methyl aminolevulinate topical PDT may be preferable for difficult-to-treat basal cell carcinoma.[15,16]

Topical PDT is effective in **Bowen's disease** (squamous cell carcinoma *in situ*), with equivalence to cryotherapy, and equivalence or superiority to topical fluorouracil; cosmetic outcome is superior to standard therapy.[7] Topical PDT is not recommended for the treatment of invasive squamous cell carcinoma.[7] Topical methyl aminolevulinate PDT was more effective and cosmetically acceptable compared with topical 5-fluorouracil for pre-malignant skin disease in a small study in organ transplant recipients.[17]

PDT using *oral* 5-aminolevulinic acid as the photosensitiser, at doses of 30 or 60 mg/kg, has been used to treat **Barrett's oesophagus**, which is a major risk factor for oesophageal adenocarcinoma (p. 705.3).[18,19] A small study found similar clinical responses with low-dose (30 mg/kg) and high-dose (60 mg/kg) oral aminolevulinic acid protocols.[20] Good long-term results have been reported with aminolevulinic acid PDT in patients with early neoplasia or high-grade intraepithelial neoplasia.[21]

Aminolevulinic acid is given *orally* for the photodynamic detection of malignant tissue during **glioma** resection (see Malignant Neoplasms of the Brain, p. 701.2).[22,23] It has also been used for the fluorescence detection of **pleural malignancies**.[24]

An *intravesical* solution of hexaminolevulinate is used in the cystoscopic detection of non-muscle invasive **bladder cancer** (p. 700.2). Detection rates are higher compared with the use of standard white light cystoscopy,[25,26] although it may be less effective in patients previously treated with intravesical chemotherapy or immunotherapy.[26] Improvements in detection and associated complete resection are also thought to be related to lower recurrence rates.[25] Intravesical solutions of aminolevulinic acid have been studied as whole-bladder photodynamic therapy in the treatment of bladder tumours[27,28] and hexaminolevulinate is under investigation.

A *topical* application of 5-aminolevulinic acid 3% has been tried in the treatment of **cervical intraepithelial neoplasia**, with poor response.[29]

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2. Gupta AK, Ryder JE. Photodynamic therapy and topical aminolevulinic acid: an overview. *Am J Clin Dermatol* 2003; **4:** 699–708.
3. Siddiqui MAA, *et al.* Topical methyl aminolevulinate. *Am J Clin Dermatol* 2004; **5:** 127–37.
4. Marmur ES, *et al.* A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. *Dermatol Surg* 2004; **30:** 264–71.
5. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; **156:** 793–801.
6. Juzeniene A, *et al.* Application of 5-aminolevulinic acid and its derivatives for photodynamic therapy in vitro and in vivo. *Methods Mol Biol* 2010; **635:** 97–106.
7. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; **159:** 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 30/09/09)
8. Tschen EH, *et al.* Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; **155:** 1262–9.
9. Tarstedt M, *et al.* A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; **85:** 424–8.
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11. Apalla Z, *et al.* Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. *Br J Dermatol* 2010; **162:** 171–5.
12. Hauschild A, *et al.* Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. *Br J Dermatol* 2009; **160:** 1066–74.
13. Szeimies R-M, *et al.* Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. *Br J Dermatol* 2010; **162:** 410–14.
14. Cappugi P, *et al.* New proposal for the treatment of nodular basal cell carcinoma with intralesional 5-aminolevulinic acid. *J Chemother* 2004; **16:** 491–3.
15. Horn M, *et al.* Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *Br J Dermatol* 2003; **149:** 1242–9.
16. Vinciullo C, *et al.* Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; **152:** 765–72.
17. Perrett CM, *et al.* Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007; **156:** 320–8.
18. Ackroyd R, *et al.* Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. *Gut* 2000; **47:** 612–17.
19. Barr H. Barrett's esophagus: treatment with 5-aminolevulinic acid photodynamic therapy. *Gastrointest Endosc Clin N Am* 2000; **10:** 421–37.
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22. Tonn J-C, Stummer W. Fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid: practical use, risks, and pitfalls. *Clin Neurosurg* 2008; **55:** 20–6.
23. Colditz MJ, Jeffree RL. Aminolevulinic acid (ALA)-protoporphyrin IX fluorescence guided tumour resection. *J Clin Neurosci* 2012; **19:** 1471–4.
24. Baas P, *et al.* Fluorescence detection of pleural malignancies using 5-aminolaevulinic acid. *Chest* 2006; **129:** 718–24.
25. Malmström P-U, *et al.* Role of hexaminolevulinate-guided fluorescence cystoscopy in bladder cancer: critical analysis of the latest data and European guidance. *Scand J Urol Nephrol* 2012; **46:** 108–16.
26. Lerner SP, *et al.* Fluorescence and white light cystoscopy for detection of carcinoma in situ of the urinary bladder. *Urol Oncol* 2012; **30:** 285–9.
27. Waidelich R, *et al.* Whole bladder photodynamic therapy with 5-aminolevulinic acid using a white light source. *Urology* 2003; **61:** 332–7.
28. Berger AP, *et al.* Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: a single-center study. *Urology* 2003; **61:** 338–41.
29. Barnett AA, *et al.* A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia. *Int J Cancer* 2003; **103:** 829–32.

Skin disorders. 5-Aminolevulinic acid has been used topically in the photodynamic therapy (PDT) of skin condi-

tions such as psoriasis, recalcitrant viral warts, acne vulgaris, and cutaneous T-cell lymphoma.[1,2] Topical PDT is considered effective for clearing the lesions of cutaneous leishmaniasis, although further studies are needed. It also appears effective in the treatment of photoageing.[2] Variable results have been reported with this therapy in patients with plaque psoriasis. In one study therapy was generally well-tolerated,[3] but in another all patients reported stinging or burning during irradiation,[4] and topical PDT is not recommended for use in psoriasis.[2] PDT with 5-aminolevulinic acid has been reported to significantly improve an infected leg ulcer resistant to conventional therapies.[5] A topical 10% solution has been used with intraurethral PDT to treat condylomata acuminata.[6] Benefit has also been reported with topical PDT, using 5-aminolevulinic acid 20%, in 10 patients with actinic cheilitis, a common condition of the lower lip, which can progress to squamous cell carcinoma.[7] Topical PDT may potentially be beneficial in skin cancer prophylaxis, although further investigation is needed.[2]

PDT using topical aminolevulinic acid or methyl aminolevulinate can be effective in the treatment of inflammatory acne of the face and back.[2] However, the optimum regimen to achieve a sustained response with minimal adverse effect has not been established. A review[8] found that most studies reported on topical use of aminolevulinic acid 20% or methyl aminolevulinate 16%, but were small and of variable quality. The authors suggested that treatment for moderate to moderately severe inflammatory acne could consist of a short contact time of 15 to 60 minutes under occlusion, followed by broad spectrum yellow and/or red light. A course of therapy could consist of 2 to 4 treatments applied at intervals of 2 to 4 weeks.

1. Ibbotson SH. Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer. *Br J Dermatol* 2002; **146:** 178–88.
2. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; **159:** 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 02/04/13)
3. Smits T, *et al.* A placebo-controlled randomized study on the clinical effectiveness, immunohistochemical changes and protoporphyrin IX accumulation in fractionated 5-aminolaevulinic acid-photodynamic therapy in patients with psoriasis. *Br J Dermatol* 2006; **155:** 429–36.
4. Radakovic-Fijan S, *et al.* Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol* 2005; **152:** 279–83.
5. Clayton TH, Harrison PV. Photodynamic therapy for infected leg ulcers. *Br J Dermatol* 2007; **156:** 384–5.
6. Wang XL, *et al.* Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol* 2004; **151:** 880–5.
7. Sotiriou E, *et al.* Actinic cheilitis treated with one cycle of 5-aminolaevulinic acid-based photodynamic therapy: report of 10 cases. *Br J Dermatol* 2008; **159:** 261–2.
8. Taylor MN, Gonzalez ML. The practicalities of photodynamic therapy in acne vulgaris. *Br J Dermatol* 2009; **160:** 1140–8.

Adverse Effects and Precautions

The mechanism of action of topical 5-aminolevulinic acid or its derivatives generally results in local phototoxicity, manifest as a localised burning or stinging sensation, erythema, oedema, pruritus, scabbing, or pain. Symptoms are usually mild to moderate, and transient. During treatment, patients should be advised to avoid sunlight or prolonged exposure to bright light.

Other common adverse effects on the skin include scaling or crusting, ulceration, suppuration, blistering, bleeding, sensation of heat, erosion or exfoliation, and skin infection. Urticaria, rash, and changes in skin pigmentation may also occur. Application site discharge, eczema, and allergic contact dermatitis have been reported. Systemic effects may occur with topical use. Paraesthesia and headache have been reported commonly; nausea, fatigue, eye swelling or eye pain, and wound haemorrhage have also occurred.

Bladder pain, cystitis, dysuria, haematuria, and abnormal urinalysis may occur with intravesical use. Anaphylactic shock has been reported. Widespread bladder inflammation should be excluded before instillation because of the potential for increased porphyrin accumulation resulting in an increased risk of local toxicity and false fluorescence.

Adverse effects associated with oral use include nausea, hypotension, and photosensitivity. Other reported effects include anaemia, thrombocytopenia, leucocytosis, and increases in bilirubin, liver enzyme, and amylase values.

Handling. US licensed product information warns that nitrile gloves should be worn during application and removal of methyl aminolevulinate hydrochloride cream; vinyl or latex gloves do not provide adequate protection.

Hypersensitivity. Allergic reactions to aminolevulinic acid[1] and methyl aminolevulinate[2] have been reported.

1. Gniazdowska B, *et al.* Allergic contact dermatitis from δ-aminolevulinic acid used for photodynamic therapy. *Contact Dermatitis* 1998; **38:** 348–9.
2. Wulf HC, Philipsen P. Allergic contact dermatitis to 5-aminolaevulinic acid methylester but not to 5-aminolaevulinic acid after photodynamic therapy. *Br J Dermatol* 2004; **150:** 143–5.

Porphyria. Licensed product information states that the use of 5-aminolevulinic acid and its derivatives is contra-indicated in patients with porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aminolevulinic acid given orally as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. However, topical methyl aminolevulinate is classified as not porphyrinogenic because of insignificant systemic absorption; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/03/13)

Interactions

Use with other known photosensitisers such as griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, and tetracyclines might increase the photosensitivity reaction commonly seen with 5-aminolevulinic acid or its derivatives.

St John's wort. A patient taking St John's wort had a pronounced phototoxic reaction consisting of an erythematous rash and swelling of the face, neck, and hands, 6 hours after receiving oral aminolevulinic acid. Although both drugs have been associated with photosensitivity, the authors suggested a synergistic effect had occurred. Tests *in vitro* appeared to confirm this.[1]

1. Ladner DP, *et al.* Synergistic toxicity of δ-aminolaevulinic acid-induced protoporphyrin IX used for photodiagnosis and hypericum extract, a herbal antidepressant. *Br J Dermatol* 2001; **144:** 916–8.

Pharmacokinetics

After intravenous and oral doses of aminolevulinic acid hydrochloride equivalent to 100 mg of aminolevulinic acid, the mean half-life of aminolevulinic acid is stated to be about 0.83 hours and 0.7 hours, respectively; oral bioavailability is about 50 to 60%. *In-vitro* studies of dermal absorption found that the mean cumulative absorption of methyl aminolevulinate through healthy human skin after 24 hours was 0.26% of a dose and a skin depot containing 4.9% of the dose was formed.

References.

1. Juzeniene A, *et al.* Topical application of 5-aminolaevulinic acid, methyl 5-aminolaevulinate and hexyl 5-aminolaevulinate on normal human skin. *Br J Dermatol* 2006; **155:** 791–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Metvix; ***Austral.***: Metvix; ***Austria***: Hexvix; Metvix; ***Belg.***: Gliolan; Hexvix; Metvix; ***Braz.***: Metvix; ***Canad.***: Levulan Kerastick; Metvix; ***Chile***: Levulan Kerastick; Metvix; ***China***: ALA (艾拉); ***Cz.***: Gliolan; Hexvix; MC 506†; Metvix; ***Denm.***: Ameluz; Gliolan; Hexvix; Metvix; ***Fin.***: Hexvix; Metvix; ***Fr.***: Gliolan; Hexvix; Metvixia; ***Ger.***: Gliolan; Hexvix; Metvix; ***Gr.***: Gliolan; Hexvix; Metvix; ***Irl.***: Alacare; Gliolan; Hexvix; Metvix; ***Ital.***: Hexvix; Metvix; ***Jpn***: Alabel; Alaglio; ***Neth.***: Ameluz; Gliolan; Hexvix; Metvix; ***Norw.***: Ameluz; Gliolan; Hexvix; Metvix; ***NZ***: Metvix; ***Pol.***: Gliolan; ***Port.***: Gliolan; Hexvix; Metvix; ***S.Afr.***: Metvix; ***Singapore***: Metvix; ***Spain***: Gliolan; Hexvix; Metvix; ***Swed.***: Gliolan; Hexvix; Metvix; ***Switz.***: Hexvix; Metvix; ***Thai.***: Levulan Kerastick; ***UK***: Ameluz; Gliolan; Hexvix; Metvix; Porphin; ***USA***: Cysview; Levulan Kerastick; Metvixia.

Amonafide *(USAN, rINN)*

Amonafida; Amonafidum; M-FA-142; Nafidimide; NSC-308847; Амонафид.

3-Amino-*N*-[2-(dimethylamino)ethyl]naphthalimide; 5-Amino-2-[2-(dimethylamino)ethyl]-1*H*-benz(de)isoquinoline-1,3(2*H*)-dione.

$C_{16}H_{17}N_3O_2$=283.3

CAS — 69408-81-7.

UNII — 1Q8D39N37L.

Amonafide Hydrochloride *(rINNM)*

Amonafide, Chlorhydrate de; Amonafide dihydrochloride; Amonafidi Hydrochloridum; Hidrocloruro de amonafida; Амонафида Гидрохлорид.

$C_{16}H_{17}N_3O_2$, 2HCl=356.2

CAS — 150091-68-2.

UNII — 2UAV344O66.

NOTE. The name Quinamed has been used as a trade mark for amonafide hydrochloride.

Amonafide Malate *(rINNM)*

Amonafide L-Malate (USAN); Amonafide, Malate d'; Amonafidi Malas; AS-1413; Malato de amonafida; XAN-02; Амонафида Малат.

$C_{16}H_{17}N_3O_2$, $C_4H_6O_5$=417.4

CAS — 618863-54-0.

UNII — LI06Q37TEG.

NOTE. The name Xanafide has been used as a trade mark for amonafide malate

Profile

Amonafide is a topoisomerase inhibitor. Amonafide malate has been investigated for the treatment of acute myeloid leukaemia, but failed to improve the rate of complete remission. Amonafide hydrochloride has also been investigated, but some studies were stopped due to serious adverse effects.

Amrubicin *(USAN, rINN)*

Amrubicina; Amrubicine; Amrubicinum; SM-5887; Амрубицин.

(+)-(7*S*,9*S*)-9-Acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione.

$C_{25}H_{25}NO_9$=483.5

CAS — 110267-81-7 (amrubicin); 110311-30-3 (amrubicin hydrochloride).

ATC — L01DB10.

ATC Vet — QL01DB10.

UNII — 93N13LB4Z2.

Profile

Amrubicin is a synthetic anthracycline derivative related to compounds such as doxorubicin (p. 782.3). Amrubicin hydrochloride is a potent topoisomerase II inhibitor that is used as an antineoplastic in the treatment of lung cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Calsed.

Amsacrine *(BAN, USAN, pINN)*

Acridinyl Anisidide; *m*-AMSA; Amsacrina; Amsacrinum; Amsakriini; Amsakrin; CI-880; NSC-249992; Амсакрин.

4′-(Acridin-9-ylamino)methanesulphon-*m*-anisidide.

$C_{21}H_{19}N_3O_3S$=393.5

CAS — 51264-14-3.

ATC — L01XX01.

ATC Vet — QL01XX01.

UNII — 00DPD30SOY.

Incompatibility. Amsacrine is incompatible with sodium chloride 0.9% injection and with other chloride-containing solutions,[1,2] apparently because of the poor solubility of the hydrochloride salt in aqueous solution.[2] Amsacrine reacts with certain plastics.[1]

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
2. Trissel LA, *et al.* Visual compatibility of amsacrine with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 2525–8.

Uses and Administration

Amsacrine is an antineoplastic agent that appears to act by intercalation with DNA and inhibition of nucleic acid synthesis. It may also exert an action on cell membranes. Cells in G_2 or S phases may be most sensitive to its actions.

It is used for the induction and maintenance of remission in adult acute leukaemias, particularly acute myeloid leukaemia.

Amsacrine is prepared as a solution in lactic acid and dimethylacetamide, and is given, diluted in glucose 5%, by intravenous infusion over 60 to 90 minutes.

For the induction of remission, amsacrine may be given at a dose of 90 mg/m² daily for 5 to 8 days, depending on clinical response. Courses may be repeated at 2- to 4-week intervals according to response, and the dose may be increased to 120 mg/m² daily in subsequent courses if tolerated. Maintenance doses of 150 mg/m² as a single dose or divided over 3 consecutive days have been given every 3 to 4 weeks, adjusted if necessary according to response.

Complete blood counts should be performed regularly, and cardiac, liver, kidney, and CNS function should be monitored.

Doses should be reduced in patients with hepatic or renal impairment (see p. 742.1).

References.
1. Ghaddar HM, *et al.* Amsacrine and continuous-infusion high-dose cytosine arabinoside as induction therapy for patients with newly-diagnosed acute myelogenous leukemia. *Leuk Lymphoma* 1996; **22:** 71–6.
2. Reman O, *et al.* Groupe d'Étude et de Traitement de la Leucémie Aiguë Lymphoblastique de l'Adulte. Rescue therapy combining intermediate-dose cytarabine with amsacrine and etoposide in relapsed adult acute lymphoblastic leukemia. *Hematol J* 2004; **5:** 123–9.
3. Sung WJ, *et al.* Phase II trial of amsacrine plus intermediate-dose Ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. *Jpn J Clin Oncol* 2005; **35:** 612–16.
4. Horstmann MA, *et al.* Amsacrine combined with etoposide and high-dose methylprednisolone as salvage therapy in acute lymphoblastic leukemia in children. *Haematologica* 2005; **90:** 1701–3.
5. Kessler T, *et al.* Amsacrine containing induction therapy in elderly AML patients: comparison to standard induction regimens in a matched-pair analysis. *Leuk Res* 2008; **32:** 491–4.

Administration in hepatic impairment. In moderate to severe hepatic impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m^2 daily.

Administration in renal impairment. In moderate to severe renal impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m^2 daily.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression is usually dose-limiting and may be severe. The nadir of the white cell count has been reported at about 12 days after treatment, with recovery usually by the 25th day. Pancytopenia and haemorrhage may develop. Nausea and vomiting (mild to moderate), stomatitis (mild to life-threatening), rashes, and alopecia may occur. Grand mal seizures, renal dysfunction, hepatotoxicity, and cardiotoxicity have also been reported. Amsacrine is irritant: there may be phlebitis and local tissue necrosis particularly when given in high concentrations.

Amsacrine should be given with caution to patients with liver or kidney disease, who may require dosage adjustments.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amsacrine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use with diuretics or nephrotoxic drugs such as the aminoglycosides may theoretically increase the risk of cardiotoxicity with amsacrine by precipitating hypokalaemia.

Pharmacokinetics

Amsacrine is poorly absorbed after oral doses. When given intravenously it has a reported terminal half-life of about 5 to 8 hours. It is metabolised in the liver and excreted mainly in the bile, mostly as metabolites. It is reported to be about 98% protein bound.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Amsidyl†; ***Belg.***: Amsidine†; ***Canad.***: Amsa PD; ***Fr.***: Amsalyo; ***Ger.***: Amsidyl; ***Gr.***: Amsidine; Amsidyl; ***Irl.***: Amsidine; ***Neth.***: Amsidine; ***Swed.***: Amekrin; ***Switz.***: Amsidyl; ***UK***: Amsidine†.

Anastrozole *(BAN, USAN, rINN)* ⊗

Anastrotsoli; Anastrozol; Anastrozolo; Anastrozolum; ICI-D1033; ZD-1033; Анастрозол.

2,2′-Dimethyl-2,2′-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(propiononitrile); α,α,α′,α′-Tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-*m*-benzenediacetonitrile.

$C_{17}H_{19}N_5$=293.4

CAS — 120511-73-1.

ATC — L02BG03.

ATC Vet — QL02BG03.

UNII — 2Z07MYW1AZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Anastrozole). A white or almost white powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; practically insoluble in cyclohexane. It shows polymorphism.

USP 36: (Anastrozole). A white to off-white crystalline powder. Freely soluble in alcohol, in methyl alcohol, in acetone, and in tetrahydrofuran; very soluble in acetonitrile.

Uses and Administration

Anastrozole is a potent and selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue. It is used in the treatment of advanced or locally advanced breast cancer, and as adjuvant treatment in hormone receptor-positive early breast cancer (p. 702.1), in postmenopausal women in an oral dose of 1 mg once daily. Responses are unlikely in patients with oestrogen receptor-negative disease, unless they had a previous positive clinical response to tamoxifen. For patients with advanced breast cancer, therapy may be continued until tumour progression. Adjuvant therapy may be continued for up to 5 years, although the optimum duration is uncertain.

References.
1. Jonat W, *et al.* Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006; **7:** 991–6. Correction. *ibid.* 2007; **8:** 6.
2. Graham PH. Anastrozole for malignant and benign conditions: present applications and future therapeutic integrations. *Expert Opin Pharmacother* 2007; **8:** 2347–57.
3. Sanford M, Plosker GL. Anastrozole: a review of its use in postmenopausal women with early-stage breast cancer. *Drugs* 2008; **68:** 1319–40.
4. Needleman SJ, Tobias JS. Review of the ATAC study: tamoxifen versus anastrozole in early-stage breast cancer. *Expert Rev Anticancer Ther* 2008; **8:** 1871–81.
5. Nabholtz JM, *et al.* Comparative review of anastrozole, letrozole and exemestane in the management of early breast cancer. *Expert Opin Pharmacother* 2009; **10:** 1435–47.
6. Kelly CM, Buzdar AU. Anastrozole. *Expert Opin Drug Safety* 2010; **9:** 995–1003.
7. Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole—of clinical importance? *Br J Cancer* 2011; **104:** 1059–66.

Administration in hepatic impairment. UK licensed product information states that no dosage adjustment of anastrozole is required for patients with mild hepatic impairment, but contra-indicates its use in those with moderate or severe hepatic disease. US licensed product information states that no change in dose is required for those with mild to moderate hepatic impairment and that anastrozole has not been studied in those with severe hepatic impairment; dosage adjustment in patients with stable hepatic cirrhosis is not considered to be necessary.

Administration in renal impairment. US licensed product information allows for unchanged doses of anastrozole in renal impairment. However, UK licensed product information contra-indicates its use in patients with severe renal impairment (those with a creatinine clearance less than 20 mL/min).

Endometriosis. In a small, open-label study,[1] *oral* anastrozole 1 mg, given daily with a low-strength oral contraceptive for 6 months, reduced pelvic pain scores in women with refractory endometriosis (p. 2264.1). Adverse effects were mild, although most patients had breakthrough bleeding, which exacerbated pain. The authors supposed that a higher dose of oral contraceptive should be considered in future studies. A randomised, controlled study to investigate the efficacy of oral anastrozole with subcutaneous goserelin after surgery for endometriosis found the combination increased the pain-free interval and decreased recurrence rates compared with goserelin alone.[2]

There are also reports of success with oral letrozole 2.5 mg daily, given with calcium and vitamin D,[3] and also with norethisterone in some cases.[4] However, use with desogestrel in a small study of women with refractory endometriosis caused the development of functional ovarian cysts, necessitating interruption of treatment.[5]

In a small pilot study of patients with rectovaginal endometriosis,[6] anastrozole 250 micrograms was given *vaginally* once daily for 6 months. Dysmenorrhoea improved significantly although chronic pelvic pain was unchanged. Adverse effects were mild.

A review[4] on the use of aromatase inhibitors for endometriosis noted that, while they may be useful in reducing pain, the long-term course of pain symptoms after interruption of therapy remains to be evaluated, and that their superiority over hormonal therapy has yet to be proven. Furthermore, permanent inhibition of aromatase activity is contra-indicated in women with endometriosis who wish to preserve their fertility, and they should only be offered to selected women who have severe pain despite previous surgical and hormonal therapy; further studies were considered necessary before routine use could be recommended.

1. Amsterdam LL, *et al.* Anastrazole [sic] and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 2005; **84:** 300–4.
2. Soysal S, *et al.* The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. *Hum Reprod* 2004; **19:** 160–7.
3. Razzi S, *et al.* Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. *BJOG* 2004; **111:** 182–4.
4. Ferrero S, *et al.* Pharmacological treatment of endometriosis: experience with aromatase inhibitors. *Drugs* 2009; **69:** 943–52.
5. Remorgida V, *et al.* Letrozole and desogestrel-only contraceptive pill for the treatment of stage IV endometriosis. *Aust N Z J Obstet Gynaecol* 2007; **47:** 222–5.
6. Hefler LA, *et al.* Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. *Fertil Steril* 2005; **84:** 1033–6.

Growth hormone deficiency. Up to 3 years of adjuvant treatment with anastrozole in adolescent boys with growth hormone deficiency (see Growth Retardation, p. 1921.3) resulted in significant gains in predicted adult height compared with placebo; the drug was well tolerated and normal pubertal progression was maintained.[1]

1. Mauras N, *et al.* Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. *J Clin Endocrinol Metab* 2008; **93:** 823–31.

Gynaecomastia. Anastrozole has been reported[1,2] to be under investigation for the treatment of gynaecomastia, but controlled studies suggest that it may be no better than placebo—see Gynaecomastia (p. 2264.3) and Gynaecomastia under Adverse Effects and Precautions of Flutamide (p. 799.1).

1. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; **2:** 643–9.
2. Mauras N, *et al.* Pharmacokinetics and pharmacodynamics of anastrozole in pubertal boys with recent-onset gynecomastia. *J Clin Endocrinol Metab* 2009; **94:** 2975–8.

Infertility. Nonsteroidal aromatase inhibitors such as anastrozole and letrozole have been investigated for their ovulation-inducing effects, see Letrozole, p. 817.2.

Precocious puberty. For a report of the effective use of anastrozole with bicalutamide in the treatment of familial male precocious puberty (testotoxicosis), see Precocious Puberty, under Bicalutamide, p. 749.2.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of anastrozole are gastrointestinal disturbances (including anorexia, nausea and vomiting, and diarrhoea), asthenia, hot flushes, dizziness, drowsiness, headache, and rash. Other commonly reported effects include hair thinning, vaginal dryness or bleeding, myalgia, arthralgia, carpal tunnel syndrome, and bone pain and/or fractures. Insomnia, depression, peripheral oedema, lymphoedema, increased cough, pharyngitis, dyspnoea, back pain, and hypertension are also common. An increased incidence of cardiovascular adverse events has been seen in women with pre-existing ischaemic heart disease and caution is advised in these patients. Abnormalities in liver enzyme values, hepatitis, thromboembolism, and hypercholesterolaemia can occur. Rare cases of erythema multiforme, Stevens-Johnson syndrome, and allergic reactions (including angioedema, urticaria, and anaphylaxis) have been reported. Other adverse reactions include thrombophlebitis, anaemia, leucopenia, anxiety, cataracts, and urinary-tract infections; bronchitis, rhinitis, and sinusitis have been reported.

Reductions in bone mineral density (BMD) can occur during use of anastrozole. Patients with or at risk of osteoporosis should therefore have their BMD assessed at the start of therapy and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be started as appropriate and carefully monitored.

The use of aromatase inhibitors such as anastrozole is generally contra-indicated in premenopausal women (particularly in pregnancy).

References.
1. Files JA, *et al.* Managing aromatase inhibitors in breast cancer survivors: not just for oncologists. *Mayo Clin Proc* 2010; **85:** 560–6.
2. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006; **7:** 633–43.

Breast feeding. Licensed product information states that it is unknown whether anastrozole is distributed into human milk; in the UK its use during breast feeding is contra-indicated while in the USA a decision to use may be made based on clinical judgement. It has been suggested[1] that if only a single dose is given, breast feeding should be withheld for 10 days.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Effects on blood lipids. For a comparison of the effects of anastrozole, letrozole, and exemestane on blood lipids see under Exemestane, p. 792.3.

Effects on the liver. A case of acute hepatitis was attributed to anastrozole, 3 weeks after starting therapy.[1] In another case[2] there was some evidence of an auto-immune mechanism.

1. de la Cruz L, *et al.* Severe acute hepatitis in a patient treated with anastrozole. *Lancet* 2007; **369:** 23–4.
2. Inno A, *et al.* Anastrozole-related acute hepatitis with autoimmune features: a case report. *BMC Gastroenterol* 2011; **11:** 32.

Effects on the musculoskeletal system. In a series of 77 postmenopausal women treated with anastrozole for metastatic breast cancer, 12 complained of joint pains within 2 months of beginning therapy. Based on this experience and the incidence of arthralgia reported during clinical studies, the authors estimated that arthralgia occurs in 10 to 15% of patients treated with anastrozole, possibly as a result of the very low oestrogen concentrations achieved.[1] It has been suggested that there may be modest differences between ethnic groups in the incidences of joint symptoms and bone fractures,[2] which seem to be lower in Japanese patients.

Adjuvant anastrozole therapy for postmenopausal women with early breast cancer was associated with accelerated bone loss, but the risk appeared to be confined to those with osteopenia at baseline.[3] A retrospective review[4] including 316 patients treated with aromatase inhibitors (anastrozole, letrozole, or exemestane) found that there was a significant association between musculoskeletal symptoms and bone mineral density (BMD) results; those with severe symptoms had an increased likelihood of having an abnormal BMD. Patients who were also taking calcium and bisphosphonates had fewer symptoms and fewer fractures, and those who had taken tamoxifen before aromatase inhibitors were less likely to develop musculoskeletal symptoms. Those taking steroidal aromatase inhibitors had significantly more arthralgia, generalised bone pain or myalgia, and bone fractures than those taking nonsteroidal aromatase inhibitors. The need to assess the risk of osteoporosis before starting therapy has been stressed.[5]

1. Donnellan PP, *et al.* Aromatase inhibitors and arthralgia. *J Clin Oncol* 2001; **19:** 2767.
2. Okishiro M, *et al.* Incidence of joint symptoms and bone fractures in Japanese postmenopausal breast cancer patients treated with adjuvant anastrozole. *J Cancer Res Clin Oncol* 2009; **135:** 823–7.
3. Eastell R, *et al.* Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008; **26:** 1051–8.
4. Muslimani AA, *et al.* Aromatase inhibitor-related musculoskeletal symptoms: is preventing osteoporosis the key to eliminating these symptoms? *Clin Breast Cancer* 2009; **9:** 34–8.
5. Chien AJ, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. *J Clin Oncol* 2006; **24:** 5305–12.

CARPAL TUNNEL SYNDROME. Carpal tunnel syndrome has been reported in postmenopausal women given anastrozole; in one study,[1] more than 3 times as many women taking anastrozole developed carpal tunnel syndrome than those taking tamoxifen, although the incidence was still low (2.6%). Most cases were of mild or moderate intensity and short duration; risk factors were an age of 60 years or younger, or previous treatment with hormone replacement therapy or chemotherapy.

1. Sestak I, *et al.* Aromatase inhibitor-induced carpal tunnel syndrome: results from the ATAC trial. *J Clin Oncol* 2009; **27:** 4961–5.

Effects on the skin. A cutaneous eruption, diagnosed as subacute cutaneous lupus erythematosus, appeared 1 month after starting anastrozole. The patient was also taking an ACE inhibitor. The condition improved slightly after stopping anastrozole and replacing the ACE inhibitor with atenolol, but reappeared with greater intensity when anastrozole was restarted. Anastrozole was stopped again and the patient was treated with hydroxychloroquine and corticosteroids; after 4 months, signs had resolved and no recurrence was seen after 1 year.[1]

1. Trancart M, *et al.* Anastrozole-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 2008; **158:** 628–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anastrozole as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Tamoxifen. In a study of postmenopausal women with breast cancer, use of *daily* tamoxifen with anastrozole reduced anastrozole concentrations by 27% compared with daily anastrozole monotherapy; however, the effect of anastrozole on estradiol suppression was similar whether used alone or with tamoxifen.[1] In another study of daily anastrozole, *weekly* tamoxifen, or the combination thereof, there was no difference in anastrozole concentration in the combination arm compared with the anastrozole monotherapy arm in the first year.[2] The authors hypothesised that when given at a daily dose, tamoxifen has a mainly oestrogenic effect in an oestrogen-deprived environment, whereas a weekly dose still provides desirable oestrogenic properties when added to anastrozole, but without impairing anastrozole bioavailability.[2]

1. DowsettM, *et al.* ATAC Trialists' Group. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex™ and tamoxifen alone or in combination' (ATAC) trial. *Br J Cancer* 2001; **85:** 317–24.
2. Bonanni B, *et al.* Randomized biomarker trial of anastrozole or low-dose tamoxifen or their combination in subjects with breast intraepithelial neoplasia. *Clin Cancer Res* 2009; **15:** 7053–60.

Pharmacokinetics

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about 2 hours. Food decreases the rate of absorption, though this is not considered clinically significant. Anastrozole is 40% bound to plasma proteins. It is metabolised in the liver by *N*-dealkylation, hydroxylation, and glucuronidation; the main metabolite is triazole, which lacks pharmacological activity (but see also Metabolism, below). Anastrozole is excreted in the urine, chiefly as metabolites. The terminal plasma elimination half-life is about 40 to 50 hours, and steady-state concentrations occur after about 7 days in patients receiving once-daily doses.

Metabolism. Anastrozole is mainly cleared by hepatic metabolism (see Pharmacokinetics, above); it has been hypothesised[1] that differences in metabolism may contribute to the interindividual variability in the drug's effects. A study to characterise anastrozole metabolism concluded that hydroxylation and *N*-glucuronidation are the main metabolic pathways.[1] *In vitro* and *in vivo* data suggested that anastrozole is hydroxylated to hydroxyanastrozole, mainly by the cytochrome P450 isoenzyme CYP3A4; there may be some involvement of CYP3A5. Hydroxyanastrozole is then rapidly and extensively conjugated probably by uridine diphosphate glucuronosyltransferases (UGTs). *N*-Glucuronidation of anastrozole to anastrozole glucuronide occurs mainly by UGT1A4, although the precise contribution of the enzyme to *in vivo* metabolism is unknown. Triazole or any *N*-dealkylated metabolites could not be detected in *in vitro* studies; the role of *N*-dealkylation in anastrozole metabolism could not be confirmed.

1. Kamdem LK, *et al.* In vitro and in vivo oxidative metabolism and glucuronidation of anastrozole. *Br J Clin Pharmacol* 2010; **70:** 854–69.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Anaskebir; Anastraze; Anebol; Arimidex; Aromenal; Cefer; Distalene; Gondonar; Leprofen; Pantestone; Puricap; Trozolite; ***Austral.:*** Anastrol; Arimidex; ***Austria:*** Anastrolan; Arimidex; ***Belg.:*** Arimidex; ***Braz.:*** Arimidex; Trozolet; ***China:*** Ai Da (艾达); Arimidex (瑞宁得); Rui Si Yi (瑞斯意); Rui Ting (瑞婷); ***Cz.:*** Acydex†; Alozex; Anabrest†; Anaprex; Anasolde†; Anastar; Anastrad; Anaya; Arimidex; Armotraz; Asnea; Betasolde†; Deltasolde; Ebezolid; Egistrozol; Epsisolde; Gammasolde; Mammozole; Mastoren; OncoFem; Trasolette†; Zelotrin†; Zenbrest; Zynzol; ***Denm.:*** Anastelb; Arimidex; Mimastran; ***Fin.:*** Anazol; Arimidex; ***Fr.:*** Arimidex; ***Ger.:*** Anablock; Anadex; Anastro; Anastromin; Arimidex; ***Gr.:*** Anastrogen; Arimidex; Astrazol; Enastros; Londer; Oxeda; Strazal; Viastrol; Zolitrat; ***Hong Kong:*** Arimidex; ***Hung.:*** Anabrest; Anamataz; Anaromat; Arilla; Arimidex; Axastrol; Mammozole; Mastoren; Nobrec; Valmidex; Zynzol†; ***India:*** Altraz; Altrol; Anabrez; Arimidex; Armotraz; ***Indon.:*** Arimidex; ***Irl.:*** Agerdex; Amidex; Anastarrow†; Arimidex; ***Israel:*** Anastrol; Anastrose; Arimidex; ***Ital.:*** Ankarma; Arimidex; Eristrol; Extroplex; Raoloz; Renazole; ***Malaysia:*** Arimidex; ***Mex.:*** Arimidex; ***Neth.:*** Anoxidil; Arimidex; Barstra; Biostrol; Brestazol; Egistrozol; Genstra†; Kirana†; Mastrol; Regost; Renazole†; Strakir; Zolkir; Zolzyn; ***Norw.:*** Arimidex; ***NZ:*** Aremed; Arimidex; ***Philipp.:*** Anzol; Arimidex; ***Pol.:*** Anastralan; AnastroGen; AnastroLek; Ansyn; Apo-Nastrol; Arimidex; Arinel†; Atrozol; Egistrozol; Mamostrol; Symanastrol; Zolastrol; ***Port.:*** Anacyne†; Arimidex; Astoz; Remidex†; ***Rus.:*** Anastera (Анастера); Arimidex (Аримидекс); Egistrazol (Эгистразол); Mammosole (Маммозол); ***S.Afr.:*** Arimidex; Stradexa; ***Singapore:*** Aremed; Arimidex; ***Spain:*** Amenur; Anabrest†; Arimidex; Curmyl†; ***Swed.:*** Anastelb; Arimidex; ***Switz.:*** Arimidex; ***Thai.:*** Aremed; Arimidex; Femizet; ***Turk.:*** Arimidex; ***UK:*** Arimidex; ***Ukr.:*** Arimidex (Аримидекс); Axastrol (Аксастрол); ***USA:*** Arimidex; ***Venez.:*** Arimidex; Trozolet.

Antineoplaston A10

3-Phenylacetylamino-2,6-piperidinedione.
$C_{13}H_{14}N_2O_3$=246.3

Profile

Antineoplaston A10, one of a group of peptide derivatives isolated from blood and urine, has been investigated for the treatment of breast cancer, brain stem glioma, and other malignant neoplasms although its value has been questioned (see below).

A critical review of the antineoplastons[1] noted that most work had been done with antineoplaston A10, which is insoluble in aqueous solutions, and its derivatives antineoplaston AS2.5 (phenylacetylglutamine), and antineoplaston AS2.1 (a 4:1 mixture of phenylacetic acid and phenylacetylglutamine), which had not been independently shown to be active against cancer. However, some interest in the antineoplastons subsequently continued.[2-4]

1. Green S. Antineoplastons: an unproved cancer therapy. *JAMA* 1992; **267:** 2924–8.
2. Buckner JC, *et al.* Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin Proc* 1999; **74:** 137–45.
3. Badria F, *et al.* Immune modulatory potentials of antineoplaston A-10 in breast cancer patients. *Cancer Lett* 2000; **157:** 57–63.
4. Burzynski SR, *et al.* Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma. *Integr Cancer Ther* 2006; **5:** 40–7.

AS-1411

AGRO-100.

Profile

AS-1411 is a selective oligonucleotide ligand (aptamer) that binds to the protein nucleolin, inducing apoptosis in cancer cells. It is under investigation for the treatment of renal cell carcinoma, pancreatic cancer, and acute myelogenous leukaemia.

References.

1. Bates PJ, *et al.* Discovery and development of the G-rich oligonucleotide AS1411 as a novel treatment for cancer. *Exp Mol Pathol* 2009; **86:** 151–64.
2. Mongelard F, Bouvet P. AS-1411, a guanosine-rich oligonucleotide aptamer targeting nucleolin for the potential treatment of cancer, including acute myeloid leukemia. *Curr Opin Mol Ther* 2010; **12:** 107–14.

Asparaginase *(USAN)*

L-Asparaginaasi; L-Asparaginas; Asparaginasa; L-Asparaginasa; L-Asparaginase; L-Asparaginasum; L-Asparaginaz; L-Asparagine Amidohydrolase; MK-965; NSC-109229; Re-82-TAD-15; Аспарагиназа.

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.
UNII — G4FQ3CKY5R.

NOTE. Asparaginase (*USAN*) is an enzyme isolated from *Escherichia coli*, or obtained from other sources. See also Colaspase and Crisantaspase, below.

Incompatibility. Asparaginase is incompatible with rubber. Licensed product information recommends that it should not be mixed with other drugs.

Storage. Asparaginase should be stored at 2 degrees to 8 degrees (see also Stability, p. 744.1).

Colaspase *(BAN)*

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Colaspase (*BAN*) is asparaginase obtained from selected strains of *Escherichia coli*, such as ATCC 9637.

Pharmacopoeias. *Chin.* includes Asparaginase obtained from *Escherichia coli* ASI 357.

Crisantaspase *(BAN, pINN)*

Asparaginase *Erwinia chrysanthemi* (USAN); Crisantaspasa; Crisantaspasum; Erwinia L-asparaginase; Krisantaspaasi; Krisantaspas; Крисантаспаза.

CAS — 9015-68-3; 1349719-22-7.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Crisantaspase (*BAN*) is asparaginase obtained from cultures of *Erwinia chrysanthemi* (*E. carotovora*).

Pegaspargase *(USAN, rINN)*

PEG-L-asparaginase; Pegaspargasa; Pégaspargase; Pegaspargasum; Пэгаспраза.

A conjugate of colaspase with a polyethylene glycol of molecular weight 5000; Monomethoxypolyethylene glycol succinimidyl L-asparaginase.
CAS — 130167-69-0.
ATC — L01XX24.
ATC Vet — QL01XX24.
UNII — 7D96IR0PPM.

Stability. Although asparaginase was routinely kept under refrigeration,[1] information from a manufacturer (*Merck Sharp & Dohme*) indicated that it would remain stable for 48 hours at 15 degrees to 30 degrees. Licensed product information for pegaspargase states it should not be used if stored at room temperature for more than 48 hours.

1. Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; **40:** 101–2.

Storage. Pegaspargase should be stored at 2 degrees to 8 degrees.

Units

One international unit of asparaginase splits 1 micromole of ammonia from L-asparagine in 1 minute under standard conditions.

Uses and Administration

Asparaginase is an enzyme that acts by breaking down the amino acid L-asparagine to aspartic acid and ammonia. It interferes with the growth of those malignant cells which, unlike most healthy cells, are unable to synthesise L-asparagine for their metabolism, but resistance to its action develops fairly rapidly. Its action is reportedly specific for the G_1 phase of the cell cycle.

Asparaginase and pegaspargase are used mainly in combination regimens for the induction of remissions in acute lymphoblastic leukaemia (p. 692.3). Pegaspargase may be used in patients who are hypersensitive to asparaginase (although hypersensitivity to pegaspargase can still occur, see Adverse Effects, below).

Crisantaspase may be given by intramuscular, intravenous, or subcutaneous injection. Colaspase may be given intramuscularly (maximum volume of 2 mL per injection), or intravenously over not less than 30 minutes into a running infusion of sodium chloride, or glucose 5%. Regimens vary, and dosage should follow local protocols, but a usual dose of asparaginase given as crisantaspase 6000 units/m² (200 units/kg) is given three times weekly for 3 weeks. Alternatively, pegaspargase may be given intramuscularly (maximum volume of 2 mL per injection) or intravenously diluted in 100 mL of sodium chloride, or glucose 5% and given over 1 to 2 hours into a running infusion, in a dose of 2500 units/m² no more frequently than every 14 days.

Asparaginase is not generally used alone as an induction agent but doses of 200 units/kg daily have been given intravenously as colaspase, for 28 days.

Many of the regimens using asparaginase or pegaspargase are for use in children; for further details see below.

Although not entirely reliable, an intradermal test dose of about 2 units has been recommended in the USA, to test for hypersensitivity before treatment with asparaginase or where more than a week has elapsed between doses. Desensitisation has been advocated in patients at increased risk of allergic reactions. The incidence of hypersensitivity is lower in patients given pegaspargase, and a test dose is not advocated.

References.

1. Muller HJ, Boos J. Use of L-asparaginase in childhood ALL. *Crit Rev Oncol Hematol* 1998; **28:** 97–113.
2. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol* 1999; **457:** 621–9.
3. Abshire TC, *et al.* Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 2000; **96:** 1709–15.
4. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet* 2005; **44:** 367–93.
5. Fu CH, Sakamoto KM. PEG-asparaginase. *Expert Opin Pharmacother* 2007; **8:** 1977–84.
6. Douer D. Is asparaginase a critical component in the treatment of acute lymphoblastic leukemia? *Best Pract Res Clin Haematol* 2008; **21:** 647–58.
7. Jaccard A, *et al.* L-asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. *Ann Oncol* 2009; **20:** 110–16. Correction. *ibid.*; 1612.
8. Zeidan A, *et al.* Pegasparaginase: where do we stand? *Expert Opin Biol Ther* 2009; **9:** 111–19.

Administration in children. Asparaginase and pegaspargase are used in children mainly in combination regimens for the induction of remission in acute lymphoblastic leukaemia. Pegaspargase may be used in children who are hypersensitive to asparaginase (although hypersensitivity to pegaspargase can still occur, see Adverse Effects, below). Regimens vary and dosage should follow local protocols, but doses are similar to those used in adults, see above. US licensed product information describes combination regimens using asparaginase with vincristine and prednisone for children with acute lymphoblastic leukaemia; typical asparaginase doses (given as colaspase) include:

- intravenous asparaginase 1000 units/kg daily for 10 days
- intramuscular asparaginase 6000 units/m² given every third day for 9 doses

Asparaginase toxicity is reported to affect children less than adults. A large study in children with acute lymphoblastic leukaemia also found that asparaginase derived from *Erwinia chrysanthemi* (crisantaspase) had a lower toxicity than that derived from *Escherichia coli* (colaspase); however, a lower survival rate was noted with crisantaspase over 5 years of treatment.[1]

1. Moghrabi A, *et al.* Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood* 2007; **109:** 896–904.

Adverse Effects

Asparaginase is a protein and may produce anaphylaxis and other hypersensitivity reactions including fever, rashes, bronchospasm, urticaria, hypotension, and laryngeal oedema. The risk of anaphylactic reactions increases with continued exposure to asparaginase, and may be increased on re-exposure to asparaginase after a drug-free interval. Patients who develop hypersensitivity to asparaginase derived from *Escherichia coli* may be able to continue treatment with that derived from *Erwinia chrysanthemi* as the enzymes are immunologically distinct. Hypersensitivity to pegaspargase is less common, but is still significant; about 30% of patients hypersensitive to asparaginase will be hypersensitive to pegaspargase too.

Liver function abnormalities occur in many patients, and there may be decreased blood concentrations of fibrinogen and clotting factors resulting in coagulopathy or thrombotic complications. There may also be alterations in blood lipids and cholesterol, and hypoalbuminaemia. Hyperammonaemia, due to the production of ammonia from asparagine, may occur. Uraemia, and occasionally renal failure, have been reported. Pancreatitis may occur and may be fatal: there may also be hyperglycaemia due to decreased insulin production, and death from ketoacidosis has occurred.

Gastrointestinal disturbances, including nausea and vomiting, and CNS disturbances, including drowsiness, depression, coma, hallucinations, seizures, and a Parkinson-like syndrome, have also been reported. Myalgia, reactive arthritis, and transient bone-marrow depression have occurred rarely, as has marked leucopenia. Fatal hyperthermia has been reported.

General references.

1. Earl M. Incidence and management of asparaginase-associated adverse events in patients with acute lymphoblastic leukemia. *Clin Adv Hematol Oncol* 2009; **7:** 600–6.

Effects on the blood. Central thrombosis or intracranial haemorrhage as well as peripheral thrombosis and haemorrhage have been reported after asparaginase therapy.[1-4] Although the precise mechanism for this effect remains unclear, asparaginase appears to deplete certain clotting factors as well as antithrombin III, plasminogen, and fibrinogen.[4] These decreases may be dependent on the formulation and resultant asparaginase activity of preparations,[5] and there is some suggestion that crisantaspase may affect coagulation factors less severely than colaspase.[6] A multicentre, retrospective survey[3] of paediatric patients with acute lymphoblastic leukaemia found that use of corticosteroids with colaspase may be an additional risk factor for thromboembolic events.

1. Priest JR, *et al.* A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr* 1982; **100:** 984–9.
2. Ott N, *et al.* Sequelae of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1988; **10:** 191–5.
3. Sutor AH, *et al.* Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr* 1999; **211:** 201–4.
4. Alberts SR, *et al.* Thrombosis related to the use of L-asparaginase in adults with acute lymphoblastic leukemia: a need to consider coagulation monitoring and clotting factor replacement. *Leuk Lymphoma* 1999; **32:** 489–96.
5. Nowak-Göttl U, *et al.* Influence of two different Escherichia coli asparaginase preparations on fibrinolytic proteins in childhood ALL. *Haematologica* 1996; **81:** 127–31.
6. Carlsson H, *et al.* Effects of Erwinia-asparaginase on the coagulation system. *Eur J Haematol* 1995; **55:** 289–93.

Hypersensitivity. Reports of a low rate of cross-sensitivity to crisantaspase in patients hypersensitive to colaspase.[1,2]

1. Billett AL, *et al.* Allergic reactions to Erwinia asparaginase in children with acute lymphoblastic leukemia who had previous allergic reactions to Escherichia coli asparaginase. *Cancer* 1992; **70:** 201–6.
2. Vrooman LM, *et al.* Erwinia asparaginase after allergy to E. coli asparaginase in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2010; **54:** 199–205.

Precautions

Asparaginase is contra-indicated in patients with pancreatitis, and should be avoided in pregnancy. It should be given cautiously to patients with hepatic impairment; liver function should be measured regularly during treatment. Treatment should be stopped if an allergic reaction occurs and not restarted with the same type of asparaginase; facilities for the management of anaphylaxis (see p. 1293.2) should be available during treatment. Some licensed product information recommends an intradermal test dose at the start of asparaginase treatment to check for hypersensitivity, as described under Uses, above, although such tests may not always be predictive. Careful observation is needed when re-treating with asparaginase after a break in therapy, as there may be an increased risk of allergic reactions. Desensitisation has been used in patients at increased risk of hypersensitivity, although it may itself be hazardous. Serum amylase and lipase concentrations should be monitored regularly as should blood glucose concentrations. Asparaginase has been reported to interfere with tests of thyroid function by transient reduction of concentrations of thyroxine-binding globulin. Routine screening of blood clotting factors should be carried out before starting treatment; if coagulopathy occurs, asparaginase should be withheld until recovery. Monitoring of blood count and bone marrow is also recommended. Measures to protect against the adverse effects of hyperuricaemia may be required (see p. 600.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies asparaginase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/11/11)

Interactions

Use of asparaginase with other drugs that affect liver function may increase the risk of hepatotoxicity and concomitant corticosteroid therapy may increase the risk of coagulation abnormalities. If asparaginase is given with methotrexate the activity of the latter may be reduced (see below). Vincristine neurotoxicity may possibly be increased by use with asparaginase (see p. 884.1).

Methotrexate. Asparaginase inhibits protein synthesis and cell replication, and therefore may interfere with the action of drugs such as methotrexate that require cell replication for their antineoplastic effect.[1] Licensed product information for asparaginase states that this effect persists as long as plasma-asparagine concentrations are suppressed and recommends that methotrexate should not be given with, or after asparaginase, while asparagine concentrations are below normal. It has been suggested that giving methotrexate 24 hours *before* asparaginase permits at least an additive therapeutic effect.[2]

1. Jolivet J, *et al.* Prevention of methotrexate cytotoxicity by asparaginase inhibition of methotrexate polyglutamate formation. *Cancer Res* 1985; **45:** 217–20.
2. Capizzi RL. Asparaginase-methotrexate in combination chemotherapy: schedule-dependent differential effects on normal versus neoplastic cells. *Cancer Treat Rep* 1981; **65** (suppl 4): 115–21.

Pharmacokinetics

After intravenous injection the plasma half-life of the native enzyme has varied from about 8 to 30 hours; half-lives of up to 49 hours may be seen after intramuscular dosage. The mean half-life of pegaspargase is reported to be between 6 and 14 days. Asparaginase is found in the lymph at about 20% of the concentration in plasma. There is virtually no diffusion into the CSF. Little is excreted in the urine.

References.

1. Panetta JC, *et al.* Comparison of native *E. coli* and PEG asparaginase pharmacokinetics and pharmacodynamics in pediatric acute lymphoblastic leukemia. *Clin Pharmacol Ther* 2009; **86:** 651–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kidrolase; Oncaspar; ***Austral.***: Leunase; ***Austria***: Erwinase; ***Belg.***: Paronal; ***Braz.***: Elspar; ***Canad.***: Erwinase; Kidrolase; ***China***: Leunase (左旋门冬酰胺酶); ***Cz.***: Kidrolase; ***Fr.***: Kidrolase; ***Ger.***: Erwinase†; Oncaspar; ***Gr.***: Erwinase; Oncaspar; ***Hong Kong***: Leunase; ***India***: L-Aspase; Leucoginase; Leunase; Oncoginase; Onconase; ***Indon.***: Leunase; ***Irl.***: Erwinase; ***Israel***: Kidrolase; ***Jpn***: Leunase; ***Malaysia***: Leunase; ***Mex.***: Elspar; Leunase; ***Neth.***: Erwinase; Paronal; ***NZ***: Erwinase; Leunase; ***Philipp.***: Leunase; ***Pol.***: Oncaspar; ***Port.***: Erwinase; ***Rus.***: Oncaspar (Онкаспар); ***S.Afr.***: Laspar; ***Singapore***: Erwinase; Leunase; ***Thai.***: Erwinase; Leunase; ***Turk.***: Leunase; ***UK***: Erwinase; ***USA***: Elspar; Erwinaze; Oncaspar.

Atiprimod (rINN)

Atiprimodum; Атипримод.
2-[3-(Diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decane.

$C_{22}H_{44}N_2$=336.6
CAS — 123018-47-3 (atiprimod); 130065-61-1 (atiprimod hydrochloride); 183063-72-1 (atiprimod maleate).
UNII — MG7D3QD743.

Profile

Atiprimod is an antineoplastic that is under investigation for the treatment of carcinoid tumours and multiple myeloma.

Atrasentan Hydrochloride *(USAN, rINNM)*

A-147627.1; Abbott-147627; ABT-627; Atrasentan, Chlorhydrate d'; Atrasentani Hydrochloridum; Hidrocloruro de atrasentán; Атразентана Гидрохлорид.
(2*R*,3*R*,4*S*)-1-[(Dibutylcarbamoyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid hydrochloride.
$C_{29}H_{38}N_2O_6$,HCl=547.1
CAS — 173937-91-2 (atrasentan); 195733-43-8 (atrasentan hydrochloride).
UNII — E4G31X93ZA.

NOTE. The name Xinlay has been used as a trademark for atrasentan hydrochloride.

Profile

Atrasentan hydrochloride is a selective endothelin-A receptor antagonist that inhibits the effect of endothelin-1, a protein that may be involved in cancer progression. It is under investigation in the treatment of prostate cancer, and has been tried in other malignant neoplasms, as well as for complications of diabetes and the metabolic syndrome.

References.

1. Samara E, *et al.* Single-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist. *J Clin Pharmacol* 2001; **41:** 397–403.
2. Carducci MA, *et al.* Atrasentan, an endothelin-receptor antagonist for refractory adenocarcinomas: safety and pharmacokinetics. *J Clin Oncol* 2002; **20:** 2171–80.
3. Carducci MA, *et al.* Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol* 2003; **21:** 679–89.
4. Zonnenberg BA, *et al.* Phase I dose-escalation study of the safety and pharmacokinetics of atrasentan: an endothelin receptor antagonist for refractory prostate cancer. *Clin Cancer Res* 2003; **9:** 2965–72.
5. Ryan CW, *et al.* Dose-ranging study of the safety and pharmacokinetics of atrasentan in patients with refractory malignancies. *Clin Cancer Res* 2004; **10:** 4406–11.
6. Michaelson MD, *et al.* Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. *Cancer* 2006; **107:** 530–5.
7. Carducci MA, *et al.* Atrasentan Phase III Study Group Institutions. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer* 2007; **110:** 1959–66.
8. Chiappori AA, *et al.* Phase I/II study of atrasentan, an endothelin A receptor antagonist, in combination with paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer. *Clin Cancer Res* 2008; **14:** 1464–9.
9. Phuphanich S, *et al.* New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Phase I safety study of escalating doses of atrasentan in adults with recurrent malignant glioma. *Neuro-oncol* 2008; **10:** 617–623.
10. Nelson JB, *et al.* Atrasentan Phase 3 Study Group. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. *Cancer* 2008; **113:** 2478–87.
11. Raichlin E, *et al.* Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis. *Hypertension* 2008; **52:** 522–8.
12. Russo A, *et al.* Anti-endothelin drugs in solid tumors. *Expert Opin Emerg Drugs* 2010; **15:** 27–40.

Axitinib *(USAN, rINN)*

AG-013736; Axitinibum; Акситиниб.
N-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethenyl]-1*H*-indazol-6-yl}sulfanyl)benzamide.
$C_{22}H_{18}N_4OS$=386.5
CAS — 319460-85-0.
UNII — C9LVQ0YUXG.

Uses and Administration

Axitinib is an inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases. It is given orally in the treatment of advanced renal cell carcinoma (p. 708.3). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The recommended initial dose is 5 mg twice daily, given at 12-hourly intervals. The dose may be increased in patients who tolerate axitinib for at least 2 consecutive weeks with no adverse effects above grade 2, are normotensive, and are not receiving antihypertensive therapy; an increase to 7 mg twice daily, and then to 10 mg twice daily may be considered. If the dose must be decreased because of adverse effects, it is suggested that 5 mg twice daily is reduced to 3 mg twice daily, and then to 2 mg twice daily, if necessary.

The use of strong inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 should be avoided in patients given axitinib. If the combination must be used then the dose of axitinib should be halved, with further adjustments made according to patient response.

The dose of axitinib should be reduced in patients with hepatic impairment (see below).

Axitinib is also under investigation for the treatment of other cancers, including thyroid and liver cancers.

References.

1. Rini BI, *et al.* Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009; **27:** 4462–8.
2. Kelly RJ, Rixe O. Axitinib (AG-013736). *Recent Results Cancer Res* 2010; **184:** 33–44.
3. Rini BI, *et al.* Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; **378:** 1931–9.

Administration in hepatic impairment. The starting dose of axitinib should be reduced in patients with moderate hepatic impairment (Child-Pugh class B) to about half the usual starting dose (see Uses and Administration, above). Further dose adjustment should be made based on individual response. Specific information on its use in severe hepatic impairment (Child-Pugh class C) is lacking.

References.

1. Tortorici MA, *et al.* Influence of mild and moderate hepatic impairment on axitinib pharmacokinetics. *Invest New Drugs* 2011; **29:** 1370–80.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of axitinib include gastrointestinal disturbances, reduced appetite, weight loss, fatigue, asthenia, dysphonia, and palmar-plantar erythrodysesthesia.

Hypertension is also common and cases of hypertensive crisis have been reported. Blood pressure should be well-controlled before starting axitinib and monitored during therapy. Antihypertensive treatment may be needed but the dose of axitinib should be reduced if hypertension persists; axitinib should be stopped if hypertension is severe and persistent or there is evidence of hypertensive crisis. Arterial and venous thromboembolism have occurred in patients given axitinib. Reported haemorrhagic events have included cerebral haemorrhage, haematuria, and gastrointestinal bleeding. Gastrointestinal perforation and fistula formation have also been reported.

Other adverse effects include thyroid dysfunction, proteinuria, and elevations of liver enzymes values; patients should be assessed for these before starting axitinib and monitored during therapy. There have also been cases of reversible posterior leukoencephalopathy syndrome in patients given axitinib.

Axitinib should be stopped at least 24 hours before surgery, because of potential impairment of wound healing.

Interactions

Plasma concentrations of axitinib may be altered by the concomitant use of drugs that affect the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Strong inhibitors of these enzymes should be avoided, but if they must be used then the dose of axitinib should be reduced (see Uses and Administration, above). Grapefruit and grapefruit juice should also be avoided. Moderate and strong inducers of these enzymes can reduce axitinib concentrations and should therefore be avoided during axitinib therapy.

Pharmacokinetics

Axitinib is absorbed from the gastrointestinal tract. It has a bioavailability of about 58% and is highly bound to plasma proteins. Axitinib is metabolised mainly in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Most of the dose is excreted as metabolites in the urine and faeces; about 12% is excreted unchanged in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Inlyta; ***Jpn***: Inlyta; ***Neth.***: Inlyta; ***Norw.***: Inlyta; ***Switz.***: Inlyta; ***UK***: Inlyta; ***USA***: Inlyta.

Azacitidine *(BAN, USAN, rINN)*

5-Azacitidina; Azacitidina; Azacitidinum; 5-Azacytidine; Ladakamycin; NSC-102816; U-18496; Азацитидин.
4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one.
$C_8H_{12}N_4O_5$=244.2
CAS — 320-67-2.
ATC — L01BC07.
ATC Vet — QL01BC07.
UNII — M801H13NRU.

Uses and Administration

Azacitidine is an antimetabolite antineoplastic with general properties similar to those of cytarabine (p. 774.1). It also inhibits cellular pyrimidine synthesis. Azacitidine is used in myelodysplastic syndromes (p. 694.3); it is also used in the treatment of acute myeloid leukaemia (p. 693.1) and chronic myelomonocytic leukaemia.

Azacitidine is given subcutaneously or intravenously in a dose of 75 mg/m^2 daily for 7 days, in 4-week cycles. For myelodysplastic syndromes, if there is no benefit after 2 cycles, and no toxicity other than nausea and vomiting has occurred, the dose may be increased to 100 mg/m^2 daily.

Treatment for at least 4 to 6 cycles is usually recommended; treatment is continued as long as the patient benefits, or until disease progression. Doses may need to be adjusted for haematological toxicity. Azacitidine should be used with caution in renal impairment and doses adjusted accordingly (see below).

References.

1. Siddiqui MAA, Scott LJ. Azacitidine: in myelodysplastic syndromes. *Drugs* 2005; **65:** 1781–9.
2. Kaminskas E, *et al.* FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist* 2005; **10:** 176–82.
3. Silverman LR, *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006; **24:** 3895–3903.
4. Abdulhaq H, Rossetti JM. The role of azacitidine in the treatment of myelodysplastic syndromes. *Expert Opin Invest Drugs* 2007; **16:** 1967–75.
5. O'Dwyer K, Maslak P. Azacitidine and the beginnings of therapeutic epigenetic modulation. *Expert Opin Pharmacother* 2008; **9:** 1981–6.
6. Lyons RM, *et al.* Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Oncol* 2009; **27:** 1850–6.
7. Fenaux P, *et al.* International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; **10:** 223–32.
8. Cataldo VD, *et al.* Azacitidine for the treatment of myelodysplastic syndrome. *Expert Rev Anticancer Ther* 2009; **9:** 875–84.
9. Keating GM. Azacitidine: a review of its use in higher-risk myelodysplastic syndromes/acute myeloid leukaemia. *Drugs* 2009; **69:** 2501–18.
10. Gurion R, *et al.* 5-azacitidine prolongs overall survival in patients with myelodysplastic syndrome—a systematic review and meta-analysis. *Haematologica* 2010; **95:** 303–10.

Administration in renal impairment. Adverse renal effects of azacitidine include abnormalities in renal-function tests, renal tubular acidosis, renal failure, and death. Licensed product information recommends that if serum-bicarbonate concentrations fall to below 20 mmol/litre, the dose of azacitidine should be halved for the next course. If there are rises in serum concentrations of urea or creatinine, the next cycle of azacitidine should be delayed until these return to normal or baseline, and the dose should be halved on the next treatment course.

Adverse Effects and Precautions

The adverse effects of azacitidine are generally similar to those seen with cytarabine (p. 775.1). Hypokalaemia, dyspnoea, and bruising are common.

Pharmacokinetics

Azacitidine is rapidly absorbed after subcutaneous use; the bioavailability relative to intravenous use is about 89%. The mean plasma half-life after subcutaneous injection is about 40 minutes. Azacitidine and its metabolites are excreted mainly in the urine; about 50% and 85% is recovered after subcutaneous and intravenous dosing, respectively. The mean elimination half-life is about 4 hours after subcutaneous or intravenous use.

References.

1. Marcucci G, *et al.* Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. *J Clin Pharmacol* 2005; **45:** 597–602.
2. Tsao CF, *et al.* Azacitidine pharmacokinetics in an adolescent patient with renal compromise. *J Pediatr Hematol Oncol* 2007; **29:** 330–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vidaza; ***Austria***: Vidaza; ***Belg.***: Vidaza; ***Braz.***: Vidaza; ***Canad.***: Vidaza; ***Cz.***: Vidaza; ***Denm.***: Vidaza; ***Fr.***: Vidaza; ***Ger.***: Vidaza; ***Gr.***: Vidaza; ***Hong Kong***: Vidaza; ***Irl.***: Vidaza; ***Israel***: Vidaza; ***Ital.***: Vidaza; ***Jpn***: Vidaza; ***Malaysia***: Vidaza; ***Neth.***: Vidaza; ***Norw.***: Vidaza; ***NZ***: Vidaza; ***Philipp.***: Vidaza; ***Pol.***: Vidaza; ***Port.***: Vidaza; ***S.Afr.***: Vidaza; ***Singapore***: Vidaza; ***Spain***: Vidaza; ***Swed.***: Vidaza; ***Switz.***: Vidaza; ***Thai.***: Vidaza; ***Turk.***: Vidaza; ***UK***: Vidaza; ***USA***: Vidaza.

Bafetinib *(USAN, rINN)*

Bafétinib; Bafetinibum; INNO-406; NS-187; Бафетиниб.
N-(3-{[(4,5′-Bipyrimidin)-2-yl]amino}-4-methylphenyl)-4-{[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]methyl}-3-(trifluoromethyl)benzamide.

$C_{30}H_{31}F_3N_8O$=576.6
CAS — 859212-16-1; 887650-05-7.
UNII — NVW4Z03I9B.

Profile

Bafetinib is an orally active tyrosine kinase inhibitor active against BCR-ABL and Lyn (part of the SRC family) kinases. It is under investigation for the treatment of malignant neoplasms such as chronic myeloid leukaemia, chronic lymphocytic leukaemia, brain cancer, and prostate cancer.

References.

1. Kantarjian H, *et al.* Phase 1 study of INNO-406, a dual Abl/Lyn kinase inhibitor, in Philadelphia chromosome-positive leukemias after imatinib resistance or intolerance. *Cancer* 2010; **116:** 2665–72.
2. Santos FP, *et al.* Bafetinib, a dual Bcr-Abl/Lyn tyrosine kinase inhibitor for the potential treatment of leukemia. *Curr Opin Investig Drugs* 2010; **11:** 1450–65.

Becatecarin *(USAN, rINN)*

Becatecarina; Bécatécarine; Becatecarinum; Betacatecarin; Betotecarin; BMS-181176; BMY-27557; DEAE-rebeccamycin; NSC-655649; XL-119; Бекатекарин.
1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-*O*-methyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione.
$C_{33}H_{34}Cl_2N_4O_7$=669.6
CAS — 119673-08-4.
UNII — A60X6M8U6G.

Profile

Becatecarin is a synthetic analogue of the antineoplastic antibiotic rebeccamycin. It is an inhibitor of the enzyme topoisomerase I, and is under investigation in the treatment of bile-duct and other tumours.

References.

1. Merchant J, *et al.* Phase I clinical and pharmacokinetic study of NSC 655649, a rebeccamycin analogue, given in both single-dose and multiple-dose formats. *Clin Cancer Res* 2002; **8:** 2193–2201.
2. Goel S, *et al.* A phase II study of rebeccamycin analog NSC 655649 in patients with metastatic colorectal cancer. *Invest New Drugs* 2003; **21:** 103–7.
3. Langevin AM, *et al.* Phase I trial of rebeccamycin analog (NSC #655649) in children with refractory solid tumors: a pediatric oncology group study. *J Pediatr Hematol Oncol* 2003; **25:** 526–33.
4. Hussain M, *et al.* A phase II study of rebeccamycin analog (NSC-655649) in metastatic renal cell cancer. *Invest New Drugs* 2003; **21:** 465–71.
5. Ricart AD, *et al.* Phase I and pharmacokinetic study of sequences of the rebeccamycin analogue NSC 655649 and cisplatin in patients with advanced solid tumors. *Clin Cancer Res* 2005; **11:** 8728–36.
6. Langevin AM, *et al.* Children's Oncology Group. A phase II trial of rebeccamycin analogue (NSC #655649) in children with solid tumors: a Children's Oncology Group study. *Pediatr Blood Cancer* 2008; **50:** 577–80.
7. Borthakur G, *et al.* Phase 1 study of XL119, a rebeccamycin analog, in patients with refractory hematologic malignancies. *Cancer* 2008; **113:** 360–6.
8. Dowlati A, *et al.* Phase II and pharmacokinetic trial of rebeccamycin analog in advanced biliary cancers. *Cancer Chemother Pharmacol* 2009; **65:** 73–8.

Belagenpumatucel-L *(USAN)*

NOTE. The name Lucanix has been used as a trade mark for belagenpumatucel-L.

Profile

Belagenpumatucel-L is an allogeneic cancer vaccine (p. 757.3) that is stated to produce improved antigen recognition because of its ability to block transforming growth factor β-2. It is under investigation for the treatment of non-small cell lung cancer.

Belinostat *(USAN, rINN)*

Bélinostat; Belinostatum; PXD-101; Белиностат.
N-Hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide.
$C_{15}H_{14}N_2O_4S$=318.3
CAS — 414864-00-9.
UNII — F4H96P17NZ.

Profile

Belinostat is a histone deacetylase inhibitor that is under investigation for the treatment of peripheral T-cell lymphomas and other malignant neoplasms.

References.

1. Steele NL, *et al.* Pharmacokinetic and pharmacodynamic properties of an oral formulation of the histone deacetylase inhibitor belinostat (PXD101). *Cancer Chemother Pharmacol* 2011; **67:** 1273–9.
2. Giaccone G, *et al.* Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors. *J Clin Oncol* 2011; **29:** 2052–9.

Belotecan *(rINN)*

Belotecán; Bélotécan; Belotecanum; CKD-602; Бельотекан.
(4*S*)-4-Ethyl-4-hydroxy-11-[2-(isopropylamino)ethyl]-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione.
$C_{25}H_{27}N_3O_4$=433.5
CAS — 256411-32-2.
UNII — 27Z82M2G1N.

NOTE. The name Camtobell has been used as a trade mark for belotecan.

Belotecan Hydrochloride *(USAN, pINNM)*

Bélotécan, Chlorhydrate de; Belotecani Hydrochloridum; CKD-602; Hidrocloruro de belotecán; Бельотекана Гидрохлорид.
(4*S*)-4-Ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione hydrochloride.
$C_{25}H_{27}N_3O_4$,HCl=470.0
CAS — 213819-48-8.
UNII — 01DZ4127G7.

Profile

Like irinotecan (p. 812.2), belotecan is a topoisomerase I inhibitor related to camptothecin. It is used for the treatment of ovarian cancer and small cell lung cancer. A liposomal formulation (S-CKD-602)is also under investigation.

References.

1. Lee DH, *et al.* A phase I and pharmacologic study of belotecan in combination with cisplatin in patients with previously untreated extensive-stage disease small cell lung cancer. *Clin Cancer Res* 2007; **13:** 6182–6.
2. Lee DH, *et al.* Belotecan, new camptothecin analogue, is active in patients with small-cell lung cancer: results of a multicenter early phase II study. *Ann Oncol* 2008; **19:** 123–7.
3. Kim SJ, *et al.* A multicenter phase II study of belotecan, new camptothecin analogue, in patients with previously untreated extensive stage disease small cell lung cancer. *Lung Cancer* 2010; **68:** 446–9.
4. Kim YM, *et al.* The efficacy and toxicity of belotecan (CKD-602), a camptothericin analogue topoisomerase I inhibitor, in patients with recurrent or refractory epithelial ovarian cancer. *J Chemother* 2010; **22:** 197–200.
5. Kim HS, *et al.* Comparison of the efficacy between topotecan- and belotecan-, a new camptothecin analog, based chemotherapies for recurrent epithelial ovarian cancer: a single institutional experience. *J Obstet Gynaecol Res* 2010; **36:** 86–93.
6. Rhee CK, *et al.* A multicenter phase II study of belotecan, a new camptothecin analogue, as a second-line therapy in patients with small cell lung cancer. *Lung Cancer* 2011; **72:** 64–7.

Bendamustine Hydrochloride

(BANM, USAN, rINNM)

Bendamustina, hidrocloruro de; Bendamustine, Chlorhydrate de; Bendamustinhydrochlorid; Bendamustini Hydrochloridum; Cytostasan; Hidrocloruro de bendamustina; IMET-3393; SDX-105; SyB-L-0501; Бендамустина Гидрохлорид.
5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid hydrochloride.
$C_{16}H_{21}Cl_2N_3O_2$, HCl=394.7
CAS — 16506-27-7 (bendamustine); 3543-75-7 (bendamustine hydrochloride).
ATC — L01AA09.
ATC Vet — QL01AA09.
UNII — 981Y8SX18M.

Stability. US licensed product information for bendamustine hydrochloride states that, once reconstituted as directed and further diluted with sodium chloride 0.9%, the final infusion solution is stable for 24 hours when refrigerated (2 degrees to 8 degrees) or for 3 hours when stored at room temperature (15 degrees to 30 degrees) and exposed to light.

Uses and Administration

Bendamustine is an antineoplastic alkylating agent used for the treatment of chronic lymphocytic leukaemia (p. 693.3) as well as for non-Hodgkin's lymphoma (p. 696.3) that has progressed during, or within 6 months of, treatment with rituximab. It may be given with prednisone for the treatment of multiple myeloma (p. 699.2) in patients older than 65 years of age who are not eligible for stem-cell transplantation and who cannot be treated with thalidomide or bortezomib. It may also be used for Hodgkin's disease and breast cancer.

Bendamustine is given intravenously as the hydrochloride. After reconstitution, it is usually diluted in 500 mL of sodium chloride 0.9%; the final concentration of bendamustine hydrochloride should be between 200 and 600 micrograms/mL. Doses should be modified or delayed in the event of toxicity until the patient has recovered, and until neutrophils and platelets have reached acceptable concentrations (see Bone-Marrow Depression, p. 730.3).

For the treatment of **chronic lymphocytic leukaemia**, bendamustine hydrochloride is given in a dose of 100 mg/m², infused over 30 to 60 minutes on days 1 and 2 of a 28-day cycle, for up to 6 cycles. For severe haematological or non-haematological toxicity, doses should be reduced to 50 mg/m² on days 1 and 2 of each cycle. If severe haematological toxicity recurs, the dose should be further reduced to 25 mg/m² on days 1 and 2 of each cycle. Dose re-escalation in subsequent cycles may be considered.

The recommended dose for **non-Hodgkin's lymphoma** is 120 mg/m², infused over 30 to 60 minutes on days 1 and 2 of a 21-day cycle, for up to 8 cycles. For severe haematological or non-haematological toxicity, doses should be reduced to 90 mg/m² on days 1 and 2 of each cycle. If severe toxicity recurs, the dose should be further reduced to 60 mg/m² on days 1 and 2 of each cycle.

For the treatment of **multiple myeloma**, bendamustine hydrochloride is given in a dose of 120 to 150 mg/m², infused over 30 to 60 minutes on days 1 and 2 of a 28-day cycle; intravenous or oral prednisone at a dose of 60 mg/m² is given on days 1 to 4 of the cycle.

References.

1. Knauf W. Bendamustine in the treatment of chronic lymphocytic leukemia. *Expert Rev Anticancer Ther* 2009; **9:** 165–74.
2. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. *J Clin Oncol* 2009; **27:** 1492–1501. Correction. *ibid.;* 2892.
3. Tageja N, Nagi J. Bendamustine: something old, something new. *Cancer Chemother Pharmacol* 2010; **66:** 413–23.
4. Cheson BD, *et al.* Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. *Clin Lymphoma Myeloma Leuk* 2010; **10:** 21–7.
5. Elefante A, Czuczman MS. Bendamustine for the treatment of indolent non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *Am J Health-Syst Pharm* 2010; **67:** 713–23.
6. Garnock-Jones KP. Bendamustine: a review of its use in the management of indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *Drugs* 2010; **70:** 1703–18.
7. NICE. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Technology Appraisal Guidance 216, issued February 2011). Available at: http://www.nice.org.uk/nicemedia/live/13343/53180/53180.pdf (accessed 22/09/11)
8. Hoy SM. Bendamustine: a review of its use in the management of chronic lymphocytic leukaemia, rituximab-refractory indolent non-Hodgkin's lymphoma and multiple myeloma. *Drugs* 2012; **72:** 1929–50.

Administration in hepatic impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in mild hepatic impairment, data are limited, and therefore caution should be exercised when using bendamustine in these patients. Bendamustine should not be used in moderate or severe hepatic impairment due to a lack of data.

Administration in renal impairment. Although no meaningful effect on the pharmacokinetics of bendamustine was seen in renal impairment, US licensed product information states that data are limited, and that caution should be exercised in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with creatinine clearance less than 40 mL/minute, due to a lack of data.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bendamustine commonly causes myelosuppression and doses may need to be reduced (see Uses and Administration, above); patients are therefore susceptible to infection. Other common adverse effects include gastrointestinal disturbances, fever, asthenia, fatigue, malaise, dry mouth, somnolence, cough, headache, mucosal inflammation, and stomatitis. Infusion reactions are common; symptoms include fever, chills, pruritus, and rash. Anaphylactic reactions have been reported rarely, especially during the second and subsequent cycles of therapy. Prophylactic antihistamines, antipyretics, and corticosteroids should be considered. If severe infusion reactions occur, therapy should be stopped. Tumour lysis syndrome has been reported, usually within the first treatment cycle, and may lead to acute renal failure and death. Adequate volume status should be maintained and potassium and uric acid concentrations should be monitored; allopurinol may be used in patients at high risk. Skin reactions such as bullous exanthema can occur with bendamustine; therapy may need to be withheld or stopped. Worsening hypertension, including hypertensive crisis, has also occurred. Increases in creatinine concentrations and liver enzyme values have been reported; bendamustine should be used with caution in patients with renal or hepatic impairment.

Interactions

Bendamustine is extensively metabolised by cytochrome P450 isoenzyme CYP1A2. Inhibitors of CYP1A2, such as fluvoxamine and ciprofloxacin, may increase exposure to bendamustine. Conversely, CYP1A2 inducers, such as omeprazole, can reduce exposure to bendamustine; tobacco smoking also may increase exposure to bendamustine.

Pharmacokinetics

Bendamustine is about 95% bound to plasma proteins; data suggest it is not likely to displace nor to be displaced by highly protein-bound drugs. Bendamustine distributes freely into human red blood cells. It is mainly metabolised by hydrolysis via the cytochrome P450 isoenzyme CYP1A2. Little or no accumulation in plasma is anticipated for intravenous doses of bendamustine given on days 1 and 2 of a 28-day cycle. About 90% of the drug is eliminated, mainly via the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Levact; ***Canad.***: Treanda; ***Cz.***: Ribomustin; ***Denm.***: Levact; ***Fin.***: Levact; ***Fr.***: Levact; ***Ger.***: Levact; Ribomustin†; ***Gr.***: Levact; Ribomustin; Treanda; ***Hong Kong***: Treanda; ***Irl.***: Levact; ***Ital.***: Levact; ***Jpn***: Treakisym; ***Neth.***: Levact; ***Norw.***: Levact; ***Rus.***: Ribomustine (Рибомустин); ***Singapore***: Symbenda; ***Spain***: Levact; ***Swed.***: Ribovact; ***Switz.***: Ribomustin; ***UK***: Levact; ***Ukr.***: Ribomustine (Рибомустин); ***USA***: Treanda.

Bevacizumab *(rINN)*

Bévacizumab; Bevacizumabum; R-435; rhuMAb-VEGF; Бевацизумаб.

Immunoglobulin G1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer.

CAS — 216974-75-3.

ATC — L01XC07.

ATC Vet — QL01XC07.

UNII — 2S9ZZM9Q9V.

Stability. UK licensed product information states that bevacizumab is chemically and physically stable for 48 hours at 2 degrees to 30 degrees in sodium chloride 0.9%, although immediate use is recommended from a microbiological point of view. If the solution is not used immediately, storage for longer than 24 hours at 2 degrees to 8 degrees cannot be recommended, unless dilution has taken place in controlled and validated aseptic conditions. In the USA, licensed product information states that bevacizumab solutions for infusion may be stored at 2 degrees to 8 degrees for up to 8 hours.

Bevacizumab should not be mixed with glucose.

A study tested the concentration change in bevacizumab when the drug was drawn up into 1-mL latex-free syringes, using a 20-gauge needle, and then capped with a 30-gauge needle, and stored at 4 degrees for varying times; 1 syringe was frozen at -10 degrees. Results were compared with an unopened vial of bevacizumab stored at 4 degrees and protected from light. Bevacizumab concentrations decreased by 1.6% at 1 week, 0% at 3 weeks, 8.8% at 3 months, and 15.9% at 6 months; the concentration in the frozen syringe decreased by 12% at 6 months.[1]

1. Bakri SJ, *et al*. Six-month stability of bevacizumab (Avastin) binding to vascular endothelial growth factor after withdrawal into a syringe and refrigeration or freezing. *Retina* 2006; **26:** 519–22.

Uses and Administration

Bevacizumab is a recombinant humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby inhibiting the angiogenesis that occurs during tumour growth. Bevacizumab is used with fluoropyrimidine-based chemotherapy in the treatment of metastatic colorectal cancer (p. 706.3). It has also been used with a taxane such as paclitaxel, for the first-line treatment of patients with metastatic breast cancer (p. 702.1). Bevacizumab may be used with platinum-based chemotherapy in the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (p. 710.2). Bevacizumab is used with interferon alfa for the first-line treatment of advanced and/or metastatic renal cell cancer (p. 708.3). Bevacizumab is also used for the treatment of progressive glioblastoma (see Malignant Neoplasms of the Brain, p. 701.2).

Bevacizumab is usually given diluted in 100mL of sodium chloride 0.9%; the final concentration should be kept within the range of 1.4 to 16.5 mg/mL. The first dose should be given as an intravenous infusion over 90 minutes; if this is well tolerated the second dose should be given over 60 minutes, and if this is well tolerated then subsequent doses may be given over 30 minutes.

In the treatment of **colorectal cancer**, bevacizumab is given in a dose of 5 or 10 mg/kg once every 2 weeks, or 7.5 or 15 mg/kg once every 3 weeks; doses depend on the combination of drugs used in the regimen.

For **breast cancer**, the recommended dose of bevacizumab is 10 mg/kg given once every 2 weeks, or 15 mg/kg given once every 3 weeks.

For **non-small cell lung cancer**, the recommended dose of bevacizumab is 7.5 or 15 mg/kg given once every 3 weeks. In the UK, combination therapy is given for up to 6 cycles, followed by bevacizumab monotherapy until disease progression.

For **renal cell carcinoma**, bevacizumab is given in a dose of 10 mg/kg once every 2 weeks.

For **glioblastoma**, the recommended dose of bevacizumab is 10 mg/kg once every 2 weeks.

There are no recommended dose reduction regimens should adverse effects occur with bevacizumab; therapy should either be permanently stopped or temporarily suspended.

Bevacizumab is under investigation for various other neoplasms, including gastric, ovarian, and prostate cancer. A related monoclonal antibody, ranibizumab (p. 2602.1) has been developed for the treatment of neovascular (wet) age-related macular degeneration, and it has been suggested that bevacizumab might also be of benefit.

A drug-eluting stent containing bevacizumab is under investigation.

References.

1. Hurwitz H, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350:** 2335–42.
2. Johnson DH, *et al*. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. *J Clin Oncol* 2004; **22:** 2184–91.
3. Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. *Ann Pharmacother* 2004; **38:** 1258–64.
4. Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. *Am J Health-Syst Pharm* 2005; **62:** 1021–32. Correction. *ibid.*; 1241.
5. Kabbinavar FF, *et al*. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23:** 3706–12.
6. Midgley R, Kerr D. Bevacizumab—current status and future directions. *Ann Oncol* 2005; **16:** 999–1004.
7. Lyseng-Williamson KA, Robinson DM. Spotlight on bevacizumab in advanced colorectal cancer, breast cancer, and non-small cell lung cancer. *BioDrugs* 2006; **20:** 193–5.
8. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther* 2006; **28:** 1779–1802.
9. Pañares RL, Garcia AA. Bevacizumab in the management of solid tumors. *Expert Rev Anticancer Ther* 2007; **7:** 433–45.
10. Cilley JC, *et al*. Bevacizumab in the treatment of colorectal cancer. *Expert Opin Biol Ther* 2007; **7:** 739–49.
11. Burger RA. Experience with bevacizumab in the management of epithelial ovarian cancer. *J Clin Oncol* 2007; **25:** 2902–8.
12. Escudier B, *et al*. AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; **370:** 2103–11.
13. Miller K, *et al*. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; **357:** 2666–76.
14. Scott LJ. Bevacizumab: in first-line treatment of metastatic breast cancer. *Drugs* 2007; **67:** 1793–9.
15. McCormack PL, Keam SJ. Bevacizumab: a review of its use in metastatic colorectal cancer. *Drugs* 2008; **68:** 487–506.
16. Di Costanzo F, *et al*. Bevacizumab in non-small cell lung cancer. *Drugs* 2008; **68:** 737–46.
17. Norden AD, *et al*. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* 2008; **70:** 779–87.
18. Buie LW, Valgus J. Bevacizumab: a treatment option for recurrent glioblastoma multiforme. *Ann Pharmacother* 2008; **42:** 1486–90.
19. Moen MD. Bevacizumab: in previously treated glioblastoma. *Drugs* 2010; **70:** 181–9.
20. Koutras AK, *et al*. Bevacizumab in the treatment of breast cancer. *Cancer Treat Rev* 2010; **36:** 75–82.
21. McDermott DF, George DJ. Bevacizumab as a treatment option in advanced renal cell carcinoma: an analysis and interpretation of clinical trial data. *Cancer Treat Rev* 2010; **36:** 216–23.
22. Iwamoto FM, Fine HA. Bevacizumab for malignant gliomas. *Arch Neurol* 2010; **67:** 285–8.

Administration. It has been suggested that bevacizumab may be safely given at an infusion rate of 500 micrograms/kg per minute; this means a dose of 5 mg/kg could be given over 10 minutes.[1]

1. Reidy DL, *et al*. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007; **25:** 2691–5.

Eye disorders. In addition to the conditions discussed below, bevacizumab is being tried in many eye disorders, mostly those associated with choroidal or retinal neovascularisation, or with macular oedema, but the number of patients is mostly small, with evidence limited to case reports or small case series.[1]

1. Gunther JB, Altaweel MM. Bevacizumab (Avastin) for the treatment of ocular disease. *Surv Ophthalmol* 2009; **54:** 372–400.

AGE-RELATED MACULAR DEGENERATION. Promising short-term results with intravenous[1,2] or intravitreal[3-9] bevacizumab to treat age-related macular degeneration (p. 880.2) or its complications were reported, and a controlled study[10] found its intravitreal use to be superior to pegaptanib or to photodynamic therapy with verteporfin. However, bevacizumab is unlicensed for this use and has been associated with adverse effects (see Effects on the Eyes, p. 748.1). Ranibizumab (p. 2602.1) is a humanised antibody fragment derived from bevacizumab that is licensed for the treatment of this disease. A multicentre comparative study[11] found that ranibizumab and bevacizumab, both given according to the same intravitreal schedule, had equivalent effects on visual acuity during 1 year of follow-up. No significant differences were seen between the 2 drugs in rates of death or thrombotic events, although the rate of serious systemic adverse events (mainly hospitalisation) was higher with bevacizumab.

1. Michels S, *et al*. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005; **112:** 1035–47.
2. Bolz M, *et al*. Effect of systemic bevacizumab therapy on retinal pigment epithelial detachment. *Br J Ophthalmol* 2007; **91:** 785–9.
3. Avery RL, *et al*. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113:** 363–72.
4. Bashshur ZF, *et al*. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006; **142:** 1–9.
5. Spaide RF, *et al*. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006; **26:** 383–90.
6. Fung AE, *et al*. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006; **90:** 1344–9.
7. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Ann Pharmacother* 2007; **41:** 614–25.
8. Madhusudhana KC, *et al*. Intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization in age-related macular degeneration: results from 118 cases. *Br J Ophthalmol* 2007; **91:** 1716–17.
9. Ávila MP, *et al*. Twelve-month short-term safety and visual-acuity results from a multicentre prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularisation secondary to age-related macular degeneration. *Br J Ophthalmol* 2009; **93:** 305–9.
10. Tufail A, *et al*. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. *BMJ* 2010; **340:** c2459.
11. Martin DF, *et al*. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; **364:** 1897–908.

GLAUCOMA. Neovascular glaucoma is a severe complication in patients affected by proliferative diabetic retinopathy or central retinal vein occlusion, and can result in complete loss of vision; treatment is unsatisfactory, and early diagnosis with aggressive control of intra-ocular pressure is crucial. In a small study of patients who had already undergone standard retinal ablative treatment, a total of 3 intravitreal injections of bevacizumab were given, at intervals of 4 weeks. Regression of corneal oedema with significant pain reduction was seen after the first injection, without any notable improvement in visual acuity; however, after the third injection, regression of iris neovascularisation as well as significant improvement of visual acuity was seen in most cases.[1]

1. Costagliola C, *et al*. Intravitreal bevacizumab (Avastin) injection for neovascular glaucoma: a survey on 23 cases throughout 12-month follow-up. *Br J Clin Pharmacol* 2008; **66:** 667–73.

PTERYGIUM. Bevacizumab has been investigated in the management of pterygium.[1]

1. Mauro J, Foster CS. Pterygia: pathogenesis and the role of subconjunctival bevacizumab in treatment. *Semin Ophthalmol* 2009; **24:** 130–4.

RETINOPATHY OF PREMATURITY. For reference to the investigational use of bevacizumab in infants with retinopathy of prematurity see p. 2120.3.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Bevacizumab has been reported to be effective.[1]

1. Stefanadis C, *et al*. Avastin-eluting stent: long-term angiographic and clinical follow up. *Hellenic J Cardiol* 2008; **49:** 188–90.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bevacizumab may impair wound healing; therapy should not be started for at least 28 days after major surgery or until the surgical incision is fully healed; it should also be withheld before elective surgery. Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation is more common in patients receiving bevacizumab; fatalities have been reported. Serious, and sometimes fatal, non-gastrointestinal fistulas can also occur, usually within the first 6 months of therapy. Bevacizumab should be stopped permanently in patients who develop gastrointestinal perforation, or fistulas, or wound dehiscence needing medical intervention. Very rare cases of nasal septum perforation have been reported.

Leucopenia, anaemia, neutropenia, thrombocytopenia, and febrile neutropenia have also occurred; severe neutropenia with infection has caused fatalities. Bevacizumab can cause two distinct patterns of bleeding. Minor

haemorrhage such as epistaxis may occur; severe or fatal bleeding including CNS haemorrhage and pulmonary haemorrhage presenting as haemoptysis has been reported. There is an increased risk of serious arterial and venous thromboembolic events associated with the use of bevacizumab including pulmonary embolism, stroke, transient ischaemic attacks, myocardial infarction, angina, and death. Bevacizumab may cause congestive heart failure; the risk is higher in those patients who have concurrent or previous treatment with anthracyclines. Hypertension, possibly dose-dependent, has occurred; blood pressure should be monitored, and therapy stopped in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria may develop; bevacizumab should be stopped in patients who develop nephrotic syndrome. Other adverse effects include asthenia, pain, abdominal pain, gastrointestinal disturbances, stomatitis, headache, taste alteration, dyspnoea, lachrymation disorder, and exfoliative dermatitis. Peripheral sensory neuropathy, syncope, somnolence, supraventricular tachycardia, palmar-plantar erythrodysesthesia syndrome, myalgia, arthralgia, and muscular weakness have been commonly reported. Mucosal inflammation, dry skin, and skin discoloration are also common. Laboratory abnormalities reported include hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, and increased INR. Infusion reactions, manifesting as hypertension, hypoxia, wheezing, chest pain, headaches, rigors, and diaphoresis may occur rarely with the first dose of bevacizumab; treatment should be interrupted.

There have been rare reports of reversible posterior leukoencephalopathy syndrome, a neurological disorder; this may present as seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Bevacizumab therapy should be stopped, and patients treated symptomatically.

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1. Hurwitz H, Saini S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. *Semin Oncol* 2006; **33** (suppl 10): S26–S34.
2. Saif MW, Mehra R. Incidence and management of bevacizumab-related toxicities in colorectal cancer. *Expert Opin Drug Safety* 2006; **5:** 553–66.
3. Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. *Ann Pharmacother* 2009; **43:** 490–501.
4. Higa GM, Abraham J. Biological mechanisms of bevacizumab-associated adverse events. *Expert Rev Anticancer Ther* 2009; **9:** 999–1007.
5. Shord SS, *et al*. Understanding and managing the possible adverse effects associated with bevacizumab. *Am J Health-Syst Pharm* 2009; **66:** 999–1013.
6. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol* 2010; **117:** 497–504.

Effects on the cardiovascular system. For a discussion of the incidence of hypertension associated with use of bevacizumab, see Effects on the Kidneys, below.

Effects on the eyes. As of November 2008, the UK manufacturer of bevacizumab (*Roche, UK*) reported on 25 Canadian cases of adverse events after the unlicensed intravitreal use of the drug; symptoms included ocular irritation, photophobia, blurred vision, and floaters associated with mild to moderate anterior and posterior cellular inflammation.[1] The US manufacturer (*Genentech, USA*) reported that, as of December 2008, there had been 36 Canadian reports of intra-ocular adverse effects, of which 32 were serious intra-ocular inflammatory reactions, after intravitreal use of bevacizumab.[2] Other adverse reactions reported after intravitreal use include retinal pigment epithelial tear[3] and submacular haemorrhage[4] after use for age-related macular degeneration, and macular ischaemia[5] after use for central retinal vein occlusion in patients with diabetes and vascular disease; retinal detachment has occurred after use for proliferative diabetic retinopathy, when used as an adjunct to vitrectomy[6] and when used for neovascular glaucoma in one patient,[7] where it was associated with macular hole.

1. Roche, UK. Reports of severe eye inflammation and sterile endophthalmitis following off-label intravitreal use of AVASTIN (bevacizumab) in Canada (issued 9th February, 2009). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON041212&RevisionSelectionMethod=Latest (accessed 04/09/09)
2. Genetech, USA. Important Drug Notification: reports of intraocular inflammatory reactions after intravitreal injection with AVASTIN (issued 19th December, 2008). Available at: http://www.gene.com/gene/products/information/pdf/avastin_ocular_letter.pdf (accessed 04/09/09)
3. Hannan SR, *et al*. Retinal pigment epithelial tear following intravitreal bevacizumab for choroidal neovascular membrane due to age-related macular degeneration. *Br J Ophthalmol* 2007; **91:** 977–8.
4. Goverdhan SV, Lochhead J. Submacular haemorrhages after intravitreal bevacizumab for large occult choroidal neovascularisation in age-related macular degeneration. *Br J Ophthalmol* 2008; **92:** 210–12.
5. Shimura M, Yasuda K. Macular ischaemia after intravitreal bevacizumab injection in patients with central retinal vein occlusion and a history of diabetes and vascular disease. *Br J Ophthalmol* 2010; **94:** 381–3.
6. Arevalo JF, *et al*. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; **92:** 213–16.
7. Mitamura Y, *et al*. Retinal detachment with macular hole following intravitreal bevacizumab in patient with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; **92:** 717–18.

Effects on the kidneys. A systematic review and subsequent meta-analysis of 7 studies in 1850 patients with various cancers estimated the incidence and risk of developing hypertension and proteinuria with bevacizumab therapy.[1] The relative risk (RR) of developing proteinuria was 1.4 with low-dose bevacizumab (95% confidence interval 1.1 to 1.7) and even higher with high-dose therapy (RR 2.2; 95% confidence interval 1.6 to 2.9). For hypertension, the RR was 3.0 for low-dose bevacizumab (95% confidence interval 2.2 to 4.2) and 7.5 for high-dose therapy (95% confidence interval 4.2 to 13.4). US licensed product information states that hypertension can persist after stopping bevacizumab; therapy should be stopped permanently in those with hypertensive crisis or hypertensive encephalopathy. (For the suggestion that hypertension is a problem with angiogenesis inhibitors in general see Effects on the Cardiovascular System in Sorafenib, p. 858.2.) The safety of continued treatment in patients with moderate to severe proteinuria has not been evaluated; therapy should be interrupted if proteinuria is equal to or greater than 2 g per 24 hours, and may be resumed when it is less than this.

Nephrotic syndrome has also been reported with use of bevacizumab;[2,3] therapy should be stopped in these patients. In one case,[3] there was evidence of a haemolytic-uraemic syndrome; renal biopsy revealed a glomerular thrombotic microangiopathy. Bevacizumab was stopped, with favourable response; however, sunitinib therapy was started but had to be stopped due to a recurrence of severe haemolytic-uraemic syndrome.

A patient who received 3 doses of bevacizumab was diagnosed with acute renal failure secondary to interstitial nephritis. His renal function resolved slowly after stopping therapy; haemodialysis was required.[4]

1. Zhu X, *et al*. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007; **49:** 186–93.
2. George BA, *et al*. Nephrotic syndrome after bevacizumab: case report and literature review. *Am J Kidney Dis* 2007; **49:** e23–e29.
3. Frangié C, *et al*. Renal thrombotic microangiopathy caused by anti-VEGF-antibody treatment for metastatic renal-cell carcinoma. *Lancet Oncol* 2007; **8:** 177–8.
4. Barakat RK, *et al*. Interstitial nephritis secondary to bevacizumab treatment in metastatic leiomyosarcoma. *Ann Pharmacother* 2007; **41:** 707–10.

Effects on the musculoskeletal system. Osteonecrosis of the jaw (similar to that seen with the bisphosphonates, see under Bisphosphonates, p. 1176.3) has been reported in 2 patients after bevacizumab therapy; neither patient had been treated with bisphosphonates.[1] Other cases have occurred when bevacizumab and bisphosphonates were given together; it has been postulated that anti-angiogenic agents such as bevacizumab and sunitinib (see also Effects on the Musculoskeletal System, under Sunitinib, p. 859.2) contribute to oral mucosal breakdown and subsequent development of osteonecrosis of the jaw.[2]

1. Estilo CL, *et al*. Osteonecrosis of the jaw related to bevacizumab. *J Clin Oncol* 2008; **26:** 4037–8.
2. Ayllon J, *et al*. Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile? *Ann Oncol* 2009; **20:** 600–1.

Effects on the nervous system. There are reports of reversible posterior leukoencephalopathy syndrome (RPLS) attributed to bevacizumab.[1,2] Presenting symptoms included lethargy, seizures, hypertension, acute bilateral loss of vision, headache, and confusion. Recovery was rapid after symptomatic treatment.

The symptoms of RPLS may be difficult to distinguish from those of uncontrolled hypertension, and patients presenting with the above signs and symptoms should be examined neurologically.[3]

1. Glusker P, *et al*. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; **354:** 980–1.
2. Ozcan C, *et al*. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; **354:** 981–2.
3. Health Canada. Association of AVASTIN(bevacizumab) with hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome (RPLS) (issued 24th October 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2006/avastin_pc-cp-eng.php (accessed 30/07/08)

Effects on the spleen. Splenic infarction has been reported in a patient given bevacizumab, fluorouracil, folinic acid, and irinotecan. Bevacizumab was stopped. Four further chemotherapy cycles were given. The splenic infarcts partially regressed, although the patient died from metastatic progression. The authors attributed the splenic infarction to bevacizumab, which has been associated with arterial thromboembolic events.[1]

1. Malka D, *et al*. Splenic infarction and bevacizumab. *Lancet Oncol* 2006; **7:** 1038.

Fistula formation. US licensed product information for bevacizumab states that the incidence of gastrointestinal perforation, including fistula formation and/or intra-abdominal abscess, in bevacizumab-treated patients with colorectal cancer or non-small cell lung cancer was 2.4% and 0.9%, respectively. Reports of other types of fistulas such as bronchopleural, urogenital, and biliary fistulas, across various indications and mostly within the first 6 months of therapy, are less common; however, reports of tracheo-oesophageal fistula formation include some fatalities.[1,2] Therapy should be permanently stopped in patients with tracheo-oesophageal or gastrointestinal fistulas.

1. Roche, Canada. Health Canada endorsed important safety information on AVASTIN (bevacizumab): association of AVASTIN (bevacizumab) with tracheo-esophageal fistula (issued June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avastin_hpc-cps_2_e.pdf (accessed 13/06/07)
2. Genentech, USA. Important drug warning regarding AVASTIN (bevacizumab) (issued April 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm153953.pdf (accessed 21/07/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bevacizumab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

The US manufacturer of bevacizumab has recommended that it should not be used with *sunitinib* after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1] UK licensed product information states that this was reversible upon stopping the 2 drugs.

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm126434.pdf (accessed 21/07/10)

Pharmacokinetics

Bevacizumab has a half-life of about 20 days. The predicted time to steady state is about 100 days. Male patients and those with a higher tumour burden have higher clearances of bevacizumab than females and those with tumour burdens below the median, respectively; although no evidence of lesser efficacy has been seen due to this higher clearance, the relationship between exposure to bevacizumab and clinical outcome is not known.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avastin; ***Austral.***: Avastin; ***Austria***: Avastin; ***Belg.***: Avastin; ***Braz.***: Avastin; ***Canad.***: Avastin; ***Chile***: Avastin; ***China***: Avastin (安维汀); ***Cz.***: Avastin; ***Denm.***: Avastin; ***Fin.***: Avastin; ***Fr.***: Avastin; ***Ger.***: Avastin; ***Gr.***: Avastin; ***Hong Kong***: Avastin; ***Hung.***: Avastin; ***Indon.***: Avastin; ***Irl.***: Avastin; ***Israel***: Avastin; ***Ital.***: Avastin; ***Jpn***: Avastin; ***Malaysia***: Avastin; ***Mex.***: Avastin; ***Neth.***: Avastin; ***Norw.***: Avastin; ***NZ***: Avastin; ***Philipp.***: Avastin; ***Pol.***: Avastin; ***Port.***: Avastin; ***Rus.***: Avastin (Авастин); ***S.Afr.***: Avastin; ***Singapore***: Avastin; ***Spain***: Avastin; ***Swed.***: Avastin; ***Switz.***: Avastin; ***Thai.***: Avastin; ***Turk.***: Altuzan; ***UK***: Avastin; ***Ukr.***: Avastin (Авастин); ***USA***: Avastin.

Bexarotene *(BAN, USAN, rINN)*

Beksaroteeni; Beksaroten; Bexaroten; Bexarotène; Bexarotено; Bexarotenum; LG-100069; LGD-1069; Бексаротен.

p-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl) vinyl]benzoic acid.

$C_{24}H_{28}O_2$=348.5

CAS — 153559-49-0.

ATC — L01XX25.

ATC Vet — QL01XX25.

UNII — A61RXM4375.

Uses and Administration

Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. It is used in the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p. 698.3), in a usual initial oral dose of 300 mg/m^2 daily as a single dose taken with a meal. Dosage is adjusted according to toxicity. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For the topical treatment of refractory disease a 1% gel may be applied on alternate days for the first week, gradually increased at weekly intervals to up to 4 times daily, depending on tolerance.

References.
1. Anonymous. Bexarotene (Targretin) for cutaneous T-cell lymphoma. *Med Lett Drugs Ther* 2000; **42:** 31–2.
2. Lowe MN, Plosker GL. Bexarotene. *Am J Clin Dermatol* 2000; **1:** 245–50.
3. Duvic M, *et al*. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 2001; **19:** 2456–71.
4. Wong S-F. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother* 2001; **35:** 1056–65.
5. Heald P, *et al*. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol* 2003; **49:** 801–15.
6. Hanifin JM, *et al*. Novel treatment of chronic severe hand dermatitis with bexarotene gel. *Br J Dermatol* 2004; **150:** 545–53.
7. Farol LT, Hymes KB. Bexarotene: a clinical review. *Expert Rev Anticancer Ther* 2004; **4:** 180–8.
8. Gniadecki R, *et al*. The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157:** 433–40.
9. Lessin SR, *et al*. Treatment of parapsoriasis with bexarotene 1% gel. *Int J Dermatol* 2008; **47:** 1325–7.
10. Abbott RA, *et al*. Bexarotene therapy for mycosis fungoides and Sézary syndrome. *Br J Dermatol* 2009; **160:** 1299–1307.
11. Talpur R, *et al*. Phase I/II randomized bilateral head-head comparison of topical bexarotene 1% gel for alopecia areata. *J Am Acad Dermatol* 2009; **61:** 592.e1–592.e9.
12. Qu L, Tang X. Bexarotene: a promising anticancer agent. *Cancer Chemother Pharmacol* 2010; **65:** 201–5.

Adverse Effects and Precautions

The main adverse effects noted after oral therapy with bexarotene include hyperlipidaemia, hypothyroidism, leucopenia, headache, oedema, altered liver function, rash, and pruritus. Exfoliative dermatitis, alopecia, and skin disorders may occur. Other common adverse effects include anaemia, insomnia, dizziness, eye or ear disorders, gastrointestinal disturbances, arthralgia, and myalgia. Acute pancreatitis has been associated with hypertriglyceridaemia, and patients with risk factors for pancreatitis should generally not be given bexarotene. If triglyceride concentrations rise during therapy, dose reductions are recommended, and lipid-lowering therapy may be instituted (with the exception of gemfibrozil, see below). The most common adverse events associated with topical therapy are rash, pruritus, and pain. Bexarotene capsules and gel should not be used during pregnancy because of the risk of fetal malformation.

References.
1. Assaf C, *et al*. Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol* 2006; **155:** 261–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bexarotene as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Gemfibrozil. Gemfibrozil inhibits clearance of bexarotene, resulting in extremely high triglyceride levels and pancreatitis.[1]

1. Talpur R, *et al*. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002; **47:** 672–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Targretin; ***Austria***: Targretin; ***Belg.***: Targretin; ***Chile***: Targretin; ***Cz.***: Targretin; ***Denm.***: Targretin; ***Fr.***: Targretin; ***Ger.***: Targretin; ***Gr.***: Targretin; ***Hung.***: Targretin; ***Irl.***: Targretin; ***Ital.***: Targretin; ***Neth.***: Targretin; ***Norw.***: Targretin; ***Pol.***: Targretin; ***Port.***: Targretin; ***Spain***: Targretin; ***Swed.***: Targretin; ***UK***: Targretin; ***USA***: Targretin.

Bicalutamide *(BAN, USAN, rINN)*

Bicalutamida; Bicalutamidum; Bikalutamid; Bikalutamidi; ICI-176334; Бикалутамид.

(*RS*)-4′-Cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

$C_{18}H_{14}F_4N_2O_4S$=430.4

CAS — 90357-06-5.

ATC — L02BB03.

ATC Vet — QL02BB03.

UNII — A0Z3NAU9DP.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Bicalutamide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol and in dichloromethane; freely soluble in acetone.

USP 36: (Bicalutamide). A fine, white to off-white powder. Sparingly to slightly soluble in alcohol; freely soluble in acetone and in tetrahydrofuran; soluble in acetonitrile. Store in airtight containers.

Uses and Administration

Bicalutamide is a nonsteroidal anti-androgen with actions and uses similar to those of flutamide (p. 798.2). It is used orally in the treatment of prostatic cancer (p. 712.3). When used with a gonadorelin analogue in the palliative treatment of advanced prostatic cancer the usual dose is 50 mg daily. In the UK treatment is started at least 3 days before starting the gonadorelin analogue to suppress any flare reaction, but in the USA treatment is started at the same time. A similar dose is used with surgical castration, starting on the same day as surgery.

Bicalutamide in a dose of 150 mg daily may be given as monotherapy or adjuvant therapy to surgery or radiotherapy in men with locally advanced disease at high risk for disease progression. It has been used as monotherapy in localised disease, but there is some evidence to suggest that in men without high risk of disease progression, who would otherwise be managed with watchful waiting, the immediate use of bicalutamide may increase the risk of death.

References.
1. Wirth M, *et al*. Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. *Urology* 2001; **58:** 146–51.
2. Boccardo F, *et al*. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. *Eur Urol* 2002; **42:** 481–90.
3. See WA, *et al*. Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *J Urol (Baltimore)* 2002; **168:** 429–35.
4. See W, *et al*. Immediate treatment with bicalutamide 150 mg as adjuvant therapy significantly reduces the risk of PSA progression in early prostate cancer. *Eur Urol* 2003; **44:** 512–17.
5. Fradet Y. Bicalutamide (Casodex) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2004; **4:** 37–48.
6. Schellhammer PF, Davis JW. An evaluation of bicalutamide in the treatment of prostate cancer. *Clin Prostate Cancer* 2004; **2:** 213–19.
7. Wirth MP, *et al*. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol (Baltimore)* 2004; **172:** 1865–70.
8. Iversen P, *et al*. Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol (Baltimore)* 2004; **172:** 1871–6.
9. Klotz L, Schellhammer P. Combined androgen blockade: the case for bicalutamide. *Clin Prostate Cancer* 2005; **3:** 215–19.
10. Wirth M, *et al*. Bicalutamide ('Casodex') 150 mg in addition to standard care in patients with nonmetastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme. *Prostate Cancer Prostatic Dis* 2005; **8:** 194–200.
11. Tyrell CJ, *et al*. Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005; **76:** 4–10.
12. McLeod DG, *et al*. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; **97:** 247–54.
13. Wellington K, Keam SJ. Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. *Drugs* 2006; **66:** 837–50.
14. Iversen P, Roder MA. The Early Prostate Cancer program: bicalutamide in nonmetastatic prostate cancer. *Expert Rev Anticancer Ther* 2008; **8:** 361–9.

Precocious puberty. Bicalutamide, with either anastrozole or letrozole, has been reported to be effective in the treatment of familial male precocious puberty (p. 2254.1); in 2 boys the combination therapy was well tolerated, stabilised bone-age advancement while allowing for continued normal linear growth, and prevented progression of virilisation.[1]

1. Lenz AM, *et al*. Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. *Pediatrics* 2010; **126:** e728–e733.

Adverse Effects and Precautions

As for Flutamide, p. 798.3. Pruritus, asthenia, alopecia, hair regrowth, and dry skin occur commonly with bicalutamide. Hypersensitivity reactions, including angioedema and urticaria, have been reported infrequently.

Cardiovascular effects including angina, heart failure, arrhythmias, and ECG changes have been reported rarely. Interstitial pneumonitis and pulmonary fibrosis have also been reported rarely.

Effects on the gastrointestinal tract. There is some evidence that bicalutamide is associated with a lower incidence of diarrhoea than flutamide.[1]

1. Schellhammer P, *et al*. A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. *Urology* 1995; **45:** 745–52.

Effects on the liver. Fulminant hepatotoxicity has been reported with bicalutamide treatment. Despite stopping the drug the patient developed secondary multiorgan failure and died.[1]

1. O'Bryant CL, *et al*. Bicalutamide-associated fulminant hepatotoxicity. *Pharmacotherapy* 2008; **28:** 1071–5.

Effects on the lungs. For a review of cases of pneumonitis associated with anti-androgens including bicalutamide, see under Flutamide, p. 798.3.

Gynaecomastia. For a discussion of gynaecomastia, a frequent adverse effect of anti-androgen therapy, and its management, see under Flutamide, p. 799.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bicalutamide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Bicalutamide inhibits various cytochrome P450 isoenzymes, particularly CYP3A4, *in vitro*, and licensed product information recommends that terfenadine, astemizole, and cisapride should not be given with bicalutamide, and that other drugs with a narrow therapeutic index that are metabolised by cytochrome P450 isoenzymes should be used with caution. *In vitro* studies have shown that bicalutamide can displace warfarin from its protein binding sites (see also Antineoplastics, p. 1532.2).

Pharmacokinetics

Bicalutamide is well absorbed after oral doses. It undergoes extensive metabolism in the liver, the active *R*-enantiomer mainly by oxidation, the inactive *S*-enantiomer mainly by glucuronidation. It is excreted as metabolites in urine and faeces. The half-life of the *R*-enantiomer is about 6 to 7 days, and may be prolonged still further in severe hepatic impairment. The *S*-enantiomer is cleared more rapidly. Bicalutamide is about 96% bound to plasma proteins.

References.
1. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. *Clin Pharmacokinet* 2004; **43:** 855–78.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bidrostat; Biolutam; Bitakebir; Bosconar; Casodex; Codebup; Dimalan; Finaband; Gepeprostin; Liberprost; Raffolutil; ***Austral.***: Calutex; Cosamide; Cosudex; ***Austria***: Androbloc; BicaluPel; Bicamed; Casodex; ***Belg.***: Casodex; ***Braz.***: Casodex; Gepeprostin; Lutamidal; ***Canad.***: Casodex; ***Chile***: Biolev; Casodex; Lutamidal; ***China***: Casodex (康士得); Yan Lie Shu (岩列舒); ***Cz.***: Atembin; Bicaluplex; Bicalutagen; Bicalutanorm; Bicalutatam; Bicamal; Bicasil; Bikalard; Bikauk; Binabic; Calumid†; Casodex; Glanuta; Lanbica; Ormandyl†; ***Denm.***: Bicalustad; Bicalutatam; Bictamid; Casodex; Nycolutamid; ***Fin.***: Alidex†; Bicadex†; Bicamid†; Bicavan; Bicusan; Bidanil†; Bikalex†; Casodex; Kandex†; Skylutamide; ***Fr.***: Casodex; Ormandyl; ***Ger.***: Androcal; Bicadex; Bicalutin; Bicamed; Casodex; ***Gr.***: Apex; Bicadex; Bicalut; Bicamide; Bicaprol; Bicatin; Bikalen; Bilumide; Casodex; Encalor; Ormandyl; Procure; Verodex; Zarmol; ***Hong Kong***: Casodex; ***Hung.***: Bicatlon; Bicusan; Bilutamid; Binabic; Calumid; Capro; Casodex; Grommar; Lanbicamid†; Sanotamid; ***India***: Biprosta; Caludec; Caluran; Calutide; Casodex; ***Indon.***: Casodex; ***Irl.***: Bicalinn; Biluta; Casodex; Casomide; ***Israel***: Bicamide; Casodex; Medimide; ***Ital.***: Casodex; Lutamid; Praxis; Safedex; ***Malaysia***: Casodex; ***Mex.***: Advanpro; Bicalem; Calutol; Casdrogen; Casodex; ***Neth.***: Bicamedica†; Bilumide; Biluron; Casodex; ***Norw.***: Casodex; ***NZ***: Bicalaccord; Bicalox; Cosudex; ***Philipp.***: Bicadex; Casodex; ***Pol.***: Binabic; Calubloc; Casodex; Neoprost; Prostide; ***Port.***: Bicastad; Casodex; Ormandyl; ***Rus.***: Bilumid (Билумид); Calumid (Калумид); Casodex (Касодекс); ***S.Afr.***: Bicadex; Bicalox; Caloxa; Casodex; ***Singapore***: Casodex; ***Spain***: Bicamylan; Bicarbex; Biobica; Casodex; Ormandyl†; Pencial; Probic; Saveprost; Wibical; ***Swed.***: Baculamyl†; Bicalustad; Bictamid; Casodex; Nycolutamid†; ***Switz.***: Bicamed; Casodex; ***Thai.***: Bypro; Calumid; Casodex; ***Turk.***: Casodex; Procalut; ***UK***: Casodex; ***Ukr.***: Areclok (Арекпок); Calumid (Калумид); Casodex (Касодекс); ***USA***: Casodex; ***Venez.***: Calutol; Casodex.

Multi-ingredient Preparations. ***Arg.***: Zolapack; ***Austral.***: ZolaCos CP; ***NZ***: ZolaCos CP.

Pharmacopoeial Preparations
BP 2014: Bicalutamide Tablets;
USP 36: Bicalutamide Tablets.

Bleomycin Sulfate *(BANM, USAN, pINNM)*

Bleomicina, sulfato de; Bleomicino sulfatas; Bleomicin-szulfát; Bleomycin Sulphate; Bléomycine, Sulfate de; Bleomycini Sulfas; Bleomycinsulfat; Bleomycin-sulfát; Bleomysiinisulfaatti; Sulfato de bleomicina; Блеомицина Сульфат.

CAS — 11056-06-7 (bleomycin); 67763-87-5 (bleomycin hydrochloride); 9041-93-4 (bleomycin sulfate).

ATC — L01DC01.

ATC Vet — QL01DC01.
UNII — 7DP3NTV15T.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Int. and *Jpn* also include Bleomycin Hydrochloride. *Chin.* includes Bleomycin A5 Hydrochloride for Injection.

Ph. Eur. 8: (Bleomycin Sulfate). The sulfate of a mixture of glycopeptides obtained by the growth of *Streptomyces verticillus* or by any other means; the two principal components of the mixture are *N*-[3-(dimethylsulphonio) propyl]bleomycinamide (bleomycin A_2) and *N*-[4-(carbamimidoylamino)butyl]bleomycinamide (bleomycin B_2). A white or yellowish-white, very hygroscopic powder. It loses not more than 3% of its weight when dried. Very soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Bleomycin Sulfate). The sulfate salt of a mixture of basic cytotoxic glycopeptides, produced by the growth of *Streptomyces verticillus* or produced by other means. It has a potency of not less than 1.5 units and not more than 2.0 units/mg. It contains between 55 and 70% of bleomycin A_2 and between 25 and 32% of bleomycin B_2; the content of bleomycin B_4 is not more than 1%. The combined percentage of bleomycin A_2 and B_2 is not less than 90%. A cream-coloured, amorphous powder. It loses not more than 6% of its weight when dried. Very soluble in water. A solution in water containing 10 units/mL has a pH of 4.5 to 6.0. Store in airtight containers.

Incompatibility. A loss of bleomycin activity was reported when bleomycin sulfate solutions were mixed with solutions of carbenicillin, cefazolin or cefalotin sodium, nafcillin sodium, benzylpenicillin sodium, methotrexate, mitomycin, hydrocortisone sodium succinate, aminophylline, ascorbic acid, or terbutaline.[1] The interactions of bleomycin have been summarised as the chelation of divalent and trivalent cations (especially copper), inactivation by compounds containing sulfhydryl groups, and precipitation by hydrophobic anions; solutions of bleomycin should not be mixed with solutions of essential amino acids, riboflavin, dexamethasone, or furosemide.[2]

1. Dorr RT, *et al.* Bleomycin compatibility with selected intravenous medications. *J Med* 1982; **13:** 121–30.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.

Stability. Bleomycin sulfate solutions appear to be equally stable in plastic or glass,[1,2] despite some earlier studies suggesting loss of potency in plastic.[3,4] There is some evidence[5] that bleomycin is more stable in sodium chloride 0.9% than glucose 5%, and sodium chloride 0.9% is the diluent recommended by the licensed product information. UK licensed product information states that bleomycin sulfate is chemically and physically stable, once reconstituted and diluted as directed, for 10 days when refrigerated at 2 degrees to 8 degrees and protected from light. From a microbiological point of view, solutions should be used immediately; storage for longer than 24 hours at 2 degrees to 8 degrees is not recommended, unless prepared under controlled and validated aseptic conditions.

1. De Vroe C, *et al.* A study on the stability of three antineoplastic drugs and on their sorption by iv delivery systems and end-line filters. *Int J Pharmaceutics* 1990; **65:** 49–56.
2. Stajich GV, *et al.* In vitro evaluation of bleomycin-induced cell lethality from plastic and glass containers. *DICP Ann Pharmacother* 1991; **25:** 14–16.
3. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
4. Adams J, *et al.* Instability of bleomycin in plastic containers. *Am J Hosp Pharm* 1982; **39:** 1636.
5. Koberda M, *et al.* Stability of bleomycin sulfate reconstituted in 5% dextrose injection or 0.9% sodium chloride injection stored in glass vials or polyvinyl chloride containers. *Am J Hosp Pharm* 1990; **47:** 2528–9.

Units

8910 units of bleomycin complex A_2/B_2 are contained in 5 mg of bleomycin complex in one ampoule of the first International Reference Preparation (1980). The Ph. Eur. 8 specifies a potency of not less than 1500 international units per mg, calculated with reference to the dried substance. These units differ from those used by the USP: Bleomycin Sulfate (USP 36) contains 1.5 to 2.0 units of bleomycin in each mg. A change in the labelling of preparations in the UK, from units equivalent to those of the USP to international units in line with the Ph. Eur., resulted in an apparent but artefactual increase in UK doses by a factor of 1000.

In some countries doses were *formerly* described in terms of mg-potency, where 1 mg-potency corresponded to 1 unit. In the original preparation 1 mg-potency was equivalent to 1 mg-weight but improvements in purification of the product led to a situation in which ampoules labelled as containing 15 mg (i.e. 15 units) contained far fewer mg-weight of bleomycin.

Uses and Administration

Bleomycin is an antineoplastic antibiotic that binds to DNA and causes strand scissions, and is probably most effective in the G_2 and M phases of the cell cycle. It is widely used to treat malignant disease; particularly squamous cell carcinomas, including those of the cervix and external genitalia, oesophagus, skin, and head and neck; Hodgkin's disease and other lymphomas; malignant neoplasms of the testis, and malignant effusions. It has also been tried in other malignancies, including carcinoma of the bladder, lung, and thyroid, and some sarcomas, including Kaposi's sarcoma.

Bleomycin is often used with other antineoplastics, notably with doxorubicin, vinblastine, and dacarbazine (ABVD) for Hodgkin's disease, and with etoposide and cisplatin (BEP) in testicular tumours. Bleomycin is given as the sulfate by either the intramuscular, intravenous, or subcutaneous route. It may also be given intra-arterially or instilled intrapleurally or intraperitoneally. If intramuscular injections are painful they may be given in a 1% solution of lidocaine.

Doses are calculated in terms of the base, and are given in ***units****, but the units used for preparations in the UK, which were formerly equivalent to those of the USP, are now international units equivalent to those of the Ph. Eur. (see Units, above). Since 1000 international units is equivalent to 1 USP unit, UK doses now appear to be 1000 times greater than those previously in use, or than those in use in the USA, and care is recommended in evaluating the literature.*

In the UK the licensed dose as a single agent for **squamous cell** or **testicular tumours** is 15 000 international units (15 USP units) three times a week, or 30 000 international units twice a week, by intramuscular or intravenous injection, although in practice treatment of malignancy will generally be with combination regimens. This may be repeated, at usual intervals of 3 to 4 weeks, up to a total cumulative dose of 500 000 international units. The dose and total cumulative dose should be reduced in those over 60 years of age (see below). Doses should be adjusted according to tolerance, and may need to be adjusted as part of combination chemotherapy. Continuous intravenous infusion at a rate of 15 000 international units per 24 hours for up to 10 days or 30 000 international units per 24 hours for up to 5 days may also be used. In patients with **lymphoma** a dose of 15 000 international units once or twice weekly by intramuscular injection has been suggested, to a total dose of 225 000 international units. Again, dosage should be reduced in older patients and in combination regimens if necessary. In the treatment of **malignant effusions** a solution of 60 000 international units in 100 mL of sodium chloride 0.9% may be instilled into the affected serous cavity. Treatment may be repeated as necessary up to a total cumulative dose of 500 000 international units depending on the patient's age. Local anaesthetics or analgesics are given concomitantly.

In the USA licensed doses for **lymphomas** as well as **squamous cell** and **testicular** neoplasms are 250 to 500 international units/kg (0.25 to 0.5 USP units/kg), or 10 000 to 20 000 international units/m^2 (10 to 20 USP units/m^2), given once or twice weekly by slow intravenous, intramuscular, or subcutaneous injection. In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, below). In patients with Hodgkin's disease, once a 50% response has been achieved it may be maintained with 1000 international units (1 USP unit) of bleomycin daily, or 5000 international units (5 USP units) weekly by slow intravenous or intramuscular injection.

In the UK, licensed product information suggests that a **total dose** of 500 000 international units (500 USP units) should not be exceeded. Total cumulative dose should not exceed 300 000 international units in those aged 60 to 69 years, 200 000 international units in those 70 to 79, and 100 000 international units in those 80 and over; the weekly dose should be no more than 60 000, 30 000 and 15 000 international units respectively. In the USA the recommended maximum total dose is 400 000 international units (400 USP units); it is generally agreed that patients receiving 400 000 international units or more are at increased risk of pulmonary toxicity (see Adverse Effects, p. 751.1).

Dosage should be reduced in patients with renal impairment (see below).

Bleomycin hydrochloride has also been given parenterally for malignant neoplasms, and bleomycin sulfate has been applied topically for the local treatment of skin tumours.

Administration. Although test doses have been suggested as a way of avoiding anaphylactoid reactions in patients with lymphoma being treated with bleomycin, a review[1] of the literature concluded that the evidence did not support such a strategy, since the onset of the reaction was unpredictable, and not associated with any particular dose. It had also been suggested that reactions were less frequent with intramuscular rather than intravenous dosage, but evidence for this was conflicting.

There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection in combination regimens may result in reduced pulmonary toxicity.[2,3]

Intralesional bleomycin is generally well tolerated; its uses by this route, which include malignancies and non-malignant skin conditions such as warts (p. 751.1) have been reviewed.[4]

1. Lam MSH. The need for routine bleomycin test dosing in the 21st century. *Ann Pharmacother* 2005; **39:** 1897–1902.
2. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; **30:** 158–60.
3. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
4. Saitta P, *et al.* Bleomycin in dermatology: a review of intralesional applications. *Dermatol Surg* 2008; **34:** 1299–1313.

Administration in renal impairment. A significant portion of a dose of bleomycin is excreted largely unchanged in the urine, and dose reduction should be considered in patients with renal impairment. UK licensed product information suggests a 50% dose reduction when the serum creatinine concentration is between 20 and 40 micrograms/mL and further reduction for serum creatinine above this. US licensed product information gives the following proposed percentages of the initial dose, based on creatinine clearance (CC):

- CC 5 to 10 mL/minute: 40%
- CC 10 to 20 mL/minute: 45%
- CC 20 to 30 mL/minute: 55%
- CC 30 to 40 mL/minute: 60%
- CC 40 to 50 mL/minute: 70%
- CC 50 mL/minute and above: 100%

Leucoplakia. Leucoplakia is used to describe a white patch or plaque in the mouth which cannot be otherwise characterised. Such lesions are of concern because they may be pre-malignant, and patients with evidence of dysplasia may be at higher risk of transformation (see also Malignant Neoplasms of the Head and Neck, p. 708.1). Leucoplakia must be distinguished from other conditions such as candidiasis, lichen planus, and oral hairy leucoplakia which is associated with HIV infection.[1]

Leucoplakia is often associated with tobacco smoking, and smoking cessation can result in regression.[1] Where active treatment is desirable, small and easily accessible lesions can be removed surgically or by laser therapy, although they may recur.[1] For extensive patches or those in which surgery would be difficult, the treatments described include topical bleomycin 1%, dissolved in dimethyl sulfoxide and applied for 5 minutes daily for 14 consecutive days. In a group of 19 patients with dysplastic leucoplakia, improvement in the appearance of lesions and histological evidence of remission of the dysplasia occurred in the majority of patients. Sustained effects were also found on long-term follow-up for up to 10 years.[2]

There have been reports of partial or complete remission of leucoplakia in studies of vitamin A or betacarotene given orally long-term,[3-5] but lesions have recurred when supplementation was stopped.[4] Topical treatment with retinoids such as tretinoin or isotretinoin has also been tried, with similar results to those of oral vitamin A and retinoid treatments.[6,7] A small open study has also suggested that topical calcipotriol may be effective.[8]

A systematic review of treatments for leucoplakia found that there were few controlled studies, and that although these treatments might be effective in the resolution of lesions, the rate of relapse was high, and there was no evidence that they prevent malignant transformation.[9]

1. Scully C, Porter S. ABC of oral health: swellings and red, white, and pigmented lesions. *BMJ* 2000; **321:** 225–8.
2. Epstein JB, *et al.* Topical bleomycin for the treatment of dysplastic oral leukoplakia. *Cancer* 1998; **83:** 629–34.
3. Issing WJ, *et al.* Long-term follow-up of larynx leukoplakia under treatment with retinyl palmitate. *Head Neck* 1996; **18:** 560–5.
4. Sankaranarayanan R, *et al.* Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment. *Oral Oncol* 1997; **33:** 231–6.
5. Garewal HS, *et al.* β -Carotene produces sustained remissions in patients with oral leukoplakia: results of a multicenter prospective trial. *Arch Otolaryngol Head Neck Surg* 1999; **125:** 1305–10.
6. Epstein JB, Gorsky M. Topical application of vitamin A to oral leukoplakia: a clinical case series. *Cancer* 1999; **86:** 921–7.
7. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; **95:** 1258–64.
8. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; **30:** 402–6.
9. Lodi G, *et al.* Interventions for treating oral leukoplakia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/05/08).

Malignant effusions. Bleomycin is used for the sclerotherapy of malignant pleural and pericardial effusions (p. 700.1).

Malignant neoplasms. Bleomycin is used in regimens for the management of Hodgkin's disease (p. 696.1), non-Hodgkin's lymphomas such as AIDS-related lympho-

mas (see p. 697.2), and for germ-cell tumours of the ovary and testis (see p. 711.2, and p. 715.1), as well as for some other malignancies including those of the head and neck, (p. 708.1), and Kaposi's sarcoma (p. 718.1).

Pneumothorax. In a patient with AIDS and pneumocystis pneumonia who developed pneumothorax, instillation of bleomycin into each pleural cavity was successful in resolving the pneumothorax after tetracycline sclerotherapy failed to do so.[1]

1. Hnatiuk OW, *et al.* Bleomycin sclerotherapy for bilateral pneumothoraces in a patient with AIDS. *Ann Intern Med* 1990; **113:** 988–90.

Warts. Several studies have examined the local use of bleomycin sulfate to treat severe or resistant warts (p. 1689.3) of the common, plane, plantar, eponychial, and mosaic types, usually by intralesional injection.[1-4] At the doses used, adverse effects, other than pain at the injection site,[1-3] do not seem to be common; however, nail dystrophy and Raynaud's phenomenon have been reported (see under Effects on the Skin, Hair, and Nails and Effects on the Vascular System, under Adverse Effects, below). Bleomycin has also been applied as a pressure-sensitive adhesive tape,[5] and various techniques for better intralesional use have been investigated.[6-8]

1. Shumack PH, Haddock MJ. Bleomycin: an effective treatment for warts. *Australas J Dermatol* 1979; **20:** 41–2.
2. Bunney MH, *et al.* The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; **111:** 197–207.
3. Munkvad M, *et al.* Locally injected bleomycin in the treatment of warts. *Dermatologica* 1983; **167:** 86–9.
4. Dhar SB, *et al.* Intralesional bleomycin in the treatment of cutaneous warts: a randomized clinical trial comparing it with cryotherapy. *Indian J Dermatol Venereol Leprol* 2009; **75:** 262–7.
5. Takigawa M, *et al.* Treatment of viral warts with pressure-sensitive adhesive tape containing bleomycin sulfate. *Arch Dermatol* 1985; **121:** 1108.
6. Munn SE, *et al.* A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; **135:** 969–71.
7. van der Velden EM, *et al.* Dermatography with bleomycin as a new treatment for verrucae vulgaris. *Int J Dermatol* 1997; **36:** 145–50.
8. Pollock B, Sheehan-Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol [sic] hand warts. *Lasers Surg Med* 2002; **30:** 135–40.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

The most frequent adverse effects with bleomycin involve the skin and mucous membranes and include rash, erythema, pruritus, vesiculation, hyperkeratosis, nail changes, alopecia, hyperpigmentation, striae, and stomatitis. Fever is also common, and acute anaphylactoid reactions with hyperpyrexia and cardiorespiratory collapse have been reported in about 1% of patients with lymphoma. There is little depression of the bone marrow. Local reactions and thrombophlebitis may occur at the site of parenteral dosage.

The most serious delayed effect is pulmonary toxicity; interstitial pneumonitis occurs in about 10% of patients and progresses to fibrosis and death in about 1% of patients treated with bleomycin. Pulmonary toxicity is more likely in elderly patients and those given total doses greater than 400 000 international units (400 USP units). It is also more likely in patients who have had previous radiotherapy to the chest.

Effects on the lungs. Pneumonitis induced by bleomycin can progress to fatal pulmonary fibrosis. The presentation is often delayed; clinical manifestations include non-productive cough, dyspnoea, and sometimes fever (see Effects on the Lungs, p. 729.1). Pneumomediastinum has also been reported as an initial manifestation of fatal pulmonary toxicity due to bleomycin.[1] Risk factors for toxicity include increased age,[2,3] deteriorating renal function,[2] and concurrent or previous radiotherapy. The reaction is dose-related, and maximum doses have been set (see Uses and Administration, p. 750.2). Other factors that may be implicated include the regimen used, concomitant oxygen supplementation, smoking history, underlying lung disease, and growth factor support.[2,3] For further details of some of these risk factors, see under Interactions, below. There is no standard treatment for bleomycin-induced pneumonitis. Bleomycin therapy is usually stopped, and corticosteroids may be given[3] although strong evidence to support their use is lacking.[2] There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection may reduce pulmonary toxicity.[2]

1. Keijzer A, Kuenen B. Fatal pulmonary toxicity in testis cancer with bleomycin-containing chemotherapy. *J Clin Oncol* 2007; **25:** 3543–4.
2. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
3. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 7614–20.

Effects on the skin, hair, and nails. Permanent nail loss and nail loss followed by regrowth with dystrophy have been reported after intralesional injection of bleomycin for periungual warts.[1-3] In 2 cases this was preceded by blistering and ulceration,[1] or swelling, severe pain, and a burning sensation.[2] All 3 patients had received injections on one or two previous occasions when 2 patients had reported only mild pain.[1,3] Other reported cutaneous adverse effects of bleomycin include flagellate erythema, Raynaud's phenomenon, gangrene, fibrotic or sclerotic skin changes, hyperpigmentation, and neutrophilic eccrine hidradenitis (an inflammatory dermatosis with erythematous plaques and nodules, neutrophilic infiltrates of eccrine glands, and degeneration of eccrine cells). Acute generalised exanthematous pustulosis and alopecia have also been reported.[4]

1. Czarnecki D. Bleomycin and periungual warts. *Med J Aust* 1984; **141:** 40.
2. Miller RAW. Nail dystrophy following intralesional injections of bleomycin for a periungual wart. *Arch Dermatol* 1984; **120:** 963–4.
3. Urbina González F, *et al.* Cutaneous toxicity of intralesional bleomycin administration in the treatment of periungual warts. *Arch Dermatol* 1986; **122:** 974–5.
4. Yamamoto T. Bleomycin and the skin. *Br J Dermatol* 2006; **155:** 869–75.

Effects on the vascular system. Although thromboembolic disorders and Raynaud's syndrome have been associated with use of bleomycin in combination regimens, particularly with cisplatin and the vinca alkaloids or etoposide (see Effects on the Cardiovascular System, p. 727.2) there is some evidence for an association of Raynaud's syndrome with the use of bleomycin alone.[1,2]

There have also been cases of Raynaud's phenomenon reported after intralesional injection of bleomycin for treatment of warts on the hands and feet.[3-6] See also Effects on the Skin, Hair, and Nails, above.

1. Sundstrup B. Raynaud's phenomenon after bleomycin treatment. *Med J Aust* 1978; **2:** 266.
2. Adoue D, Arlet P. Bleomycin and Raynaud's phenomenon. *Ann Intern Med* 1984; **100:** 770.
3. Epstein E. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1991; **24:** 785–6.
4. Gregg LJ. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1992; **26:** 279–80.
5. de Pablo P, *et al.* Raynaud's phenomenon and intralesional bleomycin. *Acta Derm Venereol (Stockh)* 1992; **72:** 465.
6. Vanhooteghem O, *et al.* Raynaud phenomenon after treatment of verruca vulgaris of the sole with intralesional injection of bleomycin. *Pediatr Dermatol* 2001; **18:** 249–51.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2.

Bleomycin should be used with caution in the elderly, in patients with renal impairment or pulmonary infection or pre-existing impairment of pulmonary function, and in those who have received radiotherapy, particularly to the thorax. Patients should undergo regular chest X-rays. If these show infiltrates, or if breathlessness occurs, bleomycin should be stopped.

In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, p. 750.2).

AIDS. Cutaneous adverse effects occurred in 12 of 50 patients being treated with bleomycin for AIDS-associated Kaposi's sarcoma and increased in severity until bleomycin was withdrawn.[1] Bleomycin should be stopped in people with AIDS if cutaneous adverse effects are seen, and rechallenge should be avoided. However, the incidence of adverse effects did not appear to be higher in these patients than in cancer patients, and patients with AIDS seem to be less sensitive to bleomycin than to antibacterials such as co-trimoxazole and penicillins.

1. Caumes E, *et al.* Cutaneous side-effects of bleomycin in AIDS patients with Kaposi's sarcoma. *Lancet* 1990; **336:** 1593.

Diving. Since the partial pressure of oxygen in the inspired air of a scuba diver increases with increasing depth, a theoretical possibility exists of a toxic [pulmonary] reaction to oxygen in bleomycin-treated patients who subsequently go diving, and such a risk would increase with the depth and duration of each dive.[1] However, the risks associated with diving after uncomplicated bleomycin-based treatment have been questioned;[2] the authors considered that resuming diving was acceptable 6 to 12 months after completing treatment with BEP (bleomycin, etoposide, and cisplatin), and recommended caution only in those who developed pulmonary function impairment when given bleomycin.

1. Zanetti CL. Scuba diving and bleomycin therapy. *JAMA* 1990; **264:** 2869.
2. de Wit R, *et al.* Bleomycin and scuba diving: where is the harm? *Lancet Oncol* 2007; **8:** 954–5.

Handling and disposal. *Urine* produced for up to 72 hours after a dose of bleomycin should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bleomycin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. For a report of use of a bleomycin-containing chemotherapy regimen in a pregnant woman and subsequent adverse effects on the infant, see Pregnancy, under Cisplatin, p. 768.2. No adverse effects were reported in another infant whose mother was treated with combination chemotherapy containing bleomycin, see Pregnancy, under Teniposide, p. 867.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. There may be an increased risk of pulmonary toxicity in patients given bleomycin who receive oxygen, for example as part of a general anaesthetic procedure; a reduction in inspired oxygen concentration has been recommended.

Antineoplastics. Enhanced pulmonary toxicity, in some cases fatal, has been reported in patients given bleomycin and *cisplatin*,[1-4] presumably because cisplatin-induced renal impairment led to a decrease in bleomycin elimination. It seems reasonable to assume that similar interactions might occur if bleomycin were given with other nephrotoxic agents. It has been suggested that apart from a decrease in bleomycin dosage if nephrotoxicity occurs with such a combination, giving bleomycin by constant infusion rather than intermittent bolus might be less toxic.[1,5]

A study to investigate whether substitution of etoposide with *gemcitabine* would lead to a less leukaemogenic BEACOPP regimen was stopped early because of unexpectedly common pulmonary toxicity; one patient died. This toxicity was considered to be due to the use of gemcitabine with bleomycin.[6]

1. Bennett WM, *et al.* Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep* 1980; **64:** 921–4.
2. van Barneveld PWC, *et al.* Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. *Oncology* 1984; **41:** 4–7.
3. Brodsky A, *et al.* Stevens-Johnson syndrome, respiratory distress and acute renal failure due to synergic bleomycin-cisplatin toxicity. *J Clin Pharmacol* 1989; **29:** 821–3.
4. Sleijfer S, *et al.* Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer* 1996; **32A:** 550–2.
5. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; **30:** 158–60.
6. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2004; **22:** 2424–9.

Colony-stimulating factors. An increased incidence of pulmonary toxicity has been reported in patients receiving bleomycin as part of the ABVD regimen (with doxorubicin, vinblastine, and dacarbazine) who were given granulocyte colony-stimulating factor to alleviate neutropenia.[1] Another case of rapidly developing and fatal pneumonitis in a patient given BEP (bleomycin, etoposide, and cisplatin) with granulocyte colony-stimulating factor has been reported.[2]

Analyses of study data failed to show increased pulmonary toxicity when granulocyte colony-stimulating factor was added to bleomycin-containing regimens in patients with germ cell tumours or non-Hodgkin's lymphomas.[3-5] In a retrospective review of patients with Hodgkin's lymphoma, however, use of bleomycin with granulocyte colony-stimulating factor was associated with a statistically significant increase of pulmonary toxicity.[6]

1. Matthews JH. Pulmonary toxicity of ABVD chemotherapy and G-CSF in Hodgkin's disease: possible synergy. *Lancet* 1993; **342:** 988.
2. Dirix LY, *et al.* Pulmonary toxicity and bleomycin. *Lancet* 1994; **344:** 56.
3. Bastion Y, *et al.* Possible toxicity with the association of G-CSF and bleomycin. *Lancet* 1994; **343:** 1221–2.
4. Bastion Y, Coiffier B. Pulmonary toxicity of bleomycin: is G-CSF a risk factor? *Lancet* 1994; **344:** 474.
5. Saxman SB, *et al.* Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* 1997; **111:** 657–60.
6. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 7614–20.

Oxygen. Because bleomycin is thought to cause pulmonary toxicity partly by induction of free radicals, use with high concentrations of oxygen could be hazardous,[1] and reductions in inspired oxygen concentration have been recommended by licensed product information where oxygen supplementation is unavoidable. *Animal* studies show an increased risk of mortality with use of bleomycin and oxygen, although data in humans are lacking. The

need for oxygen restriction in bleomycin-treated patients has, however, been questioned.[2]

1. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
2. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? *J Urol (Baltimore)* 1998; **160:** 1347–52.

Pharmacokinetics

Bleomycin is thought to be poorly absorbed from the gastrointestinal tract. Absorption is rapid after parenteral, intraperitoneal, or intrapleural use. Bioavailability is 100% and 70% after intramuscular and subcutaneous dosage, respectively. A bioavailability of 45% has been reported after intraperitoneal or intrapleural use. Plasma protein binding is low. Enzymic degradation by bleomycin hydrolase occurs, mainly in plasma, the liver and other organs, and to a much lesser extent in skin and lungs. Elimination is biphasic: mean initial and terminal half-lives of 0.5 and 4 hours respectively have been reported after an intravenous bolus. Elimination may be more prolonged after continuous intravenous infusion and mean half-lives of 1.3 and 9 hours respectively have been reported. About two-thirds of a dose is excreted unchanged in the urine; the rate of excretion is determined by renal function. Drug concentrations in the CSF are low. Bleomycin crosses the placenta.

References.

1. Broughton A, *et al.* Clinical pharmacology of bleomycin following intravenous infusion as determined by radioimmunoassay. *Cancer* 1977; **40:** 2772–8.
2. Alberts DS, *et al.* Bleomycin pharmacokinetics in man I: intravenous administration. *Cancer Chemother Pharmacol* 1978; **1:** 177–81.
3. Yee GC, *et al.* Bleomycin disposition in children with cancer. *Clin Pharmacol Ther* 1983; **33:** 668–73.

Genetic factors. Bleomycin is inactivated by bleomycin hydrolase (BLMH). Since response to chemotherapy may be determined by gene polymorphisms involved in metabolism, a study investigated whether the single nucleotide polymorphism (SNP) A1450G of the BLMH gene was associated with survival in patients with testicular cancer treated with bleomycin-containing chemotherapy. The homozygous variant G/G of this SNP was found to be associated with reduced survival and a higher prevalence of early relapses. The authors cautioned that this finding was hypothesis-generating and not yet clinically applicable.[1]

1. de Haas EC, *et al.* Variation in bleomycin hydrolase gene is associated with reduced survival after chemotherapy for testicular germ cell cancer. *J Clin Oncol* 2008; **26:** 1817–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bileco; Bleocris; Blocamicina; CytoRich; ***Austral.***: Blenamax; Blenoxane†; ***Belg.***: Bleomin†; ***Braz.***: Blenoxane; Bonar; Cinaleo; Tecnomicina; Tevableo; ***Canad.***: Blenoxane†; ***Chile***: Blexit; Nikableomicina; Oncobleocin†; ***Cz.***: Bleocin†; Bleomedac; ***Ger.***: Bleo-cell; Bleomedac; ***Gr.***: Bleocin; ***Hong Kong***: Bleocin; ***Hung.***: Bleocin†; ***India***: Bledmax; Bleochem; Bleocin; Bleocip; Bleolem; Bleonco; Bleostar-S; Bleotex; Naprobleo; Oil Bleo; Oncobleo; ***Indon.***: Blenamax; Bleocin; ***Jpn***: Bleo; Bleocin†; ***Malaysia***: Blenamax; Bleocin; ***Mex.***: Blanoxan; Bleolem; Bleomax; ***Neth.***: Bleomedac; ***NZ***: Blenoxane; ***Philipp.***: Bemocin; Blenoxane†; Bloicin-S; ***Pol.***: Bleocin†; ***Port.***: Bleocin; ***Rus.***: Blenamax (Бленамакс); Bleocin (Блеоцин); ***S.Afr.***: Blenamax; Blenoxane; Bleolem; ***Singapore***: Blenamax; Bleocin; ***Thai.***: Bleo-S†; Bleocin; Bleolem; ***Turk.***: Bleocin; Bleolem; ***UK***: Bleo; ***USA***: Blenoxane†.

Pharmacopoeial Preparations
BP 2014: Bleomycin Injection;
USP 36: Bleomycin for Injection.

Bortezomib *(BAN, USAN, rINN)*

Bortézomib; Bortezomibum; LDP-341; MG-341; MLN-341; PS-341; Бортезомиб.

N-((1*S*)-1-Benzyl-2-[[(1*R*)-1-(dihydroxyboranyl)-3-methylbutyl]amino}-2-oxoethyl)pyrazinecarboxamide; {(1*R*)-3-Methyl-1-[(2*S*)-3-phenyl-2-(pyrazin-2-carboxamido)propanamido] butyl}boronic acid.

$C_{19}H_{25}BN_4O_4$=384.2

CAS — 179324-69-7.

ATC — L01XX32.

ATC Vet — QL01XX32.

UNII — 69G8BD63PP.

Uses and Administration

Bortezomib is a reversible inhibitor of the 26S proteasome, a large protein complex in cells that is responsible for breaking down regulatory proteins of the cell cycle. Such inhibition disrupts tumour cell turnover and induces apoptosis. Bortezomib is used for the treatment of multiple myeloma (p. 699.2), either in combination with melphalan and prednisone for previously untreated patients or as monotherapy in relapsed/refractory multiple myeloma. In the USA, it is also used for mantle cell lymphoma in patients given at least one previous therapy.

In previously untreated multiple myeloma, an initial dose of bortezomib 1.3 mg/m² is given intravenously on days 1, 4, 8, 11, 22, 25, 29, and 32 of a 42-day cycle for 4 cycles. For the next 5 cycles, bortezomib is given at the same dose on days 1, 8, 22, and 29. Melphalan (9 mg/m²) and prednisone (60 mg/m²) are given orally on days 1 to 4 of each cycle.

For relapsed/refractory multiple myeloma and mantle cell lymphoma, bortezomib is given in initial bolus doses of 1.3 mg/m² intravenously on days 1, 4, 8, and 11 of a 21-day cycle. At least 72 hours should elapse between consecutive doses of bortezomib. In the UK, licensed product information recommends that patients with a confirmed complete response should receive 2 additional cycles of bortezomib, and that those who respond but do not achieve complete remission receive a total of 8 cycles. In the USA, extended therapy of more than 8 cycles may be given, either on the standard schedule recommended above, or on a maintenance schedule of one dose weekly for 4 weeks (days 1, 8, 15, and 22 of a 35-day cycle).

Before combination treatment, the platelet count should be ≥70 000 cells/mm³ and the absolute neutrophil count should be ≥1000 cells/mm³. Whether used in combination or as monotherapy, the bortezomib dose should be withheld, reduced, or treatment withdrawn, according to toxicity, particularly when peripheral neuropathy, neuropathic pain, and haematological toxicity occur (see Administration in Subsequent Cycles, below).

See also below for use in patients with hepatic impairment.

Bortezomib is under investigation for the treatment of other malignancies including non-Hodgkin's lymphoma. A subcutaneous formulation is also under investigation.

References.

1. Orlowski RZ. Bortezomib and its role in the management of patients with multiple myeloma. *Expert Rev Anticancer Ther* 2004; **4:** 171–9.
2. Jagannath S, *et al.* Bortezomib in recurrent and/or refractory multiple myeloma: initial clinical experience in patients with impaired renal function. *Cancer* 2005; **103:** 1195–1200.
3. Richardson PG, *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; **352:** 2487–98.
4. O'Connor OA. Marked clinical activity of the proteasome inhibitor bortezomib in patients with follicular and mantle-cell lymphoma. *Clin Lymphoma Myeloma* 2005; **6:** 191–9.
5. Wang M, *et al.* Use of bortezomib in B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2006; **6:** 983–91.
6. NICE. Bortezomib monotherapy for relapsed multiple myeloma (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf (accessed 23/05/08)
7. Terpos E, *et al.* Myeloma bone disease and proteasome inhibition therapies. *Blood* 2007; **110:** 1098–1104.
8. Richardson PG, *et al.* Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. *Br J Haematol* 2007; **137:** 429–35.
9. Utecht KN, Kolesar J. Bortezomib: a novel chemotherapeutic agent for hematologic malignancies. *Am J Health-Syst Pharm* 2008; **65:** 1221–31.
10. Curran MP, McKeage K. Bortezomib: a review of its use in patients with multiple myeloma. *Drugs* 2009; **69:** 859–88.
11. Laubach JP, *et al.* Clinical challenges associated with bortezomib therapy in multiple myeloma and Waldenströms macroglobulinemia. *Leuk Lymphoma* 2009; **50:** 694–702. Correction. *ibid.*; 1235.
12. Einsele H. Bortezomib. *Recent Results Cancer Res* 2010; **184:** 173–87.

Administration. Although licensed product information recommends no dose reduction of bortezomib for the elderly on the basis of age alone, toxicity often limits its use and reduced-intensity regimens have been investigated.[1-3] In combination treatment for elderly patients with untreated multiple myeloma, use of a once-weekly bortezomib regimen was well-tolerated without apparent detriment to efficacy (compared with the conventional initial twice-weekly schedule, see Uses and Administration, above).[1,2] In a retrospective review of elderly patients with relapsed disease, a once-weekly regimen of bortezomib was given with dexamethasone to patients with a median age of 80 years; toxicity and efficacy were comparable to a control cohort (median age 61 years) who were given the standard initial twice-weekly regimen (see Uses and Administration, above).[3]

1. Mateos M-V, *et al.* Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol* 2010; **11:** 934–41.
2. Bringhen S, *et al.* Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010; **116:** 4745–53.
3. Parrish C, *et al.* Feasibility and efficacy of administration of bortezomib-containing regimens to patients over the age of 70 years. *Br J Haematol* 2011; **153:** 273–5.

ROUTE. A randomised study in patients with relapsed multiple myeloma found that subcutaneous bortezomib had similar efficacy to intravenous use.[1] The subcutaneous route also seemed to have a better systemic safety profile than intravenous bortezomib; peripheral neuropathy (of all grades) was significantly less, and overall rates of gastrointestinal disorders, respiratory, and nervous system disorders were also lower with subcutaneous use. Systemic exposure was similar between routes; peak plasma concentrations were lower but more sustained with subcutaneous use.

1. Moreau P, *et al.* Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011; **12:** 431–40.

Administration in hepatic impairment. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment and close monitoring is recommended. In the UK and USA, specific recommendations are made according to the severity of impairment, defined by bilirubin and aspartate aminotransferase (AST/SGOT) concentrations:

- mild impairment, bilirubin ≤ the upper limit of normal (ULN) with AST > the ULN, or bilirubin > the ULN up to 1.5 times the ULN with any AST concentration: no dose modification required.
- moderate and severe impairment, bilirubin > 1.5 times the ULN with any AST concentration: reduce dose in the first cycle to bortezomib 700 micrograms/m² intravenously; in subsequent cycles doses can be increased up to 1 mg/m² or reduced to 500 micrograms/m² depending on tolerance.

See Uses and Administration, above for further details of dosing regimens.

Administration in subsequent cycles. When intravenous bortezomib is used *with melphalan and prednisone* for previously untreated multiple myeloma patients:

- if prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is seen in one cycle: consider reduction of the *melphalan* dose by 25% in the next cycle
- if the platelet count ≤ 30 000 cells/mm³ or absolute neutrophil count ≤ 750 cells/mm³ on a bortezomib dosing day (other than day 1): withhold bortezomib
- if several bortezomib doses in a cycle (≥ 3 doses during twice weekly dosing, or ≥ 2 doses during weekly dosing) or consecutive cycles are withheld: the bortezomib dose should be reduced by 25% (1.3 mg/m² to 1 mg/m²; 1 mg/m² to 700 micrograms/m²)

For grade 3 or more severe non-haematological toxicity (excluding neuropathy), dose modifications are as for patients on monotherapy, below

When used as *monotherapy* in relapsed/refractory multiple myeloma and mantle cell lymphoma, bortezomib should be withheld at the onset of any grade 3 non-haematological (excluding neuropathy) or grade 4 haematological toxicities. Once the toxicity has resolved, bortezomib may be restarted at a dose reduced by 25% (1.3 mg/m² to 1 mg/m²; 1 mg/m² to 700 micrograms/m²)

For those who have neuropathic pain and/or peripheral (sensory or motor) neuropathy, *whether treated with bortezomib monotherapy or as part of a combination regimen*, the following dose modifications are recommended:

- grade 1 with pain, or grade 2: reduce bortezomib dose to 1 mg/m²
- grade 2 with pain, or grade 3: withhold bortezomib until toxicity resolves; restart with a reduced dose of 700 micrograms/m² and change treatment schedule to once weekly
- grade 4 (disabling sensory neuropathy or life-threatening motor neuropathy or paralysis): stop bortezomib

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Very common adverse effects of bortezomib include haematological toxicities (especially transient thrombocytopenia, neutropenia, and anaemia), decreased appetite, gastrointestinal disturbances, peripheral neuropathy, fatigue, fever, headache, dyspnoea, and rash. Complete blood counts including platelet counts should be monitored and therapy withheld or given at reduced doses if necessary. Peripheral neuropathy may also be dose-limiting.

Other common adverse effects include hyperglycaemia, hypokalaemia, insomnia, anxiety, confusion, depression, dry mouth, blurred vision, eye pain, vertigo, dizziness, dysgeusia, tremor, epistaxis, cough, rhinorrhoea, pruritus, urticaria, erythema, and oedema. Orthostatic hypotension is also common and may require treatment; caution is advised in patients with a history of syncope, those who are dehydrated, or those who take antihypertensives. Dizziness, orthostatic hypotension, fatigue, or blurred vision can affect the performance of tasks such as driving. Hypertension is also common. Musculoskeletal adverse effects such as myalgia, arthralgia, bone pain, and cramps are often reported.

Tachycardia, arrhythmias, palpitations, angina pectoris, atrial fibrillation, and myocardial infarction have occurred. There have been isolated cases of QT-interval prolongation but causality has not been confirmed. Congestive heart failure may develop or be exacerbated and pulmonary oedema has been reported. There are rare reports of pericarditis. Pulmonary disease such as pneumonitis has

occurred, and there have been rare reports of acute respiratory distress syndrome, some of them fatal. Bortezomib should not be used in patients with acute diffuse pulmonary or pericardial disease. Renal impairment is common in patients with multiple myeloma and acute renal failure has developed in patients on bortezomib. Dysuria is also common; urinary frequency or incontinence, urinary retention, haematuria, proteinuria, and haemorrhagic cystitis have been reported. Hepatotoxicity, which may be reversible, has included increases in liver enzyme values, hyperbilirubinaemia, and acute liver failure; bortezomib should be used with caution in hepatic impairment.

Tumour lysis syndrome may occur during bortezomib treatment, and those with a high tumour burden should be monitored closely. Immune-mediated reactions such as anaphylaxis, angioedema, serum-sickness-type reactions, polyarthritis with rash, and proliferative glomerulonephritis have been reported; bortezomib should be stopped if serious reactions occur. Reversible posterior leukoencephalopathy syndrome has occurred rarely and therapy should again be stopped; symptoms include seizures, hypertension, headache, blindness, and confusion. Bacterial, viral, and fungal infections have been reported in patients on bortezomib. Reactivation of latent herpes zoster infection can occur and prophylaxis with antivirals is recommended.

Other adverse effects that have been reported include injection site reactions, electrolyte disturbances, paralysis, disseminated intravascular coagulation, hearing impairment, thrombotic or bleeding events, ischaemic colitis, paralytic ileus, acute pancreatitis, pulmonary hypertension, Sweet's syndrome (acute febrile neutrophilic dermatosis), Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions, alopecia, and erectile dysfunction have also been reported.

Effects on the nervous system. Treatment with bortezomib is often associated with peripheral neuropathy, mainly sensory, although cases of motor neuropathy have been reported. A review[1] identified risk factors for bortezomib-induced peripheral neuropathy as pre-existing neuropathy and comorbidities that cause nerve damage such as diabetes. The incidence of neuropathy with bortezomib is also higher in patients with multiple myeloma compared with solid tumours. Furthermore, high rates of peripheral neuropathy have been reported in newly diagnosed multiple myeloma patients before treatment. Results from an analysis[2] in relapsed and/or refractory multiple myeloma patients also found that the peripheral neuropathy associated with bortezomib seemed to be cumulative and dose-related, and increased in prevalence through the first 5 treatment cycles. Prolonged bortezomib exposure beyond this time did not seem to increase the incidence or severity of neuropathy. Development of neuropathy appeared to be independent of previous neurotoxic therapy. In most patients, neuropathic pain resolved or improved after dose modification or upon completion of therapy. Recovery is reported to take a median of 3 months after stopping bortezomib,[1] although some cases have taken up to 2 years for neuropathic symptoms to resolve.

Analgesics may be given symptomatically (see Choice of Analgesic, p. 4.2). For reference to use of topical menthol to relieve bortezomib-induced neuropathic pain, see p. 2553.3.

1. Argyriou AA, *et al.* Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood* 2008; **112:** 1593–9. Correction. *ibid.*; **113:** 4478.
2. Richardson PG, *et al.* Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol* 2006; **24:** 3113–20.

Effects on the skin. In 3 studies of bortezomib in patients with non-Hodgkin's lymphoma, 26 of 140 patients developed an erythematous maculopapular rash. Six patients underwent biopsy; all cases revealed a small vessel necrotising vasculitis. Although some patients had dosage reductions implemented or therapy interrupted upon development of the rash, others were treated continuously without dose reduction, with no apparent adverse clinical consequences. In fact, analysis of the data supported a strong relationship between bortezomib-associated cutaneous vasculitis and a positive clinical response in patient with non-Hodgkin's lymphoma.[1] A macular brown-red eruption developed in a patient at the site of bortezomib infusions; abundant venous flushing was given from the fourth infusion, and the eruption did not recur, although hyperpigmentation persisted for several months.[2]

1. Gerecitano J, *et al.* Drug-induced cutaneous vasculitis in patients with non-Hodgkin lymphoma treated with the novel proteasome inhibitor bortezomib: a possible surrogate marker of response? *Br J Haematol* 2006; **134:** 391–8.
2. Mataix J, *et al.* Persistent supravenous eruption induced by intravenous bortezomib therapy. *Br J Dermatol* 2008; **158:** 863–4.

Infection. A retrospective analysis[1] of data from a study in relapsed multiple myeloma revealed an increase in herpes zoster infections with bortezomib treatment compared with dexamethasone. An incidence of 13% was reported which was comparable with that reported by other studies in relapsed multiple myeloma. Similarly, a herpes zoster incidence of 13% was found in newly diagnosed multiple myeloma patients treated with bortezomib (plus melphalan and prednisone),[2] compared with 4% in the control group (melphalan and prednisone only). The incidence of herpes zoster was reduced to 3% in the bortezomib group when antiviral prophylaxis was used. A retrospective review[3] found that prophylactic use of antivirals resulted in no cases of herpes zoster in 125 multiple myeloma patients treated with bortezomib. Most patients were given aciclovir 400 mg daily, or a reduced dose of 200 mg daily in renal impairment; famciclovir 500 mg daily or valaciclovir 250 to 500 mg daily were also used.

1. Chanan-Khan A, *et al.* Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol* 2008; **26:** 4784–90.
2. San Miguel JF, *et al.* VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008; **359:** 906–17.
3. Vickrey E, *et al.* Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. *Cancer* 2009; **115:** 229–32.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bortezomib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Bortezomib is both metabolised by, and a weak inhibitor of, cytochrome P450 isoenzymes, see below. Ketoconazole (a potent CYP3A4 inhibitor) increased exposure to bortezomib, but omeprazole (a potent CYP2C19 inhibitor) did not increase exposure to bortezomib. Patients should be closely monitored for toxicities or reduced efficacy when bortezomib is given with inhibitors or inducers of CYP3A4. Although melphalan plus prednisone increased exposure to bortezomib, the increase is not thought to be clinically relevant. Hypoglycaemia and hyperglycaemia have occurred in diabetic patients receiving oral antidiabetics who were given bortezomib.

Pharmacokinetics

After a single intravenous dose of bortezomib, plasma concentrations decline in a biphasic manner; a distribution phase of less than 10 minutes is followed by a longer elimination phase of about 5 to 15 hours. Clearance decreases after multiple doses. Protein binding has been reported to be about 83%. Bortezomib has a large volume of distribution suggesting it is widely distributed to peripheral tissues. Peak proteasome inhibition occurs about 1 hour after a dose, with a mean of 61% inhibition and a half-life of about 24 hours. *In-vitro* studies indicate that bortezomib is mainly oxidatively metabolised via the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP1A2; minor metabolism via CYP2D6 and CYP2C9 also occurs. Bortezomib is also a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The major metabolic pathway is deboronation to inactive metabolites.

References.

1. Pekol T, *et al.* Human metabolism of the proteasome inhibitor bortezomib: identification of circulating metabolites. *Drug Metab Dispos* 2005; **33:** 771–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Velcade; ***Austral.***: Velcade; ***Austria***: Velcade; ***Belg.***: Velcade; ***Braz.***: Velcade; ***Canad.***: Velcade; ***Chile***: Velcade; ***China***: Velcade (万珂); ***Cz.***: Velcade; ***Denm.***: Velcade; ***Fin.***: Velcade; ***Fr.***: Velcade; ***Ger.***: Velcade; ***Gr.***: Velcade; ***Hong Kong***: Velcade; ***Hung.***: Velcade; ***India***: Bortenat; Mibor; ***Indon.***: Velcade; ***Irl.***: Velcade; ***Israel***: Velcade; ***Ital.***: Velcade; ***Malaysia***: Velcade; ***Mex.***: Velcade; ***Neth.***: Velcade; ***Norw.***: Velcade; ***NZ***: Velcade; ***Philipp.***: Velcade; ***Pol.***: Velcade; ***Port.***: Velcade; ***Rus.***: Milanfore (Милапфор); Velcade (Велкейд); ***S. Afr.***: Velcade; ***Singapore***: Velcade; ***Spain***: Velcade; ***Swed.***: Velcade; ***Switz.***: Velcade; ***Thai.***: Velcade; ***Turk.***: Velcade; ***UK***: Velcade; ***USA***: Velcade; ***Venez.***: Velcade.

Bosutinib *(USAN, rINN)*

Bosutinibum; SKI-606; Бозутиниб.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile.

$C_{26}H_{29}Cl_2N_5O_3$=530.4

CAS — 380843-75-4.
UNII — 5018V4AEZ0.

Uses and Administration

Bosutinib is an orally active dual SRC family and BCR-ABL tyrosine kinase inhibitor. It is indicated in patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive chronic myeloid leukaemia (p. 694.2) that is resistant to prior therapy or in those who are intolerant to other therapies. An oral dose of 500 mg is taken once daily with food. In the absence of grade 3 adverse effects, this dose may be increased to 600 mg once daily in patients who have an incomplete haematological response by week 8 or an incomplete cytogenetic response by week 12. The dose is reduced in those with hepatic impairment, see Administration in Hepatic Impairment below, and may need to be modified if toxicities occur, see Administration in Subsequent Cycles below. Treatment may be continued until there is disease progression or intolerance to bosutinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Bosutinib is also being investigated in solid tumours and for polycystic kidney disease.

References.

1. Keller G, *et al.* Bosutinib: a dual SRC/ABL kinase inhibitor for the treatment of chronic myeloid leukemia. *Expert Rev Hematol* 2009; **2:** 489–97.
2. Keller G, *et al.* Bosutinib. *Recent Results Cancer Res* 2010; **184:** 119–27.
3. Boschelli F, *et al.* Bosutinib: a review of preclinical studies in chronic myelogenous leukaemia. *Eur J Cancer* 2010; **46:** 1781–9.
4. Cortes JE, *et al.* Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol* 2012; **30:** 3486–92.

Administration in hepatic impairment. Exposure to bosutinib is increased in those with hepatic impairment, and a reduced oral dose of 200 mg once daily is recommended in patients with chronic myeloid leukaemia and any degree of hepatic impairment.

Dose adjustments are required if hepatotoxicity occurs during treatment, see Administration in Subsequent Cycles, below.

Administration in subsequent cycles. In chronic myeloid leukaemia, oral bosutinib dosage may need to be modified if toxicities occur.

If myelosuppression occurs, bosutinib should be withheld until the absolute neutrophil count is ≥1000 cells/mm^3 and the platelets are ≥50 000 cells/mm^3. Bosutinib is resumed at the same dose if recovery occurs within 2 weeks; if recovery takes longer than 2 weeks, the daily dose is reduced by 100 mg. If cytopenia recurs the daily dose should be reduced by a further 100 mg upon recovery.

For an increase in liver transaminases >5 times the upper limit of normal (ULN), bosutinib should be withheld until recovery to ≤2.5 times the ULN; the dose should be resumed at 400 mg once daily thereafter. Bosutinib treatment should be stopped if recovery takes longer than 4 weeks or if liver transaminases increase to ≥3 times the ULN with a bilirubin increase >2 times the ULN and alkaline phosphatase <2 times the ULN.

If grade 3 or 4 diarrhoea occurs (≥7 stools/day more than usual), bosutinib should be withheld until recovery to grade 1 or better and the dose restarted at 400 mg once daily.

For other moderate or severe non-haematological toxicities, bosutinib should be withheld until the toxicity has resolved and then resumed at a dose of 400 mg once daily. If appropriate, this may be increased to 500 mg once daily if this higher dose was previously used.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most commonly reported adverse effects with bosutinib are diarrhoea, nausea, vomiting, abdominal pain, thrombocytopenia, anaemia, rash, pyrexia, and fatigue. The gastrointestinal toxicity with bosutinib can be dose-limiting; diarrhoea may be severe. Antidiarrhoeals, antiemetics, and fluid replacement may be required to manage symptoms. Gastritis and gastrointestinal haemorrhage have also been reported.

Myelosuppression (neutropenia, anaemia, and thrombocytopenia) can occur and full blood counts should be undertaken weekly for the first month and then monthly thereafter. Increased liver enzyme values and hepatotoxicity has been seen with bosutinib and liver function tests should be carried out monthly for the first three months of treatment.

Fluid retention occurs with bosutinib and may manifest as pericardial or pleural effusion, pulmonary oedema, or peripheral oedema.

Treatment may need to be modified for gastrotoxicity, myelosuppression, hepatotoxicity, and fluid retention, see Administration in Subsequent Cycles, above.

Hypersensitivity reactions include urticaria and anaphylactic shock, and dermatological effects include pruritus, acne, erythema multiforme, exfoliative rash, and drug eruption. Chest pain, pericarditis, and a prolonged QT interval have also been reported, as have dyspnoea, respiratory failure, and pulmonary hypertension. Increases in blood creatinine levels and acute renal failure have occurred.

Other adverse effects include acute pancreatitis, arthralgia, myalgia, back pain, headache, dizziness, dysgeusia, tinnitus, cough, and hyperkalaemia.

Exposure to bosutinib is increased in patients with hepatic impairment.

Interactions

Bosutinib is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is an inhibitor and substrate for P-glycoprotein. Potent or moderate inhibitors of CYP3A4 or P-glycoprotein should be avoided as an increased plasma concentration of bosutinib is expected. Potent or moderate inducers of CYP3A4 should also be avoided as a reduction in the plasma concentration of bosutinib is expected.

Bosutinib may increase exposure to drugs that are P-glycoprotein substrates.

The bioavailability of bosutinib is pH-dependent and concomitant use with the proton pump inhibitor lansoprazole reduced exposure to bosutinib. If possible, short-acting antacids or H_2-antagonists should be used in place of proton pump inhibitors, and bosutinib doses should be separated from gastric-acid suppressants by at least 2 hours.

References.

1. Abbas R, *et al.* Effect of ketoconazole on the pharmacokinetics of oral bosutinib in healthy subjects. *J Clin Pharmacol* 2011; **51:** 1721–7.

Pharmacokinetics

Peak plasma concentrations of bosutinib occur around 4 to 6 hours after a single oral dose. Exposure increases when taken with a high-fat meal. Bosutinib is highly protein bound at around 96%, and is a P-glycoprotein inhibitor and substrate. Metabolism is mainly via the cytochrome P450 isoenzyme CYP3A4 to inactive metabolites. Over 90% of an oral dose is excreted in the faeces and 3% in the urine. The terminal elimination half-life is about 22.5 hours after a single oral dose.

References.

1. Abbas R, *et al.* A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects. *Cancer Chemother Pharmacol* 2012; **69:** 221–7.
2. Abbas R, *et al.* Evaluation of the pharmacokinetics and safety of bosutinib in patients with chronic hepatic impairment and matched healthy subjects. *Cancer Chemother Pharmacol* 2012. Available at: doi: 10.1007/s00280-012-1987-7

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Bosulif; ***USA***: Bosulif.

Brentuximab Vedotin *(rINN)*

Brentuximab Vedotina; Brentuximab Védotine; Brentuximaburn Vedotinum; cAC10-vcMMAE; SGN-35; Брентуксимаб Ведотин.

CAS — 914088-09-8.

UNII — 7XL5ISS668.

Uses and Administration

Brentuximab vedotin is an antibody-drug conjugate consisting of the chimeric CD30-specific monoclonal antibody cAC10 conjugated to monomethyl auristatin E (MMAE), a microtubule disrupting agent. Brentuximab vedotin is used for the treatment of patients with Hodgkin's disease (p. 696.1) after failure of autologous haematopoietic stem cell transplantation or after failure of at least two treatment regimens (in those deemed unsuitable for transplantation). It is also used for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one combination chemotherapy regimen.

The recommended dose is 1.8 mg/kg (up to a maximum body-weight of 100 kg) given as an intravenous infusion over 30 minutes every 3 weeks. Treatment may be continued for a maximum of 16 cycles or until disease progression or unacceptable toxicity occurs. The dose may need to be delayed or reduced (see Administration in Subsequent Cycles, below). Brentuximab vedotin is diluted before infusion to obtain a final concentration ranging from 400 micrograms/mL to 1.8 mg/mL; appropriate infusion fluids include sodium chloride 0.9%, glucose 5%, or Lactated Ringer's solution.

Brentuximab vedotin is under investigation in the treatment of cutaneous T-cell lymphoma.

References.

1. Foyil KV, Bartlett NL. Brentuximab vedotin for the treatment of CD30+ lymphomas. *Immunotherapy* 2011; **3:** 475–85.
2. Minich SS. Brentuximab vedotin: a new age in the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma. *Ann Pharmacother* 2012; **46:** 377–83.
3. Younes A, *et al.* Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; **30:** 2183–9.
4. Gopal AK, *et al.* Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. *Blood* 2012; **120:** 560–8.
5. van de Donk NW, Dhimolea E. Brentuximab vedotin. *MAbs* 2012; **4:** 458–65.

Administration in subsequent cycles. Brentuximab vedotin therapy may need to be delayed or the intravenous dose reduced if toxicity occurs. Licensed product information makes the following recommendations.

In the event of peripheral neuropathy:

- new or worsening grade 2 or 3 toxicity: treatment should be withheld until neuropathy improves to grade 1 or baseline, then brentuximab vedotin restarted at 1.2 mg/kg
- grade 4 toxicity: treatment is stopped

For neutropenia:

- grade 3 or 4 toxicity: treatment should be withheld until neutropenia improves to baseline or grade 2 or lower; growth factor support should be considered for subsequent cycles
- recurrent grade 4 neutropenia despite the use of growth factors: treatment should be stopped or the dose reduced to 1.2 mg/kg

Adverse Effects, Treatment, and Precautions

Bone marrow depression occurs commonly with brentuximab vedotin, especially neutropenia, anaemia, and thrombocytopenia. Neutropenia may be severe and prolonged and force doses to be delayed or reduced, or therapy to be stopped (see Administration in Subsequent Cycles, above). Complete blood counts should be monitored before each dose, and more frequently if neutropenia is severe. Infections occur, and can be serious; opportunistic infections have also been reported. Peripheral neuropathy is common and is mainly sensory, although cases of peripheral motor neuropathy have also been reported. Neuropathy may be cumulative and patients should be monitored for symptoms such as hypoaesthesia or hyperaesthesia, paraesthesia, burning sensations, or neuropathic pain or weakness. Therapy may need to be delayed or stopped, or a dose reduction may be warranted (see Administration in Subsequent Cycles, above).

Other common adverse effects include fatigue, gastrointestinal disturbances, cough, dyspnoea, fever, chills, lymphadenopathy, rash, pruritus, alopecia, headache, dizziness,insomnia, anxiety, myalgia, arthralgia, muscle spasms, peripheral oedema, hyperglycaemia, night sweats, and dry skin. Pain in the back, abdomen, or oropharyngeal area is also common; pain in an extremity can be serious.

Infusion-related reactions have occurred; associated symptoms include chills, nausea, dyspnoea, pruritus, fever, and cough. The infusion should be interrupted and the patient should be pre-medicated for subsequent infusions; premedication may include paracetamol, an antihistamine, and a corticosteroid. If anaphylaxis occurs, the infusion should be immediately and permanently stopped. Tumour lysis syndrome has been reported, especially in those with a high tumour burden, or rapidly proliferating disease. Stevens-Johnson syndrome has occurred; therapy should be stopped. There have been reports of fatal progressive multifocal leukoencephalopathy. Other serious adverse effects that have been reported include pulmonary embolism, pneumonitis, pneumothorax, pyelonephritis, septic shock, and supraventricular arrhythmia.

Interactions

Brentuximab vedotin contains monomethyl auristatin E (MMAE), which is mainly metabolised by cytochrome P450 isoenzyme CYP3A. Use of brentuximab vedotin with ketoconazole increased exposure to MMAE by about 30 to 70% and patients taking strong CYP3A4 inhibitors should be monitored closely for adverse reactions. Use with rifampicin, a potent CYP3A4 inducer, reduced exposure to MMAE by about 30 to 45%.

Pharmacokinetics

Brentuximab vedotin consists of a monoclonal antibody conjugated with monomethyl auristatin E (MMAE); the pharmacokinetic profile of brentuximab vedotin was similar to that of the monoclonal antibody. Peak concentrations of brentuximab vedotin were seen soon after the end of an infusion; time to peak concentrations of MMAE ranged from 1 to 3 days. Steady-state concentrations of brentuximab vedotin and MMAE occurred within 21 days when the drug was given every 3 weeks. No accumulation of brentuximab vedotin was seen with multiple dosing, and MMAE exposure decreased with continued use. Binding of MMAE to plasma proteins *in vitro* ranged from 68 to 82%. *In vivo*, only a small fraction of MMAE released from brentuximab vedotin is metabolised; this metabolism is mainly via oxidation by cytochrome P450 isoenzyme CYP3A4/5. The terminal half-life of brentuximab vedotin is about 4 to 6 days. About 24% of MMAE is recovered in both urine and faeces over a 1-week period; of this recovered MMAE, about 72% is in the faeces, and the majority of the excreted MMAE is unchanged.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Adcetris; ***Switz.***: Adcetris; ***UK***: Adcetris; ***USA***: Adcetris.

Brostallicin *(rINN)*

Brostalicina; Brostallicine; Brostallicinum; PNU-166196 (hydrochloride); Бростальлицин.

4-(2-Bromoacrylamido)-*N*‴-(2-guanidinoethyl)-1,1′,1″,1‴-tetramethyl-*N*,4′:*N*′,4″:*N*″,4‴-quater[pyrrole-2-carboxamide].

$C_{30}H_{35}BrN_{12}O_5$=723.6

CAS — 203258-60-0.

UNII — RPC6R41K4I.

Profile

Brostallicin is an antineoplastic that binds to DNA. It is under investigation for the treatment of soft-tissue sarcomas.

References.

1. ten Tije AJ, *et al.* Phase I and pharmacokinetic study of brostallicin (PNU-166196), a new DNA minor-groove binder, administered intravenously every 3 weeks to adult patients with metastatic cancer. *Clin Cancer Res* 2003; **9:** 2957–64.
2. Broggini M, *et al.* Brostallicin: a new concept in minor groove DNA binder development. *Anticancer Drugs* 2004; **15:** 1–6.
3. Leahy M, *et al.* Brostallicin, an agent with potential activity in metastatic soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2007; **43:** 308–15.
4. Lorusso D, *et al.* Brostallicin (PNU-166196), a new minor groove DNA binder: preclinical and clinical activity. *Expert Opin Invest Drugs* 2009; **18:** 1939–46.

Broxuridine *(rINN)*

Bromodeoxyuridine; Broxuridina; Broxuridinum; BUDR; NSC-38297; Броксуридин.

5-Bromo-2′-deoxyuridine; 5-Bromo-1-(2-deoxy-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione.

$C_9H_{11}BrN_2O_5$=307.1

CAS — 59-14-3.

UNII — G34N38R2N1.

Profile

Broxuridine is a thymidine analogue which acts as a radiosensitiser to enhance the effects of radiotherapy. It is also reported to possess antiviral activity. A related compound brivudine (p. 970.1) is used as an antiviral.

Broxuridine is used as a research tool for measuring DNA synthesis. It has been given by intra-arterial infusion, with radiotherapy and other antineoplastic agents, in the treatment of tumours of the brain, head, and neck; it has also been used diagnostically.

References.

1. Freese A, *et al.* The application of 5-bromodeoxyuridine in the management of CNS tumors. *J Neurooncol* 1994; **20:** 81–95.
2. Phillips TL, *et al.* Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *Int J Radiat Oncol Biol Phys* 1995; **33:** 339–48.
3. Prados MD, *et al.* Influence of bromodeoxyuridine radiosensitization on malignant glioma patient survival: a retrospective comparison of survival data from the Northern California Oncology Group (NCOG) and Radiation Therapy Oncology Group trials (RTOG) for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys* 1998; **40:** 653–9.
4. Prados MD, *et al.* Phase III randomized study of radiotherapy plus procarbazine, lomustine, and vincristine with or without BUdR for treatment of anaplastic astrocytoma: final report of RTOG 9404. *Int J Radiat Oncol Biol Phys* 2004; **58:** 1147–52.

Busulfan *(BAN, rINN)*

Bussulfam; Busulfaani; Busulfanas; Busulfano; Busulfanum; Busulphan; Buszulfán; CB-2041; GT-41; Myelosan; NSC-750; WR-19508; Бусульфан.

Tetramethylene di(methanesulphonate); Butane-1,4-diyl di(methanesulphonate).

$C_6H_{14}O_6S_2$=246.3

CAS — 55-98-1.

ATC — L01AB01.

ATC Vet — QL01AB01.
UNII — G1LN9045DK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Busulfan). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; freely soluble in acetone and in acetonitrile. Store in airtight containers. Protect from light.

USP 36: (Busulfan). A white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble 1 in 45 of acetone. Store in airtight containers.

Uses and Administration

Busulfan is an antineoplastic with a cell-cycle non-specific alkylating action unlike that of the nitrogen mustards, and having a selective depressant action on bone marrow. In small doses, it depresses granulocytopoiesis and to a lesser extent thrombocytopoiesis but has little effect on lymphocytes. With larger doses, severe bone-marrow depression eventually ensues.

Because of its selective action, busulfan has been used in the palliative treatment of chronic myeloid leukaemia (p. 694.2). It provides symptomatic relief with a reduction in spleen size and a general feeling of well-being. The fall in leucocyte count is usually accompanied by a rise in the haemoglobin concentration. Permanent remission is not induced and resistance to its beneficial effects gradually develops.

Busulfan may be used in patients with polycythaemia vera (p. 695.2) and in some patients with myelofibrosis and primary thrombocythaemia (p. 695.2). It is also used at high doses as part of a conditioning regimen to prepare patients for haematopoietic stem cell transplantation, see p. 1937.1.

Busulfan may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The licensed initial oral dosage of busulfan in **chronic myeloid leukaemia** is 60 micrograms/kg or 1.8 mg/m^2 daily, with a usual maximum single daily dose of 4 mg. This is continued until the white cell count has fallen to between 15 000 and 25 000 cells/mm^3(typically 12 to 20 weeks). It should be stopped earlier if the platelet count falls below 100 000 cells/mm^3. Higher doses may be given if the response after 3 weeks is inadequate but this increases the risk of irreversible damage to the bone marrow and calls for special vigilance. Complete blood counts should be made at least every week and the trends followed closely; if haemorrhagic tendencies occur or there is a steep fall in the white cell count indicating severe bone-marrow depression, busulfan should be withdrawn until marrow function has returned.

Once an initial remission has been attained treatment is stopped and not resumed until the white cell count returns to 50 000 cells/mm^3. If this occurs within 3 months, continuous maintenance treatment with a usual dose of 0.5 to 2 mg daily may be given; doses equating to less than 1 whole tablet may be achieved by including busulfan-free days between the treatment days.

In patients with **polycythaemia vera** the usual oral dose is 4 to 6 mg daily, continued for 4 to 6 weeks with careful monitoring of blood counts. Further courses are given when relapse occurs; alternatively, maintenance therapy may be given at half the dose required for induction. Doses of 2 to 4 mg daily have been given for **primary thrombocythaemia** or myelofibrosis.

In conditioning regimens for **haematopoietic stem cell transplantation** busulfan is given in *oral* doses of 1 mg/kg every 6 hours for 4 days, starting 7 days before transplantation; cyclophosphamide is usually given for 2 days, starting 24 hours after the final dose of busulfan. When given by *intravenous* infusion, the recommended dose is 800 micrograms/kg ideal body-weight every 6 hours for 4 days starting 7 days before transplantation. Cyclophosphamide is usually given for 2 days: UK licensed product information states that cyclophosphamide dosing should not be started for at least 24 hours after the last dose of busulfan, while US information permits earlier use although no sooner than 6 hours after the last busulfan dose. Actual body-weight is used for the calculation if it is less than the ideal weight and dose calculations for obese patients should be based on adjusted ideal body weight. Each dose should be diluted in sodium chloride 0.9% or glucose 5% to a final concentration of about 500 micrograms/mL, and given over 2 hours through a central venous catheter using an infusion pump.

For doses in children, see below.

References.

1. Buggia I, *et al.* Busulfan. *Ann Pharmacother* 1994; **28:** 1055–62.
2. Socié G, *et al.* Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood* 2001; **98:** 3569–74.
3. Ferry C, Socié G. Busulfan-cyclophosphamide versus total body irradiation-cyclophosphamide as preparative regimen before allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: what have we learned? *Exp Hematol* 2003; **31:** 1182–6.
4. Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2009; **15:** 523–36.

Administration in children. Busulfan may be given in conditioning regimens to prepare children for **haematopoietic stem cell transplantation**. UK licensed product information states that it may be given *orally* to children less than 18 years of age, in accordance with local protocols, up to a maximum dose of 37.5 mg/m^2 every 6 hours for 4 days, starting 7 days before transplantation; cyclophosphamide is usually given for 2 days, starting 24 hours after the final dose of busulfan. When given *intravenously*, busulfan is licensed for use with cyclophosphamide or melphalan. The recommended dose of busulfan for children up to 17 years of age is weight-based as follows:

- less than 9 kg: busulfan 1 mg/kg
- 9 to 16 kg: busulfan 1.2 mg/kg
- 16 to 23 kg: busulfan 1.1 mg/kg
- 23 to 34 kg: busulfan 950 micrograms/kg
- greater than 34 kg: busulfan 800 micrograms/kg

This dose is given every 6 hours over 4 days to a total of 16 doses, diluted and infused as for adults (see Uses and Administration, above); cyclophosphamide or melphalan should not be started for at least 24 hours after the final dose of busulfan.

For the treatment of **chronic myeloid leukaemia** busulfan may be given orally to paediatric patients in the same dose as that used for adults (see Uses and Administration, above).

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

The major adverse effect of busulfan with standard doses is bone-marrow depression, manifest as leucopenia, thrombocytopenia, and sometimes, anaemia. The nadir of the granulocyte count usually occurs after about 10 to 30 days with recovery occurring over up to 5 months, but busulfan has sometimes caused irreversible or extremely-prolonged bone-marrow depression.

Hyperpigmentation is common, and in a few cases after long-term therapy may be part of a syndrome simulating Addison's disease.

Rarely, progressive interstitial pulmonary fibrosis, known as 'busulfan lung', can occur on prolonged treatment. Gastrointestinal disturbances are rare at usual therapeutic doses but may be dose-limiting where high doses are given before bone marrow transplantation. Other rare adverse effects include dry skin and other skin reactions, liver damage, gynaecomastia, cataract formation, and, at high doses, CNS effects including convulsions.

Busulfan may result in impaired fertility and gonadal function. As with other alkylating agents, it is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. Haemorrhagic cystitis occurred in a patient who had received prolonged therapy with busulfan.[1] High-dose busulfan used in conditioning regimens for haematopoietic stem cell transplantation may increase the risk of late-onset haemorrhagic cystitis.[2,3]

1. Pode D, *et al.* Busulfan-induced hemorrhagic cystitis. *J Urol (Baltimore)* 1983; **130:** 347–8.
2. Kondo M, *et al.* Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 1998; **22:** 995–8.
3. Leung AYH, *et al.* Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. *Bone Marrow Transplant* 2002; **29:** 509–13.

Effects on the liver. Jaundice in the terminal phase of chronic myeloid leukaemia in a 31-year-old man was attributed to busulfan which had been taken for 6 years.[1] Busulfan toxicity involving the liver was also reported in a patient who had taken busulfan for 54 months,[2] while hepatitis possibly associated with busulfan therapy has also been described.[3] Dose-dependent veno-occlusive disease (VOD) has been reported in 20 to 40% of patients receiving high-dose busulfan before bone marrow transplantation.[4] Previous radiotherapy, progenitor cell transplantation, three cycles of chemotherapy or more, the use of multiple alkylating agents, or total doses of busulfan in excess of 16 mg/kg can increase the risk of hepatic VOD. A reduced incidence of hepatic VOD has been seen in those patients given high-dose busulfan and cyclophosphamide when the first dose of cyclophosphamide has been delayed for more than 24 hours after the last dose of busulfan.

1. Underwood JCE, *et al.* Jaundice after treatment of leukaemia with busulphan. *BMJ* 1971; **1:** 556–7.
2. Foadi MD, *et al.* Portal hypertension in a patient with chronic myeloid leukaemia. *Postgrad Med J* 1977; **53:** 267–9.
3. Morris L, Guthrie T. Busulfan-induced hepatitis. *Am J Gastroenterol* 1988; **83:** 682–3.
4. Hassan M. The role of busulfan in bone marrow transplantation. *Med Oncol* 1999; **16:** 166–76.

Effects on the nervous system. High-dose busulfan, used in conditioning regimens for bone marrow transplantation, has been associated with the development of convulsions,[1-4] both generalised[1,3,4] and myoclonic.[2,4] As a result, the use of prophylactic antiepileptic therapy has been suggested as a component of such regimens.[1,3,4] However, some have not considered the routine use of prophylactic antiepileptics justified.[5]

If an antiepileptic is given, the best drug to choose is uncertain. Many studies have used phenytoin, but the potential for phenytoin to increase the metabolism of busulfan, thereby possibly decreasing its myeloablative efficacy, has been pointed out.[6] In addition, phenytoin plasma concentrations have been found to be subtherapeutic in patients who developed convulsions despite a standard prophylactic dose,[4] and the regimen was subsequently adjusted to take account of plasma concentrations. Clobazam has been suggested as an alternative to phenytoin for prophylaxis of busulfan-induced seizures.[7] A review[8] on the optimal prevention of seizures with high-dose busulfan considered that phenytoin was not the best choice, given its adverse effects and the induction of busulfan metabolism; it was suggested that a benzodiazepine such as clonazepam or lorazepam ought to be considered, and that levetiracetam also showed some promise.

Licensed product information from one manufacturer *Otsuka, USA* states that the recommended dose of their parenteral product is based on studies in which phenytoin was given; since phenytoin increases the clearance of busulfan by 15% or more, exposure should be monitored if other anticonvulsants are used, as an increase in plasma-busulfan might be expected, with increased risk of toxicity.

1. Marcus RE, Goldman JM. Convulsions due to high-dose busulphan. *Lancet* 1984; **ii:** 1463.
2. MartellRW, *et al.* High-dose busulfan and myoclonic epilepsy. *Ann Intern Med* 1987; **106:** 173.
3. Sureda A, *et al.* High-dose busulfan and seizures. *Ann Intern Med* 1989; **111:** 543–4.
4. Grigg AP, *et al.* Busulphan and phenytoin. *Ann Intern Med* 1989; **111:** 1049–50. Correction. *ibid.*; **112:** 313.
5. Hugh-Jones K, Shaw PJ. No convulsions in children on high-dose busulphan. *Lancet* 1985; **i:** 220.
6. Fitzsimmons WE, *et al.* Anticonvulsants and busulfan. *Ann Intern Med* 1990; **112:** 552–3.
7. Schwarer AP, *et al.* Clobazam for seizure prophylaxis during busulfan chemotherapy. *Lancet* 1995; **346:** 1238.
8. Eberly AL, *et al.* Optimal prevention of seizures induced by high-dose busulfan. *Pharmacotherapy* 2008; **28:** 1502–10.

Effects on the skin and hair. For the effect of radiotherapy in precipitating skin lesions in busulfan-treated patients, see under Precautions, below.

Permanent alopecia has been reported after use of busulfan.[1]

1. Tosti A, *et al.* Permanent alopecia after busulfan chemotherapy. *Br J Dermatol* 2005; **152:** 1056–8.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Careful attention should be given to monitoring blood counts during therapy. This should be done at least weekly at the start of standard dose therapy. With high dose therapy blood counts should be monitored daily, as should liver function. Prophylactic anticonvulsants should be used during high dose therapy (see Effects on the Nervous System, above).

Busulfan should be stopped if lung toxicity develops. The use of oxygen may exacerbate possible lung toxicity; if anaesthesia is required the concentration of oxygen should be minimised.

Handling. Busulfan is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies busulfan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Radiotherapy. Severe cutaneous reactions occurred in patients given radiotherapy at least 30 days after combined chemotherapy with high-dose busulfan.[1]

It is possible that radiotherapy could worsen subclinical lung injury caused by busulfan.

1. Vassal G, *et al.* Radiosensitisation after busulphan. *Lancet* 1987; **i:** 571.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Phenytoin increases the metabolism of busulfan (see Effects on the Nervous System, above).

Antifungals. Giving *itraconazole* with busulfan resulted in a decrease in the clearance of busulfan; *fluconazole* had no such effect.[1] Busulfan doses may need to be decreased if itraconazole is also given.

1. Buggia I, *et al.* Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. *Anticancer Res* 1996; **16:** 2083–8.

Antineoplastics. When *tioguanine* was given with busulfan for chronic myeloid leukaemia, several cases of hepatic nodular regenerative hyperplasia, with abnormal liver function tests, portal hypertension, and oesophageal varices were noted. There were no cases in patients given busulfan alone, and the mechanism of this possible interaction is unclear.[1,2]

1. Key NS, *et al.* Oesophageal varices associated with busulfan-thioguanine combination therapy for chronic myeloid leukaemia. *Lancet* 1987; **ii:** 1050–2.
2. Shepherd PCA, *et al.* Thioguanine used in maintenance therapy of chronic myeloid leukaemia causes non-cirrhotic portal hypertension. *Br J Haematol* 1991; **79:** 185–92.

Antiprotozoals. In patients who received either high-dose oral or intravenous busulfan as part of a myeloablative regimen before stem cell transplantation, the use of *metronidazole* significantly increased plasma concentrations of busulfan and the degree of associated toxicity, including elevation of liver function tests, veno-occlusive disease, and/or mucositis.[1,2]

1. Nilsson C, *et al.* The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **31:** 429–35.
2. Gulbis AM, *et al.* Busulfan and metronidazole: an often forgotten but significant drug interaction. *Ann Pharmacother* 2011; **45:** e39.

Pharmacokinetics

Busulfan is well absorbed after oral dosage, although intra- and interpatient bioavailability vary widely. Busulfan is lipophilic and crosses the blood-brain barrier; concentrations in the CSF have been reported as being comparable to those in plasma. About 30% of circulating drug is irreversibly bound to plasma proteins, mainly to albumin; the level of reversible binding has been variably reported to be insignificant at around 7%, or to be about 55%. The plasma elimination half-life is about 2 to 3 hours. Busulfan is extensively metabolised in the liver, mainly by conjugation with glutathione, either spontaneously or mediated by the enzyme glutathione-S-transferase. About 12 inactive metabolites have been identified, which are excreted in the urine. About 1% of busulfan is excreted unchanged. Elimination in the faeces is considered to be negligible.

References.

1. Nath CE, *et al.* Variability in the pharmacokinetics of intravenous busulphan given as a single daily dose to paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol* 2008; **66:** 50–9.
2. Salinger DH, *et al.* Development of a population pharmacokinetics-based sampling schedule to target daily intravenous busulfan for outpatient clinic administration. *J Clin Pharmacol* 2010; **50:** 1292–1300.
3. Bartelink IH, *et al.* Body weight-dependent pharmacokinetics of busulfan in paediatric haematopoietic stem cell transplantation patients: towards individualized dosing. *Clin Pharmacokinet* 2012; **51:** 331–45.

Genetic factors. Busulfan is metabolised in the liver via conjugation with glutathione; this can be mediated via the enzyme glutathione-S-transferase (GST). Genetic variants can result in altered enzymatic activity, and affect busulfan metabolism. A pharmacokinetic study in children given intravenous busulfan found that carriers of GSTA1*B allele had a higher exposure to busulfan than non-carriers; busulfan clearance in carriers was reduced by about 30%. While genetic status may provide some explanation for pharmacokinetic variability, busulfan exposure is also dependent on age and body-weight; GSTA1*B carriers were also significantly younger and weighed less, confounding the interpretation. Nonetheless, genotype may be useful in dosing decisions.[1]

1. Johnson L, *et al.* Glutathione S-transferase A1 genetic variants reduce busulfan clearance in children undergoing hematopoietic cell transplantation. *J Clin Pharmacol* 2008; **48:** 1052–62.

Metabolism. In a study of the pharmacokinetics of high-dose busulfan in 5 patients receiving 1 mg/kg orally every six hours for 4 days, the mean elimination half-life decreased from about 3.4 hours after the first dose to about 2.3 hours after the final dose, suggesting that busulfan may induce its own metabolism.[1]

Genetic factors may also affect metabolism of busulfan, see above.

1. Hassan M, *et al.* Pharmacokinetic and metabolic studies of high-dose busulphan in adults. *Eur J Clin Pharmacol* 1989; **36:** 525–30.

Therapeutic drug monitoring. The value of therapeutic drug monitoring for busulfan in conditioning regimens for haematopoietic stem cell transplantation has been reviewed,[1,2] and suggested to maximise engraftment and minimise toxicity and relapse. In regimens using busulfan with cyclophosphamide, steady-state plasma concentrations of busulfan above 600 micrograms/litre appeared to favour engraftment.[1] A pharmacokinetic analysis found that in patients with graft rejections, busulfan trough concentrations were below 150 nanograms/mL; steady-state concentrations also tended to be lower in this group but not significantly so.[3]

The bioavailability of oral busulfan is variable, particularly in children; intravenous conditioning regimens, adjusted on the basis of first-dose pharmacokinetics and therapeutic drug monitoring, have been used to overcome this problem.[4,5] A study found a significant correlation between busulfan concentration in plasma and saliva after oral dosing in children; busulfan saliva analysis may therefore be a useful, non-invasive alternative to plasma analysis.[6]

1. McCune JS, *et al.* Plasma concentration monitoring of busulfan: does it improve clinical outcome? *Clin Pharmacokinet* 2000; **39:** 155–65.
2. Russell JA, Kangarloo SB. Therapeutic drug monitoring of busulfan in transplantation. *Curr Pharm Des* 2008; **14:** 1936–49.
3. Chandy M, *et al.* Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia—the role of busulfan pharmacokinetics in determining outcome. *Bone Marrow Transplant* 2005; **36:** 839–45.
4. Tran H, *et al.* Pharmacokinetics and individualized dose adjustment of intravenous busulfan in children with advanced hematologic malignancies undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2004; **10:** 805–12.
5. Kletzel M, *et al.* Pharmacokinetics of a test dose of intravenous busulfan guide dose modifications to achieve an optimal area under the curve of a single daily dose of intravenous busulfan in children undergoing a reduced-intensity conditioning regimen with hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2006; **12:** 472–9.
6. Rauh M, *et al.* Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children: validation of liquid chromatography tandem mass spectrometry method. *Clin Pharmacokinet* 2006; **45:** 305–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Busilvex; Myleran; ***Austral.***: Busulfex; Myleran; ***Austria***: Busilvex; Myleran; ***Belg.***: Busilvex; Myleran; ***Braz.***: Myleran; ***Canad.***: Busulfex; Myleran; ***Chile***: Myleran; ***China***: Busulfex (白舒非); Myleran (马利兰); ***Cz.***: Busilvex; Myleran; ***Denm.***: Busilvex; ***Fr.***: Busilvex; Myleran; ***Ger.***: Busilvex; Myleran; ***Gr.***: Busilvex; Myleran; ***Hong Kong***: Busulfex; Myleran; ***India***: Bucelon; Busuphan; Mylefan; Myleran; Myran; Mysulfan; ***Irl.***: Busilvex; Myleran; ***Israel***: Busulfex; Myleran; ***Ital.***: Busilvex; Myleran; ***Jpn***: Busulfex; ***Malaysia***: Busulflex; Myleran; ***Mex.***: Myleran; ***Neth.***: Busilvex; Myleran; ***Norw.***: Busilvex; ***NZ***: Myleran; ***Pol.***: Busilvex; Myleran; ***Port.***: Busilvex; Myleran; ***Rus.***: Myleran (Милеран); ***S. Afr.***: Busilvex†; Myleran; ***Singapore***: Busulfex; Myleran; ***Spain***: Busilvex; ***Swed.***: Busilvex; Myleran; ***Switz.***: Busilvex; ***Thai.***: Busulfex; Myleran; ***Turk.***: Busilvex; Busulfex; Myleran; ***UK***: Busilvex; Myleran; ***USA***: Busulfex; Myleran.

Multi-ingredient Preparations. ***Singapore***: Myran.

Pharmacopoeial Preparations
BP 2014: Busulfan Tablets;
USP 36: Busulfan Tablets.

Cabazitaxel *(USAN, rINN)*

Cabazitaxelum; RPR-116258A; XRP-6258; Кабазитаксел.
1-Hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-((2*R*,3*S*)-3-[[(*tert*-butoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate).
$C_{45}H_{57}NO_{14}$=835.9
CAS — 183133-96-2.
UNII — 51F690397J.

Uses and Administration

Cabazitaxel is a semisynthetic taxane similar to paclitaxel (see p. 839.3) that is manufactured from a taxane precursor derived from the needles of the yew tree. It is used with prednisone or prednisolone in the treatment of hormone-refractory metastatic prostate cancer (p. 712.3), in patients previously treated with a docetaxel-containing regimen.

Cabazitaxel is given by intravenous infusion over 1 hour diluted in at least 250 mL sodium chloride 0.9% or glucose 5% to a final concentration of between 100 to 260 micrograms/mL; infusion is via a 0.22 micrometre in-line filter and PVC containers and polyurethane infusion sets should not be used. Cabazitaxel 25 mg/m^2 is given every 3 weeks, with oral prednisone or prednisolone 10 mg given daily.

At least 30 minutes before each dose of cabazitaxel, an intravenous dose of an antihistamine (diphenhydramine 25 mg or equivalent), a corticosteroid (dexamethasone 8 mg or equivalent), and a histamine H_2-antagonist (ranitidine 50 mg or equivalent) should be given. Prophylaxis with an antiemetic is also recommended and can be given orally or intravenously as needed. Patients at high risk of neutropenia may need granulocyte colony-stimulating factor, see Adverse Effects, Treatment, and Precautions, below.

Toxicity may require the cabazitaxel dose to be modified, see Administration in Subsequent Cycles, below.

References.

1. de Bono JS, *et al.* TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376:** 1147–54. Correction. *ibid.* 2011; **377:** 720.
2. Agarwal N, *et al.* Cabazitaxel for the treatment of castration-resistant prostate cancer. *Future Oncol* 2011; **7:** 15–24.
3. Michielsen DP, *et al.* Cabazitaxel for the treatment of prostate cancer. *Expert Opin Pharmacother* 2011; **12:** 977–82.
4. Paller CJ, Antonarakis ES. Cabazitaxel: a novel second-line treatment for metastatic castration-resistant prostate cancer. *Drug Des Devel Ther* 2011; **5:** 117–24.
5. Oudard S. TROPIC: phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. *Future Oncol* 2011; **7:** 497–506.
6. Villanueva C, *et al.* Cabazitaxel: a novel microtubule inhibitor. *Drugs* 2011; **71:** 1251–8. Correction. *ibid.*; 1720.

Administration in subsequent cycles. Intravenous doses of cabazitaxel should be modified for the following toxicities:

- febrile neutropenia, or neutropenia of grade 3 or above for more than 1 week despite treatment including granulocyte colony-stimulating factor: delay cabazitaxel until neutrophil count is above 1500 cells/mm^3 and fever has improved or resolved, then reduce dose to 20 mg/m^2. Secondary prophylaxis with a granulocyte colony-stimulating factor is recommended.
- persistent diarrhoea (despite treatment), or diarrhoea of grade 3 or above: delay cabazitaxel until improvement or resolution of symptoms, then reduce dose to 20 mg/m^2.
- peripheral neuropathy of grade 2 or above: delay cabazitaxel until improvement or resolution of symptoms, then reduce dose to 20 mg/m^2.

If a patient continues to have any of the above adverse effects while on the reduced dose, cabazitaxel treatment should be stopped.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Neutropenia is common during cabazitaxel treatment and fatalities have been reported. Granulocyte colony-stimulating factor may be given to reduce the risk, and prophylaxis and/or treatment should be considered in high-risk patients such as those aged 65 years and over, those with poor performance status, those with extensive prior radiotherapy, or those with previous episodes of febrile neutropenia. Cabazitaxel should not be started or continued while neutrophil counts are 1500 cells/mm^3 or below; if counts increase above this level then use may be continued using a modified dose (see Uses and Administration, above). Blood counts should be monitored every week during the first treatment cycle of cabazitaxel, and before each cycle thereafter.

To prevent hypersensitivity reactions, all patients should be given premedication with an antihistamine, corticosteroid, and histamine H_2-antagonist (see Uses and Administration, above). If a severe hypersensitivity reaction occurs cabazitaxel should be stopped immediately and not restarted; symptoms include hypotension, bronchospasm, and rash, that may occur within a few minutes of the infusion. Cabazitaxel should not be used in patients hypersensitive to polysorbate 80, which is present in the formulation.

Peripheral neuropathy and gastrointestinal disturbances are common; diarrhoea may be severe and fatalities have been reported. Treatment should be delayed or the dose reduced for peripheral neuropathy, or severe or persistent diarrhoea (see Uses and Administration, above). Other common adverse effects include anaemia, leucopenia, thrombocytopenia, fatigue, haematuria, dyspnoea, dysgeusia, cough, arthralgia, myalgia, alopecia, anorexia, dehydration, hyperglycaemia, hypokalaemia, anxiety, confusion, sciatica, conjunctivitis, increased lachrymation, tinnitus, vertigo, tachycardia, hypotension or hypertension, deep-vein thrombosis, flushing, dry skin, and urinary disorders. Arrhythmias, peripheral oedema, increases in liver enzymes, urinary-tract infection, dizziness, headache, pyrexia, muscle spasms, and pain including chest pain have also been reported. Renal failure, occasionally fatal, has occurred. Other rare adverse effects that have led to death include cardiac arrest or cardiac failure, ventricular fibrillation, and cerebral haemorrhage.

Some adverse effects such as neutropenia, fatigue, pyrexia, dizziness, dehydration, and urinary-tract infections occurred more frequently in elderly patients (65 years and over), who may require additional monitoring.

Cabazitaxel is metabolised in the liver and so should not be used in patients with hepatic impairment (defined as total bilirubin > the upper limit of normal, or aspartate aminotransferase and/or alanine aminotransferase ≥1.5 times the upper limit of normal).

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3.

Cabazitaxel is mainly metabolised via the cytochrome P450 isoenzyme CYP3A4. Potent inhibitors or inducers of this enzyme may affect exposure to cabazitaxel, and their use together should be avoided. Caution is advised when cabazitaxel is used with moderate inhibitors.

In vitro studies suggest that the potential for cabazitaxel to inhibit or induce CYP isoenzymes is low.

Pharmacokinetics

Cabazitaxel is equally distributed between blood and plasma *in vitro*; binding to plasma proteins is about 90%, mainly to albumin and lipoproteins. Cabazitaxel is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4 and CYP3A5, and to a lesser extent by CYP2C8. Renal excretion of cabazitaxel and its metabolites accounts for a small portion of the dose (about 4%); most of the dose (76%) is excreted via the faeces as metabolites. After a one-hour intravenous infusion, cabazitaxel follows a three-compartment pharmacokinetic model with α, β, and γ half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

Cabazitaxel crosses the blood-brain barrier and the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Jevtana; ***Belg.***: Jevtana; ***Braz.***: Jevtana; ***Denm.***: Jevtana; ***Fr.***: Jevtana; ***Ger.***: Jevtana; ***Irl.***: Jevtana; ***Israel***: Jevtana; ***Neth.***: Jevtana; ***Norw.***: Jevtana; ***Spain***: Jevtana; ***Swed.***: Jevtana; ***Switz.***: Jevtana; ***UK***: Jevtana; ***USA***: Jevtana.

Cabozantinib *(USAN, pINN)*

Cabozantinibum; XL-184 (cabozantinib or cabozantinib s-malate); Кабозантиниб.

N-{4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

$C_{28}H_{24}FN_3O_5$=501.5

CAS — 849217-68-1.

UNII — 1C39JW444G.

Cabozantinib s-Malate *(USAN, pINNM)*

Cabozantinib, Malate de; Cabozantinibi Malas; Malato de cabozantinib; XL-184 (cabozantinib or cabozantinib s-malate); Кабозантиниба Малат.

$C_{28}H_{24}FN_3O_5,C_4H_6O_5$=635.6

CAS — 1140909-48-3.

UNII — DR7ST46X58.

Uses and Administration

Cabozantinib is a tyrosine kinase inhibitor that targets multiple receptor kinases including MET (mesenchymal-epithelial transition factor, hepatocyte growth factor receptor/HGFR), RET (rearranged during transfection), and VEGF (vascular endothelial growth factor). It is used in the treatment of progressive, metastatic medullary thyroid cancer (p. 716.1). Doses are given as the s-malate but expressed as the base; 177.4 mg of cabozantinib s-malate is equivalent to about 140 mg cabozantinib.

The usual oral dose is the equivalent of cabozantinib 140 mg once daily; capsules should be taken on an empty stomach and swallowed whole. A missed dose should not be taken within 12 hours of the next dose. Dose adjustments may be required for toxicities, see Administration in Subsequent Cycles, below. Treatment is continued until disease progression or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For patients who must also take a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, the daily dose of cabozantinib should be reduced by 40 mg. The original dose of cabozantinib may be restarted 2 or 3 days after the inhibitor has been stopped. For patients who must take a potent CYP3A4 inducer, the daily dose of cabozantinib should be increased by 40 mg to a maximum dose of 180 mg daily. The original dose of cabozantinib may be restarted 2 or 3 days after the inducer has been stopped.

Cabozantinib is also under investigation for the treatment of other solid neoplasms including prostate cancer and renal cell carcinoma.

References.
1. Durante C, *et al.* XL184 (cabozantinib) for medullary thyroid carcinoma. *Expert Opin Invest Drugs* 2011; **20:** 407–413.
2. Kurzrock R, *et al.* Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol* 2011; **29:** 2660–6.
3. Nagilla M, *et al.* Cabozantinib for the treatment of advanced medullary thyroid cancer. *Adv Therapy* 2012; **29:** 925–34.
4. Hart CD, De Boer RH. Profile of cabozantinib and its potential in the treatment of advanced medullary thyroid cancer. *Onco Targets Ther* 2013; **6:** 1–7.

Administration in subsequent cycles. Cabozantinib treatment may need to be modified if toxicities occur. It should be withheld for grade 4 haematological adverse effects, for grade 3 or higher non-haematological reactions, or for intolerable grade 2 reactions. When reactions have resolved or improved to grade 1, the oral daily dose of cabozantinib should be reduced as follows:

- in those previously taking 140 mg: resume treatment at 100 mg
- in those previously taking 100 mg: resume treatment at 60 mg
- in those previously taking 60 mg: resume treatment at 60 mg if tolerated, otherwise stop treatment

Adverse Effects and Precautions

The most commonly reported adverse effects with cabozantinib are diarrhoea or constipation, stomatitis, nausea and vomiting, abdominal pain, dysgeusia, oral pain, anorexia and decreased body weight, palmar-plantar erythrodysesthesia syndrome, fatigue, hair colour changes, and hypertension. Other less common adverse effects include other gastrointestinal disorders such as dyspepsia or dysphagia, arthralgia, muscle spasms, musculoskeletal chest pain, dizziness, peripheral neuropathy, anxiety, dysphonia, rash, dry skin, alopecia, and hypotension. Reversible posterior leucoencephalopathy syndrome has been reported, and any patients reporting seizures, headache, visual disturbances, confusion, or altered mental state should be evaluated for this. Increased concentrations of thyroid-stimulating hormone, increased liver enzyme values, hyperbilirubinaemia, neutropenia, thrombocytopenia, lymphopenia, hypocalcaemia, hypophosphataemia, hypomagnesaemia, hypokalaemia, and hyponatraemia have also been noted. Proteinuria has sometimes occurred; monitoring is recommended.

Gastrointestinal perforations and fistulas have occurred, as have tracheal or oesophageal fistulas. Serious haemorrhage has been reported and cabozantinib should not be used in patients with recent haemorrhage or haemoptysis. An increased incidence of thrombotic events, including venous and arterial thromboembolism, has also been associated with cabozantinib.

Osteonecrosis of the jaw has occurred with cabozantinib and an oral examination should be carried out before starting treatment and periodically thereafter. Wound complications have also been reported and treatment should be stopped at least 28 days before scheduled surgery, including invasive dental procedures; it may be restarted when healing is deemed adequate. Where dehiscence or wound healing complications occur during treatment, cabozantinib should be withheld.

Cabozantinib should be permanently stopped for visceral perforation or fistula formation, severe haemorrhage, serious arterial thromboembolism, nephrotic syndrome, malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite medical management, osteonecrosis of the jaw, or reversible posterior leucoencephalopathy syndrome.

Interactions

Cabozantinib is a substrate of the cytochrome P450 isoenzyme CYP3A4. Exposure to cabozantinib was increased by 38% when it was given with the CYP3A4 inhibitor ketoconazole, and potent CYP3A4 inhibitors should be avoided during treatment. Conversely, exposure to cabozantinib was decreased by 77% when it was given with the CYP3A4 inducer rifampicin and prolonged use of potent CYP3A4 inducers should avoided. The dose cabozantinib may need to be adjusted if CYP3A4 inhibitors or inducers must be used, see Uses and Administration, above.

Pharmacokinetics

Peak plasma concentrations of cabozantinib occur between 2 to 5 hours after an oral dose, and steady-state concentrations are seen by day 15. Exposure is increased when it is taken with a high-fat meal. Cabozantinib is highly-bound to plasma proteins (over 99%). It is metabolised by the cytochrome P450 isoenzyme CYP3A4; CYP2C9 is a minor route. It is excreted via the faeces and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Cometriq.

Cancer Vaccines

Vacunas contra el cáncer.

Profile

Vaccines are under investigation for many neoplastic diseases including breast, colorectal, head and neck, lung, ovarian, pancreatic, prostate, and renal cancers, lymphoma, and melanoma. Vaccines can be either preventative or therapeutic. Vaccines for the treatment of cancer are designed to stimulate an antibody response and can be allogeneic or autologous and based on dendritic cells, peptides or proteins, whole tumour cells, RNA or DNA, bacterial or viral vectors, or heat shock proteins.

BCG vaccine can be used as immunotherapy to treat bladder cancer (see p. 2378.2), and a human papillomavirus (HPV) vaccine for the prevention of cervical cancer is available in some countries (see p. 2392.2). A therapeutic vaccine targeting epidermal growth factor is used in some countries for non-small cell lung cancer. Sipuleucel-T (p. 857.1) and vitespen (p. 887.1) are examples of personalised cancer vaccines.

Reviews.
1. Eager R, *et al.* Lung cancer vaccines. *Curr Gene Ther* 2007; **7:** 469–84.
2. Lowe DB, *et al.* Towards progress on DNA vaccines for cancer. *Cell Mol Life Sci* 2007; **64:** 2391–2403.
3. Doehn C, *et al.* Prostate cancer vaccines: current status and future potential. *BioDrugs* 2008; **22:** 71–84.
4. de Gruijl TD, *et al.* Whole-cell cancer vaccination: from autologous to allogeneic tumor- and dendritic cell-based vaccines. *Cancer Immunol Immunother* 2008; **57:** 1569–77.
5. Ebben JD, *et al.* Tumour vaccine approaches for CNS malignancies: progress to date. *Drugs* 2009; **69:** 241–9.
6. Pilla L, *et al.* Multipeptide vaccination in cancer patients. *Expert Opin Biol Ther* 2009; **9:** 1043–55.
7. Shumway NM, *et al.* Therapeutic breast cancer vaccines: a new strategy for early-stage disease. *BioDrugs* 2009; **23:** 277–87.
8. Venuti A. Progress and challenges in the vaccine-based treatment of head and neck cancers. *J Exp Clin Cancer Res* 2009; **28:** 69.
9. Eggermont AM. Therapeutic vaccines in solid tumours: can they be harmful? *Eur J Cancer* 2009; **45:** 2087–90.
10. Chen X, *et al.* Novel strategies for improved cancer vaccines. *Expert Rev Vaccines* 2009; **8:** 567–76.
11. Mocellin S, *et al.* Peptide-based anticancer vaccines: recent advances and future perspectives. *Curr Med Chem* 2009; **16:** 4779–96.
12. Eksioglu EA, *et al.* Dendritic cells as therapeutic agents against cancer. *Front Biosci* 2010; **15:** 321–47.
13. Copier J, Dalgleish A. Whole-cell vaccines: a failure or a success waiting to happen? *Curr Opin Mol Ther* 2010; **12:** 14–20.
14. Rodríguez PC, *et al.* Clinical development and perspectives of CIMAvax EGF, Cuban vaccine for non-small-cell lung cancer therapy. *MEDICC Rev* 2010; **12:** 17–23.

Capecitabine *(BAN, USAN, rINN)*

Capecitabina; Capécitabine; Capecitabinum; Kapecitabin; Kapesitabiini; Kapesitabin; Ro-09-1978/000; Капецитабин.

Pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate.

$C_{15}H_{22}FN_3O_6$=359.4

CAS — 154361-50-9; 158798-73-3.

ATC — L01BC06.

ATC Vet — QL01BC06.

UNII — 6804DJ8Z9U.

Pharmacopoeias. In *US.*

USP 36: (Capecitabine). A white to off-white crystalline powder. Sparingly soluble in water; soluble in alcohol and in acetonitrile; freely soluble in methyl alcohol. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Capecitabine is a prodrug that is converted to fluorouracil (p. 795.3) in body tissues. It is given orally for the treatment of metastatic colorectal cancer (p. 706.3) and is also used for the adjuvant treatment of patients after surgery for Dukes C colon cancer. Capecitabine is given with docetaxel for the treatment of locally advanced or metastatic breast cancer (p. 702.1) after failure of anthracycline-containing chemotherapy. It may be given as monotherapy after failure of taxanes and anthracycline-containing regimens for patients with breast cancer and for whom further anthracycline-containing therapy is not indicated. Capecitabine with lapatinib (p. 815.1) is used for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress human epidermal receptor type 2 (HER2). Capecitabine is also used with a platinum-based regimen for the first-line treatment of gastric cancer (p. 706.1).

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

For *monotherapy* in **colon**, **colorectal**, or in **breast** cancer, the recommended initial oral dose is 1.25 g/m² given twice daily (for the suggestion that lower initial doses may be favoured in the USA see Administration, p. 758.1). Doses are given for 14 days, followed by a 7-day rest period.

Adjuvant treatment for colon cancer is recommended for a total of 6 months.

For *combination* therapy in **breast** cancer, when given with docetaxel, capecitabine is given in the same dose as listed above; docetaxel is given at 75 mg/m² as a 1-hour intravenous infusion every 3 weeks. However, when used with lapatinib tosilate, a different regimen is used, see Uses and Administration, under Lapatinib Tosilate, p. 815.1.

In *combination* therapy in **colorectal** or **gastric** cancer, the recommended initial oral dose of capecitabine is 0.8 to 1 g/m² twice daily for 14 days, followed by a 7-day rest period. Alternatively, capecitabine 625 mg/m² twice daily is given continuously.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Doses should be modified in subsequent cycles according to toxicity. Capecitabine doses should be reduced in patients with renal impairment (see below).

Capecitabine is also under investigation in the treatment of other malignancies.

References.

1. Sun W. Evolution of capecitabine dosing in colorectal cancer. *Clin Colorectal Cancer* 2010; **9:** 31–9.
2. Naughton M. Evolution of capecitabine dosing in breast cancer. *Clin Breast Cancer* 2010; **10:** 130–5.
3. Norman G, *et al.* Capecitabine for the treatment of advanced gastric cancer. *Health Technol Assess* 2010; **14** (suppl. 2): 11–17.
4. Ma Y, *et al.* Capecitabine for the treatment for advanced gastric cancer: efficacy, safety and ethnicity. *J Clin Pharm Ther* 2012; **37:** 266–75.
5. O'Shaughnessy JA, *et al.* Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. *Oncologist* 2012; **17:** 476–84.
6. Fernández-Martos C, *et al.* The role of capecitabine in locally advanced rectal cancer treatment: an update. *Drugs* 2012; **72:** 1057–73.
7. NICE. Capecitabine for the treatment of advanced gastric cancer (issued July 2010, reviewed May 2013). Available at: http://www.nice.org.uk/nicemedia/live/13049/49875/49875.pdf (accessed 08/10/13)
8. Li Q, *et al.* Clinical efficacy of including capecitabine in neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2013; **8:** e53403.

Administration. Severe toxicity has been reported when capecitabine was given after a fluorouracil and folinic acid regimen to patients with colorectal cancer; a comparable effect was not seen when the treatments were given in the reverse order.[1] Although the mechanism of this sequence-specific toxicity was not determined, the authors suggested that an interaction with intracellularly retained folate was a possible cause.

Interestingly, it has been suggested that aggressive dietary folate supplementation policies in the USA may also contribute to the increased rate of major toxicity seen with capecitabine in phase III studies there, compared with Europe and Asia. In contrast to European practice, oncologists in the USA therefore rarely prescribed the recommended initial oral dose of 1.25 g/m² twice daily, tending to prefer a dose of 1 g/m² twice daily.[2]

1. Hennig IM, *et al.* Severe sequence-specific toxicity when capecitabine is given after fluorouracil and leucovorin. *J Clin Oncol* 2008; **26:** 3411–17.
2. Midgley R, Kerr DJ. Capecitabine: have we got the dose right? *Nat Clin Pract Oncol* 2009; **6:** 17–24.

Administration in the elderly. A review noted that the pharmacokinetics of capecitabine were not affected by age in those patients with normal renal function. However, toxicity may be increased in some elderly patients, and reduced doses may be used.[1]

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. Renal impairment increases systemic exposure to 5′-deoxy-5-fluorouridine, a metabolite of capecitabine. An increase in the severity of adverse effects appears to correlate with decreased renal function and increased exposure to this metabolite.[1]

Licensed product information suggests the following dosage adjustments based on creatinine clearance (CC):

- mild renal impairment, CC 51 to 80 mL/minute: no dosage adjustment necessary
- moderate renal impairment, CC 30 to 50 mL/minute: when the starting dose is 1.25 g/m² twice daily, a dose reduction of 25%, to about 950 mg/m² twice daily is recommended; however, when the starting dose is 1 g/m² twice daily, no dose reduction is required
- severe renal impairment, CC below 30 mL/minute: capecitabine is contra-indicated

1. Poole C, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. *Cancer Chemother Pharmacol* 2002; **49:** 225–34.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p. 797.1. Diarrhoea (which may be severe), nausea and vomiting, abdominal pain, stomatitis, and palmar-plantar erythrodysesthesia syndrome (erythema and desquamation of hands and feet) occur commonly with capecitabine, and may be dose-limiting. Other common adverse effects include fatigue, asthenia, and anorexia. Rashes, alopecia, erythema, dryness of the skin, pruritus, skin pigmentation disorders, and nail disorders can occur. Other adverse effects are fever, pain, arthralgia, constipation, dyspepsia, paraesthesia, headache, dizziness, insomnia, depression, eye irritation, hypo- or hypercalcaemia, and dehydration. Encephalopathy, cardiotoxicity, thromboembolism, and bone-marrow depression have all been reported. Hyperbilirubinaemia has occurred. Severe toxicity has been seen in patients with dihydropyrimidine dehydrogenase deficiency.

Doses of capecitabine should be reduced in patients with moderate renal impairment and its use is contra-indicated in those with severe renal or hepatic impairment.

Effects on blood lipids. Severe hypertriglyceridaemia has been reported with oral capecitabine;[1] patients had high baseline triglyceride concentrations at the start of capecitabine. Despite the introduction of lipid-lowering therapy, triglyceride concentrations remained above baseline, and only decreased several weeks after stopping capecitabine. A prospective study suggested an incidence of hypertriglyceridaemia of 3.7% in patients treated with capecitabine, either as monotherapy or with oxaliplatin, for colorectal cancer.[2]

1. Kurt M, *et al.* Capecitabine-induced severe hypertriglyceridemia: report of two cases. *Ann Pharmacother* 2006; **40:** 328–31.
2. Michie CO, *et al.* The frequency and severity of capecitabine-induced hypertriglyceridaemia in routine clinical practice: a prospective study. *Br J Cancer* 2010; **103:** 617–21.

Effects on the eyes. A report of severe ocular irritation with corneal deposits and impaired visual acuity in 2 patients given capecitabine.[1] Symptoms resolved within several weeks of stopping the drug.

1. Waikhom B, *et al.* Severe ocular irritation and corneal deposits associated with capecitabine use. *N Engl J Med* 2000; **343:** 740–1. Correction. *ibid.*; 1428.

Effects on the heart. Acute ischaemic chest pain has been reported, usually within a few days of starting capecitabine.[1-3] Symptoms from case reports[1] and incidence in Phase III studies[4] were similar to those in patients given fluorouracil. While symptoms have generally been reported to be reversible, fatal myocardial infarction has occurred.[2] One patient had also had cardiotoxicity with fluorouracil treatment,[1] but others had no apparent risk factors.[2] Capecitabine-induced cardiotoxicity without chest pain has also been reported;[5] myocardial ischaemia and a significant decrease in ejection fraction were apparent on exertion.

1. Frickhofen N, *et al.* Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol* 2002; **13:** 797–801.
2. Kuppens IELM, *et al.* Capecitabine induces severe angina-like chest pain. *Ann Intern Med* 2004; **140:** 494–5.
3. Bertolini A, *et al.* Acute cardiotoxicity during capecitabine treatment: a case report. *Tumori* 2001; **87:** 200–6.
4. van Cutsem E, *et al.* Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol* 2002; **13:** 484–5.
5. Goldsmith YB, *et al.* Capecitabine-induced coronary vasospasm. *J Clin Oncol* 2008; **26:** 3802–4.

Effects on the nervous system. Peripheral neuropathy,[1] encephalopathy,[2,3] and cerebellar ataxia[4] have been reported with capecitabine use.

1. Saif MW, *et al.* Peripheral neuropathy associated with capecitabine. *Anticancer Drugs* 2004; **15:** 767–71.
2. Niemann B, *et al.* Toxic encephalopathy induced by capecitabine. *Oncology* 2004; **66:** 331–5.
3. Videnovic A, *et al.* Capecitabine-induced multifocal leukoencephalopathy: a report of five cases. *Neurology* 2005; **65:** 1792–4.
4. Lam MSH, *et al.* Capecitabine-associated cerebellar ataxia. *Am J Health-Syst Pharm* 2008; **65:** 2032–5.

Effects on the skin and nails. While hand-foot syndrome appears to be common in patients treated with capecitabine (see Palmar-plantar Erythrodysesthesia Syndrome, below), other skin eruptions have been rarely reported.[1] Onychomadesis (total separation of the nail-bed) and onycholysis have occurred.[2,3] Pyogenic granuloma has been seen with the use of capecitabine,[1] as has re-pigmentation of chemotherapy-induced vitiligo.[4] Stevens-Johnson syndrome has also been reported.[5]

1. Piguet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. *Br J Dermatol* 2002; **147:** 1270–2.
2. Chen G-Y, *et al.* Onychomadesis and onycholysis associated with capecitabine. *Br J Dermatol* 2001; **145:** 521–2.
3. Chen G-Y, *et al.* Exudative hyponychial dermatitis associated with capecitabine and docetaxel combination chemotherapy for metastatic breast carcinoma: report of three cases. *Br J Dermatol* 2003; **148:** 1071–3.
4. Schmid-Wendtner M-H, *et al.* Leopard-like vitiligo with capecitabine. *Lancet* 2001; **358:** 1575.
5. Sendur MA, Kilickap S. Stevens-Johnson syndrome after treatment with capecitabine. *Clin Oncol (R Coll Radiol)* 2008; **20:** 202–3.

Hypersensitivity. A patient was successfully given fluorouracil by continuous infusion despite previous hypersensitivity to capecitabine. The authors supposed that the hypersensitivity was likely to have been caused by capecitabine or intermediate metabolites, and suggested a lack of cross-sensitivity between capecitabine and fluorouracil.[1]

1. Liu CY. Fluorouracil for allergic reactions to capecitabine. *Ann Pharmacother* 2002; **36:** 1897–9.

Palmar-plantar erythrodysesthesia syndrome. Hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome, p. 730.1) has been reported to be common with use of capecitabine given either as monotherapy[1] or as part of combination chemotherapy regimens.[2,3] The syndrome developed within the first 2 cycles of monotherapy,[1] but within the first 3 cycles in combination therapy,[3] which was attributed to dose modifications of capecitabine in the latter case. Use with docetaxel, and previous chemotherapy-induced stomatitis were found to be significant risk factors for its occurrence.[3] The only effective management is treatment interruption and dose modification.[4] Supportive measures to reduce pain and discomfort and prevent secondary infection are important.[5] General recommended strategies include submersion of hands and feet in cold water, wound care, and avoidance of extreme temperature changes, tight-fitting clothing, or skin friction. Emollient creams may be of benefit for both prophylaxis and treatment. Other strategies that have been proposed include the use of amifostine, topical or systemic corticosteroids, and nicotine patches; however, use of these drugs for capecitabine-induced hand-foot syndrome remains unproven. While pyridoxine cannot be recommended for prophylaxis, some consider it a reasonable choice for treatment, since benefit has been reported with its use with topical emollients.[4] Concurrent treatment with celecoxib has been reported to reduce the incidence of hand-foot syndrome induced by capecitabine.[6,7] For reference to the use of vitamin E to alleviate palmar-plantar erythrodysesthesia syndrome caused by capecitabine and docetaxel, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p. 2120.1.

As a result of capecitabine-induced hand-foot syndrome, fingerprint misidentification has been reported.[8,9]

1. Abushullaih S, *et al.* Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. *Cancer Invest* 2002; **20:** 3–10.
2. Park YH, *et al.* High incidence of severe hand-foot syndrome during capecitabine-docetaxel combination chemotherapy. *Ann Oncol* 2003; **14:** 1691–2.
3. Heo YS, *et al.* Hand-foot syndrome in patients treated with capecitabine-containing combination chemotherapy. *J Clin Pharmacol* 2004; **44:** 1166–72.
4. Gressett SM, *et al.* Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract* 2006; **12:** 131–41.
5. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome: insights from clinical trials evaluating capecitabine. *Oncology (Huntingt)* 2004; **18:** 1161–8, 1173.
6. Lin E, *et al.* Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Huntingt)* 2002; **16** (12 suppl 14): 31–7.
7. Lin EH, *et al.* Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? *Am J Clin Oncol* 2006; **29:** 232–9.
8. García-Saénz JA, *et al.* Elementary, my dear Watson. *J Clin Oncol* 2007; **25:** 1815–6.
9. Wong M, *et al.* Travel warning with capecitabine. *Ann Oncol* 2009; **20:** 1281.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies capecitabine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Toxicity. Sequence-specific toxicity has been reported when capecitabine was given after fluorouracil and folinic acid, see Administration, above.

Tumour lysis syndrome. A fatal case of tumour lysis syndrome (p. 730.2) has been reported after the use of capecitabine.[1]

1. Kurt M, *et al.* Tumor lysis syndrome following a single dose of capecitabine. *Ann Pharmacother* 2004; **38:** 902.

Interactions

As for Fluorouracil, p. 797.3. Altered coagulation parameters and bleeding have occurred in patients on warfarin or phenprocoumon given capecitabine. Increased phenytoin plasma concentrations and symptoms of toxicity during use with capecitabine have been reported. Antacids containing aluminium or magnesium hydroxides cause a small increase in capecitabine plasma concentration. The maximum tolerated dose of capecitabine is reduced when it is given with either folinic acid or interferon alfa. Use with sorafenib increased exposure to capecitabine.

Antivirals. For reference to a fatal interaction between capecitabine and *brivudine*, see Antivirals, under Interactions of Fluorouracil, p. 797.3.

Folate. For the suggestion that an interaction between capecitabine and intracellularly retained folate led to increased toxicity in patients with colorectal cancer, see Administration, above.

Pharmacokinetics

Capecitabine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur at about 1.5 hours. Food reduces the rate and extent of absorption. Plasma protein binding of capecitabine is less than 60%. Capecitabine is hydrolysed in the liver to 5′-deoxy-5-fluorocytidine (5′-DFCR), which is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR; doxifluridine—p. 782.3) and subsequently to the active 5-fluorouracil in body tissues, via the enzyme thymidine phosphorylase. 5-Fluorouracil is further metabolised, as discussed on p. 798.1. About 3% of a dose of capecitabine is excreted in the urine unchanged.

References.

1. Reigner B, *et al.* Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998; **4:** 941–8.
2. Reigner B, *et al.* Clinical pharmacokinetics of capecitabine. *Clin Pharmacokinet* 2001; **40:** 85–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Apecitab; Capebina; Capecit; Capectan; Capefas; Categor; Catepen; Derebel; Xeloda; ***Austral.***: Xeloda; ***Austria***: Xeloda; ***Belg.***: Xeloda; ***Braz.***: Xeloda; ***Canad.***: Xeloda; ***Chile***: Xeloda; ***China***: Xeloda (希罗达); ***Cz.***: Xeloda; ***Denm.***: Xeloda; ***Fin.***: Xeloda; ***Fr.***: Xeloda; ***Ger.***: Xeloda; ***Gr.***: Xeloda; ***Hong Kong***: Xeloda; ***Hung.***: Xeloda; ***India***: Capecite; Capiibine; Captabin; Capxcel; Caxeta; Naprocap; ***Indon.***: Xeloda; ***Irl.***: Xeloda; ***Israel***: Xeloda; ***Ital.***: Xeloda; ***Jpn***: Xeloda; ***Malaysia***: Xeloda; ***Mex.***: Xeloda; ***Neth.***: Capecitastad; Coloxet; Vopecidex; Xeloda; ***Norw.***: Xeloda; ***NZ***: Xeloda; ***Philipp.***: Xeloda; ***Pol.***: Xeloda; ***Port.***: Xeloda; ***Rus.***: Xeloda (Кселода); ***S.Afr.***: Xeloda; ***Singapore***: Xeloda; ***Spain***: Xeloda; ***Swed.***: Xeloda; ***Switz.***: Xeloda; ***Thai.***: Xeloda; ***Turk.***: Xeloda; ***UK***: Xeloda; ***Ukr.***: Xeloda (Кселода); ***USA***: Xeloda; ***Venez.***: Xeloda.

Pharmacopoeial Preparations
USP 36: Capecitabine Tablets.

Carboplatin *(BAN, USAN, rINN)*

Carboplatine; Carboplatino; Carboplatinum; CBDCA; JM-8; Karboplatiini; Karboplatin; Karboplatina; Karboplatyna; NSC-241240; Карбоплатин.

cis-Diammine(cyclobutane-1,1-dicarboxylato)platinum.

$C_6H_{12}N_2O_4Pt$=371.3

CAS — 41575-94-4.

ATC — L01XA02.

ATC Vet — QL01XA02.

UNII — BG3F62OND5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Carboplatin). A colourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

USP 36: (Carboplatin). A 1% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. Carboplatin reacts with aluminium causing loss of potency and forming a precipitate. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving carboplatin.

Stability. About 5% of the initial carboplatin concentration was lost over 24 hours when solutions were diluted in sodium chloride 0.9% and stored at 25 degrees; lesser amounts of degradation were seen at lower sodium chloride concentrations, but carboplatin was apparently stable over this period if diluted with glucose 5%.[1] The authors suggested that chloride-containing infusion solutions are not suitable for carboplatin, not only because of the loss of active drug but because of the possibility that conversion to cisplatin may be occurring, with a risk of increased toxicity.[1] This has been contested by the manufacturers (*Bristol-Myers, USA*), who found that only 0.5% or 0.7%, depending on formulation, of a carboplatin solution in sodium chloride 0.9%, had been converted to cisplatin after 24 hours.[2] However, the total degradation of carboplatin was not measured. In another study, the authors calculated the time to 5% degradation of carboplatin at 25 degrees as 29.2 hours in sodium chloride 0.9% compared with 52.7 hours in water.[3] They concluded that carboplatin should not be diluted in sodium chloride 0.9% when intended for continuous infusion over a prolonged period.[3] Carboplatin in glucose 5% was reported to be stable for 7 days at 25 degrees in PVC bags when protected from light.[4]

1. Cheung Y-W, *et al.* Stability of cisplatin, iproplatin, carboplatin, and tetraplatin in commonly used intravenous solutions. *Am J Hosp Pharm* 1987; **44:** 124–30.
2. Perrone RK, *et al.* Extent of cisplatin formation in carboplatin admixtures. *Am J Hosp Pharm* 1989; **46:** 258–9.
3. Allsopp MA, *et al.* The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles. *Int J Pharmaceutics* 1991; **69:** 197–210.
4. Diaz Amador F, *et al.* Stability of carboplatin in polyvinyl chloride bags. *Am J Health-Syst Pharm* 1998; **55:** 602, 604.

Uses and Administration

Carboplatin is an analogue of cisplatin with similar actions and uses (see p. 766.2). It is used in the treatment of advanced ovarian cancers and of small-cell lung cancer, both alone and combined with other antineoplastics. It has also been tried as an alternative to cisplatin in other solid tumours (see below).

Carboplatin is given by intravenous infusion over 15 minutes to 1 hour. In the UK an initial dose of 400 mg/m^2 is licensed for use as a single agent in previously untreated patients with normal renal function, reduced by 20 to 25% (to 300 to 320 mg/m^2) in patients who have previously been treated with myelosuppressive therapy or who have poor performance status. In the USA an initial dose of 360 mg/m^2 is licensed as a single agent in previously treated patients with recurrent disease, and an initial dose of 300 mg/m^2 when used with cyclophosphamide in previously untreated patients.

Dosage adjustments are necessary in patients with renal impairment (see below) and when carboplatin is given as part of a combination regimen. The dose in mg may be calculated using the Calvert formula as described under Administration, below. Subsequent doses should be adjusted according to the nadir of the white cell and platelet counts (see also Bone-marrow Depression, p. 730.3), and should not be given more frequently than every 4 weeks.

Administration. Pharmacokinetic studies by Calvert and colleagues[1] have indicated that the dose of carboplatin to produce a desired area under the concentration-time curve (AUC) could be calculated, based on the patient's glomerular filtration rate (GFR), as:

$$\text{Dose in mg} = \text{target AUC} \times (\text{GFR} + 25)$$

It should be noted that the resultant dose is given in mg and not in mg/m^2. This formula was found to be useful in patients with higher than normal as well as reduced GFR. Suggested target AUCs were 5 mg/mL per minute in previously treated patients and 7 mg/mL per minute in those who had not previously received chemotherapy. In combination therapy the appropriate AUC value depended on the other drugs used: an AUC of 4.5 mg/mL per minute gave acceptable results when carboplatin was used with bleomycin and etoposide for testicular teratoma.

However, determination of GFR may be a problem: clearance of technetium-99m-labelled diethylenetriamine penta-acetic acid (DTPA) or chromium-51-labelled edetic acid is more accurate than 24-hour creatinine clearance, with the first of these more convenient than the second.[2] (It has been suggested that creatinine clearance should not be used to estimate GFR for the Calvert equation.[3]) Nonetheless, radioisotopic determination of GFR is still an elaborate procedure, and may be less accurate in children than adults.[4,5] Chatelut and colleagues have proposed formulas[4,6,7] for determining clearance of carboplatin in both adults and children.

It has been suggested that the Calvert and Chatelut formulas are not sufficiently accurate for use in **children**, or in adults with very severe renal impairment. Bayesian methods are the technique of choice where serum carboplatin concentrations can be monitored.[3] However, a study in children showed that dosage based on determination of the GFR results in more consistent carboplatin exposure than dosage based on body-surface.[8] A comparison of calculation methods for carboplatin dosing in children found marked differences with the use of different GFR formulas.[5] GFR calculations according to Léger with the dose formula of Newell, or dose calculation by the method of Chatelut were considered to have low bias and only small age-dependent differences, whereas calculation methods with several steps or conversion procedures were prone to considerable error; the authors stated that the usefulness of dose calculations based solely on the serum creatinine should be critically questioned, and recommended the use of limited sampling strategies, therapeutic drug monitoring, and the precise determination of GFR.[5] There has also been a report of the successful use of the Calvert formula in 2 Japanese patients undergoing haemodialysis.[9]

1. Calvert AH, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7:** 1748–56.
2. Millward MJ, *et al.* Carboplatin dosing based on measurement of renal function—experience at the Peter MacCallum Cancer Institute. *Aust N Z J Med* 1996; **26:** 372–9.
3. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 1997; **33:** 161–83.
4. Chatelut E, *et al.* Population pharmacokinetics of carboplatin in children. *Clin Pharmacol Ther* 1996; **59:** 436–43.
5. Würthwein G, *et al.* Carboplatin dosing in children: calculation by different formulae. *Onkologie* 2011; **34:** 16–22.
6. Chatelut E, *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; **87:** 573–80.
7. Hulin A, *et al.* Suivi thérapeutique pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du carboplatine. *Therapie* 2010; **65:** 157–62.
8. Thomas H, *et al.* Prospective validation of renal-function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group Trial. *J Clin Oncol* 2000; **18:** 3614–21.
9. Oguri T, *et al.* Pharmacokinetic analysis of carboplatin in patients with cancer who are undergoing hemodialysis. *Cancer Chemother Pharmacol* 2010; **66:** 813–17.

Administration in the elderly. A review[1] found no data to support dose reduction of carboplatin based on age alone and noted that the use of the Calvert and Chatelut formulas (see Administration, above) allows for safe and accurate dosing by taking into account renal function changes associated with age.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. The initial dose of carboplatin is usually determined using a formula (see Administration, above). If this approach is not adopted, US licensed product information suggests the following initial intravenous dose of carboplatin, based on creatinine clearance (CC):

- CC 41 to 59 mL/minute: 250 mg/m^2
- CC 16 to 40 mL/minute: 200 mg/m^2

The incidence of severe leucopenia, neutropenia, or thrombocytopenia has been about 25% in renally-impaired patients who received single-agent carboplatin therapy at the above doses. The data for patients with more severe renal impairment are too limited to allow dosage recommendations.

Malignant neoplasms. A preliminary review[1] of carboplatin, concluded that it was active in ovarian cancer (p. 711.2), with similar responses to those seen with cisplatin; its activity in small-cell lung cancer (p. 710.2), seminoma, and squamous cell carcinomas of the head and neck seemed likely to be comparable, whereas results in gastrointestinal and breast cancers, lymphomas and leukaemias, melanoma, mesothelioma, renal carcinoma, and sarcoma were, generally unimpressive. A subsequent review[2] suggested that in testicular cancer, where there was a prospect of cure, cisplatin, which appeared to give better results in some studies should be preferred. However, in ovarian cancer, where treatment was largely palliative, carboplatin had the advantage of being better tolerated. A further review[3] of randomised studies concurred that carboplatin was equivalent to cisplatin in suboptimally debulked ovarian cancer and extensive-stage small-cell lung cancer, and was inferior to cisplatin in testicular cancer. It was also concluded that carboplatin was inferior to cisplatin in head and neck and oesophageal cancers. There was insufficient comparative evidence for other cancers for which cisplatin has a role.

1. Wagstaff AJ, *et al.* Carboplatin: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of cancer. *Drugs* 1989; **37:** 162–90.
2. Anonymous. Cisplatin or carboplatin for ovarian and testicular cancer? *Drug Ther Bull* 1994; **32:** 62–3.
3. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; **17:** 409–22.

Adverse Effects, Treatment, and Precautions

The adverse effects of carboplatin are similar to those of cisplatin (p. 767.1); nephrotoxicity and gastrointestinal toxicity are less severe than with cisplatin and reversible myelosuppression is the dose-limiting toxicity; platelet counts reach a nadir between 14 and 21 days after a dose, with recovery within 35 days, but recovery from leucopenia may be slower. Myelosuppression may be more severe and prolonged in patients with impaired renal function. Carboplatin should therefore be given at reduced doses to these patients and should be avoided if creatinine clearance is 20 mL/minute or less. Weekly blood counts and regular renal and hepatic function tests are recommended in all patients during therapy. Neurological function including assessment of hearing should also be monitored.

Incidence of adverse effects. The manufacturers analysed the adverse effects of carboplatin in studies involving 710 patients.[1] Myelosuppression was the dose-limiting toxicity: leucopenia occurred in 55% of the evaluable patients. Leucopenia and thrombocytopenia result in symptomatic events such as infection or bleeding in a minority of patients. Anaemia was frequent (59%) and required transfusional support in about one-fifth of the patients. Nephrotoxicity and serum electrolyte loss were much less of a problem; no high-volume fluid hydration or electrolyte supplementation was given during treatment. Vomiting occurred in about half the patients, and a further 25% had nausea without vomiting. Peripheral neurotoxi-

city was reported in 6% of evaluable patients and clinical ototoxicity occurred in only 8 cases or about 1% (but see also Effects on the Ears, below). Increases in liver enzyme values have also been reported, as well as, more rarely, alopecia, rash, a flu-like syndrome, and local effects at the injection site.

1. Canetta R, *et al.* Carboplatin: the clinical spectrum to date. *Cancer Treat Rev* 1985; **12** (suppl A): 125–36.

Effects on the ears. Carboplatin is less ototoxic than cisplatin, but ototoxicity is still common with carboplatin when used in high doses, for example, as part of conditioning regimens for bone marrow transplantation.[1,2] Long-term audiometric follow-up has been advised in young children given carboplatin-based chemotherapy, as ototoxicity may only be evident some years after treatment.[3] There was some evidence that sodium thiosulfate reduced carboplatin-induced hearing loss, when carboplatin was used for CNS malignancy.[4,5]

1. Freilich RJ, *et al.* Hearing loss in children with brain tumors treated with cisplatin and carboplatin-based high-dose chemotherapy with autologous bone marrow rescue. *Med Pediatr Oncol* 1996; **26:** 95–100.
2. Parsons SK, *et al.* Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. *Bone Marrow Transplant* 1998; **22:** 669–74.
3. Jehanne M, *et al.* Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. *Pediatr Blood Cancer* 2009; **52:** 637–43.
4. Neuwelt EA, *et al.* First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. *J Pharmacol Exp Ther* 1998; **286:** 77–84.
5. Doolittle ND, *et al.* Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Res* 2001; **7:** 493–500.

Effects on the eyes. Cortical blindness developed in 2 patients with impaired renal function receiving high-dose carboplatin;[1] although 10 cases of visual disturbances in patients receiving carboplatin had been reported to the manufacturers, none of these had sudden blindness and it was thought that the effect represented CNS toxicity in the presence of poor renal excretion. It was concluded that it was unwise to give high-dose carboplatin to patients whose glomerular filtration rate is less than 50 mL/minute.

Severe ocular and orbital toxicity has been reported after intracarotid injection of carboplatin for the treatment of recurrent glioblastomas.[2]

1. O'Brien MER, *et al.* Blindness associated with high-dose carboplatin. *Lancet* 1992; **339:** 558.
2. Watanabe W, *et al.* Severe ocular and orbital toxicity after intracarotid injection of carboplatin for recurrent glioblastomas. *Graefes Arch Clin Exp Ophthalmol* 2002; **240:** 1033–5.

Effects on the heart. Atrial flutter has been reported following the first dose of a second course of carboplatin.[1] The patient spontaneously reverted to sinus rhythm after 24 hours.

1. Zakaria S, *et al.* Atrial flutter associated with carboplatin administration. *Ann Pharmacother* 2011; **45:** e59.

Effects on the kidneys. Although carboplatin is reported to be much less nephrotoxic than cisplatin it is not devoid of adverse effects on the kidney.[1-8] Salt wasting nephropathy (similar to that seen with cisplatin),[1] and decreased creatinine clearance[2] and glomerular filtration rate[3] have occurred, as has acute renal failure, including in 2 patients given intraperitoneal carboplatin[4] (although these patients had been heavily pretreated with cisplatin). It has been suggested that renal toxicity may be more likely at cumulative carboplatin doses of about 750 mg/m^2 or more,[3] and there is some evidence to suggest that intensive hydration may ameliorate nephrotoxic effects.[2]

1. Welborn J, *et al.* Renal salt wasting and carboplatinum. *Ann Intern Med* 1988; **108:** 640.
2. Reed E, Jacob J. Carboplatin and renal dysfunction. *Ann Intern Med* 1989; **110:** 409.
3. Smit EF, *et al.* Carboplatin and renal function. *Ann Intern Med* 1989; **110:** 1034.
4. McDonald BR, *et al.* Acute renal failure associated with the use of intraperitoneal carboplatin: a report of two cases and review of the literature. *Am J Med* 1991; **90:** 386–91.
5. Frenkel J, *et al.* Acute renal failure in high dose carboplatin chemotherapy. *Med Pediatr Oncol* 1995; **25:** 473–4.
6. Agraharkar M, *et al.* Carboplatin-related hematuria and acute renal failure. *Am J Kidney Dis* 1998; **32:** E5.
7. Butani L, *et al.* End-stage renal disease after high-dose carboplatinum in preparation of autologous stem cell transplantation. *Pediatr Transplant* 2003; **7:** 408–12.
8. Tarrass F, *et al.* End-stage renal disease following carboplatin chemotherapy for a nasopharyngeal carcinoma. *Ren Fail* 2007; **29:** 1049–51.

Hypersensitivity. In one series, 12% of 205 patients treated with carboplatin developed a hypersensitivity reaction after a median of 8 courses of platinum therapy.[1] Symptoms were at least moderately severe in half of the patients. Reactions to cisplatin might be anticipated in patients who have been previously sensitised to carboplatin although they do not necessarily occur (see p. 768.1). In another study,[2] patients receiving more than 7 courses of carboplatin therapy were given a skin test before each course in an attempt to identify patients at risk for hypersensitivity reactions. The test consisted of 0.02 mL of an undiluted aliquot of their planned infusion, injected intradermally 1 hour before the dose. A negative skin test accurately predicted the absence of a hypersensitivity reaction. In a further extended report[3] by the same group, the skin test had been given about 30 minutes before carboplatin doses in 126 women who had already received at least 6 courses of a platinum-based regimen for a gynaecological cancer. Of 668 negative skin tests, a hypersensitivity reaction developed on 10 occasions (in 7 patients), giving a false-negative rate of 1.5%. None of the reactions were severe. Of the 39 patients who had a positive skin test, 7 elected to receive the dose of carboplatin; 6 of these developed a hypersensitivity reaction but none were severe.

The use of a desensitisation regimen has been successful in a small number of patients,[4,5] although others have not found it useful.[6]

1. Markman M, *et al.* Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999; **17:** 1141–5.
2. Zanotti KM, *et al.* Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol* 2001; **19:** 3126–9.
3. Markman M, *et al.* Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003; **21:** 4611–14.
4. Markman M, *et al.* Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol* 2004; **130:** 25–8.
5. Genc DB, *et al.* Clinical features and management of carboplatin-related hypersensitivity reactions in pediatric low-grade glioma. *Support Care Cancer* 2012; **20:** 385–93.
6. Lafay-Cousin L, *et al.* Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. *Cancer* 2008; **112:** 892–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carboplatin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. For a report of the successful use of carboplatin-based chemotherapy during pregnancy, with no adverse effects on the infant, see Pregnancy, under Cisplatin, p. 768.2.

Interactions

As for Cisplatin, p. 768.2. When used with docetaxel, clearance of carboplatin has been reported to be about 50% higher than values reported for carboplatin monotherapy.

Pharmacokinetics

Intravenous carboplatin exhibits a biphasic elimination and is excreted mainly in the urine, about 70% of a dose being excreted within 24 hours, the majority in the first 6 hours. About a third of a dose is excreted unchanged. The terminal half-life (as free platinum) is reported to be about 6 hours. (For the effect of docetaxel on carboplatin clearance, see Interactions, above.) Platinum from carboplatin slowly becomes protein bound, and is subsequently excreted with a half-life of 5 days or more.

References.

1. van der Vijgh WJF. Clinical pharmacokinetics of carboplatin. *Clin Pharmacokinet* 1991; **21:** 242–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Carbokebir; Carboplat; Carboxtie; Omilipis; TCO-Carbo; ***Belg.***: Carbosin; ***Braz.***: B-Platin; Biocarbo; Citoplatina; Fauldcarbo; Kemocarb; Oncoplatin; Paraplatin; Platamine; Tecnocarb; Tevacarbo; Vancel; ***Chile***: Oncocarb†; Paraplatin†; ***China***: Bobei (波贝); Paraplatin (伯尔定); ***Cz.***: Carbomedac; Carbosol; Cycloplatin; ***Denm.***: Carbomedac; ***Fin.***: Carbosin; Paraplatin†; ***Fr.***: Paraplatine†; ***Ger.***: Axicarb; Carbo-cell; Carbomedac; Haemato-carb; Neocarbo†; Ribocarbo; ***Gr.***: Carboplamin; Carboplan; Carbosin; Emorzim; Megaplatin; Paraplatin; Vadeplatin; ***Hong Kong***: Paraplatin; ***Hung.***: Cycloplatin; Paraplatin†; ***India***: Biocarb; Blastocarb; Blastoplatin; Carbokem; Carbopa; Carboplan; Carboteen; Carbotinal; Cytocarb; Ducarb; Karplat; Kemocarb; Naproplat; Neocarb; Neoplatin; Oncocarbin; Paraplatin; ***Indon.***: Actoplatin; Carbosin; Paraplatin†; ***Irl.***: Paraplatin†; ***Ital.***: Paraplatin; ***Malaysia***: Carbosin†; ***Mex.***: Acoplasic; Bagotanilo†; Blastocarb; Boplatex; Carboplat; Carbotec; Ifacap†; Kemocarb; Paraplatin; ***Neth.***: Carbosin; ***NZ***: Carbaccord; Paraplatin†; ***Philipp.***: Biovinate; Bonaplatin†; Carbosin; Carbotinol; Crobextin†; Kemocarb; Naproplat; Paraplatin†; ***Pol.***: Cycloplatin†; Paraplatin†; ***Port.***: Nealorin†; Novoplatinum; ***Rus.***: Blastocarb (Бластокарб); Carbotera (Карботера); Cycloplatin (Циклоплатин); Paract (Паракт); Paraplatin (Параплатин); ***S.Afr.***: Carbosin; Paraplatin†; ***Singapore***: Carbotinol; Paraplatin; ***Spain***: Paraplatin; ***Swed.***: Paraplatin†; ***Switz.***: Paraplatin; ***Thai.***: Blastocarb; Carbosin; Kemocarb; Neoplatin; Paraplatin; ***Turk.***: Carbodex; Carbosin; Carmen; Paraplatin†; Platinwas; ***UK***: Paraplatin; ***USA***: Paraplatin; ***Venez.***: Bioplatinex; Oplat.

Pharmacopoeial Preparations
BP 2014: Carboplatin Injection;
USP 36: Carboplatin for Injection.

Carfilzomib *(USAN, rINN)*

Carfilzomibum; PR-171; Карфильзомиб.
(2*S*)-*N*-{(1*S*)-1-Benzyl-2-[{(1*S*)-3-methyl-1-[[(2*R*)-2-methyloxiran-2-yl]carbonyl}butyl)amino]-2-oxoethyl}-4-methyl-2-({(2*S*)-2-[(morpholin-4-ylacetyl)amino]-4-phenylbutanoyl}amino) pentanamide.
$C_{40}H_{57}N_5O_7$=719.9
CAS — 868540-17-4.
UNII — 72X6E3J5AR.

Uses and Administration

Carfilzomib is an irreversible inhibitor of the 20S proteasome, a core unit within the 26S proteasome (see also Bortezomib, p. 752.1), that disrupts tumour cell turnover and induces apoptosis. It is used for the treatment of multiple myeloma (p. 699.2) in patients who have received at least 2 prior therapies including bortezomib and an immune modulator, and whose disease has progressed on or within 60 days of completing the last therapy. Carfilzomib is given intravenously over 2 to 10 minutes on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest to give a 28-day treatment cycle. In cycle 1, a dose of carfilzomib 20 mg/m^2 is given. If tolerated, the dose is increased in subsequent cycles to 27 mg/m^2. Treatment may be continued until disease progression or unacceptable toxicity occurs.

The dose of carfilzomib should be calculated using the patient's actual body-surface at baseline up to a maximum of 2.2 m^2. Dose adjustments only need to be made when the patient's weight shows greater than 20% change from the previous measurement.

To reduce the incidence and severity of infusion reactions premedication with dexamethasone 4 mg orally or intravenously should be given before each dose of carfilzomib in cycle 1, and before each dose during the first cycle of dose escalation. Premedication with dexamethasone should also be used if infusion reactions develop or reappear in subsequent cycles.

Doses should be modified if toxicity occurs, see Administration in Subsequent Cycles, below.

References.

1. Khan ML, Stewart AK. Carfilzomib: a novel second-generation proteasome inhibitor. *Future Oncol* 2011; **7:** 607–12.
2. Khan RZ, Badros A. Role of carfilzomib in the treatment of multiple myeloma. *Expert Rev Hematol* 2012; **5:** 361–72.

Administration in subsequent cycles. Intravenous doses of carfilzomib should be modified if marked toxicity occurs. Doses can be decreased from 27 mg/m^2 to 20 mg/m^2 (one dose level), or from 20 mg/m^2 to 15 mg/m^2 (one dose level). For specific toxicities, the following adjustments are recommended:

For *haematological toxicity* (grade 3 or 4 neutropenia and grade 4 thrombocytopenia), carfilzomib should be withheld. If there is full recovery before the next scheduled dose, carfilzomib may be continued at the same dose. If there is recovery to grade 2 neutropenia or grade 3 thrombocytopenia, carfilzomib should be reduced by one dose level. If tolerated, the reduced dose may be increased to the previous level.

For *cardiotoxicity* (grade 3 or 4, new-onset or worsening of heart failure, decreased left ventricular function, or myocardial ischaemia), *pulmonary complications* (grade 3 or 4), *pulmonary hypertension*, *hepatotoxicity* (grade 3 or 4 increases in liver transaminases, bilirubin, or other liver abnormality), or peripheral neuropathy (grade 3 or 4), carfilzomib should be withheld until toxicity has resolved or organ function has returned to baseline. A reduction of carfilzomib by one dose level should be considered when restarting treatment. If tolerated, the reduced dose may be increased to the previous level.

For *renal toxicity* (serum creatinine ≥twice baseline), carfilzomib should be withheld until renal function has returned to grade 1 or baseline. If toxicity is due to carfilzomib, treatment should be reduced by one dose level when restarting. However, if toxicity is not due to carfilzomib, treatment may be restarted at the previous dose. If tolerated, the reduced dose may be increased to the previous level.

Adverse Effects and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of carfilzomib include fatigue, fever, gastrointestinal disturbances, and dyspnoea; treatment should be withheld if dyspnoea occurs. Anaemia

and thrombocytopenia are also very common. The platelet count should be monitored frequently during treatment; the nadir of the count usually occurs around day 8. Other haematological toxicities such as neutropenia, lymphopenia, and leucopenia also occur commonly. Neutropenia and thrombocytopenia may be dose limiting.

Other common adverse reactions include peripheral neuropathy, headache, cough, peripheral oedema, pain, insomnia, muscle spasms, asthenia, electrolyte disturbances, respiratory-tract infections, dizziness, hypoaesthesia, anorexia, hyperglycaemia, and increases in blood creatinine. Acute renal failure has been reported.

Cardiovascular adverse effects include hypertension, myocardial ischaemia, and myocardial infarction. Pulmonary hypertension and new onset or worsening of pre-existing heart failure have been reported. Carfilzomib should be withheld or stopped if serious cardiac events occur.

Infusion reactions can occur immediately following, or up to 24 hours after, carfilzomib administration. Reactions include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, dyspnoea, hypotension, syncope, chest tightness, or angina. Dexamethasone should be given before carfilzomib infusions, see Uses and Administration, p. 760.3.

Tumour lysis syndrome has been reported with carfilzomib; patients with multiple myeloma and a high tumour burden may be at increased risk. If tumour lysis syndrome occurs, treatment should be interrupted until symptoms have resolved.

Hepatotoxicity may occur with increases in liver enzyme values and bilirubin. Hepatic failure has been reported. Liver enzymes should be monitored frequently and treatment withheld for severe increases in transaminases, bilirubin, or other liver abnormalities.

Reactivation of herpes zoster has occurred and antiviral prophylaxis should be considered for patients with a history of herpes zoster infection.

Pharmacokinetics

Carfilzomib was about 97% bound to plasma proteins when tested *in vitro*. It is rapidly and extensively metabolised. The main metabolic pathways are peptidase cleavage and epoxide hydrolysis to inactive metabolites. Cytochrome P450 isoenzymes play only a minor role in the overall metabolism. Carfilzomib is rapidly cleared with a half-life of 1 hour or less on day 1 of cycle 1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Kyprolis.

Carmofur *(rINN)*

Carmofurum; HCFU; Karmofuuri; Кармофур.
5-Fluoro-*N*-hexyl-3,4-dihydro-2,4-dioxo-1-(2*H*)-pyrimidinecarboxamide; 1-Hexylcarbamoyl-5-fluorouracil.
$C_{11}H_{16}FN_3O_3$=257.3
CAS — 61422-45-5.
ATC — L01BC04.
ATC Vet — QL01BC04.
UNII — HA82M3RAB2.

Pharmacopoeias. In *Chin.* and *Jpn*.

Profile

Carmofur is an orally active derivative of fluorouracil (p. 795.2) and has similar actions. It is used in the adjuvant treatment of colorectal and breast cancer, and has also been used in ovarian cancer. Carmofur has been associated with the development of neurological disorders including leukoencephalopathy. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

References.

1. Yamada T, *et al*. Leukoencephalopathy following treatment with carmofur: a case report and review of the Japanese literature. *Asia Oceania J Obstet Gynaecol* 1989; **15:** 161–8.
2. Sakamoto J, *et al*. An individual patient data meta-analysis of long supported adjuvant chemotherapy with oral carmofur in patients with curatively resected colorectal cancer. *Oncol Rep* 2001; **8:** 697–703.
3. Nakamura T, *et al*. Optimal duration of oral adjuvant chemotherapy with Carmofur in the colorectal cancer patients: the Kansai Carmofur Study Group trial III. *Int J Oncol* 2001; **19:** 291–8.
4. Tominaga T, *et al*. Postoperative chemoendocrine therapy for women with node-positive stage II breast cancer with combined cyclophosphamide, tamoxifen, and 1-hexylcarbamoyl-5-fluorouracil. *Eur J Surg* 2001; **167:** 598–604.
5. Iwagaki H, *et al*. Post-operative adjuvant chemotherapy for colorectal cancer with 5-fluorouracil (5-FU) infusion combined with 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration after curative resection. *Anticancer Res* 2001; **21:** 4163–8.
6. Morimoto K, Koh M. Postoperative adjuvant use of carmofur for early breast cancer. *Osaka City Med J* 2003; **49:** 77–83.
7. Tominaga T, *et al*. 1-Hexylcarbamoyl-5-fluorouracil + cyclophosphamide + tamoxifen versus CMF + tamoxifen in women with lymph node-positive breast cancer after primary surgery: a randomized controlled trial. *Oncol Rep* 2004; **12:** 797–803.
8. Sakamoto J, *et al*. An individual patient data meta-analysis of adjuvant therapy with carmofur in patients with curatively resected colon cancer. *Jpn J Clin Oncol* 2005; **35:** 536–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Mifurol (唏福禄); ***Fin.***: Mirafur†; ***Jpn***: Mifurol†.

Carmustine *(BAN, USAN, rINN)*

BCNU; BiCNU; Carmustin; Carmustina; Carmustinum; Karmustiini; Karmustin; Karmustinas; Karmusztin; NSC-409962; WR-139021; Кармустин.
1,3-Bis(2-chloroethyl)-1-nitrosourea.
$C_5H_9Cl_2N_3O_2$=214.0
CAS — 154-93-8.
ATC — L01AD01.
ATC Vet — QL01AD01.
UNII — U68WG3173Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Carmustine). A yellowish, granular powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. It melts at about 31 degrees with decomposition. Store at a temperature of 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Carmustine). Light yellow powder. Freely soluble in ether. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Stability. Licensed product information states that, when reconstituted, resulting carmustine solutions (undiluted or further diluted in sodium chloride 0.9% or glucose 5%) are stable for 8 hours at room temperature, or 24 hours at 2 degrees to 8 degrees, when protected from light. Carmustine is adsorbed onto PVC giving sets and containers, and polyethylene or glass should be used.

A study has indicated that diluted solutions of carmustine undergo increased degradation in the presence of sodium bicarbonate, with only 73% of the original concentration of carmustine remaining after 90 minutes, much of the loss being in the first 15 minutes.[1]

1. Colvin M, *et al*. Stability of carmustine in the presence of sodium bicarbonate. *Am J Hosp Pharm* 1980; **37:** 677–8.

Uses and Administration

Carmustine is a cell-cycle phase non-specific antineoplastic belonging to the nitrosourea group of compounds, which are considered to function as alkylating agents. It is believed to alkylate DNA and RNA, and may also inhibit enzymatic processes by carbamoylation of amino acids in proteins. Carmustine is used in the treatment of brain tumours, and in combination chemotherapy for multiple myeloma. It may be given as second-line therapy in Hodgkin's disease, non-Hodgkin's lymphoma, and some other malignancies (see below).

Carmustine is licensed for use as a single agent either as a single dose of 150 to 200 mg/m^2 or divided into doses of 75 to 100 mg/m^2 given on 2 successive days. Doses are given by intravenous infusion over 1 to 2 hours in sodium chloride 0.9% or glucose 5%. Lower doses are usually given in combination therapy. Doses may be repeated every 6 weeks provided that blood counts have returned to acceptable levels. Subsequent doses must be adjusted according to the haematological response (see also Bone-marrow Depression, p. 730.3).

Polymer implants containing carmustine have been developed for implantation into the brain in the localised treatment of high-grade malignant glioma or recurrent glioblastoma multiforme. Each implant contains 7.7 mg of carmustine: up to 8 such implants are inserted into the cavity left by surgical removal of the tumour.

Amyloidosis. For mention of chemotherapy with epirubicin, cyclophosphamide, and carmustine to suppress amyloidosis after cardiac transplantation, see p. 819.3.

Malignant neoplasms. Carmustine has been used in chemotherapeutic regimens for several malignancies. Because of its ability to pass the blood-brain barrier it has been extensively used in malignant neoplasms of the brain (p. 701.2). As an extension of such use, carmustine-releasing wafers have been implanted directly into the brain.[1-3] In a multicentre study[4] in patients with recurrent malignant glioma, biodegradable poly(carboxyphenoxypropane/sebacic acid)anhydride polymer wafers containing carmustine implanted into the brain after tumour resection produced a median survival of 31 weeks compared with 23 weeks for placebo. A subsequent small cohort study[5] failed to find a clear survival benefit associated with wafer implantation in recurrent glioma, and reported a higher rate of complications including seizures, cerebral oedema, CSF leaks, sepsis, and wound infections. The limitations of this small study were acknowledged by the authors, and a review[6] that included these studies concluded that despite limited data, carmustine wafers do provide some survival benefit. A randomised study in 240 patients found that treatment with carmustine wafers reduced the risk of death by 28% compared with placebo;[7] this survival advantage was maintained at 1, 2, and 3 years, with statistical significance at 3 years.[8] The adverse effect profile was similar for carmustine and placebo groups,[7] and retrospective reviews[2,9] found carmustine wafers to be well tolerated with a low incidence of surgical complications such as infection. However, it was noted that, in some patients, neurological symptoms developed during an attempted tapering of dexamethasone dosage after carmustine with radiotherapy and that close supervision of patients is warranted. Treatment effects or necrosis can radiographically mimic recurrent tumour in a proportion of patients;[9] implantation of wafers caused morphological changes of the brain immediately adjacent to the implants.[10] There is considerable interest in multimodal therapy, using adjuvant temozolomide and radiotherapy after surgery and implantation of carmustine wafers.[3]

Other conditions in which carmustine has been used include malignant melanoma (p. 714.3) and Hodgkin's disease (p. 696.1).

1. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. *Expert Rev Anticancer Ther* 2008; **8:** 343–59.
2. Attenello FJ, *et al*. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol* 2008; **15:** 2887–93.
3. La Rocca RV, Mehdorn HM. Localized BCNU chemotherapy and the multimodal management of malignant glioma. *Curr Med Res Opin* 2009; **25:** 149–60.
4. Brem H, *et al*. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995; **345:** 1008–12.
5. Subach BR, *et al*. Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 1999; **45:** 17–23.
6. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. *Surg Neurol* 2000; **53:** 458–64.
7. Westphal M, *et al*. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncol* 2003; **5:** 79–88.
8. Westphal M, *et al*. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148:** 269–75.
9. Kleinberg LR, *et al*. Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 2004; **22:** 1–9.
10. Giese A, *et al*. Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004; **66:** 351–60.

Mycosis fungoides. Topical application of carmustine has been used successfully[1-5] in early mycosis fungoides (p. 698.3). Erythema and telangiectasia were the most frequent adverse effects.

1. Zackheim HS, *et al*. Topical carmustine (BCNU) for mycosis fungoides and related disorders: a 10-year experience. *J Am Acad Dermatol* 1983; **9:** 363–74.
2. Zackheim HS, *et al*. Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990; **22:** 802–10.
3. Zackheim HS. Topical carmustine (BCNU) for patch/plaque mycosis fungoides. *Semin Dermatol* 1994; **13:** 202–6.
4. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. *J Am Acad Dermatol* 2000; **42:** 283–5.
5. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. *Dermatol Ther* 2003; **16:** 299–302.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2. Delayed and cumulative bone-marrow depression is the most frequent and serious adverse effect of intravenous carmustine. Platelets and leucocytes are mainly affected, with platelet nadirs occurring at 4 to 5 weeks after a dose and leucocyte nadirs at 5 to 6 weeks; although thrombocytopenia is usually more severe, leucopenia may also be dose-limiting. Other adverse effects include pulmonary fibrosis (mainly but not exclusively at high cumulative doses—see also Effects on the Lungs, p. 729.1), renal and hepatic damage, and neuroretinitis. Nausea and vomiting, beginning up to 2 hours after a dose, is common but can be reduced by prophylactic antiemetic therapy. Venous irritation may follow intravenous injection and transient hyperpigmentation has been noted after contact of a solution with the skin. Flushing of the skin and suffusion of the conjunctiva may occur on rapid intravenous infusion. Hypotension, tachycardia, chest pain, headache, and hypersensitivity reactions have been reported.

Convulsions, cerebral oedema, and various neurological symptoms have been reported in patients given carmustine-containing polymer implants; abnormalities of wound

healing at the site of implantation, and an increased incidence of intracranial infection have also been reported.

As with other alkylating agents, carmustine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the eyes. Ocular toxicity has been reported in patients given carmustine,[1,2] and seems to be more likely when given into the carotid artery,[1,2] although it was also seen with high-dose intravenous therapy. There is some evidence that the alcohol diluent used to prepare carmustine solutions may contribute to the retinopathy.[2]

1. Shingleton BJ, *et al.* Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol* 1982; **100:** 1766–72.
2. Greenberg HS, *et al.* Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system. *J Neurosurg* 1984; **61:** 423–9.

Effects on the lungs. Studies have found a high incidence of fatal pulmonary fibrosis (see also Effects on the Lungs, p. 729.1) in patients treated with carmustine for gliomas during childhood; patients who were treated before 5 or 6 years of age were more likely to die of pulmonary fibrosis than those treated at a later age.[1,2] However, there are reports of pulmonary toxicity and upper lobe pulmonary fibrosis occurring in adults given carmustine and high-dose chemotherapy.[3]

1. O'Driscoll BR, *et al.* Late carmustine lung fibrosis: age at treatment may influence severity and survival. *Chest* 1995; **107:** 1355–7.
2. Lohani S, *et al.* 25-year study of lung fibrosis following carmustine therapy for brain tumor in childhood. *Chest* 2004; **126:** 1007.
3. Parish JM, *et al.* Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. *Mayo Clin Proc* 2003; **78:** 630–4.

Extravasation. For mention of the use of sodium bicarbonate as a specific antidote after carmustine extravasation, see under Treatment of Adverse Effects of Antineoplastics, p. 731.3.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Carmustine should be used with extreme caution in children, who are at particular risk of severe delayed pulmonary toxicity. It should also be used with caution in patients with reduced lung function. Lung function should be monitored before and frequently during therapy. Blood counts should be monitored weekly during therapy, and for at least 6 weeks after the last dose. Renal and hepatic function should also be monitored periodically.

Patients undergoing craniotomy for malignant glioma and implantation of carmustine wafers should be monitored closely for complications, including seizures, intracranial infections, abnormal wound healing, and brain oedema. Brain oedema and compression (intracerebral mass effect) due to tumour recurrence, infection, or necrosis, may require further surgery or the removal of carmustine wafers.

Handling and disposal. Carmustine has been shown to permeate latex, PVC, and rubber gloves, the degree of permeation tending to increase with time,[1-3] up to an equilibrium value.[2] The permeation rate appears not to depend solely on glove thickness and material, and may be different for different gloves made from the same material.[2] The time for initial penetration was reported to vary between 4.7 and 66.0 minutes in one study,[2] and gloves could be chosen accordingly depending on the anticipated length of exposure. Double-gloving, particularly with thicker PVC[1] or ethylmethacrylate[3] gloves, may offer some additional protection.

1. Connor TH, *et al.* Permeability of latex and polyvinyl chloride gloves to carmustine. *Am J Hosp Pharm* 1984; **41:** 676–9.
2. Thomas PH, Fenton-May V. Protection offered by various gloves to carmustine exposure. *Pharm J* 1987; **238:** 775–7.
3. Mellström GA, *et al.* Barrier effect of gloves against cytostatic drugs. *Curr Probl Dermatol* 1996; **25:** 163–9.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Cimetidine. Reductions in white cell counts and platelet counts well below those normally attributed to treatment with carmustine alone were seen in 6 of 8 patients receiving their first course of carmustine and corticosteroids with cimetidine given prophylactically,[1] and in 9 patients in a further study.[2] Cimetidine was also reported to exacerbate the neutropenia and leucopenia in a patient receiving lomustine.[3]

1. Selker RG, *et al.* Bone-marrow depression with cimetidine plus carmustine. *N Engl J Med* 1978; **299:** 834.
2. Volkin RL, *et al.* Potentiation of carmustine-cranial irradiation-induced myelosuppression by cimetidine. *Arch Intern Med* 1982; **142:** 243–5.
3. Hess WA, Kornblith PL. Combination of lomustine and cimetidine in the treatment of a patient with malignant glioblastoma: a case report. *Cancer Treat Rep* 1985; **69:** 733.

Pharmacokinetics

Intravenous carmustine is rapidly metabolised, and no intact drug is detectable after 15 minutes; metabolites have a much longer half-life and are presumed to be responsible for its activity. It is mainly excreted in the urine; some is also excreted as carbon dioxide, via the lungs. Carmustine readily crosses the blood-brain barrier, appearing in CSF in substantial concentrations almost immediately after intravenous injection. Carmustine diffuses from polymer implants into surrounding brain tissue; however, tissue and plasma concentrations after implantation have not been determined.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: BiCNU; ***Austral.***: BiCNU; Gliadel; ***Austria***: Carmubris; ***Braz.***: Becenun; ***Canad.***: BiCNU; ***Chile***: BiCNU; ***Cz.***: BiCNU; ***Fr.***: BiCNU; Gliadel; ***Ger.***: Carmubris†; Gliadel; ***Gr.***: BiCNU; Carmubris; Gliadel; Nitrumon; ***Hung.***: BiCNU; ***Irl.***: BiCNU†; Gliadel; ***Israel***: Gliadel; ***Ital.***: Gliadel; ***Jpn***: Gliadel; ***Malaysia***: Gliadel; ***Mex.***: BiCNU; ***Neth.***: Gliadel; ***NZ***: BiCNU; ***Philipp.***: BiCNU†; ***Port.***: Gliadel; ***S.Afr.***: BiCNU†; Gliadel; ***Singapore***: BiCNU; Gliadel; ***Spain***: Gliadel; ***Thai.***: Gliadel†; ***Turk.***: Nitrumon; ***UK***: Gliadel; ***USA***: BiCNU; Gliadel; ***Venez.***: BiCNU.

Pharmacopoeial Preparations
USP 36: Carmustine for Injection.

Catumaxomab *(rINN)*

Catumaxomabum; Катумаксомаб.

Immunoglobulin G2a, anti-(human antigen 17-1A) (mouse monoclonal Ho-3/TP-A-01/TPBs01 heavy chain), disulfide with mouse monoclonal Ho-3/TP-A-01/TPBs01 light chain, disulfide with immunoglobulin G2b anti-(human CD3 (antigen)) (rat monoclonal 26/II/6-1.2/TPBs01 heavy chain), bidisulfide with rat monoclonal 26/II/6-1.2/TPBs01 light chain.

CAS — 509077-98-9.
ATC — L01XC09.
ATC Vet — QL01XC09.

Uses and Administration

Catumaxomab is a rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule EpCAM, which is overexpressed in most carcinomas, and the CD3 antigen; a third binding site enables interaction with accessory immune cells. These binding properties induce a reaction against tumour cells which includes T-cell activation, antibody-dependent cell mediated cytotoxicity, complement-dependent cytotoxicity, and phagocytosis.

Catumaxomab is used for the intraperitoneal treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible. Catumaxomab is diluted with sodium chloride 0.9% in polypropylene syringes before infusion via a constant infusion pump system. Four intraperitoneal infusions are given:

- first dose (day 0): 10 micrograms in 10 mL sodium chloride (total volume 10.1 mL)
- second dose (day 3): 20 micrograms in 20 mL sodium chloride (total volume 20.2 mL)
- third dose (day 7): 50 micrograms in 49.5 mL sodium chloride (total volume 50 mL)
- fourth dose (day 10): 150 micrograms in 48.5 mL sodium chloride (total volume 50 mL)

At least 2 days must elapse between infusions; this interval can be prolonged in the event of adverse reactions, but the overall treatment period should not exceed 20 days.

Catumaxomab is also under investigation for the treatment of gastric cancer.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Infusion-related reactions characteristic of a cytokine release syndrome (including fever, nausea, vomiting, chills, dyspnoea, and hypotension or hypertension) occur commonly with catumaxomab. A systemic inflammatory response syndrome (SIRS) may also occur; this generally develops within 24 hours of infusion, and manifests as fever, tachycardia, tachypnoea, and leucocytosis. Premedication with analgesics, antipyretics, or NSAIDs is recommended as prophylaxis for both syndromes.

Myelosuppression is common with catumaxomab. Other common adverse effects include tachycardia, vertigo, gastrointestinal disturbances, hyperbilirubinaemia, hepatitis, electrolyte imbalances (hyponatraemia, hypocalcaemia, hypokalaemia), hyperglycaemia, arthralgia, myalgia, headache, dizziness, anxiety, insomnia, and renal disorders such as proteinuria and haematuria. Ileus and abdominal pain may be serious. Skin and subcutaneous reactions are also common, and may be severe. Uncommon adverse effects, which may be serious, include pulmonary embolism, pleural effusion, acute renal failure, convulsions, intestinal obstruction, gastric haemorrhage, and extravasation. Infections are common, and can be severe; use of catumaxomab is not recommended during acute infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Removab; ***Cz.***: Removab; ***Denm.***: Removab; ***Fr.***: Removab; ***Ger.***: Removab; ***Irl.***: Removab; ***Israel***: Removab; ***Neth.***: Removab; ***Norw.***: Removab; ***Pol.***: Removab; ***Port.***: Removab; ***Swed.***: Removab; ***UK***: Removab.

Cediranib *(BAN, rINN)*

AZD-2171; Cédiranib; Cediranibum; Цедираниб.

4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline.

$C_{25}H_{27}FN_4O_3$=450.5

CAS — 288383-20-0.
UNII — NQU9IPY4K9.

NOTE. The name Recentin has been used as a trade mark for cediranib.

Cediranib Maleate *(BANM, USAN, rINNM)*

AZD-2171 maleate; Cédiranib, Maléate de; Cediranibi Maleas; Maleato de cediranib; Цедираниба Малеат.

4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline(2*Z*)-but-2-enedioate.

$C_{25}H_{27}FN_4O_3,C_4H_4O_4$=566.6

CAS — 857036-77-2.
UNII — 68AYS9A614.

Profile

Cediranib is an inhibitor of tyrosine kinase associated with the vascular endothelial growth factor (VEGF) receptor. It is under investigation for the treatment of recurrent glioblastoma. It has been investigated for metastatic colorectal cancer and non-small cell lung cancer but results were disappointing. Adverse effects include hypertension and proteinuria.

References.

1. Robertson JD, *et al.* Phase III trial of FOLFOX plus bevacizumab or cediranib (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III. *Clin Colorectal Cancer* 2009; **8:** 59–60.
2. Langenberg MH, *et al.* Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: results from a phase II randomized, factorial, double-blind study of cediranib in patients with advanced solid tumors. *J Clin Oncol* 2009; **27:** 6152–9.
3. Dietrich J, *et al.* Cediranib: profile of a novel anti-angiogenic agent in patients with glioblastoma. *Expert Opin Invest Drugs* 2009; **18:** 1549–57.
4. Robinson ES, *et al.* Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clin J Am Soc Nephrol* 2010; **5:** 477–83.
5. Goss GD, *et al.* Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. *J Clin Oncol* 2010; **28:** 49–55.
6. Batchelor TT, *et al.* Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol* 2010; **28:** 2817–23.

Cetuximab *(USAN, rINN)*

C-225; Cétuximab; Cetuximabum; IMC-C225; Цетуксимаб.

Immunoglobulin G1 (human-mouse monoclonal C225 γ1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ-chain, dimer.

CAS — 205923-56-4.
ATC — L01XC06.
ATC Vet — QL01XC06.
UNII — PQX0D8J21J.

Stability. Cetuximab 2 mg/mL was physically stable when stored for 14 days at 4 degrees in either PVC infusion bags or the opened original glass vial.[1]

1. Ikesue H, *et al.* Stability of cetuximab and panitumumab in glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2010; **67:** 223–6.

Uses and Administration

Cetuximab is a chimeric monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). Signal transduction through the EGFR results in activation of the protein expressed by the wild-type *KRAS* gene (Kirsten rat sarcoma 2 viral oncogene homologue), which plays a role in cell growth regulation and angiogenesis. In patients with

KRAS gene mutations, activation of the *KRAS* protein is independent of EFGR regulation and cetuximab is ineffective. It is, however, used in the treatment of EGFR-expressing, *KRAS* wild-type, metastatic colorectal cancer (p. 706.3). Cetuximab may be used first-line with fluorouracil-based combinations such as the FOLFOX (infusional fluorouracil, folinic acid, and oxaliplatin) or FOLFIRI (fluorouracil, folinic acid, and irinotecan) regimens. It is also used with irinotecan in patients refractory to irinotecan-based chemotherapy, or as monotherapy in patients intolerant to irinotecan-based regimens or after failure of both oxaliplatin- and irinotecan-based regimens. Cetuximab with radiotherapy may be used for the treatment of locally advanced squamous cell cancer of the head and neck (p. 708.1). It is also used with platinum-based chemotherapy for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck, and as monotherapy in those for whom prior platinum-based therapy has failed. It is under investigation for non-small cell lung cancer and other solid tumours.

For all indications, cetuximab 400 mg/m^2 is given as a loading dose by intravenous infusion over 2 hours. This is followed by once weekly maintenance doses of 250 mg/m^2 given over 1 hour. The maximum infusion rate is 10 mg/min. Premedication with a histamine H_1-antagonist and corticosteroids is recommended, and patients should be closely monitored for at least 1 hour after the end of the cetuximab infusion. A low-protein-binding 0.22-micrometre in-line filter should be used, and the infusion given via an infusion or syringe pump.

In combined therapy for colorectal cancer, chemotherapy should not be given for at least 1 hour after the end of cetuximab infusion. In head and neck carcinoma, cetuximab therapy is started one week before radiation therapy and continued until the end of the radiation therapy period. Cetuximab is usually given 1 hour before radiation therapy. When used as monotherapy, cetuximab is continued until disease progression or unacceptable toxicity occurs.

The infusion rate should be permanently reduced in patients who have had a mild to moderate infusion reaction, and cetuximab should be immediately and permanently stopped if a severe reaction has occurred (see Adverse Effects and Precautions, below). When a severe acneform rash has occurred, the next dose should be delayed by 1 to 2 weeks. After the first occurrence, the full maintenance dose may be given if there has been improvement in the rash; after a second occurrence the next dose should be delayed and reduced to 200 mg/m^2; after a third occurrence the next dose should be delayed and reduced to 150 mg/m^2. If there is no improvement in the rash when therapy has been delayed, or if the rash has occurred 4 times, cetuximab should be stopped.

References.

1. NICE. Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (issued June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA145Guidance.pdf (accessed 03/09/09)
2. NICE. Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck (issued June 2009). Available at: http://www.nice.org.uk/nicemedia/live/12179/44644/44644.pdf (accessed 14/11/12)
3. NICE. Cetuximab for the first-line treatment of metastatic colorectal cancer (issued August 2009). Available at: http://www.nice.org.uk/nicemedia/live/12216/45198/45198.pdf (accessed 14/11/12)
4. Gerber DE, Choy H. Cetuximab in combination therapy: from bench to clinic. *Cancer Metastasis Rev* 2010; **29:** 171–80.
5. Frampton JE. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck. *Drugs* 2010; **70:** 1987–2010.
6. Broadbridge VT, *et al*. Cetuximab in metastatic colorectal cancer. *Expert Rev Anticancer Ther* 2012; **12:** 555–65.
7. Carillio G, *et al*. Cetuximab in non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2012; **12:** 163–75.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Adverse effects associated with cetuximab include skin reactions, asthenia, and gastrointestinal disturbances. Skin reactions present mainly as an acneform rash, and, if severe, require dosage adjustment (see Uses and Administration, p. 762.3). Sun exposure should be limited. Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. Mild reactions include chills, fever, and dyspnoea; severe reactions include bronchospasm, urticaria, hypotension or hypertension, and loss of consciousness, and fatalities have occurred. Premedication with a histamine H_1-antagonist and corticosteroids is recommended, and dose adjustment may be necessary (see Uses and Administration, p. 762.3). Cardiopulmonary arrest and/or sudden death has been reported in patients treated with cetuximab and radiation therapy, and cetuximab should be given with caution to head and neck cancer patients with coronary artery disease, congestive cardiac failure, or arrhythmias. Radiation dermatitis has also been reported with cetuximab. Cardiotoxicity may be increased when cetuximab is used with fluorouracil. When used with platinum compounds, the frequency of severe leucopenia or severe neutropenia may be increased, leading to infectious complications such as febrile neutropenia, pneumonia, and sepsis. Hypomagnesaemia can occur; patients should be monitored for this and accompanying hypocalcaemia and hypokalaemia before, during, and for up to 8 weeks after stopping therapy. Interstitial lung disease, pulmonary embolism, deep-vein thrombosis, and renal failure have been reported rarely. Common adverse effects include headache, increases in liver enzyme concentrations, and conjunctivitis.

Effects on the nervous system. A 54-year-old man had a generalised seizure within 15 minutes of starting his first infusion of cetuximab;[1] he had been pretreated with ondansetron, ranitidine, diphenhydramine, and dexamethasone. The authors considered the seizure to be an infusion reaction.

1. McClellan NH, Bell WA. Seizure activity during cetuximab infusion in a patient with metastatic colorectal cancer. *Am J Health-Syst Pharm* 2012; **69:** 1881–4.

Effects on the skin, hair, and nails. Acneform follicular rashes have been reported with cetuximab therapy;[1,2] lesions were pustular and papular,[2-4] and commonly occurred on the face, scalp, chest, and upper back.[1-5] The relative risk of developing high-grade rash was estimated to be over 20 times greater in patients given cetuximab than in controls; the incidence was higher in patients with colorectal cancer (12.6%) than in those with other malignancies (6.6%).[6] It has been suggested that there is a relationship between rash and response to therapy or survival, i.e. that rash might be a surrogate marker of cetuximab activity;[7,8] doubling the cetuximab dose in patients without severe initial skin reactions is reported to increase their response rate to therapy.[9] A few cases of lengthening eyelash and eyebrow hair[10] and abnormal growth of chest hair[11] have been described. Paronychia has also been reported,[1,5,12] as have intraoral aphthous ulcers.[1]

Treatment with oral isotretinoin 500 micrograms/kg daily has been reported to successfully clear acneform skin lesions in 2 patients; topical therapy with metronidazole 0.75% gel or erythromycin 1% was also used.[13] Prophylactic oral minocycline 100 mg daily, started on the same day as cetuximab and given for 8 weeks, significantly reduced total facial lesion counts in the first 4 weeks when compared with placebo; this difference tapered by the end of 8 weeks of treatment. Topical tazarotene showed no clinical benefit and caused local irritation that forced tazarotene to be stopped in many patients.[14]

Some have suggested that the clinical findings of papulopustular rash, nail and periungual abnormalities, alterations in hair texture and growth, and dry skin and pruritus, constitute a syndrome unique to the epidermal growth factor receptor (EGFR) inhibitors, believed to be due to EGFR inhibition in the epidermis, hair follicle, and nail matrix.[15] A retrospective study[16] of patients treated with EGFR inhibitors (erlotinib, cetuximab, or panitumumab) for more than 6 months found that all patients had cutaneous adverse effects. However, the frequency of skin changes arising from long-term use was different to effects seen soon after treatment; the incidence of folliculitis diminished over time, whereas paronychia, skin dryness, and hair modifications became more predominant.

Erythema and focal epidermolysis, progressing to severe radiation dermatitis with necrosis, has been reported in patients given radiation therapy with cetuximab.[17]

1. Busam KJ, *et al*. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; **144:** 1169–76.
2. Walon L, *et al*. Éruptions acnéiformes induites par le cétuximab. *Ann Dermatol Venereol* 2003; **130:** 443–6.
3. Kimyai-Asadi A, Jih MH. Follicular toxic effects of chimeric anti-epidermal growth factor receptor antibody cetuximab used to treat human solid tumors. *Arch Dermatol* 2002; **138:** 129–31.
4. Jacot W, *et al*. Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. *Br J Dermatol* 2004; **151:** 238–41.
5. Monti M, *et al*. Cutaneous toxicity induced by cetuximab. *J Clin Oncol* 2003; **21:** 4651–3.
6. Su X, *et al*. Risk of high-grade skin rash in cancer patients treated with cetuximab—an antibody against epidermal growth factor receptor: systemic [sic] review and meta-analysis. *Oncology* 2009; **77:** 124–33.
7. Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol* 2005; **23:** 5235–46.
8. Gatzemeier U, *et al*. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncol* 2011; **12:** 30–7.
9. Van Cutsem E, *et al*. Intrapatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. *J Clin Oncol* 2012; **30:** 2861–8.
10. Dueland S, *et al*. Epidermal growth factor receptor inhibition induces trichomegaly. *Acta Oncol* 2003; **42:** 345–6.
11. Montagut C, *et al*. Abnormal hair growth in a patient with head and neck cancer treated with the anti-epidermal growth factor receptor monoclonal antibody cetuximab. *J Clin Oncol* 2005; **23:** 5273–5.
12. Boucher KW, *et al*. Paronychia induced by cetuximab, an antiepidermal growth factor receptor antibody. *J Am Acad Dermatol* 2002; **47:** 632–3.
13. Gutzmer R, *et al*. Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol* 2005; **153:** 849–51.
14. Scope A, *et al*. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 2007; **25:** 5390–6.
15. Lacouture ME, Lai SE. The PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) syndrome. *Br J Dermatol* 2006; **155:** 852–4.
16. Osio A, *et al*. Cutaneous side-effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. *Br J Dermatol* 2009; **161:** 515–21.
17. Budach W, *et al*. Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med* 2007; **357:** 514–5.

Hypersensitivity. For limited data pointing to a lack of cross-sensitivity between cetuximab and panitumumab, see Hypersensitivity, under Panitumumab, p. 843.2.

For a report of a generalised seizure considered to be an infusion reaction, see Effects on the Nervous System, above.

Hypomagnesaemia. A patient given cetuximab developed profound hypomagnesaemia, requiring intravenous supplementation with up to 10 g magnesium sulfate daily, throughout the duration of cetuximab therapy. This case prompted a review of 154 patients treated with cetuximab, of whom 34 had their magnesium concentrations measured at least once. Among these 34 patients, 6 had grade 3 and 2 had grade 4 hypomagnesaemia; this equated to an incidence of 24% of grade 3/4 hypomagnesaemia. In each of these cases the need for supplementation subsided after stopping cetuximab, with resolution of the hypomagnesaemia within several weeks.[1] However, it was not clear whether all patients had a normal magnesium concentration before treatment, nor was there any indication of the median time to development of hypomagnesaemia.

Another retrospective review of 114 patients did address these issues.[2] It found 48 patients had normal baseline magnesium concentrations before starting cetuximab. Of these 48 evaluable patients, 13 developed grade 3 or grade 4 hypomagnesaemia (27%); median time to onset of grade 3/4 hypomagnesaemia was 5.5 months. There was a significant association between duration of cetuximab therapy and grade of hypomagnesaemia. Magnesium replacement therapy was given to those patients with grade 3/4 toxicity. Initial attempts at oral replacement with up to 1.6 g magnesium oxide three times daily were ineffective, and intravenous supplementation was needed. However, the effects of infusion did not extend beyond 48 to 72 hours, with some patients requiring daily magnesium sulfate infusions of up to 10 g daily. Furthermore, in some patients, magnesium supplementation became less effective with continued cetuximab treatment. Of 3 patients evaluable for recovery from hypomagnesaemia after stopping cetuximab, 2 were found to correct their magnesium concentrations without supplementation after 1 month. However, 1 patient required prolonged and ongoing supplementation for more than 5 months, at 4 g infused 3 times weekly (having received 8 g daily while on cetuximab).[2] A prospective study[3] found that a progressive decrease in serum magnesium concentrations was seen in 97% of patients after treatment with cetuximab, panitumumab, or matuzumab. The authors concluded that magnesium wasting was specifically due to inhibition of the epidermal growth factor receptor (EGFR), and suggested hypomagnesaemia might be a class effect of the monoclonal antibodies directed against EGFR. However, incidence and severity may vary between products. There was also high interindividual variability; increasing age was associated with more severe hypomagnesaemia.

1. Schrag D, *et al*. Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 2005; **97:** 1221–4.
2. Fakih MG, *et al*. Cetuximab-induced hypomagnesemia in patients with colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 152–6.
3. Tejpar S, *et al*. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 2007; **8:** 387–94.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cetuximab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pharmacokinetics

The pharmacokinetics of cetuximab have been reported to be non-linear and dose-dependent. Steady-state concentrations are reached after 3 weeks. Cetuximab has a long elimination half-life of about 70 to 100 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Erbitux; ***Austral.***: Erbitux; ***Austria***: Erbitux; ***Belg.***: Erbitux; ***Braz.***: Erbitux; ***Canad.***: Erbitux; ***Chile***: Erbitux; ***China***: Erbitux (爱必妥); ***Cz.***: Erbitux; ***Denm.***: Erbitux; ***Fin.***: Erbitux; ***Fr.***: Erbitux; ***Ger.***: Erbitux; ***Gr.***: Erbitux; ***Hong Kong***: Erbitux; ***Hung.***: Erbitux; ***India***: Erbitux;

Indon.: Erbitux; ***Irl.***: Erbitux; ***Israel***: Erbitux; ***Ital.***: Erbitux; ***Malaysia***: Erbitux; ***Mex.***: Erbitux; ***Neth.***: Erbitux; ***Norw.***: Erbitux; ***NZ***: Erbitux; ***Philipp.***: Erbitux; ***Pol.***: Erbitux; ***Port.***: Erbitux; ***Rus.***: Erbitux (Эрбитукс); ***S.Afr.***: Erbitux; ***Singapore***: Erbitux; ***Spain***: Erbitux; ***Swed.***: Erbitux; ***Switz.***: Erbitux; ***Thai.***: Erbitux; ***UK***: Erbitux; ***Ukr.***: Erbituks (Эрбитукс); ***USA***: Erbitux.

Chlorambucil *(BAN, rINN)*

CB-1348; Chlorambucilis; Chlorambucilum; Chlorambucyl; Chloraminophene; Chlorbutinum; Clorambucilo; Klorambucil; Klórambucil; Klorambusilil; Klorambusil; NSC-3088; WR-139013; Хлорамбуцил.

4-[4-Bis(2-chloroethyl)aminophenyl]butyric acid.

$C_{14}H_{19}Cl_2NO_2$=304.2

CAS — 305-03-3.

ATC — L01AA02.

ATC Vet — QL01AA02.

UNII — 18D05L7309.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Chlorambucil). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone. Protect from light.

USP 36: (Chlorambucil). An off-white, slightly granular powder. M.p. 65 degrees to 69 degrees. Very slightly soluble in water; soluble 1 in 2 of acetone; soluble in dilute alkali. Store in airtight containers. Protect from light.

Storage. Licensed product information recommends that tablets of chlorambucil should be stored at 2 degrees to 8 degrees and kept dry.

Uses and Administration

Chlorambucil is an oral antineoplastic derived from chlormethine (p. 765.1) and has a similar mode of action. It acts on lymphocytes and to a lesser extent on neutrophils and platelets. Chlorambucil is most valuable in those conditions associated with the proliferation of white blood cells, especially lymphocytes, and is used in the treatment of chronic lymphocytic leukaemia and lymphomas, including Hodgkin's disease. It is also used in Waldenström's macroglobulinaemia and has been given in gestational trophoblastic tumours. Although formerly widely used in the management of polycythaemia vera it has largely been superseded.

Chlorambucil also has immunosuppressant properties and has been given in auto-immune disorders including amyloidosis, Behçet's syndrome, glomerular kidney disease, primary biliary cirrhosis, polymyositis, rheumatoid arthritis, and sarcoidosis.

The use of chlorambucil in these disorders is discussed under the individual headings below.

Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Chlorambucil is better tolerated than chlormethine hydrochloride and serious bone-marrow toxicity is not usually a problem with normal doses. When used as a single-agent antineoplastic for chronic lymphocytic leukaemia and lymphomas, chlorambucil is licensed for oral use in usual initial doses of 100 to 200 micrograms/kg daily (usually 4 to 10 mg once daily), for 3 to 8 weeks. A dose of 100 micrograms/kg daily may be adequate for the treatment of non-Hodgkin's lymphoma; 150 micrograms/kg daily until the total leucocyte count falls below 10 000 cells/mm^3 may be used in chronic lymphocytic leukaemia; and in Hodgkin's disease, 200 micrograms/kg daily is usually required. Lower doses may be given as part of a combination regimen. If lymphocytic infiltration of the bone marrow is present or if the bone marrow is hypoplastic, the daily dose should not exceed 100 micrograms/kg. Alternatively, high-dose chlorambucil may be given intermittently. For example, in chronic lymphocytic leukaemia it may be given in an initial single dose of 400 micrograms/kg increased by 100 micrograms/kg at each 2- or 4-week dose interval until control of lymphocytosis is achieved or toxicity occurs.

Once a remission has been established the patient may receive continuous maintenance with 30 to 100 micrograms/kg daily. However, short intermittent courses appear to be safer and are generally preferred for maintenance.

In patients with Waldenström's macroglobulinaemia chlorambucil is licensed in an initial oral dose of 6 to 12 mg daily until leucopenia develops. Maintenance therapy with doses of 2 to 8 mg daily may then be given indefinitely.

Total and differential white cell counts and haemoglobin and platelet examinations are recommended each week during treatment with chlorambucil.

Amyloidosis. Chlorambucil may be of use in preserving kidney function and improving survival in patients with amyloidosis secondary to rheumatic disease,[1-4] the management of which is discussed in more detail on p. 819.3.

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46:** 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis; a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20:** 2051–7.
3. David J, *et al.* Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. *Clin Exp Rheumatol* 1993; **11:** 85–90.
4. Savolainen HA. Chlorambucil in severe juvenile chronic arthritis: longterm followup with special reference to amyloidosis. *J Rheumatol* 1999; **26:** 898–903.

Blood disorders, non-malignant. Chlorambucil may produce a response in cold auto-immune haemolytic anaemia (p. 1122.2).

Connective tissue and muscular disorders. Chlorambucil has been used as a corticosteroid-sparing agent in patients with Behçet's syndrome (p. 1601.1). It has occasionally been tried in polymyositis (p. 1611.1). In both these conditions, the potential benefits must be weighed against the possibility of toxicity.

Kidney disorders, non-malignant. Chlorambucil has been used in some forms of glomerular kidney disease (p. 1604.3). Minimal change nephropathy occurs mainly in young children and is the most common cause of childhood nephrotic syndrome. Treatment with cytotoxics is reserved for the most severe cases because of fears about toxicity; cyclophosphamide is generally preferred to chlorambucil because it is perceived as entailing somewhat less risk although chlorambucil has been used successfully in cyclophosphamide-resistant disease.[1] Although not licensed for use in children with relapsing corticosteroid-sensitive nephrotic syndrome, the *BNFC* suggests that children from 3 months of age may be given an oral dose of 200 micrograms/kg once daily for 8 weeks. Chlorambucil has been used with corticosteroids in patients with membranous nephropathy,[2-4] but again cyclophosphamide may be better tolerated.

1. Ueda N, *et al.* Beneficial effect of chlorambucil in steroid-dependent and cyclophosphamide-resistant minimal change nephrotic syndrome. *J Nephrol* 2009; **22:** 610–5.
2. Ponticelli C, *et al.* Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. *N Engl J Med* 1992; **327:** 599–603.
3. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328–33.
4. Ponticelli C, *et al.* A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 1995; **48:** 1600–4.

Liver disorders, non-malignant. No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p. 2638.3). Chlorambucil is one of several drugs for which reports of benefit exist.[1]

1. Hoofnagle JH, *et al.* Randomized trial of chlorambucil for primary biliary cirrhosis. *Gastroenterology* 1986; **91:** 1327–34.

Malignant neoplasms. Chlorambucil is used in the management of haematological malignancies such as chronic lymphocytic leukaemia (p. 693.3), Hodgkin's disease (p. 696.1), indolent low-grade non-Hodgkin's lymphomas (p. 696.3), and Waldenström's macroglobulinaemia (p. 699.1). It was formerly used in polycythaemia vera (p. 695.2) but is now largely superseded.

Ocular disorders, non-malignant. Chlorambucil is one of the immunosuppressants that may be considered for patients with uveitis (p. 1615.1) unresponsive to corticosteroids in tolerable doses.[1-3]

1. Mudun AB, *et al.* Short-term chlorambucil for refractory uveitis in Behcet's disease. *Ocul Immunol Inflamm* 2001; **9:** 219–29.
2. Miserocchi E, *et al.* Efficacy and safety of chlorambucil in intractable noninfectious uveitis. *Ophthalmology* 2002; **109:** 137–42.
3. Goldstein DA, *et al.* Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. *Ophthalmology* 2002; **109:** 370–7.

Pemphigus and pemphigoid. Chlorambucil with prednisone or prednisolone has been reported[1,2] to be effective in the treatment of pemphigus and pemphigoid (p. 1687.1).

1. Shah N, *et al.* The use of chlorambucil with prednisone in the treatment of pemphigus. *J Am Acad Dermatol* 2000; **42:** 85–8.
2. Chave TA, *et al.* Chlorambucil as a steroid-sparing agent in bullous pemphigoid. *Br J Dermatol* 2004; **151:** 1107–8.

Rheumatoid arthritis. Chlorambucil has been used for its immunosuppressant properties in a few patients with severe rheumatoid arthritis (p. 13.2), especially with vasculitis, who have failed to respond to other drugs. However, the use of cytotoxic immunosuppressants other than methotrexate is considered debatable.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p. 1612.2), corticosteroids are the usual treatment. Chlorambucil is one of several cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

A reversible progressive lymphocytopenia tends to develop during treatment with chlorambucil. Neutropenia may continue to develop up to 10 days after the last dose. Irreversible bone-marrow depression can occur particularly when the total dosage for the course approaches 6.5 mg/kg.

Other reported adverse effects include gastrointestinal disturbances, hepatotoxicity, skin rashes (rarely Stevens-Johnson syndrome or toxic epidermal necrolysis), peripheral neuropathy, and central neurotoxicity, including seizures. Interstitial pneumonia and pulmonary fibrosis have occurred; the latter is usually reversible but fatalities have been recorded. Chlorambucil in high doses may produce azoospermia and amenorrhoea; sterility has developed particularly when chlorambucil has been given to boys at or before puberty.

Overdosage may result in pancytopenia and in neurotoxicity, including agitation, ataxia, and grand mal seizures.

Like other alkylating agents, chlorambucil is potentially mutagenic, teratogenic, and carcinogenic, and an increased incidence of acute leukaemias and other secondary malignancies has been reported in patients who have received the drug.

Effects on the bladder. Chlorambucil-induced cystitis was reported in a 73-year-old woman given 2 mg daily for over 2 years for the treatment of lymphocytic lymphoma.[1]

1. Daoud D, *et al.* Sterile cystitis associated with chlorambucil. *Drug Intell Clin Pharm* 1977; **11:** 491.

Effects on the eyes. Visual impairment and optic atrophy in a patient who had been receiving chlorambucil for 5 years to control non-Hodgkin's lymphoma were thought to be due to the drug,[1] although ocular effects are extremely rare with chlorambucil.

1. Yiannakis PH, Larner AJ. Visual failure and optic atrophy associated with chlorambucil therapy. *BMJ* 1993; **306:** 109.

Effects on the nervous system. There have been a few reports of seizures in patients given chlorambucil. A review[1] of these suggested that in adults, patients with a history of seizures, or those given high doses of chlorambucil may be at increased risk. The reports in children consisted mainly of patients being treated for nephrotic syndrome, possibly because the condition may alter the pharmacokinetics of chlorambucil.

1. Salloum E, *et al.* Chlorambucil-induced seizures. *Cancer* 1997; **79:** 1009–13.

Hypersensitivity. Drug fever, characterised by high temperature, rigors, and malaise, may occur in patients within hours or days of starting chlorambucil, often after a drug-free interval. In 3 patients who developed symptoms of chlorambucil-induced drug fever, desensitisation, beginning with an oral dose of 500 micrograms daily, increased about every 5 days by 500 micrograms up to 2 mg was successful. In one patient the dose was successfully increased to 4 mg daily by continuing to increase by 500 micrograms every 7 days.[1]

1. Weber E, *et al.* Rapid desensitization for chlorambucil drug fever. *Haematologica* 2007; **92:** e77.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Chlorambucil should be avoided, or given with great care and at reduced doses, for at least 4 weeks after treatment with radiotherapy or other antineoplastics (unless only low doses of radiation have been given to parts remote from the bone marrow and the neutrophil and platelet counts are not depressed). The dose should be reduced if there is lymphocytic involvement of the bone marrow or if it is hypoplastic. Chlorambucil should be given with care to patients with impaired renal function; consideration should also be given to dose reduction in patients with gross hepatic dysfunction. Children with nephrotic syndrome, patients receiving high-dose pulse therapy with chlorambucil, and those with a history of seizures, may be at increased risk of seizures. Regular blood counts are required during therapy.

Handling and disposal. Chlorambucil is irritant; avoid contact with skin and mucous membranes.

Urine produced for up to 48 hours after a dose of chlorambucil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorambucil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Pregnancy. A patient with chronic lymphocytic leukaemia who was taking low-dose chlorambucil was found to be pregnant with a viable 20-week fetus during the third month of chlorambucil treatment. Treatment was stopped, and a healthy child without apparent congenital anomaly was delivered at 36 weeks by caesarean section. Development and growth had remained normal at 3 months of age.[1]

1. Ali R, *et al.* Pregnancy in chronic lymphocytic leukemia: experience with fetal exposure to chlorambucil. *Leuk Res* 2009; **33:** 567–9.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Pharmacokinetics

Chlorambucil is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses and is reported to have a terminal half-life in plasma of about 1.5 hours. It is extensively metabolised in the liver, mainly to active phenylacetic acid mustard, which has a slightly longer plasma half-life of about 1.8 to 2.5 hours, and which like chlorambucil also undergoes some spontaneous degradation to further derivatives. Chlorambucil and its metabolites are extensively protein bound. It is excreted in the urine almost entirely as metabolites with less than 1% unchanged.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Leukeran; ***Austral.***: Leukeran; ***Austria***: Leukeran; ***Belg.***: Leukeran; ***Braz.***: Leukeran; ***Canad.***: Leukeran; ***Chile***: Leukeran; ***China***: Leukeran (留可然); ***Cz.***: Leukeran; ***Denm.***: Leukeran; ***Fin.***: Leukeran; ***Ger.***: Leukeran; ***Gr.***: Leukeran; ***Hong Kong***: Leukeran; ***India***: Clokeran; Leukeran; ***Irl.***: Leukeran; ***Israel***: Leukeran; ***Ital.***: Leukeran; ***Malaysia***: Leukeran; ***Mex.***: Leukeran; ***Neth.***: Leukeran; ***Norw.***: Leukeran; ***NZ***: Leukeran; ***Philipp.***: Leukeran; ***Pol.***: Leukeran; ***Port.***: Leukeran; ***Rus.***: Leukeran (Лейкеран); ***S. Afr.***: Leukeran; ***Singapore***: Leukeran; ***Spain***: Leukeran; ***Swed.***: Leukeran; ***Switz.***: Leukeran; ***Thai.***: Leukeran; ***Turk.***: Leukeran; ***UK***: Leukeran.

Pharmacopoeial Preparations
BP 2014: Chlorambucil Tablets;
USP 36: Chlorambucil Tablets.

Chlormethine Hydrochloride

(BANM, rINNM)

Chlorethazine Hydrochloride; Chlorméthine, Chlorhydrate de; Chlormethini Hydrochloridum; Clormetina, hidrocloruro de; Hidrocloruro de clormetina; HN2 (chlormethine); Klormetin Hidroklorür; Mechlorethamine Hydrochloride; Mecloretamina (chlormethine); Mustin Hidroklorür; Mustine Hydrochloride; Nitrogen Mustard (chlormethine); NSC-762; WR-147650; Хлорметина Гидрохлорид.

Bis(2-chloroethyl)methylamine hydrochloride; 2,2′-Dichloro-*N*-methyldiethylamine hydrochloride.

$C_5H_{11}Cl_2N,HCl$=192.5

CAS — 51-75-2 (chlormethine); 55-86-7 (chlormethine hydrochloride).

ATC — L01AA05.

ATC Vet — QL01AA05.

UNII — L0MR697HHI.

Pharmacopoeias. In *Br.*, *Chin.*, *Int.*, and *US.*

BP 2014: (Chlormethine Hydrochloride). A white or almost white, hygroscopic, vesicant, crystalline powder or mass. Very soluble in water. Store at a temperature of 8 degrees to 15 degrees.

USP 36: (Mechlorethamine Hydrochloride). A white, hygroscopic, crystalline powder. A 0.2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Stability. Solutions of chlormethine hydrochloride lose their activity very rapidly, particularly at neutral or alkaline pH.

A study[1] using an assay specific for chlormethine found that a 0.1% solution in Water for Injections or sodium chloride 0.9% injection underwent a loss of about 10% when stored for 6 hours at room temperature, and of about 4 to 6% when stored for the same period at 4 degrees; similar results were obtained whether the solution was stored in glass vials or plastic syringes. Solutions in 500 mL of sodium chloride or glucose 5% injection and stored in PVC infusion bags were still less stable, with 15% and 10% degradation respectively after 6 hours at room temperature.

Chlormethine hydrochloride has been used in extemporaneous ointment preparations in the treatment of mycosis fungoides.[2] One formulation of chlormethine hydrochloride, dissolved in acetone and worked into white soft paraffin, was reported[3] to be stable for at least 84 days when stored at 4 degrees, and for at least 40 days at 37 degrees.

1. Kirk B. Stability of reconstituted Mustine Injection BP during storage. *Br J Parenter Ther* 1986; **7:** 86–92.
2. Price NM, *et al.* Ointment-based mechlorethamine treatment for mycosis fungoides. *Cancer* 1983; **52:** 2214–19.
3. Cummings J, *et al.* The long term stability of mechlorethamine hydrochloride (nitrogen mustard) ointment measured by HPLC. *J Pharm Pharmacol* 1993; **45:** 6–9.

Uses and Administration

Chlormethine belongs to the group of antineoplastic drugs described as alkylating agents. It also possesses weak immunosuppressant properties.

Chlormethine hydrochloride has been used in the treatment of advanced Hodgkin's disease (p. 696.1), historically with a vinca alkaloid, procarbazine, and prednisone or prednisolone (the MOPP regimen). Chlormethine has also been tried in non-Hodgkin's lymphomas, notably mycosis fungoides (p. 698.3), and some other malignancies including chronic leukaemias, tumours of the breast, ovary, and lung, and in polycythaemia vera. Chlormethine has been used in the management of malignant effusions but is not the agent of choice.

In the MOPP regimen chlormethine hydrochloride has been given in doses of 6 mg/m^2. However, when licensed for use as a single agent, the usual dose of chlormethine hydrochloride is 400 micrograms/kg, preferably as a single dose, although it may be divided into 2 or 4 equal doses on successive days. It is given by intravenous injection in a strength of 1 mg/mL in Water for Injections or sodium chloride 0.9%. Injection over 2 minutes into the tubing of a fast running intravenous infusion of sodium chloride 0.9% or glucose 5% may reduce the incidence of thrombophlebitis and the risk of extravasation.

The response should be assessed by the trend of the blood counts. Treatment with chlormethine may be repeated when the bone-marrow function has recovered.

Intracavitary injections of 200 to 400 micrograms/kg have been given in the treatment of malignant, especially pleural, effusions.

For topical treatment of mycosis fungoides, see below.

Histiocytic syndromes. Dilute solutions of chlormethine (200 micrograms/mL) have been applied topically for the cutaneous symptoms of Langerhans-cell histiocytosis (p. 692.1).[1,2] Such therapy was reported to effectively clear skin lesions in most patients, and be well tolerated. However, although no malignant skin disease developed during the follow-up of one group of children, the long-term effects of topical chlormethine are of concern in young patients.[2]

1. Sheehan MP, *et al.* Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 1991; **119:** 317–21.
2. Hoeger PH, *et al.* Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. *Arch Dis Child* 2000; **82:** 483–7.

Mycosis fungoides. Chlormethine is used topically in the management of mycosis fungoides (p. 698.3). A retrospective cohort analysis[1] of 203 patients treated with chlormethine found a partial response rate of 33% and a complete response rate of 50%. The median time to achieve complete response was 12 months and the time to relapse was also 12 months. Mild disease of limited skin involvement responded better than generalised patch/plaque disease, and more patients with mild disease obtained long-term remission. Maintenance therapy was used in some patients, but on cessation the relapse rate was similar to patients who did not receive maintenance therapy. Although unlicensed in the UK, guidelines[2] suggest chlormethine as a treatment option for early-stage mycosis fungoides, applied in a concentration of 0.01% or 0.02%, either as an aqueous solution in sodium chloride 0.9% or in an ointment base such as emulsifying ointment.

1. Kim YH, *et al.* Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; **139:** 165–73.
2. Whittaker SJ, *et al.* Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; **149:** 1095–1107. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Cutaneous%20T%20Cell%20Lymphoma.pdf (accessed 22/04/10)

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Chlormethine hydrochloride is extremely toxic and its use is invariably accompanied by adverse effects. Severe nausea and vomiting may begin within an hour of injection of the drug and last for some hours; antiemetics should be given before treatment. It causes varying degrees of bone-marrow depression depending on the dose. In heavily pretreated patients, or when the total dose for a single course exceeds 400 micrograms/kg, there is a risk of severe and possibly fatal depression with anaemia, lymphocytopenia, granulocytopenia, and thrombocytopenia with consequent haemorrhage. Depression of lymphocytes may be apparent within 24 hours of a dose and maximum suppression of granulocytes and platelets occurs within 7 to 21 days; haematological recovery may be adequate after 4 weeks.

Tinnitus, vertigo, deafness, headache, drowsiness, and other neurological symptoms have been reported, as have episodes of jaundice. Skin reactions to chlormethine hydrochloride include maculopapular rashes. Hypersensitivity is frequent when topical preparations are used.

Chlormethine hydrochloride has a powerful vesicant action on the skin and mucous membranes and great care must be taken to avoid contact with the eyes. Thrombophlebitis is a potential hazard of chlormethine particularly if it is not sufficiently diluted. Extravasation of the injection causes severe irritation and even sloughing. If extravasation occurs during injection, it has been suggested that the involved area should be infiltrated with an isotonic 4% solution of sodium thiosulfate, followed by the application of an ice compress intermittently for 6 to 12 hours, although the role of specific antidotes in antineoplastic extravasation is somewhat contentious (see p. 731.3).

Chlormethine hydrochloride may produce temporary or permanent inhibition of fertility. There is some evidence of mutagenicity, teratogenicity, and carcinogenicity.

Effects on the nervous system. Severe immediate neurotoxicity developed[1] in 14 of 21 evaluable patients who underwent bone marrow transplantation after preparation with cytotoxic regimens including chlormethine 0.3 to 2mg/kg. Symptoms developed a median of 4 days after treatment and included headache, hallucinations, confusion, convulsions, paraplegia, and tremor. Symptoms resolved in most, although in some they had not done so before their death. Six of the patients who recovered from acute toxicity developed a delayed neurotoxicity, beginning a median of 169 days after the first chlormethine injection and characterised by symptoms including confusion, somnolence, personality change, dementia, focal motor seizures, and hydrocephalus. Patients older than 21 years, those who had received CNS irradiation, and those treated concomitantly with other cytotoxic agents were at increased risk of neurotoxicity.

1. Sullivan KM, *et al.* Immediate and delayed neurotoxicity after mechlorethamine preparation for bone marrow transplantation. *Ann Intern Med* 1982; **97:** 182–9.

Handling and disposal. Chlormethine hydrochloride is a strong vesicant; avoid contact with skin and mucous membranes.

The manufacturers state that *unused injection* solutions of chlormethine hydrochloride may be neutralised by mixing with an equal volume of a solution containing sodium thiosulfate 5% and sodium bicarbonate 5% and allowing to stand for 45 minutes. Equipment used in the preparation and administration of such solutions may be treated similarly. Alternatively a solution containing sodium carbonate 2.5% or sodium hydroxide in a mixture of industrial methylated spirit and water has been suggested for the decontamination of equipment.

Urine produced for up to 48 hours after a dose of chlormethine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlormethine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Pharmacokinetics

On intravenous injection, chlormethine is rapidly converted to a reactive ethyleneimmonium ion. It usually disappears from the blood in a few minutes. A very small proportion is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Mustargen†; ***Fr.***: Caryolysine†; ***Gr.***: Caryolysine; ***Israel***: Mustargen; ***Switz.***: Mustargen†; ***USA***: Mustargen; Valchlor.

Pharmacopoeial Preparations
BP 2014: Chlormethine Injection;
USP 36: Mechlorethamine Hydrochloride for Injection.

Cilengitide *(USAN, rINN)*

Cilengitida; Cilengitidum; EMD-121974; Циленгитид.
Cyclo(L-arginylglycyl-L-α-aspartyl-D-phenylalanyl-*N*-methyl-L-valyl).
$C_{27}H_{40}N_8O_7$=588.7
CAS — 188968-51-6.
UNII — 4EDF46E4GI.

Profile

Cilengitide is an integrin inhibitor with anti-angiogenic actions, under investigation in the treatment of glioma, squamous cell carcinoma of the head and neck, and non-small cell lung cancer.

References.

1. Friess H, *et al.* A randomized multi-center phase II trial of the angiogenesis inhibitor cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. *BMC Cancer* 2006; **6:** 285.
2. Hariharan S, *et al.* Assessment of the biological and pharmacological effects of the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptor antagonist, cilengitide (EMD 121974), in patients with advanced solid tumors. *Ann Oncol* 2007; **18:** 1400–7.
3. MacDonald TJ, *et al.* Phase I clinical trial of cilengitide in children with refractory brain tumors: Pediatric Brain Tumor Consortium Study PBTC-012. *J Clin Oncol* 2008; **26:** 919–24.
4. Reardon DA, *et al.* Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. *Expert Opin Invest Drugs* 2008; **17:** 1225–35.

Cintredekin Besudotox *(USAN, rINN)*

Cintredekina besudotox; Cintrédékine Bésudotox; Cintredekinum Besudotoxum; IL13-PE38; IL13-PE38QQR; NK-408; Pseudomonas Exotoxin (domains II/III)-Interleukin 13 Chimeric Protein; Toxin hIL 13-PE38QQR (plasmid phuIL 13-Tx); Tredekincept Sudotox; Цинтредекин Безудотокс.
CAS — 372075-36-0.
UNII — ZL04JX89M7.

Profile

Cintredekin besudotox is a recombinant fusion protein of interleukin-13 and a bacterial toxin derived from *Pseudomonas aeruginosa.* It is under investigation for the treatment of malignant gliomas.

References.

1. Kunwar S, *et al.* Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. *J Clin Oncol* 2007; **25:** 837–44.
2. Vogelbaum MA, *et al.* Convection-enhanced delivery of cintredekin besudotox (interleukin-13-PE38QQR) followed by radiation therapy with and without temozolomide in newly diagnosed malignant gliomas: phase 1 study of final safety results. *Neurosurgery* 2007; **61:** 1031–7.
3. Mut M, *et al.* Cintredekin besudotox in treatment of malignant glioma. *Expert Opin Biol Ther* 2008; **8:** 805–12.

Cisplatin *(BAN, USAN, rINN)*

CDDP; *cis*-DDP; Cisplatina; Cisplatine; Cisplatino; Cisplatinum; Cis-platinum; Cisplatyna; Ciszplatin; DDP; Diamindicloruro de platino (II); NSC-119875; Peyrone's Salt; Platinum Diamminodichloride; Sisplatiini; Sisplatin; Цисплатин.
cis-Diamminedichloroplatinum.
$(NH_3)_2PtCl_2$=300.0
CAS — 15663-27-1.
ATC — L01XA01.
ATC Vet — QL01XA01.
UNII — Q20Q21Q62J.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Cisplatin). A yellow powder or yellow or orange-yellow crystals. Slightly soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 0.1% solution in sodium chloride 0.9% has a pH of 4.5 to 6.0 immediately after preparation. Store in airtight containers. Protect from light.

USP 36: (Cisplatin). Store in airtight containers. Protect from light.

Incompatibility. Cisplatin is rapidly degraded in the presence of bisulfite or metabisulfite,[1,2] and admixture with preparations containing these as preservatives may result in loss of activity.[2] Sodium bicarbonate may also increase the loss of cisplatin from solution, and in some cases may cause precipitation.[3] The stability of cisplatin when mixed with fluorouracil is reported to be limited, with 10% loss of cisplatin in 1.2 to 1.5 hours.[4] Mixtures with etoposide[5] in sodium chloride 0.9% injection formed a precipitate if mannitol and potassium chloride were present as additives, but not when the diluent was glucose 5% with sodium chloride 0.45%. Turbidity has been reported[6] within 4 hours of mixing 0.1% solutions of cisplatin and thiotepa in glucose 5%. Cisplatin exhibits variable incompatibility with paclitaxel, depending on the paclitaxel concentration and the temperature.[7]

Cisplatin reacts with aluminium causing loss of potency and precipitate formation. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving cisplatin.

1. Hussain AA, *et al.* Reaction of cis-platinum with sodium bisulfite. *J Pharm Sci* 1980; **69:** 364–5.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24:** 91–9.
3. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
4. Stewart CF, Fleming RA. Compatibility of cisplatin and fluorouracil in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1990; **47:** 1373–7.
5. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 1400–4.
6. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.
7. Zhang Y, *et al.* Compatibility and stability of paclitaxel combined with cisplatin and with carboplatin in infusion solutions. *Ann Pharmacother* 1997; **31:** 1465–70.

Stability. Decomposition of cisplatin in aqueous solutions is mainly due to reversible substitution of water for chloride, and its stability is enhanced in sodium chloride solutions because of the excess of chloride ions available.[1,2] A solution in sodium chloride 0.9% injection has been reported to lose 3% of the drug in less than one hour and to remain stable at this equilibrium value for 24 hours at room temperature.[1] Stability is decreased if exposed to intense light, but the effect of normal lighting conditions is apparently smaller.[1,2] It has been recommended that admixtures of cisplatin with mannitol and magnesium sulfate (in glucose 5% with sodium chloride 0.45%) stored at room temperature in PVC bags should be used within 48 hours, but may be stored for 4 days at 4 degrees or frozen and stored at -15 degrees for up to 30 days.[3] However, solutions containing 600 micrograms/mL or more of cisplatin precipitate out when refrigerated and are slow to redissolve.[1]

1. Greene RF, *et al.* Stability of cisplatin in aqueous solution. *Am J Hosp Pharm* 1979; **36:** 38–43.
2. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
3. LaFollette JM, *et al.* Stability of cisplatin admixtures in polyvinyl chloride bags. *Am J Hosp Pharm* 1985; **42:** 2652.

Uses and Administration

The antineoplastic cisplatin is a platinum-containing complex that may act similarly to the alkylating agents. Its antineoplastic actions are cell-cycle non-specific and are dependent upon its *cis* configuration; they appear to be related to its hydrolysis in the body to form reactive aquated species. Although it causes immunosuppression, stimulation of the host immune response against the tumour has been suggested as contributing to cisplatin's antineoplastic action.

Cisplatin is of value in the treatment of tumours of the testis, usually as a major component of combination chemotherapy regimens, and particularly with bleomycin and etoposide (BEP), or with bleomycin and a vinca alkaloid. It is also used in metastatic ovarian tumours, cervical tumours, lung cancer, advanced bladder cancer, and squamous cell carcinoma of the head and neck. It has been reported to be active against many other solid tumours, as indicated by the cross references given under Malignant Neoplasms, p. 767.1.

Cisplatin is given by intravenous infusion in sodium chloride 0.9% or in a mixture of sodium chloride and glucose. In monotherapy, it is usually given as a single dose of 50 to 120 mg/m^2 every 3 to 4 weeks. Alternatively, 15 to 20 mg/m^2 is given daily for 5 days, every 3 to 4 weeks. Lower doses are generally used for combination chemotherapy regimens than for single agent therapy; 20 mg/m^2 or more is given once every 3 to 4 weeks. A dose of 20 mg/m^2 daily for 5 days every 3 to 4 weeks has been used in combination chemotherapy of testicular tumours.

Licensed product information recommends that cisplatin is given in 2 litres of chloride-containing infusion fluid. In practice, volumes of less than 2 litres have been used in expert centres. The infusion may be given over 1 to 2 hours, although licensed product information generally recommends a longer infusion time of 6 to 8 hours in order to reduce renal and gastrointestinal toxicities.

To aid diuresis and protect the kidneys, 37.5 g of mannitol (e.g. 375 mL of mannitol 10%) is usually added to the infusion or is infused separately immediately before cisplatin. In order to begin diuresis the patient is usually hydrated by the infusion of 1 to 2 litres of a suitable fluid over several hours before giving cisplatin. Adequate hydration must also be maintained for up to 24 hours after a dose. Renal, haematological, auditory, and neurological function should be monitored during therapy, and dosage adjusted accordingly.

Cisplatin has also been given by the intra-arterial and intraperitoneal routes, and by instillation into the bladder. It is being investigated as a liposomal formulation, and as a collagen-based injectable gel containing cisplatin and adrenaline (MPI-5010) to localise the effect. An oral formulation of cisplatin is also under investigation.

Various analogues of cisplatin have been developed or investigated including those with fewer adverse effects (e.g. carboplatin, p. 759.1; nedaplatin, p. 834.3), an altered spectrum of activity (oxaliplatin, p. 838.1), or activity on oral dosage (satraplatin, p. 856.3).

Administration. Adjustments to the way in which cisplatin is given have been suggested in an attempt to improve efficacy while reducing toxicity.

Hydration before and after a dose of cisplatin, together with the use of mannitol to promote diuresis, is now standard (see Uses and Administration, above). Higher doses of cisplatin (up to 200 mg/m^2 per treatment cycle) have been successfully given by infusion in hypertonic sodium chloride, accompanied by intensive hydration.[1,2] Sodium chloride 3% infusion solution has been used.[3] However, while such a regimen may limit nephrotoxicity, other toxic effects, such as peripheral neuropathy, are not prevented;[1,2,4,5] myelosuppression may be less if the total dose is given in 2 divided doses rather than divided over 5 days.[2] High-dose cisplatin has been given once weekly; haematological toxicity may be dose-limiting with this regimen.[3]

Toxicity has been reported to be reduced when cisplatin was given by continuous intra-arterial[6] or intravenous[7] infusion. It has also been suggested that giving cisplatin in the evening rather than the morning results in less damage to renal function, apparently because of circadian variations in urine production.[8] However, another study[9] found that morning, rather than evening, doses of cisplatin resulted in less renal damage. Noting the inconsistency with previous reports, the authors concluded that use of a prolonged hydration protocol and concomitant furosemide might have been responsible for these results (see also under Interactions, Cardiovascular Drugs, p. 768.3). It was also found that morning dosage of cisplatin may be more emetogenic than evening dosage, although the use of prophylactic ondansetron before cisplatin reduced this apparent circadian effect on vomiting.

A suggested alternative way to increase the platinum dose without producing incapacitating toxicity has been the combination of cisplatin and carboplatin.[10] Formulation as liposomal cisplatin is also under investigation.[11]

Various drugs have been investigated to reduce toxicity, including amifostine, glutathione, and thiosulfate, as discussed under Effects on the Ears, p. 767.2 Effects on the Kidneys, p. 767.2 and Effects on the Nervous System, p. 767.3.

A retrospective study of patients with bladder cancer found that calculation of creatinine clearance (CC) by mathematical formulas was inadequate in determining renal eligibility for treatment with cisplatin, especially in patients over 65 years of age; up to 44% of patients who were treated with cisplatin based on measured CC would have been deemed ineligible using mathematical calculations.[12] The value of therapeutic drug monitoring has been reviewed.[13]

1. Ozols RF, *et al.* High-dose cisplatin in hypertonic saline. *Ann Intern Med* 1984; **100:** 19–24.
2. Gandara DR, *et al.* Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. *J Natl Cancer Inst* 1989; **81:** 790–4.
3. de Jongh FE, *et al.* Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. *Br J Cancer* 2003; **88:** 1199–1206.
4. Bagley CM, *et al.* High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; **102:** 719.
5. Ozols RF, Young RC. High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; **102:** 719.
6. Jacobs SC, *et al.* Intraarterial cisplatin infusion in the management of transitional cell carcinoma of the bladder. *Cancer* 1989; **64:** 388–91.
7. Salem P, *et al.* Cis-diamminedichloroplatinum (II) by 5-day continuous infusion: a new dose schedule with minimal toxicity. *Cancer* 1984; **53:** 837–40.
8. Hrushesky WJM, *et al.* Circadian time dependence of cisplatin urinary kinetics. *Clin Pharmacol Ther* 1982; **32:** 330–9.
9. Kobayashi M, *et al.* Cisplatin-induced vomiting depends on circadian timing. *Chronobiol Int* 2001; **18:** 851–63.
10. Piccart MJ, *et al.* Cisplatin combined with carboplatin: a new way of intensification of platinum dose in the treatment of advanced ovarian cancer. *J Natl Cancer Inst* 1990; **82:** 703–7.
11. Stathopoulos GP. Liposomal cisplatin: a new cisplatin formulation. *Anticancer Drugs* 2010; **21:** 732–6.
12. Raj GV, *et al.* Formulas calculating creatinine clearance are inadequate for determining eligibility for cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006; **24:** 3095–3100.
13. Hulin A, *et al.* Suivi thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du cisplatine. *Therapie* 2010; **65:** 151–5.

Administration in the elderly. Despite receiving less chemotherapy than their younger counterparts, selected

elderly patients have been shown to benefit from adjuvant cisplatin-based chemotherapy and studies have concluded that chemotherapy should not be withheld from patients on the basis of age.[1,2] A review[3] considered cisplatin to be a viable treatment option in selected elderly patients; renal function and the high incidence of age-related hearing loss should, however, be taken into consideration. The authors recommended that cisplatin be used at the lower range of dosage, and preferably at a reduced infusion rate (for example, over 24 hours) to avoid excessive toxicity in the elderly; hydration should be monitored to prevent fluid overload and concomitant use of nephrotoxic drugs should be avoided.

Use of mathematical formulas to determine renal eligibility for cisplatin treatment has been deemed to be inadequate, especially in patients over 65 years of age, see Administration, p. 766.3.

1. Pepe C, *et al*. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J Clin Oncol* 2007; **25:** 1553–61.
2. Früh M, *et al*. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. *J Clin Oncol* 2008; **26:** 3573–81.
3. Lichtman SM, *et al*. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. Licensed product information generally contra-indicates the use of cisplatin in patients with renal impairment. However, there are reports of the use of cisplatin with peritoneal dialysis[1] or haemodialysis[2,3] in a few patients.

1. Sebestyen J, *et al*. Cisplatin pharmacokinetics in a child receiving peritoneal dialysis. *Pediatr Nephrol* 2010; **25:** 1185–9.
2. Matsumoto K. Pharmacokinetics of cisplatin and methotrexate after M-VAC chemotherapy for advanced urothelial cancer in hemodialysis patients. *Int J Urol* 2008; **15:** 949–50.
3. Zahra MA, *et al*. Concurrent weekly cisplatin chemotherapy and radiotherapy in a haemodialysis patient with locally advanced cervix cancer. *Clin Oncol (R Coll Radiol)* 2008; **20:** 6–11.

Malignant neoplasms. Cisplatin is used in the management of many solid malignancies, notably those of the bladder, cervix, lung, ovary, and testis, as discussed on p. 700.2, p. 704.2, p. 710.2, p. 711.2, and p. 715.1 respectively. Other malignancies where cisplatin may be employed, as discussed in the introduction to this chapter, include non-Hodgkin's lymphomas (p. 696.3), tumours of brain (p. 701.2), endometrium (p. 704.3), oesophagus, stomach, and anus (p. 705.3, p. 706.1, and p. 708.1), head and neck (p. 708.1), and thymus (p. 715.3), neuroblastoma (p. 716.2), and sarcoma of bone and soft tissue (p. 717.3 and p. 718.2).

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

Severe nausea and vomiting occur in most patients during treatment with cisplatin; nausea may persist for up to a week.

Serious toxic effects on the kidneys, bone marrow, and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative.

Damage to the renal tubules may be evident during the second week after a dose of cisplatin and renal function must return to normal before further cisplatin is given. Adequate hydration, and use of osmotic diuretics such as mannitol to increase urine volume and thus decrease the urinary concentration of platinum, can reduce the incidence of nephrotoxicity. Electrolyte disturbances, particularly hypomagnesaemia and hypocalcaemia, may occur, possibly as a result of renal tubular damage. Hyperuricaemia is also seen.

Bone-marrow depression may be severe with higher doses of cisplatin. Nadirs in platelet and leucocyte counts occur between days 18 and 23 and most patients recover by day 39; anaemia is common and may be partly related to decreased production of erythropoietin after renal damage.

Ototoxicity may be more severe in children. It can manifest as tinnitus, loss of hearing in the high frequency range, and occasionally deafness or vestibular toxicity. Other neurological effects reported include peripheral neuropathies, loss of taste, seizures, and encephalopathy including reversible posterior leukoencephalopathy. Ocular toxicities include optic neuritis, papilloedema, and cerebral blindness.

Anaphylactoid reactions and cardiac abnormalities have occurred. Injection site reactions, including localised oedema, pain, erythema, skin ulceration and phlebitis may occur. Extravasation may lead to tissue cellulitis, fibrosis, and necrosis. Intra-arterial use of cisplatin has been associated with hepatobiliary disorders, including cholecystitis, biloma, and liver abscesses.

Platinum derivatives are potentially mutagenic and teratogenic, and there is some evidence they may be associated with the development of secondary leukaemias—see Carcinogenicity, p. 726.2.

Effects on the blood. Cisplatin-induced anaemia appears to be disproportionate to the effects on other blood cells, and to correlate with renal tubular dysfunction.[1] It may therefore be due to an erythropoietin deficiency state resulting from cisplatin-induced renal tubular damage. Haemolysis has also been reported.[2]

1. Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. *J Clin Invest* 1995; **95:** 1650–9.
2. Rothmann SA, Weick JK. Cisplatin toxicity for erythroid precursors. *N Engl J Med* 1981; **304:** 360.

THROMBOEMBOLISM. For discussion of thromboembolic events possibly associated with cisplatin-containing chemotherapy regimens see Effects on the Cardiovascular System, p. 727.2.

Effects on the ears. Ototoxicity is a well-established adverse effect of cisplatin.[1] It appears to be due to generation of reactive oxygen species that cause apoptosis of hair cells in the cochlea,[1] and results in hearing loss, particularly at high frequencies.[1,2] Risk factors include younger age,[1] larger cumulative doses[1] (one study[2] identified doses above 60 mg/m^2 as risk factors), pre-existing hearing loss or renal disease,[1] and irradiation of the brain or base of the skull.[1,3] Various substances including thiols, amifostine, ebselen, allopurinol, and salicylates have been investigated in *animals* for their protective effect against cisplatin-induced neurotoxicity[1] but although some promising results have been seen, benefit is yet to be shown in large clinical studies, and there is some concern about the risk of reducing the antineoplastic effect of cisplatin as well. However, a small study comparing cisplatin chemoradiation with or without sodium thiosulfate tentatively concluded that thiosulfate did seem to offer some protection against hearing loss.[4] Another study[5] in young patients with average-risk medulloblastoma found that amifostine, given before and during cisplatin infusion, significantly reduced the risk of severe ototoxicity. It was noted[6] that the cisplatin dose and schedule used for this study were different to those commonly used in other paediatric malignancies, and that amifostine might not necessarily be protective in other settings.

1. Rybak LP, *et al*. Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res* 2007; **226:** 157–67.
2. Rademaker-Lakhai JM, *et al*. Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol* 2006; **24:** 918–24.
3. Low WK, *et al*. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol* 2006; **24:** 1904–9.
4. Zuur CL, *et al*. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol* 2007; **25:** 3759–65.
5. Fouladi M, *et al*. Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma. *J Clin Oncol* 2008; **26:** 3749–55.
6. Freyer DR, *et al*. Prevention of hearing loss in children receiving cisplatin chemotherapy. *J Clin Oncol* 2009; **27:** 317–18.

Effects on electrolytes. Renal-magnesium wasting and, less commonly, symptomatic hypomagnesaemia occurs with cisplatin therapy.[1,2] Adding magnesium to the pre- and posthydration fluids has been suggested.[2] When hypocalcaemia is also present, tetany may result,[1,3] although this has responded to electrolyte infusion without the need to interrupt chemotherapy.[1] Cisplatin therapy may also be associated with significant hypokalaemia,[1] and salt-wasting,[4] and hyponatraemia.[5,6]

See also Effects on the Kidneys, below.

1. Winkler CF, *et al*. Cisplatin and renal magnesium wasting. *Ann Intern Med* 1979; **91:** 502.
2. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev* 1999; **25:** 47–58.
3. Stuart-Harris R, *et al*. Tetany associated with cis-platin. *Lancet* 1980; **ii:** 1303.
4. Hamdi T, *et al*. Cisplatin-induced renal salt wasting syndrome. *South Med J* 2010; **103:** 793–9.
5. Hutchison FN, *et al*. Renal salt wasting in patients treated with cisplatin. *Ann Intern Med* 1988; **108:** 21–5.
6. Mariette X, *et al*. Cisplatin and hyponatremia. *Ann Intern Med* 1988; **108:** 770–1.

Effects on the heart. Cases of cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, sinus tachycardia, sinus bradycardia, and third-degree heart block) have been reported following the use of cisplatin and other platinum-based antineoplastic drugs.[1,2] It was proposed that this may be due to either direct arrhythmogenicity, hypersensitivity, or electrolyte imbalances (see also Effects on Electrolytes, above).

1. Tassinari D, *et al*. Cardiac arrhythmias after cisplatin infusion: three case reports and a review of the literature. *Ann Oncol* 1997; **8:** 1263–7.
2. Zakaria S, *et al*. Atrial flutter associated with carboplatin administration. *Ann Pharmacother* 2011; **45:** e59.

Effects on the kidneys. Nephrotoxicity is a well-established adverse effect of cisplatin, may be dose-limiting, and can manifest as acute or chronic renal failure, polyuria, or chronic hypomagnesaemia.[1] The mechanism appears to involve mainly damage to the proximal renal tubule; selective magnesium loss may be due to a specific membrane or transport system abnormality. Sulfhydryl metabolism and oxidative stress play a role in toxicity, and measures that reduce glutathione depletion and scavenge intracellular free oxygen radicals have been tried in an attempt to modulate nephrotoxicity.[1-3] However, the primary measures for reducing renal damage have been aggressive hydration with chloride-containing solutions, and the use of mannitol (see also Prophylaxis, below). It has been suggested that cisplatin may mobilise lead accumulated in bone and cause temporary accumulation in the kidney, with concomitant toxicity,[4] but this has been vigorously disputed.[5-7]

See also under Effects on Electrolytes, above.

1. Anand AJ, Bashey B. Newer insights into cisplatin nephrotoxicity. *Ann Pharmacother* 1993; **27:** 1519–25.
2. Meyer KB, Madias NE. Cisplatin nephrotoxicity. *Miner Electrolyte Metab* 1994; **20:** 201–13.
3. Kuhlmann MK, *et al*. Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. *Nephrol Dial Transplant* 1997; **12:** 2478–80.
4. El-Sharkawi AM, *et al*. Unexpected mobilisation of lead during cisplatin chemotherapy. *Lancet* 1986; **ii:** 249–50.
5. Tothill P, *et al*. Is lead mobilised by cisplatin? *Lancet* 1989; **ii:** 333.
6. Tothill P, *et al*. Mobilisation of lead by cisplatin. *Lancet* 1989; **ii:** 1342.
7. Hainsworth IR, Morgan WD. Plasma lead and cisplatin. *Lancet* 1989; **ii:** 624.

PROPHYLAXIS. Hydration with 1 to 2 litres of fluid before treatment, and infusion of cisplatin in a further 2 litres of infusion fluid containing an osmotic diuretic such as mannitol reduces the nephrotoxicity of cisplatin, but does not abolish it. Maintaining adequate hydration and urinary output post-treatment is also important. It has been recommended[1] that urinary output be maintained at 3 to 4 litres daily for 2 to 3 days after a dose of cisplatin. Giving cisplatin over 6 to 8 hours rather than 1 to 2 hours may also decrease renal toxicity.

Sulfur-containing nucleophiles can inactivate cisplatin, and have therefore been investigated for their chemoprotective potential. Amifostine is a prodrug that is selectively activated by normal tissue, and has been shown to protect normal tissue (principally the kidney) against the cytotoxicity of cisplatin without affecting antitumour activity (for references, see Cytoprotection, p. 1539.3). Glutathione (p. 1555.2) is a similar agent, which may be selectively taken up by kidney and neural tissue. Sodium thiosulfate (p. 1576.1) does not show selective activation or uptake, and its use is therefore limited to situations where cisplatin is given locally (e.g. intraperitoneal[2,3]) or directly (e.g. intra-arterial[4]).

1. Launay-Vacher V, *et al*. Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. *Cancer Chemother Pharmacol* 2008; **61:** 903–9.
2. Malmstrom H, *et al*. Intraperitoneal high-dose cisplatin and etoposide with systemic thiosulfate protection in second-line treatment of advanced ovarian cancer. *Gynecol Oncol* 1993; **49:** 166–71.
3. van Rijswijk RE, *et al*. Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. *Ann Oncol* 1997; **8:** 1235–41.
4. Rohde S, *et al*. Intra-arterial high-dose chemotherapy with cisplatin as part of a palliative treatment concept in oral cancer. *Am J Neuroradiol* 2005; **26:** 1804–9.

Effects on the nervous system. The features of cisplatin-induced peripheral neuropathy are consistent with damage mainly to sensory fibres, with numbness, tingling, and decreased vibratory sensation and deep tendon reflexes, progressing in severe cases to disabling sensory ataxia.[1] The toxicity is dose-dependent, with symptoms usually appearing in patients who have received cumulative doses of 300 to 600 mg/m^2, although individuals vary in susceptibility. Neuropathy is reversible but recovery may take a year or more. The pathophysiology is unknown. Peripheral neuropathy can be a dose-limiting toxicity for cisplatin and agents such as Org-2766 (a corticotropin analogue) and amifostine (p. 1539.2) have been investigated for their potential in protecting peripheral nerves.[1-3] Vitamin E has been reported to be effective in reducing cisplatin-induced peripheral neuropathy.[4,5] Glutathione is also under investigation for the prevention of neurotoxicity (see p. 1555.2). Other drugs that have been tried include oxcarbazepine and ditiocarb sodium.[6] However, a systematic review considered that the evidence for most of the interventions intended to reduce cisplatin neurotoxicity was insufficient to show benefit.[6] Autonomic neuropathy, with, in some cases, consequent orthostatic hypotension, has also been described after treatment with cisplatin-containing regimens.[7] Apart from ototoxicity (see above), cisplatin has also been associated with central neurotoxicity, including leukoencephalopathy or focal encephalopathy, seizures, aphasia, confusion, agitation, and cortical blindness.[8-12] It has been suggested that the mechanism of focal encephalopathy may be vascular,[8] although this is uncertain.

1. Mollman JE. Cisplatin neurotoxicity. *N Engl J Med* 1990; **322:** 126–7.
2. Alberts DS, Noel JK. Cisplatin-associated neurotoxicity: can it be prevented? *Anticancer Drugs* 1995; **6:** 369–83.

3. Cavaletti G, *et al*. Neuroprotectant drugs in cisplatin neurotoxicity. *Anticancer Res* 1996; **16:** 3149–59.
4. Pace A, *et al*. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003; **21:** 927–31.
5. Pace A, *et al*. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. *Neurology* 2010; **74:** 762–6.
6. Albers JW, *et al*. Interventions for preventing neuropathy caused by cisplatin and related compounds. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 22/03/11).
7. Richardson P, Cantwell BMJ. Autonomic neuropathy after cisplatin based chemotherapy. *BMJ* 1990; **300:** 1466–7.
8. Lindeman G, *et al*. Cisplatin neurotoxicity. *N Engl J Med* 1990; **323:** 64–5.
9. Philip PA, *et al*. Convulsions and transient cortical blindness after cisplatin. *BMJ* 1991; **302:** 416.
10. Higa GM, *et al*. Severe, disabling neurologic toxicity following cisplatin retreatment. *Ann Pharmacother* 1995; **29:** 134–7.
11. Ito Y, *et al*. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol* 1998; **19:** 415–17.
12. Steeghs N, *et al*. Cisplatin-induced encephalopathy and seizures. *Anticancer Drugs* 2003; **14:** 443–6.

Extravasation. For discussion of the management of extravasation, including methods to manage cisplatin extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p. 731.3.

Hypersensitivity. Anaphylactoid reactions to intravenous cisplatin generally appear within a few minutes of dosage and have manifested as facial oedema, wheezing, tachycardia, and hypotension.[1] A high incidence of anaphylactoid reaction has also been seen after intravesical instillation in patients with bladder cancer,[2] but intraperitoneal or intrapleural use does not seem to be associated with an enhanced risk of hypersensitivity,[3] although anaphylactoid reactions have occurred when cisplatin is given intraperitoneally.[4] Anaphylactoid symptoms and ischaemia of the hands accompanied severe exfoliative dermatitis in one patient on the second cycle of cisplatin-based chemotherapy;[5] she had earlier had exfoliative dermatitis associated with carboplatin. However, it is unclear to what extent cross-sensitivity exists between platinum compounds; cisplatin has been successfully used after a hypersensitivity reaction to oxaliplatin.[6] Palmar-plantar erythrodysesthesia (p. 730.1) has also occurred with cisplatin.[7]

1. Von Hoff DD, *et al*. Allergic reactions to cis platinum. *Lancet* 1976; **i:** 90.
2. Denis L. Anaphylactic reactions to repeated intravesical instillation with cisplatin. *Lancet* 1983; **i:** 1378–9.
3. Markman M. No increase in allergic reactions with intracavitary administration of cisplatin. *Lancet* 1984; **ii:** 1164.
4. Hebert ME, *et al*. Anaphylactoid reactions with intraperitoneal cisplatin. *Ann Pharmacother* 1995; **29:** 260–3.
5. Lee TC, *et al*. Severe exfoliative dermatitis associated with hand ischemia during cisplatin therapy. *Mayo Clin Proc* 1994; **69:** 80–2.
6. Elligers KT, *et al*. Rechallenge with cisplatin in a patient with pancreatic cancer who developed a hypersensitivity reaction to oxaliplatin. Is skin test useful in this setting? *JOP* 2008; **9:** 197–202.
7. Vakalis D, *et al*. Acral erythema induced by chemotherapy with cisplatin. *Br J Dermatol* 1998; **139:** 750–1.

Nausea and vomiting. For discussion of the management of chemotherapy-induced nausea and vomiting, see under Nausea and Vomiting, p. 1814.3.

Overdosage. Fatalities have occurred with a total intravenous cisplatin dose of 640 mg given over 4 days and 750 mg given over 1 day; overdoses ranging from 180 to 480 mg/m^2 have been reported without fatalities, although significant toxicities are expected to occur. Immediate effects, in the first hours or days include nausea and vomiting, and rarely, diarrhoea. These may be followed by acute renal failure, electrolyte disturbances, hepatotoxicity, and rarely, pancreatitis, respiratory failure, and seizures. Later adverse effects that occur after days or weeks include chronic renal failure, myelosuppression, ototoxicity, peripheral neuropathy, and retinopathy. Key management strategies for a cisplatin overdose involve renal protection and enhancing drug elimination. Aggressive intravenous hydration with at least 3 to 6 litres daily is essential for reducing nephrotoxicity (for prophylaxis of nephrotoxicity with therapeutic doses, see p. 767.3). The osmotic diuretic mannitol (25 to 50 g intravenously, diluted in 250 to 500 mL of a suitable infusion fluid and given over 60 minutes) may be used to achieve a urine output of 1 to 3 mL/kg per hour for 6 to 24 hours. Sodium thiosulfate may be considered, particularly within the first 2 hours, although the optimum dose regimen has not been established. It is thought to bind free platinum thereby limiting renal tubular necrosis, and may protect against renal magnesium wasting. Plasmapheresis has been used successfully in some cases; haemodialysis, although useful for acute renal failure, is not effective at removing cisplatin from the circulation. Investigational therapies include amifostine, ditiocarb sodium, acetylcysteine, fosfomycin, and colestipol.[1]

1. Tsang RY, *et al*. Cisplatin overdose: toxicities and management. *Drug Safety* 2009; **32:** 1109–22.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Cisplatin is generally contra-indicated in patients with renal or hearing impairment, or bone-marrow depression. Renal and neurological function and hearing should be monitored during treatment, and regular blood counts performed. Electrolytes should be measured before starting therapy, and before each subsequent course. Adequate hydration and urinary output must be maintained before, and for 24 hours after, a dose.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment.

Breast feeding. Platinum concentrations in a patient receiving cisplatin were 900 nanograms/mL in breast milk and 800 nanograms/mL in plasma.[1] Although most of the platinum in breast milk is probably protein-bound the authors considered that a mother should not breast feed while receiving cisplatin. However, in another report,[2] cisplatin was undetectable in breast milk and the American Academy of Pediatrics[3] considers its use to be compatible with breast feeding.

1. de Vries EGE, *et al*. Excretion of platinum into breast milk. *Lancet* 1989; **i:** 497. Correction. *ibid.*; 798.
2. Egan PC, *et al*. Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69:** 1387–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. Methods for the destruction of *cisplatin wastes* by reduction with zinc powder under acidic conditions or by reaction with ditiocarb sodium have been described.[1] Residue produced by the degradation of cisplatin by either method showed no mutagenicity *in vitro*.

Urine produced for up to 7 days after a dose of cisplatin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al*. , eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cisplatin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. Cisplatin was given with etoposide and bleomycin to a pregnant woman at 26 weeks of gestation for carcinoma of uncertain primary origin. At 27 weeks of gestation, she developed profound neutropenia followed by septicaemia and went into premature labour. The infant had profound leucopenia and neutropenia by day 3, which was attributed to chemotherapy given 6 days before delivery; prophylactic antibacterials including gentamicin were given. Hair loss at the age of 10 days was attributed to etoposide. At 1 year of age, the child had moderate bilateral sensorineural hearing loss; this was considered to be either due to cisplatin exposure *in utero* or to gentamicin use.[1] However, there are other reports of cisplatin use during the second or third trimester of pregnancy with no subsequent apparent adverse effects on the infant.[2-5] In most cases, cisplatin had been given with cyclophosphamide,[2-4] although in one instance it was given with paclitaxel.[5] In one report, cisplatin-induced maternal ototoxicity led to it being replaced after 2 courses by carboplatin.[4]

1. Raffles A, *et al*. Transplacental effects of maternal cancer chemotherapy: case report. *Br J Obstet Gynaecol* 1989; **96:** 1099–1100.
2. Malfetano JH, Goldkrand JW. Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma. *Obstet Gynecol* 1990; **75:** 545–7.
3. King LA, *et al*. Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy. *Gynecol Oncol* 1991; **41:** 78–80.
4. Henderson CE, *et al*. Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. *Gynecol Oncol* 1993; **49:** 92–4.
5. Sood AK, *et al*. Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; **83:** 599–600.

Radiotherapy. Enhanced ototoxicity has been reported in patients given cisplatin with cranial irradiation.[1,2]

1. Granowetter L, *et al*. Enhanced cis-platinum neurotoxicity in pediatric patients with brain tumors. *J Neurooncol* 1983; **1:** 293–7.
2. Mahoney DH, *et al*. Ototoxicity with cisplatin therapy. *J Pediatr* 1983; **103:** 1006.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use with other myelosuppressive, nephrotoxic or ototoxic drugs may exacerbate the adverse effects of cisplatin. The effects of cisplatin on renal function may also affect the pharmacokinetics of other drugs excreted by the renal route.

Antibacterials. Although the use of cisplatin with other nephrotoxic or ototoxic drugs requires great caution, there is some evidence that *aminoglycosides* can be used in patients who have recently received cisplatin if appropriate supportive care is available.[1]

1. Cooper BW, *et al*. Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy. *Am J Med* 1993; **94:** 497–504.

Antineoplastics. The ototoxicity of cisplatin was reportedly enhanced by *ifosfamide*,[1] a drug that is not ototoxic when given alone, although it does have nephrotoxic potential, making reports of increased nephrotoxicity in patients who have received both unsurprising.[2,3]

For a report of increased toxicity with *etoposide*, see p. 792.1. Cisplatin may reduce the clearance of *paclitaxel*, see p. 842.2.

1. Meyer WH, *et al*. Ifosfamide and exacerbation of cisplatin-induced hearing loss. *Lancet* 1993; **341:** 754–5.
2. Rossi R, Ehrich JHH. Partial and complete de Toni-Debré-Fanconi syndrome after ifosfamide chemotherapy of childhood malignancy. *Eur J Clin Pharmacol* 1993; **44** (suppl 1): S43–S45.
3. Martinez F, *et al*. Ifosfamide nephrotoxicity: deleterious effect of previous cisplatin administration. *Lancet* 1996; **348:** 1100–1.

Cardiovascular drugs. A patient whose renal function was unaffected by cisplatin alone developed nephrotoxicity when given cisplatin and antihypertensive therapy with *furosemide*, *hydralazine*, *diazoxide*, and *propranolol*.[1] Previous results in *animals* suggest that furosemide may aggravate cisplatin nephrotoxicity, while the other antihypertensives might have contributed to a transient fall in renal-blood flow with resultant increased renal-tubular cisplatin concentration.

1. Markman M, Trump DL. Nephrotoxicity with cisplatin and antihypertensive medications. *Ann Intern Med* 1982; **96:** 257.

Gastrointestinal drugs. For mention of 2 retrospective studies, one showing a decreased area under the plasma-concentration time curve of high-dose cisplatin with *ondansetron* and the other an increase, see p. 773.3.

Pharmacokinetics

After intravenous doses cisplatin disappears from the plasma in a biphasic manner and half-lives of 25 to 49 minutes and 3 to 4 days have been reported for total platinum. More than 90% of the platinum from a dose is protein bound within 2 to 4 hours; only the unbound fraction has significant antineoplastic activity. Cisplatin is concentrated in the liver, kidneys, and large and small intestines. Penetration into the CNS appears to be poor. Excretion is mainly in the urine but is incomplete and prolonged: up to about 50% of a dose has been reported to be excreted in urine over 5 days, and platinum may be detected in tissue for several months afterwards. The unbound fraction, which is more rapidly cleared, may be actively secreted by the renal tubules. Cisplatin is well-absorbed on intraperitoneal use. Cisplatin may be distributed into breast milk (see Breast Feeding, above).

References.

1. Loh GW, *et al*. A systematic review of limited sampling strategies for platinum agents used in cancer chemotherapy. *Clin Pharmacokinet* 2007; **46:** 471–94.
2. Jehn CF, *et al*. Pharmacokinetics of liposomal cisplatin (lipoplatin) in combination with 5-FU in patients with advanced head and neck cancer: first results of a phase III study. *Anticancer Res* 2007; **27:** 471–5.
3. Royer B, *et al*. Population pharmacokinetics and dosing recommendations for cisplatin during intraperitoneal peroperative administration: development of a limited sampling strategy for toxicity risk assessment. *Clin Pharmacokinet* 2009; **48:** 169–80.
4. Cotte E, *et al*. Population pharmacokinetics and pharmacodynamics of cisplatinum during hyperthermic intraperitoneal chemotherapy using a closed abdominal procedure. *J Clin Pharmacol* 2011; **51:** 9–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ciskebir†; Elvecis; Platamine†; Platanovag; Platino II; Sicatem; ***Belg.***: Platosin†; ***Braz.***: C-Platin; Cisplatex†; Citoplax; Fauldcispla; Incel; Platiran; Platistine; Tecnoplatin; ***Chile***: Blastolem; ***China***: Fangtan (方坦); Jin Shun (金顺); Nuo Xin (诺欣); Yi Jiu Bo (益久博); ***Cz.***: Platidiam; Platosin†; ***Fin.***: Platinol†; ***Fr.***: Cisplatyl†; ***Ger.***: Cis-Gry†; Platinex†; ***Gr.***: Cisplamin; Cisplamol; Cisplasan; Cisplatyl; Oncoplat; Platamine; Platinol; Platosin; ***Hung.***: Platidiam; ***India***: Blastolem; Cadiplat; Cisget; Cisplan; Cisplat; Cisteen; Cistriz; Cytoplatin; Duplat; Kemoplat; Neoplat; Oncoplatin; Platin; ***Indon.***: Platinox; Platosin; ***Israel***: Abiplatin; ***Ital.***: Platamine; Pronto Platamine; ***Jpn***: Platosin; Randa; ***Malaysia***: Platosin; ***Mex.***: Accocit; Blastolem; Noveldexis; Platinol; Tecnoplatin; ***Neth.***: Platosin; ***NZ***: Platinol†; ***Philipp.***: Ciplexal†; Cisplagen; Cisteen; Cytosplat; Docistin; Kemoplat; Oncotin; Placitin; Platamine†; Platin; Platinol†; Platinoxan†; Platosin; ***Pol.***: Platidiam; ***Port.***: Faulplatin†; ***Rus.***: Blastolem (Бластолем)†; Kemoplat (Кемоплат); Platidiam (Платидиам); Platinol (Платинол); ***S.Afr.***: Abiplatin; Platosin; ***Singapore***: Abiplatin; ***Spain***: Neoplatin†;

Switz.: Platiblastin-S†; Platinol†; ***Thai.***: Abiplatin†; Blastolem†; Kemoplat†; Placis; Platinol†; Platosin; ***Turk.***: Oncoplatin†; Placis; Platosin-S; ***USA***: Platinol†; ***Venez.***: Cytoplatin.

Pharmacopoeial Preparations
BP 2014: Cisplatin Injection;
USP 36: Cisplatin for Injection.

Cladribine *(BAN, USAN, rINN)*

2-Chlorodeoxyadenosine; Cladribin; Cladribina; Cladribinum; Kladribiini; Kladribin; Kladrybina; RWJ-26251-000; RWJ-26251; Кладрибин.
2-Chloro-2′-deoxyadenosine.
$C_{10}H_{12}ClN_5O_3$=285.7
CAS — 4291-63-8.
ATC — L01BB04.
ATC Vet — QL01BB04.
UNII — 47M74X9YT5.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cladribine). A white or almost white crystalline powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; soluble in dimethyl sulfoxide; practically insoluble in acetonitrile. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Cladribine). Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Stability. Cladribine shows increased degradation in glucose 5%, therefore this diluent should not be used. Cladribine in sodium chloride 0.9% is stable for at least 24 hours at room temperature and ambient lighting in PVC infusion containers.

Licensed product information states that cladribine should be stored at 2 degrees to 8 degrees and protected from light.

Uses and Administration

Cladribine is a chlorinated purine nucleoside analogue that inhibits DNA synthesis and repair, particularly in lymphocytes and monocytes. It is used as an antimetabolite antineoplastic for the treatment of lymphoid malignancies including hairy-cell leukaemia (p. 694.3) and chronic lymphocytic leukaemia (p. 693.3). It has also been used in histiocytic syndromes (p. 692.1) and in Waldenström's macroglobulinaemia (p. 699.1).

The recommended intravenous dose of cladribine in **hairy-cell leukaemia** is a single course of 90 micrograms/kg (3.6 mg/m^2) daily for 7 days by continuous infusion. If the patient does not respond to the initial course, they are unlikely to respond to further doses. Cladribine is also given subcutaneously in a dose of 140 micrograms/kg (5.6 mg/m^2) daily for 5 consecutive days.

For the treatment of **chronic lymphocytic leukaemia** the recommended intravenous dose is 120 micrograms/kg (4.8 mg/m^2) daily for 5 consecutive days of a 28-day cycle; the infusion is given over 2 hours. Response should be determined every 2 cycles, and once maximum response has occurred a further 2 cycles of treatment are recommended, up to a maximum of 6 cycles. Patients who do not respond with a lymphocyte reduction of 50% or more after 2 cycles should not receive further therapy. Cladribine is also given subcutaneously in a dose of 100 micrograms/kg (4 mg/m^2) daily for 5 consecutive days. This dose of subcutaneous cladribine is also licensed in some countries for the treatment of indolent **non-Hodgkin's lymphoma** and **Waldenström's macroglobulinaemia**.

Reviews.

1. Belani R, Saven A. Cladribine in hairy cell leukemia. *Hematol Oncol Clin North Am* 2006; **20:** 1109–23.
2. Sigal DS, Saven A. Cladribine in indolent non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2008; **8:** 535–45.
3. Huynh E, *et al.* Cladribine in the treatment of hairy cell leukemia: initial and subsequent results. *Leuk Lymphoma* 2009; **50** (suppl 1): 12–17.
4. Spurgeon S, *et al.* Cladribine: not just another purine analogue? *Expert Opin Invest Drugs* 2009; **18:** 1169–81.
5. Sigal DS, *et al.* Beyond hairy cell: the activity of cladribine in other hematologic malignancies. *Blood* 2010; **116:** 2884–96.

Multiple sclerosis. Cladribine has been investigated for the treatment of multiple sclerosis (p. 996.3).

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

Cladribine produces severe myelosuppression, including neutropenia, anaemia, and thrombocytopenia, especially at high doses. Transfusion of blood products may be required. Prolonged CD4 lymphopenia with a nadir at 4 to 6 months also develops. Prolonged bone-marrow hypocellularity may also occur, although it is not clear if this is due to the drug or underlying disease. Haemolytic anaemia has also been reported. Severe infections can occur, and may be fatal. Myelodysplastic syndrome has been reported rarely.

Other adverse effects include fever, chills, diaphoresis, fatigue, malaise, mild nausea and gastrointestinal disturbances, rashes, pruritus, purpura, headache, anxiety, dizziness, abnormal breath and/or chest sounds, cough, dyspnoea, oedema, tachycardia, hypotension, arthralgia, and myalgia. Reversible, mild increases in bilirubin and hepatic transaminases are common. Rare adverse events include hepatic, renal, or cardiac failure, atrial fibrillation, and hypereosinophilia; tumour lysis syndrome can occur, and may be fatal.

Very high doses of cladribine have been associated with severe renal and nervous system toxicity as well as myelosuppression. Severe neurotoxicity is rare at currently recommended doses, but confusion, neuropathy, ataxia, insomnia, and somnolence have occurred.

Carcinogenicity. As with some other antimetabolites (see p. 726.2), Epstein-Barr virus-related lymphoma has been reported after cladribine therapy.[1] A study found that in patients with chronic lymphocytic leukaemia, treatment with cladribine did not increase the risk of secondary malignancies when compared with treatment with alkylating agents and combination therapy. However, lung cancers occurred more frequently with cladribine treatment.[2]

1. Niesvizky R, *et al.* Epstein-Barr virus-associated lymphoma after treatment of macroglobulinemia with cladribine. *N Engl J Med* 1999; **341:** 55.
2. Robak T, *et al.* Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. *Eur J Cancer* 2004; **40:** 383–9.

Precautions

For the precautions necessary with antineoplastics, see p. 732.2. Careful haematological monitoring is recommended, especially during the first 4 to 8 weeks of therapy. Renal and hepatic function should also be monitored periodically.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cladribine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

Lamivudine. A patient with chronic lymphocytic leukaemia had no decrease in lymphocyte count when cladribine was given with lamivudine, the latter being to prevent reactivation of hepatitis B. Lamivudine was stopped and, after another course of cladribine, the lymphocyte count responded. Study *in-vitro* found that lamivudine inhibited the phosphorylation of cladribine, rendering it inactive.[1]

1. Chtioui H, *et al.* Concomitant treatment with lamivudine renders cladribine inactive by inhibition of its phosphorylation. *Br J Haematol* 2009; **144:** 136–7.

Pharmacokinetics

Plasma-cladribine concentrations after intravenous infusion show either a biphasic or triphasic decline, with terminal half-lives ranging from 3 to 22 hours. A bi-exponential decline has been reported after subcutaneous injection, with an initial and terminal half-life of about 2 and 11 hours, respectively. Cladribine is extensively distributed and penetrates into the CNS. It is about 20% bound to plasma proteins. Cladribine is phosphorylated within cells by deoxycytidine kinase to form 2-chlorodeoxyadenosine-5′-monophosphate which is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chlorodeoxyadenosine-5′-triphosphate (CdATP) by nucleoside diphosphate kinase.

References.

1. Liliemark J. The clinical pharmacokinetics of cladribine. *Clin Pharmacokinet* 1997; **32:** 120–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hemobine; Intocel; Leustat; ***Austral.***: Leustatin; Litak; ***Austria***: Leustatin; Litak; ***Belg.***: Leustatin; ***Braz.***: Leustatin; ***Canad.***: Leustatin; ***China***: Ai Bo Ding (艾博定); ***Cz.***: Leustatin†; Litak; ***Denm.***: Litak; ***Fin.***: Leustatin; Litak; ***Fr.***: Leustatine; Litak; ***Ger.***: Leustatin; Litak; ***Gr.***: Leustatin; Litak; ***Hong Kong***: Leustatin; ***Irl.***: Litak; ***Israel***: Leustatin†; Litak; ***Ital.***: Leustatin; ***Neth.***: Leustatin; Litak; ***Norw.***: Leustatin; Litak; ***NZ***: Leustatin; ***Philipp.***: Leustatin†; ***Pol.***: Biodribin; Litak; ***Port.***: Leustatin; Litak; ***Rus.***: Leicladin (Лейкладин); Movectro (Мовектро); ***S.Afr.***: Leustatin; Litak; ***Singapore***: Leustatin†; ***Spain***: Leustatin; Litak; ***Swed.***: Leustatin; Litak; ***Switz.***: Leustatin; Litak; ***UK***: Leustat; Litak; ***USA***: Leustatin; ***Venez.***: Leustatin.

Clofarabine *(BAN, USAN, rINN)*

Cl-F-Ara-A; Clofarabina; Clofarabinum; Клофарабин.
2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine.
$C_{10}H_{11}ClFN_5O_3$=303.7
CAS — 123318-82-1.
ATC — L01BB06.
ATC Vet — QL01BB06.
UNII — 762RDY0Y2H.

Uses and Administration

Clofarabine, a purine nucleoside analogue, is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory acute lymphoblastic leukaemia (p. 692.3) in patients aged 1 to 21 years. A dose of 52 mg/m^2 is given daily for 5 days, by intravenous infusion (see Administration, below) over 2 hours. A longer infusion time should be considered in children weighing less than 20 kg to reduce anxiety and irritability, and to avoid high clofarabine concentrations. The course may be repeated every 2 to 6 weeks, depending on the patient's recovery from bone-marrow depression and other adverse effects (see Administration in Subsequent Cycles, p. 770.1). Treatment is usually assessed after 2 treatment cycles.

For doses in hepatic and renal impairment, see below and p. 770.1, respectively.

Clofarabine is also under investigation for the treatment of acute myeloid leukaemia. An oral formulation is under investigation for the treatment of patients with myelodysplastic syndromes.

References.

1. Harned TM, Gaynon PS. Treating refractory leukemias in childhood, role of clofarabine. *Ther Clin Risk Manag* 2008; **4:** 327–36.
2. McGregor BA, *et al.* The use of higher dose clofarabine in adults with relapsed acute lymphoblastic leukemia. *Am J Hematol* 2009; **84:** 228–30.
3. Larson ML, Venugopal P. Clofarabine: a new treatment option for patients with acute myeloid leukemia. *Expert Opin Pharmacother* 2009; **10:** 1353–7.
4. Lech-Maranda E, *et al.* Clofarabine as a novel nucleoside analogue approved to treat patients with haematological malignancies: mechanism of action and clinical activity. *Mini Rev Med Chem* 2009; **9:** 805–12.
5. Zhenchuk A, *et al.* Mechanisms of anti-cancer action and pharmacology of clofarabine. *Biochem Pharmacol* 2009; **78:** 1351–9.
6. Sampat K, *et al.* Clofarabine: emerging role in leukemias. *Expert Opin Invest Drugs* 2009; **18:** 1559–64.
7. Jeha S. Recent progress in the treatment of acute lymphoblastic leukemia: clofarabine. *Hematol Oncol Clin North Am* 2009; **23:** 1137–44.
8. Thomas X, *et al.* Clofarabine for the treatment of adult acute myeloid leukemia. *Future Oncol* 2009; **5:** 1197–1210.
9. Faderl S, *et al.* Oral clofarabine in the treatment of patients with higher-risk myelodysplastic syndrome. *J Clin Oncol* 2010; **28:** 2755–60.
10. Tiu RV, *et al.* Clofarabine for myelodysplastic syndromes. *Expert Opin Invest Drugs* 2011; **20:** 1005–14.
11. Majda K, *et al.* Clofarabine (2-chloro-2′-fluoro-2′-deoxyarabinosyladenine)—biochemical aspects of anticancer activity. *Acta Pol Pharm* 2011; **68:** 459–66.
12. O'Connor D, *et al.* Early UK experience in the use of clofarabine in the treatment of relapsed and refractory paediatric acute lymphoblastic leukaemia. *Br J Haematol* 2011; **154:** 482–5.
13. Tran H, Yang D. Clofarabine in the treatment of newly diagnosed acute myeloid leukemia in older adults. *Ann Pharmacother* 2012; **46:** 89–96.

Administration. Instructions for dilution of clofarabine for intravenous use may vary according to country. US licensed product information recommends to filter clofarabine through a 0.2 micrometre syringe filter and then dilute with either glucose 5% or sodium chloride 0.9%, to obtain a final concentration between 150 and 400 micrograms/mL. However, UK licensed product information states that, after filtration (as above), clofarabine should be diluted with sodium chloride 0.9%; total volumes are based on body-surface area as follows:

- ⩽ 1.44 m^2: 100 mL
- 1.45 to 2.4 m^2: 150 mL
- 2.41 to 2.5 m^2: 200 mL

UK licensed product information also states that if the use of a 0.2 micrometre syringe filter is unfeasible, then the concentrate may be filtered with a 5 micrometre filter, diluted as above, and then given through a 0.22 micrometre in-line filter.

Administration in children. Clofarabine is licensed for use in patients aged 1 to 21 years, see Uses and Administration, above.

Administration in hepatic impairment. Clofarabine should be used with caution in hepatic impairment, because data are limited, and there is a potential for hepatotoxicity (see Adverse Effects, p. 770.1). UK licensed product information states that use in severe hepatic impairment is therefore contra-indicated. US licensed product information states that if grade 3 (or higher) increases in bilirubin are seen, clofarabine dosage should be withheld; it may be restarted at a dose reduced by 25% once organ function has recovered (see also Administration in Subsequent Cycles, p. 770.1).

Administration in renal impairment. Clofarabine should be used with caution in renal impairment, because data are limited, and there is a potential for accumulation in patients with decreased creatinine clearance. In patients with moderate impairment (creatinine clearance 30 to 60 mL/min), a dose reduction of 50% is recommended. No dosage recommendations are made for patients with severe impairment and UK licensed product information contra-indicates its use in such patients.

If grade 3 (or higher) increases in creatinine are seen, clofarabine dosage should be withheld; it may be restarted at a dose reduced by 25% once organ function has recovered (see also Administration in Subsequent Cycles, below).

Administration in subsequent cycles. Dosage of clofarabine is determined by body-surface (see Uses and Administration, p. 769.3), based on the actual height and weight before the start of each cycle.

- Treatment cycles are repeated after recovery or return to baseline organ function, about every 2 to 6 weeks.
- Subsequent cycles should not be given sooner than 14 days from the starting day of the previous cycle.
  The absolute **neutrophil** count (ANC) should be $\geqslant$ 750 cells/mm^3 before a dose is given.
  If the ANC has not recovered after 6 weeks from the start of a cycle, a bone marrow aspirate should be performed to determine possible refractory disease; if this is not evident, and once the ANC has recovered to the above concentration, the dose for the next cycle should be reduced by 25% (of the previous dose given).
  If a patient has severe neutropenia, defined as ANC < 500 cells/mm^3, that lasts $\geqslant$ 4 weeks, the dose for the next cycle should be reduced by 25%.
- Clofarabine should be withheld in the event of a clinically significant **infection**; once controlled, treatment may be restarted at the full dose. However, if a second significant infection occurs, treatment may be restarted at a dose reduced by 25% once the infection is controlled.
- If **other** severe toxicities occur (grade 3 toxicities excluding nausea and vomiting), then clofarabine should be withheld until recovery, and restarted at a dose reduced by 25%. If the same toxicity recurs on a second occasion, treatment is withheld until recovery and a *further* 25% dose reduction is recommended.

If a severe toxicity recurs on a third occasion, or does not resolve within 14 days, or is life-threatening or disabling, then clofarabine treatment should be stopped.

Adverse Effects, Treatment, and Precautions

As for Fludarabine Phosphate, p. 794.3, although neurotoxicity is less severe. Febrile neutropenia is very common with clofarabine, as are anxiety, headache, flushing, mucosal inflammation, pruritus, and palmar-plantar erythrodysesthesia syndrome. Other common adverse effects include pain, myalgia, arthralgia, hypersensitivity reactions, haematuria, skin exfoliation, alopecia, erythema (which can be generalised), petechiae, dry skin, hyperhidrosis, dizziness, tremor, hearing loss, and epistaxis. Hypertension has also been reported. Hepatotoxicity is also common and can include hyperbilirubinaemia, jaundice, and veno-occlusive disease; patients who have received a haematopoietic stem cell transplant may be at higher risk for hepatotoxicity.

Patients should be monitored for signs and symptoms of cytokine release (including tachypnoea, tachycardia, hypotension, and pulmonary oedema) that could develop into systemic inflammatory response syndrome (SIRS) or capillary leak syndrome, which can be fatal. Symptoms of the latter include respiratory distress, hypotension, pleural and pericardial effusions, and multi-organ failure. Prophylactic corticosteroids may be useful, but clofarabine must be stopped immediately if signs or symptoms of SIRS, capillary leak syndrome, or hypotension develop; further treatment, at a lower dose (see Uses and Administration, p. 769.3), can be considered once patients are stabilised and organ function has returned to baseline. Patients with cardiac disease should be closely monitored. Enterocolitis, including neutropenic enterocolitis and *Clostridium difficile* colitis have been reported, usually within a month of treatment with clofarabine, and usually when given with other chemotherapy.

Renal and hepatic function, and complete blood counts, should be monitored during clofarabine therapy. Hydration should be maintained during treatment to minimise the risk of tumour lysis syndrome and other adverse effects.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clofarabine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

Patients taking drugs that affect blood pressure or cardiac function should be closely monitored during clofarabine therapy. Drugs that are eliminated by renal tubular secretion might interfere with the excretion of clofarabine and should be avoided.

Pharmacokinetics

Clofarabine is about 47% bound to plasma proteins, mainly to albumin. About 50 to 60% of a dose is excreted unchanged in the urine and it has a terminal half-life of about 5 hours.

References.
1. Bonate PL, *et al.* Population pharmacokinetics of clofarabine and its metabolite 6-ketoclofarabine in adult and pediatric patients with cancer. *Cancer Chemother Pharmacol* 2011; **67:** 875–90.
2. Long-Boyle J, *et al.* Pharmacokinetics of clofarabine in patients with high-risk inherited metabolic disorders undergoing brain-sparing hematopoietic cell transplantation. *J Clin Pharmacol* 2011; **51:** 679–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Evoltra; ***Austria***: Evoltra; ***Belg.***: Evoltra; ***Canad.***: Clolar; ***Cz.***: Evoltra; ***Denm.***: Evoltra; ***Fr.***: Evoltra; ***Ger.***: Evoltra; ***Gr.***: Evoltra; ***Irl.***: Evoltra; ***Israel***: Evoltra; ***Ital.***: Evoltra; ***Jpn***: Evoltra; ***Neth.***: Evoltra; ***Norw.***: Evoltra; ***NZ***: Evoltra; ***Pol.***: Evoltra; ***Port.***: Evoltra; ***Spain***: Evoltra; ***Swed.***: Evoltra; ***UK***: Evoltra; ***USA***: Clolar.

Corynebacterium parvum

C. parvum; NSC-220537; *Propionibacterium acnes*.
UNII — TRZ1AA965O.

Profile

Inactivated *Corynebacterium parvum* has been used in the treatment of malignant effusions, and has been tried as an adjuvant to cancer chemotherapy for its immunostimulant properties. It has also been used in the treatment of musculoskeletal and joint disorders.

Fever and pain have occurred after intracavitary injection. There have been reports of nephrotoxicity after intravenous use.

Crizotinib *(USAN, rINN)*

Crizotinibum; PF-02341066; Кризотиниб.
3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridine-2-amine.
$C_{21}H_{22}Cl_2FN_5O$=450.3
CAS — 877399-52-5.
UNII — 53AH36668S.

Uses and Administration

Crizotinib is an inhibitor of receptor tyrosine kinases, including ALK (anaplastic lymphoma kinase) and hepatocyte growth factor receptor (HGFR; c-Met). Crizotinib is used for the treatment of patients with locally advanced, metastatic, or advanced and refractory non-small cell lung cancer (p. 711.1) that is ALK-positive. The recommended dose is 250 mg orally twice daily; capsules should be swallowed whole. Treatment is continued until patients no longer benefit, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* If a daily dose of crizotinib is missed, no catch-up dose is recommended if it is less than 6 hours before the next dose. Doses may need to be reduced or treatment interrupted for toxicity (see Administration in Subsequent Cycles, below).

Crizotinib is also under investigation for the treatment of other solid tumours and non-Hodgkin's lymphoma.

References.
1. Kwak EL, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; **363:** 1693–1703.
2. Rodig SJ, Shapiro GI. Crizotinib, a small-molecule dual inhibitor of the c-Met and ALK receptor tyrosine kinases. *Curr Opin Investig Drugs* 2010; **11:** 1477–90.
3. Gadgeel SM, Bepler G. Crizotinib: an anaplastic lymphoma kinase inhibitor. *Future Oncol* 2011; **7:** 947–53.

Administration in subsequent cycles. The oral dose of crizotinib may need to be reduced or therapy withheld if toxicities occur. Licensed product information gives the following guidelines:
for haematological toxicities

- grade 3: withhold until recovery $\leqslant$ grade 2, then resume at the same dose schedule
- grade 4: withhold until recovery $\leqslant$ grade 2, then resume at 200 mg twice daily; in the case of recurrence, withhold again until recovery $\leqslant$ grade 2, then resume at 250 mg once daily. For further grade 4 recurrence, permanently stop crizotinib

for non-haematological toxicities

- any grade pneumonitis (that is not due to disease progression, other pulmonary disease, infection, or effects of radiation): permanently stop crizotinib
- grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with total bilirubin $\leqslant$ grade 1: withhold until recovery to $\leqslant$ grade 1 or baseline, then resume at 200 mg twice daily; in the case of recurrence, withhold again until recovery $\leqslant$ grade 1, then resume at 250 mg once daily. For further grade 3 or 4 recurrence, permanently stop crizotinib
- grade 2, 3, or 4 ALT or AST elevation with concurrent grade 2, 3, or 4 total bilirubin elevation (without evidence of cholestasis or haemolysis): permanently stop crizotinib
- grade 3 QTc prolongation: withhold until recovery to $\leqslant$ grade 1, then resume at 200 mg twice daily; in the case of recurrence, withhold again until recovery $\leqslant$ grade 1, then resume at 250 mg once daily. For further grade 3 recurrence, permanently stop crizotinib
- grade 4 QTc prolongation: permanently stop crizotinib

Adverse Effects, Treatment, and Precautions

Crizotinib has been associated with severe pneumonitis and fatalities have been reported. Patients should be monitored for pulmonary symptoms and crizotinib should be permanently stopped in those diagnosed with treatment-related pneumonitis. Other respiratory adverse effects associated with fatalities have included hypoxia, acute respiratory distress syndrome, dyspnoea, empyema, and pulmonary haemorrhage. Pulmonary embolism can occur. Increases in liver transaminases have been seen, and liver function tests should be monitored monthly, or more frequently if needed. While most patients were asymptomatic, some may require dose interruption or for therapy to be permanently stopped. QTc prolongation can occur and crizotinib should be avoided in patients with congenital long QT syndrome. Monitoring (using ECGs and electrolyte concentrations) should be considered in those with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking drugs known to prolong the QT interval. Bradycardia can occur with crizotinib therapy. Severe neutropenia, thrombocytopenia, and lymphopenia have been reported and dose modifications may be needed. For details of dose delay, dose reductions, or stoppage of therapy for adverse effects, see Administration in Subsequent Cycles, above.

The most common adverse effects associated with crizotinib are visual disorders, gastrointestinal disturbances, and oedema. Visual disorders include visual impairment, blurred vision, diplopia, photopsia, photophobia, and vitreous floaters; events have generally been reported within 2 weeks of starting crizotinib. Gastrointestinal disturbances include nausea, diarrhoea, vomiting, constipation, oesophageal disorders, abdominal pain, and stomatitis. Other common adverse effects include fatigue, decreased appetite, hypophosphataemia, dizziness, headache, dysgeusia, insomnia, upper respiratory-tract infection, dyspnoea, cough, arthralgia, and rash. Neuropathy is also common, and can include burning sensations, dysaesthesia, hypoaesthesia or hyperaesthesia, neuralgia, and paraesthesia; peripheral neuropathy can be sensory or motor. Pain (in the chest or back) and fever can occur. Renal cysts, without evidence of abnormal urinalysis or renal impairment, have been reported.

Interactions

Crizotinib is metabolised by cytochrome P450 isoenzymes CYP3A4/5. Strong CYP3A inhibitors (such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole) can increase crizotinib plasma concentrations and concomitant use should be avoided; grapefruit juice should also be avoided. Caution is advised with concomitant use of moderate CYP3A inhibitors. Strong CYP3A inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St John's Wort) can decrease crizotinib plasma concentrations and concomitant use should be avoided. Crizotinib also inhibits CYP3A and dose reduction may be needed for drugs that are mainly metabolised by CYP3A. Use of crizotinib with CYP3A substrates with narrow therapeutic indices (such as alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be avoided.

Pharmacokinetics

Peak plasma concentrations occur between 4 to 6 hours after a single oral dose of crizotinib. Mean bioavailability is about 43%. Exposure is reduced by a high-fat meal; however, crizotinib can be given with or without food. Steady-state concentrations are reached within 15 days. Plasma protein binding is about 90%. *In-vitro* data suggest that crizotinib is a substrate for P-glycoprotein, that

metabolism is mainly via the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. The main metabolic pathways are oxidation (to crizotinib lactam) and *O*-dealkylation. The mean apparent plasma terminal half-life has been reported to be about 42 hours after a single dose of crizotinib. About 63% and 22% of a single dose is recovered in faeces and urine, respectively (of which unchanged drug is about 53% and 2.3%, respectively).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Xalkori; ***Denm.***: Xalkori; ***Fr.***: Xalkori; ***Israel***: Xalkori; ***Jpn***: Xalkori; ***Neth.***: Xalkori; ***Norw.***: Xalkori; ***Switz.***: Xalkori; ***UK***: Xalkori; ***USA***: Xalkori.

Cyclophosphamide *(BAN, rINN)*

B-518; Ciclofosfamida; Ciklofosfamidas; Ciklofoszfamid; Cyclophosphamid; Cyclophosphamidum; Cyclophosphamidum Monohydricum; Cyclophosphanum; Cyklofosfamid; Cyklofosfamid monohydrát; NSC-26271; Siklofosfamid; Syklofosfamidi; WR-138719; Циклофосфамид.

2-[Bis(2-chloroethyl)amino]perhydro-1,3,2-oxazaphosphorinan 2-oxide monohydrate.

$C_7H_{15}Cl_2N_2O_2P,H_2O$=279.1

CAS — 6055-19-2 (cyclophosphamide monohydrate); 50-18-0 (anhydrous cyclophosphamide).

ATC — L01AA01.

ATC Vet — QL01AA01.

UNII — 8N3DW7272P (cyclophosphamide); 6UXW23996M (anhydrous cyclophosphamide).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Cyclophosphamide). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. A freshly prepared 2% solution in water has a pH of 4.0 to 6.0.

USP 36: (Cyclophosphamide). A white, crystalline powder. It liquefies upon loss of its water of crystallisation. Soluble in water and in alcohol. A 1% solution in water has a pH of 3.9 to 7.1 when determined 30 minutes after preparation. Store in airtight containers at 2 degrees to 30 degrees.

Uses and Administration

Cyclophosphamide is an antineoplastic that is converted in the body to active alkylating metabolites with properties similar to those of chlormethine (p. 765.2). It also possesses marked immunosuppressant properties.

Cyclophosphamide is widely used, often with other agents, in the treatment of malignant diseases. It is given for Burkitt's and other non-Hodgkin's lymphomas, multiple myeloma, and mycosis fungoides. It is also used in gestational trophoblastic tumours and malignancies of the brain, breast, endometrium, lung, and ovary; in childhood malignancies such as neuroblastoma, retinoblastoma, Wilms' tumour; and in sarcomas and some leukaemias.

The immunosuppressant properties of cyclophosphamide have been used in organ and tissue transplantation. It has also been used in the management of disorders thought to have an auto-immune component including amyloidosis, Behçet's syndrome, glomerular kidney disease, immune thrombocytopenia, aplastic anaemia, idiopathic pulmonary fibrosis, polymyositis, scleroderma, SLE, and vasculitic syndromes including the Churg-Strauss syndrome, polyarteritis nodosa, and Wegener's granulomatosis.

The use of cyclphosphamide is these disorders is further discussed under the headings below.

Cyclophosphamide is usually given orally or by intravenous injection.

In the BP 2014 the content of Cyclophosphamide Injection is expressed in terms of the equivalent amount of anhydrous cyclophosphamide whereas the content of Cyclophosphamide Tablets is given in terms of the monohydrate; the USP 36 expresses content in terms of anhydrous cyclophosphamide for both injection and tablets. Confusion has arisen when patients were changed from a preparation in which the content was expressed as the monohydrate to one in which it was expressed as the anhydrous substance (see Effects on the Bladder, p. 772.3). 53.45 mg of cyclophosphamide monohydrate is equivalent to 50 mg of anhydrous cyclophosphamide. *Doses below are given in terms of anhydrous cyclophosphamide.*

The dosage of cyclophosphamide given may vary considerably depending on the disease being treated, the condition of the patient including the state of the bone marrow, and use with radiotherapy or other chemotherapy. The white cell count is usually used to guide the dose. Every effort should be made to establish that the dose is appropriate according to the above factors. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

In the UK, examples of regimens given, generally without specific indications, in licensed product information are:

- *low-dose*: cyclophosphamide 2 to 6 mg/kg weekly as a single intravenous dose or in divided oral doses
- *moderate-dose*: 10 to 15 mg/kg weekly as a single intravenous dose.
- *high-dose*: 20 to 40 mg/kg as a single intravenous dose every 10 to 20 days, although higher doses have been used

Alternative regimens include:

- 100 to 300 mg daily in divided oral doses
- 50 to 250 mg/m^2 daily orally
- 80 to 300 mg/m^2 daily as a single intravenous dose, or daily in divided oral doses
- 300 to 600 mg/m^2 weekly as a single intravenous dose
- 600 to 1500 mg/m^2 as a single intravenous dose or short infusion at 10- to 20-day intervals

Alternative regimens used in some other European countries include:

- 3 to 6 mg/kg (about 120 to 240 mg/m^2) daily intravenously
- 10 to 15 mg/kg (about 400 to 600 mg/m^2) every 2 to 5 days intravenously

In the UK, the use of mesna is generally recommended with single doses of cyclophosphamide over 2 g, but it is used with cyclophosphamide doses as low as 10 mg/kg in some countries.

In the USA, an initial dose of 40 to 50 mg/kg has been licensed for single agent therapy of malignancy, given intravenously in divided doses over 2 to 5 days although in practice treatment of malignancy will generally be with combination regimens. Other licensed regimens include:

- 3 to 5 mg/kg twice weekly intravenously
- 10 to 15 mg/kg every 7 to 10 days intravenously
- 1 to 5 mg/kg daily orally

In patients who are to undergo haematopoietic stem cell transplantation, intravenous doses of 20 to 40 mg/kg (about 800 to 1600 mg/m^2) and higher are given, at intervals of 21 to 28 days. Alternatively, very high doses of cyclophosphamide such as 60 mg/kg daily for 2 days may be given as part of the conditioning regimen.

Cyclophosphamide has also been given intramuscularly, intraperitoneally, and intrapleurally, as well as intra-arterially, and by local perfusion (but passage through the liver is required for its activation—see Pharmacokinetics, p. 774.1). A liquid preparation of cyclophosphamide for oral use may be prepared using the powder for injection.

Regular blood counts are essential during therapy with cyclophosphamide and treatment should be withdrawn or delayed if leucopenia or thrombocytopenia becomes severe (see also Bone-marrow Depression, p. 730.3). Patients should be adequately hydrated and urine output maintained.

Administration in the elderly. Despite some suggestion that cyclophosphamide metabolism may be slower in the elderly, there appear to be no pharmacokinetic differences based on age alone. A review concluded that healthy older patients should not be denied adjuvant chemotherapy on an age basis, and that there is no solid evidence for dose reduction of cyclophosphamide based on age alone.[1]

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Amyloidosis. Although there is no unequivocally effective treatment for amyloidosis (p. 819.3), cyclophosphamide may reduce the decline in renal function and prolong survival;[1-3] it has also been used with epirubicin and carmustine to suppress the disease in a patient who had undergone heart transplantation for cardiac amyloid.[4] Good responses have also been reported to cyclophosphamide given in a regimen with thalidomide and dexamethasone.[5]

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46:** 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis; a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20:** 2051–7.
3. Chevrel G, *et al.* Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. *Rheumatology (Oxford)* 2001; **40:** 821–5.
4. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309:** 1135–7.
5. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109:** 457–64.

Blood disorders, non-malignant. Cyclophosphamide has been used in patients with immune thrombocytopenia (p. 1606.1), but cytotoxic immunosuppressants tend to be a second-line treatment option. Responses generally occur within 8 weeks.[1] In patients with refractory life-threatening disease, high-dose cyclophosphamide[1] may be tried. Combination chemotherapy including cyclophosphamide has also produced responses in a few patients.[2]

In the management of warm auto-immune haemolytic anaemia (p. 1122.2) low-dose cyclophosphamide may be used in patients refractory to corticosteroids and splenectomy. A small number of patients with severe refractory disease have been treated with high-dose cyclophosphamide with some success.[3]

Cyclophosphamide is often used in preparation for bone marrow transplantation in patients with aplastic anaemia (p. 1121.3), and complete remission has also been reported with high-dose cyclophosphamide alone.[4,5] However, a randomised study[6] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those given cyclophosphamide. Further follow-up[7] also found that relapse rates were no different.

Cyclophosphamide with a corticosteroid has been tried in the rare condition of acquired haemophilia (p. 1126.3).

1. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126:** 307–14.
2. Figueroa M, *et al.* Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med* 1993; **328:** 1226–9.
3. Moyo VM, *et al.* High-dose cyclophosphamide for refractory autoimmune hemolytic anemia. *Blood* 2002; **100:** 704–6.
4. Brodsky RA, *et al.* Durable treatment-free remission after high-dose cyclophosphamide therapy for previously untreated severe aplastic anemia. *Ann Intern Med* 2001; **135:** 477–83.
5. Savage WJ, *et al.* Treatment of hepatitis-associated aplastic anemia with high-dose cyclophosphamide. *Pediatr Blood Cancer* 2007; **49:** 947–51.
6. Tisdale JF, *et al.* High-dose cyclophosphamide in severe aplastic anaemia: a randomised trial. *Lancet* 2000; **356:** 1554–9.
7. Tisdale JF, *et al.* Late complications following treatment for severe aplastic anemia (SAA) with high-dose cyclophosphamide (Cy): follow-up of a randomized trial. *Blood* 2002; **100:** 4668–70.

Cogan's syndrome. For reference to the use of cyclophosphamide with corticosteroids for Cogan's syndrome, see p. 1603.2.

Connective tissue and muscular disorders. Cyclophosphamide is one of several immunosuppressants that have been tried for disease control in Behçet's syndrome (p. 1601.1); such drugs may permit a reduction in the use of corticosteroids, although they carry their own risks of toxicity. In polymyositis (p. 1611.1) cyclophosphamide may have a role where there is lung disease; the role of immunosuppressants other than azathioprine or methotrexate is poorly defined. In patients with SLE (p. 1613.3), cyclophosphamide has been used with some success for severe disease or disease refractory to corticosteroids alone, and appears to be more effective than corticosteroids for lupus nephritis; the evidence for its use has been critically assessed.[1,2]

1. Houssiau F. Thirty years of cyclophosphamide: assessing the evidence. *Lupus* 2007; **16:** 212–16.
2. Bargman JM. How did cyclophosphamide become the drug of choice for lupus nephritis? *Nephrol Dial Transplant* 2009; **24:** 381–4.

Kidney disorders, non-malignant. Cyclophosphamide is used with corticosteroids in the treatment of some forms of glomerular kidney disease (p. 1604.3). In children with nephrotic syndrome, oral cyclophosphamide 2 to 3 mg/kg daily for 8 weeks may be added to a course of corticosteroid therapy in relapsing disease; intravenous cyclophosphamide 500 mg/m^2 monthly for 6 months also substantially reduces the risk of relapse.[1] Addition of cyclophosphamide to corticosteroid therapy also improves the prospect of remission in focal glomerulosclerosis. Oral cyclophosphamide helps to stabilise progressive disease in patients with membranous nephropathy[2] although intermittent intravenous pulses are reported to be ineffective.[3] Such treatment is usually reserved for those whose disease is severe and progressive enough to justify it, but is probably better tolerated than other alkylating agents such as chlorambucil.[4] Cyclophosphamide has been given with methylprednisolone for rapidly progressive glomerulonephritis,[5] and has been used as part of the aggressive management of renal lesions in Goodpasture's syndrome. A systematic review[6] concluded that pulse cyclophosphamide, which allows for a reduced dose, results in good remission rates in rapidly progressive glomerulonephritis, but has an increased risk of relapse when compared with continuous use.

1. Hodson EM *et al.* Non-corticosteroid treatment for nephrotic syndrome in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 20/07/10).
2. Falk RJ, *et al.* Treatment of progressive membranous glomerulopathy: a randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. *Ann Intern Med* 1992; **116:** 438–45.
3. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328–33.
4. Schieppati A, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester; John Wiley; 2004 (accessed 22/07/09).
5. Bruns FJ, *et al.* Long-term follow-up of aggressively treated idiopathic rapidly progressive glomerulonephritis. *Am J Med* 1989; **86:** 400–6.
6. Walters G, *et al.* Interventions for renal vasculitis in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 22/07/09).

Liver disorders, non-malignant. For mention of the use of cyclophosphamide in auto-immune hepatitis inadequately

controlled by corticosteroids and azathioprine see Chronic Active Hepatitis, p. 1602.3.

Lung disorders, non-malignant. Cyclophosphamide has been used with corticosteroids in patients with idiopathic pulmonary fibrosis as mentioned under Interstitial Lung Disease, p. 1607.1.

Malignant neoplasms. Cyclophosphamide is one of the most widely used drugs for the chemotherapy of malignancy, and mention of its role may be found in the discussions of the management of gestational trophoblastic tumours (p. 691.2); the non-Hodgkin's lymphomas, including AIDS-related lymphoma, Burkitt's lymphoma, and mycosis fungoides (p. 696.3, p. 697.2, p. 697.3, p. 698.3); malignancies of the brain (p. 701.2), breast (p. 702.1), lung (p. 710.2), ovary (p. 711.2) and thymus (p. 715.3); multiple myeloma (p. 699.2); Wilms' tumour, neuroblastoma, and retinoblastoma (p. 709.1, p. 716.2, and p. 717.2 respectively); and sarcomas of bone (p. 717.3) and rhabdomyosarcoma (see Soft-tissue Sarcoma, p. 718.2). Cyclophosphamide is also used in the management of acute lymphoblastic leukaemia (p. 692.3) and chronic lymphocytic leukaemia (p. 693.3).

Neuromuscular disorders. Cyclophosphamide has been tried in myasthenia gravis (p. 684.1) in patients who require immunosuppressants but are intolerant of or unresponsive to corticosteroids and azathioprine. Cyclophosphamide has also been tried in regimens for the management of multiple sclerosis (p. 996.3), but the reported benefits have generally been slight and outweighed by toxicity, such that it is usually reserved for patients with severe disease resistant to standard therapies.

References.
1. De Feo LG, *et al*. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. *Muscle Nerve* 2002; **26:** 31–6.
2. Drachman DB, *et al*. Treatment of refractory myasthenia: "rebooting" with high-dose cyclophosphamide. *Ann Neurol* 2003; **53:** 29–34.
3. Portaccio E, *et al*. Safety and tolerability of cyclophosphamide 'pulses' in multiple sclerosis: a prospective study in a clinical cohort. *Multiple Sclerosis* 2003; **9:** 446–50.
4. Zephir H, *et al*. Treatment of progressive forms of multiple sclerosis by cyclophosphamide: a cohort study of 490 patients. *J Neurol Sci* 2004; **218:** 73–7.
5. La Mantia L, *et al*. Cyclophosphamide for multiple sclerosis. Available in The Cochrane Database of SystematicReviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Ocular disorders, non-malignant. Immunosuppressive agents, including cyclophosphamide, have been used in scleritis and uveitis (see p. 1612.3 and p. 1615.1) unresponsive to corticosteroids in tolerable doses.

Organ and tissue transplantation. Cyclophosphamide is used in high doses, usually with busulfan or irradiation, in conditioning regimens for bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1937.1). It has been tried as part of immunosuppressant regimens after transplantation of heart grafts (p. 1938.2).

Paraquat poisoning. For reference to the use of cyclophosphamide in paraquat poisoning, see p. 2159.2.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p. 1687.1). Immunosuppressive therapy, including cyclophosphamide,[1,2] has been used with corticosteroids to permit a reduction in corticosteroid dosage. Cyclophosphamide with a corticosteroid is also reported to be of value in ocular mucous membrane pemphigoid,[3] although treatment may not completely prevent cicatrisation.[4] Oral cyclophosphamide is considered an alternative to azathioprine in pemphigus vulgaris and pulsed intravenous doses might be considered in severe or recalcitrant cases.[5] There is less support for cyclophosphamide in bullous pemphigoid and it should only be considered if other treatments have failed or are contra-indicated.[6] However, oral or intravenous cyclophosphamide with corticosteroids may be considered for first-line treatment of severe or rapidly progressive mucous membrane pemphigoid.[7]

1. Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. *Arch Dermatol* 1992; **128:** 1626–30.
2. Itoh T, *et al*. Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol* 1996; **134:** 931–3.
3. Kirtschig G, *et al*. Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; **138:** 380–4.
4. Elder MJ, *et al*. Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995; **79:** 264–6.
5. Harman KE, *et al*. British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Pemphigus%20Vulgaris.pdf (accessed 20/07/10)
6. Wojnarowska F, *et al*. British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bullous%20Pemphigoid.pdf (accessed 20/07/10)
7. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; **6:** 93–103.

Retroperitoneal fibrosis. There are reports[1,2] of success with cyclophosphamide, with or without corticosteroids, in the treatment of retroperitoneal fibrosis (p. 1612.1). In one study,[2] severe or refractory disease was treated with monthly intravenous pulses of cyclophosphamide 15 mg/kg, for 6 months, followed by azathioprine; all patients went into remission.

1. Fukuda W, *et al*. Multifocal fibrosclerosis: retroperitoneal fibrosis associated with a suprasellar tumor and pachymeningitis. *Intern Med* 2003; **42:** 1006–10.
2. Warnatz K, *et al*. Immunosuppressive treatment of chronic periaortitis: a retrospective study of 20 patients with chronic periaortitis and a review of the literature. *Ann Rheum Dis* 2005; **64:** 828–33.

Rheumatoid arthritis. Cyclophosphamide has been used as a disease-modifying antirheumatic drug in rheumatoid arthritis (p. 13.2), usually in patients with severe disease unresponsive to other drugs; its severe toxicity limits its usefulness.[1] It is of most value in controlling antibody-mediated systemic complications of the disease such as vasculitis[2] through inhibition of B-cell function.

1. Suarez-Almazor ME, *et al*. Cyclophosphamide for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/05/05).
2. Choy E, Kingsley G. How do second-line agents work? *Br Med Bull* 1995; **51:** 472–92.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p. 1612.2), corticosteroids are the usual treatment. Cyclophosphamide is one of several cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy; its use has been limited by toxicity.

Scleroderma. As discussed on p. 1942.3 the role of drug treatment for scleroderma is not well determined, and it is unclear whether cyclophosphamide (with or without a corticosteroid) is useful for patients with lung involvement.

Vasculitic syndromes. Treatment of the systemic vasculitides has revolved around the use of corticosteroids and cyclophosphamide. The benefits are uncertain in polyarteritis nodosa (p. 1610.2) and Takayasu's arteritis (p. 1614.3), but the benefits of combined therapy are generally accepted in Churg-Strauss syndrome (p. 1603.1) and microscopic polyangiitis (p. 1610.2), and cyclophosphamide is the mainstay of effective treatment of Wegener's granulomatosis (p. 1615.2). Several cyclophosphamide regimens are used, with no major differences reported in outcome.[1] A pulsed regimen (intermittent high-dose intravenous therapy) was found to be as effective in antineutrophil cytoplasmic antibody-associated vasculitis as an oral daily regimen; pulsed therapy allowed for a reduced cumulative cyclophosphamide dose and caused fewer adverse effects.[2]

1. Richmond R, *et al*. Optimisation of cyclophosphamide therapy in systemic vasculitis. *Clin Pharmacokinet* 1998; **34:** 79–90.
2. de Groot K, *et al*. EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; **150:** 670–80.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2. The major dose-limiting effect is myelosuppression. After single doses the nadir of the white cell count may occur in around 1 to 2 weeks with full recovery usually in 3 to 4 weeks. Thrombocytopenia and anaemia may occur but tend to be less common and less severe.

Haemorrhagic cystitis may develop after high or prolonged dosage, and can be life-threatening. Adequate hydration to maintain urine output at 100 mL/hour and use of mesna (see p. 1557.2) are generally recommended in an attempt to reduce urotoxicity. If mesna is used, frequent emptying of the bladder should be avoided. Doses of cyclophosphamide should be given early in the day.

Alopecia occurs in about 20% of patients given low doses and in practically all patients given high doses. Hair loss starts after 3 weeks of treatment but regrowth is usually evident after 3 months, even with continued treatment. Hyperpigmentation of skin, especially that of the palms and soles, and of the nails, has been reported.

Nausea and vomiting commonly occur, and may be reduced by prophylactic antiemetics. Mucositis may also occur.

Other adverse effects include a syndrome resembling inappropriate secretion of antidiuretic hormone (which may require diuretic therapy), disturbances of carbohydrate metabolism, gonadal suppression (common and occasionally resulting in sterility), interstitial pulmonary fibrosis, and, especially at high doses, cardiotoxicity.

Cyclophosphamide, in common with other alkylating agents, has carcinogenic, mutagenic, and teratogenic potential and secondary malignancies have occurred in patients given previous antineoplastic therapy including cyclophosphamide—see p. 726.2.

Effects on the bladder. *Sterile haemorrhagic cystitis* (p. 2347.3) can occur after high-dose infusions of cyclophosphamide or after prolonged low-dose oral use.[1-4] It is believed to be secondary to renal excretion of alkylating metabolites, particularly the acrolein metabolite, that cause sloughing, thinning, and inflammation of the bladder wall. Damage ranges from minor bleeding to diffuse necrotic ulceration, and can lead to anaemia, constriction of the bladder, bladder perforation, and death.[2] Symptoms may be delayed, and have been reported to occur up to 6 months after stopping the drug.[5] An increased incidence of cystitis when patients on a high-dose cyclophosphamide regimen were transferred from one brand to another has been reported,[6] apparently because one was labelled in terms of the anhydrous substance and one as the monohydrate, resulting in a 6.4% difference in the content of active substance.[7]

Measures used to prevent haemorrhagic cystitis include intravenous hydration with diuresis, frequent voiding, or bladder catheterisation with irrigation, to increase urine output and dilute the excreted metabolites. Mesna may be used as a uroprotectant to reduce exposure to the metabolites.[2-4] If bleeding occurs, various drugs have been instilled intravesically, including sodium chloride 0.9%, alum, or prostaglandins.[2,3,8-11] Silver nitrate, formaldehyde, or phenol instillations have been used but are painful and patients require anaesthesia.[2] There is limited information to suggest that conjugated oestrogens given orally or intravenously may be effective;[2,12] oral pentosan polysulfate sodium may also be of benefit.[3] Nonpharmacological techniques are reserved for refractory cases and include arterial embolisation or surgery.[2]

In addition to the shorter term effects, cyclophosphamide has been reported to be associated with the development of *bladder carcinoma*.[1,4,13-16] A history of cyclophosphamide-induced cystitis may be associated with an increased risk of bladder carcinoma[1,4,13] but some studies have not found a link,[15] and bladder malignancies can develop in patients who have not experienced cystitis while receiving cyclophosphamide.[14] For a discussion of the carcinogenic effects of antineoplastics, including cyclophosphamide, see p. 726.2.

1. Talar-Williams C, *et al*. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; **124:** 477–84.
2. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; **17:** 696–706.
3. Mukhtar S, Woodhouse C. The management of cyclophosphamide-induced haematuria. *BJU Int* 2010; **105:** 908–12.
4. Monach PA, *et al*. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheum* 2010; **62:** 9–21.
5. Armstrong B, *et al*. Delayed cystitis due to cyclophosphamide. *N Engl J Med* 1979; **300:** 45.
6. Shaw IC, *et al*. Difference in bioactivity between two preparations of cyclophosphamide. *Lancet* 1983; **i:** 709.
7. Hilgard P, *et al*. Bioactivity of cyclophosphamide preparations. *Lancet* 1983; **i:** 1436.
8. Mohiuddin J, *et al*. Treatment of cyclophosphamide-induced cystitis with prostaglandin E_2. *Ann Intern Med* 1984; **101:** 142.
9. Miller LJ, *et al*. Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. *Ann Pharmacother* 1994; **28:** 590–4.
10. Ippoliti C, *et al*. Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46:** 811–15.
11. Laszlo D, *et al*. Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; **80:** 421–5.
12. Ordemann R, *et al*. Encouraging results in the treatment of haemorrhagic cystitis with estrogen – report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25:** 981–5.
13. Wall RL, Clausen KP. Carcinoma of the urinary bladder in patients receiving cyclophosphamide. *N Engl J Med* 1975; **293:** 271–3.
14. Plotz PH, *et al*. Bladder complications in patients receiving cyclophosphamide for systemic lupus erythematosus or rheumatoid arthritis. *Ann InternMed* 1979; **91:** 221–3.
15. Pedersen-Bjergaard J, *et al*. Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med* 1988; **318:** 1028–32.
16. Travis LB, *et al*. Bladder cancer after chemotherapy for non-Hodgkin's lymphoma. *N Engl J Med* 1989; **321:** 544–5.

Effects on the blood. Amifostine has been reported to protect against the myelosuppressive effects of cyclophosphamide, and may be used to reduce neutropenia-related infection associated with the combination of cyclophosphamide and cisplatin (see p. 1539.2).

Effects on carbohydrate metabolism. Acute onset type 1 diabetes occurred in a patient treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), and was thought to be due to the cyclophosphamide.[1]

1. Atlan-Gepner C, *et al*. A cyclophosphamide-induced autoimmune diabetes. *Lancet* 1998; **352:** 373–4.

Effects on electrolytes. Water intoxication has been reported with cyclophosphamide,[1-4] usually in high doses (30 to 50 mg/kg or more) although symptoms have been reported after a dose of 20 mg/kg in a patient with renal disease,[3] and in another patient with SLE but apparently

normal renal function who received 10 mg/kg.[4] One case of severe hyponatraemia leading to convulsions and death has been reported.[5] Symptoms resemble the syndrome of inappropriate antidiuretic hormone secretion[5] but plasma concentrations of antidiuretic hormone do not appear to be raised in these patients.[3]

1. DeFronzo RA, *et al.* Water intoxication in man after cyclophosphamide therapy: time course and relation to drug activation. *Ann Intern Med* 1973; **78:** 861–9.
2. Green TP, Mirkin BL. Prevention of cyclophosphamide-induced antidiuresis by furosemide infusion. *Clin Pharmacol Ther* 1981; **29:** 634–42.
3. Bressler RB, Huston DP. Water intoxication following moderate-dose intravenous cyclophosphamide. *Arch Intern Med* 1985; **145:** 548–9.
4. McCarron MO, *et al.* Water intoxication after low dose cyclophosphamide. *BMJ* 1995; **311:** 292.
5. Harlow PJ, *et al.* A fatal case of inappropriate ADH secretion induced by cyclophosphamide therapy. *Cancer* 1979; **44:** 896–8.

Effects on the eyes. Recurrent transient myopia, apparently due to increased hydration of the lens of the eye, was induced by an intravenous bolus of cyclophosphamide in an adolescent with SLE.[1]

CMV retinitis has occurred in patients during or after cyclophosphamide therapy; presenting symptoms included floaters and blurred or decreased vision.[2]

1. Arranz JA, *et al.* Cyclophosphamide-induced myopia. *Ann Intern Med* 1992; **116:** 92–3.
2. Agrawal A, *et al.* Visual symptoms in patients on cyclophosphamide may herald sight threatening disease. *Br J Ophthalmol* 2003; **87:** 122–3.

Effects on reproductive potential. Severe gonadal failure with transient or permanent azoospermia is common in men treated with cyclophosphamide. Suppression of germ-cell function with intramuscular testosterone in 5 men during cyclophosphamide therapy for nephrotic syndrome was associated with a more rapid return of spermatogenesis compared with 10 patients not given the androgen.[1] Others have also suggested that gonadal suppression using testosterone in men, and triptorelin in women, has some benefit in protecting against cyclophosphamide-induced damage.[2]

1. Masala A, *et al.* Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997; **126:** 292–5.
2. Cigni A, *et al.* Hormonal strategies for fertility preservation in patients receiving cyclophosphamide to treat glomerulonephritis: a nonrandomized trial and review of the literature. *Am J Kidney Dis* 2008; **52:** 887–96.

Effects on the skin. An erythematous pruritic rash, similar to the palmar-plantar erythrodysesthesia syndrome (p. 730.1) but occurring on the dorsal surfaces of the hands and feet, occurred 6 days after the first high dose of cyclophosphamide in a patient being prepared for bone marrow transplantation.[1] Previous cyclophosphamide-containing chemotherapy did not produce this reaction. The symptoms improved somewhat on treatment with triamcinolone ointment, and subsequently desquamation of the hands occurred with decreased purplish discoloration and oedema of the feet. There has also been a report of 2 patients who developed Stevens-Johnson syndrome, with some features suggestive of overlapping toxic epidermal necrolysis.[2]

For reports of subacute cutaneous lupus erythematosus after treatment with cyclophosphamide plus doxorubicin, see Effects on the Skin and Nails, under Doxorubicin, p. 784.3.

1. Matsuyama JR, Kwok KK. A variant of the chemotherapy-associated erythrodysesthesia syndrome related to high-dose cyclophosphamide. *DICP Ann Pharmacother* 1989; **23:** 776–9.
2. Assier-Bonnet H, *et al.* Stevens-Johnson syndrome induced by cyclophosphamide: report of two cases. *Br J Dermatol* 1996; **135:** 864–6.

Hypersensitivity. Occasional anaphylaxis has been reported with cyclophosphamide;[1] analysis of data by the Boston Collaborative Drug Surveillance Program detected only one allergic skin reaction among 210 patients given cyclophosphamide, resulting in a calculated incidence of 4.8 reactions per 1000 recipients.[2]

1. Jones JB, *et al.* Cyclophosphamide anaphylaxis. *DICP Ann Pharmacother* 1989; **23:** 88–9.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2.

Cyclophosphamide should not be given to patients with bone-marrow aplasia, acute infection, or drug- or radiation-induced urothelial toxicity. It should be given with care to those with diabetes mellitus. Care is also needed in elderly or debilitated patients, or those with renal or hepatic impairment or who have undergone adrenalectomy. Liberal fluid intake and frequent micturition are advised to reduce the risk of cystitis but care must be taken to avoid water retention and intoxication. Urine should be examined regularly for red cells, which may precede haemorrhagic cystitis. The haematological profile should be monitored regularly.

The use of cyclophosphamide in pregnancy should be avoided where possible.

Breast feeding. Cyclophosphamide has been detected in breast milk,[1] and there are reports of neutropenia,[2] and leucopenia and thrombocytopenia,[3] in infants who have been breast fed by women receiving cyclophosphamide. The American Academy of Pediatrics considers[4] that cyclophosphamide may interfere with cellular metabolism, causing neutropenia and possibly immune suppression in the infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Wiernik PH, Duncan JH. Cyclophosphamide in human milk. *Lancet* 1971; **1:** 912.
2. Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. *Med J Aust* 1977; **1:** 383–4.
3. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc* 1979; **71:** 165–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. *Residues* of cyclophosphamide or ifosfamide destroyed using alkaline hydrolysis in the presence of dimethylformamide showed no mutagenicity *in vitro*.[1] An alternative method, involving refluxing of cyclophosphamide with hydrochloric acid, neutralising, and then reacting with sodium thiosulfate, was effective for the degradation of cyclophosphamide, but residues from ifosfamide were still highly mutagenic *in vitro* and this second method should therefore not be used to degrade ifosfamide.

Urine and faeces produced for up to 72 hours and 5 days respectively after an oral dose of cyclophosphamide should be handled wearing protective clothing.[2] As cyclophosphamide was present in sweat and saliva, protective clothing was advised for 72 hours after a dose when bathing the patient or carrying out oral procedures.

1. Castegnaro M, *et al.* , eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclophosphamide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Pregnancy. For a report of a healthy infant born to a woman treated with a cyclophosphamide-containing regimen, see Pregnancy, under Teniposide, p. 867.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Since cyclophosphamide must undergo hepatic metabolism before it is active, interactions are possible with drugs that inhibit or stimulate the mixed function oxidase enzymes responsible. There may be an increased risk of cardiotoxicity in patients who have also received doxorubicin or other cardiotoxic drugs.

Allopurinol. Although the Boston Collaborative Drug Surveillance Program reported an increased incidence of bone-marrow depression in patients given allopurinol with cyclophosphamide than in those given cyclophosphamide without allopurinol (15 of 26 compared with only 6 of 32),[1] a subsequent study in patients given combination chemotherapy, including cyclophosphamide, for lymphomas failed to find any difference in the nadirs of the platelet and white blood cell counts in cycles in which allopurinol was given.[2] Although allopurinol pretreatment in 4 patients resulted in a longer cyclophosphamide half-life in a study in 26 patients given cyclophosphamide, urinary excretion of cyclophosphamide was unchanged.[3] A longer cyclophosphamide half-life was also seen in a study in children given allopurinol.[4]

1. Boston Collaborative Drug Surveillance Program. Allopurinol and cytotoxic drugs: interaction in relation to bone marrow depression. *JAMA* 1974; **227:** 1036–40.
2. Stolbach L, *et al.* Evaluation of bone marrow toxic reaction in patients treated with allopurinol. *JAMA* 1982; **247:** 334–6.
3. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; **33:** 226–33.
4. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Antibacterials. *Chloramphenicol* given before cyclophosphamide prolonged the mean cyclophosphamide serum half-life from 7.5 to 11.5 hours and reduced the peak activity in all of 5 subjects.[1] Giving *sulfaphenazole* before cyclophosphamide significantly inhibited the rate of biotransformation of cyclophosphamide in 2 of 7 subjects and enhanced it in 2; it remained unchanged in 3. A study in patients with non-Hodgkin's lymphoma found that giving *ciprofloxacin* before cyclophosphamide affected pharmacokinetic parameters of cyclophosphamide. The area under the concentration-time curve (AUC) of cyclophosphamide was increased and clearance was lower; AUC of the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide, was decreased and clearance increased.[2]

1. Faber OK, *et al.* The effect of chloramphenicol and sulphaphenazole on the biotransformation of cyclophosphamide in man. *Br J Clin Pharmacol* 1975; **2:** 281–5.
2. Afsharian P, *et al.* The effect of ciprofloxacin on cyclophosphamide pharmacokinetics in patients with non-Hodgkin lymphoma. *Eur J Haematol* 2005; **75:** 206–11.

Anticoagulants. For reference to the interaction of cyclophosphamide with *warfarin*, see p. 1532.2.

Antifungals. Analysis of cyclophosphamide metabolism in patients enrolled in a study comparing itraconazole with fluconazole found that those given itraconazole had higher exposure to toxic metabolites of cyclophosphamide. Both the antifungals appeared to alter cyclophosphamide metabolism and the authors cautioned against use of azole antifungals with antineoplastics that are metabolised via cytochrome P450 isoenzymes.[1]

1. Marr KA, *et al.* Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; **103:** 1557–9.

Barbiturates. Although patients receiving cyclophosphamide developed higher peak plasma concentrations of active cyclophosphamide metabolites when given enzyme-inducing agents such as barbiturates, the active metabolites also disappeared rapidly.[1]

1. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; **33:** 226–33.

Chlorpromazine. The half-life of cyclophosphamide was about 200% greater in 2 children also taking chlorpromazine than in children not given the phenothiazine.[1]

1. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Ciclosporin. For reference to the effect of cyclophosphamide on ciclosporin concentrations, see Interactions, Antineoplastics, p. 1957.2.

Colony-stimulating factors. Fatal respiratory insufficiency associated with alveolar fibrosis developed in an infant given cyclophosphamide and doxorubicin followed by *filgrastim*.[1] Since pulmonary toxicity with cyclophosphamide is normally associated with high cumulative doses it was suggested that in this case the effects might have been exacerbated by the granulocyte colony-stimulating factor. (The pulmonary toxicity of bleomycin has also been suggested to be exacerbated by colony-stimulating factors, as discussed on p. 751.3).

1. van Woensel JBM, *et al.* Acute respiratory insufficiency during doxorubicin, cyclophosphamide, and G-CSF therapy. *Lancet* 1994; **344:** 759–60.

Corticosteroids. Single doses of *prednisone* have been found to inhibit the activation of cyclophosphamide but after longer-term treatment the rate of activation has increased.[1] A study in children found that pretreatment with *dexamethasone* was associated with increased clearance of cyclophosphamide and a decrease in its half-life relative to children not given the corticosteroid.[2]

1. Faber OK, Mouridsen HT. Cyclophosphamide activation and corticosteroids. *N Engl J Med* 1974; **291:** 211.
2. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Gastrointestinal drugs. In a retrospective study in patients receiving high-dose cyclophosphamide, cisplatin, and carmustine,[1] the area under the plasma-concentration time curve (AUC) for cyclophosphamide (measured as the parent compound) was 17% lower when *ondansetron* rather than prochlorperazine was added to the antiemetic regimen. In addition, the AUC for cisplatin was 10% higher with the ondansetron regimen. In a similar study,[2] the AUCs for both cyclophosphamide and cisplatin were lower in patients receiving an antiemetic regimen including ondansetron rather than prochlorperazine. The authors of both studies noted that the relevance of these findings to toxicity and antitumour effect of the antineoplastics remained to be determined.

1. Gilbert CJ, *et al.* Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol* 1998; **42:** 497–503.
2. Cagnoni PJ, *et al.* Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics. *Bone Marrow Transplant* 1999; **24:** 1–4.

NSAIDs. Acute life-threatening water intoxication was reported in a patient given low-dose cyclophosphamide with *indometacin*.[1] The patient had previously received

treatment with cyclophosphamide (for multiple myeloma) without significant adverse effect.

1. Webberley MJ, Murray JA. Life-threatening acute hyponatraemia induced by low dose cyclophosphamide and indomethacin. *Postgrad Med J* 1989; **65:** 950–2.

Suxamethonium. For reference to a possible interaction between cyclophosphamide and suxamethonium, see under Suxamethonium Chloride, p. 2039.3.

Pharmacokinetics

After oral doses, cyclophosphamide is well absorbed from the gastrointestinal tract with a bioavailability greater than 75%. It is widely distributed in the tissues and crosses the blood-brain barrier. It undergoes activation by various cytochrome P450 isoenzymes (notably CYP2B6) in the liver. The initial metabolites are 4-hydroxycyclophosphamide and its acyclic tautomer, aldophosphamide, which both undergo further metabolism; aldophosphamide may undergo non-enzymatic conversion to active phosphoramide mustard. Acrolein is also produced and may be responsible for bladder toxicity. Cyclophosphamide is excreted principally in urine, as metabolites and some unchanged drug. It crosses the placenta, and is found in breast milk.

Reviews.

1. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38:** 291–304.
2. de Jonge ME, *et al.* Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet* 2005; **44:** 1135–64.

Absorption. Cyclophosphamide was detected in the urine of 5 patients after application to intact skin, showing that cyclophosphamide can be absorbed via this route.[1] Absorption continued after the site of application had been cleaned, suggesting that cyclophosphamide had penetrated subcutaneous lipid and was slowly released to the circulation from this depot. Cyclophosphamide was also identified in the urine of 2 oncology nurses but appeared more quickly than in patients, suggesting a faster route of absorption, perhaps by inhalation of aerosols generated during dissolution of the drug.

1. Hirst M, *et al.* Occupational exposure to cyclophosphamide. *Lancet* 1984; **i:** 186–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ciclokebir; ***Austral.***: Cycloblastin; Endoxan; ***Austria***: Endoxan; ***Belg.***: Endoxan; ***Braz.***: Evociclo; Genuxal; ***Canad.***: Cytoxan†; Procytox; ***Chile***: Endoxan; Ledoxina; ***China***: Endoxan (安道生); ***Cz.***: Endoxan; ***Denm.***: Sendoxan; ***Fin.***: Sendoxan; ***Fr.***: Endoxan; ***Ger.***: Endoxan; ***Gr.***: Cyclolest; Endoxan; ***Hong Kong***: Cycram; Endoxan; ***Hung.***: Cytoxan†; Endoxan; ***India***: Cycloxan; Cycrame; Cydoxan; Cyphos; Eldamide; Endoxan; Ledoxan; Neophos; Oncomide; Oncophos; Oncoxan; ***Indon.***: Cyclovid; Endoxan; ***Irl.***: Endoxana; ***Israel***: Endoxan; ***Ital.***: Endoxan; ***Jpn***: Endoxan; ***Mex.***: Cryofaxol; Formitex; Hidrofosmin; Ledoxina; ***Neth.***: Endoxan; ***Norw.***: Sendoxan; ***NZ***: Cycloblastin; Cytoxan; Endoxan; ***Philipp.***: Cytoxan†; Endoxan†; Ledoxan; Xyclomed; ***Pol.***: Endoxan; ***Port.***: Endoxan; ***Rus.***: Endoxan (Эндоксан); ***S. Afr.***: Cycloblastin†; Endoxan; ***Singapore***: Alkyloxan; Cycram; Endoxan; ***Spain***: Genoxal; ***Swed.***: Sendoxan; ***Switz.***: Endoxan; ***Thai.***: Endoxan; Ledoxan†; ***Turk.***: Alkyloxan; Endoxan; ***Venez.***: Biodoxan.

Pharmacopoeial Preparations

BP 2014: Cyclophosphamide Injection; Cyclophosphamide Oral Solution; Cyclophosphamide Tablets;

USP 36: Cyclophosphamide for Injection; Cyclophosphamide Tablets.

Cytarabine *(BAN, USAN, rINN)*

Ara-C; Arabinosylcytosine; Citarabin; Citarabina; Citarabinas; Citosina arabinósido; Cytarabin; Cytarabina; Cytarabine Liposome; Cytarabinum; Cytosine Arabinoside; Liposomal Cytarabine; NSC-63878 (cytarabine hydrochloride); Sitarabin; Sytarabiini; U-19920; U-19920A (cytarabine hydrochloride); WR-28453; Цитарабин.

1-β-D-Arabinofuranosylcytosine; 4-Amino-1-β-D-arabinofuranosylpyrimidin-2(1*H*)-one.

$C_9H_{13}N_3O_5$=243.2

CAS — 147-94-4 (cytarabine); 69-74-9 (cytarabine hydrochloride).

ATC — L01BC01.

ATC Vet — QL01BC01.

UNII — 04079A1RDZ.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Chin. includes the hydrochloride.

Ph. Eur. 8: (Cytarabine). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Cytarabine). An odourless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform. Protect from light.

Incompatibility. Although cytarabine has been stated in the literature to be incompatible with solutions of fluorouracil[1,2] and methotrexate[2] some studies have reported it to be stable for some hours when mixed with the latter.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Uses and Administration

Cytarabine, a pyrimidine nucleoside analogue, is an antimetabolite antineoplastic that inhibits DNA synthesis. Its actions are specific for the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Cytarabine is one of the mainstays of the treatment of acute myeloid leukaemia (p. 693.1), and is used in regimens for consolidation in patients with acute lymphoblastic leukaemia (p. 692.3). It has also been used for chronic myeloid leukaemia (p. 694.2) and the myelodysplasias (p. 694.3) (see also Low-dose Therapy, under Administration, below). It may be used in salvage regimens for Hodgkin's disease (p. 696.1), as part of the complex regimens sometimes employed in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p. 696.3 *et seq.*), and for meningeal leukaemia or lymphoma.

Cytarabine is usually given intravenously; it is also used subcutaneously. Higher doses can be tolerated when given by rapid intravenous injection rather than slow infusion, because of the rapid clearance of cytarabine, but there is little evidence of clinical advantage either way. Cytarabine (in a suitable formulation) may be given intrathecally for leukaemic or lymphomatous meningitis.

For the induction of remission in **acute leukaemias** many dosage regimens have been used: 100 mg/m^2 twice daily by rapid intravenous injection, or 100 mg/m^2 daily by continuous intravenous infusion, both for 7 days, are used in combination regimens for acute myeloid leukaemia. Cytarabine 200 mg/m^2 by continuous intravenous infusion for 5 days, at intervals of about 2 weeks, has also been used as monotherapy. Other recommended regimens include a continuous dosing regimen in which cytarabine 2 mg/kg daily is given by rapid intravenous injection for 10 days; thereafter, the dose may be increased if necessary to 4 mg/kg until a therapeutic response or toxicity is evident. Alternatively, 0.5 to 1 mg/kg may be infused daily (over 1 to 24 hours) for 10 days, increased thereafter to 2 mg/kg daily until toxicity or remission occurs. Intermittent regimens include intravenous cytarabine 3 to 5 mg/kg daily for 5 consecutive days, repeated after an interval of 2 to 9 days, until therapeutic response or toxicity occurs.

For maintenance 1 to 1.5 mg/kg once or twice weekly may be given intravenously or subcutaneously.

In the treatment of refractory non-Hodgkin's **lymphomas**, high-dose regimens have been used, with cytarabine given in doses of 3 g/m^2 every 12 hours for up to 12 doses. These doses should be given by intravenous infusion over 1 to 3 hours.

In the management of meningeal leukaemia and other **meningeal neoplasms**, cytarabine has been given by intrathecal injection in doses of 5 to 75 mg/m^2, or 30 to 100 mg, once every 2 to 7 days to once daily for 4 or 5 days. The dosage schedule is usually determined by the type and severity of CNS manifestations and the patient's response to prior therapy. A commonly used intrathecal cytarabine regimen is 10 to 30 mg/m^2 3 times weekly, or 30 mg/m^2 once every 4 days, until CSF findings are normal; the latter regimen is followed by one additional dose. If systemic toxicity occurs with intrathecal cytarabine, modification of other therapy may be necessary. A liposomal formulation is available in some countries for intrathecal use, and permits less frequent dosing because of its longer duration of action: the recommended dose for lymphomatous meningitis is 50 mg intrathecally every 2 weeks for 5 doses then every 4 weeks for 5 doses. Oral or intravenous dexamethasone 4 mg twice daily for 5 days should be given, starting on the day of the liposomal cytarabine intrathecal injection. If neurotoxicity develops, the dose may be reduced to 25 mg; if this persists, liposomal cytarabine therapy should be stopped. For discussion of use of this formulation in children, see Administration in Children, below.

White cell and platelet counts should be determined regularly during treatment with cytarabine and therapy should be stopped or modified if platelets fall below 50 000 cells/mm^3 or the polymorphonuclear granulocyte count falls below 1000 cells/mm^3.

Cytarabine ocfosfate is an orally active prodrug of cytarabine under investigation for acute and chronic myeloid leukaemia.

Administration. *INTRATHECAL.* Intrathecal cytarabine has been associated with neurotoxicity (see also Effects on the Nervous System, p. 775.2), some of which has been variously attributed to preservatives, volume, osmolality, and pH of the preparation;[1] common practice is to prepare intrathecal chemotherapy with preservative-free diluent and limit the volume of the final solution, usually to 5 mL. A study[1] evaluated pH and osmolality for cytarabine intrathecal solutions (in various diluents) at concentrations of 2, 5, 10, and 25 mg/mL. Osmolality increased with increased concentrations but was within 10% of the physiological range of the CSF. However, the pH of cytarabine at 10 and 25 mg/mL was more than 10% higher than the upper limit of the physiological pH of CSF.

Intrathecal doses of the liposomal formulation of cytarabine result in prolonged drug exposure when compared with intrathecal doses of the conventional formulation (see Pharmacokinetics, p. 775.3). In a randomised study,[2] the liposomal formulation given once every 2 weeks produced a higher response rate and improved Karnofsky score compared with the conventional formulation given twice a week in patients with lymphomatous meningitis secondary to lymphoma. The use of liposomal formulations intrathecally to treat leukaemic or lymphomatous meningitis has been reviewed.[3,4] For discussion of use of this formulation in children, see Administration in Children, below.

1. de Lemos ML, *et al.* Evaluation of osmolality and pH of various concentrations of methotrexate, cytarabine, and thiotepa prepared in normal saline, sterile water for injection, and lactated Ringer's solution for intrathecal administration. *J Oncol Pharm Pract* 2009; **15:** 45–52.
2. Glantz MJ, *et al.* Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol* 1999; **17:** 3110–16.
3. Rueda Domínguez A, *et al.* Liposomal cytarabine (DepoCyte) for the treatment of neoplastic meningitis. *Clin Transl Oncol* 2005; **7:** 232–8.
4. Benesch M, Urban C. Liposomal cytarabine for leukemic and lymphomatous meningitis: recent developments. *Expert Opin Pharmacother* 2008; **9:** 301–9.

LOW-DOSE THERAPY. Because of initial suggestions that low doses of cytarabine might induce differentiation and maturation of leukaemic cells, low-dose therapy has been tried in patients with myelodysplastic syndrome and acute myeloid leukaemia. Although complete remission may occur in about 20% of patients with myelodysplastic syndromes a similar proportion succumb to treatment-related mortality, and remissions do not appear to be particularly long-lasting. Bone-marrow suppression may be marked even at these doses.[1] Low-dose subcutaneous cytarabine (20 mg twice daily for 10 days, at intervals of 4 to 6 weeks) was found to be superior to hydroxycarbamide (with or without all-trans retinoic acid) in elderly patients with acute myeloid leukaemia. Although the authors considered the prognosis for these patients to still be unsatisfactory, they suggested that therapy with low-dose cytarabine could represent a baseline against which other promising treatments might be compared.[2]

1. Aul C, Gattermann N. The role of low-dose chemotherapy in myelodysplastic syndrome. *Leuk Res* 1992; **16:** 207–15.
2. Burnett AK, *et al.* The National Cancer Research Institute Haematological Oncology Study Group Adult Leukemia Working Party. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; **109:** 1114–24.

Administration in children. UK licensed product information for conventional formulations of cytarabine indicates that children appear to tolerate proportionally higher doses by weight or surface area than adults, and that where a range of doses is given, children should be treated at the higher dose (see Uses and Administration, above).

UK and US licensed product information for liposomal formulations of cytarabine state that safety and efficacy in children have not been established. A dose of intrathecal liposomal cytarabine 35 mg (given with oral or intravenous dexamethasone 150 micrograms/kg twice daily for 5 days) has been recommended in patients between the ages of 3 and 21 years.[1] A pilot study to determine the feasibility, safety, and pharmacokinetics of this formulation in 6 patients aged less than 3 years found that it was safe and well tolerated when given with dexamethasone; drug exposure after a dose of 25 mg intrathecally was comparable to that after 50 mg in adults and 35 mg in older children.[2]

1. Bomgaars L, *et al.* Phase I trial of intrathecal liposomal cytarabine in children with neoplastic meningitis. *J Clin Oncol* 2004; **22:** 3916–21.
2. Peyrl A, *et al.* Pharmacokinetics and safety of intrathecal liposomal cytarabine in children aged <3 years. *Clin Pharmacokinet* 2009; **48:** 265–71.

Administration in hepatic or renal impairment. For conventional formulations, UK licensed product information states that cytarabine should be used with caution in hepatic impairment, and suggests a reduced dose in patients whose liver function is poor; however, no specific

dose recommendations are given and no definition of the degree of hepatic impairment. Dosage reduction is not considered necessary in patients with renal impairment.

US licensed product information states that patients with renal or hepatic impairment may be more likely to have CNS toxicity after high-dose cytarabine, which should be used with caution and possibly at a reduced dose in these patients; no specific dose recommendations are given.

Leukoencephalopathy. There are anecdotal reports[1-3] of marked improvement in patients with progressive multifocal leukoencephalopathy secondary to AIDS or chemotherapy-induced immunosuppression who were given intravenous or intrathecal cytarabine. However, a randomised multicentre study[4] indicated that cytarabine was ineffective and had no role in this condition (see also Infections in Immunocompromised Patients, p. 960.2). Others[5] have suggested that even intrathecal dosage may not provide adequate delivery of cytarabine to target cells, and that delivering the drug directly into the brain under pressure might be an alternative. Cytarabine has also been used with cidofovir.[6]

1. O'Riordan T, *et al.* Progressive multifocal leukoencephalopathy-remission with cytarabine. *J Infect* 1990; **20:** 51–4.
2. Portegies P, *et al.* Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1991; **337:** 680–1.
3. Nicoli F, *et al.* Efficacy of cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1992; **339:** 306.
4. Hall CD, *et al.* Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N Engl J Med* 1998; **338:** 1345–51.
5. Levy RM, *et al.* Convection-enhanced intraparenchymal delivery (CEID) of cytosine arabinoside (AraC) for the treatment of HIV-related progressive multifocal leukoencephalopathy (PML). *J Neurovirol* 2001; **7:** 382–5.
6. Terrier B, *et al.* Leucoencéphalite multifocale progressive en dehors du sida: efficacité de l'association cytarabine-cidofovir. *Rev Med Interne* 2007; **28:** 488–91.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The major dose-limiting adverse effect of cytarabine is bone-marrow depression, manifest as leucopenia (particularly granulocytopenia), thrombocytopenia, and anaemia, sometimes with striking megaloblastic changes. Myelosuppression appears to be more evident after continuous infusions. Leucopenia is biphasic, with a nadir at 7 to 9 days after a dose and another, more severe, at 15 to 24 days. The nadir of the platelet count occurs at about 12 to 15 days. Recovery generally occurs in a further 10 days.

Gastrointestinal disturbances may occur: nausea and vomiting may be more severe when doses are given rapidly (but other adverse effects are reported to be worse when the drug is given by infusion). Other adverse effects reported include hepatic dysfunction, renal dysfunction, neurotoxicity, bleeding complications, rashes, oral and anal ulceration, gastrointestinal haemorrhage, oesophagitis, and conjunctivitis. A syndrome of bone and muscle pain, fever, malaise, conjunctivitis, and rash, sometimes described as flu-like, has been reported 6 to 12 hours after cytarabine doses, and may be treated or prevented with corticosteroids. Anaphylactoid reactions and pancreatitis have occurred rarely. There may be local pain, cellulitis, and thrombophlebitis at the site of injection.

Intrathecal use of the liposomal cytarabine formulation commonly causes chemical arachnoiditis manifesting as neck stiffness or pain, nausea, vomiting, headache, and fever. Dexamethasone should be used prophylactically to reduce the incidence and severity of this complication. Other rare adverse effects include encephalopathy, and focal seizures. Intrathecal use of conventional cytarabine formulations has rarely been associated with severe spinal cord toxicity, necrotising encephalopathy, blindness, and other neurotoxicities. If given intrathecally, preservative-free diluents must be used.

High-dose therapy has been associated with particularly severe gastrointestinal and CNS effects, including severe ulceration of the gastrointestinal tract, pneumatosis cystoides leading to peritonitis, necrotising colitis and bowel necrosis, peripheral neuropathy, and cerebral and cerebellar dysfunction, with personality changes, somnolence, and coma. There may also be corneal toxicity leading to punctate keratitis and haemorrhagic conjunctivitis, sepsis, liver abscess, severe skin rash leading to desquamation, alopecia, and cardiac disorders including pericarditis and fatal cardiomyopathy. Pulmonary toxicity sometimes fatal, has occurred.

Cytarabine is teratogenic in *animals* (but see Pregnancy, below).

In addition to frequent white blood cell and platelet counts, blood-uric acid should be monitored because of the risk of hyperuricaemia secondary to lysis of neoplastic cells, and renal and hepatic function should be periodically assessed. Cytarabine should be given with care to patients with impaired liver function; dosage reduction may be necessary.

The toxicity of cytarabine has been reviewed.[1] The principal toxicity of standard dosage regimens is myelosuppression but bleeding complications and gastrointestinal toxicity are also major problems at standard doses. With the high-dose regimens neurological toxicity may be dose-limiting: severe and sometimes irreversible symptoms have been seen in some 6 to 10% of patients receiving a cumulative dose of 36 g/m^2. Ocular toxicity may occur in up to 80% of patients at the highest doses. Since cytarabine toxicity is largely dose-related, low-dose cytarabine is generally well tolerated, even in elderly patients (who are more susceptible): its only significant toxicity is myelosuppression.

1. Stentoft J. The toxicity of cytarabine. *Drug Safety* 1990; **5:** 7–27.

Effects on the nervous system. Although paraplegia has been reported with intrathecal cytarabine[1] (see also under Benzyl Alcohol, p. 1740.3) and peripheral neuropathy has occurred in a patient who had received only conventional intravenous doses,[2] the majority of cases of neurotoxicity associated with cytarabine appear to be in patients given high-dose regimens.[3-7] Although some cases have manifested as demyelinating peripheral neuropathy,[3,4] including a syndrome of painful legs and involuntary movements in the toes which showed some response to carbamazepine,[3] most studies have reported in particular a syndrome of cerebellar toxicity,[5-8] with symptoms such as dysarthria, nystagmus, and ataxia. Toxicity appears to be dose-related: in one series[5] CNS toxicity occurred in none of 12 patients given total doses of up to 24 g/m^2 of cytarabine, 3 of 19 patients receiving 36 g/m^2, and 1 of 12 patients given 48 g/m^2, none of which were life-threatening or irreversible, whereas 4 of 6 patients given 54 g/m^2 (as 4.5 g/m^2 every 12 hours for 12 doses) developed neurotoxicity, which was fatal in one and irreversible in another. However, persistent, severe cerebellar toxicity has also been reported in a patient who had received a total dose of only 36 g/m^2 (as 3 g/m^2 every 12 hours).[8] There is some evidence[6] that patients aged over 50, and those who have recently received conventional-dose cytarabine[7] may be at increased risk. Intracranial hypertension (pseudotumor cerebri) has occurred rarely.[9] Neurological effects possibly related to cytarabine were seen in 2 out of 5 heavily pre-treated children given intrathecal liposomal cytarabine;[10] in 1 case, acute encephalopathy was probably caused by high-dose methotrexate but aggravated by cytarabine, and in the other case, persistent generalised seizures developed after the sixth intrathecal injection of cytarabine.

1. Saleh MN, *et al.* Intrathecal cytosine arabinoside-induced acute, rapidly reversible paralysis. *Am J Med* 1989; **86:** 729–30.
2. Russell JA, Powles RL. Neuropathy due to cytosine arabinoside. *BMJ* 1974; **4:** 652–3.
3. Malapert D, Degos JD. Jambes douloureuses et orteils instables: neuropathie induite par la cytarabine. *Rev Neurol (Paris)* 1989; **145:** 869–71.
4. Openshaw H, *et al.* Acute polyneuropathy after high dose cytosine arabinoside in patients with leukemia. *Cancer* 1996; **78:** 1899–1905.
5. Lazarus HM, *et al.* Central nervous system toxicity of high-dose systemic cytosine arabinoside. *Cancer* 1981; **48:** 2577–82.
6. Graves T, Hooks MA. Drug-induced toxicities associated with high-dose cytosine arabinoside infusions. *Pharmacotherapy* 1989; **9:** 23–8.
7. Barnett MJ, *et al.* Neurotoxicity of high-dose cytosine arabinoside. *Prog Exp Tumor Res* 1985; **29:** 177–82.
8. Dworkin LA, *et al.* Cerebellar toxicity following high-dose cytosine arabinoside. *J Clin Oncol* 1985; **3:** 613–16.
9. Fort JA, Smith LD. Pseudotumor cerebri secondary to intermediate-dose cytarabine HCl. *Ann Pharmacother* 1999; **33:** 576–8.
10. Benesch M, *et al.* Feasibility and toxicity of intrathecal liposomal cytarabine in 5 children and young adults with refractory neoplastic meningitis. *J Pediatr Hematol Oncol* 2007; **29:** 222–6.

Effects on the skin. A syndrome of pain and erythema of the palms and soles, progressing to bullae and desquamation, has been seen in patients receiving intermediate- or high-dose cytarabine.[1-3] The syndrome is similar to the palmar-plantar erythrodysesthesia syndrome (p. 730.1) reported in patients receiving chemotherapy not including cytarabine,[4] although some considered the two forms of toxicity distinct.[5] Cutaneous small vessel necrotising vasculitis[6] and Henoch-Schönlein purpura[7] have been reported after therapy with cytarabine.

1. Baer MR, *et al.* Palmar-plantar erythrodysesthesia and cytarabine. *Ann Intern Med* 1985; **102:** 556.
2. Peters WG, Willemze R. Palmar-plantar skin changes and cytarabine. *Ann Intern Med* 1985; **103:** 805.
3. Calista D, Landi C. Cytarabine-induced acral erythema: a localized form of toxic epidermal necrolysis? *J Eur Acad Dermatol Venereol* 1998; **10:** 274–5.
4. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
5. Vogelzang NJ, Ratain MJ. Cancer chemotherapy and skin changes. *Ann Intern Med* 1985; **103:** 303–4.
6. Ahmed I, *et al.* Cytosine arabinoside-induced vasculitis. *Mayo Clin Proc* 1998; **73:** 239–42.
7. Aktas B, *et al.* Severe Henoch-Schönlein purpura induced by cytarabine. *Ann Pharmacother* 2009; **43:** 792–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cytarabine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. Although there has been a report of limb and ear deformities in the infant of a woman given cytarabine at the estimated time of conception and 4 to 8 weeks later,[1] no congenital abnormalities were noted in 17 infants, 5 therapeutic abortions, and one still-birth (after pre-eclamptic toxaemia) resulting from over 20 known cases in which cytarabine was given during pregnancy.[2]

For a report of a fetal sinusoidal heart rate pattern and neonatal pancytopenia after a woman was given combination chemotherapy including cytarabine, see Pregnancy, under Etoposide, p. 791.3.

1. Wagner VM, *et al.* Congenital abnormalities in baby born to cytarabine treated mother. *Lancet* 1980; **ii:** 98–9.
2. Morgenstern G. Cytarabine in pregnancy. *Lancet* 1980; **ii:** 259.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Antifungals. Cytarabine may inhibit the action of *flucytosine*—see p. 581.3.

Antineoplastics. Acute pancreatitis has been reported in patients given cytarabine who had previously received *asparaginase* therapy.[1] Subclinical damage to the pancreas by asparaginase may have rendered it susceptible to cytarabine.

For a report of hepatic dysfunction in patients who had received cytarabine and *daunorubicin* see under Daunorubicin Hydrochloride, p. 779.3.

Giving cytarabine after *fludarabine* is reported to result in a fivefold increase in intracellular cytarabine concentrations in leukaemic cells,[2] producing improved clinical response rates.

1. Altman AJ, *et al.* Acute pancreatitis in association with cytosine arabinoside therapy. *Cancer* 1982; **49:** 1384–6.
2. Avramis VI, *et al.* Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a phase I/II study in pediatric patients with relapsed leukemias. *Clin Cancer Res* 1998; **4:** 45–52.

Pharmacokinetics

Cytarabine is not effective orally due to rapid deamination in the gastrointestinal tract; less than 20% of an oral dose is absorbed. After intravenous injection it disappears rapidly from the plasma with an initial half-life of about 10 minutes; the terminal elimination half-life ranges from 1 to 3 hours. It is converted by phosphorylation to an active form, which is rapidly deaminated, mainly in the liver and the kidneys, to inactive 1-β-D-arabinofuranosyluracil (uracil arabinoside, ara-U). The majority of an intravenous dose is excreted in the urine within 24 hours, mostly as the inactive metabolite with about 10% as unchanged cytarabine.

There is only moderate diffusion of cytarabine across the blood-brain barrier after intravenous injection, but, because of low deaminase activity in the CSF, concentrations achieved after continuous intravenous infusion or intrathecal injection are maintained for longer in the CSF than are those in plasma, with a terminal elimination half-life of 3.5 hours. After intrathecal doses of the liposomal formulation, a terminal elimination half-life of 100 to 263 hours was seen. Cytarabine also crosses the placenta.

References.

1. Slevin ML, *et al.* The pharmacokinetics of subcutaneous cytosine arabinoside in patients with acute myelogenous leukaemia. *Br J Clin Pharmacol* 1981; **12:** 507–10.
2. DeAngelis LM, *et al.* Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside. *Cancer Chemother Pharmacol* 1992; **29:** 173–7.
3. Hamada A, *et al.* Clinical pharmacokinetics of cytarabine formulations. *Clin Pharmacokinet* 2002; **41:** 705–18.
4. Peyrl A, *et al.* Pharmacokinetics and safety of intrathecal liposomal cytarabine in children aged <3 years. *Clin Pharmacokinet* 2009; **48:** 265–71.
5. Lamba JK. Genetic factors influencing cytarabine therapy. *Pharmacogenomics* 2009; **10:** 1657–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Citagenin; ***Austria***: Alexan; ARA-cell†; DepoCyte; ***Belg.***: Cytosar; DepoCyte; ***Braz.***: Aracytin; Citarax; Darbin; Fauldcita; Tabine; ***Canad.***: Cytosar; DepoCyt; ***Chile***: Alexan†; Aracytin; Laracit; ***China***: Alexan (爱力生); Cytosar (赛德萨); Saidewei (赛德威); ***Cz.***: Alexan; Cytosar; DepoCyte; ***Denm.***: Arabine; DepoCyte; ***Fin.***: Arabine†; DepoCyte; ***Fr.***: Aracytine; DepoCyte; ***Ger.***: Alexan†; ARA-cell; DepoCyte; ***Gr.***: Arace; Aracytin; Citabion; DepoCyte; ***Hong Kong***: Alexan; Cytosar; ***Hung.***: Alexan; Cytosar; DepoCyte; ***India***: Arasid; Biobin; Cancyt; Cybin; Cytabin; Cytaraside; Cytarine; Cytrosar; Oncotar; ***Indon.***: Alexan; Cytosar-U†; ***Irl.***: DepoCyte; ***Israel***: Alexan; Cytosar; ***Ital.***: Aracytin; DepoCyte; ***Jpn***: Cylocide; Starasid; ***Malaysia***: Cytosar-U; ***Mex.***: Cytosar; Ifarab†; Lar-

acit; Medsara; Mokcell; Novumtrax†; ***Neth.***: Alexan†; DepoCyte; ***Norw.***: DepoCyte; ***Philipp.***: Cancyt; Cytosar-U; Cytox; Leucyt; Tabine; ***Pol.***: Alexan; Cytosar; DepoCyte; ***Port.***: ARAcell; Citaloxan; Cytosar; DepoCyte; ***Rus.***: Alexan (Алексан); Cytosar (Цитозар); ***S.Afr.***: Alexan†; Cytosar; Laracit; ***Spain***: DepoCyte; ***Swed.***: Arabine; DepoCyte; ***Switz.***: Cytosar; DepoCyte; ***Thai.***: Alexan; Cytarine; Cytosar; ***Turk.***: Alexan; ARAcell; Cytonal; ***UK***: DepoCyte; ***Ukr.***: Cytosar (Цитозар); ***USA***: DepoCyt; ***Venez.***: Cytosar.

Pharmacopoeial Preparations
BP 2014: Cytarabine Injection;
USP 36: Cytarabine for Injection.

Dabrafenib *(USAN, pINN)*

Dabrafénib; Dabrafenibum; GSK-2118436A; Йофоластат.
N-{3-[5-(2-Aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide.
$C_{23}H_{20}F_3N_5O_2S_2$=519.6
CAS — 1195765-45-7.
UNII — QGP4HA4G1B.

Dabrafenib Mesilate *(pINNM)*

Dabrafénib, Mésilate de; Dabrafenib Mesylate (USAN); Dabrafenibi Mesilas; GSK-2118436B; Mesilato de dabrafenib; Йофоластата Мезилат.
$C_{23}H_{20}F_3N_5O_2S_2.CH_4O_3S$=615.7
CAS — 1195768-06-9.
UNII — B6DC89I63E.

Profile

Dabrafenib is an inhibitor of BRAF kinases that is used in the treatment of unresectable or metastatic melanoma (p. 714.3) with BRAF V600E mutations; it should not be used in patients with wild-type BRAF melanoma. It is given as the mesilate salt but doses are expressed as the base; 50 mg of dabrafenib is equivalent to about 59.25 mg dabrafenib mesilate. The usual oral dose is equivalent to 150 mg twice daily, taken 12 hours apart; capsules should be swallowed whole and taken on an empty stomach. A missed dose should not be taken within 6 hours of the next dose. Doses may need to be withheld or reduced if toxicity occurs. Where dose adjustment is required, the first dose reduction is to 100 mg twice daily, the second reduction to 75 mg twice daily, and the third reduction to 50 mg twice daily; dabrafenib should be stopped if the patient is unable to tolerate 50 mg twice daily. Treatment is continued until disease progression or unacceptable toxicity occurs. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Commonly reported adverse effects with dabrafenib include skin reactions, headache, fever, arthralgia, cough, and nasopharyngitis. New primary cutaneous malignancies such as squamous cell carcinoma, keratoacanthoma, and melanoma have occurred during treatment. Other effects include hyperglycaemia, uveitis, and iritis. Dabrafenib should be avoided during pregnancy and women of childbearing potential should use contraception during and for 4 weeks after treatment.

References.
1. Ballantyne AD, Garnock-Jones KP. Dabrafenib: first global approval. *Drugs* 2013; **73:** 1367–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Tafinlar; ***USA***: Tafinlar.

Dacarbazine *(BAN, USAN, rINN)*

Dacarbazin; Dacarbazina; Dacarbazinum; Dakarbatsiini; Dakarbazin; DIC; DTIC; Imidazole Carboxamide; NSC-45388; WR-139007; Дакарбазин.
5-(3,3-Dimethyltriazeno)imidazole-4-carboxamide.
$C_6H_{10}N_6O$=182.2
CAS — 4342-03-4 (dacarbazine); 64038-56-8 (dacarbazine citrate).
ATC — L01AX04.
ATC Vet — QL01AX04.
UNII — 7GR28W0FJI.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Dacarbazine). A white or slightly yellowish, crystalline powder. Slightly soluble in water and in anhydrous alcohol; practically insoluble in dichloromethane. Store at 2 degrees to 8 degrees. Protect from light.

USP 36: (Dacarbazine). Store in airtight containers at 2 degrees to 8 degrees. Protect from light.

Incompatibility. Dacarbazine has been reported to be incompatible with hydrocortisone sodium succinate but not with the sodium phosphate.[1] It has been reported to be incompatible with heparin,[2] although only with concentrated dacarbazine solutions (25 mg/mL).

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Nelson RW, *et al.* Visual incompatibility of dacarbazine and heparin. *Am J Hosp Pharm* 1987; **44:** 2028.

Stability. References to the photodegradation of dacarbazine solution.[1-4] Dacarbazine is more sensitive to direct sunlight than to artificial lighting or diffuse daylight.

1. Stevens MFG, Peatey L. Photodegradation of solutions of the antitumour drug DTIC. *J Pharm Pharmacol* 1978; **30** (suppl): 47P.
2. Horton JK, Stevens MFG. Search for drug interactions between the antitumour agent DTIC and other cytotoxic agents. *J Pharm Pharmacol* 1979; **31** (suppl): 64P.
3. Kirk B. The evaluation of a light-protecting giving set. *Intensive Therapy Clin Monit* 1987; **8:** 78–86.
4. El Aatmani M, *et al.* Stability of dacarbazine in amber glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2002; **59:** 1351–6.

Uses and Administration

Dacarbazine is a cell-cycle non-specific antineoplastic that is thought to function as an alkylating agent after it has been activated in the liver. Dacarbazine is used mainly in the treatment of metastatic malignant melanoma (p. 714.3). It is also given to patients with Hodgkin's disease (p. 696.1), notably with doxorubicin, bleomycin, and vinblastine (ABVD). Dacarbazine is used with other drugs in the treatment of soft-tissue sarcoma (p. 718.2), except mesothelioma and Kaposi's sarcoma, and may be given in neuroblastoma (p. 716.2), and other tumours.

Dacarbazine is given by the intravenous route. Injections may be given over 1 minute. The reconstituted solution can be further diluted with up to 300 mL of glucose 5% or sodium chloride 0.9% and given by infusion over 15 to 30 minutes; doses of 200 mg/m² and over are usually infused.

Dacarbazine is licensed for use as a single agent for **metastatic melanoma** in doses of 2 to 4.5 mg/kg daily for 10 days, repeated at intervals of 4 weeks, or 200 to 250 mg/m² daily for 5 days, repeated at intervals of 3 weeks. It can also be given in a dose of 850 mg/m² by intravenous infusion at 3-week intervals. In the treatment of **Hodgkin's disease** doses of 150 mg/m² daily for 5 days repeated every 4 weeks, or 375 mg/m² every 15 days have been given with other agents. In the treatment of **soft-tissue sarcoma**, dacarbazine 250 mg/m² is given daily for 5 days repeated every 3 weeks; it is usually given with doxorubicin.

References.
1. D'Incan M, Souteyrand P. Dacarbazine (Déticène). *Ann Dermatol Venereol* 2001; **128:** 517–25.
2. Eggermont AMM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? *Eur J Cancer* 2004; **40:** 1825–36.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Leucopenia and thrombocytopenia with dacarbazine, although usually moderate, may be severe. The nadir of the white cell count usually occurs 21 to 25 days after a dose. Anorexia, nausea, and vomiting occur in more than 90% of patients initially but tolerance may develop after repeated doses. Less frequent adverse effects include diarrhoea, skin reactions, alopecia, a flu-like syndrome, facial flushing and paraesthesia, headache, blurred vision, seizures, and rare but potentially fatal hepatotoxicity. There may be local pain at the injection site; extravasation produces pain and tissue damage. Anaphylaxis has occurred occasionally.

Dacarbazine should be used with caution in hepatic and renal impairment, and consideration given to reducing the dose. Haematological monitoring is required during therapy. Dacarbazine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. A report[1] of haemorrhagic cystitis associated with dacarbazine treatment for melanoma. The patient developed gross haematuria with inflammation and oedema of the bladder wall 2 weeks after completing 3 cycles of monotherapy with dacarbazine; the condition responded to symptomatic management with saline lavage and oral and intravenous hydration. Two subsequent transient episodes of haematuria resolved spontaneously.

1. Mohammadianpanah M, *et al.* Hemorrhagic cystitis in a patient receiving conventional doses of dacarbazine for metastatic malignant melanoma: case report and review of the literature. *Clin Ther* 2007; **29:** 1161–5.

Effects on the liver. Dacarbazine has been associated with fatal hepatic vascular toxicity, caused by thrombosis of the hepatic veins, necrosis, and extensive haemorrhage.[1] As the reaction usually occurs during the second course of dacarbazine it is thought to be immune mediated, and early corticosteroid treatment has been tried with a few reported cases of patient survival.[2] Other adverse hepatic effects have included[3] necrosis without inflammation, granulomatous hepatitis, and acute toxic hepatitis during the first course of dacarbazine. Morphological studies have suggested that dacarbazine may exert a toxic effect on the microfilamentous cytoskeleton of the hepatocytes.[3]

1. Ceci G, *et al.* Fatal hepatic vascular toxicity of DTIC: is it really a rare event? *Cancer* 1988; **61:** 1988–91.
2. Herishanu Y, *et al.* The role of glucocorticoids in the treatment of fulminant hepatitis induced by dacarbazine. *Anticancer Drugs* 2002; **13:** 177–9.
3. Dancygier H, *et al.* Dacarbazine (DTIC)-induced human liver injury. *Gut* 1982; **23:** A447.

Handling. Dacarbazine is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dacarbazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Levodopa. For a report of dacarbazine reducing the effects of levodopa, see Antineoplastics, p. 907.2.

Pharmacokinetics

Dacarbazine is poorly absorbed from the gastrointestinal tract. On intravenous injection it is rapidly distributed with an initial plasma half-life of about 20 minutes; the terminal half-life is reported to be about 5 hours. The volume of distribution is larger than body water content, suggesting localisation in some body tissues, probably mainly the liver. Only about 5% is bound to plasma protein. It crosses the blood-brain barrier to a limited extent; concentrations in CSF are about 14% of those in plasma. Dacarbazine is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP2E1 (and possibly in the tissues by CYP1A1) to its active metabolite 5-(3-methyltriazeno-1-yl)-imidazole-4-carboxamide (MTIC), which spontaneously decomposes to the major metabolite 5-amino-imidazole-4-carboxamide (AIC). About half of a dose is excreted unchanged in the urine by tubular secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Oncocarbil; ***Austral.***: DTIC†; ***Braz.***: Baxcarbas†; Dacarb; Evodazin; Fauldacar; ***Chile***: Deticene; ***China***: Ai Li Da (艾立达); ***Fin.***: Dacatic; ***Fr.***: Deticene; ***Ger.***: Detimedac; ***Gr.***: Dacarbion; Deticene; ***Hong Kong***: DTI; ***India***: Arzi; Dabaz; Dacarba; Dacarex; Dacarin; Dacarzine; Daczin; Decarb; Oncodac; ***Israel***: Dacin; Deticene†; ***Mex.***: Acocarb; Detilem†; Ifadac†; ***Neth.***: Deticene; ***Philipp.***: Duticin; ***Port.***: Deticene†; Fauldetic; ***S.Afr.***: DTIC-Dome; ***Singapore***: Dac; ***Switz.***: Dacin; ***Turk.***: Deticene; ***USA***: DTIC-Dome.

Pharmacopoeial Preparations
BP 2014: Dacarbazine Injection;
USP 36: Dacarbazine for Injection.

Dactinomycin *(BAN, USAN, rINN)*

Actinomicina D; Actinomycin C_1; Actinomycin D; Dactinomicina; Dactinomycine; Dactinomycinum; Daktinomisin; Daktinomycin; Daktinomysiini; Daktynomycyna; Meractinomycin; NSC-3053; Дактиномицин.
$N^{2,1}$,$N^{2',1'}$-(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyldicarbonyl)bis[threonyl-D-valylprolyl(*N*-methylglycyl)(*N*-methylvaline) 1.5→3.1-lactone].
$C_{62}H_{86}N_{12}O_{16}$=1255.4
CAS — 50-76-0.
ATC — L01DA01.
ATC Vet — QL01DA01.
UNII — 1CC1JFE158.

Description. Dactinomycin is an antineoplastic antibiotic produced by *Streptomyces parvulus* and other species of *Streptomyces.*

Cactinomycin (actinomycin C; HBF-386; NSC-18268) is a mixture of dactinomycin (actinomycin D) (10%), actinomycin C_2 (45%), and actinomycin C_3 (45%) produced by *Streptomyces chrysomallus.*

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, *Pol.*, and *US.*

USP 36: (Dactinomycin). A bright red, somewhat hygroscopic, crystalline powder, affected by light and heat. It has a potency of not less than 950 and not more than 1030 micrograms/mg, calculated on the dried basis. Soluble in water at 10 degrees and slightly soluble in water at 37 degrees; freely soluble in alcohol; very slightly soluble in

ether. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Adsorption. Dactinomycin binds to cellulose ester filters,[1] and such filtration should be avoided.[2] Although it has been suggested that significant amounts of drug may be adsorbed to glass or plastic,[3] dactinomycin is reportedly compatible with glass and PVC infusion containers,[4] and giving into the tubing of a fast-running intravenous infusion is recommended—see Uses and Administration, below.

1. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Rapp RP, *et al.* Guidelines for the administration of commonly-used intravenous drugs—1984 update. *Drug Intell Clin Pharm* 1984; **18:** 218–32.
4. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.

Uses and Administration

Dactinomycin is a highly toxic antibiotic with antineoplastic properties. It inhibits the proliferation of cells in a cell-cycle non-specific way by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis. It may enhance the cytotoxic effects of radiotherapy (see also Adverse Effects, below). Dactinomycin also has immunosuppressant properties.

It has been used, usually with other drugs or radiotherapy, in the treatment of Wilms' tumour (p. 709.1), gestational trophoblastic tumours (p. 691.2), nonseminomatous testicular cancer (p. 715.1), and sarcomas such as rhabdomyosarcoma (see Soft-tissue Sarcoma, p. 718.2) and Ewing's sarcoma (see Bone Sarcoma, p. 717.3).

In the treatment of Wilms' tumour, childhood rhabdomyosarcoma, or Ewing's sarcoma, an intravenous dose of 15 micrograms/kg daily for 5 days has been used in combination regimens. In adults, gestational trophoblastic tumours have been treated with 12 micrograms/kg daily for 5 days as a single agent, or 500 micrograms on days 1 and 2 of combination regimens. Metastatic nonseminomatous testicular cancer has been treated with 1 mg/m² on day 1 of combination regimens. The dose intensity for adults or children should not exceed 15 micrograms/kg or 400 to 600 micrograms/m² daily for 5 days per 2-week cycle, and lower doses may need to be used in some chemotherapy combinations or with radiotherapy. Using a regional perfusion technique to localise the drug has permitted the use of higher doses, 50 micrograms/kg being suggested for an isolated lower extremity or pelvis and 35 micrograms/kg for an upper extremity.

Great care must be taken to avoid extravasation and it should be given, for preference, into the tubing of a fast-running intravenous infusion. Platelet and white cell counts should be performed frequently to detect bone-marrow depression; if either count shows a marked decrease the drug should be withheld until recovery occurs, which may take up to 3 weeks (see also Bone-marrow Depression, p. 730.3).

Administration in children. Dactinomycin is used in children in the treatment of malignant diseases as outlined in Uses and Administration, above. For a discussion of dactinomycin pharmacokinetics in children, see under Pharmacokinetics, below.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Apart from nausea and vomiting adverse effects are often delayed, beginning 2 to 4 days after the completion of a course of treatment and reaching a maximum after 1 to 2 weeks. Fatalities have occurred. Haematological and gastrointestinal effects (particularly stomatitis and diarrhoea) may prove dose-limiting. Myelosuppression is apparent 1 to 7 days after therapy and may be manifest first as thrombocytopenia; the nadir of the platelet and white cell counts usually occurs within 14 to 21 days, with recovery in 21 to 25 days. Other adverse effects include oral and gastrointestinal effects such as cheilitis, oesophagitis, gastrointestinal ulceration, and proctitis; fever, malaise, hypocalcaemia, myalgia, alopecia, pneumonitis, and kidney and liver abnormalities. Skin reactions include eruptions, acne, toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Hepatotoxicity, including fatal hepatic failure, has been reported; veno-occlusive disease (mainly hepatic) may be fatal, especially in children younger than 2 years. Anaphylactoid reactions have occurred. Dactinomycin is very irritant and extravasation results in severe tissue damage. Regional perfusion therapy has also resulted in damage to soft tissues and oedema.

The effects of radiotherapy are enhanced by dactinomycin and severe reactions may follow the use of high doses. Erythema and pigmentation of the skin may occur in areas previously irradiated. An increased incidence of second primary tumours has been seen in patients treated with radiation and dactinomycin.

Dactinomycin should not be given to patients with varicella or herpes zoster, as severe and even fatal systemic disease may occur. Its use is best avoided in infants under about 1 year of age as they are reported to be highly susceptible to the toxicity of dactinomycin. Blood counts and renal and hepatic function should be monitored frequently.

Effects on the liver. Although pulsed doses (given every 3 or 6 weeks) less than about 50 micrograms/kg or 1.5 mg/m² do not seem to be associated with an unacceptable degree of hepatotoxicity,[1] giving dactinomycin as a single dose of 60 micrograms/kg (about 1.8 mg/m²) every 3 weeks to children with Wilms' tumour was associated with a high incidence of severe hepatotoxicity;[2] reduction of the dose to 45 micrograms/kg every 3 weeks reduced this incidence to levels comparable with a standard regimen of 15 micrograms/kg daily for 5 successive days.[3] Others have not seen such a high incidence of hepatotoxicity with doses of 60 micrograms/kg (despite some raised liver enzyme values), but in this case the high dose was given only every 6 weeks.[4] In general, dactinomycin should be given with caution to children with a history of antecedent liver damage, including abdominal irradiation or recent halothane anaesthesia.[1]

Reversible veno-occlusive disease has been seen particularly in children with Wilms' tumour given dactinomycin and vincristine. A literature review[5] noted a significant predominance in right-sided Wilms' tumour, possibly because the tumour mass could interfere with blood flow in the hepatic veins, which might make the liver more susceptible to the effects of dactinomycin. One study[6] found age of less than 1 year to be a risk factor and a study in children with rhabdomyosarcoma given dactinomycin, vincristine, and cyclophosphamide also found that young age (under 3 years) was associated with a greater risk of severe hepatotoxicity.[7] US licensed product information states that veno-occlusive disease (primarily hepatic) may be fatal, especially in children younger than 2 years of age.

1. Pritchard J, *et al.* Hepatotoxicity of actinomycin-D. *Lancet* 1989; **i:** 168.
2. D'Angio GJ. Hepatotoxicity with actinomycin D. *Lancet* 1987; **ii:** 104.
3. D'Angio GJ. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.
4. de Camargo B. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.
5. Tornesello A, *et al.* Veno-occlusive disease of the liver in right-sided Wilms' tumours. *Eur J Cancer* 1998; **34:** 1220–3.
6. Bisogno G, *et al.* Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol* 1997; **29:** 245–51.
7. Arndt C, *et al.* Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. *J Clin Oncol* 2004; **22:** 1894–1901. Correction [dosage error]. *ibid.*; 3434.

Handling. Dactinomycin is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dactinomycin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Pharmacokinetics

Intravenous doses of dactinomycin are rapidly distributed with high concentrations in bone marrow and nucleated cells. It undergoes only minimal metabolism and is slowly excreted in urine and bile. The terminal plasma half-life is reported to be about 36 hours. It does not cross the blood-brain barrier but is thought to cross the placenta.

In children. A study[1] involving 31 patients aged between 1 and 20 years given dactinomycin in intravenous doses of 0.7 to 1.5 mg/m² found that the pharmacokinetics of the drug were variable, but could be described by a 3-compartment model. Peak plasma concentrations varied from 3.2 to 99.2 nanograms/mL, and both peak plasma concentration and exposure were inversely related to bodyweight. Since there was evidence that exposure was also related to more severe toxicity, younger patients might be at greater risk with a regimen based on surface area; conversely the practice of capping the dose at 2 mg in older patients might result in underdosage.

For evidence that younger patients do have more liver toxicity with dactinomycin, see Effects on the Liver, above.

1. Veal GJ, *et al.* Pharmacokinetics of dactinomycin in a pediatric patient population: a United Kingdom Children's Cancer Study Group Study. *Clin Cancer Res* 2005; **11:** 5893–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cosmegen; ***Austral.***: Cosmegen; ***Austria***: Cosmegen; ***Belg.***: Lyovac Cosmegen; ***Braz.***: Cosmegen; ***Canad.***: Cosmegen; ***Fin.***: Cosmegen†; ***Gr.***: Cosmegen; ***Hong Kong***: Cosmegen; ***India***: Cosmegen; Dacmozen; Dactino; ***Irl.***: Cosmegen; ***Ital.***: Cosmegen; ***Mex.***: Ac-De†; Cosmegen; ***Neth.***: Lyovac Cosmegen†; ***Norw.***: Cosmegen†; ***NZ***: Cosmegen; ***Philipp.***: Cosmegen†; Trepar; ***Rus.***: Cosmegen (Космеген); ***S.Afr.***: Cosmegen; ***Singapore***: Cosmegen†; ***Swed.***: Cosmegen†; ***Switz.***: Cosmegen; ***Thai.***: Lyovac Cosmegen; ***Turk.***: Cosmegen; ***UK***: Cosmegen†; ***USA***: Cosmegen.

Pharmacopoeial Preparations
USP 36: Dactinomycin for Injection.

Dasatinib *(BAN, USAN, rINN)*

BMS-354825; Dasatinibum; Дазатиниб.

N-(2-Chloro-6-methylphenyl)-2-{[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino}-5-thiazolecarboxamide.

$C_{22}H_{26}ClN_7O_2S$=488.0

CAS — 302962-49-8.

ATC — L01XE06.

ATC Vet — QL01XE06.

UNII — RBZ1571X5H (dasatinib); X78UG0A0RN (anhydrous dasatinib).

Uses and Administration

Dasatinib is an oral inhibitor of several tyrosine kinases including BCR-ABL (Philadelphia chromosome) and SRC family tyrosine kinases. It is used for the treatment of adults with all phases of chronic myeloid leukaemia (CML; p. 694.2) who have resistance or intolerance to previous therapy, including imatinib, and as first-line treatment in those with Philadelphia chromosome-positive chronic phase CML. It is also used for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL; p. 692.3) who are resistant to or intolerant of prior therapy.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

The recommended oral starting dose of dasatinib in chronic phase CML is 100 mg once daily: tablets, which should be swallowed whole, not crushed or chewed, should be taken consistently either in the morning or the evening. The recommended starting dose for accelerated, myeloid, or lymphoid blast phase CML or Philadelphia chromosome-positive ALL is 140 mg once daily. Dosage may be adjusted according to response and tolerability; doses of up to 140 mg once daily have been used in patients with chronic phase CML, and up to 180 mg once daily in those with advanced phase, or with ALL. Treatment is continued until disease progression or unacceptable toxicity occurs. For dose adjustments in toxicity, see Administration in Subsequent Cycles, p. 778.1.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments are considered necessary.

- An *increased* dose of dasatinib should be considered in those patients given strong CYP3A4 inducers, and the patient should be monitored for toxicity.
- For those given a strong CYP3A4 inhibitor, the dose of dasatinib should be *reduced* to 20 mg daily in those patients taking 100 mg daily, and to 40 mg daily in those taking 140 mg daily. If this is not tolerated, then either drug should be stopped; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of dasatinib is increased.

References.

1. Talpaz M, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006; **354:** 2531–41.
2. Hochhaus A, *et al.* Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; **109:** 2303–9. Correction. *ibid.*; **110:** 1438.
3. Cortes J, *et al.* Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007; **109:** 3207–13.
4. Guilhot F, *et al.* Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007; **109:** 4143–50.
5. Ottmann O, *et al.* Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007; **110:** 2309–15.
6. Anonymous. Dasatinib (Sprycel) for CML and Ph+ALL. *Med Lett Drugs Ther* 2007; **49:** 6–7.

7. Olivieri A, Manzione L. Dasatinib: a new step in molecular target therapy. *Ann Oncol* 2007; **18** (suppl): vi42–vi46.
8. Keam SJ. Dasatinib: in chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. *BioDrugs* 2008; **22:** 59–69.
9. Tyler T. Once-daily dasatinib for treatment of patients with chronic myeloid leukemia. *Ann Pharmacother* 2009; **43:** 920–7.
10. Cortes JE, *et al*. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol* 2010; **28:** 398–404.
11. Lindauer M, Hochhaus A. Dasatinib. *Recent Results Cancer Res* 2010; **184:** 83–102.
12. Kim LC, *et al*. Dasatinib in solid tumors. *Expert Opin Invest Drugs* 2010; **19:** 415–25.

Administration in subsequent cycles. Licensed product information for dasatinib recommends adjustment of the oral dose in patients who develop marked haematological or other toxicity.

For patients with chronic phase chronic myeloid leukaemia (CML) started on a dose of 100 mg daily in whom neutrophil counts are below 500 cells/mm^3, the drug should be stopped until neutrophil counts recover to at least 1000 cells/mm^3; similarly if platelet counts are less than 50 000 cells/mm^3 the drug should be stopped until they exceed this value. If this recovery in blood counts occurs in 7 days or less, treatment should be resumed at the previous dose. If the fall in neutrophil counts recurs for more than 7 days, or the fall in platelet counts is extreme (below 25 000 cells/mm^3) treatment should again be stopped and only be resumed at a lower dose of 80 mg daily. If a second recurrence is seen, treatment should be resumed at a dose of 50 mg daily in those given dasatinib as first-line treatment; treatment should be stopped in those that are resistant to or intolerant of prior therapy.

Similarly, in patients with accelerated phase CML, blast phase CML, or Philadelphia chromosome-positive acute lymphoblastic leukaemia started on 140 mg daily, in whom neutrophil counts are below 500 cells/mm^3 or platelets below 10 000 cells/mm^3 (and in whom the cytopenia is not related to the disease), treatment should be stopped, and only restarted once cell counts are at least twice these values. Treatment is resumed at the original dose on the first occasion, but if cytopenia recurs, it should be resumed at 100 mg daily on the second occasion, and 80 mg daily on the third.

If severe non-haematological toxicity occurs, treatment should again be stopped, and only resumed, at a lower dose if appropriate, once toxicity has resolved.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of dasatinib include fluid retention, gastrointestinal disturbances, and bleeding. Fluid retention may be severe, and can result in pleural and pericardial effusion, pulmonary oedema, and ascites. Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in patients with advanced chronic myeloid leukaemia (CML) or acute lymphoblastic leukaemia than in patients in chronic phase CML. Recovery generally occurs after dose interruption and/or reduction, although treatment may need to be stopped. Febrile neutropenia and, rarely, red cell aplasia have been reported. Full blood counts should be measured weekly for the first 2 months and then monthly thereafter. Severe bleeding events, including fatal CNS and gastrointestinal haemorrhages, have been reported, mostly in conjunction with thrombocytopenia although dasatinib also causes reversible platelet dysfunction *in vivo*. Treatment interruption and blood transfusion may be required for gastrointestinal haemorrhages. Caution is required when giving dasatinib with other drugs that affect platelet function or with anticoagulants (see Interactions, below). Embolic events including pulmonary embolism and deep-vein thrombosis have also been reported.

Cardiac failure, arrhythmias, and hypertension are common; hypotension, angina, myocardial infarction (including fatalities), pericarditis, myocarditis, acute coronary syndrome, and cor pulmonale occur more rarely. Dasatinib has the potential to prolong the QT interval, and should be given with caution to patients at risk of this, such as those with hypokalaemia or hypomagnesaemia, those on antiarrhythmic therapy or other drugs that prolong the QT interval, or those receiving cumulative high doses of anthracyclines.

Other common adverse effects include headache, pyrexia, chills, musculoskeletal pain, arthralgia, myalgia, asthenia, fatigue, chest pain, electrolyte disturbances, appetite and weight disturbances, mucositis, colitis, flushing, and skin disorders such as rash, alopecia, dermatitis, pruritus, acne, dry skin, and hyperhidrosis.

Respiratory adverse effects include dyspnoea, cough, pulmonary hypertension, pneumonitis, bronchospasm, respiratory distress syndrome, and interstitial lung disease. Infections, including pneumonia, are common; sepsis, although uncommon, may be fatal. Renal failure, urinary frequency, proteinuria, and liver disorders such as hepatitis, cholecystitis, and cholestasis have been reported. CNS adverse effects include depression, insomnia, dizziness, dysgeusia, somnolence, and neuropathy, and less commonly, anxiety, confusion, decreased libido, syncope, tremor, and amnesia. Stroke, transient ischaemic attacks, convulsions, and optic neuritis have been reported rarely. Visual disturbances, dry eye, tinnitus, conjunctivitis, and vertigo have occurred.

Uncommon adverse effects include tumour lysis syndrome, hyperuricaemia, hypoalbuminaemia, pancreatitis, gynaecomastia, irregular menstruation, rhabdomyolysis, hypersensitivity including erythema nodosum, and other skin disorders such as acute febrile neutrophilic dermatosis, photosensitivity, pigmentation disorders, panniculitis, skin ulcers, bullous conditions, nail disorders, and palmar-plantar erythrodysesthesia syndrome. Rare adverse effects include livedo reticularis (a mottled blue discoloration of the skin associated with poor venous return) and protein-losing gastroenteropathy.

Caution is advised when using dasatinib in patients with hepatic impairment.

Effects on the skin. Panniculitis has been reported with the use of dasatinib, which resolved upon stopping therapy. In one case, dasatinib was restarted with prednisone, and no recurrence of panniculitis was noted. In another patient, however, a rash recurred on restarting therapy that was not sensitive to corticosteroid treatment.[1]

1. Assouline S, *et al*. Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. *N Engl J Med* 2006; **354:** 2623–4.

Lupus. A patient developed arthralgia and fatigue 3 months after starting dasatinib for chronic myeloid leukaemia. Symptoms worsened, drug-induced lupus was suspected, and dasatinib was stopped 9 months after starting therapy. Fever, arthralgia, fatigue, hepatosplenomegaly and pleuro-pericardial effusions all resolved fully within 1 month. It was suggested that the risk of developing dasatinib-associated autoimmunity be assessed prospectively by screening for autoantibodies before starting treatment with dasatinib.[1]

1. Rea D, *et al*. Dasatinib-induced lupus. *Lancet* 2008; **372:** 713–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dasatinib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Interactions

Dasatinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals, macrolide antibacterials, HIV-protease inhibitors, and nefazodone may increase blood concentrations of dasatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of dasatinib. When use with such drugs cannot be avoided, dose adjustment of dasatinib may be necessary (see Uses and Administration, p. 777.3). Since St John's wort may decrease dasatinib concentrations unpredictably, these drugs should not be given together.

Dasatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and may alter blood concentrations of other drugs that are substrates of this enzyme.

Since the solubility of dasatinib is dependent on pH, use with antacids should be avoided. If antacid therapy is needed, it should be given at least 2 hours before or 2 hours after the dose of dasatinib. Similarly, histamine H_2-receptor antagonists or proton pump inhibitors such as famotidine or omeprazole should not be given with dasatinib as long-term suppression of gastric acid secretion is likely to reduce dasatinib exposure.

Dasatinib prolongs the QT interval and the effect may be additive when given with other drugs with similar effects. Dasatinib also causes thrombocytopenia and bleeding, which may be additive with antiplatelet drugs, anticoagulants, and NSAIDs.

References.

1. Eley T, *et al*. Phase I study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. *J Clin Pharmacol* 2009; **49:** 700–9.

Pharmacokinetics

Peak plasma concentrations of dasatinib occur between 0.5 and 6 hours after an oral dose. The mean terminal half-life is about 5 hours. Consumption of a high-fat meal may increase exposure to dasatinib, but this effect is not considered to be of clinical significance. Dasatinib is extensively distributed and metabolised. Metabolism occurs mainly via the cytochrome P450 isoenzyme CYP3A4, forming an active metabolite. Plasma protein binding of dasatinib and its active metabolite is about 96% and 93%, respectively. Elimination is mainly via the faeces; about 4% is recovered in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sprycel; ***Austral.***: Sprycel; ***Austria***: Sprycel; ***Belg.***: Sprycel; ***Braz.***: Sprycel; ***Canad.***: Sprycel; ***Chile***: Sprycel; ***Cz.***: Sprycel; ***Denm.***: Sprycel; ***Fr.***: Sprycel; ***Ger.***: Sprycel; ***Gr.***: Sprycel; ***Hong Kong***: Sprycel; ***Hung.***: Sprycel; ***Indon.***: Sprycel†; ***Irl.***: Sprycel; ***Israel***: Sprycel; ***Ital.***: Sprycel; ***Malaysia***: Sprycel; ***Neth.***: Sprycel; ***Norw.***: Sprycel; ***NZ***: Sprycel; ***Pol.***: Sprycel; ***Port.***: Sprycel; ***Rus.***: Sprycel (Спрайсел); ***S.Afr.***: Sprycel; ***Singapore***: Sprycel; ***Spain***: Sprycel; ***Swed.***: Sprycel; ***Switz.***: Sprycel; ***Thai.***: Sprycel; ***Turk.***: Sprycel; ***UK***: Sprycel; ***USA***: Sprycel.

Daunorubicin *(BAN, rINN)*

Daunomycin; Daunorubicina; Daunorubicine; Daunorubicinum; Daunorubisiini; FI-6339; RP-13057; Rubidomicina; Rubidomycin; Даунорубицин.

(1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxonaphthacen-1-yl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside.

$C_{27}H_{29}NO_{10}$=527.5

CAS — 20830-81-3.

ATC — L01DB02.

ATC Vet — QL01DB02.

UNII — ZS7284E0ZP.

Daunorubicin Citrate *(BANM, rINNM)*

Citrato de daunorubicina; Daunorubicine, Citrate de; Daunorubicini Citras; Даунорубицина Цитрат.

ATC — L01DB02.

UNII — 5L84T2Z6NP.

Daunorubicin Hydrochloride

(BANM, USAN, rINNM)

Cloridrato de Daunorrubicina; Daunomycin Hydrochloride; Daunoribisin Hidroklorür; Daunorubicin hydrochlorid; Daunorubicina, hidrocloruro de; Daunorubicine, Chlorhydrate de; Daunorubicin-hidroklorid; Daunorubicinhydrochlorid; Daunorubicinhydroklorid; Daunorubicini Hydrochloridum; Daunorubicino hidrocloridas; Daunorubisiinihydrokloridi; FI-6339 (daunorubicin); Hidrocloruro de daunorubicina; NDC-0082-4155; NSC-82151; RP-13057 (daunorubicin); Rubidomycin Hydrochloride; Даунорубицина Гидрохлорид.

(1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxonaphthacen-1-yl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-pyranoside hydrochloride; (8*S*-*cis*)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)]oxy-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.

$C_{27}H_{29}NO_{10}$,HCl=564.0

CAS — 23541-50-6.

ATC — L01DB02.

ATC Vet — QL01DB02.

UNII — UD984I04LZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Daunorubicin Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It is manufactured by methods designed to minimise or eliminate the presence of histamine. An orange-red, hygroscopic, crystalline powder. It contains between 95 and 102% of the hydrochloride (anhydrous and solvent-free basis). Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Daunorubicin Hydrochloride). An orange-red, hygroscopic, crystalline powder. It has a potency equivalent to not less than 842 and not more than 1030 micrograms of the base per mg. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone; very slightly soluble in chloroform. A 0.5% solution in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Incompatibility. Daunorubicin is incompatible with heparin sodium,[1] and has also been reported to be incompatible with a solution of dexamethasone sodium phosphate.

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.

Stability. In a study[1] of the stability of anthracycline antineoplastic agents in 4 infusion fluids (glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid) daunorubicin hydrochloride was stable in all 4, the percentage remaining after 24 hours being 98.5%, 97.4%, 94.7%, and 95.4% respectively. Stability appeared to be partly related to pH; daunorubicin was more stable as the pH of the mixture became more acidic, with the best stability in glucose 5% with a pH of 4.5. Although daunorubicin solutions are degraded by light, the effect is reported not to be significant at concentrations of 500 micrograms/mL or above; however, below this concentration precautions should be taken to protect solutions from light, and storage should be in polyethylene or polypropylene containers to minimise adsorptive losses.[2] It has been suggested that formulation with the food colouring Scarlet GN, which absorbs light over the same spectral region as daunorubicin, would stabilise daunorubicin solutions to light.[3]

Liposomal daunorubicin citrate should be diluted with glucose 5% solution as aggregation of the liposomes may result with sodium chloride. In addition, licensed product information advises that liposomal daunorubicin should not be mixed with substances containing benzyl alcohol or other detergent-like molecules, which can lead to premature rupture of the liposomes.

1. Poochikian GK, *et al*. Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.
2. Wood MJ, *et al*. Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
3. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Uses and Administration

Daunorubicin is an antineoplastic anthracycline antibiotic with actions similar to those of doxorubicin (p. 783.2), to which it is closely related. It is used with other antineoplastics to induce remissions in acute leukaemias. Daunorubicin is given in combination regimens for acute lymphoblastic leukaemia (see p. 692.3) and acute myeloid leukaemias (see p. 693.1). It has also been tried in some other malignancies. A liposomal formulation of daunorubicin has been developed for use in the management of advanced Kaposi's sarcoma in patients with AIDS (see also p. 718.1).

In the conventional formulation, daunorubicin is usually given as the hydrochloride, but doses are expressed in terms of the base. Daunorubicin hydrochloride 21.4 mg is equivalent to about 20 mg daunorubicin. The liposomal formulation contains daunorubicin citrate, equivalent to about 2 mg/mL of daunorubicin base.

In US treatment regimens for adult acute lymphoblastic or myeloid leukaemia, the usual dose of *conventional* daunorubicin hydrochloride is the equivalent of daunorubicin 45 mg/m^2 daily on days 1 to 3 of the first course; in acute myeloid leukaemia, this dose is also given on days 1 and 2 of subsequent courses. Courses may be repeated if needed, after bone-marrow evaluation. In the UK, for remission induction in acute leukaemias, a dose of 40 to 60 mg/m^2 can be given on alternate days for a course of up to 3 injections. Daunorubicin hydrochloride is given as a solution in sodium chloride 0.9% into a fast-running intravenous infusion of sodium chloride 0.9% or glucose 5%.

For doses in children and the elderly, see below. Dosage should be reduced in patients with impaired hepatic or renal function (see below).

In the treatment of Kaposi's sarcoma, *liposomal* daunorubicin citrate is given intravenously every 2 weeks starting with a dose of 40 mg/m^2, and continued for as long as disease control can be maintained. It is diluted with glucose 5% (sodium chloride 0.9% should not be used) to a daunorubicin concentration between 0.2 and 1 mg/mL, and given over 30 to 60 minutes.

Blood counts should be determined frequently during treatment as daunorubicin has a potent effect on bone-marrow function (see also Bone-marrow Depression, p. 730.3). Cardiac function should be monitored at regular intervals to detect signs of cardiotoxicity. The total cumulative dose of daunorubicin in adults should not exceed 550 to 600 mg/m^2; in patients who have received radiotherapy to the chest it may be advisable to limit the total cumulative dose to about 400 mg/m^2. Product information for liposomal daunorubicin recommends determining left ventricular ejection fraction (LVEF) at baseline and after cumulative doses of 320 mg/m^2, and every 160 mg/m^2 thereafter. In patients who have received prior radiotherapy to the chest, or who have pre-existing cardiac disease, or who have had previous anthracycline therapy (equivalent to more than *doxorubicin* 300 mg/m^2) LVEF should be assessed at baseline and after every 160 mg/m^2 of liposomal daunorubicin.

Administration. *HIGH-DOSE THERAPY.* Two multicentre studies in patients with acute myeloid leukaemia compared the use of a standard induction dose of a conventional daunorubicin formulation (45 mg/m^2), with an escalated dose of 90 mg/m^2, given for 3 days in a regimen with cytarabine.[1,2] In patients aged 60 and under, the high-dose regimen was associated with an increased rate of complete remission (70.6 versus 57.3% in the conventional dose group), and improved overall survival (median values of 23.7 versus 15.7 months) on follow-up for a median of 25 months.[2] Although this study suggested little benefit in the subgroup of patients older than 50, in the other, which was restricted to those 60 and over, comparable improvements in remission and overall survival were seen with high-dose therapy in those between 60 and 65 years of age,[1] but patients older than this did not show any benefit. The higher doses of anthracycline were not associated with an increase in mortality or moderate to severe adverse events, even in older patients.

1. Löwenberg B, *et al*. Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), German AML Study Group (AMLSG), and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009; **361:** 1235–48. Correction. *ibid*. 2010; **362:** 1155. [dose]
2. Fernandez HF, *et al*. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med* 2009; **361:** 1249–59.

Administration in children. Daunorubicin hydrochloride is licensed for the induction of remission in children with acute leukaemia. Doses may vary according to country, and the combination regimen used.

In the USA, a dose of daunorubicin 25 mg/m^2 is given intravenously once a week, in combination regimens, to children with acute lymphoblastic leukaemia. Complete remission is generally obtained within 4 courses; however, if only partial remission is obtained after 4 courses, up to 2 further courses may be given. For children less than 2 years of age, or with a body-surface of less than 0.5 m^2, a dose of 1 mg/kg is used instead.

In the UK, children with acute myeloid or lymphoblastic leukaemia who are 2 years and older may be given the same dose as adults (see Uses and Administration, above). Children under 2 years of age, or with a body-surface of less than 0.5 m^2 may be given an intravenous dose of 1 mg/kg daily.

Precautions and monitoring are as for adults; cardiotoxicity may occur more frequently in children. A total cumulative dose of 300 mg/m^2 should not be exceeded; in children under 2 years, the total cumulative dose should not exceed 10 mg/kg.

The safety and efficacy of *liposomal* daunorubicin citrate in paediatric patients has not been established. However, a study in 24 patients aged between 2 and 23 years, who were given doses of 30 or 60 mg/m^2, indicated that the pharmacokinetics showed less variability than has been reported for conventional formulations, and no substantial differences related to age.[1]

1. Hempel G, *et al*. Population pharmacokinetics of liposomal daunorubicin in children. *Br J Clin Pharmacol* 2003; **56:** 370–7.

Administration in the elderly. Daunorubicin hydrochloride should be used with care in elderly patients with inadequate bone marrow reserves. In the UK, a dosage reduction of up to 50% is recommended. In the USA, for patients with acute myeloid leukaemia and aged 60 years and over, an intravenous dose of daunorubicin 30 mg/m^2 daily on days 1 to 3 of the first course, and days 1 and 2 of subsequent courses, is recommended for combination treatment regimens. Precautions and monitoring are as for younger adults (see Uses and Administration, above); cardiotoxicity may occur more frequently in the elderly. However, see also High-dose Therapy, above.

The safety and efficacy of *liposomal* daunorubicin citrate in elderly patients has not been established.

Administration in hepatic impairment. Doses of daunorubicin should be reduced in hepatic impairment. Some licensed product information for daunorubicin hydrochloride recommends that patients with serum-bilirubin concentrations of 12 to 30 micrograms/mL (or 20 to 50 micromoles/litre) should receive 75% of the usual daily dose, and those with concentrations greater than 30 micrograms/mL (or above 50 micromoles/litre) should be given 50% of the usual daily dose.

Limited data exist for liposomal daunorubicin citrate; in the USA, similar dosage reductions to those given for the hydrochloride are recommended.

Administration in renal impairment. Doses of daunorubicin should be reduced in renal impairment. Some licensed product information for daunorubicin hydrochloride recommends that patients with serum-creatinine concentrations of 12 to 30 micrograms/mL (or 105 to 265 micromoles/litre) should receive 75% of the usual daily dose, and those with concentrations greater than 30 micrograms/mL (or 265 micromoles/litre) should be given 50% of the usual daily dose.

Limited data exist for liposomal daunorubicin citrate; in the USA, similar dosage reductions to those given for the hydrochloride are recommended in patients with a serum-creatinine concentration greater than 30 micrograms/mL.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1 and p. 785.1.

Cardiotoxicity is more likely when the total cumulative dose of daunorubicin exceeds 550 to 600 mg/m^2 in adults, 300 mg/m^2 in children, or in children aged under 2 years, 10 mg/kg. The total cumulative dose should be limited to 400 mg/m^2 in patients who have had previous radiation therapy to the chest. US licensed product information for the standard formulation of daunorubicin recommends an ECG and/or determination of left ventricular ejection fraction (LVEF) before each course. Product information for liposomal daunorubicin recommends evaluating cardiac function before each course of daunorubicin and determining LVEF at baseline and after cumulative doses of 320 mg/m^2, and every 160 mg/m^2 thereafter. In patients who have pre-existing cardiac disease, or who have had previous radiotherapy to the chest or anthracycline therapy (more than 300 mg/m^2 *doxorubicin* or equivalent) LVEF should be assessed at baseline and after every 160 mg/m^2 of liposomal daunorubicin. Daunorubicin should be used in reduced doses in hepatic and renal impairment.

Liposomal formulations of daunorubicin may be associated with a reduced potential for local tissue necrosis although current clinical experience is limited and such toxicity remains a possibility. An acute syndrome of back pain, flushing, and chest tightness may occur during infusion of such products, but generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. For a discussion of the cardiotoxicity of anthracyclines, and its management, see Effects on the Heart, under Doxorubicin, p. 784.1.

Effects on the skin and nails. For reports of hyperpigmentation in patients given daunorubicin, see under Doxorubicin, p. 784.3.

Handling and disposal. Daunorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

For a method for the destruction of daunorubicin in wastes see under Doxorubicin, p. 785.1.

Pregnancy. For a report of a fetal sinusoidal heart rate pattern and neonatal pancytopenia after a woman was given combination chemotherapy including daunorubicin, see Pregnancy, under Etoposide, p. 791.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies daunorubicin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

As for Doxorubicin, p. 785.2.

Antineoplastics. Hepatic dysfunction was reported[1] in 13 patients given cumulative doses of daunorubicin 180 to 450 mg/m^2. Ten of them had also received *tioguanine* or *cytarabine*, or a combination of these. The authors also noted that other studies had suggested that the related drug doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, and thought that a similar interaction could occur between daunorubicin and tioguanine.

1. Penta JS, *et al*. Hepatotoxicity of combination chemotherapy for acute myelocytic leukemia. *Ann Intern Med* 1977; **87:** 247–8.

Pharmacokinetics

After intravenous injection, daunorubicin is rapidly distributed into body tissues, particularly the liver, lungs, kidneys, spleen, and heart with an initial distribution half-life of about 45 minutes. It is rapidly metabolised in the liver, and is excreted in bile and urine as unchanged drug and metabolites. The major metabolite, daunorubicinol, has antineoplastic activity. Up to 25% of a dose is excreted in urine in an active form over several days (the terminal plasma elimination half-lives of daunorubicin and its major metabolite are reported to be 18.5 and 26.7 hours respectively); an estimated 40% is excreted in bile.

Daunorubicin does not appear to cross the blood-brain barrier, but crosses the placenta.

The pharmacokinetics of liposomal doxorubicin are significantly different from those of the conventional drug formulation, with a decreased uptake by normal tissues (although tumour neovasculature is reported to have increased permeability to the liposomes), and a terminal half-life of 4 to 5 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daunoblastina†; Daunogobbi; Maxidauno; ***Austral.***: DaunoXome†; ***Austria***: Daunoblastin; DaunoXome†; ***Belg.***: Cerubidine; ***Braz.***: Daunoblastina; Daunocin; DaunoXome†; ***Canad.***: Cerubidine; ***Chile***: Cerubidine†; Daurocina†; Oncodaunotec†; ***China***: Daunoblastina (柔红霉素); ***Denm.***: Cerubidin; DaunoXome; ***Fin.***: DaunoXome; ***Fr.***: Cerubidine; DaunoXome; ***Ger.***: Daunoblastin; DaunoXome†; ***Gr.***: Cerubidine; Daunoblastina; DaunoXome; ***Hong Kong***: Daunoblastina; ***Hung.***: Daunoblastina; ***India***: Daunobin; Daunocin; Daunoplus; Daunorubitec; Daunoside; Daunotec; Norubin; ***Irl.***: Cerubidin; DaunoXome; ***Israel***: Cerubidine; ***Ital.***: Daunoblastina; DaunoXome; ***Mex.***: Rubilem; ***Neth.***: Cerubidine; DaunoXome; ***Norw.***: Cerubidin; DaunoXome; ***Port.***: DaunoXome; ***Rus.***: DaunoXome (Даунозом)†; ***S.Afr.***: Daunoblastin; ***Singapore***: Daunoblastina; Daunocin; ***Spain***: Daunoblastina; ***Swed.***: Cerubidin; DaunoXome†; ***Switz.***: Cerubidine†; ***UK***: DaunoXome; ***USA***: Cerubidine; DaunoXome; ***Venez.***: Daunoblastina.

Pharmacopoeial Preparations
USP 36: Daunorubicin Hydrochloride for Injection.

Decitabine *(BAN, USAN, rINN)*

5-Aza-2′-deoxycytidine; DAC; Decitabina; Décitabine; Decitabinum; NSC-127716; Децитабин.

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.

$C_8H_{12}N_4O_4$=228.2

CAS — 2353-33-5.

ATC — L01BC08.

ATC Vet — QL01BC08.

UNII — 776B62CQ27.

Uses and Administration

Decitabine is an antineoplastic antimetabolite structurally related to cytarabine (p. 774.1). It is reported to cause DNA hypomethylation by the inhibition of DNA methyltransferase, which has the potential to alter gene expression (reactivate silent genes) and limit disease progression and resistance. Decitabine is used in the treatment of myelodysplastic syndromes (p. 694.3); it is also used in the management of newly diagnosed or secondary acute myeloid leukaemia (p. 693.1) in patients 65 years of age or older who are not candidates for standard induction chemotherapy.

Decitabine is given by intravenous infusion, diluted to a final concentration of 0.1 to 1 mg/mL in sodium chloride 0.9%, glucose 5%, or lactated Ringer's injection.

For the treatment of **myelodysplastic syndromes** the recommended dose is 15 mg/m² infused over 3 hours and given every 8 hours for 3 days; this 3-day cycle is repeated every 6 weeks, for a minimum of 4 cycles. If haematological recovery from a cycle is incomplete, cycle length may be increased to as much as every 10 weeks and the dose reduced to 11 mg/m² every 8 hours upon restarting therapy; this dose may be maintained or increased in subsequent cycles as clinically indicated. An alternative regimen is decitabine 20 mg/m² infused over 1 hour and given once daily for 5 days; this 5-day cycle is repeated every 4 weeks, for at least 4 cycles. If myelosuppression occurs, subsequent cycles should be delayed until haematological recovery.

Decitabine treatment should be delayed if serum creatinine is 2 mg per 100 mL or greater, or if total bilirubin is 2 or more times the upper limit of normal, or if the patient has an active or uncontrolled infection.

For the treatment of **acute myeloid leukaemia** the recommended dose of decitabine is 20 mg/m² infused over 1 hour and given once daily for 5 days; this 5-day cycle is repeated every 4 weeks, for at least 4 cycles. If myelosuppression occurs, subsequent cycles should be delayed until haematological recovery.

Decitabine is also under investigation for the treatment of chronic myeloid leukaemia (p. 694.2). It is also reported to increase fetal haemoglobin in patients with sickle-cell disease (p. 1123.2).

References.

1. DeSimone J, *et al.* Maintenance of elevated fetal hemoglobin levels by decitabine during dose interval treatment of sickle cell anemia. *Blood* 2002; **99:** 3905–8.
2. Momparler RL. Pharmacology of 5-aza-2′-deoxycytidine (decitabine). *Semin Hematol* 2005; **42** (suppl 2): S9–S16.
3. Kantarjian HM, Issa JP. Decitabine dosing schedules. *Semin Hematol* 2005; **42** (suppl 2): S17–S22. Correction. *ibid.*; 274.
4. Lubbert M, Minden M. Decitabine in acute myeloid leukemia. *Semin Hematol* 2005; **42** (suppl 2): S38–S42.
5. Issa JP, Byrd JC. Decitabine in chronic leukemias. *Semin Hematol* 2005; **42** (suppl 2): S43–S49.
6. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39:** 1700–9.
7. Momparler RL. Epigenetic therapy of cancer with 5-aza-2′-deoxycytidine (decitabine). *Semin Oncol* 2005; **32:** 443–51.
8. Kantarjian H, *et al.* Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer* 2006; **106:** 1794–1803.
9. McKeage K, Croom KF. Decitabine in myelodysplastic syndromes. *Drugs* 2006; **66:** 951–8.
10. Jabbour E, *et al.* Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. *Cancer* 2008; **112:** 2341–51.
11. Steensma DP, *et al.* Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. *J Clin Oncol* 2009; **27:** 3842–8.
12. Santos FP, *et al.* Decitabine in the treatment of myelodysplastic syndromes. *Expert Rev Anticancer Ther* 2010; **10:** 9–22.
13. Daskalakis M, *et al.* Decitabine. *Recent Results Cancer Res* 2010; **184:** 131–57.
14. Ganetsky A. The role of decitabine for the treatment of acute myeloid leukemia. *Ann Pharmacother* 2012; **46:** 1511–17.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. The most common adverse effect of decitabine is myelosuppression, which may be severe and dose-limiting. Fatalities have been reported. Other common adverse effects include fatigue, pyrexia, gastrointestinal disturbances, petechiae, and hyperglycaemia. Cardiorespiratory arrest, increased blood bilirubin, intracranial haemorrhage, abnormal liver function tests, pulmonary oedema, atrial fibrillation, central line infection, or febrile neutropenia may force treatment to be stopped or delayed. Other adverse effects which may be dose-limiting include lethargy, oedema, tachycardia, depression, or pharyngitis.

Pharmacokinetics

On intravenous dosage decitabine shows biphasic disposition. Plasma protein binding is negligible. The exact route of metabolism and excretion is not known; one pathway appears to be deamination by cytidine deaminase, which is found principally in the liver, but also in granulocytes, the intestinal epithelium, and whole blood. A terminal elimination half-life of about 0.5 hours has been reported after a 72-hour infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dacogen; Detavi; ***Braz.***: Dacogen; ***Chile***: Dacogen; ***China***: Dacogen (达珂); ***Israel***: Dacogen; ***Malaysia***: Dacogen; ***Neth.***: Dacogen; ***Philipp.***: Dacogen; ***Rus.***: Dacogen (Дакоген); ***Switz.***: Dacogen; ***Thai.***: Dacogen; ***Turk.***: Dacogen; ***UK***: Dacogen; ***USA***: Dacogen.

Denileukin Diftitox *(USAN, rINN)*

DAB_{389}IL2; Denileucina diftitox; Denileukin Difitox (BAN); Dénileukine Diftitox; Denileukinum Diftitoxum; LY-335348; Денилейкин Дифтитокс.

CAS — 173146-27-5.

ATC — L01XX29.

ATC Vet — QL01XX29.

UNII — 25E79B5CTM.

Uses and Administration

Denileukin diftitox is a recombinant interleukin fusion toxin comprised of interleukin-2 linked to the A and B fragments of diphtheria toxin. It is given by intravenous infusion for the management of persistent or recurrent cutaneous T-cell lymphoma (see Mycosis Fungoides, p. 698.3), in patients whose malignant cells express the CD25 interleukin-2 receptor. The concentration of denileukin diftitox must be at least 15 micrograms/mL during all steps in the preparation of the solution for infusion. The recommended dose is 9 or 18 micrograms/kg daily, given over 15 minutes or more, for 5 consecutive days every 3 weeks.

References.

1. Olsen E, *et al.* Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19:** 376–88.
2. Martin A, *et al.* A multicenter dose-escalation trial with denileukin diftitox (ONTAK, DAB(389)IL-2) in patients with severe psoriasis. *J Am Acad Dermatol* 2001; **45:** 871–81.
3. Talpur R, *et al.* Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). *Leuk Lymphoma* 2002; **43:** 121–6.
4. Frankel AE, *et al.* A phase II study of DT fusion protein denileukin diftitox in patients with fludarabine-refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2003; **9:** 3555–61.
5. Eklund JW, Kuzel TM. Denileukin diftitox: a concise clinical review. *Expert Rev Anticancer Ther* 2005; **5:** 33–8.
6. Foss F. Clinical experience with denileukin diftitox (ONTAK). *Semin Oncol* 2006; **33** (suppl 3): 11–16.
7. Duvic M, Talpur R. Optimizing denileukin diftitox (Ontak) therapy. *Future Oncol* 2008; **4:** 457–69.
8. Manoukian G, Hagemeister F. Denileukin diftitox: a novel immunotoxin. *Expert Opin Biol Ther* 2009; **9:** 1445–51.
9. Prince HM, *et al.* Phase III placebo-controlled trial o f denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2010; **28:** 1870–7.

Adverse Effects and Precautions

Denileukin diftitox can cause an acute hypersensitivity reaction within 24 hours of infusion with symptoms reminiscent of a cytokine release syndrome. Anaphylaxis and death have also been reported. A more delayed flu-like syndrome may also occur up to several days after infusion. Vascular leak syndrome, characterised by hypotension, oedema, or hypoalbuminaemia, may also be delayed. Gastrointestinal disturbances, chills, fever, and asthenia are common. Other adverse effects include rash, predisposition to cutaneous infections, and thrombotic events. Visual loss has been reported; although recovery was reported in some patients, in most cases impairment persisted.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Ontak; ***USA***: Ontak.

Diaziquone *(USAN, rINN)*

Aziridinylbenzoquinone; AZQ; CI-904; Diazicuona; Diaziquonum; NSC-182986; Диазихон.

Diethyl 2,5-bis-(1-aziridinyl)-3,6-dioxo-1,4-cyclohexadiene-1,4-dicarbamate.

$C_{16}H_{20}N_4O_6$=364.4

CAS — 57998-68-2.

UNII — FQL5EUP13W.

Profile

Diaziquone has been investigated as an antineoplastic in the treatment of malignant brain tumours and acute myeloid leukaemia. It is thought to act as an alkylating agent. Adverse effects include bone-marrow suppression, manifesting chiefly as leucopenia and thrombocytopenia, gastrointestinal disturbances, and alopecia. Anaphylactoid reactions have occurred.

Docetaxel *(BAN, USAN, rINN)*

Docetaksel; Docétaxel; Docetaxelum; Docetaxol; Docetaxolum; Dosetaksel; Dosetaksoli; NSC-628503; RP-56976; Доцетаксел.

(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate; *tert*-Butyl {(1*S*,2*S*)-2-[(2*S*,5*R*,7*S*,10*R*,13*S*)-4-acetoxy-2-benzoyloxy-1,7,10-trihydroxy-9-oxo-5,20-epoxytax-11-en-13-yloxycarbonyl]-2-hydroxy-1-phenylethyl}carbamate.

$C_{43}H_{53}NO_{14}$=807.9

CAS — 114977-28-5 (anhydrous docetaxel); 148408-66-6 (docetaxel trihydrate).

ATC — L01CD02.

ATC Vet — QL01CD02.

UNII — 15H5577CQD (docetaxel); 699121PHCA (anhydrous docetaxel).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Docetaxel, Anhydrous). A white or almost white, crystalline, hygroscopic powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Docetaxel Trihydrate). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in dichloromethane. Protect from light.

USP 36: (Docetaxel). A white or almost white, crystalline powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in acetone. Protect from light.

Incompatibility and stability. Various formulations of docetaxel are available; some require an initial reconstitution of a concentrate with a solvent (resulting in a premix solution) before further dilution for infusion, whereas others are available in vials as a solution ready for further dilution for infusion. Both the premix solutions and the vials should be used as soon as possible after reconstitution and opening, respectively. However, licensed product information (*Actavis, UK*) states that the premix solution is chemically and physically stable for 8 hours when stored between 2 degrees and 8 degrees or at room temperature (below 25 degrees). The same company states for its solution formulation that physical, chemical, and microbiological stability has been shown for 28 days at 2 degrees to 8

degrees and at 25 degrees under normal lighting conditions (after the first vial opening).

Docetaxel is further diluted with sodium chloride 0.9% or glucose 5% to a concentration not exceeding 740 micrograms/mL; chemical and physical stability, and maximum storage time varies between products:

- *Actavis, UK* (premix solution formulation): 4 hours at about 25 degrees under normal lighting; 4 hours at 5 degrees ± 3 degrees, protected from light; storage not longer than 24 hours at 2 degrees to 8 degrees
- *Actavis, UK* (concentrate solution): 8 hours at about 25 degrees under normal lighting; 3 days at 2 degrees to 8 degrees, protected from light
- *Hospira, UK*: 4 hours when stored below 25 degrees; storage not longer than 24 hours at 2 degrees to 8 degrees
- *Taxotere, Sanofi-Aventis, UK*: 6 hours when stored below 25 degrees; 48 hours at 2 degrees to 8 degrees (in non-PVC bags; see below for further information)

Product literature should therefore be consulted.

The chemical and physical stability of various docetaxel infusion solutions has been studied.[1-3] The *Taxotere* formulation was diluted to 300 or 900 micrograms/mL with sodium chloride 0.9% in polyolefin containers or glass bottles, and stored at 19 degrees to 21 degrees and protected from light.[1] There was no evidence of precipitation in the first 24 hours of storage. However, after this time, HPLC assay revealed concentrations with large standard deviations for some containers, suggesting the existence of microprecipitates. Precipitation was a generalised phenomenon at day 7, especially in glass containers. The results of this study supported the use of docetaxel within 4 hours of preparation, and the authors cautioned that docetaxel (*Taxotere* formulation) was very labile and physical stability could be strongly affected by small variations in handling conditions.[1]

Many docetaxel formulations contain polysorbate 80, which has the potential to leach the plasticiser diethylhexyl phthalate (DEHP) from PVC bags, and use in such containers is to be avoided.[3] In order to minimise patient exposure to DEHP, some manufacturers (*Hospira, UK*) recommend that docetaxel be stored in glass bottles or polypropylene or polyolefin containers, and given through polyethylene-lined giving sets. Similar recommendations are made for paclitaxel, see under Incompatibility, p. 839.3.

1. Eroles AA, *et al*. Stability of docetaxel diluted to 0.3 or 0.9 mg/mL with 0.9% sodium chloride injection and stored in polyolefin or glass containers. *Am J Health-Syst Pharm* 2009; **66:** 1565–8.
2. Thiesen J, Krämer I. Physico-chemical stability of docetaxel premix solution and docetaxel infusion solutions in PVC bags and polyolefine containers. *Pharm World Sci* 1999; **21:** 137–41.
3. Dalle M, *et al*. Peut-on conditionner les solutions de docétaxel dans des poches en PVC? Can solutions of docetaxel be conditioned in PVC bags? *J Pharm Clin* 2006; **25:** 147–52.

Uses and Administration

Docetaxel is a semisynthetic taxane similar to paclitaxel (see p. 839.3). It is manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata*. Docetaxel is used for locally advanced or metastatic breast cancer (p. 702.1). It may be used as first-line treatment with doxorubicin; in the treatment of refractory disease, it is used alone or with capecitabine. In the treatment of metastatic breast cancer that overexpresses HER2 (human epidermal growth receptor 2), docetaxel may be used with trastuzumab as initial therapy. For adjuvant treatment of operable, node-positive breast cancer, docetaxel is given with doxorubicin and cyclophosphamide. Docetaxel is also indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (p. 710.2), either with cisplatin for initial treatment of unresectable disease, or after failure of previous platinum-based chemotherapy. It is used with prednisone or prednisolone in hormone-refractory metastatic prostate cancer (p. 712.3). Docetaxel is given with cisplatin and fluorouracil in the first-line treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (see Malignant Neoplasms of the Stomach, p. 706.1); it is also used in this combination for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (p. 708.1).

Docetaxel is given by intravenous infusion in glucose 5% or sodium chloride 0.9% at a concentration not exceeding 740 micrograms/mL. Infusion is normally over 1 hour. Premedication with an oral corticosteroid, such as dexamethasone 16 mg daily, for 3 days starting 1 day before docetaxel is recommended with many regimens.

The licensed dose for docetaxel as a single agent in the treatment of **breast cancer** after failure of previous chemotherapy is 60 to 100 mg/m^2 once every 3 weeks. A dose of 75 mg/m^2 once every 3 weeks is given in combination therapy with doxorubicin, or capecitabine, or when used as adjuvant therapy with doxorubicin and cyclophosphamide. When used with trastuzumab, docetaxel is given at a dose of 100 mg/m^2 once every 3 weeks.

The dose for **non-small cell lung cancer** is 75 mg/m^2 once every 3 weeks, for both first-line combination therapy and monotherapy after failure of previous chemotherapy.

For **gastric adenocarcinoma** docetaxel 75 mg/m^2 is given before cisplatin and fluorouracil; treatment is repeated every 3 weeks.

In the induction treatment of **head and neck cancer**, the recommended dose of docetaxel is 75 mg/m^2, given before cisplatin and fluorouracil; treatment is given every 3 weeks for 3 cycles, followed by chemoradiotherapy, or for 4 cycles when followed by radiotherapy alone.

For **prostate cancer**, the dose of docetaxel is 75 mg/m^2 once every 3 weeks, with prednisone or prednisolone 5 mg orally twice daily given continuously. The use of prednisone or prednisolone reduces the need for a premedication corticosteroid; dexamethasone 8 mg may be given at 12 hours, 3 hours, and 1 hour before docetaxel.

Regular blood counts are required, and dosage in subsequent courses should be reduced in patients who develop severe or febrile neutropenia (see also Bone-marrow Depression, p. 730.3), or severe cutaneous reactions or peripheral neuropathy. The dose of docetaxel should be reduced in hepatic impairment, see below. A dose reduction is also suggested when docetaxel is used with strong cytochrome P450 isoenzyme CYP3A4 inhibitors, see Administration with Other Drugs, below.

Novel formulations of docetaxel are under investigation, including a pegylated conjugate, a lyophilised emulsion, and a docetaxel prodrug nanoparticle formulation.

References. For references to taxanes as a class, see Paclitaxel, p. 840.2.

1. Montero A, *et al*. Docetaxel for treatment of solid tumours: a systematic review of clinical data. *Lancet Oncol* 2005; **6:** 229–39.
2. Engels FK, *et al*. Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. *Br J Cancer* 2005; **93:** 173–7.
3. McKeage K, Keam SJ. Docetaxel: in hormone-refractory metastatic prostate cancer. *Drugs* 2005; **65:** 2287–94.
4. Lyseng-Williamson KA, Fenton C. Docetaxel: a review of its use in metastatic breast cancer. *Drugs* 2005; **65:** 2513–31.
5. Deeks ED, Scott LJ. Docetaxel: in gastric cancer. *Drugs* 2007; **67:** 1893–1901.
6. Bernier J, Vrieling C. Docetaxel in the management of patients with head and neck squamous cell carcinoma. *Expert Rev Anticancer Ther* 2008; **8:** 1023–32.
7. Saloustros E, Georgoulias V. Docetaxel in the treatment of advanced non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2008; **8:** 1207–22.
8. De Dosso S, Berthold DR. Docetaxel in the management of prostate cancer: current standard of care and future directions. *Expert Opin Pharmacother* 2008; **9:** 1969–79.
9. Saloustros E, *et al*. Paclitaxel and docetaxel in the treatment of breast cancer. *Expert Opin Pharmacother* 2008; **9:** 2603–16.
10. Caponigro F, *et al*. Docetaxel in the management of head and neck cancer. *Anticancer Drugs* 2009; **20:** 639–45.
11. Nishiyama M, Wada S. Docetaxel: its role in current and future treatments for advanced gastric cancer. *Gastric Cancer* 2009; **12:** 132–41.
12. Galsky MD, Vogelzang NJ. Docetaxel-based combination therapy for castration-resistant prostate cancer. *Ann Oncol* 2010; **21:** 2135–44.

Administration. Docetaxel has been investigated as a low-dose weekly infusion, in patient groups such as the elderly, those with poor performance status, or refractory disease.[1-6] Weekly doses of 30 to 40 mg/m^2 are considered to be of similar efficacy to the standard three-weekly dosage regimen[7] (see also under Paclitaxel, p. 840.2). A pharmacokinetic study in 20 elderly patients suggested that a suitable starting dose might be 26 mg/m^2, increased provided there was no toxicity, but see also below.[8]

1. Hainsworth JD, *et al*. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol* 2001; **19:** 3500–5.
2. Mekhail T, *et al*. Phase I trial of weekly docetaxel and gemcitabine in patients with refractory malignancies. *Cancer* 2003; **97:** 170–8.
3. Petrioli R, *et al*. Weekly low-dose docetaxel in advanced non-small cell lung cancer previously treated with two chemotherapy regimens. *Lung Cancer* 2003; **39:** 85–9.
4. Di Maio M, *et al*. Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2007; **25:** 1377–82.
5. Abbrederis K, *et al*. Weekly docetaxel monotherapy for advanced gastric or esophagogastric junction cancer: results of a phase II study in elderly patients or patients with impaired performance status. *Crit Rev Oncol Hematol* 2008; **66:** 84–90.
6. Rivera E, *et al*. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer* 2008; **112:** 1455–61.
7. Hainsworth JD. Practical aspects of weekly docetaxel administration schedules. *Oncologist* 2004; **9:** 538–45.
8. Hurria A, *et al*. Pharmacokinetics and toxicity of weekly docetaxel in older patients. *Clin Cancer Res* 2006; **12:** 6100–5.

Administration in the elderly. A review[1] found no significant data to support dose modifications of docetaxel based on age alone. While elderly patients may be more vulnerable to adverse effects, interpatient variability appears to be more important than age-related variability.

See also Administration, above.

1. Lichtman SM, *et al*. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in hepatic impairment. UK licensed product information recommends that doses of docetaxel monotherapy should be reduced from 100 mg/m^2 to 75 mg/m^2 in mild to moderate hepatic impairment, defined as alanine aminotransferase (ALT/SGPT) and/or aspartate aminotransferase (AST/SGOT) more than 1.5 times the upper limit of normal (ULN), and alkaline phosphatase more than 2.5 times the ULN. Hepatic function should be monitored; use should be avoided if possible in severe hepatic impairment. US licensed information advises against the use of docetaxel in patients with bilirubin above ULN, or in those with mild to moderate hepatic impairment (defined as for the UK, above).

Administration with other drugs. Use of docetaxel with strong cytochrome P450 isoenzyme CYP3A4 inhibitors may affect exposure to docetaxel (see Interactions, p. 782.1). Clinical data on appropriate dose adjustment of docetaxel are limited. US licensed product information recommends a 50% dose reduction of docetaxel when use with strong CYP3A4 inhibitors cannot be avoided; this is based on extrapolation from a small pharmacokinetic study of the use of docetaxel with ketoconazole (but see Antifungals, p. 782.2).

For doses of docetaxel when given as part of licensed chemotherapy combination regimens, see Uses and Administration, above.

It has been suggested that administration with inhibitors of CYP3A4 or P-glycoprotein or both might allow *oral* administration of docetaxel to produce viable exposure to the drug; see Antiretrovirals and Immunosuppressants, p. 782.2.

Adverse Effects, Treatment, and Precautions

As for Paclitaxel, p. 841.1. Neutropenia, anaemia and skin reactions are common with docetaxel and may be severe. Fluid retention, resulting in oedema, ascites, pleural and pericardial effusion, and weight gain, is also common, and may be cumulative; premedication with a corticosteroid can reduce fluid retention as well as the severity of hypersensitivity reactions. Asthenia and fatigue have also been reported. Rare cases of ototoxicity, hearing impairment or loss have occurred. Very rare cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported with combination chemotherapy regimens containing docetaxel; haematological follow-up may be required.

Docetaxel should not be used in patients hypersensitive to polysorbate 80, which is contained in the formulation. Patients with hepatic impairment show increased sensitivity to toxic effects of docetaxel, and should be given the drug with great care and in reduced doses, if at all.

A review of 6 adverse effects that have been seen with most docetaxel-based regimens (febrile neutropenia, hypersensitivity reactions, fluid retention, nail toxicity, asthenia, and neuropathy) and their management.[1]

1. Baker J, *et al*. Docetaxel-related side effects and their management. *Eur J Oncol Nurs* 2009; **13:** 49–59.

Effects on the eyes. Excessive tear formation (epiphora) severe enough to interfere with reading and driving has been reported in patients given docetaxel. Canalicular stenosis has been described as the mechanism for this effect, and docetaxel has been measured in tear fluid suggesting that irritation of the ocular surface and fibrosis of the tear drainage ducts may be caused by direct contact with docetaxel.[1] Epiphora and canalicular stenosis are more severe and occur more frequently in patients given weekly docetaxel than in those who receive the drug every 3 weeks.[2,3] The mean cumulative dose of docetaxel was found to be higher in those patients who developed stenosis.[2] Management of this adverse effect includes probing and irrigation of the lachrymal ducts and canalicular silicone tubing placement, alone or after surgery. The condition is generally reversible and tubing can be removed 4 to 6 weeks after stopping docetaxel therapy.[4] The use of topical tobramycin and dexamethasone on a tapering regimen can sometimes eliminate the need for silicone intubation or surgery.[3]

Very rare cases of transient visual disturbances such as flashing lights and scotomata have occurred during docetaxel infusion, and in association with hypersensitivity reactions. These were reversible upon stopping the infusion. For reference to a report of glaucoma possibly related to docetaxel, see Paclitaxel, p. 841.2.

1. Esmaeli B, *et al*. Docetaxel secretion in tears: association with lacrimal drainage obstruction. *Arch Ophthalmol* 2002; **120:** 1180–2.
2. Esmaeli B, *et al*. Canalicular stenosis secondary to weekly versus every-3-weeks docetaxel in patients with metastatic breast cancer. *Ophthalmology* 2002; **109:** 1188–91.
3. Esmaeli B, *et al*. Prospective study of incidence and severity of epiphora and canalicular stenosis in patients with metastatic breast cancer receiving docetaxel. *J Clin Oncol* 2006; **24:** 3619–22.
4. Ahmadi MA, Esmaeli B. Surgical treatment of canalicular stenosis in patients receiving docetaxel weekly. *Arch Ophthalmol* 2001; **119:** 1802–4.

Effects on the gastrointestinal tract. Ischaemic colitis has occurred in patients treated with docetaxel.[1-3] Some

patients also received vinorelbine, which may have exacerbated this complication.[1,2]

1. Ibrahim NK, *et al.* Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. *Lancet* 2000; **355:** 281–3.
2. de Matteis A, *et al.* Intestinal side-effects of docetaxel/vinorelbine combination. *Lancet* 2000; **355:** 1098–9.
3. Hussein MAH, *et al.* Docetaxel-related ischemic colitis. *J Clin Oncol* 2005; **23:** 9424–5.

Effects on the heart. For comment on the increased risk of heart failure when docetaxel is given with trastuzumab and after anthracyclines, see under Interactions, below.

Effects on the lungs. Reviews[1,2] of interstitial lung disease associated with docetaxel.

1. Grande C, *et al.* Docetaxel-induced interstitial pneumonitis following non-small-cell lung cancer treatment. *Clin Transl Oncol* 2007; **9:** 578–81.
2. Alsamarai S, *et al.* Pneumonitis related to docetaxel: case report and review of the literature. *In Vivo* 2009; **23:** 635–7.

Effects on the musculoskeletal system. For reference to cases of taxane-induced arthralgia and myalgia successfully treated with gabapentin, see Paclitaxel, p. 841.3.

Effects on the skin, hair, and nails. Palmar-plantar erythrodysesthesia syndrome (p. 730.1) has been reported with the use of docetaxel.[1,2] For reference to the use of vitamin E to alleviate palmar-plantar erythrodysesthesia syndrome caused by docetaxel and capecitabine, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p. 2120.1. Cases of radiation recall dermatitis associated with docetaxel have also been reported.[3-5] There is a further report of recall dermatitis at sites previously treated with a laser.[6] A hyperpigmented eruption developed in a patient at the site of docetaxel injection after insufficient venous flushing; no eruption occurred after a second infusion with abundant venous flushing.[7] Licensed product information states that very rare cases of bullous eruption such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with docetaxel, but that other factors may have contributed to the development of these reactions.

In a multicentre study, patients given docetaxel wore a frozen glove on the right hand, leaving the left hand unprotected to serve as a control. The use of the glove significantly reduced skin and nail toxicity.[8]

For reference to reports of scleroderma, alopecia, and further adverse effects on the nails after the use of docetaxel, see Paclitaxel, p. 841.3.

1. Eich D, *et al.* Acral erythrodysesthesia syndrome caused b y intravenous infusion of docetaxel in breast cancer. *Am J Clin Oncol* 2002; **25:** 599–602.
2. Benghiat H, Al-Niaimi A. Palmar-plantar erythrodysesthesia secondary to docetaxel chemotherapy: a case report. *J Med Case Reports* 2011; **5:** 80.
3. Piroth MD, *et al.* Radiation recall dermatitis from docetaxel. *Onkologie* 2002; **25:** 438–40.
4. Kandemir EG, *et al.* Docetaxel-induced radiation recall dermatitis. *Swiss Med Wkly* 2005; **135:** 34–5.
5. Borgia F, *et al.* Radiation recall dermatitis after docetaxel administration: absolute indication to replace the drug? *Br J Dermatol* 2005; **153:** 674–5.
6. Chu C-Y, Yang C-H. Docetaxel-induced recall dermatitis on previous laser treatment sites. *Br J Dermatol* 2005; **153:** 441–3.
7. Aydogan I, *et al.* Persistent serpentine supravenous hyperpigmented eruption associated with docetaxel. *J Eur Acad Dermatol Venereol* 2005; **19:** 345–7.
8. Scotté F, *et al.* Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *J Clin Oncol* 2005; **23:** 4424–9.

Hypersensitivity. For a discussion of taxane-induced hypersensitivity, including references to desensitisation protocols, see under Paclitaxel, p. 842.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies docetaxel as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pregnancy. For discussion of the use of taxanes during pregnancy, see Paclitaxel, p. 842.1.

Tumour lysis syndrome. Fatal cases of tumour lysis syndrome (p. 730.2) have been reported after the second-line use of docetaxel.[1,2]

1. Sorscher SM. Tumor lysis syndrome following docetaxel therapy for extensive metastatic prostate cancer. *Cancer Chemother Pharmacol* 2004; **54:** 191–2.
2. Ajzensztejn D, *et al.* Tumor lysis syndrome after treatment with docetaxel for non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 2389–91.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Docetaxel is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with inducers or inhibitors or other substrates of this enzyme may affect exposure to docetaxel. It should be given with caution to patients taking strong CYP3A4 inhibitors including HIV-protease inhibitors such as ritonavir, and azole antifungals like ketoconazole or itraconazole. Ketoconazole has been reported to reduce the clearance of docetaxel (but see below); based on this, US licensed product information recommends a dose reduction of docetaxel when it is given with strong CYP3A4 inhibitors if use together cannot be avoided (see Administration with Other Drugs, p. 781.3).

References.

1. Royer I, *et al.* Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996; **56:** 58–65.

Antifungals. In a pharmacokinetic study, no consistent effects on docetaxel concentrations were seen with the addition of *ketoconazole*. Significant inter- and intrapatient variability was noted and a potential interaction could not be excluded.[1] In another study in 7 patients, however, the clearance of docetaxel was significantly reduced by 49% when given with ketoconazole.[2]

1. Van Veldhuizen PJ, *et al.* Docetaxel and ketoconazole in advanced hormone-refractory prostate carcinoma: a phase I and pharmacokinetic study. *Cancer* 2003; **98:** 1855–62.
2. Engels FK, *et al.* Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. *Clin Pharmacol Ther* 2004; **75:** 448–54.

Antineoplastics. The clearance of a dose of docetaxel was markedly reduced[1] when it was given after 4 days of treatment with *topotecan*, rather than on day 1; this resulted in worsened neutropenia.

Sorafenib may increase systemic exposure to docetaxel.

An increased incidence of febrile neutropenia and gastrointestinal disorders, including 2 fatalities, was reported in patients given docetaxel with *doxorubicin*,[2] although others[3] considered this high incidence unrepresentative of usual toxicity rates with this combination.

Heart failure has been reported in patients given docetaxel with other cytotoxic drugs, especially *trastuzumab*, and particularly after anthracycline-containing therapy. UK licensed product information therefore recommends that patients given docetaxel with trastuzumab should undergo baseline cardiac assessment and cardiac function should be monitored during treatment.

1. Zamboni WC, *et al.* Pharmacokinetic and pharmacodynamic study of the combination of docetaxel and topotecan in patients with solid tumors. *J Clin Oncol* 2000; **18:** 3288–94.
2. Brain EGC, *et al.* Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. *JAMA* 2005; **293:** 2367–71.
3. Martin M, *et al.* Life-threatening complications from doxorubicin-docetaxel chemotherapy for breast cancer. *JAMA* 2005; **294:** 2166.

Antiretrovirals. *HIV-PROTEASE INHIBITORS.* Severe toxicity has been reported after the use of intravenous docetaxel with *ritonavir*, probably due to ritonavir-induced inhibition of cytochrome P450 isoenzyme CYP3A4, causing a significant increase in exposure to docetaxel.[1]

Subsequently, the use of ritonavir to boost systemic exposure to oral docetaxel (which has a low bioavailability) has been investigated.[2,3] Use of these two drugs together was well tolerated,[2] and resulted in enhanced oral absorption and reduced elimination of docetaxel.[3] A pharmacokinetic model has been developed[3] to establish optimal combination regimens.

1. Mir O, *et al.* Severe toxicity related to a pharmacokinetic interaction between docetaxel and ritonavir in HIV-infected patients. *Br J Clin Pharmacol* 2010; **69:** 99–101.
2. Oostendorp RL, *et al.* Coadministration of ritonavir strongly enhances the apparent oral bioavailability of docetaxel in patients with solid tumors. *Clin Cancer Res* 2009; **15:** 4228–33.
3. Koolen SLW, *et al.* Population pharmacokinetics of intravenously and orally administered docetaxel with or without co-administration of ritonavir in patients with advanced cancer. *Br J Clin Pharmacol* 2010; **69:** 465–74.

Immunosuppressants. Oral bioavailability of the taxanes docetaxel and paclitaxel is low, partly due to their affinity for P-glycoprotein;[1,2] metabolism by cytochrome P450 isoenzyme CYP3A4 and poor solubility may also contribute. Studies have found that exposure to oral docetaxel[1,2] and paclitaxel[2] can be increased by use with *ciclosporin*, a P-glycoprotein inhibitor. P-glycoprotein inhibitors might be used to boost the bioavailability of an oral formulation, although ciclosporin is not an ideal candidate because of its immunosuppressive effects.[2]

1. Malingré MM, *et al.* Coadministration of cyclosporine strongly enhances the oral bioavailability of docetaxel. *J Clin Oncol* 2001; **19:** 1160–6.
2. Koolen SLW, *et al.* Intravenous-to-oral switch in anticancer chemotherapy: a focus on docetaxel and paclitaxel. *Clin Pharmacol Ther* 2010; **87:** 126–9.

Pharmacokinetics

On intravenous dosage docetaxel is rapidly distributed to body tissues. Docetaxel is more than 95% bound to plasma proteins. It is extensively metabolised via hepatic cytochrome P450 isoenzyme CYP3A4 and excreted chiefly in the faeces as metabolites. Only about 6% of a dose is excreted in urine. The terminal elimination half-life is about 11 hours. Clearance is reduced in hepatic impairment.

References.

1. Rudek MA, *et al.* Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. *Eur J Cancer* 2004; **40:** 1170–8.
2. Baker SD, *et al.* Clinical pharmacokinetics of docetaxel: recent developments. *Clin Pharmacokinet* 2006; **45:** 235–52.
3. Tran A, *et al.* Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther* 2006; **79:** 570–80.
4. Charles KA, *et al.* Predicting the toxicity of weekly docetaxel in advanced cancer. *Clin Pharmacokinet* 2006; **45:** 611–22.
5. Baker SD, *et al.* Pharmacogenetic pathway analysis of docetaxel elimination. *Clin Pharmacol Ther* 2009; **85:** 155–63.
6. Minami H, *et al.* Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice. *Cancer Sci* 2009; **100:** 144–9.
7. Franke RM, *et al.* Castration-dependent pharmacokinetics of docetaxel in patients with prostate cancer. *J Clin Oncol* 2010; **28:** 4562–7.
8. Gerritsen-van Schieveen P, Royer B. Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du docétaxel. *Therapie* 2010; **65:** 201–6.
9. Engels FK, *et al.* Therapeutic drug monitoring for the individualization of docetaxel dosing: a randomized pharmacokinetic study. *Clin Cancer Res* 2011; **17:** 353–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asodocel; Docekebir; Dolectran; Donataxel; Doxetal; Eriox; Plustaxano; Taxotere; Texot; Trazoteva; ***Austral.***: Oncotaxel; Taxotere; ***Austria***: Ebedoce; Taxotere; ***Belg.***: Taxotere; ***Braz.***: Docelibbs; Docetere; Oncodocel; Taxotere; Trixotene; ***Canad.***: Taxotere; ***Chile***: Taxotere; ***China***: Ai Su (艾素); Ao Ming Run (奥名润); Duo Pa Fei (多帕菲); Ruilibo (瑞立博); Si Qu Di (斯曲帝); Taxotere (泰索帝); Xi Cun (希存); Yi You Rui Kang (易优瑞康); ***Cz.***: Cetadocure; Docefrez; Taxotere; ***Denm.***: Cetadocure; Taxotere; ***Fin.***: Taxotere; ***Fr.***: Taxotere; ***Ger.***: Bendadocel; Docetaxin; Ribodocel; Taxceus; Taxotere; ***Gr.***: Taxotere; ***Hong Kong***: Taxotere; ***Hung.***: Taxotere; ***India***: Celtere; Daxotel; Detaxl; Docecad; Docefrez; Docet; Docetax; Docetec; Docetere; Doxel; Ferdotax; ***Indon.***: Brexel; Docetere; Taxotere; ***Irl.***: Docefim; Docefrez; Docirena; Taxotere; ***Israel***: Taxotere; ***Ital.***: Cetadocure; Taxceus; Taxotere; ***Jpn***: Taxotere; ***Malaysia***: Taxotere; ***Mex.***: Taxotere; ***Neth.***: Cetadocure†; Dincilezan; Docefim; Docefrez†; Docirena; Dostradixinol; Taxceus; Taxotere; Tevadocel; Tolnexa; ***Norw.***: Taxotere; ***NZ***: Taxotere; ***Philipp.***: Daxotel; Doci; Hentaxel; Taxotere; ***Pol.***: Docefrez; Taxotere; ***Port.***: Docefrez; Taxotere; ***Rus.***: Tautax (Таутакс); Taxotere (Таксотер); ***S.Afr.***: Docetere; Taxotere; ***Singapore***: Taxotere; ***Spain***: Taxotere; ***Swed.***: Taxotere; ***Switz.***: Taxotere; ***Thai.***: Daxotel; Taxotere; ***Turk.***: Doxel; Doxitax; Taxotere; ***UK***: Taxotere; ***Ukr.***: Taxotere (Таксотер); ***USA***: Taxotere; ***Venez.***: Daxotel; Taxotere.

Pharmacopoeial Preparations

USP 36: Docetaxel Injection.

Doxifluridine *(rINN)*

5-DFUR; Doxifluridina; Doxifluridinum; FUDR; Ro-21-9738; Доксифлуридин; 5′-Deoxy-5-fluorouridine.

$C_9H_{11}FN_2O_5$=246.2

CAS — 3094-09-5.

UNII — V1JK16Y2JP.

Pharmacopoeias. In *Jpn*.

Profile

Doxifluridine is an antineoplastic that probably acts through its conversion in the body to fluorouracil (p. 795.2). It is given orally in the management of malignant neoplasms of the breast (p. 702.1) and gastrointestinal tract (p. 705.2), and of other solid tumours, in doses of 0.8 to 1.2 g daily in divided doses. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Doxifluridine has also been given by the intravenous route.

Pharmacokinetics. Doxifluridine is metabolised to fluorouracil and 5,6-dihydrofluorouracil. It is orally active with a bioavailability of 34 to 47%.

References.

1. Sommadossi J-P, *et al.* Kinetics and metabolism of a new fluoropyrimidine, 5′-deoxy-5-fluorouridine, in humans. *Cancer Res* 1983; **43:** 930–3.
2. Van Der Heyden SAM, *et al.* Pharmacokinetics and bioavailability of oral 5′-deoxy-5-fluorouridine in cancer patients. *Br J Clin Pharmacol* 1999; **47:** 351–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: A i Feng (艾丰); Furtulon (氟铁龙); Ke Fu (可弗); Ke Tuo (克托); Qi Nuo Bi Tong (奇诺必通); Shu Qi (枢绮); Tan Nuo (坦诺); Yi Di An (谊迪安); Zhi Ai (知爱); ***Jpn***: Furtulon.

Doxorubicin *(BAN, USAN, rINN)*

Adriamycin; Doksorubisiini; Doxorubicina; Doxorubicine; Doxorubicinum; FI-106; 3-Hydroxyacetyldaunorubicin; 14-Hydroxydaunomycin; Доксорубицин.

8-Hydroxyacetyl (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione.
$C_{27}H_{29}NO_{11}$=543.5
CAS — 23214-92-8.
ATC — L01DB01.
ATC Vet — QL01DB01.
UNII — 80168379AG.

NOTE. In many countries the name Adriamycin is a trademark.

Doxorubicin Citrate *(BANM, rINNM)*

Citrato de doxorubicina; Doxorubicin Citrate Liposome; Doxorubicine, Citrate de; Doxorubicini Citras; Liposomal Doxorubicin Citrate; Доксорубицина Цитрат.
$C_{27}H_{29}NO_{11}$,$xC_6H_8O_7$
CAS — 111266-55-8.
ATC — L01DB01.
ATC Vet — QL01DB01.

NOTE. Doxorubicin citrate complex is a constituent of some liposomal products. It is prepared from doxorubicin hydrochloride (below).

Doxorubicin Hydrochloride *(BANM, rINNM)*

Cloridrato de Doxorrubicina; Doksorubicino hidrochloridas; Doksorubicyny chlorowodorek; Doksorubisiinihydrokloridi; Doksorubisin Hidroklorür; Doxorubicin Hydrochloride Liposome; Doxorubicina, hidrocloruro de; Doxorubicine, Chlorhydrate de; Doxorubicin-hidroklorid; Doxorubicin-hydrochlorid; Doxorubicinhydrochlorid; Doxorubicinhydroklorid; Doxorubicini hydrochloridum; Hidrocloruro de doxorubicina; Liposomal Doxorubicin Hydrochloride; NSC-123127; Доксорубицина Гидрохлорид.
$C_{27}H_{29}NO_{11}$,HCl=580.0
CAS — 25316-40-9.
ATC — L01DB01.
ATC Vet — QL01DB01.
UNII — 82F2G7BL4E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Doxorubicin Hydrochloride). The hydrochloride of a substance isolated from certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It contains between 98 and 102% of the hydrochloride, calculated on the anhydrous substance. An orange-red, hygroscopic, crystalline powder. Soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers.

USP 36: (Doxorubicin Hydrochloride). A red-orange, hygroscopic, crystalline or amorphous powder. It contains not less than 98% and not more than 102% of $C_{27}H_{29}NO_{11}$, HCl, calculated on the anhydrous, solvent-free basis. Soluble in water, in sodium chloride 0.9%, and in methyl alcohol; practically insoluble in chloroform, in ether, and in other organic solvents. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. It may exist in an amorphous form, which should be stored at -25 degrees to -10 degrees.

Incompatibility. Admixture of doxorubicin hydrochloride with cefalotin sodium, dexamethasone, diazepam, or hydrocortisone sodium succinate is reported to result in immediate precipitation;[1] similarly precipitation has occurred when doxorubicin hydrochloride was mixed with furosemide or heparin sodium.[2] A mixture of fluorouracil or aminophylline with doxorubicin hydrochloride is reported to darken in colour from red to purple, indicating degradation of doxorubicin.[1] For mention of the compatibility of doxorubicin with paclitaxel, see p. 839.3.

Liposomal doxorubicin differs in its incompatibilities from conventional formulations: whereas the latter are reportedly incompatible with allopurinol, cefepime, and ganciclovir, there was no visual evidence of this with the liposomal formulation. However, it was incompatible with several solutions including amphotericin B, docetaxel, gallium nitrate, hydroxyzine hydrochloride, metoclopramide hydrochloride, miconazole, mitoxantrone hydrochloride, morphine sulfate and some other opioids, paclitaxel, sodium bicarbonate, and some antibacterials.[3]

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Cohen MH, *et al.* Drug precipitation within IV tubing: a potential hazard of chemotherapy administration. *Cancer Treat Rep* 1985; **69:** 1325–6.
3. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.

Stability. Although sensitive to light at low concentrations, doxorubicin is not subject to significant photodegradation at clinical concentrations and special precautions to protect solutions from light during use do not appear to be necessary.[1,2]

UK licensed product information for conventional formulations of doxorubicin hydrochloride state that, from a microbiological perspective, reconstituted solutions should be used immediately, and that storage time should not be longer than 24 hours at 2 degrees to 8 degrees, unless dilution has taken place under controlled and validated aseptic conditions. Chemical and physical stability varies between products:

- *Hameln, UK*: 48 hours at 2 degrees to 8 degrees and 24 hours at 25 degrees, in either sodium chloride 0.9% or glucose 5%, when prepared in glass containers and protected from light
- *Hospira, UK*: 21 days at 2 degrees to 8 degrees after reconstitution in either sodium chloride 0.9% or water for injection, in glass or polypropylene containers
- Doxorubicin 0.2% solution, *Medac, UK*: undiluted, 7 days at 15 degrees to 25 degrees, in glass containers and protected from light
- Doxorubicin powder for solution for injection, *Medac, UK*: 2 mg/mL in sodium chloride 0.9%—7 days at 15 degrees to 25 degrees and 14 days at 2 degrees to 8 degrees; 500 micrograms/mL in water for injection—24 hours below 25 degrees; 50 micrograms/mL to 5 mg/mL in sodium chloride 0.9%—7 days at 15 degrees to 25 degrees

Solutions of doxorubicin in sodium chloride solution 0.9% were reported[3] to be stable for 24 days when stored in PVC minibags at 25 degrees and for even longer if stored in minibags or polypropylene syringes at 4 degrees. Stability in solution seems to be partly related to pH, with doxorubicin becoming more stable[3-5] at acid pH. A fall in pH of the solution also significantly decreases the loss of doxorubicin by adsorption and precipitation onto the surface of a positively-charged in-line filter.[6]

Pegylated liposomal doxorubicin formulations (*Caelyx, UK* and *Doxil, USA*) should be diluted only with glucose 5%. If not used immediately, they may be stored for 24 hours at 2 degrees to 8 degrees.

1. Tavoloni N, *et al.* Photolytic degradation of adriamycin. *J Pharm Pharmacol* 1980; **32:** 860–2.
2. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
3. Wood MJ, *et al.* Stability of doxorubicin, daunorubicin and epirubicin in plastic syringes and minibags. *J Clin Pharm Ther* 1990; **15:** 279–89.
4. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.
5. Beijnen JH, *et al.* Stability of anthracycline antitumour agents in infusion fluids. *J Parenter Sci Technol* 1985; **39:** 220–2.
6. Francomb MM, *et al.* Effect of pH on the adsorption of cytotoxic drugs to a 96 hour intravenous filter. *Pharm J* 1991; **247:** R26.

Uses and Administration

Doxorubicin is an anthracycline antineoplastic antibiotic. It is thought to have multiple modes of action including intercalation of DNA leading to an inhibition of DNA and RNA synthesis, inhibition of topoisomerase II, free radical formation, and alterations in cell membranes. Doxorubicin is a cell-cycle non-specific agent. It also has antibacterial and immunosuppressant properties.

Doxorubicin is effective against many tumours as indicated by the cross-references given below. It is used, often with other antineoplastics, in the treatment of Hodgkin's disease, non-Hodgkin's lymphomas, acute leukaemias, bone and soft-tissue sarcomas, neuroblastoma, Wilms' tumour, and malignant neoplasms of the bladder, breast, lung, ovary, and stomach. It has also been used in other tumours. Liposomal doxorubicin is used in the management of Kaposi's sarcoma in patients with AIDS, for the treatment of metastatic breast and ovarian cancers, and with bortezomib for the treatment of multiple myeloma.

Doxorubicin hydrochloride is given by intravenous injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 minutes or more. When used as a single agent, the dose of the *conventional* formulation is 60 to 75 mg/m^2 once every 3 or 4 weeks, or 1.2 to 2.4 mg/kg, once every 3 weeks. Alternatively, doses of 20 to 25 mg/m^2 have been given daily for 3 days every 3 or 4 weeks, although dividing the dose in this way may increase the incidence of mucositis. A regimen of 20 mg/m^2 as a single weekly dose may be used, and is reported to be associated with a lower incidence of cardiotoxicity.

Doses may need to be reduced if doxorubicin is given with other antineoplastics: a dose of 30 to 60 mg/m^2 every 3 weeks has been suggested. Obese patients may need a reduced dose, as may children, elderly patients, and patients with hepatic impairment (see below).

The total cumulative dose should not exceed 450 to 550 mg/m^2; in patients who have received radiotherapy to the chest, or other cardiotoxic drugs, it may be advisable to further limit the total cumulative dose.

In the management of AIDS-related Kaposi's sarcoma *pegylated liposomal* doxorubicin hydrochloride is given in an intravenous dose of 20 mg/m^2 infused over 30 minutes once every 2 to 3 weeks. For the treatment of breast and ovarian cancers, the suggested dose of this liposomal formulation is 50 mg/m^2 infused over 1 hour once every 4 weeks. In the treatment of multiple myeloma, liposomal doxorubicin hydrochloride is given at a dose of 30 mg/m^2 on day 4 of the bortezomib regimen (see p. 752.1); it is given as an infusion over 1 hour immediately after the bortezomib infusion. In all these conditions, treatment should be continued for as long as the patient responds satisfactorily and tolerates treatment. The pegylated liposomal formulation should be diluted only with glucose 5%; generally, doses below 90 mg are diluted in 250 mL, and doses over 90 mg are diluted in 500 mL.

A *non-pegylated liposomal* formulation is also available and contains a doxorubicin citrate complex prepared with the aid of doxorubicin hydrochloride. It is given in the treatment of metastatic breast cancer in doses equivalent to doxorubicin hydrochloride 60 to 75 mg/m^2 every 3 weeks, with cyclophosphamide 600 mg/m^2. Doses are given by intravenous infusion over 1 hour, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of 0.4 to 1.2 mg/mL doxorubicin hydrochloride.

Blood counts should be made routinely during treatment with doxorubicin (see also Bone-marrow Depression, p. 730.3) and cardiac function should be monitored at regular intervals for early signs of cardiotoxicity.

Doxorubicin hydrochloride has also been instilled into the bladder in the local treatment of malignant neoplasms. For this purpose 50 mL of a 1 mg/mL solution may be instilled into the bladder for about one hour; treatment may be given at weekly to monthly intervals. Doxorubicin has also been given intra-arterially.

Various novel formulations of doxorubicin have been investigated. Doxorubicin with carbon/iron carrier particles (MTC-DOX) is a magnetically targeted treatment, using an external magnet to keep the drug at the tumour site, that has been investigated for hepatocellular carcinoma. A polymer of doxorubicin and polyisohexylcyanoacrylate in nanoparticle form is under investigation for the treatment of hepatocellular carcinoma. Doxorubicin-eluting beads, for injection directly into the brain, and glutathione-pegylated liposomal doxorubicin are under investigation for the treatment of glioma. Hydrophilic microspheres reconstituted with a solution of doxorubicin hydrochloride have been used for chemoembolisation of hepatic tumours. Doxorubicin linked to a gonadotrophin-releasing hormone agonist is being investigated for the treatment of ovarian cancer.

Reviews of liposomal formulations.

1. Sharpe M, *et al.* Polyethylene glycol-liposomal doxorubicin: a review of its use in the management of solid and haematological malignancies and AIDS-related Kaposi's sarcoma. *Drugs* 2002; **62:** 2089–2126.
2. Forbes C, *et al.* A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technol Assess* 2002; **6:** 1–119.
3. O'Shaughnessy JA. Pegylated liposomal doxorubicin in the treatment of breast cancer. *Clin Breast Cancer* 2003; **4:** 318–28.
4. Orditura M, *et al.* Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity. *Oncol Rep* 2004; **12:** 549–56.
5. Thigpen JT, *et al.* Role of pegylated liposomal doxorubicin in ovarian cancer. *Gynecol Oncol* 2005; **96:** 10–18.
6. Soloman R, Gabizon AA. Clinical pharmacology of liposomal anthracyclines: focus on pegylated liposomal doxorubicin. *Clin Lymphoma Myeloma* 2008; **8:** 21–32.
7. Patil RR, *et al.* Engineered nanocarriers of doxorubicin: a current update. *Crit Rev Ther Drug Carrier Syst* 2008; **25:** 1–61.
8. Plosker GL. Pegylated liposomal doxorubicin: a review of its use in the treatment of relapsed or refractory multiple myeloma. *Drugs* 2008; **68:** 2535–51.
9. Leonard RCF, *et al.* Improving the therapeutic index of anthracycline chemotherapy: focus on liposomal doxorubicin (Myocet®). *Breast* 2009; **18:** 218–24.
10. Gaitanis A, Staal S. Liposomal doxorubicin and nab-paclitaxel: nanoparticle cancer chemotherapy in current clinical use. *Methods Mol Biol* 2010; **624:** 385–92.

Administration in children. Doxorubicin is used for paediatric malignancies; UK licensed product information for conventional formulations advises that adult dosage regimens (see above) may be suitable for children, but dose reductions may be needed, particularly in young children.

References.

1. Creutzig U, *et al.* Favourable outcome of patients with childhood acute promyelocytic leukaemia after treatment with reduced cumulative anthracycline doses. *Br J Haematol* 2010; **149:** 399–409.

Administration in the elderly. UK licensed product information for doxorubicin in conventional formulations advises that the dose may need to be reduced in the elderly; in patients over 70 years of age, a total cumulative dose of 450 mg/m^2 has been recommended.

Administration in hepatic impairment. Doses of doxorubicin should be adjusted as follows in patients with liver dysfunction:

- serum-bilirubin concentrations of 12 to 30 micrograms/mL: half the normal dose
- serum-bilirubin greater than 30 micrograms/mL: quarter of the usual dose.

Slightly different schedules may apply to liposomal products but may vary between preparations.

Amyloidosis. For mention of the use of doxorubicin in patients with amyloidosis (and of the increased risk this may carry in cardiac amyloidosis) see p. 819.3.

Malignant neoplasms. Doxorubicin plays a major role in combination regimens for chemotherapy of solid malignancies; it is often employed for tumours of the breast and lung (see p. 702.1 and p. 710.2) and for Wilms' tumour and neuroblastoma or retinoblastoma in children (see p. 709.1, p. 716.2, and p. 717.2) and has been used for malignancies of the bladder (p. 700.2); for various gynaecological cancers including those of the endometrium, and ovary (see p. 704.3, and p. 711.2); for cancer of the liver, stomach, and pancreas (p. 709.3, p. 706.1, p. 712.1); and for neoplasms of prostate, and thymus (p. 712.3 and p. 715.3). It is also used in the treatment of sarcomas of bone and soft-tissue (see p. 717.3 and p. 718.2) and liposomal doxorubicin is used in patients with Kaposi's sarcoma (see p. 718.1).

In addition, doxorubicin is a component of the ABVD regimen used to treat Hodgkin's disease (see p. 696.1) and is part of the CHOP regimen used for non-Hodgkin's lymphoma (p. 696.3). Doxorubicin is also used in Burkitt's lymphoma (p. 697.3), mycosis fungoides (p. 698.3), and the lymphomas associated with AIDS (see p. 697.2). It has been employed in acute lymphoblastic leukaemia (p. 692.3), in chronic lymphocytic leukaemia as part of the CHOP regimen (though with uncertain benefit—see p. 693.3), and in multiple myeloma (p. 699.2).

Adverse Effects and Treatment

For general discussions see Antineoplastics, p. 726.1 and p. 730.2.

Doxorubicin and other anthracyclines cause pronounced bone-marrow depression, which may be dose-limiting. White cell count reaches a nadir 10 to 15 days after a dose and usually recovers by about 21 days.

The anthracyclines may produce cardiotoxicity, both as an acute, usually transient disturbance of cardiac function marked by ECG abnormalities and, sometimes, arrhythmias; and as a delayed, sometimes fatal, irreversible congestive heart failure, which may occur suddenly. Severe cardiotoxicity is more likely in adults given total cumulative doses of doxorubicin greater than 450 to 550 mg/m^2, and may occur months or even years after use. However, congestive heart failure has been reported even with doses of 240 to 300 mg/m^2. Cardiotoxicity may occur at lower cumulative doses in those previously treated with other anthracyclines or antineoplastics, or with radiotherapy to the chest.

Gastrointestinal disturbances include moderate or sometimes severe nausea and vomiting; mucositis (stomatitis and oesophagitis) may progress to ulceration. Alopecia, usually reversible, occurs in the majority of patients. The urine may be coloured red. Occasional hypersensitivity reactions may occur. Hyperuricaemia may occur due to tumour lysis syndrome. Other adverse effects include conjunctivitis, lachrymation, urticarial rashes, hyperpigmentation of the oral mucosa and/or nails, onycholysis, drowsiness, renal or hepatic damage, and transient increases in liver enzymes.

Doxorubicin and other anthracyclines are very irritant and thrombophlebitis can occur; extravasation is serious and may produce extensive local necrosis and ulceration. If extravasation occurs, the injection should be immediately stopped and restarted in another vein; the appropriate management of such events is contentious (see p. 731.3) but may include ice packs, tissue irrigation, corticosteroids, and if necessary, surgery. Local erythematous streaking along the vein and facial flushing may be indicative of too rapid an injection. Intravesical instillation can cause bladder and urethral irritation, haematuria, and haemorrhagic cystitis.

Combination therapy including doxorubicin has rarely been associated with secondary acute myeloid leukaemia (see also Carcinogenicity, p. 726.2). *Animal* data have shown doxorubicin to be embryotoxic, teratogenic, and mutagenic. Doxorubicin may cause infertility.

Formulations of liposomal doxorubicin appear to be associated with a reduced potential for local tissue necrosis, and possibly a reduced incidence of cardiotoxicity. Conversely, palmar-plantar erythrodysesthesia (p. 730.1) appears to be more common, and may be dose-limiting. In addition, an acute anaphylactoid-like reaction may be seen on initial infusion, but this generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. Cardiotoxicity has been a major factor in limiting the use of the anthracyclines, doxorubicin and daunorubicin. Anthracycline derivatives have been developed with the aim of reducing the inherent cardiotoxicity of this class of compounds, including aclarubicin (p. 735.2), epirubicin (p. 787.1), idarubicin (p. 805.2), mitoxantrone (p. 833.1), and pixantrone (p. 847.2). However, although this strategy has met with some success, all these compounds exhibit some degree of cardiotoxicity.

Toxicity is essentially of 2 kinds: acute, usually reversible ECG changes, including a wide range of arrhythmias, and a delayed, usually irreversible dose-related cardiomyopathy, resulting in congestive heart failure.[1-3] The latter may be further subdivided into early-onset, occurring up to about a year afterwards, and late-onset toxicity occurring years after treatment,[2,4,5] which may be fatal. Late cardiac failure may occur up to 18 years after anthracycline therapy.[2,6,7] The 1-year mortality rate for patients with doxorubicin-induced New York Heart Association (NYHA) class III to IV heart failure is 40%, and the 2-year mortality rate is 60%.[8]

- The single most important determinant of cardiotoxicity appears to be the *total cumulative dose*, with the risk of toxicity becoming ever greater at total cumulative doxorubicin doses of 550 mg/m^2 or more.[8-14] However, patients vary widely in sensitivity,[2,10,13] and these values represent relatively arbitrary choices on a continuum of risk: there is no single safe dose.[1,5,13] Even at doses that produce no symptoms, subclinical myocardial damage may occur, and in children this may result in diminished cardiac reserve and heart disease in later life.[1,15,16]
- The *dosage schedule* also appears to be important; relatively high single doses on an infrequent schedule appear to be more cardiotoxic than lower, more closely spaced doses, suggesting that cardiotoxicity is related to peak blood concentrations of doxorubicin.[10]
- Cardiotoxicity is also reported to be more likely in *children and elderly* patients, and in those who have received prior *radiotherapy* to the chest.[3,4,9,10,12] Previous *cardiovascular disease* also increases the risk.[1,2,9] *Females* appear to be at greater risk than males.[8,17] *Other risk factors* include hypertension, liver disease, whole body hyperthermia, African American ancestry, and trisomy-21.[3,5,9]
- Use with cyclophosphamide, trastuzumab, or *other antineoplastics* with cardiotoxic potential may increase the likelihood of cardiomyopathy.[9,10]

Prevention. Much effort has gone into ways of predicting and preventing anthracycline-induced cardiotoxicity. Although ECG changes are commonly monitored, most of the changes are not predictive of cardiomyopathy and severe cardiotoxicity can occur without ECG changes. However, a persistent reduction in the voltage of the QRS wave is generally indicative of the need to perform further tests. Non-invasive cardiac *monitoring*, by means of echocardiography or radionuclide angiography, is useful in predicting the development of cardiomyopathy, but may give normal results until damage is quite advanced; sensitivity may be improved with exercise stress tests.[1-3] Measurement of left ventricular ejection fraction (LVEF) is frequently used for baseline evaluation, and at regular intervals thereafter.[9,18] Indium-111 antimyosin imaging detects abnormal cardiac uptake of indium-111 antimyosin, which can be seen even in the absence of any change in LVEF, and can be predictive of an impending fall in LVEF; this technique is highly sensitive but is time-consuming and not widely available.[10] Endomyocardial biopsy is the most sensitive indicator of cardiomyopathy, but it is invasive and again not widely available.[9,10,18] The Childrens Cancer Study Group[19] has issued guidelines for monitoring using ECG, echocardiography, and radionuclide angiocardiography in patients receiving anthracyclines. The role of such techniques in predicting late-onset cardiotoxicity remains to be clarified,[2] and there is disagreement on the best manner of monitoring anthracycline-induced cardiotoxicity. This reflects conflicting data and the scarcity of well-designed studies, but the Childrens Cancer Study Group guideline, or one that incorporates a baseline cardiac evaluation with follow-up as the anthracycline dose increases, has been advocated as a reasonable approach to monitoring anthracycline-induced cardiotoxicity.[13]

There is some preliminary evidence to suggest that concentrations of cardiac troponins and natriuretic peptides could be used as predictive markers of myocardial damage.[9,10,18,20,21]

Dexrazoxane (p. 1548.1) has shown some protective effect against the cardiotoxicity of doxorubicin and other anthracyclines, and is used to reduce cardiomyopathy in women receiving doxorubicin for metastatic breast cancer.

Alteration of the dosage schedule to weekly rather than three-weekly dosage, or the use of continuous infusion, have been advocated as ways of reducing doxorubicin cardiotoxicity; an anthracycline infusion time of six hours or longer has been shown to reduce the risk of heart failure and seemed to reduce the risk of subclinical cardiac damage.[22] Anthracyclines formulated in *liposomes* have also been used to reduce the risk.[2,5,8-11,13,18] The cardiac safety of liposomal daunorubicin has not been established, but non-pegylated liposomal doxorubicin has better cardiac safety than conventional doxorubicin,[11,21,23] while pegylated liposomal doxorubicin has a significantly reduced risk of cardiotoxicity.[11,21] (However, haematological and mucocutaneous toxicity, and palmar-plantar erythrodysesthesia are greater with liposomal formulations and may limit their use.[24])

Treatment. Management is essentially that of standard cardiac failure (p. 1262.3), with diuretics, beta blockers, ACE inhibitors, and ultimately, cardiac transplantation (p. 1938.2).[5,8,9,21]

1. Hale JP, Lewis IJ. Anthracyclines: cardiotoxicity and its prevention. *Arch Dis Child* 1994; **71:** 457–62.
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3. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998; **339:** 900–905.
4. Adams MJ, Lipshultz SE. Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. *Pediatr Blood Cancer* 2005; **44:** 600–6.
5. Lipshultz SE, *et al.* Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Heart* 2008; **94:** 525–33.
6. Goorin AM, *et al.* Initial congestive heart failure, six to ten years after doxorubicin chemotherapy for childhood cancer. *J Pediatr* 1990; **116:** 144–7.
7. Steinherz LJ, *et al.* Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991; **266:** 1672–7.
8. Wouters KA, *et al.* Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. *Br J Haematol* 2005; **131:** 561–78.
9. Birtle AJ. Anthracyclines and cardiotoxicity. *Clin Oncol (R Coll Radiol)* 2000; **12:** 146–52.
10. Jain D. Cardiotoxicity of doxorubicin and other anthracycline derivatives. *J Nucl Cardiol* 2000; **7:** 53–62.
11. Theodoulou M, Hudis C. Cardiac profiles of liposomal anthracyclines: greater cardiac safety versus conventional doxorubicin? *Cancer* 2004; **100:** 2052–63.
12. Petit T. Toxicité cardiaque des anthracyclines: anthracycline-induced cardiotoxicity. *Bull Cancer* 2004; **91** (suppl): S159–S165.
13. Jannazzo A, *et al.* Monitoring of anthracycline-induced cardiotoxicity. *Ann Pharmacother* 2008; **42:** 99–104.
14. Iarussi D, *et al.* Recent advances in the prevention of anthracycline cardiotoxicity in childhood. *Curr Med Chem* 2001; **8:** 1649–60.
15. Yeung ST, *et al.* Functional myocardial impairment in children treated with anthracyclines for cancer. *Lancet* 1991; **337:** 816–18.
16. Lipschultz SE, *et al.* Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991; **324:** 808–15.
17. Lipshultz SE, *et al.* Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995; **332:** 1738–43.
18. Ewer MS, *et al.* Cardiac safety of liposomal anthracyclines. *Semin Oncol* 2004; **31** (6 suppl 13): 161–81.
19. Steinherz LJ, *et al.* Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Childrens Cancer Study Group. *Pediatrics* 1992; **89:** 942–9.
20. Sparano JA, *et al.* Predicting cancer therapy-induced cardiotoxicity: the role of troponins and other markers. *Drug Safety* 2002; **25:** 301–11.
21. Gianni L, *et al.* Anthracycline cardiotoxicity: from bench to bedside. *J Clin Oncol* 2008; **26:** 3777–84.
22. van Dalen EC, *et al.* Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/05/10).
23. van Dalen EC, *et al.* Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 18/05/10).
24. Orditura M, *et al.* Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity (review). *Oncol Rep* 2004; **12:** 549–56.

Effects on the liver. Hepatitis and non-specific hepatocellular damage has been reported in patients receiving doxorubicin as part of combination therapy.[1] A characteristic hepatotoxicity can also be produced by the combination of radiotherapy with doxorubicin.[2]

1. Avilés A, *et al.* Hepatic injury during doxorubicin therapy. *Arch Pathol Lab Med* 1984; **108:** 912–13.
2. Price LA. Surviving malignant disease: medical and oncological aspects. *Br J Hosp Med* 1983; **30:** 8–12.

Effects on the skin and nails. Hyperpigmentation has occurred in patients given daunorubicin, doxorubicin, or idarubicin.[1-6] Reports described pigmentation of the skin and transverse hyperpigmented bands of the nails. Effects on the skin resolved over several weeks, and bands on the nails moved with normal nail growth. Dark-skinned patients appear to be more susceptible to this adverse effect. Biopsy has found an increase in melanin granules in the affected tissues. An unusual blue-grey pigmentation of the face was reported in a patient given doxorubicin.[7]

There have been reports of subacute cutaneous lupus erythematosus after treatment with doxorubicin plus cyclophosphamide for breast cancer.[8,9] A change of chemotherapy regimen and corticosteroids successfully treated some patients, but lesions continued to flare after each cycle in one patient with Sjögren's syndrome despite a change to paclitaxel and trastuzumab; symptoms eventually resolved when chemotherapy was complete.[9] In another case[8] skin lesions kept developing even after the chemotherapy regimen was complete, and although oral corticosteroids improved the lesions, they reappeared when the corticosteroids were withdrawn; complete resolution was seen with thalidomide.

For specific reference to treatment of alopecia caused by doxorubicin, and for extravasation, see p. 730.3 and p. 731.3.

1. Kelly TM, *et al.* Hyperpigmentation with daunorubicin therapy. *Arch Dermatol* 1984; **120:** 262–3.
2. Kumar L, Kochupillai V. Doxorubicin induced hyperpigmentation. *N Z Med J* 1990; **103:** 165.

3. Curran CF. Doxorubicin-associated hyperpigmentation. *N ZMed J* 1990; **103:** 517.
4. Anderson LL, *et al.* Cutaneous pigmentation after daunorubicin chemotherapy. *J Am Acad Dermatol* 1992; **26:** 255–6.
5. Borecky DJ, *et al.* Idarubicin-induced pigmentary changes of the nails. *Cutis* 1997; **59:** 203–4.
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7. Konohana A. Blue-gray pigmentation in a patient receiving doxorubicin. *J Dermatol* 1992; **19:** 250–2.
8. Guhl G, *et al.* Chemotherapy-induced subacute lupus erythematosus. *Lupus* 2009; **18:** 859–60.
9. Funke AA, *et al.* Subacute cutaneous lupus erythematosus exacerbated or induced by chemotherapy. *Arch Dermatol* 2010; **146:** 1113–16.

Palmar-plantar erythrodysesthesia syndrome. Palmar-plantar erythrodysesthesia syndrome (p. 730.1) is associated with the use of liposomal doxorubicin, and recommendations have been made for its management.[1] The most effective way of preventing the syndrome was to maintain doses at not more than 10 mg/m² weekly (typically as a single infusion of 40 mg/m² every 4 weeks). At such doses, the syndrome, if it occurred was typically mild and easily managed. Dose-intensity modification was also thought likely to be beneficial in managing the syndrome if it developed, although evidence to support this was lacking.

UK licensed product information states that pyridoxine (in daily doses of 50 to 150 mg) and corticosteroids have been used for the prophylaxis and treatment of this condition although clinical data for their efficacy are lacking; other strategies include keeping the hands and feet cool with cold water soaks or baths, avoiding heat or hot water, and not wearing socks, gloves, or tight-fitting shoes.

1. von Moos R, *et al.* Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts. *Eur J Cancer* 2008; **44:** 781–90.

Precautions

For a general discussion see Antineoplastics, p. 732.2.

Doxorubicin and other anthracyclines are generally contra-indicated in patients with heart disease. The total cumulative dose should be limited, and cardiac function, including left ventricular ejection fraction, should be assessed before and monitored during treatment (see Effects on the Heart, p. 784.1). Blood counts should be monitored and doses should not be repeated while there is bone-marrow depression or ulceration of the mouth. Doxorubicin should be given with great care in reduced doses to patients with hepatic impairment; dosage reduction may also be necessary in children and the elderly. Extravasation results in severe tissue damage and doxorubicin and other anthracyclines should not be given by intramuscular or subcutaneous injection. The adverse effects of irradiation may be enhanced by doxorubicin and skin reactions previously induced by radiotherapy may recur; the total cumulative dose should be reduced to no more than 400 mg/m² in patients who have received radiotherapy to the chest or heart. Different liposomal formulations may not be interchangeable with conventional formulations, or with each other.

Breast feeding. Doxorubicin and its metabolites have been detected in breast milk.[1] The American Academy of Pediatrics considers[2] that doxorubicin is concentrated in breast milk, that it may possibly cause immune suppression in the infant, has unknown effects on growth, and an association with carcinogenesis.

1. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69:** 1387–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. Doxorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

A method for the destruction of doxorubicin or daunorubicin *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of daunorubicin by this method showed no mutagenicity *in vitro*; some mutagenicity was seen with high concentrations of residues from doxorubicin.

Urine and faeces produced for up to 7 days after a dose of doxorubicin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.* , eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes; some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies doxorubicin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. Although doxorubicin has been reported to be undetectable in amniotic fluid[1,2] it has been found in fetal tissue (liver, kidney, and lungs) at concentrations several times those in maternal plasma,[2] indicating that it does cross the placenta. The effect of anthracyclines on the outcome of 160 pregnancies has been analysed.[3] Most women had received combination chemotherapy that included doxorubicin or daunorubicin, for haematological malignancies or breast cancer. Most outcomes (73%) were normal. There were 5 malformations, most often associated with regimens that also included antimetabolites or alkylating agents; the malformations were highly variable. Fetal toxicity was associated with chemotherapy use for solid tumours during the first trimester, and the risk of severe fetal toxicity was significantly increased with doxorubicin doses above 70 mg/m² per cycle. Fetal cardiotoxicity occurred in 2 cases and was associated with anthracycline use during the second and third trimesters. It has been suggested that the use of epirubicin may reduce the risk of fetal myocardiopathy, but a brief review of the literature[4] suggested that its toxicity profile in pregnancy was very similar to that of doxorubicin. Fetal death was more frequent in women with acute leukaemia; it was associated with disease progression and the authors recommended that chemotherapy should not be postponed.

For a report of a healthy infant born to a woman treated with a doxorubicin-containing chemotherapy regimen, see Pregnancy, under Teniposide, p. 867.2.

UK licensed product information for doxorubicin cautions against use in pregnancy. Recommendations vary, but some advise that men and women both take effective contraceptive measures during treatment and for 3 to 6 months after therapy.

1. Roboz J, *et al.* Does doxorubicin cross the placenta? *Lancet* 1979; **ii:** 1382–3.
2. D'Incalci M, *et al.* Transplacental passage of doxorubicin. *Lancet* 1983; **i:** 75.
3. Germann N, *et al.* Anthracyclines during pregnancy: embryo–fetal outcome in 160 patients. *Ann Oncol* 2004; **15:** 146–50.
4. Mir O, *et al.* Chemotherapy for breast cancer during pregnancy: is epirubicin safe? *Ann Oncol* 2008; **19:** 1814–15.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. The total cumulative dose of doxorubicin should be reduced in patients who have received other cardiotoxic drugs such as daunorubicin or cyclophosphamide. Doxorubicin is reported to inhibit the intracellular activation of stavudine and hence its antiviral effect.

Antibacterials. Hypersensitivity reactions to doxorubicin or daunorubicin have been reported in 2 patients with recent exposure to *clindamycin*, one of whom had exhibited hypersensitivity to that antibiotic.[1] The possibility of cross-sensitivity between anthracyclines and clindamycin should be considered.

1. Arena FP, Sherlock S. Doxorubicin hypersensitivity and clindamycin. *Ann Intern Med* 1990; **112:** 150.

Antineoplastics. Giving doxorubicin with or after drugs, such as *streptozocin*[1] or *methotrexate*,[2] that can impair hepatic function, has resulted in increased doxorubicin toxicity, possibly due to reduced hepatic clearance. A high incidence of cardiotoxicity (manifest as congestive heart failure) has been reported in patients given doxorubicin with *paclitaxel* (which also has cardiotoxic effects).[3] Any interaction may be schedule dependent.[4] Similarly an increased incidence of cardiotoxicity has been seen when *trastuzumab* was given with or after anthracyclines (see Effects on the Heart under Trastuzumab, p. 876.3).

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[5] found that it decreased clearance of doxorubicin and prolonged the terminal half-life, increasing exposure to doxorubicin and myelosuppressive effects. The authors suggested that the dose of doxorubicin might need to be reduced by about 60%.

Sorafenib may increase systemic exposure to doxorubicin.

For a suggestion that doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, see under Daunorubicin Hydrochloride, p. 779.3.

For a report of an increased incidence of febrile neutropenia and gastrointestinal complications when doxorubicin is used with *docetaxel*, see Antineoplastics, under Docetaxel, p. 782.2.

In a pharmacokinetic study, both paclitaxel and docetaxel increased exposure to liposomal doxorubicin, although the effect was less pronounced with docetaxel.[6]

For mention of changes in exposure to pegylated or liposomal doxorubicin and *vinflunine* when these drugs were used together, see Interactions, under Vinflunine, p. 885.2.

1. Anonymous. Two drugs may not be better than one. *JAMA* 1976; **236:** 913.
2. Robertson JH, *et al.* Toxicity of doxorubicin and methotrexate in osteogenic sarcoma. *BMJ* 1976; **1:** 23.
3. Gianni L, *et al.* Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; **13:** 2688–99.
4. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37:** 195–211.
5. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7:** 1221–9.
6. Briasoulis E, *et al.* Interaction pharmacokinetics of pegylated liposomal doxorubicin (Caelyx) on coadministration with paclitaxel or docetaxel. *Cancer Chemother Pharmacol* 2004; **53:** 452–7.

General anaesthetics. For reference to QT-interval prolongation during anaesthesia with *isoflurane* in women who had received anthracycline-based chemotherapy for breast cancer, see p. 1907.3.

Immunosuppressants. Increased plasma-doxorubicin concentrations and myelotoxicity have occurred when *ciclosporin* was used to modulate tumour resistance.[1] Severe neurological toxicity occurred in another patient given doxorubicin after long-term ciclosporin therapy.[2] It has been suggested that the use of ciclosporin or its analogues (see Antineoplastics, above for the effect of valspodar) to modulate doxorubicin resistance should be undertaken with caution.[3]

1. Rushing DA, *et al.* The effects of cyclosporine on the pharmacokinetics of doxorubicin in patients with small cell lung cancer. *Cancer* 1994; **74:** 834–41.
2. Barbui T, *et al.* Neurological symptoms and coma associated with doxorubicin administration during chronic cyclosporin therapy. *Lancet* 1992; **339:** 1421.
3. Beck WT, Kuttesch JF. Neurological symptoms associated with cyclosporin plus doxorubicin. *Lancet* 1992; **340:** 496.

Thalidomide. In a comparison of two treatment regimens for multiple myeloma (thalidomide, dexamethasone, cisplatin, cyclophosphamide, and etoposide, with or without doxorubicin), there was an increased risk of deep-vein thrombosis in those patients who received the combination that included doxorubicin.[1] The authors cited a previous study[2] in which the addition of thalidomide to an antineoplastic regimen increased the risk of deep-vein thrombosis, and concluded that patients with multiple myeloma treated with the combination of doxorubicin and thalidomide are at increased risk.

1. Zangari M, *et al.* Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 2002; **100:** 1168–71.
2. Zangari M, *et al.* Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood* 2001; **98:** 1614–15.

Pharmacokinetics

After intravenous injection, doxorubicin is rapidly cleared from the blood, and distributed into tissues including lungs, liver, heart, spleen, and kidneys. It undergoes rapid metabolism in the liver to metabolites including the active metabolite doxorubicinol (adriamycinol). About 40 to 50% of a dose is stated to be excreted in bile within 7 days, of which about half is as unchanged drug. Only about 5% of a dose is excreted in urine within 5 days. It does not cross the blood-brain barrier but may cross the placenta and is distributed into breast milk. The disappearance of doxorubicin from the blood is triphasic: mean half-lives are 12 minutes, 3.3 hours and about 30 hours.

The pharmacokinetics of *liposomal* formulations are somewhat different from the conventional drug. The use of macrogols in the surface layer of the liposomes (pegylation) reduces removal of liposomes by macrophages. This results in prolonged circulation in the plasma, with relatively little tissue distribution, but tumour neovasculature is reported to permit penetration of liposomes into tumour tissue. Pharmacokinetics are reported to be biphasic with mean half-lives of 5 hours and 55 to 75 hours respectively. A non-pegylated liposomal formulation also exists and is reported to produce higher peak plasma concentrations of total doxorubicin than conventional formulations, but lower free (not liposome-encapsulated) concentrations. Clearance is reduced, and peak plasma concentrations of doxorubicinol delayed.

References.

1. Speth PAJ, *et al.* Clinical pharmacokinetics of doxorubicin. *Clin Pharmacokinet* 1988; **15:** 15–31.
2. Rushing DA, *et al.* The disposition of doxorubicin on repeated dosing. *J Clin Pharmacol* 1993; **33:** 698–702.
3. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of doxorubicin in patients with small cell lung cancer. *Clin Pharmacol Ther* 1993; **53:** 555–61.
4. Amantea MA, *et al.* Population pharmacokinetics and pharmacodynamics of pegylated-liposomal doxorubicin in patients with AIDS-related Kaposi's sarcoma. *Clin Pharmacol Ther* 1997; **61:** 301–11.
5. Danesi R, *et al.* Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. *Clin Pharmacokinet* 2002; **41:** 431–44.

6. Swenson CE, *et al*. Pharmacokinetics of doxorubicin administered i.v. as Myocet (TLC D-99; liposome-encapsulated doxorubicin citrate) compared with conventional doxorubicin when given in combination with cyclophosphamide in patients with metastatic breast cancer. *Anticancer Drugs* 2003; **14:** 239–46.
7. Gabizon A, *et al*. Pharmacokinetics of pegylated liposomal doxorubicin: review of animal and human studies. *Clin Pharmacokinet* 2003**42:** 419–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adriblastina; Caelyx; Colhidrol; Dicladox; Doxocris; Doxokebir; Doxopeg; Doxtie; Nagun; Onkostatil; Roxorin; Varidoxo; ***Austral.***: Caelyx; ***Austria***: Adriblastin; Caelyx; DOXO-Cell†; Myocet; ***Belg.***: Adriblastina; Caelyx; Doxorubin†; Myocet; ***Braz.***: Adriblastina; Biorrub; Caelyx; Doxolem; Doxopeg; Evorubicin; Fauldoxo; Oncodox; Rubex; Rubidox; ***Canad.***: Caelyx; Myocet; ***Chile***: Adriblastina†; Caelyx; Daxotel; Doxopeg; ***China***: Caelyx (楷莱); ***Cz.***: Adriblastina; Caelyx; Doxolem†; Myocet; Xorucin; ***Denm.***: Caelyx; Myocet; ***Fin.***: Caelyx; ***Fr.***: Adriblastine; Caelyx; Myocet; ***Ger.***: Adriblastin†; Adrimedac; Axidoxo; Caelyx; DOXO-Cell; Myocet; Ribodoxo; ***Gr.***: Adriblastina; Caelyx; Doxiprol; Doxorubin; Doxosan; Doxotil; Myocet; Rubidox; ***Hong Kong***: Caelyx; Sindroxocin; ***Hung.***: Adriblastina; Caelyx; Myocet; ***India***: Adrim; Adrosal; Cadria; Caelyx; Cardia; Dobicin; Dobixin; Doxobin; Doxolem; Doxomed; Doxorex; Doxorubin; Doxulip; Doxutec; Duxocin; Lyphidox; Naprodox; Oncodox; Oncodria; ***Indon.***: Adricin; Caelyx; Pallagicin†; Rubidox†; ***Irl.***: Caelyx; Myocet; ***Israel***: Adriblastina; Doxil; Myocet; ***Ital.***: Adriblastina; Caelyx; Myocet; ***Jpn***: Adriacin; ***Malaysia***: Caelyx; Doxorubin; ***Mex.***: Adriblastina; Caelyx; Doxolem; Doxopeg; Doxotec; Doxtie†; Ifadox†; ***Neth.***: Caelyx; Debdox; Doxorubin; Myocet; ***Norw.***: Caelyx; Myocet; ***NZ***: Caelyx; Doxorubin; ***Philipp.***: AD Mycin; Adriblastina; Adrim; Adrosal; Axibin; Caelyx; Doxorubin; Rubidox†; ***Pol.***: Adriblastina; Adrimedac; Biorubina; Caelyx; Myocet; Rastocin†; ***Port.***: Caelyx; DOXO-cell; Fauldoxo; Myocet; ***Rus.***: Caelyx (Келикс); Rastocin (Растоцин); Sindroxocin (Синдроксоцин); ***S.Afr.***: Adriblastina; Caelyx; ***Singapore***: Adriblastina; Caelyx; Diox; Ebedoxo; ***Spain***: Caelyx; Farmiblastina; Myocet; ***Swed.***: Caelyx; Myocet; ***Switz.***: Adriblastin; Caelyx; ***Thai.***: AD Mycin; Adriblastina; Adrim; Caelyx; Doxolem; Doxorubin; Lipo-Dox; ***Turk.***: Adriblastina; Caelyx; Doxo-Teva; ***UK***: Caelyx; Myocet; ***Ukr.***: Adriblastina (Адрибластин)†; Caelyx (Келикс)†; Lipodox (Липодокс); ***USA***: Doxil; Lipodox; ***Venez.***: Adriblastina; Adrim; Caelyx; Doxonolver.

Pharmacopoeial Preparations
BP 2014: Doxorubicin Injection;
USP 36: Doxorubicin Hydrochloride for Injection; Doxorubicin Hydrochloride Injection.

Edrecolomab *(USAN, rINN)*

17-1A Antibody; C1; Édrécolomab; Edrecolomabum; Monoclonal Antibody 17-1A; Эдреколомаб.
Immunoglobulin G2a (mouse monoclonal 17-1A γ-chain anti-human colon cancer tumor-associated antigen), disulfide with mouse monoclonal 17-1A light chain, dimer.
CAS — 156586-89-9.
ATC — L01XC01.
ATC Vet — QL01XC01.
UNII — 0KYI9U9FSJ.

Profile

Edrecolomab is a monoclonal antibody of murine origin directed at epithelial cell surface glycoproteins that has been used as adjuvant therapy after surgery in patients with colorectal cancer (p. 706.3), although reports of improved survival do not seem to have been borne out.

References.

1. Riethmüller G, *et al*. Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. *Lancet* 1994; **343:** 1177–83.
2. Riethmüller G, *et al*. Monoclonal antibody therapy for resected Dukes' C colorectal cancer: seven-year outcome of a multicenter randomized trial. *J Clin Oncol* 1998; **16:** 1788–94.
3. Adkins JC, Spencer CM. Edrecolomab (monoclonal antibody 17-1A). *Drugs* 1998; **56:** 619–26.
4. Punt CJA, *et al*. Edrecolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: a randomised study. *Lancet* 2002; **360:** 671–7.
5. Hartung G, *et al*. Adjuvant therapy with edrecolomab versus observation in stage II colon cancer: a multicenter randomized phase III study. *Onkologie* 2005; **28:** 347–50.
6. Fields ALA, *et al*. Adjuvant therapy with the monoclonal antibody edrecolomab plus fluorouracil-based therapy does not improve overall survival of patients with stage III colon cancer. *J Clin Oncol* 2009; **27:** 1941–7.
7. Schmoll H-J, Arnold D. When wishful thinking leads to a misty-eyed appraisal: the story of the adjuvant colon cancer trials with edrecolomab. *J Clin Oncol* 2009; **27:** 1926–9.

Efaproxiral *(USAN, rINN)* ⊗

Éfaproxiral; Efaproxiralum; RSR-13; Эфапроксирал.
2-(4-{2-[(3,5-Dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methyl propanoic acid.
$C_{20}H_{23}NO_4$=341.4
CAS — 131179-95-8.
ATC — L01XD06.
ATC Vet — QL01XD06.
UNII — J81E81G364.

NOTE. The names Efaproxyn and Revaproxyn have been used as trade marks for efaproxiral.

Efaproxiral Sodium *(USAN, rINNM)* ⊗

Efaproxiral sódico; Éfaproxiral Sodique; Natrii Efaproxiralum; Натрий Эфапроксирал.
$C_{20}H_{22}NNaO_4$=363.4
CAS — 170787-99-2.
ATC — L01XD06.
ATC Vet — QL01XD06.
UNII — 3L83QP52XI.

Profile

Efaproxiral is an allosteric modifier of haemoglobin that enhances the diffusion of oxygen to hypoxic tumour tissue, making it more sensitive to radiotherapy. It has been investigated in the treatment of brain metastases from solid tumours.

Elacytarabine *(USAN, rINN)*

CP-4055; Elacitarabina; Élacytarabine; Elacytarabinum; Элацитарабин.
4-Amino-1-{5-*O*-[(9*E*)-octadec-9-enoyl]-β-D-arabinofuranosyl}pyrimidin-2(1*H*)-one.
$C_{27}H_{45}N_3O_6$=507.7
CAS — 188181-42-2.
UNII — TA7WJG93AR.

NOTE. The name Elacyt has been used as a trade mark for elacytarabine.

Profile

Elacytarabine is a lipid-conjugated derivative of cytarabine (p. 774.1) that is under investigation for the treatment of acute myeloid leukaemia.

Elesclomol *(USAN, rINN)*

Élesclomol; Elesclomolum; STA-4783; Элескломол.
Propanedioic acid, bis[2-methyl-2-(phenylthioxomethyl) hydrazide]; 1-*N*′-benzenecarbothioyl-3-(2-benzenecarbothioyl-2-methylhydrazinyl)-*N*′-methyloxopropanehydrazide.
$C_{19}H_{20}N_4O_2S_2$=400.5
CAS — 488832-69-5.
UNII — 6UK191M53P.

Profile

Elesclomol is an oxidative stress inducer that is under investigation as a treatment for metastatic melanoma.

References.

1. Berkenblit A, *et al*. Phase I clinical trial of STA-4783 in combination with paclitaxel in patients with refractory solid tumors. *Clin Cancer Res* 2007; **13:** 584–90.
2. Kirshner JR, *et al*. Elesclomol induces cancer cell apoptosis through oxidative stress. *Mol Cancer Ther* 2008; **7:** 2319–27.
3. O'Day S, *et al*. Phase II, randomized, controlled, double-blinded trial of weekly elesclomol plus paclitaxel versus paclitaxel alone for stage IV metastatic melanoma. *J Clin Oncol* 2009; **27:** 5452–8.

Endostatin

rhEndostatin (recombinant human endostatin); YH-16 (recombinant human endostatin).

NOTE. The name Endu has been used as a trade mark for recombinant human endostatin.

Profile

Endostatin is an endogenous human protein fragment of collagen type XVIII that has anti-angiogenic properties. A recombinant human form has been used for non-small cell lung cancer and is under investigation for the treatment of other malignancies such as metastatic melanoma and gastrointestinal tumours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Endostar (恩度).

Enocitabine *(rINN)*

Behenoyl Cytarabine; Behenoylcytosine Arabinoside; BH-AC; Enocitabina; Énocitabine; Enocitabinum; NSC-239336; Эноцитабин.
N-(1-β-D-Arabinofuranosyl-1,2-dihydro-2-oxo-4-pyrimidinyl) docosanamide.
$C_{31}H_{55}N_3O_6$=565.8
CAS — 55726-47-1.
UNII — 9YVR68W306.

Profile

Enocitabine is an antineoplastic that is converted in the body to cytarabine (p. 774.1). It has been used similarly in the treatment of acute leukaemias.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Sunrabin.

Entinostat *(USAN, rINN)*

Entinostatum; MS-27-275; MS-275; SNDX-275; Энтиностат.
Pyridin-3-ylmethyl {[4-[(2-aminophenyl)carbamoyl]phenyl} methyl)carbamate.
$C_{21}H_{20}N_4O_3$=376.4
CAS — 209783-80-2.
UNII — 1ZNY4FKK9H.

Profile

Entinostat is an orally active histone deacetylase inhibitor that is under investigation for the treatment of Hodgkin's disease.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Knipstein J, Gore L. Entinostat for treatment of solid tumors and hematologic malignancies. *Expert Opin Invest Drugs* 2011; **20:** 1455–67.

Enzalutamide *(USAN, pINN)*

Enzalutamida; Enzalutamidum; MDV-3100; Энзалутамид.
4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide.
$C_{21}H_{16}F_4N_4O_2S$=464.4
CAS — 915087-33-1.
UNII — 93T0T9GKNU.

Uses and Administration

Enzalutamide is a nonsteroidal anti-androgen that competitively inhibits binding to androgen receptors. It is used in the treatment of metastatic castration-resistant prostate cancer (p. 712.3) in patients who have previously been treated with docetaxel. The usual oral dose is 160 mg once daily. Treatment should be withheld if severe toxicity occurs and then restarted after 1 week, or when symptoms have improved, at either the usual dose or a reduced dose (80 or 120 mg once daily) if warranted.

Use with strong cytochrome P450 isoenzyme CYP2C8 inhibitors should be avoided. If a strong CYP2C8 inhibitor must be used, the dose of enzalutamide should be reduced to 80 mg once daily. The original dose may be resumed after the inhibitor has been stopped.

References.

1. Scher HI, *et al*. AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; **367:** 1187–97.
2. Golshayan AR, Antonarakis ES. Enzalutamide: an evidence-based review of its use in the treatment of prostate cancer. *Core Evid* 2013; **8:** 27–35.
3. Pal SK, *et al*. Enzalutamide for the treatment of prostate cancer. *Expert Opin Pharmacother* 2013; **14:** 679–85.

Adverse Effects and Precautions

The most commonly reported adverse effects with enzalutamide are asthenia or fatigue, muscular weakness, arthralgia, musculoskeletal and back pain, diarrhoea, peripheral oedema, headache, flushing, hypertension, respiratory-tract infections, dizziness, insomnia, anxiety, paraesthesia, and haematuria. Seizures have occurred in patients taking enzalutamide and it should be used with caution in those with predisposing factors.

Interactions

Enzalutamide is metabolised by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4, and use with inhibitors or inducers of these isoenzymes may affect exposure to

enzalutamide. The strong CYP2C8 inhibitor gemfibrozil increased exposure to enzalutamide and its active metabolite by 2.2-fold; consequently, the use of strong CYP2C8 inhibitors with enzalutamide should be avoided, or the dose of enzalutamide reduced if use together is necessary (see Uses and Administration, p. 786.3). The increase in exposure to enzalutamide and its active metabolite was less prominent (1.3-fold) with the strong CYP3A4 inhibitor itraconazole. The effects of strong or moderate inducers of CYP2C8 or CYP3A4 on enzalutamide have not been evaluated and licensed product information recommends that their use together should be avoided.

Enzalutamide itself is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. The exposure of drugs that are substrates of these isoenzymes may be decreased when given with enzalutamide; use with enzalutamide should be avoided for those that also have a narrow therapeutic index.

Pharmacokinetics

Peak plasma concentrations of enzalutamide occur about 1 hour after an oral dose and with daily dosing steady state is reached after 28 days. Enzalutamide is about 97% bound to plasma proteins, mainly albumin; the major active metabolite *N*-desmethyl enzalutamide is about 95% bound to plasma proteins. Enzalutamide is metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8, the latter of which is mainly responsible for the formation of the active metabolite. Over 70% of a dose is excreted as metabolites in the urine, and 14% in the faeces. The mean terminal half-life after a single dose is about 6 days for enzalutamide and about 8 days for *N*-desmethyl enzalutamide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Xtandi; ***USA***: Xtandi.

Enzastaurin Hydrochloride *(USAN, rINNM)*

Enzastaurine, Chlorhydrate d'; Enzastaurini Hydrochloridum; Hidrocloruro de enzastaurina; LY-317615; Энзастаурина Гидрохлорид.

3-(1-Methyl-1*H*-indol-3-yl)-4-{1-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1*H*-indol-3-yl}-1*H*pyrrole-2,5-dione hydrochloride.

$C_{32}H_{29}N_5O_2$,HCl=552.1

CAS — 359017-79-1.

UNII — KX7K68Z2UH.

Profile

Enzastaurin hydrochloride is a protein kinase C inhibitor that has been investigated for the treatment of gliomas and is being tried in other malignancies including non-Hodgkin's lymphoma, and with pemetrexed in non-small cell lung cancer.

References.

1. Sorbera LA, *et al.* Enzastaurin hydrochloride. *Drugs Of The Future* 2007; **32:** 297–309. Correction. *ibid.*; 751.
2. Ma S, Rosen ST. Enzastaurin. *Curr Opin Oncol* 2007; **19:** 590–5.
3. Chen YB, LaCasce AS. Enzastaurin. *Expert Opin Invest Drugs* 2008; **17:** 939–44.
4. Wick W, *et al.* Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 2010; **28:** 1168–74.
5. Galanis E, Buckner JC. Enzastaurin in the treatment of recurrent glioblastoma: a promise that did not materialize. *J Clin Oncol* 2010; **28:** 1097–8.
6. Giovannetti E, *et al.* Pharmacological aspects of the enzastaurin-pemetrexed combination in non-small cell lung cancer (NSCLC). *Curr Drug Targets* 2010; **11:** 12–28.

Epirubicin Hydrochloride

(BANM, USAN, rINNM)

Epirubicina, hidrocloruro de; Épirubicine, chlorhydrate d'; Epirubicin-hidroklorid; Epirubicin-hydrochlorid; Epirubicin-hydrochlorid; Epirubicinhydroklorid; Epirubicini Hydrochloridum; Epirubicino hidrochloridas; Epirubisiinihydrokloridi; Epirubisin Hidroklorür; Hidrocloruro de epirubicina; IMI-28; Pidorubicin Hydrochloride; Эпирубицина Гидрохлорид; 4′-Epiadriamycin Hydrochloride; 4′-Epidoxorubicin Hydrochloride.

(8*S*,10*S*)-10-(3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyloxy)-8-glycolloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxynaphthacene-5,12-dione hydrochloride.

$C_{27}H_{29}NO_{11}$,HCl=580.0

CAS — 56420-45-2 (epirubicin); 56390-09-1 (epirubicin hydrochloride).

ATC — L01DB03.

ATC Vet — QL01DB03.

UNII — 22966TX7J5.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Epirubicin Hydrochloride). A substance obtained by chemical transformation of a substance produced by certain strains of *Streptomyces peucetius*. An orange-red powder. Soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.0 to 5.5. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Epirubicin Hydrochloride). An orange-red powder. Soluble in water and methyl alcohol; slightly soluble in anhydrous alcohol; practically insoluble in acetone. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Incompatibility. Licensed product information states that epirubicin hydrochloride is incompatible with heparin or fluorouracil, resulting in precipitation, and that it is hydrolysed in alkaline solutions.

Stability. Epirubicin was not subject to significant photodegradation at clinical concentrations,[1,2] and special precautions to protect solutions from light during use do not appear to be necessary. However, photodegradation may be significant at lower concentrations (below 500 micrograms/mL).[1]

1. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
2. Pujol M, *et al.* Stability study of epirubicin in NaCl 0.9% injection. *Ann Pharmacother* 1997; **31:** 992–5.

Uses and Administration

Epirubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (p. 783.2). It is used, alone or with other antineoplastics, in acute leukaemias, lymphomas, multiple myeloma, and in solid tumours including Wilms' tumour (p. 709.1), cancer of the bladder (p. 700.2), breast (p. 702.1), and stomach (p. 706.1).

Epirubicin hydrochloride is given by intravenous injection of a solution in sodium chloride 0.9% or Water for Injections into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 to 5 minutes, or by infusion over up to 30 minutes. It is given as a single agent in usual doses of 60 to 90 mg/m² as a single dose every 3 weeks; this dose may be divided over 2 or 3 days if desired. A regimen of 20 to 30 mg/m² once a week has been tried in palliative care or in those who do not tolerate the higher dose. High-dose regimens, of 120 mg/m² or more every 3 weeks, or 45 mg/m² for 3 consecutive days every 3 weeks have been used.

Doses may need to be reduced if epirubicin is given with other antineoplastics. Doses should also be reduced in patients with liver impairment (see below) and in those whose bone-marrow function is impaired by age or previous chemotherapy or radiotherapy.

A total cumulative dose of 0.9 to 1 g/m² should not generally be exceeded, because of the risk of cardiotoxicity.

Epirubicin has also been given by intravesical instillation in the local treatment of bladder cancer. Instillation of 50 mg weekly as a 0.1% solution (in sodium chloride 0.9% or sterile water) for 8 weeks has been suggested, reduced to 30 mg in 50 mL weekly if chemical cystitis develops; for carcinoma *in-situ*, the dose may be increased, if tolerated, to 80 mg in 50 mL weekly. For the prophylaxis of recurrence in patients who have undergone transurethral resection, 50 mg weekly for 4 weeks, followed by 50 mg instilled once a month for 11 months is the suggested regimen. The solution should be retained in the bladder for 1 hour.

Blood counts should be made routinely during treatment with epirubicin (see also Bone-marrow Depression, p. 730.3) and cardiac function should be carefully monitored. Liver function should be assessed before and if possible during therapy.

References.

1. Plosker GL, Faulds D. Epirubicin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. *Drugs* 1993; **45:** 788–856.
2. Coukell AJ, Faulds D. Epirubicin: an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of breast cancer. *Drugs* 1997; **53:** 453–82.
3. Onrust SV, *et al.* Epirubicin: a review of its intravesical use in superficial bladder cancer. *Drugs Aging* 1999; **15:** 307–33.
4. Ormrod D, *et al.* Epirubicin: a review of its efficacy as adjuvant therapy and in the treatment of metastatic disease in breast cancer. *Drugs Aging* 1999; **15:** 389–416.
5. Earl H, Iddawela M. Epirubicin as adjuvant therapy in breast cancer. *Expert Rev Anticancer Ther* 2004; **4:** 189–95.

Administration in hepatic impairment. Doses of epirubicin should be halved in patients with moderate liver dysfunction (serum bilirubin concentrations of 12 to 30 micrograms/mL), while those with severe liver impairment (serum bilirubin greater than 30 micrograms/mL) should be given a quarter of the usual dose.

Amyloidosis. For reference to a regimen including epirubicin used to control disease in a patient with amyloidosis, see p. 819.3.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1. Cardiotoxicity and myelotoxicity may be less than with doxorubicin. Cardiotoxicity is more likely when the total cumulative dose exceeds 0.9 to 1 g/m².

Effects on the heart. For further discussion of the cardiotoxicity of anthracyclines, see under Adverse Effects of Doxorubicin, p. 784.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies epirubicin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

As for Doxorubicin, p. 785.2.

Antineoplastics. Increased exposure to epirubicin, and a consequent increase in myelotoxicity, has been reported in patients given epirubicin immediately after *paclitaxel*, compared with patients who received epirubicin before paclitaxel.[1] Similar interactions have been seen when paclitaxel was given before other anthracyclines.[2] These and other studies[3,4] have suggested that paclitaxel given in this way is associated with a reduced conversion of epirubicin to the less myelotoxic metabolite, epirubicinol, although the interaction is complex, and may involve both disposition and pharmacodynamics.

1. Venturini M, *et al.* Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity. *J Clin Oncol* 2000; **18:** 2116–25.
2. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37:** 195–211.
3. Grasselli G, *et al.* Clinical and pharmacologic study o f the epirubicin and paclitaxel combination in women with metastatic breast cancer. *J Clin Oncol* 2001; **19:** 2222–31.
4. Danesi R, *et al.* Pharmacokinetics and pharmacodynamics of combination chemotherapy with paclitaxel and epirubicin in breast cancer patients. *Br J Clin Pharmacol* 2002; **53:** 508–18.

Cimetidine. Cimetidine increased the formation of the active metabolite of epirubicin in a study in 8 patients; there was also a substantial increase in systemic exposure to unchanged epirubicin.[1] The mechanisms and potential clinical significance of the interaction were unclear.

1. Murray LS, *et al.* The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced breast cancer: preliminary evidence of a potentially common drug interaction. *Clin Oncol* 1998; **10:** 35–8.

Pharmacokinetics

After intravenous doses epirubicin is rapidly and extensively distributed into body tissues, and undergoes metabolism in the liver, with the formation of epirubicinol (13-hydroxyepirubicin) and appreciable amounts of glucuronide derivatives. Epirubicin is eliminated mainly in bile, with a terminal plasma elimination half-life of about 30 to 40 hours. About 10% of a dose is recovered in urine within 48 hours. Epirubicin does not cross the blood-brain barrier.

References.

1. Morris RG, *et al.* Disposition of epirubicin and metabolites with repeated courses to cancer patients. *Eur J Clin Pharmacol* 1991; **40:** 481–7.
2. Robert J. Clinical pharmacokinetics of epirubicin. *Clin Pharmacokinet* 1994; **26:** 428–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisabon; Cuatroepi; Epidoxo; Epifil; Epikebir†; Farmorubicin; Robanul; ***Austral.***: Pharmorubicin; ***Austria***: Epi-Cell†; Farmorubicin; ***Belg.***: Farmorubicine; ***Braz.***: Brecila; Farmorubicina; Nuovodox; Rubina†; Tecnomax; ***Canad.***: Pharmorubicin; ***Chile***: Farmorrubicina; ***China***: Ai Da Sheng (艾达生); Pharmorubicin (法玛新); ***Cz.***: Epimedac; Farmorubicin; ***Denm.***: Epi-cell; Farmorubicin; ***Fin.***: Farmorubicin; ***Fr.***: Farmorubicine; ***Ger.***: Axirubicin-e; Bendaepi; Epi Teva; Epi-Cell; Epi-NC†; Epimedac; Eracin; Farmorubicin; Riboepi; ***Gr.***: Cenebir; Ciazil; Epibicin; Epibra; Epimedac; Epirub; Epirud†; Farmorubicin; Megarubicin; Rubiprol; ***Hong Kong***: Episindan; Pharmorubicin; ***Hung.***: Episindan; Farmorubicin; ***India***: Alrubicin; Epirubitec; Epithra; Epricin; Farmorubicin; ***Irl.***: Pharmorubicin; ***Israel***: Farmorubicin†; ***Ital.***: Farmorubicina; ***Jpn***: Farmorubicin; ***Malaysia***: Pharmorubicin; ***Mex.***: Anthracord; Binarin; Epilem; Farmorubicin; Favicin; ***Neth.***: Farmorubicine; ***Norw.***: Farmorubicin; ***NZ***: Epiccord; Pharmorubicin; ***Philipp.***: Anthracin; E.P. Mycin; EP Mycin; Neoquabin; Pharmorubicin; ***Pol.***: Bioepicyna; Episindan; Farm-

orubicin; ***Port.***: Epi-cell; Farmorubicina; ***Rus.***: Epilem (Эпилем); Episindan (Эписиндан); Farmorubicin (Фарморубицин); ***S.Afr.***: Epicord; Farmorubicin; ***Singapore***: Eberubi; Episindan; Pharmorubicin; ***Spain***: Farmorubicina; Sendras†; ***Swed.***: Farmorubicin; ***Switz.***: Farmorubicin; ***Thai.***: Anthracin†; E.P.Mycin†; EP Mycin; Epilem; Pharmorubicin; ***Turk.***: Farmorubicin; Pirucin; Rubens; ***UK***: Pharmorubicin; ***Ukr.***: Farmorubicin (Фарморубицин); ***USA***: Ellence; ***Venez.***: Farmorubicin.

Pharmacopoeial Preparations
BP 2014: Epirubicin Injection.

Epratuzumab *(rINN)*

AMG-412; Épratuzumab; Epratuzumabum; Эпратузумаб.
Immunoglobulin G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain, dimer.
CAS — 205923-57-5.
UNII — 3062P60MH9.

Profile

Epratuzumab is a humanised anti-CD22 monoclonal antibody under investigation, alone or conjugated with yttrium-90 (p. 2230.1), for the treatment of non-Hodgkin's lymphoma. It is also under investigation for the treatment of moderate to severe SLE.

References.
1. Davies SL, Martin L. Epratuzumab. *Drugs Of The Future* 2005; **30:** 683–7.
2. Leonard JP, *et al.* Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 5044–51.
3. Lindén O, *et al.* Dose-fractionated radioimmunotherapy in non-Hodgkin's lymphoma using DOTA-conjugated, ^{90}Y-radiolabeled, humanized anti-CD22 monoclonal antibody, epratuzumab. *Clin Cancer Res* 2005; **11:** 5215–22.
4. Goldenberg DM. Epratuzumab in the therapy of oncological and immunological diseases. *Expert Rev Anticancer Ther* 2006; **6:** 1341–53.
5. Leonard JP, Goldenberg DM. Preclinical and clinical evaluation of epratuzumab (anti-CD22 IgG) in B-cell malignancies. *Oncogene* 2007; **26:** 3704–13.
6. Leonard JP, *et al.* Durable complete responses from therapy with combined epratuzumab and rituximab: final results from an international multicenter, phase 2 study in recurrent, indolent, non-Hodgkin lymphoma. *Cancer* 2008; **113:** 2714–23.

Eptaplatin *(rINN)*

Eptaplatine; Eptaplatino; Eptaplatinum; Heptaplatin; SKI-2053R; Эптаплатин.
cis-[(4*R*,5*R*)-2-Isopropyl-1,3-dioxolane-4,5-bis(methylamine)-*N*,*N*′][malonato(2−)-*O*,*O*′]platinum.
$C_{11}H_{20}N_2O_6Pt$=471.4
CAS — 146665-77-2.
UNII — 1352HON1DH.

Profile

Eptaplatin is a platinum derivative that is used as an intravenous antineoplastic in the treatment of gastric cancer. Nephrotoxicity is the main adverse effect.

References.
1. Ahn JH, *et al.* Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer. *Cancer Chemother Pharmacol* 2002; **50:** 104–10.
2. Min YJ, *et al.* Combination chemotherapy with 5-fluorouracil and heptaplatin as first-line treatment in patients with advanced gastric cancer. *J Korean Med Sci* 2004; **19:** 369–73.
3. Lee KH, *et al.* Randomized, multicenter, phase III trial of heptaplatin 1-hour infusion and 5-fluorouracil combination chemotherapy comparing with cisplatin and 5-fluorouracil combination chemotherapy in patients with advanced gastric cancer. *Cancer Res Treat* 2009; **41:** 12–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Kor.***: Sunpla.

Eribulin *(rINN)*

B-1939; ER-086526; Eribulina; Éribuline; Eribulinum; Эрибулин.
(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12-*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2′,3′:5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one.
$C_{40}H_{59}NO_{11}$=729.9
CAS — 253128-41-5.
ATC — L01XX41.
ATC Vet — QL01XX41.
UNII — LR24G6354G.

Eribulin Mesilate *(rINNM)*

E-7389; Eribulin Mesylate (USAN); Éribuline, Mésilate d'; Eribulini Mesilas; Mesilato de eribulina; Эрибулина Мезилат.
(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12-*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2′,3′:5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one methanesulfonate.
$C_{40}H_{59}NO_{11}.CH_4O_3S$=826.0
CAS — 441045-17-6.
ATC — L01XX41.
ATC Vet — QL01XX41.
UNII — AV9U0660CW.

Uses and Administration

Eribulin is a synthetic analogue of halichondrin B, a substance isolated from marine sponges. It inhibits tubulin polymerisation and is used in the treatment of refractory locally advanced or metastatic breast cancer (p. 702.1) in patients previously treated with at least 2 chemotherapy regimens, including an anthracycline and a taxane. Eribulin is given as the mesilate, although in some countries the dose is expressed as the base. The recommended dose is eribulin mesilate 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2) given by intravenous injection over 2 to 5 minutes, on days 1 and 8 of a 21-day cycle. The start of treatment should be delayed in patients with absolute neutrophil counts less than 1000 cells/mm^3, or platelet counts less than 75 000 cells/mm^3, or grade 3 or 4 non-haematological toxicity, until recovery occurs, and similar precautions apply in subsequent cycles once treatment has started. More severe toxicity may also require dose reduction (see Administration in Subsequent Cycles, below). For doses in hepatic or renal impairment, see below.

Eribulin is also under investigation for the treatment of various other malignancies including non-small cell lung cancer, prostate cancer, and sarcoma.

References.
1. Twelves C, *et al.* Phase III trials of eribulin mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. *Clin Breast Cancer* 2010; **10:** 160–3.
2. Cigler T, Vahdat LT. Eribulin mesylate for the treatment of breast cancer. *Expert Opin Pharmacother* 2010; **11:** 1587–93.
3. Cortes J, *et al.* EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; **377:** 914–23.

Administration in hepatic impairment. Exposure to eribulin is increased by hepatic impairment and lower doses are recommended. The intravenous dose of eribulin mesilate for mild impairment (Child-Pugh class A) is 1.1 mg/m^2 (equivalent to eribulin 970 micrograms/m^2), and for moderate impairment (Child-Pugh class B) 700 micrograms/m^2 (equivalent to eribulin 620 micrograms/m^2), given on days 1 and 8 of a 21-day cycle. Eribulin has not been studied in those with severe hepatic impairment (Child-Pugh class C).

Administration in renal impairment. No dose adjustment is considered necessary when eribulin is used in those with mild renal impairment, defined by US licensed product information as creatinine clearance (CC) 50 to 80 mL/min; however, exposure to eribulin is increased by moderate renal impairment (CC 30 to 50 mL/min) and a lower intravenous dose of eribulin mesilate 1.1 mg/m^2 is recommended in the USA, given on days 1 and 8 of a 21-day cycle. The safety of eribulin has not been studied in those with severe renal impairment (CC < 30 mL/min). UK licensed product information states that patients with severe renal impairment (CC < 40 mL/min) may need a reduction in dose, but gives no specific dose recommendation.

Administration in subsequent cycles. If any of the following occur after an intravenous dose of eribulin mesilate:
- absolute neutrophil count (ANC) < 500 cells/mm^3 and lasting more than 7 days
- ANC < 1000 cells/mm^3 complicated by fever or infection
- platelet count < 25 000 cells/mm^3
- platelet count < 50 000 cells/mm^3 complicated by haemorrhage or the need for transfusion
- grade 3 or 4 non-haematological toxicity

then subsequent doses should be reduced from 1.4 mg/m^2 eribulin mesilate (1.23 mg/m^2 eribulin) to 1.1 mg/m^2 eribulin mesilate (970 micrograms/m^2 eribulin).

If such toxicities recur despite dose reduction, then subsequent doses should be further reduced to 700 micrograms/m^2 eribulin mesilate (620 micrograms/m^2 eribulin); if severe toxicity continues at this lower dose, then treatment should be stopped. Doses should not be increased again in subsequent cycles once they have been reduced.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects associated with eribulin are neutropenia, anaemia, leucopenia, fatigue, fever, alopecia, peripheral neuropathy, headache, arthralgia, myalgia, anorexia, and gastrointestinal disturbances. Infections, including urinary-tract or upper respiratory-tract infections, nasopharyngitis, rhinitis, and oral candidiasis, are also common, as are pain, especially in the back, bone, chest, or oropharyngeal area, and electrolyte disturbances including hypokalaemia, hypomagnesaemia, and hypophosphataemia.

Other adverse effects include febrile neutropenia, thrombocytopenia, lymphopenia, tachycardia, hot flushes, cough, dyspnoea, abdominal pain, stomatitis, mouth ulceration, dry mouth, peripheral oedema, muscle spasms or weakness, epistaxis, rhinorrhoea, increased lachrymation, conjunctivitis, dysgeusia, vertigo, dizziness, insomnia, depression, and increased liver enzymes. Skin disorders include rash, pruritus, hyperhidrosis, dry skin, erythema, and palmar-plantar erythrodysesthesia; nail disorders have also been reported. Hyperglycaemia and dehydration have occurred, as have chills and flu-like illness.

Less common adverse effects include deep-vein thrombosis, pulmonary embolism, interstitial lung disease, hyperbilirubinaemia, angioedema, and tinnitus. Renal disorders that have been reported include dysuria, haematuria, proteinuria, and renal failure.

Complete blood counts should be measured before each dose of eribulin, and more frequently in those who develop severe cytopenias. Treatment should be delayed or the dose reduced if febrile neutropenia occurs or if severe neutropenia lasts longer than 7 days, see Uses and Administration, above. Severe neutropenia may be more common in patients with elevated liver enzymes or bilirubin.

Patients should be monitored closely for peripheral motor and sensory neuropathy. Treatment should be withheld for severe peripheral neuropathy, see Uses and Administration, above.

Eribulin may prolong the QT interval and ECG monitoring is recommended in patients at higher risk, including those with heart failure, bradyarrhythmias, electrolyte abnormalities, or patients also taking other drugs that prolong the QT interval such as some antiarrhythmics. Hypokalaemia and hypomagnesaemia should be corrected before starting eribulin, and these electrolytes monitored periodically during treatment. Eribulin should not be used in patients with congenital long QT syndrome.

Pharmacokinetics

Eribulin is a substrate for, and a weak inhibitor of, P-glycoprotein. Eribulin is rapidly distributed, and has a large volume of distribution. Plasma protein binding ranges from 49 to 65%. It is eliminated by biliary excretion, mainly as unchanged drug, with 82% of the dose in the faeces and 9% in the urine. The mean elimination half-life is about 40 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Halaven; ***Belg.***: Halaven; ***Cz.***: Halaven; ***Denm.***: Halaven; ***Fin.***: Halaven; ***Fr.***: Halaven; ***Ger.***: Halaven; ***Gr.***: Halaven; ***Hung.***: Halaven; ***Irl.***: Halaven; ***Israel***: Halaven; ***Ital.***: Halaven; ***Jpn***: Halaven; ***Neth.***: Halaven; ***Norw.***: Halaven; ***Pol.***: Halaven; ***Port.***: Halaven; ***Singapore***: Halaven; ***Spain***: Halaven; ***Swed.***: Halaven; ***Switz.***: Halaven; ***UK***: Halaven; ***USA***: Halaven.

Erlotinib Hydrochloride

(BANM, USAN, rINNM)

CP-358774-01; Erlotinib, Chlorhydrate d'; Erlotinibi Hydrochloridum; Hidrocloruro de erlotinib; NSC-718781; OSI-774; Эрлотиниба Гидрохлорид.
N-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.
$C_{22}H_{23}N_3O_4$,HCl=429.9
CAS — 183321-74-6 (erlotinib); 183319-69-9 (erlotinib hydrochloride).
ATC — L01XE03.
UNII — DA87705X9K.

Uses and Administration

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor. It is used for the management of locally advanced or metastatic non-small cell lung cancer (p. 710.2) either in disease that is unresponsive to other therapy, or, in some

countries, as maintenance monotherapy in those with stable disease after platinum-based first-line chemotherapy. It is also used with gemcitabine in the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer (p. 712.1). It is given orally as the hydrochloride but doses are expressed in terms of the base: erlotinib hydrochloride 109 mg is equivalent to about 100 mg of erlotinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The usual dose for non-small cell lung cancer is 150 mg daily, taken at least 1 hour before or 2 hours after food. In the treatment of pancreatic cancer, the recommended dose is 100 mg daily, taken at least 1 hour before or 2 hours after food. Treatment is continued until disease progression or unacceptable toxicity occurs. Where dosage adjustment is necessary, reductions are made in 50 mg steps. Caution is advised in some patients with hepatic or renal impairment (see below).

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments of erlotinib are considered necessary.

- When used with a potent CYP3A4 inhibitor, the dose of erlotinib may need to be *reduced*, especially if severe adverse effects occur.
- When given with a potent CYP3A4 inducer, *increases* in the dose of erlotinib should be considered at 2-week intervals with monitoring. The maximum daily dose of erlotinib when used with rifampicin is 450 mg. If the inducer is then stopped, the erlotinib dose will need to be immediately reduced to the indicated starting dose.

Erlotinib is also under investigation in the treatment of malignant glioma.

References.

1. Perez-Soler R. The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4238s–4240s.
2. Pérez-Soler R, *et al*. Determinants of tumor response and survival with erlotinib in patients with non—small-cell lung cancer. *J Clin Oncol* 2004; **22:** 3238–47.
3. Anonymous. Erlotinib. *Med Lett Drugs Ther* 2005; **47:** 25–6.
4. Smith J. Erlotinib: small-molecule targeted therapy in the treatment of non-small-cell lung cancer. *Clin Ther* 2005; **27:** 1513–34.
5. Brown ER, Shepherd FA. Erlotinib in the treatment of non-small cell lung cancer. *Expert Rev Anticancer Ther* 2005; **5:** 767–75.
6. Shepherd FA, *et al*. Erlotinib in previously treated non—small-cell lung cancer. *N Engl J Med* 2005; **353:** 123–32.
7. Tang PA, *et al*. A review of erlotinib and its clinical use. *Expert Opin Pharmacother* 2006; **7:** 177–93.
8. Gridelli C, *et al*. Erlotinib in non-small-cell lung cancer. *Expert Opin Pharmacother* 2007; **8:** 2579–92.
9. Saif MW, *et al*. Erlotinib: the first biologic in the management of pancreatic cancer. *Expert Opin Pharmacother* 2008; **9:** 1595–1607.
10. Waller LL, *et al*. Using erlotinib to treat patients with non-small cell lung cancer who continue to smoke. *Lung Cancer* 2010; **67:** 12–16.
11. Steins M, *et al*. Erlotinib. *Recent Results Cancer Res* 2010; **184:** 21–31.
12. Iyer R, Bharthuar A. A review of erlotinib—an oral, selective epidermal growth factor receptor tyrosine kinase inhibitor. *Expert Opin Pharmacother* 2010; **11:** 311–20.
13. Cataldo VD, *et al*. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med* 2011; **364:** 947–55.
14. Mountzios G, Syrigos KN. A benefit-risk assessment of erlotinib in non-small-cell lung cancer and pancreatic cancer. *Drug Safety* 2011; **34:** 175–86.

Administration in hepatic or renal impairment. Erlotinib is metabolised by the liver. UK licensed product information states that although erlotinib exposure was similar in patients with moderate hepatic impairment (Child-Pugh score 7 to 9) compared with those with adequate hepatic function, caution is advised when using erlotinib in hepatic impairment. Dose reduction or interruption of therapy should be considered if adverse effects occur. Use in severe hepatic impairment is not recommended due to a lack of data.

UK licensed product information also states that no dose adjustments appear necessary in patients with mild to moderate renal impairment, but that use of erlotinib in patients with severe renal impairment is not recommended. There are no data available for patients with a creatinine clearance less than 15 mL/minute or those with a serum creatinine concentration greater than 1.5 times the upper normal limit.

Malignant neoplasms of the skin. Erlotinib has been reported to initially cause inflammation at the site of actinic keratoses, followed by partial regression.[1] A patient with nonresectable, refractory, locally aggressive keratoacanthoma centrifugum marginatum of the scalp, a squamous neoplasm known to be abundant in epidermal growth factor receptors (EGFR), was treated with erlotinib. No new lesions developed and an almost complete regression of existing lesions was seen after 2 months of treatment. The authors suggested that EGFR inhibitors such as erlotinib should be considered for well-differentiated EGFR-expressing squamous skin neoplasms, especially if lesions are recalcitrant, multiple, or surgically nonresectable.[2]

1. Hermanns J-F, *et al*. Erlotinib-responsive actinic keratoses. *Oncol Rep* 2007; **18:** 581–4.
2. Bulj TK, *et al*. Refractory aggressive keratoacanthoma centrifugum marginatum of the scalp controlled with the epidermal growth factor receptor inhibitor erlotinib. *Br J Dermatol* 2010; **163:** 633–7.

Adverse Effects, Treatment, and Precautions

The most common adverse effects associated with erlotinib hydrochloride are rash and diarrhoea. Generally, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun-exposed areas; protective clothing and/or use of sunscreen is advisable, and dose reduction may be needed. Bullous, blistering, and exfoliative skin conditions have been reported, including rare cases suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis, some of which were fatal; erlotinib therapy should be interrupted or stopped if such bullous symptoms occur. Moderate or severe diarrhoea should be treated with an appropriate antidiarrhoeal such as loperamide; dose reduction may be needed. In more severe or persistent cases leading to dehydration, therapy should be stopped temporarily. Hypokalaemia and renal failure (including fatalities) have been reported; some cases were secondary to dehydration or concurrent chemotherapy. Renal function and electrolytes should be monitored in patients at risk of dehydration.

Other common adverse effects include nausea, vomiting, stomatitis, gastrointestinal bleeding, abdominal pain, anorexia, alopecia, pruritus, dry skin, paronychia, conjunctivitis, epistaxis, and fatigue. Alterations in liver function tests have occurred. Rare cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported. Liver function should be periodically monitored, and treatment interrupted or stopped if liver function changes are severe. Interstitial lung disease has also been reported; again, deaths have occurred. Erlotinib treatment should be interrupted if unexplained pulmonary symptoms occur, such as dyspnoea, cough, and fever. Cases of gastrointestinal perforation, some fatal, have occurred; patients taking anti-angiogenic drugs, taxanes, corticosteroids, or NSAIDs or with a history of peptic ulcer or diverticular disease are at increased risk. Erlotinib should be permanently stopped if perforation occurs. Ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis can also occur, and are risk factors for corneal perforation or ulceration, which has been reported very rarely; erlotinib should be interrupted or stopped in the event of acute or worsening eye pain.

Effects on the ears. Bilateral eardrum perforation with resultant hearing loss has been reported after 1 year of therapy with oral erlotinib.[1] Dosage was reduced from 150 mg daily to 100 mg daily, and 6 months later the left tympanic membrane had healed.

1. Lee SM, *et al*. Bilateral eardrum perforation after long-term treatment with erlotinib. *J Clin Oncol* 2008; **26:** 2582–4.

Effects on the liver. Acute hepatitis developed in an elderly man 12 days after starting erlotinib; he was also taking metformin for type 2 diabetes mellitus. Lactic acidosis, which may have been exacerbated by the metformin, developed rapidly, and the patient died. Liver toxicity may be worse in frail elderly patients with comorbidities and multiple medications. Careful monitoring of liver function tests and renal function was advised.[1]

The manufacturers reported on fatalities that had occurred in patients with advanced solid tumours and moderate hepatic impairment as defined by the Child-Pugh criteria; 6 of 10 patients who died had baseline bilirubin values more than 3 times the upper normal limit (ULN), suggesting severe, rather than moderate, hepatic impairment. All patients had liver involvement such as hepatocellular carcinoma, cholangiosarcoma, or liver metastases, and the manufacturers warned that there may be limitations to using Child-Pugh criteria in an oncology population.[2] US licensed product information states that patients with hepatic impairment should be closely monitored and therapy interrupted or stopped if liver function changes are severe, such as doubling of total bilirubin and/or tripling of transaminases in patients with pretreatment values outside the normal range. Therapy should also be interrupted or stopped if total bilirubin is more than 3 times the ULN and/or transaminases are greater than 5 times the ULN in those with normal pretreatment values.

1. Pellegrinotti M, *et al*. Erlotinib-induced hepatitis complicated by fatal lactic acidosis in an elderly man with lung cancer. *Ann Pharmacother* 2009; **43:** 542–5.
2. Genentech, OSI. Important safety information (issued September 2008). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM135238.pdf (accessed 22/09/09)

Effects on the skin, hair, and nails. Reviews[1-3] of erlotinib-induced skin rash and its management, including discussion of its potential value as a surrogate marker of disease response. Isotretinoin plus clindamycin has been reported to be effective in treating erlotinib-induced rash;[4] aprepitant has been reported[5] to be effective in treating and preventing associated pruritus (for further information about aprepitant for pruritus, see p. 1822.3).

For reference to other cutaneous adverse effects of epidermal growth factor receptor inhibitors, including erlotinib, see Effects on the Skin, Hair, and Nails, under Cetuximab, p. 763.2.

1. Saif MW, *et al*. Erlotinib-induced skin rash. Pathogenesis, clinical significance and management in pancreatic cancer patients. *JOP* 2008; **9:** 267–74.
2. Tsimboukis S, *et al*. Erlotinib-induced skin rash in patients with non-small-cell lung cancer: pathogenesis, clinical significance, and management. *Clin Lung Cancer* 2009; **10:** 106–11.
3. Thatcher N, *et al*. UK Erlotinib Skin Toxicity Management Consensus Group. Expert consensus on the management of erlotinib-associated cutaneous toxicity in the UK *Oncologist* 2009; **14:** 840–7.
4. Bidoli P, *et al*. Isotretinoin plus clindamycin seem highly effective against severe erlotinib-induced skin rash in advanced non-small cell lung cancer. *J Thorac Oncol* 2010; **5:** 1662–3.
5. Vincenzi B, *et al*. Aprepitant for erlotinib-induced pruritus. *N Engl J Med* 2010; **363:** 397–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies erlotinib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, can increase erlotinib concentrations and use with potent inhibitors should be avoided as increased toxicity may occur. Conversely, CYP3A4 inducers, such as rifampicin, can reduce erlotinib concentrations and may reduce its efficacy. Dose adjustments may be required (see Uses and Administration, p. 788.3). Caution is also required with ciprofloxacin or potent inhibitors of CYP1A2, as erlotinib exposure may be increased, and dose reductions may be needed if adverse effects occur. Use with P-glycoprotein inhibitors such as ciclosporin and verapamil may cause altered distribution or elimination of erlotinib. Drugs that increase the pH of the gastrointestinal tract such as antacids, H_2-receptor antagonists, or proton pump inhibitors may reduce the solubility of erlotinib and hence lower its bioavailability. Use of proton pump inhibitors with erlotinib should be avoided. If the use of antacids or H_2-receptor antagonists cannot be avoided, dosing should be staggered; licensed product information recommends that antacids should be taken at least 4 hours before or 2 hours after erlotinib, and erlotinib at least 2 hours before or 10 hours after ranitidine. Exposure to erlotinib is reduced in smokers compared with non-smokers. Exposure to erlotinib may be increased by capecitabine.

Erlotinib is a strong inhibitor of glucuronidation by the uridine diphosphate glucuronosyltransferase isoenzyme UGT1A1 *in vitro* and may affect exposure to UGT1A1 substrates. Increased INR and bleeding events have been reported with erlotinib, some associated with the use of warfarin and some with the use of NSAIDs, see p. 1532.2 and p. 107.3, respectively.

Fibrates. Progression of lung adenocarcinoma in a patient treated with erlotinib was attributed to suboptimal exposure to erlotinib, and the dose was increased. Concomitant medications included escitalopram, alprazolam, and *fenofibrate*. Given the potential induction of cytochrome P450 isoenzyme CYP3A4 by fenofibrate, this was withdrawn; a reduction in erlotinib dosage was subsequently needed.

1. Mir O, *et al*. Drug-induced effects on erlotinib metabolism. *N Engl J Med* 2011; **365:** 379–80.

Tobacco smoking. Exposure to erlotinib is reduced in smokers (see Interactions, above). A study determined that the maximum tolerated dose of oral erlotinib was 300 mg daily in lung cancer patients who were also current smokers. Steady-state trough plasma concentrations and incidence of rash and diarrhoea were similar to those in other studies of former smokers or those who had never smoked, who were taking the usual recommended dose of 150 mg daily.[1]

1. Hughes AN, *et al*. Overcoming CYP1A1/1A2 mediated induction of metabolism by escalating erlotinib dose in current smokers. *J Clin Oncol* 2009; **27:** 1220–6.

Pharmacokinetics

Erlotinib is absorbed from the gastrointestinal tract, with a bioavailability of about 60%; this may increase up to almost 100% in the presence of food. Peak plasma concentrations occur about 4 hours after a dose, and it is about 93% bound to plasma proteins. Erlotinib is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP1A2. Metabolic pathways include demethylation, to metabolites OSI-420 and OSI-413, oxidation, and aromatic hydroxylation. Erlotinib has an elimination half-life of

about 36 hours. More than 80% of a dose is excreted as metabolites in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tarceva; ***Austral.***: Tarceva; ***Austria***: Tarceva; ***Belg.***: Tarceva; ***Braz.***: Tarceva; ***Canad.***: Tarceva; ***Chile***: Tarceva; ***China***: Tarceva (特罗凯); ***Cz.***: Tarceva; ***Denm.***: Tarceva; ***Fin.***: Tarceva; ***Fr.***: Tarceva; ***Ger.***: Tarceva; ***Gr.***: Tarceva; ***Hong Kong***: Tarceva; ***Hung.***: Tarceva; ***Indon.***: Tarceva; ***Irl.***: Tarceva; ***Israel***: Tarceva; ***Ital.***: Tarceva; ***Jpn***: Tarceva; ***Malaysia***: Tarceva; ***Mex.***: Tarceva; ***Neth.***: Tarceva; ***Norw.***: Tarceva; ***NZ***: Tarceva; ***Philipp.***: Tarceva; ***Pol.***: Tarceva; ***Port.***: Tarceva; ***Rus.***: Tarceva (Тарцева); ***S.Afr.***: Tarceva; ***Singapore***: Tarceva; ***Spain***: Tarceva; ***Swed.***: Tarceva; ***Switz.***: Tarceva; ***Thai.***: Tarceva; ***Turk.***: Tarceva; ***UK***: Tarceva; ***Ukr.***: Tarceva (Тарцева); ***USA***: Tarceva.

Estramustine Sodium Phosphate

(BANM, rINNM)

Estramustin Fosfat Sodyum; Estramustina, fosfato sódico de; Estramustine, Phosphate Sodique de; Estramustine Phosphate Sodium (USAN); Fosfato sódico de estramustina; Natrii Estramustini Phosphas; NSC-89199 (estramustine phosphate); Ro-22-2296/000 (estramustine); Ro-21-8837/001; Натрия Эстрамустина Фосфат.

Estra-1,3,5(10)-triene-3,17β-diol 3-[bis(2-chloroethyl)carbamate] 17-(disodium phosphate); Disodium 3-[bis(2-chloroethyl)-carbamoyloxy]estra-1,3,5(10)-trien-17β-yl orthophosphate.

$C_{23}H_{30}Cl_2NNa_2O_6P$=564.3

CAS — 2998-57-4 (estramustine); 4891-15-0 (estramustine phosphate); 52205-73-9 (estramustine sodium phosphate).

ATC — L01XX11.

ATC Vet — QL01XX11.

UNII — 75F375MT2N.

Pharmacopoeias. In *Br.*

BP 2014: (Estramustine Sodium Phosphate). A white or almost white powder. Freely soluble in water and in methyl alcohol; very slightly soluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 8.5 to 10.0. Protect from light.

Uses and Administration

Estramustine is a combination of estradiol and normustine, a homologue of chlormethine (p. 765.1). It has weaker oestrogenic activity than estradiol and weaker antineoplastic activity than most other alkylating agents. Estramustine phosphate is given orally as the disodium salt. Doses are calculated in terms of estramustine phosphate; 108 mg of estramustine sodium phosphate is equivalent to about 100 mg of estramustine phosphate. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Estramustine phosphate with meglumine has been given by intravenous injection.

Estramustine sodium phosphate is licensed for use in the treatment of advanced prostatic carcinoma (p. 712.3). An estramustine phosphate dose of about 14 mg/kg daily in divided doses is used. The usual initial dose is 560 to 840 mg daily, which may be adjusted to between 140 mg and 1.4 g daily according to the response and gastrointestinal tolerance. It should be given not less than 1 hour before or 2 hours after meals.

References.

1. Bergenheim AT, Henriksson R. Pharmacokinetics and pharmacodynamics of estramustine phosphate. *Clin Pharmacokinet* 1998; **34:** 163–72.
2. Sangrajrang S, *et al.* Estramustine resistance. *Gen Pharmacol* 1999; **33:** 107–13.
3. Kreis W, Budman D. Daily oral estramustine and intermittent intravenous docetaxel (Taxotere) as chemotherapeutic treatment for metastatic, hormone-refractory prostate cancer. *Semin Oncol* 1999; **26** (suppl 17): 34–8.
4. Kitamura T. Necessity of re-evaluation of estramustine phosphate sodium (EMP) as a treatment option for first-line monotherapy in advanced prostate cancer. *Int J Urol* 2001; **8:** 33–6.
5. Hamilton A, Muggia F. Estramustine potentiates taxane in prostate and refractory breast cancers. *Oncology (Huntingt)* 2001; **15** (suppl 7): 40–3.
6. Kitamura T, *et al.* EMP combination chemotherapy and low-dose monotherapy in advanced prostate cancer. *Expert Rev Anticancer Ther* 2002; **2:** 59–71.
7. Petrylak DP, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–20.
8. Fizazi K, *et al.* Meta-analysis of Estramustine in Prostate Cancer (MECaP) Trialists' Collaborative Group. Addition of estramustine to chemotherapy and survival of patients with castration-refractory prostate cancer: a meta-analysis of individual patient data. *Lancet Oncol* 2007; **8:** 994–1000.

Adverse Effects, Treatment, and Precautions

Oestrogenic adverse effects with estramustine are fairly common, and may include gynaecomastia, fluid retention, and cardiovascular effects. Gastrointestinal disturbances, hepatic dysfunction, loss of libido, hypersensitivity reactions, and occasionally leucopenia and thrombocytopenia may occur. Estramustine is contra-indicated in patients with peptic ulceration and severe hepatic or cardiovascular disease. Diabetes mellitus may be exacerbated, and the drug should be given with care to patients with disorders such as congestive heart failure, epilepsy, hypertension, migraine, and renal impairment which may be adversely affected by additional fluid retention. Care is also required in patients with conditions predisposing to hypercalcaemia, and serum calcium should be monitored in hypercalcaemic patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies estramustine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Estramustine sodium phosphate should not be given with milk products or products high in calcium, which may interfere with its absorption. Hypersensitivity reactions including angioedema have occurred rarely in patients given estramustine who were also receiving an ACE inhibitor.

Pharmacokinetics

Up to 75% of a dose of estramustine sodium phosphate is absorbed from the gastrointestinal tract and rapidly dephosphorylated. Estramustine is found in the body mainly as its oxidised isomer estromustine; both forms accumulate in the prostate. Some hydrolysis of the carbamate linkage occurs in the liver, releasing estradiol, estrone, and the normustine group. Estramustine and estromustine have plasma half-lives of 10 to 20 hours, and are excreted with their metabolites mainly in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Estracyt; Estranovag; Suloprost; Tratina†; ***Austria***: Estracyt; ***Belg.***: Estracyt; ***Canad.***: Emcyt; ***Chile***: Estracyt; ***China***: Estracyt (艾去适); ***Cz.***: Estracyt; ***Denm.***: Estracyt; ***Fin.***: Estracyt; ***Fr.***: Estracyt; ***Ger.***: cellmustin; Estracyt; Medactin†; Multosin; ***Gr.***: Estracyt; ***Hong Kong***: Estracyt; ***Hung.***: Estracyt; ***India***: Estramin; X-Trant; ***Irl.***: Estracyt†; ***Israel***: Estracyt; ***Ital.***: Estracyt; ***Jpn***: Estracyt; ***Malaysia***: Estracyt; ***Mex.***: Emcyt; ***Neth.***: Estracyt; ***Norw.***: Estracyt†; ***Pol.***: Estracyt; ***Port.***: Estracyt; ***Rus.***: Estracyt (Эстрацит); ***S.Afr.***: Estracyt; ***Singapore***: Estracyt; ***Spain***: Estracyt; ***Swed.***: Estracyt; ***Switz.***: Estracyt; ***Turk.***: Estracyt; ***UK***: Estracyt; ***Ukr.***: Estracyt (Эстрацит); ***USA***: Emcyt; ***Venez.***: Estracyt.

Pharmacopoeial Preparations

BP 2014: Estramustine Phosphate Capsules.

Etanidazole *(USAN, rINN)*

Etanidazol; Étanidazole; Etanidazolum; NSC-301467; SR-2508; Этанидазол.

N-(2-Hydroxyethyl)-2-nitroimidazole-1-acetamide.

$C_7H_{10}N_4O_4$=214.2

CAS — 22668-01-5.

UNII — 30DKA3Q1HL.

Profile

Etanidazole is a radiosensitiser, structurally related to metronidazole, that is under investigation as an adjunct to radiotherapy in the treatment of cancer. Peripheral neuropathy may be dose-limiting.

References.

1. Lee DJ, *et al.* Results of an RTOG phase III trial (RTOG 85-27) comparing radiotherapy plus etanidazole with radiotherapy alone for locally advanced head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1995; **32:** 567–76.
2. Eschwege F, *et al.* Results of a European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1997; **39:** 275–81.
3. Marcus KJ, *et al.* A phase I trial of etanidazole and hyperfractionated radiotherapy in children with diffuse brainstem glioma. *Int J Radiat Oncol Biol Phys* 2003; **55:** 1182–5.
4. Drzymala RE, *et al.* Radiation Therapy Oncology Group. A phase I-B trial of the radiosensitizer: etanidazole (SR-2508) with radiosurgery for the treatment of recurrent previously irradiated primary brain tumors or brain metastases (RTOG Study 95-02). *Radiother Oncol* 2008; **87:** 89–92.

Etoposide *(BAN, USAN, rINN)*

EPEG; Etoposid; Étoposide; Etoposidi; Etoposido; Etopósido; Etoposidum; Etopozid; Etopozidas; Etopozyd; NSC-141540; VP-16; VP-16-213; Этопозид.

4′-Demethylepipodophyllotoxin 9-[4,6-*O*-(*R*)-ethylidene-β-D-glucopyranoside]; (5*S*,5a*R*,8a*S*,9*R*)-9-(4,6-*O*-Ethylidene-β-D-glucopyranosyloxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

$C_{29}H_{32}O_{13}$=588.6

CAS — 33419-42-0.

ATC — L01CB01.

ATC Vet — QL01CB01.

UNII — 6PLQ3CP4P3.

NOTE. The trivial name epipodophyllotoxin has occasionally been used incorrectly for etoposide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Etoposide). A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers.

USP 36: (Etoposide). A fine, white to off-white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, in dichloromethane, and in ethyl acetate; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Etoposide Phosphate *(USAN)*

BMY-40481; Etopósido, fosfato de.

{5*R*-[5α,5aβ,8aα,9β(*R**)]}-5-[3,5-Dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydrofuro-[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one; 4′-Demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-β-D-glucopyranoside) 4′-(dihydrogen phosphate).

$C_{29}H_{33}O_{16}P$=668.5

CAS — 117091-64-2.

ATC — L01CB01.

ATC Vet — QL01CB01.

UNII — 528XYJ8L1N.

Incompatibility. For reference to precipitation when mannitol or potassium chloride was added to mixtures of etoposide and cisplatin in sodium chloride injection, see Cisplatin, p. 766.1.

For incompatibility of etoposide formulations with various plastics see Administration, p. 791.1.

Stability. UK licensed product information states that etoposide (diluted to a concentration of 200 or 400 micrograms/mL) has been shown to be physically and chemically stable for 24 hours at 15 degrees to 25 degrees. For microbiological reasons, the diluted solution should be used immediately; if not immediately used, the solution should not be stored longer than 12 hours at 15 degrees to 25 degrees, unless it has been diluted under aseptic conditions.

US licensed product information states that etoposide, diluted to a concentration of 200 or 400 micrograms/mL, is stable for 96 and 24 hours, respectively, at room temperature (25 degrees) under normal fluorescent light in either glass or plastic containers.

Etoposide phosphate, after reconstitution and further dilution, can be stored under refrigeration (at 2 degrees to 8 degrees) or at room temperature (20 degrees to 25 degrees) for 24 hours.

Uses and Administration

Etoposide is a semisynthetic derivative of podophyllotoxin with antineoplastic properties; it interferes with the function of topoisomerase II thus inhibiting DNA synthesis, and is most active against cells in the late S and G_2 phases of the cell cycle.

It is used, usually with other antineoplastics, in the treatment of tumours of the testis, small cell cancer of the lung, and in acute leukaemias. It has also been tried in other solid tumours including those of the brain, gastrointestinal tract, ovary, and thymus, and some childhood neoplasms; in lymphomas, and in the treatment of Kaposi's sarcoma associated with AIDS. For further discussion, see the cross-references indicated under Malignant Neoplasms, p. 791.2.

Etoposide may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Etoposide is given by slow intravenous infusion over at least 30 minutes, as a solution in sodium chloride 0.9% or glucose 5% injection. In general, the concentration of the infusion should be between 200 to 400 micrograms/mL, although recommendations vary depending on the preparation; precipitation may occur at higher concentrations. Etoposide phosphate, a prodrug, has improved solubility in water. 113.6 mg of etoposide phosphate is equivalent to 100 mg of etoposide. Intravenous doses are calculated in terms of etoposide, and are identical to those of the base, but it may be given in concentrations up to the

equivalent of etoposide 20 mg/mL. Etoposide phosphate solutions may be infused over 5 minutes to 3.5 hours.

Regimens vary; the usual *intravenous* dose of etoposide ranges from 50 to 120 mg/m^2 daily for 5 days. Somewhat lower doses have been suggested in lung cancer. Alternatively, 100 mg/m^2 has been given on alternate days to a total of 300 mg/m^2. The usual *oral* dose of etoposide is 100 to 240 mg/m^2 daily for 5 consecutive days. Courses may be repeated after 3 to 4 weeks. Doses should be reduced in renal impairment (see below).

Administration. Although precipitation of etoposide may occur at high infusion concentrations (see Uses and Administration, p. 790.3), high doses of etoposide have been infused undiluted to avoid giving large volumes of fluid to the patient.[1-3] Etoposide was infused through a central line, and this method has been reported to be safe and effective;[2] pharmacokinetic studies suggested unaltered systemic bioavailability when compared with diluted infusions.[3] However, cracking of plastic syringes and infusion cassettes has been reported, possibly due to the polyethylene glycol component of the formulation. This appears particularly problematic when devices containing ABS plastic (a polymer produced from acrylonitrile, butadiene, and styrene) are used; alternative devices may be preferable.[1] Leaching of the plasticiser diethylhexyl phthalate (which is potentially toxic and carcinogenic) from PVC bags and tubing has been reported with etoposide, and it has been suggested that these should also not be used if possible when preparing and giving the drug.[4]

Etoposide has been injected into the ventricles of the brain in the treatment of patients with neoplastic meningitis.[5]

1. Schwinghammer TL, *et al.* Cracking of ABS plastic devices used to infuse undiluted etoposide injection. *Am J Hosp Pharm* 1988; **45:** 1277.
2. Creger RJ, *et al.* Infusion of high doses of undiluted etoposide through central venous catheters during preparation for bone marrow transplantation. *Cancer Invest* 1990; **8:** 13–16.
3. Ehninger G, *et al.* Unaltered pharmacokinetics after the administration of high-dose etoposide without prior dilution. *Cancer Chemother Pharmacol* 1991; **28:** 214–16.
4. de Lemos ML, *et al.* Leaching of diethylhexyl phthalate from polyvinyl chloride materials into etoposide intravenous solutions. *J Oncol Pharm Pract* 2005; **11:** 155–7.
5. Chamberlain MC, *et al.* Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer* 2006; **106:** 2021–7.

Administration in the elderly. Increasing age was reported to correlate with higher etoposide concentrations during oral therapy; increasing age and higher etoposide concentrations also correlated with lower white blood cell and absolute neutrophil counts.[1] A review noted that, compared with intravenous etoposide, there is more variability in the pharmacokinetics and toxicity of oral etoposide, and the oral route may appear less effective and more toxic as a result. In elderly patients taking etoposide, a small dose reduction and careful monitoring has thus been advised, even in those with normal renal and hepatic function.[2]

1. Miller AA, *et al.* Pharmacology of 21-day oral etoposide given in combination with i.v. cisplatin in patients with extensive-stage small cell lung cancer: a cancer and leukemia group B study (CALGB 9062). *Clin Cancer Res* 1997; **3:** 719–25.
2. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. Some licensed product information for etoposide or etoposide phosphate recommends that patients with a creatinine clearance of between 15 and 50 mL/minute be given 75% of the recommended dose. No recommendations are given for those patients having a creatinine clearance of below 15 mL/minute, although one product (*Vepesid; BMS, USA*) suggests that further dose reduction in these patients be considered.

Histiocytic syndromes. Systemic chemotherapy is often tried in patients with extensive Langerhans-cell histiocytosis (p. 692.1), although its value is uncertain. Etoposide is one of the drugs widely used for this purpose.

Hypereosinophilic syndrome. Etoposide has been reported to produce clinical responses in patients with the hypereosinophilic syndrome.[1]

1. Bourrat E, *et al.* Etoposide for treating the hypereosinophilic syndrome. *Ann Intern Med* 1994; **121:** 899–900.

Influenza. A patient was diagnosed with pandemic (H1N1) 2009 influenza infection (p. 960.2). During the course of this, he developed secondary haemophagocytic lymphohistiocytosis, and was treated with etoposide and betamethasone. He had a prompt clinical response within one week. It has been hypothesised that cytotoxic therapy might be beneficial for severe influenza infection, and the authors suggested that further studies in this area are needed.[1]

1. Henter J-I, *et al.* Cytotoxic therapy for severe swine flu A/H1N1. *Lancet* 2010; **376:** 2116.

Malignant neoplasms. Etoposide has been used for a variety of solid tumours: in particular it is part of curative regimens used in the treatment of testicular cancer and germ-cell tumours of the ovary (see p. 715.1 and p. 711.2), and is used with cisplatin and other drugs in the treatment of lung cancer (p. 710.2). Other solid neoplasms in which it is sometimes employed include those of the brain (p. 701.2), stomach (p. 706.1), and thymus (p. 715.3), as well as in neuroblastoma (p. 716.2), Wilms' tumour (p. 709.1), retinoblastoma (p. 717.2), and rhabdomyosarcoma (p. 718.2); it has also formed part of systemic regimens for bone sarcomas (p. 717.3), disseminated Kaposi's sarcoma (see p. 718.1), and gestational trophoblastic tumours (p. 691.2). Etoposide is used in regimens for Hodgkin's disease (see p. 696.1); it is also sometimes used in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p. 696.3), and may produce short-term responses in mycosis fungoides (p. 698.3). It is also used in Burkitt's lymphoma (p. 697.3). Etoposide may have benefits when added to induction protocols for acute myeloid leukaemia (p. 693.1), and when used as part of intensification therapy in acute lymphoblastic leukaemia (p. 692.3). It has formed part of salvage regimens in multiple myeloma (p. 699.2).

Vasculitic syndromes. For mention of the use of etoposide to induce remission in patients with Wegener's granulomatosis resistant to standard therapy with cyclophosphamide and corticosteroids, see p. 1615.2.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The dose-limiting toxicity of etoposide is myelosuppression, mainly seen as leucopenia, but also thrombocytopenia, and sometimes anaemia. The nadir of the granulocyte count usually occurs 7 to 14 days after a dose, with recovery by about 21 days. Nausea and vomiting are common; there may also be anorexia, diarrhoea, and mucositis. Gastrointestinal toxicity may be more common after oral dosage. Reversible alopecia occurs in about two-thirds of all patients. Hypersensitivity or anaphylactoid reactions can occur, characterised by flushing, chills, fever, tachycardia, bronchospasm, dyspnoea, and hypotension. Apnoea and fatal reactions associated with bronchospasm have been reported. Peripheral or central neuropathies, including transient cortical blindness, have been reported rarely, as have weakness, fatigue, somnolence, aftertaste, fever, rashes, urticaria, skin pigmentation, pruritus, and dysphagia. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. Tumour lysis syndrome, sometimes fatal, has been reported after use of etoposide with other chemotherapeutic drugs. Disturbances of liver function have been reported, mainly at high doses. There have been occasional reports of cardiotoxicity. Local irritation and thrombophlebitis may occur at the site of injection. Care should be taken to avoid extravasation although tissue damage (possibly associated with the vehicle) is rare.

Rapid intravenous doses may cause hypotension; etoposide should be given by infusion over at least 30 minutes. Etoposide should not be given to patients with severe hepatic impairment nor by the intracavitary route.

Some adverse effects associated with intravenous etoposide may be due to the formulation of the vehicle.

There is evidence that etoposide may be associated with the development of secondary leukaemias—see Carcinogenicity, p. 726.2.

Breast feeding. Some licensed product information states that it is unknown whether etoposide is excreted into breast milk. However, in breast milk samples from a woman given consolidation therapy, including etoposide,[1] for acute promyelocytic leukaemia, etoposide concentrations were maximal just after a dose, but decreased rapidly to undetectable levels within 24 hours on each of three days. She started to breast feed her baby 3 weeks after the completion of therapy, and no abnormalities were seen in the infant up to 16 months of age. It has been suggested[2] that breast feeding be withheld for 24 to 36 hours after a dose.

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; **48:** 131–2.
2. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Effects on the gastrointestinal tract. Pneumatosis intestinalis (the presence of gas within the bowel wall), a rare condition, has been reported after intravenous[1] and oral[2] etoposide. It is supposed that myelosuppressive drugs might interfere with the mucosal integrity of the intestinal tract, and that the intestinal mucosa might be highly sensitive to etoposide.

1. Hashimoto S, *et al.* Pneumatosis cystoides intestinalis after chemotherapy for hematological malignancies: report of 4 cases. *Intern Med* 1995; **34:** 212–15.
2. Shih I-L, *et al.* Pneumatosis coli after etoposide chemotherapy for breast cancer. *J Clin Oncol* 2007; **25:** 1623–5.

Effects on the nervous system. A report of an acute dystonic reaction in a child given etoposide as part of a combined maintenance regimen for acute lymphoblastic leukaemia;[1] the patient had been receiving the same regimen uneventfully for over a year but symptoms (which responded to diphenhydramine) recurred on rechallenge with etoposide.

1. Ascher DP, Delaney RA. Acute dystonia from etoposide. *DrugIntell Clin Pharm* 1988; **22:** 41–2.

Handling and disposal. *Urine and faeces* produced for up to 4 and 7 days respectively after a dose of etoposide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hypersensitivity. Hypersensitivity reactions to intravenous etoposide are characterised by one or more of: hypotension, bronchospasm, flushing, exanthema, dyspnoea, fever, chills, tachycardia, tightness in the chest, cyanosis, and hypertension. Although originally thought rare, some investigators[1] have reported an incidence of up to about 50%, particularly in younger patients. The mechanism is uncertain, but a literature review[1] supported the hypothesis that it might not be antibody-mediated, since reducing the rate of infusion can prevent reactions, as can reducing etoposide concentration in the infusion solution. However, an immunogenic mechanism cannot be excluded as hypersensitivity appears to have been reported less frequently with the oral formulation, which unlike the infusion does not contain polysorbate 80. In addition, there are reports[2-4] of successful use of etoposide phosphate formulations (which do not contain polysorbate 80) after hypersensitivity reactions to etoposide, suggesting that the solvent may be responsible. Successful desensitisation in a patient hypersensitive to etoposide has been reported.[5]

1. Hoetelmans RMW, *et al.* Hypersensitivity reactions to etoposide. *Ann Pharmacother* 1996; **30:** 367–71.
2. Bernstein BJ, Troner MB. Successful rechallenge with etoposide phosphate after an acute hypersensitivity reaction to etoposide. *Pharmacotherapy* 1999; **19:** 989–91.
3. Siderov J, *et al.* Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. *Br J Cancer* 2002; **86:** 12–13.
4. Collier K, *et al.* Successful treatment with etoposide phosphate in patients with previous etoposide hypersensitivity. *J Oncol Pharm Pract* 2008; **14:** 51–5.
5. Alvarez Cardona A, *et al.* Desensibilización para etopósido: comunicación de un caso. *Rev Alerg Mex* 2010; **57:** 33–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etoposide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. A 22-year-old woman, who was diagnosed with acute myelogenous leukaemia at 20 weeks of gestation, was treated with combination chemotherapy including cytarabine and daunorubicin at 22 weeks, but the response was unsatisfactory, and the regimen was altered to cytarabine, mitoxantrone, and etoposide at 31 weeks. After the second course of chemotherapy was completed, an intermittent sinusoidal fetal heart rate pattern was detected, along with intra-uterine fetal growth retardation. Complete remission was achieved at 35 weeks and a caesarean section was performed a week later due to fetal distress. The neonate was underweight and had pancytopenia requiring blood transfusion and antibacterial therapy; he was discharged at 2 months of age in good health. The authors concluded that the fetal sinusoidal heart rate pattern may have been induced by tissue hypoxia due to severe anaemia, and that the leucopenia and thrombocytopenia resulted from bone marrow suppression caused by the transplacental effects of maternal chemotherapy; they considered that mitoxantrone and etoposide might be responsible for the neonatal pancytopenia.[1]

For a report of hair loss in an infant, attributed to etoposide given to the mother before delivery, see Pregnancy, under Cisplatin, p. 768.2.

1. Hsu K-F, *et al.* Sinusoidal fetal heart rate pattern during chemotherapy in a pregnant woman with acute myelogenous leukemia. *J Formos Med Assoc* 1995; **94:** 562–5.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Phenylbutazone, salicylic acid, and sodium salicylate can affect the protein binding of etoposide.

Caution is advised when etoposide phosphate is given with drugs such as levamisole hydrochloride that are known to inhibit phosphatase activities.

Antineoplastics. Giving etoposide 2 days after a dose of *cisplatin* was associated with a marked decrease in etoposide clearance and more toxicity, compared with the same dose given 21 days after a dose of cisplatin, in a study involving 17 children.[1] There was no evidence of a persistent decrease in etoposide clearance associated with the cumulative dose of cisplatin, however. In a randomised, crossover study,[2] cisplatin or *carboplatin* were given alternately during 2 courses of etoposide. Although increases in the area under the concentration-time curve of etoposide were seen in the second course, effects were modest and, given the pharmacokinetic variability seen with etoposide, the authors considered any clinical impact to be small.

1. Relling MV, *et al.* Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther* 1994; **56:** 503–11.
2. Thomas HD, *et al.* Randomized cross-over clinical trial to study potential pharmacokinetic interactions between cisplatin or carboplatin and etoposide. *Br J Clin Pharmacol* 2002; **53:** 83–91.

Ciclosporin. High-dose ciclosporin therapy was found to increase the exposure to etoposide by 80%, and to reduce etoposide clearance by 38%. Leucopenia was increased. Etoposide doses should be halved when the drug is given with high-dose ciclosporin.[1] In a study[2] of children who received etoposide and mitoxantrone for acute myeloid leukaemia, the addition of ciclosporin with a 40% reduction in the doses of the antineoplastics still resulted in a 71% reduction in the clearance of etoposide, and a 42% reduction for mitoxantrone. However, there was wide interpatient variability, and the rates of stomatitis and infection were similar between the groups, with or without ciclosporin.

1. Lum BL, *et al.* Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate drug resistance. *J Clin Oncol* 1992; **10:** 1635–42.
2. Lacayo NJ, *et al.* Pharmacokinetic interactions of cyclosporine with etoposide and mitoxantrone in children with acute myeloid leukemia. *Leukemia* 2002; **16:** 920–7.

Grapefruit juice. In a randomised crossover study[1] of 6 patients, grapefruit juice appeared to reduce the oral bioavailability of etoposide. Initially the authors had expected the opposite since etoposide is demethylated by cytochrome P450 isoenzyme CYP3A4. Although no definite conclusions could be made due to the small number of patients studied, a possible mechanism might have been alteration of P-glycoprotein mediated transport.

1. Reif S, *et al.* Effect of grapefruit juice intake on etoposide bioavailability. *Eur J Clin Pharmacol* 2002; **58:** 491–4.

Pharmacokinetics

Absorption after oral doses is variable, but on average about 50% of the dose of etoposide is absorbed. The pharmacokinetics of etoposide are subject to considerable interindividual variation. It is rapidly distributed, and concentrations in plasma fall in a biphasic manner, with a terminal half-life of 4 to 11 hours. Etoposide is about 94% bound to plasma protein. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Etoposide is excreted in urine and faeces as unchanged drug and metabolites: about 45% of a dose is reported to be excreted in urine over 72 hours. It crosses the blood-brain barrier poorly; concentrations in CSF are 1 to 10% of those in plasma. It is distributed into breast milk (see Breast Feeding, p. 791.2).

References.

1. Toffoli G, *et al.* Pharmacokinetic optimisation of treatment with oral etoposide. *Clin Pharmacokinet* 2004; **43:** 441–66.
2. Schieveen PG, *et al.* Suivi thérapeutique pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique de l'étoposide administré par voie orale. *Therapie* 2010; **65:** 207–12.

Metabolism. Studies *in vitro* suggested that metabolic activation of etoposide by oxidation into the *O*-quinone derivative might play an essential role in its activity against DNA.[1]

1. van Maanen JMS, *et al.* Metabolic activation of anti-tumour agent VP 16-213. *Hum Toxicol* 1986; **5:** 136.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Citodox†; Etocris; Euvaxon; Neoplaxol; Percas†; Vepesid; VP-Gen; ***Austral.***: Etopophos; Vepesid; ***Austria***: Etopofos; Vepesid; ***Belg.***: Celltop; Eposin; Vepesid; ***Braz.***: Eposido; Etomorase; Etosin†; Eunades; Nexvep; Posidon; Tevaetopo; Vepesid; ***Canad.***: Vepesid; ***Chile***: Epsidox; ***China***: Bo Rui (泊瑞); Etopophos (凡毕复); Lastet (拉司太特); Vepesid (凡毕士); Wei Ke (威克); ***Cz.***: Lastet†; Vepesid†; ***Denm.***: Eposid; Etopofos†; Vepesid; ***Fin.***: Eposin; Etopofos†; Vepesid; ***Fr.***: Celltop; Etopophos; Vepeside†; ***Ger.***: Eto-cell; Eto-Gry; Etomedac; Etopophos; Lastet; Neoposid†; Riboposid; Vepesid; ***Gr.***: Celltop; Etobion; Etopofos; Vepesid; ***Hong Kong***: Sintopozid; Vepesid†; ***Hung.***: Lastet†; Sintopozid; Vepesid†; ***India***: Actitop; Beposid; Bioposide; Eside; Ethopul; Etolon; Etosid; Fytop; Fytosid; Lastet; Oncosid; Posid; ***Indon.***: Etopul; Posyd; ***Irl.***: Etopophos; Vepesid; ***Ital.***: Lastet†; Vepesid; ***Jpn***: Lastet; ***Malaysia***: Eposin; Lastet; ***Mex.***: Cryosid; Etonco†; Etopos†; Kenazol†; Tosuben; Vepesid; VP-Tec; ***Neth.***: Eposin; Etomedac; Toposin; Vepesid; ***Norw.***: Eposin; Etopofos†; Vepesid; ***NZ***: Etopophos; Vepesid; ***Philipp.***: Etopoxan†; Etopul; Fytosid; Lastet; Posid; Topresid; Vepesid†; ***Pol.***: Lastet†; Sintopozid†; Vepesid; ***Port.***: Eposin; Vepesid†; ***Rus.***: Cytoposid (Цитопозид); Fytosid (Фитозид); Lastet (Ластет); Vepesid (Вепезид); ***S.Afr.***: Eposin; Etopophos†; Vepesid; ***Singapore***: Ebeposide; Lastet; Vepesid; ***Spain***: Vepesid; ***Swed.***: Eposin; Etopofos; Vepesid; ***Switz.***: Etopophos; Vepesid; ***Thai.***: Eposin; Etopos; Fytosid; Lastet; Topo; Vepesid†; ***Turk.***: Eposin; Etosid; Lastet; Vepesid; ***UK***: Eposin; Etopophos; Vepesid; ***USA***: Etopophos; Toposar; Vepesid; ***Venez.***: Etonolver; Etosid; Fytosid.

Pharmacopoeial Preparations
BP 2014: Etoposide Capsules; Etoposide Infusion;
USP 36: Etoposide Capsules; Etoposide Injection.

Exemestane *(BAN, USAN, rINN)* ⊗

Eksemestaani; Eksemestan; Exemestan; Exémestane; Exemestano; Exemestanum; FCE-24304; Эксеместан.
6-Methyleneandrosta-1,4-diene-3,17-dione.
$C_{20}H_{24}O_2$=296.4
CAS — 107868-30-4.
ATC — L02BG06.
ATC Vet — QL02BG06.
UNII — NY22HMQ4BX.

Uses and Administration

Exemestane is a selective inhibitor of the aromatase (oestrogen synthetase) system responsible for the conversion of androgens to oestrogens in peripheral tissues, but unlike anastrozole (p. 742.2) or letrozole (p. 817.2) it has a steroidal structure. It is used in the treatment of advanced breast cancer (p. 702.1), in postmenopausal women who are no longer responsive to anti-oestrogen therapy. It is also used for adjuvant treatment of postmenopausal women with oestrogen-receptor positive early breast cancer, after 2 to 3 years of initial adjuvant tamoxifen treatment; a total of 5 years of adjuvant hormonal therapy should be given. The recommended oral dose is 25 mg once daily, preferably after a meal.

In patients receiving potent inducers of the cytochrome P450 isoenzyme CYP3A4 (such as rifampicin or phenytoin), the recommended oral dose of exemestane is 50 mg once daily, after a meal.

References.

1. Coombes RC, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350:** 1081–92. Corrections. *ibid.*; **351:** 2461 and *ibid.* 2006; **355:** 1746.
2. Bertelli G, *et al.* Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology* 2006; **69:** 471–7.
3. Bundred N. The evolving role of exemestane in the management of breast cancer. *Br J Hosp Med* 2006; **67:** 427–30.
4. Coombes RC, *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; **369:** 559–70. Correction. *ibid.*; 906.
5. Paridaens RJ, *et al.* Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008; **26:** 4883–90.
6. Deeks ED, Scott LJ. Exemestane: a review of its use in postmenopausal women with breast cancer. *Drugs* 2009; **69:** 889–918.
7. Nabholtz JM, *et al.* Comparative review of anastrozole, letrozole and exemestane in the management of early breast cancer. *Expert Opin Pharmacother* 2009; **10:** 1435–47.
8. Glück S. Exemestane as first-line therapy in postmenopausal women with recurrent or metastatic breast cancer. *Am J Clin Oncol* 2010; **33:** 314–19.
9. Bertelli G, Gangadhara S. Exemestane in postmenopausal women with early or advanced breast cancer: a review. *Expert Opin Pharmacother* 2010; **11:** 1933–42.
10. Goss PE, *et al.* NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; **364:** 2381–91.

Adverse Effects and Precautions

The adverse effects of exemestane are similar to those seen with other aromatase inhibitors such as anastrozole (p. 742.3), and similar precautions should be taken. Fatigue and increased sweating are common with exemestane. Visual disturbances have been reported. Thrombocytopenia and leucopenia have been reported rarely. For the suggestion that exemestane may have more pro-atherogenic effects on blood lipids than anastrozole or letrozole, see below.

Breast feeding. Studies show that exemestane is distributed into the milk of *rats*. Licensed product information states that it is unknown whether exemestane is excreted into human milk; in the UK use during breast feeding is contra-indicated while in the USA a decision may be made based on clinical judgement. It has been suggested[1] that breast feeding be stopped if using multiple doses of exemestane, and to withhold breast feeding for at least 5 days after the last dose.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Effects on blood lipids. A comparison of the adverse effects of letrozole, anastrozole, and exemestane in postmenopausal women indicated[1] that although all 3 had similar effects on markers of bone turnover, exemestane was associated with a markedly greater decrease in high-density lipoprotein (HDL) cholesterol. This resulted in an increase in the atherogenic ratio of low-density (LDL) to HDL-cholesterol. Since some studies have suggested that low HDL-cholesterol may be a more important risk factor for cardiovascular disease in women than men it was suggested that further study was needed to see if this difference had clinical significance.

1. McCloskey EV, *et al.* Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. *Eur J Cancer* 2007; **43:** 2523–31.

Effects on the musculoskeletal system. Exemestane therapy has been found to decrease bone mineral density (BMD) in postmenopausal women with early breast cancer.[1,2] In one study, the decrease in BMD was seen within 6 months of switching therapy from tamoxifen, and was significant at the lumbar spine and hip.[2] In a Scandinavian study, BMD loss with exemestane compared with placebo was modest from the femoral neck, and not significant at the lumbar spine;[1] however, it was noted that the changes in the placebo group were greater than expected, possibly due to the lack of calcium and vitamin D supplementation, and that there is a high incidence of hip fracture in Scandinavia. Patients starting exemestane therapy should be assessed for baseline BMD;[1] while those with normal BMD are considered to not need further assessment beyond lifestyle advice, those with osteopenia should have their BMD monitored, and therapeutic interventions made as appropriate.[2]

See also Effects on the Musculoskeletal System, under Anastrozole, p. 743.1.

1. Lønning PE, *et al.* Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005; **23:** 5126–37.
2. Coleman RE, *et al.* Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; **8:** 119–27.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies exemestane as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

The metabolism of exemestane is mediated by the cytochrome P450 isoenzyme CYP3A4. Rifampicin, a potent inducer of CYP isoenzymes, can decrease plasma concentrations of exemestane. Use with other drugs that induce this isoenzyme may reduce the efficacy of exemestane; dose adjustments are recommended in these patients (see Uses and Administration, above). Exemestane should also be used cautiously with drugs that are substrates for CYP3A4 and that have a narrow therapeutic index. Significant effects on exemestane clearance by cytochrome P450 isoenzyme inhibitors are considered unlikely. Exemestane should not be given with oestrogen-containing drugs as these would negate its pharmacological action.

Pharmacokinetics

Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is 90% bound to plasma proteins. It is metabolised via oxidation by the cytochrome P450 isoenzyme CYP3A4, and via reduction by aldoketoreductase. Metabolites are excreted in the urine and faeces, and less than 1% of a dose is excreted unchanged in the urine. Exemestane has a terminal elimination half-life of about 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aromasin; Noxetol; ***Austral.***: Aromasin; ***Austria***: Aromasin; ***Belg.***: Aromasin; ***Braz.***: Aromasin; ***Canad.***: Aromasin; ***Chile***: Aromasin; ***China***: Ao Qi (澳奇); Aromasin (阿诺新); Ke Yi (可怡); Ru Su Mei (如苏美); Su Lai (速莱); Yi Si Tan (依斯坦); You Ke Yi (优可依); ***Cz.***: Aromasin; Astexana; Exestea; Funamel; Greca; Mexinat; Netamise; Sarivanil; ***Denm.***: Aremedan; Aromasin; Exemasin; Glandex; Memelin†; Nosteron†; ***Fin.***: Aromasin; Xemestan; ***Fr.***: Aromasine; ***Ger.***: Aromasin; Exemed; Exemedac; Exestan; ***Gr.***: Aromasin; ***Hong Kong***: Aromasin; ***Hung.***: Aromasin; Exemin; Mexezon; ***Indon.***: Aromasin; ***Irl.***: Aromasin; ***Israel***: Aromasin; ***Ital.***: Aromasin; Exegen; Piextane; ***Malaysia***: Aromasin; ***Mex.***: Aromasin; ***Neth.***: Aromasin; Exanidon; Exemedica; Exeregio; Memelin†; Nateran; ***Norw.***: Aromasin; ***NZ***: Aromasin; Exaccord; Mestane; ***Philipp.***: Aromasin; ***Pol.***: Aromasin; Nosteron; ***Port.***: Aromasin; ***Rus.***: Aromasin (Аромазин); Aromeston (Ароместон); ***S.Afr.***: Aromasin; ***Singapore***: Aromasin; ***Spain***: Aromasil; Gepex; ***Swed.***: Aromasin; ***Switz.***: Aromasin; ***Thai.***: Aromasin; ***Turk.***: Aromasin; ***UK***: Aromasin; ***Ukr.***: Aromasin (Аромазин); ***USA***: Aromasin; ***Venez.***: Aromasin.

Exisulind *(rINN)*

Exisulindum; FGN-1; Sulfona de sulindac; Sulindac Sulfone; Эксисулинд.

5-Fluoro-2-methyl-1-[(*Z*)-*p*-(methylsulfonyl)benzylidene] indene-3-acetic acid.

$C_{20}H_{17}FO_4S$=372.4

CAS — 59973-80-7.

UNII — K619IIG2R9.

NOTE. The names Aptosyn and Prevatec have been used as trade marks for exisulind.

Profile

Exisulind is a sulfone metabolite of sulindac (p. 134.2) that is reported to induce apoptosis in cancerous and precancerous cells. It has been studied for the treatment of familial adenomatous polyposis, with variable results. It is also being investigated for the prevention and treatment of malignant neoplasms, including those of the breast, prostate, and lung.

References.

1. Goluboff ET. Exisulind, a selective apoptotic antineoplastic drug. *Expert Opin Invest Drugs* 2001; **10:** 1875–82.
2. Webster WS, Leibovich BC. Exisulind in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2005; **5:** 957–62.
3. Arber N, *et al*. Sporadic adenomatous polyp regression with exisulind is effective but toxic: a randomised, double blind, placebo controlled, dose-response study. *Gut* 2006; **55:** 367–73.

Ezatiostat Hydrochloride *(USAN, rINNM)*

Ézatiostat, Chlorhydrate d'; Ezatiostati Hydrochloridum; Hidrocloruro de ezatiostat; TER-199; TLK-199; Эзатиостата Гидрохлорид.

Ethyl (2*R*)-[(4*S*)-4-amino-5-ethoxy-5-oxopentanoyl]-*S*-benzyl-L-cysteinyl-2-phenylglycinate hydrochloride.

$C_{27}H_{35}N_3O_6S$,HCl=566.1

CAS — 286942-97-0.

UNII — D59N834676.

NOTE. The name Telintra has been used as a trade mark for ezatiostat.

Profile

Ezatiostat hydrochloride is an inhibitor of glutathione S-transferase P1-1. It is under investigation in the treatment of myelodysplastic syndrome and has been granted orphan drug status in the USA. Ezatiostat has been given orally and intravenously. Adverse effects following oral use have included nausea, diarrhoea, vomiting; chills, back pain, and flushing were seen following intravenous use. Ezatiostat has also been investigated in the treatment of idiopathic chronic neutropenia.

References.

1. Quddus F, *et al*. Oral ezatiostat HCl (TLK199) and myelodysplastic syndrome: a case report of sustained hematologic response following an abbreviated exposure. *J Hematol Oncol* 2010; **3:** 16.
2. Raza A, *et al*. A phase 2 randomized multicenter study of 2 extended dosing schedules of oral ezatiostat in low to intermediate-1 risk myelodysplastic syndrome. *Cancer* 2012; **118:** 2138–47.
3. Lyons RM, *et al*. Oral ezatiostat HCl (Telintra, TLK199) and idiopathic chronic neutropenia (ICN): a case report of complete response of a patient with G-CSF resistant ICN following treatment with ezatiostat, a glutathione S-transferase P1-1 (GSTP1-1) inhibitor. *J Hematol Oncol* 2011; **4:** 43.

Fadrozole Hydrochloride *(USAN, rINNM)* ⊗

CGS-16949 (fadrozole); CGS-16949A; Fadrozol, hidrocloruro de; Fadrozole, Chlorhydrate de; Fadrozoli Hydrochloridum; Hidrocloruro de fadrozol; Фадрозола Гидрохлорид.

(±)-*p*-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile monohydrochloride.

$C_{14}H_{13}N_3$,HCl=259.7

CAS — 102676-47-1 (fadrozole); 102676-96-0 (fadrozole hydrochloride).

UNII — H0Q44H4ECQ.

Profile

Fadrozole hydrochloride is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p. 742.1). It has been used for the treatment of breast cancer.

References.

1. Buzdar AU, *et al*. Fadrozole HCl (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma: results of two randomized double blind controlled multiinstitutional trials. *Cancer* 1996; **77:** 2503–13.
2. Miller AA, *et al*. Fadrozole hydrochloride in postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996; **78:** 789–93.
3. Falkson CI, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Ann Oncol* 1996; **7:** 465–9.
4. Thurlimann B, *et al*. First-line fadrozole HCl (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer: prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88. *Ann Oncol* 1996; **7:** 471–9.
5. Tominaga T, *et al*. Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Ann Oncol* 2003; **14:** 62–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Afema.

Farletuzumab *(USAN, rINN)*

Farletuzumabum; MORAb-003; Фарлетузумаб.

CAS — 896723-44-7.

UNII — 2O09BG0OWA.

Profile

Farletuzumab is a humanised monoclonal antibody that binds to and blocks the function of folate receptor alpha (FRA), a cell surface protein that is over-expressed in ovarian and other cancers. Farletuzumab is under investigation for the treatment of ovarian cancer.

References.

1. Spannuth WA, *et al*. Farletuzumab in epithelial ovarian carcinoma. *Expert Opin Biol Ther* 2010; **10:** 431–7.
2. Konner JA, *et al*. Farletuzumab, a humanized monoclonal antibody against folate receptor α , in epithelial ovarian cancer: a phase I study. *Clin Cancer Res* 2010; **16:** 5288–95.

Fenretinide *(USAN, rINN)*

Fenretinida; Fenrétinide; Fenretinidum; 4-HPR; 4-Hydroxyphenylretinamide; McN-R-1967; Фенретинид.

all-trans-4′-Hydroxyretinanilide.

$C_{26}H_{33}NO_2$=391.6

CAS — 65646-68-6.

UNII — 187EJ7QEXL.

Profile

Fenretinide is a retinoid derivative that is given orally and is being studied in the management of haematological malignancies such as lymphoma and solid malignancies such as brain and bone tumours, Ewing's sarcoma, and breast, prostate, ovarian, and cervical cancer. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Fenretinide has also been tried in oral lichen planus and leucoplakia. It is also under investigation as an adjunct to antipsychotic treatment in schizophrenia, for atrophy in age-related macular degeneration, and for insulin resistance in obese patients. It has been tried in the treatment of psoriasis, but was associated with unacceptable adverse effects such as night blindness and severe toxic erythema.

Fenretinide has been studied for the treatment of breast cancer and cutaneous malignancies but early results were disappointing and night blindness and mucocutaneous effects have been associated with this use.[1] Fenretinide has been investigated for the prevention of breast cancer (p. 703.2), but a large randomised study of secondary prevention failed to show any benefit.[2] A follow-up of the same study[3] found that patients receiving fenretinide had a lower incidence of ovarian carcinoma during the 5-year treatment period, but that this apparently protective effect disappeared after treatment was stopped. Combinations of tamoxifen and fenretinide, given intermittently (for treatment or prevention), have been reported to be well tolerated.[4-6] Its actions may be due to anti-angiogenic properties.[7]

1. Modiano MR, *et al*. Phase II study of fenretinide (N-[4-hydroxyphenyl] retinamide) in advanced breast cancer and melanoma. *Invest New Drugs* 1990; **8:** 317–19.
2. Veronesi U, *et al*. Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 1999; **91:** 1847–56.
3. De Palo G, *et al*. Effect of fenretinide on ovarian carcinoma occurrence. *Gynecol Oncol* 2002; **86:** 24–7.
4. Cobleigh MA, *et al*. Phase I/II trial of tamoxifen with or without fenretinide, an analog of vitamin A, in women with metastatic breast cancer. *J Clin Oncol* 1993; **11:** 474–7.
5. Conley B, *et al*. Pilot trial of the safety, tolerability, and retinoid levels of N-(4-hydroxyphenyl) retinamide in combination with tamoxifen in patients at high risk for developing invasive breast cancer. *J Clin Oncol* 2000; **18:** 275–83.
6. Guerrieri-Gonzaga A. *et al*. Preliminary results on safety and activity of a randomized, double-blind, 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. *J Clin Oncol* 2006; **24:** 129–35.
7. Sogno I, *et al*. Anti-angiogenic properties of chemopreventive drugs: fenretinide as a prototype. *Recent Results Cancer Res* 2009; **181:** 71–6.

Floxuridine *(USAN, rINN)*

Floxuridina; Floxuridinum; 5-Fluorouracil Deoxyriboside; FUDR; NSC-27640; WR-138720; Флоксуридин.

2′-Deoxy-5-fluorouridine; 5-Fluoro-2′-deoxyuridine; 1-(2-Deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione.

$C_9H_{11}FN_2O_5$=246.2

CAS — 50-91-9.

UNII — 039LU44I5M.

Pharmacopoeias. In *US.*

USP 36: (Floxuridine). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Floxuridine is an antineoplastic which acts as an antimetabolite, either by conversion to fluorouracil (after rapid injection), or, when given by slow intra-arterial infusion, partly via floxuridine monophosphate (F-dUMP), which produces greater inhibition of DNA synthesis.

Floxuridine is used in the palliative treatment of hepatic metastases of colorectal cancer (p. 706.3). It has been tried in some other solid neoplasms. Doses of 100 to 600 micrograms/kg daily are given by continuous hepatic arterial infusion, usually with the aid of an infusion pump, until toxicity occurs.

White cell and platelet counts should be carried out regularly during therapy and treatment should be stopped if the white cell count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p. 730.3), or if major adverse effects occur.

References.

1. Fordy C, *et al*. Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases. *Br J Cancer* 1998; **78:** 1058–60.
2. Kemeny N, *et al*. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341:** 2039–48.
3. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; **18:** 243–54.
4. Fiorentini G, *et al*. Locoregional therapy for liver metastases from colorectal cancer: the possibilities of intraarterial chemotherapy, and new hepatic-directed modalities. *Hepatogastroenterology* 2001; **48:** 305–12.
5. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; **352:** 734–5.
6. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. *Mol Cancer Ther* 2009; **8:** 1015–25.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p. 797.1. Adverse reactions after intra-arterial infusion often include local reactions, thromboembolic complications, and infection or bleeding at the catheter site, or blockage of the catheter. Erythema, stomatitis, and gastrointestinal disturbances are relatively common. There have also been signs of liver dysfunction.

Effects on the liver. Serious biliary toxicity has been reported in over half of all patients receiving hepatic arterial infusions of floxuridine, usually manifesting as sclerosing cholangitis or acalculous cholecystitis;[1] as a result some surgeons routinely remove the gallbladder at the time of infusion pump implantation.[2] Extrahepatic biliary stenosis with jaundice and cholestasis has also been described;[3] the authors suggest that this could lead to intrahepatic biliary damage from bile stasis and infection, recurrent cholangitis, and biliary sclerosis. Floxuridine infusions have also been associated with a case of fatal progressive cirrhosis of the liver in the absence of overt cholestasis.[4] Pseudoaneurysms of the hepatic artery, lead-

ing to serious retroperitoneal or gastrointestinal bleeding, have also been described.[5]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Anonymous. An implanted infusion pump for chemotherapy of liver metastases. *Med Lett Drugs Ther* 1984; **26:** 89–90.
3. Aldrighetti L, *et al.* Extrahepatic biliary stenoses after hepatic arterial infusion (HAI) of floxuridine (FUdR) for liver metastases from colorectal cancer. *Hepatogastroenterology* 2001; **48:** 1302–7.
4. Pettavel J, *et al.* Fatal liver cirrhosis associated with long-term arterial infusion of floxuridine. *Lancet* 1986; **ii:** 1162–3.
5. Samaras P, *et al.* Hemorrhage associated with hepatic artery pseudoaneurysms after regional chemotherapy with floxuridine: case report. *Int Semin Surg Oncol* 2008; **5:** 17.

Interactions

As for Fluorouracil, p. 797.3.

Pharmacokinetics

Floxuridine is poorly absorbed from the gastrointestinal tract and it is usually given by injection. Floxuridine is metabolised mainly in the liver to fluorouracil after rapid injection. When given by slow intra-arterial infusion, more of the drug is metabolised to floxuridine monophosphate (F-dUMP). It is excreted as carbon dioxide via the lungs; some is excreted, as unchanged drug and metabolites, in urine. Floxuridine crosses the blood-brain barrier to some extent and is found in CSF.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: FUDR; ***Turk.***: Floxudem; ***USA***: FUDR†.

Pharmacopoeial Preparations
USP 36: Floxuridine for Injection.

Fludarabine Phosphate

(BAN, USAN, rINNM)

2-F-ara-AMP; Fludarabiinifosfaatti; Fludarabin Fosfat; Fludarabina, fosfato de; Fludarabine Monophosphate; Fludarabine, phosphate de; Fludarabinfosfat; Fludarabin-fosfát; Fludarabini Phosphas; Fludarabino fosfatas; Fludarabinphosphat; 2-Fluoro-ara-AMP; Fosfato de fludarabina; NSC-312887; Флударабина Фосфат.

9-β-D-Arabinofuranosyl-2-fluoroadenine 5′-dihydrogenphosphate.

$C_{10}H_{13}FN_5O_7P$=365.2

CAS — 21679-14-1 (fludarabine); 75607-67-9 (fludarabine phosphate).

ATC — L01BB05.

ATC Vet — QL01BB05.

UNII — 1X9VK9O1SC.

NOTE. The name FluCam has been used for a regimen of fludarabine with alemtuzumab. Distinguish from Flucam, which is a proprietary name for ampiroxicam (p. 21.1).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fludarabine Phosphate). A white or almost white, hygroscopic, crystalline powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; freely soluble in dimethylformamide. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Fludarabine Phosphate). A white to off-white, hygroscopic, crystalline powder. Slightly soluble in water and in 0.1M hydrochloric acid; practically insoluble in dehydrated alcohol; freely soluble in dimethylformamide. Store at 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Fludarabine phosphate is a fluorinated nucleotide analogue of the antiviral vidarabine (p. 1023.1); it is a purine analogue that acts as an antimetabolite antineoplastic to inhibit DNA synthesis. Fludarabine is used for the treatment of B-cell chronic lymphocytic leukaemia (p. 693.3). Fludarabine phosphate is given intravenously or orally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* For intravenous use, fludarabine phosphate is either given by bolus injection, usually in 10 mL sodium chloride 0.9%, or by infusion over 30 minutes, usually in 100 mL sodium chloride 0.9%. The usual *intravenous* dose is 25 mg/m^2 daily for 5 consecutive days. Alternatively it may be given *orally* in a dose of 40 mg/m^2 daily for 5 consecutive days. Courses may be repeated every 28 days, usually for up to 6 cycles.

Haematological function should be monitored regularly; the dosage may need to be reduced, or further courses delayed, if blood counts indicate severe or persistent myelosuppression (see Administration in Subsequent Cycles, below). Doses should be reduced in renal impairment (see below).

General references.

1. Adkins JC, *et al.* Fludarabine: an update of its pharmacology and use in the treatment of haematological malignancies. *Drugs* 1997; **53:** 1005–37.
2. Plosker GL, Figgitt DP. Oral fludarabine. *Drugs* 2003; **63:** 2317–23.

Administration in the elderly. US licensed product information states that patients of advanced age are predisposed to increased toxicity from fludarabine, and that such patients should be monitored closely, and the dose modified accordingly. UK licensed product information states that data are limited for patients over the age of 75 years; in patients over the age of 65 years, creatinine clearance (CC) should be measured and patients treated accordingly, see Administration in Renal Impairment, below.

A review[1] stated that fludarabine may be used safely and effectively in older patients, but that supportive measures were important. Response rates tend to be lower in older patients, and dose reductions are recommended in the setting of reduced CC in an effort to minimise treatment-related toxicity.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. US licensed product information for intravenous fludarabine recommends that patients with moderate renal impairment, defined as creatinine clearance (CC) of 30 to 70 mL/min per 1.73 m^2 should have a 20% dose reduction of fludarabine. Fludarabine should not be given to those with severe renal impairment (CC less than 30 mL/min per 1.73 m^2).

UK licensed product information for intravenous and oral fludarabine states that for those patients with a CC of between 30 and 70 mL/min, the dose should be reduced by up to 50% and close haematological monitoring used to assess toxicity; the drug is contra-indicated in those with CC less than 30 mL/min.

Administration in subsequent cycles. US licensed product information for *intravenous* fludarabine states that the dose may need to be decreased or treatment delayed based on haematological or non-haematological toxicity; if neurotoxicity occurs, therapy may need to be delayed, or stopped.

UK licensed product information for *oral* fludarabine states that if cell numbers are too low at the start of a subsequent cycle and there is evidence of treatment-related myelosuppression, the planned treatment cycle should be postponed until the granulocyte count is above 1000 cells/mm^3 and the platelet count is above 100 000 cells/mm^3. Treatment should only be postponed up to a maximum of 2 weeks; if the counts have not recovered after 2 weeks, the daily dose of fludarabine phosphate should be reduced accordingly to the following:

- granulocytes 500 to 1000 cells/mm^3 and/or platelets 50 000 to 100 000 cells/mm^3: 30 mg/m^2
- granulocytes less than 500 cells/mm^3 and/or platelets less than 50 000 cells/mm^3: 20 mg/m^2

The dose is not reduced if thrombocytopenia is disease related. If the patient does not respond to treatment after 2 cycles and shows little or no haematological toxicity, the dose may be increased cautiously in subsequent cycles.

Malignant neoplasms. Fludarabine is the preferred second-line therapy for chronic lymphocytic leukaemia once initial alkylating agent therapy fails,[1] and may also be used for initial therapy (see p. 693.3). It has also been tried in other malignancies. Listed below are some references to the use of fludarabine phosphate for the treatment of chronic lymphocytic leukaemia,[2-4] and its potential activity against a variety of other malignancies, including indolent low-grade non-Hodgkin's lymphoma[5,6] (p. 696.3), mycosis fungoides,[7] heavy chain disease,[8] prolymphocytic leukaemia,[9,10] hairy cell leukaemia,[11] and Waldenström's macroglobulinaemia.[12-14]

1. NICE. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (issued September 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/NICEfludarab_E_29guidance.pdf (accessed 31/07/08)
2. Zhu Q, *et al.* Fludarabine in comparison to alkylator-based regimen as induction therapy for chronic lymphocytic leukemia: a systematic review and meta-analysis. *Leuk Lymphoma* 2004; **45:** 2239–45.
3. Richards S. Fludarabine increases complete response but not survival compared with conventional alkylator-based regimens for previously untreated chronic lymphocytic leukaemia. *Cancer Treat Rev* 2005; **31:** 332–5.
4. Ricci F, *et al.* Fludarabine in the treatment of chronic lymphocytic leukemia: a review. *Ther Clin Risk Manag* 2009; **5:** 187–207.
5. Hiddemann W, Pott-Hoeck C. Fludarabine in the management of malignant lymphomas. *Drugs* 1994; **47** (suppl 6): 50–6.
6. Anderson VR, Perry CM. Fludarabine: a review of its use in non-Hodgkin's lymphoma. *Drugs* 2007; **67:** 1633–55.
7. Scarisbrick JJ, *et al.* A trial of fludarabine and cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma. *Br J Dermatol* 2001; **144:** 1010–15.
8. Agrawal S, *et al.* First report of fludarabine in gamma-heavy chain disease. *Br J Haematol* 1994; **88:** 653–5.
9. Smith OP, Mehta AB. Fludarabine monophosphate for prolymphocytic leukaemia. *Lancet* 1990; **336:** 820.
10. Kantarjian HM, *et al.* Efficacy of fludarabine, a new adenine nucleoside analogue, in patients with prolymphocytic leukemia and the prolymphocytoid variant of chronic lymphocytic leukemia. *Am J Med* 1991; **90:** 223–8.
11. Kantarjian HM, *et al.* Fludarabine therapy in hairy cell leukemia. *Cancer* 1991; **67:** 1291–3.
12. Dhodapkar MV, *et al.* Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood* 2001; **98:** 41–8.
13. Leblond V, *et al.* Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood* 2001; **98:** 2640–4.
14. Tedeschi A, *et al.* Fludarabine-based combination therapies for Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma* 2009; **9:** 67–70.

Organ and tissue transplantation. Fludarabine is commonly used in non-myeloablative or reduced-intensity conditioning regimens before haematopoietic stem cell transplantation (p. 1937.1).[1,2] Fludarabine-based conditioning appears to be most effective in slowly proliferating malignancies, which give time for a graft-versus-leukaemia effect to develop. Although toxicity is generally mild with fludarabine, graft-versus-host disease is still a significant problem and the optimal conditioning regimen remains to be determined.[1]

1. Carella AM. Treatment of hematological malignancies with allogeneic nonmyeloablative stem cell transplantation: conditioning regimens with fludarabine. *Hematol J* 2004; **5** (suppl 1): S68–S75.
2. Blaise D, *et al.* Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica* 2007; **92:** 533–41.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow suppression from fludarabine is very common and dose-limiting, manifesting as neutropenia, thrombocytopenia, and anaemia; the nadir of the white cell and platelet counts usually occurs after about 13 and 16 days, respectively. Myelosuppression can be severe and cumulative; prolonged lymphopenia with concomitant risk of opportunistic infections may occur. Bone marrow hypoplasia or aplasia resulting in pancytopenia may sometimes be fatal. Careful haematological monitoring is required. Infections can be severe and sometimes fatal; these include opportunistic infections and reactivations of latent viral infections such as herpes zoster, Epstein-Barr virus, and JC virus (causing progressive multifocal leukoencephalopathy). Hepatitis B has been reported; in hepatitis B virus carriers, aggravation of hepatitis or fulminant hepatitis can occur.

Auto-immune disorders (including auto-immune haemolytic anaemia, thrombocytopenic purpura, acquired haemophilia, and Evan's syndrome) have been reported, and may be life-threatening or fatal. Patients should be monitored for signs of haemolysis and therapy stopped if it occurs. Use of fludarabine should be avoided in patients with decompensated haemolytic anaemia.

Peripheral neuropathy is common with fludarabine. Other neurological disturbances include agitation, confusion, visual disturbances, and seizures; high intravenous doses of fludarabine have been associated with severe neurological effects, including blindness, coma, and death.

Other common adverse effects include fever, fatigue, chills, cough, weakness, malaise, anorexia, gastrointestinal disturbances, mucositis, stomatitis, oedema, and rashes. Less commonly, pulmonary toxicity (including pulmonary fibrosis, pneumonitis, and dyspnoea), gastrointestinal haemorrhage, and abnormalities in hepatic or pancreatic enzymes can occur. Tumour lysis syndrome has been reported, especially in patients with large tumour burdens. Rarely reported effects include heart failure, arrhythmias, pemphigus, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Cerebral haemorrhage, pulmonary haemorrhage, and haemorrhagic cystitis can occur.

Exacerbation of existing skin cancer lesions as well as new onset of skin cancer has been reported in some patients. Transfusion-associated graft-versus-host disease has been seen after transfusion of non-irradiated blood in patients treated with fludarabine, and fatalities have occurred; patients should only receive irradiated blood.

Dosage should be reduced in renal impairment (see above).

Carcinogenicity. A study in patients with chronic lymphocytic leukaemia who were treated with fludarabine found that there was no significantly increased risk of secondary malignancy after therapy, despite the immunosuppressive properties of this drug.[1] A review[2] of this and other studies concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-

term follow-up of patients treated with fludarabine was needed.

1. Cheson BD, *et al*. Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukaemias. *J Clin Oncol* 1999; **17:** 2454–60.
2. Van Den Neste E, *et al*. Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; **40:** 541–50.

Effects on the eyes. See Effects on the Nervous System, below.

Effects on the lungs. Pulmonary toxicity manifest as dyspnoea, fever, hypoxaemia, and radiographic evidence of interstitial and alveolar infiltrates was diagnosed in 9 patients of a cohort of 105 treated with fludarabine.[1] Lung biopsies were performed in 6 patients and showed diffuse chronic interstitial inflammation and fibrosis. Patients with chronic lymphocytic leukaemia appeared to be at greater risk of developing this complication than those with non-Hodgkin's lymphoma.

1. Helman DL, *et al*. Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* 2002; **122:** 785–90.

Effects on the nervous system. High doses (of the order of 100 mg/m^2 daily intravenously) of fludarabine are associated with severe, life-threatening neurotoxicity. However, a few cases of progressive multifocal leukoencephalopathy have also been reported in patients given fludarabine in usual doses.[1-4] The prolonged immunosuppression caused by fludarabine might increase the risk of developing this fatal demyelinating disease, which is caused by opportunistic JC virus infection. Ocular toxicity, including irreversible loss of vision, has also been reported occasionally, including with low-dose regimens.[5]

1. Zabernigg A, *et al*. Late-onset fatal neurological toxicity of fludarabine. *Lancet* 1994; **344:** 1780.
2. Gonzalez H, *et al*. Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). *Hematol Cell Ther* 1999; **41:** 183–6.
3. Cid J, *et al*. Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol* 2000; **79:** 392–5.
4. Vidarsson B, *et al*. Progressive multifocal leukoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease. *Am J Hematol* 2002; **70:** 51–4.
5. Ding X, *et al*. Ocular toxicity of fludarabine: a purine analog. *Expert Rev Ophthalmol* 2008; **3:** 97–109.

Graft-versus-host disease. Transfusion-associated graft-versus-host disease has been reported when blood products were used in patients treated with fludarabine.[1] Fludarabine-treated patients should receive irradiated red cells and platelets (to inactivate any viable T-cells) if they require a transfusion.

1. Williamson LM, *et al*. Fludarabine treatment and transfusion-associated graft-versus-host disease. *Lancet* 1996; **348:** 472–3.

Infection. A review[1] of patients treated with fludarabine-containing regimens showed that therapy was associated with serious infections including listeriosis, pneumocystis pneumonia, mycobacterial infections, and opportunistic fungal and viral infections. The risk was exacerbated by previous or current corticosteroid therapy. Prophylactic therapy with co-trimoxazole, triazole antifungals, aciclovir, and colony-stimulating factors was recommended in at-risk patients. A high incidence of herpesvirus infections was also found in another review[2] of patients treated with fludarabine. Combination therapy using chlorambucil and fludarabine resulted in more infections than when either was used alone,[3] but single-agent fludarabine was associated with more major infections and herpesvirus infections than chlorambucil alone. The frequency of serious infection has also been reported[4] to be increased in patients after their conditions became refractory to fludarabine and they were being treated with conventional chemotherapy.

For reports of progressive multifocal leukoencephalopathy caused by opportunistic JC virus infection in patients receiving fludarabine, see Effects on the Nervous System, above.

1. Anaissie EJ, *et al*. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med* 1998; **129:** 559–66.
2. Byrd JC, *et al*. Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. *Br J Haematol* 1999; **105:** 445–7.
3. Morrison VA, *et al*. Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. *J Clin Oncol* 2001; **19:** 3611–21.
4. Perkins JG, *et al*. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer* 2002; **94:** 2033–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fludarabine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Psoriasis. Although incidental resolution of psoriatic lesions has been reported[1,2] in a few patients being treated with fludarabine, there is also a report[3] of a patient with fulminant exacerbation of psoriatic plaques and generalised erythroderma after starting fludarabine therapy. Symptoms resolved on stopping the drug and treatment with corticosteroids, emollients, and phototherapy.

1. Karadoğan I, *et al*. Resolution of psoriatic skin lesions with fludarabine. *Am J Med* 1999; **107:** 300–1.
2. Smith OP, *et al*. Fludarabine and psoriasis. *N Engl J Med* 1994; **330:** 1540–1.
3. Jordan J, *et al*. Paradoxical exacerbation of psoriasis during therapy with fludarabine. *Eur J Dermatol* 2008; **18:** 365–6.

Interactions

Increased pulmonary toxicity, sometimes fatal, has been reported in patients given fludarabine with pentostatin. Pretreatment with cytarabine may reduce the metabolic activation of fludarabine, but pretreatment with fludarabine results in increased intracellular concentrations of cytarabine—see p. 775.3. The therapeutic efficacy of fludarabine may also be reduced by dipyridamole and other inhibitors of adenosine uptake.

Aminoglycosides. Severe ototoxicity occurred when a short course of *gentamicin* was given to a patient who had recently completed a course of fludarabine.[1]

1. O'Brien RK, Sparling TG. Gentamicin and fludarabine ototoxicity. *Ann Pharmacother* 1995; **29:** 200–1.

Corticosteroids. For a suggestion that use of fludarabine with corticosteroids may increase the risk of infection, see Infection, above.

Pharmacokinetics

Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabine which is taken up by lymphocytes and rephosphorylated via the enzyme deoxycytidine kinase to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate occur about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after oral doses of the phosphate.

Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 40 to 60% of an intravenous dose is excreted in the urine. The pharmacokinetics of fludarabine show considerable interindividual variation.

References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. *Clin Pharmacokinet* 2002; **41:** 93–103.
3. Lichtman SM, *et al*. The pharmacokinetics and pharmacodynamics of fludarabine phosphate in patients with renal impairment: a prospective dose adjustment study. *Cancer Invest* 2002; **20:** 904–13.
4. Ogawa Y, *et al*. Phase I and pharmacokinetic study of oral fludarabine phosphate in relapsed indolent B-cell non-Hodgkin's lymphoma. *Ann Oncol* 2006; **17:** 330–3.
5. Salinger DH, *et al*. A limited sampling schedule to estimate individual pharmacokinetic parameters of fludarabine in hematopoietic cell transplant patients. *Clin Cancer Res* 2009; **15:** 5280–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fludakebir; Fludara; Fludarosa; Forclina; ***Austral.***: Fludara; ***Austria***: Fludara; Neoflubin; ***Belg.***: Fludara; ***Braz.***: Fludalibbs; Fludara; ***Canad.***: Fludara; ***Chile***: Fludara; ***China***: Fludara (福达华); ***Cz.***: Fludara; Tazumara†; ***Denm.***: Fludara; ***Fin.***: Fludara; ***Fr.***: Fludara; ***Ger.***: Bendarabin; Fludara; Neoflubin†; ***Gr.***: Fludara; ***Hong Kong***: Fludara; ***Hung.***: Fludara; ***India***: Fludabine; Fludacel; Fludara; Fludarin; Naprobin; ***Indon.***: Fludara; ***Irl.***: Fludara; ***Israel***: Fludara; ***Ital.***: Fludara; ***Malaysia***: Fludara; ***Mex.***: Beneflur; Fludara†; ***Neth.***: Fludara; ***Norw.***: Fludara; ***NZ***: Fludara; ***Philipp.***: Fludara; ***Pol.***: Fludalym; Fludara; ***Port.***: Fludara; ***Rus.***: Fludara (Флудара); Flugarda (Флугарда); ***S.Afr.***: Fludara; ***Singapore***: Fludara; ***Spain***: Beneflur; ***Swed.***: Fludara; ***Switz.***: Fludara†; ***Thai.***: Fludara; ***Turk.***: Fludara; Flumen; ***UK***: Fludara; ***USA***: Fludara†; Oforta†; ***Venez.***: Fludara.

Pharmacopoeial Preparations

USP 36: Fludarabine Phosphate for Injection; Fludarabine Phosphate Injection.

Fluorouracil *(BAN, USAN, rINN)*

5-Fluorouracil; Fluorouracilas; Fluorouracile; Fluorouracilo; Fluorouracilum; Fluorouracyl; Fluorourasiili; 5-Fluorourasil; Fluorourasil; Fluoruracil; 5-FU; NSC-19893; Ro-2-9757; WR-69596; Флуороурацил.

5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione.

$C_4H_3FN_2O_2$=130.1

CAS — 51-21-8.
ATC — L01BC02.
ATC Vet — QL01BC02.
UNII — U3P01618RT.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Fluorouracil). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.0. Protect from light.

USP 36: (Fluorouracil). A white to practically white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Incompatibility. Preparations of fluorouracil are alkaline, and compatibility problems may be expected with acidic drugs and preparations, or those which are unstable in the presence of alkali. Fluorouracil is reported to be incompatible with cytarabine,[1] diazepam,[2] doxorubicin[2] (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate.[3] Although fluorouracil has been stated to be incompatible with methotrexate[1] a study of the long-term stability of an admixture of the 2 drugs in sodium chloride 0.9% injection suggests otherwise.[4]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
3. Trissel LA, *et al*. Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.
4. Vincké BJ, *et al*. Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.

Stability. Despite one report[1] that fluorouracil had limited stability when dissolved in glucose 5% at room temperature (10% loss from solution in 43 hours when stored in PVC and in only 7 hours when stored in glass), others[2] found such a solution to be stable for at least 16 weeks when stored in PVC at 5 degrees. When stored at room temperature in PVC, solutions of fluorouracil may lose water by evaporation, which slowly increases their concentration.[2,3] Results of a study of fluorouracil and methotrexate admixtures in sodium chloride 0.9% suggest that extended stability (up to 13 weeks) is possible in this diluent at 5 degrees in PVC bags.[3] Commercial solutions of fluorouracil for injection have been reported to be stable for 7 days at 37 degrees in a portable infusion pump, although at 25 degrees one brand showed evidence of precipitation.[4] Fluorouracil solutions may be incompatible with synthetic elastomers: microscopic precipitation has been reported as soon as 4 hours after placement into polyisoprene reservoirs of elastomeric infusers and in polypropylene syringes with an elastomeric joint.[5] Some have questioned the validity of this finding.[6,7]

1. Benvenuto JA, *et al*. Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
2. Quebbeman EJ, *et al*. Stability of fluorouracil in plastic containers used for continuous infusion at home. *Am J Hosp Pharm* 1984; **41:** 1153–6.
3. Vincké B, *et al*. Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
4. Stiles ML, *et al*. Stability of fluorouracil administered through four portable infusion pumps. *Am J Hosp Pharm* 1989; **46:** 2036–40.
5. Corbrion V, *et al*. Precipitation of fluorouracil in elastomeric infusers with a polyisoprene reservoir and in polypropylene syringes with an elastomeric joint. *Am J Health-Syst Pharm* 1997; **54:** 1845–8.
6. Trissel LA. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55:** 1314–15.
7. Allwood MC. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55:** 1315–16.

Uses and Administration

Fluorouracil, an analogue of the pyrimidine uracil, is an antineoplastic that acts as an antimetabolite. After intracellular conversion to the active deoxynucleotide it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. It can also interfere with RNA synthesis.

Fluorouracil is used alone or in combination in the adjuvant and palliative treatment of gastrointestinal cancer. In this setting it may be combined with folinic acid (see Administration, p. 796.1). Fluorouracil is often given with cyclophosphamide and methotrexate or doxorubicin in the adjuvant treatment of breast cancer. It may also be used in the palliation of other malignant neoplasms such as those of the head and neck, liver, and pancreas. In addition, it may be used topically for treating malignant or premalignant lesions of the skin. Its use in these malignancies is further discussed under Choice of Antineoplastic as indicated by the cross-references given below.

Many dosage regimens have been used. Although it is most often given in combination regimens for the treatment of malignancy, many of the licensed dosage regimens relate to single-agent use. Such licensed regimens include:

- by *intravenous injection*, usual doses of 12 mg/kg daily (to a maximum of 0.8 to 1 g daily) for 3 or 4 days. If there is

no evidence of toxicity, this may be followed after 1 day by 6 mg/kg on alternate days for 3 or 4 further doses. An alternative schedule is to give 15 mg/kg intravenously once a week throughout the course. The course may be repeated after 4 to 6 weeks or maintenance doses of 5 to 15 mg/kg to a maximum of 1 g may be given weekly.

- by *intravenous infusion*, usual doses of 15 mg/kg daily (to a maximum of 1 g daily) being infused in 500 mL of sodium chloride 0.9% or glucose 5% over 4 hours and repeated on successive days until toxicity occurs or a total of 12 to 15 g has been given. *Continuous infusion* may also be used. The course may be repeated after 4 to 6 weeks.
- by continuous *intra-arterial infusion*, in doses of 5 to 7.5 mg/kg daily (regional perfusion).
- by *mouth*, although the parenteral route is generally preferred, a dose of 15 mg/kg, to a maximum of 1 g in one day, has been given once weekly for maintenance. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Suggested regimens with folinic acid include:

- 200 mg/m^2 of folinic acid (as calcium folinate) by slow intravenous injection followed immediately by an intravenous bolus of fluorouracil 370 mg/m^2; the treatment is given daily for 5 consecutive days, and may be repeated every 4 to 5 weeks
- lower doses of folinic acid (20 mg/m^2) followed by fluorouracil 425 mg/m^2 for 5 consecutive days, repeated every 4 to 5 weeks (the Mayo regimen)
- an initial dose of 200 mg/m^2 of folinic acid, followed by fluorouracil 400 mg/m^2 as an initial intravenous bolus injection and then 600 mg/m^2 by continuous intravenous infusion. This dosage is given for 2 consecutive days every 2 weeks (the de Gramont regimen)

The white cell count should be determined frequently during treatment with fluorouracil and therapy stopped immediately if the count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p. 730.3) or if severe adverse effects occur. Doses should be reduced by up to half in patients with poor nutritional status, impaired bone-marrow, hepatic, or renal function, and within 30 days of major surgery.

Fluorouracil is used *topically* in the treatment of solar (actinic) keratoses and other superficial tumours and premalignant conditions of the skin including Bowen's disease and superficial basal cell carcinomas. For actinic keratosis it is usually applied as a 0.5 to 5% cream or as a 1 to 5% solution in propylene glycol once or twice daily for 2 to 4 weeks; the higher strength may be applied for at least 3 to 6 weeks for superficial basal cell carcinomas.

Administration. For reference to sequence-specific toxicity when fluorouracil and folinic acid were given before capecitabine, see Administration, under Capecitabine, p. 758.1.

MODULATION. Modulation of fluorouracil by other drugs has been tried in an effort to enhance its effects, particularly in the treatment of colorectal cancer (p. 706.3).

Folinic acid has been extensively used to modulate the effects of fluorouracil, and has become the agent of choice. Various regimens have been used, modifying the fluorouracil schedule (continuous infusion versus bolus), folinic acid dose (low-dose versus high-dose) and the regimen frequency (monthly, bimonthly, or weekly). Despite many studies, the optimum regimen in terms of efficacy and tolerability has yet to be determined.

In the adjuvant setting, a large-scale randomised study[1] found low-dose folinic acid was as effective as high-dose when added to fluorouracil given either once weekly for 30 doses, or for 5 consecutive days per month over 6 months.

In the palliation of advanced disease, meta-analyses have revealed the value of the addition of folinic acid to fluorouracil,[2] and the use of infusions rather than bolus fluorouracil,[3] in terms of response rates. An updated meta-analysis confirmed the benefit of addition of folinic acid to fluorouracil in terms of response rate, and found a small but statistically significant advantage in terms of overall survival. Survival benefit was restricted to studies using the same dose of fluorouracil in the treatment arms (fluorouracil alone versus fluorouracil and folinic acid), suggesting that the benefit of modulation with folinic acid could be compensated by an increase of fluorouracil dose in the fluorouracil alone arm. However, increased toxicity from high-dose fluorouracil might occur.[4] The data for low-dose folinic acid versus high-dose are less clear.[5] In 1 randomised study,[6] a bimonthly infusion regimen of fluorouracil plus high-dose folinic acid (the de Gramont regimen[7]) was more effective than a monthly bolus regimen of fluorouracil plus low-dose folinic acid. Further studies comparing the effect of high- and low-dose folinic acid added to the same schedule of continuous infusion fluorouracil are required.

Interferon alfa also appears to modify[8] the actions of fluorouracil (see also under Interactions, p. 797.3), and has been investigated with fluorouracil and folinic acid. Although some early results were promising, later randomised controlled studies failed to show any benefit for the addition of interferon alfa to fluorouracil or fluorouracil plus folinic acid.[8] It is not clear whether interferon beta will prove of any greater benefit.

Based on the results of early adjuvant studies, *levamisole* was used as standard therapy to modulate fluorouracil, particularly in the USA. However, more recent studies indicate that levamisole is no more effective than placebo when added to fluorouracil,[1] or to fluorouracil plus folinic acid.[9]

Methotrexate has also been used to modulate fluorouracil. Meta-analysis of several studies of fluorouracil preceded by methotrexate found that the combination doubled the response rate to fluorouracil in metastatic colorectal cancer and produced some survival benefits.[10] (Combination in the reverse order, i.e. methotrexate preceded by fluorouracil, may reduce methotrexate toxicity—see Other Drugs, under Treatment of Adverse Effects, p. 827.1.)

1. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355:** 1588–96.
2. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10:** 896–903.
3. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; **16:** 301–8.
4. The Meta-Analysis Group in Cancer. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; **22:** 3766–75. Correction. *ibid.* 2005; **23:** 1337–8.
5. Rustum YM, *et al.* Rationale for treatment design: biochemical modulation of 5-fluorouracil by leucovorin. *Cancer J Sci Am* 1998; **4:** 12–18.
6. de Gramont A, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French Intergroup study. *J Clin Oncol* 1997; **15:** 808–15.
7. de Gramont A, *et al.* A review of GERCOD trials of bimonthly leucovorin plus 5-fluorouracil 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998; **34:** 619–26.
8. Makower D, Wadler S. Interferons as biomodulators of fluoropyrimidines in the treatment of colorectal cancer. *Semin Oncol* 1999; **26:** 663–71.
9. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; **17:** 3553–9.
10. Advanced Colorectal Cancer Meta-analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994; **12:** 960–9.

ROUTE. Fluorouracil can be given orally, parenterally, or topically (see Uses and Administration, p. 795.3); it has also been used intralesionally and intraurethrally in the treatment of condyloma acuminata, see Warts, below.

Administration in the elderly. A review[1] concluded that there is no pharmacokinetic basis for dose modification of fluorouracil based on age alone; data are conflicting as to whether toxicity is likely to be increased in elderly patients.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Darier's disease. Two patients with resistant Darier's disease (p. 1683.2) receiving long-term oral retinoid therapy responded to treatment with topical fluorouracil applied as a 1% cream once daily.[1] There was complete clearance of skin lesions after 3 weeks of treatment. In another case,[2] topical fluorouracil 1% cream applied every second day, alternating with clobetasol ointment, dramatically improved hyperkeratosis after 1 month; improvement persisted for 2 months after the end of treatment. Fluorouracil 1% cream has also been used as monotherapy,[3,4] leading to marked improvement or complete remission after about 4 weeks of therapy.

1. Knulst AC, *et al.* Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol* 1995; **133:** 463–6.
2. Velasco S, Guillet G. Amélioration d'une maladie de Darier traitée par 5-fluorouracil topique. *Ann Dermatol Venereol* 2006; **133:** 366–8.
3. Yoon TY, *et al.* Successful treatment of Darier disease with topical 5-fluorouracil. *Br J Dermatol* 2006; **154:** 1210–12.
4. Schmidt H, *et al.* Topical 5-fluorouracil in Darier disease. *Br J Dermatol* 2008; **158:** 1393–6.

Eye disorders. Aside from its use in glaucoma surgery (below), fluorouracil has been used adjunctively in other ocular surgery. It has also shown promising results in the treatment of ocular surface malignancies.[1]

1. Abraham LM, *et al.* The clinical applications of fluorouracil in ophthalmic practice. *Drugs* 2007; **67:** 237–55.

Glaucoma. A regimen of subconjunctival injections of fluorouracil is effective in improving the outcome of glaucoma filtering surgery[1-3] in selected patients when used as an adjunct to prevent the formation of scar tissue (see p. 1999.1). However, in view of the increased risk of late-onset conjunctival wound leaks caution has been suggested in its use in eyes with a good prognosis.[3] Although one study[4] found that fluorouracil improved the success rate of combined glaucoma filtering surgery and cataract surgery earlier studies had failed to find any advantage.[5,6] A systematic review[7] of these and 2 other studies concluded that fluorouracil reduced the risk of surgical failure of trabeculectomy in eyes at high risk of failure, and in those undergoing surgery for the first time, but noted that the methodological quality of the studies was not high, and that this practice has largely been superseded by the use of intra-operative mitomycin. However, a later survey[8] in the UK found that the use of antimetabolites in glaucoma surgery was much less common than in the USA or Japan, and that fluorouracil was strongly preferred to mitomycin.

Intra-operative topical application of fluorouracil has been tried as an alternative to subconjunctival injection with conflicting results.[9-11]

1. Ophir A, Ticho U. A randomized study of trabeculectomy and subconjunctival administration of fluorouracil in primary glaucomas. *Arch Ophthalmol* 1992; **110:** 1072–5.
2. Goldenfeld M, *et al.* 5-Fluorouracil in initial trabeculectomy: a prospective, randomized, multicenter study. *Ophthalmology* 1994; **101:** 1024–9.
3. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. *Am J Ophthalmol* 1996; **121:** 349–66.
4. Gandolfi SA, Vecchi M. 5-Fluorouracil in combined trabeculectomy and clear-cornea phacoemulsification with posterior chamber intraocular lens implantation: a one-year randomized, controlled clinical trial. *Ophthalmology* 1997; **104:** 181–6.
5. Wong PC, *et al.* 5-Fluorouracil after primary combined filtration surgery. *Am J Ophthalmol* 1994; **117:** 149–54.
6. O'Grady JM, *et al.* Trabeculectomy, phacoemulsification, and posterior chamber lens implantation with and without 5-fluorouracil. *Am J Ophthalmol* 1993; **116:** 594–9.
7. Wormald R, *et al.* Post-operative 5-fluorouracil for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 12/05/05).
8. Siriwardena D, *et al.* National survey of antimetabolite use in glaucoma surgery in the United Kingdom. *Br J Ophthalmol* 2004; **88:** 873–6.
9. Egbert PR, *et al.* A prospective trial of intraoperative fluorouracil during trabeculectomy in a black population. *Am J Ophthalmol* 1993; **116:** 612–16.
10. Lachkar Y, *et al.* Trabeculectomy with intraoperative sponge 5-fluorouracil in Afro-Caribbeans. *Br J Ophthalmol* 1997; **81:** 555–8.
11. Yorston D, Khaw PT. A randomised trial of the effect of intraoperative 5-FU on the outcome of trabeculectomy in east Africa. *Br J Ophthalmol* 2001; **85:** 1028–30.

Malignant neoplasms. Fluorouracil plays an important role in the adjuvant treatment of gastrointestinal cancer, as discussed on p. 705.2, and has been widely used in adjuvant regimens for early breast cancer (p. 702.1). It may also be employed in the management of several other malignancies including pancreatic endocrine tumours (p. 716.3), cancers of the cervix (p. 704.2) and head and neck (p. 708.1), liver metastases (p. 709.3), and tumours of the exocrine pancreas (p. 712.1). It is reported to have only modest activity in neoplasms of the kidney (p. 708.3). In addition, it is sometimes applied topically as part of the management of malignant or pre-malignant lesions of the skin (see Basal Cell and Squamous Cell Carcinoma, p. 714.2), or surface neoplasia of the eye (p. 705.1).

The role of fluorouracil in chemoradiotherapy of various malignancies has been reviewed.[1]

1. Rich TA, *et al.* Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol* 2004; **22:** 2214–32.

Toxoplasmosis. For mention of the use of fluorouracil with clindamycin to treat cerebral toxoplasmosis, see p. 271.1.

Warts. Fluorouracil has been used, as a 1% or, more usually, a 5% cream or solution in the treatment of genital warts (condylomata acuminata).[1-3] It has been tried as an adjuvant to laser therapy in severe papillomavirus-associated vulvar disease,[4] with variable results, and in men with subclinical or clinically apparent penile lesions.[5] A preparation of fluorouracil 3% in a collagen gel basis, with adrenaline as a local vasoconstrictor, has been tried by injection into genital warts.[6] Fluorouracil has also been used intraurethrally to treat intraurethral warts; preparations have included instillation of a 1% solution, 5% cream, or a 5% suppository; urethral instillation of 250 mg fluorouracil injection mixed with 0.18% lidocaine hydrochloride gel has been reported to reduce the size and number of intraurethral condyloma acuminata in 1 patient, and no new growth was seen after 6 months of follow-up.[7] A combination of fluorouracil 0.5% and salicylic acid 10% has also been stated to be effective in the topical treatment of common and plantar warts.[8] Although the evidence was weak, a systematic review found fluorouracil to be better at curing genital warts than placebo, no treatment, or podophyllum resin; use with interferon alfa-2a, or with interferon alfa-2a and carbon dioxide laser

treatment may have a better outcome.[9] For a discussion of the various agents, including cytotoxics such as fluorouracil, used to destroy warts, see p. 1689.3.

1. Kling AR. Genital warts—therapy. *Semin Dermatol* 1992; **11:** 247–55.
2. Stone KM. Human papillomavirus infection and genital warts: update on epidemiology and treatment. *Clin Infect Dis* 1995; **20** (suppl 1): S91–7.
3. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997; **102:** 28–37.
4. Reid R, *et al.* Superficial laser vulvectomy IV: extended laser vaporization and adjunctive 5-fluorouracil therapy of human papillomavirus-associated vulvar disease. *Obstet Gynecol* 1990; **76:** 439–48.
5. Bergman A, Nalick R. Genital human papillomavirus infection in men: diagnosis and treatment with a laser and 5-fluorouracil. *J Reprod Med* 1991; **36:** 363–6.
6. Swinehart JM, *et al.* Intralesional fluorouracil/epinephrine injectable gel for treatment of condylomata acuminata: a phase 3 clinical study. *Arch Dermatol* 1997; **133:** 67–73.
7. Gammon DC, *et al.* Intraurethral fluorouracil and lidocaine for intraurethral condyloma acuminata. *Am J Health-Syst Pharm* 2008; **65:** 1830–3.
8. Zschocke I, *et al.* Wirksamkeit und Nutzen eines 5-FU-/Salicylsäure-haltigen Präparates in der Therapie vulgärer und plantarer Warzen—systematische Literaturübersicht und Metaanalyse. *J Dtsch Dermatol Ges* 2004; **2:** 187–93.
9. Batista CS, *et al.* 5-FU for genital warts in non-immunocompromised individuals. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 21/06/10).

Adverse Effects and Treatment

For general discussions see Antineoplastics, p. 726.1 and p. 730.2. The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is also schedule dependent: a 5-day regimen is commonly associated with bone marrow suppression, diarrhoea, and mucositis, a weekly schedule with neutropenia. With protracted continuous infusion or high-dose boluses, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hands and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site. Leucopenia is common; the nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. It is recommended that treatment should also be stopped if falling blood counts go below 100 000 cells/mm^3 for platelets or below 3500 cells/mm^3 for white cells, but see also Bone Marrow Depression, p. 730.3. Anaemia may also occur. Nausea and vomiting are common, and may be treated with an antiemetic. Alopecia may be seen especially in females, but is generally reversible. Other adverse effects include dermatitis, changes in pigmentation, changes in the nails, ataxia, and fever. Thrombophlebitis has been reported. Ocular toxicity, including excessive lachrymation, dacryostenosis, visual changes, and photophobia can occur. A transient reversible cerebellar syndrome has been reported, and a reversible confusional state can occur rarely. Cases of leukoencephalopathy have also been reported. There have been reports of chest pain, tachycardia, breathlessness, and ECG changes after use of fluorouracil. Anaphylaxis has also occurred.

Local inflammatory reactions such as erythema, pain, pruritus, burning, irritation, and photosensitivity reactions have occurred after topical use. Telangiectasia, hyperpigmentation, and scarring have also been reported. Dermatitis and, rarely, erythema multiforme have occurred. Ocular irritation has also been reported after topical use.

Effects on the eyes. Systemic fluorouracil therapy has been associated with various types of ocular toxicity including several cases of excessive lachrymation and watering of the eyes.[1] In one patient this was associated with symptoms suggesting fibrosis of the tear duct,[1] and possibly representing local irritation due to the presence of fluorouracil in tear fluid,[2] although symptoms have not always resolved on stopping the drug.[1] More seriously a case of bilateral total corneal epithelial erosion has been described.[3] Optic neuropathy, culminating in near blindness, has also occurred in a patient given fluorouracil as part of a combination regimen.[4] Severe ulceration and corneal abscess with hyopyon has followed local injection of fluorouracil into the eye in a diabetic patient with idiopathic band keratopathy.[5]

1. HaidakDJ, *et al.* Tear-duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Ann Intern Med* 1978; **88:** 657.
2. Christophidis N, *et al.* Lacrimation and 5-fluorouracil. *Ann Intern Med* 1978; **89:** 574.
3. Hirsh A, *et al.* Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy. *Br J Ophthalmol* 1990; **74:** 638.
4. Adams JW, *et al.* Recurrent acute toxic optic neuropathy secondary to 5-FU. *Cancer Treat Rep* 1984; **68:** 565–6.
5. Hickey-Dwyer M, Wishart PK. Serious corneal complication of 5-fluorouracil. *Br J Ophthalmol* 1993; **77:** 250–1.

Effects on the heart. Life-threatening cardiotoxicity (arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischaemia) has been reported to occur in 0.55% of patients given fluorouracil,[1] although the incidence of angina and less severe cardiotoxicity associated with coronary artery spasm may be higher.[1-3] Possible risk factors include pre-existing heart disease or mediastinal radiotherapy, and prolonged infusion of the drug, but symptoms can also occur in patients without these risk factors.[2-5] Therefore, at present, it is not possible to reliably predict patients at risk.[6] Some suggest that the use of a trometamol buffer in the fluorouracil formulation may contribute to the formation of cardiotoxic degradation products.[7]

1. Keefe DL, *et al.* Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol* 1993; **33:** 1060–70.
2. McLachlan SA, *et al.* The spectrum of 5-fluorouracil cardiotoxicity. *Med J Aust* 1994; **161:** 207–9.
3. Anand AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother* 1994; **28:** 374–8.
4. Hannaford R. Sudden death associated with 5-fluorouracil. *Med J Aust* 1994; **161:** 225.
5. Dalzell JR, Samuel LM. The spectrum of 5-fluorouracil cardiotoxicity. *Anticancer Drugs* 2009; **20:** 79–80.
6. Becker K, *et al.* Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs* 1999; **57:** 475–84.
7. Lukaschek J, *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; **22:** 5022–5.

Effects on the nervous system. Central neurotoxicity, including cerebellar ataxia, confusion, disorientation, and emotional lability is reported to occur rarely in patients receiving fluorouracil, although the incidence may be increased with high-dose or intensive regimens. The dihydropyrimidine dehydrogenase gene may exist in variant forms[1] and patients with polymorphisms of this or other disorders of pyrimidine metabolism may be at increased risk of neurotoxicity.[2-4] It has also been suggested that fluorouracil may produce neurotoxicity by causing thiamine deficiency,[5] (Wernicke's encephalopathy has been reported[6]) and that thiamine may be used to treat it.[5,6]

1. Amstutz U, *et al.* Dihydropyrimidine dehydrogenase gene variation and severe 5-fluorouracil toxicity: a haplotype assessment. *Pharmacogenomics* 2009; **10:** 931–44.
2. Tuchman M, *et al.* Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. *N Engl J Med* 1985; **313:** 245–9.
3. Stéphan F, *et al.* Depressed hepatic dihydropyrimidine dehydrogenase activity and fluorouracil-related toxicities. *Am J Med* 1995; **99:** 685–8.
4. Takimoto C, *et al.* Reversible 5-fluorouracil-associated encephalopathy in a dihydropyrimidine dehydrogenase (DPD) deficient patient. *Clin Pharmacol Ther* 1996; **59:** 161.
5. Pirzada NA, *et al.* Fluorouracil-induced neurotoxicity. *Ann Pharmacother* 2000; **34:** 35–8.
6. Cho IJ, *et al.* A case of Wernicke's encephalopathy following fluorouracil-based chemotherapy. *J Korean Med Sci* 2009; **24:** 747–50.

Effects on the skin. In addition to reports of fluorouracil-associated dermatitis and photosensitivity a syndrome of erythema, pain, and desquamation of the skin of palms and soles has been reported[1-4] (the palmar-plantar erythrodysesthesia syndrome, p. 730.1). Although particularly associated with continuous infusion[1,2] the syndrome can also occur after bolus doses.[3,4] Symptoms generally respond to stopping the drug, but addition of oral pyridoxine to chemotherapy regimens has been reported to prevent or resolve symptoms,[5] as has application of a nicotine patch in one patient.[6]

Rash and confusion developing in an elderly man with malabsorption and poor nutritional intake who received fluorouracil for a biliary-tract tumour were diagnosed as pellagra.[7] Symptoms responded to nicotinic acid therapy.

1. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
2. Feldman LD, Ajani JA. Fluorouracil-associated dermatitis of the hands and feet. *JAMA* 1985; **254:** 3479.
3. Atkins JN. Fluorouracil and the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1985; **102:** 419.
4. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. *Ann Intern Med* 1989; **111:** 858.
5. Vukelja SJ, *et al.* Pyridoxine for the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1989; **111:** 688–9.
6. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; **120:** 813.
7. Stevens HP, *et al.* Pellagra secondary to 5-fluorouracil. *Br J Dermatol* 1993; **128:** 578–80.

Hypersensitivity. Although local hypersensitivity reactions are included in licensed product information as potential adverse effects of topical fluorouracil, hypersensitivity reactions to systemic fluorouracil have been reported very rarely.[1-6] For a report of the successful use of fluorouracil in a patient allergic to capecitabine, suggesting that cross-sensitivity does not occur between the two, see p. 758.2.

1. Reed WP, Morris DM. Maculopapular eruption resulting from systemic administration of 5-fluorouracil. *Cutis* 1984; **33:** 381–2.
2. Sridhar KS. Allergic reaction to 5-fluorouracil infusion. *Cancer* 1986; **58:** 862–4.
3. Milla Santos A, Sanchiz Medina F. Anaphylactic reaction following iv administration of 5-fluorouracil. *Cancer Treat Rep* 1986; **70:** 1346.
4. Duley JA, Nethersell AB. Delayed hypersensitivity to 5-fluorouracil associated with reduced dihydropyrimidine dehydrogenase (DPD) activity. *Adv Exp Med Biol* 1998; **431:** 147–50.
5. Eppinger T, Sperber K. Desensitization to 5-fluorouracil. *Allergy Asthma Proc* 1999; **20:** 189–91.
6. Biswal BM. Anaphylaxis following continuous 5-fluorouracil infusion chemotherapy. *Aust N Z J Med* 1999; **29:** 743–4.

Precautions

For general discussions see Antineoplastics, p. 732.2. Fluorouracil should be given with care to weak or malnourished patients, to those with a history of heart disease, or to those with hepatic or renal insufficiency. Patients with a history of high-dose pelvic irradiation or treatment with alkylating agents, and those with widespread metastases to the bone marrow should also be treated with extreme caution. Blood cell counts should be determined frequently during therapy. Fluorouracil should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency as this can lead to increased toxicity.

Topical fluorouracil should not be used on mucous membranes. There is a possibility of increased absorption if used excessively or on ulcerated or inflamed skin. Occlusive dressings may increase inflammatory actions. Exposure to UV light during treatment should be avoided. Creams are preferably applied using a nonmetal applicator or gloved hand; if bare fingertips are used the hands must be washed immediately afterwards.

Handling and disposal. Fluorouracil is irritant; avoid contact with skin and mucous membranes.

Urine and faeces produced for up to 48 hours and 5 days respectively after an oral dose of fluorouracil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Metabolic disorders. For reference to increased risk of neurotoxicity in patients with a defect of pyrimidine metabolism given fluorouracil, see under Effects on the Nervous System, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluorouracil as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3. The actions of fluorouracil may be modified by other drugs including allopurinol, cimetidine, folinic acid, methotrexate, and metronidazole (see also under Administration, p. 796.1). Fluorouracil and fluorouracil prodrugs should not be given with brivudine, sorivudine, and analogues as these are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD) which degrades fluorouracil, and increased fluoropyrimidine toxicity can occur (see also Precautions, above, and Antivirals, below).

References.

1. Jansman FGA, *et al.* Assessing the clinical significance of drug interactions with fluorouracil in patients with colorectal cancer. *Am J Health-Syst Pharm* 2005; **62:** 1788–93.

Antineoplastics. *Oxaliplatin,* which is given with fluorouracil and folinic acid in the treatment of colorectal cancer, reduced fluorouracil clearance in a study[1] of 29 patients with colorectal cancer. The effect was delayed and prolonged, lasting about 15 days, and an increase in toxicity correlated with raised fluorouracil concentrations. The mechanism of this interaction is unclear. In contrast, however, another study[2] found no effect of oxaliplatin on fluorouracil pharmacokinetics; the study was not designed to investigate a delayed effect and the dose of oxaliplatin was lower than that used in the first study.

Sorafenib has been reported to have variable effects on fluorouracil exposure.

For reference to the effect of fluorouracil on the action of *paclitaxel,* see Antineoplastics, p. 842.2. For the increased risk of haemolytic-uraemic syndrome that may be seen if fluorouracil is used with *mitomycin,* see Effects on the Kidneys, p. 831.3.

1. Boisdron-Celle M, *et al.* Influence of oxaliplatin on 5-fluorouracil plasma clearance and clinical consequences. *Cancer Chemother Pharmacol* 2002; **49:** 235–43.
2. Joel SP, *et al.* Lack of pharmacokinetic interaction between 5-fluorouracil and oxaliplatin. *Clin Pharmacol Ther* 2004; **76:** 45–54.

Antiprotozoals. *Metronidazole* increased the toxicity of fluorouracil in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic. No enhanced antineoplastic effect was seen with the combination *in vitro.*[1]

1. Bardakji Z, *et al.* 5-Fluorouracil–metronidazole combination therapy in metastatic colorectal cancer. *Cancer Chemother Pharmacol* 1986; **18:** 140–4.

Antivirals. Giving *interferon alfa-2b* with fluorouracil has produced a marked increase in the initial plasma concentration of fluorouracil and a decrease in fluorouracil clearance.[1]

Severe leucopenia, fatal in some cases, has been reported in patients given fluorouracil or fluorouracil prodrugs (such as tegafur) with *sorivudine*.[2,3] A metabolite of sorivudine appears to inhibit dihydropyrimidine dehydrogenase, the primary enzyme responsible for the inactivation of fluorouracil.[3] A fatality has also been reported in a patient treated with the oral prodrug capecitabine who was also given *brivudine*.[4]

1. Czejka MJ, *et al.* Clinical pharmacokinetics of 5-fluorouracil: influence of the biomodulating agents interferon, dipyridamole and folic acid alone and in combination. *Arzneimittelforschung* 1993; **43:** 387–90.
2. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342:** 1166.
3. Diasio RB. Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; **46:** 1–4.
4. Rätz Bravo AE, *et al.* Fatal drug-drug interaction of brivudine and capecitabine. *Acta Oncol* 2009; **48:** 631–3.

Gastrointestinal drugs. Pretreatment with *cimetidine* for 4 weeks increased plasma concentrations of fluorouracil after intravenous and oral doses in 6 patients.[1] The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen after single doses of cimetidine in 5 patients or pretreatment for just 1 week in 6. Care is required in patients given both drugs together.

1. Harvey VJ, *et al.* The influence of cimetidine on the pharmacokinetics of 5-fluorouracil. *Br J Clin Pharmacol* 1984; **18:** 421–30.

Pharmacokinetics

Absorption of fluorouracil from the gastrointestinal tract is unpredictable and fluorouracil is usually given intravenously. Little is absorbed when fluorouracil is applied to healthy skin.

After intravenous injection fluorouracil is cleared rapidly from plasma with a mean half-life of about 16 minutes. It is distributed throughout body tissues and fluids (including crossing the blood-brain barrier to appear in the CSF), and disappears from the plasma within about 3 hours. Within the target cell fluorouracil is converted to 5-fluorouridine monophosphate and floxuridine monophosphate (5-fluorodeoxyuridine monophosphate), the former undergoing conversion to the triphosphate which can be incorporated into RNA while the latter inhibits thymidylate synthetase. About 15% of an intravenous dose is excreted unchanged in the urine within 6 hours. The remainder is inactivated mainly in the liver and is catabolised via dihydropyrimidine dehydrogenase (DPD) similarly to endogenous uracil. A large amount is excreted as respiratory carbon dioxide; urea and other metabolites are also produced.

References.

1. Ploylearmsaeng S-A, *et al.* How may anticancer chemotherapy with fluorouracil be individualised? *Clin Pharmacokinet* 2006; **45:** 567–92.

Chronopharmacology. Plasma concentrations of fluorouracil during continuous intravenous infusion are reported to undergo circadian variations of as much as 50% of the mean, peak concentrations occurring in the middle of the night.[1] The variation may be due to a circadian variation in the activity of the enzyme dihydropyrimidine dehydrogenase in blood,[2] but striking interpatient variations in peak concentrations of fluorouracil and peak enzyme activity suggest that any adjustment of infusion times would need to be individualised.[2] It has been suggested that pharmacokinetic monitoring should be investigated as a means of individualising fluorouracil doses with the aim of improving efficacy and reducing toxicity.[3]

1. Petit E, *et al.* Circadian rhythm-varying plasma concentration of 5-fluorouracil during a five-day continuous venous infusion at a constant rate in cancer patients. *Cancer Res* 1988; **48:** 1676–9.
2. Harris BE, *et al.* Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracillevels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. *Cancer Res* 1990; **50:** 197–201.
3. Young AM, *et al.* Can pharmacokinetic monitoring improve clinical use of fluorouracil. *Clin Pharmacokinet* 1999; **36:** 391–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acler; Efudix; Oncofu†; Triosules; ***Austral.***: Efudix; ***Belg.***: Efudix; Fluracedyl; Fluroblastine; ***Braz.***: Efurix; Fauldfluor; Neugrast; ***Canad.***: Efudex; Fluoroplex†; ***Chile***: Efudix; Fluoracilo†; ***China***: An Te Fan (安特凡); Fu Ke (福可); Fu Mi Te (弗米特); Fu Ruo Xin (福若欣); Fu Shi Ke (扶时可); Gefente (格芬特); Hua Kang Da (华康达); Ning Lan Xin (宁兰欣); Pu Li Da (普力达); Sen Ting (森汀); Sinofuan (中人氟安); Zuo Ding (佐定); ***Cz.***: La-Fu†; ***Denm.***: Flurablastin; ***Fin.***: Flurablastin; ***Fr.***: Efudix; ***Ger.***: Benda; Efudix; Haemato-fu†; Neofluor†; Onkofluor†; Ribofluor; ***Gr.***: Fluracedyl; Fluroblastin; Uraciflor; ***Hong Kong***: Efudix; ***Hung.***: Efudix; ***India***: Fivefluro†; Fivocil; Fivoflu; Flocil; Flonida; Florac; Flucil; Fludin; Fluonco; Fluracil; Flutas; Kucil; Oncofluor; Oncourcil; ***Indon.***: Curacil; Fluracedyl; ***Irl.***: Efudix; ***Israel***: Efudix; ***Malaysia***: Fluracedyl; ***Mex.***: Acoflut; Carebin; Efudix; Flurox; Tecflu; ***Neth.***: Efudix; Fluracedyl; ***Norw.***: Flurablastin; ***NZ***: Efudix; ***Philipp.***: Fivoflu; Fluonco; Fluoxan†; Fluracedyl; Fluroblastin; Uflahex†; Utoral; ***Pol.***: Efudix; ***Port.***: Cinkef-U; ***Rus.***: Flurox (Флурокс); ***S.Afr.***: Efudix; Floracor; Fluracedyl; Fluroblastin; ***Singapore***: Efudix†; ***Swed.***: Flurablastin†; ***Switz.***: Efudix; ***Thai.***: Effcil; Fivoflu†; Flurox†; ***Turk.***: Fluro-5; Oncosil; Oncouracil†; ***UK***: Efudix; ***USA***: Adrucil; Carac; Efudex; Fluoroplex; ***Venez.***: Fivoflu; Fluroblastin.

Multi-ingredient Preparations. ***Austria***: Verrumal; ***Cz.***: Verrumal; ***Ger.***: Actikerall; Verrumal; ***Gr.***: Verruca Hermal; ***Hong Kong***: Verrumal; ***Hung.***: Verrumal; ***Israel***: Verrumal; ***Malaysia***: Verrumal; ***Pol.***: Verrumal; ***Port.***: Verrucare; Verrumal; ***Singapore***: Verrumal; ***Switz.***: Actikerall; Verrumal; ***Thai.***: Verrumal; ***Turk.***: Verrutol; ***UK***: Actikerall.

Pharmacopoeial Preparations

BP 2014: Fluorouracil Cream; Fluorouracil Injection;
USP 36: Fluorouracil Cream; Fluorouracil Injection; Fluorouracil Topical Solution.

Flutamide *(BAN, USAN, rINN)*

Flutamid; Flutamida; Flutamidas; Flutamidi; Flutamidum; Sch-13521; Флутамид.

α′,α′,α′-Trifluoro-4′-nitroisobutyro-*m*-toluidide; α,α,α-Trifluoro-2-methyl-4′-nitro-*m*-propionotoluidide.

$C_{11}H_{11}F_3N_2O_3$=276.2

CAS — 13311-84-7.

ATC — L02BB01.

ATC Vet — QL02BB01.

UNII — 76W6J0943E.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; practically insoluble in heptane. Protect from light.

USP 36: (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water, in liquid paraffin, and in petroleum spirit; freely soluble in acetone, in ethyl acetate, and in methyl alcohol; soluble in chloroform and in ether. Store in airtight containers. Protect from light.

Uses and Administration

Flutamide is a nonsteroidal compound with anti-androgenic properties which appears to act by inhibiting the uptake and/or binding of androgens in target tissues. It is used, usually with gonadorelin analogues, in the palliative treatment of prostatic carcinoma (p. 712.3). The usual oral dose is 250 mg three times daily. When used in combination therapy UK licensed product information recommends that flutamide treatment should be started at least 3 days before the gonadorelin analogue to suppress any 'flare' reaction; however, in some other countries it is recommended that treatment with both agents be begun simultaneously for optimum effect.

Congenital adrenal hyperplasia. For mention of the use of flutamide with testolactone to block androgenic effects in congenital adrenal hyperplasia, see p. 1603.2.

Hirsutism and alopecia. Anti-androgens (usually cyproterone or spironolactone) are widely used for the drug treatment of hirsutism (p. 2262.1). Flutamide has no particular advantage in this context;[1,2] one study has found flutamide to be more effective than spironolactone in inhibiting hirsutism,[3] but others found them to be of similar efficacy,[4,5] and the risk of hepatotoxicity with flutamide is a problem.[2] Nonetheless, flutamide has continued to be investigated.[6-10]

Flutamide has also been investigated[11] in women with female-pattern hair loss (female androgenetic alopecia).

1. Rittmaster RS. Hyperandrogenism—what is normal? *N Engl J Med* 1992; **327:** 194–6.
2. Rittmaster RS. Hirsutism. *Lancet* 1997; **349:** 191–5.
3. Cusan L, *et al.* Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertil Steril* 1994; **61:** 281–7.
4. Erenus M, *et al.* Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertil Steril* 1994; **61:** 613–6.
5. Moghetti P, *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85:** 89–94.
6. Muderris II, *et al.* Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). *Gynecol Endocrinol* 2000; **14:** 38–41.
7. Venturoli S, *et al.* Low-dose flutamide (125 mg/day) as maintenance therapy in the treatment of hirsutism. *Horm Res* 2001; **56:** 25–31.
8. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60:** 241–9.
9. Calaf J, *et al.* Spanish Working Group for Hirsutism. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *J Clin Endocrinol Metab* 2007; **92:** 3446–52.
10. Unluhizarci K, *et al.* A comparison between finasteride, flutamide, and finasteride plus flutamide combination in the treatment of hirsutism. *J Endocrinol Invest* 2009; **32:** 37–40.
11. Paradisi R, *et al.* Prospective cohort study on the effects and tolerability of flutamide in patients with female pattern hair loss. *Ann Pharmacother* 2011; **45:** 469–75.

Polycystic ovary syndrome. Flutamide has been used, usually with metformin, in the management of polycystic ovary syndrome (p. 2253.3);[1-5] additive effects have been reported with this combination.

1. Ibáñez L, *et al.* Additive effects of insulin-sensitizing and anti-androgen treatment in young nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 2002; **87:** 2870–4.
2. Ibáñez L, *et al.* Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *J Clin Endocrinol Metab* 2003; **88:** 2600–6.
3. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60:** 241–9.
4. Gambineri A, *et al.* Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *J Clin Endocrinol Metab* 2006; **91:** 3970–80.
5. Ibáñez L, *et al.* Low-dose pioglitazone, flutamide, metformin plus an estro-progestagen for non-obese young women with polycystic ovary syndrome: increasing efficacy and persistent safety over 30 months. *Gynecol Endocrinol* 2010; **26:** 869–73.

Adverse Effects and Precautions

The most frequently reported adverse effects with flutamide are hot flushes and reversible gynaecomastia or breast tenderness, sometimes accompanied by galactorrhoea. Nausea, vomiting, diarrhoea, increased appetite, anorexia, and sleep disturbances may occur. There have been reports of skin reactions, including epidermal necrolysis, and of liver damage, sometimes fatal. Other adverse effects reported in patients receiving flutamide include anaemias, haemolysis, headache, dizziness, malaise, blurred vision, anxiety, depression, decreased libido, impotence, and hypertension. Abdominal pain, chest pain, dyspnoea, and cough have been reported rarely. Discoloration of the urine to amber or yellow-green can be caused by the presence of flutamide and/or its metabolites.

Flutamide should be used with care in patients with cardiovascular disease because of the possibility of fluid retention. It should also be used with caution in patients with hepatic impairment and is contra-indicated in those with severe impairment. Regular liver function testing is recommended in all patients: therapy should be stopped or dosage reduced if there is evidence of hepatotoxicity.

Effects on the blood. A report[1] of methaemoglobinaemia in an elderly man was attributed to flutamide. A study[2] of 45 patients given flutamide found no cases of methaemoglobinaemia, but the authors noted a further 3 published case reports.

1. Schott AM, *et al.* Flutamide-induced methemoglobinemia. *DICP Ann Pharmacother* 1991; **25:** 600–1.
2. Schulz M, *et al.* Lack of methemoglobinemia with flutamide. *Ann Pharmacother* 2001; **35:** 21–5.

Effects on the liver. Hepatitis occurred in a 79-year-old man taking flutamide 750 mg daily as sole therapy after a prostatectomy,[1] but a subsequent study[2] in 1091 patients given flutamide 250 mg three times daily as part of a regimen for prostate cancer found marked signs of liver damage only in 4, of whom only 2 had clinical evidence of hepatotoxicity. In the USA, the FDA had 46 reports of patients with hepatotoxicity associated with flutamide up to December 1994. Of these patients, 20 died from progressive liver disease.[3] Further cases have continued to be reported,[4-7] including in women receiving low doses for hirsutism.[7,8] Early tapering of the dose, stopping therapy, or switching to another anti-androgen may resolve hepatotoxic effects.[9] Patients with chronic viral hepatitis may be at higher risk of developing hepatotoxicity with anti-androgen therapy.[10]

1. Hart W, Stricker BHC. Flutamide and hepatitis. *Ann Intern Med* 1989; **110:** 943–4.
2. Gomez J-L, *et al.* Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *Am J Med* 1992; **92:** 465–70.
3. Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. *J Urol (Baltimore)* 1996; **155:** 209–12. Correction *ibid:* 396.
4. Garcia Cortes M, *et al.* Flutamide-induced hepatotoxicity: report of a case series. *Rev Esp Enferm Dig* 2001; **93:** 423–32. Correction. *ibid.;* 634.
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6. Osculati A, Castiglioni C. Fatal liver complications with flutamide. *Lancet* 2006; **367:** 1140–1.
7. Brahm J, *et al.* Acute and fulminant hepatitis induced by flutamide: case series report and review of the literature. *Ann Hepatol* 2011; **10:** 93–8.
8. Castelo-Branco C, Del Pino M. Hepatotoxicity during low-dose flutamide treatment for hirsutism. *Gynecol Endocrinol* 2009; **25:** 419–22.
9. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66:** 735–40.
10. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36:** 293–7.

Effects on the lungs. In a review[1] of 78 cases of pneumonitis reported to the FDA between 1998 and 2000 that were associated with bicalutamide, flutamide, or nilutamide, it was found that 14 patients had died of respiratory failure. It was estimated that the incidence of pneumonitis

was highest for nilutamide (0.77%), but lower for flutamide (0.04%) and bicalutamide (0.01%).

1. Bennett CL, *et al.* Pneumonitis associated with nonsteroidal antiandrogens: presumptive evidence of a class effect. *Ann Intern Med* 2002; **137:** 625.

Effects on the skin. Photosensitivity reactions have been reported in patients receiving flutamide.[1,2] Some consider it to be an early manifestation of SLE.[2]

1. Fujimoto M, *et al.* Photosensitive dermatitis induced by flutamide. *Br J Dermatol* 1996; **135:** 496–7.
2. Kaur C, Thami GP. Flutamide-induced photosensitivity: is it a forme fruste of lupus? *Br J Dermatol* 2003; **148:** 603–4.

Gynaecomastia. Gynaecomastia (p. 2264.3) and breast pain are frequent adverse effects of nonsteroidal anti-androgens used to treat prostate cancer. Nearly 90% of patients treated with bicalutamide in the Early Prostate Cancer programme had breast pain, gynaecomastia, or both.[1] Some patients will accept gynaecomastia as a tolerable adverse effect of therapy but others will require specific treatment. The risk of breast changes can be reduced by the use of prophylactic low-dose irradiation of the breast area before nonsteroidal anti-androgen therapy is started. However, skin irritation can occur, and the long-term risk for development of breast cancer is unknown. Irradiation is unlikely to be effective once breast enlargement has occurred but it can help to reduce pain. Empirical use of oral analgesics or topical local anaesthetics may be considered for breast pain. Specific surgical treatment to reduce breast tissue includes liposuction and breast tissue excision.[2,3]

Hormonal therapy using tamoxifen or anastrozole has been suggested, largely based on reports of benefit in various patient groups with gynaecomastia.[1,2] Two randomised controlled studies[4,5] of men who were treated with bicalutamide for prostate cancer found that prophylactic tamoxifen was effective for the prevention of gynaecomastia and breast pain, but that anastrozole was no better than placebo. One of these studies[5] also assessed the use of these drugs as treatment and found that gynaecomastia and breast pain resolved in at least 65% of patients treated with tamoxifen, but only in about 18% of those treated with anastrozole. Tamoxifen is considered to be more effective than radiotherapy for prevention of gynaecomastia.[3]

1. Sieber PR. Treatment of bicalutamide-induced breast events. *Expert Rev Anticancer Ther* 2007; **7:** 1773–9.
2. Leibovitch I, *et al.* Management options for gynaecomastia and breast pain associated with nonsteroidal antiandrogen therapy: case studies in context. *Clin Drug Invest* 2003; **23:** 205–15.
3. Di Lorenzo G, *et al.* Management of gynaecomastia in patients with prostate cancer: a systematic review. *Lancet Oncol* 2005; **6:** 972–9.
4. Boccardo F, *et al.* Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; **23:** 808–15.
5. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; **8:** 75–83.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flutamide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Flutamide may increase the effect of warfarin, see Antineoplastics, p. 1532.2.

Pharmacokinetics

Flutamide is reported to be rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 hour after a dose. It is rapidly and extensively metabolised; the major metabolite (2-hydroxyflutamide) possesses anti-androgenic properties. The half-life of the metabolite is about 6 hours. Both flutamide and 2-hydroxyflutamide are more than 90% bound to plasma proteins. Excretion is mainly in the urine with only minor amounts appearing in the faeces.

References.

1. Radwanski E, *et al.* Single and multiple dose pharmacokinetic evaluation of flutamide in normal geriatric volunteers. *J Clin Pharmacol* 1989; **29:** 554–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asoflut; Dedile; Flutaplex; Flutepan; Flutrax; ***Austral.***: Eulexin; Flutamin; ***Austria***: Flutabene; Flutastad; Fugerel; ***Belg.***: Eulexin; Flutaplex; ***Braz.***: Eulexin; Tecnoflut; Teflut; ***Canad.***: Euflex; ***Chile***: Drogenil†; Etaconil; Flulem†; Ilidar; ***China***: Fugerel (福至尔); ***Cz.***: Andraxan†; Flucinom; Flumed; Flutaplex; Prostandril†; ***Denm.***: Eulexin†; Fluprosin; Profamid; ***Fin.***: Eulexin†; Profamid; ***Fr.***: Eulexine; Prostadirex; ***Ger.***: Flumid†; Fluta; Fugerel†; Prostica†; ***Gr.***: Adiprost†; Andraxan; Antipros; Elbat; Flucinom; Flutaplex; Palistop; Prostamide; Rikital; Rosiniol; Tremexal; ***Hong Kong***: Codalan†; Fugerel; ***Hung.***: Fluprost; Flutam; Flutasin; Fugerel; Prosztika; ***India***: Cytomid; Drogenil; Flutam; Flutide; Prostamid; ***Indon.***: Flutaplex; Fugerel; ***Irl.***: Androstat†; Drogenil; ***Ital.***: Eulexin; Fluprost; Ricalide; ***Malaysia***: Eumide; Fluta-Cell; Flutaplex; ***Mex.***: Eulexin†; Flimutal; Flulem; Tafenil; ***Neth.***: Flutaplex†; ***Norw.***: Eulexin; ***NZ***: Eulexin; Flutamin; ***Philipp.***: Fugerel; Prostanon; ***Pol.***: Apo-Flutam; Fugerel†; Prostandril†; ***Port.***: Drogenil; Eulexin; Prosneo; ***Rus.***: Flucinom (Флуцином); Flutamid (Флутамид); Flutaplex (Флутаплекс); Frugyl (фругил); ***S. Afr.***: Eulexin; Flutahexal; Flutaplex; ***Singapore***: Flutan; Fugerel; ***Spain***: Eulexin; Grisetin; Oncosal†; Prostacur; ***Swed.***: Eulexin; ***Switz.***: Flucinome†; ***Thai.***: Andraxan; Flulem; Flutan; Flutaplex; Fugerel; ***Turk.***: Andraxan; Eulexin; ***UK***: Chimax; Drogenil†; ***Ukr.***: Flutafarm (Флутафарм); ***Venez.***: Etaconil; Eulexin.

Pharmacopoeial Preparations

USP 36: Flutamide Capsules.

Formestane *(BAN, rINN)* ⊗

CGP-32349; Formestaani; Formestan; Formestano; Formestanum; 4-Hydroxyandrostenedione; 4-OHA; 4-OHAD; Форместан.

4-Hydroxyandrost-4-ene-3,17-dione.

$C_{19}H_{26}O_3$=302.4

CAS — 566-48-3.

ATC — L02BG02.

ATC Vet — QL02BG02.

UNII — PUB9T8T355.

Profile

Formestane, like exemestane (p. 792.2), is a steroidal inhibitor of the aromatase (oestrogen synthetase) system responsible for the production of oestrogens from androgens. It has been used for its anti-oestrogenic properties in the endocrine treatment of advanced breast cancer in postmenopausal women.

Irritation and pain at the site of intramuscular injection have been reported; injection into or near the sciatic nerve has resulted in pain and nerve trauma. Hypersensitivity reactions have occurred.

Reviews.

1. Wiseman LR, McTavish D. Formestane: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of breast cancer and prostatic cancer. *Drugs* 1993; **45:** 66–84.
2. Anonymous. Formestane for advanced breast cancer in postmenopausal women. *Drug Ther Bull* 1993; **31:** 85–7.
3. Carlini P, *et al.* Formestane, a steroidal aromatase inhibitor after failure of non-steroidal aromatase inhibitors (anastrozole and letrozole): is a clinical benefit still achievable? *Ann Oncol* 2001; **12:** 1539–43.

Effects on carbohydrate metabolism. Recurrent hypoglycaemic episodes developed in a diabetic patient previously well maintained on gliclazide after addition of formestane to treatment for metastatic breast cancer.[1] Episodic hypoglycaemia continued after dosage reduction, and eventually withdrawal, of gliclazide, suggesting that the effect was not simply an interaction with the sulfonylurea.

1. Brankin E, *et al.* Hypoglycaemia associated with formestane treatment. *BMJ* 1997; **314:** 869.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Lentaron†; ***Turk.***: Lentaron†.

Forodesine Hydrochloride *(USAN, rINNM)*

BCX-1777 (forodesine or forodesine hydrochloride); Forodésine, Chlorhydrate de; Forodesini Hydrochloridum; Hidrocloruro de forodesina; Фородезина Гидрохлорид.

(-)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one hydrochloride.

$C_{11}H_{14}N_4O_4$,HCl=302.7

CAS — 209799-67-7 (forodesine); 284490-13-7 (forodesine hydrochloride).

UNII — 6SN82Y9U73.

Profile

Forodesine is an inhibitor of purine nucleoside phosphorylase. It is under investigation in the treatment of T-cell lymphomas, chronic lymphocytic leukaemia, and acute lymphoblastic leukaemia.

Fosbretabulin *(rINN)*

CA4P; Combretastatin A4 Phosphate; CS-A4 (combretastatin A4); Fosbretabulina; Fosbrétabuline; Fosbretabulinum; NSC-348103 (combretastatin); Фосбретабулин.

2-Methoxy-5-[(1*Z*)-2-(3,4,5-trimethoxyphenyl)ethenyl]-phenyl dihydrogen phosphate.

$C_{18}H_{21}O_8P$=396.3

CAS — 82855-09-2 (combretastatin); 117048-59-6 (combretastatin A4); 222030-63-9 (combretastatin A4 phosphate); 168555-66-6 (combretastatin A4 disodium phosphate).

UNII — I5590ES2QZ.

NOTE. The name Zybrestat has been used as a trade mark for fosbretabulin.

Profile

Fosbretabulin is a synthetic derivative of combretastatin compounds originally isolated from the African bush-willow tree (Cape bush-willow; *Combretum caffrum*). It is described as a vascular targeting agent that reduces blood flow to tumours by disrupting the endothelial cells of newly formed blood vessels, and is under investigation for the treatment of thyroid, ovarian, and non-small cell lung cancer. It is also being investigated topically for ophthalmological disease, particularly age-related macular degeneration.

Fotemustine *(BAN, rINN)*

Fotemustin; Fotemustina; Fotémustine; Fotemustinum; S-10036; Фотемустин.

(±)-Diethyl {1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl}phosphonate.

$C_9H_{19}ClN_3O_5P$=315.7

CAS — 92118-27-9.

ATC — L01AD05.

ATC Vet — QL01AD05.

UNII — GQ7JL9P5I2.

Profile

Fotemustine is a nitrosourea derivative and alkylating agent with actions similar to those of carmustine (p. 761.2). It is used in the treatment of disseminated malignant melanoma (p. 714.3), particularly where cerebral metastases are present, and has been tried in primary malignancies of the brain (p. 701.2). When used as a single agent it is licensed for intravenous or intra-arterial infusion in usual doses of 100 mg/m^2 weekly for 3 weeks to induce remission, followed after 4 to 5 weeks, if blood counts permit, by maintenance dosage with 100 mg/m^2 every 3 weeks. Intravenous infusions are given over 1 hour and intra-arterial infusions over 4 hours. Liver function should be monitored regularly during induction treatment. Regular blood counts should be taken and dosage should be reduced or withheld if white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p. 730.3). Bone-marrow suppression may be delayed, with the nadir of the white cell counts 5 or 6 weeks after dosing. Solutions for infusion must be freshly prepared and protected from light.

References.

1. Marzolini C, *et al.* Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration. *Cancer Chemother Pharmacol* 1998; **42:** 433–40.
2. Fazeny-Dorner B, *et al.* Second-line chemotherapy with dacarbazine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme. *Anticancer Drugs* 2003; **14:** 437–42.
3. Avril MF, *et al.* Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol* 2004; **22:** 1118–25.
4. Ozkan M, *et al.* Post-operative sequential chemo-radiotherapy in high-grade cerebral gliomas with fotemustine. *J Chemother* 2004; **16:** 298–302.
5. Bonenkamp JJ, *et al.* Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol* 2004; **30:** 1107–12.
6. Peters S, *et al.* Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006; **17:** 578–83.
7. Gill S, *et al.* Long-term survival and secondary acute leukemia after fotemustine therapy for metastatic melanoma. *J Clin Oncol* 2007; **25:** 4493–4.
8. Scoccianti S, *et al.* Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience. *Anticancer Drugs* 2008; **19:** 613–20.
9. Mangiacavalli S, *et al.* Efficacy and safety of fotemustine for the treatment of relapsed and refractory multiple myeloma patients. *Eur J Haematol* 2009; **82:** 240–1.
10. Addeo R, *et al.* Fotemustine and recurrent glioblastoma: possible new opportunities for an old drug. *Cancer Chemother Pharmacol* 2009; **64:** 863–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Muforan; ***Austral.***: Muphoran; ***Austria***: Muphoran; ***Belg.***: Muphoran; ***Braz.***:

Muphoran; ***China***: Muphoran (武活龙); ***Cz.***: Mustophoran; ***Fr.***: Muphoran; ***Gr.***: Muphoran†; ***Hung.***: Mustophoran; ***Israel***: Muphoran; ***Ital.***: Muphoran; ***NZ***: Muphoran; ***Pol.***: Mustophoran; ***Port.***: Muphoran; ***Rus.***: Mustophoran (Мюстофоран); ***Spain***: Mustoforan; ***Turk.***: Muphoran; ***Ukr.***: Mustophoran (Мюстофоран).

Fulvestrant *(BAN, USAN, rINN)* ⊗

Fulvestrantum; ICI-182780; ZD-9238; ZM-182780; Фульвестрант.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

$C_{32}H_{47}F_5O_3S$=606.8

CAS — 129453-61-8.

ATC — L02BA03.

ATC Vet — QL02BA03.

UNII — 22X328QOC4.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fulvestrant). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees. Protect from light. If the substance is sterile, store in airtight containers.

USP 36: (Fulvestrant). A mixture of the diastereoisomers A and B. A white powder. Freely soluble in alcohol. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Fulvestrant is an oestrogen antagonist that downregulates the oestrogen receptor and is used for the treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women (p. 702.1); it is given when disease has relapsed or progressed during or after treatment with anti-oestrogens. Fulvestrant is given intramuscularly in a dose of 500 mg every 2 weeks for the first 3 doses, then every month thereafter. Half the dose (250 mg) is injected into each buttock concurrently. For doses in hepatic impairment, see Administration in Hepatic Impairment, below.

References.

1. Buzdar AU. Fulvestrant: a new type of estrogen receptor antagonist for the treatment of advanced breast cancer. *Drugs Today* 2004; **40:** 751–64.
2. Bundred N. Preclinical and clinical experience with fulvestrant (Faslodex) in postmenopausal women with hormone receptor-positive advanced breast cancer. *Cancer Invest* 2005; **23:** 173–81.
3. Buzdar AU, Robertson JFR. Fulvestrant: pharmacologic profile versus existing endocrine agents for the treatment of breast cancer. *Ann Pharmacother* 2006; **40:** 1572–83.
4. Flemming J, *et al*. Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: a systematic review. *Breast Cancer Res Treat* 2009; **115:** 255–68.
5. de la Haba Rodríguez JR, *et al*. Fulvestrant in advanced male breast cancer. *Ann Oncol* 2009; **20:** 1896–7.
6. Argenta PA, *et al*. A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. *Gynecol Oncol* 2009; **113:** 205–9.
7. Valachis A, *et al*. Fulvestrant in the treatment of advanced breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Oncol Hematol* 2010; **73:** 220–7.
8. Kabos P, Borges VF. Fulvestrant: a unique antiendocrine agent for estrogen-sensitive breast cancer. *Expert Opin Pharmacother* 2010; **11:** 807–16.
9. Johnston SJ, Cheung KL. Fulvestrant—a novel endocrine therapy for breast cancer. *Curr Med Chem* 2010; **17:** 902–14.
10. Gasent Blesa JM, *et al*. Experience with fulvestrant acetate in castration-resistant prostate cancer patients. *Ann Oncol* 2010; **21:** 1131–2.
11. Di Leo A, *et al*. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol* 2010; **28:** 4594–4600.
12. Wa'tn M, *et al*. Benefits of early and prolonged fulvestrant treatment in 848 postmenopausal advanced breast cancer patients. *Breast Cancer Res Treat* 2011; **125:** 127–36.
13. Masci G, *et al*. Fulvestrant for advanced male breast cancer patients: a case series. *Ann Oncol* 2011; **22:** 985.
14. Oakman C, *et al*. Fulvestrant in the management of postmenopausal women with advanced, endocrine-responsive breast cancer. *Future Oncol* 2011; **7:** 173–86.
15. Croxtall JD, McKeage K. Fulvestrant: a review of its use in the management of hormone receptor-positive metastatic breast cancer in postmenopausal women. *Drugs* 2011; **71:** 363–80.

Administration in hepatic impairment. Exposure to fulvestrant is increased in patients with moderate hepatic impairment (Child-Pugh class B), and so in the USA a reduced dose of 250 mg as a single intramuscular injection into one buttock is given every 2 weeks for the first 3 doses and monthly thereafter; however, such dose adjustment is not recommended in the UK. Fulvestrant has not been studied in those with severe hepatic impairment (Child-Pugh class C).

Adverse Effects and Precautions

The most commonly reported adverse effects of fulvestrant are gastrointestinal disturbances, headache, musculoskeletal and abdominal pain, hot flushes, cough, dyspnoea, asthenia, and increases in liver enzymes. Injection site reactions can occur. Other common adverse effects include rash, urinary-tract infections, and thromboembolic events. Hypersensitivity reactions, including angioedema and urticaria, can occur. Vaginal bleeding or infection, vertigo and leucopenia have been reported rarely.

There is a lack of data on the use of fulvestrant in those with severe hepatic impairment (Child-Pugh class C), and use in these patients is not recommended in some countries. It should be used with caution in those with lesser degrees of hepatic impairment; a reduction in dose may be required (see Administration in Hepatic Impairment, above). Fulvestrant should also be used with caution in those with severe renal impairment (creatinine clearance less than 30 mL/minute). Because it must be given by intramuscular injection, fulvestrant should be used with caution in patients with bleeding tendencies, thrombocytopenia, or who are taking anticoagulants.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fulvestrant as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pharmacokinetics

Fulvestrant is slowly absorbed after intramuscular injection and peak plasma concentrations occur after about 7 days. Steady-state concentrations are reached after about 3 to 6 doses (given monthly). Fulvestrant is highly bound to plasma proteins. It is metabolised mainly in the liver to several metabolites, some of which have oestrogen antagonist activity, and is excreted in the faeces. After intramuscular injection fulvestrant has a half-life of about 40 to 50 days.

References.

1. Robertson JFR, *et al*. Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. *Clin Pharmacokinet* 2004; **43:** 529–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Faslodex; ***Austral.***: Faslodex; ***Austria***: Faslodex; ***Belg.***: Faslodex; ***Braz.***: Faslodex; ***Canad.***: Faslodex; ***Chile***: Faslodex; ***China***: Faslodex (芙仕得); ***Cz.***: Faslodex; ***Denm.***: Faslodex; ***Fin.***: Faslodex; ***Fr.***: Faslodex; ***Ger.***: Faslodex; ***Gr.***: Faslodex; ***Hong Kong***: Faslodex; ***Hung.***: Faslodex; ***India***: Faslodex; ***Irl.***: Faslodex; ***Israel***: Faslodex; ***Ital.***: Faslodex; ***Jpn***: Faslodex; ***Malaysia***: Faslodex; ***Mex.***: Faslodex; ***Neth.***: Faslodex; ***Norw.***: Faslodex; ***NZ***: Faslodex†; ***Philipp.***: Faslodex; ***Pol.***: Faslodex; ***Port.***: Faslodex; ***Rus.***: Faslodex (Фаслодекс); ***S.Afr.***: Faslodex; ***Singapore***: Faslodex; ***Spain***: Faslodex; ***Swed.***: Faslodex; ***Switz.***: Faslodex; ***Thai.***: Faslodex; ***Turk.***: Faslodex; ***UK***: Faslodex; ***Ukr.***: Faslodex (Фаслодекс); ***USA***: Faslodex; ***Venez.***: Faslodex.

Gefitinib *(BAN, USAN, rINN)*

Géfitinib; Gefitinibum; ZD-1839; Гефитиниб.

N-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

$C_{22}H_{24}ClFN_4O_3$=446.9

CAS — 184475-35-2.

ATC — L01XE02.

ATC Vet — QL01XE02.

UNII — S65743JHBS.

Uses and Administration

Gefitinib is a selective inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR). EGFR is expressed on the surface of cells and is implicated in the process of cell growth and proliferation. Gefitinib is used for the management of locally advanced or metastatic non-small cell lung cancer (NSCLC; p. 710.2) in adults. In the UK and EU, gefitinib is indicated for those patients with tumours with activating mutations of the EGFR tyrosine kinase. In the USA, use is restricted to those patients who are currently receiving and benefiting from gefitinib, or to those who have previously benefited from therapy; it is only used after failure of both platinum-based and docetaxel chemotherapy regimens.

The recommended dose of gefitinib is 250 mg orally once daily. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For patients with diarrhoea or cutaneous adverse reactions, gefitinib therapy may be interrupted for up to 14 days, after which it may be re-instated at the same dose; if therapy is not tolerated after such an interruption, gefitinib should be stopped, and alternative treatment considered.

In patients who are given a potent CYP3A4 inducer, a dose increase of gefitinib to 500 mg orally once daily should be considered; clinical response and adverse effects should be carefully monitored.

Caution is advised in some patients with hepatic or renal impairment (see below).

References.

1. Culy CR, Faulds D. Gefitinib. *Drugs* 2002; **62:** 2237–48.
2. Kris MG, *et al*. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non–small cell lung cancer: a randomized trial. *JAMA* 2003; **290:** 2149–58.
3. Liu CY, Seen S. Gefitinib therapy for advanced non–small-cell lung cancer. *Ann Pharmacother* 2003; **37:** 1644–53.
4. Cersosimo RJ. Gefitinib: a new antineoplastic for advanced non-small-cell lung cancer. *Am J Health-Syst Pharm* 2004; **61:** 889–98.
5. Tanovic A, Alfaro V. Gefitinib: current status in the treatment of non-small cell lung cancer. *Drugs Today* 2004; **40:** 809–27.
6. Birnbaum A, Ready N. Gefitinib therapy for non-small cell lung cancer. *Curr Treat Options Oncol* 2005; **6:** 75–81.
7. Shah NT, *et al*. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005; **23:** 165–74.
8. Blackhall F, *et al*. Where next for gefitinib in patients with lung cancer? *Lancet Oncol* 2006; **7:** 499–507.
9. Maruyama R, *et al*. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008; **26:** 4244–52.
10. Kim ES, *et al*. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; **372:** 1809–18.
11. Sanford M, Scott LJ. Gefitinib: a review of its use in the treatment of locally advanced/metastatic non-small cell lung cancer. *Drugs* 2009; **69:** 2303–28.

Administration. Gefitinib tablets may be taken with or without food, and are preferably swallowed whole. However, for those patients who have difficulty swallowing, a whole tablet may be dispersed in half a glass of non-carbonated water; the tablet should not be crushed, and the glass of water should be swirled or stirred until the tablet is fully dispersed (this may take 10 to 20 minutes). The dispersion should be consumed immediately (UK licensed product information specifies this as being within 1 hour), and the glass rinsed with some more water, which should also be consumed.

This dispersion is also suitable for use through a nasogastric or gastrostomy tube.

Administration in children. For reference to the use of gefitinib with irinotecan in the treatment of children with refractory solid tumours, see Administration, under Irinotecan, p. 813.1.

Administration in hepatic impairment. UK licensed product information states that, compared with healthy control subjects, exposure to gefitinib was tripled in patients with moderate or severe hepatic impairment (classified according to Child-Pugh criteria) due to cirrhosis. In patients with tumours, gefitinib pharmacokinetics in those with hepatic impairment were similar to those patients with normal hepatic function.

US licensed product information states that no dosage adjustment is needed in patients with moderate to severe hepatic impairment due to liver metastases: in the UK, patients with moderate to severe impairment (Child-Pugh B or C) due to cirrhosis should be closely monitored for adverse effects.

Administration in renal impairment. UK licensed product information states that no dose adjustment of gefitinib is needed in patients with a creatinine clearance (CC) greater than 20 mL/minute. Caution is advised in those patients with a CC of 20 mL/minute or less, due to limited data in these patients.

US licensed product information states that, while no studies have been conducted in patients with severe renal impairment, gefitinib and its metabolites are not significantly excreted via the kidney, and no dose adjustment is required on the basis of renal function.

Adverse Effects, Treatment, and Precautions

The adverse effects of gefitinib are similar to those of erlotinib (p. 789.2), although severe hepatic and renal toxicity seems to be rare. Haemorrhage, such as epistaxis or haematuria, is common. There are also reports of tumour haemorrhage, sometimes fatal, after use of gefitinib in patients with head and neck cancer.

Other common adverse effects include nausea, vomiting, stomatitis, dry mouth, alopecia, nail disorders, asthenia, pyrexia, proteinuria, and elevations in blood creatinine.

References.

1. Inoue A, *et al*. Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; **361:** 137–9.
2. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA®) monotherapy: clinical experience in non-small-cell lung cancer. *Drug Safety* 2004; **27:** 1081–92.

Effects on survival. In chemotherapy-naive patients with advanced non-small cell lung cancer, gefitinib, given with gemcitabine plus cisplatin,[1] or paclitaxel plus carboplatin,[2] showed no survival advantage over chemotherapy

without gefitinib. In a large study in patients with non-small cell lung cancer given gefitinib or placebo, after failure of one or two previous treatment regimens, no survival benefit was shown with gefitinib;[3] recommendations restricting the use of gefitinib to selected patients have been made in the USA (see Uses and Administration, p. 800.2).[4] However, a subset analysis of study data found an improvement in survival in a subgroup of patients of Asian origin.[5] In reports of the IMEX study in patients with head and neck cancer, no survival advantage for gefitinib was found when compared with methotrexate; an increased incidence of tumour haemorrhage was seen in those treated with gefitinib.[6] Studies have suggested that there are subgroups of patients with non-small cell lung cancer who have specific biomarkers or mutations in the epidermal growth factor receptor (EGFR) gene which correlate with clinical response to gefitinib.[7-10] A subsequent study established EGFR mutation status as the most important independent predictor of survival benefit with gefitinib treatment.[11]

A small retrospective study found that further treatment with gefitinib prolonged survival in patients who were initially responsive, but who had subsequent disease progression upon stopping therapy.[12]

1. Giaccone G, *et al*. Gefitinib in combination with gemcitabine and cisplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol* 2004; **22:** 777–84.
2. Herbst RS, *et al*. Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol* 2004; **22:** 785–94.
3. Thatcher N, *et al*. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366:** 1527–37.
4. FDA Public Health Advisory. New labeling and distribution program for gefitinib (Iressa) (issued 17/06/05). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm163112.htm (accessed 21/07/10)
5. Chang A, *et al*. Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006; **1:** 847–55.
6. AstraZeneca, Canada. Health Canada endorsed important safety information on Iressa (gefitinib): lack of survival benefit and increased incidence of tumour haemorrhage in association with IRESSA in patients with squamous cell carcinoma of the head and neck (SCCHN) (issued 1st December 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/iressa_4_hpc-cps-eng.php (accessed 23/09/09)
7. Lynch TJ, *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.
8. Paez JG, *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–1500.
9. Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non–small-cell lung cancer: current knowledge and future directions. *J Clin Oncol* 2005; **23:** 2556–68.
10. Hirsch FR, *et al*. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5034–42.
11. Satouchi M, *et al*. Predictive factors associated with prolonged survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib. *Br J Cancer* 2007; **96:** 1191–6.
12. Yokouchi H, *et al*. Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. *BMC Cancer* 2007; **7:** 51.

Interactions

Gefitinib is metabolised via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Inhibitors of CYP3A4, such as itraconazole, can decrease the clearance of gefitinib and increase exposure. The increase in gefitinib plasma concentration caused by potent CYP3A4 inhibitors may be higher in patients with CYP2D6 poor-metaboliser genotype. In CYP2D6 extensive metabolisers, use of gefitinib with potent CYP2D6 inhibitors may double gefitinib concentrations. Patients taking gefitinib who are also treated with potent CYP3A4 or CYP2D6 inhibitors should be closely monitored for adverse reactions.

Conversely, CYP3A4 inducers, such as rifampicin, can reduce exposure to gefitinib. Use with potent CYP3A4 inhibitors should be avoided, but if not, dose adjustment is recommended (see Uses and Administration, p. 800.2), and the patient's response should be carefully monitored.

Substances that cause a significant and sustained elevation in gastric pH may reduce gefitinib bioavailability; high doses of short-acting antacids may have a similar effect if taken regularly and at the same time as gefitinib, and ranitidine, with or without sodium bicarbonate, decreased exposure to gefitinib by over 40%.

Elevations in INR or bleeding events have been reported in patients taking gefitinib with warfarin.

Gefitinib also has limited potential to inhibit the cytochrome P450 isoenzyme CYP2D6; substrates of CYP2D6 may need dose modification when given with gefitinib (such as metoprolol, see p. 1322.1).

References.
1. Swaisland HC, *et al*. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* 2005; **44:** 1067–81.

Pharmacokinetics

Gefitinib is slowly absorbed, and peak plasma concentrations occur 3 to 7 hours after an oral dose. Bioavailability is about 60%, and is not significantly altered by food. Gefitinib is extensively distributed throughout the body. Plasma protein binding is about 90%. Gefitinib is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6; the major metabolite is *O*-desmethylgefitinib, which is much less potent than gefitinib, and unlikely to contribute to its clinical activity. Gefitinib is excreted mainly as metabolites via the faeces; renal elimination of gefitinib and its metabolites accounts for less than 4% of the dose given. The elimination half-life is reported to be about 41 to 48 hours.

References.
1. Swaisland HC, *et al*. Single-dose clinical pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005; **44:** 1165–77.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Iressa; ***Austral.***: Iressa; ***Austria***: Iressa; ***Belg.***: Iressa; ***Braz.***: Iressa; ***Canad.***: Iressa; ***Chile***: Iressa; ***China***: Iressa (易瑞沙); ***Cz.***: Iressa; ***Denm.***: Iressa; ***Fr.***: Iressa; ***Ger.***: Iressa; ***Gr.***: Iressa; ***Hong Kong***: Iressa; ***Hung.***: Iressa; ***India***: Gefitero; Gefonib; Geftib; Geftilon; Geftinat; ***Indon.***: Iressa; ***Irl.***: Iressa; ***Israel***: Iressa; ***Malaysia***: Iressa; ***Mex.***: Iressa; ***Neth.***: Iressa; ***Norw.***: Iressa; ***NZ***: Iressa; ***Philipp.***: Iressa; ***Pol.***: Iressa; ***Port.***: Iressa; ***Rus.***: Iressa (Иресса); ***Singapore***: Iressa; ***Spain***: Iressa; ***Swed.***: Iressa; ***Switz.***: Iressa; ***Thai.***: Iressa; ***UK***: Iressa; ***USA***: Iressa†; ***Venez.***: Iressa.

Gemcitabine Hydrochloride

(BANM, USAN, rINNM)

Gemcitabina, hidrocloruro de; Gemcitabine, Chlorhydrate de; Gemcitabinhydrochlorid; Gemcitabini Hydrochloridum; Hidrocloruro de gemcitabina; LY-188011 (gemcitabine); Гемцитабина Гидрохлорид.

4-Amino-1-(2-deoxy-2,2-difluoro-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one hydrochloride; 2′-Deoxy-2′,2′-difluorocytidine hydrochloride.

$C_9H_{11}F_2N_3O_4$,HCl=299.7

CAS — 95058-81-4 (gemcitabine); 122111-03-9 (gemcitabine hydrochloride).

ATC — L01BC05.

ATC Vet — QL01BC05.

UNII — U347PV74IL.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8 (Gemcitabine Hydrochloride). A white or almost white powder. Soluble in water; slightly soluble in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 2.0 to 3.0.

USP 36: (Gemcitabine Hydrochloride). A white to off-white solid. Soluble in water; practically insoluble in alcohol and in polar organic solvents; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers.

Incompatibility. Gemcitabine hydrochloride was reported to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, cefotaxime sodium, furosemide, ganciclovir sodium, imipenem with cilastatin sodium, irinotecan, methotrexate sodium, methylprednisolone sodium succinate, mezlocillin sodium, mitomycin, piperacillin sodium, piperacillin sodium with tazobactam, and prochlorperazine edisilate during simulated Y-site administration.[1]

1. Trissel LA, *et al*. Compatibility of gemcitabine hydrochloride with 107 selected drugs during simulated Y-site injection. *J Am Pharm Assoc* 1999; **39:** 514–18.

Uses and Administration

Gemcitabine is an analogue of cytarabine (p. 774.1) that is metabolised intracellularly to active diphosphate and triphosphate nucleosides, which inhibit DNA synthesis and induce apoptosis. It is mainly active against cells in S phase. It is given in the management of solid tumours including those of the bladder, breast, lung, ovary, and pancreas (see p. 700.2, p. 702.1, p. 710.2, p. 711.2, and p. 712.1, respectively).

Gemcitabine is given intravenously as the hydrochloride. Doses are calculated in terms of the base; gemcitabine hydrochloride 1.14 g is equivalent to about 1 g of gemcitabine. Doses are reconstituted in sodium chloride 0.9%. The concentration of the infusion solution should not exceed the equivalent of gemcitabine 40 mg/mL. Gemcitabine is given by infusion over 30 to 60 minutes; doses are subsequently adjusted according to response and toxicity.

In the treatment of **pancreatic cancer**, an initial course of gemcitabine 1 g/m^2 once weekly for up to 7 weeks may be given, followed after a one-week recovery period by a regimen of infusions once weekly for 3 consecutive weeks out of 4.

In **non-small cell lung cancer**, gemcitabine may be given as a single agent; 1 g/m^2 once weekly for 3 consecutive weeks out of 4 is recommended. Alternatively, it may be given before cisplatin. Two schedules have been used; gemcitabine 1.25 g/m^2 is given on days 1 and 8 of a 21-day cycle, or gemcitabine 1 g/m^2 is given on days 1, 8 and 15 of a 28-day cycle.

In the treatment of **bladder cancer**, gemcitabine is given before cisplatin. The recommended dose of gemcitabine is 1 g/m^2 on days 1, 8, and 15 of a 28-day cycle.

In **breast cancer**, gemcitabine is usually given after a taxane such as paclitaxel. A dose of gemcitabine 1.25 g/m^2 is given on days 1 and 8 of a 21-day cycle.

In **ovarian cancer**, gemcitabine is given before carboplatin. The recommended dose of gemcitabine is 1 g/m^2 on days 1 and 8 of a 21-day cycle.

References.
1. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 15–19.
2. Hussain M, *et al*. Novel gemcitabine-containing triplets in the management of urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 20–4.
3. Hochster HS. Newer approaches to gemcitabine-based therapy of pancreatic cancer: fixed-dose-rate infusion and novel agents. *Int J Radiat Oncol Biol Phys* 2003; **56** (suppl): 24–30.
4. Yardley DA. Gemcitabine and taxanes as a new standard of care in breast cancer. *Clin Breast Cancer* 2004; **4** (suppl 3): S107–S112.
5. Natale R. A ten-year review of progress in the treatment of non-small-cell lung cancer with gemcitabine. *Lung Cancer* 2005; **50** (suppl): S2–S4.
6. Saha A, Rudd R. Gemcitabine and carboplatin: is this the best combination for non-small cell lung cancer? *Expert Rev Anticancer Ther* 2006; **6:** 165–73.
7. Kose MF, *et al*. Gemcitabine plus carboplatin in platinum-sensitive recurrent ovarian carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 437–43.
8. Wirk B, Perez E. Role of gemcitabine in breast cancer management: an update. *Semin Oncol* 2006; **33** (suppl 2): S6–S14.
9. Pfisterer J, *et al*. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006; **24:** 4699–4707.
10. Kiba T, *et al*. Single-agent gemcitabine for biliary tract cancers: study outcomes and systematic review of the literature. *Oncology* 2006; **70:** 358–65.
11. Maki RG. Gemcitabine and docetaxel in metastatic sarcoma: past, present, and future. *Oncologist* 2007; **12:** 999–1006.
12. El Karak F, Flechon A. Gemcitabine in bladder cancer. *Expert Opin Pharmacother* 2007; **8:** 3251–6.
13. Serrano A, Gerson R. Chemotherapy with gemcitabine in advanced biliary tract carcinoma. *Rev Recent Clin Trials* 2008; **3:** 70–8.
14. Hilbig A, Oettle H. Gemcitabine in the treatment of metastatic pancreatic cancer. *Expert Rev Anticancer Ther* 2008; **8:** 511–23.
15. Dent S, *et al*. Gemcitabine in the management of metastatic breast cancer: a systematic review. *Breast Cancer Res Treat* 2008; **108:** 319–31.
16. Danesi R, *et al*. Pharmacogenomics of gemcitabine in non-small-cell lung cancer and other solid tumors. *Pharmacogenomics* 2009; **10:** 69–80.
17. Wong A, *et al*. Clinical pharmacology and pharmacogenetics of gemcitabine. *Drug Metab Rev* 2009; **41:** 77–88.
18. Rivera F, *et al*. Treatment of advanced pancreatic cancer: from gemcitabine single agent to combinations and targeted therapy. *Cancer Treat Rev* 2009; **35:** 335–9.

Administration. Gemcitabine is recommended as the standard of care in patients with advanced pancreatic cancer (p. 712.1). There is some suggestion that its efficacy may be improved if it is given at a fixed dose rate of 10 mg/m^2 per minute, rather than by conventional infusion.[1] However, while this regimen has been found to be well tolerated,[2] several studies have not shown an improvement in survival compared with the standard gemcitabine infusion[3] and some do not recommend it for routine use.[4]

1. Tempero M, *et al*. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003; **21:** 3402–8.
2. Ko AH, *et al*. Phase II study of fixed dose rate gemcitabine with cisplatin for metastatic adenocarcinoma of the pancreas. *J Clin Oncol* 2006; **24:** 379–85.
3. Poplin E, *et al*. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; **27:** 3778–85.
4. Kulke MH, *et al*. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. *J Clin Oncol* 2009; **27:** 5506–12.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The major dose-limiting adverse effect of gemcitabine is bone-marrow depression, although this is reported to be modest and rarely requires stopping therapy. Gastrointestinal disturbances occur, especially nausea and vomiting, but these are usually of mild to moderate severity. Rashes, often associated with pruritus, and flu-like symptoms are relatively common; severe desquamation and bullous skin eruptions, toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred rarely. Oedema, dyspnoea, myalgia, and alopecia are commonly reported. Pulmonary oedema has been reported infrequently; interstitial pneumonitis, pulmonary fibrosis, and acute respiratory distress syndrome have occurred. Therapy should be stopped if pulmonary toxicity occurs. There are rare cases of hypotension and anaphylactoid reactions. Haematuria,

proteinuria, transient liver enzyme elevations, and serious hepatotoxicity, including liver failure and death, have been reported. It should therefore be used with caution in patients with impaired renal or hepatic function. Haemolytic-uraemic syndrome and/or thrombocytopenic purpura have been reported and have led to irreversible renal failure; gemcitabine should be stopped at the first signs of microangiopathic haemolytic anaemia. Congestive heart failure, myocardial infarction, or arrhythmias may occur rarely. Ischaemic colitis with necrosis (including fatalities), peripheral vasculitis and gangrene, and cerebrovascular accident have also been reported.

Gemcitabine may produce somnolence: patients so affected should not drive or operate machinery. Severe toxicity, in the form of potentially life-threatening oesophagitis and pneumonitis has been seen in patients given radical radiotherapy to the thorax concurrently with gemcitabine.

Effects on the nervous system. A report of autonomic neuropathy associated with gemcitabine therapy.[1] Symptoms resolved 4 weeks after stopping therapy.

1. Dormann AJ, *et al.* Gemcitabine-associated autonomic neuropathy. *Lancet* 1998; **351:** 644.

Effects on the skin. A patient who received gemcitabine a week after phototherapy developed a severe sunburn reaction in those areas exposed to UVB. The erythema resolved spontaneously, but recurred with each subsequent dose of gemcitabine, and became progressively more intense. A short course of high-dose prednisone was given with topical triamcinolone, and the patient was safely rechallenged with 2 further doses of gemcitabine.[1]

1. Badger J, *et al.* Photo therapy recall with gemcitabine following ultraviolet B treatment. *J Clin Oncol* 2005; **23:** 7224–5.

Peripheral ischaemia. Pain, coldness, colour changes, and distal claudication in the feet have been reported in patients treated with gemcitabine and cisplatin.[1] Pain and colour changes in the fingertips have also been reported after gemcitabine monotherapy.[2]

1. Barceló R, *et al.* Distal ischemic changes related to combination chemotherapy with cisplatin and gemcitabine: description of four cases. *Ann Oncol* 2000; **11:** 1191–4.
2. Yildiz R, *et al.* Digital ischemic changes after gemcitabine therapy in a patient with metastatic non-small-cell lung cancer. *Ann Pharmacother* 2007; **41:** 901–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gemcitabine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

Antineoplastics. In a study[1] of 14 patients with lung cancer, the use of *paclitaxel* before gemcitabine caused a decrease in the systemic clearance, volume of distribution, and interpatient pharmacokinetic variability of gemcitabine. This resulted in plasma concentrations of gemcitabine slightly higher than the desired range. However, there was no apparent relationship between pharmacokinetic changes and toxicity, and the clinical significance of this possible interaction is unclear.

A study investigating a modified chemotherapy regimen in which gemcitabine was substituted for etoposide was stopped because of unexpected pulmonary toxicity. This was considered to be due to the combination of gemcitabine and *bleomycin*, as the adverse effect was apparent in other studies using this combination.[2]

1. Shord SS, *et al.* Gemcitabine pharmacokinetics and interaction with paclitaxel in patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003; **51:** 328–36.
2. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's lymphoma study group. *J Clin Oncol* 2004; **22:** 2424–9.

Pharmacokinetics

After intravenous doses gemcitabine is rapidly cleared from the blood and metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues. Clearance is about 25% lower in women than in men. Almost all of the dose is excreted in urine as 2′-deoxy-2′,2′-difluorouridine (dFdU), only about 1% being found in the faeces. Intracellular metabolism produces mono-, di-, and triphosphate metabolites, the latter two active. The half-life of gemcitabine ranges from 42 to 94 minutes depending on age and gender. The intracellular half-life of the triphosphate is stated to range from 0.7 to 12 hours.

All cross-references refer to entries in Volume A

References.
1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Shamseddine AI, *et al.* Comparative pharmacokinetics and metabolic pathway of gemcitabine during intravenous and intra-arterial delivery in unresectable pancreatic cancer patients. *Clin Pharmacokinet* 2005; **44:** 957–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abine; Antoril; Eriogem; Gebina; Gemofas; Gemtro; Gestredos; Gezt; Gramagen; Nabigem; Oncoplus; ***Austral.***: Gemzar; ***Austria***: Gemzar; ***Belg.***: Gemzar; ***Braz.***: Gemcit; Gemzar; ***Canad.***: Gemzar; ***Chile***: Gemzar; Genuten; ***China***: Gemzar (健择); Yu Jie (誉捷); Ze Fei (泽菲); ***Cz.***: Citegin; Gemalata; Gemcirena; Gemibane; Gemstad; Gemtex; Gemzar; Getmisi; Gitrabin; Lungera; Naruyd; ***Denm.***: Gemabin†; Gemcit†; Gemcitelb†; Gemhal†; Gemind; Gemstada; Gemtiba†; Gemtifi†; Gemzar; Nallian†; ***Fin.***: Gemzar; ***Fr.***: Gemcirena†; Gemzar; ***Ger.***: Axigem; Bendacitabin; Gemci-Cell; Gemcitan; Gemedac; Gemzar†; Ribozar; ***Gr.***: Demozar; Gemcipen; Gemcirena; Gemnil; Gemzar†; Genvir; Medigem; Santabin; Tamcibin; ***Hong Kong***: Gemzar; Gitrabin; ***Hung.***: Dercin; Gemdex; Gemzar; Nallian; ***India***: Abingem; Biogem; Celgem; Celzar; Cytogem; Gembin; Gemcite; Gemita; Gempower; Gemtaz; Lifogem; Oncogem; ***Indon.***: Cytogem; Gemzar; ***Irl.***: Gemabin†; Gemzar; ***Israel***: Gemnil; Gemzar; Meditabine; ***Ital.***: Gemzar; Jemta; ***Malaysia***: Gemzar; ***Mex.***: Gemzar; ***Neth.***: Gemalata; Gemzar; Jemta; ***Norw.***: Gemzar; ***NZ***: Gemzar; ***Philipp.***: Gemcit; Gemita; Gemtabine; Gemzar; Oncoril; Zefei; ***Pol.***: Dercin; Gemciteva; Gemzar; Gitrabin; ***Port.***: Gemcit; Gemzar; ***Rus.***: Cytogem (Цитогем); Gemcitare (Гемцитар); Gemcitera (Гемцитера); Gemcitover (Гемцитовер); Gemzar (Гемзар); Ongecin (Онгецин); ***S. Afr.***: Cytigem; Gemtaz; Gemzar; ***Singapore***: Gemzar; ***Spain***: Gemzar; ***Swed.***: Gemzar; ***Switz.***: Gemzar; ***Thai.***: Gemcit; Gemita; Gemtaz; Gemzar; Gramagen; ***Turk.***: Gemko; Gemzar; ***UK***: Gemzar; ***Ukr.***: Cytogem (Цитогем); ***USA***: Gemzar; ***Venez.***: Gemzar.

Pharmacopoeial Preparations
USP 36: Gemcitabine for Injection.

Gemtuzumab Ozogamicin *(USAN, rINNM)*

CDP-771; CMA-676; Gemtuzumab ozogamicina; Gemtuzumab Ozogamicine; Gemtuzumab Zogamicin; Gemtuzumabum Ozogamicinum; WAY-CMA-676; Гемтузумаб Озогамицин.

Immunoglobulin G4 (human-mouse monoclonal hP67.6 κ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer conjugate with ozogamicin.

CAS — 220578-59-6.
ATC — L01XC05.
ATC Vet — QL01XC05.
UNII — 8GZG754X6M.

Uses and Administration

Gemtuzumab ozogamicin is a recombinant humanised monoclonal antibody conjugated with calicheamicin, a cytotoxic antibiotic. The antibody binds specifically to the CD33 antigen, which is expressed on leukaemic myeloblasts but not normal haematopoietic stem cells. Gemtuzumab ozogamicin has been used for the second-line treatment of CD33-positive acute myeloid leukaemia (p. 693.1) in elderly patients who are unable to tolerate conventional chemotherapy. It is given in 100 mL of sodium chloride 0.9% via a low protein-binding in-line filter. A usual dose has been 9 mg/m^2 given by intravenous infusion over 2 hours, repeated once after 14 days. Lower doses have been investigated as part of combined induction or consolidation regimens.

References.
1. McGavin JK, Spencer CM. Gemtuzumab ozogamicin. *Drugs* 2001; **61:** 1317–22.
2. Dowell JA, *et al.* Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. *J Clin Pharmacol* 2001; **41:** 1206–14.
3. Sievers EL, *et al.* Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 2001; **19:** 3244–54.
4. Sievers EL, Linenberger M. Mylotarg: antibody-targeted chemotherapy comes of age. *Curr Opin Oncol* 2001; **13:** 522–7.
5. Larson RA, *et al.* Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia* 2002; **16:** 1627–36.
6. Buckwalter M, *et al.* Pharmacokinetics of gemtuzumab ozogamicin as a single-agent treatment of pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Pharmacol* 2004; **44:** 873–80.
7. Lo-Coco F, *et al.* Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood* 2004; **104:** 1995–9.
8. Fenton C, Perry CM. Gemtuzumab ozogamicin: a review of its use in acute myeloid leukaemia. *Drugs* 2005; **65:** 2405–27.
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10. Stasi R, *et al.* Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. *Cancer Treat Rev* 2008; **34:** 49–60.
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12. Medical Research Council. AML15: Medical Research Council Working Parties on Leukaemia in Adults and Children Acute Myeloid Leukaemia Trial 15. Available at: http://www.download.bham.ac.uk/bctu/AML15/Amendment%20Nov%202007/AML15%20protocol%20version%207%20Final%20200704201%20with%20no%20track%20changes.pdf (accessed 30/07/08)

Adverse Effects and Precautions

For general discussions see Antineoplastics, p. 726.1 and p. 732.2.

Myelosuppression is common with gemtuzumab ozogamicin, and thrombocytopenia may be prolonged. Infusion-related reactions characteristic of a cytokine release syndrome (including fever, chills, dyspnoea, and hypotension) and hypersensitivity may occur; prophylactic use of an antihistamine and paracetamol is recommended. Pulmonary sequelae may be fatal. Hepatotoxicity, including severe veno-occlusive disease, has also been reported. Electrolyte imbalances, especially hypokalaemia and hypomagnesaemia, and gastrointestinal disturbances may occur.

Blood and platelet counts, electrolytes, and liver function tests should be regularly monitored.

The drug was withdrawn from the market in the USA after reports of increased mortality in patients with acute myeloid leukaemia who were given gemtuzumab ozogamicin as part of a combination regimen.

Hypersensitivity. A 75-year-old man with acute myeloid leukaemia developed severe respiratory distress and died after being given gemtuzumab ozogamicin and platelets on the same day. He had previously had the drug and platelets on separate occasions with no untoward effects. It was suggested that this combination contributed to a fatal hypersensitivity reaction.[1]

1. Hanbali A, *et al.* Fatal hypersensitivity reaction to gemtuzumab ozogamicin associated with platelet transfusion. *Am J Health-Syst Pharm* 2007; **64:** 1401–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mylotarg; ***Gr.***: Mylotarg; ***Israel***: Mylotarg; ***Singapore***: Mylotarg†; ***USA***: Mylotarg†; ***Venez.***: Mylotarg.

Gimatecan *(rINN)*

CPT-184; Gimatécan; Gimatecán; Gimatecanum; LBQ-707; ST-1481; Гиматекан.

(4*S*)-11-{(*E*)-[(1,1-Dimethylethoxy)imino]methyl}-4-ethyl-4-hydroxy-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione.

$C_{25}H_{25}N_3O_5$=447.5

CAS — 292618-32-7.
UNII — 7KKS9R192F.

Profile

Gimatecan is a camptothecin derivative that inhibits the enzyme topoisomerase I. Gimatecan is under investigation for the treatment of malignant glioma.

References.
1. Sessa C, *et al.* Concerted escalation of dose and dosing duration in a phase I study of the oral camptothecin gimatecan (ST1481) in patients with advanced solid tumors. *Ann Oncol* 2007; **18:** 561–8.
2. Zhu AX, *et al.* Phase I and pharmacokinetic study of gimatecan given orally once a week for 3 of 4 weeks in patients with advanced solid tumors. *Clin Cancer Res* 2009; **15:** 374–81.
3. Pecorelli S, *et al.* Phase II of oral gimatecan in patients with recurrent epithelial ovarian, fallopian tube or peritoneal cancer, previously treated with platinum and taxanes. *Ann Oncol* 2010; **21:** 759–65.

Girentuximab *(USAN, rINN)*

cG-250; Girentuximabum; WX-G250; Гирентуксимаб.

CAS — 916138-87-9.
UNII — 539B57DFJF.

NOTE. The name Rencarex has been used as a trade mark for girentuximab. The name Redectane has been used as a trade mark for girentuximab labelled with iodine-124.

Profile

Girentuximab is a chimeric monoclonal antibody that binds specifically to the protein carbonic anhydrase IX (CAIX, MN, or G250 antigen) expressed on the cell surface in the majority of clear-cell renal cell carcinomas; the antigen is present in various other solid tumours. Girentuximab is under investigation for the treatment of clear-cell renal cell carcinoma.

Girentuximab labelled with iodine-124 (p. 2225.2) is being studied for the imaging of renal tumours.

Givinostat *(rINN)*

Givinostatum; Гивиностат.
{6-[(Diethylamino)methyl]naphthalen-2-yl}methyl [4-(hydroxycarbamoyl)phenyl]carbamate.
$C_{24}H_{27}N_3O_4$=421.5
CAS — 497833-27-9.
UNII — 5P60F84FBH.

Profile

Givinostat is an orally active histone deacetylase inhibitor that is under investigation for the treatment of polycythaemia vera and juvenile idiopathic arthritis.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Vojinovic J, *et al.* Safety and efficacy of an oral histone deacetylase inhibitor in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2011; **63:** 1452–8.
2. Rambaldi A, *et al.* A pilot study of the histone-deacetylase inhibitor givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. *Br J Haematol* 2010; **150:** 446–55.

Glufosfamide *(rINN)*

D-19575; β-D-Glu-IPM; β-D-Glucosyl-ifosfamide Mustard; Glufosfamida; Glufosfamidum; Глуфосфамид.
β-D-Glucopyranose 1-[*N*,*N*′-bis(2-chloroethyl)phosphorodiamidate].
$C_{10}H_{21}Cl_2N_2O_7P$=383.2
CAS — 132682-98-5.
UNII — 1W5N8SZD9A.

Profile

Glufosfamide is a conjugate of glucose and the active part of the alkylating antineoplastic ifosfamide (p. 806.1). It is under investigation for the treatment of pancreatic cancer and other solid tumours.

References.

1. Chiorean EG, *et al.* A phase 1 dose-escalation trial of glufosfamide in combination with gemcitabine in solid tumors including pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* 2008; **61:** 1019–26.
2. Ciuleanu TE, *et al.* A randomised phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine. *Eur J Cancer* 2009; **45:** 1589–96.

Hydroxycarbamide *(BAN, rINN)*

Hidroksikarbamid; Hidroksikarbamidas; Hidroxicarbamida; Hidroxikarbamid; Hydroksikarbamidi; Hydroksiüre; Hydroxikarbamid; Hydroxycarbamid; Hydroxycarbamidum; Hydroxymočovina; Hydroxyurea (USAN); Hydroxyurea; NSC-32065; SQ-1089; WR-83799; Гидроксикарбамид.
$NH_2.CO.NHOH$=76.06
CAS — 127-07-1.
ATC — L01XX05.
ATC Vet — QL01XX05.
UNII — X6Q56QN5QC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Hydroxycarbamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Hydroxyurea). A white to off-white powder. It is somewhat hygroscopic and decomposes in the presence of moisture. Freely soluble in water and in hot alcohol. Store in airtight containers in a dry atmosphere.

Stability. An oral solution of hydroxycarbamide 100 mg/mL was prepared[1] by first mixing the contents of 500-mg capsules (*Hydrea; BMS, USA*) in sterile water at room temperature to produce a concentration of 200 mg/mL. The mixture was vigorously stirred for several hours and then filtered to remove insoluble excipients. Flavoured syrup (*Syrpalta without color; Humco, USA*) was added to the filtered solution to produce a final concentration of 100 mg/mL.

The resulting solution was found to have lost 5% of its chemical content of hydroxycarbamide during the first 3 months of storage at room temperature in amber plastic bottles but there was no further loss up to 9 months later. The loss of its *in-vitro* inhibitory activity was less than 5% at 3 months, less than 10% at 6 months but activity was about 80% at 9 months. In contrast a solution that had been prepared by dissolving the contents of the capsules in heated water had an immediate loss of 40% of its chemical content and over 60% of its inhibitory activity.

1. Heeney MM, *et al.* Chemical and functional analysis of hydroxyurea oral solutions. *J Pediatr Hematol Oncol* 2004; **26:** 179–84.

Uses and Administration

Hydroxycarbamide is an antineoplastic that may cause inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor. It is S-phase specific. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia, and may be used in the myeloproliferative disorders polycythaemia vera and primary (essential) thrombocythaemia. It has also been tried, often combined with radiotherapy, in some solid malignancies (see Malignant Neoplasms, p. 804.1). Hydroxycarbamide has also produced benefit in the haemoglobinopathies, particularly in sickle-cell disease (see below).

Hydroxycarbamide is given orally. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In the treatment of **chronic myeloid leukaemia** and **solid tumours**, hydroxycarbamide is given typically in a single dose of 20 to 30 mg/kg daily or in a single dose of 80 mg/kg every third day. Generally, the continuous regimen is used for chronic myeloid leukaemia, and the intermittent regimen for solid tumours. When used with radiotherapy, hydroxycarbamide is started 7 days before radiotherapy. If a beneficial effect is evident after 6 weeks, therapy may be continued indefinitely.

In **essential thrombocythaemia**, the initial dose of hydroxycarbamide is about 15 mg/kg daily; starting doses of 15 to 20 mg/kg daily are recommended for **polycythaemia vera**. Doses are subsequently adjusted according to platelet counts.

In **sickle-cell disease** initial doses of 15 mg/kg daily are suggested, increased if necessary by 2.5 to 5 mg/kg every 12 weeks according to response and blood counts; usual doses are 15 to 30 mg/kg daily with a maximum of 35 mg/kg daily. For doses in children, see below.

Blood counts and hepatic and renal function should be monitored during therapy; treatment may need to be interrupted if leucopenia or thrombocytopenia occur (see Adverse Effects, Treatment, and Precautions, p. 804.1).

Administration in children. In the UK hydroxycarbamide is licensed for use in children older than 2 years of age for the treatment of sickle-cell disease; doses are the same as for adults, see Uses and Administration, above. The *BNFC* advises that a slightly lower initial oral dose of 10 to 15 mg/kg daily may be used instead. For doses in renal impairment and for more information on hydroxycarbamide use in sickle-cell disease, see below.

For reference to the preparation and stability of an oral solution of hydroxycarbamide 100 mg/mL, see under Stability, above.

Administration in renal impairment. Results from a single-dose study in patients with sickle-cell disease indicated that systemic exposure to hydroxycarbamide correlates to renal function.[1] An initial oral dose of 7.5 mg/kg daily is recommended for adults and children over 2 years of age with sickle-cell disease and a creatinine clearance of less than 60 mL/minute. US product information also recommends this dose adjustment for adults with end-stage renal disease; on dialysis days the dose should be given after haemodialysis.

1. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45:** 434–45.

Haemoglobinopathies. Hydroxycarbamide is considered a promising treatment for the haemoglobinopathies. It can stimulate fetal haemoglobin production, which in turn can reduce haemoglobin polymerisation and the numbers of deformed, dense, and damaged erythrocytes.[1] In adult patients with **sickle-cell disease** (p. 1123.2), a randomised controlled study produced evidence that initial oral doses of 15 mg/kg daily, adjusted according to response and tolerance to up to 35 mg/kg daily, reduced the rate of sickle-cell crisis compared with placebo.[2] An observational follow-up study[3] of this group found that patients taking hydroxycarbamide for frequent sickle-cell episodes appeared to have reduced mortality. A report in 2 adults has suggested that it might reverse splenic dysfunction.[4] A systematic review[5] has noted that despite the benefits, the paucity of long-term studies limits conclusions on the toxicity of treatment with hydroxycarbamide.

Despite some concerns about giving a potential carcinogen to children,[6] studies in paediatric populations have also reported evidence of benefit in terms of decreased hospitalisation[7,8] and sickle-cell crisis.[8,9] Although the evidence for the efficacy of hydroxycarbamide in children with sickle-cell disease is not as strong as that for adults[10] and is mostly based on observational studies, a systematic review[11] concluded that there was strong evidence of an increase in haemoglobin and decreased hospitalisations, moderate evidence of decreased painful crises, and weak evidence of decreased neurological events. There was insufficient evidence to draw conclusions on the effect of hydroxycarbamide on the frequency of transfusions or mortality. Hydroxycarbamide may be considered for children with sickle-cell disease and frequent complications such as painful crises, priapism, severe anaemia, or acute chest syndrome.[12] Hydroxycarbamide has also been suggested as an alternative to blood transfusions in children who have had a stroke.[8,13,14] Although a small study[15] has suggested benefit in paediatric patients in terms of splenic preservation, long-term prevention of organ damage remains to be established.[16,17]

It has been suggested that use of the drug with erythropoietin might enhance the production of fetal haemoglobin, but results from studies of the combination have been conflicting.[18,19]

There appear to have been few studies of hydroxycarbamide specifically in **thalassaemia** (p. 1124.1). Initial oral doses of 8.2 to 10.3 mg/kg daily, increased until toxicity occurred, did produce sustained increases in fetal haemoglobin in 3 patients, but did not result in a sustained increase in total haemoglobin.[20] Others have reported[21] that rises in fetal haemoglobin did not necessarily correlate with clinical improvement. Conversely, sustained responses have been seen in other studies.[22-25] Use with sodium phenylbutyrate has produced conflicting results.[26-28]

1. Halsey C, Roberts IAG. The role of hydroxyurea in sickle cell disease. *Br J Haematol* 2003; **120:** 177–86.
2. Charache S, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; **332:** 1317–22.
3. Steinberg MH, *et al.* Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; **289:** 1645–51. Correction. *ibid.*; **290:** 756.
4. Claster S, Vichinsky E. First report of reversal of organ dysfunction in sickle cell anemia by the use of hydroxyurea: splenic regeneration. *Blood* 1996; **88:** 1951–3.
5. Lanzkron S, *et al.* Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med* 2008; **148:** 939–55.
6. Zimmerman SA, *et al.* Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004; **103:** 2039–45.
7. Scott JP, *et al.* Hydroxyurea therapy in children severely affected with sickle cell disease. *J Pediatr* 1996; **128:** 820–8.
8. Gulbis B, *et al.* Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood* 2005; **105:** 2685–90.
9. Jayabose S, *et al.* Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J Pediatr* 1996; **129:** 559–65.
10. Brawley OW, *et al.* National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008; **148:** 932–8.
11. Strouse JJ, *et al.* Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; **122:** 1332–42.
12. Mueller BU. When should hydroxyurea be used for children with sickle cell disease? *Pediatrics* 2008; **122:** 1365–6.
13. Ware RE, *et al.* Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999; **94:** 3022–6.
14. Ware RE, *et al.* Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004; **145:** 346–52.
15. Wang WC, *et al.* A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; **139:** 790–6.
16. Powars DR. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr* 2001; **139:** 763–4.
17. Kinney TR, *et al.* Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Blood* 1999; **94:** 1550–4.
18. Goldberg MA, *et al.* Treatment of sickle cell anemia with hydroxyurea and erythropoietin. *N Engl J Med* 1990; **323:** 366–72.
19. Rodgers GP, *et al.* Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle-cell disease. *N Engl J Med* 1993; **328:** 73–80.
20. Hajjar FM, Pearson HA. Pharmacologic treatment of thalassemia intermedia with hydroxyurea. *J Pediatr* 1994; **125:** 490–2.
21. de Paula EV, *et al.* Long-term hydroxyurea therapy in beta-thalassaemia patients. *Eur J Haematol* 2003; **70:** 151–5.
22. Loukopoulos D, *et al.* Hydroxyurea therapy in thalassemia. *Ann N Y Acad Sci* 1998; **30:** 120–8.
23. Rigano P, *et al.* Clinical and hematological responses to hydroxyurea in Sicilian patients with Hb S/β -thalassemia. *Hemoglobin* 2001; **25:** 9–17.
24. Loukopoulos D, *et al.* Reduction of the clinical severity of sickle cell/β -thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis* 2000; **26:** 453–66.
25. Bradai M, *et al.* Hydroxyurea can eliminate transfusion requirements in children with severe β -thalassemia. *Blood* 2003; **102:** 1529–30.
26. Olivieri NF, *et al.* Treatment of thalassaemia major with phenylbutyrate and hydroxyurea. *Lancet* 1997; **350:** 491–2.
27. Hoppe C, *et al.* Hydroxyurea and sodium phenylbutyrate therapy in thalassemia intermedia. *Am J Hematol* 1999; **62:** 221–7.
28. Dover GJ. Hemoglobin switching protocols in thalassemia. *Ann N Y Acad Sci* 1998; **850:** 80–6.

HIV infection and AIDS. Unlike most drugs used to treat HIV, which target viral enzymes, hydroxycarbamide inhibits ribonucleotide reductase, a host cellular enzyme that is less prone to mutation and subsequent development of resistance.[1] The drug acts synergistically with didanosine (p. 972.3). Of 25 HIV-positive patients given didanosine 200 mg twice daily with hydroxycarbamide 15 mg/kg daily in 2 divided doses, all showed a drop in viral load and an increase in CD4+ lymphocyte count.[2] Viraemia was not detectable in 13 of 24 patients evaluated at 6 months and 10 of 20 patients evaluated at 1 year. In 2 of these patients who subsequently received no antiviral treatments for 1 year there was no viral rebound, although some proviral DNA was detected.[3] In another study in 6 patients, didanosine 200 mg twice daily with hydroxycarbamide 250 mg

four times daily (suggested to be a better regimen because of the short half-life of the antineoplastic) produced a sharp decrease in viraemia, which was maintained for up to 72 weeks.[4] A rebound occurred in 1 patient on interrupting treatment but viral replication was again suppressed when treatment was restarted.

Combinations with didanosine and other HIV drugs have also been tried.[1] A controlled study[5] of hydroxycarbamide, didanosine, and stavudine indicated significantly enhanced activity when the antivirals were used with the antineoplastic rather than placebo. However, in a long-term follow-up[6] there was a high withdrawal rate amongst patients receiving this combination, due to virological failure and adverse effects such as peripheral neuropathy and fatigue. Another study[7] (ACTG 5025) was terminated due to the high risk of toxicity, including fatal pancreatitis, in patients receiving the hydroxycarbamide regimens. The authors noted that the use of a higher daily dosage of 1.2 g of hydroxycarbamide (rather than the usual 1 g daily) and increased exposure to didanosine (itself associated with pancreatitis) may have contributed to toxicity. An analysis of 2613 patients[8] determined that the use of hydroxycarbamide with didanosine, or didanosine and stavudine, resulted in a fourfold increase in the risk for development of pancreatitis, compared with didanosine alone. In a study of patients who had failed protease-inhibitor based regimens,[9] the addition of the antineoplastic to reverse transcriptase inhibitor-based therapy significantly improved virologic response. Despite an increased incidence of adverse events associated with its use, hydroxycarbamide was considered to be a valuable alternative in these patients. A small randomised study[10] of patients with chronic HIV infection given structured treatment interruptions with cycles of HAART, or HAART and hydroxycarbamide, found that use of the latter decreased viral load. There is some suggestion that a lower dose of hydroxycarbamide (300 mg twice daily) may have better antiretroviral activity, and fewer adverse effects, than higher doses.[11] For further discussion of the management of HIV infection and AIDS, see p. 957.2.

1. Gibbs MA, Sorensen SJ. Hydroxyurea in the treatment of HIV-1. *Ann Pharmacother* 2000; **34:** 89–93.
2. Vila J, *et al*. 1-year follow-up of the use of hydroxycarbamide and didanosine in HIV infection. *Lancet* 1996; **848:** 203–4.
3. Vila J, *et al*. Absence of viral rebound after treatment of HIV-infected patients with didanosine and hydroxycarbamide. *Lancet* 1997; **350:** 635–6.
4. Lori F, *et al*. Long-term suppression of HIV-1 by hydroxyurea and didanosine. *J AMA* 1997; **277:** 1437–8.
5. Rutschmann OT, *et al*. A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *AIDS* 1998; **12:** F71–7.
6. Rutschmann OT, *et al*. Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *AIDS* 2000; **14:** 2145–51.
7. Havlir DV, *et al*. Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001; **15:** 1379–88.
8. Moore RD, *et al*. Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS* 2001; **15:** 617–20.
9. Lafeuillade A, *et al*. The HYDILE trial: efficacy and tolerance of a quadruple combination of reverse transcriptase inhibitors versus the same regimen plus hydroxyurea or hydroxyurea and interleukin-2 in HIV-infected patients failing protease inhibitor-based combinations. *HIV Clin Trials* 2002; **3:** 263–71.
10. García F, *et al*. A cytostatic drug improves control of HIV-1 replication during structured treatment interruptions: a randomized study. *AIDS* 2003; **17:** 43–51.
11. Lisziewicz J, *et al*. Hydroxyurea in the treatment of HIV infection: clinical efficacy and safety concerns. *Drug Safety* 2003; **26:** 605–24.

Malignant neoplasms. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia (p. 694.2), and may be used in the myeloproliferative disorders polycythaemia vera (p. 695.2) and primary (essential) thrombocythaemia (p. 695.2). Hydroxycarbamide has been tried, often with radiotherapy, in some solid malignancies such as tumours of the cervix (p. 704.2), head and neck (p. 708.1), and ovary (p. 711.2).

Psoriasis. An immunosuppressant (usually methotrexate or ciclosporin) may be useful in patients with severe refractory psoriasis (p. 1688.1). Hydroxycarbamide has also been tried, although experience is limited.[1,2]

1. Layton AM, *et al*. Hydroxyurea in the management of therapy resistant psoriasis. *Br J Dermatol* 1989; **121:** 647–53.
2. Smith CH, *et al*. Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24:** 2–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow suppression, including megaloblastic changes, is the main adverse effect of hydroxycarbamide. The erythema caused by irradiation may be exacerbated. Other adverse effects reported have included gastrointestinal disturbances, impairment of renal function, pulmonary oedema, dermatological reactions, alopecia, and neurological reactions such as headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions. There are rare reports of acute pulmonary reactions consisting of pulmonary infiltrates or fibrosis, dyspnoea and fever. Symptoms resembling cutaneous vasculitis, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders treated with hydroxycarbamide, especially in those also given interferon. There are reports of hepatotoxicity and pancreatitis, some fatal, in patients with HIV infection, given hydroxycarbamide and antiretrovirals (see also HIV Infection and AIDS, p. 803.3); peripheral neuropathy has also occurred.

Pre-existing anaemia should be corrected before beginning therapy with hydroxycarbamide and the haemoglobin concentration, white cell and platelet counts, and hepatic and renal function should be determined repeatedly during treatment. Treatment should be interrupted if the white cell or platelet count fall below acceptable levels (see also Bone-marrow Depression, p. 730.3). If anaemia occurs when hydroxycarbamide is used as an antineoplastic, it may be corrected by transfusions of whole blood without stopping therapy. If anaemia (haemoglobin less than 4.5 g per 100 mL, or reticulocyte count less than 80 000 cells/mm^3 when haemoglobin is less than 9 g per 100 mL) occurs when the drug is used for sickle-cell disease, therapy should be interrupted. Megaloblastic changes are usually self-limiting.

Hydroxycarbamide should be used with caution in patients with impaired renal function. Uric acid concentrations should be monitored, and a high fluid intake maintained during treatment. The elderly may be more sensitive to its adverse effects.

Breast feeding. In breast-milk samples from a woman given hydroxycarbamide 500 mg three times daily, the mean concentration of the drug was found to be about 6 mg/litre. It was estimated that, had the infant been breast-fed, it would have received about 3 to 4 mg daily. Although this amount appears to be low, women are advised not to breast feed while taking hydroxycarbamide.[1]

1. Sylvester RK, *et al*. Excretion of hydroxyurea into milk. *Cancer* 1987; **60:** 2177–8.

Carcinogenicity. Secondary leukaemias have occurred in patients receiving hydroxycarbamide for myeloproliferative disorders, although the extent to which this is due to the treatment or the underlying disorder is unknown.

Skin cancers have also been associated with its use. These are often multiple and include both squamous cell and basal cell carcinomas.

References.

1. Liozon E, *et al*. Is treatment with hydroxyurea leukemogenic in patients with essential thrombocythemia? An analysis of three new cases of leukaemic transformation and review of the literature. *Hematol Cell Ther* 1997; **39:** 11–18.
2. Pearson TC, *et al*. Leukemic transformation in polycythemia vera. *Blood* 1998; **92:** 1837–8.
3. De Simone C, *et al*. Multiple squamous cell carcinomas of the skin during long-term treatment with hydroxyurea. *Eur J Dermatol* 1998; **8:** 114–15.
4. Best PJM, Petitt RM. Multiple skin cancers associated with hydroxyurea therapy. *Mayo Clin Proc* 1998; **73:** 961–3.

Effects on the liver. Fever and hepatitis have been reported[1,2] in patients receiving hydroxycarbamide. Symptoms recurred when patients were rechallenged with the drug.

1. Heddle R, Calvert AF. Hydroxyurea induced hepatitis. *Med J Aust* 1980; **1:** 121.
2. Westerman DA, *et al*. Hydroxyurea-induced fever and hepatitis. *Aust N Z J Med* 1998; **28:** 657–9.

Effects on the skin and nails. Reports of skin reactions with hydroxycarbamide include hyperpigmentation of the skin,[1] and of nails (melanonychia).[2]

Hydroxycarbamide therapy has been associated with scaly erythematous skin lesions often resembling those of dermatomyositis.[1,3,4] Such lesions usually occur after several years of treatment and the course is usually benign. However, withdrawal of the drug is usually necessary for healing or improvement, in which case resolution may take several months.[1,4] Hydroxycarbamide can also cause painful leg ulcers, often on the malleoli, which may require stopping treatment.[1,5,6] Leg ulcers often coexist with dermatomyositis-like eruptions and may be caused by the same mechanism,[7] although mechanical injury may have a role in malleolar ulceration.[5] Licensed product information notes that vasculitic toxicities, including vasculitic ulceration and gangrene, have been associated with hydroxycarbamide use in patients with myeloproliferative disorders (particularly if also given interferon). However, histologically, perivascular lymphocytic infiltration without vasculitis has been reported in both early dermatomyositis-like lesions[1] and in leg ulcers.[5,8]

Skin cancers have also occurred, see Carcinogenicity above.

1. Vassallo C, *et al*. Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol* 2001; **26:** 141–8.
2. Aste N, *et al*. Nail pigmentation caused by hydroxyurea: report of 9 cases. *J Am Acad Dermatol* 2002; **47:** 146–7.
3. Senet P, *et al*. Hydroxyurea-induced dermatomyositis-like eruption. *Br J Dermatol* 1995; **133:** 455–9.
4. Daoud MS, *et al*. Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 1997; **36:** 178–82.
5. Best PJ, *et al*. Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med* 1998; **128:** 29–32.
6. Chaine B, *et al*. Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001; **137:** 467–70.
7. Suehiro M, *et al*. Hydroxyurea dermopathy with a dermatomyositis-like eruption and a large leg ulcer. *Br J Dermatol* 1998; **139:** 748–9.
8. Tarumoto T, *et al*. A case of bilateral heel ulcers associated with hydroxyurea therapy for chronic myelogenous leukemia. *Jpn J Clin Oncol* 2000; **30:** 159–62.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of hydroxycarbamide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxycarbamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3.

Pharmacokinetics

Hydroxycarbamide is readily absorbed from the gastrointestinal tract and distributed throughout the body. Peak plasma concentrations are reached within 2 hours. Up to 50% of a dose is metabolised by the liver; hydroxycarbamide is excreted in urine as metabolites and unchanged drug. Some is excreted as carbon dioxide via the lungs. About 80% of a dose is reported to be excreted in the urine within 12 hours. Hydroxycarbamide crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

References.

1. Gwilt PR, Tracewell WG. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin Pharmacokinet* 1998; **34:** 347–58.
2. Gwilt PR, *et al*. Pharmacokinetics of hydroxyurea in plasma and cerebrospinal fluid of HIV-1-infected patients. *J Clin Pharmacol* 2003; **43:** 1003–7.
3. Yan J-H, *et al*. The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45:** 434–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dacrodil†; Hidrolid; ***Austral.***: Hydrea; ***Austria***: Litalir; ***Belg.***: Hydrea; ***Braz.***: Hydrea; ***Canad.***: Hydrea; ***Chile***: Hydrea; ***Cz.***: Litalir; Siklos; ***Denm.***: Hydrea; ***Fin.***: Hydrea; ***Fr.***: Hydrea; Siklos; ***Ger.***: Litalir; Siklos; Syrea; ***Gr.***: Hydrea; Hydreasyn; Siklos; ***Hong Kong***: Hydrea†; ***Hung.***: Litalir; ***India***: Cytodrox; Durea; Hondrea; Hydab; Hydran; Hydrea; Leukocel; Myelostat; Neodrea; Oxyrea; ***Indon.***: Hydrea; ***Irl.***: Hydrea; Siklos; ***Ital.***: Onco-Carbide; ***Mex.***: Hydrea; ***Neth.***: Hydrea; Siklos; ***Norw.***: Hydrea; ***NZ***: Hydrea; ***Philipp.***: Hydab; Hydrox; Krabinex; Litalir†; ***Pol.***: Siklos; ***Port.***: Hydrea†; Siklos; ***Rus.***: Gidroxyurea (Гидроксиурея)†; Hydrea (Гидреа); ***S.Afr.***: Hydrea; ***Singapore***: Hydrine; ***Spain***: Hydrea; Siklos; ***Swed.***: Hydrea; ***Switz.***: Litalir; ***Thai.***: Hydrea; ***Turk.***: Hydrea; ***UK***: Hydrea; Siklos; ***USA***: Droxia; Hydrea.

Pharmacopoeial Preparations
BP 2014: Hydroxycarbamide Capsules;
USP 36: Hydroxyurea Capsules.

Ibritumomab Tiuxetan *(BAN, USAN, rINN)*

Ibritumomab tiuxetán; Ibritumomab Tiuxétan; Ibritumomabum Tiuxetanum; IDEC-129; IDEC-Y2B8; Ибритумомаб Тиуксетан.

Immunoglobulin G1, anti(human CD20 (antigen))(mouse monoclonal IDEC-Y2B8 γ1-chain), disulfide with mouse monoclonal IDEC-Y2B8 κ-chain, dimer tiuxetan conjugate.

CAS — 206181-63-7.
UNII — 4Q52C550XK.

Uses and Administration

Ibritumomab is a murine monoclonal antibody to CD20 antigen, which is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. Radiolabelled ibritumomab tiuxetan is used in the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (p. 696.3). Patients are pretreated with a low dose of rituximab (p. 852.1). In the USA this is followed by slow intravenous injection of ibritumomab tiuxetan chelated with indium-111 (p. 2224.3) for imaging to

confirm that biodistribution of tumour cells is acceptable, but in some other countries such imaging is considered to provide relatively little useful information, and is omitted. A second rituximab treatment is given 7 to 9 days after the first, followed by ibritumomab tiuxetan chelated with yttrium-90 (p. 2230.1) for radio-immunotherapy.

References.
1. Wiseman GA, *et al*. Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Crit Rev Oncol Hematol* 2001; **39:** 181–94.
2. Wagner HN, *et al*. Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-labeled anti-CD20 monoclonal antibody. *J Nucl Med* 2002; **43:** 267–72.
3. Witzig TE, *et al*. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 2453–63.
4. Witzig TE, *et al*. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3262–9.
5. Ansell SM, *et al*. Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3885–90.
6. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today* 2004; **40:** 111–19.
7. Hagenbeek A, Lewington V. Report of a European consensus workshop to develop recommendations for the optimal use of ^{90}Y-ibritumomab tiuxetan (Zevalin) in lymphoma. *Ann Oncol* 2005; **16:** 786–92.
8. Meredith RF. Logistics of therapy with the ibritumomab tiuxetan regimen. *Int J Radiat Oncol Biol Phys* 2006; **66** (suppl): S35–S38.
9. Cheung MC, *et al*. Yttrium 90 ibritumomab tiuxetan in lymphoma. *Leuk Lymphoma* 2006; **47:** 967–77. Correction. *ibid*.; 1719–20.
10. Gisselbrecht C, *et al*. Current status and future perspectives for yttrium-90 (^{90}Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40:** 1007–17.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p. 726.1 and p. 732.2.

Myelosuppression is common after doses of ibritumomab tiuxetan, and may be prolonged. Fatal intracranial haemorrhage has occurred. Infections and hypersensitivity reactions may also be severe. As ibritumomab tiuxetan is given with rituximab, severe infusion reactions due to the cytokine release syndrome may occur (see under Rituximab, p. 854.3). Severe cutaneous and mucocutaneous reactions, some fatal, have been reported and therapy should be stopped if they occur. Gastrointestinal disturbances are common. Other adverse effects include anorexia, asthenia, fever, cough, dyspnoea, dizziness, headache, insomnia, anxiety, arthralgia, myalgia, and peripheral oedema. Patients should be monitored for signs of extravasation in order to avoid radiation-associated tissue damage. If extravasation occurs, the infusion should be stopped immediately and restarted in another vein.

Complete blood and platelet counts should be monitored weekly, or more frequently if cytopenia is present, until haematological recovery. Ibritumomab tiuxetan should not be given to patients with extensive marrow involvement, impaired bone marrow reserve, or platelet or neutrophil counts below acceptable levels (see also Bone-marrow Depression, p. 730.3). Care should be taken during and after radiolabelling with indium-111 or yttrium-90 to minimise radiation exposure.

Effects on the skin. Severe cutaneous and mucocutaneous reactions have been reported after use of ibritumomab tiuxetan with rituximab, some of them with a fatal outcome.[1,2] Reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis. Onset was reported to vary from days to months. Treatment should be stopped if any patient has such a reaction.

1. Kooijmans-Coutinho M [Biogen Idec (USA)]. Important drug warning (issued October 2005). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm164905.pdf (accessed 21/07/10)
2. Berlex, Canada. Association of severe mucocutaneous reactions with the ZEVALIN therapeutic regimen (issued 7th December 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zevalin_nth-aah_e.pdf (accessed 26/04/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zevamab; ***Austria***: Zevalin; ***Belg.***: Zevalin; ***Canad.***: Zevalin; ***Cz.***: Zevalin; ***Fin.***: Zevalin; ***Fr.***: Zevalin; ***Ger.***: Zevalin; ***Hong Kong***: Zevalin; ***Hung.***: Zevalin; ***Irl.***: Zevalin; ***Israel***: Zevalin; ***Ital.***: Zevalin; ***Neth.***: Zevalin; ***Norw.***: Zevalin; ***NZ***: Zevalin†; ***Pol.***: Zevalin; ***Port.***: Zevalin; ***S. Afr.***: Zevalin†; ***Spain***: Zevalin; ***Swed.***: Zevalin; ***Switz.***: Zevalin; ***Thai.***: Zevalin; ***Turk.***: Zevalin; ***UK***: Zevalin; ***USA***: Zevalin.

Ibrutinib *(USAN, pINN)*

CRA-032765; Ibrutinibum; PCI-32765-00; PCI-32765; Ибрутиниб.

1-{(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one.

$C_{25}H_{24}N_6O_2$=440.5

CAS — 936563-96-1.

Profile

Ibrutinib is an inhibitor of Bruton's tyrosine kinase that is used in the treatment of relapsed mantle cell lymphoma (p. 698.2). The usual dose is 560 mg orally once daily; capsules should be swallowed whole and not opened. If a daily dose is missed, the next day's dose should not be increased. If severe toxicity occurs, doses should be withheld until recovery to baseline or grade 1. For the first occurrence, treatment is restarted at the usual dose. Subsequently, the dose should be reduced to 420 mg daily after the second occurrence, and to 280 mg daily after the third occurrence. Ibrutinib should be stopped if the patient is unable to tolerate 280 mg daily. Treatment is continued until the patient no longer benefits, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Ibrutinib is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A family and use with strong or moderate inhibitors or strong inducers of these enzymes should be avoided. If use together is necessary, ibrutinib treatment may be interrupted for short-term therapy with a strong CYP3A inhibitor; the dose of ibrutinib should be reduced to 140 mg daily when used with a moderate CYP3A inhibitor.

The most commonly reported adverse effects include neutropenia, thrombocytopenia, anaemia, gastrointestinal disturbances, fatigue, musculoskeletal or abdominal pain, peripheral oedema, dyspnoea, rash, and decreased appetitie. Haemorrhage, renal failure, and second primary malignancies have occurred.

Ibrutinib is also under investigation for chronic lymphocytic leukaemia.

References.
1. Burger JA, Buggy JJ. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765). *Leuk Lymphoma* 2013; **54:** 2385–91.
2. Chavez JC, *et al*. Ibrutinib: a n evidence-based review o f its potential in the treatment of advanced chronic lymphocytic leukemia. *Core Evid* 2013; **8:** 37--45.
3. Akinleye A, *et al*. Ibrutinib and novel BTK inhibitors in clinical development. *J Hematol Oncol* 2013; **6:** 59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Imbruvica.

Idarubicin Hydrochloride

(BANM, USAN, rINNM)

4-Demethoxydaunorubicin Hydrochloride; Hidrocloruro de idarubicina; Idarubicina, hidrocloruro de; Idarubicine, chlorhydrate d'; Idarubicinhydroklorid; Idarubicini Hydrochloridum; Idarubisiinihydrokloridi; Idarubisin Hidroklorür; IMI-30; NSC-256439 (idarubicin); Идарубицина Гидрохлорид.

(7*S*,9*S*)-9-Acetyl-7-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-7,8,9,10-tetrahydro-6,9,11-trihydroxynaphthacene-5,12-dione hydrochloride.

$C_{26}H_{27}NO_9$,HCl=534.0

CAS — 58957-92-9 (idarubicin); 57852-57-0 (idarubicin hydrochloride).

ATC — L01DB06.

ATC Vet — QL01DB06.

UNII — 5VV3MDU5IE.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Idarubicin Hydrochloride). A red-orange to red-brown powder. Slightly soluble in water; insoluble in acetone and in solvent ether; soluble in methyl alcohol. A 0.5% solution in water has a pH between 5.0 and 6.5. Store in airtight containers.

Incompatibility. Licensed product information states that precipitation occurs when idarubicin hydrochloride is mixed with heparin, and that it will degrade in alkaline solution.

Uses and Administration

Idarubicin like daunorubicin (p. 778.3), of which it is an analogue, is an anthracycline antibiotic and has antineoplastic actions similar to those of doxorubicin (p. 783.2). It is used as the hydrochloride, alone or with other drugs, for the induction of remission in patients with acute myeloid leukaemias (p. 693.1). It is also used as a second-line treatment in acute lymphoblastic leukaemia (p. 692.3), and advanced breast cancer (p. 702.1).

Idarubicin hydrochloride is given by *intravenous* injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 5 to 15 minutes. The suggested dose in adult acute myeloid leukaemia is 12 mg/m^2 daily for 3 days, with cytarabine. A similar dose, as a single agent, has been given in acute lymphoblastic leukaemia. An alternative dosage schedule in acute myeloid leukaemia is 8 mg/m^2 given daily for 5 days, either alone or in combination therapy. For suggested doses in children with acute lymphoblastic leukaemia see Administration in Children, below.

When the intravenous route cannot be used, idarubicin hydrochloride may be given orally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* A suggested *oral* dose in adult acute myeloid leukaemia as a single agent is 30 mg/m^2 daily for 3 days; 15 to 30 mg/m^2 may be given daily for 3 days when used with other drugs.

In patients with breast cancer unresponsive to front-line chemotherapy not including anthracyclines, idarubicin hydrochloride has been given orally in doses of 45 mg/m^2, as a single dose or divided over 3 consecutive days; the treatment may be repeated every 3 or 4 weeks depending on the haematological recovery. A total cumulative oral dose of 400 mg/m^2 should not be exceeded.

Blood counts should be performed frequently in patients receiving idarubicin, and monitoring of cardiac, hepatic, and renal function is recommended. Doses should be reduced in patients with hepatic or renal impairment (see also below). In patients who receive a second course of idarubicin, intravenous dosage should be reduced by 25% if severe mucositis developed with the first course; therapy should be delayed until the patient has recovered from this toxicity.

The actions and uses of idarubicin have been reviewed.[1] A study in leukaemia cells *in vitro* suggested that idarubicin was more active than a conventional anthracycline, daunorubicin, against cells with the multidrug resistance (MDR) phenotype.[2] A collaborative overview of randomised studies for acute myeloid leukaemia found that idarubicin-based therapy achieved better remission rates and overall survival than daunorubicin-based regimens.[3] Its oral bioavailability has been suggested to offer an advantage in the management of malignancies in older patients.[4]

1. Cersosimo RJ. Idarubicin: an anthracycline antineoplastic agent. *Clin Pharm* 1992; **11:** 152–67.
2. Berman E, McBride M. Comparative cellular pharmacology of daunorubicin and idarubicin in human multidrug-resistant leukaemia cells. *Blood* 1992; **79:** 3267–73.
3. AML Collaborative Group. A systematic collaborative overview of randomised trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol* 1998; **103:** 100–9.
4. Crivellari D, *et al*. New oral drugs in older patients: a review of idarubicin in elderly patients. *Crit Rev Oncol Hematol* 2004; **49:** 153–63.

Administration in children. Idarubicin hydrochloride may be given as a second-line treatment to children with relapsed acute lymphoblastic leukaemia. The suggested intravenous dose for use as a single agent is 10 mg/m^2 daily for 3 days. Precautions and monitoring are as for adults, see Uses and Administration, above.

Administration in hepatic impairment. UK licensed product information for idarubicin hydrochloride recommends that a dose reduction be considered in patients with hepatic impairment. Although no specific doses are suggested, it is noted that a 50% reduction in dosage has been used with some other anthracyclines in patients whose bilirubin concentrations were between 12 and 20 micrograms/mL. Use of idarubicin is contra-indicated in patients with severe hepatic impairment.

US licensed product information states that in patients with moderate or severe hepatic impairment, the metabolism of idarubicin is expected to be reduced, leading to higher systemic drug concentrations, and that dose reduction should be considered. No specific doses are recommended; idarubicin should be withheld if bilirubin concentrations exceed 50 micrograms/mL.

Administration in renal impairment. Both UK and US licensed product information state renal impairment may affect the disposition of idarubicin and that, in many studies, treatment was contra-indicated if serum creatinine concentrations exceeded 20 micrograms/mL. US licensed product information suggests that dose reduction be considered in renal impairment, but gives no specific doses; UK licensed product information states that idarubicin should not be used in patients with severe renal impairment.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1. Raised liver enzymes and bilirubin can occur with idarubicin. Severe enterocolitis with perforation has been reported rarely. A cumulative total dose limit has not yet been defined. UK licensed

product information states that total cumulative oral doses up to 400 mg/m² have a low probability of cardiotoxicity. Cardiomyopathy has been reported in some patients with cumulative intravenous doses of 150 to 290 mg/m². It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. Idarubicin should be given with caution, and in reduced doses, to patients with renal or hepatic impairment.

Effects on the heart. Cardiotoxicity is a major factor in limiting the use of anthracyclines (see under Doxorubicin, p. 784.1). It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. However, a 34-year-old woman with no risk factors for heart disease developed severe congestive heart failure after her first exposure to idarubicin, which was given as part of an induction regimen for acute myeloid leukaemia. The patient's left ventricular ejection fraction improved after 4 months, supporting the hypothesis that, while chronic anthracycline-induced cardiomyopathy is irreversible, subacute congestive heart failure after short-term anthracycline use may be partially or totally reversible.[1]

1. Yang S-C, *et al.* The development of congestive heart failure and ventricular tachycardia after first exposure to idarubicin in a patient with acute myeloid leukaemia. *Br J Clin Pharmacol* 2010; **69:** 209–11.

Effects on the skin and nails. For a report of transverse hyperpigmented bands of the nails in a patient who received idarubicin, see under Doxorubicin, p. 784.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies idarubicin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pharmacokinetics

On intravenous dosage idarubicin is rapidly distributed into body tissues and extensively tissue bound, with a volume of distribution which may be in excess of 2000 litres. It is extensively metabolised, both in the liver and extrahepatically; the principal metabolite, idarubicinol (13-dihydroidarubicin) has equal antineoplastic activity. Peak concentrations of idarubicin and idarubicinol in bone marrow and nucleated blood cells are 400 (idarubicin) and 200 (idarubicinol) times greater than those in plasma; cellular concentrations of drug and metabolite decline with apparent terminal half-lives of 15 and 72 hours respectively, whereas plasma half-lives are reported to be 20 to 22 hours and about 45 hours respectively. Idarubicin is excreted in bile, and to a lesser extent in urine, as unchanged drug and metabolites.

Idarubicin is also absorbed orally, reaching peak plasma concentrations within 4 hours. Estimates of its oral bioavailability vary from about 20 to 40%.

References.

1. Robert J. Clinical pharmacokinetics of idarubicin. *Clin Pharmacokinet* 1993; **24:** 275–88.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Epicina; Zavedos; ***Austral.***: Zavedos; ***Austria***: Zavedos; ***Belg.***: Zavedos; ***Braz.***: Evomid; Zavedos; ***Canad.***: Idamycin; ***Chile***: Zavedos; ***China***: Ai Nuo Ning (艾诺宁); Zavedos (善唯达); ***Cz.***: Zavedos; ***Denm.***: Zavedos; ***Fin.***: Zavedos; ***Fr.***: Zavedos; ***Ger.***: Zavedos; ***Gr.***: Zavedos; ***Hong Kong***: Zavedos; ***Hung.***: Zavedos; ***Irl.***: Zavedos; ***Israel***: Zavedos; ***Ital.***: Zavedos; ***Malaysia***: Zavedos; ***Mex.***: Idamycin; Idaralem†; ***Neth.***: Zavedos; ***Norw.***: Zavedos; ***NZ***: Zavedos; ***Philipp.***: Zavedos; ***Pol.***: Zavedos; ***Port.***: Zavedos; ***Rus.***: Rubide (Рубида); Zavedos (Заведос); ***S.Afr.***: Zavedos; ***Singapore***: Zavedos; ***Spain***: Zavedos; ***Swed.***: Zavedos; ***Switz.***: Zavedos; ***Thai.***: Idaralem†; Zavedos; ***Turk.***: Idamen; Zavedos; ***UK***: Zavedos; ***Ukr.***: Zavedos (Заведос); ***USA***: Idamycin; ***Venez.***: Zavedos.

Pharmacopoeial Preparations

USP 36: Idarubicin Hydrochloride for Injection.

Ifosfamide *(BAN, USAN, rINN)*

Ifosfamid; Ifosfamida; Ifosfamidas; Ifosfamidi; Ifosfamidum; Ifoszfamid; Iphosphamide; Isophosphamide; MJF-9325; NSC-109724; Z-4942; Ифосфамид.

3-(2-Chloroethyl)-2-(2-chloroethylamino)perhydro-1,3,2-oxazaphosphorinane 2-oxide.

$C_7H_{15}Cl_2N_2O_2P$=261.1

CAS — 3778-73-2.

ATC — L01AA06.

ATC Vet — QL01AA06.

UNII — UM20QQM95Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ifosfamide). A white or almost white, hygroscopic, fine crystalline powder. Soluble in water; freely soluble in dichloromethane. Store in airtight containers.

USP 36: (Ifosfamide). A white, crystalline powder. M.p. about 40 degrees. Freely soluble in water; very soluble in alcohol, in methyl alcohol, in isopropyl alcohol, in dichloromethane, and in ethyl acetate; very slightly soluble in hexanes. A 10% solution in water has a pH of between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 25 degrees.

Incompatibility. Ifosfamide appears to be compatible when mixed in solution with mesna.[1,2] However, ifosfamide appears to be incompatible with benzyl alcohol used as a preservative in Water for Injections: solutions made up with water preserved in this way became turbid, with the formation of aqueous and oily phases, at concentrations of ifosfamide greater than 60 mg/mL.[3]

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i:** 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii:** 468.
3. Behme RJ, *et al.* Incompatibility of ifosfamide with benzyl-alcohol-preserved bacteriostatic water for injection. *Am J Hosp Pharm* 1988; **45:** 627–8.

Stability. Ifosfamide undergoes a reversible chemical rearrangement in aqueous solution, which is sensitive to changes in pH.[1] The ratio of these compounds to one another in biological fluids may have a bearing on the toxicity and efficacy of ifosfamide.

1. Küpfer A, *et al.* Intramolecular rearrangement of ifosfamide in aqueous solutions. *Lancet* 1990; **335:** 1461.

Uses and Administration

Ifosfamide is an alkylating agent with properties similar to those of cyclophosphamide (p. 771.1), of which it is a congener. It is used in the treatment of solid tumours including those of the cervix, lung, ovary, testis, and thymus, as well as in sarcoma and in the treatment of lymphomas. For further mention of these uses see the cross-references given below.

Ifosfamide is given intravenously, either by injection as a solution diluted to less than 4%, or by infusion. Licensed dosage regimens include a total dose of 8 to 12 g/m² divided over 3 to 5 days, with the course repeated at 2 to 4 week intervals; a total dose of 6 g/m² divided over 5 days, repeated every 3 weeks; and doses of 5 to 6 g/m², to a maximum of 10 g, given as a single 24-hour infusion, repeated at 3 to 4 week intervals. The interval between courses also depends on the blood count (see also Bone-marrow Depression, p. 730.3). Oral ifosfamide has also been studied but is associated with neurotoxicity (see Effects on the Nervous System, below).

Ifosfamide should be given with mesna (see Administration, below), and adequate hydration should be maintained, to avoid urological toxicity; fluid intake should not be less than 2 litres daily.

Administration. Mesna (p. 1557.2) can combine with urotoxic ifosfamide metabolites in the kidney to form stable and non-toxic compounds. It is therefore given prophylactically with ifosfamide. It has a shorter half-life than ifosfamide so repeated doses are needed to provide adequate protection of the bladder. A common schedule uses intravenous mesna at 60% of the ifosfamide dose, divided into 3 doses given with, or 15 minutes before, ifosfamide, then 4 and 8 hours after ifosfamide.[1] Mesna may also be given orally, but higher doses are required.

1. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6:** 144–54.

Malignant neoplasms. Ifosfamide may be used as an alternative to cyclophosphamide in lymphomas such as Burkitt's lymphoma (p. 697.3). It is also used in a variety of solid neoplasms, including in palliative regimens for advanced cervical cancer (p. 704.2); in the treatment of lung cancer (p. 710.2); in ovarian cancer (p. 711.2) and second-line and salvage regimens for testicular cancer (p. 715.1); in thymoma (p. 715.3); in adjuvant therapy for bone sarcomas (p. 717.3) and rhabdomyosarcoma (see Soft-tissue Sarcoma, p. 718.2).

Adverse Effects, Treatment, and Precautions

As for Cyclophosphamide, p. 772.2. Toxic effects on the urinary tract may be more severe with ifosfamide and may involve the kidneys as well as the bladder. CNS adverse effects have been reported, especially confusion, drowsiness, depressive psychosis, hallucinations, and rarely, seizures.

Effects on the heart. Severe myocardial depression, with heart failure and ventricular arrhythmias, has been reported in patients given high-dose ifosfamide.[1] Symptoms were reversible with appropriate treatment in most cases although one patient died of cardiogenic shock.

1. Quezado ZMN, *et al.* High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med* 1993; **118:** 31–6.

Effects on the kidneys. In addition to its effects on the bladder ifosfamide may be associated with serious nephrotoxicity. A prospective study found that moderate and severe nephrotoxicity are common after ifosfamide treatment in children and adolescents, affecting 28% of patients.[1] Both proximal and distal tubular damage,[2,3] and to a lesser extent glomerular effects,[3] are seen, and the Fanconi syndrome (with development of hypophosphataemic rickets in several children),[3-7] and nephrogenic diabetes insipidus[2,7] may result. Progressive chronic renal failure after high-dose ifosfamide has been described.[8] Life-threatening hypokalaemia possibly due to a renal lesion has also occurred.[9] Results in *rats* suggest that generation of toxic metabolites within the kidney itself may be responsible, and that repairable renal damage occurs after the first dose, which is aggravated by repeated toxic insults.[10] This is in agreement with clinical results, since although renal damage has been seen after a single dose, perhaps representing an idiosyncratic reaction,[11,12] most cases have been in children receiving relatively high doses long-term. Renal damage appears to persist after withdrawal of ifosfamide in these patients and may be largely irreversible.[13] Toxicity may also progress over the months or years after treatment,[14] or late renal damage may develop after treatment has stopped.[15] Proximal tubular dysfunction was the most common form of damage in patients who had received ifosfamide at least 5 years previously for childhood malignancies,[14,15] and it has been suggested that reductions in the glomerular filtration rate are secondary to this, rather than a direct result of ifosfamide toxicity.[14] Although the risk of late toxicity was considered low, the damage was moderately severe even when the cumulative dose was small (60 g/m²).[15]

Possible risk factors for nephrotoxicity have included younger age (less than 5 years), high cumulative doses, use with cisplatin, or unilateral nephrectomy.[1,14,16] The cumulative dose appears to be the most important risk factor for the development and severity of toxicity.[1,16] The maximum safe dose of ifosfamide has not been established;[1,14,16] although significant nephrotoxicity is relatively infrequent below 84 g/m², doses above 119 g/m² are associated with a high risk of severe damage. Although some found no association between age at treatment and renal damage,[1] others noted that a younger age was associated with more severe nephrotoxicity,[14,16] and suggested that caution is needed when giving cumulative doses of 45 g/m² and above to children aged under 3 years[14] or 60 g/m² and above to those under 5 years.[16] Acetylcysteine has been investigated for its potential protective effect against nephrotoxicity.[17]

1. Skinner R, *et al.* Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. *Br J Cancer* 2000; **82:** 1636–45.
2. Skinner R, *et al.* Nephrotoxicity after ifosfamide. *Arch Dis Child* 1990; **65:** 732–8.
3. Burk CD, *et al.* Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. *J Pediatr* 1990; **117:** 331–5.
4. Skinner R, *et al.* Hypophosphataemic rickets after ifosfamide treatment in children. *BMJ* 1989; **298:** 1560–1.
5. Newbury-Ecob RA, Barbor PRH. Hypophosphataemic rickets after ifosfamide treatment. *BMJ* 1989; **299:** 258.
6. Newbury-Ecob RA, *et al.* Ifosfamide-induced Fanconi syndrome. *Lancet* 1989; **i:** 1328.
7. Skinner R, *et al.* Nephrotoxicity of ifosfamide in children. *Lancet* 1989; **ii:** 159.
8. Krämer A, *et al.* Progressive renal failure in two breast cancer patients after high-dose ifosfamide. *Lancet* 1994; **334:** 1569.
9. Husband DJ, Watkin SW. Fatal hypokalaemia associated with ifosfamide/mesna chemotherapy. *Lancet* 1988; **i:** 1116.
10. Graham MI, *et al.* A proposed mechanism for isophosphamide-induced kidney toxicity. *Hum Toxicol* 1985; **4:** 545–6.
11. Heney D, *et al.* Acute ifosfamide-induced tubular toxicity. *Lancet* 1989; **ii:** 103–4.
12. Devalck C, *et al.* Acute ifosfamide-induced proximal tubular toxic reaction. *J Pediatr* 1991; **118:** 325–6.
13. Heney D, *et al.* Progressive renal toxicity due to ifosfamide. *Arch Dis Child* 1991; **66:** 966–70.
14. Loebstein R, *et al.* Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. *J Clin Pharmacol* 1999; **39:** 454–61.
15. Oberlin O, *et al.* Long-term evaluation of ifosfamide-related nephrotoxicity in children. *J Clin Oncol* 2009; **27:** 5350–5.
16. Loebstein R, Koren G. Ifosfamide-induced nephrotoxicity in children: critical review of predictive risk factors. *Pediatrics* 1998; **101:** 1067. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/6/e8 (accessed 30/06/04)
17. Chen N, *et al.* Prevention of ifosfamide nephrotoxicity by N-acetylcysteine: clinical pharmacokinetic considerations. *Can J Clin Pharmacol* 2007; **14:** e246–e250.

Effects on the nervous system. Use of ifosfamide (with or without mesna for urothelial protection) may be associated with the development of severe encephalopathy, which develops in 10 to 40% of patients receiving high doses. Symptoms include confusion, stupor, seizures, hallucinations, blurred vision, and occasionally, coma; fatalities have been reported.[1] The effect has been suggested to be due to a metabolite, chloroacetaldehyde,[1] a hypothesis

supported by the increased incidence of encephalopathy after oral rather than intravenous doses.[2] Others suggest that the dechloroethylated metabolites may contribute, and in particular the *R*-enantiomer of 3-dechloroethylifosfamide, which is a metabolite of *S*-ifosfamide.[3] There is some uncertainty about the contributory role of mesna, if any: encephalopathy has not been seen when mesna is given with cyclophosphamide,[4] and has been seen when ifosfamide is given alone,[2] but an exacerbatory role for mesna cannot be ruled out,[5] perhaps via its chelating properties.[4]

Proposed risk factors include renal and hepatic impairment, pelvic disease, brain metastases, electrolyte imbalances, and drug-drug interactions.[1] A retrospective review of 237 patients given ifosfamide, of whom 38 developed encephalopathy, found no evidence that age or ifosfamide dose influenced the development of the condition, and serum creatinine values were in the normal range in the affected group, although they were slightly higher than in those not affected; however, low serum albumin did seem to be associated with greater risk.[6] It has also been suggested that the drug be given by continuous infusion over several days where possible, since this route has by far the lowest incidence of encephalopathy (7%, versus 26% with intravenous bolus and 43% with oral doses).[7] Care may also be required when giving other antineoplastics to patients who have had encephalopathy after ifosfamide, since a case of encephalopathy with bleomycin (not normally associated with neurotoxicity) has been reported in such a patient.[8] In another case, ifosfamide neurotoxicity developed after the addition of aprepitant to a standard antiemetic regimen that included ondansetron and dexamethasone; induction of ifosfamide metabolism to neurotoxic metabolites may have accounted for the symptoms.[9] Hypoalbuminaemia has been identified as a risk factor in other case reports. A small cohort study identified hypoalbuminaemia, female sex, low total bilirubin, anaemia, and obesity as being associated with the development of ifosfamide-induced encephalopathy.[1]

Methylthioninium chloride has been tried to prevent or reverse signs of encephalopathy (see Glutaric Aciduria under Uses of Methylthioninium Chloride, p. 1559.2).

1. Sweiss KI, *et al.* Encephalopathy after high-dose ifosfamide: a retrospective cohort study and review of the literature. *Drug Safety* 2008; **31:** 989–96.
2. Lewis LD, Meanwell CA. Ifosfamide pharmacokinetics and neurotoxicity. *Lancet* 1990; **335:** 175–6.
3. Wainer IW, *et al.* Ifosfamide stereoselective dichloroethylation [sic] and neurotoxicity. *Lancet* 1994; **343:** 982–3.
4. Osborne RJ, Slevin ML. Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; **i:** 1398–9.
5. Pinkerton R, *et al.* Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; **i:** 1399.
6. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. *Am J Clin Oncol* 2005; **28:** 277–80.
7. Cerny T, *et al.* Ifosfamide by continuous infusion to prevent encephalopathy. *Lancet* 1990; **335:** 175.
8. Atherton P, *et al.* Drug-induced encephalopathy after previous ifosfamide treatment. *Lancet* 1988; **ii:** 1084.
9. Jarkowski A. Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. *Am J Health-Syst Pharm* 2008; **65:** 2229–31.

Handling and disposal. A study[1] found that ifosfamide 8% solution penetrated all of 4 brands of latex glove and one PVC glove, although the diffusion rate was 4 or more times slower than through cadaver skin. Permeation was greater through the PVC glove than the latex gloves, partly due to its lesser thickness, although permeation was not dependent on thickness alone and varied between gloves of the same brand as well as between brands. They recommended that latex gloves of a suitable brand should be worn when handling ifosfamide, and changed at least every 2 hours. For reference to a method for the destruction of ifosfamide waste, see under Cyclophosphamide, p. 773.2.

1. Corlett SA, *et al.* Permeation of ifosfamide through gloves and cadaver skin. *Pharm J* 1991; **247:** R39.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ifosfamide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

As for Cyclophosphamide, p. 773.2. For a general outline of antineoplastic drug interactions, see p. 733.3. For reference to the effects of ifosfamide on oral anticoagulants, see under Warfarin Sodium, p. 1532.2. For a report of the enhancement of cisplatin-induced ototoxicity and nephrotoxicity, see under Cisplatin, p. 768.3.

Antibacterials. Oral *rifampicin* given twice daily for 6 days, starting 3 days before intravenous ifosfamide (as a 24-hour infusion), increased the clearance of ifosfamide by over 100%; however, exposure to metabolites of ifosfamide was relatively unchanged. The authors considered that rifampicin might decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70:** 132–41.

Antifungals. *Ketoconazole* given orally for 4 days, starting 1 day before intravenous ifosfamide (given as a 24-hour infusion), decreased ifosfamide clearance. However, ifosfamide metabolism to active metabolites was decreased, and urinary excretion of ifosfamide was increased. Ketoconazole may decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70:** 132–41.

Pharmacokinetics

Ifosfamide is normally given intravenously, although it is well absorbed from the gastrointestinal tract. The pharmacokinetics of ifosfamide are reported to exhibit considerable interindividual variation. It is a prodrug that is extensively metabolised, chiefly by cytochrome P450 isoenzymes such as CYP3A4 and CYP2B6 in the liver, to both active and inactive metabolites; there is some evidence that metabolism is saturated at very high doses. Although licensed product information states that a mean terminal elimination half-life is about 15 hours after a single high-dose intravenous bolus, most studies at lower doses appear to have recorded elimination half-lives of about 4 to 8 hours. After repeated doses (fractionated therapy) there is a decrease in the elimination half-life, apparently due to autoinduction of metabolism. Ifosfamide is distributed into the CSF. It is excreted largely in urine, as unchanged drug and metabolites.

General references.

1. Wagner T. Ifosfamide clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 439–56.
2. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38:** 291–304.
3. Kerbusch T, *et al.* Clinical pharmacokinetics and pharmacodynamics of ifosfamide and its metabolites. *Clin Pharmacokinet* 2001; **40:** 41–62.

In a study[1] in 20 patients receiving intravenous ifosfamide over 3 or 5 days, the median elimination half-life of ifosfamide was 3.85 hours in patients under 60 years of age compared with 6.03 hours in those over age 60; this difference appeared to be due to an increased volume of distribution in the older age group. The autoinduction of metabolism typically seen with multiple doses of ifosfamide was not affected by age. The increased clearance seen over time during a 5-day cycle of ifosfamide treatment[2] was not sustained over the 21 days between cycles, but was reproducible and of similar magnitude in the subsequent cycle.

In another study[3] the half-life of the *S*-enantiomer of ifosfamide was found to be 5.98 hours after an intravenous bolus of the racemate, compared with 7.12 hours for the *R*-enantiomer.

1. Lind MJ, *et al.* The effect of age on the pharmacokinetics of ifosfamide. *Br J Clin Pharmacol* 1990; **30:** 140–3.
2. Lewis LD. A study of 5 day fractionated ifosfamide pharmacokinetics in consecutive treatment cycles. *Br J Clin Pharmacol* 1996; **42:** 179–86.
3. Corlett SA, *et al.* Pharmacokinetics of ifosfamide and its enantiomers following a single 1h intravenous infusion of the racemate in patients with small cell lung carcinoma. *Br J Clin Pharmacol* 1995; **39:** 452–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cuantil; Fentul†; Ifocris; Ifosmixan; IFX; ***Austral.***: Holoxan; ***Austria***: Holoxan; ***Belg.***: Holoxan; ***Braz.***: Evolox; Holoxane; ***Canad.***: Ifex; ***Chile***: Holoxan; Ifolem; ***China***: Holoxan (和乐生); Pi Fu Ping (匹服平); ***Cz.***: Holoxan; IFO-cell; ***Gr.***: Holoxan; ***Hong Kong***: Holoxan; ***Hung.***: Holoxan; ***India***: Holoxan; Ifocip; Ifos; Ipamide; ***Indon.***: Holoxan; ***Irl.***: Mitoxana; ***Israel***: Ifoxan†; ***Ital.***: Holoxan; ***Malaysia***: IFO-Cell; ***Mex.***: Alquimid; Crifty; Fosfidex†; Ifadex; Ifolem; Ifomida; ***Neth.***: Holoxan; ***Norw.***: Holoxan; ***NZ***: Holoxan; ***Philipp.***: Holoxan; Iphox; ***Pol.***: Holoxan; Macdafen; ***Port.***: Holoxan; ***Rus.***: Holoxan (Холоксан); ***S.Afr.***: Holoxan; ***Singapore***: Holoxan; ***Spain***: Tronoxal; ***Swed.***: Holoxan; ***Switz.***: Holoxan; ***Thai.***: Holoxan; IFO-cell†; Ifolem; ***Turk.***: Haloxan; Holoxan; ***USA***: Ifex.

Multi-ingredient Preparations. ***India***: Holoxan Uromitexan; Ifex-M; Ifomid-M; Ifoxan with Mesna; Ipamide with Mesna†; Isoxan.

Pharmacopoeial Preparations
BP 2014: Ifosfamide Injection;
USP 36: Ifosfamide for Injection.

Imatinib Mesilate *(BANM, rINNM)*

CGP-57-148B; CGP-57148; Imatinib, Mésilate d'; Imatinib, mesilato de; Imatinib Mesylate (USAN); Imatinib Mesylate; Imatinibi Mesilas; Mesilato de imatinib; STI-571; Иматиниба Мезилат.

α-(4-Methyl-1-piperazinyl)-3′-{[4-(3-pyridyl)-2-pyrimidinyl]amino}-*p*-tolu-*p*-toluidide methanesulfonate.

$C_{29}H_{31}N_7O,CH_4O_3S$=589.7

CAS — 152459-95-5 (imatinib); 220127-57-1 (imatinib mesilate).

ATC — L01XE01.

UNII — 8A1O1M485B.

Uses and Administration

Imatinib is a tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukaemia (p. 694.2) and acute lymphoblastic leukaemia (p. 692.3). It also inhibits the tyrosine kinase for platelet-derived growth factor and stem cell factor, c-kit (CD117), which is overexpressed in gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p. 718.2). Imatinib is also indicated for patients with myelodysplastic syndromes (p. 694.3), hypereosinophilic syndrome, aggressive systemic mastocytosis (p. 1226.3), and dermatofibrosarcoma protuberans. Imatinib is given orally as the mesilate but doses are expressed as the base. Imatinib mesilate 119.5 mg is equivalent to about 100 mg of imatinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In the treatment of **chronic myeloid leukaemia**, patients in chronic phase may be given the equivalent of 400 mg of the base daily, increased to 600 mg daily or 400 mg twice daily if required. Patients in blast crisis or accelerated phase are given 600 mg daily, increased to 400 mg twice daily if necessary.

In the treatment of patients with newly diagnosed **acute lymphoblastic leukaemia**, imatinib 600 mg daily may be given with induction, consolidation, or maintenance chemotherapy. The same dose may be given as monotherapy for patients with relapsed or refractory disease.

In the treatment of **gastrointestinal stromal tumours** (GIST), 400 mg daily is recommended. In patients with unresectable or metastatic disease that progresses at this dose, a dose increase up to 400 mg twice daily may be considered.

For patients with **myelodysplastic disease**, the recommended dose of imatinib is 400 mg daily. For **mastocytosis**, 400 mg daily is given, unless there is associated eosinophilia, in which case a starting dose of 100 mg daily is recommended, increased to 400 mg if response is inadequate. Similarly, the recommended dose for **hypereosinophilic syndrome** is 400 mg daily, although a subset of patients with FIP1L1-platelet-derived growth factor receptor-α fusion kinase should be started on 100 mg daily, increased to 400 mg if response is insufficient. Patients with **dermatofibrosarcoma protuberans** may be given 400 mg twice daily.

Doses should be taken with food, and accompanied by plenty of water, to minimise gastric irritation. Dose adjustments may be necessary if myelosuppression or hepatotoxicity occurs; blood counts and liver function should be regularly monitored (see Administration in Hepatic Impairment, p. 808.1). Doses are also adjusted in renal impairment, see p. 808.1.

Doses of imatinib should be increased by 50%, and clinical response should be carefully monitored, in patients given potent CYP3A4 inducers such as rifampicin or phenytoin. For children's doses, see Administration in Children, below.

Administration in children. In the UK, the licensed oral dose of imatinib for children with chronic myeloid leukaemia (CML) is 340 mg/m² daily, for those in chronic or advanced phase; a total dose of 800 mg should not be exceeded. The dose may be increased to 570 mg/m² daily (maximum total dose 800 mg) in children with disease progression, with unsatisfactory haematological response after at least 3 months of treatment, with no cytogenetic response after 12 months of treatment, or with loss of a previously achieved haematological or cytogenetic response.

In the USA, imatinib is given in a usual dose of 340 mg/m² daily in children with newly diagnosed CML or with chemotherapy in newly diagnosed acute lymphoblastic leukaemia; the dose should not exceed 600 mg.

Treatment can be given as a once-daily dose, or, in CML, split into morning and evening doses. There is no experience with the use of imatinib in children under 1 year of age.

Use in children has been reviewed.[1]

1. Barr RD. Imatinib mesylate in children and adolescents with cancer. *Pediatr Blood Cancer* 2010; **55:** 18–25.

Administration in hepatic impairment. Imatinib is metabolised in the liver. Licensed product information in the UK recommends that patients with mild, moderate, or severe liver impairment should be given the minimum recommended oral dose of 400 mg daily. In the USA, patients with mild and moderate impairment should be given the recommended daily dose, but in those with severe hepatic impairment, a 25% decrease in dose is recommended. In both countries, degrees of hepatic impairment are defined as:

- mild: total bilirubin equal to 1.5 times the upper limit of normal (ULN); aspartate aminotransferase (AST/SGOT) greater than ULN. AST/SGOT can be normal or less than ULN if the total bilirubin is greater than ULN
- moderate: total bilirubin > 1.5 and up to 3 times the ULN
- severe: total bilirubin > 3 to 10 times the ULN

US licensed product information also states that if, during treatment, elevations in bilirubin > 3 times the ULN or liver transaminases > 5 times the ULN occur, imatinib should be withheld until bilirubin levels have returned to less than 1.5 times the ULN and transaminase levels to less than 2.5 times the ULN. Treatment may then be continued at a reduced daily dose. In adults the dose is reduced from 800 mg to 600 mg, from 600 mg to 400 mg, and from 400 mg to 300 mg. In children, the dose should be reduced from 340 mg/m^2 daily to 260 mg/m^2 daily, or from 260 mg/m^2 daily to 200 mg/m^2 daily.

Administration in renal impairment. UK licensed product information for imatinib states that patients with mild or moderate renal impairment, defined as creatinine clearance (CC) of 20 to 59 mL/minute, may be given an initial oral dose of 400 mg daily. Patients with severe renal impairment (CC less than 20 mL/minute) or on dialysis can also be started at this dose, although caution is recommended; the dose can be adjusted as needed.

In the USA, patients with mild renal impairment (CC 40 to 59 mL/minute) should not be given a dose greater than 600 mg. Patients with moderate renal impairment (CC 20 to 39 mL/minute) should have their initial dose halved; the dose can then be adjusted as needed, although a maximum dose of 400 mg is recommended. Caution is advised in those with severe impairment; doses of 100 mg daily have been used.

Hypereosinophilic syndrome. Imatinib has been reported to produce clinical responses in patients with the hypereosinophilic syndrome (HES).[1-4] Some reports suggest that imatinib also has activity in mast-cell disease, even in the absence of associated eosinophilia.[5] However, not all patients with HES respond to imatinib.[4] Many patients with the myelodysplastic variant of HES express a novel kinase derived from an abnormal fusion of platelet-derived growth factor receptor-α gene with a neighbouring gene, FIP1L1. Almost all patients with this FIP1L1-platelet-derived growth factor receptor-α fusion kinase will respond to imatinib, but a subset of patients with HES without known imatinib targets have also been reported to respond to the drug.[6,7]

1. Gleich GJ, *et al*. Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 2002; **359:** 1577–8.
2. Cools J, *et al*. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348:** 1201–14.
3. Koury MJ, *et al*. Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003; **115:** 587–9.
4. Payne SM, Kovacs MJ. Imatinib mesylate treatment in two patients with idiopathic hypereosinophilic syndrome. *Ann Pharmacother* 2004; **38:** 1215–18.
5. Pardanani A, *et al*. Imatinib for systemic mast-cell disease. *Lancet* 2003; **362:** 535–7.
6. Müller AMS, *et al*. Imatinib mesylate as a novel treatment option for hypereosinophilic syndrome: two case reports and a comprehensive review of the literature. *Ann Hematol* 2006; **85:** 1–16.
7. Antoniu SA. Imatinib mesylate for the treatment of hypereosinophilic syndromes. *Curr Opin Investig Drugs* 2006; **7:** 980–4.

Malignant neoplasms. References.

1. Peggs K, Mackinnon S. Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. *N Engl J Med* 2003; **348:** 1048–50.
2. Deininger MW, *et al*. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003; **21:** 1637–47.
3. Deininger M, *et al*. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood* 2005; **105:** 2640–53.
4. Kantarjian HM, *et al*. New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. *Ann Intern Med* 2006; **145:** 913–23.
5. Moen MD, *et al*. Imatinib: a review of its use in chronic myeloid leukaemia. *Drugs* 2007; **67:** 299–320.
6. Siddiqui MAA, Scott LJ. Imatinib: a review of its use in the management of gastrointestinal stromal tumours. *Drugs* 2007; **67:** 805–20.
7. Cross SA, Lyseng-Williamson KA. Imatinib: in relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukaemia. *Drugs* 2007; **67:** 2645–54.
8. Jabbour E, *et al*. Suboptimal response to or failure of imatinib treatment for chronic myeloid leukemia: what is the optimal strategy? *Mayo Clin Proc* 2009; **84:** 161–9.
9. Wolf D, Rumpold H. A benefit-risk assessment of imatinib in chronic myeloid leukaemia and gastrointestinal stromal tumours. *Drug Safety* 2009; **32:** 1001–15.
10. Duffaud F, Le Cesne A. Imatinib in the treatment of solid tumours. *Target Oncol* 2009; **4:** 45–56.
11. Adenis A, *et al*. Imatinib in gastrointestinal stromal tumor: does treatment duration matter? *Oncology* 2009; **77:** 157–61.
12. Gronchi A, *et al*. The role of high-dose imatinib in the management of patients with gastrointestinal stromal tumor. *Cancer* 2010; **116:** 1847–58.
13. Osborn M, Hughes T. Managing imatinib resistance in chronic myeloid leukaemia. *Curr Opin Hematol* 2010; **17:** 97–103.
14. Sanford M, Scott LJ. Imatinib: as adjuvant therapy for gastrointestinal stromal tumour. *Drugs* 2010; **70:** 1963–72.

Pulmonary hypertension. Imatinib has produced beneficial responses in patients with pulmonary arterial hypertension (p. 1278.2) and may have a role, particularly in patients who fail to respond to other therapies.[1-4]

1. Ghofrani HA, *et al*. Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 1412–13.
2. Patterson KC, *et al*. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med* 2006; **145:** 152–3.
3. Souza R, *et al*. Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006; **61:** 736.
4. Chhina MK, *et al*. Evaluation of imatinib mesylate in the treatment of pulmonary arterial hypertension. *Future Cardiol* 2010; **6:** 19–35.

Adverse Effects and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of imatinib mesilate include gastrointestinal disturbances, myelosuppression, superficial oedema, myalgia, arthralgia, muscle cramps, rashes, fatigue, and headache. Myelosuppression usually manifests as neutropenia, thrombocytopenia, anaemia, or febrile neutropenia; haemolytic anaemia has occurred rarely. Other common adverse effects include dizziness, taste disturbances, anorexia, paraesthesia, insomnia, eye disorders or visual disturbances, epistaxis, cough, dyspnoea, dry skin, pruritus, alopecia, night sweats, pyrexia, weakness, and rigors. Hepatotoxicity may occur; fatal cases of hepatic necrosis have been reported. Aseptic necrosis of bone, mainly in the femoral head, has been reported rarely. There are reports of serious and severe skin disorders, including erythema multiforme, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, exfoliative dermatitis, and bullous eruptions. Rhabdomyolysis has also occurred. Haemorrhages are common; gastrointestinal bleeding, however, is more frequent in those patients treated for stromal tumours. Ulceration can occur; gastrointestinal perforation, fatal in some cases, has been reported rarely.

Severe fluid retention commonly occurs, and may result in pleural and pericardial effusion, pulmonary oedema, and ascites. Some fatalities have been reported, and treatment may need to be stopped if there is unexpected, rapid weight gain. Elderly patients and those with a history of cardiac disease may be at increased risk. Isolated cases of left ventricular dysfunction have been reported; patients with cardiac disease or risk factors for cardiac failure should be monitored. Other reported cardiac disorders include congestive heart failure, palpitations, tachycardia, arrhythmias, angina pectoris, and myocardial infarction. There are reports, including fatalities, of cerebral oedema, increased intracranial pressure and papilloedema. Hypothyroidism has been reported in patients on levothyroxine replacement therapy; TSH concentrations should be monitored in these patients.

Imatinib mesilate should be taken with food and a large glass of water to minimise gastrointestinal irritation. Complete blood counts and liver function should be monitored regularly.

Effects on the heart. Ten patients receiving imatinib developed severe congestive heart failure without obvious cause; all patients had normal left ventricular function before imatinib was started. Mitochondrial abnormalities were found after myocardial biopsy on 2 of the patients. These findings were confirmed by studies on *mice* and *in vitro*. The authors suggested that patients be closely followed for clinical manifestations of left ventricular dysfunction.[1]

Subsequent evaluation by the manufacturer (*Novartis*) established that the frequency of reported cardiac events was less than 1%. However, they recommended that patients with known cardiac disease or risk factors for cardiac failure be monitored accordingly, that those developing clinical manifestations suggestive of congestive cardiac failure be thoroughly evaluated and treated, and that elderly patients or those with underlying heart disease be evaluated for baseline left ventricular ejection fraction.[2]

1. Kerkelä R, *et al*. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006; **12:** 908–16.
2. Novartis, Canada. Health Canada endorsed important safety information on Gleevec (imatinib mesylate): recent safety information regarding reports of significant left ventricular ejection fraction reduction and congestive heart failure with GLEEVEC (imatinib mesylate) (issued 21st September, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/gleevec_2_hpc-cps-eng.php (accessed 01/08/08)

Effects on the kidneys. Imatinib has been associated with the development of acute renal failure, requiring haemodialysis.[1-3]

1. Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplant* 2002; **17:** 685–7.
2. Pou M, *et al*. Acute renal failure secondary to imatinib mesylate treatment in chronic myeloid leukemia. *Leuk Lymphoma* 2003; **44:** 1239–41.
3. Foringer JR, *et al*. Acute renal failure secondary to imatinib mesylate treatment in prostate cancer. *Ann Pharmacother* 2005; **39:** 2136–8.

Effects on the lungs. Interstitial pneumonitis has been reported with imatinib;[1-8] presenting symptoms included dry cough and dyspnoea. Doses of imatinib ranged from 100 mg to 600 mg daily. In most cases, the pneumonitis resolved after stopping imatinib and starting corticosteroid therapy. The mechanism was unclear, and may involve a hypersensitivity reaction. In an analysis of 27 cases of interstitial lung disease associated with imatinib therapy,[8] 30% of patients showed a hypersensitivity reaction radiological pattern. Pre-existing lung disease may be a risk factor.

1. Bergeron A, *et al*. Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol* 2002; **20:** 4271–2.
2. Rosado MF, *et al*. Imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol* 2003; **21:** 3171–3.
3. Ma CX, *et al*. Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003; **78:** 1578–9.
4. Yokoyama T, *et al*. Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia* 2004; **18:** 645–6.
5. Isshiki I, *et al*. Interstitial pneumonitis during imatinib therapy. *Br J Haematol* 2004; **125:** 420.
6. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; **79:** 80–1.
7. Lin J-T, *et al*. Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006; **47:** 1693–5.
8. Ohnishi K, *et al*. Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia* 2006; **20:** 1162–4.

Effects on reproductive potential. Oligospermia[1] and ovarian failure[2] have been reported after treatment with imatinib. Patients should be counselled before therapy about the risk of impaired fertility.

1. Seshadri T, *et al*. Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med* 2004; **351:** 2134–5.
2. Christopoulos C, *et al*. Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med* 2008; **358:** 1079–80.

Effects on the skin, hair, and nails. There are reports of acute generalised exanthematous pustulosis in patients given imatinib.[1,2] The authors noted that severe skin reactions had been reported in some other patients given the drug, and speculated that the effect might be dose-dependent and related to its pharmacological action. In subsequent reports[3-5] of cutaneous adverse effects, this dose-dependency has also been seen, with effects especially at doses of 600 mg daily and above. In a report of a livedoid pattern of rash in 3 patients taking imatinib, the authors noted that adverse skin reactions to imatinib tend to be strongly dose-dependent, are self-limiting, and do not usually affect the mucous membranes.[6] Epidermal necrolysis occurred in a patient who underwent stem cell transplantation after treatment with imatinib.[7] The authors suggested that prolonged inhibition of platelet-derived growth factor by imatinib may have impaired the repair of skin damage caused by the conditioning therapy. In a report of 19 patients with skin reactions, the authors suggested that the actions of imatinib on platelet-derived growth factor may have caused an increase in dermal interstitial fluid pressure, capable of inducing oedema and the subsequent erythema and desquamation that was seen. Rare reactions included psoriasis, hyaline cell syringoma, and malpighian epithelioma, all of which occurred after at least 1 year of therapy.[8] Follicular mucinosis[9] and panniculitis[10] have also been reported with use of imatinib, as has Stevens-Johnson syndrome.[11,12] Palmoplantar hyperkeratosis and nail dystrophy can occur,[13,14] as can lichenoid eruptions.[14] Repigmentation of grey hair has also been reported.[15]

Oral corticosteroids have been used to resolve most cases of skin eruptions.[8] In other instances, re-introduction of imatinib at low doses, gradually increased to full dosage, has been successfully tolerated.[8,12,16] In one patient, who developed exfoliative dermatitis with imatinib and had recurrent reactions despite decreased doses, a once-weekly dose of imatinib was associated with a less severe rash that eventually disappeared over a period of 4 months.[17]

1. Brouard M, Saurat J-H. Cutaneous reactions to STI571. *N Engl J Med* 2001; **345:** 618–19.
2. Schwarz M, *et al*. Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol* 2002; **69:** 254–6.
3. Valeyrie L, *et al*. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; **48:** 201–6.

4. Drummond A, *et al*. A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). *Br J Haematol* 2003; **120:** 911–13.
5. Ugurel S, *et al*. Dose-dependent severe cutaneous reactions to imatinib. *Br J Cancer* 2003; **88:** 1157–9.
6. Martínez-González MC, *et al*. Livedoid skin reaction probably due to imatinib therapy. *Ann Pharmacother* 2007; **41:** 148–52.
7. Schaich M, *et al*. Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2003; **82:** 303–4.
8. Breccia M, *et al*. Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol* 2005; **74:** 121–3.
9. Yanagi T, *et al*. Follicular mucinosis associated with imatinib (STI571). *Br J Dermatol* 2004; **151:** 1276–8.
10. Ugurel S, *et al*. Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. *Br J Dermatol* 2003; **149:** 678–9.
11. Hsiao L-T, *et al*. Stevens-Johnson syndrome after treatment with STI571: a case report. *Br J Haematol* 2002; **117:** 620–2.
12. Rule SAJ, *et al*. Managing cutaneous reactions to imatinib therapy. *Blood* 2002; **100:** 3434–5.
13. Deguchi N, *et al*. Imatinib mesylate causes palmoplantar hyperkeratosis and nail dystrophy in three patients with chronic myeloid leukaemia. *Br J Dermatol* 2006; **154:** 1216–18.
14. Kuraishi N, *et al*. Lichenoid drug eruption with palmoplantar hyperkeratosis due to imatinib mesylate: a case report and a review of the literature. *Acta Derm Venereol* 2010; **90:** 73–6.
15. Etienne G, *et al*. Imatinib mesylate and gray hair. *N Engl J Med* 2002; **347:** 446.
16. Park MA, *et al*. Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc* 2004; **25:** 345–7.
17. Tanvetyanon T, Nand S. Overcoming recurrent cutaneous reactions from imatinib using once-weekly dosing. *Ann Pharmacother* 2003; **37:** 1818–20.

Effects on the spleen. There are isolated reports of splenic rupture in patients receiving imatinib mesilate.[1]

1. Elliott MA, *et al*. Adverse events after imatinib mesylate therapy. *N Engl J Med* 2002; **346:** 712–13.

Gynaecomastia. Gynaecomastia was noted in 7 of 38 men assessed for hormone concentrations while enrolled in studies of imatinib; the authors attributed the disorder to reductions in testosterone concentrations due to imatinib.[1]

1. Gambacorti-Passerini C, *et al*. Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet* 2003; **361:** 1954–56.

Hypophosphataemia. Hypophosphataemia and associated changes in bone and mineral metabolism were reported in a study of patients receiving imatinib. Patients with normal serum-phosphate concentrations also had similar changes in bone turnover. Hypophosphataemia was apparently related to patient age and imatinib dose; it was also associated with decreased serum concentrations of calcium and vitamin D.[1] In a review of data, the manufacturers (*Novartis*) noted an incidence of 50% of patients in 2 studies; overall 1.5% had grade 4 hypophosphataemia. However, the reported incidence of hypophosphataemia as an adverse effect of imatinib was only 3%. They suggested that phosphate concentrations be monitored in patients taking imatinib until further elucidation of the effect of the drug on bone is available.[2] While some have questioned the association between treatment with imatinib and hypophosphataemia,[3] others have also reported hypophosphataemia during treatment with the drug.[4] The effect, however, appears to be reversible on stopping imatinib.

1. Berman E, *et al*. Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; **354:** 2006–13.
2. Owen S, *et al*. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
3. Tournis S, Lyritis GP. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
4. Joensuu H, Reichardt P. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 628. Correction. *ibid.*; 1627.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imatinib as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Pregnancy. Two of 3 pregnancies in 2 patients taking imatinib were successful; the infants were both small for weight, but healthy and without congenital abnormalities. In the third case, a first trimester miscarriage occurred. Both women continued imatinib throughout their pregnancies.[1]

In another report,[2] 10 women became pregnant while being treated with imatinib for chronic myeloid leukaemia. Imatinib therapy was stopped upon discovery of the pregnancy; exposure to imatinib ranged from 4 to 9 weeks. Two patients had a spontaneous abortion shortly after stopping imatinib, and another patient elected to have a therapeutic abortion. Seven other pregnancies went to term, resulting in 8 babies. One infant had hypospadias which was surgically corrected without complications; all other infants were healthy. The partners of 8 male patients also conceived while the men were receiving imatinib, one of them twice. All male patients continued therapy with imatinib. One spontaneous abortion occurred. Of the 8 babies born, 1 was found to have a mild rotation of the small intestine requiring surgery shortly after birth. The authors considered it possible that the brief exposure to imatinib may have slightly increased the risk of spontaneous abortion. While concluding that normal pregnancies are possible during imatinib therapy, the authors of both reports emphasised that possible teratogenic effects cannot be ruled out, and that patients should still be advised to use appropriate and effective contraception.

A similar warning was issued in a review of outcome data from 125 pregnancies involving exposure to imatinib. The authors noted that 63 pregnancies had resulted in the live birth of normal infants; a further 35 women terminated the pregnancy (in 3 cases because fetal abnormalities were found), and 18 ended in spontaneous abortion.[3] However, there were 9 infants with congenital abnormalities, several of which were strikingly similar, a fact that was considered to be of some concern.

1. AlKindi S, *et al*. Imatinib in pregnancy. *Eur J Haematol* 2005; **74:** 535–7.
2. Ault P, *et al*. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *J Clin Oncol* 2006; **24:** 1204–8.
3. Pye SM, *et al*. The effects of imatinib on pregnancy outcome. *Blood* 2008; **111:** 5505–8.

Syndrome of inappropriate ADH secretion. Hyponatraemia, leading to a syndrome of inappropriate ADH secretion (SIADH) has been reported after therapy with imatinib at a dose of 800 mg daily. Fluid restriction and dose reduction to 600 mg daily restored sodium concentrations to normal.[1]

1. Liapis K, *et al*. Syndrome of inappropriate secretion of antidiuretic hormone associated with imatinib. *Ann Pharmacother* 2008; **42:** 1882–6.

Tumour lysis syndrome. Tumour lysis syndrome has been reported with imatinib;[1,2] patients should be monitored closely. Allopurinol and adequate hydration have been suggested as prophylaxis in patients with a high tumour burden.[2]

1. Dann EJ, *et al*. Tumor lysis syndrome after STI571 in Philadelphia chromosome-positive acute lymphoblastic leukemia. *J Clin Oncol* 2002; **20:** 354–5.
2. Chang H, Shih L-Y. Imatinib-induced tumor lysis syndrome: report of a case and review of the literature. *Chang Gung Med J* 2008; **31:** 510–14.

Interactions

Imatinib mesilate is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals and macrolide antibacterials, may increase blood concentrations of imatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of imatinib; imatinib dosage may need to be increased in these patients (see Uses and Administration, p. 807.3).

In vitro studies have indicated that imatinib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6, and may increase blood concentrations of drugs that are substrates of these enzymes.

The dose of levothyroxine may need to be increased before imatinib is given to patients with hypothyroidism (see Antineoplastics under Interactions of Levothyroxine, p. 2341.3).

Antifungals. In a small study in healthy subjects, *ketoconazole* significantly increased imatinib exposure; mean maximum plasma concentration and area under the concentration-time curve increased, and clearance of imatinib decreased. The half-life of imatinib appeared relatively unchanged. To avoid overexposure, single subtherapeutic doses of imatinib had been used (200 mg); the authors noted that clinical significance might arise with use of imatinib in daily doses of 800 mg or more.[1]

1. Dutreix C, *et al*. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol* 2004; **54:** 290–4.

Calcium-channel blockers. For a report of a possible interaction between imatinib and *nifedipine*, see Antineoplastics under Interactions of Nifedipine, p. 1453.3.

St John's wort. Exposure to imatinib was significantly reduced when it was given after 2 weeks of treatment with St John's wort; area under the concentration-time curve was decreased, maximum plasma concentration and half-life of imatinib were reduced, and clearance increased.[1,2]

1. Frye RF, *et al*. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* 2004; **76:** 323–9.
2. Smith PF, *et al*. The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004; **24:** 1508–14.

Pharmacokinetics

Imatinib mesilate is well absorbed after oral doses and peak blood concentrations occur after 2 to 4 hours. The mean bioavailability is about 98%. Imatinib is reported to be about 95% bound to plasma proteins. Plasma elimination half-lives of imatinib and its major active metabolite, the *N*-demethylated piperazine derivative, are about 18 and 40 hours respectively. The major enzyme responsible for the metabolism of imatinib is cytochrome P450 isoenzyme CYP3A4; isoenzymes CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play a minor role. About 81% of a dose is eliminated within 7 days in the faeces (68%) and urine (13%). It is excreted mostly as metabolites, with only 25% as unchanged drug.

References.
1. Peng B, *et al*. Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol* 2004; **44:** 158–62.
2. Peng B, *et al*. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005; **44:** 879–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agacel; Glivec; Imatib; Mesinib; Tagonib; Timab; Ziatir; ***Austral.***: Glivec; ***Austria***: Glivec; ***Belg.***: Glivec; ***Braz.***: Glivec; ***Canad.***: Gleevec; ***Chile***: Glivec; ***China***: Glivec (格列卫); ***Cz.***: Glivec; ***Denm.***: Glivec; ***Fin.***: Glivec; ***Fr.***: Glivec; ***Ger.***: Glivec; ***Gr.***: Glivec; ***Hong Kong***: Glivec; ***Hung.***: Glivec; ***India***: Celonib; Glivec; Imalek; Imatib; Mesylonib; Mitinab; Zoleta†; ***Indon.***: Glivec; ***Irl.***: Glivec; ***Israel***: Glivec; ***Ital.***: Glivec; ***Jpn***: Glivec; ***Malaysia***: Glivec; ***Mex.***: Glivec; ***Neth.***: Glimatin; Glivec; Imakrebin; Tibaldix; ***Norw.***: Glivec; ***NZ***: Glivec; ***Philipp.***: Glivec; ***Pol.***: Glivec; ***Port.***: Glivec; ***Rus.***: Glivec (Гливек); ***S.Afr.***: Gleevec; ***Singapore***: Glivec; ***Spain***: Glivec; ***Swed.***: Glivec; ***Switz.***: Glivec; ***Thai.***: Glivec; ***Turk.***: Glivec; ***UK***: Glivec; ***Ukr.***: Glivec (Гливек); ***USA***: Gleevec; ***Venez.***: Glivec.

Imexon *(rINN)*

BM-06002; Imexón; Imexonum; Имексон.

(5*R*,5)-4-Amino-1,3-diazabicyclo[3.1.0]hex-3-en-2-one.

$C_4H_5N_3O$=111.1

CAS — 59643-91-3.

UNII — 8F63U28T2V.

NOTE. The name Amplimexon has been used as a trade mark for imexon.

Profile

Imexon is a cyanoaziridine compound that appears to act as an antineoplastic in several ways, one of which is by causing mitochondrial disruption in the cancer cell, thus inducing apoptosis. It is under investigation for the treatment of malignant neoplasms, including ovarian cancer, pancreatic adenocarcinoma, multiple myeloma, and metastatic malignant melanoma.

Ingenol Mebutate *(USAN, rINN)*

Ingenol Mebutato; Ingenoli Mebutas; 3-Ingenyl Angelate; Mébutate d'Ingénol; PEP-005; Ингенол Мебутат.

(1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-Dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1*H*-2,8a-methanocyclopenta[*a*]cyclopropa[*e*]cyclodecen-6-yl (2*Z*)-2-methylbut-2-enoate.

$C_{25}H_{34}O_6$=430.5

CAS — 75567-37-2.

ATC — D06BX02.

ATC Vet — QD06BX02.

UNII — 7686S50JAH.

Uses and Administration

Ingenol mebutate is a protein kinase C activator isolated from the plant *Euphorbia peplus*. It is used in the topical treatment of actinic keratosis (see Basal Cell and Squamous Cell Carcinoma, p. 714.2). A gel containing 0.015% is applied once daily for 3 consecutive days to affected areas on the face and scalp. For areas on the trunk and extremities, a 0.05% gel is applied once daily for 2 days. Patients should wash their hands immediately after applying the gel, and treated areas should not be touched or washed for 6 hours.

Ingenol mebutate is also under investigation in the treatment of non-melanoma skin cancer.

References.
1. Anderson L, *et al*. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. *J Am Acad Dermatol* 2009; **60:** 934–43.
2. Siller G, *et al*. PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. *Australas J Dermatol* 2009; **50:** 16–22.
3. Siller G, *et al*. PEP005 (ingenol mebutate) gel for the topical treatment of superficial basal cell carcinoma: results of a randomized phase IIa trial. *Australas J Dermatol* 2010; **51:** 99–105.

Adverse Effects and Precautions

The topical application of ingenol mebutate typically causes local skin reactions including erythema, flaking, crusting,

swelling, blistering, and ulceration. These effects usually occur within 1 day of starting treatment, peak up to 1 week after finishing treatment, and resolve within 2 weeks for affected areas on the face and scalp and within 4 weeks for areas on the trunk and extremities. Reactions can sometimes be severe. Ingenol mebutate should not be used until the skin is healed from any previous drug or surgical treatment.

Severe eye pain, eyelid oedema, eyelid ptosis, and periorbital oedema have occurred after inadvertent ocular exposure to ingenol mebutate gel. Patients should wash their hands well after handling the gel, and avoid transferring the drug to the eye during and after application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Picato; ***UK***: Picato; ***USA***: Picato.

Iniparib *(rINN)*

BSI-201; Iniparibum; Иниципариб.
4-Iodo-3-nitrobenzamide.
$C_7H_5IN_2O_3$=292.0
CAS — 160003-66-7.

Profile

Iniparib is a poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor that is under investigation for the treatment of several malignant neoplasms including brain, breast, ovarian, uterine, and non-small cell lung cancer. Initial studies have had mixed results.

References.

1. O'Shaughnessy J, *et al.* Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011; **364:** 205–14.
2. Liang H, Tan AR. Iniparib, a PARP1 inhibitor for the potential treatment of cancer, including triple-negative breast cancer. *IDrugs* 2010; **13:** 646–56.

Inotuzumab Ozogamicin *(USAN, rINN)*

CMC-544; Inotuzumab ozogamicina; Inotuzumab Ozogamicine; Inotuzumabum Ozogamicinum; WAY-207294; Инотузумаб Озогамицин.
Immunoglobulin G4, anti-(human CD22 (antigen)) (human-mouse monoclonal G544 heavy chain), disulfide with human-mouse monoclonal G544 κ-chain, dimer, conjugate with ozogamicin.
CAS — 635715-01-4.
UNII — P93RUU11P7.

Profile

Inotuzumab ozogamicin is a recombinant humanised monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. It is under investigation for the treatment of non-Hodgkin's lymphomas.

Interleukin-2

BG-8301 (teceleukin); Epidermal Thymocyte Activating Factor; ETAF; Factor de crecimiento de células T; IL-2; Interleucina 2; T-cell Growth Factor; TCGF; Интерлейкин-2.

Description. Interleukin-2 is a naturally-occurring 133-amino-acid glycoprotein with a molecular weight of about 15 000. It is available from natural sources or as a product of recombinant DNA technology (rIL-2).

In addition to aldesleukin (below) modified forms of interleukin-2 produced by recombinant DNA technology have included celmoleukin and teceleukin.

Aldesleukin *(BAN, USAN, rINN)*

Aldesleukiini; Aldesleukina; Aldesleukine; Aldesleukinum; Aldeslökin; Des-alanyl-1, Serine-125 Human Interleukin-2; Recombinant Interleukin-2; 125-L-Serine-2--133-interleukin 2 (human reduced); Альдеслейкин.
CAS — 110942-02-4.
ATC — L03AC01.
ATC Vet — QL03AC01.
UNII — M89N0Q7EQR.

Description. Aldesleukin (modified human recombinant interleukin-2) is produced by recombinant DNA technology using an *Escherichia coli* strain containing an analogue of the human interleukin-2 gene. It differs from native interleukin-2 in that it is not glycosylated, it has no N-terminal alanine, and it has serine substituted for cysteine at position 125.

Incompatibility. Aldesleukin 33 800 units/mL in glucose 5% lost significant biological activity when mixed with other drugs including ganciclovir sodium, lorazepam, pentamidine isetionate, prochlorperazine edisilate, and promethazine hydrochloride.[1] However, the incompatibility was not detectable by spectrophotometric methods and only lorazepam was visually incompatible, suggesting that these methods may be invalid for assessing the compatibility of proteins.

1. Alex S, *et al.* Compatibility and activity of aldesleukin (recombinant interleukin-2) in presence of selected drugs during simulated Y-site administration: evaluation of three methods. *Am J Health-Syst Pharm* 1995; **52:** 2423–6.

Stability. Aldesleukin lost 75 to 100% of activity when reconstituted with glucose 5% or sodium chloride 0.9% in a plastic syringe and given over 24 hours with a syringe driver.[1,2] Loss of activity was not seen if aldesleukin was reconstituted with water alone[2] or with the addition of albumin.[1,2] It was suggested that loss of activity could be suspected because of lack of toxicity,[1,2] and that the lack of toxicity in some published studies could be due to this.[1,3] However, the authors of these studies indicated that they had reconstituted aldesleukin with albumin.[4,5] Reconstitution with low concentrations of albumin has been advocated to avoid bioavailability problems,[1,4,6] but is not recommended for currently licensed preparations. Vials of aldesleukin are reconstituted with water for injection.

However, UK licensed product information allows for further dilution of reconstituted aldesleukin with up to 500 mL of glucose 5%, containing human albumin 0.1%, when infused over a 24-hour period; the albumin should be added and mixed with the glucose before addition of the reconstituted aldesleukin.

For short intravenous infusion, the US licensed product information indicates that dilution in glucose 5% outside of a specified range (below 30 micrograms/mL and above 70 micrograms/mL) results in increased variability in drug delivery.

Reconstitution or dilution of aldesleukin preparations with sodium chloride 0.9% is not recommended because increased aggregation occurs.

1. Miles DW, *et al.* Reconstitution of interleukin 2 with albumin for infusion. *Lancet* 1990; **335:** 1602–3.
2. Vlasveld LT, *et al.* Reconstitution of interleukin-2. *Lancet* 1990; **336:** 446.
3. Miles DW, *et al.* Toxicity and reconstitution of recombinant interleukin-2 with albumin. *Lancet* 1991; **338:** 1464.
4. Franks CR. Reconstitution of interleukin-2. *Lancet* 1990; **336:** 445–6.
5. Hamblin T. Reconstitution of interleukin-2 with albumin for infusion. *Lancet* 1990; **336:** 251.
6. Lamers CHJ, *et al.* Bioavailability of interleukin-2 after reconstitution with albumin. *Lancet* 1992; **340:** 241.

Units

100 units of human interleukin-2 are contained in one ampoule of the first International Standard Preparation (1987). The activity of interleukin-2 has also been expressed in Nutley and Cetus units: 100 international units is reportedly equivalent to about 83.3 Nutley units and to about 16.7 Cetus units. US licensed product information states that 18 million international units of aldesleukin are equivalent to 1.1 mg of protein.

Uses and Administration

Interleukin-2 is a lymphokine which stimulates the proliferation of T-lymphocytes and thus amplifies immune response to an antigen; it also has actions on B-lymphocytes, and induces the production of interferon-γ and the activation of lymphokine-activated killer (LAK) cells and natural killer (NK) cells. Interleukin-2 is used in the immunotherapy of metastatic renal cell carcinoma in selected patients (see p. 708.3). It is also used in metastatic melanoma (p. 714.3), and has been tried in non-Hodgkin's lymphoma and acute myeloid leukaemia (see also below).

Interleukin-2 is usually given by intravenous infusion or subcutaneous injection of one of its recombinant forms, such as aldesleukin.

Many dosage regimens have been tried. In the UK, the recommended dose of aldesleukin for metastatic renal cell carcinoma is 18 million units given subcutaneously once daily for 5 days, followed by 2 days rest for the first week. For the next 3 weeks, 18 million units are then given on days 1 and 2 of each week, and 9 million units on days 3 to 5 of each week, followed by 2 days rest. This 4-week cycle may be repeated after an interval of 1 week. Doses may be delayed or reduced if the regimen is not tolerated.

Intravenous infusion of aldesleukin is now rarely used because of an association with capillary leak syndrome (see Adverse Effects and Treatment, p. 811.2). If it is used, 18 million units/m^2 per 24 hours is given as a continuous intravenous infusion for 5 days, followed by 2 to 6 days of rest. Then another 5 days of infusion is given, followed by 3 weeks of rest. This constitutes one induction cycle; a second cycle may be given after the 3-week rest period of the first cycle. After either subcutaneous or intravenous use, up to 4 maintenance cycles may be given, at 4-week intervals, to patients who respond or whose disease stabilises. In the USA, aldesleukin is licensed for use by intravenous infusion for metastatic renal cell carcinoma or metastatic melanoma. The recommended dose is an infusion of 600 000 units/kg over 15 minutes, every 8 hours for up to 14 doses. This 5-day cycle is repeated after 9 days. Further courses may be given at intervals of at least 7 weeks in patients who respond. Doses should be withheld for toxicity.

Interleukin-2 given by inhalation is being investigated in the treatment of renal cell carcinoma.

Interleukin-2 has also been studied in adaptive immunotherapy with LAK cells or tumour-infiltrating lymphocytes (TIL), which are harvested from the patient, activated *ex vivo*, and then re-infused.

Interleukin-2 is also being tried in patients with HIV infection and AIDS in an attempt to restore immune response (see below) and has been given in some other infections or immune diseases.

Other interleukins are under investigation (see also Interleukin-1, p. 2533.3). Conjugates of interleukin-2 with macrogol (PEG-IL2; pegaldesleukin) have also been investigated and liposome-encapsulated interleukin-2 has also been investigated for the treatment of renal, brain and CNS tumours.

A mixture of naturally occurring cytokines, including interleukins, interferons, chemokines, and colony-stimulating factors (Multikine) is under investigation for neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck.

Reviews.

1. Noble S, Goa K. Aldesleukin (recombinant interleukin-2): a review of its pharmacological properties, clinical efficacy and tolerability in patients with metastatic melanoma. *BioDrugs* 1997; **7:** 394–422.
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4. Atkins MB, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part I: IL-2-based clinical trials. *Med Oncol* 2001; **18:** 197–207.
5. Gaffen SL, Liu KD. Overview of interleukin-2 function, production and clinical applications. *Cytokine* 2004; **28:** 109–23.
6. Eklund JW, Kuzel TM. A review of recent findings involving interleukin-2-based cancer therapy. *Curr Opin Oncol* 2004; **16:** 542–6.
7. Eklund JW, Kuzel TM. Interleukin-2 in the treatment of renal cell carcinoma and malignant melanoma. *Cancer Treat Res* 2005; **126:** 263–87.
8. Porta C. Maintenance biotherapy with interleukin-2 and interferon for metastatic renal cell cancer. *Expert Rev Anticancer Ther* 2006; **6:** 141–52.
9. McDermott DF. Update on the application of interleukin-2 in the treatment of renal cell carcinoma. *Clin Cancer Res* 2007; **13:** 716s–720s.
10. Petrella T, *et al.* Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. *Cancer Treat Rev* 2007; **33:** 484–96.

Administration. A review[1] of the administration of interleukin-2.

1. Shaker MA, Younes HM. Interleukin-2: evaluation of routes of administration and current delivery systems in cancer therapy. *J Pharm Sci* 2009; **98:** 2268–98.

Acute myeloid leukaemia. Interleukin-2 is given with histamine hydrochloride (p. 2525.2) to patients with acute myeloid leukaemia in first remission after consolidation therapy.[1,2] The role of histamine hydrochloride is to protect lymphocytes, especially NK and T cells, which are responsible for immune-mediated destruction of residual leukaemic cells.

Interleukin-2 is given by subcutaneous injection in a dose of 16 400 units/kg twice daily with a minimum of 6 hours between each dose. These doses of interleukin-2 are followed after 1 to 3 minutes by histamine hydrochloride in a dose of 500 micrograms by subcutaneous injection over 5 to 15 minutes (injection rate not to exceed 100 micrograms/min). The maximum injection time of 15 minutes for histamine hydrochloride may be necessary to reduce severe histamine-induced adverse effects (see p. 2525.3). Patients should rest for 20 minutes after the histamine dose. Histamine hydrochloride should not be injected at the same time as interleukin-2 nor into the same anatomical region. The regimen is given over a treatment cycle of 3 weeks and repeated for a total of 10 treatment cycles; the first 3 cycles are followed by a treatment-free interval of 3 weeks, increased to 6 weeks after subsequent cycles. Doses of either drug may be modified if adverse effects are severe.

1. Thorén FB, *et al.* Histamine dihydrochloride and low-dose interleukin-2 as post-consolidation immunotherapy in acute myeloid leukemia. *Expert Opin Biol Ther* 2009; **9:** 1217–23.
2. Romero AI, *et al.* Post-consolidation immunotherapy with histamine dihydrochloride and interleukin-2 in AML. *Scand J Immunol* 2009; **70:** 194–205.

HIV infection and AIDS. The immunodeficiency of HIV infection and AIDS (p. 957.2) has been associated with a defect in interleukin-2 production. Interleukin-2 stimulates the proliferation of lymphocytes and activates natural killer cells and studies have therefore examined the potential benefits of adding interleukin-2 to the treatment of patients with HIV infection.[1,2] After earlier pilot studies,

trials of antiretroviral therapy plus interleukin-2 have shown it to produce a much greater increase in CD4 cell counts than antiretroviral therapy alone,[3-7] even where therapy included HAART. However, it is not clear that this results in any additional clinical benefit. A pooled analysis[8] of earlier results showed a non-significant trend towards improved clinical outcome but the ESPRIT and SILCAAT studies[9] could not show any clinical benefit in terms of survival or risk of opportunistic disease from adding subcutaneous interleukin-2 to antiretroviral regimens, despite sustained increases in CD4 cell counts over a median of 7 years or more.

Although teceleukin has been tried[3] most studies of interleukin-2 therapy in HIV have used aldesleukin. Doses and routes have varied: in general doses seem to have ranged from 6 to 18 million units daily by intravenous infusion, or 3 to 30 million units daily subcutaneously, given in most cases for a 5-day cycle every 8 weeks. Subcutaneous dosage appears to be as effective as intravenous,[4,10] is more convenient,[4] and may be less toxic.[11] There is evidence that 5-day dose cycles of 3, 4.5 or 7.5 million units twice daily by subcutaneous injection are effective,[5,6,10,12-14] whereas cycles with a lower dose of 1.5 million units twice daily are not.[5,12,14] A meta-analysis[15] of 3 studies found that subcutaneous doses of 7.5 million units twice daily for 5 days every 8 weeks resulted in greater increases in CD4 cell counts after 3 cycles of therapy than doses of 4.5 million units or 1.5 million units. However, others have reported benefit from a dose as low as 3 million units daily when used with HAART in patients with advanced disease.[16] Continuous low-dose daily therapy appears to accelerate the normalisation of T-cell and natural killer cell concentrations over the course of several months.[11]

Adverse effects are common, particularly at higher doses and with intravenous infusion rather than subcutaneous use.[7,11] However, concerns about a potential stimulant effect on viral replication with a consequent increase in viral load do not seem to have been borne out.[4-7,10] Some studies have reported reduced viral loads in interleukin-treated patients,[6,17] including decreases in hepatitis C viral load in those HIV patients co-infected with hepatitis C.[10,18]

The macrogol conjugate of interleukin-2, PEG-IL2, has also been investigated in this context, but results have been disappointing, since it appears markedly less effective than aldesleukin in stimulating CD4 counts.[4,19]

1. Pau AK, Tavel JA. Therapeutic use of interleukin-2 in HIV-infected patients. *Curr Opin Pharmacol* 2002; **2:** 433–9.
2. Temesgen Z. Interleukin-2 for the treatment of human immunodeficiency virus infection. *Drugs Today* 2006; **42:** 791–801.
3. Bartlett JA, *et al.* Coadministration of zidovudine and interleukin-2 increases absolute CD4 cells in subjects with Walter Reed stage 2 human immunodeficiency virus infection: results of ACTG protocol 042. *J Infect Dis* 1998; **178:** 1170–3.
4. Levy Y, *et al.* Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: a randomised controlled trial. *Lancet* 1999; **353:** 1923–9.
5. Losso MH, *et al.* A randomized, controlled, phase II trial comparing escalating doses of subcutaneous interleukin-2 plus antiretrovirals versus antiretrovirals alone in human immunodeficiency virus-infected patients with CD4+ cell counts ≥350/mm³. *J Infect Dis* 2000; **181:** 1614–21. Correction. *ibid.*; 2122.
6. Davey RT, *et al.* Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: a randomized controlled trial. *JAMA* 2000; **284:** 183–9.
7. Piscitelli SC, *et al.* A risk-benefit assessment of interleukin-2 as an adjunct to antiviral therapy in HIV infection. *Drug Safety* 2000; **22:** 19–31.
8. Emery S, *et al.* Pooled analysis of 3 randomized, controlled trials of interleukin-2 therapy in adult human immunodeficiency virus type 1 disease. *J Infect Dis* 2000; **182:** 428–34.
9. Abrams D, *et al.* INSIGHT-ESPRIT Study Group. SILCAAT Scientific Committee. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med* 2009; **361:** 1548–59.
10. Tambussi G, *et al.* Efficacy of low-dose intermittent subcutaneous interleukin (IL)–2 in antiviral drug–experienced human immunodeficiency virus–infected persons with detectable virus load: a controlled study of 3 IL-2 regimens with antiviral drug therapy. *J Infect Dis* 2001; **183:** 1476–84.
11. Smith KA. Low-dose daily interleukin-2 immunotherapy: accelerating immune restoration and expanding HIV-specific T-cell immunity without toxicity. *AIDS* 2001; **15** (suppl 2): S28–S35.
12. Davey RT, *et al.* A randomized trial of high-versus low-dose subcutaneous interleukin-2 outpatient therapy for early human immunodeficiency virus type 1 infection. *J Infect Dis* 1999; **179:** 849–58.
13. David D, *et al.* Rapid effect of interleukin-2 therapy in human immunodeficiency virus–infected patients whose CD4 cell counts increase only slightly in response to combined antiretroviral treatment. *J Infect Dis* 2001; **183:** 730–5.
14. Ruxrungtham K, *et al.* A randomized, controlled 24-week study of intermittent subcutaneous interleukin-2 in HIV-1 infected patients in Thailand. *AIDS* 2000; **14:** 2509–13.
15. Arduino RC, *et al.* CD4 cell response to 3 doses of subcutaneous interleukin 2: meta-analysis of 3 Vanguard studies. *Clin Infect Dis* 2004; **39:** 115–22.
16. Arnó A, *et al.* Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with ≤250/microlitre CD4 T cells and undetectable plasma virus load. *J Infect Dis* 1999; **180:** 56–60.
17. Lafeuillade A, *et al.* Pilot study of a combination of highly active antiretroviral therapy and cytokines to induce HIV-1 remission. *J Acquir Immune Defic Syndr* 2001; **26:** 44–55.
18. Schlaak JF, *et al.* Sustained suppression of HCV replication and inflammatory activity after interleukin-2 therapy in patients with HIV/hepatitis C virus coinfection. *J Acquir Immune Defic Syndr* 2002; **29:** 145–8.
19. Carr A, *et al.* Outpatient continuous intravenous interleukin-2 or subcutaneous, polyethylene glycol-modified interleukin-2 in human immunodeficiency virus-infected patients: a randomized, controlled, multicenter study. *J Infect Dis* 1998; **178:** 992–9.

Postherpetic neuralgia. A 46-year-old HIV patient with chronic, treatment-resistant postherpetic neuralgia (p. 10.3) received 1 cycle of subcutaneous interleukin-2 (7.5 million units twice daily for 5 consecutive days) within the context of a clinical HIV study. He reported immediate resolution of his postherpetic neuralgia, and no recurrence of pain occurred during 3 years of follow-up.[1]

1. Rotty J, *et al.* Interleukin-2: a potential treatment option for postherpetic neuralgia? *Clin Infect Dis* 2006; **43:** e109–e110.

Adverse Effects and Treatment

Toxicity is related to dose and route and is often severe; fatalities have been recorded. Decreased vascular resistance and increased capillary permeability (the 'capillary leak syndrome') is common in patients given aldesleukin, and results in hypotension, reduced organ perfusion, and oedema. The incidence and severity of this syndrome is lower after subcutaneous than intravenous dosage. Fluid replacement may be necessary to treat the resultant hypovolaemia and dopamine or other pressor agents may be needed to help maintain organ perfusion. Capillary leak syndrome may also be associated with cardiac effects including tachycardia, angina, myocardial infarction; respiratory effects such as dyspnoea, pulmonary oedema, and respiratory failure; renal abnormalities including uraemia and oliguria or anuria; mental status changes including irritability, depression, confusion, and drowsiness. Therapy should be stopped if patients develop severe lethargy or somnolence, as continuing may result in coma. Raised liver enzymes, gastrointestinal disturbances, fever and flu-like symptoms (malaise, rigors, chills, arthralgia, and myalgia), rashes, pruritus, anaemia, leucopenia, and thrombocytopenia, are also relatively common. Paracetamol (but not NSAIDs, see Effects on the Kidneys, below) may be used prophylactically for fever. Pethidine may be used to control rigors. Antiemetics and antidiarrhoeals may also be required. Antihistamines may benefit some patients with pruritic rash. Injection site reactions are common after subcutaneous doses; necrosis has occurred. Aldesleukin therapy is associated with impaired neutrophil function, and an increased risk of bacterial infections (see below), including sepsis and bacterial endocarditis; this has been reported mainly after intravenous use, and antibacterial prophylaxis may be necessary.

References.

1. Sundin DJ, Wolin MJ. Toxicity management in patients receiving low-dose aldesleukin therapy. *Ann Pharmacother* 1998; **32:** 1344–52.
2. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother* 2001; **24:** 287–93.
3. Dutcher J, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part II: management of IL-2 toxicity and studies with other cytokines. *Med Oncol* 2001; **18:** 209–19.
4. Schwartz RN, *et al.* Managing toxicities of high-dose interleukin-2. *Oncology (Huntingt)* 2002; **16** (suppl 13): 11–20.

Bacterial infections. The incidence of sepsis and bacteraemia is increased in patients receiving interleukin-2 via intravenous catheters,[1,2] and possibly subcutaneously,[3] although others have not found this to be the case.[4,5] The increased incidence of nonopportunistic bacterial infection may be a particular problem in patients with AIDS who are treated with interleukin-2.[6] The mechanism is uncertain, but may be related to impairment of neutrophil function by the cytokine.[7]

1. Snydman DR, *et al.* Nosocomial sepsis associated with interleukin-2. *Ann Intern Med* 1990; **112:** 102–7.
2. Shiloni E, *et al.* Interleukin-2 therapy, central venous catheters, and nosocomial sepsis. *Ann Intern Med* 1990; **112:** 882–3.
3. Jones AL, *et al.* Infectious complications of subcutaneous interleukin-2 and interferon-alpha. *Lancet* 1992; **339:** 181–2.
4. Buter J, *et al.* Infection after subcutaneous interleukin-2. *Lancet* 1992; **339:** 552.
5. Schomburg AG, *et al.* Cytokines and infection in cancer patients. *Lancet* 1992; **339:** 1061.
6. Murphy PM, *et al.* Marked disparity in incidence of bacterial infections in patients with the acquired immunodeficiency syndrome receiving interleukin-2 or interferon-γ. *Ann Intern Med* 1988; **108:** 36–41.
7. Klempner MS, *et al.* An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. *N Engl J Med* 1990; **322:** 959–65.

Effects on the cardiovascular system. Interleukin-2 treatment can cause cardiotoxicity such as arrhythmias and acute myocardial infarction. High-dose therapy (600 000 units/kg intravenously every 8 hours) has been associated with myocarditis, which appears to be reversible; haemodynamic instability that can lead to an acute coronary syndrome has also been described. Careful screening of patients for cardiopulmonary disease is recommended.[1]

1. Eisner RM, *et al.* Case report and brief review: IL-2-induced myocarditis. *Cancer Invest* 2004; **22:** 401–4.

Effects on endocrine function. It has been suggested that patients with adrenal metastases may be particularly susceptible to adrenal haemorrhage and consequent failure during interleukin therapy.[1] Results also suggested that lack of endogenous steroid production may increase the risk of early severe interleukin-2 toxicity.[1]

Effects on thyroid function have also been reported, with the development of hypothyroidism[2-4] and goitre.[3]

1. VanderMolen LA, *et al.* Adrenal insufficiency and interleukin-2 therapy. *Ann Intern Med* 1989; **111:** 185.
2. Atkins MB, *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; **318:** 1557–63.
3. van Liessum PA, *et al.* Hypothyroidism and goitre during interleukin-2 therapy without LAK cells. *Lancet* 1989; **i:** 224.
4. Sauter NP, *et al.* Transient thyrotoxicosis and persistent hypothyroidism due to acute-autoimmune thyroiditis after interleukin-2 and interferon-α therapy for metastatic carcinoma: a case report. *Am J Med* 1992; **92:** 441–4.

Effects on the kidneys. Intravenous aldesleukin therapy was associated with varying degrees of acute renal dysfunction in almost all of 99 adult patients.[1] The clinical syndrome of hypotension, oliguria, fluid retention, and associated azotaemia with intense tubular avidity for filtered sodium all support prerenal acute renal failure as the cause of renal dysfunction. However, renal function values returned to baseline levels within 7 days in 62% of patients and in 95% by 30 days. Patients with elevated pretreatment serum-creatinine values, particularly those aged over 60 years, and those who had previously undergone a nephrectomy, were at risk of more severe and prolonged changes in renal function, and might be particularly vulnerable to the use of indometacin for associated fever and chills, which could potentiate renal impairment through its effects on intrarenal prostaglandin production. Similar effects were noted in a study[2] of 15 children given continuous infusion of aldesleukin. A further study[3] of the renal haemodynamic effects of aldesleukin infusion found it to have a specific renal vasoconstrictor effect; changes in renal prostaglandin synthesis contributed to the decreased renal blood flow.

1. Belldegrun A, *et al.* Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. *Ann Intern Med* 1987; **106:** 817–22.
2. Cochat P, *et al.* Renal effects of continuous infusion of recombinant interleukin-2 in children. *Pediatr Nephrol* 1991; **5:** 33–7.
3. Geertsen PF, *et al.* Renal haemodynamics, sodium and water reabsorption during continuous intravenous infusion of recombinant interleukin-2. *Clin Sci* 1998; **95:** 73–81.

Effects on the skin. Pseudosystemic sclerosis has been reported after use of aldesleukin; a reduction in skin thickening was seen after aldesleukin therapy was stopped and corticosteroids started.[1]

1. Marie I, *et al.* Pseudosystemic sclerosis as a complication of recombinant human interleukin 2 (aldesleukin) therapy. *Br J Dermatol* 2007; **156:** 182–3.

Precautions

Aldesleukin should be given with great care, if at all, to patients with pre-existing cardiac or pulmonary disease, and those with severe renal or hepatic impairment. It should be avoided in patients with CNS metastases or seizure disorders.

Risk factors for toxicity and poor response include restricted physical activity (Eastern Cooperative Oncology Group performance status of 1 or greater), 2 or more metastatic sites, and a period of less than 24 months between diagnosis of primary tumour and consideration for aldesleukin therapy. UK licensed product information states that aldesleukin should not be used to treat metastatic renal cell carcinoma in patients with all three of these risk factors.

Aldesleukin may worsen auto-immune diseases, and should be used with caution in patients with these conditions. Bacterial infections should be adequately treated before beginning therapy. Aldesleukin may increase effusions from serosal surfaces, and these should generally be treated before starting aldesleukin therapy.

Vital signs, blood counts, renal and hepatic function, serum electrolytes, and pulmonary and cardiac function should be monitored before starting treatment and then regularly during therapy.

Activity. For mention of the loss of activity when aldesleukin was given by continuous infusion without albumin, see Stability p. 810.2.

Inflammatory bowel disease. Two patients with a history of Crohn's disease had a recurrence of the condition when given aldesleukin. It was suggested that interleukin-2 should be contra-indicated in such patients.[1]

1. Sparano JA, *et al.* Symptomatic exacerbation of Crohn disease after treatment with high-dose interleukin-2. *Ann Intern Med* 1993; **118:** 617–18.

Psoriasis. Exacerbations of psoriasis developed in 3 patients during therapy with aldesleukin alone or with lymphokine-activated killer cells. The psoriatic symptoms remitted with topical therapy.[1]

1. Lee RE, *et al.* Interleukin 2 and psoriasis. *Arch Dermatol* 1988; **124:** 1811–15.

Interactions

Corticosteroids (which reduce some of the adverse effects of interleukin-2) may also reduce its antineoplastic properties: use together should generally be avoided. The use of iodinated contrast media after aldesleukin therapy may result in symptoms resembling the immediate adverse effects of aldesleukin. Although most events were reported to occur within 2 to 4 weeks of the last dose of aldesleukin, some occurred several months afterward.

Antivirals. For the effect of interleukin-2 on plasma concentrations of *indinavir*, see p. 987.3.

NSAIDs. NSAIDs are effective in preventing or reducing fever and myalgia caused by interleukin-2. However, there is concern that they could exacerbate renal toxicity (see also Effects on the Kidneys, p. 811.3). Use of *indometacin* in patients receiving interleukin-2 led to more severe weight gain, oliguria, and azotaemia in 1 study.[1] However, *ibuprofen* was used successfully to reduce interleukin-2 toxicity in another study.[2]

1. Sosman JA, *et al.* Repetitive weekly cycles of interleukin-2 II: clinical and immunologic effects of dose, schedule, and addition of indomethacin. *J Natl Cancer Inst* 1988; **80:** 1451–61.
2. Eberlein TJ, *et al.* Ibuprofen causes reduced toxic effects of interleukin 2 administration in patients with metastatic cancer. *Arch Surg* 1989; **124:** 542–7.

Pharmacokinetics

After intravenous bolus, the serum distribution and elimination half-lives of aldesleukin are 13 and 85 minutes, respectively. After subcutaneous doses, the absorption half-life is 45 minutes and the elimination half-life is 5.3 hours, while bioavailability ranges between 35 and 47%.

Aldesleukin is metabolised to amino acids by the kidneys.

References.
1. Anderson PM, Sorenson MA. Effects of route and formulation on clinical pharmacokinetics of interleukin-2. *Clin Pharmacokinet* 1994; **27:** 19–31.
2. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous interleukin-2 in HIV-infected patients. *Pharmacotherapy* 1996; **16:** 754–9.
3. Kirchner GI, *et al.* Pharmacokinetics of recombinant human interleukin-2 in advanced renal cell carcinoma patients following subcutaneous application. *Br J Clin Pharmacol* 1998; **46:** 5–10.
4. Kamikawa S, *et al.* Pharmacokinetic study of interleukin-2 following intravenous injection in hemodialysis patients with renal cell carcinoma. *Ther Apher Dial* 2008; **12:** 67–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ilcass; Ilgen; Proleukin†; ***Austria***: Proleukin; ***Belg.***: Proleukin; ***Braz.***: Proleukin; ***Canad.***: Proleukin; ***China***: An Jie Suo (安捷素); Bai Jie Yi (百杰依); De Lu Sheng (德路生); Inleusin (英路因); Jin Lu Kang (金路康 ???); Ju He Li (巨和粒); Luo Jin (洛金); Ou Nai Te (欧耐特); Quan Qi (泉奇); Sai Di En (赛迪恩); Te Er Kang (特尔康); Xin De Lu Sheng (新德路生); Xin Ji Er (欣吉尔); Xin Luo Er (辛洛尔); Yin Te Kang (因特康); Ying Te Kang Xin (英特康欣); Yuan Ce Xin (远策欣); Yue Kang Xian (悦康仙); ***Cz.***: Proleukin; ***Denm.***: Proleukin; ***Fin.***: Proleukin; ***Fr.***: Proleukin; ***Ger.***: Proleukin; ***Gr.***: Proleukin; ***Hong Kong***: Proleukin†; ***Hung.***: Proleukin; ***Irl.***: Proleukin; ***Israel***: Proleukin; ***Ital.***: Proleukin; ***Jpn***: Celeuk; Imunace; ***Mex.***: Proleukin; ***Neth.***: Proleukin; ***NZ***: Proleukin; ***Pol.***: Proleukin†; ***Port.***: Proleukin; ***Rus.***: Proleukin (Пролейкин); Roncoleukin (Ронколейкин); ***S.Afr.***: Chiron IL-2; ***Singapore***: Proleukin; ***Spain***: Proleukin; ***Switz.***: Proleukin; ***Turk.***: Proleukin; ***UK***: Proleukin; ***Ukr.***: Bioleukin (Биолейкин); ***USA***: Proleukin.

Ipilimumab *(USAN, rINN)*

BMS-734016; Ipilimumabum; MDX-010; MDX-CTLA-4; Ипилимумаб.

Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer.

CAS — 477202-00-9.

UNII — 6T8C155666.

Uses and Administration

Ipilimumab is a recombinant, human monoclonal antibody to the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), which is a cell surface receptor involved in the downregulation of T-cell activation. Ipilimumab is used for the treatment of unresectable or metastatic melanoma (p. 714.3). The recommended intravenous dose is 3 mg/kg every 3 weeks, to a total of 4 doses; the dose is diluted in sodium chloride 0.9% or glucose 5% to a final concentration ranging from 1 to 2 mg/mL, and the infusion given over 90 minutes, via a low-protein-binding in-line filter.

Ipilimumab may be withheld or permanently stopped if immune-mediated reactions occur, see Adverse Effects, Treatment, and Precautions, below.

Ipilimumab is also under investigation for the treatment of prostate cancer and various other solid tumours.

References.
1. Weber J, *et al.* A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res* 2009; **15:** 5591–8.
2. Wolchok JD, *et al.* Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol* 2010; **11:** 155–64.
3. Ku GY, *et al.* Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. *Cancer* 2010; **116:** 1767–75.
4. Hodi FS, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363:** 711–23. Correction. *ibid.*; 1290.
5. Robert C, *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364:** 2517–26.
6. Cameron F, *et al.* Ipilimumab: first global approval. *Drugs* 2011; **71:** 1093–1104.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of ipilimumab are fatigue, diarrhoea, pruritus, rash, and colitis. Severe, life-threatening, or fatal immune-mediated reactions, involving any organ, can occur. Enterocolitis (including intestinal perforation), hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy (including hypopituitarism and adrenal insufficiency) have been reported most commonly. Rare effects considered to be immune-mediated include pneumonitis, meningitis, nephritis, eosinophilia, and pericarditis. Myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, erythema multiforme, psoriasis, pancreatitis, arthritis, and auto-immune thyroiditis have also been reported.

Ipilimumab should be stopped permanently if any severe immune-mediated reactions occur, and the patient treated with high-dose systemic corticosteroids. Ipilimumab therapy should be withheld in those with moderate reactions; the patient may require corticosteroids and symptomatic treatment. Therapy may be resumed after complete or partial resolution of the reaction in patients who are taking prednisone at less than 7.5 mg daily (or equivalent); ipilimumab is restarted at the recommended dose, until all 4 doses are given, or until 16 weeks have elapsed from the first dose, whichever occurs earlier. If moderate disease persists, or the corticosteroid dose cannot be reduced to prednisone 7.5 mg daily (or equivalent), ipilimumab should be stopped permanently. Corticosteroid eye drops can be used to treat patients who develop uveitis, iritis, or episcleritis; ipilimumab should be stopped permanently if immune-mediated ocular disease occurs that is unresponsive to local immunosuppressive therapy. Patients should be monitored for any signs and symptoms of immune-mediated reactions. Liver function tests and thyroid function tests should be assessed at baseline and before each dose.

References.
1. Beck KE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24:** 2283–9.
2. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; **12:** 864–72.
3. Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. *Cancer Immunol Immunother* 2009; **58:** 823–30.

Pharmacokinetics

Ipilimumab steady-state concentrations occur by the third dose. Clearance was found to increase with increasing bodyweight. The mean terminal half-life is 14.7 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Yervoy; ***Belg.***: Yervoy; ***Canad.***: Yervoy; ***Denm.***: Yervoy; ***Fr.***: Yervoy; ***Ger.***: Yervoy; ***Irl.***: Yervoy; ***Israel***: Yervoy; ***Neth.***: Yervoy; ***Norw.***: Yervoy; ***Spain***: Yervoy; ***Swed.***: Yervoy; ***Switz.***: Yervoy; ***UK***: Yervoy; ***USA***: Yervoy.

Irinotecan Hydrochloride

(BANM, USAN, rINNM)

Camptothecin 11 (irinotecan); CPT-11 (irinotecan); DQ-2805; Hidrocloruro de irinotecán; Irinotécan, Chlorhydrate d'; Irinotecán, hidrocloruro de; Irinotecani Hydrochloridum; Irinotekaanihydrokloridi; Irinotekan Hidroklorür; Irinotekan-hydroklorid; U-101440E; Иринотекана Гидрохлорид.

(+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate hydrochloride trihydrate; (*S*)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6′,7′]indolizino[1,2-*b*]quinolin-9-yl [1,4′-dipiperidine]-1′-carboxylate hydrochloride trihydrate.

$C_{33}H_{38}N_4O_6,HCl,3H_2O$=677.2

CAS — 97682-44-5 (irinotecan); 136572-09-3 (irinotecan hydrochloride trihydrate).

ATC — L01XX19.

ATC Vet — QL01XX19.

UNII — 042LAQ11I5.

Pharmacopoeias. In *US*.

USP 36: (Irinotecan Hydrochloride). Pale yellow to yellow, crystalline powder. Sparingly soluble in water and in organic solvents. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Irinotecan is a semisynthetic derivative of the alkaloid camptothecin, obtained from the shrub *Camptotheca acuminata*. The camptothecin derivatives are inhibitors of the enzyme topoisomerase I and thus interfere with the coiling and uncoiling of DNA during replication and prevent nucleic acid synthesis. This action is specific for S phase.

Irinotecan is used in the treatment of advanced colorectal cancer (p. 706.3). It may be used with fluorouracil and folinic acid (with or without bevacizumab), or with capecitabine (with or without bevacizumab), as first-line therapy, and is also given as monotherapy in patients whose disease has recurred or progressed after initial fluorouracil-based therapy. It is further indicated for use with cetuximab (p. 762.3) in the treatment of EGFR-expressing, *KRAS* wild type, metastatic colorectal cancer, either first-line or after the failure of other regimens containing irinotecan. It has been tried in the management of other solid tumours including those of the lung (p. 710.2).

It is given as the hydrochloride, by intravenous infusion, in at least 250 mL of glucose 5%, or sodium chloride 0.9%. In the treatment of refractory colorectal malignancies one suggested single-agent dose regimen is irinotecan hydrochloride 125 mg/m² infused over 90 minutes once a week for 4 weeks, followed by a 2-week rest period. Additional courses may be given if required, with doses modified according to toxicity. Another regimen requires an initial dose of 350 mg/m² over 30 to 90 minutes repeated every 3 weeks and adjusted according to toxicity (for dosage in hepatic impairment, see p. 813.1).

For the suggestion that initial doses should be modified to reduce toxicity in those with certain genotypes, see Genetic Factors, p. 813.3.

Irinotecan may also be given as part of a regimen with fluorouracil and folinic acid in the first-line treatment of metastatic colorectal cancer. Many regimens exist. The irinotecan hydrochloride component of the course may be given at a dose of 180 mg/m² over 30 to 90 minutes every 2 weeks. Alternatively, 125 mg/m² may be given weekly, usually on days 1, 8, 15, and 22 of a 42-day cycle. (For reference to toxicity from such regimens see under Interactions, p. 814.1.)

Treatment cycles may be continued indefinitely as long as patients continue to benefit.

In the treatment of EGFR-expressing metastatic colorectal cancer, in patients who have failed previous treatment, irinotecan is given usually at the same dose as was used in the last cycles of the previous irinotecan-containing regimen; irinotecan should not be given for at least 1 hour after the end of the cetuximab infusion. When used first-line with cetuximab, the dose of irinotecan will depend on the specific regimen used.

A formulation of irinotecan with hyaluronic acid is being developed for colorectal cancer. A stable nanoliposomal formulation, MM-398, is under investigation for the treatment of pancreatic cancer. Also under investigation is a pegylated formulation of irinotecan (NKTR-102) for various malignancies including ovarian cancer, and irinotecan-eluting beads, for injection directly into the brain in the treatment of glioma, or for chemoembolisation in colorectal cancer.

References.
1. Douillard JY, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355:** 1041–7. Correction. *ibid.*; 1372.
2. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
3. Rothenberg ML. Irinotecan (CPT-11): recent developments and future directions—colorectal cancer and beyond. *Oncologist* 2001; **6:** 66–80.
4. Saltz LB, *et al.* Irinotecan plus fluorouracil/leucovorin for metastatic colorectal cancer: a new survival standard. *Oncologist* 2001; **6:** 81–91.
5. Cunningham D, *et al.* Optimizing the use of irinotecan in colorectal cancer. *Oncologist* 2001; **6** (suppl 4): 17–23.
6. Vanhoefer U, *et al.* Irinotecan in the treatment of colorectal cancer: clinical overview. *J Clin Oncol* 2001; **19:** 1501–18.
7. Douillard JY, *et al.* Update on European adjuvant trials with irinotecan for colorectal cancer. *Oncology (Huntingt)* 2002; **16** (suppl 3): 13–15.
8. Ulukan H, Swaan PW. Camptothecins: a review of their chemotherapeutic potential. *Drugs* 2002; **62:** 2039–57.
9. Pizzolato JF, Saltz LB. The camptothecins. *Lancet* 2003; **361:** 2235–42.
10. Glimelius B. Benefit-risk assessment of irinotecan in advanced colorectal cancer. *Drug Safety* 2005; **28:** 417–33.

11. Fuchs C, *et al*. Irinotecan in the treatment of colorectal cancer. *Cancer Treat Rev* 2006; **32:** 491–503.
12. Sato T, *et al*. Treatment of advanced or recurrent colorectal cancer with irinotecan in Japan and elsewhere. *Expert Opin Pharmacother* 2008; **9:** 1223–8.
13. Van Cutsem E, *et al*. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360:** 1408–17.
14. Hebbar M, *et al*. Current place of high-dose irinotecan chemotherapy in patients with metastatic colorectal cancer. *J Cancer Res Clin Oncol* 2009; **135:** 749–52.
15. Van Cutsem E, *et al*. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol* 2009; **27:** 3117–25.
16. Weekes J, *et al*. Irinotecan therapy and molecular targets in colorectal cancer: a systemic [sic] review. *World J Gastroenterol* 2009; **15:** 3597–602.
17. Zhuang L, *et al*. Meta-analysis of chemotherapy with irinotecan or oxaliplatin-involved regimen for untreated metastatic advanced colorectal cancer. *Oncol Res* 2010; **18:** 437–44.
18. Oostendorp LJ, *et al*. Systematic review of benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer. *Anticancer Drugs* 2010; **21:** 749–58.

Administration. The intravenous formulation of irinotecan (*Camptosar, Pfizer, USA*) has been given orally to children with refractory solid tumours.[1] The dose (typically 15 mg/m^2) was drawn up in a plastic oral syringe on the day of dosing, although the reconstituted solution has been reported to be stable for 21 days at 4 degrees in these syringes. The dose was mixed with cranberry-grape juice immediately before use.

When this single oral dose of irinotecan was given with oral *gefitinib*, median irinotecan bioavailability was significantly higher, and systemic exposure to irinotecan and its metabolite SN-38 was greater, than that seen in patients not given gefitinib.[1]

1. Furman WL, *et al*. Tyrosine kinase inhibitor enhances the bioavailability of oral irinotecan in pediatric patients with refractory solid tumors. *J Clin Oncol* 2009; **27:** 4599–4604.

Administration in the elderly. UK licensed product information states that elderly patients treated with irinotecan require more intensive monitoring, and that the dose should be chosen with care. US licensed product information reports that exposure to the active metabolite SN-38 is increased by about 11% in patients aged 65 years and older compared with younger patients. No change in the initial dose is recommended for elderly patients given weekly irinotecan, but in those given the 3-weekly schedule, a lower initial dose is recommended in patients 70 years and older based on clinical toxicity with this schedule (although the pharmacokinetics of this schedule have not been studied in a geriatric population). A review[1] found that delayed diarrhoea was increased in elderly patients, although response rates appear unaffected by age. While there were no data to support a specific dose modification, it was recommended that those older than 70 years, those with previous pelvic irradiation, or those with poor performance status, be treated with reduced initial doses.

1. Lichtman SM, *et al*. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in hepatic impairment. In patients with hyperbilirubinaemia, the clearance of irinotecan is decreased, exposure to the active metabolite SN-38 is increased, and the risk of haematological toxicity is increased. US licensed product information recommends a reduction in the initial dose of irinotecan for those patients with increased bilirubin concentrations. However, doses in patients with bilirubin greater than 2 mg per 100 mL cannot be determined due to insufficient data.

In the UK, licensed product information recommends the following dosage reduction for monotherapy regimens in which irinotecan hydrochloride is normally given at 350 mg/m^2 every 3 weeks (see Uses and Administration, p. 812.3):

- in patients with bilirubin up to 1.5 times the upper limit of normal range (ULN): no dosage reduction is considered necessary and irinotecan hydrochloride 350 mg/m^2 is recommended;
- in patients with bilirubin ranging from 1.5 to 3 times the ULN: irinotecan hydrochloride 200 mg/m^2 may be given;
- in patients with bilirubin over 3 times the ULN: the use of irinotecan is not recommended.

Administration in renal impairment. UK and US licensed product information state that irinotecan is not recommended or should be used with caution in patients with renal impairment due to a lack of data; creatinine clearance was reported[1] to be inversely related to the risk of severe neutropenia in one study. US licensed product information states that irinotecan is not recommended for use in dialysis. However, there is a report of its use in a colorectal cancer patient on long-term haemodialysis;[2] the initial intravenous dose used was irinotecan 50 mg/m^2 weekly for 3 weeks, repeated after a rest period of 1 week. This dose was well tolerated, and irinotecan was increased to 80 mg/m^2 after 2 cycles. Pharmacokinetic study showed a lower apparent clearance and a higher maximum concentration of the active metabolite SN-38, compared with patients with normal renal function. The authors concluded that an initial dose of 80 mg/m^2 (about ⅔ of the standard dose) given weekly for 3 weeks followed by a rest period of 1 week might be feasible in patients with end-stage renal failure.

1. de Jong FA, *et al*. Renal function as a predictor of irinotecan-induced neutropenia. *Clin Pharmacol Ther* 2008; **84:** 254–62.
2. Czock D, *et al*. Irinotecan in cancer patients with end-stage renal failure. *Ann Pharmacother* 2009; **43:** 363–9.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Neutropenia and diarrhoea may be dose-limiting in patients given irinotecan. The nadir of the white cell count usually occurs about 8 days after a dose, with recovery by about day 22. Leucopenia and anaemia also occur and, less commonly, thrombocytopenia. Complete blood counts should be monitored weekly during treatment. Those who are homozygous for the uridine diphosphate glucuronosyltransferase allele UGT1A1*28 are at increased risk of neutropenia (see Genetic Factors, below). Radiotherapy also increases the risk of myelosuppression. Treatment should be withheld until neutropenia recovers to at least grade 1, and further doses reduced for severe haematological toxicity.

Nausea, vomiting, and diarrhoea are common with irinotecan, and can be severe. Acute diarrhoea, occurring within 24 hours of a dose, may be part of a transient cholinergic syndrome which can also include sweating, hypersalivation, abdominal cramps, lachrymation, miosis, conjunctivitis, vasodilatation, hypotension, chills, and dizziness. These symptoms can be controlled with atropine. However, a more severe, prolonged diarrhoea may occur, beginning more than 24 hours after a dose, and can be life-threatening; prompt management with high-dose loperamide and fluid replacement is required (see Effects on the Gastrointestinal Tract, below), and irinotecan treatment should be interrupted and any further doses reduced. Elderly patients, women, those who have had abdominal or pelvic radiotherapy, those with pre-existing hyperleucocytosis, and those with poor performance status are at increased risk of diarrhoea. There is also an increased risk of infection and haematological toxicity in patients with severe diarrhoea. A prophylactic antibacterial should be given if there is diarrhoea and severe neutropenia (neutrophil count < 500 cells/mm^3) or fever. Dehydration can occur and in severe cases has led to acute renal failure, hypotension, and cardio-circulatory failure. Other gastrointestinal disturbances include toxic megacolon, colitis including typhlitis, ischaemia, and ulceration, leading to haemorrhage, obstruction, and perforation. Pseudomembraneous colitis has also been reported. Irinotecan should not be given to patients with inflammatory bowel disease or bowel obstruction.

Other adverse effects include hiccups, weakness, reversible alopecia, skin reactions, pancreatitis, and increases in liver enzymes, bilirubin, creatinine, amylase, and lipase. Liver function tests should be carried out at baseline and before each cycle. Hypertension has occurred rarely during or after infusion. There are rare reports of hypersensitivity reactions including anaphylaxis, mild injection site reactions, transient speech disorders (dysarthria), muscular contraction or cramps, and paraesthesia. Interstitial lung disease with pulmonary infiltrates is uncommon during irinotecan treatment, but can be fatal; patients with risk factors should be closely monitored. If symptoms such as dyspnoea, cough, and fever occur, irinotecan and any other chemotherapy should be withheld, and stopped permanently if interstitial lung disease is diagnosed.

Thromboembolic events have occurred, including myocardial ischaemia and infarction, cerebral infarction, pulmonary embolism, arterial thrombosis, angina, and vascular disorders.

Severe toxicity resulting in an increased number of deaths has been reported when irinotecan was given with fluorouracil and folinic acid (see under Interactions, p. 814.1).

Effects on the gastrointestinal tract. *Acute* diarrhoea occurring as part of a cholinergic syndrome with irinotecan is rarely severe. The syndrome is usually treated or prevented with atropine, but pretreatment with hyoscine butylbromide has also been tried.[1,2] In contrast, *delayed* diarrhoea can be dose-limiting or even fatal in some patients. Standard treatment involves fluid and electrolyte replacement and a high-dose loperamide regimen consisting of 4 mg loperamide immediately after the first loose stool, then 2 mg every 2 hours until 12 hours after the last liquid stool. During the night, the patient may take 4 mg every 4 hours. The high-dose therapy should not be given for more than 48 hours and should never be given prophylactically. Specific recommendations[3] state that if the diarrhoea persists for more than 24 hours despite loperamide therapy, patients should also take an oral fluoroquinolone for 7 days. If the diarrhoea persists for more than 48 hours, patients should be hospitalised for parenteral hydration. Other treatments have been tried, including acetorphan, activated charcoal, budesonide, glutamine, and octreotide.[2,4-9] A regimen of thalidomide with irinotecan has been reported to have a striking lack of gastrointestinal adverse effects such as diarrhoea and nausea.[2,10] However, a pharmacokinetic study found no decrease in gastrointestinal toxicity when these 2 drugs were given together, see Thalidomide, under Interactions, p. 814.2.

Diarrhoea may be caused by direct intestinal damage due to SN-38, the active metabolite of irinotecan; reduction of intestinal SN-38 concentrations using the poorly absorbed aminoglycoside neomycin as prophylaxis was reported to ameliorate diarrhoea in 6 of 7 patients who had this adverse effect.[11]

1. Zampa G, Magnolfi E. Premedication for irinotecan. *J Clin Oncol* 2000; **18:** 237.
2. Yang X, *et al*. Novel agents that potentially inhibit irinotecan-induced diarrhea. *Curr Med Chem* 2005; **12:** 1343–58.
3. Rothenberg ML, *et al*. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; **19:** 3801–7.
4. Saliba F, *et al*. Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment. *J Clin Oncol* 1998; **16:** 2745–51.
5. Lenfers BHM, *et al*. Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. *Ann Oncol* 1999; **10:** 1251–3.
6. Savarese D, *et al*. Glutamine for irinotecan diarrhea. *J Clin Oncol* 2000; **18:** 450–1.
7. Ychou M, *et al*. Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. *Am J Clin Oncol* 2000; **23:** 143–8.
8. Pro B, *et al*. Therapeutic response to octreotide in patients with refractory CPT-11 induced diarrhea. *Invest New Drugs* 2001; **19:** 341–3.
9. Michael M, *et al*. Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. *J Clin Oncol* 2004; **22:** 4410–17.
10. Govindarajan R, *et al*. Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; **356:** 566–7.
11. Kehrer DFS, *et al*. Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001; **7:** 1136–41.

Genetic factors. Irinotecan is hydrolysed to SN-38, an active metabolite, which is inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes.[1] Genetic variation in the UGT family may affect irinotecan pharmacodynamics. Although UGT1A1*28 polymorphism appears to be only one of several identified causes of altered SN-38 pharmacokinetics,[1,2] it has been strongly associated with the development of severe neutropenia, and genotyping has been proposed as a method of identifying patients at risk of severe toxicity from irinotecan.[3,4] However, genotyping does not predict for all toxicities, and a significant association between the UGT1A1*28 homozygous genotype and diarrhoea has not been proven. Furthermore, a normal UGT1A1 genotype does not ensure lack of toxicity, although the risk is less; the possibility of underdosing in those with the normal genotype may need to be considered.[5] Despite these limitations, it has been suggested that every patient receiving irinotecan for the first time be tested for UGT1A1 genotype.[5]

Licensed product information in the USA states that reduced initial doses should be considered for patients known to be homozygous for the UGT1A1*28 allele; however, the most appropriate dose reduction in the homozygous population is unknown. Some have suggested an initial 20% dose reduction, with escalation to full dosage in subsequent courses in the event of little or no toxicity.[5] A prospective study[6] found that the UGT1A1*28 genotype (homozygous or heterozygous) was significantly associated with haematological toxicity, but only during the first cycle of irinotecan-containing chemotherapy. This called into question the need for a dose reduction in irinotecan for patients with this genotype, particularly since homozygous patients showed a trend to improve clinical response. A study in paediatric patients[7] found that, for low-dose, protracted schedules of irinotecan (doses ranged from 15 to 75 mg/m^2 daily, given either intravenously or orally, for 5 days, for 2 consecutive weeks), UGT1A1 genotyping was not a useful prognostic indicator of severe toxicity. A similar lack of influence of UGT1A1 genotype was seen in adults given a low-dose regimen for metastatic colon cancer.[8] A meta-analysis[9] found that the risk of haematological toxicity was similar for all genotypes at lower doses of irinotecan. The authors suggested that at low doses of irinotecan, decisions about treating individual patients could be made according to standard clinical practice, whereas genotype-based decisions were advisable at higher doses. Many studies on so-called 'irinogenetics' have been conducted.[10,11] One such study[11] examined 42 common genetic variants, as well as some non-genetic variables. UGT1A1*93 was found to be a strong predictor for neutropenia, and drug

transporter polymorphisms may also have a significant impact on irinotecan pharmacokinetics and pharmacodynamics. Non-genetic factors were also found to be significant; females were more prone to neutropenia, for example, and total bilirubin may also be a factor.[11] Since smoking and other medications can also influence irinotecan disposition, it has been asked whether the drug-elimination phenotype needs to be ascertained, rather than genotype alone, and whether too many genes are involved in drug elimination for genotyping to be of practical clinical use. However, further studies might elucidate a drug elimination genotype with relevance for other drugs, not only irinotecan.[12]

1. Paoluzzi L, *et al.* Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. *J Clin Pharmacol* 2004; **44:** 854–60.
2. Ramchandani RP, *et al.* The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 2007; **47:** 78–86.
3. Innocenti F, *et al.* Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22:** 1382–8.
4. Hahn KK, *et al.* Pharmacogenetics and irinotecan therapy. *Am J Health-Syst Pharm* 2006; **63:** 2211–17.
5. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006; **24:** 4534–8.
6. Toffoli G, *et al.* The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24:** 3061–8.
7. Stewart CF, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007; **25:** 2594–2600.
8. Schulz C, *et al.* UGT1A1 gene polymorphism: impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. *World J Gastroenterol* 2009; **15:** 5058–66.
9. Hoskins JM, *et al.* UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst* 2007; **99:** 1290–5.
10. Hoskins JM, *et al.* Irinotecan pharmacogenetics: influence of pharmacodynamic genes. *Clin Cancer Res* 2008; **14:** 1788–96.
11. Innocenti F, *et al.* Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. *J Clin Oncol* 2009; **27:** 2604–14.
12. Mathijssen RHJ, Gurney H. Irinogenetics: how many stars are there in the sky? *J Clin Oncol* 2009; **27:** 2578–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies irinotecan as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Interactions

Irinotecan is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system such as carbamazepine, phenobarbital, or phenytoin reduce exposure to irinotecan and its active metabolite SN-38; use with St John's Wort is contra-indicated. Conversely, inhibitors of this system such as ketoconazole increase exposure to irinotecan and SN-38; use with ketoconazole is contra-indicated.

Antidepressants. In a small, crossover study[1] of cancer patients, use of *St John's wort* during irinotecan therapy was found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan. Myelosuppression was also reduced with this combination. The interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP3A4 by St John's wort.

1. Mathijssen RHJ, *et al.* Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; **94:** 1247–9.

Antineoplastics. Although previously reported to be effective, and not associated with excessive toxicity,[1] a regimen of irinotecan with bolus *fluorouracil* and folinic acid was found to be associated with an excess of early deaths in 2 further studies, which were consequently terminated.[2] Deaths were associated with a variety of events including dehydration (due to diarrhoea, nausea, and vomiting), neutropenia, and sepsis. It has been suggested that use of irinotecan with fluorouracil by continuous infusion might be better tolerated,[3,4] and a small study[5] found that the sequence may be important. Irinotecan followed by an infusion of fluorouracil over 48 hours, was associated with less dose-limiting toxicity, and higher maximum tolerated doses, than fluorouracil infusion followed by irinotecan.

Sorafenib may increase systemic exposure to irinotecan.

Gefitinib has been used to increase the bioavailability of *oral* irinotecan, see under Administration, p. 813.1.

1. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
2. Sargent DJ, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 144–5.
3. Ledermann JA, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 145–6.
4. Van Cutsem E, *et al.* Toxicity of irinotecan in patients with colorectal cancer. *N Engl J Med* 2001; **345:** 1351–2.
5. Falcone A, *et al.* Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients. *J Clin Oncol* 2001; **19:** 3456–62.

Smoking. A study found that tobacco smoking significantly affected the pharmacokinetics and toxicity of irinotecan.[1] Clearance of irinotecan was faster in smokers, and systemic exposure to the active metabolite SN-38 (see Pharmacokinetics, below) was almost 40% lower in smokers. This effect probably contributed to the significantly lower haematological toxicity seen in smokers; no significant difference in diarrhoea was seen between smokers and non-smokers. Smoking may induce cytochrome P450 isoenzymes, or possibly affect carboxylesterase activity. The study did not determine an effect of smoking on the outcome of treatment with irinotecan. However, smokers may need a higher dose of irinotecan relative to non-smokers, since the lower exposure to irinotecan and SN-38 may indicate a potential risk of treatment failure.

1. van der Bol JM, *et al.* Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* 2007; **25:** 2719–26.

Thalidomide. A pharmacokinetic study found that the metabolism of irinotecan to SN-38 was significantly decreased by thalidomide. Despite reports of reduced gastrointestinal toxicity when these 2 drugs were given together (see Effects on the Gastrointestinal System, p. 813.2), 3 out of 19 patients enrolled in the study had severe delayed diarrhoea after being given irinotecan with thalidomide.[1]

1. Allegrini G, *et al.* Irinotecan in combination with thalidomide in patients with advanced solid tumors: a clinical study with pharmacodynamic and pharmacokinetic evaluation. *Cancer Chemother Pharmacol* 2006; **58:** 585–93.

Pharmacokinetics

Irinotecan exhibits biphasic or triphasic pharmacokinetics, with a terminal half-life of about 14 hours. After intravenous doses it is hydrolysed by carboxylesterase in body tissues to active SN-38 (7-ethyl-10-hydroxycamptothecin), which has a biphasic elimination profile with a terminal half-life of about 14 hours. Plasma protein binding for irinotecan and SN-38 is about 65% and 95%, respectively. SN-38 is mainly eliminated by glucuronidation, predominantly by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Irinotecan is also partly metabolised by cytochrome P450 isoenzymes CYP3A4 and perhaps CYP3A5. More than 50% of an intravenous dose of irinotecan is excreted as unchanged drug, with about 30% in the faeces via the bile and about 20% in the urine.

References.
1. Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet* 1997; **33:** 245–59.
2. Rivory LP. Metabolism of CPT-11: impact on activity. *Ann N Y Acad Sci* 2000; **922:** 205–15.
3. Mathijssen RH, *et al.* Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res* 2001; **7:** 2182–94.
4. Ma MK, McLeod HL. Lessons learned from the irinotecan metabolic pathway. *Curr Med Chem* 2003; **10:** 41–9.
5. Smith NF, *et al.* Pharmacogenetics of irinotecan metabolism and transport: an update. *Toxicol In Vitro* 2006; **20:** 163–75.
6. Di Paolo A, *et al.* Clinical pharmacokinetics of irinotecan-based chemotherapy in colorectal cancer patients. *Curr Clin Pharmacol* 2006; **1:** 311–23.
7. Fujita K, Sparreboom A. Pharmacogenetics of irinotecan disposition and toxicity: a review. *Curr Clin Pharmacol* 2010; **5:** 209–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biotecan; Camptosar; Efixano; Irenax; Irinogen; Itoxaril; Kebirtecan; Pipetecan; Satigene; Sibudan; Trinotecan; Winol; ***Austral.***: Camptosar; ***Austria***: Campto; ***Belg.***: Campto; Irinosin; ***Braz.***: Biotecan; Camptosar; Irenax; Irinolibbs; Irnocam; Ironotel; Proto-Itecan; Tecnotecan; ***Canad.***: Camptosar; ***Chile***: Camptosar; Linatecan; ***China***: Ai Li (艾力); Campto (开普拓); ***Cz.***: Campto; Canri; Irinoxin; Riemid; ***Denm.***: Campto; Irinosor†; ***Fin.***: Campto; ***Fr.***: Campto; ***Ger.***: Axinotecan; Campto; Irinomedac; Irinotesin; Riboirino; ***Gr.***: Biotecan; Campto; Irinocan; Iritec; Mizantrone; Santacil; Vintecan; ***Hong Kong***: Campto; Irinotesin; ***Hung.***: Campto; Tekazol; ***India***: Irinotel; Irnocam; ***Indon.***: Campto; Irnocam; ***Irl.***: Campto; ***Israel***: Campto; Irinomed; ***Ital.***: Campto; ***Jpn***: Campto; Topotecin; ***Malaysia***: Campto; Irnocam; ***Mex.***: Camptolem†; Camptosar; Daritex A; Iraplax; Itoxaril; Terican; ***Neth.***: Campto; Cetomedica; Iricam; Iritec; Jovadolin; Narimed; Xavetta; ***Norw.***: Campto; ***NZ***: Camptosar; Irinoccord; ***Philipp.***: Campto; Irican; ***Pol.***: Campto; Irinotesin; ***Port.***: Campto; Faultenocan; Irkan; ***Rus.***: Camptera (Камптера); Campto (Кампто); Camptotecan (Камптотекан); Iriten (Иритен); Irnocam (Ирнокам); ***S.Afr.***: Campto; Irinotas; ***Singapore***: Campto; Irinotesin; ***Spain***: Campto; ***Swed.***: Campto†; ***Switz.***: Campto; ***Thai.***: Campto; Irenax†; Irino†; Irinoll; Irinotel; Irinotesin; ***Turk.***: Campto; Irinocam; Tekamen; ***UK***: Campto; ***Ukr.***: Campto (Кампто); Irnocam (Ірнокам); ***USA***: Camptosar; ***Venez.***: Camptosar; Elinatecan.

Pharmacopoeial Preparations

USP 36: Irinotecan Hydrochloride Injection.

Ixabepilone *(USAN, rINN)*

Azaepothilone B; BMS-247550-01; Ixabepilona; Ixabépilone; Ixabepilonum; Иксабепильон.

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.

$C_{27}H_{42}N_2O_5S$=506.7

CAS — 219989-84-1.

ATC — L01DC04.

ATC Vet — QL01DC04.

UNII — K27005NP0A.

Uses and Administration

Ixabepilone is an analogue of the epothilone compound patupilone (p. 843.3) that is used for the treatment of patients with metastatic or locally advanced breast cancer. It is given as monotherapy in those whose tumours are resistant or refractory to anthracyclines, taxanes, and capecitabine. Ixabepilone is also used with capecitabine in those whose tumours are resistant to anthracycline and taxanes, or in those with cancer resistant to taxanes, and for whom further anthracycline therapy is contra-indicated.

The recommended dose of ixabepilone is 40 mg/m^2 (to a maximum of 88 mg) given by intravenous infusion over 3 hours every 3 weeks. Ixabepilone is diluted with a suitable infusion fluid (pH 6 to 9), such as lactated Ringer's solution, to a final concentration of 200 to 600 micrograms/mL before infusion.

Doses are adjusted for toxicity. If moderate or severe neuropathy, or any severe toxicity (other than neuropathy) occurs, the dose should be decreased by 20%. If severe neuropathy lasts 7 days or more, or any disabling toxicity occurs, therapy should be stopped. If the neutrophil count falls below 500 cells/mm^3 for 7 days or more, if platelets fall below 25 000 cells/mm^3 (or below 50 000 cells/mm^3 with bleeding), or if febrile neutropenia occurs, the dose should be decreased by 20%. If toxicities recur, an additional 20% dose reduction should be made. Patients should not begin a new cycle of treatment unless the neutrophil count is at least 1500 cells/mm^3, the platelet count is at least 100 000 cells/mm^3, and non-haematological toxicities have improved to grade 1 (mild) or resolved.

Doses are also adjusted in hepatic impairment (see Administration in Hepatic Impairment, below).

Use of strong inhibitors of CYP3A4 should be avoided with ixabepilone. If no alternative is available, a dose reduction of ixabepilone to 20 mg/m^2 should be considered. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of ixabepilone is increased back to the original dose.

Use of strong CYP3A4 inducers should also be avoided with ixabepilone, but if they must be used, the dose of ixabepilone may be gradually increased up to 60 mg/m^2; increased doses should be given as an intravenous infusion over 4 hours. Once the inducer is stopped, ixabepilone should be reduced to the original dose.

References.
1. Gianni L. Ixabepilone and the narrow path to developing new cytotoxic drugs. *J Clin Oncol* 2007; **25:** 3389–91.
2. Fornier MN. Ixabepilone, first in a new class of antineoplastic agents: the natural epothilones and their analogues. *Clin Breast Cancer* 2007; **7:** 757–63.
3. Thomas ES, *et al.* Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007; **25:** 5210–17.
4. Moen MD. Ixabepilone: in locally advanced or metastatic breast cancer. *Drugs* 2009; **69:** 1471–81.

Administration in hepatic impairment. Ixabepilone and capecitabine *combination therapy* is contra-indicated in patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2.5 times the upper limit of normal (ULN), or in those with bilirubin greater than the ULN. Patients with values equal to or below these figures may be given the standard dose of ixabepilone.

In *monotherapy*, the following doses of ixabepilone may be given:

- mild; AST and ALT up to 2.5 times the ULN, and normal bilirubin: 40 mg/m^2 *or* AST or ALT equal to or less than 10 times the ULN and bilirubin equal to or less than 1.5 times the ULN: 32 mg/m^2
- moderate; AST and ALT equal to or less than 10 times the ULN and bilirubin greater than 1.5 times the ULN, but equal to or less than 3 times the ULN: patients should be started at 20 mg/m^2, and the dosage in subsequent cycles escalated up to, but not exceeding, 30 mg/m^2 if tolerated
- severe; AST or ALT greater than 10 times the ULN or bilirubin greater than 3 times the ULN: not recommended

Data are limited for patients with a baseline AST or ALT greater than 5 times the ULN.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Peripheral neuropathy is common with ixabepilone, but is generally reversible. Dose reduction, or delaying or stopping treatment may be necessary (see Uses and Administration, p. 814.3). Dose-dependent myelosuppression can occur, manifested mainly as neutropenia; febrile neutropenia and fatalities have been reported. Frequent blood counts are recommended. Ixabepilone is formulated in polyoxyl castor oil and should be avoided in patients hypersensitive to this substance; patients should be premedicated with a histamine H_1-and histamine H_2-antagonist about 1 hour before infusion. Therapy should be stopped if a hypersensitivity reaction occurs, and symptomatic treatment given. Subsequent cycles may be given with additional corticosteroid therapy, and extension of the infusion time should be considered.

Cardiac adverse effects such as hypotension, myocardial ischaemia, myocardial infarction, arrhythmias, ventricular dysfunction, and cardiomyopathy have been reported. Caution is advised in patients with a history of cardiac disease and therapy may need to be stopped if cardiac effects occur. Effects on the respiratory system include dyspnoea, cough, pneumonitis, pulmonary oedema, and respiratory failure. Increases in hepatic enzymes, jaundice, and acute hepatic failure have occurred, as has renal failure.

Other adverse effects include gastrointestinal disturbances, anorexia, myalgia, arthralgia, fatigue, alopecia, insomnia, headache, taste disorders, dizziness, increased lachrymation, hot flushes, nail disorders, skin disorders including rashes, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, pruritus, and skin exfoliation or hyperpigmentation, renal calculi, electrolyte disturbances, coagulopathy, cognitive disorders, syncope, thrombotic or haemorrhagic events, and vasculitis.

Interactions

Ixabepilone undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to ixabepilone. Conversely, CYP3A4 inducers can reduce exposure to ixabepilone. Use of ixabepilone with strong inhibitors or inducers of CYP3A4 should be avoided. If strong inhibitors are used, dose adjustments may be required (see Uses and Administration, p. 814.3). Grapefruit juice may also increase plasma concentrations of ixabepilone and should be avoided. St John's wort may decrease plasma concentrations of ixabepilone unpredictably and should also be avoided.

Pharmacokinetics

Ixabepilone is extensively distributed. Plasma protein binding is about 67 to 77%. It is extensively metabolised in the liver, mainly by oxidation via cytochrome P450 isoenzyme CYP3A4. It is eliminated mainly as metabolites; about 86% of a dose is eliminated within 7 days, 65% in faeces, and 21% in the urine. The terminal elimination half-life is reported to be about 52 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ixempra; ***Chile***: Ixempra; ***Fr.***: Ixempra†; ***Israel***: Ixempra; ***NZ***: Ixempra; ***Singapore***: Ixempra; ***Switz.***: Ixempra; ***Thai.***: Ixempra; ***USA***: Ixempra.

Lapatinib Tosilate *(rINNM)*

GW-572016F; Lapatinib Ditosylate (USAN); Lapatinib, Tosilate de; Lapatinibi Tosilas; Tosilato de lapatinib; Лапатиниба Тозилат.

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)furan-2-yl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate.

$C_{29}H_{26}ClFN_4O_4S,2C_7H_8O_3S,H_2O$=943.5

CAS — 231277-92-2 (lapatinib); 388082-78-8 (lapatinib tosilate).

UNII — G873GX646R.

Uses and Administration

Lapatinib tosilate is a dual tyrosine kinase inhibitor directed against two members of the human epidermal growth factor receptor family, namely epidermal growth factor receptor (EGFR; ErbB1) and human epidermal receptor type 2 (HER2; ErbB2). Lapatinib is used in the treatment of breast cancer (p. 702.1) that overexpresses HER2, either with capecitabine (p. 757.3) in patients with advanced or metastatic disease who have had previous therapy including an anthracycline, a taxane, and trastuzumab, or, in some countries, with an aromatase inhibitor in postmenopausal women with hormone-receptor positive metastatic disease.

Doses of lapatinib tosilate are expressed in terms of the base; lapatinib tosilate 405 mg is equivalent to about 250 mg of lapatinib. It is given orally, at least one hour before or one hour after food. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

When given with capecitabine, the recommended dose of lapatinib is 1.25 g once daily on days 1 to 21 of a 21-day cycle. Capecitabine is given at a dose of 2 g/m² daily (given orally in 2 doses about 12 hours apart, with food or within 30 minutes after food) on days 1 to 14 of the cycle. Treatment may be continued until disease progression or unacceptable toxicity occurs. If a daily dose is missed, the next day's dose should not be doubled.

When given with an aromatase inhibitor, the recommended dose of lapatinib is 1.5 g given orally once daily.

Dosage should be reduced in patients with severe hepatic impairment (see Administration in Hepatic Impairment, below). Treatment with lapatinib should be stopped in patients who develop a decreased left ventricular ejection fraction (LVEF); however, patients may be restarted at a reduced dose of lapatinib after a minimum of 2 weeks if the LVEF recovers to normal and if the patient is asymptomatic. When given with capecitabine, lapatinib is restarted at 1 g daily, or when given with an aromatase inhibitor, lapatinib 1.25 g daily is used. Lapatinib may need to be stopped or treatment interrupted if other severe toxicities develop. Patients can be restarted at the recommended dose when the toxicity improves. However, if toxicity recurs, lapatinib should be restarted at a lower dose; when given with capecitabine, lapatinib is restarted at 1 g daily, or when given with an aromatase inhibitor, lapatinib 1.25 g daily is used.

If use with potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, US licensed product information recommends dose adjustments of lapatinib based on pharmacokinetic studies. Lapatinib should be given at a dose of 500 mg daily when given with a potent CYP3A4 inhibitor; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the lapatinib dose is increased to the usual recommended dose. When given with a potent inducer of this isoenzyme, the dose of lapatinib should be increased gradually, based on tolerability. When given with capecitabine, lapatinib is titrated from 1.25 g daily up to 4.5 g daily; when given with the aromatase inhibitor letrozole, lapatinib is titrated from 1.5 g daily up to 5.5 g daily. If the inducer is stopped, the dose of lapatinib should be reduced to the usual recommended dose.

Lapatinib is also under investigation for the treatment of gastric cancer and head and neck squamous cell carcinoma.

References.

1. Nelson MH, Dolder CR. Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. *Ann Pharmacother* 2006; **40:** 261–9.
2. Moy B, Goss PE. Lapatinib: current status and future directions in breast cancer. *Oncologist* 2006; **11:** 1047–57.
3. Geyer CE, *et al.* Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; **355:** 2733–43.
4. Montemurro F, *et al.* Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. *Expert Opin Biol Ther* 2007; **7:** 257–68.
5. Ito Y, *et al.* Does lapatinib, a small-molecule tyrosine kinase inhibitor, constitute a breakthrough in the treatment of breast cancer? *Breast Cancer* 2007; **14:** 156–62.
6. Dhillon S, Wagstaff AJ. Lapatinib. *Drugs* 2007; **67:** 2101–8.
7. Paul B, *et al.* Lapatinib: a dual tyrosine kinase inhibitor for metastatic breast cancer. *Am J Health-Syst Pharm* 2008; **65:** 1703–10.
8. Frampton JE. Lapatinib: a review of its use in the treatment of HER2-overexpressing, trastuzumab-refractory, advanced or metastatic breast cancer. *Drugs* 2009; **69:** 2125–48.

Administration in hepatic impairment. US licensed product information states that systemic exposure to lapatinib after a single 100-mg oral dose increased by about 14% and 63% in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, when compared with healthy control subjects. Caution is advised when lapatinib is given to patients with severe hepatic impairment. Oral doses should be reduced; when given with capecitabine, lapatinib is reduced to 750 mg daily, or when given with letrozole, a dose of lapatinib 1 g daily is used. However, licensed product information warns that there are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of lapatinib tosilate are gastrointestinal disturbances, dermatological reactions such as palmar-plantar erythrodysesthesia and rash, and fatigue. Diarrhoea may be severe and dose-limiting. Decreases in left ventricular ejection fraction (LVEF) have been reported with lapatinib, usually within the first 12 weeks of treatment. LVEF should be evaluated in all patients before therapy is started, and periodically evaluated during treatment. Prolongation of the QT interval has also been reported, and lapatinib should be given with caution to those patients with relevant risk factors such as hypokalaemia or hypomagnesaemia, congenital QT prolongation, use of antiarrhythmics, or cumulative high-dose anthracycline therapy. Other reported adverse effects include stomatitis, mucosal inflammation, pain in extremities, back pain, dyspnoea, insomnia, epistaxis, alopecia, nail disorders such as paronychia, and hypersensitivity reactions including anaphylaxis. Lapatinib has been associated with interstitial lung disease and pneumonitis, and treatment should be stopped if severe pulmonary symptoms develop. Hepatotoxicity has occurred and may be severe; deaths have been reported. Liver function should be monitored before, and every 4 to 6 weeks during, treatment. If severe hepatotoxicity develops during treatment, lapatinib should be permanently stopped. Lapatinib should be given with caution to those with pre-existing severe hepatic impairment; doses may need to be reduced.

Effects on the heart. A pooled analysis[1] of data from 44 studies, involving 3689 subjects given lapatinib, found that asymptomatic changes in ventricular ejection fraction occurred in 53 cases and symptomatic events in 7 cases; there were no cardiac deaths attributed to the drug. Of the symptomatic cases 5 were receiving monotherapy and 2 were also taking letrozole or paclitaxel. Symptoms, which included dyspnoea, heart failure, or palpitations, lasted for 2 and 6 weeks respectively in 2 patients who recovered fully, and one of these patients subsequently restarted lapatinib treatment. Of the remaining 5, 2 died due to disease progression (including one in whom lapatinib was not withdrawn as in the other cases), 2 had partial recovery (one of whom later restarted lapatinib), and one remained symptomatic. The frequency of cardiac events was similar in control patients who did not take lapatinib, and there was no evidence of cumulative cardiotoxicity with the drug, nor did previous anthracycline or trastuzumab treatment seem to increase the risk of a reaction in this relatively small group of patients. Despite these results, which suggested a reassuringly low level of cardiotoxicity, the authors considered that cardiac monitoring every 3 months during lapatinib treatment should still be recommended until more data were available.

1. Perez EA, *et al.* Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008; **83:** 679–86.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lapatinib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Interactions

Lapatinib tosilate undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to lapatinib. Conversely, CYP3A4 inducers, such as carbamazepine, can reduce exposure to lapatinib. Use of lapatinib with strong inhibitors or inducers of CYP3A4 should be avoided; if they are to be given together, dose adjustments may be required (see Uses and Administration, above). Grapefruit juice may also increase plasma concentrations of lapatinib and should be avoided. *In vitro* studies indicate that lapatinib itself inhibits CYP3A4 and CYP2C8; it should be used cautiously with substrates of these isoenzymes that have a narrow therapeutic index.

Lapatinib is a substrate of P-glycoprotein and P-glycoprotein inhibitors can increase plasma concentrations of lapatinib. Lapatinib itself also inhibits human P-glycoprotein and may in turn increase plasma concentrations of drugs that are substrates of P-glycoprotein.

References.

1. Smith DA, *et al.* Effects of ketoconazole and carbamazepine on lapatinib pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2009; **67:** 421–6.

Pharmacokinetics

Absorption after an oral dose of lapatinib tosilate is variable and incomplete. Peak plasma concentrations occur after about 4 hours. Systemic exposure to lapatinib is increased when it is given with food. It is highly protein bound. Lapatinib undergoes extensive metabolism, mainly by cytochrome P450 isoenzymes CYP3A4 and CYP3A5; CYP2C19 and CYP2C8 account for some minor metabolism. The terminal half-life after a single dose has been reported to be about 14 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours. About 27% and 14% of an oral dose is recovered in the faeces, as parent

lapatinib and metabolites, respectively; renal excretion is negligible.

References.
1. Koch KM, *et al.* Effects of food on the relative bioavailability of lapatinib in cancer patients. *J Clin Oncol* 2009; **27:** 1191–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tykerb; ***Austria***: Tyverb; ***Belg.***: Tyverb; ***Braz.***: Tykerb; ***Canad.***: Tykerb; ***Chile***: Tykerb; ***Cz.***: Tyverb; ***Denm.***: Tyverb; ***Fr.***: Tyverb; ***Ger.***: Tyverb; ***Gr.***: Tyverb; ***Hong Kong***: Tykerb; ***Hung.***: Tyverb; ***Indon.***: Tykerb; ***Irl.***: Tyverb; ***Israel***: Tykerb; ***Ital.***: Tyverb; ***Jpn***: Tykerb; ***Malaysia***: Tykerb; ***Mex.***: Tykerb; ***Neth.***: Tyverb; ***Norw.***: Tyverb; ***NZ***: Tykerb; ***Philipp.***: Tykerb; ***Pol.***: Tyverb; ***Port.***: Tyverb; ***Rus.***: Tyverb (Тайверб); ***Singapore***: Tykerb; ***Spain***: Tyverb; ***Swed.***: Tyverb; ***Switz.***: Tyverb; ***Thai.***: Tykerb; ***Turk.***: Tykerb; ***UK***: Tyverb; ***Ukr.***: Tyverb (Тайверб); ***USA***: Tykerb.

Laromustine *(USAN, rINN)*

Laromustina; Laromustinum; 101-M; VNP-40101M; Ларомустин.

2′-(2-Chloroethyl)-*N*-methyl-1′,2′-bis(methylsulfonyl)carbamohydrazide.

$C_6H_{14}ClN_3O_5S_2$=307.8

CAS — *173424-77-6.*

UNII — *14J2G0U3NQ.*

NOTE. The name Cloretazine has been used as a trade mark for laromustine; it should not be confused with chlorethazine, which is a synonym for chlormethine (p. 765.1).

Profile

Laromustine is an alkylating agent that is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndromes, and brain cancer.

References.
1. Pigneux A. Laromustine, a sulfonyl hydrolyzing alkylating prodrug for cancer therapy. *IDrugs* 2009; **12:** 39–53.
2. Giles F, *et al.* Phase 3 randomized, placebo-controlled, double-blind study of high-dose continuous infusion cytarabine alone or with laromustine (VNP40101M) in patients with acute myeloid leukemia in first relapse. *Blood* 2009; **114:** 4027–33.
3. Schiller GJ, *et al.* Single-agent laromustine, a novel alkylating agent, has significant activity in older patients with previously untreated poor-risk acute myeloid leukemia. *J Clin Oncol* 2010; **28:** 815–21.
4. Vey N, Giles F. Laromustine (cloretazine). *Expert Opin Pharmacother* 2010; **11:** 657–67.

Lenalidomide *(BAN, USAN, rINN)*

CC-5013; CDC-501; CDC-5013; ENMD-0997; IMiD-3; Lenalidomid; Lenalidomida; Lénalidomide; Lenalidomidum; Леналидомид.

3-(4-Amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione.

$C_{13}H_{13}N_3O_3$=259.3

CAS — *191732-72-6.*

ATC — *L04AX04.*

ATC Vet — *QL04AX04.*

UNII — *F0P408N6V4.*

NOTE. IMiD-3 has also been used as a synonym for pomalidomide (p. 847.3).

Uses and Administration

Lenalidomide is an analogue of thalidomide (p. 867.3) that has immunomodulatory and antiangiogenic properties. It is used for the treatment of transfusion-dependent anaemia due to myelodysplastic syndromes (p. 694.3) associated with certain abnormalities of chromosome 5 (deletion 5q abnormalities), and is given with dexamethasone for multiple myeloma (p. 699.2) in patients who have received at least one prior therapy. Lenalidomide is also used for relapsed or refractory mantle cell lymphoma (p. 698.2).

Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

For transfusion-dependent anaemia due to myelodysplastic syndromes the recommended initial oral dose is 10 mg daily; UK licensed product information recommends that this is given for 21 days of a 28-day cycle, whereas in the USA it is given continuously.

For multiple myeloma or mantle cell lymphoma the recommended initial oral dose of lenalidomide is 25 mg daily, given for 21 days of a 28-day cycle. In multiple myeloma it is given with oral dexamethasone at a dose of 40 mg daily on days 1 to 4, days 9 to 12, and days 17 to 20 of each 28-day cycle, for the first 4 cycles, and then 40 mg daily on days 1 to 4 of each 28-day cycle thereafter.

Lenalidomide is associated with significant neutropenia and thrombocytopenia, and dosage is adjusted according to haematological toxicity. Doses are also adjusted for some other severe toxicities and for renal impairment (see Administration in Renal Impairment, below).

References.
1. Anderson KC. Lenalidomide and thalidomide: mechanisms of action—similarities and differences. *Semin Hematol* 2005; **42** (suppl 4): S3–S8.
2. Zeldis JB, *et al.* Lenalidomide in multiple myeloma: current role and future directions. *Expert Opin Pharmacother* 2010; **11:** 829–42.
3. Komrokji RS, List AF. Lenalidomide for treatment of myelodysplastic syndromes: current status and future directions. *Hematol Oncol Clin North Am* 2010; **24:** 377–88.
4. Scott LJ, Lyseng-Williamson KA. Lenalidomide: a review of its use in the treatment of relapsed or refractory multiple myeloma. *Drugs* 2011; **71:** 625–49.
5. Komrokji RS, List AF. Lenalidomide for treatment of myelodysplastic syndromes. *Curr Pharm Des* 2012; **18:** 3198–203.
6. Syed YY, Scott LJ. Lenalidomide: a review of its use in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndrome associated with 5q chromosome deletion. *Drugs* 2013; **73:** 1183–96.

Administration in renal impairment. Lenalidomide is eliminated mainly via the kidneys as unchanged drug. Clearance decreases as renal function decreases, prolonging the half-life and increasing exposure to the drug. A study recommended that dose adjustments be made for patients with creatinine clearance (CC) less than 50 mL/minute; a 40% reduction to 60% of the starting dose was recommended for these patients. For those with CC less than 30 mL/minute, the reduced dose should be given at extended dosing intervals. About 30% of circulating lenalidomide was removed by a 4-hour session of haemodialysis.[1]

Licensed product information also recommends that doses are adjusted according to the degree of renal impairment; moderate impairment is defined as CC from 30 to less than 50 mL/minute in UK product information or from 30 to less than 60 mL/minute in US literature, severe as CC less than 30 mL/minute, and end-stage renal disease as CC less than 30 mL/minute and requiring dialysis. In patients with **multiple myeloma** or **mantle cell lymphoma**, initial oral doses are adjusted as follows:
- moderate renal impairment: 10 mg once daily. In multiple myeloma this dose may be increased to 15 mg once daily after 2 cycles if the patient is not responding to treatment, but is tolerating lenalidomide
- severe renal impairment: 7.5 mg once daily or 15 mg every other day. In multiple myeloma this dose may be increased to 10 mg daily if tolerated
- end-stage renal disease: 5 mg once daily; on dialysis days the dose should be given after haemodialysis

In **myelodysplastic syndromes**, initial oral doses are adjusted as follows:
- moderate impairment: 5 mg once daily
- severe impairment and end-stage renal disease: 2.5 mg once daily; on dialysis days the dose should be given after haemodialysis

1. Chen N, *et al.* Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; **47:** 1466–75.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Because of potential teratogenicity lenalidomide use is restricted in women of child-bearing potential and similar precautions to thalidomide are required, see p. 869.2.

Lenalidomide is associated with significant neutropenia and thrombocytopenia. Anaemia is also common and other haematological toxicities can occur. Dose reduction or delaying or stopping therapy may be needed; supportive therapy such as growth factors may be necessary. Full blood counts should be monitored at baseline, weekly for the first 8 weeks of therapy, and monthly thereafter. In multiple myeloma patients given lenalidomide with dexamethasone, US product information recommends monitoring full blood counts every 2 weeks for the first 12 weeks, and then monthly thereafter. There is also an increased risk of thrombotic events with lenalidomide, particularly deep-vein thrombosis and pulmonary embolism in multiple myeloma patients; prophylactic therapy may be considered. Haemorrhagic disorders have also occurred. Cardiac disorders including hypotension or hypertension, arrhythmias, myocardial infarction, and heart failure have also been reported.

Renal failure has been reported during lenalidomide treatment. Caution is advised in patients with renal impairment as lenalidomide is excreted via the kidneys; dose adjustments may be required, see above. Hepatotoxicity has also been reported; liver function should be monitored.

Peripheral neuropathy, insomnia, headache, hypoaesthesia, dizziness, and changes to mental status such as depression, hallucinations, mood swings, dysgeusia, and tremor have occurred.

Endocrine disorders that may occur include hirsutism and hypothyroidism; thyroid function should be monitored. Erectile dysfunction has occurred.

Tumour flare reactions and tumour lysis syndrome (p. 730.2) may be seen, and those with a high tumour burden should be monitored closely and appropriate precautions taken, see p. 732.2. An increased rate of second primary malignancies has been noted in some multiple myeloma patients including those taking lenalidomide plus dexamethasone (mainly skin cancers and solid tumours), those taking lenalidomide plus melphalan (acute myeloid leukaemia, myelodysplastic syndromes, and solid tumours), or those taking lenalidomide after high-dose melphalan and stem cell transplantation (B-cell malignancies including Hodgkin's disease).

Lenalidomide has been associated with hypersensitivity reactions including angioedema and severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. If these are suspected, or if a severe, exfoliative, or bullous rash develops, lenalidomide treatment should be permanently stopped. For other forms of skin reaction, lenalidomide should be withheld or stopped depending on the severity. Cross sensitivity may occur in patients with previous hypersensitivity to thalidomide, and such patients should be monitored closely; patients who have previously had a severe skin reaction with thalidomide should not be treated with lenalidomide.

Other adverse effects include gastrointestinal disturbances, pruritus, fatigue, dyspnoea, respiratory distress, cough, interstitial pneumonitis, skin hyperpigmentation, dry skin, hyperhidrosis, cerebrovascular accident, pancreatitis, infections such as pneumonia and herpes, alopecia, peripheral oedema, pyrexia, electrolyte disturbances, and vertigo. Eye disorders include blurred vision, irritation, cataracts, and loss of vision. Musculoskeletal effects include muscle cramps, myopathy, myalgia, arthralgia, and musculoskeletal pain.

Elderly patients may be more susceptible to adverse effects.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lenalidomide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Tumour flare. Tumour flare characterised by painful lymphadenopathy, and sometimes accompanied by musculoskeletal pain and fever, has been reported in patients receiving lenalidomide for relapsed or refractory chronic lymphocytic leukaemia (CLL)[1-3] or for refractory Hodgkin's disease.[4] A lower incidence was noted in CLL patients given a low-dose continuous oral regimen (10 mg once daily for 28 days, increased as tolerated by 5 mg every 28 days to a maximum of 25 mg daily) compared with those given 25 mg once daily orally for 21 days of a 28-day cycle.[1,2] Although serious consequences have been reported in some cases, including one fatality,[3] most cases were not severe and responded to treatment with corticosteroids or NSAIDs;[1,2,4] a reduction in lenalidomide dose has also allowed continued treatment.[4] Lenalidomide-induced B-cell activation has been suggested as contributing to the reaction.[3]

1. Chanan-Khan A, *et al.* Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. *J Clin Oncol* 2006; **24:** 5343–9.
2. Ferrajoli A, *et al.* Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. *Blood* 2008; **111:** 5291–7.
3. Andritsos LA, *et al.* Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. *J Clin Oncol* 2008; **26:** 2519–25.
4. Corazzelli G, *et al.* Tumor flare reactions and response to lenalidomide in patients with refractory classic Hodgkin lymphoma. *Am J Hematol* 2010; **85:** 87–90.

Interactions

Lenalidomide may increase peak plasma concentrations of digoxin. Epoetins or other drugs that increase the risk of thrombosis should be used with caution in patients taking lenalidomide.

Pharmacokinetics

Lenalidomide is rapidly absorbed with peak plasma concentrations occurring between about 0.6 and 1.5 hours after an oral dose. Giving lenalidomide with food does not alter the extent of absorption. Binding to plasma proteins is about 30%. About 80% of a dose is eliminated unchanged through the kidneys. The mean half-life is 3 hours in healthy subjects and 3 to 5 hours in patients with multiple myeloma, myelodysplastic syndromes, or mantle cell lymphoma. Clearance decreases proportionally with renal function. Lenalidomide is distributed into the semen in

small amounts, less than 0.01% of the dose, and semen-concentrations are undetectable 3 days after stopping treatment (male patients should use barrier methods of contraception, see Adverse Effects and Precautions, under Thalidomide, p. 869.2).

References.
1. Chen N, *et al.* Distribution of lenalidomide into semen of healthy men after multiple oral doses. *J Clin Pharmacol* 2010; **50:** 767–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ladevina; ***Austral.***: Revlimid; ***Austria***: Revlimid; ***Belg.***: Revlimid; ***Canad.***: Revlimid; ***Chile***: Revlimid; ***Cz.***: Revlimid; ***Denm.***: Revlimid; ***Fr.***: Revlimid; ***Ger.***: Revlimid; ***Gr.***: Revlimid; ***Hong Kong***: Revlimid; ***India***: Lenangio; Lenid; Mydolen; ***Irl.***: Revlimid; ***Israel***: Revlimid; ***Ital.***: Revlimid; ***Malaysia***: Revlimid; ***Neth.***: Revlimid; ***Norw.***: Revlimid; ***NZ***: Revlimid; ***Philipp.***: Revlimid; ***Pol.***: Revlimid; ***Port.***: Revlimid; ***Rus.***: Revlimid (Ревлимид); ***Singapore***: Revlimid; ***Spain***: Revlimid; ***Swed.***: Revlimid; ***Switz.***: Revlimid; ***Thai.***: Revlimid; ***UK***: Revlimid; ***USA***: Revlimid.

Lenvatinib *(USAN, rINN)*

ER-203492-00; Lenvatinibum; Ленватиниб.
N-[4-[(6-Carbamoyl-7-methoxyquinolin-4-yl)oxy]-2-chlorophenyl}-*N'*-cyclopropylurea.
$C_{21}H_{19}ClN_4O_4$=426.9
CAS — 417716-92-8.
UNII — EE083865G2.

Lenvatinib Mesilate *(rINNM)*

E-7080; Lenvatinib, Mesilate de; Lenvatinib Mesylate (USAN); Lenvatinibi Mesilas; Mesilato de lenvatinib; Ленватиниба Мезилат.
N-[4-[(6-Carbamoyl-7-methoxyquinolin-4-yl)oxy]-2-chlorophenyl}-*N'*-cyclopropylurea monomethanesulfonate.
$C_{21}H_{19}ClN_4O_4.CH_4O_3S$=523.0
CAS — 857890-39-2.
UNII — 3J78384F61.

Profile

Lenvatinib is an oral tyrosine kinase inhibitor that targets the vascular endothelial growth receptor VEGFR2, and several other kinases involved in angiogenesis and tumour proliferation. Lenvatinib is under investigation for the treatment of various solid tumours, including thyroid cancer, melanoma, glioma, and endometrial cancer.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Lestaurtinib *(USAN, rINN)*

A-154475.0; CEP-701; KT-5555; Lestaurtinibum; SP-924; Лестауртиниб.
(9*S*,10*S*,12*R*)-10-Hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydro-1*H*-9,12-epoxydiindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one.
$C_{26}H_{21}N_3O_4$=439.5
CAS — 111358-88-4.
UNII — DO989GC5D1.

Profile

Lestaurtinib is a tyrosine kinase inhibitor directed against the FLT3 receptor, that is under investigation for the treatment of acute myeloid leukaemia.

Letrozole *(BAN, USAN, rINN)* ⊗

CGS-20267; Letrotsoli; Letrozol; Létrozole; Letrozolum; Летрозол.
4,4'-(1*H*-1,2,4-Triazol-1-ylmethylene)dibenzonitrile.
$C_{17}H_{11}N_5$=285.3
CAS — 112809-51-5.
ATC — L02BG04.
ATC Vet — QL02BG04.
UNII — 7LKK855W8I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Letrozole). A white or yellowish, crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol; freely soluble in dichloromethane.

USP 36: (Letrozole). A white to yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

Uses and Administration

Letrozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p. 742.2). It is used in the treatment of advanced or locally advanced breast cancer (p. 702.1) in postmenopausal women. It may be given as neoadjuvant (pre-operative) therapy to those with localised hormone-receptor positive disease, to allow subsequent breast-conserving surgery. Letrozole is also used for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer; treatment is generally given for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. In postmenopausal women given 5 years of adjuvant tamoxifen for early breast cancer, letrozole may be used as extended adjuvant therapy; treatment should continue for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. The usual oral dose is 2.5 mg daily.

References.
1. Nabholtz JM, *et al.* Comparative review of anastrozole, letrozole and exemestane in the management of early breast cancer. *Expert Opin Pharmacother* 2009; **10:** 1435–47.
2. Keating GM. Letrozole: a review of its use in the treatment of postmenopausal women with hormone-responsive early breast cancer. *Drugs* 2009; **69:** 1681–1705.
3. Dellapasqua S, Colleoni M. Letrozole. *Expert Opin Drug Metab Toxicol* 2010; **6:** 251–9.
4. Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole----of clinical importance? *Br J Cancer* 2011; **104:** 1059–66.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dosage adjustment of letrozole is required for patients with mild to moderate hepatic impairment (Child-Pugh category A and B). While letrozole is contra-indicated in the UK in severe hepatic impairment (Child-Pugh category C), in the USA, it is recommended that the dose of letrozole be reduced by 50% in those patients with cirrhosis and severe hepatic impairment; the recommended oral dose for these patients is 2.5 mg given every other day.

Endometriosis. Aromatase inhibitors have been investigated for the treatment of endometriosis, see under Uses of Anastrozole, p. 742.2.

Infertility. Letrozole has been investigated[1-5] as an adjunct to assisted reproduction technologies in the management of infertility (p. 2253.1). A systematic review and meta-analysis[6] concluded that there was insufficient evidence to judge the benefits of letrozole and other aromatase inhibitors in ovulation induction, although use appeared to be associated with a higher number of mono-ovulatory cycles. A recommended regimen for intra-uterine insemination was letrozole 2.5 mg daily from day 3 to day 7 of the cycle, followed by follicle-stimulating hormone from day 8; this might be an attractive alternative to the use of gonadotrophins because of the reduced risk of ovarian hyperstimulation syndrome and multiple gestation.

Aromatase inhibitors such as anastrozole and letrozole have been used for infertility associated with polycystic ovary syndrome;[7] although there is not enough evidence to recommend them routinely for ovulation induction, they may be considered in women who have not responded to clomifene, or where other treatments are not suitable. Letrozole has also been tried successfully[8] in a male patient with azoospermia.

However, concerns about unlicensed use have been raised by the Canadian manufacturer (*Novartis, Canad.*) because of the potential for maternal and fetal toxicity, and fetal malformations:[9] licensed product information contra-indicates the use of letrozole in premenopausal women, and there have been reports of congenital anomalies in the infants of women treated with letrozole for infertility.

1. Healey S, *et al.* Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril* 2003; **80:** 1325–9.
2. Al-Fozan H, *et al.* A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril* 2004; **82:** 1561–3.
3. Garcia-Velasco JA, *et al.* The aromatase inhibitor letrozole increases the concentration of intraovarian androgens and improves in vitro fertilization outcome in low responder patients: a pilot study. *Fertil Steril* 2005; **84:** 82–7.
4. Al-Fadhli R, *et al.* A randomized trial of superovulation with two different doses of letrozole. *Fertil Steril* 2006; **85:** 161–4.
5. Pritts EA. Letrozole for ovulation induction and controlled ovarian hyperstimulation. *Curr Opin Obstet Gynecol* 2010; **22:** 289–94.
6. Requena A, *et al.* Reproductive Endocrinology Interest Group of Spanish Society of Fertility. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. *Hum Reprod Update* 2008; **14:** 571–82.
7. Eckmann KR, Kockler DR. Aromatase inhibitors for ovulation and pregnancy in polycystic ovary syndrome. *Ann Pharmacother* 2009; **43:** 1338–46.
8. Patry G, *et al.* Use of the aromatase inhibitor letrozole to treat male infertility. *Fertil Steril* 2009; **92:** 829.e1–829.e2.
9. Novartis, Canada. Health Canada endorsed important safety information: contraindication of Femara (letrozole) in premenopausal women (issued 17th November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/femara_hpc-cps-eng.pdf (accessed 31/07/08)

Precocious puberty. A pilot study assessing the use of letrozole in the treatment of 9 girls with precocious puberty (p. 2254.1) due to the McCune-Albright syndrome concluded that it could be an effective initial therapy and might offer an alternative for those who fail to respond to tamoxifen. Possible adverse effects included ovarian enlargement and cyst formation, and further studies were considered necessary.[1]

For a report of the effective use of letrozole with bicalutamide in the treatment of familial male precocious puberty (testotoxicosis), see Precocious Puberty, under Bicalutamide, p. 749.2.

1. Feuillan P, *et al.* Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. *J Clin Endocrinol Metab* 2007; **92:** 2100–6.

Adverse Effects, Treatment, and Precautions

As for Anastrozole, p. 742.3.

Breast feeding. Licensed product information states that it is unknown whether letrozole is distributed into human milk; in the UK its use during breast feeding is contra-indicated while in the USA a decision to use may be made based on clinical judgement.

Effects on blood lipids. For a comparison of the effects of anastrozole, letrozole, and exemestane on blood lipids see under Exemestane, p. 792.3.

Effects on the musculoskeletal system. Postmenopausal women with primary breast cancer were reported to have significant decreases in bone mineral density at the hip and lumbar spine after 24 months of letrozole therapy.[1]

See also Effects on the Musculoskeletal System, under Anastrozole, p. 743.1.

1. Perez EA, *et al.* Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. *J Clin Oncol* 2006; **24:** 3629–35.

Effects on the skin. Toxic epidermal necrolysis, attributed to letrozole, has been reported in a patient with breast cancer who was also receiving dexamethasone and omeprazole.[1] She had been switched from tamoxifen to letrozole a few weeks before the reaction occurred.

1. Chia WK, *et al.* Toxic epidermal necrolysis in patient with breast cancer receiving letrozole. *Lancet Oncol* 2006; **7:** 184–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies letrozole as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Tamoxifen. In a study[1] of postmenopausal women with breast cancer, the addition of tamoxifen reduced letrozole plasma concentrations by a mean of about 38%, but the effect of letrozole on hormone concentrations was unchanged. The mechanism and possible clinical effect of this interaction are unknown.

1. Dowsett M, *et al.* Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. *Clin Cancer Res* 1999; **5:** 2338–43.

Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. Food decreases the rate but not the extent of absorption. About 60% of letrozole in the circulation is bound to plasma protein, mainly albumin. Letrozole is rapidly and extensively distributed to tissues. *In vitro* data suggest that it is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2A6. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days, and steady-state concentrations occur within 2 to 6 weeks.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cendalon; Fecinole; Femara; Kebirzol; Letrofarm; Veuen; ***Austral.***: Femara; Fera; ***Austria***: Femara; ***Belg.***: Femara; ***Braz.***: Femara; ***Canad.***: Femara; ***Chile***: Femara; ***China***: Femara (弗隆); Fu Rui (芙瑞); ***Cz.***: Aletro; Arofek; Attozette; Brenea; Britagal; Britapons; Clarzole; Dracenax; Etruzil; Femara; Femtozette†; Garion; Helzette; Lerana; Lestara; Letmylan; Letride; Letroger†; Letromedac; Letrovena; Letrozette; Loosyn; Loxelza; Luro; Mamira; Ninivet;

OncoZol; Oralet; Symletrol; Trozara; Trozel; ***Denm.***: Femar; Femara; Letregio; ***Fin.***: Femar; Letrolan; ***Fr.***: Femara; ***Ger.***: Femara; Letro-cell; Letroarom; Letroblock; Letromedac; ***Gr.***: Aramef; Aromed; Femaplex; Femara; Leoncon; Letrafem; Letropen; Letrozin; Levinox; Linol; Mimor; Religan; Stefaplex; Trezor; Viobrest; ***Hong Kong***: Femara; ***Hung.***: Etruzil; Famos; Femara; Letromataz; Letronorm; Lexeroll; Ninivet; Picozone; ***India***: Femara; Fempro; Feofer; Letocor; Letoripe; Letroz; Lets; Letz; Letzol; Momazol; Oncolet; Oreta; Trozet; ***Indon.***: Femara; ***Irl.***: Eirfem; Femara; Letzo; ***Israel***: Femara; Femozol; ***Ital.***: Femara; ***Jpn***: Femara; ***Malaysia***: Femara; ***Mex.***: Femara; Zolstro; ***Neth.***: Etruzil; Femara; Letaris†; Letrazan; Letregio; Letroman; Letromedica; Letronofi; Letroregiozol; Letroveres; Letrozin; Regioletrozol; ***Norw.***: Femar; Femara; ***NZ***: Femara; Letara; Letraccord; ***Philipp.***: Femara; Hentrozole; Letoripe; Lezol; Trozet; ***Pol.***: Apo-Letro; Aromek; Clarzole; Etruzil; Femara; Lameta; Letralan; Letrodotril; Letrofem; Lostar; Mionic; Trozel; ***Port.***: Cetezol; Femara; Lambda; Loosyn; Nucleus†; ***Rus.***: Extraza (Экстраза); Femara (Фемара); Letrose (Летроза); Letrotera (Летротера); ***S.Afr.***: Femara; Femzole; Laradex; ***Singapore***: Femara; ***Spain***: Devazol; Femara; Galdar; Loxifan; ***Swed.***: Femar; ***Switz.***: Femara; ***Thai.***: Femara; Trozet; ***Turk.***: Femara; Letroks; ***UK***: Femara; ***Ukr.***: Femara (Фемара); Letromara (Летромара); ***USA***: Femara; ***Venez.***: Femara.

Pharmacopoeial Preparations
USP 36: Letrozole Tablets.

Lintuzumab *(rINN)*

HuM-195; Lintuzumabum; SGN-33; Линтузумаб.
Immunoglobulin G1, anti-(human CD33 (antigen)) (human-mouse monoclonal HuM195γ1-chain), disulfide with human-mouse monoclonal HuM195κ-chain, dimer.
CAS — 166089-32-3.

Profile

Lintuzumab is a humanised anti-CD33 monoclonal antibody that is under investigation for the treatment of myelodysplastic syndromes and acute myeloid leukaemia.

References.

1. Feldman EJ, *et al.* Phase III randomized multicenter study of a humanized anti-CD33 monoclonal antibody, lintuzumab, in combination with chemotherapy, versus chemotherapy alone in patients with refractory or first-relapsed acute myeloid leukemia. *J Clin Oncol* 2005; **23:** 4110–16.

Lobaplatin *(rINN)*

D-19466; Lobaplatine; Lobaplatino; Lobaplatinum; Лобаплатин.
cis-[*trans*-1,2-Cyclobutanebis(methylamine)][(*S*)-lactato-O^1,O^1]platinum.
$C_9H_{18}N_2O_3Pt$=397.3
CAS — 135558-11-1.
UNII — OX5XK1JD8C.

Profile

Lobaplatin is a platinum derivative that is used as an antineoplastic in the treatment of breast cancer, small cell lung cancer, and chronic myelogenous leukaemia. The main adverse effect is thrombocytopenia. Lobaplatin is reported to show some cytotoxic effect upon cisplatin-resistant cells.

References.

1. Welink J, *et al.* Pharmacokinetics and pharmacodynamics of lobaplatin (D-19466) in patients with advanced solid tumors, including patients with impaired renal or liver function. *Clin Cancer Res* 1999; **5:** 2349–58.
2. McKeage MJ. Lobaplatin: a new antitumour platinum drug. *Expert Opin Invest Drugs* 2001; **10:** 119–28.
3. Anonymous. Lobaplatin: D 19466. *Drugs R D* 2003; **4:** 369–72.
4. Zhou B, *et al.* Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. *J Vasc Interv Radiol* 2010; **21:** 333–8.

Lomustine *(BAN, USAN, rINN)*

CCNU; Łomustiini; Lomustin; Lomustina; Lomustinas; Lomustinum; Lomustyna; Lomusztin; NSC-79037; RB-1509; WR-139017; Ломустин.
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.
$C_9H_{16}ClN_3O_2$=233.7
CAS — 13010-47-4.
ATC — L01AD02.
ATC Vet — QL01AD02.
UNII — 78RF0Z81KG.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Lomustine). A yellow, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Lomustine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone, and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Lomustine is a nitrosourea with actions and uses similar to those of carmustine (p. 761.2). It has been used in the treatment of brain tumours (p. 701.2) and resistant or relapsed Hodgkin's disease and other lymphomas (p. 696.1), and also lung cancer (p. 710.2), malignant melanoma (p. 714.3), and various solid tumours.

When given as a single agent, lomustine is licensed for oral use in adults and children as a single dose of 120 to 130 mg/m^2; division of the dose over 3 consecutive days may reduce gastrointestinal effects. A dose of 100 mg/m^2 should be given to patients with compromised bone-marrow function. Doses are also generally reduced when lomustine is given as part of a combination regimen. Providing blood counts have returned to acceptable levels, doses may be repeated every 6 to 8 weeks, and should be adjusted according to the haematological response (see also Bone-marrow Depression, p. 730.3).

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Adverse Effects, Treatment, and Precautions

As for Carmustine, p. 761.3. Neurological reactions such as confusion and lethargy have been reported.

Handling and disposal. A method for the destruction of lomustine *waste* by reaction with hydrobromic acid in glacial acetic acid has been described.[1] The residue produced by the degradation of lomustine by this method showed no mutagenicity. This method is not suitable for the degradation of carmustine.

1. Castegnaro M, *et al.* , eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.

Overdosage. A patient who inadvertently received 200 mg of lomustine for 7 days instead of a single 200-mg dose developed pancytopenia and subsequent multiorgan dysfunction including liver dysfunction, abdominal pain, pulmonary toxicity with tachypnoea and hypoxaemia, and CNS toxicity leading to confusion and disorientation.[1] Although the white cell count recovered other signs of toxicity did not and the patient developed fever and hypotension and died 59 days after the initial dose of lomustine. In another case of accidental overdose, a 30-year old female received a cumulative dose of 28 mg/kg over 7 days.[2] Severe myelosuppression developed soon after the overdose and lasted for 50 days. The patient was treated with granulocyte colony-stimulating factor and antibacterial cover, norethisterone (to prevent menstruation), and acetylcysteine (to protect against organ toxicity). Gastrointestinal necrosis occurred, and liver enzymes remained elevated even after recovery from the overdose, but the patient survived and her tumour regressed without further chemotherapy.

1. Trent KC, *et al.* Multiorgan failure associated with lomustine overdose. *Ann Pharmacother* 1995; **29:** 384–6.
2. Abele M, *et al.* CCNU overdose during PCV chemotherapy for anaplastic astrocytoma. *J Neurol* 1998; **245:** 236–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lomustine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Cimetidine. For a report of a possible interaction between lomustine and cimetidine, see under Carmustine, p. 762.1.

Theophylline. Leucopenia and thrombocytopenia in a 45-year-old woman were believed to have been secondary to an interaction between theophylline and lomustine.[1]

1. Zeltzer PM, Feig SA. Theophylline-induced lomustine toxicity. *Lancet* 1979; **ii:** 960–1.

Pharmacokinetics

Lomustine is absorbed from the gastrointestinal tract and is rapidly metabolised, with peak plasma concentrations of metabolites occurring within 4 hours of an oral dose. Metabolites have a prolonged plasma half-life reported to range from 16 to 48 hours. Active metabolites readily cross the blood-brain barrier and appear in the CSF in concentrations higher than those in plasma. About half a dose is excreted as metabolites in the urine within 24 hours and about 75% is excreted within 4 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: CeeNU; ***Austral.***: CeeNU; ***Braz.***: Citostal; ***Canad.***: CeeNU; ***Chile***: CeeNU†; ***Cz.***: CeeNU; ***Fr.***: Belustine; ***Ger.***: Cecenu; ***Gr.***: Cecenu; CeeNU; Prava; ***India***: Lomtin; Lustine; ***Mex.***: CeeNU; ***Neth.***: Belustine; ***NZ***: CeeNU; ***Philipp.***: CeeNU†; ***S.Afr.***: CeeNU†; ***Singapore***: CeeNU; ***Switz.***: CeeNU†; ***UK***: CCNU; ***USA***: CeeNU.

Pharmacopoeial Preparations
BP 2014: Lomustine Capsules;
USP 36: Lomustine Capsules.

Lonidamine *(BAN, rINN)*

AF-1890; Diclondazolic Acid; Lonidamina; Lonidaminum; TH-070; Лонидамин.
1-(2,4-Dichlorobenzyl)indazole-3-carboxylic acid.
$C_{15}H_{10}Cl_2N_2O_2$=321.2
CAS — 50264-69-2.
ATC — L01XX07.
ATC Vet — QL01XX07.
UNII — U78804BIDR.

Profile

Lonidamine is an antineoplastic that is thought to act by inhibiting mitochondrial function in tumour cells. It has been given orally in the treatment of various solid neoplasms, including those of the lung, breast, prostate, and brain. It has also been used as a radiosensitiser.

Lumiliximab *(USAN, rINN)*

Gomiliximab; IDEC-152; Lumiliximabum; Лумиликсимаб.
Immunoglobulin G1, anti-(human immunoglobulin E receptor type II) (human-*Macaca irus* monoclonal IDEC-152 γ1-chain), disulfide with human-*Macaca irus* monoclonal IDEC-152 κ-chain, dimer.
CAS — 357613-86-6.
UNII — 8Z13S29R5A.

Profile

Lumiliximab is a chimeric anti-CD23 monoclonal antibody that is under investigation for the treatment of chronic lymphocytic leukaemia.

References.

1. Byrd JC, *et al.* Phase 1 study of lumiliximab with detailed pharmacokinetic and pharmacodynamic measurements in patients with relapsed or refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2007; **13:** 4448–55.
2. Byrd JC, *et al.* Phase 1/2 study of lumiliximab combined with fludarabine, cyclophosphamide, and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia. *Blood* 2010; **115:** 489–95.

Mafosfamide *(rINN)*

Mafosfamid; Mafosfamida; Mafosfamidi; Mafosfamidum; Мафосфамид.
(±)-2-([2-[Bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-4-yl]thio)ethanesulphonic acid *P-cis* oxide.
$C_9H_{19}Cl_2N_2O_5PS_2$=401.3
CAS — 88859-04-5.
UNII — 5970HH9923.

Profile

Mafosfamide is a derivative of cyclophosphamide (p. 771.1) that has been used to treat bone marrow for transplantation. Intrathecal mafosfamide has been investigated for the treatment of meningeal tumours.

Marimastat *(BAN, USAN, rINN)*

BB-2516; Marimastatum; TA-2516; Маримастат.
(2*S*,3*R*)-3-[(*S*)-[2,2-Dimethyl-1-(methylcarbamoyl)propyl]carbamoyl]-2-hydroxy-5-methylhexanohydroxamic acid.
$C_{15}H_{29}N_3O_5$=331.4
CAS — 154039-60-8.
UNII — D5EQV23TDS.

Profile

Marimastat is an oral inhibitor of matrix metalloproteinases, enzymes which are thought to play a role in the metastasis of cancer cells. It has been investigated in various malignant disorders.

Masitinib (rINN)

AB-1010; Masitinibum; Маситиниб.
4-[(4-Methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}phenyl)benzamide.
$C_{28}H_{30}N_6OS$=498.6
CAS — 790299-79-5.
ATC — L01XE22.
ATC Vet — QL01XE22.
UNII — M59NC4E26P.

Profile

Masitinib is a tyrosine kinase inhibitor active against c-kit and platelet-derived growth factor tyrosine kinases, that is under investigation for the treatment of malignancies such as gastrointestinal stromal tumours, pancreatic cancer, and multiple myeloma. It is also being investigated in inflammatory conditions such as asthma, mastocytosis, and rheumatoid arthritis.

Melphalan (BAN, USAN, rINN)

CB-3025; Melfalaani; Melfalan; Melfalán; Melphalanum; NSC-8806 (melphalan hydrochloride); PAM; Phenylalanine Mustard; Phenylalanine Nitrogen Mustard; L-Sarcolysine; WR-19813; Мелфалан.
4-Bis(2-chloroethyl)amino-L-phenylalanine.
$C_{13}H_{18}Cl_2N_2O_2$=305.2
CAS — 148-82-3 (melphalan); 3223-07-2 (melphalan hydrochloride).
ATC — L01AA03.
ATC Vet — QL01AA03.
UNII — Q41OR9510P.

NOTE. Merphalan (CB-3007; NSC-14210; sarcolysine) is the racemic form of melphalan; Medphalan (CB-3026; NSC-35051) is the D-isomer of melphalan.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Melphalan). A white or almost white, hygroscopic powder. Practically insoluble in water; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Store in airtight containers. Protect from light.

USP 36: (Melphalan). An off-white to buff powder with a faint odour. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol; soluble in dilute mineral acids. Store in airtight, glass containers. Protect from light.

Stability. A study of the stability of melphalan 40 and 400 micrograms/mL in infusion fluids reported that the time for a 10% loss of drug at 20 degrees in sodium chloride 0.9% injection was 4.5 hours, compared with 2.9 hours in lactated Ringer's injection, which has a considerably lower chloride ion content, and only 1.5 hours in glucose 5% injection.[1] At 25 degrees the corresponding figures were 2.4, 1.5, and 0.6 hours, and at 37 degrees they were 0.6, 0.4, and 0.3 hours. It was concluded that melphalan is sufficiently stable at 20 degrees in sodium chloride injection to permit infusion, but that increased temperature and decreased chloride ion concentration were associated with faster degradation rates.[1] Another study recommended that solutions of melphalan be handled at temperatures above 5 degrees for the minimum time but found that a solution containing 20 micrograms/mL in sodium chloride 0.9% could be stored for at least 6 months at -20 degrees without significant deterioration.[2] A more recent study, while recommending storage at 4 degrees between preparation and use of the infusion, considered that giving it at a room temperature of 20 degrees or below, and use of hypertonic (3%) saline as a diluent, would be sufficient to allow prolonged infusion.[3] The practicalities of such a procedure were not addressed.

1. Tabibi SE, Cradock JC. Stability of melphalan in infusion fluids. *Am J Hosp Pharm* 1984; **41:** 1380–2.
2. Bosanquet AG. Stability of melphalan solutions during preparation and storage. *J Pharm Sci* 1985; **74:** 348–51.
3. Pinguet F, *et al.* Effect of sodium chloride concentration and temperature on melphalan stability during storage and use. *Am J Hosp Pharm* 1994; **51:** 2701–4.

Uses and Administration

Melphalan is an antineoplastic that acts as a bifunctional alkylating agent. It is used mainly in the treatment of multiple myeloma. Melphalan has also been given to patients with carcinoma of the breast and ovary, neuroblastoma, Hodgkin's disease, and in polycythaemia vera, and has been given by intra-arterial regional perfusion for malignant melanoma and soft-tissue sarcomas. See also the cross-references given below. Melphalan is also used in the treatment of amyloidosis, see below.

Melphalan is usually given orally as a single daily dose or in divided doses; it is also given intravenously as the hydrochloride. Doses are calculated in terms of the base; 1.12 mg of melphalan hydrochloride is equivalent to about 1 mg of melphalan. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Frequent blood counts are essential and dosage should be adjusted according to haematological response. Therapy should be interrupted if the platelet or white cell count fall below acceptable levels (see also Bone-marrow Depression, p. 730.3). It should be given with great caution if the neutrophil count has recently been depressed by chemotherapy or radiotherapy.

Many conventional-dose regimens have been tried for the treatment of multiple myeloma and there is still uncertainty as to the best schedule. Melphalan is usually combined with corticosteroids. Licensed **oral** dosage regimens that have been used include:

- 150 micrograms/kg daily in divided doses for 4 days, repeated at 6-week intervals
- 150 micrograms/kg daily for 7 days followed by a rest period of at least 14 days, or as long as 5 to 6 weeks; a maintenance dose of 50 micrograms/kg daily or less is given when the white blood cells and platelet counts increase with further adjustments according to the blood count
- 250 micrograms/kg daily for 4 days *or* 200 micrograms/kg daily for 5 days, for a total dose per course of 1 mg/kg; the course is repeated at intervals of 4 to 6 weeks according to the blood count
- 6 mg daily for 2 to 3 weeks adjusted according to the blood count; treatment is then stopped for up to 4 weeks until the white blood cells and platelet counts increase, after which a maintenance dose of 2 mg daily may be started
- 10 mg daily for 7 to 10 days followed by a maintenance dose of 2 mg daily when the white blood cells and platelet counts exceed 4000 cells/mm^3 and 100 000 cells/mm^3, respectively; the dose should then be further adjusted to 1 to 3 mg daily, according to blood counts

For optimum effect, therapy is usually adjusted to produce a moderate leucopenia, with white cell counts in the range 3000 to 3500 cells/mm^3.

In the treatment of breast cancer, licensed doses of 150 micrograms/kg daily or 6 mg/m^2 daily for 5 days, repeated every 6 weeks have been used. Doses of 200 micrograms/kg daily for 5 days every 4 to 8 weeks may be given to patients with ovarian carcinoma.

In patients with polycythaemia vera, doses of 6 to 10 mg daily for 5 to 7 days, and then 2 to 4 mg daily, have been used for remission induction; a dose of 2 to 6 mg weekly has been used for maintenance.

Melphalan is also given **intravenously**; for ovarian adenocarcinoma a single dose of 1 mg/kg, repeated at 4-week intervals if the platelet and neutrophil counts permit, may be given as monotherapy. It can be infused in sodium chloride 0.9% or injected slowly into the tubing of a fast-running drip; when given by infusion the time from reconstitution of the solution to completion of infusion should not exceed 1.5 hours and prolonged infusions should be carried out with several batches of solution, each freshly prepared. In multiple myeloma, the licensed dose for use as a single agent is an intravenous dose of 400 micrograms/kg or 16 mg/m^2, infused over 15 to 20 minutes; the first 4 doses may be given at 2-week intervals, but further doses should be given at 4-week intervals depending on toxicity.

High-dose melphalan has been given intravenously in some malignancies: doses of 100 to 240 mg/m^2 have been licensed in neuroblastoma, and 100 to 200 mg/m^2 in multiple myeloma, generally followed by autologous stem cell rescue, which becomes essential where doses exceed 140 mg/m^2. High doses should be given through a central venous catheter.

Melphalan may be given by **regional arterial perfusion** in the management of melanoma and soft-tissue sarcomas. A typical dosage range for hyperthermic regional perfusion for upper extremity perfusions is 0.6 to 1 mg/kg, whereas for lower extremity perfusions doses of 0.8 to 1.5 mg/kg (in melanoma) or 1 to 1.4 mg/kg (in sarcoma) are typically used.

The dose of melphalan should be reduced in patients with **renal impairment** (see below).

Administration in the elderly. Higher toxicity, mainly myelosuppression, has been reported when melphalan is used in patients older than 70 years, but a review concluded that dose modification is not recommended on the basis of age alone.[1] Dose reduction of melphalan is recommended for declining renal function (see Administration in Renal Impairment, below).

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. The initial dose of intravenous melphalan should be reduced by about 50% in patients with renal impairment and dosage reduction should be considered when giving it orally. For high-dose intravenous melphalan regimens (melphalan 100 to 140 mg/m^2) given **without** stem cell rescue to patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min), UK licensed product information advises that the dose is also usually reduced by 50%.

High-dose intravenous melphalan (up to 200 mg/m^2) **with** stem cell rescue has been used successfully without dose reductions in patients with severe renal impairment (creatinine clearance less than 20 mL/min), including those on dialysis.[1]

1. Bird JM, *et al.* The clinical outcome and toxicity of high-dose chemotherapy and autologous stem cell transplantation in patients with myeloma or amyloid and severe renal impairment: a British Society of Blood and Marrow Transplantation study. *Br J Haematol* 2006; **134:** 385–90.

Amyloidosis. Amyloidosis refers to a group of conditions characterised by accumulation of a waxy proteinaceous infiltrate within body tissues.[1-3] They include:

- primary or AL amyloidosis, in which the amyloid is derived from immunoglobulin light chains
- ATTR amyloidosis (a familial form), in which amyloid is derived from transthyretin
- AA amyloidosis, which is most often secondary to chronic inflammation, such as that associated with rheumatoid arthritis, tuberculosis, or familial Mediterranean fever (p. 605.1)

Symptoms vary, depending on where the amyloid is deposited. The organs most commonly affected are the heart and kidneys. Renal amyloidosis can present as proteinuria, leading to nephrotic syndrome and renal failure. While renal disease is common in the AA and AL forms, it is less prevalent in ATTR amyloidosis, which commonly presents with neuropathy. Cardiac involvement, rare in AA amyloidosis, is variable in the ATTR form, and common in the AL form; it manifests as restrictive cardiomyopathy, leading to congestive heart failure. Painful peripheral sensory neuropathy and carpal tunnel syndrome also occur frequently. Amyloid deposition in the gastrointestinal tract can lead to malabsorption. Hepatomegaly is common. Macroglossia, due to deposition of amyloid in the tongue, occurs only in the AL form.[1,2]

Management depends to some extent upon the type of amyloidosis involved, and the site, but no drug or combination of drugs is unequivocally effective.

Liver transplantation is the definitive therapy for patients with ATTR amyloidosis.[1,4] Tafamidis meglumine is used for the treatment of ATTR amyloidosis in adult patients with symptomatic polyneuropathy to delay peripheral neurological impairment; it is used before liver transplantation.

Treatment for AA amyloidosis secondary to chronic inflammation is aimed at the underlying disease; immunosuppressants such as chlorambucil, cyclophosphamide, and methotrexate have been used, as well as inhibitors of tumour necrosis factor and interleukin-1 receptor antagonists.[5] Colchicine is effective in the treatment of AA amyloidosis complicating familial Mediterranean fever, but is not considered to be of benefit in other forms of amyloidosis.[1,6]

Melphalan plus prednisone or prednisolone has been shown to increase median survival in primary amyloidosis patients.[7] It is considered the treatment of choice in AL amyloidosis for patients in whom more intensive chemotherapy is not appropriate; evidence of benefit from the addition of a corticosteroid has not been evaluated and in some patients, it may be reasonable not to include a corticosteroid.[6] Melphalan, prednisone, and colchicine was found to be more effective than colchicine alone in the treatment of AL amyloidosis,[8] but a later study[9] found no benefit in adding colchicine to the standard therapy.

Addition of multiple alkylating agents such as vincristine, carmustine, and cyclophosphamide to the standard therapy[10] did not improve survival or response. Evidence to support the use of alkylating-based combination chemotherapy for primary amyloidosis is lacking.[6] Alternatively, cycles of vincristine, doxorubicin, and dexamethasone (VAD) may be effective, but patients with cardiac amyloidosis may be at increased risk of anthracycline toxicity.[11] In the UK, VAD is considered as first-line therapy in patients under the age of 70 years who do not have cardiac failure, autonomic neuropathy, or peripheral neuropathy.[6]

High-dose intravenous melphalan with autologous haematopoietic stem cell transplantation (HSCT) has been used;[12] it may result in complete remission of primary amyloidosis.[13-15] Some[1] consider it the treatment of choice, but while it may improve renal disease,[13] the therapy remains very toxic; patient selection on the basis of limited organ disease and no significant cardiac involvement may reduce morbidity and mortality.[6,14] The outcome of treatment with high-dose intravenous melphalan with

autologous HSCT was not superior to standard-dose oral melphalan plus oral dexamethasone in patients with newly diagnosed AL amyloidosis.[16]

High-dose dexamethasone or thalidomide may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those refractory to chemotherapy;[6] good results have been reported in patients with AL amyloidosis given a regimen combining cyclophosphamide with dexamethasone and thalidomide.[17] Local application or oral dosage of dimethyl sulfoxide, and 4′-iodo-4′-deoxydoxorubicin has been investigated.[1,11]

Symptomatic management is also important. Care must be taken to avoid digitalis toxicity when cardiac amyloid is present, as well as to avoid salt and water depletion through injudicious use of diuretics. Calcium-channel blockers and beta blockers should be avoided.[1] Renal transplantation may be considered in end-stage renal failure due to amyloidosis, but unless amyloid production has been stopped disease is likely to recur in the new kidney. Cardiac transplantation, and subsequent chemotherapy with epirubicin, carmustine, and cyclophosphamide to suppress the underlying disease and control amyloid deposition in the graft has also been described.[18]

Because amyloid deposits contain a plasma glycoprotein serum amyloid P component (SAP) that contributes to the stability of the deposits, and thus contributes to the pathogenesis of amyloidosis, future therapeutic approaches include the targeting of SAP to deplete it from the tissues and clear it from the plasma. Ro-63-8695 (CPHPC) is being investigated.[3,19] Eprodisate disodium is under investigation for AA amyloidosis.[20]

1. Khan MF, Falk RH. Amyloidosis. *Postgrad Med J* 2001; **77:** 686–93.
2. Falk RH, Skinner M. The systemic amyloidoses: an overview. *Adv Intern Med* 2000; **45:** 107–37.
3. Gillmore JD, Hawkins PN. Drug Insight: emerging therapies for amyloidosis. *Nat Clin Pract Nephrol* 2006; **2:** 263–70.
4. Suhr OB, *et al.* Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; **6:** 263–76.
5. Lachmann HJ, *et al.* Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356:** 2361–71.
6. British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. *Br J Haematol* 2004; **125:** 681–700. Also available at: http://www.bcshguidelines.com/pdf/ALamyloidosis_210604.pdf (accessed 07/03/06)
7. Gertz MA, Rajkumar SV. Primary systemic amyloidosis. *Curr Treat Options Oncol* 2002; **3:** 261–71.
8. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100:** 290–8.
9. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; **336:** 1202–7.
10. Gertz MA, *et al.* Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis. *J Clin Oncol* 1999; **17:** 262–7.
11. Sezer O, *et al.* New therapeutic approaches in primary systemic AL amyloidosis. *Ann Hematol* 2000; **79:** 1–6.
12. Sanchorawala V, Seldin DC. An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. *Amyloid* 2007; **14:** 261–9.
13. Dember LM, *et al.* Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. *Ann Intern Med* 2001; **134:** 746–53.
14. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002; **99:** 4276–82.
15. Skinner M, *et al.* High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004; **140:** 85–93.
16. Jaccard A, *et al.* Myélome Autogreffe (MAG) and Intergroupe Francophone du Myélome (IFM) Intergroup. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; **357:** 1083–93.
17. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109:** 457–64.
18. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309:** 1135–7.
19. Pepys MB, *et al.* Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* 2002; **417:** 254–9.
20. Dember LM, *et al.* Eprodisate for AA Amyloidosis Trial Group. Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; **356:** 2349–60.

Bone disorders, non-malignant. Fibrogenesis imperfecta ossium is a rare progressive bone disease in which disorders of bone collagen and mineralisation, and subsequent abnormal bone structure, result in bone pain and fractures. A patient responded to melphalan 10 mg and prednisolone 20 or 30 mg given daily, in 7-day courses every 2 months.[1,2] Another showed some improvement with intermittent 5-day courses of melphalan 10 mg daily and prednisolone 40 mg daily.[3] However, melphalan alone was reported to be ineffective in 2 other patients; both had bone-marrow depression.[3,4]

1. Stamp TCB, *et al.* Fibrogenesis imperfecta ossium: remission with melphalan. *Lancet* 1985; **i:** 582–3.
2. Ralphs JR, *et al.* Ultrastructural features of the osteoid of patients with fibrogenesis imperfecta ossium. *Bone* 1989; **10:** 243–9.
3. Carr AJ, *et al.* Fibrogenesis imperfecta ossium. *J Bone Joint Surg Br* 1995; **77:** 820–9.
4. Lafage-Proust M-H, *et al.* Fibrogenesis imperfecta ossium: ineffectiveness of melphalan. *Calcif Tissue Int* 1996; **59:** 240–4.

Malignant neoplasms. The important role played by melphalan in the management of multiple myeloma is discussed on p. 699.2. Melphalan is also used as part of salvage regimens for relapsed Hodgkin's disease (see p. 696.1), in ovarian cancer (p. 711.2), and for local perfusion of melanoma (p. 714.3).

Organ and tissue transplantation. Melphalan is used as part of non-myeloablative or reduced intensity conditioning regimens before haematopoietic stem cell transplantation, see p. 1937.1.

Adverse Effects and Treatment

For general discussions see Antineoplastics, p. 726.1 and p. 730.2.

The onset of neutropenia and thrombocytopenia is variable; the nadir of bone-marrow depression usually occurs at 2 to 3 weeks after starting treatment with melphalan, with recovery after 4 to 5 weeks.

Skin rashes and hypersensitivity reactions, including anaphylaxis, may occur. Cardiac arrest has been reported in association with such effects. Gastrointestinal disturbances may sometimes occur, particularly at high doses where diarrhoea, vomiting, and stomatitis may become dose-limiting. Haemolytic anaemia, vasculitis, pulmonary fibrosis, and hepatic disorders including hepatitis and jaundice have been reported. Suppression of ovarian function is common in premenopausal women; temporary or permanent sterility may occur in male patients. Extravasation of melphalan injection can cause skin ulceration and necrosis. As with other alkylating agents, melphalan also has carcinogenic, mutagenic, and teratogenic potential.

Mucositis. Amifostine has been shown to reduce the frequency and severity of melphalan-induced oral mucositis.[1]

1. Spencer A, *et al.* Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplant* 2005; **35:** 971–7.

Overdosage. A 12-month old child given melphalan 140 mg intravenously (a tenfold overdose) developed pronounced lymphopenia within 24 hours but had no other significant adverse effects until the seventh day, when neutropenia, thrombocytopenia, oral ulceration, and diarrhoea developed.[1] Bone marrow recovered within 40 days. Treatment was by vigorous hyperalimentation and close surveillance during this period and the patient subsequently remained well 9 months afterwards, without complications. Cases of intravenous melphalan overdose have also been reported in adults,[2] resulting in bone-marrow depression, haemorrhagic diarrhoea, and electrolyte disturbances. Bone-marrow depression has also been reported after cumulative oral doses of 360 mg over 3 weeks,[3] and 560 mg over 2 weeks.[4] Filgrastim was used in one of these cases to stimulate bone-marrow recovery.[4]

1. Coates TD. Survival from melphalan overdose. *Lancet* 1984; **ii:** 1048.
2. Jost LM. Überdosierung von Melphalan (Alkeran): Symptome und Behandlung: eine Übersicht. *Onkologie* 1990; **13:** 96–101.
3. Grimes DJ, *et al.* Complete remission of paraproteinaemia and neuropathy following iatrogenic oral melphalan overdose. *Br J Haematol* 1993; **83:** 675–7.
4. Jirillo A, *et al.* Accidental overdose of melphalan per os in a 69-year-old woman treated for advanced endometrial carcinoma. *Tumori* 1998; **84:** 611.

Precautions

For general discussions see Antineoplastics, p. 732.2.

Care is required in patients with impaired renal function.

Handling and disposal. *Urine and faeces* produced for up to 48 hours and 7 days respectively after an oral dose of melphalan should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies melphalan as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Use of nalidixic acid with high-dose intravenous melphalan in children has resulted in fatal haemorrhagic enterocolitis.

Ciclosporin. For reference to enhanced toxicity when melphalan was given with ciclosporin, see under Ciclosporin, p. 1957.2.

Food. The bioavailability of oral melphalan is significantly reduced, by up to 45%, by food. Some recommend that melphalan should not be taken with food, and that if dosage is switched from after to before food patients should be monitored for increased toxicity.[1]

1. Nathan C, Betmouni R. Melphalan: avoid with food. *Pharm J* 1996; **257:** 264.

Interferons. The fever induced by interferon alfa resulted in a reduction in the area under the plasma concentration-time curve for melphalan in a study of 10 patients, although the peak plasma concentration and time to peak concentration were not affected.[1] The effect was thought to represent increased chemical reactivity of melphalan at the elevated temperature.

1. Ehrsson H, *et al.* Oral melphalan pharmacokinetics: influence of interferon-induced fever. *Clin Pharmacol Ther* 1990; **47:** 86–90.

Pharmacokinetics

Absorption of melphalan from the gastrointestinal tract is variable; the mean bioavailability is reported to be 56% but it may range from 25 to 89%. Absorption is reduced by the presence of food (see above). On absorption it is rapidly distributed throughout body water with a volume of distribution of about 0.5 litres/kg, and has been reported to be inactivated mainly by spontaneous hydrolysis. About 60 to 90% is bound to plasma proteins, mainly albumin. The terminal plasma half-life of melphalan has been reported to be about 30 to 150 minutes. Melphalan is excreted in the urine, about 10% as unchanged drug.

References.
1. Nath CE, *et al.* Melphalan pharmacokinetics in children with malignant disease: influence of body weight, renal function, carboplatin therapy and total body irradiation. *Br J Clin Pharmacol* 2005; **59:** 314–24.
2. Nath CE, *et al.* Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol* 2007; **64:** 151–64.
3. Padussis JC, *et al.* Pharmacokinetics and drug resistance of melphalan in regional chemotherapy: ILP versus ILI. *Int J Hyperthermia* 2008; **24:** 239–49.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alkerana; Eriolan; Melfoma; ***Austral.***: Alkeran; ***Austria***: Alkeran; ***Belg.***: Alkeran; ***Braz.***: Alkeran; ***Canad.***: Alkeran; ***Chile***: Alkeran; ***China***: Alkeran (爱克兰); ***Cz.***: Alkeran; ***Denm.***: Alkeran; ***Fin.***: Alkeran; ***Fr.***: Alkeran; ***Ger.***: Alkeran; ***Gr.***: Alkeran; ***Hong Kong***: Alkeran; ***India***: Alkacel; Alkeran; Alphalan; ***Irl.***: Alkeran; ***Israel***: Alkeran; ***Ital.***: Alkeran; ***Malaysia***: Alkeran; ***Mex.***: Alkeran; ***Neth.***: Alkeran; ***Norw.***: Alkeran; ***NZ***: Alkeran; ***Philipp.***: Alkeran; ***Pol.***: Alkeran; ***Port.***: Alkeran; ***Rus.***: Alkeran (Алкеран); Sarcolysin (Сарколизин); ***S.Afr.***: Alkeran; ***Singapore***: Alkeran; ***Swed.***: Alkeran; ***Switz.***: Alkeran; ***Thai.***: Alkeran; ***Turk.***: Alkeran; ***UK***: Alkeran; ***USA***: Alkeran.

Pharmacopoeial Preparations
BP 2014: Melphalan Injection; Melphalan Tablets;
USP 36: Melphalan Tablets.

Mercaptopurine *(BAN, rINN)*

6MP; Mercaptopurin; Mercaptopurina; Mercaptopurinum; Mercaptopurinum Monohydricum; Merkaptopuriini; Merkaptopürin; Merkaptopurin; Merkaptopurin monohydrát; Merkaptopurinas; Merkaptopuryna; NSC-755; Purinethiol; WR-2785; Меркаптопурин.

6-Mercaptopurine monohydrate; Purine-6-thiol monohydrate; 1,7-Dihydro-6*H*-purine-6-thione monohydrate.

$C_5H_4N_4S,H_2O$=170.2

CAS — 50-44-2 (anhydrous mercaptopurine); 6112-76-1 (mercaptopurine monohydrate).

ATC — L01BB02.

ATC Vet — QL01BB02.

UNII — E7WED276I5 (mercaptopurine); PKK6MUZ20G (anhydrous mercaptopurine).

NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine and mercaptamine (formerly cysteamine, p. 2554.3) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Mercaptopurine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 36: (Mercaptopurine). A yellow, odourless or practically odourless, crystalline powder. Insoluble in water, in acetone, and in ether; soluble in hot alcohol and in dilute alkali solutions; slightly soluble in 2N sulfuric acid. Store in airtight containers. Protect from light.

Uses and Administration

Mercaptopurine is an antineoplastic that acts as an antimetabolite. It is an analogue of the natural purines hypoxanthine and adenine. After the intracellular conversion of mercaptopurine to active tioguanine nucleotides, including thioinosinic acid, it appears to have a variety of actions including interfering with nucleic acid synthesis. It also has immunosuppressant properties. Its actions are specific for cells in S phase.

Mercaptopurine is used, usually with other agents, in the treatment of leukaemia. It can be used for remission induction in acute lymphoblastic and myeloid leukaemias (p. 692.3 and p. 693.1, respectively) but other agents are generally preferred and its main use is in maintenance programmes, commonly with methotrexate. It may also be effective in chronic myeloid leukaemia (p. 694.2). There is cross-resistance between mercaptopurine and tioguanine (p. 872.1).

Mercaptopurine has been used for its immunosuppressant properties in the treatment of auto-immune disorders such as inflammatory bowel disease (see below for doses) but has been largely replaced by azathioprine.

Mercaptopurine is given orally usually as tablets; although oral suspensions are available, they are not bioequivalent to tablets and close haematological monitoring is advised when changing between formulations. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* The usual initial antineoplastic dose of mercaptopurine is 2.5 mg/kg or 50 to 75 mg/m^2 daily but dose and duration depend on the combination regimen used; dosage is adjusted according to individual response and tolerance. In maintenance schedules the dose may vary from 1.5 to 2.5 mg/kg daily. Blood counts should be taken daily during remission induction and weekly during maintenance; if there is a steep fall in the white cell count or severe bone-marrow depression mercaptopurine should be stopped immediately.

For dose reductions when mercaptopurine is used with allopurinol, see Interactions, below.

It has been used intravenously as mercaptopurine sodium. Thioinosine (mercaptopurine riboside) has also been used.

Administration in children. Mercaptopurine is given to children for the treatment of leukaemias in the same dose by weight or surface area as that used for adults (see Uses and Administration, above).

There is evidence[1] that the maintenance dosage of mercaptopurine should be tailored individually to achieve an appropriate systemic exposure in children with acute lymphoblastic leukaemia (although this would involve determining mercaptopurine pharmacokinetics in each child). Improvements in survival since 1980 may be associated with changes in the prescribing of mercaptopurine which have resulted in greater cumulative doses being given;[2] some children may have been undertreated in the past because of variations in the pharmacokinetics of mercaptopurine (particularly boys, who tolerate mercaptopurine better than girls,[3] but who have a poorer prognosis).[2] The concentration of tioguanine nucleotide metabolites in the erythrocytes has been shown to be directly related to the risk of relapse in children with acute lymphoblastic leukaemia.[4] Thiopurine methyltransferase (TPMT) activity (which results in methylation and inactivation of mercaptopurine rather than the formation of active nucleotides) may play a substantial role in this variation,[5] but titration of the dose of mercaptopurine until myelotoxicity occurs may prevent the problem:[2] despite gaps in therapy caused by more frequent drug withdrawal, it appears to result in greater accumulation of tioguanine nucleotides in the cells.[6] A pharmacokinetic model has been proposed as offering a more rational approach for mercaptopurine dosing in children, by taking into account body-surface as well as TPMT genotype.[7]

Mercaptopurine is also used for inflammatory bowel disease in children, see below.

1. Koren G, *et al.* Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *N Engl J Med* 1990; **323:** 17–21.
2. Hale JP, Lilleyman JS. Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. *Arch Dis Child* 1991; **66:** 462–6.
3. Lilleyman JS, *et al.* Childhood lymphoblastic leukaemia: sex difference in 6-mercaptopurine utilization. *Br J Cancer* 1984; **49:** 703–7.
4. Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet* 1994; **343:** 1188–90.
5. Lennard L, *et al.* Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet* 1990; **336:** 225–9.
6. Lennard L, *et al.* Mercaptopurine in childhood leukaemia: the effects of dose escalation on thioguanine nucleotide metabolites. *Br J Clin Pharmacol* 1996; **42:** 525–7.
7. Hawwa AF, *et al.* Population pharmacokinetic and pharmacogenetic analysis of 6-mercaptopurine in paediatric patients with acute lymphoblastic leukaemia. *Br J Clin Pharmacol* 2008; **66:** 826–37.

Administration in hepatic or renal impairment. Both UK and US licensed product information suggest that consideration be given to reducing the dosage of mercaptopurine in patients with hepatic or renal impairment, but no specific dose recommendations are given.

Inflammatory bowel disease. Mercaptopurine has been reported to be of benefit in ulcerative colitis[1,2] (although the quality of the evidence was considered low by a systematic review[3]) and Crohn's disease,[4-6] although azathioprine has generally been preferred (see p. 1945.1). Although unlicensed in the UK, the *BNF* and the *BNFC* state that mercaptopurine may be given to adults and children from 2 years of age for severe Crohn's disease or ulcerative colitis in an oral dose of 1 to 1.5 mg/kg once daily; in children up to 18 years of age an initial maximum of 50 mg daily is advised, increasing only up to 75 mg daily if necessary.

1. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; **85:** 717–22.
2. George J, *et al.* The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; **91:** 1711–14.
3. Timmer A, *et al.* Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 07/07/10).
4. Peyrin-Biroulet L, *et al.* Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2009; **104:** 2089–96.
5. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 07/07/10).
6. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 07/07/10).

Polymyositis. Mercaptopurine has been tried in a few patients with polymyositis but has not been formally assessed.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression with mercaptopurine, manifesting as leucopenia, thrombocytopenia, and anaemia, may be delayed; hypoplasia may occur. Mercaptopurine is less toxic to the gastrointestinal tract than the folic acid antagonists or fluorouracil but gastrointestinal disturbances may occur. Hepatotoxicity has been reported, with cholestatic jaundice and necrosis, sometimes fatal. Gastrointestinal and hepatic toxicity are reported to be more frequent in adults than in children, and are more likely at higher doses. Crystalluria with haematuria has been seen rarely as have skin disorders including hyperpigmentation. Fever may occur.

Mercaptopurine should be used with care in patients with impaired hepatic or renal function. Hepatic function should be monitored periodically.

Breast feeding. For information about the use of mercaptopurine during breast-feeding, see Azathioprine, p. 1946.3.

Effects on the blood. Measurement of the activity of thiopurine methyltransferase (TPMT) or the concentration of its substrate, tioguanine nucleotide, has been suggested as a way of predicting those individuals likely to have severe myelotoxicity with mercaptopurine and related drugs (see Azathioprine, p. 1946.2). Patients with an inherited deficiency of the TPMT enzyme may be at increased risk of myelosuppression from mercaptopurine. TPMT testing may be carried out in patients with evidence of toxicity; dose reductions should be considered in those with TPMT deficiency, although optimal initial doses have not been established for these patients. Tests for TPMT deficiency have not been shown to identify all patients at risk of severe toxicity; close monitoring of blood counts should still be performed.

Effects on the pancreas. Pancreatitis occurred in 13 of 396 patients given mercaptopurine for inflammatory bowel disease.[1] Symptoms resolved on withdrawal but recurred in 7 who were re-challenged with mercaptopurine or azathioprine. Acute pancreatitis has also been reported in 2 children given mercaptopurine during maintenance chemotherapy for acute lymphoblastic leukaemia.[2] They had also suffered pancreatitis from asparaginase during earlier therapy, and the authors suggested that subclinical damage to the pancreas by asparaginase may have been exacerbated by mercaptopurine, but also noted that most patients who develop asparaginase-induced pancreatitis receive mercaptopurine without developing this complication.

1. Present DH, *et al.* 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111:** 641–9.
2. Willert JR, *et al.* Recurrent mercaptopurine-induced acute pancreatitis: a rare complication of chemotherapy for acute lymphoblastic leukemia in children. *Med Pediatr Oncol* 2002; **38:** 73–4.

Handling and disposal. A method for the destruction of mercaptopurine or tioguanine in *wastes* by oxidation with potassium permanganate in sulfuric acid.[1] Residues produced by this method had no mutagenic activity. *Urine and faeces* produced for up to 48 hours and 5 days, respectively after a dose of mercaptopurine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Overdosage. Despite substantial overdose, no acute renal or hepatic toxicity occurred in 2 children. In one case, in which no specific detoxification measures were implemented, neutrophils reached a nadir on day 11 followed by a gradual recovery to normal by day 46. In the other case, gastric lavage was performed and activated charcoal was given; no evidence of neutropenia was seen. The authors recommended that management of acute accidental ingestion should include gastric lavage if the patient presents within 1 hour or if the amount ingested is large. Haemodialysis may be considered if the patient presents within 3 hours of ingestion. Liver function should be monitored. Severe myelosuppression may be managed with granulocyte colony-stimulating factor and a bone-marrow harvest may be of benefit if performed within several hours of the overdose.[1]

1. Chow LML, *et al.* Toxic ingestion of 6-mercaptopurine by young siblings of pediatric oncology patients. *J Pediatr* 2004; **144:** 669–71.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mercaptopurine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. For discussion of the safety of mercaptopurine in pregnancy, see Azathioprine, p. 1947.1.

Interactions

Mercaptopurine should be given with particular caution with other hepatotoxic drugs. Its effects are enhanced by allopurinol and the dose of mercaptopurine should be reduced to one-third to one-quarter of the usual dose when allopurinol is also given.

Allopurinol. Mercaptopurine plasma concentrations were markedly increased by allopurinol when mercaptopurine was given orally but not when it was given intravenously.[1] The results appear to indicate that allopurinol inhibits the first-pass metabolism of mercaptopurine.

The use of allopurinol to promote formation of 6-thioguanine nucleotides rather than 6-methylmercaptopurine nucleotides in patients with preferential metabolism via the latter has been investigated.[2,3]

1. Zimm S, *et al.* Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. *Clin Pharmacol Ther* 1983; **34:** 810–17.
2. Gerich ME, *et al.* A prospective evaluation of the impact of allopurinol in pediatric and adult IBD patients with preferential metabolism of 6-mercaptopurine to 6-methylmercaptopurine. *J Crohns Colitis* 2010; **4:** 546–52.
3. Gardiner SJ, *et al.* Allopurinol might improve response to azathioprine and 6-mercaptopurine by correcting an unfavorable metabolite ratio. *J Gastroenterol Hepatol* 2011; **26:** 49–54.

Anticoagulants. For reference to mercaptopurine diminishing the activity of *warfarin*, see p. 1532.2.

Antineoplastics. For a suggestion that *doxorubicin* might enhance the hepatotoxicity of mercaptopurine, see under Daunorubicin Hydrochloride, p. 779.3.

Giving mercaptopurine with low-dose oral *methotrexate* increased mean peak plasma concentrations of mercaptopurine by 26% compared with the same dose of mercaptopurine alone in a study in 14 patients with acute lymphoblastic leukaemia.[1] The effect was probably due to inhibition of the first-pass metabolism of mercaptopurine by methotrexate, which is a potent inhibitor of xanthine oxidase. In another study[2] of 10 children with acute lymphoblastic leukaemia, high-dose intravenous methotrexate (2 or 5 g/m^2) increased the peak plasma concentrations of mercaptopurine by 108 and 121% respectively. However, the clinical effect of this pharmacokinetic interaction is probably only minor because of the low, and highly variable, mercaptopurine bioavailability and the lack of correlation between mercaptopurine plasma concentrations and effect.[3] Mercaptopurine and methotrexate have been widely used in combination chemother-

apy regimens for acute lymphoblastic leukaemia for their synergistic pharmacodynamic interaction.

1. Balis FM, *et al*. The effect of methotrexate on the bioavailability of oral 6-mercaptopurine. *Clin Pharmacol Ther* 1987; **41:** 384–7.
2. Innocenti F, *et al*. Clinical and experimental pharmacokinetic interaction between 6-mercaptopurine and methotrexate. *Cancer Chemother Pharmacol* 1996; **37:** 409–14.
3. Giverhaug T, *et al*. The interaction of 6-mercaptopurine (6-MP) and methotrexate (MTX). *Gen Pharmacol* 1999; **33:** 341–6.

Azathioprine. For a report of a fatality when a patient was prescribed mercaptopurine and azathioprine by separate practitioners, see Interactions, under Azathioprine, p. 1947.2.

Gastrointestinal drugs. The enzyme thiopurine methyltransferase is inhibited *in vitro* by *sulfasalazine* and *mesalazine*, raising the possibility of an interaction in patients treated simultaneously with an aminosalicylate and a thiopurine such as mercaptopurine or azathioprine.[1] Myelotoxicity has been reported in a patient receiving mercaptopurine and *olsalazine*.[2] Similarly, severe pancytopenia has occurred in a 13-year-old boy when azathioprine was added to mesalazine therapy.[3] In a study[4] of 34 patients with Crohn's disease in which *balsalazide*, mesalazine, or sulfasalazine was added to established azathioprine or mercaptopurine therapy, mild leucopenia was common in patients given mesalazine or sulfasalazine, and whole blood concentrations of tioguanine nucleotide were found to be increased, probably due to thiopurine methyltransferase inhibition. These effects were not statistically significant in patients given balsalazide.

1. Szumlanski C, Weinshilboum RM. Sulfasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; **39:** 456–9.
2. Lewis LD, *et al*. Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. *Clin Pharmacol Ther* 1997; **62:** 464–75.
3. Chouraqui JP, *et al*. Azathioprine toxicity in a child with ulcerative colitis: interaction with mesalazine. *Gastroenterology* 1996; **110** (suppl): A883.
4. Lowry PW, *et al*. Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. *Gut* 2001; **49:** 656–64.

Pharmacokinetics

Mercaptopurine is variably and incompletely absorbed from the gastrointestinal tract; about 50% of an oral dose has been reported to be absorbed, but the absolute bioavailability is somewhat lower, probably due to gastrointestinal or first-pass metabolism, and is also subject to wide interindividual variation. Once absorbed it is widely distributed throughout body water and tissues. Plasma half-lives ranging from about 20 to 90 minutes have been reported after intravenous injection and the drug is not found in plasma after about 8 hours but this is of limited significance since mercaptopurine is activated intracellularly by conversion to nucleotide derivatives which persist for much longer. It is rapidly and extensively metabolised in the liver, by methylation and oxidation as well as by the formation of inorganic sulfates. Thiol methylation is catalysed by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. Patients with little or no detectable enzyme activity may accumulate excessive cellular concentrations of active tioguanine nucleotides, predisposing them to mercaptopurine toxicity. Considerable amounts of mercaptopurine are also oxidised to thiouric acid by the enzyme xanthine oxidase. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Mercaptopurine crosses the blood-brain barrier to some extent and is found in the CSF, but only in subtherapeutic concentrations.

Therapeutic drug monitoring. For a discussion of therapeutic drug monitoring for mercaptopurine, see under Azathioprine, p. 1947.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Puri-Nethol; Varimer; ***Austral.***: Puri-Nethol; ***Austria***: Puri-Nethol; ***Belg.***: Puri-Nethol; ***Braz.***: Puri-Nethol; ***Canad.***: Purinethol; ***Chile***: Puri-Nethol; ***Cz.***: Puri-Nethol; ***Denm.***: Xaluprine; ***Fr.***: Puri-Nethol; ***Ger.***: Puri-Nethol; ***Gr.***: Puri-Nethol; ***Hong Kong***: Puri-Nethol; ***India***: Empurine; Mercapto; Puri-Nethol; ***Irl.***: Puri-Nethol; ***Israel***: Puri-Nethol; ***Ital.***: Puri-Nethol; ***Mex.***: Puri-Nethol; ***Neth.***: Puri-Nethol; Xaluprine; ***Norw.***: Puri-Nethol; Xaluprine; ***NZ***: Puri-Nethol; ***Philipp.***: Capmerin; Empurine; Merpurin; Puri-Nethol; ***Rus.***: Puri-Nethol (Пури-нетол); ***S.Afr.***: Puri-Nethol; ***Singapore***: Puri-Nethol; Purinetone; ***Swed.***: Puri-Nethol; ***Switz.***: Puri-Nethol; ***Thai.***: Empurine†; Puri-Nethol; ***Turk.***: Puri-Nethol; ***UK***: Puri-Nethol†; Xaluprine; ***USA***: Purinethol.

Pharmacopoeial Preparations

BP 2014: Mercaptopurine Oral Suspension; Mercaptopurine Tablets;

USP 36: Mercaptopurine Tablets.

Methotrexate *(BAN, USAN, rINN)*

Amethopterin; Ametopterina; 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid; 4-Amino-10-methylfolic Acid; CL-14377; α-Methopterin; Methotrexat; Methotrexát; Méthotrexate; Methotrexatum; Metotreksaatti; Metotreksatas; Metotrexat; Metotrexát; Metotrexato; MTX; NSC-740; WR-19039; Метотрексат.

N-{4-[(2,4-Diamino-6-pteridinylmethyl)methylamino]benzoyl}-L-glutamic acid.

$C_{20}H_{22}N_8O_5$=454.4

CAS — 59-05-2.

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

UNII — YL5FZ2Y5U1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Methotrexate). A yellow or orange, hygroscopic, crystalline powder. It contains not more than 13% of water. Practically insoluble in water, in alcohol, and in dichloromethane; dissolves in dilute solutions of mineral acids and of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

USP 36: (Methotrexate). It is a mixture of 4-amino-10-methylfolic acid and closely related substances; it contains not less than 98% and not more than 102% of $C_{20}H_{22}N_8O_5$, calculated on the anhydrous basis. A yellow or orange-brown crystalline powder. It contains not more than 12% of water. Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. Store in airtight containers. Protect from light.

Methotrexate Sodium *(BANM, rINNM)*

Méthotrexate de Sodium; Methotrexate Disodium; Metotreksat Sodyum; Metotrexate sodium; Metotrexato disódico; Metotrexato sódico; Natrii Methotrexatum; Натрий Метотрексат.

$C_{20}H_{20}N_8Na_2O_5$=498.4

CAS — 7413-34-5 (methotrexate disodium); 15475-56-6 (methotrexate sodium, xNa).

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

UNII — 3IG1E710ZN.

Incompatibility. Methotrexate sodium has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate;[1] however, another study suggests it is compatible with fluorouracil.[2] Furthermore a mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25 degrees, although precipitation did occur on storage for several days.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Vincké BJ, *et al*. Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
3. Cheung Y-W, *et al*. Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Stability to light. Methotrexate undergoes photodegradation when stored in the light in diluted solutions, although undiluted commercial preparations are reported to show negligible photodegradation.[1] The bicarbonate ion catalyses this reaction and such admixtures should be avoided if possible, although they may be stable in light for 12 hours. Storage of solutions diluted in sodium chloride 0.9% injection in PVC bags was reported to protect against photodegradation although the length of the study was only 4 hours.[2] Photodegradation can take place under normal lighting, but is more rapid in direct sunlight, with about 11% drug loss from a 1 mg/mL solution after 7 hours; storage under normal lighting resulted in little change in drug concentration over 24 hours with a decrease of up to 12% by 48 hours.[3] Loss was greatest from unprotected polybutadiene tubing, with almost 80% drug loss in 48 hours.

1. Chatterji DC, Gallelli JF. Thermal and photolytic decomposition of methotrexate in aqueous solutions. *J Pharm Sci* 1978; **67:** 526–31.
2. Dyvik O, *et al*. Methotrexate in infusion solutions—a stability test for the hospital pharmacy. *J Clin Hosp Pharm* 1986; **11:** 343–8.
3. McElnay JC, *et al*. Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Uses and Administration

Methotrexate is an antimetabolite antineoplastic that acts as an antagonist of folic acid. It also has immunosuppressant properties. Within the cell, folic acid is reduced to dihydrofolic and then tetrahydrofolic acid. Methotrexate competitively inhibits the enzyme dihydrofolate reductase and prevents the formation of tetrahydrofolate which is necessary for purine and pyrimidine synthesis and consequently the formation of DNA and RNA. It is most active against cells in the S phase of the cell cycle. Folinic acid (the 5-formyl derivative of tetrahydrofolic acid) has been given after high doses to bypass the block in tetrahydrofolate production in normal cells and prevent the adverse effects of methotrexate. A suggested schedule for *folinic acid rescue* is described under Folinic Acid, p. 2067.1. (See also Treatment of Adverse Effects, p. 826.3). Methotrexate, in very high doses, followed by folinic acid rescue, is used in treating some malignant diseases.

Methotrexate is used in the management of acute lymphoblastic leukaemia. It is seldom used for the induction of remission but is employed in maintenance programmes and in the prophylaxis and treatment of meningeal leukaemia. It may be used for Burkitt's and other non-Hodgkin's lymphomas. In the solid neoplasms it is an important part of curative regimens for choriocarcinoma and other gestational trophoblastic tumours, and for the adjuvant therapy of osteosarcoma and breast cancer. It may also be used in other malignant neoplasms, see Malignant Neoplasms, p. 824.1.

Methotrexate is of value in the treatment of psoriasis but because of the risks associated with this use, it should only be given when the disease is severe and has not responded to other forms of treatment. It is widely used as a disease-modifying antirheumatic drug in rheumatoid arthritis. Methotrexate may be used to prevent graft-versus-host disease after bone marrow transplantation and may be used as a cytotoxic immunosuppressant and corticosteroid-sparing agent in non-malignant diseases.

Methotrexate has a role in the management of ectopic pregnancy (see p. 823.3) and in the termination of early pregnancy (see p. 824.3).

Methotrexate may be given *orally* as the base or the sodium salt, or by *injection* as the sodium salt. Doses are calculated in terms of methotrexate. Methotrexate sodium 16.5 mg is equivalent to about 15 mg of methotrexate. The doses and regimens used vary enormously, and may need to be adjusted according to bone marrow or other toxicity (see also under Bone-marrow Depression, p. 730.3). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Methotrexate regimens are often described as low-, moderate-, and high-dose, although what is meant by these terms may vary slightly. Some UK licensed product information has defined them as follows:

- low-dose: individual doses under 100 mg/m²
- moderate-dose: individual doses between 100 mg/m² and 1 g/m²
- high-dose: individual doses above 1 g/m²

Doses larger than 100 mg are usually given partly or wholly by intravenous infusion over not more than 24 hours.

Some common methotrexate doses are as follows:

For maintenance therapy in **acute lymphoblastic leukaemia**:

- 15 mg/m² orally or intramuscularly twice weekly
- 20 to 30 mg/m² orally or intramuscularly twice weekly
- 2.5 mg/kg intravenously every 14 days

For **meningeal leukaemia**:

- 12 mg/m² intrathecally once weekly for 2 weeks, then once monthly
- 200 to 500 micrograms/kg intrathecally at intervals of 2 to 5 days until the cell count of the CSF returns to normal; one additional dose is advised thereafter
- 12 mg intrathecally once weekly until the cell count of the CSF returns to normal; one additional dose is advised thereafter

For **Burkitt's lymphoma**:

- stages I to II: 10 to 25 mg orally daily for 4 to 8 days
- stage III (with other drugs): 0.625 to 2.5 mg/kg orally daily

In all stages, courses are usually repeated several times at intervals of 7 to 10 days.

For **lymphosarcoma**:

- (with other drugs): 0.625 to 2.5 mg/kg intravenously or intramuscularly daily

For **choriocarcinoma** and similar trophoblastic diseases:

- 15 to 30 mg orally or intramuscularly daily for 5 days, repeated after an interval of 1 week or longer, for 3 to 5 courses

For **osteosarcoma**:

- 8 to 12 g/m² intravenously once weekly, with folinic acid rescue

For **breast cancer**:
- (with cyclophosphamide and fluorouracil in the CMF regimen, see Table 1, p. 719) 40 mg/m² intravenously on days 1 and 8
- (with other drugs in cyclical regimens) 10 to 60 mg/m² intravenously

For **mycosis fungoides**:
- 2.5 to 10 mg orally daily for weeks or months, adjusted according to response and toxicity
- 50 mg intramuscularly weekly, as a single dose, or in two divided doses

For **psoriasis**:
- 10 to 25 mg orally, intramuscularly, or intravenously once weekly, adjusted according to response and toxicity; a suggested test dose in the range of 5 to 10 mg is recommended one week before the start of therapy
- 7.5 to 20 mg (increased as needed to a maximum of 25 to 30 mg) orally weekly, given as 3 divided doses over 24 hours, or as 3 divided doses at 12-hour intervals, or as 4 divided doses at 8-hour intervals; some suggest a test dose of 2.5 to 5 mg
- 2 to 5 mg (maximum 6.25 mg) orally daily for 5 days, followed by an interval of at least 2 days

For **rheumatoid arthritis**:
- 7.5 mg once weekly, given as a single oral, subcutaneous, intramuscular, or intravenous dose, or as 2.5 mg orally every 12 hours for 3 doses, adjusted according to response to a usual maximum of 20 mg weekly

In psoriasis and rheumatoid arthritis, once an adequate response is seen, the dose should be reduced to the lowest possible effective dose.

For doses in children, see below.

It is essential that blood counts and tests of renal and liver function should be made before, during, and after each course of treatment with methotrexate (see Precautions, p. 827.1). For further information on dosing in hepatic and renal impairment, see below.

Administration in children. Methotrexate is used in some countries for cancer chemotherapy in children, either alone or in combination regimens, and in juvenile idiopathic arthritis, for patients with active polyarticular rheumatoid disease.

For use in cancer chemotherapy such as for **acute lymphoblastic leukaemia** dosage is usually based on body-weight or body-surface in similar doses to those used in adults (see Uses and Administration, p. 822.3); alternatively, an oral or parenteral dose of methotrexate 15 mg/m² once weekly (with other drugs) has been suggested. For **meningeal leukaemia**, some UK licensed product information states that the dose of intrathecal methotrexate is constant regardless of age or body-surface in patients over the age of 3 years, and that those under 3 years be treated in accordance with combination chemotherapy protocols. For **non-Hodgkin's lymphoma** in children, methotrexate is given according to the disease phase and histological type; single intravenous doses range from 300 mg/m² to 5 g/m².

For juvenile **rheumatoid arthritis** the recommended starting oral or parenteral dose in the USA is 10 mg/m² once weekly. Dosage is adjusted gradually to achieve an optimal response. Children have been given doses up to 30 mg/m² weekly, but data are too limited to assess how doses over 20 mg/m² weekly might affect the risk of serious toxicity, although there is some suggestion that children given 20 to 30 mg/m² weekly (0.65 to 1 mg/kg weekly) may have better absorption and fewer gastrointestinal adverse effects if methotrexate is given either intramuscularly or subcutaneously. In the UK, methotrexate is licensed for children aged 3 to 16 years in the treatment of polyarticular juvenile idiopathic arthritis; a usual dose of 10 to 15 mg/m² once weekly by subcutaneous or intramuscular injection can be increased up to a maximum of 20 mg/m² once weekly. While stating that methotrexate is not licensed for use in children with other non-malignant conditions, the *BNFC* recommends a dose for juvenile idiopathic arthritis, juvenile dermatomyositis, vasculitis, uveitis, SLE, localised scleroderma, and sarcoidosis; children aged 1 month to 18 years may be given 10 to 15 mg/m² once weekly initially, increased if needed to a maximum of 25 mg/m² once weekly. Doses may be given orally, subcutaneously, or intramuscularly.

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. See also Neonates, under Benzyl Alcohol, p. 1741.1.

For **psoriasis**, although methotrexate is unlicensed in the UK for this use in children, the *BNFC* allows for specialist use in severe uncontrolled refractory disease. Children aged 2 to 18 years may be given an initial oral dose of 200 micrograms/kg (maximum 10 mg) once weekly, increased according to response to 400 micrograms/kg (maximum 25 mg) once weekly.

For suggested doses in the treatment of **Crohn's disease** in children, see Inflammatory Bowel Disease, p. 824.1.

Administration in the elderly. Licensed product information states that methotrexate should be used with extreme caution in the elderly, and that dosage reduction should be considered. Folate reserves are lower in older people and dosage reduction may be needed based on reduced liver and kidney function. Concomitant disease or drug therapy may contribute to these factors. There is some suggestion that adverse effects such as bone marrow suppression, thrombocytopenia, and pneumonitis may be increased in elderly patients.

A review[1] also states that increased toxicity has been seen in elderly patients given long-term low-dose methotrexate, and that half-life and clearance are significantly prolonged in older patients. A dose reduction based on renal function is recommended, and an alternative dosing formula using creatinine clearance (CC) has been proposed, namely:

adjusted dose = normal dose X CC / 70

See also Administration in Renal Impairment, below.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in hepatic impairment. Methotrexate is hepatotoxic, and liver function should be monitored during therapy (see Precautions, p. 827.1). Methotrexate should not be given to patients with severe or significant hepatic impairment, or to those with liver disease, including fibrosis, cirrhosis, or hepatitis. UK licensed product information for one injectable formulation (*Metoject; Medac, UK*) specifies that methotrexate should not be used if the bilirubin concentration is greater than 5 mg per 100 mL (85.5 micromoles/litre). Most UK licensed product information advises that methotrexate therapy be suspended for at least 2 weeks if substantial hepatic function abnormalities develop.

Administration in renal impairment. Methotrexate is renally excreted, and renal function should be monitored before, during, and after treatment. High-dose methotrexate therapy can affect the kidneys, and measures to prevent this may be required, see Effects on the Kidneys, p. 825.2.

Most UK licensed product information contra-indicates use in severe or significant renal impairment and states that doses of methotrexate should be reduced in patients with renal impairment, but gives no specific dose recommendations. However, licensed product information for one injectable formulation (*Metoject; Medac, UK*) gives the following recommendations based on creatinine clearance (CC):
- CC > 50 mL/min: 100% of the usual dose
- CC between 20 and 50 mL/min: 50% of the usual dose
- CC < 20 mL/min: use contra-indicated

Some advise adjustment of dose according to the CC and serum methotrexate concentrations. For a suggested dose in elderly patients based on CC, see Administration in the Elderly, above.

Asthma. Various immunosuppressants, including methotrexate, have been tried for their anti-inflammatory and corticosteroid-sparing properties in chronic asthma (p. 1195.2), but because of fears about toxicity are largely reserved for certain patients dependent upon systemic corticosteroids. Results of individual studies with methotrexate have been conflicting, but it appears that some patients may benefit from the corticosteroid-sparing effects of methotrexate.[1-5] However, some reviewers considered that the reduction in corticosteroid dose was insufficient to offset the adverse effects of methotrexate.[6] Methotrexate therapy must be given for at least 3 months for an adequate assessment of efficacy.

1. Shulimzon TR, Shiner RJ. A risk-benefit assessment of methotrexate in corticosteroid-dependent asthma. *Drug Safety* 1996; **15:** 283–90.
2. Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997; **112:** 29–33.
3. Corrigan CJ, *et al.* Methotrexate therapy of oral corticosteroid-dependent asthmatics reduces serum immunoglobulins: correlation with clinical response to therapy. *Clin Exp Allergy* 2005; **35:** 579–84.
4. Comet R, *et al.* Benefits of low weekly doses of methotrexate in steroid-dependent asthmatic patients: a double-blind, randomized, placebo-controlled study. *Respir Med* 2006; **100:** 411–19.
5. Domingo C, *et al.* Twelve years' experience with methotrexate for GINA treatment step 5 asthma patients. *Curr Med Res Opin* 2009; **25:** 367–74.
6. Davies H, *et al.* Methotrexate as a steroid sparing agent for asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 12/05/05).

Connective tissue and muscular disorders. Reports in a limited number of patients indicate that methotrexate given once weekly in low to moderate doses may be of benefit in patients with SLE (p. 1613.3), with benefit reported particularly for joint and mucocutaneous symptoms.[1,2] In a retrospective analysis of patients with cutaneous lupus erythematosus, low doses of methotrexate significantly decreased disease activity.[3]

Methotrexate therapy has been investigated for its potential corticosteroid-sparing properties in polymyalgia rheumatica (p. 1610.3). Different regimens have been tried and although one study[4] reported benefit, others[5,6] found no evidence of clinical efficacy or a corticosteroid-sparing effect. Guidelines from the 3E Initiative[2] considered it effective and recommended its use as a corticosteroid-sparing agent in polymyalgia rheumatica and giant-cell arteritis.

Methotrexate is widely used in rheumatoid arthritis (see p. 824.2) and in polymyositis (p. 1611.1), and has been tried in Cogan's syndrome (p. 1603.2).

1. Sato EI. Methotrexate therapy in systemic lupus erythematosus. *Lupus* 2001; **10:** 162–4.
2. Visser K, *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; **68:** 1086–93.
3. Wenzel J, *et al.* Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol* 2005; **153:** 157–62.
4. Ferraccioli G, *et al.* Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol* 1996; **23:** 624–8.
5. Feinberg HL, *et al.* The use of methotrexate in polymyalgia rheumatica. *J Rheumatol* 1996; **23:** 1550–2.
6. van der Veen MJ, *et al.* Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis* 1996; **55:** 218–23.

Ectopic pregnancy. Ectopic pregnancy occurs when the fertilised ovum implants outside the uterus, usually in the fallopian tube itself (tubal pregnancy). Earlier detection has become possible due to improved diagnostic techniques. In many countries, there has been a rise in the rate of ectopic pregnancies followed by a decline; this may be partly due to increasing rates of infection with *Chlamydia*, followed by the effect of prevention, and changes in the popularity of intra-uterine devices.[1] Although ectopic pregnancies may spontaneously abort early, without clinical sequelae, the potential adverse effects are serious, ranging from pelvic pain and bleeding at 5 to 6 weeks of gestation (indistinguishable from spontaneous abortion), to potentially fatal intra-abdominal haemorrhage later in the course of an otherwise asymptomatic pregnancy.

Laparoscopic surgery remains the standard treatment.[1-4] In some countries non-surgical methods are increasing in popularity because of earlier diagnosis.[1,5] Perhaps the most experience of the latter has been with methotrexate. Management with intramuscular methotrexate may be appropriate for selected women with small unruptured tubal pregnancies who are haemodynamically stable, have low serum-chorionic gonadotrophin concentrations, and lack contra-indications to methotrexate use.[2-7] Surgery is preferred where there is cardiac activity in the conceptus, since a living embryo increases resistance to methotrexate.[6,7] Two regimens of intramuscular methotrexate have been described. A multiple-dose regimen of 1 mg/kg on 4 alternate days, with folinic acid rescue,[1] has similar efficacy to surgery.[3] A single dose of 50 mg/m² can be used instead[1,5] but systematic reviews have indicated that it has a higher failure rate than surgery[3,8] and about 20% of patients will require more than one cycle of treatment.[5] Some suggest that it is best reserved for women with serum-chorionic gonadotrophin concentrations below 1.5 units/mL.[4] The addition of an oral dose of mifepristone to single-dose methotrexate has been investigated[1,9,10] and may reduce treatment failure rates.

Methotrexate has been given by local injection directly into the ectopic (salpingocentesis). Doses of 1 mg/kg or 50 mg have been used[11] but this technique is significantly less successful than surgery.[3] Systemic methotrexate (with folinic acid rescue) has also been reported to be effective in resolving persistent ectopic pregnancy unsuccessfully treated with surgery.

The role of other agents in the management of ectopic pregnancy is less well established. Local instillation of glucose 50% by salpingocentesis has also been used in the treatment of ectopic pregnancy,[11,12] but one study was stopped because of a higher failure rate with glucose treatment compared with local methotrexate.[13]

Methotrexate may also be used in the termination of early uterine pregnancy (see p. 824.3).

1. Farquhar CM. Ectopic pregnancy. *Lancet* 2005; **366:** 583–91.
2. Tay JI, *et al.* Ectopic pregnancy. *BMJ* 2000; **320:** 916–9. Correction. *ibid.*; **321:** 424.
3. Hajenius PJ, *et al.* Interventions for tubal ectopic pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 19/05/08).
4. Mol F, *et al.* Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. *Hum Reprod Update* 2008; **14:** 309–19.
5. Lipscomb GH, *et al.* Nonsurgical treatment of ectopic pregnancy. *N Engl J Med* 2000; **343:** 1325–9.
6. Lipscomb GH, *et al.* Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999; **341:** 1974–8.
7. American College of Obstetricians and Gynecologists. ACOG practice bulletin: medical management of tubal pregnancy. Number 3, December 1998. *Int J Gynecol Obstet* 1999; **65:** 97–103.

8. Parker J, *et al.* A systematic review of single-dose intramuscular methotrexate for the treatment of ectopic pregnancy. *Aust N Z J Obstet Gynaecol* 1998; **38:** 145–50.
9. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; **13:** 1987–90.
10. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; **179:** 640–3.
11. Natofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; **42:** 39–47.
12. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; **76:** 797–800.
13. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; **265:** 82–4.

Inflammatory bowel disease. Methotrexate (given intramuscularly once weekly in a dose of 25 mg) was reported to improve symptoms and reduce corticosteroid requirements in a large controlled study in patients with chronic active *Crohn's disease*.[1] Those patients who were in remission after 16 weeks of methotrexate treatment were entered into a further placebo-controlled study[2] of methotrexate 15 mg weekly by intramuscular injection. During 40 weeks of follow-up, a higher proportion of patients receiving methotrexate remained in remission, and had fewer relapses. Smaller studies have also reported modest benefit for oral methotrexate 12.5 to 22.5 mg/week in chronic active disease.[3,4] Subcutaneous methotrexate has also been used.[5] A review[6] concluded that low-dose methotrexate could be recommended for induction of remission and for its corticosteroid-sparing effect in refractory and corticosteroid-dependent Crohn's disease, although the precise indications, dose, and route for its use were still unclear.

Although methotrexate is unlicensed in the UK for Crohn's disease, the *BNF* suggests the following doses in adults over 18 years of age with severe disease:

- induction of remission: 25 mg intramuscularly once weekly
- maintenance of remission: 10 to 25 mg orally once weekly, or 15 mg intramuscularly once weekly

The *BNFC* suggests the following doses for children aged 7 to 18 years:

- induction of remission: 15 mg/m² (maximum 25 mg) once weekly, by subcutaneous or intramuscular injection
- maintenance of remission: 15 mg/m²(maximum 25 mg) once weekly, either orally or by subcutaneous or intramuscular injection; the dose is reduced according to response to the lowest effective dose

The value of methotrexate in *ulcerative colitis* is doubtful: although benefits have been seen in some patients,[5,7] a study in active ulcerative colitis found no significant differences between oral methotrexate 12.5 mg/week and placebo.[8] For a discussion of inflammatory bowel disease, see p. 1811.3.

1. Feagan BG, *et al.* Methotrexate for the treatment of Crohn's disease. *N Engl J Med* 1995; **332:** 292–7.
2. Feagan BG, *et al.* A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *N Engl J Med* 2000; **342:** 1627–32.
3. Oren R, *et al.* Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; **92:** 2203–9.
4. Arora S, *et al.* Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46:** 1724–9.
5. Egan LJ, *et al.* A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 1999; **13:** 1597–1604.
6. Egan LJ, Sandborn WJ. Methotrexate for inflammatory bowel disease: pharmacology and preliminary results. *Mayo Clin Proc* 1996; **71:** 69–80.
7. Kozarek RA. Methotrexate for refractory Crohn's disease: preliminary answers to definitive questions. *Mayo Clin Proc* 1996; **71:** 104–5.
8. Oren R, *et al.* Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; **110:** 1416–21.

Malignant neoplasms. Methotrexate is extensively used in the management of malignant disease. In acute lymphoblastic leukaemia it is used for maintenance therapy, and intrathecally for prophylaxis of CNS relapse, as discussed on p. 692.3, while it also forms part of several regimens used for non-Hodgkin's lymphomas such as Burkitt's lymphoma (p. 697.3), mycosis fungoides (p. 698.3) and those associated with AIDS (p. 697.2). In the solid neoplasms it is an important part of curative regimens for gestational trophoblastic tumours (p. 691.2), the adjuvant therapy of osteosarcoma (p. 717.3) and is used in regimens for tumours of the bladder (p. 700.2), brain (p. 701.2), breast (p. 702.1), stomach (p. 706.1), and head and neck (p. 708.1).

Multiple sclerosis. Results suggest that oral methotrexate 7.5 mg weekly may be of benefit[1] in slowing the progression of multiple sclerosis (p. 996.3). Although the results of studies of immunosuppressant therapy in this condition have tended to be disappointing, it has been pointed out that benefit was assessed differently in the methotrexate study,[2] which may have a bearing on its more favourable conclusions.

1. Goodkin DE, *et al.* Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol* 1995; **37:** 30–40.
2. Whitaker JN, *et al.* Clinical outcomes and documentation of partial beneficial effects of immunotherapy for multiple sclerosis. *Ann Neurol* 1995; **37:** 5–6.

Myasthenia gravis. Methotrexate has been tried in the management of myasthenia gravis (p. 684.1) in patients who require immunosuppression but are intolerant of or unresponsive to corticosteroids and azathioprine.

Organ and tissue transplantation. For reference to the use of methotrexate (usually with ciclosporin) in bone marrow transplantation, see Haematopoietic Stem Cell Transplantation, p. 1937.1.

Primary biliary cirrhosis. Like other drugs used for primary biliary cirrhosis (p. 2638.3) methotrexate has been associated with biochemical improvement but evidence of clinical and in particular histological improvement is harder to show, and the toxicity of immunosuppressants such as methotrexate is problematic. A randomised study comparing methotrexate with colchicine found a slightly lower survival with methotrexate after 10 years of treatment;[1] a systematic review[2] concluded that methotrexate had no effect on mortality or the need for liver transplantation in patients with primary biliary cirrhosis and that there was no evidence to support its use.

1. Kaplan MM, *et al.* A randomized controlled trial of colchicine plus ursodiol versus methotrexate plus ursodiol in primary biliary cirrhosis: ten-year results. *Hepatology* 2004; **39:** 915–23.
2. Giljaca V, *et al.* Methotrexate for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 07/07/10).

Psoriatic arthritis. Methotrexate may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p. 14.3) when the arthritis is not controlled by physical therapy and NSAIDs, although toxicity may limit long-term use in some patients.

Retroperitoneal fibrosis. There are reports[1,2] of success with low-dose weekly methotrexate in the treatment of retroperitoneal fibrosis (p. 1612.1); corticosteroids were also given, but tapered off in one case.[1]

1. Scavalli AS, *et al.* Long-term follow-up of low-dose methotrexate therapy in one case of idiopathic retroperitoneal fibrosis. *Clin Rheumatol* 1995; **14:** 481–4.
2. Vaglio A, *et al.* Post-treatment residual tissue in idiopathic retroperitoneal fibrosis: active residual disease or silent "scar" ? A study using ^{18}F-fluorodeoxyglucose positron emission tomography. *Clin Exp Rheumatol* 2005; **23:** 231–4.

Rheumatoid arthritis. Therapy of rheumatoid arthritis (p. 13.2) is conventionally begun with an analgesic and an NSAID for symptomatic relief, to which a disease-modifying antirheumatic drug (DMARD) is subsequently added in an attempt to retard the disease process. It is now clear that irreversible joint damage commonly occurs in early disease and rheumatologists now generally add the DMARD shortly after rheumatoid arthritis has been diagnosed. Methotrexate is widely used,[1] and is the DMARD of first choice in many patients. Systematic review has confirmed that methotrexate has significant benefit in the short-term treatment of the disease.[2] Multinational recommendations for its use[3] produced by the 3E Initiative included beginning oral therapy at 10 to 15 mg weekly and increasing this dose by 5 mg every 2 to 4 weeks up to a maximum of 20 to 30 mg weekly (this is somewhat higher than the licensed doses recommended in Uses and Administration, p. 822.3); the Initiative also considered that at least 5 mg of folic acid weekly should be given as a supplement. These recommendations considered that monotherapy was preferable to combination of methotrexate with other DMARDs in DMARD-naive patients,[3] with methotrexate-based combinations used when monotherapy was ineffective. Methotrexate has been tried with ciclosporin, hydroxychloroquine and sulfasalazine, leflunomide, etanercept, and infliximab. Studies have shown improved responses to these combinations compared with methotrexate alone, but long-term efficacy and safety has not been studied.[4] For debate on the value of initial combination therapy versus monotherapy see p. 13.2. A randomised controlled study[5] found that subcutaneous methotrexate was significantly more effective than the same dose of oral methotrexate in patients with active rheumatoid arthritis.

Methotrexate may be of benefit[6-8] in juvenile idiopathic arthritis (p. 12.1): for doses, see Administration in Children, p. 823.1.

Methotrexate may also be of value in the management of associated uveitis (see p. 825.1).

1. Anonymous. Modifying disease in rheumatoid arthritis. *Drug Ther Bull* 1998; **36:** 3–6.
2. Suarez-Almazor ME, *et al.* Methotrexate for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 15/10/09).
3. Visser K, *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; **68:** 1086–93.
4. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001; **134:** 695–706.
5. Braun J, *et al.* MC-MTX.6/RH Study Group. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; **58:** 73–81.
6. Ravelli A, *et al.* Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. *J Pediatr* 1998; **133:** 262–5.
7. Takken T, *et al.* Methotrexate for treating juvenile idiopathic arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 15/10/09).
8. Ramanan AV, *et al.* Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; **88:** 197–200.

Sarcoidosis. Where therapy is required for sarcoidosis (p. 1612.2) corticosteroids are the first choice of drug; methotrexate is one of the preferred second-line immunosuppressants.

References.
1. Webster GF, *et al.* Methotrexate therapy in cutaneous sarcoidosis. *Ann Intern Med* 1989; **111:** 538–9.
2. Soriano FG, *et al.* Neurosarcoidosis: therapeutic success with methotrexate. *Postgrad Med J* 1990; **66:** 142–3.
3. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; **155:** 846–51.
4. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999; **54:** 742–6.

Scleroderma. There is some evidence of benefit with methotrexate in patients with scleroderma (p. 1942.3), particularly for cutaneous symptoms, although not all studies have shown clear value.

References.
1. van den Hoogen FH, *et al.* Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996; **35:** 364–72.
2. Seyger MMB, *et al.* Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol* 1998; **39:** 220–5.
3. Uziel Y, *et al.* Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; **136:** 91–5.
4. Pope JE, *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; **44:** 1351–8.
5. Weibel L, *et al.* Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol* 2006; **155:** 1013–20.

Skin disorders, non-malignant. Methotrexate is widely used in the treatment of severe refractory psoriasis. As discussed on p. 1688.1 the aim of such therapy is to bring the disease under control, enabling a return to other therapy. For use in psoriatic arthritis see above. Methotrexate is also used with corticosteroids in the management of pemphigus and pemphigoid (p. 1687.1).

Termination of pregnancy. Methotrexate has been investigated as an alternative to mifepristone for use with misoprostol for the termination of early pregnancy (p. 2131.3). Intramuscular methotrexate followed 3 days later by intravaginal misoprostol was more effective than misoprostol alone for termination at 56 days or less;[1] the combination was reported to be less successful after 57 to 63 days of gestation.[2] Later studies[3,4] however found the combination to be safe and effective in terminating pregnancies up to 63 days of gestation; in these the misoprostol was given up to 7 days after the methotrexate. Oral methotrexate is also effective.[5-7] However, the efficacy of methotrexate followed by misoprostol does appear to diminish with increasing gestational age,[8] and the time to complete abortion generally takes longer with regimens using methotrexate compared with mifepristone.[9] The American College of Obstetricians and Gynecologists[10] recommends that methotrexate with misoprostol may be used in pregnancies of up to 49 days of gestation, the usual regimen being methotrexate, either 50 mg/m² intramuscularly or 50 mg orally, followed 3 to 7 days later by misoprostol 800 micrograms vaginally. The College also advises that it may take up to 4 weeks for complete abortion to occur in about 15 to 25% of women given such regimens.

For the role of methotrexate in the management of ectopic pregnancy, see p. 823.3.

1. Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion: a randomized controlled trial. *JAMA* 1994; **272:** 1190–5.
2. Creinin MD. Methotrexate and misoprostol for abortion at 57-63 days gestation. *Contraception* 1994; **50:** 511–15.
3. Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. *N Engl J Med* 1995; **333:** 537–40.
4. Creinin MD, *et al.* A randomized trial comparing misoprostol three and seven days after methotrexate for early abortion. *Am J Obstet Gynecol* 1995; **173:** 1578–84.
5. Creinin MD. Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1996; **54:** 15–18.
6. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90:** 611–16.
7. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; **57:** 83–8.

8. Creinin MD, *et al.* Methotrexate and misoprostol for early abortion: a multicenter trial. *Contraception* 1996; **53:** 321–7.
9. Wiebe E, *et al.* Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002; **99:** 813–19.
10. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, October 2005). *Obstet Gynecol* 2005; **106:** 871–82.

Uveitis. Methotrexate has been reported to be safe and effective[1-3] when used to treat uveitis (p. 1615.1) in small numbers of patients.

1. Samson CM, *et al.* Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. *Ophthalmology* 2001; **108:** 1134–9.
2. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005; **32:** 362–5.
3. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol* 2005; **89:** 806–8.

Vasculitic syndromes. In giant cell arteritis (p. 1604.2), improved clinical response and a corticosteroid-sparing effect have been reported with the addition of methotrexate to corticosteroid therapy,[1] but other studies using different designs and dosages[2,3] have failed to find any benefit. Guidelines from the 3E Initiative[4] considered it effective and recommended its use as a corticosteroid-sparing agent in polymyalgia rheumatica and giant-cell arteritis. For the use of methotrexate in Takayasu's arteritis and Wegener's granulomatosis see p. 1614.3 and p. 1615.2, respectively.

1. Jover JA, *et al.* Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; **134:** 106–14.
2. Spiera RF, *et al.* A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; **19:** 495–501.
3. Hoffman GS, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; **46:** 1309–18.
4. Visser K, *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; **68:** 1086–93.

Adverse Effects

For general discussions see Antineoplastics, p. 726.1.

The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may show an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death.

Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given. Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors it is teratogenic, and it has been associated with fetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned (see Carcinogenicity, below).

Carcinogenicity. There are reports of lymphomas associated with low-dose methotrexate therapy for rheumatic disorders,[1-4] which in some cases have been associated with concomitant Epstein-Barr virus infection.[2] Transitional cell bladder cancer has also been associated with such therapy.[5] However, a retrospective analysis involving 16 263 patients with rheumatoid arthritis found no evidence of a relationship between the use of methotrexate as an antirheumatic and the development of haematological malignancy.[6] Nonetheless, the spontaneous remission of lymphoma after withdrawal of methotrexate in some patients seems to support an association[7] A later prospective study[8] of all new cases of lymphoma, detected over 3 years in patients treated with methotrexate for rheumatoid arthritis, also found a higher incidence of Hodgkin's disease compared with the general population. An Australian cohort study[9] in rheumatoid arthritis patients treated with methotrexate found an overall increased incidence of malignancy with a fivefold increased risk of non-Hodgkin's lymphoma, a threefold increased risk of lung cancer, and a threefold increased risk of melanoma relative to the general population. Further investigation was considered necessary to determine whether the findings with respect to melanoma were unique to Australia and what role methotrexate, immunosuppression, and environmental factors such as exposure to UV radiation have in the development thereof. The carcinogenic risk with antimetabolites such as methotrexate has generally been considered less than with alkylating agents (p. 726.2).

1. Zimmer-Galler I, Lie JT. Choroidal infiltrates as the initial manifestation of lymphoma in rheumatoid arthritis after treatment with low-dose methotrexate. *Mayo Clin Proc* 1994; **69:** 258–61.
2. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; **328:** 1317–21.
3. Viraben R, *et al.* Reversible cutaneous lymphoma occurring during methotrexate therapy. *Br J Dermatol* 1996; **135:** 116–18.
4. Ebeo CT, *et al.* Methotrexate-induced pulmonary lymphoma. *Chest* 2003; **123:** 2150–3.
5. Millard RJ, McCredie S. Bladder cancer in patients on low-dose methotrexate and corticosteroids. *Lancet* 1994; **343:** 1222–3.
6. Moder KG, *et al.* Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: a retrospective study. *Am J Med* 1995; **99:** 276–81.
7. Georgescu L, Paget SA. Lymphoma in patients with rheumatoid arthritis: what is the evidence of a link with methotrexate? *Drug Safety* 1999; **20:** 475–87.
8. Mariette X, *et al.* Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002; **99:** 3909–15.
9. Buchbinder R, *et al.* Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 2008; **59:** 794–9.

Effects on the blood. Although serious and sometimes fatal blood dyscrasias are a well-known consequence of high-dose methotrexate therapy the UK CSM[1] stated in September 1997 that it was also aware of 83 reports of blood dyscrasias associated with low-dose methotrexate used to treat psoriasis or rheumatoid arthritis; there were 36 fatalities. Many of the cases had contributing factors such as advanced age, renal impairment, or use with interacting drugs.

1. CSM/MCA. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232406&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

MEGALOBLASTIC ANAEMIA. Megaloblastic anaemia, usually with marked macrocytosis, has been reported in mainly elderly patients given long-term weekly methotrexate therapy.[1-3] It has been suggested that therapy should be withdrawn if the mean corpuscular volume exceeds 106 femtolitres.[1] Symptoms appear to be associated with folate depletion by methotrexate,[2,4,5] probably due to increased excretion,[6] and in one case megaloblastic anaemia developed after starting a weight-reducing diet poor in folate.[4] Folate supplementation, conversely, may permit continuation of methotrexate therapy with resolution of the anaemia.[5]

1. Dodd HJ, *et al.* Megaloblastic anaemia in psoriatic patients treated with methotrexate. *Br J Dermatol* 1985; **112:** 630.
2. Dahl MGC. Folate depletion in psoriatics on methotrexate. *Br J Dermatol* 1984; **111** (suppl 26): 18.
3. Casserly CM, *et al.* Severe megaloblastic anemia in a patient receiving low-dose methotrexate for psoriasis. *J Am Acad Dermatol* 1993; **29:** 477–80.
4. Fulton RA. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; **114:** 267–8.
5. Oxholm A, Thomsen K. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; **114:** 268–9.
6. Duhra P, *et al.* Intestinal folate absorption in methotrexate treated psoriatic patients. *Br J Dermatol* 1988; **119:** 327–32.

Effects on the gastrointestinal tract. Although gastrointestinal toxicity is well recognised as an effect of high-dose regimens, oral ulceration has also been reported after low-dose (weekly) methotrexate use.[1,2] In some instances it was related to overdosage; symptoms resolved upon correction of the dose and with folate supplementation.[1] Folate deficiency may increase the oral toxicity of methotrexate, and folate supplementation may also avoid the need to stop low-dose methotrexate.[2]

1. Deeming GMJ, *et al.* Methotrexate and oral ulceration. *Br Dent J* 2005; **198:** 83–5.
2. Kalantzis A, *et al.* Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100:** 52–62.

Effects on the kidneys. High-dose methotrexate therapy can result in supersaturation of the urine with methotrexate and its metabolites leading to crystal formation.[1] These crystals can cause intrarenal obstruction and are a factor in the development of acute renal failure. Risk factors for crystal formation are acid urine, volume depletion, and renal impairment. Adequate hydration, and urinary alkalinisation with sodium bicarbonate or acetazolamide play an important role in minimising nephrotoxicity in high-dose methotrexate regimens. A study found that the incidence of severe toxicity was reduced in patients given greater hydration and alkalinisation. However, this more intensive hydration regimen also significantly lowered methotrexate plasma concentrations.[2] Glucarpidase, a recombinant glutamate carboxypeptidase, is used in the management of methotrexate-induced renal dysfunction when methotrexate concentrations are very high (see Treatment of Adverse Effects, p. 826.3).[3]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; **106:** 459–65.
2. Christensen ML, *et al.* Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. *J Clin Oncol* 1988; **6:** 797–801.
3. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist* 2006; **11:** 694–703.

Effects on the liver. Methotrexate is well established as a cause of hepatotoxicity, including periportal fibrosis, when given in relatively high doses as an antineoplastic, and it has become clear that its long-term use in lower doses for disorders such as psoriasis and rheumatoid arthritis can also be associated with liver toxicity.[1,2] There has been some difficulty in these patients in distinguishing the effects of the drug from the effects of the disease, but there is good evidence that the risk is increased in patients given doses on a daily rather than a weekly regimen, and in those with a high alcohol intake.[1] Pre-existing liver disease, obesity (especially if associated with diabetes mellitus), renal impairment, and increasing total cumulative dose may also increase the risk of hepatotoxicity.[1] A lower incidence of hepatotoxicity in patients with rheumatoid arthritis (compared with older studies in patients with psoriasis) may be due to improved dosage regimens and greater awareness of the risks.[1]

In order to minimise the risks of serious liver damage various guidelines and recommendations have been issued for the use of methotrexate in psoriasis and rheumatoid arthritis, and the appropriate monitoring.

- For patients with *psoriasis*, 1988 US guidelines[3] recommended a liver biopsy at the beginning of treatment and after each cumulative dose of 1 to 1.5 g, with monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, and albumin. However, the need to repeat routine liver biopsies was questioned[4] and some[5] recommended omitting the baseline biopsy in patients with no risk factors. A 2009 consensus[6] suggests that patients being considered for methotrexate therapy be divided into 2 groups based on their risk factors for liver injury. Patients with a low risk for hepatotoxicity are monitored similarly to rheumatoid arthritis patients (see below), with an option for liver biopsy upon reaching a cumulative dose of 3.5 to 4 g. For those with one or more risk factors for hepatotoxicity, guidelines remain more stringent, with the first consideration being the feasibility of using another drug. If methotrexate is used, it is advisable that a liver biopsy be performed, at or near the start of therapy; since some patients will stop methotrexate after 2 to 6 months because of adverse effects or lack of efficacy, the liver biopsy may be postponed until after this period. A repeat biopsy should be performed after a cumulative dose of 1 to 1.5 g, and with every additional 1 to 1.5 g thereafter. Methotrexate should be stopped if liver changes are moderate to severe. Practice in the UK has focused on monitoring of the aminoterminal peptide of type III procollagen (PIIINP), a serological marker of hepatic fibrosis,[7] and this is recommended by the British Association of Dermatologists[8] as a safer alternative to liver biopsy. PIIINP values should be determined before starting methotrexate and then every 2 to 3 months during treatment. A liver biopsy may then be considered in those with persistently abnormal values. However, some[7] have said that larger studies of the value of PIIINP assays should be undertaken before definitive recommendations can be made.
- In patients with *rheumatoid arthritis* US guidelines[9,10] suggest an initial biopsy only in patients with a history of excessive alcohol consumption, persistently abnormal AST or ALT values or chronic hepatitis B or C infection. All patients should have liver function tests (LFTs) monitored monthly for the first 6 months and then every 1 to 2 months thereafter. For minor elevations in AST or ALT (less than twofold the upper limit of normal), LFTs are repeated in 2 to 4 weeks; for moderate elevations in AST or ALT (greater than twofold but less than threefold the upper limit of normal), close monitoring, repeat LFTs in 2 to 4 weeks, and reduction of the dose as needed are advocated. A biopsy should be performed if 5 of 9 (or 6 of 12) measurements of AST are elevated in a 12-month

interval or if there is a decline in serum albumin (with normal nutritional status) below the normal range; if liver changes are moderate to severe, methotrexate should be stopped. Options for patients with normal findings include continuing to follow the above guidelines without biopsy, or the first biopsy may be performed at a cumulative dose of 3.5 to 4g of methotrexate, or methotrexate can be stopped after this cumulative dose, or patients switched to alternative therapy. However, some rheumatologists[11,12] consider that less stringent monitoring may be warranted, especially in those with no risk factors for hepatotoxicity. Similarly, although these guidelines have been widely adopted for use in children with juvenile idiopathic arthritis, some[13] consider that routine blood tests every 4 to 8 weeks are unnecessarily frequent.

The UK CSM advised in 1997 that LFTs (with blood count and renal-function testing) should be performed before beginning long-term low-dose methotrexate therapy and repeated weekly until therapy was stabilised, and thereafter every 2 to 3 months.[14]

1. West SG, *et al.* Methotrexate hepatotoxicity. *Rheum Dis Clin North Am* 1997; **23:** 883–915.
2. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. *Clin Exp Rheumatol* 2009; **27:** 1017–25.
3. Roenigk HH, *et al.* American Academy of Dermatology. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; **19:** 145–6.
4. Boffa MJ, *et al.* Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; **133:** 774–8.
5. Roenigk HH, *et al.* Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998; **38:** 478–85.
6. Kalb RE, *et al.* Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009; **60:** 824–37.
7. Maurice PDL, *et al.* Monitoring patients on methotrexate: hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. *Br J Dermatol* 2005; **152:** 451–8.
8. British Association of Dermatologists. Psoriasis—General Management—Methotrexate. Available at: http://www.bad.org.uk/site/1121/default.aspx (accessed 20/07/10)
9. Kremer JM, *et al.* American College of Rheumatology. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; **37:** 316–28.
10. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002; **46:** 328–46.
11. Yazici Y, *et al.* Monitoring by rheumatologists for methotrexate-, etanercept-, infliximab-, and anakinra-associated adverse events. *Arthritis Rheum* 2003; **48:** 2769–72.
12. Yazici Y, *et al.* Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities. *Clin Exp Rheumatol* 2005; **23:** 517–20.
13. Ortiz-Alvarez O, *et al.* Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol* 2004; **31:** 2501–6.
14. CSM/MCA. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

Effects on the lungs. Pulmonary toxicity due to methotrexate has been well described.[1-3] A review[1] of over 120 reports of methotrexate pneumonitis found that onset usually occurred during treatment, presenting as dyspnoea, cough, and fever. Examination often found tachypnoea and crackles, eosinophilia, reduced pulmonary function, interstitial and alveolar infiltrates on chest radiography, and interstitial inflammation and fibrosis. The majority of cases were managed with cessation of methotrexate with or without corticosteroid therapy; most patients improved, but there were 16 deaths caused by respiratory disease. Methotrexate was restarted in 16 patients, and pneumonitis recurred in 4 of these.

Up to 25 April 2003, the UK CSM had received 90 reports of parenchymal lung disorders, including 52 reports of pneumonitis, 21 of pulmonary fibrosis, 5 of interstitial lung disease, and 3 of interstitial pneumonitis. The CSM has suggested that patients should seek medical attention if symptoms such as dyspnoea, dry, nonproductive cough, or fever develop; methotrexate should be stopped and corticosteroids given in the event of suspected pneumonitis.[4]

A multicentre case-control study[5] which examined 29 cases of methotrexate-induced lung injury among rheumatoid arthritis patients found that risk factors included age over 60 years, pleuropulmonary disease (or to a lesser extent other extra-articular disease), previous use of other disease-modifying antirheumatic drugs, and low serum-albumin; an association with smoking, nonsedentary occupations, and diabetes mellitus was also noted. The mechanisms of methotrexate-induced pulmonary inflammation have been investigated *in vitro*,[6] and suggested to be due to stimulation of the p38 mitogen-activated protein kinase pathway, with increased production of the pro-inflammatory cytokines interleukin-1β and interleukin-8, and inhibition of the anti-inflammatory interleukin-4.

1. Imokawa S, *et al.* Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000; **15:** 373–81.
2. Lateef O, *et al.* Methotrexate pulmonary toxicity. *Expert Opin Drug Safety* 2005; **4:** 723–30.
3. Kim Y-J, *et al.* Mechanisms underlying methotrexate-induced pulmonary toxicity. *Expert Opin Drug Safety* 2009; **8:** 451–8.
4. CSM/MHRA. Methotrexate and pneumonitis. *Current Problems* 2003; **29:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
5. Alarcón GS, *et al.* Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis: a multicenter, case-control study. *Ann Intern Med* 1997; **127:** 356–64.
6. Kim Y-J, *et al.* Inflammation in methotrexate-induced pulmonary toxicity occurs via the p38 MAPK pathway. *Toxicology* 2009; **256:** 183–90.

Effects on mental function. Children who had received intrathecal methotrexate with cranial irradiation for the prophylaxis of CNS leukaemia, had a significant intellectual deficit compared with their siblings.[1] There was no corresponding significant reduction in IQ in a group of children who had received systemic chemotherapy and radiotherapy when compared with their sibling controls. The results suggest that intrathecal methotrexate and cranial irradiation cause intellectual problems, particularly on the higher, more complex and integrated intellectual functions, and that the repercussions are greater in younger children. Subsequent results in these patients indicated that although the lowering of IQ had persisted, it had not progressed since the original study.[2] A further study confirmed the adverse neurological effects of leukaemia treatment, and its effects on IQ, and did not find a reduced radiation dose to be any less toxic.[3] Neurotoxicity appeared to be greater when systemic therapy with intramuscular rather than oral methotrexate was given with CNS prophylaxis. A study[4] of children who underwent surgery, chemotherapy, and craniospinal radiotherapy for medulloblastoma also found that those patients who received intrathecal methotrexate had significantly worse cognitive deficits than those who did not, and all patients performed worse than a control group of cousins and siblings.

In a small study[5] of children treated for leukaemia with chemotherapy that included intrathecal methotrexate, but without irradiation, there were lower cognitive scores in some measures compared with a group of healthy controls, but overall no major cognitive impairment was found.

A study in 20 patients receiving intermittent oral methotrexate for psoriasis found no evidence of psychological impairment.[6]

1. Twaddle V, *et al.* Intellectual function after treatment for leukaemia or solid tumours. *Arch Dis Child* 1983; **58:** 949–52.
2. Twaddle V, *et al.* Intellect after malignancy. *Arch Dis Child* 1986; **61:** 700–2.
3. Chessells JM, *et al.* Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation. *Arch Dis Child* 1990; **65:** 416–22.
4. Riva D, *et al.* Intrathecal methotrexate affects cognitive function in children with medulloblastoma. *Neurology* 2002; **59:** 48–53.
5. Kingma A, *et al.* No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. *J Pediatr Hematol Oncol* 2002; **24:** 106–14.
6. Duller P, van de Kerkhof PCM. The impact of methotrexate on psychoorganic functioning. *Br J Dermatol* 1985; **113:** 503–4.

Effects on the nervous system. Methotrexate has a cumulative toxic effect on the nervous system, and generalised and focal neurotoxic reactions are associated with intrathecal and high-dose intravenous use.[1] An immediate, usually transient, effect occurring within a day of high intravenous doses can cause nausea and vomiting, headache, somnolence, lethargy, confusion, disorientation, seizures, and increased intracranial pressure. Reversible acute meningitis can follow intrathecal use, with similar results.[1] Aseptic meningitis has also been reported after intramuscular methotrexate.[2] Spinal cord myelopathy resulting in transient or permanent paraplegia has also followed intrathecal methotrexate use, especially if other neurotoxic treatments have also been used. A subacute form of toxic reaction can occur up to several weeks after treatment. It is usually transient and characterised by seizures, varying degrees of paresis, aphasia, anaesthesia, blurred vision, and pseudobulbar palsy. A more delayed syndrome occurs weeks to months after treatment and is of variable severity, but can progress to lethargy, seizures, spasticity, paresis, drooling, and dementia. This condition is characterised by leukoencephalopathy and chronic calcification of brain tissue. It is dose-related, and more severe if the patient has also received radiotherapy.[1]

See also Effects on Mental Function, above.

1. Shuper A, *et al.* Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *J Child Neurol* 2000; **15:** 573–80.
2. Hawboldt J, Bader M. Intramuscular methotrexate-induced aseptic meningitis. *Ann Pharmacother* 2007; **41:** 1906–11.

Effects on the skin. There are rare reports[1,2] of painful erythema of the hands and feet, particularly the fingertips, with progression to blistering and desquamation (palmar-plantar erythrodysesthesia syndrome, p. 730.1) after the use of high-dose intravenous methotrexate. Purpuric skin lesions due to vasculitis have occurred after both high-dose[3] and low-dose[4,5] methotrexate. Accelerated rheumatoid nodulosis has been reported[6,7] after the use of methotrexate in patients with rheumatoid arthritis. Erosion of psoriatic plaques, accompanied by pain and erythema, has been seen[8,9] after low-dose methotrexate therapy; blistering and necrosis consistent with toxic epidermal necrolysis has occurred.[8] Possible exacerbation of a photosensitivity reaction to ciprofloxacin has been described,[10] and reactivation of sunburn has also been reported[11] in several cases where methotrexate was given within 2 to 5 days after the initial sunburn.

1. Doyle LA, *et al.* Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983; **98:** 611–12.
2. Millot F, *et al.* Acral erythema in children receiving high-dose methotrexate. *Pediatr Dermatol* 1999; **16:** 398–400.
3. Navarro M, *et al.* Leukocytoclastic vasculitis after high-dose methotrexate. *Ann Intern Med* 1986; **105:** 471–2.
4. Marks CR, *et al.* Small-vessel vasculitis and methotrexate. *Ann Intern Med* 1984; **100:** 916.
5. Torner O, *et al.* Methotrexate related cutaneous vasculitis. *Clin Rheumatol* 1997; **16:** 108–9.
6. Williams FM, *et al.* Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. *J Am Acad Dermatol* 1998; **39:** 359–62.
7. Filosa G, *et al.* Accelerated nodulosis during methotrexate therapy for refractory rheumatoid arthritis: a case report. *Adv Exp Med Biol* 1999; **455:** 521–4.
8. Reed KM, Sober AJ. Methotrexate-induced necrolysis. *J Am Acad Dermatol* 1983; **8:** 677–9.
9. Pearce HP, Wilson BB. Erosion of psoriatic plaques: an early sign of methotrexate toxicity. *J Am Acad Dermatol* 1996; **35:** 835–8.
10. Nedorost ST, *et al.* Drug-induced photosensitivity reaction. *Arch Dermatol* 1989; **125:** 433–4.
11. Khan AJ, *et al.* Methotrexate and the photodermatitis reactivation reaction: a case report and review of the literature. *Cutis* 2000; **66:** 379–82.

Hypersensitivity. There are rare reports of anaphylactic reactions in patients given methotrexate. Reactions have usually occurred in patients who had previous exposure to methotrexate, but there are also reports of reaction during initial exposure to high-dose intravenous therapy.[1] Serious reactions have also been described after low-dose intravenous[2] and intrathecal[3] use. Desensitisation may be possible.[4] A 9-year-old patient with osteosarcoma who had previously tolerated 5 courses of high-dose methotrexate (12 g/m^2 over 4 hours) developed urticaria, repeated on rechallenge, but no oedema or respiratory symptoms during the sixth. She was successfully managed by premedication with diphenhydramine and corticosteroids, followed by 1/1000 of the total methotrexate dose over 90 minutes, 1/100 over 90 minutes, 1/10 over 6 hours, and the remainder over 18 hours.[4]

1. Alkins SA, *et al.* Anaphylactoid reactions to methotrexate. *Cancer* 1996; **77:** 2123–6.
2. Cohn JR, *et al.* Systemic anaphylaxis from low dose methotrexate. *Ann Allergy* 1993; **70:** 384–5.
3. Devecioğlu Ö, *et al.* Systemic near-fatal anaphylactic reaction after intrathecal methotrexate administration. *Med Pediatr Oncol* 2000; **34:** 151–2.
4. Bouchireb K, *et al.* Management and successful desensitization in methotrexate-induced anaphylaxis. *Pediatr Blood Cancer* 2009; **52:** 295–7.

Treatment of Adverse Effects

For general guidelines, see p. 730.2.

Folinic acid neutralises the immediate toxic effects of methotrexate on the bone marrow. It is given as sodium or calcium folinate orally, intramuscularly, by intravenous bolus injection, or by infusion. When overdosage is suspected the dose of folinate should be at least as high as that of methotrexate and should be given as soon as possible; further doses are given as required preferably based on serum-methotrexate concentrations. Folinate should be continued until serum-methotrexate concentrations fall below 0.05 to 0.1 micromol/litre, which may necessitate prolonged treatment in patients with delayed elimination. Other dosage regimens, given intramuscularly or orally, may be appropriate for more modest toxicity associated with conventional doses of methotrexate. For details, see under Folinic Acid, p. 2067.1. After intrathecal overdose, the drainage of 30 mL of CSF within 15 minutes removes about 95% of methotrexate; but methotrexate rapidly enters the systemic circulation and folinic acid treatment should be based on serum-methotrexate concentrations.

Folinic acid is usually given with high-dose methotrexate regimens to prevent damage to normal tissue ('folinic acid rescue') and this is discussed in Uses and Administration, p. 822.3.

An adequate flow of alkaline urine should be maintained after high doses of methotrexate to prevent precipitation of methotrexate or its metabolites in the renal tubules; in addition to adequate hydration, the use of acetazolamide or sodium bicarbonate is recommended.

The recombinant glutamate carboxypeptidase glucarpidase (p. 1555.1) is used in addition to folinic acid in the management of methotrexate toxicity. It rapidly hydrolyses methotrexate to its inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid and glutamate which are metabo-

lised by the liver thus providing a non-renal pathway for methotrexate elimination.

Desensitisation. For mention of desensitisation to the drug in a patient with methotrexate-induced anaphylaxis see Hypersensitivity, p. 826.3.

Folate supplementation. A discussion of the selection of the appropriate route for folinic acid rescue with *high-dose methotrexate* regimens.[1] The general objective is to give folinic acid (as folinate) at doses that maintain plasma concentrations of reduced folates at a level equivalent to or greater than the plasma-methotrexate concentration. In any clinical situation suggesting impaired gastrointestinal function calcium folinate should be given by injection. Although absorption of intramuscular doses is relatively complete and rapid the intravenous route is usually preferable for other reasons, such as a reduced risk of bleeding at injection sites. In the absence of impaired gastrointestinal function, and where there are no concomitant risk factors for methotrexate toxicity, the oral route may be used provided that methotrexate concentrations are expected to be less than 1 micromol/litre. For very high dose methotrexate regimens it is generally appropriate to begin folinic acid rescue intravenously to ensure adequate initial therapy, but the majority of the dosage regimen can generally be given orally.

There is no consensus on the use of folate supplementation in patients taking *low-dose methotrexate*,[2] although reviews have concluded that supplementation with either folic or folinic acid reduces adverse effects related to the liver function tests, gastrointestinal tract and oral mucosa.[2,3] However, a study found that while folate supplementation reduced the incidence of methotrexate-related liver enzyme elevations, it had no effect on incidence, severity, or duration of other adverse effects.[4] Effects of folate supplementation on the efficacy of methotrexate have been inconclusive;[3] some consider the effect to be small.[4,5] There is some suggestion that folinic acid, but not folic acid, may reduce the efficacy of methotrexate.[2] However, an analysis[6] of two studies found a reduction in efficacy with folic acid supplementation. The issue of supplementation remains controversial, with some recommending routine folic acid,[2,5,7] and others suggesting that folate only be added when demand for folate increases, such as during infection or with antibacterial use.[8]

1. Rodman JH, Crom WR. Selecting an administration route for leucovorin rescue. *Clin Pharm* 1989; **8:** 617, 621.
2. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004; **43:** 267–71.
3. Ortiz Z, *et al.* Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 08/02/06).
4. van Ede AE, *et al.* Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; **44:** 1515–24.
5. Griffith SM, *et al.* Do patients with rheumatoid arthritis established on methotrexate and folic acid 5 mg daily need to continue folic acid supplements long term? *Rheumatology (Oxford)* 2000; **39:** 1102–9.
6. Khanna D, *et al.* Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. *Arthritis Rheum* 2005; **52:** 3030–8.
7. Hornung N, *et al.* Folate, homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. *J Rheumatol* 2004; **31:** 2374–81.
8. Manna R, *et al.* Folic acid supplementation during methotrexate treatment: nonsense? *Rheumatology (Oxford)* 2005; **44:** 563–4.

Other drugs. Pretreatment with fluorouracil is reported to reduce the toxicity of methotrexate sufficiently to permit high-dose methotrexate without the need for folinic acid rescue.[1] Methotrexate has also been given before fluorouracil to modulate its activity (see Administration, in Fluorouracil, p. 796.1).

The acute neurotoxic effects of methotrexate have been reported to be relieved by intravenous aminophylline or oral theophylline in some children.[2]

For reference to the inefficacy of diltiazem in preventing the nephrotoxicity due to high-dose methotrexate, see Kidney Disorders, under Diltiazem p. 1360.1.

For evidence that colestyramine might decrease serum-methotrexate concentrations, see Interactions, p. 828.1. For reference to the use of glucarpidase to manage methotrexate-induced renal toxicity see Effects on the Kidneys, p. 825.2.

1. White RM. 5-Fluorouracil modulates the toxicity of high dose methotrexate. *J Clin Pharmacol* 1995; **35:** 1156–65.
2. Bernini JC, *et al.* Aminophylline for methotrexate-induced neurotoxicity. *Lancet* 1995; **345:** 544–7.

Precautions

For general discussions see p. 732.2.

Methotrexate should be used with great care in patients with bone-marrow, hepatic, or renal impairment. It should also be used cautiously in ulcerative disorders of the gastrointestinal tract, and in the elderly and the very young. Pleural or ascitic effusions may act as a depot for methotrexate and produce enhanced toxicity, and should be drained before treatment.

Regular monitoring of haematological, renal, and hepatic function, and gastrointestinal toxicity is advisable. Treatment should be interrupted if myelosuppression, diarrhoea, or stomatitis occur. Dyspnoea or cough may be a sign of pulmonary toxicity and patients should be advised to contact their doctor if they develop these symptoms. Treatment should be withdrawn and the patient investigated to exclude infection. If methotrexate-induced lung disease is suspected corticosteroid therapy may be started and further treatment with methotrexate should not be given. Patients or their carers should report any symptoms or signs suggestive of infection, especially sore throat.

In patients receiving **low-dose methotrexate for psoriasis or rheumatoid arthritis** full blood counts and renal and liver function tests should be performed before starting treatment and repeated regularly thereafter (for discussion of guidelines for monitoring in these patients see Effects on the Liver, p. 825.3). Treatment should be interrupted if myelosuppression, stomatitis, or any abnormality of liver function is detected. Methotrexate should not be used to treat rheumatoid arthritis or psoriasis in patients with alcoholism, liver disease or persistent abnormal liver function tests, or in those with significant renal impairment, immunodeficiency, or blood disorders. A test dose has been recommended. Severe or fatal toxicity has resulted from overdosage when doses intended for a low-dose weekly regimen were mistakenly taken daily, and particular care should be taken to avoid confusion about dosage frequency.

With **high-dose regimens**, serum concentrations of methotrexate should be monitored. Maintenance of an adequate flow of alkaline urine is essential (see Treatment of Adverse Effects, p. 826.3).

Methotrexate is a potent teratogen and should be avoided in **pregnancy**. While some licensed product information includes advice that conception should be avoided for at least 6 months after therapy some considers 3 months adequate.

Blood products. Enhanced toxicity was seen in 2 of 14 patients receiving methotrexate by 24-hour infusion when packed red cells were transfused immediately after the methotrexate infusion.[1] Erythrocytes act as reservoirs for methotrexate and probably resulted in the prolonged high serum-methotrexate concentrations seen in these patients. Great care should be exercised whenever packed red blood cells and methotrexate are given concurrently.

1. Yap AKL, *et al.* Methotrexate toxicity coincident with packed red cell transfusions. *Lancet* 1986; **ii:** 641.

Breast feeding. Methotrexate has been detected in breast milk in low concentrations.[1] The American Academy of Pediatrics considers[2] that methotrexate may interfere with cellular metabolism, causing neutropenia and possibly immunosuppression in the nursing infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Johns DG, *et al.* Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972; **112:** 978–80.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/04)

Handling and disposal. Care should be taken to avoid inhalation of methotrexate or contact with skin and mucous membranes. It may cause irritation of the eyes.

Methods have been published for the oxidative destruction of methotrexate *wastes* using potassium permanganate and sulfuric acid, aqueous alkaline potassium permanganate, or sodium hypochlorite.[1] The first method may also be used for dichloromethotrexate. Residues produced by the degradation of methotrexate by these methods showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 72 hours and 7 days respectively after a dose of methotrexate should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.* eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hepatitis. Reactivation of hepatitis B infection, with the development of hepatocellular necrosis and fulminant hepatic failure requiring liver transplantation, developed on stopping low-dose methotrexate therapy in a patient with rheumatoid arthritis who was also an asymptomatic chronic hepatitis B carrier.[1] It was suggested that all patients being considered for low-dose methotrexate therapy should be screened for the presence of serum HBsAg before beginning therapy. However, a similar case of fatal reactivation has been reported[2] in a patient negative for HBsAg.

1. Flowers MA, *et al.* Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; **112:** 381–2.
2. Gwak GY, *et al.* Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. *Clin Exp Rheumatol* 2007; **25:** 888–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methotrexate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. The use of methotrexate in pregnancy is contra-indicated (see Precautions, above). There is a report of a healthy infant born to a woman who was treated with *intrathecal* methotrexate, see Pregnancy, under Teniposide, p. 867.2.

PUVA. Of a total of 94 patients with psoriasis and 38 with mycosis fungoides treated with PUVA therapy (methoxsalen and ultraviolet light) 2 of the former also given methotrexate developed skin cancers.[1] It was suggested that the combination of methotrexate and PUVA may be synergistic in inducing cutaneous malignancy. However, in a cohort study[2] of patients with severe psoriasis, exposure to methotrexate for at least 4 years was associated with an increase in risk of squamous cell carcinoma but not basal cell carcinoma, and no interaction was found between methotrexate and PUVA.

1. Fitzsimons CP, *et al.* Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet* 1983; **i:** 235–6.
2. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73:** 2759–64.

Radiation. Analysis of neutrophil counts for 18 months in children with acute lymphoblastic leukaemia showed that methotrexate-induced neutropenia was significantly greater in patients given CNS irradiation and was considered to have contributed to 3 of 5 deaths during remission.[1]

For the effect of cranial irradiation and intrathecal methotrexate on intellectual development, see Effects on Mental Function, p. 826.2.

1. Report to the Medical Research Council of the Working Party on Leukaemia in Childhood. Analysis of treatment in childhood leukaemia: I—predisposition to methotrexate-induced neutropenia after craniospinal irradiation. *BMJ* 1975; **3:** 563–6.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. The effects of methotrexate may be enhanced by drugs that decrease its renal excretion, such as NSAIDs and salicylates, probenecid, and some penicillins. Fatal toxicity has occurred in patients given NSAIDs with methotrexate (see p. 828.2). Severe toxicity has occurred rarely when co-trimoxazole or trimethoprim was given with methotrexate. Use with other myelotoxic, hepatotoxic, or nephrotoxic agents may increase the risk of toxicity. Folic acid and its derivatives may decrease the efficacy of methotrexate, although they are often used together to reduce methotrexate toxicity (see Treatment of Adverse Effects, p. 826.3).

Animal studies suggested methotrexate toxicity may be increased by chloramphenicol, para-aminobenzoic acid, and hypoglycaemics, but there does not appear to be any evidence of this clinically.

Antibacterials. The oral *aminoglycosides* neomycin[1] and paromomycin[2] have been reported to reduce the gastrointestinal absorption of methotrexate. Various *penicillins* have been reported to markedly decrease the clearance of methotrexate given intravenously for treatment of neoplasms,[3-6] although *ceftazidime* may not.[4] There have also been a few reports of penicillins possibly exacerbating the toxicity of low-dose methotrexate in patients being treated for psoriasis or rheumatoid arthritis, but a small study found that although flucloxacillin decreased methotrexate clearance slightly, this was not clinically significant.[7] Methotrexate toxicity has been reported in a patient receiving low-dose methotrexate after a course of *tetracycline*.[8] In a patient receiving high-dose methotrexate, giving *doxycycline* before the eleventh cycle was believed to be responsible for an exacerbation of methotrexate toxicity, with raised plasma concentrations and reduced clearance of methotrexate.[9] *Sulfonamides* such as sulfafurazole and sulfamethoxazole may displace methotrexate from binding sites[10] and reduce renal clearance.[11] Megaloblastic pancytopenia has been reported on several occasions when methotrexate was given with *co-trimoxazole*[12-14] or *trimethoprim*;[13,15,16] possible mechanisms involved include an addi-

tive antifolate effect, in addition to the effect of the sulfamethoxazole component in the case of co-trimoxazole.

1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; **3:** 1–13.
2. Cohen MH, *et al.* Effect of oral prophylactic broad spectrum nonabsorbable antibiotics on the gastrointestinal absorption of nutrients and methotrexate in small cell bronchogenic carcinoma patients. *Cancer* 1976; **38:** 1556.
3. Bloom EJ, *et al.* Delayed clearance (CL) of methotrexate (MTX) associated with antibiotics and antiinflammatory agents. *Clin Res* 1986; **34:** 560A.
4. Yamamoto K, *et al.* Delayed elimination of methotrexate associated with piperacillin administration. *Ann Pharmacother* 1997; **31:** 1261–2.
5. Dean R, *et al.* Possible methotrexate-mezlocillin interaction. *Am J Pediatr Hematol Oncol* 1992; **14:** 88–9.
6. Ronchera CL, *et al.* Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. *Ther Drug Monit* 1993; **15:** 375–9.
7. Herrick AL, *et al.* Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1996; **41:** 223–7.
8. Turck M. Successful psoriasis treatment then sudden 'cytotoxicity'. *Hosp Pract* 1984; **19:** 175–6.
9. Tortajada-Ituren JJ, *et al.* High-dose methotrexate—doxycycline interaction. *Ann Pharmacother* 1999; **33:** 804–8.
10. Liegler DG, *et al.* The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* 1969; **10:** 849–57.
11. Ferrazzini G, *et al.* Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* 1990; **117:** 823–6.
12. Liddle BJ, Marsden JR. Drug interactions with methotrexate. *Br J Dermatol* 1989; **120:** 582–3.
13. Jeurissen ME, *et al.* Pancytopenia and methotrexate with trimethoprim-sulfamethoxazole. *Ann Intern Med* 1989; **111:** 261.
14. Groenendal H, Rampen FHJ. Methotrexate and trimethoprim–sulphamethoxazole—a potentially hazardous combination. *Clin Exp Dermatol* 1990; **15:** 358–60.
15. Steuer A, Gumpel JM. Methotrexate and trimethoprim: a fatal interaction. *Br J Rheumatol* 1998; **37:** 105–6.
16. Govert JA, *et al.* Pancytopenia from using trimethoprim and methotrexate. *Ann Intern Med* 1992; **117:** 877–8.

Antiepileptics. For mention of the reduction in serum-*valproate* concentration produced by methotrexate see p. 557.3.

Antineoplastics. Enhanced methotrexate toxicity might be expected with nephrotoxic agents (such as *cisplatin*) that can reduce methotrexate excretion by impairing renal function. Sequential use of methotrexate and *fluorouracil* may result in synergistic enhancement of effect (see Administration, in Fluorouracil, p. 796.1), and equally, fluorouracil before methotrexate may reduce its toxicity (see Other Drugs, under Treatment of Adverse Effects, p. 827.1), but if *asparaginase* (p. 744.3) is given before methotrexate the cytotoxic effect of methotrexate may be reduced.

Methotrexate may increase the bioavailability of *mercaptopurine*, probably by interference with first-pass metabolism (see p. 821.3).

Colestyramine. Serum-methotrexate concentrations were markedly reduced in 3 patients given colestyramine to treat methotrexate toxicity.[1,2] Colestyramine appears to bind methotrexate and reduce its enterohepatic recirculation.

1. Erttmann R, Landbeck G. Effect of oral cholestyramine on the elimination of high-dose methotrexate. *J Cancer Res Clin Oncol* 1985; **110:** 48–50.
2. Shinozaki T, *et al.* Successful rescue by oral cholestyramine of a patient with methotrexate nephrotoxicity: nonrenal excretion of serum methotrexate. *Med Pediatr Oncol* 2000; **34:** 226–8.

Dantrolene. Dantrolene was considered to have caused methotrexate toxicity in a patient given high-dose methotrexate.[1]

1. André N, *et al.* Can dantrolene contribute to methotrexate toxicity? *Ann Pharmacother* 2006; **40:** 1695–6.

Gastrointestinal drugs. Elevated serum concentrations of methotrexate were reported when it was given to 2 patients also receiving *omeprazole*.[1,2] The effect was not seen with subsequent cycles of methotrexate therapy once omeprazole had been stopped. In another case[3] however, raised methotrexate concentrations were thought to be due to an interaction with omeprazole, but were identical during a second cycle after omeprazole had been withdrawn. Severe generalised myalgia and bone pain were reported in a patient who received methotrexate and *pantoprazole*.[4] The same reaction occurred on rechallenge with the combination, but not with methotrexate alone. Although methotrexate concentrations were unchanged, concentrations of the metabolite 7-hydroxymethotrexate were raised suggesting an interaction with its renal elimination. *Lansoprazole* has been reported not to affect the pharmacokinetics of methotrexate.[5] A Japanese study found that use of proton pump inhibitors (including omeprazole, lansoprazole, and *rabeprazole*) was associated with delayed plasma elimination of methotrexate in patients given high-dose methotrexate therapy.[6]

1. Reid T, *et al.* Impact of omeprazole on the plasma clearance of methotrexate. *Cancer Chemother Pharmacol* 1993; **33:** 82–4.
2. Beorlegui B, *et al.* Potential interaction between methotrexate and omeprazole. *Ann Pharmacother* 2000; **34:** 1024–7.
3. Whelan J, *et al.* Omeprazole does not alter plasma methotrexate clearance. *Cancer Chemother Pharmacol* 1999; **44:** 88–9.
4. Tröger U, *et al.* Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. *BMJ* 2002; **324:** 1497.
5. Vakily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 1179–86.
6. Suzuki K, *et al.* Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol* 2009; **67:** 44–9.

Glutamine. Drugs with the potential to lower urinary pH, such as glutamine, may decrease clearance of methotrexate and cause it to precipitate in the renal tubules. Acute nephrotoxicity[1] followed failure to adjust urinary pH during high-dose methotrexate infusion in a patient also taking glutamine. Urinary pH should be continually checked in patients receiving both drugs and adjusted with bicarbonate if necessary.

1. Marín Pozo JF, *et al.* Hazards of concomitant administration of methotrexate and glutamine. *Am J Health-Syst Pharm* 2010; **67:** 601–2.

Immunosuppressants. For reports of enhanced toxicity with *ciclosporin* in patients who have received methotrexate see p. 1957.2.

Leflunomide. For a report of the effect of methotrexate in patients receiving leflunomide, see p. 82.3.

Nitrous oxide. Severe unpredictable myelosuppression and stomatitis have been attributed to the use of nitrous oxide anaesthesia in patients receiving methotrexate, potentiating the effects of methotrexate on folate metabolism.[1] The effect could be reduced by the use of folinic acid rescue.

1. Goldhirsch A, *et al.* Methotrexate/nitrous-oxide toxic interaction in perioperative chemotherapy for early breast cancer. *Lancet* 1987; **ii:** 151.

NSAIDs. Severe, and in some cases fatal, aggravation of methotrexate toxicity has been reported when it was given with various NSAIDs including *aspirin* and other *salicylates*,[1,2] *azapropazone*,[3] *diclofenac*,[4] *indometacin*,[4,5] and *ketoprofen*.[6] The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an effect of NSAIDs on the kidney resulting in reduced methotrexate excretion.[6,7] *Naproxen* has been reported not to affect the pharmacokinetics of methotrexate,[8,9] but a fatal interaction has nonetheless been reported.[10] Despite the risks, some commentators have pointed out that methotrexate and NSAIDs are frequently used together in the treatment of rheumatoid arthritis,[11,12] and that provided this is done with caution, in low doses, and patients are appropriately monitored and cautioned to avoid additional 'over-the-counter' analgesics, such combinations need not be contra-indicated. A study in patients receiving low-dose methotrexate for rheumatoid arthritis suggested that *flurbiprofen, ketoprofen,* or *piroxicam* did not influence methotrexate clearance.[13] A case of methotrexate toxicity has nevertheless been described[14] in an elderly woman when flurbiprofen was added to low-dose methotrexate therapy.

Manufacturers of methotrexate generally contra-indicate the use of NSAIDs with high-dose methotrexate.

1. Baker H. Intermittent high dose oral methotrexate therapy in psoriasis. *Br J Dermatol* 1970; **82:** 65–9.
2. Zuik M, Mandel MA. Methotrexate-salicylate interaction: a clinical and experimental study. *Surg Forum* 1975; **26:** 567–9.
3. Daly HM, *et al.* Methotrexate toxicity precipitated by azapropazone. *Br J Dermatol* 1986; **114:** 733–5.
4. Gabrielli A, *et al.* Methotrexate and nonsteroidal anti-inflammatory drugs. *BMJ* 1987; **294:** 776.
5. Maiche AG. Acute renal failure due to concomitant action of methotrexate and indomethacin. *Lancet* 1986; **i:** 1390.
6. Thyss A, *et al.* Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. *Lancet* 1986; **i:** 256–8.
7. Furst DE, *et al.* Effect of aspirin and sulindac on methotrexate clearance. *J Pharm Sci* 1990; **79:** 782–6.
8. Stewart CF, *et al.* Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. *Clin Pharmacol Ther* 1990; **47:** 540–6.
9. Vakily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 1179–86.
10. Singh RR, *et al.* Fatal interaction between methotrexate and naproxen. *Lancet* 1986; **i:** 1390.
11. Tully M. NSAIDs. *Pharm J* 1991; **247:** 746.
12. Zachariae H. Methotrexate and nonsteroidal anti-inflammatory drugs. *Br J Dermatol* 1992; **126:** 95.
13. Tracy TS, *et al.* Methotrexate disposition following concomitant administration of ketoprofen, piroxicam and flurbiprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1994; **37:** 453–6.
14. Frenia ML, Long KS. Methotrexate and nonsteroidal antiinflammatory drug interactions. *Ann Pharmacother* 1992; **26:** 234–7.

Probenecid. Probenecid can produce two- to fourfold increases in serum-methotrexate concentrations,[1-3] presumably by inhibiting renal excretion of methotrexate. Although probenecid has been shown to reduce protein binding of methotrexate,[4] usual doses of probenecid are unlikely to significantly affect methotrexate elimination by this mechanism. A woman receiving low-dose weekly methotrexate for rheumatoid arthritis developed severe pancytopenia when probenecid was given for asymptomatic hyperuricaemia.[5]

1. Aherne GW, *et al.* Prolongation and enhancement of serum methotrexate concentrations by probenecid. *BMJ* 1978; **1:** 1097–9.
2. Howell SB, *et al.* Effect of probenecid on cerebrospinal fluid methotrexate kinetics. *Clin Pharmacol Ther* 1979; **26:** 641–6.
3. Lilly MB, Omura GA. Clinical pharmacology of oral intermediate-dose methotrexate with or without probenecid. *Cancer Chemother Pharmacol* 1985; **15:** 220–2.
4. Paxton JW. Interaction of probenecid with the protein binding of methotrexate. *Pharmacology* 1984; **28:** 86–9.
5. Basin KS, *et al.* Severe pancytopenia in a patient taking low dose methotrexate and probenecid. *J Rheumatol* 1991; **18:** 609–10.

Retinoids. An increased risk of hepatotoxicity has been reported when methotrexate and *etretinate* are given together,[1] possibly due to increased plasma concentrations of methotrexate.[2,3]

1. Zachariae H. Dangers of methotrexate/etretinate combination therapy. *Lancet* 1988; **i:** 422.
2. Harrison PV, *et al.* Methotrexate and retinoids in combination for psoriasis. *Lancet* 1987; **ii:** 512.
3. Larsen FG, *et al.* Interaction of etretinate with methotrexate pharmacokinetics in psoriatic patients. *J Clin Pharmacol* 1990; **30:** 802–7.

Xanthines. For mention of the effect of methotrexate on the clearance of theophylline, see Antineoplastics, under Interactions of Theophylline, p. 1235.2.

Pharmacokinetics

When given in low doses, methotrexate is rapidly absorbed from the gastrointestinal tract, but higher doses are less well absorbed. It is also rapidly and completely absorbed after intramuscular doses. Peak serum concentrations occur 1 to 2 hours after an oral dose, and 30 to 60 minutes after an intramuscular one.

Methotrexate is distributed to tissues and extracellular fluid with a steady-state volume of distribution of 0.4 to 0.8 litres/kg; it penetrates ascitic fluid and effusions, which may act as a depot and thus enhance toxicity. Clearance from plasma is reported to be triphasic, with a terminal elimination half-life of between 3 and 10 hours after doses less than 30 mg/m² or 8 to 15 hours after high-dose parenteral therapy. It is about 50% bound to plasma protein. Methotrexate enters the cells in part by an active transport mechanism and is bound as polyglutamate conjugates: bound drug may remain in the body for several months, particularly in the liver.

Only small or insignificant amounts cross the blood-brain barrier and enter the CSF after oral or parenteral doses, although this may be increased by giving higher doses; however, after intrathecal doses there is significant passage into the systemic circulation.

Methotrexate has been detected in very small amounts in saliva and breast milk. It crosses the placenta.

Methotrexate does not appear to undergo significant metabolism at low doses; after high-dose therapy the 7-hydroxy metabolite has been detected. Methotrexate may be partly metabolised by the intestinal flora after oral doses. It is excreted mainly in the urine, by glomerular filtration and active tubular secretion. Small amounts are excreted in bile and found in faeces; there is some evidence for enterohepatic recirculation.

Considerable interindividual variation exists in the pharmacokinetics of methotrexate: those patients in whom clearance is delayed are at increased risk of toxicity.

References.

1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; **3:** 1–13.
2. Balis FM, *et al.* Clinical pharmacokinetics of commonly used anticancer drugs. *Clin Pharmacokinet* 1983; **8:** 202–32.
3. Wang Y-M, Fujimoto T. Clinical pharmacokinetics of methotrexate in children. *Clin Pharmacokinet* 1984; **9:** 335–48.
4. Witter FR. Clinical pharmacokinetics in the treatment of rheumatoid arthritis in pregnancy. *Clin Pharmacokinet* 1993; **25:** 444–9.
5. Bannwarth B, *et al.* Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis. *Clin Pharmacokinet* 1996; **30:** 194–210.
6. Chládek J, *et al.* Pharmacokinetics and pharmacodynamics of low-dose methotrexate in the treatment of psoriasis. *Br J Clin Pharmacol* 2002; **54:** 147–56.
7. Grim J, *et al.* Pharmacokinetics and pharmacodynamics of methotrexate in non-neoplastic diseases. *Clin Pharmacokinet* 2003; **42:** 139–51.
8. Aumente D, *et al.* Population pharmacokinetics of high-dose methotrexate in children with acute lymphoblastic leukaemia. *Clin Pharmacokinet* 2006; **45:** 1227–38.
9. Thompson PA, *et al.* Methotrexate pharmacokinetics in infants with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 2007; **59:** 847–53.
10. Hider SL, *et al.* The pharmacogenetics of methotrexate. *Rheumatology (Oxford)* 2007; **46:** 1520–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Artrait; Ervemin; Metodik; Trixate; Xantromid; ***Austral.***: Ledertrexate†; Methohlastin; ***Austria***: Ebetrexat; Metoject†; ***Belg.***: Emthexate; Ledertrexate; ***Braz.***: Biometrox; Emthexate†; Fauldmetro; Hytas; Metrexato; Miantrex; Reutrexato; Tecnomet; Tevametho; ***Canad.***: Metoject; ***Chile***: Metoject; Trixilem; ***China***: Meisusheng (美素生); Midu (密都); ***Cz.***: Metoject; Trexan; ***Denm.***: Ebetrex; Emthex-

ate; Metex; Metoject†; ***Fin.***: Ebetrex; Emthexat†; Metoject; Trexan; ***Fr.***: Imeth; Ledertrexate; Metoject; Novatrex; ***Ger.***: Bendatrexat†; Lantarel; Metex; MTX; Neotrexat†; ***Gr.***: Emthexate; Methobion; Methoblastin; Metoject; ***Hung.***: Metoject; Trexan; ***India***: Alltrex; Biotrexate; Caditrex; Dermatrex; Dermotrex; Folitrax; Hi-Trex; Imutrex; Merex; Methocel; Methocip; Methorex; Metorex; Metrex; Mexate; Neotrexate; Oncotrex; Onotrex; ***Indon.***: Emthexate; ***Irl.***: Metoject; ***Israel***: Abitrexate; Metoject; ***Ital.***: Reumaflex; Sactiva; Securact; ***Jpn***: Metolate; ***Malaysia***: Emthexate; ***Mex.***: Atrexel; Ifamet†; Ledertrexate; Medsatrexate; Otaxem; Texate; Trixilem; ***Neth.***: Ebetrexat†; Emthexate; Metoject; ***Norw.***: Ebetrex; Metex; Metoject†; ***NZ***: Emthexate; Methoblastin; ***Philipp.***: Alltrex; Emthexate; Hextrate†; Methobax†; Pterin; Zexate; ***Pol.***: Metex; Metoject; Trexan; ***Port.***: Fauldexato; Ledertrexato; Metex; Metoject; ***Rus.***: Metoject (Методжект); Zexat (Зексат); ***S.Afr.***: Abitrexate; Emthexate†; Methacor; Methacor; ***Singapore***: Abitrexate; Ebetrexat; Emthexate; MTX; ***Spain***: Bertanel; Emthexate†; Metoject; ***Swed.***: Ebetrex; Metoject; Metotab; ***Switz.***: Metoject; ***Thai.***: Abitrexate; Alltrex; Emthexate; Metrex; Neometho; Onkomet; Trixilem; Zexate†; ***Turk.***: Emthexate; Metoart; Metoject; MTX; Trexan; ***UK***: Ebetrex†; Matrex; Maxtrex; Metoject; ***USA***: Otrexup; Rheumatrex; Trexall; ***Venez.***: Zexate.

Pharmacopoeial Preparations
BP 2014: Methotrexate Injection; Methotrexate Tablets;
USP 36: Methotrexate for Injection; Methotrexate Injection; Methotrexate Tablets.

2-Methoxyoestradiol

2-ME2; 2-Methoxyestradiol; NSC-659853; 2-Метоксиэстрадиол.
(17β)-2-Methoxyestra-1,3,5(10)-triene-3,17-diol.
$C_{19}H_{26}O_3$=302.4
CAS — 362-07-2.
UNII — 6I2QW73SR5.

NOTE. The names Panzem and PulmoLAR have been used as trade marks for 2-methoxyoestradiol.

Profile

2-Methoxyoestradiol is a metabolite of oestradiol (p. 2271.1). It does not have direct oestrogenic activity, but works through multiple cellular pathways to produce antineoplastic effects, including inhibition of angiogenesis and induction of apoptosis. 2-Methoxyoestradiol is under investigation in the treatment of various diseases, including glioblastoma, multiple myeloma, carcinoid tumours, as well as ovarian, prostate, breast, and renal cell cancers. It is also under investigation for pulmonary arterial hypertension and rheumatoid arthritis.

Midostaurin *(USAN, rINN)*

Benzoylstaurosporine; CGP-41251; Midostaurina; Midostaurine; Midostaurinum; PKC-412; Мидостаурин.
N-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3′,2′,1′-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide.
$C_{35}H_{30}N_4O_4$=570.6
CAS — 120685-11-2.
UNII — ID91255VON.

Profile

Midostaurin is a multikinase inhibitor effective against tyrosine kinase and protein kinase C, and those of receptors for growth factors including vascular endothelial growth factor and platelet-derived growth factor. It is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndrome, and systemic mastocytosis.

Mifamurtide *(BAN, rINN)*

Mifamurtida; Mifamurtidum; MTP-PE; Muramyl Tripeptide Phosphatidyl Ethanolamine; Muramyl Tripeptide Phosphatidyl Monoethanolamine; Мифамуртид.
2-[(*N*-{(2*R*)-[(2-Acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate.
$C_{59}H_{109}N_6O_{19}P$=1237.5
CAS — 83461-56-7.
ATC — L03AX15.
ATC Vet — QL03AX15.
UNII — 1LM890Q4FY.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt. The name Junovan has been used as a trade mark for mifamurtide.

Mifamurtide Sodium *(rINNM)*

CGP-19835A; L-MTP-PE (liposomal mifamurtide sodium); Mifamurtida sódica; Mifamurtide (USAN); Mifamurtide Sodique; Mifamurtidum Natricum; Мифамуртид Натрий.
2-[(*N*-{(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(Acetylamino)-2,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yloxy]propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexanoyloxy)propyl sodium phosphate hydrate.
$C_{59}H_{108}N_6NaO_{19}P.xH_2O$=1259.5 (anhydrous)
CAS — 838853-48-8.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Uses and Administration

Mifamurtide is an immunomodulator that activates monocytes and macrophages to increase their capacity to destroy cancer cells. A liposomal formulation of mifamurtide is used with other chemotherapy to treat non-metastatic, resected osteosarcoma in patients from 2 to 30 years of age. The reconstituted suspension is filtered then diluted in 50 mL sodium chloride 0.9% and given by intravenous infusion over 1 hour. Mifamurtide 2 mg/m^2 is given twice weekly (at least 3 days apart) for 12 weeks, followed by once weekly for an additional 24 weeks. A total of 48 infusions is given in 36 weeks.

References.

1. Meyers PA. Muramyl tripeptide (mifamurtide) for the treatment of osteosarcoma. *Expert Rev Anticancer Ther* 2009; **9:** 1035–49.
2. Frampton JE. Mifamurtide: a review of its use in the treatment of osteosarcoma. *Paediatr Drugs* 2010; **12:** 141–53.
3. Chou AJ, *et al.* Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. *Cancer* 2009; **115:** 5339–48.

Administration in children. Mifamurtide is given in a liposomal formulation to children aged from 2 years with osteosarcoma; see above for dosage details.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Common adverse effects with mifamurtide include blood disorders such as anaemia, thrombocytopenia, granulocytopenia, transient neutropenia, and leucopenia; CNS disorders such as headache, dizziness, paraesthesia, hypoaesthesia, somnolence or insomnia, tremor, fatigue, confusion, depression, and anxiety; musculoskeletal disorders such as pain, spasm, arthralgia, and myalgia; and skin disorders such as rash, pruritus, dry skin, alopecia, and hyperhidrosis. Gastrointestinal disturbances such as nausea, vomiting, diarrhoea or constipation, abdominal pain, and anorexia are very common.

Other adverse effects that occur commonly during treatment include infusion-site reactions, phlebitis, flushing, dehydration, hypokalaemia, vertigo, tinnitus, hearing loss, blurred vision, hepatic pain, dysmenorrhoea, haematuria, dysuria, pollakiuria, fever, chills, and oedema.

Common respiratory disorders include dyspnoea or tachypnoea, cough, haemoptysis, epistaxis, sinus or nasal congestion, pleural effusion, or pharyngolaryngeal pain. Respiratory distress has been reported occasionally in patients with pre-existing asthma; mifamurtide therapy should be stopped if a severe respiratory reaction occurs. Prophylactic bronchodilators may be considered in those with a history of reversible airways obstruction.

Cardiac disorders such as tachycardia and hypertension or hypotension are common. Subacute thrombosis has been reported very rarely. Patients with a history of venous thrombosis, vasculitis, or unstable cardiovascular disease should be closely monitored, and treatment delayed or stopped if symptoms are persistent or worsening. Clotting parameters should be monitored after the first dose and again after several doses.

Mifamurtide has occasionally been associated with an inflammatory response, including pericarditis and pleuritis, and it should be used with caution in those with a history of auto-immune disorders, inflammatory disease, or other collagen vascular diseases. Patients should be monitored for signs of uncontrolled inflammatory reactions such as arthritis or synovitis. Allergic reactions also have occurred occasionally with mifamurtide; symptoms include rash, dyspnoea, and severe hypertension.

Caution is required in patients with hepatic or renal impairment due to a lack of data; hepatic and renal function should be monitored until treatment is complete.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Mifamurtide modulates the immune system and its use is not recommended with calcineurin inhibitors or with regular use of corticosteroids. The use of mifamurtide with high-dose NSAIDs is also not recommended as *in vitro* studies have shown that high-dose NSAIDs can block the macrophage-activating action of mifamurtide.

Licensed product information suggests liposomal mifamurtide should not be administered at the same time as other lipophilic formulations.

Pharmacokinetics

Mifamurtide is rapidly cleared from the plasma after intravenous injection and is distributed into the liver, spleen, nasopharynx, thyroid, and to a lesser extent, into the lungs. The cells of the reticuloendothelial system clear mifamurtide liposomes by phagocytosis. The mean half-life is biphasic, that for the initial phase being about 15 minutes while the terminal half-life is about 18 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Mepact; ***Cz.***: Mepact; ***Denm.***: Mepact; ***Ger.***: Mepact; ***Gr.***: Mepact; ***Irl.***: Mepact; ***Israel***: Mepact; ***Ital.***: Mepact; ***Neth.***: Mepact; ***Norw.***: Mepact; ***Pol.***: Mepact; ***Port.***: Mepact; ***Spain***: Mepact; ***Swed.***: Mepact; ***Switz.***: Mepact; ***UK***: Mepact.

Milatuzumab *(USAN, rINN)*

Immu-115; Milatuzumabum; Милатузумаб.
Immunoglobulin G1, anti-(human class II antigen invariant chain) (human-mouse monoclonal hLL1 heavy chain), disulfide with human-mouse monoclonal hLL1 κ-chain, dimer.
CAS — 899796-83-9.
UNII — 2OP4E0GC6V.

Profile

Milatuzumab is a humanised monoclonal antibody directed against the CD74 antigen. It is under investigation for the treatment of multiple myeloma, chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma. Milatuzumab conjugated to doxorubicin (p. 782.3) is also being studied for multiple myeloma treatment.

References.

1. Berkova Z, *et al.* Milatuzumab—a promising new immunotherapeutic agent. *Expert Opin Invest Drugs* 2010; **19:** 141–9.

Miltefosine *(BAN, rINN)*

D-18506; HDPC; Hexadecilfosfocolina; Hexadecylphosphocholine; Miltefosiini; Miltefosin; Miltefosina; Miltéfosine; Miltefosinum; Мильтефозин.
[2-(Trimethylammonio)ethyl][hexadecyloxyphosphonate].
$C_{21}H_{46}NO_4P$=407.6
CAS — 58066-85-6.
ATC — L01XX09.
ATC Vet — QL01XX09.
UNII — 53EY29W7EC.

Profile

Miltefosine is a phospholipid derivative that is structurally related to the phospholipid components of the cell membrane and is thought to exert its antineoplastic actions by disruption of cell-membrane function. A 6% solution is applied once or twice daily as a topical antineoplastic agent for skin metastases of breast cancer. Topical miltefosine is also being investigated for the treatment of cutaneous T-cell lymphoma and *Acanthamoeba* keratitis (p. 919.3); topical and oral formulations have been tried for disseminated amoebic infections (p. 920.1). Systemic miltefosine is being investigated for urticaria. Oral miltefosine is used for the treatment of visceral and cutaneous leishmaniasis in a dose of 1.5 to 2.5 mg/kg daily (maximum daily dose 150 mg) for 28 days.

Acanthamoeba infections. References[1,2] to the potential value of miltefosine against *Acanthamoeba* infections (p. 920.1).

1. Aichelburg AC, *et al.* Successful treatment of disseminated Acanthamoeba sp. infection with miltefosine. *Emerg Infect Dis* 2008; **14:** 1743–6.
2. Walochnik J, *et al.* Anti-acanthamoeba efficacy and toxicity of miltefosine in an organotypic skin equivalent. *J Antimicrob Chemother* 2009; **64:** 539–45.

Leishmaniasis. Miltefosine, given orally in doses of 50 to 150 mg daily, or about 2.5 mg/kg daily, for 28 days, appears to be of benefit[1-7] in the treatment of visceral leishmaniasis (p. 923.1), and has been licensed for this purpose in India and Germany. Benefit has also been reported in patients given similar doses for New World cutaneous leishmaniasis,[8] (p. 922.1) and it has also been licensed in some South American countries, but success may depend on the infecting *Leishmania* species.[9] A small

study[10] in Iran found oral miltefosine to be at least as good as intramuscular meglumine antimonate for the treatment of infections caused by *L. major*. Another retrospective, observational study[11] reported successful treatment with oral miltefosine in 30 of 34 patients (most of whom had not responded to initial treatment with intralesional antimony alone or with cryotherapy) for *L. major* infection acquired in northern Afghanistan. A further 4 patients were cured after receiving additional doses of either intralesional or intravenous antimony. The use of longer courses of miltefosine in the treatment of patients with both leishmaniasis and HIV infection has been reported.[12]

After recovery from visceral leishmaniasis caused by *L. donovani* patients may develop post-kala-azar dermal leishmaniasis; further treatment is needed in these patients as they represent a human reservoir for the disease. A small study[13] of 24 patients in Bihar, India reported that an oral dose of miltefosine 50 mg three times daily for 60 days (or 50 mg twice daily for 90 days in those who had intolerable adverse effects) achieved a cure in 96% of the patients. There were no relapses at 1-year follow-up.

1. Sundar S, *et al.* Trial of oral miltefosine for visceral leishmaniasis. *Lancet* 1998; **352:** 1821–3.
2. Jha TK, *et al.* Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; **341:** 1795–1800.
3. Thakur CP, *et al.* Miltefosine in a case of visceral leishmaniasis with HIV co-infection; and rising incidence of this disease in India. *Trans R Soc Trop Med Hyg* 2000; **94:** 696–7.
4. Sundar S, *et al.* Short-course of oral miltefosine for treatment of visceral leishmaniasis. *Clin Infect Dis* 2000; **31:** 1110–13.
5. Sundar S, *et al.* Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med* 2002; **347:** 1739–46.
6. Bhattacharya SK, *et al.* Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clin Infect Dis* 2004; **38:** 217–21.
7. Ritmeijer K, *et al.* A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis* 2006; **43:** 357–64.
8. Soto J, *et al.* Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis* 2001; **33:** e57–e61. Available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/322689 (accessed 01/08/08)
9. Soto J, *et al.* Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 2004; **38:** 1266–72.
10. Mohebali M, *et al.* Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. *Acta Trop* 2007; **103:** 33–40.
11. van Thiel PP, *et al.* Miltefosine treatment of *Leishmania major* infection: an observational study involving Dutch military personnel returning from northern Afghanistan. *Clin Infect Dis* 2010; **50:** 80–3.
12. Sindermann H, *et al.* Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis* 2004; **39:** 1520–3.
13. Ramesh V, *et al.* Miltefosine as an effective choice in the treatment of post-kala-azar dermal leishmaniasis. *Br J Dermatol* 2011; **165:** 411–14.

Malignant neoplasms. References to the use of topical miltefosine in breast cancer.

1. Terwogt JM, *et al.* Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast cancer. *Br J Cancer* 1999; **79:** 1158–61.
2. Smorenburg CH, *et al.* Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients. *Anticancer Drugs* 2000; **11:** 825–8.
3. Leonard R, *et al.* Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol* 2001; **19:** 4150–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies miltefosine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Miltex; ***Braz.***: Miltex†; ***Chile***: Miltex; ***Fin.***: Miltex†; ***Fr.***: Miltex; ***Ger.***: Impavido; Miltex; ***Hung.***: Miltex; ***Israel***: Miltex†; ***Ital.***: Miltex; ***Philipp.***: Miltex†; ***Singapore***: Miltex; ***Spain***: Miltex†; ***Swed.***: Miltex†; ***UK***: Miltex†.

Miriplatin *(rINN)*

Miriplatine; Miriplatino; Miriplatinum; SM-11355; Мириплатин.
(*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-N,N′]bis(tetradecanoato-*O*)platinum.
$C_{34}H_{68}N_2O_4Pt$=764.0
CAS — 141977-79-9.

Miriplatin Hydrate *(rINNM)*

D-06294; Miriplatine, Hydrate de; Miriplatini Hydratum; Miriplatino hidratada; Мириплатина Гидрат.
$C_{34}H_{68}N_2O_4Pt,H_2O$=782.0
CAS — 250159-48-9.

Profile

Miriplatin is a platinum derivative used as an antineoplastic in the treatment of hepatocellular carcinoma. It is given as the hydrate but doses are expressed as the base; 1 mg of miriplatin hydrate is equivalent to about 1.02 mg of miriplatin. A usual dose of 70 mg is given once daily by hepatic intra-arterial injection. Hepatic dysfunction, hepatobiliary disorders, and hepatic failure can occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Miripla.

Mitobronitol *(BAN, rINN)*

DBM; Dibromomannitol; Mitobronitolum; NSC-94100; R-54; WR-220057; Митобронитол.
1,6-Dibromo-1,6-dideoxy-D-mannitol.
$C_6H_{12}Br_2O_4$=308.0
CAS — 488-41-5.
ATC — L01AX01.
ATC Vet — QL01AX01.
UNII — 5UP30YED7N.

Pharmacopoeias. In *Br.*

BP 2014: (Mitobronitol). A white or almost white crystalline solid. Slightly soluble in water, in alcohol, and in acetone; practically insoluble in chloroform. Protect from light.

Profile

Mitobronitol is an antineoplastic that appears to act as an alkylating agent, perhaps by epoxide formation. It has been used in the management of thrombocythaemia, both primary, and secondary to chronic myeloid leukaemia or polycythaemia vera.

The usual oral dose is 250 mg daily until the platelet count falls to acceptable levels. Intermittent dosage has been given for maintenance therapy, adjusted according to the blood count. Frequent examination of the blood should be performed during treatment. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Mitobronitol is well absorbed from the gastrointestinal tract and is excreted through the liver into the bile, with reabsorption from the small intestine. It is eliminated as unchanged drug and some bromine-containing metabolites in the urine over several days.

Carcinogenicity. Long-term follow-up of a cooperative study[1] involving 350 patients with polycythaemia vera and treated with mitobronitol was thought to indicate that mitobronitol was less likely than phosphorus-32 or busulfan to induce acute myeloid leukaemia.

For a discussion of the usual management of polycythaemia vera, see p. 695.2.

1. Kelemen E, *et al.* Decreasing risk of leukaemia during prolonged follow-up after mitobronitol therapy for polycythaemia vera. *Lancet* 1987; **ii:** 625.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Myelobromol.

Pharmacopoeial Preparations
BP 2014: Mitobronitol Tablets.

Mitoguazone Dihydrochloride *(rINNM)*

Dihidrocloruro de mitoguazona; Methyl-GAG; Methylglyoxal Bisguanylhydrazone (mitoguazone); MGBG; Mitoguazona, dihidrocloruro de; Mitoguazone, Dichlorhydrate de; Mitoguazoni Dihydrochloridum; NSC-32946; Митогуазона Дигидрохлорид.
1,1′-[(Methylethanediylidene)dinitrilo]diguanidine dihydrochloride.
$C_5H_{12}N_8$,2HCl=257.1
CAS — 459-86-9 (mitoguazone); 7059-23-6 (mitoguazone dihydrochloride).
ATC — L01XX16.
ATC Vet — QL01XX16.
UNII — NNI098FX5Q.

Profile

Mitoguazone is an antineoplastic that may exert its cytotoxic effects by its ability to inhibit polyamine biosynthesis. It has been tried as the dihydrochloride monohydrate or the acetate, in the treatment of leukaemias, lymphomas, and some solid tumours.

Mitoguazone may produce hypoglycaemia and should be given dissolved in glucose-containing infusion fluids; sugar may be taken orally if hypoglycaemia develops during infusion. Granulocytopenia and thrombocytopenia are generally mild and reversible on stopping treatment. Gastrointestinal effects frequently occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Methyl-Gag†.

Mitolactol *(rINN)*

DBD; Dibromodulcitol; Mitolactolum; NSC-104800; WR-138743; Митолактол.
1,6-Dibromo-1,6-dideoxy-D-galactitol.
$C_6H_{12}Br_2O_4$=308.0
CAS — 10318-26-0.
UNII — LJ2P1SIK8Y.

Profile

Mitolactol is an antineoplastic that may act by alkylation, probably as epoxide metabolites including dianhydrogalactitol. It has been given orally in the treatment of metastatic breast and cervical carcinoma, although other drugs are usually preferred, and has also been tried in other malignant neoplasms, notably those of the brain. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In addition to myelosuppression, which is usually dose-limiting, and manifests chiefly as leucopenia and thrombocytopenia, adverse effects include gastrointestinal disturbances, skin rashes, grey pigmentation of the skin, transient disturbances of hepatic function, elevated blood-urea nitrogen (BUN), and hypersensitivity reactions. Blood counts should be taken regularly during treatment and mitolactol withdrawn if bone-marrow depression occurs.

Mitomycin *(BAN, USAN, rINN)*

Mitomicina; Mitomicina C; Mitomicinas; Mitomicinum; Mitomisin; Mitomycin C; Mitomycine; Mitomycine C; Mitomycinum; Mitomysiini; NSC-26980; Митомицин.
6-Amino-1,1a,2,8,8a,8b-hexahydro-8-hydroxymethyl-8a-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione carbamate; (1*S*,2*S*,9*S*,9a*R*)-7-Amino-2,3,5,8,9,9a-hexahydro-9a-methoxy-6-methyl-5,8-dioxo-1,2-epimino-1-*H*-pyrrolo[1,2-*a*]indol-9-ylmethyl carbamate.
$C_{15}H_{18}N_4O_5$=334.3
CAS — 50-07-7.
ATC — L01DC03.
ATC Vet — QL01DC03.
UNII — 50SG9535K6.

Description. Mitomycin is an antineoplastic antibiotic produced by the growth of *Streptomyces caespitosus.*

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Mitomycin). A substance produced by a strain of *Streptomyces caespitosus.* Blue-violet crystals or crystalline powder. Slightly soluble in water and in acetone; freely soluble in dimethylacetamide; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 7.5. Protect from light.

USP 36: (Mitomycin). A blue-violet crystalline powder. It has a potency of not less than 970 micrograms/mg. Slightly soluble in water; soluble in acetone, in butyl acetate, in cyclohexanone, and in methyl alcohol. A 0.5% suspension in water has a pH of 6.0 to 7.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Mitomycin may be incompatible with drugs that are acid in solution—for a report of incompatibility with topotecan, see p. 872.3.

Stability. Mitomycin undergoes degradation in acid solution,[1] and two studies[2,3] suggested that mitomycin was much less stable in glucose 5% injection than in sodium chloride 0.9%. These findings were queried by a manufacturer (*Bristol, USA*) whose own results suggested[4] that mitomycin was stable for 48 hours in glucose injection 5% at 25 degrees, and it is uncertain whether different manufacturers' formulations differ in stability, or, as has been suggested, that an unsuitable assay was used by the manufacturer to measure stability.[5]

1. Beijnen JH, Underberg WJM. Degradation of mitomycin C in acidic solution. *Int J Pharmaceutics* 1985; **24:** 219–29.
2. Benvenuto JA, *et al.* Stability and compatibility of antitumour agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
3. Quebbeman EJ, *et al.* Stability of mitomycin admixtures. *Am J Hosp Pharm* 1985; **42:** 1750–4.

4. Keller JH. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; **43:** 59,64.
5. Quebbeman EJ, Hoffman NE. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; **43:** 64.

Uses and Administration

Mitomycin is a highly toxic antibiotic with antineoplastic properties. It acts as an alkylating agent after activation *in vivo* and suppresses the synthesis of nucleic acids. It is a cell-cycle non-specific agent, but is most active in the late G_1 and early S phases.

Mitomycin is used, with other antineoplastic agents, in the treatment of many solid tumours including those of the bladder, breast, cervix, eye, stomach, and prostate as indicated by the cross-references given below. Mitomycin has been tried in other neoplasms including those of the gastrointestinal tract, head and neck, pancreas, in melanoma, sarcomas, and in leukaemias.

Dosage regimens include an initial dose of 10 to 20 mg/m^2 intravenously; subsequent doses are repeated at intervals of 6 to 8 weeks if blood counts permit, and should be reduced according to the previous haematological response. Usual doses in other regimens range from 4 to 10 mg (60 to 150 micrograms/kg) given at 1- to 6-week intervals. Other regimens may be used, particularly in combination.

Doses are adjusted according to the effect on bone marrow and treatment should not be repeated until the leucocyte and platelet counts are above acceptable levels (see also Bone-marrow Depression, p. 730.3).

Mitomycin is also used as a bladder instillation: 20 to 40 mg is instilled once weekly or three times a week for a total of 20 doses in the treatment of superficial bladder tumours. These doses are usually given in 20 to 40 mL of water for injection. The solution should be retained in the bladder for at least 1 hour. For the prevention of recurrent bladder tumours 20 mg may be instilled every 2 weeks, or 40 mg monthly or 3-monthly. Alternatively 4 to 10 mg has been instilled once weekly or three times a week.

Mitomycin has been given by the intra-arterial route in the treatment of liver tumours, sometimes as an infusion of microcapsules designed to produce localised embolisation.

Mitomycin is used for its effect on fibroblasts to improve outcomes and reduce scarring in certain types of surgery, notably in glaucoma (see below).

Mitomycin is also used topically in the form of 0.02% or 0.04% eye drops to treat conjunctival or corneal squamous cell carcinoma.

References.
1. Abraham LM, *et al.* Mitomycin: clinical applications in ophthalmic practice. *Drugs* 2006; **66:** 321–40.
2. Bolenz C, *et al.* Intravesical mitomycin C for superficial transitional cell carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 1273–82.
3. Tabaee A, *et al.* Mitomycin C and endoscopic sinus surgery: where are we? *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 40–3.
4. Warner D, Brietzke SE. Mitomycin C and airway surgery: how well does it work? *Otolaryngol Head Neck Surg* 2008; **138:** 700–9.
5. Teus MA, *et al.* Mitomycin C in corneal refractive surgery. *Surv Ophthalmol* 2009; **54:** 487–502.

Glaucoma. Mitomycin, like fluorouracil, is effective in improving the outcome of glaucoma filtering surgery in selected patients when used as an adjunct to prevent the formation of scar tissue (see p. 1999.1). Fluorouracil is usually given as a regimen of multiple injections but mitomycin given as a single intra-operative topical application in usual concentrations ranging from 200 to 500 micrograms/mL appears to be of similar efficacy.[1,2] A systematic review of 11 studies concluded that intra-operative mitomycin reduced the chances of failure in high-risk patients, and in those having their first trabeculectomy.[3] However it was noted that the nature of the data might have led to overestimation of the effect and that there was some evidence of an increased risk of cataract with mitomycin. Late hypotony is also a problem.[4] For other potential complications see Effects on the Eye, below.

1. Skuta GL, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992; **99:** 438–44.
2. Katz GJ, *et al.* Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery: extended follow-up. *Ophthalmology* 1995; **102:** 1263–9.
3. Wilkins M, *et al.* Intra-operative mitomycin C for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 25/04/06).
4. Bindlish R, *et al.* Efficacy and safety of mitomycin-C in primary trabeculectomy: five-year follow-up. *Ophthalmology* 2002; **109:** 1336–42.

Keratectomy. Mitomycin has been used as an adjunct to laser keratectomy (photorefractive or phototherapeutic keratectomy) to prevent the subsequent formation of corneal haze due to fibroblast proliferation. Although earlier studies used brief intraoperative local application of a 0.02% solution, a lower dose solution (0.002%) also appears to be effective, and may reduce the risk of adverse effects.

References.
1. Kottler UB, Dick HB. Mitomycin C bei oberflächlichen Hornhautablationen mit dem Excimer-Laser: Eigene Erfahrungen und Literaturübersicht. *Klin Monbl Augenheilkd* 2005; **222:** 499–504.
2. Wallau AD, *et al.* Mitomicina C e "Excimer laser". *Arq Bras Oftalmol* 2005; **68:** 867–72.
3. Bedei A, *et al.* Photorefractive keratectomy in high myopic defects with or without intraoperative mitomycin C: 1-year results. *Eur J Ophthalmol* 2006; **16:** 229–34.
4. Thornton I, *et al.* Low-dose mitomycin C as a prophylaxis for corneal haze in myopic surface ablation. *Am J Ophthalmol* 2007; **144:** 673–681.
5. Thornton I, *et al.* Comparison of standard (0.02%) and low dose (0.002%) mitomycin C in the prevention of corneal haze following surface ablation for myopia. *J Refract Surg* 2008; **24:** S68–S76.
6. Srinivasan S, *et al.* Photorefractive keratectomy with 0.02% mitomycin C for treatment of residual refractive errors after LASIK. *J Refract Surg* 2008; **24:** S64–S67.
7. Leccisotti A. Mitomycin C in photorefractive keratectomy: effect on epithelialization and predictability. *Cornea* 2008; **27:** 288–91.
8. Wallau AD, Campos M. Photorefractive keratectomy with mitomycin C versus LASIK in custom surgeries for myopia: a bilateral prospective randomized clinical trial. *J Refract Surg* 2008; **24:** 326–36.
9. Wallau AD, Campos M. One-year outcomes of a bilateral randomised prospective clinical trial comparing PRK with mitomycin C and LASIK. *Br J Ophthalmol* 2009; **93:** 1634–8.
10. Virasch VV, *et al.* Reduced application time for prophylactic mitomycin C in photorefractive keratectomy. *Ophthalmology* 2010; **117:** 885–9.
11. Shah RA, Wilson SE. Use of mitomycin-C for phototherapeutic keratectomy and photorefractive keratectomy surgery. *Curr Opin Ophthalmol* 2010; **21:** 269–73.

Malignant neoplasms. Mitomycin is used in the prevention of recurrent bladder cancer (p. 700.2), in the palliative therapy of advanced breast cancer (p. 702.1), in malignancies of the cervix (p. 704.2), eye (p. 705.1), and stomach and anus (p. 706.1 and p. 708.1), and has been tried in advanced prostatic cancer (see p. 712.3).

Pterygium. Pterygium is a degenerative condition of subconjunctival tissues that results in a vascularised overgrowth of the conjunctiva and cornea. It is cosmetically unappealing but does not usually require treatment. However, if it affects the pupillary area it can be treated surgically. Pterygium often recurs after removal and methods used to prevent recurrence include radiotherapy or the topical application of mitomycin or thiotepa.[1]

Thiotepa has been applied postoperatively as 0.05% eye drops for several weeks, but pterygium may still recur[2] and adverse effects include conjunctival injection, granuloma, hypertrophic conjunctiva, and black deposits in the conjunctival fornix.[1] Depigmentation of the eyelids may also be a problem, so patients should avoid direct sunlight during thiotepa use.[1]

Mitomycin has been applied topically to the surgical site, or given as eye drops postoperatively.[1] The optimal intraoperative exposure time and concentration are uncertain: concentrations of 0.02 or 0.04% have been applied for up to 5 minutes,[1,3] and low-dose treatment with mitomycin 0.02% for 30 seconds has been reported to be effective with few complications.[4] Postoperative treatment has generally been given as 0.02, 0.04, or 0.1% eye drops for up to 2 weeks, but the higher concentrations and longer treatment periods have been associated with more adverse effects,[1] some of which may be severe and sight-threatening (see also Effects on the Eyes, below). Comparisons of intraoperative with postoperative use suggest that pterygium recurrence rates are similar.[1,5]

A range of β-irradiation doses and fractionation methods have been used. Long-term complications include posterior subcapsular changes of the lens, atrophy and ulceration of the sclera, and scleral necrosis leading to endophthalmitis.[1] In one retrospective study,[6] intra-operative use of 0.04% mitomycin was more effective than β-irradiation in preventing recurrence after surgery. In another study,[7] postoperative mitomycin 0.02% for one week was less effective than radiation therapy.

1. Hoffman RS, Power WJ. Current options in pterygium management. *Int Ophthalmol Clin* 1999; **39:** 15–26.
2. Chapman-Smith JS. Pterygium treatment with triethylene thiophosphoramide. *Aust N Z J Ophthalmol* 1992; **20:** 129–31.
3. Anduze AL. Pterygium surgery with mitomycin-C: ten-year results. *Ophthalmic Surg Lasers* 2001; **32:** 341–5.
4. Cheng H-C, *et al.* Low-dose intraoperative mitomycin C as chemoadjuvant for pterygium surgery. *Cornea* 2001; **20:** 24–9.
5. Oguz H, *et al.* Intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. *Acta Ophthalmol Scand* 1999; **77:** 147–50.
6. Amano S, *et al.* Comparative study of intraoperative mitomycin C and β irradiation in pterygium surgery. *Br J Ophthalmol* 2000; **84:** 618–21.
7. Şimşek T, *et al.* Comparative efficacy of β -irradiation and mitomycin-C in primary and recurrent pterygium. *Eur J Ophthalmol* 2001; **11:** 126–32.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The main adverse effect of mitomycin is delayed cumulative bone-marrow suppression. Profound leucopenia and thrombocytopenia occurs after about 4 weeks with recovery in about 8 to 10 weeks after a dose. Therapy should be withheld until platelets and white blood cells recover to at least 100 000 cells/mm^3 and 4000 cells/mm^3, respectively. Blood counts may not recover in about one-quarter of patients. Other serious adverse effects include renal damage and pulmonary toxicity; a potentially fatal haemolytic-uraemic syndrome has been reported in some patients. US licensed product information states that the degree of renal impairment does not appear to be related to dose or duration of therapy although it has been suggested that the risk of renal toxicity is low with cumulative doses less than 50 mg/m^2, but increases with higher cumulative doses (see also Effects on the Kidneys, below). Gastrointestinal toxicity, dermatitis, alopecia, fever, malaise, and rarely cardiotoxicity may also occur. Local tissue necrosis, ulceration, and cellulitis may follow extravasation. Intra-arterial use can cause skin disorders such as pain, redness, erythema, blisters, erosion, and ulceration; skin and/or muscle necrosis may develop. Injection into the hepatic artery can cause liver and biliary tract disorders such as cholecystitis, cholangitis, and bile duct necrosis.

Mitomycin is contra-indicated in patients with impaired renal function or coagulation disorders. Renal function should be tested before beginning treatment and after each course.

Effects on the bladder. Intravesical instillation of mitomycin after resection of superficial bladder tumours has led to the development of indolent asymptomatic ulcers at the resection site which may persist for months, and must be distinguished from persistent infiltrating bladder cancer.[1,2] Persistent ulceration, inflammation, necrosis, and pain has also occurred, possibly because of mitomycin extravasation at the resection site.[3] Fistula formation has also been described.[4] There are also a few reports[5] of eosinophilic cystitis, in which eosinophilic infiltration of the mucosa and muscle were accompanied by oedema, inflammation, muscle necrosis and fibrosis. Severe bladder contracture is a rare, and often irreversible, complication of intravesical mitomycin;[6] urinary diversion may be required in cases of intolerable urinary frequency.[7] Formation of papillary-like calcifications at the resection site,[8] and calcification of the bladder wall have also been described after the use of mitomycin for superficial transitional cell carcinoma of the bladder.

See also under Effects on the Skin, p. 832.1.

1. Richards B, Tolley D. Benign ulcers after bladder instillation of mitomycin C. *Lancet* 1986; **i:** 45.
2. Hetherington JW, Whelan P. Persistent ulcers after bladder instillation of mitomycin C. *Lancet* 1986; **i:** 324.
3. Cliff AM, *et al.* Perivesical inflammation after early mitomycin C instillation. *BJU Int* 2000; **85:** 556–7.
4. Dangle PP, *et al.* Vesicoenteric, vesicovaginal, vesicocutaneousfistula -an unusual complication with intravesical mitomycin. *Can J Urol* 2008; **15:** 4269–72.
5. Ülker V, *et al.* Eosinophilic cystitis induced by mitomycin-C. *Int Urol Nephrol* 1996; **28:** 755–9.
6. Punga-Maole ML, *et al.* Rétraction vésicale, complication de la chimioprophylaxie du cancer vésical superficiel par mitomycine C endovésicale: a propos d'un cas et revue de la littérature. *Prog Urol* 1995; **5:** 580–5.
7. Wajsman Z, *et al.* Severely contracted bladder following intravesical mitomycin C therapy. *J Urol (Baltimore)* 1983; **130:** 340–1.
8. Fiore AA, *et al.* Papillary-like bladder calcifications following intravesical mitomycin C: a case report. *Minerva Urol Nefrol* 1993; **45:** 171–3.

Effects on the eyes. Early complications after the topical use of mitomycin with glaucoma filtering surgery (see Glaucoma, above) include hypotony, shallow anterior chamber, cataract formation, choroidal effusions, hypotonous maculopathy, and suprachoroidal haemorrhage.[1] Late complications include bleb leak, blebitis, and endophthalmitis.[2] Complications from the topical use of mitomycin with or after pterygium surgery (see Pterygium, above) commonly include irritation and photophobia. Other effects include delayed epithelial healing, avascularity of the sclera and cornea, scleral calcification and ulceration, necrotising scleritis, corneal or scleral perforation, iridocyclitis, cataract formation, glaucoma, and symblepharon.[1] Some of these effects may be severe and sight-threatening, and require further surgery.[3] Complications most commonly reported after the use of topical mitomycin in ocular surface neoplasia were hypersensitivity reactions and epiphora (an overflow of tears) secondary to stenosis of the lachrymal punctum.[4]

1. Hardten DR, Samuelson TW. Ocular toxicity of mitomycin-C. *Int Ophthalmol Clin* 1999; **39:** 79–90.
2. DeBry PW, *et al.* Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. *Arch Ophthalmol* 2002; **120:** 297–300.
3. Rubinfeld RS, *et al.* Serious complications of topical mitomycin C after pterygium surgery. *Ophthalmology* 1992; **99:** 1647–54.
4. Khong JJ, Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. *Br J Ophthalmol* 2006; **90:** 819–22.

Effects on the kidneys. A syndrome of thrombotic microangiopathy resembling the haemolytic-uraemic syndrome has been seen in patients receiving mitomycin, either alone[1] or more often with other drugs, particularly fluorouracil[2] or tamoxifen.[3,4] The syndrome is characterised by haemolytic anaemia, thrombocytopenia, and progressive renal failure, and may be accompanied by hypertension, pulmonary oedema, and neurological effects including confusion, headache, and seizures.[1,2] Onset is usually delayed, sometimes occurring several months after the end of a course of mitomycin.[1,2]

There is some uncertainty as to whether mitomycin dose is significant, but one study[1] found that all of 25 cases they

reported had received total doses of 70 mg or more, and another[2] reported that 74 of 83 cases had received 60 mg or more.

Symptoms may be exacerbated by blood transfusions.[2] The use of erythropoietin allowed the cessation of blood transfusion, with subsequent haematological improvement and slower progression of chronic renal failure in one case report.[5] Plasma exchange has been suggested as possibly helpful,[1] although only a minority of patients may benefit from this treatment.[2] Extracorporeal protein A immunoadsorption has also been tried.[6] Captopril therapy may also be useful.[7]

1. Cordonnier D, *et al.* La néphrotoxicité de la mitomycine C (à propos de 25 observations): résultats d'une enquête multicentrique organisée par la société de néphrologie. *Nephrologie* 1985; **6:** 19–26.
2. Lesesne JB, *et al.* Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989; **7:** 781–9.
3. Montes A, *et al.* A toxic interaction between mitomycin C and tamoxifen causing the haemolytic uraemic syndrome. *Eur J Cancer* 1993; **29A:** 1854–7.
4. Ellis PA, *et al.* Haemolytic uraemic syndrome in a patient with lung cancer: further evidence for a toxic interaction between mitomycin-C and tamoxifen. *Clin Oncol (R Coll Radiol)* 1996; **8:** 402–3.
5. Catalano C, *et al.* Erythropoietin is beneficial in mitomycin-induced hemolytic-uremic syndrome. *Nephron* 2002; **91:** 324–6.
6. Kasper S, *et al.* Protein A immunoadsorption therapy for refractory, mitomycin C-associated thrombotic microangiopathy. *Transfusion* 2007; **47:** 1263–7.
7. Schiebe ME, *et al.* Mitomycin C-related hemolytic uremic syndrome in cancer patients. *Anticancer Drugs* 1998; **9:** 433–5.

Effects on the liver. Hepatic veno-occlusive disease developed in 6 of 29 patients given intensive mitomycin therapy and autologous bone marrow transplantation.[1] The effect was manifest as abdominal pain, hepatomegaly, and ascites, and liver failure was progressive and fatal in 3. A further patient, who had no symptoms, was found to have veno-occlusive disease at post mortem.

1. Lazarus HM, *et al.* Veno-occlusive disease of the liver after high-dose mitomycin C therapy and autologous bone marrow transplantation. *Cancer* 1982; **49:** 1789–95.

Effects on respiratory function. Mitomycin-induced pulmonary toxicity has been reviewed.[1,2] There have been reports of toxicity at total dosages as low as 20 mg/m² of mitomycin,[2] although others report[1] that the average cumulative dose associated with toxicity is 78 mg. Premedication with corticosteroids may reduce the incidence of lung toxicity.[2] Interstitial lung disease associated with intravesical mitomycin has also been described.[3]

See also Effects on the Lungs, p. 729.1. For reference to the respiratory effects of mitomycin used with a vinca alkaloid see Interactions, Antineoplastics, under Vinblastine Sulfate, p. 882.2.

1. Linette DC, *et al.* Mitomycin-induced pulmonary toxicity: case report and review of the literature. *Ann Pharmacother* 1992; **26:** 481–4.
2. Okuno SH, Frytak S. Mitomycin lung toxicity: acute and chronic phases. *Am J Clin Oncol* 1997; **20:** 282–4.
3. Janeiro Pais JM, *et al.* Mitomicina C endovesical y fibrosis pulmonar. *Actas Urol Esp* 2009; **33:** 822–5.

Effects on the skin. Severe eczema of the hands and feet and generalised rash have been reported in patients receiving intravesical mitomycin.[1,2] These symptoms appear to be due to a delayed hypersensitivity (type IV) reaction,[1,2] which is probably also responsible for the bladder irritation and cystitis that may follow intravesical mitomycin[1] (see p. 831.3). Leucocytoclastic vasculitis caused by an immune-complex mediated (type III) reaction and presenting as purpuric papules has also been described.[2]

1. Colver GB, *et al.* Dermatitis due to intravesical mitomycin C: a delayed-type hypersensitivity reaction? *Br J Dermatol* 1990; **122:** 217–24.
2. Kunkeler L, *et al.* Type III and type IV hypersensitivity reactions due to mitomycin C. *Contact Dermatitis* 2000; **42:** 74–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mitomycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Antineoplastics. Cardiotoxicity developed in 14 of 91 patients who received mitomycin therapy as second-line treatment for breast cancer after the failure of *doxorubicin*-containing regimens, compared with 3 of 89 similar patients whose second-line treatment did not include mitomycin.[1]

For reports of acute bronchospasm after injection of a *vinca alkaloid* in patients pretreated with mitomycin see Vinblastine Sulfate, p. 882.2. For the increased risk of haemolytic-uraemic syndrome that may occur if mitomycin is given with *fluorouracil* or *tamoxifen* see under Effects on the Kidneys, p. 831.3.

1. Buzdar AU, *et al.* Adriamycin and mitomycin C: possible synergistic cardiotoxicity. *Cancer Treat Rep* 1978; **62:** 1005–8.

Pharmacokinetics

Mitomycin disappears rapidly from the blood after intravenous injection with an initial (distribution) half-life of 17 minutes. It is widely distributed but does not appear to cross the blood-brain barrier. Mitomycin is metabolised mainly but not exclusively in the liver. The terminal half-life is about 50 minutes. After normal doses about 10% of a dose is excreted unchanged in the urine; small amounts are also present in bile and faeces. With increasing doses metabolic pathways are saturated, and more drug is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asomutan; Crisofimina; Maximiton; Mitocyna; Mitokebir; Mitonovag; Mitotie; Sintemicina; Vetio; ***Braz.***: Baxmicin†; Mitocin; ***Fin.***: Mitostat; ***Fr.***: Ametycine; ***Ger.***: Ametycine; Mitem; Mito-extra; Mito-medac; ***India***: Almito; Mitocin; Mitodus; Mitonco; Oncocin; ***Mex.***: Mitocin-C†; Mitolem; Mitotie; Mixandex; ***Philipp.***: Mytoxid; ***Thai.***: Mitocin; Vesimycin; ***USA***: Mitosol; Mitozytrex†; Mutamycin†.

Pharmacopoeial Preparations
USP 36: Mitomycin for Injection.

Mitotane *(BAN, USAN, rINN)*

CB-313; Mitotaani; Mitotan; Mitotano; Mitotanum; NSC-38721; o,p'DDD; WR-13045; Митотан.

1,1-Dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane.

$C_{14}H_{10}Cl_4$=320.0

CAS — 53-19-0.

ATC — L01XX23.

ATC Vet — QL01XX23.

UNII — 78E4J5IB5J.

Pharmacopoeias. In *US.*

USP 36: (Mitotane). A white crystalline powder with a slight aromatic odour. M.p. is between 75 degrees and 81 degrees. Practically insoluble in water; soluble in alcohol, in ether, in petroleum spirit, and in fixed oils and fats. Store in airtight containers. Protect from light.

Uses and Administration

Mitotane is an oral antineoplastic that directly suppresses the adrenal cortex. It may also modify peripheral steroid metabolism. It is given in the treatment of advanced adrenocortical tumours. Dosing schedules vary. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In the UK, mitotane is given in an initial oral dose of 2 to 3 g daily in patients with adrenocortical tumours, increased at 2-week intervals until plasma mitotane concentrations reach the target range of 14 to 20 micrograms/mL. For rapid control of Cushing's symptoms in these patients, an initial oral dose of 4 to 6 g daily may be necessary, and can be increased as often as every week to achieve the target concentration range. The total daily dose is given in 2 or 3 divided doses with meals containing fat-rich foods. Corticosteroid therapy may also be required for adrenal insufficiency, see Precautions, below. Mitotane plasma concentrations should be measured at frequent intervals (after each dose adjustment) until the target concentration range is reached, usually within 3 to 5 months. Regular monitoring of plasma concentrations should continue once the maintenance dose is established. If severe toxicity occurs, mitotane treatment should be withheld and restarted when plasma concentrations are within the target range. For mild toxicity the dose should be reduced until the maximum tolerated dose is reached. Mitotane treatment may be continued for as long as there is benefit. If there is no benefit after 3 months at an optimal dose, treatment should be stopped. For doses in children, see below.

In the USA, the usual initial oral dosage is 2 to 6 g daily in 3 or 4 divided doses. Doses are usually increased to 9 to 10 g daily, unless adverse effects necessitate dose reduction. The maximum tolerated dose ranges from about 2 to 16 g daily.

Administration in children. Mitotane is used in children and adolescents for the treatment of advanced adrenocortical tumours. In the UK, an initial oral dose of 1.5 to 3.5 g/m² daily can be increased up to a target dose of 4 g/m² daily. The total daily dose is given in 2 or 3 divided doses with meals containing fat-rich foods. Plasma concentrations of mitotane should be monitored as for adults, see above; a sharp increase in mitotane concentration may be seen when 10 micrograms/mL is reached. The dose may be reduced after 2 or 3 months depending on mitotane concentrations or toxicity.

Malignant neoplasms of the adrenal gland. Adrenocortical carcinoma is a rare and aggressive malignancy, and there are few prospective studies of its treatment. Surgery is the treatment of choice and the only curative option for localised disease.[1] Retrospective studies of adjuvant mitotane after resection with curative intent have shown mixed results. Some investigators found that mitotane had no effect on survival[2] or recurrence rate,[3] while others reported significantly improved recurrence-free survival.[4] Nevertheless, mitotane is often suggested as adjuvant therapy because of the high risk of recurrence, although it might be considered unnecessary following complete resection of localised small tumours.[1,5]

Mitotane has been reported to be of benefit in patients undergoing palliative surgery,[2] and is the drug of choice when the tumour cannot be completely removed surgically[1,5] although tumour reduction may be minimal.[5] Response rates range from 13 to 30% in metastatic disease, but most are of limited duration and complete response is rare.[1] It is also used in metastatic disease to control symptoms but adverse effects can limit its use. Mitotane has also been tried with cytotoxic chemotherapy, and various regimens are under investigation.[1]

1. Zini L, *et al.* Contemporary management of adrenocortical carcinoma. *Eur Urol* 2011; **60:** 1055–65.
2. Icard P, *et al.* Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg* 2001; **25:** 891–7.
3. Grubbs EG, *et al.* Recurrence of adrenal cortical carcinoma following resection: surgery alone can achieve results equal to surgery plus mitotane. *Ann Surg Oncol* 2010; **17:** 263–70.
4. Terzolo M, *et al.* Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007; **356:** 2372–80.
5. Veytsman I, *et al.* Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. *J Clin Oncol* 2009; **27:** 4619–29.

Adverse Effects

Almost all patients given mitotane have anorexia, nausea and vomiting, and sometimes diarrhoea, and about 40% suffer some central toxicity with dizziness, vertigo, sedation, lethargy, ataxia, and paraesthesia. Brain damage and impaired function can occur after prolonged use of high doses. Other common adverse effects include leucopenia, thrombocytopenia, anaemia, hypercholesterolaemia, hypertriglyceridaemia, mucositis, gynaecomastia, and headache. Bleeding time may be prolonged, but the mechanism of this effect is unknown. Ocular adverse effects may occur including blurred vision, diplopia, lenticular opacities, maculopathy, and retinopathy. Other adverse effects include hypersensitivity reactions, rashes, fever, myalgia, myasthenia, haemorrhagic cystitis, haematuria, albuminuria, flushing, hypertension, orthostatic hypotension, and hypersalivation. Liver enzymes are commonly increased with mitotane, and there have been reports of auto-immune hepatitis and cholestatic hepatitis. Hypothyroidism has occurred.

Precautions

Mitotane inhibits the adrenal cortex and adrenocortical insufficiency may develop during treatment; corticosteroid therapy is often required. In trauma, infection, or shock the drug should be temporarily withdrawn and corticosteroids should be given systemically. Mitotane should be given with care to patients with renal or hepatic impairment. Before mitotane therapy is begun, all possible tumour tissue from large metastases should be surgically removed, in order to minimise possible infarction or haemorrhage in the tumour. Patients should not drive or operate machinery. Behavioural and neurological assessments should be carried out regularly in patients who have been receiving treatment for 2 years or more, especially when mitotane plasma concentrations exceed 20 micrograms/mL. Plasma concentrations should be monitored to guide dosage; the therapeutic window lies between 14 and 20 micrograms/mL (see also Therapeutic Drug Monitoring, p. 833.1). Fetal adrenal abnormalities have been reported after exposure during pregnancy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mitotane as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Mitotane can induce hepatic microsomal enzymes such as cytochrome P450 isoenzymes. This may enhance the

metabolism of some other drugs, including coumarin anticoagulants.

Spironolactone. Mitotane in a dose of up to 3 g daily in a 65-year-old patient with Cushing's syndrome appeared to be ineffective and did not produce the usual adverse effects associated with mitotane while the patient was also receiving spironolactone.[1]

1. Wortsman J, Soler NG. Mitotane: spironolactone antagonism in Cushing's syndrome. *JAMA* 1977; **238:** 2527.

Pharmacokinetics

Up to 40% of a dose of mitotane is absorbed from the gastrointestinal tract; absorption increases with food. After daily doses of 5 to 15 g, concentrations in the blood of 7 to 90 micrograms/mL of unchanged drug and 29 to 54 micrograms/mL of metabolite have been reported. It is widely distributed and appears to be stored mainly in fatty tissues. It is metabolised in the liver and other tissues and excreted as metabolites in urine and bile. From 10 to 25% of a dose has been recovered in the urine as a water-soluble metabolite. As it is slowly released from storage sites, terminal plasma half-lives ranging from 18 to 159 days have been reported. In most patients mitotane is no longer detected in plasma about 6 to 9 weeks after stopping therapy.

Therapeutic drug monitoring. Monitoring of mitotane and its major metabolite *o,p'*-DDE in 2 patients receiving mitotane in low doses for Cushing's disease found that there is a prolonged lag time in the plasma concentration changes in response to alterations in dosage,[1] presumably because of the lipophilicity of both compounds which leads to accumulation in adipose tissue. A study[2] in adrenal carcinoma found that mitotane is preferentially distributed into the very-low-density lipoprotein (VLDL) fraction of the serum of patients with hypertriglyceridaemia, whereas under normolipidaemic conditions, it is bound to high-density lipoproteins and albumin. Because VLDL is not incorporated into the human adrenal cells, mitotane's lipophilicity has implications for treatment and monitoring in patients with hypertriglyceridaemia. In some studies[3,4] tumour responses were seen only in those patients with a serum concentration of mitotane above 14 micrograms/mL, and a small prospective study[5] found that therapeutic concentrations (defined as between 14 and 20 micrograms/mL) could be reached by sustained low doses (1 to 3 g daily), thus limiting adverse effects.

1. Benecke R, *et al.* Plasma level monitoring of mitotane (o,p'-DDD) and its metabolite (o,p'-DDE) during long-term treatment of Cushing's disease with low doses. *Eur J Clin Pharmacol* 1991; **41:** 259–61.
2. Gebhardt DOE, *et al.* The distribution of *o,p'*-DDD (mitotane) among serum lipoproteins in normo-and hypertriglyceridemia. *Cancer Chemother Pharmacol* 1992; **29:** 331–4.
3. Haak HR, *et al.* Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. *Br J Cancer* 1994; **69:** 947–51.
4. Baudin E, *et al.* Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer* 2001; **92:** 1385–92.
5. Terzolo M, *et al.* Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. *J Clin Endocrinol Metab* 2000; **85:** 2234–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lysodren; ***Belg.***: Lysodren; ***Braz.***: Lisodren; ***Canad.***: Lysodren; ***Cz.***: Lysodren; ***Denm.***: Lysodren; ***Fin.***: Lysodren; ***Fr.***: Lysodren; ***Ger.***: Lysodren†; ***Gr.***: Lysodren; ***Hong Kong***: Lysodren†; ***Hung.***: Lysodren; ***Irl.***: Lysodren; ***Ital.***: Lysodren; ***Neth.***: Lysodren; ***Norw.***: Lysodren; ***Pol.***: Lysodren; ***Port.***: Lysodren; ***Spain***: Lysodren; ***Switz.***: Lysodren; ***UK***: Lysodren; ***USA***: Lysodren.

Pharmacopoeial Preparations
USP 36: Mitotane Tablets.

Mitoxantrone Hydrochloride

(BANM, USAN, rINNM)

CL-232315; DHAD; Dihydroxyanthracenedione Dihydrochloride; Hidrocloruro de mitoxantrona; Mitoksantron Hidroklorür; Mitoksantronihydrokloridi; Mitoksantrono hidrochloridas; Mitoxantron dihydrochlorid; Mitoxantrona, hidrocloruro de; Mitoxantrone, Chlorhydrate de; Mitoxantronhidrokloríd; Mitoxantronhydrochlorid; Mitoxantronhydroklorid; Mitoxantroni Dihydrochloridum; Mitoxantroni hydrochloridum; Mitozantron Hidroklorür; Mitozantrone Hydrochloride; NSC-301739; Митоксантрона Гидрохлорид.

1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino] anthraquinone dihydrochloride.

$C_{22}H_{28}N_4O_6.2HCl$=517.4

CAS — 65271-80-9 (mitoxantrone); 70476-82-3 (mitoxantrone hydrochloride).

ATC — L01DB07.

ATC Vet — QL01DB07.

UNII — U6USW86RD0.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Mitoxantrone Hydrochloride). A dark-blue, electrostatic, hygroscopic powder. Sparingly soluble in water; practically insoluble in acetone; slightly soluble in methyl alcohol. Store in airtight containers.

USP 36: (Mitoxantrone Hydrochloride). A dark-blue powder. Sparingly soluble in water; practically insoluble in acetone, in acetonitrile, and in chloroform; slightly soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Mitoxantrone is an anthracenedione antineoplastic structurally related to doxorubicin (p. 782.3). It inhibits topoisomerase II and causes DNA strand breakage, as well as intercalating with DNA. It is cell-cycle non-specific but is most active against cells in the late S phase.

It is used in the treatment of metastatic breast cancer (p. 702.1), and of non-Hodgkin's lymphomas (p. 696.3), alone or with other agents. It may also be given to treat adult acute myeloid leukaemias (p. 693.1). Mitoxantrone has also been used in patients with hormone-refractory prostate cancer (p. 712.3), liver cancer (p. 709.3), and ovarian cancer (p. 711.2).

In addition, mitoxantrone is used in the management of secondary progressive or relapsing multiple sclerosis (see below), to reduce neurological disability or the frequency of relapses.

Mitoxantrone is given as the hydrochloride, but doses are expressed in terms of the base; 1.2 mg of the hydrochloride is equivalent to about 1 mg of mitoxantrone. In the treatment of breast **cancer**, prostate cancer, liver cancer, and lymphomas, a dose equivalent to mitoxantrone 14 mg/m² is given initially, then repeated every 3 weeks. It is diluted to at least 50 mL in sodium chloride 0.9% or glucose 5% and injected over at least 3 minutes into a freely-running intravenous infusion of either. Subsequent doses may be adjusted according to the degree of myelosuppression produced. Initial dosage may need to be reduced to 12 mg/m² in debilitated patients or those who have had previous chemotherapy. Doses should also probably be reduced when mitoxantrone is given as part of a combination regimen: initial doses should generally be reduced by 2 to 4 mg/m² below those recommended for single-agent use.

In the treatment of patients with acute myeloid leukaemia an intravenous dose of 12 mg/m² daily for 5 days may be given as monotherapy to induce remission; alternatively 10 to 12 mg/m² may be given for 3 days with a 7-day course of cytarabine.

All patients should have cardiac function assessed before starting therapy, including left ventricular ejection fraction (LVEF) evaluation. Regular cardiac examinations are recommended in all patients at increased risk of cardiotoxicity and in those who receive a cumulative dose of mitoxantrone greater than 160 mg/m². Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p. 730.3).

In the management of **multiple sclerosis**, the recommended dose is the equivalent of mitoxantrone 12 mg/m² by intravenous infusion over 5 to 15 minutes. This dose may be given once every 3 months initially provided that neutrophil counts are above 1500 cells/mm³ and that LVEF is greater than 50%. Blood counts and liver function should be monitored before each dose. LVEF should be evaluated before beginning mitoxantrone therapy and before all subsequent doses; a total cumulative dose in excess of 140 mg/m² should be avoided. LVEF should also be measured if signs or symptoms of heart failure develop.

References.

1. Faulds D, *et al.* Mitoxantrone: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs* 1991; **41:** 400–49.
2. Fox EJ. Mechanism of action of mitoxantrone. *Neurology* 2004; **63** (suppl): S15–S18.

Multiple sclerosis. Mitoxantrone has produced clinical benefit[1-4] in terms of reduced relapse rate and a slowing of disease progression in patients with multiple sclerosis (p. 996.3). It has been given intravenously in doses of 5 or 12 mg/m² every 3 months, or 8 mg/m² every month. Patients with progressive relapsing disease may benefit from rapid induction with 12 mg/m² monthly for 3 months.[5] Benefit has also been found when used with corticosteroids,[6] although the combination was not compared with mitoxantrone alone. However, cardiotoxicity limits the dose that can be given[7,8] (see Uses and Administration, above). Because of this and other adverse effects, such as possible secondary malignancy or potentially permanent amenorrhoea, some consider the use of mitoxantrone in multiple sclerosis to be unproven[9] and others have cautioned[10] that alternative immunomodulators have less severe toxicities. A systematic review[11] concluded that mitoxantrone was moderately effective in the short-term treatment of multiple sclerosis, but that information on its long-term effects was lacking; use should be limited to patients with worsening relapsing-remitting or secondary progressive disease with evidence of worsening disability.

1. Millefiorini E, *et al.* Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997; **244:** 153–9.
2. van de Wyngaert FA, *et al.* A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg* 2001; **101:** 210–16.
3. Hartung H-P, *et al.* Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; **360:** 2018–25.
4. Jeffery DR, Herndon R. Review of mitoxantrone in the treatment of multiple sclerosis. *Neurology* 2004; **63** (suppl): S19–S24.
5. Rizvi SA, *et al.* Mitoxantrone for multiple sclerosis in clinical practice. *Neurology* 2004; **63** (suppl): S25–S27.
6. Edan G, *et al.* Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; **62:** 112–118.
7. Ghalie RG, *et al.* Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 2002; **59:** 909–13.
8. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. *Neurology* 2004; **63** (suppl): S28–S32.
9. Chaudhuri A, Behan PO. Mitoxantrone trial in multiple sclerosis. *Lancet* 2003; **361:** 1133–4.
10. Marriott JJ, *et al.* The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; **74:** 1463–70.
11. Martinelli Boneschi F, *et al.* Mitoxantrone for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/03/06).

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1. Mitoxantrone is reported to be better tolerated than doxorubicin. The nadir of the white cell count usually occurs about 10 days after a dose, with recovery by day 21. Elevation in liver enzyme values may occur; there are occasional reports of severe hepatic impairment in patients with leukaemia, in whom doses are generally higher and adverse effects of mitoxantrone may be more frequent and severe.

Transient blue-green coloration of the urine, and occasionally the sclerae, may occur. Blue discoloration of the skin (which can also occur after extravasation) and nails have been reported. Nail dystrophy and onycholysis can occur.

Severe neurotoxicity has resulted from erroneous intrathecal dosage; local or regional neuropathy has followed intra-arterial injection. Care is required in patients with pre-existing heart disease, or who have had prior anthracycline treatment or radiotherapy to the chest, as they are at increased risk of cardiotoxicity; regular cardiac examinations, including left ventricular ejection fraction (LVEF) evaluation, should be performed in these patients from the start of therapy. All patients should be assessed for cardiac signs and symptoms; multiple sclerosis patients with a baseline LVEF below the lower limit of normal should not be treated with mitoxantrone. UK licensed product information states that cardiac monitoring should also be performed in patients without identifiable cardiac risk factors who receive a total cumulative dose of mitoxantrone in excess of 160 mg/m²; US licensed product information states that the risk of symptomatic congestive heart failure is higher after a cumulative dose of 140 mg/m² and that multiple sclerosis patients should not receive a total cumulative dose greater than this. Care is also required in patients with hepatic impairment. Regular blood counts should be performed during treatment. Treatment with mitoxantrone, either alone or with other antineoplastics and/or radiotherapy, has been associated with an increased risk of development of secondary acute myeloid leukaemia.

Alopecia. Two patients receiving therapy with mitoxantrone developed selective alopecia of white but not of dark hair.[1]

1. Arlin ZA, *et al.* Selective alopecia with mitoxantrone. *N Engl J Med* 1984; **310:** 1464.

Breast feeding. Mitoxantrone was detected in the breast milk of a woman with acute promyelocytic leukaemia in remission who was given consolidation chemotherapy that included mitoxantrone 6 mg/m² on days 1 to 3. Concentrations were 120 nanograms/mL just after the third dose and 18 nanograms/mL 28 days after treatment. Although she breast fed her neonate from 3 weeks after the completion of the course of treatment and no adverse effects were seen, the authors recommended that women treated with mitoxantrone should not breast feed.[1]

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; **48:** 131–2.

Effects on the heart. Data from over 4000 patients treated with mitoxantrone included 172 reports of cardiac events, including 42 cases of congestive heart failure and 66 of

decreased ejection fraction.[1] Previous anthracycline therapy increased the risk, and congestive heart failure seemed to be more likely in patients exposed to a cumulative mitoxantrone dose of 160 mg/m², or 100 mg/m² in those already given anthracyclines. The risk of symptomatic congestive heart failure in cancer patients has been estimated to be 2.6% for patients receiving a cumulative dose of up to 140 mg/m²; the US manufacturer recommended that patients with multiple sclerosis should not receive a total cumulative dose greater than this.[2] In a further 78 patients,[3] clinical heart failure developed in 2 after cumulative doses of 174 and 243 mg/m². Four of 9 other patients given mitoxantrone in doses above 100 mg/m² showed signs of cardiotoxicity, and a further patient previously given doxorubicin 313 mg/m² had a fall in stress ejection fraction after only 47 mg/m² of mitoxantrone. However, cardiotoxicity has also been seen after lower doses; sinus bradycardia occurred[4] in 2 previously untreated patients after starting continuous infusions of mitoxantrone 10 mg/m², and severe acute heart failure[5] in a patient with multiple sclerosis, 2 months after a second dose of mitoxantrone 12 mg/m² was given. Late cardiotoxicity can also occur; dilated cardiomyopathy, with a left ventricular ejection fraction of 20%, developed[6] in a patient with multiple sclerosis 2 years after a course of mitoxantrone with a cumulative dose of 72 mg/m². For information on the cardiotoxicity of anthracyclines, to which mitoxantrone is structurally related, see under Adverse Effects and Treatment of Doxorubicin, p. 784.1.

1. Crossley RJ. Clinical safety and tolerance of mitoxantrone. *Semin Oncol* 1984; **11:** (suppl 1): 54–8.
2. Lammers P (Serono, USA). Novantrone: mitoxantrone for injection concentrate (issued April 2005). Available at: http://www.novantrone.com/assets/pdf/healthcare_professional_letter.pdf (accessed 11/08/09)
3. Stuart-Harris R, *et al.* Cardiotoxicity associated with mitoxantrone. *Lancet* 1984; **ii:** 219–20.
4. Benekli M, *et al.* Mitoxantrone-induced bradycardia. *Ann Intern Med* 1997; **126:** 409.
5. Dörr J, *et al.* Severe cardiac failure in a patient with multiple sclerosis following low-dose mitoxantrone treatment. *Neurology* 2009; **73:** 991–3.
6. Killestein J, *et al.* Severe cardiac failure in a patient with multiple sclerosis following low-dose mitoxantrone treatment. *Neurology* 2010; **74:** 934.

Handling and disposal. *Urine and faeces* produced for up to 7 days after a dose of mitoxantrone should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hypersensitivity. In a report of 3 patients, allergic-type reactions to mitoxantrone included vasculitis, facial oedema and skin rashes, and in one, breathlessness, tachypnoea, cyanosis, and unrecordable pulse and blood pressure.[1] Allergic reactions to the drug appear to be rare.

1. Taylor WB, *et al.* Allergic reactions to mitoxantrone. *Lancet* 1986; **i:** 1439.

Pregnancy. For a report of a fetal sinusoidal heart rate pattern and neonatal pancytopenia after a woman was given combination chemotherapy including mitoxantrone, see Pregnancy, under Etoposide, p. 791.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mitoxantrone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

For a report of the effect of ciclosporin in patients receiving mitoxantrone and etoposide, see p. 792.1.

Pharmacokinetics

After intravenous doses mitoxantrone is rapidly and extensively distributed to body tissues, and slowly excreted in urine and bile as unchanged drug and metabolites. The elimination half-life is reported to range from 5 to 18 days. Between 6 and 11% of a dose has been recovered from urine, and 13 to 25% in faeces, within 5 days. It does not appear to cross the blood-brain barrier, but it is distributed into breast milk.

References.

1. Ehninger G, *et al.* Pharmacokinetics and metabolism of mitoxantrone: a review. *Clin Pharmacokinet* 1990; **18:** 365–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Batinel†; Micraleve; Mitoxgen; Mitoxmar†; ***Austral.***: Novantrone†; Onkotrone; ***Austria***: Ebexantron; ***Belg.***: Xantrosin; ***Braz.***: Evomixan; Misostol; Mitoxal†; ***China***: Heng En (恒恩); Mi Xi Ning (米西宁); Novantrone (诺肖林); Ze Kang (泽康); ***Cz.***: Onkotrone†; Refador†; ***Fin.***: Novantrone; ***Fr.***: Elsep; Novantrone; ***Ger.***: Haemato-tron†; Novantron; Onkotrone; Ralenova; ***Gr.***: Genefadrone; Mitoxan; Novantrone; Zyneva; ***Hong Kong***: Novantrone†; Santrone; ***Hung.***: Novantrone†; Onkotrone; Refador†; ***India***: Mitozan; Oncotron; ***Indon.***: Norexan†; ***Irl.***: Novantrone†; ***Israel***: Novantrone; ***Ital.***: Novantrone; Onkotrone; ***Mex.***: Formyxan; Mitoxgen; Mitroxone; Neotalem; ***Norw.***: Novantrone; ***NZ***: Novantrone; Onkotrone; ***Philipp.***: Domitrone; Onkotrone†; ***Port.***: Mitroxene†; Novantrone†; ***Rus.***: Oncotrone (Онкотрон); ***S.Afr.***: Novantrone†; ***Singapore***: Ebexantron†; ***Spain***: Novantrone; Pralifan; ***Swed.***: Novantrone; ***Switz.***: Novantron; ***Thai.***: Neotalem; ***Turk.***: Neotalem; Novantrone; Oncocarbin; Oncotron; ***UK***: Onkotrone; ***USA***: Novantrone†; ***Venez.***: Misostol.

Pharmacopoeial Preparations
BP 2014: Mitoxantrone Infusion;
USP 36: Mitoxantrone Injection.

Mogamulizumab *(USAN, rINN)*

AMG-761; KM-8761; KW-0761; Mogamulizumabum; Могамулизумаб.

Immunoglobulin G1, anti-(CC chemokine receptor CCR4) (human-mouse monoclonal KW-0761 heavy chain), disulfide with human-mouse monoclonal KW-0761 κ-chain, dimer.

CAS — 1159266-37-1.
UNII — YI437801BE.

Profile

Mogamulizumab is a humanised monoclonal antibody directed against the CCR4 chemokine receptor. It is used in the treatment of relapsed or refractory adult T-cell leukaemia/lymphoma. It is also under investigation for the treatment of asthma.

References.

1. Ishida T, *et al.* Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol* 2012; **30:** 837–42.
2. Tobinai K, *et al.* Targeting chemokine receptor CCR4 in adult T-cell leukemia-lymphoma and other T-cell lymphomas. *Curr Hematol Malig Rep* 2012; **7:** 235–40.
3. Subramaniam JM, *et al.* Mogamulizumab: first global approval. *Drugs* 2012; **72:** 1293–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Poteligeo.

Motesanib *(USAN, rINN)*

AMG-706; Motésanib; Motesanibum; Мотезаниб.

N-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-6-yl)-2-[(pyridine-4-ylmethyl)amino]pyridine-3-carboxamide.

$C_{22}H_{23}N_5O$=373.5
CAS — 453562-69-1.
UNII — U1JK633AYI.

Motesanib Diphosphate *(USAN, rINN)*

AMG-706; Difosfato de motesanib; Motésanib, Diphosphate de; Motesanibi Diphosphas; Мотезаниба Дифосфат.

Motesanib phosphate (1:2).

$C_{22}H_{23}N_5O,2H_3O_4P$=569.4
CAS — 857876-30-3.
UNII — T6Q3060U91.

Profile

Motesanib is a tyrosine kinase inhibitor that targets the receptors of vascular endothelial growth factor, platelet-derived growth factor, and other growth factors, thereby inhibiting angiogenesis. It is under investigation for the treatment of solid malignancies such as non-squamous non-small cell lung cancer and breast cancer.

Muparfostat

PI-88.

CAS — 185077-23-0.

Profile

Muparfostat is a heparanase inhibitor derived from the yeast *Pichia holstii* that is under investigation for the treatment of malignancies such as liver cancer and advanced melanoma.

Naptumomab Estafenatox *(rINN)*

ABR-217620; Naptumomab Estafénatox; Naptumomabum Estafenatoxum; Наптумомаб Эстафенатокс.

Immunoglobulin fragment, anti-[trophoblast glycoprotein (TPBG, 5T4)] monoclonal 5T4 gamma1 heavy chain fragment fusion protein [*Mus musculus* VH (5T4V14: H41>P, S44>G, I69>T, V113>G)-IGHG1_CH1] - [Glycyl-Glycyl-Prolyl] -superantigen SEA/E-120 (synthetic), non-disulfide linked with monoclonal 5T4 kappa light chain [*Mus musculus* V-KAPPA (5T4V18: F10>S, T45>K, I63>S, F73>L, T77>S, L78>V, L83>A)-IGKC].

CAS — 676258-98-3.
UNII — 93T929W6LC.

Profile

Naptumomab estafenatox is a murine monoclonal antibody conjugated with a bacterial superantigen, a modified variant of staphylococcal enterotoxin A that acts as a target for T-cell activation. The antibody is directed against a tumour-specific antigen 5T4. Naptumomab estafenatox is under investigation for the treatment of renal cell carcinoma.

References.

1. Borghaei H, *et al.* Phase I dose escalation, pharmacokinetic and pharmacodynamic study of naptumomab estafenatox alone in patients with advanced cancer and with docetaxel in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2009; **27:** 4116–23.
2. Robinson MK, *et al.* Naptumomab estafenatox: a new immunoconjugate. *Expert Opin Biol Ther* 2010; **10:** 273–9.
3. Forsberg G, *et al.* Naptumomab estafenatox, an engineered antibody-superantigen fusion protein with low toxicity and reduced antigenicity. *J Immunother* 2010; **33:** 492–9.

Nedaplatin *(rINN)*

Nédaplatine; Nedaplatino; Nedaplatinum; NSC-3751010; 254-S; Недаплатин.

cis-Diammine(glycolato-*O*¹,*O*²)platinum.

$C_2H_8N_2O_3Pt$=303.2
CAS — 95734-82-0.
UNII — 8UQ3W6JXAN.

Profile

Nedaplatin is a platinum derivative with general properties similar to those of cisplatin (p. 766.1) although it may be associated with less nephrotoxicity. It is used in the treatment of a variety of malignant neoplasms. It is given by intravenous infusion over 1 hour or more, dissolved in at least 300 mL of an appropriate infusion solution, in doses of 80 to 100 mg/m². The infusion should be followed by infusion of at least 1 litre of fluid to ensure adequate hydration and reduce the risk of renal damage.

References.

1. Ishibashi T, *et al.* Determination of optimal dosage for nedaplatin based on pharmacokinetic and toxicodynamic analysis. *Anticancer Res* 2005; **25:** 1273–81.
2. Shirai T, *et al.* Phase II study of the combination of gemcitabine and nedaplatin for advanced non-small-cell lung cancer. *Lung Cancer* 2006; **52:** 181–7.
3. Fuwa N, *et al.* Chemoradiation therapy using radiotherapy, systemic chemotherapy with 5-fluorouracil and nedaplatin, and intra-arterial infusion using carboplatin for locally advanced head and neck cancer–Phase II study. *Oral Oncol* 2007; **43:** 1014–20.
4. Oshita F, *et al.* Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer. *Cancer Chemother Pharmacol* 2008; **62:** 465–70.
5. Yokoyama Y, *et al.* A phase II multicenter trial of concurrent chemoradiotherapy with weekly nedaplatin in advanced uterine cervical carcinoma: Tohoku Gynecologic Cancer Unit Study. *Oncol Rep* 2008; **19:** 1551–6.
6. Yamamoto N, *et al.* A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 2009; **65:** 79–88.
7. Hirose T, *et al.* Phase II study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer. *Anticancer Res* 2009; **29:** 1733–8.
8. Cao W, *et al.* A phase II study of paclitaxel and nedaplatin as first-line chemotherapy in patients with advanced esophageal cancer. *Jpn J Clin Oncol* 2009; **39:** 582–7.
9. Shiraishi T, *et al.* Salvage chemotherapy with paclitaxel and gemcitabine plus nedaplatin (TGN) as part of multidisciplinary therapy in patients with heavily pretreated cisplatin-refractory germ cell tumors. *Int J Clin Oncol* 2009; **14:** 436–41.
10. Osawa S, *et al.* Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma. *BMC Cancer* 2009; **9:** 408.
11. Zhang M-Q, *et al.* Concurrent chemoradiotherapy with paclitaxel and nedaplatin followed by consolidation chemotherapy in locally advanced squamous cell carcinoma of the uterine cervix: preliminary results of a phase II study. *Int J Radiat Oncol Biol Phys* 2010; **78:** 821–7.
12. Oshita F, *et al.* Phase II study of nedaplatin and irinotecan with concurrent thoracic radiotherapy in patients with locally advanced non-small-cell lung cancer. *Br J Cancer* 2010; **103:** 1325–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Xian Da (奥先达); Jepaso (捷佰舒); Lu Bei (鲁贝); Quan Bo (泉铂); ***Jpn***: Aqupla.

Nelarabine *(BAN, USAN, rINN)*

506U; 506U78; GW-506U; GW-506U78; MAY; Nelarabina; Nélarabine; Nelarabinum; Nelzarabine; Неларабин.

2-Amino-9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine.

$C_{11}H_{15}N_5O_5$=297.3

CAS — 121032-29-9.
ATC — L01BB07.
ATC Vet — QL01BB07.
UNII — 60158CV180.

Uses and Administration

Nelarabine is a prodrug of ara-G, a purine nucleoside analogue that is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma. A dose of 1.5 g/m² is given undiluted by intravenous infusion over 2 hours in adults, on days 1, 3, and 5 of a 21-day cycle. For doses in children, see below.

Nelarabine should be stopped at the first sign of moderate to severe neurological toxicity. Dosage may be delayed for other toxicities, including haematological toxicity.

References.
1. Gandhi V, *et al.* Evaluation of the combination of nelarabine and fludarabine in leukemias: clinical response, pharmacokinetics, and pharmacodynamics in leukemia cells. *J Clin Oncol* 2001; **19:** 2142–52.
2. Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. *Ann Pharmacother* 2005; **39:** 1056–63.
3. Sanford M, Lyseng-Williamson KA. Nelarabine. *Drugs* 2008; **68:** 439–47.
4. DeAngelo DJ, *et al.* Nelarabine for the treatment of patients with relapsed or refractory T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma. *Hematol Oncol Clin North Am* 2009; **23:** 1121–35.

Administration in children. Nelarabine is given to children for the treatment of relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma. It is given undiluted by intravenous infusion over 1 hour, at a dose of 650 mg/m² daily for 5 consecutive days, and repeated every 21 days.

UK licensed product information recommends the above dose for those aged 21 years and younger, and the adult dose (see Uses and Administration, above) in those aged 16 years and older; in studies, for those patients in the age range of 16 to 21 years either dose has been used.

Adverse Effects, Treatment, and Precautions

Neurotoxicity is common with nelarabine and may be dose-limiting. Signs and symptoms include somnolence, confusion, convulsions, ataxia, paraesthesias, and hypoaesthesia. Severe toxicity can manifest as coma, status epilepticus (which may be fatal), craniospinal demyelination, or ascending neuropathy. Risk of neurotoxicity is increased by previous or current intrathecal chemotherapy or previous radiation to the spine or brain. Leucopenia, thrombocytopenia, anaemia, and neutropenia are common, especially in children. Full blood counts should be regularly monitored. Other common adverse events include fatigue, gastrointestinal disorders, respiratory disorders, pyrexia, headache, hypokalaemia, hypoalbuminaemia, hyperbilirubinaemia, and increased liver enzyme values. Fatal cerebral haemorrhage has been reported. Appropriate measures to avoid hyperuricaemia (especially in patients considered at risk for tumour lysis syndrome) include adequate hydration, urinary alkalinisation, and possible prophylaxis with allopurinol.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nelarabine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pharmacokinetics

In adult patients with leukaemia or lymphoma, nelarabine is rapidly eliminated from the plasma, with a half-life of about 30 minutes; no data are available for paediatric patients although the mean clearance is reported to be about 30% higher in children. Nelarabine is rapidly and extensively demethylated via the enzyme adenosine deaminase to the active metabolite 9-β-D-arabinofuranosylguanine (ara-G; arabinosylguanine; arabinofuranosylguanine; guanine arabinoside); both nelarabine and ara-G are widely distributed throughout the body. Ara-G has an elimination half-life from plasma of about 3 hours. Plasma protein binding is not significant. Nelarabine also undergoes hydrolysis to form methylguanine. Both methylguanine and ara-G undergo further metabolism to guanine, which is deaminated to form xanthine, itself further oxidised to uric acid. Nelarabine and ara-G are partially eliminated by the kidneys; mean apparent clearance is lower in patients with mild to moderate renal impairment.

References.
1. Kisor DF, *et al.* Pharmacokinetics of nelarabine and 9-beta-D-arabinofuranosyl guanine in pediatric and adult patients during a phase I study of nelarabine for the treatment of refractory hematologic malignancies. *J Clin Oncol* 2000; **18:** 995–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Atriance; ***Belg.***: Atriance; ***Canad.***: Atriance; ***Cz.***: Atriance; ***Denm.***: Atriance; ***Fr.***: Atriance; ***Ger.***: Atriance; ***Gr.***: Atriance; ***Irl.***: Atriance; ***Israel***: Atriance; ***Ital.***: Atriance; ***Jpn***: Arranon; ***Neth.***: Atriance; ***Norw.***: Atriance; ***Pol.***: Atriance; ***Port.***: Atriance; ***Rus.***: Atriance (Атрианс); ***Spain***: Atriance; ***Swed.***: Atriance; ***Switz.***: Atriance; ***UK***: Atriance; ***USA***: Arranon.

Neratinib *(USAN, rINN)*

HKI-272; Nératinib; Neratinibum; Нератиниб.
(2*E*)-*N*-[4-({3-Chloro-4-[(pyridine-2-yl)methoxy]phenyl} amino)-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino) but-2-enamide.
$C_{30}H_{29}ClN_6O_3$=557.1
CAS — 698387-09-6.
UNII — JJH94R3PWB.

Profile

Neratinib is an orally active tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) family, including HER1, HER2 and HER4. It is under investigation for the treatment of breast cancer and other solid tumours.

References.
1. Wong K-K, *et al.* A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. *Clin Cancer Res* 2009; **15:** 2552–8.
2. Bose P, Ozer H. Neratinib: an oral, irreversible dual EGFR/HER2 inhibitor for breast and non-small cell lung cancer. *Expert Opin Invest Drugs* 2009; **18:** 1735–51.
3. Burstein HJ, *et al.* Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol* 2010; **28:** 1301–7.
4. Sequist LV, *et al.* Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28:** 3076–83.

Nilotinib *(BAN, USAN, rINN)*

AMN-107; Nilotinibum; Nilotynib; Нильотиниб.
4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzamide.
$C_{28}H_{22}F_3N_7O$=529.5
CAS — 641571-10-0.
ATC — L01XE08.
ATC Vet — QL01XE08.
UNII — F41401512X.

Nilotinib Hydrochloride *(rINNM)*

Hidrocloruro de nilotinib; Nilotinib, Chlorhydrate de; Nilotinibi Hydrochloridum; Нильотиниба Гидрохлорид.
Nilotinib Hydrochloride Monohydrate.
$C_{28}H_{22}F_3N_7O,HCl,H_2O$=584.0
CAS — 923288-90-8.
ATC — L01XE08.
ATC Vet — QL01XE08.
UNII — K37N7BYX3X (anhydrous nilotinib hydrochloride); 5JHU0N1R6K (nilotinib hydrochloride monohydrate).

Uses and Administration

Nilotinib is a potent inhibitor of BCR-ABL tyrosine kinase. Nilotinib is used for the treatment of adults with Philadelphia chromosome-positive chronic myeloid leukaemia (CML; p. 694.2), both as first-line treatment of chronic phase, and in the treatment of chronic or accelerated phase in those who are resistant to, or intolerant of, previous imatinib-based treatment. Nilotinib is given orally as the hydrochloride, but doses are expressed in terms of the base; 100 mg of nilotinib is equivalent to about 110 mg of nilotinib hydrochloride monohydrate. Doses are given at least 1 hour before or 2 hours after food. Capsules should usually be swallowed whole, but if patients have difficulty swallowing then capsules can be opened and the contents dispersed in one teaspoon of apple sauce; the mixture should be taken immediately (within 15 minutes). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For first-line treatment of chronic phase CML, nilotinib hydrochloride is given in an oral dose equivalent to nilotinib 300 mg twice daily. In the treatment of patients with chronic or accelerated phase CML resistant to prior treatment or where there has been intolerance to therapy, a dose equivalent to nilotinib 400 mg twice daily is used. If a dose is missed, no catch-up dose is recommended; the next dose should be taken as usual. Treatment may be continued until disease progression. Doses may need to be adjusted or treatment withheld for toxicity, see below. For doses in hepatic impairment, see below.

Nilotinib is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4. Use with strong CYP3A4 inhibitors or inducers should be avoided. If a strong CYP3A4 inhibitor is required, nilotinib treatment should be interrupted. If a strong CYP3A4 inhibitor must be used with nilotinib, US licensed product information suggests reducing the dose of nilotinib as follows:

- In first-line treatment of chronic phase CML, consider a dose reduction to 200 mg once daily
- In the treatment of patients with chronic or accelerated phase CML resistant to prior treatment or where there has been intolerance to therapy, consider a dose reduction to 300 mg once daily

Once the inhibitor is stopped, a washout period should be allowed before nilotinib is increased to the original dose.

Increasing the dose of nilotinib is considered unlikely to compensate for the loss of nilotinib exposure when strong CYP3A4 inducers are used, and their use together is not recommended.

Nilotinib has been investigated for the treatment of gastrointestinal stromal tumours.

References.
1. Weisberg E, *et al.* AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer* 2006; **94:** 1765–9.
2. Kantarjian H, *et al.* Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; **354:** 2542–51.
3. Kantarjian HM, *et al.* Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; **110:** 3540–6.
4. Plosker GL, Robinson DM. Nilotinib. *Drugs* 2008; **68:** 449–59.
5. Deremer DL, *et al.* Nilotinib: a second-generation tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia. *Clin Ther* 2008; **30:** 1956–75.
6. Breccia M, Alimena G. Nilotinib therapy in chronic myelogenous leukemia: the strength of high selectivity on BCR/ABL. *Curr Drug Targets* 2009; **10:** 530–6.
7. Fava C, *et al.* Development and targeted use of nilotinib in chronic myeloid leukemia. *Drug Des Devel Ther* 2009; **2:** 233–43.
8. Rosti G, *et al.* GIMEMA CML Working Party. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. *Blood* 2009; **114:** 4933–8.
9. Cortes JE, *et al.* Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol* 2010; **28:** 392–7.
10. Saglio G, *et al.* ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; **362:** 2251–9.
11. Quintás-Cardama A, *et al.* Nilotinib. *Recent Results Cancer Res* 2010; **184:** 103–17.
12. Breccia M, Alimena G. Nilotinib: a second-generation tyrosine kinase inhibitor for chronic myeloid leukemia. *Leuk Res* 2010; **34:** 129–34.

Administration in hepatic impairment. Exposure to nilotinib is increased in hepatic impairment and US licensed product information recommends a lower initial dose in patients with impairment at baseline. For first-line treatment of chronic phase chronic myeloid leukaemia (CML), those with mild, moderate, or severe impairment (Child-Pugh classes A, B, and C, respectively) are given an initial oral dose equivalent to nilotinib 200 mg twice daily which can be increased up to the usual dose of 300 mg twice daily if tolerated. In the treatment of patients with chronic or accelerated phase CML resistant to prior treatment or where there has been intolerance to therapy, those with mild or moderate impairment are given an initial oral dose equivalent to nilotinib 300 mg twice daily which can be increased up to the usual dose of 400 mg twice daily if tolerated; those with severe impairment are given an initial oral dose equivalent to nilotinib 200 mg twice daily which can be increased up to 300 mg twice daily, and then 400 mg twice daily, as tolerated.

UK licensed product information states that dose adjustments of nilotinib are not necessary in hepatic impairment, although caution is advised.

Dose adjustments may also be required if liver function deteriorates during treatment, see Administration in Toxicity, below.

Administration in toxicity. Nilotinib should be withheld or the dose reduced if haematological toxicity that is not related to the underlying leukemia occurs during treatment of chronic myeloid leukaemia (CML). In chronic phase CML (either when nilotinib is used first-line or when there has been resistance to or intolerance of prior treatment), nilotinib should be withheld when the absolute neutrophil count (ANC) falls to < 1000 cells/mm³ and/or platelets to $< 50\,000$ cells/mm³. If values increase above these levels within 2 weeks, treatment may be resumed using the previous oral dose, but if blood counts remain low for more than 2 weeks, a dose reduction to 400 mg once daily may be required.

Accelerated phase CML in patients that are resistant to or intolerant of prior treatment is managed as for chronic phase in the USA (see above). However, in the UK, nilotinib is withheld when the ANC falls to < 500 cells/mm³ and/or platelets to $< 10\,000$ cells/mm³. If the ANC increases to > 1000 cells/mm³ and/or platelets increase to $> 20\,000$ cells/mm³ within 2 weeks, treatment may be

resumed using the previous dose, but if blood counts remain low for more than 2 weeks, a dose reduction to 400 mg once daily may be required.

Nilotinib treatment may need to be withheld or the dose reduced to 400 mg once daily for increases (grade 3 or above) in serum lipase or amylase, bilirubin, and/or liver enzymes; if withheld, treatment may be restarted at 400 mg once daily when values return to grade 1 or below. Similarly, for other moderate to severe non-haematological toxicity, nilotinib should be withheld, and treatment restarted at 400 mg once daily when toxicity has resolved; if appropriate the dose may be increased back up to the usual recommended dose (see Uses and Administration, p. 835.2).

Nilotinib can prolong the QT interval and US licensed product information recommends withholding treatment for a corrected QT (QTcF) of > 480 milliseconds. If the QTcF interval returns to < 450 milliseconds and to within 20 milliseconds of the baseline value within 2 weeks, nilotinib can be restarted at the previous dose. If the QTcF interval is between 450 and 480 milliseconds after 2 weeks, the dose should be restarted at a lower dose of 400 mg once daily, and treatment stopped if the QTcF increases again to > 480 milliseconds. An ECG should be carried out about 7 days after any dose adjustment.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of nilotinib are rash, pruritus, fatigue, headache, and gastrointestinal disturbances. Other common adverse effects include fever, alopecia, asthenia, muscle spasms, myalgia, arthralgia, pain including musculoskeletal or chest pain, oedema, folliculitis, papilloma, insomnia, anxiety, dizziness, paraesthesia, conjunctivitis, dry eye, vertigo, flushing, dyspnoea, cough, hyperhidrosis, dry skin, urticaria, and acne. Myelosuppression occurs (commonly thrombocytopenia, neutropenia, and anaemia), but is generally reversible and can be managed by withholding therapy or dose reduction, see Administration in Toxicity, p. 835.3. Complete blood counts should be performed every fortnight for the first 2 months and monthly thereafter. Nilotinib can prolong the QT interval, which may result in ventricular tachycardia (torsade de pointes), causing syncope, seizures, and/or death; treatment may be withheld or the dose reduced (p. 835.3). Nilotinib should not be used in patients at high risk of developing QT prolongation such as those with hypokalaemia or hypomagnesaemia, congenital long QT syndrome, uncontrolled or significant cardiac disease, or those taking other medicines that prolong the QT interval. Taking nilotinib with substances that increase the concentration of nilotinib, such as food or inhibitors of the cytochrome P450 isoenzyme CYP3A4, may increase the risk of QT prolongation, see Interactions, below. ECGs should be obtained at baseline, 1 week after starting nilotinib, and periodically thereafter including after dose adjustments. Other cardiac adverse effects include arrhythmias, palpitations, angina, hypertension, cardiac failure, pericarditis,and myocardial infarction. Sudden death has occurred rarely and may be related to ventricular repolarisation abnormalities. Thrombotic disorders or haemorrhage have been reported.

Tumour lysis syndrome has occurred rarely, and adequate hydration and treatment of elevated uric acid concentrations are recommended before starting nilotinib. Electrolyte abnormalities can occur and electrolytes should be monitored during therapy. Hepatotoxicity has been reported. Pancreatitis can occur and serum lipase should be monitored; caution is recommended in patients with a history of pancreatitis. Other adverse effects that have been reported include pleural or pericardial effusion, interstitial lung disease, mucosal ulceration or inflammation, hypersensitivity, thyroid and/or parathyroid disorders, dyslipidaemia, hyperglycaemia or hypoglycaemia, gout, depression, amnesia, tremor, peripheral neuropathy, chorioretinopathy, tinnitus, visual or hearing impairment, epistaxis, urinary disorders, erectile dysfunction, gynaecomastia, menorrhagia, erythema multiforme, erythema nodosum, palmar-plantar erythrodysesthesia, photosensitivity, and skin changes such as discoloration, hyperpigmentation, exfoliation, hypertrophy, or atrophy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nilotinib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Interactions

Nilotinib is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with strong inhibitors or inducers of CYP3A4 should be avoided. If strong CYP3A4 inhibitors must be used, dose adjustments may be required (see Uses and Administration, p. 835.2). Grapefruit juice may increase plasma concentrations of nilotinib and should be avoided. St John's wort should also be avoided. *In vitro*, nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and of the uridine diphosphate glucuronosyltransferase isoenzyme UGT1A1; exposure to substrates of these enzymes may be altered by nilotinib. Nilotinib is a substrate for P-glycoprotein and exposure may be affected by drugs that modulate P-glycoprotein. Nilotinib should not be given with drugs that prolong the QT interval.

The solubility of nilotinib is affected by pH, with a reduced solubility at higher pH, and drugs that suppress gastric acid may lead to lower exposure to nilotinib. However, nilotinib absorption was only modestly decreased by esomeprazole despite a marked increase in gastric pH, and nilotinib may be used with esomeprazole or other proton pump inhibitors.

References.

1. Yin OQP, *et al.* Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib. *J Clin Pharmacol* 2010; **50:** 960–7.
2. Tanaka C, *et al.* Effects of rifampin and ketoconazole on the pharmacokinetics of nilotinib in healthy participants. *J Clin Pharmacol* 2011; **51:** 75–83.

Pharmacokinetics

Peak plasma concentrations occur about 3 hours after an oral dose of nilotinib. Bioavailability is about 30% and is increased almost twofold when given with food. Plasma protein binding is about 98%. The apparent elimination half-life is about 17 hours. It is metabolised in the liver via oxidation and hydroxylation, in which cytochrome P450 isoenzyme CYP3A4 plays an important role. Most of an oral dose is eliminated unchanged in the faeces within 7 days.

References.

1. Tanaka C, *et al.* Clinical pharmacokinetics of the BCR-ABL tyrosine kinase inhibitor nilotinib. *Clin Pharmacol Ther* 2010; **87:** 197–203.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tasigna; ***Austral.***: Tasigna; ***Austria***: Tasigna; ***Belg.***: Tasigna; ***Braz.***: Tasigna; ***Canad.***: Tasigna; ***Chile***: Tasigna; ***China***: Tasigna (达希纳); ***Cz.***: Tasigna; ***Denm.***: Tasigna; ***Fr.***: Tasigna; ***Ger.***: Tasigna; ***Gr.***: Tasigna; ***Hong Kong***: Tasigna; ***Hung.***: Tasigna; ***Indon.***: Tasigna; ***Irl.***: Tasigna; ***Israel***: Tasigna; ***Ital.***: Tasigna; ***Malaysia***: Tasigna; ***Neth.***: Tasigna; ***Norw.***: Tasigna; ***NZ***: Tasigna; ***Philipp.***: Tasigna; ***Pol.***: Tasigna; ***Port.***: Tasigna; ***Rus.***: Tasigna (Тасигна); ***Singapore***: Tasigna; ***Spain***: Tasigna; ***Swed.***: Tasigna; ***Switz.***: Tasigna; ***Thai.***: Tasigna; ***Turk.***: Tasigna; ***UK***: Tasigna; ***Ukr.***: Tasigna (Тасигна); ***USA***: Tasigna.

Nilutamide *(BAN, USAN, rINN)*

Nilutamid; Nilutamida; Nilutamidi; Nilutamidum; RU-23908; Нилутамид.

5,5-Dimethyl-3-(α,α,α-trifluoro-4-nitro-*m*-tolyl)-imidazolidine-2,4-dione.

$C_{12}H_{10}F_3N_3O_4$=317.2

CAS — 63612-50-0.

ATC — L02BB02.

ATC Vet — QL02BB02.

UNII — 51G6I8B902.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nilutamide). A white or almost white powder. Very slightly soluble in water; freely soluble in acetone; soluble in anhydrous ethanol. Protect from light.

Uses and Administration

Nilutamide is a nonsteroidal anti-androgen that is used similarly to flutamide (p. 798.2) in the treatment of prostatic carcinoma (p. 712.3). It is given orally in a dose of 300 mg daily, usually starting on the same day as orchidectomy or starting treatment with a gonadorelin analogue. Dosage may be reduced to 150 mg daily after 1 month.

References.

1. Dole EJ, Holdsworth MT. Nilutamide: an antiandrogen for the treatment of prostate cancer. *Ann Pharmacother* 1997; **31:** 65–75.
2. Desai A, *et al.* Nilutamide: possible utility as a second-line hormonal agent. *Urology* 2001; **58:** 1016–20.
3. Kassouf W, *et al.* Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol (Baltimore)* 2003; **169:** 1742–4.
4. Nakabayashi M, *et al.* Efficacy of nilutamide as secondary hormonal therapy in androgen-independent prostate cancer. *BJU Int* 2005; **96:** 783–6.

Adverse Effects and Precautions

As for Flutamide, p. 798.3. Interstitial pneumonitis has occurred in patients receiving nilutamide, and the drug is contra-indicated in those with severe respiratory insufficiency.

Effects on the eyes. Reversible visual disturbances, particularly delayed dark adaptation, have been associated with nilutamide.[1-3] Although some consider such visual disturbances to be mild and generally well tolerated,[4] others suggest that these, together with alcohol intolerance and, more seriously, effects on the lung, mean that other nonsteroidal anti-androgens should be preferred.[5]

1. Harnois C, *et al.* Ocular toxicity of Anandron in patients treated for prostatic cancer. *Br J Ophthalmol* 1986; **70:** 471–3.
2. Brisset JM, *et al.* Ocular toxicity of Anandron. *Br J Ophthalmol* 1987; **71:** 639.
3. Chan P, Odel JG. Delayed dark adaptation caused by nilutamide. *J Neuroophthalmol* 2008; **28:** 158–9.
4. Dijkman GA, *et al.* Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31:** 1550–1.
5. Dole EJ, Holdsworth MT. Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31:** 1551–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nilutamide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Patients receiving nilutamide may exhibit intolerance to alcohol.

Pharmacokinetics

Nilutamide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively metabolised although it may inhibit its own metabolism to some extent after multiple doses. About 60% of an oral dose of nilutamide is eliminated in the urine and less than 10% in the faeces, with an elimination half-life of 41 to 49 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Anandron; ***Braz.***: Anandron; ***Canad.***: Anandron; ***Fr.***: Anandron; ***Gr.***: Anandron; ***Hung.***: Anandron; ***Mex.***: Anandron; ***Neth.***: Anandron; ***Port.***: Anandron; ***USA***: Nilandron.

Nimotuzumab *(rINN)*

Cimazumab; h-R3; Nimotutsumabi; Nimótúzúmab; Nimotuzumabas; Nimotuzumabs; Nimotuzumabum; Нимотузумаб.

Immunoglobulin G1, anti-(humanized mouse monoclonal hR3 β1 chain anti-human epidermal growth factor receptor), disulfide with humanized mouse monoclonal hR3 κ-chain, dimer.

CAS — 828933-51-3.

Profile

Nimotuzumab is a humanised monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It may be used in some countries for the treatment of glioma and cancers of the head and neck. It is also under investigation for pancreatic cancer, non-small cell lung cancer, oesophageal cancer, and gastric cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: CIMAher; ***Braz.***: Cimaher; ***China***: Taixinsheng (泰欣生); ***India***: Biomab EGFR; ***Indon.***: TheraCIM; ***Philipp.***: Theracim; ***Thai.***: TheraCIM.

Nimustine Hydrochloride *(rINNM)*

ACNU; Hidrocloruro de nimustina; Nimustiinihydrokloridi; Nimustina, hidrocloruro de; Nimustine, Chlorhydrate de; Nimustinhydroklorid; Nimustini Hydrochloridum; NSC-245382; Pimustine Hydrochloride; Нимустина Гидрохлорид.

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride.

$C_9H_{13}ClN_6O_2$,HCl=309.2

CAS — 42471-28-3 (nimustine); 55661-38-6 (nimustine hydrochloride).

ATC — L01AD06.

ATC Vet — QL01AD06.

UNII — DFR965WKBU.

Profile

Nimustine is a nitrosourea antineoplastic with actions and uses similar to those of carmustine (p. 761.2). It is licensed for use in the treatment of malignant glioma. Nimustine hydrochloride is given in doses of 2 to 3 mg/kg or 90 to

100 mg/m² as a single dose by slow intravenous injection, repeated at intervals of 6 weeks depending on haematological response.

References.
1. Anders K, *et al.* Accelerated radiotherapy with concomitant ACNU/Ara-C for the treatment of malignant glioma. *J Neurooncol* 2000; **48:** 63–73.
2. Kochii M, *et al.* Randomized comparison of intra-arterial versus intravenous infusion of ACNU for newly diagnosed patients with glioblastoma. *J Neurooncol* 2000; **49:** 63–70.
3. Silvani A, *et al.* Intra-arterial ACNU and carboplatin versus intravenous chemotherapy with cisplatin and BCNU in newly diagnosed patients with glioblastoma. *Neurol Sci* 2002; **23:** 219–24.
4. Weller M, *et al.* Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol* 2003; **21:** 3276–84.
5. Watanabe T, *et al.* Human interferon beta, nimustine hydrochloride, and radiation therapy in the treatment of newly diagnosed malignant astrocytomas. *J Neurooncol* 2005; **72:** 57–62.
6. Glas M, *et al.* Nimustine (ACNU) plus teniposide (VM26) in recurrent glioblastoma. *Oncology* 2009; **76:** 184–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Nidran (宁得朗); ***Ger.***: ACNU†; ***Jpn***: Nidran.

Nolatrexed *(rINN)*

AG-337 (nolatrexed dihydrochloride); Nolatrexedum; Нолатрексед.

2-Amino-6-methyl-5-(4-pyridylthio)-4(3*H*)-quinazolinone.

$C_{14}H_{12}N_4OS$=284.3

CAS — 147149-76-6 (nolatrexed); 152946-68-4 (nolatrexed dihydrochloride).

UNII — K75ZUN743Q.

Profile

Nolatrexed is, like raltitrexed (p. 850.3), a selective inhibitor of thymidylate synthase. It has been investigated as an antimetabolite antineoplastic for the treatment of hepatocellular carcinoma and other solid tumours, although results of single-agent studies have been disappointing.

References.
1. Hughes AN, *et al.* Clinical pharmacokinetic and in vitro combination studies of nolatrexed dihydrochloride (AG337, Thymitaq) and paclitaxel. *Br J Cancer* 2000; **82:** 1519–27.
2. Estlin EJ, *et al.* A phase I study of nolatrexed dihydrochloride in children with advanced cancer. *Br J Cancer* 2001; **84:** 11–18.
3. Pivot X, *et al.* Result of two randomized trials comparing nolatrexed (Thymitaq) versus methotrexate in patients with recurrent head and neck cancer. *Ann Oncol* 2001; **12:** 1595–9.
4. Gish RG, *et al.* Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; **25:** 3069–75.

Obinutuzumab *(USAN, rINN)*

Afutuzumab; GA-101; huMAB<CD20>; Obinutuzumabum; RG-7159; Ro-5072759; Обинутузумаб.

CAS — 949142-50-1.

UNII — O43472U9X8.

Profile

Obinutuzumab is a humanised anti-CD20 monoclonal antibody that is under investigation for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Gazyva.

Oblimersen Sodium *(USAN, rINNM)*

G-3139; Natrii Oblimersenum; Oblimersen sódico; Oblimersén sódico; Oblimersen Sodique; Натрий Облимерсен.

P-Thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-thymidine sodium.

$C_{172}H_{204}N_{62}Na_{17}O_{91}P_{17}S_{17}$=6058.3

CAS — 190977-41-4.

UNII — SH55B0RQ9K.

NOTE. The name Genasense has been used as a trade mark for oblimersen sodium.

Profile

Oblimersen sodium is an antisense oligonucleotide that blocks the production of BCL-2, a mitochondrial protein that prevents apoptosis. It is under investigation for the treatment of various malignant neoplasms, including leukaemias and malignant melanoma.

References.
1. Frankel SR. Oblimersen sodium (G3139 Bcl-2 antisense oligonucleotide) therapy in Waldenstrom's macroglobulinemia: a targeted approach to enhance apoptosis. *Semin Oncol* 2003; **30:** 300–304.
2. Büchele T. Proapoptotische Therapie mit Oblimersen (bcl-2-Antisense-Oligonukleotid)—Übersicht über präklinische und klinische Daten. *Onkologie* 2003; **26** (suppl 7): 60–9.
3. Herbst RS, Frankel SR. Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): a rational therapeutic to enhance apoptosis in therapy of lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4245s–4248s.
4. Chi KN. Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. *World J Urol* 2005; **23:** 33–7.
5. O'Brien SM, *et al.* Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol* 2005; **23:** 7697–7702.
6. Mita MM, *et al.* A phase I, pharmacokinetic and biologic correlative study of oblimersen sodium (Genasense, G3139) and irinotecan in patients with metastatic colorectal cancer. *Ann Oncol* 2006; **17:** 313–21.
7. Bedikian AY, *et al.* Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24:** 4738–45.
8. O'Brien S, *et al.* Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25:** 1114–20. Correction. *ibid.* 2008; **26:** 820.
9. O'Brien S, *et al.* 5-year survival in patients with relapsed or refractory chronic lymphocytic leukemia in a randomized, phase III trial of fludarabine plus cyclophosphamide with or without oblimersen. *J Clin Oncol* 2009; **27:** 5208–12.

Ofatumumab *(BAN, USAN, rINN)*

2F2; GSK-1841157; HuMax-CD20; Ofatumumabum; Офатумумаб.

Immunoglobulin G1, anti-(human CD20 (antigen))(human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer.

CAS — 679818-59-8.

ATC — L01XC10.

ATC Vet — QL01XC10.

UNII — M95KG522R0.

Uses and Administration

Ofatumumab is a human anti-CD20 monoclonal antibody that is used in the treatment of refractory chronic lymphocytic leukaemia (p. 693.3) in patients refractory to fludarabine and alemtuzumab. An initial intravenous infusion of ofatumumab 300 mg is given for the first dose, followed after 1 week by 2 g once weekly for a further 7 doses. After a 4- or 5-week interval, 2 g is given every 4 weeks for a further 4 doses. The drug is given via an infusion pump and an in-line 0.2-micrometre filter, and is diluted in 1 litre of sodium chloride 0.9% (giving a concentration of 0.3 mg/mL for the first infusion and 2 mg/mL for subsequent infusions). An initial infusion rate of 12 mL/hour is recommended for the first 2 infusions; this rate can be doubled every 30 minutes until a rate of 200 mL/hour is reached, providing no infusion reactions occur. Subsequent doses may be begun at a rate of 25 mL/hour, and doubled every 30 minutes to a maximum of 400 mL/hour. The infusion rate should be reduced if infusion reactions occur, and premedication with a corticosteroid, analgesic, and an antihistamine is recommended, see Adverse Effects below.

It is also under investigation for non-Hodgkin's lymphoma, rheumatoid arthritis, and multiple sclerosis.

References.
1. Coiffier B, *et al.* Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood* 2008; **111:** 1094–1100.
2. Hagenbeek A, *et al.* First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 2008; **111:** 5486–95.
3. Robak T. Ofatumumab, a human monoclonal antibody for lymphoid malignancies and autoimmune disorders. *Curr Opin Mol Ther* 2008; **10:** 294–309.
4. Castillo J, *et al.* Ofatumumab, a second-generation anti-CD20 monoclonal antibody, for the treatment of lymphoproliferative and autoimmune disorders. *Expert Opin Invest Drugs* 2009; **18:** 491–500.

Adverse Effects, Treatment, and Precautions

As for Rituximab, see p. 854.1. Premedication with an intravenous corticosteroid, an oral analgesic, and an oral or intravenous antihistamine is recommended 30 to 120 minutes before every ofatumumab infusion; the corticosteroid dose may be reduced for later infusions if a severe infusion reaction did not occur with the previous dose. If an infusion-related adverse effect does occur, treatment should be interrupted until the patient is stable. After a mild or moderate reaction, the infusion should be restarted either at half the infusion rate being used at the time of the reaction, or the usual initial rate (12 mL/hour) if this was being used at the time of the reaction. For severe reactions, treatment should either be restarted at 12 mL/hour, regardless of the rate being used before (US recommendation for grade 3 reactions and UK recommendation), or treatment stopped (US recommendation for grade 4 reactions). If restarted, infusion rates can then be increased as usual, according to tolerance (see Uses and Administration, above).

Other adverse effects that have occurred with ofatumumab include agranulocytosis, red cell aplasia, coagulopathy, and hyperhidrosis.

Pharmacokinetics

Peak plasma concentrations of ofatumumab occur at or shortly after the end of the infusion. Ofatumumab is eliminated by proteolytic enzymes and via binding to B-cells. There is a rapid and sustained depletion of CD20 B-cells after the first infusion, leaving a reduced number for binding at subsequent infusions. As a result, clearance and half-life decrease with repeated dosing, and there is increased exposure to ofatumumab, although there is considerable interindividual variation. The mean half-life is reported to be about 1.3 days after the first infusion, and about 14 days after the twelfth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Arzerra; ***Cz.***: Arzerra; ***Denm.***: Arzerra; ***Fr.***: Arzerra; ***Ger.***: Arzerra; ***Gr.***: Arzerra; ***Irl.***: Arzerra; ***Israel***: Arzerra; ***Jpn***: Arzerra; ***Neth.***: Arzerra; ***Norw.***: Arzerra; ***Pol.***: Arzerra; ***Port.***: Arzerra; ***Spain***: Arzerra†; ***Swed.***: Arzerra; ***Switz.***: Arzerra; ***UK***: Arzerra; ***USA***: Arzerra.

Olaparib *(rINN)*

AZD-2281; KU-0059436; Olaparibum; Олапариб.

4-[(3-{[4-(Cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one.

$C_{24}H_{23}FN_4O_3$=434.5

CAS — 763113-22-0.

UNII — WOH1JD9AR8.

Profile

Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that is under investigation as an antineoplastic for the treatment of breast and ovarian cancer.

References.
1. Fong PC, *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009; **361:** 123–34.
2. Fong PC, *et al.* Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol* 2010; **28:** 2512–19.

Omacetaxine Mepesuccinate *(rINN)*

CGX-635; HHT; Homoharringtonine; Mepesuccinato de omacetaxina; NSC-141633; Omacétaxine, Mépésuccinate d'; Omacetaxini mepesuccinas; Омацетаксина Мепесукцинат.

1-[(1*S*,3a*R*,14b*S*)-2-Methoxy-1,5,6,8,9,14b-hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)butanedioate.

$C_{29}H_{39}NO_9$=545.6

CAS — 26833-87-4.

ATC — L01XX40.

ATC Vet — QL01XX40.

UNII — 6FG804155B.

NOTE. The name Ceflatonin has been used as a trade mark for omacetaxine mepesuccinate.

Pharmacopoeias. In *Chin.*

Uses and Administration

Omacetaxine mepesuccinate is a semisynthetic formulation of homoharringtonine, which is an alkaloid derived from the tree *Cephalotaxus harringtonia*, and related species. It is thought to induce apoptosis by inhibition of protein synthesis.

It is used for the treatment of chronic myeloid leukaemia (p. 694.2) when there is resistance or intolerance to tyrosine kinase inhibitors. The recommended starting dose of omacetaxine mepesuccinate is 1.25 mg/m² twice daily, by subcutaneous injection, for 14 consecutive days of a 28-day cycle. Cycles should be repeated every 28 days until there is a haematological response. The maintenance dose should be 1.25 mg/m² twice daily for 7 consecutive days of a 28-day cycle, repeated as long as there is clinical benefit. Complete blood counts should be performed weekly during induction and initial maintenance therapy, and every two weeks or as needed after initial maintenance cycles; the dose should be adjusted when toxicity occurs (see Administration in Subsequent Cycles, p. 838.1).

Omacetaxine mepesuccinate has also been tried in the treatment of acute leukaemias and other neoplastic disorders. The related compounds harringtonine, isoharringtonine, and deoxyharringtonine have also been investigated.

References.
1. Quintás-Cardama A, Cortes J. Homoharringtonine for the treatment of chronic myelogenous leukemia. *Expert Opin Pharmacother* 2008; **9:** 1029–37.
2. Quintás-Cardama A, Cortes J. Omacetaxine mepesuccinate -a semisynthetic formulation of the natural antitumoral alkaloid homoharringtonine, for chronic myelocytic leukemia and other myeloid malignancies. *IDrugs* 2008; **11:** 356–72.
3. Li Y-F, *et al*. The effect of homoharringtonine in patients with chronic myeloid leukemia who have failed or responded suboptimally to imatinib therapy. *Leuk Lymphoma* 2009; **50:** 1889–91.
4. Quintás-Cardama A, *et al*. Homoharringtonine, omacetaxine mepesuccinate, and chronic myeloid leukemia circa 2009. *Cancer* 2009; **115:** 5382–93.
5. Kim TD, *et al*. Omacetaxine mepesuccinate for the treatment of leukemia. *Expert Opin Pharmacother* 2011; **12:** 2381–92.

Administration in subsequent cycles. If the absolute neutrophil count (ANC) falls to < 500 cells/mm³ or the platelet count falls to < 50 000 cells/mm³ during treatment with omacetaxine mepesuccinate, then the next cycle should be delayed until the ANC is ≥1000 cells/mm³ and the platelet count ≥ 50 000 cells/mm³. The number of dosing days should also be reduced by 2 days for the next cycle.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Omacetaxine mepesuccinate causes myelosuppression, resulting in thrombocytopenia, neutropenia, and anaemia in a significant proportion of patients. Severe thrombocytopenia has resulted in gastrointestinal haemorrhage and cases of fatal cerebral haemorrhage. Other common adverse effects include diarrhoea, nausea, fatigue, asthenia, arthralgia, headache, alopecia, rash, and convulsions. Glucose intolerance and severe hyperglycaemia have been reported Injection site reactions can occur.

Complete blood counts should be monitored regularly. Blood-glucose should also be monitored, particularly in patients with diabetes or risk factors for diabetes.

Pharmacokinetics

Peak plasma concentrations of omacetaxine mepesuccinate occur about 30 minutes after subcutaneous injection. Plasma protein binding is less than or equal to 50%. Omacetaxine mepesuccinate is hydrolysed by plasma esterases, but the major elimination route is unknown. The mean elimination half-life after subcutaneous use is about 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Chuan Shan Ning (川山宁); Fu Er (扶尔); Gao Rui Te (高瑞特); Hua Pu Le (华普乐); Jin Nuo Xing (金诺星); Sai Lan (赛兰); Wo Ting (沃汀); ***USA***: Synribo.

Oregovomab *(USAN, rINN)*

MAb-B43.13; Orégovomab; Oregovomabum; Ореговомаб.

Immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ1-chain), disulfide with mouse monoclonal B43.13 κ-chain, dimer.

CAS — 213327-37-8.

Profile

Oregovomab is a murine monoclonal antibody that binds to CA-125, an antigen that is overexpressed in the majority of ovarian cancer patients, and stimulates an immune response to the tumour cells. It has been investigated for the treatment of ovarian cancer.

Oxaliplatin *(BAN, USAN, rINN)*

JM-83; NSC-266046; *l*-OHP; Oksaliplatiini; Oksaliplatin; Oksaliplatina; Oxalato-platinum; Oxaliplatina; Oxaliplatine; Oxaliplatino; Oxaliplatinum; RP-54780; SR-96669; Оксалиплатин.

[(1*R*,2*R*)-1,2-Cyclohexanediamine-*N*,*N*'][oxalato(2-)-*O*,*O*']platinum.

$C_8H_{14}N_2O_4Pt$=397.3

CAS — 61825-94-3.

ATC — L01XA03.

ATC Vet — QL01XA03.

UNII — 04ZR38536J.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Oxaliplatin). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol; very slightly soluble in methyl alcohol.

USP 36: (Oxaliplatin). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol; very slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Incompatibility. Licensed product information states that oxaliplatin should not be mixed with chloride-containing solutions (including sodium chloride) or alkaline drugs or solutions. In particular, oxaliplatin should not be mixed with fluorouracil or any trometamol salts. While oxaliplatin may be infused through a Y-site with folinic acid (in glucose 5% solution), they may not be mixed in the same infusion bag, and folinic acid must not contain trometamol as an excipient. The infusion line should be flushed with glucose 5% before giving any other medication. Oxaliplatin may degrade on contact with aluminium, and injection equipment containing aluminium should not be used.

Stability. UK licensed product information states that oxaliplatin must be diluted in glucose 5% to give a concentration not less than 200 micrograms/mL. From a microbiological point of view, the infusion preparation should be used immediately; the infusion should not be stored for longer than 24 hours at 2 degrees to 8 degrees unless it has been prepared in controlled and validated aseptic conditions. Chemical and physical stability has been shown for 48 hours at 2 degrees to 8 degrees, and for 24 hours at 25 degrees. US licensed product information states that, after dilution in 250 to 500 mL of glucose 5%, oxaliplatin infusion solutions have a shelf-life of 6 hours at room temperature (20 degrees to 25 degrees) and up to 24 hours when refrigerated (2 degrees to 8 degrees), and that protection from light is not required.

A study[1] found that oxaliplatin solutions at 700 micrograms/mL in polyolefin infusion bags of glucose 5% were chemically stable for at least 30 days at both 3 degrees to 7 degrees and 20 degrees to 24 degrees without regard to light. Another study[2] found that oxaliplatin solutions at 250 micrograms/mL in 5% glucose, in polyolefin bags, were stable at 4 degrees as well as at room temperature (either protected or unprotected from light) for 90 days. Additionally, oxaliplatin solutions diluted to 200 micrograms/mL and 1.3 mg/mL in glucose 5% were found to be stable in PVC, polyethylene, and polypropylene infusion bags for at least 14 days at both 4 degrees and 20 degrees, either protected or unprotected from light.[3]

1. André P, *et al*. Stability of oxaliplatin in infusion bags containing 5% dextrose injection. *Am J Health-Syst Pharm* 2007; **64:** 1950–4.
2. Junker A, *et al*. Stability of oxaliplatin solution. *Ann Pharmacother* 2009; **43:** 390–1.
3. Eiden C, *et al*. Physicochemical stability of oxaliplatin in 5% dextrose injection stored in polyvinyl chloride, polyethylene, and polypropylene infusion bags. *Am J Health-Syst Pharm* 2009; **66:** 1929–33.

Uses and Administration

Oxaliplatin is a platinum-containing complex similar to cisplatin (see p. 766.1). It is given with fluorouracil and folinic acid in the treatment of metastatic colorectal cancer and in the adjuvant treatment of stage III (Dukes C) colon cancer (p. 706.3). The recommended dose is 85 mg/m² by intravenous infusion over 2 to 6 hours, dissolved in 250 to 500 mL of glucose 5%. The dose may be repeated at intervals of 2 weeks if toxicity permits, reduced according to tolerance. In the adjuvant setting, oxaliplatin is given for 12 cycles. After persistent neurotoxicity or recovery from severe adverse effects licensed product information recommends an initial reduction to 65 mg/m² in metastatic colorectal cancer, and to 75 mg/m² when given as adjuvant treatment. Oxaliplatin should always be given before fluoropyrimidines.

Oxaliplatin is under investigation for the treatment of ovarian and lung cancer. A liposomal formulation of oxaliplatin is in development.

References.
1. Culy CR, *et al*. Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60:** 895–924.
2. Simpson D, *et al*. Oxaliplatin: a review of its use in combination therapy for advanced metastatic colorectal cancer. *Drugs* 2003; **63:** 2127–56.
3. Keam SJ, *et al*. Oxaliplatin: in operable colorectal cancer. *Drugs* 2005; **65:** 89–96.
4. Fu S, *et al*. Clinical application of oxaliplatin in epithelial ovarian cancer. *Int J Gynecol Cancer* 2006; **16:** 1717–32.
5. Kim GP, Erlichman C. Oxaliplatin in the treatment of colorectal cancer. *Expert Opin Drug Metab Toxicol* 2007; **3:** 281–94.
6. Stordal B, *et al*. Oxaliplatin for the treatment of cisplatin-resistant cancer: a systematic review. *Cancer Treat Rev* 2007; **33:** 347–57.
7. Cortinovis D, *et al*. Oxaliplatin doublets in non-small cell lung cancer: a literature review. *Lung Cancer* 2008; **60:** 325–31.
8. Capdevila J, *et al*. Oxaliplatin-based chemotherapy in the management of colorectal cancer. *Expert Rev Anticancer Ther* 2008; **8:** 1223–36.
9. Raez LE, *et al*. Oxaliplatin in first-line therapy for advanced non-small-cell lung cancer. *Clin Lung Cancer* 2010; **11:** 18–24.
10. Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. *Curr Oncol* 2011; **18:** 18–25.

Administration in the elderly. A review[1] concluded that there are no data to support dose reduction of oxaliplatin based on age alone, other than any dosage adjustment considered necessary for renal impairment (see Administration in Renal Impairment, below).

1. Lichtman SM, *et al*. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in renal impairment. The primary route of platinum elimination is renal, and clearance of platinum is decreased in patients with renal impairment. However, a study determined that increased platinum exposure in patients with renal impairment was not associated with increased oxaliplatin toxicity. Dose reduction was not considered to be necessary in patients with mild to moderate renal impairment (as defined by creatinine clearance of 20 mL/minute or more).[1] UK licensed product information concurs that no dose adjustment is necessary in mild to moderate renal impairment, but contra-indicates the use of oxaliplatin in severe renal impairment (defined as creatinine clearance of less than 30 mL/minute), due to lack of data.

1. Takimoto CH, *et al*. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute organ dysfunction working group study. *J Clin Oncol* 2003; **21:** 2664–72.

Adverse Effects and Precautions

The adverse effects of oxaliplatin are similar to those of cisplatin (p. 767.1) but nausea and vomiting, nephrotoxicity, and myelosuppression, seem to be less marked. Raised liver enzyme values may occur. Neurotoxicity can be dose-limiting. Peripheral neuropathy occurs in 85 to 95% of patients given oxaliplatin; pain, functional impairment, and loss of tendon reflexes may develop. Pulmonary fibrosis, potentially fatal, has also been reported. Extravasation of oxaliplatin can cause local pain and inflammation; complications may sometimes be severe, including necrosis.

Neurological examinations should be carried out at regular intervals during treatment and the dose should be reduced if symptoms are prolonged or severe. Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p. 730.3). Oxaliplatin should not be given to patients with pre-existing sensory neuropathies or myelosuppression, nor to those with severe renal impairment. Renal function and toxicity should be carefully monitored in those with more moderate degrees of renal impairment.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment for men and for 4 months for women.

Effects on the blood. Acute haemolysis, with[1-5] and without[6] anaemia, has been reported with the use of oxaliplatin. The reactions were considered to be immune-mediated. Evan's syndrome (immune-mediated thrombocytopenia and haemolytic anaemia) has also been reported,[7] as has sudden onset of pancytopenia with resultant intracranial haemorrhage.[8]

See also under Hypersensitivity, p. 839.2.

1. Desrame J, *et al*. Oxaliplatin-induced haemolytic anaemia. *Lancet* 1999; **354:** 1179–80.
2. Garufi C, *et al*. Immunohemolytic anemia following oxaliplatin administration. *Ann Oncol* 2000; **11:** 497.
3. Hofheinz R-D, *et al*. Two potential mechanisms of oxaliplatin-induced haemolytic anaemia in a single patient. *Cancer Chemother Pharmacol* 2004; **53:** 276–7.
4. Chen VMY, *et al*. An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion* 2004; **44:** 838–43.
5. Lai J-I, Wang W-S. Acute hemolysis after receiving oxaliplatin treatment: a case report and literature review. *Pharm World Sci* 2009; **31:** 538–41.
6. Koutras AK, *et al*. Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis: a case report and review of the literature. *Oncology* 2004; **67:** 179–82.
7. Earle CC, *et al*. Oxaliplatin-induced Evan's syndrome. *Br J Cancer* 2001; **84:** 441.
8. Teng CJ, *et al*. Sudden-onset pancytopenia with intracranial hemorrhage after oxaliplatin treatment: a case report and literature review. *Jpn J Clin Oncol* 2011; **41:** 125–9.

Effects on the liver. The development of ascites, portal hypertension, and hepatic lesions in a patient with colorectal cancer was considered to be due to oxaliplatin; metastatic or recurrent cancer had been originally suspected.[1]

1. Tisman G, *et al*. Oxaliplatin toxicity masquerading as recurrent colon cancer. *J Clin Oncol* 2004; **22:** 3202–4.

Effects on the nervous system. Neurological toxicity is the principal dose-limiting adverse effect with oxaliplatin.[1-4] The toxicity is biphasic:

- acute paraesthesias or dysaesthesias of the extremities, triggered or exacerbated by cold, are seen in 85 to 95% of patients within hours of infusion, but are normally mild and resolve within hours or days. Some patients also

have distressing laryngopharyngeal symptoms, such as difficulty in breathing or swallowing.
- with increasing cumulative dose, peripheral sensory symptoms increase in duration and intensity. Symptoms are sometimes associated with pain and cramps, and may progress to functional impairment (loss of fine sensorimotor coordination). Dosage reduction may be required, but in clinical practice the onset of functional impairment often occurs after the maximum response to therapy has been attained. Cumulative neurotoxicity is reversible in most cases, and about 80% of patients exhibit symptom regression within 4 to 6 months.

The incidence of neurotoxicity may be higher when oxaliplatin is given with fluorouracil. There is some evidence that more prolonged infusion of oxaliplatin can reduce acute toxicity, particularly laryngopharyngeal symptoms. Antiepileptics such as carbamazepine (see Neuropathic Pain, p. 513.2) or gabapentin have been investigated in the management of oxaliplatin-induced neurotoxicity, although results have been inconclusive.[5] Other drugs that have been tried include amifostine, glutathione, acetylcarnitine, thioctic acid, celecoxib, and ginkgo biloba extract.[5] Initial results have been promising for some of these substances,[5] but, similarly to cisplatin (see p. 767.3), conclusive data are lacking for most interventions. Intravenous calcium gluconate and magnesium chloride infusions have been used to prevent acute oxaliplatin neuropathy with good initial results; similarly, intravenous calcium gluconate and magnesium sulfate have been reported to dramatically improve oxaliplatin-associated neuropathy.[6-8] However, a study designed to evaluate potential reduction of cumulative neurotoxicity associated with oxaliplatin, using calcium and magnesium salts, was terminated after those patients receiving calcium and magnesium reported a significantly lower response to chemotherapy (which consisted of oxaliplatin, folinic acid, fluorouracil, and bevacizumab). Although these results need confirmation, the possibility that calcium and magnesium may reduce the activity of certain drugs in the treatment of colorectal cancer should be considered.[9] Others[10,11] have contended that calcium and magnesium therapy does not affect the antitumour efficacy of oxaliplatin-containing regimens; further studies are planned.

1. Extra JM, *et al.* Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol* 1998; **25** (suppl 5): 13–22.
2. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60:** 895–924.
3. Cassidy J, Misset J-L. Oxaliplatin-related side effects: characteristics and management. *Semin Oncol* 2002; **29** (suppl 15): 11–20.
4. Argyriou AA, *et al.* A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev* 2008; **34:** 368–77.
5. Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. *Ther Clin Risk Manag* 2005; **1:** 249–58.
6. Gamelin L, *et al.* Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res* 2004; **10:** 4055–61.
7. Cersosimo RJ. Oxaliplatin-associated neuropathy: a review. *Ann Pharmacother* 2005; **39:** 128–35.
8. Gamelin L, *et al.* Neurotoxicité de l'oxaliplatine. *Bull Cancer* 2006; **93** (suppl 1): S17–S22.
9. Hochster HS, *et al.* Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. *J Clin Oncol* 2007; **25:** 4028–9.
10. Gamelin L, *et al.* Oxaliplatin-related neurotoxicity: interest of calcium-magnesium infusion and no impact on its efficacy. *J Clin Oncol* 2008; **26:** 1188–9.
11. Grothey A, *et al.* Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. *J Clin Oncol* 2011; **29:** 421–7.

GUILLAIN-BARRÉ SYNDROME. A patient with metastatic colon cancer developed Guillain-Barré syndrome after weekly treatment with oxaliplatin-based chemotherapy;[1] he recovered after treatment with intravenous immunoglobulin.

1. Christodoulou C, *et al.* Guillain-Barré syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy. *Anticancer Drugs* 2004; **15:** 997–9.

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME. Reversible posterior leukoencephalopathy syndrome (RPLS) was diagnosed in a woman given oxaliplatin with bevacizumab, and capecitabine. She tolerated further therapy with bevacizumab and irinotecan with no complications. The authors attributed the RPLS to oxaliplatin.[1]

1. Pinedo DM, *et al.* Reversible posterior leukoencephalopathy syndrome associated with oxaliplatin. *J Clin Oncol* 2007; **25:** 5320–1.

Extravasation. Although oxaliplatin was originally considered to be non-vesicant, there have been reports of extravasation causing inflammation, sclerosis, or, in some cases, severe necrosis.[1-4] Some consider it to be a vesicant drug,[1,2] although others state oxaliplatin extravasation to be less harmful than that of more classic vesicants.[4]

For discussion of the management of extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p. 731.3.

1. Baur M, *et al.* Extravasation of oxaliplatin (Eloxatin)–clinical course. *Onkologie* 2000; **23:** 468–71.
2. Foo KF, *et al.* A case report of oxaliplatin extravasation. *Ann Oncol* 2003; **14:** 961–2.
3. Kennedy JG, *et al.* Vesicant characteristics of oxapliplatin [sic] following antecubital extravasation. *Clin Oncol (R Coll Radiol)* 2003; **15:** 237–9.
4. Kretzschmar A, *et al.* Extravasations of oxaliplatin. *J Clin Oncol* 2003; **21:** 4068–9.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, have been reported with oxaliplatin,[1-18] usually after several cycles of treatment. Symptoms include hypotension, tachycardia, dyspnoea, burning sensations, pruritus, erythema, sweating, and dizziness.[1,2,7,8] Rashes have also been reported[5,6,12] as have fever and chills.[9,10] While the mechanism of hypersensitivity to oxaliplatin is not clear, it has been suggested that reactions are characterised by development of symptoms during or shortly after the infusion, and are possibly due to a type I IgE-mediated reaction.[7,10] Idiosyncratic or infusional reactions, which are delayed until hours after the infusion,[6,10] are considered to be associated with cytokine release.[7,10] Cases have generally resolved on stopping oxaliplatin and giving appropriate treatment. Acute thrombocytopenia, occurring after the onset of hypersensitivity, has been reported in 2 patients,[15] both of whom were found to have oxaliplatin-dependent IgG platelet antibodies; see also Effects on the Blood, p. 838.3.

Prophylaxis before further oxaliplatin therapy, with corticosteroids and/or antihistamines, has shown variable efficacy.[4-7,9,10] Desensitisation protocols using dilute solutions and longer infusion times have been reported to be successful.[10,11,13,14] For the successful use of cisplatin in a patient hypersensitive to oxaliplatin see p. 768.1.

Intradermal skin testing has been used to identify patients with suspected hypersensitivity to oxaliplatin; however, in some patients with negative skin tests, reactions have occurred upon rechallenge.[6,8]

1. Tournigand C, *et al.* Severe anaphylactic reactions to oxaliplatin. *Eur J Cancer* 1998; **34:** 1297–8.
2. Médioni J, *et al.* Anaphylaxis after oxaliplatin. *Ann Oncol* 1999; **10:** 610.
3. Larzillière I, *et al.* Anaphylactic reaction to oxaliplatin: a case report. *Am J Gastroenterol* 1999; **94:** 3387–8.
4. Stahl M, *et al.* Reaction after oxaliplatin—prevention with corticosteroids? *Ann Oncol* 2001; **12:** 874.
5. Alliot C, *et al.* Severe anaphylactic reaction to oxaliplatin. *Clin Oncol (R Coll Radiol)* 2001; **13:** 236.
6. Thomas RR, *et al.* Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003; **97:** 2301–7.
7. Brandi G, *et al.* Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003; **89:** 477–81.
8. Garufi C, *et al.* Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol* 2003; **14:** 497–8.
9. Lenz G, *et al.* Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. *Anticancer Drugs* 2003; **14:** 731–3.
10. Lim K-H, *et al.* Hypersensitivity reactions to oxaliplatin: a case report and the success of a continuous infusional desensitization schedule. *Anticancer Drugs* 2004; **15:** 605–7.
11. Gammon D, *et al.* Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004; **9:** 546–9.
12. Ng CVT. Hypersensitivity reactions to oxaliplatin in two Asian patients. *Ann Pharmacother* 2005; **39:** 1114–18.
13. Mis L, *et al.* Successful desensitization to oxaliplatin. *Ann Pharmacother* 2005; **39:** 966–9.
14. Syrigou EI, *et al.* Hypersensitivity reactions to oxaliplatin: a retrospective study and the development of a desensitization protocol. *Clin Colorectal Cancer* 2009; **8:** 106–9.
15. Bautista MA, *et al.* Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. *J Hematol Oncol* 2010; **3:** 12.
16. Shao Y-Y, *et al.* Characteristics and risk factors of oxaliplatin-related hypersensitivity reactions. *J Formos Med Assoc* 2010; **109:** 362–8.
17. Mori Y, *et al.* Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. *Oncology* 2010; **79:** 136–43.
18. Seki K, *et al.* Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. *Int J Med Sci* 2011; **8:** 210–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxaliplatin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Interactions

For reference to the effect of oxaliplatin on fluorouracil, see Antineoplastics, p. 797.3.

Pharmacokinetics

After intravenous doses, oxaliplatin is widely distributed throughout the body. It binds irreversibly to red blood cells, which can prolong the half-life of the drug. The mean terminal half-life has been variously stated to be 273 hours and 391 hours.

Oxaliplatin is extensively metabolised to both inactive and active compounds and is mainly excreted in the urine.

References.

1. Lévi F, *et al.* Oxaliplatin: pharmacokinetics and chronopharmacological aspects. *Clin Pharmacokinet* 2000; **38:** 1–21.
2. Graham MA, *et al.* Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res* 2000; **6:** 1205–18.
3. Jerremalm E, *et al.* New insights into the biotransformation and pharmacokinetics of oxaliplatin. *J Pharm Sci* 2009; **98:** 3879–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisapla; Dabenzol; Dacplat; Goxyral; Kebir; Metaplatin; Mitog; O-Plat; Oxaltie; Platinostyl; Plusplatin; Uxalun; Xaliplat; ***Austral.***: Eloxatin; Oxalatin; ***Austria***: Eloxatin; ***Belg.***: Eloxatin; ***Braz.***: Eloxatin; Ezulen; O-Plat; Oxalibbs; Tevaoxali; Uxalun; ***Canad.***: Eloxatin; ***Chile***: Eloxatin; O-Plat; ***China***: Ai Heng (艾恒); Ai Ke Bo Kang (艾克博康); Ao Zheng Nan (奥正南); Cao Bo (草铂); Chen Ya (辰雅); Duo Ling (多令); Eloxatin (乐沙定); Jia Le Tong Tai (佳乐同泰); Olatin (优铂廷); ***Cz.***: Ebeoxal; Eloxatin; Livellin; Oxaliquid; Oxiplat†; Platox; Rezidol; ***Denm.***: Eloxatin; Olatin; Rezidol; ***Fin.***: Eloxatin†; Oxitropic†; ***Fr.***: Eloxatine; ***Ger.***: Axiplatin; Bendaplatin; Croloxat; Eloxatin; Medoxa; Oxaliplan; Riboxatin; ***Gr.***: Axoplan; Eloxatin; Oxaliprol; Oxaltina; Plaxitin; Rectoxal; Rexap; Veraxatin; ***Hong Kong***: Eloxatin; Sindoxplatin; ***Hung.***: Eloxatin; Gessedil; Livellin†; Sinoxal; ***India***: Celdach; Dacotin; Fexoplat; Glenoxal; Kinaplat; Oplatin; Oxamil; Oxiplat; Oxitan; Oxoplan; ***Indon.***: Eloxatin; Rexta; ***Irl.***: Eloxatin; Oxamed†; ***Israel***: Eloxatin; ***Ital.***: Eloxatin; ***Jpn***: Elplat; ***Malaysia***: Eloxatin; ***Mex.***: Eloxatin; Entia; Olipcis; Oxitan; Riptam; ***Neth.***: Eloxatin; Foxantal†; Osigilatin†; Oxalisin; Oxiplasol†; ***Norw.***: Eloxatin; ***NZ***: Eloxatin; Oxaliccord; ***Philipp.***: Eloxatin; Henplatin; Oxalem; Oxitel; Platinox; Zildox; ***Pol.***: Eloxatin; Gessedil; ***Port.***: Eloxatin; Oxalix; ***Rus.***: Eloxatine (Элоксатин); Exorum (Экзорум); Oxatera (Оксатера); Plaksat (Плаксат); Platicad (Платикад); ***S.Afr.***: Eloxatin; Exiplat; Oxaliwin; ***Singapore***: Eloxatin; ***Spain***: Eloxatin; Oxitropic†; ***Swed.***: Eloxatin; ***Switz.***: Eloxatine; ***Thai.***: Eloxatin; Entia; Oxalip; Oxitan; Oxol; Oxplatin; ***Turk.***: Eloxatin; Linoxa; Oxalimedac; Oxalpin; Oxaqual; Oxebewe; Oxerol; Ploxal; ***UK***: Eloxatin†; ***Ukr.***: Eloxatine (Элоксатин); ***USA***: Eloxatin; ***Venez.***: Eloxatin.

Pharmacopoeial Preparations

USP 36: Oxaliplatin for Injection; Oxaliplatin Injection.

Paclitaxel *(BAN, USAN, rINN)*

BMS-181339-01; NSC-125973; Paclitaxelum; Paklitakseeli; Paklitaksel; Paklitaxel; Taxol; Taxol A; Паклитаксел.

(2*S*,5*R*,7*S*,10*R*,13*S*)-10,20-Bis(acetoxy)-2-benzoyloxy-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-13-yl (3*S*)-3-benzoylamino-3-phenyl-D-lactate.

$C_{47}H_{51}NO_{14}$=853.9

CAS — 33069-62-4.

ATC — L01CD01.

ATC Vet — QL01CD01.

UNII — P88XT4IS4D.

NOTE. Paclitaxel was formerly referred to as taxol, but the use of this name is now limited, as Taxol is a trademark.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Paclitaxel). Isolated from natural sources or produced by fermentation or by a semisynthetic process. A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Paclitaxel). A white to off-white powder. Insoluble in water; soluble in alcohol. Store in airtight containers at a temperature between 20 degrees and 25 degrees. Protect from light.

Incompatibility. The vehicle for conventional paclitaxel injection, which contains alcohol and polyoxl castor oil, was found to leach the plasticiser diethylhexyl phthalate (DEHP) from some plastic giving sets.[1,2] Consequently, licensed product information recommends the use of non-PVC containers and giving sets; the use of filter devices which incorporate short inlet and/or short outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Paclitaxel was found to be compatible with doxorubicin for at least 24 hours, but microcrystalline precipitation of paclitaxel occurred after 3 to 5 days.[3] For mention of the incompatibility of paclitaxel and cisplatin see p. 766.1.

1. Trissel LA, *et al.* Compatibility of paclitaxel injection vehicle with intravenous administration and extension sets. *Am J Hosp Pharm* 1994; **51:** 2804–10.
2. Mazzo DJ, *et al.* Compatibility of docetaxel and paclitaxel in intravenous solutions with polyvinyl chloride infusion materials. *Am J Health-Syst Pharm* 1997; **54:** 566–9.
3. Trissel LA, *et al.* Compatibility and stability of paclitaxel combined with doxorubicin hydrochloride in infusion solutions. *Ann Pharmacother* 1998; **32:** 1013–6.

Uses and Administration

Paclitaxel is a taxane originally derived from the bark of the Pacific yew tree *Taxus brevifolia* (Taxaceae), and now obtained semisynthetically from a taxane precursor derived from the needles of the European yew, *Taxus baccata.* Paclitaxel's antineoplastic action arises from induction of microtubule formation and stabilisation of microtubules, thereby disrupting normal cell division in the G_2 and M phases of the cell cycle.

Paclitaxel is used for the primary treatment of advanced ovarian cancer (p. 711.2) with cisplatin or carboplatin, and for secondary treatment, usually after failure of standard platinum-containing therapy. In the treatment of node-positive breast cancer (p. 702.1), paclitaxel is used for adjuvant therapy after anthracycline-containing chemotherapy. In locally advanced or metastatic breast cancer, it is used first-line with an anthracycline, or as a second-line single-agent, usually after failure of anthracycline-based therapy. In patients with locally advanced or metastatic disease who overexpress HER2 (human epidermal growth receptor 2) it may be used with trastuzumab as initial therapy. Paclitaxel is used with cisplatin or carboplatin, for the primary treatment of non-small cell lung cancer (p. 710.2) in patients who are not candidates for potentially curative surgery and/or radiotherapy. In metastatic adenocarcinoma of the pancreas (p. 712.1) it is used first-line with gemcitabine. It may be used for the second-line treatment of AIDS-related Kaposi's sarcoma (p. 718.1), and has been tried in other neoplasms including cancers of the head and neck, and relapsed germ-cell tumours.

The conventional formulation of paclitaxel with polyoxyl castor oil and alcohol is usually given intravenously. It is diluted, usually with sodium chloride 0.9% or glucose 5%, to a final concentration of 0.3 to 1.2 mg/mL, in a non-PVC container and given through an in-line filter (of not greater than 0.22 micrometres). In licensed regimens it is generally given at 3-week intervals although there is increasing evidence that use at smaller intervals of 1 week may be advantageous (see Administration, below). An injectable suspension of albumin-bound paclitaxel nanoparticles (*Abraxane; Celgene, UK and USA*; ABI-007) is also available. It is usually given intravenously over 30 minutes. PVC or non-PVC containers may be used; an in-line filter is not necessary.

The recommended dose of conventional paclitaxel for the primary treatment of **ovarian cancer** is 135 mg/m^2 infused over 24 hours, followed by cisplatin, and repeated at 3-week intervals. Alternatively 175 mg/m^2 may be infused over 3 hours, followed by cisplatin, every 3 weeks. For the secondary treatment of ovarian cancer, the suggested dose as a single agent is 135 or 175 mg/m^2 infused over 3 hours once every 3 weeks.

Paclitaxel has also been given intraperitoneally for the treatment of ovarian cancer.

For **breast cancer**, an intravenous dose of conventional paclitaxel 175 mg/m^2 infused over 3 hours once every 3 weeks is recommended for adjuvant treatment (for 4 courses), for second-line monotherapy, and for first-line treatment with trastuzumab; paclitaxel is given the day after the first dose of trastuzumab, or immediately after subsequent doses if well-tolerated. When used first-line with doxorubicin, paclitaxel 220 mg/m^2 is infused over 3 hours once every 3 weeks; the dose is given 24 hours after doxorubicin.

Albumin-bound paclitaxel nanoparticles are also used for the treatment of refractory or relapsed metastatic breast cancer. The dose is 260 mg/m^2 given intravenously over 30 minutes every 3 weeks.

In **non-small cell lung cancer**, the recommended dose of conventional paclitaxel is 135 mg/m^2 over 24 hours, or 175 mg/m^2 over 3 hours, followed by cisplatin, and repeated at 3-week intervals.

Albumin-bound paclitaxel nanoparticles may also be used with carboplatin as a first-line option for locally advanced or metastatic non-small cell lung cancer. A dose of 100 mg/m^2 is infused intravenously over 30 minutes on days 1, 8, and 15 of a 21-day cycle.

For the first-line treatment of metastatic **pancreatic adenocarcinoma**, albumin-bound paclitaxel nanoparticles are given in a dose of 125 mg/m^2 infused intravenously over 30 to 40 minutes, and followed immediately after by gemcitabine, on days 1, 8, and 15 of a 28-day cycle.

A dose of conventional paclitaxel 135 mg/m^2 over 3 hours once every 3 weeks has been suggested for AIDS-related **Kaposi's sarcoma**. Alternatively, 100 mg/m^2 over 3 hours every 2 weeks may be given, especially in patients with poor performance status.

Regular blood counts should be performed, and dosage should not be given or repeated until the neutrophil and platelet counts are at acceptable levels; see Administration in Subsequent Cycles, below. Pretreatment with corticosteroids, antihistamines, and histamine H_2-antagonists is needed for the conventional formulation of paclitaxel, but not for the albumin-bound nanoparticle formulation.

The dose of paclitaxel may need to be reduced in patients with hepatic impairment (see below).

Various formulations have been developed to avoid the use of polyoxyl castor oil and improve the efficacy and safety of paclitaxel. In addition to the albumin-bound formulation referred to above, formulations in development include paclitaxel linked to docosahexaenoic acid (DHA-paclitaxel) or biodegradable polymers (such as paclitaxel poliglumex, CT-2103), micellar and liposomal formulations, and an oral dosage form. An injectable gel containing a modified-release formulation of paclitaxel is also under investigation, for direct injection into tumours.

Paclitaxel-releasing stents may be used to reduce restenosis after coronary artery stent placement.

References to paclitaxel, and to taxanes as a class.

1. Hayes DF, *et al.* Cancer and Leukemia Group B (CALGB) Investigators. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med* 2007; **357:** 1496–1506.
2. Saloustros E, *et al.* Paclitaxel and docetaxel in the treatment of breast cancer. *Expert Opin Pharmacother* 2008; **9:** 2603–16.
3. Sakamoto J, *et al.* Paclitaxel chemotherapy for the treatment of gastric cancer. *Gastric Cancer* 2009; **12:** 69–78.
4. Fu Y, *et al.* Medicinal chemistry of paclitaxel and its analogues. *Curr Med Chem* 2009; **16:** 3966–85.
5. Gaitanis A, Staal S. Liposomal doxorubicin and nab-paclitaxel: nanoparticle cancer chemotherapy in current clinical use. *Methods Mol Biol* 2010; **624:** 385–92.
6. Montero AJ, *et al.* Nab-paclitaxel in the treatment of metastatic breast cancer: a comprehensive review. *Expert Rev Clin Pharmacol* 2011; **4:** 329–34.
7. Huang TC, Campbell TC. Comparison of weekly versus every 3 weeks paclitaxel in the treatment of advanced solid tumors: a meta-analysis. *Cancer Treat Rev* 2012; **38:** 613–17.
8. Socinski MA, *et al.* Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012; **30:** 2055–62.
9. Gradishar WJ. Taxanes for the treatment of metastatic breast cancer. *Breast Cancer (Auckl)* 2012; **6:** 159–71.
10. Von Hoff DD, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369:** 1691–1703.

Administration. Although many of the original studies of conventional paclitaxel employed a 24-hour infusion regimen, the use of *3-hour infusions* has subsequently become widespread. A systematic review[1] noted that although it was difficult to compare efficacy in studies of unlike malignancies there was no conclusive evidence of a difference in efficacy with differing length of infusion; however, there were differences in the adverse effect profile, neutropenia being much less marked with the shorter infusion, although neurotoxic effects were reduced with 24-hour administration. (Note that albumin-bound paclitaxel can be given over 30 minutes, see p. 839.3).

There has also been considerable interest in evaluating the use of conventional paclitaxel in reduced-dose *weekly* schedules.[2-14] Various dosage regimens have been tried: most have found that doses of between 50 and about 100 mg/m^2 weekly, usually by infusion over 1 hour rather than a conventional 3-hour infusion, can be given with relatively modest toxicity. Although higher doses have been tried, neurotoxicity and myelosuppression become problematic and tend to limit dose intensity. Several studies have addressed the use of weekly paclitaxel with other antineoplastics, for example with trastuzumab in breast cancer, estramustine in prostate cancer, and with platinum compounds or gemcitabine in other solid tumours such as those of the ovary or lung. In a randomised controlled study[13] in patients with metastatic breast cancer, weekly paclitaxel (80 mg/m^2) with or without trastuzumab nearly doubled time to progression from 5 to 9 months compared with a 3-weekly regimen, and had better response rates and overall survival. Neuropathy was the main toxicity (see also Effects on the Nervous System, p. 841.3). A meta-analysis[14] of weekly versus 3-weekly taxane regimens in advanced breast cancer found that although the objective response rate was better with a 3-week regimen of paclitaxel, giving the drug weekly produced higher overall survival and was associated with fewer serious adverse effects. There appeared to be little difference between a weekly and a 3-weekly regimen for docetaxel, but it was impossible to come to firm conclusions because of scanty data.

The use of weekly paclitaxel with radiotherapy is also under investigation in the management of lung cancer and glioblastoma multiforme.

For the suggestion that inhibitors of P-glycoprotein (such as ciclosporin) might be used to boost bioavailability and allow the use of *oral* paclitaxel see Immunosuppressants, under Interactions of Docetaxel, p. 782.2.

1. Williams C, *et al.* Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2011 (accessed 29/06/11).
2. Seidman AD, *et al.* Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 1998; **16:** 3353–61.
3. Fountzilas G, *et al.* Radiation and concomitant weekly administration of paclitaxel in patients with glioblastoma multiforme: a phase II study. *J Neurooncol* 1999; **45:** 159–65.
4. Markman M. Weekly paclitaxel in the management of ovarian cancer. *Semin Oncol* 2000; **27** (suppl 7): 37–40.
5. De Pas T, *et al.* Phase I and pharmacologic study of weekly gemcitabine and paclitaxel in chemo-naive patients with advanced non-small-cell lung cancer. *Ann Oncol* 2000; **11:** 821–7.
6. Langer CJ, *et al.* Paclitaxel by 1-h infusion in combination with carboplatin in advanced non-small cell lung carcinoma (NSCLC). *Eur J Cancer* 2000; **36:** 183–93.
7. Akerley W. Recent developments in weekly paclitaxel therapy in lung cancer. *Curr Oncol Rep* 2001; **3:** 165–9.
8. Haas N, *et al.* Phase I trial of weekly paclitaxel plus oral estramustine phosphate in patients with hormone-refractory prostate cancer. *Urology* 2001; **58:** 59–64.
9. Seidman AD, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; **19:** 2587–95.
10. Kouroussis C, *et al.* A dose-finding study of the weekly administration of paclitaxel in patients with advanced solid tumors. *Am J Clin Oncol* 2001; **24:** 404–7.
11. Brambilla L, *et al.* Weekly paclitaxel for advanced aggressive classic Kaposi sarcoma: experience in 17 cases. *Br J Dermatol* 2008; **158:** 1339–44.
12. Sparano JA, *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; **358:** 1663–71. Correction. *ibid.*; **359:** 106. Correction. *ibid.* 2009; **360:** 1685.
13. Seidman AD, *et al.* Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008; **26:** 1642–9.
14. Mauri D, *et al.* Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev* 2010; **36:** 69–74.

Administration in the elderly. A review[1] stated that data are conflicting regarding the impact of age on paclitaxel clearance. However, studies indicate that both weekly and 3-weekly dosing regimens are feasible in elderly patients, and no dose reduction of paclitaxel is needed on the basis of age alone.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in hepatic impairment. Total bilirubin has been shown to be a good predictor of paclitaxel elimination capacity and of individual susceptibility to paclitaxel-related myelosuppression.[1]

UK licensed product information for the conventional formulation of paclitaxel states that there are inadequate data available to recommend dose adjustment in mild to moderate hepatic impairment. Paclitaxel is not recommended in patients with severe hepatic impairment. US licensed product information makes recommendations for initial dosage adjustment of some paclitaxel regimens in patients with hepatic impairment, according to transaminase and bilirubin concentrations. They suggest the conventional formulation of paclitaxel should not be given if transaminase values are > 10 times the upper limit of normal (ULN), or if bilirubin is > 7.5 mg per 100 mL or 5 times the ULN.

In US licensed product information for the albumin-bound paclitaxel nanoparticle formulation recommendations vary depending on the indication and the degree of hepatic impairment; in patients with aspartate aminotransferase (AST/SGOT) < 10 times ULN and the following bilirubin concentrations:

- bilirubin > ULN to 1.25 times ULN (mild impairment): usual initial dose (see Uses and Administration, p. 839.3)
- 1.26 to 2 times ULN (moderate impairment): an initial dose of 200 mg/m^2 in breast cancer and 75 mg/m^2 in non-small cell lung cancer (NSCLC); not recommended for pancreatic adenocarcinoma
- 2.01 to 5 times ULN (severe impairment): an initial dose of 130 mg/m^2 in breast cancer and 50 mg/m^2 in NSCLC; not recommended for pancreatic adenocarcinoma

Treatment with the albumin-bound formulation is not recommended in any patients with AST/SGOT > 10 times ULN or bilirubin > 5 times ULN. Further dose adjustments in subsequent cycles are based on individual tolerance; in severe impairment, an increase up to 200 mg/m^2 in breast cancer and 75 mg/m^2 in NSCLC can be considered if the initial dose is tolerated.

UK licensed product information for this formulation states that a dose reduction must be considered in patients with bilirubin concentrations more than twice the ULN; patients with bilirubin > 5 times the ULN or with transaminase concentrations > 10 times the ULN should not be treated, due to a lack of data.

1. Joerger M, *et al.* Safety and pharmacology of paclitaxel in patients with impaired liver function: a population pharmacokinetic-pharmacodynamic study. *Br J Clin Pharmacol* 2007; **64:** 622–33.

Administration in subsequent cycles. In general, if toxicity occurs paclitaxel doses are withheld until the patient has recovered or symptoms have improved; treatment may be restarted at a reduced dose. If the toxicity is persistent despite dose reductions treatment should be stopped.

Conventional paclitaxel should not be given to patients with baseline neutrophil counts < 1500 cells/mm^3; some manufacturers also contra-indicate use in patients with platelets < 100 000 cells/mm^3. In patients with Kaposi's sarcoma, conventional paclitaxel should not be given if baseline neutrophil counts are < 1000 cells/mm^3 or platelets are < 75 000 cells/mm^3. Subsequent doses should not be given until the neutrophil and platelet counts reach these values or greater. Patients who have severe neutropenia (< 500 cells/mm^3 for a minimum of 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses; for patients with Kaposi's sarcoma, a dose reduction of 25% is recommended.

Albumin-bound paclitaxel should also not be given to patients with baseline neutrophil counts < 1500 cells/mm^3.

- In patients with **breast cancer**, treatment is modified if severe neutropenia or severe sensory neuropathy occur. Doses are reduced in steps of 40 mg/m².
- In patients with **non-small cell lung cancer** treatment is modified for neutropenia, thrombocytopenia, or severe sensory neuropathy. Doses are reduced in steps of 25 mg/m².
- In patients with **pancreatic adenocarcinoma** treatment is modified for neutropenia, thrombocytopenia, severe peripheral neuropathy, grade 2 or 3 cutaneous toxicity, or grade 3 mucositis or diarrhoea. Doses are reduced in steps of 25 mg/m².

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Coronary stents that elute paclitaxel effectively reduce restenosis and have been widely used, although there is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis.[1-3] In a study compared with bare metal stents, paclitaxel-releasing stents reduced the risk of restenosis and the need for repeat revascularisation procedures, although the follow-up rates of death from cardiac causes or myocardial infarction were not significantly reduced at 9 months[4] and 1 year.[5] However, between 9 months and 1 year, major cardiac adverse events were significantly reduced in the paclitaxel-releasing stent group compared with controls.[5] A larger multicentre study[6] in patients with acute myocardial infarction confirmed the reduced risk of restenosis and recurrent ischaemia with paclitaxel-releasing as against bare-metal stents; no evidence of differences in mortality or stent thrombosis was seen at 1 year of follow-up. A review[7] of various stent designs concluded that safety of paclitaxel-releasing stents was independent of design, dose-density, or presence or absence of a polymer carrier system; however, those without a polymer carrier were unable to show a positive effect on clinical outcome in patients with de novo coronary lesions. However, in a paclitaxel-releasing stent system, failure of the stent-delivery balloon to deflate has been associated with serious injuries and 1 fatality.[8] The risk of late stent thrombosis may also be increased with drug eluting stents,[9] although the evidence is controversial,[10] and their role in complex interventions is not yet established.[11,12]

Positive effects on restenosis have also been reported[13] with use of a paclitaxel-coated angioplasty balloon.

1. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; **353:** 653–62.
2. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353:** 663–70.
3. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
4. Stone GW, *et al.* A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350:** 221–31.
5. Stone GW, *et al.* One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004; **109:** 1942–7.
6. Stone GW, *et al.* HORIZONS-AMI Trial Investigators. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 2009; **360:** 1946–59.
7. Silber S. Paclitaxel-eluting stents: are they all equal? An analysis of six randomized controlled trials in de novo lesions of 3,319 patients. *J Interv Cardiol* 2003; **16:** 485–90.
8. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; **351:** 1593–5.
9. Stone GW, *et al.* Safety and efficacy of sirolimus-and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356:** 998–1008.
10. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; **356:** 1020–9.
11. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297:** 1992–2000.
12. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297:** 2001–9.
13. Scheller B, *et al.* Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006; **355:** 2113–24.

Adverse Effects, Treatment, and Precautions

Paclitaxel is available as two formulations: a conventional formulation and an albumin-bound form. The two formulations are not interchangeable and one cannot be substituted for the other. While adverse effects are similar, the frequency of these effects can vary between formulations.

Conventional paclitaxel commonly produces severe dose-limiting myelosuppression, mainly neutropenia. The nadir of the white cell count usually occurs after about 11 days, with recovery usually by day 15 to 21 after a dose. Neutropenia may be less frequent when infusions are given over 3 rather than 24 hours. Blood counts should be monitored frequently.

Peripheral neuropathy can also be severe, and occasionally dose-limiting. Neurotoxicity appears to be more frequent and more severe when infusions are given over 3 hours rather than 24 hours. Hypersensitivity reactions, with flushing, rash, chills, dyspnoea, hypotension (or hypertension), chest pain, back pain, tachycardia, generalised urticaria, and angioedema may occur; anaphylaxis has been reported. All patients should be given initial premedication with corticosteroids, antihistamines, and histamine H_2-antagonists. Mild hypersensitivity reactions do not require interruption of therapy, but serious reactions (which may be fatal, and can occur despite premedication) require treatment to be stopped; patients who have serious reactions should not be re-treated with paclitaxel. Conventional paclitaxel is formulated in polyoxyl castor oil and it should be avoided in patients hypersensitive to this substance.

Cardiac disorders include bradycardia, arrhythmias, myocardial infarction, and heart failure; severe cardiac conduction disorders occur rarely and require continuous cardiac monitoring.

Common adverse effects include alopecia, arthralgia and myalgia, gastrointestinal disturbances, transient mild nail and skin changes, and elevation of liver enzyme values. Infections are also common, and fatalities have been reported. Injection site reactions and mucositis may occur more frequently with the 24-hour infusion than the 3-hour infusion. Manifestations include localised oedema, pain, erythema, and induration; extravasation may result in tissue damage.

Rare adverse events include febrile neutropenia, motor or autonomic neuropathy (which can result in paralytic ileus and orthostatic hypotension), seizures, encephalopathy, dizziness, headache, ataxia, severe thrombotic events, optic nerve and/or visual disturbances (especially at high doses), ototoxicity, bowel obstruction or perforation, pancreatitis, interstitial pneumonia, and pseudomembranous colitis. There are reports of hepatic necrosis and hepatic encephalopathy, some of which have been fatal. Increases in bilirubin and blood creatinine have been reported. Severe skin disorders include Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, and exfoliative dermatitis.

Albumin-bound paclitaxel also causes myelosuppression, mainly neutropenia which is rapidly reversible and dose-dependent. Febrile neutropenia is common. Sensory neuropathy occurs frequently, but is usually mild and does not generally require dose modification. Hypersensitivity is uncommon, and premedication is not required. Patients who have a severe hypersensitivity reaction to paclitaxel should not be given the drug again. Tachycardia and arrhythmias occur commonly; bradycardia, cardiac arrest, congestive heart failure, and left ventricular dysfunction are rare, but cardiac monitoring may be required, especially if patients have underlying cardiac disease or previous exposure to anthracyclines.

As with conventional paclitaxel, adverse effects such as alopecia, arthralgia, myalgia, gastrointestinal disturbances, nail and skin disorders, infections, and increases in liver enzyme values are common. Other common adverse effects include anorexia, hypokalaemia, stomatitis, flushing, hypertension, oedema (including lymphoedema), dyspnoea, epistaxis, cough, rhinitis, rhinorrhoea, fatigue, eye disorders, vertigo, and pain. Headache, ataxia, dizziness, dysgeusia, insomnia or somnolence, depression, and anxiety are also common.

Rare adverse effects include hypotension, thrombotic events, injection site reactions, and interstitial pneumonia. Other uncommon adverse effects include glucose and electrolyte disturbances, increases in bilirubin and blood creatinine, and urinary disorders. There have been rare reports of stroke and transient ischaemic attacks, cranial nerve palsies, and vocal cord paresis.

Both conventional and albumin-bound paclitaxel should be used with caution in patients with hepatic impairment (see Administration in Hepatic Impairment, p. 840.3).

Alcohol intoxication. Acute alcohol intoxication resulting from high-dose paclitaxel infusion has been reported;[1] it was calculated that the dose used (348 mg/m²) supplied 50 mL of alcohol, or the equivalent of about 3 drinks (half a bottle of wine).

1. Wilson DB, *et al.* Paclitaxel formulation as a cause of ethanol intoxication. *Ann Pharmacother* 1997; **31:** 873–5.

Effects on the eyes. Optic neuritis has occurred with paclitaxel. There is a report of glaucoma possibly related to the use of docetaxel and paclitaxel in a patient also receiving corticosteroids.[1]

1. Fabre-Guillevin E, *et al.* Taxane-induced glaucoma. *Lancet* 1999; **354:** 1181–2.

Effects on the heart. Infusion of paclitaxel has been associated with sinus bradycardia, atrial arrhythmias, ventricular tachycardia, heart block, myocardial infarction, and sudden death.[1,2] Symptoms of heart failure have been reported.[3] In another report sudden death 7 days after paclitaxel treatment raised the question of whether paclitaxel might have had a delayed effect.[4] There is some evidence of cellular damage to the myocardium of a patient with paclitaxel-associated cardiac symptoms.[3] Licensed product information notes that severe cardiovascular events have been seen more frequently after the use of paclitaxel in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

1. Rowinsky EK, *et al.* Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991; **9:** 1704–12.
2. Arbuck SG, *et al.* A reassessment of cardiac toxicity associated with Taxol. *J Natl Cancer Inst Monogr* 1993; **15:** 117–30.
3. Jekunen A, *et al.* Paclitaxel-induced myocardial damage detected by electron microscopy. *Lancet* 1994; **343:** 727–8.
4. Alagaratnam TT. Sudden death 7 days after paclitaxel infusion for breast cancer. *Lancet* 1993; **342:** 1232–3.

Effects on the musculoskeletal system. For discussion of paclitaxel-induced arthralgia and myalgia (also referred to as paclitaxel-acute pain syndrome), and its association with neuropathic pain, see Effects on the Nervous System, below.

Effects on the nervous system. Neurotoxicity, usually manifesting as cumulative sensory peripheral neuropathy, is the most important non-haematological toxicity associated with use of paclitaxel, particularly when given in weekly dose-dense regimens,[1] where it is often dose-limiting (see also Administration, p. 840.2). The risk appears to be greater in older patients, those with diabetes, and those with co-existing alcohol abuse. Motor neuropathy is much less common than sensory symptoms, which may include numbness, paraesthesia, and burning sensations in a symmetric glove-and-stocking pattern that usually affects the lower limbs first. Orthostatic hypotension, arrhythmias, and ileus have sometimes been reported as possible signs of autonomic neuropathy. Although mild sensory neuropathy is generally reversible within a few months, more severe cases may persist much longer. Treatment options are lacking and close monitoring of patients to avoid the development of severe symptoms is important.[1]

Paclitaxel-acute pain syndrome (also called paclitaxel-induced arthralgia and myalgia), has been described as a diffuse aching discomfort that is most often felt in the legs, hips, and lower back. Symptoms usually develop over 1 to 4 days of treatment and resolve over a similar timeframe. It has been noted that the intensity of pain felt with the first paclitaxel infusion appeared to predict the later severity of sensory-predominant peripheral neuropathy (particularly shooting or burning pain) that gradually developed over a 12-week course of therapy, supporting the hypothesis that paclitaxel-acute pain syndrome is a form of neurotoxicity.[2,3] Gabapentin has been reported to be of benefit in the management of taxane-induced arthralgia and myalgia.[4,5]

Acute encephalopathy, manifesting between 5 hours and 16 days after infusion, has also been reported rarely in patients given paclitaxel.[6] Symptoms have included disorientation, mood disorders, language disorders, delirium, hallucinations, and coma.

1. Mielke S, *et al.* Peripheral neuropathy: a persisting challenge in paclitaxel-based regimes. *Eur J Cancer* 2006; **42:** 24–30.
2. Loprinzi CL, *et al.* Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. *J Clin Oncol* 2011; **29:** 1472–8.
3. Reeves BN, *et al.* Further data supporting that paclitaxel-associated acute pain syndrome is associated with development of peripheral neuropathy: North Central Cancer Treatment Group trial N08C1. *Cancer* 2012; **118:** 5171–8.
4. van Deventer H, Bernard S. Use of gabapentin to treat taxane-induced myalgias. *J Clin Oncol* 1999; **17:** 434–5.
5. Nguyen VH, Lawrence HJ. Use of gabapentin in the prevention of taxane-induced arthralgias and myalgias. *J Clin Oncol* 2004; **22:** 1767–9.
6. Lachkar S, *et al.* Encéphalopathie aiguë après injection de paclitaxel. *Rev Mal Respir* 2006; **23:** 73–7.

Effects on the respiratory system. Acute bilateral interstitial pneumonitis has been reported rarely in patients receiving paclitaxel, despite premedication with corticosteroids and histamine antagonists.[1] Symptoms resolved on treatment with parenteral corticosteroids.

1. Khan A, *et al.* Paclitaxel-induced acute bilateral pneumonitis. *Ann Pharmacother* 1997; **31:** 1471–4.

Effects on the skin, hair, and nails. Nail changes, noted as pigmentation or discoloration of the nail-bed, may occur with paclitaxel. Onycholysis (separation of the nail from the nail-bed) has also been reported.[1] Discoloration and onycholysis can also occur after docetaxel use, and there are reports of subungual hyperkeratosis and haemorrhage.[2-4]

Localised oedema evolving into skin sclerosis, mimicking systemic sclerosis, has been reported after taxane use.[5,6] In most patients, the sclerosis developed mainly on the extremities, and especially the lower extremities. Joint contracture may occur. The total cumulative dose of the taxane may contribute to the onset.[5]

Severe and irreversible alopecia has been reported after use of docetaxel or paclitaxel in patients with breast cancer.[7]

1. Flory SM, *et al.* Onycholysis associated with weekly administration of paclitaxel. *Ann Pharmacother* 1999; **33:** 584–5.
2. Wasner G, *et al.* Clinical picture: nail changes secondary to docetaxel. *Lancet* 2001; **357:** 910.
3. Pavithran K, Doval DC. Nail changes due to docetaxel. *Br J Dermatol* 2002; **146:** 709–10.
4. Leonard GD, Zujewski JA. Docetaxel-related skin, nail, and vascular toxicity. *Ann Pharmacother* 2003; **37:** 148.

5. Itoh M, *et al.* Taxane-induced scleroderma. *Br J Dermatol* 2007; **156:** 363–7.
6. Takahashi T, *et al.* A case of taxane-induced scleroderma: a different expression profile of Fli1 proteins in dermal fibroblasts and microvascular endothelial cells compared with systemic sclerosis. *Br J Dermatol* 2011; **164:** 1393–5.
7. Prevezas C, *et al.* Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009; **160:** 883–5.

Hypersensitivity. Despite premedication with corticosteroids, antihistamines, and H_2-antagonists, hypersensitivity reactions are common in patients given conventional paclitaxel; up to about 40% of patients may have a mild reaction and about 2% a severe reaction. Fatalities have been reported. There are rare reports of delayed hypersensitivity reactions with paclitaxel; necrotic ulceration has occurred, without evidence of extravasation.[1] Some consider the cause to be the polyoxyl castor oil diluent for paclitaxel, and docetaxel has been suggested as a suitable alternative.[2] However, hypersensitivity reactions have also occurred with docetaxel and taxane cross-reactivity has been reported.[3,4] Although the manufacturers of both drugs consider further use to be contra-indicated after a severe reaction, strategies for continuation of treatment and desensitisation have been described.[5,6]

Hypersensitivity reactions to paclitaxel-eluting stents have also been reported;[7] however, the incidence is low, and some consider the polymer coating of the stent to be the likely cause.[8]

1. Beri R, *et al.* Severe dermatologic reactions at multiple sites after paclitaxel administration. *Ann Pharmacother* 2004; **38:** 238–41.
2. Bernstein BJ. Docetaxel as an alternative to paclitaxel after acute hypersensitivity reactions. *Ann Pharmacother* 2000; **34:** 1332–5.
3. Denman JP, *et al.* Hypersensitivity reaction (HSR) to docetaxel after a previous HSR to paclitaxel. *J Clin Oncol* 2002; **20:** 2760–1.
4. Karacan Ö, *et al.* Acute interstitial pneumopathy associated with docetaxel hypersensitivity. *Onkologie* 2004; **27:** 563–5.
5. Markman M, *et al.* Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000; **18:** 102–5.
6. Feldweg AM, *et al.* Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005; **96:** 824–9.
7. Nebeker JR, *et al.* Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006; **47:** 175–81.
8. Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents: is it the pill or the polymer? *J Am Coll Cardiol* 2006; **47:** 182–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paclitaxel as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pregnancy. Paclitaxel has been shown to be embryotoxic and fetotoxic in *animal* studies, but, although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus. A retrospective study[1] of 15 women who were given taxane chemotherapy for breast and ovarian cancer during the second and third trimesters of pregnancy found no differences in birth-weight, gestational age at delivery, rate of growth restriction, congenital anomalies and incidence of maternal and neonatal neutropenia for taxanes when compared with conventional chemotherapy. A systematic review[2] of taxane use for ovarian cancer during 12 pregnancies (11 for paclitaxel and 1 for docetaxel) found that in 92% of cases a healthy child was born; in 6 out of 8 cases with survival data, the mother was alive and disease free at the end of follow-up (median 20 months, and ranging from 9.75 to 45 months). The authors concluded that taxanes may be valuable for treatment of ovarian cancer during the second and third trimesters, but use in early pregnancy is associated with an increased risk of abortion or congenital abnormalities.

Oligohydramnios has been reported[3] with paclitaxel in a pregnant woman with breast cancer. From 24 weeks of gestation the patient received four cycles of doxorubicin and cyclophosphamide and was then started on a weekly regimen of paclitaxel; growth factor support was given throughout chemotherapy. Oligohydramnios was noted after the fourth week of paclitaxel. A healthy infant was delivered at 36 weeks of gestation.

1. Cardonick E, *et al.* Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012; **23:** 3016–23.
2. Zagouri F, *et al.* Taxanes for ovarian cancer during pregnancy: a systematic review. *Oncology* 2012; **83:** 234–8.
3. Shieh MP, Mehta RS. Oligohydramnios associated with administration of weekly paclitaxel for triple-negative breast cancer during pregnancy. *Ann Oncol* 2011; **22:** 2151–2.

Sickle-cell disease. A patient with previously undiagnosed sickle-cell disease had a painful crisis after being given conventional paclitaxel as part of a chemotherapy regimen for breast cancer.[1] It was unclear if the reaction was due to paclitaxel or its vehicle, and whether an alternative taxane or albumin-bound paclitaxel would cause a similar effect.

1. Wilson NM, *et al.* Paclitaxel-induced sickle cell crisis. *Am J Health-Syst Pharm* 2008; **65:** 1333–6.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Pretreatment with cisplatin may reduce the clearance of paclitaxel, resulting in increased toxicity, and when both drugs are given, paclitaxel should be given first.

Paclitaxel is metabolised by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. No clinically relevant interactions with other CYP2C8 substrates are likely. While use with ketoconazole (a potent inhibitor of CYP3A4) does not affect paclitaxel elimination, data are limited on use with other CYP3A4 inhibitors or inducers, and caution is advised when paclitaxel is used with these drugs.

Antineoplastics. For reference to enhanced cardiotoxicity when paclitaxel was given with *doxorubicin*, see p. 785.2. For the pharmacokinetic changes reported when paclitaxel was given with *gemcitabine*, see p. 802.1.

Pretreatment with *fluorouracil* has been reported to inhibit paclitaxel's cytotoxic action, possibly by preventing tumour cells from entering the G_2-M phases of the cell cycle.[1] The effect also occurred when the 2 drugs were given simultaneously, suggesting that combination therapy might not be appropriate.

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[2] found that it decreased clearance of paclitaxel and prolonged the terminal half-life, increasing exposure to paclitaxel and myelosuppressive effects. The authors suggested that the dose of paclitaxel may need to be reduced by about 60%.

Variable effects on paclitaxel pharmacokinetics have been seen when it has been given with *carboplatin* plus *sorafenib*; see under Interactions of Sorafenib, p. 858.2.

1. Johnson KR, *et al.* 5-Fluorouracil interferes with paclitaxel cytotoxicity against human solid tumor cells. *Clin Cancer Res* 1997; **3:** 1739–45.
2. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7:** 1221–9.

Antiretrovirals. In a patient given various antiretrovirals during paclitaxel treatment for Kaposi's sarcoma, pharmacokinetic parameters of paclitaxel were not significantly different when compared with historical controls.[1] The first course of therapy combined paclitaxel with *lamivudine*, *stavudine*, and the HIV-protease inhibitors *ritonavir* and *saquinavir*. In subsequent courses, paclitaxel was given with *nevirapine*, and the final course consisted of paclitaxel given with ritonavir and *indinavir*.

However, licensed product information for paclitaxel states that studies suggest that systemic clearance of paclitaxel was significantly lower in the presence of *nelfinavir* and ritonavir, but not indinavir, and that paclitaxel should be given with caution to patients taking HIV-protease inhibitors. HIV-protease inhibitors are metabolised by the cytochrome P450 isoenzyme CYP3A4, but are also reported to inhibit CYP3A activity. This may lead to increased adverse effects when given with taxanes; the combination of *delavirdine* and saquinavir has been reported to cause serious mucositis, severe myalgia, alopecia, and leucopenia when given with paclitaxel.[2] In other case reports, one patient tolerated *lopinavir*, ritonavir, delavirdine, and *didanosine* without complications until the addition of paclitaxel caused fatal toxicity. In another patient taking indinavir, ritonavir, stavudine, and lamivudine, the addition of paclitaxel caused profound cytopenia and total body alopecia; further courses of paclitaxel were given at a reduced dose with no sequelae.[3]

1. Nannan Panday VR, *et al.* Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma—drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study. *Cancer Chemother Pharmacol* 1999; **43:** 516–19.
2. Schwartz JD, *et al.* Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma. *AIDS* 1999; **13:** 283–4.
3. Bundow D, Aboulafia DM. Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated Kaposi sarcoma. *Am J Clin Oncol* 2004; **27:** 81–4.

Immunosuppressants. For the effect of ciclosporin on the oral absorption of paclitaxel, see Immunosuppressants, under Interactions of Docetaxel, p. 782.2.

For the effects of *valspodar* (an analogue of ciclosporin) on paclitaxel, see Antineoplastics, above.

Pharmacokinetics

Intravenous paclitaxel exhibits a biphasic decline in plasma concentrations, with a mean terminal half-life of anywhere between about 3 and 50 hours. The pharmacokinetics are non-linear. The steady-state volume of distribution is reported to range from 200 to 700 litres/m^2, indicating extensive extravascular distribution, tissue binding, or both. Paclitaxel is 89% or more bound to plasma protein *in vitro*. The elimination of paclitaxel has not been fully elucidated; only about 1 to 12% of a dose is reported to be excreted in urine, as unchanged drug, indicating extensive non-renal clearance. Paclitaxel is metabolised in the liver, with the major metabolic pathway apparently mediated by the cytochrome P450 isoenzyme CYP2C8, although CYP3A4 may play a minor role. Metabolites are excreted in the faeces via the bile, the primary metabolite being 6α-hydroxypaclitaxel.

The clearance and volume of distribution of albumin-bound paclitaxel nanoparticles are reported to be markedly greater (by about 45 and 55% respectively) than those from conventional formulations. In addition, the fraction of free (unbound) paclitaxel in the blood has been reported to be higher than with conventional paclitaxel.

References.
1. Sonnichsen DS, Relling MV. Clinical pharmacokinetics of paclitaxel. *Clin Pharmacokinet* 1994; **27:** 256–69.
2. Walle T, *et al.* Taxol metabolism and disposition in cancer patients. *Drug Metab Dispos* 1995; **23:** 506–12.
3. Sonnichsen DS, *et al.* Variability in human cytochrome P450 paclitaxel metabolism. *J Pharmacol Exp Ther* 1995; **275:** 566–75.
4. Henningsson A, *et al.* Mechanism-based pharmacokinetic model for paclitaxel. *J Clin Oncol* 2001; **19:** 4065–73.
5. Gerritsen-van Schieveen P, Royer B. Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du paclitaxel. *Therapie* 2010; **65:** 195–200.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asotax; Clitaxel; Dalys; Drifen; Erioxal; Paclikebir; Pacliteva; Paklitaxfil; Panataxel; Tarvexol; Taxocris; Taxol; Taycovit; ***Austral.***: Abraxane; Anzatax; Taxol; ***Austria***: Ebetaxel; Taxol; ***Belg.***: Paclitaxin; Paxene†; Taxol; ***Braz.***: Biopaxel; Evotaxel; Ontax; Onxel; Paclitax; Pantium; Parexel; Tarvexol; Taxilan; Taxol; Tevapacli; ***Canad.***: Abraxane; Taxol; ***Chile***: Britaxol; Oncoplaxel†; Praxel; Taxodiol; ***China***: Anzatax (安素泰); Li Pu Su (力扑素); Medaxol (紫素); Taxol (泰素); Te Su (特素); ***Cz.***: Abraxane; Anzatax; Brevitax; Egilitax; Eucol; OncoTax; Onxol†; Paclimedac; Pacline; Paxene†; Taxol; ***Denm.***: Abraxane; Cantaxel†; Paclimedac; Tacli; ***Fin.***: Paclitaxin; Taxol†; ***Fr.***: Abraxane; Paxene†; Taxol; ***Ger.***: Abraxane; Axitaxel; Bendatax; celltaxel; NeoTaxan†; Paclit; Ribotax; Taxol†; Taxomedac; ***Gr.***: Abraxane; Biotaxel; Cedol; Oncotaxen; Ovapac; Pacline; Paclit; Paclitaxin; Paclitol; Paclixel; Pataxel; Paxene; Paxital; Ribotal; Taxogen; Taxol; Taxoprol; Xenius; ***Hong Kong***: Anzatax; Ebetaxel; Intaxel†; Sindaxel; Taxol; ***Hung.***: Genexol; Intaxel†; Paxene†; Taxol†; ***India***: Abraxane; Altaxel; Betaxel; Cansure; Cantaxel; Celtax; Cytax; Dutaxel; Intaxel; Mitotax; Nanoxel; Napro-Tax; Neotaxl; Oncotaxel; Paclicad; Pacliron; Paclitax; Paclitec; Paclitrust; Petaxel; ***Indon.***: Anzatax; Ebetaxel; Paxus; Sindaxel; Taxol†; ***Irl.***: Abraxane; Cantaxel; Ebetaxel; Palat; Paxene†; Taxol†; ***Israel***: Biotax†; Ebetaxel; Medixel; Paciavenir; ***Ital.***: Anzatax; Taxol; ***Jpn***: Taxol; ***Malaysia***: Anzatax; Formoxol; Mitotax; Taxol; ***Mex.***: Aclixel†; Acoexcel; Asotax; BrisTaxol; Cryoxet; Daburex; Ifaxol†; Paclisan; Praxel; ***Neth.***: Abraxane; Paclitaxin; Paxene†; Taxol; ***Norw.***: Abraxane; ***NZ***: Abraxane; Anzatax; Taxol; ***Philipp.***: Intaxel; Nanoxel; Napro-Tax; Paclitaxin; Palitax; Paxel; Taxol†; Unitaxel; ***Pol.***: Abraxane; Poltaxel†; Sindaxel; Taxol; ***Port.***: Abraxane; Paxene†; Taxobine; Taxol; ***Rus.***: Abitaxel (Абитаксел); Intaxel (Интаксел); Mitotax (Митотакс); Paclitax (Паклитакс); Paclitera (Паклитера); Paxene (Паксен); Sindaxel (Синдаксел); Taxacad (Таксакад); Taxol (Таксол); ***S.Afr.***: Anzatax; Biolyse; Ebetaxel; Paxitas; Paxitas; Taxol; ***Singapore***: Aclipak; Anzatax; Ebetaxel; Genexol; Mitotax; Paclitaxin; Taxol; ***Spain***: Abraxane; Paxene†; Taxol; ***Swed.***: Abraxane; Paxene†; Taxol†; ***Switz.***: Taxol; ***Thai.***: Anzatax; Genetaxyl; Inoxel; Intaxel; Oncotaxel†; Paclitaxin; Paxoll; Praxel; Sindaxel; Taxol; ***Turk.***: Anzatax; Ebetaxel; Taksen; Taxol; Vitax; ***UK***: Abraxane; Paxene†; ***Ukr.***: Mitotax (Митотакс); ***USA***: Abraxane; Onxol†; Taxol†; ***Venez.***: Clitaxel; Intaxel; Paclitax.

Pharmacopoeial Preparations
USP 36: Paclitaxel Injection.

Palifosfamide *(USAN, rINN)*

IPM; Palifosfamida; Palifosfamidum; ZIO-201; Палифосфамид.

N,N′-Bis(2-chloroethyl)phosphorodiamidic acid.

$C_4H_{11}Cl_2N_2O_2P$=221.0

CAS — 31645-39-3.

UNII — 6A4U6NN813.

Profile

Palifosfamide is an active metabolite of ifosfamide (p. 806.1) that is under investigation for the treatment of soft-tissue sarcoma.

Panitumumab *(BAN, USAN, rINN)*

ABX-EGF; E7.6.3; Panitumumabum; rHuMAb-EGFr; Панитумумаб.

Immunoglobulin, anti-(human epidermal growth factor receptor) (human monoclonal ABX-EGF heavy chain), disulfide with human monoclonal ABX-EGF light chain, dimer.

CAS — 339177-26-3.
ATC — L01XC08.
ATC Vet — QL01XC08.
UNII — 6A901E312A.

Stability. Panitumumab was physically stable when stored for 14 days at 4 degrees in either PVC infusion bags at a concentration of 2.5 mg/mL in sodium chloride 0.9%, or the opened original glass vial at a concentration of 20 mg/mL.[1]

1. Ikesue H, *et al.* Stability of cetuximab and panitumumab in glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2010; **67:** 223–6.

Uses and Administration

Panitumumab is a recombinant human monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). Like cetuximab (p. 762.3), panitumumab can therefore affect cell growth regulation and angiogenesis in patients with wild-type (non-mutated) *RAS* (rat sarcoma) oncogene but it is ineffective in patients who have *RAS* gene mutations. It is used in the treatment of EGFR-expressing, *RAS* wild type, metastatic colorectal cancer (p. 706.3) either with fluoropyrimidine-containing chemotherapy as first- or second-line therapy, or as monotherapy in patients with disease progression after fluoropyrimidine-, oxaliplatin-, or irinotecan-containing regimens.

The recommended dose is 6 mg/kg given as an intravenous infusion every 14 days. Doses up to and including 1 g are given in 100 mL sodium chloride 0.9% over 60 minutes whereas doses above 1 g are diluted in 150 mL and given over 90 minutes; the final concentration of the infusion should not exceed 10 mg/mL. The infusion should be given via an infusion pump using a low-protein-binding 0.2 or 0.22 micrometre in-line filter. It may be given through a peripheral line or indwelling catheter; the line should be flushed with sodium chloride 0.9% before and after giving panitumumab. The infusion rate should be reduced by 50% in patients who have a mild to moderate infusion reaction, and stopped immediately and permanently if a severe reaction occurs.

Panitumumab should be withheld if severe dermatological toxicity develops, and permanently stopped if toxicity does not improve within 1 month. If toxicity improves after withholding no more than 2 doses of panitumumab, treatment may be restarted, either at the same dose or at a reduced dose; recommendations for dose modifications vary between countries.

References.

1. Gibson TB, *et al.* Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 29–31.
2. Saif MW, Cohenuram M. Role of panitumumab in the management of metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 118–24.
3. Saadeh CE, Lee HS. Panitumumab: a fully human monoclonal antibody with activity in metastatic colorectal cancer. *Ann Pharmacother* 2007; **41:** 606–13.
4. Giusti RM, *et al.* FDA drug approval summary: panitumumab (Vectibix™). *Oncologist* 2007; **12:** 577–83.
5. Peeters M, *et al.* Review article: panitumumab—a fully human anti-EGFR monoclonal antibody for treatment of metastatic colorectal cancer. *Aliment Pharmacol Ther* 2008; **28:** 269–81.
6. Hecht JR, *et al.* A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009; **27:** 672–80.
7. Peeters M, *et al.* Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. *Cancer* 2009; **115:** 1544–54.
8. Keating GM. Panitumumab: a review of its use in metastatic colorectal cancer. *Drugs* 2010; **70:** 1059–78.

Adverse Effects, Treatment, and Precautions

As for Cetuximab, p. 763.1, although the use of premedication for prevention of infusion reactions with panitumumab has not been standardised. The infusion rate should be reduced by 50% in patients who have mild to moderate infusion reactions and this lower rate should be maintained for subsequent infusions. If a severe reaction occurs, the drug should be stopped immediately and permanently. Fatal angioedema has been reported. In patients who developed skin reactions, infectious complications including abscesses and sepsis, also in some cases fatal, have been reported. Fatigue is very common, as is paronychia; the latter may be severe enough to require stoppage of therapy. Panitumumab should not be used in patients with interstitial pneumonitis or pulmonary fibrosis, and therapy should be permanently stopped in patients who develop interstitial lung disease, pneumonitis, or lung infiltrates; fatalities have been reported. Eye disorders are common and include conjunctivitis, ocular hyperaemia, increased lachrymation, dry eye, eye pruritus, and eyelash growth. There are rare reports of keratitis and ulcerative keratitis with panitumumab, and therapy should be interrupted or stopped if this occurs; contact lens use is a risk factor for development of keratitis and ulceration.

Wild-type *RAS* (rat sarcoma oncogene) status should be confirmed before starting treatment as panitumumab is ineffective in patients who have *RAS* mutations. Panitumumab should not be used with some chemotherapy regimens; for details of the adverse effects associated with such combinations, see Interactions, below.

Effects on the skin, hair, and nails. For reference to cutaneous adverse effects of epidermal growth factor receptor inhibitors, including panitumumab, see under Cetuximab, p. 763.2.

Hypersensitivity. Although infusion reactions and hypersensitivity have been reported with panitumumab (see above) there is evidence from a limited number of patients that there is no cross-sensitivity between panitumumab and cetuximab,[1-4] and that therefore the former can be used in those with severe reactions to the latter. Successful use of cetuximab in those with reactions to panitumumab has also been reported.[5] Despite this, fatal hypersensitivity reactions have occurred after panitumumab; one was in a patient who had previously reacted to cetuximab.[6]

1. Cartwright TH, Genther R. Successful administration of panitumumab alone after severe infusion reaction to cetuximab in a patient with metastatic colorectal cancer. *Clin Colorectal Cancer* 2008; **7:** 202–3.
2. Saif MW, *et al.* Successful re-challenge with panitumumab in patients who developed hypersensitivity reactions to cetuximab: report of three cases and review of literature. *Cancer Chemother Pharmacol* 2009; **63:** 1017–22.
3. Langerak A, *et al.* Panitumumab monotherapy in patients with metastatic colorectal cancer and cetuximab infusion reactions: a series of four case reports. *Clin Colorectal Cancer* 2009; **8:** 49–54.
4. Nielsen DL, *et al.* Six cases of treatment with panitumumab in patients with severe hypersensitivity reactions to cetuximab. *Ann Oncol* 2009; **20:** 798.
5. Saif MW, *et al.* Successful desensitization with cetuximab after an infusion reaction to panitumumab in patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2009; **65:** 107–12.
6. MHRA/CHM. Panitumumab (Vectibix): serious hypersensitivity reactions. *Drug Safety Update* 2010; **3**(10): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON081866&RevisionSelectionMethod=LatestReleased (accessed 26/05/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies panitumumab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

Panitumumab should not be used with some chemotherapy regimens. A high incidence of severe diarrhoea occurred in patients given panitumumab with fluorouracil, folinic acid, and irinotecan (the IFL regimen, see Table 1, Common Chemotherapy Regimens for Malignant Disease, p. 719). Increased toxicity and risk of death occurred when panitumumab was given with bevacizumab. A reduced survival-time was reported in patients with tumours expressing *RAS* gene mutations or with unknown *RAS* status who were given panitumumab with oxaliplatin-based chemotherapy for metastatic colorectal cancer.

Pharmacokinetics

The pharmacokinetics of panitumumab are reported to be non-linear. Steady-state concentrations were reached by the third infusion with the recommended dose regimen. The elimination half-life was about 7.5 days.

References.

1. Ma P, *et al.* Population pharmacokinetic analysis of panitumumab in patients with advanced solid tumors. *J Clin Pharmacol* 2009; **49:** 1142–56.
2. Yang B-B, *et al.* Pharmacokinetic and pharmacodynamic perspectives on the clinical drug development of panitumumab. *Clin Pharmacokinet* 2010; **49:** 729–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vectibix; ***Austria***: Vectibix; ***Belg.***: Vectibix; ***Braz.***: Vectibix; ***Canad.***: Vectibix; ***Cz.***: Vectibix; ***Denm.***: Vectibix; ***Fr.***: Vectibix; ***Ger.***: Vectibix; ***Gr.***: Vectibix; ***Hung.***: Vectibix; ***Irl.***: Vectibix; ***Israel***: Vectibix; ***Ital.***: Vectibix; ***Jpn***: Vectibix; ***Norw.***: Vectibix; ***Pol.***: Vectibix; ***Port.***: Vectibix; ***Rus.***: Vectibix (Вектибикс); ***Spain***: Vectibix; ***Swed.***: Vectibix; ***Switz.***: Vectibix; ***UK***: Vectibix; ***USA***: Vectibix.

Panobinostat *(USAN, rINN)*

LBH-589; Panobinostatum; Панобиностат.

(2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide.

$C_{21}H_{23}N_3O_2$=349.4

CAS — 404950-80-7.
UNII — 9647FM7Y3Z.

Profile

Panobinostat is a histone deacetylase inhibitor that is under investigation as an antineoplastic for the treatment of malignancies such as cutaneous T-cell lymphoma.

Patupilone *(rINN)*

EPO-906; Epothilone B; Patupilona; Patupilonum; Патупильон.

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

$C_{27}H_{41}NO_6S$=507.7

CAS — 152044-54-7.
UNII — UEC0H0URSE.

Profile

Patupilone is a metabolite isolated from the bacterium *Sorangium cellulosum*, with microtubule stabilising activity similar to that of the taxanes. It is under investigation as an antineoplastic for the treatment of malignancies such as ovarian cancer.

References.

1. Rubin EH, *et al.* Phase I dose-finding study of weekly single-agent patupilone in patients with advanced solid tumors. *J Clin Oncol* 2005; **23:** 9120–9.
2. Forster M, *et al.* A phase Ib and pharmacokinetic trial of patupilone combined with carboplatin in patients with advanced cancer. *Clin Cancer Res* 2007; **13:** 4178–84.
3. Schelman W, *et al.* A phase I trial of gemcitabine in combination with patupilone in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2008; **62:** 727–33.
4. Hussain A, *et al.* Phase II trial of weekly patupilone in patients with castration-resistant prostate cancer. *Ann Oncol* 2009; **20:** 492–7.
5. ten Bokkel Huinink WW, *et al.* Safety and efficacy of patupilone in patients with advanced ovarian, primary fallopian, or primary peritoneal cancer: a phase I, open-label, dose-escalation study. *J Clin Oncol* 2009; **27:** 3097–3103.

Pazopanib Hydrochloride

(BANM, USAN, rINNM)

GW-786034B; Hidrocloruro de pazopanib; Pazopanib, Chlorhydrate de; Pazopanibi Hydrochloridum; Пазопаниба Гидрохлорид.

5-({4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide hydrochloride.

$C_{21}H_{23}N_7O_2S,HCl$=474.0

CAS — 444731-52-6 (pazopanib); 635702-64-6 (pazopanib hydrochloride).
ATC — L01XE11.
ATC Vet — QL01XE11.
UNII — 33Y9ANM545.

Uses and Administration

Pazopanib hydrochloride is an inhibitor of multiple tyrosine kinases including those associated with the vascular epidermal growth factor receptor (VEGFR). It is used in the treatment of advanced renal cell carcinoma (p. 708.3). It may also be used in advanced soft-tissue sarcoma (p. 718.2), although efficacy in adipocytic soft-tissue sarcoma or gastrointestinal stromal tumours has not been shown.

Doses are expressed in terms of the base; 1 mg pazopanib is equivalent to about 1.08 mg pazopanib hydrochloride. The recommended oral dose of pazopanib is 800 mg once daily at least 1 hour before or 2 hours after food. Dose modifications should be in steps of 200 mg, although US licensed product information allows for an initial dose reduction to 400 mg once daily if needed in patients with renal cell carcinoma. The daily dose should not exceed 800 mg. Tablets should be swallowed whole and not crushed. If a daily dose is missed and it is less than 12 hours until the next dose, the missed dose should be omitted and the next daily dose taken as usual. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

If a potent cytochrome P450 isoenzyme CYP3A4 inhibitor must also be used, US licensed product information recommends that the pazopanib dose should be reduced to 400 mg once daily; the dose may be reduced further if adverse effects occur.

For dose adjustments in hepatic impairment or if hepatotoxicity occurs, see p. 844.1.

Pazopanib eye drops are under investigation for the treatment of age-related macular degeneration.

References.
1. Sonpavde G, *et al*. Pazopanib, a potent orally administered small-molecule multitargeted tyrosine kinase inhibitor for renal cell carcinoma. *Expert Opin Invest Drugs* 2008; **17:** 253–61.
2. Sloan B, Scheinfeld NS. Pazopanib, a VEGF receptor tyrosine kinase inhibitor for cancer therapy. *Curr Opin Investig Drugs* 2008; **9:** 1324–35.
3. Sleijfer S, *et al*. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol* 2009; **27:** 3126–32.
4. Sternberg CN, *et al*. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; **28:** 1061–8.
5. Keisner SV, Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. *Drugs* 2011; **71:** 443–54.
6. NICE. Pazopanib for the first-line treatment of advanced renal cell carcinoma. Technology Appraisal Guidance 215 (issued February 2011). Available at: http://www.nice.org.uk/nicemedia/live/13346/53185/53185.pdf (accessed 30/04/12)

Administration in hepatic impairment. Patients with mild hepatic impairment, defined as either normal bilirubin and any degree of alanine aminotransferase (ALT) elevation or an elevation of bilirubin up to 1.5 times the upper limit of normal (ULN) regardless of the ALT value, have been shown to have similar pazopanib pharmacokinetics to patients with normal hepatic function, and therefore can be given the usual initial recommended dose of pazopanib (see Uses and Administration, p. 843.3). Clearance of pazopanib is reduced by about 50% in patients with moderate hepatic impairment, and patients with pre-existing moderate impairment (defined as an elevation of bilirubin > 1.5 to 3 times the ULN, regardless of ALT values) should be given a lower initial oral dose of pazopanib 200 mg once daily. Due to poor tolerability, pazopanib is not recommended in those with pre-existing severe impairment, defined as total bilirubin > 3 times the ULN.

Hepatotoxicity may occur during pazopanib treatment at the usual recommended dose, and liver function should be monitored before and during treatment, see Adverse Effects and Precautions, below. The following adjustments are recommended, according to increases in ALT and bilirubin concentrations:

- For isolated ALT increases of between 3 and 8 times the ULN, the current pazopanib dose may be continued, with weekly monitoring of liver function until ALT returns to grade 1 or baseline.
- For isolated ALT increases of > 8 times the ULN, treatment should be withheld until ALT returns to grade 1 or baseline. If the benefit of continued treatment is thought to outweigh the risk of hepatotoxicity, pazopanib can be restarted at a dose of no more than 400 mg once daily, and liver function monitored weekly for 8 weeks. If ALT increases of > 3 times the ULN recur, pazopanib should be stopped permanently.
- For ALT increases of > 3 times the ULN with bilirubin increases of > 2 times the ULN, pazopanib should be stopped permanently. Liver function should be monitored until toxicity has resolved.

Patients with Gilbert's syndrome (mild unconjugated hyperbilirubinaemia), and an increase in ALT > 3 times the ULN, should be managed according to the above recommendations.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects with pazopanib include diarrhoea and other gastrointestinal disturbances, headache, hair colour changes, fatigue, asthenia, anorexia, dysgeusia, and abdominal pain. Hypertension has also occurred commonly and hypertensive crisis may develop; patients should be monitored and treated with antihypertensives as required. If hypertension persists despite treatment, the dose of pazopanib may be reduced; pazopanib should be stopped for severe hypertension despite treatment and dose reduction. QT prolongation and torsade de pointes have occurred, and caution is required in those with cardiac disease or a history of QT prolongation, those taking antiarrhythmics, or those taking other medicines that prolong the QT interval. ECGs and electrolytes should be monitored before starting pazopanib and periodically during treatment. Pazopanib has been associated with cardiac dysfunction such as a reduction in left ventricular ejection fraction and congestive heart failure in some patients. Arterial thrombotic adverse effects have been reported, including myocardial infarction, angina, ischaemic stroke, and transient ischaemic attacks; fatalities have occurred. Caution is required in patients with risk factors for thrombosis, and use is not recommended in those who have suffered an event in the previous 6 months. Cases of venous thrombosis and pulmonary embolism have also occurred. Haemorrhagic adverse effects including fatal haemorrhages have also been reported with pazopanib, and use is not recommended in those who have suffered haemoptysis, cerebral haemorrhage, or significant gastrointestinal haemorrhage in the previous 6 months.

Use of pazopanib is not recommended in those with pre-existing severe hepatic impairment. Hepatotoxicity, manifested as raised serum transaminases and bilirubin, has been reported during treatment and can be severe; fatalities have occurred. Liver function should be monitored before starting treatment, at least once every 4 weeks for the first 4 months, and periodically thereafter. Treatment may need to be stopped or the dose reduced for severe hepatotoxicity, see Administration in Hepatic Impairment, above.

Hypothyroidism has been reported with pazopanib and monitoring of thyroid function is recommended. Monitoring for proteinuria is also recommended, before and during treatment, and pazopanib should be stopped permanently if severe proteinuria develops.

Other common adverse effects include alopecia, chest pain, oedema, palmar-plantar erythrodysesthesia, rash, skin depigmentation, and changes in electrolyte and glucose concentrations. Pazopanib has been associated with gastrointestinal perforation and fistula, including some fatalities. Thrombocytopenia, neutropenia, leucopenia, dizziness, paraesthesia, hot flushes, epistaxis, dysphonia, erythema, pruritus, dry skin, hyperhidrosis, myalgia, muscle spasms, mucosal inflammation, and increased blood creatinine have also commonly occurred. Less commonly reported effects include bradycardia, pancreatitis, peritonitis, photosensitivity reactions, and skin exfoliation. Reversible posterior leukoencephalopathy syndrome, which presents with visual and neurological disturbances, has been reported.

Vascular endothelial growth factor receptor inhibitors such as pazopanib may impair healing, and it is recommended that treatment is stopped at least 7 days before surgery; pazopanib should be stopped permanently if wound dehiscence develops.

Interactions

Pazopanib is metabolised by cytochrome P450 isoenzymes, mainly CYP3A4, and inhibitors or inducers of CYP3A4 may affect exposure to pazopanib. Pazopanib is also a substrate for P-glycoprotein (PgP) and breast cancer resistance protein (BCRP) and use with potent PgP or BCRP inhibitors or inducers may alter exposure and distribution of pazopanib.

Use of pazopanib eye drops with ketoconazole (a potent CYP3A4 inhibitor and a PgP inhibitor) increased exposure to pazopanib. Use of lapatinib (a substrate for and weak inhibitor of CYP3A4 and PgP, and a potent inhibitor of BCRP) also substantially increased exposure to pazopanib. Combination of pazopanib with strong CYP3A4, PgP, or BCRP inhibitors should therefore be avoided. If use together cannot be avoided, US licensed product information states that a dose reduction of pazopanib can be considered, see Uses and Administration, p. 843.3. Grapefruit juice inhibits CYP3A4 activity and it should be avoided during treatment with pazopanib.

Combination of pazopanib with strong CYP3A4, PgP, or BCRP inducers is also not recommended.

In vitro, pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 and may affect exposure to substrates of these enzymes. It is also an inhibitor of glucuronidation by the enzyme UGT1A1, and inhibits the organic anion transporting polypeptide (OATP) 1B1.

Concomitant use of pazopanib with simvastatin increases the incidence of elevations of alanine aminotransferase. In such cases the dose of pazopanib should be adjusted (see Administration in Hepatic Impairment, above), and consideration given to stopping simvastatin. The effect of pazopanib use with other statins is unknown.

Pharmacokinetics

Peak plasma concentrations occur about 2 to 4 hours after an oral dose of pazopanib. Absorption and bioavailability are increased when tablets are crushed and systemic exposure is increased when given with food. Pazopanib is highly protein bound (> 99%) and is a substrate for P-glycoprotein and breast cancer resistant protein (BCRP). Metabolism occurs via cytochrome P450 isoenzymes, mainly CYP3A4, with a minor contribution from CYP1A2 and CYP2C8. Elimination is mostly via the faeces with less than 4% in the urine. Pazopanib has a mean half-life of about 31 hours after an oral dose.

References.
1. Di Gion P, *et al*. Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines and pyrroles. *Clin Pharmacokinet* 2011; **50:** 551–603.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Votrient; ***Austria***: Votrient; ***Belg.***: Votrient; ***Canad.***: Votrient; ***Cz.***: Votrient; ***Denm.***: Votrient; ***Fr.***: Votrient; ***Ger.***: Votrient; ***Gr.***: Votrient; ***Irl.***: Votrient; ***Israel***: Votrient; ***Jpn***: Votrient; ***Neth.***: Votrient; ***Norw.***: Votrient; ***NZ***: Votrient; ***Pol.***: Votrient; ***Port.***: Votrient; ***Singapore***: Votrient; ***Spain***: Votrient; ***Swed.***: Votrient; ***Switz.***: Votrient; ***Thai.***: Votrient; ***Turk.***: Votrient; ***UK***: Votrient; ***Ukr.***: Votrient (Вотриент); ***USA***: Votrient.

Pemetrexed Disodium

(BANM, USAN, rINNM)

LY-231514 (pemetrexed or pemetrexed disodium); MTA; Multi-targeted Antifolate; Pemetreksed Disodyum; Pemetrexed disódico; Pémétrexed Disodique; Pemetrexedum Dinatricum; Динатрий Пеметрексед.

Disodium *N*-[*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamate.

$C_{20}H_{19}N_5Na_2O_6$=471.4

CAS — 137281-23-3 (pemetrexed); 150399-23-8 (pemetrexed disodium); 357166-29-1 (pemetrexed disodium heptahydrate).

ATC — L01BA04.

ATC Vet — QL01BA04.

UNII — 2PKU919BA9 (pemetrexed disodium); 9T47E4OM16 (pemetrexed disodium heptahydrate).

NOTE. In practice, pemetrexed is given as the disodium heptahydrate ($C_{20}H_{19}N_5Na_2O_6,7H_2O$ = 597.5).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pemetrexed Disodium Heptahydrate). A white or almost white powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane. pH of a 5.6% solution in water is 7.5 to 8.4.

Incompatibility. Licensed product information states that pemetrexed is physically incompatible with diluents containing calcium, including Ringer's solution and lactated Ringer's solution. A study[1] found pemetrexed disodium 20 mg/mL to be physically incompatible with 24 drugs resulting in precipitation or colour change during simulated Y-site administration. These drugs include amphotericin B, some cephalosporin and cephamycin antibacterials, chlorpromazine hydrochloride, ciprofloxacin, dobutamine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, gemcitabine hydrochloride, gentamicin sulfate, irinotecan hydrochloride, metronidazole, minocycline hydrochloride, mitoxantrone hydrochloride, nalbuphine hydrochloride, ondansetron hydrochloride, prochlorperazine edisilate, tobramycin sulfate, and topotecan hydrochloride.

1. Trissel LA, *et al*. Physical compatibility of pemetrexed disodium with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; **61:** 2289–93.

Stability. Licensed product information states that pemetrexed is chemically and physically stable, once reconstituted and diluted, for 24 hours either refrigerated at 2 degrees to 8 degrees or at 25 degrees; from a microbiological point of view, solutions should be used immediately, unless prepared under controlled and validated aseptic conditions.

Pemetrexed, reconstituted in polypropylene syringes with sodium chloride 0.9% to a concentration of 25 mg/mL, was found to be both chemically and physically stable for 2 days when stored at room temperature, and for 31 days when refrigerated.[1] Although pemetrexed solutions of 2, 10, and 20 mg/mL in glucose 5% and sodium chloride 0.9% in PVC bags were chemically stable for 90 days when frozen at -20 degrees, microparticulates formed, possibly related to the PVC containers. Pemetrexed solutions should therefore not be frozen.[2]

1. Zhang Y, Trissel LA. Physical and chemical stability of pemetrexed solutions in plastic syringes. *Ann Pharmacother* 2005; **39:** 2026–8.
2. Zhang Y, Trissel LA. Physical instability of frozen pemetrexed solutions in PVC bags. *Ann Pharmacother* 2006; **40:** 1289–92.

Uses and Administration

Pemetrexed is mainly a thymidylate synthase inhibitor like raltitrexed (p. 850.3), but it also inhibits other folate-dependent enzymes involved in purine synthesis such as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. It is used as second-line monotherapy or first-line with cisplatin in the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (p. 710.2); it is also used as maintenance monotherapy in patients whose disease has not progressed after platinum-based first-line chemotherapy. Pemetrexed is also used with cisplatin in the first-line treatment of unresectable malignant pleural mesothelioma (p. 711.2).

Pemetrexed is given as the disodium heptahydrate but doses are expressed in terms of the base: pemetrexed disodium heptahydrate 1.4 g is equivalent to about 1 g of pemetrexed. A dose of pemetrexed 500 mg/m^2 is given by intravenous infusion over 10 minutes. The dose may be repeated in 21-day cycles, and should be adjusted according to toxicity. In combination therapy, cisplatin (at a dose of

75 mg/m² infused over 2 hours) is given about 30 minutes after the end of pemetrexed infusion. Doses may need to be modified according to toxicity, see Administration in Subsequent Cycles, below. For further information on use in renal impairment, see below.

Pretreatment with oral dexamethasone 4 mg twice daily for 3 days is recommended, starting the day before pemetrexed. At least 5 doses of oral folic acid (350 micrograms to 1 mg) should be taken during the 7 days before the first dose of pemetrexed; dosing should continue throughout pemetrexed therapy, and for 21 days after the last pemetrexed dose. Patients should also receive an intramuscular injection of vitamin B_{12} 1 mg in the week before the first pemetrexed dose, and once every 3 cycles thereafter; subsequent injections may be given on the same day as pemetrexed.

Pemetrexed is under investigation as an antifolate antimetabolite in the treatment of colon, pancreatic, breast, and head and neck cancer.

References.

1. Hochster HS. The role of pemetrexed in the treatment of gastrointestinal malignancy. *Clin Colorectal Cancer* 2004; **4:** 190–5.
2. Rollins KD, Lindley C. Pemetrexed: a multitargeted antifolate. *Clin Ther* 2005; **27:** 1343–82.
3. Martin M. Clinical experience with pemetrexed in breast cancer. *Semin Oncol* 2006; **33** (suppl 2): S15–S18.
4. Dundar Y, *et al*. Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. *Health Technol Assess* 2007; **11:** 1–90.
5. Green J, *et al*. Pemetrexed disodium in combination with cisplatin versus other cytotoxic agents or supportive care for the treatment of malignant pleural mesothelioma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/08/07).
6. Longo-Sorbello GS, *et al*. Role of pemetrexed in non-small cell lung cancer. *Cancer Invest* 2007; **25:** 59–66.
7. Meriggi F, *et al*. The potential role of pemetrexed in gastrointestinal cancer. *Chemotherapy* 2008; **54:** 1–8.
8. Baldwin CM, Perry CM. Pemetrexed: a review of its use in the management of advanced non-squamous non-small cell lung cancer. *Drugs* 2009; **69:** 2279–2302.
9. Tomao F, *et al*. Emerging role of pemetrexed in ovarian cancer. *Expert Rev Anticancer Ther* 2009; **9:** 1727–35.

Administration in the elderly. A retrospective analysis found pemetrexed to be effective as a second-line therapy in non-small cell lung cancer patients aged 70 years or older, with a more favourable toxicity profile than docetaxel.[1]

UK licensed product information states that there are no data to suggest that patients aged 65 years or older are at increased risk of adverse effects compared with younger patients; no dose reductions are recommended on the basis of age alone.

1. Weiss GJ, *et al*. Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 4405–11.

Administration in renal impairment. A pharmacokinetic study[1] found that pemetrexed clearance decreased with declining renal function. Although systemic exposure increased in these patients, this was not associated with an increase in drug-related dose-limiting toxicities for patients with a GFR of 40 mL/minute or more and receiving vitamin supplementation (folic acid and vitamin B_{12} supplementation appears to reduce toxicity without altering pemetrexed pharmacokinetics). Patients with a GFR of 80 mL/minute or more tolerated a dose of pemetrexed 600 mg/m², given intravenously every 3 weeks, whereas patients with a GFR of 40 to 79 mL/minute tolerated 500 mg/m² every 3 weeks. One patient with a GFR of 19 mL/minute died as a result of treatment-related toxicity and accrual into this group was stopped. As a result, no data were available for patients with a GFR below 40 mL/minute.

Licensed product information states that no dose adjustment is necessary in patients with a creatinine clearance (CC) of 45 mL/minute or more. Use in patients with a CC of less than 45 mL/minute is not recommended due to lack of data. Caution is advised when giving pemetrexed with NSAIDs in patients whose CC is less than 80 mL/minute (see Interactions, below).

1. Mita AC, *et al*. Phase I and pharmacokinetic study of pemetrexed administered every 3 weeks to advanced cancer patients with normal and impaired renal function. *J Clin Oncol* 2006; **24:** 552–62.

Administration in subsequent cycles. Complete blood counts should be performed in all patients given pemetrexed. Patients should not begin a new cycle unless:

- the absolute neutrophil count (ANC) is ⩾ 1500 cells/mm³
- the platelet count is ⩾ 100 000 cells/mm³
- creatinine clearance is ⩾ 45 mL/min (see also Administration in Renal Impairment, above)

Dose adjustments at the start of a subsequent cycle should be based on nadir haematological counts or maximum non-haematological toxicity from the preceding cycle of therapy. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, patients are treated according to the following recommendations, which are suitable for pemetrexed monotherapy or use with cisplatin. For **haematological** toxicities:

- nadir ANC < 500 cells/mm³ and nadir platelets ⩾ 50 000 cells/mm³; 75% of previous dose (pemetrexed and cisplatin)
- nadir platelets < 50 000 cells/mm³ without bleeding, regardless of nadir ANC; 75% of previous dose (pemetrexed and cisplatin)
- nadir platelets < 50 000 cells/mm³ with bleeding, regardless of nadir ANC; 50% of previous dose (pemetrexed and cisplatin)

If **non-haematological** toxicities (excluding neurotoxicity) are severe, treatment should be withheld until resolution, and treatment resumed according to the following recommendations:

- any grade 3 or 4 toxicities except mucositis; 75% of previous dose (pemetrexed and cisplatin)
- any diarrhoea requiring hospitalisation, or grade 3 or 4 diarrhoea; 75% of previous dose (pemetrexed and cisplatin)
- grade 3 or 4 mucositis; 50% of previous pemetrexed dose and 100% of previous cisplatin dose

Patients should stop therapy if **neurotoxicity** is severe (grade 3 or 4); otherwise doses are adjusted as follows:

- grade 0 to 1; 100% of previous dose (pemetrexed and cisplatin)
- grade 2; 100% of previous pemetrexed dose and 50% of previous cisplatin dose

Pemetrexed should be stopped if patients have any severe haematological or non-haematological toxicities after 2 dose reductions.

Adverse Effects, Treatment, and Precautions

As for Raltitrexed, p. 851.1. Neutropenia and febrile neutropenia are common and myelosuppression may be dose-limiting.

Pemetrexed may also cause fatigue, stomatitis, pharyngitis, oesophagitis, chest pain, and neuropathy. Rare cases of hepatitis, colitis, and interstitial pneumonitis have occurred; fatalities have been reported. Bullous skin conditions have been reported, including Stevens-Johnson syndrome and toxic epidermal necrolysis, which in some cases were fatal. Serious renal events, including acute renal failure, have been reported with pemetrexed when it was used either alone or with other cytotoxic drugs; most patients had underlying risk factors such as dehydration, hypertension, or diabetes. Cardiovascular events, including myocardial infarction and cerebrovascular events, have occurred rarely, usually when pemetrexed was used with other cytotoxic drugs and in patients with cardiovascular risk factors. Arrhythmias have been reported. Cases of radiation pneumonitis or oesophagitis, and radiation recall have been reported in patients treated with radiotherapy. Hypersensitivity reactions may occur. Cases of peripheral ischaemia leading to extremity necrosis have been reported. The effect of pleural effusions or ascites on pemetrexed is unknown; in those patients with significant third-space fluid, draining of any effusions before treatment with pemetrexed should be considered.

Complete blood cell counts should be monitored, and folate and vitamin B_{12} are given as prophylaxis against haematological and gastrointestinal toxicity during pemetrexed therapy. Pretreatment with a corticosteroid, such as oral dexamethasone, reduces the incidence and severity of skin reactions. (For dosing details, see Uses and Administration, p. 844.3.) Gastrointestinal toxicity may be severe, leading to dehydration, and antiemetics and appropriate hydration should be given before and after treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pemetrexed as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

High doses of NSAIDs and aspirin may decrease pemetrexed elimination. In patients with mild to moderate renal impairment (creatinine clearance 45 to 79 mL/minute) high doses of NSAIDs and aspirin should be avoided from 2 days before until 2 days after pemetrexed use, and NSAIDs that have longer half-lives, such as piroxicam, should be avoided from 5 days before until 2 days after pemetrexed.

Analgesics. Enteric-coated *aspirin* 325 mg given orally every 6 hours for a total of 9 doses before pemetrexed, did not affect the pharmacokinetic profile of pemetrexed in an interaction study; the authors considered no dose adjustment necessary when moderate doses of aspirin were given with pemetrexed. However, this result could not be extrapolated to high-dose aspirin regimens, as the interaction might be dependent on salicylate concentrations. In contrast, oral *ibuprofen* 400 mg every 6 hours for a total of 9 doses before pemetrexed significantly reduced systemic pemetrexed clearance. Despite an increase in pemetrexed exposure, no increase in toxicity was seen. Dose adjustments were not considered necessary in patients with normal renal function (defined as creatinine clearance of 80 mL/minute or greater). However, in patients with pre-existing reduced pemetrexed clearance due to renal impairment, giving ibuprofen may result in further increases in pemetrexed exposure; the authors advised caution when using these 2 drugs together in patients with a creatinine clearance of less than 80 mL/minute.[1] For licensed product information regarding the use of aspirin and NSAIDs with pemetrexed, see above.

1. Sweeney CJ, *et al*. Two drug interaction studies evaluating the pharmacokinetics and toxicity of pemetrexed when coadministered with aspirin or ibuprofen in patients with advanced cancer. *Clin Cancer Res* 2006; **12:** 536–42.

Pharmacokinetics

Pemetrexed has a plasma elimination half-life of 3.5 hours in patients with normal renal function. *In-vitro* data indicate that pemetrexed is about 81% bound to plasma proteins. It undergoes limited hepatic metabolism, and about 70 to 90% of a dose is eliminated unchanged in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alimta; Enzastar; Trexam; ***Austral.***: Alimta; ***Austria***: Alimta; ***Belg.***: Alimta; ***Braz.***: Alimta; ***Canad.***: Alimta; ***Chile***: Alimta; ***China***: Alimta (力比泰); Jepale (捷佰立); Pu Lai Le (普来乐); Yiluoze (怡罗泽); ***Cz.***: Alimta; ***Denm.***: Alimta; ***Fin.***: Alimta; ***Fr.***: Alimta; ***Ger.***: Alimta; ***Gr.***: Alimta; ***Hong Kong***: Alimta; ***Hung.***: Alimta; ***India***: Alimta; Pamifect; ***Irl.***: Alimta; ***Israel***: Alimta; ***Ital.***: Alimta; ***Malaysia***: Alimta; ***Mex.***: Alimta; ***Neth.***: Alimta; ***Norw.***: Alimta; ***NZ***: Alimta; ***Philipp.***: Alimta; ***Pol.***: Alimta; ***Port.***: Alimta; ***Rus.***: Alimta (Алимта); ***S.Afr.***: Alimta; ***Singapore***: Alimta; ***Spain***: Alimta; ***Swed.***: Alimta; ***Switz.***: Alimta; ***Thai.***: Alimta; ***Turk.***: Alimta; Pemtrex; ***UK***: Alimta; ***Ukr.***: Alimta (Алимта); ***USA***: Alimta.

Pentostatin *(BAN, USAN, rINN)*

CI-825; Co-vidarabine; Covidarabine; Deoxycoformycin; NSC-218321; PD-81565; Pentostatina; Pentostatine; Pentostatinum; 2′-Deoxycoformycin; YK-176; Пентостатин.

(*R*)-3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol; 1,2-Dideoxy-1-[(*R*)-3,6,7,8-tetrahydro-8-hydroxyimidazo[4,5-*d*][1,3]diazepin-3-yl]-D-*erythro*-pentofuranose.

$C_{11}H_{16}N_4O_4$=268.3

CAS — 53910-25-1.

ATC — L01XX08.

ATC Vet — QL01XX08.

UNII — 395575MZO7.

Uses and Administration

Pentostatin is a potent inhibitor of the enzyme adenosine deaminase and probably exerts its cytotoxic actions through the interruption of normal purine metabolism and DNA synthesis. Lymphocytes are particularly sensitive to its actions.

Pentostatin is used as a single agent in the treatment of hairy-cell leukaemia (p. 694.3), in usual doses of 4 mg/m² every other week. The dose is given as an intravenous bolus injection, or as an infusion over 20 to 30 minutes. Hydration with 500 mL to 1 litre of glucose 5% in sodium chloride 0.18 or 0.9%, or equivalent, is recommended beforehand; a further 500 mL of the hydration solution should be infused once the drug has been given.

Pentostatin has been tried in cutaneous T-cell lymphomas (see Mycosis Fungoides, p. 698.3). It is also under investigation in some other lymphoid malignancies, including chronic lymphocytic leukaemia (p. 693.3), and for the management of chronic graft-versus-host disease following haematopoietic stem cell transplantation (p. 1937.1).

References.

1. Grever MR, *et al*. Pentostatin in the treatment of hairy-cell leukemia. *Best Pract Res Clin Haematol* 2003; **16:** 91–9.
2. Drapkin R, *et al*. Results of a phase II multicenter trial of pentostatin and rituximab in patients with low grade B-cell non-Hodgkin's lymphoma: an effective and minimally toxic regimen. *Clin Lymphoma* 2003; **4:** 169–75.
3. Tsimberidou AM, *et al*. Phase II study of pentostatin in advanced T-cell lymphoid malignancies: update of an MD Anderson Cancer Center series. *Cancer* 2004; **100:** 342–9.

4. Tsiara SN, *et al.* Treatment of resistant/relapsing chronic lymphocytic leukemia with a combination regimen containing deoxycoformycin and rituximab. *Acta Haematol (Basel)* 2004; **111:** 185–8.
5. Dillman RO. Pentostatin (Nipent™) in the treatment of chronic lymphocyte leukemia and hairy cell leukemia. *Expert Rev Anticancer Ther* 2004; **4:** 27–36.
6. Higman M, *et al.* Pentostatin—pharmacology, immunology, and clinical effects in graft-versus-host disease. *Expert Opin Pharmacother* 2004; **5:** 2605–13.
7. Ho AD, Hensel M. Pentostatin and purine analogs for indolent lymphoid malignancies. *Future Oncol* 2006; **2:** 169–83.
8. Grever MR. Pentostatin: impact on outcome in hairy cell leukemia. *Hematol Oncol Clin North Am* 2006; **20:** 1099–1108.
9. Sauter C, *et al.* Pentostatin in chronic lymphocytic leukemia. *Expert Opin Drug Metab Toxicol* 2008; **4:** 1217–22.
10. Lamanna N, Kay NE. Pentostatin treatment combinations in chronic lymphocytic leukemia. *Clin Adv Hematol Oncol* 2009; **7:** 386–92.

Adverse Effects and Precautions

The most common adverse effects in patients given pentostatin include myelosuppression (and in particular suppression of the CD4+ lymphocyte subset), headache, abdominal pain, fever and chills, gastrointestinal disturbances (notably diarrhoea and nausea and vomiting), hypersensitivity reactions, and hepatotoxicity. Central neurotoxicity may manifest as tiredness, anxiety, depression, sleep disturbances, and paraesthesias: treatment should be withheld or stopped in such patients. Impaired renal function and pulmonary toxicity (cough, dyspnoea, and pneumonia) may occur. Severe toxicity in early studies, affecting mainly the CNS, kidneys, liver, and lungs, was associated with the use of doses higher than those currently recommended and produced some fatalities.

Other adverse effects reported with pentostatin include dry skin and rashes (sometimes severe and worsening with continued treatment), pruritus, conjunctivitis, alopecia, arthralgia and myalgia, peripheral oedema, thrombophlebitis, and cardiovascular disorders including arrhythmias, angina pectoris, and heart failure.

Pentostatin should not be given to patients with impaired renal function, or in active infection. It is teratogenic in *animals* and potentially genotoxic: it is therefore contra-indicated in pregnancy and men given pentostatin should not father children for 6 months after therapy.

Interactions

Pentostatin should not be given with fludarabine, as the combination may increase pulmonary toxicity. A similar increase in toxicity is expected when pentostatin is used with vidarabine.

Use of pentostatin with carmustine, etoposide and high-dose cyclophosphamide, has produced acute pulmonary oedema and hypotension, leading to death. Pentostatin should therefore not be given with high-dose cyclophosphamide.

Allopurinol. Fatal acute necrotising arteritis developed in a patient given pentostatin and allopurinol.[1] Although the hypersensitivity vasculitis may have been due to allopurinol alone there is circumstantial evidence to suggest that pentostatin may predispose patients to drug hypersensitivity and it may be wise to avoid this combination, and to observe pentostatin-treated patients closely for allergic manifestations.

1. Steinmetz JC, *et al.* Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; **86:** 498–9.

Pharmacokinetics

After intravenous injection, pentostatin has an elimination half-life of about 6 hours. About 90% of a dose is excreted in the urine as unchanged drug and metabolites. Pentostatin crosses the blood-brain barrier and can be measured in the CSF.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Nipent; ***Fr.***: Nipent; ***Ger.***: Nipent; ***Gr.***: Nipent; ***Irl.***: Nipent; ***Ital.***: Nipent; ***Neth.***: Nipent; ***Port.***: Nipent; ***Spain***: Nipent; ***UK***: Nipent; ***USA***: Nipent.

Peplomycin Sulfate *(USAN, rINNM)*

NK-631; Pepleomycin Sulphate; Peplomicina, sulfato de; Peplomycin Sulphate; Péplomycine, Sulfate de; Peplomycini Sulfas; Sulfato de peplomicina; Пепломицина Сульфат.

N^1-{3-[(*S*)-(α-Methylbenzyl)amino]propyl}bleomycinamide sulphate.

$C_{61}H_{88}N_{18}O_{21}S_2.H_2SO_4$=1571.7

CAS — 68247-85-8 (peplomycin); 70384-29-1 (peplomycin sulfate).

UNII — 6A668951HW.

Pharmacopoeias. In *Jpn*.

Profile

Peplomycin is an antineoplastic derived from bleomycin (p. 749.3) and with similar properties. It has been given as the sulfate in the treatment of a variety of malignant neoplasms, including lymphomas and tumours of the head and neck, breast, cervix, lung, oesophagus, prostate, and skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Pepleo.

Peretinoin *(rINN)*

Ácido poliprénico; Acyclic Retinoid; E-5166; NIK-333; Peretinoína; Pérétinoïne; Peretinoinum; Polyprenic Acid; Polyprenoic Acid; Полипреноевая Кислота; Перетиноин.

(*all-E*)-3,7,11,15-Tetramethyl-2,4,6,10,14-hexadecapentaenoic acid.

$C_{20}H_{30}O_2$=302.5

CAS — 81485-25-8.

UNII — 11ALM7A4RV.

Profile

Peretinoin is a retinoid that has been tried in psoriasis and keratoderma and is being studied in the treatment of liver cancers.

References.
1. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. *N Engl J Med* 1996; **334:** 1561–7.
2. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N Engl J Med* 1999; **340:** 1046–7.
3. Takai K, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma: updated analysis of the long-term follow-up data. *Intervirology* 2005; **48:** 39–45.

Perifosine *(rINN)*

D-21266; KRX-0401; Perifosina; Périfosine; Perifosinum; Перифозин.

4-Hydroxy-1,1-dimethylpiperidinium hydroxide octadecyl hydrogen phosphate inner salt.

$C_{25}H_{52}NO_4P$=461.7

CAS — 157716-52-4.

UNII — 2GWV496552.

Profile

Perifosine is an oral alkylphospholipid compound that is structurally related to miltefosine (p. 829.3); it has similarities to the phospholipid components of the cell membrane and exerts its antineoplastic action by disruption of cell-membrane functions. It is under investigation for the treatment of multiple myeloma and advanced metastatic colorectal cancer.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.
1. Ghobrial IM, *et al.* Clinical and translational studies of a phase II trial of the novel oral Akt inhibitor perifosine in relapsed or relapsed/refractory Waldenstrom's macroglobulinemia. *Clin Cancer Res* 2010; **16:** 1033–41.
2. Unger C, *et al.* First-time-in-man and pharmacokinetic study of weekly oral perifosine in patients with solid tumours. *Eur J Cancer* 2010; **46:** 920–5.

Pertuzumab *(BAN, USAN, rINN)*

2C4; Pertuzumabum; R-1273; rhuMAb-2C4; Пертузумаб.

Immunoglobulin G1, anti-(human v (receptor)) (human-mouse monoclonal 2C4 heavy chain), disulfide with human-mouse monoclonal 2C4 κ-chain, dimer.

CAS — 380610-27-5.

ATC — L01XC13.

ATC Vet — QL01XC13.

UNII — K16AIQ8CTM.

NOTE. The name Omnitarg has been used as a trade mark for pertuzumab.

Uses and Administration

Pertuzumab is a humanised monoclonal antibody and a human epidermal growth factor receptor (HER) dimerisation inhibitor. It inhibits HER2 heterodimerisation with other HER family receptors, thereby preventing the activation of HER signalling pathways. Pertuzumab is used with trastuzumab and docetaxel in the treatment of HER2-positive metastatic breast cancer (p. 702.1), in patients who have not been given anti-HER2 therapy or chemotherapy.

The initial dose of pertuzumab is 840 mg given by intravenous infusion over 60 minutes. This is followed by a dose of 420 mg given by infusion over 30 to 60 minutes once every 3 weeks. If a dose is delayed or missed then treatment should be resumed as soon as possible, but if the time between doses is 6 weeks or more then pertuzumab should be restarted at 840 mg followed by 420 mg once every 3 weeks.

Pertuzumab should be withheld or stopped if trastuzumab is withheld or stopped. Pertuzumab and trastuzumab should be withheld for at least 3 weeks if there is a drop in left ventricular ejection fraction (LVEF) to less than 40%, or if LVEF is 40 to 45% with a 10% or greater absolute decrease below pretreatment values. Pertuzumab may be restarted if the LVEF has recovered to more than 45%, or to 40 to 45% associated with less than a 10% absolute decrease below pretreatment values. If the LVEF has not improved, or has declined further, after about 3 weeks then stopping pertuzumab and trastuzumab permanently should be strongly considered.

Pertuzumab is under investigation in the treatment of HER2-positive gastric cancer.

References.
1. Baselga J, *et al.* CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; **366:** 109–19.
2. Keating GM. Pertuzumab: in the first-line treatment of HER2-positive metastatic breast cancer. *Drugs* 2012; **72:** 353–60.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Hypersensitivity and infusion reactions have been reported in patients given pertuzumab. Patients should be monitored for 60 minutes after the first dose, and for 30 minutes after subsequent doses. Other adverse effects reported in patients given pertuzumab (with trastuzumab and docetaxel) include diarrhoea, nausea, neutropenia, fatigue, rash, and peripheral neuropathy. Decreases in left ventricular ejection fraction (LVEF) have occurred in patients who have been given drugs that block HER2 activity, including pertuzumab; LVEF should be assessed before starting pertuzumab and regularly during treatment (see also Uses and Administration, above).

Licensed product information warns against the use of pertuzumab during pregnancy, based on reports of oligohydramnios, delayed fetal kidney development, and embryo-fetal death in *animal* studies.

References.
1. Drucker AM, *et al.* Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. *Breast Cancer Res Treat* 2012; **135:** 347–54.

Effects on the heart. Pertuzumab is anticipated to have adverse cardiac effects because of its inhibition of human epidermal growth factor receptor 2 dimerisation, which has a role in cardiac myocyte homoeostasis. Cardiac safety data from 598 patients in phase 2 studies of pertuzumab have been pooled and analysed.[1] Pertuzumab had been given as monotherapy and in combination regimens with non-anthracycline cytotoxics, trastuzumab, or erlotinib, for various malignancies including metastatic breast cancer. In 331 patients given monotherapy there were 23 cases (6.9%) of asymptomatic left ventricular systolic dysfunction and 1 case (1.4%) of symptomatic heart failure. The incidence of cardiac dysfunction was not significantly different when pertuzumab was given in combination therapy. The median time to these effects was about cycle 4.

However, these studies included patients with a lifetime exposure to anthracyclines up to doxorubicin 360 mg/m^2 or equivalent and excluded those with cardiac comorbidities, which probably contributed to the low rates of cardiac events. In addition, where patients had a history of anthracycline treatment, it had generally been given several months or years before pertuzumab therapy. The effects of regimens containing pertuzumab and anthracyclines is under investigation.

See Effects on the Heart under Trastuzumab (p. 876.3) and Doxorubicin (p. 784.1, for anthracyclines) for further information about the cardiotoxicity of these other drugs.

1. Lenihan D, *et al.* Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol* 2012; **23:** 791–800.

Pharmacokinetics

Pertuzumab has a half-life of about 18 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Perjeta; ***Jpn***: Perjeta; ***Switz.***: Perjeta; ***UK***: Perjeta; ***USA***: Perjeta.

Picoplatin *(BAN, USAN, rINN)*

AMD-473; NX-473; Picoplatine; Picoplatino; Picoplatinum; ZD-0473; Пикоплатин.

cis-Amminedichloro(2-methylpyridine)platinum(II).

$C_6H_{10}Cl_2N_2Pt$=376.1

CAS — 181630-15-9.

UNII — B5TAN0L720.

Profile

Picoplatin is a platinum derivative that is under investigation as an intravenous antineoplastic for the treatment of small-cell lung cancer, and other solid tumours such as colorectal, ovarian, and prostate cancer. An oral dosage form is also being developed.

References.

1. Kelland L. Broadening the clinical use of platinum drug-based chemotherapy with new analogues: satraplatin and picoplatin. *Expert Opin Invest Drugs* 2007; **16:** 1009–21.
2. Eckardt JR, *et al.* Phase II study of picoplatin as second-line therapy for patients with small-cell lung cancer. *J Clin Oncol* 2009; **27:** 2046–51.

Pipobroman *(USAN, pINN)*

A-8103; NSC-25154; Pipobromán; Pipobromanum; Пипоброман.

1,4-Bis(3-bromopropionyl)piperazine.

$C_{10}H_{16}Br_2N_2O_2$=356.1

CAS — 54-91-1.

ATC — L01AX02.

ATC Vet — QL01AX02.

UNII — 6Q99RDT97R.

Profile

Pipobroman is an antineoplastic which appears to act by alkylation. It may be used in the treatment of polycythaemia vera (p. 695.2), in patients requiring myelosuppressive therapy, and in refractory chronic myeloid leukaemia (p. 694.2).

The usual initial dose for polycythaemia vera is 1 mg/kg daily, given orally, and increased to 3 mg/kg, if necessary, according to response. Maintenance dosage is 100 to 200 micrograms/kg daily. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The main adverse effect is moderate bone-marrow depression, which may develop 4 weeks or more from starting treatment. Anaemia may be marked at higher doses and is usually accompanied by leucopenia. Thrombocytopenia and haemolysis have occurred. In the initial stages of treatment, white cell and platelet counts should be determined on alternate days and complete blood counts once or twice weekly. Dosage should be stopped if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p. 730.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vercyte; ***Gr.***: Vercite; ***Ital.***: Vercite.

Pirarubicin *(rINN)*

Pirarubicina; Pirarubicine; Pirarubicinum; 1609-RB; Tepirubicin; THP-ADM; THP-doxorubicin; Пирарубицин.

(8*S*,10*S*)-10-{[3-Amino-2,3,6-trideoxy-4-*O*-(2*R*-tetrahydro-2*H*-pyran-2-yl)-α-L-*lyxo*-hexopyranosyl]oxy}-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione.

$C_{32}H_{37}NO_{12}$=627.6

CAS — 72496-41-4.

ATC — L01DB08.

ATC Vet — QL01DB08.

UNII — D58G680W0G.

Pharmacopoeias. In *Jpn*.

Profile

Pirarubicin is an antineoplastic anthracycline antibiotic that is a structural analogue of doxorubicin (p. 782.3), and has similar properties. It is used in the management of breast cancer and has also been tried in other solid neoplasms, acute leukaemias and lymphomas.

Pirarubicin is formulated as the hydrochloride but doses are in terms of the base. A usual dose of 25 to 50 mg/m² every 3 to 4 weeks has been recommended in breast cancer, but other dosage regimens have been used. Doses may be given by intravenous injection over 5 to 10 minutes into a rapidly-flowing intravenous infusion of glucose 5%. Patients should undergo regular blood counts and monitoring of cardiac function: at cumulative doses above 600 mg/m² ventricular ejection fraction should be checked before each course. Pirarubicin has also been given by the intra-arterial and intravesical routes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Theprubicine†; ***Jpn***: Therarubicin.

Pixantrone *(BAN, USAN, rINN)*

BBR-2778; Pixantrona; Pixantronum; Пиксантрон.

6,9-Bis[(2-aminoethyl)amino]benzo[*g*]isoquinoline-5,10-dione.

$C_{17}H_{19}N_5O_2$=325.4

CAS — 144510-96-3.

ATC — L01DB11.

ATC Vet — QL01DB11.

UNII — F5SXN2KNMR.

Pixantrone Maleate *(BANM, rINNM)*

BBR-2778 (pixantrone or pixantrone maleate); Maleato de pixantrona; Pixantrone Dimaleate (USAN); Pixantrone, Maléate de; Pixantroni Maleas; Пиксантрона Малеат.

6,9-bis[(2-Aminoethyl)amino]benzo[*g*]isoquinoline-5,10-dione (2*Z*)-but-2-endioate (1:2).

$C_{17}H_{19}N_5O_2.2C_4H_4O_4$=557.5

CAS — 144675-97-8.

ATC — L01DB11.

ATC Vet — QL01DB11.

UNII — P0R64C4CR9.

Profile

Pixantrone is an aza-anthracenedione anthracycline derivative that is structurally similar to mitoxantrone (p. 833.1). However, it lacks the 5,8-dihydroxy substitution groups thought to be responsible for mitoxantrone-induced cardiotoxicity. It is a weak inhibitor of topoisomerase II that directly alkylates DNA to form stable DNA adducts and cross-strand breaks.

Pixantrone is given as monotherapy for the treatment of patients with relapsed or refractory aggressive non-Hodgkin's B-cell lymphomas (p. 696.3).

Pixantrone is given as the dimaleate, but doses are expressed in terms of the base; 1.7 mg of the dimaleate is equivalent to about 1 mg of pixantrone. It is given in a dose equivalent to pixantrone 50 mg/m² on days 1, 8, and 15 of each 28-day cycle, for up to 6 cycles. It is diluted to 250 mL in sodium chloride 0.9% and given by slow intravenous infusion over at least 60 minutes.

Doses may need to be delayed or adjusted according to the degree of toxicity produced.

References.

1. Engert A, *et al.* EXTEND PIX301: a phase III randomized trial of pixantrone versus other chemotherapeutic agents as third-line monotherapy in patients with relapsed, aggressive non-Hodgkin's lymphoma. *Clin Lymphoma Myeloma* 2006; **7:** 152–4.
2. El-Helw LM, Hancock BW. Pixantrone: a novel aza-anthracenedione in the treatment of non-Hodgkin's lymphomas. *Expert Opin Invest Drugs* 2007; **16:** 1683–91.
3. El-Helw LM, Hancock BW. Pixantrone: a promising drug in the treatment of non-Hodgkin lymphomas. *Future Oncol* 2009; **5:** 445–53.
4. Mukherji D, Pettengell R. Pixantrone maleate for non-Hodgkin's lymphoma. *Drugs Today* 2009; **45:** 797–805.
5. Cabanillas F. Pixantrone: a new agent for relapsed aggressive lymphomas. *Lancet Oncol* 2012; **13:** 654–6.
6. Pettengell R, *et al.* Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol* 2012; **13:** 696–706. Correction. *ibid.*; e285.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Pixuvri; ***Neth.***: Pixuvri; ***Norw.***: Pixuvri; ***Spain***: Pixuvri; ***UK***: Pixuvri.

Plevitrexed *(BAN, rINN)*

BGC-9331; plevitredex; Plévitrexed; Plevitrexedum; ZD-9331; Плевитрексед.

(2*S*)-2-[(4-{[[2,7-Dimethyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl](prop-2-ynyl)amino}-2-fluorobenzoyl)amino]-4-(1*H*-tetrazol-5-yl)butanoic acid.

$C_{26}H_{25}FN_8O_4$=532.5

CAS — 153537-73-6.

UNII — L9P2881C3H.

Profile

Plevitrexed is a thymidylate synthase inhibitor that is under investigation for the treatment of stomach and ovarian cancers.

Plitidepsin *(BAN, rINN)*

Aplidine; Dehydrodidemnin B; Plitidepsina; Plitidepsine; Plitidepsinum; Плитиденсин.

3,6-Anhydro(*N*-{(2*S*,4*S*)-4-[{3*S*,4*R*,5*S*)-3-hydroxy-4-[[*N*-(2-oxopropanoyl)-L-prolyl-*N*-methyl-D-leucyl-L-threonyl]amino}-5-methylheptanoyloxy}-2,5-dimethyl-3-oxohexanoyl}-L-leucyl-L-prolyl-*N*,*O*-dimethyl-L-tyrosine).

$C_{57}H_{87}N_7O_{15}$=1110.4

CAS — 137219-37-5.

UNII — Y76ID234HW.

NOTE. The name Aplidin has been used as a trade mark for plitidepsin.

Profile

Plitidepsin is an antineoplastic isolated from the marine tunicate *Aplidium albicans*. It is under investigation in the treatment of acute lymphoblastic leukaemia, multiple myeloma, and solid tumours.

References.

1. Muñoz-Alonso MJ, *et al.* The mechanism of action of plitidepsin. *Curr Opin Investig Drugs* 2009; **10:** 536–42.
2. Eisen T, *et al.* Phase II study of weekly plitidepsin as second-line therapy for small cell lung cancer. *Lung Cancer* 2009; **64:** 60–5.
3. Schöffski P, *et al.* Phase II randomized study of Plitidepsin (Aplidin), alone or in association with L-carnitine, in patients with unresectable advanced renal cell carcinoma. *Mar Drugs* 2009; **7:** 57–70.
4. Eisen T, *et al.* Phase II study of biweekly plitidepsin as second-line therapy in patients with advanced malignant melanoma. *Melanoma Res* 2009; **19:** 185–92.
5. Dumez H, *et al.* Phase II study of biweekly plitidepsin as second-line therapy for advanced or metastatic transitional cell carcinoma of the urothelium. *Mar Drugs* 2009; **7:** 451–63.
6. Baudin E, *et al.* Phase II study of plitidepsin 3-hour infusion every 2 weeks in patients with unresectable advanced medullary thyroid carcinoma. *Am J Clin Oncol* 2010; **33:** 83–8.
7. Le Tourneau C, *et al.* Reports of clinical benefit of plitidepsin (Aplidine), a new marine-derived anticancer agent, in patients with advanced medullary thyroid carcinoma. *Am J Clin Oncol* 2010; **33:** 132–6.
8. Mateos MV, *et al.* Phase II clinical and pharmacokinetic study of plitidepsin 3-hour infusion every two weeks alone or with dexamethasone in relapsed and refractory multiple myeloma. *Clin Cancer Res* 2010; **16:** 3260–9.

Pomalidomide *(USAN, rINN)*

CC-4047; IMiD-3; Pomalidomid; Pomalidomida; Pomalidomidum; Помалидомид.

4-Amino-2-[(3*RS*)-2,6-dioxopiperidin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione.

$C_{13}H_{11}N_3O_4$=273.2

CAS — 19171-19-8.

UNII — D2UX06XLB5.

NOTE. IMiD-3 has also been used as a synonym for lenalidomide (p. 816.1).

Uses and Administration

Pomalidomide is a derivative of thalidomide (p. 867.3) that has immunomodulatory and antiangiogenic properties. It is used with dexamethasone or as monotherapy for the treatment of multiple myeloma (p. 699.2) in patients who have been treated with at least 2 other therapies including lenalidomide and bortezomib, and whose disease has progressed within 60 days of completing the last therapy. A usual oral dose of pomalidomide is 4 mg once daily taken on an empty stomach, for 21 days of a 28-day cycle. The dose may need to be modified if toxicities occur, see Administration in Subsequent Cycles, p. 848.1. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Pomalidomide is also under investigation in myelofibrosis.

References.

1. Lacy MQ, *et al.* Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia* 2010; **24:** 1934–9.
2. Begna KH, *et al.* A phase-2 trial of low-dose pomalidomide in myelofibrosis. *Leukemia* 2011; **25:** 301–4.
3. Lacy MQ, Tefferi A. Pomalidomide therapy for multiple myeloma and myelofibrosis: an update. *Leuk Lymphoma* 2011; **52:** 560–6.
4. Lacy MQ, *et al.* Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood* 2011; **118:** 2970–5.
5. Schey S, Ramasamy K. Pomalidomide therapy for myeloma. *Expert Opin Invest Drugs* 2011; **20:** 691–700.
6. Leleu X, *et al.* Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. *Blood* 2013; **121:** 1968–75.
7. Elkinson S, McCormack PL. Pomalidomide: first global approval. *Drugs* 2013; **73:** 595–604.

Administration in subsequent cycles. The usual oral dose of pomalidomide may need to be modified if toxicity occurs.

If haematological toxicity occurs, the absolute neutrophil count (ANC) must be at least 500 cells/mm³ and the platelet count must be at least 50 000 cells/mm³ before a dose of pomalidomide is given. The following dose modifications are required when values fall below these concentrations.

- For ANC < 500 cells/mm³, ANC < 1000 cells/mm³ with fever ⩾ 38.5 degrees, or platelets < 25 000 cells/mm³: pomalidomide should be withheld until values recover and then resumed at a dose of 3 mg once daily.
- For each subsequent fall (ANC < 500 cells/mm³ or platelets < 25 000 cells/mm³): pomalidomide should be withheld until values recover and then resumed at a daily dose 1 mg less than the previous dose. If toxicities occur at a dose of 1 mg once daily, treatment should be stopped.

If other grade 3 or 4 toxicities occur, pomalidomide should be withheld until values recover to at least grade 2 and then resumed at a daily dose 1 mg less than the previous dose. If toxicities occur at a dose of 1 mg once daily, treatment should be stopped.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Because of its potential teratogenicity, pomalidomide use is restricted in women of child-bearing potential and similar precautions to thalidomide are required, see p. 869.2.

Pomalidomide is associated with haematological toxicity, particularly neutropenia, anaemia, and thrombocytopenia. Full blood counts should be monitored weekly for the first 8 weeks of treatment and then monthly thereafter; dose adjustments may be required, see Administration in Subsequent Cycles, above. Venous thromboembolism has occurred during pomalidomide treatment, and prophylactic measures should be considered in those at increased risk.

Neuropathy, including peripheral neuropathy, has been reported with pomalidomide. Dizziness, confusion, anxiety, insomnia, and headache have occurred.

Other common adverse effects include fatigue, pyrexia, chills, gastrointestinal disorders, anorexia, changes in body weight, muscle spasm or weakness, arthralgia, pain including bone and muscle pain, dyspnoea, cough, epistaxis, hyperhidrosis, rash, dry skin, pruritus, electrolyte disturbances, hyperglycaemia, increases in blood creatinine, and renal failure. Vertigo, increases in bilirubin and hepatic enzymes, and interstitial lung disease have also occurred.

Licensed product information recommends that pomalidomide should be avoided in patients with serum creatinine greater than 3 mg/dL, or with serum bilirubin greater than 2 mg/dL and aspartate aminotransferase or alanine aminotransferase greater than 3 times the upper limit of normal, due to a lack of data in such patients.

There have been reports of acute myeloid leukaemia in patients treated with pomalidomide.

Effects on the lungs. For reports of respiratory toxicity associated with pomalidomide, see under Thalidomide, p. 870.1.

Interactions

Pomalidomide is mainly metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4; potent inhibitors or inducers of these isoenzymes may affect exposure to pomalidomide. Tobacco smoking may reduce pomalidomide exposure due to induction of CYP1A2.

Pomalidomide is a substrate of P-glycoprotein and other drugs that inhibit or induce P-glycoprotein may affect its exposure.

Pharmacokinetics

Maximum serum concentrations of pomalidomide occur 2 to 3 hours after an oral dose. Plasma protein binding ranges from 12 to 44%. Pomalidomide is distributed into the semen. It is mainly metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4, with CYP2C19 and CYP2D6 playing a minor role. Pomalidomide is excreted via the kidneys with a plasma half-life of about 9.5 hours in healthy adults and 7.5 hours in those with multiple myeloma. About 73% of a dose was eliminated in the urine and 15% in the faeces, mainly as metabolites with a small portion as unchanged drug.

References.

1. Hoffmann M, *et al.* Absorption, metabolism and excretion of [^{14}C] pomalidomide in humans following oral administration. *Cancer Chemother Pharmacol* 2013; **71:** 489–501.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Imnovid; ***USA***: Pomalyst.

Ponatinib *(USAN, rINN)*

AP-24534; Ponatinibum; Понатиниб.

3-[2-(Imidazo[1,2-*b*]pyridazin-3-yl)ethynyl]-4-methyl-*N*-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide.

$C_{29}H_{27}F_3N_6O$=532.6

CAS — 943319-70-8.

UNII — 4340891KFS.

Ponatinib Hydrochloride *(USAN, rINNM)*

Hidrocloruro de ponatinib; Ponatinib, Chlorhydrate de; Ponatinibi Hydrochloridum; Понатиниба Гидрохлорид.

$C_{29}H_{27}F_3N_6O,HCl$=569.0

CAS — 1114544-31-8.

UNII — 96R6PU3D8J.

Uses and Administration

Ponatinib is a BCR-ABL tyrosine kinase inhibitor that is used for the treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia, or Philadelphia chromosome-positive acute lymphoblastic leukaemia, that is resistant to, or in patients who are intolerant of, prior tyrosine kinase inhibitor therapy. An oral dose of 45 mg once daily is used and continued until disease progression is noted. Treatment may need to be modified if toxicities occur (see Administration in Subsequent Cycles, below).

If ponatinib is used with a potent cytochrome P450 isoenzyme CYP3A inhibitor, a reduced oral dose of 30 mg once daily is recommended.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Cortes JE, *et al.* Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 2012; **367:** 2075–88.

Administration in subsequent cycles. The oral dose of ponatinib may need to be modified if toxicity occurs during treatment for chronic myeloid leukaemia, or Philadelphia chromosome-positive acute lymphoblastic leukaemia.

If myelosuppression occurs with the absolute neutrophil count (ANC) falling below 1000 cells/mm³ or platelets falling below 50 000 cells/mm³, interrupt ponatinib until the ANC recovers to at least 1500 cells/mm³ and platelets recover to at least 75 000 cells/mm³. When restarting, the dose should be adjusted as follows:

- for the first occurrence, resume ponatinib at the usual dose of 45 mg once daily
- for the second occurrence, resume ponatinib at a reduced dose of 30 mg once daily
- for the third occurrence, resume ponatinib at a further reduced dose of 15 mg once daily

Treatment modifications for other toxicities are as follows:

- if hepatotoxicity occurs with liver transaminases increased to > 3 times the upper limit of normal (ULN), interrupt ponatinib until transaminases have recovered to < 3 times the ULN
- for asymptomatic grade 1 or 2 increases in serum lipase, consider interruption or dose reduction of ponatinib
- for asymptomatic grade 3 or 4 increases in serum lipase (> 2 times the ULN) or asymptomatic grade 2 pancreatitis, interrupt ponatinib until lipase has recovered to < 1.5 times the ULN
- for symptomatic grade 3 pancreatitis, interrupt ponatinib until symptoms have completely resolved and lipase has recovered to < 1.5 times the ULN
- for grade 4 pancreatitis, stop ponatinib treatment

When restarting therapy, the dose should be adjusted as follows:

- when toxicity occurs on a dose of 45 mg once daily, resume ponatinib at a reduced dose of 30 mg once daily
- when toxicity occurs on a dose of 30 mg once daily, resume ponatinib at a further reduced dose of 15 mg once daily
- when toxicity occurs on a dose of 15 mg once daily, stop ponatinib treatment

Adverse Effects, Treatment, and Precautions

The most common adverse effects with ponatinib are gastrointestinal disorders such as constipation and nausea, hypertension, rash, dry skin, abdominal pain, fatigue, headache, arthralgia, and pyrexia. Other commonly reported effects include arterial ischaemia, heart failure, peripheral oedema, myelosuppression, infections, peripheral neuropathy, dizziness, cough, dyspnoea, myalgia, muscle spasm, pain including back pain and bone pain, mucositis, anorexia, and insomnia. Abnormalities associated with ponatinib treatment include increased liver and pancreatic enzyme values, increased bilirubin, decreased albumin, increased creatinine, increased triglycerides, and electrolyte and blood glucose abnormalities.

Severe myelosuppression has occurred in nearly half of patients treated with ponatinib. Thrombocytopenia, neutropenia, leucopenia, anaemia, and lymphopenia have been seen. Blood counts should be measured every 2 weeks for the first 3 months and then monthly or as clinically indicated, and the dose adjusted as necessary, see Administration in Subsequent Cycles, above.

Arterial thrombotic events have included cardiovascular, cerebrovascular, and peripheral thrombosis, including myocardial infarction and stroke. Most of the patients who developed arterial thrombosis had one or more cardiovascular risk factors. Ponatinib should be interrupted or stopped if such events occur. Venous thromboembolism including deep-vein thrombosis and pulmonary embolism has also occurred, and may require dose modification or treatment to be stopped. Serious bleeding events have been reported, particularly cerebral or gastrointestinal haemorrhage, and were most often seen in patients with severe thrombocytopenia; treatment should be interrupted if bleeding occurs.

Cardiovascular adverse effects include cardiac arrhythmias such as bradyarrhythmias and supraventricular tachyarrhythmias, congestive heart failure or left ventricular dysfunction, and hypertension sometimes leading to hypertensive crisis. Blood pressure should be monitored, and treatment may need to be stopped for severe heart failure. Fluid retention has been seen, particularly peripheral oedema, and pleural or pericardial effusion.

Hepatotoxicity and acute liver failure have occurred and liver function tests should be checked at baseline and at least monthly thereafter; treatment should be adjusted as necessary. Ponatinib is metabolised in the liver and use should be avoided in those with moderate to severe hepatic impairment due to the risk of increased exposure. Pancreatitis has been reported; lipase concentrations may be increased and should be monitored every 2 weeks for the first 2 months and then monthly thereafter or as needed, and treatment modified as necessary.

Hyperuricaemia has occurred, and tumour lysis syndrome has developed occasionally. Ponatinib could compromise wound healing, and gastrointestinal perforation has occurred over a month after abdominal surgery was carried out. Treatment should be stopped at least 1 week before major surgery, and reintroduced once wound healing is deemed adequate.

Interactions

In vitro studies have suggested that ponatinib is a substrate for the cytochrome P450 isoenzyme family CYP3A. Exposure to ponatinib was increased when given with the potent CYP3A4 inhibitor ketoconazole, and ponatinib dose adjustments are required when used with a potent CYP3A inhibitor; for further details, see Uses and Administration, above. Potent inducers of the CYP3A family should be avoided where possible during ponatinib treatment due to the risk of reduced efficacy.

An increase in gastric pH may reduce the bioavailability of, and exposure to, ponatinib and caution is advised with drugs that increase gastric pH such as proton pump inhibitors, histamine H_2-antagonists, or antacids.

Pharmacokinetics

Peak plasma concentrations of ponatinib are seen within 6 hours of an oral dose. Solubility is pH dependent, with higher pH resulting in lower solubility. It is more than 99% bound to plasma proteins *in vitro*, and is a weak substrate for, and an inhibitor of, P-glycoprotein and breast cancer resistance protein (BCRP or ABCG2). Ponatinib is metabolised by the cytochrome P450 isoenzymes CYP3A4 and to a lesser extent CYP3A5, CYP2C8, and CYP2D6, as well as by esterases and amidases. The elimination half-life ranged from 12 to 66 hours (mean 24 hours) once steady state was achieved. Ponatinib is excreted mainly in the faeces (nearly 90%), with a small amount in the urine (about 5%).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Iclusig; ***USA***: Iclusig.

Porfimer Sodium *(BAN, USAN, rINN)*

CL-184116; Dihaematoporphyrin Ether; Éter de dihematoporfirina; Porfimeerinatrium; Porfimère Sodique; Porfimerna-

trium; Porfímero sódico; Porfimerum Natricum; Порфимер Натрий.
CAS — 87806-31-3.
ATC — L01XD01.
ATC Vet — QL01XD01.
UNII — Y3834SIK5F.

Uses and Administration

Porfimer sodium is a haematoporphyrin derivative that reportedly accumulates in malignant tissue on injection. It is then activated by laser light to release oxygen radicals within malignant cells, producing cytotoxicity. Porfimer sodium is used as a photosensitiser in the photodynamic therapy of endobronchial non-small cell lung cancer (p. 710.2), oesophageal cancer (p. 705.3), and superficial bladder cancer (p. 700.2). It is also used for the treatment of dysplasia associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p. 1810.2).

Porfimer sodium should be reconstituted with glucose 5% or sodium chloride 0.9% to a final concentration of 2.5 mg/mL. It is given by slow intravenous injection at a dose of 2 mg/kg. This is followed, 40 to 50 hours later, by activation using a laser tuned to a wavelength of 630 nanometres and delivered to the area of the tumour using a fibre optic guide. Residual tumour may subsequently be debrided surgically. A second laser treatment may be given 96 to 120 hours after the original injection. A maximum of 3 courses of photodynamic therapy may be used, with each injection separated by a minimum of 30 days for oesophageal and endobronchial tumours, and a minimum of 90 days for dysplasia in Barrett's oesophagus. However, in the treatment of superficial bladder cancer, only one dose of drug and light is given due to an increased risk of bladder contracture, and no surgical debridement is performed.

For further information about use in hepatic or renal impairment, see below.

Administration in hepatic impairment. US licensed product information states that hepatic impairment could prolong the elimination of porfimer, and that patients with mild to severe hepatic impairment should be warned that the precautions for photosensitivity (see below) may need to be followed for longer than 90 days. EU licensed product information recommends similar warnings for those with mild to moderate impairment; use is contra-indicated in severe hepatic impairment.

Administration in renal impairment. EU licensed product information for some porfimer products (*Photofrin, Axcan*) states that, because excretion of porfimer is mainly via the faecal route, no special precautions are necessary in patients with renal impairment. However, EU licensed product information for other porfimer products (*Photo-Barr*, Axcan) contra-indicates use in severe renal impairment, as it has not been evaluated. US licensed product information (*Photofrin, Axcan*) states that renal impairment could prolong the elimination of porfimer, and that patients with severe renal impairment should be warned that the precautions for photosensitivity (see below) may need to be followed for longer than 90 days.

Photodynamic therapy. Photodynamic therapy (PDT) probably has the greatest potential of the various forms of light-activated treatment.[1] Photosensitising drugs are given intravenously, orally, or topically, and are selectively retained by tumour cells. When exposed to the correct wavelength of light the drug produces toxic oxygen radicals that destroy cell membranes and thereby kill the tumour cells. Vascular damage and immune-mediated injury may also occur.[2-4] Tumour cells must have an adequate supply of oxygen to be sensitive to PDT,[2] and as light penetration is usually limited, early or superficial malignant lesions respond best to therapy.[1,2] Photodynamic therapy has been tried in skin, gastrointestinal, head and neck, bladder, gynaecological, pancreatic, pulmonary, and various intraperitoneal malignancies[2,3,5-12] It is also used for the treatment of Barrett's oesophagus[12-14] and for the treatment of age-related macular degeneration (p. 880.2); it has been tried for other ocular disorders.[15] There is also an interesting report of cytotoxicity against leukaemic cells *in vitro* when exposure to porfimer sodium was combined with ultrasound.[6]

The main adverse effect of photosensitisers such as porfimer is photosensitivity lasting 4 to 8 weeks; patients should be advised to avoid sunlight during this period and therapy is best delayed until the darker winter months if possible.[1] Newer photosensitisers are being developed to show increased tissue penetration and less prolonged photosensitivity.[2] The natural haem precursor 5-aminolevulinic acid (p. 740.1) has the advantage that photosensitivity lasts only a few hours.

1. Bown SG. New techniques in laser therapy. *BMJ* 1998; **316:** 754–7.
2. Hsi RA, *et al.* Photodynamic therapy in the treatment of cancer: current state of the art. *Drugs* 1999; **57:** 725–34.
3. Ost D, *et al.* Photodynamic therapy in lung cancer. *Oncology* 2000; **14:** 379–86.
4. Brown SB, Ibbotson SH. Photodynamic therapy and cancer. *BMJ* 2009; **339:** b2459.
5. Wilson JHP, *et al.* Photodynamic therapy for gastrointestinal tumors. *Scand J Gastroenterol* 1991; **26** (suppl 188): 20–5.
6. Tachibana K, *et al.* Eliminating adult T-cell leukaemia cells with ultrasound. *Lancet* 1997; **349:** 325.
7. Walther MM. The role of photodynamic therapy in the treatment of recurrent superficial bladder cancer. *Urol Clin North Am* 2000; **27:** 163–70.
8. Metz JM, Friedberg JS. Endobronchial photodynamic therapy for the treatment of lung cancer. *Chest Surg Clin North Am* 2001; **11:** 829–39.
9. Biel MA. Photodynamic therapy in head and neck cancer. *Curr Oncol Rep* 2002; **4:** 87–96.
10. Moghissi K. Role of bronchoscopic photodynamic therapy in lung cancer management. *Curr Opin Pulm Med* 2004; **10:** 256–60.
11. Bown SG, *et al.* Photodynamic therapy for cancer of the pancreas. *Gut* 2002; **50:** 549–57.
12. Brown SB, *et al.* The present and future role of photodynamic therapy in cancer treatment. *Lancet Oncol* 2004; **5:** 497–508.
13. Wolfsen HC, *et al.* Photodynamic therapy for dysplastic Barrett esophagus and early esophageal adenocarcinoma. *Mayo Clin Proc* 2002; **77:** 1176–81.
14. Kelty CJ, *et al.* Photodynamic therapy for Barrett's esophagus: a review. *Dis Esophagus* 2002; **15:** 137–44.
15. Sivaprasad S, Hykin P. The role of photodynamic therapy in ophthalmology. *Br J Hosp Med* 2006; **67:** 647–50.

Adverse Effects and Precautions

Photosensitivity occurs in all patients treated with porfimer sodium. This effect is likely to be prolonged, and patients should avoid sunlight or bright indoor light for at least 30 days. Some patients may remain photosensitive for longer, and may need to follow these precautions for at least 90 days. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Other reported adverse effects include local inflammation and pain, including chest, back, or abdominal pain, respiratory insufficiency or distress (including dyspnoea), dehydration, dysphagia, constipation, nausea and vomiting, fever, tachycardia, atrial fibrillation, pleural effusion, and anaemia due to tumour bleeding. Pneumonia, bronchitis, anxiety, insomnia, cardiac failure, and peripheral or generalised oedema have also been reported. Photodynamic therapy with porfimer sodium is contra-indicated in patients with porphyria, oesophageal or gastric varices, large oesophageal ulcers, oesophageal fistulas, erosion of major blood vessels, or severe acute respiratory distress. Sufficient time should be allowed between photodynamic therapy and radiotherapy to allow inflammatory reactions from either treatment to subside.

Porphyria. Licensed product information states that the use of porfimer sodium is contra-indicated in patients with porphyria.

Interactions

Use of porfimer sodium with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

Porfimer sodium is distributed and eliminated slowly after intravenous injection, with plasma elimination half-life reported to be between 11 and 28 days. *In vitro* studies indicate that plasma protein binding is about 90%. Excretion occurs mainly via the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Photofrin; ***Canad.***: Photofrin; ***Cz.***: PhotoBarr; ***Fr.***: Photobarr†; Photofrin; ***Ger.***: Photofrin†; ***Gr.***: Photofrin; ***Hung.***: Photobarr; Photofrin; ***Irl.***: Photobarr; Photofrin; ***Israel***: Photofrin†; ***Mex.***: Photofrin; ***Neth.***: Photobarr†; ***Pol.***: PhotoBarr; ***Port.***: Photobarr; Photofrin; ***UK***: Photofrin; ***USA***: Photofrin.

Porfiromycin *(BAN, USAN, rINN)*

Methyl Mitomycin; NSC-56410; Porfiromicina; Porfiromycine; Porfiromycinum; U-14743; Порфиромицин.
6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-1,5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]-indole-4,7-dione carbamate ester.
$C_{16}H_{20}N_4O_5$=348.4
CAS — 801-52-5.
UNII — H1WK901OA6.

Profile

Porfiromycin is an antibiotic antineoplastic structurally related to mitomycin (p. 830.3). It is under investigation for the treatment of malignant neoplasms of the cervix, and the head and neck.

References.
1. Haffty BG, *et al.* Bioreductive alkylating agent porfiromycin in combination with radiation therapy for the management of squamous cell carcinoma of the head and neck. *Radiat Oncol Invest* 1997; **5:** 235–45.
2. Haffty BG, *et al.* Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial. *Int J Radiat Oncol Biol Phys* 2005; **61:** 119–28.

Pralatrexate *(USAN, rINN)*

PDX; Pralatrexato; Pralatrexatum; Пралатрексат.
(2*S*)-2-[(4-{(1*RS*)-1-[(2,4-Diaminopteridin-6-yl)methyl]but-3-ynyl}benzoyl)amino]pentanedioic acid.
$C_{23}H_{23}N_7O_5$=477.5
CAS — 146464-95-1.
ATC — L01BA05.
ATC Vet — QL01BA05.
UNII — A8Q8I19Q20.

Uses and Administration

Pralatrexate is an antineoplastic that acts as an antimetabolite of folic acid; it competitively inhibits the enzyme dihydrofolate reductase. Pralatrexate is used for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. It is given as an intravenous bolus over 3 to 5 minutes into a free-flowing infusion of sodium chloride 0.9%. The recommended dose is 30 mg/m^2 once weekly for 6 weeks, in 7-week cycles.

Patients are also given oral folic acid 1 to 1.25 mg daily, which should be started up to 10 days before starting pralatrexate, and continued until 30 days after the last dose. In addition, an intramuscular dose of vitamin B_{12} 1 mg, is given no more than 10 weeks before starting pralatrexate, and every 8 to 10 weeks thereafter; doses may be given on the same day as pralatrexate.

Doses of pralatrexate are modified according to toxicity (see Administration in Subsequent Cycles, below); once the dose is reduced, it should not be increased again.

Pralatrexate is also under investigation for diffuse large B-cell lymphoma, follicular lymphoma, and non-papillary transitional cell carcinoma of the urinary bladder.

References.
1. O'Connor OA, *et al.* Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma. *Br J Haematol* 2007; **139:** 425–8.
2. Mould DR, *et al.* A population pharmacokinetic and pharmacodynamic evaluation of pralatrexate in patients with relapsed or refractory non-Hodgkin's or Hodgkin's lymphoma. *Clin Pharmacol Ther* 2009; **86:** 190–6.
3. O'Connor OA, *et al.* Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. *J Clin Oncol* 2009; **27:** 4357–64.
4. Rueda A, *et al.* Pralatrexate, a new hope for aggressive T-cell lymphomas? *Clin Transl Oncol* 2009; **11:** 215–20.
5. Zain J, O'Connor O. Pralatrexate: basic understanding and clinical development. *Expert Opin Pharmacother* 2010; **11:** 1705–14.

Administration in subsequent cycles. Before any dose of pralatrexate is given, the following conditions are required:
- mucositis must be grade 1 or less
- platelet count should be at least 100 000 cells/mm^3 for the first dose, and 50 000 cells/mm^3 for all subsequent doses
- absolute neutrophil count (ANC) should be at least 1000 cells/mm^3

Doses are omitted or reduced according to toxicity, as outlined below. Once the dose is reduced, it is not increased again.

For **mucositis**, according to grade on the day of treatment, and upon recovery to grade 1 or better, respectively:
- grade 2: omit dose, restart at previous dose
- grade 2 recurrence, or grade 3: omit dose, reduce next dose to 20 mg/m^2
- grade 4: stop therapy

For **haematological toxicity**, according to blood count on the day of treatment, duration, and dose upon restarting:
- platelets < 50 000 cells/mm^3:
  for 1 week: omit dose, restart at previous dose
  for 2 weeks: omit dose, reduce next dose to 20 mg/m^2
  for 3 weeks: stop therapy
- ANC 500 to 1000 cells/mm^3 and no fever for 1 week: omit dose, restart at previous dose
- ANC 500 to 1000 cells/mm^3 with fever, or ANC < 500 cells/mm^3:
  for 1 week: omit dose, give colony-stimulating factor (CSF) support, and restart with previous dose (with CSF support)
  for 2 weeks, or recurrence: omit dose, give CSF support, and reduce next dose to 20 mg/m^2 (with CSF support)
  for 3 weeks or at second recurrence: stop therapy

For all **other** toxicities, based on grade on day of treatment, and upon recovery to grade 2 or less:

- grade 3: omit dose, restart with 20 mg/m²
- grade 4: stop therapy

Adverse Effects, Treatment, and Precautions

As for Methotrexate, p. 825.1, p. 826.3, and p. 827.1. Patients treated with pralatrexate are also given folic acid and vitamin B_{12} (see Uses and Administration, p. 849.3) to reduce treatment-related haematological toxicity and mucositis.

Interactions

As for Methotrexate, p. 827.3.

Pharmacokinetics

Pralatrexate exposure and peak plasma concentrations have been reported to increase proportionally with dose. Pralatrexate is about 67% bound to plasma proteins. The terminal elimination half-life is about 12 to 18 hours after a single intravenous dose. It is excreted in the urine and clearance decreases with decreasing creatinine clearance.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel:*** Difolta; ***USA:*** Folotyn.

Prednimustine *(USAN, rINN)*

Leo-1031; NSC-134087; Prednimustiini; Prednimustin; Prednimustina; Prednimustinum; Преднимустин.

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-{4-[bis(2-chloroethyl)amino]phenyl}butyrate).

$C_{35}H_{45}Cl_2NO_6$=646.6

CAS — 29069-24-7.

ATC — L01AA08.

ATC Vet — QL01AA08.

UNII — 9403SIO2S8.

Profile

Prednimustine is the prednisolone ester of chlorambucil, (p. 764.1) and has been given orally in the treatment of various malignant diseases.

Procarbazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de procarbazina; Ibenzmethyzin Hydrochloride; NSC-77213; Procarbazina, hidrocloruro de; Procarbazine, Chlorhydrate de; Procarbazini Hydrochloridum; Ro-4-6467/1; Прокарбазина Гидрохлорид.

N-Isopropyl-α-(2-methylhydrazino)-*p*-toluamide hydrochloride.

$C_{12}H_{19}N_3O$,HCl=257.8

CAS — 671-16-9 (procarbazine); 366-70-1 (procarbazine hydrochloride).

ATC — L01XB01.

ATC Vet — QL01XB01.

UNII — XH0NPH5ZX8.

Pharmacopoeias. In *Chin., Int., Jpn,* and *US.*

USP 36: (Procarbazine Hydrochloride). Store in airtight containers. Protect from light.

Uses and Administration

Procarbazine hydrochloride is a methylhydrazine derivative whose antineoplastic effect, although not fully understood, may resemble that of the alkylating agents; it appears to inhibit protein and nucleic acid synthesis and suppress mitosis. It does not show cross-resistance with other cytotoxic drugs.

Its main use is the treatment of Hodgkin's disease (p. 696.1) when it is usually given with other drugs. Procarbazine has also been used in the treatment of non-Hodgkin's lymphomas (p. 696.3) and refractory solid tumours.

Doses of procarbazine hydrochloride are calculated in terms of procarbazine; procarbazine hydrochloride 116 mg is equivalent to about 100 mg of procarbazine. Procarbazine is given orally. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* In combination regimens such as MOPP (with chlormethine, vincristine, and prednisone), procarbazine hydrochloride is given in doses equivalent to procarbazine 100 mg/m² daily for 10 to 14 days of each 4- to 6-week cycle. If used as a single agent, a dose equivalent to 50 mg of procarbazine daily, increased by 50 mg daily to 250 to 300 mg daily in divided doses has been suggested in the UK, while in the USA the recommended regimen is 2 to 4 mg/kg daily for the first week, subsequently increased to 4 to 6 mg/kg daily, doses being given to the nearest 50 mg. These doses are continued until maximum response is achieved or leucopenia, thrombocytopenia, or other signs of toxicity occur. Maintenance doses are usually 50 to 150 mg daily in the UK, given until a total dose of at least 6 g has been reached; in the USA maintenance doses of 1 to 2 mg/kg daily are given. Procarbazine treatment should be withheld if toxicity occurs, and restarted upon recovery. For doses in children, see below.

Administration in children. Procarbazine hydrochloride is used in children mainly for Hodgkin's disease when it is usually given with other drugs. It has also been used for other advanced lymphomas or solid tumours. In combination regimens such as MOPP (with chlormethine, vincristine, and prednisone), procarbazine hydrochloride is given to children in equivalent doses to adults, see above. If used as a single agent, an initial oral dose equivalent to procarbazine 50 mg/m² daily for the first week is suggested in the USA (UK licensed product information suggests a dose of 50 mg), increased to 100 mg/m² thereafter until maximum response or toxicity occurs. US licensed product information suggests the dose may be reduced to 50 mg/m² for maintenance when maximum response has been obtained. Procarbazine treatment should be withheld if toxicity occurs, and restarted upon recovery.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects associated with procarbazine are gastrointestinal disturbances such as anorexia, nausea and vomiting (although patients may soon become tolerant), and bone-marrow depression. Leucopenia and thrombocytopenia may be delayed with a nadir at about 4 weeks after a dose, and recovery usually within 6 weeks. Anaemia, haemolysis, and bleeding tendencies have been reported.

Neurotoxicity is also common, with central effects such as somnolence, depression, nervousness or confusion, headache, hallucinations, and dizziness, and peripheral neuropathies including paraesthesias and decreased reflexes. Lethargy, ataxia, and sleep disorders have also occurred, and tremors, convulsions, and coma have been reported.

Other adverse effects reported include fever and myalgia, pulmonary fibrosis or pneumonitis, haematuria, urinary frequency, skin reactions including dermatitis, pruritus, and hyperpigmentation, tachycardia, orthostatic hypotension, ocular defects, infertility, and hepatic impairment.

Procarbazine is a carcinogen, mutagen, and teratogen.

Procarbazine should be used with caution in patients with hepatic or renal impairment, and is contra-indicated if impairment is severe. The haematological status of the patient should be determined at least every 3 or 4 days and hepatic and renal function determined weekly. Care is also advisable in patients with phaeochromocytoma, epilepsy, or cardiovascular or cerebrovascular disease. Treatment should be interrupted if allergic skin reactions occur.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of procarbazine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Procarbazine is a weak MAOI and the possibility of reactions with other drugs and food, although very rare, must be borne in mind—for details of MAOI reactions see p. 444.3 and p. 445.1. Procarbazine may enhance the sedative effects of other CNS depressants. A disulfiram-like reaction has been reported with alcohol and the effects of antihypertensive agents may be enhanced.

Antiepileptics. Use with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine, possibly through a reactive intermediate generated by induction of the cytochrome P450 isoenzyme CYP3A subfamily.[1] Non-enzyme-inducing antiepileptics might be more appropriate in patients with brain tumours in whom procarbazine therapy is anticipated.

1. Lehmann DF, *et al.* Anticonvulsant usage is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumors. *Clin Pharmacol Ther* 1997; **62:** 225–9.

Pharmacokinetics

Procarbazine is readily absorbed from the gastrointestinal tract. It crosses the blood-brain barrier and diffuses into the CSF. A plasma half-life of about 10 minutes has been reported. Procarbazine is rapidly metabolised (mainly in liver and kidneys) and only about 5% is excreted unchanged in the urine. The remainder is oxidised to *N*-isopropylterephthalamic acid and excreted in the urine, up to about 70% of a dose being excreted in 24 hours. Some of the drug is excreted as carbon dioxide and methane via the lungs. During oxidative breakdown in the body hydrogen peroxide is formed which may account for some of the drug's actions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.:*** Natulan†; ***Canad.:*** Matulane; ***Fr.:*** Natulan; ***Ger.:*** Natulan; ***Gr.:*** Natulan; ***Ital.:*** Natulan; ***Neth.:*** Natulan; ***Rus.:*** Natulan (Натулан); ***S.Afr.:*** Natulan; ***Singapore:*** Natulan; ***Spain:*** Natulan†; ***Switz.:*** Natulan; ***USA:*** Matulane.

Pharmacopoeial Preparations

USP 36: Procarbazine Hydrochloride Capsules.

Raltitrexed *(BAN, USAN, rINN)*

D-1694; ICI-D1694; Raltitreksed; Raltitreksedi; Raltitrexedum; ZD-1694; Ралтитрексед.

N-{5-[3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl (methyl)amino]-2-thenoyl}-L-glutamic acid.

$C_{21}H_{22}N_4O_6S$=458.5

CAS — 112887-68-0.

ATC — L01BA03.

ATC Vet — QL01BA03.

UNII — FCB9EGG971.

Uses and Administration

Raltitrexed is a folate analogue that is a potent and specific inhibitor of the enzyme thymidylate synthase, which is involved in the synthesis of DNA. It has been used in the treatment of advanced colorectal cancer (p. 706.3) and has also been tried in breast cancer (p. 702.1) and other solid neoplasms.

The recommended initial dose of raltitrexed in patients with normal renal function is 3 mg/m² given by intravenous infusion over 15 minutes. Subsequent doses, which should be reduced by up to 50% depending on the severity of initial toxicity, may be given at intervals of 3 weeks provided toxicity has resolved.

A full blood count should be performed before each dose and treatment withheld if the white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p. 730.3). Hepatic and renal function should also be tested. It is essential that doses be adjusted in renal impairment (see below).

References.

1. Gunasekara NS, Faulds D. Raltitrexed: a review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1998; **55:** 423–35.
2. Cunningham D, *et al.* Efficacy, tolerability and management of raltitrexed (Tomudex) monotherapy in patients with advanced colorectal cancer: a review of phase II/III trials. *Eur J Cancer* 2002; **38:** 478–86.
3. Scheithauer W, *et al.* Randomized multicenter phase II trial of oxaliplatin plus irinotecan versus raltitrexed as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2002; **20:** 165–72.
4. Feliu J, *et al.* Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen. *Eur J Cancer* 2002; **38:** 1204–11.
5. Comella P, *et al.* Oxaliplatin plus raltitrexed and leucovorin-modulated 5-fluorouracil i.v. bolus: a salvage regimen for colorectal cancer patients. *Br J Cancer* 2002; **86:** 1871–5.
6. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.
7. van Meerbeeck JP, *et al.* Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; **23:** 6881–9.
8. Ducreux M, *et al.* FFCD 9601 Collaborative Group. Randomised trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 trial. *Oncology* 2006; **70:** 222–30.
9. Wilson KS, *et al.* Adjuvant therapy with raltitrexed in patients with colorectal cancer intolerant of 5-fluorouracil: British Columbia Cancer Agency experience. *Cancer Invest* 2007; **25:** 711–14.
10. Hind D, *et al.* The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2008; **12:** 1–182.
11. Popov I, *et al.* Raltitrexed (Tomudex) versus standard leucovorin-modulated bolus 5-fluorouracil: results from the randomised phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1). *Eur J Cancer* 2008; **44:** 2204–11.
12. Wilson KS, Malfair Taylor SC. Raltitrexed: optimism and reality. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1447–54.

Administration in renal impairment. It is essential that doses of raltitrexed be adjusted in renal impairment (creatinine clearance less than 65 mL/minute) as fatalities have been associated with the failure to make such adjustments (see Toxicity, under Adverse Effects, p. 851.1). The dosage

interval should be increased from 3 to 4 weeks and the dose adjusted on the basis of creatinine clearance (CC) as follows:
- CC of 55 to 65 mL/minute, 2.25 mg/m²
- CC of 25 to 54 mL/minute, 1.5 mg/m²(in some countries, adjustment of the dose to a percentage of the full dose equivalent to the value of the CC in mL/minute is suggested in this group, e.g. reduction to 30% in those with a CC of 30 mL/minute, or 40% if CC is 40 mL/minute)
- CC less than 25 mL/minute, treatment contra-indicated

Adverse Effects, Treatment, and Precautions

Raltitrexed produces bone marrow depression, usually mild to moderate, with leucopenia, anaemia, and, less frequently, thrombocytopenia. The nadir of the white cell count usually occurs 7 to 14 days after a dose, with recovery by the third week. Full blood counts should be monitored before each dose, and treatment may be withheld and restarted at reduced doses if needed (see Uses and Administration, p. 850.3). Gastrointestinal toxicity is also common, with nausea and vomiting, diarrhoea, and anorexia; mucositis may occur. Gastrointestinal bleeding has been reported rarely. Reversible increases in liver enzyme values have occurred. Other adverse effects include weakness and malaise, fever, pain, headache, rashes, desquamation, arthralgia, muscle cramps, weight loss, dehydration, peripheral oedema, alopecia, increased sweating, taste disturbance, and conjunctivitis. Cellulitis and sepsis have been reported. The use of folinic acid 25 mg/m² every 6 hours intravenously has been suggested in licensed product information for patients who develop very severe toxicity.

Raltitrexed should be given with care to patients with hepatic impairment and should be avoided if impairment is severe. It should also be avoided in severe renal impairment and be given in reduced doses in moderate impairment, based on creatinine clearance (see Administration in Renal Impairment, p. 850.3). Care is also advisable in debilitated or elderly patients or in patients who have had radiotherapy.

Raltitrexed is teratogenic; pregnancy should be avoided while either partner is receiving the drug and for at least 6 months after treatment. It may impair male fertility.

Toxicity. A large multicentre study comparing raltitrexed with fluorouracil plus folinic acid was suspended in 1999 due to an excess of deaths in the raltitrexed arm.[1] This decision has led to some controversy,[1-3] as in 11 of the 17 deaths in patients taking raltitrexed there was evidence that the dose had not been correctly adjusted to take account of renal function. In addition, and further confusing the issue, the incidence of reported serious adverse effects was lower in raltitrexed-treated patients than in controls. A further study[4] reported an increased rate of raltitrexed-related deaths compared with fluorouracil-based regimens. Almost all of the 18 deaths were caused by gastrointestinal and haematological toxicity, and in 3 of these the dose of raltitrexed had not been adjusted for toxicity.

1. Anonymous. Drug-company decision to end cancer trial. *Lancet* 1999; **354:** 1045.
2. Ford HER, Cunningham D. Safety of raltitrexed. *Lancet* 1999; **354:** 1824–5.
3. Kerr D. Safety of raltitrexed. *Lancet* 1999; **354:** 1825.
4. Maughan TS, *et al*. Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.

Interactions

Raltitrexed should not be given with folic or folinic acid, which may impair its cytotoxic action. (For the deliberate use of folinic acid to counteract the effects of raltitrexed in patients with severe toxicity, see above.)

Pharmacokinetics

After intravenous doses raltitrexed has triphasic pharmacokinetics, with an initial rapid decline from peak plasma concentrations followed by a slow terminal elimination phase. Raltitrexed is actively transported into cells and metabolised to active polyglutamate forms. The remainder of a dose is excreted unchanged, about 50% of a dose appearing in the urine, and about 15% in the faeces. The terminal elimination half-life is about 8 days. Clearance is markedly reduced in renal impairment.

References.
1. Clarke SJ, *et al*. Clinical and preclinical pharmacokinetics of raltitrexed. *Clin Pharmacokinet* 2000; **39:** 429–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tomudex; ***Austral.***: Tomudex; ***Austria***: Tomudex; ***Belg.***: Tomudex; ***Braz.***: Tomudex; ***Canad.***: Tomudex; ***Cz.***: Tomudex; ***Fr.***: Tomudex; ***Hung.***: Tomudex; ***Irl.***: Tomudex; ***Ital.***: Tomudex; ***Mex.***: Tomudex; ***Norw.***: Tomudex; ***Philipp.***: Tomudex†; ***Port.***: Tomudex; ***Rus.***: Tomudex (Томудекс); ***Singapore***: Tomudex; ***Spain***: Tomudex; ***Switz.***: Tomudex; ***Turk.***: Tomudex; ***UK***: Tomudex.

Ramucirumab *(USAN, rINN)*

IMC-1121B; Ramucirumabum; Рамуцирумаб.
CAS — 947687-13-0.
UNII — D99YVK4L0X.

Profile

Ramucirumab is a human monoclonal antibody that targets the vascular endothelial growth factor receptor-2 (VEGFR-2). It is under investigation for the treatment of various solid tumours, including those of the breast, gastrointestinal tract, and lung.

References.
1. Krupitskaya Y, Wakelee HA. Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR-2 for the potential treatment of cancer. *Curr Opin Investig Drugs* 2009; **10:** 597–605.
2. Spratlin JL, *et al*. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G_1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28:** 780–7.
3. Spratlin J. Ramucirumab (IMC-1121B): monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. *Curr Oncol Rep* 2011; **13:** 97–102.

Ranimustine *(rINN)*

MCNU; NSC-0270516; Ranimustina; Ranimustinum; Ranomustine; Ранимустин.
Methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-α-D-glucopyranoside.
$C_{10}H_{18}ClN_3O_7$=327.7
CAS — 58994-96-0.
ATC — L01AD07.
ATC Vet — QL01AD07.
UNII — RYH2T97J77.

Profile

Ranimustine is a nitrosourea derivative with general properties similar to those of carmustine (p. 761.2). It is used intravenously in the treatment of malignant neoplasms in usual doses of 50 to 90 mg/m² every 6 to 8 weeks according to haematological response.

References.
1. Wada M, *et al*. Induction therapy consisting of alternating cycles of ranimustine, vincristine, melphalan, dexamethasone and interferon alpha (ROAD-IN) and a randomized comparison of interferon alpha maintenance in multiple myeloma: a co-operative study in Japan. *Br J Haematol* 2000; **109:** 805–14.
2. Hatano N, *et al*. Efficacy of post operative adjuvant therapy with human interferon beta, MCNU and radiation (IMR) for malignant glioma: comparison among three protocols. *Acta Neurochir (Wien)* 2000; **142:** 633–8.
3. Wakabayashi T, *et al*. Initial and maintenance combination treatment with interferon-beta, MCNU (ranimustine), and radiotherapy for patients with previously untreated malignant glioma. *J Neurooncol* 2000; **49:** 57–62.
4. Mizuno H, *et al*. Superior efficacy of MMCP regimen compared with VMCP and MMPP regimens in the treatment of multiple myeloma. *Intern Med* 2002; **41:** 290–4.
5. Takenaka T, *et al*. Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301. *Int J Hematol* 2004; **79:** 165–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cymerin.

Ranpirnase *(USAN, rINN)*

P-30 Protein; Ranpirnasa; Ranpirnasum; Рапирназа.
CAS — 196488-72-9.

NOTE. Ranpirnase has been incorrectly stated to contain ergotamine. The name Onconase has been used as a trade mark for ranpirnase.

Profile

Ranpirnase is a ribonuclease reported to have antineoplastic properties. It is under investigation in the treatment of malignant mesothelioma. Ranpirnase has also been investigated in the management of solid tumours. It is also reported to have activity *in vitro* against HIV.

Regorafenib *(USAN, rINN)*

Bay-73-4506; Régorafénib; Regorafenibum; Регорафениб.
4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide.
$C_{21}H_{15}ClF_4N_4O_3$=482.8
CAS — 755037-03-7 (anhydrous regorafenib); 1019206-88-2 (regorafenib hydrate).
ATC — L01XE21.
ATC Vet — QL01XE21.
UNII — 24T2A1DOYB.

Profile

Regorafenib is an oral inhibitor of several receptor tyrosine kinases. It is used for the treatment of patients with metastatic colorectal cancer (p. 706.3) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, a vascular endothelial growth factor inhibitor, and an epidermal growth factor receptor inhibitor (if *KRAS* wild-type). Regorafenib is also used in those with locally-advanced unresectable or metastatic gastrointestinal stromal tumours (see Soft Tissue Sarcoma, p. 718.2) that have been previously treated with imatinib and sunitinib. The recommended dose is 160 mg orally once daily for the first 21 days of each 28-day cycle. Treatment is continued until patients no longer benefit, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Regorafenib should be taken at the same time each day with a low-fat meal. If a daily dose is missed, the next day's dose should not be doubled. Doses may need to be adjusted or treatment withheld or permanently stopped for severe toxicity.

It is also under investigation for the treatment of various other malignant neoplasms.

Hepatotoxicity has occurred and may be severe; deaths have been reported. Liver function should be monitored before, and every 2 weeks during the first 2 months of treatment; thereafter, monitoring should be monthly. Regorafenib is metabolised by the cytochrome P450 isoenzyme CYP3A4 and by the uridine diphosphate glucuronosyltransferase enzyme UGT1A9 and concomitant use of strong CYP3A4 inhibitors and inducers should be avoided.

References.
1. Wilhelm SM, *et al*. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; **129:** 245–55.
2. Grothey A. Regorafenib in metastatic colorectal cancer. *Clin Adv Hematol Oncol* 2012; **10:** 324–5.
3. Grothey A, *et al*. CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 303–12.
4. Demetri GD, *et al*. GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 295–302.
5. Festino L, *et al*. Critical appraisal of the use of regorafenib in the management of colorectal cancer. *Cancer Manag Res* 2013; **5:** 49–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Stivarga; ***Switz.***: Stivarga; ***UK***: Stivarga; ***USA***: Stivarga.

Ridaforolimus *(USAN, rINN)*

AP-23573; Deforolimus; MK-8669; Ridaforolimusum; Ридафоролимус.
(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*)-12-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-[(Dimethylphosphinoyl)oxy]-3-methoxycyclohexyl]-1-methylethyl}-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone.
$C_{53}H_{84}NO_{14}P$=990.2
CAS — 572924-54-0.
ATC — L01XE19.
ATC Vet — QL01XE19.
UNII — 48Z35KB15K.

NOTE. The name Jenzyl has been used as a trade mark for ridaforolimus.

Profile

Ridaforolimus is an analogue of sirolimus (p. 1970.2). It inhibits the 'mammalian target of rapamycin' (mTOR), interfering with the cell cycle, and is under investigation for the treatment of malignancies such as breast, endometrial, prostate, and lung cancer.

References.
1. Mita MM, *et al*. Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. *J Clin Oncol* 2008; **26:** 361–7.
2. Rizzieri DA, *et al*. A phase 2 clinical trial of deforolimus (AP23573, MK-8669), a novel mammalian target of rapamycin inhibitor, in patients with relapsed or refractory hematologic malignancies. *Clin Cancer Res* 2008; **14:** 2756–62.

3. Hartford CM, *et al*. A phase I trial to determine the safety, tolerability, and maximum tolerated dose of deforolimus in patients with advanced malignancies. *Clin Cancer Res* 2009; **15:** 1428–34.
4. Mahalingam D, *et al*. Targeting the mTOR pathway using deforolimus in cancer therapy. *Future Oncol* 2009; **5:** 291–303.

Rituximab *(BAN, USAN, rINN)*

IDEC-102; IDEC-C2B8; R-105; Rituksimab; Rituksimabi; Rituximabum; Ритуксимаб.

Immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer.

CAS — 174722-31-7.
ATC — L01XC02.
ATC Vet — QL01XC02.
UNII — 4F4X42SYQ6.

Uses and Administration

Rituximab is a chimeric monoclonal antibody that binds specifically to the CD20 antigen. Rituximab is used in the treatment of non-Hodgkin's lymphomas (p. 696.3), as monotherapy in relapsed or refractory low-grade or follicular lymphoma, or in first-line regimens for follicular lymphoma with combination chemotherapy, such as CVP (cyclophosphamide, vincristine, and prednisolone). Rituximab monotherapy may also be used in patients with low-grade stable disease after first-line treatment with CVP chemotherapy. It is also indicated for maintenance therapy in patients with follicular lymphoma who respond to induction chemotherapy that may or may not have contained rituximab. Rituximab is also used with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) or other anthracycline-based regimens for CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. Rituximab also forms part of the combination regimen employing ibritumomab tiuxetan (p. 804.3). Rituximab is also used with combination chemotherapy for chronic lymphocytic leukaemia (p. 693.3). Rituximab with methotrexate is used in adults with severe active rheumatoid arthritis (p. 853.3) who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least one TNF inhibitor; in the USA, it may also be used in moderate disease. Rituximab plus corticosteroids is used in adults with Wegener's granulomatosis (p. 1615.2) and microscopic polyangiitis (p. 1610.2).

Rituximab is licensed for use by intravenous infusion over several hours, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of between 1 and 4 mg/mL. The first infusion is normally begun at a rate of 50 mg/hour; this may be increased in increments of 50 mg/hour every 30 minutes to a maximum of 400 mg/hour, if well tolerated. Subsequent doses may be begun at a rate of 100 mg/hour, and increased in increments of 100 mg/hour every 30 minutes to a maximum of 400 mg/hour.

In the UK for the *treatment* of refractory or relapsed follicular **lymphoma**, rituximab is given as a single agent in a usual dose of 375 mg/m^2 once weekly for 4 doses; in the USA 4 or 8 doses may be given. Patients in either country may be re-treated after relapse for a further 4 doses. When given with combination chemotherapy for previously untreated follicular lymphoma, or for diffuse large B-cell lymphoma (with CHOP), rituximab 375 mg/m^2 is given on day 1 of the chemotherapy cycle, after the corticosteroid component of the regimen, for up to a total of 8 cycles. In patients previously treated with 6 to 8 cycles of CVP chemotherapy for low-grade lymphoma and who have not progressed, rituximab 375 mg/m^2 may be given once weekly for 4 doses, repeated every 6 months, for up to 16 doses.

In the regimen with ibritumomab tiuxetan, rituximab is usually given at a dose of 250 mg/m^2, within 4 hours before the ibritumomab infusions.

For *maintenance* treatment in those with follicular lymphoma who have responded to induction chemotherapy, rituximab is given as monotherapy. In previously untreated patients rituximab 375 mg/m^2 is started 2 months after the last dose of induction chemotherapy and given once every 2 months. In the UK this is continued until disease progression or for a maximum of 2 years, whereas in the USA, 12 doses of rituximab are given for maintenance. In the UK rituximab maintenance is also used in those with refractory or relapsed disease that responds to subsequent induction treatment with a combination regimen; 375 mg/m^2 is started 3 months after the last dose of induction chemotherapy and given once every 3 months. Maintenance treatment is continued until disease progression or for a maximum of 2 years.

In the treatment of **chronic lymphocytic leukaemia**, the recommended dose of rituximab is 375 mg/m^2, given on the day before chemotherapy in cycle 1, followed by 500 mg/m^2 given on day 1 of each subsequent cycle, for up to 6 cycles in total; chemotherapy is given after the rituximab infusion. Prophylactic hydration and allopurinol or rasburicase is recommended, starting 48 hours before rituximab, to reduce the risk of tumour lysis syndrome; in the UK, those with high lymphocyte counts are given intravenous corticosteroids before rituximab to reduce the incidence and severity of infusion reactions.

In the treatment of **rheumatoid arthritis**, rituximab is given in a dose of 1 g, for 2 doses; the infusions are separated by 2 weeks. It is given with methotrexate, and intravenous corticosteroids are recommended before each infusion to reduce the incidence and severity of infusion reactions. Licensed product information states that subsequent courses should be given every 24 weeks or based on clinical evaluation, but no sooner than every 16 weeks; however, guidance issued by NICE in the UK recommends that rituximab should be given no more often than every 6 months.

For the treatment of **Wegener's granulomatosis** and **microscopic polyangiitis**, rituximab is given in a dose of 375 mg/m^2 once weekly for 4 doses; corticosteroids are also given to treat severe vasculitic symptoms, preferably beginning within 14 days before rituximab is started, and continuing during and after rituximab therapy.

General reviews.

1. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
2. McDonald V, Leandro M. Rituximab in non-haematological disorders of adults and its mode of action. *Br J Haematol* 2009; **146:** 233–46.

Administration. *RATE.* Licensed product information states that rituximab infusions should be given at a specific rate (see Uses and Administration, above). In an effort to reduce infusion times, faster rates have been investigated. One study gave the first infusion of rituximab in cycle 1 as in the licensed product information, but subsequent infusions were given over 90 minutes, with 20% of the dose given in the first 30 minutes, and the remaining 80% over 60 minutes; the total dose was delivered in 250 mL. Rapid infusion was well tolerated with no serious infusion reactions; 10 out of 150 patients who had an adverse reaction with the first cycle (given at the standard licensed rate) tolerated subsequent rapid infusion without event, and 8 patients were not premedicated with corticosteroids.[1] Another study also reported that rituximab infusions given over 90 minutes, with or without corticosteroids, were well tolerated and safe.[2] In another study, 40 patients were given rituximab; the first infusion was given as licensed and averaged 5 hours. All subsequent infusions were given over 1 hour. It was reported that even those patients who had shown some hypersensitivity during the first infusion were able to tolerate the rapid infusion without problems.[3] A survey found that the majority of chemotherapy units in the UK were infusing second and subsequent rituximab infusions over 90 minutes if patients had no significant reactions to the initial rituximab infusion. In this study 54 patients were given an initial infusion over 90 minutes and, if no serious reactions were noted, were given subsequent infusions over 60 minutes; the 1-hour infusion was well tolerated in all patients.[4]

1. Sehn LH, *et al*. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood* 2007; **109:** 4171–3.
2. Salar A, *et al*. Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. *Eur J Haematol* 2006; **77:** 338–40.
3. Provencio M, *et al*. Rapid-infusion rituximab in lymphoma treatment. *Ann Oncol* 2006; **17:** 1027–8.
4. Tuthill M, *et al*. Rapid infusion of rituximab over 60 min. *Eur J Haematol* 2009; **82:** 322–5.

ROUTE. Rituximab has been used *intralesionally* in the treatment of cutaneous B-cell lymphoma. There are reports of benefit, with long-term remission in some patients,[1] but rapid recurrence in others.[2] In a study of 8 patients, intralesional rituximab was given to 6 patients, in doses of 10 to 30 mg per lesion, 3 times weekly; if clinical remission was incomplete, another cycle of 3 injections was given 1 month later. Two patients were treated intravenously with weekly infusions for 4 weeks. Complete remission was seen in all 8 patients. No relapse was seen in those given intravenous therapy, but recurrences were seen in 4 of the 6 patients treated intralesionally. Moderate pain was reported during intralesional injection.[3]

Rituximab has also been used *intrapleurally* for the treatment of malignant pleural effusions in a patient with non-Hodgkin's lymphoma, in whom effusions continued to increase despite systemic chemotherapy and chest drainage. An initial test dose of rituximab 50 mg in 50 mL of sterile saline was given as a bolus into the right pleural cavity on day 1. This was followed by 200 mg in 100 mL on day 2 into the left cavity, and 400 mg in 100 mL on day 3 into the right cavity; both doses were given over 5 minutes. The therapy was well tolerated, and the effusions resolved within 2 weeks. The patient received 4 courses of intravenous rituximab consolidation therapy during a follow-up of 6 months; the effusions did not recur.[4]

Massive ascites developed in a patient with stage IV mantle cell lymphoma that was refractory to conventional chemotherapy (including intravenous rituximab added to the CHOP regimen). A palliative experimental treatment with *intraperitoneal* rituximab was given in a dose of 600 mg in 500 mL of sodium chloride 0.9%, and instilled over 4 hours. This was applied weekly for 11 courses, each time after drainage of ascites. No systemic adverse effects were noted, and the general status of the patient improved significantly; ascites resolved completely and partial remission of intra-abdominal lymph nodes and splenomegaly was noted. The patient remained asymptomatic for more than 6 months.[5]

Patients with CNS lymphoma have been treated with *intraventricular* or *intrathecal* doses of rituximab. Doses ranged from 10 to 40 mg in volumes of 1 to 4 mL, and an equivalent volume of CSF was removed before intraventricular use. Rituximab therapy was reported to be effective in those with leptomeningeal involvement, but solid parenchymal tumours progressed or showed only minor response.[6] A further study of intrathecal rituximab in 7 patients with acute lymphoblastic leukaemia and CNS disease reported complete remission in 5 patients, with no clinical evidence of neurotoxicity after 2 years of follow-up. Rituximab 10 mg was diluted in 6 mL of saline and given intrathecally every week for 4 consecutive weeks.[7]

1. Paul T, *et al*. Intralesional rituximab for cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144:** 1239–43.
2. Roguedas AM, *et al*. Intralesional therapy with anti-CD20 monoclonal antibody rituximab: local and systemic efficacy in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2005; **152:** 541–4.
3. Kerl K, *et al*. Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. *Br J Dermatol* 2006; **155:** 1197–1200.
4. Schmidt HH, *et al*. Intrapleural instillation of rituximab for the treatment of malignant pleural effusions in NHL. *Haematologica* 2004; **89:** e133–e134.
5. Crysandt M, *et al*. Intraperitoneal application of rituximab in refractory mantle cell lymphoma with massive ascites resulting in local and systemic response. *Eur J Haematol* 2007; **79:** 546–9.
6. Schulz H, *et al*. Intraventricular treatment of relapsed central nervous system lymphoma with the anti-CD20 antibody rituximab. *Haematologica* 2004; **89:** 753–4.
7. Jaime-Pérez JC, *et al*. Effectiveness of intrathecal rituximab in patients with acute lymphoblastic leukaemia relapsed to the CNS and resistant to conventional therapy. *Br J Haematol* 2009; **144:** 794–5.

Administration in children. Although not licensed in the UK or the USA for use in children, there are reports of benefit in children with various diseases, such as autoimmune haemolytic anaemia, immune thrombocytopenia (see also below and p. 853.1, respectively), and post-transplantation lymphoproliferative disease,[1] as well as rheumatoid arthritis, and SLE.[2] Standard doses of 375 mg/m^2 weekly have usually been given, in most cases for a median course of 4 doses.

1. Giulino LB, *et al*. Treatment with rituximab in benign and malignant hematologic disorders in children. *J Pediatr* 2007; **150:** 338–44.
2. El-Hallak M, *et al*. Clinical effects and safety of rituximab for treatment of refractory pediatric autoimmune diseases. *J Pediatr* 2007; **150:** 376–82.

Blood disorders, non-malignant. *HAEMOLYTIC ANAEMIA.* Rituximab has been used in the treatment of both adults and children with severe refractory auto-immune haemolytic anaemia (p. 1122.2) of various causes,[1] including warm,[2-4] cold,[5-7] and mixed[8,9] disease.

1. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
2. Quartier P, *et al*. Treatment of childhood autoimmune haemolytic anaemia with rituximab. *Lancet* 2001; **358:** 1511–13.
3. Gottardo NG, *et al*. Successful induction and maintenance of long-term remission in a child with chronic relapsing autoimmune hemolytic anemia using rituximab. *Pediatr Hematol Oncol* 2003; **20:** 557–61.
4. Svahn J, *et al*. Rituximab-based immunosuppression for autoimmune haemolytic anaemia in infants. *Br J Haematol* 2009; **145:** 96–100.
5. Sparling TG, *et al*. Remission of cold hemagglutinin disease induced by rituximab therapy. *Can Med Assoc J* 2001; **164:** 1405.
6. Engelhardt M, *et al*. Severe cold hemagglutinin disease (CHD) successfully treated with rituximab. *Blood* 2002; **100:** 1922–3.
7. Berentsen S, *et al*. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004; **103:** 2925–8.
8. Morselli M, *et al*. Mixed warm and cold autoimmune hemolytic anemia: complete recovery after 2 courses of rituximab treatment. *Blood* 2002; **99:** 3478–9.
9. Webster D, *et al*. Prompt response to rituximab of severe hemolytic anemia with both cold and warm autoantibodies. *Am J Hematol* 2004; **75:** 258–9.

HAEMORRHAGIC DISORDERS. Although data are limited, reports suggest that rituximab may be an effective alternative for the treatment of acquired haemophilia (p. 1126.3) after established therapies have failed.[1,2] Durable responses have been reported after rituximab was used first-line or as salvage therapy;[3] the usual intravenous dose used was 375 mg/m^2 once weekly for 4 weeks. Patients with high autoantibody titres may only achieve a partial response, or be slow to respond, but increasing the number of doses of rituximab or using it with cyclophosphamide and/or corticosteroids may improve response. Rituximab may be an effective alternative for those patients unable to have cytotoxic therapy.

An analysis[4] of the use of rituximab in 49 patients with congenital haemophilia (haemophilia A or B) concluded

that about half of haemophiliacs with inhibitors resistant to previous immune tolerance regimens could be durably rescued with rituximab, and that the highest responses were seen in adult haemophiliacs with mild or moderate disease who were given rituximab as part of a protocol that included factor VIII concentrates or other immunosuppressive drugs.

1. Maillard H, *et al*. Rituximab in postpartum-related acquired hemophilia. *Am J Med* 2006; **119:** 86–8.
2. Stachnik JM. Rituximab in the treatment of acquired hemophilia. *Ann Pharmacother* 2006; **40:** 1151–7.
3. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
4. Franchini M, *et al*. Immune tolerance with rituximab in congenital haemophilia with inhibitors: a systematic literature review based on individual patients' analysis. *Haemophilia* 2008; **14:** 903–12.

IMMUNE THROMBOCYTOPENIA. Rituximab has been reported[1-3] to be effective in patients, including children and infants, with immune thrombocytopenia (p. 1606.1) refractory to standard treatments. Some consider it to be a possible alternative treatment, with good response rates and durable responses obtained in both adults and children.[4] Two patterns of response have been seen; within 4 weeks, or until several weeks or even months after the start of rituximab, suggesting additional mechanisms of action besides depletion of autoantibodies. While most studies used rituximab in a usual intravenous dose of 375 mg/m^2 once weekly for 4 weeks, lower doses (including a single dose regimen for children) have been used. Re-treatment of patients who relapse after an initial response to rituximab is also an option, and rituximab has been used alone or with other drugs.[4] However, a review[5] cautioned against the indiscriminate use of rituximab in this patient population, given the lack of controlled data.

1. Zaja F, *et al*. The B-cell compartment as the selective target for the treatment of immune thrombocytopenias. *Haematologica* 2003; **88:** 538–46.
2. Bengtson KL, *et al*. Successful use of anti-CD20 (rituximab) in severe, life-threatening childhood immune thrombocytopenic purpura. *J Pediatr* 2003; **143:** 670–3.
3. Wang J, *et al*. Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr* 2005; **146:** 217–21.
4. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
5. Arnold DM, *et al*. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med* 2007; **146:** 25–33.

THROMBOTIC MICROANGIOPATHIES. Rituximab has been reported[1-3] to be of benefit in relapsed or refractory thrombotic thrombocytopenic purpura (see under Plasma, p. 1159.1). Time to response has ranged from less than 1 week to about 13 weeks;[4] durable remissions have been reported.[5] Most patients are reported to have received the standard intravenous dose of rituximab 375 mg/m^2 once weekly for 4 weeks; however, some patients required prolonged therapy, whereas others responded with only 1 or 2 doses.[4]

1. Zheng X, *et al*. Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. *Ann Intern Med* 2003; **138:** 105–8.
2. Reddy PS, *et al*. Rituximab in the treatment of relapsed thrombotic thrombocytopenic purpura. *Ann Hematol* 2005; **84:** 232–5.
3. Kosugi S, *et al*. Rituximab provided long-term remission in a patient with refractory relapsing thrombotic thrombocytopenic purpura. *Int J Hematol* 2005; **81:** 433–6.
4. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
5. Ling HT, *et al*. Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: a report of 13 cases and review of the literature. *Am J Hematol* 2009; **84:** 418–21.

Castleman's disease. Castleman's disease is a rare lymphoproliferative disorder, often associated with HIV infection (p. 957.2) and thought to be caused by the same virus (human herpesvirus 8) as Kaposi's sarcoma. No standard treatment has been established. Responses to rituximab therapy have been reported in two small open-label studies in patients with HIV-associated Castleman's disease;[1,2] rituximab 375 mg/m^2 was given intravenously once weekly for 4 weeks. However, exacerbation of Kaposi's sarcoma lesions may be a problem.

1. Gérard L, *et al*. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus-associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. *J Clin Oncol* 2007; **25:** 3350–6.
2. Bower M, *et al*. Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med* 2007; **147:** 836–9.

Eye disorders. Orbital pseudolymphomas are uncommon benign tumours which usually affect the lachrymal gland, orbital soft tissue, or extra-ocular muscles. Clinical presentation includes painless onset of ptosis, proptosis, diplopia, or eyelid swelling. There are reports of durable response to rituximab.[1]

1. Witzig TE, *et al*. Treatment of benign orbital pseudolymphomas with the monoclonal anti-CD20 antibody rituximab. *Mayo Clin Proc* 2007; **82:** 692–9.

Glomerular kidney disease. In a report of 5 patients with corticosteroid-resistant nephrotic syndrome, 4 patients had a complete remission and 1 patient had a partial remission after treatment with rituximab in standard doses for 4 weeks. Complete remission was maintained in 3 patients, despite tapering of corticosteroids and calcineurin inhibitors.[1] The limited evidence for such use has subsequently been reviewed.[2]

1. Bagga A, *et al*. Rituximab in patients with the steroid-resistant nephrotic syndrome. *N Engl J Med* 2007; **356:** 2751–2.
2. Haffner D, Fischer DC. Nephrotic syndrome and rituximab: facts and perspectives. *Pediatr Nephrol* 2009; **24:** 1433–8.

Malignant neoplasms. Reviews.

1. NICE. Rituximab for aggressive non-Hodgkin's lymphoma (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/65_rituximab_nonhodgkins_fullguidance.pdf (accessed 07/09/09)
2. Avivi I, *et al*. Clinical use of rituximab in haematological malignancies. *Br J Cancer* 2003; **89:** 1389–94.
3. Held G, *et al*. Rituximab for the treatment of diffuse large B-cell lymphomas. *Expert Rev Anticancer Ther* 2006; **6:** 1175–86.
4. van Oers MH. Rituximab maintenance in indolent lymphoma: indications and controversies. *Curr Oncol Rep* 2007; **9:** 378–83.
5. Schulz H, *et al*. Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/07/08).
6. Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. *Annu Rev Med* 2008; **59:** 237–50.
7. NICE. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkins lymphoma: review of technology appraisal guidance 37 (issued February 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA137guidance.pdf (accessed 07/09/09)
8. Kapoor P, *et al*. Anti-CD20 monoclonal antibody therapy in multiple myeloma. *Br J Haematol* 2008; **141:** 135–48.
9. Gisselbrecht C. Use of rituximab in diffuse large B-cell lymphoma in the salvage setting. *Br J Haematol* 2008; **143:** 607–21.
10. Vidal L, *et al*. Rituximab as maintenance therapy for patients with follicular lymphoma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 07/09/09).
11. NICE. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (issued July 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/TA174FullGuidance.pdf (accessed 07/09/09)
12. Hagemeister F. Rituximab for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2010; **70:** 261–72.
13. Gao G, *et al*. A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma. *Acta Oncol* 2010; **49:** 3–12.
14. Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. *Drugs* 2010; **70:** 1445–76.

Multiple sclerosis. A single course of rituximab has been reported to reduce inflammatory brain lesions and clinical relapses in relapsing-remitting multiple sclerosis (p. 996.3);[1] the small study was not designed to assess long-term safety or uncommon adverse effects.

1. Hauser SL, *et al*. HERMES Trial Group. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; **358:** 676–88.

Myasthenia gravis. Rituximab has been tried[1] in a few patients with myasthenia gravis (p. 684.1).

1. Nelson RP, *et al*. Rituximab for the treatment of thymoma-associated and de novo myasthenia gravis: 3 cases and review. *J Clin Neuromusc Dis* 2009; **10:** 170–7.

Organ and tissue transplantation. Rituximab is a treatment option for patients with chronic graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p. 1937.1). Available data suggest that rituximab may be particularly effective for patients with extensive corticosteroid-refractory chronic GVHD manifesting as thrombocytopenia, or for those with sclerodermatous, cutaneous, or rheumatological involvement.[1] Post-transplant lymphoproliferative disorder (PTLD) after solid organ transplantation (see p. 1936.2 *et seq*) is rare but life-threatening; many cases, especially more aggressive lymphomas, do not respond to the usual first-line therapy of reduction in immunosuppression. Rituximab and/or chemotherapy have been used for PTLD. Some recommend that patients with Epstein-Barr virus (EBV) positive and early-onset PTLD be given rituximab monotherapy if reduction in immunosuppression fails; treatment with chemotherapy is reserved for those who fail to respond to rituximab. More aggressive treatment, including the use of rituximab with combination chemotherapy (given sequentially or concurrently), should be considered initially, along with reduction of immunosuppressive treatment, in those patients with CD20-positive or high-grade PTLDs. The use of granulocyte colony-stimulating factors and antibacterials as prophylaxis against infectious complications should be considered in this high-risk population.[2] Rituximab has been investigated as induction therapy for patients undergoing renal transplantation, but a small study reported an excess risk of acute cellular rejection in those given rituximab.[3]

1. Bates JS, *et al*. Clinical utility of rituximab in chronic graft-versus-host disease. *Ann Pharmacother* 2009; **43:** 316–21.
2. Lee J-J, *et al*. Role of chemotherapy and rituximab for treatment of posttransplant lymphoproliferative disorder in solid organ transplantation. *Ann Pharmacother* 2007; **41:** 1648–59.
3. Clatworthy MR, *et al*. B-cell-depleting induction therapy and acute cellular rejection. *N Engl J Med* 2009; **360:** 2683–5.

Pemphigus. Rituximab has been reported to be of benefit in pemphigus vulgaris (p. 1687.1) and its use has been reviewed.[1,2] In a review of 17 cases, it was used in patients with severe and widespread disease that had not responded to usual therapy with corticosteroids and immunosuppressants. A dose of 375 mg/m^2 once weekly was used and most patients were given a course of 4 doses. Most patients showed some improvement from rituximab, including 9 who were free of clinical disease for more than 6 months and 5 who had a partial response. However, although concomitant therapy could be reduced in 8 patients, only 2 were able to stop systemic corticosteroids and immunosuppressants; in 6 cases this information was not reported. Rituximab might therefore be useful for remission induction when corticosteroids have not been effective, but long-term follow-up is needed. Rituximab with normal immunoglobulins has also been reported to be effective in patients with refractory pemphigus vulgaris.[3]

Rituximab has also been reported to be of benefit in pemphigus foliaceus,[4-6] a less common variant of pemphigus. A single cycle of 4 weekly infusions of rituximab was reported to achieve complete remission in 12 of 14 patients with pemphigus vulgaris and 6 of 7 patients with pemphigus foliaceus; 2 patients in the former group achieved delayed complete remission. Of these 20 patients, 6 with pemphigus vulgaris and 3 with pemphigus foliaceus had a relapse; 2 of these 9 patients were given a second course of rituximab and again achieved complete remission. After 34 months of follow-up, 18 patients were free of disease, and 8 of these were not receiving any systemic therapy.[7]

1. El Tal AK, *et al*. Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006; **55:** 449–59.
2. Schmidt E, *et al*. Rituximab in severe pemphigus. *Ann N Y Acad Sci* 2009; **1173:** 683–91.
3. Ahmed AR, *et al*. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355:** 1772–9.
4. Goebeler M, *et al*. Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. *Br J Dermatol* 2003; **149:** 899–901.
5. Arin MJ, *et al*. Anti-CD20 monoclonal antibody (rituximab) in the treatment of pemphigus. *Br J Dermatol* 2005; **153:** 620–5.
6. Fernando SL, O'Connor KS. Treatment of severe pemphigus foliaceus with rituximab. *Med J Aust* 2008; **189:** 289–90.
7. Joly P, *et al*. A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med* 2007; **357:** 545–52.

Rheumatoid arthritis. Rituximab is of benefit in patients with rheumatoid arthritis (p. 13.2) refractory to standard therapy.[1-4] The ability of rituximab to prevent articular damage, its efficacy for extra-articular manifestations, the efficacy and safety of repeated courses, and long-term effects on the immune system remain to be determined.[5] Radiographic data from a placebo-controlled study showed a trend towards less progression of structural joint damage with a course of rituximab (2 doses); assessment was made at 24 weeks.[6] In a consensus statement, European and Canadian rheumatologists stated that re-treatment with rituximab may be considered after week 24 in those who respond to initial therapy.[7]

1. Edwards JCW, *et al*. Efficacy of B-cell—targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; **350:** 2572–81.
2. Summers KM, Kockler DR. Rituximab treatment of refractory rheumatoid arthritis. *Ann Pharmacother* 2005; **39:** 2091–5.
3. Higashida J, *et al*. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-α treatment. *J Rheumatol* 2005; **32:** 2109–15.
4. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
5. Looney RJ. B cell-targeted therapy for rheumatoid arthritis: an update on the evidence. *Drugs* 2006; **66:** 625–39.
6. Cohen SB, *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; **54:** 2793–2806.
7. Smolen JS, *et al*. Working Group on the Rituximab Consensus Statement. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; **66:** 143–50.

Scleroderma. Rituximab is under investigation for the management of scleroderma (p. 1942.3).

Skin disorders. In addition to reports of efficacy in pemphigus (see above), rituximab has been reported to be of benefit in refractory cases of pemphigoid[1] and epidermolysis bullosa acquisita.[2,3]

1. Schmidt E, *et al*. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156:** 352–6.
2. Crichlow SM, *et al*. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol* 2007; **156:** 194–6.
3. Sadler E, *et al*. Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol* 2007; **157:** 417–19.

Systemic lupus erythematosus. Rituximab has been investigated for the treatment of SLE (p. 1613.3),[1-3] but results of controlled studies have been disappointing.

1. Sfikakis PP, *et al*. Rituximab anti-B-cell therapy in systemic lupus erythematosus: pointing to the future. *Curr Opin Rheumatol* 2005; **17:** 550–7.
2. García-Carrasco M, *et al*. Use of rituximab in patients with systemic lupus erythematosus: an update. *Autoimmun Rev* 2009; **8:** 343–8.
3. Hughes G. Rituximab in lupus and beyond: the state of the art. *Lupus* 2009; **18:** 639–44.

Thyroid disorders. Rituximab has been investigated in the management of Graves' disease (see Hyperthyroidism, p. 2332.2), including Graves' ophthalmopathy.[1,2]

1. Nielsen CH, *et al.* B-cell depletion with rituximab in the treatment of autoimmune diseases: Graves' ophthalmopathy the latest addition to an expanding family. *Expert Opin Biol Ther* 2007; **7:** 1061–78.
2. Heemstra KA, *et al.* Rituximab in relapsing Graves' disease, a phase II study. *Eur J Endocrinol* 2008; **159:** 609–15.

Vasculitic syndromes. Rituximab has been reported to be of benefit in treating vasculitic syndromes (p. 1615.2), including those associated with antineutrophil cytoplasmic antibodies (ANCA-associated vasculitis).[1-4] Similar efficacy to cyclophosphamide has been reported,[3,4] with some suggestion that rituximab may be more effective in relapsing disease.[4] Successful treatment of scleritis associated with Wegener's granulomatosis has also been described.[5] Safety and efficacy have also been reported[6] with the use of rituximab in patients with refractory Henoch-Schönlein purpura (see Hypersensitivity Vasculitis, p. 1606.1).

1. Keogh KA, *et al.* Induction of remission b y B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; **52:** 262–8.
2. Ferraro AJ, *et al.* Effective therapeutic use of rituximab in refractory Wegener's granulomatosis. *Nephrol Dial Transplant* 2005; **20:** 622–5.
3. Jones RB, *et al.* European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; **363:** 211–20.
4. Stone JH, *et al.* RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; **363:** 221–32.
5. Cheung CMG, *et al.* Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. *Br J Ophthalmol* 2005; **89:** 1542.
6. Donnithorne KJ, *et al.* Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. *J Pediatr* 2009; **155:** 136–9.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Infusion of rituximab has been associated with a cytokine release syndrome of fever, chills, and rigors, usually within 2 hours of beginning therapy (see also Infusion-related Reactions, below). Other reported symptoms include pruritus, urticaria, rashes, dyspnoea, bronchospasm, angioedema, transient hypotension, and flushing; myocardial infarction, ventricular fibrillation, and cardiogenic shock can occur. Asthenia, headache, rhinitis, and hypertension may also be associated with infusion reactions. Severe cases may be associated with tumour lysis syndrome (and its associated electrolyte abnormalities such as hyperuricaemia, hyperkalaemia, hypocalcaemia, and hyperphosphataemia), acute renal failure, acute respiratory failure, and death. Hypersensitivity reactions manifest similarly to the cytokine release syndrome, but usually occur within minutes of starting infusion. Mucocutaneous reactions, some fatal, and including Stevens-Johnson syndrome or toxic epidermal necrolysis have also occurred. A reaction resembling serum sickness has been reported.

Patients with an extensive tumour burden, pulmonary tumour infiltration or pulmonary insufficiency may be at increased risk of severe infusion reactions and should be treated with caution and possibly a decreased initial infusion rate. Therapy should be interrupted in patients who develop severe symptoms and only resumed, at up to half the previous rate, once all signs and symptoms have resolved. Premedication with analgesics, antihistamines, and possibly corticosteroids is recommended in all patients before receiving rituximab.

Use of rituximab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), and fatalities have been reported. In most cases, patients had multiple risk factors, including long-term treatment with combination chemotherapy or immunosuppression, or were undergoing haematopoietic stem cell transplantation. Patients should be monitored regularly for new or worsening neurological clinical manifestations suggestive of PML; rituximab should be permanently stopped if PML develops.

Reactivation of hepatitis B virus (HBV) has occurred in some patients; fulminant hepatitis, hepatic failure, and fatalities have been reported. Patients at high risk of HBV infection should be screened before starting rituximab therapy and carriers should be monitored for signs of active infection or hepatitis during and for several months after therapy. Rituximab should be stopped if viral hepatitis develops. Other serious infections, which may be fatal, can occur with rituximab.

Haematological adverse effects including lymphopenia, leucopenia, neutropenia, thrombocytopenia, and anaemia have occurred in some patients; effects are usually considered mild and reversible. Complete blood and platelet counts should be monitored regularly. Exacerbation of heart failure and angina pectoris has also been reported, and other cardiac events include arrhythmias and tachycardia. Gastrointestinal disturbances may also occur. Abdominal pain, bowel obstruction, and perforation, in some cases fatal, have been reported with rituximab, usually with combination chemotherapy.

All cross-references refer to entries in Volume A

References.

1. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; **7** (suppl 3): S19–S25.
2. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; **31:** 456–73.
3. Ram R, *et al.* The late adverse events of rituximab therapy—rare but there! *Leuk Lymphoma* 2009; **50:** 1083–95.

Effects on the blood. Late-onset neutropenia (defined as neutropenia occurring 30 days after the last dose) has been reported in patients receiving rituximab.[1] Acute and potentially severe thrombocytopenia associated with rituximab therapy has also been reported occasionally.[2,3] Haemolytic anaemia occurred in a patient given 4 doses of rituximab, plus corticosteroid therapy, for refractory pemphigus vulgaris.[4] Although there was a drop in haemoglobin after the first and second doses of rituximab, concentrations then stabilised; the reticulocyte count remained high throughout treatment.

1. Rios-Fernández R, *et al.* Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. *Br J Dermatol* 2007; **157:** 1271–3.
2. Dhand S, Bahrain H. Rituximab-induced severe acute thrombocytopenia: a case report and review of literature. *Cancer Invest* 2008; **26:** 913–15.
3. Ram R, *et al.* Rituximab-associated acute thrombocytopenia: an underdiagnosed phenomenon. *Am J Hematol* 2009; **84:** 247–50.
4. Li WW, *et al.* Haemolytic anaemia following rituximab treatment in a patient with pemphigus vulgaris. *Br J Dermatol* 2009; **161:** 205–6.

Effects on the eyes. About 20 minutes after the start of a rituximab infusion, a patient developed bilateral conjunctivitis without pain, lachrymation, or discharge. No other clinical manifestations of a hypersensitivity reaction were apparent, and the conjunctivitis resolved spontaneously, about 30 minutes after the end of the infusion. No recurrence was evident with subsequent rituximab therapy.[1]

1. Marinella MA. Bilateral conjunctivitis due to rituximab. *Ann Pharmacother* 2007; **41:** 1318.

Effects on the gastrointestinal tract. In November 2006 the manufacturer noted that 47 cases of bowel obstruction (9 fatal) and 37 cases of gastrointestinal perforation (4 fatal) had been reported in patients given rituximab.[1] Interpretation of data was difficult due to confounding factors; however, a contributory role of rituximab could not be excluded. The mean time to onset of symptoms was 6 days (range 1 to 77 days) for documented perforation. Complaints of abdominal pain, especially early in a course of rituximab treatment, should prompt thorough diagnostic evaluation and treatment.

There have been reports of ulcerative colitis when rituximab was used to deplete B-lymphocytes in Graves' disease[2] and nephrotic syndrome.[3] A severe exacerbation of pre-existing ulcerative colitis occurred in a patient with refractory disease given rituximab as salvage therapy.[4]

1. Roche, Canada. Reports of bowel obstruction and gastrointestinal perforation with RITUXAN (rituximab) (issued 10th November 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/rituxan_3_hpc-cps-eng.php (accessed 30/07/08)
2. El Fassi D, *et al.* Ulcerative colitis following B lymphocyte depletion with rituximab in a patient with Graves' disease. *Gut* 2008; **57:** 714–15.
3. Ardelean DS, *et al.* Severe ulcerative colitis after rituximab therapy. *Pediatrics* 2010; **126:** e243–e246.
4. Goetz M, *et al.* Exacerbation of ulcerative colitis after rituximab salvage therapy. *Inflamm Bowel Dis* 2007; **13:** 1365–8.

Effects on the lungs. Pulmonary reactions have been reported with rituximab use,[1] including reversible interstitial pneumonia[2-4] and interstitial fibrosis.[5] A fatal intra-alveolar haemorrhage in 1 patient was attributed to a hypersensitivity reaction to rituximab;[6] a further case of alveolar haemorrhage associated with interstitial lung disease has been reported.[7]

1. Wagner SA, *et al.* Rituximab-induced interstitial lung disease. *Am J Hematol* 2007; **82:** 916–19.
2. Burton C, *et al.* Interstitial pneumonitis related to rituximab therapy. *N Engl J Med* 2003; **348:** 2690–1.
3. Jullien V, *et al.* Une pneumopathie alvéolo-interstitielle hypoxémiante associée à la prise de rituximab. *Rev Mal Respir* 2004; **21:** 407–10.
4. Swords R, *et al.* Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2004; **77:** 103–4.
5. Leon RJ, *et al.* Rituximab-induced acute pulmonary fibrosis. *Mayo Clin Proc* 2004; **79:** 949, 953.
6. Alexandrescu DT, *et al.* Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. *Leuk Lymphoma* 2004; **45:** 2321–5.
7. Heresi GA, *et al.* Interstitial pneumonitis and alveolar hemorrhage complicating use of rituximab: case report and review of the literature. *Respiration* 2008; **76:** 449–53.

Effects on the nervous system. As of December 2006, the FDA had received a total of 24 reports of progressive multifocal leukoencephalopathy (PML) in patients given rituximab.[1] PML is a fatal demyelinating disease that follows reactivation of latent JC or PK polyomavirus (also known as papovavirus) in the CNS; the virus is present in about 80% of adults. In the first 12 cases reported to the FDA, 10 patients tested positive for the JC virus and 1 had confirmed BK virus. PML presents with rapidly progressive focal neurological deficits including hemiparesis, paraesthesias, visual-field deficits, ataxia, and behavioural and cognitive changes.[2] In a report of 57 cases,[3] 52 patients had haematological malignancies and 5 had auto-immune disorders; all patients had received previous immunosuppressive therapies, including alkylating agents, purine analogues, corticosteroids, or drugs to prevent allogeneic stem cell or solid organ rejection. The case-fatality rate was 90%.

There have also been reports[4,5] of *reversible* posterior leukoencephalopathy syndrome with rituximab. Symptoms have varied between patients, with drowsiness, confusion, hallucinations, nausea, and vomiting occurring in one,[4] and hypertension, headache, blurred vision, and seizures in another.[5]

1. FDA. Rituximab (marketed as Rituxan): progressive multifocal leukoencephalopathy (PML). *FDA Drug Safety Newsletter* 2007; **1:** 3–5. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109158.pdf (accessed 21/07/10)
2. MHRA/CHM. Rituximab and efalizumab: progressive multifocal leukoencephalopathy. *Drug Safety Update* 2008; **2** (5): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON033504&RevisionSelectionMethod=LatestReleased (accessed 07/09/09)
3. Carson KR, *et al.* Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009; **113:** 4834–40.
4. Sánchez-Carteyron A, *et al.* Posterior reversible encephalopathy syndrome after rituximab infusion in neuromyelitis optica. *Neurology* 2010; **74:** 1471–3.
5. Mavragani CP, *et al.* A case of reversible posterior leucoencephalopathy syndrome after rituximab infusion. *Rheumatology (Oxford)* 2004; **43:** 1450–1.

Infection. In addition to progressive multifocal leukoencephalopathy associated with JC or BK virus reactivation (see Effects on the Nervous System, above), rituximab therapy for lymphomas is associated with an increased risk of viral infection or reactivation, notably from hepatitis B and CMV;[1,2] there is less evidence of any increased risk of serious infection in patients treated with rituximab for rheumatoid arthritis.[3]

Hepatitis C reactivation has also been reported in a patient after rituximab was added to the chemotherapy regimen.[4] In another patient, chronic hepatitis was caused by a persistent hepatitis E infection with active viral replication, in a patient receiving maintenance therapy for lymphoma with rituximab.[5]

1. Aksoy S, *et al.* Rituximab-related viral infections in lymphoma patients. *Leuk Lymphoma* 2007; **48:** 1307–12.
2. Aksoy S, *et al.* Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. *Leuk Lymphoma* 2009; **50:** 357–65.
3. Salliot C, *et al.* Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* 2009; **68:** 25–32.
4. Hsieh C-Y, *et al.* Rituximab-induced hepatitis C virus reactivation after spontaneous remission in diffuse large B-cell lymphoma. *J Clin Oncol* 2008; **26:** 2584–6.
5. Ollier L, *et al.* Chronic hepatitis after hepatitis E virus infection in a patient with non-Hodgkin lymphoma taking rituximab. *Ann Intern Med* 2009; **150:** 430–1.

Infusion-related reactions. By November 1998 there had been 74 cases of serious infusion-related reactions to rituximab reported worldwide, with 8 fatal cases.[1] An estimated 12 000 to 14 000 patients had been treated.

The reaction usually occurs within the first 2 hours of infusion and the underlying mechanism is believed to be a severe cytokine release syndrome, with some elements of tumour lysis syndrome.[1-3] In one series of cases tumour necrosis factor-α and interleukin-6 levels were found to peak 90 minutes after the onset of the infusion, and these elevated cytokine levels coincided with infusion-related symptoms.[2] The reaction is usually most marked after the first infusion and subsequent infusions are usually tolerated, emphasising that this is not a true hypersensitivity reaction.[4]

Patients with a high tumour burden (lesions over 10 cm in diameter or more than 500 000 circulating malignant cells/mm^3), a history of pulmonary infiltration or insufficiency, or underlying cardiac disease are believed to be at greater risk of severe reactions.[1,2,4] The UK CSM recommends that premedication with an analgesic and an antihistamine should always be given before rituximab, and corticosteroids should be considered.[1] However, serious or fatal reactions have occurred despite such premedication.[3,4] Alternative infusion schedules and/or combination therapy with chemotherapeutic drugs may be required to decrease the tumour burden before rituximab therapy.[2,4]

1. CSM/MCA. Rituximab (MabThera): serious infusion-related adverse reactions. *Current Problems* 1999; **25:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 26/04/06)
2. Winkler U, *et al.* Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukaemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999; **94:** 2217–24.
3. Lim L-C, *et al.* Fatal cytokine release syndrome with chimeric anti-CD20 monoclonal antibody rituximab in a 71-year-old patient with chronic lymphocytic leukaemia. *J Clin Oncol* 1999; **17:** 1962–3.
4. Byrd JC, *et al.* Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-

related side effects and rapid blood tumor clearance. *J Clin Oncol* 1999; **17:** 791–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rituximab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. Giving 4 cycles of rituximab (with doxorubicin, vincristine, and prednisolone) to a pregnant woman with lymphoma, from 21 weeks of gestation until delivery at 35 weeks, resulted in no adverse effects to either the mother or the infant.[1] In another report, a 31-year-old woman was diagnosed with non-Hodgkin's lymphoma during pregnancy. She received 6 cycles of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Two months after treatment, she spontaneously delivered a premature but healthy infant. Patient and child were clinically assessed every 3 months; the infant's B cells were severely diminished at birth but recovered over 6 to 12 weeks. Rituximab concentrations in both mother and child also decreased as expected. No adverse effects were seen during 16 months of follow-up.[2] In 2 case reports of rituximab use during the first trimester of pregnancy, no significant adverse effects on the neonates were seen; transient granulocytopenia and lymphopenia were reported.[3,4] A 35-year-old woman diagnosed with Burkitt's lymphoma in week 15 of pregnancy received 4 weekly infusions of rituximab starting in week 16, followed by four courses of rituximab with CHOP, and then 2 courses of CHOP alone. In week 41, a healthy infant was delivered by caesarean section. Both the mother and child had very high serum concentrations of rituximab at birth with a complete absence of B cells; rituximab levels in the cord blood serum were three times that in the mother's serum. However, B-cell recovery was reported to be rapid, and no overt infectious complications were seen in the child up to the age of 26 months; growth and developmental status were also normal.[5] Nonetheless, licensed product information advises against rituximab use during pregnancy, given the potential for B-cell depletion in the fetus; women of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months after therapy.

1. Herold M, *et al.* Efficacy and safety of a combined rituximab chemotherapy during pregnancy. *J Clin Oncol* 2001; **19:** 3439.
2. Decker M, *et al.* Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *Lancet Oncol* 2006; **7:** 693–4. Correction. *ibid.*; 706.
3. Kimby E, *et al.* Safety of rituximab therapy during the first trimester of pregnancy: a case history. *Eur J Haematol* 2004; **72:** 292–5.
4. Ojeda-Uribe M, *et al.* Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. *J Perinatol* 2006; **26:** 252–5.
5. Friedrichs B, *et al.* The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* 2006; **91:** 1426–7.

Interactions

Statins. It has been reported that, in a laboratory study, statins significantly decreased rituximab cytotoxicity, suggesting that statins may induce conformational changes in CD20 through cholesterol depletion, resulting in impaired binding of rituximab. While noting that there are no clinical data to support withholding statins during rituximab therapy, the authors advised that it might be prudent to consider doing so.[1] However, a subsequent prospective study[2] found no evidence that concomitant statin therapy in patients with diffuse large B-cell lymphoma or follicular lymphoma had any adverse effect on response to rituximab-based therapy; event-free survival was actually improved in patients with follicular lymphoma who took statins, regardless of other therapy.

1. Rabinowitz I. Interaction between statins and rituximab in non-Hodgkin's lymphoma. *J Clin Oncol* 2008; **26:** 5486.
2. Nowakowski GS, *et al.* Statin use and prognosis in patients with diffuse large B-cell lymphoma and follicular lymphoma in the rituximab era. *J Clin Oncol* 2010; **28:** 412–17.

Pharmacokinetics

The mean peak plasma concentration of rituximab has been reported to increase with successive infusions; however, considerable interindividual variation is seen. Serum concentrations are negatively correlated with tumour burden and the number of circulating B-cells. The mean terminal half-life is about 20 days. Rituximab is bound to B lymphocytes, and is detectable in the body for 3 to 6 months after treatment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: MabThera; ***Austral.***: MabThera; ***Austria***: MabThera; ***Belg.***: MabThera; ***Braz.***: MabThera; ***Canad.***: Rituxan; ***Chile***: MabThera; ***Cz.***: MabThera; ***Denm.***: MabThera; ***Fin.***: MabThera; ***Fr.***: MabThera; ***Ger.***: MabThera; ***Gr.***: MabThera; ***Hong Kong***: MabThera; ***Hung.***: MabThera; ***India***: MabThera; ***Indon.***: MabThera; ***Irl.***: MabThera; ***Israel***: MabThera; ***Ital.***: MabThera; ***Jpn***: Rituxan; ***Malaysia***: MabThera; ***Mex.***: MabThera; ***Neth.***: MabThera; ***Norw.***: MabThera; ***NZ***: MabThera; ***Philipp.***: MabThera; ***Pol.***: MabThera; ***Port.***: MabThera; ***Rus.***: MabThera (Мабтера); ***S.Afr.***: MabThera; ***Singapore***: MabThera; ***Spain***: MabThera; ***Swed.***: MabThera; ***Switz.***: MabThera; ***Thai.***: MabThera; ***Turk.***: MabThera; ***UK***: MabThera; ***Ukr.***: MabThera (Мабтера); ***USA***: Rituxan; ***Venez.***: MabThera.

Romidepsin *(USAN, rINN)*

Depsipeptide; FK-228; FR-901228; NSC-630176; Romidepsina; Romidepsine; Romidepsinum; Ромидепсин.

(1*S*,4*S*,10*S*,16*E*,21*R*)-7-[(2*Z*)Ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone.

$C_{24}H_{36}N_4O_6S_2$=540.7

CAS — 128517-07-7.

ATC — L01XX39.

ATC Vet — QL01XX39.

UNII — CX3T89XQBK.

NOTE. The name Chromadax has been used as a trade mark for romidepsin.

Uses and Administration

Romidepsin is a histone deacetylase inhibitor used for the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p. 698.3) and peripheral T-cell lymphoma. It is given intravenously; the reconstituted solution is diluted in 500 mL of sodium chloride 0.9% and infused over 4 hours. The initial dose is romidepsin 14 mg/m² on days 1, 8, and 15 of a 28-day cycle. Treatment should be withheld for severe haematological toxicity or for moderate or severe non-haematological toxicity, except alopecia, see below. Romidepsin may be continued for as long as there is benefit from treatment and toxicity allows.

Romidepsin is under investigation in the treatment of solid tumours.

References.

1. Piekarz RL, *et al.* Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2009; **27:** 5410–17.
2. Whittaker SJ, *et al.* Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* 201 0; **28:** 4485–91.
3. Piekarz RL, *et al.* Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood* 2011; **117:** 5827–34.
4. Yang LPH. Romidepsin: in the treatment of T-cell lymphoma. *Drugs* 2011; **71:** 1469–80.
5. Coiffier B, *et al.* Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 2012; **30:** 631–6.

Administration in subsequent cycles. Romidepsin treatment should be withheld for severe haematological toxicity or for moderate or severe non-haematological toxicity, except alopecia.

- For grade 3 or 4 neutropenia or thrombocytopenia, romidepsin may be restarted at 14 mg/m² when the cytopenia returns to an absolute neutrophil count of 1500 cells/mm³ and/or a platelet count of 75000 cells/mm³
- For grade 4 febrile neutropenia or thrombocytopenia that requires a platelet transfusion, treatment should be delayed until the cytopenia has returned to baseline measurements or grade 1 or less, and the romidepsin dose permanently reduced to 10 mg/m²
- For grade 2 or 3 non-haematological toxicity, romidepsin may be restarted at 14 mg/m² when toxicity has returned to baseline measurements or grade 1 or less
- For grade 4 non-haematological toxicity, or if grade 3 toxicity recurs, treatment should be delayed until toxicity has returned to baseline measurements or grade 1 or less, and the romidepsin dose permanently reduced to 10 mg/m²

Romidepsin treatment should be stopped if grade 3 or 4 non-haematological toxicities recur after dose reduction.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Romidepsin can cause haematological adverse effects such as thrombocytopenia, leucopenia, and anaemia; blood counts should be monitored during treatment and the dose adjusted if necessary, see above. Arrhythmias, QT prolongation, and other ECG changes have also been noted during romidepsin treatment. Potassium and magnesium concentrations should be within the normal range before starting treatment, and ECG and electrolyte monitoring should be considered at baseline and periodically during treatment in patients with congenital long QT syndrome, a history of cardiovascular disease, or those taking antiarrhythmics or medicines that prolong the QT interval. Electrolyte disturbances such as hypokalaemia and hypophosphataemia have also been reported during treatment. Hyperuricaemia can occur, and patients with advanced-stage disease or high tumour burden should be monitored for the development of tumour lysis syndrome.

Gastrointestinal disturbances, fatigue, fever, and infections are common adverse effects of romidepsin. Other reported effects include oedema, dyspnoea, taste disturbances, hypotension, dermatitis, pruritus, increases in liver enzyme concentrations, hypoalbuminaemia, and hyperglycaemia. There have been isolated cases of cardiopulmonary adverse events and acute renal failure, including fatalities.

Due to a lack of data romidepsin should be used with caution in patients with end-stage renal disease or with moderate or severe hepatic impairment.

Interactions

Romidepsin is metabolised by the cytochrome P450 isoenzyme CYP3A4 and its concentration may be affected by CYP3A4 inhibitors or inducers given at the same time. Strong CYP3A4 inhibitors and inducers should be avoided during romidepsin treatment, and caution is advised if moderate CYP3A4 inhibitors are given. Romidepsin is also a substrate of P-glycoprotein, and caution is advised if it is given with P-glycoprotein inhibitors as increased concentrations of romidepsin are likely.

A prolonged prothrombin time (PT) and an elevated international normalised ratio (INR) has been reported in a patient given romidepsin while taking warfarin; monitoring of these parameters is advised if romidepsin is to be given with a coumarin anticoagulant.

Pharmacokinetics

Romidepsin is highly bound to plasma proteins (about 93%). It is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP3A5, CYP1A1, CYP2B6, and CYP2C19 play a minor role. During usual intravenous dosing, the terminal half-life is about 3 hours.

References.

1. Klimek VM, *et al.* Tolerability, pharmacodynamics, and pharmacokinetics studies of depsipeptide (romidepsin) in patients with acute myelogenous leukemia or advanced myelodysplastic syndromes. *Clin Cancer Res* 2008; **14:** 826–32.
2. Woo S, *et al.* Population pharmacokinetics of romidepsin in patients with cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma. *Clin Cancer Res* 2009; **15:** 1496–1503.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Istodax.

Rostaporfin *(USAN, rINN)*

Rostaporfina; Rostaporfine; Rostaporfinum; SnET2; Tin Ethyl Etiopurpurin; Tin etiopurpurin dichloride; Ростапорфин.

(*OC*-6-13)-Dichloro[ethyl (18*RS*,19*SR*)-3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato (2-)-N^{23},N^{24},N^{25},N^{26}]tin.

$C_{37}H_{42}Cl_2N_4O_2Sn$=764.4

CAS — 284041-10-7; 114494-17-6.

UNII — 466G63QE7G.

NOTE. The names Photrex and Purlytin have been used as trade marks for rostaporfin.

Profile

Rostaporfin is a photosensitiser that is under investigation in the photodynamic therapy of neovascular (wet) age-related macular degeneration (p. 880.2). It has also been investigated for photodynamic therapy of malignant neoplasms.

Ruxolitinib Phosphate *(USAN, rINN/M)*

Fosfato de ruxolitinib; INC-424 (ruxolitinib); INCB-018424 salt; Ruxolitinib, Phosphate de; Ruxolitinibi Phosphas; Руксолитиниба Фосфат.

(3*R*)-3-Cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile phosphate (1:1).

$C_{17}H_{18}N_6.H_3O_4P$=404.4

CAS — 941678-49-5 (ruxolitinib); 1092939-17-7 (ruxolitinib phosphate).

UNII — 436LRU32H5.

Uses and Administration

Ruxolitinib is an inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2, and is used in the treatment of intermediate- or high-risk myelofibrosis (p. 856.1). It is

given orally as the phosphate, but doses are expressed in terms of the base; 13.2 mg of ruxolitinib phosphate is equivalent to about 10 mg of ruxolitinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The recommended starting dose for myelofibrosis is based on platelet count:
- > 200 000 cells/mm³: 20 mg orally twice daily
- 100 000 to 200 000 cells/mm³: 15 mg orally twice daily

The dose is adjusted according to efficacy and tolerability. If efficacy is insufficient, and providing platelet and neutrophil counts are adequate, the daily dose may be increased in 10-mg increments to a maximum of 25 mg twice daily. Doses should not be increased in the first 4 weeks of treatment and, after that, not more often than every 2 weeks. Treatment should be stopped after 6 months if there has been no reduction in spleen size or improvement in symptoms.

Doses should be reduced if platelet counts fall, to avoid thrombocytopenia (see Administration in Toxicity, below). If ruxolitinib is stopped for reasons other than thrombocytopenia, the dose may be reduced gradually; a reduction of 10 mg each week has been suggested. Doses should also be reduced in patients with hepatic or renal impairment (see below).

If a potent cytochrome P450 isoenzyme inhibitor must also be used, ruxolitinib should be started at a dose of 10 mg twice daily in patients with a platelet count of ≥100 000 cells/mm³; those with a count below this should avoid ruxolitinib altogether.

Ruxolitinib is under investigation in the treatment of polycythaemia vera.

Administration in hepatic impairment. A starting dose of ruxolitinib 10 mg orally twice daily is suggested for patients with hepatic impairment and a platelet count of 100 000 to 150 000 cells/mm³. Ruxolitinib should be avoided in patients with hepatic impairment and lower platelet counts.

Administration in renal impairment. The dose of ruxolitinib should be reduced in patients with renal impairment. Starting doses (given below) have been recommended based on platelet count and renal function. Further dose adjustment should be made according to response.

Patients with renal impairment that is moderate (creatinine clearance 30 to 59 mL/min) or severe (15 to 29 mL/min):
- platelet count 100 000 to 150 000 cells/mm³: 10 mg orally twice daily
- platelet count < 100 000 cells/mm³: avoid ruxolitinib

Ruxolitinib should not be given to patients with end-stage renal disease not requiring dialysis (creatinine clearance < 15 mL/min).

Patients with end-stage renal disease on dialysis:
- platelet count > 200 000 cells/mm³: 20 mg orally
- platelet count 100 000 to 200 000 cells/mm³: 15 mg orally
- subsequent doses should be given on dialysis days, after the dialysis session

Administration in toxicity. The dose of ruxolitinib may need to be reduced to avoid thrombocytopenia during therapy. Adjustments are made in relation to the platelet count and the dose of ruxolitinib at the time of platelet decline.
- platelets 100 000 to < 125 000 cells/mm³: the dose should be no more than 15 mg orally twice daily (or 20 mg twice daily if the dose at the time of platelet decline was 25 mg twice daily)
- platelets 75 000 to < 100 000 cells/mm³: the dose should be no more than 10 mg orally twice daily
- platelets 50 000 to < 75 000 cells/mm³: the dose should be no more than 5 mg orally twice daily
- platelets < 50 000 cells/mm³: withhold ruxolitinib

If ruxolitinib treatment has been interrupted because of thrombocytopenia, it may be restarted after the platelet count rises to an acceptable level above 50 000 cells/mm³. The dose used should be at least 5 mg twice daily below the dose at interruption, and no more than the following maximum recommended doses:
- platelets ≥ 125 000 cells/mm³: maximum 20 mg orally twice daily
- platelets 100 000 to < 125 000 cells/mm³: maximum 15 mg orally twice daily
- platelets 75 000 to < 100 000 cells/mm³: maximum 10 mg orally twice daily for at least 2 weeks, which may be increased to 15 mg twice daily if stable
- platelets 50 000 to < 75 000 cells/mm³: 5 mg orally twice daily for at least 2 weeks, which may be increased to 10 mg twice daily if stable
- platelets < 50 000 cells/mm³: continue to withhold ruxolitinib

Myelofibrosis. An early phase study of ruxolitinib in 153 patients reported improvements in signs and symptoms of advanced myelofibrosis[1] (p. 695.1). However, follow-up over 3 years in 51 of these patients found that treatment had been stopped in 40% because of disease progression or loss or lack of response, and in 34% because of toxicity with or without disease progression or lack of response.[2]

1. Verstovsek S, *et al*. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med* 2010; **363:** 1117–27.
2. Tefferi A, *et al*. Long-term outcome of treatment with ruxolitinib in myelofibrosis. *N Engl J Med* 2011; **365:** 1455–7.

Adverse Effects, Treatment, and Precautions

The most common adverse effect of ruxolitinib phosphate is myelosuppression, which is manifest as thrombocytopenia and anaemia to some degree in most patients while neutropenia occurs less frequently. These effects are dose-related and generally managed by dose reduction or withholding treatment. Complete blood counts and platelet counts should be measured before starting ruxolitinib, every 2 to 4 weeks until doses are stabilised, then as clinically indicated.

Bruising is common in patients given ruxolitinib; petechiae, ecchymosis, contusion, haematoma, and injection-site haematoma have all been reported. Other adverse effects include dizziness, headache, weight gain, and flatulence. Low-grade elevations of alanine and aspartate transaminases and cholesterol have also been reported. Patients given ruxolitinib are at risk of developing serious infection, and any active infection should be treated before starting ruxolitinib.

Dose reductions are recommended in patients with hepatic or renal impairment.

Withdrawal. Withdrawal effects after stopping ruxolitinib have been described in 5 patients being treated for myelofibrosis.[1] Acute relapse of symptoms and splenomegaly were accompanied by other signs and symptoms that included worsening of cytopenias, respiratory distress, pleural and pericardial effusion, and syndromes similar to septic shock and disseminated intravascular coagulation. The effects generally started within days after ruxolitinib was stopped because of loss of treatment benefit or adverse effects, even after the dose had been tapered in some cases.

1. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. *Mayo Clin Proc* 2011; **86:** 1188–91.

Interactions

Ruxolitinib phosphate is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4 can increase the concentrations and prolong the half-life of ruxolitinib. The dose of ruxolitinib should be adjusted when it is used with potent inhibitors such as ketoconazole (see Uses and Administration, p. 855.3). No dose adjustment is considered necessary in general when ruxolitinib is given with mild or moderate inhibitors such as erythromycin.

Inducers of CYP3A4 such as rifampicin can reduce concentrations of ruxolitinib but with an associated increase in exposure to its active metabolites. Patients should be closely monitored and the dose of ruxolitinib adjusted as necessary.

Pharmacokinetics

Ruxolitinib phosphate is well absorbed from the gastrointestinal tract, with a peak plasma concentration occurring 1 to 2 hours after an oral dose. It is about 97% bound to plasma proteins, mainly albumin. Ruxolitinib is eliminated by metabolism, mainly through the cytochrome P450 isoenzyme CYP3A4. There are several active metabolites that together contribute 18% of the overall pharmacodynamics of ruxolitinib. About 74% of a dose is excreted in the urine and about 22% via the faeces. The mean elimination half-life of ruxolitinib is about 3 hours, but that of ruxolitinib plus its metabolites is about 5.8 hours.

References.
1. Shilling AD, *et al*. Metabolism, excretion, and pharmacokinetics of [^{14}C] INCB018424, a selective Janus tyrosine kinase 1/2 inhibitor, in humans. *Drug Metab Dispos* 2010; **38:** 2023–31.
2. Shi JG, *et al*. The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers. *J Clin Pharmacol* 2011; **51:** 1644–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Jakavi; ***Norw.***: Jakavi; ***Switz.***: Jakavi; ***UK***: Jakavi; ***USA***: Jakafi.

Sabarubicin *(rINN)*

MEN-10755; Sabarubicina; Sabarubicine; Sabarubicinum; Сабарубицин.

(7*S*,9*S*)-7-[[4-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]oxy)-6,9,11-trihydroxy-9-(hydroxyacetyl)-7,8,9,10-tetrahydrotetracene-5,12-dione.

$C_{32}H_{37}NO_{13}$=643.6

CAS — 211100-13-9.

UNII — XS499WOZ93.

Profile

Sabarubicin, an anthracycline, is an analogue of doxorubicin (p. 782.3). It acts as a potent topoisomerase II inhibitor and is under investigation for the treatment of various solid tumours, such as cancers of the lung, ovary, breast, and prostate. Myelosuppression is the main adverse effect.

References.
1. Jones K. MEN-10755. Menarini. *Curr Opin Investig Drugs* 2003; **4:** 1473–8.
2. Caponigro F, *et al*. A phase II study of sabarubicin (MEN-10755) as second line therapy in patients with locally advanced or metastatic platinum/taxane resistant ovarian cancer. *Invest New Drugs* 2005; **23:** 85–9.
3. Fiedler W, *et al*. A study from the EORTC new drug development group: open label phase II study of sabarubicin (MEN-10755) in patients with progressive hormone refractory prostate cancer. *Eur J Cancer* 2006; **42:** 200–204.

Sapacitabine *(USAN, rINN)*

CS-682; CYC-682; Sapacitabina; Sapacitabinum; Сапацитабин.

N-[1-(2-Cyano-2-deoxy-β-D-arabinofuranosyl)-2-oxo-1,2-dihydropyrimidin-4-yl]hexadecanamide.

$C_{26}H_{42}N_4O_5$=490.6

CAS — 151823-14-2.

UNII — W335P73C3L.

Profile

Sapacitabine is an oral nucleoside analogue that is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndromes, cutaneous T-cell lymphoma, and lung cancer.

References.
1. Delaunoit T, *et al*. A phase I clinical and pharmacokinetic study of CS-682 administered orally in advanced malignant solid tumors. *Invest New Drugs* 2006; **24:** 327–33.
2. Kantarjian H, *et al*. Phase I clinical and pharmacokinetic study of oral sapacitabine in patients with acute leukemia and myelodysplastic syndrome. *J Clin Oncol* 2010; **28:** 285–91.

Satraplatin *(USAN, rINN)*

BMS-182751; BMY-45594; JM-216; Satraplatine; Satraplatino; Satraplatinum; Сатраплатин.

(*OC*-6-43)-Bis(acetato)amminedichloro(cyclohexylamine)platinum.

$C_{10}H_{22}Cl_2N_2O_4Pt$=500.3

CAS — 129580-63-8.

ATC — L01XA04.

ATC Vet — QL01XA04.

UNII — 8D7B37T28G.

NOTE. The name Orplatna has been used as a trade mark for satraplatin.

Profile

Satraplatin is an analogue of cisplatin (p. 766.1) with generally similar properties, but which is well absorbed after oral dosage. It has been investigated for its antineoplastic properties in the treatment of prostate cancer and other solid tumours. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

References.
1. Kelland LR. An update on satraplatin: the first orally available platinum anticancer drug. *Expert Opin Invest Drugs* 2000; **9:** 1373–82.
2. Vouillamoz-Lorenz S, *et al*. Pharmacokinetics of satraplatin (JM216), an oral platinum (IV) complex under daily oral administration for 5 or 14 days. *Anticancer Res* 2003; **23:** 2757–65.
3. Sternberg CN, *et al*. Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology* 2005; **68:** 2–9.
4. Sternberg CN. Satraplatin in the treatment of hormone-refractory prostate cancer. *BJU Int* 2005; **96:** 990–4.
5. McKeage MJ. Satraplatin in hormone-refractory prostate cancer and other tumour types: pharmacological properties and clinical evaluation. *Drugs* 2007; **67:** 859–69.
6. Ricart AD, *et al*. Satraplatin, an oral platinum, administered on a five-day every-five-week schedule: a pharmacokinetic and food effect study. *Clin Cancer Res* 2009; **15:** 3866–71.
7. Sternberg CN, *et al*. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2009; **27:** 5431–8.
8. Bhargava A, Vaishampayan UN. Satraplatin: leading the new generation of oral platinum agents. *Expert Opin Invest Drugs* 2009; **18:** 1787–97.

Seocalcitol *(BAN, rINN)*

CB-1089; EB-1089; Séocalcitol; Seocalcitolum; Сеокальцитол.
(5*Z*,7*E*,22*E*,24*E*)-24a,26a,27a-Trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1α,3β,25-triol.
$C_{30}H_{46}O_3$=454.7
CAS — 134404-52-7.
UNII — Q0OZ0D9223.

Profile

Seocalcitol is a vitamin D analogue that has been investigated for the treatment of hepatocellular carcinoma and prostate cancer.

Siplizumab *(USAN, rINN)*

Medi-507; Siplizumabum; Сиплизумаб.
CAS — 288392-69-8.

Profile

Siplizumab is a humanised anti-CD2 monoclonal antibody under investigation for the treatment of non-Hodgkin's lymphoma and psoriasis, as well as for its immunomodulatory effects after transplantation.

References.

1. Pruett TL, *et al.* Safety profile, pharmacokinetics, and pharmacodynamics of siplizumab, a humanized anti-CD2 monoclonal antibody, in renal allograft recipients. *Transplant Proc* 2009; **41:** 3655–61.
2. Adkins D, *et al.* Safety profile and clinical outcomes in a phase I, placebo-controlled study of siplizumab in acute graft-versus-host disease. *Transplantation* 2009; **88:** 198–202.
3. O'Mahony D, *et al.* EBV-related lymphoproliferative disease complicating therapy with the anti-CD2 monoclonal antibody, siplizumab, in patients with T-cell malignancies. *Clin Cancer Res* 2009; **15:** 2514–22.
4. Langley RG, *et al.* Safety profile of intravenous and subcutaneous siplizumab, an anti-CD2 monoclonal antibody, for the treatment of plaque psoriasis: results of two randomized, double-blind, placebo-controlled studies. *Int J Dermatol* 2010; **49:** 818–28.
5. Brochstein JA, *et al.* Phase-1 study of siplizumab in the treatment of pediatric patients with at least grade II newly diagnosed acute graft-versus-host disease. *Pediatr Transplant* 2010; **14:** 233–41.

Sipuleucel-T *(USAN)*

APC-8015.
CAS — 917381-47-6.
UNII — 8Q622VDR18.

Pharmacopoeias. In *US.*

USP 36: (Sipuleucel-T). The active components of sipuleucel-T are autologous antigen presenting cells (APCs) and a recombinant protein, PAP-GM-CSF that consists of human prostatic acid phosphatase (PAP) fused through the *C*-terminus to the *N*-terminus of human granulocyte-macrophage colony-stimulating factor (GM-CSF) by a Gly-Ser linker. It is prepared using a patient's own peripheral blood mononuclear cells. Store at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Sipuleucel-T is a personalised cancer vaccine (p. 757.3) prepared by combining a recombinant human fusion protein with antigen-presenting cells isolated from the patient's blood. It is used in the treatment of metastatic, hormone-refractory prostate cancer (p. 712.3). The patient's peripheral blood cells are sampled by leucapheresis about 3 days before the scheduled dose and sent for combination with the protein. The resulting suspension is given as 3 infusions, at intervals of about 2 weeks. Doses are given intravenously over 60 minutes; an in-line filter should not be used. Premedication is recommended (see below), and the infusion rate may be decreased or the infusion stopped if an infusion reaction occurs.

References.

1. Patel PH, Kockler DR. Sipuleucel-T: a vaccine for metastatic, asymptomatic, androgen-independent prostate cancer. *Ann Pharmacother* 2008; **42:** 91–8.
2. Higano CS, *et al.* Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009; **115:** 3670–9.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions have occurred frequently with sipuleucel-T, including fever, chills, dyspnoea, bronchospasm, nausea, vomiting, fatigue, asthenia, dizziness, headache, muscle ache, hypertension, and tachycardia. Patients with cardiac or pulmonary conditions should be closely monitored. Oral premedication with paracetamol and an antihistamine is recommended, about 30 minutes before infusion. If an infusion reaction occurs, the infusion rate may be decreased, or the infusion stopped depending on the severity of the reaction. Supportive care should also be given.

Cerebrovascular adverse effects have also been reported, such as haemorrhagic and ischaemic strokes. There have been isolated cases of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumour flare. Other possible adverse effects (some of which may be associated with the accompanying leucapheresis procedure) include pain, haematuria, anaemia, muscle spasms, rash, tremor, paraesthesia, citrate toxicity, gastrointestinal disturbances, peripheral oedema, cough, and respiratory-tract and urinary-tract infections. Some patients who required a central venous catheter for treatment with sipuleucel-T developed infections, including sepsis.

Sipuleucel-T is a personalised treatment, and is only suitable for autologous use. It is not routinely tested for transmissible infectious diseases, and healthcare workers should observe handling precautions. Use with immunosuppressants or chemotherapy has not been studied, and caution is advised, as sipuleucel-T is designed to stimulate the immune system. Consideration should be given to stopping or reducing immunosuppressant therapy, if appropriate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Provenge.

Sizofiran *(rINN)*

Schizophyllan; Sizofirán; Sizofiranum; Сизофиран.
Poly[3→-(*O*-β-D-glucopyranosyl-(1→3)-*O*-[β-D-glucopyranosyl-(1→6)]-*O*-β-D-glucopyranosyl-(1→3)-*O*-β-D-glucopyranosyl)→1].
$(C_{24}H_{40}O_{20})_n$
CAS — 9050-67-3.

Profile

Sizofiran is a polysaccharide obtained from cultures of the basidiomycete fungus *Schizophyllum commune.* It is reported to have antineoplastic and immunomodulating activity and is given with radiotherapy in malignant neoplasms of the cervix (p. 704.2). It is given by intramuscular injection in usual doses of 40 mg weekly. It has also been tried with chemotherapy or radiotherapy in other malignant neoplasms. Hypersensitivity reactions, including anaphylactoid shock, may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Sonifilan.

Sobuzoxane *(rINN)*

MST-16; Sobuzoxano; Sobuzoxanum; Собузоксан.
4,4′-Ethylenebis[1-(hydroxymethyl)-2,6-piperazinedione] bis(isobutyl carbonate).
$C_{22}H_{34}N_4O_{10}$=514.5
CAS — 98631-95-9.
UNII — R1308VH37P.

Profile

Sobuzoxane is an orally active inhibitor of topoisomerase II that is used for its antineoplastic properties in the treatment of non-Hodgkin's lymphomas and adult T-cell leukaemia/lymphoma. Adverse effects include myelosuppression, bleeding tendency, renal and hepatic dysfunction, gastrointestinal disturbances, alopecia, headache, and fever.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Okamoto T, *et al.* Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin's lymphoma. *Acta Haematol (Basel)* 2000; **104:** 128–30.
2. Inoue Y, *et al.* Durable remission by sobuzoxane in an HIV-seronegative patient with human herpesvirus 8-negative primary effusion lymphoma. *Int J Hematol* 2004; **79:** 271–5.
3. Swift LP, *et al.* The cardio-protecting agent and topoisomerase II catalytic inhibitor sobuzoxane enhances doxorubicin-DNA adduct mediated cytotoxicity. *Cancer Chemother Pharmacol* 2008; **61:** 739–49.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Perazolin.

Sorafenib *(BAN, USAN, rINN)*

BAY-43-9006; Sorafénib; Sorafenibum; Сорафениб.
4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide.
$C_{21}H_{16}ClF_3N_4O_3$=464.8
CAS — 284461-73-0.
ATC — L01XE05.
ATC Vet — QL01XE05.
UNII — 9ZOQ3TZI87.

Sorafenib Tosilate *(BANM, rINNM)*

BAY-54-9085; Sorafénib, Tosilate de; Sorafenib, tosilato de; Sorafenib Tosylate (USAN); Sorafenibi Tosilas; Сорафениба Тозилат.
4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.
$C_{21}H_{16}ClF_3N_4O_3$, $C_7H_8O_3S$=637.0
CAS — 475207-59-1.
ATC — L01XE05.
ATC Vet — QL01XE05.
UNII — 5T62Q3B36J.

Uses and Administration

Sorafenib is an inhibitor of multiple intracellular and cell surface kinases thought to be involved in angiogenesis. It is given orally as the tosilate but doses are expressed in terms of the base; sorafenib tosilate 274 mg is equivalent to about 200 mg of sorafenib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Sorafenib is used in the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. The recommended oral dose is 400 mg twice daily, given at least 1 hour before or 2 hours after food. Treatment is continued until no clinical benefit is seen or until unacceptable toxicity occurs. Doses are reduced to 400 mg once daily if toxicity occurs; further reduction to a single dose of 400 mg every other day may be necessary.

Sorafenib is under investigation for the treatment of locally unresectable and metastatic melanoma.

References.

1. Rini BI. Sorafenib. *Expert Opin Pharmacother* 2006; **7:** 453–61.
2. Escudier B, *et al.* TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356:** 125–34. Correction. *ibid.*; **357:** 203.
3. McKeage K, Wagstaff AJ. Sorafenib: in advanced renal cancer. *Drugs* 2007; **67:** 475–83.
4. Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. *Pharmacotherapy* 2007; **27:** 1125–44.
5. Takimoto CH, Awada A. Safety and anti-tumor activity of sorafenib (Nexavar) in combination with other anti-cancer agents: a review of clinical trials. *Cancer Chemother Pharmacol* 2008; **61:** 535–48.
6. Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am J Health-Syst Pharm* 2008; **65:** 123–31.
7. Keating GM, Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma. *Drugs* 2009; **69:** 223–40.
8. Escudier B, *et al.* TARGET Study Group. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009; **27:** 3312–18.
9. Merseburger AS, *et al.* Sorafenib reveals efficacy in sequential treatment of metastatic renal cell cancer. *Expert Rev Anticancer Ther* 2009; **9:** 1429–34.
10. Hasskarl J. Sorafenib. *Recent Results Cancer Res* 2010; **184:** 61–70.

Administration in hepatic or renal impairment. Sorafenib is mainly metabolised in the liver. Hepatic impairment might reduce exposure to sorafenib. However, exposure is comparable in patients with mild or moderate (Child-Pugh A and B) impairment to that in patients with normal hepatic function. Licensed product information therefore states that no dose adjustment is needed in patients with mild to moderate impairment. No data are available on patients with severe (Child-Pugh C) hepatic impairment.

Licensed product information states that no dose adjustment is needed in patients with mild, moderate, or severe renal impairment, but that no data are available for patients on dialysis.

A study[1] involving patients with varying degrees of hepatic or renal impairment recommended the following empirical starting doses of oral sorafenib, based on tolerability and the development of dose-limiting toxicity in patient cohorts with hepatic impairment:

- mild hepatic dysfunction (bilirubin between upper limit of normal (ULN) and 1.5 X ULN and/or AST > ULN): a standard dose of 400 mg twice daily
- moderate hepatic dysfunction (bilirubin between 1.5 and 3 X ULN, any value of AST): 200 mg twice daily
- severe dysfunction (bilirubin over 3 X ULN, any value of AST): patients were unable to tolerate even 200 mg every third day; however, a separate cohort defined as having very severe dysfunction (albumin less than 25 micro-

grams/mL and any values of bilirubin and AST) were able to tolerate 200 mg daily

Based on the patient cohorts with renal impairment, the following empirical recommendations for initial dose were made:

- mild renal impairment (creatinine clearance (CC) between 59 and 40 mL/minute): the standard dose of 400 mg twice daily
- moderate renal impairment (CC between 39 and 20 mL/minute): 200 mg twice daily
- severe renal impairment (CC less than 20 mL/minute): a dose could not be defined due to low patient numbers enrolled in this cohort
- patients on haemodialysis: 200 mg daily

1. Miller AA, *et al.* Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Oncol* 2009; **27:** 1800–5.

Age-related macular degeneration. Two patients with recurrent exudative age-related macular degeneration (AMD; p. 880.2) elected to have oral sorafenib added to their treatment in an attempt to decrease the number of intra-ocular injections; they were treated with 200 mg three times weekly. Vision stabilised or improved in both patients, and neither patient developed serious adverse effects. Although oral sorafenib is not licensed for AMD, the authors suggested that further study of this regimen for refractory or recurrent exudative AMD was warranted.[1]

1. Diago T, *et al.* Ranibizumab combined with low-dose sorafenib for exudative age-related macular degeneration. *Mayo Clin Proc* 2008; **83:** 231–4.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Diarrhoea and dermatological toxicities such as palmar-plantar syndrome and rash are the most common adverse effects with sorafenib. Treatment may include topical therapies, or dose adjustment, or temporary interruption of sorafenib. Congestive heart failure, cardiac ischaemia, and myocardial infarction have been reported with sorafenib, and treatment should be interrupted or stopped in patients who develop ischaemia and/or infarction. Mild to moderate hypertension can occur, which may be manageable with antihypertensive therapy, but severe or persistent hypertension or hypertensive crisis despite treatment, may force sorafenib to be stopped. Blood pressure should be regularly monitored. There is an increased risk of bleeding with sorafenib and fatalities have been reported; if severe enough to need intervention, the drug should be permanently stopped. Leucopenia, lymphopenia, anaemia, neutropenia, and thrombocytopenia are common. Hypophosphataemia and transient disturbances in liver function tests can occur. Elevations in lipase and amylase concentrations are very common. Fatal hepatitis has been reported. Pancreatitis can occur. Renal failure is common. Other adverse effects include alopecia, pruritus, dry skin, erythema, acne, flushing, exfoliative dermatitis, hoarseness, gastrointestinal disturbances, arthralgia, myalgia, asthenia, pain, and peripheral neuropathy. Tinnitus, depression, and erectile dysfunction are often reported, as are pyrexia, flu-like illness, and weight decrease. Gastrointestinal perforation has been reported rarely; therapy should be stopped if it occurs. Reversible posterior leukoencephalopathy has also occurred rarely, as have symptoms suggestive of interstitial lung disease, including pneumonitis and acute respiratory distress syndrome. Other uncommon adverse events include hypersensitivity reactions, changes in thyroid function, hyponatraemia, gynaecomastia, rhinorrhoea, Stevens-Johnson syndrome, and squamous cell carcinoma of the skin. Angioedema and radiation-recall dermatitis can also occur.

References.

1. Robert C, *et al.* Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; **6:** 491–500.
2. Strumberg D, *et al.* Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? *Eur J Cancer* 2006; **42:** 548–56.
3. Veronese ML, *et al.* Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006; **24:** 1363–9.
4. Yang C-H, *et al.* Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008; **158:** 592–6.
5. Lipworth AD, *et al.* Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology* 2009; **77:** 257–71.
6. Lee WJ, *et al.* Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Br J Dermatol* 2009; **161:** 1045–51.

Effects on the blood. Reversible erythrocytosis occurred in 5 patients treated with sorafenib or sunitinib; onset was relatively rapid over 1 to 2 weeks, reaching a peak at 4 to 9 weeks after the start of tyrosine kinase inhibitor treatment.[1]

1. Alexandrescu DT, *et al.* Secondary erythrocytosis produced by the tyrosine kinase inhibitors sunitinib and sorafenib. *J Clin Oncol* 2008; **26:** 4047–8.

Effects on the cardiovascular system. A meta-analysis[1] of data involving 4599 patients indicated that 23.4% of those given *sorafenib* developed hypertension; about 5% of sorafenib-treated patients developed severe (grade 3 or 4) hypertension. This represented a relative risk of developing high blood pressure 6.1 times that of patients not given sorafenib. Hypertension may also develop with other angiogenesis inhibitors; relative risk has been shown to be similar with high-dose *bevacizumab*, and there is evidence of a slightly smaller risk (incidence of hypertension 22.5%, relative risk 3.89) with *sunitinib*.

An observational study[2] in patients taking either sorafenib or sunitinib found that about a third of patients had a cardiovascular event; median duration of tyrosine kinase inhibitor therapy at event occurrence was 8 weeks. Some patients were asymptomatic, with biochemical signs and ECG changes only, whereas others had mild to life-threatening clinical symptoms. All symptomatic and some asymptomatic patients received cardiovascular treatment, recovered, and were considered eligible to resume treatment with the tyrosine kinase inhibitor. The authors considered cardiovascular monitoring as well as prophylactic treatment to be essential; this might allow for continued treatment of the underlying cancer. It was also noted that cardiotoxicity might mimic disease progression.

For reference to the incidence of cardiotoxicity with *lapatinib* see Effects on the Heart, p. 815.3.

1. Wu S, *et al.* Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol* 2008; **9:** 117–23.
2. Schmidinger M, *et al.* Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2008; **26:** 5204–12.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sorafenib as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3. Sorafenib is metabolised by the cytochrome P450 isoenzyme CYP3A4. Rifampicin can reduce exposure to sorafenib. Other inducers of this enzyme (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, and phenytoin) may also reduce blood concentrations of sorafenib. However, ketoconazole did not alter exposure to sorafenib and other drugs that inhibit CYP3A4 are considered unlikely to alter the metabolism of sorafenib.

In vitro studies have indicated that sorafenib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP2D6, but use of sorafenib with midazolam, or omeprazole, or dextromethorphan did not alter the exposure to any of these drugs; interactions with drugs that are substrates of these enzymes are considered unlikely.

Sorafenib inhibits the cytochrome P450 isoenzyme CYP2C9 *in vitro*, and may increase concentrations of its substrates. Use with warfarin may affect the INR, see Antineoplastics, under Warfarin, p. 1532.2.

Sorafenib also inhibits the isoenzymes CYP2B6 and CYP2C8 *in vitro*, and drug interactions with substrates of these may occur.

Sorafenib may increase exposure to docetaxel, doxorubicin, and irinotecan; variable effects on fluorouracil have been reported. Variable effects have also been seen with paclitaxel; use of continuous sorafenib with paclitaxel and carboplatin caused an increase in sorafenib exposure, an increase in paclitaxel exposure, and an increase in the exposure to 6α-hydroxypaclitaxel, while carboplatin pharmacokinetics were unaffected. Licensed product information states that the clinical significance of these increases is unknown. However, when sorafenib was given 2 days before, and then on the same day as carboplatin plus paclitaxel, it had no significant effect on the pharmacokinetics of paclitaxel; licensed product information advocates no dose adjustments when these 3 drugs are given in this way. Higher mortality was seen in a subset of patients with squamous cell lung carcinoma treated with sorafenib, carboplatin, and paclitaxel compared with those treated with carboplatin plus paclitaxel alone; no definitive cause was identified.

Neomycin interferes with enterohepatic recycling of sorafenib, resulting in decreased exposure to sorafenib.

Pharmacokinetics

Peak plasma concentrations of sorafenib occur about 3 hours after an oral dose. Absorption is reduced by about 30% after a high-fat meal. Plasma protein binding is about 99.5%. Sorafenib is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP3A4. It also undergoes glucuronidation. The elimination half-life of sorafenib is about 25 to 48 hours. About 96% of a dose is excreted within 14 days, with 77%, mostly as unchanged drug, recovered in the faeces, and 19% in the urine as glucuronidated metabolites.

References.

1. Clark JW, *et al.* Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. *Clin Cancer Res* 2005; **11:** 5472–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nexavar; ***Austral.***: Nexavar; ***Austria***: Nexavar; ***Belg.***: Nexavar; ***Braz.***: Nexavar; ***Canad.***: Nexavar; ***Chile***: Nexavar; ***China***: Nexavar (多吉美); ***Cz.***: Nexavar; ***Denm.***: Nexavar; ***Fr.***: Nexavar; ***Ger.***: Nexavar; ***Gr.***: Nexavar; ***Hong Kong***: Nexavar; ***Hung.***: Nexavar; ***Indon.***: Nexavar; ***Irl.***: Nexavar; ***Israel***: Nexavar; ***Ital.***: Nexavar; ***Malaysia***: Nexavar; ***Mex.***: Nexavar; ***Neth.***: Nexavar; ***Norw.***: Nexavar; ***NZ***: Nexavar; ***Philipp.***: Nexavar; ***Pol.***: Nexavar; ***Port.***: Nexavar; ***Rus.***: Nexavar (Нексавар); ***S.Afr.***: Nexavar; ***Singapore***: Nexavar; ***Spain***: Nexavar; ***Swed.***: Nexavar; ***Switz.***: Nexavar; ***Thai.***: Nexavar; ***Turk.***: Nexavar; ***UK***: Nexavar; ***USA***: Nexavar.

Streptozocin *(USAN, rINN)*

Estreptozocina; NSC-85998; Streptotsosiini; Streptozocine; Streptozocinum; Streptozosin; Streptozotocin; U-9889; Стрептозоцин.

2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose.

$C_8H_{15}N_3O_7$=265.2

CAS — 18883-66-4.

ATC — L01AD04.

ATC Vet — QL01AD04.

UNII — 5W494URQ81.

Storage. Licensed product information recommends that the freeze-dried streptozocin preparation be stored at 2 degrees to 8 degrees and protected from light.

Uses and Administration

Streptozocin is an antibiotic antineoplastic belonging to the nitrosoureas (see Carmustine, p. 761.2) and is used, alone or with other antineoplastics, mainly in the treatment of pancreatic endocrine (islet-cell) tumours (p. 716.3). It is given by intravenous injection or infusion in doses of 1 g/m² weekly, increased if necessary after 2 weeks to up to 1.5 g/m². Alternatively doses of 500 mg/m² may be given daily for 5 days and repeated every 6 weeks.

It has also been tried in other tumours including exocrine pancreatic cancer and prostate cancer.

Streptozocin has also been given by intra-arterial infusion (but see Adverse Effects below).

Full blood counts, and renal and hepatic function tests should be performed routinely during treatment; doses should be reduced or treatment withdrawn if renal toxicity occurs.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Cumulative nephrotoxicity is common with streptozocin and may be severe and irreversible. Mild proteinuria may be the first sign of toxicity. Intra-arterial use may be associated with more rapid development of nephrotoxicity.

Other adverse effects include severe nausea and vomiting and alterations in liver function or occasionally severe hepatotoxicity. Myelosuppression may occur but is rarely severe. Confusion, lethargy, and depression have been reported in some patients given streptozocin by 5-day continuous infusion. Streptozocin may affect glucose metabolism. A diabetogenic effect has been reported; hypoglycaemia attributed to the release of insulin from damaged cells has also occurred.

Streptozocin is irritant to tissues and extravasation may lead to local ulceration and necrosis.

Streptozocin should be used with extreme care in patients with pre-existing renal impairment.

Handling and disposal. Methods for the destruction of streptozocin *waste* by reaction with hydrobromic acid in glacial acetic acid or by oxidation with a solution of potas-

sium permanganate in sulfuric acid.[1] Residues produced by either method were free of mutagenic activity.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.

Interactions

Streptozocin should not be given with other potentially nephrotoxic drugs. For increased doxorubicin toxicity when given with streptozocin see p. 785.2.

Phenytoin. It has been suggested that because phenytoin appeared to protect the beta cells of the pancreas from the cytotoxic effects of streptozocin, its use with streptozocin should be avoided in patients being treated for pancreatic tumours.[1]

1. Koranyi L, Gero L. Influence of diphenylhydantoin on the effect of streptozotocin. *BMJ* 1979; **1:** 127.

Pharmacokinetics

After intravenous doses streptozocin is rapidly cleared from the blood and distributed to body tissues, particularly the liver, kidneys, intestines, and pancreas. It is extensively metabolised, mainly in the liver and perhaps the kidney, and excreted principally in the urine as metabolites and a small amount of unchanged drug. About 60 to 70% of an intravenous dose is excreted in urine within 24 hours. Some is also excreted via the lungs. Streptozocin itself does not cross the blood-brain barrier but its metabolites are found in the CSF.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Zanosar; ***Fr.***: Zanosar; ***Gr.***: Zanosar; ***Israel***: Zanosar†; ***Switz.***: Zanosar†; ***USA***: Zanosar.

Sunitinib Malate *(BANM, USAN, rINNM)*

Malato de sunitinib; PHA-290940AD; SU-010398; SU-011248 (sunitinib); Sunitinib, Malate de; Sunitinibi Malas; Сунитиниба Малат.

N-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide hydrogen (2*S*)-2-hydroxybutanedioate.

$C_{22}H_{27}FN_4O_2,C_4H_6O_5$=532.6

CAS — 557795-19-4 (sunitinib); 341031-54-7 (sunitinib malate).

ATC — L01XE04.

ATC Vet — QL01XE04.

UNII — LVX8N1UT73.

Uses and Administration

Sunitinib malate is an inhibitor of several receptor tyrosine kinases. It is used for the treatment of gastrointestinal stromal tumours (GIST; see Soft-tissue Sarcoma, p. 718.2) after disease progression during imatinib treatment, or in patients intolerant to imatinib. It is also used for the treatment of advanced and/or metastatic renal cell carcinoma (RCC; p. 708.3). It is also licensed in some countries for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET; p. 716.3).

Sunitinib is given orally as the malate, but doses are expressed in terms of the base; sunitinib malate 66.8 mg is equal to about 50 mg of sunitinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For the treatment of GISTs or RCC, the recommended dose is 50 mg once daily, for 4 weeks of a 6-week treatment cycle. Doses may be increased or decreased in steps of 12.5 mg, based on individual tolerability. UK licensed product information recommends that the daily dose should not normally exceed 75 mg nor be decreased below 25 mg.

For the treatment of pNETs, the recommended dose of sunitinib is 37.5 mg once daily; doses are given continuously. Dose modification is made in steps of 12.5 mg, based on individual tolerability; doses above 50 mg daily in pNETs have not been evaluated.

Use of inhibitors or inducers of CYP3A4 may increase or decrease sunitinib plasma concentrations. If no alternative is available, a dose reduction of sunitinib to a minimum of 37.5 mg daily for GIST or RCC, or 25 mg daily for pNET, should be considered if it is given with a strong CYP3A4 inhibitor. Doses can be increased to a maximum of 87.5 mg daily for GIST or RCC, or 62.5 mg daily for pNET, if sunitinib is given with a CYP3A4 inducer; the patient should be closely monitored for toxicity.

References.

1. Motzer RJ, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24:** 16–24.
2. Faivre S, *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; **24:** 25–35.
3. Motzer RJ, *et al.* Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Expert Opin Invest Drugs* 2006; **15:** 553–61.
4. Motzer RJ, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295:** 2516–24.
5. Deeks ED, Keating GM. Sunitinib. *Drugs* 2006; **66:** 2255–66.
6. Demetri GD, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368:** 1329–38.
7. Motzer RJ, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356:** 115–24.
8. Goodman VL, *et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007; **13:** 1367–73.
9. O'Brien MF, *et al.* Sunitinib therapy in renal cell carcinoma. *BJU Int* 2008; **101:** 1339–42.
10. Socinski MA. The current status and evolving role of sunitinib in non-small cell lung cancer. *J Thorac Oncol* 2008; **3** (suppl 2): S119–S123.
11. Kulke MH, *et al.* Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol* 2008; **26:** 3403–10.

Adverse Effects, Treatment, and Precautions

Common adverse effects of sunitinib include gastrointestinal disturbances, anorexia, headache, fatigue, fever, hypertension, hypothyroidism, mouth pain or irritation, dry mouth, mucosal inflammation, oedema, taste disturbances, arthralgia, and myalgia. Myelosuppression is common, and complete blood counts should be performed at the beginning of each treatment cycle. Other effects include dizziness, paraesthesia, dyspnoea, alopecia, Yellow skin discoloration and chromaturia can occur. Other dermatological effects include depigmentation of the hair or skin, dryness, rash, exfoliative dermatitis, or palmar-planter syndrome. Gastrointestinal perforation has been reported rarely; fatalities have been reported in patients with intra-abdominal malignancies.

Decreases in left ventricular ejection fraction (LVEF) have occurred with sunitinib; baseline and periodic evaluations of LVEF should be taken. Patients should be monitored for signs of congestive cardiac failure and therapy interrupted or stopped if they occur. Dose reductions may be necessary in patients who show no signs of heart failure but who show decreases in LVEF. Sunitinib may prolong the QT interval and should be used with caution in patients with a history of this, who are taking antiarrhythmics, or who have pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

There is an increased risk of bleeding at all sites; epistaxis is the most common treatment-related bleeding event but fatal pulmonary haemorrhage has occurred in patients with lung cancer. Pulmonary embolism or venous thromboembolic events may occur. Patients under stresses such as surgery, trauma, or severe infection should be monitored for adrenal insufficiency. Increases in serum amylase and lipase concentrations have been seen and there are rare reports of pancreatitis and hepatic failure. There are also rare reports of seizures and reversible posterior leukoencephalopathy syndrome.

Effects on the blood. For a report of reversible erythrocytosis in patients given sunitinib or sorafenib, see Effects on the Blood, under Sorafenib, p. 858.1.

Effects on the cardiovascular system. A retrospective review in 75 patients given repeating cycles of sunitinib in phase I/II studies of its efficacy for gastrointestinal stromal tumours found that cardiovascular events occurred in 8, of whom 6 developed congestive heart failure.[1] Of 36 patients given the subsequently approved dose, 10 had reductions in left ventricular ejection fraction of at least 10%. Hypertension developed in 35 of the 75 patients, and it was suggested that left ventricular dysfunction might be due to a combination of hypertension and a direct toxic effect on heart muscle.

For the relative risk of developing hypertension with sunitinib, and results of a study analysing cardiotoxicity of sunitinib and sorafenib, see under Sorafenib, p. 858.2.

1. Chu TF, *et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; **370:** 2011–19.

Effects on the kidneys. For a report of haemolytic-uraemic syndrome after the use of bevacizumab and sunitinib, see Effects on the Kidneys, under Bevacizumab, p. 748.2.

Effects on the musculoskeletal system. As of 31st January 2010, the German manufacturer (*Pfizer*) reported 27 cases of osteonecrosis of the jaw (similar to that seen with the bisphosphonates, see under Bisphosphonates, p. 1176.3) related to sunitinib therapy.[1] There are other reports in cancer patients treated with sunitinib,[2-6] the majority of whom had also received treatment with intravenous bisphosphonates.However, in one case,[4] the patient had never received bisphosphonates, but had previously had dental extraction.

There have been similar reports of bisphosphonate-related osteonecrosis of the jaw in patients given bevacizumab (see under Bevacizumab, p. 748.2) and it has been postulated that the strong anti-angiogenic action of these drugs contributed to oral mucosal breakdown and the subsequent development of osteonecrosis of the jaw.[3] Caution is advised when sunitinib and bisphosphonates are used together or sequentially,[1] and dental care precautions similar to those in patients prescribed bisphosphonates (see under Bisphosphonates, p. 1175.2) are recommended.

1. Kalanovic D, Fricker R. Pfizer, Germany. Mögliches Risiko für das Auftreten einer Kieferosteonekrose bei mit Sunitinib (Sutent) behandelten Krebspatienten bei gleichzeitiger oder vorheriger Anwendung von Bisphosphonaten (issued 30/11/2010). Available at: http://www.bfarm.de/SharedDocs/1_Downloads/DE/Pharmakovigilanz/rote-HandBriefe/2010/sunitinib.pdf?__blob=publicationFile (accessed 17/12/10)
2. Brunello A, *et al.* Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma. *Bone* 2009; **44:** 173–5.
3. Ayllon J, *et al.* Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile? *Ann Oncol* 2009; **20:** 600–1.
4. Koch FP, *et al.* Osteonecrosis of the jaw related to sunitinib. *Oral Maxillofac Surg* 2011; **15:** 63–6.
5. Bozas G, *et al.* Osteonecrosis of the jaw after a single bisphosphonate infusion in a patient with metastatic renal cancer treated with sunitinib. *Onkologie* 2010; **33:** 321–3.
6. Hoefert S, Eufinger H. Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: presentation of three cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **110:** 463–9.

Effects on the nervous system. Coma has been reported with sunitinib; therapy was immediately stopped and the patient regained consciousness within 24 hours.[1]

1. Arnaud L, *et al.* Transient sunitinib-induced coma in a patient with fibromyxoid sarcoma. *J Clin Oncol* 2008; **26:** 1569–71.

Effects on the skin. Palmar-plantar syndrome is a well-recognised adverse effect of several tyrosine kinase inhibitors, including sunitinib.[1] A patient developed palmar-plantar syndrome and rashes resembling seborrhoeic dermatitis while taking sunitinib. Therapy was stopped and the rash was treated with a topical corticosteroid; blisters on the palms and soles resolved with desquamation.[2] In another report,[3] 5 out of 40 patients treated with sunitinib developed erythema and desquamation in the scrotal and inguinal areas; these effects decreased or disappeared after the drug was stopped, and reappeared upon restarting sunitinib. Histological analysis of 3 specimens mimicked the pathological features of psoriasis. Pyoderma gangrenosum has also been reported.[4]

1. Lipworth AD, *et al.* Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology* 2009; **77:** 257–71.
2. Tsai K-Y, *et al.* Hand-foot syndrome and seborrheic dermatitis-like rash induced by sunitinib in a patient with advanced renal cell carcinoma. *J Clin Oncol* 2006; **24:** 5786–8.
3. Billemont B, *et al.* Scrotal cutaneous side effects of sunitinib. *N Engl J Med* 2008; **359:** 975–6.
4. ten Freyhaus K, *et al.* Pyoderma gangrenosum: another cutaneous side-effect of sunitinib? *Br J Dermatol* 2008; **159:** 242–3.

Effects on thyroid function. Hypothyroidism is common after sunitinib therapy. A cohort study found that 36% of patients developed hypothyroidism after an average of 50 weeks of therapy. The incidence of hypothyroidism increased with the duration of therapy, and the effect was not transient; patients needed replacement therapy with levothyroxine. Mild thyrotoxicosis may precede the onset of hypothyroidism. Although the mechanism is not clear, the drug may cause destructive thyroiditis. Patients should be screened for hypothyroidism and serum concentrations of thyroid-stimulating hormone (TSH) measured at suggested intervals of 2 to 3 months.[1]

1. Desai J, *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med* 2006; **145:** 660–4.

Mucositis. Sunitinib has been reported to cause stomatitis, characterised by bullous and erosive lesions with widespread lichenoid and necrotising areas.[1]

1. Mignogna MD, *et al.* Sunitinib adverse event: oral bullous and lichenoid mucositis. *Ann Pharmacother* 2009; **43:** 546–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sunitinib as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/09/11)

Tumour lysis syndrome. Tumour lysis syndrome has been reported after treatment with sunitinib; electrolytes and renal function should be closely monitored.[1,2]

1. Nicholaou T, *et al.* Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. *Lancet* 2007; **369:** 1923–4.
2. Saylor PJ, Reid TR. Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. *J Clin Oncol* 2007; **25:** 3544–6.

Interactions

Sunitinib is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4 to produce an active metabolite, which is further metabolised by CYP3A4. Ketoconazole increased exposure to sunitinib, and use with other potent inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sunitinib concentrations. Conversely, use with rifampicin decreased exposure to sunitinib, and inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, phenobarbital, or St John's wort) may decrease plasma sunitinib concentrations. If the use of alternative drugs is not feasible, dose adjustments of sunitinib may be necessary (see Uses and Administration, p. 859.1).

Antineoplastics. The US manufacturer of *bevacizumab* has recommended that it should not be used with sunitinib after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm126434.pdf (accessed 21/07/10)

Pharmacokinetics

Peak plasma concentrations occur 6 to 12 hours after an oral dose of sunitinib. Bioavailability is unaffected by food. Sunitinib is metabolised mainly via the cytochrome P450 isoenzyme CYP3A4 to its primary active metabolite, which itself is then further metabolised via CYP3A4. Plasma protein binding of sunitinib and its metabolite is about 95% and 90%, respectively; plasma elimination half-lives are 40 to 60 hours, and 80 to 110 hours, respectively. Sunitinib is excreted mainly in faeces; about 16% is found in urine, as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sutent; ***Austral.***: Sutent; ***Austria***: Sutent; ***Belg.***: Sutent; ***Braz.***: Sutent; ***Canad.***: Sutent; ***Chile***: Sutent; ***China***: Sutent (索坦); ***Cz.***: Sutent; ***Denm.***: Sutent; ***Fr.***: Sutent; ***Ger.***: Sutent; ***Gr.***: Sutent; ***Hong Kong***: Sutent; ***Hung.***: Sutent; ***Irl.***: Sutent; ***Israel***: Sutent; ***Ital.***: Sutent; ***Jpn***: Sutent; ***Malaysia***: Sutent; ***Mex.***: Sutent; ***Neth.***: Sutent; ***Norw.***: Sutent; ***NZ***: Sutent; ***Philipp.***: Sutent; ***Pol.***: Sutent; ***Port.***: Sutent; ***Rus.***: Sutent (Сутент); ***S.Afr.***: Sutent; ***Singapore***: Sutent; ***Spain***: Sutent; ***Swed.***: Sutent; ***Switz.***: Sutent; ***Thai.***: Sutent; ***Turk.***: Sutent; ***UK***: Sutent; ***Ukr.***: Sutent (Сутент); ***USA***: Sutent.

Talactoferrin Alfa *(USAN, rINN)*

LF-00; rhLF; Talactoferrin; Talactoferrina alfa; Talactoferrine Alfa; Talactoferrinum Alfa; Талактоферрин Альфа.

Lactoferrin (recombinant human LF00).

CAS — 308240-58-6.

UNII — 7A05SA9QRR.

Profile

Talactoferrin alfa is a recombinant form of human lactoferrin (p. 2539.3) that acts on the immune system as a dendritic cell recruiter and activator. An oral formulation is under investigation for the treatment of malignancies such as non-small cell lung cancer and renal cell carcinoma. It is also being investigated as an oral treatment for sepsis, and topically as a wound healing agent for diabetic foot ulcers.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Hayes TG, *et al.* Phase I trial of oral talactoferrin alfa in refractory solid tumors. *Invest New Drugs* 2006; **24:** 233–40.
2. Lyons TE, *et al.* Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *Am J Surg* 2007; **193:** 49–54.
3. Jonasch E, *et al.* Phase 2 trial of talactoferrin in previously treated patients with metastatic renal cell carcinoma. *Cancer* 2008; **113:** 72–7.
4. Hayes TG, *et al.* Phase IB trial of oral talactoferrin in the treatment of patients with metastatic solid tumors. *Invest New Drugs* 2010; **28:** 156–62.

Talaporfin Sodium *(USAN, rINNM)*

LS-11; ME-2906; Monoaspartyl Chlorin e6 (talaporfin); Mono-L-aspartyl chlorin (talaporfin); Natrii Talaporfinum; NPe-6 (talaporfin); Talaporfina sódica; Talaporfine Sodique; Taporfin Sodium; Натрий Талапорфин.

Tetrasodium *N*-{[(7*S*,8*S*)-3-carboxy-7-(2-carboxyethyl)-13-ethenyl-18-ethyl-7,8-dihydro-2,8,12,17-tetramethyl-21*H*,23*H*-porphin-5-yl]acetyl}-L-aspartate.

$C_{38}H_{41}N_5Na_4O_9$=803.7

CAS — 110230-98-3 (talaporfin); 220201-34-3 (talaporfin sodium).

UNII — L63605PZ70.

NOTE. The names Aptocine and Laserphyrin have been used as trade marks for talaporfin sodium.

Profile

Talaporfin sodium is a photosensitiser that is used for the photodynamic therapy (see under Porfimer Sodium, p. 849.1) of lung cancer. It is also under investigation for the treatment of other tumours, such as hepatocellular carcinoma and metastatic colorectal cancer.

References.

1. Wang S, *et al.* Talaporfin sodium. *Expert Opin Pharmacother* 2010; **11:** 133–40.

Tamibarotene *(rINN)*

AM-80; NSC-608000; Tamibarotène; Tamibaroteno; Tamibarotenum; Тамибаротен.

N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)terephthalamic acid.

$C_{22}H_{25}NO_3$=351.4

CAS — 94497-51-5.

UNII — 08V52GZ3H9.

Profile

Tamibarotene is a synthetic retinoid that is given orally for the treatment of relapsed or refractory acute promyelocytic leukaemia. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Malignant neoplasms. Tamibarotene has been used to induce remission in patients with acute promyelocytic leukaemia (see Acute Myeloid Leukaemias, p. 693.1) who relapsed after successful remission induction with tretinoin.[1,2] Twenty-four patients received tamibarotene at a daily oral dose of 6 mg/m^2; 14 patients obtained complete remission after a median of 41 days.[1] Reported adverse effects include hypercholesterolaemia, hypertriglyceridaemia,[1,3] cheilitis, xerosis, gastrointestinal disturbances, bone pain, headache, dermatitis, liver damage, and leucocytosis; in one case, retinoic acid syndrome occurred.[1]

1. Tobita T, *et al.* Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood* 1997; **90:** 967–73.
2. Shinjo K, *et al.* Good prognosis of patients with acute promyelocytic leukemia who achieved second complete remission (CR) with a new retinoid, Am80, after relapse from CR induced by all-trans-retinoic acid. *Int J Hematol* 2000; **72:** 470–3.
3. Takeuchi M, *et al.* Relapsed acute promyelocytic leukemia previously treated with all-trans retinoic acid: clinical experience with a new synthetic retinoid, Am-80. *Leuk Lymphoma* 1998; **31:** 441–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Amnolake.

Tamoxifen Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de tamoxifeno; ICI-46474; Tamoksifeenisitraatti; Tamoksifen Sitrat; Tamoksifeno citratas; Tamoxifen citrát; Tamoxifencitrat; Tamoxifén-citrát; Tamoxifène, citrate de; Tamoxifeni Citras; Tamoxifeno, citrato de; Тамоксифена Цитрат.

(*Z*)-2-[4-(1,2-Diphenylbut-1-enyl)phenoxy]ethyldimethylamine citrate.

$C_{26}H_{29}NO,C_6H_8O_7$=563.6

CAS — 10540-29-1 (tamoxifen); 54965-24-1 (tamoxifen citrate).

ATC — L02BA01.

ATC Vet — QL02BA01.

UNII — 7FRV7310N6.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Tamoxifen Citrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water and in acetone; soluble in methyl alcohol.

USP 36: (Tamoxifen Citrate). A white, fine, crystalline powder. Very slightly soluble in water, in alcohol, in acetone, and in chloroform; soluble in methyl alcohol. Protect from light.

Uses and Administration

Tamoxifen is an oestrogen antagonist with actions similar to those of clomifene citrate (see p. 2259.1). It may also inhibit the production or release of cellular growth factors and induce apoptosis. It is used in the adjuvant endocrine therapy of node-positive breast cancer, in the treatment of metastatic disease, and for prophylaxis in women at increased risk including those with ductal carcinoma in situ. It has been tried in some other malignancies including tumours of the ovary and in malignant melanoma. Tamoxifen is also used to stimulate ovulation in women with anovulatory infertility. See also the cross-references below.

Tamoxifen is given orally as the citrate but doses are calculated in terms of the base; tamoxifen citrate 15.2 mg is equivalent to about 10 mg of tamoxifen. In the treatment of **breast cancer**, usual doses are tamoxifen 20 mg daily, in 2 divided doses or as a single daily dose. Doses of up to 40 mg daily may be given but no additional benefit has been found. Adjuvant therapy is normally continued for up to 5 years, although the optimum duration is still uncertain (p. 702.1). To reduce breast cancer incidence in women at high risk of the disease, the licensed dose of tamoxifen is 20 mg daily for 5 years.

In the treatment of anovulatory **infertility** the usual dose is tamoxifen 20 mg daily on days 2 to 5 of the menstrual cycle, increased if necessary in subsequent cycles up to 80 mg daily. In women with irregular menstruation the initial course may be begun on any day, and a second course begun at a higher dose after 45 days if there has been no response. If the patient responds with menstruation, subsequent courses may begin on day 2 of the cycle.

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation for the treatment of cyclic mastalgia.

An oral formulation of the tamoxifen metabolite, endoxifen, is under investigation, see Metabolism, p. 864.1.

Reviews.

1. Kramer R, Brown P. Should tamoxifen be used in breast cancer prevention? *Drug Safety* 2004; **27:** 979–89.
2. Singh Ranger G. Current concepts in the endocrine therapy of breast cancer: tamoxifen and aromatase inhibitors. *J Clin Pharm Ther* 2005; **30:** 313–17.
3. Morales L, *et al.* Choosing between an aromatase inhibitor and tamoxifen in the adjuvant setting. *Curr Opin Oncol* 2005; **17:** 559–65.
4. Poole R, Paridaens R. The use of third-generation aromatase inhibitors and tamoxifen in the adjuvant treatment of postmenopausal patients with hormone-dependent breast cancer: evidence based review. *Curr Opin Oncol* 2007; **19:** 564–72.
5. MunshiA, Singh P. Tamoxifen in breast cancer: not so easy to write off. *Breast* 2008; **17:** 121–4.
6. Beguerie JR, *et al.* Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis. *Int J Dermatol* 2010; **49:** 1194–1202.

Breast disorders, non-malignant. *GYNAECOMASTIA.* Tamoxifen, usually in doses of 10 mg twice daily, has been reported to be effective[1-7] in reducing pain, swelling, and breast size in men or pubertal boys with gynaecomastia (p. 2264.3). Tamoxifen has been recommended as a drug of choice in patients requiring drug therapy, given for 3 months to see if a response occurs.[7] It has also been reported to be effective for the prevention and treatment of gynaecomastia and breast pain caused by the nonsteroidal anti-androgen bicalutamide,[8-11] which is used in the treatment of prostate cancer (see Gynaecomastia under Adverse Effects and Precautions of Flutamide, p. 799.1). A randomised study[12] in patients with prostate cancer treated with bicalutamide found that a daily schedule of tamoxifen was more effective than a weekly schedule in preventing gynaecomastia. In addition, switching to a weekly schedule after a daily schedule was followed by a dramatic increase in the development of gynaecomastia and mastalgia; this became apparent after 6 months of treatment, probably as a result of the study design, in which 2 months of daily treatment was given before switching to the weekly schedule, causing a loading effect.

1. Jefferys DB. Painful gynaecomastia treated with tamoxifen. *BMJ* 1979; **1:** 1119–20.
2. Hooper PD. Puberty gynaecomastia. *J R Coll Gen Pract* 1985; **35:** 142.
3. McDermott MT, *et al.* Tamoxifen therapy for painful idiopathic gynecomastia. *South Med J* 1990; **83:** 1283–5.
4. Ting AC, *et al.* Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. *Am Surg* 2000; **66:** 38–40.
5. Lawrence SE, *et al.* Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; **145:** 71–6.
6. Hanavadi S, *et al.* The role of tamoxifen in the management of gynaecomastia. *Breast* 2006; **15:** 276–80.
7. Braunstein GD. Gynecomastia. *N Engl J Med* 2007; **357:** 1229–37.
8. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; **8:** 75–83.
9. Perdonà S, *et al.* Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; **6:** 295–300.
10. Di Lorenzo G, *et al.* Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; **174:** 2197–2203.
11. Fradet Y, *et al.* Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol* 2007; **52:** 106–14.
12. Bedognetti D, *et al.* An open, randomised, multicentre, phase 3 trial comparing the efficacy of two tamoxifen schedules in preventing gynaecomastia induced by bicalutamide monotherapy in prostate cancer patients. *Eur Urol* 2010; **57:** 238–45.

MASTALGIA. Tamoxifen 20 mg daily has been shown to be effective in patients with both cyclic and non-cyclic mastalgia,[1] and improvement has also been reported at a lower dose of 10 mg daily.[2] However, there is concern about the use of tamoxifen in otherwise healthy premenopausal women,[3-5] particularly since many patients relapse on withdrawal,[2] and it has been recommended[6,7] that tamoxifen be reserved for patients who fail to respond to other drugs (see p. 2265.1).

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation in the treatment of cyclic mastalgia.

1. Fentiman IS, *et al.* Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet* 1986; **i:** 287–8.
2. Fentiman IS, *et al.* Studies of tamoxifen in women with mastalgia. *Br J Clin Pract* 1989; **43** (suppl 68): 34–6.
3. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; **i:** 305.
4. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; **i:** 680–1.
5. Fentiman IS, *et al.* Tamoxifen for mastalgia. *Lancet* 1986; **i:** 681.
6. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; **47:** 284–94.
7. Anonymous. Cyclical breast pain: what works and what doesn't. *Drug Ther Bull* 1992; **30:** 1–3.

Cardiovascular disorders. Tamoxifen has been reported to have a generally favourable effect on lipid profiles (see Effects on Blood Lipids, under Adverse Effects, p. 862.1) suggesting it may have cardiovascular benefits.[1] A cohort study of adjuvant tamoxifen found that the drug reduced the incidence of myocardial infarction,[2] and a randomised study of the same therapy also showed a trend towards a decrease in mortality from coronary heart disease.[3] However, in a much larger breast cancer prevention study, tamoxifen did not reduce the risk of, and mortality from, ischaemic heart disease, neither of which differed between placebo and tamoxifen recipients.[4,5] This lack of difference was independent of pre-existing cardiovascular disease.[5] A review[6] noted that while the available data suggested an overall benefit, most of them came from studies in women at low absolute risk of myocardial infarction; studies in men at high absolute risk would be needed to determine whether tamoxifen and related drugs were suitable as cardioprotectants.

1. Pritchard KI, Abramson BL. Cardiovascular health and aromatase inhibitors. *Drugs* 2006; **66:** 1727–40.
2. McDonald CC, *et al.* Scottish Cancer Trials Breast Group. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. *BMJ* 1995; **311:** 977–80.
3. Costantino JP, *et al.* Coronary heart disease mortality and adjuvant tamoxifen therapy. *J Natl Cancer Inst* 1997; **89:** 776–82.
4. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
5. Reis SE, *et al.* Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. *J Natl Cancer Inst* 2001; **93:** 16–21.
6. Grainger DJ, Schofield PM. Tamoxifen for the prevention of myocardial infarction in humans: preclinical and early clinical evidence. *Circulation* 2005; **112:** 3018–24.

Disorders related to the menstrual cycle. Apart from cyclic mastalgia (see above) tamoxifen has been used in cases in which disorders were linked to the hormonal changes of the menstrual cycle, including menorrhagia due to myometrial hypertrophy,[1] an auto-immune dermatitis due to post-ovulatory rises in serum progesterone[2,3] (see Effects on the Skin under Progesterone, p. 2301.3), and premenstrual migraine.[4] However, tamoxifen was thought to be a cause of recurrent migraines in another patient, because of its action at oestrogen receptors.[5] Tamoxifen has also been tried in primary dysmenorrhoea.[6]

1. Fraser IS. Menorrhagia due to myometrial hypertrophy: treatment with tamoxifen. *Obstet Gynecol* 1987; **70:** 505–6.
2. Wojnarowska F, *et al.* Progesterone-induced erythema multiforme. *J R Soc Med* 1985; **78:** 407–8.
3. Stephens CJM, *et al.* Autoimmune progesterone dermatitis responding to tamoxifen. *Br J Dermatol* 1989; **121:** 135–7.
4. O'Dea JPK, Davis EH. Tamoxifen in the treatment of menstrual migraine. *Neurology* 1990; **40:** 1470–1.
5. Mathew P, Fung F. Recapitulation of menstrual migraine with tamoxifen. *Lancet* 1999; **353:** 467–8.
6. Pierzyński P, *et al.* Effect of short-term, low-dose treatment with tamoxifen in patients with primary dysmenorrhea. *Gynecol Endocrinol* 2006; **22:** 698–703.

Infertility. Tamoxifen is reported to be as effective as clomifene in the treatment of anovulatory infertility (p. 2253.1) in women,[1-3] and may be useful in women in whom abnormal cervical mucus acts as a barrier to spermatozoa.[4] In infertile men, however, results are reportedly contradictory, with some studies reporting increase in sperm density and improved pregnancy rates while others failed to find any effect.[5] The addition of testosterone may improve outcomes, however, and a later study of men with idiopathic oligozoospermia reported that tamoxifen with testosterone improved sperm variables and pregnancy rates compared with a placebo group (there was no comparison with tamoxifen alone).[6]

1. Messinis IE, Nillius SJ. Comparison between tamoxifen and clomiphene for induction of ovulation. *Acta Obstet Gynecol Scand* 1982; **61:** 377–9.
2. Boostanfar R, *et al.* A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. *Fertil Steril* 2001; **75:** 1024–6.
3. Steiner AZ, *et al.* Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. *Hum Reprod* 2005; **20:** 1511–15.
4. Annapurna V, *et al.* Effect of two anti-estrogens, clomiphene citrate and tamoxifen, on cervical mucus and sperm-cervical mucus interaction. *Int J Fertil* 1997; **42:** 215–18.
5. Howards SS. Treatment of male infertility. *N Engl J Med* 1995; 312–17.
6. Adamopoulos DA, *et al.* Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertil Steril* 2003; **80:** 914–20.

Malignant neoplasms. For reference to the use of tamoxifen in malignant neoplasms of breast, ovary, and in cutaneous melanoma, see p. 702.1, p. 711.2, and p. 714.3. The most common use of tamoxifen is for the endocrine therapy of oestrogen-receptor positive early or advanced breast cancer, where there seems to be a clear benefit. How long such therapy should be continued remains uncertain although continuing therapy beyond 5 years may not increase the overall benefit. However, extending therapy by following 5 years of tamoxifen therapy with several years of an aromatase inhibitor such as letrozole (see, p. 817.2) does seem to provide additional benefit.

Extension of tamoxifen use to the attempted prophylaxis of breast cancer has proved controversial (see p. 703.2). Nonetheless, evidence that tamoxifen can reduce short-term incidence of breast cancer in some women at increased risk has been seen, and tamoxifen has been approved for such use in the USA.

Osteoporosis. Tamoxifen has been reported to have favourable effects on bone mass,[1-3] and current use has been associated with a substantial reduction in osteoporotic fractures.[4] However, any general role in the prevention of osteoporosis (p. 1168.1) seems unlikely given concerns about the carcinogenicity of tamoxifen. The effects are reported to be comparable in magnitude to those of calcium supplementation, and less than those of oestrogens (see also p. 2246.1) or bisphosphonates. It has been suggested that such an effect on bone would provide an additional benefit in women receiving tamoxifen for the prophylaxis of breast cancer,[5] although others dispute the benefits.[6]

1. Love RR, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; **326:** 852–6.
2. Love RR, *et al.* Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Arch Intern Med* 1994; **154:** 2585–8.
3. Grey AB, *et al.* The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995; **99:** 636–41.
4. Cooke AL, *et al.* Tamoxifen use and osteoporotic fracture risk: a population-based analysis. *J Clin Oncol* 2008; **26:** 5227–32.
5. Powles TJ. The case for clinical trials of tamoxifen for prevention of breast cancer. *Lancet* 1992; **340:** 1145–7.
6. Fugh-Berman A, Epstein S. Tamoxifen: disease prevention or disease substitution? *Lancet* 1992; **340:** 1143–5.

Precocious puberty. Tamoxifen has been reported to be beneficial in the treatment of precocious puberty (p. 2254.1).

Retroperitoneal fibrosis. Tamoxifen may be a viable therapeutic option in the treatment of adults with retroperitoneal fibrosis (p. 1612.1).[1-3] Tamoxifen was successful in treating a prepubertal child with disease that was unresponsive to high-dose corticosteroids.[4]

1. Moroni G, *et al.* Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches. *Nephrol Dial Transplant* 2006; **21:** 2485–90.
2. van Bommel EFH, *et al.* Brief communication: tamoxifen therapy for nonmalignant retroperitoneal fibrosis. *Ann Intern Med* 2006; **144:** 101–6.
3. Costanzi S, *et al.* A paraneoplastic retroperitoneal fibrosis resistant to corticosteroids treated with tamoxifen. *Clin Nephrol* 2008; **70:** 172–5.
4. Dedeoglu F, *et al.* Successful treatment of retroperitoneal fibrosis with tamoxifen in a child. *J Rheumatol* 2001; **28:** 1693–5.

Adverse Effects

The most frequent adverse effects of tamoxifen are hot flushes. Other adverse effects include fluid retention, nausea, gastrointestinal intolerance, vaginal bleeding or discharge, pruritus vulvae, rashes, dry skin, and alopecia. There have also been reports of dizziness, headache, depression, confusion, fatigue, and muscle cramps. There may be an increased tendency to thromboembolism, and pulmonary embolism has occurred. Tumour pain and flare may be a sign of response, but hypercalcaemia, sometimes severe, has developed in patients with bony metastases. Transient thrombocytopenia and leucopenia have been reported. Blurred vision and loss of visual acuity, corneal opacities, retinopathies, and cataracts have occurred rarely. Tamoxifen has been associated with increased liver enzymes, and rarely with cholestasis and hepatitis. Hypertriglyceridaemia has occurred. Uterine fibroids and endometrial changes including hyperplasia and polyps may occur, and an increased incidence of endometrial carcinoma, and rarely uterine sarcoma, has been reported. Suppression of menstruation may occur in premenopausal women and cystic ovarian swellings have occasionally occurred. Very rare cases of interstitial pneumonitis have been reported.

Carcinogenicity. Tamoxifen has a stimulant effect on the endometrium (probably by acting as a partial oestrogen agonist) and its use has been associated with the development of endometrial polyps[1,2] and endometriosis,[3] and an increased risk of endometrial cancer.[4-6] The risk, which increases with duration of therapy, is generally agreed to be modest, and the clinical benefit in women with breast cancer outweighs any increased risk of endometrial neoplasm.[7-10] Women taking tamoxifen to prevent breast cancer have been estimated to have a 2.53-fold greater risk of developing endometrial carcinoma than untreated women.[11] The risk may increase with more prolonged use and a case-control study has reported that long-term (over 2 years) users may have a worse prognosis if endometrial cancer develops, due to less favourable history and stage.[12] Another case-control study showed that the relative risk of endometrial cancer increased with duration of tamoxifen treatment, up to at least 10 years. Risk was not associated with the daily dose of tamoxifen, and was comparable in pre- and postmenopausal women.[13]

It has been recommended that women with breast cancer taking tamoxifen should have annual gynaecological examinations, and any unusual symptoms, including abnormal bleeding or spotting should be investigated promptly.[14] Women taking tamoxifen for prophylaxis of breast cancer should be monitored carefully for endometrial hyperplasia. If atypical hyperplasia develops, tamoxifen should be stopped while the condition is treated and a hysterectomy should be considered before tamoxifen is re-started.[14] However, up to 39% of postmenopausal women taking tamoxifen show endometrial changes and as these seldom progress to cancer, the value of routine endometrial biopsies has been questioned.[8,9,14,15] Transvaginal ultrasonography has been used as a noninvasive method of endometrial screening, but has a high rate of false-positive results.[16] It has been suggested that colour doppler ultrasonography, which distinguishes vascularised lesions such as polyps and carcinomas from avascular atrophic lesions, may be a useful alternative.[17] There is some evidence that a levonorgestrel-releasing intra-uterine device can protect against benign endometrial polyps induced by tamoxifen.[18]

Although rare, there is an increase in the risk of uterine sarcoma in women receiving tamoxifen. Between 1978, when tamoxifen was first marketed in the USA, and April 2001, the FDA was aware of 43 cases in women who had been receiving tamoxifen; there had also been reports in 116 women in other countries.[19] Although less than the expected rate in this population, this was considered to be due to underreporting. An evaluation of data from 39451 breast cancer patients initially treated with tamoxifen found that the overall risk of uterine corpus cancer was more than doubled with the use of tamoxifen; the risk of rare but aggressive forms of uterine tumours, notably malignant mixed mullerian tumours, was increased more than fourfold.[20]

Tamoxifen has been shown to form DNA adducts in *rat* livers, and there has been speculation that it may cause liver cancer in humans. However, there is considerable interspecies variation in the metabolism of tamoxifen and several large-scale clinical studies did not find an increase in liver carcinogenicity in humans.[10] No substantial increase in liver or colorectal cancer has been seen in tamoxifen-treated patients,[21] and there is little evidence of any increased risk for oesophageal cancer.[21,22] Stomach cancer was the most frequently seen secondary cancer in a Japanese cohort study,[21] and a Swedish cohort study concluded that women with breast cancer were at increased risk of gastric adenocarcinoma, and that tamoxifen therapy might play a role.[22] Results from a case-control study in the UK suggested that tamoxifen treatment did not increase the risk of ovarian cancer (although non-hormonal chemotherapy might).[23]

Although in treated women with breast cancer adjuvant tamoxifen reduces the risk of developing a second primary malignancy in the contralateral breast, a case-control study has suggested that 5 or more years of tamoxifen treatment increases the risk, should such a malignancy develop, that it will be oestrogen-receptor negative, and hence harder to treat.[24]

1. Corley D, *et al.* Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. *Obstet Gynecol* 1992; **79:** 111–16.
2. Buijs C, *et al.* Tamoxifen and uterine abnormalities. *J Clin Oncol* 2004; **22:** 2505–7.
3. Cano A, *et al.* Tamoxifen and the uterus and endometrium. *Lancet* 1989, **i:** 376.
4. Fornander T, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989; **i:** 117–20.
5. Gusberg SB. Tamoxifen for breast cancer: associated endometrial cancer. *Cancer* 1990; **65:** 1463–4.
6. van Leeuwen FE, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994; **343:** 448–52.
7. Baum M, *et al.* Endometrial cancer during tamoxifen treatment. *Lancet* 1994; **343:** 1291.
8. Bissett D, *et al.* Gynaecological monitoring during tamoxifen therapy. *Lancet* 1994; **344:** 1244.
9. Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? *Lancet* 1998; **351:** 155–7.

10. Stearns V, Gelmann EP. Does tamoxifen cause cancer in humans? *J Clin Oncol* 1998; **16:** 779–92.
11. Fisher B, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
12. Bergman L, *et al*. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 2000; **356:** 881–7.
13. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. *J Natl Cancer Inst* 2005; **97:** 375–84.
14. American College of Obstetrics and Gynaecologists. ACOG Committee Opinion: tamoxifen and endometrial cancer. *Int J Gynaecol Obstet* 1996; **53:** 197–9.
15. Barakat RR, *et al*. Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000; **18:** 3459–63.
16. Gerber B, *et al*. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000; **18:** 3464–70.
17. Aleem FA, Predanic M. Endometrial changes in patients on tamoxifen. *Lancet* 1995; **346:** 1292–3.
18. Chin J, *et al*. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 20/04/10).
19. Wysowski DK, *et al*. Uterine sarcoma associated with tamoxifen use. *N Engl J Med* 2002; **346:** 1832–3.
20. Curtis RE, *et al*. Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; **96:** 70–4.
21. Matsuyama Y, *et al*. Second cancers after adjuvant tamoxifen therapy for breast cancer in Japan. *Ann Oncol* 2000; **11:** 1537–43.
22. Chandanos E, *et al*. Tamoxifen exposure and risk of oesophageal and gastric adenocarcinoma: a population-based cohort study of breast cancer patients in Sweden. *Br J Cancer* 2006; **95:** 118–22.
23. Swerdlow AJ, Jones ME. Ovarian cancer risk in premenopausal and perimenopausal women treated with Tamoxifen: a case-control study. *Br J Cancer* 2007; **96:** 850–5.
24. Li CI, *et al*. Adjuvant hormonal therapy for breast cancer and risk of hormone receptor-specific subtypes of contralateral breast cancer. *Cancer Res* 2009; **69:** 6865–70.

Effects on the blood. Pancytopenia developed shortly after beginning tamoxifen therapy in an elderly woman, and persisted for some years;[1] the patient eventually developed very severe leucopenia and died of infection. Thrombocytopenia has also been reported.[2]

1. Miké V, *et al*. Fatal neutropenia associated with long-term tamoxifen therapy. *Lancet* 1994; **344:** 541–2.
2. Nasiroğlu N, *et al*. Tamoxifen induced-thrombocytopenia: it does occur. *Med Oncol* 2007; **24:** 453–4.

Effects on blood lipids. Tamoxifen has been reported to have a generally favourable effect on serum lipid profiles.[1] Patients with breast cancer and subsequent chemotherapy-induced ovarian failure developed marked increases in total cholesterol and low-density lipoprotein levels; adjuvant tamoxifen was found to decrease these serum lipid concentrations to below baseline concentrations. No significant changes in high-density lipoprotein or serum triglyceride concentrations were seen.[2] However, some cases of increased serum triglycerides, mainly in women with pre-existing hypertriglyceridaemia, have been reported.[3-5] Pancreatitis has also resulted.[5] It has been suggested that tamoxifen should be used with caution in patients with hypertriglyceridaemia.[3,4]

1. Love RR, *et al*. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Intern Med* 1991; **115:** 860–4.
2. Vehmanen L, *et al*. Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids. *Br J Cancer* 2004; **91:** 476–81.
3. Kanel KT, *et al*. Delayed severe hypertriglyceridaemia from tamoxifen. *N Engl J Med* 1997; **337:** 281.
4. Colls BM, George PM. Severe hypertriglyceridaemia and hypercholesterolaemia associated with tamoxifen use. *Clin Oncol* 1998; **10:** 270–1.
5. Sakhri J, *et al*. Severe acute pancreatitis due to tamoxifen-induced hypertriglyceridemia with positive rechallenge. *JOP* 2010; **11:** 382–4.

Effects on bones and joints. Arthralgia has been reported as an adverse effect of generic tamoxifen therapy; however, a crossover study[1] involving 121 postmenopausal women who developed new onset arthralgia during tamoxifen treatment for breast cancer found that arthralgia resolved in 114 when generic tamoxifen was swapped for another brand (*Nolvadex; AstraZeneca, UK*). Arthralgia recurred when the patients resumed taking a generic. It was suggested that possibly the generic tablets included an excipient responsible for symptoms, or Nolvadex contained an excipient with a protective effect.

1. Blencowe NS, *et al*. The use of Nolvadex in the treatment of generic Tamoxifen-associated small joint arthralgia. *Breast* 2010; **19:** 243–5.

Effects on the cardiovascular system. *ISCHAEMIC HEART DISEASE.* For discussion of whether the effects of tamoxifen on lipid profiles can alter the incidence of ischaemic heart disease, see Cardiovascular Disorders under Uses and Administration, p. 861.1.

STROKE. An excess risk of stroke was seen in tamoxifen compared with placebo recipients (5 cases versus 1) in a study of adjuvant tamoxifen.[1] A statistically non-significant increase in stroke was also seen in a study on the use of tamoxifen for breast cancer prevention (0.5 excess cases per 1000 women per year).[2] A meta-analysis[3] of 9 studies for prevention or treatment of breast cancer, involved data from 39 601 women, of whom 19 954 received tamoxifen. It concluded that use of tamoxifen increased the risk of ischaemic stroke by 82%, and the risk of any stroke by 29%; however, the absolute increase in risk was small.

In contrast, a case-control study of 11 045 women with breast cancer, found that tamoxifen use was not associated with an increased risk of first stroke.[4]

A time-dependent effect of adjuvant tamoxifen has been seen, with significantly increased morbidity and mortality from cerebrovascular disease, including stroke, during the active treatment period; risk was significantly decreased after treatment was stopped.[5]

1. Dignam JJ, Fisher B. Occurrence of stroke with tamoxifen in NSABP B-24. *Lancet* 2000; **355:** 848–9.
2. Fisher B, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
3. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004; **63:** 1230–3.
4. Geiger AM, *et al*. Stroke risk and tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; **96:** 1528–36.
5. Rosell J, *et al*. Time dependent effects of adjuvant tamoxifen therapy on cerebrovascular disease: results from a randomised trial. *Br J Cancer* 2011; **104:** 899–902.

THROMBOEMBOLISM. A case control study,[1] involving 25 cases of deep-vein thrombosis or pulmonary embolism among more than 10 000 women with breast cancer, suggested that current use of tamoxifen was associated with an estimated relative risk of developing idiopathic venous thromboembolism of 7.1 (95% confidence interval 1.5 to 33). Past use of tamoxifen was not associated with a materially increased risk. In a randomised placebo-controlled study, there was an increase in pulmonary emboli in women receiving tamoxifen for cancer prevention (excess of 0.46 cases per 1000 women per year).[2] The fatality rate from pulmonary emboli in tamoxifen recipients was about 17%. In this study, there was also a trend towards more deep-vein thrombosis in tamoxifen recipients. In another controlled study[3] of breast cancer prevention, tamoxifen approximately doubled the risk of developing a major thromboembolic event such as pulmonary embolism, deep-vein thrombosis, or retinal thrombosis. Cerebral sinus thrombosis has also been reported.[4] An analysis[5] of 4 tamoxifen prevention studies also found that venous thromboembolic events were increased in all studies, with a relative risk of 1.9 for those taking tamoxifen compared with placebo. However, another randomised study[6] found only a borderline significantly higher risk of developing venous thromboembolic events in those women allocated to tamoxifen; most of these events were superficial thrombophlebitis. Furthermore, women already at risk for atherosclerosis had a higher risk of venous thromboembolism. While the authors could not exclude a selection bias for healthier subjects in the study, they commented that the prothrombotic effect of tamoxifen may depend on the patient's existing endocrine status, and may be attenuated in those women taking HRT, especially when it is used transdermally.

1. Meier CR, Jick H. Tamoxifen and risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 1998; **45:** 608–12.
2. Fisher B, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
3. Duggan C, *et al*. Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. *J Clin Oncol* 2003; **21:** 3588–93.
4. Masjuan J, *et al*. Tamoxifen: a new risk factor for cerebral sinus thrombosis. *Neurology* 2004; **62:** 334–5.
5. Cuzick J, *et al*. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003; **361:** 296–300.
6. Decensi A, *et al*. Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. *Circulation* 2005; **111:** 650–6.

Effects on the eyes. Tamoxifen has been reported to be associated with decreased visual acuity, corneal opacities and cataract, and retinopathy. The latter is sometimes progressive although in most cases it has shown improvement once the drug was stopped.[1] A prospective study in 63 patients taking tamoxifen 20 mg daily found evidence of decreased visual acuity, macular oedema, and retinal opacities in 4, occurring after 10 to 35 months of therapy.[2] A small excess risk of developing cataracts (3.1 extra per year per 1000 women) and of requiring cataract surgery (1.7 per year per 1000 women) was found in women taking tamoxifen for up to 5 years to reduce the risk of breast cancer.[3] Studies *in vitro* have suggested that cataract formation may be due to inhibition of chloride channels in the lens by tamoxifen or its hydroxy metabolite.[4] Retinopathy after high-dose tamoxifen treatment may be associated with crystalline deposition of the drug in the retina.[5]

1. Mihm LM, Barton TL. Tamoxifen-induced ocular toxicity. *Ann Pharmacother* 1994; **28:** 740–2.
2. Pavlidis NA, *et al*. Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. *Cancer* 1992; **69:** 2961–4.
3. Fisher B, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
4. Zhang JJ, *et al*. Tamoxifen blocks chloride channels: a possible mechanism for cataract formation. *J Clin Invest* 1994; **94:** 1690–7.
5. Bourla DH, *et al*. Peripheral retinopathy and maculopathy in high-dose tamoxifen therapy. *Am J Ophthalmol* 2007; **144:** 126–8.

Effects on the genito-urinary system. Persistent nocturnal priapism was reported in a man receiving tamoxifen 20 mg daily.[1] Symptoms abated within 24 hours of withdrawing the drug. Impotence has been reported in men receiving tamoxifen, and has been attributed to a paradoxical oestrogenic effect.[2]

1. Fernando IN, Tobias JS. Priapism in patient on tamoxifen. *Lancet* 1989; **i:** 436.
2. Collinson MP, *et al*. Two case reports of tamoxifen as a cause of impotence in male subjects with carcinoma of the breast. *Breast* 1993; **2:** 48–9.

Effects on the liver. Cholestasis and increased liver enzyme values have been reported on use of tamoxifen in a 75-year-old patient.[1] Enzyme activity rose again on rechallenge with tamoxifen. Fatal hepatocellular necrosis and agranulocytosis, possibly exacerbated by continuing to take the drug once jaundice developed, has also been reported;[2] the authors noted that 4 cases of hepatic failure (3 fatal) and 5 cases of hepatitis (1 fatal) had been reported to the UK CSM. Patients taking tamoxifen may also develop steatohepatitis,[3-7] which must be distinguished from alcohol-induced liver disease. Steatohepatitis is reversible on withdrawal of tamoxifen.[3,5,6] A study in healthy women who had had hysterectomies found the risk of steatohepatitis to be particularly high among obese women, moderately high among overweight women, and similar to that with placebo in women of normal weight.[8] Bezafibrate has been tried to prevent progression of steatohepatitis and permit continued use of tamoxifen.[9]

For a report of peliosis hepatis and liver haemorrhage in a patient receiving tamoxifen and warfarin, see Anticoagulants, under Interactions, p. 863.2.

For reference to studies in *animals* suggesting that tamoxifen has the potential to cause liver cancer, see Carcinogenicity, p. 861.3.

1. Blackburn AM, *et al*. Tamoxifen and liver damage. *BMJ* 1984; **289:** 288.
2. Ching CK, *et al*. Tamoxifen-associated hepatocellular damage and agranulocytosis. *Lancet* 1992; **339:** 940.
3. Pratt DS, *et al*. Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1995; **123:** 236.
4. Van Hoof M, *et al*. Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1996; **124:** 855–6.
5. Ogawa Y, *et al*. Tamoxifen-induced fatty liver in patients with breast cancer. *Lancet* 1998; **351:** 725.
6. Oien KA, *et al*. Cirrhosis with steatohepatitis after adjuvant tamoxifen. *Lancet* 1999; **353:** 36–7.
7. Osman KA, *et al*. Tamoxifen-induced non-alcoholic steatohepatitis: where are we now and where are we going? *Expert Opin Drug Safety* 2007; **6:** 1–4.
8. Bruno S, *et al*. Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. *BMJ* 2005; **330:** 932–5.
9. Saibara T, *et al*. Bezafibrate for tamoxifen-induced non-alcoholic steatohepatitis. *Lancet* 1999; **353:** 1802.

Effects on the ovaries. Ovarian cysts are relatively common as an adverse effect in women receiving adjuvant tamoxifen: a study[1] in 95 such women reported the development of ovarian cysts in 6 of 16 (37.5%) who were premenopausal and in 5 of 79 postmenopausal women (6.3%). In 2 of the premenopausal women the cysts were complex. Two women underwent laparotomy for persistent cysts that were found to be benign, and 1 for leiomyoma; the cysts in the other 8 women resolved after withdrawal of tamoxifen. A study of 142 breast cancer patients receiving tamoxifen found ovarian cysts in 24 patients after treatment. Cyst development was more common in pre-menopausal women, patients with high oestrogen levels, and patients who did not receive high-dose chemotherapy.[2] There is little evidence that tamoxifen increases the risk of ovarian cancer (see Carcinogenicity, p. 861.3).

1. Shushan A, *et al*. Ovarian cysts in premenopausal and postmenopausal tamoxifen-treated women with breast cancer. *Am J Obstet Gynecol* 1996; **174:** 141–4.
2. Mourits MJE, *et al*. Ovarian cysts in women receiving tamoxifen for breast cancer. *Br J Cancer* 1999; **79:** 1761–64.

Effects on the skin and hair. Vasculitis has been reported in patients given tamoxifen.[1,2] Withdrawal of the drug resulted in complete clearance of the lesions;[1,2] in one case, on re-introduction, purpura developed again within a few days.[1] The results suggest that tamoxifen can produce immune-mediated vascular damage.

In another report a patient with white hair developed darkening and repigmentation of the hair after about 2½ years of tamoxifen therapy.[3] Alopecia has also been reported in women given tamoxifen,[4,5] and in older patients the follicle may not recover.[4]

1. Drago F, *et al*. Tamoxifen and purpuric vasculitis. *Ann Intern Med* 1990; **112:** 965–6.
2. Baptista MZ, *et al*. Tamoxifen-related vasculitis. *J Clin Oncol* 2006; **24:** 3504–5.
3. Hampson JP, *et al*. Tamoxifen-induced hair colour change. *Br J Dermatol* 1995; **132:** 483–4.
4. Gateley CA, Bundred NJ. Alopecia and breast disease. *BMJ* 1997; **314:** 481.
5. Ayoub J-PM, *et al*. Tamoxifen-induced female androgeneticalopecia in a patient with breast cancer. *Ann Intern Med* 1997; **126:** 745–6.

Precautions

All patients being considered for treatment with tamoxifen should be assessed for any increased risk of thromboembolism. Tamoxifen should not be used for treatment of infertility or the prophylaxis of breast cancer in women with a history of thromboembolic events. When used to treat breast cancer in such women, the risks and benefits should be considered; in some patients, especially those given cytotoxic drugs, prophylactic anticoagulation may be justified. Care is also needed during or immediately after major surgery or prolonged immobility; all patients should be given prophylaxis against thrombosis. In patients being treated for infertility, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility and only restarted when the patient is fully mobile. Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness or any pain in the calf of one leg. Tamoxifen should be withdrawn immediately in any patient developing thromboembolism and appropriate treatment given. Treatment should not usually be restarted for infertility therapy but resumption of tamoxifen with prophylactic anticoagulation may be justified in selected patients with breast cancer.

Women treated with tamoxifen should have routine gynaecological monitoring, and any abnormal symptoms such as menstrual irregularities, abnormal vaginal bleeding or discharge, or pelvic pain should be investigated (see also under Carcinogenicity, p. 861.3). Periodic complete blood counts and liver function tests have been suggested.

Abuse. Although the supervised use of tamoxifen for the treatment of gynaecomastia resulting from the abuse of anabolic steroids has been reported[1] it also appears to be widely used without medical supervision. Tamoxifen can be used to treat idiopathic gynaecomastia and gynaecomastia resulting as an adverse effect of nonsteroidal anti-androgens used to treat prostate cancer (see under Breast Disorders, Non-malignant, p. 860.3).

1. de Luis DA, *et al.* Anabolizantes esteroideos y ginecomastia: revisión de la literatura. *An Med Interna* 2001; **18:** 489–91.

Breast feeding. Tamoxifen was shown to inhibit lactation in 60 puerperal women.[1] Licensed product information recommends that it should not be given to lactating women as it is unknown if tamoxifen appears in breast milk.

1. Masala A, *et al.* Inhibition of lactation and inhibition of prolactin release after mechanical breast stimulation in puerperal women given tamoxifen or placebo. *Br J Obstet Gynaecol* 1978; **85:** 134–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tamoxifen as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pregnancy. Tamoxifen is contra-indicated in pregnancy. Ambiguous genitalia have been reported in an infant exposed to tamoxifen *in utero*, although no causal link was found.[1] Another infant was born with Goldenhar's syndrome (oculoauriculovertebral dysplasia) after exposure to tamoxifen throughout a 26-week pregnancy.[2] The mother had also taken cocaine and marijuana during the first 6 weeks of pregnancy, and a bone scan using technetium (^{99m}Tc) medronate had been performed. The US manufacturer of tamoxifen (*Zeneca, USA*) was aware of 50 pregnancies in patients taking tamoxifen, resulting in 19 normal births, 8 terminations, 13 unknown outcomes and 10 infants with fetal or neonatal abnormalities.[2]

Tamoxifen has also been used to stimulate ovulation in women with luteal phase dysfunction. In one study tamoxifen was given to 40 women, resulting in 14 pregnancies. Although 9 infants were born with no congenital abnormalities, there were 5 spontaneous abortions, which the authors felt was unacceptably high.[3] Another study, using lower doses of tamoxifen (in some cases sequentially with clomifene), reported 32 pregnancies and only 3 spontaneous abortions in 65 treated patients.[4]

1. Tewari K, *et al.* Ambiguous genitalia in infant exposed to tamoxifen in utero. *Lancet* 1997; **350:** 183.
2. Cullins SL, *et al.* Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994; **271:** 1905–6.
3. Ruiz-Velasco V, *et al.* Chemical inducers of ovulation: comparative results. *Int J Fertil* 1979; **24:** 61–64.
4. Wu CH. Less miscarriage in pregnancy following tamoxifen treatment of infertile patients with luteal phase dysfunction as compared to clomiphene treatment. *Early Pregnancy* 1997; **3:** 301–5.

Radiotherapy. There are reports of radiation recall, with erythema at the site of previous radiotherapy, in patients receiving tamoxifen.[1-3]

1. Parry BR. Radiation recall induced by tamoxifen. *Lancet* 1992; **340:** 49.
2. Extermann M, *et al.* Radiation recall in a patient with breast cancer treated for tuberculosis. *Eur J Clin Pharmacol* 1995; **48:** 77–8.
3. Singer EA, *et al.* Tamoxifen-induced radiation recall dermatitis. *Breast J* 2004; **10:** 170–1.

Interactions

There is a risk of increased anticoagulant effect if tamoxifen is given with coumarin anticoagulants. Conversely, use with cytotoxic drugs may increase the risk of thromboembolic events; prophylactic anticoagulation should be considered. In order to avoid bleeding during a possible thrombocytopenic episode, platelet aggregation inhibitors should not be used with tamoxifen. Tamoxifen increases the dopaminergic effect of bromocriptine; bromocriptine increases serum concentrations of tamoxifen and its major metabolite *N*-desmethyltamoxifen (see Pharmacokinetics, below). Use with inhibitors of cytochrome P450 isoenzyme CYP2D6 has been shown to reduce plasma concentrations of endoxifen, a tamoxifen metabolite (see Pharmacokinetics, below); while the clinical relevance is unclear, a reduced effect of tamoxifen cannot be excluded, and use with potent CYP2D6 inhibitors should be avoided if possible.

Tamoxifen is metabolised by CYP3A4 and care is required when it is used with CYP3A4 inducers, as tamoxifen concentrations may be reduced; plasma concentrations of tamoxifen may be increased by use with CYP3A4 inhibitors.

Preparations of sex hormones, especially oestrogens, should not be used with tamoxifen as a mutual decrease in effect is possible. Medroxyprogesterone decreases concentrations of *N*-desmethyltamoxifen, but not of tamoxifen.

Tamoxifen is metabolised by cytochrome P450 isoenzymes, including CYP2D6 (see Pharmacokinetics, below), and drugs which inhibit CYP2D6 can reduce metabolism and potentially increase the risk of breast cancer recurrence. Recommendations regarding the use of these drugs with tamoxifen have been made:[1]

Potent inhibitors should be avoided; these include the SSRIs paroxetine, fluoxetine, bupropion, and duloxetine (see also Antidepressants, below), and other drugs such as perphenazine, pimozide, thioridazine, quinidine, ticlopidine, terbinafine, and cinacalcet.

Weak to moderate inhibitors should be used with caution, especially in patients considered to be CYP2D6 intermediate metabolisers (see Genetic Factors, below). These include the SSRIs sertraline, citalopram, and fluvoxamine, the tricyclic antidepressants clomipramine, doxepin, desipramine, imipramine, amitriptyline, and nortriptyline, as well as other drugs such as chlorpromazine, fluphenazine, haloperidol, amiodarone, amlodipine, felodipine, nicardipine, nifedipine, verapamil, chloroquine, halofantrine, ritonavir, cimetidine, clemastine, diphenylpyraline, hydroxyzine, promethazine, tripelennamine, and celecoxib.

1. Sideras K, *et al.* Coprescription of tamoxifen and medications that inhibit CYP2D6. *J Clin Oncol* 2010; **28:** 2768–76. Correction. *ibid.*; 3543.

Allopurinol. For reference to exacerbation of hepatotoxicity when tamoxifen was given with allopurinol, see p. 603.1.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of tamoxifen in 10 healthy subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Anticoagulants. Cases of a potentially life-threatening interaction between tamoxifen and *warfarin*, with marked prolongation of prothrombin times, haematuria, and haematoma, have been reported.[1-3] It has been suggested that in addition to enhancement of the effects of warfarin, competition for the same metabolic enzyme systems might reduce the activity of tamoxifen against tumours,[2] but this remains speculative.

Peliosis hepatis and fatal liver haemorrhage have been reported in a patient who was receiving tamoxifen with warfarin and a liothyronine-levothyroxine preparation.[4]

1. Lodwick R, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1987; **295:** 1141.
2. Tenni P, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1989; **298:** 93.
3. Ritchie LD, Grant SMT. Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file. *BMJ* 1989; **298:** 1253.
4. Loomus GN, *et al.* A case of peliosis hepatis in association with tamoxifen therapy. *Am J Clin Pathol* 1983; **80:** 881–3.

Antidepressants. Some antidepressants, particularly *SSRIs*, may inhibit the bioactivation of tamoxifen via the cytochrome P450 isoenzyme CYP2D6. The metabolism of tamoxifen to an active metabolite, 4-hydroxy-*N*-desmethyltamoxifen (endoxifen), may be inhibited by *paroxetine*, a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6.[1] However, the clinical consequences of this are not fully established. A case-control study[2] found that patients taking tamoxifen with known inhibitors of CYP isoenzymes, including CYP2D6, were no more likely to relapse than those not receiving a CYP inhibitor. However, a retrospective cohort study[3] found that paroxetine use during tamoxifen treatment was associated with an increased risk of death from breast cancer. The increased risk was directly related to the duration of combined use, and supports the hypothesis that irreversible CYP2D6 inhibition by paroxetine can reduce or abolish the survival advantage conferred by long-term tamoxifen treatment in patients with breast cancer. In contrast, no such risk was seen with other antidepressants (*citalopram, fluoxetine, fluvoxamine, sertraline*, and *venlafaxine*), although smaller sample sizes for some may have influenced results. Some consider that potent CYP2D6 inhibitors such as bupropion, paroxetine, and fluoxetine should be avoided in women with breast cancer taking tamoxifen, and antidepressants with a low potential to inhibit CYP2D6 (such as venlafaxine or citalopram) should be considered instead.[4-6] Caution is warranted even with moderate CYP2D6 inhibitors such as duloxetine and sertraline.[6]

For further reference to use of CYPD26 inhibitors with tamoxifen, including a slightly different classification for some of the SSRIs mentioned here, see above.

1. Stearns V, *et al.* Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003; **95:** 1758–64.
2. Lehmann D, *et al.* Lack of attenuation in the antitumor effect of tamoxifen by chronic CYP isoform inhibition. *J Clin Pharmacol* 2004; **44:** 861–5.
3. Kelly CM, *et al.* Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 2010; **340:** c693. Available at: http://www.bmj.com/cgi/reprint/340/feb08_1/c693 (accessed 20/04/10)
4. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. *J Clin Psychiatry* 2009; **70:** 1688–97.
5. Andersohn F, Willich SN. Interaction of serotonin reuptake inhibitors with tamoxifen. *BMJ* 2010; **340:** c783. Available at: http://www.bmj.com/cgi/section_pdf/340/feb08_3/c783.pdf (accessed 20/04/10)
6. Anonymous. Drug interaction between tamoxifen and antidepressants. *Aust Prescriber* 2011; **34:** 23.

Antineoplastics. *Aminoglutethimide* reduces serum tamoxifen concentrations, possibly by increasing its metabolism.[1] For mention of an increased risk of haemolytic-uraemic syndrome in patients who received therapy with tamoxifen and *mitomycin* see Effects on the Kidneys, under Mitomycin, p. 831.3. Tamoxifen has been reported to affect plasma concentrations of *anastrozole* and *letrozole*, see p. 743.1 and p. 817.3, respectively.

1. Lien EA, *et al.* Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. *Cancer Res* 1990; **50:** 5851–7.

Herbal medicines. Some authors have expressed concern that herbs such as *dong quai* (which has been used to relieve hot flushes after chemotherapy for breast cancer), *agnus castus, cimicifuga, ginseng*, and *lupulus* have shown significant oestrogenic activity in studies in *animals* and *in vitro*,[1-3] and might interfere with competitive oestrogen receptor antagonists such as tamoxifen.[1]

1. Boyle FM. Adverse interaction of herbal medicine with breast cancer treatment. *Med J Aust* 1997; **167:** 286.
2. Eagon CL, *et al.* Medicinal botanicals: estrogenicity in rat uterus and liver. *Proc Am Assoc Cancer Res* 1997; **38:** 293.
3. Doyle BJ, *et al.* Estrogenic effects of herbal medicines from Costa Rica used for the management of menopausal symptoms. *Menopause* 2009; **16:** 748–55.

Immunosuppressants. For the results of a study *in vitro* suggesting that tamoxifen might inhibit the metabolism of *tacrolimus* by inhibiting the cytochrome P450 isoenzyme system, see under Interactions of Tacrolimus, p. 1977.3.

Neuromuscular blockers. For reference to prolonged neuromuscular blockade in a patient given *atracurium* while receiving tamoxifen, see p. 2032.2.

Pharmacokinetics

Peak plasma concentrations of tamoxifen occur 4 to 7 hours after an oral dose. It is extensively protein bound. Plasma clearance is reported to be biphasic and the terminal half-life may be up to 7 days. It is extensively metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6. The major serum metabolite, *N*-desmethyltamoxifen is formed mainly via CYP3A4; it has a half-life at steady state of about 14 days. 4-Hydroxytamoxifen is a minor metabolite. *N*-Desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised (via CYP2D6 and the CYP3A family, respectively) to 4-hydroxy-*N*-desmethyltamoxifen (endoxifen). Several of the metabolites are stated to have similar pharmacological activity to the parent compound, and endoxifen has been proposed as an alternative treatment to avoid differences in metabolism (see Metabolism, p. 864.1). Tamoxifen is excreted slowly in the faeces, mainly as conjugates. Small amounts are excreted in urine. Tamoxifen appears to undergo enterohepatic circulation.

Genetic factors. Tamoxifen is metabolised by the cytochrome P450 isoenzymes, and its metabolites may play a role in its antineoplastic effect. Studies have suggested that

patients with low or absent CYP2D6 activity or who are being treated with CYP2D6 inhibitors have lower concentrations of endoxifen. Patients with CYP2D6*3, *4, *5, and *6 alleles are designated as poor metabolisers, those with *9, *10, *17, *29, and *41 as intermediate metabolisers, and those with *1, *2, and *35 as extensive metabolisers.[1,2] Genetic polymorphism in the enzymes responsible for tamoxifen biotransformation has the potential to affect clinical outcomes. While a small study[3] showed a decreased risk of breast cancer recurrence in patients with the CYP2D6*4 allele when treated with tamoxifen, another[4] found that this allele was an independent predictor of a higher risk of disease relapse and a lower incidence of hot flashes in postmenopausal women with breast cancer. A further study[5] found that carriers of CYP2D6 alleles *4 or *5 showed a greater risk for breast cancer relapse. Furthermore, carriers of the CYP2C19*17 genotype had a more favourable clinical outcome. A retrospective cohort study found that poor metabolisers had an almost twofold increased risk of breast cancer recurrence compared with extensive metabolisers; those with decreased CYP2D6 activity (intermediate and poor metabolisers) also had worse disease-free survival compared with extensive metabolisers, although there was no significant difference in overall survival.[6] The Clinical Pharmacology Subcommittee of the US FDA Advisory Committee for Pharmaceutical Science has advised that availability of genotypic testing be included in licensed product information for tamoxifen.[7,8] Some have commented[8] that it would seem reasonable to confine CYP2D6 testing to situations where it might guide the choice between tamoxifen and an alternative.

It has been suggested[9] that genetic variation in uridine diphosphate glucuronosyltransferase (UGT) enzymes, which are important in the glucuronidation of tamoxifen and its metabolites, may also play a role in interindividual differences in response to the drug.

1. Borges S, *et al*. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther* 2006; **80:** 61–74.
2. Goetz MP, *et al*. Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. *Clin Pharmacol Ther* 2008; **83:** 160–6.
3. Wegman P, *et al*. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res* 2005; **7:** R284–R290.
4. Goetz MP, *et al*. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; **23:** 9312–18.
5. Schroth W, *et al*. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol* 2007; **25:** 5187–93.
6. Schroth W, *et al*. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA* 2009; **302:** 1429–36.
7. Young D. Genetics examined in tamoxifen's effectiveness: recurrence warning urged for labeling. *Am J Health-Syst Pharm* 2006; **63:** 2286, 2296.
8. Desta Z, Flockhart DA. Germline pharmacogenetics of tamoxifen response: have we learned enough? *J Clin Oncol* 2007; **25:** 5147–9.
9. Lazarus P, *et al*. Potential role of UGT pharmacogenetics in cancer treatment and prevention: focus on tamoxifen. *Ann N Y Acad Sci* 2009; **1155:** 99–111.

Metabolism. Tamoxifen is extensively metabolised by cytochrome P450 isoenzymes, to active metabolites that include *N*-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-*N*-desmethyltamoxifen (endoxifen).[1,2] *In-vitro* studies suggest that both *N*-desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised to endoxifen.[3] There is growing interest in how genetic polymorphism might influence the efficacy and toxicity of tamoxifen and its metabolites (see Genetic Factors, p. 863.3). Substitution of endoxifen for tamoxifen has been proposed as a treatment option for patients with breast cancer in order to avoid any effects of genetic polymorphisms as well as any interactions with cytochrome P450 isoenzyme CYP2D6 inhibitors (see under Interactions, p. 863.2). The safety, tolerability, and bioavailability of an oral formulation of endoxifen has been evaluated; a daily dose of 4 mg endoxifen citrate has been proposed as being appropriate for breast cancer prevention and therapy.[2]

1. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. *Clin Pharmacokinet* 2005; **44:** 349–66.
2. Ahmad A, *et al*. Endoxifen, a new cornerstone of breast cancer therapy: demonstration of safety, tolerability, and systemic bioavailability in healthy human subjects. *Clin Pharmacol Ther* 2010; **88:** 814–7.
3. Desta Z, *et al*. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther* 2004; **310:** 1062–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisafeno; Diemon†; Ginarsan; Nolvadex; Rolap†; Tamoxis; Taxfeno†; Trimetrox†; ***Austral.***: Genox; Nolvadex; Tamosin; Tamoxen; ***Austria***: Ebefen; Nolvadex; ***Belg.***: Doctamoxifene†; Nolvadex; Tamizam; Tamoplex; ***Braz.***: Bioxifeno†; Festone; Kessar†; Nolvadex; Tamoxin; Taxofen; Tecnotax; ***Canad.***: Apo-Tamox; Nolvadex; Tamofen†; ***Chile***: Kessar; Nolvadex; Oncotamox†; Taxus; ***China***: De Fu Ling (德孚伶); Tamofen (特茉芬); Xifen (昔芬); ***Cz.***: Nolvadex†; Tamoplex; Zitazonium†; ***Fin.***: Tadex; Tamexin†; Tamofen; ***Fr.***: Nolvadex; ***Ger.***: Mandofen†; Nolvadex; Tamokadin†; Tamox†; Tamoxistad†; ***Gr.***: Adifen; Defarol; Kessar; Nolvadex; Puretam; Tamoplex; Terimon; Zymoplex; ***Hong Kong***: Apo-Tamox; Nolvadex; Novofen†; Zitazonium; ***Hung.***: Zitazonium; ***India***: Blastofen; Caditam; Cytotam; Eldtam; Mamofen; Moxifen; Neotam; Nolvadex; Oncomox; Oncotam; Tamodex; ***Indon.***: Nolvadex†; Tamofen; Tamoplex; Taxen†; ***Irl.***: Moxelle; Nolvadex; Soltamox; Tamox; ***Israel***: Nolvadex†; Tamofen†; Tamoxi†; ***Ital.***: Kessar; Nolvadex; Nomafen; Tamoxene; ***Malaysia***: Genox†; Nolvadex; Novofen; Tamoplex; Zitazonium; ***Mex.***: Bagotam†; Bilem; Cryoxifeno; Fenobest; Luzamoxin; Nolvadex; Ralsifen-X; Taxus; Tecnofen; ***Neth.***: Nolvadex†; Soltamox; ***Norw.***: Nolvadex; ***NZ***: Genox; Nolvadex†; Tamofen†; ***Philipp.***: Cytrolic†; Fenahex; Gynatam; Gyraxen; Kessar†; Medtax; Nolvadex; Tamoplex; Tamoxsta†; Xifen; Zitazonium; ***Pol.***: Nolvadex; ***Port.***: Mastofen†; Nolvadex; Tamoxan; ***Rus.***: Tamifen (Тамифен)†; Zitazonium (Зитазониум); ***S.Afr.***: Kessar; Neophedan; Nolvadex; Tamoplex; TamoxiHexal; ***Singapore***: Apo-Tamox†; Nolvadex; Novofen; Tamofen†; ***Spain***: Nolvadex; Yacesal†; ***Swed.***: Nolvadex; ***Switz.***: Nolvadex; Tamec; ***Thai.***: Bilem; Gynatam†; Mamofen; Moxafen†; Nolvadex; Novofen; Tamoplex; Tuosomin†; Zitazonium; ***Turk.***: Nolvadex; Tadex; Tamofen†; Tamoplex; Tamoxifencell; ***UAE***: Tamophar; ***UK***: Nolvadex†; Soltamox; ***USA***: Soltamox; ***Venez.***: Gynatam; Nolvadex; Taxus.

Pharmacopoeial Preparations
BP 2014: Tamoxifen Tablets;
USP 36: Tamoxifen Citrate Tablets.

Tegafur *(BAN, USAN, rINN)*

FT-207; Ftorafur; MJF-12264; NSC-148958; Tegafúr; Tégafur; Tegafuras; Tegafūrs; Tegafurum; Tegafuuri; WR-220066; Терафур.

5-Fluoro-1-(tetrahydro-2-furyl)uracil; 5-Fluoro-1-(tetrahydro-2-furyl)pyrimidine-2,4(1*H*,3*H*)-dione.

$C_8H_9FN_2O_3$=200.2

CAS — 17902-23-7.

ATC — L01BC03.

ATC Vet — QL01BC03.

UNII — 1548R74NSZ.

NOTE. The name S-1 has been used for a mixture of tegafur, gimeracil, and oteracil potassium.

Pharmacopoeias. In *Chin.* and *Jpn*.

Uses and Administration

Tegafur is considered to be an orally active prodrug of fluorouracil (p. 795.3). It has been used in the management of malignant neoplasms including those of the breast, gallbladder, gastrointestinal tract, head and neck, liver, and pancreas. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Tegafur has been given orally in doses up to 1 g/m^2 daily. It is often given with uracil (UFT; p. 2637.3). Tegafur 300 mg/m^2 daily, with uracil 672 mg/m^2 daily, may be given in 3 divided oral doses, together with calcium folinate, in the management of metastatic colorectal cancer. Doses are given for a cycle of 28 days, followed by 7 days without treatment. The drugs should be taken 1 hour before or after meals, and doses modified according to toxicity. Doses of tegafur 1 to 3 g/m^2 daily for 5 days have been given **intravenously**.

Administration. Tegafur is an orally active prodrug of fluorouracil. Although it has been given as a single agent, it is more often used with drugs that modify its bioavailability and toxicity.[1] These include uracil (p. 2637.3) and gimeracil (5-chloro-2,4-dihydroxypyridine, CDHP, gimestat), which can increase fluorouracil concentrations by inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for its further catabolism,[1-4] and oteracil (oxonic acid), which inhibits another enzyme, orotate pyrimidine phosphoribosyl transferase, thought to play a role in the gastrointestinal toxicity of fluorouracil and its prodrugs.[2]

UFT consists of tegafur and uracil in the optimal molar ratio 1:4.[1] It is available for the treatment of colorectal cancer (p. 706.3)—for doses, see above. A preliminary analysis of a large study comparing oral UFT and calcium folinate therapy with intravenous fluorouracil and calcium folinate found both regimens to be well tolerated with similar levels of toxicity.[5] It is also used as adjuvant therapy for gastrointestinal and other solid tumours,[6] including being tried in hepatocellular carcinoma;[7] it appears to improve survival in patients with adenocarcinoma of the lung[8] and node-negative breast cancer.[9] The efficacy of tegafur-based adjuvant therapy in Japanese patients with stomach cancer has been reviewed.[10]

A combination of tegafur, gimeracil, and oteracil potassium in the molar ratio 10:4:10 (TS-1, *Taiho Jpn*) has been tried in gastric and colorectal cancers.[2-4,11] Initial results have suggested comparable activity to fluorouracil and calcium folinate in induction regimens but the incidence of diarrhoea and stomatitis was reduced.

1. Adjei AA. A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer. *Br J Clin Pharmacol* 1999; **48:** 265–77.
2. Sakata Y, *et al*. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34:** 1715–20.
3. Sugimachi K, *et al*. An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999; **57:** 202–10.
4. Osugi H, *et al*. Oral fluoropyrimidine anticancer drug TS-1 for gastric cancer patients with peritoneal dissemination. *Oncol Rep* 2002; **9:** 811–15.
5. Smith R, *et al*. UFT plus calcium folinate vs 5-FU plus calcium folinate in colon cancer. *Oncology (Huntingt)* 1999; **13** (suppl 3): 44–7.
6. Tanaka F. UFT (tegafur and uracil) as postoperative adjuvant chemotherapy for solid tumors (carcinoma of the lung, stomach, colon/rectum, and breast): clinical evidence, mechanism of action, and future direction. *Surg Today* 2007; **37:** 923–43.
7. Ishikawa T. Chemotherapy with enteric-coated tegafur/uracil for advanced hepatocellular carcinoma. *World J Gastroenterol* 2008; **14:** 2797–2801.
8. Kato H, *et al*. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350:** 1713–21.
9. Noguchi S, *et al*. Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. *J Clin Oncol* 2005; **23:** 2172–84.
10. Oba K. Efficacy of adjuvant chemotherapy using tegafur-based regimen for curatively resected gastric cancer: update of a meta-analysis. *Int J Clin Oncol* 2009; **14:** 85–9.
11. Shibahara K, *et al*. Retrospective study of S-1 versus tegafur/uracil and oral leucovorin in patients with metastatic colorectal cancer. *Anticancer Res* 2008; **28:** 1779–83.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p. 797.1.

Bone-marrow depression may be less severe with tegafur but gastrointestinal toxicity is often dose-limiting and central neurotoxicity is more common. Peripheral oedema and dyspnoea occur commonly. Increases in liver function test values are common and there are reports of fatal fulminant hepatitis. Liver function should be monitored in patients with hepatic impairment given tegafur; it should not be given in severe hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tegafur as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

Tegafur should not be used with drugs that inhibit dihydropyrimidine dehydrogenase; fatalities have occurred in patients given tegafur and sorivudine (see Antivirals under Interactions of Fluorouracil, p. 797.3). For the effect of tegafur with uracil on phenytoin, see p. 544.1.

Pharmacokinetics

Tegafur is well absorbed from the gastrointestinal tract after oral doses. After an intravenous dose it is reported to have a prolonged plasma half-life of 6 to 16 hours. Tegafur appears to be slowly metabolised in the liver to fluorouracil (p. 798.1), and some intracellular conversion to fluorouracil may also occur. Tegafur crosses the blood-brain barrier and is found in the CSF.

References.

1. Etienne-Grimaldi M-C, *et al*. A clinical pharmacokinetic analysis of tegafur-uracil (UFT) plus leucovorin given in a new twice-daily oral administration schedule. *Clin Pharmacokinet* 2007; **46:** 953–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Aisiwan (爱斯万)†; Qi Xing (岐星); ***Cz.***: Ftorafur; ***Gr.***: Ftorafur; ***Hong Kong***: Futraful†; ***Hung.***: Ftorafur; ***Indon.***: Futraful; ***Jpn***: Futraful; ***Rus.***: Ftorafur (Фторафур); ***Spain***: Utefos; ***Ukr.***: Ftorafur (Фторафур).

Multi-ingredient Preparations. ***Arg.***: Asofurtal; Fimer; UFT; ***Austria***: UFT; ***Belg.***: UFT; ***Braz.***: UFT; ***China***: S-1 (爱斯万); Weikangda (维康达); ***Cz.***: Teysuno; UFT†; ***Denm.***: Teysuno; UFT; Uftoral†; ***Fr.***: UFT; ***Ger.***: UFT; ***Gr.***: UFT; ***Hong Kong***: UFT†; ***Hung.***: UFT†; ***Irl.***: Teysuno; UFT†; ***Israel***: UFT; ***Ital.***: UFT; ***Jpn***: TS-1; UFT; ***Malaysia***: UFT; ***Mex.***: UFT; ***Neth.***: Teysuno; UFT; ***Norw.***: Teysuno; UFT†; ***Philipp.***: Tefudex; UFT; ***Pol.***: UFT; ***Port.***: UFT; ***Rus.***: UFT (УФТ); ***S.Afr.***: UFT; ***Singapore***: TS-One; UFT; ***Spain***: UFT†; ***Swed.***: Teysuno; UFT†; ***Thai.***: TS-One; UFT†; UFUR; ***Turk.***: UFT; ***UK***: Teysuno; Uftoral†.

Temoporfin *(BAN, USAN, rINN)*

EF-9; *meso*-Tetrahydroxyphenylchlorin; *meta*-Tetrahydroxyphenylchlorin; mTHPC; Temoporfiini; Temoporfina; Témoporfine; Temoporfinum; Темопорфин.

3,3′,3″,3‴-(7,8-Dihydroporphyrin-5,10,15,20-tetrayl)tetraphenol; 7,8-Dihydro-5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin.

$C_{44}H_{32}N_4O_4$=680.8

CAS — 122341-38-2.

ATC — L01XD05.

ATC Vet — QL01XD05.

UNII — FU21S769PF.

Uses and Administration

Temoporfin is a porphyrin derivative. It is used palliatively as a photosensitiser in the photodynamic therapy (see under Porfimer Sodium, p. 849.1) of refractory squamous cell carcinoma of the head and neck (p. 708.1), that cannot be treated with radiotherapy, surgery, or systemic chemotherapy. It is also under investigation in the treatment of various other malignant neoplasms. Temoporfin is given by slow intravenous injection over at least 6 minutes, at a dose of 150 micrograms/kg. This is followed 96 hours later by activation using a laser tuned to a wavelength of 652 nanometres for about 200 seconds, sufficient to supply a dose of 20 J/cm^2. This should take place not less than 90 hours and not more than 110 hours after injection. Treatment may be repeated once after at least 4 weeks if necessary.

Liposomal formulations for topical delivery of temoporfin are under investigation.

References.

1. Kubler AC, *et al*. Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers Surg Med* 1999; **25:** 60–8.
2. Baas P, *et al*. Photodynamic therapy with *meta*-tetrahydroxyphenylchlorin for basal cell carcinoma: a phase I/II study. *Br J Dermatol* 2001; **145:** 75–8.
3. Kubler AC, *et al*. Treatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy. *Int J Oral Maxillofac Surg* 2001; **30:** 504–9.
4. Javaid B, *et al*. Photodynamic therapy (PDT) for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. *Lasers Med Sci* 2002; **17:** 51–6.
5. Friedberg JS, *et al*. A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma. *Ann Thorac Surg* 2003; **75:** 952–9.
6. Copper MP, *et al*. Meta-tetra(hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2003; **129:** 709–11.
7. D'Cruz AK, *et al*. mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. *Head Neck* 2004; **26:** 232–40.
8. Etienne J, *et al*. Photodynamic therapy with green light and m-tetrahydroxyphenyl chlorin for intramucosal adenocarcinoma and high-grade dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2004; **59:** 880–9. Correction. *ibid.*; **60:** 1042.
9. Hopper C, *et al*. mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma. *Int J Cancer* 2004; **111:** 138–46.
10. Lou PJ, *et al*. Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. *Br J Cancer* 2004; **91:** 441–6.
11. Campbell SM, *et al*. Photodynamic therapy using meta-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; **151:** 1076–80.
12. Naim R. Photodynamische Therapie mit m-THPC (Foscan): Behandlung von Plattenepithelkarzinomen im Kopf-Hals-Bereich. *HNO* 2008; **56:** 490–2.

Adverse Effects and Precautions

Adverse effects of temoporfin include photosensitivity, local inflammatory reactions, and gastrointestinal disturbances. Patients should be advised to avoid direct sunlight or bright indoor light for 15 days, and to protect the injection site from light for at least 3 months if extravasation has occurred.

Porphyria. Licensed product information states that the use of temoporfin is contra-indicated in patients with porphyria.

Interactions

Use of temoporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased; this has been reported with topical fluorouracil.

Pharmacokinetics

Peak plasma concentrations of temoporfin occur about 2 to 4 hours after intravenous infusion. Thereafter, elimination is bi-exponential, with a terminal plasma half-life of about 65 hours. Plasma protein binding is about 85%. *Animal* data indicate that temoporfin is metabolised in the liver and excreted in the faeces via the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Foscan; ***Belg.***: Foscan; ***Cz.***: Foscan; ***Denm.***: Foscan; ***Fr.***: Foscan†; ***Ger.***: Foscan; ***Gr.***: Foscan; ***Hung.***: Foscan; ***Irl.***: Foscan; ***Israel***: Foscan; ***Ital.***: Foscan; ***Neth.***: Foscan; ***Norw.***: Foscan; ***Pol.***: Foscan; ***Port.***: Foscan; ***UK***: Foscan.

Temozolomide *(BAN, USAN, rINN)*

CCRG-81045; M&B-39831; NSC-362856; Sch-52365; Temotsolomidi; Temozolomid; Temozolomida; Témozolomide; Temozolomidum; Темозоломид.

3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxamide.

$C_6H_6N_6O_2$=194.2

CAS — 85622-93-1.

ATC — L01AX03.

ATC Vet — QL01AX03.

UNII — YF1K15M17Y.

Pharmacopoeias. In *US*.

USP 36: (Temozolomide). A white to light pink or light tan powder. Sparingly soluble in water; practically insoluble in toluene; soluble in dimethyl sulfoxide.

Uses and Administration

Temozolomide is a prodrug that is converted to MTIC (see Pharmacokinetics, p. 866.1), the active metabolite of dacarbazine (p. 776.1). MTIC acts as an alkylating agent. Temozolomide is licensed for the treatment of malignant gliomas (below) such as glioblastoma multiforme and anaplastic astrocytoma, and metastatic malignant melanoma (below).

Temozolomide may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In adult patients with *newly diagnosed* **glioblastoma multiforme**, temozolomide is given initially with focal radiotherapy (the *concomitant phase*) in an oral or intravenous dose of 75 mg/m^2 daily for 42 days. Treatment may be interrupted or stopped depending on toxicity. Complete blood counts should be monitored weekly. Four weeks after completing the concomitant phase, temozolomide *monotherapy* is begun at an oral or intravenous dose of 150 mg/m^2 once daily for 5 days of a 28-day cycle. In cycle 2, the dose is increased to 200 mg/m^2 for 5 days, if toxicity allows. If the dose cannot be increased in cycle 2, it should not be increased in subsequent cycles. The dose used at cycle 2 is then given every 28 days, toxicity allowing. Up to 6 cycles of temozolomide monotherapy may be given.

The usual oral dose for *recurrent or progressive* malignant gliomas in adults previously untreated with chemotherapy is 200 mg/m^2 once daily for 5 days, repeated every 28 days. In patients who have received previous courses of chemotherapy the initial oral or intravenous dose is 150 mg/m^2 once daily for 5 days, for the first cycle of therapy, but may be increased to 200 mg/m^2 for subsequent courses if there is no haematological toxicity.

An oral dose of 200 mg/m^2 once daily for 5 days every 28 days is also used for metastatic **malignant melanoma**.

Administration. References[1,2] to the use of temozolomide in dose-dense regimens, designed to maximise exposure to the drug and consequent efficacy. In contrast to the original 5-day regimen (150 to 200 mg/m^2 daily for 5 days of a 28-day cycle) used in glioma, these have included 75 mg/m^2 daily for 6 to 7 weeks[1] (this is now recommended by licensed product information for the initial phase of glioma treatment) and regimens in which 150 mg/m^2 was given for 5 or 7 days of a 14-day cycle, or 100 mg/m^2 for 21 days of a 28-day cycle.[1] However, the increased dose intensity may be associated with increased adverse effects and the clinical benefits are still uncertain.

1. Wick W, *et al*. New (alternative) temozolomide regimens for the treatment of glioma. *Neuro Oncol* 2009; **11:** 69–79.
2. Neyns B, *et al*. Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects. *Cancer* 2010; **116:** 2868–77.

Administration in children. In the UK, temozolomide may be given to children aged 3 years or older for the treatment of malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, that recurs or progresses after standard therapy. It is given orally in the same dose as that used for adults (see Uses and Administration, above).

Malignant neoplasms. Temozolomide has been studied[1-9] particularly in the management of malignant neoplasms of the brain (p. 701.2). In the UK, guidance has been issued[10] on its use in patients with recurrent progressive malignant glioma who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of adverse effects). A systematic review[11] concluded that temozolomide is an effective primary therapy for newly diagnosed glioblastoma multiforme; it prolongs survival and delays progression. For recurrent disease, data from a single study indicate that it delays progression but does not affect overall survival. Another review[12] concluded that although there was good evidence for the use of temozolomide in both high- and low-grade gliomas, value could not be shown for other brain tumours, including metastases.

1. Dinnes J, *et al*. A rapid and systematic review of the effectiveness of temozolomide for the treatment of recurrent malignant glioma. *Br J Cancer* 2002; **86:** 501–5.
2. Wick W, *et al*. One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. *Neurology* 2004; **62:** 2113–15.
3. Levin N, *et al*. Chemotherapy as initial treatment in gliomatosis cerebri: results with temozolomide. *Neurology* 2004; **63:** 354–6.
4. Agarwala SS, *et al*. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol* 2004; **22:** 2101–7.
5. Stupp R, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352:** 987–96.
6. Athanassiou H, *et al*. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol* 2005; **23:** 2372–7.
7. Tosoni A, *et al*. Is protracted low-dose temozolomide feasible in glioma patients? *Neurology* 2006; **66:** 427–9.
8. Wick A, *et al*. Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol* 2007; **25:** 3357–61.
9. Sher DJ, *et al*. The added value of concurrently administered temozolomide versus adjuvant temozolomide alone in newly diagnosed glioblastoma. *J Neurooncol* 2008; **88:** 43–50.
10. NICE. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (issued April 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/temozolomideguidance.pdf (accessed 30/07/08)
11. Hart MG, *et al*. Temozolomide for high grade glioma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/07/09).
12. Tilleul P, *et al*. Guide de prescription et de bon usage du témozolomide dans les tumeurs cérébrales. *Bull Cancer* 2009; **96:** 579–89.

MELANOMA. Temozolomide has been studied[1-3] as a treatment for advanced metastatic melanoma (p. 714.3). A phase III study compared the overall survival-time in 305 patients treated with either oral temozolomide or intravenous dacarbazine in standard doses for up to 12 cycles of therapy. Temozolomide was found to be at least equivalent to dacarbazine in these patients, and there were no major differences in adverse effects.[2] However, median survival-times were short in both groups (7.7 months and 6.4 months respectively). Another phase III study comparing temozolomide alone or with interferon alfa in 282 patients also found modest median survival-times of 8.4 and 9.7 months respectively.[4] Studies in *animals* have investigated isolated limb infusion of temozolomide, plus hyperthermia, for regional therapy of melanoma of the extremities.[5]

1. Bleehen NM, *et al*. Cancer research campaign phase II trial of temozolomide in metastatic melanoma. *J Clin Oncol* 1995; **13:** 910–13.
2. Middleton MR, *et al*. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; **18:** 158–66.
3. Quirt I, *et al*. Temozolomide for the treatment of metastatic melanoma: a systematic review. *Oncologist* 2007; **12:** 1114–23.
4. Kaufmann R, *et al*. Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. *J Clin Oncol* 2005; **23:** 9001–7.
5. Ko SH, *et al*. Optimizing a novel regional chemotherapeutic agent against melanoma: hyperthermia-induced enhancement of temozolomide cytotoxicity. *Clin Cancer Res* 2006; **12:** 289–97.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Myelosuppression is common with temozolomide and is dose-limiting. Blood counts should be obtained before the start of treatment and monitored throughout. The nadir of cell counts usually occurs 21 to 28 days after treatment, with recovery within the next 1 to 2 weeks. Patients over 70 years of age are thought to be more susceptible to severe myelosuppression. Prolonged pancytopenia may result in aplastic anaemia, and fatalities have been reported. Opportunistic infections can occur; pneumocystis pneumonia has been reported in patients also given radiotherapy or corticosteroids, or during a longer dosing regimen of temozolomide. Prophylaxis against pneumocystis pneumonia should be given to all patients receiving temozolomide with radiotherapy, regardless of lymphocyte count.

Nausea and vomiting are very common; antiemetic therapy may be given before or during treatment. Other common adverse effects include constipation, diarrhoea, anorexia, alopecia, fatigue, headache, rashes, convulsions, and insomnia or somnolence. Anxiety, depression, confusion, dizziness, hemiparesis, aphasia, dysphagia, peripheral neuropathy, paraesthesia, neurological and/or speech disorders, tremor, and concentration or memory impairment can occur, as can visual field defects, blurred vision, diplopia, hearing impairment, or tinnitus. Deafness has been reported. Vascular disorders such as haemorrhage, deep venous thrombosis, and peripheral oedema can occur; pulmonary embolism has been reported. Other commonly reported adverse effects include dyspnoea, coughing, dry skin, pruritus, arthralgia and/or myalgia, urinary incontinence, fever, pain, and dysgeusia. Liver enzyme values can

increase, and hyperglycaemia may occur. Cushingoid disorders have occurred uncommonly. Hypersensitivity reactions, including rare cases of anaphylaxis, can occur. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported rarely. Cases of interstitial pneumonitis have also been reported. Temozolomide has carcinogenic, mutagenic, and teratogenic potential. Use in pregnancy should be avoided, and men should be advised not to father a child for up to 6 months after receiving the final dose; sperm preservation before treatment should be considered as temozolomide may cause irreversible infertility.

Carcinogenicity. Antineoplastic drugs such as alkylating agents are associated with the development of secondary malignancies (see Carcinogenicity, p. 726.2). Myelodysplastic syndrome and myeloid leukaemia have been reported in patients treated with regimens containing temozolomide. Three patients with glioma developed malignant lymphoma after treatment with temozolomide.[1]

1. Neyns B, *et al.* Non-Hodgkin's lymphoma i n patients with glioma treated with temozolomide. *J Clin Oncol* 2008; **26:** 4518–19. Correction. *ibid.* 2009; **27:** 3070.

Effects on the lungs. After completing 2 cycles of temozolomide therapy for glioblastoma multiforme, an 88-year-old man presented with a 4-week history of fever, weakness, shortness of breath, and non-productive cough. Auscultation of the lungs revealed inspiratory crackles without wheezing or rub. Drug-associated organising pneumonitis was suspected, and temozolomide therapy was stopped. Prednisolone was started, with prophylaxis against *Pneumocystis jirovecii*, and the patient improved dramatically.[1] Others have subsequently reported temozolomide-associated hypersensitivity pneumonitis.[2]

1. Maldonado F, *et al.* Temozolomide-associated organizing pneumonitis. *Mayo Clin Proc* 2007; **82:** 771–3.
2. Koschel D, *et al.* Hypersensitivity pneumonitis associated with the use of temozolomide. *Eur Respir J* 2009; **33:** 931–4.

Hepatitis. Hepatitis B reactivation has been associated with the use of temozolomide plus radiotherapy.[1,2] In one case, corticosteroid treatment may have played a role in reactivation,[1] and in another case, which was fatal, hepatotoxicity from valproic acid or temozolomide itself could have contributed.[2]

1. Chheda MG, *et al.* Hepatitis B reactivation during glioblastoma treatment with temozolomide: a cautionary note. *Neurology* 2007; **68:** 955–6.
2. Grewal J, *et al.* Fatal reactivation of hepatitis B with temozolomide. *N Engl J Med* 2007; **356:** 1591–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies temozolomide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Valproic acid decreases oral clearance of temozolomide by about 5%; the clinical significance is unknown.

Pharmacokinetics

Temozolomide is rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 0.5 to 1.5 hours after a dose. Food reduces the rate and extent of absorption. Temozolomide readily crosses the blood-brain barrier and can be detected in the CSF. The plasma elimination half-life is about 1.8 hours. Plasma protein binding is about 10 to 20%. Temozolomide undergoes spontaneous hydrolysis to its active metabolite 5-(3-methyl-triazen-1-yl)-imidazole-4-carboxamide (MTIC), which is then further hydrolysed to 5-amino-imidazole-4-carboxamide (AIC) and methylhydrazine. Temozolomide is largely eliminated by the kidneys, about 5 to 10% as unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dralitem; Temodal; Temola; Tezulina; Tocitrap; Zolom; ***Austral.***: Temodal; ***Austria***: Temodal; ***Belg.***: Temodal; ***Braz.***: Temodal; ***Canad.***: Temodal; ***Chile***: Dralitem; Temodal; ***China***: Diqing (蒂清); Temodal (泰道); ***Cz.***: Onkmoeck; Temodal; Temomedac; Temostad; ***Denm.***: Onkmoeck; Temodal; Temomedac; ***Fin.***: Temodal; ***Fr.***: Temodal; ***Ger.***: Temodal; Temomedac; Temozo-cell; ***Gr.***: Temodal; Temomedac; ***Hong Kong***: Temodal; ***Hung.***: Temodal; ***India***: Emzolam; Gliotem; Glioz; ***Indon.***: Temodal; ***Irl.***: Temodal; Temomedac; ***Israel***: Temo; Temodal; ***Ital.***: Temodal; ***Malaysia***: Temodal; ***Mex.***: Temodal; ***Neth.***: Blastomat; Nogron; Ridoca; Temodal; Temomedac; ***Norw.***: Temodal; ***NZ***: Temaccord; Temodal; ***Philipp.***: Temodal; Temozam; ***Pol.***: Temodal; Temomedac; ***Port.***: Temodal; Temomedac; ***Rus.***: Temodal (Темодал); Temomid (Темомид); ***S.Afr.***: Temodal; ***Singapore***: Temodal; ***Spain***: Temodal; Temomedac; ***Swed.***: Temodal; Temomedac; ***Switz.***: Temodal; ***Thai.***: Temodal; ***Turk.***: Temodal; ***UK***: Temodal; ***Ukr.***: Temodal (Темодал); ***USA***: Temodar; ***Venez.***: Temodal.

Temsirolimus *(BAN, USAN, rINN)*

CCI-779; Temsirolimusum; Темсиролимус.

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone 4′[2,2-bis(hydroxymethyl)propionate].

$C_{56}H_{87}NO_{16}$=1030.3

CAS — 162635-04-3.

ATC — L01XE09.

ATC Vet — QL01XE09.

UNII — 624KN6GM2T.

Incompatibility. The formulation of temsirolimus injection contains polysorbate 80, which increases the rate of extraction of the plasticiser di-2-ethylhexylphthalate (DEHP) from PVC. In order to minimise exposure to DEHP, the infusion should be given in glass, polyolefin, or polyethylene containers, through non-DEHP giving sets with an in-line polyethersulfone filter of not greater than 5 micrometres.

Uses and Administration

Temsirolimus is an ester analogue of sirolimus (p. 1970.2) that is used for the treatment of advanced renal cell carcinoma and relapsed and/or refractory mantle cell lymphoma. It is given intravenously, diluted in 250 mL sodium chloride 0.9% and infused over 30 to 60 minutes, preferably via an infusion pump.

For **renal cell carcinoma**, temsirolimus 25 mg is given once weekly. Treatment should be interrupted and the dose reduced if toxicity occurs. US licensed product information recommends withholding the dose if the absolute neutrophil count falls below 1000 cells/mm^3, or the platelet count falls below 75 000 cells/mm^3, or if grade 3 toxicity occurs. Once these have resolved to grade 2 or less, temsirolimus may be restarted with the dose reduced by 5 mg weekly, to a dose no lower than 15 mg weekly.

Use of strong inhibitors or inducers of CYP3A4 may increase or decrease exposure to sirolimus, the active metabolite of temsirolimus. If no alternative is available, US licensed product information suggests dose adjustments for renal cell carcinoma patients. A reduction of temsirolimus to 12.5 mg weekly should be considered if it is given with a strong CYP3A4 inhibitor. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before temsirolimus is increased back to the original dose. A dose increase of temsirolimus to 50 mg weekly should be considered if it is given with a strong CYP3A4 inducer; once the inducer is stopped, temsirolimus should be decreased to the original dose.

In the UK, temsirolimus is also licensed for **mantle cell lymphoma**; the recommended dose is 175 mg once weekly for 3 weeks followed by 75 mg once weekly thereafter. Treatment should be interrupted and the dose reduced for absolute neutrophil counts below 1000 cells/mm^3 and/or platelet counts below 50 000 cells/mm^3. Once these counts have returned to these levels or higher, temsirolimus may be restarted with the weekly dose reduced in the following way:

- last dose 175 mg, reduce to 75 mg
- last dose 75 mg, reduce to 50 mg
- last dose 50 mg, reduce to 25 mg

If neutrophil and platelet counts are not maintained at or above these levels on the new dose, then treatment should be withheld and the next lower dose given once the counts have recovered. Inhibitors and inducers of CYP3A4 should be avoided in patients given temsirolimus for mantle cell lymphoma.

Temsirolimus treatment may continue until disease progression or toxicity occurs.

For doses in patients with hepatic impairment see below.

References.

1. Hudes G, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356:** 2271–81.
2. Simpson D, Curran MP. Temsirolimus: in advanced renal cell carcinoma. *Drugs* 2008; **68:** 631–8.
3. Boni JP, *et al.* Intravenous temsirolimus in cancer patients: clinical pharmacology and dosing considerations. *Semin Oncol* 2009; **36** (suppl 3): S18–S25.
4. Dancey JE, *et al.* Evaluating temsirolimus activity in multiple tumors: a review of clinical trials. *Semin Oncol* 2009; **36** (suppl 3): S46–S58.
5. Thompson Coon J, *et al.* Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. *Health Technol Assess* 2010; **14:** 1–208.
6. Ravaud A, *et al.* Inhibiteurs de mTOR: temsirolimus et évérolimus dans le traitement du cancer du rein. *Bull Cancer* 2010; **97:** 45–51.
7. Stock C, *et al.* Temsirolimus. *Recent Results Cancer Res* 2010; **184:** 189–97.
8. Borders EB, *et al.* Mammalian target of rapamycin: biological function and target for novel anticancer agents. *Am J Health-Syst Pharm* 2010; **67:** 2095–2106.
9. Hoy SM, McKeage K. Temsirolimus: in relapsed and/or refractory mantle cell lymphoma. *Drugs* 2010; **70:** 1819–29.

Administration in hepatic impairment. Temsirolimus is mainly metabolised in the liver, and should be used with caution in patients with hepatic impairment. In the treatment of renal cell carcinoma, UK licensed product information considers that no dose adjustment is required for mild or moderate hepatic impairment (Child-Pugh class A or B). For severe impairment (Child-Pugh class C) and a baseline platelet count ≥100 000 cells/mm^3, a reduced dose of temsirolimus 10 mg intravenously once weekly is recommended. Temsirolimus is contra-indicated for treatment of mantle cell lymphoma in patients with moderate or severe hepatic impairment.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Temsirolimus is metabolised to sirolimus; for adverse effects of sirolimus, see p. 1971.2. Additional adverse effects reported with temsirolimus include lymphopenia, myalgia, hypocalcaemia, anorexia, asthenia, nail disorders, dry skin, pruritus, and conjunctivitis. Cataracts have occurred in patients given temsirolimus with interferon alfa. Effects on the nervous system include insomnia, anxiety, depression, dysgeusia, paraesthesia, dizziness, and ageusia. Although hepatotoxicity has not been reported with temsirolimus, raised liver transaminase concentrations are common.

Hypersensitivity reactions to temsirolimus may be life-threatening; symptoms include anaphylaxis, dyspnoea, flushing, and chest pain. Antihistamines should be given about 30 minutes before the start of the infusion. If the patient develops a hypersensitivity reaction, the infusion should be stopped and the patient observed for 30 to 60 minutes. If appropriate, treatment may be restarted about 30 minutes after a further dose of an antihistamine and/or an H_2-antagonist. The infusion may be restarted at a slower infusion rate (up to 60 minutes) and completed within 6 hours of preparation. Cases of fatal bowel perforation have occurred; patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhoea, and/or acute abdomen. Patients with CNS tumours and/or those given anticoagulants may be at increased risk of developing intracranial bleeding, which may be fatal.

Serum glucose, cholesterol, and triglycerides should be monitored before and during treatment with temsirolimus.

Effects on the lungs. Eight out of 22 patients given temsirolimus developed pulmonary abnormalities compatible with drug-induced pneumonitis. Dyspnoea and dry cough were the most common symptoms, although 4 patients were asymptomatic. The risk of developing pulmonary toxicity is increased in those with abnormal pretreatment pulmonary function, or a history of lung disease.[1] A retrospective review[2] found that 29% of patients developed radiographically diagnosed temsirolimus-related pneumonitis; radiographic changes were not necessarily associated with symptoms. The onset of drug-related pneumonitis occurred within the first 8 weeks of temsirolimus treatment in 60% of patients.

1. Duran I, *et al.* Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006; **42:** 1875–80.
2. Maroto JP, *et al.* Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. *J Clin Oncol* 2011; **29:** 1750–6.

Interactions

Both temsirolimus and its main active metabolite, sirolimus, are metabolised by cytochrome P450 isoenzyme CYP3A4, and inducers or inhibitors of CYP3A4 may affect exposure, see Interactions, under Sirolimus, p. 1972.1. If the use of alternative drugs is not feasible, dose adjustments of temsirolimus may be necessary, see Uses and Administration, above.

References.

1. Boni J, *et al.* Pharmacokinetic profile of temsirolimus with concomitant administration of cytochrome P450-inducing medications. *J Clin Pharmacol* 2007; **47:** 1430–9.
2. Boni JP, *et al.* Differential effects of ketoconazole on exposure to temsirolimus following intravenous infusion of temsirolimus. *Br J Cancer* 2008; **98:** 1797–1802.

Pharmacokinetics

Temsirolimus is mainly metabolised by cytochrome P450 isoenzyme CYP3A4 to 5 metabolites; sirolimus is the main active metabolite. The mean half-life of temsirolimus is about 17 hours. Exposure to sirolimus may be much greater than that of temsirolimus, due principally to the longer half-life of sirolimus (see p. 1972.1). Elimination is mainly in faeces; about 5% is recovered in the urine.

All cross-references refer to entries in Volume A

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Torisel; ***Austral.***: Torisel; ***Austria***: Torisel; ***Belg.***: Torisel; ***Braz.***: Torisel; ***Canad.***: Torisel; ***Chile***: Torisel; ***Cz.***: Torisel; ***Denm.***: Torisel; ***Fr.***: Torisel; ***Ger.***: Torisel; ***Gr.***: Torisel; ***Hong Kong***: Torisel; ***Hung.***: Torisel; ***Irl.***: Torisel; ***Israel***: Torisel; ***Ital.***: Torisel; ***Malaysia***: Torisel; ***Neth.***: Torisel; ***Norw.***: Torisel; ***Philipp.***: Torisel; ***Pol.***: Torisel; ***Port.***: Torisel; ***Rus.***: Torisel (Торизел); ***Singapore***: Torisel; ***Spain***: Torisel; ***Swed.***: Torisel; ***Switz.***: Torisel; ***Thai.***: Torisel; ***Turk.***: Torisel; ***UK***: Torisel; ***USA***: Torisel.

Teniposide *(BAN, USAN, rINN)*

ETP; NSC-122819; Teniposid; Téniposide; Teniposidi; Teniposido; Tenipósido; Teniposidum; VM-26; Тенипозид.

(5*S*,5a*R*,8a*S*,9*R*)-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-(4,6-*O*-thenylidene-β-D-glucopyranosyloxy)isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

$C_{32}H_{32}O_{13}S$=656.7

CAS — 29767-20-2.

ATC — L01CB02.

ATC Vet — QL01CB02.

UNII — 957E6438QA.

Stability. Precipitation occurred repeatedly in preparations for infusion containing teniposide 200 micrograms/mL in either glucose 5% or sodium chloride 0.9% injection, although previously such preparations had been used uneventfully.[1] Dilution of teniposide solutions to 100 micrograms/mL or less reduced the frequency of the problem, which could not be attributed to a change in formulation and remained unexplained.

1. Strong DK, Morris LA. Precipitation of teniposide during infusion. *Am J Hosp Pharm* 1990; **47:** 512,518.

Uses and Administration

Teniposide is an antineoplastic agent with general properties similar to those of etoposide (p. 790.2). It is given as monotherapy or part of a combination regimen for refractory non-Hodgkin's lymphoma (p. 696.3), and with other antineoplastic agents in the treatment of refractory acute lymphoblastic leukaemia (p. 692.3). Teniposide is also used in solid tumours including neuroblastoma (p. 716.2), and has been used in retinoblastoma (p. 717.2).

Teniposide is given by slow intravenous infusion over at least 30 to 60 minutes, as a solution of up to 1 mg/mL in sodium chloride 0.9% or glucose 5%. Dosage regimens vary.

For non-Hodgkin's **lymphoma**, the following monotherapy regimens have been used:

- 30 mg/m² daily for 10 days
- 30 mg/m² daily every five days
- 50 to 100 mg/m² once weekly

Doses in combination regimens have generally been given once weekly, at 60 to 70 mg/m².

In the treatment of refractory acute lymphoblastic **leukaemia**, the following combination regimens have been used:

- 165 mg/m² twice weekly for 8 to 9 doses, with cytarabine
- 250 mg/m² weekly for 4 to 8 weeks, with vincristine and prednisone

For **neuroblastoma**, doses as a single agent range from 130 to 180 mg/m² once weekly.

Adverse Effects, Treatment, and Precautions

As for Etoposide, p. 791.2. There is some evidence that teniposide may be a more potent mutagen and carcinogen than etoposide.

Breast feeding. US licensed product information states that it is unknown whether teniposide is excreted in human milk. It has been suggested[1] that breast feeding be withheld for 30 to 48 hours after a dose.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Hypersensitivity. Haemolytic anaemia and acute renal failure with tubular necrosis has been reported in a patient who developed an antibody to teniposide.[1] As with etoposide (p. 791.3) hypersensitivity or infusion reactions occur, sometimes with the first dose, and may be severe;[2,3] the frequency may be as high as 13% in neuroblastoma patients.[2] Although it has been suggested that hypersensitivity reactions might be due to the polyoxyl castor oil in the injection vehicle,[2] studies *in vitro* suggest that it is the drug rather than the vehicle that is responsible.[3]

1. Habibi B, *et al.* Immune hemolytic anemia and renal failure due to teniposide. *N Engl J Med* 1982; **306:** 1091–3.
2. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; **i:** 394.
3. Carstensen H, *et al.* Teniposide-induced hypersensitivity reactions in children. *Lancet* 1989; **ii:** 55.

Pregnancy. A 32-year-old woman was diagnosed with Burkitt's lymphoma at 22 weeks of gestation. She was treated with combination chemotherapy, including doxorubicin, vincristine, teniposide, cyclophosphamide, and prednisolone; courses were given every 2.5 or 3 weeks depending on haematological recovery, for a total of 6 courses. At 35 weeks, she was given intrathecal methotrexate for a total of 7 doses, and bleomycin for a total of 4 doses. The infant was healthy, fully developed, with no physical abnormalities, and had a normal heart, and a normal blood count.[1]

1. Lowenthal RM, *et al.* Normal infant after combination chemotherapy including teniposide for Burkitt's lymphoma in pregnancy. *Med Pediatr Oncol* 1982; **10:** 165–9.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Salicylic acid, sulfamethizole, and tolbutamide may affect the protein binding of teniposide, potentially increasing free teniposide in plasma and resulting in toxicity; caution is advised when giving any of these drugs with teniposide.

Antiepileptics. Clearance of teniposide was markedly increased by *phenytoin* or *phenobarbital*; the resultant decrease in systemic exposure to the antineoplastic might reduce its efficacy, and increased dosage would be needed in patients receiving these drugs to guarantee equivalent exposure.[1]

1. Baker DK, *et al.* Increased teniposide clearance with concomitant anticonvulsant therapy. *J Clin Oncol* 1992; **10:** 311–15.

Ciclosporin. Use of ciclosporin with teniposide has been reported[1] to produce a decrease in the clearance of the latter, with increased terminal half-life, peak plasma concentrations, and toxicity.

1. Toffoli G, *et al.* Cyclosporin A as a multidrug-resistant modulator in patients with renal cell carcinoma treated with teniposide. *Br J Cancer* 1997; **75:** 715–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vumon; ***Austral.***: Vumon; ***Austria***: Vumon†; ***Braz.***: Vumon; ***Canad.***: Vumon; ***Chile***: Vumon†; ***China***: Bang Lai (邦莱); Vumon (卫萌); ***Gr.***: Vumon; ***Hong Kong***: Vumon†; ***Mex.***: Vumon; ***Neth.***: Vumon; ***NZ***: Vumon; ***Pol.***: Vumon; ***Port.***: Vumon†; ***S.Afr.***: Vumon†; ***Spain***: Vumon†; ***USA***: Vumon.

Testolactone *(USAN, rINN)* ⊗

1-Dehydrotestololactone; NSC-23759; SQ-9538; Testolactona; Testolactonum; Testolakton; Testolaktoni; Тестолактон.

D-Homo-17a-oxaandrosta-1,4-diene-3,17-dione.

$C_{19}H_{24}O_3$=300.4

CAS — 968-93-4.

UNII — 6J9BLA949Q.

Pharmacopoeias. In *US.*

USP 36: (Testolactone). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 4050 of water; soluble in alcohol and in chloroform; slightly soluble in benzyl alcohol; insoluble in ether and in petroleum spirit. Store in airtight containers.

Profile

Testolactone is a derivative of testosterone (see p. 2305.1). It is reported to be an aromatase inhibitor that reduces peripheral oestrogen synthesis but has no significant androgenic activity. It has been given orally in the palliative treatment of advanced breast cancer in postmenopausal women (p. 702.1).

It is unsuitable for men with breast cancer.

Peripheral neuropathies have occurred in patients given testolactone; gastrointestinal disturbances, pain or oedema of the extremities, hypertension, malaise, maculopapular erythema, and glossitis have also been reported.

Congenital adrenal hyperplasia. For mention of the use of testolactone with flutamide to block androgenic effects in congenital adrenal hyperplasia, see p. 1603.2.

Precocious puberty. Encouraging results have been reported using testolactone in the treatment of 5 girls with precocious puberty (p. 2254.1) due to the McCune-Albright syndrome.[1] Testolactone is an aromatase inhibitor and blocks the synthesis of oestrogens from androgens. Long-term therapy (for up to 5 years) was associated with continued benefit in many patients; however, signs of puberty were not always completely suppressed, in some cases perhaps because of difficulties in maintaining the dosage regimen.[2] Encouraging results were also obtained using testolactone with spironolactone in the treatment of familial precocious puberty in boys, although neither agent was successful when used alone.[3] Again, signs of a reduced response to longer-term therapy have occurred; in this case control was restored by addition of a gonadorelin analogue.[4] Another study[5] in 10 boys who were treated for at least 6 years with spironolactone and testolactone, with deslorelin added at the onset of secondary central precocious puberty, found normalisation in growth rate and bone maturation, and improvements in predicted adult height.

1. Feuillan PP, *et al.* Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone. *N Engl J Med* 1986; **315:** 1115–19.
2. Feuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; **77:** 647–51.
3. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
4. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
5. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Preparations

Pharmacopoeial Preparations

USP 36: Testolactone Tablets.

Thalidomide *(BAN, USAN, rINN)*

E-217; K-17; NSC-66847; Talidomid; Talidomida; Talidomidi; Thalidomidum; Талидомид.

2-Phthalimidoglutarimide.

$C_{13}H_{10}N_2O_4$=258.2

CAS — 50-35-1.

ATC — L04AX02.

ATC Vet — QL04AX02.

UNII — 4Z8R6ORS6L.

Pharmacopoeias. In *US.*

USP 36: (Thalidomide). A white to off-white powder. Sparingly soluble in water, in dehydrated alcohol, in acetone, in butyl acetate, in ethyl acetate, in glacial acetic acid, and in methyl alcohol; practically insoluble in chloroform, in ether, and in benzene; very soluble in dimethylformamide, in dioxan, and in pyridine. Store in airtight containers. Protect from light.

Stability. An extemporaneously prepared oral suspension of thalidomide 20 mg/mL was reported to be stable for at least 35 days when stored in amber plastic bottles under refrigeration (3 degrees to 5 degrees). The contents of capsules (*Thalomid; Celgene, USA*) were suspended in a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (*Paddock, USA*). Appropriate precautions should be taken during preparation and handling, because of the risks associated with this drug.[1]

1. Kraft S, *et al.* Stability of an extemporaneously prepared thalidomide suspension. *Am J Health-Syst Pharm* 2012; **69:** 56–8.

Uses and Administration

Thalidomide has immunomodulating, anti-inflammatory, and anti-angiogenic activities. It should always be given under appropriately supervised and controlled conditions because of the teratogenic risks and other potential adverse effects (see Adverse Effects and Precautions, p. 869.2). Thalidomide is given orally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Thalidomide is used in the treatment of **multiple myeloma** (see Malignant Neoplasms, p. 868.3). In disease that is refractory to standard therapies, it is given as monotherapy in an initial oral dose of 200 mg once daily. The dose may be increased by 100 mg at weekly intervals up to a maximum dose of 400 mg daily, as tolerated. Thalidomide may be used with melphalan and prednisone in patients with newly diagnosed multiple myeloma who are over 65 years of age or ineligible for high-dose chemotherapy; thalidomide in a dose of 200 mg daily is given continuously for a maximum of 12 treatment cycles of 6 weeks each. Thalidomide may also be used with dexamethasone in the treatment of patients with newly diagnosed multiple myeloma. Thalidomide 200 mg is given once daily, with dexamethasone 40 mg given orally on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle. Four cycles of a thalidomide and dexamethasone regimen may be used as induction therapy before high-dose chemotherapy with autologous stem cell rescue.

Thalidomide is also used for the treatment of acute cutaneous manifestations of moderate to severe type 2 (erythema nodosum leprosum) **lepra reactions** (see Leprosy, p. 188.3), but should not be given as monotherapy if moderate to severe neuritis is present; in such cases, corticosteroid therapy should also be given and continued

until neuritis improves. Thalidomide may also be used for maintenance therapy for prevention and suppression of the cutaneous manifestations of recurrent type 2 lepra reactions. It is of no value in type 1 lepra reactions. It may be given orally in usual initial doses of 100 to 300 mg once daily. In severe cases up to 400 mg daily may be given. The dose should be reduced gradually by 50 mg every 2 to 4 weeks once a satisfactory response has been achieved. An alternative regimen is to start treatment with 100 mg once daily, and if symptoms are not controlled, increase the dose by increments of 100 mg at weekly intervals up to a maximum of 400 mg once daily.

Thalidomide should preferably be given at bedtime and at least 1 hour after the evening meal.

Thalidomide has been used in several other conditions whose aetiology may involve the immune system, such as treatment and prevention of graft-versus-host disease, treatment and prevention of recurrent aphthous stomatitis in severely and terminally immunocompromised patients, treatment of the clinical manifestations of both tuberculous and non-tuberculous mycobacterial infection, treatment of myelodysplastic syndrome and treatment of HIV-associated wasting syndrome, Kaposi's sarcoma, and Crohn's disease. It has also been used in the treatment of primary brain malignancies. Thalidomide is being investigated in some other malignancies.

Guidelines on the clinical use of thalidomide.

1. Powell RJ, Gardner-Medwin JMM. Guideline for the clinical use and dispensing of thalidomide. *Postgrad Med J* 1994; **70:** 901–4.
2. Lary JM, *et al*. The return of thalidomide: can birth defects be prevented? *Drug Safety* 1999; **21:** 161–9.
3. Zeldis JB, *et al*. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther* 1999; **21:** 319–30. Further information available at: http://www.thalomid.com/steps_program.aspx (accessed 27/05/08)
4. Chave TA, *et al*. All-Wales Dermatology Audit Committee. Thalidomide usage in Wales: the need to follow guidelines. *Br J Dermatol* 2001; **144:** 310–15.

Action. The mechanism of action of thalidomide is not completely understood, although investigations have shown that it has anti-inflammatory and immunomodulating effects, including inhibition of the synthesis of tumour necrosis factor (TNF)-α. However, this inhibition is incomplete and selective, and increased plasma-TNF-α concentrations have been seen in some patient groups. Other immunomodulatory and anti-inflammatory properties include inhibition of leucocyte chemotaxis into the site of inflammation and reduction of phagocytosis by polymorphonuclear leucocytes. Thalidomide also appears to modulate interleukins, although results of investigations into its effect on specific interleukins and interferon gamma have so far been equivocal. Effects on CD4+ cells and variable effects on other mediators of intercellular reactions have also been implicated. Thalidomide also inhibits angiogenesis, which may have implications in solid tumours and other diseases.

General references to the mechanism of action and uses of thalidomide.[1-8]

1. Schuler U, Ehninger G. Thalidomide: rationale for renewed use in immunological disorders. *Drug Safety* 1995; **12:** 364–9.
2. Calabrese L, Fleischer AB. Thalidomide: current and potential clinical applications. *Am J Med* 2000; **108:** 487–95.
3. Peuckmann V, *et al*. Potential novel uses of thalidomide: focus on palliative care. *Drugs* 2000; **60:** 273–92.
4. Franks ME, *et al*. Thalidomide. *Lancet* 2004; **363:** 1802–11.
5. Rajkumar SV. Thalidomide: tragic past and promising future. *Mayo Clin Proc* 2004; **79:** 899–903.
6. Joglekar S, Levin M. The promise of thalidomide: evolving indications. *Drugs Today* 2004; **40:** 197–204.
7. Bessmertny O, Pham T. Thalidomide use in pediatric patients. *Ann Pharmacother* 2002; **36:** 521–5.
8. Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J* 2005; **7:** E14–E19.

Behçet's syndrome. Thalidomide was effective for the treatment of oral and genital ulceration and follicular lesions in a randomised, double-blind, placebo-controlled study[1] in 96 male patients with Behçet's syndrome (p. 1601.1). It was also noted that the development of new oral and genital ulcers was prevented, although relapses may occur on cessation of therapy. Thalidomide has also been reported[2,3] to be of benefit for severe oral and genital ulceration in children with Behçet's syndrome unresponsive to other treatments. Thalidomide also improved symptoms in a woman with Behçet's syndrome who had recurrent perforating intestinal ulcers.[4]

1. Hamuryudan V, *et al*. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128:** 443–50.
2. Shek LP-C, *et al*. Thalidomide responsiveness in an infant with Behçet's syndrome. *Pediatrics* 1999; **103:** 1295–7.
3. Kari JA, *et al*. Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology (Oxford)* 2001; **40:** 933–8.
4. Sayarlioglu M, *et al*. Treatment of recurrent perforating intestinal ulcers with thalidomide in Behçet's disease. *Ann Pharmacother* 2004; **38:** 808–11.

Cachexia. For the use of thalidomide in HIV-associated wasting, see HIV-associated Complications, below, and in cancer-related cachexia, see Malignant Neoplasms, below.

Gastrointestinal bleeding. Thalidomide has been used to control refractory bleeding in patients with gastrointestinal vascular malformations including angiodysplasia. Studies in small groups of patients have shown reductions in the number and size of angiodysplasias and in transfusion requirements. Doses of 50 to 200 mg orally daily have generally been used.[1-3] At least 8 weeks of treatment may be needed for a beneficial effect; the optimum duration of therapy is unknown but thalidomide has been continued for up to 6 months.[1] However, adverse effects may limit its use.[1,3]

1. Kamalaporn P, *et al*. Thalidomide for the treatment of chronic gastrointestinal bleeding from angiodysplasias: a case series. *Eur J Gastroenterol Hepatol* 2009; **21:** 1347–50.
2. Ge Z-Z, *et al*. Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. *Gastroenterology* 2011; **141:** 1629–37.
3. Garrido A, *et al*. Thalidomide in refractory bleeding due to gastrointestinal angiodysplasias. *Rev Esp Enferm Dig* 2012; **104:** 69–71.

Graft-versus-host disease. A review[1] of studies investigating the use of thalidomide in chronic graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1937.1) concluded that although thalidomide appeared to be of benefit in some patients unresponsive to other treatments, doses greater than 200 mg daily are poorly tolerated in most patients. Giving thalidomide as prophylaxis led to poor survival, possibly through interfering with development of tolerance. Thalidomide was not of benefit when given as treatment for newly diagnosed disease.

1. Flowers MED, Martin PJ. Evaluation of thalidomide for treatment or prevention of chronic graft-versus-host disease. *Leuk Lymphoma* 2003; **44:** 1141–6.

HIV-associated complications. It has been proposed that thalidomide's inhibitory activity against TNF-α may explain its anti-HIV effect. However, there are conflicting reports as both decreased and increased TNF-α levels, as well as unchanged levels, have been seen in HIV-patients.[1] Nevertheless, thalidomide has shown some promise as a therapeutic agent for some AIDS-related diseases. It is an effective treatment for severe ulceration of the mouth (p. 1814.2), oropharynx, and oesophagus in patients with HIV-infection.[2-5] Of concern though is the finding that modest increases in plasma HIV RNA levels have been seen in some patients, which correlated with increases in TNF-α levels.[2,4] Thalidomide has also been tried with some success in HIV-infected patients with prurigo nodularis,[6] alopecia areata[7] (p. 1682.3), and hypertrophic genital herpes[8] (p. 955.2). It has also proved to be of benefit in HIV-associated wasting[9] (p. 959.1), and has shown promise in high doses for the treatment of AIDS-related Kaposi's sarcoma[10] (p. 718.1). Thalidomide was also of benefit in 3 patients with severe idiopathic HIV-associated colitis.[11]

1. Ravot E, *et al*. New uses for old drugs in HIV infection: the role of hydroxyurea, cyclosporin and thalidomide. *Drugs* 1999; **58:** 953–63.
2. Jacobson JM, *et al*. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med* 1997; **336:** 1487–93.
3. Ramirez-Amador VA, *et al*. Thalidomide as therapy for human immunodeficiency virus-related oral ulcers: a double-blind placebo-controlled clinical trial. *Clin Infect Dis* 1999; **28:** 892–4.
4. Jacobson JM, *et al*. Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. *J Infect Dis* 1999; **180:** 61–7.
5. Shetty K. Thalidomide in the management of recurrent aphthous ulcerations in patients who are HIV-positive: a review and case reports. *Spec Care Dentist* 2005; **25:** 236–41.
6. Maurer T, *et al*. Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. *Arch Dermatol* 2004; **140:** 845–9.
7. Baranda L, *et al*. Severe and unresponsive HIV-associated alopecia areata successfully treated with thalidomide. *Acta Derm Venereol* 2005; **85:** 277–8.
8. Holmes A, *et al*. Thalidomide therapy for the treatment of hypertrophic herpes simplex virus-related genitalis in HIV-infected individuals. *Clin Infect Dis* 2007; **44:** e96–e99. Available at: http://www.journals.uchicago.edu/doi/abs/10.1086/517513 (accessed 18/01/08)
9. Reyes-Terán G, *et al*. Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind, placebo-controlled trial. *AIDS* 1996; **10:** 1501–7.
10. Little RF, *et al*. Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000; **18:** 2593–2602.
11. Johnson L, *et al*. Thalidomide treatment for refractory HIV-associated colitis: a case series. *Clin Infect Dis* 2008; **47:** 133–6.

Inflammatory bowel disease. Small open-label studies[1-3] have shown efficacy of thalidomide in patients with refractory Crohn's disease (see under Inflammatory Bowel Disease, p. 1811.3). In many of those patients already receiving corticosteroids the dosage could be reduced and in some corticosteroids could be stopped completely. Reduction of TNF-α and interleukin-12 by thalidomide may be responsible for its clinical effects in Crohn's disease.[4] Thalidomide has also been reported[5] to be of benefit in children and young adults with intractable inflammatory bowel disease (both Crohn's disease and ulcerative colitis).

1. Ehrenpreis ED, *et al*. Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* 1999; **117:** 1271–7.
2. Vasiliauskas EA, *et al*. An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999; **117:** 1278–87.
3. Bariol C, *et al*. Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; **17:** 135–9.
4. Bauditz J, *et al*. Thalidomide reduces tumour necrosis factor α and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002; **50:** 196–200.
5. Lazzerini M, *et al*. Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. *Aliment Pharmacol Ther* 2007; **25:** 419–27.

Kaposi's sarcoma. See under HIV-associated complications, above and under Malignant Neoplasms, below.

Lupus erythematosus. Thalidomide has been found to be of benefit in lupus erythematosus, including chronic discoid lupus erythematosus,[1,2] lupus erythematosus profundus,[3,4] SLE[5] (p. 1613.3), and cutaneous lupus erythematosus.[6-11] The beneficial effect of thalidomide on cutaneous lupus erythematosus may be partly mediated through protection against UV-induced inflammation.[11]

1. Knop J, *et al*. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108:** 461–6.
2. Brocard A, *et al*. Lupus érythémateux chronique: traitement par thalidomide. *Ann Dermatol Venereol* 2005; **132:** 853–6.
3. Burrows NP, *et al*. Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol* 1991; **125:** 62–7.
4. Wienert S, *et al*. Facetten des Lupus erythematodes: Pannikulitis mit gutem Ansprechen auf Thalidomid. *J Dtsch Dermatol Ges* 2008; **6** 214–16.
5. Bessis D, *et al*. Thalidomide for systemic lupus erythematosus. *Lancet* 1992; **339:** 549–50.
6. Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. *Clin Exp Rheumatol* 1993; **11:** 487–93.
7. Stevens RJ, *et al*. Thalidomide in the treatment of the cutaneous manifestations of lupus erythematosus: experience in sixteen consecutive patients. *Br J Rheumatol* 1997; **36:** 353–9.
8. Duong DJ, *et al*. American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. *Arch Dermatol* 1999; **135:** 1079–87.
9. Pelle MT, Werth VP. Thalidomide in cutaneous lupus erythematosus. *Am J Clin Dermatol* 2003; **4:** 379–87.
10. Cuadrado MJ, *et al*. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med* 2005; **118:** 246–50.
11. Cummins DL, Gaspari AA. Photoprotection by thalidomide in patients with chronic cutaneous and systemic lupus erythematosus: discordant effects on minimal erythema dose and sunburn cell formation. *Br J Dermatol* 2004; **151:** 458–64.

Malignant neoplasms. Thalidomide has shown benefit in the treatment of patients with multiple myeloma (p. 699.2).[1] In relapsed or refractory disease, a review[2] of uncontrolled studies showed that thalidomide monotherapy may achieve complete or partial responses in about 29% of patients, and found at 12 months after starting therapy an overall survival rate of about 60% and event-free survival of about 35%. The response improves when dexamethasone is added, increasing the complete or partial response rate to about 46% without a significant increase in toxicity.[3] The combination of thalidomide and dexamethasone has also been used in newly-diagnosed patients, with response rates of at least 63% reported.[4-6] This combination may be used as induction therapy before autologous haematopoietic stem cell transplantation.[4] After transplantation, thalidomide has been studied for maintenance therapy and found to reduce the risk for disease progression, but the effect on overall survival has been mixed.[7] It has been suggested that the lowest effective maintenance dose is 50 mg orally daily, that therapy should be given for 1 year or less to limit the risk of significant toxicity, and that thalidomide should not be used in patients with FISH-defined poor-risk cytogenetics; however, the situation for elderly patients is less clear.[7] Improved response rates have been found when thalidomide was added to cycles of melphalan and prednisone in newly-diagnosed elderly patients (when transplantation is generally unsuitable), extending survival-time by about 20% (about 6 to 7 months).[8]

Thalidomide has also been tried in the treatment of several non-plasma cell malignancies with variable results.[9] It has shown promise in patients with recurrent high-grade gliomas[10] (p. 701.2) and is under investigation for non-AIDS-related Kaposi's sarcoma[11,12] (p. 718.1), metastic melanoma[13] (p. 714.3), myelofibrosis with myeloid metaplasia,[14-16] and androgen-independent prostate cancer[17,18] (p. 712.3).

Thalidomide has shown some benefit in the treatment of cancer-related cachexia (see under Megestrol, p. 2289.3) in patients with pancreatic cancer.[19]

1. Palumbo A, *et al*. Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008; **111:** 3968–77.
2. Glasmacher A, *et al*. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *Br J Haematol* 2006; **132:** 584–93.
3. von Lilienfeld-Toal M, *et al*. A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. *Eur J Haematol* 2008; **81:** 247–52.
4. Rajkumar SV, *et al*. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*.2006; **24:** 431–6.

5. Rajkumar SV, *et al.* Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol* 2008; **26:** 2171–7.
6. Ludwig H, *et al.* Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood* 2009; **113:** 3435–42.
7. Ludwig H, *et al.* International Myeloma Working Group. IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012; **119:** 3003–15.
8. Fayers PM, *et al.* Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood* 2011; **118:** 1239–47.
9. Kumar S, *et al.* Thalidomid: current role in the treatment of non-plasma cell malignancies. *J Clin Oncol* 2004; **22:** 2477–88. Correction. *ibid.*; 2973. [title]
10. Fine HA, *et al.* Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000; **18:** 708–15.
11. Ben M'barek L, *et al.* A retrospective analysis of thalidomide therapy in non-HIV-related Kaposi's sarcoma. *Dermatology* 2007; **215:** 202–5.
12. Rubegni P, *et al.* Thalidomide in the treatment of Kaposi's sarcoma. *Dermatology* 2007; **215:** 240–4.
13. Danson S, *et al.* Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol* 2003; **21:** 2551–7.
14. Mesa RA, *et al.* Durable responses to thalidomide-based drug therapy for myelofibrosis with myeloid metaplasia. *Mayo Clin Proc* 2004; **79:** 883–9.
15. Marchetti M, *et al.* Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. *J Clin Oncol* 2004; **22:** 424–31.
16. Thomas DA, *et al.* Thalidomide therapy for myelofibrosis with myeloid metaplasia. *Cancer* 2006; **106:** 1974–84.
17. Figg WD. The 2005 Leon I. Goldberg Young Investigator Award Lecture: Development of thalidomide as an angiogenesis inhibitor for the treatment of androgen-independent prostate cancer. *Clin Pharmacol Ther* 2006; **79:** 1–8.
18. Cox MC, *et al.* The use of thalidomide in androgen-independent prostate cancer. *Urol Oncol* 2006; **24:** 246–9.
19. Gordon JN, *et al.* Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54:** 540–5.

Mouth ulceration. See under Behçet's syndrome p. 868.1 and under HIV-associated complications, p. 868.2.

Oesophageal ulceration. Thalidomide has been shown to be of benefit in the treatment of idiopathic oesophageal ulcers in patients with AIDS (see under HIV-associated complications, p. 868.2). Thalidomide has also been reported to have healed an oesophageal ulcer refractory to other treatments in an immunocompetent patient,[1] and in an immunocompromised patient after liver transplant.[2]

1. Ollivier S, *et al.* Idiopathic giant oesophageal ulcer in an immunocompetent patient: the efficacy of thalidomide treatment. *Gut* 1999; **45:** 463–4.
2. Atiq M, *et al.* Successful treatment with thalidomide in a liver transplant recipient with giant esophageal ulcers. *Liver Transpl* 2006; **12:** 987–8.

Rheumatic disorders. Beneficial responses to thalidomide have been reported in the treatment of refractory rheumatoid arthritis[1] and adult-onset Still's disease.[2] Thalidomide also improved symptoms in 2 children with systemic onset juvenile rheumatoid arthritis, in whom other therapy, including etanercept, had been ineffective.[3] Efficacy was also shown in a further 11 children with refractory disease who were able to reduce their use of prednisone.[4]

1. Gutiérrez-Rodríguez O, *et al.* Treatment of refractory rheumatoid arthritis—the thalidomide experience. *J Rheumatol* 1989; **16:** 158–63.
2. Stambe C, Wicks IP. TNF α and response of treatment-resistant adult-onset Still's disease to thalidomide. *Lancet* 1998; **352:** 544–5.
3. Lehman TJA, *et al.* Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis. *J Pediatr* 2002; **140:** 125–7.
4. Lehman TJ, *et al.* Thalidomide for severe systemic onset juvenile rheumatoid arthritis: a multicenter study. *J Pediatr* 2004; **145:** 856–7.

Sarcoidosis. Case reports[1-5] of thalidomide in the treatment of sarcoidosis suggest that it might be of benefit.

1. Carlesimo M, *et al.* Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *J Am Acad Dermatol* 1995; **32:** 866–9.
2. Baughman RP, *et al.* Thalidomide for chronic sarcoidosis. *Chest* 2002; **122:** 227–32.
3. Walter MC, *et al.* Successful treatment of muscle sarcoidosis with thalidomide. *Acta Myol* 2003; **22:** 22–5.
4. Nguyen YT, *et al.* Treatment of cutaneous sarcoidosis with thalidomide. *J Am Acad Dermatol* 2004; **50:** 235–41.
5. Hammond ER, *et al.* Thalidomide for acute treatment of neurosarcoidosis. *Spinal Cord* 2007; **45:** 802–3.

Skin disorders. Thalidomide has shown efficacy in several severe dermatological disorders refractory to conventional therapies.[1,2] A review[3] of studies of thalidomide in the treatment of severe type 2 (erythema nodosum leprosum) lepra reactions concluded that it is an effective alternative to corticosteroid therapy. It has also been investigated in other severe skin disorders and beneficial responses have been reported in erythema multiforme[4,5] (p. 1684.3), pruritus associated with uraemia,[6] Langerhans-cell histiocytosis[7] (p. 692.1), epidermolysis bullosa and its variants,[8-10] prurigo nodularis,[11,12] pyoderma gangrenosum[13,14] (p. 1688.3), and Schnitzler's syndrome.[15] Thalidomide has been reported[16] to be of benefit in the treatment of erythema nodosum-like lesions attributed to immune reconstitution inflammatory syndrome that developed in a patient after initiation of antibacterial therapy for Whipple's disease.

1. Wu JJ, *et al.* Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153:** 254–73.
2. FaverIR, *et al.* Thalidomide for dermatology: a review of clinical uses and adverse effects. *Int J Dermatol* 2005; **44:** 61–7.
3. Walker SL, *et al.* The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev* 2007; **78:** 197–215.
4. Bahmer FA, *et al.* Thalidomide treatment of recurrent erythema multiforme. *Acta Derm Venereol (Stockh)* 1982; **62:** 449–50.
5. Moisson YF, *et al.* Thalidomide for recurrent erythema multiforme. *Br J Dermatol* 1992; **126:** 92–3.
6. Silva SRB, *et al.* Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron* 1994; **67:** 270–3.
7. McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **48:** 44–9.
8. Goulden V, *et al.* Linear prurigo simulating dermatitis artefacta in dominant dystrophic epidermolysis bullosa. *Br J Dermatol* 1993; **129:** 443–6.
9. Ozanic Bulic S, *et al.* Thalidomide in the management of epidermolysis bullosa pruriginosa. *Br J Dermatol* 2005; **152:** 1332–4.
10. Strauss RM, *et al.* A child with laryngo-onychocutaneous syndrome partially responsive to treatment with thalidomide. *Br J Dermatol* 2006; **155:** 1283–6.
11. Ferrándiz C, *et al.* Sequential combined therapy with thalidomide and narrow-band (TL01) UVB in the treatment of prurigo nodularis. *Dermatology* 1997; **195:** 359–61.
12. Lan C-CE, *et al.* Treatment of idiopathic prurigo nodularis in Taiwanese patients with low-dose thalidomide. *J Dermatol* 2007; **34:** 237–42.
13. Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. *Mayo Clin Proc* 2000; **75:** 842–4.
14. Koca E, *et al.* Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum. *Neth J Med* 2006; **64:** 422–4.
15. Worm M, Kolde G. Schnitzler's syndrome: successful treatment of two patients using thalidomide. *Br J Dermatol* 2003; **148:** 601–2.
16. Lagier J-C, *et al.* Successful treatment of immune reconstitution inflammatory syndrome in Whipple's disease using thalidomide. *J Infect* 2010; **60:** 79–82.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Thalidomide was withdrawn from use as a hypnotic in the early 1960s after it was discovered that it produced teratogenic effects when given in early pregnancy. These effects, which could develop after a single dose, involved mainly malformations of the limbs and defects of the ears, eyes, and internal organs. Death at or shortly after birth was also common. Further abnormalities and problems, including effects on the CNS, developed in later life.

Thalidomide was reintroduced in 1998 for use as an immunomodulator but because of its severe teratogenic effects, it should not be used in women of child-bearing potential, or if such use is absolutely essential then stringent contraceptive measures must be used, including the simultaneous use of 2 reliable forms of contraception for at least 4 weeks before, during, and for 4 weeks after, thalidomide therapy. A pregnancy test must be carried out before starting thalidomide treatment (preferably within 24 hours, and no more than 3 days before), and regular tests carried out during treatment. If pregnancy occurs during thalidomide therapy the drug must be stopped immediately and the patient given appropriate evaluation and counselling. As thalidomide is present in semen, male patients receiving thalidomide should use barrier methods of contraception even after successful vasectomy if their partner is of child-bearing potential. Patients should not donate blood or sperm during thalidomide therapy, or for 4 weeks after stopping.

The other major adverse effect of thalidomide is peripheral neuropathy, which can be severe and irreversible, and dose modifications should be considered. If there is no loss of function (grade 1), the patient should be monitored and doses reduced if symptoms worsen. If function deteriorates but daily living activities are not compromised (grade 2), the dose should be reduced or treatment interrupted and the patient monitored; treatment should be discontinued if there is no improvement, or it may be restarted if neuropathy resolves. Treatment should be discontinued when the neuropathy interferes with daily activities (grade 3) or is disabling (grade 4).

Venous thromboembolism has been reported in a significant number of patients receiving thalidomide for multiple myeloma, particularly in those also receiving chemotherapeutic drugs, including dexamethasone. Arterial thromboembolic events, including myocardial infarction and stroke, have also occurred, especially in patients with pre-existing risk factors for these; thromboprophylaxis should be considered, particularly in the first few months of treatment (see Effects on the Cardiovascular System, below).

Thalidomide is a centrally active hypnotic sedative and frequently causes drowsiness and somnolence; affected patients should not drive or operate machinery. Other common adverse effects include constipation, dizziness, and orthostatic hypotension. Hypersensitivity reactions have occurred. An erythematous macular rash may develop, usually 2 to 10 days after initiation of therapy. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported, and therefore thalidomide should be stopped if a rash develops and only restarted after appropriate clinical evaluation. Thalidomide therapy should not be resumed if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Neutropenia and an increase in the viral load in HIV-infected patients have also been reported; thalidomide therapy should not be started in neutropenic patients. Bradycardia, heart failure, renal failure, seizures, worsening of Parkinson's disease symptoms, and hearing impairment or deafness, have also been reported. Patients with a high tumour burden before treatment are at increased risk of tumour lysis syndrome.

Although human data for breast feeding while taking thalidomide are lacking, licensed product information recommends that it should be avoided in view of the potential for serious adverse effects in the infant.

Reviews.

1. Günzler V. Thalidomide in human immunodeficiency virus (HIV) patients: a review of safety considerations. *Drug Safety* 1992; **7:** 116–34.
2. Clark TE, *et al.* Thalomid(thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24:** 87–117.
3. Grover JK, *et al.* The adverse effects of thalidomide in relapsed and refractory patients of multiple myeloma. *Ann Oncol* 2002; **13:** 1636–40.
4. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. *J Support Oncol* 2003; **1:** 194–205.
5. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. *Am J Med* 2004; **117:** 508–15.
6. Uhl K, *et al.* Thalidomide use in the US: experience with pregnancy testing in the S.T.E.P.S. programme. *Drug Safety* 2006; **29:** 321–9.

Effects on the blood. Thrombocytopenia has been reported in patients given thalidomide for multiple myeloma.[1,2]

1. Duyvendak M, *et al.* Thalidomide-associated thrombocytopenia. *Ann Pharmacother* 2005; **39:** 1936–9.
2. Prasad HK, *et al.* Isolated thrombocytopenia induced by thalidomide in a patient with multiple myeloma: case report and review of literature. *Am J Hematol* 2007; **82:** 855–7.

Effects on the cardiovascular system. Use of thalidomide in patients with malignant neoplastic disease has been associated with an increased risk of **venous** thromboembolic events such as deep-vein thrombosis. There were 27 spontaneous reports of thromboembolic events in the first 18 months of thalidomide returning to the US market in July 1998; 26 of these were in patients with malignancies.[1] A review[2] of thromboembolic events associated with thalidomide identified 67 such reports from a total of 2075 adverse events reported to the FDA between October 1998 and June 2001; a further 29 cases were identified from clinical study data. Deep-vein thrombosis occurred in 48 of these patients, pulmonary embolism in 25, and 23 developed both. The most common primary diagnoses among these patients were multiple myeloma and renal cell carcinoma. However, it should be noted that patients with cancer are known to be at increased risk of venous thromboembolism and some chemotherapeutic regimens may further increase this risk. The contribution of thalidomide to the development of venous thromboembolism remains to be fully evaluated in controlled studies. Further reviews[3,4] of reports of venous thromboembolism associated with thalidomide concluded that the incidence of venous thromboembolism in patients with multiple myeloma is higher when thalidomide is given with chemotherapeutic drugs such as dexamethasone, melphalan, or doxorubicin.

Patients given thalidomide have also been reported to be at increased risk of **arterial** thromboembolic events such as myocardial infarction and stroke. This risk appeared to be greatest in the first 5 months of treatment, and most patients who had such effects had pre-existing thromboembolic risk factors. It is recommended that measures should be taken to reduce modifiable risk factors such as hypertension, hyperlipidaemia, and smoking in those given thalidomide, and that candidates for thalidomide treatment be given appropriate thromboprophylaxis at least for the first 5 months, especially those with thromboembolic risk factors additional to their underlying pathology.[5]

Studies suggest that prophylactic use of a low-molecular-weight heparin (enoxaparin),[6] low-dose aspirin,[7] or low-dose warfarin[8] may reduce the incidence of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapeutic drugs. A comparison of these 3 drugs in patients who did not have any other clear indication for prophylaxis showed them to be equally effective in reducing serious thromboembolic events, acute cardiovascular events, and sudden death.[9]

Bradycardia has been associated with thalidomide therapy in some patients, although symptoms may be managed by a reduction in dose.[10,11] See also under Effects on the Endocrine System, p. 870.1.

1. Clark TE, *et al.* Thalomid(thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24:** 87–117.
2. Bennett CL, *et al.* Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med* 2002; **113:** 603–6.
3. Bennett CL, *et al.* Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA* 2006; **296:** 2558–60.
4. Rajkumar SV. Thalidomide therapy and deep venous thrombosis in multiple myeloma. *Mayo Clin Proc* 2005; **80:** 1549–51.
5. Celgene, Fr. Thalidomide Celgene(thalidomide) et effets indésirables thromboemboliques artériels et veineux (issued May 2011). Available at: http://www.afssaps.fr/var/afssaps_site/storage/original/application/e9fe25485f5b263201af9b1395909881.pdf (accessed 12/05/11)

6. Zangari M, *et al.* Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. *Br J Haematol* 2004; **126:** 715–21.
7. Baz R, *et al.* The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc* 2005; **80:** 1568–74.
8. Ikhlaque N, *et al.* Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. *Am J Hematol* 2006; **81:** 420–2.
9. Palumbo A, *et al.* Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol* 2011; **29:** 986–93.
10. Coutsouvelis J, Corallo CE. Thalidomide-induced bradycardia and its management. *Med J Aust* 2004; **180:** 366–7.
11. Fahdi IE, *et al.* Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol* 2004; **93:** 1052–5.

Effects on the endocrine system. Amenorrhoea has been reported[1,2] in women taking thalidomide for severe dermatological conditions; menses resumed 2 to 3 months after stopping thalidomide.[2]

Hypothyroidism has been associated with thalidomide use in patients with multiple myeloma,[3,4] and it was suggested[3] that some adverse effects of thalidomide, such as bradycardia and constipation, may be manifestations of hypothyroidism.

Severe hyperglycaemia has been reported[5] in a 70-year-old man 4 weeks after starting thalidomide for multiple myeloma. Plasma-glucose concentrations returned to normal after treatment with insulin and an oral antidiabetic and he continued with thalidomide therapy.

1. Passeron T, *et al.* Thalidomide-induced amenorrhoea: two cases. *Br J Dermatol* 2001; **144:** 1292–3.
2. Francès C, *et al.* Transient secondary amenorrhea in women treated by thalidomide. *Eur J Dermatol* 2002; **12:** 63–5.
3. Badros AZ, *et al.* Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. *Am J Med* 2002; **112:** 412–13.
4. de Savary N, *et al.* Severe hypothyroidism after thalidomide treatment. *J R Soc Med* 2004; **97:** 443.
5. Pathak RD, *et al.* Thalidomide-associated hyperglycemia and diabetes: case report and review of literature. *Diabetes Care* 2003; **26:** 1322–3.

Effects on the gastrointestinal tract. Bowel perforation requiring surgery has been reported[1] in 3 patients taking thalidomide for malignant neoplasms. A fourth case of acute abdominal pain and suspected bowel perforation is also described but the patient died of a cardiac arrest before surgery.

1. McClay H, Cervi P. Thalidomide and bowel perforation: four cases in one hospital. *Br J Haematol* 2008; **140:** 360–1.

Effects on the liver. Hepatitis has been reported[1] in a 58-year-old woman taking thalidomide for end-stage plasma cell leukaemia. In another report of hepatotoxicity,[2] a 76-year-old woman with multiple myeloma being treated with thalidomide and dexamethasone developed jaundice and acute increases in liver enzymes, which returned to normal when thalidomide was stopped. Fatal fulminant hepatic failure with encephalopathy that appeared to be associated with thalidomide developed in a 64-year-old woman being treated for multiple myeloma.[3]

1. Fowler R, Imrie K. Thalidomide-associated hepatitis: a case report. *Am J Hematol* 2001; **66:** 300–2.
2. Hanje AJ, *et al.* Thalidomide-induced severe hepatotoxicity. *Pharmacotherapy* 2006; **26:** 1018–22.
3. Hamadani M, *et al.* Thalidomide-induced fulminant hepatic failure. *Mayo Clin Proc* 2007; **82:** 638.

Effects on the lungs. Interstitial pneumonitis,[1] including interstitial pneumonia,[2] has been reported in patients taking *thalidomide* for multiple myeloma. There have also been reports of dyspnoea in women taking thalidomide for ovarian cancer; resolution of symptoms occurred on drug withdrawal and some patients were able to continue therapy when reintroduced at a reduced dose.[3]

There have also been reports of respiratory toxicity associated with *pomalidomide* therapy for multiple myeloma.[4] One patient abruptly developed dyspnoea, pyrexia, and chills about 4 months after starting pomalidomide plus dexamethasone treatment; lung infiltrates consistent with pneumonitis were noted. Pomalidomide was stopped and symptoms resolved quickly with corticosteroid treatment. Treatment was later restarted with a reduced dose of pomalidomide without recurrence of symptoms. Another patient developed dyspnoea 16 months after starting pomalidomide plus dexamethasone treatment. Symptoms resolved when treatment was withdrawn but recurred with 2 further rechallenges, one using a lower dose of pomalidomide.

1. Onozawa M, *et al.* Thalidomide-induced interstitial pneumonitis. *J Clin Oncol* 2005; **23:** 2425–6.
2. Sasaki M, *et al.* Thalidomide may induce interstitial pneumonia preferentially in Japanese patients. *Eur J Haematol* 2009; **82:** 73–4.
3. Gordinier ME, Dizon DS. Dyspnea during thalidomide treatment for advanced ovarian cancer. *Ann Pharmacother* 2005; **39:** 962–5.
4. Geyer HL, *et al.* Acute lung toxicity related to pomalidomide. *Chest* 2011; **140:** 529–33.

Effects on mental function. Symptoms of dementia appeared in a patient who had been taking thalidomide for about 2 months for the treatment of multiple myeloma.[1] Dementia later resolved completely within 48 hours of stopping thalidomide.

1. Morgan AE, *et al.* Reversible dementia due to thalidomide therapy for multiple myeloma. *N Engl J Med* 2003; **348:** 1821–2.

Effects on the nervous system. Peripheral neuropathy is a major adverse effect of thalidomide therapy, although the underlying mechanisms, risk factors, and optimum management are still not clear.[1] One prospective study[2] in patients with cutaneous lupus erythematosus or SLE concluded that the cumulative dose of thalidomide had no effect on the incidence of peripheral neuropathy, whereas results from a retrospective study[3] in patients with SLE or multiple myeloma showed that the risk of developing neurotoxicity as well as severity of symptoms did correlate with cumulative dose. However, the latter study[3] examined a range of doses and found that this correlation was most significant at cumulative doses over 20 g but either absent or equivocal at lower doses, which might explain the discrepancies in results between studies using different doses. Two further studies[4,5] in patients with multiple myeloma concluded that neurotoxicity was associated with duration of treatment of greater than 6 to 12 months rather than dose-intensity or total cumulative dose. Conversely, another study,[6] also in multiple myeloma patients, found electrophysiologic evidence of peripheral neuropathy in two-thirds of patients as early as 4 months from the start of treatment, and in all of them by 7 months; many patients also had clinical symptoms.

Central neurotoxicity has also been reported[7] in a patient who developed encephalopathy after receiving thalidomide monotherapy for multiple myeloma over 21 months.

1. Apfel SC, Zochodne DW. Thalidomide neuropathy: too much or too long? *Neurology* 2004; **62:** 2158–9.
2. Briani C, *et al.* Thalidomide neurotoxicity: prospective study in patients with lupus erythematosus. *Neurology* 2004; **62:** 2288–90.
3. Cavaletti G, *et al.* Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. *Neurology* 2004; **62:** 2291–3.
4. Tosi P, *et al.* Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol* 2005; **74:** 212–16.
5. Mileshkin L, *et al.* Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol* 2006; **24:** 4507–14.
6. Plasmati R, *et al.* Neuropathy in multiple myeloma treated with thalidomide: a prospective study. *Neurology* 2007; **69:** 573–81.
7. Sohlbach K, *et al.* Encephalopathy in a patient after long-term treatment with thalidomide. *J Clin Oncol* 2006; **24:** 4942–4.

Effects on sexual function. Dose-related sexual dysfunction, including loss of libido, loss of penile rigidity, and premature ejaculation, was associated with thalidomide use in 2 male patients.[1] Erectile dysfunction has been reported[2] in 6 patients within 4 weeks of starting thalidomide therapy.

1. Pouaha J, *et al.* Thalidomide and sexual dysfunction in men. *Br J Dermatol* 2002; **146:** 1112–13.
2. Murphy PT, O'Donnell JR. Thalidomide induced impotence in male hematology patients: a common but ignored complication? *Haematologica* 2007; **92:** 1440.

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a 62-year-old woman about 5 weeks after starting thalidomide for the treatment of a glioblastoma. Although she was taking several other drugs, including dexamethasone, thalidomide was considered responsible since its use had the closest temporal relationship to the adverse effect. Toxic epidermal necrolysis has also been reported[2] in a 64-year-old patient 24 days after starting thalidomide and dexamethasone for myeloma. It was suggested that there might be an adverse interaction between thalidomide and dexamethasone. Thalidomide had previously been studied[3] for the *treatment* of toxic epidermal necrolysis, but the study was prematurely terminated because of significantly higher mortality in the thalidomide group; the causes of death were those usually attributed to the disease itself. Thalidomide had been chosen as an investigative drug because it is a potent inhibitor of TNF-α, which has been implicated in the pathogenesis of this condition. However, the authors noted that there was a tendency for plasma concentrations of TNF-α to increase after treatment with thalidomide compared with the placebo group, and postulated that thalidomide might paradoxically enhance TNF-α production in these patients.

Exacerbation of psoriasis by thalidomide, reported, in 2 patients might also have been due to an increase in TNF-α production.[4,5]

In an open-label study in 87 patients with multiple myeloma[6] comparing thalidomide given as monotherapy or given with dexamethasone, minor to moderate skin eruptions were noted in about 45% of patients in each group, and included morbilliform, seborrhoeic, maculopapular, and non-specific dermatitis. Three patients receiving thalidomide and dexamethasone developed severe skin reactions (exfoliative erythroderma, erythema multiforme, or toxic epidermal necrolysis) that required treatment to be stopped.

1. Horowitz SB, Stirling AL. Thalidomide-induced toxic epidermal necrolysis. *Pharmacotherapy* 1999; **19:** 1177–80.
2. Rajkumar SV, *et al.* Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. *N Engl J Med* 2000; **343:** 972–3.
3. Wolkenstein P, *et al.* Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352:** 1586–9.
4. Dobson CM, Parslew RA. Exacerbation of psoriasis by thalidomide in Behçet's syndrome. *Br J Dermatol* 2003; **149:** 432–3.
5. Varma K, Finlay AY. Exacerbation of psoriasis by thalidomide in a patient with erythema multiforme. *Br J Dermatol* 2006; **154:** 789–90.
6. Hall VC, *et al.* Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; **48:** 548–52.

Migraine. Migraine attacks were associated with thalidomide use in a 36-year-old man.[1]

1. García-Albea E, *et al.* Jaqueca típica y talidomida. *Med Clin (Barc)* 1993; **100:** 557.

Mutagenicity. Reports of the birth of 3 malformed infants to parents who had themselves been exposed to thalidomide *in utero*[1,2] provoked fears that thalidomide may be a mutagen. However, the limb malformations seen in the infants were not typical of mutagenesis[3] and the teratogenic effect of thalidomide was likely to be associated with interference with angiogenesis in the fetus rather than mutation.[4] Review[5] of the evidence up to 1998 concluded that there was no scientific basis for the hypothesis that thalidomide is a mutagen and birth defects appeared to be no more common in children born to thalidomide-affected parents than in the population as a whole. Further support for the counter-argument came in 2002 from a Swedish retrospective study in which malformations or functional anomalies consistent with thalidomide embryopathy were not found in 64 children born to 34 parents with thalidomide embryopathy.[6]

1. McBride WG. Thalidomide may be a mutagen. *BMJ* 1994; **308:** 1635–6.
2. Tenconi R, *et al.* Amniotic band sequence in child of thalidomide victim. *BMJ* 1994; **309:** 1442.
3. Read AP. Thalidomide may be a mutagen. *BMJ* 1994; **308:** 1636.
4. D'Amato RJ, *et al.* Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994; **91:** 4082–5.
5. Smithells D. Does thalidomide cause second generation birth defects? *Drug Safety* 1998; **19:** 339–41.
6. Strömland K, *et al.* Offspring of male and female parents with thalidomide embryopathy: birth defects and functional anomalies. *Teratology* 2002; **66:** 115–21.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thalidomide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

The sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine has been reported to be enhanced by thalidomide. Use with other drugs that have the potential to cause peripheral neuropathy should be undertaken cautiously.

Antineoplastics. There may be an increased risk of deep-vein thrombosis from the use of thalidomide with *doxorubicin* (see p. 785.3). See also Effects on the Cardiovascular System, p. 869.3.

For the effect of thalidomide on the metabolism of *irinotecan*, see under Interactions of Irinotecan, p. 814.2.

Corticosteroids. For reference to a possible interaction between thalidomide and *dexamethasone*, see under Effects on the Skin, above.

Hormonal contraceptives. Thalidomide does *not* alter the metabolism of ethinylestradiol and norethisterone,[1,2] and so the efficacy of oral contraceptives should not be affected by thalidomide therapy. Nevertheless, 2 reliable forms of contraception should always be used simultaneously when taking thalidomide (see Adverse Effects and Precautions, p. 869.2), bearing in mind that the reliability of hormonal contraceptives may be compromised by drugs other than thalidomide (see p. 2242.3).

1. Trapnell CB, *et al.* Thalidomide does not alter the pharmacokinetics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 1998; **64:** 597–602.
2. Scheffler MR, *et al.* Thalidomide does not alter estrogen-progesterone hormone single-dose pharmacokinetics. *Clin Pharmacol Ther* 1999; **65:** 483–90.

Interferons. Neurological toxicity was reported[1] in 4 of 13 patients in a phase II study of thalidomide and interferon alfa-2a used together in the treatment of renal cell carcinoma. It was suggested that the membrane-destabilising properties of both drugs could have produced such serious toxicity since it exceeded that expected from either drug alone. A fifth patient had a Stevens-Johnson reaction that was also attributed to the combination. The study was halted as a result of these serious adverse effects.

Severe bone marrow depression has been reported[2] in a patient given thalidomide with peginterferon alfa-2b that was also attributed to the combined effect of the 2 drugs.

1. Nathan PD, *et al.* Unexpected toxicity of combination thalidomide and interferon alfa-2a treatment in metastatic renal cell carcinoma. *J Clin Oncol* 2002; **20:** 1429–30.
2. Gómez-Rangel JD, *et al.* Pegylated-interferon induced severe bone marrow hypoplasia in a patient with multiple myeloma receiving thalidomide. *Am J Hematol* 2003; **74:** 290–1.

Pharmacokinetics

Thalidomide is slowly absorbed from the gastrointestinal tract; peak plasma concentrations occur within about 3 to 6 hours of an oral dose. It crosses the placenta and is distributed into the semen. The exact metabolic route and fate of thalidomide is unknown, although it appears to undergo non-enzymatic hydrolysis in plasma. The elimination half-life is about 5 to 7 hours.

References.
1. Aweeka F, *et al.* Pharmacokinetics and pharmacodynamics of thalidomide in HIV patients treated for oral aphthous ulcers: ACTG protocol 251. *J Clin Pharmacol* 2001; **41:** 1091–7.
2. Wohl DA, *et al.* Safety, tolerability, and pharmacokinetic effects of thalidomide in patients infected with human immunodeficiency virus: AIDS Clinical Trials Group 267. *J Infect Dis* 2002; **185:** 1359–63.
3. Teo SK, *et al.* Clinical pharmacokinetics of thalidomide. *Clin Pharmacokinet* 2004; **43:** 311–27.
4. Kamikawa R, *et al.* The pharmacokinetics of low-dose thalidomide in Japanese patients with refractory multiple myeloma. *Biol Pharm Bull* 2006; **29:** 2331–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Thalomid; ***Canad.***: Thalomid; ***Chile***: Inmunoprin; ***India***: Oncothal; Thalix; ***Jpn***: Thaled; ***Mex.***: Inmunoprin; Talizer; ***NZ***: Thalomid; ***Philipp.***: Thalix; ***UK***: Talidex; ***USA***: Thalomid.

Pharmacopoeial Preparations
USP 36: Thalidomide Capsules.

Thiotepa *(BAN, rINN)*

NSC-6396; TESPA; Thiophosphamide; Thiotépa; Thiotepum; Tiotepa; Triethylenethiophosphoramide; TSPA; WR-45312; Тиотепа.

Phosphorothioic tri(ethyleneamide); Tris(aziridin-1-yl)phosphine sulphide.

$C_6H_{12}N_3PS$=189.2

CAS — 52-24-4.

ATC — L01AC01.

ATC Vet — QL01AC01.

UNII — 905Z5W3GKH.

Pharmacopoeias. In *Br., Chin., Fr., Jpn,* and *US.*

BP 2014: (Thiotepa). Fine white, crystalline flakes. M.p. 52 degrees to 57 degrees. Freely soluble in water, in alcohol, and in chloroform. Store at 2 degrees to 8 degrees. At higher temperatures it polymerises and becomes inactive.

USP 36: (Thiotepa). Fine white, crystalline flakes, having a faint odour. M.p. 52 degrees to 57 degrees. Soluble 1 in 13 of water, 1 in about 8 of alcohol, 1 in about 2 of chloroform, and 1 in about 4 of ether. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Incompatibility. Lyophilised thiotepa 1 mg/mL in glucose 5% was incompatible when mixed with solutions of cisplatin or minocycline hydrochloride.[1]

1. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.

Stability. A solution of a lyophilised thiotepa preparation 500 micrograms/mL in glucose 5% was considered to be stable (less than 10% loss of thiotepa) for 8 hours at both 4 degrees and 23 degrees.[1] After 24 hours losses ranged between about 10 and 17%. A higher thiotepa concentration (5 mg/mL) was stable for 3 days at 23 degrees and 14 days at 4 degrees. Another study found that solutions containing 1 or 3 mg/mL of thiotepa in sodium chloride 0.9% were stable for 24 hours at 25 degrees and 48 hours at 8 degrees, but solutions containing 0.5% thiotepa needed to be used immediately.[2]

1. Xu QA, *et al.* Stability of thiotepa (lyophilized) in 5% dextrose injection at 4 and 23 degreesC. *Am J Health-Syst Pharm* 1996; **53:** 2728–30.
2. Murray KM, *et al.* Stability of thiotepa (lyophilized) in 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1997; **54:** 2588–91.

Uses and Administration

Thiotepa is an ethyleneimine compound whose antineoplastic effect is related to its alkylating action. It has generally been replaced by cyclophosphamide (p. 771.1) or other drugs. It is not a vesicant and may be given by all parenteral routes, as well as directly into tumour masses.

Thiotepa has been given parenterally in the palliative treatment of various solid tumours, including those of breast and ovary (p. 702.1 and p. 711.2). It may also be given intravenously with other antineoplastic drugs, with or without total body irradiation, as a conditioning therapy before autologous or allogeneic haematopoietic progenitor cell transplantation (HPCT). Instillations of thiotepa may be used in the adjuvant treatment of superficial tumours of the bladder (p. 700.2) and in the control of malignant effusions (p. 700.1). It has also been given intrathecally to patients with malignant meningeal disease, and has been used, in the form of eye drops, as an adjunct to the surgical removal of pterygium, to prevent recurrence (see p. 831.2). Thiotepa has also been used in the treatment of condylomata acuminata (p. 1689.3).

Thiotepa is given in a variety of dosage schedules for the **palliative treatment** of various solid tumours. In general, initial doses to suit the individual patient are followed by maintenance doses given at intervals of 1 to 4 weeks. Blood counts are recommended before and during therapy and should continue for at least 3 weeks after stopping. Thiotepa should not be given if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p. 730.3) and treatment should be stopped if the white cell count falls rapidly. Dosage should be reduced in patients with lesser degrees of leucopenia.

Intramuscular and intravenous dosage regimens vary considerably; several regimens have used courses of 15 mg daily for 4 days. In the USA a licensed dose of 300 to 400 micrograms/kg may be given intravenously at 1- to 4-week intervals. A solution containing 1 mg/mL in sterile water has been tried intrathecally in doses of up to 10 mg given on alternate days, for up to 4 doses (see also Administration, below).

The following doses, given by intravenous infusion over 2 to 4 hours, are recommended for use as **conditioning therapy**:

- for haematological diseases:
  - 125 to 300 mg/m² daily, given as a single infusion, for 2 to 4 days before *autologous* HPCT to a maximum cumulative dose of 900 mg/m² for the entire conditioning treatment, *or*
  - 185 to 481 mg/m² daily, given in one or two infusions, for 1 to 3 days before *allogeneic* HPCT to a maximum cumulative dose of 555 mg/m² for the entire conditioning treatment
- for solid tumours:
  - 120 to 250 mg/m² daily, given in one or two infusions, for 2 to 5 days before autologous HPCT to a maximum cumulative dose of 800 mg/m² for the entire conditioning treatment

For doses of thiotepa given as conditioning therapy in children, see below.

In the treatment of **bladder cancer** thiotepa in doses up to 60 mg may be instilled in 30 to 60 mL of sterile water or sodium chloride 0.9% into the bladder of a patient previously dehydrated for 8 to 12 hours, and retained if possible for 2 hours. The instillation may be repeated weekly for up to 4 weeks. Similar instillations have been given at intervals of 1 to 2 weeks, for up to 8 instillations in the prophylaxis of recurrence after surgical removal of bladder cancer. Single doses of 90 mg in 100 mL of sterile water have also been used prophylactically. For **malignant effusions**, doses of up to 60 mg of thiotepa in 20 to 60 mL of sterile water may be instilled after aspiration; in the USA the licensed dose is 600 to 800 micrograms/kg, a dose similar to that suggested for injection directly into tumours. Thiotepa for local use may be mixed with solutions of procaine and adrenaline.

Thiotepa 0.05% in sterile Ringer's solution has been instilled as eye drops every 3 hours for up to 6 weeks after surgical removal of **pterygium** in order to reduce the likelihood of recurrence.

A dose of 60 mg in a gel has been instilled weekly into the urethra for the treatment of **condylomata acuminata** (genital warts). Topical application of thiotepa has also been used for condylomata.

Administration. Neurotoxicity of intrathecal chemotherapy has been variously attributed to preservatives, volume, osmolality, and pH of the preparation; common practice is to prepare intrathecal chemotherapy with preservative-free diluent and limit the volume of the final solution, usually to 5 mL. A study evaluated pH and osmolality for thiotepa intrathecal solutions (in various diluents) at concentrations commonly used in practice: 1, 2, and 5 mg/mL. The concentration of thiotepa or the diluent used did not significantly change the pH of the injection; however, osmolality was generally lower than the physiological range of the CSF.[1]

1. de Lemos ML, *et al.* Evaluation of osmolality and pH of various concentrations of methotrexate, cytarabine, and thiotepa prepared in normal saline, sterile water for injection, and lactated Ringer's solution for intrathecal administration. *J Oncol Pharm Pract* 2009; **15:** 45–52.

Administration in children. Thiotepa may be given with other antineoplastic drugs, with or without total body irradiation, to children as a conditioning therapy before autologous or allogeneic haematopoietic progenitor cell transplantation (HPCT). The following doses, given by intravenous infusion over 2 to 4 hours, are recommended:

- for haematological diseases: 125 to 250 mg/m² daily, given in one or two infusions, for 1 to 3 days before *allogeneic* HPCT to a maximum cumulative dose of 375 mg/m² for the entire conditioning treatment
- for solid tumours: 150 to 350 mg/m² daily, given as a single infusion, for 2 to 3 days before *autologous* HPCT to a maximum cumulative dose of 1050 mg/m² for the entire conditioning treatment

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression may be delayed; the nadir of white cell and platelet counts may occur up to 30 days after thiotepa has been stopped. Bone-marrow depression has been reported after intravesical as well as parenteral use, and has occasionally been prolonged or fatal.

Gastrointestinal disturbances, fatigue, weakness, headache and dizziness, hypersensitivity reactions, blurred vision and conjunctivitis may occur. Amenorrhoea and impaired fertility have also been reported. Local irritation, and rarely frank chemical or haemorrhagic cystitis may follow intravesical instillation. Depigmentation of periorbital skin has occurred after the use of thiotepa eye drops. As with other alkylating agents, thiotepa is potentially mutagenic, teratogenic, and carcinogenic.

Thiotepa should be given with extreme care, if at all, to patients with pre-existing impairment of hepatic, renal, or bone-marrow function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiotepa as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Pharmacokinetics

The absorption of thiotepa from the gastrointestinal tract is incomplete and unreliable; variable absorption also occurs from intramuscular injection sites. Absorption through serous membranes such as the bladder and pleura occurs to some extent. After intravenous doses it is rapidly cleared from plasma, with an elimination half-life of about 2.4 hours. It is extensively metabolised: triethylenephosphoramide (TEPA), the primary metabolite, and some of the other metabolites have cytotoxicactivity and are eliminated more slowly than the parent compound. It is excreted in the urine: less than 2% of a dose is reported to be present as unchanged drug or its primary metabolite.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Tepadina; ***Cz.***: Tepadina; ***Denm.***: Tepadina; ***Ger.***: Tepadina; ***Gr.***: Thioplex; ***Irl.***: Tepadina; ***Ital.***: Thioplex; ***Neth.***: Ledertepa; Tepadina; ***Norw.***: Tepadina; ***Pol.***: Tepadina; ***Port.***: Tepadina; ***Spain***: Tepadina; ***UK***: Tepadina; ***USA***: Thioplex.

Pharmacopoeial Preparations
BP 2014: Thiotepa Injection;
USP 36: Thiotepa for Injection.

Tioguanine *(BAN, rINN)*

NSC-752; 6-TG; 6-Thioguanine; Thioguanine (USAN); Tioguaniini; Tioguanin; Tioguanina; Tioguaninum; WR-1141; Тиогуанин.

2-Aminopurine-6(1*H*)-thione; 2-Amino-6-mercaptopurine; 2-Aminopurine-6-thiol.

$C_5H_5N_5S$=167.2

CAS — 154-42-7 (anhydrous tioguanine); 5580-03-0 (tioguanine hemihydrate).

ATC — L01BB03.

ATC Vet — QL01BB03.

UNII — FTK8U1GZNX (thoguanine); WIX31ZPX66 (anhydrous thioguanine).

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2014: (Tioguanine). A pale yellow, crystalline powder. Practically insoluble in water, in alcohol, and in chloroform; dissolves in dilute solutions of alkali hydroxides.

USP 36: (Thioguanine). It is anhydrous or contains one-half molecule of water of hydration. A pale yellow, odourless or practically odourless, crystalline powder. Insoluble in water and in chloroform; soluble 1 in 7700 of alcohol; freely

soluble in dilute solutions of alkali hydroxides. Store in airtight containers.

Uses and Administration

Tioguanine is an analogue of the naturally occurring purine, guanine, and is an antimetabolite antineoplastic with actions and uses similar to those of mercaptopurine (p. 821.1). It appears to cause fewer gastrointestinal reactions but cross-resistance exists so that patients who do not respond to one are unlikely to respond to the other.

Tioguanine is given *orally*, usually with other antineoplastics, in the induction and consolidation of remissions in acute myeloid leukaemia (p. 693.1). It has also been used in other malignancies including acute lymphoblastic leukaemia (p. 692.3) and chronic myeloid leukaemia (p. 694.2). *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Doses of between 100 and 200 mg/m^2 daily have been given at various stages of treatment for short term cycles. A dose of 2 mg/kg daily increased after 4 weeks to 3 mg/kg daily if there is no response and toxicity allows, may be given in those rare cases when single agent therapy is considered appropriate.

Blood counts should be made frequently, particularly during induction and when tioguanine is given with other antineoplastics. Therapy should be withdrawn at the first sign of severe bone-marrow depression. Tioguanine is not recommended for maintenance or similar long-term continuous therapy because of the high risk of hepatotoxicity (see Effects on the Liver, below).

Tioguanine has been given *intravenously* as the sodium salt.

Administration in children. Tioguanine is given orally in the treatment of acute childhood leukaemias in the same doses as those used for adults (see Uses and Administration, above).

Administration in the elderly. UK licensed product information states that tioguanine has been used in elderly patients with acute leukaemia at the same doses as those used for younger patients, and that there are no dosage recommendations based on age alone. US licensed product information states that dose selection for elderly patients should be made cautiously, in view of the greater possibility of decreased hepatic, renal, or cardiac function, and suggests that initial doses be at the lower end of the dosing range.

Administration in hepatic or renal impairment. UK licensed product information states that reduced doses should be considered in patients with hepatic or renal impairment, but makes no specific dose recommendations. US licensed product information makes no recommendations for dose adjustment in hepatic or renal impairment, aside from advising caution in elderly patients who might have reduced hepatic or renal function (see Administration in the Elderly, above).

Psoriasis. A report of the use of tioguanine, in oral doses ranging from 20 mg twice weekly to 120 mg daily, in the management of patients with refractory psoriasis.[1] Dramatic improvement occurred in 14 of 18 patients, but a further 2 were unable to tolerate the drug. Myelosuppression was the principal toxic effect and it was suggested that thiopurine methyltransferase activity could be measured as a basis to determine initial dosage and the risk of toxicity. For the conventional management of psoriasis see p. 1688.1.

1. Mason C, Krueger GG. Thioguanine for refractory psoriasis. *J Am Acad Dermatol* 2001; **44:** 67–72.

Adverse Effects, Treatment, and Precautions

As for Mercaptopurine, p. 821.2.

In some patients, gastrointestinal reactions are reported to be less frequent than with mercaptopurine.

Effects on the blood. For the view that it may be possible to predict those individuals likely to have severe bone-marrow depression with tioguanine based on measurement of the activity of thiopurine methyltransferase or the concentration of tioguanine nucleotide, see under Azathioprine, p. 1946.2.

Effects on the liver. The use of tioguanine has been limited by reports of hepatic veno-occlusive disease attributed to the drug.[1-4] The manufacturer (*GlaxoSmithKline*) has stated that, in most cases, liver toxicity is reversible upon withdrawal of chemotherapy. A comparison with mercaptopurine in the maintenance treatment of children with acute lymphoblastic leukaemia found that of 95 patients who developed veno-occlusive disease, 82 were receiving tioguanine, representing about 11% of all patients assigned to the drug.[5] In addition, although tioguanine was associated with fewer CNS relapses, patients in the tioguanine arm were more likely to develop fatal infections.

Centrilobular hepatic necrosis has also been reported; reports are confounded by the use of high doses of tioguanine, other antineoplastics, oral contraceptives, and chronic alcohol abuse.

1. Gill RA, *et al.* Hepatic veno-occlusive disease caused by 6-thioguanine. *Ann Intern Med* 1982; **96:** 58–60.
2. Krivoy N, *et al.* Reversible hepatic veno-occlusive disease and 6-thioguanine. *Ann Intern Med* 1982; **96:** 788.
3. Kao NL, Rosenblate HJ. 6-Thioguanine therapy for psoriasis causing toxic hepatic venoocclusive disease. *J Am Acad Dermatol* 1993; **28:** 1017–18.
4. Romagosa R, *et al.* Treatment of psoriasis with 6-thioguanine and hepatic venoocclusive disease. *J Am Acad Dermatol* 2002; **47:** 970–2.
5. Vora A, *et al.* Medical Research Council/National Cancer Research Network Childhood Leukaemia Working Party. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006; **368:** 1339–48.

Handling and disposal. For reference to a method for the destruction of tioguanine in wastes, see Mercaptopurine, p. 821.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tioguanine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Interactions

Unlike mercaptopurine (p. 821.3), normal doses of tioguanine may be used with allopurinol.

Several cases of portal hypertension with hepatic nodular regenerative hyperplasia have been reported in patients who received tioguanine with busulfan (see p. 756.1).

It has been suggested that daunorubicin might enhance the hepatotoxicity of tioguanine (see p. 779.3).

Pharmacokinetics

Tioguanine is incompletely and variably absorbed from the gastrointestinal tract; on average about 30% of a dose is absorbed after oral doses. It is rapidly activated in the body by intracellular conversion to its nucleotide, thioguanylic acid and its thioguanosine phosphate derivatives. With repeated doses increasing amounts of the nucleotide are incorporated into DNA. Very little unchanged tioguanine has been detected circulating in the blood but the half-life of the nucleotide in the tissues is prolonged. Tioguanine is inactivated mainly by methylation to aminomethylthiopurine; small amounts are deaminated to thioxanthine, and may go on to be oxidised by xanthine oxidase to thiouric acid, but inactivation is essentially independent of xanthine oxidase and is not affected by inhibition of the enzyme.

It is excreted in the urine almost entirely as metabolites; only negligible amounts of tioguanine have been detected. Tioguanine does not appear to cross the blood-brain barrier to a significant extent; very little is found in CSF after normal clinical doses. It crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lanvis; ***Austral.***: Lanvis; ***Belg.***: Lanvis; ***Braz.***: Lanvis; ***Canad.***: Lanvis; ***Chile***: Lanvis; ***Cz.***: Lanvis; ***Fr.***: Lanvis; ***Gr.***: Lanvis; ***Hong Kong***: Lanvis; ***Irl.***: Lanvis; ***Israel***: Lanvis; ***Malaysia***: Lanvis; ***Neth.***: Lanvis; ***NZ***: Lanvis; ***Pol.***: Lanvis; ***S.Afr.***: Lanvis; ***Swed.***: Lanvis; ***Switz.***: Lanvis; ***Thai.***: Lanvis; ***Turk.***: Lanvis; ***UK***: Lanvis†; ***USA***: Tabloid†.

Pharmacopoeial Preparations
BP 2014: Tioguanine Tablets;
USP 36: Thioguanine Tablets.

Tipifarnib *(USAN, rINN)*

R-115777; Tipifarnibum; Типифарниб.
(+)-6-[(*R*)-Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone.
$C_{27}H_{22}Cl_2N_4O$=489.5
CAS — 192185-72-1.
UNII — MAT637500A.

NOTE. The name Zarnestra has been used as a trade mark for tipifarnib.

Profile

Tipifarnib is a farnesyl transferase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

References.
1. Zhang S, *et al.* Pharmacokinetics of tipifarnib after oral and intravenous administration in subjects with advanced cancer. *J Clin Pharmacol* 2006; **46:** 1116–27.
2. Siegel-Lakhai WS, *et al.* Clinical and pharmacologic study of the farnesyltransferase inhibitor tipifarnib in cancer patients with normal or mildly or moderately impaired hepatic function. *J Clin Oncol* 2006; **24:** 4558–64.
3. Perez-Ruixo JJ, *et al.* Exposure-toxicity relationships for tipifarnib in cancer patients. *Br J Clin Pharmacol* 2007; **64:** 219–32.
4. Martinelli G, *et al.* Farnesyltransferase inhibition in hematologic malignancies: the clinical experience with tipifarnib. *Clin Adv Hematol Oncol* 2008; **6:** 303–10.
5. Harousseau JL, *et al.* FIGHT-AML-301 Investigators. A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older. *Blood* 2009; **114:** 1166–73.
6. Epling-Burnette PK, Loughran TP. Suppression of farnesyltransferase activity in acute myeloid leukemia and myelodysplastic syndrome: current understanding and recommended use of tipifarnib. *Expert Opin Invest Drugs* 2010; **19:** 689–98.

Tirapazamine *(USAN, rINN)*

SR-4233; Tirapazamina; Tirapazaminum; Win-59075; Тирапазамин.
3-Amino-1,2,4-benzotriazine 1,4-dioxide.
$C_7H_6N_4O_2$=178.2
CAS — 27314-97-2.
UNII — 1UD32YR59G.

Profile

Tirapazamine is reported to be reduced in hypoxic cells to an active anion that causes DNA strand breaks. It sensitises hypoxic tumour cells to the cytotoxic activity of other drugs. It is under investigation for its cytotoxic actions, alone or with cisplatin or radiotherapy. Adverse effects reported with tirapazamine include nausea and vomiting, diarrhoea, rashes, muscle cramps and fatigue; myelosuppression is said to be rare.

Reviews.
1. Gandara DR, *et al.* Tirapazamine: prototype for a novel class of therapeutic agents targeting tumor hypoxia. *Semin Oncol* 2002; **29** (suppl 4): 102–9.
2. Marcu L, Olver I. Tirapazamine: from bench to clinical trials. *Curr Clin Pharmacol* 2006; **1:** 71–9.
3. Reddy SB, Williamson SK. Tirapazamine: a novel agent targeting hypoxic tumor cells. *Expert Opin Invest Drugs* 2009; **18:** 77–87.

Tivozanib *(USAN, rINN)*

AV-951 (tivozanib hydrochloride); Kil-8951; Tivozanibum; Тивозаниб.
1-{2-Chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-3-(5-methyl-1,2-oxazol-3-yl)urea.
$C_{22}H_{19}ClN_4O_5$=454.9
CAS — 475108-18-0.
UNII — 172030934T.

Profile

Tivozanib is an orally active tyrosine kinase inhibitor that targets vascular epidermal growth factor receptors 1, 2, and 3. It is under investigation for the treatment of renal cell carcinoma and other solid tumours.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.
1. De Luca A, Normanno N. Tivozanib, a pan-VEGFR tyrosine kinase inhibitor for the potential treatment of solid tumors. *IDrugs* 2010; **13:** 636–45.

Topotecan Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de topotecán; Nogitecan Hydrochloride; SKF-104864A; SKF5-104864-A; Topotecán, hidrocloruro de; Topotécane, Chlorhydrate de; Topotecani Hydrochloridum; Topotekaanihydrokloridi; Topotekanhydroklorid; Топотекана Гидрохлорид.
(*S*)-10-Dimethylaminomethyl-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2*b*]quinoline-3,14(4*H*,12*H*)-dione hydrochloride.
$C_{23}H_{23}N_3O_5$,HCl=457.9
CAS — 123948-87-8 (topotecan); 119413-54-6 (topotecan hydrochloride).
ATC — L01XX17.
ATC Vet — QL01XX17.
UNII — 9565425ZCY.

Incompatibility. Topotecan hydrochloride was found to degrade to 88.7% of its original concentration over 4 hours when mixed with ticarcillin sodium or potassium clavulanate. It was also found to be incompatible with dexamethasone sodium phosphate and fluorouracil.[1]

When mixed with mitomycin solution an immediate colour change took place and concentrations of mitomycin fell by 15 to 20% over 4 hours. The pH of the mixtures remained constant at 3.3 to 3.5.

1. Mayron D, Gennaro AR. Stability and compatibility of topotecan hydrochloride with selected drugs. *Am J Health-Syst Pharm* 1999; **56:** 875–81.

Uses and Administration

Like irinotecan (p. 812.3), topotecan is a semisynthetic derivative of the alkaloid camptothecin that exerts its antineoplastic activity by inhibition of topoisomerase I. It is used in the treatment of metastatic carcinoma of the ovary refractory to other therapy (see p. 711.2) and in relapsed small cell lung cancer (p. 710.2) after standard therapy. Topotecan is given with cisplatin in the treatment of metastatic, recurrent, or persistent carcinoma of the cervix (p. 704.2) that is not amenable to curative treatment with surgery and/or radiation therapy. Topotecan is also under investigation in the management of myelodysplastic syndromes.

Topotecan is given as the hydrochloride but doses are expressed in terms of the base. Topotecan hydrochloride 1.09 mg is equivalent to about 1 mg of topotecan. Topotecan may be given orally or intravenously. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* When given by intravenous infusion, topotecan is diluted in sodium chloride 0.9% or glucose 5%; a final concentration of between 25 and 50 micrograms/mL is specified in the UK.

In **ovarian** and **small cell lung cancer**, topotecan hydrochloride may be given *intravenously* in an initial dose equivalent to topotecan 1.5 mg/m², infused over 30 minutes, on days 1 to 5 of a 21-day course. A minimum of 4 courses should be given, in the absence of tumour progression, and provided that blood counts and haemoglobin have recovered adequately (see also Bone-marrow Depression, p. 730.3). If severe neutropenia occurs in any course, or if the platelet count falls below 25 000 cells/mm³, the dose in the subsequent courses may be reduced by 250 micrograms/m² to 1.25 mg/m² daily, and subsequently to 1 mg/m² daily if necessary. Alternatively, in the event of severe neutropenia, a granulocyte colony-stimulating factor may be given from day 6 of the course, 24 hours after topotecan dosage is complete. If severe toxicity recurs once the dose has been reduced to 1 mg/m² withdrawal of topotecan may be required. Dosage should also be reduced in patients with renal impairment (see below).

Topotecan may also be given *orally* for small cell lung cancer. The recommended dose is 2.3 mg/m² once daily for 5 consecutive days, repeated every 21 days. If neutropenia occurs, or if the platelet count falls below 25 000 cells/mm³, or for patients with severe diarrhoea, the daily dose should be reduced by 400 micrograms/m²(to 1.9 mg/m² daily, and subsequently to 1.5 mg/m² daily if necessary) for subsequent courses.

In **cervical cancer**, topotecan is given in an intravenous dose of 750 micrograms/m², infused over 30 minutes, on days 1, 2, and 3 of a 21-day course; cisplatin 50 mg/m² is given by intravenous infusion after topotecan on day 1. Dosage adjustments for subsequent courses are specific for each drug; for cisplatin, see p. 766.2. If severe neutropenia occurs, or if the platelet count falls below 25 000 cells/mm³, the topotecan dose should be reduced to 600 micrograms/m², and subsequently to 450 micrograms/m² if necessary. Alternatively, in the event of severe febrile neutropenia, granulocyte colony-stimulating factor may be given from day 4 of the course, 24 hours after completion of the topotecan infusion.

References.
1. Long HJ, *et al.* Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2005; **23:** 4626–33.
2. Randall-Whitis LM, Monk BJ. Topotecan in the management of cervical cancer. *Expert Opin Pharmacother* 2007; **8:** 227–36.
3. Eckardt JR, *et al.* Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007; **25:** 2086–92. Correction. *ibid.;* 3387.
4. Nicum SJ, O'Brien ME. Topotecan for the treatment of small-cell lung cancer. *Expert Rev Anticancer Ther* 2007; **7:** 795–801.
5. O'Brien M, *et al.* Recent advances with topotecan in the treatment of lung cancer. *Oncologist* 2007; **12:** 1194–204.
6. Ackermann S, *et al.* Topotecan in cervical cancer. *Int J Gynecol Cancer* 2007; **17:** 1215–23.
7. Peng LH, *et al.* Topotecan for ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).
8. Sehouli J, Oskay-Özcelik G. Current role and future aspects of topotecan in relapsed ovarian cancer. *Curr Med Res Opin* 2009; **25:** 639–51.
9. Lorusso D, *et al.* Review role of topotecan in gynaecological cancers: current indications and perspectives. *Crit Rev Oncol Hematol* 2010; **74:** 163–74.
10. Loveman E, *et al.* The clinical effectiveness and cost-effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation. *Health Technol Assess* 2010; **14:** 1–204.
11. Paton F, *et al.* Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix. *Health Technol Assess* 2010; **14** (suppl 1): 55–62.

Administration. In an attempt to reduce haematological toxicity, various schedule modifications of topotecan have been investigated, one of the most commonly studied being a regimen of intravenous topotecan 4 mg/m² over 30 minutes, once weekly for 3 weeks, followed by a week of rest.[1] A pharmacokinetic study found this dose to be well tolerated in patients with advanced solid tumours, although clinical efficacy was not assessed.[1] A study compared the conventional schedule of topotecan (see Uses and Administration, above), at a reduced dose of 1.25 mg/m² on days 1 to 5 of a 21-day cycle, with a weekly schedule of 4 mg/m² on days 1, 8 and 15 of a 28-day cycle in patients with platinum-resistant ovarian cancer.[2] Haematological toxicity was less with the weekly regimen. Slightly lower efficacy in terms of response rates and progression-free survival was seen with the weekly regimen, although these differences were not statistically significant, and there was no notable differences in overall survival between the two regimens. The authors concluded that weekly topotecan is a viable treatment option in this setting, allowing therapy to be geared towards goals of management.[2]

1. Curtis KK, *et al.* A phase I study to characterize the safety, tolerability, and pharmacokinetics of topotecan at 4 mg/m² administered weekly as a 30-minute intravenous infusion in patients with cancer. *J Clin Pharmacol* 2010; **50:** 268–75.
2. Sehouli J, *et al.* Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol* 2011; **29:** 242–8.

Administration in renal impairment. Licensed product information for *intravenous* topotecan recommends the following for patients with **ovarian or small cell lung cancer** according to creatinine clearance (CC):
- mild renal impairment (CC 40 to 60 mL/minute): no dosage adjustment
- moderate renal impairment (CC 20 to 39 mL/minute): 750 micrograms/m² daily for 5 consecutive days

For patients with small cell lung cancer given *oral* topotecan, the following is suggested:
- mild renal impairment (CC 50 to 80 mL/minute): no dosage adjustment
- moderate renal impairment (CC 30 to 49 mL/minute): 1.8 mg/m² once daily for 5 consecutive days

Data are insufficient to make dose recommendations in patients with severe renal impairment.

In patients with **cervical cancer**, treatment with topotecan and cisplatin should only be started in those with a serum creatinine of 1.5 mg or less per 100 mL.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Neutropenia is very common with topotecan and is usually dose-limiting. The nadir of white cell count usually occurs about 9 to 12 days after a dose. Febrile neutropenia, sepsis, and neutropenic colitis can occur; fatalities have been reported. Thrombocytopenia, anaemia, and leucopenia also occur commonly. Topotecan should not be given to those patients with pre-existing bone-marrow depression, and blood counts should be monitored regularly. Gastrointestinal disturbances and anorexia are also common with topotecan, and may be severe; oral topotecan is associated with severe diarrhoea.

Interstitial lung disease has been reported, and can be fatal; underlying risk factors include pulmonary fibrosis, lung cancer, thoracic radiation, and use of other drugs toxic to the lungs or of colony-stimulating factors. Patients should be monitored for signs and symptoms such as cough, fever, dyspnoea, or hypoxia, and treatment should be stopped if interstitial lung disease is suspected.

Other adverse effects include fatigue and weakness, alopecia, malaise, pruritus, pyrexia, and hyperbilirubinaemia. Hypersensitivity reactions including rashes have been reported; anaphylaxis, angioedema, and urticaria may occur rarely.

Licensed product information recommends that topotecan should not be given to patients with severe hepatic or renal impairment, due to a lack of data in these patients. Its use in breast feeding is contra-indicated for the same reason. Topotecan has been reported to produce fetal death and malformations in *animals*.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies topotecan as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Interactions

For a report of topotecan reducing the clearance of docetaxel, see Antineoplastics, p. 782.2.

Greater myelosuppression is seen when topotecan is used with other cytotoxic drugs, which may require dosage reductions of either drug. However, with platinum drugs, there is a sequence-dependent interaction: giving a platinum drug on the first day of topotecan dosage requires lower doses of each, compared with giving it on the fifth day.

Granulocyte colony-stimulating factor can prolong the duration of neutropenia if given with topotecan, so if used, it should not be started until, 24 hours after topotecan dosage is complete.

Ciclosporin has been reported to increase exposure to topotecan.

Pharmacokinetics

Topotecan is rapidly absorbed after oral doses; peak plasma concentrations occur after about 1 to 2 hours. The oral bioavailability is about 40%. Food does not appreciably affect topotecan pharmacokinetics. Topotecan is widely distributed after intravenous doses. Plasma protein binding is about 35%. The drug undergoes reversible hydrolysis of the lactone ring to the inactive hydroxy acid form; only small amounts are demethylated in the liver. A significant proportion of a dose is excreted in urine. The terminal half-life has been reported to be 2 to 3 hours for the intravenous formulation, and 3 to 6 hours for the oral formulation.

References.
1. Herben VMM, *et al.* Clinical pharmacokinetics of topotecan. *Clin Pharmacokinet* 1996; **31:** 85–102.
2. Mould DR, *et al.* Population pharmacokinetic and adverse event analysis of topotecan in patients with solid tumors. *Clin Pharmacol Ther* 2002; **71:** 334–48.
3. Herben VM, *et al.* Urinary and fecal excretion of topotecan in patients with malignant solid tumours. *Cancer Chemother Pharmacol* 2002; **50:** 59–64.
4. Léger F, *et al.* Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. *Br J Cancer* 2004; **90:** 343–7.
5. Schaiquevich P, *et al.* Population pharmacokinetic analysis of topotecan in pediatric cancer patients. *Clin Cancer Res* 2007; **13:** 6703–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asotecan; Hycamtin; Potekam; Tisogen; Topokebir; ***Austral.***: Hycamtin; ***Austria***: Hycamtin; ***Belg.***: Hycamtin; ***Braz.***: Evotecan; Hycamtin; Toporan; ***Canad.***: Hycamtin; ***Chile***: Hycamtin; ***China***: Ai Tuo (艾妥); Aoluona (奥罗那); Bo En (卜恩); Hycamtin (和美新); Jin Xi Su (金喜素); Sheng Cheng (胜城); Xinze (欣泽); ***Cz.***: Hycamtin; Potactasol; ***Denm.***: Hycamtin; ***Fin.***: Hycamtin; ***Fr.***: Hycamtin; Potactasol; ***Ger.***: Hycamtin; ***Gr.***: Hycamtin; ***Hong Kong***: Hycamtin; ***Hung.***: Hycamtin; Viatopin†; ***India***: Cantop; Topotel; ***Irl.***: Hycamtin; Potactasol; ***Israel***: Hycamtin; Potactasol; ***Ital.***: Hycamtin; ***Mex.***: Toranex; ***Neth.***: Hycamtin; Potactasol; ***Norw.***: Hycamtin; Potactasol; ***Philipp.***: Hycamtin; Topotel; ***Pol.***: Hycamtin; Potactasol; ***Port.***: Hycamtin; Potactasol; ***Rus.***: Hycamtin (Гикамтин); Verotekan (Веротекан); ***S.Afr.***: Hycamtin; ***Singapore***: Hycamtin; ***Spain***: Hycamtin; ***Swed.***: Hycamtin; ***Switz.***: Hycamtin; ***Thai.***: Hycamtin; Topotel; ***Turk.***: Hycamtin; ***UK***: Hycamtin; Potactasol; ***Ukr.***: Hycamtin (Гикамтин); ***USA***: Hycamtin.

Toremifene Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de toremifeno; FC-1157a; Toremifen Sitrat; Torémifène, Citrate de; Toremifeni Citras; Toremifeno, citrato de; Торемифена Цитрат.

2-{*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy}-*N*,*N*-dimethylethylamine citrate.

$C_{26}H_{28}ClNO,C_6H_8O_7$=598.1

CAS — 89778-26-7 (toremifene); 89778-27-8 (toremifene citrate).

ATC — L02BA02.

ATC Vet — QL02BA02.

UNII — 2498Y783QT.

Uses and Administration

Toremifene is a selective oestrogen receptor modulator with properties similar to those of tamoxifen (p. 860.2). It is used in the treatment of metastatic breast cancer (p. 702.1) in postmenopausal women with oestrogen-receptor positive tumours.

Toremifene is given orally as the citrate, but doses are calculated in terms of the base; 88.4 mg of toremifene citrate is equivalent to about 60 mg of toremifene. A dose of toremifene 60 mg once daily is used.

Toremifene is also under investigation for the prevention of prostate cancer in men with high-grade intraepithelial neoplasia, as well as for the treatment of adverse effects related to androgen deprivation therapy.

References.
1. Wiseman LR, Goa KL. Toremifene: a review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. *Drugs* 1997; **54:** 141–60.
2. Holli K, *et al*. Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 2000; **18:** 3487–94.
3. Taneja SS, *et al*. Toremifene—a promising therapy for the prevention of prostate cancer and complications of androgen deprivation therapy. *Expert Opin Invest Drugs* 2006; **15:** 293–305.
4. Smith MR, *et al*. Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. *J Urol (Baltimore)* 2008; **179:** 152–5.
5. Smith MR, *et al*. Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: interim analysis of a multicenter phase III study. *J Clin Oncol* 2008; **26:** 1824–9.
6. Lewis JD, *et al*. Excellent outcomes with adjuvant toremifene or tamoxifen in early stage breast cancer. *Cancer* 2010; **116:** 2307–15.
7. Yamamoto Y, *et al*. Clinical usefulness of high-dose toremifene in patients relapsed on treatment with an aromatase inhibitor. *Breast Cancer* 2010; **17:** 254–60.
8. Smith MR, *et al*. Toremifene to reduce fracture risk in men receiving androgen deprivation therapy for prostate cancer. *J Urol (Baltimore)* 2010; **184:** 1316–21.

Mastalgia. For reports of efficacy with toremifene in the management of mastalgia, see under Danazol, p. 2265.1.

Adverse Effects and Precautions

As for Tamoxifen Citrate, p. 861.2. Increased sweating occurs very commonly with toremifene.

Use of toremifene is contra-indicated in patients with pre-existing endometrial hyperplasia, or in those with severe thromboembolic disease or severe hepatic impairment. Toremifene has been shown to prolong the QT interval in a dose-dependent manner. Its use is therefore contra-indicated in patients with QT prolongation, electrolyte disturbances (especially uncorrected hypokalaemia), or in those with bradycardia, heart failure, or a history of arrhythmias. Toremifene should also be used with caution in those with conditions such as myocardial ischaemia, as treatment may lead to an increased risk for ventricular arrhythmias such as torsade de pointes and cardiac arrest; if cardiac arrhythmia occurs during therapy, toremifene should be stopped and an ECG should be performed. Patients with bone metastases should be monitored for signs and symptoms of hypercalcaemia.

Breast feeding. Licensed product information states that toremifene is excreted in the milk of *rats*, and that bodyweight gain of the rat offspring was seen during lactation. It is unknown whether the drug is excreted in human milk, and use is contra-indicated during breast feeding. It has been suggested[1] that breast feeding be withheld for a minimum of 25 to 30 days after a dose.

1. *et al*., eds. *Drugs during pregnancy and lactation: treatment options and risk assessment*. 2nd ed. London: Elsevier, 2007.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies toremifene as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Toremifene is metabolised by cytochrome P450 isoenzyme CYP3A4, and potent enzyme-inducing drugs such as phenytoin, phenobarbital and carbamazepine, can increase toremifene metabolism, thereby lowering the serum concentration; dose adjustment of toremifene may be needed. Conversely, azole antifungals and macrolide antibacterials may theoretically inhibit toremifene metabolism by inhibiting the isoenzyme.

Toremifene should not be used with drugs that prolong the QT interval, such as antiarrhythmics, antipsychotics (such as phenothiazines, pimozide, sertindole, haloperidol, and sultopride), certain antimicrobials (such as moxifloxacin, erythromycin, pentamidine, and antimalarials, particularly halofantrine), certain antihistamines (terfenadine, astemizole, mizolastine) and other drugs such as cisapride, vincamine, bepridil, and diphemanil.

Use with drugs that decrease renal calcium excretion, such as thiazide diuretics, may increase the incidence of hypercalcaemia. Use with coumarin anticoagulants should be avoided as there is a risk of increased bleeding time.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of toremifene in 9 subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al*. Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Pharmacokinetics

Toremifene citrate is well absorbed from the gastrointestinal tract and peak plasma concentrations of toremifene occur within 3 hours. Food intake may delay peak plasma concentrations by up to 2 hours but has no effect on the extent of absorption. Plasma concentration declines biexponentially; the mean distribution half-life is about 4 hours and the elimination half-life is about 5 days. It is extensively bound to plasma proteins, mainly albumin. Toremifene is metabolised principally by the cytochrome P450 isoenzyme CYP3A4. The main metabolite is *N*-demethyltoremifene, which is reported to have similar anti-oestrogenic activity but weaker anti-tumour activity than toremifene; it is even more extensively bound to plasma proteins. Minor metabolites of toremifene include (deaminohydroxy)-toremifene, 4-hydroxytoremifene, and *N*,*N*-didemethyltoremifene; concentrations of these are considered to be too low to have biological effects. Toremifene undergoes enterohepatic circulation and is eliminated mainly in the faeces as metabolites. About 10% is excreted in the urine.

Reviews.
1. Taras TL, *et al*. Clinical pharmacokinetics of toremifene. *Clin Pharmacokinet* 2000; **39:** 327–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fareston; ***Austria***: Fareston; ***Belg.***: Fareston†; ***China***: Fareston (法乐通); ShuRui (枢瑞); ***Cz.***: Fareston; ***Fin.***: Fareston; ***Fr.***: Fareston; ***Ger.***: Fareston†; ***Gr.***: Fareston; ***Hung.***: Fareston; ***Irl.***: Fareston; ***Ital.***: Fareston; ***Mex.***: Fareston†; ***Neth.***: Fareston; ***NZ***: Fareston; ***Pol.***: Fareston; ***Port.***: Fareston; ***Rus.***: Fareston (Фарестон); ***S.Afr.***: Fareston; ***Spain***: Fareston†; ***Swed.***: Fareston; ***Switz.***: Fareston†; ***Thai.***: Fareston; ***Turk.***: Fareston; ***UK***: Fareston; ***Ukr.***: Fareston (Фарестон); ***USA***: Fareston.

Tositumomab *(rINN)*

B-1; Tositumomabum; Тositумомаб.
Immunoglobulin G2a anti-(human antigen CD 20) (mouse monoclonal clone B1R1 γ2a-chain), disulfide with mouse monoclonal clone B1R1 λ_2-chain, dimer.
CAS — 192391-48-3.
UNII — 0343IGH41U.

Uses and Administration

Tositumomab is an anti-B1 monoclonal antibody that is directed against the CD20 antigen found on the surface of B lymphocytes. It is radiolabelled with iodine-131 (p. 2225.3) for the treatment of patients with CD20 antigen-expressing, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma (p. 696.3), and including those patients who have disease refractory to rituximab.

The regimen consists of a dosimetric step, followed 7 to 14 days later by a therapeutic step. The dosimetric step consists of 450 mg of tositumomab given intravenously in 50 mL sodium chloride 0.9% over 60 minutes. Tositumomab 35 mg radiolabelled with iodine-131 is then given intravenously in 30 mL sodium chloride 0.9% over 20 minutes. This is followed by whole body imaging to determine whether biodistribution is acceptable, and to allow calculation of the therapeutic dose of radiolabelled tositumomab. In the therapeutic step, tositumomab 450 mg is given again, and followed by the calculated dose of radiolabelled tositumomab.

The rate of infusion may be halved for mild to moderate infusional toxicity, and stopped if this is severe; the infusions may be restarted at half the rate once toxicity resolves. Patients are pretreated with thyroid protective agents at least 24 hours before the first radiolabelled dose of tositumomab; treatment is continued until 2 weeks after the radiolabelled therapeutic dose. Analgesics and antihistamines are also given orally 30 minutes before doses of tositumomab.

References.
1. Kaminski MS, *et al*. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001; **19:** 3918–28.
2. Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin Oncol* 2003; **30** (suppl): 31–8.
3. Davies AJ, *et al*. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2004; **22:** 1469–79.
4. Vose JM. Bexxar: novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma. *Oncologist* 2004; **9:** 160–72.
5. Horning SJ, *et al*. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; **23:** 712–19.
6. Kaminski MS, *et al*. ^{131}I-Tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005; **352:** 441–9.
7. Fisher RI, *et al*. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol* 2005; **23:** 7565–73.
8. Dosik AD, *et al*. Subsequent therapy can be administered after tositumomab and iodine I-131 tositumomab for non-Hodgkin lymphoma. *Cancer* 2005; **106:** 616–22.
9. Davies AJ. A review of tositumomab and I^{131} tositumomab radioimmunotherapy for the treatment of follicular lymphoma. *Expert Opin Biol Ther* 2005; **5:** 577–88.
10. Smith S, Sweetenham JW. Iodine 131 tositumomab in the treatment of non-Hodgkin's lymphoma. *Future Oncol* 2007; **3:** 255–62.
11. Cheung MC, *et al*. Members of the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. ^{131}I-Tositumomab in lymphoma. *Curr Oncol* 2009; **16:** 32–47.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Infusion reactions suggestive of a cytokine release syndrome, and other hypersensitivity reactions including anaphylaxis, have been reported with tositumomab. Prolonged and severe neutropenia, thrombocytopenia, and anaemia occur commonly; full blood counts should be monitored weekly for up to 12 weeks. Other adverse effects include gastrointestinal disturbances, dehydration, abdominal pain, pleural effusion, and increased susceptibility to infection. Delayed adverse effects such as the development of secondary malignancies, leukaemia, or myelodysplastic syndrome may occur. Patients receiving the radiolabelled regimen may be susceptible to hypothyroidism and pretreatment with thyroid blocking drugs is recommended (see Uses and Administration, above); levels of thyroid-stimulating hormone should be measured before treatment and annually thereafter.

Hypersensitivity. A report of successful use of tositumomab in a patient who had repeated infusion reactions to rituximab[1] suggests a possible lack of cross-sensitivity between the 2 anti-CD20 antibodies.

1. Hayslip J, Fenning R. Safe administration of iodine-131 tositumomab after repeated infusion-related reactions to rituximab. *Oncologist* 2007; **12:** 338–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Bexxar; ***USA***: Bexxar.

Trabectedin *(BAN, USAN, rINN)*

Ecteinascidin-743; ET-743; NSC-64B766; Trabectedina; Trabectédine; Trabectedinum; Трабектедин.
(1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6′,8,14-Trihydroxy-7′,9-dimethoxy-4,10,23-trimethyl-19-oxo-3′,4′,6,7,12,13,14,16-octahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino-6a*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1′(2′*H*)-isoquinolin]-5-yl acetate.
$C_{39}H_{43}N_3O_{11}S$=761.8
CAS — 114899-77-3.
ATC — L01CX01.
ATC Vet — QL01CX01.
UNII — ID0YZQ2TCP.

Uses and Administration

Trabectedin is a novel DNA-binding agent derived from the marine tunicate, *Ecteinascidia turbinata*. It is used for the treatment of advanced soft-tissue sarcomas, after failure of anthracyclines or ifosfamide, or in patients for whom these drugs are unsuitable. It is also licensed for use with liposomal doxorubicin in the treatment of relapsed platinum-sensitive ovarian cancer.

For treatment of **soft-tissue sarcomas**, the recommended dose is 1.5 mg/m², given as an intravenous infusion over 24 hours.

For the treatment of **ovarian cancer** trabectedin is given in a dose of 1.1 mg/m² as an intravenous infusion over 3 hours immediately following an infusion of pegylated liposomal doxorubicin 30 mg/m².

Treatment may be repeated at 3-week intervals as long as clinical benefit persists, provided haematological, hepatic, and renal function parameters are met. If these baseline criteria are not met, treatment must be delayed for up to 3 weeks, until the criteria are met. If severe toxicity occurs at any time between cycles, the dose for subsequent cycles must be reduced (see Administration in Subsequent Cycles, p. 875.1).

If trabectedin is given via a central venous line, which is the preferred method, the dose should be diluted in at least 50 mL of sodium chloride 0.9% or glucose 5%. If central access is unfeasible, and it is given peripherally, the dose should be diluted in at least 1 litre of diluent. Dexamethasone 20 mg is given intravenously 30 minutes before treatment with trabectedin (or before liposomal doxorubicin in patients treated for ovarian cancer), to reduce nausea and hepatotoxicity.

References.
1. van Kesteren C, *et al.* Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. *Anticancer Drugs* 2003; **14:** 487–502.
2. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Invest Drugs* 2003; **12:** 1843–53.
3. Beumer JH, *et al.* Hepatotoxicity and metabolism of trabectedin: a literature review. *Pharmacol Res* 2005; **51:** 391–8.
4. Fayette J, *et al.* ET-743: a novel agent with activity in soft tissue sarcomas. *Oncologist* 2005; **10:** 827–32.
5. Schöffski P, *et al.* Trabectedin (ET-743): evaluation of its use in advanced soft-tissue sarcoma. *Future Oncol* 2007; **3:** 381–92.
6. Schöffski P, *et al.* Clinical impact of trabectedin (ecteinascidin-743) in advanced/metastatic soft tissue sarcoma. *Expert Opin Pharmacother* 2008; **9:** 1609–18.
7. Boudou L, *et al.* Trabectedin for the management of soft-tissue sarcoma. *Expert Rev Anticancer Ther* 2009; **9:** 727–37.
8. Chuk MK, *et al.* Trabectedin. *Oncologist* 2009; **14:** 794–9. Correction. *ibid.*; 949.
9. Ganjoo KN, Patel SR. Trabectedin: an anticancer drug from the sea. *Expert Opin Pharmacother* 2009; **10:** 2735–43.
10. Carter NJ, Keam SJ. Trabectedin: a review of its use in soft tissue sarcoma and ovarian cancer. *Drugs* 2010; **70:** 355–76.

Administration in hepatic impairment. Licensed product information states that there are no studies of trabectedin in hepatic impairment and data are unavailable to recommend doses in these patients. However, since systemic exposure is likely to be increased in these patients, thus increasing the risk of hepatotoxicity, caution is advised and dose adjustments may be needed. Trabectedin should not be given to patients with hyperbilirubinaemia.

Administration in renal impairment. Licensed product information for trabectedin states that no dose adjustments are needed when used as monotherapy in patients with mild or moderate renal impairment, but that trabectedin should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) as no data are available for this population. For similar reasons, combination therapy is not recommended in those with creatinine clearance less than 60 mL/min.

Administration in subsequent cycles. Initial criteria for administration of trabectedin are:
- absolute neutrophil count: at least 1500 cells/mm^3
- platelet count: at least 100 000 cells/mm^3
- bilirubin: less than or equal to upper limit of normal (ULN)
- alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase: less than or equal to 2.5 X ULN
- albumin: 25 mg/mL or more
- creatine phosphokinase: less than or equal to 2.5 X ULN
- haemoglobin: 9 g/dL
- creatinine clearance: at least 30 mL/minute for monotherapy or 60 mL/minute for combination therapy with liposomal doxorubicin

These baseline criteria must also be met before re-treating the patient in subsequent cycles. If serious toxicity occurs between cycles, e.g neutropenia of less than 500 cells/mm^3 lasting more than 5 days or associated with fever or infection, thrombocytopenia below 25 000 cells/mm^3, bilirubin above the ULN or alkaline phosphatase > 2.5 X ULN, or increase in aminotransferases above 2.5 X ULN for monotherapy or 5 X ULN for combination therapy, then subsequent doses must be reduced as follows:
- for **soft-tissue sarcoma** the dose of trabectedin is reduced from 1.5 mg/m^2 to 1.2 mg/m^2 initially, and then to 1 mg/m^2 if necessary. If severe toxicity still continues, stopping treatment should be considered
- for **ovarian cancer**, the initial dose of 1.1 mg/m^2 is reduced to 900 micrograms/m^2 (with a reduction in liposomal doxorubicin dose to 25 mg/m^2), and then to 750 micrograms/m^2 (with liposomal doxorubicin 20 mg/m^2). Again, consideration should be given to stopping treatment if further reduction is necessary

Once a dose has been reduced for toxicity, re-escalation in subsequent cycles is inadvisable.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Neutropenia, thrombocytopenia, anaemia, and leucopenia are very common with trabectedin; febrile neutropenia often occurs. Full blood counts should be performed at baseline, weekly for the first 2 cycles, and then once between cycles thereafter. Dose reductions may be needed in those with haematological toxicity. Hepatobiliary disorders are also very common, and include hyperbilirubinaemia and alterations in liver function tests, which are mostly transient. Patients with liver disease should be closely monitored, and trabectedin should not be given to those with hyperbilirubinaemia.

Other very common adverse effects include gastrointestinal disturbances, anorexia, headache, and fatigue. Antiemetic prophylaxis with dexamethasone should be given to all patients. Peripheral sensory neuropathy, paraesthesia, dysgeusia, dizziness, pyrexia, and oedema are common, as are dyspnoea, cough, alopecia, myalgia, arthralgia, dehydration, hypokalaemia, hypotension, and flushing. Injection site reactions can occur, and the use of a central line is recommended.

Deaths associated with trabectedin treatment have often involved a combination of adverse events including pancytopenia, febrile neutropenia, and in some cases sepsis, hepatic involvement, renal failure, and rhabdomyolysis.

Trabectedin may cause serious birth defects if given during pregnancy, although data are limited. Women and men of fertile age are advised to use effective contraception during treatment, and for 3 and 5 months, respectively, after stopping treatment. Breast feeding is contra-indicated due to lack of data, and should be avoided for the duration of treatment and for 3 months after therapy is stopped.

Extravasation. A report[1] of severe local tissue inflammation and necrosis in 2 patients, associated with extravasation of trabectedin from central venous access devices. Both patients had full thickness injuries that required surgical debridement of affected skin, subcutaneous tissue, and pectoral muscle, suggesting that trabectedin should be considered a vesicant.

1. Theman TA, *et al.* Recognition of a new chemotherapeutic vesicant: trabectedin (ecteinascidin-743) extravasation with skin and soft tissue damage. *J Clin Oncol* 2009; **27:** e198–e200.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trabectedin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Interactions

Trabectedin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme (such as azole antifungals, macrolide antibacterials, or ritonavir) may increase blood concentrations of trabectedin. Equally, inducers of CYP3A4 (such as rifampicin, phenobarbital, and St John's wort) may decrease systemic exposure to trabectedin. Trabectedin is a substrate of P-glycoprotein, and use with P-glycoprotein inhibitors (such as ciclosporin and verapamil) may alter trabectedin pharmacokinetics, although the clinical significance of this interaction has not been established. Alcohol and other hepatotoxic drugs should be avoided during trabectedin treatment due to possible potentiation of hepatotoxicity. Use with live attenuated vaccines is not recommended, and use with yellow fever vaccine is specifically contra-indicated. For the effect of trabectedin on phenytoin, see p. 544.1.

Pharmacokinetics

Trabectedin is extensively distributed in the tissues. Plasma protein binding is about 94 to 98%. It is metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4. The terminal half-life is about 180 hours. Trabectedin is excreted mainly in the faeces, with a small amount in the urine, of which less than 1% is unchanged drug.

References.
1. Beumer JH, *et al.* Metabolism of trabectedin (ET-743, Yondelis) in patients with advanced cancer. *Cancer Chemother Pharmacol* 2007; **59:** 825–37.
2. Perez-Ruixo JJ, *et al.* Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet* 2007; **46:** 867–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Yondelis; ***Austria***: Yondelis; ***Belg.***: Yondelis; ***Canad.***: Yondelis; ***Chile***: Yondelis; ***Cz.***: Yondelis; ***Denm.***: Yondelis; ***Fr.***: Yondelis; ***Ger.***: Yondelis; ***Gr.***: Yondelis; ***Hung.***: Yondelis; ***Irl.***: Yondelis; ***Israel***: Yondelis; ***Ital.***: Yondelis; ***Neth.***: Yondelis; ***Norw.***: Yondelis; ***Pol.***: Yondelis; ***Port.***: Yondelis; ***Rus.***: Yondelis (Йонделис); ***Singapore***: Yondelis; ***Spain***: Yondelis; ***Swed.***: Yondelis; ***Switz.***: Yondelis; ***Thai.***: Yondelis; ***UK***: Yondelis.

Trabedersen *(BAN, rINN)*

AP-12009; TGF-β2 antisense oligonucleotide; Trabédersen; Trabedersén; Trabedersenum; Transforming growth factor-β2-specific phosphorothioate antisense oligodeoxynucleotide; Трабедерсен.

2′-Deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxyadenosine.

CAS — 925681-61-4.

NOTE. The name Oncomun has been used as a trade mark for trabedersen.

Profile

Trabedersen is an antisense oligonucleotide that specifically suppresses the production of transforming growth factor-beta-2, an immunosuppressive protein produced by tumour cells. It is under investigation for the treatment of high-grade glioma (see Malignant Neoplasms of the Brain, p. 701.2) and other neoplasms such as pancreatic cancer.

Trametinib *(USAN, pINN)*

GSK-1120212; Tramétinib; Trametinibum; Траметиниб.

N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide.

$C_{26}H_{23}FIN_5O_4$=615.4

CAS — 871700-17-3.

UNII — 33E86K87QN.

Trametinib Dimethyl Sulfoxide *(USAN, pINNM)*

GSK-1120212B.

$C_{26}H_{23}FIN_5O_4.C_2H_6OS$=693.5

CAS — 1187431-43-1.

UNII — BSB9VJ5TUT.

Profile

Trametinib is an inhibitor of mitogen-activated extracellular kinases (MEK 1 and 2) that is used in the treatment of unresectable or metastatic melanoma (p. 714.3) with BRAF V600E or V600K mutations; it should not be used in patients who have previously been treated with a BRAF inhibitor. It is given as the compound trametinib dimethyl sulfoxide but doses are expressed as the non-solvated base; 2 mg of trametinib is equivalent to about 2.25 mg trametinib dimethyl sulfoxide. The usual oral dose is equivalent to 2 mg once daily; tablets should be swallowed whole and taken on an empty stomach. A missed dose should not be taken within 12 hours of the next dose. Doses may need to be withheld or reduced if toxicity occurs. Where dose adjustment is required, reductions are made in steps of 500 micrograms. Treatment is continued until disease progression or unacceptable toxicity occurs. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Commonly reported adverse effects with trametinib are skin reactions such as rash, dry skin, and pruritus, paronychia, lymphoedema, hypertension, haemorrhage, and gastrointestinal disturbances, particularly diarrhoea. Severe skin toxicity, cardiomyopathy, interstitial lung disease, retinal pigment epithelial detachment, and retinal vein occlusion have also occurred. Trametinib should be avoided during pregnancy and women of child-bearing potential should use contraception during and for 4 months after treatment.

References.
1. Wright CJ, McCormack PL. Trametinib: first global approval. *Drugs* 2013; **73:** 1245–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Mekinist.

Trastuzumab *(BAN, USAN, rINN)*

Anticuerpo monoclonal HER2; HER-2 Monoclonal Antibody; rhuMAb HER2; Trastutsumabi; Trastuzumabum; Трастузумаб.

Immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ_1-chain anti-human p185$^{c\text{-}erbB2}$ receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer.

CAS — 180288-69-1.

ATC — L01XC03.

ATC Vet — QL01XC03.

UNII — P188ANX8CK.

Trastuzumab Emtansine *(USAN, rINN)*

Ado-trastuzumab Emtansine; PRO-132365; RG-3502; T-DM1; Trastuzumab-DM1; Trastuzumab Emtansina; Trastuzumab-

MCC-DM1; Trastuzumabum Emtansinum; Трастузумаб Эмтанзин.
CAS — 1018448-65-1.
UNII — SE2KH7T06F.

NOTE. Trastuzumab emtansine contains trastuzumab covalently linked to the microtubule inhibitory drug DM1, via the stable thioether linker MCC (4-[*N*-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex.

Trastuzumab and trastuzumab emtansine are not interchangeable.

Uses and Administration

Trastuzumab is a humanised monoclonal antibody directed against a cell surface protein produced by the human epidermal growth factor receptor 2 (HER2) gene. HER2 protein is overexpressed in about one-third of all breast cancers. Trastuzumab is used in the treatment of breast cancer (p. 702.1) with such characteristics. It is also used with combination chemotherapy in HER2-positive metastatic gastric cancer (p. 706.1). Trastuzumab emtansine (also called ado-trastuzumab emtansine) consists of trastuzumab conjugated to DM1, a maytansine derivative and cytotoxic microtubule inhibitor. It is used in the treatment of metastatic HER2-positive breast cancer.

Note that trastuzumab and trastuzumab emtansine are not interchangeable.

Trastuzumab is generally given in either a weekly or 3-weekly infusion schedule. Doses should be added to 250 mL of sodium chloride 0.9% for intravenous infusion. The initial dose is given over 90 minutes and subsequent doses may be given over 30 to 90 minutes. Alternatively, for some indications, it may be given subcutaneously once every 3 weeks; injection sites should be alternated between thighs, and the dose injected over 2 to 5 minutes. Preparations for subcutaneous injection contain recombinant human hyaluronidase and are not suitable for intravenous use.

- Weekly infusion schedule: 4 mg/kg initially, followed after 1 week by a maintenance dose of 2 mg/kg at weekly intervals.
- 3-Weekly infusion schedule: 8 mg/kg initially, followed after 3 weeks by a maintenance dose of 6 mg/kg once every 3 weeks.
- 3-Weekly subcutaneous schedule: 600 mg once every 3 weeks (no loading dose is required).

In metastatic breast cancer, trastuzumab may be given alone or with a taxane or an aromatase inhibitor. It is given in either a weekly or 3-weekly schedule, and continued until disease progression.

In the adjuvant treatment of early breast cancer, trastuzumab may be given in a weekly schedule with docetaxel or paclitaxel for 12 weeks, starting after 4 cycles of the AC regimen (doxorubicin and cyclophosphamide). Alternatively, weekly trastuzumab may be given with docetaxel and carboplatin for 18 weeks. One week after the completion of either of these treatment courses, trastuzumab may be continued at 6 mg/kg by infusion every 3 weeks. A 3-weekly trastuzumab regimen may also be given as adjuvant monotherapy after multimodal therapy including surgery, chemotherapy, and radiotherapy if applicable. In locally advanced disease, a 3-weekly trastuzumab regimen has been used with neoadjuvant chemotherapy followed by adjuvant trastuzumab; however, the concurrent use of trastuzumab with anthracyclines should be limited to chemotherapy-naive patients and only using low-dose anthracycline regimens. Trastuzumab therapy is given for 1 year in total or until disease recurs, whichever occurs first.

In metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, trastuzumab is given in a 3-weekly infusion schedule with cisplatin and either capecitabine or 5-fluorouracil. Treatment is continued until disease progression.

If the patient misses an infusion dose of trastuzumab by 1 week or less, then the usual maintenance dose should be given as soon as possible, without waiting until the next planned cycle. Subsequent cycles are then given according to the previous schedule.

If the infusion dose is missed by more than 1 week, a reloading dose of trastuzumab should be given, and subsequent maintenance doses given thereafter.

If a subcutaneous dose is missed, it should be given as soon as possible; the interval between doses should not be less than 3 weeks.

Trastuzumab emtansine (ado-trastuzumab emtansine) is given alone in the treatment of metastatic breast cancer. A dose of 3.6 mg/kg is given every 3 weeks until disease progression or there is unacceptable toxicity. The dose should be added to 250 mL of sodium chloride 0.9% for intravenous infusion. The first dose is infused over 90 minutes; subsequent doses may be given over 30 minutes if tolerated.

If a dose of trastuzumab emtansine is missed or delayed, it should be given as soon as possible and the schedule adjusted to keep an interval of 3 weeks between subsequent doses.

The dose of trastuzumab or trastuzumab emtansine may need to be delayed or reduced because of toxicity (see Administration in Subsequent Cycles, below).

References.
1. Smith I, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369:** 29–36.
2. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007; **357:** 39–51.
3. Orman JS, Perry CM. Trastuzumab: i n HER2 and hormone receptor co-positive metastatic breast cancer. *Drugs* 2007; **67:** 2781–9.
4. von Minckwitz G, *et al.* Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 study. *J Clin Oncol* 2009; **27:** 1999–2006.
5. Garnock-Jones KP, *et al.* Trastuzumab: a review of its use as adjuvant treatment in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. *Drugs* 2010; **70:** 215–39. Correction. *ibid.* 2011; **71:** 1578.
6. Bang Y-J, *et al.* ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376:** 687–97. Correction. *ibid.*; 1302.
7. Croxtall JD, McKeage K. Trastuzumab: in HER2-positive metastatic gastric cancer. *Drugs* 2010; **70:** 2259–67.
8. Slamon D, *et al.* Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; **365:** 1273–83.
9. Verma S, *et al.* EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; **367:** 1783–91.
10. Ballantyne A, Dhillon S. Trastuzumab emtansine: first global approval. *Drugs* 2013; **73:** 755–65.
11. Hamizi S, *et al.* Subcutaneous trastuzumab: development of a new formulation for treatment of HER2-positive early breast cancer. *Onco Targets Ther* 2013; **6:** 89–94.

Administration. Intrathecal trastuzumab has been tried in the treatment of leptomeningeal carcinomatosis in HER2-positive metastatic breast cancer. A review[1] of 17 case reports found that it had been given as monotherapy or in various regimens with other systemic or intrathecal treatments. Individual doses of trastuzumab ranged from 4 to 150 mg, and total doses ranging from 35 to 1110 mg (mean 399.8 mg) were reported. Slightly higher doses were recorded in 4 of the patients given intrathecal trastuzumab readministration beyond CNS progression (mean dose of 560 mg and cumulative dose of 1040 mg). Clinical and radiological improvement was reported in more than half of the patients and overall survival was prolonged to a median of 13.5 months compared with 5.9 months for published historical groups. Treatment was well tolerated.

1. Zagouri F, *et al.* Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. *Breast Cancer Res Treat* 2013; **139:** 13–22.

Administration in subsequent cycles. *Trastuzumab* infusion may need to be slowed or stopped in patients who develop infusion reactions. Parenteral treatment may need to be withheld or stopped if ventricular function deteriorates.

Similarly, *trastuzumab emtansine* infusion should be slowed or stopped for infusion reactions. The dose may need to be delayed or reduced for other adverse effects. The dose may be reduced step-wise from 3.6 mg/kg to 3 mg/kg, then to 2.4 mg/kg; if a further dose reduction is needed then trastuzumab emtansine should be stopped. The following modifications have been recommended in patients who develop increases in serum transaminases, hyperbilirubinaemia, or thrombocytopenia:

- serum transaminases > 2.5 to ⩽ 5 X upper limit of normal (ULN): continue trastuzumab emtansine at the same dose
- serum transaminases > 5 to ⩽ 20 X ULN: withhold until recovery to at least ⩽ 5 X ULN and then reduce the dose by one step
- serum transaminases > 20 X ULN: permanently stop trastuzumab emtansine
- total bilirubin > 1.5 to ⩽ 3 X ULN: withold until recovery to at least < 1.5 X ULN, then treat at the same dose
- total bilirubin > 3 to ⩽ 10 X ULN: withold until recovery to at least < 1.5 X ULN, then reduce the dose by one step
- total bilirubin > 10 X ULN: permanently stop trastuzumab emtansine
- serum transaminases > 3 X ULN and total bilirubin > 2 X ULN: permanently stop trastuzumab emtansine
- patients diagnosed with nodular regenerative hyperplasia: permanently stop trastuzumab emtansine
- platelets 25 000 to < 50 000 cells/mm^3: withhold until ⩾ 75 000 cells/mm^3 and then treat at the same dose
- platelets < 25 000 cells/mm^3: withhold until ⩾ 75 000 cells/mm^3 and then reduce the dose by one step

In patients with left ventricular dysfunction, trastuzumab emtansine should be withheld if left ventricular ejection fraction is less than 40%, or between 40% and 45% and also 10% or more points below baseline. Treatment should be stopped if there is symptomatic congestive heart failure, or if function has not recovered in less than 3 weeks to within 10% points from baseline or to more than 40%.

Trastuzumab emtansine should be withheld in patients who develop grade 3 or 4 peripheral neuropathy, and permanently stopped in those who develop pulmonary toxicity.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2 and p. 732.2.

Trastuzumab has been associated with fatal hypersensitivity reactions, infusion reactions characteristic of a cytokine release syndrome, and pulmonary events including acute respiratory distress syndrome. These usually occur after the first dose of trastuzumab and are more common in patients with reduced lung function. Systemic and local reactions have occurred after subcutaneous injection. Use of trastuzumab is contra-indicated in patients with severe dyspnoea at rest. Cardiac dysfunction and congestive heart failure may also occur and left ventricular function should be monitored before and during therapy. The risk of cardiotoxicity is increased if trastuzumab is given with anthracyclines or cyclophosphamide (see below).

There is an increase in the incidence of leucopenia, thrombocytopenia, anaemia, and febrile neutropenia when trastuzumab is given with chemotherapy, but it infrequently causes myelosuppression when used alone. Diarrhoea occurs in about 25% of patients given trastuzumab as monotherapy; the incidence increases with combination therapy. Other gastrointestinal disturbances are common, as are chills, fever, headache, arthralgia, myalgia, and rashes. Asthenia, chest pain, and renal or liver disorders have also been reported.

The adverse effects of trastuzumab are also reported for *trastuzumab emtansine*. However, thrombocytopenia and hepatotoxicity are very common and may require dose adjustment. Peripheral neuropathy is also commonly reported with trastuzumab emtansine; it is generally a sensory neuropathy and may be severe in a small percentage of patients.

Effects on the heart. Cardiac events related to the use of trastuzumab include asymptomatic decreases in left ventricular ejection fraction, tachycardia, palpitations, dyspnoea, and chest pain. Congestive heart failure may develop.[1] Complete left bundle branch block, mimicking an acute coronary syndrome, has also been seen.[2]

In a pivotal comparative study,[3] an increased incidence of cardiac adverse events prompted a retrospective analysis. This independent review identified cardiac dysfunction in 27% of patients given trastuzumab, an anthracycline, and cyclophosphamide, compared with only 8% given an anthracycline and cyclophosphamide. In patients given trastuzumab and paclitaxel, 13% developed cardiac dysfunction compared with 1% of patients given paclitaxel alone, although all these patients had previously received an anthracycline. The incidence of severe dysfunction was highest in those patients given trastuzumab, an anthracycline, and cyclophosphamide.

Further analysis[4] of this and 6 other studies found that, in a total of 1219 patients, 10 heart-related deaths had been reported, and that 9 of these were patients who had taken trastuzumab. However, the risk of developing cardiotoxicity was less when trastuzumab was given alone than when given with anthracyclines. Advanced age was found to be a significant risk factor, whereas giving trastuzumab and the anthracycline at different times appeared to decrease the rate of cardiotoxicity.

Licensed product information for trastuzumab warns that patients who have previously had anthracyclines may also be at increased risk of cardiotoxicity with trastuzumab treatment. Furthermore, because the half-life of trastuzumab is about 4 to 5 weeks, trastuzumab may persist in the circulation for up to 20 to 25 weeks, and patients given anthracyclines after stopping trastuzumab may still be at increased risk of cardiotoxicity. If anthracyclines are used, the patient's cardiac function should be carefully monitored. Patients with pre-existing cardiovascular disease should also be treated with caution.

However, the majority of patients who develop congestive heart failure improve with standard treatment, including the use of ACE inhibitors, beta blockers, cardiac glycosides and diuretics.[1,5,6] Cardiotoxicity may improve even in those patients who continue with trastuzumab therapy.[5,6] A small retrospective study found that cardiotoxicity appeared to be largely reversible once trastuzumab was stopped, and that therapy might even be restarted. Findings from myocardial biopsy suggested that, while the mechanism of cardiotoxicity with trastuzumab remained uncertain, it differed from that with anthracyclines.[7] A retrospective review[8] of 173 patients with metastatic breast cancer who were treated with trastuzumab-based therapy for at least 1 year found that 28% of patients had a cardiac event; 10.9% had grade 3 cardiotoxicity, including 1 cardiac-related death. However, cardiotoxicity, whether symptomatic or not, was generally

reversible, with or without specific therapy, suggesting that maintenance or re-treatment with trastuzumab may be feasible in those patients for whom no alternative therapeutic options are available.

Analysis of symptomatic heart failure with trastuzumab suggests a lower incidence than that previously reported with retrospective data; however, this may be due to over-reported events in pivotal studies and the more recent exclusion of patients at risk of cardiotoxicity.[5] Analysis from a large study of patients given adjuvant chemotherapy with or without 1 year of trastuzumab found a cumulative incidence of cardiac events (defined as confirmed New York Heart Association class III or IV cardiac dysfunction, or cardiac death) with trastuzumab of 4.1% at 3 years. The difference in cumulative incidence was 3.3% when compared with the control group.[9] Additional follow-up to 7 years included some further reports of cardiac events in both groups, but the late development of heart failure in patients given trastuzumab was uncommon.[10] Cardiac function returned to the normal range in the majority of patients who had stopped trastuzumab because of dysfunction, although some decline from baseline persisted. In similar studies,[11,12] follow-up analyses at around 3 years also confirmed a higher incidence of cardiac events in patients given 1 year of trastuzumab therapy, but it remained low and cardiac dysfunction appeared to be reversible.

Reviews[13,14] have concluded that trastuzumab-induced cardiotoxicity is not dose-related and is generally reversible once the drug is stopped. However, others[15,16] have challenged the concept that cardiotoxicity is reversible, and the need for longer-term follow-up data, especially with respect to asymptomatic left ventricular dysfunction, has been emphasised.[13,15] As well as routine monitoring of cardiac function and for symptoms of heart failure, some suggest that increases in serum concentrations of troponin I during trastuzumab treatment are predictive of cardiotoxicity, and that further investigation of troponin I monitoring is warranted.[16]

1. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002; **95:** 1592–1600.
2. Tu C-M, *et al*. Trastuzumab (Herceptin)-associated cardiomyopathy presented as new onset of complete left bundle-branch block mimicking acute coronary syndrome: a case report and literature review. *Am J Emerg Med* 2009; **27:** 903.e1–903.e3.
3. Slamon DJ, *et al*. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
4. Seidman A, *et al*. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20:** 1215–21.
5. Suter TM, *et al*. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 2004; **13:** 173–83.
6. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004; **22:** 322–9.
7. Ewer MS, *et al*. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; **23:** 7820–6.
8. Guarneri V, *et al*. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol* 2006; **24:** 4107–15.
9. Tan-Chiu E, *et al*. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23:** 7811–19.
10. Romond EH, *et al*. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012; **30:** 3792–9.
11. Perez EA, *et al*. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008; **26:** 1231–8.
12. Procter M, *et al*. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. *J Clin Oncol* 2010; **28:** 3422–8.
13. Sengupta PP, *et al*. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. *Mayo Clin Proc* 2008; **83:** 197–203.
14. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. *Drug Safety* 2008; **31:** 459–67.
15. Telli ML, *et al*. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007; **25:** 3525–33.
16. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. *J Natl Compr Canc Netw* 2011; **9:** 243–9.

Effects on the liver. A 54-year-old African American woman was treated with 8 weeks of trastuzumab therapy. Her liver enzyme concentrations were normal before treatment was started but increased until trastuzumab had to be stopped, after which they returned to normal. Upon re-challenge, liver enzyme concentrations increased again. Liver function tests with close monitoring are advised during trastuzumab therapy.[1]

1. Srinivasan S, *et al*. Trastuzumab-induced hepatotoxicity. *Ann Pharmacother* 2008; **42:** 1497–1501.

Metastatic disease. There is some suggestion that patients treated with trastuzumab for metastatic breast cancer have a higher incidence of cerebral metastases. This may reflect increased survival of patients given trastuzumab, and the lack of CNS penetration by the drug,[1,2] or tumours overexpressing human epidermal growth receptor 2 (HER2) may be more likely to metastasise to the CNS.[2] A comparison[1] of trastuzumab-treated patients with a control group found that, although trastuzumab reduced the incidence of bone metastases, the development of brain metastases was similar in both groups. However, trastuzumab improved overall survival in all patients developing metastases, including those with brain metastases. A retrospective review[2] found an association between the development of cerebral metastases and both hormone-receptor negative status and the presence of visceral disease.

For the intrathecal use of trastuzumab in leptomeningeal carcinomatosis in metastatic breast cancer, see Administration under Uses and Administration, p. 876.2.

1. Lower EE, *et al*. Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival. *Clin Breast Cancer* 2003; **4:** 114–19.
2. Clayton AJ, *et al*. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004; **91:** 639–43.

Peripheral vascular toxicity. A woman developed a painless prominence of the veins in her left arm and hand 3 days after receiving trastuzumab via a left hand vein. The veins were thickened and rope-like on palpation but there was no tenderness, oedema, or skin changes; there was no evidence of thrombus. She had previously received intravenous chemotherapy into left hand veins without sequelae. Biopsy suggested venous wall injury. Cardiac function was preserved, suggesting the mechanism of vascular injury was unrelated to cardiac dysfunction. Trastuzumab therapy was stopped permanently and her symptoms gradually resolved over the course of a year.[1]

1. Pansegrau GK, *et al*. Trastuzumab-associated peripheral vascular toxicity. *J Clin Oncol* 2007; **25:** 1438–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trastuzumab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/09/11)

Pregnancy. Fetal exposure to *trastuzumab* in 18 pregnancies (19 newborns) has been reviewed.[1] The duration of maternal trastuzumab treatment ranged from 1 to 31 weeks, with a mean duration of 14.8 weeks, and it was given either alone or with other antineoplastics. Oligohydramnios and anhydramnios were the most commonly reported adverse events, affecting 11 of the 15 pregnancies exposed to trastuzumab in the second or third trimester. There was a trend towards an increase in risk with a longer duration of trastuzumab use. However, oligohydramnios seemed to be reversible after stopping the drug. There appeared to be no significant difference between weekly and 3-weekly exposure in relation to oligohydramnios and anhydramnios. Some cases showed intra-uterine growth restriction, dystrophy, and pulmonary hypoplasia. Conditions reported at birth in 9 neonates included respiratory distress, renal failure, and infection; 4 of these infants died within 6 months. The remaining 10 neonates were healthy at birth and at follow-up.

No adverse effects were found in the 3 cases exposed to trastuzumab during the first trimester only (up to 6 weeks of gestational age).[1] The authors suggested that this might be related to the poor trans-placental transfer of monoclonal antibodies during early pregnancy compared with later gestation. Also, the inhibitory effect of trastuzumab on epidermal growth factor receptors in the fetal kidney, which might inhibit amniotic fluid production, would only be significant after month 4 (before this the amniotic fluid is produced maternally). Nevertheless, the limited number of reports precludes any definite conclusion about the safety of trastuzumab in the first trimester.

Licensed product information advises the use of contraception during trastuzumab therapy and for at least 6 months after stopping treatment.

Information about fetal exposure to *trastuzumab emtansine* is lacking. However, in addition to the potential effects of trastuzumab, the cytotoxic component DM1 is expected to cause embryo-fetal toxicity.

1. Zagouri F, *et al*. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013; **137:** 349–57.

Interactions

For reports of trastuzumab enhancing the effect of warfarin, see p. 1532.2.

Based on *in-vitro* studies, it is suggested that the concomitant use of strong inhibitors of the cytochrome P450 isoenzyme CYP3A4 and trastuzumab emtansine should be avoided if possible, because of the potential for an increased exposure to the DM1 component.

Pharmacokinetics

The pharmacokinetics of *trastuzumab* are non-linear, and clearance decreases with increasing dose. The half-life after short-duration intravenous infusions was found to be about 2 days after weekly 10-mg doses and 12 days after 500-mg doses. It has also been reported to be about 6 days with the recommended weekly infusion schedule (4 mg/kg initially, followed by 2 mg/kg weekly), and about 16 days with the 3-weekly infusion schedule (8 mg/kg initially, followed by 6 mg/kg every 3 weeks). However, limited sampling may underestimate terminal half-life. Population pharmacokinetic modelling, based on pooled data in a two-compartment model to take account of accumulation with long-term dosing, estimates a terminal elimination half-life of about 28.5 days. When given subcutaneously, trastuzumab peak plasma concentrations occur about 3 days after injection, but with high interindividual variability ranging from 1 to 14 days. It has an estimated bioavailability of about 82%.

Detectable concentrations of the cell surface protein of the HER2 receptor (shed antigen) have been found in patients' serum; those patients with higher baseline values for shed antigen had lower serum trough concentrations of trastuzumab, although target trastuzumab concentrations were still achieved after weekly dosing, and no relationship to clinical response was seen.

Trastuzumab emtansine has a shorter half-life than trastuzumab, of about 4 days. The small molecule component, DM1, is metabolised via the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 and is a substrate of P-glycoprotein.

References.

1. Baselga J, *et al*. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol* 2005; **23:** 2162–71.
2. Bruno R, *et al*. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol* 2005; **56:** 361–9.
3. Chudasama VL, *et al*. Semi-mechanistic population pharmacokinetic model of multivalent trastuzumab emtansine in patients with metastatic breast cancer. *Clin Pharmacol Ther* 2012; **92:** 520–7.
4. Lu D, *et al*. An integrated multiple-analyte pharmacokinetic model to characterize trastuzumab emtansine (T-DM1) clearance pathways and to evaluate reduced pharmacokinetic sampling in patients with HER2-positive metastatic breast cancer. *Clin Pharmacokinet* 2013; **52:** 657–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Herceptin; ***Austral.***: Herceptin; ***Austria***: Herceptin; ***Belg.***: Herceptin; ***Braz.***: Herceptin; ***Canad.***: Herceptin; ***Chile***: Herceptin; ***China***: Herceptin (赫赛汀); ***Cz.***: Herceptin; ***Denm.***: Herceptin; ***Fin.***: Herceptin; ***Fr.***: Herceptin; ***Ger.***: Herceptin; ***Gr.***: Herceptin; ***Hong Kong***: Herceptin; ***Hung.***: Herceptin; ***India***: Herceptin; ***Indon.***: Herceptin; ***Irl.***: Herceptin; ***Israel***: Herceptin; ***Ital.***: Herceptin; ***Jpn***: Herceptin; ***Malaysia***: Herceptin; ***Mex.***: Herceptin; ***Neth.***: Herceptin; ***Norw.***: Herceptin; ***NZ***: Herceptin; ***Philipp.***: Herceptin; ***Pol.***: Herceptin; ***Port.***: Herceptin; ***Rus.***: Herceptin (Герцептин); ***S.Afr.***: Herceptin; ***Singapore***: Herceptin; ***Spain***: Herceptin; ***Swed.***: Herceptin; ***Switz.***: Herceptin; ***Thai.***: Herceptin; ***Turk.***: Herceptin; ***UK***: Herceptin; ***Ukr.***: Herceptin (Герцептин); ***USA***: Herceptin; Kadcyla; ***Venez.***: Herceptin.

Treosulfan *(BAN, rINN)*

Dihydroxybusulphan; NSC-39069; Treosulfaani; Tréosulfan; Treosulfano; Treosulfanum; Треосульфан.

L-Threitol 1,4-dimethanesulphonate.

$C_6H_{14}O_8S_2$=278.3

CAS — 299-75-2.

ATC — L01AB02.

ATC Vet — QL01AB02.

UNII — CO61ER3EPI.

Profile

Treosulfan is an antineoplastic agent related to busulfan (p. 754.3), which is reported to act by alkylation after conversion *in vivo* to epoxide compounds. It is used palliatively or as an adjunct to surgery mainly in the treatment of ovarian cancer (p. 711.2).

Treosulfan may be given orally, intravenously, or intraperitoneally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Treosulfan 1 g daily is licensed for *oral* use in 4 divided doses for 2 or 4 weeks followed by the same period without treatment. Alternatively 1.5 g daily in 3 divided doses may be given for 1 week, followed by 3 weeks without therapy. The cycle is then repeated, the dose being adjusted if necessary according to the effect on bone marrow. Doses of 3 to 8 g/m² may instead be given *intravenously* every 1 to 3 weeks. Doses larger than 3 g/m² should be given by infusion at a rate of 3 g/m² every 5 to 10 minutes. Doses up to 1.5 g/m² have been given *intraperitoneally*. Lower doses

should be used if treatment with other antineoplastic drugs or radiotherapy is being given.

Regular blood counts should be made and treatment should be interrupted if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p. 730.3). Because bone-marrow depression may be cumulative the interval between blood counts should be reduced after the second course of treatment with treosulfan.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Ovastat.

Trofosfamide *(rINN)*

A-4828; NSC-109723; Trilophosphamide; Trofosfamid; Trofosfamida; Trofosfamidi; Trofosfamidum; Trophosphamide; Z-4828; Трофосфамид.

3-(2-Chloroethyl)-2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine-2-oxide.

$C_9H_{18}Cl_3N_2O_2P$=323.6

CAS — 22089-22-1.

ATC — L01AA07.

ATC Vet — QL01AA07.

UNII — H64JRU6GJ0.

Profile

Trofosfamide is a derivative of cyclophosphamide (p. 771.1) and has the same general properties. It is used in the treatment of malignant disorders in usual initial oral doses of 300 to 400 mg daily. Doses of 50 to 150 mg daily have been given for maintenance therapy.

Uses. References[1-10] to the use of trofosfamide, including its investigational use with pioglitazone and rofecoxib as antiangiogenic therapy.[4,5,7]

1. Gunsilius E, *et al.* Palliative chemotherapy in pretreated patients with advanced cancer: oral trofosfamide is effective in ovarian carcinoma. *Cancer Invest* 2001; **19:** 808–11.
2. Reichardt P, *et al.* Oral trofosfamide: an active and well-tolerated maintenance therapy for adult patients with advanced bone and soft tissue sarcomas: results of a retrospective analysis. *Onkologie* 2002; **25:** 541–6.
3. Andersson PO, *et al.* Trofosfamide as salvage therapy for anaplastic large cell lymphoma relapsing after high-dose chemotherapy. *Leuk Lymphoma* 2002; **43:** 2351–3.
4. Vogt T, *et al.* Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. *Cancer* 2003; **98:** 2251–6.
5. Reichle A, *et al.* Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer* 2004; **101:** 2247–56.
6. Latz D, *et al.* Trofosfamide in the palliative treatment of cancer: a review of the literature. *Onkologie* 2004; **27:** 572–6.
7. Coras B, *et al.* Antiangiogenic therapy with pioglitazone, rofecoxib, and trofosfamide in a patient with endemic kaposi sarcoma. *Arch Dermatol* 2004; **140:** 1504–7.
8. Jahnke K, *et al.* Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. *Ann Oncol* 2005; **16:** 1974–8.
9. Salminen EK, *et al.* Palliative chemotherapy with trofosfamide in advanced prostate cancer. *Anticancer Res* 2006; **26:** 539–42.
10. Görn M, *et al.* A pilot study of docetaxel and trofosfamide as second-line 'metronomic' chemotherapy in the treatment of metastatic non-small cell lung cancer (NSCLC). *Onkologie* 2008; **31:** 185–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trofosfamide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Ixoten; ***Gr.***: Ixoten.

Tumour Necrosis Factor

Factor de necrosis tumoral; TNF.

Tasonermin *(BAN, rINN)*

Tasonermiini; Tasonermina; Tasonermine; Tasonerminum; TNFα-1a; Тазонермин.

$C_{778}H_{1225}N_{215}O_{231}S_2$=17350.8

CAS — 94948-59-1.

ATC — L03AX11.

ATC Vet — QL03AX11.

UNII — 23CA79S88F.

Profile

Tumour necrosis factor is a cytokine of which 2 forms have been identified with similar biological properties: TNFα or cachectin, which is produced mainly by macrophages, and TNFβ or lymphotoxin, which is produced by lymphocytes. Various recombinant forms of TNFα, both human and mouse, are available: the names sonermin and sertenef have been used for such products.

The antitumour effects of tumour necrosis factor *in vitro* and in *animals* have prompted investigation of recombinant TNFα in the treatment of cancer either alone or with other cytokines such as interleukin-2 or the interferons. Tasonermin is a recombinant TNFα used with melphalan (p. 819.1) for soft tissue sarcomas. It is given by mildly hyperthermic isolated limb perfusion at a total dose of 3 mg for an upper limb and 4 mg for a lower limb.

Leakage of tasonermin into the systemic circulation should not exceed 10%, as severe toxicity may occur. Local adverse effects include skin reactions, oedema, and pain; less commonly, vascular thrombosis, onycholysis, or severe tissue damage have occurred. Systemic effects include fever, chills, nausea and vomiting, arrhythmias, hepatotoxicity, and infections. Shock or hypotension, neurological disorders, thrombocytopenia, leucopenia, acute renal failure, and hypersensitivity reactions have all been reported.

References.

1. van Der Veen AH, *et al.* An overview on the use of TNF-alpha: our experience with regional administration and developments towards new opportunities for systemic application. *Anticancer Res* 2000; **20:** 3467–74.
2. Eggermont AM, ten Hagen TL. Tumor necrosis factor-based isolated limb perfusion for soft tissue sarcoma and melanoma: ten years of successful antivascular therapy. *Curr Oncol Rep* 2003; **5:** 79–80.
3. ten Hagen TL, Eggermont AM. Solid tumor therapy: manipulation of the vasculature with TNF. *Technol Cancer Res Treat* 2003; **2:** 195–203.
4. Corti A. Strategies for improving the anti-neoplastic activity of TNF by tumor targeting. *Methods Mol Med* 2004; **98:** 247–64.
5. Lejeune FJ, *et al.* Efficiency of recombinant human TNF in human cancer therapy. *Cancer Immun* 2006; **6:** 6.
6. van Horssen R, *et al.* TNF-α in cancer treatment: molecular insights, antitumor effects, and clinical utility. *Oncologist* 2006; **11:** 397–408.
7. Lejeune FJ, Rüegg C. Recombinant human tumor necrosis factor: an efficient agent for cancer treatment. *Bull Cancer* 2006; **93:** E90–E100.
8. Pilati P, *et al.* Strategies to enhance the anticancer potential of TNF. *Front Biosci* 2008; **13:** 3181–93.
9. Grünhagen DJ, *et al.* Isolated limb perfusion with TNF-alpha and melphalan in locally advanced soft tissue sarcomas of the extremities. *Recent Results Cancer Res* 2009; **179:** 257–70.
10. Bellavance EC, Alexander HR. TNF-based isolated hepatic perfusion. *Front Biosci* 2009; **14:** 1771–84.

Units. The first International Standard for human tumour necrosis factor α, which contained 40 000 international units/ampoule, was considered unsuitable for the assay of recombinant *mouse* tumour necrosis factor α, for human tumour necrosis factor β, or for preparations of tumour necrosis factor α of modified structure.[1] The second International Standard for human tumour necrosis factor α has been established as having a potency of 46 500 international units/ampoule.[2]

The first Reference Reagent for tumour necrosis factor β had an assigned potency of 150 000 units/ampoule.[3]

1. WHO. WHO expert committee on biological standardization: forty-second report. *WHO Tech Rep Ser 822* 1992. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf (accessed 01/08/08)
2. WHO. WHO expert committee on biological standardization: fifty-fourth report. *WHO Tech Rep Ser 927* 2005. Available at: http//whqlibdoc.who.int/trs/WHO_TRS_927_eng.pdf (accessed 01/08/08)
3. WHO. WHO expert committee on biological standardization: forty-seventh report. *WHO Tech Rep Ser 878* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_878.pdf (accessed 01/08/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tasonermin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Beromun; ***China***: Na Ke Si (纳科思); Tian En Fu (天恩福); ***Cz.***: Beromun; ***Gr.***: Beromun; ***Irl.***: Beromun; ***Ital.***: Beromun; ***Neth.***: Beromun; ***Pol.***: Beromun; ***Port.***: Beromun; ***Rus.***: Refnot (Рефнот); ***Spain***: Beromun; ***Swed.***: Beromun; ***UK***: Beromun.

Ubenimex *(rINN)*

NK-421; NSC-265489; Ubénimex; Ubenimexum; Убенимекс.

(-)-*N*-[(2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine.

$C_{16}H_{24}N_2O_4$=308.4

CAS — 58970-76-6.

UNII — I0J33N5627.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Ubenimex is a peptide derived from *Streptomyces olivoreticuli.* It is reported to have antineoplastic and immunostimulant properties. It has been used in the adjuvant treatment of acute myeloid leukaemia and is under investigation for the treatment of lung cancer. Adverse effects include gastrointestinal and hepatic function disturbances, skin rashes, headache, and paraesthesias.

References.

1. Ichinose Y, *et al.* Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *J Natl Cancer Inst* 2003; **95:** 605–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bai Shi Xin (百士欣); ***Jpn***: Bestatin.

Valrubicin *(USAN, rINN)*

AD-32; NSC-246131; *N*-Trifluoroacetyladriamycin-14-valerate; *N*-Trifluoroacetyldoxorubicin-14-valerate; Valrubicina; Valrubicine; Valrubicinum; Вальрубицин.

(8*S*,10*S*)-8-Glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-{[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy}-5,12-naphthacenedione 8^2-valerate.

$C_{34}H_{36}F_3NO_{13}$=723.7

CAS — 56124-62-0.

ATC — L01DB09.

ATC Vet — QL01DB09.

UNII — 2C6NUM6878.

Pharmacopoeias. In *US.*

USP 36: (Valrubicin). An orange to orange-red crystalline powder. Very slightly soluble in water, in hexane, and in petroleum spirit; soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Valrubicin is a semisynthetic analogue of the anthracycline doxorubicin (p. 782.3). It is used for carcinoma *in situ* (CIS) of the bladder (p. 700.2) refractory to BCG vaccine, when surgery is contra-indicated, although only about 20% of such patients exhibit a complete response. A dose of 800 mg is given intravesically once a week for 6 weeks. Valrubicin is diluted with sodium chloride 0.9% to a total volume of 75 mL. The solution should be retained for 2 hours if possible before voiding.

Because of the risk of metastasis, cystectomy should be reconsidered for patients with CIS who do not respond completely to valrubicin treatment after 3 months.

References.

1. Steinberg G, *et al.* Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol (Baltimore)* 2000; **163:** 761–7.
2. Kuznetsov DD, *et al.* Intravesical valrubicin in the treatment of carcinoma in situ of the bladder. *Expert Opin Pharmacother* 2001; **2:** 1009–13.

Adverse Effects, Treatment, and Precautions

Increased urinary frequency and urgency, dysuria, bladder spasm and pain may follow intravesical use of valrubicin due to local irritation of the bladder, and usually resolve within 1 to 7 days of treatment. Gross haematuria has occurred rarely but should be distinguished from drug-induced red coloration of the urine. Abdominal pain and nausea may occur.

Myelosuppression similar to that seen with other anthracyclines (see Adverse Effects of Doxorubicin, p. 784.1) is possible if significant systemic exposure occurs. Therefore valrubicin should not be given to patients with a perforated bladder or compromised bladder mucosa.

Because of the risk of metastasis, cystectomy should be reconsidered for patients with carcinoma *in situ* who do not respond completely to valrubicin treatment after 3 months.

Pharmacokinetics

On intravesical use valrubicin penetrates the bladder wall but systemic absorption is low in patients who have an intact bladder mucosa. The drug is almost entirely excreted by voiding after the installation period.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Valtaxin; ***Israel***: Valstar†; ***USA***: Valstar.

Pharmacopoeial Preparations

USP 36: Valrubicin Intravesical Solution.

Vandetanib *(BAN, USAN, rINN)*

AZD-6474; Vandétanib; Vandetanibum; ZD-6474; Вандетаниб.

N-(4-Bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine.

$C_{22}H_{24}BrFN_4O_2$=475.4

CAS — 338992-00-0; 443913-73-3.

ATC — L01XE12.

ATC Vet — QL01XE12.

UNII — YO460OQ37K.

NOTE. The name Zactima has been used as a trade mark for vandetanib.

Uses and Administration

Vandetanib is a tyrosine kinase inhibitor targeted at receptors for vascular endothelial growth factor and epidermal growth factor. It is used for the treatment of symptomatic or progressive medullary thyroid cancer (p. 716.1) in patients with unresectable locally advanced or metastatic disease. The recommended dose is 300 mg orally once daily. Treatment is continued until patients no longer benefit, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* If a daily dose of vandetanib is missed, no catch-up dose is recommended if it is less than 12 hours before the next dose. In the event of severe toxicity, treatment is interrupted until toxicity resolves or improves; dosage may be resumed at 200 mg once daily; doses may be reduced further to 100 mg once daily if needed. For use in hepatic and renal impairment, see below. In the event of a corrected QT interval (QTcF) greater than 500 milliseconds, treatment should be interrupted until the QTcF returns to less than 450 milliseconds; treatment is resumed at a reduced dose.

Vandetanib is also under investigation in the treatment of other solid malignancies.

Reviews.

1. Herbst RS, *et al.* Vandetanib (ZD6474): an orally available receptor tyrosine kinase inhibitor that selectively targets pathways critical for tumor growth and angiogenesis. *Expert Opin Invest Drugs* 2007; **16:** 239–49.
2. Hanrahan EO, Heymach JV. Vascular endothelial growth factor receptor tyrosine kinase inhibitors vandetanib (ZD6474) and AZD2171 in lung cancer. *Clin Cancer Res* 2007; **13** (15 suppl): s4617–s4622.
3. Natale RB. Dual targeting of the vascular endothelial growth factor receptor and epidermal growth factor receptor pathways with vandetinib [sic] (ZD6474) in patients with advanced or metastatic non-small cell lung cancer. *J Thorac Oncol* 2008; **3** (suppl 2): S128–S130.
4. Morabito A, *et al.* Vandetanib (ZD6474), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases: current status and future directions. *Oncologist* 2009; **14:** 378–90.
5. Morabito A, *et al.* Vandetanib: an overview of its clinical development in NSCLC and other tumors. *Drugs Today* 2010; **46:** 683–98.
6. Commander H, *et al.* Vandetanib: first global approval. *Drugs* 2011; **71:** 1355–65.

Administration. As for Gefitinib, p. 800.3.

Administration in hepatic impairment. A pharmacokinetic study[1] in subjects given a single oral dose of vandetanib 800 mg found that hepatic impairment was associated with reduced peak plasma concentrations, especially in those with severe disease, but that the area under the concentration-time curve was unaltered. Exposure to *N*-desmethylvandetanib (see Pharmacokinetics, below) was reduced in subjects with hepatic impairment, consistent with impaired oxidative drug metabolism. It was concluded that, while hepatic impairment would not affect the magnitude of steady-state exposure, the time taken to achieve it would be increased, especially in those with severe disease. The authors concluded that no dose adjustment would be needed in patients with hepatic impairment.

US licensed product information states that data are limited in patients with hepatic impairment (serum bilirubin > 1.5 times the upper limit of normal) and that vandetanib is not recommended for use in patients with moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment, as safety and efficacy have not been established.

1. Weil A, *et al.* Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clin Pharmacokinet* 2010; **49:** 607–18.

Administration in renal impairment. A pharmacokinetic study[1] in subjects given a single oral dose of vandetanib 800 mg found that renal impairment resulted in statistically significant increased exposure and reduced plasma clearance. Mean area under the concentration-time curve values were 46%, 62%, and 79% higher in subjects with mild, moderate, and severe renal impairment, respectively.

US licensed product information states that the initial dose of vandetanib (see Uses and Administration, above) should be reduced to 200 mg orally once daily in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

1. Weil A, *et al.* Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clin Pharmacokinet* 2010; **49:** 607–18.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with vandetanib are gastrointestinal disturbances, abdominal pain, rash, acne, headache, fatigue, and decreased appetite. Diarrhoea can be severe, and routine anti-diarrhoeals are recommended; vandetanib may need to be interrupted, and treatment resumed at a reduced dose upon improvement. Hypertension is also common, and hypertensive crisis has been reported; dose reduction or interruption of therapy may be needed, and if blood pressure cannot be controlled, vandetanib should not be restarted. Other adverse effects include hypocalcaemia, proteinuria, pancreatitis, blurred vision, and depression. Electrolyte abnormalities, decreased glucose, increased alanine aminotransferase (ALT) concentrations, increased bilirubin, and increased creatinine can occur.

Vandetanib can prolong the QT interval; because of the drug's long half-life (see Pharmacokinetics, below), this and other adverse effects may not resolve quickly. ECG monitoring is recommended at baseline, after 2 to 4 weeks, again at 8 to 12 weeks after starting treatment, and every 3 months thereafter. Torsade de pointes, ventricular tachycardia, and sudden death have been reported. Vandetanib therapy should not be started in patients whose corrected QT interval (QTcF) is greater than 450 milliseconds (see also Uses and Administration, above), and the drug should not be given to those with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated cardiac failure. It should also not be given if the patient has hypocalcaemia, hypokalaemia, or hypomagnesaemia, which should be corrected before starting therapy with vandetanib, and periodically monitored.

Severe skin reactions, including Stevens-Johnson syndrome, have occurred with vandetanib; fatalities have been reported. Treatment involves stopping therapy and the use of systemic corticosteroids. If vandetanib is restarted, a reduced dose should be used. Mild to moderate reactions can include rash, dry skin, dermatitis, pruritus, photosensitivity reactions, and palmar-plantar erythrodysesthesia syndrome; these may be treated with topical and systemic corticosteroids, oral antihistamines, and topical and systemic antibacterial therapy. Sunscreens and protective clothing are advised if the patient is exposed to sunlight; this should continue for 4 months after vandetanib therapy is stopped.

Fatalities due to cardiac failure, ischaemic cerebrovascular events, or serious haemorrhage have been reported in patients taking vandetanib; therapy should be stopped. Interstitial lung disease has also occurred, in some cases fatal, and patients should be advised to report any new or worsening respiratory symptoms. Therapy may need to be interrupted or stopped permanently in severe cases; corticosteroids and antibacterials may be indicated for management.

Reversible posterior leukoencephalopathy syndrome (RPLS) has also been seen, and this diagnosis should be considered if patients present with seizures, headache, visual disturbances, or confusion. Therapy may need to be stopped if RPLS occurs.

Patients who are treated with vandetanib and who have had a thyroidectomy have required higher doses of thyroid hormone replacement therapy; thyroid stimulating hormone concentrations should be measured at baseline, at 2 to 4 weeks, at 8 to 12 weeks, and every 3 months thereafter.

Vandetanib may be fetotoxic; women should be advised to avoid pregnancy during treatment and for at least 4 months after the last dose.

Interactions

Vandetanib is metabolised by the cytochrome P450 isoenzyme CYP3A4. Inducers of this isoenzyme can reduce plasma vandetanib concentrations and use with potent CYP3A4 inducers (such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifabutin, rifampicin, and rifapentine) should be avoided. St John's wort can decrease vandetanib exposure unpredictably and use together is not recommended. No significant interaction was seen between vandetanib and the potent CYP3A4 inhibitor itraconazole in healthy subjects. Vandetanib can prolong the QT interval and use with antiarrhythmic drugs (such as amiodarone, disopyramide, dofetilide, procainamide, and sotalol) and other drugs that prolong the QT interval (such as chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide) should be avoided.

Pharmacokinetics

Absorption of vandetanib after oral ingestion is slow, with peak plasma concentrations occurring at about 6 hours (range 4 to 10 hours) after dosing. Steady-state concentrations occur at about 3 months. Plasma protein binding is about 90%. Vandetanib is metabolised by cytochrome P450 isoenzyme CYP3A4, mainly to *N*-desmethylvandetanib, and by flavin-containing mono-oxygenase enzymes FM01 and FM03 to vandetanib-*N*-oxide. The plasma half-life is about 19 days. Vandetanib and its metabolites are slowly excreted in the urine and faeces. Exposure to vandetanib is increased by renal impairment. Japanese and Chinese patients have been reported to have higher exposure to vandetanib compared with Caucasian patients.

References.

1. Weil A, *et al.* Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clin Pharmacokinet* 2010; **49:** 607–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Caprelsa; ***Canad.***: Caprelsa; ***Denm.***: Caprelsa; ***Fr.***: Caprelsa; ***Israel***: Caprelsa; ***Neth.***: Caprelsa; ***Norw.***: Caprelsa; ***Swed.***: Caprelsa; ***Switz.***: Caprelsa; ***UK***: Caprelsa; ***USA***: Caprelsa.

Veltuzumab *(USAN, rINN)*

Immu-106; Veltuzumabum; Велтузумаб.

Immunoglobulin G1, anti-(human CD20 (antigen)) (human-mouse monoclonal hA20 heavy chain), disulfide with human-mouse monoclonal hA20 κ-chain, dimer.

CAS — 728917-18-8.

UNII — BPD4DGQ314.

Profile

Veltuzumab is a humanised monoclonal antibody that targets CD20 receptors on B-lymphocytes. It is under investigation for the treatment of chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, idiopathic thrombocytopenia purpura, and rheumatoid arthritis.

References.

1. Goldenberg DM, *et al.* Properties and structure-function relationships of veltuzumab (hA20), a humanized anti-CD20 monoclonal antibody. *Blood* 2009; **113:** 1062–70. Correction. *ibid.*; 5368.
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Vemurafenib *(USAN, rINN)*

PLX-4032; RG-7204; RO-5185426; Vémurafénib; Vemurafenibum; Вемурафениб.

N-{3-[5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-carbonyl]-2,4-difluorophenyl}propane-1-sulfonamide.

$C_{23}H_{18}ClF_2N_3O_3S$=489.9

CAS — 918504-65-1.

UNII — 207SMY3FQT.

Uses and Administration

Vemurafenib is a BRAF kinase inhibitor that is used for the treatment of unresectable or metastatic melanoma (p. 714.3) with $BRAF^{V600}$ mutation. The recommended oral dose is 960 mg twice daily. A missed dose may be taken up to 4 hours before the next dose. Tablets should be swallowed whole and not crushed or chewed. Vemurafenib may be taken with or without food, but regularly taking both daily doses on an empty stomach should be avoided as this may reduce its exposure (see Pharmacokinetics, p. 880.2). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Treatment is continued until disease progression or unacceptable toxicity occurs. The dose may need to be modified or withheld if toxicity occurs, see Administration in Subsequent Cycles, p. 880.1.

Vemurafenib is also under investigation for the treatment of thyroid cancer.

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Administration in subsequent cycles. Oral doses of vemurafenib may need to be withheld, reduced, or treatment stopped if toxicity occurs.

- For grade 3 or intolerable grade 2 adverse effects: withhold treatment until effects have resolved to ⩽ grade 1. Treatment may be resumed at a dose of 720 mg twice daily after the first occurrence; after the second occurrence treatment should be resumed at 480 mg twice daily. If the same adverse effect recurs for a third time, vemurafenib should be permanently stopped.
- For grade 4 adverse effects: either permanently stop vemurafenib, or withhold until effects have resolved to ⩽ grade 1 and then resume treatment at a dose of 480 mg twice daily. If the same adverse effect recurs for a second time, vemurafenib should be permanently stopped.
- For those with a QTc > 500 milliseconds during treatment: vemurafenib should be withheld and risk factors for QT interval prolongation controlled. Once the QTc has recovered to < 500 milliseconds, treatment may be resumed at a dose of 720 mg twice daily after the first occurrence; after the second occurrence treatment should be resumed at 480 mg twice daily. If QT interval prolongation recurs for a third time, vemurafenib should be permanently stopped. If, after risk factors for QT interval prolongation have been controlled, the QTc is still > 500 milliseconds and there is > 60 milliseconds increase from pretreatment values, vemurafenib should be permanently stopped.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with vemurafenib are arthralgia, alopecia, fatigue, nausea, rash, photosensitivity, pruritus, and skin papilloma. Patients should avoid sun exposure, wear protective clothing, and apply sunscreen when outdoors to avoid photosensitivity. For intolerable grade 2 erythema, dose modifications are recommended, see Administration in Subsequent Cycles, above. Other effects on the skin include dry skin, actinic keratosis, palmar-plantar erythrodysesthesia syndrome, keratosis pilaris, seborrhoeic keratosis, and erythema nodosum. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely; treatment should be permanently stopped in those who have a severe skin reaction.

Cutaneous squamous cell carcinomas have been reported in patients treated with vemurafenib, usually early in the course of treatment with a median time to first appearance of 7 to 8 weeks. Non-cutaneous squamous cell carcinoma, basal cell carcinoma, and new primary cases of malignant melanoma have also occurred. Monitoring for malignancies should be undertaken before, during, and for up to 6 months after treatment.

Hypersensitivity reactions include anaphylaxis, rash, erythema, and hypotension; treatment should be permanently stopped in those who have a severe reaction.

QT prolongation has been seen with vemurafenib, and treatment is not recommended in those with long QT syndrome, uncorrected electrolyte abnormalities, or those taking other medicines known to prolong the QT interval. ECG and electrolytes should be monitored before starting vemurafenib and after changing the dose. ECGs should also be checked 15 days after the start of treatment, monthly during the first 3 months of treatment, and then every 3 months thereafter (or more often if needed). Treatment should not be started in those with a QTc > 500 milliseconds; the dose may need to be withheld or reduced, or vemurafenib stopped, in those with a prolonged QT interval during treatment, see Administration in Subsequent Cycles, above.

Abnormalities in liver function tests have occurred during vemurafenib treatment, and liver function should be measured before starting treatment, and monthly during treatment or as needed. Vemurafenib may need to be withheld, the dose reduced, or treatment stopped if abnormalities occur, see Administration in Subsequent Cycles, above.

Effects on the eyes include blurred vision, iritis, photophobia, retinal vein occlusion, and uveitis. Patients should be monitored for signs of uveitis; treatment with corticosteroid and mydriatic eye drops may be required if uveitis occurs.

Other adverse effects that have occurred with vemurafenib include myalgia, musculoskeletal pain, oedema, fever, headache, dysgeusia, gastrointestinal disorders, cough, dizziness, peripheral neuropathy, Bell's palsy, folliculitis, vasculitis, and atrial fibrillation.

References.
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Interactions

In-vitro studies indicate that vemurafenib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and therefore inhibitors or inducers of this enzyme may alter vemurafenib concentrations. Caution is required when vemurafenib is used with strong CYP3A4 inhibitors or inducers.

Vemurafenib is also a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor, and a CYP3A4 inducer; use is not recommended with drugs that are metabolised via these routes and have a narrow therapeutic window. Exposure to caffeine (a CYP1A2 substrate) and dextromethorphan (a CYP2D6 substrate) was increased when given with vemurafenib, and a reduced dose of CYP1A2 and CYP2D6 substrates may be required if they must be given with vemurafenib. Exposure to midazolam (a CYP3A4 substrate) was decreased with vemurafenib.

Pharmacokinetics

When vemurafenib is taken orally at usual doses, peak plasma concentrations occur after about 3 to 4 hours and steady state is achieved in 15 to 22 days. Regularly taking vemurafenib on an empty stomach may lead to significantly lower steady state exposure than when taken with or just after food. Vemurafenib is highly protein bound (> 99%) to albumin and α-1 acid glycoprotein. *In-vitro* studies have shown that vemurafenib is a substrate and an inhibitor of P-glycoprotein. Only 5% of a dose of vemurafenib is metabolised; 94% of the dose is excreted in the faeces and 1% in the urine. The median elimination half-life is about 57 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zelboraf; ***Belg.***: Zelboraf; ***Canad.***: Zelboraf; ***Denm.***: Zelboraf; ***Fr.***: Zelboraf; ***Israel***: Zelboraf; ***Neth.***: Zelboraf; ***Norw.***: Zelboraf; ***Swed.***: Zelboraf; ***Switz.***: Zelboraf; ***UK***: Zelboraf; ***USA***: Zelboraf.

Verteporfin *(BAN, USAN, rINN)*

Benzoporphyrin Derivative; BPD; CL-318952; Verteporfiini; Verteporfina; Vertéporfine; Verteporfinum; Вертепорфин.

trans-18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoic acid monomethyl ester.

$C_{41}H_{42}N_4O_8$=718.8

CAS — 129497-78-5.

ATC — S01LA01.

ATC Vet — QS01LA01.

UNII — 0X9PA28K43.

Pharmacopoeias. In *US.*

USP 36: (Verteporfin). Store at a temperature between -25 degrees and -10 degrees in airtight containers.

Uses and Administration

Verteporfin is a photosensitiser used in photodynamic therapy (see under Porfimer Sodium, p. 849.1). It is used to treat neovascular (wet) age-related macular degeneration (see below). After intravenous dosage verteporfin accumulates preferentially in the endothelial cells of actively growing blood vessels, including those in the choroid. When activated by laser light it produces local vascular occlusion and this inhibits neovascularisation and reduces the decline in visual acuity. It is given by intravenous infusion over 10 minutes at a dose of 6 mg/m². This is followed 15 minutes after the start of the infusion by activation using a laser tuned to a wavelength of 689 nanometres and delivered to the eye via a fibre optic device and a slit lamp, together with a suitable contact lens. The recommended light dose is 50 J/cm², given over 83 seconds. Therapy may be repeated every 3 months for recurrent choroidal neovascular leakage. Verteporfin has also been investigated in the photodynamic therapy of a variety of other disorders including malignant neoplasms.

Age-related macular degeneration. Age-related macular degeneration (AMD) is a degenerative disease usually occurring in people over the age of 50 years.[1-3] The central portion of the retina (the macula) deteriorates[2,4,5] and it is a major cause of severe visual loss in people over 60 years old in North America and Europe.[4,6] There are two main types of AMD.[2,4,6-9]

- In geographic atrophy or *non-neovascular* or *non-exudative (dry) AMD*, which occurs at an early stage of AMD, the retinal pigment epithelium is lost completely in localised areas, causing a gradual loss of central vision in the affected eye(s). It is characterised by retinal hypo- or hyperpigmentation, and yellow deposits of acellular amorphous debris beneath the retina, called drusen. These are usually large, or soft (with indistinct margins); small hard drusen occur naturally with ageing but, unlike drusen in AMD, do not progress.
- In *neovascular* or *exudative (wet) AMD*, new blood vessels develop in the choroidal layer beneath the retina; leaks or haemorrhage from these lead to macular oedema, retinal scarring, and often acute, significant loss of vision. This process of *choroidal neovascularisation* (CNV) is defined as classic or occult according to its appearance on fluorescein angiography;[2,5,8,10] the classic form is associated with more rapid progression than the occult form.[2,8] CNV lesions are also classified according to their location relative to the fovea.[1,2,11] Although the neovascular form accounts for only about 20% of all cases of AMD, the risk of severe visual loss with this form is much higher than with dry AMD.[1,8,12] However, about 10 to 20% of patients with dry AMD can progress to the neovascular form,[1,9] and both forms can occasionally co-exist in the same patient.[10]

Risk factors, besides older age, include a family history of the disorder, polymorphisms in either the complement factor H (CFH) or age-related maculopathy susceptibility 2 (ARMS2 or LOC387715) genes, smoking, white race, and increased body-mass index;[3,12,13] female sex, atherosclerosis, dietary fat or fish intake, alcohol or caffeine consumption, refractive error, iris colour, and increased exposure to sunlight have also been proposed as risk factors but have not consistently been related to development of AMD.[13]

There is currently no **treatment** that effectively prevents visual loss or improves vision in all patients with AMD.[14]

- Laser photocoagulation treatment is of proven efficacy for neovascular AMD, especially for extrafoveal CNV;[15] however, rates of recurrence are high.[1,6,13,14]
- Photodynamic therapy (see under Porfimer Sodium, p. 849.1) with verteporfin has been shown to decrease the risk of visual loss in patients with neovascular AMD, including subfoveal CNV.[1,4,8,10,11,14,16-20] Systematic reviews have noted that although photodynamic therapy with verteporfin is probably effective in preventing visual loss in those with classic and occult CNV due to AMD, the size of the effect remains in doubt.[5,21] Furthermore, the therapy can only be effective during the proliferative stage of the disease while the neovascular process is active.[5]

  In the UK, NICE guidelines considered the evidence to show a larger treatment effect in patients with classic CNV, and recommend photodynamic therapy in those patients with neovascular AMD with a confirmed diagnosis of classic, with no occult, subfoveal CNV.[2] However, other guidelines[22] on the use of verteporfin recommend that verteporfin treatment be considered for patients with minimally classic subfoveal CNV who have relatively small lesions, or where the proportion of classic CNV is increasing. For those patients with occult CNV and who are presumed to have recent disease progression, verteporfin may be considered in those with smaller lesions or lower levels of visual acuity; for those with large occult lesions, treatment may be considered if levels of visual acuity are rapidly decreasing. Patients should be followed up at least as often as every 3 months after initial therapy, and re-treated if necessary.[22] Subsequent results suggest that verteporfin is ineffective in occult lesions.[20]

  While photodynamic therapy is considered to have minimal adverse effects and a low complication rate, some have cautioned that patients should be counselled that verteporfin therapy rarely leads to an improvement in vision.[23]
- Vascular endothelial growth factor (VEGF) plays a role in the development of CNV secondary to AMD; pegaptanib and ranibizumab are VEGF inhibitors used in the treatment of neovascular (wet) AMD.[24-26] Systematic reviews[27,28] of randomised controlled studies of these drugs concluded that both show benefit in slowing or stopping the progression of disease. Greater effect was seen with ranibizumab than with pegaptanib, although head-to-head comparative studies are needed to confirm this. Use of pegaptanib is not recommended by NICE in the UK.[29] Early studies have reported benefit from the use of aflibercept.[30,31] Bevacizumab is also used, although its use is unlicensed and controversial.[6,15,24,32] (For further discussion, see Age-related Macular Degeneration, under Bevacizumab, p. 747.2.) Triamcinolone acetonide, a corticosteroid that may also downregulate VEGF, has been given intravitreally with variable results; combination treatment with photodynamic therapy is under investigation,[9,13,33] and initial results have been promising.[15]
- Angiogenesis inhibitors such as anecortave[3,9,13,14,33] and squalamine[15] are under investigation for neovascular AMD. Interferon alfa gave encouraging preliminary results, but controlled data showed no benefit.[9,13] Thalidomide has been tried, but studies were stopped due to adverse effects.[9,13]
- Vitamin and mineral supplements may be of use in selected patients; the AREDS study found that antoxidants (vitamin C, vitamin E, and betacarotene) plus zinc modestly benefited those with moderate to severe signs of the disease.[10,12,14] However, betacarotene

should be avoided in smokers,[3,6,9] and high doses of vitamins may have adverse effects.[12] The carotenoids, lutein and zeaxanthin, have been promoted as retinal protectants, but controlled data are lacking.[9,10,14,34,35] Some recommend that those at risk of AMD should be encouraged to stop smoking and to consume a diet including vegetables, fish, whole grains, and nuts, and to reduce consumption of fats especially vegetable oil.[7,12,34] A prospective cohort study found that a high dietary intake of vitamin E and zinc, or an above-median intake of the combination of vitamins C and E, betacarotene, and zinc were associated with a lower risk of incident AMD.[36] Daily supplementation with folic acid, pyridoxine, and cyanocobalamin during an average of 7.3 years of follow-up reduced the risk of AMD in a large cohort of women at increased risk for vascular disease; benefit emerged at about 2 years of follow-up and persisted throughout the study.[37] However, systematic reviews[38,39] have found no evidence to support the role of antoxidant vitamin and mineral supplements in the primary prevention of AMD.

- Retinal or macular surgery, and transpupillary thermotherapy have been investigated;[1,10,13,14,33] however, long-term data are lacking for surgery,[12] and use of transpupillary thermotherapy is not recommended.[15] Radiotherapy has also been tried with mixed results.[9,13] Retinal transplantation is under investigation.[6,10,14] Gene silencing with bevasiranib, a short interfering RNA (siRNA) therapeutic designed to turn off or silence the gene that produces VEGF, is also under investigation for wet AMD.[12,40,41]

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Adverse Effects and Precautions

Photosensitivity will occur in all patients treated with verteporfin and patients should not be exposed to direct sunlight for 2 to 5 days after treatment. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Headaches, injection site reactions, and visual disturbances occur frequently. Extravasation at the injection site may produce severe pain and inflammation and requires interruption of therapy. Patients who have a severe decrease in vision should not be re-treated until their vision recovers. Other reported adverse effects include hypersensitivity, infusion-related pain (mainly presenting as back pain), chest pain, gastrointestinal disturbances, atrial fibrillation, hypertension, decreased hearing, and anaemia. Verteporfin should be used with care in patients with hepatic impairment and may be contra-indicated if impairment is severe.

Porphyria. Licensed product information states that the use of verteporfin is contra-indicated in patients with porphyria. However, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies verteporfin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/11/11)

Interactions

Use of verteporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

After intravenous doses, elimination of verteporfin is bi-exponential, with a terminal plasma elimination half-life of about 5 to 6 hours. Protein binding is about 90%. It is metabolised in the liver. It is excreted in faeces via the bile, mostly as unchanged drug, with less than 1% of a dose recovered in the urine.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Visudyne; ***Austral.***: Visudyne; ***Austria***: Visudyne; ***Belg.***: Visudyne; ***Braz.***: Visudyne; ***Canad.***: Visudyne; ***Chile***: Visudyne†; ***China***: Visudyne (维速达尔); ***Cz.***: Visudyne; ***Denm.***: Visudyne; ***Fin.***: Visudyne; ***Fr.***: Visudyne; ***Ger.***: Visudyne; ***Gr.***: Visudine; ***Hong Kong***: Visudyne; ***Hung.***: Visudyne; ***Indon.***: Visudyne; ***Irl.***: Visudyne; ***Israel***: Visudyne; ***Ital.***: Visudyne; ***Jpn***: Visudyne; ***Malaysia***: Visudyne; ***Neth.***: Visudyne; ***Norw.***: Visudyne; ***NZ***: Visudyne; ***Philipp.***: Visudyne; ***Pol.***: Visudyne; ***Port.***: Visudyne; ***Rus.***: Visudyne (Визудин); ***S.Afr.***: Visudyne; ***Singapore***: Visudyne; ***Spain***: Visudyne; ***Swed.***: Visudyne; ***Switz.***: Visudyne; ***Thai.***: Visudyne; ***Turk.***: Visudyne; ***UK***: Visudyne; ***USA***: Visudyne; ***Venez.***: Visudyne.

Pharmacopoeial Preparations

USP 36: Verteporfin for Injection.

Vinblastine Sulfate *(BANM, USAN, rINNM)*

29060-LE; NSC-49842; Sulfato de Vimblastina; Sulfato de vinblastina; Vinblastiinisulfaatti; Vinblastin Sülfat; Vinblastina, sulfato de; Vinblastine, Sulfate de; Vinblastine Sulphate; Vinblastini Sulfas; Vinblastino sulfatas; Vinblastinsulfat; Vinblastin-sulfát; Vinblasztin-szulfát; Vincaleukoblastine Sulphate; VLB (vinblastine); Winblastyny siarczan; Винбластина Сульфат.

$C_{46}H_{58}N_4O_9,H_2SO_4$=909.1

CAS — 865-21-4 (vinblastine); 143-67-9 (vinblastine sulfate).

ATC — L01CA01.

ATC Vet — QL01CA01.

UNII — N00W22YO2B.

Description. Vinblastine sulfate is the sulfate of an alkaloid, vincaleukoblastine, extracted from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Vinblastine Sulfate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water; practically insoluble in alcohol. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature not exceeding -20 degrees in airtight glass containers. Protect from light.

USP 36: (Vinblastine Sulfate). A white or slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature between -25 degrees and -10 degrees in airtight containers. Protect from light.

Stability. Between about 5 and 20% of active drug was lost from solution when a solution of vinblastine sulfate 3 micrograms/mL in glucose 5% injection was stored for 48 hours in a range of intravenous burette giving sets, the highest loss being from cellulose propionate sets and the lowest from one made from methacrylate butadiene styrene.[1] Similarly, storage in PVC tubing led to a 42 to 44% loss from solution whereas only about 6% was lost over the 48 hours in polybutadiene tubing. The losses appeared to be due to drug sorption, and were therefore greater from the tubing which had a greater surface-area-to-volume ratio than the burettes.

1. McElnay JC, *et al*. Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Uses and Administration

Vinblastine sulfate is an antineoplastic vinca alkaloid that apparently acts by binding to the microtubular proteins of the spindle and arresting mitosis at the metaphase; it is thus specific for the M phase of the cell cycle. It also interferes with amino acid metabolism and possibly nucleic acid synthesis, and has some immunosuppressant activity. Multidrug resistance may occur.

Vinblastine sulfate is used, usually with other antineoplastics, in the treatment of Hodgkin's disease and other lymphomas, for some inoperable malignant neoplasms including those of the breast, bladder, and kidney, and in non-small cell lung cancer, choriocarcinoma, and Kaposi's sarcoma; vinblastine has also been used in the management of Langerhans-cell histiocytosis and advanced mycosis fungoides. It was formerly used with bleomycin and cisplatin (PVB) for testicular cancer, but other regimens are now preferred. See the cross-references given below.

Vinblastine sulfate is given by **intravenous** injection. Care should be taken to avoid extravasation and the intravenous injection may be given over 1 minute into a freely-running infusion of sodium chloride 0.9% if preferred. However, UK guidelines recommend that for adults and adolescents, the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% and infused intravenously over 5 to 10 minutes. (For adolescents treated in specialised paediatric units, see Administration in Children, p. 882.1.)

The usual dose of vinblastine sulfate is about 6 mg/m², not more often than once every 7 days. Single doses starting at 3.7 mg/m² and increasing at weekly intervals, over 4 weeks, to a usual maximum dose of 11.1 mg/m² have been given; doses have been increased above this, but should not exceed 18.5 mg/m². If a maintenance dose is required, it may be given every 7 days provided white cell counts permit (see below), and should be the maximum dose that the patient is able to tolerate without serious leucopenia occurring.

For doses in children, see p. 882.1.

White cell counts should be made before each injection and some sources suggest a repeat dose should not be given

unless the count has risen to at least 4000 cells/mm³ (but see also Bone-marrow Depression, p. 730.3). Dosage reduction is recommended in patients with hepatic impairment (see below).

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in children. Doses of vinblastine sulfate in children vary according to the disease treated, the schedule used, and whether it is used as a single agent or as part of a combination chemotherapy regimen. The usual dose is about 6 mg/m² given **intravenously**, not more often than once every 7 days. Single doses starting at 2.5 mg/m² and increasing at weekly intervals, over 4 weeks, to a usual maximum dose of 7.5 mg/m² have been given; doses have been increased above this, but should not exceed 12.5 mg/m².

UK guidelines state that doses of vinca alkaloids may be given via a syringe to children and adolescents treated in paediatric units.[1] For adolescents treated in adolescent or adult units, recommendations for administration are as for adults (see Uses and Administration, p. 881.3).

1. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Administration in hepatic impairment. Licensed product information states that the dose of vinblastine should be reduced by 50% in patients having a direct serum bilirubin value above 3 mg per 100 mL.

Blood disorders, non-malignant. The vinca alkaloids vinblastine and vincristine have been used in the treatment of auto-immune blood disorders such as immune thrombocytopenia (p. 1606.1). There are also reports of the haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura responding to treatment with intravenous injection of vincristine.[1-3] For further details on the treatment of thrombotic microangiopathies, see under Plasma, p. 1159.1. Vincristine has been given with normal immunoglobulin in the management of a patient with life-threatening thrombocytopenia due to sarcoidosis.[4] Vincristine has also been used for life-threatening haemangioma (p. 1605.3).

1. Gutterman LA, *et al*. The hemolytic-uremic syndrome: recovery after treatment with vincristine. *Ann Intern Med* 1983; **98:** 612–13.
2. Ferrara F, *et al*. Vincristine as salvage treatment for refractory thrombotic thrombocytopenic purpura. *Ann Hematol* 1999; **78:** 521–3.
3. Ferrara F, *et al*. Vincristine as treatment for recurrent episodes of thrombotic thrombocytopenic purpura. *Ann Hematol* 2002; **81:** 7–10.
4. Larner AJ. Life threatening thrombocytopenia in sarcoidosis. *BMJ* 1990; **300:** 317–19.

Histiocytic syndromes. The value of systemic chemotherapy in patients with Langerhans-cell histiocytosis (p. 692.1) is uncertain; however, it is certainly widely used in extensive disease, vinblastine being one of the drugs often employed.[1,2]

1. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996; **75:** 17–24.
2. Gadner H, *et al*. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; **138:** 728–34. Correction. *ibid.*; **139:** 170.

Malignant neoplasms. Vinblastine plays an important role in the ABVD regimen in patients with Hodgkin's disease (p. 696.1). It also formed part of the effective, if toxic, PVB regimen used to treat germ cell (ovarian or testicular) cancer, p. 711.2 and p. 715.1 respectively, although other regimens tend now to be preferred. The vinca alkaloids are also active in gestational trophoblastic tumours (p. 691.2), and vinblastine is also used in the therapy of invasive bladder cancer (p. 700.2); it may be used in the adjuvant or palliative treatment of non-small-cell lung cancer (p. 710.2) and in the palliative care of advanced breast cancer (p. 702.1). It has been used in malignancies of the kidney (p. 708.3). Vinca alkaloids are also used to treat Kaposi's sarcoma (p. 718.1).

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression, especially leucopenia, is the most common adverse effect with vinblastine and tends to be dose-limiting. Maximum depression occurs 5 to 10 days after a dose with recovery in a further 7 to 14 days. Leucopenia may be more severe in patients with cachexia or extensive skin ulceration: vinblastine should not be used in elderly patients with these conditions. Stomatitis, gastrointestinal bleeding, and abdominal pain may occur; nausea and vomiting respond to treatment with antiemetics.

The vinca alkaloids can produce central and peripheral (including autonomic) neurotoxicity, although these effects are less frequent with vinblastine. Symptoms include malaise, weakness, headache, depression, paraesthesia and numbness, loss of deep tendon reflexes, peripheral neuropathies, constipation and adynamic ileus, jaw pain, and convulsions. Damage to the eighth cranial nerve may result in vestibular and auditory toxicity leading to dizziness, nystagmus, vertigo, and partial or total deafness. A routine prophylactic regimen against constipation is recommended in patients receiving high doses of vinblastine. Overdosage has caused permanent damage to the CNS. Intrathecal use of the vinca alkaloids is contra-indicated because of the likelihood of fatal neurotoxicity (see Administration Error, below).

Other reported effects include skin reactions, alopecia, ischaemic cardiotoxicity, hypertension, dyspnoea and bronchospasm, and bone and tumour pain. A syndrome of inappropriate secretion of antidiuretic hormone has occurred at high doses, and may be relieved by fluid restriction and, if necessary, a suitable diuretic. Rare cases of anaphylaxis and anaphylactoid-type reactions have been reported with the vinca alkaloids.

Vinblastine is irritant to the skin and mucous membranes and extravasation may cause necrosis, cellulitis, and sloughing. The application of warmth and local injection of hyaluronidase may be of benefit in relieving the effects of extravasation. By analogy with its use in the management of vincristine overdosage (see p. 883.2), folinic acid has been suggested for use in overdosage with vinblastine.

Vinblastine should not be injected into an extremity with impaired circulation because of an increased risk of thrombosis. It should be given with caution and at reduced dosage to patients with hepatic impairment (see under Uses, above).

Administration error. *Intrathecal doses of vinca alkaloids, including vinblastine, result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK guidelines on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

Handling and disposal. A method for the destruction of vincristine or vinblastine *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of either drug by this method showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vinblastine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vinblastine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use with drugs that inhibit cytochrome P450 isoenzymes of the CYP3A subfamily may result in decreased metabolism of vinblastine and increased toxicity. Use with cisplatin has been reported to increase vinblastine plasma concentrations. For a report of the possible contribution of vinblastine to reduced plasma concentrations of phenytoin, see p. 544.1.

Analgesics. A report of enhanced hepatotoxicity in patients treated with interferon alfa and vinblastine who were given *paracetamol*.[1]

1. Kellokumpu-Lehtinen P, *et al*. Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; **i:** 1143.

Antibacterials. There is a report of severe vinblastine toxicity in 3 patients who received vinblastine and ciclosporin with *erythromycin*.[1] Adverse effects resolved on stopping erythromycin and recurred in 1 patient who was rechallenged with erythromycin.

1. Tobe SW, *et al*. Vinblastine and erythromycin: an unrecognised serious drug interaction. *Cancer Chemother Pharmacol* 1995; **35:** 188–90.

Antineoplastics. Acute bronchospastic reactions after injection of a vinca alkaloid have been reported, usually in patients also given *mitomycin*,[1] and presenting as acute respiratory distress, cyanosis, and dyspnoea, often with the development of pulmonary infiltrates and pneumonitis.[2,3] Several fatalities due to respiratory complications have occurred. For reports of vascular toxicity and Raynaud's syndrome associated with the use of vinca alkaloids with *bleomycin* and other drugs, see Effects on the Cardiovascular System, p. 727.2.

1. Dyke RW. Acute bronchospasm after a vinca alkaloid in patients previously treated with mitomycin. *N Engl J Med* 1984; **310:** 389.
2. Konits PH, *et al*. Possible pulmonary toxicity secondary to vinblastine. *Cancer* 1982; **50:** 2771–4.
3. Ozols RF, *et al*. MVP (mitomycin, vinblastine, and progesterone): a second-line regimen in ovarian cancer with a high incidence of pulmonary toxicity. *Cancer Treat Rep* 1983; **67:** 721–2.

Antivirals. Severe myelosuppression has occurred in patients given relatively high doses of vinblastine with *interferon alfa-n1*.

A patient who had been given vinblastine 6 mg/m² every 3 weeks had severe gastrointestinal and haematological toxicity and moderate renal failure when *HAART* with zidovudine, lamivudine, abacavir, nevirapine, and lopinavir with ritonavir was reintroduced.[1] The vinblastine dosage was eventually stabilised at 2 mg/m² during HAART without toxicity.

1. Kotb R, *et al*. Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. *Eur J Haematol* 2006; **76:** 269–71.

Pharmacokinetics

Vinblastine is not reliably absorbed from the gastrointestinal tract. After intravenous use it is rapidly cleared from the blood and distributed to tissues; it is reported to be concentrated in blood platelets. It is extensively protein bound. Vinblastine is metabolised in the liver, by cytochrome P450 isoenzymes of the CYP3A subfamily, to an active metabolite desacetylvinblastine, and is excreted in faeces via the bile, and in urine; some is excreted as unchanged drug. The terminal half-life is reported to be about 25 hours. It does not cross the blood-brain barrier in significant amounts.

References.

1. Levêque D, Jehl F. Molecular pharmacokinetics of Catharanthus (vinca) alkaloids. *J Clin Pharmacol* 2007; **47:** 579–88.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Blastovin; ***Austral.***: Velbe†; ***Austria***: Velbe; ***Belg.***: Vinblasin†; ***Braz.***: Faulblastina; Velban; Vinatin; ***Chile***: Lemblastine; ***China***: Weibaoding (威保啶); ***Denm.***: Velbe; ***Fin.***: Velbe; ***Fr.***: Velbe; ***Gr.***: Velbe; ***Hong Kong***: Velbastine; ***India***: Cytoblastin; ***Israel***: Blastovin; ***Ital.***: Velbe; ***Mex.***: Lemblastine; ***Neth.***: Blastivin†; ***Norw.***: Velbe; ***Philipp.***: Oncostin; Velbastine; ***Port.***: Solblastin; ***S.Afr.***: Cytoblastin; ***Singapore***: Velbastine; ***Swed.***: Velbe; ***Switz.***: Velbe; ***Turk.***: Vinko; ***UK***: Velbe; ***USA***: Velban.

Pharmacopoeial Preparations
BP 2014: Vinblastine Injection;
USP 36: Vinblastine Sulfate for Injection.

Vincristine Sulfate *(BANM, USAN, rINNM)*

Compound 37231; Leurocristine Sulphate; NSC-67574; 22-Oxovincaleukoblastine Sulphate; Sulfato de leurocristina; Sulfato de vincristina; Vincristina, sulfato de; Vincristine, Sulfate de; Vincristine Sulphate; Vincristini sulfas; Vincristinsulfat; Vinkristiinisulfaatti; Vinkristin Sülfat; Vinkristino sulfatas; Vinkristinsulfat; Vinkristin-sulfát; Vinkrisztin-szulfát; Winkrystyny siarczan; Винкристина Сульфат.

$C_{46}H_{56}N_4O_{10},H_2SO_4$=923.0

CAS — 57-22-7 (vincristine); 2068-78-2 (vincristine sulfate).

ATC — L01CA02.

ATC Vet — QL01CA02.

UNII — T5IRO3534A.

Description. Vincristine sulfate is the sulfate of an alkaloid, 22-oxovincaleukoblastine, obtained from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Vincristine Sulfate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding -20 degrees in airtight glass containers. Protect from light.

USP 36: (Vincristine Sulfate). A white to slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature between -25 degrees and -20 degrees in airtight containers. Protect from light.

Uses and Administration

Vincristine is an antineoplastic vinca alkaloid that may act similarly to vinblastine (p. 881.3) by arresting mitosis at the metaphase.

Vincristine sulfate is used mainly in combination chemotherapy regimens for acute and chronic leukaemias, lymphomas, including Hodgkin's disease and non-Hodgkin's lymphomas, and multiple myeloma. It is also used for tumours of the breast, lung, head and neck, and soft-tissue sarcomas, as well as for paediatric solid tumours including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumour, retinoblastoma, and medulloblastoma. Vincristine has also been used in immune thrombocytopenia refractory to other agents. See also the cross-references given below.

Vincristine sulfate is given by **intravenous** injection. Care should be taken to avoid extravasation and the injection may be given over 1 minute into a freely-running intravenous infusion (usually sodium chloride 0.9%) if preferred. However, UK guidelines recommend that for adults and adolescents, the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% and infused intravenously over 5 to 10 minutes. (For adolescents treated in specialised paediatric units, see Administration in Children, below.)

The usual dose of vincristine sulfate is 1.4 to 1.5 mg/m^2 once weekly, up to a maximum weekly dose of 2 mg (see also Administration, below).

For doses in children, see below.

Blood counts should be carried out before giving each dose. Dosage reduction is recommended in patients with hepatic impairment (see below).

A *liposomal* formulation of vincristine is used in the treatment of patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia who have had at least 2 relapses or whose disease has progressed following 2 or more anti-leukaemia therapies. Vincristine sulfate liposome injection is given by intravenous infusion (in sodium chloride 0.9% or glucose 5%) over 1 hour in a dose of 2.25 mg/m^2 once every 7 days. Doses may need to be modified if toxicity occurs. A liposomal formulation is also under investigation for metastatic uveal melanoma.

Action. Results *in vitro* suggested[1] a selective action of vincristine against lymphocytes of patients with chronic lymphocytic leukaemia; lymphocytes of healthy subjects were not so affected. A further study[2] confirmed these findings, and also found marked variation in vincristine susceptibility among individual chronic lymphocytic leukaemic cells. This suggests that vincristine may have effects other than arrest of mitosis.

1. Vilpo J, Vilpo L. Selective toxicity of vincristine against chronic lymphocytic leukaemia in vitro. *Lancet* 1996; **347:** 1491–2.
2. Vilpo JA, *et al*. Selective toxicity of vincristine against chronic lymphocytic leukemia cells in vitro. *Eur J Haematol* 2000; **65:** 370–8.

Administration. Although a maximum single dose of 2 mg is recommended for vincristine sulfate to reduce neurotoxicity, a review[1] has suggested that this guideline is overly rigid, since it does not take into account interindividual variations in pharmacokinetics and susceptibility to toxicity, which may be considerable. Furthermore the authors considered the evidence for effectiveness of this dosage limitation to be equivocal. They suggested beginning therapy at 1.4 mg/m^2 and adjusting subsequent doses according to toxicity.

Administration errors have occurred with the vinca alkaloids. For UK guidelines on dilution of intravenous vinca alkaloids to avoid inadvertent intrathecal use, see Administration Error, under Adverse Effects, below.

1. McCune JS, Lindley C. Appropriateness of maximum-dose guidelines for vincristine. *Am J Health-Syst Pharm* 1997; **54:** 1755–8.

Administration in children. The suggested dose of vincristine sulfate for the treatment of paediatric tumours in children weighing over 10 kg is 1.4 to 2 mg/m^2, given **intravenously** once weekly, up to a maximum weekly dose of 2 mg. For those weighing 10 kg or less, the suggested initial dose is 50 micrograms/kg, given once weekly.

UK guidelines state that doses of vinca alkaloids may be given via a syringe to children and adolescents treated in paediatric units.[1] For adolescents treated in adolescent or adult units, recommendations for administration are as for adults (see Uses and Administration, above).

1. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Administration in hepatic impairment. Licensed product information states that the dose of vincristine should be reduced by 50% in patients having a serum bilirubin value above 3 mg per 100 mL (51 micromoles/litre).

Amyloidosis. For mention of regimens including vincristine used in the management of amyloidosis, see p. 819.3.

Blood disorders, non-malignant. Vincristine may be employed in the treatment of various auto-immune blood disorders, see under Vinblastine, p. 882.1.

Malignant neoplasms. Vincristine is widely used in the treatment of malignant neoplasms. It is a fundamental part of potentially curative regimens for acute lymphoblastic leukaemia, Hodgkin's disease and aggressive non-Hodgkins lymphomas (see p. 692.3, p. 696.1 and p. 696.3). It has also been used in chronic lymphocytic leukaemia (p. 693.3) and in other non-Hodgkin's lymphomas including AIDS-related lymphoma (p. 697.2), Burkitt's lymphoma (p. 697.3) and mycosis fungoides (p. 698.3). Other haematological malignancies in which it may be tried include multiple myeloma (p. 699.2). Among the solid neoplasms, vincristine is used in regimens to treat gestational trophoblastic tumours (p. 691.2), tumours of the brain (p. 701.2), head and neck (p. 708.1), Wilms' tumour (p. 709.1), small-cell lung cancer (p. 710.2), and thymoma (p. 715.3). It is also employed in regimens for neuroblastoma (p. 716.2), retinoblastoma (p. 717.2), and some sarcomas including sarcomas of bone, Kaposi's sarcoma, and rhabdomyosarcoma (see p. 717.3, p. 718.1, and p. 718.2).

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1.

Bone-marrow depression occurs less commonly than with vinblastine but neurological and neuromuscular effects are more severe with vincristine and are dose-limiting. Walking may be impaired and the neurological effects may not be reversed for several months after the drug is stopped. Convulsions, often with hypertension, have occurred. Constipation is common and there may be abdominal pain. Urinary disturbances have occurred and alopecia is frequent.

Folinic acid has been given for the treatment of overdosage: suggested doses are as much as 100 mg of folinic acid intravenously every 3 hours for 24 hours, then every 6 hours for at least 48 hours. However, this is unlikely to be of benefit in reversing neuromuscular toxicity. For mention of the use of glutamic acid in managing the usually fatal consequences of inadvertent intrathecal dosage, see below.

Because severe constipation and impaction of faeces often occur with vincristine, laxatives or enemas may be necessary to ensure regular bowel function. Vincristine should be given with caution to patients with pre-existing neuromuscular disease and is contra-indicated in patients with the demyelinating form of Charcot-Marie-Tooth syndrome (see under Effects on the Nervous System, below). Doses may need to be adjusted in patients with hepatic impairment. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity.

A liposomal formulation of vincristine has been associated with hepatotoxicity and increased liver enzyme tests; hepatic function should be monitored.

Administration error. *Inadvertent intrathecal doses of vincristine result in ascending paralysis and death.*[1-3] However, in one case[1] treatment immediately after the error, and consisting of removal of contaminated spinal fluid and flushing with lactated Ringer's solution and fresh frozen plasma diluted in lactated Ringer's solution, plus intravenous and oral glutamic acid, was reported successful in stabilising neurological dysfunction and preventing death. A similar case of successful treatment has subsequently been reported,[4] in which immediate CSF aspiration and irrigation (with lactated Ringer's solution containing fresh frozen plasma to bind vincristine) for 6 days was combined with intravenous folate, glutamic acid, and pyridoxine.

Licensed product information therefore recommends the following treatment as soon as possible after inadvertent intrathecal injection:

- removal of as much CSF as is safely possible through the lumbar access
- CSF irrigation with lactated Ringer's solution, by continuous infusion at a rate of 150 mL/hour
- as soon as it is available, 25 mL of fresh frozen plasma should be added to every 1 litre of lactated Ringer's solution and infused at a rate of 75 mL/hour; the rate of infusion should then be adjusted to maintain a spinal fluid protein concentration of 150 mg per 100 mL

While stating that the roles of the following drugs in the reduction of neurotoxicity are uncertain, licensed product information also allows the use of:

- glutamic acid 10 g intravenously over 24 hours, followed by 500 mg orally, three times daily, for one month or until the neurological dysfunction has stabilised
- folinic acid 100 mg as an intravenous bolus, and then infused at a rate of 25 mg/hour for 24 hours, then 25 mg intravenously every six hours for 1 week
- pyridoxine 50 mg intravenously over 30 minutes, every 8 hours

While early recognition and immediate treatment with cerebrospinal fluid drainage and exchange may improve survival,[5] fatalities still occur despite these measures.[5,6] Recommendations[2,6] have been made in order to prevent further errors occurring, including restrictions on the prescription, administration, and storage of intrathecal drugs. In the UK, recommendations state that when vinca alkaloids are prescribed for adults and adolescents, syringes should not be used to administer the dose; instead, the required dose of vinca alkaloid should be supplied in a 50 mL infusion bag of sodium chloride 0.9%, and infused over 5 to 10 minutes. All vinca alkaloids should be labelled as being for intravenous use only, with a clear warning of the consequences of use by other routes. However, for children and adolescents being treated in specialised paediatric units, the use of syringes to administer vinca alkaloids is permitted.[7]

1. Dyke RW. Treatment of inadvertent intrathecal injection of vincristine. *N Engl J Med* 1989; **321:** 1270–1.
2. DoH. Updated national guidance on the safe administration of intrathecal chemotherapy (HSC 2008/001, issued 11th August, 2008). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_086844.pdf (accessed 16/09/09)
3. Hennipman B, *et al*. Intrathecal vincristine: 3 fatal cases and a review of the literature. *J Pediatr Hematol Oncol* 2009; **31:** 816–19.
4. Qweider M, *et al*. Inadvertent intrathecal vincristine administration: a neurosurgical emergency. Case report. *J Neurosurg Spine* 2007; **6:** 280–3.
5. Alcaraz A, *et al*. Intrathecal vincristine: fatal myeloencephalopathy despite cerebrospinal fluid perfusion. *J Toxicol Clin Toxicol* 2002; **40:** 557–61.
6. Fernandez CV, *et al*. Intrathecal vincristine: an analysis of reasons for recurrent fatal chemotherapeutic error with recommendations for prevention. *J Pediatr Hematol Oncol* 1998; **20:** 587–90.
7. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Effects on the nervous system. In its most typical form, vincristine neurotoxicity[1] manifests as a mixed sensorimotor neuropathy of the distal type. The earliest symptoms are sensory changes in the form of paraesthesias, accompanied by impairment and ultimately loss of deep tendon reflexes. In more severe forms, impairment of motor function occurs with wrist drop and foot drop, ataxia and gait abnormalities, and occasionally progressive quadriparesis.

In contrast to these peripheral neuropathies, which are usually associated with long-term usage, there may be short-term autonomic neuropathy resulting in constipation and occasionally ileus, abdominal pain, atony of the urinary bladder (which may lead to urinary retention), orthostatic hypotension, and rarely, impotence. Effects on the cranial nerves may result in ptosis, hoarseness (due to laryngeal nerve paralysis), or optic neuropathies. Effects on the CNS are rare, probably in part because of poor penetration into CSF, but include excessive release of antidiuretic hormone and consequent hyponatraemia.

Hallucinations have occurred[2] and effects on the special senses have been reported: both bilateral optic atrophy and blindness,[3] and profound neurological deafness (which was largely reversible on drug withdrawal)[4] have occurred. Convulsions associated with hypertension are another feature of vincristine toxicity.[5]

Toxicity is related to both the cumulative and the individual dose.[1] It usually begins in adults after receiving a total of 5 to 6 mg, and is significant by the time a cumulative dose of 15 to 20 mg is reached. If individual doses are low (less than 2 mg) or intervals between doses are longer than the usual week, patients can tolerate higher cumulative doses. Children tolerate vincristine better than adults, but the elderly are particularly prone to neurotoxicity. Patients with existing neurological disorders such as poliomyelitis or the Charcot-Marie-Tooth syndrome may be at increased risk of neurotoxicity.[6-9] It has been suggested that increased neurotoxicity may be associated with the use of ready-to-use solutions rather than reconstituted lyophilised preparations but this is unproven.[10-14]

There is no good treatment for the effects of vincristine on the nervous system: symptoms are largely reversible once dosage is interrupted, and should be managed with appropriate symptomatic care.[1] However, there is some suggestion that glutamic acid may be of benefit in treating neurotoxicity[15]—see also Administration Error, above. For the use of dinoprost to alleviate ileus induced by vinca alkaloids, see p. 2134.1.

1. Legha SS. Vincristine neurotoxicity: pathophysiology and management. *Med Toxicol* 1986; **1:** 421–7.
2. Holland JF, *et al*. Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res* 1973; **33:** 1258–64.
3. Awidi AS. Blindness and vincristine. *Ann Intern Med* 1980; **93:** 781.
4. Yousif H, *et al*. Partially reversible nerve deafness due to vincristine. *Postgrad Med J* 1990; **66:** 688–9.
5. Ito S, *et al*. Seizures and hypertension complicating vincristine therapy in children. *Clin Pharmacol Ther* 1995; **57:** 208.
6. Hogan-Dann CM, *et al*. Polyneuropathy following vincristine therapy in two patients with Charcot-Marie-Tooth syndrome. *JAMA* 1984; **252:** 2862–3.

7. Miller BR. Neurotoxicity and vincristine. *JAMA* 1985; **253:** 2045.
8. Chauncey TR, *et al*. Vincristine neurotoxicity. *JAMA* 1985; **254:** 507.
9. Griffiths JD, *et al*. Vincristine neurotoxicity in Charcot-Marie-Tooth syndrome. *Med J Aust* 1985; **143:** 305–6.
10. Arnold AM, *et al*. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 346.
11. Jalihal S, Roebuck N. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 637.
12. Davies CE, *et al*. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 637–8.
13. Warrier RP, Ducos R. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 980.
14. Gennery BA. Vincristine neurotoxicity. *Lancet* 1985; **ii:** 385.
15. Jackson DV, *et al*. Amelioration of vincristine neurotoxicity by glutamic acid. *Am J Med* 1988; **84:** 1016–22.

Handling and disposal. For a method for the destruction of vincristine *wastes*, see under Vinblastine Sulfate, p. 882.2.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vincristine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vincristine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/09/11)

Pregnancy. For a report of a healthy infant born to a woman treated with a vincristine-containing chemotherapy regimen, see Pregnancy, under Teniposide, p. 867.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use of vincristine with drugs that inhibit cytochromes of the CYP3A subfamily may result in decreased metabolism of vincristine and increased toxicity. If vincristine is used with asparaginase it should be given 12 to 24 hours before the enzyme: giving asparaginase with or before vincristine may reduce vincristine clearance and increase toxicity. For reports of vascular toxicity and Raynaud's syndrome associated with the use of vinca alkaloids with bleomycin and other drugs see Effects on the Cardiovascular System, p. 727.2.

Antibacterials. Severe neurotoxicity has occurred when *isoniazid* was added to the regimen of a patient receiving vincristine.[1]

1. Carrión C, *et al*. Possible vincristine-isoniazid interaction. *Ann Pharmacother* 1995; **29:** 201.

Antiepileptics. A pharmacokinetic study showed that systemic clearance of vincristine was 63% higher when it was given with *phenytoin* or *carbamazepine*, two inducers of the cytochrome P450 isoenzyme CYP3A4. The clinical significance of this finding is unknown.[1]

1. Villikka K, *et al*. Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumours. *Clin Pharmacol Ther* 1999; **66:** 589–93.

Antifungals. Toxicity has been reported to be increased in children who received *itraconazole* with or without nifedipine during treatment involving vincristine.[1-4] Itraconazole is presumed to potentiate the toxicity of vincristine either by inhibition of cytochrome P450 isoenzymes, thus reducing the clearance of vincristine,[1-4] or by inhibiting the P-glycoprotein efflux pump,[2,3] and increasing intracellular concentrations of vincristine. Nifedipine also decreases the clearance of vincristine, by similar mechanisms,[1,3,4] and can theoretically further potentiate toxicity.

1. Murphy JA, *et al*. Vincristine toxicity in five children with acute lymphoblastic leukaemia. *Lancet* 1995; **346:** 443.
2. Jeng MR, Feusner J. Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2001; **18:** 137–42.
3. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. *Pediatr Hematol Oncol* 2001; **18:** 543–6.
4. Kamaluddin M, *et al*. Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. *Acta Paediatr* 2001; **90:** 1204–7.

Nifedipine. Vincristine toxicity may be potentiated by nifedipine, see Antifungals, above.

Pharmacokinetics

Vincristine is not reliably absorbed from the gastrointestinal tract. After intravenous injection it disappears rapidly from the blood. It is extensively protein bound and is reported to be concentrated in blood platelets. It is metabolised in the liver chiefly by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 and excreted mainly in the bile; about 70 to 80% of a dose is found in faeces, as unchanged drug and metabolites, while 10 to 20% appears in the urine. The terminal half-life is reported to be about 85 hours but may range from about 19 to 155 hours. Vincristine does not appear to cross the blood-brain barrier in significant amounts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vincesᵗ; ***Austral.***: Oncovinᵗ; ***Austria***: Oncovin; ***Belg.***: Oncovinᵗ; Vincrisin; ***Braz.***: Dabaz; Fauldvincri; Oncovin; Tecnocris; Vincizina; ***Chile***: Citomidᵗ; ***Denm.***: Oncovin; ***Fin.***: Oncovin; ***Fr.***: Oncovin; ***Ger.***: Cellcristin; Onkocristinᵗ; ***Gr.***: Oncovin; ***Hong Kong***: Vinracine; ***India***: Alcrist; Biocristin; Cytocristin; Neocristinᵗ; Oncocristin; ***Malaysia***: Vinracineᵗ; ***Mex.***: Citomidᵗ; Crivosinᵗ; Oncovin; Vintec; ***Philipp.***: Alcavixin; Nevexitinᵗ; Vinsulgen; ***Rus.***: Citomid (Цитомид); ***Singapore***: Vinracine; ***Spain***: Vincrisulᵗ; ***Swed.***: Oncovin; ***Switz.***: Oncovin; ***Thai.***: Citomidᵗ; VCS; ***Turk.***: Oncocristinᵗ; Oncovin; ***UK***: Oncovin; ***USA***: Marqibo; Oncovin; Vincasar PFS.

Pharmacopoeial Preparations
BP 2014: Vincristine Injection;
USP 36: Vincristine Sulfate for Injection; Vincristine Sulfate Injection.

Vindesine Sulfate *(BANM, USAN, rINNM)*

Compound 112531 (vindesine); Desacetyl Vinblastine Amide Sulfate; LY-099094; NSC-245467 (vindesine or vindesine sulfate); Sulfato de vindesina; Vindesiinisulfaatti; Vindesina, sulfato de; Vindésine, sulfate de; Vindesine Sulphate; Vindesini Sulfas; Vindesinsulfat; Vindesin-sulfát; Vindezino sulfatas; Vindezin-szulfát; Виндезина Сульфат.

3-Carbamoyl-4-*O*-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine sulfate.

$C_{43}H_{55}N_5O_7,H_2SO_4$=852.0

CAS — 53643-48-4 (vindesine); 59917-39-4 (vindesine sulfate).

ATC — L01CA03.

ATC Vet — QL01CA03.

UNII — CPH2U7DNDY.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Vindesine Sulfate). A white or almost white, hygroscopic, amorphous substance. Freely soluble in water and in methyl alcohol; practically insoluble in cyclohexane. The pH of a 0.5% solution in water is 3.5 to 5.5. Store in airtight polypropylene containers with a polypropylene cap, at a temperature not exceeding -50 degrees.

Uses and Administration

Vindesine sulfate is an antineoplastic agent derived from vinblastine (see p. 881.3); like the other vinca alkaloids it causes mitotic arrest in metaphase by binding to microtubular protein. It is used, alone or with other antineoplastics, in the treatment of refractory acute lymphoblastic leukaemia, blast crises of chronic myeloid leukaemia, malignant melanoma unresponsive to other therapy, and advanced carcinoma of the breast, unresponsive to surgery and/or hormonal therapy. See also the cross references given below.

Vindesine sulfate is given by **intravenous** injection. Care should be taken to avoid extravasation and the intravenous injection may be given over 1 to 3 minutes into a freely-running infusion (usually sodium chloride 0.9% or glucose 5%) if preferred. However, UK guidelines recommend that for adults and adolescents, the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% and infused intravenously over 5 to 10 minutes. (For adolescents treated in specialised paediatric units, see Administration in Children, below.) The usual starting dose of vindesine sulfate is 3 mg/m² which may be raised by increments of 500 micrograms/m² weekly providing that the granulocyte and platelet counts do not fall below 1500 cells/mm³ and 100 000 cells/mm³, respectively (see also Bone-marrow Depression, p. 730.3), and providing the patient has no acute abdominal pain; the maximum total weekly dose is 4 mg/m².

For doses in children, see below.

Blood counts should be made before each injection. It may be necessary to reduce initial doses in patients with significantly impaired hepatic function.

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in children. An initial dose of vindesine sulfate 4 mg/m² **intravenously** may be given to children for the treatment of acute lymphoblastic leukaemia (resistant to other drugs). This may be increased in weekly increments of 500 micrograms/m² providing granulocyte and platelet counts do not fall below acceptable levels and provided the patient has no acute abdominal pain. The weekly dose for children usually ranges between 4 and 5 mg/m².

UK guidelines state that doses of vinca alkaloids may be given via a syringe to children and adolescents treated in paediatric units.[1] For adolescents treated in adolescent or adult units, recommendations for administration are as for adults (see Uses and Administration, above).

1. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): usingvincaalkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Malignant neoplasms. Vindesine has been tried in refractory metastatic melanoma (p. 714.3), childhood acute lymphoblastic leukaemia (p. 692.3), chronic myeloid leukaemia in blastic crisis (p. 694.2), and neuroblastoma (p. 716.2). It is also under investigation in lung cancer, particularly non-small cell lung cancer (p. 710.2) and responses have been reported in advanced breast cancer (p. 702.1).

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1.

The main dose-limiting effect of vindesine is granulocytopenia, with the nadir of the white cell count usually occurring 3 to 5 days after a dose and recovery after a further 4 to 5 days. Although neurotoxicity occurs it may be less severe than that seen with vincristine (see p. 883.2). Alopecia is the most common adverse effect.

Folinic acid has been suggested for the treatment of overdosage by analogy with vincristine.

Vindesine should not be given by the intrathecal route, as this may produce fatal toxicity. Care should be taken if acute abdominal pain occurs: further doses may result in paralytic ileus.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* In a 10-year-old child accidentally given an intrathecal injection of vindesine, treatment with folinic acid and dexamethasone produced transient recovery but symptoms subsequently recurred and the patient died of progressive ascending paralysis.[1] The CNS showed changes at necropsy similar to those seen after intrathecal vincristine. Other fatal cases[2,3] have subsequently been reported. For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

1. Robbins G. Accidental intrathecal injection of vindesine. *BMJ* 1985; **291:** 1094.
2. Tournel G, *et al*. Fatal accidental intrathecal injection of vindesine. *J Forensic Sci* 2006; **51:** 1166–8.
3. Nisse P, *et al*. Administration accidentelle intrathécale de vindésine: à propos de 2 cas mortels. *Therapie* 2007; **62:** 360–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vindesine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/09/11)

Interactions

As for Vinblastine Sulfate, p. 882.2.

Pharmacokinetics

The pharmacokinetics of vindesine are similar to those of the other vinca alkaloids. After intravenous doses elimination from the blood is triphasic; the drug is rapidly distributed to body tissues. The terminal half-life is reported to be about 20 hours. It is metabolised mainly in the liver and excreted in bile and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Eldisin; ***Belg.***: Eldisine; ***China***: Ai De Xin (艾得新); Xi Ai Ke (西艾克); ***Fin.***: Eldisine; ***Fr.***: Eldisine; ***Ger.***: Eldisine; ***Gr.***: Eldisine; Enison; Gesidine; ***Irl.***: Eldisineᵗ; ***Ital.***: Eldisine; ***Port.***: Gesidineᵗ; ***Spain***: Enison; ***Swed.***: Eldisine; ***Switz.***: Eldisine; ***UK***: Eldisine.

Pharmacopoeial Preparations
BP 2014: Vindesine Injection.

Vinflunine *(BAN, rINN)*

F-12158; F-13840; L-0070; Vinflunina; Vinfluninum; Винфлунин.

4′-Deoxy-20′,20′-difluoro-8′-norvincaleukoblastine.

$C_{45}H_{54}F_2N_4O_8$=816.9

CAS — 162652-95-1.

ATC — L01CA05.
ATC Vet — QL01CA05.
UNII — 5BF646324K.

Vinflunine Tartrate *(rINNM)*

BMS-710485; F-12158; Tartrato de vinflunina; Vinflunine Ditartrate (BANM); Vinflunine Ditartrate (USAN); Vinflunine, Tartrate de; Vinflunini Tartras; Винфлунина Тартрат.

$C_{45}H_{54}F_2N_4O_8.2C_4H_6O_6$=1117.1

CAS — 194468-36-5.
ATC — L01CA05.
ATC Vet — QL01CA05.
UNII — 33MG53C7XW.

Uses and Administration

Vinflunine is a fluorinated vinca alkaloid derived from vinorelbine that has a similar antineoplastic action to vinblastine (p. 881.3). It is used in the treatment of advanced or metastatic bladder cancer (p. 700.2), as monotherapy after failure of a platinum-containing regimen. Vinflunine is given as the ditartrate but doses are expressed as the base; 1.37 mg of vinflunine ditartrate is equivalent to about 1 mg of vinflunine. It is given by **intravenous** infusion over 20 minutes, diluted in 100 mL sodium chloride 0.9% or glucose 5%, in a usual initial dose of vinflunine 320 mg/m² every 3 weeks. A lower initial dose of 280 mg/m² is given to patients with a performance status of 1 or less and prior pelvic irradiation; this can be increased thereafter to 320 mg/m² every 3 weeks in the absence of any toxicities.

Full blood counts should be monitored before each injection and the dose adjusted or delayed based on results; other toxicities may also affect the dose regimen (see Administration in Subsequent Cycles, below).

For dosage in patients with hepatic or renal impairment, see below.

Vinflunine is also being investigated in other neoplasms including non-small cell lung cancer and breast cancer.

References.
1. Bellmunt J, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009; **27:** 4454–61. Correction. *ibid.* 2010; **28:** 182.
2. Jordan MA, *et al.* Exploring the mechanisms of action of the novel microtubule inhibitor vinflunine. *Semin Oncol* 2008; **35** (suppl 3): S6–S12.
3. Bellmunt J, *et al.* Clinical activity of vinflunine in transitional cell carcinoma of the urothelium and other solid tumors. *Semin Oncol* 2008; **35** (suppl 3): S34–S43.
4. Lobert S, Puozzo C. Pharmacokinetics, metabolites, and preclinical safety of vinflunine. *Semin Oncol* 2008; **35** (suppl 3): S28–S33.

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in hepatic impairment. The dose of vinflunine should be reduced in patients with hepatic impairment, according to Child Pugh class or based on prothrombin time, bilirubin, transaminase, and gamma glutamyl transferase (GGT) values.

The usual intravenous dose of vinflunine 320 mg/m² every 3 weeks is given to patients with the following hepatic parameters:
- prothrombin time > 70% of the normal value
  and
- bilirubin > the upper limit of normal (ULN) and ≤ 1.5 times the ULN
  and/or
- transaminases > 1.5 times the ULN and ≤ 2.5 times the ULN
  and/or
- GGT > the ULN and ≤ 5 times the ULN

A reduced intravenous dose of 250 mg/m² every 3 weeks is given to those with hepatic impairment defined as:
- Child Pugh class A
  or
- prothrombin time ≥ 60% of the normal value
  and
- bilirubin > 1.5 times the ULN and ≤ 3 times the ULN
  and
- transaminases > the ULN
  and/or
- GGT > 5 times the ULN

A reduced intravenous dose of 200 mg/m² every 3 weeks is given to those with hepatic impairment defined as:
- Child Pugh class B
  or
- prothrombin time ≥ 50% of the normal value
  and
- bilirubin > 3 times the ULN
  and
- transaminases > the ULN
  and
- GGT > the ULN

Vinflunine has not been studied in patients with Child Pugh class C, or in those with a prothrombin time < 50% of the normal value or with bilirubin > 5 times the ULN or with transaminases > 6 times the ULN or with GGT > 15 times the ULN.

Administration in renal impairment. The dose of vinflunine should be reduced in patients with renal impairment. UK licensed product information recommends the following based on creatinine clearance (CC):
- CC > 60 mL/min: usual intravenous dose of vinflunine 320 mg/m² every 3 weeks
- CC 40 to 60 mL/min: 280 mg/m² every 3 weeks
- CC 20 to 39 mL/min: 250 mg/m² every 3 weeks
- CC < 20 mL/min: not specified

Administration in subsequent cycles. Complete blood counts should be performed in all patients given vinflunine. Patients should not begin a new cycle if their absolute neutrophil count (ANC) is < 1000 cells/mm³ or if platelets are < 100 000 cells/mm³; treatment should be delayed until blood counts reach these levels or above. If recovery has not occurred within 2 weeks, treatment should be permanently stopped.

Dose adjustments are required for the following toxicities:
- grade 4 neutropenia (ANC < 500 cells/mm³) for > 7 days
- febrile neutropenia (ANC < 1000 cells/mm³ and fever ≥ 38.5 degrees)
- grade 2 mucositis or constipation for ≥ 5 days, or ≥ grade 3 for any duration
- any other toxicity that is ≥ grade 3, except grade 3 nausea or vomiting

If one of the above toxicities occurs in a patient whose initial intravenous dose of vinflunine was 320 mg/m² (the usual initial dose), a reduced dose of vinflunine 280 mg/m² is given. This is further reduced to 250 mg/m² if a toxicity occurs again in the next cycle; treatment should be permanently stopped for toxicities occurring in 3 consecutive cycles.

If one of the above toxicities occurs in a patient whose initial intravenous dose of vinflunine was 280 mg/m², a reduced dose of 250 mg/m² is given; treatment should be permanently stopped for toxicities occurring in 2 consecutive cycles.

For organ toxicity that is ≥ grade 2 on the day the next vinflunine dose is due, treatment should be delayed until recovery to ≤ grade 1.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1.

The main dose-limiting effect of vinflunine is neutropenia, and the dose should be adjusted according to regular blood counts. Use is contra-indicated in patients with a baseline absolute neutrophil count < 1500 cells/mm³ or a platelet count < 100 000 cells/mm³. Gastrointestinal adverse effects are also common; regular laxatives are recommended to prevent constipation. Other adverse effects include musculoskeletal adverse effects such as pain, myalgia, and arthralgia, and cardiovascular effects such as QT prolongation, tachycardia, ischaemia, and myocardial infarction; vinflunine should be used with caution in patients with pre-existing cardiac disease, or those with risk factors for QT prolongation. It should also not be given with other medicines that prolong the QT interval, or with potent inhibitors or inducers of the cytochrome P450 isoenzyme CYP3A4 (see under Interactions, below). Patients with hepatic or renal impairment may need a reduced dose of vinflunine (see under Uses, above and above).

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Vinflunine is metabolised by the cytochrome P450 isoenzyme CYP3A4; exposure to vinflunine or its active metabolite 4-*O*-deacetyl-vinflunine (DVFL) may be affected by inhibitors or inducers of this enzyme and their use with vinflunine is not recommended.

Caution is required when vinflunine is used with pegylated or liposomal doxorubicin, as exposure to vinflunine was increased and exposure to doxorubicin decreased with this combination. *In vitro* data have suggested that this could be due to adsorption of vinflunine on the liposomes and a change in the distribution of both drugs in the blood.

Vinflunine should not be given with other medicines that prolong the QT interval.

Pharmacokinetics

Vinflunine is moderately bound to plasma proteins, mainly high-density lipoproteins and serum albumin, and it is extensively distributed into the tissues. The main metabolite of vinflunine is 4-*O*-deacetyl-vinflunine (DVFL), which has some antineoplastic activity and is formed by multiple esterases. All other metabolites are inactive and are formed by the cytochrome P450 isoenzyme CYP3A4. Vinflunine has a terminal elimination half-life of about 40 hours, while DVFL is eliminated more slowly, with a half-life of about 120 hours. Excretion occurs via the faeces (about two-thirds) and the urine (about one-third).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Javlor; ***Cz.***: Javlor; ***Denm.***: Javlor; ***Fr.***: Javlor; ***Ger.***: Javlor; ***Gr.***: Javlor; ***Irl.***: Javlor; ***Israel***: Javlor; ***Ital.***: Javlor; ***Neth.***: Javlor; ***Norw.***: Javlor; ***Pol.***: Javlor; ***Port.***: Javlor; ***Spain***: Javlor; ***Swed.***: Javlor; ***UK***: Javlor.

Vinorelbine Tartrate *(BANM, USAN, rINNM)*

Tartrato de vinorelbina; Vinorelbiinitartraatti; Vinorelbin Bitartrat; Vinorelbina, tartrato de; Vinorelbin-ditartarát; Vinorelbine Ditartrate; Vinorelbine, tartrate de; Vinorelbini Ditartras; Vinorelbini Tartras; Vinorelbino tartratas; Vinorelbintartrat; Винорелбина Тартрат; 5′-Nor-anhydrovinblastine Tartrate.

3′,4′-Didehydro-4′-deoxy-8′-norvincaleukoblastine ditartrate.

$C_{45}H_{54}N_4O_8.2C_4H_6O_6$=1079.1

CAS — 71486-22-1 (vinorelbine); 125317-39-7 (vinorelbine tartrate).
ATC — L01CA04.
ATC Vet — QL01CA04.
UNII — 253GQW851Q.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Vinorelbine Tartrate). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in hexane. A 1.4% solution in water has a pH of 3.3 to 3.8. Store under an inert gas at a temperature not exceeding -15 degrees. Protect from light.

USP 36: (Vinorelbine Tartrate). A white to yellow or light brown amorphous powder. Freely soluble in water. pH of a 1% solution in water is between 3.3 and 3.8. Store at a temperature between -25 degrees and -10 degrees in airtight containers. Protect from light.

Uses and Administration

Vinorelbine is a semisynthetic vinca alkaloid with antineoplastic activity similar to vinblastine (p. 881.3). It is used, alone or with other antineoplastics, in the first-line treatment of non-small cell lung cancer (p. 710.2) and in the treatment of advanced breast cancer (p. 702.1) that has relapsed or is refractory to an anthracycline-containing regimen.

Vinorelbine is given as the tartrate but doses are calculated in terms of vinorelbine: vinorelbine tartrate 1.385 mg is equivalent to about 1 mg of vinorelbine. Vinorelbine may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

It may be given by **intravenous** injection over 5 to 10 minutes, as a solution containing the equivalent of vinorelbine 1.5 to 3 mg/mL in glucose 5% or sodium chloride 0.9% injection, into a freely-running intravenous infusion. However, UK guidelines recommend that the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% or glucose 5% and infused intravenously over 5 to 10 minutes. It may also be given by intravenous infusion over 20 to 30 minutes after dilution in 125 mL of glucose 5% or sodium chloride 0.9%.

The usual initial intravenous dose in the treatment of breast cancer or non-small cell lung cancer is the equivalent of vinorelbine 25 to 30 mg/m² (maximum 60 mg) once weekly. Doses may be adjusted or delayed based on blood counts (see Administration in Subsequent Cycles, p. 886.1).

The drug is also given **orally** as a single agent in a dose of 60 mg/m² (maximum 120 mg) once weekly for 3 weeks. Subsequent doses may be increased to 80 mg/m² (maximum 160 mg), based on neutrophil counts (see Administration in Subsequent Cycles, p. 886.1). The dose and schedule may vary in combination regimens.

For dosage in patients with hepatic impairment or with massive liver metastases, see p. 886.1.

References.
1. Gregory RK, Smith IE. Vinorelbine—a clinical review. *Br J Cancer* 2000; **82:** 1907–13.
2. Sarris AH, *et al*. Infusional vinorelbine in relapsed or refractory lymphomas. *Leuk Lymphoma* 2000; **39:** 291–9.
3. Sorensen P, *et al*. Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. *Gynecol Oncol* 2001; **81:** 58–62.
4. Oudard S, *et al*. Phase II study of vinorelbine in patients with androgen-independent prostate cancer. *Ann Oncol* 2001; **12:** 847–52.
5. Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. *Clin Breast Cancer* 2001; **2:** 113–28.
6. Aapro MS, *et al*. Developments in cytotoxic chemotherapy: advances in treatment utilising vinorelbine. *Crit Rev Oncol Hematol* 2001; **40:** 251–63.
7. Freyer G, *et al*. Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 2003; **21:** 35–40.
8. Gebbia V, Puozzo C. Oral versus intravenous vinorelbine: clinical safety profile. *Expert Opin Drug Safety* 2005; **4:** 915–28.
9. Aapro MS, *et al*. Oral vinorelbine: role in the management of metastatic breast cancer. *Drugs* 2007; **67:** 657–67.
10. Gralla RJ, *et al*. Oral vinorelbine in the treatment of non-small cell lung cancer: rationale and implications for patient management. *Drugs* 2007; **67:** 1403–10.
11. Bonneterre J, Penel N. Vinorelbine in breast cancer. *Expert Opin Pharmacother* 2008; **9:** 2901–10.
12. Piccirillo MC, *et al*. Vinorelbine for non-small cell lung cancer. *Expert Opin Drug Safety* 2010; **9:** 493–510.

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in the elderly. UK licensed product information states that, while no relevant differences in response rates to vinorelbine have been seen in the elderly, greater sensitivity of some older patients cannot be ruled out; age is stated to not affect the pharmacokinetics of vinorelbine. A review[1] found conflicting data on the effect of age on pharmacokinetics of intravenous vinorelbine, yet concluded that no dose modification was required on the basis of age.

1. Lichtman SM, *et al*. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.

Administration in hepatic impairment. Clearance of intravenous vinorelbine was markedly reduced in patients with diffuse liver metastases and hence severely altered hepatic function: a 50% dose reduction was probably appropriate in such patients even if hyperbilirubinaemia was not marked.[1] However, reduced doses were not necessary in patients with moderate liver involvement in whom liver function, as measured by lidocaine metabolism, was not markedly reduced. Others have also confirmed that doses need not be reduced in mild to moderate hepatic impairment.[2]

Licensed product information in the UK suggests that the *intravenous* dose be reduced by one-third in patients with severe hepatic impairment (defined as bilirubin greater than twice the upper limit of normal (ULN) and/or transaminases greater than five times the ULN), or in those with massive liver metastases (more than 75% of liver volume replaced by tumour cells). In the USA, licensed product information recommends that the intravenous dose of vinorelbine be reduced by 50% in patients with total bilirubin values of 2.1 to 3 mg per 100 mL and by 75% in those with total bilirubin greater than 3 mg per 100 mL.

UK licensed product information recommends the following *oral* weekly doses of vinorelbine for patients with hepatic impairment:
- mild (bilirubin less than 1.5 times the ULN and transaminases from 1.5 to 2.5 times the ULN): 60 mg/m² (the standard dose)
- moderate (bilirubin 1.5 to 3 times the ULN): 50 mg/m²
- severe: use is contra-indicated

1. Robieux I, *et al*. Pharmacokinetics of vinorelbine in patients with liver metastases. *Clin Pharmacol Ther* 1996; **59:** 32–40.
2. Kitzen JJ, *et al*. Mild to moderate liver dysfunction does not require dose reduction of oral or intravenous vinorelbine: results of a pharmacokinetic study. *Eur J Cancer* 2010; **46:** 266–9.

Administration in subsequent cycles. Use of vinorelbine is contra-indicated if blood counts fall below acceptable levels.

In the UK, **intravenous** use is contra-indicated if platelet counts are less than 75 000 cells/mm³, or if neutrophils are less than 1500 to 2000 cells/mm³ (this varies slightly according to manufacturer), and treatment is delayed until recovery.

In the USA, dose adjustments (expressed as a percentage of the starting dose) are based on granulocyte counts as follows:
- ⩾ 1500 cells/mm³: 100%
- 1000 to 1499 cells/mm³: 50%
- < 1000 cells/mm³: dose should be omitted. Granulocyte counts are repeated in 1 week; if 3 consecutive counts are below this value, vinorelbine therapy should be stopped

For patients who, during treatment, had fever and/or sepsis while granulocytopenic, or had 2 consecutive weekly doses not given due to granulocytopenia, subsequent doses (expressed as a percentage of the starting dose) are:
- ⩾ 1500 cells/mm³: 75%
- 1000 to 1499 cells/mm³: 37.5%
- < 1000 cells/mm³: dose should be omitted. Granulocyte counts are repeated in 1 week, and if 3 consecutive weekly doses cannot be given, vinorelbine should be stopped altogether

For **oral** therapy, use is also contra-indicated if platelet counts are less than 75 000 cells/mm³ or if neutrophil counts are less than 1500 cells/mm³. For the recommended initial 3 doses, see Uses and Administration, p. 885.3. Subsequent doses are based on neutrophil counts. The recommended dose for the fourth week based on the neutrophil count during the first 3 doses (of 60 mg/m² weekly) is as follows:
- > 1000 cells/mm³: 80 mg/m²
- ⩾ 500 and < 1000 cells/mm³(1 episode): 80 mg/m²
- ⩾ 500 and < 1000 cells/mm³(2 episodes): 60 mg/m²
- < 500 cells/mm³: 60 mg/m²

Similarly, for any dose thereafter planned to be given as 80 mg/m², if the neutrophil count is below 1500 cells/mm³ and/or the platelet count is between 75 000 and 100 000 cells/mm³, then the treatment should be delayed until recovery. If the neutrophil count is below 500 cells/mm³ or more than once is between 500 and 1000 cells/mm³, the dose should be delayed until recovery and the dose reduced from 80 to 60 mg/m² weekly for the next 3 doses.

It is possible to re-escalate the weekly dose from 60 to 80 mg/m² if the neutrophil count did not drop below 500 cells/mm³, or to between 500 and 1000 cells/mm³ more than once, during 3 doses given at 60 mg/m².

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1. The main dose-limiting effect of vinorelbine is neutropenia. The nadir of the neutrophil count occurs 5 to 10 days after a dose, with recovery usually after a further 7 to 14 days. The drug should be stopped if moderate or severe neurotoxicity develops. Other common adverse effects include taste disorders, dysphagia, insomnia, visual disorders, hypotension, cough, genito-urinary disorders such as dysuria, and chills. Severe hyponatraemia may occur. Local pain and thrombophlebitis may be seen with repeated injection of vinorelbine. Gastrointestinal effects such as nausea and vomiting are common with the oral formulation; giving capsules with food may reduce the incidence, and prophylaxis with antiemetics is recommended. Capsules should not be opened or chewed as the contents are irritant.

Care should be taken when using vinorelbine in patients with a history of ischaemic heart disease. Vinorelbine should not be given with radiotherapy if the treatment field includes the liver, and its use is contra-indicated in severe hepatic impairment, see Administration in Hepatic Impairment, above.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

Effects on the gastrointestinal tract. For reference to a report of vinorelbine possibly exacerbating ischaemic colitis in patients receiving docetaxel, see p. 781.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vinorelbine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/09/11)

Interactions

As for Vinblastine Sulfate, p. 882.2. Vinorelbine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with strong inhibitors or inducers of CYP3A4 may affect exposure to vinorelbine; caution is advised.

Antibacterials. A retrospective cohort study in Japan[1] found that patients given *clarithromycin* with vinorelbine were at greater risk for severe neutropenia than those given vinorelbine alone.

1. Yano R, *et al*. Evaluation of potential interaction between vinorelbine and clarithromycin. *Ann Pharmacother* 2009; **43:** 453–8.

Pharmacokinetics

As with the other vinca alkaloids, vinorelbine exhibits triphasic pharmacokinetics after intravenous injection. Vinorelbine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur 1.5 to 3 hours after oral doses. The absolute bioavailability is about 40%; food does not alter exposure to vinorelbine. Comparable blood concentrations occur with oral vinorelbine doses of 60 and 80 mg/m² and intravenous doses of 25 and 30 mg/m², respectively. Vinorelbine is extensively distributed, especially into pulmonary tissues; however, it is not found in the CNS. Binding to plasma proteins is 13.5% but it is strongly bound to blood cells; binding to platelets is about 78%. Vinorelbine is metabolised via the cytochrome P450 isoenzyme CYP3A4. The metabolite 4-*O*-deacetylvinorelbine (deacetylvinorelbine), which has antineoplastic activity, is thought to be formed by carboxylesterases. The mean terminal half-life of vinorelbine is about 40 hours. Vinorelbine and its metabolites are excreted mainly in faeces via the bile but a small amount (less than 20% of a dose) is found in the urine, largely as unchanged drug.

References.
1. Levêque D, Jehl F. Clinical pharmacokinetics of vinorelbine. *Clin Pharmacokinet* 1996; **31:** 184–97.
2. Marty M, *et al*. Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors. *Ann Oncol* 2001; **12:** 1643–9.
3. Bugat R, *et al*. The effects of food on the pharmacokinetic profile of oral vinorelbine. *Cancer Chemother Pharmacol* 2002; **50:** 285–90.
4. Variol P, *et al*. A simultaneous oral/intravenous population pharmacokinetic model for vinorelbine. *Eur J Clin Pharmacol* 2002; **58:** 467–76.
5. Wong M, *et al*. Predictors of vinorelbine pharmacokinetics and pharmacodynamics in patients with cancer. *J Clin Oncol* 2006; **24:** 2448–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Filcrin; Navelbine; Neocitec; Sulcoline; Vilne; Vinarine; Vinkebir; Vinorel; Vinorgen; ***Austral.***: Navelbine; ***Austria***: Eberelbin; Navelbine; ***Belg.***: Navelbine; ***Braz.***: Evotabina; Navelbine; Neocitec; Norelbin; Oncobine; Tevavinor; ***Canad.***: Navelbine; ***Chile***: Navelbine; ***China***: Ai Ke Ning (艾克宁); Gai Nuo (盖诺); Jie Bin (杰宾); Kang Neng (康能); LeWei (乐唯); Min Nuo Bin (民诺宾); Navelbine (诺维本); Rui Ze (瑞择); Sui Bin (穗宾); Tai Bin (泰宾); ***Cz.***: Navelbine; Navirel; Nibrevin†; Oncobine; ***Denm.***: Navelbine; Navirel; ***Fin.***: Navelbine; Navirel; ***Fr.***: Navelbine; ***Ger.***: Bendarelbin; Navelbine; Navin; Navirel; ***Gr.***: Eunades; Navelbine; Zaolin; ***Hong Kong***: Navelbine; ***Hung.***: Navelbine; ***India***: Navelbine; Vinelbine; ***Indon.***: Navelbine; ***Irl.***: Navelbine; ***Israel***: Navelbine; ***Ital.***: Navelbine; ***Jpn***: Navelbine; ***Malaysia***: Navelbine; ***Mex.***: Bagovir†; Navelbine; Navildez; Vieby; Viessia; Vinilex; ***Neth.***: Navelbine; Navirel; ***Norw.***: Navelbine; Navirel; ***NZ***: Navelbine; ***Philipp.***: Navelbine; Vinotel; ***Pol.***: Navelbine; Navirel; ***Port.***: Navelbine; Navirel; Vinorel; ***Rus.***: Maverex (Маверекс); Navelbine (Навельбин); Velbin (Велбин); Vincatera (Винкатера); Vinelbin (Винельбин); ***S.Afr.***: Carcyt; Navelbine; Vinorel; ***Singapore***: Navelbine; ***Spain***: Navelbine; ***Swed.***: Navelbine; Navirel; ***Switz.***: Navelbine; ***Thai.***: Navelbine; Viessia; Vinelbine†; ***Turk.***: Navelbine; Renovel; ***UK***: Navelbine; ***Ukr.***: Navelbine (Навельбин); ***USA***: Navelbine.

Pharmacopoeial Preparations
USP 36: Vinorelbine Injection.

Vismodegib *(rINN)*

GDC-0449; RG-3616; Vismodégib; Vismodegibum; Висмодегиб.

2-Chloro-*N*-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methanesulfonyl)benzamide.

$C_{19}H_{14}Cl_2N_2O_3S$=421.3

CAS — 879085-55-9.

ATC — L01XX43.

ATC Vet — QL01XX43.

UNII — 25X868M3DS.

Uses and Administration

Vismodegib is an orally active hedgehog pathway inhibitor that is used for the treatment of basal cell carcinoma (p. 714.2).

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Vismodegib is used to treat patients with metastatic basal cell carcinoma, or with locally advanced disease that has recurred after surgery or who are not candidates for surgery, and who are not candidates for radiation. It is given in a dose of 150 mg once daily until there is disease progression or unacceptable toxicity. If a dose is missed it should be omitted and the next dose taken as scheduled. Capsules should be swallowed whole, and not opened or crushed.

References.
1. De Smaele E, *et al*. Vismodegib, a small-molecule inhibitor of the hedgehog pathway for the treatment of advanced cancers. *Curr Opin Investig Drugs* 2010; **11:** 707–18.
2. Graham RA, *et al*. Pharmacokinetics of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors: the role of alpha-1-acid glycoprotein binding. *Clin Cancer Res* 2011; **17:** 2512–20.
3. Metcalfe C, de Sauvage FJ. Hedgehog fights back: mechanisms of acquired resistance against Smoothened antagonists. *Cancer Res* 2011; **71:** 5057–61.

4. Lorusso PM, *et al.* Pharmacokinetic dose-scheduling study of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors. *Clin Cancer Res* 2011; **17:** 5774–82.

Adverse Effects and Precautions

The most common adverse effects of vismodegib are muscle spasms, arthralgias, alopecia, fatigue, gastrointestinal disturbances, taste disturbances, reduced appetite, and weight loss. Amenorrhoea has been reported in some premenopausal women. Hyponatraemia, hypokalaemia, and azotaemia have also been found in some patients given vismodegib.

Vismodegib is expected to cause embryo-fetal death and severe birth defects, based on its mechanism of action and *animal* studies. Pregnancy should be excluded before starting vismodegib in female patients and highly effective contraception used during and for 7 months after therapy. The same potential risks apply to female partners of male patients, who can be exposed to vismodegib in semen; condoms with spermicide should be used, even after vasectomy, during and for 2 months after stopping vismodegib therapy.

Patients should also be advised not to donate blood or blood products during therapy and for 7 months after stopping vismodegib.

Interactions

The solubility of vismodegib is pH dependent and drugs that affect gastric pH, such as antacids, histamine H_2-antagonists, and proton pump inhibitors, may reduce its bioavailability. Drugs that inhibit P-glycoprotein might increase systemic exposure to vismodegib.

Pharmacokinetics

Vismodegib is absorbed from the gastrointestinal tract, but with an absolute bioavailability of only about 32% after a single dose. It is highly bound to plasma proteins. Vismodegib is excreted mainly as unchanged drug via the liver; about 82% of a dose is eliminated in the faeces and about 4.4% in the urine. The elimination half-life is about 12 days after a single dose, but 4 days after continuous once-daily dosing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Erivedge; ***UK***: Erivedge; ***USA***: Erivedge.

Vitespen *(USAN)*

gp-96; HSPPC-96.
Glucose regulated protein 94 (grp 94); Endoplasmin (human tumor rejection antigen 1).
CAS — 492448-75-6.
UNII — H3598Y1TLJ.

NOTE. The name Oncophage has been used as a trade mark for vitespen.

Profile

Vitespen is a personalised cancer vaccine (p. 757.3) prepared from heat shock glycoprotein 96 and associated peptides isolated from the patient's tumour, that stimulates an immune response to tumour cells. It is under investigation for the treatment of renal cell carcinoma, metastatic melanoma, and various other solid neoplasms.

References.

1. Wood C, *et al.* C-100-12 RCC Study Group. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet* 2008; **372:** 145–54.
2. di Pietro A, *et al.* Oncophage: step to the future for vaccine therapy in melanoma. *Expert Opin Biol Ther* 2008; **8:** 1973–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Oncophage (Онкофаг).

Vosaroxin *(USAN, rINN)*

AG-7352; SNS-595; SPC-595; Voreloxin; Vosaroxina; Vosaroxine; Vosaroxinum; Ворелоксин.
(+)-7-[(3*S*,4*S*)-3-Methoxy-4-(methylamino)pyrrolidin-1-yl]-4-oxo-1-(thiazol-2-yl)-1,4-dihydro-1,8-napthyridine-3-carboxylic acid.
$C_{18}H_{19}N_5O_4S$=401.4
CAS — 175414-77-4.
UNII — K6A90IIZ19.

Profile

Vosaroxin is a quinolone derivative that inhibits topoisomerase II. It is under investigation for its antineoplastic properties in the treatment of malignant neoplasms such as acute myeloid leukemia and ovarian cancer.

References.

1. Advani RH, *et al.* Voreloxin, a first-in-class anticancer quinolone derivative, in relapsed/refractory solid tumors: a report on two dosing schedules. *Clin Cancer Res* 2010; **16:** 2167–75.
2. Hawtin RE, *et al.* Voreloxin is an anticancer quinolone derivative that intercalates DNA and poisons topoisomerase II. *PLoS One* 2010; **5:** e10186.
3. Krug LM, *et al.* Phase II multicenter trial of voreloxin as second-line therapy in chemotherapy-sensitive or refractory small cell lung cancer. *J Thorac Oncol* 2011; **6:** 384–6.

Vorinostat *(USAN, rINN)*

SAHA; Suberoylanilide Hydroxamic Acid; Vorinostatum; Вориностат.
N-Hydroxy-*N'*-phenyl octanediamide.
$C_{14}H_{20}N_2O_3$=264.3
CAS — 149647-78-9.
ATC — L01XX38.
ATC Vet — QL01XX38.
UNII — 58IFB293JI.

Uses and Administration

Vorinostat is a histone deacetylase inhibitor used for the treatment of cutaneous T-cell lymphoma (see Non-Hodgkin's Lymphomas, p. 696.3). The recommended dose is 400 mg orally, given once daily with food. This may be reduced to 300 mg once daily, with a further reduction to 300 mg once daily for 5 consecutive days of each week, if needed. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Vorinostat is also under investigation for the treatment of multiple myeloma and mesothelioma.

References.

1. O'Connor OA. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *J Clin Oncol* 2006; **24:** 166–73.
2. Krug LM, *et al.* Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. *Clin Lung Cancer* 2006; **7:** 257–61.
3. Richon VM. Cancer biology: mechanism of antitumour action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor. *Br J Cancer* 2006; **95** (suppl): S2–S6.
4. O'Connor OA. Clinical experience with the novel histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in patients with relapsed lymphoma. *Br J Cancer* 2006; **95** (suppl): S7–S12.
5. Duvic M, Zhang C. Clinical and laboratory experience of vorinostat (suberoylanilide hydroxamic acid) in the treatment of cutaneous T-cell lymphoma. *Br J Cancer* 2006; **95** (suppl): S13–S19.
6. Anonymous. Vorinostat (Zolinza) for cutaneous T-Cell lymphoma. *Med Lett Drugs Ther* 2007; **49:** 23–4.
7. Duvic M, Vu J. Vorinostat: a new oral histone deacetylase inhibitor approved for cutaneous T-cell lymphoma. *Expert Opin Invest Drugs* 2007; **16:** 1111–20.
8. Richon VM, *et al.* Development of vorinostat: current applications and future perspectives for cancer therapy. *Cancer Lett* 2009; **280:** 201–10.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of vorinostat are gastrointestinal disturbances, fatigue, chills, dry mouth and taste disorders. Thrombocytopenia and anaemia are also common, and are dose-related; dose reductions may be necessary and in some instances, therapy may need to be stopped. Pulmonary embolism and deep-vein thrombosis have occurred. Other adverse effects include muscle spasms, alopecia, dizziness, peripheral oedema, headache, pruritus, cough, upper respiratory-tract infection, and pyrexia. Increases in serum creatinine, hypokalaemia, and hyperglycaemia have been reported, as has prolongation of the QT interval. Blood cell counts, electrolytes, glucose, and serum creatinine should be monitored every 2 weeks during the first 2 months of therapy and monthly thereafter.

Interactions

Severe thrombocytopenia and gastrointestinal bleeding have been reported when vorinostat has been given with other histone deacetylase inhibitors such as valproic acid; platelet counts should be monitored every 2 weeks for the first 2 months of therapy. Vorinostat may prolong prothrombin time and affect the INR in patients receiving coumarin anticoagulants.

Pharmacokinetics

After an oral dose of vorinostat with a high-fat meal, mean time to peak plasma concentration was about 4 hours; this was reduced to 1.5 hours after fasting. Aside from this decrease in the rate of absorption, a high-fat meal also increased the extent of absorption. While these results were stated not to be clinically significant, licensed product information recommends that vorinostat be taken with food. Plasma protein binding is about 71%. Vorinostat is metabolised by glucuronidation and hydrolysis followed by oxidation; metabolites are pharmacologically inactive. Less than 1% of a dose is recovered in the urine as unchanged drug. The mean terminal half-life is about 2 hours for vorinostat.

References.

1. Rubin EH, *et al.* A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res* 2006; **12:** 7039–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zolinza; ***Canad.***: Zolinza; ***Gr.***: Zolinza; ***Jpn***: Zolinza; ***USA***: Zolinza.

Zalutumumab *(USAN, rINN)*

2F8; HuMax-EGFr; Zalutumumabum; Залутумумаб.
Immunoglobulin G1, anti-(human epidermal growth factor receptor)(human monoclonal 2F8 heavy chain), disulfide with human monoclonal 2F8 κ-chain, dimer.
CAS — 667901-13-5.

Profile

Zalutumumab is a human monoclonal antibody targeted at the epidermal growth factor receptor (EGFR). EGFR is found on the surface of many cancer cells, and activation thereof promotes tumour cell growth. Zalutumumab is under investigation for the treatment of head and neck cancer.

References.

1. Rivera F, *et al.* Current situation of zalutumumab. *Expert Opin Biol Ther* 2009; **9:** 667–74.

Zibotentan *(USAN, rINN)*

ZD-4054; Zibotentán; Zibotentanum; Зиботентан.
N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide.
$C_{19}H_{16}N_6O_4S$=424.4
CAS — 186497-07-4.
UNII — 8054MM4902.

Profile

Zibotentan is an endothelin-A receptor antagonist that is under investigation for the treatment of hormone-resistant prostate cancer and other solid tumours, although initial results have been disappointing.

References.

1. Morris CD, *et al.* Specific inhibition of the endothelin A receptor with ZD4054: clinical and pre-clinical evidence. *Br J Cancer* 2005; **92:** 2148–52.
2. Warren R, Liu G. ZD4054: a specific endothelin A receptor antagonist with promising activity in metastatic castration-resistant prostate cancer. *Expert Opin Invest Drugs* 2008; **17:** 1237–45.

Zinostatin *(USAN, rINN)*

Neocarzinostatin; NSC-69856; NSC-157365; Zinostatina; Zinostatine; Zinostatinum; Зиностатин.
CAS — 9014-02-2.
UNII — PP082U6W1L.

Description. Zinostatin is an antineoplastic antibiotic obtained from *Streptomyces carzinostaticus.*

Pharmacopoeias. *Jpn* includes zinostatin stimalamer.

Profile

Zinostatin is an antibiotic with antineoplastic activity and has been used in the treatment of malignant neoplasms.

Zinostatin stimalamer, a conjugate of zinostatin with a styrene-maleic acid polymer, is given by hepatic intra-arterial injection for the treatment of liver cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: SMANCS.

Zorubicin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de zorubicina; NSC-164011; RP-22050 (zorubicin); Zorubicina, hidrocloruro de; Zorubicine, Chlorhydrate de; Zorubicini Hydrochloridum; Зорубицина Гидрохлорид.

Benzoic acid (2*S*-*cis*)-{1-[4-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxonaphthacen-2-yl]ethylidene}hydrazide hydrochloride.

$C_{34}H_{35}N_3O_{10}$,HCl=682.1

CAS — 54083-22-6 (zorubicin); 36508-71-1 (zorubicin hydrochloride).

ATC — L01DB05.

ATC Vet — QL01DB05.

UNII — WXM8D9M6DE.

Profile

Zorubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (see p. 782.3). It has been used as the hydrochloride in the treatment of acute leukaemias.

Antiparkinsonian Drugs

The antiparkinsonian drugs described in this chapter can be broadly divided into 2 groups; the **dopaminergics**, drugs that are used to potentiate the actions of dopamine, and the **antimuscarinics**, drugs that are used to reduce excessive central cholinergic effects.

Dopamine is a key neurotransmitter in the CNS; in particular, striatal dopamine depletion is associated with the clinical condition of parkinsonism. Dopamine also inhibits prolactin release from the pituitary and is believed to be the prolactin-release inhibiting factor (PRIF or PIF); dopamine deficiency in the pituitary is associated with conditions characterised by hyperprolactinaemia. Accordingly, drugs that replenish central dopamine or that can act as stimulants of dopamine receptors (dopamine agonists), may alleviate the symptoms of parkinsonism (see below), hyperprolactinaemia (p. 2252.2), and related disorders.

At least 5 subtypes of dopamine receptor are thought to exist: D_1 receptors appear to stimulate adenylate cyclase activity; D_2 receptors activate various systems and inhibit adenylate cyclase activity. D_3, D_4, and D_5 receptors have been less well studied but D_3 and D_4 are similar to D_2, forming the D_2-like group, whereas D_1 and D_5 form the D_1-like group. D_2 receptors have been implicated in the pathophysiology of parkinsonism and schizophrenia.

Dopaminergics, or drugs that enhance their actions, described in this chapter include:

- levodopa, which is converted by decarboxylation into dopamine in the body, and which, unlike dopamine itself, can penetrate the blood-brain barrier and supply a source of dopamine to the brain
- the peripheral dopa-decarboxylase inhibitors, benserazide and carbidopa, which have no dopaminergic action of their own but increase the availability of levodopa
- apomorphine, which is structurally related to dopamine and acts as a dopamine agonist
- the adamantanamine, amantadine, which may augment dopaminergic activity
- the ergot derivatives, bromocriptine, cabergoline, lisuride, and pergolide, which act as dopamine agonists
- various other non-ergot dopamine agonists, such as piribedil, pramipexole, ropinirole, rotigotine, talipexole, and terguride
- the specific monoamine oxidase type B inhibitors, rasagiline and selegiline, which enhance the action of dopamine and levodopa
- the catechol-*O*-methyltransferase inhibitors (COMT-inhibitors), entacapone and tolcapone, which enhance the action of levodopa

Antimuscarinic drugs are used in Parkinson's disease (idiopathic or primary parkinsonism) and, particularly, drug-induced parkinsonism. They act by reducing the excessive central cholinergic effects of dopamine deficiency. Antimuscarinics described in this chapter include the tertiary amines, such as benzatropine, orphenadrine, procyclidine, and trihexyphenidyl, which are the most commonly used in the treatment of parkinsonism.

Drugs targeting non-dopaminergic pathways are being developed to reduce the impact of the motor complications associated with dopaminergic drugs. These include istradefylline, a selective adenosine A_{2A}-receptor antagonist that is given as an adjunct to levodopa therapy.

Parkinsonism

The syndrome of parkinsonism is characterised by tremor, rigidity, akinesia or bradykinesia, and loss of postural reflexes, associated with reduced dopamine activity in the brain. It may be **classified** as follows:

- primary (idiopathic) parkinsonism, usually referred to as Parkinson's disease (formerly paralysis agitans)
- secondary (acquired) parkinsonism, including postencephalitic parkinsonism, drug-induced parkinsonism, and symptoms associated with manganese poisoning
- 'parkinsonism-plus' syndromes where parkinsonism is a feature of other degenerative diseases of the CNS, such as progressive supranuclear palsy and multiple system atrophy

'Arteriosclerotic parkinsonism' has been used to describe parkinsonism associated with cerebrovascular disease, although this may be confusing since vascular brain damage is not a cause of Parkinson's disease.

The term parkinsonism is often used for the idiopathic form, that is, Parkinson's disease. Parkinson's disease and postencephalitic parkinsonism have been attributed mainly to depletion of striatal dopamine in the basal ganglia as a result of the loss of neurones in the substantia nigra. Striatal dopamine deficiency results in loss of the normal functional balance between dopaminergic and cholinergic activity and the aim of treatment is to increase the former and/or decrease the latter.

The **cause** of *Parkinson's disease* is not established, although environmental and genetic factors are probably superimposed on a background of neuronal loss related to ageing. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a contaminant of an illicitly produced pethidine analogue MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), causes irreversible parkinsonism similar to Parkinson's disease. This effect appears to follow conversion by monoamine oxidase B to the neurotoxic methylphenylpyridinium ion, which is selectively concentrated in dopaminergic neurones in the substantia nigra. It has been proposed that free radicals produced during normal metabolism of dopamine in the brain by monoamine oxidase B might be similarly neurotoxic to dopaminergic neurones in the substantia nigra (the oxidant stress hypothesis). This has led to concern that use of levodopa, by increasing the supply of dopamine, might therefore exacerbate neurodegeneration and hasten the progression of Parkinson's disease but compelling evidence of such an effect is lacking.

Drug-induced parkinsonism (see Extrapyramidal Disorders, p. 1049.2) can arise from depletion of presynaptic dopamine, as with reserpine and tetrabenazine, or from blockade of postsynaptic dopamine receptors in the striatum, as by antipsychotics and some antiemetics such as metoclopramide. It is generally reversible on drug withdrawal or dose reduction and may sometimes disappear gradually despite continuous drug therapy. Although the use of levodopa to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, it has generally been reported to be ineffective or to increase psychiatric symptoms. Antimuscarinics may provide relief from the extrapyramidal symptoms that occur as adverse effects of antipsychotic therapy; however, they do not relieve the symptoms of tardive dyskinesia and should be withdrawn if it develops.

There is no cure for Parkinson's disease. Although the possibility of using drug therapy to slow neurodegeneration is being investigated, no drug so far has a proven neuroprotective effect. **Treatment** is palliative and symptomatic and consists mainly of drug therapy supplemented when necessary with physical treatment such as physiotherapy and speech therapy. Surgery is occasionally used and there is growing interest in the use of transplantation and in electrical devices for the control of tremor.

Drugs used in Parkinson's disease. Drug therapy consists largely of the use of dopaminergics or antimuscarinics in an attempt to restore the normal balance between dopaminergic and cholinergic activity. Dopaminergics may act by direct replacement of dopamine, by delaying the metabolism of endogenous dopamine, by stimulation of dopamine receptors directly, or by enhancement of release of endogenous dopamine. Drugs with differing actions are often used together to achieve optimum control of symptoms.

- *Levodopa* is the most effective symptomatic treatment. It is converted by decarboxylation into dopamine and, unlike dopamine, can penetrate the blood-brain barrier and supply a source of dopamine to the brain. Levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as *benserazide* or *carbidopa*. These drugs are unable to penetrate the blood-brain barrier and therefore prevent only extracerebral conversion of levodopa to dopamine. This allows effective concentrations of dopamine to be achieved in the brain with lower doses of levodopa and also reduces nausea and vomiting and other adverse effects associated with peripheral formation of dopamine.

  The majority of patients respond initially to levodopa and its use has improved the quality and duration of life. However, after 2 years or more, benefit is reduced as the disease progresses and late complications emerge. Apart from dyskinesias and psychiatric effects, a major problem with long-term levodopa treatment is the appearance of fluctuations in mobility, the two predominant forms being 'end-of-dose' deterioration ('wearing-off' effect) and the 'on-off' phenomenon (see Complications of Treatment, below). Thus, views differ as to the best time to start treatment and the dosage to use in order to limit the long-term complications.

  Catechol-*O*-methyltransferase (COMT) inhibitors, such as *entacapone* and *tolcapone*, are selective and reversible inhibitors of COMT, with mainly peripheral actions. They are given as adjunctive therapy to patients with fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations; because of the risk of serious hepatotoxicity, tolcapone should be restricted to when other adjunctive therapy is ineffective or contra-indicated. When levodopa is used with a peripheral dopa-decarboxylase inhibitor, *O*-methylation becomes the predominant form of metabolism of levodopa; adding a peripheral COMT inhibitor can thus extend the duration and effect of levodopa in the brain, and allow lower and less frequent doses of levodopa. They therefore can help to stabilise patients, especially those with 'end-of-dose' deterioration.
- *Rasagiline* and *selegiline* are selective inhibitors of monoamine oxidase type B, an enzyme involved in the metabolism of dopamine in the brain. When used with levodopa in severe parkinsonism they have a dose-sparing effect and are of value in patients with fluctuations in mobility. Early treatment with selegiline may delay the need for levodopa and there has been much interest in the possibility that these drugs might have neuroprotective effects, but it is difficult to separate any putative effect on disease progression from symptomatic benefits, and at present there is insufficient evidence to show that any treatment can slow progression of the disease. Used alone, selegiline produces few adverse effects but when used with levodopa it can provoke or worsen dyskinesias or psychiatric symptoms and doubts have been expressed on the safety of long-term use.
- Dopamine agonists such as *bromocriptine*, *cabergoline*, *pergolide*, *pramipexole*, *ropinirole*, and *rotigotine* act by direct stimulation of remaining postsynaptic dopamine receptors. Dopamine agonists are increasingly used in the early treatment of younger patients with parkinsonism in an attempt to delay therapy with levodopa (younger patients are at an increased risk of motor complications with levodopa). However, their efficacy often decreases after a few years. In older patients they may be reserved for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating fluctuations in mobility in the later stages of the disease. *Apomorphine* is a potent dopamine agonist, but must be given parenterally and with an antiemetic. Although this restricts its use, it has a role in stabilising patients who suffer unpredictable 'on-off' effects. It is also used in the differential diagnosis of parkinsonism.
- *Antimuscarinics* are considered to have a weak antiparkinsonian effect compared with levodopa. They may reduce tremor but have little effect on bradykinesia. They may be of use alone or with other drugs in the initial treatment of patients with mild symptoms, especially when tremor is pronounced, or later as an adjunct to levodopa, such as in patients with refractory tremor or dystonias. Antimuscarinic adverse effects, particularly cognitive impairment, occur frequently and can limit their use. However, some antimuscarinic effects can ameliorate complications associated with Parkinson's disease; dry mouth may be an advantage in patients with sialorrhoea. There appear to be no important differences in the efficacy of antimuscarinics for Parkinson's disease but some patients may tolerate one drug better than another. Those commonly used for Parkinson's disease include *benzatropine*, *orphenadrine*, *procyclidine*, and *trihexyphenidyl*.
- *Amantadine* is a weak dopamine agonist with some antimuscarinic activity although its activity as an antagonist of *N*-methyl-D-aspartate may also have a beneficial effect in Parkinson's disease. It has mild antiparkinsonian effects compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity but only a small proportion of patients derive much benefit. It is used similarly to antimuscarinics in early disease when symptoms are mild, but tolerance to its effects can occur rapidly.
- *Istradefylline* is a selective adenosine A_{2A}-receptor antagonist given as an adjunct to levodopa therapy. Drugs targeting non-dopaminergic pathways, such as the adenosine pathway, are being developed in order to reduce the impact of the motor complications associated with dopaminergic drugs.

Choice and implementation of drug treatment. If symptoms are mild, drug therapy may not be required in the early stages of the disease. When symptoms become troublesome but are still relatively mild *amantadine* or an *antimuscarinic* may be started; antimuscarinics are useful when tremor predominates but are generally more suitable for younger patients and in drug-induced rather than idiopathic parkinsonism. Some have begun treatment with

selegiline immediately, but there have been doubts over whether it has a neuroprotective effect, as postulated, and also over long-term safety. There is no consensus on when to start dopaminergic treatment or whether to begin with *levodopa* or a *dopamine agonist*. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms.

When levodopa does become necessary, the usual practice is to start with small doses, given with a peripheral dopa-decarboxylase inhibitor, and increase slowly to a dose which reduces disability to an acceptable level. Variations in response and diminishing efficacy over the years necessitate careful adjustment of the size and form of the dose and the dosage schedule.

Complications of treatment. Fluctuations in mobility have been reported in more than half of patients on levodopa after 5 years of therapy. They generally proceed through predictable **'end-of-dose'** deterioration to the **'on-off'** phenomenon with marked very sudden swings from mobility to immobility. The cause of the fluctuations is not known, but multiple factors including desensitisation of dopamine receptors, interference with the response to dopamine by other levodopa metabolites such as 3-*O*-methyldopa, fluctuating plasma concentrations, and erratic transport of levodopa from blood to the brain have been suggested. It appears that as the disease progresses the capacity of the nigrostriatal dopaminergic system to synthesise and store dopamine, and to act as a buffer in maintaining dopamine brain concentrations, declines. Dopamine concentrations therefore become more dependent on levodopa dosage and the pattern of response will come to reflect more closely the rise and fall in levodopa concentrations. Eventually the effect of various factors that produce even small changes in plasma concentrations of levodopa will progressively become more pronounced.

Approaches to the management of 'end-of-dose' fluctuations include more frequent but smaller doses and the use of modified-release preparations. Addition of selegiline or partial replacement of levodopa by a dopamine agonist with a more prolonged action may also be tried.

Various attempts have been made to overcome the 'on-off' phenomenon. Those speculating that long-term treatment results in altered dopamine receptor sensitivity have used controlled withdrawal of levodopa for short periods ('drug holidays') but it is a dangerous procedure of doubtful value and no longer recommended.

Others have linked the 'on-off' phenomenon to variable plasma concentrations although, since transfer of levodopa into the brain involves active transport mechanisms, concentrations in plasma may not necessarily reflect those in the brain. Continuous intraduodenal or intravenous infusion of levodopa has been shown to reduce fluctuations in mobility, which suggests that dopamine receptors are still sensitive, although this is not practical for day-to-day management (but see below). However, there is evidence that some patients may benefit from modified-release formulations of levodopa with a peripheral dopa-decarboxylase or COMT inhibitor. As levodopa competes with amino acids for uptake into the brain, attempts to lessen fluctuations in dopamine brain concentrations have included taking levodopa on an empty stomach and also delaying most of a day's protein consumption until the evening. Addition of entacapone, rasagiline, selegiline, or a dopamine agonist may also help to reduce 'on-off' phenomena. If fluctuations remain a problem subcutaneous apomorphine is often effective. In some countries a gel formulation of levodopa with carbidopa is available for continuous infusion by an ambulatory pump into the duodenum when other available combination therapy has not been satisfactory.

Other complications of treatment with levodopa can include **dyskinesia**, which may respond to dosage adjustment or partial replacement of levodopa with a dopamine agonist. Amantadine may also be considered, although evidence is lacking. Some patients with Parkinson's disease may have **severe pain** and **dystonia**; measures to increase 'on' periods can help reduce or eliminate pain in most patients.

Patients with Parkinson's disease can suffer from a range of **psychiatric effects**, such as depression, dementia, sleep disturbances, and psychosis, due to the adverse effects of drug therapy and to disease progression. It has been recommended that if patients develop psychotic reactions, an attempt to adjust their antiparkinsonian drugs should be tried before resorting to the use of antipsychotics. Although classical antipsychotics are usually contra-indicated because they can exacerbate parkinsonism, atypical antipsychotics such as clozapine and quetiapine may be used in treatment-resistant psychosis—see Disturbed Behaviour, p. 1030.2. The cholinesterase inhibitor rivastigmine is licensed in some countries for the symptomatic treatment of mild to moderately severe dementia in Parkinson's disease. **Excessive daytime sleepiness** and **sudden onset of sleep** have been reported with dopamine agonists, as have **behavioural disturbances** including intense urges to gamble and increased sexual urges, and patients should be warned of the possible risks (see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2). **Fibrotic reactions** resulting in cardiovascular and pulmonary adverse effects have been reported with ergot derivatives and patients should be monitored (see Fibrosis, under Adverse Effects of Bromocriptine, p. 897.3). **Nausea and vomiting** induced by dopaminergics may be minimised by introducing the drug gradually and giving the dose with food, but if this is ineffective or apomorphine is being used these effects can be controlled by the antiemetic domperidone. Domperidone does not readily cross the blood-brain barrier and therefore acts mainly as a peripheral dopamine antagonist. Tolerance to the nausea usually develops after a few weeks and domperidone may then be withdrawn.

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Amantadine *(BAN, pINN)*

Amantadiini; Amantadin; Amantadina; Amantadinum; Амантадин.

Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine.

$C_{10}H_{17}N$=151.3

CAS — 768-94-5.

ATC — N04BB01.

ATC Vet — QN04BB01.

UNII — BF4C9Z1J53.

Amantadine Hydrochloride

(BANM, USAN, pINNM)

1-Adamantanamine Hydrochloride; Amantadiinihydroklor-idi; Amantadina, hidrocloruro de; Amantadine, chlorhydrate d'; Amantadin-hidroklorid; Amantadin-hydrochlorid; Amantadinhydrochlorid; Amantadinhydroklorid; Amantadini Hydrochloridum; Amantadino hidrochloridas; EXP-105-1; Hidrocloruro de amantadina; NSC-83653; Амантадина Гидрохлорид.

Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine hydrochloride.

$C_{10}H_{17}N,HCl$=187.7

CAS — 665-66-7.

ATC — N04BB01.

ATC Vet — QN04BB01.

UNII — M6Q1EO9TD0.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Amantadine Hydrochloride). A white or almost white crystalline powder. It sublimes on heating. Freely soluble in water and in alcohol.

USP 36: (Amantadine Hydrochloride). A white or practically white crystalline powder. Soluble 1 in 2.5 of water, 1 in 5.1 of alcohol, 1 in 18 of chloroform, and 1 in 70 of macrogol 400. pH of a 20% solution in water is between 3.0 and 5.5.

Amantadine Sulfate *(pINNM)*

Amantadina, sulfato de; Amantadine, Sulfate d'; Amantadine Sulphate; Amantadini Sulfas; Sulfato de amantadina; Амантадина Сульфат.

$(C_{10}H_{17}N)_2SO_4$=398.6

CAS — 31377-23-8.

ATC — N04BB01.

ATC Vet — QN04BB01.

UNII — 9921T5P019.

Uses and Administration

Amantadine is a weak dopamine agonist with some antimuscarinic activity; it is also an antagonist at *N*-methyl-D-aspartate receptors. Amantadine has mild antiparkinsonian activity and is used in the management of parkinsonism (p. 891.2), mainly in early disease when symptoms are mild. It may improve bradykinesia, rigidity, and tremor but tolerance can develop.

Amantadine is also an antiviral that inhibits replication of influenza type A virus; it has very little or no activity against influenza type B virus. It is used prophylactically against infection with influenza type A virus and to ameliorate symptoms when given during the early stages of infection (but see p. 891.2).

Amantadine has also been used in the management of herpes zoster (see Varicella-zoster Infections, p. 956.2).

Amantadine is usually given orally as the hydrochloride and the doses below are expressed in terms of this salt.

In **parkinsonism**, treatment is usually started with 100 mg daily, increasing to 100 mg twice daily after a week or more. Doses up to a maximum of 400 mg daily have occasionally been used. The lowest effective dose should be used in patients over 65 years of age because of the potential for reduced renal clearance in this age group. Withdrawal of

amantadine treatment for parkinsonism should be gradual to avoid exacerbating the condition; UK licensed product information suggests decreasing the dose by half at weekly intervals.

The dose of amantadine in the UK for the treatment of **influenza A** is 100 mg daily, usually given for about 5 days. For the prophylaxis of influenza A the same dose is given for as long as protection from infection is required, which may be for about 6 weeks. If amantadine is being given with influenza vaccination then it is usually only given for up to 3 weeks after vaccination. Children aged 10 to 15 years may also be given 100 mg daily for the recommended period. A daily dose of less than 100 mg or 100 mg given at intervals greater than one day has been recommended for patients over 65 years of age.

Doses in the USA are higher than those in the UK: for the treatment of influenza A the daily dose is 200 mg daily as a single dose or in two divided doses, continued for 24 to 48 hours after the disappearance of symptoms. The same dose is given for the prophylaxis of influenza A for at least 10 days after exposure. If given with vaccination then amantadine should be taken for the next 2 to 4 weeks. The dose of amantadine should be reduced to 100 mg daily in patients aged 65 years and over, and in those who show intolerance to the higher dose. US licensed product information recommends that children aged 1 to 9 years may be given 4.4 to 8.8 mg/kg daily to a maximum of 150 mg daily, although the CDC suggests 5 mg/kg daily (maximum 150 mg daily) to reduce the risk of toxicity. Older children may be given 100 mg twice daily; CDC suggests that children weighing less than 40 kg should be given a dose of 5 mg/kg daily, regardless of their age.

In **herpes zoster**, treatment with 100 mg twice daily may be given for 14 days; if pain persists, treatment may be continued for a further 14 days.

The dosage of amantadine should be reduced in patients with renal impairment (see below).

Amantadine sulfate has been used similarly to the hydrochloride; it has been given orally or by intravenous infusion.

Administration. Amantadine sulfate has been used successfully in doses of up to 600 mg daily by intravenous infusion in the management of akinetic crisis in patients with Parkinson's disease.[1]

1. Gadoth N, *et al.* I.V. amantidine [sic] sulfate for extrapyramidal crisis. *Clin Pharm* 1985; **4:** 146.

Administration in children. For doses of amantadine hydrochloride in the prophylaxis and treatment of influenza A in children, see p. 890.3.

Administration in renal impairment. The oral dose of amantadine hydrochloride should be reduced in patients with renal impairment by either reducing the total daily dose or by increasing the dosage interval in accordance with their creatinine clearance (CC).

In the UK the following doses are recommended:

- CC over 35 mL/min: 100 mg daily
- CC 15 to 35 mL/min: 100 mg every 2 to 3 days
- CC less than 15 mL/min: not recommended

In the USA the following doses are recommended:

- CC 30 to 50 mL/min: 200 mg on the first day followed by 100 mg daily thereafter
- CC 15 to 29 mL/min: 200 mg on the first day followed by 100 mg on alternate days
- CC less than 15 mL/min or those on haemodialysis: 200 mg every 7 days

See also under Precautions, p. 892.2.

Extrapyramidal disorders. Amantadine has been used as an alternative to antimuscarinics[1] in the short-term management of *drug-induced extrapyramidal symptoms* (p. 1049.2). US licensed product information has recommended a usual oral dose of 200 mg daily in 2 divided doses increased up to 300 mg daily if necessary. However, the development of tolerance has limited its usefulness. See also Parkinsonism, below.

Amantadine has been investigated in the management of *chorea* in patients with Huntington's disease.[2,3]

1. König P, *et al.* Amantadine versus biperiden: a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. *Neuropsychobiology* 1996; **33:** 80–4.
2. Magnet MK, *et al.* Amantadine in the akinetic-rigid variant of Huntington's disease. *Ann Pharmacother* 2004; **38:** 1194–6.
3. Heckmann JM, *et al.* IV amantadine improves chorea in Huntington's disease: an acute randomized, controlled study. *Neurology* 2004; **63:** 597–8.

Hepatitis C. Amantadine has been investigated[1-4] as an addition to interferon-based antiviral regimens in the treatment of chronic hepatitis C infection (p. 952.1). A meta-analysis[1] concluded that it was of no value in treatment-naive patients or relapsers, but that triple therapy with amantadine, ribavirin, and interferon improved sustained responses in patients previously unresponsive to therapy.

1. Deltenre P, *et al.* Evaluation of amantadine in chronic hepatitis C: a meta-analysis. *J Hepatol* 2004; **41:** 462–73.
2. Stauber RE, *et al.* Retreatment of patients with chronic hepatitis C not responding to interferon/ribavirin combination therapy with daily interferon plus ribavirin plus amantadine. *Wien Klin Wochenschr* 2004; **116:** 530–5.
3. Herrine SK, *et al.* Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci* 2005; **50:** 719–26.
4. Mangia A, *et al.* A randomized controlled trial of pegylated interferon alpha-2a (40 KD) or interferon alpha-2a plus ribavirin and amantadine vs interferon alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. *J Viral Hepatitis* 2005; **12:** 292–9.

Hiccup. Amantadine[1] has been reported to have produced beneficial results in patients with intractable hiccups. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

1. Askenasy JJM, *et al.* Persistent hiccup cured by amantadine. *N Engl J Med* 1988; **318:** 711.

Influenza. Amantadine has been used similarly to rimantadine (p. 1012.2) in the prophylaxis and treatment of influenza A (p. 960.2). In adults, the two drugs are equally effective, but amantadine is associated with more adverse effects;[1] further study on their safety and efficacy in children and the elderly is considered warranted.[2] Amantadine reduced the duration of influenza A symptoms when given in a dose of 200 mg daily within 48 hours of the onset of symptoms.[3] However, although amantadine is licensed in the UK and USA for the prophylaxis and treatment of influenza A, its use for such purposes is not recommended by authorities in these countries because of resistance in circulating influenza A virus strains.[4-6]

Resistance to amantadine may occur rapidly.[7] For further information see Resistance, under Rimantadine, p. 1013.1.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 21/06/06).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 29/05/08).
3. Nicholson KG, Wiselka MJ. Amantadine for influenza A. *BMJ* 1991; **302:** 425–6.
4. CDC. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; **60** (RR-1): 1–26. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf (accessed 09/02/11)
5. NICE. Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza—includes a review of NICE technology appraisal guidance 67: NICE Technology Appraisal Guidance 158 (issued September 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA158Guidance.pdf (accessed 20/08/09)
6. NICE. Amantadine, oseltamivir and zanamivir for the treatment of influenza—review of NICE technology appraisal guidance 58: NICE Technology Appraisal Guidance 168 (issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/TA168fullguidance.pdf (accessed 20/08/09)
7. Bright RA, *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.

Multiple sclerosis. Amantadine has been used to alleviate fatigue associated with multiple sclerosis (p. 996.3). However, a systematic review[1] concluded that there was insufficient evidence to support its use in reducing fatigue in patients with multiple sclerosis; further large controlled studies are considered warranted.

1. Pucci E, *et al.* Amantadine for fatigue in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 29/05/08).

Neuroleptic malignant syndrome. Amantadine has been tried[1-3] in the treatment of the neuroleptic malignant syndrome (p. 1050.2).

1. McCarron MM, *et al.* A case of neuroleptic malignant syndrome successfully treated with amantadine. *J Clin Psychiatry* 1982; **43:** 381–2.
2. Amdurski S, *et al.* A therapeutic trial of amantadine in haloperidol-induced malignant neuroleptic syndrome. *Curr Ther Res* 1983; **33:** 225–9.
3. Woo J, *et al.* Neuroleptic malignant syndrome successfully treated with amantadine. *Postgrad Med J* 1986; **62:** 809–10.

Parkinsonism. Amantadine's mechanism of action in parkinsonism (p. 889.1) is unclear but may be due to its antimuscarinic activity and alterations in dopamine release and reuptake. It has also been suggested that its action as a non-competitive antagonist of *N*-methyl-D-aspartate may have a beneficial effect.[1,2] It has mild antiparkinsonian activity compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity and is used in a similar manner to antimuscarinics mainly in the treatment of patients with early Parkinson's disease when symptoms are mild. It may also be useful for dyskinesias in more advanced disease.[3] However, few patients obtain much benefit and tolerance to its effects can occur. Moreover, two systematic reviews[4,5] concluded that there was insufficient evidence from randomised controlled studies on the safety and efficacy of amantadine in the treatment of both Parkinson's disease and levodopa-induced dyskinesias in late disease.

Licensed product information suggests that the efficacy of amantadine may be prolonged by withdrawing it for 3 to 4 weeks, continuing with existing antiparkinsonian therapy or starting low-dose levodopa treatment if clinically necessary in the meantime.

1. Laing P. Stroke treatment. *Lancet* 1991; **337:** 1601.
2. Greenamyre JT, O'Brien CF. N-Methyl-D-aspartate antagonists in the treatment of Parkinson's disease. *Arch Neurol* 1991; **48:** 977–81.
3. Thomas A, *et al.* Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; **75:** 141–3.
4. Crosby NJ, *et al.* Amantadine in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).
5. Crosby NJ, *et al.* Amantadine for dyskinesia in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/02/06).

Withdrawal syndromes. *COCAINE.* Despite some early promising results a systematic review[1] considered that there was no evidence to support the use of dopamine agonists, including amantadine, in the treatment of cocaine dependence (p. 1990.1).

1. Soares B, *et al.* Dopamine agonists for cocaine dependence. [Withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 23/08/10).

Adverse Effects

Most adverse effects associated with amantadine therapy appear to be dose-related and relatively mild; some resemble those of antimuscarinic drugs. They may be reversed by withdrawing therapy but many resolve despite continuation.

Livedo reticularis, sometimes associated with ankle oedema, is quite common in patients given very high doses of amantadine or with long-term therapy. CNS effects such as anxiety, inability to concentrate, dizziness, insomnia, nightmares, headache, and changes in mood may occur. Psychotic reactions, hallucinations, and confusion have been reported, especially in the elderly, patients with renal impairment or psychiatric disorders, and those also receiving antimuscarinics.

Other adverse effects reported have included orthostatic hypotension, palpitations, urinary retention, slurred speech, ataxia, lethargy, anorexia, nausea, vomiting, dry mouth, constipation, rash, diaphoresis, and blurred vision. There have been isolated reports of congestive heart failure, photosensitisation leucopenia, neutropenia, dyskinesias, oculogyric episodes, and convulsions.

Effects on the cardiovascular system. Congestive heart failure has been reported with amantadine;[1] the patient had been receiving combined treatment with amantadine, levodopa, and orphenadrine for 4 years. Others have considered that while amantadine sometimes causes ankle oedema, an association between amantadine and heart failure is not proven.[2] Livedo reticularis, a mottled blue discoloration of the skin due to prominence of the normal pattern of venous drainage, has been reported[2] to occur in about 50% of all elderly patients given amantadine 100 to 300 mg daily for 2 to 6 weeks and was associated with oedema in 5 to 10%. Both livedo and oedema have usually been confined to the legs and may result from the catecholamine-releasing action of amantadine in certain vascular beds; the oedema was unlikely to be due to heart failure. Angina, dyspnoea, pulmonary congestion, or distension of neck veins has also been reported[2] in 4 of 89 parkinsonian patients treated with amantadine; only 2 of these 4 had had ankle oedema before heart failure developed. No patient had been seen in whom heart failure seemed due directly to amantadine.

See also Overdosage, p. 892.1.

1. Vale JA, Maclean KS. Amantadine-induced heart-failure. *Lancet* 1977; **i:** 548.
2. Parkes JD, *et al.* Amantadine-induced heart-failure. *Lancet* 1977; **i:** 904.

Effects on electrolytes. For a report of a patient who developed hyponatraemia when given amantadine or levodopa, see Effects on Kidney Function under Levodopa, p. 905.2.

Effects on the eyes. Superficial punctate keratitis and corneal abrasion with loss of visual acuity was seen in both eyes of a 64-year-old man about 3 weeks after starting treatment with amantadine 100 mg daily.[1] Symptoms resolved on stopping amantadine but recurred when retreatment with amantadine was attempted. In another report,[2] a 14-year-old boy developed bilateral corneal oedema with visual loss associated with amantadine treatment. He had been taking amantadine 300 mg daily for several months with many other drugs; symptoms resolved when amantadine was stopped.

1. Nogaki H, Morimatsu M. Superficial punctate keratitis and corneal abrasion due to amantadine hydrochloride. *J Neurol* 1993; **240:** 388–9.
2. Hughes B, *et al.* Reversible amantadine-induced corneal edema in an adolescent. *Cornea* 2004; **23:** 823–4.

Effects on mental function. It has been suggested[1] that the ability of amantadine and memantine to cause psychotic

disturbances in patients with Parkinson's disease might be related to their action as *N*-methyl-D-aspartate antagonists.

For reference to disturbed behaviour including excessive gambling, and to daytime somnolence reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

1. Riederer P, *et al*. Pharmacotoxic psychosis after memantine in Parkinson's disease. *Lancet* 1991; **338:** 1022–3.

Effects on the nervous system. Peripheral sensory motor neuropathy secondary to long-term (8 years) use of amantadine has been reported[1] in a 48-year-old woman with parkinsonism. Trophic skin ulcers, paraesthesias, and distal weakness resolved on stopping amantadine.

1. Shulman LM, *et al*. Amantadine-induced peripheral neuropathy. *Neurology* 1999; **53:** 1862–5.

Overdosage. A patient with postencephalitic parkinsonism who had taken an estimated 2.8 g of amantadine hydrochloride in a suicide attempt developed acute toxic psychosis with disorientation, visual hallucinations, and aggressive behaviour.[1] Convulsions did not occur, possibly because he had been receiving phenytoin, which was continued. The patient was treated with hydration and chlorpromazine and recovered in 4 days.

A 2-year-old child who had ingested 600 mg of amantadine hydrochloride developed symptoms of acute toxicity, including agitation and dystonic posturing, despite emesis with 'syrup of ipecac'.[2] She responded immediately to physostigmine 500 micrograms intravenously, repeated after 10 minutes. Her pupils remained moderately dilated until about 20 hours after the ingestion; thereafter she made a full recovery.

Cardiac arrest developed 4 hours after a 37-year-old woman ingested 2.5 g of amantadine hydrochloride and was treated successfully.[3] However, ventricular arrhythmias, including torsade de pointes, continued over the ensuing 48 hours and may have been exacerbated by use of isoprenaline and dopamine. The patient was subsequently stabilised with lidocaine by intravenous infusion, but died of respiratory failure 10 days after admission.

1. Fahn S, *et al*. Acute toxic psychosis from suicidal overdosage of amantadine. *Arch Neurol* 1971; **25:** 45–8.
2. Berkowitz CD. Treatment of acute amantadine toxicity with physostigmine. *J Pediatr* 1979; **95:** 144–5.
3. Sartori M, *et al*. Torsade de pointe: malignant cardiac arrhythmia induced by amantadine poisoning. *Am J Med* 1984; **77:** 388–91.

Precautions

Amantadine is usually contra-indicated in severe renal disease and in patients with a history of epilepsy or other seizure disorders, or gastric ulceration. It should also not be given to patients with untreated angle-closure glaucoma. Amantadine should be used with caution in patients with cardiovascular or liver disease, renal impairment, recurrent eczema, or psychiatric disorders. Suicide attempts, in some cases fatal, and suicidal ideation have been reported in patients taking amantadine. Care should be taken in all elderly patients, who may be more sensitive to antimuscarinic effects, and in whom renal clearance is likely to be reduced.

In common with other drugs having antimuscarinic properties amantadine may cause blurred vision or impair alertness; patients so affected should not drive or operate machinery.

Treatment with amantadine should not be stopped abruptly in parkinsonian patients since a sudden marked clinical deterioration may occur. There have been isolated reports of a neuroleptic malignant-like syndrome associated with abrupt withdrawal of amantadine, especially in patients also receiving antipsychotics.

Antiviral resistance. See Influenza under Uses and Administration, p. 891.2.

Breast feeding. Amantadine is distributed into breast milk and licensed product information states that adverse effects have occurred in breast-fed infants of mothers taking amantadine.

Pregnancy. Amantadine should not be used during pregnancy; embryotoxicity and teratogenicity have been reported in *rats* given high doses.[1]

A complex cardiovascular lesion occurred in an infant whose mother had taken amantadine hydrochloride 100 mg daily during the first 3 months of pregnancy.[1] In another case, tetralogy of Fallot and limb deformities were seen in the neonate of a mother who was given amantadine hydrochloride 100 mg daily for 7 days during the 4th and 6th weeks of gestation.[2] However, a report of the use of amantadine during 2 separate pregnancies by a woman with multiple sclerosis noted no abnormalities in either infant.[3]

1. Nora JJ, *et al*. Cardiovascular maldevelopment associated with maternal exposure to amantadine. *Lancet* 1975; **ii:** 607.
2. Pandit PB, *et al*. Tibial hemimelia and tetralogy of Fallot associated with first trimester exposure to amantadine. *Reprod Toxicol* 1994; **8:** 89–92.
3. Levy M, *et al*. Fetal outcome following intrauterine amantadine exposure. *Reprod Toxicol* 1991; **5:** 79–81.

Renal impairment. Evidence of extremely limited excretion of amantadine was found in 12 patients who were either anephric or had negligible renal function after a single 100-mg dose of amantadine hydrochloride.[1] Only small amounts were removed by dialysis. It was suggested that amantadine should be given with caution to patients requiring maintenance haemodialysis; a single dose may provide adequate plasma concentrations for many days.[1]

Dosage regimens based on creatinine clearance[2] or fixed doses at extended intervals[3] have been published. However, both regimens have been criticised and a conservative approach to amantadine dosage in these patients recommended[4] (for the regimens in licensed product information, see Administration in Renal Impairment, p. 891.1). The need for caution in using amantadine in patients with renal impairment is highlighted by a report of a patient with end-stage renal disease who progressed from delirium to coma after receiving amantadine 100 mg twice daily for 3 days.[5]

1. Soung L-S, *et al*. Amantadine hydrochloride pharmacokinetics in hemodialysis patients. *Ann Intern Med* 1980; **93:** 46–9.
2. Horadam VW, *et al*. Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. *Ann Intern Med* 1981; **94:** 454–8.
3. Wu MJ, *et al*. Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. *Clin Nephrol* 1982; **17:** 19–23.
4. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; **14:** 35–51.
5. Macchio GJ, *et al*. Amantadine-induced coma. *Arch Phys Med Rehabil* 1993; **74:** 1119–20.

Withdrawal. Neuroleptic malignant syndrome occurred in a patient being treated for heat stroke when all his medication, including antipsychotics and amantadine, was withdrawn.[1] It is suggested that dopamine agonists should not be stopped in patients with hyperpyrexia at risk from this syndrome. In another report,[2] a 14-year-old boy being treated with amantadine for influenza A encephalopathy developed neuroleptic malignant syndrome when the drug was stopped after 5 days; the patient improved when amantadine treatment was resumed. The authors recommended a gradual reduction in dosage when stopping amantadine therapy.

Acute delirium developed in 3 elderly patients with Parkinson's disease after gradual withdrawal of long-term amantadine therapy;[3] symptoms resolved when amantadine was restarted.

1. Simpson DM, Davis GC. Case report of neuroleptic malignant syndrome associated with withdrawal from amantadine. *Am J Psychiatry* 1984; **141:** 796–7.
2. Ito T, *et al*. Neuroleptic malignant syndrome following withdrawal of amantadine in a patient with influenza A encephalopathy. *Eur J Pediatr* 2001; **160:** 401.
3. Factor SA, *et al*. Acute delirium after withdrawal of amantadine in Parkinson's disease. *Neurology* 1998; **50:** 1456–8.

Interactions

Amantadine may enhance the adverse effects of antimuscarinics and the dose of these drugs should be reduced when used with amantadine; adverse effects of levodopa may also be exacerbated.

Licensed product information states that amantadine should be used with caution in patients receiving drugs that affect the CNS. The rate of excretion of amantadine may be reduced by drugs that raise urinary pH.

Antiarrhythmics. *Quinine* and *quinidine* have been reported to reduce the renal clearance of amantadine in healthy male, but not female, subjects.[1] Patients taking these drugs together should be observed for signs of amantadine toxicity.

1. Gaudry SE, *et al*. Gender and age as factors in the inhibition of renal clearance of amantadine by quinine and quinidine. *Clin Pharmacol Ther* 1993; **54:** 23–7.

Antimalarials. For the possible effects of the use of *quinine* and *quinidine* with amantadine, see Antiarrhythmics, above.

Diuretics. A patient with Parkinson's disease, previously stabilised on amantadine hydrochloride 300 mg daily, developed symptoms of amantadine toxicity, including ataxia, myoclonus, and confusion, 7 days after starting treatment with a preparation containing *triamterene* and *hydrochlorothiazide* (*Dyazide*).[1] It was postulated that the effect was due to reduction of the tubular secretion of amantadine.

1. Wilson TW, Rajput AH. Amantadine-Dyazide interaction. *Can Med Assoc J* 1983; **129:** 974–5.

MAOIs. Hypertension occurred about 48 hours after starting treatment with *phenelzine sulfate* in a patient already receiving amantadine.[1]

1. Jack RA, Daniel DG. Possible interaction between phenelzine and amantadine. *Arch Gen Psychiatry* 1984; **41:** 726.

Pharmacokinetics

Amantadine hydrochloride is well absorbed from the gastrointestinal tract; peak concentrations in the plasma appear within about 4 hours after oral doses. Plasma protein binding is reported to be about 67%, with a substantial amount bound to erythrocytes; the concentration is about 2.7 times higher in erythrocytes than in plasma. It is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion although small amounts of an acetylated metabolite have also been detected in urine; the plasma elimination half-life is reported to be about 15 hours in patients with normal renal function but is significantly prolonged in the elderly and in patients with renal impairment. The rate of elimination may be increased by acidification of the urine. Amantadine crosses the placenta and the blood-brain barrier. It is also distributed into breast milk.

References.

1. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; **14:** 35–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actison; Ampakine; Virosol; ***Austral.***: Symmetrel; ***Austria***: Hofcomant; PK-Merz; ***Belg.***: Amantan†; ***Braz.***: Mantidan; ***Chile***: Prayanol; ***Cz.***: Amantadol†; PK-Merz; Viregyt-K; ***Fin.***: Atarin†; ***Fr.***: Mantadix; ***Ger.***: Amantagamma†; Amixx; PK-Merz; tregor; ***Gr.***: Hofcomant; PK-Merz; Symmetrel; ***Hong Kong***: PK-Merz; Topharmin†; ***Hung.***: PK-Merz; Viregyt; ***India***: Amantrel; ***Irl.***: Symmetrel†; ***Israel***: Paritrel†; PK-Merz; ***Ital.***: Mantadan; ***Malaysia***: PK-Merz; ***Mex.***: Kinestrel; PK-Merz; ***Neth.***: Symmetrel; ***NZ***: Symmetrel; ***Philipp.***: PK-Merz; ***Pol.***: Amantix; Viregyt K; ***Port.***: Parkadina; PK-Merz; ***S.Afr.***: Symadin; Symmetrel; ***Singapore***: Symmetrel; ***Switz.***: PK-Merz; Symmetrel; ***Turk.***: PK-Merz; ***UK***: Lysovir; Symmetrel; ***Ukr.***: Neomidantan (Неомидантан); PK-Merz (ПК-Мерц); ***USA***: Symmetrel.

Multi-ingredient Preparations. ***China***: Bi Li Kang (必利康); Ke Li Ke (可立克); Qing Lang (清朗); Tai Ke (泰克); You Ka Dan (优卡丹); ***Mex.***: Antiflu-Des; Fluviatol; Fluviatol; Rosel.

Pharmacopoeial Preparations

BP 2014: Amantadine Capsules; Amantadine Oral Solution;
USP 36: Amantadine Hydrochloride Capsules; Amantadine Hydrochloride Syrup.

Apomorphine Hydrochloride *(BANM)*

Apomorfiinihydrokloridi; Apomorfin Hidroklorür; Apomorfina, hidrocloruro de; Apomorfin-hidroklorid; Apomorfinhydrochlorid hemihydrát; Apomorfinhydroklorid; Apomorfino hidrochloridas; Apomorfiny chlorowodorek; Apomorphine, chlorhydrate d'; Apomorphinhydrochlorid; Apomorphini hydrochloridum; Apomorphini Hydrochloridum Hemihydricum; Апоморфина Гидрохлорид.

6aβ-Aporphine-10,11-diol hydrochloride hemihydrate; (*R*)-10,11-Dihydroxy-6a-aporphine hydrochloride hemihydrate; (6a*R*)-5,6,6a,7-Tetrahydro-6-methyl-4*H*-dibenzo[*de,g*]quinoline-10,11-diol hydrochloride hemihydrate.

$C_{17}H_{17}NO_2$,HCl,½H_2O=312.8

CAS — 58-00-4 (apomorphine); 314-19-2 (anhydrous apomorphine hydrochloride); 41372-20-7 (apomorphine hydrochloride, hemihydrate).

ATC — G04BE07; N04BC07.

ATC Vet — QG04BE07; QN04BC07.

UNII — F39049Y068 (apomorphine hydrochloride hemihydrate); 9K13MD7A0D (anhydrous apomorphine hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Br. also includes a form for homoeopathic preparations.

Ph. Eur. 8: (Apomorphine Hydrochloride Hemihydrate). White or slightly yellowish-brown or green-tinged greyish crystals or crystalline powder, the green tinge becoming more pronounced on exposure to air and light. Sparingly soluble in water and in alcohol; practically insoluble in toluene. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

USP 36: (Apomorphine Hydrochloride). Odourless, minute white or greyish-white, glistening crystals or white powder. It gradually acquires a green colour on exposure to light and air. Soluble 1 in 50 of water and 1 in 20 of water at 80 degrees; soluble 1 in 50 of alcohol; very slightly soluble in ether and in chloroform. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

BP 2014: (Apomorphine Hydrochloride for Homoeopathic Preparations; Apomorphinum Muriaticum for Homoeopathic Preparations).

Stability. Aqueous solutions of apomorphine hydrochloride decompose on storage and should not be used if they turn green or brown or contain a precipitate.

Uses and Administration

Apomorphine is a morphine derivative with structural similarities to dopamine. It is a potent dopamine D_1- and D_2-receptor agonist used in the management of parkinsonism (below), especially in the control of the 'on-off' effect. It has also been used in the management of erectile dysfunction. Apomorphine is given as the hydrochloride and doses are expressed in terms of this salt. The regimen for parkinsonism given below applies to the UK preparation and doses are given subcutaneously; a similar preparation is available in the USA although the licensed maximum single and daily doses are less than those in the UK.

The optimal dose of apomorphine in the management of 'off' periods in parkinsonism should be established individually under specialist care. At least 2 days of pretreatment with the antiemetic domperidone is advised before starting apomorphine. After withholding antiparkinsonian therapy overnight to provoke an 'off' period, a test dose of 1 mg is given initially, followed by a second dose of 2 mg after 30 minutes, if necessary. Subsequent incremental increases should then be given at intervals of at least 40 minutes, as necessary, to determine the lowest dose producing a satisfactory motor response. Once the patient's normal antiparkinsonian therapy is re-established, the effective dose of apomorphine hydrochloride is given at the first signs of an 'off' period.

The dose and frequency are further adjusted according to response; patients typically require 3 to 30 mg daily in divided doses but individual injections should not be greater than 10 mg. Patients who require more than 10 injections daily or those whose overall control of symptoms remains unsatisfactory with intermittent injections may benefit from continuous subcutaneous infusion. The infusion is started at a rate of 1 mg/hour and this may be increased in steps of up to 500 micrograms/hour at intervals of not less than 4 hours to a maximum rate of 4 mg/hour. It is advised that infusions should only be given during waking hours and that the infusion site should be changed every 12 hours; 24-hour infusions are not advised unless there are severe night-time symptoms. Patients usually need to supplement the infusion with intermittent bolus injections but the recommended maximum total daily dose given by infusion and/or injection is 100 mg.

Apomorphine stimulates the chemoreceptor trigger zone in the brain and can produce emesis within a few minutes of a dose. However, the use of apomorphine for the induction of emesis in poisoning is considered dangerous owing to the risk of inducing protracted vomiting and shock, and is not recommended.

Homoeopathy

Apomorphine has been used in homoeopathic medicines.

Erectile dysfunction. Apomorphine is among many drugs that have been used in the management of erectile dysfunction[1-5] (p. 2348.2) with some beneficial results. It is usually given sublingually although it has also been given subcutaneously.[1] Inhaled apomorphine is also under investigation.[6]

1. Segraves RT, *et al.* Effect of apomorphine on penile tumescence in men with psychogenic impotence. *J Urol (Baltimore)* 1991; **145:** 1174–5.
2. Heaton JPW, *et al.* Recovery of erectile function by the oral administration of apomorphine. *Urology* 1995; **45:** 200–6.
3. Dula E, *et al.* Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. *Urology* 2000; **56:** 130–5.
4. Martinez R, *et al.* Clinical experience with apomorphine hydrochloride: the first 107 patients. *J Urol (Baltimore)* 2003; **170:** 2352–5.
5. Gontero P, *et al.* Clinical efficacy of apomorphine SL in erectile dysfunction of diabetic men. *Int J Impot Res* 2005; **17:** 80–5.
6. Riley A, *et al.* Inhalation device allows novel administration of apomorphine in men with erectile dysfunction: efficacy and safety findings. *J Sex Med* 2010; **7:** 1508–17.

Parkinsonism. *DIAGNOSIS.* Test doses of subcutaneous apomorphine have been used in the differential diagnosis of parkinsonian syndromes,[1-4] to distinguish forms responsive to dopaminergics from other parkinsonian syndromes such as Wilson's disease, corticobasal degeneration, and diffuse Lewy-body dementia. Oral challenge with levodopa is still the best test of dopaminergic responsiveness[5,6] but apomorphine has proved of value in re-assessing patients who have become less responsive to levodopa.[1,4]

1. Barker R, *et al.* Subcutaneous apomorphine as a diagnostic test for dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1989; **i:** 675.
2. Oertel WH, *et al.* Apomorphine test for dopaminergic responsiveness. *Lancet* 1989; **i:** 1262–3.
3. Frankel JP, *et al.* Use of apomorphine to test for dopamine responsiveness in Wilson's disease. *Lancet* 1989; **ii:** 801–2.
4. Hughes AJ, *et al.* Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1990; **336:** 32–4.
5. Steiger MJ, Quinn NP. Levodopa challenge test in Parkinson's disease. *Lancet* 1992; **339:** 751–2.
6. Müller T, *et al.* Repeated rating improves value of diagnostic dopaminergic challenge tests in Parkinson's disease. *J Neural Transm* 2003; **110:** 603–9.

TREATMENT. Although apomorphine has produced benefit in Parkinson's disease (p. 889.1) when given orally, the high doses required to overcome extensive first-pass hepatic metabolism (up to 1.4 g daily in one study[1]), were associated with uraemia. The use of apomorphine in Parkinson's disease has therefore been limited by the need for parenteral dosage. The current main use of apomorphine in Parkinson's disease is for the stabilisation of patients with 'on-off' fluctuations unresponsive to other dopamine agonists. It is usually given subcutaneously either by injection or infusion but a review[2] of the use of apomorphine in Parkinson's disease also discussed studies of rectal, sublingual, and intranasal use. Inhaled apomorphine is also under investigation.

1. Cotzias GC, *et al.* Treatment of Parkinson's disease with aporphines. *N Engl J Med* 1976; **294:** 567–72.
2. Koller W, Stacy M. Other formulations and future considerations for apomorphine for subcutaneous injection therapy. *Neurology* 2004; **62** (suppl 4): S22–S26.

Adverse Effects

Treatment of parkinsonism. Apomorphine usually produces nausea and vomiting when given in therapeutic doses but these effects can be controlled by treatment with domperidone or trimethobenzamide. Transient sedation can be common during the first few weeks of treatment. Increased salivation and perspiration have also been reported. Apomorphine can produce neuropsychiatric disturbances including increasing cognitive impairment, personality changes, confusion, and hallucinations. Signs of CNS stimulation including euphoria, lightheadedness, restlessness, tremor, tachycardia, and tachypnoea occur less frequently. Apomorphine may induce dyskinesias during 'on' periods in patients with parkinsonism and these may be severe enough to require stopping therapy; postural instability and falls may also be a problem. Transient orthostatic hypotension may also occur infrequently. Eosinophilia has occurred rarely. The use of apomorphine with levodopa may cause haemolytic anaemia and treatment may need to be stopped if this cannot be satisfactorily controlled through dosage adjustment. Induration, nodule formation, and panniculitis, sometimes leading to ulceration, often develops at the site of subcutaneous injection.

Management of erectile dysfunction. The most common adverse effects have been nausea, headache, and dizziness. Other effects reported include yawning, rhinitis, pharyngitis, somnolence, infection, pain, increased cough, flushing, taste disturbances, and sweating. Fainting and syncope (vasovagal syndrome) have also occurred.

Overdosage with apomorphine can produce persistent vomiting, respiratory depression, bradycardia, hypotension, and coma; death may occur.

Akinesia. A 60-year-old man who was being investigated for parkinsonian symptoms became totally immobile and mute 15 minutes after receiving apomorphine 4 mg subcutaneously.[1] He remained conscious but was drowsy and sweating. Similar profound akinesia occurred on rechallenge with 2- and 6-mg doses. A diagnosis of probable nigrostriatal degeneration was made as the patient had previously shown no improvement with levodopa, but the mechanism of the idiosyncratic reaction to apomorphine was unclear.

1. Jenkins JR, Pearce JMS. Paradoxical akinetic response to apomorphine in parkinsonism. *J Neurol Neurosurg Psychiatry* 1992; **55:** 414–15.

Effects on the heart. A 67-year-old man developed palpitations with cold perspiration and chest pain, in addition to asthenia, salivation, nausea and vomiting, 5 minutes after receiving 3 mg apomorphine subcutaneously. An ECG showed atrial fibrillation with a ventricular frequency of 140 beats/minute.[1]

1. Stocchi F, *et al.* Transient atrial fibrillation after subcutaneous apomorphine bolus. *Mov Disord* 1996; **11:** 584–5.

Effects on mental function. Severe confusion, hallucinations, and acute psychosis were reported in 4 of 6 parkinsonian patients given subcutaneous apomorphine.[1] Three of the 4 had previously had mental disturbances while receiving lisuride. However, other studies failed to note effects on mental function in parkinsonian patients given apomorphine[2,3] and it has been suggested that the risk of psychosis in patients with no history of confusion or hallucinations is low.[3] UK licensed product information notes that apomorphine has been reported to exacerbate neuropsychiatric disturbances in patients with parkinsonism.

For reference to disturbed behaviour including excessive gambling, and to daytime somnolence reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

1. Ruggieri S, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **i:** 566.
2. Stibe CMH, *et al.* Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988; **i:** 403–6.
3. Poewe W, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **i:** 1084–5.

Hypersensitivity. Allergic reactions including contact dermatitis, severe rhinitis, and respiratory distress have been reported in 2 workers who came into contact with apomorphine powder.[1] Contact allergy has also been reported in a patient who developed a swollen nose and lips after intranasal use of apomorphine.[2] Skin testing in all these cases[1,2] gave a positive reaction to apomorphine. Biopsy of subcutaneous nodules, which develop at the site of injection in most patients using apomorphine subcutaneously, has not been able to clarify what type of reaction was responsible for the development of panniculitis.[3] Although the nodules may slowly resolve the sites are often unsuitable for reuse as absorption from them is unpredictable; concern has been expressed that this may limit long-term use of apomorphine.[3]

1. Dahlquist I. Allergic reactions to apomorphine. *Contact Dermatitis* 1977; **3:** 349–50.
2. van Laar T, *et al.* Nasolabiale allergische reactie op intranasale toediening van apomorfine bij de ziekte van Parkinson. *Ned Tijdschr Geneeskd* 1992; **136** (suppl 47): 26–7.
3. Acland KM, *et al.* Panniculitis in association with apomorphine infusion. *Br J Dermatol* 1998; **138:** 480–2.

Oedema. Severe reversible oedema of the lower limbs developed in a patient receiving subcutaneous apomorphine.[1] Oedema recurred when apomorphine was reintroduced, but to a lesser extent.

1. Vermersch P. Severe oedema after subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **ii:** 802.

Stomatitis. Stomatitis, severe enough to warrant stopping treatment, occurred in 4 of 8 patients after 2 to 6 months of therapy with sublingual apomorphine.[1]

1. Montastruc JL, *et al.* Sublingual apomorphine in Parkinson's disease: a clinical and pharmacokinetic study. *Clin Neuropharmacol* 1991; **14:** 432–7.

Treatment of Adverse Effects

In the UK, domperidone is usually given to control nausea and vomiting when apomorphine is used in the management of Parkinson's disease; pretreatment with domperidone for at least 2 days is advised before starting treatment with apomorphine. Usually domperidone can be withdrawn gradually over several weeks or longer although some patients may need to continue treatment indefinitely. In the USA, trimethobenzamide hydrochloride is used similarly, beginning 3 days before starting apomorphine treatment.

In overdosage an opioid antagonist such as naloxone has been given to treat excessive vomiting, and CNS and respiratory depression.

References.

1. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; **14:** 442–9.

Precautions

Apomorphine should not be given to patients with respiratory or CNS depression, hypersensitivity to opioids, neuropsychiatric problems, or dementia. It should be used with caution in patients prone to nausea and vomiting or when vomiting is likely to pose a risk. Apomorphine should also be used with care in patients with pulmonary, cardiovascular, or endocrine disease or with renal or hepatic impairment. Extra care is needed when starting treatment in elderly or debilitated patients and in those with a history of orthostatic hypotension. Patients who suffer dizziness, lightheadedness, or syncope should not drive or operate machinery.

Treatment of parkinsonism. Apomorphine is not suitable for use in patients who have an 'on' response to levodopa marred by severe dyskinesia, hypotonia, or psychiatric effects; it should also not be used in those with hepatic impairment. Periodic monitoring of hepatic, renal, haematopoietic, and cardiovascular function has been advised and the *BNF* recommends that patients receiving apomorphine with levodopa should be screened for haemolytic anaemia and thrombocytopenia on starting treatment and then every 6 months. Patients who develop anaemia, or those who have continuing confusion or hallucinations during treatment with apomorphine require observation and dosage adjustment under specialist supervision; treatment may need to be stopped. Excessive daytime sleepiness and sudden onset of sleep may also occur with apomorphine and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Local subcutaneous reactions can sometimes be reduced by using sodium chloride 0.9% to dilute injection solutions, by rotating injection sites, and possibly by use of ultrasound in areas of nodularity and induration.

Management of erectile dysfunction. UK licensed product information has warned that drugs for erectile dysfunction should be used with caution in patients with anatomical penile deformity.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies apomorphine as probably not porphyrinogenic when given sublingually; it may be used as a drug of first choice and no precautions are needed.[1] No classification is offered when used in injectable form.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

Apomorphine should be used with caution in patients receiving antihypertensives or organic nitrates as it may potentiate their hypotensive effects. Enhanced hypotensive effects may also occur when alcohol is given with apomorphine. The therapeutic effects of apomorphine may be antagonised by antipsychotics and other drugs that act as CNS dopamine inhibitors. The effect of apomorphine is possibly enhanced by entacapone and memantine.

Antiemetics. *Domperidone* (in the UK) and *trimethobenzamide* (in the USA) are used with apomorphine to control nausea and vomiting when it is prescribed for the management of parkinsonism. However, whether other antiemetics may safely be used is less clear. US licensed product information contra-indicates the use of *ondansetron* and related 5-HT_3 antagonists with apomorphine, on the grounds that profound hypotension and loss of consciousness have been reported in patients given this combination. However, UK licensed product information makes no mention of such a contra-indication, and licensed information for lower-dose products used in the management of erectile dysfunction notes that on the basis of interaction studies, ondansetron hydrochloride or *prochlorperazine maleate* may safely be given to patients receiving apomorphine for this indication.

Pharmacokinetics

Apomorphine is well absorbed after subcutaneous injection but undergoes extensive first-pass hepatic metabolism when given by mouth and oral bioavailability is low. However, it is readily absorbed after sublingual doses and peak plasma concentrations occur in about 40 to 60 minutes; bioavailability is reported to be about 17 to 18% compared with subcutaneous injection. Apomorphine is about 90% bound to plasma proteins, mainly to albumin.

Apomorphine is extensively metabolised in the liver, mainly by conjugation with glucuronic acid or sulfate; the major metabolite is apomorphine sulfate. It is also demethylated to produce norapomorphine. Most of a dose is excreted in urine, mainly as metabolites.

References.

1. Neef C, van Laar T. Pharmacokinetic-pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. *Clin Pharmacokinet* 1999; **37:** 257–71.
2. Argiolas A, Hedlund H. The pharmacology and clinical pharmacokinetics of apomorphine SL. *BJU Int* 2001; **88** (suppl 3): 18–21.
3. LeWitt PA. Subcutaneously administered apomorphine: pharmacokinetics and metabolism. *Neurology* 2004; **62** (suppl 4): S8–S11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Apokinon; ***Austral.***: Apomine; ***Austria***: APO-go; ***Braz.***: Uprima; ***Chile***: APO-go; Noc; ***China***: Li Ke Ji (丽科吉); ***Cz.***: APO-go; ***Denm.***: APO-go; ***Fin.***: APO-go; ***Fr.***: Apokinon; ***Ger.***: APO-go; ***Gr.***: APO-go; ***Hong Kong***: APO-go; ***Irl.***: APO-go; ***Israel***: APO-go; ***Ital.***: Apofin; ***Jpn***: Apokyn; Ixense†; ***Mex.***: Taluvian; ***Neth.***: APO-go; Dacepton; ***Norw.***: Britaject; ***NZ***: APO-go†; Apomine; ***Port.***: APO-go; ***Spain***: APO-go; ***Swed.***: APO-go; ***Thai.***: APO-go; Ixense; Uprima; ***Turk.***: APO-go; ***UK***: APO-go; ***USA***: Apokyn.

Homoeopathic Preparations. ***Austral.***: Travellers Relief; ***Austria***: Vomitusheel; ***Fr.***: Apomorphinum Complexe No 97†; Bilinum Complexe No 113; ***Ger.***: Homvio-Em; Vomistop; ***Switz.***: Nelsons Travella†; Vomitusheel; ***UK***: Travella.

Pharmacopoeial Preparations

USP 36: Apomorphine Hydrochloride Tablets.

Benserazide *(BAN, USAN, rINN)*

Benseratsidi; Benserazid; Benserazida; Bensérazide; Benserazidum; Ro-4-4602; Бенсеразид.

DL-Serine 2-(2,3,4-trihydroxybenzyl)hydrazide; 2-Amino-3-hydroxy-2′-(2,3,4-trihydroxybenzyl)propionohydrazide.

$C_{10}H_{15}N_3O_5$=257.2

CAS — 322-35-0.

UNII — 762OS3ZEJU.

Benserazide Hydrochloride *(BANM, rINNM)*

Benseratsidihydrokloridi; Benserazida, hidrocloruro de; Bensérazide, chlorhydrate de; Benserazid-hydrochlorid; Benserazidhydrochlorid; Benserazidhydroklorid; Benserazidi Hydrochloridum; Benserazido hidrochloridas; Benszerazid-hidroklorid; Hidrocloruro de benserazida; Serazide Hydrochloride; Бенсеразида Гидрохлорид.

$C_{10}H_{15}N_3O_5$,HCl=293.7

CAS — 14919-77-8; 14046-64-1.

UNII — B66E5RK36Q.

NOTE. Compounded preparations of benserazide hydrochloride may be represented by the following names:

- Co-beneldopa *(BAN)*—benserazide 1 part and levodopa 4 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Benserazide Hydrochloride). A white or yellowish-white or orange-white crystalline powder. It shows polymorphism. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

Solubility. Benserazide is unstable in a neutral, alkaline, or strongly acidic medium.[1]

1. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; **28:** 302–7.

Uses and Administration

Benserazide hydrochloride is a peripheral dopa-decarboxylase inhibitor with actions similar to those of carbidopa (p. 900.3) and is used similarly as an adjunct to levodopa in the treatment of parkinsonism (p. 889.1). For details of dosage, see Levodopa, p. 902.3.

References.

1. Dingemanse J, *et al.* Pharmacodynamics of benserazide assessed by its effects on endogenous and exogenous levodopa pharmacokinetics. *Br J Clin Pharmacol* 1997; **44:** 41–8.

Adverse Effects and Precautions

Early reports[1] noted developmental abnormalities of the *rat* skeleton, but others found no evidence of any disorder involving bone metabolism in man.[2] Nevertheless, licensed product information recommends that benserazide should not be given to patients under 25 years of age, nor to pregnant women or to women of child-bearing potential in the absence of adequate contraception.

1. Theiss E, Schärer K. Toxicity of L-dopa and a decarboxylase inhibitor in animal experiments. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson.* Geneva: Georg, 1971: 497–504.
2. Ziegler WH, *et al.* Toxicity of L-dopa and a dopa decarboxylase inhibitor in humans. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson.* Geneva: Georg, 1971: 505–16.

Pharmacokinetics

Pharmacokinetic and metabolic studies[1,2] in *animals* and man have shown that, after oral doses in parkinsonian patients, benserazide was rapidly absorbed to the extent of about 58%; giving it with levodopa tended to increase this slightly. Benserazide was rapidly excreted in the urine in the form of metabolites, mostly within the first 6 hours; 85% of urinary excretion had occurred within 12 hours. It is mainly metabolised in the gut and appears to protect levodopa against decarboxylation primarily in the gut, but also in the rest of the organism, mainly by way of its metabolite trihydroxybenzylhydrazine. Benserazide did not cross the blood-brain barrier in *rats*.

1. Schwartz DE, *et al.* Pharmacokinetics of the decarboxylase benserazide in man: its tissue distribution in the rat. *Eur J Clin Pharmacol* 1974; **7:** 39–45.
2. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; **28:** 302–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Restex.

Multi-ingredient Preparations. ***Arg.***: Madopar; ***Austral.***: Madopar; ***Austria***: Madopar; Restex; ***Belg.***: Prolopa; ***Braz.***: Prolopa; ***Canad.***: Prolopa; ***Chile***: Melitase; Prolopa; ***Cz.***: Madopar; ***Denm.***: Madopar; ***Fin.***: Madopar; ***Fr.***: Modopar; ***Ger.***: Levodopa comp B†; Levopar†; Madopar; PK-Levo†; ***Gr.***: Madopar; ***Hong Kong***: Madopar; ***Hung.***: Madopar; ***India***: Benspar; Madopar-F; ***Indon.***: Leparson; Levazide; Levopar; Madopar; Pardoz; ***Irl.***: Madopar; ***Israel***: Levopar Plus; ***Ital.***: Madopar; ***Malaysia***: Madopar; ***Mex.***: Madopar; ***Neth.***: Madopar; Modopar†; ***Norw.***: Madopar; ***NZ***: Madopar; ***Philipp.***: Madopar; ***Pol.***: Madopar; ***Port.***: Madopar; ***Rus.***: Madopar (Мадопар); ***S.Afr.***: Madopar; ***Singapore***: Madopar; ***Spain***: Madopar; ***Swed.***: Madopark; ***Switz.***: Madopar; ***Thai.***: Madopar; Udopar-250; Vopar; ***Turk.***: Madopar; ***UK***: Madopar; ***Ukr.***: Madopar (Мадопар); ***Venez.***: Madopar.

Pharmacopoeial Preparations

BP 2014: Co-beneldopa Capsules; Dispersible Co-beneldopa Tablets; Prolonged-release Co-beneldopa Capsules.

Benzatropine Mesilate *(BANM, rINNM)*

Benzatropina, mesilato de; Benzatropine, Mésilate de; Benzatropine Methanesulfonate; Benzatropini Mesilas; Benztropine Mesylate; Mesilato de benzatropina; Бензатропина Мезилат.

(1*R*,3*r*,5*S*)-3-Benzhydryloxytropane methanesulphonate.

$C_{21}H_{25}NO,CH_4O_3S$=403.5

CAS — 86-13-5 (benzatropine); 132-17-2 (benzatropine mesilate).

ATC — N04AC01.

ATC Vet — QN04AC01.

UNII — WMJ8TL7510.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Benzatropine Mesilate). A white, odourless or almost odourless, crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in ether.

USP 36: (Benztropine Mesylate). A white, slightly hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether. Store in airtight containers.

Uses and Administration

Benzatropine mesilate is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3); it also has antihistaminic properties.

Benzatropine is used for the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias.

Benzatropine mesilate is given orally or, if necessary, by intramuscular or intravenous injection.

The usual oral daily dose of benzatropine mesilate in **parkinsonism** is 1 to 2 mg, with a range of 0.5 to 6 mg. In arteriosclerotic and idiopathic parkinsonism the usual initial daily dose is 0.5 to 1 mg at bedtime, although some patients may require an initial daily dose of 4 to 6 mg. Patients with post-encephalitic parkinsonism often tolerate an initial daily dose of 2 mg, given in one or more doses, although highly-sensitive patients may initially be given 500 micrograms at bedtime. The actions of benzatropine are cumulative, and may not be evident for several days after beginning therapy. Doses may be gradually increased by 500 micrograms every 5 to 6 days to a maximum of 6 mg daily if necessary. Maintenance therapy may be given as a single daily dose at bedtime or in divided doses 2 to 4 times daily. Similar doses may also be given intramuscularly, if appropriate.

In the management of **drug-induced extrapyramidal symptoms** doses of 1 to 4 mg once or twice daily have been given orally or parenterally. Therapy should be stopped after 1 to 2 weeks to assess whether it is still necessary.

In an emergency such as **acute dystonia**, benzatropine mesilate may be injected intramuscularly or intravenously in a dose of 1 to 2 mg; intramuscular injection is reported to produce an effect as quickly as intravenous dosage so the latter is rarely necessary.

Benzatropine has also been given as the hydrochloride.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Drowsiness may be severe in some patients and patients so affected should not drive or operate machinery. Mental disturbances and excitement may occur with large doses or in susceptible patients.

Abuse. For mention of abuse of benzatropine see under Trihexyphenidyl Hydrochloride, p. 918.1.

Effects on the heart. Paradoxical sinus bradycardia in a patient with depression and psychotic symptoms was attributed to benzatropine since it persisted despite modification to other treatment and resolved only when benzatropine was withdrawn.[1]

1. Voinov H, *et al.* Sinus bradycardia related to the use of benztropine mesylate. *Am J Psychiatry* 1992; **149:** 711.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies benzatropine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Antidepressants. A report[1] of 5 patients who developed delirium while taking an antipsychotic, an *SSRI*, and benzatropine suggested that there might be an interaction between SSRIs and benzatropine.

1. Roth A, *et al.* Delirium associated with the combination of a neuroleptic, an SSRI, and benztropine. *J Clin Psychiatry* 1994; **55:** 492–5.

Antipsychotics. Fatal heat stroke after exposure to an ambient temperature of over 29 degrees has been reported[1,2] in patients receiving benzatropine with antipsychotics. Paralytic ileus, sometimes fatal, has also been seen in patients taking benzatropine with antipsychotics.[3]

1. Stadnyk AN, Glezos JD. Drug-induced heat stroke. *Can Med Assoc J* 1983; **128:** 957–9.
2. Tyndel F, Labonté R. Drug-facilitated heat stroke. *Can Med Assoc J* 1983; **129:** 680.
3. Wade LC, Ellenor GL. Combination mesoridazine- and benztropine mesylate-induced paralytic ileus: two case reports. *Drug Intell Clin Pharm* 1980; **14:** 17–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Benztrop; Cogentin; ***Austria***: Cogentin†; ***Cz.***: Apo-Benztropine†; ***Hong Kong***: Cogentin; ***NZ***: Benztrop; Cogentin; ***Singapore***: Cogentin; ***Thai.***: Cogentin; ***UK***: Cogentin; ***USA***: Cogentin.

Pharmacopoeial Preparations
BP 2014: Benzatropine Injection; Benzatropine Tablets;
USP 36: Benztropine Mesylate Injection; Benztropine Mesylate Tablets.

Biperiden *(BAN, rINN)*

Biperideeni; Bipéridène; Biperideno; Biperidenum; Бипериден.
1-(Bicyclo[2.2.1]hept-5-en-2-yl)-1-phenyl-3-piperidinopropan-1-ol.
$C_{21}H_{29}NO$=311.5
CAS — 514-65-8.
ATC — N04AA02.
ATC Vet — QN04AA02.
UNII — 0FRP6G56LD.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Biperiden). A white, practically odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform. Protect from light.

Biperiden Hydrochloride *(BANM, rINNM)*

Biperideenihydrokloridi; Biperiden Hidroklorür; Bipéridène, Chlorhydrate de; Biperidén-hidroklorid; Biperidenhydrochlorid; Biperiden-hydrochlorid; Biperidenhydroklorid; Biperideni Hydrochloridum; Biperideno hidrochloridas; Biperideno, hidrocloruro de; Hidrocloruro de biperideno; Бипериден Гидрохлорид.
$C_{21}H_{29}NO,HCl$=347.9
CAS — 1235-82-1.
ATC — N04AA02.
ATC Vet — QN04AA02.
UNII — K35N76CUHF.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Biperiden Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol; very slightly soluble in dichloromethane. A 0.2% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Biperiden Hydrochloride). A white, practically odourless, crystalline powder. Slightly soluble in water, in alcohol, in chloroform, and in ether; sparingly soluble in methyl alcohol. Protect from light.

Biperiden Lactate *(BANM, rINNM)*

Biperiden Laktat; Bipéridène, Lactate de; Biperideni Lactas; Biperideno, lactato de; Lactato de biperideno; Бипериден Лактат.
$C_{21}H_{29}NO,C_3H_6O_3$=401.5
CAS — 7085-45-2.
ATC — N04AA02.
ATC Vet — QN04AA02.
UNII — 09TD6C5147.

Pharmacopoeias. *US* includes Biperiden Lactate Injection.

Uses and Administration

Biperiden is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3) but with more potent antinicotinic properties.

Biperiden is used in the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias.

Biperiden is given orally as the hydrochloride and by injection as the lactate; doses are expressed in terms of the relevant salt.

US licensed product information gives the initial oral dose for **Parkinson's disease** as 2 mg of the hydrochloride 3 or 4 times daily which can then be increased according to response to a maximum of 16 mg daily. In some countries a much lower initial oral dose of 1 mg twice daily is recommended. In the USA the recommended oral dose for **drug-induced extrapyramidal symptoms** is 2 mg of the hydrochloride 1 to 3 times daily. In other countries a wider dose range of 1 to 4 mg 1 to 4 times daily is used. Modified-release tablets with different dose schedules are available in some countries.

In severe cases, or when biperiden cannot be given orally, the lactate can be given by intramuscular or slow intravenous injection; total daily doses of up to 10 to 20 mg daily have been used.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Parenteral use may be followed by slight transient hypotension.

Abuse. Abuse of biperiden has been reported in psychiatric patients.[1,2]

1. Pullen GP, *et al.* Anticholinergic drug abuse: a common problem? *BMJ* 1984; **289**: 612–13.
2. Ozucelik DN, *et al.* Gluteal abscess following intramuscular injection of dissolved biperiden tablets. *Int J Clin Pract* 2007; **61:** 1417–18.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies biperiden as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Biperiden is readily absorbed from the gastrointestinal tract, but bioavailability is only about 30% suggesting that it undergoes extensive first-pass metabolism. Biperiden has an elimination half-life of about 20 hours.

References.
1. Hollmann M, *et al.* Biperiden effects and plasma levels in volunteers. *Eur J Clin Pharmacol* 1984; **27:** 619–21.
2. Grimaldi R, *et al.* Pharmacokinetic and pharmacodynamic studies following the intravenous and oral administration of the antiparkinsonian drug biperiden to normal subjects. *Eur J Clin Pharmacol* 1986; **29:** 735–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Akineton; Berofin; Darcipireno†; Denzolam; Sinekin; ***Austral.***: Akineton; ***Austria***: Akineton; ***Belg.***: Akineton; ***Braz.***: Akineton; Cinetol; Parkinsol; Propark; ***Chile***: Akineton†; ***Cz.***: Akineton; ***Denm.***: Akineton; ***Fin.***: Akineton; Ipsatol; ***Fr.***: Akineton; ***Ger.***: Akineton; ***Gr.***: Akineton; ***Hung.***: Akineton; ***Irl.***: Akineton; ***Israel***: Dekinet; ***Ital.***: Akineton; ***Mex.***: Akineton; Bikipen†; Kinex; ***Neth.***: Akineton; ***Norw.***: Akineton; ***Philipp.***: Aketon; Akidin; Akineton; ***Pol.***: Akineton; ***Port.***: Akineton; ***Rus.***: Akineton (Акинетон); Mendilex (Мендилекс); ***S.Afr.***: Akineton; ***Spain***: Akineton; ***Swed.***: Akineton; ***Switz.***: Akineton; ***Turk.***: Akineton; ***USA***: Akineton; ***Venez.***: Akineton.

Pharmacopoeial Preparations
USP 36: Biperiden Hydrochloride Tablets; Biperiden Lactate Injection.

Bornaprine Hydrochloride *(BANM, rINNM)*

Bornaprin Hidroklorür; Bornaprina, hidrocloruro de; Bornaprine, Chlorhydrate de; Bornaprini Hydrochloridum; Hidrocloruro de bornaprina; Борнаприна Гидрохлорид.
3-Diethylaminopropyl 2-phenylbicyclo[2.2.1]heptane-2-carboxylate hydrochloride.
$C_{21}H_{31}NO_2,HCl$=365.9
CAS — 20448-86-6 (bornaprine); 26908-91-8 (bornaprine hydrochloride).
ATC — N04AA11.
ATC Vet — QN04AA11.
UNII — R99RGW1B2Q.

Profile

Bornaprine hydrochloride is a quaternary ammonium antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It is used in the symptomatic treatment of **parkinsonism** (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias; it is claimed to be mainly effective against tremor. Bornaprine hydrochloride is given orally in initial doses of 2 mg daily gradually increased to 6 to 12 mg daily according to response. It is also used in the treatment of **hyperhidrosis** (p. 1685.1) in a dose of 4 to 8 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Sormodren; ***Ger.***: Sormodren; ***Gr.***: Sormodren; ***Ital.***: Sormodren; ***Turk.***: Sormodren.

Bromocriptine Mesilate *(BANM, rINNM)*

Bromocriptina, mesilato de; Bromocriptine, mésilate de; Bromocriptine Mesylate (USAN); Bromocriptine Methanesulphonate; Bromocriptini Mesilas; Bromocriptinmesilat; Bromocryptine Mesylate; 2-Bromo-α-ergocryptine Mesylate; 2-Bromoergocryptine Monomethanesulfonate; Bromokriptiinimesilaatti; Bromokriptin Mesilat; Bromokriptinmesilat; Bromokriptin-mesylát; Brómokriptin-mezilát; Bromokriptino mesilatas; CB-154 (bromocriptine); Mesilato de bromocriptina; Бромокриптина Мезилат.
(5′*S*)-2-Bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-ergotaman-3′,6′,18-trione methanesulphonate.
$C_{32}H_{40}BrN_5O_5,CH_4O_3S$=750.7
CAS — 25614-03-3 (bromocriptine); 22260-51-1 (bromocriptine mesilate).
ATC — G02CB01; N04BC01.
ATC Vet — QG02CB01; QN04BC01.
UNII — FFP983J3OD.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Bromocriptine Mesilate). A white or slightly coloured fine crystalline powder. Practically insoluble in water; soluble in alcohol; sparingly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in a mixture of 2 parts methyl alcohol to 8 of water has a pH of 3.1 to 3.8. Store in airtight containers at a temperature not exceeding -15 degrees. Protect from light.

USP 36: (Bromocriptine Mesylate). A white or slightly coloured fine crystalline powder; odourless or having a weak characteristic odour. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Uses and Administration

Bromocriptine, an ergot derivative (p. 2137.1), is a dopamine D_2-agonist. It inhibits the secretion of prolactin (p. 2145.1) from the anterior pituitary and is used in the treatment of prolactinoma and endocrinological disorders associated with hyperprolactinaemia (p. 896.2), including amenorrhoea, galactorrhoea, hypogonadism, and infertility in both men and women. Bromocriptine is also used to suppress puerperal lactation for medical reasons (p. 896.2); it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support. Growth hormone secretion may be suppressed by bromocriptine in some patients with acromegaly (p. 896.1). Because of its dopaminergic activity bromocriptine is also used in the management of Parkinson's disease (p. 896.3). It is used in some countries as an adjunct to diet and exercise to improve glycaemic control in type 2 diabetes mellitus (p. 459.1) but its exact mode of action is unknown.

Bromocriptine is usually given orally as the mesilate; doses are expressed in terms of the base. Bromocriptine mesilate 2.87 mg is equivalent to about 2.5 mg of bromocriptine. Oral doses should be taken with food. Bromocriptine mesilate has also been given intramuscularly as a depot injection for disorders associated with hyperprolactinaemia.

For the **prevention of puerperal lactation** bromocriptine 2.5 mg is given on the day of delivery followed by 2.5 mg twice daily for 14 days. The risk of hypotension and, more rarely, hypertension must be borne in mind and it has been recommended that bromocriptine should not be given until at least 4 hours after delivery. For the **suppression of established lactation** it is given in a dose of 2.5 mg daily for 2 to 3 days subsequently increased to 2.5 mg twice daily for 14 days.

For the treatment of other conditions (see below) the dose of bromocriptine is usually increased gradually. In the UK, typically, an initial dose of 1 to 1.25 mg at night is given,

increased to 2 to 2.5 mg at night after 2 to 3 days, and subsequently increased by 1 to 2.5 mg every 2 to 3 days to a dose of 2.5 mg twice daily, or more if necessary. In the USA, a usual starting dose is 1.25 to 2.5 mg daily increased by 2.5 mg every 2 to 7 days.

In the **treatment of hypogonadism and galactorrhoea syndromes and infertility** bromocriptine is introduced gradually as described above. Most patients with hyperprolactinaemia respond to 7.5 mg daily but up to 30 mg daily may be required. Infertile patients without raised serum concentrations of prolactin are usually given 2.5 mg twice daily. In patients known to have **prolactinomas** the dose is also introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days to a dose of 5 mg every 6 hours but occasionally patients may require up to 30 mg daily. Although unlicensed in the UK and USA, bromocriptine is used in some countries for **cyclical benign breast and menstrual disorders**. In benign breast disease bromocriptine is introduced gradually up to a daily dosage of 5 to 7.5 mg if necessary. In the treatment of premenstrual symptoms therapy should begin on day 14 of the cycle and introduced gradually up to a usual dosage of 2.5 mg twice daily until menstruation begins.

Bromocriptine may be used as an adjunct to surgery and radiotherapy to reduce plasma-growth hormone concentrations in **acromegalic patients**. In the UK, it is introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days if necessary up to 5 mg every 6 hours, according to response. In the USA, the usual starting dose (see above) may be increased by 1.25 to 2.5 mg every 3 to 7 days to a maximum daily dose of 100 mg if necessary; the usual dosage range is 20 to 30 mg daily.

In **Parkinson's disease** bromocriptine has been used alone, although it is usually given as an adjunct to levodopa treatment. It should be introduced even more gradually than the regimen above, and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved. In the UK, a suggested initial dose is the equivalent of 1 to 1.25 mg of bromocriptine at night during week 1, increased to 2 to 2.5 mg at night for week 2, 2.5 mg twice daily for week 3, and for week 4, 2.5 mg three times daily; the dose may be increased thereafter by 2.5 mg every 3 to 14 days according to response. The EMEA has recommended a maximum dose of 30 mg daily. In the USA, a usual starting dose is 1.25 mg twice daily increased by 2.5 mg every 14 to 28 days to a maximum dose of 100 mg daily if necessary.

In the USA, bromocriptine is used as an adjunct in **type 2 diabetes mellitus**. An initial oral dose of 800 micrograms daily is increased in weekly steps of 800 micrograms, according to tolerance, to a daily dose of between 1.6 to 4.8 mg; doses are given once daily within 2 hours of waking in the morning.

For details of uses and associated doses in children and adolescents, see below.

Administration in children. In the UK, bromocriptine is licensed for the treatment of prolactinomas and gigantism (acromegaly), under specialist supervision, in children and adolescents aged 7 to 17 years. For prolactinomas, an initial oral dose of 1 mg is given 2 or 3 times daily. A higher starting dose of 1.25 mg given 2 or 3 times daily is suggested for gigantism. Thereafter, the dose may be gradually increased according to response; a maximum of 20 mg daily is recommended in those aged 13 years or older, regardless of indication, while younger children may be given a maximum dose of 5 mg daily for prolactinomas and 10 mg daily for gigantism.

In the USA, bromocriptine is licensed for the treatment of prolactinomas in children and adolescents aged 11 to 15 years. An initial oral dose of 1.25 to 2.5 mg daily may be gradually increased, according to response, to a usual range of 2.5 to 10 mg daily.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and bromocriptine has been used in acromegaly (p. 1921.1) as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels. While it is less effective than somatostatin analogues, it can be given orally and is therefore more convenient to administer.

Cushing's syndrome. There have been occasional reports of benefit with the use of bromocriptine in the treatment of Cushing's syndrome (p. 2559.1). Remission of ACTH-dependent Cushing's syndrome was maintained for 6 years by bromocriptine 2.5 mg twice daily in a patient who had initially received pituitary irradiation.[1] However, the same group subsequently reported that they had found that bromocriptine did not effectively reduce ACTH secretion following bilateral adrenalectomy.[2]

1. Atkinson AB, *et al.* Six year remission of ACTH-dependent Cushing's syndrome using bromocriptine. *Postgrad Med J* 1985; **61:** 239–42.
2. Atkinson AB. The treatment of Cushing's syndrome. *Clin Endocrinol (Oxf)* 1991; **34:** 507–13.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as bromocriptine in the management of hepatic encephalopathy see p. 1811.2.

Hyperprolactinaemia and prolactinomas. Prolactinomas (prolactin-secreting pituitary adenomas) are among the commonest causes of hyperprolactinaemia. Raised serum-prolactin concentrations can result in reduced gonadotrophin production, which in turn may suppress gonadal function. Consequences may include oligomenorrhoea or amenorrhoea, and infertility in either sex. Galactorrhoea may also result from high prolactin levels and can occur in men as well as women.

Dopamine is the major inhibitory factor in the hypothalamus and directly inhibits the secretion of prolactin. Bromocriptine, a dopamine agonist, has been the first choice of treatment in many centres for the treatment of hyperprolactinaemia secondary to a prolactinoma although cabergoline is now preferred by some. Bromocriptine is extremely effective in controlling elevated circulating prolactin concentrations and restoring gonadal function; although it is rarely curative, it may produce considerable shrinkage of the adenoma.[1]

The sensitivity of hyperprolactinaemia to bromocriptine therapy can vary considerably between patients and this is reflected in the wide range of oral doses required to reduce prolactin concentrations to normal levels. Although beginning therapy with gradually increasing doses can minimise adverse effects it has been reported that about 5 to 10% of patients are unable to tolerate oral bromocriptine;[2] other dosage routes have therefore been investigated. Bromocriptine is well absorbed from standard oral tablets placed in the vagina and appears to be both effective in lowering prolactin concentrations and well tolerated when given by this route.[3] However, limitations are considered to be the relatively short duration of action and the relatively low dose that can be given.[2] A depot preparation given intramuscularly in a dose of 50 to 250 mg monthly has been found to be effective and well tolerated in long-term studies;[4,5] it is reported to be used in some centres to begin treatment for macroprolactinomas.[2]

For discussions of the management of hyperprolactinaemia and associated disorders see p. 2252.2 (hyperprolactinaemia), p. 2251.3 (amenorrhoea), p. 2252.3 (hypogonadism), p. 2348.2 (erectile dysfunction), and p. 2253.1 (infertility).

1. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. *Pituitary* 2002; **5:** 55–65.
2. Ciccarelli E, Camanni F. Diagnosis and drug therapy of prolactinoma. *Drugs* 1996; **51:** 954–65.
3. Ginsburg J, *et al.* Vaginal bromocriptine. *Lancet* 1991; **338:** 1205–6.
4. Ciccarelli E, *et al.* Long term therapy of patients with macroprolactinoma using repeatable injectable bromocriptine. *J Clin Endocrinol Metab* 1993; **76:** 484–8.
5. Ciccarelli E, *et al.* Double blind randomized study using oral or injectable bromocriptine in patients with hyperprolactinaemia. *Clin Endocrinol (Oxf)* 1994; **40:** 193–8.

PREGNANCY. References to the management of prolactinoma during pregnancy.[1-3] Bromocriptine has been successfully used for management in pregnant women, particularly if there is symptomatic enlargement of the tumour, although there continues to be debate on the appropriateness of continuous therapy in less high-risk individuals.

1. Randeva HS, *et al.* Prolactinoma and pregnancy. *Br J Obstet Gynaecol* 2000; **107:** 1064–8.
2. Bronstein MD, *et al.* Medical management of pituitary adenomas: the special case of management of the pregnant woman. *Pituitary* 2002; **5:** 99–107.
3. Chiodini I, Liuzzi A. PRL-secreting pituitary adenomas in pregnancy. *J Endocrinol Invest* 2003; **26:** 96–9.

Lactation inhibition. Because of its effects on prolactin, bromocriptine is a potent suppressor of lactation and has been widely used for the prevention of lactation in women who choose not to breast feed post partum. However, bromocriptine has been associated with severe adverse effects in some women, and its use to suppress a physiological state has been criticised (see p. 2130.1). Consequently, licensed product information from some countries recommends that bromocriptine should only be used to suppress puerperal lactation for medical reasons; it is also not recommended for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support.

Mastalgia. Since mastalgia (p. 2265.1) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months. Bromocriptine is one of the drugs that may be used to treat mastalgia.[1,2] It may improve symptoms in up to about 50% of patients with cyclical mastalgia, but is less effective in the non-cyclical form.[3,4] Adverse effects can be severe in some patients.

1. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; **47:** 284–94.
2. Anonymous. Cyclical breast pain—what works and what doesn't. *Drug Ther Bull* 1992; **30:** 1–3.
3. Pye JK, *et al.* Clinical experience of drug treatments for mastalgia. *Lancet* 1985; **ii:** 373–7.
4. Mansel RE, Dogliotti L. European multicentre trial of bromocriptine in cyclical mastalgia. *Lancet* 1990; **335:** 190–3.

Neuroleptic malignant syndrome. Bromocriptine has been used in doses of up to 30 mg daily,[1-6] usually alone or with dantrolene, in the treatment of neuroleptic malignant syndrome (p. 1050.2) although some workers have not found it to be of use.[7]

1. Mueller PS, *et al.* Neuroleptic malignant syndrome: successful treatment with bromocriptine. *JAMA* 1983; **249:** 386–8.
2. Dhib-Jalbut S, *et al.* Treatment of the neuroleptic malignant syndrome with bromocriptine. *JAMA* 1983; **250:** 484–5.
3. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; **ii:** 969–70.
4. Guerrero RM, Shifrar KA. Diagnosis and treatment of neuroleptic malignant syndrome. *Clin Pharm* 1988; **7:** 697–701.
5. Lo TCM, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; **65:** 653–5.
6. Chandran GJ, *et al.* Neuroleptic malignant syndrome: case report and discussion. *Can Med Assoc J* 2003; **169:** 439–42.
7. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.

Parkinsonism. Dopamine agonists such as bromocriptine are often used to begin treatment of parkinsonism (p. 889.1), particularly in younger patients, in an attempt to delay therapy with levodopa. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease. However, in early disease, there is no evidence that adjunctive bromocriptine prevents or delays the onset of motor complications associated with levodopa monotherapy.

References.

1. Temlett JA, *et al.* Adjunctive therapy with bromocriptine in Parkinson's disease. *S Afr Med J* 1990; **78:** 680–5.
2. Hely MA, *et al.* The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *J Neurol Neurosurg Psychiatry* 1994; **57:** 903–10.
3. Montastruc JL, *et al.* A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. *J Neurol Neurosurg Psychiatry* 1994; **57:** 1034–8.
4. Giménez-Roldán S, *et al.* Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clin Neuropharmacol* 1997; **20:** 67–76.
5. Ogawa N, *et al.* Nationwide multicenter prospective study on the long-term effects of bromocriptine for Parkinson's disease: final report of a ten-year follow-up. *Eur Neurol* 1997; **38** (suppl 2): 37–49.
6. Lees AJ, *et al.* Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology* 2001; **57:** 1687–94.
7. van Hilten, *et al.* Bromocriptine versus levodopa in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).
8. van Hilten, *et al.* Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).

Polycystic ovary syndrome. Bromocriptine has been tried in women with the polycystic ovary syndrome (p. 2253.3) who have mild basal hyperprolactinaemia without evidence of a pituitary tumour.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical but dopaminergic therapy has emerged as a common first-line choice. Bromocriptine showed some benefit in a small study.[1]

1. Walters AS, *et al.* A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Ann Neurol* 1988;**24:** 455–8.

Withdrawal syndromes. *ALCOHOL* Studies of the efficacy of bromocriptine as an aid in the maintenance of abstinence from alcohol (p. 1735.1) have yielded conflicting results.[1-4] However, it has been suggested[3] that response to bromocriptine might be linked to a specific genotype of the D_2 dopamine receptor.

1. Dongier M, *et al.* Bromocriptine in the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1991; **15:** 970–7.
2. Naranjo CA, *et al.* Long-acting bromocriptine (B) does not reduce relapse in alcoholics. *Clin Pharmacol Ther* 1995; **57:** 161.
3. Lawford BR, *et al.* Bromocriptine in the treatment of alcoholics with the D_2 dopamine receptor A1 allele. *Nat Med* 1995; **1:** 337–41.
4. Powell BJ, *et al.* A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcohol Clin Exp Res* 1995; **19:** 462–8.

Adverse Effects

Nausea is the most common adverse effect at the beginning of treatment with bromocriptine, but vomiting, dizziness, and orthostatic hypotension may also occur. Syncope has followed initial doses.

Adverse effects are generally dose-related and may therefore be more frequent with the higher doses that have been used in the treatment of parkinsonism and acromegaly. Reduction of the dosage, followed in a few days by a more gradual increase, may alleviate many adverse effects. Nausea may be reduced by taking bromocriptine with food; domperidone may also be given at least 1 hour before bromocriptine, for the first few days of therapy.

Bromocriptine and similar drugs are vasoconstrictors; Raynaud's syndrome or digital vasospasm, induced by cold, and leg cramps have been reported. Other cardiovascular effects have included erythromelalgia, prolonged severe hypotension, arrhythmias, and exacerbation of angina. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and psychiatric disorders have been reported in postpartum women given bromocriptine.

The use of ergot derivatives such as bromocriptine has been associated with retroperitoneal fibrosis, pleural thickening and effusions, and pericarditis and pericardial effusions.

Other adverse effects reported include headache, nasal congestion, drowsiness, dry mouth, constipation, diarrhoea, and altered liver-function tests. Dyskinesias and psychomotor excitation have occurred in patients suffering from parkinsonism. Gastrointestinal bleeding has been reported in acromegalic patients. Psychosis, with hallucinations, delusions, and confusion, occurs particularly when high doses are used to treat parkinsonism, but has also been reported with low doses. A neuroleptic malignant-like syndrome associated with abrupt withdrawal of bromocriptine has been reported very rarely.

Incidence of adverse effects. In 27 published studies of the treatment of Parkinson's disease, 217 of the 790 patients given bromocriptine had adverse effects.[1] Mental changes were noted in 90 patients, dyskinesia in 20, orthostatic hypotension in 40, and gastrointestinal effects in 40. The fewest adverse effects (9%) occurred with low-dose bromocriptine, more occurred with high-dose bromocriptine (27%) or with low-dose bromocriptine with levodopa (26%), and the most occurred with high-dose bromocriptine and levodopa (32%). However, those on high doses had more advanced disease and might have been more susceptible to mental changes and dyskinesias.

An analysis by the manufacturer of published reports on patients treated with bromocriptine for 1 to 10 years concluded that in general, adverse effects noted were no different from those associated with short-term treatment.[2]

1. Lieberman AN, Goldstein M. Bromocriptine in Parkinson disease. *Pharmacol Rev* 1985; **37:** 217–27.
2. Weil C. The safety of bromocriptine in long-term use: a review of the literature. *Curr Med Res Opin* 1986; **10:** 25–51.

Effects on the blood. Severe leucopenia and mild thrombocytopenia developed in a 23-year-old woman after treatment with bromocriptine 7.5 to 10 mg daily for about 3 months.[1]

1. Giampietro O, *et al.* Severe leukopenia and mild thrombocytopenia after chronic bromocriptine (CB-154) administration. *Am J Med Sci* 1981; **281:** 169–72.

Effects on the cardiovascular system. An early review noted that asymptomatic **hypotension** occurred in many subjects given bromocriptine.[1] However, faintness and dizziness, sometimes accompanied by *nausea* and *vomiting*, were common at the start of treatment with bromocriptine and these symptoms rather than an anaphylactic type of reaction were likely to account for the collapse that occurred in a few sensitive patients. Two of 53 patients with Parkinson's disease fainted after an initial dose of 1.25 or 2.5 mg, but the exact incidence of shock-like syndromes was difficult to assess; the manufacturers had stated that 22 of over 10 000 subjects given bromocriptine had had hypotension and collapse, mainly at the start of treatment.

- All patients starting treatment should be warned of the possibility of fainting. The initial dose should not exceed 1.25 to 2.5 mg and should be taken with food and in bed.

If fainting does occur recovery is usually rapid and spontaneous. Tolerance to adverse effects such as hypotension and nausea may develop rapidly.

Hypertension, seizures, stroke, and *myocardial infarction* have been associated with bromocriptine therapy, notably in postpartum women.[2-4] A study involving 1813 women suggested that the risk of **postpartum hypertension** was increased in women who had pregnancy-induced hypertension and that this risk was further increased in those who took bromocriptine for suppression of lactation.[5] A case-controlled study[6] involving 43 of the women who had had postpartum seizures while taking bromocriptine found that while the initial risk of seizures appeared to be lower in patients taking bromocriptine there was a small positive association with seizures occurring more than 72 hours after delivery.

- Although a causal relationship between the use of bromocriptine and these adverse effects in postpartum women has not been established, licensed product information recommends that bromocriptine should not be used post partum or in the puerperium in women with high blood pressure, coronary artery disease or other severe cardiovascular disorders, or symptoms or history of serious psychiatric disorders.
- It is also recommended that when bromocriptine is used in postpartum women blood pressure should be carefully monitored, especially during the first few days and if hypertension, unremitting headache, or signs of CNS toxicity develop, treatment should be discontinued immediately.

Severe dilated **cardiomyopathy** has been reported in a patient being treated with bromocriptine for microprolactinoma.[7]

For details of **fibrotic reactions** resulting in cardiovascular adverse effects, see Fibrosis, below.

1. Parkes D. Side effects of bromocriptine. *N Engl J Med* 1980; **302:** 749–50.
2. Anonymous. Postpartum hypertension, seizures, strokes reported with bromocriptine. *FDA Drug Bull* 1984; **14:** 3.
3. Ruch A, Duhring JL. Postpartum myocardial infarction in a patient receiving bromocriptine. *Obstet Gynecol* 1989; **74:** 448–51.
4. Larrazet F, *et al.* Possible bromocriptine-induced myocardial infarction. *Ann Intern Med* 1993; **118:** 199–200.
5. Watson DL, *et al.* Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? *Obstet Gynecol* 1989; **74:** 573–6.
6. Rothman KJ, *et al.* Bromocriptine and puerperal seizures. *Epidemiology* 1990; **1:** 232–8.
7. Kaushik P, *et al.* Acute onset of severe dilated cardiomyopathy during bromocriptine therapy. *Ann Pharmacother* 2004; **38:** 1219–21.

Effects on the ears. Audiometric evidence of bilateral sensorineural hearing loss was reported in 3 patients receiving bromocriptine 15 or 20 mg daily for chronic hepatic encephalopathy.[1] Hearing improved when the dose was reduced to 10 mg daily.

1. Lanthier PL, *et al.* Bromocriptine-associated ototoxicity. *J Laryngol Otol* 1984; **98:** 399–404.

Effects on electrolytes. There have been isolated reports of severe hyponatraemia associated with the use of bromocriptine.[1,2]

1. Marshall AW, *et al.* Bromocriptine-associated hyponatraemia in cirrhosis. *BMJ* 1982; **285:** 1534–5.
2. Damase-Michel C, *et al.* Hyponatraemia in a patient treated with bromocriptine. *Drug Invest* 1993; **5:** 285–7.

Effects on the eyes. Blurred vision and diplopia have been reported in several patients receiving bromocriptine.[1] Reversible myopia also developed in a patient with hyperprolactinaemia given bromocriptine.[2]

Licensed product information states that visual field impairment associated with macroprolactinoma usually resolves with bromocriptine treatment. However, in a patient with progressive visual loss due to compression of the optic chiasm by a large pituitary tumour, bromocriptine caused total visual loss within hours.[3] Vision slowly returned to normal when the patient was placed in the supine position; the most likely cause of the visual loss was thought to be orthostatic hypotension with resultant decrease in perfusion pressure to the visual system. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Bromocriptine has been reported to cause visual cortical disturbances.[4] In some cases blurred vision and transient cortical blindness have preceded seizures and strokes.

1. Calne DB, *et al.* Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; **i:** 735–7.
2. Manor RS, *et al.* Myopia during bromocriptine treatment. *Lancet* 1981; **i:** 102.
3. Couldwell WT, Weiss MH. Visual loss associated with bromocriptine. *Lancet* 1992; **340:** 1410–11.
4. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Effects on mental function. High doses of bromocriptine are well known to cause **psychotic reactions** in patients with parkinsonism.[1] However, mania has also been associated with the use of bromocriptine post partum[2,3] and it has been stated that psychological symptoms can occur with doses of only 2.5 to 5 mg daily.[4] It was also noted that, unlike the relatively mild and transient symptoms associated with levodopa, bromocriptine produces a severe psychosis in which the patient is violent and aggressive, suffering from intense delusions which are often hostile and violent; complete withdrawal of bromocriptine may still leave a residue of severe psychotic illness persisting for 1 to 3 weeks. Psychosis associated with low doses of bromocriptine has often occurred in patients with a history of psychotic illness or disturbances in behaviour and mood.[5-7] Drug-related psychotic reactions have also been reported in patients with no psychiatric history;[8,9] of 600 patients given bromocriptine or lisuride for the treatment of acromegaly or prolactinoma, 8 developed symptoms including anxiety, depression, auditory hallucinations, delusions, hyperactivity, disinhibition, euphoria, and insomnia and 4 had received doses only previously associated with psychosis in susceptible patients.[9]

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including bromocriptine, see under Levodopa, p. 905.2.

1. Calne DB, *et al.* Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; **i:** 735–7.
2. Vlissides DN, *et al.* Bromocriptine-induced mania? *BMJ* 1978; **1:** 510.
3. Brook NM, Cookson IB. Bromocriptine-induced mania? *BMJ* 1978; **1:** 790.
4. Pearce I, Pearce JMS. Bromocriptine in parkinsonism. *BMJ* 1978; **1:** 1402–4.
5. Pearson KC. Mental disorders from low-dose bromocriptine. *N Engl J Med* 1981; **305:** 173.
6. Le Feuvre CM, *et al.* Bromocriptine-induced psychosis in acromegaly. *BMJ* 1982; **285:** 1315.
7. Procter AW, *et al.* Bromocriptine induced psychosis in acromegaly. *BMJ* 1983; **286:** 50. Correction. *ibid.;* 311.
8. Einarson TR, Turchet EN. Psychotic reaction to low-dose bromocriptine. *Clin Pharm* 1983; **2:** 273–4.
9. Turner TH, *et al.* Psychotic reactions during treatment of pituitary tumours with dopamine agonists. *BMJ* 1984; **289:** 1101–3.

Effects on the nervous system. CSF rhinorrhoea has been associated with bromocriptine therapy in patients with invasive prolactinomas. A report of 3 cases found 13 further cases on reviewing the literature;[1] of these, 7 patients had developed rhinorrhoea within 1 month of starting bromocriptine and 2 cases developed after 12 months.

For reference to seizures associated with the use of bromocriptine in postpartum women, see Effects on the Cardiovascular System, above.

1. Barlas O, *et al.* Bromocriptine-induced cerebrospinal fluid fistula in patients with macroprolactinomas: report of three cases and a review of the literature. *Surg Neurol* 1994; **41:** 486–9.

Effects on the respiratory system. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including bromocriptine, see Fibrosis, below.

Effects on sexual function. For reports of the effects of dopamine agonists on sexual function, see under Levodopa, p. 906.1.

Effects on the urinary tract. Constant dribbling urinary incontinence developed in a woman receiving bromocriptine 2.5 mg daily for a recurrent pituitary growth; symptoms resolved on stopping the drug and recurred on rechallenge.[1] Bromocriptine has been shown to have two effects, one on the bladder outflow tract and one on the detrusor muscle, that could predispose to urinary incontinence.[2]

1. Sandyk R, Gillman MA. Urinary incontinence in patient on long-term bromocriptine. *Lancet* 1983; **ii:** 1260–1.
2. Caine M. Bromocriptine and urinary incontinence. *Lancet* 1984; **i:** 228.

Fibrosis. Fibrosis has been associated with the long-term use of ergot derivatives (see under Methysergide, p. 677.2). Fibrotic reactions such as cardiac valvulopathy and pleuropulmonary effusion have been reported with bromocriptine, cabergoline, lisuride, and pergolide therapy in patients with Parkinson's disease.

Constrictive pericarditis[1] was reported in 2 patients who had received *bromocriptine* for 2 and 4 years, respectively; the latter still had slight pleural effusion 13 months after the drug was stopped. Valvular heart disease[2] developed in another patient who had received bromocriptine for 5 years; symptoms resolved 6 months after stopping the drug. Interstitial lung disease, with dyspnoea, chest pain, cough, and pulmonary fibrosis was reported[3] in a patient after use of relatively high doses of bromocriptine (62 mg daily). Respiratory symptoms largely resolved on withdrawal of the drug, although functional respiratory changes and moderate dyspnoea persisted after 6 months. A review of the literature revealed several other reports of pleuropulmonary fibrosis associated with relatively high doses of bromocriptine which occurred after between 15 days and up to 3 years of treatment. Although the incidence of this effect did not seem to be high, similar cases have continued to be reported.[4-6] In June 2008 the EMEA recommended that for long-term use in conditions such as Parkinson's disease, the maximum dose should be 30 mg daily.[7]

A patient developed pleuropulmonary disease 16 months after starting treatment with *cabergoline;*[8] he had previously received bromocriptine for 10 years and had had a normal chest X-ray at the time of transfer to cabergoline treatment. In another report, 2 cases of pleural effusion/pulmonary fibrosis, occurring after 10 to 11 months of treatment, were described.[9] One patient had modest pretreatment lung alterations attributed to previous bromocriptine therapy. Withdrawal was associated with improvement in both cases. Congestive heart failure secondary to constrictive pericarditis, and severe pleuropulmonary fibrosis that resulted in

dyspnoea, persistent in one case,[10] have also been reported in 2 patients receiving long-term cabergoline.[10,11] Another patient developed cardiac valvulopathy after taking cabergoline for a total of 20 months;[12] her dosage was 4 mg daily for the last 7 months. Cardiac symptoms slowly improved on withdrawal of the drug, although some evidence of valvular defects was still present 23 months later. Valvular heart disease has also been reported in a 74-year-old man after 4 months of therapy with cabergoline [dosage not stated].[13] By December 2005, 86 cases of suspected adverse reactions to cabergoline had been reported to the Australian Drug Reactions Advisory Committee (ADRAC),[14] of which 15 described pleural or pulmonary fibrosis/effusion, or pneumonitis; time to onset ranged from a few days to over 3 years with a median of 4 months. There had been no reports of fibrotic complications associated with low-dose cabergoline in the treatment of lactation suppression and hyperprolactinaemia. The UK MHRA considers the risk of cardiac valvulopathy to be high and UK labelling for cabergoline has been amended accordingly (see p. 900.2) with the EMEA in June 2008 recommending a maximum dose of 3 mg daily.[7]

A woman developed bilateral pleural effusions after taking *lisuride* 4 mg daily for about 17 months.[8] Her condition improved on stopping lisuride.

The UK CSM[15] reported in 2003 that *pergolide* had been associated with cases of cardiac valvulopathy; since 1989, valvulopathy had been reported in fewer than 5 in 100 000 patients. The CSM also referred to a published case series[16] which reported on 3 patients with severe tricuspid regurgitation after long-term pergolide treatment. The authors of this case series and the CSM both considered that, based on the available evidence, there was a potential association between pergolide and cardiac valvulopathy. Subsequently, the FDA[17] stated that, up to the end of 2002, it was aware of 15 cases of valvular heart disease with pergolide treatment; this figure included the 3 cases reported in the above series and 4 cases from the UK. A later study[18] that examined 78 patients taking pergolide for Parkinson's disease found evidence of restrictive valvular heart disease in 15 of 52 (29%) patients taking doses less than 5 mg daily and in 11 of 26 (42%) receiving doses of 5 mg or more daily. Pulmonary fibrosis and retroperitoneal fibrosis have also been associated with pergolide treatment;[19-21] in most cases, symptoms improved when the drug was stopped. Duration of exposure to pergolide ranged from 6 months[20] to 11 years.[21]

In April 2002 the CSM[22] calculated crude reporting rates of fibrotic reactions associated with the ergot derivative dopamine agonists (bromocriptine, cabergoline, lisuride, and pergolide), based on data submitted to its Yellow Card scheme and estimated drug exposure. Pergolide was found to be associated with a higher reporting rate of fibrotic reactions compared with the other ergot derivatives; however, this result needed further investigation to see if it reflected a true increase in risk or was due to factors such as reporting biases. There is some evidence that the incidence of reactions to pergolide are dose-related; doses are restricted in many countries (see p. 910.3) and in June 2008 the EMEA recommended a maximum dose of 3 mg daily.[7] Pergolide was withdrawn from the market in the USA and Canada. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with this class of drugs.

1. Champagne S, *et al.* Chronic constrictive pericarditis induced by long-term bromocriptine therapy: report of two cases. *Ann Pharmacother* 1999; **33:** 1050–4.
2. Serratrice J, *et al.* Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev* 2002; **10:** 334–6.
3. Vergeret J, *et al.* Fibrose pleuro-pulmonaire et bromocriptine. *Sem Hop Paris* 1984; **60:** 741–4.
4. Kinnunen E, Viljanen A. Pleuropulmonary involvement during bromocriptine treatment. *Chest* 1988; **94:** 1034–6.
5. Macak IA, *et al.* Bromocriptine-induced pulmonary disease. *Can J Hosp Pharm* 1991; **44:** 37–8, xxiv.
6. Debove P, *et al.* Pleuropneumopathie à la bromocriptine chez un parkinsonien: revue de la littérature à propos d'une nouvelle observation. *Ann Med Interne (Paris)* 1998; **149:** 167–71.
7. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)
8. Bhatt MH, *et al.* Pleuropulmonary disease associated with dopamine agonist therapy. *Ann Neurol* 1991; **30:** 613–16.
9. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.
10. Ling LH, *et al.* Constrictive pericarditis and pleuropulmonary disease linked to ergot dopamine agonist therapy (cabergoline) for Parkinson's disease. *Mayo Clin Proc* 1999; **74:** 371–5.
11. Townsend M, MacIver DH. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart* 2004; **90:** e47.
12. Horvath J, *et al.* Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord* 2004; **19:** 656–62.
13. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; **353:** 1976–7.
14. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Ergot derivatives and fibrotic reactions. *Aust Adverse Drug React Bull* 2006; **25:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 30/05/08)
15. CSM/MHRA. Pergolide (Celance) and cardiac valvulopathy. *Current Problems* 2003; **29:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
16. Pritchett AM, *et al.* Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002; **77:** 1280–6.
17. Flowers CM, *et al.* The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. *Mayo Clin Proc* 2003; **78:** 730–1.
18. Van Camp G, *et al.* Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet* 2004; **363:** 1179–83.
19. Agarwal P, *et al.* Diagnosis and management of pergolide-induced fibrosis. *Mov Disord* 2004; **19:** 699–704.
20. Simcock D, Paviour D. Rapid onset of pergolide-induced pulmonary fibrosis in a patient with corticobasal degeneration. *Hosp Med* 2004; **65:** 372–3.
21. Tintner R, *et al.* Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson disease. *Arch Neurol* 2005; **62:** 1290–5.
22. CSM/MCA. Fibrotic reactions with pergolide and other ergot-derived receptor agonists. *Current Problems* 2002; **28:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)

Hypersensitivity. An allergic reaction developed in a 26-year-old woman being treated with bromocriptine for a prolactin-secreting microadenoma.[1] The patient reacted similarly to lisuride and treatment was continued with quinagolide.

1. Merola B, *et al.* Allergy to ergot-derived dopamine agonists. *Lancet* 1992; **339:** 620.

Oedema. Oedema poorly responsive to diuretics has been reported[1] in a patient given bromocriptine as part of treatment for prolactinoma. The oedema improved on substitution of pergolide but worsened with higher doses. Oedema resolved when treatment was changed to quinagolide. The reaction was considered to be idiosyncratic since enquiries by the author of the report had revealed only one similar case. In a subsequent report[2] a patient with Parkinson's disease who had been receiving bromocriptine for 5 years developed marked lower leg oedema, and subsequently cough, dyspnoea, and chest pain associated with an exudative pleural effusion; there was no evidence of fibrosis. Both oedema and effusion had largely resolved within 4 weeks of stopping bromocriptine.

1. Blackard WG. Edema—an infrequently recognized complication of bromocriptine and other ergot dopaminergic drugs. *Am J Med* 1993; **94:** 445.
2. Messiaen T, *et al.* Épanchement pleural et importants œdèmes des membres inférieurs induits par la bromocriptine. *Rev Med Interne* 1996; **17:** 680–3.

Overdosage. The most striking symptom in two children aged 2 and 2½ years who accidentally ingested an estimated 25 and 7.5 mg of bromocriptine, respectively, was lethargy with altered mental status.[1] The first child vomited and became sleepy. On admission he was markedly lethargic, but combative when disturbed, and also had hypotension, shallow breathing, dilated pupils, and hyperreflexic lower extremities. Nasogastric lavage was promptly performed, and activated charcoal and then magnesium citrate given. Blood pressure and ECG were monitored, and glucose and sodium chloride solution infused. The other child vomited, became lethargic, and had dilated pupils. Ipecacuanha was given, and activated charcoal followed by magnesium citrate given by nasogastric tube. Both children recovered completely.

1. Vermund SH, *et al.* Accidental bromocriptine ingestion in childhood. *J Pediatr* 1984; **105:** 838–40.

Withdrawal syndromes. Transient galactorrhoea and hyperprolactinaemia occurred in a young woman after withdrawal of bromocriptine therapy for Parkinson's disease.[1] It was suggested the effects were due to a rebound phenomenon. For discussion of a syndrome resembling neuroleptic malignant syndrome that has developed on withdrawal of bromocriptine and other antiparkinsonian drugs, see under Levodopa, p. 906.2.

1. Pentland B, Sawers JSA. Galactorrhoea after withdrawal of bromocriptine. *BMJ* 1980; **281:** 716.

Precautions

Patients with hyperprolactinaemia should be investigated for the possibility of a pituitary tumour before treatment with bromocriptine. Malignancy must be excluded in patients with cyclical benign breast disorders such as mastalgia. Annual gynaecological examinations (or every 6 months for postmenopausal women) are recommended. Treatment of women with hyperprolactinaemic amenorrhoea results in ovulation; patients not wishing to conceive should be advised to use contraceptive measures although oral contraceptives should be avoided because they may increase prolactin levels. Acromegalic patients should be checked for symptoms of peptic ulceration before therapy and should immediately report symptoms of gastrointestinal discomfort during therapy.

In general, bromocriptine should be given with caution to patients with cardiovascular disease, Raynaud's syndrome, or a history of psychosis. It is contra-indicated in patients with hypersensitivity to bromocriptine or other ergot alkaloids, and in those with uncontrolled hypertension.

Bromocriptine is contra-indicated in the toxaemia of pregnancy. It should also not be used postpartum or in the puerperium in women with hypertension, coronary artery disease, or symptoms or a history of serious psychiatric disorders. When used, blood pressure should be monitored carefully, especially during the first few days in postpartum women. Particular caution is necessary in patients who are receiving or who have recently received drugs that can alter blood pressure; use with ergot alkaloids during the puerperium is not recommended. Treatment in postpartum women should be stopped immediately if hypertension, unremitting headache, or signs of CNS toxicity develop.

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and those who drive or operate machinery should be warned of the possibility of dizziness and fainting during this period. Excessive daytime sleepiness and sudden onset of sleep may also occur with bromocriptine and other dopaminergic agonists, and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring. A reduction in dosage or withdrawal of the drug may be appropriate. Because of the risk of fibrosis bromocriptine is contra-indicated in patients with pre-existing valve problems.

Patients on long-term, high-dose therapy should be monitored for signs of progressive fibrotic disorders such as retroperitoneal fibrosis and bromocriptine withdrawn if fibrotic changes are diagnosed or suspected. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with bromocriptine. Periodic monitoring of cardiovascular, haematopoietic, hepatic, and renal function is also recommended. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Breast feeding. The American Academy of Pediatrics[1] considers that bromocriptine should be given with caution to breast-feeding mothers, since it suppresses lactation and may be hazardous to the mother.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/02/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bromocriptine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Pregnancy. Details of various surveys of the effect of the use of bromocriptine during pregnancy have been published by the manufacturer.[1,2] The first survey was based on spontaneous reporting of all pregnancies between 1973 and 1980 in women who had taken bromocriptine after conception.[1] Information was obtained on 1410 pregnancies in 1335 women, the majority of whom had been treated for hyperprolactinaemic conditions, while in 256 pregnancies pituitary tumours and acromegaly were the primary diagnosis. Bromocriptine was generally taken at some time in the first 8 weeks after conception, the mean duration of treatment being 21 days. In 4 patients bromocriptine was not prescribed until late in pregnancy and in 9 with acromegaly and pituitary microadenoma it was taken continuously throughout gestation. There were 157 (11.1%) spontaneous abortions, 12 (0.9%) extrauterine pregnancies, 2 patients with 3 hydatidiform moles (0.2%), and an incidence of twin pregnancies of 1.8%. Major congenital abnormalities were detected in 12 (1%) infants at birth and minor abnormalities in 31 (2.5%). A second survey,[2] which consisted of formal monitoring of the use of bromocriptine at 33 clinics between 1979 and 1980, collected data on a further 743 pregnancies in 668 women and had similar findings. The incidence rates reported in these surveys were comparable with those quoted for normal populations and the data indicate that the use of bromocriptine in the treatment of women with infertility is not associated with an increased risk of abortion, multiple pregnancy, or congenital abnormalities. Furthermore, follow-up, for up to 9 years, of 546 children exposed to bromocriptine *in utero* found no evidence that bromocriptine had any adverse effect on postnatal development.[2] Nevertheless, since the risk of abortion is not increased by interruption of treatment, licensed product information recommends that bromocriptine therapy be stopped as soon as pregnancy is confirmed unless there is a definite indication for its continuation.

See also Pregnancy, under Hyperprolactinaemia and Prolactinomas, p. 896.2.

1. Turkalj I, *et al*. Surveillance of bromocriptine in pregnancy. *JAMA* 1982; **247:** 1589–91.
2. Krupp P, Monka C. Bromocriptine in pregnancy: safety aspects. *Klin Wochenschr* 1987; **65:** 823–7.

Interactions

Dopamine antagonists such as the phenothiazines, butyrophenones, thioxanthenes, and metoclopramide (but see below) might be expected to reduce the prolactin-lowering and the antiparkinsonian effects of bromocriptine and domperidone might reduce its prolactin-lowering effect. Memantine may enhance the effects of bromocriptine. Stimulants of gastrointestinal motility such as macrolide antibacterials or octreotide can increase the bioavailability of bromocriptine.

Alcohol. Alcohol intolerance was noted in 5 of 73 patients receiving bromocriptine 10 to 60 mg daily for the treatment of acromegaly.[1] Two patients who had gastrointestinal adverse effects while taking low doses of bromocriptine had a marked reduction in their symptoms and were able to tolerate higher doses when they refrained completely from alcohol.[2]

1. Wass JAH, *et al*. Long-term treatment of acromegaly with bromocriptine. *BMJ* 1977; **1:** 875–8.
2. Ayres J, Maisey MN. Alcohol increases bromocriptine's side effects. *N Engl J Med* 1980; **302:** 806.

Antibacterials. Drowsiness, dystonia, choreoathetoid dyskinesias, and visual hallucinations occurred when *josamycin* was given to a patient receiving bromocriptine.[1]

The systemic bioavailability of a single oral dose of bromocriptine 5 mg was markedly increased in 5 healthy subjects after treatment with *erythromycin estolate* 250 mg four times daily for 4 days;[2] clearance of bromocriptine was decreased and peak plasma concentrations of bromocriptine were more than 4 times higher than when given alone.

1. Montastruc JL, Rascol A. Traitement de la maladie de Parkinson par doses élevées de bromocriptine: interaction possible avec la josamycine. *Presse Med* 1984; **13:** 2267–8.
2. Nelson MV, *et al*. Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* 1990; **47:** 694–7.

Antifungals. The response to bromocriptine was blocked in a patient who was also receiving *griseofulvin*.[1]

1. Schwinn G, *et al*. Metabolic and clinical studies on patients with acromegaly treated with bromocriptine over 22 months. *Eur J Clin Invest* 1977; **7:** 101–7.

Antineoplastics. *Tamoxifen* may increase the dopaminergic effect of bromocriptine; for the effect of bromocriptine on tamoxifen, see Interactions, under Tamoxifen, p. 863.2.

Antipsychotics. Serum concentrations of prolactin rose and visual fields deteriorated when *thioridazine* was given to a 40-year-old man receiving bromocriptine therapy for a large prolactinoma.[1]

For a discussion of the effect of bromocriptine on patients receiving antipsychotics, see Antiparkinsonian Drugs under Chlorpromazine on p. 1052.3.

1. Robbins RJ, *et al*. Interactions between thioridazine and bromocriptine in a patient with a prolactin-secreting pituitary adenoma. *Am J Med* 1984; **76:** 921–3.

Metoclopramide. As noted in Interactions, above, there are theoretical reasons to suppose that dopamine antagonists such as metoclopramide might reduce the effects of bromocriptine. However, an early study[1] in 10 patients with Parkinson's disease given single doses of bromocriptine 12.5 to 100 mg found that pretreatment with metoclopramide 60 mg had no consistent effect upon plasma concentrations of bromocriptine or growth hormone and no consistent effect upon clinical response.

1. Price P, *et al*. Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; **6:** 303–9.

Sympathomimetics. There have been isolated reports[1,2] of severe hypertension, with headache and life-threatening complications, in patients taking bromocriptine with *isometheptene mucate* or *phenylpropanolamine*.

1. Kulig K, *et al*. Bromocriptine-associated headache: possible life-threatening sympathomimetic interaction. *Obstet Gynecol* 1991; **78:** 941–3.
2. Chan JCN, *et al*. Postpartum hypertension, bromocriptine and phenylpropanolamine. *Drug Invest* 1994; **8:** 254–6.

Pharmacokinetics

Bromocriptine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 3 hours after oral doses. However, only about 30% of an oral dose is absorbed and, owing to extensive first-pass metabolism, the bioavailability is only about 6%. It has been reported to be 90 to 96% bound to serum albumin *in vitro*. It is metabolised in the liver, mainly by hydrolysis to lysergic acid and peptides. The elimination of bromocriptine is biphasic; half-lives of about 4 to 4.5 hours and 15 hours, respectively have been reported for the 2 phases. It is excreted mainly in faeces via the bile, with small amounts in urine.

In a study involving 10 patients with Parkinson's disease, single oral doses of bromocriptine 12.5, 25, 50, and 100 mg resulted in very variable peak plasma concentrations ranging from 1.3 to 5.3, 1.4 to 3.5, 2.6 to 19.7, and 6.5 to 24.6 nanograms/mL, respectively, 30 to 210 minutes (mean 102 minutes) after dosage.[1] After 4 hours plasma concentrations were about 75% of the peak values. Clinical improvement was evident within 30 to 90 minutes of a dose with peak effect at about 130 minutes and in most patients improvement persisted throughout the 4-hour study period. Peak clinical response, peak fall in blood pressure, and peak rise in plasma concentrations of growth hormone occurred about 30, 60, and 70 minutes, respectively after peak plasma-bromocriptine concentrations but there was no significant relationship between them. However, there was a significant relationship between plasma concentrations and concurrent changes in clinical response compared with pretreatment scores. Dyskinesias occurred within 90 to 180 minutes of dosage in 5 of 10 patients.

Bromocriptine is well absorbed from standard oral tablets placed in the vagina and plasma concentrations sufficient to lower plasma prolactin concentrations have been achieved using this route.[2,3]

1. Price P, *et al*. Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; **6:** 303–9.
2. Vermesh M, *et al*. Vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. *Obstet Gynecol* 1988; **72:** 693–8.
3. Katz E, *et al*. Successful treatment of a prolactin-producing pituitary macroadenoma with intravaginal bromocriptine mesylate: a novel approach to intolerance of oral therapy. *Obstet Gynecol* 1989; **73:** 517–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Parlodel; ***Austral.***: Bromohexal†; Kripton; Parlodel; ***Austria***: Parlodel; Umprel; ***Belg.***: Parlodel; ***Braz.***: Bagren†; Parlodel; ***Chile***: Criten; Grifocriptina; Kriptonal; Parlodel; Prigost; ***China***: Baimoting (佰莫亭)†; Parlodel; ***Cz.***: Medocriptine; Parlodel; ***Denm.***: Parlodel; ***Fin.***: Parlodel; ***Fr.***: Bromo-Kin; Parlodel; ***Ger.***: kirim gyn†; kirim; Pravidel; ***Gr.***: Parlodel; Serocryptin; ***Hong Kong***: Bromergon; Medocriptine; Parlodel; Syntocriptine; ***India***: Briptin; Brom; Bromogen; Criptal; Encript; Kripti; Ovucript; Sicriptin; ***Indon.***: Cripsa; Parlodel; ***Irl.***: Parlodel; ***Israel***: Parilac†; Parlodel†; ***Ital.***: Parlodel; ***Jpn***: Parlodel; ***Malaysia***: Medocriptine; Parlodel; ***Mex.***: Biodel; Broptin; Crilem†; Cryocriptina†; Kriptiser†; Mesiken; Parlodel; ***Neth.***: Parlodel; ***Norw.***: Parlodel; ***Philipp.***: Parlodel; Provasyn; ***Pol.***: Bromergon; Bromocorn; Ergolaktyna†; Parlodel; ***Port.***: Parlodel; ***Rus.***: Bromergon (Бромэргон); Parlodel (Парлодел); ***S.Afr.***: Parlodel; ***Singapore***: Brameston; Butin†; Parlodel; ***Spain***: Parlodel; ***Swed.***: Pravidel; ***Switz.***: Parlodel; ***Thai.***: Brocaden†; Bromergon; Parlodel; Suplac; ***Turk.***: Galaktomin; Gynodel; Parlodel; ***UAE***: Antiprotin; ***UK***: Parlodel; ***Ukr.***: Parlodel (Парлодел)†; ***USA***: Cycloset; Parlodel; ***Venez.***: Parlodel.

Pharmacopoeial Preparations

BP 2014: Bromocriptine Capsules; Bromocriptine Tablets;
USP 36: Bromocriptine Mesylate Capsules; Bromocriptine Mesylate Tablets.

Budipine *(rINN)*

Budipino; Budipinum; Будипин.
1-*tert*-Butyl-4,4-diphenylpiperidine.
$C_{21}H_{27}N$=293.5
CAS — 57982-78-2.
ATC — N04BX03.
ATC Vet — QN04BX03.
UNII — L9026OPI2Z.

Profile

Budipine is a phenylpiperidine derivative used as an adjunct in the treatment of parkinsonism (p. 889.1). It is given orally as the hydrochloride in daily doses of up to 60 mg. Budipine has been reported to prolong the QT interval.

References.
1. Spieker S, *et al*. Tremorlytic activity of budipine: a quantitative study with long-term tremor recordings. *Clin Neuropharmacol* 1995; **18:** 266–72.
2. Groen H, *et al*. A study to investigate the pharmacokinetics and metabolism of budipine after administration of a single oral dose of [^{14}C]-B757-01 to six healthy volunteers. *Br J Clin Pharmacol* 1999; **48:** 771P–772P.
3. Malsch U, *et al*. Monotherapie der Parkinsonschen Erkrankung mit Budipin: ein randomisierter Doppelblindvergleich mit Amantadin. *Fortschr Neurol Psychiatr* 2001; **69:** 86–9.
4. Przuntek H, *et al*. Budipine provides additional benefit in patients with Parkinson disease receiving a stable optimum dopaminergic drug regimen. *Arch Neurol* 2002; **59:** 803–6.
5. Reichmann H. Budipine in Parkinson's tremor. *J Neurol Sci* 2006; **248:** 53–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Parkinsan.

Cabergoline *(BAN, USAN, rINN)*

Cabergolin; Cabergolina; Cabergolinum; FCE-21336; Kabergoliini; Kabergolin; Kabergolina; Каберголин.
1-[(6-Allylergolin-8β-yl)carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea; (8*R*)-6-Allyl-*N*-[3-(dimethylamino)propyl]-*N*-(ethylcarbamoyl)ergoline-8-carboxamide.
$C_{26}H_{37}N_5O_2$=451.6
CAS — 81409-90-7.
ATC — G02CB03; N04BC06.
ATC Vet — QG02CB03; QN04BC06.
UNII — LL60K9J05T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cabergoline). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in alcohol; very slightly soluble in *n*-hexane. It is slightly soluble in 0.1M hydrochloric acid. Protect from light.

USP 36: (Cabergoline). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; slightly soluble in 0.1M hydrochloric acid; very slightly soluble in hexane. Store in airtight containers. Protect from light.

Uses and Administration

Cabergoline, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p. 895.3). It is a potent and long-lasting inhibitor of prolactin secretion used in the management of disorders associated with hyperprolactinaemia (p. 900.1). It is also used to suppress puerperal lactation for medical reasons (p. 900.1); it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support. Cabergoline is also used in the management of Parkinson's disease (p. 900.1) as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response; in the UK cabergoline is restricted to patients who are intolerant of, or who do not respond to, non-ergot drug treatment.

Cabergoline is given orally and should be taken with food.

To **inhibit physiological lactation**, cabergoline is given as a single 1-mg dose on the first day post partum. For **suppression of established lactation**, the dose is 250 micrograms every 12 hours for 2 days.

In the treatment of **disorders associated with hyperprolactinaemia**, the initial dose of cabergoline is 500 micrograms weekly. The dose is then increased at monthly intervals in increments of 500 micrograms weekly according to response. The weekly dose may be given on a single occasion or divided into 2 or more doses on separate days according to tolerance; doses over 1 mg should be given as divided doses although the maximum single daily dose should not exceed 3 mg. The usual dose is 1 mg weekly but up to 4.5 mg weekly has been used.

In **Parkinson's disease**, cabergoline should be introduced gradually and during this period the dose of levodopa may be reduced gradually until an optimal response is achieved. A suggested initial dose of cabergoline given as a single daily dose is 500 micrograms in monotherapy or 1 mg in adjunctive therapy. The dose may be increased in increments of 0.5 or 1 mg, at intervals of 7 or 14 days, to 2 to 3 mg daily. The EMEA has recommended a maximum dose of 3 mg daily.

Doses of cabergoline may need to be reduced in patients with severe hepatic impairment (see below).

Administration in hepatic impairment. Licensed product information recommends caution in patients with severe hepatic impairment (Child-Pugh category C), and doses of cabergoline should be adjusted accordingly.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone concentrations, although they are less effective than somatostatin analogues (p. 1921.1).

A small study comparing cabergoline with depot bromocriptine and quinagolide failed to find evidence of its efficacy.[1] However, in a later open study[2] there was a good response in about 40% of patients treated with cabergoline, which is better than the response usually reported for bromocriptine. The addition of cabergoline has

also been beneficial in acromegaly that is resistant to somatostatin analogue therapy.[3]

1. Colao A, *et al.* Effect of different dopaminergic agents in the treatment of acromegaly. *J Clin Endocrinol Metab* 1997; **82:** 518–23.
2. Abs R, *et al.* Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab* 1998; **83:** 374–8.
3. Cozzi R, *et al.* Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clin Endocrinol (Oxf)* 2004; **61:** 209–15.

Hyperprolactinaemia and prolactinomas. Dopamine agonists are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (see p. 2252.2). Although bromocriptine has been the first choice for this indication, some now prefer cabergoline,[1] which appears to be more effective and better tolerated.[2,3]

Further references.[4-11]

1. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; **14:** 228–38. Correction. *ibid.*, 342.
2. Pascal-Vigneron V, *et al.* Amenorrhée hyperprolactinémique: traitement par cabergoline versus bromocriptine. *Presse Med* 1995; **24:** 753–7.
3. di Sarno A, *et al.* Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab* 2001; **86:** 5256–61.
4. Webster J, *et al.* The efficacy and tolerability of long-term cabergoline therapy in hyperprolactinaemic disorders: an open, uncontrolled, multicentre study. *Clin Endocrinol (Oxf)* 1993; **39:** 323–9.
5. Webster J, *et al.* A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1994; **331:** 904–9.
6. Verhelst J, *et al.* Cabergoline in the treatment of hyperprolactinaemia: a study in 455 patients. *J Clin Endocrinol Metab* 1999; **84:** 2518–22.
7. Colao A, *et al.* Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J Clin Endocrinol Metab* 2000; **85:** 2247–52.
8. Colao A, *et al.* Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 2003; **349:** 2023–33.
9. Colao A, *et al.* Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. *J Clin Endocrinol Metab* 2004; **89:** 1704–11.
10. Ono M, *et al.* Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J Clin Endocrinol Metab* 2008; **93:** 4721–7.
11. Kharlip J, *et al.* Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. *J Clin Endocrinol Metab* 2009; **94:** 2428–36.

Lactation inhibition. A single 1-mg dose of cabergoline was found to be as effective as bromocriptine 2.5 mg given twice daily for 14 days for preventing puerperal lactation in a double-blind multicentre study involving 272 women.[1] It has been suggested that cabergoline would be a better choice than bromocriptine for lactation inhibition.[2] However, as discussed on p. 2130.1, the routine use of dopaminergics such as bromocriptine or cabergoline is not recommended for the suppression of physiological lactation.

1. European Multicentre Study Group for Cabergoline in Lactation Inhibition. Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study. *BMJ* 1991; **302:** 1367–71.
2. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; **14:** 228–38. Correction. *ibid.*; 342.

Parkinsonism. Cabergoline is used as a long-acting dopamine agonist in Parkinson's disease (p. 889.1). Dopamine agonists are often used to begin treatment in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stages of the disease.

References.

1. Inzelberg R, *et al.* Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. *Neurology* 1996; **47:** 785–8.
2. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.
3. Hutton JT, *et al.* Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology* 1996; **46:** 1062–5.
4. Marsden CD. Clinical experience with cabergoline in patients with advanced Parkinson's disease treated with levodopa. *Drugs* 1998; **55** (suppl 1): 17–22.
5. Rinne UK, *et al.* Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications: results of a double-blind levodopa controlled trial. *Drugs* 1998; **55** (suppl 1): 23–30.
6. Clarke CE, Deane K. Cabergoline for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane K. Cabergoline versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Bracco F, *et al.* The long-acting dopamine receptor agonist cabergoline in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study. *CNS Drugs* 2004; **18:** 733–46. Correction. *ibid.* 2005; **19:** 633.
9. Curran MP, Perry CM. Cabergoline: a review of its use in the treatment of Parkinson's disease. *Drugs* 2004; **64:** 2125–41.
10. Odin P, *et al.* Efficacy and safety of high-dose cabergoline in Parkinson's disease. *Acta Neurol Scand* 2006; **113:** 18–24.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has been largely empirical but dopaminergic therapy has emerged as a common first-line choice. Long-acting drugs such as cabergoline may be preferred in order to avoid the complications associated with levodopa therapy. Randomised multicentre studies[1,2] in patients with idiopathic RLS concluded that a single evening dose of cabergoline for 5 weeks markedly reduced symptoms during the night and the next day compared with placebo. Results from follow-up analysis of one study[1] after 1 year of treatment suggested that cabergoline at a median dose of 2 mg daily has a high rate of remission and is well tolerated; the authors recommended an initial dose of cabergoline 500 micrograms in the evening increased in increments of 500 micrograms weekly according to response.

1. Stiasny-Kolster K, *et al.* Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology* 2004; **63:** 2272–9.
2. Oertel WH, *et al.* Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). *Neurology* 2006; **67:** 1040–6.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3, although patients unable to tolerate bromocriptine may tolerate cabergoline (and vice versa).

Licensed product information states that conception should be avoided for at least one month after treatment.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including cabergoline, see under Levodopa, p. 905.2.

For reference to **pathological gambling** reported in patients with Parkinson's disease receiving dopamine agonists including cabergoline, see under Levodopa, p. 905.2.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including cabergoline, see under Bromocriptine, p. 897.3.

In 2007, based on further evidence from 3 studies,[1-3] the UK MHRA[4] considered the risk of cardiac valvulopathy to be high and clinically significant with cabergoline and pergolide, and the risks of treatment with these 2 drugs to be similar. This resulted in the following changes to UK labelling for cabergoline products in Parkinson's disease:

- restricted to second-line treatment in patients intolerant of, or who do not respond to, non-ergot drug treatment
- contra-indicated in patients with a history of pulmonary, pericardial, and retroperitoneal fibrotic disorders, or in those with anatomical evidence of cardiac valvulopathy
- monitoring for development of valvular disease or fibrosis recommended: echocardiography should be performed within 3 to 6 months of starting treatment and every 6 to 12 months thereafter

In June 2008 the EMEA further recommended that the maximum dose should be 3 mg daily.[5]

1. Yamamoto M, *et al.* Dopamine agonists and cardiac valvulopathy in Parkinson disease: a case-control study. *Neurology* 2006; **67:** 1225–9.
2. Schade R, *et al.* Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; **356:** 29–38.
3. Zanettini R, *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; **356:** 39–46.
4. MHRA/CHM. Cabergoline: cardiovalvulopathy. *Drug Safety Update* 2007: **1** (1): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2031801&RevisionSelectionMethod=LatestReleased (accessed 23/08/10)
5. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)

Oedema. Three cases of lower limb oedema after chronic treatment with cabergoline have been reported.[1] In one case the oedema was severe enough to necessitate withdrawal of therapy.

1. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cabergoline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Cabergoline is absorbed from the gastrointestinal tract and mean peak plasma concentrations occur within 2 to 3 hours. It is subject to first-pass metabolism and is extensively metabolised to several metabolites that do not appear to contribute to its pharmacological activity. Plasma protein binding has been estimated to be about 40%. Cabergoline is mainly eliminated via the faeces; a small proportion is excreted in the urine. In *rats*, cabergoline has been reported to cross the placenta and to be distributed into breast milk.

General references.

1. Del Dotto P, Bonuccelli U. Clinical pharmacokinetics of cabergoline. *Clin Pharmacokinet* 2003; **42:** 633–45.

Half-life. Pharmacokinetic studies of cabergoline have been hampered by lack of an assay method sensitive enough to detect plasma concentrations of cabergoline after therapeutic doses. However, the plasma elimination half-life of cabergoline has been estimated indirectly to be 63 to 68 hours in healthy subjects and 79 to 115 hours in patients with hyperprolactinaemia.[1]

1. Rains CP, *et al.* Cabergoline: a review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation. *Drugs* 1995; **49:** 255–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cabaser; Caberpar; Cabertrix; Cieldom; Dostinex; Lac Stop; Lactamax; Triaspar; ***Austral.***: Bergoline; Cabaser; Cobasol; Dostan; Dostinex; Tinexa; ***Austria***: Cabaseril; Dostinex; ***Belg.***: Dostinex; Sostilar; ***Braz.***: Dostinex; ***Canad.***: Dostinex; ***Chile***: Cabertrix; Dostinex; ***Cz.***: Cabera†; Dostinex; ***Denm.***: Cabaser; Cabergin; Dostinex; ***Fin.***: Cabaser; Dostinex; ***Fr.***: Dostinex; ***Ger.***: Cabaseril; Cabergo-TEVA†; Dostinex; ***Gr.***: Dostinex; ***Hong Kong***: Dostinex; ***India***: Caberlin; Cabgolin; Camforte; CB-Lin; Parcar; ***Irl.***: Cabaser; Caberex; Dalzior; Dostinex; Eflavex; ***Israel***: Cabaser; Cabotrim; Dostinex; ***Ital.***: Actualene; Cabaser; Dostinex; ***Malaysia***: Dostinex; ***Mex.***: Dostinex; ***Neth.***: Dostinex; ***Norw.***: Cabaser; Dostinex; ***NZ***: Dostinex; ***Pol.***: Dostinex; ***Port.***: Dostinex; ***Rus.***: Agalates (Агалатес); Dostinex (Достинекс); ***S.Afr.***: Arigoline; Dostinex; ***Singapore***: Dostinex; ***Spain***: Dostinex; Sogilen; ***Swed.***: Cabaser; Dostinex; ***Switz.***: Cabaser; Dostinex; ***Turk.***: Cabaser; Dostinex; ***UK***: Cabaser; Dostinex; ***Ukr.***: Alactin (Алактин); Dostinex (Достинекс); ***Venez.***: Dostinex.

Pharmacopoeial Preparations

USP 36: Cabergoline Tablets.

Carbidopa *(BAN, USAN, rINN)*

Carbidopa-Monohydrat; Carbidopum Monohydricum; Karbidopa; Karbidopa monohydrát; α-Methyldopa Hydrazine; MK-486; Карбидопа.

(+)-2-(3,4-Dihydroxybenzyl)-2-hydrazinopropionic acid monohydrate; (-)-L-α-Hydrazino-3,4-dihydroxy-α-methylhydrocinnamic acid monohydrate.

$C_{10}H_{14}N_2O_4,H_2O$=244.2

CAS — 28860-95-9 (anhydrous); 38821-49-7 (monohydrate).

UNII — MNX7R8C5VO (carbidopa monohydrate); KR87B45RGH (anhydrous carbidopa).

NOTE. The synonym MK-485 has been used for the racemic mixture.

Compounded preparations of carbidopa and levodopa may be represented by the following names:

- Co-careldopa *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Carbidopa). A white or yellowish-white powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane; dissolves in dilute solutions of mineral acids. Protect from light.

USP 36: (Carbidopa). A white to creamy-white, odourless or practically odourless powder. Slightly soluble in water and in methyl alcohol; practically insoluble in alcohol, in acetone, in chloroform, and in ether; freely soluble in 3N hydrochloric acid. Protect from light.

Uses and Administration

Carbidopa is a peripheral dopa-decarboxylase inhibitor with little or no pharmacological activity when given alone in usual doses. It inhibits the peripheral decarboxylation of levodopa to dopamine and as, unlike levodopa, it does not cross the blood-brain barrier, effective brain concentrations of dopamine are produced with lower doses of levodopa. At the same time reduced peripheral formation of dopamine reduces peripheral adverse effects, notably nausea and vomiting, and cardiac arrhythmias, although the dyskinesias and adverse mental effects associated with levodopa therapy tend to develop earlier. Contrary to its effect in patients on levodopa alone, pyridoxine does not inhibit the response to levodopa in patients also receiving a peripheral dopa-decarboxylase inhibitor.

In the treatment of parkinsonism (p. 889.1) carbidopa is given with levodopa to enable a lower dosage of the latter to be used, a more rapid response to be obtained, and to decrease adverse effects. For details of administration and dosage, see Levodopa, p. 902.3.

Carbidopa also inhibits the peripheral decarboxylation of the serotonin precursor oxitriptan (p. 440.3).

General references.
1. Pinder RM, *et al.* Levodopa and decarboxylase inhibitors: a review of their clinical pharmacology and use in the treatment of parkinsonism. *Drugs* 1976; **11:** 329–77.
2. Boshes B. Sinemet and the treatment of parkinsonism. *Ann Intern Med* 1981; **94:** 364–70.

Adverse Effects

Hypersensitivity. Henoch-Schönlein purpura that developed in a 68-year-old patient being treated for Parkinson's disease appeared to be due to either carbidopa or an excipient of the carbidopa preparation (*Sinemet*).[1]

1. Niedermaier G, Briner V. Henoch-Schönlein syndrome induced by carbidopa/levodopa. *Lancet* 1997; **349:** 1071–2.

Pharmacokinetics

Carbidopa is rapidly but incompletely absorbed from the gastrointestinal tract. It is rapidly excreted in the urine both unchanged and in the form of metabolites. It does not cross the blood-brain barrier. In *rats*, carbidopa has been reported to cross the placenta and to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prikap; ***Irl.***: Duodopa; ***Pol.***: Nakom; ***UK***: Apodespan; ***USA***: Lodosyn.

Multi-ingredient Preparations. ***Arg.***: Carlevod; Lebocar; Lecarge; Nervocur; Parkinel; Sinemet; Stalevo; ***Austral.***: Duodopa; Kinson; Levohexal†; Sinemet; Stalevo; ***Austria***: Duodopa; Levocar; Sinemet; Stalevo; ***Belg.***: Duodopa; Sinemet; Stalevo; ***Braz.***: Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Sinemet; Stalevo; ***Canad.***: Apo-Levocarb; Duodopa; Novo-Levocarbidopa†; Nu-Levocarb; Pro-Levocarb; Sinemet; Stalevo; ***Chile***: Grifoparkin; Levofamil; Protonis†; Saniter Compuesto; Sinemet; Stalevo; ***China***: Sinemet (息宁); Xi Lai Mei (西莱美); ***Cz.***: Apo-Levocarb; Dopalux†; Duodopa; Isicom; Lecardop; Nakom; Sinemet; Stalevo; ***Denm.***: Duodopa; Sinemet; Stalevo; ***Fin.***: Duodopa; Kardopal; Levocar; Sinemet; Stalevo; ***Fr.***: Duodopa; Sinemet; Stalevo; ***Ger.***: Duodopa; Isicom; Levo-C; Levobeta C; Levocarb†; Levocomp†; Levodop; Levodopa comp C†; Levodopa Comp; Nacom; Stalevo; Striaton†; ***Gr.***: Duodopa; Sinemet; Stalevo; Zimox; ***Hong Kong***: Apo-Levocarb; Levomed; Levomet; Sinedopa†; Sinemet; Stalevo; ***Hung.***: Duellin†; Duodopa; Sinemet†; Stalevo; ***India***: LCD; Levopa-C; Neocare; Syndopa; ***Indon.***: Stalevo; ***Irl.***: Half Sinemet; Sinemet; Stalevo; ***Israel***: Dopicar; Duodopa; Sinemet; Stalevo; ***Ital.***: Duodopa; Sinemet; Sirio; Stalevo; ***Malaysia***: Apo-Levocarb; Levomed; Sinedopa; Sinemet; Stalevo; ***Mex.***: Cloisone; Lemdopa†; Racovel; Sinemet; Stalevo; Ternovag; ***Neth.***: Duodopa; Sinemet; Stalevo; ***Norw.***: Duodopa; Sinemet; Stalevo; ***NZ***: Apo-Levocarb†; Sindopa; Sinemet; ***Philipp.***: Ledocar; Sinemet; Stalev; Tidomet; ***Pol.***: Sinemet; Stalevo; ***Port.***: Duodopa; Ledopsan; Sinemet; Stalevo; ***Rus.***: Duellin (Дуэллин); Nakom (Наком); Sinemet (Синемет); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); ***S.Afr.***: Carbilev; Sinemet; Stalevo; ***Singapore***: Cardopar; Credanil; Levomet; Sinemet; Stalevo; Tidomet; ***Spain***: Duodopa; Ledopsan†; Sinemet; Stalevo; ***Swed.***: Duodopa; Levocar; Sinemet; Stalevo; ***Switz.***: Duodopa; Sinemet; Stalevo; ***Thai.***: Levomed; Levomet; Sinemet; Stalevo; Syndopa; Tidomet; ***Turk.***: Sinemet; Stalevo; ***UK***: Duodopa; Half Sinemet; Sinemet; Stalevo; ***Ukr.***: Levocarbhexal (Левокарбгексал)†; Levokom (Левоком); Nakom (Наком); Stalevo (Сталево); ***USA***: Atamet; Parcopa; Sinemet; Stalevo; ***Venez.***: Sinemet; Stalevo.

Pharmacopoeial Preparations
BP 2014: Co-careldopa Tablets;
USP 36: Carbidopa and Levodopa Orally Disintegrating Tablets; Carbidopa and Levodopa Tablets.

Dexetimide *(BAN, USAN, rINN)*

Dexetimida; Dexétimide; Dexetimidum; Дексэтимид.
(*S*)-2-(1-Benzyl-4-piperidyl)-2-phenylglutarimide; (*S*)-3-Phenyl-1′-(phenylmethyl)-(3,4′-bipiperidine)-2,6-dione.
$C_{23}H_{26}N_2O_2$=362.5
CAS — 21888-98-2.
ATC — N04AA08.
ATC Vet — QN04AA08.
UNII — 43477QYX3D.

Dexetimide Hydrochloride *(BANM, rINNM)*

Dexbenzetimide Hydrochloride; Dexetimida, hidrocloruro de; Dexétimide, Chlorhydrate de; Dexetimidi Hydrochloridum; Hidrocloruro de dexetimida; R-16470; Дексэтимида Гидрохлорид.
$C_{23}H_{26}N_2O_2$,HCl=398.9
CAS — 21888-96-0.
ATC — N04AA08.
ATC Vet — QN04AA08.
UNII — B987A3XX7D.

Profile

Dexetimide is a tertiary antimuscarinic with actions similar to those of trihexyphenidyl (p. 917.3). It has been used to alleviate drug-induced extrapyramidal symptoms (see under Chlorpromazine, p. 1049.2), but, like other antimuscarinics, is of no value against tardive dyskinesias. Dexetimide hydrochloride has been given orally and by intramuscular injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Tremblex†.

Diethazine Hydrochloride *(BANM, rINNM)*

Diaethazinium Chloratum; Dietazina, hidrocloruro de; Diéthazine, Chlorhydrate de; Diethazini Hydrochloridum; Eazamine Hydrochloride; Hidrocloruro de dietazina; RP-2987; Диэтазина Гидрохлорид.
10-(2-Diethylaminoethyl)phenothiazine hydrochloride.
$C_{18}H_{22}N_2S$,HCl=334.9
CAS — 60-91-3 (diethazine); 341-70-8 (diethazine hydrochloride).
UNII — S88072126Q.

Profile

Diethazine hydrochloride is an antimuscarinic with actions similar to those of profenamine hydrochloride (p. 912.3), but it is more toxic and bone-marrow depression may occur. It has been used in the treatment of parkinsonism.

Droxidopa *(USAN, rINN)*

DOPS; Droxidopum; L-DOPS; L-*threo*-DOPS; L-*threo*-3,4-Dihydroxyphenylserine; Дроксидопа.
(-)-*threo*-3-(3,4-Dihydroxyphenyl)-L-serine.
$C_9H_{11}NO_5$=213.2
CAS — 23651-95-8.
UNII — J7A92W69L7.

Profile

Droxidopa is a precursor of noradrenaline that is used in the treatment of parkinsonism (p. 889.1) and some forms of orthostatic hypotension (p. 1634.3). The usual oral maintenance dose is 600 mg daily for the treatment of parkinsonism and 300 to 600 mg daily in orthostatic hypotension; daily doses should be divided.

The racemic form (DL-*threo*-3,4-dihydroxyphenylserine) has also been studied for orthostatic hypotension.

References.
1. Iida N, *et al.* Treatment of dialysis-induced hypotension with L-threo-3, 4-dihydroxyphenylserine. *Nephrol Dial Transplant* 1994; **9:** 1130–5.
2. Freeman R, *et al.* The treatment of neurogenic orthostatic hypotension with 3,4-DL-threo-dihydroxyphenylserine: a randomized, placebo-controlled, crossover trial. *Neurology* 1999; **10:** 2151–7.
3. Akizawa T, *et al.* Clinical effects of L-threo-3,4-dihydroxyphenylserine on orthostatic hypotension in hemodialysis patients. *Nephron* 2002; **90:** 384–90.
4. Kaufmann H, *et al.* Norepinephrine precursor therapy in neurogenic orthostatic hypotension. *Circulation* 2003; **108:** 724–8.
5. Goldstein DS, *et al.* Clinical pharmacokinetics of the norepinephrine precursor L-threo-DOPS in primary chronic autonomic failure. *Clin Auton Res* 2004; **14:** 363–8.
6. Kaufmann H. L-dihydroxyphenylserine (Droxidopa): a new therapy for neurogenic orthostatic hypotension: the US experience. *Clin Auton Res* 2008; **18** (suppl 1): 19–24.
7. Mathias CJ. L-dihydroxyphenylserine (Droxidopa) in the treatment of orthostatic hypotension: the European experience. *Clin Auton Res* 2008; **18** (suppl 1): 25–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Dops.

Entacapone *(BAN, USAN, rINN)*

Entacapona; Entacaponum; Entakapon; Entakaponi; OR-611; Энтакапон.
(*E*)-α-Cyano-*N*,*N*-diethyl-3,4-dihydroxy-5-nitrocinnamamide; (*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylacrylamide.
$C_{14}H_{15}N_3O_5$=305.3
CAS — 130929-57-6.
ATC — N04BX02.
ATC Vet — QN04BX02.
UNII — 4975G9NM6T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Entacapone). A greenish-yellow or yellow powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in anhydrous ethanol; soluble or sparingly soluble in acetone. Protect from light.

USP 36: (Entacapone). A greenish yellow to yellow powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, in ether, and in isopropyl alcohol; sparingly soluble in acetone and in methyl alcohol; very slightly soluble in toluene. Store in airtight containers.

Uses and Administration

Entacapone is a selective, reversible, peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to combination preparations of levodopa and dopa-decarboxylase inhibitors, in patients with Parkinson's disease (below) and 'end-of-dose' motor fluctuations who cannot be stabilised on levodopa combinations alone. Entacapone is given orally in a dosage of 200 mg at the same time as each dose of levodopa with dopa-decarboxylase inhibitor, up to a maximum of 200 mg ten times daily. It is often necessary to gradually reduce the dosage of levodopa by about 10 to 30% within the first few weeks after starting treatment with entacapone; this effect may be more marked in the presence of benserazide than of carbidopa.

Entacapone may also be given as a combination preparation with carbidopa and levodopa; for dosage details, see Levodopa, p. 902.3.

Parkinsonism. Entacapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT), with mainly peripheral actions. It is given as adjunctive therapy to patients with Parkinson's disease (p. 889.1) having fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. When levodopa is given with a peripheral dopa-decarboxylase inhibitor, *O*-methylation then becomes the predominant form of metabolism of levodopa; therefore adding a peripheral COMT inhibitor such as entacapone potentially extends the duration and effect of levodopa in the brain, and thus allows levodopa to be given less often and in lower doses.

References.
1. Holm KJ, Spencer CM. Entacapone: a review of its use in Parkinson's disease. *Drugs* 1999; **58:** 159–177.
2. Anonymous. Entacapone for Parkinson's disease. *Med Lett Drugs Ther* 2000; **42:** 7–8.
3. Chong BS, Mersfelder TL. Entacapone. *Ann Pharmacother* 2000; **34:** 1056–65.
4. Myllyla VV, *et al.* Twelve-month safety of entacapone in patients with Parkinson's disease. *Eur J Neurol* 2001; **8:** 53–60.
5. Poewe WH, *et al.* Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). *Acta Neurol Scand* 2002; **105:** 245–55.
6. Brooks DJ, *et al.* Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1071–9.
7. Fenelon G, *et al.* Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations: a randomized, double-blind, multicentre study. *J Neural Transm* 2003; **110:** 239–51.
8. Olanow CW, Stocchi F. COMT inhibitors in Parkinson's disease: can they prevent and/or reverse levodopa-induced motor complications? *Neurology* 2004; **62** (suppl 1): S72–S81.
9. Deane K, *et al.* Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).
10. Poewe W. The role of COMT inhibition in the treatment of Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S31–S38.
11. Schrag A. Entacapone in the treatment of Parkinson's disease. *Lancet Neurol* 2005; **4:** 366–70.

Adverse Effects

The most frequent adverse effects produced by entacapone relate to increased dopaminergic activity and occur most commonly at the start of treatment; reduction of the levodopa dosage may reduce the severity and frequency of such effects. Adverse effects may include nausea, vomiting, abdominal pain, constipation, diarrhoea, colitis, dry mouth, and dyskinesias. Other commonly reported adverse effects include dizziness, insomnia, nightmares, hallucinations, confusion, fatigue, and increased sweating. Behavioural disturbances including intense urges to gamble and increased sexual urges have also been reported (see Effects on Mental Function, in Levodopa, p. 905.2). There have been rare reports of agitation, urticaria, erythematous or maculopapular rash, anorexia, and weight decrease. Increases in liver enzyme values have been reported rarely; there have also been isolated cases of cholestatic hepatitis. Isolated cases of neuroleptic malignant syndrome have been reported after abrupt reduction or withdrawal of entacapone; there have also been isolated cases of rhabdomyolysis. It may produce a harmless reddish-brown discoloration of the urine. Skin, hair, beard, and nail discolorations have been reported.

References.
1. Brooks DJ. Safety and tolerability of COMT inhibitors. *Neurology* 2004; **62** (Suppl 1): S39–S46.

Carcinogenicity. The FDA[1] reported that it is continuing to review data from the STRIDE-PD study, which suggested that parkinsonian patients who were taking the combination preparation containing entacapone, carbidopa, and levodopa (*Stalevo; Novartis, USA*) had an increased risk of prostate cancer when compared with those who were taking carbidopa with levodopa. The FDA commented that previous studies of shorter duration did not find such an association with entacapone, and that prostate cancer is most commonly diagnosed in men of the same age as those in the STRIDE-PD study.

1. FDA. FDA drug safety communication: ongoing safety review of Stalevo (entacapone/carbidopa/levodopa) and possible development of prostate cancer (issued 31st March, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm206363.htm (accessed 14/05/10)

Effects on the cardiovascular system. The FDA[1] is continuing to evaluate data from clinical studies that initially suggest that patients taking a combination preparation containing entacapone, carbidopa, and levodopa (*Stalevo; Novartis, USA*) are at an increased risk of cardiovascular events compared with those taking carbidopa with levodopa. The FDA commented that most patients had pre-existing risk factors for cardiovascular disease.

1. FDA. FDA drug safety communication: ongoing safety review of Stalevo and possible increased cardiovascular risk (issued 20th August, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm223060.htm (accessed 24/08/10)

Precautions

Entacapone is contra-indicated in patients with phaeochromocytoma and in patients with a history of neuroleptic malignant syndrome or nontraumatic rhabdomyolysis. It should be avoided in patients with hepatic impairment, and given with caution to patients with biliary obstruction. A general medical evaluation, including liver function, should be considered in those who develop progressive anorexia, asthenia, and weight decrease within a relatively short period of time. Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Treatment with entacapone should not be stopped abruptly; when necessary withdrawal should be made gradually, increasing the dose of levodopa as required.

Genetic polymorphism. For reference to slow metabolisers being more susceptible to COMT-inhibitor induced hepatotoxicity, see under Tolcapone, p. 917.2.

Interactions

Use of entacapone with a non-selective MAOI is contra-indicated. Entacapone should be used with caution in patients receiving drugs metabolised by catechol-*O*-methyltransferase (COMT) including adrenaline, apomorphine, dobutamine, dopamine, isoprenaline, methyldopa, noradrenaline, paroxetine, and rimiterol. Caution is also advised when used with certain antidepressants including the tricyclics, reversible inhibitors of monoamine oxidase type A, and noradrenaline reuptake inhibitors such as venlafaxine.

Entacapone may aggravate levodopa-induced orthostatic hypotension and should be used cautiously in patients who are taking other drugs that may cause orthostatic hypotension.

Entacapone may form chelates with iron preparations in the gastrointestinal tract; the two drugs should be taken at least 2 to 3 hours apart.

Pharmacokinetics

There are large intra- and interindividual variations in the absorption of entacapone. Peak plasma concentrations occur about one hour after oral doses. Entacapone undergoes extensive first-pass metabolism and oral bioavailability is about 35%. Absorption is not affected significantly by food. Entacapone is about 98% bound to plasma proteins. It is eliminated mainly in the faeces with about 10 to 20% being excreted in the urine, mainly as glucuronide conjugates. Entacapone is thought to be distributed into breast milk on the basis of studies in *rats*.

Entacapone is rapidly absorbed from the gastrointestinal tract and bioavailability after oral doses has been reported to range from 29 to 46%. It does not cross the blood-brain barrier. Over half of a dose appears in the faeces with smaller amounts being excreted in the urine as glucuronides of entacapone and its (*Z*)-isomer. Elimination half-lives of about 1.6 to 3.4 hours have been reported for entacapone.

References.
1. Wikberg T, *et al.* Identification of major metabolites of the catechol-O-methyltransferase inhibitor entacapone in rats and humans. *Drug Metab Dispos* 1993; **21:** 81–92.
2. Keränen T, *et al.* Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. *Eur J Clin Pharmacol* 1994; **46:** 151–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Comtan; ***Austral.***: Comtan; ***Austria***: Comtan; ***Belg.***: Comtan; ***Braz.***: Comtan; Entarkin; ***Canad.***: Comtan; ***China***: Comtan (珂丹); ***Cz.***: Comtan; Comtess; ***Denm.***: Comtan†; Comtess; ***Fin.***: Comtess; ***Fr.***: Comtan; ***Ger.***: Comtess; ***Gr.***: Comtan; ***Hong Kong***: Comtan; ***Hung.***: Comtan; ***India***: Adcapone; Entacom; ***Indon.***: Comtan; ***Irl.***: Comtan; Comtess; ***Israel***: Comtan; ***Ital.***: Comtan; ***Malaysia***: Comtan; ***Mex.***: Comtan; ***Neth.***: Comtan; Comtess; ***Norw.***: Comtess; ***NZ***: Comtan; ***Philipp.***: Comtan; ***Pol.***: Comtan; Comtess; ***Port.***: Comtan; Comtess; ***S.Afr.***: Comtan; ***Singapore***: Comtan; ***Spain***: Comtan; ***Swed.***: Comtess; ***Switz.***: Comtan; ***Thai.***: Comtan; ***Turk.***: Comtan; ***UK***: Comtess; ***Ukr.***: Contan (Комтан)†; ***USA***: Comtan; ***Venez.***: Comtan.

Multi-ingredient Preparations. ***Arg.***: Stalevo; ***Austral.***: Stalevo; ***Austria***: Stalevo; ***Belg.***: Stalevo; ***Braz.***: Stalevo; ***Canad.***: Stalevo; ***Chile***: Stalevo; ***Cz.***: Stalevo; ***Denm.***: Stalevo; ***Fin.***: Stalevo; ***Fr.***: Stalevo; ***Ger.***: Stalevo; ***Gr.***: Stalevo; ***Hong Kong***: Stalevo; ***Hung.***: Stalevo; ***Indon.***: Stalevo; ***Irl.***: Stalevo; ***Israel***: Stalevo; ***Ital.***: Stalevo; ***Malaysia***: Stalevo; ***Mex.***: Stalevo; ***Neth.***: Stalevo; ***Norw.***: Stalevo; ***Philipp.***: Stalev; ***Pol.***: Stalevo; ***Port.***: Stalevo; ***Rus.***: Stalevo (Сталево); ***S.Afr.***: Stalevo; ***Singapore***: Stalevo; ***Spain***: Stalevo; ***Swed.***: Stalevo; ***Switz.***: Stalevo; ***Thai.***: Stalevo; ***Turk.***: Stalevo; ***UK***: Stalevo; ***Ukr.***: Stalevo (Сталево); ***USA***: Stalevo; ***Venez.***: Stalevo.

Pharmacopoeial Preparations
USP 36: Entacapone Tablets.

Istradefylline *(USAN, rINN)*

Istradefilina; Istradéfylline; Istradefyllinum; KW-6002; Истрадефиллин.

8-[(1*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]-1,3-diethyl-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione.

$C_{20}H_{24}N_4O_4$=384.4

CAS — 155270-99-8.

UNII — 2GZ0LIK7T4.

Profile

Istradefylline is a selective adenosine A_{2A}-receptor antagonist given to reduce 'end-of-dose' deterioration with levodopa therapy in the treatment of Parkinson's disease (p. 889.1). Istradefylline is given orally in a usual dose of 20 mg once daily, which can be increased to 40 mg daily if necessary.

References.
1. Park A, Stacy M. Istradefylline for the treatment of Parkinson's disease. *Expert Opin Pharmacother* 2012; **13:** 111–14.
2. Chen W, *et al.* Istradefylline, an adenosine A_{2A} receptor antagonist, for patients with Parkinson's disease: a meta-analysis. *J Neurol Sci* 2013; **324:** 21–8.
3. Dungo R, Deeks ED. Istradefylline: first global approval. *Drugs* 2013; **73:** 875–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Nouriast.

Levodopa *(BAN, USAN, rINN)*

Dihydroxyphenylalanine; L-Dopa; 3-Hydroxy-L-tyrosine; Laevo-dopa; Lévodopa; Levodopum; Леводопа.

(-)-3-(3,4-Dihydroxyphenyl)-L-alanine.

$C_9H_{11}NO_4$=197.2

CAS — 59-92-7.

ATC — N04BA01.

ATC Vet — QN04BA01.

UNII — 46627O600J.

NOTE. Compounded preparations of levodopa may be represented by the following names:
- Co-beneldopa (*BAN*)—benserazide 1 part and levodopa 4 parts (w/w)
- Co-careldopa *x*/*y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa, respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Levodopa). A white or slightly cream-coloured, crystalline powder. Slightly soluble in water; freely soluble in 1M hydrochloric acid but sparingly soluble in 0.1M hydrochloric acid; practically insoluble in alcohol. A 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 36: (Levodopa). A white to off-white, odourless, crystalline powder. In the presence of moisture, it is rapidly oxidised by atmospheric oxygen and darkens. Slightly soluble in water; freely soluble in 3N hydrochloric acid; insoluble in alcohol. Store in a dry place in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Stability. Extemporaneously prepared oral liquid dosage forms may be unstable and manufacturers' formulations should be used where possible.[1] Water dispersible formulations of levodopa with benserazide are available in some countries but a method that can be used by patients to prepare daily solutions of levodopa with carbidopa has been suggested:[2] one litre of a solution in potable water may be prepared with ten crushed standard tablets of levodopa 100 mg with carbidopa 25 mg and 2 g of ascorbic acid added to stabilise the levodopa.

1. Walls TJ, *et al.* Problems with inactivation of drugs used in Parkinson's disease. *BMJ* 1985; **290:** 444–5.
2. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.

Uses and Administration

Levodopa, a naturally occurring amino acid, is the immediate precursor of the neurotransmitter dopamine. The actions of levodopa are mainly those of dopamine (p. 1367.2).

Unlike dopamine, levodopa readily enters the CNS and is used in the treatment of conditions, such as Parkinson's disease (p. 904.1), that are associated with depletion of dopamine in the brain. Levodopa is rapidly decarboxylated by peripheral enzymes so that very little unchanged drug is available to cross the blood-brain barrier for central conversion into dopamine. Consequently, levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as benserazide (p. 894.1) or carbidopa (p. 900.3) to increase the proportion of levodopa that can enter the brain. This enables the dosage of levodopa to be reduced and may diminish peripheral adverse effects, such as nausea and vomiting and cardiac arrhythmias, by blocking the peripheral production of dopamine. It may also provide a more rapid response at the start of therapy.

The majority of patients with Parkinson's disease benefit from levodopa therapy, but after 2 years or more, improvement in disability is gradually lost as the disease progresses and fluctuations in mobility emerge. Postencephalitic parkinsonism responds to levodopa, but a higher incidence of adverse effects has been reported than in the idiopathic form so smaller doses are generally used. Levodopa has also been used to control the neurological symptoms of chronic manganese poisoning, which resemble those of parkinsonism. It should not be used in antipsychotic-induced parkinsonism.

Levodopa has an effect on pituitary function as a result of its conversion to dopamine. It may enhance growth hormone secretion and has been used diagnostically as a provocative test for growth hormone deficiency. Levodopa also inhibits prolactin secretion.

Response to levodopa varies considerably between patients. **Treatment of parkinsonism** should begin with small doses increased gradually, ideally to a dose that improves mobility without producing adverse effects. Levodopa should be taken with or after meals, although in later disease, it may be preferable to take it on an empty stomach (see Precautions, p. 906.3). Once established, maintenance doses may need to be reduced as the patient ages. When given **without a peripheral dopa-decarboxylase inhibitor** (which is rare) a suggested initial oral dose is 125 mg twice daily increased gradually every 3 to 7 days, according to response, to up to 8 g daily in divided doses. The intervals between doses should be adjusted to meet individual needs; many patients find 4 or 5 divided doses daily to be satisfactory although some may require smaller, more frequent doses in order to control fluctuations in mobility. Maximum improvement may take up to 6 months or longer to occur.

When given **with a peripheral dopa-decarboxylase inhibitor** lower doses of levodopa are used. As high central dopamine concentrations can be achieved more quickly, both beneficial and adverse effects tend to occur more rapidly than with levodopa alone and patients should be monitored carefully. In those already receiving levodopa the drug should be stopped and benserazide or carbidopa with levodopa started on the next day or after 24 hours if the patient was receiving a modified-release preparation of levodopa.

Benserazide is given as the hydrochloride but doses are expressed in terms of the base. Benserazide hydrochloride 28.5 mg is equivalent to about 25 mg of benserazide. Benserazide is usually given with levodopa in the ratio of 1 part of benserazide base to 4 parts of levodopa (co-beneldopa) and the doses for co-beneldopa that follow are expressed in terms of the levodopa component.

- An initial oral dose for *patients not previously treated with levodopa* is levodopa 50 mg three or four times daily increased gradually in increments of levodopa 100 mg once or twice weekly, according to response. If the disease is at an advanced stage, the initial starting dose may be increased to levodopa 100 mg three times daily. For some elderly patients, an initial dose of levodopa 50 mg once or twice daily, increased by 50 mg every third or fourth day, may be suitable. Maintenance doses usually lie within the range of levodopa 400 to 800 mg daily in divided doses, although most patients require no more than 600 mg daily. If optimal improvement has not been achieved after several weeks at the average dose, further increases may be made with caution; it is rarely necessary to give more than 1 g of levodopa daily.
- The initial dose of levodopa given with benserazide in *patients previously treated with levodopa alone* should be about 10 to 15% of the dose previously being taken, thus levodopa 300 mg would be appropriate for a patient previously taking levodopa 2 g daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose is levodopa 50 mg given three or four times daily. In either situation, the dose may then be adjusted in a similar manner as described for previously untreated patients.
- Modified-release capsules containing the equivalent of benserazide 25 mg with levodopa 100 mg are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* the initial dose is one capsule three times daily adjusted every 2 to 3 days according to response; it is recommended that initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of levodopa with benserazide, initially one capsule should be substituted for every 100 mg of levodopa and should be given at the same dosage frequency as before; increases in dosage can then be made every 2 to 3 days according to response. An average of 50% more levodopa may be required compared with previous therapy and titration may take up to 4 weeks. *Supplementary doses* of an immediate-release preparation of benserazide with levodopa may also be required with the first morning dose.

Carbidopa is usually given with levodopa (co-careldopa) as tablets in the ratio of 1 to 4 or 1 to 10, which allows dosage adjustments of either drug for individual patients. Carbidopa is given as the hydrous base although doses are expressed in terms of the anhydrous base; hydrous carbidopa 10.8 mg is equivalent to about 10 mg of anhydrous carbidopa. Full inhibition of peripheral dopa-decarboxylase is reported to be achieved with 70 to 100 mg of carbidopa daily.

- A suggested initial oral dose for *patients not previously treated with levodopa* is carbidopa 25 mg with levodopa 100 mg three times daily, increased gradually, in increments of carbidopa 12.5 mg with levodopa 50 mg or carbidopa 25 mg with levodopa 100 mg every day or on alternate days, as necessary, until a total daily dose of carbidopa 200 mg with levodopa 800 mg is reached. Maintenance therapy should be individualised and adjusted gradually according to response. Carbidopa doses greater than 200 mg daily are not generally exceeded.
- The initial dose of levodopa with carbidopa in *patients previously treated with levodopa alone* should be about 20 to 25% of the dose previously being taken, thus for patients taking less than 1.5 g of levodopa daily a suggested initial dose is carbidopa 25 mg with levodopa 100 mg given three or four times daily; a suggested initial dose for patients taking more than 1.5 g of levodopa daily is carbidopa 25 mg with levodopa 250 mg given three or four times daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose should provide a similar daily amount of levodopa.
- Modified-release tablets containing carbidopa with levodopa in the ratio of 1 to 4 are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* therapy, or for *those currently receiving levodopa alone*, the initial dose is carbidopa 50 mg with levodopa 200 mg twice daily, adjusted according to response, at intervals of not less than 3 days. It is recommended that for patients who are not already receiving levodopa initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of carbidopa with levodopa, the initial dose of the modified-release preparation should provide a similar daily amount of levodopa, but the dosing intervals should be prolonged and are normally between 4 to 12 hours. The initial substitution dose of the modified-release preparation should provide no greater than 10% more levodopa than was previously given for doses of levodopa exceeding 900 mg daily. Doses and intervals may then be altered according to clinical response, allowing at least 3 days between adjustments. Up to 30% more levodopa may be required in the modified-release preparation than was previously given in the immediate-release preparation. Average maintenance doses of modified-release preparations lie within the range of carbidopa 100 mg with levodopa 400 mg to carbidopa 400 mg with levodopa 1.6 g daily in divided doses. *Supplementary doses* of an immediate-release preparation of carbidopa with levodopa may be required in some patients.

Combination preparations of levodopa with carbidopa and the catechol-*O*-methyltransferase (COMT) inhibitor **entacapone** are also available; each tablet contains levodopa and carbidopa in a ratio of 4 to 1 with entacapone 200 mg. Such preparations are indicated for patients with end-of-dose motor fluctuations not stabilised on levodopa/peripheral dopa-decarboxylase inhibitor treatment. Patients should only take one combination tablet for each dose.

- *Patients previously treated with an immediate-release preparation of levodopa with a peripheral dopa-decarboxylase inhibitor and separate entacapone* should be transferred to the combination preparation at a dose that provides similar or slightly higher amounts of levodopa.
- For *patients not currently taking entacapone*, the dose of the combination preparation should normally provide a similar or slightly lower dose of levodopa to that previously taken. However, patients with *dyskinesia* or taking *levodopa in doses above 800 mg daily* should start entacapone as a separate medication before being transferred to the combination preparation, as a 10 to 30% reduction in their levodopa dose may be needed when starting combination therapy, especially if levodopa is being given with benserazide.

In some countries a gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available for *continuous infusion* by an ambulatory pump into the duodenum. It is indicated for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations when other available combination therapy has not been satisfactory. A positive test of the clinical response via a temporary nasoduodenal tube is required before a permanent tube is inserted into the duodenum or upper jejunum. The total daily dose comprises of 3 individually-adjusted doses, which are expressed in terms of the levodopa component as follows:

- the *morning bolus dose*, based on the patient's previous morning intake of levodopa, is usually 100 to 200 mg and should not exceed 300 mg in total; the therapeutic dose level is achieved within 10 to 30 minutes
- the *continuous maintenance dose*, based on the patient's previous daily intake of levodopa, is usually 40 to 120 mg/hour infused over 16 hours, adjustable in steps of 2 mg/hour to within a range of 20 to 200 mg/hour; higher doses may be needed in exceptional cases
- *extra bolus doses*, given when required, are usually between 10 to 40 mg although higher doses may be needed in exceptional cases; the maintenance dose should be increased if more than 5 bolus doses are needed daily

After the initial dose setting, further dose adjustments should be made over a few weeks. If medically justified, it may be administered during the night.

Melevodopa, the methyl ester of levodopa, has been used orally as the hydrochloride with carbidopa in some countries for parkinsonism. The ethyl ester of levodopa, etilevodopa, has also been studied.

Administration. A small crossover study involving 24 patients with severe Parkinson's disease found that daytime intraduodenal infusion of a levodopa and carbidopa gel preparation for 3 weeks was clinically superior to individually optimised conventional regimens.[1] Another small case series of 5 patients found that continuous 24-hour intraduodenal infusion was also generally well-tolerated and improved motor fluctuations without the development of clinically significant tolerance to its effects.[2] Long-term experience (up to 7 years) in a limited number of patients has suggested that intraduodenal infusion is a good alternative for those with advanced disease and disabling motor fluctuations.[3] A gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available in some countries for intraduodenal infusion.

1. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64:** 216–23.
2. Nyholm D, *et al.* Long-term 24-hour duodenal infusion of levodopa: outcome and dose requirements. *Neurology* 2005; **65:** 1506–7.
3. Nilsson D, *et al.* Duodenal levodopa infusion in Parkinson's disease: long-term experience. *Acta Neurol Scand* 2001; **104:** 343–8.

Administration in children. Although unlicensed, levodopa has been tried for various conditions in neonates, children, and adolescents. For further details and suggested doses, see Amino Acid Metabolic Disorders (below), Dystonias (below), and Pituitary and Hypothalamic Disorders (p. 904.2).

Amino acid metabolic disorders. Although not licensed for the treatment of defects in tetrahydrobiopterin synthesis and dihydrobiopterin reductase deficiency, the *BNFC* suggests that neonates, children, and adolescents up to the age of 18 years may be given initial oral doses of 250 to 500 micrograms/kg of levodopa (with carbidopa in the ratio of 4 to 1) four times daily increased according to response every 4 to 5 days to a maintenance dose of 2.5 to 3 mg/kg four times daily. Preparations containing levodopa with carbidopa in the ratio of 10 to 1 should be considered at higher doses. Treatment should be reviewed regularly every 3 to 6 months during early childhood.

Drug-induced extrapyramidal disorders. The management of drug-induced extrapyramidal disorders is discussed under the Adverse Effects of Chlorpromazine on p. 1049.2. Although the use of dopamine agonists, especially levodopa, to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, levodopa has generally been reported to be ineffective or to increase psychiatric symptoms.

Dysphagia. Results of a small study[1] have suggested that levodopa may improve the impaired swallowing reflex in patients with basal ganglia infarctions and thereby help to prevent aspiration pneumonia.

1. Kobayashi H, *et al.* Levodopa and swallowing reflex. *Lancet* 1996; **348:** 1320–1.

Dystonias. A dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures; it may also have additional myoclonic or tremulous components. Typically it starts as a focal dystonia localised in one part of the body and to begin with may appear only during a specific motor act (action dystonia). If the syndrome is progressive the dystonias may become apparent at rest and spread first to more than one part of the body (segmental dystonia) and may eventually affect most or all of the body (generalised dystonia). Progression of the dystonia appears to be related to age of onset. Dystonia beginning in childhood usually starts in the legs and progresses to become segmental or generalised, whereas in adults the dystonia usually starts in other parts of the body and rarely becomes generalised. Examples of focal dystonias are blepharospasm (affecting the eye and surrounding facial muscles), writer's cramp (hand and arm), spasmodic torticollis (neck), spasmodic dysphonia, or dystonic dysphagia (larynx or pharynx), and leg dystonias. Some dystonias may be associated with metabolic disorders such as Wilson's disease or Lesch-Nyhan syndrome; with neurological disorders such as Huntington's disease; or with other causes including head trauma, manganese or carbon disulfide toxicity, or the adverse effects of antipsychotics or antiparkinsonian drugs. However, in the majority of cases the disease is idiopathic.

There are no cures for most types of dystonia, but with appropriate **management** symptomatic relief is possible in many patients.[1-5]

- It has been suggested that all children and adolescents presenting with dystonia, particularly starting in the legs, should first be given a trial with *levodopa*.[1,3,5] Although not licensed for children in the UK, the *BNFC* states that children aged 3 months and older with dopamine-sensitive dystonias, including dystonic cerebral palsy, may be given 250 micrograms/kg of levodopa (with carbidopa in the ratio of 4 to 1) orally two or three times daily increased according to response every 2 to 3 days to a maximum of 1 mg/kg of levodopa three times daily. Another suggested regimen is to gradually build up to a dose of levodopa 200 mg with carbidopa 50 mg given three times daily and to maintain this dose for 3 months; if there is no useful response in this period the drug is withdrawn.[1] Where there is benefit it is usually dramatic and is sustained as long as the drug is taken, which may be more than 10 years in some cases, in general without the long-term problems associated with levodopa for parkinsonism (see p. 889.1).
- In children and adolescents who fail to respond to levodopa an *antimuscarinic* such as trihexyphenidyl is second choice; the *BNFC* also suggests using procyclidine. Adverse effects are minimised by starting with a low dose which is then gradually increased. General experience indicates that about half of all children and adolescents benefit from antimuscarinics; adults tolerate the drug less well and only about a fifth of adult patients with focal dystonia benefit.
- In patients who do not respond to levodopa or high-dose antimuscarinics other drugs may be used. Many benefit from *benzodiazepines* such as diazepam; a few have responded to *baclofen* or *carbamazepine*. *Antipsychotics* are sometimes useful but carry the risk of inducing tardive dyskinesia. *Tetrabenazine* carries less risk of tardive dyskinesia but may induce depression. In very severe dystonia combination therapy may be required: tetrabenazine with pimozide and trihexyphenidyl is sometimes effective.

- In patients refractory to oral therapy *intrathecal* baclofen, or surgery may be tried.
- The response in patients with adult onset focal dystonia is usually poor. However, the use of *botulinum A toxin* can produce relief in blepharospasm, spasmodic torticollis, and spasmodic dysphonia, and is under investigation for writer's cramp and other occupational dystonias. In some patients with generalised and segmental dystonia, botulinum A toxin injected into the most disabling or painful muscles has been used as adjunctive therapy. Local injections into the affected muscles produce weakness over the next week or so, thereby reducing or abolishing dystonic spasms. The effect lasts some 2 to 4 months. *Botulinum B toxin* has also been used in the management of spasmodic torticollis.

Further details of the management of blepharospasm and spasmodic torticollis can be found under Botulinum Toxins on p. 2018.1 and p. 2019.2, respectively. For a discussion of the management of antipsychotic-induced dystonic reactions, see Extrapyramidal Disorders, under Adverse Effects of Chlorpromazine, p. 1049.2.

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.
2. Williams A. Consensus statement for the management of focal dystonias. *Br J Hosp Med* 1993; **50:** 655–9.
3. Bressman SB. Dystonia update. *Clin Neuropharmacol* 2000; **23:** 239–51.
4. Tarsy D, Simon DK. Dystonia. *N Engl J Med* 2006; **355:** 818–29.
5. Jankovic J. Treatment of dystonia. *Lancet Neurol* 2006; **5:** 864–72.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as levodopa in the management of hepatic encephalopathy see p. 1811.2.

Neuroleptic malignant syndrome. There have been isolated reports[1-4] that levodopa used alone or with bromocriptine has been successful in the treatment of patients with neuroleptic malignant syndrome (p. 1050.2). However, bromocriptine is usually preferred when a dopaminergic is required for the treatment of this condition.

1. Knezevic W, *et al.* Neuroleptic malignant syndrome. *Med J Aust* 1984; **140:** 28–30.
2. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; **ii:** 969–70.
3. Lo TCN, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; **65:** 653–5.
4. Shoop SA, Cernek PK. Carbidopa/levodopa in the treatment of neuroleptic malignant syndrome. *Ann Pharmacother* 1997; **31:** 119.

Parkinsonism. Levodopa is the mainstay in the treatment of Parkinson's disease (p. 889.1) but opinion varies on when it should be used in the course of the disease. Most patients respond to levodopa initially but after a few years benefit may be reduced. There may be problems with dyskinesias and psychiatric effects and fluctuations in mobility necessitating careful dosage adjustment or the use of adjunctive drugs. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms. Levodopa should be given with a peripheral dopa-decarboxylase inhibitor; a peripheral catechol-*O*-methyltransferase (COMT) inhibitor may also be necessary for patients with fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. The various methods used for the pharmacokinetic optimisation of levodopa therapy as Parkinson's disease progresses include timing of doses, the use of modified-release formulations, oral solutions (but see Stability, p. 902.3) and dispersible formulations for immediate absorption, the timing of food intake, and the use of other drugs to increase the absorption of levodopa. In some countries a gel formulation of levodopa with carbidopa is available for intraduodenal infusion.

References.

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.
2. Contin M, *et al.* Pharmacokinetic optimisation in the treatment of Parkinson's disease. *Clin Pharmacokinet* 1996; **30:** 463–81.
3. Murer MG, *et al.* Levodopa in Parkinson's disease: neurotoxicity issue laid to rest? *Drug Safety* 1999; **21:** 339–52.
4. Furlanut M, *et al.* Monitoring of L-dopa concentrations in Parkinson's disease. *Pharmacol Res* 2001; **43:** 423–7. Correction. *ibid.*; **44:** 149.
5. Carlsson A. Treatment of Parkinson's with L-DOPA: the early discovery phase, and a comment on current problems. *J Neural Transm* 2002; **109:** 777–87.
6. Katzenschlager R, Lees AJ. Treatment of Parkinson's disease: levodopa as the first choice. *J Neurol* 2002; **249** (suppl 2): II19–II24.
7. van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. *CNS Drugs* 2003; **17:** 475–89.
8. LeWitt PA, Nyholm D. New developments in levodopa therapy. *Neurology* 2004; **62** (suppl 1): S9–S16.
9. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S56–S63.
10. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64:** 216–23.
11. LeWitt PA. Levodopa for the treatment of Parkinson's disease. *N Engl J Med* 2008; **359:** 2468–76.

Pituitary and hypothalamic disorders. *DIAGNOSIS AND TESTING.* Diminished growth hormone reserve is one of the earliest functional abnormalities in anterior pituitary failure and, since dopamine is believed to stimulate growth hormone secretion, levodopa has been used as a provocative test for the diagnosis of growth hormone deficiency.[1,2] Levodopa 500 mg has been given orally after an overnight fast and serum concentrations of growth hormone measured hourly at 0 to 3 hours; children may be given 10 mg/kg to a maximum of 500 mg. Transient nausea, vomiting, vertigo, and hypotension may occur and the patient should be kept recumbent during the test. A normal response is an increase in serum concentration of growth hormone of more than 5 nanograms/mL or to a level of more than 10 nanograms/mL, although 10 to 15% of normal subjects may not respond. However, there is some dispute as to whether stimulated growth hormone secretion tests are superior to measurements of circulating somatomedins in detecting growth hormone deficiency.[3-5] For a discussion of the management of growth retardation, including the problems of accurate diagnosis, see p. 1921.3.

1. Abboud CF. Laboratory diagnosis of hypopituitarism. *Mayo Clin Proc* 1986; **61:** 35–48.
2. Müller EE, *et al.* Involvement of brain catecholamines and acetylcholine in growth hormone deficiency states: pathophysiological, diagnostic and therapeutic implications. *Drugs* 1991; **41:** 161–77.
3. Hoffmann DM, *et al.* Diagnosis of growth-hormone deficiency in adults. *Lancet* 1994; **343:** 1064–8. Correction. *ibid.*, **344:** 206.
4. de Boer H, *et al.* Diagnosis of growth hormone deficiency in adults. *Lancet* 1994; **343:** 1645–6.
5. Rosenfeld RG, *et al.* Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab* 1995; **80:** 1532–40.

Sleep-associated movement disorders. The aetiology of *restless legs syndrome* and *periodic limb movements in sleep* is obscure and treatment has been largely empirical (p. 1034.2). Few of the treatments tried in these often co-existent disorders have been studied in a controlled manner but small controlled studies[1-6] have reported beneficial effects such as improved sleep quality and reduced leg movements from levodopa used with a peripheral dopa-decarboxylase inhibitor. Most patients received a bedtime dose of 50 to 200 mg of levodopa with possible additional doses during the night. A 1-year open-label extension study[7] confirmed the continued efficacy and safety of levodopa in patients with restless legs syndrome; the authors recommended a maximum daily dose of 400 mg levodopa to decrease the risk of exacerbation or rebound symptoms during the day. However, long-acting dopaminergic agonists are preferred in order to avoid the complications associated with levodopa.

Levodopa has also been reported to have been of benefit in a study of 10 patients with *sleep bruxism*.[8]

1. von Scheele C. Levodopa in restless legs. *Lancet* 1986; **ii:** 426–7.
2. Brodeur C, *et al.* Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind controlled study. *Neurology* 1988; **38:** 1845–8.
3. Kaplan PW, *et al.* A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993; **16:** 717–23.
4. Trenkwalder C, *et al.* L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind crossover trial. *Sleep* 1995; **18:** 681–8.
5. Beneš H, *et al.* Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep* 1999; **22:** 1073–81.
6. Janzen L, *et al.* An overview of levodopa in the management of restless legs syndrome in a dialysis population: pharmacokinetics, clinical trials, and complications of therapy. *Ann Pharmacother* 1999; **33:** 86–92.
7. Trenkwalder C, *et al.* One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? *Mov Disord* 2003; **18:** 1184–9.
8. Lobbezoo F, *et al.* The effect of the catecholamine precursor L-dopa on sleep bruxism: a controlled clinical trial. *Mov Disord* 1997; **12:** 73–8.

Strabismus. Experimental studies have shown that centrally acting drugs such as levodopa may improve vision in patients with amblyopia (see Strabismus, p. 2000.3). However, their role in clinical practice is not established.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2:** 91–100.

Tourette's syndrome. Levodopa has been studied in the management of Tourette's syndrome (see Tics, p. 1030.1). A small pilot study[1] has produced encouraging results.

1. Black KJ, *et al.* Response to levodopa challenge in Tourette syndrome. *Mov Disord* 2000; **15:** 1194–8.

Adverse Effects

Gastrointestinal effects, notably nausea, vomiting, and anorexia are common early in treatment with levodopa, particularly if the dosage is increased too rapidly. Gastrointestinal bleeding has been reported in patients with a history of peptic ulcer disease.

The commonest cardiovascular effect is orthostatic hypotension, which is usually asymptomatic, but may be associated with faintness and dizziness. Cardiac arrhythmias have been reported and hypertension has occasionally occurred.

Psychiatric symptoms occur in a high proportion of patients, especially the elderly, and include agitation, anxiety, euphoria, nightmares, insomnia or sometimes drowsiness, and depression. More serious effects, usually requiring a reduction in dosage or withdrawal of levodopa, include aggression, paranoid delusions, hallucinations, delirium, severe depression, with or without suicidal behaviour, and unmasking of psychoses. Psychotic reactions are more likely in patients with postencephalitic parkinsonism or a history of mental disorders. Excessive daytime sleepiness and sudden onset of sleep have been reported very rarely, as have pathological gambling, increased libido, and hypersexuality.

Abnormal involuntary movements or dyskinesias are the most serious dose-limiting adverse effects of levodopa and are very common at the optimum dose required to control parkinsonism; their frequency increases with duration of treatment. Involuntary movements of the face, tongue, lips, and jaw often appear first and those of the trunk and extremities later. Severe generalised choreoathetoid and dystonic movements may occur after prolonged use. Muscle twitching and blepharospasm may be early signs of excessive dosage. Exaggerated respiratory movements and exacerbated oculogyric crises have been reported in patients with postencephalitic parkinsonism. Bradykinesia and akinesia, in the form of 'end-of-dose' deterioration and the 'on-off' phenomenon, may re-emerge in patients with parkinsonism as a complication of long-term treatment, but may be due to progression of the disease rather than to levodopa (see also Parkinsonism, p. 889.1).

A positive response to the direct Coombs' test may occur, usually without evidence of haemolysis although autoimmune haemolytic anaemia has occasionally been reported. Transient leucopenia and thrombocytopenia have occurred rarely. The effects of levodopa on liver and kidney function are generally slight; transient increases in liver enzymes, and in blood-urea nitrogen and serum-uric acid concentrations, have been reported. Levodopa may cause discoloration of the urine; reddish at first then darkening on standing. Other body fluids may also be discoloured.

Some of the adverse effects reported may not be attributable directly to levodopa, but rather to the use of antimuscarinics, to increased mobility, or to the unmasking of underlying conditions as parkinsonism improves. Use with a peripheral dopa-decarboxylase inhibitor may reduce the severity of peripheral symptoms such as gastrointestinal and cardiovascular effects, but central effects such as dyskinesias and mental disturbances may occur earlier in treatment.

Incidence of adverse effects. The major adverse effects of levodopa are dyskinesia in 75% of patients and psychiatric disturbances in 25%.[1] Nausea and vomiting in 40 to 50% gradually regress and hypotension in 25 to 30% is generally asymptomatic. Less common adverse effects include cardiac arrhythmias, particularly atrial and ventricular ectopic beats and less commonly atrial flutter and fibrillation; palpitations and flushing often accompanied by excessive sweating; hypertension; polyuria, incontinence, and urinary retention, although antimuscarinic drugs often contribute to problems with micturition; and dark coloration of the urine and saliva. Rare adverse effects include abdominal pain, constipation, and diarrhoea; mydriasis, blurred vision, diplopia, and precipitation of glaucoma; headache; stridor; tachypnoea; and paraesthesias.

1. Calne DB, Reid JL. Antiparkinsonian drugs: pharmacological and therapeutic aspects. *Drugs* 1972; **4:** 49–74.

Abnormal coloration. Black pigmentation of rib cartilage has been noted at necropsy in patients treated with levodopa.[1,2] Abnormal pigmentation is generally not seen at other sites[2] but there have been isolated reports[2,3] of patients who also had pigmentation of the intervertebral discs. Although the pigmentation appears to be irreversible it was considered to be probably harmless.[2] It has been suggested that the pigmentation was due to deposition of dihydroxyphenylalanine (DOPA) in the cartilage.[1] It is known that DOPA will readily auto-oxidise *in vitro* in the presence of oxygen to a black pigment and this can also happen *in vivo* since black urine is a well known adverse effect of levodopa. Dark sweat and pigmentation of the skin and teeth are also known adverse effects.

See also Effects on the Skin and Hair, p. 906.1.

1. Connolly CE, *et al.* Black cartilage associated with levodopa. *Lancet* 1986; **i:** 690.
2. Rausing A, Rosén U. Black cartilage after therapy with levodopa and methyldopa. *Arch Pathol Lab Med* 1994; **118:** 531–5.
3. Keen CE. *BMJ* 1998; **316:** 240.

Dysgeusia. A change in taste sensation was reported[1] in 23 of 514 patients treated with levodopa and a peripheral dopa-decarboxylase inhibitor; 2 of the 23 had total loss of taste initially. The altered taste, often described as insipid, metallic, or plastic, was first noted 3 to 32 weeks after

beginning treatment, and lasted for 2 to 40 weeks. In an earlier report, 22 of 100 patients receiving levodopa alone had had changes in taste.[2]

1. Siegfried J, Zumstein H. Changes in taste under L-DOPA therapy. *Z Neurol* 1971; **200:** 345–8.
2. Barbeau A. L-DOPA therapy: past, present and future. *Ariz Med* 1970; **27:** 1–4.

Effects on the blood. Reports of effects of levodopa on the blood are mostly confined to individual case reports. A study in 365 patients, receiving levodopa in a mean daily dosage of 4.04 g, found that 32 developed a positive direct Coombs' test, the majority after between 3 and 12 months of therapy, but none developed haemolytic anaemia.[1] However, occasional cases of auto-immune haemolytic anaemia have been reported;[2-4] in one case, dosage reduction and addition of a peripheral dopa-decarboxylase inhibitor largely abolished haemolysis,[3] but in another, haemolysis recurred on re-institution of levodopa with carbidopa and required corticosteroid treatment.[4] A case of severe acute non-haemolytic anaemia related to levodopa therapy has also been reported.[5]

Levodopa is widely stated to produce leucopenia in some patients; however, there are few published reports. Transient minor decreases in total leucocyte counts were reported in 3 of a group of 80 patients receiving levodopa.[6]

Severe thrombocytopenia has been reported in 2 patients who had received levodopa for 3 and 2 years respectively;[7,8] the condition was apparently an auto-immune response and responded to prednisone therapy and withdrawal of levodopa.

1. Joseph C. Occurrence of positive Coombs test in patients treated with levodopa. *N Engl J Med* 1972; **286:** 1401–2.
2. Territo MC, *et al*. Autoimmune hemolytic anemia due to levodopa therapy. *JAMA* 1973; **226:** 1347–8.
3. Lindström FD, *et al*. Dose-related levodopa-induced haemolytic anaemia. *Ann Intern Med* 1977; **86:** 298–300.
4. Bernstein RM. Reversible haemolytic anaemia after levodopa-carbidopa. *BMJ* 1979; **1:** 1461–2.
5. Alkalay I, Zipoli T. Levodopa-induced acute non-hemolytic anemia. *Ann Allergy* 1977; **39:** 191.
6. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101:** 791–800.
7. Wanamaker WM, *et al*. Thrombocytopenia associated with long-term levodopa therapy. *JAMA* 1976; **235:** 2217–19.
8. Giner V, *et al*. Thrombocytopenia associated with levodopa treatment. *Arch Intern Med* 2003; **163:** 735–6.

Effects on the cardiovascular system. There have been conflicting reports on the effects of peripheral dopa-decarboxylase inhibitors on orthostatic hypotension attributed to levodopa therapy. In a study,[1] supine and erect systolic blood pressure was found to be significantly higher in parkinsonian patients given levodopa with carbidopa than in those receiving levodopa alone, suggesting that the peripheral actions of dopamine contribute to levodopa-induced hypotension. However, another study[2] found no change in the incidence and degree of orthostatic hypotension after giving levodopa with carbidopa and, similarly, no difference in the frequency of ventricular arrhythmias.

See also Effects on Kidney Function, below and Cardiovascular Disorders, under Precautions, p. 907.1.

1. Calne DB, *et al*. Action of L-α-methyldopahydrazine on the blood pressure of patients receiving levodopa. *Br J Pharmacol* 1972; **44:** 162–4.
2. Leibowitz M, Lieberman A. Comparison of dopa decarboxylase inhibitor (carbidopa) combined with levodopa and levodopa alone on the cardiovascular system of patients with Parkinson's disease. *Neurology* 1975; **25:** 917–21.

Effects on electrolytes. See Effects on Kidney Function, below.

Effects on the endocrine system. Single doses of levodopa given to healthy subjects cause an increase in plasma concentrations of glucose, insulin, and glucagon, as well as of growth hormone[1] and there has been concern over the potential endocrine effects of levodopa therapy in patients with Parkinson's disease.[2] A study of carbohydrate metabolism in 24 patients with Parkinson's disease indicated that these patients had abnormally low rates of **glucose utilisation** when untreated, apparently due to impaired insulin release, and this was not altered when levodopa therapy was given.[3] However, a similar study completed by 19 patients[2] noted increased impairment of glucose utilisation after levodopa therapy for 1 year with a delayed hypersecretion of insulin in response to a glucose load similar to the metabolic changes of acromegaly. It was considered that patients given levodopa for parkinsonism should be monitored for evidence of diabetes mellitus or frank acromegaly.[2]

Postmenopausal bleeding occurred in varying degrees in 12 of 47 women treated with levodopa.[4] In one case bleeding was severe enough to warrant interrupting treatment and subsequent dosage reduction.

1. Rayfield EJ, *et al*. L-Dopa stimulation of glucagon secretion in man. *N Engl J Med* 1975; **293:** 589–91.
2. Sirtori CR, *et al*. Metabolic responses to acute and chronic L-dopa administration in patients with parkinsonism. *N Engl J Med* 1972; **287:** 729–33.
3. Van Woert MH, Mueller PS. Glucose, insulin, and free fatty acid metabolism in Parkinson's disease treated with levodopa. *Clin Pharmacol Ther* 1971; **12:** 360–7.
4. Wajsbort J. Post-menopausal bleeding after L-dopa. *N Engl J Med* 1972; **286:** 784.

Effects on the eyes. Both miosis[1] and mydriasis[2] have been reported with levodopa.

For a report of the exacerbation of oculogyric crises by levodopa, see under Extrapyramidal Effects, p. 906.2.

1. Spiers ASD, *et al*. Miosis during L-dopa therapy. *BMJ* 1970; **2:** 639–40.
2. Weintraub MI, *et al*. Pupillary effects of levodopa therapy: development of anisocoria in latent Horner's syndrome. *N Engl J Med* 1970; **283:** 120–3.

Effects on the gastrointestinal tract. Although gastrointestinal bleeding has more commonly been reported in patients with a history of peptic ulceration, there is a rare report[1] of acute melaena and non-specific gastritis associated with levodopa therapy in a 56-year-old man without any previous evidence of a gastric disorder.

See also Dysgeusia, p. 904.3.

1. Riddoch D. Gastritis and L-dopa. *BMJ* 1972; **1:** 53–4.

Effects on kidney function. Levodopa 1 to 2 g given to 7 patients with idiopathic or postencephalitic Parkinson's disease produced significant increases in renal plasma flow, glomerular filtration rate, and sodium and potassium excretion.[1] It was considered that the natriuretic effects could contribute to the orthostatic hypotension commonly seen in patients receiving levodopa. There is a report of a patient who developed hyponatraemia when given levodopa with carbidopa.[2] The patient had previously had a similar reaction with amantadine. On each occasion symptoms disappeared when dopaminergic medication was withdrawn and recurred on rechallenge. Inappropriate secretion of antidiuretic hormone was suggested as a possible mechanism.

Levodopa has also been reported to have a kaliuretic effect, resulting in hypokalaemia, in some parkinsonian patients;[3] the effect could be prevented by also giving a peripheral dopa-decarboxylase inhibitor.

1. Finlay GD, *et al*. Augmentation of sodium and potassium excretion, glomerular filtration rate and renal plasma flow by levodopa. *N Engl J Med* 1971; **284:** 865–70.
2. Lammers GJ, Roos RAC. Hyponatraemia due to amantadine hydrochloride and L-dopa/carbidopa. *Lancet* 1993; **342:** 439.
3. Granérus A-K, *et al*. Kaliuretic effect of L-dopa treatment in parkinsonian patients. *Acta Med Scand* 1977; **201:** 291–7.

Effects on mental function. **Psychiatric complications** were the single commonest reason for stopping levodopa treatment in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Within 2 years, levodopa was withdrawn because of toxic confusional states (21 patients), paranoid psychosis (6 patients), unipolar depression (2 patients), and mania (1 patient). The incidence of visual hallucinations increased as treatment continued but, as with toxic confusional states, patients generally improved when levodopa was withdrawn. Before treatment, 40 patients had suffered severe depression and levodopa produced sustained improvement in only 2. After 6 years, 20 of the 81 patients remaining were moderately or severely depressed and were rarely improved by withdrawal or reduction in dosage of levodopa. Increasing dementia affected 26 of the 81 patients after 6 years; withdrawal of levodopa in 5 failed to improve cognitive disabilities, but increased parkinsonism.

Another study[2] reported that 141 of 400 patients being treated for Parkinson's disease developed mental disorders. In this study certain acute states, particularly anxiety, on-off hallucinations, and fits of delirium were linked to treatment with levodopa, whereas dementia and depression were not.

Long-term use of levodopa and dopamine agonists has been associated with various **behavioural disturbances**, including hypersexuality (see Effects on Sexual Function, p. 906.1), punding (purposeless repetitive acts), excessive gambling or shopping (see below), and other obsessive behaviour such as compulsive eating.[3-5] Risk factors include male gender, young age at onset of Parkinson's disease, underlying personality traits, and a personal or family history of addictive disorders.[4] Reduction in dopaminergic therapy can lead to cessation or improvement in symptoms. Some patients may develop dopamine dysregulation syndrome (see Abuse, under Precautions, p. 906.3).

A 12-month study of 1281 patients in the USA treated with dopamine agonists for Parkinson's disease found that 9 were suffering from **excessive gambling**.[6] All patients had received levodopa, 8 pramipexole, and the remaining patient pergolide. The rate of pathological gambling was 1.5% in the 529 patients taking pramipexole. The authors considered that this was not unexpected given the general availability of casinos in the local area and an incidence in the general US population of 0.3 to 1.3%. An analysis[7] of 11 patients who began pathological gambling after starting therapy with pramipexole (9 cases) or ropinirole (2 cases) found that in 8 patients such behaviour resolved when the drug was tapered or stopped; follow-up was not available in the other 3. In 7 patients the symptoms had developed within 1 to 3 months of achieving maintenance dose or after dose increases of dopamine agonist therapy. Of the 11 patients, 3 had not received levodopa. Cabergoline therapy has also been associated with pathological gambling.[8] Similar behaviour described as being markedly increased in "on" periods has been reported in other patients treated with levodopa.[9] Pathological gambling has also been associated with misuse of dopaminergics.[10]

Sleep-related complaints have occurred and were reported by 74 of 100 patients with Parkinson's disease.[11] All 74 were on levodopa and the prevalence of symptoms increased with the duration of treatment. Symptoms included insomnia, excessive daytime somnolence, altered dream phenomena, nocturnal vocalisation, involuntary myoclonic movements, and rarely, sleepwalking. Sleep fragmentation, which includes insomnia and somnolence, was the most common symptom overall. It has been suggested[12] that in patients with mild to moderate disease levodopa and dopamine agonists could cause sleep disruption. However, these drugs produce beneficial effects on nocturnal disabilities in patients with more severe disease. Reports[13-19] of daytime somnolence or sudden onset of sleep with various other dopamine agonists, including apomorphine, bromocriptine, cabergoline, lisuride, pergolide, piribedil, pramipexole, quinagolide, and ropinirole, suggest that this is a class effect of dopaminergic antiparkinsonian therapy, and patients should be warned of the possible risks (see Precautions, p. 906.3). The risk of somnolence may be increased in those patients taking combinations of dopaminergics.[18,20]

1. Shaw KM, *et al*. The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49:** 283–93.
2. Rondot P, *et al*. Mental disorders in Parkinson's disease after treatment with L-Dopa. *Adv Neurol* 1984; **40:** 259–69.
3. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17:** 172–80.
4. Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug Safety* 2009; **32:** 475–88.
5. MHRA. Public Assessment Report—Dopamine agonists: pathological gambling and increased libido (issued 7th November, 2006). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2025150&RevisionSelectionMethod=LatestReleased (accessed 23/08/10)
6. Driver-Dunckley E, *et al*. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003; **61:** 422–3.
7. Dodd ML, *et al*. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; **62:** 1377–81.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Pathological gambling with cabergoline. *Aust Adverse Drug React Bull* 2005; **24:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 16/02/06)
9. Molina JA, *et al*. Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov Disord* 2000; **15:** 869–72.
10. Gschwandtner U, *et al*. Pathologic gambling in patients with Parkinson's disease. *Clin Neuropharmacol* 2001; **24:** 170–2.
11. Nausieda PA, *et al*. Psychiatric complications of levodopa therapy of Parkinson's disease. *Adv Neurol* 1984; **40:** 271–7.
12. van Hilten B, *et al*. Sleep disruption in Parkinson's disease: assessment by continuous activity monitoring. *Arch Neurol* 1994; **51:** 922–8.
13. Frucht S, *et al*. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; **52:** 1908–10.
14. Schapira AHV. Sleep attacks (sleep episodes) with pergolide. *Lancet* 2000; **355:** 1332–3.
15. Ferreira JJ, *et al*. Sleep attacks and Parkinson's disease treatment. *Lancet* 2000; **355:** 1333–4.
16. Pirker W, Happe S. Sleep attacks in Parkinson's disease. *Lancet* 2000; **356:** 597–8.
17. Houmann CN. *et al*. Sleep attacks in patients taking dopamine agonists: review. *BMJ* 2002; **324:** 1483–7.
18. CSM/MHRA. Dopaminergic drugs and sudden sleep onset. *Current Problems* 2003; **29:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
19. Plowman BK, *et al*. Sleep attacks in patients receiving dopamine-receptor agonists. *Am J Health-Syst Pharm* 2005; **62:** 537–40.
20. Etminan M, *et al*. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomised controlled trials. *Drug Safety* 2001; **24:** 863–8.

Effects on respiration. Respiratory crises, including attacks of gasping, panting, sniffing, puffing, and breath-holding, occurred in 12 of 25 patients with postencephalitic parkinsonism during treatment with levodopa.[1] A further 8 developed respiratory and phonatory tics, including sudden deep breaths, yawns, coughs, giggles, sighing, grunting, and moaning. All 20 patients also suffered tachypnoea, bradypnoea, and asymmetrical movement of both sides of the chest, paradoxical diaphragmatic movements, and reversal of inspiratory and expiratory phases. The induction of respiratory crises may be prompt or greatly delayed; 3 patients only developed crises after more than 9 months of treatment with levodopa. Crises were readily precipitated by psychophysiological arousals such as rage and exertion. Most of the patients who developed marked respiratory disorders had shown slight irregularities of respiratory rhythm, rate, and force before receiving levodopa.

In another report a distressing dose-related irregularity in the rate and depth of breathing occurred when a patient with Parkinson's disease was given levodopa with benserazide.[2] The respiratory abnormality was completely suppressed by use of tiapride, with no reduction in the efficacy of levodopa.

1. Sacks OW, *et al*. Side-effects of L-dopa in postencephalitic parkinsonism. *Lancet* 1970; **i:** 1006.
2. De Keyser J, Vincken W. L-Dopa-induced respiratory disturbance in Parkinson's disease suppressed by tiapride. *Neurology* 1985; **35:** 235–7.

Effects on sexual function. An increase in libido, over and above the effects of improved mobility and well-being, has been reported in parkinsonian patients receiving levodopa or dopamine agonists. One report noted increased libido but no improvement in sexual performance in 4 of 80 patients receiving levodopa[1] while another reported a moderate increase in sexual interest in 4 of 7 male patients.[2] There have also been reports of hypersexuality and deviant sexual behaviour in patients with Parkinson's disease receiving levodopa or dopamine agonists.[3-6] In some cases this was associated with increased dosage and possibly abuse of the drugs. Symptoms often improved on dosage reduction or withdrawal. Hypersexual behaviour and hypergenitalism have also been reported in a pre-pubertal boy given levodopa for behavioural disturbances.[7]

Some workers[8] have commented that dopaminergics such as cabergoline are being promoted illegally on the Internet for male sexual enhancement and warn of the potential for abuse and serious adverse effects.

Clitoral tumescence and increased libido has been noted in a woman receiving bromocriptine to suppress lactation[9] but there has been a report of sexual dissatisfaction and decreased libido in 3 women receiving bromocriptine for hyperprolactinaemia.[10]

1. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101:** 791–9.
2. Brown E, *et al*. Sexual function and affect in parkinsonian men treated with L-dopa. *Am J Psychiatry* 1978; **135:** 1552–5.
3. Vogel HP, Schiffter R. Hypersexuality—a complication of dopaminergic therapy in Parkinson's disease. *Pharmacopsychiatry* 1983; **16:** 107–10.
4. Jiménez-Jiménez FJ, *et al*. Possible zoophilia associated with dopaminergic therapy in Parkinson disease. *Ann Pharmacother* 2002; **36:** 1178–9.
5. Kañovský P, *et al*. Penile erections and hypersexuality induced by pergolide treatment in advanced, fluctuating Parkinson's disease. *J Neurol* 2002; **249:** 112–14.
6. Berger C, *et al*. Sexuelle Delinquenz und Morbus Parkinson. *Nervenarzt* 2003; **74:** 370–5.
7. Korten JJ, *et al*. Undesirable prepubertal effects of levodopa. *JAMA* 1973; **226:** 355.
8. Pinero A, *et al*. Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; **353:** 1976–7.
9. Blin O, *et al*. Painful clitoral tumescence during bromocriptine therapy. *Lancet* 1991; **337:** 1231–2.
10. Saleh AK, Moussa MAA. Sexual dysfunction in women due to bromocriptine. *BMJ* 1984; **289:** 228.

Effects on the skin and hair. Two women who were given levodopa, up to 3 g daily, developed diffuse alopecia in addition to other adverse effects.[1] Repigmentation of hair has occurred in a white-bearded man after being treated with levodopa 1.5 g daily for 8 months.[2] Vitiligo has been reported[3] in a patient with Parkinson's disease following addition of tolcapone to his levodopa/carbidopa regimen. The development of vitiligo was attributed to the increase in plasma-levodopa concentrations brought about by concomitant use of tolcapone.

See also Melanoma, under Precautions, p. 907.1.

1. Marshall A, Williams MJ. Alopecia and levodopa. *BMJ* 1971; **2:** 47.
2. Grainger KM. Pigmentation in Parkinson's disease treated with levodopa. *Lancet* 1973; **i:** 97–8.
3. Sabaté M, *et al*. Vitiligo associated with tolcapone and levodopa in a patient with Parkinson's disease. *Ann Pharmacother* 1999; **33:** 1228–9.

Extrapyramidal effects. Choreiform movements were the major dose-limiting complication of long-term treatment with levodopa in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Dyskinesias usually appeared in the first year and became more severe and generalised with time. Certain distinctive patterns of involuntary movements occurred as follows:

- peak-dose movements affected 65 of the 81 patients and were dose-related. Movements were usually choreic, affecting the face and limbs, but dystonic and ballistic movements were also seen; characteristically they began 20 to 90 minutes after an oral dose and lasted from 10 minutes to 4 hours with a tendency to be more severe mid-way through the interdose period
- biphasic movements presenting as 2 distinct episodes of chorea or dystonia within each interdose period occurred in only 3 patients
- early morning and 'end-of-dose' dystonia was present in 15 patients after 6 years of treatment with levodopa, but rarely developed during the first 3 years
- nocturnal myoclonus occurred in 12 patients

The frequency, intensity, and complexity of spontaneous fluctuations in performance were greatly enhanced by long-term levodopa therapy. Two clinically distinct types of fluctuation, 'end-of-dose' deterioration and the 'on-off' phenomenon, were related to treatment. 'End-of-dose' deterioration or the 'wearing-off' effect affected 52 patients after 6 years of treatment and was characterised by progressive reduction in the duration of benefit from each dose with a gradual return of nocturnal and early morning disability in some patients. The 'on-off' phenomenon affected 14 patients who had completely unpredictable swings from relative mobility, usually accompanied by involuntary movements, to periods of profound bradykinesia and hypotonia. In addition, 'freezing episodes' and abrupt falls became increasingly common and affected 50 patients after 6 years compared with 33 before therapy.

1. Shaw KM, *et al*. The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49:** 283–93.

OCULOGYRIC CRISIS. After initial remission, oculogyric crises in 5 of 25 patients with postencephalitic parkinsonism recurred and were subsequently severely exacerbated during treatment with levodopa.[1] One patient, who previously had not had oculogyric crises, developed severe crises in the fourth month of therapy with levodopa. During these crises forced gaze deviation was always accompanied by severe neurological and mental symptoms, some of which were scarcely tolerable.

1. Sacks OW, Kohl M. L-Dopa and oculogyric crises. *Lancet* 1970; **ii:** 215–16.

Gout. There have been reports of elevated serum uric acid concentrations in patients receiving levodopa, but some of these are of doubtful significance since levodopa has been shown to give falsely-elevated uric acid concentrations by colorimetric methods.[1] However, hyperuricaemia as measured by more specific methods,[2,3] with a few cases of overt gout,[2,3] has also been reported.

1. Cawein MJ, Hewins J. False rise in serum uric acid after L-dopa. *N Engl J Med* 1969; **281:** 1489–90.
2. Honda H, Gindin RA. Gout while receiving levodopa for parkinsonism. *JAMA* 1972; **219:** 55–7.
3. Calne DB, Fermaglich J. Gout induced by L-dopa and decarboxylase inhibitors. *Postgrad Med J* 1976; **52:** 232–3.

Hypersensitivity. Reports of hypersensitivity reactions to levodopa have included a vasculitis characterised by neuromyopathy, periarteriolitis with eosinophilia,[1] and a lupus-like auto-immune syndrome.[2]

1. Wolf S, *et al*. Neuromyopathy and periarteriolitis in a patient receiving levodopa. *Arch Intern Med* 1976; **136:** 1055–7.
2. Massarotti G, *et al*. Lupus-like autoimmune syndrome after levodopa and benserazide. *BMJ* 1979; **2:** 553.

Overdosage. Adverse effects after ingestion of 80 to 100 g of levodopa over a 12-hour period by a parkinsonian patient included hypertension initially, followed by hypotension of a few hours' duration, sinus tachycardia, and symptomatic orthostatic hypotension for more than a week.[1] Marked confusion, agitation, insomnia, and restlessness were the most prominent clinical symptoms and did not disappear completely for over a week; severe anorexia and insomnia persisted for 2 to 3 weeks. After the overdose the patient had virtually no signs of parkinsonism and received no levodopa or antimuscarinic medication for 6 days; rigidity and akinesia began to recur on the fourth day.

1. Hoehn MM, Rutledge CO. Acute overdose with levodopa: clinical and biochemical consequences. *Neurology* 1975; **25:** 792–4.

Withdrawal syndromes. Withdrawal of antiparkinsonian drugs, particularly levodopa, has been implicated in the development of a syndrome resembling the neuroleptic malignant syndrome,[1-6] characterised by fever, muscle rigidity, profuse sweating, tachycardia, tachypnoea, and elevated muscle enzyme values.[2] Several fatalities have occurred.[1,2] It has been suggested that the neuroleptic malignant syndrome is associated with blockade of dopamine receptors in the striatum, leading to increased rigidity and heat production, and in the hypothalamus, resulting in impaired thermoregulation[7] and it seems reasonable that withdrawal of levodopa might have a similar effect in patients with depleted central dopamine concentrations. Thus, the use of a 'drug holiday' to manage fluctuations in response to levodopa (see Parkinsonism, p. 889.1) is no longer recommended.

Fever, extrapyramidal symptoms and raised creatine kinase concentrations, resembling a very mild form of the neuroleptic malignant syndrome, have also been reported in parkinsonian patients exposed to stress such as dehydration or infection but without any change in medication.[8]

1. Sechi GP, *et al*. Fatal hyperpyrexia after withdrawal of levodopa. *Neurology* 1984; **34:** 249–51.
2. Friedman JH, *et al*. A neuroleptic malignantlike syndrome due to levodopa therapy withdrawal. *JAMA* 1985; **254:** 2792–5.
3. Figà-Talamanca L, *et al*. Hyperthermia after discontinuance of levodopa and bromocriptine therapy: impaired dopamine receptors a possible cause. *Neurology* 1985; **35:** 258–61.
4. Gibb WRG, Griffith DNW. Levodopa withdrawal syndrome identical to neuroleptic malignant syndrome. *Postgrad Med J* 1986; **62:** 59–60.
5. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal: clinical features in 11 patients. *Parkinsonism Relat Disord* 2003; **9:** 175–8.
6. Mizuno Y, *et al*. Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord* 2003; **9** (suppl 1): S3–S9.
7. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology* 1981; **31:** 132–7.
8. Mezaki T, *et al*. Benign type of malignant syndrome. *Lancet* 1989; **i:** 49–50.

Treatment of Adverse Effects

Reduction in dosage reverses most of the adverse effects of levodopa. Nausea and vomiting may be diminished by increasing the dose of levodopa gradually, and/or by taking with or after meals, although taking levodopa on a full stomach may lead to lower plasma concentrations. Gastrointestinal effects may also be reduced by giving an antiemetic such as cyclizine or domperidone but not a phenothiazine (see Antipsychotics, under Interactions, p. 907.3). Use with a peripheral dopa-decarboxylase inhibitor reduces peripheral but not central adverse effects. Orthostatic hypotension may respond to the use of elastic stockings.

The benefits of gastric decontamination after an overdose of levodopa are uncertain. However, activated charcoal should be considered in adults who have ingested more than 2 g (or more than the total daily dose, whichever is greater), and in children who have taken more than 200 mg, if they present within 1 hour of ingestion. Supportive measures should also be instituted. Pyridoxine may increase the metabolism of levodopa (see Nutritional Agents, under Interactions, p. 908.1) but its value in overdosage has not been established; it does not reduce the effects of levodopa given with a peripheral dopa-decarboxylase inhibitor.

Nausea and vomiting. For reference to the use of domperidone in the management of nausea and vomiting associated with levodopa in patients with Parkinson's disease, see under Uses and Administration of Domperidone, p. 1841.2.

Psychosis. Atypical antipsychotics such as clozapine (p. 1058.1) have been tried in the management of psychosis occurring as a complication of parkinsonism and of drugs such as levodopa used in its treatment.

Precautions

Levodopa is contra-indicated in patients with angle-closure glaucoma and should be used with caution in open-angle glaucoma. Caution is also required in patients with cardiovascular disease, pulmonary disease, endocrine disorders, psychiatric disturbances, osteomalacia, hepatic or renal disease, or a history of peptic ulceration. Periodic evaluations of hepatic, psychiatric, haematological, renal, and cardiovascular functions have been advised.

Since an association between levodopa and activation of malignant melanoma has been suspected (although not confirmed), it is generally recommended that levodopa should not be given to patients with (or with a history of) the disease or with skin disorders suggestive of it.

Parkinsonian patients who benefit from levodopa therapy should be warned to resume normal activities gradually to avoid the risk of injury. Treatment with levodopa should not be stopped abruptly.

Excessive daytime sleepiness and sudden onset of sleep may occur with levodopa and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Levodopa inhibits prolactin secretion and may therefore interfere with lactation.

Food interferes with the absorption of levodopa, though levodopa is usually given with or immediately after meals to reduce nausea and vomiting. However, patients with the 'on-off' phenomenon may benefit from dosage on an empty stomach (see Parkinsonism, p. 889.1).

Abuse. Abuse of levodopa and dopamine agonists in patients with Parkinson's disease has been reported.[1-6] The term dopamine dysregulation syndrome, has been used to describe a condition where there is a compulsive and dysregulated use of dopaminergic drugs beyond that needed to achieve relief of motor symptoms and which is harmful to the patient.[7] Patients have progressively increased the dosage of levodopa to obtain psychotropic effects such as euphoria despite accompanying dystonia and other extrapyramidal adverse effects. Withdrawal often led to craving, drug-seeking behaviour, and mood disturbances such as depression, features resembling a psychological dependence syndrome. Abuse in patients without parkinsonism has also occurred.[8]

See also Effects on Sexual Function, under Adverse Effects, above.

1. Nausieda PA. Sinemet "abusers". *Clin Neuropharmacol* 1985; **8:** 318–27.

2. Soyka M, Huppert D. L-dopa abuse in a patient with former alcoholism. *Br J Addict* 1992; **87:** 117–18.
3. Spigset O, von Schéele C. Levodopa dependence and abuse in Parkinson's disease. *Pharmacotherapy* 1997; **17:** 1027–30.
4. Merims D, *et al.* Is there addiction to levodopa in patients with Parkinson's disease? *Mov Disord* 2000; **15:** 1014–16.
5. Müller U, *et al.* Levodopa-Abhängigkeit bei Parkinsonkrankheit: Fallbericht und Literaturübersicht. *Nervenarzt* 2002; **73:** 887–91.
6. Borek LL, Friedman JH. Levodopa addiction in idiopathic Parkinson disease. *Neurology* 2005; **65:** 1508.
7. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17:** 172–80.
8. Steiner I, Wirguin I. Levodopa addiction in non-parkinsonian patients. *Neurology* 2003; **61:** 1451.

Cardiovascular disorders. A high incidence of cardiovascular adverse effects was reported in early studies of levodopa, but both Parkinson's disease and heart disease are common in the elderly and adverse cardiac effects of levodopa may be less prevalent than was first thought. A study in 40 patients[1] concluded that, apart from those with severe orthostatic hypotension or unstable coronary disease, levodopa may be used safely in parkinsonian patients with heart disease. Others[2] noted that levodopa and bromocriptine cause cardiac arrhythmias in less than 1% of all patients, the incidence for levodopa with a peripheral dopa-decarboxylase inhibitor being lower still. Nevertheless, caution is advised in patients with cardiovascular disease.

1. Jenkins RB, *et al.* Levodopa therapy of patients with parkinsonism and heart disease. *BMJ* 1972; **3:** 512–14.
2. Parkes JD, *et al.* Amantadine-induced heart failure. *Lancet* 1977; **i:** 904.

Diabetes mellitus. For reference to concern over the potential of levodopa to impair glucose utilisation, see Effects on the Endocrine System under Adverse Effects, p. 905.1.

Melanoma. There has been concern over the effects of levodopa on melanoma in view of the ability of malignant melanoma cells to convert levodopa to melanin and isolated reports of melanoma developing or being exacerbated during levodopa therapy continue to appear. However, in a survey of 1099 patients with primary cutaneous malignant melanoma only one had taken levodopa.[1] It was concluded that levodopa therapy is not an important factor in the induction of malignant melanoma. Furthermore, use of levodopa in daily doses of up to 4g with carbidopa in 17 patients with metastatic melanoma failed to provide any evidence that levodopa accelerated the progression of the disease.[2] Reviews[3,4] of these and later reports concluded that the purported link between levodopa and malignant melanoma was tenuous.

For a report of antineoplastic chemotherapy used for the treatment of melanoma reducing the efficacy of levodopa, see under Interactions, below.

1. Sober AJ, Wick MM. Levodopa therapy and malignant melanoma. *JAMA* 1978; **240:** 554–5.
2. Gurney H, *et al.* The use of L-dopa and carbidopa in metastatic malignant melanoma. *J Invest Dermatol* 1991; **96:** 85–7.
3. Siple JF, *et al.* Levodopa therapy and the risk of malignant melanoma. *Ann Pharmacother* 2000; **34:** 382–5.
4. Fiala KH, *et al.* Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? *Parkinsonism Relat Disord* 2003; **9:** 321–7.

Pregnancy. Levodopa alone and with carbidopa has been associated with fetal abnormalities in *animals* given high doses; no teratogenic effect has been noted with carbidopa alone. However, 2 women with parkinsonism who received levodopa with carbidopa or levodopa alone throughout their pregnancies gave birth to normal infants.[1]

1. Cook DG, Klawans HL. Levodopa during pregnancy. *Clin Neuropharmacol* 1985; **8:** 93–5.

Withdrawal. For adverse effects associated with withdrawal of levodopa, see under Adverse Effects, p. 906.2.

Interactions

The therapeutic or adverse effects of levodopa may be affected by interactions with a variety of drugs. Mechanisms may include effects on catecholamine metabolising enzymes, neurotransmitters, or receptor sites, effects on the endocrine system, and effects on gastrointestinal absorption. Drugs that modify gastric emptying may affect the absorption of levodopa.

Antibacterials. A study[1] in 7 healthy subjects showed that use of *spiramycin* with levodopa and carbidopa resulted in reduced plasma-levodopa concentrations and an increase in its peripheral metabolism.

A hypertensive reaction and severe tremor occurred when *isoniazid* was given to a patient receiving levodopa;[2] it was not certain whether isoniazid was acting as an MAOI.

1. Brion N, *et al.* Effect of a macrolide (spiramycin) on the pharmacokinetics of L-dopa and carbidopa in healthy volunteers. *Clin Neuropharmacol* 1992; **15:** 229–35.
2. Morgan JP. Isoniazid and levodopa. *Ann Intern Med* 1980; **92:** 434.

Antidepressants. *BUPROPION.* Caution has been advised with bupropion because of reports of a higher incidence of adverse effects during use with levodopa.

MAOIS. Giving levodopa with non-specific MAOIs such as *phenelzine, nialamide,* or *tranylcypromine* may cause dangerous hypertension;[1-4] it is recommended that levodopa should not be given with, or within at least 14 days of stopping, an MAOI. Hypertensive reactions to levodopa with tranylcypromine were inhibited by carbidopa,[5] but licensed product information for preparations containing levodopa with carbidopa or benserazide still contra-indicates their use with MAOIs. The incidence of adverse effects may be increased if levodopa is used with *moclobemide,* a monoamine oxidase type A inhibitor (see Dopaminergics, p. 438.2). *Selegiline,* a monoamine oxidase type B inhibitor, is used to enhance the antiparkinsonian effect of levodopa, see p. 914.3.

1. Hodge JV. Use of monoamine oxidase inhibitors. *Lancet* 1965; **i:** 764–5.
2. Friend DG, *et al.* The action of L-dihydroxyphenylalanine in patients receiving nialamide. *Clin Pharmacol Ther* 1965; **6:** 362–6.
3. Hunter KR, *et al.* Monoamine oxidase inhibitors and L-dopa. *BMJ* 1970; **3:** 388.
4. Sharpe J, *et al.* Idiopathic orthostatic hypotension treated with levodopa and MAO inhibitor: a preliminary report. *Can Med Assoc J* 1972; **107:** 296–300.
5. Teychenne PF, *et al.* Interactions of levodopa with inhibitors of monoamine oxidase and L-aromatic amino acid decarboxylase. *Clin Pharmacol Ther* 1975; **18:** 273–7.

SSRIS. There was some evidence from a prescribing study that SSRIs might exacerbate parkinsonism resulting in increased doses of levodopa or addition of adjunctive drugs.[1]

1. van de Vijver DAMC, *et al.* Start of a selective serotonin reuptake inhibitor (SSRI) and increase of antiparkinsonian drug treatment in patients on levodopa. *Br J Clin Pharmacol* 2002; **54:** 168–70.

TRICYCLIC ANTIDEPRESSANTS. Although tricyclic antidepressants have generally been used safely with levodopa,[1] hypertensive crises have occurred in some rare cases. Such events have been reported in patients receiving *amitriptyline* or *imipramine* and levodopa with carbidopa.[2,3] Imipramine has been reported to impair the rate of levodopa absorption,[4] presumably due to its antimuscarinic properties (for the effect of antimuscarinics on the absorption of levodopa, see below).

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Rampton DS. Hypertensive crisis in a patient given Sinemet, metoclopramide, and amitriptyline. *BMJ* 1977; **2:** 607–8.
3. Edwards M. Adverse interaction of levodopa with tricyclic antidepressants. *Practitioner* 1982; **226:** 1447–8.
4. Morgan JP, *et al.* Imipramine-mediated interference with levodopa absorption from the gastrointestinal tract in man. *Neurology* 1975; **25:** 1029–34.

TRYPTOPHAN. See Amino Acids under Nutritional Agents, below.

Antiepileptics. *Phenytoin* has been shown to diminish the therapeutic effect of levodopa in patients with parkinsonism or chronic manganese poisoning.[1] The mechanism of the interaction was considered uncertain.

1. Mendez JS. Diphenylhydantoin: blocking of levodopa effects. *Arch Neurol* 1975; **32:** 44–6.

Antihypertensives. Use of levodopa with *guanethidine* may cause increased hypotension.[1] *Clonidine* has been reported to inhibit the therapeutic effect of levodopa, possibly by stimulating central alpha-adrenoceptors.[2] *Methyldopa* and levodopa may enhance each other's therapeutic or adverse effects, although there has been mention of the inhibitory effect of methyldopa on the therapeutic response to levodopa.[3,4] *Reserpine and other rauwolfia alkaloids* may oppose the antiparkinsonian effects of levodopa by central depletion of dopamine; UK licensed product information advises that use together should be avoided.

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Shoulson I, Chase TN. Clonidine and the anti-parkinsonian response to L-dopa or piribedil. *Neuropharmacology* 1976; **15:** 25–7.
3. Cotzias GC, *et al.* L-Dopa in Parkinson's syndrome. *N Engl J Med* 1969; **281:** 272.
4. Kofman O. Treatment of Parkinson's disease with L-dopa: a current appraisal. *Can Med Assoc J* 1971; **104:** 483–7.

Antimuscarinics. Antimuscarinic antiparkinsonian drugs may enhance the therapeutic effects of levodopa but by delaying gastric emptying they may also reduce its absorption.[1]

1. Algeri S, *et al.* Effect of anticholinergic drugs on gastro-intestinal absorption of L-dopa in rats and in man. *Eur J Pharmacol* 1976; **35:** 293–9.

Antineoplastics. A patient with Parkinson's disease noted[1] that the efficacy of levodopa was reduced each time he received *dacarbazine* for the treatment of melanoma. As serum-dopamine concentrations were unchanged it was suggested[1] that dacarbazine might compete with levodopa at the blood-brain barrier.

1. Merello M, *et al.* Impaired levodopa response in Parkinson's disease during melanoma therapy. *Clin Neuropharmacol* 1992; **15:** 69–74.

Antipsychotics. The therapeutic effects of levodopa may be diminished by CNS dopamine inhibitors including phenothiazine derivatives[1] such as *prochlorperazine.*[2] Butyrophenones such as *haloperidol* and thioxanthenes such as *flupentixol* might be expected to have a similar effect due to their antidopaminergic properties.

1. Yahr MD, Duvoisin RC. Drug therapy of parkinsonism. *N Engl J Med* 1972; **287:** 20–4.
2. Duvoisin RC. Diphenidol for levodopa induced nausea and vomiting. *JAMA* 1972; **221:** 1408.

Anxiolytics. Reversible deterioration of parkinsonism has been reported in patients receiving levodopa who were also given *benzodiazepines* such as *diazepam,*[1,2] *nitrazepam*[1] (although the evidence was equivocal), or *chlordiazepoxide.*[3] In one case parkinsonian symptoms resolved without alteration in the medication.[1]

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Wodak J, *et al.* Review of 12 months' treatment with L-dopa in Parkinson's disease, with remarks on unusual side effects. *Med J Aust* 1972; **2:** 1277–82.
3. Yosselson-Superstine S, Lipman AG. Chlordiazepoxide interaction with levodopa. *Ann Intern Med* 1982; **96:** 259–60.

Baclofen. Adverse effects including hallucinations, confusion, headache, and nausea and worsening of symptoms have been reported[1,2] in patients with Parkinson's disease taking levodopa when also given baclofen.

1. Skausig OB, Korsgaard S. Hallucinations and baclofen. *Lancet* 1977; **i:** 1258.
2. Lees AJ, *et al.* Baclofen in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1978; **41:** 707–8.

Gastrointestinal drugs. *ANTACIDS.* Some studies have suggested that taking an antacid before a dose of levodopa enhances the absorption of levodopa, apparently by enhancing gastric emptying and reducing metabolism of levodopa in the stomach.[1,2] This was particularly marked in a case report in a patient with prolonged gastric emptying time.[1] However, another study in 8 patients with presumably normal gastric motility, only 3 of whom had Parkinson's disease, found no significant increase in overall absorption of levodopa when given with an antacid although there was some evidence of increased absorption in some of the patients.[3] UK licensed product information (*Madopar CR; Roche*) states that antacids reduce the absorption of levodopa from the modified-release preparation by 32%.

1. Rivera-Calimlim L, *et al.* L-Dopa treatment failure: explanation and correction. *BMJ* 1970; **4:** 93–4.
2. Pocelinko R, *et al.* The effect of an antacid on the absorption and metabolism of levodopa. *Clin Pharmacol Ther* 1972; **13:** 149.
3. Leon AS, Spiegel HE. The effect of antacid administration on the absorption and metabolism of levodopa. *J Clin Pharmacol* 1972; **12:** 263–7.

ANTIEMETICS. Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms including parkinsonism; however, it accelerates gastric emptying and has been reported[1] to increase the rate of levodopa absorption. The importance of timing has been noted[2] since levodopa delays gastric emptying and metoclopramide antagonises this effect. Licensed product information advises caution when using metoclopramide with levodopa. *Domperidone* has been reported to increase the bioavailability of levodopa slightly.[3]

1. Morris JGL, *et al.* Plasma dopa concentrations after different preparations of levodopa in normal subjects. *Br J Clin Pharmacol* 1976; **3:** 983–90.
2. Berkowitz DM, McCallum RW. Interaction of levodopa and metoclopramide on gastric emptying. *Clin Pharmacol Ther* 1980; **27:** 414–20.
3. Shindler JS, *et al.* Domperidone and levodopa in Parkinson's disease. *Br J Clin Pharmacol* 1984; **18:** 959–62.

PROKINETICS. Maximum plasma concentrations of levodopa are increased by *cisapride.*[1]

See also Metoclopramide and Domperidone, under Antiemetics, above.

1. Neira WD, *et al.* The effects of cisapride on plasma L-dopa levels and the clinical response in Parkinson's disease. *Mov Disord* 1995; **10:** 66–70.

General anaesthetics. The general anaesthetics *cyclopropane* and *halothane* lower the threshold for ventricular arrhythmias to sympathomimetic amines, including dopamine, and should probably not be used within 6 to 8 hours of levodopa.[1,2] Although other general anaesthetics are now usually preferred, it was suggested that, in any case, levodopa could safely be taken before surgery when given with a peripheral dopa-decarboxylase inhibitor.[3]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12:** 376–82.
2. Bianchine JR, Sunyapridakul L. Interactions between levodopa and other drugs: significance in the treatment of Parkinson's disease. *Drugs* 1973; **6:** 364–88.
3. Anonymous. Surgery and long-term medication. *Drug Ther Bull* 1984; **22:** 73–6.

Nutritional agents. *AMINO ACIDS.* The transport of levodopa into the brain is subject to competition from chemically related L-amino acids, especially the other aromatic amino acids *phenylalanine, tyrosine, tryptophan,* and *histidine.*[1] A high-protein diet or the large neutral amino acids pheny-

lalanine, *leucine*, or *isoleucine* have been shown to reduce the therapeutic effect of levodopa given by intravenous infusion to parkinsonian patients; such alterations in the absorption and transport of levodopa may contribute to the fluctuating responses seen in Parkinson's disease, the so-called 'on-off' phenomenon[2] (see also Parkinsonism, p. 889.1). In contrast, a study in healthy subjects[3] found that while a low-protein meal appeared to cause a small reduction in levodopa absorption, a high-protein meal had no such effect. Other reported interactions with amino acids include *methionine*-antagonism of the therapeutic effect of levodopa in parkinsonism[4] and *tryptophan*-reduced blood concentrations of levodopa.[5]

1. Daniel PM, *et al.* Do changes in blood levels of other aromatic aminoacids influence levodopa therapy? *Lancet* 1976; **i:** 95.
2. Nutt JG, *et al.* The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984; **310:** 483–8.
3. Robertson DRC, *et al.* The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* 1991; **31:** 413–17.
4. Pearce LA, Waterbury LD. L-methionine: a possible levodopa antagonist. *Neurology* 1974; **24:** 640–1.
5. Weitbrecht W-U, Weigel K. Der Einfluss von L-Tryptophan auf die L-Dopa-Resorption. *Dtsch Med Wochenschr* 1976; **101:** 20–2.

IRON SALTS. Levodopa forms complexes with iron salts and *ferrous sulfate* has reduced bioavailability of levodopa by about 50% in healthy subjects.[1] Giving ferrous sulfate to 9 patients with Parkinson's disease receiving levodopa with carbidopa reduced the area under the concentration-time curve for levodopa by 30%; the reduction was greater than 75% for carbidopa. Although this was associated with deterioration in some patients' disability, the average reduction in efficacy of therapy did not achieve statistical significance.[2]

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; **31:** 251–5.
2. Campbell NRC, *et al.* Sinemet-ferrous sulphate interaction in patients with Parkinson's disease. *Br J Clin Pharmacol* 1990; **30:** 599–605.

PYRIDOXINE. The enzyme responsible for the decarboxylation of levodopa, L-amino acid decarboxylase, is dependent on pyridoxine and pyridoxine supplements have been reported to enhance the peripheral metabolism of levodopa to dopamine leaving less available to cross the blood-brain barrier for central conversion to dopamine;[1-4] pyridoxine therefore inhibits the action of levodopa but this can be stopped by use of a peripheral dopa-decarboxylase inhibitor.[2,3]

1. Leon AS, *et al.* Pyridoxine antagonism of levodopa in parkinsonism. *JAMA* 1971; **218:** 1924–7.
2. Cotzias GC, Papavasiliou PS. Blocking the negative effects of pyridoxine on patients receiving levodopa. *JAMA* 1971; **215:** 1504–5.
3. Yahr MD, Duvoisin RC. Pyridoxine, levodopa, and L-α-methyldopa hydrazine regimen in parkinsonism. *JAMA* 1971; **216:** 2141.
4. Carter AB. Pyridoxine and parkinsonism. *BMJ* 1973; **4:** 236.

Papaverine. Antagonism of the beneficial effects of levodopa in parkinsonism has been reported when patients were also given papaverine,[1,2] and it was recommended that the combination should be avoided. However, a later study[3] in 9 patients receiving levodopa with a peripheral dopa-decarboxylase inhibitor found no changes in the control of Parkinson's disease when they were also given papaverine for 3 weeks.

1. Duvoisin RC. Antagonism of levodopa by papaverine. *JAMA* 1975; **231:** 845.
2. Posner DM. Antagonism of levodopa by papaverine. *JAMA* 1975; **233:** 768.
3. Montastruc JL, *et al.* Does papaverine interact with levodopa in Parkinson's disease? *Ann Neurol* 1987; **22:** 558–9.

Penicillamine. Isolated case reports suggest that penicillamine increases plasma-levodopa concentrations.[1]

1. Mizuta E, *et al.* Effect of D-penicillamine on pharmacokinetics of levodopa in Parkinson's disease. *Clin Neuropharmacol* 1993; **16:** 448–50.

Sympathomimetics. It has been suggested that sympathomimetics such as *adrenaline* or *isoprenaline* may enhance the cardiac adverse effects of levodopa.[1]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12:** 376–82.

Pharmacokinetics

Levodopa is rapidly absorbed from the gastrointestinal tract by an active transport system. Most absorption takes place in the small intestine; absorption is very limited from the stomach, and since decarboxylation may take place in the stomach wall, delays in gastric emptying may reduce the amount of levodopa available for absorption. Peak plasma concentrations occur within 2 hours of oral doses. Levodopa is about 10 to 30% bound to plasma proteins.

Levodopa is rapidly decarboxylated by the enzyme aromatic L-amino acid decarboxylase, mostly in the gut, liver, and kidney, to dopamine, which is metabolised in turn, principally to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Other routes of metabolism include *O*-methylation, transamination, and oxidation, producing a variety of minor metabolites including noradrenaline and 3-*O*-methyldopa; the latter may accumulate in the CNS due to its relatively long half-life. The elimination half-life of levodopa itself is reported to be about 30 to 60 minutes.

Unlike dopamine, levodopa is actively transported across the blood-brain barrier, but because of the extent of peripheral decarboxylation very little is available to enter the CNS unless it is given with a peripheral dopa-decarboxylase inhibitor. In the presence of a peripheral dopa-decarboxylase inhibitor the major route of metabolism of levodopa becomes the formation of 3-*O*-methyldopa by the enzyme catechol-*O*-methyltransferase.

About 80% of an oral dose of levodopa is excreted in the urine within 24 hours, mainly as dihydroxyphenylacetic and homovanillic acids. Only small amounts of levodopa are excreted unchanged in the faeces.

Levodopa crosses the placenta and is distributed into breast milk.

General references.

1. Nutt JG, Fellman JH. Pharmacokinetics of levodopa. *Clin Neuropharmacol* 1984; **7:** 35–49.
2. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. *Clin Pharmacokinet* 1987; **13:** 141–78.
3. Robertson DRC, *et al.* The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa. *Br J Clin Pharmacol* 1989; **28:** 61–9.
4. Robertson DRC, *et al.* The influence of levodopa on gastric emptying in man. *Br J Clin Pharmacol* 1990; **29:** 47–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prikap; ***China***: Symblyopia (思利巴); ***Ger.***: Restex; ***India***: Bidopal; ***Irl.***: Duodopa; ***Jpn***: Doparl†; ***Pol.***: Nakom; ***UK***: Apodespan.

Multi-ingredient Preparations. ***Arg.***: Carlevod; Lebocar; Lecarge; Madopar; Nervocur; Parkinel; Sinemet; Stalevo; ***Austral.***: Duodopa; Kinson; Levohexal†; Madopar; Sinemet; Stalevo; ***Austria***: Duodopa; Levocar; Madopar; Restex; Sinemet; Stalevo; ***Belg.***: Duodopa; Prolopa; Sinemet; Stalevo; ***Braz.***: Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Prolopa; Sinemet; Stalevo; ***Canad.***: Apo-Levocarb; Duodopa; Novo-Levocarbidopa†; Nu-Levocarb; Pro-Levocarb; Prolopa; Sinemet; Stalevo; ***Chile***: Grifoparkin; Levofamil; Melitase; Prolopa; Protonis†; Saniter Compuesto; Sinemet; Stalevo; ***China***: Sinemet (息宁); Xi Lai Mei (西莱美); ***Cz.***: Apo-Levocarb; Dopalux†; Duodopa; Isicom; Lecardop; Madopar; Nakom; Sinemet; Stalevo; ***Denm.***: Duodopa; Madopar; Sinemet; Stalevo; ***Fin.***: Duodopa; Kardopal; Levocar; Madopar; Sinemet; Stalevo; ***Fr.***: Duodopa; Modopar; Sinemet; Stalevo; ***Ger.***: Duodopa; Isicom; Levo-C; Levobeta C; Levocarb†; Levocomp†; Levodop; Levodopa comp B†; Levodopa comp C†; Levodopa Comp; Levopar†; Madopar; Nacom; PK-Levo†; Stalevo; Striaton†; ***Gr.***: Duodopa; Madopar; Sinemet; Stalevo; Zimox; ***Hong Kong***: Apo-Levocarb; Levomed; Levomet; Madopar; Sinedopa†; Sinemet; Stalevo; ***Hung.***: Duellin†; Duodopa; Madopar; Sinemet†; Stalevo; ***India***: Benspar; LCD; Levopa-C; Madopar-F; Neocare; Syndopa; ***Indon.***: Leparson; Levazide; Levopar; Madopar; Pardoz; Stalevo; ***Irl.***: Half Sinemet; Madopar; Sinemet; Stalevo; ***Israel***: Dopicar; Duodopa; Levopar Plus; Sinemet; Stalevo; ***Ital.***: Duodopa; Madopar; Sinemet; Sirio; Stalevo; ***Malaysia***: Apo-Levocarb; Levomed; Madopar; Sinedopa; Sinemet; Stalevo; ***Mex.***: Cloisone; Lemdopa†; Madopar; Racovel; Sinemet; Stalevo; Ternovag; ***Neth.***: Duodopa; Madopar; Modopar†; Sinemet; Stalevo; ***Norw.***: Duodopa; Madopar; Sinemet; Stalevo; ***NZ***: Apo-Levocarb†; Madopar; Sindopa; Sinemet; ***Philipp.***: Ledocar; Madopar; Sinemet; Stalev; Tidomet; ***Pol.***: Madopar; Sinemet; Stalevo; ***Port.***: Duodopa; Ledopsan; Madopar; Sinemet; Stalevo; ***Rus.***: Duellin (Дуэллин); Madopar (Мадопар); Nakom (Наком); Sinemet (Синемет); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); ***S.Afr.***: Carbilev; Madopar; Sinemet; Stalevo; ***Singapore***: Cardopar; Credanil; Levomet; Madopar; Sinemet; Stalevo; Tidomet; ***Spain***: Duodopa; Ledopsan†; Madopar; Sinemet; Stalevo; ***Swed.***: Duodopa; Levocar; Madopark; Sinemet; Stalevo; ***Switz.***: Duodopa; Madopar; Sinemet; Stalevo; ***Thai.***: Levomed; Levomet; Madopar; Sinemet; Stalevo; Syndopa; Tidomet; Udopar-250; Vopar; ***Turk.***: Madopar; Sinemet; Stalevo; ***UK***: Duodopa; Half Sinemet; Madopar; Sinemet; Stalevo; ***Ukr.***: Levocarbhexal (Левокарбгексал)†; Levokom (Левоком); Madopar (Мадопар); Nakom (Наком); Stalevo (Сталево); ***USA***: Atamet; Parcopa; Sinemet; Stalevo; ***Venez.***: Madopar; Sinemet; Stalevo.

Pharmacopoeial Preparations

BP 2014: Co-beneldopa Capsules; Co-careldopa Tablets; Dispersible Co-beneldopa Tablets; Levodopa Capsules; Levodopa Tablets; Prolonged-release Co-beneldopa Capsules;

USP 36: Carbidopa and Levodopa Orally Disintegrating Tablets; Carbidopa and Levodopa Tablets; Levodopa Capsules; Levodopa Tablets.

Lisuride Maleate *(BANM, rINNM)*

Lisurid Maleat; Lisurida, maleato de; Lisuride, Maléate de; Lisuridi Hydrogenomaleas; Lisuridi Maleas; Lisuridivetymaleaatti; Lisuridvätemaleat; Lysuride Maleate; Maleato de lisurida; Methylergol Carbamide Maleate; Лизурида Малеат.

3-(9,10-Didehydro-6-methylergolin-8α-yl)-1,1-diethylurea hydrogen maleate; 8-Decarboxamido-8-(3,3-diethylureido)-D-lysergamide maleate.

$C_{20}H_{26}N_4O,C_4H_4O_4$=454.5

CAS — 18016-80-3 (lisuride); 19875-60-6 (lisuride maleate).
ATC — G02CB02; N02CA07.
ATC Vet — QG02CB02; QN02CA07.
UNII — UV1635N8XW.

Uses and Administration

Lisuride maleate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p. 895.3). It is also reported to have serotonergic activity. It is used similarly in the management of Parkinson's disease (p. 909.1) and has been used in disorders associated with hyperprolactinaemia (below), including amenorrhoea, galactorrhoea, and infertility. It is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that can be adequately relieved with simple analgesics and breast support. Lisuride has been used in some countries for the treatment of acromegaly, and for the prophylaxis of migraine. It is normally given orally; doses should be taken with food.

In the management of **Parkinson's disease**, lisuride maleate has been added to treatment with levodopa or other antiparkinsonian drugs. Initially 100 micrograms is taken at bedtime and additional doses of 100 micrograms may be added, at intervals of one week, first in the morning and then at midday. Further increases are made, until an optimum response is obtained, by adding 100 micrograms each week using the same sequence of increases, starting with the bedtime dose; dosage should not normally exceed 2 mg daily given in 3 or 4 divided doses.

When used to **suppress lactation**, the usual dose of lisuride maleate is 200 micrograms two or three times daily for 14 days; treatment should be started within the first 24 hours of delivery.

In the treatment of disorders associated with **hyperprolactinaemia**, 100 micrograms of lisuride maleate may be given in the evening of the first day, followed by 100 micrograms at midday and in the evening of the second day, and 100 micrograms in the morning, at midday, and in the evening of the third day; thereafter doses may be adjusted according to prolactin levels. Similar doses are also used in **acromegaly** with adjustments made according to growth hormone levels (see also below).

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p. 1921.1). While bromocriptine and cabergoline have been the main dopamine agonists used, lisuride has been used in some countries.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p. 2252.2). Lisuride has been used as an alternative to bromocriptine. There is a report of plasma-prolactin concentrations being reduced to normal in 4 female patients with macroprolactinomas given lisuride 400 to 800 micrograms daily for 2 years.[1] Subsequent dosage reduction in 3 was followed by a rise in prolactin values. In the fourth patient prolactin remained in the normal range when the dose was progressively reduced from 400 to 50 micrograms daily, although complete withdrawal was followed by an increase in prolactin concentration within 3 months.

Vaginal dosage of lisuride has been studied in an attempt to avoid adverse effects associated with oral therapy. In a study[2] involving 40 women with hyperprolactinaemia a 200-microgram standard oral tablet placed in the vagina at night produced a similar reduction in prolactin concentrations to that obtained with 400 micrograms taken orally and was better tolerated.

1. Liuzzi A, *et al.* Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985; **313:** 656–9.
2. Tasdemir M, *et al.* Vaginal lisuride for hyperprolactinaemia. *Lancet* 1995; **346:** 1362.

Lactation inhibition. Lisuride is used in some countries for the prevention of puerperal lactation (p. 2130.1). However, the routine use of dopaminergics is not recommended for the suppression of physiological lactation.

References.

1. Venturini PL, *et al.* Effects of lisuride and bromocriptine on inhibition of lactation and on serum prolactin levels: comparative double-blind study. *Eur J Obstet Gynecol Reprod Biol* 1981; **11:** 395–400.

Mastalgia. In a small placebo-controlled study,[1] lisuride 200 micrograms daily was effective in the treatment of cyclical mastalgia. However, since mastalgia (p. 2265.1) can improve spontaneously, treatment should rarely be

considered unless pain has been present for about 6 months.

1. Kaleli S, *et al.* Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; **75:** 718–23.

Migraine. Although lisuride has been used in some countries for the prophylaxis of migraine (p. 670.3) it is not usually considered to be the drug of choice or even one of the main alternatives.

Parkinsonism. While some neurologists use dopamine agonists such as lisuride early in the treatment of parkinsonism (p. 889.1) in an attempt to delay therapy with levodopa, others reserve them for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease.

References.

1. Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology* 1989; **39:** 336–9.
2. Clarke CE, Speller J. Lisuride for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
3. Clarke CE, *et al.* Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
4. Allain H, *et al.* Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *Eur Neurol* 2000; **44:** 22–30.

ADMINISTRATION. Lisuride has been of benefit when given by continuous intravenous or subcutaneous infusion in patients having fluctuations in mobility with levodopa therapy[1-4] but severe psychiatric effects have been associated with the use of these routes.[3] Transdermal lisuride has also been investigated for the treatment of Parkinson's disease and restless legs syndrome.[5,6]

1. Obeso JA, *et al.* Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol* 1986; **19:** 31–5.
2. Obeso JA, *et al.* Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. *Lancet* 1986; **i:** 467–70.
3. Critchley P, *et al.* Psychosis and the lisuride pump. *Lancet* 1986; **i:** 349.
4. Stocchi F, *et al.* Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain* 2002; **125:** 2058–66.
5. Woitalla D, *et al.* Transdermal lisuride delivery in the treatment of Parkinson's disease. *J Neural Transm Suppl* 2004; **68:** 89–95.
6. Benes H. Transdermal lisuride: short-term efficacy and tolerability study in patients with severe restless legs syndrome. *Sleep Med* 2006; **7:** 31–5.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3. Infusion of lisuride in parkinsonian patients has been associated with severe psychiatric adverse effects.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including lisuride, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including lisuride, see under Adverse Effects of Bromocriptine, p. 897.3.

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Plasma concentrations varied widely after a single oral dose of lisuride maleate 300 micrograms in 11 patients with Parkinson's disease.[1] Absorption was rapid and the mean plasma elimination half-life was 2.2 hours. Only a mean of 0.05% of the dose was excreted unchanged in the urine in 24 hours. The mean oral bioavailability of lisuride maleate has been reported[2] to be 10% after a 100-microgram dose and 22% after a 300-microgram dose.

A single dose of lisuride 25 micrograms given by intravenous, intramuscular, or subcutaneous injection reduced plasma-prolactin concentrations by up to 60% in 11 of 12 healthy subjects, the effect lasting for about 10 hours.[3] Plasma-lisuride concentrations after intravenous injection fell in 2 phases with half-lives of 14 minutes and 1.5 hours, respectively. Peak plasma concentrations after subcutaneous and intramuscular injection were obtained after 12 and 15 minutes, respectively.

1. Burns RS, *et al.* Disposition of oral lisuride in Parkinson's disease. *Clin Pharmacol Ther* 1984; **35:** 548–56.
2. Hümpel M, *et al.* Radioimmunoassay of plasma lisuride in man following intravenous and oral administration of lisuride hydrogen maleate; effect on plasma prolactin level. *Eur J Clin Pharmacol* 1981; **20:** 47–51.
3. Krause W, *et al.* The pharmacokinetics and pharmacodynamics of lisuride in healthy volunteers after intravenous, intramuscular, and subcutaneous injection. *Eur J Clin Pharmacol* 1991; **40:** 399–403.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dopergin; ***Fr.***: Arolac; Dopergine; ***Ger.***: Dopergin; ***Gr.***: Dipergon; ***Ital.***: Dopergin; ***Mex.***: Dopergin; ***NZ***: Dopergin; ***Spain***: Dopergin; ***Turk.***: Dopergin.

Metixene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metixeno; Methixene Hydrochloride (USAN); Methixene Hydrochloride; Methixene Hydrochloride Monohydrate; Metikseenihydrokloridi; Metikseno hidrochloridas; Métixène, Chlorhydrate de; Metixén-hidroklorid; Metixenhydrochlorid; Metixen-hydrochlorid monohydrát; Metixenhydroklorid; Metixeni Hydrochloridum; Metixeni Hydrochloridum Monohydricum; Metixeno, hidrocloruro de; NSC-78194; SJ-1977; Метиксена Гидрохлорид.

(*RS*)-9-(1-Methyl-3-piperidylmethyl)thioxanthene hydrochloride monohydrate.

$C_{30}H_{32}NS,HCl,H_2O$=363.9

CAS — 4969-02-2 (metixene); 1553-34-0 (anhydrous metixene hydrochloride); 7081-40-5 (metixene hydrochloride monohydrate).

ATC — N04AA03.

ATC Vet — QN04AA03.

UNII — 84L8XK6N1G.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Metixene Hydrochloride). A white or almost white, crystalline or fine crystalline powder. Soluble in water, in alcohol, and in dichloromethane. A 1.8% solution in water has a pH of 4.4 to 5.8. Protect from light.

Profile

Metixene hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p. 1312.1); it also has antihistaminic and direct antispasmodic properties.

It is used for the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The usual oral dose of metixene hydrochloride is 2.5 mg three to six times daily initially, gradually increased according to response to a total of 20 to 60 mg daily in divided doses.

Metixene hydrochloride has also been used in preparations to relieve gastrointestinal spasms.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metixene as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Tremarit†; ***Hung.***: Tremaril; ***Ital.***: Tremaril.

Multi-ingredient Preparations. ***Philipp.***: Spasmo-Canulase; ***Port.***: Espasmo Canulase†; ***S.Afr.***: Spasmo-Canulase†; ***Switz.***: Spasmo-Canulase.

Orphenadrine Citrate *(BANM, rINNM)*

Citrato de orfenadrina; Mephenamine Citrate; Orfenadriinisitraatti; Orfenadrina, citrato de; Orfenadrincitrat; Orfenadrincitrát; Orfenadrino citratas; Orphenadin Citrate; Orphenadrincitrat; Orphénadrine, Citrate d'; Orphenadrini Citras; Орфенадрина Цитрат.

(*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine dihydrogen citrate.

$C_{18}H_{23}NO,C_6H_8O_7$=461.5

CAS — 83-98-7 (orphenadrine); 4682-36-4 (orphenadrine citrate).

ATC — M03BC01.

ATC Vet — QM03BC01.

UNII — X0A40NBI4S.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Orphenadrine Citrate). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Orphenadrine Citrate). A white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Orphenadrine Hydrochloride *(BANM, rINNM)*

BS-5930; Hidrocloruro de orfenadrina; Mephenamine Hydrochloride; Orfenadriinihydrokloridi; Orfenadrina, hidrocloruro de; Orfenadrin-hidroklorid; Orfenadrin-hydrochlorid; Orfenadrinhydroklorid; Orfenadrino hidrochloridas; Orphenadin Hydrochloride; Orphénadrine, Chlorhydrate d'; Orphenadrinhydrochlorid; Orphenadrini Hydrochloridum; Орфенадрина Гидрохлорид.

(*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine hydrochloride.

$C_{18}H_{23}NO,HCl$=305.8

CAS — 341-69-5.

ATC — N04AB02.

ATC Vet — QN04AB02.

UNII — UBY910DUXH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Orphenadrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. Protect from light.

Uses and Administration

Orphenadrine, which is a congener of diphenhydramine (p. 626.1) without sharing its soporific effect, is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It also has weak antihistaminic and local anaesthetic properties. Orphenadrine is used as the hydrochloride and the citrate; doses are expressed in terms of the relevant salt.

Orphenadrine is used as the hydrochloride in the symptomatic treatment of **parkinsonism** (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The initial oral dose of orphenadrine hydrochloride is 150 mg daily in divided doses gradually increased by 50 mg every 2 or 3 days according to response; the usual maintenance dose is in the range of 150 to 300 mg daily, but some patients may require a total of up to 400 mg daily. Orphenadrine hydrochloride has also been given intramuscularly.

Orphenadrine is also used as the citrate to relieve pain due to **skeletal muscle spasm** (below). It is given orally in a dose of 100 mg twice daily or by intramuscular or slow intravenous injection in a dose of 60 mg which has been repeated every 12 hours.

Combinations of orphenadrine with an NSAID, usually diclofenac, or with paracetamol, have been used in the treatment of musculoskeletal and joint disorders.

Hiccup. Orphenadrine citrate has been used in some countries for the treatment of intractable hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

Muscle and joint disorders. References to the use of orphenadrine in the management of leg cramps and other painful conditions associated with skeletal muscle spasm,[1,2] and with diclofenac in osteoarthritis and other musculoskeletal disorders.[3,4]

1. Latta D, Turner E. An alternative to quinine in nocturnal leg cramps. *Curr Ther Res* 1989; **45:** 833–7.
2. Hunskaar S, Donnell D. Clinical and pharmacological review of the efficacy of orphenadrine and its combination with paracetamol in painful conditions. *J Int Med Res* 1991; **19:** 71–87.
3. Uitz E, *et al.* Diclofenac/Orphenadrin-Infusionstherapie bei Patienten mit aktivierten Arthrosen. *Wien Med Wochenschr* 1998; **148:** 179–82.
4. Aglas F, *et al.* Ergebnisse einer Anwendungsbeobachtung mit Diclofenac/Orphenadrin-Infusionen bei Patienten mit muskuloskelettalen Krankheiten und Funktionsstorungen. *Acta Med Austriaca* 1998; **25:** 86–90.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Orphenadrine may cause insomnia.

Abuse. A 23-year-old schizophrenic man, whose treatment included orphenadrine 100 mg three times daily, obtained illicit supplies and increased the dose for euphoric effect.[1] On one occasion he had an epileptic convulsion after a 600-mg dose.

See also under Trihexyphenidyl Hydrochloride, p. 918.1.

1. Shariatmadari ME. Orphenadrine dependence. *BMJ* 1975; **3:** 486.

Overdosage. A report[1] of acute poisoning with orphenadrine after massive overdosage in a schizophrenic patient, who responded to intensive supportive treatment, including large doses of adrenaline, dopamine, and dobutamine to restore blood pressure following asystole. Between 1977

and 1980 twelve deaths due to orphenadrine were recorded by the UK National Poisons Unit.

1. Clarke B, *et al.* Acute poisoning with orphenadrine. *Lancet* 1985; **i:** 1386.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies orphenadrine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Withdrawal. A suspected withdrawal syndrome was reported in a 56-year-old woman who showed slow neurological postoperative recovery after her orphenadrine treatment had been stopped abruptly;[1] her status improved when the drug was restarted.

1. Esler MD, *et al.* Postoperative orphenadrine withdrawal. *Br J Anaesth* 2000; **85:** 497.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Orphenadrine is an inhibitor of the cytochrome P450 isoenzyme CYP2B6, which is involved in the metabolism of bupropion to its major metabolite; licensed product information advises that orphenadrine should be used with caution in patients also receiving bupropion.

Chlorpromazine. For the effect of orphenadrine on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p. 1052.3.

Dextropropoxyphene. A suggested interaction between orphenadrine and dextropropoxyphene was open to question.[1,2]

1. Pearson RE, Salter FJ. Drug interaction? — orphenadrine with propoxyphene. *N Engl J Med* 1970; **282:** 1215.
2. Puckett WH, Visconti JA. Orphenadrine and propoxyphene (cont.). *N Engl J Med* 1970; **283:** 544.

Pharmacokinetics

Orphenadrine is readily absorbed from the gastrointestinal tract and after intramuscular injection. It is almost completely metabolised to at least 8 metabolites. It is mainly excreted in the urine as metabolites and small amounts of unchanged drug. The half-life of orphenadrine has been reported to be 14 hours (but see below).

Half-life. While the mean elimination half-life of orphenadrine in 5 healthy subjects given a single dose of the hydrochloride was found to be 15.5 hours, elimination half-lives of 30.5 and 40 hours were calculated in 2 patients given repeated oral doses.[1]

1. Labout JJM, *et al.* Difference between single and multiple dose pharmacokinetics of orphenadrine hydrochloride in man. *Eur J Clin Pharmacol* 1982; **21:** 343–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Norflex; ***Canad.***: Norflex; Orfenace; ***Chile***: Plenactol†; ***Denm.***: Lysantin; ***Fin.***: Norflex; ***Ger.***: Norflex; ***Gr.***: Disipal; Norflex; ***India***: Orphipal; ***Israel***: Flexin; ***Ital.***: Disipal; ***Malaysia***: Norflex; ***Mex.***: Norflex; ***NZ***: Disipal; Norflex; ***S.Afr.***: Disipal; Norflex; Phenerine†; ***Singapore***: Onadrine; ***Swed.***: Norflex; ***Thai.***: Norflex; Ofee; Orfenal; Phemax; Sinogesic; ***UK***: Biorphen; Disipal; ***USA***: Banflex; Flexon; Norflex; ***Venez.***: Norflex.

Multi-ingredient Preparations. ***Arg.***: Belmalen; Flogodisten; Mio Aldoron; Mio-Virobron; ***Austral.***: Norgesic; ***Austria***: Neodolpasse; Norgesic; ***Braz.***: Ana-Flex; Bioflex; Dalgex†; Doralgex; Dorciflex†; Dorflex; Doricin; Dorzone; Flexalgex; Flexdor; Miorrelax; Nevralgex; Novralflex; Reflex; Relaflex; Rheumafim; Rielex; Royflex; Sedalex; ***Chile***: Norgesic†; ***Cz.***: Neodolpasse; ***Fin.***: Dolan; Norgesic; ***Gr.***: Norgesic; ***Hong Kong***: Myodrine†; Norgesic; Pormus; ***Hung.***: Neodolpasse; ***India***: Orphamol; ***Israel***: Muscol; Norgesic†; ***Malaysia***: Anarex; Cetagesic; Norgesic; Orphenadol; Paragesic; Suniton†; ***Mex.***: Norflex Plus; ***NZ***: Norgesic; ***Philipp.***: Norgesic; ***S.Afr.***: Besemax; Besenol; Norflex Co; Uniflex; ***Singapore***: Anarex; Camgesic; Cetagesic; Norgesic; Norphen; Orcigesic; Orphenadol; Suniton; ***Swed.***: Norgesic; ***Thai.***: Cenasic; Corilax; Dorpane; Dysmenic; Fagesic†; GPO Gesic; M-Gesic; Medgesic; Muscol; Muscolic; Muslexac; Myodrine; Myoflex; Myopa; Myopas; Myosic; Myospa; Mypara Plus; Nabesac; Neosec; Noraphen; Norgesic; Norgetex; Norgic; Norphen; Norsica; Nuosic; Nurasic; Orano; Orapa; Orflex; Orgesic; Ornadine; Orpar; Orphengesic; Orphensic; Paradine; Parina; Patargesic; Poli-Relaxane; Polydol; Pormus; Pronadrine; Prospa; Relar; Relaxic; Rena; Rexodrin; Togesic; ***UAE***: Muscadol; ***USA***: Norgesic†; Orphenadrine Compound; Orphengesic†; ***Venez.***: Norgesic.

Pharmacopoeial Preparations

BP 2014: Orphenadrine Hydrochloride Tablets;
USP 36: Orphenadrine Citrate Extended-Release Tablets; Orphenadrine Citrate Injection; Orphenadrine Citrate, Aspirin, and Caffeine Tablets.

Pergolide Mesilate *(BANM, rINNM)*

LY-127809; Mesilato de pergolida; Pergolid Mesilat; Pergolid mesylát; Pergolida, mesilato de; Pergolide, mésilate de; Pergolide Mesylate (USAN); Pergolidi Mesilas; Pergolidimesilatti; Pergolidmesilat; Pergolid-mezilát; Pergolido mesilatas; Перголида Мезилат.

8β-Methylthiomethyl-6-propylergoline methanesulphonate; Methyl (8*R*,10*R*)-6-propylergolin-8-ylmethyl sulphide methanesulphonate.

$C_{19}H_{26}N_2S,CH_4O_3S$=410.6

CAS — 66104-22-1 (pergolide); 66104-23-2 (pergolide mesilate).

ATC — N04BC02.

ATC Vet — QN04BC02.

UNII — 55B9HQY616.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Pergolide Mesilate). A white or almost white crystalline powder. Slightly soluble in water, in alcohol, and in dichloromethane; very slightly soluble in acetone; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Pergolide Mesylate). A white to off-white powder. Slightly soluble in water, in dehydrated alcohol, and in chloroform; very slightly soluble in acetone; practically insoluble in ether; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Pergolide mesilate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p. 895.3), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. Pergolide is used in the management of Parkinson's disease (below) as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response; in the UK pergolide is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment. Pergolide is given orally as the mesilate with doses expressed as the base. Pergolide mesilate 65.3 mg is equivalent to about 50 mg pergolide.

For use as *monotherapy* an initial dose equivalent to 50 micrograms of pergolide is given on the first evening of therapy. The dose is thereafter gradually increased: 50 micrograms twice daily is taken on days 2 to 4, then increased by 100 to 250 micrograms every 3 or 4 days, given in 3 divided doses, up to a daily dose of 1.5 mg at day 28. After day 30, the dose should be increased further by a maximum of 250 micrograms twice a week until an optimum response is achieved. Usual maintenance doses are 2.1 to 2.5 mg daily; doses above 3 mg daily are not recommended by the EMEA. The daily dose is usually given in 3 divided doses.

For use as *adjunctive therapy* with levodopa, pergolide should be introduced gradually and during this period patients can have their levodopa dosage decreased gradually until an optimum response is achieved. The initial dose of pergolide is the equivalent of 50 micrograms daily for the first 2 days, increased gradually by 100 or 150 micrograms every third day over the next 12 days of therapy. Further increases of 250 micrograms may then be made every third day until an optimum response is achieved. A usual maintenance dose is 3 mg daily; doses above 3 mg daily are not recommended by the EMEA. The daily dose is usually given in 3 divided doses.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p. 1921.1). While bromocriptine and cabergoline have been the main dopamine agonists used pergolide has also been tried.[1]

1. Kleinberg DL, *et al.* Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. *N Engl J Med* 1983; **309:** 704–9.

Hyperprolactinaemia and prolactinomas. Dopamine agonists are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p. 2252.2). Pergolide has been suggested as an alternative to bromocriptine in this condition.

Studies[1-3] of pergolide mesilate in patients with hyperprolactinaemia indicate that single doses reduce serum-prolactin concentrations for more than 24 hours. In most patients, the effective dose was between 50 and 150 micrograms daily. Adverse effects were similar to those seen with bromocriptine, although some patients who could not take bromocriptine were able to tolerate pergolide (and vice versa). Pergolide reportedly lost favour for this indication after reports of an increased incidence of uterine neoplasms in *rodents* receiving high doses. However, licensed product information states that no cases of uterine malignancies have to date been reported in humans receiving pergolide. The long-term outcome of treatment of macroprolactinomas with pergolide has been examined in 23 patients,[4] and efficacy and relative safety of pergolide was shown after an average of 27 months (range: 9 to 64 months) treatment.

1. Franks S, *et al.* Treatment of hyperprolactinaemia with pergolide mesylate: acute effects and preliminary evaluation of long-term treatment. *Lancet* 1981; **ii:** 659–61.
2. Franks S, *et al.* Effectiveness of pergolide mesylate in long-term treatment of hyperprolactinaemia. *BMJ* 1983; **286:** 1177–9.
3. Kleinberg DL, *et al.* Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. *N Engl J Med* 1983; **309:** 704–9.
4. Freda PU, *et al.* Long-term treatment of prolactin-secreting macroadenomas with pergolide. *J Clin Endocrinol Metab* 2000; **85:** 8–13.

Parkinsonism. Dopamine agonists such as pergolide are often used to begin the treatment of parkinsonism (p. 889.1) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease. Pergolide has a relatively long duration of action compared with other dopamine agonists commonly used. Although the duration of the clinical antiparkinsonian effect of pergolide remains to be determined, studies suggest it is of the order of 5 to 8 hours. Depending on the dose used the response to other dopamine agonists in late parkinsonism is 1 to 4 hours for levodopa, 2 to 4 hours for lisuride, and 4 to 6 hours for bromocriptine.

References.

1. Anonymous. Pergolide (Celance)—a third dopamine agonist. *Drug Ther Bull* 1991; **29:** 79.
2. Markham A, Benfield P. Pergolide: a review of its pharmacology and therapeutic use in Parkinson's disease. *CNS Drugs* 1997; **7:** 328–40.
3. Barone P, *et al.* Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. *Neurology* 1999; **53:** 573–9.
4. Clarke CE, Speller J. Pergolide for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews, Issue 2. Chichester: John Wiley; 1999 (accessed 16/02/06).
5. Clarke CE, Speller J. Pergolide versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 16/02/06).

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Pergolide has produced some benefit in several studies.[1-6] In a randomised placebo-controlled study,[6] therapeutic effects were seen with mean daily doses of pergolide 400 micrograms after 6 weeks and maintained after 12 months with doses of up to 720 micrograms daily.

1. Silber MH, *et al.* Pergolide in the management of restless legs syndrome: an extended study. *Sleep* 1997; **20:** 878–82.
2. Winkelmann J, *et al.* Treatment of restless legs syndrome with pergolide—an open clinical trial. *Mov Disord* 1998; **13:** 566–9.
3. Earley CJ, *et al.* Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology* 1998; **51:** 1599–1602.
4. Wetter TC, *et al.* A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 1999; **52:** 944–50.
5. Stiasny K, *et al.* Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 2001; **56:** 1399–1402.
6. Trenkwalder C, *et al.* Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS study. *Neurology* 2004; **62:** 1391–7.

Tourette's syndrome. Pergolide has been studied in the management of Tourette's syndrome (see Tics, p. 1030.1). A preliminary study[1] produced encouraging results, subsequently confirmed by placebo-controlled studies in children and adolescents.[2,3]

1. Lipinski JF, *et al.* Dopamine agonist treatment of Tourette disorder in children: results of an open-label trial of pergolide. *Mov Disord* 1997; **12:** 402–7.
2. Gilbert DL, *et al.* Tourette's syndrome improvement with pergolide in a randomized, double-blind, crossover trial. *Neurology* 2000; **54:** 1310–15.
3. Gilbert DL, *et al.* Tic reduction with pergolide in a randomized controlled trial in children. *Neurology* 2003; **60:** 606–11.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3.

An increased incidence of uterine neoplasms has been reported in *rodents* given high doses of pergolide mesilate.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including pergolide, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including pergolide, see under Adverse Effects of Bromocriptine, p. 897.3.

In Australia,[1] Canada,[2] and Europe[3] regulatory authorities recommended that patients undergo a cardiovascular evaluation before starting treatment with pergolide; periodic clinical monitoring for development of valvular disease or fibrosis is also recommended. Doses of pergolide above 3 mg daily are not recommended by the EMEA.[3] Furthermore, use is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment and it is contra-indicated in patients with a history of fibrotic disorders or in those with anatomical evidence of cardiac valvulopathy.[4] In 2007, based on further evidence from 2 studies,[5,6] pergolide was withdrawn from the market in the USA[7] and Canada.[8]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cardiac valvulopathy with pergolide. *Aust Adverse Drug React Bull* 2004; **23:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.pdf (accessed 16/02/06)
2. Shire, Canada. New Safety information regarding Permax and occurrence of cardiac valvulopathy/fibrosis: update on the use of Permax (pergolide mesylate) (issued 12th October, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/shire_permax_2_hpc-cps-eng.pdf (accessed 12/08/08)
3. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)
4. MHRA. Dopamine agonists for Parkinson's disease (issued 30th March, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/GeneralsafetyinformationandadvicePlus/Product-specificinformationandadvice/DopamineagonistsforParkinson146sdisease/CON2030729 (accessed 03/06/08)
5. Schade R, *et al.* Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; **356:** 29–38.
6. Zanettini R, *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; **356:** 39–46.
7. FDA. FDA public health advisory: pergolide (marketed as Permax) (issued 29th March, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/UCM051285 (accessed 24/08/10)
8. Eli Lilly, Canada. Health Canada-mandated important safety information on Permax (pergolide mesylate) (issued 10th August, 2007). Available at: http://www.lilly.ca/servlets/sfs;jsessionid=9E0E83CA662673A89F439C68DAA3AC4B?t=/documentManager/sfdoc.file.supply&e=UTF-8&i=1233164768976&l=0&s=S62tYOHmUjqiTRlfa&fileID=1251138472378 (accessed 23/08/10)

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Pergolide mesilate is absorbed from the gastrointestinal tract. It is reported to be about 90% bound to plasma proteins. It is excreted mainly in the urine in the form of metabolites.

References.
1. Blin O. The pharmacokinetics of pergolide in Parkinson's disease. *Curr Opin Neurol* 2003; **16** (suppl 1): S9–S12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aroltex; Celance; Geranil; ***Austral.***: Permax; ***Austria***: Permax; ***Belg.***: Permax; ***Braz.***: Celance†; ***Cz.***: Permax; ***Fr.***: Celance†; ***Ger.***: Parkotil†; ***Gr.***: Celance†; ***Irl.***: Celance; ***Ital.***: Nopar; ***Mex.***: Permax; ***Neth.***: Permax†; ***NZ***: Permax; ***Port.***: Permax; ***S.Afr.***: Permax†; ***Singapore***: Celance; ***Spain***: Pharken†; ***Switz.***: Permax†; ***Turk.***: Permax; ***UK***: Celance†.

Pharmacopoeial Preparations
USP 36: Pergolide Tablets.

Piribedil *(rINN)*

ET-495; EU-4200; Piribédil; Piribedilum; Пирибедил.
2-(4-Piperonylpiperazin-1-yl)pyrimidine.
$C_{16}H_{18}N_4O_2$=298.3
CAS — 3605-01-4.
ATC — N04BC08.
ATC Vet — QN04BC08.
UNII — DO22K1PRDJ.

Profile

Piribedil is a non-ergot dopamine agonist that has been given orally in the treatment of parkinsonism (below) and in circulatory disorders. Piribedil mesilate has been given by injection for circulatory disorders. Preparations of piribedil are licensed in some countries for the management of impaired memory and cognitive function in the elderly.

Adverse effects reported include nausea and vomiting, dizziness, hallucinations, confusion, drowsiness, hypothermia, dyskinesias, and occasional changes in liver function.

When used as monotherapy in Parkinson's disease a usual daily oral dose of piribedil is 150 to 250 mg in divided doses; a daily dose of 80 to 140 mg may be suitable when used as an adjunct to levodopa.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including piribedil, see under Adverse Effects of Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Adverse Effects of Levodopa, p. 905.2.

Parkinsonism. Piribedil is a dopamine D_2-agonist while its metabolite is reported to act on D_1 receptors. It has been mainly used as an adjunct to levodopa therapy in the treatment of Parkinson's disease (p. 889.1).

References.
1. Montastruc JL, *et al.* Current status of dopamine agonists in Parkinson's disease management. *Drugs* 1993; **46:** 384–93.
2. Montastruc JL, *et al.* A randomized, double-blind study of a skin patch of a dopaminergic agonist, piribedil, in Parkinson's disease. *Mov Disord* 1999; **14:** 336–41.
3. Ziegler M, Rondot P. Activité du piribédil dans la maladie de Parkinson: étude multicentrique. *Presse Med* 1999; **28:** 1414–18.
4. Ziegler M, *et al.* Efficacy of piribedil as early combination to levodopa in patients with stable Parkinson's disease: a 6-month, randomized, placebo-controlled study. *Mov Disord* 2003; **18:** 418–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Trastoner; Trivastal; ***Braz.***: Trivastal; ***China***: Trastal (泰舒达); ***Fr.***: Trivastal; ***Ger.***: Clarium; ***Gr.***: Trivastal; ***India***: Trivastal; ***Ital.***: Trivastan; ***Malaysia***: Trivastal; ***Philipp.***: Trivastal; ***Pol.***: Pronoran; ***Port.***: Trivastal; ***Rus.***: Pronoran (Пронoран); ***Singapore***: Trivastal; ***Thai.***: Trivastal; ***Turk.***: Trivastal; ***Ukr.***: Pronoran (Пронoран); ***Venez.***: Trivastal.

Pramipexole Hydrochloride

(BANM, rINNM)

Hidrocloruro de pramipexol; PNU-98528-E; Pramipexol, hidrocloruro de; Pramipexole, Chlorhydrate de; Pramipexole, dichlorhydrate de; Pramipexole Dihydrochloride (USAN); Pramipexoli dihydrochloridum; Pramipexoli Hydrochloridum; SND-919-CL-2Y (pramipexole hydrochloride); SUD-919Y (pramipexole); Прамипексола Гидрохлорид.
(*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate.
$C_{10}H_{17}N_3S,2HCl, H_2O$=302.3
CAS — 104632-26-0 (pramipexole); 104632-25-9 (anhydrous pramipexole hydrochloride); 191217-81-9 (pramipexole hydrochloride monohydrate).
ATC — N04BC05.
ATC Vet — QN04BC05.
UNII — 3D867NP06J.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pramipexole Dihydrochloride Monohydrate). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble to slightly soluble in alcohol; soluble in methyl alcohol; practically insoluble in dichloromethane. pH of a 2% solution in water is 2.8 to 3.4.

USP 36: (Pramipexole Dihydrochloride). A white to almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol; practically insoluble in dichloromethane. Protect from moisture and light.

Uses and Administration

Pramipexole is a non-ergot dopamine agonist with actions similar to those of bromocriptine (p. 895.3). It is used similarly in the management of Parkinson's disease (below), either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response. Pramipexole is also used for the treatment of moderate to severe restless legs syndrome (below). It is given orally as the hydrochloride; doses have been described in terms of the hydrochloride (as below) or of the base. In terms of equivalency:

- pramipexole hydrochloride 125 micrograms is equivalent to about 88 micrograms of pramipexole
- pramipexole hydrochloride 250 micrograms is equivalent to about 180 micrograms of pramipexole
- pramipexole hydrochloride 500 micrograms is equivalent to about 350 micrograms of pramipexole
- pramipexole hydrochloride 1 mg is equivalent to about 700 micrograms of pramipexole

In the treatment of **Parkinson's disease**, the dose of pramipexole should be increased gradually and the dose of levodopa gradually reduced during the dose-titration and maintenance phases until an optimum response is achieved. The initial dose of pramipexole *hydrochloride* is 125 micrograms three times daily increased to 250 micrograms three times daily in the second week and then to 500 micrograms three times daily in the third week according to response. Thereafter the daily dose may be increased if necessary by 750 micrograms at weekly intervals to a maximum of 4.5 mg daily. Modified-release preparations are also available for once-daily use. The dosage should be reduced in patients with renal impairment (see below).

If it is necessary to stop pramipexole therapy, it should be withdrawn gradually. The dose of pramipexole hydrochloride should be tapered off at a rate of 750 micrograms daily until a daily dose of 750 micrograms has been reached; thereafter, the dose should be reduced by 375 micrograms daily.

Pramipexole is also given as a single daily dose, 2 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of pramipexole *hydrochloride* is 125 micrograms daily. This may be increased if necessary after 4 to 7 days to 250 micrograms daily. Subsequent doses may be increased if necessary by 250 micrograms every 4 to 7 days to a maximum of 750 micrograms daily. Response to therapy should be evaluated after 3 months; if treatment is interrupted for more than a few days, it should be restarted at 125 micrograms daily, and then increased, if required, as described above. For this indication, pramipexole may be withdrawn without gradual tapering of the dose.

Administration in renal impairment. The elimination of pramipexole is dependent on renal function and the oral dosage of pramipexole hydrochloride should therefore be reduced in patients with renal impairment.

In the treatment of *Parkinson's disease*, the following dosage schedule has been suggested in UK licensed product information adjusted according to the patient's creatinine clearance (CC):

- CC 20 to 50 mL/minute: initially 125 micrograms twice daily increased, if necessary, to a maximum of 2.25 mg daily
- CC less than 20 mL/minute: initially 125 micrograms once daily increased, if necessary, to a maximum of 1.5 mg daily

Similar reductions are suggested in US licensed information for patients with a CC of 30 to 50 mL/minute and 15 to less than 30 mL/minute, respectively; no recommendation is made for those with a CC of less than 15 mL/minute.

If renal function declines during maintenance therapy it is recommended that the daily dose of pramipexole should be reduced by the same percentage as the decline in CC.

Lower doses are used in the treatment of *restless legs syndrome* and UK licensed information considers dosage reductions unnecessary in patients with CC of more than 20 mL/minute. US licensed information recommends that the interval between titration steps is increased to 14 days in those patients with CC of 20 to 60 mL/minute.

Parkinsonism. Pramipexole is a dopamine agonist used in the treatment of Parkinson's disease (p. 889.1) as an adjunct to levodopa therapy to reduce 'off' periods with levodopa and ameliorate other fluctuations of mobility in the later stages of the disease. It is also used as monotherapy early in the course of the disease in an attempt to delay therapy with levodopa.

References.
1. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease: a randomized dose-ranging study. *JAMA* 1997; **278:** 125–30.
2. Lieberman A, *et al.* Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology* 1997; **49:** 162–8.
3. Shannon KM, *et al.* Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology* 1997; **49:** 724–8.
4. Guttman M. International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology* 1997; **49:** 1060–5.
5. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000; **284:** 1931–8.
6. Clarke CE, *et al.* Pramipexole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
7. Clarke CE, *et al.* Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
8. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* 2004; **61:** 1044–53. Correction. *ibid.* 2005; **62:** 430.
9. Moller JC, *et al.* Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. *Mov Disord* 2005; **20:** 602–10.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical, although dopaminergic therapy has emerged as a common first-line choice. Low-dose pramipexole has produced some benefit in several studies[1-8] and is licensed for the treatment of moderate to severe RLS in some countries.

1. Lin S-C, *et al.* Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clin Proc* 1998; **73:** 497–500.
2. Montplaisir J, *et al.* Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 1999; **52:** 938–43.

3. Montplaisir J, *et al*. Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol* 2000; **7** (suppl 1): 27–31.
4. Saletu M, *et al*. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *Eur Arch Psychiatry Clin Neurosci* 2002; **252:** 185–94.
5. Silber MH, *et al*. Pramipexole in the management of restless legs syndrome: an extended study. *Sleep* 2003; **26:** 819–21.
6. Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome: an open label trial. *Neuropsychobiology* 2004; **50:** 65–70.
7. Winkelman JW, *et al*. Efficacy and safety of pramipexole in restless legs syndrome. *Neurology* 2006; **67:** 1034–9.
8. Oertel WH, *et al*. Pramipexole RLS Study Group. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). *Mov Disord* 2007; **22:** 213–19.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3.

Pramipexole should be used with caution in patients with renal impairment and reduced doses are recommended.

Ophthalmological monitoring is recommended at regular intervals or if vision abnormalities occur.

Incidence of adverse effects. References.

1. Etminan M, *et al*. Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26:** 439–44.

Effects on mental function. Pramipexole has been associated with attacks of sudden onset of sleep, sometimes without any prior feeling of drowsiness, that can occur at any time during treatment. Licensed product information states that the incidence of **daytime somnolence** is increased at daily doses of pramipexole hydrochloride higher than 1.5 mg. A retrospective analysis[1] of data to evaluate the incidence and nature of somnolence in patients receiving pramipexole in clinical studies showed that for patients with moderate or severe somnolence, the onset of worst-reported somnolence occurred at a mean daily dose of around 4 mg (range: 0.75 to 4.5 mg).

For further reports of daytime somnolence occurring in patients receiving dopamine agonists including pramipexole, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, including pramipexole, see under Levodopa, p. 905.2.

1. Hauser RA, *et al*. Pramipexole-induced somnolence and episodes of daytime sleep. *Mov Disord* 2000; **15:** 658–63.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pramipexole as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

As for Bromocriptine, p. 899.1. Cimetidine is reported to reduce the renal clearance of pramipexole.

Caution is advised when other sedating drugs or alcohol are used with pramipexole because of possible additive effects and the risk of precipitating sudden onset of sleep (see above).

References.

1. Wright CE, *et al*. Influence of probenecid and cimetidine on pramipexole pharmacokinetics. *Clin Pharmacol Ther* 1996; **59:** 183.

Pharmacokinetics

Pramipexole is readily absorbed from the gastrointestinal tract and peak plasma concentrations have occurred within about 2 hours in fasting patients and in about 3 hours when given with food. Oral bioavailability is reported to be about 90%. Pramipexole is widely distributed throughout the body and plasma-protein binding is less than 20%. Metabolism is minimal and more than 90% of a dose is excreted via renal tubular secretion unchanged into the urine. Elimination half-lives of 8 to 12 hours have been reported. On the basis of studies in *rats*, it is thought to be distributed into breast milk.

References.

1. Wright CE, *et al*. Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. *J Clin Pharmacol* 1997; **37:** 520–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Maxtenk; Neurosomat; Nixol; Noxopran; Nulipar; Parfeno; Parmital; Parxium†; Portiv; Proats; Sifrol; Treminel; ***Austral.***: Sifrol; ***Austria***: Sifrol; ***Belg.***: Sifrol; ***Braz.***: Livipark; Mirapex; Sifrol; ***Canad.***: Mirapex; ***Chile***: Biopsol; Intaxel; Sifrol; ***China***: Sifrol (森福罗); ***Cz.***: Aperixon; Emwepel; Glepark; Medopexol; Mirapexin; Oprymea; Pexogies; Pexopaul; Pramigen; Pramithan; Pramixil; Ritmorest; Sifrol; ***Denm.***: Derinik; Mirapexin; Neliprax†; Oprymea; Pramithon; Sifrol; Tifripex†; ***Fin.***: Derinik; Glepark; Pramigen; Sifrol; ***Fr.***: Sifrol; ***Ger.***: Oprymea; Pramip; Sifrol; ***Gr.***: Glepark; Mariprax; Medopexol; Miraleton; Miraparkin; Mirapexin; ***Hong Kong***: Mirapex; ***Hung.***: Mirapexin; Oprymea; Pramitenorm; ***Indon.***: Sifrol; ***Irl.***: Glepark; Meroximer; Miramel; Mirapexin; Mirole; Oprymea; Sifrol; ***Israel***: Sifrol; Trimexol; ***Ital.***: Ezaprev; Mariprax; Miparkan; Miraper; Mirapexin; Miviren; Pramigen; Ramixole; ***Jpn***: BI-Sifrol; Mirapex; ***Malaysia***: Sifrol; ***Mex.***: Sifrol; ***Neth.***: Glepark; Mirapexin; Oprymea; Pramipexolane; Pramithon; Sifrol; ***Norw.***: Sifrol; ***NZ***: Sifrol; ***Philipp.***: Sifrol; ***Pol.***: Miparkan; Mirapexin; Neliprax; Oprymea; Pramixil; Ritmorest; Sifrol; ***Port.***: Ezaprev; Mirapexin; Oprymea; Sifrol; ***Rus.***: Mirapex (Мирапекс); ***S.Afr.***: Pexola; ***Singapore***: Sifrol; ***Spain***: Mirapexin; ***Swed.***: Derinik; Oprymea; Sifrol; ***Switz.***: Sifrol; ***Thai.***: Sifrol; ***Turk.***: Parkyn; Parson; Pexola; ***UK***: Mirapexin; ***Ukr.***: Mirapex (Мирапекс); Miraxol (Мираксол); ***USA***: Mirapex; ***Venez.***: Sifrol/Mirapex.

Procyclidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de prociclidina; Prociclidina, hidrocloruro de; Procyclidine, Chlorhydrate de; Procyclidini Hydrochloridum; Проциклидина Гидрохлорид.

1-Cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl)propan-1-ol hydrochloride.

$C_{19}H_{29}NO,HCl$=323.9

CAS — 77-37-2 (procyclidine); 1508-76-5 (procyclidine hydrochloride).

ATC — N04AA04.

ATC Vet — QN04AA04.

UNII — CQC932Z7YW.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Procyclidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 6.5.

USP 36: (Procyclidine Hydrochloride). A white crystalline powder, having a moderate characteristic odour. Soluble 1 in 35 of water, 1 in 9 of alcohol, 1 in 6 of chloroform, and 1 in 11 000 of ether; insoluble in acetone. pH of a 1% solution in water is between 5.0 and 6.5. Store in a dry place in airtight containers. Protect from light.

Uses and Administration

Procyclidine hydrochloride is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It is used for the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias (but see under Uses and Administration of Levodopa, p. 903.3); for doses in children, see below.

In **parkinsonism**, the initial oral dose of 2.5 mg three times daily may be increased gradually by 2.5 to 5 mg every 2 or 3 days (or by 2.5 mg daily if used for drug-induced extrapyramidal syndrome) until the optimum maintenance dose, usually 10 to 30 mg daily in 3 (or occasionally 4) divided doses, is reached; daily doses of up to 60 mg have occasionally been required. As a rule, postencephalitic patients tolerate and require the larger doses; elderly and arteriosclerotic patients may require smaller doses.

In an emergency such as **acute dystonias**, 5 to 10 mg may be given by intravenous injection; higher doses have sometimes been used. The intramuscular route has also been employed: 5 to 10 mg may be given as a single injection, repeated if necessary after 20 minutes to a maximum of 20 mg daily. Parenteral doses are usually effective within 5 to 10 minutes but may need 30 minutes to produce relief.

Administration in children. Although procyclidine hydrochloride is not licensed in the UK for management of dystonias (p. 903.3) in children, the *BNFC* suggests that oral doses of 1.25 mg 3 times daily may be given to those aged 7 to 12 years, and 2.5 mg 3 times daily to those aged 12 to 18 years. In an emergency, a single dose may be given by intramuscular or intravenous injection according to age as follows: under 2 years, 0.5 to 2 mg; 2 to 10 years, 2 to 5 mg; 10 to 18 years, 5 to 10 mg or occasionally more. Parenteral doses are usually effective within 5 to 10 minutes but may need 30 minutes to produce relief.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Psychotic episodes may be precipitated in patients with mental disorders when procyclidine is used for the treatment of drug-induced extrapyramidal syndrome.

Abuse. Like other antimuscarinics (see also under Trihexyphenidyl Hydrochloride, p. 918.1) procyclidine has been abused for its euphoriant effects.[1,2]

1. McGucken RB, *et al*. Teenage procyclidine abuse. *Lancet* 1985; **i:** 1514.
2. Dooris B, Reid C. Feigning dystonia to feed an unusual drug addiction. *J Accid Emerg Med* 2000; **17:** 311.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Paroxetine increases plasma-procyclidine concentrations and it is recommended that the dose of procyclidine should be reduced if antimuscarinic effects are seen in patients receiving both drugs.

Pharmacokinetics

Procyclidine hydrochloride is absorbed from the gastrointestinal tract and bioavailability has been reported to be 75% after oral doses; it disappears rapidly from the tissues. Procyclidine given intravenously acts within 5 to 20 minutes and has a duration of effect of up to 4 hours. The mean plasma elimination half-life after oral or intravenous doses is about 12 hours. About one-fifth of an oral dose is metabolised in the liver, mainly by the cytochrome P450 isoenzymes, followed by conjugation with glucuronic acid. A small amount of unchanged drug is excreted in the urine.

References.

1. Whiteman PD, *et al*. Pharmacokinetics and pharmacodynamics of procyclidine in man. *Eur J Clin Pharmacol* 1985; **28:** 73–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kemadrin; ***Belg.***: Kemadrin; ***Cz.***: Kemadrin; ***Denm.***: Kemadrin; ***Ger.***: Osnervan; ***Hung.***: Kemadrin; ***India***: Kemadrin; ***Irl.***: Kemadrin; ***Israel***: Kemadrin; ***NZ***: Kemadrin; ***Spain***: Kemadren; ***Switz.***: Kemadrin; ***UK***: Arpicolin; Kemadrin.

Pharmacopoeial Preparations

BP 2014: Procyclidine Injection; Procyclidine Tablets;
USP 36: Procyclidine Hydrochloride Tablets.

Profenamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Profenamina; Ethopropazine Hydrochloride; Hidrocloruro de profenamina; Isothazine Hydrochloride; Profenamina, hidrocloruro de; Profénamine, Chlorhydrate de; Profenamini Hydrochloridum; Prophenamini Chloridum; Профенамина Гидрохлорид.

10-(2-Diethylaminopropyl)phenothiazine hydrochloride.

$C_{19}H_{24}N_2S,HCl$=348.9

CAS — 522-00-9 (profenamine); 1094-08-2 (profenamine hydrochloride).

ATC — N04AA05.

ATC Vet — QN04AA05.

UNII — O00T1I1VRN.

Profile

Profenamine hydrochloride is a phenothiazine derivative with antimuscarinic, adrenergic-blocking, antihistaminic, local anaesthetic, and ganglion-blocking properties. Adverse effects associated with phenothiazines may occur, especially with high doses (see under Chlorpromazine, p. 1047.2). Profenamine has been used in the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as other phenothiazines, but, like other antimuscarinics (see Atropine Sulfate, p. 1310.2), is of no value against tardive dyskinesias. It has been used in a usual initial oral dose of 50 mg three times daily, gradually increased to 500 mg or more daily in divided doses, according to response.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Parsitan.

Rasagiline Mesilate *(rINNM)*

Mesilato de rasagilina; Rasagiline, Mésilate de; Rasagiline Mesylate (USAN); Rasagilini Mesilas; TV-1030 (rasagiline); TVP-1012; Разагилина Мезилат.

(*R*)-*N*-2-Propynyl-1-indanamine methanesulfonate.

$C_{12}H_{13}N,CH_4O_3S$=267.3

CAS — 136236-51-6 (rasagiline); 161735-79-1 (rasagiline mesilate).

ATC — N04BD02.

ATC Vet — QN04BD02.

UNII — LH8C2JI290.

Uses and Administration

Rasagiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease (p. 889.1), either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' fluctuations in response. Rasagiline is given orally as the mesilate and doses are expressed in terms of the base; rasagiline mesilate 1.56 mg is equivalent to about 1 mg of rasagiline. The usual dose is the equivalent of rasagiline 1 mg once daily. In the USA, an initial daily dose of 500 micrograms is recommended for adjunctive therapy.

The dose of rasagiline may need to be reduced when given with drugs that inhibit the cytochrome P450 isoenzyme CYP1A2 (see Interactions, below for details) and in patients with hepatic impairment (see below).

References.

1. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 2002; **59:** 1937–43.
2. Stern MB, *et al.* Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord* 2004; **19:** 916–23.
3. Thebault JJ, *et al.* Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. *Pharmacotherapy* 2004; **24:** 1295–1305.
4. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol* 2004; **61:** 561–6.
5. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 2005; **62:** 241–8.
6. Rascol O, *et al.* Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* 2005; **365:** 947–54.
7. Rascol O. Rasagiline in the pharmacotherapy of Parkinson's disease: a review. *Expert Opin Pharmacother* 2005; **6:** 2061–75.
8. Chen JJ, *et al.* Clinical pharmacology of rasagiline: a novel, second-generation propargylamine for the treatment of Parkinson disease. *J Clin Pharmacol* 2005; **45:** 878–94.
9. Siderowf A, Stern M. Clinical trials with rasagiline: evidence for short-term and long-term effects. *Neurology* 2006; **66** (suppl 4): S80–S88.
10. Goetz CG, *et al.* Parkinson Study Group TEMPO and PRESTO Investigators. Safety of rasagiline in elderly patients with Parkinson disease. *Neurology* 2006; **66:** 1427–9.
11. Oldfield V, *et al.* Rasagiline: a review of its use in the management of Parkinson's disease. *Drugs* 2007; **67:** 1725–47.
12. Olanow CW, *et al.* ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; **361:** 1268–78.
13. Ahlskog JE, Uitti RJ. Rasagiline, Parkinson neuroprotection, and delayed-start trials: still no satisfaction? *Neurology* 2010; **74:** 1143–8.

Administration in hepatic impairment. UK licensed product information for rasagiline advises caution when used in patients with mild hepatic impairment whereas US licensed information recommends that the oral dose be reduced to 500 micrograms daily. Rasagiline should not be used in those with moderate or severe impairment.

Adverse Effects and Precautions

Common adverse effects reported with rasagiline monotherapy include headache, flu-like syndrome, malaise, neck pain, angina pectoris, dyspepsia, anorexia, leucopenia, arthralgia, arthritis, depression, vertigo, rhinitis, conjunctivitis, skin rashes, melanoma, and urinary urgency. Cerebrovascular accidents and myocardial infarction have been reported rarely. Other adverse effects include orthostatic hypotension and hallucinations.

Rasagiline should not be used in patients with severe hepatic impairment; use in moderate impairment should also be avoided. It should be used with caution in patients with mild hepatic impairment and therapy should be stopped in those who progress to moderate impairment.

Interactions

As for Selegiline Hydrochloride, p. 916.1. Unlike the non-selective MAOIs, such as phenelzine, rasagiline can be used safely without dietary tyramine restrictions, although these have been recommended in some countries.

Rasagiline should not be given with other MAOIs because of the risk of non-selective MAO inhibition that may lead to hypertensive reactions.

It is metabolised by the cytochrome P450 isoenzyme CYP1A2 and potent inhibitors of this enzyme such as ciprofloxacin may increase the plasma levels of rasagiline. UK licensed product information for rasagiline advises caution when such drugs are used with rasagiline whereas US licensed product information recommends that the dose of rasagiline be reduced to 500 micrograms daily when given with CYP1A2 inhibitors. Tobacco smoking induces hepatic metabolic enzymes and may decrease the plasma levels of rasagiline.

Entacapone has been reported to increase the clearance of oral rasagiline by 28% when used together.

Pharmacokinetics

Rasagiline is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur in about 30 minutes to 1 hour. Bioavailability is reported to be about 36%. Rasagiline is about 60 to 70% bound to plasma proteins.

It is extensively metabolised in the liver by *N*-dealkylation and hydroxylation, via the cytochrome P450 isoenzyme CYP1A2, and conjugation. 1-Aminoindan is a major metabolite and is stated to be active although it is not a monoamine oxidase B inhibitor. Metabolites are excreted mainly in the urine and partly in the faeces; less than 1% of a dose is excreted as unchanged drug in the urine. The terminal half-life is 0.6 to 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Elbrus; Rasax; ***Austria***: Azilect; ***Belg.***: Azilect; ***Canad.***: Azilect; ***Cz.***: Azilect; ***Denm.***: Azilect; ***Fin.***: Azilect; ***Fr.***: Azilect; ***Ger.***: Azilect; ***Gr.***: Azilect; ***Hung.***: Azilect; ***Irl.***: Azilect; ***Israel***: Azilect; ***Ital.***: Azilect; ***Mex.***: Azilect; ***Neth.***: Azilect; ***Norw.***: Azilect; ***Pol.***: Azilect; ***Port.***: Azilect; ***Rus.***: Azilect (Азилект); ***S.Afr.***: Azilect; ***Spain***: Azilect; ***Swed.***: Azilect; ***Switz.***: Azilect; ***Thai.***: Azilect; ***Turk.***: Azilect; ***UK***: Azilect; ***USA***: Azilect.

Ropinirole Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de ropinirol; Ropinirol, hidrocloruro de; Ropinirole, Chlorhydrate de; Ropiniroli Hydrochloridum; SKF-101468 (ropinirole); SKF-0101468-A (ropinirole hydrochloride); Ропинирола Гидрохлорид.

4-[2-(Dipropylamino)ethyl]-2-indolinone hydrochloride.

$C_{16}H_{24}N_2O,HCl$=296.8

CAS — 91374-21-9 (ropinirole); 91374-20-8 (ropinirole hydrochloride).

ATC — N04BC04.

ATC Vet — QN04BC04.

UNII — D7ZD41RZI9.

Pharmacopoeias. In *US.*

USP 36: (Ropinirole Hydrochloride). A pale cream to yellow powder. Soluble in water.

Uses and Administration

Ropinirole is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p. 895.3), but in contrast to bromocriptine it also has agonist properties at D_3 receptors. It is used similarly in the management of Parkinson's disease (below), either alone or as an adjunct to reduce 'on-off' fluctuations in levodopa response. Ropinirole is also used for the treatment of moderate to severe idiopathic restless legs syndrome (below). It is given orally as the hydrochloride; doses are expressed in terms of the base. Ropinirole hydrochloride 1.14 mg is equivalent to about 1 mg of ropinirole.

In the treatment of **Parkinson's disease**, ropinirole should be introduced gradually and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved; the concurrent dose of levodopa may be reduced by about 20 to 30%. The daily dosage of ropinirole should be given in three divided doses, preferably with food. The initial daily dose of ropinirole is 750 micrograms increased at weekly intervals in steps of 750 micrograms for the first 4 weeks. After week 4, the weekly increments may be made in steps of 1.5 mg up to a dose of 9 mg daily according to response; subsequent weekly increments may be made in steps of up to 3 mg. The daily dosage should not exceed 24 mg. Optimal response is usually achieved within the range of 3 to 9 mg daily; higher doses may be required if used with levodopa. If it is necessary to stop ropinirole therapy, it should be withdrawn gradually by reducing the number of daily doses over a period of 1 week. Once adequate symptomatic control has been established, ropinirole may be given as once-daily modified-release tablets.

Ropinirole is also given as a single daily dose, 1 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of ropinirole is 250 micrograms daily for 2 days; if tolerated, the dose is then increased to 500 micrograms daily for the rest of the first week. Dosage is then increased as necessary up to a maximum of 4 mg daily. Increases are made weekly in steps of 500 micrograms up to a dose of 3 mg daily; a final increase after one further week of 1 mg to a dose of 4 mg daily can then be made. In the UK, it has been recommended that treatment should be reassessed 3 months after starting therapy. For this indication, ropinirole may be withdrawn without gradual tapering of the dose.

If treatment with ropinirole is interrupted for more than a few days it should be restarted at the low initial dose and increased gradually as required.

Reviews.

1. Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. *Neurology* 1997; **49** (suppl 1): S58–S62.

Parkinsonism. Dopamine agonists such as ropinirole may be used to begin treatment of parkinsonism (p. 889.1) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease.

References.

1. Rascol O, *et al.* A placebo-controlled study of ropinirole a new D_2 agonist, in the treatment of motor fluctuations of L-DOPA-treated parkinsonian patients. *Adv Neurol* 1996; **69:** 531–4.
2. Adler CH, *et al.* The Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; **49:** 393–9.
3. Rascol O, *et al.* Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord* 1998; **13:** 39–45.
4. Korczyn AD, *et al.* A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999; **53:** 364–70.
5. Matheson AJ, Spencer CM. Ropinirole: a review of its use in the management of Parkinson's disease. *Drugs* 2000; **60:** 115–37.
6. Clarke CE, Deane K. Ropinirole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane K. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Whone AL, *et al.* Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol* 2003; **54:** 93–101.
9. Pahwa R, *et al.* Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007; **68:** 1108–15.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Ropinirole is licensed for the treatment of moderate to severe RLS in some countries.

References.

1. Trenkwalder C, *et al.* Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004; **75:** 92–7.
2. Cheer SM, *et al.* Ropinirole: for the treatment of restless legs syndrome. *CNS Drugs* 2004; **18:** 747–54.
3. Walters AS, *et al.* Ropinirole is effective in the treatment of restless legs syndrome—TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004; **19:** 1414–23.
4. Bogan RK, *et al.* TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81:** 17–27.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3. Hypersensitivity reactions including angioedema, pruritus, rash, and urticaria have been reported with ropinirole therapy. Licensed product information states that the pharmacokinetics of ropinirole have not been studied in patients with hepatic or severe renal impairment and therefore it should be used with caution, if at all, in such patients. No pharmacokinetic changes were noted in those with mild to moderate renal impairment.

In the treatment of restless legs syndrome, earlier onset of symptoms in the afternoon or evening (augmentation) and recurrence of symptoms in the early morning hours (rebound) have been reported with ropinirole.

Incidence of adverse effects. References.

1. Etminan M, *et al.* Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26:** 439–44.
2. Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials. *Drug Safety* 2010; **33:** 147–61.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including ropinirole, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ropinirole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

Since it is a dopamine agonist, ropinirole may share some of the pharmacological interactions of bromocriptine, p. 899.1. In addition, high doses of oestrogens can increase plasma concentrations of ropinirole and dosage adjustments may be necessary if oestrogen therapy is started or withdrawn during treatment with ropinirole. Ropinirole is metabolised by the cytochrome P450 isoenzyme CYP1A2 and there is therefore the potential for interactions between ropinirole and other drugs that are metabolised similarly or more particularly with inducers or inhibitors of this enzyme. Dosage adjustments may be necessary if therapy with such drugs is started or withdrawn during treatment with ropinirole.

Pharmacokinetics

Ropinirole is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have occurred 1.5 hours after oral doses; the rate of absorption, but not the extent, may be reduced if taken with food. Bioavailability is reported to be about 50%. It is widely distributed throughout the body and plasma protein binding is low (10 to 40%).

Ropinirole is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2, and excreted in the urine as inactive metabolites; less than 10% of an oral dose is excreted as unchanged drug. A mean elimination half-life of about 6 hours has been reported for ropinirole. It is thought to be distributed into breast milk on the basis of studies in *rats*.

References.

1. Brefel C, *et al.* Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol* 1998; **45:** 412–15.
2. Hubble J, *et al.* Linear pharmacokinetic behavior of ropinirole during multiple dosing in patients with Parkinson's disease. *J Clin Pharmacol* 2000; **40:** 641–6.
3. Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet* 2000; **39:** 243–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Requip; ***Austral.***: Appese; Repreve; ***Austria***: Requip; ***Belg.***: Requip; ***Canad.***: Requip; ***Chile***: Requip; ***Cz.***: Adartrel; Aropilo; Aropix; Lirona†; Requip; Rolpryna; Ropinstad; Ropison; ***Denm.***: Adartrel; Requip; Ropinict; ***Fin.***: Adartrel†; Requip; ***Fr.***: Adartrel; Requip; ***Ger.***: Adartrel; Ralnea; Requip; Ropinal; ***Gr.***: Adartrel; Requip; ***Hong Kong***: Requip; ***Hung.***: Aropilo; Ralnea; Requip; Romyl; Ropidopin; ***Irl.***: Adartrel†; Eironil†; Requip; Rolpryna; Roni†; Ropirade; ***Israel***: Requip; ***Ital.***: Adartrel†; Requip; Roprima; ***Jpn***: ReQuip; ***Malaysia***: Requip; ***Mex.***: Requip; ***Neth.***: Adartrel; Requip; Ropison; Sonirol†; ***Norw.***: Adartrel; Requip; ***NZ***: Requip; Ropaccord; Ropin; ***Philipp.***: Requip; ***Pol.***: Adartrel; Aropilo; Aropix; Contexine; Parnirol; Requip; ***Port.***: Adartrel; Requip; Ropimed; Zyatrol†; ***Rus.***: Requip (Реквип); ***S.Afr.***: Requip; Resure; ***Singapore***: Requip; ***Spain***: Adartrel; Niromylan†; Requip; Rolpryna; Ropigen†; ***Swed.***: Adartrel; Requip; ***Switz.***: Adartrel; Requip; ***Thai.***: Requip; ***Turk.***: Requip; ***UK***: Adartrel; Aimpart; Ralnea; Raponer; Repinex; Requip; ***USA***: Requip.

Pharmacopoeial Preparations

USP 36: Ropinirole Tablets.

Rotigotine *(BAN, USAN, rINN)*

N-0923; Rotigotina; Rotigotinum; SPM-962; Ротиготин.

(-)-(*S*)-5,6,7,8-Tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol.

$C_{19}H_{25}NOS$=315.5

CAS — 99755-59-6 (rotigotine); 125572-93-2 (rotigotine hydrochloride).

ATC — N04BC09.

ATC Vet — QN04BC09.

UNII — 87T4T8BO2E.

Uses and Administration

Rotigotine is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p. 895.3), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. It is used as monotherapy in the management of Parkinson's disease (p. 889.1), mainly in the early stage. It may also be used as an adjunct to levodopa therapy. Rotigotine is also used for the treatment of moderate to severe idiopathic restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2). Rotigotine is given as transdermal patches delivering amounts ranging from 1 to 8 mg per 24 hours.

In the treatment of **Parkinson's disease**, when given as *monotherapy*, the initial dose is 2 mg daily, increased in weekly steps of 2 mg if necessary, to a maximum of 8 mg daily. Rotigotine may also be used as *adjunctive therapy* with levodopa in an initial dose of 4 mg daily, increased in weekly steps of 2 mg if necessary, to a maximum of 16 mg daily. Treatment with rotigotine should be withdrawn gradually; the daily dose should be reduced in steps of 2 mg every other day until complete withdrawal is achieved.

In the treatment of **restless legs syndrome**, the initial dose is 1 mg daily, increased in weekly steps of 1 mg according to response, to a maximum of 3 mg daily. The need for treatment continuation should be assessed every 6 months. If stopping treatment, the daily dose should be reduced in steps of 1 mg every other day until complete withdrawal is achieved.

Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site.

References.

1. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* 2003; **60:** 1721–8.
2. Stiasny-Kolster K, *et al.* Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Mov Disord* 2004; **19:** 1432–8.
3. Poewe W, Leussi F. Clinical studies with transdermal rotigotine in early Parkinson's disease. *Neurology* 2005; **65** (suppl 1): S11–S14. Correction. *ibid.*; 1328.
4. Watts RL, *et al.* Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 2007; **68:** 272–6. Correction. *ibid.*; **69:** 617.
5. Splinter MY. Rotigotine: transdermal dopamine agonist treatment of Parkinson's disease and restless legs syndrome. *Ann Pharmacother* 2007; **41:** 285–95.
6. LeWitt PA, *et al.* Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology* 2007; **68:** 1262–7.
7. Trenkwalder C, *et al.* Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord* 2008; **23:** 2267–2302.
8. Reading P. Treating restless legs syndrome with rotigotine. *Br J Hosp Med* 2010; **71:** 216–19.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3. Reactions may occur at the site of application and are usually mild or moderate in intensity. The site should be rotated on a daily basis and the same site should not be used within 14 days.

Licensed product information recommends that rotigotine should be used with caution in patients with severe hepatic impairment and reduced doses may be necessary in cases of worsening impairment; however, this is based on a lack of evidence in such patients.

Interactions

Since it is a dopamine agonist, rotigotine may share some of the pharmacological interactions of bromocriptine, p. 899.1.

Caution is advised when other sedating drugs or alcohol are used with rotigotine because of possible additive effects.

Pharmacokinetics

Rotigotine has poor oral bioavailability as it undergoes extensive first-pass metabolism via glucuronidation in the gut wall and liver. Peak plasma concentrations occur 24 hours after transdermal application. Steady-state concentrations are reached after 24 to 48 hours of continuous daily application. It undergoes *N*-dealkylation and conjugation to form inactive metabolites. Rotigotine is excreted mainly in the urine and about 23% appears in the faeces. The elimination half-life is 5 to 7 hours. It is distributed into milk of *rats*.

References.

1. Cawello W, *et al.* Transdermal administration of radiolabelled [^{14}C] rotigotine by a patch formulation: a mass balance trial. *Clin Pharmacokinet* 2007; **46:** 851–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Neupro; ***Austria***: Neupro; ***Belg.***: Neupro; ***Cz.***: Neupro; ***Denm.***: Neupro; ***Fr.***: Neupro; ***Ger.***: Leganto; Neupro; ***Gr.***: Neupro; ***Hong Kong***: Neupro; ***Hung.***: Neupro; ***Irl.***: Leganto; Neupro; ***Israel***: Neupro; ***Ital.***: Neupro; ***Jpn***: Neupro; ***Neth.***: Neupro; ***Norw.***: Neupro; ***Pol.***: Neupro; ***Port.***: Neupro; ***Spain***: Neupro; ***Swed.***: Neupro; ***Switz.***: Neupro; ***Thai.***: Neupro; ***UK***: Neupro; ***Ukr.***: Neupro (Неупро); ***USA***: Neupro.

Selegiline Hydrochloride

(BANM, USAN, rINNM) ⊗

Deprenilo; Deprenyl; L-Deprenyl; Hidrocloruro de selegilina; Selegiliinihydrokloridi; Selegilin Hidroklorür; Selegilin hydrochlorid; Selegilina, hidrocloruro de; Sélégiline, Chlorhydrate de; Selegilinhydrochlorid; Selegilini Hydrochloridum; Selegilino hidrochloridas; Szelegilin-hidroklorid; Селегилина Гидрохлорид.

(-)-(*R*)-*N*,α-Dimethyl-*N*-(prop-2-ynyl)phenethylamine hydrochloride; (*R*)-Methyl(α-methylphenethyl)prop-2-ynylamine hydrochloride.

$C_{13}H_{17}N,HCl$=223.7

CAS — 14611-51-9 (selegiline); 2079-54-1 (selegiline hydrochloride); 14611-52-0 (selegiline hydrochloride).

ATC — N04BD01.

ATC Vet — QN04BD01.

UNII — 6W731X367Q ((-)-selegiline hydorchloride); 63G7R4955A ((±)-selegiline hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Selegiline Hydrochloride). A white or almost white, crystalline powder. M.p. about 143 degrees. Freely soluble in water and in methyl alcohol; slightly soluble in acetone and in ethyl acetate. A 2% solution in water has a pH of 3.5 to 4.5. Protect from light.

USP 36: (Selegiline Hydrochloride). A white, odourless crystalline powder. Freely soluble in water, in chloroform, and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Selegiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease mainly as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response, but see Parkinsonism, p. 915.1. Addition of selegiline to levodopa therapy may enable the dosage of levodopa to be reduced by about 10 to 30%. Selegiline may be given alone in early Parkinson's disease in an attempt to delay the need for levodopa therapy. It is also used in the treatment of depression (p. 915.1).

In the treatment of **Parkinson's disease**, selegiline hydrochloride is given orally as conventional preparations such as capsules, tablets, or liquid, or as lyophilisate tablets. The dose of the conventional preparations is 10 mg daily, either as a single dose in the morning or in 2 divided doses of 5 mg at breakfast and lunchtime. The initial dose of the oral lyophilisate tablets is 1.25 mg daily at least 5 minutes before breakfast; patients already receiving 10 mg of conventional preparations can be transferred to 1.25 mg of the oral lyophilisate. US product information states that the initial oral lyophilisate dose of 1.25 mg daily may be increased, after at least 6 weeks, to 2.5 mg given once daily, if necessary.

In the USA, transdermal patches delivering 6, 9, or 12 mg of selegiline over 24 hours are available for the treatment of **depression**. The initial dose is 6 mg daily, increased in steps of 3 mg every 2 weeks if necessary, to a maximum of 12 mg daily. Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site. Dose increases should be made with caution in the elderly and patients should be closely observed for postural changes in blood pressure during treatment. Dietary restrictions are necessary at doses of 9 mg daily and above, see Interactions, p. 916.1.

Other conditions in which selegiline has been tried include dementia.

Some references to the actions of selegiline.

1. Youdim MBH, Finberg JPM. Pharmacological actions of l-deprenyl (selegiline) and other selective monoamine oxidase B inhibitors. *Clin Pharmacol Ther* 1994; **56:** 725–33.
2. Lange KW, *et al.* Biochemical actions of l-deprenyl (selegiline). *Clin Pharmacol Ther* 1994; **56:** 734–41.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; selegiline is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (p. 1990.1).

References.

1. Houtsmuller EJ, *et al.* Transdermal selegiline and intravenous cocaine: safety and interactions. *Psychopharmacology (Berl)* 2004; **172:** 31–40.

Dementia. The hypothesis that neurodegeneration in Alzheimer's disease (p. 388.1) might be due to free radical formation has led to drugs such as selegiline being tried as antoxidant therapy.

Early double-blind studies[1,2] indicated that oral selegiline 10 mg daily might produce beneficial effects in patients with Alzheimer's disease but it was suggested that improvements in mood and cognitive function may have been due to a reduction in tension and depression.[3] A 15-month study in Alzheimers's patients with mild cognitive impairment showed oral selegiline 10 mg daily to have little effect,[4] although the authors pointed out that those with more severe dementia have shown more response in other studies. The conclusion of a later study[5] that oral selegiline 10 mg daily slowed progression in patients with moderate disease has been criticised[6] on the grounds that any effect was only evident after statistical adjustment to the original analysis. In addition a systematic review[7] examining the effects of selegiline concluded that there was no meaningful evidence of a beneficial effect of oral selegiline in patients with Alzheimer's disease. They also considered that there

was no longer any justification for its use in patients with Alzheimer's disease.

1. Piccinin GL, *et al.* Neuropsychological effects of L-deprenyl in Alzheimer's-type dementia. *Clin Neuropharmacol* 1990; **13:** 147–63.
2. Mangoni A, *et al.* Effects of a MAO-B inhibitor in the treatment of Alzheimer disease. *Eur Neurol* 1991; **31:** 100–107.
3. Anonymous. Drugs for Alzheimer's disease. *Drug Ther Bull* 1990; **28:** 42–4.
4. Burke WJ, *et al.* L-Deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. *J Am Geriatr Soc* 1993; **41:** 1219–25.
5. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; **336:** 1216–22.
6. Pincus MM. Alpha-tocopherol and Alzheimer's disease. *N Engl J Med* 1997; **337:** 572.
7. Birks J, Flicker L. Selegiline for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).

Depression. Selegiline is a selective inhibitor of monoamine oxidase type B and there are reports[1-3] of it producing improvement in depression (p. 398.1). However, at the doses usually required to produce an antidepressant effect the specificity of oral selegiline is reported to be lost and it has been suggested that the efficacy of selegiline as an antidepressant might depend on inhibition of monoamine oxidase A rather than inhibition of monoamine oxidase B alone. Such a loss of specificity would mean that patients taking selegiline for depression would need to observe the dietary restrictions applicable to non-selective MAOIs.

To overcome the problems associated with the oral route, transdermal selegiline has also been tried and may be more effective than placebo in the treatment of depression.[4] The use of the transdermal route allows sustained blood levels of selegiline to be delivered without extensive inhibition of peripheral monoamine oxidase A. Transdermal patches of selegiline are licensed for the treatment of depression in the USA.

1. Mendlewicz J, Youdim MBH. L-Deprenil, a selective monoamine oxidase type B inhibitor, in the treatment of depression: a double-blind evaluation. *Br J Psychiatry* 1983; **142:** 508–11.
2. Mann JJ, *et al.* A controlled study of the antidepressant efficacy and side-effects of (-)-deprenyl. *Arch Gen Psychiatry* 1989; **46:** 45–50.
3. Sunderland T, *et al.* High-dose selegiline in treatment-resistant older depressive patients. *Arch Gen Psychiatry* 1994; **51:** 607–15.
4. Frampton JE, Plosker GL. Selegiline transdermal system: in the treatment of major depressive disorder. *Drugs* 2007; **67:** 257–65.

Narcoleptic syndrome. Small controlled studies[1,2] have suggested that oral selegiline 20 to 40 mg daily has a beneficial effect on symptoms of narcolepsy and cataplexy (p. 2314.3); at such a dosage a low-tyramine diet is considered necessary.

1. Hublin C, *et al.* Selegiline in the treatment of narcolepsy. *Neurology* 1994; **44:** 2095–2101.
2. Mayer G, *et al.* Selegeline [sic] hydrochloride treatment in narcolepsy: a double-blind, placebo-controlled study. *Clin Neuropharmacol* 1995; **18:** 306–19.

Parkinsonism. As a selective monoamine oxidase type B inhibitor, selegiline reduces the metabolism of dopamine and thereby enhances its actions. It reduces levodopa's 'end-of-dose' effect and has a dose-sparing effect. Some have used it as **monotherapy** in an attempt to delay the need for levodopa. If progression of Parkinson's disease (p. 889.1) were due to a cytotoxic effect of free radicals, generated during the metabolism of dopamine, on dopaminergic neurones in the substantia nigra, selegiline might slow the process by reducing their formation. In a large early study,[1] the DATATOP study, selegiline monotherapy delayed the need to start levodopa in patients with early Parkinson's disease. These findings were corroborated by other smaller studies.[2,3] There has been much debate over whether the benefit was due to a neuroprotective or symptomatic effect. Re-analysis of the DATATOP data by independent workers[4,5] and findings of other studies[6] supported a symptomatic effect. Subsequent studies involving DATATOP patients were also consistent with a symptomatic effect; any benefit produced by selegiline appeared to be less pronounced as the duration of treatment increased[7] and was lost completely long term.[8,9] However, a later study[10] designed to minimise any symptomatic effect cast doubt on whether the delay in progression of the signs and symptoms of Parkinson's disease obtained with selegiline was entirely due to a symptomatic effect.

Studies of the use of selegiline as an **adjunct** to levodopa therapy[6,11,12] indicate that selegiline permits a modest reduction in the dosage requirements of levodopa. An interim analysis of a study of the early addition of selegiline to levodopa has also suggested that selegiline might stabilise the long-term daily levodopa dosage.[13] As with monotherapy, combined therapy has been reported to slow symptom progression.[14]

The use of selegiline in Parkinson's disease has been questioned after a UK study[11] found an unexpected increase in mortality in patients taking levodopa with selegiline compared with those taking levodopa alone. No difference in mortality had been detected at the 3-year follow-up[15] but after an average follow-up time of 5.6 years[11] mortality was 60% higher in the group also receiving selegiline. The study has been criticised on many grounds including the fact that mortality was very high in both arms of the study[16] and has been the subject of much debate.[17,18] The authors of the study[11] had stated that they would advise the study patients to withdraw selegiline therapy. Analysis of follow-up data[19] until the selegiline arm of the study was terminated (average 6.8 years) found an excess mortality of about 35%, a figure calculated[20] to be no longer significant. However, because of the premature termination of the study such results were considered[21] to be biased. Whether any excess in mortality is causally related to selegiline is still unclear. Some consider that changes in prescribing practice based on this study are not warranted.[17] Others[21] have made a cautious recommendation not to start combination treatment in patients with newly diagnosed Parkinson's disease but consider that there is little evidence to advise patients who have been using selegiline with levodopa for years without problem to change their treatment. An evaluation of mortality among patients taking antiparkinsonian drugs (using the UK General Practice Research Database) provided evidence against there being substantial excess mortality associated with the use of selegiline.[22] These results are supported by systematic reviews[23,24] and meta-analyses[25,26] of randomised, double-blind studies which found no increase in mortality associated with selegiline treatment regardless of concurrent levodopa. Furthermore, increased mortality was not seen in patients in the original DATATOP study[1] after an average follow-up time of 8.2 years. However, it was noted that the delay of disability seen in the early phase of selegiline therapy[1,7] was not associated with longer life during follow-up.[27] A later systematic review[23] has also found no convincing evidence that selective monoamine oxidase type B inhibitors (selegiline and lazabemide) significantly delay disease progression in early Parkinson's disease and routine use is not recommended. Similarly, another recent systematic review[24] found insufficient evidence to recommend the routine use of selegiline over the use of levodopa and dopamine agonists (bromocriptine and lisuride) in early disease.

1. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989; **321:** 1364–71.
2. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989; **245:** 519–22.
3. Allain H, *et al.* Selegiline in de novo parkinsonian patients: the French selegiline multicenter trial (FSMT). *Acta Neurol Scand* 1991; **84** (suppl 136): 73–8.
4. Schulzer M, *et al.* The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Ann Neurol* 1992; **32:** 795–8.
5. Ward CD. Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994; **57:** 217–20.
6. Brannan T, Yahr MD. Comparative study of selegiline plus L-dopa–carbidopa versus L-dopa–carbidopa alone in the treatment of Parkinson's disease. *Ann Neurol* 1995; **37:** 95–8.
7. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.
8. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. *Ann Neurol* 1996; **39:** 29–36.
9. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996; **39:** 37–45.
10. Olanow CW, *et al.* The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1996; **38:** 771–7.
11. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.
12. Myllylä VV, *et al.* Early selegiline therapy reduces levodopa dose requirement in Parkinson's disease. *Acta Neurol Scand* 1995; **91:** 177–82.
13. Larsen JP, Boas J. Norwegian-Danish Study Group. The effects of early selegiline therapy on long-term treatment and parkinsonian disability: an interim analysis of a Norwegian-Danish 5-year study. *Mov Disord* 1997; **12:** 175–82.
14. Pålhagen S, *et al.* Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology* 2006; **66:** 1200–6.
15. Parkinson's Disease Research Group in the United Kingdom. Comparisons of the therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993; **307:** 467–72.
16. Olanow CW, *et al.* Patients taking selegiline may have received more levodopa than necessary. *BMJ* 1996; **312:** 702–3.
17. Ahlskog JE. Treatment of early Parkinson's disease: are complicated strategies justified? *Mayo Clin Proc* 1996; **71:** 659–70.
18. Mizuno Y, Kondo T. Mortality associated with selegiline in Parkinson's disease: what do the available data mean? *Drug Safety* 1997; **16:** 289–94.
19. Ben-Shlomo Y, *et al.* Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *BMJ* 1998; **316:** 1191–6.
20. Abrams KR. Monitoring randomised controlled trials. *BMJ* 1998; **316:** 1183–4.
21. Breteler MMB. Selegiline, or the problem of early termination of clinical trials. *BMJ* 1998; **316:** 1182–3.
22. Thorogood M, *et al.* Mortality in people taking selegiline: observational study. *BMJ* 1998; **317:** 252–4.
23. Macleod A, *et al.* Monoamine oxidase B inhibitors for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/02/06).
24. Caslake R, *et al.* Monoamine oxidase B inhibitors versus other dopaminergic agents in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/05/10).
25. Olanow CW, *et al.* Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998; **51:** 825–30.
26. Ives NJ, *et al.* Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ* 2004; **329:** 593–6.
27. The Parkinson Study Group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. *Ann Neurol* 1998; **43:** 318–25.

Smoking cessation. Selegiline has been investigated as an aid to smoking cessation (p. 2570.2).

References.
1. George TP, *et al.* A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biol Psychiatry* 2003; **53:** 136–43.
2. Biberman R, *et al.* A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. *Addiction* 2003; **98:** 1403–7.

Adverse Effects

Selegiline is often given as an adjunct to levodopa therapy and many of the adverse effects reported may be attributed to enhanced levodopa activity; dosage of levodopa may have to be reduced. However, most reported adverse effects, with the possible exception of increased dyskinesias and cardiac arrhythmias, have also been seen with selegiline monotherapy. Adverse effects have included orthostatic hypotension, chest pain, nausea, vomiting, constipation, diarrhoea, confusion, headache, tremor, vertigo, dizziness, psychosis, depression, hallucinations, agitation, dry mouth, sore throat, difficulty in micturition, skin reactions, back pain, muscle cramps, joint pain, and myopathy. The amfetamine metabolites of selegiline may cause insomnia and abnormal dreams; evening doses should be avoided. Transient increases in liver enzymes have been reported. Mouth ulcers and stomatitis may occur with the oral lyophilisate.

Since the selectivity of selegiline is lost at higher doses, signs and symptoms of overdosage may resemble those of non-selective MAOIs such as phenelzine (see p. 442.2).

Effects on carbohydrate metabolism. Profound hypoglycaemia developed in a 70-year-old man after selegiline was added to his existing medication for Parkinson's disease.[1] Hypoglycaemia was accompanied by hyperinsulinaemia and resolved 1 week after stopping selegiline.

1. Rowland MJ, *et al.* Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? *J Clin Pharmacol* 1994; **34:** 80–5.

Effects on mortality. For reference to a study that found an increased mortality rate in patients with Parkinson's disease taking selegiline and levodopa compared with those taking levodopa alone, see Parkinsonism, under Uses and Administration, above.

Precautions

Selegiline should be used with caution in patients with a history of peptic ulceration and avoided in those with active ulceration. It should also be used with caution in uncontrolled hypertension, arrhythmias, angina, severe liver or kidney dysfunction, or psychosis.

When selegiline is used in the management of depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1.

Cardiovascular disorders. An investigation[1] of the autonomic effects of selegiline as a potential cause of the unexpected mortality seen in a study[2] in patients with Parkinson's disease receiving selegiline and levodopa (see Parkinsonism, above) suggested that the risk of orthostatic hypotension with this combination may have been underestimated. It was considered prudent to withdraw selegiline from those with symptomatic orthostatic hypotension or cardiovascular or cerebrovascular disease. For those without symptomatic morbidity, but a greater than 20 mmHg fall in blood pressure on standing for 2 minutes, gradual withdrawal of selegiline with adjustment of levodopa dosage should be considered.

1. Churchyard A, *et al.* Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **63:** 228–34.
2. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies selegiline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

Selegiline is less likely than non-selective MAOIs, such as phenelzine, to interact with tyramine in food; such hypertensive reactions have been reported rarely at usual doses but UK licensed product information for oral formulations states that its selectivity is lost at higher doses and it must be assumed that selegiline can usually only be used safely without dietary restrictions at doses of up to 10 mg daily. US licensed information for the transdermal preparation states that dietary restrictions are necessary at doses of 9 mg daily and above: patients should be warned not to eat any tyramine-rich foods while being treated with, and for at least 14 days after discontinuation of, these doses or after dose reduction to 6 mg daily. For further details on dietary restrictions applicable to patients taking MAOIs, see p. 444.3.

Even when given in therapeutic doses life-threatening interactions can occur between selegiline and pethidine. Serious reactions, sometimes fatal, have also been reported when selegiline was used with tricyclic antidepressants or serotonin reuptake inhibitors including the SSRIs and venlafaxine. Licensed product information states that 14 days should elapse between stopping selegiline and starting treatment with tricyclic or serotonergic antidepressants. Conversely, selegiline should not be given to patients who have recently received these antidepressants; at least 5 weeks should elapse between stopping fluoxetine and starting treatment with selegiline. Use of selegiline with non-selective MAOIs may cause severe hypotension and such use is not recommended.

Antidepressants. Although there have been studies in which patients with parkinsonism have received selegiline with *SSRIs* such as fluoxetine[1] or paroxetine[2] (apparently without any problems) there have been reports of reactions[3-5] such as shivering and sweating, hypertension, hyperactivity, and ataxia occurring when selegiline and fluoxetine have been used together. The FDA noted[6] that reactions similar to those between SSRIs and non-selective MAOIs had also been reported in patients taking selegiline with paroxetine or sertraline.

Severe reactions, sometimes fatal, have also occurred in patients taking selegiline and *tricyclic antidepressants*.[6] For a report of serotonin syndrome developing when *venlafaxine* was given after selegiline (despite a drug-free period), see p. 457.1.

There has been a report[7] of a patient receiving the non-selective MAOI *iproniazid* who had severe orthostatic hypotension when given selegiline. Selegiline given with the reversible MAOI *moclobemide* to healthy subjects markedly increased the pressor response to tyramine compared with the effects of each drug used alone.[8] The authors concluded that dietary restriction of tyramine-containing foods would be necessary if these drugs were to be used together.

One UK manufacturer (*Cephalon, UK*) states that oral selegiline should not be given with any type of antidepressant, while another (*Orion, UK*) advises that use with SSRIs or venlafaxine be avoided and recommends caution when used with the tricyclics. The US manufacturer of transdermal selegiline (*Bristol-Myers Squibb, USA*), used for depression, states that use with other antidepressants such as *bupropion*, *mirtazapine*, serotonin reuptake inhibitors, *St John's wort*, and tricyclics is contra-indicated.

1. Waters CH. Fluoxetine and selegiline—lack of significant interaction. *Can J Neurol Sci* 1994; **21:** 259–61.
2. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* 1994; **28:** 405–6.
3. Suchowersky O, de Vries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* 1990; **35:** 571–2.
4. Jermain DM, *et al.* Potential fluoxetine-selegiline interaction. *Ann Pharmacother* 1992; **26:** 1300.
5. Montastruc JL, *et al.* Pseudophaeochromocytoma in parkinsonian patient treated with fluoxetine plus selegiline. *Lancet* 1993; **341:** 555.
6. Anonymous. Eldepryl and antidepressant interaction. *FDA Med Bull* 1995; **25** (Feb.): 6.
7. Pare CMB, *et al.* Attempts to attenuate the 'cheese effect': combined drug therapy in depressive illness. *J Affect Disord* 1985; **9:** 137–41.
8. Korn A, *et al.* Tyramine pressor sensitivity in healthy subjects during combined treatment with moclobemide and selegiline. *Eur J Clin Pharmacol* 1996; **49:** 273–8.

Antimigraine drugs. Some serotonin agonists including *rizatriptan*, *sumatriptan*, and *zolmitriptan* are metabolised via monoamine oxidase type A and therefore it is considered unlikely that selegiline, a monoamine oxidase type B inhibitor, would interact with these drugs. Nevertheless, one manufacturer (*Cephalon, UK*) of oral selegiline contra-indicates its use in patients also receiving serotonin agonists; it is also recommended that at least 24 hours should elapse between stopping selegiline and starting treatment with these drugs.

Opioid analgesics. Selegiline can produce life-threatening reactions when given with *pethidine*.[1]

Some manufacturers contra-indicate use of selegiline with pethidine and other opioid analgesics such as *dextropropoxyphene*, *methadone*, and *tramadol*.

1. Zornberg GL, *et al.* Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337:** 246. Correction. *ibid.*; 440.

Oral contraceptives. The total area under the concentration-time curve for selegiline given in single doses of 5 to 40 mg was raised ten- to twentyfold in 4 women who were using oral hormonal contraceptives when compared with 4 women receiving no other medication.[1] It was suggested that use of selegiline and oral hormonal contraceptives should be avoided or the dosage of selegiline reduced.

1. Laine K, *et al.* Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids. *Br J Clin Pharmacol* 1999; **47:** 249–54.

Sympathomimetics. Licensed information for a US product (*Eldepryl; Somerset, USA*) states that there has been a report of hypertensive crisis in a patient taking recommended doses of selegiline and *ephedrine*. A hypertensive reaction after low-dose *dopamine* infusion has been reported[1] in a 75-year-old patient taking selegiline 10 mg daily for Parkinson's disease. The authors suggest that this may indicate a non-specific action of selegiline at usual doses on peripheral monoamine oxidase type-A. UK licensed product information states that dopamine should be used with caution in patients taking selegiline.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; **34:** 1020–4.

Pharmacokinetics

Selegiline is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur in 30 minutes after oral doses of conventional preparations. Although subject to large interindividual variation, bioavailability is about 10% and is increased when given with food. Selegiline is rapidly distributed throughout the body and crosses the blood-brain barrier. It undergoes extensive first-pass metabolism in the liver to produce at least 5 metabolites, including *l*-(-)-desmethylselegiline (norselegiline), *l*- (-)-*N*-methylamfetamine, and *l*- (-)-amfetamine. Plasma concentrations of selegiline metabolites are greatly reduced after doses of the oral lyophilisate preparation, the majority of which undergoes absorption through the buccal mucosa. Topical use also avoids first-pass metabolism and about 25 to 30% of the stated content is available systemically. Selegiline is excreted as metabolites mainly in the urine and about 15% appears in the faeces. At steady state the elimination half-life is reported to be 10 hours.

References.

1. Heinonen EH, *et al.* Pharmacokinetic aspects of l-deprenyl (selegiline) and its metabolites. *Clin Pharmacol Ther* 1994; **56:** 742–9.
2. Mahmood I, *et al.* Clinical pharmacokinetics and pharmacodynamics of selegiline: an update. *Clin Pharmacokinet* 1997; **33:** 91–102.
3. Anttila M, *et al.* Marked effect of liver and kidney function on the pharmacokinetics of selegiline. *Clin Pharmacol Ther* 2005; **77:** 54–62.
4. Azzaro AJ, *et al.* Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with the selegiline transdermal system (6 mg/24 h): a comparison with oral selegiline capsules. *J Clin Pharmacol* 2007; **47:** 1256–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Brintenal; Jumex; Zelapar; ***Austral.***: Eldepryl; Selgene; ***Austria***: Amboneural; Cognitiv; Jumex; Xilopar; ***Belg.***: Eldepryl; ***Braz.***: Deprilan; Elepril; Jumexil; Niar; Parkexin; ***Chile***: Selgina; ***China***: Eldepryl (咪多吡); Fu An (辅安); Jin Si Ping (金思平); ***Cz.***: Apo-Seleg; Cognitiv; Jumex; Niar†; ***Denm.***: Eldepryl; ***Fin.***: Eldepryl; ***Fr.***: Deprenyl; Otrasel; ***Ger.***: Antiparkin; Jutagilin†; Movergan; Selepark†; Selgimed†; Xilopar; ***Gr.***: Calaquin; Cosmopril; Ermolax; Feliselin; Krautin; Legil; Procythol; Resostyl; ***Hong Kong***: Julab†; Jumex; Sefmex; Selegos; ***Hung.***: Cognitiv†; Jumex; ***India***: Eldepryl; Elegelin; Jumax; Jumex; Selerin; Selgin; ***Indon.***: Jumex; ***Irl.***: Eldepryl; ***Israel***: Selgin; ***Ital.***: Egibren; Jumex; Selecom; Seledat; Xilopar; ***Jpn***: FP Tab; ***Malaysia***: Jumex; Sefmex; ***Mex.***: Niar; ***Neth.***: Eldepryl; ***Norw.***: Eldepryl; ***NZ***: Eldepryl; ***Philipp.***: Jumex; ***Pol.***: Apo-Selin; Jumex; Segan; Selerin; Selgin†; Selgres; ***Port.***: Jumex; Niponeurin†; Xilopar; ***Rus.***: Cognitiv (Когнитив); Jumex (Юмекс); Segan (Сеган)†; Selegos (Селегос)†; ***S.Afr.***: Eldepryl; Parkilyne; ***Singapore***: Jumex; Selegos; ***Spain***: Plurimen; ***Swed.***: Eldepryl; ***Switz.***: Jumexal†; ***Thai.***: Julab; Jumex; Sefmex; ***Turk.***: Moverdin; Seldepar; ***UK***: Eldepryl; Zelapar; ***Ukr.***: Eldepryl (Эльдеприл); Segan (Сеган); ***USA***: Atapryl; Carbex†; Eldepryl; Emsam; Zelapar; ***Venez.***: Jumex.

Pharmacopoeial Preparations
BP 2014: Selegiline Oral Solution; Selegiline Tablets;
USP 36: Selegiline Hydrochloride Tablets.

Talipexole Hydrochloride *(rINNM)*

Alefexole Hydrochloride; B-HT-920; Hidrocloruro de talipexol; Talipexol, hidrocloruro de; Talipexole, Chlorhydrate de; Talipexoli Hydrochloridum; Талипексола Гидрохлорид.

6-Allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine dihydrochloride.
$C_{10}H_{15}N_3S,2HCl$=282.2
CAS — 101626-70-4 (talipexole); 36085-73-1 (talipexole hydrochloride).
UNII — 9R6E1D8H1O.

Profile

Talipexole hydrochloride is a dopamine D_2-agonist that is used in the management of parkinsonism (p. 889.1); it is given orally in usual maintenance doses of 1.2 to 3.6 mg daily, in divided doses. It has also been investigated in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Domin.

Terguride *(rINN)*

Tergurida; Terguridum; Теругид.
1,1-Diethyl-3-(6-methylergolin-8α-yl) urea.
$C_{20}H_{28}N_4O$=340.5
CAS — 37686-84-3.
ATC — G02CB06.
ATC Vet — QG02CB06.
UNII — 21OJT43Q88.

Profile

Terguride, an ergot derivative, is a partial dopamine agonist with general properties similar to those of bromocriptine (p. 895.3). It is used in the treatment of disorders related to hyperprolactinaemia (p. 2252.2) in a usual oral dose of 500 micrograms twice daily. It is also being investigated in the management of parkinsonism and pulmonary hypertension.

References.

1. Krause W, *et al.* Pharmacokinetics and endocrine effects of terguride in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 609–15.
2. Baronti F, *et al.* Partial dopamine agonist therapy of levodopa-induced dyskinesias. *Neurology* 1992; **42:** 1241–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Teluron.

Tolcapone *(BAN, USAN, rINN)*

Ro-40-7592; Tolcapona; Tolcaponum; Tolkapon; Tolkaponi; Толкапон.
3,4-Dihydroxy-4′-methyl-5-nitrobenzophenone; 3,4-Dihydroxy-5-nitrophenyl(4-methylphenyl)methanone.
$C_{14}H_{11}NO_5$=273.2
CAS — 134308-13-7.
ATC — N04BX01.
ATC Vet — QN04BX01.
UNII — CIF6334OLY.

Pharmacopoeias. In *US*.

USP 36: (Tolcapone). A yellow, fine powder or fine powder with lumps. Insoluble in water and in *n*-hexane; Freely soluble in acetone and in tetrahydrofuran; sparingly soluble in chloroform and in dichloromethane; soluble in methyl alcohol and in ethyl acetate. Store in airtight containers at a temperature between 20 degrees and 25 degrees. Protect from light.

Uses and Administration

Tolcapone is a peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to levodopa and dopa-decarboxylase inhibitor combinations in the management of Parkinson's disease (p. 917.1) for patients who cannot be stabilised on these levodopa combinations or for those who have 'end-of-dose' deterioration. Because of the risk of serious hepatotoxicity (see Effects on the Liver, p. 917.1) the FDA in the USA restricted its use to when other adjunctive therapy was ineffective or contra-indicated. In the EU, tolcapone was withdrawn from the market in November 1998 and subsequently returned in 2004, its use being similarly restricted to patients who fail to respond to, or are intolerant of, other COMT inhibitors.

The usual recommended dosage of tolcapone is 100 mg given orally three times daily; up to a maximum of 200 mg three times daily may be considered if the clinical benefit justifies the increased risk of hepatotoxicity. The first dose of the day should be taken at the same time as the combined levodopa preparation. Most patients already taking more

than 600 mg of levodopa daily will require a reduction in their dosage of levodopa; patients on lower levodopa doses may also require a dose reduction.

Tolcapone should be withdrawn if a substantial clinical benefit is not obtained within the first 3 weeks of treatment. An adjustment in the levodopa dose may be necessary following tolcapone withdrawal.

Parkinsonism. Tolcapone is a reversible peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of levodopa and dopamine.[1] It appears to differ from entacapone (p. 901.2) by being a more potent COMT inhibitor in the periphery and by penetrating into the brain (although the significance of any central effects of COMT inhibition are not known).[1] When given to patients with Parkinson's disease (p. 889.1) and levodopa-related fluctuations in disability or 'end-of-dose' effects, it has prolonged the clinical benefit obtained with levodopa and allowed the total daily dosage of levodopa to be reduced.[2,3] Benefit has also been reported[4] when added to levodopa therapy in patients with stable Parkinson's disease. However, a systematic review[5] concluded that there were insufficient data to show any significant difference in efficacy between tolcapone and bromocriptine or pergolide in the adjunctive treatment of levodopa-induced motor complications.

The use of tolcapone is restricted in some countries because of the risk of serious hepatotoxicity (see Effects on the Liver, below).

1. Nutt JG. Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; **351:** 1221–2.
2. Kurth MC, *et al.* Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. *Neurology* 1997; **48:** 81–7.
3. Rajput AH, *et al.* Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind placebo-controlled, multicenter trial. *Neurology* 1997; **49:** 1066–71.
4. Waters CH, *et al.* Tolcapone Stable Study Group. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1997; **49:** 665–71.
5. Deane K, *et al.* Catechol-O-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).

Adverse Effects

The most common adverse effects associated with tolcapone are diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth, anorexia, dyskinesia, dystonia, dizziness, orthostatic hypotension, hallucinations, confusion, excessive dreaming, somnolence, headache, increased sweating, and sleep disorders. Diarrhoea may be severe enough for treatment to be stopped. Behavioural disturbances including intense urges to gamble and increased sexual urges have also been reported (see Effects on Mental Function, in Levodopa, p. 905.2). Increases in liver enzyme values have occurred and hepatitis and hepatic failure, sometimes fatal, have been reported. Isolated cases of neuroleptic malignant syndrome have also been reported after dose reduction or stopping tolcapone; rhabdomyolysis may develop as a complication of the syndrome. Tolcapone and its metabolites can produce a yellow intensification in the colour of urine.

Effects on the liver. The UK CSM had noted[1] that, after a report[2] in September 1998 of fatal acute hepatic failure associated with tolcapone, the European Committee for Proprietary Medicinal Products (CPMP) had reviewed all reports of hepatic injury with tolcapone. There had been 10 reports of serious hepatic adverse reactions since tolcapone was marketed in October 1997, which included 7 reports of hepatitis, 3 of which had a fatal outcome. Serious hepatic reactions occurred unpredictably and their development was not always predicted by liver function monitoring. Consequently, in the EU, the marketing authorisation for tolcapone was suspended in November 1998. This suspension was lifted in April 2004 by the CPMP after further review.

In some countries such as the USA, tolcapone has always remained available albeit with restricted indications and strict monitoring requirements (see Precautions, below). Up to 2003, there had been no further reports of fatal hepatic failure after the introduction of these measures although the number of patients eligible to receive the drug has been reduced.[3]

1. CSM/MCA. Withdrawal of tolcapone (Tasmar). *Current Problems* 1999; **25:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. Assal F, *et al.* Tolcapone and fulminant hepatitis. *Lancet* 1998; **352:** 958.
3. Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. *Drug Safety* 2003; **26:** 743–7.

Effects on the skin. For reference to the development of vitiligo in a patient following addition of tolcapone to levodopa/carbidopa treatment, see under Levodopa, p. 906.1.

Precautions

Tolcapone should not be given to patients with hepatic impairment or raised liver enzyme values. Liver enzymes should be monitored:

- when starting treatment with tolcapone or on increasing the dose to 200 mg three times daily
- every 2 weeks during the first year of therapy
- every 4 weeks for a further 6 months
- every 8 weeks thereafter

Tolcapone should be stopped if liver enzyme levels exceed the upper limit of normal or if signs or symptoms suggestive of the onset of hepatic failure occur. Patients who have developed evidence of hepatic injury while receiving tolcapone should not be given the drug again.

Tolcapone should be used with caution in patients with severe renal impairment.

It is contra-indicated in patients with severe dyskinesia or with a history of neuroleptic malignant syndrome (NMS). It is also contra-indicated in patients with a history of nontraumatic rhabdomyolysis or symptoms of hyperpyrexia and confusion possibly related to NMS. Patients with phaeochromocytoma should not be given tolcapone.

Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Abrupt withdrawal or dose reduction of tolcapone should be monitored carefully because of the risk of developing symptoms resembling NMS.

The elderly. Confusion occurred in 3 elderly patients with severe Parkinson's disease after the addition of tolcapone to their antiparkinsonian therapy.[1] It was suggested that a starting dose of tolcapone 100 mg daily might be more suitable in frail patients with severe disease. It was noted[2] that a reduction in levodopa dosage is generally recommended when tolcapone is given to patients such as these, who were receiving 500 to 600 mg of levodopa daily.

1. Henry C, Wilson JA. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **351:** 1965–6.
2. Harper J, Vieira B. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **352:** 578.

Genetic polymorphism. Two patients who developed elevated liver enzyme values while receiving tolcapone, one of whom also had hepatic dysfunction while receiving entacapone, were found to be poor metabolisers with regard to UDP-glucuronosyltransferase activity.[1] Such patients may be predisposed to COMT-inhibitor induced hepatotoxicity.

1. Martignoni E, *et al.* Two patients with COMT inhibitor-induced hepatic dysfunction and UGT1A9 genetic polymorphism. *Neurology* 2005; **65:** 1820–2.

Interactions

Tolcapone may influence the pharmacokinetics of drugs metabolised by catechol-*O*-methyltransferase; a dose reduction of such drugs should be considered when given with tolcapone. Increased concentrations of benserazide and its active metabolite have been reported when given with tolcapone. Licensed product information advises that non-selective MAOIs should not be used with tolcapone.

Pharmacokinetics

Tolcapone is rapidly absorbed from the gastrointestinal tract and maximum plasma concentrations have occurred within 2 hours of an oral dose; food delays and decreases the absorption. Absolute bioavailability is reported to be about 65%. Tolcapone is more than 99% bound to plasma proteins (mainly albumin) and is not widely distributed into body tissues. It is extensively metabolised, mainly by conjugation to the inactive glucuronide, but methylation by catechol-*O*-methyltransferase to 3-*O*-methyltolcapone and metabolism by cytochrome P450 isoenzymes CYP3A4 and CYP2A6 also occurs. About 60% of a dose is excreted in the urine with the remainder appearing in the faeces. The elimination half-life has been reported to be about 2 to 3 hours. The clearance of unbound tolcapone may be reduced by 50% in patients with moderate cirrhotic liver disorders.

References.
1. Dingemanse J, *et al.* Integrated pharmacokinetics and pharmacodynamics of the novel catechol-O-methyltransferase inhibitor tolcapone during first administration to humans. *Clin Pharmacol Ther* 1995; **57:** 508–17.
2. Jorga KM, *et al.* Effect of liver impairment on the pharmacokinetics of tolcapone and its metabolites. *Clin Pharmacol Ther* 1998; **63:** 646–54.
3. Jorga K, *et al.* Metabolism and excretion of tolcapone, a novel inhibitor of catechol-O-methyltransferase. *Br J Clin Pharmacol* 1999; **48:** 513–20.
4. Jorga K, *et al.* Population pharmacokinetics of tolcapone in parkinsonian patients in dose finding studies. *Br J Clin Pharmacol* 2000; **49:** 39–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tasmar†; ***Austria***: Tasmar; ***Belg.***: Tasmar; ***Braz.***: Tasmar; ***Chile***: Tasmar; ***China***: Sen De Ning (森得宁); Tasmar (答是美); ***Cz.***: Tasmar; ***Denm.***: Tasmar; ***Fr.***: Tasmar; ***Ger.***: Tasmar; ***Gr.***: Tasmar; ***Hung.***: Tasmar; ***Irl.***: Tasmar; ***Ital.***: Tasmar; ***Mex.***: Tasmar; ***Neth.***: Tasmar; ***Norw.***: Tasmar; ***NZ***: Tasmar; ***Philipp.***: Tasmar; ***Pol.***: Tasmar; ***Port.***: Tasmar; ***Rus.***: Tasmar (Тасмар); ***S.Afr.***: Tasmar†; ***Spain***: Tasmar; ***Swed.***: Tasmar; ***Switz.***: Tasmar; ***UK***: Tasmar; ***USA***: Tasmar.

Pharmacopoeial Preparations
USP 36: Tolcapone Tablets.

Trihexyphenidyl Hydrochloride

(BANM, rINNM)

Benzhexol Hydrochloride; Cloridrato de Triexilfenidila; Cyclodolum; Hidrocloruro de trihexifenidilo; Triheksifenidilio hidrochloridas; Triheksyfenidylu chlorowodorek; Triheksyfenidyylihydrokloridi; Trihexifenidilhidroklorid; Trihexifenidilo, hidrocloruro de; Trihexyfenidyl-hydrochlorid; Trihexyfenidyl-hydroklorid; Trihexyphénidyle, chlorhydrate de; Trihexyphenidylhydrochlorid; Trihexyphenidyli Hydrochloridum; Trihexyphenidylium Chloratum; Тригексифенидила Гидрохлорид.

1-Cyclohexyl-1-phenyl-3-piperidinopropan-1-ol hydrochloride.

$C_{20}H_{31}NO,HCl$=337.9

CAS — 144-11-6 (trihexyphenidyl); 52-49-3 (trihexyphenidyl hydrochloride).

ATC — N04AA01.

ATC Vet — QN04AA01.

UNII — AO61G82577.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of trihexyphenidyl:

Artanes.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Trihexyphenidyl Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.2 to 6.2.

USP 36: (Trihexyphenidyl Hydrochloride). A white or slightly off-white, crystalline powder, having not more than a very faint odour. Slightly soluble in water; soluble in alcohol and in chloroform. Store in airtight containers.

Uses and Administration

Trihexyphenidyl hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3). It also has a direct antispasmodic action on smooth muscle.

Trihexyphenidyl hydrochloride is given orally in the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias in adults and children, but see p. 918.1. Trihexyphenidyl hydrochloride is given in 3 or 4 divided doses daily before or with food.

In **Parkinson's disease** the usual initial dose of 1 mg daily is gradually increased at intervals of 3 to 5 days by increments of 2 mg to 6 to 10 mg daily, according to response; for advanced cases, 12 to 15 mg daily or even more (up to 20 mg daily) may be needed. As a rule, postencephalitic patients tolerate and require the larger doses.

Usual doses for **drug-induced extrapyramidal symptoms** lie within the range of 5 to 15 mg daily, although as little as 1 mg daily may be sufficient in some cases.

Since the elderly and arteriosclerotic patients are more susceptible to the adverse effects of antimuscarinics a dose at the lower end of the range is usually recommended.

Antimuscarinic treatment of parkinsonism should never be terminated suddenly and it is usual when changing from one drug to another to withdraw one in small amounts while gradually increasing the dose of the other.

Trihexyphenidyl hydrochloride may be given with other drugs used for the relief of parkinsonism, such as levodopa, but the dose of each drug may need to be reduced. Trihexyphenidyl hydrochloride 3 to 6 mg daily is usually adequate.

Administration in children. Although unlicensed, trihexyphenidyl hydrochloride has been used for the management of dystonias in children; for suggested doses, see p. 918.1.

Dystonias. Antimuscarinics such as trihexyphenidyl are used in the management of dystonias (p. 903.3) although only about half of all children and adolescents, and fewer adults (who tolerate antimuscarinics less well) show any response. Adverse effects may be limited by starting with a low dose: one suggested regimen[1] starts with trihexyphenidyl 1 mg daily and rises up to 12 mg daily over the next 4 to 6 weeks; some patients may require up to 60 to 100 mg daily. The *BNFC* suggests that children aged 3 months to 18 years may be given oral doses of 1 to 2 mg daily as a single dose or in 2 divided doses; if necessary, the dose can be increased every 3 to 7 days by 1 mg daily to a maximum of 2 mg/kg daily.

1. Jankovic J. Dystonia: medical therapy and botulinum toxin. *Adv Neurol* 2004; **94:** 275–86.

Adverse Effects, Treatment and Precautions

As for Atropine Sulfate, p. 1312.1. In some patients, such as those with arteriosclerosis or a history of drug idiosyncrasy, trihexyphenidyl may produce mental disturbances, excitement, or nausea and vomiting; such patients should be allowed to develop a tolerance by starting with a small initial dose and gradually increasing it until an effective level is reached. If a severe reaction occurs, trihexyphenidyl should be stopped for a few days and resumed at a lower dose. Trihexyphenidyl may provoke or exacerbate tardive dyskinesia.

Abuse. Trihexyphenidyl hydrochloride has been abused for its euphoric effect[1,2] especially by psychiatric patients.[3] Its abuse potential in schizophrenic patients has been questioned[4] and its unpleasant antimuscarinic effects tend to limit its repeated use,[5] but a small survey among psychiatric patients found that trihexyphenidyl was reported to be the antimuscarinic most frequently abused;[6] procyclidine, benzatropine, and orphenadrine (in decreasing order of frequency) were also misused. A later analysis of health insurance data from one region of France[7] examined prescriptions for trihexyphenidyl in 3028 subjects, most of whom were also receiving antipsychotics, and concluded that there was evidence of an abnormal pattern of use in about 2%. Patients in this subgroup were mostly young, male, and also receiving benzodiazepines or high doses of buprenorphine.

1. Crawshaw JA, Mullen PE. A study of benzhexol abuse. *Br J Psychiatry* 1984; **145:** 300–3.
2. Nappo SA, *et al*. Trihexyphenidyl (Artane): a Brazilian study of its abuse. *Subst Use Misuse* 2005; **40:** 473–82.
3. Pullen GP, *et al*. Anticholinergic drug abuse: a common problem? *BMJ* 1984; **289:** 612–13.
4. Goff DC, *et al*. A placebo-controlled trial of trihexyphenidyl in unmedicated patients with schizophrenia. *Am J Psychiatry* 1994; **151:** 429–31.
5. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995.
6. Buhrich N, *et al*. Misuse of anticholinergic drugs by people with serious mental illness. *Psychiatr Serv* 2000; **51:** 928–9.
7. Frauger E, *et al*. Détournement d'usage du trihexyphénidyle (Artane, Parkinane): tendances récentes. *Therapie* 2003; **58:** 541–7.

Effects on the heart. Paradoxical sinus bradycardia developed in a schizophrenic patient after receiving trihexyphenidyl for extrapyramidal effects due to antipsychotic medication.[1] Normal sinus rhythm was restored after trihexyphenidyl was stopped. The patient had previously received trihexyphenidyl and suffered bradycardia which at the time was attributed to haloperidol.

1. Blumensohn R, *et al*. Bradycardia due to trihexyphenidyl hydrochloride. *Drug Intell Clin Pharm* 1986; **20:** 786–7.

Effects on mental function. Oral trihexyphenidyl 2 mg significantly impaired memory function compared with placebo in a study in 13 elderly patients.[1] Impairment of memory has also been noted in patients with Parkinson's disease given antimuscarinics such as trihexyphenidyl.[2] However, impairment may be reversible on stopping the antimuscarinic (see Atropine, p. 1312.2).

1. Potamianos G, Kellett JM. Anti-cholinergic drugs and memory: the effects of benzhexol on memory in a group of geriatric patients. *Br J Psychiatry* 1982; **140:** 470–2.
2. Sadeh M, *et al*. Effects of anticholinergic drugs on memory in Parkinson's disease. *Arch Neurol* 1982; **39:** 666–7.

Overdosage. A 34-year-old woman developed a toxic reaction with widely dilated pupils, dry skin, and visual hallucinations within 24 hours of taking about 300 mg of trihexyphenidyl hydrochloride with suicidal intent.[1] After 3 to 4 days the hallucinations were replaced by illusions; complete recovery occurred after a week, with no special treatment. Death associated with moderate blood concentrations of trihexyphenidyl (0.12 micrograms/mL) has been reported[2] in a schizophrenic patient recovering from a respiratory infection. It was thought possible that he had increased his dose to counteract developing tardive dyskinesia, and that the toxic effects had been exacerbated by respiratory inflammation; there was no evidence of suicidal intent.

1. Ananth JV, *et al*. Toxic psychosis induced by benzhexol hydrochloride. *Can Med Assoc J* 1970; **103:** 771.
2. Gall JAM, *et al*. Death due to benzhexol toxicity. *Forensic Sci Int* 1995; **71:** 9–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trihexyphenidyl as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Withdrawal. A 61-year-old woman who had taken trihexyphenidyl 6 mg daily for a year for Parkinson's disease developed encephalopathy and miosis on two occasions when treatment was abruptly withdrawn.[1] Slowly tapered withdrawal avoided these effects.

1. Johkura K, *et al*. Trihexyphenidyl withdrawal encephalopathy. *Ann Neurol* 1997; **41:** 133–4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Chlorpromazine. For the effect of trihexyphenidyl on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p. 1052.3.

Pharmacokinetics

Trihexyphenidyl hydrochloride is well absorbed from the gastrointestinal tract and has been stated to exert an effect within 1 hour of an oral dose.

Half-life. The reported half-life of trihexyphenidyl has varied according to the assay method used. Values reported when using radioreceptor and chromatographic techniques have ranged from about 1 to more than 24 hours[1] and from 10 to 29 hours,[2] respectively, but the sensitivity and specificity of these methods have been criticised.[3] With a more recently developed radio immunoassay it was found that after oral doses there was an initial elimination phase with an estimated half-life of 5.33 hours followed by a terminal elimination phase with an estimated half-life of 32.7 hours.

1. Burke RE, Fahn S. Pharmacokinetics of trihexyphenidyl after short-term and long-term administration to dystonic patients. *Ann Neurol* 1985; **18:** 35–40.
2. Garbarg S, *et al*. Comparaison pharmacoclinique de deux formes galéniques de trihexyphénidyle. *Encephale* 1983; **IX:** 167–74.
3. He H, *et al*. Development and application of a specific and sensitive radioimmunoassay for trihexyphenidyl to a pharmacokinetic study in humans. *J Pharm Sci* 1995; **84:** 561–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Artane; ***Austral.***: Artane; ***Belg.***: Artane; ***Braz.***: Artane; Triexidyl; ***Canad.***: Apo-Trihex; ***Chile***: Tenvatil; Tonaril; ***Fr.***: Artane; Parkinane; Trihexy; ***Ger.***: Artane; Parkopan; ***Gr.***: Artane; ***Hong Kong***: Adtendyl†; ***India***: Barohexy; Bexol; Dyskinil; Dystonil; Lahexy; Manohexy; Pacitane; Parales; Parnon; ***Indon.***: Arkine; Artane†; Hexymer; ***Israel***: Partane; Rodenal; ***Ital.***: Artane; ***Malaysia***: Aca; Apo-Trihex; ***Mex.***: Hipokinon; Kexidil; ***Neth.***: Artane; ***Pol.***: Parkopan†; ***Port.***: Artane; ***Rus.***: Cyclodol (Циклодол); ***S.Afr.***: Artane†; ***Singapore***: Apo-Trihex; B-Hex; Beahexol; ***Spain***: Artane; ***Swed.***: Pargitan; ***Thai.***: Aca; Acamed; Artane; Pozhexol; Tridyl; ***UK***: Broflex†; ***Ukr.***: Parkopan (Паркопан)†; ***USA***: Trihexy.

Multi-ingredient Preparations. ***India***: Benzyzine; Chlorectil Plus; Cinris Forte; Cizoren Plus; Clozine Forte; Clozine Plus; Combidol; Don Forte; Don Plus; Don-LS; Emetil DS; Emetil Plus; Etores-TR; F Plus; Gencalm Plus; Genrest Plus; Genrest-LS; Halotex; Hexidol Forte; Hexidol Kit; Hexidol Plus; Kaytrix-C; Lacalm Plus; Lacalm; Manocalm Forte; Manocalm Plus; Manodol; Mindol Forte; Mindol Plus; Neocalm Forte; Neocalm Plus; Sycot; Trinicalm Forte; Trinicalm Plus.

Pharmacopoeial Preparations

BP 2014: Trihexyphenidyl Tablets;

USP 36: Trihexyphenidyl Hydrochloride Elixir; Trihexyphenidyl Hydrochloride Extended-release Capsules; Trihexyphenidyl Hydrochloride Tablets.

Tropatepine Hydrochloride *(rINNM)*

Hidrocloruro de tropatepina; SD-1248-17; Tropatepina, hidrocloruro de; Tropatépine, Chlorhydrate de; Tropatepini Hydrochloridum; Тропатепина Гидрохлорид.

3-(Dibenzo[*b*,*e*]thiepin-11(6*H*)-ylidene)tropane hydrochloride.

$C_{22}H_{23}NS,HCl$=370.0

CAS — 27574-24-9 (tropatepine); 27574-25-0 (tropatepine hydrochloride).

ATC — N04AA12.

ATC Vet — QN04AA12.

UNII — 17N1U39U3Z.

Profile

Tropatepine hydrochloride is an antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It is used in the management of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value in tardive dyskinesias. Tropatepine hydrochloride is given orally in usual doses of 10 to 30 mg daily; it is also given intramuscularly or by slow intravenous injection in doses of 10 to 20 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Lepticur.

Antiprotozoals

Amoebic infections, p. 919
Amoebiasis, p. 919
Acanthamoeba keratitis, p. 919
Disseminated amoebic infections, p. 920
Primary amoebic meningoencephalitis, p. 920
Babesiosis, p. 920
Balantidiasis, p. 920
Blastocystis hominis infection, p. 920
Coccidiosis, p. 921
Cryptosporidiosis, p. 921
Cyclosporiasis, p. 921
Gastro-enteritis, p. 921
Giardiasis, p. 921
Infections in immunocompromised patients, p. 921
Isosporiasis, p. 921
Leishmaniasis, p. 922
Malaria, p. 924
Microsparidiosis, p. 924
Pneumocystis pneumonia, p. 924
Toxoplasmosis, p. 924
Trichomoniasis, p. 925
African trypanosomiasis, p. 925
American trypanosomiasis, p. 925

The drugs described in this chapter are those used mainly in the treatment of parasitic protozoal infections. In addition to their use as antiprotozoals, metronidazole and related nitroimidazole derivatives are also important in the treatment of anaerobic bacterial infections. Some veterinary antiprotozoal drugs are included. Drugs used in the treatment of malaria are described in the Antimalarials chapter; some of these are also used in other protozoal infections.

The principal antiprotozoal drugs are listed in Table 1, below.

Choice of Antiprotozoal

Protozoal infections occur throughout the world and are a major cause of morbidity and mortality in some regions. The choice of treatment for the principal protozoal diseases in humans is discussed below.

Amoebic infections

The most common amoebic infection of man is **amoebiasis** caused by infection with the protozoan parasite *Entamoeba histolytica* and related species. Free-living amoebae occur worldwide and are distributed in soil and water. They can also cause disease in man, though these infections are rare. Diseases include:

- **amoebic keratitis** caused by *Acanthamoeba* spp.
- **disseminated amoebic infections** including granulomatous amoebic encephalitis and cutaneous, pulmonary, and nasopharyngeal infections caused by *Acanthamoeba* spp., *Balamuthia mandrillaris* (previously referred to as leptomyxid amoebae), and very rarely by *Sappinia diploidea*
- **primary amoebic meningoencephalitis** caused by *Naegleria fowleri*

Amoebiasis. Amoebiasis[1-3] is a parasitic infection caused mainly by the protozoan *Entamoeba histolytica*. Although about 10% of the world's population is infected with *Entamoeba* spp., most individuals are infected with *E. dispar*, one of 2 non-pathogenic species recognised in humans (the other being *E. moshkovskii*). Transmission of *E. histolytica* is usually by the faeco-oral route and infection results from the ingestion of cysts, usually in contaminated food and water. Amoebiasis occurs throughout the world, but the incidence is higher in developing countries and is closely related to sanitation and socio-economic status.

Colonisation of the bowel lumen with *E. histolytica* usually results in asymptomatic infection, although infected people chronically pass cysts in stools. In about 10% of cases symptomatic (invasive) disease may occur days to years after the initial infection; factors increasing susceptibility to tissue invasion include malnutrition, immunosuppression, and pregnancy. Symptomatic (invasive) amoebiasis may be classified as intestinal or extra-intestinal amoebiasis.

- *Intestinal amoebiasis* comprises two main states, amoebic dysentery and non-dysenteric amoebic colitis; amoeboma, a localised form of intestinal amoebiasis, and amoebic appendicitis may also occur. A few patients may develop fulminant or necrotising amoebic colitis which is associated with a mortality rate of more than 40%.
- The most common form o f *extra-intestinal amoebic disease* is hepatic amoebiasis, which may present as acute non-suppurative disease or as amoebic liver abscess. Amoebic infection is a less common cause of liver abscess than bacterial infection. Amoebiasis may also involve the skin, genito-urinary tract, or organs such as the lungs and brain.

Drugs used in the **treatment** of amoebiasis may be classified according to their site of action as follows:

- *luminal amoebicides* acting mainly in the bowel lumen. Diloxanide furoate is widely used as the luminal amoebicide of choice, although clefamide, etofamide, and teclozan are also effective. Paromomycin and diiodohydroxyquinoline have also been used[1,2] although most oral preparations of halogenated hydroxyquinolines have been withdrawn because of the association between clioquinol and subacute myelo-opticoneuropathy
- *tissue* or *systemic amoebicides* acting mainly in the intestinal wall and liver. These have included the alkaloid emetine, its synthetic derivative dehydroemetine, and the antimalarial chloroquine which acts mainly in the liver
- *mixed amoebicides* acting at all sites of infection, that is within the intestinal lumen and in the intestinal wall and other tissues. These have included metronidazole and other 5-nitroimidazole derivatives (such as ornidazole, secnidazole, and tinidazole). However, because of their rapid absorption from the gastrointestinal tract, the nitroimidazoles are less effective against parasites in the lumen

Patients with proven *E. histolytica* **asymptomatic** amoebiasis should be treated with a luminal amoebicide to prevent transmission of cysts to others and because of the small but definite risk of potentially severe invasive disease.[2,3] The choice of drug is influenced by availability; diloxanide furoate is generally used in the UK while diiodohydroxyquinoline or paromomycin are also used in the USA.[4] Infection with *E. dispar* and probably infection with *E. moshkovskii* do not need treatment.[3] Those with symptomatic intestinal or extraintestinal **invasive** disease should be treated with a 5-nitroimidazole derivative (usually metronidazole), followed by a luminal amoebicide to eradicate any surviving organisms from the lumen of the large intestine and prevent relapse.[1-3] However, a systematic review[5] to evaluate antiamoebic drugs for the treatment of amoebic colitis found that tinidazole was more effective than metronidazole in reducing clinical failure and better tolerated. Uncomplicated cases usually respond to a 5-day treatment course with metronidazole, while more severe infections are treated for 10 days.[3] In cases of **fulminant** or necrotising amoebic colitis and for severely ill patients, broad-spectrum antibacterials are given with a systemic amoebicide to decrease the risk of superinfection with bowel flora and peritonitis.[1-3] Nitazoxanide has been used in mild to moderate intestinal disease.[4] Standard treatment for amoebic **liver abscess** is metronidazole followed by a luminal amoebicide. The majority of patients with amoebic liver abscess defervesce after 3 to 4 days of treatment with metronidazole.[2,3]

In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2.

Table 1. Classification of principal antiprotozoals.

Antimony compounds	*Nitrofurans*
Meglumine antimonate	Furazolidone
Sodium stibogluconate	Nifuratel
	Nifurtimox
Aromatic diamidines	
Pentamidine	*5-Nitroimidazoles*
	Metronidazole
Arsenicals, pentavalent	Nimorazole
Acetarsol	Ornidazole
Tryparsamide	Secnidazole
	Tinidazole
Arsenicals, trivalent	
Melarsoprol	*Miscellaneous*
	Atovaquone
Dichloroacetamides	Benznidazole
Diloxanide	Dehydroemetine
	Eflornithine
Halogenated hydroxyquinolines	Mepacrine
Diiodohydroxyquinoline	Nitazoxanide
	Paromomycin
	Suramin

1. Stanley SL. Amoebiasis. *Lancet* 2003; **361:** 1025–34.
2. Haque R, *et al.* Amebiasis. *N Engl J Med* 2003; **348:** 1565–73.
3. Pritt BS, Clark CG. Amebiasis. *Mayo Clin Proc* 2008; **83:** 1154–9.
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Acanthamoeba keratitis. *Acanthamoeba* keratitis may result from corneal trauma or exposure to contaminated water, but is most commonly associated with the wearing of soft contact lenses as well as the use of home-made sodium chloride solutions for cleaning them. Infection usually occurs in otherwise healthy persons. Rare cases have been associated with laser-assisted *in-situ* keratomileusis. Keratitis is a local infection that typically begins with a foreign-body sensation followed by pain, tearing, photophobia, and blurred vision. The infection may progress to involve the sclera and loss of vision may follow.

If the disease is recognised early it usually responds well to topical **antiamoebic treatment**; severe infection and late-presenting cases may require penetrating keratoplasty.[1,2] A combination of antiamoebic drugs is generally used because the cyst form is highly resistant to therapy and may persist for years. Two weeks may be required before a response is seen, and the total duration of therapy is a minimum of 3 to 4 weeks; some recommend treating for 3 to 4 months,[3] or even longer. Infection can recur after treatment due to persistence of the cystic form.

The first drug used with some success was 0.1% propamidine isetionate applied topically.[1,4] It was used with an aminoglycoside such as neomycin or a neomycin-polymyxin-gramicidin preparation and a cure was achieved in about 50% of cases. However, most cysts are resistant to neomycin and due to surface toxicity and poor *in-vitro* sensitivity,[1,5] neomycin is no longer recommended.[1,6] Since then the biguanide cationic antiseptics, chlorhexidine and polihexanide have also been shown to be effective in a 0.02% concentration against trophozoites and cysts and have become the drugs of choice.[2,3,5,7] Propamidine has been tried with these agents, however, poor cysticidal activity, chronic conjunctival infection, and resistance to some strains of *Acanthamoeba* to propamidine has prompted the suggestion that it should be replaced by another diamidine such as hexamidine.[1] Biguanides may also be used alone,[6] and are particularly effective in early infection.

Other drugs that have been tried include the topical imidazoles; when applied in a 1% solution they may be effective against trophozoites but probably not against cysts.[1,5] They should never be used as monotherapy. Voriconazole 1% eye drops have, however, been effective for salvage therapy.[8] Oral ketoconazole and, to a lesser extent, itraconazole penetrate into the cornea and have been used as adjunctive therapy to polihexanide and chlorhexidine, but the levels obtained in the cornea are probably too low to be trophozoiticidal.[2] Possible new therapies include antineoplastic and antimalarial drugs; the biguanide antidiabetic drugs metformin and phenformin, and the antibacterial ofloxacin have been shown to have activity against trophozoites *in vitro*, but not against cysts.[1]

Topical cycloplegic therapy and oral NSAIDs may be given for **symptomatic management** of pain, although opioid analgesics are often necessary.[2] Some authorities suggest the use of topical NSAIDs.[1] The use of topical corticosteroids to control inflammation remains controversial because they suppress macrophage activity, which is essential in scavenging and destroying the amoeba.[1] It is recommended that the use of corticosteroids should be delayed and limited as much as possible. They may be considered with antiamoebic agents in those patients with severe pain, scleritis, or severe anterior-chamber inflammation.[2,9,10] A retrospective study[9] found that the use of topical corticosteroids was not associated with treatment failure, but was associated with a prolonged course of antiamoebic therapy. In patients with severe scleral involvement, systemic immunosuppressants such as oral corticosteroids, ciclosporin, and azathioprine may be needed.[11]

Acanthamoeba keratitis in contact lens wearers should be **preventable** by good lens hygiene (see Contact Lens Care, p. 1731.2).

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Disseminated amoebic infections. Granulomatous amoebic encephalitis (GAE) and disseminated granulomatous amoebic disease (involving the skin, lungs, and sinuses) are caused by infection with free-living amoebae, usually *Acanthamoeba* spp. or sometimes *Balamuthia mandrillaris* (previously referred to as leptomyxid amoebae). They are opportunistic infections occurring mainly in debilitated or immunocompromised individuals. In GAE the protozoa spread haematogenously to the CNS from the sinuses, lungs, or skin lesions and produce focal neurological deficits that progress over days or weeks to a diffuse meningoencephalitis. The infection is usually fatal and most cases have been diagnosed postmortem so little is known about effective treatments, although many drugs have been tried.

Drugs that have been used in combinations to **treat** disseminated and CNS infections caused by *Acanthamoeba* spp. include co-trimoxazole, pentamidine, sulfadiazine, flucytosine, rifampicin, and azoles such as ketoconazole, itraconazole, or fluconazole;[1,2] susceptibilities of species and strains appear to vary widely, and susceptibility testing is advisable.

Successful treatment has been reported in 2 apparently immunocompetent children with chronic meningitis caused by *Acanthamoeba* after prolonged treatment with oral co-trimoxazole, rifampicin, and ketoconazole.[3] Successful treatment has also been reported with topical and oral miltefosine in an immunocompromised patient with disseminated acanthamoebiasis, amoebic encephalitis, and underlying miliary tuberculosis and tuberculous meningitis; the patient initially failed treatment with parenteral co-trimoxazole (later changed to oral sulfadiazine), fluconazole, liposomal amphotericin B, and flucytosine.[4]

Similar drugs have been used to treat CNS infections caused by *B. mandrillaris* and 2 patients have been successfully treated with pentamidine, sulfadiazine, flucytosine, fluconazole, a macrolide (such as azithromycin or clarithromycin), and a phenothiazine (such as thioridazine or trifluoperazine).[5]

Clinical responses to chemotherapy have also been reported in a few patients[6-9] with disseminated infection but no evidence of CNS involvement. Disseminated *Acanthamoeba* infection in an immunocompromised patient was successfully treated with intravenous pentamidine followed by maintenance therapy with oral itraconazole.[6] Skin lesions were treated topically with chlorhexidine and ketoconazole.[1] Clinical improvement of disseminated acanthamoebiasis in a patient with AIDS followed treatment with intravenous pentamidine and oral flucytosine; an infant with HIV infection was treated with fluconazole, flucytosine, and sulfadiazine.[7] A lung transplant patient with disseminated acanthamoebiasis was also successfully treated with pentamidine, flucytosine, and azithromycin, plus topical chlorhexidine and ketoconazole.[8] A case of granulomatous dermatitis secondary to *Acanthamoeba* infection in a lung transplant recipient has been successfully treated with a prolonged course of amphotericin B lipid complex and voriconazole.[9]

The use of RNA interference aimed at *Acanthamoeba* genes, using a combination of short-strand interfering RNAs (siRNAs), has been proposed following promising results *in vitro*.[10]

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Primary amoebic meningoencephalitis. Primary amoebic meningoencephalitis is a rare infection usually caused by the free-living amoeba *Naegleria fowleri*. It occurs mainly in healthy children and young adults and is usually associated with swimming in warm fresh water. The protozoa invade the CNS directly through the nasal mucosa to produce a meningoencephalitis that is usually rapidly fatal (7 to 10 days).

A few cases of successful treatment have been reported, and have generally involved intravenous[1-5] and usually intrathecal[1-3] amphotericin B; some patients were also given oral rifampicin,[2-5] intravenous and intrathecal miconazole,[2] intravenous chloramphenicol,[5] or ornidazole.[4]

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Babesiosis

Babesiosis (piroplasmosis) is an infection caused by intraerythrocytic protozoa of the *Babesia* genus, which are transmitted to man by the bite of infected *Ixodes* ticks. Transmission by blood transfusion has also been reported. *Ixodes scapularis*, one of the ticks that may cause babesiosis, may also be infected with, and transmit, *Anaplasma phagocytophilum* and/or *Borrelia burgdorferi* and therefore the bite from this tick may lead to babesiosis, human granulocytic anaplasmosis (see Ehrlichiosis, p. 179.1), or Lyme disease (p. 190.1) as a single infection or as a co-infection.[1] Babesiosis occurs worldwide in animals. In the US, human infection is most commonly due to *B. microti*; the disease is much rarer in Europe where it is usually caused by *B. divergens* or *B. bovis*.[1-3] Infection with the babesia-like piroplasms WA-1 and MO-1 has also been reported in the USA.[1,2]

Clinical features of babesiosis acquired in the USA differ from that acquired in Europe. Infection in the USA is often asymptomatic and self-limiting, but may produce prolonged severe viral-like illness with fever and haemolytic anaemia, particularly in patients who are asplenic, elderly, debilitated, or immunocompromised (including those infected with HIV). Symptoms include chills, sweating, myalgia, arthralgia, weakness, fatigue, anorexia, nausea, vomiting, jaundice, and headache. The most common complications are heart failure, disseminated intravascular coagulation, acute respiratory distress syndrome, and renal failure.[1-3] Co-infection with *B. microti* and *Borrelia burgdorferi* has resulted in more severe symptoms. In Europe, infections have mostly been described in asplenic persons, in many of whom the infection was rapidly fatal. Clinical features include severe haemolytic anaemia, jaundice, pulmonary oedema, and renal failure.

There is no established specific **treatment** for babesiosis. Treatment is not recommended for asymptomatic patients although all symptomatic patients should be treated with antibacterials to prevent the development of complications.[1] For serious infections, supportive therapies include red blood cell exchange transfusions to reduce parasitaemia. *Clindamycin with quinine* was the first regimen used[4] for the treatment of *B. microti* infections, but has been associated with significant toxicity. A prospective randomised study[5] in 58 patients found *azithromycin with atovaquone* to be as effective as clindamycin and quinine and associated with less toxicity. *Azithromycin with quinine* has been reported to be effective in 2 patients who had not responded to quinine plus clindamycin.[6,7] *Pentamidine* has also been reported to produce clinical improvement in patients with *B. microti* infection,[8] but the efficacy and safety of pentamidine has been questioned.[9] *Other drugs* that have been tried with variable results include chloroquine, primaquine, pyrimethamine, sulfadiazine, and tetracycline.[2,3]

The Infectious Diseases Society of America[1] recommends a combination of either clindamycin plus quinine or atovaquone plus azithromycin, both orally for 7 to 10 days; the combination of intravenous clindamycin plus oral quinine should be used in severe babesiosis. In immunocompromised patients higher doses of azithromycin may be used; they are prone to relapsing disease, and treatment should be given for 6 weeks or more, including 2 weeks after parasites are no longer detectable in blood smears.[10] Partial or complete exchange transfusion may also be given. Patients with persistent infection should be re-treated.

Patients *co-infected* or suspected to be co-infected with *Anaplasma phagocytophilum* and/or *Borrelia burgdorferi* should also be given doxycycline for 10 days.[1,3] For information on the treatment of co-infected patients see Lyme Disease, p. 190.1. In *B. divergens* infections, treatment is complicated by the rapid progression of the disease. Antiprotozoal and antimalarial drugs have been tried with limited success, although pentamidine with co-trimoxazole was successful in a patient,[11] and a marked reduction in parasite load was seen in a patient treated with pentamidine plus exchange transfusions.[12] The combination of clindamycin plus quinine with exchange transfusion has also been suggested.[2]

Preventive measures against babesiosis include the use of tick repellents, physical protection, and prompt removal of attached ticks.[1]

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Balantidiasis

Balantidiasis is an uncommon infectious disease of the large intestine caused by a ciliated protozoan, *Balantidium coli*, that frequently infects pigs. Humans and usually resistant but may become infected by eating food or drinking water that has been contaminated by human or animal faeces containing *B. coli* cysts, or by handling infected animals. Those with poor nutrition and achlorhydria appear more vulnerable to infection.

Most cases of balantidiasis are asymptomatic and the organism lives in the large intestine as a luminal commensal, however, asymptomatic people can transmit the disease. Those with symptomatic infections may develop a chronic illness characterised by intermittent diarrhoea, abdominal cramps, and weight loss; colitis with mucus and bloody stools occurs less commonly. Colonic ulceration resulting in a syndrome resembling amoebic dysentery may occur in some individuals, while others may develop a fulminating form of balantidiasis. Untreated cases have proved fatal.

Oral tetracycline for 10 days is the **treatment** of choice; metronidazole, diiodohydroxyquinoline,[1] paromomycin, or nitazoxanide are alternatives. Treatment courses of up to 20 days may be required in immunosuppressed patients, including those who are infected with HIV.

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Blastocystis hominis infection

There is controversy over whether the protozoan parasite *Blastocystis hominis* is a pathogen or a harmless commensal of the intestinal tract. It has been reported both in immunocompetent and immunocompromised subjects,[1,2] with transmission probably by the faeco-oral route. Diarrhoea and other gastrointestinal symptoms have been ascribed to the organism.

Treatment with standard antiprotozoals, especially metronidazole, has had variable success; metronidazole resistance may occur.[3,4] Co-trimoxazole was reported to have eliminated *B. hominis* from the stools of all but one of 47 otherwise healthy subjects with diarrhoea in one study,[5] and similarly in 36 of 38 children, and 14 of 15 adults, in another.[6] In patients heavily infected with *B. hominis*, only 4 of 12 treated with metronidazole and 2 of 9 given co-trimoxazole achieved eradication of the organism.[7] Diiodohydroxyquinoline,[8] nitazoxanide,[4,9] or paromomycin[4] may be effective in some cases.

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Coccidiosis

Coccidiosis is a term sometimes applied to infections with protozoa of the order *Eucoccidiorida.* The predominant coccidian infections in man are caused by *Cryptosporidium* (below), *Cyclospora cayetanensis* (below), *Isospora* (below), *Plasmodium* (see Malaria, p. 644.1), and *Toxoplasma* (p. 924.2). Coccidian protozoa, mainly *Eimeria,* cause economically important infections in domesticated animals.

Cryptosporidiosis

Cryptosporidiosis[1] is a gastrointestinal infection caused by species of the coccidian protozoan parasite *Cryptosporidium.* It has a worldwide distribution and occurs in many animal species as well as in man. Infection is acquired through ingestion, and perhaps inhalation, of oocysts. Infection in immunocompetent individuals usually causes a self-limiting watery, non-bloody diarrhoea lasting up to 2 weeks. In immunocompromised patients and particularly AIDS patients with a CD4+ count below 100 cells/microlitre, there may be profuse and persistent diarrhoea (for 2 months or longer), profound weight loss, and severe abdominal pain, and the infection may be life-threatening. Other sites of infection include the respiratory and biliary tracts.

There is currently no consistently effective specific **treatment**[2,3] and priority should be given to maintaining hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Beneficial responses to octreotide have been reported in a few cases,[4-6] but US guidelines for the prevention and treatment of opportunistic infection in HIV-infected patients[7] consider that octreotide is no more effective than oral antidiarrhoeals and its use is not recommended. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2. In patients with AIDS the severity of the infection may be controlled if the immune function is improved with HAART,[2,3,7,8] but where this is not possible, therapy with an antimicrobial and an antidiarrhoeal drug continues to be standard.[2] Several drugs have been studied in small clinical studies; for nitazoxanide, paromomycin,[7,8] spiramycin,[7] and azithromycin,[9,10] benefits were at best moderate,[2] although evidence is perhaps best for nitazoxanide,[11] particularly in patients not infected with HIV.[3] Other treatments reported to have produced benefit in a few patients include hyperimmune bovine colostrum,[12-16] eflornithine,[17] rifabutin or rifaximin,[3] or normal immunoglobulin with high cryptosporidium antibody titres.[18]

Guidelines for the treatment of opportunistic infection in HIV-infected patients in the USA suggest that, in addition to optimising the HAART regimen, the addition of nitazoxanide[7,8] or alternatively paromomycin[7] therapy may be considered; azithromycin[8] is not recommended.

Clarithromycin and rifabutin may be useful for disease prophylaxis,[19] although the efficacy of clarithromycin has been questioned.[20] Guidelines for the prevention and treatment of opportunistic infection in HIV-infected patients in the USA[7,8] consider that the data on these drugs are insufficient to recommend their use for chemoprophylaxis.

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Cyclosporiasis

An organism originally described as cyanobacterium-like or coccidian-like bodies, but now identified as the coccidian protozoan *Cyclospora cayetanensis,* has been reported to be a cause of diarrhoea in both immunocompromised and immunocompetent patients. Infection results from ingestion of spores or oocysts in contaminated food or water and can result in diarrhoea, nausea, vomiting, abdominal cramps, loss of appetite, and flu-like symptoms. In immunocompetent patients, infection may be asymptomatic or self-limiting while immunocompromised patients may develop severe or persistent symptoms. Prolonged *C. cayetanensis* infection has been associated with various extraintestinal complications including biliary disease, acalculous cholecystitis, Guillain-Barré syndrome, and reactive arthritis.

Successful **treatment** of cyclosporiasis has been reported with oral co-trimoxazole;[1-4] treatment is usually given for 7 to 10 days, but HIV-infected patients can relapse after treatment and higher doses[4] or long-term suppressive treatment may be required. Alternative treatments have not yet been found for those allergic to sulfonamides.[1,3] However, a small, randomised study[2] comparing co-trimoxazole and ciprofloxacin for treatment of and secondary prophylaxis for *Cyclospora* infection in HIV infected patients found ciprofloxacin to be moderately effective, but less active than co-trimoxazole. Successful use of nitazoxanide has also been reported.[5]

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Gastro-enteritis

Although bacteria and viruses are responsible for many cases of infective diarrhoea, protozoal infections are also a cause of diarrhoea,[1,2] which can be severe (especially in immunocompromised patients, including those with AIDS). Patients with diarrhoea lasting for more than 7 days should be tested for protozoal parasites.[3] In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly.[3] Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2. Specific therapy with antiprotozoals may also be necessary to control enteric protozoal infections.

For the management of the protozoal infections that are generally associated with diarrhoea, see under Amoebiasis (p. 919.1), Balantidiasis (p. 920.3), *Blastocystis hominis* infections (p. 920.3), Cryptosporidiosis (above), Cyclosporiasis (above), Giardiasis (below), Isosporiasis (below), and Microsporidiosis (p. 924.1).

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Giardiasis

Infection with *Giardia intestinalis* (*G. duodenalis, G. lamblia; Lamblia intestinalis*) is one of the commonest intestinal protozoal infections throughout the world, especially in areas with poor sanitation and unsafe water. Infection is acquired by oral ingestion of *Giardia* cysts, either from direct contact with infected animals or humans, or by ingestion of water and foodstuffs contaminated by the faeces of infected animals or humans.

Many infected people are asymptomatic and most infections are self-limited. However, asymptomatic people may still act as carriers. Symptomatic giardiasis is usually characterised by diarrhoea, fatigue, abdominal cramps, bloating, nausea, and weight loss. Symptoms usually improve in 2 to 6 weeks but some people have chronic symptoms. Malabsorption of fat, lactose, and vitamins A and B_{12}, and failure of children to thrive have been reported in those with chronic giardiasis.

Priority in the **management** of acute diarrhoea of any aetiology is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2.

One of the most effective antiprotozoal treatments is metronidazole or another nitroimidazole derivative such as tinidazole,[1-3] ornidazole, and secnidazole.[1] Nitazoxanide is also effective[4-6] and some consider it a drug of choice.[3] Other alternatives include furazolidone, and mepacrine.[1,3] Paromomycin has been suggested;[3] although it is less effective than other drugs, it is not absorbed systemically and may be a useful alternative in resistant infection and during pregnancy.[1] The benzimidazoles (albendazole and mebendazole) have been tried with mixed results, but they might be useful in the developing world where their broad antiparasitic effect would be an advantage,[1] and some suggest[7] that albendazole is comparable in efficacy to metronidazole. Treatment may sometimes need to be repeated, possibly due to resistance or relapse,[1] and drug combinations such as a nitroimidazole with mepacrine[1,8] have been reported to be of value in such cases.

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Infections in immunocompromised patients

Patients with a defective immune system are at particular risk of infection. Primary immune deficiency is rare, whereas secondary deficiency is more common: immunosuppressive therapy, cancer and its treatment, HIV infection, and splenectomy may all cause neutropenia and impaired humoral and cellular immunity in varying degrees. The risk of infection is linked to the duration and severity of neutropenia. Most protozoal infections present in a more severe form in immunocompromised patients than in immunocompetent patients. Those of particular concern in patients with HIV infection include Cryptosporidiosis (above), Isosporiasis (below), Leishmaniasis (p. 922.1), Microsporidiosis (p. 924.1), and Toxoplasmosis (p. 924.2).

Detailed guidelines for the treatment and prevention of opportunistic infections (including some protozoal infections) among HIV-infected adults, adolescents, and children have been developed in the USA.[1,2]

1. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 17/09/13)
2. CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR* 2009; **58** (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 05/08/10)

Isosporiasis

Isosporiasis is a coccidian protozoal infection of the gastrointestinal tract caused by *Cystoisospora belli,* formerly

called *Isospora belli*. It has a worldwide distribution but occurs more frequently in tropical and subtropical regions. Oocysts are excreted in faeces and infection is acquired when sporulated oocysts are ingested.

In immunocompetent individuals the infection is usually mild and self-limiting but in immunocompromised patients, including those with AIDS, the infection can vary from a chronic and intermittent illness to a severe, life-threatening diarrhoeal disease.

Treatment is usually with co-trimoxazole for 10 days.[1-3] Immunocompromised patients may need higher doses and treatment for up to 3 to 4 weeks.[2,3] Ciprofloxacin may be an alternative in those unable to tolerate co-trimoxazole, although it is somewhat less effective.[1,2] Pyrimethamine has been used successfully in individual patients with sulfonamide sensitivity.[2] In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2.

HIV-infected patients with a CD4+ count below 200 cells/microlitre should receive long-term suppressive therapy (secondary **prophylaxis**) with co-trimoxazole. Pyrimethamine may be used in patients allergic to sulfonamides; ciprofloxacin may be given as an alternative.[2] Secondary prophylaxis may be stopped in those patients taking effective antiretroviral therapy who have a CD4+ count above 200 cells/microlitre for at least 6 months.[2]

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2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://aidsinfo.nih.gov/contentfiles/adult_oi.pdf (accessed 23/08/13)
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Leishmaniasis

Leishmaniasis[1,2] is caused by parasitic protozoa of the genus *Leishmania*; the species involved depends on the geographical distribution. It occurs throughout Africa, the Middle East, Central Asia, and the Mediterranean (Old World leishmaniasis), and throughout Central and South America (New World leishmaniasis). In endemic areas there is generally a reservoir of disease in a mammalian host, often dogs or rodents. The usual vectors are sandflies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World. Some species of *Leishmania* may also be transmitted by blood transfusions or contaminated needles; congenital transmission has been reported.

Leishmaniasis ranges from self-limiting, localised, cutaneous ulcers to widely disseminated progressive disease with involvement of the reticuloendothelial system, and can be categorised as:

- cutaneous (below)
- mucocutaneous (mucosal) (p. 923.1)

or

- visceral (p. 923.1)

Incubation periods can be prolonged, with clinical features not appearing until several months or even years after the primary infection.

Leishmaniasis has also emerged as an opportunistic infection in immunocompromised patients (including HIV and AIDS), in whom it is particularly difficult to treat. For further information see also p. 923.3. The most common clinical presentation of leishmaniasis in persons with AIDS is visceral disease, but the distribution varies geographically; in Europe visceral disease has been reported in 95% of cases, while in Brazil, mucocutaneous (43%) and cutaneous (20%) are common. Clinical manifestations in patients with AIDS may be atypical and severe, and relapse after treatment is common. Since the introduction of HAART the incidence of leishmaniasis has decreased substantially in developed countries, but co-infection is a growing problem in Asia and Africa.

In endemic areas an integrated approach to controlling leishmaniasis involves case detection and treatment of patients, vector and animal reservoir control, environmental management to reduce suitable vector habitats, and personal protection against sandfly bites including the use of insect repellents and bednets. Strategies aimed at controlling malaria are believed to have reduced leishmaniasis transmission dramatically.

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Cutaneous leishmaniasis. Cutaneous leishmaniasis is caused by various species of *Leishmania*. Old World disease is normally caused by *L. tropica, L. major*, or *L. aethiopica*, although cutaneous lesions due to *L. infantum* and *L. donovani* have been reported. New World cutaneous leishmaniasis (American cutaneous leishmaniasis) is caused by many species and subspecies of *Leishmania* including *L. braziliensis, L. mexicana, L. panamensis*, and *L. peruviana*. Worldwide, about 90% of cases occur in Algeria, Pakistan, Saudi Arabia, Syria, Afghanistan, Brazil, and Peru. In general, New World forms tend to be more severe and longer lasting than Old World forms.

Cutaneous leishmaniasis has been categorised into different clinical forms:

- *localised* disease is confined to the skin and lesions are mainly on exposed parts of the body. The disease ranges from single, self-healing lesions which are troublesome and unsightly but not a threat to life, to multiple, deep, and destructive ulcers which cause considerable disfigurement and disability. A 'classical' lesion starts as a nodule at the site of inoculation. A crust develops centrally which may fall away exposing an ulcer which heals gradually. Satellite nodules at the edge of the lesion are common
- *diffuse* cutaneous leishmaniasis occurs occasionally after infection with *L. aethiopica* or members of the *L. mexicana* complex and involves dissemination of the disease from the original site of infection to distant skin sites, typically the face and exterior surfaces of the limbs. The lesions resemble lepromatous leprosy, do not heal spontaneously, and are resistant to treatment
- *leishmaniasis recidivans* is a lupoid or tuberculoid form caused by infection with *L. tropica*. This chronic disease often occurs as slowly progressive, destructive and disfiguring lesions on the face which are very resistant to most forms of therapy

There is no consensus on the optimum **treatment** for cutaneous leishmaniasis[1] and a systematic review[2] on the treatment of Old World cutaneous leishmaniasis found 49 randomised controlled studies covering at least 19 different treatments. Current methods include physical interventions, topical ointments, local injection, and systemic anti-protozoals;[3] vaccines containing *Leishmania* spp. are under investigation, see p. 2397.2. The decision to treat depends upon the site and extent of the lesions and the likelihood of dissemination. Small lesions, particularly in Old World cutaneous leishmaniasis, may be left untreated if they are not troublesome to the patient; most lesions heal spontaneously within 2 to 15 months depending on the infecting species. The aim of treatment is to accelerate cure, reduce scarring, and prevent parasitic dissemination or relapse. Treatment is usually given to those patients with persistent lesions (6 months or more), lesions located over joints or on the face, or multiple or large lesions. Systemic therapy should be given to those with large and disfiguring lesions and those caused by *L. braziliensis* or other New World *Leishmania* species associated with mucocutaneous disease. Healing occurs slowly and may be incomplete at the end of a treatment course; patients who fail to respond after the initial course may be given a second or third treatment course of the same drug or treatment with an alternative drug. Drugs mainly used for the treatment of cutaneous leishmaniasis include:[1,2,4]

- intralesional, intramuscular, or intravenous pentavalent antimonials (meglumine antimonate, sodium stibogluconate)
- oral azoles
- topical paromomycin
- oral miltefosine
- intramuscular pentamidine

Old World cutaneous leishmaniasis. The pentavalent antimonials have been widely used and are the current mainstays of systemic treatment. Lesions at exposed sites that are small and few in number have been successfully treated with intralesional pentavalent antimonials.[3,5,6] Oral azole antifungals have been investigated for potential use in cutaneous leishmaniasis. Ketoconazole given for 4 to 6 weeks has been reported to be effective in about 70% of patients with *L. major* infections, but is not effective against infections caused by *L. tropica* and *L. aethiopica*.[7,8] Itraconazole has been found to be effective[9,10] and a systematic review[2] reported that for *L. tropica* infections there was reasonable evidence that a 6-week itraconazole regimen was more effective than placebo. Similarly a 6-week course of fluconazole was more effective than placebo for infections caused by *L. major*.[11] Conventional amphotericin B is an effective alternative, but has been associated with substantial toxicity and there is little experience with liposomal amphotericin B. The use of oral miltefosine is being investigated[1] and there is a case report of successful treatment in a patient with infection caused by *L. major*.[12] A small study[13] in Iran found oral miltefosine to be at least as good as intramuscular meglumine antimonate for the treatment of infections caused by *L. major*; another retrospective, observational study[14] also reported successful treatment with oral miltefosine of *L. major* infection acquired in northern Afghanistan. Topical paromomycin has been studied with variable results;[3,15-18] the vehicle may affect benefit. A systematic review[2] reported that for *L. major* infections there was reasonable evidence that topical paromomycin (15%) with methylbenzethonium (12%) twice daily for 28 days was more effective than placebo. Oral nitazoxanide has also been tried.[19] Local cryotherapy or, alternatively, application of heat to bring the temperature of the lesion to about 40 degrees which may aid healing have been tried for both Old World[20] and New World leishmaniasis.[3] Some suggest a step-wise approach to treatment of Old World cutaneous leishmaniasis.[21] They propose that patients with single, small lesions of short duration (less than 6 months) may be treated with cryotherapy, while those with multiple, atypical, large or extensive lesions, recidivans-type lesions, and relapsed cases should be treated with a combination of systemic and topical treatments. Combination therapies found to be effective are topical imiquimod (5%) with either oral dapsone or oral itraconazole, and cryotherapy with oral itraconazole.[21]

New World cutaneous leishmaniasis. Disease caused by *L. mexicana* may be treated with a parenteral pentavalent antimonial for 10 days, while disease caused by other species is treated for 20 days.[1] (However, a systematic review,[22] while noting the poor quality of the evidence, failed to find a significant difference in cure rates of *L. braziliensis* or *L. panamensis* infections when treated for 10 versus 20 days with parenteral antimonials.) In regions where the risk for mucosal disease is very low, topical treatment with paromomycin sulfate 15% plus methylbenzethonium chloride 12% has produced promising responses;[23,24] but in Columbia, the addition of topical paromomycin did not augment the clinical response to a short course of treatment with parenteral meglumine antimonate.[25] The addition of topical imiquimod to a standard treatment regimen with parenteral meglumine antimonate accelerated healing of lesions and decreased scar prominence in patients who had failed an initial course of antimony therapy[26] and in those with newly diagnosed disease.[27] Patients treated only with imiquimod cream all relapsed after treatment was stopped.[27] Results for the use of oral miltefosine have varied. A placebo-controlled study[28] found oral miltefosine to be effective (91%) in Columbia but much less effective in Guatemala (53%). Another study[29] in Bolivia reported that cure rates with miltefosine (88%) were similar to those with an intramuscular pentavalent antimonial (94%) in the treatment of infection caused by *L. braziliensis*. The authors concluded that oral miltefosine was more effective for *L. braziliensis* in Bolivia than for *L. braziliensis* in Guatemala. A small study[30] in Venezuela reported good initial cure rates with oral miltefosine given daily for between 75 and 218 days in patients with diffuse cutaneous leishmaniasis; however, most patients developed new lesions after treatment was stopped. Another small study[31] in Brazil reported that high-dose oral fluconazole, given daily for a median duration of 6 weeks, was effective for infections caused by *L. braziliensis*. There is limited and sometimes inconsistent evidence of benefit from the use of oral allopurinol or oral pentoxifylline as an adjuvant to parenteral antimonial therapy.[22]

Among the **non-specific therapies** tried in cutaneous leishmaniasis, topical application of the nitric oxide donor *S*-nitroso-*N*-acetylpenicillamine (SNAP)[32] and intralesional injection of hypertonic sodium chloride solution[33] have produced beneficial responses. Immunomodulation using leishmania antigens mixed with BCG,[34] or interferon gamma,[35] has produced encouraging results.

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Mucocutaneous leishmaniasis. Mucocutaneous leishmaniasis of the New World (espundia) is most commonly caused by *L. braziliensis* with about 90% of cases occurring in Brazil, Bolivia, and Peru. In mucocutaneous leishmaniasis the primary lesions do not heal spontaneously. Metastatic spread to the mucosa may occur during the presence of the primary lesion or up to 30 years later. The nasal mucosa is always affected. Ulceration and erosion progressively destroy the soft tissue and cartilage of the oronasal/pharyngeal cavity. Mutilation is severe and secondary bacterial infection is frequent and can be fatal.

The most commonly used drugs for the **treatment** of mucocutaneous leishmaniasis are:[1-3]

- intramuscular or intravenous pentavalent antimonials (meglumine antimonate, sodium stibogluconate)
- intravenous amphotericin B (conventional and liposomal)

Mucocutaneous leishmaniasis responds poorly to treatment and relapses are common. Initial treatment with pentavalent antimony for 28 days usually results in a cure in 75% of mild cases.[1] Failure to respond is an indication to use amphotericin B[1] or pentamidine, but toxicity limits the use of the latter. A non-randomised study[4] in 72 Bolivian patients given oral miltefosine daily for 28 days reported a cure rate of 83% in those who had mild disease (affecting nasal skin and nasal mucosa) and 58% in those with more extensive disease (involving the palate, pharynx, and larynx); treatment was at least as effective as a course of parenteral amphotericin B. Mucosal disease in Old World leishmaniasis is much less common than visceral or cutaneous forms, but treatment with antimony compounds or ketoconazole has been described.[5]

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Visceral leishmaniasis. Visceral leishmaniasis[1-4] is caused by *L. donovani* in the Indian subcontinent, Asia, and Africa and by *L. infantum* or *L. chagasi* elsewhere in the New and Old World. The majority of cases occur in Bangladesh, Brazil, Ethiopia, India, Nepal, and Sudan. The incubation period typically varies from 3 to 8 months, and many infections result in sub-clinical or self-limiting disease. Fever, malaise, shivering or chills, weight loss, anorexia, and discomfort in the left hypochondrium are common; there is often non-tender splenomegaly with or without hepatomegaly, wasting, pallor of mucous membranes, anaemia, leucopenia, and lymphadenopathy. Continued deterioration can lead to potentially fatal secondary infection. Darkening of the skin of the face, hands, feet, and abdomen (kala-azar = black sickness) is uncommon and has only been described in patients from the Indian subcontinent. Rare complications can include severe acute haemolytic anaemia, acute renal damage, and severe mucosal haemorrhage.

A small percentage of patients in India and about 50% of those in the Sudan develop post-kala-azar dermal leishmaniasis after recovery from visceral leishmaniasis caused by *L. donovani* and such patients represent a human reservoir for the disease. Longer treatment courses are needed in Indian post-kala-azar dermal leishmaniasis.

The most commonly used drugs for the **treatment** of visceral leishmaniasis are:[1-3]

- intramuscular or intravenous pentavalent antimonials (meglumine antimonate, sodium stibogluconate)
- intravenous amphotericin B (conventional, liposomal and lipid complex formulations)
- intramuscular paromomycin
- oral miltefosine
- intramuscular or intravenous pentamidine

The pentavalent antimonials, given daily for 28 days, are the traditional first-line drugs for the treatment of visceral leishmaniasis.[1-4] Patients relapsing after the initial course of treatment may be given a further course, or treated with an alternative drug. There is growing evidence that responsiveness to the antimonials is declining and they are no longer effective in some parts of India.[5]

The use of pentavalent antimonials has also declined in Europe, the USA, and other developed countries where treatment with liposomal amphotericin B is preferred.[1,2,4] The conventional formulation of amphotericin B is also highly effective,[6] but lipid formulations of amphotericin B are better tolerated than conventional amphotericin B, and are likely to be preferred when the toxicity and duration of therapy with conventional forms would compromise patient compliance.

Intramuscular paromomycin has been used alone[7-9] or with a pentavalent antimonial[3,10] and could be an effective alternative for pentavalent antimonials or amphotericin B. Combination treatment with a single dose of liposomal amphotericin B followed by 10 days of paromomycin was found to have a cure rate of 97.5% in patients treated in Bihar, India, where visceral leishmaniasis is more difficult to treat. The combination of paromomycin for 10 days plus oral miltefosine (see below) for 10 days was found to have a cure rate of 98.7%.[11]

Miltefosine is the first oral preparation shown to be effective against Indian visceral leishmaniasis,[12-14] including infections in children[15,16] and those previously treated with pentavalent antimonials.[14] Combination treatment with a single dose of liposomal amphotericin B followed by 7 to 14 days of miltefosine was found to be effective in more than 95% of patients treated in Bihar.[11,17] Longer treatment courses with miltefosine have also been successfully used in the treatment of post-kala-azar dermal leishmaniasis in Bihar.[18]

Pentamidine has been used as a second-line drug but its usefulness as alternative first-line therapy is doubtful[19] given its toxicity, increasing failure rates, and slow disease response. It has been suggested as an alternative for long-term secondary prophylaxis in patients with HIV infection.[20]

Sitamaquine is an orally active 8-aminoquinoline analogue that is under investigation.[3,4] Oral azoles (ketoconazole, itraconazole, and fluconazole) and allopurinol have weak activity against *Leishmania* but have not been found to be effective when used as single-drug therapy.[3] Another line of investigation has been to boost the immune response to the parasite by adding interferon gamma to conventional treatment, although results have been variable.[21-24]

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Treatment of leishmaniasis in HIV co-infected patients. For HIV-infected patients with *visceral leishmaniasis*, the efficacy of conventional, liposomal, and lipid complex formulations of amphotericin B appears to be similar to that of the pentavalent antimonials, however, liposomal amphotericin B is regarded by many as the drug of choice.[1] Alternative treatments include miltefosine and paromomycin.[1] A study[2] in Ethiopia found miltefosine to be safer but less effective than sodium stibogluconate in HIV co-infected patients. Oral miltefosine was given to 39 patients with both leishmaniasis and HIV who were resistant to, or had repeatedly relapsed after, treatment with other drugs (usually amphotericin B). Initial parasitological cure was achieved in 16 patients (41%), and 9 patients (23%) had initial improvement in both parasitological and clinical status. A similar cure and improvement rate was achieved in patients who were re-treated with additional courses of miltefosine.[3] For HIV-infected patients with *cutaneous, mucocutaneous, disseminated cutaneous leishmaniasis*, and localised cutaneous disease caused by *L. braziliensis*, US guidelines[1] recommend first-line parenteral treatment with liposomal amphotericin B or a pentavalent antimonial. Alternative drugs for cutaneous leishmaniasis are miltefosine, topical paromomycin, intralesional pentavalent antimonials, and local heat therapy.[1] Patients who fail to respond to initial therapy or have a relapse after initial treatment may be given a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy.[1]

Relapse after treatment is common, therefore US guidelines[1] recommend secondary prophylaxis with an effective antileishmanial drug (given at least every 2 to 4 weeks), particularly for patients with visceral leishmaniasis and CD4+ count less than 200 cells/microlitre. US guidelines note that there are insufficient data to provide a recommendation as to when secondary prophylaxis can be stopped, but that it might be considered after a sustained (more than 3 to 6 months) increase in the CD4+ count to levels more than 200 to 350 cells/microlitre after starting treatment with HAART.[1]

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Malaria

For a discussion of malaria, its prophylaxis and treatment, see p. 644.1.

Microsporidiosis

Microsporidia are obligate intracellular spore-forming protozoal parasites. They were mainly regarded as a cause of disease in nonhuman species but some genera, including *Brachiola, Encephalitozoon, Enterocytozoon, Microsporidium, Nosema, Pleistophora, Trachipleistophora,* and *Vittaforma* spp., are now recognised as human pathogens. Transmission is believed to be mainly faeco-oral although inhalation and direct inoculation also occur. Infections usually occur only in immunocompromised patients and in particular those with AIDS and a CD4+ T lymphocyte count of less than 100 cells/microlitre. However, infections have also been reported in non-HIV-infected individuals including children, the elderly, and organ transplant recipients. Small bowel infection with *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* have been reported in AIDS patients as causes of chronic diarrhoea and weight loss. Other manifestations of microsporidiosis in AIDS include keratoconjunctivitis, respiratory-tract infections, renal and urinary-tract infections, encephalitis, peritonitis, cholangitis, granulomatous hepatitis, and disseminated myositis.

There is no established treatment[1-3] and supportive care should be given to maintain hydration and correct electrolyte loss. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2. In patients with AIDS the best treatment is improvement of immune function with HAART.[2,3] Beneficial responses have been reported with albendazole[4-8] and US guidelines for the treatment of opportunistic infections in HIV-infected patients recommend it for treatment of intestinal and disseminated infections caused by microsporidia other than *E. bieneusi* and *Vittaforma corneae*.[2,3] Itraconazole plus albendazole may be useful for disseminated disease.[2] There have also been reports of successful treatment of *E. bieneusi* with nitazoxanide[9] and fumagillin[10,11] (and its synthetic analogue TNP-470).[2]

Topical treatment of keratoconjunctivitis has been disappointing, although there are reports of individual patients responding to topical propamidine isetionate,[12] topical fumagillin,[13,14] oral albendazole,[15] oral albendazole plus topical fumagillin,[16] or oral itraconazole plus topical antibacterials.[17] US guidelines[2,3] recommend the use of topical fumagillin plus oral albendazole for eye infections. Treatment for these should be continued indefinitely in those with a CD4 + T lymphocyte count of less than 200 cells/microlitre, because of the risk of recurrence or relapse if treatment is stopped; treatment may be stopped in those with a relatively competent immune system (CD4+ T lymphocyte count greater than 200 cells/microlitre) once the eye infection has resolved.[2]

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Pneumocystis pneumonia

Although *Pneumocystis jirovecii* was formerly classified as a protozoan, it is now accepted to be a fungus. For the management of pneumocystis pneumonia, see p. 567.2.

Toxoplasmosis

Toxoplasmosis[1] is a zoonosis with a worldwide distribution caused by the protozoan *Toxoplasma gondii*, an intestinal parasite of cats for which other mammals may act as intermediate hosts. In man, infection is usually acquired through accidental swallowing of oocysts after contact with infected cat faeces or contaminated soil, from eating raw or undercooked meat from infected animals, or from drinking contaminated water. Congenital transmission may also occur if infection is acquired for the first time during pregnancy.

Toxoplasma infection is common; in immunocompetent individuals it is usually asymptomatic and if symptoms (such as fever, headache, malaise, and lymphadenopathy) do occur they are usually self-limiting, although latent (cystic) disease may become reactivated throughout the host's lifetime. Very rarely myocarditis or encephalitis may occur. Immunocompromised patients may develop serious complications such as encephalitis, chorioretinitis, myocarditis, and pneumonitis. Toxoplasmic encephalitis is the most common presentation in patients with AIDS.

Primary infection during early pregnancy is serious because of the risk of transplacental transmission which may result in fetal death or congenital toxoplasmosis. Primary infection during later pregnancy can also result in congenital infection, although this often only becomes symptomatic later in life. Rarely, reactivation of latent infection in chronically infected severely immunocompromised women has resulted in congenital transmission.[2]

The sequelae in live-born infants with signs of infection are generally severe and include a potentially fatal syndrome in which hydrocephalus, hepatosplenomegaly with jaundice, mental retardation, and chorioretinitis may occur. Congenital disease that becomes clinically evident later in life is usually less severe, but often results in ocular or neurological impairment. Infection in the pregnant woman is usually asymptomatic and antenatal screening programmes have been set up in some countries for the diagnosis of acute infections during pregnancy. However, the value and practicality of such schemes has been debated.[2-7]

Ocular toxoplasmosis causes chorioretinitis and is often a result of congenital infection; patients may be asymptomatic until later in life.

Treatment. Toxoplasmosis in immunocompetent patients is not usually treated unless symptoms are severe. Currently there is no drug active against the cystic form, so any treatment is directed against the acute forms of the disease. Active toxoplasmosis in immunocompromised patients requires prompt treatment.

- Toxoplasmosis is normally treated with a regimen of pyrimethamine plus sulfadiazine;[8,9] folinic acid is also a standard component of regimens including pyrimethamine to counteract associated megaloblastic anaemia.
- Clindamycin plus pyrimethamine and folinic acid has been used as an alternative in patients unable to take the sulfonamide.[8,9]
- Other regimens have been studied and have been found to have activity in toxoplasmic encephalitis, notably co-trimoxazole, atovaquone plus pyrimethamine and folinic acid, or atovaquone plus sulfadiazine, or azithromycin plus pyrimethamine and folinic acid. Atovaquone has also been given alone in patients unable to tolerate pyrimethamine or sulfadiazine.[8]
- Severely ill patients needing parenteral therapy have been given intravenous co-trimoxazole or clindamycin with oral pyrimethamine.[8]

Adjunctive corticosteroids may be given occasionally for treatment of a mass effect associated with focal lesions or oedema, but should be stopped as soon as possible because of their immunosuppressant effect. Anticonvulsants should be given to patients with a history of seizures.[8,9] Acute treatment is ideally continued for 6 weeks, or for longer if disease is extensive or response is incomplete.[8,9]

Immunocompromised patients who have successfully completed a 6-week course of acute therapy should be given chronic *maintenance* therapy, which should ideally be with pyrimethamine plus sulfadiazine and folinic acid,[8,9] but alternatives are pyrimethamine plus clindamycin and folinic acid, co-trimoxazole, or atovaquone, with or without sulfadiazine or pyrimethamine and folinic acid.[8] Chronic maintenance therapy should be lifelong unless immune reconstitution occurs because of antiretroviral therapy, in which case consideration may be given to stopping prophylaxis. It should, however, be restarted if the CD4+ count falls to below 200 cells/microlitre.[8]

The management of maternal and fetal infection may vary considerably from country to country and even within a country.[1] A systematic review[10] of the treatment of women during **pregnancy** involved small studies with variations in period of gestation, duration of follow-up, and other aspects of methodology, making comparison of data problematical; consequently the evidence was inconclusive as to whether treatment was effective in preventing fetal infection or overt neonatal disease. A meta-analysis of individual patients' treatment data reported only a weak association between early treatment and reduced risk of congenital toxoplasmosis. Furthermore, it found no evidence that prenatal treatment significantly reduced the risk of clinical signs and symptoms in infected newborn infants.[11]

If treatment is given, pyrimethamine should not be used to treat primary toxoplasmosis during the first and early second trimester of pregnancy. Spiramycin has been used throughout the first 18 weeks of pregnancy but, although it reduces the risk of congenital transmission, it does not readily penetrate the cerebrospinal space and does not prevent toxoplasmic encephalitis in immunocompromised women. After 14 to 18 weeks of gestation a pyrimethamine regimen with sulfadiazine may be given.[2] Some countries advise that spiramycin be continued throughout the pregnancy, while others recommend changing to the pyrimethamine plus sulfadiazine regimen at 17 weeks of gestation.[1]

When there is evidence of placental or fetal infection acquired in late second or third trimester, treatment is usually with the pyrimethamine plus sulfadiazine regimen; some advise that pyrimethamine plus sulfadiazine treatment may be alternated with courses of spiramycin until term.[1]

In **neonates** with congenital toxoplasmosis, the preferred treatment is also a pyrimethamine plus sulfadiazine regimen.[9] Infants without HIV infection should be treated for 12 months. In infants with mild toxoplasmosis, some experts recommend alternating the pyrimethamine-sulfadiazine regimen with spiramycin on a monthly basis from months 7 to 12, in order to reduce the risk of bone marrow suppression. However, infants with HIV infection and moderate to severe toxoplasmosis should receive the full 12-month regimen of pyrimethamine-sulfadiazine.[9] Longer courses of treatment may be given in cases of extensive disease. A corticosteroid, usually dexamethasone or prednisolone, has been added in children with CNS involvement.[9]

In immunocompetent individuals, **ocular toxoplasmosis** is a self-limiting disease and requires no treatment, unless visual acuity is threatened or there is a large retinal lesion with marked vitritis.[12-14] A systematic review[15] found a lack of evidence to support routine treatment for acute toxoplasma retinochoroiditis in immunocompetent patients, but did find weak evidence to suggest that long-term treatment of patients with chronic recurrent disease may reduce recurrence. All immunocompromised patients should be treated and prolonged treatment is necessary to prevent recrudescence. The best drug regimen is unknown. The most commonly used regimens give pyrimethamine with sulfadiazine or clindamycin (which is concentrated in the choroid). Benefit has been reported from clindamycin with corticosteroids,[16] although corticosteroids should never be used alone since fulminant cases may occur. Spiramycin is not indicated for ocular toxoplasmosis.

Prophylaxis. Primary prophylaxis against *T. gondii* infection has been investigated in AIDS patients and recipients of organ transplants. In HIV-infected adults and adolescents who are seropositive for *Toxoplasma* and who have a CD4+ count of less than 100 cells/microlitre, primary prophylaxis against encephalitis should be given.[8] Primary prophylaxis should also be given to seropositive children with a CD4 percentage less than 15%.[9]

Co-trimoxazole, in regimens designed for pneumocystis pneumonia prophylaxis, was found to be effective and is therefore recommended.[8,9] Alternatively, a regimen using pyrimethamine plus dapsone, or perhaps atovaquone, with or without pyrimethamine, can also be considered.[8,9] A regimen involving pyrimethamine plus sulfadoxine has also been tried, with promising results.[17]

Toxoplasma-seronegative persons who are not receiving a pneumocystis prophylactic regimen known to be active against toxoplasmic encephalitis should be retested for *Toxoplasma* should their CD4+ count fall below 100 cells/microlitre and if they have seroconverted primary prophylaxis should be started.[8] Primary prophylaxis should be stopped in adult and adolescent patients whose CD4+ count rises in response to antiretroviral therapy to more than 200 cells/microlitre for 3 months or more. If the count subsequently falls to below 200 cells/microlitre it should be restarted.[8] Similarly, primary prophylaxis may be stopped in children whose CD4 percentage rises to above 15% and should be restarted if the CD4 percentage subsequently falls below 15%.[9]

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Trichomoniasis

Trichomoniasis is caused by invasion of the genito-urinary tract with the protozoan *Trichomonas vaginalis*. Transmission is mainly sexual. Trichomoniasis is a common cause of vaginitis and vaginal discharge but infections vary in severity from asymptomatic (in up to 50% of cases) to an acute inflammatory vaginitis. Men are usually asymptomatic, although they may have urethritis. Asymptomatic infection in either sex should still be treated to prevent sexual transmission and symptomatic infection. *T. vaginalis* infection has been associated with HIV acquisition and adverse pregnancy outcomes, particularly premature rupture of the membranes, preterm delivery, and low birth-weight.

Guidelines for the **treatment** of trichomoniasis have been produced by an expert group in the UK,[1] by WHO,[2] and by the CDC in the USA.[3] Treatment is usually with a nitroimidazole such as metronidazole or tinidazole, often as a single oral dose of 2 g.[1-4] Alternative treatment regimens include standard oral doses of metronidazole or tinidazole given twice daily for 5 to 7 days.[1-3] Sexual partners should also be treated.[1-3] In HIV-infected women with trichomoniasis, there is evidence that metronidazole 500 mg orally given twice daily for 7 days is superior to a single 2-g oral dose; therefore, a multidose treatment regimen should be considered for HIV-infected women.[3]

Some strains of *T. vaginalis* have reduced susceptibility to nitroimidazoles[1-3] and patients who fail to respond to the first course of treatment may be re-treated with a repeat course of the initial regimen[1] or an alternative standard treatment.[2,3] If this fails and re-infection has been excluded patients may be given:

- a broad-spectrum antibacterial (such as erythromycin or amoxicillin) before re-treatment with metronidazole[1]
- oral metronidazole 400 mg three times daily with rectal metronidazole 1 g daily for 7 days or longer (zinc sulfate 1% vaginal douches or vaginal washes with 3% acetic acid may be added to the regimen)[1]
- high dose oral metronidazole[1,3] or tinidazole[3] (2 g) daily for 3 to 5 days
- high dose intravenous metronidazole[1]
- high dose oral tinidazole (2 g) twice daily for 2 weeks, with or without intravaginal tinidazole[1]
- a single dose of oral metronidazole plus intravaginal metronidazole applied at night, each for 3 to 7 days[2]

A patient with metronidazole- and tinidazole-resistant infection was successfully treated with paromomycin.[5] Vaginal preparations of metronidazole are only recommended for the treatment of refractory infections.[2] A trichomoniasis vaccine containing inactivated *Lactobacillus* spp. is available in some countries for the prophylaxis of recurrent vaginal trichomoniasis, see p. 2422.2.

Patients with hypersensitivity to nitroimidazoles can be managed by desensitisation with incremental doses of oral or intravenous metronidazole. Alternative topical therapies have been tried, but cure rates are low (less than 50%).[3,6]

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African trypanosomiasis

Human African trypanosomiasis (HAT or sleeping sickness)[1] is caused by subspecies of the protozoan *Trypanosoma brucei*, transmitted by the bite of infected tsetse flies (*Glossina* spp.). Infection can follow blood transfusion and congenital trypanosomiasis has also occurred. Infection does not appear to confer immunity.

Infection can be divided into the early, first, or haematolymphatic stage (infection of the bloodstream and lymph nodes), with bouts of fever, lymphadenopathy, pruritus, headache, and muscle and joint pain, and the late, second, or meningoencephalitic stage which starts when the parasite invades the CNS. Signs and symptoms include sleep disturbances, confusion, incoordination, psychiatric disorders, and eventual deterioration of consciousness. Without treatment the patient undergoes progressive neurological degeneration and death.

HAT takes two forms that are clinically distinct, depending on the parasite involved:

- *Trypanosoma brucei gambiense* (Gambian or West African sleeping sickness) occurs in west and central Africa and causes more than 90% of reported cases of HAT. It is a chronic infection and a person may be infected for months or years without major signs or symptoms of the disease; the disease stages are relatively distinct. When symptoms do appear, the patient is often in an advanced disease stage with CNS involvement
- *Trypanosoma brucei rhodesiense* (Rhodesian or East African sleeping sickness) occurs in eastern and southern Africa and causes less than 10% of reported cases of HAT. It is an acute infection with the first signs and symptoms appearing after a few weeks or months; disease stages are indistinct. The disease progresses rapidly and invades the CNS; if left untreated, it will usually lead to death in a matter of weeks or months

Although it has proven impractical to eliminate trypanosomiasis from endemic areas, the intensity of transmission can be reduced by active and passive case detection and treatment.[2] Vector control activities have had some success in controlling *T. b. rhodesiense* disease, but seem to be less effective and less widely applied for the control of *T.b. gambiense*.[3]

The **treatment** of HAT involves the use of 5 drugs depending on the form and stage of the disease:[1-6]

- intramuscular ***pentamidine*** is used for the first stage when caused by *T. b. gambiense*
- intravenous ***suramin*** is used for the first stage when caused by *T. b. rhodesiense* and in areas where pentamidine resistance occurs, suramin may be used for *T. b. gambiense* HAT
- intravenous ***melarsoprol*** is used for the second stage caused by *T. b. rhodesiense* or in second-stage *T. b. gambiense* disease when eflornithine treatment has failed or is unavailable
- intravenous ***eflornithine*** is used for the second stage if caused by *T. b. gambiense*
- oral ***nifurtimox***, used with eflornithine in second-stage disease caused by *T. b. gambiense*, including melarsoprol-refractory disease

The treatment of patients with suramin or pentamidine in the first stage of HAT is relatively easy and safe, but diagnosis is difficult and infection often goes unnoticed since symptoms may be mild or confused with other conditions.[2] Treatment can be curative if started before the CNS has become involved. Most patients, however, are diagnosed after second-stage symptoms have occurred.[2,5] Suramin or pentamidine penetrate the blood-brain barrier poorly and cannot be used to treat second-stage disease, and the other drugs used to treat this stage have limitations.

Intravenous injections with melarsoprol are painful and are associated with severe adverse effects; about 5 to 10% of patients will suffer from reactive encephalopathy during treatment, with an average case-fatality rate of 50%.[2,3,7] Some degree of protection against this toxicity may be provided by prophylaxis with prednisolone.[8,9] High rates of melarsoprol treatment failure (up to 50%) have been reported in several regions, including the Sudan, Uganda, the Democratic Republic of Congo, and Angola.[2]

Eflornithine is also effective and is safer than melarsoprol in the treatment of second-stage *T. b. gambiense* HAT,[10-12] but is not generally used for *T. b. rhodesiense* HAT[3] because of reduced susceptibility of the parasite.[2] Eflornithine is difficult to use as it needs to be given by slow intravenous infusion every 6 hours for 14 days, and requires close patient monitoring. If relapse occurs after treatment with eflornithine, use of melarsoprol should be considered.[4]

There is concern that long-term use of eflornithine monotherapy may result in the development of resistance, and it is less effective in areas with a high prevalence of HIV infection.[10] Oral nifurtimox has been used for treatment of late stage *T.b. gambiense* HAT,[13,14] but is considered not effective enough to be used as monotherapy.[2] However, promising results have been obtained from a randomised controlled study[15] for the treatment of second stage *T.b. gambiense* infection with oral nifurtimox for 10 days plus intravenous eflornithine (given 12-hourly for 7 days). Combination therapy (NECT) required fewer eflornithine doses and the duration of treatment was reduced. Furthermore, resistance was also less likely to develop as the drugs have different modes of action.[2] Given the high incidence of adverse effects with melarsoprol, NECT was considered a candidate to replace it, although the combination still requires access to appropriate healthcare facilities.[7]

Patients should be seen every 6 months for a follow-up period of at least 2 years, to ascertain if treatment has been successful.

Various potential antitrypanosomal drugs are under investigation, including diamidine derivatives[16] and the nitroimidazole fexinidazole.[17]

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American trypanosomiasis

American trypanosomiasis (Chagas' disease)[1-7] is a zoonosis caused by *Trypanosoma cruzi*, carried by Central or South American reduviid or triatomine bugs. Infected bugs defecate on the human host while feeding on blood and metacyclic trypanosomes that are shed enter the host through broken skin or by direct penetration of mucous membranes such as the conjunctiva. Infection may also occur through blood transfusion or less commonly transplanted organs; vertical transmission from infected mother to fetus can also occur. In endemic areas infection is usually acquired in childhood. Control measures include case detection and treatment, vector control by insecticide

applications within domestic buildings, and screening of blood donors.

In the early *acute phase* of infection parasites are present in the blood; clinical symptoms may or may not be apparent and most people recover spontaneously within 4 to 8 weeks. Symptomatic infection in the acute phase is characterised by fever, malaise, rash, lymphadenopathy, and hepatosplenomegaly. A swelling or chagoma may occur at the site of infection, which is often on the face; if this site is the conjunctiva a unilateral periorbital oedema occurs (Romañas sign). More rarely acute heart failure or meningoencephalitis occur and may be fatal in children. After a few months an asymptomatic latent or *indeterminate phase* develops and parasitaemia falls to low or undetectable levels. In 10 to 20 years about 15 to 30% of chronically infected persons develop *chronic* Chagas' disease (also called the chronic symptomatic phase) which is characterised by irreversible alterations of heart muscle (Chagasic cardiomyopathy) and gastrointestinal disease (mainly enlargement of the oesophagus or the rectosigmoid colon). In immunocompromised patients (including those with HIV infection) symptomatic reactivation of chronic, latent *T. cruzi* may occur.

Available **treatment** is generally unsatisfactory but, despite their toxicity, oral nifurtimox or oral benznidazole are of value especially in the acute phase; it is not certain whether trypanocidal treatment during the indeterminate phase can prevent the development of chronic disease although favourable results were obtained in a small study in children given benznidazole.[8] A systematic review[9] found that when given either nifurtimox or benznidazole, parasitological cure occurred in about 60 to 85% of patients in the acute phase and in more than 90% of congenitally infected infants treated in their first year of life. Although it is generally felt that there is no benefit from treatment in the chronic phase, treatment during the early chronic phase was reported to be beneficial,[10] and long-term follow-up of patients who had received benznidazole showed a reduction in cardiac complications and parasitaemia.[11]

Following a systematic review[9] it has been suggested that indications for treatment with benznidazole or nifurtimox include all cases of acute and congenital infection, reactivated infection, and all children 18 years of age or less with chronic infection; antitrypanocidal treatment should also generally be offered to adults aged 19 to 50 without advanced Chagasic cardiomyopathy, and may be considered in older adults although the risks of drug therapy are greater in the last group. It is not recommended for advanced Chagasic cardiomyopathy, since the existing pathology will not benefit, but the potential to reduce development of cardiomyopathy should be considered in patients with gastrointestinal involvement. In laboratory workers at risk of an infection after an accident, treatment with benznidazole for 10 days should be started immediately.[1]

Guidelines for the treatment of opportunistic infection in HIV-infected patients in the USA[12] suggest treatment with benznidazole or nifurtimox to reduce parasitaemia and prevent clinical symptoms in those with acute, early chronic, and reactivated disease. Re-treatment with either one of these drugs is recommended for HIV-infected patients who do not respond or who relapse after their initial therapy. Disease reactivation is also a problem in patients undergoing organ transplantation and the risk depends mainly on the degree of immunosuppression. Many experts advise close post-transplantation laboratory and clinical monitoring and treatment if reactivation is shown.[9,13] Some experts suggest treatment should be given to patients in whom future immunosuppression is anticipated, such as previously untreated *T. cruzi*-infected patients awaiting organ transplantation, or HIV-infected patients.[9]

The efficacy of treatment varies from country to country and may be linked to variations in the sensitivity of different strains of *T. cruzi*. Treatment is said to be successful when both parasitaemia and serological tests become negative and remain so for at least one year after the end of treatment.

Allopurinol, allopurinol riboside, and itraconazole have been tried for the treatment of American trypanosomiasis since they have shown trypanocidal activity in laboratory and *animal* studies; a prodrug of ravuconazole, E-1224, is also being studied. Initial clinical studies reported that oral allopurinol (600 or 900 mg daily for 60 days) was as effective as nifurtimox or benznidazole in reducing parasitaemia during the indeterminate phase and was better tolerated.[14] However, a later randomised, placebo-controlled study[15] in a small number of patients with chronic Chagas' disease reported that oral allopurinol was no more effective in clearing infection than placebo. A placebo-controlled study[16] in 404 patients with chronic Chagas' disease treated with either oral itraconazole (6 mg/kg daily for 120 days), oral allopurinol (8.5 mg/kg daily for 60 days), or placebo reported parasitologic cure in 44% and ECG normalisation in 36.5% of patients treated with allopurinol; for those given itraconazole a parasitologic cure of 53% and ECG normalisation of 48.2% was reported. A follow-up study[17] of the cardiac benefits in patients with chronic Chagas' disease 9 years after treatment with either oral itraconazole or oral allopurinol found that itraconazole and allopurinol were equally effective at reversing ECG changes but itraconazole appeared more protective against developing new ECG abnormalities in patients with a normal ECG at baseline. A further evaluation 11 years after treatment concluded that itraconazole was no less effective at preventing cardiomyopathy than allopurinol but had fewer adverse effects.[18] Posaconazole has also been tried.[19]

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Acetarsol *(BAN, rINN)*

Acetaminohydroxyphenylarsonsäure; Acétarsol; Acetarsolum; Acetarsona; Acetarsone; Acetphenarsinum; Asetarsoli; Osarsolum; Ацетарсол.

3-Acetamido-4-hydroxyphenylarsonic acid.

$C_8H_{10}AsNO_5$=275.1

CAS — 97-44-9.

ATC — A07AX02; G01AB01; P01CD02.

ATC Vet — QA07AX02; QG01AB01; QP51AD05.

UNII — 806529YU1N.

Profile

Acetarsol, a pentavalent organic arsenical derivative, has been given orally in the treatment of intestinal amoebiasis and vaginally in the treatment of trichomoniasis, but the use of pentavalent arsenical compounds has generally been abandoned in favour of more effective and less toxic drugs. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p. 2448.3.

Acetarsol suppositories were once tried in the treatment of proctitis. Acetarsol lithium and acetarsol sodium have been included in some preparations for minor mouth infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Osarbon (Осарбон); Osarcid (Осарцид).

Aminitrozole *(BAN, rINN)*

Acinitrazole; Aminitrozol; Aminitrozolum; CL-5279; Nithiamide (USAN); Nithiamide; Аминитрозол.

N-(5-Nitrothiazol-2-yl)acetamide.

$C_5H_5N_3O_3S$=187.2

CAS — 140-40-9.

UNII — 9CBM60191Z.

Profile

Aminitrozole is an antiprotozoal that is used topically, often with sulfanilamide (p. 368.1), in the treatment of susceptible skin and soft tissue infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ukr.***: Nitacid (Нитацид); Streptonitol (Стрептонитол).

Amprolium Hydrochloride *(BANM, rINNM)*

Amprolii Hydrochloridum; Amprolio, hidrocloruro de; Amprolium, Chlorhydrate d'; Hidrocloruro de amprolio; Ампролия Гидрохлорид.

1-(4-Amino-2-propylpyrimidin-5-ylmethyl)-2-methylpyridinium chloride hydrochloride.

$C_{14}H_{19}ClN_4$,HCl=315.2

CAS — 121-25-5 (amprolium); 137-88-2 (amprolium hydrochloride).

Pharmacopoeias. In *Fr.* and *US* for veterinary use only. Also in *BP(Vet)*.

BP(Vet) 2014: (Amprolium Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform; very slightly soluble in ether.

USP 36: (Amprolium). A white to light yellow powder. Freely soluble in water, in alcohol, in dimethylformamide and in methyl alcohol; sparingly soluble in dehydrated alcohol; practically insoluble in acetone, in butyl alcohol, and in isopropyl alcohol.

Profile

Amprolium hydrochloride is an antiprotozoal used in veterinary practice, for the treatment and control of coccidiosis caused by *Eimeria* spp. It is a structural analogue of thiamine and prolonged high doses may cause thiamine deficiency. Neurological symptoms reported after overdose in *dogs* were treatable with intravenous or intramuscular thiamine.

Pentavalent Antimony Compounds

Antimonio pentavalente, compuestos de; Пятивалентной Сурьмы Соединений.

Meglumine Antimonate

Antimoniato de meglumina; Antimony Meglumine; Meglumine Antimoniate; Protostib; RP-2168; Меглумина Антимонат.

1-Deoxy-1-methylamino-D-glucitol antimonate.

$C_7H_{18}NO_8Sb$=366.0

CAS — 133-51-7.

ATC — P01CB01.

ATC Vet — QP51AB01.

UNII — 75G4TW236W.

Sodium Stibogluconate *(BAN, rINN)*

Estibogluconato de sodio; Natrii Stibogluconas; Natriumstiboglukonaatti; Natriumstiboglukonat; Sod. Stibogluc.; Sodium Antimony Gluconate; Sodyum Stiboglukonat; Stibogluconat-Natrium; Stibogluconate de Sodium; Натрия Стибоглюконат.

CAS — 16037-91-5.

ATC — P01CB02.

ATC Vet — QP51AB02.

UNII — V083S0159D.

Description. A pentavalent antimony compound of indefinite composition. It has been represented by the formula $C_6H_9Na_2O_9Sb$ but usually there are less than 2 atoms of Na for each atom of Sb. Solutions may be sterilised by autoclaving.

Pharmacopoeias. In *Br., Chin., Int.*, and *It.*

BP 2014: (Sodium Stibogluconate). It is mainly the disodium salt of μ-oxy-bis[gluconato(3-)O^2,O^3,O^4-hydroxoantimony]. It contains not less than 30.0% and not more than 34.0% of antimony(V), calculated with reference to the dried and methanol-free substance. It is a colourless, odourless or almost odourless, mostly amorphous powder. Very soluble in water; practically insoluble in alcohol and in ether. A solution in water containing 10% of pentavalent antimony has a pH of 5.0 to 5.6 after autoclaving.

Uses and Administration

Pentavalent antimony, as sodium stibogluconate or meglumine antimonate, is used as first-line treatment for most forms of leishmaniasis (see below). Cutaneous and diffuse cutaneous leishmaniasis caused by *Leishmania aethiopica* infections do not respond to standard treatment with pentavalent antimony compounds, but may respond slowly if higher doses are used.

For systemic use, meglumine antimonate or sodium stibogluconate may be given by deep intramuscular injection or by intravenous injection. Intravenous injections must be given very slowly (over at least 5 minutes) and preferably through a fine needle to avoid thrombophlebitis; as with trivalent antimony compounds, they should be stopped immediately if coughing, vomiting, or substernal pain occurs. Both products may be injected intralesionally. Meglumine antimonate and sodium stibogluconate are given as solutions containing the equivalent of pentavalent antimony 85 mg/mL and 100 mg/mL respectively. Doses are expressed in terms of the equivalent amount of pentavalent antimony.

Local variations exist in treatment schedules but WHO recommends the following regimens:

- In **visceral leishmaniasis**, initial treatment is based on daily intramuscular injection of pentavalent antimony 20 mg/kg (but see below) usually given for 28 days. The length of treatment varies from one endemic area to another, but is continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals. Patients who relapse are re-treated at the same dose.
- Early non-inflamed lesions of **cutaneous leishmaniasis** due to all forms of *Leishmania* except *L. aethiopica*, *L. amazonensis*, and *L. braziliensis* may be treated by infiltration with intralesional injections of 1 to 3 mL of sodium stibogluconate or meglumine antimonate (about 100 to 300 mg of pentavalent antimony), repeated once or twice if necessary at intervals of 1 to 2 days. Systemic therapy with intramuscular pentavalent antimony 10 to 20 mg/kg daily is given if the lesions are more severe and continued until a few days after clinical and parasitological cure is achieved. In cutaneous leishmaniasis due to *L. braziliensis*, prolonged systemic treatment with intramuscular pentavalent antimony 20 mg/kg daily for a minimum of 4 weeks is indicated. Similar doses are required for **diffuse cutaneous leishmaniasis** due to *L. amazonensis* and are continued for several months after clinical improvement occurs. Relapses should be expected until immunity develops.
- In **mucocutaneous leishmaniasis**, daily doses of intramuscular pentavalent antimony 20 mg/kg are given for a minimum of 4 weeks; if the response is poor, 10 to 15 mg/kg may be given every 12 hours for the same period. Relapses are well known and have generally been associated with inadequate or interrupted treatment; they are treated with the same drug given for at least twice as long as the original treatment. Only when that fails should alternative treatment be given.

Administration in children. Doses of pentavalent antimony products, such as meglumine antimonate and sodium stibogluconate, for the treatment of leishmaniasis in children are usually the same as those for adults, see Uses and Administration, above. However, for those children with visceral leishmaniasis and weighing less than 10 kg the minimum daily dose is 200 mg.

Leishmaniasis. The main treatment for leishmaniasis (p. 922.1) is a pentavalent antimony compound such as meglumine antimonate or sodium stibogluconate. A maximum daily dose of 850 mg was initially recommended by WHO and is still recommended in the UK licensed product information. However, higher doses of antimony compounds have been tried in order to overcome the unresponsiveness of leishmaniasis to therapy. In the USA, the use of 20 mg/kg daily of pentavalent antimony has been recommended, without restriction to an 850-mg maximum daily dose;[1] this is now also the dose currently suggested by WHO. At 20 mg/kg daily the most common adverse effects are musculoskeletal disorders, elevated liver enzyme values, and T-wave changes on the ECG, and the CDC recommends that the ECG, blood chemistry, and blood count should be monitored throughout therapy if resources permit.[1] Severe cardiotoxicity is rare at this dose but fatal cardiotoxicity has been reported with doses of up to 60 mg/kg daily (see under Effects on the Heart, below). Drug-resistant strains of *Leishmania infantum* have been associated with unresponsiveness to treatment with meglumine antimonate.[2] It was suggested[3] that the use of suboptimal doses may be increasing the prevalence of drug-resistant strains of the parasite. However, low doses of antimony compounds (5 mg/kg daily for 30 days) have produced long-term cure in patients with cutaneous *L. braziliensis* infection followed for up to 10 years.[4]

INTRALESIONAL ADMINISTRATION. Intralesional infiltration of 3 doses of sodium stibogluconate on alternate days or once weekly was more effective than daily treatment in a study of 96 patients with cutaneous leishmaniasis in Saudi Arabia.[5] Others have reported on the use of intralesional stibogluconate in cases from Israel[6] and twice-weekly intralesional sodium stibogluconate has been suggested for the treatment of cutaneous leishmaniasis caused by *L. tropica* in India.[7] Local infiltration of meglumine antimonate in usual doses of 150 to 900 mg (maximum 1.5 g) once each week for up to 6 weeks produced microbiological and clinical cures in all of 45 patients in Italy with cutaneous leishmaniasis.[8]

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4. Oliveira-Neto MP, *et al.* A low-dose antimony treatment in 159 patients with American cutaneous leishmaniasis: extensive follow-up studies (up to 10 years). *Am J Trop Med Hyg* 1997; **57:** 651–5.
5. Tallab TM, *et al.* Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate. *Int J Dermatol* 1996; **35:** 594–7.
6. Solomon M, *et al.* Treatment of cutaneous leishmaniasis with intralesional sodium stibogluconate. *J Eur Acad Dermatol Venereol* 2009; **23:** 1189–92.
7. Bumb RA, *et al.* Efficacy of short-duration (twice weekly) intralesional sodium stibogluconate in treatment of cutaneous leishmaniasis in India. *Br J Dermatol* 2010; 854–8.
8. Aste N, *et al.* Intralesional treatment of cutaneous leishmaniasis with meglumine antimoniate. *Br J Dermatol* 1998; **138:** 370–1.

Adverse Effects, Treatment, and Precautions

As for Trivalent Antimony Compounds, p. 151.3.

Adverse effects are generally less frequent and less severe with the pentavalent antimony compounds sodium stibogluconate and meglumine antimonate than with trivalent compounds such as antimony sodium tartrate. Nevertheless, similar precautions should be observed, especially in patients on high-dose therapy.

Intramuscular injections of sodium stibogluconate can be painful and intravenous use has been associated with thrombophlebitis. Elevations in serum lipase and amylase usually occur during treatment and symptomatic pancreatitis has been reported in some patients. Successful treatment of mucocutaneous leishmaniasis may cause severe inflammation around the lesion and involvement of the pharynx or trachea may be life-threatening.

Common adverse effects of pentavalent antimony are anorexia, vomiting, nausea, malaise, arthralgia and myalgia, headache, lethargy, and abdominal pain. ECG changes are dose-dependent and most commonly include T-wave flattening and inversion and prolonged QT interval. Renal damage is a rarely reported toxic effect. Serious adverse effects have involved the liver, musculoskeletal system, pancreas, or the heart;[1,2] when they occur it is prudent to interrupt the course temporarily.[1] Pentavalent antimony is usually well tolerated,[1] although a study[2] of 96 patients treated with sodium stibogluconate for leishmaniasis reported significant, but generally reversible, adverse effects; treatment was interrupted in 28% of the patients.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 21/01/09)
2. Aronson NE, *et al.* Safety and efficacy of intravenous sodium stibogluconate in the treatment of leishmaniasis: recent US military experience. *Clin Infect Dis* 1998; **27:** 1457–64.

Breast feeding. The amount of antimony distributed into the breast milk of a patient given sodium stibogluconate was considered not to constitute a hazard and oral absorption was not detected in an *animal* study.[1] The last available guidance from the American Academy of Pediatrics also considered that the use of antimony is usually compatible with breast feeding.[2] Others, however, have felt that more safety evaluation was required before antimony could be considered completely safe during breast feeding.[3]

1. Berman JD, *et al.* Concentration of Pentostam in human breast milk. *Trans R Soc Trop Med Hyg* 1989; **83:** 784–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)
3. Verschoyle RD. Comment. *Trop Dis Bull* 1990; **87:** 919.

Effects on the blood. Although thrombocytopenia is associated with leishmaniasis, there are also case reports associating it with sodium stibogluconate.[1,2] Eosinophilia and lymphocytosis were common in a small study in Brazilian patients given intravenous or intralesional meglumine antimonate for cutaneous leishmaniasis.[3]

1. Braconier JH, Miörner H. Recurrent episodes of thrombocytopenia during treatment with sodium stibogluconate. *J Antimicrob Chemother* 1993; **31:** 187–8.
2. Hepburn NC. Thrombocytopenia complicating sodium stibogluconate therapy for cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1993; **87:** 691.
3. Neves DB, *et al.* Antimony in plasma and skin of patients with cutaneous leishmaniasis—relationship with side effects after treatment with meglumine antimoniate. *Trop Med Int Health* 2009; **14:** 1515–22.

Effects on the heart. The ECG was monitored during 65 courses of treatment with sodium stibogluconate in 59 Kenyan patients with leishmaniasis.[1] ECG abnormalities developed during 35 treatment courses. They were qualitatively similar to those previously described during treatment with trivalent antimonial drugs, but occurred less frequently and later during the course of treatment. The most common abnormality was inversion and/or decreased amplitude of T waves. Incidence was related to total daily dose and duration of treatment. One patient died suddenly during the 4th week of treatment with antimony 60 mg/kg daily. Other deaths probably related to cardiotoxicity have been reported in patients receiving 60 mg/kg daily[2] and 30 mg/kg daily.[3] It has been recommended[1] that for treatment with sodium stibogluconate ECGs should be obtained every 3 to 4 days in patients given antimony 20 mg/kg daily for more than 20 days or a higher dose for more than 10 days. If Stokes-Adams attacks or ventricular tachyarrhythmias develop, sodium stibogluconate should be stopped and appropriate treatment given. A retrospective study[4] in patients treated with sodium stibogluconate for mostly cutaneous leishmaniasis found that the mean QT_c interval steadily increased throughout the period of treatment, reaching a potentially toxic threshold by the third week, but cardiotoxicity was seen only in one elderly patient who had hypokalaemia and pre-existing cardiovascular morbidity. Identification before treatment of factors that may increase cardiovascular risk is important. For further information on the cumulative cardiotoxicity of sodium stibogluconate and amphotericin B see Antifungals, under Interactions, p. 928.1.

1. Chulay JD, *et al.* Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). *Am J Trop Med Hyg* 1985; **34:** 702–9.
2. Bryceson ADM, *et al.* Visceral leishmaniasis unresponsive to antimonial drugs II: response to high dosage sodium stibogluconate or prolonged treatment with pentamidine. *Trans R Soc Trop Med Hyg* 1985; **79:** 705–14.
3. Thakur CP. Harmful effect of high stibogluconate treatment of kala-azar in India. *Trans R Soc Trop Med Hyg* 1986; **80:** 672–3.
4. Lawn SD, *et al.* Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. *Trans R Soc Trop Med Hyg* 2006; **100:** 264–9.

Effects on the kidneys. Sodium stibogluconate given for 10 days to 16 young men with cutaneous leishmaniasis had no apparent adverse effect on glomerular or tubular renal function.[1] However, evidence of renal tubular dysfunction has been reported in patients with mucocutaneous leishmaniasis given meglumine antimonate or sodium stibogluconate for 30 days or more[2] and acute renal failure has occurred in patients both with,[3] and without,[4] pre-existing renal impairment, the latter resulting in death.

1. Joliffe DS. Nephrotoxicity of pentavalent antimonials. *Lancet* 1985; **i:** 584.
2. Veiga JPR, *et al.* Renal tubular dysfunction in patients with mucocutaneous leishmaniasis treated with pentavalent antimonials. *Lancet* 1983; **ii:** 569.
3. Balzan M, Fenech F. Acute renal failure in visceral leishmaniasis treated with sodium stibogluconate. *Trans R Soc Trop Med Hyg* 1992; **86:** 515–16.
4. Rodrigues MLO, *et al.* Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 33–7.

Effects on the liver. WHO has reported that when serious adverse effects occur with sodium stibogluconate they often involve the liver or the heart.[1] There have been reports of disturbed liver function[2,3] in patients given sodium stibogluconate, although there has also been a report[4] that signs of altered liver function, which may be a feature of visceral leishmaniasis, improved during treatment with sodium stibogluconate.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 17/07/08)
2. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii:** 13–16.
3. Hepburn NC, *et al.* Hepatotoxicity of sodium stibogluconate in leishmaniasis. *Lancet* 1993; **342:** 238–9.
4. Misbahuddin M, *et al.* Stibogluconate for leishmaniasis. *Lancet* 1993; **342:** 804.

Effects on the musculoskeletal system. Arthralgia is common with pentavalent antimony compounds. It is usually dose-dependent[1] but a patient has been described who had symptoms early in treatment.[2] Palindromic arthropathy with effusion was associated with sodium stibogluconate treatment in another patient.[3]

1. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii:** 13–16.
2. Castro C, *et al.* Severe arthralgia, not related to dose, associated with pentavalent antimonial therapy for mucosal leishmaniasis. *Trans R Soc Trop Med Hyg* 1990; **84:** 362.

3. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; **21:** 107–10.

Effects on the nervous system. Peripheral neuropathy developed in a patient about 8 days after starting therapy with sodium stibogluconate.[1] The symptoms were generally reversible when treatment was stopped (after 17 days), although there was some slight persistent hypoaesthesia in the toes. An interaction with a single dose of amitriptyline, taken on the second day of stibogluconate therapy, seemed unlikely but could not be ruled out. Two cases of cerebellar ataxia have been reported during treatment with sodium stibogluconate for visceral leishmaniasis; toxicity might have been partly due to the neurological manifestations of the disease.[2]

1. Brummitt CF, *et al.* Reversible peripheral neuropathy associated with sodium stibogluconate therapy for American cutaneous leishmaniasis. *Clin Infect Dis* 1996; **22:** 878–9.
2. Khalil EA, *et al.* Antimony-induced cerebellar ataxia. *Saudi Med J* 2006; **27:** 90–2.

Effects on the pancreas. Pancreatitis has been associated with sodium stibogluconate treatment.[1-3] Stopping treatment usually resulted in resolution of pancreatitis.

1. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; **21:** 107–10.
2. Gasser RA, *et al.* Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis* 1994; **18:** 83–90.
3. Domingo P, *et al.* Treatment of Indian kala-azar with pentavalent antimony. *Lancet* 1995; **345:** 584–5.

Interactions

Antifungals. Cardiotoxicity, including some fatalities, has been reported in about 8 to 17% of patients treated with the standard dose of sodium stibogluconate for visceral leishmaniasis, and patients may remain at risk for cardiotoxicity for about 2 months after stopping treatment due to its slow terminal elimination phase. In contrast, cardiotoxicity is uncommon with *amphotericin B*, although it may occur in patients with pre-existing cardiopulmonary disease or electrolyte abnormalities. Cumulative cardiotoxicity, resulting in sudden clinical deterioration and death, has been reported in 3 previously stable young children given intravenous amphotericin B up to 15 days after stopping treatment with sodium stibogluconate for the treatment of visceral leishmaniasis.[1] One child had a documented ventricular tachycardia on day 2 of amphotericin B treatment, while the other children had signs and symptoms suggestive of a fatal arrhythmia on days 4 and 6 of treatment with amphotericin B. It was suggested that sodium stibogluconate increased the susceptibility of the myocardium to damage by amphotericin B. A rest period of about 14 days (or longer if ECG changes persist) and correction of electrolyte abnormalities was advised when switching treatment from sodium stibogluconate to amphotericin B.[1]

1. Maheshwari A, *et al.* Cumulative cardiac toxicity of sodium stibogluconate and amphotericin B in treatment of kala-azar. *Pediatr Infect Dis J* 2011; **30:** 180–1.

Pharmacokinetics

The pentavalent antimony compounds are poorly absorbed from the gastrointestinal tract but are rapidly absorbed and distributed by the intravenous and the intramuscular routes, which have similar pharmacokinetics. Elimination occurs in two phases; a rapid initial phase, in which the majority of a dose is excreted via the kidneys within 12 hours, and a slower phase, possibly reflecting reduction to trivalent antimony. The elimination half-life of the initial phase is about 2 hours and that of the slow terminal phase is about 33 to 76 hours. Accumulation occurs on daily use and maximum tissue concentrations may not be reached for 7 days or more. Antimony has been detected in breast milk (see Breast Feeding, p. 927.2).

References.

1. Rees PH, *et al.* Renal clearance of pentavalent antimony (sodium stibogluconate). *Lancet* 1980; **ii:** 226–9.
2. Chulay JD, *et al.* Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. *Trans R Soc Trop Med Hyg* 1988; **82:** 69–72.
3. Al Jaser M, *et al.* Pharmacokinetics of antimony in patients treated with sodium stibogluconate for cutaneous leishmaniasis. *Pharm Res* 1995; **12:** 113–16.
4. Cruz A, *et al.* Pharmacokinetics of antimony in children treated for leishmaniasis with meglumine antimoniate. *J Infect Dis* 2007; **195:** 602–8.
5. Zaghloul IY, *et al.* Clinical efficacy and pharmacokinetics of antimony in cutaneous leishmaniasis patients treated with sodium stibogluconate. *J Clin Pharmacol* 2010; **50:** 1230–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Glucantime; ***Fr.***: Glucantime; ***Gr.***: Glucantime; ***Israel***: Pentostam; ***Spain***: Glucantime; ***UK***: Pentostam; ***Venez.***: Glucantime.

Pharmacopoeial Preparations
BP 2014: Sodium Stibogluconate Injection.

Atovaquone *(BAN, USAN, rINN)*

566C; 566C80; Atovacuona; Atovakon; Atovakvon; Atovakvoni; Atovaquonum; BW-566C; BW-566C80; BW-A566C; Атоваxон.

2-[*trans*-4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

$C_{22}H_{19}O_3Cl$=366.8

CAS — 95233-18-4.

ATC — P01AX06.

UNII — Y883P1Z2LT.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Atovaquone). A yellow, crystalline powder. Practically insoluble in water; sparingly soluble in dichloromethane; very slightly soluble in methyl alcohol. It shows polymorphism.

USP 36: (Atovaquone). A yellow powder. Insoluble in water; slightly soluble in alcohol, in butanediol, in ethyl acetate, in glycerol, in octanol, and in macrogol 200; sparingly soluble in acetone, in di-*n*butyl adipate, in dimethyl sulfoxide, and in macrogol 400; soluble in chloroform; freely soluble in *N*-methylpyrrolidone and in tetrahydrofuran; very slightly soluble in 0.1N sodium hydroxide. Store in airtight containers. Protect from light.

Uses and Administration

Atovaquone is a hydroxynaphthoquinone antiprotozoal that is also active against the fungus *Pneumocystis jirovecii*. It is used in the treatment and prophylaxis of pneumocystis pneumonia in patients unable to tolerate co-trimoxazole, and with proguanil in the treatment and prophylaxis of malaria. As well as these established uses atovaquone is also used in other protozoal infections including babesiosis and toxoplasmosis. For further information see below.

In the treatment of mild to moderate **pneumocystis pneumonia**, atovaquone is given orally in a dose of 750 mg with food twice daily as a suspension, for 21 days. For prophylaxis 1500 mg of the suspension is given once daily with food.

For the ***prophylaxis*** of falciparum **malaria** in adults over 40 kg oral atovaquone 250 mg with oral proguanil hydrochloride 100 mg is given once daily. The course should start 1 to 2 days before travel to the malarious area, continue daily throughout exposure, and for 7 days after leaving the area.

In the ***treatment*** of uncomplicated falciparum malaria in adults over 40 kg oral atovaquone 1 g with oral proguanil hydrochloride 400 mg is given as a single daily dose for 3 days.

For details of doses in children, see below.

Atovaquone with proguanil is one of the antimalarial drug combinations recommended by some experts to be carried as a ***standby*** for the emergency treatment of malaria. The dose recommended for self-treatment is the same as that for treatment of uncomplicated falciparum malaria.

Reviews.

1. Haile LG, Flaherty JF. Atovaquone: a review. *Ann Pharmacother* 1993; **27:** 1488–94.
2. Artymowicz RJ, James VE. Atovaquone: a new antipneumocystis agent. *Clin Pharm* 1993; **12:** 563–70.
3. Spencer CM, Goa KL. Atovaquone: a review of its pharmacological properties and therapeutic efficacy in opportunistic infections. *Drugs* 1995; **50:** 176–96.
4. Baggish AL, Hill DR. Antiparasitic agent atovaquone. *Antimicrob Agents Chemother* 2002; **46:** 1163–73.
5. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
6. Marra F, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.
7. Boggild AK, *et al.* Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). *Am J Trop Med Hyg* 2007; **76:** 208–23.

Administration in children. Children may be given atovaquone with proguanil for the ***prophylaxis*** of falciparum **malaria** in the following licensed oral doses, based on the adult dose of 250 mg of atovaquone daily:

- children weighing 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- over 40 kg: the adult dose The course should start 1 to 2 days before travel to the malarious area, continue daily throughout exposure, and for 7 days after leaving the area.

Licensed oral doses of atovaquone with proguanil for the ***treatment*** of uncomplicated falciparum malaria, based on the adult dose of 1 g of atovaquone daily for 3 days, are:

- children weighing 5 to 8 kg: one-eighth the adult dose
- 9 to 10 kg: three-sixteenths the adult dose
- 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- over 40 kg: the adult dose

For doses in children with **babesiosis** or for prophylaxis of **pneumocystis pneumonia** see below.

Babesiosis. Atovaquone 750 mg twice daily with azithromycin 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, both orally for 7 to 10 days, has been recommended by some experts[1] in the USA for the treatment of babesiosis infections; higher doses of azithromycin should be used in immunocompromised patients (see Babesiosis, under Uses and Administration of Azithromycin, p. 221.3). Children may be given atovaquone 20 mg/kg (maximum 750 mg) twice daily with azithromycin 10 mg/kg (maximum 500 mg) on day 1 followed by 5 mg/kg (maximum 250 mg) once daily thereafter, both orally for 7 to 10 days.[1,2] In a prospective, randomised study[3] involving 58 patients with babesiosis (p. 920.2), atovaquone with azithromycin was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Atovaquone with azithromycin, both given for 10 days, was also effective in the treatment of an 8-month-old child with transfusion-associated babesiosis.[4] However, the emergence of resistance to the combination has been reported in immunocompromised patients.[5]

1. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 23/08/13)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; **343:** 1454–8.
4. Raju M, *et al.* Atovaquone and azithromycin treatment for babesiosis in an infant. *Pediatr Infect Dis J* 2007; **26:** 181–3.
5. Wormser GP, *et al.* Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis* 2010; **50:** 381–6.

Malaria. Atovaquone with proguanil (*Malarone*) is used in the treatment and prophylaxis of uncomplicated malaria caused by *Plasmodium falciparum* (see p. 644.1).

Atovaquone, a blood schizontocide, is associated with an unacceptably high rate of recrudescence when used alone[1,2] for *treatment* but is more successful in malaria when used with proguanil,[2,3] including that produced by multidrug-resistant strains.[4] Use of the combination to treat *P. ovale* and *P. malariae* malarias has also been studied.[5] Atovaquone with proguanil followed by primaquine may also be effective for the treatment of *P. vivax* malaria.[6] Some authorities recommend this combination as an alternative treatment option in patients not responsing to chloroquine monotherapy[7] or for those with chloroquine-resistant infections.[7,8]

1. Chiodini PL, *et al.* Evaluation of atovaquone in the treatment of patients with uncomplicated Plasmodium falciparum malaria. *J Antimicrob Chemother* 1995; **36;** 1073–5.
2. Looareesuwan S, *et al.* Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996; **54:** 62–6.
3. Radloff PD, *et al.* Atovaquone and proguanil for Plasmodium falciparum malaria. *Lancet* 1996; **347:** 1511–14.
4. Sabchareon A, *et al.* Efficacy and pharmacokinetics of atovaquone and proguanil in children with multidrug-resistant Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 201–6.
5. Radloff PD, *et al.* Atovaquone plus proguanil is an effective treatment for Plasmodium ovale and P. malariae malaria. *Trans R Soc Trop Med Hyg* 1996; **90:** 682.
6. Looareesuwan S, *et al.* Atovaquone and proguanil hydrochloride followed by primaquine for treatment of plasmodium vivax malaria in Thailand. *Trans R Soc Trop Med Hyg* 1999; **93:** 637–40.
7. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (updated April 2011). Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 27/07/11)
8. Lalloo DG, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; **54:** 111–21. Correction. [primaquine dose]. Corrected version available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947343507 (accessed 15/11/10)

Pneumocystis pneumonia. Atovaquone is one alternative to co-trimoxazole for the treatment of pneumocystis pneumonia (p. 567.2). In open studies, a clinical response to atovaquone was reported in 78% of patients with mild to moderate disease and in 56% of patients with severe disease who were intolerant of, or who failed to respond to, both co-trimoxazole and pentamidine.[1] Comparative studies have shown atovaquone to be less effective than co-trimoxazole[2] and probably less effective than pentamidine,[3,4] but to produce fewer treatment-limiting adverse effects than either.

Atovaquone is also an alternative to co-trimoxazole for both primary or secondary *prophylaxis*, and was as effective as dapsone[5] or inhaled pentamidine[6] in studies in patients intolerant of co-trimoxazole. Atovaquone 30 mg/kg daily plus azithromycin 5 mg/kg daily was found to be possibly as

effective as co-trimoxazole in prophylaxis of pneumocystis pneumonia in HIV-infected children.[7]

1. White A, *et al.* Clinical experience with atovaquone on a treatment investigational new drug protocol for Pneumocystis carinii pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **9:** 280–5.
2. Hughes W, *et al.* Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med* 1993; **328:** 1521–7.
3. Dohn MN, *et al.* Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. *Ann Intern Med* 1994; **121:** 174–80.
4. Lederman MM, van der Horst C. Atovaquone for Pneumocystis carinii pneumonia. *Ann Intern Med* 1995; **122:** 314.
5. El-Sadr WM, *et al.* Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998; **339:** 1889–95.
6. Chan C, *et al.* Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis* 1999; **180:** 369–76.
7. Hughes WT, *et al.* Comparison of atovaquone and azithromycin with trimethoprim-sulfamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clin Infect Dis* 2005; **40:** 136–45.

Toxoplasmosis. Atovaquone, either alone or with pyrimethamine or sulfadiazine, has produced encouraging results for treatment[1-4] or long-term suppression[4-6] of toxoplasmosis (p. 924.2) in patients with AIDS. US guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents[4] suggest atovaquone with either pyrimethamine or sulfadiazine may be considered as an alternate regimen for treatment of toxoplasmosis; atovaquone may be given alone in patients unable to tolerate pyrimethamine and sulfadiazine. Atovaquone with or without pyrimethamine can be considered as an alternate regimen for primary prophylaxis, while atovaquone, with or without either pyrimethamine or sulfadiazine, may be considered as an alternate regimen for secondary prophylaxis of toxoplasmosis.[4] However, failure of atovaquone prophylaxis following haematopoietic stem-cell transplantation has been reported.[7] It has also been tried for the treatment of toxoplasmic retinochoroiditis in immunocompetent patients.[6]

For details of doses used with pyrimethamine for the prevention of toxoplasmosis, see under Pyrimethamine, p. 663.1.

1. Kovacs JA, *et al.* Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. *Lancet* 1992; **340:** 637–8.
2. Torres RA, *et al.* Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1997; **24:** 422–9.
3. Chirgwin K, *et al.* Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002; **34:** 1243–50.
4. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 17/09/13)
5. Katlama C, *et al.* Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. *AIDS* 1996; **10:** 1107–12.
6. Winterhalter S, *et al.* Does atovaquone prolong the disease-free interval of toxoplasmic retinochoroiditis? *Graefes Arch Clin Exp Ophthalmol* 2010; **248:** 1187–92.
7. Garcia de la Fuente I, *et al.* Acute disseminated fatal toxoplasmosis after haploidentical stem cell transplantation despite atovaquone prophylaxis in a young man. *Pediatr Infect Dis J* 2010; **29:** 1059–60.

Adverse Effects and Precautions

The most common adverse effects associated with the use of atovaquone plus proguanil are headache, coughing, and gastrointestinal effects such as nausea, diarrhoea, and vomiting. Other commonly occurring adverse effects include anorexia, depression, dizziness, fever, insomnia, rashes, raised liver enzyme values, hyponatraemia, and haematological disturbances such as anaemia and neutropenia. Rare cases of allergic reactions (such as angioedema, anaphylaxis, urticaria, and vasculitis), cholestasis, and hepatitis have been reported. Hepatic failure requiring liver transplantation has also been reported. Similar adverse effects have been reported in patients taking atovaquone without proguanil for prevention and treatment of pneumocystis pneumonia. Atovaquone should be avoided in patients with gastrointestinal disorders that may limit absorption of the drug. In patients with severe renal impairment, atovaquone plus proguanil is contra-indicated for the prophylaxis of malaria; it should be used with caution in the treatment of malaria.

Effects on the skin. Stevens-Johnson syndrome has been reported[1] in a patient after a few days of taking atovaquone with proguanil for malaria prophylaxis. A case[2] of bullous erythema multiforme has also been reported in a patient given atovaquone with proguanil for malaria treatment; pruritus occurred after the first and second doses and bullae developed after the third dose.

1. Emberger M, *et al.* Stevens-Johnson syndrome associated with Malarone antimalarial prophylaxis. Abstract: *Clin Infect Dis* 2003; **37:** 158. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/07/08)
2. Remich SA, *et al.* Bullous erythema multiforme after treatment with Malarone, a combination antimalarial composed of atovaquone and proguanil hydrochloride. *Trop Doct* 2008; **38:** 190–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atovaquone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

Use of atovaquone with either metoclopramide, tetracycline, rifampicin, or rifabutin results in decreases in plasma-atovaquone concentrations. Reduced concentrations of atovaquone with proguanil have been reported in HIV-positive patients also taking efavirenz or ritonavir-boosted atazanavir or lopinavir. Other drugs which have produced small reductions in plasma-atovaquone concentrations include aciclovir, antidiarrhoeals, benzodiazepines, cephalosporins, laxatives, opioids, and paracetamol.

Atovaquone is reported to decrease the metabolism of zidovudine resulting in moderate increases in zidovudine plasma concentrations. A decrease in trough concentrations of indinavir, and in the area under the indinavir time-concentration curve has been reported when atovaquone was also given. Small decreases in the plasma concentrations of co-trimoxazole (not considered to be clinically significant) have been noted in patients taking atovaquone. There is a theoretical possibility that atovaquone could displace other highly protein-bound drugs from plasma-protein binding sites.

Anticoagulants. For reference to a case of atovaquone increasing the effect of *warfarin*, see Antiprotozoals, p. 1532.3.

Pharmacokinetics

Atovaquone is a highly lipophilic compound with a low aqueous solubility. Oral bioavailability of atovaquone shows considerable interindividual variation. Bioavailability from commercial oral liquid formulations is better than from tablets and can be further improved if taken with food, particularly meals with a high fat content. The absolute bioavailability of the tablet and liquid formulations is 23% and 47% respectively, when taken with food. Atovaquone is more than 99% bound to plasma proteins. There is indirect evidence that atovaquone may undergo limited metabolism, however, no specific metabolites have been identified. It has a long plasma half-life of 2 to 3 days in adults and 1 to 2 days in children, thought to be due to enterohepatic recycling. It is excreted almost exclusively in faeces as unchanged drug.

References.

1. Rolan PE, *et al.* Examination of some factors responsible for a food-induced increase in absorption of atovaquone. *Br J Clin Pharmacol* 1994; **37:** 13–20.
2. Dixon R, *et al.* Single-dose and steady-state pharmacokinetics of a novel microfluidized suspension of atovaquone in human immunodeficiency virus-seropositive patients. *Antimicrob Agents Chemother* 1996; **40:** 556–60.
3. Hussein Z, *et al.* Population pharmacokinetics of atovaquone in patients with acute malaria caused by Plasmodium falciparum. *Clin Pharmacol Ther* 1997; **61:** 518–30.
4. Rolan PE, *et al.* Disposition of atovaquone in humans. *Antimicrob Agents Chemother* 1997; **41:** 1319–21.
5. Thapar MM, *et al.* Time-dependent pharmacokinetics and drug metabolism of atovaquone plus proguanil (Malarone) when taken as chemoprophylaxis. *Eur J Clin Pharmacol* 2002; **58:** 19–27.
6. McGready R, *et al.* The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. *Eur J Clin Pharmacol* 2003; **59:** 545–52.
7. Na-Bangchang K, *et al.* The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. *Eur J Clin Pharmacol* 2005; **61:** 573–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Wellvone; ***Belg.***: Wellvone; ***Canad.***: Mepron; ***Fr.***: Wellvone; ***Ger.***: Wellvone; ***Gr.***: Wellvone; ***Ital.***: Wellvone; ***Jpn***: Samtirel; ***Neth.***: Wellvone; ***Port.***: Wellvone; ***S.Afr.***: Wellvone; ***Spain***: Wellvone; ***Swed.***: Wellvone; ***Switz.***: Wellvone; ***UK***: Wellvone; ***USA***: Mepron.

Multi-ingredient Preparations. ***Austral.***: Malarone; ***Austria***: Malarone; ***Belg.***: Malarone; ***Canad.***: Malarone; ***Chile***: Malarone; ***Cz.***: Malarone; ***Denm.***: Malarone; ***Fin.***: Malarone; ***Fr.***: Malarone; ***Ger.***: Malarone; ***Gr.***: Malarone; ***Hong Kong***: Malarone; ***Hung.***: Malarone; ***Irl.***: Malarone; ***Israel***: Malarone; ***Ital.***: Malarone; ***Jpn***: Malarone; ***Malaysia***: Malarone; ***Neth.***: Malarone; ***Norw.***: Malarone; ***NZ***: Malarone; ***Pol.***: Malarone; ***Port.***: Malarone; ***S.Afr.***: Malanil; ***Singapore***: Malarone; ***Spain***: Malarone; ***Swed.***: Malarone; ***Switz.***: Malarone; ***Thai.***: Malanil; ***UK***: Malarone; Reprapog; ***USA***: Malarone.

Pharmacopoeial Preparations

USP 36: Atovaquone Oral Suspension.

Azanidazole *(BAN, USAN, rINN)*

Azanidazol; Azanidazolo; Azanidazolum; F-4; Азанидазол.

4-[(*E*)-2-(1-Methyl-5-nitroimidazol-2-yl)vinyl]pyrimidin-2-ylamine.

$C_{10}H_{10}N_6O_2$=246.2

CAS — 62973-76-6.

ATC — G01AF13; P01AB04.

ATC Vet — QG01AF13; QP51AA04.

UNII — YP2Y0DRX4S.

Profile

Azanidazole is a 5-nitroimidazole derivative similar to metronidazole (p. 936.1) and has been used in the treatment of trichomoniasis in usual oral doses of 200 mg twice daily or 250 mg once daily intravaginally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Triclose.

Benznidazole *(rINN)*

Benznidazol; Benznidazolum; Ro-7-1051; Бензнидазол.

N-Benzyl-2-(2-nitroimidazol-1-yl)acetamide.

$C_{12}H_{12}N_4O_3$=260.3

CAS — 22994-85-0.

ATC — P01CA02.

UNII — YC42NRJ1ZD.

Pharmacopoeias. In *Int.*

Uses and Administration

Benznidazole is a 2-nitroimidazole derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease—see below), especially during the early acute stage of the disease.

In the *acute* stage of the disease, uncomplicated cases in patients weighing up to 40 kg may be given benznidazole orally in a dose of 7.5 mg/kg daily while those weighing more than 40 kg should be given 5 mg/kg daily. Patients with acute meningoencephalitis should be given a dose of up to 25 mg/kg daily. Benznidazole should be given orally in equally divided doses every 8 or 12 hours and is usually given for 60 days (but see also American Trypanosomiasis, below).

Trypanosoma cruzi infected organ transplant donors should be treated for 2 weeks before the donation and recipients for 2 weeks after it. In laboratory workers at risk of an infection after an accident, treatment with benznidazole (7 to 10 mg/kg daily) for 10 days should be started immediately.

Treatment of patients in the *chronic* phase of the disease with oral benznidazole (5 mg/kg daily in equally divided doses every 8 or 12 hours) may be considered in areas where transmission by the vector has been interrupted and the 60-day treatment course can be completed under medical supervision.

For details of doses in children, see below.

Administration in children. For the treatment of the acute phase of American trypanosomiasis (Chagas' disease) in children, benznidazole may be given orally at a dose of 5 to 10 mg/kg daily in two equally divided doses for 60 days. In congenital cases, full-term neonates are given 10 mg/kg daily; treatment is started at a dose of 5 mg/kg daily and may be increased to 10 mg/kg daily after 3 days of treatment if the patient does not develop leucopenia or thrombocytopenia.

American trypanosomiasis. Available treatment for American trypanosomiasis (p. 925.3) is generally unsatisfactory, but benznidazole is of value especially in the acute phase. Guidelines[1,2] recommend that benznidazole should be given for 60 days. Although the duration of treatment has not been studied in patients co-infected with HIV, a treatment course of 30 to 60 days is recommended in these patients.[3] Treatment is usually confined to the acute phase of the disease. However, therapy during the early chronic phase was reported to be beneficial[4] (although a meta-analysis[5] suggested that benefit in late chronic phase was probably marginal); prospective long-term follow-up in patients with indeterminate- or chronic-stage disease who had received benznidazole has

shown that treatment may reduce the risk for progression of heart disease and reduce parasitaemia.[6]

1. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 17/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 17/09/13)
4. de Andrade ALSS, *et al.* Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. *Lancet* 1996; **348:** 1407–13.
5. Pérez-Molina JA, *et al.* Use of benznidazole to treat chronic Chagas' disease: a systematic review with a meta-analysis. *J Antimicrob Chemother* 2009; **64:** 1139–47.
6. Viotti R, *et al.* Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006; **144:** 724–34.

Adverse Effects

Benznidazole has adverse effects similar to those of metronidazole (p. 937.3).

The most commonly reported adverse effect is a hypersensitivity reaction characterised by dermatitis with cutaneous eruptions (usually appearing 5 to 10 days after starting treatment), fever, generalized oedema, lymphadenopathy, and joint and muscle pain. The most severe adverse effects are bone marrow depression, thrombocytopenic purpura, and agranulocytosis. Other reported adverse effects include polyneuropathy, paraesthesia, and peripheral neuropathy.

Like metronidazole, benznidazole is considered to be mutagenic and should be avoided during pregnancy. Patients are also advised not to drink alcoholic beverages while taking benznidazole.

A study[1] involving 20 patients with chronic American trypanosomiasis given benznidazole 5 mg/kg daily had to be stopped because of the high incidence of rashes and neurological symptoms. A severe, debilitating pain syndrome has also been reported in a patient after treatment with benznidazole for 5 weeks.[2]

1. Apt W, *et al.* Clinical trial of benznidazole and an immunopotentiator against Chagas disease in Chile. *Trans R Soc Trop Med Hyg* 1986; **80:** 1010.
2. Moll C, *et al.* Severe invalidating pain syndrome associated with benznidazole therapy for Chagas' disease. *Clin Rheumatol* 2008; **27:** 269–70.

Pharmacokinetics

Benznidazole is absorbed from the gastrointestinal tract after oral doses (> 90% bioavailability) and is widely distributed throughout the body. More than 40% of the drug is bound to plasma protein. The peak plasma concentration occurs after 3 to 4 hours and the half-life is about 12 hours. It is metabolised in the liver and more than 70% of the metabolites are excreted by the kidneys; about 30% of a dose is excreted in the faeces.

References.

1. Raaflaub J, Ziegler WH. Single-dose pharmacokinetics of the trypanosomicide benznidazole in man. *Arzneimittelforschung* 1979; **29:** 1611–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Radanil; ***Braz.:*** Rochagan†; ***Ecuad.:*** Ragonil.

Buparvaquone *(BAN, rINN)*

Buparvacuona; Buparvaquonum; BW-720C; Бупарвахон.

trans-2-(4-*tert*-Butylcyclohexylmethyl)-3-hydroxy-1,4-naphthoquinone.

$C_{21}H_{26}O_3$=326.4

CAS — 88426-33-9.

ATC Vet — QP51AX22.

UNII — 0354RT7LG4.

Profile

Buparvaquone is an antiprotozoal used in veterinary practice for the treatment of theileriosis in cattle. Topical formulations are being evaluated for the treatment of visceral and cutaneous leishmaniasis.

Carnidazole *(BAN, USAN, pINN)*

Carnidazol; Carnidazolum; R-25831; R-28096 (carnidazole hydrochloride); Карнидазол.

O-Methyl [2-(2-methyl-5-nitroimidazol-1-yl)ethyl]thiocarbamate.

$C_8H_{12}N_4O_3S$=244.3

CAS — 42116-76-7.

ATC Vet — QP51AA09.

UNII — RH5KI819JG.

Profile

Carnidazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the treatment and prevention of trichomoniasis in pigeons.

Clazuril *(BAN, USAN, rINN)*

Clazurilo; Clazurilum; Klatsuriili; Klazuril; R-62690; Клазурил.

(±)-[2-Chloro-4-(4,5-dihydro-3,5-dioxo-*as*-triazin-2(3*H*)-yl)phenyl]-(*p*-chlorophenyl)acetonitrile.

$C_{17}H_{10}Cl_2N_4O_2$=373.2

CAS — 101831-36-1.

ATC Vet — QP51AJ02.

UNII — O8W0R05772.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Clazuril for Veterinary Use; Clazuril BP(Vet) 2014). A white or light yellow powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Clazuril is an antiprotozoal used in veterinary practice for the treatment and prophylaxis of coccidiosis in pigeons.

Clefamide *(BAN, rINN)*

Chlorphenoxamide; Clefamida; Cléfamide; Clefamidum; Клефамид.

2,2-Dichloro-*N*-(2-hydroxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl]acetamide.

$C_{17}H_{16}Cl_2N_2O_5$=399.2

CAS — 3576-64-5.

ATC — P01AC02.

UNII — 4AZ2V8K4EK.

Profile

Clefamide is an antiprotozoal that has been used as a luminal amoebicide in the treatment of *Entamoeba histolytica* infections.

Clopidol *(BAN, USAN, rINN)*

Clopidolum; Clopindol; Meticlorpindol; Клопидол.

3,5-Dichloro-2,6-dimethylpyridin-4-ol.

$C_7H_7Cl_2NO$=192.0

CAS — 2971-90-6.

UNII — 8J763HFF5N.

Profile

Clopidol is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Decoquinate *(BAN, USAN, rINN)*

Décoquinate; Decoquinato; Decoquinatum; HC-1528; M&B-15497; Декохинат.

Ethyl 6-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate.

$C_{24}H_{35}NO_5$=417.5

CAS — 18507-89-6.

ATC Vet — QP51AX14.

UNII — 534I52PVWH.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet).*

BP(Vet) 2014: (Decoquinate). A cream to buff-coloured, odourless or almost odourless, microcrystalline powder. Insoluble in water; practically insoluble in alcohol; very slightly soluble in chloroform and in ether.

USP 36: (Decoquinate). Store in airtight containers.

Profile

Decoquinate is an antiprotozoal used in veterinary practice for the treatment and prophylaxis of coccidiosis in calves and lambs, and for prophylaxis of coccidiosis in chickens. It is also used for prevention of abortions due to toxoplasmosis in sheep.

Dehydroemetine Hydrochloride *(BANM, rINNM)*

BT-436; Dehidroemetina, hidrocloruro de; Déhydroémétine, Chlorhydrate de; 2,3-Dehydroemetine Hydrochloride; Dehydroemetini Hydrochloridum; DHE; Hidrocloruro de dehidroemetina; Ro-1-9334; Дегидроэметина Гидрохлорид.

2,3-Didehydro-6′,7′,10,11-tetramethoxyemetan dihydrochloride; 3-Ethyl-1,6,7,11b-tetrahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl)-4*H*-benzo[*a*]quinolizine dihydrochloride.

$C_{29}H_{38}N_2O_4$,2HCl=551.5

CAS — 4914-30-1 (dehydroemetine); 2228-39-9 (dehydroemetine hydrochloride).

NOTE. The name DHE has been used to denote a preparation of dihydroergotamine mesilate.

Pharmacopoeias. In *Int.*

Profile

Dehydroemetine, a synthetic derivative of emetine (p. 932.3), is a tissue amoebicide with similar actions and uses, although probably of a lower toxicity.

Dehydroemetine should be avoided in patients with cardiac, renal, or neuromuscular disease and patients should be monitored for cardiotoxicity during treatment.

When used in the treatment of amoebiasis (p. 919.1), dehydroemetine hydrochloride is given by intramuscular injection in a dose of 1 mg/kg daily (maximum daily dose of 60 mg), generally for 6 to 10 days, but for no more than 5 days in children. A dose of 500 micrograms/kg has been suggested for elderly or severely ill patients. At least 6 weeks should elapse before treatment is repeated. After treatment with dehydroemetine, patients should receive a luminal amoebicide to eliminate organisms from the colon. Patients with hepatic abscesses may be given supplementary treatment with chloroquine. Dehydroemetine has also been used with metronidazole.

Administration in children. Doses of dehydroemetine for the treatment of amoebiasis in children are the same as those for adults, although it may be used for shorter periods, see above.

Liver fluke infections. Dehydroemetine has been given[1,2] in the treatment of the liver fluke infection fascioliasis (see p. 146.2).

1. Farid Z, *et al.* Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; **82:** 299.
2. Cruz López O, *et al.* Fasciolosis hepática diagnosticada en fase de estado. *Rev Gastroenterol Mex* 2006; **71:** 59–62.

Diaveridine *(BAN, USAN, rINN)*

BW-49-210; Diaveridina; Diavéridine; Diaveridinum; NSC-408735; Диаверидин.

5-Veratrylpyrimidine-2,4-diyldiamine.

$C_{13}H_{16}N_4O_2$=260.3

CAS — 5355-16-8.

ATC Vet — QP51AX18.

UNII — 7KVX81XA87.

Pharmacopoeias. In *Fr.* for veterinary use.

Profile

Diaveridine is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.

Diclazuril *(BAN, USAN, rINN)*

Diclazurilo; Diclazurilum; Diklatsuriili; Diklazuril; R-64433; Диклазурил.

(±)-4-Chlorophenyl[2,6-dichloro-4-(2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-2-yl)phenyl]acetonitrile.

$C_{17}H_9Cl_3N_4O_2$=407.6

CAS — 101831-37-2.

ATC Vet — QP51AJ03.

UNII — K110K1B1VE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Diclazuril for Veterinary Use; Diclazuril BP(Vet) 2014). A white or light yellow powder. Practically insoluble in water, in alcohol, and in dichloromethane; sparingly soluble in dimethylformamide. Protect from light.

USP 36: (Diclazuril). White to yellow powder. Practically insoluble in water, in alcohol, and in dichloromethane; sparingly soluble in dimethylformamide.

Profile

Diclazuril is an antiprotozoal that has been tried in AIDS patients for the management of diarrhoea associated with

protozoal infection. It is used in veterinary practice for the control of coccidiosis.

References.
1. Kayembe K, *et al.* Diclazuril for Isospora belli infections in AIDS. *Lancet* 1989; **i:** 1397.
2. Connolly GM, *et al.* Diclazuril in the treatment of severe cryptosporidial diarrhoea in AIDS patients. *AIDS* 1990; **4:** 700–701.
3. Menichetti F, *et al.* Diclazuril for cryptosporidiosis in AIDS. *Am J Med* 1991; **90:** 271–2.
4. Limson-Pobre RNR, *et al.* Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis* 1995; **20:** 201–2.

Diiodohydroxyquinoline *(rINN)*

Diiodohidroxiquinoleína; Diiodohydroxyquin; Diiodohydroxyquinoléine; Di-iodohydroxyquinoline (BAN); Diiodohydroxyquinolinum; Diiodoidrossichinolina; Di-iodoxychinolinum; Diiodoxyquinoléine; Diiyodohidroksikinolin; Dijodhydroxikinolin; Dijodihydroksikinoliini; Iodoquinol (USAN); Yodoquinol; Дийодогидроксихинолин.

5,7-Di-iodoquinolin-8-ol.

$C_9H_5I_2NO$=397.0

CAS — 83-73-8.

ATC — G01AC01.

ATC Vet — QG01AC01.

UNII — 63W7IE88K8.

Pharmacopoeias. In *US.*

USP 36: (Iodoquinol). A light yellowish to tan, microcrystalline powder, not readily wetted in water, odourless or has a faint odour. Practically insoluble in water; sparingly soluble in alcohol and in ether.

Uses and Administration

Diiodohydroxyquinoline, a halogenated hydroxyquinoline, is a luminal amoebicide acting mainly in the bowel lumen and is used in the treatment of intestinal amoebiasis, (p. 919.1) although less toxic amoebicides such as diloxanide furoate or paromomycin are usually preferred, especially in children (see Precautions, below). It is given alone in the treatment of asymptomatic cyst passers, or as follow-up treatment after an amoebicide that acts in the tissues, such as metronidazole, in patients with symptomatic (invasive) amoebiasis. The usual oral dosage is 630 or 650 mg three times daily for 20 days.

For details of doses in children, see below.

Diiodohydroxyquinoline has also been given in the treatment of *Dientamoeba fragilis* infections, in balantidiasis (p. 920.3) as an alternative to tetracycline, and has been tried in *Blastocystis hominis* infections (p. 920.3).

Diiodohydroxyquinoline was formerly used in the treatment of acrodermatitis enteropathica; it is reported to act by enhancing zinc absorption and has now been superseded by oral zinc therapy.

Diiodohydroxyquinoline is claimed to have some antibacterial and antifungal activity and has been used topically (but see Children, under Precautions, below).

Administration in children. Diiodohydroxyquinoline is licensed in the USA and some other countries for the treatment of amoebiasis in children; however, there is concern over its safety in children (see Children, under Precautions, below).

For the treatment of asymptomatic amoebiasis (including asymptomatic cyst passers) and as follow-up treatment after a tissue amoebicide in the management of symptomatic intestinal or invasive amoebiasis, diiodohydroxyquinoline is given in the usual oral dose of 10 to 13.3 mg/kg three times daily (to a maximum of 1.95 g daily) for 20 days.

Adverse Effects

Major concerns have been expressed about the safety of the halogenated hydroxyquinolines since the recognition of severe neurotoxicity with clioquinol (p. 273.1). In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are mainly those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms such as paraesthesias in the legs, progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disability.

It was suggested that the Japanese epidemic might have been due to genetic susceptibility, but a few cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, including broxyquinoline and diiodohydroxyquinoline, have been reported elsewhere.

Diiodohydroxyquinoline has also been associated with gastrointestinal effects such as abdominal cramps, nausea, and diarrhoea. Adverse effects which may be attributable to the iodine content of diiodohydroxyquinoline include pruritus ani, skin eruptions, and enlargement of the thyroid gland. Fever, chills, headache, and vertigo have also occurred.

Effects on the nervous system. Hypertensive encephalopathy and seizures have been reported in a 10-year-old boy taking oral diiodohydroxyquinoline for a *Dientamoeba fragilis* infection.[1] Fourteen days after starting treatment the boy had abdominal cramps and muscle pain. Four days later a pins-and-needles sensation in his feet, ataxic gait, foot drop, stiff legs, general weakness, and headache developed. These symptoms were shortly followed by tonic-clonic seizures and results from additional investigations indicated a hypertensive encephalopathy. Five months after stopping diiodohydroxyquinoline, results from a neurologic examination were normal, but the boy still had tingling and sensitivities in his legs.

1. Health Canada. Iodoquinol: suspected association with hypertensive encephalopathy and seizures. *Can Adverse React News* 2006; **16** (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v16n3-eng.pdf (accessed 11/02/09)

Precautions

Diiodohydroxyquinoline is contra-indicated in patients known to be hypersensitive to iodine or halogenated hydroxyquinolines and in those with hepatic or renal impairment. It should be used with caution in thyroid disease and may interfere with determinations of protein-bound iodine in tests for thyroid function for up to 6 months after therapy. Its use is best avoided in patients with neurological disorders. Long-term use should be avoided.

Children. Last available guidance from the Committee on Drugs of the American Academy of Pediatrics[1] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

WHO considers that the use of halogenated hydroxyquinolines for the treatment of acute diarrhoea or amoebiasis in children cannot be justified.[2] There is no evidence of their efficacy in acute diarrhoea and they have been associated with severe neurological effects. On the rare occasions when a luminal amoebicide is required, other less toxic and more effective agents are available.

1. Kauffman RE, *et al.* American Academy of Pediatrics Committee on Drugs. Clioquinol (iodochlorhydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; **86:** 797–8. [Re-affirmed October 2006, Retired January 2011] Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;86/5/797.pdf (accessed 15/02/11)
2. WHO. The rational use of drugs in the management of acute diarrhoea in children. Geneva: WHO, 1990.

Pharmacokinetics

Diiodohydroxyquinoline is poorly absorbed from the gastrointestinal tract. Concern has been expressed about possible absorption after application to the skin (see Children, under Precautions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Diodoquin; ***Mex.***: Ameban; Antidifar; Carsuquin; Diameb†; Diodoquin; Diyosul†; Entero-Diyod; Entodiba†; Exoquin; Quinosul; Versamiv; ***Turk.***: Floraquin; ***USA***: Aloquin; Sebaquin; Yodoxin; ***Venez.***: Diodoquin.

Multi-ingredient Preparations. ***Arg.***: Hipoglos Cicatrizante; ***Chile***: Dexagin; ***Hong Kong***: Anlina†; ***India***: Enteroguanidine; ***Mex.***: Ameban; Amebyl; Bontal; Coralzul; Depofin; Dialgin†; Diodolina; Dipecfur; Facetin-D; Farmeban; Flagenase 400; Flagocil†; Lambliquin; Metodine; Metrodiyod; Norecil; Novageon; Stomffler Plus; Threchop†; ***S.Afr.***: Vagarsol; Viocort; Viodor†; ***Thai.***: Coccila; Disento; Gynecon-T; Gynecon; Gynoco†; Gynova†; Gyonep; Gyracon; Nystin; Pataryer; Quinradon-N†; Vagicin; VG Med; ***USA***: Alcortin A; Hydro-Iodoquinol; Vytone.

Pharmacopoeial Preparations
USP 36: Iodoquinol Tablets.

Diloxanide Furoate *(BANM, rINNM)*

Diloksanid Furoat; Diloxanida, furoato de; Diloxanide, Furoate de; Diloxanidi Furoas; Furoato de diloxanida; Дилоксанида фуроат.

4-(*N*-Methyl-2,2-dichloroacetamido)phenyl 2-furoate.

$C_{14}H_{11}Cl_2NO_4$=328.1

CAS — 579-38-4 (diloxanide); 3736-81-0 (diloxanide furoate).

ATC — P01AC01.

UNII — YP4N72IW34.

Pharmacopoeias. In *Br., Int.,* and *US.*

BP 2014: (Diloxanide Furoate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Protect from light.

USP 36: (Diloxanide Furoate). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Diloxanide furoate, a dichloroacetamide derivative, is a luminal amoebicide acting mainly in the bowel lumen and is used in the treatment of intestinal amoebiasis (p. 919.1). It is given alone in the treatment of asymptomatic cyst passers or after an amoebicide that acts in the tissues, such as metronidazole, in patients with symptomatic (invasive) amoebiasis.

Diloxanide furoate is given orally in a dosage of 500 mg three times daily for 10 days. The course of treatment may be repeated if necessary.

For details of doses in children, see below.

Administration in children. Diloxanide furoate may be given orally to children for the treatment of asymptomatic amoebiasis (including asymptomatic cyst passers) and as follow-up treatment after a tissue amoebicide in the management of symptomatic (invasive) amoebiasis in dose of 20 mg/kg daily, in 3 divided doses, for 10 days. UK licensed product information stipulates diloxanide furoate may only be given to children weighing more than 25 kg while the *BNFC* suggests it may be given to children from the age of 1 month.

Adverse Effects

Flatulence is the most common adverse effect during treatment with diloxanide furoate. Vomiting, pruritus, and urticaria may occasionally occur.

Pharmacokinetics

Diloxanide furoate is hydrolysed before absorption from the gastrointestinal tract. The resulting diloxanide is readily absorbed and excreted mainly in the urine as the glucuronide; less than 10% of a dose appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Amicline.

Multi-ingredient Preparations. ***India***: Aldezol-DF; Amebis Forte; Amicline Plus; Antibic-DF; Aristogyl Plus; Dialox; DLotin MPS; Dyrade-M; Eldazole; Entamizole†; Entrolate; Idometrin-D; Metrogyl Compound; Metron-DF; Novogyl-MPS; Qugyl; Tinidafyl Plus; Wotinex.

Pharmacopoeial Preparations
BP 2014: Diloxanide Tablets.

Dimetridazole *(BAN, pINN)*

Dimetridatsoli; Dimetridazol; Dimétridazole; Dimetridazolum; Диметридазол.

1,2-Dimethyl-5-nitroimidazole.

$C_5H_7N_3O_2$=141.1

CAS — 551-92-8.

ATC Vet — QP51AA07.

UNII — K59P7XNB8X.

Pharmacopoeias. In *Fr.* for veterinary use. Also in *BP(Vet).*

BP(Vet) 2014: (Dimetridazole). An almost white to brownish-yellow, odourless or almost odourless powder which darkens on exposure to light. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light.

Profile

Dimetridazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the control of various protozoal infections in birds, fish, and reptiles. It has also been used for swine dysentery. Dimetridazole is considered to be potentially carcinogenic and use in food-producing animals has been banned in some countries.

Diminazene Aceturate *(BANM, rINNM)*

Aceturato de diminazeno; Diminazène, Acéturate de; Diminazeni Aceturas; Diminazeno, aceturato de; Диминазена Ацетурат.

1,3-Bis(4-amidinophenyl)triazene bis(*N*-acetylglycinate).

$C_{22}H_{29}N_9O_6$=515.5

CAS — 536-71-0 (diminazene); 908-54-3 (diminazene aceturate).

UNII — JI8SAD85NO.

NOTE. Diminazene aceturate is often referred to by its veterinary proprietary name Berenil.

Profile

Diminazene aceturate, an aromatic diamidine derivative related to pentamidine, is an antiprotozoal used in veterinary practice in the treatment of trypanosomiasis and babesiosis. It has also been tried in human infections.

Dinitolmide *(BAN, rINN)*

Dinitolmida; Dinitolmidum; Dinitrotoluamida; Dinitrotoluamide; Methyldinitrobenzamide; Динитолмид.

3,5-Dinitro-*o*-toluamide.

$C_8H_7N_3O_5$=225.2

CAS — 148-01-6.

ATC Vet — QP51AX12.

UNII — AOX68RY4TV.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Dinitolmide). A cream to light tan powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, and in ether; soluble in acetone.

Profile

Dinitolmide is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Eflornithine Hydrochloride

(BANM, USAN, rINNM)

DFMO; α-Difluoromethylornithine Hydrochloride; Éflornithine, Chlorhydrate d'; Eflornithini Hydrochloridum; Eflornitina, hidrocloruro de; Hidrocloruro de eflornitina; MDL-71782; MDL-71782A; RMI-71782; Эфлорнитина Гидрохлорид.

2-(Difluoromethyl)-DL-ornithine monohydrochloride monohydrate.

$C_6H_{12}F_2N_2O_2$,HCl,H_2O=236.6

CAS — 67037-37-0 (eflornithine); 96020-91-6 (eflornithine hydrochloride).

ATC — D11AX16; P01CX03.

ATC Vet — QD11AX16.

UNII — 4NH22NDW9H.

Uses and Administration

Eflornithine is an antiprotozoal that acts as an irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis; trypanosomes are more susceptible to the effects of eflornithine than are humans, probably because of their slower turnover of this enzyme.

Eflornithine is used in **African trypanosomiasis** due to *Trypanosoma brucei gambiense* (see below). It is effective in the late stage of the disease (when there is CNS involvement).

In the treatment of African trypanosomiasis, eflornithine hydrochloride is given by intravenous infusion. The dose is 100 mg/kg every 6 hours for at least 14 days. Each dose should be given over a period of at least 45 minutes. Dosage should be reduced in patients with renal impairment.

Eflornithine hydrochloride is also applied topically twice daily for the reduction of unwanted **facial hair** in women (see Hirsutism, below). It is available as a cream containing 15% eflornithine hydrochloride monohydrate; in the UK this content is expressed as 11.5% eflornithine and in the USA as 13.9% anhydrous eflornithine hydrochloride.

Oral formulations of eflornithine are under investigation for the treatment of familial adenomatous polyposis (see Malignant Neoplasms of the Colon and Rectum, p. 706.3).

Cryptosporidiosis. Eflornithine has been tried in the treatment of cryptosporidiosis (p. 921.1) in AIDS patients.[1]

1. Rolston KVI, *et al.* Intestinal cryptosporidiosis treated with eflornithine: a prospective study among patients with AIDS. *J Acquir Immune Defic Syndr* 1989; **2:** 426–30.

Hirsutism. Topical eflornithine hydrochloride applied twice daily as a 13.9% cream is effective in reducing the growth of unwanted facial hair in females (see Hirsutism, p. 2262.1), although it must be used indefinitely to prevent regrowth.[1] Its action is thought to be due to the irreversible inhibition of ornithine decarboxylase in hair follicles. It has also been used successfully with laser hair removal.[2]

1. Barman Balfour JA, McClellan K. Topical eflornithine. *Am J Clin Dermatol* 2001; **2:** 197–201.
2. Hamzavi I, *et al.* A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *J Am Acad Dermatol* 2007; **57:** 54–9.

Malignant neoplasms. Eflornithine has antimetabolic activity and is being studied as a potential chemopreventive agent in patients at high risk of a variety of malignant diseases, including cancer of the bladder, breast, cervix, colon, oesophagus, prostate, and skin.[1,2] It has been investigated with NSAIDs such as sulindac in the prevention of colon cancer.

1. Meyskens FL, Gerner EW. Development of difluoromethylornithine (DFMO) as a chemoprevention agent. *Clin Cancer Res* 1999; **5:** 945–51.
2. Raul F. Revival of 2-(difluoromethyl)ornithine (DFMO), an inhibitor of polyamine biosynthesis, as a cancer chemopreventive agent. *Biochem Soc Trans* 2007; **35:** 353–5.

African trypanosomiasis. Eflornithine is effective in the treatment of *Trypanosoma brucei gambiense* infections (p. 925.2), and is particularly valuable in providing an alternative to melarsoprol in meningoencephalitic disease.[1-3] Eflornithine 100 mg/kg intravenously every 6 hours for 7 days, rather than the standard 14 days, produced long-term responses in 42 of 47 patients who had relapsed after other treatment regimens.[4] Similar positive results in relapsing cases were obtained with a short 7-day course in a multicentre randomised controlled study,[5] although this short course was inferior to the 14-day course for new cases, in whom it could not be recommended. A patient who had relapsed after treatment with melarsoprol and eflornithine given singly was cured when the drugs were given together.[6] Eflornithine given for 4 days followed by 3 daily injections of melarsoprol, was associated with a cure rate of 93% in 42 patients with melarsoprol-resistant Gambian trypanosomiasis. Efficacy and toxicity were considered to be similar to a 7-day course of eflornithine monotherapy.[7] Promising results have been reported from use of eflornithine 400 mg/kg daily (200 mg/kg every 12 hours) intravenously for 7 days with oral nifurtimox 15 mg/kg daily (5 mg/kg every 8 hours) for 10 days;[8,9] this drug combination has now been included in the WHO List of Essential Medicines for the treatment of human African trypanosomiasis.[10]

Eflornithine is not effective when given alone in *T. b. rhodesiense* infections, and early reports of its use with suramin were not encouraging.[11]

1. Chappuis F, *et al.* Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clin Infect Dis* 2005; **41:** 748–51.
2. Balasegaram M, *et al.* Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bull WHO* 2006; **84:** 783–91.
3. Priotto G, *et al.* Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. *BMJ* 2008; **336:** 705–8.
4. Khonde N, *et al.* A seven days course of eflornithine for relapsing Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1997; **91:** 212–13.
5. Pepin J, *et al.* Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bull WHO* 2000; **78:** 1284–95.
6. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 315.
7. Mpia B, Pépin J. Combination of eflornithine and melarsoprol for melarsoprol-resistant Gambian trypanosomiasis. *Trop Med Int Health* 2002; **7:** 775–9.
8. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; **45:** 1435–42.
9. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009; **374:** 56–64.
10. WHO. WHO Model List of Essential Medicines; 16th list (updated March 2010). Available at: http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf (accessed 08/07/10)
11. Clerinx J, *et al.* Treatment of late stage rhodesiense trypanosomiasis using suramin and eflornithine: report of six cases. *Trans R Soc Trop Med Hyg* 1998; **92:** 449–50.

Adverse Effects and Precautions

Intravenous eflornithine commonly causes myelosuppression that may lead to anaemia, leucopenia, and thrombocytopenia. Some patients have had hearing loss and alopecia. Gastrointestinal disturbances, especially diarrhoea, may occur. Seizures have occurred in about 8% of patients given eflornithine but they may have been related to the disease rather than treatment.

Dosage should be reduced in patients with renal impairment.

Acne and skin irritation, such as erythema or a stinging or burning sensation, has been reported after topical application of eflornithine; however, adverse effects are generally mild and usually resolve without medical treatment or stopping eflornithine.

Effects on the ears. A study in 58 patients[1] given oral eflornithine alone or with interferon alfa for the treatment of metastatic melanoma found that hearing loss was related to the cumulative dose of eflornithine and was worse in patients with pre-existing hearing deficit. Temporary hearing loss usually occurs with daily doses above 2 g/m^2 and when the cumulative dose exceeds 250 g/m^2. A case of irreversible hearing loss has been reported in a patient with Barrett's oesophagus after taking [oral] eflornithine 500 mg/m^2 daily for about 13 weeks (cumulative dose of 45 g/m^2) for the prevention of oesophageal cancer.[2]

1. Croghan MK, *et al.* Dose-related α -difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991; **14:** 331–5.
2. Lao CD, *et al.* Irreversible ototoxicity associated with difluoromethylornithine. *Cancer Epidemiol Biomarkers Prev* 2004; **13:** 1250–2.

Effects on the heart. An AIDS patient with pneumocystis pneumonia had a fatal cardiac arrest during an intravenous infusion of eflornithine 100 mg/kg over 1 hour.[1] Sudden death after infusion of eflornithine had occurred in several other critically ill patients with AIDS.

1. Barbarash RA, *et al.* Alpha-difluoromethylornithine infusion and cardiac arrest. *Ann Intern Med* 1986; **105:** 141–2.

Pharmacokinetics

Eflornithine hydrochloride is absorbed from the gastrointestinal tract. After intravenous doses about 80% is excreted unchanged in the urine in 24 hours. The terminal elimination half-life is about 3 hours. It is distributed to the CSF.

Less than 1% of a dose is absorbed after topical application.

References.

1. Haegele KD, *et al.* Kinetics of α -difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. *Clin Pharmacol Ther* 1981; **30:** 210–17.
2. Milord F, *et al.* Eflornithine concentrations in serum and cerebrospinal fluid of 63 patients treated for Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1993; **87:** 473–7.
3. Malhotra B, *et al.* Percutaneous absorption and pharmacokinetics of eflornithine HCl 13.9% cream in women with unwanted facial hair. *J Clin Pharmacol* 2001; **41:** 972–8.
4. Na-Bangchang K, *et al.* The pharmacokinetics of eflornithine (alpha-difluoromethylornithine) in patients with late-stage T.b. gambiense sleeping sickness. *Eur J Clin Pharmacol* 2004; **60:** 269–78.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vaniqa; ***Austral.***: Vaniqa; ***Austria***: Vaniqa; ***Belg.***: Vaniqa; ***Canad.***: Vaniqa; ***Chile***: Sessor; Vaniqa; ***Cz.***: Vaniqa; ***Denm.***: Vaniqa; ***Fr.***: Vaniqa; ***Ger.***: Vaniqa; ***India***: Eflora; Elyn; ***Irl.***: Vaniqa; ***Israel***: Vaniqa; ***Ital.***: Vaniqa; ***Neth.***: Vaniqa; ***Norw.***: Vaniqa; ***Pol.***: Vaniqa; ***Port.***: Vaniqa; ***Spain***: Vaniqa; ***Swed.***: Vaniqa; ***Switz.***: Vaniqa; ***UK***: Vaniqa; ***USA***: Ornidyl†; Vaniqa.

Emetine Hydrochloride *(BANM)*

Cloridrato de Emetina; Emet. Hydrochlor.; Emetiinihydrokloridi; Emetina, hidrocloruro de; Emetin-dihydrochlorid; Émétine, chlorhydrate d'; Emetine Dihydrochloride; Emetinhidroklorid; Emetinhydroklorid; Emetini Chloridum; Emetini Dihydrochloridum; Emetini hydrochloridum; Emetino hidrocloridas; Emetyny dichlorowodorek; Ipecine Hydrochloride; Methylcephaëline Hydrochloride; Эметина Гидрохлорид.

6′,7′,10,11-Tetramethoxyemetan dihydrochloride heptahydrate; (2*S*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(1*R*)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl]-2*H*-benzo[*a*]quinolizine dihydrochloride heptahydrate.

$C_{29}H_{40}N_2O_4$,2HCl,$7H_2O$=679.7

CAS — 483-18-1 (emetine); 316-42-7 (anhydrous emetine hydrochloride); 7083-71-8 (emetine hydrochloride, hydrate); 79300-08-6 (emetine hydrochloride, heptahydrate).

ATC — P01AX02.

UNII — U52OG12P96 (anhydrous emetine hydrochloride); J636CC0C64 (emetine hydrochloride heptahydrate); 07DUY5KO8X (emetine hydrochloride pentahydrate).

Pharmacopoeias. In *Chin.* and *Viet.*

Eur. has a monograph for Emetine Hydrochloride Pentahydrate;

Int. permits the heptahydrate or pentahydrate in the same monograph. *US* has a monograph for the anhydrous salt.

Ph. Eur. 8: (Emetine Hydrochloride Pentahydrate). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 2% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Emetine Hydrochloride). The hydrochloride of an alkaloid obtained from ipecacuanha, or prepared by methylation of cephaëline, or prepared synthetically. Anhydrous emetine hydrochloride is a white or slightly yellowish, odourless, crystalline powder. Freely soluble in

water and in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Emetine, an alkaloid of ipecacuanha (p. 1667.2), is a tissue amoebicide acting mainly in the bowel wall and in the liver. It has been given by deep subcutaneous or intramuscular injection in the treatment of severe invasive amoebiasis (p. 919.1), including hepatic amoebiasis in patients who do not respond to metronidazole, but safer drugs have generally replaced it. Emetine was formerly given orally as emetine and bismuth iodide.

Emetine has also been included in combination preparations for the symptomatic relief of cough.

Adverse Effects

Emetine hydrochloride is commonly associated with muscle pain and weakness around the injection site; there may be necrosis and abscess formation. After injection, diarrhoea and nausea and vomiting, sometimes with dizziness and headache, are common. There may be more generalised myalgia and weakness, and, more rarely, mild sensory disturbances. Eczematous, urticarial, and purpuric skin lesions have been reported.

Cardiotoxicity may be marked by precordial pain, dyspnoea, tachycardia, and hypotension. ECG changes, particularly flattening or inversion of the T-wave and prolongation of the QT interval, occur in many patients. Accumulation after large doses or prolonged use may cause lesions of the heart, gastrointestinal tract, kidneys, liver, and skeletal muscle. Severe acute degenerative myocarditis may occur and give rise to sudden cardiac failure and death. In some patients cardiotoxic effects have appeared after the completion of treatment with therapeutic doses.

Emetine hydrochloride is very irritant and contact with mucous membranes should be avoided.

Precautions

Emetine is contra-indicated in cardiac, renal, or neuromuscular disease, in pregnancy, and in children except in severe amoebic dysentery unresponsive to other drugs. It should be used with great caution in old or debilitated patients. Patients given emetine should be closely supervised; ECG monitoring is advisable during treatment.

Pharmacokinetics

After injection emetine hydrochloride is concentrated in the liver, and to some extent in kidney, lung, and spleen. Excretion is slow and detectable amounts may persist in urine 40 to 60 days after treatment has been stopped.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Spirbon†; ***Hung.***: Radipon†; ***Switz.***: Sano Tuss.

Pharmacopoeial Preparations
USP 36: Emetine Hydrochloride Injection.

Ethopabate *(BAN)*

Etopabato; Этопабат.
Methyl 4-acetamido-2-ethoxybenzoate.
$C_{12}H_{15}NO_4$=237.3
CAS — 59-06-3.
ATC Vet — QP51AX17.
UNII — F4X3L6068O.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet)*.

BP(Vet) 2014: (Ethopabate). A white or pinkish-white powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol; slightly soluble in ether.

USP 36: (Ethopabate). A white or pinkish-white, odourless or practically odourless, powder. Very slightly soluble in water; soluble in dehydrated alcohol, in acetone, in methyl alcohol, and in acetonitrile; slightly soluble in ether; sparingly soluble in dichloromethane, in dioxan, in ethyl acetate, and in isopropyl alcohol. Protect from light.

Profile

Ethopabate is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.

Etofamide *(rINN)*

Ethychlordiphene; Etofamida; Étofamide; Etofamidum; K-430; Этофамид.
2,2-Dichloro-*N*-(2-ethoxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl] acetamide.
$C_{19}H_{20}Cl_2N_2O_5$=427.3
CAS — 25287-60-9.
ATC — P01AC03.
UNII — 03F36JH21U.

Profile

Etofamide, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p. 931.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Kitnos; ***Mex.***: Kitnos; ***Philipp.***: Kitnos.

Fumagillin *(BAN, rINN)*

Fumagilina; Fumagilliini; Fumagilline; Fumagillinum; Фумагиллин.
4-(1,2-Epoxy-1,6-dimethylhex-4-enyl)-5-methoxy-1-oxaspiro [2.5]oct-6-yl hydrogen deca-2,4,6,8-tetraenedioate.
$C_{26}H_{34}O_7$=458.6
CAS — 23110-15-8.
ATC — P01AX10.
ATC Vet — QP51AX23.
UNII — 7OW73204U1.

Profile

Fumagillin is an alicyclic antibiotic produced by certain strains of *Aspergillus fumigatus*. It has activity against microsporidia and is used in veterinary practice to control *Nosema apis* infection in honeybees.

Fumagillin is given in an oral dose of 20 mg three times daily for 14 days in the treatment of diarrhoea due to intestinal microsporidial infection (see below) with *Enterocytozoon bieneusi* in patients with HIV infection. It has also been tried in humans in the topical treatment of microsporidial keratoconjunctivitis. It was formerly given orally in the treatment of intestinal amoebiasis, but produced an unacceptably high frequency of adverse effects. Analogues of fumagillin have been studied for effects on angiogenesis in solid tumours.

Microsporidiosis. As discussed on p. 924.1, topical treatment of microsporidial keratoconjunctivitis has been disappointing. There have been several reports of successful treatment in individual patients using fumagillin topically,[1-3] usually as a solution of bicyclohexylammonium fumagillin containing the equivalent of fumagillin 70 micrograms/mL.

Oral fumagillin has been effective in the treatment of diarrhoea due to intestinal microsporidial infection with *Enterocytozoon bieneusi* in immunocompromised patients, including those with HIV infection[4-6] and solid organ transplant recipients.[6-8] US guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents[9] recommend the use of topical fumagillin plus oral albendazole for microsporidial eye infections.

1. Rosberger DF, *et al.* Successful treatment of microsporidial keratoconjunctivitis with topical fumagillin in a patient with AIDS. *Cornea* 1993; **12:** 261–5.
2. Diesenhouse MC, *et al.* Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol* 1993; **115:** 293–8.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Flisint.

Furazolidone *(BAN, rINN)*

Furatsolidoni; Furazolidon; Furazolidona; Furazolidonum; Nifurazolidonum; Фуразолидон.
3-(5-Nitrofurfurylideneamino)-2-oxazolidone.
$C_8H_7N_3O_5$=225.2
CAS — 67-45-8.
ATC — G01AX06.
ATC Vet — QG01AX06; QJ01XE90.
UNII — 5J9CPU3RE0.

Pharmacopoeias. In *Br.*, *Fr.*, and *US*.

BP 2014: (Furazolidone). A yellow odourless or almost odourless crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. The filtrate from a 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 36: (Furazolidone). A yellow, odourless, crystalline powder. Practically insoluble in water, in alcohol, and in carbon tetrachloride. Store in airtight containers. Protect from light and avoid exposure to direct sunlight.

Uses and Administration

Furazolidone is a nitrofuran derivative with antiprotozoal and antibacterial activity. It is active against the protozoan *Giardia intestinalis* (*Giardia lamblia*) and against a range of enteric bacteria *in vitro*, including staphylococci, enterococci, *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Vibrio cholerae*. Furazolidone is bactericidal and appears to act by interfering with bacterial enzyme systems. Resistance is reported to be limited. It is used in the treatment of giardiasis (p. 921.3) and cholera (p. 184.2). It has been suggested for other bacterial gastrointestinal infections, but antibacterial therapy is regarded as unnecessary in mild and self-limiting gastro-enteritis (see p. 182.2).

Furazolidone is given orally in a dose of 100 mg four times daily. It is usually given for 2 to 5 days, but may be given for up to 7 days in some patients, or for up to 10 days for giardiasis.

For details of doses in children see below.

Administration in children. For the treatment of giardiasis, cholera, and other diarrhoeal diseases caused by susceptible organisms, children and infants from 1 month of age may be given oral furazolidone at a dose of 1.25 to 1.5 mg/kg four times daily for 2 to 5 days. Some patients may need 7 days of treatment, or up to 10 days for giardiasis.

Peptic ulcer disease. Furazolidone is not one of the main antibacterials used in *Helicobacter pylori* eradication regimens for peptic ulceration (p. 1816.2), but there are some studies suggesting its efficacy in adults,[1-7] children,[8,9] and in patients unresponsive to standard first- or second-line eradication regimens.[10-14]

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7. Lu H, *et al.* One-week regimens containing ranitidine bismuth citrate, furazolidone and either amoxicillin or tetracycline effectively eradicate Helicobacter pylori: a multicentre, randomized, double-blind study. *Aliment Pharmacol Ther* 2001; **15:** 1975–9.
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9. Machado RS, *et al.* Furazolidone, tetracycline and omeprazole: a low-cost alternative for Helicobacter pylori eradication in children. *J Pediatr (Rio J)* 2008; **84:** 160–5.
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12. Eisig JN, *et al.* A furazolidone-based quadruple therapy for Helicobacter pylori retreatment in patients with peptic ulcer disease. *Clinics* 2005; **60:** 485–8.
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Adverse Effects

Adverse effects of furazolidone are usually mild and transient. The most common involve the gastrointestinal tract and include nausea and vomiting. Dizziness, drowsiness, headache, and a general malaise have also been reported.

Allergic reactions, most commonly skin reactions such as rashes or angioedema, may occur. There have been instances of acute pulmonary reactions, similar to those seen with the structurally related drug nitrofurantoin, and of hepatotoxicity. Agranulocytosis has been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given furazolidone.

Darkening of the urine has been attributed to the presence of metabolites.

Precautions

Furazolidone should be used with caution in those with G6PD deficiency because of the risk of haemolytic anaemia. It should not be given to infants under 1 month of age since their enzyme systems are immature.

Interactions

A disulfiram-like reaction has been reported in patients taking alcohol while on furazolidone therapy; alcohol should be avoided during, and for a short period after, treatment with furazolidone.

A metabolite of furazolidone is an MAOI and the cautions advised for these drugs regarding use with other drugs, especially indirect-acting sympathomimetic amines, and the consumption of food and drink containing tyramine, should be followed (see Phenelzine Sulfate, p. 444.3 and p. 445.1). However, there appear to be no reports of hypertensive crises in patients receiving furazolidone and it has been suggested that, since furazolidone inhibits monoamine oxidase gradually over several days, the risks are small if treatment is limited to a 5-day course. Toxic psychosis has been reported in a patient receiving furazolidone and amitriptyline (see Antiprotozoals, under Interactions of Amitriptyline, p. 406.3). Omeprazole modestly decreases serum concentrations of furazolidone; other proton pump inhibitors could interact similarly.

Pharmacokinetics

Although furazolidone has been considered to be largely unabsorbed when given orally, the occurrence of systemic adverse effects and coloured metabolites in the urine suggest that this may not be the case. Rapid and extensive metabolism, possibly in the intestine, has been proposed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Giardil; ***Braz.***: Giarlam; Neo Furasil; ***Chile***: Furoxona; ***India***: Furoxone; ***Indon.***: Diralox; Neo Prodiar; ***Mex.***: Furoxona; Fuxol; Kaodin; Salmocide†; ***Philipp.***: Diafuran; Diapectolin; Furoxone; ***Thai.***: Furasian; Furion; ***Turk.***: Furoksan; ***Venez.***: Furoxil; Furoxona.

Multi-ingredient Preparations. ***Braz.***: Colestase; ***Chile***: Furazolidona; ***Hong Kong***: Berber CO†; Enterocin Compound†; ***India***: Aldiamycin; Alfumet; Amibex; Anaerid-F; Aristogyl-F; Aristogyl-F; C-Met; Dependal-M; Diaglow; Enterofuran-M; Flagyl-F; Fumestar; Inseptin-MF; Kaltin MF; Lomofen; Lomostop-MF; Megyl-F; Metrogyl-F; ***Mex.***: Caopecfar†; Colfur†; Coralzul; Dialgin†; Dibapec Compuesto†; Estibal; Exofur; Furoxona CP; Kapecfuran; Neokap; Optazol; Reuginal; Solfurol; Threchop†; Yodozona; ***Spain***: Desinvag†; ***Thai.***: Coccila; Coccila; Diaropect; Diaropect; Difuran; Diocin; Disento PF; Disento; Furamed; Furasian; Furopectal; Furopectin; Patarlin; Profura; Suratin.

Pharmacopoeial Preparations

USP 36: Furazolidone Oral Suspension; Furazolidone Tablets.

Halofuginone Hydrobromide

(BANM, USAN, rINNM)

Halofuginona, hidrobromuro de; Halofuginone, Bromhydrate d'; Halofuginoni Hydrobromidum; Hidrobromuro de halofuginona; RU-19110; Галофугинона Гидробромид.

(±)-*trans*-7-Bromo-6-chloro-3-[3-(3-hydroxy-2-piperidyl)acetonyl]quinazolin-4(3*H*)-one hydrobromide.

$C_{16}H_{17}BrClN_3O_3,HBr$=495.6

CAS — 55837-20-2 (halofuginone); 64924-67-0 (halofuginone hydrobromide).

UNII — PTC2969MV1.

Profile

Halofuginone is an antiprotozoal used as the hydrobromide in veterinary practice for the prevention of coccidiosis in poultry and for the treatment and prevention of cryptosporidiosis in calves. It is also under investigation for use in neoplastic disease in humans and in the treatment of scleroderma (p. 1942.3).

Imidocarb *(BAN, rINN)*

BRN-0964732; Imidocarbe; Imidocarbo; Imidocarbum; Имидокарб.

1,3-Bis[3-(2-imidazolin-2-yl)phenyl]urea.

$C_{19}H_{20}N_6O$=348.4

CAS — 27885-92-3.

ATC Vet — QP51AE01.

UNII — 8USS3K0VDH.

Imidocarb Dipropionate *(BANM, rINNM)*

Dipropionato de imidocarbo; Imidocarbe, Dipropionate d'; Imidocarbi Dipropionas; Имидокарба Дипропионат.

$C_{19}H_{20}N_6O,2C_3H_6O_2$=496.6

CAS — 55750-06-6.

UNII — ZSM1M03SHC.

Imidocarb Hydrochloride *(BANM, USAN, rINNM)*

4A65; Hidrocloruro de imidocarbo; Imidocarbe, Chlorhydrate d'; Imidocarbi Hydrochloridum; Имидокарба Гидрохлорид.

3,3'-Di(2-imidazolin-2-yl)carbanilide dihydrochloride.

$C_{19}H_{20}N_6O,2HCl$=421.3

CAS — 5318-76-3.

UNII — KCC1V76AH8.

Profile

Imidocarb has antiprotozoal and antibacterial activity and is used as the dipropionate in veterinary practice in the treatment of babesiosis and anaplasmosis. Imidocarb hydrochloride has also been used.

Isometamidium Chloride *(BAN, rINN)*

Cloruro de isometamidio; Isometamidii Chloridum; Isometamidio, cloruro de; Isometamidium; Isométamidium, Chlorure d'; Изометамидия Хлорид.

8-[3-(*m*-Amidinophenyl)-2-triazeno]3-amino-5-ethyl-6-phenylphenanthridinium chloride.

$C_{28}H_{26}ClN_7$=496.0

CAS — 34301-55-8.

UNII — 7NH28I651F.

Profile

Isometamidium is an antiprotozoal used as the chloride in veterinary practice for the control of trypanosomiasis.

Lasalocid *(BAN, USAN, rINN)*

Lasalocide; Lasalócido; Lasalocidum; Ro-02-2985; Лазалоцид.

6-[(3*R*,4*S*,5*S*,7*R*)-7-[(2*S*,3*S*,5*S*)-5-Ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]tetrahydro-3-methyl-2-furyl]-4-hydroxy-3,5-dimethyl-6-oxononyl]-2-hydroxy-*m*-toluic acid.

$C_{34}H_{54}O_8$=590.8

CAS — 11054-70-9; 25999-31-9.

ATC Vet — QP51AH02.

UNII — W7V2ZZ2FWB.

Lasalocid Sodium *(BANM, rINNM)*

Lasalocid sódico; Lasalocide Sodique; Lasalocidum Natricum; Лазалоцид Натрий.

$C_{34}H_{53}NaO_8$=612.8

CAS — 25999-20-6.

ATC Vet — QP51AH02.

UNII — W2S5C71Y3G.

Profile

Lasalocid, an antibiotic produced by *Streptomyces lasaliensis*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in birds.

Maduramicin *(BAN, USAN, rINN)*

CL-273703; Maduramicin Ammonium; Maduramicina; Maduramicine; Maduramicinum; Мадурамицин.

Ammonium (2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2-hydroxy-6-{(*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)-9-hydroxy-2,8-dimethyl-2-{(2*S*,2'*R*,3'*S*,5*R*,5'*R*)-octahydro-2-methyl-3'-[(2*R*,4*S*,5*S*,6*S*)-tetrahydro-4,5-dimethoxy-6-methyl-2*H*-pyran-2-yl]oxy}-5'-[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl](2,2'-bifuran-5-yl)-1,6-dioxaspiro[4.5]dec-7-yl]ethyl}-4,5-dimethoxy-3-methyl-2*H*-pyran-2-acetate.

$C_{47}H_{80}O_{17},NH_3$=934.2

CAS — 84878-61-5.

ATC Vet — QP51AX10.

UNII — 5U912U22T2.

NOTE. The name maduramicin has also been used to denote the acid.

Profile

Maduramicin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry. Accidental ingestion by humans has resulted in muscle weakness, polyneuropathy, myonecrosis and rhabdomyolysis, and acute renal failure; fatalities have been reported.

Melarsoprol *(BAN, rINN)*

Mel B; Melarsen Oxide-BAL; Mélarsoprol; Melarsoprolum; RP-3854; Меларсопрол.

2-[4-(4,6-Diamino-1,3,5-triazin-2-ylamino)phenyl]-1,3,2-dithiarsolan-4-ylmethanol.

$C_{12}H_{15}AsN_6OS_2$=398.3

CAS — 494-79-1.

ATC — P01CD01.

ATC Vet — QP51AD04.

UNII — ZF3786Q2E8.

Uses and Administration

Melarsoprol, a trivalent arsenical derivative, is a trypanocide that appears to act by inhibiting trypanosomal pyruvate kinase. It is effective in the treatment of all stages of African trypanosomiasis due to *Trypanosoma brucei gambiense* or *T. brucei rhodesiense* (see below), but because of its toxicity its use is usually reserved for stages of the disease involving the CNS. Resistance has been reported to develop.

Patients undergoing therapy with melarsoprol should be treated in hospital. Melarsoprol is given by intravenous injection as a 3.6% solution in propylene glycol. The injection should be given slowly, care being taken to prevent leakage into the surrounding tissues, and the patient should remain supine and fasting for several hours after the injection.

Treatment protocols vary, but in general melarsoprol is given in low doses initially (0.36 to 1.8 mg/kg daily), especially in children and debilitated patients, increased gradually to the maximum daily dose of 3.6 mg/kg. For **intermittent** cyclic therapy, doses are given daily for 3 or 4 days and the course repeated 2 or 3 times with an interval of 7 to 10 days between courses. Since massive destruction of parasites resulting in a Jarisch-Herxheimer reaction is particularly dangerous during treatment with melarsoprol, several doses of suramin or pentamidine may be given to induce the reaction before melarsoprol is started.

An alternative 10-day **consecutive** treatment course of intravenous melarsoprol 2.2 mg/kg daily, for the treatment of *T. b. gambiense*, has been endorsed by many authorities, since it shortens patients' time in hospital and reduces the total amount of drug given. See also below.

Melarsonyl potassium is a water-soluble derivative of melarsoprol which was formerly used as an alternative to melarsoprol but was probably more toxic and less effective.

African trypanosomiasis. Melarsoprol, which is effective against both *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, is usually only given to treat the meningoencephalitic stage of African trypanosomiasis (p. 925.2) because it may produce potentially fatal encephalopathy. However, protection against this toxicity may be provided by prophylaxis with prednisolone.[1,2] Therapy with melarsoprol and eflornithine was reported to be effective in a patient who had not responded to either drug alone.[3] A study[4] to evaluate the efficacy and toxicity of a combination of eflornithine for 4 days followed by 3 daily injections of melarsoprol in 42 patients with melarsoprol-resistant Gambian trypanosomiasis, was associated with cure in 93% of patients. Efficacy and toxicity were considered to be similar to a 7-day course of eflornithine monotherapy. A comparative study[5] in 500 patients with second-stage infection with *T. b. gambiense* found that an alternative dosage regimen of melarsoprol 2.2 mg/kg daily, as a single course over 10 consecutive days, was similar in efficacy to intermittent cyclic regimens of 1.2 to 3.6 mg/kg daily for 3 or 4 days repeated twice over a 26-day period with 7-day intervals between series, although there was no difference between the regimens in the incidence of associated encephalopathy. Follow-up involving 442 of these patients indicated that results of the 2 regimens continued to be comparable; relapse after 1 year occurred in 3% of those given standard treatment and in 2% given alternative treatment; relapse rates after 2 years were

reported to be 5% and 6% respectively.[6] A further uncontrolled, multinational drug-utilisation study[7] in 2020 patients with late-stage African trypanosomiasis treated with the 10-day consecutive melarsoprol regimen reported a 93.9% cure rate 24 hours after completing treatment and an 86.2% cure rate after 2 years, however, nearly half of the patients were lost to follow-up. The overall reported fatality rate was 5.9%; encephalopathic syndrome was reported for 8.7% of patients and it was fatal in about half of all cases.

1. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; **i:** 1246–50.
2. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; **89:** 92–7.
3. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 315.
4. Mpia B, Pépin J. Combination of eflornithine and melarsoprol for melarsoprol-resistant Gambian trypanosomiasis. *Trop Med Int Health* 2002; **7:** 775–9.
5. Burri C, *et al.* Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by Trypanosoma brucei gambiense: a randomised trial. *Lancet* 2000; **355:** 1419–25.
6. Schmid C, *et al.* Efficacy of 10-day melarsoprol schedule 2 years after treatment for late-stage gambiense sleeping sickness. *Lancet* 2004; **364:** 789–90.
7. Schmid C, *et al.* Effectiveness of a 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: confirmation from a multinational study (IMPAMEL II). *J Infect Dis* 2005; **191:** 1922–31.

Adverse Effects and Treatment

Adverse effects are common and may be severe during the treatment of African trypanosomiasis with melarsoprol. It may be difficult to distinguish between effects of the disease, Jarisch-Herxheimer reactions resulting from the release of antigens from trypanosomes killed by melarsoprol, and adverse effects due to the drug's arsenic content or to hypersensitivity. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p. 2448.3.

A severe febrile reaction may occur after the first injection of melarsoprol, especially in patients with large numbers of trypanosomes in their blood. For those patients receiving intermittent cyclic treatment it is common practice to give 2 or 3 injections of suramin or pentamidine before starting melarsoprol therapy.

The most serious adverse effect is reactive encephalopathy, which occurs in about 3 to 10% of patients treated with melarsoprol and is usually seen between the end of the first 3- or 4-day course of injections and the start of the second course in those patients receiving intermittent cyclic treatment and from day 8 to 10 in those receiving the 10-day consecutive schedule. (For further information on treatment schedules see Uses and Administration, p. 934.3.) Encephalopathy may be sudden in onset or develop slowly. Symptoms include fever, headache, tremor, slurring of speech, convulsions, and coma; death has occurred in up to 5% of patients treated with melarsoprol. Less commonly, haemorrhagic encephalopathy may occur. The prophylactic use of corticosteroids has been suggested during treatment courses of melarsoprol (see African Trypanosomiasis, p. 934.3). Treatment of reactive encephalopathy has included the use of corticosteroids, hypertonic solutions to combat cerebral oedema, anticonvulsants such as diazepam, and subcutaneous adrenaline; dimercaprol has been given on the assumption that encephalopathy resulted from arsenic poisoning, but has not generally been of benefit.

Hypersensitivity reactions to melarsoprol may occur during the second and subsequent courses of treatment. Desensitisation with gradually increasing doses of melarsoprol has been attempted; corticosteroids may help to control symptoms during this procedure. Some authorities consider that the use of small doses of melarsoprol may increase the risk of resistance.

Melarsoprol injection is very irritant and extravasation during intravenous use should be avoided. Vomiting and abdominal colic may occur if it is injected too rapidly. Other adverse effects reported include agranulocytosis, hypertension, peripheral neuropathy, proteinuria, severe diarrhoea, myocardial damage, exfoliative dermatitis, and renal and hepatic disturbances.

References.
1. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; **i:** 1246–50.
2. Pepin J, Milord F. African trypanosomiasis and drug-induced encephalopathy: risk factors and pathogenesis. *Trans R Soc Trop Med Hyg* 1991; **85:** 222–4.
3. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; **89:** 92–7.

Precautions

Use of melarsoprol in febrile patients has been associated with an increased incidence of reactive encephalopathy, and therefore it should not be given during epidemics of influenza. Intercurrent infections such as malaria and pneumonia should be treated before melarsoprol is used. Severe haemolytic reactions have been reported in patients with G6PD deficiency. It may precipitate erythema nodosum when given to patients with leprosy.

Patients should be in hospital when they are treated with melarsoprol and dosage decided after taking into account their general condition.

Treatment of pregnant women with trypanosomiasis should be deferred until after delivery. Pregnant women with meningoencephalitis may be treated with pentamidine (*Trypanosoma brucei gambiense*) or suramin (*T. b. rhodesiense*).

Pharmacokinetics

Melarsoprol is reported to be unreliably absorbed if given orally and is usually given by intravenous injection. A small amount penetrates into the CSF where it has a local trypanocidal action. It is a prodrug and is rapidly metabolised to the active form, melarsen oxide. Melarsoprol itself has a plasma half-life of 30 minutes and is excreted in the faeces and urine.

The pharmacokinetics of melarsoprol have not been fully evaluated. Using biological assay and atomic absorption spectrometry, the terminal half-life of melarsoprol was originally calculated to be 35 hours and low trypanocidal activity was detected in the CSF. These methods, however, cannot distinguish melarsoprol from other substances such as melarsoprol metabolites that also have trypanocidal activity. When the terminal half-life was calculated by high-performance liquid chromatography (HPLC), melarsoprol was found to be eliminated from the plasma within 1 hour.[1,2] Based on these findings it is thought that melarsoprol is rapidly eliminated from the plasma and transformed into metabolites with trypanocidal activity.[1] Melarsen oxide has been identified by HPLC as a metabolite; the peak plasma concentration was reached 15 minutes after a dose and the half-life of free melarsen oxide was 3.9 hours.[2]

1. Bronner U, *et al.* Discrepancy in plasma melarsoprol concentrations between HPLC and bioassay methods in patients with T. gambiense sleeping sickness indicates that melarsoprol is metabolized. *Trop Med Int Health* 1998; **3:** 913–7.
2. Keiser J, *et al.* Investigations of the metabolites of the trypanocidal drug melarsoprol. *Clin Pharmacol Ther* 2000; **67:** 478–88.

Mepacrine Hydrochloride *(BANM, rINNM)*

Acrichinum; Acrinamine; Antimalarinae Chlorhydras; Chinacrina; Hidrocloruro de atatabrina; Hidrocloruro de mepacrina; Hidrocloruro de quinacrina; Mepacrina, hidrocloruro de; Mépacrine, Chlorhydrate de; Mepacrini Hydrochloridum; Mepakrin Hidroklorür; Quinacrine Hydrochloride; Мепакрина Гидрохлорид.

6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate.

$C_{23}H_{30}ClN_3O,2HCl,2H_2O$=508.9

CAS — 83-89-6 (mepacrine); 69-05-6 (anhydrous mepacrine dihydrochloride); 6151-30-0 (mepacrine dihydrochloride dihydrate).

ATC — P01AX05.

UNII — G6242H2NAA (mepacrine hydrochloride dihydrate); 81A613ZZ6X (anhydrous mepacrine hydrochloride).

Uses and Administration

Mepacrine is a 9-aminoacridine antiprotozoal used as the hydrochloride mainly as an alternative to the nitroimidazoles in the treatment of giardiasis (p. 921.3).

In giardiasis, mepacrine hydrochloride is given orally in doses of 100 mg three times daily after food for 5 to 7 days.

For details of doses in children, see below.

Mepacrine hydrochloride may also be used for the treatment of some cutaneous forms of lupus erythematosus and for SLE (see below). It has also been used locally in the treatment of some forms of cutaneous leishmaniasis, as a sterilisation technique for contraception, and in the management of malignant pleural effusions. For further information on such uses see below. It was formerly used to treat malaria.

The mesilate was also formerly used.

Mepacrine is under investigation for the treatment of variant Creutzfeldt-Jakob Disease.

Administration in children. As an alternative drug for the treatment of giardiasis, mepacrine hydrochloride may be given orally to children at a dose of 2 mg/kg three times daily after food (to a maximum 300 mg daily) for 5 days.

Contraception. Sterilisation with intra-uterine mepacrine has been attempted as an irreversible method of contraception (p. 2232.3). It produces occlusion of the fallopian tube and has been reported to be an effective non-surgical means of female sterilisation,[1] although it may be less effective than other methods.[2] There has been speculation about the risk of cancer from this technique but there appeared to be no evidence to confirm such a risk.[3-5] However, the method remains controversial and a full evaluation of its safety and efficacy has been recommended.[6] The Indian government has banned the use of mepacrine for sterilisation.[7]

1. Hieu DT, *et al.* 31 781 Cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; **342:** 213–17.
2. Sokal DC, *et al.* Contraceptive effectiveness of two insertions of quinacrine: results from 10-year follow-up in Vietnam. *Contraception* 2008; **78:** 61–5.
3. Anonymous. Death of a study: WHO, what, and why. *Lancet* 1994; **343:** 987–8.
4. Hieu DT. Quinacrine method of family planning. *Lancet* 1994; **343:** 1040.
5. Sokal DC, *et al.* Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. *Contraception* 2008; **78:** 66–72.
6. Benagiano G. Sterilisation by quinacrine. *Lancet* 1994; **344:** 689.
7. WHO. *Pharmaceuticals: restrictions in use and availability.* Geneva: WHO, 2001. Available at: http://whqlibdoc.who.int/hq/2001/EDM_QSM_2001.3.pdf (accessed 6/03/09)

Leishmaniasis. Mepacrine has historically been suggested for intralesional injection in the treatment of early noninflamed nodular lesions of cutaneous leishmaniasis (p. 922.1) due to *Leishmania tropica*, *L. major*, *L. mexicana*, *L. panamensis*, or *L. peruviana*.[1] The suggested course of treatment was 3 intralesional injections of a 5% solution of mepacrine given at intervals of 3 to 5 days. However, local infiltration of drugs can be difficult and painful.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 27/07/09)

Lupus erythematosus. Mepacrine may be added to the treatment regimen of patients with some forms of cutaneous lupus erythematosus. Treatment is usually started with hydroxychloroquine and if no improvement occurs after about 2 months mepacrine is added at an initial dosage of 100 mg daily. If this combination treatment is effective the dose of both drugs may be decreased after 1 month to reduce any adverse effects. Chloroquine may be used as an alternative to hydroxychloroquine and can also be combined with mepacrine.[1,2] Mepacrine has also been used as monotherapy, in a similar dose, in patients with visual disorders in whom treatment with hydroxychloroquine or chloroquine was considered unsuitable.[2]

Mepacrine has also been used as an alternative to standard treatments in SLE (p. 1613.3). A small study[3] reported that 5 of 6 patients with SLE unresponsive to treatment with hydroxychloroquine plus prednisone and either azathioprine or methotrexate, had complete remission of their disease when mepacrine (100 mg daily) was added to their existing treatment. Other small studies[4,5] in patients with stable SLE disease found that the addition of mepacrine to their current treatment reduced the SLE disease activity index and lowered serum levels of B lymphocyte activating factor and anticardiolipin antibody titres in some patients.

1. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther* 2007; **20:** 160–74.
2. González-Sixto B, *et al.* Aspectos prácticos de la quinacrina como tratamiento del lupus eritematoso cutáneo: serie de casos. *Actas Dermosifiliogr* 2010; **101:** 54–8.
3. Toubi E, *et al.* The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients. *Lupus* 2000; **9:** 92–5.
4. Toubi E, *et al.* Quinacrine added to ongoing therapeutic regimens attenuates anticardiolipin antibody production in SLE. *Lupus* 2003; **12:** 297–301.
5. Toubi E, *et al.* The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. *Scand J Immunol* 2006; **63:** 299–303.

Sclerotherapy. Intrapleural instillations of mepacrine hydrochloride or mesilate have been used as sclerosants in the management of malignant pleural effusions (p. 700.1) and recurrent pneumothorax but the treatment is associated with pain and a high frequency of toxic effects.

Adverse Effects

The most common adverse effects associated with mepacrine are dizziness, headache, and gastrointestinal disturbances such as nausea and vomiting. Reversible yellow discoloration of the skin, conjunctiva, and urine may occur during long-term use or after large doses; blue/black discoloration of the palate and discoloration of the nails have also been reported. Doses such as those used in the treatment of giardiasis may occasionally cause transient acute toxic psychosis. CNS stimulation and convulsions have been reported at high parenteral doses. Retinopathy similar to that seen with chloroquine (p. 651.2) and chronic dermatoses, including severe exfoliative dermatitis and lichenoid eruptions, have also occurred after prolonged use of mepacrine. Aplastic anaemia has also been reported after long term use, often preceded by such dermatoses. Hepatitis and hepatic necrosis occur rarely.

Effects on the nervous system. Two patients had convulsions a few hours after mepacrine hydrochloride 400 mg was given intrapleurally for malignant effusions.

One developed status epilepticus and died and the other was successfully treated with anticonvulsants.[1]

1. Borda I, Krant M. Convulsions following intrapleural administration of quinacrine hydrochloride. *JAMA* 1967; **201:** 1049–50.

Precautions

Mepacrine should be used with caution in elderly patients or patients with a history of psychosis, or in the presence of hepatic disease. Mepacrine can cause exacerbation of psoriasis and should be avoided in psoriatic patients.

Interactions

Mepacrine has been reported to produce a mild disulfiram-like reaction (see p. 2496.1) when taken with alcohol.

Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Pharmacokinetics

Mepacrine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur in 1 to 3 hours. It is widely distributed throughout the body. It accumulates in body tissues, particularly the liver, and is liberated slowly. Protein binding is 85%. It is excreted slowly mainly in the urine, with an elimination half-life of 5 days, and is still detectable in the urine after 2 months. Mepacrine crosses the placenta.

Intrapleural administration. Peak plasma concentrations of mepacrine far above those associated with CNS effects were rapidly attained in 3 of 4 patients after intrapleural instillation of a solution of mepacrine hydrochloride and remained at these levels for several hours.[1]

1. Björkman S, *et al.* Pharmacokinetics of quinacrine after intrapleural instillation in rabbits and man. *J Pharm Pharmacol* 1989; **41:** 160–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Maladin.

Methyl Benzoquate *(BAN)*

AY-20385; ICI-55052; Metilbenzocuato; Nequinate (pINN); Nequinate (USAN); Néquinate; Nequinato; Nequinatum; Нехинат.

Methyl 7-benzyloxy-6-butyl-1,4-dihydro-4-oxoquinoline-3-carboxylate.

$C_{22}H_{23}NO_4$=365.4

CAS — 13997-19-8.

UNII — 91ZE013933.

Profile

Methyl benzoquate is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Metronidazole *(BAN, USAN, rINN)*

Bayer-5360; Metronidatsoli; Metronidazol; Metronidazolas; Métronidazole; Metronidazolo; Metronidazolum; NSC-50364; RP-8823; SC-10295; Метронидазол.

2-(2-Methyl-5-nitroimidazol-1-yl)ethanol.

$C_6H_9N_3O_3$=171.2

CAS — 443-48-1.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

UNII — 140QMO216E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Metronidazole). A white or yellowish, crystalline powder. Slightly soluble in water, in alcohol, in acetone, and in dichloromethane. Protect from light.

USP 36: (Metronidazole). White to pale yellow, odourless crystals or crystalline powder. It darkens on exposure to light. Sparingly soluble in water and in alcohol; slightly soluble in chloroform and in ether; soluble in dilute hydrochloric acid (1 in 2). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. See below.

Metronidazole Benzoate *(BAN, rINNM)*

Benzoato de metronidazol; Benzoyl Metronidazole; Metronidatsolibentsoaatti; Metronidazol, benzoato de; Metronidazolbensoat; Metronidazolbenzoat; Metronidazol-benzoát; Métronidazole, benzoate de; Metronidazoli Benzoas; Metronidazolo benzoatas; RP-9712; Метронидазола бензоат.

2-(2-Methyl-5-nitroimidazol-1-yl)ethyl benzoate.

$C_{13}H_{13}N_3O_4$=275.3

CAS — 13182-89-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

UNII — A355C835XC.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Metronidazole Benzoate). White or slightly yellowish, crystalline powder or flakes. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Metronidazole Benzoate). A white to slightly yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; very slightly soluble in solvent ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Metronidazole Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de metronidazol; Metronidazol, hidrocloruro de; Métronidazole, Chlorhydrate de; Metronidazoli Hydrochloridum; SC-32642; Метронидазола Гидрохлорид.

$C_6H_9N_3O_3$,HCl=207.6

CAS — 69198-10-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

UNII — 76JC1633UF.

Incompatibility. Solutions of metronidazole hydrochloride have a low pH, usually of less than 2.0, before dilution and neutralisation for intravenous use. These undiluted solutions react with aluminium in equipment such as needles and produce reddish-brown discoloration, and a precipitate has been reported with ready-to-use preparations of metronidazole hydrochloride, although this occurred after contact for 6 hours or more.[1,2]

Several studies have assessed the compatibility of antibacterial injections and other drugs when added to metronidazole solution for intravenous infusion.[3-7] Results have varied according to the criteria applied and the preparations and conditions used. Physical incompatibilities due to the low pH of metronidazole injections appear to be more of a problem than chemical incompatibility. Regardless of these studies, it is generally recommended that other drugs should not be added to intravenous solutions of metronidazole or its hydrochloride. Specific information on the compatibility of individual formulations may be found in the manufacturers' literature.

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bisaillon S, Sarrazin R. Compatibility of several antibiotics or hydrocortisone when added to metronidazole solution for intravenous infusion. *J Parenter Sci Technol* 1983; **37:** 129–32.
4. Gupta VD, Stewart KR. Chemical stabilities of hydrocortisone sodium succinate and several antibiotics when mixed with metronidazole injection for intravenous infusion. *J Parenter Sci Technol* 1985; **39:** 145–8.
5. Gupta VD, *et al.* Chemical stabilities of cefamandole nafate and metronidazole when mixed together for intravenous infusion. *J Clin Hosp Pharm* 1985; **10:** 379–83.
6. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; **15:** 187–96.
7. Nahata MC, *et al.* Stability of metronidazole and ceftizoxime sodium in ready-to-use metronidazole bags stored at 4 and 25 degrees C. *Am J Health-Syst Pharm* 1996; **53:** 1046–8.

Uses and Administration

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa (see Antimicrobial Action, p. 939.3); it also has a radiosensitising effect and has been tried in the treatment of malignant neoplasms. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced.

Metronidazole is used in the treatment of susceptible protozoal infections such as amoebiasis, balantidiasis, *Blastocystis hominis* infections, giardiasis, and trichomoniasis; it has also been tried in leishmaniasis and microsporidiosis. For details of these infections and their treatment see under Choice of Antiprotozoal, p. 919.1. Metronidazole is also used in the treatment and prophylaxis of anaerobic bacterial infections. Specific bacterial infections treated with metronidazole include acute necrotising ulcerative gingivitis, bacterial vaginosis, pelvic inflammatory disease, urethritis (nongonococcal), tetanus, and antibiotic-associated colitis. For details of these infections and their treatment see under Choice of Antibacterial, p. 172.2.

Metronidazole is used to eradicate *Helicobacter pylori* in peptic ulcer disease (with other antimicrobials, and either bismuth compounds or proton pump inhibitors) and in the management of malodorous tumours and ulcers where there is anaerobic infection. It is also used in the treatment of rosacea and of dracunculiasis (guinea-worm infection) and has been given orally in the treatment of hepatic encephalopathy and perianal Crohn's disease; a topical ointment containing 10% metronidazole is also under investigation for the treatment of perianal Crohn's disease. See also below for these miscellaneous uses.

ADMINISTRATION AND DOSAGE. Metronidazole is given orally in tablets, capsules, or extended release tablets or, as metronidazole benzoate, in oral suspension; the tablets are taken with or after food and the suspension at least 1 hour before food. Extended-release tablets should be given at least 1 hour before or 2 hours after meals. Metronidazole is also given rectally in suppositories, intravaginally as a gel or cream, applied topically as a cream or gel, or given by intravenous infusion of metronidazole or metronidazole hydrochloride. Doses are expressed in terms of metronidazole base.

In **amoebiasis**, metronidazole acts as an amoebicide at all sites of infection with *Entamoeba histolytica*. Because of its rapid absorption it is probably less effective against parasites in the bowel lumen and is therefore used with a luminal amoebicide such as diloxanide furoate or diiodohydroxyquinoline in the treatment of symptomatic (invasive) amoebiasis. For the treatment of invasive intestinal amoebiasis, metronidazole is given in oral doses of 800 mg every 8 hours for 5 days; for extra-intestinal amoebiasis (including liver abscess) a dose of 400 to 800 mg every 8 hours for 5 to 10 days is given.

In **balantidiasis** and ***Blastocystis hominis* infection**, metronidazole has been given orally in a dose of 750 mg three times daily for 5 and 10 days, respectively.

In **giardiasis**, the usual oral dose of metronidazole is 2 g once daily for 3 successive days, or 400 mg three times daily for 5 days, or 500 mg twice daily for 7 to 10 days.

In **trichomoniasis**, metronidazole is given orally either as a single 2-g dose, as a 7-day course of 200 mg every 8 hours, or at a dose of 400 to 500 mg every 12 hours for 5 to 7 days. Sexual partners should also be treated. If treatment needs to be repeated, an interval of 4 to 6 weeks between courses has been recommended. Vaginal preparations containing metronidazole are available for the treatment of vaginal trichomoniasis in some countries.

Bacterial vaginosis is treated similarly to vaginal trichomoniasis with which it may co-exist; metronidazole is usually given orally as a single 2-g dose or as a 5 to 7-day course of 400 or 500 mg twice daily. Alternatively it may be applied locally as 5 g of a 0.75% gel once or twice daily for 5 days.

In **acute necrotising ulcerative gingivitis**, metronidazole 200 to 250 mg three times daily is given orally for 3 days; similar doses are used in acute oral infections. A 25% dental gel has also been used as an adjunct to the treatment of chronic periodontal infections.

For the treatment of most **anaerobic bacterial infections**, metronidazole is given orally in an initial dose of 800 mg followed by 400 mg every 8 hours, usually for about 7 days. A regimen of 500 mg every 8 hours is an alternative. When oral therapy is precluded metronidazole may be given intravenously, 500 mg being infused as 100 mL of a 5 mg/mL solution at a rate of 5 mL/minute every 8 hours, or rectally as a 1-g suppository every 8 hours for 3 days; if rectal use needs to be continued for more than 3 days, the dose should be reduced to 1 g 12 hourly. Alternative adult doses of metronidazole are 7.5 mg/kg every 6 to 8 hours orally or 15 mg/kg by intravenous infusion followed by 7.5 mg/kg every 6 hours, doses being infused over 1 hour; by either route a total dose of 4 g in 24 hours should not be exceeded. In mixed anaerobic and aerobic infections metronidazole is given with the appropriate antibacterials.

For details of doses in children, see p. 937.1.

For the **prevention of postoperative anaerobic bacterial infections**, especially in patients undergoing abdominal or gynaecological surgery, metronidazole is given orally, intravenously, or rectally in doses similar to those used for treatment, usually with a beta-lactam or an aminoglycoside antibacterial. Various schedules have been employed. In the UK, licensed doses for adults are:

- orally 400 mg every 8 hours in the 24 hours before surgery followed postoperatively by intravenous or rectal dosage until oral therapy is possible
- by intravenous infusion, 500 mg shortly before operation and repeated every 8 hours, oral doses of 200 or 400 mg every 8 hours being substituted as soon as possible
- by rectum, 1 g every 8 hours starting 2 hours before surgery.

The *BNF*, however, recommends that oral doses should be started only 2 hours before the operation and that the

number of doses for all dose routes be limited to a total of four. In the USA the recommended schedule for adults undergoing colorectal surgery is metronidazole 15 mg/kg by intravenous infusion over 30 to 60 minutes, completed about 1 hour before surgery, followed by two further intravenous doses of 7.5 mg/kg infused at 6 and 12 hours after the initial dose.

In **peptic ulcer disease**, metronidazole is used in combination therapy to eradicate *Helicobacter pylori*. Typical regimens include metronidazole plus another antibacterial (clarithromycin or amoxicillin) and a proton pump inhibitor. The usual dose of metronidazole is 400 mg twice daily except when given with omeprazole and amoxicillin, when metronidazole 400 mg three times daily is used. Initial treatment is given for 1 week.

For **leg ulcers** and **pressure sores** infected with anaerobic bacteria, oral metronidazole 400 mg may be given three times daily for 7 days. Metronidazole is also applied topically as a 0.75% or 0.8% gel to reduce the odour associated with anaerobic infection in **fungating tumours**.

In the treatment of **rosacea** metronidazole is given orally or applied topically.

General references.

1. Löfmark S, *et al.* Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clin Infect Dis* 2010; **50** (suppl 1): S16–S23.

Administration in children. Metronidazole may be given to children for the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections.

In **invasive intestinal amoebiasis** and **extra-intestinal amoebiasis**, the *BNFC* recommends oral metronidazole, for 5 days for intestinal infection or 5 to 10 days for extra-intestinal infection, in the following doses:

- children aged 1 to 3 years: 200 mg 3 times daily
- those aged 3 to 7 years: 200 mg 4 times daily
- those aged 7 to 10 years: 400 mg 3 times daily
- those more than 10 years: 800 mg 3 times daily

Alternatively experts in the USA[1] recommend oral metronidazole 35 to 50 mg/kg daily in 3 divided doses for 7 to 10 days.

In **giardiasis**, the *BNFC* recommends oral metronidazole in the following doses:

- children aged 1 to 3 years: 500 mg once daily for 3 days
- those aged 3 to 7 years: 600 to 800 mg once daily for 3 days
- those aged 7 to 10 years: 1 g once daily for 3 days
- those aged more than 10 years: 2 g once daily for 3 days, or 400 mg 3 times daily for 5 days, or 500 mg twice daily for 7 to 10 days

Alternatively experts in the USA[1] recommend oral metronidazole 15 mg/kg daily in 3 divided doses for 5 to 7 days.

In **trichomoniasis**, the *BNFC* recommends oral metronidazole in the following doses:

- children aged 1 to 3 years: 50 mg 3 times daily for 7 days
- those aged 3 to 7 years: 100 mg twice daily for 7 days
- those aged 7 to 10 years: 100 mg 3 times daily for 7 days
- those more than 10 years: 200 mg 3 times daily for 7 days or 400 to 500 mg twice daily for 5 to 7 days, or 2 g as a single dose

Alternatively experts in the USA[1] recommend oral metronidazole 15 mg/kg daily in 3 divided doses for 7 days.

For the treatment of most **anaerobic bacterial infections**, the *BNFC* recommends metronidazole is given (usually for 7 days but for 10 to 14 days in antibiotic-associated colitis) in the following doses:

- neonates: 7.5 mg/kg by intravenous infusion every 12 hours
- children 1 to 2 months of age: 7.5 mg/kg orally every 12 hours, *or* 7.5 mg/kg by intravenous infusion every 12 hours
- children aged 2 months and older: 7.5 mg/kg orally (to a maximum of 400 mg) every 8 hours, *or* 7.5 mg/kg by intravenous infusion (to a maximum of 500 mg) every 8 hours

or alternatively

- rectal doses may be given 3 times daily for 3 days, then twice daily thereafter in the following doses: children aged 1 month to 1 year may be given 125 mg, those 1 to 5 years, 250 mg, those 5 to 10 years, 500 mg, and those more than 10 years may be given 1 g

Alternative doses recommended by the American Academy of Pediatrics[2] are:

- for neonates aged ⩽7 days and weighing ⩽2 kg: a loading dose of 15 mg/kg followed by 7.5 mg/kg given intravenously every 24 to 48 hours; a dosing interval of 48 hours is suggested for extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged ⩽7 days and weighing >2 kg: 15 mg/kg given intravenously every 24 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 15 mg/kg given intravenously every 24 hours; a dosing interval of 48 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 15 mg/kg given intravenously every 12 hours
- children 1 month and older: 30 to 50 mg/kg given orally in 3 divided doses (to a maximum daily dose of 0.75 to 2.25 g) *or* 22.5 to 40 mg/kg given intravenously in 3 divided doses (to a maximum daily dose of 1.5 g)

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter,2013.
2. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in hepatic impairment. Since metronidazole is mainly metabolised by hepatic oxidation, accumulation of metronidazole and its metabolites is likely in patients with severely impaired hepatic function. Metronidazole should therefore be given with caution and at reduced doses to patients with severe hepatic impairment, and especially hepatic encephalopathy when adverse affects of metronidazole can add to the symptoms of the disease. One-third of the usual daily dose may be given once daily in these patients. For patients with lesser degrees of hepatic impairment, pharmacokinetic studies have not produced consistent results (see under Pharmacokinetics, p. 940.2) and no recommendations about dosage reduction have been made in either the UK or US licensed product information.

Administration in renal impairment. The elimination of metronidazole is largely unchanged in patients with renal impairment, although metabolites may accumulate in patients with end-stage renal disease on dialysis (see under Pharmacokinetics, p. 940.2). Dosage reductions are therefore not usually recommended for patients with renal impairment or for those undergoing peritoneal dialysis. However, both metronidazole and its metabolites are removed by haemodialysis, doses need to be given immediately after haemodialysis.

Dracunculiasis. Metronidazole may be beneficial in the management of dracunculiasis (p. 145.1). It provides symptomatic relief and is also thought to weaken the anchorage of the worms within subcutaneous tissue, thus allowing them to be removed more quickly.

Metronidazole has been given in a variety of regimens, including doses of 400 mg three times daily for 5 days,[1] 40 mg/kg daily in three divided doses (to a maximum daily dose of 2.4 g) for 3 days,[2] and 400 mg daily for 10 to 20 days.[3] WHO recommends 25 mg/kg daily for 10 days;[4] a dose of 250 mg three times daily for 10 days has also been recommended.

1. Padonu KO. A controlled trial of metronidazole in the treatment of dracontiasis in Nigeria. *Am J Trop Med Hyg* 1973; **22:** 42–4.
2. Kale OO. A controlled field trial of the treatment of dracontiasis with metronidazole and niridazole. *Ann Trop Med Parasitol* 1974; **68:** 91–5.
3. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57:** 683–9.
4. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 21/04/09)

Hepatic encephalopathy. The treatment of hepatic encephalopathy is discussed on p. 1811.2. It includes the use of an antimicrobial such as metronidazole to reduce the intestinal flora.

Inflammatory bowel disease. Oral metronidazole is used in the treatment of perineal Crohn's disease (see Inflammatory Bowel Disease, p. 1811.3) and may also be used in colonic Crohn's disease, when it has been tried with ciprofloxacin. It has also proved effective for the prevention of postsurgical recurrence. Duration of therapy is usually limited to 3 months.

Metronidazole ointment is being investigated in the management of perianal Crohn's disease.[1]

1. Maeda Y, *et al.* Randomized clinical trial of metronidazole ointment versus placebo in perianal Crohn's disease. *Br J Surg* 2010; **97:** 1340–7.

Metabolic disorders. Children with excesses of methylmalonic[1-3] and propionic[3,4] acid in their blood or urine have shown clinical improvement when given metronidazole, which reduced the excretion of faecal propionate and urinary methylmalonate. Metronidazole is considered to act through its antimicrobial effect on gut anaerobes that are involved in propionate production; such propionate cannot be handled by these children who are deficient in the relevant enzyme.

1. Bain MD, *et al.* Contribution of gut bacterial metabolism to human metabolic disease. *Lancet* 1988; **i:** 1078–9.
2. Koletzko B, *et al.* Antibiotic therapy for improvement of metabolic control in methylmalonic aciduria. *J Pediatr* 1990; **117:** 99–101.
3. Deodato F, *et al.* Methylmalonic and propionic aciduria. *Am J Med Genet C Semin Med Genet* 2006; **142C:** 104–12.
4. Mellon AF, *et al.* Effect of oral antibiotics on intestinal production of propionic acid. *Arch Dis Child* 2000; **82:** 169–72.

Mouth disorders and infections. Ciclosporin-induced gingival hyperplasia resolved in several patients after treatment with metronidazole.[1,2]

Metronidazole is considered to be effective for the treatment of acute necrotising ulcerative gingivitis and is an alternative to penicillin in other dental infections (see Mouth Infections, p. 192.3).

1. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343:** 986.
2. Cecchin E, *et al.* Treatment of cyclosporine-induced gingival hypertrophy. *Ann Intern Med* 1997; **126:** 409–10.

Peptic ulcer disease. The use of metronidazole is well established in regimens for eradicating *Helicobacter pylori* (see Peptic Ulcer Disease, p. 1816.2). However, the emergence of metronidazole-resistant strains of *H. pylori* has been associated with an increased rate of treatment failures with some regimens.[1-4] The *Helicobacter pylori* Antimicrobial Resistance Monitoring Program (HARP) in the USA[5] reported about a 25% metronidazole resistance rate in clinical *H. pylori* isolates collected from December 1998 through 2002. Difficulties arise in assessing metronidazole resistance and in correlating *in-vitro* results with clinical response.[6] In populations in which the incidence of resistance is high, it may become necessary to use alternative regimens,[7] but in other areas, such as the UK, regimens including metronidazole continue to be among the standard alternatives (although the *BNF* recommends that they should not be used for initial treatment in patients who have been given metronidazole for other infections).

1. Buckley MJM, *et al.* Metronidazole resistance reduces efficacy of triple therapy and leads to secondary clarithromycin resistance. *Dig Dis Sci* 1997; **42:** 2111–15.
2. Lerang F, *et al.* Highly effective twice-daily triple therapies for Helicobacter pylori infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? *Am J Gastroenterol* 1997; **92:** 248–53.
3. Misiewicz JJ, *et al.* One week triple therapy for Helicobacter pylori: a multicentre comparative study. *Gut* 1997; **41:** 735–9.
4. van Zanten SV, *et al.* Adding once-daily omeprazole 20 mg to metronidazole/amoxicillin treatment for Helicobacter pylori gastritis: a randomized, double-blind trial showing the importance of metronidazole resistance. *Am J Gastroenterol* 1998; **93:** 5–10.
5. Duck WM, *et al.* Antimicrobial resistance incidence and risk factors among Helicobacter pylori-infected persons, United States. *Emerg Infect Dis* 2004; **10:** 1088–94.
6. Goddard AF, Logan RPH. Antimicrobial resistance and Helicobacter pylori. *J Antimicrob Chemother* 1996; **37:** 639–43.
7. Fennerty MB. Should we abandon metronidazole containing Helicobacter pylori treatment regimens? The clinical relevance of metronidazole resistance. *Am J Gastroenterol* 1998; **93:** 2–3.

Skin disorders. Metronidazole may be effective in the management of malodorous anaerobic skin infections associated with ulceration (p. 207.1), including *pressure sores* and *fungating tumours*. Both the oral and topical routes have been employed but the evidence in favour of its use is largely anecdotal as few randomised controlled studies have yet been performed.[1,2]

Metronidazole has also been used[3] in the treatment of *rosacea* (p. 1688.3). Oral metronidazole 200 mg twice daily was more effective than placebo[4] and as effective as oral oxytetracycline.[5] Similarly, topical preparations (for example, 0.75% cream, gel, or lotion or 1% cream) have been found to be better than placebo and as effective as oral oxytetracycline.[6,7]

Oral metronidazole has been tried in the management of *lichen planus*.[8]

1. Clark J. Metronidazole gel in managing malodorous fungating wounds. *Br J Nurs* 200211 (suppl): S54–S60.
2. Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy Wound Manage* 2008; **54:** 18–27.
3. Conde JF, *et al.* Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. *J Drugs Dermatol* 2007; **6:** 495–8.
4. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet* 1976; **i:** 1211–12.
5. Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol* 1980; **102:** 443–5.
6. McClellan KJ, Noble S. Topical metronidazole: a review of its use in rosacea. *Am J Clin Dermatol* 2000; **1:** 191–9.
7. Dahl MV, *et al.* Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. *J Am Acad Dermatol* 2001; **45:** 723–30.
8. Rasi A, *et al.* Efficacy of oral metronidazole in treatment of cutaneous and mucosal lichen planus. *J Drugs Dermatol* 2010; **9:** 1186–90.

Surgical infection. Metronidazole and related nitroimidazoles are used in surgical infection prophylaxis (p. 209.1) to reduce the rate of wound infection.

HAEMORRHOIDECTOMY. Prophylactic metronidazole reduced pain after haemorrhoidectomy in a small study.[1]

1. Carapeti EA, *et al.* Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. *Lancet* 1998; **351:** 169–72.

Adverse Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastrointestinal disturbances, especially nausea and an unpleasant metallic taste. Abdominal pain, anorexia, vomiting, and diarrhoea or constipation may also occur. A furred tongue, glossitis, and

stomatitis may be associated with an overgrowth of *Candida*. There have been rare reports of antibiotic-associated colitis associated with metronidazole, although it is also used in the treatment of this condition.

Weakness, dizziness, ataxia, headache, drowsiness, insomnia, hallucinations, and changes in mood or mental state such as depression or confusion have also been reported. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures have been associated with high doses of metronidazole or prolonged treatment.

There have been rare case reports of agranulocytosis, leucopenia, pancytopenia, and thrombocytopenia, often reversible on stopping of the drug; however, fatalities have occurred. Rashes, urticaria, and pruritus occur occasionally and erythema multiforme, angioedema, and anaphylaxis have been reported rarely. Other adverse effects include urethral discomfort and darkening of the urine. Raised liver enzyme values, cholestatic hepatitis, jaundice, and pancreatitis have occasionally been reported. Thrombophlebitis may follow intravenous use of metronidazole. Other very rarely reported adverse effects include myalgia, arthralgia, and transient visual disorders such as diplopia and myopia.

Studies have shown metronidazole to be mutagenic in bacteria and carcinogenic in some *animals*.

Carcinogenicity and mutagenicity. Metronidazole is mutagenic in bacterial assays, and its hydroxy metabolite even more so, but studies of mammalian cells *in vitro* and *in vivo* have not consistently shown a mutagenic effect. Similarly, there is no uniformity in the limited data concerning genotoxicity in humans,[1] and although metronidazole has been classified as a carcinogen in *animals*, the evidence of human carcinogenicity is ambiguous. There was no appreciable increase in the incidence of cancer in a retrospective study of 771 patients given metronidazole for vaginal trichomoniasis,[2] nor in another similar study of 2460 patients.[3] The first study[2] did show an excess of cases of lung cancer, although all 4 were in women who were smokers. Subsequent follow-up[4] to 1984, covering a period of 15 to 25 years, still showed an excess of lung cancer cases even after allowing for smoking status. However, this follow-up also continued to show no significant increase overall in cancer-related morbidity or mortality. Follow-up[5] of the patients from the second study for 11 to 15 years to 1984 also showed no increase in the overall incidence of cancers nor did it confirm any increase in lung cancer.

Risks to the fetus are discussed under Pregnancy in Precautions, p. 939.2.

1. Bendesky A, *et al*. Is metronidazole carcinogenic? *Mutat Res* 2002; **511:** 133–44.
2. Beard CM, *et al*. Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 1979; **301:** 519–22.
3. Friedman GD. Cancer after metronidazole. *N Engl J Med* 1980; **302:** 519.
4. Beard CM, *et al*. Cancer after exposure to metronidazole. *Mayo Clin Proc* 1988; **63:** 147–53.
5. Friedman GD, Selby JV. Metronidazole and cancer. *JAMA* 1989; **261:** 866.

Effects on the blood. Adverse haematological effects associated with metronidazole therapy include a report of bone marrow aplasia, with leucopenia and markedly reduced erythropoiesis and granulopoiesis,[1] aplastic anaemia,[2] and the haemolytic-uraemic syndrome.[3]

1. White CM, *et al*. Bone marrow aplasia associated with metronidazole. *BMJ* 1980; **280:** 647.
2. Raman R, *et al*. Metronidazole induced aplastic anaemia. *Clinician* 1982; **46:** 464–8.
3. Powell HR, *et al*. Haemolytic-uraemic syndrome after treatment with metronidazole. *Med J Aust* 1988; **149:** 222–3.

Effects on the ears. A review of reports of ototoxicity notified to the Australian Adverse Drug Reactions Advisory Committee revealed cases of deafness associated with the use of metronidazole.[1] Two cases of bilateral moderate to severe sensorineural deafness after taking oral metronidazole have been reported; in both patients hearing recovered gradually after the drug was stopped.[2]

1. Anonymous. Drug-induced ototoxicity. *WHO Drug Inf* 1991; **5:** 12.
2. Iqbal SM, *et al*. Metronidazole ototoxicity–report of two cases. *J Laryngol Otol* 1999; **113:** 355–7.

Effects on the eyes. Myopia that developed in a patient after 11 days of oral metronidazole for trichomoniasis had resolved 4 days after withdrawal of treatment, but recurred when she resumed treatment.[1]

Optic neuropathies have also occurred.[2,3] In one report, retrobulbar or optic neuritis was seen in 7 patients given oral metronidazole.[2] Dosage varied from 0.75 to 1 g daily and duration of treatment from 7 days to a year. Abnormalities included defects in colour vision, decreased vision, and scotomas. Vision improved on withdrawal of metronidazole, although there was a residual deficit in 2 patients.

1. Grinbaum A, *et al*. Transient myopia following metronidazole treatment for Trichomonas vaginalis. *JAMA* 1992; **267:** 511–12.
2. Putnam D, *et al*. Metronidazole and optic neuritis. *Am J Ophthalmol* 1991; **112:** 737.
3. McGrath NM, *et al*. Reversible optic neuropathy due to metronidazole. *Clin Experiment Ophthalmol* 2007; **35:** 585–6.

Effects on the gastrointestinal tract. *ANTIBIOTIC-ASSOCIATED COLITIS.* Exposure to antibacterials, particularly broad-spectrum antibacterials, is the most significant risk factor for development of antibiotic-associated colitis (AAC). Antibacterials usually used to treat the disease such as vancomycin and metronidazole have also been shown to cause AAC. AAC has been reported after a 4-day prophylactic course of metronidazole, given rectally[1] and after a 7-day course of oral metronidazole[2]; the condition resolved in both cases after treatment with oral vancomycin for 5 to 7 days. A 25-year-old woman developed AAC after a course of vancomycin and metronidazole, both orally, for pelvic inflammatory disease. The condition resolved after treatment with vancomycin given alone.[3] For further reports on AAC caused by vancomycin see under Vancomycin, p. 385.3.

1. Thomson G, *et al*. Pseudomembranous colitis after treatment with metronidazole. *BMJ* 1981; **282:** 864–5.
2. Daly JJ, Chowdary KVS. Pseudomembranous colitis secondary to metronidazole. *Dig Dis Sci* 1983; **28:** 573–4.
3. Bingley PJ, Harding GM. Clostridium difficile colitis following treatment with metronidazole and vancomycin. *Postgrad Med J* 1987; **63:** 993–4.

Effects on the liver. Severely elevated liver enzyme values, consistent with a drug-induced hepatitis, occurred in a patient given metronidazole hydrochloride 500 mg every 6 hours intravenously for 4 days. He was also receiving cefapirin sodium and tobramycin sulfate.[1] A case of reversible hepatotoxicity caused by an overdose of metronidazole 12.5 g has also been reported.[2] Fatal acute fulminant liver failure probably due to metronidazole occurred in a young woman who had also developed jaundice two years earlier after taking metronidazole.[3]

1. Appleby DH, Vogtland HD. Suspected metronidazole toxicity. *Clin Pharm* 1983; **2:** 373–4.
2. Lam S, Bank S. Hepatotoxicity caused by metronidazole overdose. *Ann Intern Med* 1995; **122:** 803.
3. Björnsson E, *et al*. Metronidazol as a probable cause of severe liver injury. *Hepatogastroenterology* 2002; **49:** 252–4.

Effects on the lungs. Report of a patient who had haemoptysis after ornidazole treatment for lambliasis;[1] he had also had dyspnoea and haemoptysis after similar treatment with metronidazole 10 months previously. Bronchoscopy findings were consistent with diffuse alveolar haemorrhage.

1. Uyar M, *et al*. Diffuse alveolar haemorrhage due to 5-nitroimidazole treatment. *Respirology* 2009; **14:** 612–13.

Effects on the nervous system. *ASEPTIC MENINGITIS.* A 42-year-old man had 3 episodes of aseptic meningitis during treatment with oral metronidazole as part of an eradication regimen for *Helicobacter pylori* infection.[1] On each occasion his symptoms resolved spontaneously when eradication treatment was stopped and recurred when treatment was restarted. The aseptic meningitis was attributed to the metronidazole and the patient later tolerated an eradication treatment regimen containing a proton pump inhibitor and a macrolide.

1. Khan S, *et al*. Metronidazole-induced aseptic meningitis during Helicobacter pylori eradication therapy. *Ann Intern Med* 2007; **146:** 395–6.

CEREBELLAR TOXICITY. Ataxia and dysarthria have been reported in 2 patients given oral metronidazole plus intravenous cefepime or oral levofloxacin.[1] Symptoms occurred about one month after starting treatment and resolved 2 to 5 weeks after stopping metronidazole. A later report[2] of a patient who developed cerebellar toxicity with objective abnormalities on MRI scanning during metronidazole therapy also identified 10 cases in the literature (including those referred to above). The age range of the patients was 17 to 74 years and most presented with symptoms of ataxia and dysarthria. Cerebellar toxicity in these reports appeared to be related to high cumulative doses of metronidazole (between 25 and 1080 g). Further cases have been reported.[3-5]

1. Woodruff BK, *et al*. Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med* 2002; **346:** 68–9.
2. Patel K, *et al*. Cerebellar ataxia following prolonged use of metronidazole: case report and literature review. *Int J Infect Dis* 2008; **12:** e111–e1114.
3. Graves TD, *et al*. Reversible metronidazole-induced cerebellar toxicity in a multiple transplant recipient. *J Neurol Sci* 2009; **285:** 238–40.
4. Sarna JR, *et al*. Cases: reversible cerebellar syndrome caused by metronidazole. *CMAJ* 2009; **181:** 611–3.
5. Chatzkel JA, Vossough A. Metronidazole-induced cerebellar toxicity. *Pediatr Radiol* 2010; **40:** 1453.

CONVULSIONS. Reports[1-6] of convulsions associated with metronidazole therapy (usually in high doses or in patients with renal impairment).

1. Halloran TJ. Convulsions associated with high cumulative doses of metronidazole. *Drug Intell Clin Pharm* 1982; **16:** 409.
2. Wienbren M, *et al*. Convulsions and encephalopathy in a patient with leukemia after treatment with metronidazole. *J Clin Pathol* 1985; **38:** 1076.
3. Ferroir JP, *et al*. Polynévrite, crises convulsives et syndrome cérébelleux, complications d'un traitement par le métronidazole. *Presse Med* 1985; **14:** 2108.
4. Moulin B, *et al*. Risque neurotoxique du métronidazole (MN) au cours de l'insuffisance rénale sévère. *Ann Med Interne (Paris)* 1988; **139:** 369.
5. Sopena B, *et al*. Convulsiones inducidas por la asociación de metronidazol y cloroquina. *Med Clin (Barc)* 1990; **95:** 675.
6. Beloosesky Y, *et al*. Convulsions induced by metronidazole treatment for Clostridium difficile-associated disease in chronic renal failure. *Am J Med Sci* 2000; **319:** 338–9.

EFFECTS ON MENTAL FUNCTION. Although metronidazole is sometimes used to reduce colonic flora in the treatment of hepatic encephalopathy, impaired metabolism of metronidazole in such patients can result in elevated plasma concentrations and consequent toxicity. Psychosis and manic behaviour were reported in a patient during treatment for hepatic encephalopathy with metronidazole and lactulose, although plasma-metronidazole concentrations were not found to be raised (24 micrograms/mL).[1] Symptoms resolved when metronidazole was stopped. Acute psychosis has also been reported in a patient after a 5-day course of intravenous metronidazole 1 g daily for a gynaecological disorder[2] and in an 18- year-old woman after 2 days of [oral] treatment for pelvic inflammatory disease with metronidazole 400 mg three times daily and ofloxacin 400 mg twice daily.[3] In another patient who developed probable metronidazole-associated encephalopathy after taking oral metronidazole, the symptoms gradually resolved over a period of 2 to 4 months.[4] Hallucinations[5] and confusion[5,6] have also been reported in other patients without hepatic encephalopathy; in undernourished patients it has been suggested that metronidazole-induced encephalopathy might involve a common pathway with Wernicke's encephalopathy,[7] from which it must be distinguished. Irreversible metronidazole-associated encephalopathy leading to death has been reported in a patient given 1.5 g as a single intravenous dose daily over 10 weeks as part of a regimen to treat osteomyelitis.[8] It has been suggested[9] that patients taking metronidazole for prolonged durations may be at increased risk of encephalopathy.

1. Uhl MD, Riely CA. Metronidazole in treating portosystemic encephalopathy. *Ann Intern Med* 1996; **124:** 455.
2. Schreiber W, Spernal J. Metronidazole-induced psychotic disorder. *Am J Psychiatry* 1997; **154:** 1170–1.
3. Koul S, *et al*. Organic psychosis induced by ofloxacin and metronidazole. *Br J Hosp Med* 2009; **70:** 236–7.
4. Khodakaram K, Barmano N. Uncommon reaction to a common prescription. *Lancet* 2011; **378:** 288.
5. Mahl TC, Ummadi S. Metronidazole and mental confusion. *J Clin Gastroenterol* 2003; **36:** 373–4.
6. Kim DW, *et al*. Metronidazole-induced encephalopathy. *J Neurol Sci* 2004; **224:** 107–11.
7. Zuccoli G, *et al*. Metronidazole-induced and Wernicke encephalopathy: two different entities sharing the same metabolic pathway? *AJNR Am J Neuroradiol* 2008; **29:** E84.
8. Groothoff MV, *et al*. Irreversible encephalopathy after treatment with high-dose intravenous metronidazole. *Clin Ther* 2010; **32:** 60–4.
9. Bottenberg MM, *et al*. Metronidazole-induced encephalopathy: a case report and review of the literature. *J Clin Pharmacol* 2011; **51:** 112–6.

PERIPHERAL NEUROPATHY. Peripheral neuropathy has been reported in patients given metronidazole, usually for long periods.[1-7] Stopping metronidazole or lowering the dose usually results in complete resolution or improvement of the neuropathy but in some patients it may persist despite these measures. For reports of retrobulbar or optic neuritis associated with metronidazole, see Effects on the Eyes, above.

1. Duffy LF, *et al*. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. *Gastroenterology* 1985; **88:** 681–4.
2. Boyce EG, *et al*. Persistent metronidazole-induced peripheral neuropathy. *DICP Ann Pharmacother* 1990; **24:** 19–21.
3. Learned-Coughlin S. Peripheral neuropathy induced by metronidazole. *Ann Pharmacother* 1994; **28:** 536.
4. Dreger LM, *et al*. Intermittent-dose metronidazole-induced peripheral neuropathy. *Ann Pharmacother* 1998; **32:** 267–8.
5. Zivkovic SA, *et al*. Sensory neuropathy associated with metronidazole: report of four cases and review of the literature. *J Clin Neuromusc Dis* 2001; **3:** 8–12.
6. Sarma GRK, Kamath V. Acute painful peripheral neuropathy due to metronidazole. *Neurol India* 2005; **53:** 372–3.
7. Toumi S, *et al*. Lésions cérébelleuses réversibles et neuropathie périphérique induites par le métronidazole. *Med Mal Infect* 2009; **39:** 906–8.

Effects on the pancreas. A small number of cases of acute pancreatitis associated with metronidazole, in some cases recurrent on rechallenge, have been reported.[1-8] The delay between metronidazole exposure and the onset of pancreatitis ranged from 12 hours to 38 days. All cases of pancreatitis were moderate and resolved after stopping the metronidazole. No cases were found in a retrospective study of about 6500 patients given metronidazole.[9] However, another retrospective analysis[10] of 3083 patients found that metronidazole may increase the risk of acute pancreatitis, but mainly when it is used with other drugs for the eradication of *Helicobacter pylori*.

1. Plotnick BH, *et al*. Metronidazole-induced pancreatitis. *Ann Intern Med* 1985; **103:** 891–2.
2. Sanford KA, *et al*. Metronidazole-associated pancreatitis. *Ann Intern Med* 1988; **109:** 756–7.
3. Sura ME, *et al*. Metronidazole-associated pancreatitis. *Ann Pharmacother* 2000; **34:** 1152–5.

4. Tsesmeli NE, *et al.* Acute pancreatitis as a possible consequence of metronidazole during a relapse of ulcerative colitis. *Eur J Gastroenterol Hepatol* 2007; **19:** 805–6.
5. Feola DJ, Thornton AC. Metronidazole-induced pancreatitis in a patient with recurrent vaginal trichomoniasis. *Pharmacotherapy* 2002; **22:** 1508–10.
6. Nigwekar SU, Casey KJ. Metronidazole-induced pancreatitis. A case report and review of literature. *JOP* 2004; **5:** 516–9.
7. Loulergue P, Mir O. Metronidazole-induced pancreatitis during HIV infection. *AIDS* 2008; **22:** 545–6.
8. O'Halloran E, *et al.* Metronidazole-induced pancreatitis. *HPB Surg* 2010; **2010:** 523468.
9. Friedman G, Selby JV. How often does metronidazole induce pancreatitis? *Gastroenterology* 1990; **98:** 1702–3.
10. Nørgaard M, *et al.* Metronidazole and risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2005; **21:** 415–20.

Gynaecomastia. Gynaecomastia occurred in a 36-year-old man with ulcerative colitis after taking metronidazole for about a month.[1]

1. Fagan TC, *et al.* Metronidazole-induced gynecomastia. *JAMA* 1985; **254:** 3217.

Hypersensitivity. A hypersensitivity reaction with chills, fever, generalised erythema, and a maculopapular rash developed after a single oral dose of metronidazole in a patient who had previously developed a rash during treatment with intravaginal metronidazole.[1] There have been a few case reports of fixed drug eruptions with oral metronidazole[2,3] and ornidazole[4] with cross-sensitivity to other nitroimidazoles (but not necessarily all of them); provocation or patch tests may be done with care to establish cross-sensitivity. Cutaneous exanthemas[5] in patients taking metronidazole have also been reported. Anaphylaxis has been reported,[6,7] including a case after an oral dose of metronidazole and spiramycin in which the subsequent skin prick test was positive for metronidazole.[6] Allergic contact dermatitis has been reported after application of topical metronidazole formulations.[8]

1. Knowles S, *et al.* Metronidazole hypersensitivity. *Ann Pharmacother* 1994; **28:** 325–6.
2. Sehgal VN, *et al.* Bullous fixed drug eruption (BFDE) following per-oral metronidazole. *J Eur Acad Dermatol Venereol* 2003; **17:** 607–9.
3. Prieto A, *et al.* Recurrent fixed drug eruption due to metronidazole elicited by patch test with tinidazole. *Contact Dermatitis* 2005; **53:** 169–70.
4. Sanmukhani J, *et al.* Fixed drug eruption with ornidazole having cross-sensitivity to secnidazole but not to other nitro-imidazole compounds: a case report. *Br J Clin Pharmacol* 2010; **69:** 703–4.
5. García-Rubio I, *et al.* Hypersensitivity reactions to metronidazole. *Allergol Immunopathol (Madr)* 2006; **34:** 70–2.
6. Asensio Sánchez T, *et al.* Anaphylaxis due to metronidazole with positive skin prick test. *J Investig Allergol Clin Immunol* 2008; **18:** 138–9.
7. Schmutz JL, *et al.* Réaction anaphylactique au métronidazole. *Ann Dermatol Venereol* 2009; **136:** 759.
8. Madsen JT, *et al.* Allergic contact dermatitis to topical metronidazole - 3 cases. *Contact Dermatitis* 2007; **56:** 364–6.

Precautions

Neurotoxic symptoms including peripheral neuropathy and transient epileptiform seizures, and other serious effects such as leucopenia have sometimes been associated with prolonged or intensive treatment with metronidazole (see Adverse Effects, p. 937.3). Clinical and laboratory monitoring is advised in patients given metronidazole for more than 10 days. Metronidazole should be used with caution in patients with blood dyscrasias or CNS disease; it should be stopped in those who develop abnormal neurological signs. Doses should be reduced in patients with severe hepatic impairment.

It is suggested that the use of metronidazole should be avoided during pregnancy, and this caution applies especially to use during the first trimester and to the use of high-dose regimens (see also below).

Patients are advised not to drink alcoholic beverages while taking metronidazole (see under Interactions, below).

Breast feeding. Metronidazole is distributed into breast milk giving it a bitter taste that may impair feeding.[1] The last available guidance from the American Academy of Pediatrics considered that although the effects of metronidazole on breast-fed infants were unknown they might be of concern. It recommended that breast feeding should be stopped for 12 to 24 hours when single-dose therapy was used;[2] no specific recommendations were given for long-term treatment. Unnecessary exposure to metronidazole should be avoided because it has been found to be mutagenic and carcinogenic in some studies (see under Adverse Effects, p. 938.1).

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; **293:** 1415–17.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/02/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metronidazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Pregnancy. Metronidazole is mutagenic in bacteria and carcinogenic in *rodents*. It readily crosses the placenta achieving similar concentrations in the placental cord and maternal plasma and its use in pregnancy is controversial. Meta-analyses of studies involving the use of metronidazole in the first trimester of pregnancy[1,2] concluded that there did not appear to be an increased risk of teratogenicity. Furthermore, a small study[3] that reviewed the use of metronidazole in 922 women during pregnancy found no association between metronidazole treatment at any stage of pregnancy and preterm birth, low birth weight, or congenital anomalies.However, in the USA licensed product information considers metronidazole to be contra-indicated during the first trimester in patients with trichomoniasis; use for trichomoniasis during the second and third trimesters may be acceptable. For other indications the risks and benefits of treatment with metronidazole should be weighed carefully, especially in the first trimester. In the UK, the *National Teratology Information Service* notes that the limited available data do not indicate an increased risk to the fetus from maternal use of metronidazole during pregnancy (although high-dose regimens for bacterial vaginosis are not recommended), and recommends that the drug should not be withheld in pregnancy if there is a compelling indication for its use.[4]

1. Burtin P, *et al.* Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995; **172:** 525–9.
2. Caro-Patón T, *et al.* Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997; **44:** 179–82.
3. Koss CA, *et al.* Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrob Agents Chemother* 2012; **56:** 4800–5.
4. National Teratology Information Service. Use of metronidazole in pregnancy (issued October 2012). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Metronidazole%202012.pdf (accessed 12/06/13)

Interactions

When given with alcohol, metronidazole may provoke a disulfiram-like reaction in some patients. Acute psychoses or confusion have been associated with the use of metronidazole and disulfiram together.

Metronidazole is reported to impair the metabolism or excretion of several drugs including coumarins and warfarin (p. 1532.3), phenytoin (p. 544.1), lithium (see Antimicrobials, p. 431.3), ciclosporin, and fluorouracil (p. 797.3), with the consequent potential for an increased incidence of adverse effects. There is some evidence that phenytoin might accelerate the elimination of metronidazole. Plasma concentrations of metronidazole are decreased by phenobarbital, with a consequent reduction in the efficacy of metronidazole. Cimetidine has increased plasma concentrations of metronidazole.

For incompatibilities between metronidazole and other drugs in solutions for injection, see p. 936.2.

Alcohol. Metronidazole may provoke a disulfiram-like reaction in some individuals when given with alcohol; reactions have occurred after the use of preparations formulated with alcohol, including injections, as well as after drinking alcohol.[1] Acute psychosis or confusional state was reported in 6 of 29 alcoholic patients who were also taking disulfiram.[2] However, an analysis of published reports[3] and a study in healthy subjects[4] both found that there was no convincing evidence of a disulfiram-like reaction between metronidazole and alcohol, although caution was still advised.

Licensed product information for some other 5-nitroimidazole derivatives warns of a potential interaction with alcohol but apart from an isolated report for ornidazole[5] there do not appear to be any other published reports to support this.

1. Edwards DL, *et al.* Disulfiram-like reaction associated with intravenous trimethoprim-sulfamethoxazole and metronidazole. *Clin Pharm* 1986; **5:** 999–1000.
2. Rothstein E, Clancy DD. Toxicity of disulfiram combined with metronidazole. *N Engl J Med* 1969; **280:** 1006–7.
3. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother* 2000; **34:** 255–7.
4. Visapää J-P, *et al.* Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother* 2002; **36:** 971–4.
5. Sharma V, *et al.* Disulfiram-like reaction with ornidazole. *J Postgrad Med* 2009; **55:** 292–3.

Antiepileptics. For a report of a possible interaction between metronidazole and *carbamazepine*, see p. 517.2.

An increase in the rate of metabolism of metronidazole, resulting in treatment failure, was reported in a patient taking *phenobarbital*.[1] In a retrospective survey of patients who had not responded to treatment with metronidazole, 80% were found to be on long-term phenobarbital therapy.[2] Up to 3 times the usual dose was required to produce a parasitological cure of giardiasis in such patients.

In addition to conflicting reports on the effects of metronidazole on the metabolism of *phenytoin* (p. 544.1), increased metabolism of metronidazole was reported in a patient during treatment with phenytoin.[3]

1. Mead PB, *et al.* Possible alteration of metronidazole metabolism by phenobarbital. *N Engl J Med* 1982; **306:** 1490.
2. Gupte S. Phenobarbital and metabolism of metronidazole. *N Engl J Med* 1983; **308:** 529.
3. Wheeler LA, *et al.* Use of high-pressure liquid chromatography to determine plasma levels of metronidazole and metabolites after intravenous administration. *Antimicrob Agents Chemother* 1978; **13:** 205–9.

Antineoplastics. For reference to the effect of metronidazole on *busulfan*, see p. 756.1.

Disulfiram. For a report of acute psychosis or confusional state after metronidazole treatment in alcoholic patients receiving disulfiram, see under Alcohol, above.

Gastrointestinal drugs. In a study in 6 healthy subjects metronidazole plasma concentrations were increased by twice-daily doses of *cimetidine*. The effect was presumed to be due to inhibition of cytochrome P450 isoenzymes responsible for metronidazole metabolism.[1] However, cimetidine was not found to affect the pharmacokinetics of metronidazole in a study in patients with Crohn's disease[2] nor in a single-dose study in healthy subjects.[3]

Although concentrations in plasma and saliva of metronidazole and its hydroxy metabolite were unaffected by *omeprazole* in healthy subjects, those in gastric juice were substantially lowered, possibly as a result of a reduction in transfer from the plasma.[4] However, this may be of limited clinical significance during treatment of *Helicobacter pylori* infections.

1. Gugler R, Jansen JC. Interaction between cimetidine and metronidazole. *N Engl J Med* 1983; **309:** 1518–19.
2. Eradiri O, *et al.* Interaction of metronidazole with cimetidine and phenobarbital in Crohn's disease. *Clin Pharmacol Ther* 1987; **41:** 235.
3. Loft S, *et al.* Lack of effect of cimetidine on the pharmacokinetics and metabolism of a single oral dose of metronidazole. *Eur J Clin Pharmacol* 1988; **35:** 65–8.
4. Jessa MJ, *et al.* The effect of omeprazole on the pharmacokinetics of metronidazole and hydroxymetronidazole in human plasma, saliva and gastric juice. *Br J Clin Pharmacol* 1997; **44:** 245–53.

Immunosuppressants. For details of a pharmacokinetic study reporting reduced exposure to *mycophenolate mofetil* when given with metronidazole or metronidazole plus norfloxacin, see Antibacterials, p. 1968.2.

Antimicrobial Action

Metronidazole is active against most anaerobic protozoa including *Balantidium coli*, *Blastocystis hominis*, *Entamoeba histolytica*, *Giardia intestinalis* (*Giardia lamblia*), and *Trichomonas vaginalis*. Anaerobic bacteria which are typically sensitive are Gram-negative anaerobes belonging to the *Bacteroides fragilis* group, *Prevotella* spp., and *Fusobacterium* spp. and Gram-positive anaerobes such as *Peptococcus niger*, *Peptostreptococcus*, *Clostridium* spp., and susceptible strains of *Eubacterium*. It is bactericidal. It also has variable activity against the facultative anaerobes *Gardnerella vaginalis* and *Helicobacter pylori*.

Resistance has been reported and about 70 to 75% of *Actinomyces* spp. and *Propionibacterium propionica* are resistant to metronidazole. Cross-resistance to other nitroimidazoles, such as tinidazole, may occur.

Metronidazole is considered to be a prodrug that needs to be activated by susceptible organisms. The mechanism of action is not entirely clear, but is thought to involve reduction by bacterial 'nitroreductases' to an unstable intermediate which interacts with DNA, effectively preventing further replication.[1] Several factors affect the sensitivity of micro-organisms to metronidazole *in vitro*. Anaerobic conditions are important for optimal activity. Interactions between micro-organisms and metronidazole have been described, including inhibition of *Escherichia coli* by metronidazole in the presence of *B. fragilis* and enhancement of the rate of killing of *B. fragilis* by metronidazole in the presence of *E. coli*. The oxidative metabolites of metronidazole also have antibacterial activity; the hydroxy metabolite has been reported to be consistently more active than metronidazole against strains of *G. vaginalis*.[2,3]

Resistance to metronidazole has developed in sensitive species including the *B. fragilis* group,[4-10] other *Bacteroides* spp.[11-13] (now known as *Prevotella* spp.), and rarely to *C. difficile*.[14,15] Metronidazole resistance has also been documented for *T. vaginalis*[16-19] and *Giardia* strains.[19] Nitroimidazole resistance in *Helicobacter pylori* has been increasing and may be associated with reduced response rates to anti-*Helicobacter* therapy for peptic ulcer disease in some populations (see Peptic Ulcer Disease under Uses, p. 937.3).

1. Ingham HR, *et al.* Interactions between micro-organisms and metronidazole. *J Antimicrob Chemother* 1982; **10:** 84–7.
2. Ralph ED, Amatnieks YE. Relative susceptibilities of Gardnerella vaginalis (Haemophilus vaginalis), Neisseria gonorrhoeae, and Bac-

teroides fragilis to metronidazole and its two major metabolites. *Sex Transm Dis* 1980; **7:** 157–60.
3. Shanker S, Munro R. Sensitivity of Gardnerella vaginalis to metabolites of metronidazole and tinidazole. *Lancet* 1982; **i:** 167.
4. Ingham HR, *et al*. Bacteroides fragilis resistance to metronidazole after long-term therapy. *Lancet* 1978; **i:** 214.
5. Eme A, *et al*. Bacteroides fragilis resistant to metronidazole. *J Antimicrob Chemother* 1983; **12:** 523–5.
6. Lamothe F, *et al*. Bacteroides fragilis resistant to both metronidazole and imipenem. *J Antimicrob Chemother* 1986; **18:** 642–3.
7. Brogan O, *et al*. Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; **23:** 660–2.
8. Hickey MM, *et al*. Metronidazole resistant Bacteroides fragilis infection of a prosthetic hip joint. *J Infect* 1990; **20:** 129–33.
9. Turner P, *et al*. Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of Bacteroides fragilis. *Lancet* 1995; **345:** 1275–7.
10. Schapiro JM, *et al*. Isolation of metronidazole-resistant Bacteroides fragilis carrying the nimA nitroreductase gene from a patient in Washington State. *J Clin Microbiol* 2004; **42:** 4127–9.
11. Sprott MS, *et al*. Metronidazole-resistant anaerobes. *Lancet* 1983; **i:** 1220.
12. McWalter PW, Baird DR. Metronidazole-resistant anaerobes. *Lancet* 1983; **i:** 1220.
13. Sprott MS, Kearns AM. Metronidazole-resistant Bacteroides melaninogenicus. *J Antimicrob Chemother* 1988; **22:** 951–2.
14. Peláez T, *et al*. Reassessment of Clostridium difficile susceptibility to metronidazole and vancomycin. *Antimicrob Agents Chemother* 2002; **46:** 1647–50.
15. Brazier JS, *et al*. Reduced susceptibility of Clostridium difficile to metronidazole. *J Antimicrob Chemother* 2001; **48:** 741–2.
16. Cudmore SL, *et al*. Treatment of infections caused by metronidazole-resistant Trichomonas vaginalis. *Clin Microbiol Rev* 2004; **17:** 783–93.
17. Schwebke JR, Barrientes FJ. Prevalence of Trichomonas vaginalis isolates with resistance to metronidazole and tinidazole. *Antimicrob Agents Chemother* 2006; **50:** 4209–10.
18. Crowell AL, *et al*. In vitro metronidazole and tinidazole activities against metronidazole-resistant strains of Trichomonas vaginalis. *Antimicrob Agents Chemother* 2003; **47:** 1407–9.
19. Upcroft P, Upcroft JA. Drug targets and mechanisms of resistance in the anaerobic protozoa. *Clin Microbiol Rev* 2001; **14:** 150–64.

Pharmacokinetics

Metronidazole is readily and almost completely absorbed after oral doses. Peak plasma concentrations of about 6 and 12 micrograms/mL occur, usually within 1 to 2 hours, after single doses of 250 and 500 mg respectively. Some accumulation occurs and consequently there are higher concentrations when multiple doses are given. Absorption may be delayed, but is not reduced overall by food. Metronidazole benzoate suspension given orally is hydrolysed in the gastrointestinal tract to release metronidazole, which in turn is then absorbed.

Peak steady-state plasma concentrations of about 25 micrograms/mL with trough concentrations of about 18 micrograms/mL have been reported in patients given an intravenous loading dose of 15 mg/kg followed by 7.5 mg/kg every 6 hours. The bioavailability of metronidazole from rectal suppositories is 60 to 80%; peak plasma concentrations are half those achieved with equivalent oral doses and effective concentrations occur after about 5 to 12 hours. Absorption from vaginal pessaries is poor with a reported bioavailability of about 20 to 25%; absorption is gradual producing peak plasma concentrations of about 2 micrograms/mL after a dose of 500 mg. An intravaginal gel formulation providing a dose of 37.5 mg metronidazole produced peak plasma concentrations of 300 nanograms/mL at 8 hours, with a bioavailability of 56%.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast milk, cerebral abscesses, CSF, liver and liver abscesses, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma. It also crosses the placenta and rapidly enters the fetal circulation. No more than 20% is bound to plasma proteins.

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The principal oxidative metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the hydroxy metabolite), which has antibacterial activity and is detected in plasma and urine, and 2-methyl-5-nitroimidazole-1-acetic acid (the acid metabolite), which has virtually no antibacterial activity and is often not detected in plasma, but is excreted in urine. Small amounts of reduced metabolites, acetamide and *N*-(2-hydroxyethyl)oxamic acid (HOA), have also been detected in urine and are probably formed by the intestinal flora.

The elimination half-life of metronidazole is about 8 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates (see below) and in patients with severe hepatic impairment (see below); that of the hydroxy metabolite is prolonged in patients with substantial renal impairment (see below).

The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

References.
1. Cunningham FE, *et al*. Pharmacokinetics of intravaginal metronidazole gel. *J Clin Pharmacol* 1994; **34:** 1060–5.
2. Lamp KC, *et al*. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999; **36:** 353–73.

Hepatic impairment. There have been differing results from pharmacokinetic studies of the elimination of metronidazole in patients with hepatic impairment. No marked difference was reported[1] between patients with cirrhosis or hepatosplenic schistosomiasis given a single 500-mg oral dose of metronidazole when compared with healthy subjects; this suggested that, in the absence of renal impairment, dosage adjustment was not needed in patients with hepatic impairment. However, others found[2] that elimination of metronidazole, given intravenously, was considerably impaired in a study of 10 patients with alcoholic liver disease or chronic active hepatitis, 7 of whom also had reduced creatinine clearance. Responding to the comment[3] that these differing results were probably due to impaired renal elimination, the authors suggested[4] that impaired elimination of metronidazole was due to impaired hepatic metabolism rather than decreased renal clearance; other studies have shown metronidazole clearance to be normal in renal impairment. They nevertheless agreed that reduction in the dosage of metronidazole is required only when hepatic function is very poor, particularly when renal function is impaired. A study in 10 severely ill patients with or without impaired hepatic and/or renal function[5] also suggested that hepatic function is a very important determinant of metronidazole elimination.

1. Daneshmend TK, *et al*. Disposition of oral metronidazole in hepatic cirrhosis and in hepatosplenic schistosomiasis. *Gut* 1982; **23:** 807–13.
2. Farrell G, *et al*. Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1983; **287:** 1845.
3. Daneshmend TK, Roberts CJC. Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984; **288:** 405.
4. Farrell G, *et al*. Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984, **288:** 1009.
5. Ljungberg B, *et al*. Metronidazole: pharmacokinetic observations in severely ill patients. *J Antimicrob Chemother* 1984; **14:** 275–83.

Infants and children. A single intravenous dose of 15 mg/kg has been suggested for neonates,[1] which would produce therapeutic concentrations of metronidazole for about 24 hours in term neonates and 48 hours in preterm neonates. Renal and hepatic function is incompletely developed in newborn infants and consequently the elimination half-life of metronidazole is prolonged and has been reported to range from 25 to 109 hours.[1] Elimination half-life is inversely proportional to gestational age[1,2] and as the infant matures half-life is reduced to values closer to those in adults.[1,3]

1. Jager-Roman E, *et al*. Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr* 1982; **100:** 651–4.
2. Hall P, *et al*. Intravenous metronidazole in the newborn. *Arch Dis Child* 1983; **58:** 529–31.
3. Amon I, *et al*. Disposition kinetics of metronidazole in children. *Eur J Clin Pharmacol* 1983; **24:** 113–19.

Renal impairment. Pharmacokinetic studies have indicated that doses of metronidazole need not be altered in patients with renal impairment,[1] although adjustments might be required in patients undergoing haemodialysis, since metronidazole and its hydroxy metabolite are efficiently cleared and extensively removed in such patients.[2] However, in another study[3] the amount of metronidazole and its hydroxy metabolite cleared was found to depend on the type of dialysis membrane used; the authors concluded that dosage supplementation may be needed only for seriously ill patients undergoing haemodialysis with a membrane having high metronidazole clearance.

Routine adjustment of dosage was not considered necessary in patients undergoing peritoneal dialysis.[4] However, the potential for metabolites to accumulate was noted in patients on continuous ambulatory peritoneal dialysis[5] and it was suggested that dosage reduction may be necessary if excessive concentrations of metabolites are found to be toxic.

1. Houghton GW, *et al*. Pharmacokinetics of metronidazole in patients with varying degrees of renal failure. *Br J Clin Pharmacol* 1985; **19:** 203–9.
2. Somogyi A, *et al*. Disposition and removal of metronidazole in patients undergoing haemodialysis. *Eur J Clin Pharmacol* 1983; **25:** 683–7.
3. Lau AH, *et al*. Hemodialysis clearance of metronidazole and its metabolites. *Antimicrob Agents Chemother* 1986; **29:** 235–8.
4. Cassey JG, *et al*. Pharmacokinetics of metronidazole in patients undergoing peritoneal dialysis. *Antimicrob Agents Chemother* 1983; **24:** 950–1.
5. Guay DR, *et al*. Pharmacokinetics of metronidazole in patients undergoing continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 1984; **25:** 306–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bexon; Colpofilin; Dazotron†; Etronil; Flagyl; Format; Ginkan; Gynotran; Metral; Metrizol; Metrocev; Metrodermic; Metrolocal; Nalox; Ovufem; Padet; Repligen; Rozex; Rupezol; Taremis; Tolbin; Tricofin; ***Austral.***: Flagyl; Metrogyl; Metronide; Rozex; Zidoval; ***Austria***: Anaerobex; Ariline; Elyzol†; Nidazea; Rozex; Trichex; ***Belg.***: Flagyl; Nidazea; Rosaced; Rozex; ***Braz.***: Canderm; Candifen; Dalzolston; Flagimax; Flagyl; Flanizol; Helmizol; Metronide†; Metroniflex†; Metronil; Metronin†; Metronix; Metroval; Metrozol†; Neo Metrodazol; Odonid†; Rozex; Trinodazol; ***Canad.***: Flagyl; Florazole; MetroCream; MetroGel; MetroLotion; NidaGel; Noritate; Novo-Nidazol; Trikacide†; ***Chile***: Deprocid†; Flagyl; Geloderm; Kabizol; Medazol; Metrocream; Metrogel; Metropast; ***China***: Ai Di (艾迪); Ao Ke An (奥可安); Fu Shu Da (孚舒达); Hua Shi (华适); Hui He (慧和); Jia Le Ning (佳乐宁); Le Yi Fu (乐易扶); LiFu (丽芙); Mi Er Tuo (迷尔脱); Ni Mei Xin (尼美欣); Noritate (耐瑞); Shu Rui Te (舒瑞特); Tian Li Ning (天力宁); Wei Di Le (威迪乐); Ya Kang (牙康); Yi Fu Qing (一孚晴); ***Cz.***: Efloran; Entizol; Rosalox; Rozex; ***Denm.***: Elyzol†; Flagyl; Rozex; Zidoval; ***Fin.***: Elyzol†; Flagyl; Rosazol; Rozex; Trikozol; Zidoval; ***Fr.***: Collazole†; Flagyl; Grinazole; Imizine; Metrocol; Metrogene; Rosiced; Rozacreme; Rozagel; Rozex; ***Ger.***: Arilin; Clont; Elyzol†; Flagyl; Infectoclont†; Metrocreme; Metrogel; Metrolotion; Metronour†; Metrosa; Rosiced; Vagi-Metro; Vagimid; ***Gr.***: Acsacea; Colpocin-T; Dermaskin; Elyzol; Emedal; Flagolin; Flagyl; Gnostol; Metrazol; Metrogyl; Pedryl; Periotret; Robaz; Rosiced; Trichovagil; Tricodazole; Unitrim; ***Hong Kong***: Elyzol†; Fitgyl†; Flagyl; Frotin; Gynoplix; Marphazole†; Metole†; Metro†; Metrogyl; Metrozole†; Nizole†; Noritate†; Qualigyl; Rozex; Syneodalin†; Unigo; ***Hung.***: Klion; Metrosa; Rozex; Supplin; ***India***: Aldezole; Anaerid-S; Antamebin; Aristogyl; Avimet; Balgyl; Compeba; Flagyl; Glucogyl; Intagyl; Ivmetro; Lupigyl; Met; Metgyl; Metris; Metrogyl; Metron; Monizole; ***Indon.***: Anmerob†; Biatron; Corsagyl; Dumozol; Farnat; Fladex; Flagsol; Flagyl; Flametia†; Fortagyl; Metrofusin; Molazol; Nidazole; Promuba; Supplin; Tismazol; Trichodazol; Trogiar; Trogyl; Vadazol; Vagizol; ***Irl.***: Flagyl; Metrogel; Metronide; Metrotop†; Rozex; ***Israel***: Elyzol†; Flagyl; Metrogyl; Noritate; Rozex; Venogyl†; Zidoval; ***Ital.***: Deflamon; Elyzol; Flagyl; Rosiced; Rozex; Vagilen; Zidoval; ***Malaysia***: Flagyl†; Fogyl; Frotin; Metronol; Protogyl†; Rozex; ***Mex.***: Ameblin; Biomona; Biotazol; Dasmetrol; Dualizol; Elyzol; Epaq; Fagizol; Fartricon; Flagenase; Flagenol; Flagepat; Flagyl; Flaxtec; Fresenizol; Hemestal; Lagylan; Lamblit; Lozad†; Medazol†; Medizol†; Messeldazol; Metricom; Metrizol; Metrobendizol; Metrocream; Metrogel; Metroson; Milezzol; Nidralon-V; Nidrozol†; Nitromidager; Ortrizol; Otrozol; Ovazol-V†; Planizol; Promibasol; Prozolin; Samonil; Servizol†; Solumidazol†; Stomffler; Valpar; Vanestrin-V; Vertisal; ***Neth.***: Flagyl; Nidazea; Rosiced; Rozex; ***Norw.***: Elyzol†; Flagyl; Rozex; Zidoval; ***NZ***: Flagyl; Rozex; Trichozole; ***Philipp.***: Ameryl; Anerobia†; Anerobizol; Bacimex; Clovizole; Dazomet; Flacel; Flagyl; Flamibazid; Foramebex; Globazol†; Medgyl; Metrinox; Metrodal; Metroxid; Metrozol; Microzol; Norstene; Nozol; Panazole; Patryl; Protozole; Robaz; Rodazid; Seltrozol; Servizol; Trichomar; Tricomycin; Triconex; Tridel; Vamogyl†; Zol; Zolnid; ***Pol.***: Arilin; Metrosept†; Rozex; ***Port.***: Dumozol; Elyzol†; Flagyl; Metroderme; Norstene; Rodermil; Roseless†; Rosiced; ***Rus.***: Bacimex (Бацимекс); Ciptrogil (Сиптрогил); Efloran (Эфлоран); Flagyl (Флагил); Klion (Клион); Metrogyl (Метрогил); Metrolacare (Метролакэр); Metron (Метрон); Metroseptol (Метросептол); Metrovagin (Метровагин); Metrovit (Метровит); Metrozol (Метрозол); Rosamet (Розамет); Rozex (Розекс); Tricho-PIN (Трихо-ПИН); Trichobrol (Трихоброл); Trichopol (Трихопол); ***S.Afr.***: Acuzole; Adco-Metrostat; Ambral; Amzole; Anaerobyl; Bemetrazole; Dynametron; Flagyl; Intramed Trichazole; Medamet; Metagyl; Metazol; Metrazole; Metris; Metrogel V; Narobic; Rozex; Suprazole; Trichazole; Zagyl†; Zobacide†; ***Singapore***: Fladex; Flagyl; Medazole; Nizole; Protogyl; Rozex; Stanzil; Syneodalin; Trinazole; ***Spain***: Amotein†; Flagyl; Rozex; Tricowas B†; Zidoval; ***Swed.***: Elyzol†; Flagyl; Rosazol; Rozex; Zidoval; ***Switz.***: Arilin; Dumozol; Elyzol†; Flagyl; Metrolag; Nidazea; Perilox; Rosalox; Rozex; ***Thai.***: Asiazole; Biogyl†; Flagyl; Kana-P; Medazole; Medizole; Mefiron; Menisole†; Mepagyl; Metrazole; Metrizone; Metrocide; Metrogyl; Metrolex; Metrovid†; Milanidazole; Nidazole; Nidazone; Novamet; Robaz; Temonas; Tricomed; Unigo†; Vagil; Vagilan; Vagyl†; ***Turk.***: Flagyl; Metrajil; Metrazol; Metrosel†; Nidazol†; Roza; ***UAE***: Negazole; ***UK***: Acea; Anabact; Elyzol; Flagyl; Metrogel; Metrolyl; Metrosa; Metrotop†; Metrozol; Noritate; Norzol; Rosiced; Rozex; Vaginyl; Zidoval; Zyomet; ***Ukr.***: Efloran (Эфлоран); Flagyl (Флагил); Gravagin (Гравагин); Klion (Клион)†; Metrogyl (Метрогил); Trichopol (Трихопол); ***USA***: Flagyl; Metrocream; Metrogel Vaginal; Metrogel; Noritate; Protostat; Rosadan; Vandazole; Vitazol†; ***Venez.***: Bactrizol; Flegyl; Menizol; Metren; Metris; Metrogyl; Metrovax; Rozek.

Multi-ingredient Preparations. ***Arg.***: Bexon; Ciprocort; Colpofilin Max; Estilomicin; Fangan Plus; Farm-X Duo; Farm-X Ginecologico; Flagystatin; Ginal Cent; Ginkan; Linfol Cicatrizante; Linfol; Linfol; Mailen; Metanis; Monizol Cort; Naxo TV; Neo Pelvicillin; Ovufem; Ovumix; Pelvicillin NF; Pentol; Septigyn; Tratomax; Tratomax; Vagicural Plus; Vagilen; ***Austral.***: Somac-MA†; ***Braz.***: Bio-Vagin; Colpatrin; Colpist; Colpistar; Colpistatin; Donnagel; Flagyl Nistatina; Fungimax; Ginestatin†; Kolpitrat; Periodontil; Tricolpex; Tricomax; Trinodazol Nistatina; Trinodazol; Vagi Biotic; Vagimax†; ***Canad.***: Flagystatin; Losec 1-2-3 M; Rosasol; ***China***: Bi Jie (碧洁); Shan Qing (山庆); Shuang Zuo Tai (双唑泰); Ya Zhou Kang (牙周康); ***Cz.***: Klion-D; ***Fin.***: Flagyl Comp; Helipak A; Helipak T; ***Fr.***: Bi Missilor; Birodogyl; Missilor; Rodogyl; Tergynan; ***Hung.***: Klion-D; ***India***: A-Flox M; Abdogyl-N; Actinor-MZ; Aldezol-DF; Aldiagram; Aldiamycin; Alfumet; Amibex-NA; Amibex; Anaerid-F; Aristogyl Plus; Aristogyl-F; Aristogyl-F; Atodine-M; Aviflox-M; Avilox-M; Bacter-M; Bactomet; Balvidine-M; Bekker-M; Bestodin-M; Biosin; Broflox Plus; Burnoff; C-Dial; C-Flox-M; C-Met; Clingen Plus; Clofcin-M; Darmed; Dentasep; Dependal-M; Diaba-M; Diaglow; Diarlop Plus; Digyl; Dinemet-M; Diof; Drez-V; Drez; Dyrade-M; E-Dine-M; Ecoseptic; Entakon-M; Entamizole†; Enterofuran-M; Entrozyme-M; Fastaid; Fenigyl; Flagyl-F; Floxole-MZ; Floxzen-M; Fogum; Fumestar; Gastogyl-M; Gramogyl; Gramogyl; Gramoneg-M; Heal; Healin; Heximet; Inseptin-MF; Iocandin Sol; Iocandin-M; Kaltin MF; Klassak; Lomostop-MF; Lotinor; Loxamet; Maghex-M; Mangogyl; Mapgyl; Matinor; Matrix-MN;

Medilop; Megaflox-M; Megyl-F; Meklin; Melam; Metnox; Metro Plus; Metro-P; Metro; Metrogyl Compound; Metrogyl-DG; Metrogyl-F; Metrogyl-P; Metrohex; Metrokind-P; Metron-DF; Metronor-P; Mexidin; Mezodin; Misodine-M; Mupimet; N-TZ; Nalidys; Negadix-M; Neocip M; Nex-M; Nitra-Met; NM Power; Nogit-M; Nor-Metrogyl; Noragyl; Norbit; Norfagyl; Norfazole; Norgrade; Norin-MZ; Normint; Norrit; Notty; Novogyl-MPS; Noxigyl; NTD; Nugit-M; Obit-M; Of-M; Ofacin-M; Oflact-M; Oflamed-MN; Oflaquin-M; Oflatoon-MZ; Oflavid; Oflee-M; Oflo-M; Oflomet; Oflostar-M; OFM; Oftec-M; Okaflox M; Okagyl; Olife-M; Orahex; Orex-M; Ovidine-M; Oxo-M; Pantop-HP; Powergyl; Qugyl; ***Indon.***: Fladystin; Flagystatin; Neo Gynoxa; Provagin; Trichostatic; Vagistin; ***Irl.***: Pylera; ***Ital.***: Meclon; ***Malaysia***: Neo-Penotran; Rodogyl; ***Mex.***: Acenil; Amebyl; Diodolina; Eskapar Compuesto; Flagenase 400; Flagocil†; Flagystatin V; Gynotran; Lambliquin; Madecassol C; Metodine; Metrodiyod; Metrofur†; Norecil; Nysmosons-V; Promibasol-Plus†; Rodogyl; Stomffler Plus; Vagitrol-V; ***Philipp.***: Flagystatin; Neo-Penotran; ***Pol.***: Gynalgin; ***Rus.***: Dentamet (Дентамет); Gynalgin (Гиналгин); Gyterna (Гитерна); Klion-D (Клион-Д); Metrogyl Denta (Метрогил Дента); Metrogyl Plus (Метрогил Плюс); Metrohex (Метрогекс); Neo-Penotran (Нео-Пенотран); ***Singapore***: Flagystatin; Neo-Penotran; ***Spain***: Blastoestimulina; Rhodogil; ***Turk.***: Gynotran; Neo-Penotran; Nidazol-M; ***Ukr.***: Dentagel (Дентагель); Gynalgin (Гиналгин); Klion-D (Клион-Д); Metrogyl Denta (Метрогил Дента); Micogynax (Микожинакс); Neo-Penotran (Нео-Пенотран); ***USA***: Helidac; Pylera.

Pharmacopoeial Preparations

BP 2014: Metronidazole Gel; Metronidazole Infusion; Metronidazole Oral Suspension; Metronidazole Suppositories; Metronidazole Tablets;

USP 36: Metronidazole Capsules; Metronidazole Gel; Metronidazole Injection; Metronidazole Tablets.

Monensin *(BAN, USAN, rINN)*

Lilly-67314; Monensina; Monensinum; Монензин.

4-{2-[2-Ethyl-3′-methyl-5′-(tetrahydro-6-hydroxy-6-hydroxymethyl-3,5-dimethylpyran-2-yl)perhydro-2,2′-bifuran-5-yl]-9-hydroxy-2,8-dimethyl-1,6-dioxaspiro[4.5]dec-7-yl}3-methoxy-2-methylpentanoic acid.

$C_{36}H_{62}O_{11}$=670.9

CAS — 17090-79-8.

ATC Vet — QA16QA06; QP51AH03.

UNII — 906O0YJ6ZP.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Monensin). A mixture of antibiotic substances produced by *Streptomyces cinnamonensis*.

Monensin Sodium *(BANM, rINNM)*

Monensin Sodique; Monensina sódica; Natrii Monensinum; Натрий Монензин.

$C_{36}H_{61}NaO_{11}$=692.9

CAS — 22373-78-0.

ATC Vet — QA16QA06; QP51AH03.

UNII — 1GS872GAFV.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Monensin Sodium). An off-white to tan crystalline powder. Slightly soluble in water; soluble in chloroform and in methyl alcohol; practically insoluble in petroleum spirit. Avoid moisture and excessive heat.

Profile

Monensin is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor for cattle.

Narasin *(BAN, USAN, rINN)*

Compound 79891; Lilly-79891; Narasina; Narasine; Narasinum; Наразин.

2-(6-{5-[2-(5-Ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl}tetrahydro-3,5-dimethylpyran-2-yl)butyric acid.

$C_{43}H_{72}O_{11}$=765.0

CAS — 55134-13-9.

ATC Vet — QP51AH04.

UNII — DZY9VU539P.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Narasin Granular). It contains narasin mixed with suitable carriers and inactive ingredients prepared in a granular form that is free-flowing and free of aggregates. Narasin is a white to off-white crystalline powder. Soluble in water and in methyl alcohol.

Profile

Narasin, an antibiotic produced by *Streptomyces aureofaciens*, is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in chickens.

Nicarbazin *(BAN)*

Nicarbazina; Никарбазин.

An equimolecular complex of 1,3-bis(4-nitrophenyl)urea ($C_{13}H_{10}N_4O_5$) and 4,6-dimethylpyrimidin-2-ol ($C_6H_8N_2O$).

$C_{19}H_{18}N_6O_6$=426.4

CAS — 330-95-0.

ATC Vet — QP51AE03.

UNII — 11P9NUA12U.

Profile

Nicarbazin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Nifuratel *(BAN, USAN, rINN)*

Methylmercadone; Nifurateeli; Nifuratelum; Нифурател.

5-Methylthiomethyl-3-(5-nitrofurfurylideneamino)-2-oxazolidone.

$C_{10}H_{11}N_3O_5S$=285.3

CAS — 4936-47-4.

ATC — G01AX05.

ATC Vet — QG01AX05.

UNII — U60U6P08SP.

Uses and Administration

Nifuratel is a nitrofuran derivative with a broad antimicrobial spectrum. It is active against the protozoan *Trichomonas vaginalis* and has an antibacterial spectrum similar to that of nitrofurantoin and some antifungal activity against *Candida albicans*. Although other drugs are preferred, nifuratel has been used to treat susceptible infections of the genito-urinary tract in oral doses of 200 to 400 mg three times daily. It has also been given vaginally.

Adverse Effects

Adverse effects associated with nifuratel include gastrointestinal disturbances, peripheral neuropathy, and thrombocytopenic purpura. Allergic reactions, hepatotoxicity, blood dyscrasias, and pulmonary reactions similar to those seen with the structurally related drug nitrofurantoin have been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given nifuratel.

Hypersensitivity. There have been a few reports of contact dermatitis associated with nifuratel,[1] including one of a man with contact dermatitis of the genitals occurring 5 hours after the first use of nifuratel ointment; the man's wife was being treated with nifuratel vaginal pessaries.[2] Vulvovaginal allergic contact dermatitis has also been reported 8 days after the first use of nifuratel vaginal suppositories.[1]

1. Helbig D, *et al.* Vulvovaginal allergic contact dermatitis from nifuratel: report of a case and review of the literature. *Contact Dermatitis* 2008; **58:** 251–2.
2. Bedello PG, *et al.* Contact dermatitis from nifuratel. *Contact Dermatitis* 1983; **9:** 166.

Precautions

Nifuratel should not be given to patients with renal impairment, neuropathies, or G6PD deficiency.

Interactions

A disulfiram-like reaction may occur in patients taking alcohol while on nifuratel therapy.

Pharmacokinetics

When taken orally nifuratel is absorbed from the gastrointestinal tract. A metabolite, with activity against bacteria but not against trichomonads, is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Macmiror; ***Ger.***: Inimur†; ***Hong Kong***: Macmiror; ***Ital.***: Inimur; Macmiror; ***Mex.***: Macmiror; ***Pol.***: Macmiror; ***Rus.***: Macmiror (Макмирор); ***Ukr.***: Macmiror (Макмирор).

Multi-ingredient Preparations. ***China***: Lang Yi (朗依); Shui Qing (水青); ***Cz.***: Macmiror Complex; ***Hong Kong***: Macmiror Complex; ***Ital.***: Inimur Complex; Macmiror Complex; ***Mex.***: Macmiror Complex V; ***Pol.***: Macmiror Complex; ***Port.***: Dafnegil; ***Rus.***: Macmiror Complex (Макмирор Комплекс); ***Turk.***: Macmiror Complex; ***Ukr.***: Macmiror Complex (Макмирор Комплекс).

Nifursol *(BAN, USAN, pINN)*

Nifursolum; Нифурсол.

3,5-Dinitro-2′-(5-nitrofurfurylidene)salicylohydrazide.

$C_{12}H_7N_5O_9$=365.2

CAS — 16915-70-1.

ATC Vet — QP51AX05.

UNII — TG99GOU55Z.

Profile

Nifursol is an antiprotozoal that has been used in veterinary practice for the prevention of blackhead (histomoniasis) in poultry. Nifursol has been banned from use in food-producing animals in some countries because it is potentially mutagenic, carcinogenic, and genotoxic.

Nifurtimox *(BAN, rINN)*

Bayer-2502; Nifurtimoxum; Нифуртимокс.

Tetrahydro-3-methyl-4-(5-nitrofurfurylideneamino)-1,4-thiazine 1,1-dioxide.

$C_{10}H_{13}N_3O_5S$=287.3

CAS — 23256-30-6.

ATC — P01CC01.

ATC Vet — QP51AC01.

UNII — M84I3K7C2O.

Pharmacopoeias. In *Fr.* and *Int.*

Uses and Administration

Nifurtimox is a nitrofuran derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease) due to infection by *Trypanosoma cruzi*, especially the early acute stage of the disease (see p. 925.3). In African trypanosomiasis it has some activity against *T. brucei gambiense*, the organism responsible for West African sleeping sickness.

Nifurtimox is given orally in 3 to 4 divided doses. It is better tolerated by children than by adults. Treatment for **American trypanosomiasis** is given for 90 days for acute infections and 120 days for chronic infections. Doses for adults are 8 to 10 mg/kg daily. For doses in **African trypanosomiasis** see below.

For details of doses in children, see below.

Administration in children. For the treatment of American trypanosomiasis (Chagas' disease) in children, nifurtimox may be given orally in 3 or 4 divided doses for 90 to 120 days. Doses are based on age and weight:

- children from 1 to 10 years of age: 15 to 20 mg/kg
- children from 11 to 16 years of age: 12.5 to 15 mg/kg

Leishmaniasis. Mucocutaneous leishmaniasis of the New World (p. 922.1) is usually treated with pentavalent antimony or, in those who do not respond, with amphotericin B or pentamidine. However, nifurtimox 10 mg/kg daily for a minimum of 4 weeks has been shown to be effective in cases of mucocutaneous leishmaniasis in Colombia and Brazil. Despite this, toxic effects with nifurtimox are common and its role as a second-line drug or with pentavalent antimony has not been established.[1]

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793*, 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 27/07/09)

Neuroblastoma. Nifurtimox is under investigation[1] in the management of neuroblastoma (p. 716.2).

1. Saulnier Sholler GL, *et al.* A phase 1 study of nifurtimox in patients with relapsed/refractory neuroblastoma. *J Pediatr Hematol Oncol* 2011; **33:** 25–30.

African trypanosomiasis. Nifurtimox has been tried as an alternative to melarsoprol or eflornithine in the meningoencephalitic stage of *Trypanosoma brucei gambiense* infection (p. 925.2), but higher doses than those used in American trypanosomiasis are necessary. A good initial response was achieved[1] in 25 patients with nifurtimox 15 mg/kg daily for 60 days, but 3 patients relapsed while still receiving nifurtimox and a further 12 of 19 patients who were followed up relapsed subsequently. An attempt[2] to improve the response by increasing the daily dose even higher to 30 mg/kg for 30 days resulted in substantial toxicity and only a modest improvement in results, with 9 of 25 patients relapsing. Promising results have been reported[3,4] from use of oral nifurtimox 15 mg/kg daily (5 mg/kg every 8 hours) for 10 days with eflornithine 400 mg/kg daily (200 mg/kg every 12 hours) intravenously for 7 days; this drug combination (NECT) has now been included in the WHO List of Essential Medicines for the

The symbol † denotes a preparation no longer actively marketed

treatment of human African trypanosomiasis,[5] and may be a candidate to replace melarsoprol in this condition.[6]

1. Pepin J, *et al.* An open clinical trial of nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness in central Zaire. *Trans R Soc Trop Med Hyg* 1989; **83:** 514–17.
2. Pépin J, *et al.* High-dose nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness: an open trial in central Zaire. *Trans R Soc Trop Med Hyg* 1992; **86:** 254–6.
3. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randonized clinical trial in Congo. *Clin Infect Dis* 2007; **45:** 1435–42.
4. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009; **374:** 56–64.
5. WHO. WHO Model List of Essential Medicines; 16th list (updated March 2010). Available at: http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf (accessed 08/07/10)
6. Lutje V, *et al.* Chemotherapy for second-stage human African trypanosomiasis. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 02/02/11).

Adverse Effects and Precautions

Adverse effects are common with nifurtimox and include gastrointestinal effects such as anorexia, loss of weight, abdominal pain, nausea and vomiting, and effects on the nervous system, such as memory loss, insomnia, CNS excitement, convulsions, and psychotic behaviour. Long-term treatment has been associated with peripheral nervous system effects such as tremor, muscle weakness, mild paraesthesia, and polyneuropathy. Haematological adverse effects, skin rashes, and other allergic reactions may occur. Patients are advised not to drink alcoholic beverages while taking nifurtimox.

Breast feeding. Women being treated with nifurtimox for American trypanosomiasis are discouraged from breast feeding. However, based on theoretical models to estimate breast milk concentrations and milk-plasma ratio, the risk for significant infant exposure to nifurtimox through breast milk was calculated to be small and below the level of exposure of infants receiving nifurtimox treatment for American trypanosomiasis.[1] In view of these findings it was recommended that the risk of stopping breast feeding should be carefully evaluated against its benefits, particularly in poor communities with limited services.

1. Garcia-Bournissen F, *et al.* Is use of nifurtimox for the treatment of Chagas disease compatible with breast feeding? A population pharmacokinetics analysis. *Arch Dis Child* 2010; **95:** 224–8.

Mutagenicity. An increase in chromosomal aberrations has been seen in children given nifurtimox.[1]

1. Gorla NB, *et al.* Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res* 1989; **224:** 263–7.

Pharmacokinetics

Oral nifurtimox is well absorbed and peak serum concentrations occur after 4 hours. It is rapidly and extensively metabolised and relatively low concentrations of nifurtimox appear in the plasma and tissues. It is presumed to cross the blood-brain barrier. Less than 1% of an oral dose is excreted unchanged in the urine. The half-life is about 3 hours and is not significantly altered in those with severe renal impairment.

References.

1. Paulas C, *et al.* Pharmacokinetics of a nitrofuran compound, nifurtimox, in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 454–7.
2. Gonzalez-Martin G, *et al.* The pharmacokinetics of nifurtimox in chronic renal failure. *Eur J Clin Pharmacol* 1992; **42:** 671–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Lampit.

Nimorazole *(BAN, rINN)*

Nimorazol; Nimorazolo; Nimorazolum; Nitrimidazina; Nitrimidazine; Ниморазол.

4-[2-(5-Nitroimidazol-1-yl)ethyl]morpholine.

$C_9H_{14}N_4O_3$=226.2

CAS — 6506-37-2.

ATC — P01AB06.

ATC Vet — QP51AA06.

UNII — 469ULX0H4G.

Pharmacopoeias. In *It.*

Uses and Administration

Nimorazole is a 5-nitroimidazole derivative. It has antimicrobial actions and uses similar to those of metronidazole (p. 936.2). It is also used as a radiosensitiser.

In the treatment of **trichomoniasis**, the usual dose of nimorazole is 2 g orally as a single dose with a main meal. It may alternatively be given in a dose of 1 g every 12 hours for three doses, or 250 mg three times daily for 5 to 7 days. In **amoebiasis**, nimorazole 1 g is given twice daily, usually for 5 to 10 days and in **giardiasis** a dose of 500 mg is given twice daily, usually for 5 to 7 days.

Nimorazole may also be used in the treatment of **acute ulcerative gingivitis** in a dose of 500 mg twice daily for 2 days.

Radiosensitisation. References to the use of nimorazole as a radiosensitiser in the management of head and neck cancer.

1. Overgaard J, *et al.* A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma: results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. *Radiother Oncol* 1998; **46:** 135–46.
2. Henk JM, *et al.* Treatment of head and neck cancer with CHART and nimorazole: phase II study. *Radiother Oncol* 2003; **66:** 65–70.
3. Overgaard J, *et al.* Plasma osteopontin, hypoxia, and response to the hypoxia sensitiser nimorazole in radiotherapy of head and neck cancer: results from the DAHANCA 5 randomised double-blind placebo-controlled trial. *Lancet Oncol* 2005; **6:** 757–64.
4. Bjarnason NH, *et al.* The nimorazole regimen in patients with head and neck cancer can increase the effect of vitamin K antagonists. *Acta Oncol* 2008; **47:** 150–1.

Adverse Effects and Precautions

As for Metronidazole, p. 937.3.

Pharmacokinetics

Nimorazole is readily absorbed from the gastrointestinal tract. Peak blood concentrations occur within 2 hours, and high concentrations are reported to occur in salivary and vaginal secretions. Trichomonicidal urinary concentrations may persist for up to 48 hours after a dose. It is mainly excreted in the urine as metabolites that also have some antiprotozoal and antibacterial activity. Unchanged drug and metabolites also appear in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Naxogin; ***Belg.***: Naxogin†; ***Braz.***: Naxogin; ***Gr.***: Naxogin; ***Rus.***: Naxogin (Наксоджин); ***Turk.***: Naksojin; ***Ukr.***: Naxogin (Наксоджин).

Multi-ingredient Preparations. ***Braz.***: Naxogin Composto; ***Chile***: Naxogin Compositum†; ***Indon.***: Gynoxa; Naxogin Complex.

Nitazoxanide *(BAN, USAN, rINN)*

Nitazoxanida; Nitazoxanidum; PH-5776; Нитазоксанид.

N-(5-Nitro-2-thiazolyl)salicylamide acetate.

$C_{12}H_9N_3O_5S$=307.3

CAS — 55981-09-4.

ATC — P01AX11.

UNII — SOA12P041N.

Uses and Administration

Nitazoxanide is used for the treatment of cryptosporidiosis (p. 921.1) and giardiasis (p. 921.3). It is given orally and should be taken with food; the usual dose is 500 mg twice daily for 3 days.

For details of doses in children, see below.

Nitazoxanide has also been tried in several other protozoal and helminth infections, particularly in immunocompromised patients, including those with HIV infection. It is also being investigated for the treatment of chronic hepatitis C, rotavirus disease, and *Clostridium difficile* colitis. For further information see below.

Reviews.

1. Bailey JM, Erramouspe J. Nitazoxanide treatment for giardiasis and cryptosporidiosis in children. *Ann Pharmacother* 2004; **38:** 634–40.
2. Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis* 2005; **40:** 1173–80.
3. Musher DM, *et al.* Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006; **43:** 421–7.
4. Anderson VR, Curran MP. Nitazoxanide: a review of its use in the treatment of gastrointestinal infections. *Drugs* 2007; **67:** 1947–67.

Administration in children. For the treatment of cryptosporidiosis and giardiasis in children, nitazoxanide is given orally with food. Doses are 100 mg twice daily for 3 days in those aged 1 to 3 years and 200 mg twice daily for 3 days in those aged 4 to 11 years.

Antibiotic-associated colitis. *Clostridium difficile* colitis is usually treated with metronidazole but treatment failures are increasingly being reported and there is concern over the emergence of vancomycin resistance if it is used for treatment instead. Nitazoxanide is therefore being investigated as a possible alternative to metronidazole. A prospective, randomised, double-blind study[1] found that nitazoxanide (at an oral dose of 500 mg twice daily for 7 to 10 days) was at least as effective as metronidazole given at a dose of 250 mg 4 times daily for 10 days. A further study[2] in 35 patients who failed treatment with metronidazole for *C. difficile* colitis and were then treated with nitazoxanide reported initial cure rates of 74% after 10 days. However, 7 patients later had recurrent disease. Three of the patients who failed initial treatment and one of those who had recurrent disease were re-treated and responded to nitazoxanide, giving an aggregate cure with nitazoxanide of 66%.

1. Musher DM, *et al.* Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006; **43:** 421–7.
2. Musher DM, *et al.* Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide. *J Antimicrob Chemother* 2007; **59:** 705–10.

Hepatitis C. Nitazoxanide, given orally, either as monotherapy or with peginterferon alfa-2a (with or without ribavirin) is being investigated for the treatment of chronic hepatitis C (p. 952.1).

Nitazoxanide monotherapy (500 mg twice daily for 24 weeks) in patients with chronic hepatitis C genotype 4 resulted in sustained virologic response (undetectable serum hepatitis C virus RNA 24 weeks after the end of therapy) in 17% (4 of 23) of patients; all responders had baseline serum hepatitis C virus RNA levels ≤400 000 IU/mL.[1] A later phase II study,[2] in treatment-naive patients with chronic hepatitis C genotype 4, given 12 weeks of lead-in treatment with nitazoxanide monotherapy followed by a further 36 weeks of treatment with additional peginterferon alfa-2a (with or without ribavirin) reported an increase in the percentage of patients with sustained virologic response compared with standard therapy of peginterferon alfa-2a plus ribavirin for 48 weeks. A similar study[3] in patients with mainly hepatitis C genotype 4 infection found that the lead-in treatment time for nitazoxanide monotherapy could be reduced from 12 weeks to 4 weeks without compromising sustained virologic response rates.

1. Rossignol JF, *et al.* Clinical trial: randomized, double-blind, placebo-controlled study of nitazoxanide monotherapy for the treatment of patients with chronic hepatitis C genotype 4. *Aliment Pharmacol Ther* 2008; **28:** 574–80.
2. Rossignol JF, *et al.* Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon, and ribavirin. *Gastroenterology* 2009; **136:** 856–62.
3. Rossignol JF, *et al.* Treatment of chronic hepatitis C using a 4-week lead-in with nitazoxanide before peginterferon plus nitazoxanide. *J Clin Gastroenterol* 2010; **44:** 504–9.

Protozoal infections. As well as its established use in cryptosporidiosis (p. 921.1) and giardiasis (p. 921.3), nitazoxanide has been used in other protozoal infections including intestinal amoebiasis (p. 919.1), blastocystosis (p. 920.3), cutaneous leishmaniasis (p. 922.1), and microsporidiosis (p. 924.1).

Rotavirus diarrhoea. A randomised double-blind placebo-controlled study[1] in 38 children (median age 11 months) with confirmed rotavirus diarrhoea found that oral nitazoxanide 7.5 mg/kg twice daily for 3 days significantly reduced the duration of rotavirus disease. The median time to resolution of illness after the first dose was 31 hours for those given nitazoxanide compared with 75 hours for those given placebo. Another, single-blind study[2] involving 147 children found nitazoxanide tended to be more effective than probiotics in reducing duration of diarrhoea and time in hospital.

1. Rossignol J-F, *et al.* Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. *Lancet* 2006; **368:** 124–9.
2. Teran CG, *et al.* Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *Int J Infect Dis* 2009; **13:** 518–23.

Worm infections. Nitazoxanide has been used in various helminthiases, including ascariasis (p. 143.3), hymenolepiasis (p. 146.1), the liver fluke infection fascioliasis (p. 146.2), and trichuriasis (p. 149.1).

Adverse Effects

The most common adverse effects associated with nitazoxanide are abdominal pain, diarrhoea, nausea, vomiting, and headache. Other less commonly reported adverse effects include anorexia, fever, flatulence, pruritus, and dizziness. Spontaneous bone fracture and discoloration of urine and of the eyes have been reported rarely. Increased creatinine and liver enzyme values have been noted.

Pharmacokinetics

Nitazoxanide is absorbed from the gastrointestinal tract after oral dosage and is rapidly hydrolysed to an active desacetyl metabolite, tizoxanide. Tizoxanide then partially undergoes conjugation, mainly by glucuronidation. The extent of absorption is enhanced if given with food and peak plasma concentrations of tizoxanide and the glucuronide are seen 1 to 4 hours after an oral dose. The parent drug is not detected in plasma. Tizoxanide is more than 99% bound to plasma proteins. About two-thirds of an oral dose of nitazoxanide is eliminated in the faeces and one-third in the urine; tizoxanide is excreted in the urine, bile, and faeces, while the glucuronide is excreted in only the urine and bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nixoran; ***Braz.***: Annita; ***India***: Netazox; Nitacure; Nitarid; Nitazet; Nitzix; Nizonide; Nozoa; ***Mex.***: Avisan; Bionit; Daxon; Dexidex; Kidonax; Mitafar; Padovan Ton; Paramix; Parsenida; Rosanil; Zotanixin; ***USA***: Alinia; ***Venez.***: Celectan.

Multi-ingredient Preparations. ***India***: Abof-NZ; Bacter-NZ; Bestoflox N; Flagynor; Floxine-NT; Floxole-NT; Inflobid-NXT; Netazox-OF; Nita-O; Nitazet-O; Nitzix-O; Nizonide-O; Ofcare-NT; Oflee-NT; Olpit-NZ; Osani-NT; Oxalic-NZ; ***Mex.***: Heliton.

Ornidazole *(USAN, rINN)*

Ornidatsoli; Ornidazol; Ornidazolum; Ro-7-0207; Орнидазол.

1-Chloro-3-(2-methyl-5-nitroimidazol-1-yl)propan-2-ol.

$C_7H_{10}ClN_3O_3$=219.6

CAS — 16773-42-5.

ATC — G01AF06; J01XD03; P01AB03.

ATC Vet — QG01AF06; QJ01XD03; QP51AA03.

UNII — 62XCK0G93T.

Uses and Administration

Ornidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p. 936.2) in the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections (p. 173.1).

It is given orally after food, or intravenously. Intravenous solutions of ornidazole should be diluted to 5 mg or less per mL and 100 or 200 mL infused over 15 to 30 minutes.

In **amoebiasis** (p. 919.1), 500 mg of ornidazole is given orally twice daily for 5 to 10 days. Patients with amoebic dysentery may be given 1.5 g as a single daily dose for 3 days. An alternative regimen for adults over 60 kg is 1 g twice daily for 3 days. In severe amoebic dysentery and amoebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 0.5 to 1 g initially, followed by 500 mg every 12 hours for 3 to 6 days.

In **giardiasis** (p. 921.3), 1 or 1.5 g of ornidazole is given orally as a single daily dose for 1 or 2 days.

In **trichomoniasis** (p. 925.1), a single oral dose of 1.5 g is given; alternatively, a 5-day oral course of ornidazole 500 mg twice daily may be used. Sexual partners should also be treated.

For the *treatment* of **anaerobic bacterial infections,** ornidazole is given by intravenous infusion in an initial dose of 0.5 to 1 g, followed by 1 g daily as a single dose or in two divided doses for 5 to 10 days; oral therapy with 500 mg every 12 hours should be substituted as soon as possible.

For the *prevention* of postoperative anaerobic bacterial infections, 1 g is given by intravenous infusion about 30 minutes before surgery. An alternative oral regimen is 1.5 g given 12 hours before surgery, then 500 mg every 12 hours for 3 to 5 days after the surgery.

For details of doses in **children**, see below.

Administration in children. Ornidazole is licensed in several countries in children weighing up to 35 kg for the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections. It is given orally after food or intravenously. Children weighing over 35 kg may be given the adult dose (above).

In **amoebiasis** children may be given an oral dose of 25 mg/kg as a single daily dose for 5 to 10 days. Those with amoebic dysentery may be given 40 mg/kg as a single daily dose for 3 days. In severe amoebic dysentery and amoebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 20 to 30 mg/kg daily for 3 to 6 days. In **giardiasis**, 30 or 40 mg/kg is given orally as a single daily dose for 1 or 2 days and in **trichomoniasis**, a single oral dose of 25 mg/kg is given.

For the treatment of **anaerobic bacterial infections**, ornidazole is given by intravenous infusion in a dose of 10 mg/kg every 12 hours for 5 to 10 days or orally at a dose of 20 to 30 mg/kg daily. For the prevention of postoperative anaerobic bacterial infections, 20 to 30 mg/kg may be given orally or intravenously 12 hours before surgery; after surgery a dose of 20 to 30 mg/kg is given every 12 hours for 3 days.

Administration in hepatic impairment. In view of the prolonged half-life and reduced clearance of ornidazole reported in patients with hepatic dysfunction (see below), the interval between doses should be doubled in patients with severe hepatic impairment.

Administration in renal impairment. The elimination of ornidazole is reported to be largely unaltered in patients with impaired renal function (see under Pharmacokinetics, below). Dosage adjustment is therefore usually unnecessary, although patients receiving haemodialysis should be given a supplemental dose of ornidazole (oral or intravenous formulations) with each dialysis run; licensed product information for an oral formulation of ornidazole suggests a supplemental dose of 500 mg should be given if the daily dose is 2 g daily or 250 mg should be given if the daily dose is 1 g daily.

Rheumatoid arthritis. Rheumatoid arthritis is common in patients with periodontitis and many pathological aspects of the diseases are similar. Furthermore, high concentrations of antibodies to anaerobic bacteria have been found in the serum and synovial fluid of patients with rheumatoid arthritis. To evaluate the efficacy of ornidazole, a randomised, double-blind, placebo-controlled study[1] was carried out in 160 patients with active rheumatoid arthritis. Significantly more patients given oral ornidazole 1 g daily met the American College of Rheumatology criteria for 20, 50 and 70% improvement at 3 months compared with those taking placebo. Ornidazole treatment was also associated with significant reductions in pain, duration of morning stiffness, and disease activity and improved quality of life.

1. Ogrendik M. Treatment of rheumatoid arthritis with ornidazole: a randomized, double-blind, placebo-controlled study. *Rheumatol Int* 2006; **26:** 1132–7.

Adverse Effects and Precautions

As for Metronidazole, p. 937.3.

Effects on the liver. Auto-immune hepatitis occurred in a 35-year-old woman after treatment with ornidazole for diarrhoea and a further episode occurred after treatment for a vaginal infection.[1] A few cases of acute cholestatic hepatitis have also been reported; all the patients improved 1 to 2 months after stopping treatment.[2] Severe hepatitis with prolonged cholestasis and bile duct injury has been reported after long-term use (8 weeks) of ornidazole.[3]

1. Koşar Y, *et al*. Ornidazole-induced autoimmune hepatitis. *Eur J Gastroenterol Hepatol* 2001; **13:** 737–9.
2. Tabak F, *et al*. Ornidazole-induced liver damage: report of three cases and review of the literature. *Liver Int* 2003; **23:** 351–4.
3. Harputluoglu MM, *et al*. Severe hepatitis with prolonged cholestasis and bile duct injury due the long-term use of ornidazole. *Acta Gastroenterol Belg* 2007; **70:** 293–5.

Pharmacokinetics

Ornidazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within 3 hours. After repeated oral doses of 500 mg every 12 hours, steady-state peak and trough concentrations are 14 and 6 micrograms/mL respectively.

The plasma elimination half-life of ornidazole is 12 to 14 hours. Less than 15% is bound to plasma proteins. It is widely distributed in body tissues and fluids, including the CSF.

Ornidazole is metabolised in the liver and is excreted in the urine, mainly as conjugates and metabolites, and to a lesser extent in the faeces. Biliary excretion may be important in the elimination of ornidazole and its metabolites.

References.

1. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy* 1976; **22:** 19–29.
2. Matheson I, *et al*. Plasma levels after a single oral dose of 1.5 g ornidazole. *Br J Vener Dis* 1977; **53:** 236–9.
3. Schwartz DE, *et al*. Metabolic studies of ornidazole in the rat, in the dog and in man. *Xenobiotica* 1979; **9:** 571–81.
4. Turcant A, *et al*. Pharmacokinetics of ornidazole in neonates and infants after a single intravenous infusion. *Eur J Clin Pharmacol* 1987; **32:** 111–13.
5. Martin C, *et al*. Pharmacokinetics and tissue penetration of a single dose of ornidazole (1,000 milligrams intravenously) for antibiotic prophylaxis in colorectal surgery. *Antimicrob Agents Chemother* 1990; **34:** 1921–4.
6. Bourget P, *et al*. Disposition of ornidazole and its metabolites during pregnancy. *J Antimicrob Chemother* 1995; **35:** 691–6.

Hepatic impairment. The elimination of ornidazole after a single intravenous dose of 500 mg was impaired in 10 patients with severe liver cirrhosis when compared with 10 healthy subjects; mean half-lives were 21.9 hours and 14.1 hours respectively.[1] These results suggested that the interval between doses of ornidazole should be doubled in patients with marked hepatic impairment. The need for dose adjustment was confirmed in further studies of patients with other forms of liver disease.[2,3]

1. Taburet AM, *et al*. Pharmacokinetics of ornidazole in patients with severe liver cirrhosis. *Clin Pharmacol Ther* 1986; **40:** 359–64.
2. Bourget P, *et al*. Ornidazole pharmacokinetics in several hepatic diseases. *J Pharmacol Clin* 1988; **7:** 25–32.
3. Taburet AM, *et al*. Pharmacokinetics of ornidazole in patients with acute viral hepatitis, alcoholic cirrhosis, and extrahepatic cholestasis. *Clin Pharmacol Ther* 1989; **45:** 373–9.

Renal impairment. The half-life of intravenous ornidazole was not prolonged in a study in patients with advanced chronic renal failure, including those on continuous ambulatory peritoneal dialysis, although total plasma clearance was halved; modification of the usual dosage is not necessary in such patients. However, the drug was removed by haemodialysis and ornidazole should be given after the dialysis session rather than before.[1] In another study[2] the systemic availability and total body clearance of ornidazole were unaffected in chronic renal failure; it was considered that an additional dose should be given before haemodialysis to compensate for removal during that procedure.

1. Merdjan H, *et al*. Pharmacokinetics of ornidazole in patients with renal insufficiency; influence of haemodialysis and peritoneal dialysis. *Br J Clin Pharmacol* 1985; **19:** 211–17.
2. Horber FF, *et al*. High haemodialysis clearance of ornidazole in the presence of a negligible renal clearance. *Eur J Clin Pharmacol* 1989; **36:** 389–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mebaxol; ***Belg.***: Tiberal; ***Chile***: Invigan†; ***China***: Ao Bo Lin (奥博林); Ao Li Tuo (奥立妥); AoNing (傲宁); Gu Te (固特); Heng Bo Lai (衡博来); Jin Da (今达); Mei Er Kai (美尔凯); Nei De Zi (内德滋); Pusili (普司立); Qi Ke (齐克); Rui Shen (瑞申); Sheng Nuo (圣诺); Sheng Nuo An (圣诺安); Sheng Nuo Kang (圣诺康); Tai Fang (泰方); Tuo Su (妥苏); Xiao Ran (潇然); Ya Jie (亚洁); You Lun (优伦); ***Cz.***: Avrazor†; ***Fr.***: Tiberal; ***Gr.***: Betiral; ***India***: Asiflox-OZ; Aurnida; CGDole; Dazolic; Entamizole Plus; Giro; Horn; Nidazole; Nidoba; Oflatoon-OZ; Onidaz; Oniz; Orbest; Ord; Orizole; Orni; Ornida; Orniden; Ornimax; Ornivir; Ornizen; Zil; ***NZ***: Tiberal; ***Rus.***: Dazolic (Дазолик); Giro (Гайро); Lornizol (Лорнизол); Orniona (Орниона); Ornisid (Орнисид); Tiberal (Тиберал); ***Switz.***: Tiberal; ***Turk.***: Bitazol; Biteral; Borneral; Ornidone; Orniject; Ornisid; Ornitop; Pronizol; ***Ukr.***: Ornigil (Орнигил); Ornisid (Орнісид); Ornizol (Орнизол); Tiberal (Тиберал)†.

Multi-ingredient Preparations. ***India***: A-Flox-OZ; Abof-OZ; Adeflox-O; AF-Kit; Aflox-OZ; Aleflox-OZ; Alocin-OZ; Alox-OD; Ariflox-OZ; Arilif-OZ; Armbid OZ; Arviflox-OZ; Atoflox-OZ; Avidox-OZ; Aviflox-OZ; Bacter-OZ; Bactezoa-LB; Bactoff-OZ; Baseflox OZ; Bekker-OZ; Biofast-OZ; Bonflox; Brakke; Bru-OZ; C-Flox-OZ; Candifem; Canocin-OZ; Casflox-OZ; Cefit-OZ; Chekmet-O; Cifran-OZ; Cinflox-OZ; Cipnet-OZ; Covax-OZ; Cozan-O; Cucin-O; Diragyl; Dox-M-OZ; Ducidal-OZ; Duochek; Ecoflox-OZ; Edilox-OZ; Essasin-OZ; Esterflox-OZ; Eufox-O; Evopic-OZ; Fatiflox-OZ; Fern; Festive-OZ; Fixiflox-OZ; Flex-OZ; Flexril-Ord; Flobacin-OZ; Flogard-O; Flow-OZ; Floxaquin-O; Floxar-OZ; Floxine-OZ; Floxole-OZ; Floxzen-OZ; Fouz; Fungid-OR; Fynal-OZ; Garnid; Gatigram-OZ; Gatikind-OZ; Gatimore-OZ; Gatiquin Oz Kit; Gatri-OZ; Gatrid-OZ; Gatrix; Gazal-O; Geryl-O; GFlox-OZ; Gic-O; Glofty-OZ; Hoflo-O; Hoflox-O; Indocin-OZ; Indof OZ; Inflobact-OZ; Inflobid-OZ; Inflox-OZ; Infoxin-OZ; Inogat-O; Intragat-O; Jflo-OZ; Kareof-OZ; Kooz; Kureflox-OZ; Kylevo-OZ; L-Cin-OZ; Laflox-O; Lamizol-O; Lebact-O; Lefosym-OZ; Lek-OZ; Levact-OZ; Levocide-OZ; Levocos-OZ; Levoflox Oz; Levogyl; Levospan-OZ; Levosym-OZ; Lexof-OZ; Logflox-OZ; Loobid; Lumigard; Magof-OZ; Mahacef-OZ; MCFlox-OZ; Meganor; Meuflox-OZ; Mintof-OZ; Mof-OZ; Moflo-OZ; Myconor-4; NBox-OZ; Neva-OZ; Niolox-OZ; Noff-OR; Noragyl-OZ; Normet; Norrit-Ord; Novaflox-OZ; Nuforce-3 Kit; O & O; O-Cebran-O; O-Cebran-OZ; O-Fact-OZ; O2; O2H; Obactin-OZ; Obid-OZ; Obit-OZ; Ocimix; Ociz-OR; Odicip-OZ; Ofac-O; Ofacin-O; Ofal-M; Ofal-OZ; Ofbid-OZ; Ofcare-OD; Ofcura-OZ; Ofdaz; Ofet-O; Ofia-OZ; Ofkab-OZ; Ofkair-OZ; Ofla-OZ; Oflab-OZ; Oflact-OZ; Oflagard-O; Oflagard-OL; Oflage-OZ; Oflamed-OZ; Oflaquin-OZ; Oflark-O; Oflas-OZ; Oflaset-OZ; Oflawin-OZ; Oflee-OZ; Oflem-OZ; Oflict-OZ; Oflina-OZ; Oflo-OZ; Oflocos-OZ; Ofloday-OZ; Ofloden-O; Ofloine-OZ; Oflomil-OZ; Oflon-OZ; Oflopar-OR; Oflopip-O; Ofloren-OZ; Oflostar-OZ; Oflotas-OZ; Oflotec-OZ; Ofly-OZ; Ofmed-OZ; Ofnet-OZ; Ofnida-LB; Ofnida; Ofnis-OZ; Ofo-OZ; Ofor-OZ; Ofpil-O; Ofral-OZ; Ofran-OZ; Ofsis-OZ; Ofspan-OZ; Ofspin-OZ; Oftacin-OZ; Oftech-OZ; Oftum-OZ; Oftwo; Ofwin-OZ; Ofzac-OZ; Ofzen-OZ; Ofzo; Ojen-OZ; Okil-OZ; Oks-OZ; Oley-OZ; Olfi-O; Olfic-OZ; Olfon-OR; Olife-OZ; Olpit-OZ; On-OZ; Oniz-O; Opeq-OZ; Ophar-OZ; OQN-O; Oqueen-OZ; Orflaz Kit; Orflo; Orflo; Orin-O; Orni-O; Ornicef; Ornidox; Orniflox; Ornilox; Ornof; Oroflox-OZ; Osani-O; Osflox-OR; Osiflox-OZ; Ospol-OZ; Ot; Otago-O; Otic-O; Oxacin-OZ; Oxcin-Ord; Oxdrin-Ord; Oxiflox-OZ; Oxit-OZ; Oxo-Ord; Oxoism-OZ; Oxwal-OZ; Oxyna; Oza-O; Tariflox Plus; ***Ukr.***: Neotrizol (Неотризол); Ofor (Офор); Onristat (Орністат)†; Orcipol (Орципол); Tiflox (Тифлокс)†.

Paromomycin Sulfate *(BANM, rINNM)*

Aminosidin Sulphate; Aminosidine Sulphate; Catenulin Sulphate; Crestomycin Sulphate; Estomycin Sulphate; Hydroxymycin Sulphate; Monomycin A Sulphate; Neomycin E Sulphate; Paromomicina, sulfato de; Paromomycin Sulphate; Paromomycine, Sulfate de; Paromomycini Sulfas; Paucimycin Sulphate; Sulfato de aminosidina; Sulfato de catelubina; Sulfato de estomicina; Sulfato de hidroximicina; Sulfato de paromomicina; Sulfato de povicimina; Паромомицина Сульфат.

O-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-*O*-β-D-ribofuranosyl-(1→5)-*O*-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine sulphate.

$C_{23}H_{45}N_5O_{14}.xH_2SO_4$

CAS — 59-04-1 (paromomycin); 7542-37-2 (paromomycin); 1263-89-4 (paromomycin sulfate).
ATC — A07AA06.
ATC Vet — QA07AA06.
UNII — 845NU6GJPS.

Pharmacopoeias. In *Chin.*, *Int.*, *It.*, and *US*.

USP 36: (Paromomycin Sulfate). The sulfate salt of an antibiotic substance produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, or a mixture of two or more such salts.

A creamy-white to light yellow, odourless or practically odourless, very hygroscopic powder. It loses not more than 5% of its weight on drying. Very soluble in water; insoluble in alcohol, in chloroform, and in ether. pH of a 3% solution in water is between 5.0 and 7.5. Store in airtight containers.

Uses and Administration

Paromomycin is an aminoglycoside antibacterial that has been given orally in the treatment of intestinal protozoal infections, including amoebiasis, cryptosporidiosis, and giardiasis. It has also been tried parenterally for visceral, and topically for cutaneous, leishmaniasis (below). For details of these infections and their treatment, see under Choice of Antiprotozoal, p. 919.1. It has been used in the treatment of beef or pork tapeworm infection (p. 148.2), but it is not the treatment of choice. Like neomycin (p. 330.1), it has been used in the suppression of intestinal flora pre-operatively and as adjunctive therapy in the management of hepatic encephalopathy.

Paromomycin is given as the sulfate although doses are expressed in terms of the base. In intestinal **amoebiasis**, the dose for both adults and children is the equivalent of paromomycin 25 to 35 mg/kg daily in 3 divided oral doses with meals for 5 to 10 days. Similar doses have been tried in **cryptosporidiosis**.

In taeniasis and other **tapeworm infections**, a dose of 4 g is given orally as a single dose or in divided doses over the course of one hour.

For **hepatic coma**, 4 g is given daily in divided oral doses at regular intervals for 5 to 6 days.

Administration in children. Paromomycin may be given to children for the treatment of intestinal **amoebiasis**. Oral doses used are the same as those for adults, above. For the treatment of **visceral leishmaniasis** in the Indian subcontinent, WHO recommends an intramuscular dose of paromomycin of 11 mg/kg daily for 21 days for children weighing more than 5 kg; for visceral leishmaniasis in east Africa the same intramuscular dose is recommended (with pentavalent antimonials) for 17 days.[1]

1. WHO. *WHO model formulary for children.* Geneva: WHO, 2010. Also available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 13/12/10)

Leishmaniasis. Topical treatment with paromomycin 15% plus methylbenzethonium chloride 5 or 12% has produced variable results[1-4] in **cutaneous leishmaniasis** (p. 922.1); paromomycin 12 to 15% with urea 10% was better tolerated,[5,6] however, benefit has not been seen in all studies.[4,6] Treatment with topical paromomycin plus systemic meglumine antimonate was initially promising in patients with New World cutaneous leishmaniasis;[7] however, a subsequent study[8] found no clear advantage over treatment with meglumine antimonate alone. Good responses to parenteral paromomycin 14 mg/kg daily, with sodium stibogluconate 10 mg/kg daily, in cases of *diffuse* cutaneous leishmaniasis have also been reported.[9]

Paromomycin has also been used intramuscularly, either alone[10] or with sodium stibogluconate,[11] in the treatment of **visceral leishmaniasis** (p. 923.1) in an area of India with increasing resistance to pentavalent antimony compounds. The authors of one study[10] found paromomycin 16 or 20 mg/kg daily for 21 days to be significantly more effective than sodium stibogluconate 20 mg/kg daily for 30 days, while another study[12] found intramuscular paromomycin (11 mg/kg) daily for 21 days to be no less effective than treatment with intravenous amphotericin B (1 mg/kg) on alternate days for 30 days. Although patients given intramuscular paromomycin (11 mg/kg) daily for 14 days showed significant improvement in clinical and biomedical parameters, they had a statistically significant lower cure rate than those given treatment for 21 days; this 14-day treatment regimen is therefore not recommended as monotherapy.[13] WHO recommends an intramuscular dose of 11 mg/kg daily for 21 days for all patients weighing more than 5 kg.[14] Oral paromomycin plus intravenous pentamidine was reported to be effective in the treatment of amphotericin-resistant visceral leishmaniasis in an HIV-infected patient.[15]

1. El-On J, *et al.* Topical treatment of Old World cutaneous leishmaniasis caused by Leishmania major: a double-blind control study. *J Am Acad Dermatol* 1992; **27:** 227–31.
2. Krause G, Kroeger A. Topical treatment of American cutaneous leishmaniasis with paromomycin and methylbenzethonium chloride: a clinical study under field conditions in Ecuador. *Trans R Soc Trop Med Hyg* 1994; **88:** 92–4.
3. Arana BA, *et al.* Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. *Am J Trop Med Hyg* 2001; **65:** 466–70.
4. Asilian A, *et al.* A randomized, placebo-controlled trial of a two week reginen of aminosidine (paromomycin) ointment for treatment of cutaneous leishmaniasis in Iran. *Am J Trop Med Hyg* 1995; **53:** 648–51.
5. Bryceson ADM, *et al.* Treatment of Old World cutaneous leishmaniasis with aminosidine ointment: results of an open study in London. *Trans R Soc Trop Med Hyg* 1994; **88:** 226–8.
6. Ben Salah A, *et al.* A randomized, placebo-controlled trial in Tunisia treating cutaneous leishmaniasis with paromomycin ointment. *Am J Trop Med Hyg* 1995; **53:** 162–6.
7. Soto J, *et al.* Successful treatment of New World cutaneous leishmaniasis with a combination of topical paromomycin/methylbenzethonium chloride and injectable meglumine antimonate. *Clin Infect Dis* 1995; **20:** 47–51.
8. Soto J, *et al.* Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimonate as treatment for American cutaneous leishmaniasis: controlled study. *Clin Infect Dis* 1998; **26:** 56–8.
9. Teklemariam S, *et al.* Aminosidine and its combination with sodium stibogluconate in the treatment of diffuse cutaneous leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1994; **88:** 334–9.
10. Jha TK, *et al.* Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. *BMJ* 1998; **316:** 1200–5.
11. Thakur CP, *et al.* A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. *Trans R Soc Trop Med Hyg* 2000; **94:** 429–31.
12. Sundar S, *et al.* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; **356:** 2571–81.
13. Sundar S, *et al.* Short-course paromomycin treatment of visceral leishmaniasis in India: 14-day vs 21-day treatment. *Clin Infect Dis* 2009; **49:** 914–18.
14. WHO. *WHO model formulary.* Geneva: WHO, 2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/12/10)
15. Manfredi R, *et al.* Diffuse cutaneous dissemination of visceral leishmaniasis during human immunodeficiency virus (HIV) infection, despite negligible immunodeficiency: repeated failure of liposomal amphotericin B administration, followed by successful long-term pentamidine and paromomycin administration. *Int J Antimicrob Agents* 2008; **31:** 590–2.

Trichomoniasis. Local application of a paromomycin cream has been tried in a small number of patients with metronidazole-resistant vaginal trichomoniasis (p. 925.1) with moderate success.[1] Intravaginal use of 250-mg oral tablets of paromomycin twice daily in a similar patient has also been reported.[2] The patient became asymptomatic within 3 weeks of starting paromomycin despite stopping treatment after 10 days because of vaginal soreness.

1. Nyirjesy P, *et al.* Difficult-to-treat trichomoniasis: results with paromomycin cream. *Clin Infect Dis* 1998; **26:** 986–8.
2. Tayal SC, *et al.* Paromomycin treatment of recalcitrant *Trichomonas vaginalis*. *Int J STD AIDS* 2010; **21:** 217–18.

Adverse Effects, Treatment, and Precautions

As for Neomycin, p. 330.2.

Effects on electrolytes. Three cases of tetany have been described in patients being treated for leishmaniasis with parenteral paromomycin. Symptoms resolved after treatment with intravenous calcium gluconate and paromomycin treatment could be continued with oral calcium supplementation.[1] The authors consider that paromomycin may cause temporary renal tubular damage leading to hypocalcaemia.

1. Thakur CP. Tetany in kala azar patients treated with paromomycin. *Indian J Med Res* 2008; **127:** 489–93.

Effects on the pancreas. Pancreatitis was associated with use of paromomycin during treatment of cryptosporidiosis in a patient with HIV infection.[1]

1. Tan WW, *et al.* Paromomycin-associated pancreatitis in HIV-related cryptosporidiosis. *Ann Pharmacother* 1995; **29:** 22–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paromomycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for Neomycin, p. 330.3.

Antimicrobial Action

Paromomycin is active against various protozoa including *Leishmania* spp., *Entamoeba histolytica*, and *Cryptosporidium* spp. In addition, it has an antibacterial spectrum similar to that of neomycin (p. 330.3). There is cross-resistance between paromomycin and kanamycin, framycetin, neomycin, and streptomycin.

Paromomycin also has anthelmintic properties against tapeworms.

Pharmacokinetics

Paromomycin is poorly absorbed from the gastrointestinal tract and most of an oral dose is eliminated unchanged in the faeces; about 0.1% of an oral daily dose is excreted renally. Oral absorption may be increased in conditions which damage or inflame the mucosa or disrupt gastrointestinal motility.

Peak plasma concentrations are reached within 0.5 to 1.5 hours after an intramuscular injection. After intramuscular use it distributes well into extracellular fluid, but penetrates poorly into the CNS and lungs. Paromomycin crosses the placenta and may accumulate in amniotic fluid and fetal plasma. The plasma elimination half-life is 2.62 hours. Paromomycin does not appear to be metabolised and is excreted virtually unchanged in the urine by glomerular filtration.

Parenteral administration. References.

1. Kanyok TP, *et al.* Pharmacokinetics of intramuscularly administered aminosidine in healthy subjects. *Antimicrob Agents Chemother* 1997; **41:** 982–6.
2. Sundar S, *et al.* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; **356:** 2571–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Humatin; ***Belg.***: Gabbroral; ***Canad.***: Humatin; ***Ger.***: Humatin; ***Gr.***: Humatin; ***Indon.***: Gabbryl; ***Ital.***: Gabbroral; Humatin; Kaman; ***Jpn***: Ameparomo; ***Spain***: Humatin; ***Switz.***: Humatin; ***USA***: Humatin.

Multi-ingredient Preparations. ***Israel***: Leshcutan.

Pharmacopoeial Preparations

USP 36: Paromomycin Sulfate Capsules; Paromomycin Sulfate Syrup.

Pentamidine Isetionate *(BANM, rINNM)*

Isetionato de pentamidina; M&B-800; Pentamidiinidiisetionaatti; Pentamidin Izetiyonat; Pentamidina, isetionato de; Pentamidindiisetionat; Pentamidin-diisetionát; Pentamidin-diizetionát; Pentamidine Diisetionate; Pentamidine, diisétionate de; Pentamidine Isethionate (USAN); Pentamidine, Isétionate de; Pentamidini diisetionas; Pentamidini Isethionas; Pentamidini Isetionas; Pentamidino diizetionatas; Pentamidyny diizetionian; Пентамидина Изетионат.

4,4′-(Pentamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).

$C_{19}H_{24}N_4O_2,2C_2H_6O_4S$=592.7

CAS — 100-33-4 (pentamidine); 140-64-7 (pentamidine isetionate).
ATC — P01CX01.
UNII — V2P3K60DA2.

Pharmacopoeias. In *Eur.* (see p. vii), *Int*, and *US*.

Ph. Eur. 8: (Pentamidine Diisetionate; Pentamidine Isetionate BP 2014). A white or almost white powder or colourless crystals; it is hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers.

USP 36: (Pentamidine Isethionate). A white or almost white powder or colourless crystals. It is hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% carbon dioxide-free aqueous solution has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Immediate precipitation occurred when a solution of pentamidine isetionate 3 mg/mL in glucose 5% was mixed with each of 5 cephalosporin and 1 cephamycin injections.[1]

Pentamidine isetionate is reported to be incompatible with foscarnet.

1. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.

Pentamidine Mesilate *(BANM, rINNM)*

Mesilato de pentamidina; Pentamidina, mesilato de; Pentamidine Dimethylsulphonate; Pentamidine, Mésilate de; Pentamidine Mesylate; Pentamidine Methanesulphonate; Pentamidini Mesilas; RP-2512; Пентамидина Мезилат.

Pentamidine dimethanesulphonate.

$C_{19}H_{24}N_4O_2,2CH_3SO_3H$=532.6

CAS — 6823-79-6.
UNII — 863QBB4D0A.

Pharmacopoeias. In *Int.*

Uses and Administration

Pentamidine, an aromatic diamidine derivative, is an antiprotozoal thought to act by several mechanisms, including interference with protozoal DNA and folate transformation and by inhibition of RNA and protein synthesis. It is used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma brucei gambiense* infections, in some forms of leishmaniasis, and in the treatment and prophylaxis of pneumocystis pneumonia. Pentamidine has also been tried in other protozoal infections including *Acanthamoeba* infection and babesiosis. For further information on these diseases see below.

Pentamidine has been given as the isetionate or mesilate salt. It was registered in 1950 as the mesilate, but had been used in protozoal diseases before this. The drug was re-evaluated and commercialised as the isetionate salt in 1984; this form is the one now available in most countries. Pentamidine isetionate 4 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base; pentamidine mesilate 3.6 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base.

Pentamidine isetionate is given by deep intramuscular injection or by slow intravenous infusion over at least 60 minutes; direct intravenous injection must be avoided. Patients should be lying down. The mesilate has usually been given intramuscularly.

In the treatment of early **African trypanosomiasis** due to *T. b. gambiense*, pentamidine isetionate 4 mg/kg may be given daily or on alternate days by intramuscular injection or intravenous infusion to a total of 7 to 10 doses. Pentamidine is not effective in trypanosomiasis with CNS involvement.

In the treatment of *visceral* **leishmaniasis**, and of *mucocutaneous* leishmaniasis due to *Leishmania braziliensis* or *L. aethiopica* that have not responded to antimonials, pentamidine isetionate 4 mg/kg may be given, by intravenous infusion or intramuscular injection three times weekly, for 5 to 25 weeks or longer. An alternative regimen in visceral leishmaniasis is to give 3 to 4 mg/kg, preferably by intramuscular injection, on alternate days to a maximum of 10 injections; the course may need to be repeated. In *cutaneous* leishmaniasis due to *L. aethiopica* or *L. guyanensis*, pentamidine isetionate 3 to 4 mg/kg may be given, preferably intramuscularly once or twice weekly, until the condition resolves. A weekly dose of 3 to 4 mg/kg is also used for diffuse cutaneous leishmaniasis due to *L. aethiopica* and should be continued for at least 4 months after parasites are no longer detectable on skin smears.

In the treatment of **pneumocystis pneumonia**, pentamidine isetionate 4 mg/kg is given once daily for 14 days or longer, by intramuscular injection or preferably slow intravenous infusion. Pentamidine isetionate is given by inhalation through a nebuliser to prevent pneumocystis pneumonia in HIV-positive patients in a dose of 300 mg once every 4 weeks; in those who cannot tolerate this dose 150 mg every 2 weeks may be used. It has also occasionally been used by this route for treating mild to moderate *P. jirovecii* infection in a dose of 600 mg daily for 3 weeks. Nebuliser design can affect the droplet size delivered and hence the amount of pentamidine reaching sites of action within the lungs. The optimal particle size is 1 to 2 micrometres. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to the drug.

Administration in children. The indications for use and doses of pentamidine in infants and children are the same as those for adults, see above.

Administration in renal impairment. Since renal clearance accounts for only a small proportion of pentamidine elimination, dosage adjustment is not generally considered necessary for mild to moderate degrees of renal impairment. UK licensed product information recommends dosage reductions in patients with pneumocystis pneumonia who have a creatinine clearance of less than 10 mL/minute. In patients with life-threatening disease the recommended dose of 4 mg/kg daily should be given for 7 to 10 days and then on alternate days for the remainder of the 14-dose course. In less severe disease the suggested dose is 4 mg/kg on alternate days for 14 doses.

Amoebic infections. *ACANTHAMOEBA INFECTIONS.* There have been a few case reports of intravenous pentamidine being used successfully to treat disseminated *Acanthamoeba* infection (p. 920.1) without evidence of CNS involvement in immunocompromised patients.[1,2] It is unlikely that pentamidine would be effective in infections involving the CNS.

1. Slater CA, *et al*. Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; **331:** 85–7.
2. Murakawa GJ, *et al*. Disseminated Acanthamoeba in patients with AIDS: a report of five cases and a review of the literature. *Arch Dermatol* 1995; **131:** 1291–6.

Babesiosis. Pentamidine has been tried for babesiosis (p. 920.2), but while some patients showed clinical improvements,[1-3] the efficacy and safety of pentamidine in this infection has been questioned.[4]

1. Francioli PB, *et al*. Response of babesiosis to pentamidine therapy. *Ann Intern Med* 1981; **94:** 326–30.
2. Raoult D, *et al*. Babesiosis, pentamidine, and cotrimoxazole. *Ann Intern Med* 1987; **107:** 944.
3. Clarke CS, *et al*. Babesiosis: under-reporting or case-clustering? *Postgrad Med J* 1989; **65:** 591–3.
4. Teutsch SM, Juranek DD. Babesiosis. *Ann Intern Med* 1981; **95:** 241.

Leishmaniasis. Pentamidine has been used in the treatment of **visceral** leishmaniasis (p. 923.1) in patients who have failed to respond to antimonials alone.[1] It has also been suggested as an alternative for long-term secondary prophylaxis in patients with HIV infection.[2]

A systematic review and meta-analysis[3] to determine the best drug management in the treatment of **cutaneous** leishmaniasis (p. 922.1) in Latin America reported similar cure rates for pentamidine and the pentavalent antimonials. Pentamidine has been extensively used and studied in French Guyana, where *L. guyanensis* causes most disease and cure rates higher than 90% have been reported after 2 doses of pentamidine. Pentamidine may be considered for treatment of patients with recurrent disease and was found to be superior to re-treatment with pentavalent antimonials in those who failed the treatment with the latter.[3] A short course of intramuscular pentamidine (3 to 4 mg/kg initially and repeated once 2 days later) was successful in treating 2 patients with Old World cutaneous leishmaniasis resistant to initial treatment with pentavalent antimonials or oral fluconazole.[4] A 73% cure rate was reported in 11 patients infected with *L. infantum*, *L. major*, or *L. tropica*.[5]

Diffuse cutaneous or **mucocutaneous** disease (p. 923.1) which is unresponsive to antimonials may respond to pentamidine.[1]

For mention of the use of pentamidine with paromomycin to treat visceral leishmaniasis in an HIV-infected patient, see p. 944.1.

1. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 15/04/09)
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 17/09/13)
3. Tuon FF, *et al*. Treatment of New World cutaneous leishmaniasis–a systematic review with a meta-analysis. *Int J Dermatol* 2008; **47:** 109–24.
4. Jaurégui berry S, *et al*. Efficacy of short-course intramuscular pentamidine isethionate treatment on Old World localized cutaneous leishmaniasis in 2 patients. *Clin Infect Dis* 2006; **42:** 1812–13.
5. Hellier I, *et al*. Treatment of Old World cutaneous leishmaniasis by pentamidine isethionate: an open study of 11 patients. *Dermatology* 2000; **200:** 120–3.

Pneumocystis pneumonia. In the **treatment** of pneumocystis pneumonia (p. 567.2) intravenous pentamidine is generally reserved for patients with moderate to severe disease who do not respond to, or cannot tolerate, co-trimoxazole. Co-trimoxazole with pentamidine is no more effective than pentamidine alone in these patients and is potentially more toxic than either drug.[1] Inhaled pentamidine has occasionally been suggested for mild to moderate infection, but is now generally only used for prophylaxis. However, patients given inhaled pentamidine may be prone to extrapulmonary *Pneumocystis* infections.[2,3]

In both primary and secondary **prophylaxis** of pneumocystis pneumonia in immunocompromised patients, co-trimoxazole is preferred to inhaled pentamidine. Comparative studies have shown that, in the short term, inhaled pentamidine has been less effective than co-trimoxazole[4,5] and no more effective than another common prophylactic drug, dapsone.[6,7] In addition, both co-trimoxazole and dapsone (given with pyrimethamine) also provide protection against toxoplasmosis and extrapulmonary pneumocystis infections. However, inhaled pentamidine is better tolerated than either of these, and studies have suggested that in the long term the efficacy of the three drugs is comparable,[8,9] at least in patients with CD4+ T lymphocyte counts of more than 100 cells/microlitre. Increasing the dose of pentamidine from 300 mg every four weeks to 300 mg every two weeks[10,11] or 600 mg every week[12] may improve efficacy further. Intermittent parenteral dosage of pentamidine has been used when the more usual drugs cannot be given.[13]

1. Glatt AE, Chirgwin K. Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Arch Intern Med* 1990; **150:** 271–9.
2. Witt K, *et al*. Dissemination of Pneumocystis carinii in patients with AIDS. *Scand J Infect Dis* 1991; **23:** 691–5.
3. Sha BE, *et al*. Pneumocystis carinii choroiditis in patients with AIDS: clinical features, response to therapy, and outcome. *J Acquir Immune Defic Syndr Hum Retrovirol* 1992; **5:** 1051–8.
4. Schneider MME, *et al*. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992; **327:** 1836–41.
5. Hardy WD, *et al*. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992; **327:** 1842–8.
6. Girard P-M, *et al*. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; **328:** 1514–20.
7. Torres RA, *et al*. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Am J Med* 1993; **95:** 573–83.
8. Bozzette SA, *et al*. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; **332:** 693–9.
9. Rizzardi GP, *et al*. Risks and benefits of aerosolized pentamidine and cotrimoxazole in primary prophylaxis of Pneumocystis carinii pneumonia in HIV-1-infected patients: a two-year Italian multicentric randomized controlled trial. *J Infect* 1996; **32:** 123–31.
10. Kronawitter U, *et al*. Low incidence of Pneumocystis carinii pneumonia in HIV patients receiving 300 mg pentamidine aerosol every 2 weeks. *Clin Investig* 1992; **70:** 1089–91.
11. Rizzardi GP, *et al*. Better efficacy of twice-monthly than monthly aerosolised pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with AIDS: an Italian multicentric randomised controlled trial. *J Infect* 1995; **31:** 99–105.
12. Ong ELC, *et al*. Efficacy and effects on pulmonary function tests of weekly 600 mg aerosol pentamidine as prophylaxis against Pneumocystis carinii pneumonia. *Infection* 1992; **20:** 136–9.
13. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 12/04/09)

African trypanosomiasis. Pentamidine is used for the early or haematolymphatic phase of African trypanosomiasis caused by *Trypanosoma brucei gambiense* (p. 925.2).[1] It is reported to be less effective against *T. b. rhodesiense* and in some areas resistance of *T. b. gambiense* to pentamidine is increasing. Pentamidine has been used with suramin for *T. b. gambiense* infections but this has not been shown to be clinically superior to pentamidine alone.[2]

1. WHO. Control and surveillance of African trypanosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 881* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_881.pdf (accessed 27/07/09)
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; **90:** 183–6.

Adverse Effects

Pentamidine is a toxic drug and adverse effects are frequent and sometimes severe when given parenterally; toxicity is more common in patients with AIDS. Fatalities due to severe hypotension, hypoglycaemia, acute pancreatitis, and cardiac arrhythmias have been reported.

Rapid intravenous injection has resulted in sudden hypotension and immediate reactions such as flushing, dizziness, headache, vomiting, breathlessness, tachycardia, and fainting. Hypotension may also occur when pentamidine is given intramuscularly or by slow intravenous infusion. Pentamidine may prolong the QT interval and isolated cases of torsade de pointes have been reported. Renal impairment is common (over 20% of patients), usually manifesting as mild and reversible raised blood urea nitrogen and serum creatinine concentrations, but acute renal failure can occur. Hypoglycaemia, sometimes followed by hyperglycaemia and type 1 diabetes mellitus, is well documented. Other severe adverse effects include leucopenia, thrombocytopenia, and hypocalcaemia; possible Stevens-Johnson syndrome has also been reported. Less severe adverse effects include azotaemia, raised liver enzyme values, anaemia, macroscopic haematuria, hypomagnesaemia, hyperkalaemia, nausea and vomiting, rashes, and taste disturbances. Rhabdomyolysis has been rarely reported after intramuscular use. Intramuscular pentamidine often causes pain, swelling, sterile abscess formation, and tissue necrosis at the site of injection. Similar damage can follow extravasation during intravenous dosage.

Pentamidine is not as toxic when given by inhalation for the prophylaxis of pneumocystis pneumonia. The commonest adverse effects with this route are cough and bronchoconstriction (particularly in patients with a history of smoking or asthma) and may be controlled by a bronchodilator. Inhalation may leave a bitter taste. Pneumothorax has been reported, but may be associated with the disease. There have been rare reports of adverse effects such as those seen when pentamidine is given by injection.

Incidence of adverse effects. Adverse effects were seen in 46.8% of 404 patients given pentamidine parenterally for the treatment of pneumocystis pneumonia, according to an analysis from the CDC in the USA.[1] The reactions included impaired renal function (23.5% of patients),

abnormal liver function (9.6%), hypoglycaemia (6.2%), haematological disturbances (4.2%), rashes (1.5%), and hypocalcaemia (1.2%). Local reactions at injection sites such as pain and abscess occurred in 18.3% and immediate adverse effects such as hypotension in 9.6%.

Retrospective studies[2-4] suggest that adverse reactions occur more commonly in patients with AIDS.

An evaluation of pentamidine in the treatment of 82 patients with visceral leishmaniasis further illustrates its toxicity.[5] Cardiotoxicity (tachycardia, hypotension, and ECG changes of non-specific myocarditis), occurred in about 23% of patients. No hypoglycaemic reaction was noted, but 4 patients developed diabetes mellitus and 3 of them were found to be insulin-dependent. Other adverse reactions included gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain, or diarrhoea) in about 78%, CNS effects (headache associated with flushing, delirium, or sensory disturbances resembling pins and needles [paraesthesias]) in about 24%, mild reversible albuminuria in about 7%, and allergic manifestations (generalised urticaria, itching, and conjunctival congestion) in about 5%. One patient had severe anaphylaxis.

1. Walzer PD, *et al*. Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80:** 83–93.
2. Lachaal M, Venuto RC. Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. *Am J Med* 1989; **87:** 260–3.
3. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; **25:** 1171–4.
4. O'Brien JG, *et al*. A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; **24:** 854–9.
5. Jha TK. Evaluation of diamidine compound (pentamidine isethionate) in the treatment of resistant cases of kala-azar occurring in North Bihar, India. *Trans R Soc Trop Med Hyg* 1983; **77:** 167–70.

Effects on the blood. Haemolytic anaemia has been reported in a 55-year-old man with AIDS being treated with intravenous pentamidine for pneumocystis pneumonia. Symptoms developed after a cumulative dose of 3740 mg of pentamidine had been given and resolved several days after stopping the pentamidine.[1] Megaloblastic anaemia after intravenous pentamidine has also been reported.[2]

1. Taguchi H, *et al*. Pentamidine-induced hemolytic anemia in an AIDS patient. *Ann Pharmacother* 1999; **33:** 503.
2. Au WY, *et al*. Intravenous pentamidine induced megaloblastic anaemia. *Haematologica* 2002; **87:** ECR06.

Effects on carbohydrate metabolism. As reported under Incidence of Adverse Effects, p. 945.3, pentamidine can have a range of effects on carbohydrate metabolism. Four patients receiving pentamidine for pneumocystis pneumonia developed severe fasting hypoglycaemia followed later by hyperglycaemia and type 1 diabetes mellitus.[1] It has been suggested that pentamidine has a toxic effect on the β-cells of the pancreatic islets and can induce an early cytolytic release of insulin and hypoglycaemia, followed by β-cell destruction, insulin deficiency, and diabetes mellitus.[1,2] AIDS patients appear to be highly susceptible and have a higher incidence of hypoglycaemia due to pentamidine.[3] The action on the pancreas has led to fatal acute *pancreatitis*;[4-6] fatal hypoglycaemia has also been reported.[7] These reports[1-5,7] involved pentamidine given by injection; pancreatitis[8,9] and diabetes mellitus[10,11] have also been reported in patients given pentamidine by aerosol inhalation.

1. Bouchard P, *et al*. Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes* 1982; **31:** 40–5.
2. Osei K, *et al*. Diabetogenic effect of pentamidine: in vitro and in vivo studies in a patient with malignant insulinoma. *Am J Med* 1984; **77:** 41–6.
3. Stahl-Bayliss CM, *et al*. Pentamidine-induced hypoglycemia in patients with the acquired immune deficiency syndrome. *Clin Pharmacol Ther* 1986; **39:** 271–5.
4. Salmeron S, *et al*. Pentamidine and pancreatitis. *Ann Intern Med* 1986; **105:** 140–1.
5. Zuger A, *et al*. Pentamidine-associated fatal acute pancreatitis. *JAMA* 1986; **256:** 2383–5.
6. Sauleda J, *et al*. Probable pentamidine-induced acute pancreatitis. *Ann Pharmacother* 1994; **28:** 52–3.
7. Sattler FR, Waskin H. Pentamidine and fatal hypoglycemia. *Ann Intern Med* 1987; **107:** 789–90.
8. Herer B, *et al*. Pancreatitis associated with pentamidine by aerosol. *BMJ* 1989; **298:** 605.
9. Hart CC. Aerosolized pentamidine and pancreatitis. *Ann Intern Med* 1989; **111:** 691.
10. Fisch A. Diabetes mellitus in a patient with AIDS after treatment with pentamidine aerosol. *BMJ* 1990; **301:** 875.
11. Chen JP, *et al*. Diabetes after aerosolized pentamidine. *Ann Intern Med* 1991; **114:** 913–14.

Effects on the cardiovascular system. *Hypotension* is a problem with intravenous pentamidine, but can be reduced by infusing the dose over 60 minutes, when the incidence of hypotension appears to be similar to that with the intramuscular route.[1,2] Intravenous pentamidine has also been associated with *torsade de pointes*.[3-6] *Sinus bradycardia* and second-degree *heart block* has been described in an HIV-positive patient treated with intravenous pentamidine for pneumocystis pneumonia.[7]

1. Navin TR, Fontaine RE. Intravenous versus intramuscular administration of pentamidine. *N Engl J Med* 1984; **311:** 1701.
2. Helmick CG, Green JK. Pentamidine-associated hypotension and route of administration. *Ann Intern Med* 1985; **103:** 480.
3. Harel Y, *et al*. Pentamidine-induced torsade de pointes. *Pediatr Infect Dis J* 1993; **12:** 692–4.
4. Miller HC. Cardiac arrest after intravenous pentamidine in an infant. *Pediatr Infect Dis J* 1993; **12:** 694–6.
5. Zanetti LAF, Oliphant CM. Pentamidine-induced torsade de pointes. *Ann Pharmacother* 1994; **28:** 282–3.
6. Otsuka M, *et al*. Torsades de pointes complicating pentamidine therapy of Pneumocystis carinii pneumonia in acute myelogenous leukemia. *Intern Med* 1997; **36:** 705–8.
7. Antoniou T, Gough KA. Early-onset pentamidine-associated second-degree heart block and sinus bradycardia: case report and review of the literature. *Pharmacotherapy* 2005; **25:** 899–903.

Effects on the kidneys. In an analysis[1] of the adverse effects of parenteral pentamidine (see also under Incidence of Adverse Effects p. 945.3), nephrotoxicity was often the most serious adverse reaction, although it was impossible to attribute it solely to pentamidine. Severe renal impairment occurred in 15 of 404 patients and contributed materially to 12 of 14 ensuing deaths. However, elevation of blood urea nitrogen was usually relatively mild and reversible in those patients who had normal pretreatment renal function and had received no other nephrotoxic agents. In two studies in patients with AIDS,[2,3] severe nephrotoxicity (increase in serum creatinine concentration of 500 micrograms per 100 mL) was reported in about 40% of patients. Analysis of risk factors suggested that the development of adverse reactions to parenteral pentamidine is correlated with the total dose received and the duration of treatment,[2,3] but not with the initial degree of renal function.[2] It has been noted that renal toxicity is more common when pentamidine is given intramuscularly, rather than intravenously, to AIDS patients with diarrhoea, suggesting that fluid status might have an important role.[4] There have been instances of renal failure occurring when pentamidine is inhaled as an aerosol for its local effect.[5,6]

1. Walzer PD, *et al*. Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80:** 83–93.
2. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; **25:** 1171–4.
3. O'Brien JG, *et al*. A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; **24:** 854–9.
4. Stehr-Green JK, Helmick CG. Pentamidine and renal toxicity. *N Engl J Med* 1985; **313:** 694–5.
5. Miller RF, *et al*. Acute renal failure after nebulised pentamidine. *Lancet* 1989; **i:** 1271–2.
6. Chapelon C, *et al*. Renal insufficiency with nebulised pentamidine. *Lancet* 1989; **ii:** 1045–6.

Effects on the nervous system. Paraesthesias, including perioral paraesthesias,[1,2] have been reported with pentamidine therapy. Perioral numbness occurred in a patient soon after starting the third intravenous infusion of pentamidine for treatment of pneumocystis pneumonia and disappeared after the end of the infusion; numbness recurred with all subsequent pentamidine infusions.[1]

See also under Incidence, p. 945.3.

1. Milligan KS, Phillips DL. Perioral numbness associated with intravenous pentamidine administration. *Ann Pharmacother* 2007; **41:** 153–6.
2. Brown E, *et al*. Perioral and facial parasthesias associated with intravenous pentamidine use for pneumocystis prophylaxis. *Pediatr Hematol Oncol* 2010; **27:** 658–60.

Effects on the respiratory system. Although inhaled pentamidine has produced reactions that are normally associated with the parenteral route, the main problem after inhalation is bronchoconstriction;[1] it can be prevented by prior use of a bronchodilator. Acute eosinophilic pneumonia associated with nebulised pentamidine has been reported in a patient.[2] Concern has also been expressed at the risks to those who are with the patient at the time of inhalation and are exposed to nebulised pentamidine.[3-5]

1. Smith DE, *et al*. Reversible bronchoconstriction with nebulised pentamidine. *Lancet* 1988; **ii:** 905.
2. Dupon M, *et al*. Acute eosinophilic pneumonia induced by inhaled pentamidine isethionate. *BMJ* 1993; **306:** 109.
3. McDiarmid MA, Jacobson-Kram D. Aerosolised pentamidine and public health. *Lancet* 1989; **ii:** 863–4.
4. Thomas SHL, *et al*. Aerosolised pentamidine. *Lancet* 1989; **ii:** 1284.
5. Smaldone GC, *et al*. Detection of inhaled pentamidine in health care workers. *N Engl J Med* 1991; **325:** 891–2.

Effects on the skin. Toxic epidermal necrolysis occurred in a man with SLE the day after being given aerosolised pentamidine for the prophylaxis of pneumocystis pneumonia. A lymphocyte stimulating test was performed on all candidate drugs, and was positive for pentamidine. Treatment with pentamidine was stopped and the patient was given plasma exchange, corticosteroids, and normal immunoglobulin. The eruption slowly resolved over 3 to 4 weeks.[1]

1. Watarai A, *et al*. Toxic epidermal necrolysis caused by aerosolized pentamidine. *Am J Med* 2009; **122:** e1–e2.

Precautions

Pentamidine should be used under close supervision and great care is necessary if it is used in patients suffering from any condition likely to be exacerbated by its adverse effects. The CSF should be checked for signs of CNS involvement before giving pentamidine for trypanosomiasis, since it is unlikely to be effective in such cases. Patients should be lying down while it is given and their blood pressure should be monitored. Kidney and liver function, blood-glucose concentrations, blood and platelet counts, and other parameters indicative of developing toxicity, such as serum-calcium, -magnesium, and -potassium concentrations and the ECG, should also be assessed regularly during courses of treatment with pentamidine. Particular caution and continuous cardiac monitoring is advised if the patient's QT interval exceeds 500 milliseconds while receiving treatment; alternative regimens should be used if the QT interval exceeds 550 milliseconds.

Patients with a history of asthma or smoking may be at increased risk of cough and bronchospasm during inhalation of nebulised pentamidine. Symptoms may be controlled by giving a bronchodilator before pentamidine. Pentamidine solution should not be mixed with other drugs nor should a bronchodilator be given in the same nebuliser. Extrapulmonary *Pneumocystis jirovecii* infections may occur in patients given nebulised pentamidine and should be considered in patients with unexplained signs and symptoms. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to pentamidine.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pentamidine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

Use of pentamidine with other nephrotoxic drugs such as amphotericin B or foscarnet should preferably be avoided. Extreme caution is also necessary if pentamidine is given with other drugs, such as foscarnet, that can cause hypocalcaemia. There is an increased risk of ventricular arrhythmias if pentamidine is given with drugs which prolong the QT interval such as intravenous erythromycin, fluoroquinolones, amiodarone, tricyclic antidepressants, phenothiazines, or terfenadine. There may be an increased risk of pancreatitis when intravenous pentamidine is used with didanosine, stavudine, or zalcitabine and such combinations should be avoided. Pentamidine is structurally similar to amiloride and therefore use with potassium-sparing diuretics may result in severe hyperkalaemia.

Pharmacokinetics

After parenteral doses of the isetionate, pentamidine is widely distributed in the body. During repeated dosing accumulation is believed to occur, particularly in the liver and kidneys. After intravenous injection plasma concentrations fall rapidly to one twentieth of peak values during the first 2 hours, followed by a much slower decline thereafter. On intramuscular injection peak concentrations occur after about 1 hour and the serum concentration remains the same for about 24 hours. The apparent volume of distribution of pentamidine after intramuscular injection is more than 3 times that seen after intravenous use. Elimination half-lives of 6 hours after intravenous infusion and 9 hours after intramuscular injection have been cited, but probably represent an intermediate value, and terminal elimination half-lives of between several days and weeks have been reported. After multiple intravenous doses the half-life was 12.5 days. Only a small amount is slowly excreted unchanged in the urine.

Distribution to the lung is relatively poor after injection. Systemic absorption after inhalation is reported to result in peak plasma concentrations of 5 to 10% of those after parenteral use, and there have been a few reports of systemic adverse effects. The half-life of aerosolised pentamidine in bronchial alveolar lavage fluid is more than 10 to 14 days. Particle or droplet size appears to be important in achieving adequate pulmonary distribution.

References.

1. O'Doherty MJ, *et al*. Differences in relative efficiency of nebulisers for pentamidine administration. *Lancet* 1988; **ii:** 1283–6.
2. Simonds AK, *et al*. Aerosolised pentamidine. *Lancet* 1989; **i:** 221–2.
3. Baskin MI, *et al*. Regional deposition of aerosolized pentamidine: effects of body position and breathing pattern. *Ann Intern Med* 1990; **113:** 677–83.
4. Bronner U, *et al*. Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of Trypanosoma gambiense in Côte d'Ivoire. *Trans R Soc Trop Med Hyg* 1991; **85:** 608–11.

5. Lidman C, *et al*. Plasma pentamidine concentrations vary between individuals with Pneumocystis carinii pneumonia and the drug is actively secreted by the kidney. *J Antimicrob Chemother* 1994; **33:** 803–10.
6. Bronner U, *et al*. Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. *Br J Clin Pharmacol* 1995; **39:** 289–95.
7. Conte JE, Golden JA. Intrapulmonary and systemic pharmacokinetics of aerosolized pentamidine used for prophylaxis of Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus. *J Clin Pharmacol* 1995; **35:** 1166–73.

Renal impairment. In a study[1] of patients with normal renal function or on haemodialysis, renal clearance of pentamidine during the 24 hours after intravenous use was 2.1% of the plasma clearance in those with normal renal function, suggesting that pentamidine elimination would be largely unaffected by renal impairment. In those with end-stage renal disease on haemodialysis the terminal elimination half-life after a single dose was prolonged to about 75 hours, compared with 30 hours in the patients with normal renal function, but the volumes of distribution and area under the concentration-time curve were not significantly different. In patients with normal or mildly impaired renal function who had received between 12 and 21 doses, the terminal elimination half-life after the final dose was about 12 days and pentamidine was still detectable in the plasma after 6 weeks. There was evidence of accumulation of pentamidine during repeated daily dosing.

1. Conte JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. *J Infect Dis* 1991; **163:** 169–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Pentacarinat; ***Braz.***: Pentacarinat; ***Fr.***: Pentacarinat; ***Ger.***: Pentacarinat; ***Gr.***: Pentacarinat; Pentam; ***Hong Kong***: Pentacarinat; ***Irl.***: Pentacarinat†; ***Ital.***: Pentacarinat; ***Neth.***: Pentacarinat; ***NZ***: Pentacarinat; ***Port.***: Pentamina†; ***Spain***: Pentacarinat; ***Swed.***: Pentacarinat; ***Switz.***: Pentacarinat; ***Thai.***: Pentacarinat; ***UK***: Pentacarinat; ***USA***: NebuPent; Pentacarinat; Pentam.

Pharmacopoeial Preparations
BP 2014: Pentamidine Injection.

Quinfamide *(USAN, rINN)*

Quinfamida; Quinfamidum; Win-40014; Хинфамид.
1-(Dichloroacetyl)-1,2,3,4-tetrahydroquinolin-6-ol 2-furoic acid ester.
$C_{16}H_{13}Cl_2NO_4$=354.2
CAS — 62265-68-3.
UNII — O1ZB1046R1.

Profile

Quinfamide is a luminal amoebicide. It is given orally for intestinal amoebiasis in a dose of 300 mg, either as a single dose or as three divided doses over 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Amefin; Amefur†; Amenox; Amofarma; Amofur†; Bisidim; Celemin†; Doffler; Falacid†; Luminovag; Protosin; Quocel; Serphamida.

Multi-ingredient Preparations. ***Mex.***: Amoebriz; Bensolmin Complex; Farmiver; Oxal; Vermox-Plus.

Robenidine Hydrochloride

(BANM, USAN, rINNM)

CL-78116; Hidrocloruro de robenidina; Robenidina, hidrocloruro de; Robénidine, Chlorhydrate de; Robenidini Hydrochloridum; Robenzidene Hydrochloride; Робенидина Гидрохлорид.
1,3-Bis(4-chlorobenzylideneamino)guanidine hydrochloride.
$C_{15}H_{13}Cl_2N_5$,HCl=370.7
CAS — 25875-51-8 (robenidine); 25875-50-7 (robenidine hydrochloride).
UNII — 8STT15Y392.

Profile

Robenidine is an antiprotozoal used as the hydrochloride in veterinary practice for the prevention of coccidiosis in poultry and rabbits.

Ronidazole *(BAN, USAN, pINN)*

Ronidazol; Ronidazolum; Ронидазол.
(1-Methyl-5-nitroimidazol-2-yl)methyl carbamate.
$C_6H_8N_4O_4$=200.2
CAS — 7681-76-7.
ATC Vet — QP51AA08.
UNII — E01R4M1063.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Ronidazole). A white to yellowish-brown, odourless or almost odourless powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Protect from light.

Profile

Ronidazole is a 5-nitroimidazole antiprotozoal that is used in veterinary practice for the control of trichomoniasis in cage birds and pigeons. It has also been added to turkey feeding stuffs and has been used for the control of swine dysentery. Ronidazole is considered to be carcinogenic and its use in food-producing animals has been banned in some countries.

Salinomycin Sodium *(BANM, rINNM)*

AHR-3096 (salinomycin); K-364 (salinomycin); K-748364A (salinomycin); Natrii Salinomycinum; Salinomicina sódica; Salinomycine Sodique; Натрий Салиномицин.
Sodium (2*R*)-2-{(2*R*,5*S*,6*R*)-6-[(1*S*,2*S*,3*S*,5*R*)-5-{(2*S*,5*S*,7*R*,9*S*,10*S*,12*R*,15*R*)-2-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl]-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl}-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-5-methylpyran-2-yl} butyrate.
$C_{42}H_{69}NaO_{11}$=773.0
CAS — 53003-10-4 (salinomycin); 55721-31-8 (salinomycin sodium).
UNII — 92UOD3BMEK.

Profile

Salinomycin, an ionophore antibiotic produced by *Streptomyces albus*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor in pigs.

Poisoning. Ionophore antibacterials selectively bind certain ions causing intra- and extracellular biochemical disturbances. Salinomycin preferentially binds to potassium and interferes with potassium transport across mitochondrial membranes; the sodium/calcium ion exchange mechanism may also be disrupted. It also has potent sympathomimetic effects. Animal poisonings with ionophore antibacterials have been reported, with skeletal muscle in all animals and cardiac muscle in some animals being affected.[1] In humans, prolonged rhabdomyolysis (40 days), pain, and disability were reported in a healthy man after he accidentally inhaled and swallowed about 1 mg/kg of salinomycin. Supportive treatment (with activated charcoal, oxygen, and intravenous fluids) is recommended, as well as aggressive management of myoglobinuria (with urinary alkalinisation) and prolonged bed rest to reduce metabolic demand on the muscle; an early baseline cardiac ECG is also recommended.[1]

1. Story P, Doube A. A case of human poisoning by salinomycin, an agricultural antibiotic. *N Z Med J* 2004; **117:** U799.

Satranidazole *(rINN)*

C 10213-Go; CG-10213-Go; Go-10213; Satranidazol; Satranidazolum; Сатранидазол.
1-(1-Methyl-5-nitroimidazol-2-yl)-3-(methylsulfonyl)-2-imidazolidinone.
$C_8H_{11}N_5O_5S$=289.3
CAS — 56302-13-7.
UNII — 4N7G8A6439.

Profile

Satranidazole is a 5-nitroimidazole derivative with properties similar to those of metronidazole (p. 936.1). It is used in the treatment of amoebiasis, giardiasis, and trichomoniasis.

References.

1. Muzaffar J, *et al*. Randomized, single-blind, placebo-controlled multicenter trial to compare the efficacy and safety of metronidazole and satranidazole in patients with amebic liver abscess. *Dig Dis Sci* 2006; **51:** 2270–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Satrogyl; Satromax.

Multi-ingredient Preparations. ***India***: Satrogyl-O; Satromax-O.

Secnidazole *(BAN, rINN)*

PM-185184; 14539-RP; RP-14539; Secnidazol; Secnidazolum; Seknidazol; Секнидазол.
1-(2-Methyl-5-nitroimidazol-1-yl)propan-2-ol.
$C_7H_{11}N_3O_3$=185.2
CAS — 3366-95-8.
ATC — P01AB07.
UNII — R3459K699K.

Profile

Secnidazole is a 5-nitroimidazole derivative with properties similar to those of metronidazole (p. 936.1), apart from a much longer plasma half-life of 20 hours or more. It is used in the treatment of amoebiasis, giardiasis, and trichomoniasis.

For the treatment of intestinal amoebiasis and trichomoniasis in adults, secnidazole is given orally, usually as a single dose of 2 g; for hepatic amoebiasis an oral dose of 1.5 g daily is given in single or divided doses for 5 days. For the treatment of intestinal amoebiasis and giardiasis in children 30 mg/kg may be given as a single oral dose; in hepatic amoebiasis an oral dose of 30 mg/kg daily is given in single or divided doses for 5 days.

References.

1. Gillis JC, Wiseman LR. Secnidazole: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. *Drugs* 1996; **51:** 621–38.
2. Girginkardeşler N, *et al*. *Dientamoeba fragilis*, a neglected cause of diarrhea, successfully treated with secnidazole. *Clin Microbiol Infect* 2003; **9:** 110–13.
3. Escobedo AA, *et al*. A randomized trial comparing mebendazole and secnidazole for the treatment of giardiasis. *Ann Trop Med Parasitol* 2003; **97:** 499–504.
4. Núñez JT, Gómez G. Low-dose secnidazole in the treatment of bacterial vaginosis. *Int J Gynaecol Obstet* 2005; **88:** 281–5.
5. Slim R, *et al*. Secnidazole-induced acute pancreatitis: a new side-effect for an old drug? *JOP* 2010; **11:** 85–6.
6. Bohbot J-M, *et al*. Treatment of bacterial vaginosis: a multicenter, double-blind, double-dummy, randomised phase III study comparing secnidazole and metronidazole. *Infect Dis Obstet Gynecol* 2010; **2010:** 705692.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flagentyl; ***Braz.***: Deprozol; Neodazol; Secfar; Secnal; Secnaxidol; Secni-Plus; Secnics; Secnidal; Secnidalin; Secnihexal; Secnitec; Secnix; Secnizol; Sectil; Tecnid; Unigyn; ***China***: Ke Ni (可尼); Kelisaike (可立塞克); Ming Jie (明捷); Sai Ta Le (赛他乐); Sha Ba Ke (沙巴克); Xi Ni Di (西尼迪); Xin Shuang (信爽); You Ke Xin (优克欣); ***Fr.***: Secnol; ***India***: Ambiform; Amitab; Entosec; Etisec; Flagentyl; Noameba-DS†; Secnil; ***Indon.***: Sentyl†; ***Mex.***: Conamvag; Gisistin; Minovag; Sabima; Secnidal; ***Philipp.***: Flagentyl; ***Port.***: Flagentyl; ***Rus.***: Tagera (Tarepa); ***Turk.***: Flagentyl; ***Ukr.***: Secnidox (Секнидокс); ***Venez.***: Ambese; Daksol; Fazol; Secnidal; Secnivax; Seczol; Unidazol.

Multi-ingredient Preparations. ***Arg.***: Gynerium UD; Gynerium; ***Braz.***: Gynopac; ***India***: Azintra-3; Azithral XP; Eradikit; Eve Kit; Fas-3 Kit; FC-Kit; Fiscon Tab; Flunec Combikit; Fulkit; Fygek-AS; Gyn-3; Gynotrim Kit; Hif-AS; Kit-3D; Od-Kit; Saf Kit; ***Mex.***: C Cobistal; Gitrasek; Sepia; Sporasec; ***Rus.***: Safocid (Сафоцид); ***Ukr.***: Ginekit (Гинекит); ***Venez.***: Sporasec.

Semduramicin *(BAN, USAN, rINN)*

Semduramicina; Semduramicine; Semduramicinum; UK-61689-2 (semduramicin sodium); UK-61689; Семдурамицин.
(2*R*,3*S*,4*S*,5*R*,6*S*)-Tetrahydro-2,4-dihydroxy-6-{(*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)-9-hydroxy-2,8-dimethyl-2-{(2*S*,2′*R*,3′*S*,5′*R*)-octahydro-2-methyl-5′-[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-3′-[(2*S*,5*S*,6*R*)-tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy]-2,2′-bifuran-5-yl}-1,6-dioxaspiro[4.5]dec-7-yl]ethyl}-5-methoxy-3-methyl-2*H*-pyran-2-ylacetic acid.
$C_{45}H_{76}O_{16}$=873.1
CAS — 113378-31-7 (semduramicin); 119068-77-8 (semduramicin sodium).
UNII — P6VXL377WL.

Profile

Semduramicin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry. It is also used as the sodium salt.

Suramin Sodium *(rINN)*

Antrypol; Bayer-205; Cl-1003; Fourneau-309; Naganinum; Naganol; NSC-34936; Suramin Hexasodium (USAN); Suramina sódica; Suramine Sodique; Suraminum Natricum; Сурамин Натрий.
The symmetrical 3″-urea of the sodium salt of 8-(3-benzamido-4-methylbenzamido)naphthalene-1,3,5-trisul-

phonic acid; Hexasodium 8,8′-{carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]}bis(1,3,5-naphthalenetrisulfonate).
$C_{51}H_{34}N_6Na_6O_{23}S_6$=1429.2
CAS — 145-63-1 (suramin); 129-46-4 (suramin sodium).
ATC — P01CX02.
ATC Vet — QP51AE02.
UNII — 89521262IH.

Pharmacopoeias. In *Fr.*, *Int.*, and *It.*

Uses and Administration

Suramin is a trypanocide used in the treatment of African trypanosomiasis and as an anthelmintic in the treatment of onchocerciasis (see below).

Suramin is given as suramin sodium by slow intravenous injection, usually as a 10% solution. Because of the danger of severe reactions it is advisable to give a test dose before starting treatment.

In **African trypanosomiasis** suramin is used mainly for the early (haematolymphatic) stages of *Trypanosoma brucei rhodesiense* infection; pentamidine may be preferred for early-stage treatment of *T. b. gambiense* infection. Suramin is not used for late-stage infections with CNS involvement. Early-stage trypanosomiasis treatment begins with a (test) dose of 5 mg/kg of suramin on day 1. This is given with a pause of at least 1 minute after injecting the first few microlitres; the next 0.5 mL is given over 30 seconds with a wait of one minute before injecting the remainder of the dose over several minutes. If the test dose is tolerated 10 mg/kg is given on day 3, then 20 mg/kg on days 5, 11, 17, 23, and 30. Another schedule consists of a test dose of 100 to 200 mg and then 5 doses of 1 g given on days 1, 3, 7, 14, and 21.

For doses used in children, and in **onchocerciasis** see below.

General references.

1. McGeary RP, *et al.* Suramin: clinical uses and structure-activity relationships. *Mini Rev Med Chem* 2008; **8:** 1384–94.

Administration in children. For the treatment of early-stage African trypanosomiasis in children, suramin may be given by slow intravenous injection. A (test) dose of 5 mg/kg is given on day 1 (see above), 10 mg/kg on day 3, and 20 mg/kg on days 5, 11, 17, 23, and 30. Another schedule consists of a test dose of 100 to 200 mg and then 5 doses of 20 mg/kg given on days 1, 3, 7, 14, and 21.

Malignant neoplasms. Suramin is reported to have antineoplastic activity and has been studied in several malignant neoplasms, in particular hormone-resistant prostatic cancer (p. 712.3).[1-9] However, its clinical usefulness is hindered by dose-limiting toxicity and problems in developing a simple dose schedule. It has also been investigated as a chemosensitiser.[10-12]

1. Stein CA, *et al.* Suramin: an anticancer drug with a unique mechanism of action. *J Clin Oncol* 1989; **7:** 499–508.
2. Kilbourn RG. Suramin: new therapeutic concepts for an old drug. *Cancer Bull* 1991; **43:** 265–7.
3. Rapoport BL, *et al.* Suramin in combination with mitomycin C in hormone-resistant prostate cancer: a phase II clinical study. *Ann Oncol* 1993; **4:** 567–73.
4. Woll PJ, *et al.* Suramin for breast and prostate cancer: a pilot study of intermittent short infusions without adaptive controls. *Ann Oncol* 1994; **5:** 597–600.
5. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41:** 299–307.
6. Eisenberger MA, Reyno LM. Suramin. *Cancer Treat Rev* 1994; **20:** 259–73.
7. Rosen PJ, *et al.* Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. *J Clin Oncol* 1996; **14:** 1626–36.
8. Small EJ, *et al.* Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol* 2000; **18:** 1440–50.
9. Kaur M, *et al.* Suramin's development: what did we learn? *Invest New Drugs* 2002; **20:** 209–19.
10. Villalona-Calero MA, *et al.* Noncytotoxic suramin as a chemosensitizer in patients with advanced non-small-cell lung cancer: a phase II study. *Ann Oncol* 2008; **19:** 1903–9.
11. George S, *et al.* Phase I/II trial of 5-fluorouracil and a noncytotoxic dose level of suramin in patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2008; **6:** 79–85.
12. Lam ET, *et al.* Phase I trial of non-cytotoxic suramin as a modulator of docetaxel and gemcitabine therapy in previously treated patients with non-small cell lung cancer. *Cancer Chemother Pharmacol* 2010; **66:** 1019–29.

Onchocerciasis. Although suramin is the only drug in clinical use for onchocerciasis that is effective against adult worms, its use is restricted because of the frequency of associated complications and its intrinsic toxicity. Treatment of onchocerciasis (p. 147.2) is currently based on continuous suppression of microfilariae by regular use of ivermectin. WHO[1] advises that suramin should only be considered for the curative treatment of individuals in areas without transmission of onchocerciasis and of individuals leaving an endemic area, and for severe hyperreactive onchodermatitis where symptoms are not adequately controlled with ivermectin. WHO[2] also recommends that it should not be used to treat onchocerciasis in the elderly or infirm, in patients with severe liver or renal disease, in totally blind patients (unless they require relief from intensely itchy lesions), or in pregnant women (who should be treated after delivery).

A total dose of 66.7 mg/kg in six incremental weekly doses is recommended.[1,2] The first (test) dose of suramin sodium 3.3 mg/kg should be given very cautiously by slow intravenous injection; this is followed at weekly intervals by incremental doses of 6.7 mg/kg, 10.0 mg/kg, 13.3 mg/kg, 16.7 mg/kg and 16.7 mg/kg.[2]

1. WHO. Onchocerciasis and its control: report of a WHO expert committee. *WHO Tech Rep Ser 852* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_852.pdf (accessed 27/07/09)
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/04/09)

African trypanosomiasis. Suramin is used in the treatment of the early haematolymphatic phase of African trypanosomiasis (p. 925.2) caused by *Trypanosoma brucei rhodesiense* and for *T. b. gambiense* infections which are resistant to pentamidine.[1] In some regions, suramin has been used with pentamidine for *T. b. gambiense* infections but it has not been shown to be clinically superior to pentamidine alone.[2] Case reports have suggested that suramin with metronidazole[3] or eflornithine[4] could be useful in *T. b. rhodesiense* infections, although response to suramin plus eflornithine was disappointing in a study involving 6 patients.[5]

1. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/04/09)
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; **90:** 183–6.
3. Foulkes JR. Metronidazole and suramin combination in the treatment of arsenical refractory rhodesian sleeping sickness—a case study. *Trans R Soc Trop Med Hyg* 1996; **90:** 422.
4. Taelman H, *et al.* Combination treatment with suramin and eflornithine in late stage rhodesian trypanosomiasis: case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 572–3.
5. Clerinx J, *et al.* Treatment of late stage rhodesiense trypanosomiasis using suramin and eflornithine: report of six cases. *Trans R Soc Trop Med Hyg* 1998; **92:** 449–50.

Adverse Effects

An immediate and potentially fatal reaction, with nausea, vomiting, shock, seizures, and loss of consciousness, may occur during the first injection of suramin sodium in some patients and thus it is usual practice to give a small test dose before starting treatment; toxicity is more likely in malnourished patients.

Abdominal pain, mouth ulceration, and skin reactions such as urticaria and pruritus may occur.

Other adverse effects include paraesthesia and hyperaesthesia of the palms and soles, skin eruptions, blood dyscrasias, fever, polyuria, increased thirst, raised liver enzyme values, fatigue, and effects on the eye including photophobia and lachrymation. Proteinuria is common; haematuria and casts in the urine may also occur. There have been occasional reports of adrenal insufficiency.

Effects on the blood. Thrombocytopenia has been reported in patients receiving suramin, generally during treatment for AIDS or cancer.[1-5] An immune-mediated mechanism has been proposed[3] although there is evidence that multiple mechanisms may be involved.[4] Other adverse effects on the blood include leucopenia or neutropenia,[1,5,6] anaemia,[1] deterioration of pre-existing lymphocytopenia,[6] and fatal myelosuppression.[6] Agranulocytosis and haemolytic anaemia have occurred rarely.

1. Levine AM, *et al.* Suramin antiviral therapy in the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; **105:** 32–7.
2. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41:** 299–307.
3. Seidman AD, *et al.* Immune-mediated thrombocytopenia secondary to suramin. *Cancer* 1993; **71:** 851–4.
4. Tisdale JF, *et al.* Severe thrombocytopenia in patients treated with suramin: evidence for an immune mechanism in one. *Am J Hematol* 1996; **51:** 152–7.
5. Garcia-Schürmann JM, *et al.* Suramin treatment in hormone- and chemotherapy-refractory prostate cancer. *Urology* 1999; **53:** 535–41.
6. Rosen PJ, *et al.* Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. *J Clin Oncol* 1996; **14:** 1626–36.

Effects on the eyes. Late effects on the eyes associated with suramin include photophobia, lachrymation, and palpebral oedema. Keratopathy characterised by corneal deposits has been reported in patients receiving suramin. In a study of 114 patients receiving suramin for prostatic cancer, 13 developed corneal deposits similar to those reported with chloroquine therapy after 34 to 98 days of therapy.[1] Symptoms in 10 of the 13 included lachrymation and foreign body sensation. The remaining 3 patients were asymptomatic. Shifts in refractive error were also found. Keratopathy has also been reported in patients with AIDS receiving suramin.[2] In patients treated with suramin for ocular onchocerciasis, the incidence of optic atrophy was higher after 3 years than in untreated patients.[3] A prolonged inflammatory response to dying microfilariae in the optic nerve might be responsible, although a direct toxic or allergic effect could not be ruled out.

1. Hemady RK, *et al.* Ocular symptoms and signs associated with suramin sodium treatment for metastatic cancer of the prostate. *Am J Ophthalmol* 1996; **121:** 291–6.
2. Teich SA, *et al.* Toxic keratopathy associated with suramin therapy. *N Engl J Med* 1986; **314:** 1455–6.
3. Thylefors B, Rolland A. The risk of optic atrophy following suramin treatment of ocular onchocerciasis. *Bull WHO* 1979; **57:** 479–80.

Effects on the kidneys. In addition to the proteinuria commonly seen during suramin therapy, there have been reports of individual cases of renal glycosuria[1] and of acute renal failure.[2,3]

1. Awadzi K, *et al.* The chemotherapy of onchocerciasis XVIII: aspects of treatment with suramin. *Trop Med Parasitol* 1995; **46:** 19–26.
2. Figg WD, *et al.* Acute renal toxicity associated with suramin in the treatment of prostate cancer. *Cancer* 1994; **74:** 1612–14.
3. Smith A, *et al.* Acute renal failure in a patient receiving treatment with suramin. *Am J Clin Oncol* 1997; **20:** 433–4.

Effects on the nervous system. Neurological disorders reported in patients receiving parenteral suramin for the treatment of malignancies include a mild, distal axonal neuropathy and a more severe, inflammatory demyelinating neuropathy that is partially reversible and may resemble Guillain-Barré syndrome.[1] Severe polyneuropathy with generalised flaccid paralysis is dose dependent and has generally been associated with serum-suramin concentrations greater than 350 micrograms/mL,[2,3] but motor neuropathy was reported in 8 patients with serum concentrations of 275 micrograms/mL.[4]

1. Chaudhry V, *et al.* A prospective study of suramin-induced peripheral neuropathy. *Brain* 1996; **119:** 2039–52.
2. La Rocca RV, *et al.* Suramin-induced polyneuropathy. *Neurology* 1990; **40:** 954–60.
3. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41:** 299–307.
4. Bitton RJ, *et al.* Pharmacologic variables associated with the development of neurologic toxicity in patients treated with suramin. *J Clin Oncol* 1995; **13:** 2223–9.

Effects on the skin. Pruritus and urticaria may occur as hypersensitivity reactions to suramin. A prospective study[1] in 60 patients given high doses of intravenous suramin for the treatment of malignancies reported skin reactions, most commonly morbilliform reactions, in 82% of patients. Other reported skin effects were keratotic papules, UV recall, and urticaria. Most reactions occurred within the first 24 hours of therapy and resolved despite continued treatment. Late skin reactions include erythematous maculopapular rashes.[2] Severe reactions including erythema multiforme,[3] exfoliative dermatitis, and fatal toxic epidermal necrolysis[4,5] have been reported.

1. Lowitt MH, *et al.* Cutaneous eruptions from suramin: a clinical and histopathologic study of 60 patients. *Arch Dermatol* 1995; **131:** 1147–53.
2. O'Donnell BP, *et al.* Suramin-induced skin reactions. *Arch Dermatol* 1992; **128:** 75–9.
3. Katz SK, *et al.* Erythema multiforme induced by suramin. *J Am Acad Dermatol* 1995; **32:** 292–3.
4. May E, Allolio B. Fatal toxic epidermal necrolysis during suramin therapy. *Eur J Cancer* 1991; **27:** 1338.
5. Falkson G, Rapoport BL. Lethal toxic epidermal necrolysis during suramin treatment. *Eur J Cancer* 1992; **28A:** 1294.

Precautions

Suramin sodium should be used under close supervision, and the general condition of patients improved as far as possible before treatment starts. Patients who have a severe reaction to the first dose should never receive suramin again. It should not be used in elderly or infirm patients or in the presence of severe hepatic or renal disease. The urine should be tested before treatment starts and weekly during treatment; dosage should be reduced if moderate proteinuria develops and stopped if it becomes severe or if casts appear in the urine.

Pregnancy. Suramin has been reported to be teratogenic in *mice* but not in *rats*.[1] WHO[2] recommends that when necessary suramin should be used in pregnant women with *T. b. rhodesiense* trypanosomiasis, even those with meningoencephalitic disease, because melarsoprol is contra-indicated; in onchocerciasis, suramin treatment should be delayed until after delivery.

1. Mercier-Parot L, Tuchmann-Duplessis H. Action abortive et tératogène d'un trypanocide, la suramine. *C R Soc Biol* 1973; **167:** 1518–22.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 07/04/09)

Pharmacokinetics

After intravenous injection, suramin becomes bound to plasma proteins and plasma concentrations over 100 micrograms/mL are maintained for several weeks. Unbound suramin is excreted in the urine; small amounts are excreted in the faeces. Suramin is widely distributed; concentrations in the kidney and adrenal glands are higher than those in other tissues. Penetration of suramin into the CSF appears to be poor.

The clinical pharmacokinetics of suramin were studied in 4 patients with AIDS given 6.2 g intravenously over 5 weeks.[1] Suramin accumulated during treatment and plasma concentrations exceeded 100 micrograms/mL for several weeks. After the last dose the terminal half-life of suramin ranged from 44 to 54 days. At least 99.7% was bound to plasma proteins. Renal clearance accounted for most of the elimination of suramin from the body. There appeared to be little or no metabolism of suramin.

In another study,[2] ten male patients with onchocerciasis received weekly infusions of suramin for 6 weeks, according to the dose regimen recommended by WHO (see p. 948.1). In these patients the median elimination half-life was about 92 days, and in each case, the peak plasma concentration remained below 300 micrograms/mL.

1. Collins JM, *et al.* Clinical pharmacokinetics of suramin in patients with HTLV-III/LAV infection. *J Clin Pharmacol* 1986; **26:** 22–6.
2. Chijioke CP, *et al.* Clinical pharmacokinetics of suramin in patients with onchocerciasis. *Eur J Clin Pharmacol* 1998; **54:** 249–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Germanin.

Teclozan *(USAN, rINN)*

NSC-107433; Téclozan; Teclozán; Teclozanum; Win-13146; Теклозан.
NN′-p-Phenylenedimethylenebis[2,2-dichloro-*N*-(2-ethoxyethyl)acetamide].
$C_{20}H_{28}Cl_4N_2O_4$=502.3
CAS — 5560-78-1.
ATC — P01AC04.
UNII — K9RIF0COUB.

Profile

Teclozan, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p. 931.2). It has been given orally in the treatment of intestinal amoebiasis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Falmonox; ***Venez.***: Falmonox.

Tenonitrozole *(rINN)*

TC-109; Tenonitrozol; Ténonitrozole; Tenonitrozolo; Tenonitrozolum; Thenitrazole; Тенонитрозол.
N-(5-Nitrothiazol-2-yl)thiophene-2-carboxamide.
$C_8H_5N_3O_3S_2$=255.3
CAS — 3810-35-3.
ATC — P01AX08.
UNII — PBQ7WLE1WP.

Profile

Tenonitrozole is an antiprotozoal given in the treatment of trichomoniasis (p. 925.1). It is given orally in a dose of 250 mg twice daily with meals, for 4 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Atrican; ***Rus.***: Atrican (Атрикан); ***Ukr.***: Atrican (Атрикан).

Ternidazole *(rINN)*

Ternidazol; Ternidazolum; Тернидазол.
2-Methyl-5-nitroimidazole-1-propanol.
$C_7H_{11}N_3O_3$=185.2
CAS — 1077-93-6.
UNII — 4N8R018QB0.

Profile

Ternidazole is a 5-nitroimidazole antiprotozoal with properties similar to those of metronidazole (p. 936.1). It is an ingredient of preparations used for the treatment of vaginitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Tergynan (Тержинан); ***Ukr.***: Tergynan (Тержинан).

Tilbroquinol *(pINN)*

Tilbroquinolum; Тильброхинол.
7-Bromo-5-methylquinolin-8-ol.
$C_{10}H_8BrNO$=238.1
CAS — 7175-09-9.
ATC — P01AA05.
UNII — P6SB125NHA.

Profile

Tilbroquinol is a halogenated hydroxyquinoline antiprotozoal with properties similar to those of diiodohydroxyquinoline (p. 931.1). It has been used with tiliquinol (below) in the treatment of intestinal infections including amoebiasis but less toxic drugs are preferred.

Adverse effects. A report of neurotoxicity, considered to be subacute myelo-opticoneuropathy, in a patient who had taken tilbroquinol with tiliquinol for 4 years.[1] Hepatotoxicity has also been reported[2] with this combination.

1. Soffer M, *et al.* Oxyquinoline toxicity. *Lancet* 1983; **i:** 709.
2. Caroli-Bosc F-X, *et al.* Hépatite aiguë due à l'association de tiliquinol et tilbroquinol (Intétrix). *Gastroenterol Clin Biol* 1996; **20:** 605–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Intetrix; ***Rus.***: Intetrix (Интетрикс); ***Ukr.***: Intetrix (Интетрикс).

Tiliquinol *(rINN)*

Tiliquinolum; Тилихинол.
5-Methylquinolin-8-ol.
$C_{10}H_9NO$=159.2
CAS — 5541-67-3.
UNII — 813OG1OGVG.

Profile

Tiliquinol has been used with tilbroquinol (above) in the treatment of intestinal infections including amoebiasis but less toxic drugs are preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Intetrix; ***Rus.***: Intetrix (Интетрикс); ***Ukr.***: Intetrix (Интетрикс).

Tinidazole *(BAN, USAN, rINN)*

CP-12574; Tinidatsoli; Tinidazol; Tinidazolas; Tinidazolo; Tinidazolum; Tynidazol; Тинидазол.
1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole.
$C_8H_{13}N_3O_4S$=247.3
CAS — 19387-91-8.
ATC — J01XD02; P01AB02.
ATC Vet — QJ01XD02; QP51AA02.
UNII — 033KF7V46H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tinidazole). An almost white or pale yellow, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Tinidazole). An almost white or pale yellow crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Tinidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p. 936.2) in the treatment of susceptible protozoal infections such as amoebiasis (p. 919.1), giardiasis (p. 921.3), and trichomoniasis (p. 925.1), and bacterial vaginosis (p. 174.1), and in the treatment and prophylaxis of anaerobic bacterial infections (p. 173.1). It has also been used in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease (p. 1816.2).

Tinidazole is usually given as a single daily oral dose with or after food; it is also given by intravenous infusion and as vaginal pessaries.

In symptomatic (invasive) **amoebiasis**, tinidazole treatment is usually followed with a luminal amoebicide. In intestinal amoebiasis, a single daily dose of 2 g is given orally for 2 or 3 days; in hepatic amoebiasis, 1.5 to 2 g as a single daily dose may be given for 3 days or occasionally up to 6 days.

A single dose of tinidazole 2 g is given orally in the treatment of **giardiasis**, **trichomoniasis**, and acute necrotising **ulcerative gingivitis**. In trichomoniasis, sexual partners should also be treated.

For details of doses in children, see below.

In **bacterial vaginosis**, a single 2-g dose of tinidazole is usually given orally, although higher cure rates have been achieved with a 2-g dose on 2 successive days or 1 g daily for 5 days.

For the treatment of most **anaerobic bacterial infections**, tinidazole is given orally, usually for 5 or 6 days, in an initial dose of 2 g followed on subsequent days by 1 g daily or 500 mg twice daily. If oral therapy is not possible, tinidazole may be given intravenously, 800 mg being infused as 400 mL of a 2 mg/mL solution at a rate of 10 mL/minute; this initial dose is followed by 800 mg daily or 400 mg twice daily until oral therapy can be substituted. For the *prevention* of postoperative anaerobic bacterial infections, 2 g is given orally about 12 hours before surgery. Alternatively 1.6 g is given as a single intravenous infusion before surgery.

For the treatment of **peptic ulcer disease**, tinidazole 500 mg twice daily has been given with clarithromycin and omeprazole for 7 days. Due to problems with resistance to tinidazole and macrolides a sequential regimen of a proton pump inhibitor with amoxicillin for 5 days, followed by the proton pump inhibitor with tinidazole (500 mg twice daily) and clarithromycin for a further 5 days has also been recommended.

Reviews.

1. Manes G, Balzano A. Tinidazole: from protozoa to Helicobacter pylori—the past, present and future of a nitroimidazole with peculiarities. *Expert Rev Anti Infect Ther* 2004; **2:** 695–705.
2. Fung HB, Doan TL. Tinidazole: a nitroimidazole antiprotozoal agent. *Clin Ther* 2005; **27:** 1859–84.
3. Nailor MD, Sobel JD. Tinidazole for bacterial vaginosis. *Expert Rev Anti Infect Ther* 2007; **5:** 343–8.
4. Granizo JJ, *et al.* Tinidazol: un anaerobicida clásico con múltiples usos potenciales en la actualidad. *Rev Esp Quimioter* 2009; **22:** 106–14.
5. Dickey LJ, *et al.* Guidelines for the treatment of bacterial vaginosis: focus on tinidazole. *Ther Clin Risk Manag* 2009; **5:** 485–9.
6. Armstrong NR, Wilson JD. Tinidazole in the treatment of bacterial vaginosis. *Int J Womens Health* 2010; **1:** 59–65.

Administration in children. Tinidazole may be given to children for the treatment of susceptible protozoal infections. For intestinal or hepatic **amoebiasis** an oral dose of 50 to 60 mg/kg daily (to a maximum of 2 g) is given. Intestinal amoebiasis is treated for 3 days and hepatic amoebiasis for 5 days. Treatment of symptomatic (invasive) amoebiasis must be followed by a luminal amoebicide to eradicate any surviving organisms from the lumen of the large intestine.

In the treatment of **giardiasis** or **trichomoniasis** 50 to 75 mg/kg (to a maximum of 2 g) as a single oral dose is given; it may sometimes be necessary to repeat this dose once.

Administration in renal impairment. The elimination of tinidazole is largely unchanged in patients with impaired renal function (see under Pharmacokinetics, p. 950.1) and dosage adjustment is not generally considered necessary. However tinidazole is removed by haemodialysis, and patients may need additional doses to compensate; a dose equivalent to 50% of the recommended dose may be given at the end of haemodialysis.

Adverse Effects and Precautions

As for Metronidazole, p. 937.3.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that the use of tinidazole by mothers during breast feeding may be of concern, since it is mutagenic *in vitro*. After single-dose therapy, breast feeding may be stopped for 12 to 24 hours to allow excretion of the dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/06/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tinidazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Shock. An acute severe toxic reaction, considered not to be allergic, occurred in a healthy subject shortly after the intravenous infusion of tinidazole 1.6 g over 80 minutes.[1] He fainted for about 10 seconds and low blood pressure, nausea, and tiredness persisted for several hours. He had spasms in the left arm but no generalised convulsions. Anaphylactic shock has also been reported,[2] with severe

bronchospasm and subsequent development of Stevens-Johnson syndrome, in a patient who had reactions of increasing severity after 3 separate exposures to oral tinidazole.

1. Aase S, *et al*. Severe toxic reaction to tinidazole. *Eur J Clin Pharmacol* 1983; **24:** 425–7.
2. Singbal SS, Rataboli PV. Anaphylaxis and hypersensitivity syndrome reactions in increasing severity following repeated exposure to tinidazole. *J Postgrad Med* 2005; **51:** 243–4.

Interactions

Although licensed product information suggests that tinidazole may, like metronidazole (p. 939.2), produce a disulfiram-like reaction with alcohol there do not appear to be any published reports to support this.

Pharmacokinetics

The pharmacokinetics of tinidazole resemble those of metronidazole although the half-life is longer.

Tinidazole is rapidly and almost completely absorbed after oral doses and, typically, a peak plasma concentration of about 40 micrograms/mL occurs 2 hours after a single 2-g dose, falling to about 10 micrograms/mL at 24 hours and 2.5 micrograms/mL at 48 hours; concentrations above 8 micrograms/mL are maintained by daily maintenance doses of 1 g. Comparable concentrations occur with equivalent intravenous doses. The plasma elimination half-life of tinidazole is 12 to 14 hours.

Tinidazole is widely distributed and concentrations similar to those in plasma have been achieved in bile, breast milk, CSF, saliva, and a variety of body tissues; it also crosses the placenta and blood-brain barrier. Only 12% is reported to be bound to plasma proteins. An active hydroxy metabolite has been identified.

Unchanged drug and metabolites are excreted in the urine and, to a lesser extent, in the faeces.

References.

1. Wood BA, *et al*. The pharmacokinetics, metabolism and tissue distribution of tinidazole. *J Antimicrob Chemother* 1982; **10** (suppl A): 43–57.
2. Karhunen M. Placental transfer of metronidazole and tinidazole in early human pregnancy after a single infusion. *Br J Clin Pharmacol* 1984; **18:** 254–7.
3. Evaldson GR, *et al*. Tinidazole milk excretion and pharmacokinetics in lactating women. *Br J Clin Pharmacol* 1985; **19:** 503–7.
4. Wood SG, *et al*. Pharmacokinetics and metabolism of ^{14}C-tinidazole in humans. *J Antimicrob Chemother* 1986; **17:** 801–9.

Renal impairment. Single-dose studies indicate that the pharmacokinetics of tinidazole in patients with chronic renal failure are not significantly different from those in healthy subjects and that no modification of tinidazole dosage is necessary. However, tinidazole is rapidly removed by haemodialysis.[1,2]

1. Flouvat BL, *et al*. Pharmacokinetics of tinidazole in chronic renal failure and in patients on haemodialysis. *Br J Clin Pharmacol* 1983; **15:** 735–41.
2. Robson RA, *et al*. Tinidazole pharmacokinetics in severe renal failure. *Clin Pharmacokinet* 1984; **9:** 88–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fasigyn; Gynormal; Ladylen Duo; ***Austral.***: Fasigyn; Simplotan; ***Belg.***: Fasigyn; ***Braz.***: Amplium; Facyl; Fasigyn; Ginosutin†; Pletil; Tinoral; ***Chile***: Fasigyn; Troxxil; ***China***: Bi Shi (比适); Dabao (达保); Dikexin (迪克新); Fu Lu Ning (福路宁); Hua Er Fu (华尔复); Ji De (济得); Jie Luo Lin (捷洛林); JieLi (捷力); JinHe (津和); Kai Fu Xin (凯服新); Ke Li Tai (可立泰); Le Jing Yi (乐净怡); Login (乐净); Pu Luo Shi (普洛施); Shuanghedida (双鹤荻达); Tinijing (替尼津); Xi Pu Ning (希普宁); Xiaoli (晓力); Yi Qi (益祺); Yu Ning (裕宁); ***Fr.***: Fasigyne; ***Gr.***: Fasigyn; Trichogin; ***Hong Kong***: Fasigyn; ***India***: Amebamagma; Costini; Cozit; Datisole; Enidazol; Fasigyn; Norigyl; Tiniba; Tinidafyl; Tinifas; Tinvista; ***Indon.***: Fasigyn†; Flatin†; ***Israel***: Fasigyn†; Protocide; ***Ital.***: Trimonase; ***Malaysia***: Tindol; ***Mex.***: Amebysol†; Ametricid; Estovyn-T; Fasigyn; Induken; Trinigyn; Triseptil; ***NZ***: Dyzole; ***Port.***: Fasigyn; ***Rus.***: Fasigyn (Фазижин); Tiniba (Тинибa); ***S.Afr.***: Fasigyn; ***Singapore***: Fasigyn; ***Spain***: Tricolam; ***Swed.***: Fasigyn; ***Switz.***: Fasigyne†; ***Thai.***: Asiazole-TN; Fasigyn; Funida; Gynogena; Idazole; Leuco; Pagyn; Sporinex†; Tinazole; Tivagil; TM Dazole; Tonid†; Trichonas; Tricogyn; Tricozone; ***Turk.***: Fasigyn; ***UK***: Fasigyn; ***USA***: Tindamax; ***Venez.***: Fasigyn; Pangamil.

Multi-ingredient Preparations. ***Arg.***: Aduar; Fasigyn Nistatina; Gynormal; Helmint Compuesto; Ladylen; Mebutar Compuesto; Nistinol†; Tru Compuesto; ***Braz.***: Amplium-G; Anfugine; Cartrax; Colpolase†; Duozol; Facyl M; Ginec; Gino-Colon; Gino-Pletil; Ginosutin-M†; Gynben; Gynomax; Gynopac; Poliginax; Seczol; Takil; Tinin; Tiotrax; Travogyn; Trinizol M; Vulnagen; ***Chile***: Doxifen; Exomicol; Famidal; Ginecopast Dual; Ginecopast; Ginedazol Dual; Ginedazol; Medidos; Mizonase; Tinidazol Compuesto; ***China***: Weisanlian (胃三联); ***India***: Actiflox-T; Actinor-TZ; Adcip-TZ; AFlox-TZ; Alcip-TZ; Alcipro-TN; Alof-T; Alvi; Amebis Forte; Amibex-TZ; Amicline Plus; Antibic-DF; Aricip-TZ; Atocip-TZ; Aviflox-TZ; Avilox-TZ; Azostat; Bacter-TZ; Baycip-TZ; Biocip-TZ; Bioflox-TZ; C-Nor Plus; Cancap-Kit; Candizole-T†; Caniron-TZ; Casflox-TZ; Caspro-TZ; Cbic-TZ; Cebect-TZ; Cebran-TN; Ceepro-TZ; Ceflox-TZ; Cefobac-TD; Cefobac-TDH; Ceplox-TZ; Cezel-PT; Cidalox-TZ; Ciflon-TZ; Cifomed-TZ; Cifran-CT-H; Cifran-CT; Cina-TZ; Cinant-TZ; Cinodin-TZ; Cinzole; Cip-TZ; Cipcin-TNZ; Cipcot-TZ; Cipflox-TZ; Cipgen TZ; Cipglow-TZ; Ciplox TZ; Cipro-TZ; Ciprobid-TZ; Ciprobiotic-TN; Ciprodac-TZ; Ciprodex-TZ; Ciprogyl; Ciprolar-T; Ciprolet-A; Ciprolet-AH; Cipronat-TZ; Cipronij-TZ; Ciropet-TZ; Ciprosym-TZ; Ciprotini; Ciprotiz; Ciprotum-TZ; Ciprova-T; Ciprovec-TZ; Ciprowin-TZ; Ciprozee-TZ; Ciptam-CT; Ciptech-CT; Cipti; Ciptini; Cipure-TZ; Cipven-TZ; Cipwin-TZ; Cipzy-TZ; Ciral-TZ; Citi; Citibid; Citizol; Ciwi-TZ; Clodaz-V6; Clofcin-T; Conaz; Cozan-T; CPF-TZ; CT-Robes; Cucin-T; Cymex-TZ; Cyprin-TD; Dandrid; Dazonor; Depci-TZ; Diaba; Dialox; Diarlop-CT; DLotin MPS; Doact-TZ; Donnagyl-H; Dox-M TZ; Doxylin-TZ; DTO; Duonor; Dysnilox; E-Cip-TZ; Eldazole; Elnor-TZ; Elquin-TZ; Emdox-TZ; Emflox-TZ; Emucin-TN; Entamizole TN; Enteroflox-T; Entrolate; Eufox-TZ; Falcon-TZ; Festive-TZ; Flobacin-TZ; Flocin-TZ; Flocipron-T; Flocy TZ; Flontin; Florida-T; Floxur-TZ; Flucos-TZ; Flucoti; Flutini Kit; Fluzon-T; Forcan TZ; Formax; Ftz; Fusys-TZ; Gastrogyl Plus; Gastrogyl; Genflox TZ; Ginal-V; Ginal-V; Ginlac-V; Glocip-TZ; Gramoneg-TN; Harflox-T; Harpoon-DD; Harpoon-TZ; Helibact; Heligo; Helikit; Helipac; Hicip-TZ; Hill-V; HP Kit; Idometrin-D; Inflobid TZ; Jox-TZ; K-Cip-TZ; Kurecip-TZ; L-Cot; Labocip-TZ; Lansi Kit; Lexflox-TZ; Lexof-TZ; Locip-TZ; Lokit-Kit; Lomet-CT; Loxitin-P; Loxitin; Loxone-T; LTC-Kit; Lucipro-T; Mapci-TZ; Mapgyl; Matrix; Megaflox-TZ; Meganeg; Microcip-TZ; Microflox-CT; Mini-Citizol; Mintocip-TZ; Mofcare-TZ; N-Flox TZ; N-Tiz; Nedge; Neflox-TZ; Nexcip-TZ; Nitdin-TZ; Nor T; Nor-T; Noragyl; Norazol; Norbactin-Z; Nordys; Norfen TZ; Norflox TZ; Norilet-A; Norin-TD; Norlex-TZ; Norlon; Normax TZ; Normide-CZ; Normide; Nornij-TZ; Nort; Norzee-TZ; Notisym-LB; Nox-TZ; NT-Z; NTD; Nucip-TZ; Nuforce Kit; Obactin-TZ; Obit-TZ; Ofac-T; Ofacin-TZ; Ofal-TZ; Ofax-TZ; Ofet-T; Ofla-TZ; Oflabin-TZ; Oflamed-TZ; Oflavid-TZ; Oflawin-TZ; Ofler-TZ; Oflin-TZ; Oflo-TZ; Oflocos-TZ; Ofloden-T; Oflomac-TZ; Oflon-TZ; Ofloren-TZ; Oflostar-TZ; Oflox TZ; Oflxcin-TZ; Ofo-TZ; Ofpil-TZ; Ofral-TZ; Ofspan-TZ; Oft; Oftini; Oftum-TZ; Ofven-TZ; Ojen-TZ; Okaflox-TZ; Olfi TZ; Olife-TZ; Oltaur-TZH; Omepraz-HP Kit; Omibact-TZ; Omniflox-CT; Omoxitin; Oniflox; Orpic-T; Osani-T; Osiflox-TZ; OTC HP Kit; Oxiflox-TZ; Oxo-TZ; Oxwal-TZ; Panzer-TZ; Parabact†; Pylokit; Tinidafyl Plus; Tinvista-CF; Tinvista-NF; Wotinex; ***Indon.***: Fasigyn-Nystatin†; ***Ital.***: Fasigin N; ***Malaysia***: Pylobact Combi; ***Mex.***: Afumix; Fasigyn VT; Mebeciclol; ***Rus.***: Ciprolet A (Ципролет А); Pylobact (Пилобакт); ***Turk.***: Gynomax; ***Ukr.***: Cifran CT (Цифран CT).

Toltrazuril *(BAN, USAN, rINN)*

Bay-Vi-9142; Toltrazurilo; Toltrazurilum; Тольтразурил.

1-Methyl-3-(4-{*p*-[(trifluoromethyl)thio]phenoxy}-*m*-tolyl)-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.

$C_{18}H_{14}F_3N_3O_4S$=425.4

CAS — 69004-03-1.

ATC Vet — QP51AJ01.

UNII — QVZ3IAR3JS.

Profile

Toltrazuril is an antiprotozoal used in veterinary practice for the treatment of coccidiosis in poultry and calves, and to treat coccidian infections, including isosporiasis, in piglets.

Tryparsamide *(rINN)*

Glyphenarsine; Triparsamida; Tryparsam.; Tryparsamidum; Tryparsone; Трипарсамид.

Sodium hydrogen 4-(carbamoylmethylamino)phenylarsonate hemihydrate.

$C_8H_{10}AsN_2NaO_4.½H_2O$=305.1

CAS — 554-72-3 (anhydrous tryparsamide); 6159-29-1 (tryparsamide hemihydrate).

UNII — 4NN21HAX16.

Profile

Tryparsamide, a pentavalent arsenical compound, is a trypanocide which penetrates into the CSF and has been used with suramin in the treatment of late-stage African trypanosomiasis due to *Trypanosoma brucei gambiense*, as an alternative to melarsoprol or eflornithine (see p. 925.2). However, because of its toxicity, especially the risk of blindness resulting from damage to the optic nerve, other drugs are preferred.

For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p. 2448.3. Like melarsoprol, tryparsamide can cause encephalopathy.

Antivirals

Common cold, p. 951
Encephalitis, p. 951
Gastro-enteritis, p. 951
Haemorrhagic fevers, p. 952
Hepatitis, p. 952
Herpesvirus infections, p. 954
Cercopithecine herpesvirus 1 infections, p. 954
Cytomegalovirus infections, p. 954
Epstein-Barr virus infections, p. 955
Herpes simplex infections, p. 955
Varicella-zoster infections, p. 956
HIV infection and AIDS, p. 957
HIV-associated infections and complications, p. 958
HIV-associated malignancies, p. 959
HIV-associated wasting, p. 959
HIV infection prophylaxis, p. 959
Infections in immunocompromised patients, p. 960
Influenza, p. 960
Measles, p. 961
Respiratory syncytial virus infection, p. 961
SARS, p. 962
Warts, p. 962

The drugs described in this chapter are used in the treatment of viral infections; they may also be used to provide protection, usually for a brief period only, against infection. For most viral infections drug treatment has to be started early in the infection to be effective and inhibit the replicating virus. There is little evidence that antiviral drugs affect latent or nonreplicating viruses. They do not provide an alternative to available immunisation for the long-term prophylaxis of viral infection—for details of such treatment see the chapter on Vaccines Immunoglobulins and Antisera, p. 2373.1.

Choice of Antiviral

Antiviral drugs are effective for the treatment and prophylaxis of a range of viral infections as described below. Non-specific symptomatic and supportive treatments are also important in the management of viral infections. Those viral infections not amenable to antiviral drug therapy include mumps, poliomyelitis, rabies, and rubella.

Common cold

The common cold is a term used for viral upper respiratory tract illness. Rhinoviruses are the commonest cause in all age groups. Adenoviruses, coronaviruses, enteroviruses, and metapneumovirus may also be responsible. Infecting organisms in these groups may be of many different serotypes.

Colds are usually self-limiting and last for 4 to 10 days. Symptoms include nasal discharge and stuffiness, sneezing, sore throat, and cough (see also p. 1651.2); there is little or no malaise, headache, or fever. Colds may predispose to concurrent or subsequent bacterial infection of the upper respiratory tract; exacerbation of asthma or chronic obstructive pulmonary disease may also occur. Acute otitis media or acute sinusitis may result from obstruction of the Eustachian tube and mucosal swelling.

The successful development of a single cure or vaccine is unlikely, given the variety of causative viruses and large number of serotypes. Treatment is symptomatic. Analgesics, cough suppressants, antihistamines, and decongestants relieve symptoms but do not tend to reduce the duration of illness. Antibacterial and antiviral therapy has consistently failed to show any benefit and antibacterials are indicated only if there is secondary bacterial infection.[1] Very large doses of vitamin C have been widely used to prevent and treat colds but a systematic review[2] has concluded that, despite some evidence of benefit in published studies, its failure to reduce the incidence of colds in the normal population indicated that routine high-dose prophylaxis was not justified for community use; it might, however, be of use in persons exposed to brief periods of severe physical exercise or to cold environments. For treatment, no benefit has been found for doses up to 4 g, although one study reported equivocal benefit from a dose of 8 g given at the onset of symptoms.[2] Other drugs[3] tried have included mast-cell stabilisers, interferon alfa-2b, and zinc salts. Intranasal interferons have shown some benefit in prophylactic use, but high incidences of unacceptable nasal adverse effects have resulted in interferons failing to fulfill their early promise. Results of studies of oral or intranasal zinc treatment have been variable, although a systematic review concluded that oral zinc reduced the duration and severity of common cold symptoms when used therapeutically, and that it reduced the incidence of the common cold in healthy children when used prophylactically.[4] There is little consistent evidence to support the use of *Echinacea* for treatment or prevention of colds.[5,6] However, available *Echinacea* products differ greatly and there is some evidence that treatment with those based on the aerial parts of *E. purpurea* might be effective in adults if started early.[5] Pleconaril, a viral capsid binder, has also been studied but there have been concerns with the oral formulation over viral resistance and interactions with oral contraceptives; the intranasal formulation appears more promising.[7]

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Encephalitis

Encephalitis refers to an acute inflammatory process affecting the brain parenchyma; it is distinct from meningitis which is an inflammation of the meninges. Meningoencephalitis involves both the brain parenchyma and meninges. Viral infection is the commonest cause of encephalitis,[1-5] with the herpes simplex virus (p. 955.2) being the commonest organism involved in immunocompetent individuals. Other viruses that may cause encephalitis include enteroviruses (e.g. poliovirus), Epstein-Barr, influenza, Lassa fever, measles and mumps (paramyxoviruses), rabies, rubella, and varicella zoster. CMV and HIV cause encephalitis almost exclusively in immunocompromised individuals. In the 1990s, Hendra virus and Nipah virus, which belong to the paramyxoviridae family, were newly discovered causes of encephalitis. The reservoir for these viruses is *bats*, but transmission to humans can occur via close contact with secondary hosts such as *horses* and *pigs*. A group of viruses known as the arthropod-borne encephalitis viruses (arboviruses) may cause infections in which encephalitis is a major clinical feature. They include:

- bunyaviruses including California encephalitis virus and La Crosse virus (both transmitted by mosquitoes)
- flaviviruses (previously arbovirus Group B) including Japanese encephalitis virus, St Louis encephalitis virus, Murray Valley encephalitis virus, Rocio virus, and West Nile virus (all transmitted by mosquitoes) and the tick-borne viruses of this group, louping ill virus, Powassan virus, and the Eastern and Western subtype viruses
- reoviruses including Colorado tick fever virus (transmitted by ticks)
- togaviruses including Eastern, Western, and Venezuelan equine viruses (transmitted by mosquitoes)

In endemic regions viral encephalitis should be suspected in patients presenting with fever, headache, neck rigidity, altered level of consciousness (which may range from drowsiness to coma), and signs of diffuse cerebral dysfunction (hallucinations, psychosis, personality changes, and agitation). Seizures are common and patients who recover from encephalitis may be left with permanent neurological damage.

Since herpes simplex virus is the commonest cause of viral encephalitis, it is recommended that patients with encephalitis be given intravenous aciclovir empirically until the causative virus has been identified. (Antibacterial treatment for meningitis may also be given empirically until the cause of symptoms has been established; doxycycline should be used if rickettsial or ehrlichial infections are suspected.)[5] No specific treatment exists for non-herpetic encephalitis (although investigational treatments, including passive immunisation and the use of inhibitory RNA molecules, are under development[6]), and patients must be managed with vigorous supportive care. Corticosteroids are advocated in some circumstances,[4] but their use is controversial. Oseltamivir may be considered for infections caused by the influenza virus, ribavirin for infections with measles or Nipah virus, and interferon alfa-2 for infections caused by the St Louis encephalitis virus.[5] Pleconaril is under investigation for use in enteroviral encephalitis. Control of mosquito and tick populations in endemic areas and minimising contact with these vectors are important means of preventing infections. Japanese encephalitis vaccine and tick-borne encephalitis vaccine are available for active immunisation of individuals at risk of infection and tick-borne encephalitis immunoglobulins are available in some countries for passive immunisation against infection.

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Gastro-enteritis

Gastro-enteritis (inflammation of the stomach and intestines) may be caused by viruses, bacteria, or protozoa.[1,2] Viral gastro-enteritis is an important cause of diarrhoea, especially in children and immunocompromised patients. Viruses causing diarrhoea and other gastrointestinal symptoms include calicivirus (such as norovirus and sapovirus), and rotavirus, as well as adenovirus and astrovirus.

- Rotavirus infection is recognised as a prominent cause of endemic acute diarrhoea in infants and young children and may occasionally cause acute or chronic diarrhoea in AIDS patients. Infection may be subclinical, although symptomatic rotavirus infection usually presents with fever and vomiting for 2 to 3 days, followed by watery diarrhoea that lasts for 4 to 5 days. Other symptoms include abdominal cramps and headache.
- Noroviruses (such as the Norwalk virus) are a more common cause of viral gastro-enteritis in older children and adults, but do not appear to cause severe disease in infants. They have been the cause of waterborne outbreaks of gastro-enteritis in nursing homes, military bases, and cruise ships.
- Sapoviruses (such as the Sapporo virus) are more commonly seen in young children. While illness resulting from these viruses is usually mild and lasts for 24 to 72 hours, the presenting symptoms are usually nausea and abdominal cramps. Other symptoms include diarrhoea, vomiting, headache, myalgias, and low-grade fever.
- CMV is an important cause of diarrhoea in AIDS (see HIV-associated Wasting, p. 959.1).

In acute diarrhoea of any cause it is most important to maintain hydration by preventing and replacing fluid and electrolyte loss, especially in infants and the elderly (see p. 1808.2). For further discussion see Oral Rehydration Solutions, p. 1782.1. Antivirals are not used in the management of viral diarrhoeas, except for that caused by CMV, where ganciclovir, valganciclovir, or foscarnet may be beneficial. A 3-day course of oral nitazoxanide was found to significantly reduce the duration of rotavirus disease in young children.[3] Frequent handwashing and good personal hygiene may prevent person-to-person spread of infection. Washing of contaminated clothing and surfaces, and boiling of contaminated water will also assist in preventing infection. Several live oral rotavirus vaccines (p. 2416.1) for use in the prevention of childhood diarrhoea have been developed and some are now licensed.

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Haemorrhagic fevers

The viral haemorrhagic fevers are a group of viral illnesses characterised by a febrile illness that in some patients may be followed by severe bleeding, progressive organ failure, and death. The viruses are typically transmitted by mosquitoes, ticks, or rodents, and are largely geographically restricted. The more important viruses responsible for haemorrhagic fevers in man include:

- arenaviruses causing South American haemorrhagic fever syndromes (including Argentine, Bolivian, Brazilian, and Venezuelan haemorrhagic fever) and Lassa fever (transmitted by rodents)
- filoviruses causing Ebola and Marburg haemorrhagic fever, the natural host for which is unknown
- flaviviruses (previously arbovirus Group B) causing dengue fever and yellow fever (transmitted by mosquitoes), and Kyasanur forest fever and Omsk haemorrhagic fever (transmitted by ticks)
- hantaviruses causing haemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (transmitted by rodents)
- nairovirus causing Crimean Congo haemorrhagic fever (transmitted by ticks)
- phlebovirus causing Rift Valley fever (transmitted by mosquitoes)

Specific symptoms and the incubation time vary according to the infecting virus; in general the incubation time is short (up to 21 days but commonly less than 7 days) and followed by sudden (or, in the case of Lassa fever, more gradual) onset of fever, headache, myalgia, rash, and gastrointestinal disturbances such as abdominal pain, anorexia, diarrhoea, nausea, and vomiting. In patients who develop severe haemorrhagic manifestations (skin or mucosal bleeding, haematemesis, haematuria, or melaena), hepatitis, circulatory, renal, and respiratory failure, and coma are common. Depending on the causative virus, jaundice (yellow fever and Crimean Congo fever), muscle and joint pains (dengue fever), or pulmonary symptoms (hantavirus) may be more pronounced. Mortality is variable and ranges from less than 5% in dengue haemorrhagic fever and Lassa fever with optimal supportive care, to 15 to 30% in yellow fever and Crimean Congo haemorrhagic fever, and 70 to 80% in severe Ebola and Marburg virus infections.

Infection precautions, source isolation, and optimal supportive care are cornerstones of the management of viral haemorrhagic fevers. Vector control and prevention of bites are very important. There is generally no specific drug treatment for haemorrhagic fevers, although ribavirin may reduce mortality in patients with Lassa fever or haemorrhagic fever with renal syndrome, and possibly in Crimean Congo and Bolivian haemorrhagic fevers. Vaccines have been developed for the active immunisation of individuals at risk of Argentine haemorrhagic fever, Rift Valley fever, and yellow fever, and others are being developed for dengue fever and haemorrhagic fever with renal syndrome. Studies are ongoing for a vaccine against Ebola and Marburg viruses. Crimean Congo haemorrhagic fever immunoglobulins are available in some countries for passive immunisation against the disease. Guidelines for the prevention, control, and treatment of dengue and yellow fevers have been produced by WHO[1,2] and related organisations.[3] Guidelines for the management of haemorrhagic fevers have been published for some European countries.[4,5] The Pan American Health Organization[6] and the CDC[7] have also produced guidelines for the management of hantavirus pulmonary syndrome.

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Hepatitis

Though hepatitis may have many causes, viral hepatitis describes infections caused by viruses that mainly target the liver. Five hepatitis viruses are recognised to be primarily responsible for infection in humans and have been named hepatitis A, B, C, D, and E. Hepatitis may also occur as part of the clinical course of other viral infections, including CMV, Epstein-Barr virus, herpes simplex virus, rubella, varicella-zoster, and yellow fever infections.

Hepatitis A and E are spread via the faecal-oral route. Hepatitis B, C, and D are spread via contaminated blood and blood products, perinatal transmission, or sexual contact. All of these viruses may cause acute and occasionally fulminant hepatitis; hepatitis B, C, and D viruses can also cause chronic hepatitis. The herpesviruses may cause hepatitis during primary infection or during reactivation of a latent infection in immunocompromised persons. (For discussion on the management of herpesvirus infections, see p. 954.1.) Yellow fever virus is transmitted by mosquitoes and may cause fulminant hepatitis in non-immunised persons.

Acute viral hepatitis results in hepatocyte necrosis and inflammation of the liver. Clinical presentation ranges widely from asymptomatic infection to fulminant hepatic failure. Symptomatic acute hepatitis is characterised by abdominal pain, anorexia, fatigue, jaundice, low-grade fever, nausea, vomiting, and raised liver enzymes (AST and ALT). Chronic viral hepatitis is commonly asymptomatic but may result in hepatic fibrosis, cirrhosis, or hepatocellular carcinoma. Acute and chronic hepatitis may be complicated by fulminant hepatitis and liver failure, characterised by hepatic encephalopathy, coma, and death. As HIV and hepatitis B and C share risk factors for transmission, there are a significant number of people co-infected with 2 or all 3 viruses. HIV and hepatitis B or C co-infected patients have been found to have higher rates of hepatitis-related morbidity and mortality, with accelerated progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[1]

Viral hepatitis can be **prevented** by active immunisation against hepatitis A, hepatitis B, and yellow fever. Vaccination against hepatitis A is recommended, for example, for travellers to endemic regions, haemophiliacs, and for those considered to be at high risk due to their occupation or lifestyle (see p. 2388.3). Postexposure prophylaxis with hepatitis A immunoglobulin is recommended in some countries for household and intimate contacts of patients with hepatitis A infection, while others recommend normal immunoglobulins. Vaccination with hepatitis B vaccine is frequently recommended as part of the infant immunisation schedules and for non-immunised infants and adults at risk of infection (see, p. 2389.3). Hepatitis B immunoglobulin is recommended for passive immunisation of individuals exposed to a patient infected with the hepatitis B virus and after liver transplantation in persons infected with the hepatitis B virus, in order to prevent hepatitis B virus induced damage to the grafted liver (see, p. 2389.2). Yellow fever vaccination is recommended for persons at high risk of infection, including travellers to endemic areas and may be considered as part of the standard infant immunisation schedule in countries where the virus is endemic (see, p. 2424.3).

The **treatment of acute hepatitis** infections is largely symptomatic, as no effective antiviral therapy is available. Acute hepatitis B infection resolves without therapy in the majority of immunocompetent adults. A small pilot study[2] reported rapid clinical and biochemical responses to *lamivudine* in 13 of 15 patients with severe acute hepatitis B infection. Acute hepatitis C[3] is more commonly asymptomatic but, if diagnosed, therapy with an *interferon alfa* may be considered[4] as there is some evidence that they may reduce the risk of progression to chronic infection.[5] A study[6] in a small number of patients with acute hepatitis C concluded that if spontaneous clearance has not occurred by 12 weeks, a 6-month course of peginterferon alfa-2b should be given, as response rates to antiviral therapy are higher in patients with acute infection compared with those with established infection. The American Association for the Study of Liver Diseases (AASLD)[5] has stated that either interferon or peginterferon given for a period of 12 or 24 weeks may be considered for the treatment of acute hepatitis C if the infection persists 2 to 3 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[7] and by the Scottish Intercollegiate Guidelines Network.[8] The AASLD also states that no recommendation can be made for or against the addition of ribavirin and its use should be evaluated on a case-by-case basis.[5]

Treatment of chronic hepatitis B aims to achieve seroconversion from e antigen (HBeAg)-positive to e antigen-negative chronic infection (which is associated with lower rates of viral replication and lower rates of disease progression), to suppress viral replication, to delay the progression of chronic hepatitis to cirrhosis or hepatocellular carcinoma, and to treat extrahepatic complications such as glomerulonephritis. Complete suppression of viral replication is important to reduce the risk of viral resistance. Treatment is only recommended in patients with active or advanced liver disease and with high levels of HBV DNA. Drugs used for the treatment of chronic hepatitis B include immune modulators (interferon alfa-2b and peginterferon alfa-2a) and nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir).[9-11] Emtricitabine is being investigated for use in chronic hepatitis B[9,10] but studies with clevudine have been stopped due to serious toxicity.[12]

Interferon alfa was the first drug approved for the management of chronic hepatitis B. A meta-analysis[13] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HBeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels.[12] Studies have suggested that subcutaneous *peginterferon alfa* is as effective or slightly more effective than interferon alfa given subcutaneously.[12] Results from various studies[14] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[15] and HBeAg-negative patients with chronic hepatitis B,[16] when peginterferon alfa was given subcutaneously once weekly for 48 weeks.

Oral *lamivudine* has a similar efficacy to interferon but fewer adverse effects. Studies[17,18] have shown favourable effects on histologic, virologic, and biochemical features of the disease from long-term therapy, including decreased disease progression and progression to hepatocellular carcinoma in patients with cirrhosis or advanced fibrosis. In HBeAg-positive patients, treatment with lamivudine is generally continued for at least 6 months after seroconversion, while HBeAg-negative patients may need indefinite treatment due to high relapse rates when treatment is stopped.[12]

Studies with daily oral *adefovir dipivoxil* for 48 weeks have shown a mean drop in hepatitis B viral DNA of about 3.5 logs (factors of 10) in patients with HBeAg-positive chronic hepatitis B[19] and of about 4 logs in patients with HBeAg-negative chronic hepatitis B.[20] When adefovir dipivoxil was continued in HBeAg-negative patients for 144 weeks benefit was maintained whereas viral load rebounded in those patients who stopped treatment at 48 weeks.[20] Hepatitis B virus DNA was undetectable in 71% and 79% of patients after 96 and 144 weeks of treatment respectively.[20] Most HBeAg-positive and HBeAg-negative patients also had improvements in serum-ALT and liver histology.[19,20]

Other oral antiviral drugs approved for the treatment of chronic hepatitis B, including in patients with lamivudine-resistant disease, are entecavir and telbivudine. Studies with daily oral *entecavir* for 48 weeks have shown a mean drop in hepatitis B viral DNA of about 6.9 logs in patients with HBeAg-positive chronic hepatitis B[21] and of about 5 logs in patients with HBeAg-negative chronic hepatitis B.[22] Entecavir treatment continued through to 96 weeks, in those patients with HBeAg-positive hepatitis B, continued to show benefit.[23] In both these studies entecavir was found to be more potent than oral lamivudine in suppressing hepatitis B virus. *Telbivudine* was reported to be superior to lamivudine in patients with HBeAg-positive chronic hepatitis B and as effective as lamivudine in those with HBeAg-negative disease after 52 weeks of treatment;[24] after 104 weeks of treatment telbivudine was reported to be superior to lamivudine in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B.[25] A small open label study[26] with telbivudine or adefovir for 52 weeks, or adefovir for 24 weeks followed by telbivudine for 28 weeks, in patients with HBeAg-positive hepatitis B, reported greater and more consistent reductions in HBV DNA with telbivudine than with adefovir after 24 weeks of treatment. After 52 weeks, HBV DNA suppression was greater in patients given continuous telbivudine or who switched from adefovir to telbivudine after 24 weeks than in those given adefovir for 52 weeks. The most recent oral antiviral drug to be approved for the treatment of chronic hepatitis B is *tenofovir disoproxil fumarate*. Studies with daily oral tenofovir for 48 weeks reported superior antiviral efficacy compared with adefovir dipivoxil.[27] A systematic review and meta-analysis[28] compared the relative short-term (1-year) treatment efficacy of lamivudine, peginterferon alfa, adefovir, entecavir, telbivudine, and tenofovir in treatment-naive patients with chronic hepatitis B. Tenofovir was the most effective treatment in HBeAg-negative patients; in those who were HBeAg-positive, tenofovir and entecavir were judged most potent.

The development of antiviral ***resistance*** is a concern with long-term nucleoside/nucleotide treatment. Some 14 to 32% of patients who initially respond to lamivudine develop drug resistance within the first year of therapy and resistance increases to about 80% after 5 years of treatment;[29] lamivudine is therefore generally not recommended as first-line treatment.[30] Adefovir dipivoxil showed no resistance after 1 year of treatment, but the rate increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively.[19,20,31,32] Long-term therapy with

adefovir dipivoxil resulted in the development of resistance mutations in less than 6% of patients and it was effective in patients who had previously developed resistance to lamivudine.[20] Entecavir showed negligible resistance up to 6 years of treatment in previously treatment-naive patients, although resistance is reported to be much higher (nearly 60% after 6 years) in patients with lamivudine-resistant disease.[29] The resistance rate with telbivudine is reported to be 2 to 4% after 1 year of treatment,[33] and about 9% (in HBeAg-negative patients) to 21% (in HBeAg-positive cases) after 2 years.[29] Preliminary results also suggest negligible resistance at 48 weeks with tenofovir.[29] Combination therapy with different nucleoside and nucleotide analogues is being investigated in order to prevent drug resistance and improve efficacy.[29,34] The addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[16,35,36] The combination of lamivudine and adefovir was found to be as effective as lamivudine monotherapy.[37] The combination of lamivudine and telbivudine was less effective than telbivudine alone[38] but emtricitabine and adefovir was more effective than adefovir alone.[37]

While the AASLD[12] states that all the approved treatments may be given as initial therapy, their preferred ***choice*** is peginterferon alfa or the nucleoside analogues tenofovir or entecavir, in adults with HBeAg-positive or -negative chronic hepatitis B. In children with HBeAg-positive chronic hepatitis B, standard interferon alfa or lamivudine are recommended. In patients who are HBeAg-positive interferon is given for a defined duration (interferon alfa is given for 4 months and peginterferon alfa for 12 months), while a nucleoside/nucleotide analogue is usually given for an additional 6 months after HBeAg seroconversion. Most patients who are HBeAg-negative will relapse after treatment is stopped. In these patients interferon is also given for a defined duration (both interferon and peginterferon alfa are given for 12 months), but treatment with a nucleoside or nucleotide analogue is indefinite. Patients who have not responded to interferon alfa (standard or pegylated) therapy may be re-treated with a nucleoside analogue. Those who fail to respond after 6 months treatment should be switched to an alternative regimen. Adefovir[30,39] or tenofovir[39] may be given with lamivudine in those patients with lamivudine-resistant hepatitis B virus. Interferon alfa is not recommended in patients with compensated cirrhosis as it may cause hepatitis flares and hepatic decompensation. Guidelines are also available for other countries.[7,40-43]

Hepatitis B patients co-infected with **hepatitis D virus** are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[44] with high-dose interferon alfa (9 million units) given 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[45]

Treatment of chronic hepatitis C aims to decrease viral replication or eradicate hepatitis C virus, delay the progression to cirrhosis, and thereby decrease the frequency of hepatocellular carcinoma, and to treat extrahepatic complications of infection. The first available treatment was *interferon* alfa-2b, and this was followed by interferon alfa-2a, given subcutaneously 3 times a week. Patients treated with these interferons had a 10 to 20% chance of obtaining a sustained virological response (SVR), but had a high relapse rate. The combination of daily oral *ribavirin* with non-pegylated interferon alfa improved the rate of SVR after 48 weeks of treatment to about 40%. Further improvements in the SVR rates to about 60% have been reported since the introduction of weekly subcutaneous peginterferon alfa given with daily oral ribavirin. Studies[46,47] have found peginterferon alfa and ribavirin (SVR of 54 to 56%) to be more effective than interferon alfa and ribavirin (SVR of 44 to 47%). Factors predictive of a poor SVR are viral genotype 1, a high pretreatment viral load, increased body-weight, and the presence of cirrhosis. A study[46] with peginterferon alfa-2b or interferon alfa-2b and ribavirin showed an SVR of 42% in patients with genotype 1, compared with about 80% in patients with genotypes 2 and 3. Furthermore, patients infected with hepatitis C virus genotype 1 require treatment for 48 weeks with the standard dose of ribavirin (1 or 1.2 g daily) compared with 24 weeks of ribavirin 800 mg daily in those infected with genotypes 2 or 3.[48] Other studies[49-53] suggest that SVR can be achieved in some patients infected with genotypes 2 and 3 with a 12 to 16 week course of treatment. This is particularly true for patients in whom hepatitis C virus RNA is undetectable after 4 weeks of treatment. In patients with genotype 1 infection, longer durations of therapy (up to 72 weeks), may be appropriate in slow responders (patients who achieved a 2 log fall in the viral load but in whom viral RNA is still detectable by week 12).[54,55] In one study,[54] a SVR rate of 44% was reported for slow responders who continued treatment for 72 weeks, compared with a SVR rate of 28% in those who received 48 weeks of treatment.

Detailed guidelines have been produced in the UK,[8,56-58] Canada,[59] and in the USA[5,60] for the management of chronic hepatitis C. They all recommend weekly subcutaneous peginterferon alfa plus daily oral ribavirin as the first choice of treatment in patients with moderate to severe chronic hepatitis C. The decision to treat those with mild chronic hepatitis should be individualised; if treatment is given, subcutaneous peginterferon alfa plus oral ribavirin is again preferred.

For genotype 2 and 3 infection, 24 weeks of treatment is usually recommended[5,56] but some[8,60] suggest that 12 or 16 weeks of therapy may be sufficient in patients with genotypes 2 and 3 with undetectable viral RNA at week 4. For genotype 1, treatment for 48 weeks is generally recommended. An early prediction of treatment failure in patients with genotype 1 infection is detectable hepatitis C virus RNA with less than a 2-log fall in viral load after 12 weeks of treatment. Some[5,8,57] suggest that stopping treatment in these patients may be considered at this point, while the British Society for Gastroenterology[56] recommends stopping treatment after 24 weeks if hepatitis C virus RNA is still detectable. Some guidelines[5,8] suggest re-treatment (with peginterferon and ribavirin) of nonresponders and relapsers who have significant fibrosis or cirrhosis and who initially received (non-pegylated) interferon with or without ribavirin[5,8] or monotherapy with pegylated interferon.[5] Patients with other genotype infections should be treated with combination therapy for 48 weeks.[57,60]

Thymalfasin is being investigated as an adjunct to conventional therapy for the treatment of chronic hepatitis B and C. Telaprevir[61-63] and boceprevir,[28,64-66] specific inhibitors of hepatitis C virus serine protease, have been developed and are used as adjuncts to conventional therapy in the treatment of chronic hepatitis C genotype 1.

Treatment of chronic hepatitis in HIV co-infected patients. HIV infection reduces the efficacy of current therapies for **hepatitis B**; it decreases response to interferon alfa and increases the incidence of lamivudine-resistant hepatitis B mutations.[1] Guidelines for the management of HIV and hepatitis B co-infection have been developed by various expert groups.[67-69] The British HIV Association guidelines[67] discuss appropriate choice of antivirals and their activity against hepatitis B virus and HIV. In patients not requiring HIV therapy, hepatitis B treatment should be with drugs that have no anti-HIV activity. *Peginterferon alfa* for 12 months is considered suitable for HBeAg-positive patients with minimal fibrosis, raised ALT, low hepatitis B virus DNA, and genotype A (if tested). Treatment should be stopped if there is no hepatitis B virus DNA response (less than 1 log reduction at 12 weeks and more than 2000 international units/litre at 24 weeks). Long-term treatment with *adefovir dipivoxil* may be given as an alternative to interferon therapy and is the drug of choice in patients with significant fibrosis. Adefovir dipivoxil may be given with *telbivudine*, but telbivudine should not be used alone because of the high rate of hepatitis B viral resistance. Starting a HAART regimen (including tenofovir and emtricitabine) early may be considered for antiretroviral-naive patients with wild-type HIV. Patients who require both HIV and hepatitis B therapy may be given *tenofovir* alone or with either *lamivudine* or *emtricitabine*, as part of, or in addition to, their antiretroviral regimen. Lamivudine or emtricitabine should not be used as the only active drug against hepatitis B virus in a HAART regimen, in order to prevent the development of viral resistance. *Entecavir* may be given when tenofovir has to be stopped due to toxicity, but it must be given with a fully-suppressive HAART regimen.[67] Successful treatment of HIV with HAART may result in severe exacerbation of hepatitis B in co-infected patients.

Treatment of **hepatitis C** in HIV co-infected patients has been associated with an increased rate of adverse effects and reduced response rates. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[70-72] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[71,72] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[70] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[70,72] Guidelines for the treatment and management of HIV and hepatitis C co-infection have been developed by various expert groups.[5,8,67,73] In general, they all recommend combination therapy with *peginterferon alfa* and *ribavirin*, usually for 48 weeks. Virological response should be reassessed at weeks 4 and 12 and treatment should only be continued beyond 12 weeks in those with an early virological response. Shorter periods of treatment (24 weeks) may be considered in patients with genotypes 2 or 3 infection who have a rapid virological response (response within 4 weeks). Patients with genotype 1 and 4 who have no virological response at 4 weeks but response at 12 and 24 weeks may be given a longer treatment course of 60 to 72 weeks. Significant haemolytic anaemia may occur with ribavirin, and therefore concurrent use with zidovudine should be avoided and when possible stavudine should be replaced. Didanosine should never be given with ribavirin due to potentially life-threatening complications, such as lactic acidosis, myopathy, neuropathy, pancreatitis, and steatosis.[67,73,74] Abacavir with ribavirin should be avoided if possible. If efavirenz is given with interferon the patient should be carefully monitored for increased CNS toxicity.[67]

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Herpesvirus infections

Established herpesvirus pathogens discussed below include Cercopithecine herpesvirus 1 (below), CMV (below), Epstein-Barr virus (p. 955.1), herpes simplex virus (p. 955.2), and varicella-zoster virus (p. 956.2). Herpesviruses 6, 7, and 8 have also emerged as potential pathogens and have been associated with a variety of disorders including childhood febrile illnesses, various malignancies including Kaposi's sarcoma (p. 718.1), and multiple sclerosis (p. 996.3).

Cercopithecine herpesvirus 1 infections. *Cercopithecine herpesvirus 1* (herpesvirus simiae, monkey B virus, herpes B virus) is a herpesvirus that usually infects macaque monkeys, but may rarely be transmitted to man by laboratory accidents or bites or scratches from infected monkeys. Initial symptoms and signs may include vesicles at the site of the bite or scratch, fatigue, fever, headache, and myalgia. Lymphadenitis or lymphadenopathy, abdominal pain, nausea, and vomiting may occur. As the infection spreads to the CNS there is increasing neurological involvement that can lead to encephalitis, coma, and death. Those patients who survive usually have serious neurologic impairment.

Initial **treatment**[1-3] should be prompt with thorough cleaning of the wound or exposure site. Intravenous high-dose *aciclovir* or *ganciclovir*, followed by oral therapy, is recommended for symptomatic or culture-confirmed infection. Ganciclovir is recommended in patients who have signs or symptoms of peripheral nervous system or CNS involvement. Routine **prophylactic** use of antivirals is not recommended, although postexposure prophylaxis with oral *valaciclovir* started within a few hours of exposure and given for 14 days may be considered for potential exposures. Vaccines against the virus have been investigated.

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Cytomegalovirus infections. Cytomegalovirus (CMV) is a member of the herpesvirus group. Infection may be by intra-uterine, perinatal, or sexual transmission, by oral contact with the saliva of infected individuals, by blood transfusion, or by transplantation of infected tissue. After infection, viral DNA becomes incorporated into the host cell DNA where it persists, with occasional reactivation, for the life of the individual. Primary infections in immunocompetent adolescents and adults are generally asymptomatic, although they may occasionally present as infectious mononucleosis, lymphocytosis, or lymphadenopathy. Most congenitally infected infants are also asymptomatic, but some may present with intra-uterine growth retardation, jaundice, hepatosplenomegaly, encephalitis, and thrombocytopenia. Conversely, CMV is a major cause of morbidity and mortality in immunocompromised persons, particularly transplant recipients and patients with AIDS where it may present as CMV retinitis, colitis, oesophagitis, hepatitis, pneumonitis, or neurological disease in the form of dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy. Pneumonitis is more common in transplant recipients while retinitis is most frequent in AIDS patients.

Treatment for CMV disease is usually only given to immunocompromised patients, in whom relapses are likely to occur after treatment is stopped due to the latent nature of the virus. Ganciclovir and its oral prodrug valganciclovir are used in the treatment of severe infections in transplant recipients and patients with AIDS but ganciclovir may cause neutropenia. Foscarnet is an alternative to ganciclovir with similar efficacy and does not produce myelosuppression, although nephrotoxicity and electrolyte disturbances are common. Cidofovir may also be used for the treatment of CMV retinitis, and has the advantage of intermittent use. However, long-term treatment may be limited by renal toxicity.

HIV-infected patients. US guidelines[1] for the **initial treatment** of ***CMV retinitis*** in HIV-infected adults and adolescents recommend, for immediate sight-threatening lesions, intravitreal injections of ganciclovir along with oral valganciclovir. For patients with peripheral retinal lesions, oral valganciclovir alone is recommended. Alternatives are intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, or intravenous cidofovir. For HIV-infected children, intravenous ganciclovir is recommended; intravenous foscarnet is an alternative and valganciclovir with or without an intraocular ganciclovir implant may be considered for children old enough to be given an adult dose of oral valganciclovir.[2]

After induction therapy, **maintenance therapy** (secondary prophylaxis) is recommended in AIDS patients with CMV retinitis until immune reconstitution as a result of antiretroviral therapy has been achieved or for life if it is not. The drug of choice is oral valganciclovir; alternatives include intravenous ganciclovir with or without foscarnet, intravenous foscarnet, or intravenous cidofovir.[1] Maintenance therapy may be stopped in patients with inactive CMV disease who have an increase in CD4+ T lymphocyte count to more than 100 cells/microlitre sustained for 3 to 6 months or more, although continued ophthalmic monitoring should be performed. Maintenance therapy should begin again if the CD4+ T lymphocyte count falls below 100 cells/microlitre.[1]

Early **relapse** of CMV retinitis in patients with persistent immunodeficiency is common and is generally due to poor penetration of drugs into the eye when given systemically, rather than drug resistance. Hence, re-induction and maintenance treatment with the same systemic drug used initially is recommended in patients who relapse after systemic treatment. An alternative drug should only be considered if drug resistance is suspected or toxicity precludes use of the initial drug. Combined ganciclovir and foscarnet may be considered for patients who are not suitable for other alternatives, but is associated with greater toxicity. Relapse later in therapy is usually due to drug resistance and patients with high-level ganciclovir-resistant isolates should be switched to an alternative therapy.[1]

In HIV-infected adults and adolescents, ***CMV colitis*** or ***oesophagitis*** should be treated initially with intravenous ganciclovir or foscarnet, or with oral valganciclovir.[1] Chronic maintenance therapy is not routinely recommended but should be considered if relapse occurs.[1] For ***neurological*** disease, starting therapy promptly is critical for an optimal clinical response. Combination treatment with intravenous ganciclovir and foscarnet is currently favoured. The optimal duration of therapy has not been established.[1] Treatment of CMV ***pneumonitis*** is usually reserved for patients with cytological or histological evidence of CMV disease who do not respond to treatment for other pathogens; treatment is usually with intravenous ganciclovir or foscarnet. The role of maintenance in these patients is yet to be established.[1]

In HIV-infected adults and adolescents, ***primary prophylaxis*** with oral valganciclovir is not usually recommended because of the cost, the potential to induce CMV resistance, and the lack of proven survival advantage.[1]

Transplant recipients. Primary **prophylaxis** of CMV disease in high-risk patients, particularly transplant recipients, has been reported using intravenous ganciclovir,[3-5] valganciclovir,[6,7] foscarnet,[8] valaciclovir,[9-13] and CMV immunoglobulins.[14,15] Oral ganciclovir has also been used for primary prophylaxis and for *pre-emptive therapy* (treatment when active CMV infection is documented but disease has not yet been evident) in some transplant patients.[16-18] A systematic review[19] found that giving CMV immunoglobulins did not reduce the risk of CMV disease or all-cause mortality in solid organ transplant recipients and adding them to aciclovir or ganciclovir was not more effective than an antiviral given as monotherapy.

The British Transplantation Society (BTS)[20] and other expert groups, including an international consensus group of the Transplantation Society,[21] have published recommendations for the prevention and management of CMV disease after ***solid organ transplantation***. These recommend that the highest risk patients, such as CMV-seronegative recipients of a solid organ transplant from a seropositive donor, should be offered primary prophylaxis. The following options are available in the UK and are recommended by the BTS:[20]

- oral valganciclovir for 100 days (in heart, kidney, kidney/pancreas, or liver transplant recipients)
- valaciclovir for 90 days (heart, kidney, kidney/pancreas, liver, or lung)
- intravenous ganciclovir for at least 28 days (heart, kidney, kidney/pancreas, liver, or lung)
- high-dose oral aciclovir for 12 weeks (kidney)
- intermittent CMV hyperimmune globulin for 12 weeks (kidney)

Frequent monitoring and possible pre-emptive treatment, usually with intravenous ganciclovir, may also be required.[20]

The above regimens are also used to prevent CMV disease when the donor and recipient are both CMV-seropositive and the patient is being treated with antithymocyte globulin, antilymphocyte immunoglobulin, or muromonab-CD3. If these drugs are not used, the BTS considers that no prophylaxis is needed for CMV-seropositive recipients of kidney, kidney and pancreas, liver, or heart transplants from seropositive donors; lung transplant recipients should be given chemoprophylaxis as for seronegative patients above.[20]

The BTS also recommended oral ganciclovir for 90 days as an option for prophylaxis after heart, kidney, kidney/pancreas, liver, or lung transplant, but acknowledged in their recommendations that, during their preparation, the UK manufacturer ceased production of oral ganciclovir; it was, however, retained as an option in the recommendations in case of availability in the future.[20]

Recommendations have also been produced for the management of CMV infection in recipients of allogeneic

stem cell transplantation by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation.[22] For treatment of CMV pneumonia, normal immunoglobulin is given with ganciclovir, but normal immunoglobulin is not required in other forms of CMV disease.[22] For prevention of CMV disease, pre-emptive therapy with either intravenous ganciclovir or foscarnet rather than primary prophylaxis, is the recommended approach. Intravenous ganciclovir is, however, effective for primary prophylaxis but should be reserved for patients at high risk of developing disease. Aciclovir or valaciclovir may also be used for primary prophylaxis but their use must be combined with monitoring and pre-emptive therapy with either intravenous ganciclovir or foscarnet. If, however, ganciclovir has been given for primary prophylaxis then foscarnet should be used for first-line pre-emptive therapy. The use of valganciclovir for primary prophylaxis is under investigation, but if it is given then foscarnet should be used subsequently for first-line pre-emptive therapy. Cidofovir may be used as second-line pre-emptive therapy.[22]

CMV vaccines are currently in development.

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Epstein-Barr virus infections. Epstein-Barr virus (EBV) is a DNA virus of the herpesvirus group occurring worldwide. EBV is the causative agent in infectious mononucleosis and many people acquire a non-symptomatic infection, frequently in childhood. After primary exposure the individual becomes a lifelong carrier of the virus. Chronic EBV infection, particularly in immunocompromised individuals, is associated with several malignant diseases including Burkitt's lymphoma, nasopharyngeal carcinoma, lymphoproliferative diseases, Hodgkin's disease, T-cell lymphomas, and some gastric cancers. EBV is also associated with chronic interstitial pneumonitis in infants with AIDS and with oral hairy leucoplakia and CNS lymphomas in older AIDS patients.

Infectious mononucleosis (glandular fever) is an acute, self-limiting, lymphoproliferative infection that is seen when primary infection occurs in adolescents or young adults.[1,2] Transmission is by intimate oral contact and the incubation period ranges from 30 to 50 days. Illness is characterised by fever, sore throat, and lymphadenopathy. Other signs and symptoms include malaise, myalgias, jaundice, rash, and hepatosplenomegaly. Symptoms may last for about 2 to 3 weeks and most patients recover uneventfully with only supportive treatment, although fatigue may continue for some months. Complications, including encephalitis, anaemias, or cytopenias, may occur in a few patients but are rarely fatal. Very rarely the illness may become chronic. Chronic active EBV is defined as severe illness lasting longer than 6 months, evidence of major organ involvement, and elevated titres of antibody to EBV. Prognosis in these patients is poor and many die due to progressive pancytopenia and hypogammaglobulinaemia, or lymphomatous disease.

There is no specific **treatment** for EBV infections[1] although various experimental approaches have been investigated.[3] Treatment is generally symptomatic: hydration, paracetamol or NSAIDs, and throat lozenges or sprays. A meta-analysis[4] of five randomised controlled studies involving 339 patients with mild, moderate, or severe EBV infection, found that patients who took aciclovir had less oropharyngeal shedding, but clinical benefit was marginal and not sustained on stopping treatment. In a small number of patients with chronic active EBV, ganciclovir[5,6] and interferons[7,8] appeared to have a beneficial effect on symptoms or EBV replication. Corticosteroids are generally not indicated in uncomplicated EBV infection[9] but may be useful in patients with airways obstruction.[1,10] They may also be considered in systemic complications such as autoimmune haemolytic anaemia, aplastic anaemia, and thrombocytopenia and some also consider that they may be used for CNS involvement, myocarditis or pericarditis. However, concern has been expressed that they may impair immunity, resulting in a larger reservoir of latent virus and thereby potentially increasing the risk of developing EBV-related tumours in later years.

Concurrent throat infection with streptococci should not be treated with amoxicillin or ampicillin since they may cause a maculopapular rash in patients with infectious mononucleosis.

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Herpes simplex infections. Herpes simplex virus (HSV, herpesvirus hominis) is a DNA virus belonging to the herpesviridae family and occurs worldwide.[1] HSV can be divided into serotypes HSV-1 and HSV-2. Both viruses establish chronic infection of sensory nerve ganglia from where they may be reactivated by triggers such as stress, bacterial infection, fever, irradiation (including sunlight), menstruation, and immunosuppression. The primary infection may therefore be followed by recurrent episodes in the same area.

Primary HSV infection is acquired through direct contact with lesions or mucosal secretions of persons with active HSV lesions or persons shedding virus asymptomatically. Primary HSV-1 infections usually occur in the perioral area, and HSV-2 in the genital area, but infection may be acquired at other sites, including the fingers (whitlow), and rectum (herpes proctitis) after anal intercourse. The incubation period for both viruses ranges from 2 to 12 days and most primary HSV infections are asymptomatic.

- HSV-1 commonly causes symptomatic *oropharyngeal herpes* presenting as acute gingivostomatitis or pharyngitis and characterised by lesions of the buccal and gingival mucosa, fever, and cervical adenopathy.
  HSV-1 infections are common among immunocompromised patients, especially organ transplant recipients and those undergoing chemotherapy. In these patients infection may be more severe with extensive mucocutaneous and disseminated disease.
- *Genital herpes* is characterised by a painful ulcerative rash, and may be accompanied by dysuria, vaginal or urethral discharge, and tender inguinal lymphadenopathy. Genital herpes is most commonly caused by HSV-2 but may also be caused by HSV-1. Genital herpes tends to be more extensive when caused by HSV-2 and may include complications such as aseptic meningitis, disseminated disease, extragenital lesions, and bacterial superinfection.
  Herpes lesions are common among HIV-positive patients and may be severe, painful, and atypical; HSV recurrences and asymptomatic shedding are also increased.
- *Ocular herpes* is generally caused by HSV-1. It usually affects only one eye and most often occurs on the cornea resulting in epithelial or stromal keratitis. Epithelial keratitis usually heals without scarring whereas stromal keratitis infection involves the deeper layers and may lead to scarring, loss of vision, and occasionally blindness. Less commonly, HSV may also cause uveitis, chorioretinitis, or acute necrotising retinitis.
- HSV has been identified as one of the commonest causes of Bell's palsy and acute, sporadic viral *encephalitis*. Both HSV-1 and HSV-2 may cause encephalitis and if left untreated it is often fatal or may result in neurologic sequelae, especially in those over 35 years of age.
- *Neonatal herpes* may result from transmission of HSV-2 (or HSV-1) from mother to child during the perinatal period. Risk of neonatal herpes is highest when the mother develops primary genital herpes near the time of delivery whereas risk is much reduced with recurrent episodes. Neonatal herpes is a severe disseminated infection and often results in CNS disease. Untreated it is often fatal and survivors often have persistent ocular disease.

Recurrent herpes results from **reactivation** of latent infection and is usually milder and the duration is shorter than the primary infection. Reactivation is frequently associated with prodromal signs and symptoms, ranging from a mild tingling sensation to shooting pains. Systemic symptoms and lymphadenopathy are rare. *Herpes labialis*, also known as fever blisters or cold sores, are the most common infection resulting from reactivation of HSV-1. Recurrence o f genital herpes is more likely with HSV- 2 than HSV-1 infections.

Management. The most widely used antiviral for herpes simplex infections is aciclovir. Alternatives with improved bioavailability include famciclovir and valaciclovir. Antiviral treatment of primary herpes simplex infections, while relieving symptoms and reducing the duration of viral shedding, does not prevent recurrences. Antiviral therapy is generally more effective for primary infections than for recurrences, and should be given as early as possible during the course of an active infection, preferably within 3 days of the onset of symptoms. Resistance to aciclovir is emerging, mainly in immunocompromised patients.[2] Herpes simplex vaccines have also been tried but with generally disappointing results.

- **Orofacial herpes simplex infection.** Primary mucocutaneous HSV infection can be treated with topical, oral, or intravenous aciclovir. Oral famciclovir and valaciclovir have similar efficacy to oral aciclovir and are recommended alternatives.[1] Mucocutaneous HSV in HIV co-infected patients may be treated with intravenous or oral aciclovir, oral famciclovir, or oral valaciclovir.[3] Recurrent episodes of herpes labialis are usually self-limiting and rarely require antiviral therapy. In immunocompetent patients careful hygiene, symptomatic treatment with analgesics, and the use of antiseptics to reduce secondary infection will usually suffice. The use of sunscreens may also reduce the frequency of recurrences. If antivirals are used they should be started early in the prodromal phase. Topical antivirals, including aciclovir, penciclovir, and tromantadine, have been used and are most effective when started during the prodromal phase.[4] Docosanol may be a further alternative for topical use.[5] Oral antivirals (aciclovir, famciclovir, and valaciclovir) may shorten the duration of symptomatic lesions by about 1 day.[4] High-dose oral valaciclovir has also been reported to be effective for suppression of recurrences and may provide the convenience of single-day treatment.[6] In immunocompromised patients with primary symptomatic infection or recurrent episodes of infection, intravenous or oral aciclovir, oral famciclovir, or valaciclovir may be used. An oral antiviral (aciclovir, famciclovir, or

valaciclovir) is recommended for patients with herpes labialis and concurrent HIV infection.[3]

- **Genital herpes** is usually treated with oral aciclovir, famciclovir, or valaciclovir.[3,7-9] Intravenous aciclovir is given for severe disease or neurological complications. A study[10] found that both oral aciclovir and oral valaciclovir were effective in suppressing the frequency of recurrences and amount of HSV shedding. However, treatment of the primary HSV infection appears to have no effect on subsequent recurrences. Symptomatic recurrences in patients with a recognisable prodrome may be aborted or the severity reduced by episodic treatment with a 5-day course of oral aciclovir, famciclovir, or valaciclovir begun by the patient.[7-9] Alternative regimens (for HIV-negative patients) include high oral doses of aciclovir for 2 days,[7,8,11] famciclovir for 1 day, or valaciclovir for 3 days.[7,8]
  In HIV-negative patients without a prodrome, or those with frequent recurrences, continuous suppressive therapy with aciclovir, famciclovir, or valaciclovir should be considered.[7-9] Once-daily suppressive therapy with valaciclovir was found to significantly reduce the risk of transmission of genital herpes among heterosexual, HSV-2-discordant couples.[12]
  Symptomatic HSV recurrences in HIV-positive patients respond more slowly to anti-HSV treatment and longer treatment courses and higher doses of antivirals are needed.[8,13] Suppressive or episodic therapy should be considered for all HIV-infected persons.[3,7,13]
- **Ocular herpes simplex infections** usually require treatment with antivirals and/or interferons. Topical antivirals include aciclovir, brivudine ganciclovir, and trifluridine; these have similar efficacy and are more effective than idoxuridine or vidarabine.[14] Systemic antivirals include aciclovir, famciclovir, and valaciclovir. Other systemic antivirals that have been evaluated are ganciclovir, foscarnet, and cidofovir.[14] HSV epithelial keratitis can be treated with a topical antiviral, a topical interferon (alfa or beta), or a combination of both. Benefit appears to be similar after 7 days of treatment with either an interferon or antiviral monotherapy, but combination therapy with interferon and an antiviral produces faster healing than a topical antiviral alone.[14] Trifluridine eye drops are the treatment of choice for herpes simplex epithelial keratitis in HIV-infected patients.[15]
  Topical corticosteroid monotherapy is contra-indicated for epithelial keratitis as disease severity can be increased; however, the treatment for stromal keratitis does consists of both topical trifluridine and topical corticosteroids. The Herpes Eye Disease Study[16] reported that the addition of topical prednisolone to trifluridine reduced the risk of persistent or progressive stromal kerato-uveitis by 68%, while the further addition of oral aciclovir provided no additional benefit.[17] Stromal keratitis or iritis was not prevented by the addition of oral aciclovir in patients with epithelial keratitis and currently receiving topical trifluridine.[18] Oral aciclovir, however, was effective in reducing the rate of recurrent HSV ocular disease, particularly in patients with prior stromal keratitis,[19] and may be of benefit to patients in uveitis when added to topical corticosteroid and antiviral therapy.[20]
- **Severe or disseminated herpes simplex infections**, particularly in immunocompromised patients, require intravenous therapy. Aciclovir is given for CNS infections and disseminated HSV infections.[1,3,15] Intravenous foscarnet is recommended for infections resistant to aciclovir; intravenous cidofovir is an alternative.[3] Prolonged applications of topical trifluridine, cidofovir, or imiquimod also have been used successfully for lesions on external surfaces.[3] Neonates with evidence of herpes infection should be given high-dose intravenous aciclovir.[7,9,15] Immunocompromised patients with frequent or disabling recurrences may benefit from prophylactic oral aciclovir, valaciclovir, or famciclovir.[3,15]

Prevention. Intravenous aciclovir is recommended for all HSV-seropositive patients undergoing allogeneic haematopoietic stem cell transplants to prevent reactivation of latent HSV. Aciclovir may also be considered for HSV-seropositive patients undergoing autologous haematopoietic stem cell transplantation who are at risk of developing severe mucositis from the conditioning chemotherapy.[21] Oral aciclovir, famciclovir, or valaciclovir may be given to patients who can tolerate oral therapy. A systematic review[22] of interventions for the prevention and treatment of HSV in patients being treated for cancer found aciclovir to be effective; valaciclovir was found to be no more effective than aciclovir and high doses of valaciclovir were no better than low doses. There is a risk of neonatal herpes in the infants of mothers with genital herpes infection. Although clinical studies have shown that oral aciclovir or valaciclovir used near term reduce viral shedding and recurrence at labour and birth and the use of caesarean section these studies were not sufficiently powered to determine if they reduce the occurrence of neonatal herpes.[23,24] Prophylactic use of antivirals in late pregnancy is therefore not routinely recommended.[15]

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Varicella-zoster infections. Varicella-zoster virus (VZV) belongs to the herpesviridae and causes 2 separate diseases: chickenpox (varicella) and herpes zoster (zoster, shingles). Infection may be acquired through the respiratory tract via airborne droplets or by close contact with infected individuals. Primary infection with VZV usually occurs in childhood and results in chickenpox. In immunocompetent persons chickenpox is self-limiting and results in lifelong immunity. However, the virus is not eliminated and remains dormant within sensory nerve ganglia. In later life or in immunocompromised persons, reactivation of the virus from the sensory nerve may occur and give rise to nerve pain and a dermatomal rash (herpes zoster). Immunocompromised patients may develop a second episode of chickenpox.

The incubation period for *chickenpox* is about 14 to 15 days. In children it usually presents with a generalised rash, fever, and malaise. The rash rapidly progresses from macules to papules and then to vesicular lesions before crusting, with successive crops appearing over several days. Chickenpox acquired in childhood is commonly a mild disease lasting 3 to 5 days, with secondary bacterial skin infections the commonest complication. Chickenpox in adults may be more severe, and have a higher incidence of complications. Immunocompromised individuals may develop severe chickenpox with multiple organ involvement, high fever, more extensive vesicular skin eruption, severe pneumonia, and encephalitis.

Primary varicella infection in the first 20 weeks of pregnancy has been associated rarely with congenital varicella syndrome, characterised by skin scarring, local muscular atrophy, chorioretinitis, encephalitis, cortical atrophy, and microcephaly. Maternal infection until at least 5 days before delivery may result in a mild neonatal infection, while maternal infection from 7 days before to 7 days after delivery may result in a severe infection of the neonate with a reported fatality of about 30%.

Herpes zoster is characterised by painful vesicular eruptions in a dermatomal distribution. It may be preceded by a prodromal phase with fever and malaise or pain over the affected dermatome. Lesions continue to form over a period of 3 to 5 days, and disappear, often with a degree of scarring, after 10 to 15 days. Chronic pain that may persist after the rash has healed is termed postherpetic neuralgia (p. 10.3) and occurs in about 10% of patients. Involvement of the trigeminal nerve can lead to sight-threatening ophthalmic herpes zoster. Herpes zoster may be more severe and extensive in immunocompromised patients but is rarely fatal.

Treatment. Recommendations for the treatment of ***chickenpox*** in children,[1] adults,[2] and during pregnancy[2,3] have been developed. Treatment in otherwise healthy patients is usually symptomatic using antipyretics, analgesics, and antipruritics and is aimed at reducing complications. Antibacterials may be required for secondary skin infections. Antivirals are not recommended for the treatment of uncomplicated chickenpox in otherwise healthy children.[1] However, oral aciclovir may shorten the duration of fever and the number of lesions when given within 24 hours of onset of symptoms.[4] Antivirals do not reduce the incidence of chickenpox-associated complications in otherwise healthy children but may be useful in adults or immunocompromised patients. Intravenous therapy may be used in severe chickenpox.

The place of antivirals in the treatment of ***herpes zoster*** is well established; recommendations and guidelines on management have been produced.[5-8] Antiviral treatment can reduce the severity and duration of acute pain, minimise complications and propagation of the rash, and reduce viral shedding.[5] Systemic antivirals are recommended for all immunocompetent patients who are over 50 years of age, have moderate to severe pain or rash, or have nontruncal involvement. Treatment should be started within 72 hours of the onset of the rash and is usually continued for 7 to 10 days. Antiviral therapy may also be considered in those presenting 72 hours after the onset of the rash when there are skin, motor, neurological, or ocular complications, when new vesicles are still forming, in the elderly, or in those with severe pain.[7] Topical antivirals are not recommended.

Aciclovir may be given orally or intravenously, depending upon the severity of the infection. Oral famciclovir, valaciclovir, or brivudine are alternatives.[7] Bioavailabilities of these drugs are better than aciclovir and they also appear to be superior in terms of healing lesions and equally or more effective in relieving pain.[7,9-12]

There has been controversy over the use of oral aciclovir to prevent **postherpetic neuralgia** and ocular complications. A meta-analysis suggested that treatment of herpes zoster with oral aciclovir within 72 hours of the onset of rash could reduce the *incidence* of residual pain at 6 months by 46% in immunocompetent adults.[13] Subsequent analyses found little[14] or no[15] evidence that aciclovir decreased the incidence of postherpetic neuralgia and none for a reduction in incidence with either famciclovir[14,15] or valaciclovir.[14] It is, however, generally agreed that antivirals do reduce the *duration* of postherpetic neuralgia[14] and some experts recommend antivirals even in patients at low risk for developing postherpetic neuralgia and other complications.[7] The addition of corticosteroids to antiviral therapy does not reduce the incidence or duration of postherpetic neuralgia, but may improve the rate of resolution of the neuritis or improve pain control.[16,17]

Severely **immunocompromised** patients or others at high risk of severe or disseminated herpes zoster should receive intravenous aciclovir. Oral aciclovir, famciclovir, or valaciclovir may be considered in less severely immunocompromised patients.[7] Sorivudine and brivudine are also effective against zoster infections.[18] Brivudine is as effective, if not more, than aciclovir in immunocompromised patients[19] but is not recommended in such patients because of a potentially fatal interaction with fluorouracil (and related drugs).[7] Sorivudine has been withdrawn from the market after deaths in patients also taking fluorouracil. Foscarnet may be of value in aciclovir-resistant varicella-zoster infections[20-22] although treatment failures have been reported.[23]

Ophthalmic herpes zoster is treated with an oral antiviral, given within 72 hours of the onset of the rash; additional treatment with topical aciclovir to the eye may also be considered. Oral aciclovir, famciclovir, and

valaciclovir are all effective in reducing the pain associated with ophthalmic zoster.[24,25]

Prevention. Varicella-zoster immunoglobulins are used for the prevention of chickenpox in patients at high risk of developing complications, such as the immunocompromised, neonates whose mothers developed chickenpox 7 days before to 7 days after delivery, and in susceptible pregnant women after significant exposure. There have been reports of severe chickenpox occurring in patients undergoing corticosteroid therapy. In the UK, use of varicella-zoster immunoglobulins is recommended in persons exposed to the virus who have received high doses of corticosteroids within the previous 3 months[26] (see also Varicella, under Precautions for Corticosteroids, p. 1619.2).

Varicella-zoster vaccines are available in some countries and in the UK vaccination is recommended for active immunisation against chickenpox in persons considered to be at high risk of either infection or complications, including healthy contacts of immunocompromised patients. In the USA, a 2-dose vaccination regimen is recommended as part of the primary immunisation schedule of infants and children. Routine vaccination is also recommended for persons over the age of 13 years without evidence of immunity[27] and a high-potency vaccine against herpes zoster is recommended for persons 60 years of age and older.[28] For further discussion of varicella-zoster vaccines, see p. 2423.3.

Transmission of chickenpox to household contacts is not prevented by giving aciclovir to the primary case but there is evidence to suggest that transmission can be suppressed by giving aciclovir to susceptible contacts during the incubation period.[29,30] Although the need for such prophylaxis has been questioned, especially in otherwise healthy children,[31] prophylaxis or early treatment with antivirals may be useful for household contacts in whom the infection might prove to be more severe.[1,32,33]

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HIV infection and AIDS

The causative agent of AIDS (acquired immunodeficiency syndrome) is the human immunodeficiency virus (HIV; previously known as HTLV-III or LAV), a retrovirus transmitted by sexual contact, blood and blood products, the use of contaminated needles, or vertically from mother to fetus. Two subtypes of HIV have been identified. The most common is HIV-1, which occurs worldwide. HIV-2 is found mainly in West Africa and is associated with a slower progression to AIDS than HIV-1.

HIV uses the CD4 receptor and the CCR5 or CXCR4 co-receptors to enter T lymphocytes and monocytes/macrophages, where viral RNA is reverse transcribed into DNA and inserted into the host genome. Viral replication results in immune activation and progressive depletion of CD4+ T lymphocytes. Primary HIV infection is characterised by the development of non-neutralising HIV antibodies (seroconversion), and in some patients may manifest as a transient rash, sore throat, and lymphadenopathy (seroconversion illness). Primary HIV infection is usually followed by a largely asymptomatic chronic infection, during which persistent generalised lymphadenopathy may be noted. Chronic HIV infection is characterised by gradual depletion of CD4+ T lymphocytes resulting in progressive immunodeficiency. This may become clinically apparent when symptoms such as fatigue, weight loss, recurrent fever, diarrhoea, or thrush occur. Alternatively, patients may develop severe opportunistic infections such as pneumocystis pneumonia, toxoplasma encephalitis, oesophageal candidiasis, cryptococcal meningitis, CMV retinitis, *Mycobacterium avium* complex, recurrent bacterial pneumonia, pulmonary or extrapulmonary tuberculosis, or neoplasms such as Kaposi's sarcoma, cervical carcinoma, and lymphomas; these are collectively referred to as AIDS-defining illnesses. AIDS-defining illnesses generally do not occur until severe immunodeficiency is present (CD4+ T lymphocyte count of less than 200 cells/microlitre or less than 14% of the total lymphocyte count). Most AIDS-defining events can therefore be prevented if effective HIV treatment is started before the CD4+ count has fallen to this level. Since the availability of highly active antiretroviral therapy (HAART), the incidence of AIDS-defining illnesses has markedly declined. However, antiretroviral therapy may result in toxicity or paradoxical worsening of underlying opportunistic infections.

During the course of chronic HIV infection, measurement of the CD4+ count and HIV RNA (viral load) will aid prognosis. The absolute CD4+ count or CD4% reflects the susceptibility to opportunistic infections while a high HIV viral load is associated with a more rapid decline in CD4+ count and more rapid clinical disease progression. The HIV viral load is also used to monitor success of antiretroviral therapy, where the goal is complete suppression of viral replication (resulting in undetectable HIV viral loads). CD4+ counts and viral loads are both taken into consideration in the decision to start antiretroviral therapy.

TREATMENT.

The following discussion relates to the use of antiretrovirals in HIV infection and AIDS. The treatment of secondary and opportunistic infections and other complications is covered under the relevant sections, below.

Treatment strategies for HIV infection are changing rapidly and frequently updated guidelines for the treatment of HIV infection are published for the USA,[1-3] for the UK,[4] by the European AIDS Clinical Society (EACS),[5] and by WHO.[6,7]

Data from clinical studies in support of treatment of *acute* HIV infection are limited. Treatment of the primary HIV infection may be beneficial in relieving symptoms due to HIV during the seroconversion illness; it may restrict damage to the immune system, reduce the viral load set point once treatment is stopped and reduce the rate of viral mutation and risk of HIV transmission to sexual partners.[8] The UK guidelines do not routinely recommend early treatment of acute HIV infection, but suggest that treatment may be considered in patients with neurological involvement, any AIDS-defining illness, or a CD4+ count less than 200 cells/microlitre for 3 months or more.[4] US guidelines[2] state that treatment of acute infection is optional.

In *chronic* infection, the goal of antiretroviral therapy is to prevent or reverse immunodeficiency, prevent opportunistic infections, and prolong survival. The decision of when to start antiretroviral therapy should be individualised to take into account patient-specific relative risks and benefits of treatment. Guidelines[1,2,4-6] recommend that antiretroviral treatment should be given to patients whose CD4+ counts have fallen below 200 to 350 cells/microlitre or who have symptomatic disease, irrespective of their viral load or CD4+ count. Treatment is generally not indicated for asymptomatic patients with a CD4+ count greater than 350 cells/microlitre but may be considered for patients with a high viral load (more than 100 000 copies/microlitre), rapid CD4+ count decline (more than 100 to 120 microlitres per year), co-infection with hepatitis B or C virus, HIV-associated nephropathy, or risk factors for non-AIDS diseases, particularly cardiovascular diseases.[2,4] However, some experts in the USA[1] recommend antiretroviral treatment should be given to asymptomatic patients with CD4+ counts of 500 cells/microlitre or less and that it should also be considered in those with CD4+ counts above 500 cells/microlitre.

Combination therapy with antiretroviral drugs aims to improve potency, minimise toxicity, and delay drug resistance. The drugs used in combination therapy are:

- nucleoside reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine, and zidovudine) or the nucleotide reverse transcriptase inhibitor tenofovir
- HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir)
- non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine, and etravirine)
- the entry inhibitors, including the HIV-fusion inhibitor enfuvirtide, the CCR5-antagonist maraviroc, and the HIV-integrase inhibitors dolutegravir, raltegravir, and elvitegravir

Although ritonavir inhibits HIV-protease when given in high doses, it is almost exclusively used in low doses for its CYP450 inhibitory properties, to boost the plasma concentrations of co-administered HIV-protease inhibitors. Combination of three antiretrovirals, typically two nucleoside/nucleotide reverse transcriptase inhibitors (NsRTI/NtRTI) plus either a (ritonavir-boosted) HIV-protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), is referred to as ***highly active antiretroviral therapy*** (***HAART***). Such regimens have produced sustained reductions in viral load often to levels below the limit of detection, and have been associated with improvements in CD4+ count, immune function, and clinical well-being. This is reflected by the decline in morbidity and mortality among patients with HIV infection since the availability of HAART. Triple therapy regimens, consisting of at least 2 classes of antiretrovirals, are superior to monotherapy, dual therapy, or triple NRTI therapy. Quadruple therapy regimens may be of benefit in some patients but are likely to increase toxicity. Complete suppression of viral replication minimises the emergence of drug-resistant HIV.[9-11]

When considering combination antiretroviral therapy several factors need to be taken into consideration. Drug combinations should provide additive or synergistic antiviral activity without increased toxicity or pharmacokinetic interactions that may affect the efficacy of co-administered drugs. Drugs with maximal potency should be combined so as to minimise the risk of drug resistance developing. The patient's ability to adhere to a regimen, comorbid conditions, results of genotypic drug resistance testing, and the likelihood of pregnancy should also be taken into consideration.

In the developed world the availability of co-formulations of zidovudine with lamivudine, abacavir with lamivudine, and tenofovir with emtricitabine, and concerns over the toxicity of stavudine and zalcitabine have resulted in most treatment-naive patients starting with one of these combinations. There has been a shift from zidovudine/lamivudine to abacavir/lamivudine or to tenofovir/emtricitabine because of concern over the adverse effects and long-term toxicity (lipoatrophy) associated with zidovudine. Some experts in the USA[2] consider abacavir/lamivudine to be a second-line combination because abacavir is associated with an increased risk of myocardial infarction in patients with high cardiac risk factors. Furthermore there is concern regarding the effectiveness of abacavir/lamivudine in patients with baseline viral loads more than 100 000 copies/microlitre.[1,2,4] Similarly, among the NNRTIs, delavirdine is now rarely used and a shift from nevirapine to efavirenz has occurred because of the potential of nevirapine to cause severe skin and liver toxicity. Efavirenz is the preferred NNRTI except for

pregnant women (especially during the first trimester) or women with a high pregnancy potential. A co-formulated tablet containing tenofovir, emtricitabine, and efavirenz is available and taken once daily. HIV-protease inhibitors are almost exclusively used with ritonavir boosting. Giving amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, or tipranavir, with ritonavir, improves the pharmacokinetic properties and clinical efficacy of these HIV-protease inhibitors. Acceptable PIs for treatment-naive patients are ritonavir-boosted atazanavir, darunavir, fosamprenavir, lopinavir,[1,2,4] or saquinavir.[2,4] Randomised, controlled studies indicate that triple NRTI treatment with zidovudine, lamivudine, and abacavir is less potent than combining two NRTIs with either an NNRTI or a PI, with higher rates of virological failure and its use is not recommended.[2,4] Triple or quadruple NRTI treatment regimens are not recommended,[1] but may be used in exceptional circumstances when a PI- or NNRTI-based HAART regimen cannot be given.[4] In the USA, raltegravir and two NRTIs, preferably tenofovir and emtricitabine, may also be given as an initial treatment regimen.[1,2] Maraviroc with zidovudine plus lamivudine was found to be as effective as efavirenz when used exclusively in patients with CCR5-tropic HIV infection; in this patient group maraviroc may be considered for treatment-experienced patients or if primary drug resistance is present.[1]

WHO guidelines[6] recommend that treatment-naive patients be started on a triple therapy regimen, consisting of two NRTIs and one NNRTI. Suggested regimens include zidovudine, lamivudine, and efavirenz or nevirapine, *or* tenofovir, lamivudine or emtricitabine, and efavirenz or nevirapine.

Treatment failure. Although HAART regimens are generally most effective in antiretroviral-naive patients, good responses can also be achieved in treatment-experienced patients.[1,2] In patients who have an inadequate response to therapy, adherence needs to be carefully assessed and reasons for potential non-adherence addressed. If a patient has drug toxicity, intolerance to therapy, or for any other reason is unable to adhere to therapy, a change of drugs should be considered. Change of treatment should also be considered if the patient has a suboptimal virologic response to their current antiretroviral therapy and may be considered in those with limited gains or decreases in their CD4+ count or clinical deterioration while on fully suppressive regimens. Resistance testing is needed to determine which antiretroviral drugs will possibly be the most active.

Choice of second-line regimen is essentially empirical, since there is limited evidence from controlled studies.[13] Addition of a single antiretroviral drug to a failing combination regimen is generally not recommended because further resistance may result.[1,2,4] When a new regimen is started, 2 to 3 drugs should be included to which the patient has not been exposed or to which the virus is not resistant.

- A failing regimen of two NRTIs and an NNRTI may be replaced by a ritonavir-boosted PI with one or two different fully active NRTIs.[1,2,4,6]
- In a failing NNRTI regimen, the NNRTI should be replaced with a drug with different mechanism of action, most commonly a ritonavir-boosted PI, but newer drugs such as the integrase inhibitor raltegravir, the CCR5 antagonist maraviroc, or the NNRTI etravirine may be tried. Etravirine must be given with a potent ritonavir-boosted PI-containing regimen.[1]
- For patients who fail on a ritonavir-boosted PI based regimen, treatment options are to change to a NNRTI-based regimen (if not previously used), substitute the HIV-PI for one with limited cross-resistance (such as ritonavir-boosted atazanavir, darunavir, lopinavir, or tipranavir), and/or add a drug with a different mechanism of action, such as the HIV-fusion inhibitor enfuvirtide, raltegravir, or the CCR5 antagonist maraviroc.[2,4]

In **multidrug-experienced patients** the goal of treatment is still to suppress HIV-1 RNA to less than 50 copies/mL. In these patients treatment regimens should include at least 2, and ideally 3, fully active drugs, and at least 1 drug from a different class, such as enfuvirtide, etravirine, maraviroc, or raltegravir, should be included.[1,4] Ritonavir-boosted PIs with activity against resistant viruses are usually the basis of a new regimen.[1,2] Ritonavir-boosted tipranavir[14,15] or darunavir,[16] when used as part of a combination regimen with at least one (preferably two) active agents such as enfuvirtide, result in better viral suppression and CD4+ count increases in patients with multidrug resistant HIV-1 infection than standard ritonavir-boosted PIs.[17,18] Etravirine, which may be used depending on the number of NNRTI-associated resistance mutations present, must be given with a potent ritonavir-boosted PI; darunavir, but not tipranavir, is suitable.[1] There is no evidence for the use of two HIV-PIs,[1] but some consider that they may be an alternative for patients with limited therapeutic options living in resource-limited countries, where the newer more expensive drugs are not available.[19]

While HAART maintains plasma viral load at undetectable levels in most patients, viral replication rapidly returns to pretreatment levels once treatment is stopped. *Treatment interruption* may be associated with a precipitous decline of CD4+ count, clinical disease progression, and the development of drug resistance. Structured long-term treatment interruptions (or planned breaks) are generally not recommended in patients with HIV infection, even if drug-resistance results in chronic non-suppression of HIV RNA.[1,2,4,20] The continued efficacy of any HAART regimen is dependent on strict adherence to treatment. The improved formulation and co-formulation of several antiretrovirals has reduced the pill burden and newer drugs tend to have fewer adverse effects. However, the cost of treatment is high and access to effective treatment in developing countries with high burdens of disease, although improving, remains limited.

Newer antiretroviral drugs to further reduce pill burden and limit toxicity are in development. In addition, research continues into further drugs with enhanced activity against resistant isolates, such as HIV-entry inhibitors (that inhibit the three steps of HIV entry: CD4 attachment, chemokine receptor binding, and membrane fusion) and HIV-integrase inhibitors.[21,22] Interleukin-2 may improve the CD4+ count in patients with advanced HIV infection, or preserve CD4+ counts in patients with early HIV infection. However, it is not clear that this results in any additional clinical benefit to patients on antiretroviral therapy (see p. 810.3). Some vaccines aimed at preventing HIV infection or reducing the HIV viral load are currently under investigation (see AIDS Vaccines, p. 2376.1).

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HIV-associated infections and complications. Infections. Patients with HIV infection and AIDS are at increased risk of specific bacterial, fungal, protozoal, and viral infections largely as a result of impaired cell-mediated immunity. With the introduction of antimicrobial prophylaxis and HAART there has been a significant decrease in the incidence of most AIDS-defining opportunistic infections, especially in the developed world. However, HIV-related opportunistic infections and deaths still occur in patients newly diagnosed with HIV infection, in those in the early course of HAART, in those non-adherent to their HIV treatment, or in those with drug-resistant HIV infection; deaths also result from non-opportunistic infections and chronic viral hepatitis.[1]

- Infections affecting the *lungs* include recurrent bacterial pneumonia (p. 200.1), pneumocystis pneumonia (p. 567.2), and pulmonary tuberculosis (p. 210.2).
- Many pathogens cause *gastrointestinal-tract disease* in HIV-infected patients, including candida oesophagitis (p. 564.1), CMV colitis (p. 954.2), and amoebiasis (p. 919.1), cryptosporidiosis (p. 921.1), giardiasis (p. 921.3), isosporiasis (p. 921.3), or microsporidiosis (p. 924.1).
- AIDS-defining *neurological* infections include AIDS dementia complex (HIV encephalopathy), cryptococcal meningitis (p. 565.2), cerebral toxoplasmosis (p. 924.2), and progressive multifocal leukoencephalopathy (see Infections in Immunocompromised Patients, p. 960.2).
- *Systemic* opportunistic infections in AIDS patients include tuberculosis, coccidioidomycosis (p. 565.1), histoplasmosis (p. 566.1), and *Mycobacterium avium* complex infections (see Nontuberculous Mycobacterial Infections, p. 194.1). CMV retinitis (p. 954.2) may be a cause of blindness, while chronic herpesvirus infections (p. 954.1) may affect the skin and gastrointestinal tract.

Recommendations have been published for both treatment and prophylaxis of opportunistic infections in AIDS patients.[2-4] Recovery of immune function in patients responding to HAART may be sufficient to protect against certain opportunistic infections and to allow primary or secondary prophylaxis to be stopped.

Other complications. Non-infectious complications of HIV infection include cardiovascular events, renal disease, metabolic and skeletal disorders, toxicities of HAART, and malignancies (p. 959.1).

HIV infection and adverse effects of HAART may accelerate the typical problems associated with ageing and in particular *cardiovascular disease*.[5] HIV infection appears to increase the risk of coronary heart disease by up to twofold compared with uninfected persons and the mean age at which it develops is more than 10 years earlier (at about 50 years of age) in HIV-infected persons.

Black patients with HIV infection may develop chronic or end-stage *renal disease* due to HIV-associated nephropathy (HIVAN) or thrombotic microangiopathy; antiretroviral therapy can improve renal function in HIVAN and may slow or even stop its progression. Acute renal failure is common in hospitalised patients with (opportunistic) infections, malignancies, or hepatitis C co-infection, while proteinuria is common in all HIV patients and may reflect an increased risk of cardiovascular events. Antiretrovirals, in particular tenofovir and indinavir, may cause renal dysfunction.[6-9] Guidelines for the management of chronic kidney disease in HIV-infected patients have been developed by the HIV Medicine Association of the Infectious Diseases Society of America.[6]

Metabolic complications associated with HIV infection and HAART include dyslipidaemia, abnormal glucose metabolism (insulin resistance, impaired glucose tolerance, and diabetes mellitus), and bone disorders (osteopenia, osteoporosis, and osteonecrosis); hepatic steatosis may occur with or without lipodystrophy in the form of lipohypertrophy (fat accumulation) or lipoatrophy (fat loss). HAART may occasionally cause lactic acidosis.[10,11]

Pancytopenia is commonly seen in patients with advanced HIV infection, and *neurological syndromes* such as aseptic meningitis, headache, neuropathy, myopathy, and Guillain-Barré syndrome, may occur at any stage of the infection.

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HIV-associated malignancies. There is an increased incidence of certain malignancies in patients with HIV infection. Malignancies commonly associated with HIV infection are Kaposi's sarcoma (p. 718.1), Hodgkin's disease, non-Hodgkin's lymphoma and primary CNS lymphoma (see AIDS-related Lymphomas, p. 697.2), invasive cervical cancer (p. 704.2), and anal cancer (see Malignant Neoplasms of the Anus, p. 708.1). Some tumours may regress in response to effective antiretroviral therapy. Guidelines for the management of HIV-associated malignancies have also been issued by the British HIV association.[1]

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HIV-associated wasting. Severe malnutrition in HIV-infected patients is recognised as wasting syndrome[1-4] and has been defined as an involuntary loss of body-weight of 10% or more (of both lean and fat tissue) and may be associated with fatigue, fever, and diarrhoea (not explained by another cause). However, there is some debate as to whether it should be defined as the loss of 5 or 10% of usual weight and whether changes in body composition, rather than weight alone, better define the syndrome. Wasting is associated with morbidity and mortality in advanced HIV infection and AIDS. Wasting syndrome has been associated with inadequate oral intake, malabsorption syndrome, metabolic disorders, hypogonadism, and increased cytokine production. Weight loss and malnutrition tend to be less severe in patients taking HAART. However, loss of body cell mass may occur in patients given HAART and needs to be differentiated from fat redistribution (lipodystrophy).

Since HIV replication is central to the pathogenesis of wasting syndrome, antiretroviral therapy is indicated. Nutritional intervention, exercise, and drug treatment may be indicated in patients who have an incomplete response to antiretroviral therapy. Drugs that have been tried include growth hormone, the appetite stimulants dronabinol and megestrol, the growth hormone mediator mecasermin, steroid hormones (testosterone and testosterone analogues), synthetic anabolic steroids (nandrolone, oxandrolone, and oxymetholone), and drugs that decrease cytokine production such as pentoxifylline and thalidomide. A suggested initial approach to the management of wasting[3] is to increase dietary intake of protein or total calories. Nutritional supplementation and exercise should always be considered and encouraged before drug treatment is started. Testosterone replacement may be given to HIV-infected men with significant weight loss and low testosterone levels, and megestrol may be given to patients who are unable to voluntarily increase or maintain total energy intake. Other drug treatments such as growth hormone and anabolic steroids may be considered where rapid weight loss is associated with acute infection and in severe cases of continued weight loss refractory to non-drug therapies.

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HIV infection prophylaxis

Non-occupational exposure to HIV. Behavioural changes are the most effective methods of reducing the spread of HIV infection in the general population. These include the promotion of safe sex practices and needle exchange schemes for intravenous drug users. Guidelines have been published in the USA[1] for postexposure prophylaxis (PEP) after sexual activity, intravenous drug use, or other non-occupational exposure to HIV amongst the general population:

- a 28-day course of HAART is recommended for persons who have had non-occupational exposure to potentially infected body fluids of a person known or suspected to have HIV infection when there is a substantial risk of transmission and when the person presents within 72 hours of exposure
- for persons seeking care within 72 hours of non-occupational exposure from a person of unknown HIV status, or when such exposure would represent a substantial risk for transmission if the source were HIV-infected, it is recommended that risks and benefits of PEP be evaluated on an individual case basis
- PEP is generally not recommended for persons seeking care where there is no substantial risk for HIV transmission or for those presenting more than 72 hours after exposure (although it may be considered for persons seeking care after more than 72 hours if the exposure represents a substantial risk for transmission)

Guidelines for non-occupational PEP have also been produced in the UK[2,3] for exposure outside the healthcare setting and are similar to those for occupational exposures (see below); when given, PEP should be started as soon as possible after exposure.

Occupational exposure to HIV. The risk of seroconversion is estimated at about 0.3 to 0.4% after percutaneous contamination with HIV-infected blood and considerably less for accidents involving contamination of intact skin or mucous membranes. In view of potential toxicity of antiretrovirals, the decision whether to give PEP should balance the risk of infection against the potential drug toxicity and PEP should generally only be offered to intermediate to high-risk cases. Factors associated with increased risk of occupationally-acquired HIV infection include:

- deep injury
- visible blood on the device which caused the injury
- injury with a needle which had been placed in a source patient's artery or vein
- primary HIV infection or terminal HIV-related illness in the source patient

If PEP is given it should be started as soon as possible after the exposure. Zidovudine monotherapy has been extensively used for PEP and reduces seroconversion after percutaneous exposure by 79%. PEP with combination antiretroviral drugs is now preferred as it results in more complete suppression of viral replication and is more likely to afford some protection against drug-resistant HIV strains.

Guidelines for the UK[2] recommend a 4-week course of antiretroviral therapy after occupational percutaneous, mucous membrane, or broken skin site exposure to high-risk body fluids or tissues known to be, or suspected of being, infected with HIV. They advise that PEP emergency starter packs should contain two nucleoside reverse transcriptase inhibitors (NsRTIs) (tenofovir and emtricitabine) and a boosted HIV-protease inhibitor (lopinavir-ritonavir).

Guidelines in the USA[4] recommend selection of PEP regimens based on the level of risk of transmission presented by the exposure and other considerations such as possible antiretroviral drug resistance in the source. Most occupational HIV exposures can be managed with a two-drug regimen, using two NsRTIs or one NsRTI and one nucleotide reverse transcriptase inhibitor (NtRTI). Although there are no definitive data to show increased efficacy of 3-drug PEP regimens over 2-drug regimens, the addition of further drugs may be considered for exposures that pose an increased risk of transmission or if antiretroviral drug resistance is likely. HIV-protease inhibitors are recommended as the preferred drug for inclusion into 3- or 4- drug regimens but the NNRTI, efavirenz, may be considered when resistance to HIV-protease inhibitors in the source person is known or suspected. Due to the higher risk for potentially serious or life-threatening adverse effects abacavir, delavirdine, nevirapine, zalcitabine, and the combination of didanosine and stavudine, are not recommended for PEP.

Measures aimed at reducing **vertical transmission** of HIV from mothers to their infants include antiretroviral therapy to the mother and baby, elective caesarean section, and avoidance of breast feeding when replacement feeding is acceptable, affordable, and safe.[5-9]

The risk of vertical transmission is directly proportional to the maternal plasma HIV viral load at the time of delivery, and very few HIV-infected children are born to mothers whose HIV viral load is undetectable. The benefit of elective caesarean section is therefore most profound in women with detectable or high HIV viral loads. In contrast, zidovudine monotherapy given during pregnancy and labour, and to the infant postpartum, reduces the rate of vertical transmission by about 70%, irrespective of maternal viral load or CD4+ count.[10,11] However, zidovudine monotherapy is suboptimal for mothers with high viral loads, in whom combination antiretroviral therapy should be used to prevent vertical transmission.

In resource-limited settings, infants born to HIV-infected mothers who are not breast fed are at very high risk for mortality or morbidity. This risk can exceed that associated with HIV-infection and WHO therefore recommends exclusive breast feeding for infants born to HIV-infected women for the first 6 months of life if replacement feeding is not acceptable, feasible, affordable, sustainable and safe.[12] However, breast feeding continues to expose the infant to the risk of HIV infection and studies are ongoing to determine if extending the duration of antiretroviral prophylaxis will reduce HIV transmission via breast feeding. Extended prophylaxis for the first 14 weeks of life with nevirapine or with nevirapine plus zidovudine significantly reduced postnatal HIV infection in 9-month-old infants,[13] but extended treatment for the first 6 weeks of life with nevirapine did not reduce the risk of HIV transmission at 6 months of age.[14] The use of nevirapine in this manner is controversial because it rapidly induces resistance to NNRTIs.[15] Extended prophylactic treatment of infants with lamivudine, for a maximum of 6 months during breastfeeding, was found to be effective in reducing HIV transmission.[16] Another approach being investigated to prevent postnatal HIV transmission is to continue HAART treatment during breastfeeding in those HIV-infected mothers who received HAART during pregnancy solely for prophylaxis of perinatal HIV transmission.[17]

Guidelines for the management of HIV infection in pregnant women and for the prevention of transmission of HIV from mother to child have been developed for the USA[7] and the UK.[9] The ***US guidelines***[7] recommend that zidovudine-based therapy is of proven benefit in preventing perinatal HIV transmission, but three-drug combination drug regimens should be considered the standard of care for both treatment of HIV infection in pregnant women and prevention of perinatal HIV transmission. Treatment to prevent the latter should be offered to all women, regardless of CD4 count and viral load:

- women who are taking HAART and become pregnant should continue with their regimen, although regimens with potentially teratogenic drugs such as efavirenz should be substituted in the first trimester, as should combinations with known adverse potential for the mother, such as stavudine/didanosine. If an HIV-protease inhibitor is required, ritonavir-boosted lopinavir is the drug of choice; alternatives include ritonavir-boosted atazanavir, indinavir, or saquinavir. Treatment should be continued both during labour (with zidovudine given intravenously and other antiretroviral drugs given orally), and postpartum
- women who have not had antiretroviral treatment and have indications for therapy should also begin HAART, subject to the same precautions as above; those who do not require HAART for their own health should be offered it for prevention of perinatal transmission, but treatment may be delayed until after the first trimester, and should be stopped postpartum unless indications for continuing it develop. If the regimen includes a long half-life NNRTI, consideration should be given to continuing NRTIs for at least 7 days after stopping the former
- women who have previously had antiretrovirals should be offered an HAART regimen based on resistance testing; use of zidovudine as a component of the regimen is recommended when feasible. Need for continuing therapy should be evaluated postpartum
- in all cases above, the *infant* should be treated with zidovudine intravenously or orally for 6 weeks, starting 6 to 12 hours after birth; the course may be reduced to 4 weeks where adherence or toxicity is a problem
- in women who have had no antiretroviral therapy before labour, treatment should be offered with:
  - *mother*: continuous infusion of zidovudine during labour; *infant*: zidovudine for 6 weeks started within 6 to 12 hours of birth
  or
  - *mother*: continuous infusion of zidovudine during labour, plus a single dose of nevirapine at onset; consideration should be given to adding lamivudine during labour and zidovudine and lamivudine for 7 days postpartum, to reduce development of nevirapine resistance; *infant*: single oral dose of nevirapine at 2 to 3 days after birth, plus zidovudine for 6 weeks
- if the mother has no antiretroviral therapy either before or during labour, the infant should still be given zidovudine for 6 weeks, started as soon as possible after birth. The use of other drugs for prophylaxis in infants requires specialist consultation

While similar to those of the USA, the ***UK guidelines***[9] recommend that zidovudine monotherapy combined with elective caesarean section may still be an option for pregnant women in whom HAART is contra-indicated and whose HIV viral load is less than 10 000 copies/mL, or for women not wishing to take HAART during pregnancy. Infants born to HIV-infected mothers should be given zidovudine for 4 weeks after birth. Alternative antiretroviral

therapy may be given to infants whose mothers did not take zidovudine in their treatment regimen and triple therapy may be considered for infants whose mothers had no antiretroviral therapy or whose mothers are infected with drug-resistant HIV.

WHO has published guidelines on the use of antiretrovirals in pregnancy and for preventing HIV transmission to infants in *resource-limited settings*[8] and has updated them in line with available evidence.[5]

- In countries where HAART is available, women with a CD4+ T lymphocyte count below 350 cells/microlitre and those with a CD4+ T lymphocyte count greater than 350 cells/microlitre who have other indications for antiretroviral treatment should start HAART during their pregnancy. The preferred regimens are zidovudine plus lamivudine and either nevirapine or efavirenz. Alternative recommended regimens include tenofovir, plus lamivudine or emtricitabine, and nevirapine or efavirenz.[5] However, efavirenz-based regimens should not be started during the first trimester of pregnancy.
  Women already taking antiretrovirals should continue their therapy; but consideration should be given to switching those who are in the first trimester of pregnancy and taking efavirenz to a nevirapine-containing regimen
  Non-breast fed infants born to these mothers should be given zidovudine or nevirapine from birth until 6 weeks of age; breast-fed infants should be given nevirapine from birth until 6 weeks of age[5]
- Women in whom maternal HAART is not indicated, or those living in countries where HAART is not available, should be given short-course zidovudine starting at 14 weeks of pregnancy or as soon as feasible thereafter and continued into labour. A single dose of nevirapine should be given at the onset of labour to the mother. Zidovudine and lamivudine are given during labour and delivery and then for 7 days postpartum to reduce the emergence of nevirapine resistance. The single dose of nevirapine, and the zidovudine plus lamivudine given intra- and postpartum, can be left out if the mother has received more than 4 weeks of zidovudine during pregnancy
  Non-breast fed infants born to these mothers should be given zidovudine or nevirapine from birth until 6 weeks of age; breast-fed infants should be given nevirapine from birth until 1 week after exposure to breast milk is stopped[5]
- Another option for HIV-infected women being treated to prevent perinatal transmission to the infant, but not in need of therapy for their own health is triple antiretroviral therapy starting from as early as 14 weeks of gestation until one week after all exposure to breast milk has ended. The recommended regimens include zidovudine, lamivudine plus either ritonavir-boosted lopinavir, abacavir or efavirenz, *or* alternatively tenofovir, emtricitabine or lamivudine, plus efavirenz
  Non-breast fed infants born to these mothers should be given zidovudine or nevirapine from birth until 6 weeks of age; breast-fed infants should be given nevirapine from birth until 6 weeks of age.[5]

Other measures necessary to minimise the transmission of infection include the rigorous selection of blood donors, microbiological screening of blood, and, where possible, heat treatment of blood products. Maternal vitamin A deficiency has been identified as a risk factor for vertical transmission in Africa (see p. 2100.2). Nutritional intervention and vaginal cleansing during labour could reduce vertical transmission in regions where zidovudine therapy is not readily available.

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Infections in immunocompromised patients

Most viral infections present in a more severe form in immunocompromised patients than in immunocompetent patients. Among the viral infections that may be a particular problem in immunocompromised patients are hepatitis, herpesvirus infections (including CMV and Epstein-Barr virus infections), measles, and RSV infections. For further information and treatment of these infections, see under the individual diseases. For secondary infections occurring in HIV-infected patients, see p. 958.3.

Persistent infection with human **parvovirus B19** can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients; treatment with immunoglobulin has been reported to be successful.

Infection with a polyomavirus (JC virus)[1,2] can cause **progressive multifocal leukoencephalopathy**. Although no treatment has been consistently successful,[1] prolonged survival has been reported in patients receiving interferon alfa[3] and in those receiving HAART.[4-6] Cidofovir may be of benefit in patients unresponsive to HAART.[7,8] Rarely, JC virus, and much more commonly a related polyomavirus, BK virus,[9] have been associated with **polyomavirus-associated nephropathy** (PVAN) in renal transplant patients, a condition associated with poor prognosis for graft survival. BK virus is also associated with haemorrhagic cystitis after stem-cell transplantation.[10] Cidofovir[11] has been investigated for management of BK virus infections.

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Influenza

Influenza is an acute respiratory-tract infection caused by RNA viruses of the family Orthomyxoviridae. Three types of influenza virus, A, B, and C, have been classified. Type A causes most infections in man; type B causes a similar though possibly milder infection than type A; type C generally only causes mild infection. Epidemic influenza is usually caused by the type A influenza virus. Outbreaks of influenza due to the type A virus occur in most years while those due to the type B virus tend to occur at intervals of several years. Influenza viruses are antigenically labile with the principal surface antigens, haemagglutinin and neuraminidase, undergoing frequent changes. Major changes (antigenic shifts) in these surface antigens occur periodically and are responsible for the emergence of the subtypes of virus which may cause pandemic influenza; minor changes (antigenic drift) occur more frequently and are responsible for the annual epidemic outbreaks of influenza.

Influenza is transmitted from person to person in respiratory droplets with an incubation period of 1 to 2 days. Infection with influenza A or B virus usually lasts for about 1 to 2 weeks and is characterised by sudden onset of fever, chills, headache, malaise, myalgia, dry cough, nasal obstruction, and a dry or sore throat. Infections are usually acute but self-limiting and persons with pre-existing immunity, or those who have received influenza vaccine, have less severe symptoms. Complications that may occur in the course of infection include primary viral pneumonia, secondary bacterial pneumonia, croup, exacerbation of asthma or chronic bronchitis, myositis, Reye's syndrome, and the toxic shock syndrome. Patients at high risk of complications include the elderly, children less than 5 years of age and particularly those less than 2 years of age, persons 18 years of age or less who are receiving long-term aspirin therapy, those who are morbidly obese, women who are pregnant or up to 2 weeks postpartum, persons with haemoglobinopathies, immunocompromised individuals, and those with heart disease, chronic chest disease, metabolic disorders, chronic renal disease, chronic liver disease, and certain neurological disorders.

Since 1997, infection of humans with avian influenza virus H5N1 (so-called 'bird flu') has been reported, initially in Hong Kong. Avian influenza may cause severe illness and is associated with high mortality. Since then cases have also been reported in other Asian countries and in the near East. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic.[1,2] In April 2009 an influenza outbreak in humans, first detected in Mexico, and termed pandemic (H1N1) 2009 influenza (previously referred to as novel influenza A (H1N1) and also known as swine flu), was caused by a new strain of influenza A virus, subtype H1N1. Infections had been reported worldwide and on 11th June 2009 WHO declared a worldwide pandemic. Because there was little or no pre-existing immunity to the virus the impact of the infection has occurred in a wider age range than seasonal influenza (particularly children and young adults). Additionally, it can infect the lower respiratory tract and cause rapidly progressive pneumonia especially in children and young to middle-aged adults. Although most patients have a milder disease and recover without antiviral treatment or medical care, severe complications including fatal outcomes have occurred. In those who required hospitalisation, more than half had underlying health conditions or weak immune systems. However, about a third of those with very severe illness admitted to an intensive care unit were previously healthy. By August 2010 epidemiological data indicated that the behaviour of the virus and its patterns of transmission were transitioning towards that of seasonal influenza and WHO announced that the (H1N1) 2009 influenza pandemic was over. However, sporadic and localised outbreaks may continue to cause serious disease in high-risk groups in the post-pandemic period.[3] WHO has developed detailed guidelines for the pharmacological management of avian influenza[4,5] and pandemic (H1N1) 2009 influenza[6,7] in humans. Similar guidelines for the management of an influenza pandemic have been developed in many countries.[8-10]

The most effective means of **preventing** influenza is to provide seasonal vaccination with *influenza vaccine* adjusted to take account of current antigenic drifts and shifts and to provide protection against both influenza A and B. WHO[11] recommends that elderly individuals and persons of any age who are considered to be at high risk of influenza-related complications should be vaccinated. Similar recommendations have been made in the UK[12] and USA.[13-15]

In healthy adults living in industrialised countries, protective efficacy of influenza vaccine is about 70 to 90%, and vaccination of the elderly living in the community reduces the number of hospitalisations by 25 to 39% and death by 39 to 75%.[11] Vaccines have been developed against 2009 pandemic (H1N1) influenza and avian influenza. For further information see under Influenza Vaccines, p. 2393.3.

Four antiviral drugs are available for the prevention of influenza: the M2 ion channel inhibitors, amantadine and rimantadine (adamantanes), and the neuraminidase inhibitors, oseltamivir and zanamivir. Antivirals appear to act independently of vaccination and provide additional barriers to the virus, but should not be used as a substitute for vaccination. They may be considered for postexposure prophylaxis, for seasonal prophylaxis in unvaccinated individuals at high risk, for persons who take care of those at

high risk, and in vaccinated individuals if an influenza outbreak occurs less than 2 weeks after vaccination with an inactivated vaccine, or if circulating influenza strains are thought to be different to the vaccine strain. Prophylaxis with antivirals may also be considered in vaccinated immunocompromised individuals whose antibody response to the vaccine is likely to be incomplete.[16,17] Postexposure prophylaxis should be started within 48 hours of the most recent exposure and is given for no more than 10 days.[18] Preexposure prophylaxis should be given for the duration of time when exposure might occur.[18]

Amantadine and *rimantadine*, when started before exposure and continued throughout the period of exposure, are effective in preventing influenza A in 60 to 90% of patients. They are ineffective against influenza B and therefore cannot be considered as a substitute for vaccination unless the vaccine is contra-indicated.[19] Additional problems with these drugs are the rapid development of viral resistance and subsequent spread of resistant virus to close contacts and the potential to cause serious CNS adverse effects. All strains of influenza anticipated to circulate during the 2011-2012 winter influenza seasons, including pandemic (H1N1) 2009 influenza strains, are resistant to adamantanes.[13]

A systematic review[20] of clinical studies in healthy adults and children indicated that both the neuraminidase inhibitors, *oseltamivir* and *zanamivir*, were effective in preventing and treating the symptoms of influenza A and B but they do not prevent pneumonia or stop influenza viruses from spreading from person-to-person.

In the USA, all 4 antiviral drugs are licensed for postexposure prophylaxis of influenza but only oseltamivir and zanamivir are recommended by the Advisory Committee on Immunization Practices[18] and the American Academy of Pediatrics.[13] In the UK, amantadine, zanamivir, and oseltamivir are licensed for prophylaxis, but only oseltamivir and zanamivir were recommended by NICE[21] for postexposure prophylaxis in those at high risk of complications of influenza. Recommendations did not favour use for seasonal prophylaxis of influenza.

For most people **treatment** of influenza is largely symptomatic and supportive. However, antivirals may be used for the treatment of vaccinated or unvaccinated individuals who develop symptoms. *Amantadine* and *rimantadine* have been shown to reduce the duration of uncomplicated influenza A infection when given within 48 hours of the onset of symptoms. These drugs may be considered for patients at high risk of complications. Treatment failures may be due to the rapid emergence of drug resistance.[19,22] They are not effective against influenza B,[16] seasonal influenza A (H3N2), or the pandemic (H1N1) 2009 strain.[6] *Oseltamivir* and *zanamivir* given within 48 hours of the onset of symptoms are active against both influenza A and B viruses and reduce the duration of uncomplicated influenza by about 1 day in healthy adults and adolescents. Data are limited and inconclusive for all 4 drugs in terms of efficacy when given to individuals at high risk of complications of influenza. Neuraminidase inhibitors have several advantages compared with amantadine, including reduced viral resistance, additional efficacy against influenza B, fewer adverse effects (including CNS effects), and reduction in clinical symptoms. Viral strains resistant to amantadine and rimantadine generally remain susceptible to neuraminidase inhibitors.[20,22]

In the UK, oseltamivir and zanamivir are recommended[23] for the treatment of those at risk of complications of influenza who can start treatment within 48 hours (or within 36 hours for zanamivir treatment in children) of the onset of symptoms. In the UK NICE does not recommend the use of amantadine for the treatment of influenza. In the USA, the Advisory Committee on Immunization Practices[18] and the American Academy of Pediatrics[13] recommend oseltamivir or zanamivir for treatment of acute illness caused by influenza A and B. Treatment is given for 5 days, although longer treatment regimens might be needed in hospitalised and immunosuppressed patients. Treatment should be started as soon as possible (ideally within 48 hours of illness onset), but treatment may still be of benefit in patients with severe or progressive illness and in hospitalised patients if started after 48 hours.[18] Neuraminidase inhibitors have also been effective against some strains of avian influenza in *animal* studies and may be considered for both prophylaxis and treatment of suspected infections,[2] although WHO recommends oseltamivir as the treatment of choice.[5]

Peramivir is a neuraminidase inhibitor that is given intravenously; although it has not yet been approved for marketing in the USA, the FDA has authorised its emergency use to treat certain adult and paediatric patients with suspected or laboratory-confirmed pandemic (H1N1) 2009 influenza, or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology. Laninamivir octanoate has been licensed for use in Japan. It is a long-acting neuraminidase inhibitor given as a single oral inhalation for the treatment of influenza. Intravenous formulations of oseltamivir and zanamivir are under investigation and available on a compassionate use basis in some countries for the treatment of influenza.[6,16]

Pregnant women with confirmed or suspected influenza should be given antiviral treatment as they are known to be at higher risk for complications from infection.[6,18] Oseltamivir is preferred for treatment of pregnant women although zanamivir might be preferred by some providers because of its limited systemic absorption.[18]

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Measles

Measles[1] is an acute viral illness caused by an RNA virus of the Morbillivirus genus and of the family Paramyxoviridae. It is a highly contagious disease spread by airborne droplets or direct contact with respiratory secretions of infected persons. Infection confers lifelong immunity.

The incubation period for measles is about 8 to 12 days followed by a prodromal phase lasting several days. This phase is usually characterised by malaise, fever, conjunctivitis, cough, rhinitis, congestion, and later Koplik's spots on the buccal mucosa. An erythematous, maculopapular rash appears towards the end of the prodromal phase, starting on the face and spreading over the trunk and limbs. Measles is generally benign and uncomplicated and recovery usually takes place during the week after the rash's appearance. However, severe disease and complications may develop and are more common in adults and in children who are undernourished or immunocompromised. Most complications occur when the measles virus further suppresses host immune responses, resulting in a reactivation of latent infections or superinfection by bacteria. Respiratory complications include giant cell pneumonia, bronchopneumonia, and laryngotracheobronchitis, while neurological complications include febrile seizures, acute encephalitis, progressive subacute encephalitis, and the more slowly progressive subacute sclerosing panencephalitis (SSPE) which may develop several years after the original measles infection. Other complications include diarrhoea, otitis media, thrombocytopenia with purpura and bleeding, hepatitis, myocarditis, pericarditis, and severe keratitis that may progress to blindness.

Measles can be **prevented** by active immunisation with measles vaccine, and measles immunoglobulins may be used for passive immunisation against measles. Normal immunoglobulins may be used to prevent, or possibly modify, an attack of measles in those at risk of developing severe or fatal disease such as immunocompromised patients.

Measles usually requires only symptomatic and supportive **treatment** such as antipyretics and fluid replacement. *Vitamin A* treatment for children with measles in developing countries has been associated with a significant reduction in mortality (see p. 2100.3). A systematic review of randomised studies concluded that a dose of 200 000 units of vitamin A given on 2 consecutive days reduced mortality in children under 2 years with measles.[2] WHO recommends that supplementary vitamin A be given to all children with measles in developing countries in order to prevent keratitis and blindness. A recent review has suggested that prophylactic antibacterials may be of benefit in preventing complications such as pneumonia, purulent otitis media, and tonsillitis in children with measles but of no benefit for conjunctivitis or gastroenteritis;[3] evidence from earlier reviews did not support such use.[4,5] However, prompt antibacterial therapy should be given to those patients who develop keratitis, otitis media, or pneumonia. There appears to be no good evidence for the use of antivirals, although there are case reports of ribavirin being used to treat severely affected and immunocompromised adults with acute measles[6] or patients with subacute sclerosing panencephalitis (intravenous ribavirin plus intrathecal high-dose interferon alfa[7] or intraventricular ribavirin[8]). No controlled studies have been conducted and the use of ribavirin should be considered experimental.

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Respiratory syncytial virus infection

Respiratory syncytial virus (RSV) is an RNA virus of the family Paramyxoviridae and occurs worldwide. RSV is a prominent cause of respiratory infections in infants and young children and is generally confined to the respiratory tract. However, disease may occur at any age, and it has been recognised as a cause of morbidity and mortality among the elderly,[1] as well as among children and adults with compromised cardiac, respiratory, or immune systems. RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated environmental surfaces. RSV infection is highly contagious and may result in extensive nosocomial transmission. RSV outbreaks tend to occur annually, usually from late autumn through to early spring.

Primary infection in infants and young children is characterised by fever, cough, runny or congested nose, vomiting, and sometimes wheezing. During the primary infection up to 50% of infants develop lower respiratory-tract disease, most commonly bronchiolitis and pneumonia, and about 1 to 2% of these infants may require hospitalisation. Most infants needing hospitalisation are less than 6 months old or at risk of severe infection, for example because of a history of prematurity, or pre-existing cardiac or respiratory diseases or immunodeficiency. Otitis media and persistent wheezing are common complications of RSV infection in infants and young children. RSV

infection may trigger acute respiratory distress syndrome and exacerbate pre-existing, underlying cardiac, renal (nephrotic syndrome), or lung (cystic fibrosis) disease. Acquired immunity does not prevent re-infection, although subsequent infections are typically milder.

The **management** of mild RSV infection in infants and children[2-7] consists of supportive care such as fever control and adequate hydration. Children with more severe lower respiratory-tract disease may require hospitalisation for supplementary oxygen. Measures to limit the spread of infection in hospitals and institutions are important. Pharmacological therapies are of limited benefit. $Beta_2$-agonist *bronchodilators* are often used in the management of bronchiolitis even though systematic reviews and meta-analyses of studies have indicated only modest short-term benefit of clinical symptoms and no reduction in hospital admission rates, length of hospital stay, or improvement in oxygen saturation.[2,8] A review[9] of the use of the anticholinergic bronchodilator ipratropium bromide reported no proven efficacy. An evaluation of clinical studies[2] using nebulised or intravenous adrenaline to treat RSV infection has reported clinical benefit in some infants, as well as a reduction in hospital admission or stay. However, a systematic review[10] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients. If a bronchodilator or inhaled adrenaline is tried, it should be stopped if no response is evident after 1 or 2 treatments.[2,4]

Nebulised hypertonic *saline* is thought to increase clearance of mucus and a systematic review[11] of 4 randomised studies involving 254 infants up to 24 months of age suggested that nebulised 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score of acute viral bronchiolitis.

Systemic *corticosteroids* are also widely used despite a lack of documented clear benefit. A systematic review[12] found little benefit in terms of length of hospital stay or admission rate and no evidence of improvement in clinical scores, respiratory rate, or oxygen saturation when compared with placebo. Although a later study[13] found that a 3-day course of oral prednisolone given to children aged 6 to 35 months with respiratory distress reduced disease severity, length of hospital stay, and the duration of symptoms another[14] showed that a single oral dose of dexamethasone was of no benefit in infants with moderate to severe bronchiolitis. A double-blind, placebo-controlled study[15] in 800 infants with bronchiolitis suggested that treatment with oral dexamethasone plus nebulised epinephrine might significantly reduce hospital admissions. The routine use of systemic corticosteroids is not recommended by expert groups.[4,5] *Inhaled corticosteroids* given during the initial acute phase of bronchiolitis did not prevent post-bronchiolitic wheezing.[16]

Ribavirin is the only antiviral drug that has been licensed for the treatment of infants and children with severe RSV bronchiolitis (and it is only available in some countries). Although some studies with aerosolised ribavirin have shown some clinical benefit in infants with lower respiratory-tract RSV infection, days of hospitalisation and short-term outcomes have not been affected.[2] Due to the small number of patients enrolled in these studies, evaluation of the effects has been difficult. Also, there are some difficulties in giving the drug, and concerns about occupational health and safety, and the high cost. Routine use is not recommended;[4,5] but it may be used for selected infants and children at risk of severe disease and complications. If used, ribavirin should be started early in the course of the disease.[2-4]

Antibacterials, although often used in the management of bronchiolitis, are not routinely recommended.[4,5] The results from three small studies[17-19] suggest that *surfactant* may reduce duration of ventilation and length of intensive care stay.

Prevention of RSV infection involves good infection control practices and use of *RSV immunoglobulin* and a human monoclonal antibody to RSV, *palivizumab*. Both RSV immunoglobulin and palivizumab can be given during an RSV outbreak to prevent serious complications of infection in infants and children considered at high risk. The efficacy of RSV immunoglobulin[20] and palivizumab[21] were tested in randomised, placebo-controlled clinical studies involving high-risk infants and children (history of prematurity or with bronchopulmonary dysplasia). A 41% overall reduction in hospital admissions was reported in those given RSV immunoglobulin prophylaxis. Prophylaxis with palivizumab resulted in a 55% overall reduction in hospitalisation; reduction rates were 39% and 78% in those with and without bronchopulmonary dysplasia respectively. Respiratory severity scores, hospital days, days of oxygen requirement, and the rate of intensive care admission were also significantly lower in the palivizumab group than for the placebo group. Prophylaxis with palivizumab was also found to reduce post-bronchiolitic wheezing in premature infants.[22] It is recommended by some expert groups for prophylaxis in infants and children at high risk of severe RSV infections.[4,5,23] Vaccines to prevent RSV infection are currently under development.

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SARS

Severe acute respiratory syndrome (SARS)[1,2] is a respiratory illness caused by a coronavirus (SARS-CoV). SARS presents mainly in previously healthy adults although there have been some cases reported in children. SARS-CoV is transmitted by contact or droplets and transmission mainly occurs during the second week of illness. The incubation period for SARS is usually 2 to 10 days but may be as long as 16 days. The disease manifests initially as flu-like prodromal symptoms, usually characterised by fever, malaise, myalgia, headache, and rigors. Cough (initially dry), dyspnoea, and diarrhoea may be present in the first week but are more commonly present in the second week of illness. Severe cases develop rapidly progressive respiratory distress and hypoxia and up to about 20% of patients may require intubation or mechanical ventilation. About 20% of patients develop large volume, watery diarrhoea. The overall fatality rate during the 2002–2003 SARS outbreak was about 9.5%.

There is currently no consensus on the optimal treatment for SARS and treatment recommendations are based on the experience gained during the 2002–2003 SARS outbreak. Guidelines for the **surveillance and management** of SARS have been developed by WHO.[3] In the UK guidelines[4] have been issued for the hospital management of adults with SARS, and others have also been developed by clinicians involved in the SARS outbreak in Hong Kong.[5] Because SARS is indistinguishable from pneumonia caused by viral and bacterial pathogens, empirical antibacterial treatment in accordance with local guidelines for severe community-acquired pneumonia (p. 200.1) is recommended. Fluids and oxygen therapy should be given as required. Other treatments tried have included corticosteroids, ribavirin, interferons, normal immunoglobulins, and the co-formulated HIV-protease inhibitor ritonavir-boosted lopinavir. Corticosteroids, usually with ribavirin, were widely used and the timely use of high-dose corticosteroids may decrease fever, improve radiographic appearances, and reduce oxygen requirements.[6-8] There is, however, concern that high-dose and long-term use of corticosteroids may suppress the patient's immune system resulting in increased viral replication and possible bacterial or fungal super-infection. The UK guidelines recommend that their use be considered in moderate doses in severely ill patients with increased oxygen requirements.[4] Additionally there is no convincing clinical evidence that the use of ribavirin alters clinical outcome and the UK guidelines state that its routine use is not recommended.[4] Although interferon beta shows greater *in-vitro* antiviral activity against SARS-CoV, most experience during the 2002–2003 outbreak was with interferon alfa with or without normal immunoglobulins.[6] An open study[9] using interferon-alfacon-1 and high-dose pulse methylprednisolone reported more rapid improvement in radiographic appearance and oxygenation than corticosteroids alone. Better clinical improvement was reported in patients treated with daily interferon alfa plus high-dose corticosteroids than in those given interferon plus low-dose or limited corticosteroids.[8] The UK guidelines state that no recommendation can be given regarding the use of interferons.[4] Although normal immunoglobulins have been used in SARS their efficacy cannot be established as they were usually given with other therapies.[6] A preliminary open study[10] with ritonavir-boosted lopinavir in 41 patients with probable SARS and receiving the local standard treatment of ribavirin and corticosteroids, reported an improved outcome at 21 days and reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections. Chloroquine and niclosamide have both been reported to have some activity against the virus *in vitro*,[11] but have not been tried clinically. Newer antivirals specific for coronaviruses[12,13] and vaccines against SARS-CoV[14] have been investigated.

1. Peiris JSM, *et al.* The severe acute respiratory syndrome. *N Engl J Med* 2003; **349:** 2431–41.
2. Christian MD, *et al.* Severe acute respiratory syndrome. *Clin Infect Dis* 2004; **38:** 1420–7.
3. WHO. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS): updated recommendations October 2004. Available at: http://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1.pdf (accessed 03/04/08)
4. Lim WS, *et al.* The British Thoracic Society, the British Infection Society, and the Health Protection Agency. Hospital management of adults with severe acute respiratory syndrome (SARS) if SARS re-emerges—updated 10 February 2004. *J Infect* 2004; **49:** 1–7. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Severe%20Acute%20Resp%20Syndrome/Guidelines/sars0304.pdf (accessed 03/04/08)
5. So LK-Y, *et al.* Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet* 2003; **361:** 1615–17.
6. Kamps BS, Hoffmann, eds. *SARS Reference—10/2003.* 3rd ed. Available at: http://www.sarsreference.com/sarsreference.pdf (accessed 03/04/08)
7. Sung JJY, *et al.* Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* 2004; **59:** 414–20.
8. Zhao Z, *et al.* Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003; **52:** 715–20.
9. Loutfy MR, *et al.* Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA* 2003; **290:** 3222–8.
10. Chu CM, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:** 252–6.
11. Wong SS, Yuen KY. The management of coronavirus infections with particular reference to SARS. *J Antimicrob Chemother* 2008; **62:** 437–41.
12. Tong TR. Therapies for coronaviruses. Part I of II—viral entry inhibitors. *Expert Opin Ther Pat* 2009; **19:** 357–67.
13. Tong TR. Therapies for coronaviruses. Part 2: Inhibitors of intracellular life cycle. *Expert Opin Ther Pat* 2009; **19:** 415–31.
14. Roper RL, Rehm KE. SARS vaccines: where are we? *Expert Rev Vaccines* 2009; **8:** 887–98.

Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Anogenital warts are known as condylomata acuminata. Treatment generally relies on some form of local tissue destruction (see p. 1689.3). Interferons have also been used (see p. 992.1).

Abacavir *(BAN, rINN)*

Abacavirum; Abakaviiri; Abakavir; Abakawir; Абакавир.

{(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl}methanol.

$C_{14}H_{18}N_6O$=286.3

CAS — 136470-78-5.

ATC — J05AF06.

ATC Vet — QJ05AF06.

UNII — WR2TIP26VS.

NOTE. The code 1592U89 has been applied to abacavir but is more properly reserved for abacavir sulfate.

Abacavir Succinate *(BANM, USAN, rINNM)*

Abacavir, Succinate d'; Abacavir, succinato de; Abacaviri Succinas; Succinato de abacavir; Абакавира Суксинат.

$C_{14}H_{18}N_6O.C_4H_6O_4$=404.4

CAS — 168146-84-7.

ATC — J05AF06.

ATC Vet — QJ05AF06.

UNII — 40FH6D8CHK.

NOTE. The code 1592U89 has been applied to abacavir succinate but is more properly reserved for abacavir sulfate.

Abacavir Sulfate *(BANM, USAN, rINNM)*

1592U89; Abacavir, Sulfate d'; Abacavir, sulfato de; Abacavir Sulphate; Abacaviri Sulfas; Sulfato de abacavir; Абакавира Сульфат.

$(C_{14}H_{18}N_6O)_2.H_2SO_4$=670.8

CAS — 188062-50-2.

ATC — J05AF06.

ATC Vet — QJ05AF06.

UNII — J220T4J9Q2.

NOTE. The code 1592U89 and its abbreviated form, 1592, have also been applied to abacavir and abacavir succinate.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Abacavir Sulfate). A white or almost white powder. Soluble in water; practically insoluble in alcohol and in dichloromethane.

USP 36: (Abacavir Sulfate). A white to off-white powder. Soluble in water, in absolute alcohol, in methylalcohol, and in ethyl acetate.

Uses and Administration

Abacavir is a nucleoside reverse transcriptase inhibitor with antiretroviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when abacavir is used alone, and it is therefore used with other antiretrovirals.

Abacavir is given orally as the sulfate but doses are expressed in terms of the base; 1.17 g of abacavir sulfate is equivalent to about 1 g of abacavir. The adult dose is 300 mg twice daily or 600 mg once daily. For details of doses in children, see below. Doses should be reduced in patients with hepatic impairment (see below).

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing abacavir in combination with lamivudine and with lamivudine and zidovudine are available in some countries.

Reviews.

1. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; **60:** 447–79.
2. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; **65:** 285–302.
3. Castillo SA, *et al.* Long-term safety and tolerability of the lamivudine/abacavir combination as components of highly active antiretroviral therapy. *Drug Safety* 2006; **29:** 811–26.
4. Shey M, *et al.* A combination drug of abacavir-lamivudine-zidovudine (Trizivir) for treating HIV infection and AIDS. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 05/10/09).
5. Sivasubramanian G, *et al.* Abacavir/lamivudine combination in the treatment of HIV: a review. *Ther Clin Risk Manag* 2010; **6:** 83–94.

Administration in children. For the treatment of HIV infection in children 3 months of age and older, abacavir may be given orally as a tablet or solution with other antiretroviral drugs. Doses are based on body-weight:

- 14 to 21 kg: 150 mg (half a tablet) twice daily
- 22 to 29 kg: 150 mg (half a tablet) in the morning and 300 mg (1 tablet) in the evening
- 30 kg or more: 300 mg (1 tablet) twice daily

or

- the solution may be given in a dose of 8 mg/kg twice daily to a maximum dose of 300 mg twice daily

Administration in hepatic impairment. Abacavir should not be used in patients with moderate to severe hepatic impairment, although reduced oral doses of 200 mg twice daily may be given to patients with mild impairment (Child-Pugh score 5 to 6).

Adverse Effects

The most significant adverse effects associated with antiretroviral regimens containing abacavir are severe and sometimes fatal hypersensitivity reactions that may occur especially (but not exclusively) during the first 6 weeks of treatment, or during intermittent therapy (see also below). Symptoms of hypersensitivity often include fever, rash, cough, dyspnoea, lethargy, malaise, headache, myalgia, and gastrointestinal disturbances, particularly nausea and vomiting, diarrhoea, and abdominal pain. Anaphylaxis has occurred. Caution is needed as hypersensitivity may be misdiagnosed as influenza, respiratory disease, or gastroenteritis. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Other adverse effects associated with abacavir include pancreatitis and raised liver enzyme values. Lactic acidosis, sometimes fatal and usually associated with severe hepatomegaly and steatosis, has been reported in patients receiving NRTIs, but is thought to be less likely with abacavir than with others such as didanosine, stavudine, or zidovudine.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including abacavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, although the risk associated with abacavir use is relatively low. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the heart. For the possible risk of myocardial infarction in patients taking abacavir, see Effects on the Heart under Adverse Effects of Zidovudine, p. 1025.2.

Effects on the skin. Stevens-Johnson syndrome occurring in a patient receiving antiretroviral therapy with abacavir, lamivudine, and zidovudine was probably associated with abacavir.[1] Resolution occurred upon stopping antiretroviral therapy and the condition did not recur upon rechallenge with an alternative regimen also containing lamivudine and zidovudine.

1. Bossi P, *et al.* Stevens-Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; **35:** 902.

Hypersensitivity. Hypersensitivity reactions occur in about 5% of patients starting treatment with abacavir,[1,2] generally within the first 6 weeks.[2] Symptoms typically occur suddenly and worsen with each consecutive abacavir dose.[2] Re-starting abacavir in a patient with a history of hypersensitivity syndrome can cause severe, rapidly progressive, and potentially fatal reactions.

Risk of developing hypersensitivity to abacavir appears to be related to race, and history of antiretroviral use; it is thought to be lower in antiretroviral-experienced patients, and those of African descent.[1,2] Carriage of the major histocompatibility complex class I allele HLA-B(*)5701 has been found to be the most significant predictor of whether or not a patient will be hypersensitive to abacavir.[2] The multicentre PREDICT-1 study[3] confirmed that prospective HLA-B(*)5701 screening was effective in reducing the incidence of abacavir hypersensitivity reaction.

1. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002; **34:** 1137–42.
2. Hughes CA, *et al.* Abacavir hypersensitivity reaction: an update. *Ann Pharmacother* 2008; **42:** 387–96.
3. Mallal S, *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358:** 568–79.

Precautions

Patients considered to be at increased risk for an abacavir hypersensitivity reaction are those that carry the human leucocyte antigen HLA-B(*)5701 allele; screening patients for this allele before starting treatment with abacavir has been shown to reduce the risk of hypersensitivity reactions. Routine screening of all patients before starting treatment with an abacavir-containing product is therefore recommended including in those who tolerated previous treatment with abacavir but have unknown HLA-B(*)5701 status. Abacavir should be stopped immediately if symptoms associated with hypersensitivity occur and should *never be restarted* in patients who have stopped therapy due to a hypersensitivity reaction. Patients should be closely monitored for signs of hypersensitivity during the first 2 months of treatment, although such reactions can occur at any time. Patients restarting therapy after an interruption are at particular risk even if they have not previously had symptoms of hypersensitivity. Since intermittent therapy may increase the risk of reactions patients should be advised of the importance of regular dosing.

Although the suggestion in some studies that use of abacavir in the previous 6 months was associated with an increased risk of myocardial infarction does not seem to have been borne out (see Effects on the Heart under Adverse Effects of Zidovudine, p. 1025.2), underlying risk of cardiovascular disease should be considered and efforts made to minimise risk factors.

Abacavir should not be used in patients with moderate to severe hepatic impairment, and should be used with caution and reduced doses in those with lesser degrees of impairment and those with risk factors for liver disease. Treatment should be stopped if liver function deteriorates rapidly or if hepatomegaly or unexplained metabolic acidosis develop.

Abacavir should be avoided in patients with end-stage renal disease.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies abacavir as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Use of alcohol with abacavir may result in decreased elimination of abacavir and consequent increases in exposure. Abacavir increases the systemic clearance of oral methadone and patients should be monitored for signs of withdrawal symptoms. The dose of methadone may need to be increased in some patients.

Alcohol. References.

1. McDowell JA, *et al.* Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000; **44:** 1686–90.

Antiviral Action

Abacavir is converted intracellularly in stages to its active form carbovir triphosphate. This halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

References.

1. Faletto MB, *et al.* Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. *Antimicrob Agents Chemother* 1997; **41:** 1099–1107.

Pharmacokinetics

Abacavir is rapidly absorbed after oral doses with a bioavailability of about 80%. Absorption is delayed slightly by food but the extent is unaffected. Abacavir crosses the blood-brain barrier. It is about 50% bound to plasma proteins. The elimination half-life is about 1.5 hours after a single dose. Abacavir undergoes intracellular metabolism to the active antiviral metabolite carbovir triphosphate. Elimination is via hepatic metabolism mainly by alcohol dehydrogenase and by glucuronidation and the metabolites are excreted mainly in the urine. There is no significant metabolism by hepatic cytochrome P450 isoenzymes.

References.

1. Yuen GJ, *et al.* A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; **47:** 351–71.
2. Sleasman JW, *et al.* Abacavir pharmacokinetics during chronic therapy in HIV-1-infected adolescents and young adults. *Clin Pharmacol Ther* 2009; **85:** 394–401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Filabac; Finecil; Panka; Plusabcir; Zepril; Ziagenavir; ***Austral.***: Ziagen; ***Austria***: Ziagen; ***Belg.***: Ziagen; ***Braz.***: Ziagenavir; ***Canad.***: Ziagen; ***Chile***: Ziagen; ***China***: Ziagen (赛进); ***Cz.***: Ziagen; ***Denm.***: Ziagen; ***Fin.***: Ziagen; ***Fr.***: Ziagen; ***Ger.***: Kivexa; Ziagen; ***Gr.***: Ziagen; ***Hong Kong***: Ziagen; ***Hung.***: Ziagen; ***India***: Abamune; Abec; ***Irl.***: Ziagen; ***Israel***: Ziagen; ***Ital.***: Ziagen; ***Mex.***: Vurtas; Ziagenavir; ***Neth.***: Ziagen; ***Norw.***: Ziagen; ***NZ***: Ziagen; ***Pol.***: Ziagen; ***Port.***: Ziagen; ***Rus.***: Ziagen (Зиаген); ***S.Afr.***: Ziagen; ***Singapore***: Ziagen; ***Spain***: Ziagen; ***Swed.***: Ziagen; ***Switz.***: Ziagen; ***Thai.***: Ziagenavir; ***Turk.***: Ziagen; ***UK***: Ziagen; ***USA***: Ziagen; ***Venez.***: Ziagen.

Multi-ingredient Preparations. ***Arg.***: Kivexa; Tricivir; Trilaxis; Trivudin; Zidomuv; ***Austral.***: Kivexa; Trizivir; ***Austria***: Kivexa; Trizivir; ***Belg.***: Kivexa; Trizivir; ***Braz.***: Kivexa; ***Canad.***: Kivexa; Trizivir; ***Chile***: Kivexa; Tricivir; ***China***: Trizivir (三协唯); ***Cz.***: Kivexa; Trizivir; ***Denm.***: Kivexa; Trizivir; ***Fin.***: Kivexa; Trizivir; ***Fr.***: Kivexa; Trizivir; ***Ger.***: Trizivir; ***Gr.***: Kivexa; Trizivir; ***Hong Kong***: Kivexa; Trizivir; ***Hung.***: Kivexa; Trizivir; ***Irl.***: Kivexa; Trizivir; ***Israel***: Kivexa; Trizivir; ***Ital.***: Kivexa; Trizivir; ***Mex.***: Kivexa; Trizivir; ***Neth.***: Kivexa; Trizivir; ***Norw.***: Kivexa; Trizivir; ***NZ***: Kivexa; Trizivir; ***Pol.***: Kivexa; Trizivir; ***Port.***: Kivexa; Trizivir; ***Rus.***: Kivexa (Кивекса); Trizivir (Тризивир); ***S.Afr.***: Kivexa; Sonke Abaclamizid; Trizivar; ***Singapore***: Kivexa; Trizivir; ***Spain***: Kivexa; Trizivir; ***Swed.***: Kivexa; Trizivir; ***Switz.***: Kivexa; Trizivir;

Thai.: Kivexa; ***Turk.***: Trizivir; ***UK***: Kivexa; Trizivir; ***USA***: Epzicom; Trizivir; ***Venez.***: Trizivir.

Pharmacopoeial Preparations
BP 2014: Abacavir Oral Solution; Abacavir Tablets;
USP 36: Abacavir Oral Solution; Abacavir Tablets.

Aciclovir *(BAN, rINN)*

Aciclo guanosina; Aciclovirum; Aciklovir; Aciklovír; Acikloviras; Acycloguanosine; Acyclovir (USAN); Acyklowir; Asikloviiri; Asiklovir; BW-248U; Ацикловир.
9-[(2-Hydroxyethoxy)methyl]guanine; 2-Amino-1,9-dihydro-9-(2-hydroxyethoxymethyl)-6*H*-purin-6-one.
$C_8H_{11}N_5O_3$=225.2
CAS — 59277-89-3.
ATC — D06BB03; J05AB01; S01AD03.
ATC Vet — QD06BB03; QJ05AB01; QS01AD03.
UNII — X4HES1O11F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Aciclovir). A white to almost white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in heptane; soluble in dilute solutions of alkali hydroxides and mineral acids.

USP 36: (Acyclovir). A white to off-white crystalline powder. Slightly soluble in water; insoluble in alcohol; soluble in dilute hydrochloric acid. Store in airtight containers. Protect from light and moisture.

Aciclovir Sodium *(BANM, rINNM)*

Aciclovir sódico; Aciclovir Sodique; Acyclovir Sodium (USAN); Natrii Aciclovirum; Натрий Ацикловир.
$C_8H_{10}N_5NaO_3$=247.2
CAS — 69657-51-8.
ATC — D06BB03; J05AB01; S01AD03.
ATC Vet — QD06BB03; QJ05AB01; QS01AD03.
UNII — 927L42J563.

Incompatibility. Aciclovir is reported to be incompatible with foscarnet.[1,2] Visual incompatibility has also been reported[3] on simulated Y-site injection between aciclovir and ciclosporin, diphenhydramine, gentamicin, granisetron, or metoclopramide.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47:** 2075–7.
3. Canann D, *et al.* Visual compatibility of iv medications routinely used in bone marrow transplant recipients. *Am J Health-Syst Pharm* 2009; **66:** 727–9. Correction. *ibid.*; 1431.

Stability. A study[1] found that aciclovir sodium solutions prepared with sodium chloride 0.9% and with dextrose 5% were stable for 7 and 21 days respectively when stored at 23 degrees. Solutions stored at 4 degrees were found to be stable for 35 days although subsequent storage at room temperature produced irreversible precipitation. Precipitation may also occur when freshly prepared solutions are refrigerated but the precipitate redissolves at room temperature. US licensed product information recommends that diluted solutions be used within 24 hours of preparation.

1. Zhang Y, *et al.* Stability of acyclovir sodium 1, 7, and 10 mg/mL in 5% dextrose injection and 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1998; **55:** 574–7.

Uses and Administration

Aciclovir is a synthetic purine nucleoside analogue structurally related to guanine. It is used mainly for the treatment and prophylaxis of viral infections due to herpes simplex virus types 1 and 2 (p. 955.2) and varicella-zoster virus (herpes zoster and chickenpox—p. 956.2).

Herpes simplex infections, including herpes keratitis, herpes labialis, and genital herpes, respond to aciclovir by the intravenous, oral, or topical route, given as soon as possible after symptoms appear. Both initial and recurrent infections can be successfully treated. Prolonged treatment can reduce the incidence of recurrence which is particularly important in immunocompromised patients. However, when prolonged treatment is withdrawn, infections may recur. In addition, prolonged or repeated courses in severely immunocompromised patients may result in the selection of virus strains with reduced sensitivity and patients may, therefore, not respond to continued treatment.

Aciclovir also improves the healing of herpes zoster lesions and reduces acute pain when given intravenously or orally; use to prevent postherpetic neuralgia is controversial (see p. 10.3). Beneficial effects may be more marked in immunocompromised patients.

When used by ***intravenous infusion*** aciclovir is given as the sodium salt but doses are expressed in terms of the base. Aciclovir sodium 1.1 g is equivalent to about 1 g of aciclovir. Solutions for infusion are usually prepared to give a concentration of aciclovir of 25 or 50 mg/mL; this must then be further diluted to a final concentration not greater than about 5 mg/mL (0.5%) and given over 1 hour. Alternatively, a solution containing 25 mg/mL may be given by injection using a controlled-rate infusion pump, over 1 hour. In obese patients the dose should be calculated on the basis of ideal body-weight, to avoid overdosage.

For **herpes simplex infections** in the *immunocompromised*, and for severe initial *genital herpes*, or for *prophylaxis* of herpes simplex infections in *immunocompromised* patients the dose by the intravenous route is 5 mg/kg given every 8 hours, and recommended periods of treatment range from 5 to 7 days. A higher dose of 10 mg/kg every 8 hours is given in the treatment of *herpes simplex encephalitis*, and treatment is usually continued for 10 days.

For **varicella-zoster infections** in immunocompetent patients, a dose of 5 mg/kg every 8 hours may also be given. In *immunocompromised* patients the higher dose of 10 mg/kg every 8 hours should be used.

Oral doses of aciclovir also vary according to indication. In **herpes simplex infections**:

- for treatment of *primary infections*, including genital herpes, the usual oral dose is 200 mg five times daily (usually every 4 hours while awake) for 5 to 10 days
- severely *immunocompromised* patients or those with *impaired absorption* may be given 400 mg five times daily for 5 days
- for *suppression* of recurrent herpes simplex in *immunocompetent* patients, the oral dose is 800 mg daily in two to four divided doses; dosage reduction to 400 to 600 mg daily can be tried. Higher doses of 1 g daily have also been used. Therapy should be interrupted every 6 to 12 months for reassessment of the condition
  Chronic suppressive treatment is not suitable for mild or infrequent recurrences of herpes simplex. In such cases *episodic treatment* of recurrences may be preferred; a dose of 200 mg five times daily for 5 days has been recommended, preferably begun during the prodromal period.
- for *prophylaxis* of herpes simplex in *immunocompromised* patients, the dose is 200 to 400 mg four times daily.

The usual oral dose of aciclovir for treatment of **chickenpox** is 800 mg four or five times daily for 5 to 7 days; for herpes zoster 800 mg five times daily may be given for 7 to 10 days.

For the treatment of recurrent **herpes labialis** in *immunocompetent* patients, aciclovir is available as a 50 mg mucoadhesive ***buccal*** tablet. One tablet should be applied as a single dose to the upper gum region within one hour of onset of prodromal symptoms. Once applied, the tablet gradually dissolves during the day; it should not be crushed, sucked, chewed, or swallowed.

In **herpes simplex infections of the skin**, including genital herpes and herpes labialis, ***topical treatment*** with an ointment or cream containing aciclovir 5% may be applied 5 or 6 times daily for periods of 5 to 10 days, preferably beginning in the prodromal period as soon as signs or symptoms occur. In herpes simplex **keratitis** a 3% eye ointment may be applied 5 times daily until 3 days after healing.

Doses should be reduced in *renal impairment* (see below).

For details of doses in children, see Administration in Children, below.

Reviews.
1. Wagstaff AJ, *et al.* Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 153–205.
2. Leflore S, *et al.* A risk-benefit evaluation of aciclovir for the treatment and prophylaxis of herpes simplex virus infections. *Drug Safety* 2000; **23:** 131–42.
3. Nasser M, *et al.* Acyclovir for treating primary herpetic gingivostomatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 29/10/09).

Administration in children. Aciclovir is licensed for use in infants and children for the treatment of herpes simplex and varicella-zoster infections, and for the prophylaxis of herpes simplex infections in the immunocompromised. It may be given by slow intravenous infusion over 1 hour, or orally.

Recommended ***intravenous doses*** vary according to country and age of the patient. They are generally given every 8 hours.

In the *UK* the 8-hourly dose for children aged 3 months to 12 years is calculated by body-surface. The usual course of treatment is 5 to 10 days:

- herpes simplex and varicella-zoster infections in immunocompetent patients: 250 mg/m^2
- varicella-zoster infection in immunocompromised children or those with herpes simplex encephalitis: 500 mg/m^2

In the *USA*, the 8-hourly intravenous dose for children aged 3 months to 12 years is calculated by body-weight:

- herpes simplex infections: 10 mg/kg for 7 days
- varicella-zoster infections in immunocompromised children: 20 mg/kg for 7 days
- herpes simplex encephalitis: 20 mg/kg for 10 days

In the *UK* and the *USA* the intravenous dose for neonates and infants up to 3 months of age is calculated by body-weight; an 8-hourly intravenous dose of 10 mg/kg may be given for the treatment of herpes simplex infections. Treatment for neonatal herpes simplex usually continues for 10 days. Higher intravenous doses of 20 mg/kg every 8 hours for 14 days (21 days for CNS involvement) have been recommended by the *BNFC* for the treatment of herpes simplex infection in neonates and children up to 3 months of age. Similarly, 10 to 20 mg/kg intravenously every 8 hours is also recommended, for at least 7 days, for the treatment of herpes zoster infection in this age group.

In the *UK* the following ***oral doses*** are permitted in the treatment of herpes simplex infections, and in the prophylaxis of herpes simplex infections in the immunocompromised:

- 2 years and over: usual adult dose (see above)
- under 2 years: half usual adult dose

In the *UK* and the *USA* the oral doses for the treatment of chickenpox are:

- over 2 years: 20 mg/kg, up to a maximum of 800 mg, four times daily for 5 days

Alternatively, the following oral doses may be used:

- under 2 years: 200 mg four times daily
- 2 to 5 years: 400 mg four times daily
- 6 years and over: 800 mg four times daily

Although not a licensed indication, in the UK the *BNFC* recommends that aciclovir may also be given for postexposure attenuation of chickenpox, where varicella-zoster immunoglobulin cannot be used, in children from 1 month to 18 years of age; a dose of 10 mg/kg 4 times daily for 7 days is suggested, starting 1 week after chickenpox exposure.

Administration in renal impairment. Doses of aciclovir should be reduced in renal impairment according to creatinine clearance (CC) and licensed product information gives the following guidance:

intravenous dosage:

- CC between 25 and 50 mL/minute: the interval between infusions may be increased to 12 hours
- CC 10 to 25 mL/minute: the interval between infusions may be increased to 24 hours
- CC less than 10 mL/minute: patients on *peritoneal dialysis* should receive half the usual appropriate dose given once every 24 hours; patients on *haemodialysis* should receive half the usual dose every 24 hours plus an extra half-dose after haemodialysis

oral dosage:

- CC less than 10 mL/minute: *herpes simplex infections*: 200 mg every 12 hours; *varicella-zoster infections*: 800 mg every 12 hours
- CC between 10 and 25 mL/minute: *varicella-zoster infections*: 800 mg three times daily every 8 hours

For critically ill patients receiving renal replacement therapy, the following aciclovir doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 5 to 10 mg/kg every 24 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 5 to 10 mg/kg every 12 to 24 hours
- intermittent haemodialysis: 2.5 to 5 mg/kg every 24 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Erythema multiforme. For patients with recurrent erythema multiforme (p. 1684.3) associated with herpes simplex infection a 5-day course of oral aciclovir at the start of the infection has been proposed to prevent the subsequent skin lesions.[1] If this fails, a 6-month course of oral aciclovir has been found to be of benefit,[2] even if the association with herpes is not obvious. It should be noted, however, that erythema multiforme may occur as an adverse effect of systemic aciclovir.

1. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.
2. Tatnall FM, *et al.* A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol* 1995; **132:** 267–70.

HIV infection. Herpes simplex virus type 2 (HSV-2) seroprevalence among HIV-1 infected persons ranges from 50 to 90%. HSV-2 reactivations are common and often asymptomatic among HIV-1 infected persons. During HSV-2 reactivations plasma and genital HIV-1 levels increase and may increase HIV-1 transmissibility and disease progression. HSV-2 suppression has therefore been considered as a potential strategy to reduce HIV-1 viral load, slow HIV-1 disease progression, and possibly delay the need to start HAART.[1] Randomised studies[2-5] among

HIV-1 and HSV-2 co-infected persons not taking antiretroviral therapy (ART) and not severely immunocompromised found that standard HSV-2 suppressive therapy with oral aciclovir (400 mg twice daily) or oral valaciclovir (500 mg twice daily) for 8 to 12 weeks significantly reduced plasma and genital HIV-1 levels. However, another study[6] reported that standard suppressive treatment with oral aciclovir for 12 weeks had no effect on the rate of HIV genital shedding despite a reduction in genital HSV-2. A further study[7,8] in southern and east Africa in heterosexual, discordant (for HIV-1) couples where one partner was co-infected with HSV-2 and HIV-1, had a CD4 + count of 250 cells/microlitre or more, and was not taking ART, reported that standard daily suppressive treatment for HSV-2 with oral aciclovir, given for up to 24 months, reduced the risk of HIV-1 disease progression by 16% when compared with placebo treatment.[7] However, the incidence of transmission of HIV-1 to the previously uninfected sexual partner was not reduced.[8]

1. Tan DH, *et al.* Can herpes simplex virus type 2 suppression slow HIV disease progression: a study protocol for the valacyclovir in delaying antiretroviral treatment entry (VALIDATE) trial. *Trials* 2010; **11:** 113.
2. Nagot N, *et al.* Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007; **356:** 790–9.
3. Zuckerman RA, *et al.* Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. *J Infect Dis* 2007; **196:** 1500–8.
4. Baeten JM, *et al.* Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. *J Infect Dis* 2008; **198:** 1804–8.
5. Delany S, *et al.* Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. *AIDS* 2009; **23:** 461–9.
6. Cowan FM, *et al.* A randomised placebo-controlled trial to explore the effect of suppressive therapy with acyclovir on genital shedding of HIV-1 and herpes simplex virus type 2 among Zimbabwean sex workers. *Sex Transm Infect* 2008; **84:** 548–53.
7. Lingappa JR, *et al.* Daily acyclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet* 2010; **375:** 824-.33.
8. Celum C, *et al.* Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010; **362:** 427–39.

Adverse Effects

Aciclovir is generally well tolerated. When given intravenously as aciclovir sodium it may cause local reactions at the injection site with inflammation and phlebitis; these reactions may be associated with extravasation that can lead to tissue necrosis.

Renal impairment may be associated with systemic use of aciclovir in some patients; it is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. The risk of renal toxicity is increased by conditions favouring deposition of aciclovir crystals in the tubules such as when the patient is poorly hydrated or has existing renal impairment, or when the drug is given at a high dosage or by rapid or bolus injection. Some patients taking systemic aciclovir may have transient increases in blood concentrations of urea and creatinine although this is more acute with intravenous dosage.

Occasional adverse effects after systemic use include increased serum bilirubin and liver enzymes, haematological changes, rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), fever, headache, dizziness, and gastrointestinal effects such as nausea, vomiting, and diarrhoea. Hepatitis and jaundice have been reported rarely. Anaphylaxis and angioedema have occurred. Reversible neurological effects including lethargy, somnolence, confusion, hallucinations, agitation, tremors, psychosis, convulsions, and coma have been reported in a small number of patients, particularly in those given intravenous aciclovir and with predisposing factors such as renal impairment; these effects may be more marked in older patients. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, sometimes resulting in death, have occurred in immunocompromised patients given high parenteral doses of aciclovir. Accelerated diffuse hair loss has also been reported.

Topical application of aciclovir may produce transient stinging, burning, itching, or erythema. Eye ointments may occasionally produce transient stinging, superficial punctate keratopathy, blepharitis, or conjunctivitis.

Effects on the blood. There has been no evidence of bone-marrow toxicity in patients given aciclovir after bone marrow transplantation.[1,2] However, megaloblastic haematopoiesis was seen in the bone marrow of 3 patients given aciclovir for suspected or proven herpes simplex encephalitis.[3] There has also been a report of inhibition of human peripheral blood lymphocytes in samples taken from healthy subjects given aciclovir.[4]

1. Serota FT, *et al.* Acyclovir treatment of herpes zoster infections: use in children undergoing bone marrow transplantation. *JAMA* 1982; **247:** 2132–5.
2. Gluckman E, *et al.* Oral acyclovir prophylactic treatment of herpes simplex infection after bone marrow transplantation. *J Antimicrob Chemother* 1983; **12** (suppl B): 161–7.
3. Amos RJ, Amess JAL. Megaloblastic haemopoiesis due to acyclovir. *Lancet* 1983; **i:** 242–3.
4. Tauris P, *et al.* Evaluation of the acyclovir-induced modulation of the plaque-forming cell response of human peripheral blood lymphocytes. *J Antimicrob Chemother* 1984; **13:** 71–7.

Effects on the kidneys. Aciclovir is excreted mostly by the kidney, and reaches high concentrations in the tubular lumen, but is relatively insoluble in urine and may therefore cause intratubular precipitation of crystals in the kidney and renal damage which may result in acute renal failure within 24 to 48 hours. High doses, dehydration, or pre-existing renal impairment increase the risk of aciclovir-associated acute renal failure, which has been reported in 12 to 48% of patients in some series. Although usually asymptomatic there may be nausea, vomiting, and flank pain, together with haematuria and pyuria. Most patients recover on stopping the drug and rehydration, though some need temporary dialysis; use of a loop diuretic may be helpful in some cases. Slow infusion and adequate hydration can help to prevent crystal precipitation, and doses should be reduced in patients with underlying renal impairment.[1-3] An obese man developed acute renal failure after seven 1-g doses (calculated according to his actual body-weight) of intravenous aciclovir. Aciclovir distributes mainly into water and therefore dosing based on actual rather than ideal body-weight may result in a significant overdose and thereby increase the risk for renal impairment.[2]

There are also occasional reports of renal toxicity apparently unrelated to crystal precipitation.[4-6]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; **106:** 459–65.
2. Hernandez JO, *et al.* Acyclovir-induced renal failure in an obese patient. *Am J Health-Syst Pharm* 2009; **66:** 1288–91.
3. Fleischer R, Johnson M. Acyclovir nephrotoxicity: a case report highlighting the importance of prevention, detection, and treatment of acyclovir-induced nephropathy. *Case Report Med* 2010; **2010:** 602783.
4. Giustina A, *et al.* Low-dose acyclovir and acute renal failure. *Ann Intern Med* 1988; **108:** 312.
5. Eck P, *et al.* Acute renal failure and coma after a high dose of oral acyclovir. *N Engl J Med* 1991; **325:** 1178.
6. Johnson GL, *et al.* Acute renal failure and neurotoxicity following oral acyclovir. *Ann Pharmacother* 1994; **28:** 460–3.

Effects on the nervous system. Neurotoxicity, including tremor, confusion, myoclonus, agitation, lethargy, or hallucination, is an uncommon adverse effect of aciclovir, and may be hard to distinguish from progression of the underlying disease state. Renal impairment may increase the risk, although no clear relationship with peak plasma concentrations has been shown; cases are also more common in elderly patients and those taking other neurotoxic drugs.[1] Of 143 patients given aciclovir by intravenous infusion in doses ranging from 0.75 to 3.6 g/m^2 daily for the treatment of herpesvirus infections after bone marrow transplantation, 6 developed reversible neurological symptoms including tremor, agitation, nausea, lethargy, mild disorientation, autonomic instability, hemiparaesthesia, and slurred speech.[2] EEGs were diffusely abnormal in all 6. Symptoms improved in all patients on withdrawing aciclovir; reinstituting aciclovir in 2 produced a recurrence of symptoms. Concomitant therapy included irradiation and methotrexate intrathecally for all 6, interferon alfa for 3, and ciclosporin for 1. It has been suggested that if it is difficult to distinguish worsening encephalitis from aciclovir neurotoxicity, a trial of haemodialysis might be appropriate.[3] Development of neurotoxic symptoms has been reported[4] to be associated with increased concentrations of the metabolite 9-carboxymethoxymethylguanine in serum and CSF.

1. Ernst ME, Franey RJ. Acyclovir- and ganciclovir-induced neurotoxicity. *Ann Pharmacother* 1998; **32:** 111–13.
2. Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. *Ann Intern Med* 1983; **98:** 921–5.
3. Brady M, Main J. Aciclovir neurotoxicity is an important side effect of therapy in patients with renal impairment. *Clin Med* 2009; **9:** 630. Correction. *ibid.* 2010; **10:** 205.
4. Helldén A, *et al.* The aciclovir metabolite CMMG is detectable in the CSF of subjects with neuropsychiatric symptoms during aciclovir and valaciclovir treatment. *J Antimicrob Chemother* 2006; **57:** 945–9.

Effects on the skin. Vesicular or bullous lesions have been associated with intravenous use of aciclovir in patients thought to have herpes simplex encephalitis.[1,2] Careful evaluation is necessary to differentiate the reaction from herpetic lesions. Recall dermatitis in an area previously affected by herpes zoster lesions has also been associated with aciclovir.[3]

See also Hypersensitivity, below.

1. Buck ML, *et al.* Vesicular eruptions following acyclovir administration. *Ann Pharmacother* 1993; **27:** 1458–9.
2. Armingaud P, *et al.* Eruption bulleuse localisée après injection intraveineuse d'aciclovir: mécanisme toxique ou immunoallergique? *Ann Dermatol Venereol* 2000; **127:** 496–8.
3. Carrasco L, *et al.* Drug eruption secondary to aciclovir with recall phenomenon in a dermatome previously affected by herpes zoster. *Clin Exp Dermatol* 2002; **27:** 132–4.

Hypersensitivity. Hypersensitivity reactions,[1-3] including maculopapular rash and itching, anaphylaxis, and angioedema have been associated with the use of aciclovir. Cross-sensitivity to famciclovir[4] and to the prodrug valaciclovir[5,6] may occur; although some patients hypersensitive to aciclovir have been treated with famciclovir as an alternative.[7] Successful induction of tolerance to oral aciclovir has been described.[1,4]

1. Henry RE, *et al.* Successful oral acyclovir desensitization. *Ann Allergy* 1993; **70:** 386–8.
2. Schuster J, *et al.* Allergic drug eruption secondary to intravenous acyclovir. *Acta Derm Venereol* 2008; **88:** 196–8.
3. Jen SP, *et al.* Probable acyclovir-induced angioedema in a patient with HIV infection and suspected varicella-zoster virus encephalitis. *Am J Health-Syst Pharm* 2011; **68:** 2257–60.
4. Kawsar M, *et al.* Graded challenge in an aciclovir allergic patient. *Sex Transm Infect* 2001; **77:** 204–5.
5. Lammintausta K, *et al.* Rapid systemic valaciclovir reaction subsequent to aciclovir contact allergy. *Contact Dermatitis* 2001; **45:** 181.
6. Ebo DG, *et al.* Immediate allergy from valacyclovir. *Allergy* 2008; **63:** 941–2.
7. Bayrou O, *et al.* Famciclovir as a possible alternative treatment in some cases of allergy to acyclovir. *Contact Dermatitis* 2000; **42:** 42.

Vasculitis. Aciclovir has been associated with vasculitis. In one patient[1] it was one of many drugs given that may have caused a necrotising vasculitis. In another report an immunocompromised child with chickenpox given aciclovir by infusion developed a vasculitic rash which diminished on withdrawal of the drug.[2]

For a report of peripheral neuropathy associated with vasculitis due to the prodrug valaciclovir, see Effects on the Nervous System, p. 1021.3.

1. von Schulthess GK, Sauter C. Acyclovir and herpes zoster. *N Engl J Med* 1981; **305:** 1349.
2. Platt MPW, Eden OB. Vasculitis in association with chickenpox treatment in childhood acute lymphoblastic leukaemia. *Lancet* 1982; **ii:** 763–4.

Precautions

Systemic aciclovir should be used with caution and in reduced doses in patients with renal impairment (see Administration in Renal Impairment, p. 964.3). The elderly and patients with existing renal impairment should be closely monitored for neurological adverse effects. Adequate hydration should be maintained in patients given parenteral or high oral doses of aciclovir. Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir in the kidney; rapid or bolus injection should be avoided. The risk of renal impairment is increased by use with other nephrotoxic drugs. Doses of intravenous aciclovir based on actual body-weight may be excessive in obese patients, especially those with renal impairment; doses for obese patients should be calculated according to their ideal body-weight (see also under Effects on the Kidneys, above). Intravenous aciclovir should also be used with caution in patients with underlying neurological abnormalities, with significant hypoxia, or with serious hepatic or electrolyte abnormalities. In severely immunocompromised patients, prolonged or repeated courses of aciclovir may result in the selection of virus strains with reduced sensitivity; patients may, therefore, not respond to continued treatment.

Breast feeding. Aciclovir is distributed into breast milk[1-4] and in some instances concentrations are higher than in maternal serum.[1-3] Licensed product information reports that a maternal oral dose of 200 mg five times daily could expose a breast-fed infant to 300 micrograms/kg daily and advises caution when giving nursing mothers aciclovir. However, no adverse effects have been seen in breast-fed infants of mothers taking aciclovir, and the last available guidance from the American Academy of Pediatrics considered[5] that it was therefore usually compatible with breast feeding.

1. Lau RJ, *et al.* Unexpected accumulation of acyclovir in breast milk with estimation of infant exposure. *Obstet Gynecol* 1987; **69:** 468–71.
2. Meyer LJ, *et al.* Acyclovir in human breast milk. *Am J Obstet Gynecol* 1988; **158:** 586–8.
3. Bork K, Benes P. Concentration and kinetic studies of intravenous acyclovir in serum and breast milk of a patient with eczema herpeticum. *J Am Acad Dermatol* 1995; **32:** 1053–5.
4. Taddio A, *et al.* Acyclovir excretion in human breast milk. *Ann Pharmacother* 1994; **28:** 585–7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/04/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Pregnancy. The incidence of congenital abnormality and spontaneous fetal loss in 1246 cases of prenatal exposure to oral or intravenous aciclovir (as recorded by the International Acyclovir Pregnancy Registry between 1 June 1984 and 30 June 1998) did not significantly differ from

those in the general population.[1] A large population-based historical cohort study[2] of live-born infants in Denmark from January 1996 to September 2008 found exposure to oral aciclovir (1561 exposures), valaciclovir (229 exposures), or famciclovir (26 exposures) in the first trimester of pregnancy was not associated with an increased risk of major birth defects diagnosed within the first year of life. Forty of 1804 infants (2.2%) exposed to aciclovir, valaciclovir, or famciclovir in the first trimester were identified with a major birth defect compared with 19 920 of about 800 000 (2.4%) unexposed infants. Similarly, use of aciclovir cream in the first trimester of pregnancy was not associated with birth defects but there were too few exposures to penciclovir cream to evaluate its safety.

The Royal College of Obstetricians and Gynaecologists[3] recommends that systemic aciclovir may be given to pregnant women who present with a first episode of genital herpes, however, caution is advised when giving aciclovir before 20 weeks of gestation. Daily use over the last four weeks of pregnancy to reduce the risk of recurrence at term is, however, not routinely recommended. Due to an apparent increase in risk and severity of varicella pneumonitis in the latter half of pregnancy, the UK Advisory Group on Chickenpox[4] recommends oral aciclovir for all pregnant women with chickenpox who present within 24 hours of the onset of a rash if pregnancy is at more than 20 weeks of gestation.

1. Stone KM, *et al.* Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the International Acyclovir Pregnancy Registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol* 2004; **70:** 201–7.
2. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *J AMA* 2010; **304:** 859–66.
3. Royal College of Obstetricians and Gynaecologists. Green-top guideline no. 30: management of genital herpes in pregnancy (revised September 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT30GenitalHerpes2007.pdf (accessed 01/03/11)
4. Nathwani D, *et al.* Varicella infections in pregnancy and the newborn: a review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998; **36** (suppl 1): 59–71.

Sodium content. Each g of aciclovir sodium contains 4.05 mmol of sodium.

Interactions

Probenecid is reported to block the renal clearance of aciclovir. The risk of renal impairment is increased by use with other nephrotoxic drugs.

Antivirals. Use of *zidovudine* with aciclovir is not generally associated with additional toxicity.[1] However, there is a report[2] of a patient who had overwhelming fatigue when given aciclovir and zidovudine together; no such effect occurred when each drug was given alone.

Former product information for *interferon alfa-n1* reported progressive renal failure in patients also given aciclovir.

1. Tartaglione TA, *et al.* Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; **35:** 2225–31.
2. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; **316:** 547.

Theophylline. For reference to evidence that aciclovir inhibits *theophylline* metabolism, resulting in accumulation, see p. 1235.2.

Antiviral Action

Aciclovir is active against herpes simplex virus type 1 and type 2 and against varicella-zoster virus. This activity requires intracellular conversion of aciclovir by viral thymidine kinase to the monophosphate with subsequent conversion by cellular enzymes to the diphosphate and the active triphosphate. This active form inhibits viral DNA synthesis and replication by inhibiting the herpesvirus DNA polymerase enzyme as well as being incorporated into viral DNA. This process is highly selective for infected cells. Studies in *animals* and *in vitro* have found various sensitivities but show that target viruses are inhibited by concentrations of aciclovir that are readily achieved clinically. Herpes simplex virus type 1 appears to be the most susceptible, then type 2, followed by varicella-zoster virus.

The Epstein-Barr virus and CMV are also susceptible to aciclovir to a lesser extent. However, for CMV it does not appear to be activated by thymidine kinase and may act via a different mechanism. Epstein-Barr virus may have reduced thymidine kinase activity but its DNA polymerase is very sensitive to inhibition by aciclovir triphosphate, which may account for the partial activity.

Aciclovir has no activity against latent viruses, but there is some evidence that it inhibits latent herpes simplex virus at an early stage of reactivation.

Herpes simplex virus develops resistance to aciclovir *in vitro* and *in vivo* by selection of mutants deficient in thymidine kinase. Other mechanisms of resistance include altered substrate specificity of thymidine kinase and reduced sensitivity of viral DNA polymerase. Resistance has also been reported with varicella-zoster virus, probably by similar mechanisms.

Although occasional treatment failures have been reported, resistance has not yet emerged as a major problem in treating herpes simplex infections in immunocompetent patients. However, resistant viruses are more likely to be a problem in patients with a suppressed immune response.

There is virtually complete cross-resistance of herpes simplex strains between aciclovir and penciclovir, although it is not universal. Cross-resistance is also nearly universal between aciclovir and brivudine. However, cross-resistance is not usually seen in aciclovir-resistant thymidine kinase mutants to cidofovir, foscarnet, or vidarabine, which either do not require intracellular activation, or are not activated by thymidine kinase. If resistance does occur, it must be due to DNA polymerase mutation. Aciclovir-resistant thymidine-kinase mutants of herpes simplex are often cross-resistant to ganciclovir, whereas aciclovir-resistant polymerase mutants often retain sensitivity to the latter. Cross-resistance in strains of varicella zoster virus between aciclovir and penciclovir has been reported.

Resistance. References.

1. Bacon TH, *et al.* Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbiol Rev* 2003; **16:** 114–28.
2. Malvy D, *et al.* A retrospective, case-control study of acyclovir resistance in herpes simplex virus. *Clin Infect Dis* 2005; **41:** 320–6.

Pharmacokinetics

Aciclovir is poorly absorbed from the gastrointestinal tract after oral doses. Bioavailability of oral aciclovir is about 10 to 20%; orally active prodrugs such as valaciclovir (p. 1021.1) have been developed to overcome this poor absorption.

After intravenous dosage as aciclovir sodium it is widely distributed to body tissues and fluids including the CSF where concentrations are about 50% of those in plasma. Protein binding is reported to range from 9 to 33%.

Aciclovir is excreted largely unchanged in the urine, by glomerular filtration and some active tubular secretion, with up to 14% appearing in the urine as the inactive metabolite 9-carboxymethoxymethylguanine. In patients with normal renal function, the half-life is about 2 to 3 hours. In patients with chronic renal failure, this value is increased and may be up to 19.5 hours in anuric patients. During haemodialysis the half-life has been reported to be reduced to 5.7 hours, with 60% of a dose of aciclovir being removed. Faecal excretion may account for about 2% of a dose.

Probenecid increases the half-life and the area under the plasma concentration-time curve of aciclovir.

Aciclovir crosses the placenta and is distributed into breast milk in concentrations about 3 times higher than those in maternal serum.

Absorption of aciclovir is usually slight after topical application to intact skin, although it may be increased by changes in formulation. Aciclovir is absorbed after application of a 3% ointment to the eye giving a relatively high concentration in the aqueous humour but negligible amounts in the blood.

Reviews.

1. de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother* 1983; **12** (suppl B): 29–37.
2. Laskin OL. Clinical pharmacokinetics of acyclovir. *Clin Pharmacokinet* 1983; **8:** 187–201.
3. Wagstaff AJ, *et al.* Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 153–205.

Distribution. The pharmacokinetics of oral aciclovir and its distribution into the eye.[1]

1. Hung SO, *et al.* Pharmacokinetics of oral acyclovir (Zovirax) in the eye. *Br J Ophthalmol* 1984; **68:** 192–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acerpes; Aciclo; Aciclotex; Apofarm; Dioxis; Duolip; Lafevir; Lisovyr; Oralsone Herpes; Poviral; Trixviral; Virostatic; Xiclovir; Zovirax; ***Austral.***: Acihexal; Acivir; Acyclo-V; Blistex Antiviral; Chemists Own Cold Sore; Lovir; Nyal Antiviral Cold Sore; Ozvir; Zovirax; Zyclir†; ***Austria***: Acic; Aciclobene; Aciclostad; Activir; Herpomed; Nycovir†; ViroMed; Xorox; Zovirax; ***Belg.***: Aciclomed; Docaciclo†; Viratop; Zovirax; ***Braz.***: Aciclofar; Aciclomed; Aciclor; Aciveral; Acivirax; Anclomax; Antivirax; Aviral; Clovir; Ductovirax; Exavir; Ezopen; Heclivir; Herpesil; Hervirax; Hpvir; Uni Vir; Zovirax; ***Canad.***: Zovirax; ***Chile***: Eurovir; Lisovyr; Oftavir; Vironida; Zovirax; ***China***: A Lun (阿仑); A Te Mi An (阿特米安); Ai Bei Qing (艾贝清); Ai Er Xin (爱尔新); Aisike (艾思克); Asile (阿思乐); Bangna (邦纳); Bao Zhen Kang (葆珍康); Bo Shi Duo Wei (博仕多为); De Er Li Wei (得尔力伟); Dong Yao Qi Rui (东药琦锐); Gantai (甘泰); He Gu (和谷); Jie Ke (洁珂); Jie Luo Wei (洁罗维); Jimin Weixin (济民维新); Kang Da Wei (康达威); Keduxing (克毒星); Li Ke Ping (丽科平); Li Ke Xin (丽科欣); Luo Fu (洛芙); Nai Ge (奈格); Qiang Ni (强尼); Qing Lin (清林); Sha Wei Luo (沙威洛); Sheng Nuo Wei (圣诺韦); Tiancheng Xi Er (天诚惜尔); Wei Ping (韦平); Wei Xin (韦信); Wei-Jia (唯甲); You Kang (佑康); Zhengda Jiepu (正大捷普); Zhu Li (注力); Zovirax (苏维乐); Zylovir (西洛伟); ***Cz.***: Acyclostad; Herpesin; Provirsan; Ranvir†; Virolex†; Zovirax; ***Denm.***: Aciclodan; Acivir; Avirox; Geavir; Herpavir; Zovir; Zovirax; ***Fin.***: Aclotad; Aclovir; Acyclostad; Acyrax; Antix; Herpolips; Zovirax; ***Fr.***: Aciclovivax†; Activir; Herpevir; Kendix; Remex; Virucalm; Zovirax; ***Ger.***: Acerpes†; Acic-Ophtal; Acic†; Aciclo†; Acicloveta; Aciclostad; Acivir†; AciVision; Supraviran†; Virupos; Virzin; Zoliparin†; Zovirax; ***Gr.***: Abduce; Amitrox; Biozirox; Cargosil; Cevinolon; Clovirax; Cycloviran; Erpaclovir; Erpizon; Etasisen; Fibrilan; Hagevir; Helposol; Herzkur; Neldim; Pulibex; Uniplex; Verpir; Virusteril; Xorox; Zeramil; Zicoten; Zidovimm; Zovirax; ***Hong Kong***: Acilax; Aclovirax†; Avorax; Clinovir†; Cusiviral; Cyclovax; Declovir; Entir; Euroclovir; Fanovir†; Lovir; Medovir; Qualiclovir; Saforax†; Synclovir†; Vidaclovir†; Virest; Viroclear; Virucid; Wariviron†; Zevin†; Zoral; Zoraxin†; Zostin†; Zostinol†; Zovirax; ***Hung.***: Acyclostad; Herpesin; Telviran; Virolex; Zovirax; ***India***: Aciv; Acivir; ACV; Acvirall; Alovir; Axovir; Cevirin; Civir; Cutivir; Cyclovir; Herperax; Herpex; Herpil; Herzovir; KayVir; Koviran; Lovir; Nisivir; Ocurax; Ocuvir; Okavir; Ovir; Zovirax; ***Indon.***: Acifar; Azovir†; Clinovir; Clopes; Danovir; Herax; Herpiclof; Kenrovir†; Licovir; Matrovir†; Molavir; Nevirz†; Palovir; Poviral; Quavir†; Scanovir; Temiral; Viralis; Vircella†; Vircovir; Virdam; Vireth; Virpes; Virtaz; Virules; Zorel†; Zoter; Zovirax; Zumasid†; Zyclorax; ***Irl.***: Acic; Bellvirax; Herpetad†; Soothelip; Viralief; Zovirax; ***Israel***: Acivir; Acyclo-V; Acyclovenir; Cyclomed; Supra-Vir†; V-Ral; Zovirax; ***Ital.***: Aciclin; Aciclinlabiale; ACY; Acyvir†; Alovir; Amodivyr; Avirase; Avix; Avyclor; Avyplus; Cycloviran; Dravyr; Efriviral; Esavir; Euclivir†; Fuviron; Herpesnil; Iliaclor; Neclovir; Neviran; Riduvir; Sanavir; Voraclor; Zovirax; ***Jpn***: Zovirax; ***Malaysia***: Acylete; Avorax; Cusiviral; Declovir; Hepirax; Herpevex; Lovir; Medovir; Vacrax; Virless; Virucid; Zevin; Zoral; Zoraxin; Zovirax; ***Mex.***: Acifur†; Akevir; Apo-Vir; Avirex-T; Bioviraz; Brimex; Cicloferon; Clirbest; Clociver; Clovex; Clyvorax; Dyskly; Epsin†; Erser; Firex†; Hercivir; Herpilem†; Isavir; Jersin†; Kerastil; Laciken; Landvir; Lesaclor; Maclov; Opthavir; Seracic; Sinarden; Sophivir; Soviclor; Vicloran; Viclovir; Viremix; Virestat; Virgangel; Viroxil; Zirconia; Ziverone; Zovirax; ***Neth.***: Acyclostad; Herpolips; Kruidvat Koortslipcreme; Zovirax; ***Norw.***: Antix; Zovirax; ***NZ***: Lovir; Viraban; Zolaten; Zovirax; ***Phil'ipp.***: Aciherpin; Acyhex†; Clovir; Cloviron; Covelay; Cyclostad; Herpex; Klozivex; Lovir; Terclovir†; Virest; Zealor; Zoteran; Zovirax; ***Pol.***: Abbovir†; Acix; Antivir; Awirol†; Cusiviral†; Hascovir; Herpesin; Herpex; Heviran; Virolex; Viru-POS; Xorovir†; Zovirax; ***Port.***: Aciclosina; Aciclovax; Briclofar; Cicloviral; Divicil; Faulviral; Hermix-Sofex; Milavir; Vidovir†; Zov800; Zovirax; ***Rus.***: Citivir (Цитивир); Cyclovir (Цикловир); Herperax (Герперакс); Herpesin (Герпесин)†; Herpevir (Герпевир)†; Lovir (Ловир); Medovir (Медовир); Provirsan (Провирсан); Virolex (Виролекс); Vivorax (Виворакс); Zovirax (Зовиракс); ***S.Afr.***: Acitab; Acitop; Activir; Cyclivex; Lovire; Vyrohexal; Zovirax; ***Singapore***: Avorax; BeaRAX; Cusiviral; Declovir; Dravyr; Entir; Erlvirax; Lovir; Medovir; SP-Virac; Vacrax; Virest; Virless; Vivorax†; Zoral; Zorax; Zoraxin; Zovirax; ***Spain***: Aciclostad; Bel Labial†; Herpial; Maynar†; Virherpes; Virmen†; Viruderm; Zovicrem; Zovirax; ***Swed.***: Anti; Geavir; Zovirax; ***Switz.***: Acivir; Aviral; Helvevir; Virucalm; Zovirax; ***Thai.***: ACV; Acyvir; Azovax; Azycin†; Clinovir; Clovin; Clovira; Colsor; Covir; Cyclorax†; Declovir; Entir; Falerm; Herpenon; Herperax; Herpirax; Herpizyg; Lermex; M-Zavir; Marvir; Monirax; Norum; Paviria; Ranvir; Reclovax; Vermis; Vilerm; Viraxy; Virless; Virofik; Virogon; Virolan†; Viromed; Vironil; Vivax†; Vivir; Vizo; Zevin; Zocovin; Zovirax; Zyvirpac; ***Turk.***: Acyl; Aklovir; Asiviral; Hernovir; Herpeks†; Klovireks-L; Provir; Silovir; Virosil; Virupos; Xorox; Zovirax; ***UAE***: Lovrak; ***UK***: Aviral†; Clearsore; Cymex Ultra; Herpetad; Soothelip; Virasorb; Virovir; Zovirax; ***Ukr.***: Acic (Ацик); Acivir (Ацивир); Herpevir (Герпевир); Heviran (Гевиран); Virolex (Виролекс); Zovirax (Зовиракс); ***USA***: Sitavig; Xerese; Zovirax; ***Venez.***: Aciclor; Avir; Cloryvil; Herpin; Zovirax.

Multi-ingredient Preparations. *Cz.*: Xerclear; ***Denm.***: Xerclear; ***India***: Clovirax; ***Rus.***: Herpferon (Герпферон); ***Swed.***: Xerclear; ***Ukr.***: Herpferon (Герпферон)†.

Pharmacopoeial Preparations

BP 2014: Aciclovir Cream; Aciclovir Eye Ointment; Aciclovir Infusion; Aciclovir Oral Suspension; Aciclovir Tablets; Dispersible Aciclovir Tablets;

USP 36: Acyclovir Capsules; Acyclovir for Injection; Acyclovir Ointment; Acyclovir Oral Suspension; Acyclovir Tablets.

Adefovir *(BAN, USAN, rINN)*

Adéfovir; Adefovirum; GS-0393; PMEA; Адефовир.

{[2-(6-Amino-9*H*-purin-9-yl)ethoxy]methyl}phosphonic acid; 9-[2-(Phosphonomethoxy)ethyl]adenine.

$C_8H_{12}N_5O_4P$=273.2

CAS — 106941-25-7.

ATC — J05AF08.

ATC Vet — QJ05AF08.

UNII — 6GQP90I798.

Adefovir Dipivoxil (BANM, USAN, rINNM)

Adefovir Dipivoksil; Adéfovir Dipivoxil; Adefovir, dipivoxilo de; Adefovirum Dipivoxilum; *Bis* (POM)PMEA; Dipivoxilo de adefovir; GS-0840; Piv2PMEA; Адефовир Дипивоксил.

9-[2-({Bis[(pivaloyloxy)methoxy]phosphinyl}methoxy)ethyl] adenine.

$C_{20}H_{32}N_5O_8P$=501.5

CAS — 142340-99-6.

ATC — J05AF08.

ATC Vet — QJ05AF08.

UNII — U6Q8Z01514.

Uses and Administration

Adefovir is a nucleotide reverse transcriptase inhibitor, structurally related to adenine, that is given orally as the prodrug adefovir dipivoxil for the treatment of chronic **hepatitis B** (p. 952.1). It is used in adults with decompensated liver disease, or with compensated liver disease with evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of adefovir dipivoxil is 10 mg once daily. For details of dosage modification in patients with renal impairment, see below.

Adefovir was initially investigated for the treatment of **HIV infection**, but its use is limited by nephrotoxicity due to the high doses needed.

References.

1. Dando TM, Plosker GL. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; **63:** 2215–34.
2. Rivkin AM. Adefovir dipivoxil in the treatment of chronic hepatitis B. *Ann Pharmacother* 2004; **38:** 625–33.
3. Danta M, Dusheiko G. Adefovir dipivoxil: review of a novel acyclic nucleoside analogue. *Int J Clin Pract* 2004; **58:** 877–86.
4. Jones J, *et al.* Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. *Health Technol Assess* 2009; **13:** 1–172.

Administration in renal impairment. The oral dose of adefovir dipivoxil should be reduced in patients with renal impairment. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: usual 10 mg once-daily dosage (above)
- CC 30 to 49 mL/minute: 10 mg every 48 hours
- CC 10 to 29 mL/minute: 10 mg every 72 hours
- haemodialysis patients: 10 mg every 7 days after dialysis

Adverse Effects

The most common adverse effects reported from adefovir have been gastrointestinal effects including nausea, flatulence, diarrhoea, dyspepsia, vomiting, and abdominal pain. Other common adverse effects are headache and asthenia. There have also been reports of pruritus and skin rashes. Increases in serum-creatinine concentrations may occur and there have been instances of renal impairment and acute renal failure; proximal renal tubulopathy, Fanconi syndrome, and hypophosphataemia have also been reported. Raised liver enzyme concentrations may occur and severe acute exacerbation of hepatitis has been reported after stopping treatment with adefovir.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p. 1024.3).

Precautions

Adefovir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Adefovir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients whose liver enzyme values increase due to response to treatment must be distinguished from those in whom these indicate toxicity. Exacerbation of hepatitis has been reported in patients who developed resistance to adefovir and in those who stopped adefovir; patients who stop treatment should be monitored closely for an appropriate period. In order to minimise the risk of resistance in patients with lamivudine-resistant hepatitis B, adefovir should be used with lamivudine and not as monotherapy. Patients taking adefovir with normal renal function should be monitored every 3 months for signs of deteriorating renal function; patients at risk of renal impairment should be monitored more frequently and particular care should be exercised in patients with a creatinine clearance of less than 50 mL/minute, who may require dosage modification, and in those receiving other drugs that may affect renal function.

Use of adefovir to treat chronic hepatitis B infection in patients with undiagnosed or untreated HIV infection may result in the emergence of resistant strains of HIV. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with adefovir.

Breast feeding. It is unknown whether adefovir is distributed into breast milk but licensed product information recommends that mothers should not breast feed if taking adefovir.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adefovir dipivoxil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Studies in *rodents* given high intravenous doses of adefovir (systemic exposure 38 times that in the human) have found it to be fetotoxic or embryotoxic; neither high oral doses (systemic exposure 23 to 40 times that in the human) nor lower intravenous doses (systemic exposure 12 times that in the human) produced evidence of teratogenicity or embryotoxicity. There are no studies available on the use of adefovir in pregnant women and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk.

Interactions

Caution should be exercised when adefovir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug. Care is required when adefovir is given with other drugs with the potential for nephrotoxicity; licensed product information advises against use with tenofovir.

Antiviral Action

Adefovir is converted intracellularly in stages to the diphosphate, which then inhibits the DNA synthesis of hepatitis B virus through competitive inhibition of reverse transcriptase and incorporation into viral DNA. At high doses it has some activity against HIV.

Antiviral resistance. The development of antiviral resistance is a concern with long-term nucleoside or nucleotide treatment for chronic hepatitis B. Studies[1-4] in patients with chronic hepatitis B showed no resistance to adefovir after 1 year of treatment, but resistance rates increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively. Adefovir was found to be effective in patients who had previously developed resistance to lamivudine.[4]

1. Marcellin P, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348:** 808–16. Correction. *ibid.*: 1192.
2. Hadziyannis SJ, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348:** 800–7. Correction. *ibid.*; 1192.
3. Hadziyannis SJ, *et al.* Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005; **352:** 2673–81.
4. Delaney WE. Progress in the treatment of chronic hepatitis B: long-term experience with adefovir dipivoxil. *J Antimicrob Chemother* 2007; **59:** 827–32.

Pharmacokinetics

After oral doses adefovir dipivoxil is rapidly converted to adefovir. Peak plasma concentrations of adefovir occur after about 0.6 to 4 hours. Bioavailability is reported to be 59% after a single oral dose. Absorption is delayed but not reduced when given with food. Adefovir is widely distributed to body tissues, particularly into the kidneys, liver, and intestines. Less than 4% is bound to plasma or serum proteins. Adefovir is excreted renally by glomerular filtration and active tubular secretion; the terminal elimination half-life is reported to be about 7 hours. Adefovir is partially removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biovir; Hepsera; Revervir†; ***Austral.***: Hepsera; ***Austria***: Hepsera; ***Belg.***: Hepsera; ***Braz.***: Hepsera; ***Canad.***: Hepsera; ***Chile***: Hepsera; ***China***: A Di Xian (阿迪仙); A Gan Ding (阿甘定); Ailuwei (爱路韦); Dai Ding (代丁); Dinghe (丁贺); Hepsera (贺维力); Lifuzhi (利福之); Ming Zheng (名正); Xinfunuo (欣复诺); Yilaifen (亿来芬); Youheding (优贺丁); Yue Bao (粤宝); ***Cz.***: Hepsera; ***Denm.***: Hepsera; ***Fin.***: Hepsera; ***Fr.***: Hepsera; ***Ger.***: Hepsera; ***Gr.***: Hepsera; ***Hong Kong***: Hepsera; ***Hung.***: Hepsera; ***India***: Adesera; Adfovir; Adheb; ***Indon.***: Hepsera; ***Irl.***: Hepsera; ***Israel***: Hepsera; ***Ital.***: Hepsera; ***Malaysia***: Hepsera; ***Mex.***: Hepsera; ***Neth.***: Hepsera; ***Norw.***: Hepsera; ***NZ***: Hepsera; ***Philipp.***: Hepsera; ***Pol.***: Hepsera; ***Port.***: Hepsera; ***Singapore***: Hepsera; ***Spain***: Hepsera; ***Swed.***: Hepsera; ***Switz.***: Hepsera; ***Thai.***: Hepsera; ***Turk.***: Hepsera; ***UK***: Hepsera; ***USA***: Hepsera; ***Venez.***: Hepsera.

Amprenavir (BAN, USAN, rINN)

141W94; Amprenaviiri; Amprénavir; Amprenavirum; Amprenawir; KVX-478; VX-478; Ампренавир.

(3*S*)-Tetrahydro-3-furyl{(*S*)-α-[(1*R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl}carbamate.

$C_{25}H_{35}N_3O_6S$=505.6

CAS — 161814-49-9.

ATC — J05AE05.

ATC Vet — QJ05AE05.

UNII — 5S0W860XNR.

Uses and Administration

Amprenavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when amprenavir is used alone, and it is therefore used with other antiretrovirals.

Amprenavir has been given orally as capsules or solution but the bioavailability of these formulations (*Agenerase, GlaxoSmithKline*) differ and their doses are not interchangeable.

- In adults and adolescents (13 to 16 years) weighing 50 kg or more the *capsules* have been given in a dose of 1.2 g twice daily; when given with ritonavir (ritonavir-boosted amprenavir) the recommended dose is amprenavir 600 mg with ritonavir 100 mg twice daily or amprenavir 1.2 g with ritonavir 200 mg once daily.
- The *oral solution* has been given in a dose of 17 mg/kg three times daily (maximum daily dose 2.8 g) or 1.4 g twice daily.

For details of doses in children and patients weighing less than 50 kg, see below. For dosage in hepatic impairment, also see below.

Amprenavir is now mostly used in the form of the prodrug fosamprenavir (see p. 980.1), which may aid compliance by reducing adverse effects and increasing flexibility of dosing.

Reviews.

1. Noble S, Goa KL. Amprenavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; **60:** 1383–1410.
2. Arvieux C, Tribut O. Amprenavir or fosamprenavir plus ritonavir in HIV infection: pharmacology, efficacy and tolerability profile. *Drugs* 2005; **65:** 633–59.

Administration in children. For the treatment of HIV infection in children 4 to 12 years of age and in adolescents (13 to 16 years) weighing less than 50 kg, amprenavir has been given daily with other antiretroviral drugs. Doses are based on body-weight:

- the *capsules* in an oral dose of 20 mg/kg twice daily or 15 mg/kg three times daily, to a maximum daily dose of 2.4 g, or
- the *solution* in an oral dose of 22.5 mg/kg twice daily or 17 mg/kg three times daily, to a maximum daily dose of 2.8 g

Administration in hepatic impairment. Amprenavir should be used with caution and in reduced doses in patients with hepatic impairment. Additionally, the oral solution contains propylene glycol and extra restrictions may apply.

The following doses have been recommended in UK licensed product information:

oral solution:

- do not use

capsules:

- moderate impairment: 450 mg twice daily
- severe impairment: 300 mg twice daily

The following doses have been recommended in US product information:

oral solution:

- Child-Pugh score 5 to 8: 513 mg twice daily
- Child-Pugh score 9 to 12: 342 mg twice daily
- hepatic failure: do not use

capsules:

- Child-Pugh score 5 to 8: 450 mg twice daily
- Child-Pugh score 9 to 12: 300 mg twice daily

Adverse Effects

As for Fosamprenavir, p. 980.3.

Precautions

As for Fosamprenavir, p. 980.3. For further information on cross-reactivity between sulfonamide drugs see Hypersensitivity, under Sulfamethoxazole, p. 365.3. The oral solution and capsule formulations of amprenavir (*Agenerase, GlaxoSmithKline*) also provide high daily doses of vitamin E (with its attendant adverse effects, see p. 2121.2). The oral solution has a high content of propylene glycol, present as an excipient, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further

information on propylene glycol toxicity, see Adverse Effects and Precautions, p. 2205.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amprenavir as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Amprenavir has been associated with teratogenicity in *animals*. The solution is contra-indicated in pregnancy due to the high propylene glycol content.

Interactions

As for Fosamprenavir, p. 980.3.

Agenerase oral solution (*GlaxoSmithKline*) is contra-indicated in patients taking disulfiram or other products that reduce alcohol metabolism (such as metronidazole) and in those taking alcohol-containing products (such as ritonavir oral solution) because of the potential risk of toxicity from its propylene glycol content.

Antiviral Action

As for Fosamprenavir, p. 980.3.

Pharmacokinetics

Amprenavir is rapidly and well absorbed from the gastrointestinal tract after oral doses. Absorption is impaired by ingestion with a high-fat meal. Amprenavir capsules and oral solution are not bioequivalent; oral bioavailability is about 14% lower from the oral solution formulation than from the capsule formulation (*Agenerase, GlaxoSmithKline*). Peak plasma concentrations occur 1 to 2 hours after a single dose. It is about 90% bound to plasma proteins. Amprenavir is metabolised by hepatic cytochrome P450 isoenzyme CYP3A4. It is excreted mainly in the faeces as metabolites. The plasma elimination half-life is 7.1 to 10.6 hours.

References.
1. Sadler BM, Stein DS. Clinical pharmacology and pharmacokinetics of amprenavir. *Ann Pharmacother* 2002; **36:** 102–18.
2. Stein DS, *et al*. Pharmacokinetic and pharmacodynamic analysis of amprenavir-containing combination therapy in HIV-1-infected children. *J Clin Pharmacol* 2004; **44:** 1301–8.
3. Yogev R, *et al*. Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother* 2005; **49:** 336–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agenerase; ***Austral.***: Agenerase; ***Austria***: Agenerase†; ***Braz.***: Agenerase; ***Chile***: Agenerase†; ***Cz.***: Agenerase†; ***Fin.***: Agenerase†; ***Ger.***: Agenerase†; ***Gr.***: Agenerase; ***Irl.***: Agenerase†; ***Israel***: Agenerase; ***Mex.***: Agenerase†; ***Neth.***: Agenerase†; ***NZ***: Agenerase; ***Pol.***: Agenerase†; ***Port.***: Agenerase†; ***Rus.***: Agenerase (Агенераза); ***Spain***: Agenerase†; ***Switz.***: Agenerase†; ***Turk.***: Agenerase†; ***Venez.***: Agenerase.

Atazanavir Sulfate *(BANM, USAN, rINNM)*

Atazanavir, Sulfate d'; Atazanavir, sulfato de; Atazanavir Sulphate; Atazanaviri Sulfas; BMS-232632-05; BMS-232632 (atazanavir); Sulfato de atazanavir; Атазанавира Сульфат.

Dimethyl (3*S*,8*S*,9*S*,12*S*)-9-Benzyl-3,12-di-*tert*-butyl-8-hydroxy-4,11-dioxo-6-(*p*-2-pyridylbenzyl)-2,5,6,10,13-pentaazatetradecanedioate sulfate (1:1).

$C_{38}H_{52}N_6O_7,H_2SO_4$=802.9

CAS — 198904-31-3 (atazanavir); 229975-97-7 (atazanavir sulfate).

ATC — J05AE08.

ATC Vet — QJ05AE08.

UNII — 4MT4VIE29P.

Uses and Administration

Atazanavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when atazanavir is used alone, and it is therefore used with other antiretrovirals.

Atazanavir is given orally as the sulfate with food, but doses are expressed in terms of atazanavir; 228 mg of atazanavir sulfate is equivalent to about 200 mg of atazanavir.

The usual adult dose in both treatment-naive and treatment-experienced patients is atazanavir 300 mg, given with ritonavir 100 mg, once daily. In the USA, unboosted atazanavir 400 mg once daily may also be considered for treatment-naive patients who are unable to tolerate ritonavir.

Atazanavir should generally be ritonavir-boosted if it must be given with efavirenz, tenofovir, H_2-receptor antagonists, or proton pump inhibitors. While the use of atazanavir with efavirenz is generally not recommended (see Interactions, below) increasing the dose of atazanavir to 400 mg (with ritonavir 100 mg) once daily for use with efavirenz is considered acceptable in the USA for treatment-naive patients only. Atazanavir 400 mg with ritonavir 100 mg once daily has also been suggested when use with an H_2-receptor antagonist with tenofovir cannot be avoided, and UK licensed product information also suggests this regimen if use with a proton pump inhibitor or high-dose H_2-receptor antagonist (exceeding the equivalent of famotidine 40 mg/day) is essential.

For details of doses in children and adolescents, see below.

For details of recommended doses of atazanavir in patients with hepatic or renal impairment, see below and below respectively.

Reviews.
1. Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis* 2004; **38:** 1599–1604.
2. Musial BL, *et al*. Atazanavir: a new protease inhibitor to treat HIV infection. *Am J Health-Syst Pharm* 2004; **61:** 1365–74.
3. Orrick JJ, Steinhart CR. Atazanavir. *Ann Pharmacother* 2004; **38:** 1664–74.
4. Swainston Harrison T, Scott LJ. Atazanavir: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 2309–36.
5. Croom KF, *et al*. Atazanavir: a review of its use in the management of HIV-1 infection. *Drugs* 2009; **69:** 1107–40.
6. Bentué-Ferrer D, *et al*. Clinical pharmacology, efficacy and safety of atazanavir: a review. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1455–68.

Administration in children. For the treatment of HIV infection in children 6 years of age and older and adolescents, atazanavir is given orally with food. Doses are based on body-weight.

In the USA the recommended dosage of atazanavir with ritonavir in *treatment-naive* patients at least 6 years of age is:
- 15 to 24 kg: atazanavir 150 mg once daily with ritonavir 80 mg once daily
- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

For *treatment-naive* patients at least 13 years of age and 39 kg, who are unable to tolerate ritonavir, the recommended dose is atazanavir 400 mg once daily.

The recommended dosage of atazanavir with ritonavir in *treatment-experienced* patients at least 6 years of age is:
- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

Although the overall range of doses recommended in the UK is the same as in the US, fewer body-weight divisions are suggested.

Administration in hepatic impairment. In treatment-naive patients the oral dose of atazanavir should be adjusted in hepatic impairment as follows:
- mild hepatic impairment (Child-Pugh category A): use with caution (no specific reduction recommended)
- moderate impairment (Child-Pugh category B): atazanavir 300 mg daily
- severe hepatic impairment (Child-Pugh category C): not recommended

Ritonavir-boosted atazanavir regimens should be used with caution in patients with mild hepatic impairment and should not be used in those with moderate to severe hepatic impairment.

Administration in renal impairment. Oral dose adjustments are not usually necessary for patients with renal impairment. However, US licensed product information recommends that treatment-naive patients on haemodialysis should be given atazanavir 300 mg once daily with ritonavir 100 mg once daily and that atazanavir should not be used in treatment-experienced patients on haemodialysis.

Adverse Effects

Commonly reported adverse effects of moderate or greater intensity associated with antiretroviral regimens containing atazanavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, and jaundice), headache, insomnia, and peripheral neurological symptoms, and scleral icterus. Other commonly reported adverse effects are asthenia and fatigue. Mild to moderate rashes (usually maculopapular) generally occurring after 8 weeks of treatment and resolving within 1 to 2 weeks have been reported. Stevens-Johnson syndrome and erythema multiforme have also been reported in patients given atazanavir. Atazanavir may prolong the PR interval of the ECG and asymptomatic first-degree AV block has been reported in some patients. There have also been rare reports of QT interval prolongation and torsade de pointes. Cases of nephrolithiasis have occurred. Most patients taking atazanavir have asymptomatic elevations in unconjugated bilirubin, which is reversible upon stopping treatment. Other abnormal laboratory results include elevated amylase and lipase, elevated liver enzymes, and low neutrophils.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including atazanavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including atazanavir. Metabolic abnormalities such as insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported; unboosted atazanavir generally does not appear to have a negative effect on lipid levels. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

In the USA, atazanavir is contra-indicated in patients with severe hepatic impairment, and UK licensed product information advises that use in those with moderate liver impairment should also be avoided. It should be used with caution, and liver enzymes values monitored, in patients with milder liver disease. The use of ritonavir-boosted atazanavir has not been studied in hepatic impairment; while US licensed product information recommends avoiding use in patients with any degree of hepatic insufficiency, UK licensed product information allows use, with caution, in those with mild impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Caution should be exercised in patients with pre-existing cardiac conduction disorders or in those taking drugs that prolong the PR or increase the QT intervals. Patients developing jaundice or scleral icterus associated with hyperbilirubinaemia should be tried on an alternative antiretroviral; dose reductions of atazanavir should not be considered.

Pregnancy. Atazanavir has not been associated with teratogenicity in *animals*. Although there are theoretical concerns that atazanavir given to mothers may exacerbate physiologic hyperbilirubinaemia and lead to kernicterus in neonates and young infants, these effects have so far not occurred in clinical studies.[1]

For further information on the use of HIV-protease inhibitors in pregnancy, see under Indinavir, p. 987.1.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 05/10/09)

Interactions

Atazanavir is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and inhibits CYP3A4, CYP2C8, and UGT1A1. Use with drugs mainly metabolised by these isoenzymes may result in increases in their plasma concentrations, while drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations. When ritonavir-boosted atazanavir is given, the drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of atazanavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include
- antiarrhythmics (amiodarone, bepridil, and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)

- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated.

Owing to the potential for increased serum concentrations of sildenafil, atazanavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, atazanavir may increase serum concentrations of inhaled fluticasone and salmeterol and combination with either is not recommended. Ritonavir-boosted atazanavir should not be used with drugs having narrow therapeutic windows that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide and propafenone. Proton pump inhibitors, the NNRTIs efavirenz and nevirapine, rifampicin, and St John's wort decrease the concentration of atazanavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance. H_2-receptor antagonists may also substantially reduce serum concentrations of atazanavir. Careful consideration needs to be given to both the size and timing of the H_2-receptor antagonist dose when use with atazanavir is required, and where the antiretroviral regimen also includes tenofovir, use with a H_2-receptor antagonist is best avoided entirely. For information on doses used in management of drug interactions, see Uses and Administration, p. 968.1.

Atazanavir should also not be given to patients taking indinavir, as indirect hyperbilirubinaemia may result. Atazanavir is also contra-indicated with irinotecan as atazanavir's inhibition of UGT1A1 may increase irinotecan toxicity.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Atazanavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Atazanavir is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur after 2 to 2.5 hours. On multiple dosing with a ritonavir-boosted regimen peak plasma concentrations occur after 3 hours. Bioavailability (of both ritonavir-boosted and non-boosted regimens) is enhanced if given with food. Atazanavir is reported to be 86% bound to serum proteins. It is distributed into semen and into the CSF. Atazanavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme family CYP3A; the metabolites appear to be inactive. Atazanavir is mainly excreted in faeces, mostly as metabolites, and to a smaller extent in the urine. The terminal elimination half-life of atazanavir is reported to be about 7 hours and 8.6 hours after a ritonavir-boosted regimen.

Reviews.
1. Le Tiec C, *et al.* Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet* 2005; **44:** 1035–50.
2. Avihingsanon A, *et al.* A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. *Clin Pharmacol Ther* 2009; **85:** 402–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Reyataz; ***Austral.***: Reyataz; ***Austria***: Reyataz; ***Belg.***: Reyataz; ***Braz.***: Reyataz; ***Canad.***: Reyataz; ***Chile***: Reyataz; ***China***: Reyataz (锐艾妥); ***Cz.***: Reyataz; ***Denm.***: Reyataz; ***Fin.***: Reyataz; ***Fr.***: Reyataz; ***Ger.***: Reyataz; ***Gr.***: Reyataz; ***Hong Kong***: Reyataz; ***Hung.***: Reyataz; ***India***: Atazor; ***Indon.***: Reyataz†; ***Irl.***: Reyataz; ***Israel***: Reyataz; ***Ital.***: Reyataz; ***Jpn***: Reyataz; ***Malaysia***: Reyataz; ***Mex.***: Reyataz; ***Neth.***: Reyataz; ***Norw.***: Reyataz; ***NZ***: Reyataz; ***Pol.***: Reyataz; ***Port.***: Reyataz; ***Rus.***: Reyataz (Реатаз); ***S.Afr.***: Reyataz; ***Singapore***: Reyataz; ***Spain***: Reyataz; ***Swed.***: Reyataz; ***Switz.***: Reyataz; ***Thai.***: Reyataz; ***UK***: Reyataz; ***USA***: Reyataz.

Boceprevir *(USAN, rINN)*

Bocéprévir; Boceprevirum; SCH-503034; Боцепревир.

(1*R*,2*S*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-((2*S*)-2-{[(1,1-dimethylethyl)carbamoyl]amino}-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide.

$C_{27}H_{45}N_5O_5$=519.7

CAS — 394730-60-0.

ATC — J05AE12.

ATC Vet — QJ05AE12.

UNII — 89BT58KELH.

Uses and Administration

Boceprevir is an oral peptidomimetic HCV-protease inhibitor effective against hepatitis C virus (HCV) protease NS3/4A. It is used in the treatment of chronic hepatitis C (p. 952.1) genotype 1 infection in adults with compensated liver disease, including cirrhosis. Boceprevir is given in an oral dose of 800 mg three times daily (once every 7 to 9 hours) with food in a combined regimen with peginterferon alfa and ribavirin.

Patients **without cirrhosis** who are previously untreated or who have failed previous treatment with peginterferon alfa and ribavirin should be given an initial 4 weeks of treatment with peginterferon alfa and ribavirin (bi-therapy). Boceprevir is then added to the regimen (tri-therapy), after which the course is determined by the patient's clinical situation and hepatitis C-RNA (HCV-RNA) response to therapy. UK- and US-licensed product information recommend the following approach:

Previously untreated patients

- where HCV-RNA is undetectable at weeks 8 and 24: complete tri-therapy until the end of week 28
- where HCV-RNA is detectable at week 8, but undetectable at week 24: continue tri-therapy to the end of week 36, then switch to bi-therapy until the end of week 48

Patients who have failed previous therapy with peginterferon alfa and ribavirin

- where HCV-RNA is undetectable at weeks 8 and 24: UK licensed product information advises tri-therapy up to the end of week 36, then bi-therapy until the end of week 48; US licensed product information advises tri-therapy up to the end of week 36
- where HCV-RNA is detectable at week 8, but undetectable at week 24: continue tri-therapy up to the end of week 36, then switch to bi-therapy until the end of week 48

Patients with **cirrhosis** should be given an initial 4 weeks of bi-therapy, followed by 44 weeks of tri-therapy. The duration of tri-therapy should not be less than 32 weeks; if tri-therapy is not tolerated, a switch to bi-therapy for the remaining 12 weeks can be considered.

In all patients, HCV-RNA levels ≥100 units/mL at week 12, or detectable HCV-RNA levels at week 24 are an indication of treatment futility, in which case tri-therapy should be abandoned.

References.
1. Kwo PY, *et al.* Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010; **376:** 705–16. Correction. *ibid.*; 1224.
2. Bacon BR, *et al.* HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364:** 1207–17.
3. Poordad F, *et al.* SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364:** 1195–206.

Adverse Effects

The addition of an HCV-protease inhibitor to a regimen of peginterferon alfa and ribavirin can result in significant additional toxicity, particularly dermatological, gastrointestinal, and haematological.

Adverse effects associated with the use of boceprevir with peginterferon alfa and ribavirin are wide ranging, but the most common adverse effects reported in clinical studies were anaemia, fatigue, headache, nausea, and taste disturbances. Other common effects that have been reported include increased incidence of infection, blood dyscrasias (including neutropenia, leucopenia, and thrombocytopenia), dry eyes or changes in vision, thyroid disturbances, reduced appetite, weight loss, dehydration, metabolic disturbances (such as hyperglycaemia, hypertriglyceridaemia, and hyperuricaemia), palpitations and changes in blood pressure, psychiatric disturbances, respiratory effects (including cough and dyspnoea), various CNS effects (such as dizziness, syncope, hypoaesthesia, or paraesthesia), tinnitus, gastrointestinal disturbances, effects on the skin (including alopecia, dry skin, pruritus, and rash), muscle and joint pain, frequent urination, erectile dysfunction, weakness, fever, chills, and malaise. Rare, but potentially serious adverse effects can include deafness, haemolysis, thyroid neoplasms, cardiac arrhythmias, thrombotic disorders (including deep-vein thrombosis and pulmonary embolism), pleural fibrosis and pleuritic pain, retinopathy, cerebral and retinal ischaemia, myocardial infarction, cholecystitis, pancreatitis, and gastritis.

Precautions

Boceprevir must not be used as monotherapy as there is a high likelihood of viral resistance developing. It is contra-indicated in patients with auto-immune hepatitis. Because boceprevir is given with peginterferon alfa and ribavirin, precautions with respect to the use of these medications must be observed (see p. 995.1 and p. 1011.2, respectively). Boceprevir-containing regimens generally increase the incidence and degree of anaemia and neutropenia compared with peginterferon alfa and ribavirin alone; complete blood counts should therefore be obtained before, and periodically throughout, treatment. Prompt evaluation and treatment of infections is necessary.

Boceprevir may have proarrhythmic effects and care is warranted in patients at risk for QT-interval prolongation.

Interactions

Boceprevir is a strong inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5; boceprevir in combination with peginterferon alfa and ribavirin is contra-indicated with drugs that are highly dependent on these enzymes for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. Although specific guidance may vary between licensing authorities, these drugs may include

- the alpha$_1$-adrenoceptor antagonist alfuzosin
- antimalarials (halofantrine and lumefantrine)
- antineoplastics (tyrosine kinase inhibitors)
- antipsychotics (pimozide)
- calcium-channel blockers (bepridil)
- the oral contraceptive hormone drospirenone
- ergot derivatives (dihydroergotamine, ergonovine, ergotamine, and methylergonovine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (lovastatin and simvastatin)

Owing to the potential for increased serum concentrations of phosphodiesterase type-5 inhibitor (such as sildenafil and tadalafil), boceprevir should also be avoided with these drugs when given at the doses needed for the treatment of pulmonary hypertension. Similarly, boceprevir may increase serum concentrations of inhaled budesonide, fluticasone, or salmeterol; combination with any of these is not recommended.

Boceprevir is partly metabolised by CYP3A4 and CYP3A5; as a result, drugs that induce or inhibit these enzymes might be expected to decrease or increase exposure to boceprevir. In particular, use with potent inducers of CYP3A4 and CYP3A5 (such as carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin, rifabutin, or St Johns wort) should be avoided.

Caution should be observed if boceprevir is to be given with drugs known to prolong the QT-interval (such as amiodarone, methadone, pentamidine, quinidine, and some antipsychotics).

Antiviral action

Boceprevir is a competitive inhibitor of the NS3/4A protease of hepatitis C virus (HCV) genotype 1, a protein involved in the post-translational processing of HCV polyproteins that is required for viral replication. The drug has no clinically significant activity against other HCV genotypes and must be used with peginterferon alfa and ribavirin to minimise the emergence of viral resistance.

Pharmacokinetics

Boceprevir is given as an equal mixture of two diastereomers, SCH534128 and SCH534129, only the first of which is pharmacologically active. It is well absorbed after oral administration and peak-plasma concentrations occur after a median 2 hours; in plasma, the diastereomer ratio changes to 2:1, favouring the active diastereomer SCH534128. Plasma concentrations increase in a less-than-dose-proportional manner, indicating that larger doses are not absorbed as well as smaller ones. Food enhances its absorption by up to 65% at a dose of 800 mg three times daily. Steady-state concentrations of boceprevir occur after about 1 day of regular dosing. It has a mean volume of distribution of about 772 litres and is about 75% bound to plasma proteins.

Boceprevir is metabolised through the aldo-ketoreductase (AKR)-mediated pathway to inactive ketone-reduced metabolites; to a lesser extent, it also undergoes oxidative metabolism via CYP3A4/5. It has a mean elimination half-life of about 3.4 hours, and is excreted mainly in the faeces as metabolites with less than 10% as unchanged drug. Renal excretion of boceprevir is relatively insignificant, and the drug is not removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Victrelis; ***Belg.***: Victrelis; ***Denm.***: Victrelis; ***Fr.***: Victrelis; ***Ger.***: Victrelis; ***Irl.***: Victrelis; ***Israel***: Victrelis; ***Neth.***: Victrelis; ***Norw.***: Victrelis; ***Singapore***: Victrelis; ***Spain***: Victrelis; ***Swed.***: Victrelis; ***Switz.***: Victrelis; ***UK***: Victrelis; ***USA***: Victrelis.

Brivudine *(rINN)*

Brivudin; Brivudina; Brivudinum; BVDU; Бривудин.
(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine.
$C_{11}H_{13}BrN_2O_5$=333.1
CAS — 69304-47-8.
ATC — J05AB15.
ATC Vet — QJ05AB15.
UNII — 2M3055079H.

Profile

Brivudine is a nucleoside analogue effective *in vitro* against herpes simplex virus type 1 and varicella-zoster virus; other viruses including herpes simplex virus type 2 have been reported to be sensitive, but only at relatively high concentrations. The activity appears to be due, at least in part, to selective phosphorylation of brivudine by viral deoxythymidine kinase in preference to cellular kinases. Cross-resistance is common between brivudine and aciclovir because of some similar features in their mode of action (see p. 966.1).

Brivudine is given orally in the treatment of herpes zoster (p. 956.2) in a dose of 125 mg daily for 7 days. It has also been given orally for herpes simplex infection and has been used topically.

Brivudine has been investigated for the treatment of pancreatic cancer (p. 712.1) and has been granted orphan drug status by the EMA for this indication. When given with other antineoplastic drugs it acts by blocking heat shock protein 27 (Hsp27) which is found in high amounts in pancreatic cancer cells and plays an important role in chemoresistance.

References.
1. Keam SJ, *et al.* Brivudin (bromovinyl deoxyuridine). *Drugs* 2004; **64:** 2091–7.
2. Wassilew S. Collaborative Brivudin PHN Study Group. Brivudin compared with famciclovir in the treatment of herpes zoster: effects in acute disease and chronic pain in immunocompetent patients. A randomized, double-blind, multinational study. *J Eur Acad Dermatol Venereol* 2005; **19:** 47–55.
3. Mottu A, *et al.* Acute hepatitis due to brivudin: a case report. *J Hepatol* 2009; **51:** 967–9.
4. Fahrig R, *et al.* RP101 improves the efficacy of chemotherapy in pancreas carcinoma cell lines and pancreatic cancer patients. *Anticancer Drugs* 2006; **17:** 1045–56.

Interactions. For reference to a fatality when brivudine was given with *capecitabine* see under Interactions, Antivirals, in Fluorouracil, p. 797.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zostydol; ***Austria***: Mevir; Zostex; ***Belg.***: Zerpex; Zonavir; ***China***: Zostex (左伐); ***Cz.***: Zostevir; ***Ger.***: Zostex; ***Gr.***: Brivir; Zostevir; ***Ital.***: Brivirac; Zecovir; ***Port.***: Bridic; Zostex; ***Spain***: Nervinex; ***Switz.***: Brivex; ***Turk.***: Zostex.

Cidofovir *(BAN, USAN, rINN)*

Cidofovirum; Cydofowir; GS-0504; GS-504; HPMPC; Sidofoviiri; Sidofovir; Цидофовир.
{[(*S*)-2-(4-Amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl}phosphonic acid; 1-[(*S*)-3-Hydroxy-2-(phosphonomethoxy)propyl]-cytosine.
$C_8H_{14}N_3O_6P$=279.2
CAS — 113852-37-2 (anhydrous cidofovir); 149394-66-1 (cidofovir dihydrate).
ATC — J05AB12.
ATC Vet — QJ05AB12.
UNII — JIL713Q00N (cidofovir); 768M1V522C (anhydrous cidofovir).

Uses and Administration

Cidofovir is a nucleoside analogue that is active against herpesviruses. It is used in the treatment of CMV retinitis (p. 954.2) in patients with AIDS, and is being investigated for ocular herpes simplex and other viral infections.

In the treatment of CMV retinitis, cidofovir is given in a dose of 5 mg/kg by intravenous infusion over 1 hour once a week for 2 consecutive weeks, then once every 2 weeks for maintenance. Probenecid 2 g is given orally 3 hours before each dose of cidofovir and further 1-g doses of probenecid at 2 and 8 hours after completion of the infusion. To ensure adequate hydration, 1 litre of sodium chloride 0.9% is given by intravenous infusion over 1 to 2 hours immediately before each infusion of cidofovir; if the additional fluid load can be tolerated, a further 1 litre of sodium chloride 0.9% may be infused over 1 to 3 hours, starting at the same time as (or immediately after) the cidofovir infusion. For details of modified use of cidofovir in patients with renal impairment, see below.

Cidofovir has also been given experimentally by intravitreal injection but the commercially available formulation is unsuitable for use by this route and licensed product information advises against it (see Precautions, below).

An orally active prodrug of cidofovir known as cyclic-HPMPC (GS-930) is under investigation; a lipophilic analogue, 3-hexadecyloxy-1-propanol cidofovir (CMX-001) is also under investigation for its potential activity against a range of viruses including herpes viruses (such as CMV), BK virus, and smallpox. Cidofovir has been investigated for topical use.

Reviews.
1. Lea AP, Bryson HM. Cidofovir. *Drugs* 1996; **52:** 225–30.
2. Kendle JB, Fan-Havard P. Cidofovir in the treatment of cytomegaloviral disease. *Ann Pharmacother* 1998; **32:** 1181–92.
3. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. *Drugs* 1999; **58:** 325–45.
4. De Clercq E. Cidofovir in the treatment of poxvirus infections. *Antiviral Res* 2002; **55:** 1–13.
5. Snoeck R, De Clercq E. Role of cidofovir in the treatment of DNA virus infections, other than CMV infections, in immunocompromised patients. *Curr Opin Investig Drugs* 2002; **3:** 1561–6.
6. Toro JR, *et al.* Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox. *Dermatol Clin* 2003; **21:** 301–9.
7. Cha S, *et al.* Treatment of verruca vulgaris with topical cidofovir in an immunocompromised patient: a case report and review of the literature. *Transpl Infect Dis* 2005; **7:** 158–61.
8. Soma MA, Albert DM. Cidofovir: to use or not to use? *Curr Opin Otolaryngol Head Neck Surg* 2008; **16:** 86–90.
9. Donne AJ, *et al.* Scientific and clinical aspects of the use of cidofovir in recurrent respiratory papillomatosis. *Int J Pediatr Otorhinolaryngol* 2008; **72:** 939–44.
10. Lamoth F, *et al.* Low-dose cidofovir for the treatment of polyomavirus-associated nephropathy: two case reports and review of the literature. *Antivir Ther* 2008; **13:** 1001–9.
11. Coremans G, Snoeck R. Cidofovir: clinical experience and future perspectives on an acyclic nucleoside phosphonate analog of cytosine in the treatment of refractory and premalignant HPV-associated anal lesions. *Expert Opin Pharmacother* 2009; **10:** 1343–52.
12. Moyo TK, *et al.* Review: use of cidofovir for the treatment of HIV-negative human herpes virus-8-associated primary effusion lymphoma. *Clin Adv Hematol Oncol* 2010; **8:** 372–4.

Administration in renal impairment. Cidofovir is contra-indicated in patients with pre-existing renal impairment (serum creatinine more than 1.5 mg/dL, creatinine clearance of 55 mL/min or less, or urine protein of 100 mg/dL or more) and should be interrupted or stopped if serum creatinine increases by 500 micrograms/dL or more during therapy, or if significant proteinuria develops; in the USA, a reduction in the maintenance dose from 5 to 3 mg/kg intravenously is permitted for increases of serum creatinine of 300 to 400 micrograms/dL above baseline.

Viral infections. In addition to its use in CMV retinitis, systemic cidofovir has also been studied in herpes simplex infections,[1-4] progressive multifocal leukoencephalopathy,[5-9] BK polyomavirus-associated haemorrhagic cystitis,[4,10] and papillomavirus infections.[11] Topical formulations of cidofovir, in concentrations ranging from 0.3 to 5%, have also been used for the treatment of herpes simplex[12,13] and papillomavirus infections,[14-20] and molluscum contagiosum.[18,21,22]

See also reviews listed above.

1. Lalezari JP, *et al.* Treatment with intravenous (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]-cytosine of acyclovir-resistant mucocutaneous infection with herpes simplex virus in a patient with AIDS. *J Infect Dis* 1994; **170:** 570–2.
2. Bryant P, *et al.* Successful treatment of foscarnet-resistant herpes simplex stomatitis with intravenous cidofovir in a child. *Pediatr Infect Dis J* 2001; **20:** 1083–6.
3. Kopp T, *et al.* Successful treatment of an aciclovir-resistant herpes simplex type 2 infection with cidofovir in an AIDS patient. *Br J Dermatol* 2002; **147:** 134–8.
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5. Segarra-Newnham M, Vodolo KM. Use of cidofovir in progressive multifocal leukoencephalopathy. *Ann Pharmacother* 2001; **35:** 741–4.
6. Razonable RR, *et al.* Cidofovir treatment of progressive multifocal leukoencephalopathy in a patient receiving highly active antiretroviral therapy. *Mayo Clin Proc* 2001; **76:** 1171–5.
7. Marra CM, *et al.* Adult AIDS Clinical Trials Group 363 Team. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002; **16:** 1791–7.
8. Garvey L, *et al.* Progressive multifocal leukoencephalopathy: prolonged survival in patients treated with protease inhibitors and cidofovir: a case series. *AIDS* 2006; **20:** 791–3.
9. Viallard JF, *et al.* Improvement of progressive multifocal leukoencephalopathy after cidofovir therapy in a patient with a destructive polyarthritis. *Infection* 2007; **35:** 33–6.
10. Cesaro S, *et al.* Cidofovir for BK virus-associated hemorrhagic cystitis: a retrospective study. *Clin Infect Dis* 2009; **49:** 233–40.
11. Kottke MD, Parker SRS. Intravenous cidofovir-induced resolution of disfiguring cutaneous human papillomavirus infection. *J Am Acad Dermatol* 2006; **55:** 533–6.
12. Lalezari J, *et al.* A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis* 1997; **176:** 892–8.
13. Sacks SL, *et al.* A multicenter phase I/II dose escalation study of single-dose cidofovir gel for treatment of recurrent genital herpes. *Antimicrob Agents Chemother* 1998; **42:** 2996–9.
14. Snoeck R, *et al.* Treatment of anogenital papillomavirus infections with an acyclic nucleoside phosphonate analogue. *N Engl J Med* 1995; **333:** 943–4.
15. Davis MDP, *et al.* Large plantar wart caused by human papillomavirus-66 and resolution by topical cidofovir therapy. *J Am Acad Dermatol* 2000; **43:** 340–3.
16. Descamps V, *et al.* Topical cidofovir for bowenoid papulosis in an HIV-infected patient. *Br J Dermatol* 2001; **144:** 642–3.
17. Snoeck R, *et al.* Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. *Clin Infect Dis* 2001; **33:** 597–602.
18. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS: a pilot study. *J Eur Acad Dermatol Venereol* 2000; **14:** 484–8.
19. Husak R, *et al.* Refractory human papillomavirus-associated oral warts treated topically with 1-3% cidofovir solutions in human immunodeficiency virus type 1-infected patients. *Br J Dermatol* 2005; **152:** 590–1.
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21. Davies EG, *et al.* Topical cidofovir for severe molluscum contagiosum. *Lancet* 1999; **353:** 2042.
22. Toro JR, *et al.* Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. *Arch Dermatol* 2000; **136:** 983–5.

Adverse Effects

The most serious dose-limiting adverse effect of cidofovir is nephrotoxicity, the incidence and severity of which can be reduced by use with probenecid and by ensuring adequate hydration. Accumulation of cidofovir in the renal tubules can also be prevented by using an intermittent dosing schedule (see the licensed doses in Uses and Administration, above). There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Cases of nephrotoxicity have also been reported after off-label use of topical applications (creams or ointments) of cidofovir. Ocular toxicity and neutropenia have also been reported after use for off-label indications or by unlicensed routes of administration. Low plasma-bicarbonate concentrations and metabolic acidosis, sometimes associated with proximal tubule injury and renal wasting syndrome (including Fanconi's syndrome) or with liver dysfunction and pancreatitis, have been reported. Reversible neutropenia has also occurred. Other adverse effects include diarrhoea, headache, nausea and vomiting, fever, chills, asthenia, rash, dyspnoea, alopecia, and ocular hypotony (decreased intraocular pressure). Iritis or uveitis has been reported.

Cidofovir is carcinogenic and embryotoxic in *animals* and may have the potential to cause male infertility (see Precautions, below).

Effects on the eyes. Ocular adverse effects associated with intravenous use of cidofovir include iritis,[1] uveitis,[2-4] and ocular hypotony.[4] While development of ocular hypotony is considered to warrant withdrawal of cidofovir,[2] uveitis or iritis alone may respond to topical corticosteroids and cycloplegics thus allowing antiviral therapy to be continued; cidofovir must be stopped if there is no response or worsening of symptoms.

1. Tseng AL, *et al.* Iritis associated with intravenous cidofovir. *Ann Pharmacother* 1999; **33:** 167–71.
2. Ambati J, *et al.* Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. *Br J Ophthalmol* 1999; **83:** 1153–8.
3. Rougier M-B, *et al.* Uvéite antérieure et cidofovir. *J Fr Ophtalmol* 2001; **24:** 491–5.
4. Rapp P, *et al.* Uvéite bilatérale et hypotonie définitive due au cidofovir intraveineux: à propos d'un cas. *J Fr Ophtalmol* 2003; **26:** 717–19.

Effects on the kidneys. Dose-related nephrotoxicity is the most severe adverse effect of cidofovir and marked proteinuria has been reported in up to 50% of patients. There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Fanconi's syndrome associated with renal tubular damage has been reported in 2% of patients and, in one such patient, occurred on the third injection of cidofovir and resulted in irreversible renal impairment.[1] Reversible renal impairment with persisting Fanconi syndrome was reported in another.[2] A case of nephrogenic diabetes insipidus without premonitory laboratory abnormalities has also been reported in a patient given cidofovir.[3]

1. Vittecoq D, *et al.* Fanconi syndrome associated with cidofovir therapy. *Antimicrob Agents Chemother* 1997; **41:** 1846.
2. Kazory A, *et al.* Simultaneous development of Fanconi syndrome and acute renal failure associated with cidofovir. *J Antimicrob Chemother* 2007; **60:** 193–4.
3. Schliefer K, *et al.* Nephrogenic diabetes insipidus in a patient taking cidofovir. *Lancet* 1997; **350:** 413–14. Correction. *ibid.*; 1558.

Precautions

Cidofovir is contra-indicated in patients with renal impairment. Renal function should be measured before each dose. In the UK it is recommended that treatment should be interrupted or stopped if renal function deteriorates, but in the USA reduction of the dosage is permitted for increases in serum creatinine up to 300 to 400 micrograms/dL above baseline. Patients should receive oral probenecid and intravenous hydration with each dose of cidofovir; if probenecid cannot be used due to clinically significant hypersensitivity (to it or another sulfonamide drug), the use of cidofovir is also contra-indicated. Cidofovir should not be given with tenofovir disoproxil fumarate due

to the increased risk of Fanconi syndrome. Neutrophil counts should also be monitored and regular ophthalmological follow-up is recommended. Patients with diabetes mellitus are at increased risk of ocular hypotony.

Cidofovir is carcinogenic and embryotoxic in *animals*. Cidofovir should not be given during pregnancy and both sexes should use effective methods of contraception during treatment; in addition, effective contraception should be used, for 1 month by women and for 3 months by men, after the end of treatment. There is also a possibility that cidofovir may cause male infertility.

Cidofovir should be given intravenously only; direct intra-ocular injection has been associated with significant ocular hypotony and visual impairment and is contra-indicated.

Interactions

Additive nephrotoxicity may occur if cidofovir is used with other nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, vancomycin, or NSAIDs. Potentially nephrotoxic drugs should be stopped at least 7 days before starting cidofovir. Probenecid, which is given with cidofovir, may alter the clearance of other drugs (see Interactions under Probenecid, p. 608.2). Renal excretion of cidofovir may possibly also be affected by other drugs that are excreted by glomerular filtration and/or tubular secretion.

Patients with CMV retinitis are at increased risk of adverse inflammatory effects if cidofovir is given within 2 to 4 weeks of intravitreal fomivirsen.

Antiviral Action

Cidofovir undergoes intracellular phosphorylation by cellular kinases to the antiviral metabolite, cidofovir diphosphate, which acts as a competitive inhibitor of viral DNA polymerase. It is active against a range of herpesviruses including CMV, and, since its activity is not reliant on viral enzymes, may retain activity against some aciclovir- and foscarnet-resistant viruses. Cross-resistance with ganciclovir is common.

References.

1. Cherrington JM, *et al.* In vitro antiviral susceptibilities of isolates from cytomegalovirus retinitis patients receiving first- or second-line cidofovir therapy: relationship to clinical outcome. *J Infect Dis* 1998; **178:** 1821–5.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42:** 2240–4.

Pharmacokinetics

After intravenous doses of cidofovir, serum concentrations decline with a reported terminal half-life of about 2.2 hours (the intracellular half-life of the active diphosphate may be up to 65 hours). Cidofovir is eliminated mainly by renal excretion, both by glomerular filtration and tubular secretion. About 80 to 100% of a dose is recovered unchanged from the urine within 24 hours. Use with probenecid may reduce the excretion of cidofovir to some extent by blocking tubular secretion, although 70 to 85% has still been reported to be excreted unchanged in the urine within 24 hours.

References.

1. Cundy KC. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovir and adefovir. *Clin Pharmacokinet* 1999; **36:** 127–43.
2. Brody SR, *et al.* Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis. *Clin Pharmacol Ther* 1999; **65:** 21–8.
3. Wolf DL, *et al.* Pharmacokinetics and renal effects of cidofovir with a reduced dose of probenecid in HIV-infected patients with cytomegalovirus retinitis. *J Clin Pharmacol* 2003; **43:** 43–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vistide; ***Austria***: Vistide; ***Belg.***: Vistide; ***Cz.***: Vistide; ***Denm.***: Vistide; ***Fr.***: Vistide; ***Ger.***: Vistide; ***Gr.***: Vistide; ***Irl.***: Vistide; ***Ital.***: Vistide; ***Neth.***: Vistide; ***Pol.***: Vistide; ***Port.***: Vistide; ***Spain***: Vistide; ***Swed.***: Vistide; ***Switz.***: Vistide; ***UK***: Vistide; ***USA***: Vistide.

Daclatasvir *(USAN, pINN)*

BMS-790052; Daclatasvirum; Даклатасвир.

Dimethyl *N,N'*-(biphenyl-4,4'-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-1-(1-methylethyl)-2-oxoethane-2,1-diyl]})dicarbamate.

$C_{40}H_{50}N_8O_6$=738.9

CAS — 1009119-64-5.

UNII — LI2427F9CI.

Profile

Daclatasvir is an oral replication complex inhibitor of hepatitis C virus (HCV) protein NS5A. It is used, combined with other antivirals, for the treatment of chronic hepatitis C (p. 952.1) infection; it has broad genotypic coverage. An oral dose of daclatasvir 60 mg once daily, given with sofosbuvir (p. 1015.2), has been used in clinical studies.

References.

1. Lee C. Daclatasvir: potential role in hepatitis C. *Drug Des Devel Ther* 2013; **7:** 1223–33.
2. Herbst DA, Reddy KR. NS5A inhibitor, daclatasvir, for the treatment of chronic hepatitis C virus infection. *Expert Opin Invest Drugs* 2013; **22:** 1337–46.

Darunavir *(BAN, USAN, rINN)*

Darunavirum; TMC-114; UIC-94017; Дарунавир.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-(*N*^{1}-isobutylsulfanilamido)propyl]carbamate.

$C_{27}H_{37}N_3O_7S$=547.7

CAS — 206361-99-1.

ATC — J05AE10.

ATC Vet — QJ05AE10.

UNII — YO603Y8113.

Darunavir Ethanolate *(BANM, rINNM)*

Darunavir monoethanolate.

$C_{27}H_{37}N_3O_7S,C_2H_5OH$=593.7

ATC — J05AE10.

ATC Vet — QJ05AE10.

UNII — 33O78XF0BW.

Uses and Administration

Darunavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when darunavir is used alone, and it is therefore used with other antiretrovirals.

Darunavir is boosted with low-dose ritonavir, which acts as a pharmacokinetic enhancer. It is given orally as the ethanolate, but doses are expressed in terms of the base; 325 mg of darunavir ethanolate is equivalent to about 300 mg of darunavir.

In treatment-naive patients, the recommended dose of darunavir is 800 mg (with ritonavir 100 mg) once daily with food. In treatment-experienced patients doses are generally chosen based on the degree of darunavir resistance seen via genotypic testing; however where testing is not feasible, a dose of 600 mg (with ritonavir 100 mg) twice daily is recommended.

For details of doses in children, see below.

References.

1. Clotet B, *et al.* Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369:** 1169–78.
2. Busse KH, Penzak SR. Darunavir: a second-generation protease inhibitor. *Am J Health-Syst Pharm* 2007; **64:** 1593–602.
3. McKeage K, *et al.* Darunavir: a review of its use in the management of HIV infection in adults. *Drugs* 2009; **69:** 477–503.
4. Fullerton DS, *et al.* Pharmacoeconomics of darunavir. *Expert Rev Pharmacoecon Outcomes Res* 2011; **11:** 27–39.

Administration in children. Ritonavir-boosted darunavir may be used, with other antiretroviral drugs, for the treatment of HIV infection in children 6 years of age and older and weighing at least 20 kg. In the UK, it is further recommended that use of darunavir be reserved for treatment-experienced children only. The following oral doses are recommended, based on body-weight, and should not exceed the recommended adult dose for treatment-experienced patients (see above):

- 20 to less than 30 kg: darunavir 375 mg (with ritonavir 50 mg) twice daily
- 30 to less than 40 kg: darunavir 450 mg (with ritonavir 60 mg) twice daily
- 40 kg and over: darunavir 600 mg (with ritonavir 100 mg) twice daily

Further references to use in children.

1. Blanche S, *et al.* Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS* 2009; **23:** 2005–13.
2. Neely M, Kovacs A. Managing treatment-experienced pediatric and adolescent HIV patients: role of darunavir. *Ther Clin Risk Manag* 2009; **5:** 595–615.
3. McKeage K, Scott LJ. Darunavir: in treatment-experienced pediatric patients with HIV-1 infection. *Paediatr Drugs* 2010; **12:** 123–31.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing darunavir are gastrointestinal disturbances (abdominal pain, diarrhoea, nausea, and vomiting), nasopharyngitis, and hypertriglyceridaemia. Rashes (usually of mild to moderate severity) are seen in about 5 to 10% of patients, typically occurring within the first 4 weeks of treatment and resolving without stopping treatment. Severe rashes, including erythema multiforme and Stevens-Johnson syndrome, have occurred more rarely; treatment should be stopped if severe rash develops.

Other reported adverse effects are asthenia, dizziness, fatigue, headache, and insomnia. Less frequently reported adverse effects include folliculitis, myocardial infarction, osteopenia, osteoporosis, polyuria, somnolence, tachycardia, transient ischaemic attacks, and vertigo. Cases of drug-induced hepatitis, including fatalities, have been reported. Abnormal liver and pancreatic function tests, anaemia, neutropenia, and thrombocytopenia have also occurred.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including darunavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including darunavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Patients should undergo liver function tests before starting and during treatment with darunavir. It should not be used in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution (and liver enzymes values monitored), in those with mild to moderate impairment (Child-Pugh A or B) and those with chronic hepatitis B or C co-infection. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. All patients should be instructed to seek medical advice if symptoms suggestive of new or worsening hepatotoxicity occur.

Darunavir contains a sulfonamide moiety and should be used with caution in patients with known sulfonamide hypersensitivity, although its cross-sensitivity potential with sulfonamide drugs is unknown. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.) Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. An association with erythema multiforme and Stevens-Johnson syndrome has been reported and treatment should be stopped in patients who develop severe rashes.

Interactions

Darunavir inhibits, and is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It may affect the clearance of other drugs metabolised by this enzyme, potentially resulting in increased plasma concentrations and toxicity.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted darunavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- antiarrhythmics (amiodarone, bepridil, quinidine, and systemic lidocaine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide and sertindole)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated. Owing to the potential for increased serum concentrations of sildenafil, ritonavir-boosted darunavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir-boosted darunavir may increase serum concentrations of inhaled fluticasone and salmeterol and combination with either is not recommended. Ritonavir-boosted lopinavir, rifampicin, saquinavir, antiepileptics (phenobarbital and phenytoin), and St John's wort decrease the concentration of darunavir; use

with darunavir is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Darunavir is a selective inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance may develop between some HIV-protease inhibitors, but mechanisms of resistance to darunavir may differ from those to other drugs of the class.

Pharmacokinetics

Darunavir is rapidly absorbed after oral doses, resulting in a bioavailability of 82% when taken with recommended doses of ritonavir; food increases the bioavailability. Peak plasma concentrations occur within 2.5 to 4 hours. Darunavir is about 95% bound to plasma proteins. It is metabolised by oxidation by the cytochrome P450 system (mainly the isoenzyme CYP3A4), with at least 3 metabolites showing some antiretroviral activity. About 80% of a dose is excreted in the faeces, with 41.2% of this as unchanged drug; 14% is excreted in the urine, with 7.7% being unchanged drug. The mean terminal elimination half-life of darunavir is about 15 hours.

Reviews.

1. Rittweger M, Arastéh K. Clinical pharmacokinetics of darunavir. *Clin Pharmacokinet* 2007; **46:** 739–56.
2. Vermeir M, *et al.* Absorption, metabolism, and excretion of darunavir, a new protease inhibitor, administered alone and with low-dose ritonavir in healthy subjects. *Drug Metab Dispos* 2009; **37:** 809–20.
3. Yilmaz A, *et al.* Darunavir concentrations in cerebrospinal fluid and blood in HIV-1-infected individuals. *AIDS Res Hum Retroviruses* 2009; **25:** 457–61.
4. Giguère P, *et al.* Pharmacokinetics of darunavir, etravirine and raltegravir in an HIV-infected patient on haemodialysis. *AIDS* 2009; **23:** 740–2.
5. Ripamonti D, *et al.* Transplacental passage of ritonavir-boosted darunavir in two pregnant women. *Int J STD AIDS* 2009; **20:** 215–16.
6. Sekar V, *et al.* Pharmacokinetics of multiple-dose darunavir in combination with low-dose ritonavir in individuals with mild-to-moderate hepatic impairment. *Clin Pharmacokinet* 2010; **49:** 343–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prezista; ***Austral.***: Prezista; ***Austria***: Prezista; ***Belg.***: Prezista; ***Braz.***: Prezista; ***Canad.***: Prezista; ***Chile***: Prezista; ***China***: Prezista (预力); ***Cz.***: Prezista; ***Denm.***: Prezista; ***Fr.***: Prezista; ***Ger.***: Prezista; ***Gr.***: Prezista; ***Hung.***: Prezista; ***Irl.***: Prezista; ***Israel***: Prezista; ***Ital.***: Prezista; ***Malaysia***: Prezista; ***Neth.***: Prezista; ***Norw.***: Prezista; ***NZ***: Prezista; ***Pol.***: Prezista; ***Port.***: Prezista; ***Rus.***: Prezista (Презиста); ***Singapore***: Prezista; ***Spain***: Prezista; ***Swed.***: Prezista; ***Switz.***: Prezista; ***Thai.***: Prezista; ***Turk.***: Prezista; ***UK***: Prezista; ***USA***: Prezista.

Delavirdine Mesilate *(rINNM)*

Delavirdina, mesilato de; Délavirdine, Mésilate de; Delavirdine Mesylate (USAN); Delavirdini Mesilas; Mesilato de delavirdina; U-90152S; Делавирдина Мезилат.

1-[3-(Isopropylamino)-2-pyridyl]-4-[(5-methanesulfonamidoindol-2-yl)carbonyl]-piperazine monomethanesulfonate.

$C_{22}H_{28}N_6O_3S,CH_4O_3S$=552.7

CAS — 136817-59-9 (delavirdine); 147221-93-0 (delavirdine mesilate).

ATC — J05AG02.

ATC Vet — QJ05AG02.

UNII — 421105KRQE.

Uses and Administration

Delavirdine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Viral resistance emerges rapidly when delavirdine is used alone, and it is therefore used with other antiretrovirals for combination therapy of HIV infection and AIDS (p. 957.2).

Delavirdine is given orally as the mesilate in a usual dose of 400 mg three times daily. Some tablet formulations may be dispersed in water before use in order to increase bioavailability (see below).

Reviews.

1. Scott LJ, Perry CM. Delavirdine: a review of its use in HIV infection. *Drugs* 2000; **60:** 1411–44.

Adverse Effects

Adverse effects associated with antiretroviral regimens containing delavirdine are mostly mild to moderate. The most common adverse effect of delavirdine is rash, (usually diffuse, maculopapular, erythematous, and often pruritic), generally appearing within the first 3 weeks of starting therapy and resolving in 3 to 14 days. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse effects of moderate to severe intensity include generalised abdominal pain, asthenia, fatigue, fever, flu syndrome, headache, and localised pain. Other reported adverse effects include gastrointestinal disturbances (diarrhoea, nausea, vomiting), increased liver enzyme values, anxiety, depressive symptoms, insomnia, and respiratory effects (bronchitis, cough, pharyngitis, sinusitis, and upper respiratory-tract infections). Liver failure, haemolytic anaemia, rhabdomyolysis, and acute renal failure have been reported during postmarketing use.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including delavirdine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including delavirdine.

Precautions

Delavirdine should be stopped if a severe rash develops or if a rash is accompanied by fever, blistering, oral lesions, conjunctivitis, swelling, or muscle or joint aches. Delavirdine should be used with caution in patients with hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies delavirdine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Delavirdine has been shown to be teratogenic in *animals*. Clinical studies and postmarketing data have identified 10 infants born to mothers who took delavirdine during pregnancy. Eight of the infants were born healthy, 1 infant was born HIV-positive but had no congenital abnormalities, and 1 infant was born prematurely with a small muscular ventricular septal defect that spontaneously resolved.

Interactions

Delavirdine is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. Consequently it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of delavirdine. The absorption of delavirdine is reduced by drugs that raise gastric pH such as antacids, histamine H_2-antagonists, and proton pump inhibitors.

Delavirdine is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life threatening events. These drugs include antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (alprazolam, midazolam, triazolam). The antiepileptics carbamazepine, phenytoin, and phenobarbital, the antimycobacterials rifabutin and rifampicin, and St John's wort decrease the concentration of delavirdine; use with the antiretroviral is not recommended due to the possible loss of antiviral activity and development of resistance.

Antibacterials. Plasma concentrations of *dapsone* and *rifabutin* may be increased by delavirdine; *rifabutin* and *rifampicin*[1] may reduce delavirdine plasma concentrations and the use of either of these drugs with delavirdine is not recommended. For further information see under Rifampicin, p. 353.2 and Rifabutin, p. 350.1.

1. Borin MT, *et al.* Pharmacokinetic study of the interaction between rifampin and delavirdine mesylate. *Clin Pharmacol Ther* 1997; **61:** 544–53.

Antivirals. Use of delavirdine with buffered *didanosine* may result in reduced plasma concentrations of both drugs[1] and they should be given at least 1 hour apart.

Plasma concentrations of *HIV-protease inhibitors* may be increased by delavirdine (see Antivirals, under Interactions of Indinavir, p. 988.1). Doses of indinavir should therefore be reduced; with saquinavir, liver function should be monitored.

In return, *nelfinavir*, and *fosamprenavir* have been reported to decrease plasma concentrations of delavirdine; UK licensed product information for nelfinavir advises that use with delavirdine is not recommended, while US licensed product information for fosamprenavir contra-indicates use with delavirdine due to possible loss of virological response with development of delavirdine resistance.

1. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 169–74.

Antiviral Action

Delavirdine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to delavirdine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Delavirdine is rapidly absorbed after oral doses and peak plasma concentrations occur after about 1 hour. The bioavailability of delavirdine tablets is about 85% of that from an oral solution after a single dose. The bioavailability of the 100-mg tablet can be increased by about 20% by dissolving it in water before use; the 200-mg tablets do not readily disperse in water and should be swallowed intact. Delavirdine is about 98% bound to plasma proteins. It is extensively metabolised by hepatic microsomal enzymes, mainly by the cytochrome P450 isoenzyme CYP3A4 (although CYP2D6 may play some role), to several inactive metabolites. The plasma half-life after usual dosage is about 5.8 hours and ranges from 2 to 11 hours. Delavirdine is excreted as metabolites in the urine and faeces. Less than 5% is excreted in the urine unchanged.

Reviews.

1. Voorman RL, *et al.* Metabolism of delavirdine, a human immunodeficiency virus type-1 reverse transcriptase inhibitor, by microsomal cytochrome P450 in humans, rats, and other species: probable involvement of CYP2D6 and CYP3A. *Drug Metab Dispos* 1998; **26:** 631–9.
2. Tran JQ, *et al.* Delavirdine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2001; **40:** 207–26.
3. Shelton MJ, *et al.* Pharmacokinetics of ritonavir and delavirdine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2003; **47:** 1694–9.
4. Smith PF, *et al.* Population pharmacokinetics of delavirdine and N-delavirdine in HIV-infected individuals. *Clin Pharmacokinet* 2005; **44:** 99–109.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Rescriptor; ***Canad.***: Rescriptor; ***USA***: Rescriptor.

Denotivir *(pINN)*

Dénotivir; Denotivirum; Денотивир.

5-Benzamido-4′-chloro-3-methyl-4-isothiazolecarboxanilide.

$C_{18}H_{14}ClN_3O_2S$=371.8

CAS — 51287-57-1.

UNII — W656S9I00W.

Profile

Denotivir has antiviral, antibacterial, and anti-inflammatory properties. It is used topically as a 3% cream in the treatment of herpes virus infections and in other skin disorders complicated by bacterial infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Polvir†; Vratizolin; ***Ukr.***: Vratizolin (Вратизолин).

Didanosine *(BAN, USAN, rINN)*

BMY-40900; DDI; ddIno; Didanocin; Didanosiini; Didanosin; Didanosina; Didanosinum; Didanozin; Didanozinas; Dideoxyinosine; Didesoxinosina; NSC-612049; Диданозин.

2′,3′-Dideoxyinosine.

$C_{10}H_{12}N_4O_3$=236.2

CAS — 69655-05-6.

ATC — J05AF02.

ATC Vet — QJ05AF02.

UNII — K3GDH6OH08.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Didanosine). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in dimethyl sulfoxide.

USP 36: (Didanosine). A white to off-white crystalline powder. Practically insoluble or insoluble in acetone and in methyl alcohol; very soluble in dimethyl sulfoxide. Store at

a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Didanosine is a nucleoside reverse transcriptase inhibitor structurally related to inosine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when didanosine is used alone, and it is therefore used with other antiretrovirals.

Didanosine is given orally, usually as buffered chewable/dispersible tablets or enteric-coated capsules. Doses should be taken at least 30 minutes before, or 2 hours after, a meal. The total daily dose may be given as either a single dose or as two divided doses, the choice being dependent upon both the formulation and the strength used. For those weighing more than 60 kg the recommended dose is 400 mg daily and for those under 60 kg, 250 mg daily is given. In the USA, it is recommended that enteric-coated capsules (*Videx EC, BMS*) be given in a single, daily dose of 200 mg to those weighing less than 25 kg.

For details of doses in children, see below.

Doses of didanosine may need to be amended when given with some other antiretrovirals. For further details see under Interactions, below.

Dosage reduction may be necessary in patients with renal (see below) or hepatic impairment, although no specific dose reductions are recommended in patients with hepatic impairment and close monitoring is required.

Reviews.

1. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection. *Drugs* 1999; **58:** 1099–1135.
2. Moreno S, *et al*. Didanosine enteric-coated capsule: current role in patients with HIV-1 infection. *Drugs* 2007; **67:** 1441–62.

Administration in children. For the treatment of HIV infection in children, didanosine is given daily with other antiretroviral drugs; doses are taken orally on an empty stomach.

In the USA an oral solution or enteric-coated tablet are available for use:

- the oral solution may be given to children from 2 weeks of age in the following doses based on age, and body-surface:
  - those between 2 weeks and 8 months of age: 100 mg/m² twice daily
  - those over 8 months of age: 120 mg/m² twice daily
- enteric-coated capsules may be given orally to children weighing at least 20 kg in the following doses based on body-weight:
  - 20 to less than 25 kg: 200 mg once daily
  - 25 to less than 60 kg: 250 mg once daily
  - 60 kg or more: 400 mg once daily

In the UK chewable or dispersible tablets or enteric-coated capsules are available for use; doses are based on body-surface:

- the chewable or dispersible tablets may be given orally to children older than 3 months of age, as either a single dose or as two divided doses, in a dose of 240 mg/m² daily *or* 180 mg/m² daily if given with zidovudine
- enteric-coated capsules may be given orally to children older than 6 years of age in a dose of 240 mg/m² daily *or* 180 mg/m² daily if given with zidovudine

Alternatively, the *BNFC* gives the following doses:

- 1 to 8 months of age: 50 to 100 mg/m² twice daily
- over 8 months of age: 180 to 240 mg/m² once daily to a maximum of 400 mg daily

Doses for children should not exceed those recommended for adults (see Uses and Administration, above).

Administration in renal impairment. Dosage of didanosine should be reduced in patients with renal impairment. The following oral doses are recommended based on the patient's weight and creatinine clearance (CC):

Adults weighing 60 kg or more:

- CC 60 mL/minute or more: usual adult doses
- CC 30 to 59 mL/minute: 200 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 150 mg once daily
- CC less than 10 mL/minute: 100 mg once daily

Adults less than 60 kg:

- CC 60 mL/minute or more: usual adult doses
- CC 30 to 59 mL/minute: 150 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 100 mg once daily
- CC less than 10 mL/minute: 75 mg once daily

For patients requiring intermittent haemodialysis or continuous ambulatory peritoneal dialysis, dosing recommendations for CC less than 10 mL/min may be used; doses should preferably be given after the dialysis run.

Adverse Effects

The most common serious adverse effects of didanosine are peripheral neuropathy and potentially fatal pancreatitis. Other commonly reported adverse effects include abdominal pain, diarrhoea, fatigue, headache, nausea, rash, and vomiting. Abnormal liver function tests may occur and hepatitis or fatal hepatic failure has been reported rarely; fatalities were reported most often in patients taking didanosine with stavudine and hydroxycarbamide. Non-cirrhotic portal hypertension, including cases resulting in liver transplantation or death, has also occurred. Retinal and optic-nerve changes have been reported in children, particularly in those taking higher than recommended doses; retinal depigmentation has been reported in adult patients. Other adverse effects include alopecia, anaemia, asthenia, dry mouth, fever, flatulence, parotid gland enlargement, leucopenia, hypersensitivity reactions including anaphylaxis, hyperuricaemia, and thrombocytopenia. Lactic acidosis usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs; it has sometimes been fatal, and generally occurs after some months of treatment.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including didanosine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including didanosine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the blood. In general, haematological abnormalities are less common in patients taking didanosine than in those taking zidovudine. However, there have been reports of thrombocytopenia associated with didanosine.[1-3]

1. Butler KM, *et al*. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med* 1991; **324:** 137–44.
2. Lor E, Liu YQ. Didanosine-associated eosinophilia with acute thrombocytopenia. *Ann Pharmacother* 1993; **27:** 23–5.
3. Herranz P, *et al*. Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344:** 680.

Effects on the eyes. Retinal lesions with atrophy of the retinal pigment epithelium at the periphery of the retina were reported in 4 children receiving didanosine doses of 270 to 540 mg/m² daily.[1]

1. Whitcup SM, *et al*. Retinal lesions in children treated with dideoxyinosine. *N Engl J Med* 1992; **326:** 1226–7.

Effects on the heart. For the possible risk of myocardial infarction in patients taking didanosine, see Effects on the Heart under Adverse Effects of Zidovudine, p. 1025.2.

Effects on the liver. Fatal fulminant hepatic failure was reported[1] in a patient receiving didanosine. A further 14 cases had been noted by the manufacturer, and elevated liver enzymes have been recorded during clinical studies.[2-5]

Potentially fatal non-cirrhotic portal hypertension (NCPH) has been reported in some HIV-infected individuals. In a nested, case-control study including 15 patients with NCPH and 75 matched control subjects, prolonged exposure to didanosine was found to be the only independent risk factor for NCPH in patients with HIV.[6]

1. Lai KK, *et al*. Fulminant hepatic failure associated with 2′,3′-dideoxyinosine (ddI). *Ann Intern Med* 1991; **115:** 283–4.
2. Dolin R, *et al*. Zidovudine compared with didanosine in patients with advanced HIV type 1 infection and little or no experience with zidovudine. *Arch Intern Med* 1995; **155:** 961–74.
3. Jablonowski H, *et al*. A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; **9:** 463–9.
4. Alpha International Coordinating Committee. The Alpha trial: European/Australian randomized double-blind trial of two doses of didanosine in zidovudine-intolerant patients with symptomatic HIV disease. *AIDS* 1996; **10:** 867–80.
5. Gatell JM, *et al*. Switching from zidovudine to didanosine in patients with symptomatic HIV infection and disease progression. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **12:** 249–58.
6. Kovari H, *et al*. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis* 2009; **49:** 626–35.

Effects on mental state. Recurrent mania associated with didanosine treatment has been reported in a patient.[1]

1. Brouillette MJ, *et al*. Didanosine-induced mania in HIV infection. *Am J Psychiatry* 1994; **151:** 1839–40.

Effects on the mouth. Xerostomia (dry mouth) may be a troublesome effect in patients receiving didanosine.[1,2]

1. Dodd CL, *et al*. Xerostomia associated with didanosine. *Lancet* 1992; **340:** 790.
2. Valentine C, *et al*. Xerostomia associated with didanosine. *Lancet* 1992; **340:** 1542.

Effects on the pancreas. Pancreatitis is recognised as being the most serious adverse effect of didanosine and can be fatal.[1-3] It appears to be dose-related, occurring in up to 13% of patients receiving 750 mg of didanosine daily.[2,4] Pancreatitis can resolve if didanosine is withdrawn[5] and cautious reintroduction of didanosine has been possible in some patients.[6] Raised amylase concentrations[3] and glucose intolerance have been reported in patients who subsequently developed pancreatitis.

1. Bouvet E, *et al*. Fatal case of 2′,3′-dideoxyinosine-associated pancreatitis. *Lancet* 1990; **336:** 1515.
2. Kahn JO, *et al*. A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *N Engl J Med* 1992; **327:** 581–7.
3. Dolin R, *et al*. Zidovudine compared with didanosine in patients with advanced HIV-type 1 infection and little or no previous experience with zidovudine. *Arch Intern Med* 1995; **155:** 961–74.
4. Jablonowski H, *et al*. A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; **9:** 463–9.
5. Nguyen B-Y, *et al*. Five-year follow-up of a phase I study of didanosine in patients with advanced human immunodeficiency virus infection. *J Infect Dis* 1995; **171:** 1180–9.
6. Butler KM, *et al*. Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics* 1993; **91:** 747–51.

Effects on the skin. Didanosine has been implicated in a case of Stevens-Johnson syndrome[1] and of cutaneous vasculitis.[2]

1. Parneix-Spake A, *et al*. Didanosine as probable cause of Stevens-Johnson syndrome. *Lancet* 1992; **340:** 857–8.
2. Herranz P, *et al*. Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344:** 680.

Precautions

Didanosine should be used with extreme caution in patients with a history of pancreatitis and those with increased triglyceride concentrations should be observed carefully for signs of pancreatitis and treatment with didanosine interrupted in all patients with signs and symptoms of possible pancreatitis, until it has been excluded. Alternative treatment regimens should also be considered in patients who develop symptoms of peripheral neuropathy. Use with other drugs likely to cause pancreatitis or peripheral neuropathy (see Interactions, below) should preferably be avoided; treatment with didanosine should be suspended if possible when use of such drugs is essential.

Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. However, cases of non-cirrhotic portal hypertension (some leading to liver transplantation or death) have also been reported in patients with no evidence of viral hepatitis. Didanosine should be given with caution to patients with hepatomegaly or other risk factors for liver disease and patients with hepatic impairment. Regular checks of liver function are recommended. If liver enzymes increase to more than 5 times the upper limit of normal during treatment then didanosine should be stopped. Patients should also be monitored for early signs of portal hypertension (including thrombocytopenia or splenomegaly). Didanosine should be stopped in patients with evidence of portal hypertension. Treatment with didanosine may be associated with lactic acidosis and should also be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, steatosis, or metabolic or lactic acidosis of unknown aetiology. Dosage reduction may be necessary in renal impairment.

To monitor for retinal or optic nerve changes, ophthalmic examination (including visual acuity, colour vision, and dilated fundus examination) should be considered annually in patients taking didanosine, as well as when any changes in vision are reported. didanosine withdrawn if they occur. Monitoring should also be considered in adults.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies didanosine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Use of didanosine with other drugs known to cause pancreatitis (for example intravenous pentamidine) or with drugs that may cause peripheral neuropathy (for example metronidazole, isoniazid, and vincristine) should be avoided. If co-administration is unavoidable, patients should be monitored carefully for these adverse effects.

An increase in the area under the plasma concentration-time curve for didanosine has been reported when allopurinol or other xanthine oxidase inhibitors are given concurrently; because of the risk of toxicity, use of didanosine with allopurinol is not recommended.

Plasma concentrations of didanosine may be reduced by methadone and increased by ganciclovir or valganciclovir, although the degree may vary with specific didanosine preparations. The paediatric powder for oral solution (*Videx; BMS, USA*) should not be given with methadone or ganciclovir, although the enteric-coated tablet (*Videx; BMS, USA*) could be used, if necessary, with careful monitoring.

Didanosine formulations (chewable or dispersible preparation) contain an antacid and other drugs that could be affected by an increased gastric pH (for example some HIV-protease inhibitors, ketoconazole, itraconazole, and fluoroquinolone antibacterials) should be given at least 2 hours before didanosine. Didanosine preparations containing magnesium or aluminium antacids should not be given with tetracyclines.

Use of didanosine with tenofovir results in increased plasma concentrations of didanosine and consequently an increased risk of didanosine-related adverse effects such as peripheral neuropathy, pancreatitis, and lactic acidosis. Fatalities have been reported. There have also been reports of virological failure and emergence of resistance at an early stage of treatment when didanosine and tenofovir were given with lamivudine as part of a once daily triple nucleoside regimen. UK licensed product information for both didanosine and tenofovir does not recommend co-administration of these drugs either at standard or reduced doses of didanosine. A 250-mg daily dose of didanosine had been evaluated, but resulted in virological failure and the emergence of resistance. US product information for didanosine, however, recommends that co-administration may be undertaken with caution in patients with normal renal function. For patients weighing greater than 60 kg the dose of didanosine should be reduced to 250 mg daily, while for those weighing less than 60 kg a dose of 200 mg daily is recommended. US product information for tenofovir advises against using didanosine with tenofovir in patients under 60 kg due to a lack of data.

Ribavirin has been shown *in vitro* to increase the intracellular triphosphate levels of didanosine and to potentially increase the risk of adverse effects related to didanosine; concurrent use should be avoided.

See also below for interactions with other antivirals.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antivirals. Plasma concentrations of didanosine are roughly doubled when given with *ganciclovir*.[1-3] *Valganciclovir*, the prodrug of ganciclovir, inhibits purine nucleoside phosphorylase and increases didanosine concentrations. Significant CD4+ T lymphocyte count decline and symptoms of didanosine toxicity, despite complete viral suppression, occurred in an HIV-positive patient given an antiretroviral regimen containing didanosine plus valganciclovir for the treatment of CMV enteritis. Complete CD4 + count recovery and resolution of symptoms occurred when didanosine was replaced with abacavir.[4]

Changes in the pharmacokinetics of didanosine and *zidovudine* have occurred when these drugs are given together, but results of studies have not been consistent, and the effects have generally been of limited clinical significance. For further details, see under Interactions in Zidovudine, p. 1026.3.

Tenofovir has been reported to significantly increase plasma concentrations of didanosine,[5] (see also p. 973.3) and may increase the risk of pancreatitis associated with didanosine.[6,7] There has also been a report of acute renal failure and fatal lactic acidosis when tenofovir was added to a regimen containing didanosine.[8]

Use of didanosine with *delavirdine* resulted in reductions in the area under the concentration-time curve for both drugs in a single-dose study.[9] Licensed product information for delavirdine recommends that these two drugs should be given at least 1 hour apart.

Absorption of some *HIV-protease inhibitors* may be reduced by the buffers in some didanosine formulations and they should therefore be given 1 or more hours apart, depending on the drug (see p. 988.1).

1. Griffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; **10** (suppl 4): S3–S6.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1057–62.
3. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 227–34.
4. Tseng AL, Salit IE. CD4+ cell count decline despite HIV suppression: a probable didanosine-valganciclovir interaction. *Ann Pharmacother* 2007; **41:** 512–17.
5. Pecora Fulco P, Kirian MA. Effect of tenofovir on didanosine absorption in patients with HIV. *Ann Pharmacother* 2003; **37:** 1325–8.
6. Blanchard JN, *et al.* Pancreatitis with didanosine and tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; **37:** e57–e62. Correction. *ibid.*: 995. [title of paper corrected]
7. Kirian MA, *et al.* Acute onset of pancreatitis with concomitant use of tenofovir and didanosine. *Ann Pharmacother* 2004; **38:** 1660–3.
8. Murphy MD, *et al.* Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis* 2003; **36:** 1082–5.
9. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 169–74.

Antiviral Action

Didanosine is converted intracellularly to its active form dideoxyadenosine triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

Didanosine-resistant strains of HIV emerge during didanosine therapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. Evidence for the development of didanosine-resistant HIV was reported in 36 of 64 patients with advanced HIV infection within 24 weeks of switching from zidovudine to didanosine monotherapy.[1] Patients with the didanosine resistance mutation for HIV reverse transcriptase showed a greater decline in CD4+ T cell count and increase in viral burden than those without.

Multiple-drug resistant mutations have been found in patients taking long-term combination antiretroviral therapy containing didanosine.[2]

1. Kozal MJ, *et al.* Didanosine resistance in HIV-infected patients switched from zidovudine to didanosine monotherapy. *Ann Intern Med* 1994; **121:** 263–8.
2. Kavlick MF, *et al.* Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; **98:** 1506–13.

Pharmacokinetics

Didanosine is rapidly hydrolysed in the acid medium of the stomach and is therefore given orally with pH buffers or antacids. Bioavailability is reported to range from 20 to 40% depending on the formulation used; the bioavailability is substantially reduced with some formulations if taken with or after food. Peak plasma concentrations occur about 1 hour after oral dosage. Binding to plasma proteins is reported to be less than 5%. Didanosine has been reported not to cross the blood brain barrier.

Didanosine is metabolised intracellularly to the active antiviral metabolite dideoxyadenosine triphosphate. The plasma elimination half-life is reported to be about 1.5 hours. Renal clearance is by glomerular filtration and active tubular secretion; about 20% of an oral dose is recovered in the urine. Didanosine is partially cleared by haemodialysis but not by peritoneal dialysis.

References.

1. Balis FM, *et al.* Clinical pharmacology of 2′,3′-dideoxyinosine in human immunodeficiency virus-infected children. *J Infect Dis* 1992; **165:** 99–104.
2. Morse GD, *et al.* Comparative pharmacokinetics of antiviral nucleoside analogues. *Clin Pharmacokinet* 1993; **24:** 101–23.
3. Mueller BU, *et al.* Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics* 1994; **94:** 724–31.
4. Knupp CA, *et al.* Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: influence of hemodialysis and continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther* 1996; **60:** 535–42.
5. Wintergerst U, *et al.* Lack of absorption of didanosine after rectal administration in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; **43:** 699–701.
6. Abreu T, *et al.* Bioavailability of once- and twice-daily regimens of didanosine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2000; **44:** 1375–6.
7. Hernández-Novoa B, *et al.* Effect of food on the antiviral activity of didanosine enteric-coated capsules: a pilot comparative study. *HIV Med* 2008; **9:** 187–91.

Pregnancy. Fetal blood concentrations of 14 and 19% of the maternal serum-didanosine concentrations have been reported.[1] There is evidence of extensive metabolism in the placenta.[2]

1. Pons JC, *et al.* Fetoplacental passage of 2′,3′-dideoxyinosine. *Lancet* 1991; **337:** 732.
2. Dancis J, *et al.* Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J Acquir Immune Defic Syndr* 1993; **6:** 2–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dinosin; Videx; ***Austral.***: Videx; ***Austria***: Videx; ***Belg.***: Videx; ***Braz.***: Videx; ***Canad.***: Videx; ***Chile***: Videx; ***China***: Ai Lue (艾略); Hate (哈特); Videx (惠妥滋); ZhengYuan (正元); ***Cz.***: Videx; ***Denm.***: Videx; ***Fin.***: Videx; ***Fr.***: Videx; ***Ger.***: Videx; ***Gr.***: Videx; ***Hong Kong***: Videx; ***Hung.***: Videx; ***India***: D-Sine; DDRetro; Dinex; ***Indon.***: Videx†; ***Irl.***: Videx; ***Ital.***: Videx; ***Malaysia***: Videx; ***Mex.***: Didasten†; Dinocin; Videx; ***Neth.***: Videx; ***Norw.***: Videx; ***NZ***: Videx; ***Pol.***: Videx†; ***Port.***: Videx; ***Rus.***: Videx (Видекс); ***S.Afr.***: Deladex; Videx; ***Spain***: Videx; ***Swed.***: Videx; ***Switz.***: Videx; ***Thai.***: Divir; Videx; ***Turk.***: Videx; ***UK***: Videx; ***USA***: Videx; ***Venez.***: Videx.

Multi-ingredient Preparations. ***India***: Odivir Kit.

Pharmacopoeial Preparations

USP 36: Didanosine Delayed-Release Capsules; Didanosine for Oral Solution; Didanosine Tablets for Oral Suspension.

Docosanol *(USAN)*

Behenyl Alcohol; *n*-Docosanol; Docosyl Alcohol; IK-2; Докозанол.

1-Docosanol.

$C_{22}H_{46}O$=326.6

CAS — 661-19-8.

ATC — D06BB11.

ATC Vet — QD06BB11.

UNII — 9G1OE216XY.

Profile

Docosanol is an antiviral used topically five times daily as a 10% cream in the treatment of recurrent herpes labialis (see Herpes Simplex Infections, p. 955.2). Docosanol is reported to act by inhibiting fusion between the cell plasma membrane and the herpes simplex virus, thereby preventing viral entry into cells and subsequent viral replication. It has been investigated for genital herpes.

References.

1. Habbema L, *et al.* n-Docosanol 10% cream in the treatment of recurrent herpes labialis: a randomised, double-blind, placebo-controlled study. *Acta Derm Venereol* 1996; **76:** 479–81.
2. Sacks SL, *et al.* Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2001; **45:** 222–30.
3. Leung DT, Sacks SL. Docosanol: a topical antiviral for herpes labialis. *Expert Opin Pharmacother* 2004; **5:** 2567–71.
4. Treister NS, Woo SB. Topical n-docosanol for management of recurrent herpes labialis. *Expert Opin Pharmacother* 2010; **11:** 853–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Abreva; ***Cz.***: Erazaban; ***Fr.***: Erazaban; ***Gr.***: Healip; ***Irl.***: Erazaban; ***Neth.***: Erazaban; ***Norw.***: Heloc†; ***Pol.***: Erazaban; ***Port.***: Erazaban; ***Swed.***: Healip†; ***UK***: Blistex Cold Sore Cream; ***Ukr.***: Priora (Приора); ***USA***: Abreva.

Dolutegravir *(USAN, rINN)*

Dolutégravir; Dolutegravirum; GSK-1349572; S-349572; Долутегравир.

(4*R*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1′,2′:4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide.

$C_{20}H_{19}F_2N_3O_5$=419.4

CAS — 1051375-16-6.

UNII — DKO1W9H7M1.

Dolutegravir Sodium *(USAN, rINNM)*

Dolutegravir Sódico; Dolutégravir Sodique; GSK-1349572A; Natrii Dolutegravirum; Натрий Долутегравир.

$C_{20}H_{18}F_2N_3NaO_5$=441.4

CAS — 1051375-19-9.

UNII — 1Q1V9V5WYQ.

Profile

Dolutegravir is an inhibitor of HIV integrase, an enzyme essential for insertion of viral DNA into the host genome, and thus for replication. It is used with other antiretrovirals for treatment of HIV infection and AIDS (p. 957.2) and is licensed for use in both treatment-naive and treatment-experienced patients.

It is given orally as the sodium salt but doses are expressed in terms of the free acid; 52.6 mg of dolutegravir sodium is equivalent to about 50 mg of dolutegravir. The usual dose is the equivalent of 50 mg of dolutegravir once daily, given with or without food. When used in integrase strand transfer inhibitor (INSTI)-experienced patients with certain INSTI-associated resistance substitutions or suspected INSTI resistance, a dose of 50 mg twice daily is recommended. This dose is also suggested when dolutegravir is given with efavirenz, ritonavir-boosted fosamprenavir or tipranavir, or rifampicin.

Dolutegravir increases the serum concentration of dofetilide (p. 1367.1) with the possible risk of serious and/or life-threatening events.

References.

1. Ballantyne AD, Perry CM. Dolutegravir: first global approval. *Drugs* 2013; **73:** 1627–37.

2. Cahn P, *et al.* Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet* 2013; **382:** 700–8.
3. Raffi F, *et al.* Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013; **13:** 927–35.
4. Eron JJ, *et al.* Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *J Infect Dis* 2013; **207:** 740–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Tivicay.

Efavirenz *(BAN, rINN)*

5B706; DMP-266; Efavirentsi; Éfavirenz; Efavirenzum; Efawirenz; L-743; L-743726; Эфавиренз.

(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

$C_{14}H_9ClF_3NO_2$=315.7

CAS — 154598-52-4.

ATC — J05AG03.

ATC Vet — QJ05AG03.

UNII — JE6H2O27P8.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Efavirenz). A white to slightly pink crystalline powder. Practically insoluble in water; soluble in methyl alcohol. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Efavirenz is a non-nucleoside reverse transcriptase inhibitor with activity against HIV. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS (p. 957.2).

Efavirenz is given orally as *capsules* or *tablets* in a dose of 600 mg once daily; alternatively, it may be given as an *oral solution* in a dose of 720 mg once daily. Efavirenz tablets and capsules should be given on an empty stomach. Dosing at bedtime is recommended during the first 2 to 4 weeks of therapy to improve tolerability. Bioavailability of efavirenz from the oral solution is less than that from the capsule and so proportionately higher doses of the solution are used.

Licensed product information notes that the dose of efavirenz may need to be adjusted to manage significant drug interactions:

- a decreased dose of 300 mg once daily is recommended when efavirenz is given with voriconazole (in contrast, the maintenance dose of voriconazole should be increased; for details, see Uses and Administration of Voriconazole, p. 597.2)
- for use with rifampicin, the dose of efavirenz should be increased to 800 mg daily in patients weighing 50 kg or more

For a dose-escalation protocol suggested to reduce efavirenz-related neuropsychiatric adverse effects, see Effects on the Nervous System, below.

For details of doses in children and adolescents, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing efavirenz in combination with emtricitabine and tenofovir are available in some countries.

References.
1. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. *Drugs* 2006; **66:** 1501–12.
2. Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. *J Antimicrob Chemother* 2009; **64:** 910–28.
3. Mbuagbaw LCE, *et al.* Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 26/01/11).
4. Deeks ED, Perry CM. Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla): a review of its use in the management of HIV infection. *Drugs* 2010; **70:** 2315–38.

Administration. The bioavailability of a single 600-mg dose of efavirenz given as the capsule contents sprinkled and mixed with a small amount of suitable food vehicle (such as apple sauce, grape jelly, yogurt, or infant formula) was found to be bioequivalent to a 600-mg efavirenz dose given as intact capsules under fasting conditions in healthy adults.[1]

1. Kaul S, *et al.* Bioavailability in healthy adults of efavirenz capsule contents mixed with a small amount of food. *Am J Health-Syst Pharm* 2010; **67:** 217–22.

Administration in children. For the treatment of HIV infection in children 3 years of age and older and adolescents efavirenz is given daily with other antiretroviral drugs. In the USA oral *capsules* and *tablets* are available and the dose is based on body-weight:

- 10 to 14 kg: 200 mg once daily
- 15 to 19 kg: 250 mg once daily
- 20 to 24 kg: 300 mg once daily
- 25 to 32.4 kg: 350 mg once daily
- 32.5 to 39 kg: 400 mg once daily
- 40 kg or more: as for adults (above)

Capsules are also available in the UK for use in children and adolescents; doses are similar to those used in the USA.

In the UK an *oral solution* is also available; the dose ranges, which are again calculated in terms of body-weight, also depend on the age range:

- 13 to 14 kg: children less than 5 years, 360 mg daily; children 5 years and older, 270 mg once daily
- 15 to 19 kg: children less than 5 years, 390 mg daily; children 5 years and older, 300 mg once daily
- 20 to 24 kg: children less than 5 years, 450 mg daily; children 5 years and older, 360 mg once daily
- 25 to 32.4 kg: children less than 5 years, 510 mg daily; children 5 years and older, 450 mg once daily
- 32.5 to 39 kg: children 5 years and older, 510 mg once daily
- 40 kg or more: children 5 years and older, as for adults, above

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing efavirenz are rashes and psychiatric or CNS disturbances. Mild to moderate rashes (usually maculopapular eruptions) generally appear within the first 2 weeks of starting therapy and may resolve within a month of continued treatment; severe forms including erythema multiforme and Stevens-Johnson syndrome have been reported occasionally. Adverse CNS include agitation, amnesia, confusion, dizziness, euphoria, headache, insomnia or somnolence, impaired concentration, abnormal thinking or dreaming, convulsions, depersonalisation, and hallucinations. Such effects usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks; they may occur more frequently when efavirenz is taken with meals, possibly due to increased efavirenz plasma concentrations. Serious psychiatric adverse effects include severe depression, suicidal ideation and attempts, aggressive behaviour, and psychotic reactions including paranoia and mania. Other adverse effects include nausea and vomiting, diarrhoea, fatigue, and pancreatitis. Raised liver enzyme values and raised serum-cholesterol and -triglyceride concentrations have been reported. Hepatic failure and photoallergic dermatitis have occurred.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including efavirenz, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including efavirenz. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported.

Effects on the mouth. Burning mouth syndrome was diagnosed in a patient 2 weeks after adding efavirenz to her long-standing combination antiretroviral treatment regimen.[1] Efavirenz was stopped and the syndrome resolved within 1 week.

1. Borrás-Blasco J, *et al.* Burning mouth syndrome due to efavirenz therapy. *Ann Pharmacother* 2006; **40:** 1471–2.

Effects on the nervous system. More than 50% of patients starting efavirenz therapy have efavirenz-related neuropsychiatric adverse events. These may be severe enough to lead to patients stopping treatment, although the risk of exacerbating anxiety or depression has been questioned. Symptoms are generally transient and resolve within 4 weeks of beginning therapy.[1] The results of a randomised, double-blind, multicentre study,[2] suggested that step-wise dose escalation of oral efavirenz over 2 weeks (200 mg daily on days 1 to 6, 400 mg daily on days 7 to 13, and 600 mg daily on day 14 and beyond) might reduce the incidence and intensity of efavirenz-related neuropsychiatric adverse effects, with no apparent decrease in antiviral efficacy. However, there has been some concern about longer term neurotoxicity. A cohort study[3] in 146 asymptomatic HIV-infected subjects, most of whom had been receiving combination antiretroviral therapy for more than a year, found that about half of them had some degree of cognitive impairment, and this was strongly associated with use of efavirenz.

1. Clifford DB, *et al.* Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005; **143:** 714–21.
2. Gutiérrez-Valencia A, *et al.* Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. *Ann Intern Med* 2009; **151:** 149–56.
3. Ciccarelli N, *et al.* Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011; **76:** 1403–9.

Effects on vitamin D metabolism. In a cross-sectional study of 1077 HIV-infected patients,[1] inclusion of efavirenz in antiretroviral regimens was found to nearly double the risk of severe vitamin D deficiency. A subsequent observational cohort study[2] also found an association between vitamin D insufficiency and use of an efavirenz-based antiretroviral regimen.

1. Welz T, *et al.* Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *AIDS* 2010; **24:** 1923–8.
2. Dao CN, *et al.* Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. *Clin Infect Dis* 2011; **52:** 396–405.

Hyperhidrosis. Severe night sweats in a patient being treated with efavirenz resolved when the dose was reduced; the patient had higher than normal plasma-efavirenz concentrations at standard dosage, perhaps due to a abnormal allele of the cytochrome P450 isoenzyme CYP2D6.[1]

1. Martín AF, *et al.* Hyperhidrosis in association with efavirenz. *AIDS Patient Care STDS* 2009; **23:** 143–5.

Hypersensitivity. Hypersensitivity syndromes suggestive of DRESS (drug rash with eosinophilia and systemic symptoms) have been reported with efavirenz;[1-5] systemic symptoms may include renal impairment, respiratory failure, and hepatitis. In some cases, systemic manifestations have occurred without evident rash or eosinophilia.[3]

1. Bossi P, *et al.* Hypersensitivity syndrome associated with efavirenz therapy. *Clin Infect Dis* 2000; **30:** 227–8.
2. Behrens GM, *et al.* Pulmonary hypersensitivity reaction induced by efavirenz. *Lancet* 2001; **357:** 1503–4. Correction. *ibid.*; 2060.
3. Angel-Moreno-Maroto A, *et al.* Severe efavirenz-induced hypersensitivity syndrome (not-DRESS) with acute renal failure. *J Infect* 2006; **52:** e39–e40.
4. Curry E, *et al.* Renal impairment and hypersensitivity reaction due to efavirenz. *Nephrology (Carlton)* 2008; **13:** 541.
5. Leung JM, *et al.* Efavirenz-induced hypersensitivity reaction manifesting in rash and hepatitis in a Latino male. *Ann Pharmacother* 2008; **42:** 425–9.

Precautions

Efavirenz is contra-indicated in patients with severe hepatic impairment (Child-Pugh class C), and is not recommended in those with moderate impairment; it should be used with caution, and liver enzymes values monitored, in patients with mild liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution should be exercised in patients with a history of seizures or psychiatric disorders including depression. Efavirenz should be stopped if a severe rash, associated with blistering, desquamation, mucosal involvement, or fever, develops. Monitoring of serum lipids and blood-glucose may be considered during efavirenz treatment. Food may increase exposure to efavirenz and lead to an increase in the frequency of undesirable effects.

False-positive results in some urinary cannabinoid tests have been reported in subjects receiving efavirenz.

Abuse. Efavirenz has reportedly been used as an ingredient in 'Whoonga', a highly addictive street drug used in some parts of Africa to enhance the hallucinogenic effects of cannabis (p. 2467.1). These reports have been questioned by some authorities, citing tests of samples from South Africa where no efavirenz was identified.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies efavirenz as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Licensed product information states that efavirenz has been associated with teratogenicity in *animals.* No specific malformation pattern was noted in more than 500 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen. However, retrospective analysis of these pregnancies noted a few cases of neural tube defects, including meningomyelocele. US guidelines for use of antiretroviral drugs in pregnant HIV-infected women[1] recommend that use of efavirenz be avoided in the first trimester, although use later in the

pregnancy may be considered if no better alternatives exist. The use of adequate contraceptive measures is recommended during, and for 12 weeks after, treatment with regimens containing efavirenz.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Efavirenz is metabolised mainly by cytochrome P450 isoenzymes including CYP3A4. Consequently, it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Enzyme inducers may decrease plasma concentrations of efavirenz; efavirenz itself acts as an enzyme inducer and can reduce plasma concentrations of other drugs. Inhibition of some P450 isoenzymes has also been found *in vitro*.

Efavirenz is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antihistamines (astemizole and terfenadine), calcium-channel blockers (bepridil), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (midazolam and triazolam). St John's wort decreases the concentration of efavirenz; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Antibacterials. Plasma concentrations of efavirenz may be reduced by *rifampicin* and may necessitate an increase in the dose of efavirenz; for specific dosing guidance, see Uses and Administration, p. 975.1. Concurrent use with *rifabutin* does not appear to significantly affect efavirenz concentrations, but for the effect of efavirenz on rifabutin, see p. 350.1.

Use of efavirenz with *clarithromycin* has resulted in a decrease in the plasma concentration of clarithromycin and an increase in its active hydroxy metabolite. The combination has been associated with a high incidence of rashes.

Antiepileptics. A small crossover study[1] in healthy subjects reported that both efavirenz and carbamazepine exposure was significantly reduced when efavirenz 600 mg daily was given with carbamazepine titrated to 400 mg daily. Both drugs are metabolised by cytochrome P450 isoenzymes and they appear to induce each other's metabolism. However, no significant effect was seen in the pharmacokinetics of the 10,11-epoxide metabolite of carbamazepine. It was recommended that an alternative antiepileptic drug (such as vigabatrin or gabapentin) be considered or the dose of carbamazepine be titrated to a higher dose if given with efavirenz.

1. Ji P, *et al*. Pharmacokinetic interaction between efavirenz and carbamazepine after multiple-dose administration in healthy subjects. *J Clin Pharmacol* 2008; **48:** 948–56.

Antifungals. When efavirenz and *voriconazole* are given together the concentration of efavirenz is increased and that of voriconazole reduced.[1] For the adjusted doses recommended for managing this interaction, see Uses and Administration of Efavirenz (p. 975.1) and Voriconazole (p. 597.2).

Efavirenz also significantly decreased the concentrations of *itraconazole* and *posaconazole*; as no suitable dose adjustments for these drugs have been established, use of alternative antifungals should be considered. Efavirenz may also have the potential to decrease concentrations of *ketoconazole*.

1. Damle B, *et al*. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. *Br J Clin Pharmacol* 2008; **65:** 523–30.

Antivirals. For the effect of efavirenz on *HIV-protease inhibitors*, see p. 988.1.

Grapefruit. The metabolism of efavirenz may be inhibited by concomitant ingestion of grapefruit juice.

Antiviral Action

Efavirenz acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to efavirenz and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Efavirenz is absorbed after oral doses and peak plasma concentrations occur after about 3 to 5 hours. Steady-state plasma concentrations are reached in 6 to 7 days after multiple dosing. Food increases the bioavailability of efavirenz. Efavirenz is more than 99% bound to plasma proteins and is distributed into the CSF. It is metabolised mainly by hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2B6 into inactive hydroxylated, metabolites. Efavirenz acts as an enzyme inducer and induces its own metabolism resulting in a terminal half-life of 40 to 55 hours after multiple doses compared with 52 to 76 hours after a single dose. About 14 to 34% of a dose is excreted in the urine (less than 1% unchanged), and 16 to 61% in the faeces (mainly as unchanged drug).

References.

1. Kappelhoff BS, *et al*. Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2005; **44:** 849–61.
2. Almond LM, *et al*. Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. *J Antimicrob Chemother* 2005; **56:** 738–44.
3. Burger D, *et al*. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* 2006; **61:** 148–54.
4. Back DJ, *et al*. Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2006; **45:** 213–14.
5. Wintergerst U, *et al*. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother* 2008; **61:** 1336–9.
6. Ngaimisi E, *et al*. Long-term efavirenz autoinduction and its effect on plasma exposure in HIV patients. *Clin Pharmacol Ther* 2010; **88:** 676–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Efavilea†; Filginase; Stocrin; Sulfinav; Virorrever; Zuletel; ***Austral.***: Stocrin; ***Austria***: Stocrin; ***Belg.***: Stocrin; ***Braz.***: Evir; Stocrin; ***Canad.***: Sustiva; ***Chile***: Stocrin; ***China***: Stocrin (施多宁); ***Cz.***: Stocrin; Sustiva; ***Denm.***: Stocrin; ***Fin.***: Stocrin; ***Fr.***: Sustiva; ***Ger.***: Sustiva; ***Gr.***: Stocrin; Sustiva; ***Hong Kong***: Stocrin; ***Hung.***: Stocrin; ***India***: EF; Efavir; Efcure; Efferven; Evirenz; ***Irl.***: Stocrin; Sustiva; ***Israel***: Stocrin; ***Ital.***: Sustiva; ***Malaysia***: Stocrin; ***Mex.***: Stocrin; ***Neth.***: Stocrin; Sustiva; ***Norw.***: Stocrin; ***NZ***: Stocrin; ***Pol.***: Stocrin; Sustiva; ***Port.***: Stocrin; Sustiva; ***Rus.***: Stocrin (Стокрин); ***S.Afr.***: Erige; Hevaz; Stocrin; ***Singapore***: Stocrin; ***Spain***: Sustiva; ***Swed.***: Stocrin; ***Switz.***: Stocrin; ***Thai.***: Stocrin; ***Turk.***: Stocrin; ***UK***: Sustiva; ***USA***: Sustiva; ***Venez.***: Efavir; Stocrin.

Multi-ingredient Preparations. ***Austral.***: Atripla; ***Austria***: Atripla; ***Belg.***: Atripla; ***Canad.***: Atripla; ***Cz.***: Atripla; ***Denm.***: Atripla; ***Fr.***: Atripla; ***Ger.***: Atripla; ***Gr.***: Atripla; ***Hong Kong***: Atripla; ***India***: Cytocom-E; Duovir-E; Emduo-E; Lazid-E; Odivir Kit; ***Irl.***: Atripla; ***Israel***: Atripla; ***Ital.***: Atripla; ***Neth.***: Atripla; ***Norw.***: Atripla; ***NZ***: Atripla; ***Pol.***: Atripla; ***Port.***: Atripla; ***Spain***: Atripla; ***Swed.***: Atripla; ***Switz.***: Atripla; ***Thai.***: Atripla; ***UK***: Atripla; ***USA***: Atripla.

Pharmacopoeial Preparations
USP 36: Efavirenz Capsules.

Elvitegravir *(USAN, rINN)*

Elvitégravir; Elvitegravirum; GS-9137; JTK-303; Элвитегравир.

6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

$C_{23}H_{23}ClFNO_5$=447.9

CAS — 697761-98-1.

ATC — J05AX11.

ATC Vet — QJ05AX11.

UNII — 4GDQ854U53.

Profile

Elvitegravir is an HIV-integrase inhibitor with antiretroviral activity against HIV-1. Elvitegravir (150 mg) may be given as a component of a four-drug, fixed-dose combination product (*Stribild, Gilead, USA* and also referred to as the Quad pill) with the pharmacokinetic enhancer cobicistat (p. 2482.3) and the NRTIs emtricitabine (below) and tenofovir (p. 1018.1) for the treatment of HIV infection and AIDS (p. 957.2) in antiretroviral treatment-naive patients. The recommended dose is one tablet taken orally once daily with food. It is also being studied with low-dose ritonavir acting as a pharmacokinetic enhancer.

Elvitegravir is metabolised by the cytochrome P450 isoenzyme CYP3A and drugs that induce CYP3A may decrease its plasma concentration, while drugs that inhibit CYP3A may increase its plasma concentration. It is also a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

References.

1. Ramanathan S, *et al*. Pharmacokinetics of coadministered ritonavir-boosted elvitegravir and zidovudine, didanosine, stavudine, or abacavir. *J Acquir Immune Defic Syndr* 2007; **46:** 160–6.
2. Shimura K, *et al*. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *J Virol* 2008; **82:** 764–74.
3. Shimura K, Kodama EN. Elvitegravir: a new HIV integrase inhibitor. *Antiviral Chem Chemother* 2009; **20:** 79–85.
4. Klibanov OM. Elvitegravir, an oral HIV integrase inhibitor, for the potential treatment of HIV infection. *Curr Opin Investig Drugs* 2009; **10:** 190–200.
5. Zolopa AR, *et al*. Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. *J Infect Dis* 2010; **201:** 814–22.
6. Ramanathan S, *et al*. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet* 2011; **50:** 229–44.
7. Olin JL, *et al*. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet for HIV-1 infection treatment. *Ann Pharmacother* 2012; **46:** 1671–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Vitekta.

Multi-ingredient Preparations. ***Jpn***: Stribild; ***UK***: Stribild; ***USA***: Stribild.

Emtricitabine *(USAN, rINN)*

BW-524W91; Emtricitabin; Emtricitabina; Emtricitabinum; Emtrisitabin; (-)-FTC; FTC-(-); FTC; Эмтрицитабин.

5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine.

$C_8H_{10}FN_3O_3S$=247.2

CAS — 143491-57-0.

ATC — J05AF09.

ATC Vet — QJ05AF09.

UNII — G70B4ETF4S.

Uses and Administration

Emtricitabine is a nucleoside reverse transcriptase inhibitor related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when emtricitabine is used alone, and it is therefore used with other antiretrovirals.

Emtricitabine is given orally once daily as capsules in a usual adult dose of 200 mg or 240 mg as oral solution.

For details of doses in infants, children, and adolescents, see below.

For details of doses of emtricitabine to be used in patients with renal impairment, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing emtricitabine with tenofovir, and with efavirenz plus tenofovir are available in some countries. It is also a component of a four-drug, fixed-dose combination product with elvitegravir and tenofovir and the pharmacokinetic enhancer cobicistat (p. 2482.3).

Reviews.

1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64:** 2075–82.
2. Modrzejewski KA, Herman RA. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. *Ann Pharmacother* 2004; **38:** 1006–14.
3. Frampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1427–48.
4. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. *Clin Infect Dis* 2006; **42:** 126–31.
5. Perry CM. Emtricitabine/tenofovir disoproxil fumarate: in combination with a protease inhibitor in HIV-1 infection. *Drugs* 2009; **69:** 843–57.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents emtricitabine is given with other antiretroviral drugs. Doses, given once daily, are based on body-weight:

- in infants up to 3 months of age the *oral solution* is given in a dose of 3 mg/kg daily
- in infants, children, and adolescents over 3 months of age the oral solution is given in a dose of 6 mg/kg daily to a maximum daily dose of 240 mg
- the *capsules* may be given to children and adolescents weighing more then 33 kg in the usual adult dose of 200 mg daily.

Administration in renal impairment. Doses of emtricitabine should be reduced in patients with renal impairment, according to the patient's creatinine clearance (CC):

- CC at least 50 mL/minute: usual adult doses (as capsules or solution)
- CC 30 to 49 mL/minute: 200 mg every 48 hours (capsules) or 120 mg every 24 hours (oral solution)
- CC 15 to 29 mL/minute: 200 mg every 72 hours (capsules) or 80 mg every 24 hours (oral solution)
- CC less than 15 mL/minute: 200 mg every 96 hours (capsules) or 60 mg every 24 hours (oral solution)

Hepatitis B. For mention of the use of emtricitabine with tenofovir in the management of treatment-experienced patients with hepatitis B, see under Tenofovir, p. 1018.2.

Prevention of HIV transmission. For discussion of the use of emtricitabine with tenofovir to reduce transmission of HIV infection, see under Tenofovir, p. 1018.2.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing emtricitabine are headache, diarrhoea, and nausea; hyperpigmented skin discoloration is very common in children and common in adults. Other common adverse effects include abdominal pain, vomiting, dyspepsia, abnormal dreams, asthenia, dizziness, insomnia, pain, allergic skin reactions, pruritus, rashes, and urticaria. Abnormal laboratory test results associated with emtricitabine-containing regimens include hyperbilirubinaemia, increases in serum lipase and pancreatic amylase, and raised liver enzymes. There have also been reports of neutropenia and anaemia. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including emtricitabine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including emtricitabine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Precautions

Treatment with emtricitabine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Emtricitabine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events; treatment should be interrupted or stopped if there is evidence of exacerbation of liver disease. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment is begun. Acute and sometimes severe exacerbations of hepatitis have been reported in hepatitis B-infected patients after stopping treatment with emtricitabine; patients co-infected with HIV and hepatitis B should be closely monitored for several months after stopping treatment. Emtricitabine should be used with caution and doses adjusted in patients with renal impairment.

Interactions

Caution should be exercised when emtricitabine is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Emtricitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase. Emtricitabine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Emtricitabine is rapidly and extensively absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur after 1 to 2 hours. Bioavailability is reported to be 93% for the capsules. Binding to plasma proteins is reported to be less than 4%. The plasma elimination half-life is about 10 hours. Emtricitabine is metabolised to a limited degree, but is excreted largely unchanged in the urine and to a lesser extent in the faeces. It is partially removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Emtriva; ***Austral.***: Emtriva; ***Austria***: Emtriva; ***Belg.***: Emtriva; ***Canad.***: Emtriva; ***China***: Hui Er Ding (惠尔丁); Xin Luo Shu (新罗舒); ***Cz.***: Emtriva; ***Denm.***: Emtriva; Eviplera; ***Fin.***: Emtriva; ***Fr.***: Emtriva; ***Ger.***: Emtriva; ***Gr.***: Emtriva; ***Hung.***: Emtriva; ***Irl.***: Emtriva; ***Ital.***: Emtriva; ***Mex.***: Emtriva; ***Neth.***: Emtriva; ***Norw.***: Emtriva; ***NZ***: Emtriva; ***Pol.***: Emtriva; ***Port.***: Emtriva; ***Spain***: Emtriva; ***Swed.***: Emtriva; ***Switz.***: Emtriva; ***UK***: Emtriva; ***USA***: Emtriva.

Multi-ingredient Preparations. ***Arg.***: Truvada; ***Austral.***: Atripla; Truvada; ***Austria***: Atripla; Truvada; ***Belg.***: Atripla; Truvada; ***Canad.***: Atripla; Truvada; ***Chile***: Truvada; ***Cz.***: Atripla; Truvada; ***Denm.***: Atripla; Truvada; ***Fin.***: Truvada; ***Fr.***: Atripla; Truvada; ***Ger.***: Atripla; Eviplera; Truvada; ***Gr.***: Atripla; Truvada; ***Hong Kong***: Atripla; Truvada; ***Irl.***: Atripla; Truvada; ***Israel***: Atripla; Eviplera; Truvada; ***Ital.***: Atripla; Truvada; ***Jpn***: Stribild; ***Mex.***: Truvada; ***Neth.***: Atripla; Truvada; ***Norw.***: Atripla; Eviplera; Truvada; ***NZ***: Atripla; Truvada; ***Pol.***: Atripla; Truvada; ***Port.***: Atripla; Truvada; ***S.Afr.***: Adco Emtevir; Didivir; Truvada; Tyricten; ***Spain***: Atripla; Truvada; ***Swed.***: Atripla; Eviplera; Truvada; ***Switz.***: Atripla; Eviplera; Truvada; ***Thai.***: Atripla; Ricovir-Em; Truvada; ***UK***: Atripla; Eviplera; Stribild; Truvada; ***USA***: Atripla; Complera; Stribild; Truvada.

Enfuvirtide *(BAN, USAN, rINN)*

DP-178; Enfuvirtid; Enfuvirtida; Enfuvirtidum; Enfuwirtyd; Pentafusida; Pentafuside; T-20; Энфувиртид.

$C_{204}H_{301}N_{51}O_{64}$=4491.9

CAS — 159519-65-0.

ATC — J05AX07.

ATC Vet — QJ05AX07.

UNII — 19OWO1T3ZE.

Uses and Administration

Enfuvirtide is a synthetic 36-amino acid peptide that blocks HIV cell fusion and viral entry. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS (p. 957.2). Enfuvirtide is given by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a usual dose of 90 mg twice daily. Each injection should be given at a different site from the preceding one. For details of doses in children and adolescents, see below.

References.

1. Oldfield V, *et al.* Enfuvirtide: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1139–60.
2. Reynes J, *et al.* TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS* 2007; **21:** 533–43.
3. Wiznia A, *et al.* T20-310 Study Group. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J* 2007; **26:** 799–805.
4. Rockstroh J, *et al.* Adherence to enfuvirtide and its impact on treatment efficacy. *AIDS Res Hum Retroviruses* 2008; **24:** 141–8.
5. Saberi P, *et al.* Immunologic benefits of enfuvirtide in patients enrolled in a drug assistance program. *Ann Pharmacother* 2008; **42:** 621–6.
6. Kitchen CM, *et al.* Enfuvirtide antiretroviral therapy in HIV-1 infection. *Ther Clin Risk Manag* 2008; **4:** 433–9.
7. Makinson A, Reynes J. The fusion inhibitor enfuvirtide in recent antiretroviral strategies. *Curr Opin HIV AIDS* 2009; **4:** 150–8.
8. Joly V, *et al.* Enfuvirtide: from basic investigations to current clinical use. *Expert Opin Pharmacother* 2010; **11:** 2701–13.

Administration in children. For the treatment of HIV infection, enfuvirtide may be given to children 6 to 16 years of age by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a dose of 2 mg/kg twice daily (to a maximum of 90 mg twice daily). Each injection should be given at a different site from the preceding one.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing enfuvirtide are local injection site reactions with resultant pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis. These reactions have been reported to occur in 98% of patients, but only a small minority needed to stop therapy. Other very common adverse effects include nausea, diarrhoea, weight loss, and peripheral neuropathy. Anorexia, abdominal pain, constipation, pancreatitis, myalgia, weakness or loss of strength, lymphadenopathy, insomnia, depression, 'flu-like' illness, sinusitis, and conjunctivitis are also common. An increased incidence of some bacterial infections, in particular of pneumonia, has occurred in patients receiving enfuvirtide. Hypersensitivity reactions have occurred in about 1% of patients. Other adverse effects have included anxiety, hyperglycaemia, hypertriglyceridaemia, and eosinophilia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy in HIV-infected patients with severe immune deficiency. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

References.

1. Maggi P, *et al.* Cutaneous injection site reactions to long-term therapy with enfuvirtide. *J Antimicrob Chemother* 2004; **53:** 678–81.
2. Morilla ME, *et al.* Localized amyloidosis at the site of enfuvirtide injection. *Ann Intern Med* 2009; **151:** 515–16.
3. Kousignian I, *et al.* Does enfuvirtide increase the risk of bacterial pneumonia in patients receiving combination antiretroviral therapy? *J Antimicrob Chemother* 2010; **65:** 138–44.
4. Wallace BJ, *et al.* Enfuvirtide injection site reactions: a clinical and histopathological appraisal. *Australas J Dermatol* 2011; **52:** 19–26.

Precautions

Enfuvirtide should be stopped immediately and should not be restarted in patients who develop signs of a systemic hypersensitivity reaction. An increased incidence of some bacterial infections, in particular of pneumonia, has been seen and patients receiving enfuvirtide should be closely monitored for signs of pneumonia. UK licensed product information recommends that enfuvirtide be used with caution in patients with hepatic impairment and in those with moderate to severe renal impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Antiviral Action

Enfuvirtide is an HIV fusion inhibitor that interferes with entry of HIV into cells by binding to the gp41 subunit of the viral envelope glycoprotein, thereby inhibiting fusion of viral and cellular membranes. Strains of HIV with reduced susceptibility to enfuvirtide have been isolated in patients receiving the drug but, owing to the different mode of action of enfuvirtide and the fact that it does not require intracellular activation for its activity, cross-resistance with other antiretrovirals may occur less frequently.

Resistance. References to the development of resistance to enfuvirtide.

1. Greenberg ML, Cammack N. Resistance to enfuvirtide, the first HIV fusion inhibitor. *J Antimicrob Chemother* 2004; **54:** 333–40.
2. van Lelyveld SF, *et al.* Therapy failure following selection of enfuvirtide-resistant HIV-1 in cerebrospinal fluid. *Clin Infect Dis* 2010; **50:** 387–90.
3. Leung PH, *et al.* High prevalence of primary enfuvirtide (ENF) resistance-associated mutations in HIV-1-infected patients in Hong Kong. *J Clin Virol* 2010; **47:** 273–5.

Pharmacokinetics

Enfuvirtide is absorbed after subcutaneous injection with a mean absolute bioavailability of 84%. It is 92% bound to plasma proteins. Enfuvirtide is a peptide and is metabolised by hydrolysis; it does not inhibit cytochrome P450 isoenzymes. The elimination half-life is 3.8 hours after subcutaneous use, although elimination pathways have yet to be identified.

References.

1. Patel IH, *et al.* Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clin Pharmacokinet* 2005; **44:** 175–86.
2. Zhang X, *et al.* Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol* 2007; **47:** 510–17.
3. Weizsaecker K, *et al.* Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS* 2011; **22:** 294–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fuzeon; ***Austral.***: Fuzeon; ***Austria***: Fuzeon; ***Belg.***: Fuzeon; ***Braz.***: Fuzeon; ***Canad.***: Fuzeon; ***Chile***: Fuzeon; ***China***: Fuzeon (恩夫韦肽); ***Cz.***: Fuzeon; ***Denm.***: Fuzeon; ***Fin.***: Fuzeon; ***Fr.***: Fuzeon; ***Ger.***: Fuzeon; ***Gr.***: Fuzeon; ***Hung.***: Fuzeon; ***Irl.***: Fuzeon; ***Israel***: Fuzeon; ***Ital.***: Fuzeon; ***Mex.***: Fuzeon; ***Neth.***: Fuzeon; ***Norw.***: Fuzeon†; ***NZ***: Fuzeon; ***Pol.***: Fuzeon; ***Port.***: Fuzeon; ***Rus.***: Fuzeon (Фузеон); ***Singapore***: Fuzeon; ***Spain***: Fuzeon; ***Swed.***: Fuzeon; ***Switz.***: Fuzeon; ***Thai.***: Fuzeon; ***UK***: Fuzeon; ***USA***: Fuzeon.

Entecavir *(USAN, rINN)*

BMS-200475-01; Entécavir; Entecavirum; SQ-34676; Энтекавир.

9-[(1*S*,3*R*,4*S*)-4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine monohydrate.

$C_{12}H_{15}N_5O_3,H_2O$=295.3

CAS — 142217-69-4 (anhydrous entecavir); 209216-23-9 (entecavir monohydrate).

ATC — J05AF10.

ATC Vet — QJ05AF10.

UNII — 5968Y6H45M (entecavir); NNU2O4609D (anhydrous entecavir).

Uses and Administration

Entecavir is a nucleoside reverse transcriptase inhibitor, structurally related to guanosine with selective antiviral activity against hepatitis B virus. It is used for the treatment of chronic hepatitis B (p. 952.1) in adults with compensated liver disease with evidence of active viral replication, persistently elevated liver enzyme values, and histologically active disease, including those resistant to lamivudine; it may also be used in those with decompensated liver disease. The usual oral dose of entecavir in patients with:

- compensated liver disease and who are nucleoside treatment-naive is 500 micrograms once daily, either with or without food. In patients with a history of hepatitis B viraemia during lamivudine therapy or with known resistance to lamivudine, a dose of 1 mg once daily on an empty stomach should be used
- decompensated liver disease is 1 mg once daily on an empty stomach

For details of reduced doses to be used in patients with renal impairment, see below.

Reviews.

1. Sims KA, Woodland AM. Entecavir: a new nucleoside analog for the treatment of chronic hepatitis B infection. *Pharmacotherapy* 2006; **26:** 1745–57.
2. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; **28:** 184–203.
3. Scott LJ, Keating GM. Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2009; **69:** 1003–33.
4. Cornberg M, Manns MP. Entecavir— Möglichkeiten und Grenzen einer effektiven Therapie der chronischen Hepatitis B. *Dtsch Med Wochenschr* 2010; **135:** 32–7.
5. Woo G, *et al.* Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010; **139:** 1218–29.
6. Keating GM. Entecavir: a review of its use in the treatment of chronic hepatitis B in patients with decompensated liver disease. *Drugs* 2011; **71:** 2511–29.

Administration in renal impairment. Oral doses of entecavir should be reduced in patients with renal impairment according to creatinine clearance (CC).

In those with compensated liver disease and a CC of:

- 30 to 49 mL/minute: 250 micrograms once daily or 500 micrograms every 48 hours in nucleoside treatment-naive patients; 500 micrograms once daily or 1 mg every 48 hours in lamivudine-refractory patients
- 10 to 29 mL/minute: 150 micrograms once daily or 500 micrograms every 72 hours in nucleoside treatment-naive patients; 300 micrograms once daily, 500 micrograms every 48 hours, or 1 mg every 72 hours in lamivudine-refractory patients
- less than 10 mL/minute (and patients on haemodialysis or continuous ambulatory peritoneal dialysis): 50 micrograms once daily or 500 micrograms every 5 to 7 days in nucleoside treatment-naive patients; 100 micrograms once daily, 500 micrograms every 72 hours, or 1 mg every 7 days in lamivudine-refractory patients

In those with decompensated disease, doses are the same as those for patients with lamivudine-resistant compensated disease.

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Adverse Effects

The most common adverse effects of entecavir have been headache, fatigue, dizziness, and nausea. Other adverse effects include diarrhoea, dyspepsia, insomnia, somnolence, and vomiting.

Raised liver enzyme concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with entecavir. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p. 1024.3). Patients with decompensated liver disease may be at a higher risk of serious hepatic adverse effects, lactic acidosis, and specific renal adverse effects such as hepatorenal syndrome.

Entecavir is carcinogenic in *rodents*, but a relationship with human cancer has not been established.

Precautions

Entecavir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Entecavir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients whose liver enzyme values increase due to response to treatment must be distinguished from those in whom this indicates toxicity. Exacerbation of hepatitis B has been reported both during and after stopping treatment with entecavir. Hepatic function should be monitored closely while on treatment and for several months after treatment is stopped. Dosage reduction may be necessary in patients with renal impairment.

Limited clinical experience suggests there is a potential for HIV to develop resistance to NRTIs if entecavir is used to treat chronic hepatitis B virus infection in patients with undiagnosed or untreated HIV infection. Treatment with entecavir is not recommended for co-infected patients who are not also receiving HAART. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with entecavir.

HIV-infected patients. It was initially thought that entecavir did not inhibit replication of HIV-1 at clinically relevant doses. However, a small consistent decrease in HIV-1 RNA was noted in 3 patients with HIV-1 and hepatitis B virus co-infection being treated with entecavir monotherapy.[1] In one of them, an HIV variant containing the M184V resistance substitution was found. Subsequent *in vitro* analyses showed that HIV-1 strains containing M184V were resistant to entecavir.

1. McMahon MA, *et al.* The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med* 2007; **356:** 2614–21.

Interactions

Caution should be exercised when entecavir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Entecavir is phosphorylated intracellularly to the active triphosphate form which competes with deoxyguanosine triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby inhibiting every stage of the enzyme's activity.

Although initially thought to be inactive against HIV at clinically relevant doses, entecavir may have sufficient action to result in the selection of resistant HIV variants (see HIV-infected Patients, under Precautions, above).

Pharmacokinetics

Entecavir is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur 30 to 90 minutes after an oral dose and steady state concentrations after 6 to 10 days of treatment. Absorption is both delayed and reduced by food; this is not considered to be clinically relevant in nucleoside treatment-naive patients but may affect efficacy in lamivudine-refractory patients in whom entecavir should be taken on an empty stomach. Bioavailability of the tablet formulation is equal to that of the oral solution and they may be given interchangeably. Binding of entecavir to plasma proteins is about 13% *in vitro*. Entecavir is not metabolised by the cytochrome P450 system. It is mainly eliminated by the kidneys by glomerular filtration and active tubular secretion, with a terminal elimination half-life of 128 to 149 hours. Small amounts of glucuronide and sulfate conjugates are formed. Entecavir is partially removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Baraclude; Teneir; ***Austral.***: Baraclude; ***Austria***: Baraclude; ***Belg.***: Baraclude; ***Braz.***: Baraclude; ***Canad.***: Baraclude; ***Chile***: Baraclude; ***China***: Baraclude (博路定); ***Cz.***: Baraclude; ***Denm.***: Baraclude; ***Fr.***: Baraclude; ***Ger.***: Baraclude; ***Gr.***: Baraclude; ***Hong Kong***: Baraclude; ***Hung.***: Baraclude; ***India***: Baraclude; ***Indon.***: Baraclude; ***Irl.***: Baraclude; ***Israel***: Baraclude; ***Ital.***: Baraclude; ***Malaysia***: Baraclude; ***Neth.***: Baraclude; ***Norw.***: Baraclude; ***NZ***: Baraclude; ***Philipp.***: Baraclude; ***Pol.***: Baraclude; ***Port.***: Baraclude; ***Rus.***: Baraclude (Бараклюд); ***S.Afr.***: Baraclude; ***Singapore***: Baraclude; ***Spain***: Baraclude; ***Swed.***: Baraclude; ***Switz.***: Baraclude; ***Thai.***: Baraclude; ***Turk.***: Baraclude; ***UK***: Baraclude; ***USA***: Baraclude.

Etravirine *(BAN, USAN, rINN)*

Etravirin; Etravirina; Étravirine; Etravirinum; R-165335; TMC-125; Этравирин.

4-[6-Amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile.

$C_{20}H_{15}BrN_6O$=435.3

CAS — 269055-15-4.

ATC — J05AG04.

ATC Vet — QJ05AG04.

UNII — 0C50HW4FO1.

Uses and Administration

Etravirine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is given with other antiretrovirals for the treatment of HIV infection and AIDS (p. 957.2) in treatment-experienced patients, who have evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretrovirals. Etravirine is given orally in a usual dose of 200 mg twice daily after food.

For details of doses in children and adolescents, see below.

References.

1. Deeks ED, Keating GM. Etravirine. *Drugs* 2008; **68:** 2357–72.
2. Johnson LB, Saravolatz LD. Etravirine, a next-generation nonnucleoside reverse-transcriptase inhibitor. *Clin Infect Dis* 2009; **48:** 1123–8.
3. Harris M, *et al.* Canadian consensus guidelines for the optimal use of etravirine in the treatment of HIV-infected adults. *Can J Infect Dis Med Microbiol* 2009; **20:** e24–e34.
4. Martínez E, Nelson M. Simplification of antiretroviral therapy with etravirine. *AIDS Rev* 2010; **12:** 52–9.
5. Tseng A, Macarthur RD. Profile of etravirine for the treatment of HIV infection. *Ther Clin Risk Manag* 2010; **6:** 49–58.
6. Towner W, *et al.* Efficacy, safety, and tolerability of etravirine with and without darunavir/ritonavir or raltegravir in treatment-experienced patients: analysis of the etravirine early access program in the United States. *J Acquir Immune Defic Syndr* 2010; **53:** 614–18.
7. Elsayed RK, Caldwell DJ. Etravirine: a novel nonnucleoside reverse transcriptase inhibitor for managing human immunodeficiency virus infection. *Am J Health-Syst Pharm* 2010; **67:** 193–205.

Licensed product information states etravirine tablets may be dispersed in a suitable liquid in patients with swallowing difficulties. The tablets should first be dispersed in a small amount of water (about 5 mL or just enough to cover tablet); thereafter, the mixture may be further diluted with more water, orange juice, or milk, although the use of grapefruit juice, and warm or carbonated beverages should be avoided. The mixture should be stirred well and the entire contents given to the patient immediately after preparation.

Administration in children. Etravirine is given orally with other antiretroviral drugs in the management of HIV infection and AIDS in treatment-experienced children and adolescents aged 6 to 18 years. Doses should be taken after food and are based on body-weight:

- 16 to less than 20 kg: 100 mg twice daily
- 20 to less than 25 kg: 125 mg twice daily
- 25 to less than 30 kg: 150 mg twice daily
- at least 30 kg: 200 mg twice daily (maximum dose)

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing etravirine are nausea and rash (usually mild to moderate) and generally appearing in the second week of treatment and resolving within 1 to 2 weeks. Severe and potentially life-threatening skin reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Severe systemic hypersensitivity reactions (DRESS syndrome—drug rash with eosinophilia and systemic symptoms), including cases resulting in liver failure, have also occurred. There have also been reports of rhabdomyolysis. Additional adverse events of moderate to severe intensity reported by at least 2% of patients receiving etravirine in clinical studies included gastrointestinal complaints (abdominal pain, diarrhoea, nausea, and vomiting), fatigue, headache, hypertension, and peripheral neuropathy. Raised liver enzyme values, glucose levels, and serum-cholesterol and -triglyceride concentrations have been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including etravirine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including etravirine.

General references.

1. Grinsztejn B, *et al.* A review of the safety and tolerability profile of the next-generation NNRTI etravirine. *AIDS Res Hum Retroviruses* 2010; **26:** 725–33.

Precautions

Etravirine should be stopped immediately if a severe skin reaction or other signs or symptoms of hypersensitivity occur, including severe rash or rash accompanied by fever, malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, or eosinophilia. Etravirine is not recommended in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution in patients with mild to moderate liver disease. Patients who have virologic failure on a NNRTI-containing regimen should not be given etravirine in a regimen containing only NRTIs.

Interactions

Etravirine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19. It is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19. Consequently it may compete with other drugs metabolised by these systems, potentially resulting in

mutually altered plasma concentrations and possibly toxicity. Enzyme inducers may decrease plasma concentrations of etravirine. Carbamazepine, phenobarbital, phenytoin, rifampicin, rifapentine, and St John's wort may significantly decrease the concentration of etravirine; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Etravirine should not be given with other NNRTIs or with HIV-protease inhibitors given without ritonavir-boosting. US licensed product information also recommends that use with ritonavir-boosted atazanavir, fosamprenavir, or tipranavir be avoided; however, UK licensed product information suggests that ritonavir-boosted atazanavir may be used with etravirine and requires no dose adjustment, and that ritonavir-boosted fosamprenavir may also be used, although dose reductions may be required.

Reviews.
1. Kakuda TN, *et al.* Pharmacokinetic interactions between etravirine and non-antiretroviral drugs. *Clin Pharmacokinet* 2011; **50:** 25–39.

Antibacterials. For information on the interactions of etravirine with *rifabutin* and *rifampicin*, see p. 350.1 and p. 353.2 respectively.

Antiviral Action

Etravirine acts by inhibition of HIV-1 reverse transcriptase and blocks viral RNA- and DNA-dependent DNA polymerase activities. It is a flexible molecule designed to fit in the active pocket of viral reverse transcriptase in different ways, even when the shape of that pocket changes because of viral mutations. This is considered to reduce the risk of the development of resistance; phase II studies in treatment-experienced patients have shown activity against HIV resistant to other NNRTIs (delavirdine, efavirenz, and nevirapine).

Pharmacokinetics

Etravirine is readily absorbed after oral doses and peak plasma concentrations occur after about 2.5 to 4 hours; absorption is increased by food. It is about 99.9% bound to plasma proteins. Etravirine is extensively metabolised by hepatic microsomal enzymes, mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19 families, to substantially less active metabolites. The mean plasma half-life after usual dosage is about 41 hours and ranges from 21 to 61 hours. About 93.7% of a dose appears in the faeces (81.2 to 86.4% as unchanged drug), and 1.2% in the urine (unchanged drug was not detected in the urine).

References.
1. Schöller-Gyüre M, *et al.* Clinical pharmacokinetics and pharmacodynamics of etravirine. *Clin Pharmacokinet* 2009; **48:** 561–74.
2. Kakuda TN, *et al.* Pharmacokinetics and pharmacodynamics of the non-nucleoside reverse-transcriptase inhibitor etravirine in treatment-experienced HIV-1-infected patients. *Clin Pharmacol Ther* 2010; **88:** 695–703.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Intelence; ***Austral.***: Intelence; ***Austria***: Intelence; ***Belg.***: Intelence; ***Braz.***: Intelence; ***Canad.***: Intelence; ***Chile***: Intelence; ***China***: Intelence (英特莱); ***Cz.***: Intelence; ***Denm.***: Intelence; ***Fr.***: Intelence; ***Ger.***: Intelence; ***Gr.***: Intelence; ***Hung.***: Intelence; ***Irl.***: Intelence; ***Israel***: Intelence; ***Ital.***: Intelence; ***Neth.***: Intelence; ***Norw.***: Intelence; ***NZ***: Intelence; ***Pol.***: Intelence; ***Port.***: Intelence; ***Rus.***: Intelence (Интеленс); ***Spain***: Intelence; ***Swed.***: Intelence; ***Switz.***: Intelence; ***Thai.***: Intelence; ***UK***: Intelence; ***USA***: Intelence.

Famciclovir *(BAN, USAN, rINN)*

AV-42810; BRL-42810; Famciclovirum; Famciklovir; Famsikloviiri; Famsiklovir; Fanciclovir; Фамцикловир.

2[2-(2-Amino-9*H*-purin-9-yl)ethyl]trimethylene diacetate.

$C_{14}H_{19}N_5O_4$=321.3

CAS — 104227-87-4.

ATC — J05AB09; S01AD07.

ATC Vet — QJ05AB09; QS01AD07.

UNII — QIC03ANI02.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Famciclovir). A white to pale yellow solid. Freely soluble in methyl alcohol and in acetone; sparingly soluble in alcohol and in isopropyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Famciclovir is a prodrug of the antiviral penciclovir (p. 1008.2). It is given orally in the treatment of herpes zoster (see Varicella-zoster Infections, p. 956.2) and genital and mucocutaneous herpes (see Herpes Simplex Infections, p. 955.2).

For **herpes zoster**, famciclovir is given in a dose of 500 mg three times daily for 7 days; immunocompromised patients are given 500 mg three times daily for 10 days.

For **herpes simplex infections**, famciclovir is given in a dose of 250 mg three times daily for 5 days for first episodes of genital herpes; immunocompromised patients may be given 500 mg twice daily for 7 days. For acute treatment of recurrent episodes of genital herpes, 125 mg is given twice daily for 5 days (in the USA, the recommended dose is 1 g twice daily for 1 day and the *BNF* also gives this as an alternative regimen). Treatment should start in the prodromal period as soon as the first signs or symptoms appear. Immunocompromised patients may be given 500 mg twice daily for 7 days. For suppression of recurrent episodes of genital herpes, 250 mg is given twice daily; immunocompromised patients may be given 500 mg twice daily. Such suppressive treatment is interrupted every 6 to 12 months to observe possible changes in the natural history of the disease.

For acute treatment of recurrent mucocutaneous herpes in HIV-infected patients, 500 mg is given twice daily for 7 days.

In the USA, famciclovir may also be given orally for the treatment of recurrent herpes labialis as a single 1.5 g dose, preferably begun in the prodromal period.

Doses of famciclovir should be reduced in patients with renal impairment (see below).

Reviews.
1. Perry CM, Wagstaff AJ. Famciclovir: a review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. *Drugs* 1995; **50:** 396–415.
2. Faro S. A review of famciclovir in the management of genital herpes. *Infect Dis Obstet Gynecol* 1998; **6:** 38–43.
3. Vinh DC, Aoki FY. Famciclovir for the treatment of recurrent genital herpes: a clinical and pharmacological perspective. *Expert Opin Pharmacother* 2006; **7:** 2271–86.
4. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006; **66:** 2397–2416.
5. Chacko M, Weinberg JM. Famciclovir for cutaneous herpesvirus infections: an update and review of new single-day dosing indications. *Cutis* 2007; **80:** 77–81.
6. Aoki FY. The continuing evolution of antiviral therapy for recurrent genital herpes: 1-day patient-initiated treatment with famciclovir. *Herpes* 2007; **14:** 62–5.
7. Mubareka S, *et al.* Famciclovir: a focus on efficacy and safety. *Expert Opin Drug Safety* 2010; **9:** 643–58.

Administration in renal impairment. Doses of famciclovir need to be reduced in patients with renal impairment. The following oral doses based on creatinine clearance (CC) are recommended:

Immunocompetent patients:

Herpes zoster
- CC 40 to 59 mL/minute: 500 mg twice daily for 7 days
- CC 20 to 39 mL/minute: 500 mg once daily for 7 days
- CC < 20 mL/minute: 250 mg once daily for 7 days
- patients on haemodialysis: 250 mg is given immediately after each dialysis run during 7 days

Initial episode of genital herpes
- CC 20 to 39 mL/minute: 250 mg twice daily for 5 days
- CC < 20 mL/minute: 250 mg once daily for 5 days
- patients on haemodialysis: 250 mg is given immediately after each dialysis run during 5 days

Acute recurrent genital herpes, treatment
- CC ⩾ 20 mL/minute: 125 mg twice daily for 5 days
- CC < 20 mL/minute: 125 mg once daily for 5 days
- patients on haemodialysis: 125 mg is given immediately after each dialysis run during 5 days

Recurrent genital herpes, suppression
- CC 20 to 39 mL/minute: 125 mg twice daily
- CC < 20 mL/minute: 125 mg once daily
- patients on haemodialysis: 125 mg is given immediately after each dialysis run

For single-day dose regimens for recurrent genital herpes
- 40 to 59 mL/minute: 500 mg every 12 hours for 1 day
- 20 to 39 mL/minute: 500 mg as a single dose
- < 20 mL/minute: 250 mg as a single dose
- patients on haemodialysis: 250 mg is given immediately after the dialysis run

For single-dose treatment for recurrent herpes labialis
- 40 to 59 mL/minute: 750 mg as a single dose
- 20 to 39 mL/minute: 500 mg as a single dose
- < 20 mL/minute: 250 mg as a single dose
- patients on haemodialysis: 250 mg is given immediately after the dialysis run

Immunocompromised patients:

Herpes zoster
- as for immunocompetent patients, above, but treatment is given for 10 days

Acute recurrent genital or orofacial herpes, treatment
- CC 20 to 39 mL/minute: 500 mg once daily for 7 days
- CC < 20 mL/minute: 250 mg once daily for 7 days
- patients on haemodialysis: 250 mg is given immediately after each dialysis run during 7 days

Recurrent genital herpes, suppression
- CC 20 to 39 mL/minute: 500 mg once daily
- CC < 20 mL/minute: 250 mg once daily
- patients on haemodialysis: 250 mg is given immediately after each dialysis run

Adverse Effects and Precautions

The most common adverse effects of famciclovir are headache and nausea. Other adverse effects rarely reported include jaundice, vomiting, dizziness, rash, pruritus, urticaria, somnolence, confusion, thrombocytopenia, and hallucinations. In addition, abdominal pain and fever have been reported in immunocompromised patients given famciclovir. There have been case reports of serious skin reactions such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Dosage should be reduced in patients with renal impairment. Acute renal failure has occurred in patients with renal impairment taking inappropriately high doses of famciclovir.

References.
1. Saltzman R, *et al.* Safety of famciclovir in patients with herpes zoster and genital herpes. *Antimicrob Agents Chemother* 1994; **38:** 2454–7.

Hypersensitivity. See Vasculitis, below. For conflicting findings regarding cross-sensitivity to famciclovir in patients hypersensitive to aciclovir, see p. 965.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies famciclovir as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Pregnancy. For information on the use of famciclovir in pregnancy see under Precautions of Aciclovir, p. 965.3.

Vasculitis. Leucocytoclastic (or hypersensitivity) vasculitis, a type of cutaneous small vessel vasculitis, occurred in an elderly woman 3 days after starting famciclovir 500 mg orally 3 times daily for treatment of shingles;[1] symptoms improved after about 2 months with oral corticosteroid treatment. The report authors identified famciclovir as the most likely cause, and based on a previous case report,[2] suggested that the risk of reaction may be dose dependent.

1. Te CC, *et al.* Famciclovir-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2008; **42:** 1323–6.
2. Ali SO, *et al.* Case reports: cutaneous small vessel vasculitis due to famciclovir therapy. *J Drugs Dermatol* 2005; **4:** 486–9.

Interactions

When given with famciclovir, probenecid may reduce renal excretion of the active metabolite penciclovir, leading to increased plasma concentrations. The conversion of famciclovir to penciclovir is, in part, mediated by aldehyde oxidase, and strong inhibitors of this enzyme (such as raloxifene) may potentially reduce the formation of penciclovir.

Antiviral Action

As for Penciclovir, p. 1008.3.

Pharmacokinetics

Famciclovir is rapidly absorbed after oral doses. Absorption is delayed but not reduced by food. Famciclovir is rapidly converted to penciclovir (see p. 1008.3) and peak plasma concentrations occur within about 1 hour of a dose; virtually no famciclovir is detectable in the plasma or urine. Bioavailability of penciclovir is reported to be 77%. Famciclovir is mainly excreted in the urine (partly by renal tubular secretion) as penciclovir and its 6-deoxy precursor; elimination is reduced in patients with renal impairment.

References.
1. Pue MA, Benet LZ. Pharmacokinetics of famciclovir in man. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 47–55.
2. Boike SC, *et al.* Pharmacokinetics of famciclovir in subjects with varying degrees of renal impairment. *Clin Pharmacol Ther* 1994; **55:** 418–26.
3. Boike SC, *et al.* Pharmacokinetics of famciclovir in subjects with chronic hepatic disease. *J Clin Pharmacol* 1994; **34:** 1199–1207.
4. Gill KS, Wood MJ. The clinical pharmacokinetics of famciclovir. *Clin Pharmacokinet* 1996; **31:** 1–8.
5. Sáez-Llorens X, *et al.* Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. *Antimicrob Agents Chemother* 2009; **53:** 1912–20.
6. Ogungbenro K, *et al.* Population pharmacokinetics and optimal design of paediatric studies for famciclovir. *Br J Clin Pharmacol* 2009; **68:** 546–60.
7. Blumer J, *et al.* Single-dose pharmacokinetics of famciclovir in infants and population pharmacokinetic analysis in infants and children. *Antimicrob Agents Chemother* 2010; **54:** 2032–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pentavir; ***Austral.***: Ezovir; Famvir; Favic; ***Austria***: Famvir; ***Braz.***: Famvir; Fanclomax; Penvir; ***Canad.***: Famvir; ***China***: Fanle (凡乐); Lizhufeng (丽珠风); Ming Li Xin (明立欣); Nuo Ke (诺克); Pixin (彼欣); Wan Qi (万祺); Weike (韦克); Xian Lin Na (仙林纳); ***Cz.***: Famvir†; ***Denm.***:

Famvir; ***Fin.***: Famvir; ***Fr.***: Oravir; ***Ger.***: Famvir; ***Gr.***: Famcilet; Famvir; ***Hong Kong***: Famvir; ***Hung.***: Famvir; ***India***: Famirax; Famtrex; Microvir; ***Indon.***: Famvir; ***Irl.***: Famlov; Famvir; Myclovear†; ***Ital.***: Famvir; Ziravir†; ***Jpn***: Famvir; ***Neth.***: Famvir†; ***NZ***: Famvir; ***Port.***: Famvir†; Zyvir†; ***Rus.***: Famvir (Фамвир); ***S.Afr.***: Famvir; ***Spain***: Ancivin†; Famvir; ***Swed.***: Famvir; ***Switz.***: Famvir; ***Thai.***: Famvir; ***Turk.***: Famvir; ***UK***: Famvir; ***Ukr.***: Famvir (Фамвир); ***USA***: Famvir.

Fomivirsen Sodium *(BANM, USAN, rINNM)*

Fomivirseeninatrium; Fomivirsén sódico; Fomivirsen Sodique; Fomivirsennatrium; Fomivirseno sódico; Fomivirsenum Natricum; Isis-2922; Natrii Fomivirsenum; Натрий Фомивирсен.

$C_{204}H_{243}N_{63}Na_{20}O_{114}P_{20}S_{20}$=7122.0

CAS — 144245-52-3 (fomivirsen); 160369-77-7 (fomivirsen sodium).

ATC — S01AD08.

ATC Vet — QS01AD08.

UNII — 3Z6W3S36X5.

Uses and Administration

Fomivirsen is an antisense oligonucleotide that has been used as the sodium salt for the local treatment of CMV retinitis (p. 954.2) in patients with AIDS. For newly diagnosed disease, a dose of 165 micrograms has been given by intravitreal injection into the affected eye once each week for 3 weeks, then on alternate weeks thereafter. For previously treated disease, 330 micrograms has been injected into the affected eye; this dose may be repeated once after 2 weeks and then once every 4 weeks thereafter.

Reviews.

1. Perry CM, Barman Balfour JA. Fomivirsen. *Drugs* 1999; **57:** 375–80.
2. Geary RS, *et al.* Fomivirsen: clinical pharmacology and potential drug interactions. *Clin Pharmacokinet* 2002; **41:** 255–60.

Adverse Effects and Precautions

Adverse effects after intra-ocular injection of fomivirsen are confined to the treated eye. They include intra-ocular inflammation, transient increases in intra-ocular pressure, retinal detachment and oedema, and visual abnormalities. Other adverse effects associated with the intravitreal injection procedure include vitreal haemorrhage, endophthalmitis, uveitis, and cataract formation.

Patients should be monitored during treatment for changes in intra-ocular pressure and visual field and for extra-ocular CMV disease or disease in the contralateral eye.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fomivirsen as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Interactions

In order to reduce the risk of inflammation, intra-ocular use of fomivirsen is not recommended within 2 to 4 weeks of cidofovir treatment.

Antiviral Action

Fomivirsen is an antisense oligonucleotide that inhibits human CMV replication. It is active against strains of CMV resistant to ganciclovir, foscarnet, and cidofovir. Resistance to fomivirsen has been induced *in vitro*, but cross-resistance to antivirals with other modes of action is unlikely.

Fosamprenavir Calcium *(USAN, rINNM)*

Calcii Fosamprenavirum; Fosamprenavir cálcico; Fosamprénavir Calcique; GW-433908G; Кальций Фосампренавир.

(3*S*)-Tetrahydro-3-furyl{(α*S*)-α-[(1*R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl}carbamate calcium phosphate (1:1).

$C_{25}H_{36}CaN_3O_9PS$=625.7

CAS — 226700-79-4 (fosamprenavir); 226700-81-8 (fosamprenavir calcium).

ATC — J05AE07.

ATC Vet — QJ05AE07.

UNII — ID1GU2627N.

Uses and Administration

Fosamprenavir is a prodrug of amprenavir, which is an HIV-protease inhibitor with antiviral activity against HIV. Fosamprenavir is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when fosamprenavir is used alone, and it is therefore used with other antiretrovirals.

Fosamprenavir may be given with or without food. It is given orally as the calcium salt, but doses are expressed in terms of the base. Fosamprenavir calcium 748 mg is equivalent to about 700 mg of fosamprenavir. Licensed product information states that this is equivalent to about 600 mg of amprenavir.

In the UK, the recommended dose of ritonavir-boosted fosamprenavir in both treatment-experienced and treatment-naive adult patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

In the USA, recommended doses in treatment-naive adult patients are:

- fosamprenavir 1.4 g twice daily *without ritonavir*, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 200 mg once daily, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 100 mg once daily, or
- fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily

The recommended dose in treatment-experienced patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

For details of doses in children and adolescents, see below.

Doses should be reduced in patients with hepatic impairment (see below).

Reviews.

1. Chapman TM, *et al.* Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. *Drugs* 2004; **64:** 2101–24.
2. Hester EK, *et al.* Fosamprenavir: drug development for adherence. *Ann Pharmacother* 2006; **40:** 1301–10.
3. Torres HA, Arduino RC. Fosamprenavir calcium plus ritonavir for HIV infection. *Expert Rev Anti Infect Ther* 2007; **5:** 349–63.

Administration in children. For the treatment of HIV infection in children and adolescents, fosamprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight and totals should not exceed the adult dose (see Uses and Administration, above).

In the UK, the recommended dose of fosamprenavir oral solution in children and adolescents weighing 25 to 38 kg is 18 mg/kg twice daily *plus* ritonavir oral solution 3 mg/kg twice daily. Children and adolescents weighing at least 39 kg may be given the adult fosamprenavir tablet dose, see above. It is not licensed for use in children below 25 kg in weight or 6 years of age.

In the USA, fosamprenavir oral solution is licensed for use in infants born at 38-weeks gestation or greater and who are at least 28 days old. For the treatment of *protease inhibitor-naive* infants and children from 4 weeks of age and *protease inhibitor-experienced* infants and children from 6 months of age the recommended doses are:

- those weighing less than 11 kg: fosamprenavir 45 mg/kg twice daily plus ritonavir 7 mg/kg twice daily
- those weighing 11 to less than 15 kg: fosamprenavir 30 mg/kg twice daily plus ritonavir 3 mg/kg twice daily
- those weighing 15 to less than 20 kg: fosamprenavir 23 mg/kg twice daily plus ritonavir 3 mg/kg twice daily
- those weighing 20 kg or more: fosamprenavir 18 mg/kg twice daily plus ritonavir 3 mg/kg twice daily

Alternatively, *protease inhibitor-naive* children from 2 years of age may be given 30 mg/kg twice daily of fosamprenavir without ritonavir.

Ritonavir 100-mg capsules may be given to children and adolescents taking fosamprenavir oral suspension if they weigh at least 33 kg.

Administration in hepatic impairment. Fosamprenavir should be used with caution in all patients with hepatic impairment.

UK licensed product information recommends:

- in patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with severe hepatic impairment (Child-Pugh score 10 to 15): fosamprenavir 300 mg twice daily *plus* ritonavir 100 mg once daily

US licensed product information recommends:

- in treatment-naive patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *without ritonavir*, or *plus* ritonavir 100 mg once daily
- in HIV-protease inhibitor-experienced patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 700 mg twice daily *without ritonavir*, or fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in HIV-protease inhibitor-experienced patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with severe hepatic impairment (Child-Pugh score 10 to 15): fosamprenavir 350 mg twice daily *without ritonavir*, or fosamprenavir 300 mg twice daily *plus* ritonavir 100 mg once daily
- in protease-inhibitor experienced patients with severe hepatic impairment (Child-Pugh score 10 to 15): fosamprenavir 300 mg twice daily *plus* ritonavir 100 mg once daily

Adverse Effects

Adverse effects associated with antiretroviral regimens containing fosamprenavir or amprenavir are mostly mild to moderate. The most common adverse effects are gastrointestinal disturbances such as diarrhoea, flatulence, nausea and vomiting. Other commonly reported adverse effects include fatigue, headache, oral paraesthesia, and taste disorders, while the most frequently reported adverse effects include peripheral paraesthesias and mood disorders (including depression). Mild to moderate rashes (usually erythematous or maculopapular and sometimes pruritic), generally occur during the second week of treatment and resolve within 2 weeks. A possible association with Stevens-Johnson syndrome has been reported.

For further information on adverse effects associated with HIV-protease inhibitors, see under Indinavir Sulfate, p. 986.2

Precautions

Amprenavir or fosamprenavir should be used with caution (and liver enzyme values monitored), in patients with hepatic impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Treatment with amprenavir should be permanently stopped in patients who develop a severe or life-threatening rash or a rash with associated systemic or allergic symptoms or mucosal involvement.

Amprenavir is a sulfonamide and the drugs should be used with caution in patients known to be allergic to sulfonamides. For further information on cross-reactivity between sulfonamide drugs see Hypersensitivity, under Sulfamethoxazole, p. 365.3.

Interactions

Drugs interacting with amprenavir might reasonably also be expected to interact with fosamprenavir. Amprenavir is reported to be metabolised by the cytochrome P450 isoenzyme CYP3A4. It is also a modest inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that affect these isoenzymes may modify amprenavir plasma concentrations and amprenavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system.

Amprenavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergotamine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam) and statins (simvastatin and lovastatin). Similarly, ritonavir-boosted amprenavir should not be used with drugs having narrow therapeutic windows that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide and propafenone. Rifampicin and St John's wort decrease the concentration of amprenavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Fosamprenavir is a prodrug that is rapidly hydrolysed to amprenavir by cellular phosphatases in the gut epithelium as it is absorbed; it has little or no antiviral activity of its own *in vitro* Amprenavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance between HIV-protease inhibitors may occur, but cross-

resistance between HIV-protease inhibitors and reverse transcriptase inhibitors is considered unlikely. Mechanisms of resistance to amprenavir may differ from those of other HIV-protease inhibitors.

Pharmacokinetics

After oral doses, fosamprenavir is rapidly hydrolysed to amprenavir in the gastrointestinal epithelium as it is absorbed. Peak plasma concentrations of amprenavir occur after 1.5 to 4 hours. Fosamprenavir may be given with or without food. For details of the pharmacokinetics of amprenavir, see p. 968.1.

References.

1. Wire MB, *et al.* Fosamprenavir: clinical pharmacokinetics and drug interactions of the amprenavir prodrug. *Clin Pharmacokinet* 2006; **45:** 137–68.
2. Pérez-Elías MJ, *et al.* Pharmacokinetics of fosamprenavir plus ritonavir in human immunodeficiency virus type 1-infected adult subjects with hepatic impairment. *Antimicrob Agents Chemother* 2009; **53:** 5185–96.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Telzir; ***Austral.***: Telzir; ***Austria***: Telzir; ***Belg.***: Telzir; ***Braz.***: Telzir; ***Canad.***: Telzir; ***Chile***: Telzir; ***Cz.***: Telzir; ***Denm.***: Telzir; ***Fin.***: Telzir; ***Fr.***: Telzir; ***Ger.***: Telzir; ***Gr.***: Telzir; ***Hung.***: Telzir; ***Irl.***: Telzir; ***Israel***: Lexiva; ***Ital.***: Telzir; ***Mex.***: Telzer; ***Neth.***: Telzir; ***Norw.***: Telzir; ***Pol.***: Telzir; ***Port.***: Telzir; ***Rus.***: Telzir (Телзир); ***Spain***: Telzir; ***Swed.***: Telzir; ***Switz.***: Telzir; ***Turk.***: Telzir; ***UK***: Telzir; ***USA***: Lexiva.

Foscarnet Sodium *(BAN, USAN, rINN)*

A-29622; EHB-776 (anhydrous and hexahydrate); Foscarnet sódico; Foscarnet Sodique; Foscarnet sodique hexahydraté; Foscarnetum Natricum; Foscarnetum Natricum Hexahydricum; Foskarneettinatriumheksahydraatti; Foskarnet sodná sůl hexahydrát; Foskarnet Sodyum; Foskarnetnatriumhexahydrat; Foskarneto natrio druska heksahidratas; Foszkarnetnátrium; Phosphonatoformate Trisodium; Phosphonoformate Trisodium; Фоскарнет Натрий.

Trisodium phosphonatoformate hexahydrate.

$CNa_3O_5P,6H_2O=300.0$

CAS — 63585-09-1 (foscarnet sodium); 34156-56-4 (foscarnet sodium hexahydrate).

ATC — J05AD01.

ATC Vet — QJ05AD01.

UNII — 964YS0OOG1.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Foscarnet Sodium Hexahydrate; Foscarnet Sodium BP 2014). A white or almost white crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Protect from light.

USP 36: (Foscarnet Sodium). A white to almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Store in airtight containers. Protect from light.

Incompatibility. Foscarnet sodium has been found to be visually incompatible with some commonly used injectable drugs including amphotericin B, aciclovir sodium, cotrimoxazole, ganciclovir, and pentamidine isetionate;[1,2] licensed product information also lists incompatibilities with vancomycin, glucose 30% solution, and solutions containing calcium. It is therefore recommended that foscarnet should not be infused via an intravenous line with any other drug.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47:** 2075–7.

Uses and Administration

Foscarnet is a non-nucleoside pyrophosphate analogue active against herpesviruses. It is used as the trisodium salt mainly for the treatment of CMV retinitis in AIDS patients (see below) and for aciclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients (see below).

Foscarnet is given by intravenous infusion. A solution containing foscarnet sodium 24 mg/mL may be given via a central vein or diluted with glucose 5% or sodium chloride 0.9% to a concentration of 12 mg/mL and given via a peripheral vein. Hydration with 0.5 to 1 litre of sodium chloride 0.9% is recommended with each infusion to reduce renal toxicity.

For the treatment of **CMV retinitis** in patients with normal renal function, the usual dose is 60 mg/kg infused over at least 1 hour every 8 hours, or 90 mg/kg infused over 1½ to 2 hours every 12 hours, for 2 to 3 weeks; this should then be followed by maintenance therapy with 60 mg/kg daily, increasing to 90 to 120 mg/kg daily infused over 2 hours if tolerated.

For the treatment of aciclovir-resistant mucocutaneous **herpes simplex virus infections** in patients with normal renal function, a dose of 40 mg/kg, infused over at least 1 hour every 8 or 12 hours is given for 2 to 3 weeks or until lesions have healed.

Doses of foscarnet should be reduced in patients with renal impairment (see below).

Reviews.

1. Chrisp P, Clissold SP. Foscarnet: a review of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. *Drugs* 1991; **41:** 104–29.
2. Wagstaff AJ, Bryson HM. Foscarnet: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs* 1994; **48:** 199–226.

Administration in children. Foscarnet is not licensed for use in children in the UK. However, the *BNFC* considers that it may be used if necessary for CMV disease or mucocutaneous herpes simplex infection in children from 1 month of age. For CMV infection, foscarnet may be given in an induction dose of 60 mg/kg by intravenous infusion every 8 hours for 2 to 3 weeks, followed by maintenance in similar doses to those recommended for adults with CMV retinitis (see Uses and Administration, above). For mucocutaneous herpes simplex it recommends 40 mg/kg given every 8 hours for 2 to 3 weeks, or until lesions heal.

Administration in renal impairment. Doses of intravenous foscarnet sodium may need to be reduced in patients with renal impairment.

Treatment of CMV retinitis:

The following doses, given every 8 hours for treatment and once daily for maintenance, are suggested by the UK licensed product information according to creatinine clearance (CC):

- CC more than 1.6 mL/kg per minute: 60 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 55 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 49 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 42 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 35 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 28 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 21 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

Treatment of aciclovir-resistant mucocutaneous herpes simplex infections:

The following doses, given every 8 hours, are suggested by the UK licensed product information according to CC:

- CC more than 1.6 mL/kg per minute: 40 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 37 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 33 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 28 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 24 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 19 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 14 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

In the USA modification of doses by extending the dose interval has been recommended, resulting in proportional reductions in daily dose similar to those in the UK.

Cytomegalovirus infections. Foscarnet is used in the treatment of severe CMV infections (p. 954.2) in immunocompromised patients and appears to possess similar efficacy to ganciclovir[1] (see also under Ganciclovir, p. 983.1). It has been particularly useful in patients who require antiretroviral therapy for AIDS and are unable to tolerate ganciclovir (because of haematological toxicity). For patients unable to tolerate systemic therapy foscarnet has been tried as an intravitreal injection.[2-4] Beneficial responses have been reported with various regimens including intravitreal injections of foscarnet 1.2 mg every 48 hours for 4 doses[2] or induction with 2.4 mg twice weekly[4] or every 72 hours for 6 doses,[3] then once weekly maintenance thereafter.[3,4] Combined treatment with foscarnet and ganciclovir each given intravitreally has also been reported to be effective;[5] however, although combination systemic therapy has been widely used where resistance to ganciclovir is suspected, the evidence for a synergistic effect against CMV is not very strong.[6]

Foscarnet has also been investigated for primary prophylaxis of CMV infection in bone marrow transplant recipients at high risk of infection.[7,8]

1. Reusser P, *et al.* Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood* 2002; **99:** 1159–64.
2. Lieberman RM, *et al.* Efficacy of intravitreal foscarnet in a patient with AIDS. *N Engl J Med* 1994; **330:** 868–9.
3. Diaz-Llopis M, *et al.* High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS. *Br J Ophthalmol* 1994; **78:** 120–4.
4. Ausayakhun S, *et al.* Intravitreal foscarnet for cytomegalovirus retinitis in patients with AIDS. *J Med Assoc Thai* 2005; **88:** 103–7.
5. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
6. Drew WL. Is combination antiviral therapy for CMV superior to monotherapy? *J Clin Virol* 2006; **35:** 485–8.
7. Ippoliti C, *et al.* Foscarnet for prevention of cytomegalovirus infection in allogeneic marrow transplant recipients unable to receive ganciclovir. *Bone Marrow Transplant* 1997; **20:** 491–5.
8. Bregante S, *et al.* Foscarnet prophylaxis of cytomegalovirus infections in patients undergoing allogeneic bone marrow transplantation (BMT): a dose-finding study. *Bone Marrow Transplant* 2000; **26:** 23–9.

Herpes simplex infections. Although foscarnet is effective in the treatment of herpes simplex infections it is usually reserved for severe or disseminated herpes simplex infections, particularly in immunocompromised patients who have infections resistant to aciclovir (see p. 955.2). A 2% cream applied topically is effective in the treatment of refractory herpes simplex infections of the skin,[1] and is licensed for such use in some countries. Topical use of a 1% foscarnet cream has also been investigated.[2] For mention of intravitreal foscarnet in the management of herpes-simplex-induced acute retinal necrosis see under Varicella-zoster Infections, below.

1. Gross G, Braun D. Wirksamkeit und Verträglichkeit von topisch appliziertem Foscarnet-Natrium bei der Behandlung von Herpes labialis. Ergebnisse einer Anwendungsbeobachtung. *Hautarzt* 2006; **57:** 40–6.
2. Javaly K, *et al.* Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr* 1999; **21:** 301–6.

HIV infection. Foscarnet has some activity against HIV reverse transcriptase and in patients with HIV infection (p. 957.2) that has become resistant to multiple antiretrovirals, it has been investigated[1-3] in salvage regimens; there is some evidence that response depends on the number and nature of any thymidine-associated mutations present in the virus.

1. Canestri A, *et al.* Foscarnet salvage therapy for patients with late-stage HIV disease and multiple drug resistance. *Antivir Ther* 2006; **11:** 561–6.
2. Mathiesen S, *et al.* Long-term foscarnet therapy remodels thymidine analogue mutations and alters resistance to zidovudine and lamivudine in HIV-1. *Antivir Ther* 2007; **12:** 335–43.
3. Charpentier C, *et al.* Foscarnet salvage therapy efficacy is associated with the presence of thymidine-associated mutations (TAMs) in HIV-infected patients. *J Clin Virol* 2008; **43:** 212–5.

Varicella-zoster infections. Intravenous foscarnet is the recommended treatment for aciclovir-resistant varicella-zoster infections (p. 956.2). In a study[1] of 5 patients with AIDS and aciclovir-resistant zoster infection complete healing was reported for 3 patients after treatment with foscarnet 120 mg/kg daily for 14 to 26 days. Two patients relapsed 7 and 14 days respectively after stopping treatment. In another study[2] 10 of 13 HIV-infected patients with aciclovir-resistant zoster infection had complete healing after treatment with 100 mg/kg twice daily of foscarnet for 12 to 30 days. Five of the patients relapsed after stopping treatment with the median time to relapse being 110 days. Intravitreal foscarnet has been suggested as a useful adjunct in preventing retinal detachment in patients with varicella-zoster-induced acute retinal necrosis; it was unclear if it was of similar value in those with herpes-simplex-induced disease.[3]

1. Safrin S, *et al.* Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann Intern Med* 1991; **115:** 19–21.
2. Breton G, *et al.* Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis* 1998; **27:** 1525–7.
3. Wong R, *et al.* Acute retinal necrosis: the effects of intravitreal foscarnet and virus type on outcome. *Ophthalmology* 2010; **117:** 556–60.

Adverse Effects and Treatment

The most serious common adverse effect of foscarnet sodium is renal impairment, which may be severe. Anaemia may be common and granulocytopenia and thrombocytopenia have been reported. Foscarnet can chelate bivalent metal ions, and may be associated with an acute decrease in ionised calcium in the plasma that is not necessarily reflected by measurements of total calcium; the decrease is proportional to the rate of infusion. Other electrolyte disturbances may occur (see p. 982.1). Some patients may have convulsions. Excretion of high concentrations in the urine can cause local irritation and genital ulceration. Other adverse effects reported include nausea, vomiting, diarrhoea, malaise, fatigue, fever, headache, dizziness, paraesthesia, tremor, mood disturbances, rash, abnormal liver function tests, blood pressure and ECG changes, and isolated reports of pancreatitis. Intravenous injection may cause phlebitis at the site of injection.

In cases of overdosage it is important to maintain hydration. Foscarnet elimination may be increased by haemodialysis.

Effects on the CNS. Convulsions may occur in up to 10% of AIDS patients receiving foscarnet and have been reported after overdoses. Contributing factors include underlying CNS pathology (HIV-related encephalopathy or other infections) and foscarnet-related electrolyte disturbances. However, seizures have occurred in patients without apparent risk factors.[1]

An acute dystonic reaction has also been reported[2] in a patient treated with foscarnet.

1. Lor E, Liu YQ. Neurologic sequelae associated with foscarnet therapy. *Ann Pharmacother* 1994; **28:** 1035–7.
2. Dubow JS, *et al.* Acute dystonic reaction associated with foscarnet administration. *Am J Ther* 2008; **15:** 184–6.

Effects on electrolyte balance. Acute hypocalcaemia has been reported to occur in about 30% of AIDS patients receiving foscarnet. Other electrolyte disturbances include hypokalaemia and hypomagnesaemia (each in about 15%), hypophosphataemia (8%), and hyperphosphataemia (6%). Hypocalcaemia may cause paraesthesias and, together with hypomagnesaemia and hypokalaemia, may predispose to seizures and cardiovascular disturbances.

Electrolyte abnormalities (increased calcium, magnesium, phosphate, and potassium requirements, and a reduction in the need for sodium) have been reported to be dramatically accelerated by foscarnet in a patient being given total parenteral nutrition.[1]

1. Matarese LE, *et al.* Foscarnet-induced electrolyte abnormalities in a bone marrow transplant patient receiving parenteral nutrition. *J Parenter Enteral Nutr* 2000; **24:** 170–3.

Effects on the kidneys. The most serious common adverse effect of foscarnet sodium is nephrotoxicity. Clinically significant increases in serum-creatinine concentrations occur in about 30% of patients, and the incidence of nephrotoxicity tends to increase with increasing dose[1] and with duration of therapy.[2] Foscarnet sodium is excreted unchanged in the urine and tubulo-interstitial lesions and deposition of crystals in the glomerular capillary lumen have been implicated.[3] Acute renal failure has occurred and haemodialysis has been reported to have reduced plasma-foscarnet concentrations.[4] The risk of nephrotoxicity can be minimised by ensuring adequate hydration, the use of intermittent dosing schedules,[5] and by adjusting the dose according to serum-creatinine concentrations. Nephrogenic diabetes insipidus and renal tubular acidosis associated with foscarnet have been reported.[6-8]

1. Jacobson MA, *et al.* A dose-ranging study of daily maintenance intravenous foscarnet therapy for cytomegalovirus retinitis in AIDS. *J Infect Dis* 1993; **168:** 444–8.
2. Gaub J, *et al.* The effect of foscarnet (phosphonoformate) on human immunodeficiency virus isolation, T-cell subsets and lymphocyte function in AIDS patients. *AIDS* 1987; **1:** 27–33.
3. Beaufils H, *et al.* Foscarnet and crystals in glomerular capillary lumens. *Lancet* 1990; **336:** 755.
4. Deray G, *et al.* Foscarnet-induced acute renal failure and effectiveness of haemodialysis. *Lancet* 1987; **ii:** 216.
5. Deray G, *et al.* Prevention of foscarnet nephrotoxicity. *Ann Intern Med* 1990; **113:** 332.
6. Farese RV, *et al.* Nephrogenic diabetes insipidus associated with foscarnet treatment of cytomegalovirus retinitis. *Ann Intern Med* 1990; **112:** 955–6.
7. Conn J, *et al.* Nephrogenic diabetes insipidus associated with foscarnet—a case report. *J Antimicrob Chemother* 1996; **37:** 1180–1.
8. Navarro JF, *et al.* Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996; **27:** 431–4.

Effects on the skin and mucous membranes. A generalised pruritic macular rash was reported in a patient given foscarnet, which subsided after the drug was withdrawn.[1]

There have been several reports of genital ulceration,[2-8] possibly related to local toxicity arising from high concentrations of foscarnet in the urine. Oral ulceration, usually with genital ulceration, has occurred during foscarnet treatment.[3-5] Uvular and oesophageal ulcerations have also been reported.[4,9]

1. Green ST, *et al.* Generalised cutaneous rash associated with foscarnet usage in AIDS. *J Infect* 1990; **21:** 227–8.
2. Van Der Pijl JW, *et al.* Foscarnet and penile ulceration. *Lancet* 1990; **335:** 286.
3. Gilquin J, *et al.* Genital and oral erosions induced by foscarnet. *Lancet* 1990; **335:** 287.
4. Fégueux S, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; **335:** 547.
5. Moyle G, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; **335:** 547–8.
6. Lacey HB, *et al.* Vulval ulceration associated with foscarnet. *Genitourin Med* 1992; **68:** 182.
7. Caumes E, *et al.* Foscarnet-induced vulvar erosion. *J Am Acad Dermatol* 1993; **28:** 799.
8. Hick RW, Prose N. Penile erosions associated with foscarnet therapy in a child. *Pediatr Dermatol* 2010; **27:** 302–3.
9. Saint-Marc T, *et al.* Uvula and oesophageal ulcerations with foscarnet. *Lancet* 1992; **340:** 970–1.

Precautions

Foscarnet sodium should be used with caution in renal impairment and doses should be reduced if serum creatinine is raised. Serum-creatinine concentrations should be measured on alternate days throughout induction treatment; monitoring may be weekly during maintenance therapy. An adequate state of hydration must be maintained during therapy to prevent renal toxicity. Electrolytes, especially calcium and magnesium, should also be monitored and deficiencies corrected before and during foscarnet therapy.

Electrolyte content. Each g of foscarnet sodium (hexahydrate) contains about 10 mmol of sodium and about 3.3 mmol of phosphate.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies foscarnet as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Interactions

Foscarnet should not be given with other nephrotoxic drugs such as aminoglycosides, amphotericin B, and ciclosporin, or with other drugs that can affect serum-calcium concentrations. Intravenous pentamidine can produce both of these effects and severe additive toxicity may result from its use with foscarnet; fatalities have occurred.

Ciprofloxacin. Tonic-clonic seizures associated with foscarnet use in 2 patients receiving multiple antimicrobial drugs were thought to have been exacerbated by the concurrent use of ciprofloxacin.[1]

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; **28:** 869–72.

Parenteral nutrition. For mention that foscarnet may exacerbate the need for electrolyte replacement in patients receiving total parenteral nutrition see Effects on Electrolyte Balance, above.

Antiviral Action

Foscarnet inhibits replication of human herpesviruses including CMV, herpes simplex virus types 1 and 2, herpesviruses 6 and 8, Epstein-Barr virus, and varicella-zoster virus. Activity is also reported against hepatitis B virus and HIV. Foscarnet acts by inhibition of virus-specific DNA polymerases and reverse transcriptases: unlike the nucleoside reverse transcriptase inhibitors and ganciclovir, foscarnet does not require intracellular conversion to an active triphosphate.

References.

1. Balfour HH, *et al.* Effect of foscarnet on quantities of cytomegalovirus and human immunodeficiency virus in blood of persons with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 2721–6.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42:** 2240–4.

Pharmacokinetics

The pharmacokinetics of foscarnet are complicated by the high incidence of renal impairment induced during therapy and by the deposition and subsequent gradual release of foscarnet from bone. Thus the estimation of half-life depends upon the duration of foscarnet therapy and the duration of the observation period. The plasma half-life in patients with normal renal function is about 2 to 4 hours, but terminal half-lives up to about 8 days have been reported when accumulation in bone has taken place. Plasma protein binding is about 14 to 17%. Foscarnet crosses the blood-brain barrier in variable amounts; CSF concentrations ranging from zero to more than 3 times the plasma concentration have been reported. Foscarnet is mostly excreted unchanged in the urine mainly through glomerular filtration.

In 13 HIV-infected male patients with lymphadenopathy or AIDS-related complex[1] foscarnet [sodium] by continuous intravenous infusion (140 to 190 micrograms/kg per minute) produced plasma-foscarnet concentrations of about 100 to 500 nanomol/mL. There appeared to be a link between the degree of adverse effects and plasma-foscarnet concentrations above 350 nanomol/mL. Foscarnet was excreted mainly via the kidneys. It was thought that up to 20% of the cumulative intravenous dose may have been deposited in bone 7 days after the end of infusion.

Penetration of foscarnet into the CSF is very variable and in 5 patients[1] CSF concentrations of foscarnet were found to be 13 to 68% of those in the plasma. Subsequent studies showed that CSF concentrations of foscarnet would be virostatic in most patients,[2] attaining a mean concentration of about 25% of plasma concentration after a single infusion[2,3] and 66% under steady state conditions.[3] CSF concentrations ranged from 0 to 340%[2] and 5 to 72%[3] of those in plasma. There was a correlation between the amount of foscarnet in the CSF and inflammation of the meninges in one study,[2] and with the HIV infection stage in another,[3] but neither reported a correlation with plasma concentration.

1. Sjövall J, *et al.* Pharmacokinetics of foscarnet and distribution to cerebrospinal fluid after intravenous infusion in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1989; **33:** 1023–31.
2. Raffi F, *et al.* Penetration of foscarnet into cerebrospinal fluid of AIDS patients. *Antimicrob Agents Chemother* 1993; **37:** 1777–80.
3. Hengge UR, *et al.* Foscarnet penetrates the blood-brain barrier: rationale for therapy of cytomegalovirus encephalitis. *Antimicrob Agents Chemother* 1993; **37:** 1010–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Foscavir; ***Belg.***: Foscavir; ***Braz.***: Foscavir; ***China***: Anji (安济); Carnet (可耐); Fu Shi Ling (扶适灵); Ka Nai Xin (卡奈信); Yi Ke Ya (易可亚); ***Fr.***: Foscavir; ***Ger.***: Foscavir†; Triapten; ***Gr.***: Foscavir; ***Hung.***: Foscavir; ***Israel***: Foscavir; ***Ital.***: Foscavir; ***Jpn***: Foscavir; ***Neth.***: Foscavir; ***Norw.***: Foscavir†; ***NZ***: Foscavir; ***Port.***: Foscavir; ***Singapore***: Foscavir; ***Spain***: Foscavir; ***Swed.***: Foscavir; ***Switz.***: Foscavir; ***UK***: Foscavir; ***USA***: Foscavir.

Pharmacopoeial Preparations
BP 2014: Foscarnet Infusion.

Ganciclovir *(BAN, USAN, rINN)*

BIOLF-62; BN-B759V; BW-759; BW-759U; BWB-759U; DHPG; 9-(1,3-Dihydroxy-2-propoxymethyl)guanine; Dihydroxypropoxymethylguanine; Ganciclovirum; Gancyklovir; Gancyklowir; Gansikloviiri; Gansiklovir; RS-21592; Ганцикловир; 2′-NDG; 2′-Nor-2′-deoxyguanosine.

9-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine.

$C_9H_{13}N_5O_4$=255.2

CAS — 82410-32-0.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

UNII — P9G3CKZ4P5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Ganciclovir). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; very slightly soluble in alcohol; dissolves in dilute solutions of mineral acids and alkali hydroxides. Store in airtight containers.

USP 36: (Ganciclovir). A white to off-white crystalline powder. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Ganciclovir Sodium *(BANM, USAN, rINNM)*

Ganciclovir sódico; Ganciclovir Sodique; Natrii Ganciclovirum; Натрий Ганцикловир.

$C_9H_{12}N_5NaO_4$=277.2

CAS — 107910-75-8.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

UNII — 02L083W284.

Incompatibility. Ganciclovir is reported to be incompatible with foscarnet.

Stability. Ganciclovir sodium solution in sodium chloride 0.9% was found[1] to be stable when stored in polypropylene infusion-pump syringes for 12 hours at 25 degrees and for 10 days at 4 degrees. Little variation was found in ganciclovir concentration after storage of a 2% solution at room temperature, 5 degrees, and -8 degrees for 10 to 24 days.[2]

1. Mulye NV, *et al.* Stability of ganciclovir sodium in an infusion-pump syringe. *Am J Hosp Pharm* 1994; **51:** 1348–9.
2. Morlet N, *et al.* High dose intravitreal ganciclovir for CMV retinitis: a shelf life and cost comparison study. *Br J Ophthalmol* 1995; **79:** 753–5.

Uses and Administration

Ganciclovir is a synthetic nucleoside analogue of guanine closely related to aciclovir (p. 964.1), but has greater activity against CMV. It is used for the treatment and suppression of life-threatening or sight-threatening CMV infections in immunocompromised patients, including those with AIDS and those with iatrogenic immunosuppression associated with organ transplantation or chemotherapy of neoplastic disease (see also p. 983.1). It has also been used for superficial ocular herpes simplex infections.

Ganciclovir is given by intravenous infusion as the sodium salt but doses are expressed in terms of ganciclovir; 54.3 mg of ganciclovir sodium is equivalent to about 50 mg of ganciclovir. Solutions for infusion are usually prepared to give a concentration of ganciclovir of 50 mg/mL, then further diluted to contain not more than 10 mg/mL. An intravenous solution is given over 1 hour.

In **CMV infections**, the usual initial dose for ***treatment*** is 5 mg/kg by intravenous infusion every 12 hours for 14 to 21 days. This induction period may be followed by *maintenance* therapy to prevent recurrence or progression of the disease. The usual maintenance dosage is 5 mg/kg by intravenous infusion as a single daily dose for 7 days each week or 6 mg/kg daily for 5 days each week. If retinitis recurs or progresses a further induction course of ganciclovir may be given. AIDS patients who have received initial treatment with intravenous ganciclovir, and who have stable CMV retinitis following at least 3 weeks of intravenous therapy, may be given oral valganciclovir. In

some countries oral formulations of ganciclovir are available for maintenance; typical dosage is 3 g daily in divided doses.

For ***prevention*** of CMV infection in immunocompromised patients, specifically those receiving immunosuppressive therapy after organ transplantation, ganciclovir may be given in an *initial* dose of 5 mg/kg by intravenous infusion every 12 hours for 7 to 14 days, followed by intravenous *maintenance* therapy as above.

Doses of ganciclovir should be reduced in renal impairment (see below).

Intravitreal implants providing controlled release of ganciclovir are available for those patients with CMV retinitis who are unable to tolerate systemic therapy; the implants are designed to release ganciclovir over a period of 5 to 8 months.

Ganciclovir is also used as a topical ophthalmic 0.15% gel for the treatment of acute herpes simplex keratitis; the gel is usually applied 5 times daily until corneal healing occurs, then 3 times daily for a further 7 days.

For doses in children, see below.

General references.
1. Faulds D, Heel RC. Ganciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs* 1990; **39:** 597–638.
2. Markham A, Faulds D. Ganciclovir: an update of its therapeutic use in cytomegalovirus infection. *Drugs* 1994; **48:** 455–84.
3. Crumpacker CS. Ganciclovir. *N Engl J Med* 1996; **335:** 721–9.
4. McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 2001; **61:** 1153–83.

Administration in children. Ganciclovir is not licensed for use in children in the UK. However, the *BNFC* considers that it may be given for prevention or treatment of CMV infections in children from 1 month of age when necessary, in doses equivalent to those in adults (p. 982.3). For congenital CMV infection of the CNS in neonates a dose of 6 mg/kg by intravenous infusion every 12 hours is recommended, for a total of 6 weeks.

Administration in renal impairment. Doses of ganciclovir should be reduced in renal impairment. Licensed product information recommends the following intravenous doses based on creatinine clearance (CC):

- CC 70 mL/minute or more: 5 mg/kg every 12 hours for induction, followed by 5 mg/kg every 24 hours for maintenance
- CC 50 to 69 mL/minute: 2.5 mg/kg every 12 hours for induction, 2.5 mg/kg every 24 hours for maintenance
- CC 25 to 49 mL/minute: 2.5 mg/kg every 24 hours for induction, 1.25 mg/kg every 24 hours for maintenance
- CC 10 to 24 mL/minute: 1.25 mg/kg every 24 hours for induction, 625 micrograms/kg every 24 hours for maintenance
- dialysis patients: on days when dialysis is performed 1.25 mg/kg for induction, or 625 micrograms/kg for maintenance, in each case given shortly after the end of dialysis. In the USA, a maximum of 3 doses each week is recommended

For critically ill patients with CMV infection who are undergoing continuous renal replacement therapy, the following doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 2.5 mg/kg (induction) or 1.25 mg/kg (maintenance) every 24 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 2.5 mg/kg every 12 hours for induction or every 24 hours for maintenance

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Cytomegalovirus infections. Ganciclovir is used in both the treatment and prophylaxis of CMV infections (p. 954.2) in immunocompromised patients although the prodrug valganciclovir, which is as effective as ganciclovir and has a more convenient oral dosage regimen, may now be preferred.

As with other herpesvirus infections, antiviral treatment tends to be suppressive rather than curative, and long-term maintenance therapy is necessary. Treatment in patients with AIDS is complicated by the additive haematological toxicity of ganciclovir and zidovudine. Clinical studies comparing ganciclovir with foscarnet for AIDS-related CMV retinopathy have shown higher mortality rates in patients given ganciclovir than in those given foscarnet.[1,2] The use of ganciclovir with CMV immunoglobulins[3,4] or normal immunoglobulins,[5] or with foscarnet[6,7] has been reported to improve both efficacy and tolerance.

An alternative is the use of *intravitreal* controlled-release ganciclovir implants[8-11] to avoid systemic adverse effects. Intravitreal ganciclovir used with intravitreal foscarnet has been reported to be effective.[12]

Oral preparations of ganciclovir have been tried for maintenance therapy and may be a useful adjunct to prevent systemic infection in patients treated with the intravitreal implants[13] (but see under Resistance, p. 984.2). The use of oral ganciclovir in high doses has been investigated;[14] daily doses of up to 6 g have been reported to be of benefit, although a conclusive comparison with standard intravenous doses could not be made. CMV infections at other sites in AIDS patients, including gastrointestinal and pulmonary infections, respond less well to ganciclovir than does retinitis.

Ganciclovir is also valuable for prophylaxis and early treatment of CMV infections in *transplant recipients*.[7,15-22] It is not clear whether pre-emptive therapy in infected patients is a better strategy than prophylaxis.[23] For established infections, ganciclovir is reported to be more effective in solid organ transplant recipients than in bone marrow transplant recipients. Ganciclovir has also been tried for prevention of CMV infection in patients with AIDS, although results are conflicting.[24,25]

Treatment of *congenital infections* has a generally poor outcome. Prolonged treatment periods may improve the response, but the safety of extended treatment with ganciclovir in this age group has not been fully evaluated and there is a need for further randomised controlled studies.[26] There is some evidence[27,28] that a 6-week course started in neonates with clinically apparent disease affecting the CNS prevents hearing deterioration at 6 months and may also prevent deterioration at or beyond 1 year of age.

1. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. *N Engl J Med* 1992; **326:** 213–20.
2. Polis MA, *et al.* Increased survival of a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis who received sodium phosphonoformate (foscarnet). *Am J Med* 1993; **94:** 175–80.
3. D'Alessandro AM, *et al.* Successful treatment of severe cytomegalovirus infections with ganciclovir and CMV hyperimmune globulin in liver transplant recipients. *Transplant Proc* 1989; **21:** 3560–1.
4. Salmela K, *et al.* Ganciclovir in the treatment of severe cytomegalovirus disease in liver transplant patients. *Transplant Proc* 1990; **22:** 238–40.
5. Emanuel D, *et al.* Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; **109:** 777–82.
6. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS: the Cytomegalovirus Retreatment Trial. *Arch Ophthalmol* 1996; **114:** 23–33.
7. Mylonakis E, *et al.* Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. *Clin Infect Dis* 2002; **34:** 1337–41.
8. Anand R, *et al.* Control of cytomegalovirus retinitis using sustained release of intraocular gancyclovir. *Arch Ophthalmol* 1993; **111:** 223–7.
9. Martin DF, *et al.* Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol* 1994; **112:** 1531–9.
10. Musch DC, *et al.* Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. *N Engl J Med* 1997; **337:** 83–90.
11. Ausayakhun S, *et al.* Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. *J Med Assoc Thai* 2005; **88** (suppl 9): S15–S20.
12. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
13. Martin DF, *et al.* Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999; **340:** 1063–70.
14. Lalezari JP, *et al.* High dose oral ganciclovir treatment for cytomegalovirus retinitis. *J Clin Virol* 2002; **24:** 67–77.
15. Goodrich JM, *et al.* Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med* 1993; **118:** 173–8.
16. Winston DJ, *et al.* Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. *Ann Intern Med* 1993; **118:** 179–84.
17. Hibberd PL, *et al.* Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; **123:** 18–26.
18. Winston DJ, *et al.* Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995; **346:** 69–74.
19. Gane E, *et al.* Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. *Lancet* 1997; **350:** 1729–33.
20. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. *Clin Infect Dis* 2001; **32:** 742–51.
21. Paya CV, *et al.* Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002; **185:** 854–60.
22. Keven K, *et al.* Cytomegalovirus prophylaxis using oral ganciclovir or valganciclovir in kidney and pancreas-kidney transplantation under antibody preconditioning. *Transplant Proc* 2004; **36:** 3107–12.
23. Monforte V, *et al.* Preemptive therapy with intravenous ganciclovir for the prevention of cytomegalovirus disease in lung transplant recipients. *Transplant Proc* 2005; **37:** 4039–42.
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26. Michaels MG, *et al.* Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 2003; **22:** 504–8.
27. Kimberlin DW, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; **143:** 16–25.
28. Oliver SE, *et al.* National Institute of Allergy, Infectious Diseases Collaborative Antiviral Study Group. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009; **46** (suppl 4): S22–S26.

Epstein-Barr virus infections. There have been anecdotal reports[1-4] of some improvement in patients with Epstein-Barr virus (EBV) infection given ganciclovir, although no antiviral therapy is entirely satisfactory (p. 955.1).

1. Pirsch JD, *et al.* Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir: two cases after solid organ transplantation. *Am J Med* 1989; **86:** 241–4.
2. Ishida Y, *et al.* Ganciclovir for chronic active Epstein-Barr virus infection. *Lancet* 1993; **341:** 560–1.
3. MacGinley R, *et al.* Epstein-Barr virus encephalitis in a renal allograft recipient diagnosed by polymerase chain reaction on cerebrospinal fluid and successfully treated with ganciclovir. *Nephrol Dial Transplant* 2001; **16:** 197–8.
4. Adams LA, *et al.* Ganciclovir and the treatment of Epstein-Barr virus hepatitis. *J Gastroenterol Hepatol* 2006; **21:** 1758–60.

Herpesvirus infections. The treatment of acute herpetic epithelial keratitis with topical ganciclovir 0.15% gel has been reviewed.[1,2] Ganciclovir gel is licensed in many countries for the treatment of superficial ocular infections with herpes simplex (p. 955.2). Studies have suggested that it is as effective as 3% aciclovir ointment, and may perhaps be better tolerated.[1]

1. Colin J. Ganciclovir ophthalmic gel, 0.15%: a valuable tool for treating ocular herpes. *Clin Ophthalmol* 2007; **1:** 441–53.
2. Tabbara KF, Al Balushi N. Topical ganciclovir in the treatment of acute herpetic keratitis. *Clin Ophthalmol* 2010; **4:** 905–12.

Adverse Effects and Treatment

The most common adverse effects of systemic ganciclovir are haematological and include neutropenia and thrombocytopenia; anaemia also occurs. Neutropenia affects up to 50% of patients given ganciclovir, most commonly starting in the first or second week of use. It is usually reversible but may be prolonged or irreversible and can lead to potentially fatal infections. AIDS patients may be at a greater risk of neutropenia than other immunosuppressed patients. Thrombocytopenia occurs in about 20% of patients given ganciclovir. Those with iatrogenic immunosuppression may be more at risk of developing thrombocytopenia than AIDS patients. Other adverse effects occurring in patients given systemic ganciclovir include dyspnoea, headache, fever, rash, pruritus, asthenia, CNS and gastrointestinal disturbances, infection, increased serum-creatinine concentration, and abnormal liver function tests. Less frequent adverse effects reported include anaphylaxis, arrhythmias, hypotension, pancreatitis, haematuria, as well as metabolic, musculoskeletal, urogenital, and cutaneous symptoms. When given intravenously, irritation or phlebitis may occur at the site of injection due to the high pH.

Local adverse effects have been associated with the insertion of ocular implants of ganciclovir and use of the topical eye gel.

Animal studies have suggested that there may be a risk of adverse testicular effects with temporary or permanent inhibition of spermatogenesis. Female fertility may also be affected. Such studies also suggest that ganciclovir is a potential mutagen, teratogen, and carcinogen.

Haemodialysis and hydration may be useful in reducing plasma concentrations of ganciclovir. Haematological adverse effects may be reversed in some patients by stopping treatment or reducing dosage; blood cell counts should return to normal within 3 to 7 days.

Colony-stimulating factors have been given with ganciclovir to limit its haematological toxicity.

Effects on the blood. Ganciclovir-induced neutropenia was successfully treated in a patient with CMV retinitis and bone-marrow suppression by *molgramostim* 5 micrograms/kg daily by intravenous infusion.[1] In a multicentre, randomised placebo-controlled study[2] in 69 AIDS patients with CMV infection who developed neutropenia from ganciclovir therapy, *lenograstim* given in a daily dose of 50 micrograms/m^2 subcutaneously yielded similar positive results.

1. Russo CL, *et al.* Treatment of neutropenia associated with dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor. *Lancet* 1990; **336:** 751–2.
2. Dubreuil-Lemaire M-L, *et al.* Lenograstim for the treatment of neutropenia in patients receiving ganciclovir for cytomegalovirus infection: a randomised, placebo-controlled trial in AIDS patients. *Eur J Haematol* 2000; **65:** 337–43.

Effects on mental function. Psychosis has been associated with intravenous ganciclovir use in 2 patients with normal renal function.[1,2] In both cases, psychotic symptoms such as agitation, confusion, and hallucination, occurred within 2 to 6 days of starting treatment with ganciclovir; symptoms resolved after ganciclovir was stopped.

1. Hansen BA, *et al.* Ganciclovir-induced psychosis. *N Engl J Med* 1996; **335:** 1397.
2. Southworth MR, Dunlap SH. Psychotic symptoms and confusion associated with intravenous ganciclovir in a heart transplant recipient. *Pharmacotherapy* 2000; **20:** 479–83.

Effects on the skin. An interstitial granulomatous drug reaction was reported[1] in a 57-year old woman after about one month of treatment with intravenous ganciclovir for CMV pneumonia. No other new drugs were given before

the onset of the lesions and they resolved spontaneously within 2 weeks of stopping the ganciclovir.

1. Marcollo Pini A, *et al.* Interstitial granulomatous drug reaction following intravenous ganciclovir. *Br J Dermatol* 2008; **158:** 1391–3.

Precautions

Ganciclovir should be used with caution in patients with renal impairment and doses should be adjusted according to creatinine clearance. It should not be given by rapid or bolus injection and adequate hydration should be maintained during intravenous infusion. It should be given with caution to patients with low blood counts or with a history of cytopenic reactions to drugs. Complete blood and platelet counts should be performed every 2 days or daily during the first 14 days of intravenous therapy and once weekly thereafter; ganciclovir should be withdrawn if the neutrophil count falls below 500 cells/microlitre or the platelet count falls below 25 000 cells/microlitre. Patients receiving oral ganciclovir should also be monitored regularly.

Ganciclovir is contra-indicated in pregnancy; contraception is recommended during ganciclovir treatment and, additionally for men, for 90 days thereafter. Adverse effects have occurred in the offspring of *animals* given ganciclovir during pregnancy and lactation.

Because of the risk of carcinogenicity and the high pH of the solution, contact with the skin and eyes should be avoided during the reconstitution of ganciclovir sodium injection.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ganciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Sodium content. Each g of ganciclovir sodium contains about 3.6 mmol of sodium.

Interactions

Zidovudine given with ganciclovir may have an additive neutropenic effect and should not normally be given during intravenous ganciclovir induction therapy, although it has been given with caution during oral maintenance therapy. Probenecid and other drugs that inhibit renal tubular secretion and resorption may reduce the renal clearance of ganciclovir, and so increase its serum concentrations. Use of intravenous ganciclovir with oral mycophenolate mofetil may result in increased plasma concentrations of both drugs due to competition for renal tubular secretion. Drugs that inhibit rapid cell division such as amphotericin B, some antineoplastic drugs, co-trimoxazole, dapsone, flucytosine, hydroxycarbamide, nucleoside analogues, and pentamidine may have additive toxic effects if given with ganciclovir. Convulsions have been reported when ganciclovir was given with imipenem and cilastatin.

Antivirals. Additive haematological toxicity, including neutropenia, may occur if ganciclovir is given with *zidovudine* (see Zidovudine, p. 1026.3), and there are reports of increased plasma concentrations of *didanosine* when given with ganciclovir (see p. 974.1). There has also been a report[1] of decreased blood concentrations of ganciclovir when didanosine (200 mg every 12 hours) was given orally 2 hours before oral ganciclovir (1 g every 8 hours) but not when the two drugs were given at the same time. However, a later study[2] using twice the dose of oral ganciclovir found no effect irrespective of whether ganciclovir was given 2 hours before or 2 hours after didanosine.

When ganciclovir was given orally with *zalcitabine*, a 22% increase in the area under the concentration-time curve for ganciclovir was noted although it was believed that this did not necessitate any dosage modification.[3] No pharmacokinetic changes were reported when ganciclovir was given orally with *stavudine*.[3]

1. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 227–34.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1057–62.
3. Jung D, *et al.* The pharmacokinetics and safety profile of oral ganciclovir combined with zalcitabine or stavudine in asymptomatic HIV- and CMV-seropositive patients. *J Clin Pharmacol* 1999; **39:** 505–12.

Ciclosporin. Reversible acute unilateral or bilateral eye movement disorders typical of sixth cranial nerve palsies[1] occurred in 4 patients who received ciclosporin and ganciclovir after bone marrow transplantation.

1. Openshaw H, *et al.* Eye movement disorders in bone marrow transplant patients on cyclosporin and ganciclovir. *Bone Marrow Transpl* 1997; **19:** 503–5.

Antiviral Action

Ganciclovir inhibits replication of human herpesviruses *in vivo* and *in vitro*. It is active against CMV, herpes simplex virus types 1 and 2, Epstein-Barr virus, varicella-zoster virus, herpesvirus 6, 7, and 8, and hepatitis B virus. This activity is due to intracellular conversion of ganciclovir by viral thymidine kinase (in herpes simplex and varicella-zoster infected cells) or possibly by cellular deoxyguanosine kinase (in Epstein-Barr infected cells) to ganciclovir monophosphate with subsequent cellular conversion to the diphosphate and the active triphosphate. Ganciclovir triphosphate inhibits viral DNA synthesis by inhibiting the viral DNA polymerase enzyme as well as being incorporated into the viral DNA. This process is selective for infected cells; the concentration of ganciclovir triphosphate may be up to a hundredfold higher in CMV-infected cells than in uninfected cells.

Ganciclovir has a similar spectrum of activity to aciclovir, herpes simplex virus types 1 and 2 being the most susceptible of the herpesviruses. However, CMV is much more susceptible to ganciclovir than aciclovir.

Resistance to ganciclovir has been found *in vitro* in herpes simplex viruses, varicella-zoster virus, and CMV. Possible mechanisms of resistance include a reduction in the phosphorylation of ganciclovir to the active form and reduced sensitivity of viral DNA polymerase. Resistance has been reported in CMV strains isolated from patients receiving ganciclovir for prolonged periods and in those with an initially high viral load. It has also been seen in AIDS patients with CMV retinitis who have never previously received the drug. Ganciclovir-resistant strains of CMV are cross-resistant to aciclovir (even at the highest doses); cross-resistance with cidofovir and foscarnet have been described, however, other studies have found ganciclovir-resistant strains remain susceptible to cidofovir, foscarnet, and vidarabine.

Resistance. The development of CMV resistance to ganciclovir may be a factor in disease progression in patients receiving prolonged therapy with ganciclovir and the incidence of resistance is reported to increase with duration of therapy.[1] A ganciclovir-resistant isolate of CMV was detected in about 30% of 95 patients after 9 months of treatment and this correlated with dissemination of infection to the contralateral eye.[2] Treatment of unilateral retinitis with systemic ganciclovir (intravenously, or orally together with an implant) was associated with a higher incidence of ganciclovir-resistant CMV infection developing in the contralateral eye, compared with treatment with ganciclovir implant alone.[3]

Ganciclovir-resistant CMV has been reported[4] to be an important cause of late morbidity in seronegative patients who received CMV-seropositive organ transplants; in one study,[5] 5 of 67 seronegative recipients developed ganciclovir-resistant CMV disease compared with none of 173 seropositive subjects. The management of ganciclovir-resistant CMV has been reviewed.[6]

1. Drew WL. Cytomegalovirus resistance to antiviral therapies. *Am J Health-SystPharm* 1996; **53** (suppl 2): S17–S23.
2. Jabs DA, *et al.* Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. *J Infect Dis* 1998; **177:** 770–3.
3. Imai Y, *et al.* Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. *J Infect Dis* 2004; **189:** 611–15.
4. Limaye AP. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. *Clin Infect Dis* 2002; **35:** 866–72.
5. Limaye AP, *et al.* Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; **356:** 645–9.
6. Avery RK. Update in management of ganciclovir-resistant cytomegalovirus infection. *Curr Opin Infect Dis* 2008; **21:** 433–7.

Resistance

Resistance to ganciclovir has been found *in vitro* in herpes simplex viruses, varicella-zoster virus, and CMV. Possible mechanisms of resistance include a reduction in the phosphorylation of ganciclovir to the active form and reduced sensitivity of viral DNA polymerase. Resistance has been reported in CMV strains isolated from patients receiving ganciclovir for prolonged periods and in those with an initially high viral load. It has also been seen in AIDS patients with CMV retinitis who have never previously received the drug. Cross-resistance with cidofovir is common.

Pharmacokinetics

Ganciclovir is poorly absorbed from the gastrointestinal tract after oral doses and there is minimal systemic absorption after intravitreal injection. Bioavailability of oral ganciclovir is about 5%, and is increased by intake with food to 6 to 9%. After intravenous dosage as ganciclovir sodium it is widely distributed to body tissues and fluids including intra-ocular fluid and CSF. Binding to plasma proteins is reported to be 1 to 2%. Ganciclovir is excreted unchanged in the urine mainly by glomerular filtration and also active tubular secretion. In patients with normal renal function the half-life is about 2.5 to 4.5 hours after intravenous doses and about 4 to 5.7 hours after oral doses. In patients with renal impairment, the renal clearance decreases and the half-life increases; a half-life of 28.5 hours has been reported when the serum-creatinine concentration was greater than 398 micromol/litre.

Haemodialysis has been reported to reduce plasma-ganciclovir concentrations by about 50%.

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1. Arevalo JF, *et al.* Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. *J Infect Dis* 1995; **172:** 951–6.
2. Morlet N, *et al.* High dose intravitreal ganciclovir injection provides a prolonged therapeutic intraocular concentration. *Br J Ophthalmol* 1996; **80:** 214–16.
3. Lavelle J, *et al.* Effect of food on the relative bioavailability of oral ganciclovir. *J Clin Pharmacol* 1996; **36:** 238–41.
4. Zhou X-J, *et al.* Population pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infection. *Antimicrob Agents Chemother* 1996; **40:** 2202–5.
5. Giffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; **10** (suppl 4): S3–S6.
6. Jung D, *et al.* Steady-state relative bioavailability of three oral ganciclovir dosage regimens delivering 6,000 mg/day in patients with human immunodeficiency virus. *J Clin Pharmacol* 1998; **38:** 1021–4.
7. Jung D, *et al.* Absolute bioavailability and dose proportionality of oral ganciclovir after ascending multiple doses in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1122–8.
8. Jung D, *et al.* Effect of food on high-dose oral ganciclovir disposition in HIV-positive subjects. *J Clin Pharmacol* 1999; **39:** 161–5.
9. Snell GI, *et al.* Pharmacokinetic assessment of oral ganciclovir in lung transplant recipients with cystic fibrosis. *J Antimicrob Chemother* 2000; **45:** 511–16.
10. Wiltshire H, *et al.* Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; **44:** 495–507.
11. Asano-Mori Y, *et al.* Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment. *J Antimicrob Chemother* 2006; **57:** 1004–7.
12. Caldés A, *et al.* Population pharmacokinetics of ganciclovir after intravenous ganciclovir and oral valganciclovir administration in solid organ transplant patients infected with cytomegalovirus. *Antimicrob Agents Chemother* 2009; **53:** 4816–24.
13. Pescovitz MD, *et al.* Pharmacokinetics of oral valganciclovir solution and intravenous ganciclovir in pediatric renal and liver transplant recipients. *Transpl Infect Dis* 2010; **12:** 195–203.
14. Welker H, *et al.* Ganciclovir pharmacokinetic parameters do not change when extending valganciclovir cytomegalovirus prophylaxis from 100 to 200 days. *Transplantation* 2010; **90:** 1414–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ciganclor; Cymevene; Gasmilen; Grinevel; Neagel; Virgan; ***Austral.***: Cymevene; Vitrasert; Vitrisert; ***Austria***: Cymevene; ***Belg.***: Cymevene; Virgan; ***Braz.***: Cymevene; Ganciclotrat; Ganvirax; ***Canad.***: Cytovene; ***Chile***: Cymevene; ***China***: Ai Lin Wei (艾林维); Ao Xi Tong (奥西彤); Bo Ying (博应); Cheng Li Kang (诚力康); Cymevene (赛美维); Di Du (迪都); Du Ya Xin (独雅欣); Fu Er Ling (孚尔灵); Gen Le Wei (更乐韦); He Pu Xin (荷普欣); He Yuan (贺元); Heng Kang (恒抗); Hong Kang Wei; Hui Teng (辉腾); Ji Xi Tong (集希通); Jun Fen (君芬); Kai Ji Wei (凯济维); Le Fan (了凡); Li Bai Lu (利百路); Li Jian (利健); Li Ke Le (丽科乐); Li Ke Ming (丽科明); Li Ke Qing (丽科清); Li Ke Wei (丽科伟); Lin Ke Hong (林可宏); Luoheng (罗恒); Mei Li Neng (美立能); Mei Si Bo Wei (美斯博维); Mei Ti Bo Wei (美替博伟); Ning Dan Xin (宁丹欣); Nuo Bei Qi (诺贝奇); Nuo Hao (诺好); Nuowei (诺伟); Pu Gen Xin (普更欣); Rui Sheng Yi (瑞圣亿); Shi De (实得); Si Ze (思泽); Wei Ke Rui Da (威克锐达); Wei Ru (维如); Weisi (韦斯); Xi Wei (希韦); Xin Qing Yu (新青羽); You Ni Da (尤尼达); Zhong Jia Tai (中佳太); ***Cz.***: Cymevene; Virgan; ***Denm.***: Cymevene; ***Fin.***: Cymevene; ***Fr.***: Cymevan; Virgan; ***Ger.***: Cymeven; Virgan; ***Gr.***: Cymevene; Virgan; ***Hong Kong***: Cymevene; Virgan†; ***Hung.***: Cymevene; Virgan; ***India***: Cymevene; Ganguard; Gavir; Natclovir; ***Indon.***: Cymevene; ***Irl.***: Cymevene; ***Israel***: Cymevene; ***Ital.***: Citovirax; Cymevene; Virgan; ***Malaysia***: Cymevene; ***Mex.***: Cymevene†; Umecortil; ***Neth.***: Cymevene; ***Norw.***: Cymevene; ***NZ***: Cymevene; ***Philipp.***: Cymevene; Virgan; ***Pol.***: Cymevene; Virgan; ***Port.***: Cymevene; Virgan; ***Rus.***: Cymevene (Цимевен); ***S.Afr.***: Cymevene; ***Singapore***: Cymevene; ***Spain***: Cymevene; Virgan; ***Swed.***: Cymevene; ***Switz.***: Cymevene; ***Thai.***: Cymevene; ***Turk.***: Cymevene; ***UK***: Cymevene; Virgan; ***Ukr.***: Cymevene (Цимевен); ***USA***: Cytovene; Vitrasert†; Zirgan; ***Venez.***: Cymevene.

Pharmacopoeial Preparations

USP 36: Ganciclovir for Injection; Ganciclovir Oral Suspension.

Ibacitabine *(rINN)*

Ibacitabin; Ibacitabina; Ibacitabinum; Iododesoxycytidine; Ибацитабин.

2′-Deoxy-5-iodocytidine.

$C_9H_{12}IN_3O_4$=353.1

CAS — 611-53-0.

ATC — D06BB08.

ATC Vet — QD06BB08.

UNII — 3EK8532DZV.

Profile

Ibacitabine is an antiviral used topically as a 1% gel in the treatment of herpes labialis (see Herpes Simplex Infections, p. 955.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cuterpes; ***Gr.***: Marenil.

Idoxuridine *(BAN, USAN, rINN)*

Allergan 211; GF-I115; Idoksuridiini; Idoksuridinas; Idoxuridin; Idoxuridina; Idoxuridinum; IDU; 5-IDUR; 5-IUDR; NSC-39661; SKF-14287; Идоксуридин.

2′-Deoxy-5-iodouridine.

$C_9H_{11}IN_2O_5$=354.1

CAS — 54-42-2.

ATC — D06BB01; J05AB02; S01AD01.

ATC Vet — QD06BB01; QJ05AB02; QS01AD01.

UNII — LGP81V5245.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. & (Idoxuridine). A white or almost white crystalline powder. M.p. about 180 degrees, with decomposition. Slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 36: (Idoxuridine). A white, practically odourless, crystalline powder. Slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Iodine vapour is liberated on heating idoxuridine. It has been reported that some decomposition products such as iodouracil are more toxic than idoxuridine and reduce its antiviral activity.

Uses and Administration

Idoxuridine is a pyrimidine nucleoside structurally related to thymidine. It is used topically in the treatment of herpes simplex keratitis and cutaneous infections with herpes simplex (p. 955.2) and herpes zoster (see Varicella-zoster Infections, p. 956.2), but has generally been superseded by other antivirals.

In the treatment of herpes simplex keratitis, idoxuridine is applied as a 0.1% ophthalmic solution and has also been used as a 0.5% eye ointment.

Idoxuridine 5% in dimethyl sulfoxide (to aid absorption) may be painted onto the lesions of cutaneous herpes simplex and herpes zoster four times daily for 4 days.

Adverse Effects

Hypersensitivity reactions such as irritation, pain, and pruritus may occur occasionally when idoxuridine is applied to the eyes. Other adverse effects include stinging, conjunctivitis, oedema and inflammation of the eye or eyelids, photophobia, pruritus, and rarely, occlusion of the lachrymal duct. Prolonged or excessive use may damage the cornea.

Idoxuridine applied to the skin may produce irritation, stinging, and hypersensitivity reactions. Taste disturbance may also occur. Excessive application of topical idoxuridine to the skin may cause skin maceration.

Idoxuridine is a potential carcinogen and teratogen.

Carcinogenicity. Squamous cell carcinoma developed in a young woman after topical applications of idoxuridine for 4 days for the treatment of herpes simplex labialis.[1]

1. Koppang HS, Aas E. Squamous carcinoma induced by topical idoxuridine therapy? *Br J Dermatol* 1983; **108:** 501–3.

Precautions

Idoxuridine should be used with caution in conditions where there is deep ulceration involving the stromal layers of the cornea, as delayed healing has resulted in corneal perforation. Prolonged topical use should be avoided.

The potential teratogenicity of idoxuridine should be taken into account when treating pregnant patients or patients likely to become pregnant. Corticosteroids should be applied with caution in patients also receiving idoxuridine as they may accelerate the spread of viral infection.

Interactions

Preparations containing boric acid should not be applied to the eye in patients also receiving ocular preparations of idoxuridine as irritation ensues.

Antiviral Action

After intracellular phosphorylation to the triphosphate, idoxuridine is incorporated into viral DNA instead of thymidine so inhibiting replication of sensitive viral strains. Idoxuridine is also incorporated into mammalian DNA. Idoxuridine is active against herpes simplex and varicella zoster viruses. It has also been shown to inhibit vaccinia virus, CMV, and adenovirus.

Pharmacokinetics

Penetration of idoxuridine into the cornea and skin is reported to be poor. Idoxuridine is rapidly metabolised in the body to iodouracil, uracil, and iodide, which are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Idulea; ***Austral.***: Stoxil†; ***Braz.***: Herpesine; ***Canad.***: Herplex†; ***Ger.***: Virunguent†; ***India***: Idurin; Ridinox†; ***Indon.***: Isotic Ixodine†; ***Ital.***: Iducher; Idustatin; ***Neth.***: Virexen†; ***NZ***: Virasolve; ***Rus.***: Oftan IDU (Офтан ИДУ); ***Singapore***: Virunguent; ***Spain***: Virexen; ***Switz.***: Virunguent†; ***UK***: Herpid†.

Multi-ingredient Preparations. ***Austral.***: Virasolve.

Pharmacopoeial Preparations

BP 2014: Idoxuridine Eye Drops;

USP 36: Idoxuridine Ophthalmic Ointment; Idoxuridine Ophthalmic Solution.

Imiquimod *(BAN, USAN, rINN)*

Imikimod; Imikimodi; Imiquimodum; R-837; S-26308; Имихимод.

4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline.

$C_{14}H_{16}N_4$=240.3

CAS — 99011-02-6.

ATC — D06BB10.

ATC Vet — QD06BB10.

UNII — P1QW714R7M.

Uses and Administration

Imiquimod is an immune response modifier used topically in the treatment of external genital and perianal warts (p. 1689.3), superficial basal cell carcinomas, and actinic keratoses (see Malignant Neoplasms of the Skin, below). For the treatment of genital and perianal **warts**, it is applied as a 5% cream three times each week for up to 16 weeks and is left on the skin for 6 to 10 hours. For the management of superficial **basal cell carcinoma**, a 5% cream is applied 5 times each week for 6 weeks and left on the skin for about 8 hours. For the treatment of **actinic keratoses** on the face or scalp, a 5% cream is also used and is again left on the skin for 8 hours. In the UK, this is applied 3 times each week for 4 weeks, repeated after a 4-week break for a further 4 weeks if necessary; in the USA, application twice a week for 16 weeks is recommended.

Imiquimod is also under investigation for the treatment of other squamous cell carcinomas.

References

1. Tyring S, *et al.* Imiquimod; an international update on therapeutic uses in dermatology. *Int J Dermatol* 2002; **41:** 810–16.
2. Garland SM. Imiquimod. *Curr Opin Infect Dis* 2003; **16:** 85–9.
3. Wagstaff AJ, Perry CM. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. *Drugs* 2007; **67:** 2187–2210.
4. Schön MP, Schön M. Imiquimod: mode of action. *Br J Dermatol* 2007; **157** (suppl 2): 8–13.
5. Harwood CA, *et al.* Imiquimod cream 5% for recalcitrant cutaneous warts in immunosuppressed individuals. *Br J Dermatol* 2005; **152:** 122–9.
6. Ulrich C, *et al.* Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. *Br J Dermatol* 2007; **157** (suppl 2): 25–31.
7. Stockfleth E, *et al.* Multicentre, open-label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head. *Br J Dermatol* 2007; **157** (suppl 2): 41–6.
8. Schöfer H. Evaluation of imiquimod for the therapy of external genital and anal warts in comparison with destructive therapies. *Br J Dermatol* 2007; **157** (suppl 2): 52–5.
9. Ganjian S, *et al.* Off-label indications for imiquimod. *Dermatol Online J* 2009; **15:** 4.
10. Trakatelli M, *et al.* Efforts to counteract locally the effects of systemic immunosupression: a review on the use of imiquimod, a topical immunostimulator in organ transplant recipients. *Int J Immunopathol Pharmacol* 2010; **23:** 387–96.

Leishmaniasis. Evidence from small studies[1,2] suggests that topical imiquimod 5 or 7.5% cream with parenteral meglumine antimonate (p. 926.3) may be of use in the management of cutaneous leishmaniasis (p. 922.1).

For mention of the use of imiquimod with dapsone in itraconazole for treatment of cutaneous leishmaniasis, see under Dapsone, p. 281.3 and Itraconazole, p. 584.2, respectively.

1. Miranda-Verástegui C, *et al.* Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. *Clin Infect Dis* 2005; **40:** 1395–1403.
2. Arevalo I, *et al.* Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clin Infect Dis* 2007; **44:** 1549–54.

Malignant neoplasms of the skin. Imiquimod is indicated in the treatment of actinic keratosis[1-4] and basal cell carcinoma (p. 714.2).[5-9] It has also been reported to be effective in the treatment of cutaneous T-cell lymphomas such as mycosis fungoides (p. 698.3)[10-12] and in a patient with CD30+ anaplastic large cell lymphoma.[12] Two patients with cutaneous B-cell lymphoma had a partial remission after treatment with topical imiquimod, while one did not respond to therapy;[12] however, a patient with primary cutaneous follicle centre lymphoma was successfully treated.[13] Imiquimod is under investigation for the treatment of Bowen's disease.[14] It has also been tried in lentigo maligna[15] and other forms of localised or *in-situ* melanoma,[16,17] and there are also reports of investigational use in the management of metastatic melanoma.[18,19] and in anal and vulvar intraepithelial neoplasia.[20-22]

1. Lebwohl M, *et al.* Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004; **50:** 714–21.
2. Korman N, *et al.* Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol* 2005; **141:** 467–73.
3. Krawtchenko N, *et al.* A randomised study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol* 2007; **157** (suppl 2): 34–40.
4. Alomar A, *et al.* Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. *Br J Dermatol* 2007; **157:** 133–41.
5. Chen TM, *et al.* Treatment of a large superficial basal cell carcinoma with 5% imiquimod: a case report and review of the literature. *Dermatol Surg* 2002; **28:** 344–6.
6. Drehs MM, *et al.* Successful treatment of multiple superficial basal cell carcinomas with topical imiquimod: case report and review of the literature. *Dermatol Surg* 2002; **28:** 427–9.
7. Schulze HJ, *et al.* Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol* 2005; **152:** 939–47.
8. Bath-Hextall FJ, *et al.* Interventions for basal cell carcinoma of the skin. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
9. Love WE, *et al.* Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol* 2009; **145:** 1431–8.
10. Deeths MJ, *et al.* Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. *J Am Acad Dermatol* 2005; **52:** 275–80.
11. Martínez-González MC, *et al.* Imiquimod in mycosis fungoides. *Eur J Dermatol* 2008; **18:** 148–52.
12. Coors EA, *et al.* Topical imiquimod as treatment for different kinds of cutaneous lymphoma. *Eur J Dermatol* 2006; **16:** 391–3.
13. Stavrakoglou A, *et al.* Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. *Br J Dermatol* 2007; **157:** 620–2.
14. Mackenzie-Wood A, *et al.* Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol* 2001; **44:** 462–70.
15. Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; **155:** 653–6.
16. Lonsdale-Eccles AA, *et al.* Successful treatment of vulval melanoma in situ with topical 5% imiquimod cream. *Br J Dermatol* 2006; **155:** 215–17.
17. Spieth K, *et al.* Topical imiquimod: effectiveness in intraepithelial melanoma of oral mucosa. *Lancet Oncol* 2006; **7:** 1036–7.
18. Zeitouni NC, *et al.* Treatment of cutaneous metastatic melanoma with imiquimod 5% cream and the pulsed-dye laser. *Br J Dermatol* 2005; **152:** 376–7.
19. Utikal J, *et al.* Complete remission of multiple satellite and in-transit melanoma metastases after sequential treatment with isolated limb perfusion and topical imiquimod. *Br J Dermatol* 2006; **155:** 488–91.
20. Wieland U, *et al.* Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006; **142:** 1438–44.
21. van Seters M, *et al.* Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008; **358:** 1465–73.
22. Mahto M, *et al.* More than a decade on: review of the use of imiquimod in lower anogenital intraepithelial neoplasia. *Int J STD AIDS* 2010; **21:** 8–16.

Skin disorders. Applications of imiquimod 5% have shown some benefit in a few patients with localised scleroderma (morphoea).[1] It has also been successfully used to treat lesions of human papillomavirus type 5 in a patient with familial benign pemphigus (Hailey-Hailey disease)[2]; intra-oral applications were used in patients with human papillomavirus-associated oral leucoplakia to reduce the area of leucoplakia and thereby facilitate surgical removal of the residual lesions if necessary.[3]

Topical imiquimod appears to have antiangiogenic properties and has been tried for treatment of some infants with infantile haemangiomas[4-6] and a patient with capillary malformations;[7] treatment was beneficial in most patients.

1. Dytoc M, *et al.* First case series on the use of imiquimod for morphoea. *Br J Dermatol* 2005; **153:** 815–20.
2. Chan CC, *et al.* Human papillomavirus type 5 infection in a patient with Hailey-Hailey disease successfully treated with imiquimod. *Br J Dermatol* 2007; **156:** 579–81.
3. Allam JP, *et al.* Successful treatment of extensive human papillomavirus-associated oral leucoplakia with imiquimod. *Br J Dermatol* 2008; **158:** 644–6.

4. Welsh O, *et al.* Treatment of infantile hemangiomas with short-term application of imiquimod 5% cream. *J Am Acad Dermatol* 2004; **51:** 639–42.
5. Ho NT, *et al.* Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. *J Am Acad Dermatol* 2007; **56:** 63–8.
6. Martinez MI, *et al.* Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol* 2002; **138:** 881–4.
7. Kouba DJ, *et al.* Topical imiquimod in the treatment of a long-standing capillary malformation. *Br J Dermatol* 2007; **157:** 1071–2.

Adverse Effects and Precautions

Adverse effects after topical application of imiquimod include local skin erosion, erythema, excoriation, flaking, and oedema. There have been reports of localised hypopigmentation and hyperpigmentation. Skin reactions away from the site of application have been reported. Systemic effects after topical application include headache, flu-like symptoms, and myalgia. Hepato-biliary disorders, including severe cases, have been reported rarely after topical imiquimod use.

Hypotension has occurred after repeated ingestion.

Hypersensitivity. Angioedema, initially of both the hands and feet and later the tongue, occurred in a 61-year-old man 3 weeks after starting treatment with a 5% imiquimod cream for squamous cell carcinoma *in situ* (Bowen's disease).[1]

1. Barton JC. Angioedema associated with imiquimod. *J A m Acad Dermatol* 2004; **51:** 477–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imiquimod as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aldara; Imimore; Miquimod; Quinilan; Virosupril; ***Austral.***: Aldara; ***Austria***: Aldara; ***Belg.***: Aldara; ***Braz.***: Aldara; Imoxy; Ixium; Modik; ***Canad.***: Aldara; Vyloma; Zyclara; ***Chile***: Aldara†; Imimor; Labimiq; Tocasol; ***China***: Aldara (艾达乐); Li Di (利迪); Li Ke Jie (丽科杰); Nan Bo (南博); Tian Rui (天锐); Youbiqing (忧必青); ***Cz.***: Aldara; ***Denm.***: Aldara; ***Fin.***: Aldara; ***Fr.***: Aldara; ***Ger.***: Aldara; ***Gr.***: Aldara; ***Hong Kong***: Aldara; ***Hung.***: Aldara; ***India***: Imiquad; Nilwart; ***Irl.***: Aldara; ***Israel***: Aldara; Aquimod; ***Ital.***: Aldara; ***Jpn***: Beselna; ***Malaysia***: Aldara; ***Mex.***: Aldara; Vetland; ***Neth.***: Aldara; ***Norw.***: Aldara; ***NZ***: Aldara; ***Philipp.***: Aldara; ***Pol.***: Aldara; ***Port.***: Aldara; ***S.Afr.***: Aldara; ***Singapore***: Aldara; ***Spain***: Aldara; ***Swed.***: Aldara; ***Switz.***: Aldara; ***Thai.***: Aldara; ***Turk.***: Aldara; ***UK***: Aldara; Zyclara; ***Ukr.***: Aldara (Альдара); ***USA***: Aldara; Zyclara.

Indinavir Sulfate *(BANM, USAN, pINNM)*

Indinavir, sulfate d'; Indinavir, sulfato de; Indinavir Sulphate; Indinaviri sulfas; Indinavirsulfat; L-735524; MK-0639; MK-639; Sulfato de indinavir; Индинавира Сульфат.

(αR,γS,2S)-α-Benzyl-2-(*tert*-butylcarbamoyl)-γ-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinevaleramide sulfate (1:1).

$C_{36}H_{47}N_5O_4,H_2SO_4$=711.9

CAS — 150378-17-9 (indinavir); 157810-81-6 (indinavir sulfate).

ATC — J05AE02.

ATC Vet — QJ05AE02.

UNII — 771H53976Q.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Indinavir Sulfate). A white or almost white, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 36: (Indinavir Sulfate). A white or almost white, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from moisture.

Uses and Administration

Indinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when indinavir is used alone, and it is therefore used with other antiretrovirals.

Indinavir is given orally as the sulfate, but doses are expressed in terms of the base; 116 mg of indinavir sulfate is equivalent to about 100 mg of indinavir. It is given in a usual adult dose of 800 mg every 8 hours. Doses of indinavir may need to be adjusted to manage significant drug interactions. If used with delavirdine, a *reduced* indinavir dose of 400 to 600 mg every 8 hours should be considered. Similarly, a dose of 600 mg every 8 hours is recommended when indinavir is used with itraconazole or ketoconazole; restriction of the azole doses should also be considered (see Uses and Administration of Itraconazole, p. 583.3, and Ketoconazole, p. 585.3, respectively). If given with rifabutin, indinavir doses should be *increased* to 1 g every 8 hours (the dose of rifabutin must also be adjusted, see under Uses and Administration of Rifabutin, p. 349.1). Indinavir should be given either 1 hour before or 2 hours after meals, or with a light, low-fat meal. Adequate hydration should be maintained. Treatment may have to be interrupted if acute episodes of nephrolithiasis occur.

For details of doses in children and adolescents, see below. For details of modified dosage to be used in patients with hepatic impairment, see below.

References.
1. Rayner CR, *et al.* A critical evaluation of the therapeutic range of indinavir. *Ann Pharmacother* 2002; **36:** 1230–7.
2. Boyd M. Indinavir: the forgotten HIV-protease inhibitor: does it still have a role? *Expert Opin Pharmacother* 2007; **8:** 957–64.
3. Cressey TR, *et al.* Indinavir/ritonavir remains an important component of HAART for the treatment of HIV/AIDS, particularly in resource-limited settings. *Expert Opin Drug Metab Toxicol* 2007; **3:** 347–61.

Administration in children. For the treatment of HIV infection in children 4 years of age and older indinavir is given orally with other antiretroviral drugs. A dose of 500 mg/m^2 every 8 hours is recommended; doses should not exceed the adult dose (see above).

Administration in hepatic impairment. A reduction in the oral dose of indinavir to 600 mg every 8 hours is recommended for patients with mild to moderate hepatic insufficiency due to cirrhosis.

Adverse Effects

The most commonly reported adverse effects associated with antiretroviral regimens containing indinavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea and vomiting), taste disturbances, headache, and dizziness. Nephrolithiasis, often with flank pain and occurring with or without haematuria, is the most frequently reported serious adverse effect. It appears to be dose-related and is more frequent in patients taking more than 2.4 g daily; it also occurs more often in children. Temporarily stopping treatment and giving fluids often resolve the symptoms, but interstitial nephritis and acute renal failure have been reported. Dry skin and rashes occur commonly and may occasionally be severe. Cases of Stevens-Johnson syndrome and erythema multiforme have also been reported. Hypersensitivity reactions, including vasculitis and sometimes anaphylaxis, have been associated with indinavir. Hepatitis, including cases resulting in hepatic failure and death has occurred. Cases of acute haemolytic anaemia have been reported again with some fatalities. Other commonly reported adverse effects are dry mouth, dysuria, fatigue, flatulence, hypoaesthesia, insomnia, paraesthesia, pruritus, and acid regurgitation. Neutrophil counts may be reduced and mean corpuscular volume increased. Abnormal laboratory test results associated with indinavir-containing regimens have included crystalluria, haematuria, proteinuria, raised liver enzymes, and asymptomatic hyperbilirubinaemia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including indinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including indinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Reviews.
1. Moyle GJ, Gazzard BG. A risk-benefit assessment of HIV protease inhibitors. *Drug Safety* 1999; **20:** 299–321.

Effects on carbohydrate and lipid metabolism. HIV-protease inhibitors have been associated with a lipodystrophy syndrome characterised by peripheral fat wasting, central adiposity and the so called 'buffalo hump', hyperlipidaemia, and insulin resistance.[1]

A survey of 113 HIV-infected patients receiving HIV-protease inhibitors found lipodystrophy in 83% (severe in 11%) and impaired glucose tolerance in 23% (including diabetes mellitus in 7%) after a mean of 21 months of therapy.[2]

A systematic review[3] of published material has concluded that use of HIV-protease inhibitors is associated with increased concentrations of total cholesterol, triglycerides, and low-density lipoprotein; that use is often associated with morphological signs of cardiovascular disease such as increased carotid intima thickness or atherosclerotic lesions. Comparison of the effect of specific HIV-protease inhibitors showed that ritonavir was consistently associated with elevated lipids and that, although some studies showed that saquinavir was associated with elevated lipids, it was to a lesser degree than other drugs. Guidelines[4] have been published outlining the management, including drug therapy, of antiretroviral-induced lipid disorders in HIV-infected patients.

Impaired glucose tolerance has been linked to reduction in insulin sensitivity[5] and has responded to treatment with sulfonylureas or insulin.[6] Insulin resistance has been reported with some HIV-protease inhibitors (such as indinavir and ritonavir-boosted lopinavir), but not all; atazanavir has not been found to alter insulin sensitivity, regardless of whether it is ritonavir-boosted or not.[7]

1. Carr A, *et al.* Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; **351:** 1881–3.
2. Carr A, *et al.* Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353:** 2093–9.
3. Rhew DC, *et al.* Association between protease inhibitor use and increased cardiovascular risk in patients infected with human immunodeficiency virus: a systematic review. *Clin Infect Dis* 2003; **37:** 959–72.
4. Dubé MP, *et al.* Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; **37:** 613–27. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/378131 (accessed 28/08/08)
5. Walli R, *et al.* Impaired glucose tolerance and protease inhibitors. *Ann Intern Med* 1998; **129:** 837–8.
6. Dubé MP, *et al.* Protease inhibitor-associated hyperglycaemia. *Lancet* 1997; **350:** 713–14.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)

Effects on the cardiovascular system. Use of HIV-protease inhibitors has been associated with myocardial infarction and stroke in some cohort studies; risk appears to be greatest among patients with other risk factors for cardiovascular disease.[1] In a nested case-control study,[2] the risk of myocardial infarction was increased by cumulative exposure to all studied HIV-protease inhibitors except saquinavir, and particularly to ritonavir-boosted lopinavir and boosted or unboosted amprenavir/fosamprenavir.

For adverse effects of HIV-protease inhibitors on carbohydrate and lipid metabolism that increase the risk of coronary vascular disease, see above.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)
2. Lang S, *et al.* Clinical Epidemiology Group of the French Hospital Database on HIV. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch InternMed* 2010; **170:** 1228–38.

Effects on the kidneys. Nephrolithiasis has been reported in about 10% of patients receiving indinavir, and the incidence may be higher in patients with haemophilia or hepatitis C infection.[1] In some cases, indinavir-induced nephrolithiasis may occur years after stopping the drug.[2] There have also been reports of nephrolithiasis in patients given atazanavir or fosamprenavir. Both asymptomatic[3] and symptomatic[4,5] crystalluria have been reported in patients receiving indinavir, with symptomatic urinary-tract disease in 8%. Indinavir has been identified as the major constituent of both urinary crystals[3] and calculi.[6] In addition there have been reports of acute interstitial nephritis associated with indinavir[7] and deterioration of renal function associated with both indinavir[8] and ritonavir.[9,10] Renal atrophy was associated with long-term treatment with indinavir.[11,12]

Factors that may increase the risk of indinavir crystallisation in the urine include volume depletion, hepatic insufficiency, low urinary pH, renal insufficiency or tubular cell injury, and low lean body-mass.[2]

1. Brodie SB, *et al.* Variation in incidence of indinavir-associated nephrolithiasis among HIV-positive patients. *AIDS* 1998; **12:** 2433–7.
2. Huynh J, *et al.* Indinavir-induced nephrolithiasis three and one-half years after cessation of indinavir therapy. *Int Urol Nephrol* 2010. Available at: http://www.springerlink.com/content/54x727175v5j2362/fulltext.pdf (accessed 08/02/11)
3. Kopp JB, *et al.* Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997; **127:** 119–25.

4. Hachey DM, *et al*. Indinavir crystalluria in an HIV-positive man. *Ann Pharmacother* 2000; **34:** 403.
5. Famularo G, *et al*. Symptomatic crystalluria associated with indinavir. *Ann Pharmacother* 2000; **34:** 1414–18.
6. Daudon M, *et al*. Urinary stones in HIV-1-positive patients treated with indinavir. *Lancet* 1997; **349:** 1294–5.
7. Marroni M, *et al*. Acute interstitial nephritis secondary to the administration of indinavir. *Ann Pharmacother* 1998; **32:** 843–4.
8. Boubaker K, *et al*. Changes in renal function associated with indinavir. *AIDS* 1998; **12:** F249–F254.
9. Duong M, *et al*. Renal failure after treatment with ritonavir. *Lancet* 1996; **348:** 693–4.
10. Chugh S, *et al*. Ritonavir and renal failure. *N Engl J Med* 1997; **336:** 138.
11. Hanabusa H, *et al*. Renal atrophy associated with long-term treatment with indinavir. *N Engl J Med* 1999; **340:** 392–3.
12. Cattelan AM, *et al*. Severe hypertension and renal atrophy associated with indinavir. *Clin Infect Dis* 2000; **30:** 619–21.

Effects on the menstrual cycle. Irregular, prolonged, or heavy menstruation[1] in 4 patients receiving ritonavir subsequently returned to normal in the 3 who were transferred to a different HIV-protease inhibitor.

1. Nielsen H. Hypermenorrhoea associated with ritonavir. *Lancet* 1999; **353:** 811–12.

Effects on mental state. Acute paranoid reactions occurred on two occasions in a patient receiving saquinavir.[1]

1. Finlayson JA, Laing RBS. Acute paranoid reaction to saquinavir. *Am J Health-Syst Pharm* 1998; **55:** 2016–17.

Effects on the pancreas. Pancreatitis was associated with use of ritonavir with saquinavir in 1 patient,[1] and with ritonavir (other drugs unspecified) in 2 others,[2] and was believed to be secondary to hyperlipidaemia (see Effects on Carbohydrate and Lipid Metabolism, p. 986.2).

1. McBride M, *et al*. Lipid lowering therapy in patients with HIV infection. *Lancet* 1998; **352:** 1782–3.
2. Di Perri G, *et al*. HIV-protease inhibitors. *N Engl J Med* 1998; **339:** 773–4.

Effects on sexual function. Sexual dysfunction has been reported in patients given combination therapy with HIV-protease inhibitors and reverse transcriptase inhibitors.[1,2]

1. Martínez E, *et al*. Sexual dysfunction with protease inhibitors. *Lancet* 1999; **353:** 810–11.
2. Colebunders R, *et al*. Sexual dysfunction with protease inhibitors. *Lancet* 1999; **353:** 1802.

Effects on the skin. Rashes have been reported in about 20% of patients receiving indinavir and in 3 to 5% of patients receiving nelfinavir or saquinavir. Rash is described as a frequent adverse effect of ritonavir. In patients taking indinavir who reported rashes,[1] the rash commonly appeared within 2 weeks of starting treatment, was frequently accompanied by pruritus, and was usually self-limiting, commonly resolving within 4 weeks. Similar patterns have been reported with amprenavir/fosamprenavir (see p. 980.3).

Paronychia and pyogenic granuloma of the great toes has been reported in patients receiving indinavir.[2]

1. Gajewski LK, *et al*. Characterization of rash with indinavir in a national patient cohort. *Ann Pharmacother* 1999; **33:** 17–21.
2. Bouscarat F, *et al*. Paronychia and pyogenic granuloma of the great toes in patients treated with indinavir. *N Engl J Med* 1998; **338:** 1776–7.

Precautions

Indinavir is mainly metabolised in the liver and therefore caution and possible dosage reduction are required in hepatic impairment. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Although renal excretion is a relatively minor route of elimination, adequate hydration is recommended to reduce the risk of nephrolithiasis; monitoring is advised in the presence of renal impairment. Treatment may need to be temporarily interrupted or stopped completely in patients developing nephrolithiasis. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies indinavir as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. A retrospective survey[1] involving 89 women who received HIV-protease inhibitors during pregnancy indicated that these antivirals appeared generally safe. In the USA, guidelines[2] for the use of antiretroviral drugs in pregnant HIV-infected women suggest that when an HIV-protease inhibitor is required as part of an antiretroviral drug regimen for either maternal health or prevention of neonatal HIV transmission (see p. 959.1), ritonavir-boosted lopinavir is a drug of choice; suitable alternative HIV-protease inhibitors include nelfinavir, or ritonavir-boosted atazanavir, indinavir, or saquinavir.

1. Morris AB, *et al*. Multicenter review of protease inhibitors in 89 pregnancies. *J Acquir Immune Defic Syndr* 2000; **25:** 306–11.
2. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Indinavir is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. It may compete for the same metabolic pathways with many drugs that are metabolised similarly, often resulting in mutually increased plasma concentrations. A drug that is a significant inducer of microsomal enzymes, particularly CYP3A4, may reduce plasma concentrations of indinavir. HIV-protease inhibitors may themselves induce metabolism and may reduce plasma concentrations of other drugs.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of HIV-protease inhibitors, including indinavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These include

- the alpha$_1$-adrenoceptor antagonist alfuzosin
- antiarrhythmics (amiodarone)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (alprazolam, oral midazolam, and triazolam)
- statins (lovastatin and simvastatin)

When indinavir is boosted with ritonavir, use with bepridil, clozapine, dextropropoxyphene, fusidic acid, diazepam, estazolam, flurazepam, quinidine, pethidine, and piroxicam should also be avoided. Similarly, ritonavir-boosted indinavir should not be used with drugs having narrow therapeutic windows that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics encainide, flecainide, and propafenone. Owing to the potential for increased serum concentrations of sildenafil, indinavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, indinavir may increase serum concentrations of inhaled salmeterol and the combination is not recommended. Use of indinavir with rosuvastatin should also be avoided. Rifampicin and St John's wort decrease the concentration of indinavir; use with the antiretroviral is contra-indicated due to the possible loss of its activity and development of resistance. Use of indinavir with atazanavir is contra-indicated as both drugs have been associated with indirect hyperbilirubinaemia.

Other HIV-protease inhibitors may have similar interactions. The principal interactions that have been reported as a risk for one or more of the various HIV-protease inhibitors are listed below.

References to interactions associated with HIV-protease inhibitors.

1. Eagling VA, *et al*. Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *Br J Clin Pharmacol* 1997; **44:** 190–4.
2. von Moltke LL, *et al*. Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. *J Clin Pharmacol* 1998; **38:** 106–11.
3. Malaty LI, Kuper JJ. Drug interactions of HIV protease inhibitors. *Drug Safety* 1999; **20:** 147–69.
4. Jackson A, *et al*. Pharmacokinetics and pharmacodynamics of drug interactions involving HIV-1 protease inhibitors. *AIDS Rev* 2004; **6:** 208–17.

Amfetamines. For mention of interactions, including a fatal serotonergic reaction, with *methylenedioxymethamfetamine* (Ecstasy) in patients receiving ritonavir, see p. 2325.3.

Analgesics. Ritonavir and possibly other HIV-protease inhibitors produce complex and potentially serious interactions with some opioids (see p. 111.2). Interactions between ritonavir and *dextropropoxyphene* (p. 45.1) or *pethidine* (p. 123.2) are considered to be especially hazardous. Ritonavir might also prolong *fentanyl*-induced respiratory depression (see p. 63.2). Amprenavir, nelfinavir, ritonavir, and ritonavir-boosted HIV-protease inhibitors may reduce plasma concentrations of *methadone* (see p. 91.1). For the effect of some HIV-protease inhibitors on the pharmacokinetics of *buprenorphine*, see p. 32.3.

Use of ritonavir with *piroxicam* can result in potentially toxic concentrations of piroxicam (see p. 126.3).

Antiarrhythmics. Use of HIV-protease inhibitors with the antiarrhythmics *amiodarone, encainide, flecainide, propafenone*, or *quinidine* may result in potentially toxic plasma concentrations of these drugs with an increased risk of ventricular arrhythmias.

Antibacterials. Plasma concentrations of HIV-protease inhibitors may be reduced to subtherapeutic levels by *rifampicin*; boosting with ritonavir does not overcome the interaction and increases the risk of hepatotoxicity.[1] *Rifabutin* generally has less effect but may reduce plasma concentrations of unboosted indinavir, saquinavir, and nelfinavir; conversely, it has been suggested that use of rifabutin may increase plasma concentrations of ritonavir-boosted lopinavir (see p. 1003.1). In addition, plasma concentrations of ritonavir-boosted rifabutin are generally increased by most HIV-protease inhibitors, with a consequent risk of uveitis. In general, HIV-protease inhibitors should not be used with rifampicin (p. 353.2) and dose reduction of rifabutin is generally required when it is given with an HIV-protease inhibitor (see under Uses and Administration of Rifabutin, p. 349.1). Increased doses of indinavir have been suggested for use with rifabutin, for details see Uses and Administration, p. 986.1.

HIV-protease inhibitors may inhibit the metabolism of *clarithromycin* (p. 267.3) and possibly other macrolides.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)

Antidepressants. HIV-protease inhibitors may inhibit the metabolism of *desipramine* and other tricyclic antidepressants (p. 406.3). Interactions may also occur between HIV-protease inhibitors and SSRIs such as *fluoxetine* (p. 424.3), and have also occurred with *bupropion* (p. 410.2) and *trazodone* (p. 452.2).

Plasma concentrations of HIV-protease inhibitors may be reduced by *St John's wort* as a result of induction of cytochrome P450; concomitant use should be avoided.[1] It should be noted that the inducing effect of St. John's wort may persist for at least 2 weeks after treatment is stopped.

1. Piscitelli SC, *et al*. Indinavir concentrations and St John's wort. *Lancet* 2000; **355:** 547–8. Correction. *ibid*. 2001; **357:** 1210.

Antiepileptics. Reduced plasma concentrations of HIV-protease inhibitors may be anticipated if the enzyme inducers *carbamazepine, phenobarbital*, or *phenytoin* are given concurrently; in particular, once daily regimens of ritonavir-boosted lopinavir should be avoided with any of these drugs.[1]

Plasma concentrations of antiepileptics may also be altered when they are used with HIV-protease inhibitors. For further information, see under Carbamazepine (p. 517.2), Phenobarbital (p. 537.3), Phenytoin (p. 544.1), Lamotrigine (p. 530.2), and Valproate (p. 558.1).

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)

Antifungals. Plasma concentrations of HIV-protease inhibitors may be increased by azole antifungals. Reduced doses of indinavir have been recommended for use with *itraconazole*, and may also be considered for use with *ketoconazole*—for further information see under Uses and Administration (p. 986.1).

Conversely, plasma concentrations of ketoconazole, and possibly itraconazole may be increased by some HIV-protease inhibitors, and in particular ritonavir. US licensed product information for ritonavir advises that itraconazole or ketoconazole doses greater than 200 mg daily are not recommended. Similarly, *fluconazole* can cause significant increases in tipranavir concentrations, and it has therefore been suggested that if this combination is used, fluconazole doses should not exceed 200 mg daily. In contrast, HIV-protease inhibitors (and especially ritonavir) may substantially decrease concentrations of *voriconazole*; use with ritonavir or any ritonavir-boosted HIV-protease inhibitor should be avoided.

Antihistamines. HIV-protease inhibitors inhibit the metabolism of non-sedating antihistamines such as *astemizole* and *terfenadine* resulting in increased plasma concentrations of these drugs and an increased risk of serious ventricular arrhythmias. Such combinations should be avoided.

Antimalarials. For a discussion of possible interactions between HIV-protease inhibitors and *quinine*, see p. 668.1.

Antineoplastics. Plasma concentrations of indinavir were increased[1] during use with *interleukin-2*. Plasma concentrations of the vinca alkaloids, *vincristine* and *vinblastine*, (see p. 882.3) may also be increased when given with ritonavir, potentially leading to significant haematological or gastrointestinal adverse effects. For the effect of HIV-pro-

tease inhibitors on *paclitaxel*, see Interactions, Antivirals, p. 842.2.

1. Piscitelli SC, *et al.* Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. *Pharmacotherapy* 1998; **18:** 1212–16.

Antipsychotics. Ritonavir and possibly other HIV-protease inhibitors may increase plasma concentrations of *clozapine* (but see p. 1061.3), *pimozide* (p. 1097.2), and *sertindole* (p. 1107.3) resulting in increased toxicity. Concomitant use should be avoided. Plasma concentrations of *thioridazine* may also be increased when given with some HIV-protease inhibitors.

Antivirals. HIV-protease inhibitors can inhibit metabolism of other drugs from the same class[1] and increases in adverse effects have resulted.

Plasma concentrations of atazanavir, amprenavir/fosamprenavir, indinavir,[2] and lopinavir-ritonavir may be reduced by *nevirapine*; although increased doses of ritonavir-boosted lopinavir can be considered to manage the interaction (see under Uses and Administration of Lopinavir, p. 1002.1), licensed product information advises that use of atazanavir or unboosted fosamprenavir with nevirapine should be avoided.

Plasma concentrations of amprenavir/fosamprenavir, indinavir,[3] lopinavir, nelfinavir, ritonavir, and saquinavir may be increased by *delavirdine*; a decreased dose of indinavir is recommended when it is used with delavirdine (see Uses and Administration, p. 986.1) and the UK licensed information for saquinavir recommends that liver function should be monitored if saquinavir is given with delavirdine. Fosamprenavir and nelfinavir may in contrast decrease plasma concentrations of delavirdine (for further information see under Interactions of Delavirdine, p. 972.2).

Plasma concentrations of amprenavir/fosamprenavir, atazanavir, darunavir, indinavir, *lopinavir*, and saquinavir are decreased when given with *efavirenz*. Dose adjustments can be considered when efavirenz is used with ritonavir-boosted lopinavir, or in some cases, with ritonavir-boosted atazanavir; for further information, see Uses and Administration of Lopinavir (p. 1002.1) and Atazanavir (p. 968.1), respectively. The use of efavirenz with ritonavir is associated with an increased frequency of adverse effects, presumably due to competitive inhibition of metabolism, and liver enzymes should be monitored in patients receiving this combination. Plasma concentrations of nelfinavir are increased when given with efavirenz, but the combination is usually well tolerated at standard doses.

Plasma concentrations of HIV-protease inhibitors may also be altered by *etravirine*; use with certain HIV-protease inhibitors should be avoided entirely (see Interactions of Etravirine, p. 978.3).

Although there is no direct interaction between HIV-protease inhibitors and *didanosine*, the buffer included in the didanosine formulation can impair their absorption; doses should be separated by at least 1 to 2 hours from didanosine doses, which should be given on an empty stomach.

For a report of reduced area under the plasma concentration-time curve for *zidovudine* in patients receiving ritonavir, see p. 1026.3.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)
2. Murphy RL, *et al.* Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1. *J Infect Dis* 1999; **179:** 1116–23.
3. Ferry JJ, *et al.* Pharmacokinetic drug-drug interaction study of delavirdine and indinavir in healthy subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18:** 252–9.

Benzodiazepines. For the effect of HIV-protease inhibitors on benzodiazepines, see Diazepam, p. 1069.2.

Cardiac glycosides. For details of a possible interaction between ritonavir and *digoxin*, see p. 1357.1.

Corticosteroids. Corticosteroids, in particular *dexamethasone*, may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations. For the effect of ritonavir on plasma concentrations of *fluticasone*, see p. 1620.1

Ergot alkaloids. For reports of ergotism in patients receiving HIV-protease inhibitors and ergotamine, see Ergotamine, p. 675.3.

Gastrointestinal drugs. The antidiarrhoeal *loperamide* markedly reduced exposure to saquinavir in 12 healthy subjects given a single dose of both drugs.[1] Exposure was reduced by about 54%, a reduction of the same order of magnitude as seen with enzyme inducers such as rifampicin, although the mechanism in this case was thought likely to be impaired absorption of the antiviral. Prolonged use of loperamide might lead to substantial reductions in saquinavir plasma concentrations, and reduced clinical efficacy. Plasma concentrations of loperamide were also increased, and those of its metabolite desmethylloperamide correspondingly reduced, but this was thought unlikely to be of clinical significance.

Atazanavir and indinavir depend on acid pH in the stomach for adequate absorption, and acid-suppressive therapies such as *histamine H_2-antagonists* and *proton pump inhibitors* may significantly reduce their absorption; if acid-suppressive therapy is necessary, it has been suggested that these HIV-protease inhibitors be boosted with low-dose ritonavir to ensure adequate antiretroviral activity.[2] In the case of atazanavir, a dose increase of the antiretroviral may also be necessary if use with an acid-suppressive therapy cannot be avoided; for further information, see Uses and Administration of Atazanavir (p. 968.1). A review[3] suggested a similar precaution (or giving the two drugs at suitably separated intervals) for fosamprenavir; there was conflicting evidence for a decrease in plasma concentrations of lopinavir and tipranavir with increased gastric pH and any clinical significance was uncertain. It considered that nelfinavir should not be given with a proton pump inhibitor.[3] A pharmacokinetic study in 12 patients with HIV reported an increased exposure to saquinavir when omeprazole was given with, or 2 hours before, a regular dose of ritonavir-boosted saquinavir. The mechanism for this interaction is unclear; inhibition of cytochrome P450 isoenzymes by omeprazole could play a role.[4] Licensed product information suggests caution when using omeprazole and ritonavir-boosted saquinavir together, and recommends monitoring for saquinavir toxicity.

For the effect of HIV-protease inhibitors on *cisapride*, see p. 1835.3.

1. Mikus G, *et al.* Reduction of saquinavir exposure by coadministration of loperamide: a two-way pharmacokinetic interaction. *Clin Pharmacokinet* 2004; **43:** 1015–24.
2. Fulco PP, *et al.* Acid suppressive therapy and the effects on protease inhibitors. *Ann Pharmacother* 2006; **40:** 1974–83.
3. Falcon RW, Kakuda TN. Drug interactions between HIV protease inhibitors and acid-reducing agents. *Clin Pharmacokinet* 2008; **47:** 75–89.
4. Singh K, *et al.* Pharmacokinetics and safety of saquinavir/ritonavir and omeprazole in HIV-infected subjects. *Clin Pharmacol Ther* 2008; **83:** 867–72.

Grapefruit. Exposure to saquinavir was increased by 50% when taken with grapefruit juice;[1] however, licensed product information does not recommend any adjustment of dosage of saquinavir.

1. Kupferschmidt HHT, *et al.* Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in men. *Br J Clin Pharmacol* 1998; **45:** 355–9.

Hormonal contraceptives. For the effect of HIV-protease inhibitors on the efficacy of hormonal contraceptives, see p. 2243.3.

Immunosuppressants. Mutual increases in the area under the plasma concentration-time curves for saquinavir and *ciclosporin* were reported in a kidney transplant recipient.[1] The resultant adverse effects subsided when doses of both drugs were reduced by half. Similar interactions have occurred with other HIV-protease inhibitors.

HIV-protease inhibitors may inhibit the metabolism of *tacrolimus* (see Antivirals, p. 1978.1).

1. Brinkman K, *et al.* Pharmacokinetic interaction between saquinavir and cyclosporine. *Ann Intern Med* 1998; **129:** 914–15.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals including indinavir, see Stavudine, p. 1016.2.

Statins. HIV-protease inhibitors may inhibit the metabolism of statins metabolised by CYP3A4 isoenzymes resulting in an increased risk of myopathy. Although those statins less dependent on CYP3A4 for metabolism may be used in certain circumstances to manage HIV-protease inhibitor-induced lipid disorders, in general use with lovastatin or simvastatin should be avoided, and HIV-protease inhibitors should be given with caution in patients receiving atorvastatin or rosuvastatin.

Theophylline. For a potential effect of ritonavir on theophylline, see p. 1235.2.

Urological drugs. Serum concentrations of the phosphodiesterase type-5 inhibitors *sildenafil, tadalafil,* and *vardenafil* may be increased when some HIV-protease inhibitors, particularly ritonavir, are given concurrently.

For the effect of HIV-protease inhibitors on sildenafil, including a report of fatal myocardial infarction after sildenafil in a patient receiving ritonavir and saquinavir, see p. 2366.3.

Where use of sildenafil, tadalafil, or vardenafil with a potent CYP3A4 inhibitor (such as indinavir or ritonavir) cannot be avoided, reduced doses have been suggested; use of HIV-protease inhibitors (particularly ritonavir) is contra-indicated in those using sildenafil for the treatment of pulmonary hypertension. For further information, see under Uses and Administration of Sildenafil (p. 2364.2), Tadalafil (p. 2368.2), and Vardenafil (p. 2372.1).

Vasopressin receptor antagonists. HIV-protease inhibitors may inhibit the metabolism of conivaptan (see p. 2486.2) and tolvaptan (see p. 2633.1).

Warfarin. For the effect of HIV-protease inhibitors on the response to warfarin and other anticoagulants, see p. 1533.1.

Antiviral Action

Indinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 proteases with a tenfold greater selectivity for HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Indinavir is rapidly absorbed after oral doses and peak plasma concentrations occur in 0.8 hours (range 0.5 to 1.1 hours). Bioavailability is about 65% after a single 800-mg dose. Absorption is reduced if given with a meal high in calories, fat, and protein but is less affected by a light meal (for the effect of pH see Gastrointestinal Drugs under Interactions, above). At doses up to 1 g, increases in plasma concentration are proportionately greater than increases in dose. Plasma protein binding is about 60%. Indinavir is reported to cross the blood-brain barrier. It undergoes oxidative metabolism by cytochrome P450 isoenzyme CYP3A4 and glucuronidation. At least seven metabolites (1 glucuronide and 6 oxidative metabolites) have been identified. The elimination half-life is 1.8 hours. Less than 20% of the absorbed dose is excreted in the urine, about half of this as unchanged drug. The remainder is excreted in the faeces.

References.
1. Ståhle L, *et al.* Indinavir in cerebrospinal fluid of HIV-1-infected patients. *Lancet* 1997; **350:** 1823.
2. Bernard L, *et al.* Indinavir concentrations in hair from patients receiving highly active antiretroviral therapy. *Lancet* 1998; **352:** 1757–8.
3. Wintergerst U, *et al.* Use of saliva specimens for monitoring indinavir therapy in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2000; **44:** 2572–4.
4. Haas DW, *et al.* Steady-state pharmacokinetics of indinavir in cerebrospinal fluid and plasma among adults with human immunodeficiency virus type 1 infection. *Clin Pharmacol Ther* 2000; **68:** 367–74.
5. Burger DM, *et al.* Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2001; **45:** 701–5.
6. Kappelhoff BS, *et al.* Population pharmacokinetics of indinavir alone and in combination with ritonavir in HIV-1-infected patients. *Br J Clin Pharmacol* 2005; **60:** 276–86.
7. Unadkat JD, *et al.* Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2007; **51:** 783–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avural; Crixivan; Elvenavir; Forli; Indilea†; Inhibisam†; ***Austral.***: Crixivan; ***Austria***: Crixivan; ***Belg.***: Crixivan; ***Braz.***: Crixivan; Indinax; ***Canad.***: Crixivan; ***Chile***: Crixivan; ***China***: Ai Hao (艾好); Crixivan (佳息患); Ou Zhi (欧直); YouXin (又欣); ***Cz.***: Crixivan; ***Denm.***: Crixivan; ***Fin.***: Crixivan; ***Fr.***: Crixivan; ***Ger.***: Crixivan; ***Gr.***: Crixivan; ***Hong Kong***: Crixivan; ***Hung.***: Crixivan; ***India***: Inbec; Ind; Indease; Indivan; ***Irl.***: Crixivan; ***Israel***: Crixivan; ***Ital.***: Crixivan; ***Malaysia***: Crixivan; ***Mex.***: Aviran†; Crixivan; Indilan; ***Neth.***: Crixivan; ***Norw.***: Crixivan; ***NZ***: Crixivan; ***Philipp.***: Crixivan; ***Pol.***: Crixivan; ***Port.***: Crixivan; ***Rus.***: Crixivan (Криксиван); ***S. Afr.***: Crixivan; ***Singapore***: Crixivan; ***Spain***: Crixivan; ***Swed.***: Crixivan; ***Switz.***: Crixivan; ***Thai.***: Crixivan†; Inavir; ***Turk.***: Crixivan; ***UK***: Crixivan; ***USA***: Crixivan; ***Venez.***: Crixivan; Indivan.

Inosine Pranobex *(BAN)*

Inosin Pranobeks; Inosina dimepranol acedobén; Inosina pranobex; Inosine Acédobène Dimépranol; Inosine Dimepranol Acedoben (pINNM); Inosinum Dimepranolum Acedobenum; Inosinum pranobexum; Inosiplex; Isoprinosine; Methisoprinol; Metisoprinol; NP-113; NPT-10381; Pranobeks Inozyny; Инозин Димепранол Ацедобен.

Inosine 2-hydroxypropyldimethylammonium 4-acetamidobenzoate (1:3).

$C_{10}H_{12}N_4O_5$:$C_{14}H_{22}N_2O_4$ (1:3)=1115.2

CAS — 36703-88-5.

ATC — J05AX05.

ATC Vet — QJ05AX05.

UNII — W1SO0V223F.

NOTE. Dimepranol Acedoben is *pINN* and *USAN*.

Uses and Administration

Inosine pranobex is a complex of inosine (p. 2533.1) with dimepranol acedoben ((±)-1-(dimethylamino)-2-propanol *p*-acetamidobenzoate). It has been used in the treatment of various viral infections, including herpes simplex (p. 955.2), genital warts (below), and subacute sclerosing panencephalitis (below), although other treatments or measures are preferred. The oral dose in mucocutaneous herpes simplex is 1 g four times daily for 7 to 14 days. An oral dose of 1 g three times daily is given for 14 to 28 days as an adjunct to standard topical treatment for genital warts. In subacute sclerosing panencephalitis, the oral dose is 50 to 100 mg/kg daily in divided doses given every 4 hours.

Reviews.

1. Campoli-Richards DM, *et al.* Inosine pranobex: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1986; **32:** 383–424.

Alopecia. Oral inosine pranobex (50 mg/kg daily in 5 divided doses for 12 weeks) has been investigated[1] with some apparent benefit in the treatment of recalcitrant alopecia areata (p. 1682.3).

1. Georgala S, *et al.* Inosiplex for treatment of alopecia areata: a randomized placebo-controlled study. *Acta Derm Venereol* 2006; **86:** 422–4.

Subacute sclerosing panencephalitis. Inosine pranobex has been tried[1,2] in the treatment of subacute sclerosing panencephalitis, a complication of measles (p. 961.2), but the results of clinical studies have been equivocal. Some success has been reported when inosine pranobex has been given with interferons and other antivirals. However, a randomised study involving 121 patients, of whom 67 completed analysis, was unable to show any difference between an oral regimen of inosine pranobex 100 mg/kg daily in 3 divided doses (up to a maximum of 3 g daily) for 6 months, and the same dose combined with intraventricular interferon alfa, although the outcomes, which were considered satisfactory in about 35% of cases, were better than the 10% remission rate in historical controls, implying some benefit with either treatment.[3]

1. Haddad FS, Risk WS. Isoprinosine treatment in 18 patients with subacute sclerosing panencephalitis: a controlled study. *Ann Neurol* 1980; **7:** 185–8.
2. Jones CE, *et al.* Inosiplex therapy in subacute sclerosing panencephalitis: a multicentre, non-randomised study in 98 patients. *Lancet* 1982; **i:** 1034–7.
3. Gascon GG. International Consortium on Subacute Sclerosing Panencephalitis. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-α in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol* 2003; **18:** 819–27. Correction. *ibid.* 2004; **19:** 342.

Warts. Although of no apparent benefit in the treatment of palmar/plantar warts,[1] oral inosine pranobex has been shown to be of value in the treatment of refractory genital warts (p. 1689.3) in the cervix,[2] as well as producing some apparent epithelial morphological improvement in women with subclinical human papillomavirus infection of the vulva.[3]

1. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; **127:** 262–5.
2. Georgala S, *et al.* Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial. *BJOG* 2006; **113:** 1088–91.
3. Tay SK. Efficacy of inosine pranobex oral therapy in subclinical human papillomavirus infection of the vulva: a randomized double-blinded placebo controlled study. *Int J STD AIDS* 1996; **7:** 276–80.

Adverse Effects and Precautions

Some patients have had transient nausea, vomiting, headaches, arthralgia, fatigue, vertigo, raised liver enzymes, pruritus, and rashes. Metabolism of the inosine content of inosine pranobex leads to increased serum and urine concentrations of uric acid; caution is therefore recommended in treating patients with renal impairment, gout, or hyperuricaemia.

Antiviral Action

Inosine pranobex appears to owe its activity in viral infections more to its capacity to modify or stimulate cell-mediated immune processes than to a direct action on the virus.

Pharmacokinetics

Inosine pranobex is reported to be rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 hour after an oral dose. It is also rapidly metabolised with a plasma half-life of 50 minutes, the inosine portion of the complex yielding uric acid; the other components undergo oxidation and glucuronidation. The metabolites are excreted in the urine.

References.

1. Nielsen P, Beckett AH. The metabolism and excretion in man of NN-dimethylamino-isopropanol and p-acetamido-benzoic acid after administration of isoprinosine. *J Pharm Pharmacol* 1981; **33:** 549–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Isoprinosine; ***Canad.***: Imunovir; ***Chile***: Isoprinosine; ***Cz.***: Isoprinosine; ***Fr.***: Isoprinosine; ***Ger.***: delimmun; Isoprinosine†; ***Gr.***: Cicloxab; Iostop†; Isoprinosine; ***Hong Kong***: Qualiprinol; ***Hung.***: Isoprinosine; ***Indon.***: Isoprinosine; Isprinol; ***Irl.***: Imunovir†; Isoprinosine; ***Ital.***: Viruxan; ***Mex.***: Isoprinosine; Pranosine; ***NZ***: Imunovir; ***Philipp.***: Immunosin; Isoprinosine; ***Pol.***: Groprinosin; Neosine; ***Rus.***: Groprinosin (Гроприносин); Isoprinosine (Изопринозин); ***Singapore***: Imin; ***UK***: Imunovir; ***Ukr.***: Groprinosin (Гроприносин); Isoprinosine (Изопринозин).

Multi-ingredient Preparations. ***Philipp.***: Isoflu (Combipack).

Interferon Alfa *(BAN, rINN)*

IFN-α; Interferón-α; Interferon-α; Interferón alfa; Interféron Alfa; Interferon alpha; Interferoni Alfa; Interferonialfa; Interferonum Alfa; Ro-22-8181 (interferon alfa-2a); Sch-30500 (interferon alfa-2b); Интерферон Альфа.

CAS — 74899-72-2 (interferon alfa); 76543-88-9 (interferon alfa-2a); 99210-65-8 (interferon alfa-2b); 118390-30-0 (interferon alfacon-1); 198153-51-4 (peginterferon alfa-2a); 215647-85-1 (peginterferon alfa-2b).

ATC — L03AB01 (natural); L03AB04 (2a); L03AB05 (2b); L03AB06 (n1); L03AB09 (alfacon-1); L03AB10 (peginterferon alfa-2b); L03AB11 (peginterferon alfa-2a).

ATC Vet — QL03AB01 (natural); QL03AB04 (2a); QL03AB05 (2b); QL03AB06 (n1); QL03AB09 (alfacon-1); QL03AB10 (peginterferon alfa-2b); QL03AB11 (peginterferon alfa-2a).

UNII — 47RRR83SK7 (interferon alfa-2a); 43K1W2T1M6 (interferon alfa-2b).

NOTE. Interferon alfa was previously known as leucocyte interferon or lymphoblastoid interferon.

Interferon alfa-2a, alfa-2b, alfa-n1, and alfa-n3 are *USAN*.

Interferon alfacon-1 (*BAN, USAN, rINN*) is a recombinant non-naturally occurring alfa interferon. Peginterferon alfa-2a (*BAN, USAN, rINN*) and peginterferon alfa-2b (*BAN, rINN*) are interferons pegylated by conjugation with macrogols.

Pharmacopoeias. *Chin.* includes monographs for recombinant human alfa-2a and alfa-2b. *Eur.* (see p. vii) includes Interferon Alfa-2 Concentrated Solution.

Ph. Eur. 8: (Interferon Alfa-2 Concentrated Solution; Interferoni Alfa-2 Solutio Concentrata). It is produced by a method based on recombinant DNA technology using bacteria as host cells. A solution of a protein that is produced according to the information coded by the alfa-2 sub-species of interferon alfa gene. Interferon alfa-2a has a lysine residue at position 23 and interferon alfa-2b has an arginine residue. The concentrated solution contains a minimum of $2X10^8$ units/mL and has a minimum potency of $1.4X10^8$ units/mg of protein. A clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of -20 degrees or below. Protect from light.

Nomenclature. Interferon alfa may be derived from leucocytes or lymphoblasts, or produced by recombinant DNA technology. Sub-species of the human alfa gene may produce interferon alfa with protein variants or a mixture of proteins. The protein variants may be designated by a number (as in interferon alfa-2) which may be further qualified by a letter to indicate the amino-acid sequences at positions 23 and 34:

- interferon alfa-2a has lysine at 23 and histidine at 34
- interferon alfa-2b has arginine at 23 and histidine at 34
- interferon alfa-2c has arginine at both positions

In the case of a mixture of proteins an alphanumeric designation is given (as in interferon alfa-n1). Interferon alfacon-1 varies from interferon alfa-2 in 20 of 166 amino acids.

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology; (lns) indicates production from cultured lymphoblasts from the Namalwa cell line that have been stimulated by a Sendai virus; (bls) indicates production from leucocytes from human blood that have been stimulated by a Sendai virus.

References.

1. Finter NB. The naming of cats—and alpha-interferons. *Lancet* 1996; **348:** 348–9.

Uses and Administration

The interferons are cytokines that have a range of activities. In addition to their action against viruses they are active against malignant neoplasms and have an immunomodulating effect. Several alfa interferons are available: interferon alfa-2a (rbe), interferon alfa-2b (rbe), alfa-n3 (bls), alfacon-1 (rbe), and the pegylated interferons peginterferon alfa-2a (rbe) and peginterferon alfa-2b (rbe).

Alfa interferons are used in chronic hepatitis B and chronic hepatitis C; in several malignant neoplasms including AIDS-related Kaposi's sarcoma, hairy-cell leukaemia, chronic myeloid leukaemia, follicular lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, melanoma, multiple myeloma, and renal cell carcinoma, and in condylomata acuminata.

ADMINISTRATION AND DOSAGE. Dosage regimens for alfa interferons are as follows:

- **Chronic active hepatitis B.** *Interferon alfa-2a* is given in a dose of 2.5 to 5 million units/m^2 three times weekly by subcutaneous injection for 4 to 6 months. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously for 48 weeks. *Interferon alfa-2b* is given in a dose of 5 to 10 million units three times weekly for 4 to 6 months, or 5 million units daily for 16 weeks, by subcutaneous or intramuscular injection.
- **Chronic hepatitis C.** *Interferon alfa-2a* is given in a dose of 3 to 4.5 million units three times weekly by subcutaneous injection for 6 months when it is used with ribavirin. In patients unable to tolerate ribavirin, interferon alfa-2a monotherapy is given either in an initial dose of 3 to 6 million units three times weekly for 6 months followed by 3 million units three times weekly for an additional 6 months, or in a dose of 3 million units three times weekly for 12 months, by subcutaneous injection. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously, with ribavirin or as monotherapy, for 24 to 48 weeks (depending on genotype). *Interferon alfa-2b* is given in a dose of 3 million units three times weekly for 6 to 12 months (depending on genotype) with ribavirin or, when given as monotherapy, for 6 to 18 months, or for up to 24 months (depending on genotype), by subcutaneous or intramuscular injection. *Peginterferon alfa-2b* is given subcutaneously in a dose of 1.5 micrograms/kg once weekly for 24 to 48 weeks with ribavirin, or in a dose of 0.5 or 1 microgram/kg once weekly for 24 to 48 weeks when given as monotherapy. *Interferon alfacon-1* is given in a dose of 9 micrograms three times weekly by subcutaneous injection for 24 weeks followed by 15 micrograms three times weekly for up to 48 weeks if necessary.

  For information on the dose of ribavirin used in the treatment of chronic hepatitis C see under Ribavirin, p. 1010.2.
- **AIDS-related Kaposi's sarcoma.** *Interferon alfa-2a* is usually given in an escalating dose of 3 million units daily for 3 days, 9 million units daily for 3 days, 18 million units daily for 3 days, and 36 million units daily, if tolerated, on days 10 to 84, by subcutaneous injection; thereafter the maximum tolerated dose (up to 36 million units) may be given three times weekly. *Interferon alfa-2b* is given in a dose of 30 million units/m^2 three times weekly, by subcutaneous or intramuscular injection.
- **Hairy-cell leukaemia.** *Interferon alfa-2a* is given in an initial subcutaneous dose of 3 million units daily for 16 to 24 weeks, then the same dose three times weekly, by subcutaneous injection. Treatment has continued for up to 24 months. *Interferon alfa-2b* is given in a dose of 2 million units/m^2 three times weekly by subcutaneous or intramuscular injection for up to 6 months or more.
- **Chronic myeloid leukaemia.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, 6 million units daily for 3 days, and 9 million units daily thereafter. Patients showing a response after 12 weeks should continue treatment until a complete haematological response is achieved or for a maximum of 18 months; those who achieve a complete haematological response should continue on 9 million units daily (or a minimum of 9 million units three times weekly) in order to achieve a cytogenetic response. *Interferon alfa-2b* is given in a dose of 4 to 5 million units/m^2 daily by subcutaneous injection, continuing at the maximum tolerated dose to maintain remission (usually 4 to 5 million units/m^2 daily).
- **Follicular lymphoma.** *Interferon alfa-2a* is given as an adjunct to chemotherapy in a dose of 6 million units/m^2 daily by subcutaneous injection on days 22 to 26 of each 28-day chemotherapy cycle. *Interferon alfa-2b* is given as an adjunct to chemotherapy in a dose of 5 million units three times weekly by subcutaneous injection for 18 months.
- **Cutaneous T-cell lymphoma.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, then 9 million units daily for 3 days, and then 18 million units daily to complete 12 weeks of treatment. The maximum tolerated dose (up to 18 million units) is then given three times weekly for a minimum of 12 months in responding patients.
- **Carcinoid tumours.** *Interferon alfa-2b* is given in a dose of 3 to 9 million units (usually 5 million units) three times

weekly by subcutaneous injection. In advanced disease, 5 million units may be given daily.

- **Melanoma.** *Interferon alfa-2a* is given in a dose of 3 million units three times weekly by subcutaneous injection for 18 months. Treatment should start no later than 6 weeks after surgery. *Interferon alfa-2b* is given in an initial dose of 20 million units/m^2 daily on 5 days each week for 4 weeks by intravenous infusion over 20 minutes, and then for maintenance 10 million units/m^2 three times weekly by subcutaneous injection for 48 weeks. *Peginterferon alfa-2b* is given as adjuvant treatment in an initial dose of 6 micrograms/kg once weekly by subcutaneous injection for 8 doses, followed by a maintenance dose of 3 micrograms/kg once weekly by subcutaneous injection for up to 5 years.
- **Multiple myeloma.** *Interferon alfa-2b* is given as maintenance treatment following chemotherapy induction at a dose of 3 million units/m^2 three times weekly by subcutaneous injection.
- **Renal cell carcinoma.** *Interferon alfa-2a* is given as an adjunct to cytotoxic chemotherapy (vinblastine) in an escalating dose of 3 million units three times weekly for one week, then 9 million units three times weekly for one week, then 18 million units three times weekly thereafter for 3 to 12 months, by subcutaneous injection; if tolerance is poor, the dose may subsequently be reduced to 9 million units three times weekly. As an adjunct to bevacizumab, *interferon alfa-2a* may be given at a dose of 9 million units subcutaneously three times weekly (following a dose escalation period, if required, of not more than 2 weeks). Treatment may be continued until disease progression, or up to a maximum of 12 months. If tolerance is poor, the dose may be reduced to a minimum of 3 million units three times weekly.
- **Condylomata acuminata.** *Interferon alfa-2b* is given in a dose of 1 million units injected into each lesion three times weekly for 3 weeks, and repeated after 12 to 16 weeks if necessary. No more than 5 lesions should be treated in each treatment course. *Interferon alfa-n3* is given in a dose of 0.25 million units per lesion twice weekly for up to 8 weeks, to a maximum of 2.5 million units in each session.

See below for further details of these as well as some other uses of alfa interferons.

General reviews of interferons.

1. Volz MA, Kirkpatrick CH. Interferons 1992: how much of the promise has been realised? *Drugs* 1992; **43:** 285–94.
2. Dorr RT. Interferon-α malignant and viral diseases: a review. *Drugs* 1993; **45:** 177–211.
3. Haria M, Benfield P. Interferon-α-2a: a review of its pharmacological properties and therapeutic use in the management of viral hepatitis. *Drugs* 1995; **50:** 873–96.
4. Ruszczak Z, Schwartz RA. Interferons in dermatology: biology, pharmacology, and clinical applications. *Adv Dermatol* 1997; **13:** 235–88.
5. Edwards L. The interferons. *Dermatol Clin* 2001; **19:** 139–46, ix.
6. Moschos S, *et al*. Interferons in the treatment of solid tumors. *Cancer Treat Res* 2005; **126:** 207–41.
7. Pestka S. The interferons: 50 years after their discovery, there is much more to learn. *J Biol Chem* 2007; **282:** 20047–51.
8. Friedman RM. Clinical uses of interferons. *Br J Clin Pharmacol* 2008; **65:** 158–62.
9. Antonelli G. Biological basis for a proper clinical application of alpha interferons. *New Microbiol* 2008; **31:** 305–18.
10. Fensterl V, Sen GC. Interferons and viral infections. *Biofactors* 2009; **35:** 14–20.
11. Keating GM. Peginterferon-α-2a (40 kD): a review of its use in chronic hepatitis B. *Drugs* 2009; **69:** 2633–60.
12. Foster GR. Pegylated interferons for the treatment of chronic hepatitis C: pharmacological and clinical differences between peginterferon-α-2a and peginterferon-α-2b. *Drugs* 2010; **70:** 147–65.

Administration in children. Interferon alfa products are licensed in some countries for use in children for the treatment of chronic hepatitis B and chronic hepatitis C; they should always be used under the close supervision of a specialist. For information on the use of interferon alfa for the treatment of haemangiomas in children, see below.

Chronic hepatitis B

In the USA interferon alfa-2b (*Intron A; Schering-Plough*) is licensed for the treatment of chronic hepatitis B. The indication is based on a study in children from 1 to 17 years of age. The dose (based on body surface area) given by subcutaneous injection was 3 million units/m^2 three times a week for the first week of therapy followed by a dose increase to 6 million units/m^2 three times a week (to a maximum of 10 million units three times a week).

Treatment for chronic hepatitis B is usually given for 4 to 6 months.

Chronic hepatitis C

Interferon and peginterferon alfa-2b may be used in children from 3 to 17 years of age, with ribavirin, for the treatment of chronic hepatitis C. Duration of treatment may be influenced by the genotype of the hepatitis C virus. In hepatitis C mono-infection, patients with viral genotype 1 should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks. The recommended doses are based on body-surface; for interferon alfa-2b 3 million units/m^2 given subcutaneously 3 times a week while the dose for peginterferon alfa-2b is 60 micrograms/m^2 given subcutaneously once a week.

For information on the dose of ribavirin used in the treatment of chronic hepatitis C in children see under Ribavirin, p. 1010.3.

Age-related macular degeneration. In age-related macular degeneration (senile macular degeneration), a common cause of visual impairment in the elderly, there is a gradual and progressive deterioration of central vision usually affecting both eyes (p. 880.2). Despite encouraging preliminary results[1-4] with interferon alfa, controlled data showed no benefit after treatment for a year.[5]

1. Fine SL, *et al*. Age-related macular degeneration. *N Engl J Med* 2000 **342:** 483–92.
2. Arnold JJ, Sarks SH. Extracts from "clinical evidence": age related macular degeneration. *BMJ* 2000**321:** 741–4.
3. Comer GM, *et al*. Current and future treatment options for nonexudative and exudative age-related macular degeneration. *Drugs Aging* 2004**21:** 967–92.
4. Sun JK, Miller JW. Medical treatment of choroidal neovascularization secondary to age-related macular degeneration. *Int Ophthalmol Clin* 2005**45:** 115–32.
5. Pharmacological Therapy for Macular Degeneration Study Group. Interferon alfa-2a in ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective randomized placebo-controlled clinical trial. *Arch Ophthalmol* 1997; **115:** 865–72.

Angiomatous disease. Encouraging responses were reported in 4 of 5 children treated with interferon alfa-2a for various angiomatous diseases.[1] Regression of haemangioma size by more than 50% was achieved in 11 of 18 infants and children given interferon alfa-2a for 1 to 5 months,[2] and in 11 of 19 children treated for at least 4 months.[3] Interferon alfa-2b has also been found to cause regression of haemangioma in 27 of 38 children treated for at least 6 months.[4] In addition, there have been reports of the successful use of interferon alfa-2b to treat infantile giant cell angioblastoma[5] and pelvic metastases of adult haemangioendothelioma of the liver.[6]

The use of interferons as anti-angiogenic agents has been reviewed.[7]

1. White CW, *et al*. Treatment of childhood angiomatous diseases with recombinant interferon alfa-2a. *J Pediatr* 1991; **118:** 59–66.
2. Deb G, *et al*. Treatment of hemangiomas of infants and babies with interferon alfa-2a: preliminary results. *Int J Pediatr Hematol/Oncol* 1996; **3:** 109–13.
3. Greinwald JH, *et al*. An update on the treatment of hemangiomas in children with interferon alfa-2a. *Arch Otolaryngol Head Neck Surg* 1999; **125:** 21–7.
4. Garmendía G, *et al*. Regression of infancy hemangiomas with recombinant IFN-α 2b. *J Interferon Cytokine Res* 2001; **21:** 31–8.
5. Marler JJ, *et al*. Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of 2 cases. *Pediatrics* 2002; **109:** e37. Also available at: http://pediatrics.aappublications.org/cgi/content/full/109/2/e37 (accessed 12/06/08)
6. Kayler LK, *et al*. Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. *Transplantation* 2002; **74:** 128–30.
7. Lindner DJ. Interferons as antiangiogenic agents. *Curr Oncol Rep* 2002; **4:** 510–14.

Behçet's syndrome. Behçet's syndrome (p. 1601.1) is a systemic inflammatory disorder characterised by recurrent attacks of oral aphthous ulcers, genital ulcers, skin lesions, uveitis or other manifestations affecting the blood vessels, gastrointestinal tract, and respiratory and central nervous systems. Treatment is essentially symptomatic and empirical. A review of the literature[1] identified 338 patients who had been given interferon alfa (264 patients had received interferon alfa-2a and 74 interferon alfa-2b). Mucocutaneous symptoms improved in 86% of the patients; articular manifestations were present in 90 patients and 95% of them showed a partial or complete response to interferon alfa treatment. Ocular manifestations were present in 182 patients and 94% of them showed a partial or complete response to treatment.[1] Maximum response has been seen about 2 to 4 months after starting treatment.[2] Higher doses have been found to be more effective than low-dose regimens,[1,2] but the optimum duration of therapy remains to be determined. The best results were seen in patients with severe or refractory ocular disease.[2] Another review[3] on the management of Behçet's syndrome reported that treatment with interferon-alfa during an inflammatory attack improved the duration of and pain associated with oral aphthous ulcers; beneficial effects were also reported in patients with ocular manifestations. Randomised, controlled studies had shown that interferon alfa prevented recurrent attacks and it was considered to be effective in suppressing more severe systemic features, as well as mucocutaneous ones. Open studies with interferon alfa indicated that it might be of benefit in patients with disease resistant to conventional immunosuppressive treatments.

1. Kötter I, *et al*. The use of interferon alpha in Behçet disease: review of the literature. *Semin Arthritis Rheum* 2004; **33:** 320–35.
2. Yang DS, *et al*. Interferon-alpha in the management of patients with Behçet's disease. *Br J Hosp Med* 2008; **69:** 575–9.
3. Gul A. Standard and novel therapeutic approaches to Behçet's disease. *Drugs* 2007; **67:** 2013–22.

Blood disorders. Interferon alfa may be used in the management of the myeloproliferative disorders such as *primary (essential) thrombocythaemia*[1-4] (p. 695.2), *polycythaemia vera*,[1-5] (p. 695.2) and *agnogenic myeloid metaplasia*.[2] Benefit has also been reported with interferon alfa in patients with HIV-associated thrombocytopenia,[6] although interferons have been reported to induce immune thrombocytopenia, and there has been a report of bleeding in a patient with this condition (see Effects on the Blood under Adverse Effects, p. 992.3).

In addition to case reports of interferon alfa producing improvements in patients with idiopathic *hypereosinophilic syndrome*[7-9] who had not responded to corticosteroids or hydroxycarbamide, studies have also shown beneficial responses to interferon alfa used alone[10] or with corticosteroids or hydroxycarbamide.[11,12]

See also under Malignant Neoplasms, p. 991.3.

Paradoxically, interferon alfa has also been used with some success in patients with *thrombocytopenia* associated with hepatitis C.[13-15]

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6. Marroni M, *et al*. Interferon-α is effective in the treatment of HIV-1-related, severe, zidovudine-resistant thrombocytopenia. *Ann Intern Med* 1994; **121:** 423–9.
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12. Baratta L, *et al*. Favorable response to high-dose interferon-alpha in idiopathic hypereosinophilic syndrome with restrictive cardiomyopathy: case report and literature review. *Angiology* 2002; **53:** 465–70.
13. Uygun A, *et al*. Interferon treatment for thrombocytopenia associated with chronic HCV infection. *Int J Clin Pract* 2000; **54:** 683–4.
14. Rajan S, Liebman HA. Treatment of hepatitis C related thrombocytopenia with interferon alpha. *Am J Hematol* 2001; **68:** 202–9.
15. Benci A, *et al*. Thrombocytopenia in patients with HCV-positive chronic hepatitis: efficacy of leucocyte interferon-α treatment. *Int J Clin Pract* 2003; **57:** 17–19.

Churg-Strauss syndrome. For reports that interferon alfa may be beneficial in Churg-Strauss syndrome, see p. 1603.1.

Hepatitis. Interferon alfa (including peginterferon alfa) is one of the main drugs used in the treatment of viral hepatitis B and C and chronic hepatitis B and C co-infection with HIV (p. 952.1).

Interferon alfa was the first drug approved for the management of chronic **hepatitis B**. A meta-analysis[1] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HbeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels. Studies have suggested that subcutaneous peginterferon alfa is as effective or slightly more effective than interferon alfa given subcutaneously.[2] Results from various studies[3] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[4] and HBeAg-negative patients with chronic hepatitis B,[5] when peginterferon alfa was given subcutaneously, once weekly for 48 weeks. However, the addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[5,6] Interferon alfa can produce benefit in some patients co-infected with chronic **hepatitis B and D**.[7] However, these co-infected patients are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[7] with high-dose interferon alfa-2a (9 million units) given intramuscularly 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[8]

The first available treatment for **chronic hepatitis C** was interferon alfa-2b, and this was followed by interferon

alfa-2a, given subcutaneously 3 times a week. A meta-analysis[9] of studies involving interferon treatment of hepatitis C suggested that treatment with interferon alfa 3 million units three times weekly for at least 12 months had the best risk-benefit ratio for patients with chronic hepatitis C. Studies[10,11] with once-weekly peginterferon alfa showed it to be more effective than interferon alfa given three times weekly in patients with chronic hepatitis C, including those with cirrhosis or extensive fibrosis.[12]

Combination therapy with interferon alfa and oral ribavirin for the treatment of chronic hepatitis C is more effective than either drug alone with sustained responses having been recorded.[13] Meta-analyses have also concluded that the combination is more effective both in patients who had failed to respond to interferon alone or to other previous treatment,[14] and in patients with milder disease.[15] There is good evidence[16-18] that combining ribavirin with peginterferon alfa may be more effective than combination with interferon alfa. The British Society for Gastroenterology[19] and the American Association for the Study of Liver Diseases (AASLD)[20] therefore recommend weekly subcutaneous peginterferon alfa with daily oral ribavirin as the first choice of treatment for chronic hepatitis C. However, some have questioned whether this is true for all genotypes of the virus, suggesting that the benefit of peginterferon alfa is largely confined to patients with the less responsive genotype 1, rather than patients infected with genotypes 2 or 3.[21] (One study[16] suggested a sustained virological response (SVR) of around 42% in patients with genotype 1, versus about 80% with genotypes 2 and 3.) Rates of sustained virologic response and tolerability did not differ significantly between peginterferon alfa-2a and -2b (both given with ribavirin) in a study in patients with genotype 1 infection, treated for 48 weeks.[22]

Guidelines for the management of **HIV and hepatitis B** co-infection have been developed by various expert groups.[23-25] In patients not requiring HIV therapy peginterferon alfa for 12 months is considered an option for non-cirrhotic HBeAg-positive patients.[23] Treatment of **HIV and hepatitis C** co-infected patients has been associated with a high rate of intolerance and a low rate of response. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[26-28] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[26,28] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[27] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[27,28] Guidelines for the treatment and management of HIV and hepatitis C co-infection have been developed by various expert groups.[20,23,25,29] In general, they all recommend combination therapy with peginterferon alfa and ribavirin usually for 48 weeks. For further discussion on the management of chronic hepatitis B and C patients co-infected with HIV, see p. 952.1.

Although antivirals are generally not required in **acute hepatitis**, treatment of acute hepatitis C with interferon alfa has been shown to produce more rapid resolution of viraemia[30] and may decrease the risk of chronic hepatitis developing.[31] Studies[32] with peginterferon alfa-2b, in a small number of patients with acute hepatitis C, have shown similar efficacy. The AASLD[20] recommends that either interferon or peginterferon alfa given for a period of at least 6 months should be considered for the treatment of acute hepatitis C if the infection persists 2 to 4 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[33] and by the Scottish Intercollegiate Guidelines Network.[29]

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6. Janssen HLA, *et al.* Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005; **365:** 123–9.
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8. Farci P, *et al.* Long-term benefit of interferon α therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology* 2004; **126:** 1740–9.
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11. Perry CM, Jarvis B. Peginterferon-α -2a (40 kD): a review of its use in the management of chronic hepatitis C. *Drugs* 2001; **61:** 2263–88.
12. Heathcote EJ, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000; **343:** 1673–80.
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14. Cummings KJ, *et al.* Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C previously nonresponsive to interferon: a meta-analysis of randomized trials. *JAMA* 2001; **285:** 193–9.
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25. Alberti A, *et al.* Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005; **42:** 615–24. Correction. *ibid.;* **43:** 1098.
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27. Torriani FJ, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; **351:** 438–50.
28. Chung RT, *et al.* Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; **351:** 451–9.
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30. Myers RP, *et al.* Interferon for acute hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/08).
31. Jaeckel E, *et al.* Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345:** 1452–7.
32. Santantonio T, *et al.* Efficacy of a 24-week course of PEG-interferon α -2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 2005; **42:** 329–33.
33. Clinical Effectiveness Group (British Association of Sexual Health and HIV). United Kingdom national guideline on the management of the viral hepatitides A, B & C 2008. Available at: http://www.bashh.org/documents/1927 (accessed 02/11/09)

Herpes simplex infections. Herpes simplex infections are commonly treated with aciclovir (see p. 955.2), but beneficial responses to topical interferon alfa have been reported in genital herpes, although results are mixed.[1] Interferon alfa has also been reported to have benefit in the treatment of herpes keratitis. A systematic review[2] of interventions for herpes simplex epithelial keratitis found that interferon monotherapy had a slightly beneficial effect on dendritic epithelial keratitis, but no more than that of other antivirals and concluded that the use of an antiviral nucleoside with interferon seemed to speed healing.

1. Leung DT, Sacks SL. Current recommendations for the treatment of genital herpes. *Drugs* 2000; **60:** 1329–52.
2. Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 15/03/11).

HIV infection and AIDS. Interferons have been tried with some success in the management of Kaposi's sarcoma and mycobacterial infections in patients with AIDS (see below and under Interferon Gamma, p. 999.2, respectively).

Inflammatory bowel disease. Interferon alfa is one of many drugs that have been tried in inflammatory bowel disease (p. 1811.3). A study[1] found that clinical remission was achieved in 26 of 28 patients with ulcerative colitis after 6 to 12 months of treatment with interferon alfa-2a. Partial remission was reported in 2 of 5 patients with Crohn's disease[2] given interferon alfa, but in another study in 12 patients[3] interferon alfa was of no benefit. Although some results with interferon beta suggest benefit in the treatment of ulcerative colitis unresponsive to corticosteroids,[4,5] a controlled study with interferon beta-1a in patients with moderately active disease did not find any significant benefit.[6]

1. Sümer N, Palabiyikoğlu M. Induction of remission by interferon-α in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol* 1995; **7:** 597–602.
2. Davidsen B, *et al.* Tolerability of interferon alpha-2b, a possible new treatment of active Crohn's disease. *Aliment Pharmacol Ther* 1995; **9:** 75–9.
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4. Musch E, *et al.* Induction and maintenance of clinical remission by interferon-β in patients with steroid-refractory active ulcerative colitis—an open long-term pilot trial. *Aliment Pharmacol Ther* 2002; **16:** 1233–9.
5. Musch E, *et al.* Successful treatment of steroid refractory active ulcerative colitis with natural interferon-β —an open long-term trial. *Z Gastroenterol* 2007; **45:** 1235–40.
6. Pena-Rossi C, *et al.* Clinical trial: a multicentre, randomized, double-blind, placebo-controlled, dose-finding, phase II study of subcutaneous interferon-β-1a in moderately active ulcerative colitis. *Aliment Pharmacol Ther* 2008; **28:** 758–67.

Kaposi's sarcoma. The various treatments used for Kaposi's sarcoma, including the role of HAART as first-line therapy in the AIDS-related form, are discussed on p. 718.1. Interferon alfa has been used in AIDS-related Kaposi's sarcoma and in patients with the classical, nonepidemic form. In patients with AIDS-related Kaposi's sarcoma interferon alfa, either as monotherapy or with zidovudine, has shown benefit in HIV-positive patients provided they possess relatively elevated CD4+ T lymphocyte counts (greater than 150 cells/microlitre),[1] although other drugs have generally replaced interferon alfa as treatment for Kaposi's sarcoma.[2] Systemic and local therapy such as interferon alfa and chemotherapy may be combined with HAART.[3]

1. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist* 2001; **6:** 34–55.
2. Krown SE. AIDS-associated Kaposi's sarcoma: is there still a role for interferon alfa? *Cytokine Growth Factor Rev* 2007; **18:** 395–402.
3. Aldenhoven M, *et al.* Therapeutic strategies for epidemic Kaposi's sarcoma. *Int J STD AIDS* 2006; 571–8.

Malignant neoplasms. Many reports have been published on the effects of interferons on various neoplasms; most have involved interferon alfa.

Interferons have become established in the treatment of a few malignant disorders, notably hairy-cell leukaemia (but see p. 694.3), Kaposi's sarcoma (see above), and chronic myeloid leukaemia (p. 694.2). Alfa interferons may improve the duration of remission in multiple myeloma,[1-4] but not necessarily survival.[2,5] Combination therapy including interferons has also been used in indolent low-grade non-Hodgkin's lymphoma (p. 696.3) and interferon alfa has been used alone to maintain remission. In renal cell carcinoma (p. 708.3) response to interferon alfa used with interleukin-2 has been promising, but toxicity high; interferon alfa alone produces very modest benefit.[6] Very modest improvements in survival have been seen when interferon alfa was combined with bevacizumab.[7,8] Interferon alfa is also used in other neoplasms including melanoma (p. 714.3); neuroendocrine tumours[9] (p. 716.3); myelodysplasia; cutaneous T cell lymphomas including mycosis fungoides (p. 698.3); and in meningioma.[10,11] Interferons have been given locally as an adjunct to surgery for superficial bladder tumours (p. 700.2) and intralesionally or perilesionally in basal cell carcinoma[12-14] and also for keloid scars.[15,16] They may be used as an adjunct to curative therapy for hepatocellular carcinoma in patients with viral hepatitis.[17] Use of interferon alfa with fluorouracil has been tried in inoperable colorectal cancer but does not appear to be more beneficial than fluorouracil alone.[18] Interferon alfa given with zidovudine has produced encouraging results in adult T-cell leukaemia/lymphoma.[19] Peginterferon alfa has also been shown to be effective in the management of chronic myeloid leukaemia and solid tumours, including metastatic melanoma and renal cell carcinoma.[20]

1. Mandelli F, *et al.* Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 1990; **322:** 1430–4.
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5. Österborg A, *et al.* Natural interferon-α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: a randomized study from the myeloma group of central Sweden. *Blood* 1993; **81:** 1428–34.
6. Medical Research Council Renal Cancer Collaborators. Interferon-α and survival in metastatic renal carcinoma: early results of a randomised controlled study. *Lancet* 1999; **353:** 14–17.

7. Rini BI, *et al*. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol* 2010; **28:** 2137–43.
8. Escudier B, *et al*. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol* 2010; **28:** 2144–50.
9. Kölby L, *et al*. Randomized clinical trial of the effect of interferon α on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg* 2003; **90:** 687–93.
10. Wöber-Bingöl Ç, *et al*. Interferon-alfa-2b for meningioma. *Lancet* 1995; **345:** 331.
11. Kaba SE, *et al*. The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery* 1997; **40:** 271–5.
12. Kowalzick L, *et al*. Intralesional recombinant interferon beta-1a in the treatment of basal cell carcinoma: results of an open-label multicentre study. *Eur J Dermatol* 2002; **12:** 558–61.
13. Bostanci S, *et al*. Treatment of basal cell carcinoma located in the head and neck region with intralesional interferon alpha-2a: evaluation of long-term follow-up results. *Clin Drug Investig* 2005; **25:** 661–7.
14. Tucker SB, *et al*. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006; **54:** 1033–8.
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16. Larrabee WF, *et al*. Intralesional interferon gamma treatment for keloids and hypertrophic scars. *Arch Otolaryngol Head Neck Surg* 1990; **116:** 1159–62.
17. Breitenstein S, *et al*. Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. *Br J Surg* 2009; **96:** 975–81.
18. Thirion P, *et al*. Alpha-interferon does not increase the efficacy of 5-fluorouracil in advanced colorectal cancer: Meta-analysis Group in Cancer. *Br J Cancer* 2001; **84:** 611–20.
19. Gill PS, *et al*. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. *N Engl J Med* 1995; **332:** 1744–8.
20. Bukowski RM, *et al*. Treating cancer with PEG Intron: pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. *Cancer* 2002; **95:** 389–96.

Mycobacterial infections. For the use of interferon alfa in mycobacterial infections, see Interferon Gamma, p. 999.2.

Progressive multifocal leukoencephalopathy. Beneficial responses were reported in patients with HIV-associated progressive multifocal leukoencephalopathy (PML) after treatment with interferon alfa.[1] Daily intramuscular interferon alfa therapy for 2 weeks also resulted in some neurologic improvement in a patient identified as an asymptomatic human T-lymphotropic virus type I carrier, who developed PML and pneumocystis pneumonia.[2] However, in a retrospective analysis[3] of the relative value of HAART and interferon alfa in the treatment of PML associated with AIDS, prolonged survival associated with interferon alfa was found to be not independent of the effects of HAART and it was concluded that interferon alfa provided no additional benefit.

1. Huang SS, *et al*. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol* 1998; **4:** 324–32.
2. Kimura A, *et al*. Progressive multifocal leukoencephalopathy in an HTLV-I carrier. *Clin Neurol Neurosurg* 2006; **108:** 768–71.
3. Geschwind MD, *et al*. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol* 2001; **7:** 353–7.

Skin disorders. For the use of interferon alfa in skin disorders associated with raised IgE concentrations, see Interferon Gamma, p. 1000.1.

Warts. Various interferons have been tried by various routes in the treatment of anogenital warts (condylomata acuminata) (p. 1689.3).

Intralesional injection has been used to ensure relatively high concentrations of interferon in the wart but the occurrence of systemic adverse effects shows that there is absorption from this site. Complete responses were reported[1] in 36% of patients given intralesional interferon alfa-2b compared with 17% given placebo, and a corresponding overall reduction in the affected area of 62.4% compared with 1.2% respectively. However, follow-up was not sufficiently long to comment on relapse rates. Another study[2] found similar responses using interferons alfa-2b, alfa-n1, or beta in patients with refractory warts, with complete responses in 47% of patients given intralesional interferons compared with 22% of patients given placebo. A study[3] evaluating two different doses of intralesional interferon beta-1a given three times weekly for 3 weeks reported complete responses in 63% of lesions injected with 1 million units compared with 38% of lesions injected with 33 000 units. Good responses have also been reported in patients with both refractory and recurrent warts given intralesional interferon alfa-n3.[4] Relapses were delayed and fewer warts recurred in patients who had received interferon rather than placebo. Intralesional interferon alfa-2b used with podophyllum was more effective that podophyllum alone,[5] although about 66% of patients in each group subsequently relapsed. A systematic review concluded that based on limited available evidence intralesional interferons may have a therapeutic effect, but have no significant advantage over simpler and safer treatments.[6]

Topical application of interferon alfa has also been reported to be more effective than podophyllotoxin.[7,8] Interferon beta has also been applied topically after surgical removal of warts.[9]

Theoretically, *systemic* use should have advantages in controlling subclinical infections and reducing relapses. However, responses to subcutaneous interferon alfa have generally been disappointing[10-12] although responses comparable with cauterisation and a reduction in relapse rates with either subcutaneous or intramuscular interferon alfa-2b have been obtained.[13] Information on the use of systemic interferons as an adjunct to conventional therapy is scarce but a study in 97 patients[14] with recurrent warts found no difference in either response or relapse rates in patients given cryotherapy with subcutaneous interferon alfa or cryotherapy alone. A study comparing subcutaneous interferon alfa, beta, and gamma used with cryotherapy found no significant difference in response rate, although patients given interferon beta or gamma developed new warts at a lower frequency.[15]

Intralesional plus subcutaneous interferon alfa has also been tried in treatment of oral warts; 4 HIV-positive patients with recurrent oral warts that had failed to respond to surgery and other treatments responded to interferon alfa treatment.[16]

1. Eron LJ, *et al*. Interferon therapy for condylomata acuminata. *N Engl J Med* 1986; **315:** 1059–64.
2. Reichman RC, *et al*. Treatment of condyloma acuminatum with three different interferons administered intralesionally: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 675–9.
3. Monsonego J, *et al*. Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. *Genitourin Med* 1996; **72:** 111–14.
4. Friedman-Kien AE, *et al*. Natural interferon alfa for treatment of condylomata acuminata. *JAMA* 1988; **259:** 533–8.
5. Douglas JM, *et al*. A randomized trial of combination therapy with intralesional interferon α_{2b} and podophyllin versus podophyllin alone for the therapy of anogenital warts. *J Infect Dis* 1990; **162:** 52–9.
6. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
7. Syed TA, *et al*. Human leukocyte interferon-alpha versus podophyllotoxin in cream for the treatment of genital warts in males: a placebo-controlled, double-blind, comparative study. *Dermatology* 1995; **191:** 129–32.
8. Syed TA, *et al*. Management of genital warts in women with human leukocyte interferon-α vs podophyllotoxin in cream: a placebo-controlled, double-blind, comparative study. *J Mol Med* 1995; **73:** 255–8.
9. Gross G, *et al*. Recombinant interferon beta gel as an adjuvant in the treatment of recurrent genital warts: results of a placebo-controlled double-blind study in 120 patients. *Dermatology* 1998; **196:** 330–4.
10. Reichman RC, *et al*. Treatment of condyloma acuminatum with three different interferon-α preparations administered parenterally: a double-blind, placebo-controlled trial. *J Infect Dis* 1990; **162:** 1270–6.
11. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alfa-2a: a multicenter double-blind placebo-controlled clinical trial. *JAMA* 1991; **265:** 2684–7.
12. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alpha-2a: a multicenter double-blind placebo-controlled clinical trial. *Acta Derm Venereol (Stockh)* 1993; **73:** 223–6.
13. Panici PB, *et al*. Randomized clinical trial comparing systemic interferon with diathermocoagulation in primary multiple and widespread anogenital condyloma. *Obstet Gynecol* 1989; **74:** 393–7.
14. Eron LJ, *et al*. Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon. *Genitourin Med* 1993; **69:** 91–3.
15. Bonnez W, *et al*. A randomized, double-blind, placebo-controlled trial of systemically administered interferon-α, -β, or -γ in combination with cryotherapy for the treatment of condyloma acuminatum. *J Infect Dis* 1995; **171:** 1081–9.
16. Lozada-Nur F, *et al*. Use of intralesional interferon-alpha for the treatment of recalcitrant oral warts in patients with AIDS: a report of 4 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92:** 617–22.

Adverse Effects and Treatment

The adverse effects of interferon are varied and the natural products appear to be less toxic than the pure synthetic compounds. The frequency and severity of adverse effects of peginterferon alfa appear to be similar to those for interferon alfa although dose-related neutropenia and thrombocytopenia and injection site reactions are more common. Clinical experience suggests that interferons beta and gamma have similar adverse effects.

Adverse effects are generally mild and reversible at doses less than 5 million international units/day. The majority of patients on interferon treatment have 'flu-like' symptoms such as loss of appetite, fever, chills, fatigue, headache, malaise, myalgia, arthralgia, and sweating. These symptoms tend to be dose-related, are most likely to occur at the start of treatment, and mostly respond to paracetamol (but for a possible interaction with paracetamol, see Interactions, p. 995.2).

Other common adverse effects are alopecia, asthenia, weight loss, anxiety, depression, dermatitis, diarrhoea, irritability, nausea, nervousness, neutropenia, pruritus, sleep disturbances, taste alteration, and vomiting. Serious adverse effects reported include neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, and suicide) and neurological disturbances (confusion, coma, and seizures), severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anaemia), cardiovascular disorders (hypo- or hypertension, supraventricular arrhythmias and myocardial infarction), endocrine disorders (such as thyroid disorders and diabetes mellitus), pulmonary disorders (dyspnoea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic or ischaemic colitis), pancreatitis, and ophthalmologic disorders (such as decrease or loss of vision, retinopathy including macular oedema and retinal thrombosis or haemorrhages, optic neuritis and papilloedema).

Hypersensitivity reactions, including anaphylaxis, have occurred, and interferon therapy may cause or exacerbate auto-immune disorders (such as immune thrombocytopenia, thrombotic thrombocytopenic purpura, psoriasis, SLE, rheumatoid arthritis, and interstitial nephritis).

Hypertriglyceridaemia, sometimes severe, has been seen. High doses may cause electrolyte disturbances including decreased calcium concentrations. There may be signs of altered liver function and hepatitis has been reported. Renal failure and nephrotic syndrome have also occurred. Interferons may impair fertility and menstrual irregularities have been reported, particularly with interferon beta. Subcutaneous injection may produce a reaction at the injection site, mainly mild inflammation or erythema, but pain, hypersensitivity, and other non-specific reactions have been reported. The reaction is reported frequently with interferon beta, which can produce severe reactions including local necrosis.

Adverse effects of peginterferon alfa (alone or with ribavirin) reported in patients co-infected with hepatitis C virus and HIV, are similar to those reported in patients infected only with hepatitis C virus. Although haematological adverse effects such as neutropenia, thrombocytopenia, and anaemia occurred more often in co-infected patients, most patients could be managed by dose adjustments. Other adverse effects reported in co-infected patients given peginterferon and ribavirin include apathy, raised blood amylase, chapped lips, chromaturia, raised gamma-glutamyltransferase and hepatitis, influenza, lactic acidosis (including hyperlactacidaemia), lipodystrophy, mood alteration, pain in the pharynx, larynx, back, and limbs, pneumonia, and tinnitus. Peginterferon treatment was associated with decreases in CD4+ cell counts within the first 4 weeks that were reversible when the dose was reduced or stopped; no negative impact was noted on the control of HIV viraemia during treatment or follow-up.

Nasal dosage may produce mucosal irritation and damage.

Reviews.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Pardo M, *et al*. Risks and benefits of interferon-α in the treatment of hepatitis. *Drug Safety* 1995; **13:** 304–16.
3. Kirkwood JM, *et al*. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002; **20:** 3703–18.
4. Sleijfer S, *et al*. Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; **27:** 423–31.
5. Hauschild A, *et al*. Practical guidelines for the management of interferon-α-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. *Cancer* 2008; **112:** 982–94.

Effects on the blood. Interferon alfa has myelosuppressive effects and the commonest haematological adverse effects associated with its use are dose-related leucopenia, neutropenia, and thrombocytopenia; anaemia is rarely reported. Other reported effects associated with interferon alfa include immune haemolytic anaemia[1] and immune thrombocytopenia.[2,3] Haemorrhage occurred in a patient with immune thrombocytopenia treated with interferon alfa,[4] and it was thought prudent to use interferons with caution, if at all, in this condition.[3,4] Reports of clotting disorders are rare; bleeding associated with induction of factor VIII inhibitor has been seen in a patient given interferon alfa to enhance hydroxycarbamide therapy for chronic myeloid leukaemia.[5] Thrombosis associated with interferon alfa has also been reported.[6]

Restoration of bone-marrow function after marrow transplantation was delayed in 3 patients given a human interferon alfa preparation.[7] Laboratory results showed an inhibition of granulocyte colony growth by human leucocyte interferon alfa. It was considered that interferon alfa was contra-indicated in patients with severe bone-marrow insufficiency and should not be given to marrow transplant patients before the graft was fully functional. However, in another 5 patients recombinant interferon alfa did not affect bone marrow transplants, although 3 patients had fever and chills, 4 had more than a 60% reduction in absolute peripheral granulocyte counts, and 4 had a 37 to 80% reduction in absolute platelet counts.[8] Lymphocytes were increased in all patients; blood counts returned to normal when interferon therapy stopped. Interferon alfa produced a decline in CD4+ T-lymphocytes resulting in opportunistic infections in 2 HIV-positive patients being treated for chronic hepatitis C.[9]

1. Akard LP, *et al*. Alpha-interferon and immune hemolytic anemia. *Ann Intern Med* 1986; **105:** 306.

2. McLaughlin P, *et al.* Immune thrombocytopenia following α -interferon therapy in patients with cancer. *JAMA* 1985; **254:** 1353–4.
3. Färkkilä M, Iivanainen M. Thrombocytopenia and interferon. *BMJ* 1988; **296:** 642.
4. Matthey F, *et al.* Bleeding in immune thrombocytopenic purpura after alpha-interferon. *Lancet* 1990; **335:** 471–2.
5. English KE, *et al.* Acquired factor VIII inhibitor in a patient with chronic myelogenous leukaemia receiving interferon-alfa therapy. *Ann Pharmacother* 2000; **34:** 737–9.
6. Durand JM, *et al.* Thrombosis and recombinant interferon- α . *Am J Med* 1993; **95:** 115.
7. Nissen C, *et al.* Toxicity of human leucocyte interferon preparations in human bone-marrow cultures. *Lancet* 1977; **i:** 203–4.
8. Winston DJ, *et al.* Safety and tolerance of recombinant leukocyte A interferon in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1983; **23:** 846–51.
9. Pesce A, *et al.* Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet* 1993; **341:** 1597.

Effects on the cardiovascular system. Hypotension or hypertension, tachycardia, and distal cyanosis are the most commonly reported cardiovascular adverse effects. Other reported cardiac complications include cardiac arrhythmias, atrioventricular block, symptoms of ischaemic heart disease, including myocardial infarction and sudden death, congestive heart failure, acute dyspnoea, pericardial effusion,[1,2] and cardiomyopathy.[1,3,4] Cardiotoxicity was not related to the daily or cumulative total dose, or duration of treatment and is usually reversible on stopping interferon treatment.[1]

Peripheral vascular complications such as Raynaud's syndrome[5-9] have been associated with interferon alfa therapy and other types of interferon.

1. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest* 1991; **99:** 557–61.
2. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
3. Angulo MP, *et al.* Reversible cardiomyopathy secondary to α -interferon in an infant. *Pediatr Cardiol* 1999; **20:** 293–4.
4. Kuwata A, *et al.* A case of reversible dilated cardiomyopathy after α -interferon therapy in a patient with renal cell carcinoma. *Am J Med Sci* 2002; **324:** 331–4.
5. Bachmeyer C, *et al.* Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996; **135:** 481–3.
6. Linden D. Severe Raynaud's phenomenon associated with interferon- β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.
7. Kruit WH, *et al.* Interferon- α induced Raynaud's syndrome. *Ann Oncol* 2000; **11:** 1501–2.
8. Schapira D, *et al.* Interferon-induced Raynaud's syndrome. *Semin Arthritis Rheum* 2002; **32:** 157–62.
9. Iorio R, *et al.* Severe Raynaud's phenomenon with chronic hepatitis C disease treated with interferon. *Pediatr Infect Dis J* 2003; **22:** 195–7.

Effects on the endocrine system. Both hypothyroidism and hyperthyroidism have been associated with interferon alfa therapy.[1] Thyroid disorders are usually minor and regress on stopping the interferon (with or without other specific treatment). However, patients with interferon alfa-induced Graves' disease may be less likely to remit once the drug is stopped.[1] Most such cases have occurred in patients being treated for hepatitis C,[1] and long-lasting ophthalmopathy has been reported in one patient.[2]

The development of type 1 diabetes has also been associated with interferon alfa therapy,[3-6] and exacerbation of existing type 2 diabetes has been reported.[7,8] Reversible hypopituitarism has been reported in patients receiving interferon alfa.[9,10] Recombinant interferon gamma was reported not to affect thyroid function.[11]

1. Tomer Y, *et al.* Interferon alpha treatment and thyroid dysfunction. *Endocrinol Metab Clin North Am* 2007; **36:** 1051–66.
2. Binaghi M, *et al.* Ophtalmopathie de Basedow sévère liée à l'interféron alpha. *J Fr Ophtalmol* 2002; **25:** 412–15.
3. Fabris P, *et al.* Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; **340:** 548.
4. Guerci A-P, *et al.* Onset of insulin-dependent diabetes mellitus after interferon-alfa therapy for hairy cell leukaemia. *Lancet* 1994; **343:** 1167–8.
5. Gori A, *et al.* Reversible diabetes in patient with AIDS-related Kaposi's sarcoma treated with interferon α -2a. *Lancet* 1995; **345:** 1438–9.
6. Murakami M, *et al.* Diabetes mellitus and interferon- α therapy. *Ann Intern Med* 1995; **123:** 318.
7. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.
8. Lopes EPA, *et al.* Exacerbation of type 2 diabetes mellitus during interferon-alfa therapy for chronic hepatitis B. *Lancet* 1994; **343:** 244. Correction. *ibid.*: 680.
9. Sakane N, *et al.* Reversible hypopituitarism after interferon-alfa therapy. *Lancet* 1995; **345:** 1305.
10. Concha LB, *et al.* Interferon-induced hypopituitarism. *Am J Med* 2003; **114:** 161–3.
11. Bhakri H, *et al.* Recombinant gamma interferon and autoimmune thyroid disease. *Lancet* 1985; **ii:** 457.

Effects on the eyes. The most typical ocular adverse effect associated with interferon alfa treatment is retinopathy, which is characterised by cotton wool spots and superficial retinal haemorrhages. Reports of interferon-associated retinopathy have been reviewed.[1,2] Reduced vision or complete visual loss is rare or limited and is usually reversible after stopping treatment. In a study of 43 patients with chronic hepatitis given interferon alfa, retinopathy developed in 11 of 37 non-diabetic patients and in 3 of 6 diabetic patients after about 8 to 10 weeks of therapy.[3] None of the patients had had retinopathy before treatment; the condition was reversible in the non-diabetic patients on stopping therapy. Visual acuity remained unchanged. Subconjunctival haemorrhage occurred in a further 3 of the non-diabetic patients. Severe irreversible loss of vision has been reported in a non-diabetic patient given interferon alfa.[4] A prospective study[5] of 156 patients treated with interferon alfa or peginterferon alfa (with or without ribavirin) reported signs of retinopathy in 24% of the patients; 29 patients developed cotton-wool spots, 7 developed retinal haemorrhage, and 2 patients developed both lesions during treatment; none of the patients had retinopathy before starting treatment. The lesions remained asymptomatic and resolved in all the patients. Patient age above 45 years, hypertension, and the use of pegylated alpha-interferon were identified as risk factors for retinopathy. Neurovisual impairment was present in 31 patients before interferon treatment and in 74 patients during treatment. Another study[6] of 19 patients reported that 8 patients developed asymptomatic retinopathy while on treatment with interferon alfa (with or without ribavirin); patients who had previously failed to respond to interferon monotherapy seemed more likely to develop retinopathy when given combined therapy than patients who had responded and then relapsed. The changes were transient and sometimes disappeared while the patients were still on treatment. Retinopathy has occasionally been reported in patients being treated with interferon beta for the management of multiple sclerosis.[7-9] Symptoms also resolved after stopping treatment.

Pain in one eyeball leading to exophthalmos and complete visual loss has been reported in a patient given interferon alfa;[10] despite withdrawal of interferon and instigation of antibacterial and corticosteroid treatment, the eyeball subsequently ruptured necessitating ophthalmectomy. Other severe ocular effects reported during interferon alfa treatment include a disorder resembling Vogt-Koyanagi-Harada disease, central retinal vein occlusion, central retinal artery occlusion, and bilateral ischaemic optic neuropathy with severe visual impairment.[11]

Interferon-alfa is not usually known to cause ocular surface toxicity, however, epithelial microcyst formation has been reported in a patient after using topical interferon alfa-2b for 4 weeks.[12]

1. Hayasaka S, *et al.* Interferon associated retinopathy. *Br J Ophthalmol* 1998; **82:** 323–5.
2. Savant V, Gillow T. Interferon-associated retinopathy. *Eye* 2003; **17:** 534–6.
3. Hayasaka S, *et al.* Retinopathy and subconjunctival haemorrhage in patients with chronic viral hepatitis receiving interferon alfa. *Br J Ophthalmol* 1995; **79:** 150–2.
4. Lohmann CP, *et al.* Severe loss of vision during adjuvant interferon alfa-2b treatment for malignant melanoma. *Lancet* 1999; **353:** 1326.
5. d'Alteroche L, *et al.* Ophthalmologic side effects during alpha-interferon therapy for viral hepatitis. *J Hepatol* 2006; **44:** 56–61.
6. Jain K, *et al.* Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001; **85:** 1171–3.
7. Saito H, *et al.* Retinopathy in a multiple sclerosis patient undergoing interferon-therapy. *Multiple Sclerosis* 2007; **13:** 939–40.
8. Longmuir R, *et al.* Cotton wool spots associated with interferon beta-1 alpha therapy. *Semin Ophthalmol* 2007; **22:** 49–53.
9. Folden DV, *et al.* Interferon beta-associated retinopathy in patients treated for multiple sclerosis. *Neurology* 2008; **70:** 1153–5.
10. Yamada H, *et al.* Acute onset of ocular complications with interferon. *Lancet* 1994; **343:** 914.
11. Sène D, *et al.* Intraocular complications of IFN-alpha and ribavirin therapy in patients with chronic viral hepatitis C. *World J Gastroenterol* 2007; **13:** 3137–40.
12. Aldave AJ, Nguyen A. Ocular surface toxicity associated with topical interferon alpha-2b. *Br J Ophthalmol* 2007; **91:** 1087–8.

Effects on the gastrointestinal tract. Mild and transient gastrointestinal adverse effects such as nausea, diarrhoea, vomiting, and anorexia occur in about 30 to 40% of patients being treated with interferon alfa. There have been reports[1-4] of the onset of coeliac disease during treatment of hepatitis C with interferon or peginterferon alfa, in some cases used with ribavirin. Symptoms generally resolved after interferon was stopped and a gluten-free diet started. A case[5] of eosinophilic enteritis has been reported in a patient, with no history of digestive disorders, after 12 weeks of recombinant interferon alfa-2b treatment; symptoms resolved after stopping interferon and on treatment with prednisolone. New[6,7] or exacerbated[8] cases of ulcerative colitis have been reported in patients on interferon or peginterferon alfa treatment (with or without ribavirin). Treatment with interferon was usually stopped[7,8] and symptoms tended to resolve or improve with appropriate therapy (such as mesalazine and/or corticosteroids).[6-8] Cases of ischaemic colitis associated with interferon or peginterferon alpha have been reported rarely.[9]

1. Bardella MT, *et al.* Celiac disease during interferon treatment. *Ann Intern Med* 1999; **131:** 157–8.
2. Cammarota G, *et al.* Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *Lancet* 2000; **356:** 1494–5.
3. Bourlière M, *et al.* Onset of coeliac disease and interferon treatment. *Lancet* 2001; **357:** 803–4.
4. Martins EV, Gaburri AK. Celiac disease onset after pegylated interferon and ribavirin treatment of chronic hepatitis C. *Arq Gastroenterol* 2004; **41:** 132–3.
5. Kakumitsu S, *et al.* Eosinophilic enteritis observed during alpha-interferon therapy for chronic hepatitis C. *J Gastroenterol* 2000; **35:** 548–51.
6. Mavrogiannis C, *et al.* Ulcerative colitis associated with interferon treatment for chronic hepatitis C. *J Hepatol* 2001; **34:** 964–5.
7. Sprenger R, *et al.* Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis. *Gut* 2005; **54:** 438–9.
8. Watanabe T, *et al.* A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon alpha-2b and ribavirin. *Gut* 2006; **55:** 1682–3.
9. Leung Y, *et al.* Ischemic colitis during pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Can J Gastroenterol* 2006; **20:** 661–3.

Effects on the hair. Excessive temporary loss of telogen hair causing moderate and reversible alopecia occurs in about 7 to 30% of patients on interferon or peginterferon alfa treatment. Alopecia areata[1-3] and alopecia universalis[4,5] have occasionally been reported; complete regrowth of the hair usually occurs on completing interferon treatment. Alopecia has also been reported after use of topical interferon alfa eye drops for 3 months.[6]

A report of marked greying of the hair in a patient beginning after 5 months of treatment with interferon alfa for metastatic malignant melanoma; on completion of interferon therapy the hair regrowth returned to its normal colour.[7] Marked straightening of scalp and body hair has been reported in 2 patients after combined treatment with interferon alfa-2b or peginterferon alfa-2b and ribavirin for chronic hepatitis C.[8] In the first patient, there was also diffuse thinning of scalp hair, change in hair texture, increased greying of the hair, and eyebrow lengthening; the original curly hair began to regrow 6 months after stopping treatment, but the hair abnormalities recurred on rechallenge despite switching from interferon alfa-2b to peginterferon alfa-2b. In the second patient, treatment with peginterferon alfa-2b and ribavirin was associated with straightening of scalp hair, eyebrow hair, and pubic hair.[8] Lengthening and thickening of eyelashes has also been reported with interferon alfa therapy.[9,10] A case of eyelid and eyebrow trichomegaly has also been reported[11] in a patient treated with peginterferon alfa and ribavirin.

1. Radny P, *et al.* Alopecia areata induced by adjuvant treatment with alpha-interferon in malignant melanoma? *Dermatology* 2004; **209:** 249–50.
2. Agesta N, *et al.* Alopecia areata during interferon alpha-2b/ribavirin therapy. *Dermatology* 2002; **205:** 300–1.
3. Kernland KH, Hunziker T. Alopecia areata induced by interferon alpha? *Dermatology* 1999; **198:** 418–19.
4. Taliani G, *et al.* Reversible alopecia universalis during treatment with PEG-interferon and ribavirin for chronic hepatitis C. *J Chemother* 2005; **17:** 212–14.
5. Kartal ED, *et al.* Reversible alopecia universalis secondary to PEG-interferon alpha-2b and ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Eur J Gastroenterol Hepatol* 2007; **19:** 817–20.
6. Finger PT, Reichstein D. Interferon alpha eye drops: treatment of atypical lymphoid hyperplasia with secondary alopecia. *Br J Ophthalmol* 2007; **91:** 1085–6.
7. Fleming CJ, MacKie RM. Alpha interferon-induced hair discolouration. *Br J Dermatol* 1996; **135:** 337–8.
8. Bessis D, *et al.* Straight hair associated with interferon-alfa plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002; **147:** 392–3.
9. Hernández-Núñez A, *et al.* Trichomegaly following treatment with interferon alpha-2b. *Lancet* 2002; **359:** 1107.
10. Dikici B, *et al.* Interferon alpha and hypertrichosis of eyelashes. *Pediatr Infect Dis J* 2002; **21:** 448–9.
11. Howaizi M. Pegylated interferon-induced eyelid and eyebrow trichomegaly during chronic hepatitis C. *J Gastroenterol Hepatol* 2005; **20:** 1945–6.

Effects on hearing. Sensorineural hearing loss, mostly unilateral, has been rarely reported in patients treated with interferon or peginterferon. A prospective study[1] reported sensorineural hearing loss in 18 of 49 patients and tinnitus in 14 of 49 patients given interferons. The authors reported that effects were more common in those given interferon beta than in those given interferon alfa, and resolved in all patients on stopping therapy. A report[2] of 6 patients who had sudden hearing loss while on treatment with peginterferon alfa plus ribavirin found that hearing loss did not fully resolve after stopping treatment; but neither did it worsen in those who continued their treatment. A case report[3] of a patient who had acute sensorineural hearing loss 2 months after starting treatment with peginterferon alfa and ribavirin found that when treatment was re-started 4 months after stopping, the patient did not have further hearing loss and hearing on the left-side was unaffected. In another case report[4] a patient who developed hearing loss 22 weeks after starting treatment with peginterferon alfa, continued with treatment and symptoms did not worsen. Hearing loss resolved within 2 weeks of stopping treatment.

1. Kanda Y, *et al.* Sudden hearing loss associated with interferon. *Lancet* 1994; **343:** 1134–5.
2. Formann E, *et al.* Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin. *Am J Gastroenterol* 2004; **99:** 873–7.
3. Wong VK, *et al.* Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. *World J Gastroenterol* 2005; **11:** 5392–3.
4. Elloumi H, *et al.* Sudden hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment. *World J Gastroenterol* 2007; **13:** 5411–12.

Effects on the kidneys. Renal adverse effects associated with interferon alfa are usually limited to mild, asymptomatic proteinuria and moderate increases in serum creat-

inine in 15 to 20% of patients. Dose-related asymptomatic proteinuria has been reported with interferon gamma treatment.[1] Acute renal failure and nephrotic syndrome associated with interferon alfa treatment is rare and has mostly been reported in patients with underlying renal disease, or malignancies,[2-5] and in those receiving high doses.[6] Cases have also been reported in patients receiving interferon or peginterferon alfa treatment for chronic hepatitis C.[7-9] Nephrotic syndrome has also occurred after use of interferon beta.[10-12] Renal dysfunction usually resolves after stopping treatment, but incomplete resolution and fatalities have been reported.[5,8]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Averbuch SD, *et al*. Acute interstitial nephritis with the nephrotic syndrome following recombinant leukocyte A interferon therapy for mycosis fungoides. *N Engl J Med* 1984; **310:** 32–5.
3. Selby P, *et al*. Nephrotic syndrome during treatment with interferon. *BMJ* 1985; **290:** 1180.
4. Herrman J, Gabriel F. Membranoproliferative glomerulonephritis in a patient with hairy-cell leukemia treated with alpha-II interferon. *N Engl J Med* 1987; **316:** 112–13.
5. Colovic M, *et al*. Interferon alpha sensitisation induced fatal renal insufficiency in a patient with chronic myeloid leukaemia: case report and review of literature. *J Clin Pathol* 2006; **59:** 879–81.
6. Kramer P, *et al*. Recombinant leucocyte interferon A induces steroid-resistant acute vascular rejection episodes in renal transplant recipients. *Lancet* 1984; **i:** 989–90.
7. Endo M, *et al*. Appearance of nephrotic syndrome following interferon-α therapy in a patient with hepatitis B virus and hepatitis C virus coinfection. *Am J Nephrol* 1998; **18:** 439–43.
8. Fisher ME, *et al*. A woman with chronic hepatitis C infection and nephrotic syndrome who developed multiple renal lesions after interferon alfa therapy. *Am J Kidney Dis* 2004; **44:** 567–73.
9. Couto CA, *et al*. Life-threatening thrombocytopenia and nephrotic syndrome due to focal segmental glomerulosclerosis associated with pegylated interferon alpha-2b and ribavirin treatment for hepatitis C. *Liver Int* 2006; **26:** 1294–7.
10. Nakao K, *et al*. Minimal change nephrotic syndrome developing during postoperative interferon-beta therapy for malignant melanoma. *Nephron* 2002; **90:** 498–500.
11. Auty A, Saleh A. Nephrotic syndrome in a multiple sclerosis patient treated with interferon beta 1a. *Can J Neurol Sci* 2005; **32:** 366–8.
12. Kumasaka R, *et al*. Nephrotic syndrome associated with interferon-beta-1b therapy for multiple sclerosis. *Clin Exp Nephrol* 2006; **10:** 222–5.

Effects on lipids. Cases[1-3] of reversible hypertriglyceridaemia (with or without elevation of total cholesterol level) have been reported with interferon alfa treatment. Hypertriglyceridaemia more often occurs with longer treatment durations and does not appear to be related to pre-existing cardiovascular disorders or baseline dyslipidaemia; frequency and severity are not dose dependent. Lifestyle modifications and drug treatment with a fibrate or statin are usually needed to reduce triglyceride levels. A small study[4] reported that taking omega-3 fatty acid supplements (3 g daily for 6 months) reduced serum triglyceride levels in patients on interferon alfa for the management of chronic hepatitis C.

1. Graessle D, *et al*. Alpha-interferon and reversible hypertriglyceridemia. *Ann Intern Med* 1993; **118:** 316–17.
2. Junghans V, Rünger TM. Hypertriglyceridaemia following adjuvant interferon-α treatment in two patients with malignant melanoma. *Br J Dermatol* 1999; **140:** 183–4.
3. Wong SF, *et al*. Management of hypertriglyceridemia in patients receiving interferon for malignant melanoma. *Ann Pharmacother* 2004; **38:** 1655–9.
4. Malaguarnera M, *et al*. Fish oil treatment of interferon-alpha-induced dyslipidaemia: study in patients with chronic hepatitis C. *BioDrugs* 1999; **11:** 285–91.

Effects on the liver. Mild hepatotoxicity with an asymptomatic and reversible rise in serum aminotransferases has been reported in about 25 to 30% of patients receiving interferon alfa; severe hepatotoxicity is rare[1] but cases of fatal liver failure have been reported,[2-5] sometimes due to severe exacerbation of chronic hepatitis B and/or C infection.[4,5] An analysis of the toxicity of adjuvant high-dose interferon alfa in 40 patients being treated for melanoma reported hepatotoxicity in 39 patients, with 26 patients having grade 3 to 4 hepatotoxicity.[6] Cases[7,8] of peginterferon alfa-induced auto-immune hepatitis have been reported in patients receiving treatment for chronic hepatitis C.

Raised serum-alanine aminotransferase values have been reported in about 37% of patients given interferon beta therapy for the treatment of multiple sclerosis, with grade 3 to 4 hepatotoxicity being reported in about 1.4% of patients.[9]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Durand JM, *et al*. Liver failure due to recombinant alpha interferon. *Lancet* 1991; **338:** 1268–9.
3. Wandl UB, *et al*. Liver failure due to recombinant alpha interferon for chronic myelogenous leukaemia. *Lancet* 1992; **339:** 123–4.
4. Marcellin P, *et al*. Fatal exacerbation of chronic hepatitis B induced by recombinant alpha-interferon. *Lancet* 1991; **338:** 828.
5. Janssen HLA, *et al*. Fatal hepatic decompensation associated with interferon alfa. *BMJ* 1993; **306:** 107–8.
6. Jonasch E, *et al*. Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma. *Cancer J* 2000; **6:** 139–45.
7. Kogure T, *et al*. Fulminant hepatic failure in a case of autoimmune hepatitis in hepatitis C during peg-interferon-alpha 2b plus ribavirin treatment. *World J Gastroenterol* 2007; **13:** 4394–7.
8. Kontorinis N, *et al*. Pegylated interferon-induced immune-mediated hepatitis post-liver transplantation. *Liver Transpl* 2006; **12:** 827–30.
9. Byrnes V, *et al*. Drug induced liver injury secondary to interferon-beta (IFN-beta) in multiple sclerosis. *Ann Hepatol* 2006; **5:** 56–9.

Effects on the nervous system and mental state. Neurological adverse effects have been reported with interferon alfa treatment for chronic hepatitis C virus or for malignant diseases;[1-5] notably, an acute confusional state may develop rapidly after starting high-dose interferon alfa treatment and a depressive syndrome may develop more slowly over weeks to months of treatment. Less commonly a manic condition, usually characterised by extreme irritability and agitation but also occasionally by euphoria, may occur.

Acute interferon alfa-induced confusional states are typically characterised by disorientation, lethargy, difficulties with speaking and writing, parkinsonism, psychomotor retardation, psychotic symptoms (such as hallucinations), and somnolence.

Depression[5-9] occurs in about 16 to 58% of patients receiving interferon alfa. Patients considered to be at risk for developing depression are those with pre-existing symptoms of mood and anxiety disorders, those with a history of major depression, and those receiving higher doses of interferon alfa or on long treatment regimens. SSRIs have been used successfully to both treat patients with interferon-associated depression, thus allowing therapy to be continued,[10,11] and as pretreatment to prevent its occurrence.[12]

Should manic symptoms[13] occur, interferon alfa and antidepressant treatment should be stopped and a mood stabiliser given. Interferon alfa-induced mood disorders may also consist of an overlap between depressive and manic symptoms. A prospective study[14] of 93 patients treated with peginterferon alfa plus ribavirin for chronic hepatitis C reported that mood disorders occurred in 30 patients; 3 cases of mania, 15 cases of irritable hypomania, and 12 cases of mixed depressive states. The distinction between the 2 states is important in terms of management as depression-specific symptoms respond well to SSRIs, whereas antidepressants may worsen manic or hypomanic states.

Seizures[15-17] attributed to interferon alfa have been described.

Cases of neurological toxicity have been reported in patients receiving interferon beta,[1,18] although interferon beta is considered to be slightly less neurotoxic.

Chronic hepatitis C virus infection may be complicated by the development of systemic vasculitis caused by mixed cryoglobulinemia or of a non-cryoglobulinemic vasculitis resembling polyarteritis nodosa. Successful treatment of the hepatitis infection with interferon alfa usually results in the improvement of vasculitic symptoms, including neuropathy. However, vasculitis may also be precipitated or exacerbated by treatment with interferon (including peginterferon alfa)[19-22] resulting in development of vasculitic neuropathy. Non-vasculitic peripheral neuropathies, including cranial neuropathies; have also been reported.[20-23] Others[24] have reported no association between peginterferon alfa and peripheral neuropathy. In most cases symptoms improved on treatment with corticosteroids or spontaneously, but fatal exacerbations of vasculitis have occurred despite stopping the interferon treatment and giving immunosuppressants.[21]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Dieperink E, *et al*. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. *Am J Psychiatry* 2000; **157:** 867–76.
3. Malek-Ahmadi P. Mood disorders associated with interferon treatment: theoretical and practical considerations. *Ann Pharmacother* 2001; **35:** 489–95.
4. Van Gool AR, *et al*. Neuropsychiatric side effects of interferon-alfa therapy. *Pharm World Sci* 2003; **25:** 11–20.
5. Raison CL, *et al*. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs* 2005; **19:** 105–23.
6. Janssen HLA, *et al*. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994; **21:** 241–3.
7. Renault PF, *et al*. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987; **147:** 1577–80.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Depression with interferon. *Aust Adverse Drug React Bull* 1999; **18:** 6.
9. Capuron L, Ravaud A. Prediction of the depressive effects of interferon alfa therapy by the patient's initial affective state. *N Engl J Med* 1999; **340:** 1370.
10. Levenson JL, Fallon HJ. Fluoxetine treatment of depression caused by interferon-α. *Am J Gastroenterol* 1993; **88:** 760–1.
11. Schramm TM, *et al*. Sertraline treatment of interferon-alfa-induced depressive disorder. *Med J Aust* 2000; **173:** 359–61.
12. Musselman DL, *et al*. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001; **344:** 961–6.
13. Kingsley D. Interferon-alpha induced 'tertiary mania'. *Hosp Med* 1999; **60:** 381–2.
14. Constant A, *et al*. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry* 2005; **66:** 1050–7.
15. Janssen HLA, *et al*. Seizures associated with low-dose α-interferon. *Lancet* 1990; **336:** 1580.
16. Brouwers PJ, *et al*. Photosensitive seizures associated with interferon alpha-2a. *Ann Pharmacother* 1999; **33:** 113–14.
17. Ameen M, Russell-Jones R. Seizures associated with interferon-α treatment of cutaneous malignancies. *Br J Dermatol* 1999; **141:** 386–7.
18. Goeb JL, *et al*. Psychiatric side effects of interferon-beta in multiple sclerosis. *Eur Psychiatry* 2006; **21:** 186–93.
19. Batisse D, *et al*. Sustained exacerbation of cryoglobulinaemia-related vasculitis following treatment of hepatitis C with peginterferon alfa. *Eur J Gastroenterol Hepatol* 2004; **16:** 701–3.
20. Boonyapisit K, Katirji B. Severe exacerbation of hepatitis C-associated vasculitic neuropathy following treatment with interferon alpha: a case report and literature review. *Muscle Nerve* 2002; **25:** 909–13.
21. Beuthien W, *et al*. Vasculitic complications of interferon-alpha treatment for chronic hepatitis C virus infection: case report and review of the literature. *Clin Rheumatol* 2005; **24:** 507–15.
22. Stübgen JP. Interferon alpha and neuromuscular disorders. *J Neuroimmunol* 2009; **207:** 3–17.
23. Gastineau DA, *et al*. Severe neuropathy associated with low-dose recombinant interferon-alpha. *Am J Med* 1989; **87:** 116.
24. Briani C, *et al*. Peripheral neurotoxicity of pegylated interferon alpha: a prospective study in patients with HCV. *Neurology* 2006; **67:** 781–5.

Effects on the oral mucosa. Painful oral ulcers, necessitating withdrawal of interferon alfa therapy, have occurred in a patient treated for chronic hepatitis.[1] Interferon alfa treatment has been reported to exacerbate pre-existing lichen planus associated with chronic hepatitis C.[2,3] New cases of oral lichen planus have been reported in patients receiving interferon alfa treatment for malignant diseases[4] and chronic hepatitis.[5]

1. Qaseem T, *et al*. A case report of painful oral ulcerations associated with the use of alpha interferon in a patient with chronic hepatitis due to non-A non-B non-C virus. *Mil Med* 1993; **158:** 126–7.
2. Areias J, *et al*. Lichen planus and chronic hepatitis C: exacerbation of the lichen under interferon-alpha-2a therapy. *Eur J Gastroenterol Hepatol* 1996; **8:** 825–8.
3. Nagao Y, *et al*. Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C. *Int J Mol Med* 2005; **15:** 237–41.
4. Kütting B, *et al*. Oropharyngeal lichen planus associated with interferon-α treatment for mycosis fungoides: a rare side-effect in the therapy of cutaneous lymphomas. *Br J Dermatol* 1997; **137:** 836–7.
5. Guijarro Guijarro B, *et al*. Aparición de un liquen plano erosivo durante el tratamiento con interferón alfa-2a por una hepatitis C crónica. *Med Oral* 2001; **6:** 358–63.

Effects on the respiratory system. Pulmonary adverse effects have occasionally been reported with interferon or peginterferon alfa treatment. A literature review[1] found that the most commonly reported adverse effect was interstitial pneumonitis, followed by a sarcoid-like reaction with non-caseating granuloma formation. Other, less commonly reported events were asthma exacerbation, pleural effusion, bronchiolitis obliterans with organizing pneumonia, and a case of fatal acute respiratory distress-like syndrome (ARDS). A subsequent case of ARDS associated with peginterferon alfa therapy has also been reported.[2]

1. Midturi J, *et al*. Spectrum of pulmonary toxicity associated with the use of interferon therapy for hepatitis C: case report and review of the literature. *Clin Infect Dis* 2004; **39:** 1724–9.
2. Vartany E, *et al*. Adult respiratory distress syndrome after treatment with pegylated interferon α-2a and ribavirin. *Heart Lung* 2008; **37:** 153–6.

Effects on skeletal muscle. Myalgia is one of the 'flu-like' symptoms frequently associated with interferons. Rhabdomyolysis[1-3] has occurred in patients being treated with interferon alfa and proved fatal when associated with multiple organ failure in a patient receiving adjuvant high-dose interferon alfa for multiple myeloma.[1] Rhabdomyolysis has also been reported in a patient receiving interferon beta for the treatment of multiple sclerosis.[4] Other rarely reported muscular disorders associated with interferon alfa therapy include inflammatory myopathies, polymyositis-like symptoms, and a case of mitochondrial myopathy.[5]

1. Reinhold U, *et al*. Fatal rhabdomyolysis and multiple organ failure associated with adjuvant high-dose interferon alfa in malignant melanoma. *Lancet* 1997; **349:** 540–1.
2. Gabrielli M, *et al*. Acute reversible rhabdomyolysis during interferon alpha2b therapy for hepatitis C. *Am J Gastroenterol* 2003; **98:** 940.
3. Ozdag F, *et al*. Acute rhabdomyolysis during the treatment of scleromyxedema with interferon alfa. *J Dermatolog Treat* 2001; **12:** 167–9.
4. Lünemann JD, *et al*. Rhabdomyolysis during interferon-beta 1a treatment. *J Neurol Neurosurg Psychiatry* 2002; **72:** 274. Correction. *ibid*.; **73;** 354.
5. Stübgen JP. Interferon alpha and neuromuscular disorders. *J Neuroimmunol* 2009; **207:** 3–17.

Effects on the skin. Dermatological adverse effects such as dryness, erythema, rash, or urticaria, have been reported in about 5 to 12% of patients given interferon alfa; severe events occur rarely.[1] Exacerbation or development of psoriasis was reported in patients given recombinant interferon alfa[2-4] peginterferon alfa,[5] and interferon beta-1a.[6] However, no such effect was seen in 7 patients given interferon gamma.[7] Both vitiligo and psoriasis developed in a 10-year-old girl with chronic hepatitis B infection given interferon alfa; the skin conditions did not improve on stopping the interferon treatment.[8] A case[9] of vitiligo occurring during the third month of treatment for chronic hepatitis C with peginterferon alfa and ribavirin has been reported; the condition persisted after treatment with peginterferon was completed. Exacerbation of lichen planus has also been reported[10] during interferon alfa treatment (see also Effects on the Oral Mucosa, above). Cases of cutaneous sarcoidosis have been reported in patients with chronic hepatitis C being treated with interferon or pegylated interferon alfa plus ribavirin; skin lesions are usually benign and treatment with interferon alfa may sometimes be continued with resolution of the skin lesions occurring

spontaneously or within a few months of completing treatment.[11,12] Cutaneous vascular lesions with punctate telangiectasias were noted in 18 of 44 patients treated with interferon alfa-2a; lesions did not appear at the injection site.[13] Severe necrotising cutaneous lesions were reported at injection sites in a patient given recombinant interferon beta-1b; the lesions healed when interferon alfa-n3 was substituted.[14] However, cutaneous necrosis has also been associated with interferon alfa[15,16] and peginterferon alfa.[17] Five cases[18] of a self-resolving cutaneous lesion at the injection site of interferon, mimicking lupus erythematosus, have been reported; 3 of them involved interferon alfa therapy for malignant melanoma and the other 2 patients were being given interferon beta for multiple sclerosis. Fatal paraneoplastic pemphigus developed in a patient given interferon alfa-2a.[19] Hyperpigmentation of the skin and tongue has been described[20] in 2 dark-skinned patients during treatment with interferon alfa and ribavirin.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet* 1986; **i:** 1466–8.
3. Funk J, *et al*. Psoriasis induced by interferon-α . *Br J Dermatol* 1991; **125:** 463–5.
4. Taylor C, *et al*. Extensive psoriasis induced by interferon alfa treatment for chronic hepatitis C. *Postgrad Med J* 2000; **76:** 365–6.
5. Ketikoglou I, *et al*. Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol* 2005; **15:** 107–9.
6. López-Lerma I, *et al*. New-onset psoriasis in a patient treated with interferon beta-1a. *Br J Dermatol* 2009; **160:** 716–7.
7. Schulze H-J, Mahrle G. Gamma interferon and psoriasis. *Lancet* 1986; **ii:** 926–7.
8. Seçkin D, *et al*. Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. *Pediatr Dermatol* 2004; **21:** 577–9.
9. Tomasiewicz K, *et al*. Vitiligo associated with pegylated interferon and ribavirin treatment of patients with chronic hepatitis C: a case report. *Adv Therapy* 2006; **23:** 139–42.
10. Protzer U, *et al*. Exacerbation of lichen planus during interferon alfa-2a therapy for chronic active hepatitis C. *Gastroenterology* 1993; **104:** 903–5.
11. Eberlein-König B, *et al*. Cutaneous sarcoid foreign body granulomas developing in sites of previous skin injury after systemic interferon-alpha treatment for chronic hepatitis C. *Br J Dermatol* 1999; **140:** 370–2.
12. Hurst EA, Mauro T. Sarcoidosis associated with pegylated interferon alfa and ribavirin treatment for chronic hepatitis C: a case report and review of the literature. *Arch Dermatol* 2005; **141:** 865–8.
13. Dreno B, *et al*. Alpha-interferon therapy and cutaneous vascular lesions. *Ann Intern Med* 1989; **111:** 95–6.
14. Sheremata WA, *et al*. Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. *N Engl J Med* 1995; **332:** 1584.
15. Shinohara K. More on interferon-induced cutaneous necrosis. *N Engl J Med* 1995; **333:** 1222.
16. Sasseville D, *et al*. Interferon-induced cutaneous necrosis. *J Cutan Med Surg* 1999; **3:** 320–3.
17. Bessis D, *et al*. Necrotizing cutaneous lesions complicating treatment with pegylated-interferon alfa in an HIV-infected patient. *Eur J Dermatol* 2002; **12:** 99–102.
18. Arrue I, *et al*. Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol* 2007; **34** (suppl 1): 18–21.
19. Kirsner RS, *et al*. Treatment with alpha interferon associated with the development of paraneoplastic pemphigus. *Br J Dermatol* 1995; **132:** 474–8.
20. Willems M, *et al*. Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; **149:** 390–4.

Shock. Fatal non-cardiogenic shock occurred after the third dose of interferon alfa-2b in a patient with malignant melanoma.[1] There were similarities to a fatal reaction reported in another patient with malignant melanoma (see under Effects on Skeletal Muscle, p. 994.3).

1. Carson JJ, *et al*. Fatality and interferon α for malignant melanoma. *Lancet* 1998; **352:** 1443–4.

Precautions

Interferons should be used with caution or avoided altogether in patients with depression or psychiatric disorders, epilepsy or other CNS diseases, severe renal or hepatic impairment, chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver, auto-immune hepatitis, cardiac disorders, myelosuppression, poorly controlled thyroid dysfunction, pulmonary disease, diabetes mellitus, auto-immune diseases, coagulation disorders, or a history of these conditions.

All patients receiving interferons should be closely monitored for any signs or symptoms of psychiatric disorders; if psychiatric symptoms continue or worsen, or suicidal ideation is identified, then interferon therapy should be stopped.

Interferon treatment is not advised for patients whose hypoglycaemia, hyperglycaemia and/or diabetes mellitus is not effectively controlled; if these conditions develop during treatment and cannot be controlled with medication then interferon treatment should be stopped. Standard blood and biochemical laboratory tests (including thyroid function) should be done before starting treatment with interferon and then periodically during therapy. Interferon should be used with caution in patients also receiving other potentially myelosuppressive agents.

Assessment of cardiac function is advised before treatment is started in patients with pre-existing cardiac abnormalities and if there is any deterioration of cardiovascular status interferon should be suspended or stopped.

Hepatic and renal function should be monitored during treatment with interferons. Interferon treatment should be stopped in patients who develop evidence of liver decompensation during treatment. Treatment should also be stopped in those patients who despite the dose of interferon being reduced still have progressive and clinically significant increases in serum-alanine aminotransferase.

Patients receiving interferons who have visual disturbances should undergo eye examination. A baseline ocular examination is recommended before treatment, and periodic eye examinations should be performed throughout treatment in patients predisposed to retinopathy, such as those with diabetes mellitus or hypertension; treatment should be stopped in patients who develop new or worsening ophthalmologic disorders.

Patients with psoriasis or sarcoidosis have been reported to have exacerbations during interferon alfa therapy.

Patients should receive adequate fluids to maintain hydration during treatment with interferon alfa since hypotension related to fluid depletion has been seen in some patients.

Interferons may affect the ability to drive or operate machinery.

Antibodies may develop to exogenous interferon that reduce its activity.

Asthma. For a report of severe exacerbation of asthma in patients receiving interferon alfa, see Effects on the Respiratory System, p. 994.3.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of interferon alfa by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. It has been suggested that interferons are too large in molecular weight to transfer into breast milk in clinically relevant amounts.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 12/06/08)
2. Kumar AR, *et al*. Transfer of interferon alfa into human breast milk. *J Hum Lact* 2000; **16:** 226–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies interferon alfa-2a and peginterferon alfa-2a as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed. Interferon alfa-2b and peginterferon alfa-2b are classified as possibly porphyrinogenic; they should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Psychiatric disorders. For comment on the risk of mood disorders in patients with a history of such disorders, see Effects on the Nervous System and Mental State, p. 994.2.

Interactions

Interactions involving interferons have not been fully evaluated, but it is known that they can inhibit hepatic oxidative metabolism via cytochrome P450 enzymes; the clinical relevance of this interaction is unclear and thus caution should be exercised during use with drugs metabolised in this way. Studies with peginterferon alfa showed increased activity of the cytochrome P450 isoenzymes CYP2C8/9 and CYP2D6; caution is advised when giving peginterferon alfa with drugs that are metabolised by these isoenzymes, such as warfarin, phenytoin, and flecainide. Interferon and peginterferon alfa have been shown to inhibit the metabolism of theophylline which is metabolised via the cytochrome P450 isoenzyme CYP1A2. Drugs likely to exacerbate the haematological effects of interferons, such as ribavirin and zidovudine, should also be used with caution. Interferons may also increase the neurotoxic and cardiotoxic effects of other drugs.

ACE inhibitors. For a report of possible synergistic haematological toxicity in patients receiving interferon alfa and ACE inhibitors, see p. 1288.3.

Analgesics. Three patients had increases in liver enzyme values when given *paracetamol* 1 g two or three times daily on the same three days each week as interferon alfa; vinblastine was also given every third week.[1] Paracetamol has also been found to enhance the antiviral effect of interferon alfa in healthy subjects.[2]

1. Kellokumpu-Lehtinen P, *et al*. Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; **i:** 1143.
2. Hendrix CW, *et al*. Modulation of α -interferon's antiviral and clinical effects by aspirin, acetaminophen, and prednisone in healthy volunteers. *Antiviral Res* 1995; **28:** 121–31.

Anticoagulants. For reference to potentiation of *acenocoumarol* or *warfarin* necessitating dosage reduction in patients also receiving interferon alfa, see p. 1533.1.

Antineoplastics. For reduction in the area under the plasma concentration-time curve for *melphalan* in patients receiving interferon alfa, see p. 820.3.

Antivirals. For a report of synergistic bone-marrow toxicity with interferon alfa and *zidovudine*, see p. 1026.3.

Thalidomide. For reports of toxicity associated with interferons and thalidomide, see p. 870.3.

Theophylline. For reference to reduced clearance of theophylline in patients receiving interferon alfa, see p. 1235.2.

Antiviral Action

Interferons are naturally occurring proteins produced by eukaryotic cells in response to viral infection and other biological inducers that confer protection on uninfected cells of the same species. They are cytokines that affect many cell functions and have, in addition to their antiviral activity, antiproliferative and immunoregulatory properties. Three major classes have been identified: alfa, beta and gamma. Interferon alfa and beta are classified as Type I interferons and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities; interferon gamma in particular is a potent macrophage-stimulating factor.

Interferons exert their biological effect by binding to specific receptors on the surface of human cells. After binding, a cascade of intracellular events, including the induction of certain enzymes, occurs. This process is thought to be responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Pegylated interferons have similar, but possibly slightly weaker, actions to the native forms.

Studies have shown interferons to have benefit in infections with hepatitis B virus, hepatitis C virus, herpes simplex viruses, varicella-zoster virus, CMV, rhinoviruses, and papillomaviruses.

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. More than 80% of a subcutaneous or intramuscular dose of interferon alfa is absorbed. After intramuscular injection, interferon alfa produced by recombinant techniques and that from cultured leucocytes produce similar plasma concentrations although there is a large interindividual variation. Plasma concentrations are dose-related; and peak concentrations usually occur within 4 to 8 hours, returning to baseline by 16 to 24 hours. After intravenous doses, serum interferon levels decline at a slightly faster rate than after subcutaneous or intramuscular use and are undetectable 4 hours after infusion. After systemic use low levels of interferon are detected in respiratory secretions, CSF, eye, and brain. The elimination half-life of interferon alfa is about 2 to 7 hours after subcutaneous or intramuscular injections and 2 hours after intravenous infusion. Interferon alfa undergoes renal catabolism and negligible amounts of interferons are excreted in the urine; biliary excretion and liver metabolism are minor pathways of elimination.

The attachment of interferon to large inert macrogol (polyethylene glycol; PEG) molecules, termed pegylation, substantially reduces the rate of absorption and excretion of interferon and increases the plasma concentration. After a subcutaneous dose of peginterferon alfa-2b the maximum serum concentration occurs in about 15 to 44 hours and high concentrations are sustained for 48 to 72 hours; the mean elimination half-life is about 40 hours. The maximum serum concentration of peginterferon alfa-2a occurs about 72 to 96 hours after subcutaneous dosing and the mean terminal half-life is approximately 160 hours. The absolute bioavailability of peginterferon alfa-2a is 84% and is similar to that of unmodified interferon alfa-2a.

Reviews.

1. Zeuzem S, *et al*. Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003; **23** (suppl 1): 23–8.

2. Pedder SC. Pegylation of interferon alfa: structural and pharmacokinetic properties. *Semin Liver Dis* 2003; **23** (suppl 1): 19–22.
3. Caliceti P. Pharmacokinetics of pegylated interferons: what is misleading? *Dig Liver Dis* 2004; **36** (suppl 3): S334–9.
4. Bressler B, *et al*. Pharmacokinetics and response of obese patients with chronic hepatitis C treated with different doses of PEG-IFN alpha-2a (40KD) (PEGASYS). *Br J Clin Pharmacol* 2009; **67:** 280–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avirostat; Bioferon; INF; Infostat; Inter 2-B; Intron A Peg; Pegasys; ***Austral.***: Intron A; Pegasys; PegIntron; Roferon-A; ***Austria***: IntronA; Pegasys; PegIntron; Roferon-A; ***Belg.***: IntronA; Pegasys; PegIntron; Roferon-A; ***Braz.***: Beferon†; Blauferon; Intron A; Kinnoferon 2A; Pegasys; PegIntron; Roferon-A; ***Canad.***: Infergen†; Intron A; Pegasys; Unitron PEG†; ***Chile***: Intermax-Alpha†; IntronA; Pegasys; PegIntron; Roferon-A; ***China***: An Da Fen (安达芬); An Fu Long (安福隆); An Te Fu (安特芙); Bei Er Fen (贝尔芬); Chang Sheng De Jia (长生德佳); Chang Sheng Fu Kang (长生扶康); Chang Sheng Fu Ming (长生扶明); Di En An (迪恩安); Di Ning (滴宁); Fu Li Sheng (复力生); Hapgen (运德素); Infergen (干复津); Intefen (因特芬); Interlong (英特龙); Intron A (甘乐能); Jie Fu (捷抚); Kaifu (凯孚); Lai Fu Long (莱福隆); Li Fen Neng (利分能); Li Ya Mei (里亚美); Longhuanuo (隆化诺); Opin (奥平); Pegasys (派罗欣); PegIntron (佩乐能); Roferon-A (罗尧愫); Sai Ruo Jin (赛若金); Shu Run (淑润); Shuangyinjie (爽因洁); Wan Fu Luo (万复洛); Wan Fu Yin (万复因); Xin Fu Ning (辛复宁); Xin Hua Nuo (辛化诺); Yi Sheng (益生); YiLin (忆林); You Jing An (尤靖安); You Ni Long (尤尼隆); Yuan Ce Su (远策素); ***Cz.***: Alfaferone†; IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; Viraferon†; ViraferonPeg; ***Denm.***: IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; ***Fin.***: IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; ***Fr.***: IntronA; Pegasys; Roferon-A; ViraferonPeg; ***Ger.***: IntronA; Pegasys; PegIntron; Roferon-A; ***Gr.***: Advaferon; Inferax; Infergen; IntronA; Pegasys; PegIntron; Roferon-A; ***Hong Kong***: Intron A; Pegasys; PegIntron; Roferon-A†; ***Hung.***: Egiferon; Intron A; Pegasys; PegIntron; Roferon-A; ***India***: Alferon; Intalfa; Intron A; Intron A; LG Intermax Alpha; Roferon-A; ***Indon.***: Interferon Alfanative†; IntronA; Kalferon; Pegasys; PegIntron; ***Irl.***: IntronA; Pegasys; PegIntron; Roferon-A; ViraferonPeg; ***Israel***: Intron A; Pegasys; PegIntron; Roferon-A; ***Ital.***: Alfaferone; IntronA; Pegasys; PegIntron; Roferon-A; ***Jpn***: Canferon†; OIF; Pegasys; PegIntron; Roferon-A†; Sumiferon; ***Malaysia***: Intron A; Pegasys; PegIntron; Roferon-A; ***Mex.***: Alferon; FNI 2B†; Heberon Alfa; Intron A; Lemeron†; Nisoftat†; Pegasys; Pegtron; Proquiferon; Roferon-A†; Urifron; ***Neth.***: IntronA; Pegasys; PegIntron; Roferon-A; ViraferonPeg; ***Norw.***: IntronA; Multiferon; Pegasys; PegIntron; Roceron; ***NZ***: Intron A; Pegasys; PegIntron; Roferon-A; ***Philipp.***: Intron A; Pegasys; PegIntron; Roferon-A; Shanferon; Uniferon; ***Pol.***: Alfaferone; Intron A; Pegasys; PegIntron; Roferon-A; ViraferonPeg; ***Port.***: Intron A; Pegasys; PegIntron; Roferon-A; Viraferon†; Viraferon-Peg; ***Rus.***: Alfaferone (Альфаферон); Alfarona (Альфарона); Altevir (Альтевир); Infagel (Инфагель); Inferon (Инферон); Interal (Интераль); Intron A (Интрон А); Leucinferon (Лейкинферон); Lifferon (Лайфферон); Locferon (Локферон); Pegasys (Пегасис); PegIntron (Пегинтрон); Reaferon Lipint (Реаферон Липинт); Realdiron (Реальдирон); Roferon-A (Роферон-А); Viferon (Виферон); Wellferon (Вэллферон)†; ***S.Afr.***: Intron A; Multiferon†; Pegasys; PegIntron; Roferon-A; ***Singapore***: Intron A; Pegasys; PegIntron; Roferon-A; ***Spain***: Intron A; Pegasys; PegIntron; Roferon-A; ***Swed.***: IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; ***Switz.***: Cylatron; Intron A; Pegasys; PegIntron; Roferon-A; ***Thai.***: Bioferon; INF†; Intron A; Pegasys; PegIntron; ***Turk.***: Intron A; Pegasys; PegIntron; Roferon-A; ***UK***: IntronA; Pegasys; PegIntron; Roferon-A; Viraferon-Peg; ***Ukr.***: Alfiron (Альфирон); Alpharekin (Альфарекин); Genferon (Генферон); Intron A (Интрон-а); Laferobion (Лаферобион); Laferon (Лаферон); Lipoferon (Липоферон); Nazoferon (Назоферон); Ophthalmoferon (Офтальмоферон); Pegasys (Пегасис); PegIntron (Пегинтрон); Realdiron (Реальдирон); Roferon-A (Роферон-А); Viferon (Виферон); Virogel (Вирогель); ***USA***: Alferon N†; Infergen; Intron A; Pegasys; PegIntron; Sylatron; ***Venez.***: Intron A; Intron; Pegasys; PegIntron; Roferon-A.

Multi-ingredient Preparations. ***Arg.***: Bioferon Hepakit; ***Austral.***: Pegasys RBV; Pegatron; Rebetron†; ***Canad.***: Pegasys RBV; Pegetron; ***Hong Kong***: Rebetron†; ***Mex.***: Hepatron C†; Pegtron Cotronak Kit; ***NZ***: Pegasys RBV; Pegatron; Rebetron†; Roferon-A RBV; ***Philipp.***: Pegasys RBV; ***Rus.***: Genferon (Генферон); Genferon Light (Генферон Лайт); Herpferon (Герпферон); Hyaferone (Гиаферон); Kipferon (Кипферон); Ophtalmoferon (Офтальмоферон); ***Ukr.***: Herpferon (Герпферон)†.

Pharmacopoeial Preparations
BP 2014: Interferon Alfa-2a Injection.

Interferon Beta *(BAN, rINN)*

IFN-β; Interferón-β; Interferon-β; Interferón beta; Interféron Bêta; Interferoni beta; Interferonum Beta; SH-Y-579A (interferon beta-1b); Интерферон Бета.

CAS — 74899-71-1 (interferon beta); 145258-61-3 (interferon beta-1a); 145155-23-3 (interferon beta-1b); 90598-63-3 (interferon beta-1b).

ATC — L03AB02 (natural); L03AB07 (1a); L03AB08 (1b).

ATC Vet — QL03AB02 (natural); QL03AB07 (1a); QL03AB08 (1b).

UNII — XRO4566Q4R (interferon beta-1a); TTD90R31WZ (interferon beta-1b).

NOTE. Interferon beta was previously known as fibroblast interferon.

Interferon beta-1a and Interferon beta-1b are both *USAN*.

Pharmacopoeias. *Eur.* (see p. vii) includes Interferon Beta-1a Concentrated Solution.

Ph. Eur. 8: (Interferon Beta-1a Concentrated Solution). A solution of a glycosylated protein having the same amino acid sequence and disulphide bridge and a similar glycosylation pattern as interferon beta produced by human diploid fibroblasts in response to viral infections and various other inducers. It is produced by a method based on recombinant DNA technology, using mammalian cells in culture. It contains a minimum 0.20 mg of protein per mL, and has a minimum potency of $1.5X10^8$ units per mg of protein. It may contain buffer salts. A clear or slightly opalescent, colourless or slightly yellowish liquid. Store in airtight containers at a temperature below -70 degrees. Protect from light.

Nomenclature. Interferon beta may be derived from fibroblasts, or produced by recombinant DNA technology. Subspecies of the human beta gene produce interferon beta with protein variants designated by a number (as in interferon beta-1). Interferon beta-1 is further qualified by a letter to indicate the amino-acid sequences at positions 1 and 17, and to indicate whether or not glycosylation is present:

- interferon beta-1a has methionine at position 1 and cysteine at 17 and is glycosylated at position 80
- interferon beta-1b has serine at position 17 and is not glycosylated

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rch) indicates production from genetically engineered Chinese hamster ovary cells; (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology.

Uses and Administration

Interferon beta is a cytokine with antiviral and immunomodulating activities. Two forms of interferon beta are available: interferon beta-1a and interferon beta-1b (see Nomenclature, above). Interferon beta is mainly used in the management of relapsing-remitting multiple sclerosis (below), although its mode of action is unclear; pegylated interferon beta-1a is also being investigated. In the UK interferon beta-1b is also licensed for use in secondary progressive multiple sclerosis.

Interferon beta-1a is given in relapsing-remitting multiple sclerosis in a dose dependent upon the formulation used:

- *Avonex* (*Biogen*) is given in a dose of 6 million units (30 micrograms) once weekly by intramuscular injection.
- *Rebif* (*Serono*) is given in an escalating dose over 4 weeks, to 12 million units (44 micrograms) three times weekly by subcutaneous injection, or to 6 million units (22 micrograms) three times weekly by subcutaneous injection in patients unable to tolerate the higher dose.

Interferon beta-1b is given in both relapsing-remitting and in secondary progressive multiple sclerosis in an escalating dose over 3 to 6 weeks to a dose of 8 million units (250 micrograms) on alternate days by subcutaneous injection.

In the UK interferon beta-1a and interferon beta-1b are also indicated for the treatment of patients who have had a single demyelinating event with an active inflammatory process if it is sufficiently severe to warrant intravenous corticosteroids.

Reviews.

1. Goodkin DE. Interferon beta-1b. *Lancet* 1994; **344:** 1057–60.
2. Etheridge LJ, *et al*. The use of interferon beta in relapsing-remitting multiple sclerosis. *Arch Dis Child* 2004; **89:** 789–91.
3. Markowitz CE. Interferon-beta: mechanism of action and dosing issues. *Neurology* 2007; **68** (suppl 4): S8–S11.
4. Bertolotto A, Gilli F. Interferon-beta responders and non-responders: a biological approach. *Neurol Sci* 2008; **29** (suppl 2): S216–S217.
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6. Smith D. Interferon-beta therapy for multiple sclerosis—is the injection site the relevant action site? *J Neuroimmunol* 2009; **215:** 117–21.
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Guillain-Barré syndrome. Rapid improvement in motor function was reported during use of interferon beta-1a in a patient with Guillain-Barré syndrome associated with *Campylobacter jejuni* infection.[1] However, the relative contributions of interferon therapy and a course of plasma exchange that immediately preceded it could not be assessed.[2] Successful treatment of Guillain-Barré syndrome was reported in a patient after interferon beta-1a was added to treatment with intravenous immunoglobulin.[3] A small randomised, placebo-controlled pilot study[4] of subcutaneous interferon beta-1a or placebo, in addition to intravenous immunoglobulin, in patients with Guillain-Barré syndrome reported no significant difference in the rate of improvement.

1. Créange A, *et al*. Treatment of Guillain-Barré syndrome with interferon-β. *Lancet* 1998; **352:** 368.
2. Sawaya RA. Interferon beta for Guillain-Barré syndrome. *Lancet* 1998; **352:** 1550–1.
3. Schaller B, *et al*. Successful treatment of Guillain-Barré syndrome with combined administration of interferon-β-1a and intravenous immunoglobulin. *Eur Neurol* 2001; **46:** 167–8.
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Multiple sclerosis. Multiple sclerosis (MS)[1-4] is a chronic inflammatory and demyelinating disease affecting the CNS. It is the most common disabling neurological disease among young adults and is most often diagnosed in those between the ages of 20 and 40, with women being almost twice as likely to develop it as men. Although the etiology and pathogenesis of MS is poorly understood, it is thought that the disease has an immunological basis and occurs in genetically susceptible individuals. MS is characterised by multiple areas of inflammation and demyelination; activated T-cells enter the CNS and produce an immune cascade resulting in localised loss of myelin, oligodendrocytes, and axons. The resulting lesions (plaques) accumulate over time, with impairment or less electrical transmission along the nerve fibres (axons).

Patients with MS commonly present with an individual mix of **symptoms**, which tend to progress over years to decades. The type and number of symptoms may vary according to the areas affected but typically include bowel and bladder dysfunction, changes in cognitive function, dizziness, depression, fatigue, difficulties with walking and balance, paraesthesias, pain, sexual dysfunction, spasticity, problems with speech and swallowing, tremor, and visual impairment, notably from optic neuritis. Most patients improve to some degree after the initial attack but the course and severity of the disease are unpredictable.

People with MS generally follow one of four clinical **courses** of disease, which in turn may be mild, moderate, or severe. In about 85% of patients the disease follows a *relapsing-remitting course (RR-MS)* in which there are recurrent exacerbations (flare-ups) followed by clinical improvement and relatively long periods of remission. After about 10 to 15 years up to 50% of patients develop progressive neurological deterioration, categorised as *secondary progressive disease (SP-MS)*. However, about 15% of people with RR-MS will have a mild course with little or no disability after 15 years *(benign MS)*. About 10 to 15% of patients present without relapses but have slow continuous deterioration, classified as *primary progressive disease (PP-MS)*. In about 5% of patients the disease is described as *progressive relapsing*; people with this type of MS have steadily worsening disease from the onset but also have acute exacerbations.

Choice of treatment.

Drugs with immunological actions (disease-modifying drugs) have been tried in the treatment of MS itself with the aim of improving recovery from acute attacks, preventing or reducing further attacks (relapses), and halting the progression of the underlying pathology.[5] Different therapies are used for patients having acute attacks, for patients who have RR-MS, for patients who have the progressive subtypes, and for symptomatic management. Combination therapies are also being investigated, particularly in patients who have failed treatment with a single immunomodulatory agent.

Corticosteroids are used for their immunomodulatory and anti-inflammatory effects in acute attacks (relapses). Corticosteroid therapy reduces the duration of the episode and accelerates recovery, but it is unknown whether it alters the course of the disease in the long term.[6] The drug of choice is methylprednisolone; usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days and sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g daily have been tried.[7] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis,[8] although the effect was not sustained beyond 2 years.[9] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[10] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[11] A small clinical study indicated that the bioavailability attained after large doses of oral prednisone may be similar to that of high dose intravenous methylprednisolone.[12] In patients with PP-MS, the benefits of short-course methylprednisolone lasted no longer than 3 months[13] although, in patients with SP-MS, a preliminary study has suggested that progression may be

delayed by intermittent high-dose methylprednisolone therapy.[14]

Interferon beta has become established for treatment of RR-MS in selected patients, and is also used in SP-MS. Studies[15-17] in patients with active RR-MS have shown the efficacy of interferon *beta-1b* given subcutaneously and at different doses. Similar results in RR-MS have been obtained with interferon *beta-1a* given by either subcutaneous or intramuscular routes;[18-20] although comparative studies[21,22] have suggested that subcutaneous interferon beta-1a (44 micrograms given three times a week) is more effective than intramuscular interferon beta-1a (30 micrograms weekly). A prospective, randomised, multicentre study[23] comparing the different frequencies of dosing with interferon beta-1a and beta-1b concluded that high-dose interferon beta-1b given on alternate days was more effective in RR-MS than once-weekly interferon beta-1a. Studies[24-26] in patients presenting with a first demyelinating event (clinically isolated syndrome), or other manifestation of early disease, have shown that treatment with interferon beta may reduce the rate of progression to clinical MS, a view confirmed by a recent systematic review.[27] A 3-year follow-up analysis[28] of one study[26] found that early treatment with interferon beta-1b prevented the development of confirmed disability.

Concern has been expressed over the detection of neutralising antibodies against interferon in up to 46% of patients;[29-31] development of neutralising antibodies correlates with reduced treatment efficacy and the possibility for renewed disease activity. The development of neutralising antibodies is greater in patients treated with higher doses of interferon and in those treated with interferon beta-1b.[32] Recommendations have been made on using antibody titres to guide treatment.[33]

Some encouraging results have also been obtained with interferon beta in patients with SP-MS.[34] However, no effect has been found on disability progression from use of interferon beta (-1a or -1b) in SP-MS[35,36] or PP-MS.[37]

Results of studies[38,39] with *glatiramer* in patients with RR-MS have shown that it can reduce the number of relapses and may produce some improvements in neurological disability. Follow-up of these patients for about 3 years continued to show a beneficial effect on disease relapse rate. MRI data supported the beneficial clinical results.[40,41] When compared, interferon beta-1b and glatiramer acetate had similar clinical efficacy and led to similar suppression of disease activity as shown on monthly brain MRI in patients with RR-MS.[41] These benefits are produced in different ways leading to expectations of possible treatment with both drugs. Early treatment with glatiramer has also been shown to be effective in delaying conversion to clinical multiple sclerosis in patients presenting with clinically isolated syndrome and MRI-detected brain lesions.[42]

Natalizumab is a humanised monoclonal antibody that has been found to decrease the frequency of exacerbations in RR-MS. A 2-year randomised, placebo-controlled study[43] to assess the safety and efficacy of intravenous natalizumab reported a 68% likelihood of remaining relapse-free and a 83% reduction in the number of new or enlarging brain lesions on MRI; the cumulative probability of sustained disability progression was 17% in the natalizumab patient group compared with 29% in the placebo group. Another 2-year study[44] reported that natalizumab plus intramuscular interferon beta-1a was more effective than interferon beta-1a monotherapy. Patients receiving combination therapy were 55% less likely to relapse and had a 83% reduction in the number of new or enlarging brain lesions on MRI compared with monotherapy. A 23% probability of progression of disability was reported for the combination treatment group compared with 29% for interferon alone. Although the combination of natalizumab and glatiramer acetate is considered to be potentially antagonistic, a phase II, randomised, double-blind, placebo-controlled study found that natalizumab added to existing glatiramer acetate therapy, in patients with RR-MS who had had at least one relapse, was well tolerated and showed no apparent loss in efficacy during the 6-month study period.[45] Natalizumab has, however, been associated with an increased risk of progressive multifocal leukoencephalopathy and its use is therefore limited to patients with highly active RR-MS who have had an inadequate response to, or are unable to tolerate, other therapies.

Although some studies have shown modest benefits with *immunosuppressants*, the general conclusions of large controlled studies have tended to be that any slight benefits of existing therapies with immunosuppressants such as azathioprine, ciclosporin, cyclophosphamide, and methotrexate are outweighed by the toxicity of the doses required to have an effect.[46-53] However, a systematic review[54] concluded that azathioprine reduced the number of patients who had relapses and the number who progressed during the first 2 to 3 years of treatment. It considered that azathioprine might be given as an alternative to interferon beta for maintenance treatment for patients who frequently relapse and require corticosteroids. Long-term toxicity (including the risk of malignancy) may be related to cumulative doses above 600 g and treatment for longer than 10 years. Mitoxantrone (given by intravenous infusion) has been studied in patients with RR-, PR-, and SP-MS and found to be moderately effective in reducing disease progression and the frequency of relapses.[55,56] Its use may, however, be limited by dose-related cardiotoxicity and the risk of therapy-related acute leukaemia;[57] it is suggested that mitoxantrone be used to treat patients with rapidly progressive disease or those not responding to high-dose interferon. While most current recognised treatments are only available for parenteral use, fingolimod[58-60] is an oral immunomodulator used to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate, which binds to sphingosine 1-phosphate receptors blocking the emergence of lymphocytes from the lymph nodes thereby reducing the number of lymphocytes into peripheral blood. It is presumed that this reduces the migration of lymphocytes into the CNS. Fingolimod has been shown to reduce relapse rates and improve MRI outcomes in RR-MS compared with intramuscular interferon beta.[60] Teriflunomide is an oral pyrimidine synthesis inhibitor with immunomodulatory effects. It has reduced relapse rates, reduced the risk of disability progression (at the higher dose of 14 mg daily), and improved MRI measures of disease activity in patients with RR-MS.[61] Clinical studies have been carried out with other oral drugs including the immunosuppressants cladribine[62,63] and laquinimod.[64,65] A review[62] of cladribine indicated that it reduced the number of enhancing lesions but also had significantly more adverse effects (including myelosuppression) than placebo. The authors suggested that cladribine might have a role in the treatment of refractory patients with SP-MS. In the randomised, placebo-controlled, multicentre CLARITY study,[63] treatment with oral cladribine significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity at 96 weeks in patients with RR-MS. An increased incidence of lymphocytopenia and herpes zoster was also noted. A phase II placebo-controlled study[64] determined that oral laquinimod (300 micrograms) daily was effective in suppressing development of active lesions in RR-MS and a later study[65] reported that a daily dose of 600 micrograms laquinimod significantly reduced MRI-measured disease activity.

Other immunological approaches evaluated have included the use of monoclonal antibodies such as alemtuzumab, daclizumab, and rituximab, and immunosuppressants such as mycophenolate mofetil. Although alemtuzumab was found to be more effective than interferon beta-1a in patients with early RR-MS, the study had to be stopped early due to 6 cases of immune thrombocytopenic purpura, including one death, in those receiving alemtuzumab.[66] HMG-CoA reductase inhibitors (statins) have immunomodulatory effects and a small study[67] reported that simvastatin significantly decreases the number and volume of new MRI lesions in patients with RR-MS. An open label study in a few patients with RR-MS and breakthrough disease found that adding doxycycline to their current treatment with interferon beta-1a was safe and effective.[68] Dimethyl fumarate is thought to have immunomodulatory and neuroprotective effects, partly through activation of cellular defence against oxidative stress. In placebo-controlled studies[69,70] it has reduced relapse rates and improved some other outcome measures in RR-MS.

A systematic review[71] on the use of intermittent intravenous normal immunoglobulins in patients with RR-MS concluded that there was a reduction in relapse rate and an increased time to relapse, but no evidence that immunoglobulin treatment reduces the progression of MS or reverses existing damage. Intravenous normal immunoglobulins are not effective in SP-MS.[72] Autologous haematopoietic stem cell transplantation has shown benefit in some patients with progressive MS.[73,74]

Guidelines for the management of multiple sclerosis have been produced in the UK,[75,76] the USA,[77] and other countries.[78,79]

Symptomatic treatment.

MS can produce a wide range of symptoms, many of which are manageable; symptomatic treatment is aimed at the management of spasticity, ataxia, tremor, paroxysmal symptoms, pain, fatigue, and bladder dysfunction. Baclofen, dantrolene, diazepam, and tizanidine are the usual drugs given for spasticity (see p. 2014.2). Nabiximols (a mixture of cannabis extracts containing dronabinol and cannabidiol) is used as adjunctive treatment for spasticity and neuropathic pain in multiple sclerosis. While there is some anecdotal evidence to suggest that cannabis and individual cannabinoids, including synthetic cannabinoids such as nabilone, may improve pain and spasticity,[80] a review[81] considered evidence of efficacy to be lacking. Patients with MS can suffer from different types of pain, including pain from spasticity, and therapy must be individualised for each specific pain syndrome (see Choice of Analgesic, p. 4.2). Pain, spasms, and spasticity have responded to gabapentin in preliminary studies.[82-87] A review has noted, however, that the absolute and comparative efficacy and tolerability of anti-spasticity drugs is poorly documented.[88] Paraesthesia and dysaesthesia, which can be common, may respond to tricyclic antidepressants or antiepileptics. Amantadine, modafinil, pemoline, and fampridine have all been investigated for the management of fatigue associated with MS.[89] Treatment of bladder dysfunction may include an alpha blocker such as phenoxybenzamine and appropriate parasympathomimetic or antimuscarinic (such as oxybutynin) therapy to control bladder contractions (see Urinary Incontinence and Retention, p. 2349.2). Fampridine and amifampridine have been reported to produce beneficial symptomatic responses such as improvement in walking, dexterity, and vision, possibly as a result of potassium-channel blocking activity but an early systematic review[90] was unable to come to a conclusion about safety and efficacy, noting that publication bias posed a problem. However, subsequent to positive findings in further multicentre randomised controlled studies, fampridine is licensed for use in patients with MS who have difficulty walking.

Conventional treatments are only partially effective and may produce adverse effects, and many patients with MS try alternative therapies. The most common *dietary interventions* are supplementation with polyunsaturated fatty acids (such as omega-3 and omega-6 fatty acids, often as fish, evening primrose, or sunflower oils), allergen-free diets, vitamins, and micronutrients and antoxidants (such as selenium, ginkgo biloba extracts, and coenzyme Q10). A review of the relationship between these dietary interventions and MS concluded that there was insufficient evidence to determine their benefits or risks.[91] Polyunsaturated fatty acids seem to have no major effect on disease progression and recurrence of exacerbations over 2 years. Research into the value of vitamin D is ongoing after findings that higher levels of serum vitamin D are associated with a lower risk of MS.[92]

The use of *hyperbaric oxygen* therapy in MS was a matter of debate for many years. Some workers reported benefit, especially in bladder and bowel function or in cerebellar function whereas others were unable to substantiate any long-term benefit and reviews have concluded that there is no convincing evidence that hyperbaric oxygen therapy is useful.[93,94]

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92. Munger KL, *et al.* Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296:** 2832–8.
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Rheumatoid arthritis. Preliminary studies suggested that interferon beta might have a beneficial effect on rheumatoid arthritis,[1] the conventional management of which is described on p. 13.2. However, a subsequent randomised, double-blind study[2] found that adding subcutaneous interferon beta to methotrexate treatment in patients with rheumatoid arthritis had no clinical or radiological benefit over adding placebo.

1. van Holten J, *et al.* Interferon-β for treatment of rheumatoid arthritis? *Arthritis Res* 2002; **4:** 346–52.
2. van Holten J, *et al.* A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; **64:** 64–9.

Warts. For the use of interferon beta in the management of warts, see Interferon Alfa, p. 992.1.

Adverse Effects

As for interferons in general (see Interferon Alfa, p. 992.2).

Severe local reactions at injection sites, including tissue necrosis, have been reported. Menstrual irregularities have been associated with interferon beta use. On injection, transient neurological symptoms that may mimic an exacerbation of multiple sclerosis have been reported. In addition transient episodes of hypertonia and/or severe muscular weakness may occur at any time during treatment.

Reviews.
1. Bayas A, Rieckmann P. Managing the adverse effects of interferon-beta therapy in multiple sclerosis. *Drug Safety* 2000; **22:** 149–59.

Auto-immune disorders. Reversible subacute cutaneous lupus erythematosus[1] and SLE[2] have been reported in patients given interferon beta. A case[3] of lupus erythematosus profundus has been reported in a patient after 4 years of treatment with interferon beta-1b for multiple sclerosis; the neurological symptoms and subcutaneous nodules resolved after stopping treatment. There have been case reports of patients developing myasthenia gravis while receiving interferon beta; the patients responded to treatment with pyridostigmine.[4]

1. Nousari HC, *et al.* Subacute cutaneous lupus erythematosus associated with interferon beta-1a. *Lancet* 1998; **352:** 1825–6.
2. Crispín JC, Díaz-Jouanen E. Systemic lupus erythematosus induced by therapy with interferon-β in a patient with multiple sclerosis. *Lupus* 2005; **14:** 495–6.
3. Gono T, *et al.* Lupus erythematosus profundus (lupus panniculitis) induced by interferon-β in a multiple sclerosis patient. *J Clin Neurosci* 2007; **14:** 997–1000.
4. Dionisiotis J, *et al.* Development of myasthenia gravis in two patients with multiple sclerosis following interferon β treatment. *J Neurol Neurosurg Psychiatry* 2004; **75:** 1079.

Effects on the blood. Aplastic anaemia occurred[1] in a patient with multiple sclerosis after treatment with interferon beta-1a for about a year. The interferon was stopped and the patient had a good response to immunosuppressant treatment. The haematological effects of subcutaneous interferon beta-1a in multiple sclerosis patients have been reviewed.[2]

1. Aslam AK, Singh T. Aplastic anemia associated with interferon beta-1a. *Am J Ther* 2002; **9:** 522–3.
2. Rieckmann P, *et al.* Haematological effects of interferon-beta-1a (Rebif) therapy in multiple sclerosis. *Drug Safety* 2004; **27:** 745–56.

Effects on the cardiovascular system. Severe Raynaud's syndrome developed in a patient during treatment with interferon beta.[1] Symptoms subsided once interferon beta was stopped.

1. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.

Effects on the eyes. Interferon beta does not typically cause retinopathy but some cases have been reported, see Interferon Alfa, p. 993.1.

Effects on hearing. For a report of sensorineural hearing loss in patients receiving interferon beta, see Interferon Alfa, p. 993.3.

Effects on the liver. Hepatotoxicity, sometimes severe and in rare cases fatal, has been reported with interferons and its association specifically with the use of interferon beta-1a in multiple sclerosis patients has been reviewed.[1]

1. Francis GS, *et al.* Hepatic reactions during treatment of multiple sclerosis with interferon-β -1a: incidence and clinical significance. *Drug Safety* 2003; **26:** 815–27.

Effects on the skin. Calcified subcutaneous nodules have been reported in a patient after 3 years of treatment with subcutaneous interferon beta-1a for the treatment of multiple sclerosis.[1] For reports of severe necrotising cutaneous lesions at injection sites, and the development of psoriasis, in patients receiving interferon beta, see Interferon Alfa, p. 994.3. See also Auto-immune Disorders, above for a report of cutaneous lupus erythematosus associated with interferon beta.

1. Macbeth AE, *et al.* Calcified subcutaneous nodules: a long-term complication of interferon beta-1a therapy. *Br J Dermatol* 2007; **157:** 624–5.

Precautions

As for interferons in general (see Interferon Alfa, p. 995.1).

Interferon beta in high doses is fetotoxic and abortifacient in *primates* and should be avoided during pregnancy.

Antibody formation. For comment on the formation of neutralising antibodies to interferon beta, and their influence on its efficacy, see Multiple Sclerosis under Uses, p. 996.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies interferon beta-1a and -1b as probably not porphyrinogenic; they may be

used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for interferons in general (see Interferon Alfa, p. 995.2).

Antiviral Action

As for interferons in general (see Interferon Alfa, p. 995.3).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. About 50% of a subcutaneous dose and 40% of an intramuscular dose of interferon beta is absorbed. For some formulations of interferon beta-1a, bioavailability and area under the plasma concentration-time curves are equivalent for subcutaneous and intramuscular dosage, but for others, intramuscular doses produce higher values than subcutaneous doses and subcutaneous doses therefore cannot be substituted for intramuscular doses. Peak serum concentrations of interferon beta-1a have been reported to occur 3 hours after subcutaneous injection and between 3 and 15 hours after intramuscular injection, and those for beta-1b have been reported to occur 1 to 8 hours after subcutaneous injection. The elimination half-life for intramuscular interferon beta-1a is about 10 hours. Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avonex; Betaferon; Blastoferon; Rebif; ***Austral.***: Avonex; Betaferon; Rebif; ***Austria***: Avonex; Betaferon; Extavia; Rebif; ***Belg.***: Avonex; Betaferon; Extavia; Rebif; ***Braz.***: Avonex; Betaferon; Rebif; Serobif†; ***Canad.***: Avonex; Betaseron; Extavia; Rebif; ***Chile***: Avonex; Betaferon; Blastoferon; ***China***: Betaferon (倍泰龙); Rebif (利比); ***Cz.***: Avonex; Betaferon; Extavia; Rebif; ***Denm.***: Avonex; Betaferon; Extavia; Rebif; ***Fin.***: Avonex; Betaferon; Rebif; ***Fr.***: Avonex; Betaferon; Extavia; Rebif; ***Ger.***: Avonex; Betaferon; Extavia; Fiblaferon†; Rebif; ***Gr.***: Avonex; Betaferon; Extavia; Rebif; ***Hong Kong***: Betaferon; Rebif; ***Hung.***: Avonex; Betaferon; Extavia; Rebif; ***India***: Betaferon†; Rebif; ***Indon.***: Betaferon; Rebif; ***Irl.***: Avonex; Betaferon; Extavia; Rebif; ***Israel***: Avonex; Betaferon; Extavia; Rebif; ***Ital.***: Avonex; Betaferon; Extavia; Rebif; Serobif†; ***Jpn***: Feron; ***Malaysia***: Betaferon; Rebif; ***Mex.***: Avonex; Betaferon; Emaxem; Jumtab; Rebif; Uribeta; Xerfelan; ***Neth.***: Avonex; Betaferon; Extavia; Rebif; ***Norw.***: Avonex; Betaferon; Extavia; Rebif; ***NZ***: Avonex; Betaferon; Rebif†; ***Philipp.***: Betaferon; Rebif; ***Pol.***: Avonex; Betaferon; Extavia; Rebif; ***Port.***: Avonex; Betaferon; Extavia; Rebif; ***Rus.***: Avonex (Авонекс); Betaferon (Бетаферон); Extavia (Экставиа); Genfaxon (Генфаксон); Rebif (Ребиф); Ronbetal (Ронбетал); ***S.Afr.***: Avonex; Betaferon; Rebif; ***Singapore***: Betaferon; Rebif; ***Spain***: Avonex; Betaferon; Extavia; Rebif; ***Swed.***: Avonex; Betaferon; Extavia; Rebif; ***Switz.***: Avonex; Betaferon; Rebif; ***Thai.***: Betaferon; Rebif; ***Turk.***: Avonex; Betaferon; Rebif; ***UK***: Avonex; Betaferon; Extavia; Rebif; ***Ukr.***: β-Imunoferon 1a (β-Иммуноферон 1a); β-Imunoferon 1b (β-Иммуноферон 1b); Avonex (Авонекс); Betpher-1a (Бетфер-1a); Betpher-1b (Бетфер-1b); ***USA***: Avonex; Betaseron; Extavia; Rebif; ***Venez.***: Avonex; Rebif.

Interferon Gamma *(BAN, rINN)*

IFN-γ; Interferón-γ; Interferon-γ; Interferón gamma; Interféron gamma; Interferoni gamma; Interferonigamma; Interferonum Gamma; Интерферон Гамма.

CAS — 98059-18-8 (interferon gamma-1a); 98059-61-1 (interferon gamma-1b).

ATC — L03AB03.

ATC Vet — QL03AB03.

UNII — 21K6M2I7AG (interferon gamma-1b).

NOTE. Interferon gamma was previously known as immune interferon.

Interferon gamma-1b is *USAN* and was previously known as interferon gamma-2a.

Pharmacopoeias. *Eur.* (see p. vii) includes Interferon Gamma-1b Concentrated Solution.

Ph. Eur. 8: (Interferon Gamma-1b Concentrated Solution; Interferoni Gamma-1b Solutio Concentrata). It is a solution of the *N*-terminal methionyl form of interferon gamma. It is produced by a method based on recombinant DNA technology using bacteria as host cells. It contains a minimum of $30X10^6$ units/mg of protein. A clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of -70 degrees. Protect from light.

Nomenclature. Interferon gamma may be derived from immunologically stimulated T-lymphocytes (hence its former name of immune interferon) or produced by recombinant DNA technology. Similarly to interferon alfa, protein variants of interferon gamma are designated by a number and further qualified by a letter to indicate the amino-acid sequences at terminal positions 1 and 139:

- interferon gamma-1a has at position 1 hydrogen, cysteine, tyrosine, and cysteine and at position 139 arginine, alanine, serine, glutamine, and a hydroxyl group
- interferon gamma-1b, formerly known as interferon gamma-2a, has at position 1 hydrogen and methionine and at position 139 a hydroxyl group

Interferon gamma derived through recombinant DNA technology is labelled (rbe).

Uses and Administration

Interferon gamma is a cytokine with antiviral and immunomodulating effects. Interferon gamma-1b is used for its action as a macrophage-stimulating factor as an adjunct to antimicrobial therapy in chronic granulomatous disease. It is also used to delay time to disease progression and reduce the frequency of serious infections in patients with severe malignant osteopetrosis.

Interferon gamma-1b is given in a dose of 50 micrograms/m^2 body-surface (1 million units/m^2) three times weekly by subcutaneous injection. Patients with a body-surface less than 0.5 m^2 should receive 1.5 micrograms/kg three times weekly.

Interferon gamma-1b is also under investigation for the treatment of idiopathic pulmonary fibrosis (see below).

Interferon gamma-n1 has also been used for the treatment of cutaneous T-cell lymphomas.

Reviews.

1. Marciano BE, *et al.* Long-term interferon-γ therapy for patients with chronic granulomatous disease. *Clin Infect Dis* 2004; **39:** 692–9.
2. Errante PR, *et al.* The use of interferon-gamma therapy in chronic granulomatous disease. *Recent Pat Antiinfect Drug Discov* 2008; **3:** 225–30.
3. Hastie C. Interferon gamma, a possible therapeutic approach for late-stage prostate cancer? *Anticancer Res* 2008; **28:** 2843–9.
4. Miller CH, *et al.* Clinical use of interferon-gamma. *Ann N Y Acad Sci* 2009; **1182:** 69–79.
5. Kane A, Yang I. Interferon-gamma in brain tumor immunotherapy. *Neurosurg Clin N Am* 2010; **21:** 77–86.

Bacterial infections. In addition to its use to control infections in chronic granulomatous disease, interferon gamma was used with some success as an adjunct to antibacterials in a patient with Whipple's disease[1] but was of no benefit in a study in burn-related infections.[2] For the conventional management of these infections, see Whipple's Disease, p. 213.3 and Skin Infections, p. 207.1.

1. Schneider T, *et al.* Treatment of refractory Whipple disease with interferon-γ. *Ann Intern Med* 1998; **129:** 875–7.
2. Wasserman D, *et al.* Interferon-γ in the prevention of severe burn-related infections: a European phase III multicenter trial. *Crit Care Med* 1998; **26:** 434–9.

MYCOBACTERIAL INFECTIONS. Experience with interferons for *nontuberculous mycobacterial infections* in patients with AIDS is limited. Interferon gamma given with antimycobacterials has produced beneficial responses in patients with *Mycobacterium avium* complex infections, but produced no response or only a transient response in others given interferon gamma alone.[1-3] Benefit has been see when combined with interleukin-2.[4]

Beneficial responses have also been reported after use of interferon alfa[5] or gamma[6,7] as an adjunct to antimycobacterial therapy in HIV-negative patients with mycobacterial infections unresponsive to conventional therapy. Interferon alfa has been tried as an adjunct to conventional therapy in *multibacillary leprosy*.[8]

Inhaled interferon alfa[9] or gamma[10] may be a useful adjunct to conventional antimycobacterial treatment for *pulmonary tuberculosis*.

For discussion of these infections and their standard treatment, see Leprosy, p. 188.3, Nontuberculous Mycobacterial Infections, p. 194.1, and Tuberculosis, p. 210.2.

1. Squires KE, *et al.* Interferon-γ and Mycobacterium avium-intracellulare infection. *J Infect Dis* 1989; **159:** 599–600.
2. Squires KE, *et al.* Interferon-γ treatment for Mycobacterium avium-intracellulare complex bacillemia in patients with AIDS. *J Infect Dis* 1992; **166:** 686–7.
3. Lauw FN, *et al.* No beneficial effect of interferon-gamma treatment in 2 human immunodeficiency virus-infected patients with Mycobacterium avium complex infection. *Clin Infect Dis* 2001; **32:** e81–e82.
4. Sekiguchi Y, *et al.* Effective combination therapy using interferon-gamma and interleukin-2 for disseminated Mycobacterium avium complex infection in a pediatric patient with AIDS. *Clin Infect Dis* 2005; **41:** e104–e106.
5. Maziarz RT, *et al.* Reversal of infection with Mycobacterium avium intracellulare by treatment with alpha-interferon in a patient with hairy cell leukemia. *Ann Intern Med* 1988; **109:** 292–4.
6. Holland SM, *et al.* Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma: a preliminary report. *N Engl J Med* 1994; **330:** 1348–55.
7. Milanés-Virelles MT, *et al.* Adjuvant interferon gamma in patients with pulmonary atypical mycobacteriosis: a randomized, double-blind, placebo-controlled study. *BMC Infect Dis* 2008; **8:** 17. Available at: http://www.biomedcentral.com/content/pdf/1471-2334-8-17.pdf (accessed 26/01/10)
8. Ganapati R, *et al.* A multicenter study of recombinant interferon-alpha2b in the treatment of multibacillary leprosy. *Int J Lepr* 1997; **65:** 495–7.
9. Giosuè S, *et al.* Effects of aerosolized interferon-α in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 1998; **158:** 1156–62.
10. Condos R, *et al.* Treatment of multidrug-resistant pulmonary tuberculosis with interferon-γ via aerosol. *Lancet* 1997; **349:** 1513–15.

Idiopathic pulmonary fibrosis. In a preliminary study[1] in patients with idiopathic pulmonary fibrosis (IPF; see Interstitial Lung Disease, p. 1607.1) who had not responded to treatment with corticosteroids or to other immunosuppressive therapy, lung capacity increased in 9 patients given interferon gamma-1b with prednisolone for 12 months, but deteriorated in 9 who were treated with prednisolone alone for the same period. The study was, however, criticised for its methodology and the statistical significance of its findings questioned.[2] A later study[3] involving 330 patients with IPF found that interferon gamma-1b did not affect progression-free survival or pulmonary function; however, a trend toward lower mortality was seen in patients who received interferon gamma-1b compared with those given placebo. A subsequent study[4] to characterise the molecular effects of subcutaneous interferon gamma-1b versus placebo reported that interferon gamma-1b affected IPF through multiple pathways and could be of potential benefit. A randomised, prospective study[5] comparing interferon gamma-1b and colchicine (given for 24 months) in patients with mild-to-moderate IPF reported that 15.6% of patients treated with interferon gamma-1b and 38.8% of those given colchicine died. Patients treated with interferon gamma-1b also showed a higher forced vital capacity after 24 months of treatment. A review[6] of the use of interferon gamma-1b in the management of CFA found that efficacy of interferon gamma-1b was inconsistent with regard to changes in pulmonary function and mortality, although studies suggested that interferon gamma-1b may be of benefit in earlier-stage disease. A meta-analysis[7] of randomised controlled studies evaluating the use of interferon gamma-1b in the treatment of IPF concluded that interferon gamma-1b therapy was associated with reduced mortality. However, a later large randomised, placebo-controlled study,[8] to assess the effect of interferon gamma-1b on survival in patients with IPF and mild to moderate impairment in their baseline pulmonary function, had to be stopped early after the second interim analysis; after a median treatment duration of 64 weeks, 15% (80/551) of patients on interferon gamma-1b and 13% (35/275) of those on placebo had died.

1. Ziesche R, *et al.* A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 1999; **341:** 1264–9.
2. King TE. Interferon gamma-1b for the treatment of idiopathic pulmonary fibrosis. *N Engl J Med* 2000; **342:** 974–5.
3. Raghu G, *et al.* A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004; **350:** 125–33.
4. Strieter RM, *et al.* Effects of interferon-γ 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; **170:** 133–40.
5. Antoniou KM, *et al.* Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; **28:** 496–504.
6. Pacanowski MA, Amsden GW. Interferon gamma-1b in the treatment of idiopathic pulmonary fibrosis. *Ann Pharmacother* 2005; **39:** 1678–86.
7. Bajwa EK, *et al.* Interferon-γ 1b therapy in idiopathic pulmonary fibrosis: a metaanalysis. *Chest* 2005; **128:** 203–6.
8. King TE, *et al.* Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; **374:** 222–8.

Leishmaniasis. Interferon gamma has been tried both systemically and locally as an adjunct to standard treatment of leishmaniasis (p. 922.1) with encouraging results. A review[1] of the use of interferon gamma in non-viral infections concluded that interferon gamma was effective when combined with antimony compounds for treatment failures in visceral leishmaniasis (p. 923.1) and could enhance the response to initial therapy in untreated patients. However, the response to adjunctive interferon gamma was limited in patients with a high degree of resistance to antimony compounds.[2] For cutaneous infections (p. 922.1), intralesional interferon gamma has been shown to be effective[3] but less so than intralesional antimony compounds.[4] Subcutaneous interferon gamma (with antimony given intravenously) was no more effective than antimony alone when given as a short course over 10 days.[5] However, encouraging responses have been reported in patients who have failed to respond to antimony compounds alone.[6]

1. Murray HW. Interferon-gamma and host antimicrobial defense: current and future clinical applications. *Am J Med* 1994; **97:** 459–67.
2. Sundar S, *et al.* Response to interferon-γ plus pentavalent antimony in Indian visceral leishmaniasis. *J Infect Dis* 1997; **176:** 1117–19.
3. Harms G, *et al.* Effects of intradermal gamma-interferon in cutaneous leishmaniasis. *Lancet* 1989; **i:** 1287–92.
4. Harms G, *et al.* A randomized trial comparing a pentavalent antimonial drug and recombinant interferon-γ in the local treatment of cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1991; **85:** 214–16.
5. Arana BA, *et al.* Efficacy of a short course (10 days) of high-dose meglumine antimonate with or without interferon-γ in treating cutaneous leishmaniasis in Guatemala. *Clin Infect Dis* 1994; **18:** 381–4.
6. Falcoff E, *et al.* Clinical healing of antimony-resistant cutaneous or mucocutaneous leishmaniasis following the combined administration of interferon-γ and pentavalent antimonial compounds. *Trans R Soc Trop Med Hyg* 1994; **88:** 95–7.

Osteopetrosis. Interferon gamma has been tried in the treatment of malignant osteopetrosis (p. 1609.3). A study[1] in 14 patients found that interferon gamma-1b increased bone resorption. In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

1. Key LL, *et al.* Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med* 1995; **332:** 1594–9.

Skin disorders. Interferons have been tried in skin disorders in which IgE levels are raised. Subcutaneous interferon gamma improved *eczema* and reduced serum-IgE concentration in one patient, but the condition gradually returned within a week of stopping treatment.[1] In two studies[2,3] subcutaneous interferon gamma given to patients with severe atopic dermatitis and raised serum-IgE concentrations resulted in improvement of the skin condition; IgE concentrations were reduced in one study[2] but remained high in the other.[3] Subcutaneous interferon alfa, however, was unsuccessful in 2 patients with very severe atopic dermatitis; serum-IgE concentrations and severity of the skin condition remained unaffected.[4] Interferon alfa has been tried in subacute *cutaneous lupus erythematosus*[5,6] and *discoid lupus erythematosus*.[6] Although marked improvement generally occurred, the condition tended to recur within several weeks of stopping treatment. For discussion of the conventional treatment of eczema, see p. 1684.1 and of lupus erythematosus, see Systemic Lupus Erythematosus, p. 1613.3.

There have been reports[7,8] of the successful use of interferon alfa to control the symptoms of *urticaria* associated with mastocytosis (p. 1226.3).

Interferons have also been proposed for antifibrotic therapy in the management of diffuse *scleroderma* (see p. 1942.3). A multicentre study of interferon gamma in scleroderma[9] found that cutaneous symptoms might be improved but that treatment was associated with an unacceptable incidence of adverse effects. Interferon gamma has also been tried in *eosinophilic pustular folliculitis*.[10]

Interferons have also been used for the treatment of warts (see under Interferon Alfa, p. 992.1).

1. Souillet G, *et al.* Alpha-interferon treatment of patient with hyper IgE syndrome. *Lancet* 1989; **i:** 1384.
2. Reinhold U, *et al.* Recombinant interferon-γ in severe atopic dermatitis. *Lancet* 1990; **335:** 1282.
3. Boguniewicz M, *et al.* Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. *Am J Med* 1990; **88:** 365–70.
4. MacKie RM. Interferon-α for atopic dermatitis. *Lancet* 1990; **335:** 1282–3.
5. Nicolas J-F, Thivolet J. Interferon alfa therapy in severe unresponsive subacute cutaneous lupus erythematosus. *N Engl J Med* 1989; **321:** 1550–1.
6. Thivolet J, *et al.* Recombinant interferon α 2a is effective in the treatment of discoid and subacute cutaneous lupus erythematosus. *Br J Dermatol* 1990; **122:** 405–9.
7. Kolde G, *et al.* Treatment of urticaria pigmentosa using interferon alpha. *Br J Dermatol* 1995; **133:** 91–4.
8. Lippert U, Henz BM. Long-term effect of interferon alpha treatment in mastocytosis. *Br J Dermatol* 1996; **134:** 1164–5.
9. Polisson RP, *et al.* A multicenter trial of recombinant human interferon gamma in patients with systemic sclerosis: effects on cutaneous fibrosis and interleukin 2 receptor levels. *J Rheumatol* 1996; **23:** 654–8.
10. Fushimi M, *et al.* Eosinophilic pustular folliculitis effectively treated with recombinant interferon-γ: suppression of mRNA expression of interleukin 5 in peripheral blood mononuclear cells. *Br J Dermatol* 1996; **134:** 766–72.

Adverse Effects

As for interferons in general (see Interferon Alfa, p. 992.2)

Precautions

As for interferons in general (see Interferon Alfa, p. 995.1). Interferon gamma in high doses has been shown to increase the incidence of abortions in *primates* and should be avoided during pregnancy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies interferon gamma as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for interferons in general (see Interferon Alfa, p. 995.2).

Antiviral Action

As for interferons in general (see Interferon Alfa, p. 995.3).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. Peak plasma concentrations of interferon gamma-1b occur about 4 hours after intramuscular injection and about 7 to 8 hours after subcutaneous injection. Half-lives of 38 minutes (intravenous dosage), 2.9 hours (intramuscular dosage), and 4.9 to 5.9 hours (subcutaneous dosage) have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Imukin; ***Austral.:*** Imukin; ***Austria***: Imukin; ***Belg.***: Immukine; ***China***: Gama (伽玛); Lizhu Yindefu (丽珠因得福); Shang Sheng Lei Tai (上生雷泰); ***Cz.:*** Imukin†; ***Denm.:*** Imukin; ***Fin.:*** Imukin; ***Fr.:*** Imukin; ***Ger.:*** Imukin; ***Gr.:*** Imukin; ***Hong Kong***: Immukin; ***Hung.:*** Imukin; ***Irl.:*** Immukin; ***Ital.:*** Imukin; ***Jpn***: Biogamma†; ***Neth.:*** Immukine; Imukin†; ***Norw.:*** Imukin; ***NZ***: Imukin; ***Port.:*** Imukin; ***Rus.:*** Ingaron (Ингарон); ***Singapore***: Imukin; ***Spain***: Imukin; ***Swed.:*** Imukin; ***Switz.:*** Imukin; ***UK***: Immukin; ***USA***: Actimmune.

Lamivudine *(BAN, USAN, rINN)*

3TC; GR-109714X; Lamivudiini; Lamivudin; Lamivudina; Lamivudinum; Lamivudyna; Lavmivudin; Ламивудин; (-)-2′-Deoxy-3′-thiacytidine.

(-)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

$C_8H_{11}N_3O_3S$=229.3

CAS — 131086-21-0; 134678-17-4.

ATC — J05AF05.

ATC Vet — QJ05AF05.

UNII — 2T8Q726O95.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Lamivudine). A white or almost white powder. It exhibits polymorphism. Soluble in water, slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Lamivudine). A white to off-white solid. Soluble in water. Protect from light.

Uses and Administration

Lamivudine is a nucleoside reverse transcriptase inhibitor structurally related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used orally in the treatment of HIV infection and AIDS, (p. 957.2) and chronic hepatitis B infection (p. 952.1). Viral resistance emerges rapidly when lamivudine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

For **HIV infection**, the dose of lamivudine for adults is 300 mg daily as a single dose or in two divided doses.

For chronic **hepatitis B**, the adult dose is 100 mg once daily. In patients with concomitant HIV and hepatitis B infection the dosage regimen appropriate for HIV should be used.

For details of doses in infants, children, and adolescents see below.

Reduction of dosage is recommended for patients with renal impairment (see below).

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing lamivudine in combination with zidovudine or abacavir and with abacavir plus zidovudine are available in some countries.

Reviews.

1. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; **65:** 285–302.
2. Shey M, *et al.* A combination drug of abacavir-lamivudine-zidovudine (Trizivir) for treating HIV infection and AIDS. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 14/10/09).
3. Somboonwit C, *et al.* Abacavir and lamivudine combination. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1599–1606.
4. Kumar PN, Patel P. Lamivudine for the treatment of HIV. *Expert Opin Drug Metab Toxicol* 2010; **6:** 105–14.
5. Achenbach CJ, *et al.* Abacavir/lamivudine fixed-dose combination antiretroviral therapy for the treatment of HIV. *Adv Therapy* 2010; **27:** 1–16. Correction. *ibid.*; 127.

Administration in children. For the treatment of **HIV infection** in infants and children lamivudine is given orally either as tablets or a solution, with other antiretroviral drugs. Doses are based on body-weight:

- in infants and children over 3 months of age and weighing less than 14 kg or in those unable to swallow tablets the oral solution may be given in a dose of 4 mg/kg twice daily to a maximum daily dose of 300 mg
- in children weighing 14 to 21 kg the tablet formulation may be given in a dose of 75 mg twice daily
- in children weighing 21 to 30 kg the tablet formulation may be given in a dose of 75 mg in the morning and 150 mg at night
- in children weighing over 30 kg the tablet formulation may be given in a dose of 150 mg twice daily

The *BNFC* states that children 1 to 3 months old may be given 4 mg/kg twice daily and that for older children the total daily doses cited above may be given as a single dose once daily.

Dosage of lamivudine should be reduced in HIV-infected patients (at least 3 months of age and weighing less than 30 kg) with moderate to severe *renal impairment* (creatinine clearance (CC) below 50 mL/minute):

- CC 30 to 49 mL/minute: 4 mg/kg for the first dose then 4 mg/kg once daily
- CC 15 to 29 mL/minute: 4 mg/kg for the first dose then 2.6 mg/kg once daily
- CC 5 to 14 mL/minute: 4 mg/kg for the first dose then 1.3 mg/kg once daily
- CC less than 5 mL/minute: 1.3 mg/kg for the first dose then 700 micrograms/kg once daily

For the treatment of chronic **hepatitis B** infection in children and adolescents aged between 2 and 17 years, US licensed product information recommends an oral dose of lamivudine of 3 mg/kg once daily to a maximum daily dose of 100 mg. Dosage reduction would need to be considered in those with renal impairment. UK licensed product information does not recommend the use of lamivudine for the treatment of chronic hepatitis B in those under 17 years of age.

Administration in renal impairment. Dosage of lamivudine should be reduced in patients with moderate to severe renal impairment (creatinine clearance (CC) below 50 mL/minute).

adults: HIV infection:

- CC 30 to 49 mL/minute: 150 mg for the first dose then 150 mg once daily
- CC 15 to 29 mL/minute: 150 mg for the first dose then 100 mg once daily
- CC 5 to 14 mL/minute: 150 mg for the first dose then 50 mg once daily
- CC less than 5 mL/minute: 50 mg for the first dose then 25 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

adults: chronic hepatitis B infection:

- CC 30 to 49 mL/minute: 100 mg for the first dose then 50 mg once daily
- CC 15 to 29 mL/minute: 100 mg for the first dose then 25 mg once daily
- CC 5 to 14 mL/minute: 35 mg for the first dose then 15 mg once daily
- CC less than 5 mL/minute: 35 mg for the first dose then 10 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

children:

- see Administration in Children, above

Hepatitis. Lamivudine is one of the antivirals being used as an alternative to interferon alfa in the treatment of chronic hepatitis B (p. 952.1).[1-3] In a preliminary study, lamivudine 100 or 300 mg daily reduced hepatitis B virus DNA to low or undetectable levels.[4] In a 1-year double-blind study involving about 350 patients with chronic hepatitis B, lamivudine 100 mg daily was associated with substantial histological improvement in many patients; a dose of 25 mg daily was less effective.[5] Relapses have been reported once treatment with lamivudine is stopped, and a case of reactivation of hepatitis B infection has been reported.[6] Lamivudine has also been used[7] with thymalfasin (p. 2630.1); the combination may be more effective than lamivudine alone. Lamivudine may also be effective in preventing re-infection with hepatitis B in patients during chemotherapy[8-10] and in those who have had liver transplants,[11,12] and beneficial responses have been seen in transplant patients with acute hepatitis B infection treated with lamivudine 100 mg daily for prolonged periods.[13]

1. Dienstag JL, *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **341:** 1256–63.
2. Hagmeyer KO, Pan Y-Y. Role of lamivudine in the treatment of chronic hepatitis B virus infection. *Ann Pharmacother* 1999; **33:** 1104–12.
3. Jonas MM, *et al.* Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; **346:** 1706–13. Correction. *ibid.*; **347:** 955.
4. Dienstag JL, *et al.* A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995; **333:** 1657–61.
5. Lai C-L, *et al.* A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998; **339:** 61–8.
6. Honkoop P, *et al.* Hepatitis B reactivation after lamivudine. *Lancet* 1995; **346:** 1156–7.
7. Zhang YY, *et al.* Treatment with lamivudine versus lamivudine and thymosin alpha-1 for e antigen-positive chronic hepatitis B patients: a meta-analysis. *Virol J* 2009; **6:** 63.
8. Yeo W, *et al.* Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 2004; **22:** 927–34.
9. Idilman R. Lamivudine prophylaxis in HBV carriers with haemato-oncological malignancies who receive chemotherapy. *J Antimicrob Chemother* 2005; **55:** 828–31.
10. Loomba R, *et al.* Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148:** 519–28. Correction. *ibid.* 2009; **150:** 657–8.
11. Grellier L, *et al.* Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996; **348:** 1212–15. Correction. *ibid.* 1997; **349:** 364.

12. Perrillo RP, *et al.* A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; **33:** 424–32.
13. Andreone P, *et al.* Lamivudine treatment for acute hepatitis B after liver transplantation. *J Hepatol* 1998; **29:** 985–9.

HIV infection and AIDS. Lamivudine is a potent inhibitor of HIV-1 and HIV-2 *in vitro*, including variants resistant to zidovudine.[1] Resistance emerges rapidly when lamivudine is given alone to patients with HIV infections,[2] although sustained responses have been reported despite the emergence of resistance.[3] As discussed on p. 957.2, NRTIs, including lamivudine, are now used in combination antiretroviral drug regimens for the management of HIV infection, typically with one other NRTI and either a NNRTI or an HIV-protease inhibitor.

Lamivudine is also used in prophylactic regimens after occupational exposure to HIV infection and has been tried for reducing vertical transmission from mother to neonate;[4,5] for further information see p. 959.1.

1. Anonymous. Lamivudine: impressive benefits in combination with zidovudine. *WHO Drug Inf* 1996; **10:** 5–7.
2. Wainberg MA, *et al.* Development of HIV-1 resistance to (-)2′-deoxy-3′-thiacytidine in patients with AIDS or advanced AIDS-related complex. *AIDS* 1995; **9:** 351–7.
3. Ingrand D, *et al.* Phase I/II study of 3TC (lamivudine) in HIV-positive, asymptomatic or mild AIDS-related complex patients: sustained reduction in viral markers. *AIDS* 1995; **9:** 1323–9.
4. Mandelbrot L, *et al.* Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; **285:** 2083–93.
5. The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002; **359:** 1178–86.

Adverse Effects

Lamivudine is generally very well tolerated. However, adverse effects that may be associated with lamivudine either as monotherapy or with other antiretrovirals for the treatment of HIV include abdominal pain, nausea, vomiting, diarrhoea, headache, fever, rash, alopecia, malaise, insomnia, cough, nasal symptoms, arthralgia, and musculoskeletal pain. There have also been reports of pancreatitis, anaemia, neutropenia, and thrombocytopenia. Increases in liver enzymes and serum amylase may occur. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been reported during treatment with nucleoside reverse transcriptase inhibitors.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including lamivudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including lamivudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia, but this may be less likely with lamivudine than with other NRTIs such as didanosine, stavudine, or zalcitabine. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Patients taking a lower dose of lamivudine for the treatment of chronic hepatitis B often have abdominal discomfort and pain, diarrhoea, fatigue, headache, nausea, malaise, respiratory-tract infections, and vomiting. The most frequently reported laboratory abnormalities are elevated creatine phosphokinase, increases in serum lipase, and raised liver enzymes, in particular alanine aminotransferase. There have been rare reports of lactic acidosis, pancreatitis, and muscle disorders such as cramps, myalgia, and rhabdomyolysis.

Effects on the blood. Although anaemia associated with lamivudine usually occurs when it is used with zidovudine, there has been a report[1] of severe anaemia in a 62-year-old HIV-infected man given lamivudine alone.

1. Weitzel T, *et al.* Severe anaemia as a newly recognized side-effect caused by lamivudine. *AIDS* 1999; **13:** 2309–11.

Effects on the hair. Hair loss was associated with lamivudine treatment in 5 patients.[1]

1. Fong IW. Hair loss associated with lamivudine. *Lancet* 1994; **344:** 1702.

Effects on the nervous system. Exacerbation of peripheral neuropathy has been reported in a patient after substitution of lamivudine for zalcitabine.[1] A severe exacerbation, associated with mitochondrial toxicity and eventual death, has also been reported in a patient with previously mild neuropathy, occurring 3 months after starting lamivudine for treatment of hepatitis.[2]

1. Cupler EJ, Dalakas MC. Exacerbation of peripheral neuropathy by lamivudine. *Lancet* 1995; **345:** 460–1.
2. Fodale V, *et al.* Fatal exacerbation of peripheral neuropathy during lamivudine therapy: evidence for iatrogenic mitochondrial damage. *Anaesthesia* 2005; **60:** 806–10.

Hypersensitivity. Angioedema, urticaria, and anaphylactoid reaction occurred in a patient 30 minutes after receiving the first dose of lamivudine.[1]

1. Kainer MA, Mijch A. Anaphylactoid reaction, angioedema, and urticaria associated with lamivudine. *Lancet* 1996; **348:** 1519.

Precautions

Lamivudine therapy should be stopped in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded.

Treatment with lamivudine may be associated with lactic acidosis and should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, or metabolic or lactic acidosis of unknown aetiology. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Patients co-infected with HIV and chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In patients with chronic hepatitis B, there is a risk of rebound hepatitis when lamivudine is stopped, and liver function should be monitored in such patients. The possibility of HIV infection should be excluded before beginning lamivudine therapy for hepatitis B, since the lower doses used to treat the latter may permit the development of lamivudine-resistant strains of HIV.

Dosage reduction may be necessary in patients with impaired renal function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lamivudine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

The renal excretion of lamivudine may be inhibited by other drugs mainly eliminated by active renal secretion, for example trimethoprim. Usual prophylactic doses of trimethoprim are unlikely to necessitate reductions in lamivudine dosage unless the patient has renal impairment, but the co-administration of lamivudine with the high doses of trimethoprim (as co-trimoxazole) used in pneumocystis pneumonia and toxoplasmosis should be avoided. Although there is usually no clinically significant interaction with zidovudine, severe anaemia has occasionally been reported in patients given lamivudine with zidovudine (see Zidovudine, Interactions, p. 1026.3). Lamivudine may antagonise the antiviral action of zalcitabine and the two drugs should not be used together. Once daily triple nucleoside regimens of lamivudine and tenofovir with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should be avoided.

Antineoplastics. For a reported interaction between lamivudine and *cladribine*, see p. 769.2.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals, see Stavudine, p. 1016.2.

Antiviral Action

Lamivudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Lamivudine is also active against hepatitis B virus. Resistance to lamivudine has been reported in isolates of HIV and hepatitis B virus.

Pharmacokinetics

Lamivudine is rapidly absorbed after oral doses and peak plasma concentrations occur in about 1 hour. Absorption is delayed, but not reduced, by ingestion with food. Bioavailability is between 80 and 87%. Binding to plasma protein is reported to be up to 36%. Lamivudine crosses the blood-brain barrier with a ratio of CSF to serum concentrations of about 0.12. It crosses the placenta and is distributed into breast milk.

Lamivudine is metabolised intracellularly to the active antiviral triphosphate. Hepatic metabolism is low and it is cleared mainly unchanged by active renal excretion. An elimination half-life of 5 to 7 hours has been reported after a single dose.

References.
1. Mueller BU, *et al.* Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1998; **42:** 3187–92.
2. Johnson MA, *et al.* Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet* 1999; **36:** 41–66.
3. Bruno R, *et al.* Comparison of the plasma pharmacokinetics of lamivudine during twice and once daily administration in patients with HIV. *Clin Pharmacokinet* 2001; **40:** 695–700.
4. Asari A, *et al.* Pharmacokinetics of lamivudine in subjects receiving peritoneal dialysis in end-stage renal failure. *Br J Clin Pharmacol* 2007; **64:** 738–44.
5. Burger DM, *et al.* Age-dependent pharmacokinetics of lamivudine in HIV-infected children. *Clin Pharmacol Ther* 2007; **81:** 517–20.
6. Tremoulet AH, *et al.* Pediatric AIDS Clinical Trials Group. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; **51:** 4297–4302.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: 3TC; Amilitrap; Ganvirel; Heptodine; Imunoxa†; Kess; Lamibergen; Lamilea; Oralmuv; Ultraviral†; Vuclodir; ***Austral.***: 3TC; Zeffix; ***Austria***: Epivir; Zeffix; ***Belg.***: Epivir; Zeffix; ***Braz.***: Epivir; Lami; Vudirax; ***Canad.***: 3TC; Heptovir; ***Chile***: 3TC/Epivir; ***China***: Epivir (益平维); Heptodin (贺普丁); ***Cz.***: Epivir; Zeffix; ***Denm.***: Epivir; Zeffix; ***Fin.***: Epivir; Zeffix; ***Fr.***: Epivir; Zeffix; ***Ger.***: Epivir; Kivexa; Zeffix; ***Gr.***: Epivir; Zeffix; ***Hong Kong***: 3TC; Zeffix; ***Hung.***: Epivir; Zeffix; ***India***: Hepavud; Hepitec; Ladiwin; Lamda; Lami; Lamidac; Lamivir; Lamivox; Lamuvid; Lavir; Lazid; ***Indon.***: 3TC-HBV; 3TC; ***Irl.***: Epivir; Zeffix; ***Israel***: Epivir; Zeffix; ***Ital.***: Epivir; Zeffix; ***Jpn***: Epivir; ***Malaysia***: 3TC; Zeffix; ***Mex.***: 3TC; ***Neth.***: Epivir; Zeffix; ***Norw.***: Epivir; Zeffix; ***NZ***: 3TC; Zeffix; ***Philipp.***: Zeffix; ***Pol.***: Epivir; Zeffix; ***Port.***: Epivir; Zeffix; ***Rus.***: Epivir (Эпивир); Zeffix (Зеффикс); ***S.Afr.***: 3TC; Legram; ***Singapore***: Epivir; Zeffix; ***Spain***: Epivir; Zeffix; ***Swed.***: Epivir; Zeffix; ***Switz.***: 3TC; Zeffix; ***Thai.***: Epivir; Lahep; Lamivir; Zeffix; ***Turk.***: Epivir; Medovir; Mivux; Zeffix; Zefomen; ***UK***: Epivir; Zeffix; ***USA***: Epivir; ***Venez.***: Epivir; Lamivir.

Multi-ingredient Preparations. ***Arg.***: 3TC Complex; 3TC/AZT†; Ganvirel Duo; Imunoxa Complex†; Kess Complex; Kivexa; Lazinevir; Muvidina; Tricivir; Trilaxis; Trivudin; Ultraviral Duo†; Zetavudin; Zidomuv; ***Austral.***: Combivir; Kivexa; Trizivir; ***Austria***: Combivir; Kivexa; Trizivir; ***Belg.***: Combivir; Kivexa; Trizivir; ***Braz.***: Biovir; Kivexa; Zidolam; ***Canad.***: Combivir; Kivexa; Trizivir; ***Chile***: Combivir; Kivexa; Tricivir; ***China***: Combivir (双汰芝); Trizivir (三协唯); ***Cz.***: Combivir; Kivexa; Trizivir; ***Denm.***: Combivir; Kivexa; Trizivir; ***Fin.***: Combivir; Kivexa; Trizivir; ***Fr.***: Combivir; Kivexa; Trizivir; ***Ger.***: Combivir; Trizivir; ***Gr.***: Combivir; Kivexa; Trizivir; ***Hong Kong***: Combivir; Kivexa; Trizivir; ***Hung.***: Combivir; Kivexa; Trizivir; ***India***: Combivir; Cytocom-E; Cytocom-N; Cytocom; Duovir N; Duovir-E; Duovir; Emduo-E; Emduo-N; Emduo; Emtri; Lamda-Z; Lami Plus; Lamivir S; Lamostad-N; Lamostad; Lamsyn-Z; Lamuzid; Lazid-E; Lazid-N; Odivir Kit; Triomune; ***Irl.***: Combivir; Kivexa; Trizivir; ***Israel***: Combivir; Kivexa; Trizivir; ***Ital.***: Combivir; Kivexa; Trizivir; ***Malaysia***: Combivir; ***Mex.***: Combivir; Kivexa; Trizivir; ***Neth.***: Combivir; Kivexa; Trizivir; ***Norw.***: Combivir; Kivexa; Trizivir; ***NZ***: Combivir; Kivexa; Trizivir; ***Philipp.***: Combivir; ***Pol.***: Combivir; Kivexa; Trizivir; ***Port.***: Combivir; Kivexa; Trizivir; ***Rus.***: Combivir (Комбивир); Kivexa (Кивекса); Trizivir (Тризивир); ***S.Afr.***: Cipla-Duovir; Colamziv; Combivir; Combozil; Kivexa; Lamzid; Lodiz; Retrovir/3TC Post-HIV Exposure; Sonke Abaclamizid; Sonke-LamiNevStav; Triomune; Trizivar; Virtrium; ***Singapore***: Combivir; Kivexa; Trizivir; ***Spain***: Combivir; Kivexa; Trizivir; ***Swed.***: Combivir; Kivexa; Trizivir; ***Switz.***: Combivir; Kivexa; Trizivir; ***Thai.***: Combid; GPO-Vir S; GPO-Vir Z; Kivexa; La-Stavir; Zilavir; Zovilam; ***Turk.***: Combivir; Trizivir; ***UK***: Combivir; Kivexa; Trizivir; ***USA***: Combivir; Epzicom; Trizivir; ***Venez.***: Combivir; Duovir; Triomune; Trizivir.

Pharmacopoeial Preparations

BP 2014: Lamivudine Tablets; Zidovudine and Lamivudine Tablets;

USP 36: Lamivudine and Zidovudine Tablets; Lamivudine Oral Solution.

Laninamivir *(rINN)*

Laninamivirum; R-125489; Ланинамивир.

(2*R*,3*R*,4*S*)-3-Acetamido-2-[(1*R*,2*R*)-2,3-dihydroxy-1-methoxypropyl]-4-guanidino-3,4-dihydro-2*H*-pyran-6-carboxylic acid.

$C_{13}H_{22}N_4O_7$=346.3

CAS — 203120-17-6.

UNII — B408IW3GL5.

Laninamivir Octanoate *(rINNM)*

CS-8958; Laninamivir Octanoate Hydrate.
(2*R*,3*R*,4*S*)-3-Acetamido-4-guanidino-2-[(1*R*,2*R*)-2-hydroxy-1-methoxy-3-(octanoyloxy)propyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid monohydrate.
$C_{21}H_{36}N_4O_8.H_2O$=490.6
CAS — 203120-46-1 (anhydrous laninamivir octanoate); 371755-92-9 (laninamivir octanoate hydrate).

Profile

Laninamivir octanoate is the prodrug of laninamivir, a long-acting neuraminidase inhibitor available in Japan for the treatment of influenza A and B, (p. 960.2) including oseltamivir-resistant and pandemic (H1N1) 2009 influenza viruses. It is given as a single dose of 40 mg by oral inhalation; children may be given 20 mg.

References.
1. Watanabe A, *et al.* Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: a double-blind, randomized, noninferiority clinical trial. *Clin Infect Dis* 2010; **51:** 1167–75.
2. Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. *Antimicrob Agents Chemother* 2010; **54:** 2575–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Inavir.

Lopinavir *(BAN, USAN, rINN)*

A-157378.0; ABT-378; Lopinaviiri; Lopinavirum; Лопинавир.
(αS)-Tetrahydro-*N*-((αS)-α-{(2S,3S)-2-hydroxy-4-phenyl-3-[2-(2,6-xylyloxy)acetamido]butyl}phenethyl)-α-isopropyl-2-oxo-1(2*H*)-pyrimidineacetamide.
$C_{37}H_{48}N_4O_5$=628.8
CAS — 192725-17-0.
ATC — J05AE06.
ATC Vet — QJ05AE06.
UNII — 2494G1JF75.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lopinavir). A white or yellowish-white, slightly hygroscopic powder. It shows polymorphism. Practically insoluble in water; very soluble in methyl alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Lopinavir). A white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol; soluble in isopropyl alcohol. Store in airtight containers.

Uses and Administration

Lopinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is formulated with low-dose ritonavir, which acts as a pharmacokinetic enhancer. The combination is used in the treatment of HIV infection and AIDS (p. 957.2). Ritonavir-boosted lopinavir is also recommended for HIV postexposure prophylaxis (p. 959.1). Viral resistance emerges rapidly when ritonavir-boosted lopinavir is used alone, and it is therefore used with other antiretrovirals.

The oral dose in treatment-naive and -experienced adults is lopinavir 400 mg (with ritonavir 100 mg) twice daily. Alternatively, a once-daily dose of lopinavir 800 mg (with ritonavir 200 mg) may be considered for patients having only very few (less than 3) HIV-protease inhibitor-associated resistance mutations.

US licensed product information recommends that if the tablets are given in a treatment regimen with either *amprenavir*, *nelfinavir*, *efavirenz*, or *nevirapine* consideration be given to increasing the dose of lopinavir to 500 mg (with ritonavir 125 mg) twice daily. For patients taking the oral solution in such regimens the dose should be increased to lopinavir 533 mg (with ritonavir 133 mg) twice daily. When used with any of these drugs, the once-daily regimen of lopinavir should not be used.

Lopinavir film-coated tablets may be taken with or without food; the soft capsules and solution should be taken with food.

For a discussion of dosing in pregnant women, see Pregnancy under Pharmacokinetics, p. 1003.1.

For details of doses in children, see below.

Reviews.
1. Oldfield V, Plosker GL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs* 2006; **66:** 1275–99.
2. Schechter M, Nunes EP. Monotherapy with lopinavir/ritonavir. *Expert Opin Invest Drugs* 2007; **16:** 735–41.
3. Barragan P, Podzamczer D. Lopinavir/ritonavir: a protease inhibitor for HIV-1 treatment. *Expert Opin Pharmacother* 2008; **9:** 2363–75.
4. Croxtall JD, Perry CM. Lopinavir/ritonavir: a review of its use in the management of HIV-1 infection. *Drugs* 2010; **70:** 1885–1915.

Administration in children. For the treatment of HIV infection in children, ritonavir-boosted lopinavir is given twice daily with other antiretroviral drugs. The US licensed product information permits use in infants as young as 14 days old, whereas in the UK the age is 2 years. The dose given should not exceed the maximum adult dose (see above).

In the UK the use of the oral solution is preferred to the tablets as a more accurate dose may be given. Doses are based on body-surface.

- In children 2 years of age or more the recommended dose of the *oral solution* is lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily with food. A dose increase to 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily with food should be considered when given with *efavirenz* or *nevirapine*

In the USA the dose is based on body-weight or body-surface as follows:

- given without interacting antiretrovirals
  - 14 days to 6 months of age: lopinavir 16 mg/kg (with ritonavir 4 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - 6 months or older and less than 15 kg: lopinavir 12 mg/kg (with ritonavir 3 mg/kg) twice daily or lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily
  - 15 to 40 kg: lopinavir 10 mg/kg (with ritonavir 2.5 mg/kg) twice daily or lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily
  - over 40 kg: normal adult dose
- given in a treatment regimen with either *amprenavir*, *efavirenz*, *nelfinavir*, or *nevirapine* (requiring the dose of lopinavir/ritonavir to be increased):
  - 6 months or older and less than 15 kg: lopinavir 13 mg/kg (with ritonavir 3.25 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - 15 to 45 kg: lopinavir 11 mg/kg (with ritonavir 2.75 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - over 45 kg: as for adults, above

It has been suggested that HIV-protease inhibitor experienced children may have inadequate drug exposure on standard doses of ritonavir-boosted lopinavir; for further information, see under Pharmacokinetics, p. 1003.1.

SARS. In a preliminary open study[1] 41 patients with probable SARS were given ritonavir-boosted lopinavir as well as the local standard treatment of ribavirin and corticosteroids. At 21 days there was improved outcome with reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections.

1. Chu CM, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:** 252–6.

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing lopinavir (formulated with ritonavir) is diarrhoea of mild to moderate severity. Pancreatitis has been seen in patients receiving lopinavir, including those who developed marked triglyceride elevations; in some cases fatalities have occurred. Severe, and in some cases fatal hepatotoxicity has also been reported in patients given ritonavir-boosted lopinavir, particularly in the setting of pre-existing chronic liver disease. Other commonly reported adverse effects include asthenia, headache, insomnia, pain, paraesthesia, gastrointestinal disturbances, acne, and rash. Abnormal laboratory test results associated with lopinavir-containing regimens include increases in serum cholesterol and triglycerides and raised liver enzymes. ECG abnormalities such as prolongation of the PR interval, in some cases progressing to second- and third-degree AV block, have occurred in some patients; QT-interval prolongation and torsade de pointes have also been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including lopinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including lopinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during treatment with ritonavir-boosted lopinavir. Such therapy should be stopped if symptoms of pancreatitis occur.

Patients with pre-existing liver dysfunction or markedly elevated liver enzymes are at increased risk for further hepatotoxicity and should be monitored carefully; stopping treatment should be considered if there is evidence of worsening liver function. In the UK, ritonavir-boosted lopinavir is contra-indicated in patients with severe hepatic impairment.

Due to the potential for ECG abnormality and potential cardiac arrhythmia, ritonavir-boosted lopinavir should be used with caution in patients with underlying heart disease or conduction system abnormalities, or in those using other drugs known to prolong the PR interval. Use should also be avoided in those with congenital long-QT syndrome, hypokalaemia, or using other QT-interval prolonging drugs.

The oral solution (*Kaletra, Abbott*) has a high content of alcohol and propylene glycol, present as excipients, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further information on propylene glycol toxicity, see Adverse Effects and Precautions, p. 2205.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lopinavir as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Licensed product information notes that in *rats* given toxic doses of ritonavir-boosted lopinavir, there was early resorption, decreased fetal viability and body weight, and an increased incidence of skeletal variation and delayed skeletal ossification in the offspring. However, US guidelines[1] for the use of antiretroviral drugs in pregnant HIV-infected women note that there appears to be no evidence of human teratogenicity, and consider ritonavir-boosted lopinavir to be a drug of choice for use in HIV drug regimens required during pregnancy (see under Indinavir, p. 987.1). For evidence that doses should be increased during the latter part of pregnancy see under Pharmacokinetics, p. 1003.1.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Lopinavir is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It is formulated with low-dose ritonavir, which inhibits this enzyme and thus increases exposure. The combination is an inhibitor of CYP3A4 and increases plasma concentration of drugs mainly metabolised by this isoenzyme. It has also been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolised by cytochrome P450 isoenzymes and by glucuronidation. Drugs that strongly induce CYP3A4 may result in decreased plasma concentrations of the combination.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted lopinavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA licensed product information also contra-indicates use with the alpha$_1$-adrenoceptor antagonist alfuzosin. Owing to the potential for increased serum concentrations of sildenafil, ritonavir-boosted lopinavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir-boosted lopinavir may increase serum

concentrations of inhaled salmeterol and the combination is not recommended. Rifampicin and St John's wort decrease the concentration of lopinavir; use with the antiretroviral is best avoided due to the possible loss of its activity and development of resistance. UK licensed product information contra-indicates the use of vardenafil and amiodarone with ritonavir-boosted lopinavir.

When ritonavir-boosted lopinavir is used with some other antiretrovirals (such as efavirenz, nevirapine, amprenavir/fosamprenavir, and nelfinavir), decreased concentrations of lopinavir may occur. In some cases this may result in the need for dose modification (see p. 1002.1). Use with ritonavir-boosted fosamprenavir or tipranavir is not recommended.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antibacterials. Although *rifabutin* may reduce the plasma concentrations of some HIV-protease inhibitors (see under Indinavir, p. 987.3), a retrospective study[1] found an association between use of rifabutin with ritonavir-boosted lopinavir and *increased* plasma-lopinavir concentrations.

1. Stöhr W, *et al.* UK CHIC Steering Committee. Factors influencing lopinavir and atazanavir plasma concentration. *J Antimicrob Chemother* 2010; **65:** 129–37.

Antiviral Action

Lopinavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Lopinavir is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur after 4 hours. Bioavailability is enhanced when given with a high fat meal. Lopinavir is reported to be 98 to 99% bound to serum proteins. Lopinavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme CYP3A4; 13 metabolites have been identified with some, such as 4-oxylopinavir and 4-hydroxylopinavir, having antiviral activity. Lopinavir is mainly excreted in faeces and to a smaller extent in the urine; unchanged lopinavir accounts for about 2.2% of a dose excreted in the urine and 19.8% in the faeces. After multiple dosing, less than 3% of the absorbed lopinavir dose is excreted unchanged in the urine. The terminal elimination half-life of lopinavir is reported to be about 5 to 6 hours.

Children. The pharmacokinetics of lopinavir have been reported to vary greatly during childhood, with decreased drug exposure a concern in certain subpopulations.[1] Although there is clinical evidence for good antiviral efficacy of ritonavir-boosted lopinavir in children at the recommended standard doses, a pharmacokinetic model[2] of lopinavir in children 4 years of age and older has suggested that, although these doses are likely to be sufficient for children infected with wild-type virus, they may not provide adequate inhibitory concentrations for even moderately resistant HIV; the authors suggested that HIV-protease inhibitor experienced children might therefore benefit from routine monitoring of serum drug levels and evaluations for resistance.

1. Jullien V, *et al.* Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother* 2006; **50:** 3548–55.
2. Rakhmanina N, *et al.* Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2009; **53:** 2532–8.

Pregnancy. Due to the lack of data addressing whether serum-drug concentrations of the tablet formulation are adequate, US guidelines[1] recommend that once-daily ritonavir-boosted lopinavir dosing regimens be avoided in pregnant women. A twice-daily dose regimen should be used; and while some experts advocate the use of standard doses (see Uses and Administration, p. 1002.1) with serum concentration monitoring, empirical use of increased doses have been recommended by others.

A small study[2] in pregnant patients suggested that an increased dose of the tablet formulation of ritonavir-boosted lopinavir (a twice-daily dose of 600 mg of lopinavir with 150 mg of ritonavir) was needed during the second and third trimesters of pregnancy in order to provide equivalent exposure to that seen in non-pregnant patients taking usual doses of 400 mg of lopinavir with 100 mg ritonavir twice daily. The dose could be reduced to standard dosage within 2 weeks of delivery.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)
2. Best BM, *et al.* International Maternal Pediatric Adolescent AIDS Clinical Trials Group 1026s Study Team. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr* 2010; **54:** 381–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Kaletra; ***Austral.***: Kaletra; ***Austria***: Kaletra; ***Belg.***: Kaletra; ***Braz.***: Kaletra; ***Canad.***: Kaletra; ***Chile***: Kaletra; ***China***: Aluvia (克力芝); ***Cz.***: Kaletra; ***Denm.***: Kaletra; ***Fin.***: Kaletra; ***Fr.***: Kaletra; ***Ger.***: Kaletra; ***Gr.***: Kaletra; ***Hong Kong***: Kaletra; ***Hung.***: Kaletra; ***India***: Emletra; Lopimune; Ritomax-L; ***Irl.***: Kaletra; ***Israel***: Kaletra; ***Ital.***: Kaletra; ***Malaysia***: Kaletra; ***Mex.***: Kaletra; ***Neth.***: Kaletra; ***Norw.***: Kaletra; ***NZ***: Kaletra; ***Pol.***: Kaletra; ***Port.***: Kaletra; ***Rus.***: Kaletra (Калетра); ***S. Afr.***: Aluvia; Kaletra; ***Singapore***: Kaletra; ***Spain***: Kaletra; ***Swed.***: Kaletra; ***Switz.***: Kaletra; ***Thai.***: Aluvia; Kaletra; ***Turk.***: Kaletra; ***UK***: Kaletra; ***USA***: Kaletra; ***Venez.***: Kaletra.

Pharmacopoeial Preparations
USP 36: Lopinavir and Ritonavir Tablets.

Maraviroc *(BAN, USAN, rINN)*

Maravirocum; Maravirok; Marawirok; UK-427857; Маравирок.

4,4-Difluoro-*N*-((1*S*)-3-[(1*R*,3*s*,5*S*)-3-[3-methyl-5-(propan-2-yl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octan-8-yl]-1-phenylpropyl)cyclohexanecarboxamide.

$C_{29}H_{41}F_2N_5O$=513.7

CAS — 376348-65-1.

ATC — J05AX09.

ATC Vet — QJ05AX09.

UNII — MD6P741W8A.

Uses and Administration

Maraviroc is an antagonist of the CCR5 chemokine receptor (see Antiviral Action, below). It is used, with other antiretrovirals, for the treatment of HIV infection and AIDS (p. 957.2) in adult patients with exclusively CCR5-tropic HIV-1 infection. Co-receptor tropism should be determined by specific testing before maraviroc is used.

Maraviroc is given orally in a dose of 300 mg twice daily, although dose adjustments may be needed depending on interactions with other medicines; recommendations for these may vary, but for guidance the following doses have been recommended in the UK or USA:

- For patients also taking potent CYP3A4 inhibitors such as HIV-protease inhibitors (other than ritonavir-boosted fosamprenavir or tipranavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin, the recommended dose is 150 mg twice daily. These reductions generally apply even if a CYP3A4 inducer such as efavirenz or etravirine is also being given.
- In those whose therapy includes CYP3A4 inducers such as efavirenz, rifampicin, carbamazepine, phenobarbital, and phenytoin *without* a CYP3A4 inhibitor, the recommended dose is 600 mg twice daily.
- Patients taking other antiretrovirals (including ritonavir-boosted fosamprenavir or tipranavir), or other drugs, may be given the standard dose of 300 mg twice daily.

Licensed doses in the USA are generally similar to those in the UK, but US licensed product information does not exclude ritonavir-boosted fosamprenavir from the drugs considered to be potent inhibitors of CYP3A4; therefore the recommended dose of maraviroc when they are given together is 150 mg twice daily.

References.
1. Carter NJ, Keating GM. Maraviroc. *Drugs* 2007; **67:** 2277–88.
2. Vandekerckhove L, *et al.* Maraviroc: integration of a new antiretroviral drug class into clinical practice. *J Antimicrob Chemother* 2008; **61:** 1187–90.
3. MacArthur RD, Novak RM. Maraviroc: the first of a new class of antiretroviral agents. *Clin Infect Dis* 2008; **47:** 236–41.
4. Dau B, Holodniy M. Novel targets for antiretroviral therapy: clinical progress to date. *Drugs* 2009; **69:** 31–50.
5. Yost R, *et al.* Maraviroc: a coreceptor CCR5 antagonist for management of HIV infection. *Am J Health-Syst Pharm* 2009; **66:** 715–26.
6. Perry CM. Maraviroc: a review of its use in the management of CCR5-tropic HIV-1 infection. *Drugs* 2010; **70:** 1189–1213.

Administration in renal impairment. UK licensed product information recommends that the oral dose of maraviroc be adjusted in patients with renal impairment who are also taking potent inhibitors of cytochrome P450 isoenzyme CYP3A4. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- For patients also taking potent CYP3A4 inhibitors such as ritonavir-boosted HIV-protease inhibitors (other than fosamprenavir or tipranavir), ketoconazole, itraconazole, clarithromycin, and telithromycin and who have a CC < 80 mL/minute: 150 mg every 24 hours
- For patients also taking ritonavir-boosted fosamprenavir who have a CC < 80 mL/minute: 150 mg every 12 hours

Alternatively, US licensed product information has recommended that patients taking potent CYP3A inhibitors (including ritonavir-boosted fosamprenavir) with or without a CYP3A inducer, who have a CC of 30 to 80 mL/minute should be given a dose of 150 mg twice daily. Maraviroc is not recommended in patients with CC < 30 mL/minute who are taking potent CYP3A inhibitors or inducers.

Although dose adjustment is generally not recommended for renal impairment in patients not using potent CYP3A inhibitors or inducers, US licensed product information recommends that patients with CC < 30 mL/minute who have orthostatic hypotension while taking maraviroc should have their dose reduced to 150 mg twice daily.

No adjustment is necessary when maraviroc is given without potent CYP3A4 inhibitors or with tipranavir.

Adverse Effects and Precautions

On the basis of limited data, maraviroc appears to be well tolerated; non-specific adverse effects associated with maraviroc-based regimens include asthenia, cough and upper respiratory-tract infections, dizziness, abdominal pain and distension, constipation, diarrhoea, dyspepsia, nausea, vomiting, fever, headache, insomnia, somnolence, muscle spasms and back pain, pruritus, and rash. Less frequently reported adverse effects include bone marrow depression, myositis and rhabdomyolysis, osteonecrosis, and cardiovascular effects such as myocardial ischaemia and myocardial infarction; cardiac adverse effects were reported mainly for patients with pre-existing cardiac disease or risk factors. Maraviroc should be used cautiously in patients with a history of orthostatic hypotension, or those on blood pressure lowering medications.

Hepatobiliary disorders, including hepatic cirrhosis, cholestatic jaundice, and portal vein thrombosis have occurred rarely. Hepatotoxicity, sometimes preceded by evidence of systemic allergic reaction, has also been reported; stopping maraviroc should be considered in patients with signs or symptoms of hepatitis, or increased liver transaminases with rash or other systemic symptoms. Caution is also advised in patients with pre-existing liver dysfunction or co-infection with hepatitis B or C.

Although renal clearance normally accounts for only a small proportion of the dose, maraviroc should be used with caution in patients with renal impairment (creatinine clearance less than 80 mL/minute) who are also taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 as concentrations of maraviroc may be significantly increased. If the impairment is severe (creatinine clearance < 30 mL/minute) patients are at increased risk of orthostatic hypotension, which may lead to further cardiovascular adverse effects; US licensed product information therefore advises that maraviroc may only be considered for use in such cases if they are not also receiving potent inhibitors or inducers of these cytochromes, and where no alternative treatment options exist.

Due to its mechanism of action, maraviroc may impair the immune response to infections and possibly lead to an increased risk of malignancy.

Interactions

Maraviroc is a substrate for the cytochrome P450 isoenzyme CYP3A4 and for P-glycoprotein, and may therefore have several clinically significant interactions. Inhibitors of CYP3A4, such as HIV-protease inhibitors (other than tipranavir), increase the serum concentration of maraviroc. Inducers of CYP3A4 such as efavirenz may decrease serum maraviroc concentrations. No clinically significant interaction is expected between maraviroc and NRTIs, nevirapine, or boosted fosamprenavir or tipranavir.

Non-antiretroviral medications that significantly alter maraviroc metabolism include the CYP3A4 inhibitors ketoconazole, itraconazole, clarithromycin, and nefazodone and the CYP3A4 inducers rifampicin and St John's wort. Maraviroc does not appear to cause clinically significant changes in concentrations of other medications.

Antiviral Action

Maraviroc is an antagonist of the CCR5 chemokine receptor. During infection, HIV binds to the CD4 receptor on the surface of host cells, and then interacts with one of two co-receptors, CCR5 or CXCR4, to allow cell membrane fusion and entry to the cell. By binding to CCR5, maraviroc inhibits this process and prevents strains of HIV-1 that use CCR5 (CCR5-tropic viruses), which appear to be more common in early infection, from entering the cell. It is not active against CXCR4-tropic strains or those with dual or mixed tropism.

Pharmacokinetics

Maraviroc is absorbed after oral doses and peak concentrations occur in 0.5 to 4 hours. There is considerable interindividual variation in the pharmacokinetics. It is 76% bound to plasma proteins. Maraviroc is metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to inactive metabolites. It is excreted in both urine (20%) and faeces (76%) as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Celsentri; ***Austral.***: Celsentri; ***Austria***: Celsentri; ***Belg.***: Celsentri; ***Braz.***: Celsentri; ***Canad.***: Celsentri; ***Chile***: Celsentri; ***China***: Celsentri (善瑞); ***Cz.***: Celsentri; ***Denm.***: Celsentri; ***Fr.***: Celsentri; ***Ger.***: Celsentri; ***Gr.***: Celsentri; ***Hong Kong***: Celsentri; ***Hung.***: Celsentri; ***Irl.***: Celsentri; ***Israel***: Celsentri; ***Ital.***: Celsentri; ***Neth.***: Celsentri; ***Norw.***: Celsentri; ***Pol.***: Celsentri; ***Port.***: Celsentri; ***Spain***: Celsentri; ***Swed.***: Celsentri; ***Switz.***: Celsentri; ***Thai.***: Celsentri; ***UK***: Celsentri; ***USA***: Selzentry.

Moroxydine *(BAN, rINN)*

Moroksidiini; Moroxidin; Moroxidina; Moroxydinum; Мороксидин.

$C_6H_{13}N_5O$=171.2

CAS — 3731-59-7.

ATC — J05AX01.

ATC Vet — QJ05AX01.

UNII — O611591WAH.

Moroxydine Hydrochloride *(BANM, rINNM)*

Abitilguanide Hydrochloride; ABOB; Hidrocloruro de moroxidina; Moroxidina, hidrocloruro de; Moroxydine, Chlorhydrate de; Moroxydini Hydrochloridum; Мороксидина Гидрохлорид.

1-(Morpholinoformimidoyl)guanidine hydrochloride.

$C_6H_{13}N_5O,HCl$=207.7

CAS — 3160-91-6.

ATC — J05AX01.

ATC Vet — QJ05AX01.

Profile

Moroxydine hydrochloride has been given orally in the treatment of herpes simplex and varicella-zoster infections. It has also been used topically. It is included as an ingredient in preparations for the treatment of cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Virulex Forte; ***Mex.***: Amgrip†; Singril; Singril; Singrilen; ***S.Afr.***: Corenza C.

Nelfinavir Mesilate *(BANM, rINNM)*

AG-1343 (nelfinavir or nelfinavir mesilate); Mesilato de nelfinavir; Nelfinavir, Mésilate de; Nelfinavir, mesilato de; Nelfinavir Mesylate (USAN); Nelfinavir Mesylate; Nelfinaviri Mesilas; Нелфинавира Мезилат.

3*S*[2(2*S**,3*S**),3α,4aβ,8aβ]-*N*-(1,1-Dimethylethyl)decahydro-2-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl-3-isoquinolinecarboxamide monomethanesulphonate; (3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyldecahydro-2-[(2*R*,3*R*)-3-(3-hydroxy-o-toluamido)-2-hydroxy-4-(phenylthio)butyl]isoquinoline-3-carboxamide monomethanesulphonate.

$C_{32}H_{45}N_3O_4S,CH_4O_3S$=663.9

CAS — 159989-64-7 (nelfinavir); 159989-65-8 (nelfinavir mesilate).

ATC — J05AE04.

ATC Vet — QJ05AE04.

UNII — 98D603VP8V.

NOTE. Nelfinavir should not be confused with nevirapine (p. 1005.1).

Pharmacopoeias. In *Int.*

Uses and Administration

Nelfinavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when nelfinavir is used alone, and it is therefore used with other antiretrovirals.

Nelfinavir is given orally as the mesilate, but doses are expressed in terms of the base. Nelfinavir mesilate 292 mg is equivalent to about 250 mg of nelfinavir. Nelfinavir is available as tablets and oral powder. The oral powder should not be taken with acidic foods or drinks as this may result in a bitter taste. Nelfinavir is given in an adult dose of 1.25 g twice daily or 750 mg three times daily with food.

For details of doses in children, see below.

Reviews.

1. Pai VB, Nahata MC. Nelfinavir mesylate: a protease inhibitor. *Ann Pharmacother* 1999; **33:** 325–39.
2. Perry CM, *et al*. Nelfinavir: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 2209–44.
3. Olmo M, Podzamczer D. A review of nelfinavir for the treatment of HIV infection. *Expert Opin Drug Metab Toxicol* 2006; **2:** 285–300.
4. Brüning A, *et al*. New prospects for nelfinavir in non-HIV-related diseases. *Curr Mol Pharmacol* 2010; **3:** 91–7.

Administration in children. For the treatment of HIV infection in children nelfinavir is given orally with other antiretroviral drugs. US licensed product information permits the use of nelfinavir in children 2 years of age and older; the recommended dose is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily with food.

Malignant neoplasms. There has been some interest[1-3] in the potential of nelfinavir as an antineoplastic.

1. Gills JJ, *et al*. Nelfinavir, a new anti-cancer drug with pleiotropic effects and many paths to autophagy. *Autophagy* 2008; **4:** 107–9.
2. Brunner TB, *et al*. Phase I trial of the human immunodeficiency virus protease inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer. *J Clin Oncol* 2008; **26:** 2699–706.
3. Wu W, *et al*. Nelfinavir: a magic bullet to annihilate cancer cells? *Cancer Biol Ther* 2009; **8:** 233–5.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing nelfinavir are diarrhoea, flatulence, nausea, and rash. Raised liver enzymes and decreases in white blood cell counts have also been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including nelfinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including nelfinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Contamination. In June 2007, high levels of ethyl mesilate (ethyl methanesulfonate; EMS) were detected in European-made nelfinavir (*Viracept; Roche*). EMS may cause cancer in humans and has caused birth defects and cancer in *animals*. Nelfinavir was subsequently recalled from the European market in August 2007.[1] The manufacturer later identified and rectified the source of contamination and in September 2007 the EMEA recommended the lifting of the drug's suspension.[2] It was later determined that the exposure to EMS caused by the contaminated product were well below the threshold required for DNA damage to occur.[3] The US manufacturer (*Pfizer, USA*) notified doctors in September 2007 that EMS had been detected in nelfinavir manufactured in the USA but in much lower amounts than in European-made nelfinavir.[4] At the time the FDA considered the risk of stopping nelfinavir therapy resulting from a drug recall to be greater than the risk of taking US-made nelfinavir, but issued recommendations restricting its use specifically in children and pregnant women. However, as of March 31, 2008, all nelfinavir manufactured in the US by Pfizer meets new EMS limits established by the FDA for all patient populations, and these recommendations no longer apply.[5]

1. EMEA. European Medicines Agency agrees on action plan following the recall of Viracept and recommends suspension of the marketing authorisation (issued 21st June, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014204.pdf (accessed 18/08/10)
2. EMEA. European medicines agency recommends lifting of suspension for Viracept (issued 20th September, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014100.pdf (accessed 18/08/10)
3. EMEA. Studies assessed by the EMEA indicate no increased risk of developing cancer for patients who have taken Viracept contaminated with ethyl mesilate (issued 24th July, 2008). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Viracept/38225608en.pdf (accessed 19/10/09)
4. Pfizer, USA. Viracept (nelfinavir mesylate) 250 mg, 625 mg tablets, and powder for oral suspension: important information for prescribers (issued 10th September, 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM154880.pdf (accessed 18/08/10)
5. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Precautions

Nelfinavir should be used with caution, and liver enzyme values monitored, in patients with moderate liver disease; in the USA, the use of nelfinavir in patients with moderate or severe liver disease is not advised. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

For cautions concerning use in children and in pregnancy see under Contamination, above

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nelfinavir as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Nelfinavir is reported to be metabolised in part by cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that induce these isoenzymes may reduce the plasma concentration of nelfinavir. Conversely, when nelfinavir is given with drugs that inhibit CYP3A4 plasma concentrations, nelfinavir concentrations may be increased. It may also alter the pharmacokinetics of drugs metabolised by this isoenzyme system and possibly cause serious adverse effects.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of nelfinavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- the alpha$_1$-adrenoceptor antagonist alfuzosin
- antiarrhythmics (amiodarone and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal motility agents (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

Owing to the potential for increased serum concentrations of sildenafil, nelfinavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, nelfinavir may increase serum concentrations of inhaled salmeterol and the combination is not recommended. Omeprazole, rifampicin, and St John's wort decrease the concentration of nelfinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Nelfinavir is a selective, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Mechanisms of resistance to nelfinavir may differ sufficiently from those to other HIV-protease inhibitors to reduce the occurrence of cross-resistance between nelfinavir and other HIV-protease inhibitors. Cross-resistance between nelfinavir and NNRTIs is unlikely because they target different enzymes.

Pharmacokinetics

Nelfinavir is absorbed from the gastrointestinal tract and peak plasma concentrations occur in 2 to 4 hours. Absorption is enhanced when given with food. Nelfinavir is extensively bound to plasma proteins (more than 98%). It is metabolised by oxidation by cytochrome P450 isoenzymes including CYP3A4 and CYP2C19. The major oxidative metabolite has *in-vitro* antiviral activity equal to that of nelfinavir. In patients 13 years of age and older the plasma terminal half-life is 3.5 to 5 hours; in children 2 to 13 years of age, clearance is two to three times greater than in adults. Nelfinavir is excreted mainly in the faeces both as

unchanged drug (22%) and as metabolites (78%). Only about 1 to 2% is excreted in the urine, mainly as unchanged drug.

References.
1. Panhard X, *et al.* Population pharmacokinetic analysis for nelfinavir and its metabolite M8 in virologically controlled HIV-infected patients on HAART. *Br J Clin Pharmacol* 2005; **60:** 390–403.
2. Goujard C, *et al.* High variability of indinavir and nelfinavir pharmacokinetics in HIV-infected patients with a sustained virological response on highly active antiretroviral therapy. *Clin Pharmacokinet* 2005; **44:** 1267–78.
3. Regazzi M, *et al.* Clinical pharmacokinetics of nelfinavir and its metabolite M8 in human immunodeficiency virus (HIV)-positive and HIV-hepatitis C virus-coinfected subjects. *Antimicrob Agents Chemother* 2005; **49:** 643–9.
4. Damle B, *et al.* Pharmacokinetics of nelfinavir in subjects with hepatic impairment. *J Clin Pharmacol* 2006; **46:** 1241–9.
5. Fletcher CV, *et al.* Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther* 2008; **83:** 300–6.
6. Hirt D, *et al.* Pharmacokinetic modelling of the placental transfer of nelfinavir and its M8 metabolite: a population study using 75 maternal-cord plasma samples. *Br J Clin Pharmacol* 2007; **64:** 634–44.
7. Hirt D, *et al.* Effect of CYP2C19 polymorphism on nelfinavir to M8 biotransformation in HIV patients. *Br J Clin Pharmacol* 2008; **65:** 548–57.
8. Read JS, *et al.* Pharmacokinetics of new 625 mg nelfinavir formulation during pregnancy and postpartum. *HIV Med* 2008; **9:** 875–82.
9. Damle BD, *et al.* Influence of CYP2C19 polymorphism on the pharmacokinetics of nelfinavir and its active metabolite. *Br J Clin Pharmacol* 2009; **68:** 682–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Filosfil; Nalvir; Nelfilea; Nemacina; Retroinhi; ***Austral.***: Viracept†; ***Austria***: Viracept†; ***Belg.***: Viracept†; ***Braz.***: Viracept; ***Canad.***: Viracept; ***Chile***: Viracept†; ***China***: Viracept (泛罗赛); ***Cz.***: Viracept†; ***Fr.***: Viracept†; ***Ger.***: Viracept†; ***Gr.***: Viracept†; ***Hong Kong***: Viracept; ***Hung.***: Viracept†; ***India***: Emnel; Neivex; Nel; Nelvir; ***Irl.***: Viracept†; ***Israel***: Viracept†; ***Ital.***: Viracept†; ***Jpn***: Viracept; ***Malaysia***: Viracept; ***Mex.***: Viracept†; ***Neth.***: Viracept†; ***NZ***: Viracept†; ***Philipp.***: Viracept†; ***Pol.***: Viracept†; ***Port.***: Viracept†; ***Rus.***: Viracept (Вирацепт); ***S.Afr.***: Viracept; ***Singapore***: Viracept; ***Spain***: Viracept†; ***Switz.***: Viracept†; ***Thai.***: Nafavir; Viracept†; ***UK***: Viracept†; ***Ukr.***: Viracept (Вирацепт)†; ***USA***: Viracept; ***Venez.***: Nelvir; Viracept.

Nevirapine *(BAN, USAN, rINN)*

BIRG-0587; BI-RG-587; Nevirapiini; Nevirapiini, vedetön; Nevirapin; Nevirapin bezvodý; Nevirapin, vattenfritt; Nevirapina; Névirapine; Névirapine anhydre; Nevirapinum; Nevirapinum Anhydricum; Newirapina bezwodna; Невирапин.

11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one.

$C_{15}H_{14}N_4O$=266.3

CAS — 129618-40-2.

ATC — J05AG01.

ATC Vet — QJ05AG01.

UNII — 99DK7FVK1H.

NOTE. Nevirapine should not be confused with nelfinavir (p. 1004.1).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Eur. permits anhydrous or the hemihydrate.

Ph. Eur. 8: (Nevirapine, Anhydrous). A white or almost white powder. Practically insoluble in water; sparingly soluble or slightly soluble in dichloromethane; slightly soluble in methyl alcohol.

Ph. Eur. 8: (Nevirapine Hemihydrate). A white or almost white powder. Practically insoluble in water; slightly soluble in dichloromethane and in methyl alcohol.

USP 36: (Nevirapine). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white, odourless to nearly odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. The hydrous form is also slightly insoluble in propylene glycol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when nevirapine is used alone, and it is therefore used with other antiretrovirals.

Nevirapine is given orally in an adult dose of 200 mg once daily for the first 14 days, then increased to 200 mg twice daily provided that no rash is present (but see Precautions, below).

If treatment is interrupted for more than 7 days, it should be reintroduced using the lower dose for the first 14 days as for new treatment.

For details of doses in infants, children, and adolescents, see below.

Nevirapine is often used in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection. In women in whom HAART is not indicated, or where it is not available, a single oral dose of nevirapine 200 mg may be given at the onset of labour, with a course of zidovudine and lamivudine, for perinatal cover (see HIV Infection Prophylaxis, p. 959.1).

References.
1. Guay LA, *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999; **354:** 795–802.
2. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs* 2000; **2:** 373–407.
3. Dorenbaum A, *et al.* Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* 2002; **288:** 189–98.
4. Moodley D, *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; **187:** 725–35.
5. Taha TE, *et al.* Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 2003; **362:** 1171–7.
6. Lallemant M, *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; **351:** 217–28.
7. Shapiro RL, *et al.* Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS* 2006; **20:** 1281–8.
8. Lockman S, *et al.* Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007; **356:** 135–47.
9. Parienti JJ, *et al.* SIROCCO study team. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. *Clin Infect Dis* 2007; **45:** 263–6.
10. Dart Trial Team. Twenty-four-week safety and tolerability of nevirapine vs. abacavir in combination with zidovudine/lamivudine as first-line antiretroviral therapy: a randomized double-blind trial (NORA). *Trop Med Int Health* 2008; **13:** 6–16.
11. Ena J, *et al.* Switching from suppressive protease inhibitor-based regimens to nevirapine-based regimens: a meta-analysis of randomized controlled trials. *HIV Med* 2008; **9:** 747–56.
12. Rodríguez-Arrondo F, *et al.* Long-term effectiveness and safety outcomes in HIV-1-infected patients after a median time of 6 years on nevirapine. *Curr HIV Res* 2009; **7:** 526–32.
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Administration in children. For the treatment of HIV infection in infants, children, and adolescents nevirapine is given orally with other antiretroviral drugs. The following doses by body-weight have been suggested according to age:

- from 15 days to 8 years: 4 mg/kg once daily for 14 days and then, if no rash is present, 7 mg/kg twice daily
- 8 to 16 years: 4 mg/kg once daily for 14 days then 4 mg/kg twice daily thereafter

Alternatively, the dose may be calculated according to body-surface; an oral dose of 150 mg/m² once daily for two weeks is given followed by 150 mg/m² twice daily thereafter if no rash is present. A total dose of 400 mg daily should not be exceeded. The *BNFC* suggests higher doses of 150 to 200 mg/m² once daily for two weeks and 150 to 200 mg/m² twice daily thereafter if no rash is present also with a daily maximum of 400 mg.

For information on the use of nevirapine in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection see HIV Infection Prophylaxis, p. 959.1.

Administration in renal impairment. Dose adjustments are not required for patients with a creatinine clearance more than 20 mL/min. Patients on dialysis should receive an additional 200 mg of nevirapine after each dialysis session.

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing nevirapine is rash (usually mild to moderate, maculopapular, erythematous, and sometimes pruritic), generally occurring within 6 weeks of starting therapy. Severe and life-threatening skin reactions (with some fatalities) have occurred, including Stevens-Johnson syndrome and, more rarely, toxic epidermal necrolysis. Hypersensitivity reactions including angioedema, urticaria, and anaphylaxis have been reported. Rashes may occur alone or in the context of hypersensitivity reactions when they may be accompanied by other symptoms such as fever, arthralgia, myalgia, lymphadenopathy, eosinophilia, granulocytopenia, or renal dysfunction. Granulocytopenia occurs more commonly in children than in adults. Severe hepatotoxicity, including hepatitis and hepatic necrosis, occasionally fatal, has occurred and may be more prevalent in women and patients with high CD4+ counts at the start of treatment. Serious hepatotoxicity has also been reported in HIV-uninfected persons taking multiple doses of nevirapine for HIV postexposure-prophylaxis. Rhabdomyolysis has occurred in patients with skin and/or liver reactions. Other common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, fatigue, drowsiness, fever, myalgia, and headache.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including nevirapine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including nevirapine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the liver. The FDA has noted[1] that symptomatic liver toxicity is more frequent with nevirapine than with other antiretrovirals. Toxicity consists of elevated liver enzyme values plus at least one other symptom such as rash, flu-like symptoms, or fever, and may progress to rapidly occurring liver failure despite monitoring. It typically occurs after a few weeks of dosing, and women and patients with higher CD4+ counts are at greater risk. Deaths have occurred, including some in pregnant women (see also Pregnancy, p. 1006.1), but serious toxicity has not been reported after single doses or in HIV-infected children.

Further references.[2-7]

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Precautions

Patients taking nevirapine should be closely monitored for adverse skin reactions and hepatotoxicity during the first 18 weeks of treatment; extra vigilance is advised during the first 6 weeks of treatment. Nevirapine should be used with extreme caution in patients with moderate hepatic impairment (Child-Pugh class B); it is contra-indicated in those with severe hepatic impairment (Child-Pugh class C). Patients with high CD4+ counts (greater than 250 cells/microlitre in women or 400 cells/microlitre in men), particularly those with a detectable viral load, are at increased risk for hepatotoxicity; nevirapine should not be

started in these patients unless the benefit clearly outweighs the risk. Patients with elevated transaminase levels at the start of nevirapine therapy, and those who are co-infected with chronic hepatitis B or C are also at a higher risk of hepatotoxicity. The UK licensed product information suggests that liver function should be monitored every 2 weeks during the first 2 months of treatment, again at 3 months, and then regularly thereafter.

Treatment should be permanently stopped in patients who suffer a severe rash, rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise), hypersensitivity reactions, or clinical hepatitis. Transaminase levels should be checked for all patients who develop a rash in the first 18 weeks of treatment and nevirapine should be temporarily stopped if liver enzyme levels increase to greater than 5 times the upper limit of normal or the patient has symptoms suggestive of hepatitis. In some patients treatment may be restarted at the initial dose if liver function returns to baseline values and the patient has no clinical symptoms of hepatitis or signs of a rash (although permanent stoppage is necessary if abnormalities recur). In some cases hepatic injury progresses despite stopping the drug. Dose escalation should not be attempted in patients developing any rash during the first 14 days of treatment until the rash has resolved, however, if dose escalation is not possible within 28 days of starting therapy an alternative regimen should be sought. Patients or their carers should be counselled on how to recognise hypersensitivity reactions and instructed to seek immediate medical attention if they occur. Doses may need to be modified in patients on renal dialysis.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nevirapine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Nevirapine has not been associated with teratogenicity in *animals* Licensed product information states that the Antiretroviral Pregnancy Registry has not found an increased risk of birth defects after first trimester exposures to nevirapine and the prevalence of birth defects after exposure in any trimester was comparable to the prevalence in the general population.

Significant and potentially life-threatening maternal toxicity may occur in women using nevirapine-containing treatment regimens, particularly when nevirapine is used for the first time,[1] although others[2] have not found the risk of hepatotoxicity in pregnant women given nevirapine-based regimens to be any greater than with other antiretrovirals. Due to the risk of severe hepatotoxicity, US guidelines for use of antiretroviral drugs in pregnant HIV-infected women[3] advise against starting nevirapine in pregnant women with CD4+ counts greater than 250 cells/microlitre unless the benefit clearly outweighs the risk; women who become pregnant while on a well-tolerated nevirapine-containing regimen may continue therapy, regardless of CD4+ count.

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Interactions

Nevirapine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6. Consequently it may compete with other drugs metabolised by this system, possibly resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of nevirapine; nevirapine itself acts as a mild to moderate enzyme inducer and may thus reduce plasma concentrations of other drugs.

Rifampicin and St John's wort decrease the concentration of nevirapine; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Antivirals. For the effect of nevirapine on *HIV-protease inhibitors,* see p. 988.1.

Opioids. Nevirapine may induce the metabolism of *methadone* (p. 91.1) resulting in reduced plasma-methadone concentrations.

Antiviral Action

Nevirapine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to nevirapine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Nevirapine is readily absorbed after oral doses and absorption is not affected by food or antacids. Bioavailability is greater than 90%. Nevirapine tablets and oral suspension are comparably bioavailable and interchangeable at doses up to 200 mg. Peak plasma concentrations occur 4 hours after a single dose. Nevirapine is about 60% bound to plasma proteins. Concentrations in the CSF are about 45% of those in plasma. Nevirapine crosses the placenta and is distributed into breast milk. It is extensively metabolised by hepatic microsomal enzymes, mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, to several hydroxylated metabolites. Autoinduction of these enzymes results in a 1.5- to 2-fold increase in apparent oral clearance after 2 to 4 weeks at usual dosage, and a decrease in terminal half-life from 45 hours to 25 to 30 hours over the same period. Nevirapine is mainly excreted in the urine as glucuronide conjugates of the hydroxylated metabolites.

In children, nevirapine elimination accelerates during the first years of life, reaching a maximum at around 2 years of age, followed by a gradual decline during the rest of childhood; values in children under 8 years are about twice those in adults.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Filide; Nerapin; Protease; Ritvir; Virainhi; Viramune; ***Austral.***: Viramune; ***Austria***: Viramune; ***Belg.***: Viramune; ***Braz.***: Neviral; Viramune; ***Canad.***: Viramune; ***Chile***: Viramune; ***China***: Ai Ji (艾极); Ai Tai (艾太); Ai Wei Ning (艾韦宁); Li Wei Er (立维尔); Nuo Lan Pin (诺兰频); Viramune (维乐命); Wei Le Si (伟乐司); ***Cz.***: Viramune; ***Denm.***: Viramune; ***Fin.***: Viramune; ***Fr.***: Viramune; ***Ger.***: Viramune; ***Gr.***: Viramune; ***Hong Kong***: Viramune; ***Hung.***: Viramune; ***India***: Nev; Neve; Nevimune; Nevipan; Nevir; Neviretro; ***Indon.***: Viramune†; ***Irl.***: Viramune; ***Israel***: Viramune; ***Ital.***: Viramune; ***Jpn***: Viramune; ***Malaysia***: Hirapine; Nevipan; Viramune; ***Mex.***: Viramune; ***Neth.***: Viramune; ***Norw.***: Viramune; ***NZ***: Viramune; ***Pol.***: Viramune; ***Port.***: Viramune; ***Rus.***: Viramune (Вирамун); ***S.Afr.***: Nevivir; Viramune; Viropon; ***Singapore***: Viramune; ***Spain***: Viramune; ***Swed.***: Viramune; ***Switz.***: Viramune; ***Thai.***: Neravir; Viramune; ***Turk.***: Viramune; ***UK***: Viramune; ***Ukr.***: Viramune (Вирамун); ***USA***: Viramune; ***Venez.***: Nevimune; Viramune.

Multi-ingredient Preparations. ***Arg.***: Lazinevir; ***India***: Cytocom-N; Duovir N; Emduo-N; Emtri; Lami Plus; Lamostad-N; Lazid-N; Triomune; ***S.Afr.***: Sonke-LamiNevStav; Triomune; Virtrium; ***Thai.***: GPO-Vir S; GPO-Vir Z; ***Venez.***: Triomune.

Pharmacopoeial Preparations

USP 36: Nevirapine Oral Suspension; Nevirapine Tablets.

Oseltamivir Phosphate

(BANM, USAN, rINNM)

Fosfato de oseltamivir; GS-4104/002; Oseltamivir, fosfato de; Oséltamivir, Phosphate d'; Oseltamiviri Phosphas; Ro-64-0796/002; Осельтамивира Фосфат.

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (1:1).

$C_{16}H_{28}N_2O_4,H_3PO_4$=410.4

CAS — 196618-13-0 (oseltamivir); 204255-11-8 (oseltamivir phosphate).

ATC — J05AH02.

ATC Vet — QJ05AH02.

UNII — 4A3O49NGEZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Oseltamivir Phosphate). A white or almost white powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Oseltamivir Phosphate). White to off-white powder. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol, in dimethyl sulfoxide, and in propylene glycol; sparingly soluble in dimethylformamide; very slightly soluble in isopropyl alcohol and in macrogol 400; practically insoluble in acetonitrile, in acetone, in dichloromethane, and in *n*-hexane. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Oseltamivir is a prodrug of oseltamivir carboxylate, an inhibitor of the enzyme neuraminidase (sialidase), which has a role in the infectivity and replication of influenza A and B viruses. It is used for the treatment and postexposure prophylaxis of influenza A and B (p. 1007.1), including pandemic strains.

Oseltamivir is given orally as the phosphate, but doses are expressed in terms of the base. Oseltamivir phosphate 98.5 mg is equivalent to about 75 mg of oseltamivir. For *treatment* a dose of 75 mg is given twice daily for 5 days, beginning as soon as possible (within 48 hours) after the onset of symptoms. For *postexposure prophylaxis* the usual dose is 75 mg given once daily for at least 10 days and for up to 6 weeks during an epidemic; therapy should begin within 48 hours of exposure. In the EU intravenous oseltamivir phosphate is also available for use in patients from 1 year of age on compassionate grounds.

For details of doses in children, see below.

Dosage should be reduced in patients with renal impairment (see p. 1007.1).

Oseltamivir has been tried both for prophylaxis and treatment of H5N1 disease (avian influenza) and has been proposed as a measure to contain any potential pandemic until an effective vaccine could be developed.

Administration. Emergency compounding of an oral suspension from oseltamivir capsules may be necessary during situations when commercially manufactured oral suspension is not readily available. UK licensed product information suggests those who are unable to swallow capsules may be given the appropriate doses of oseltamivir by opening oseltamivir capsules and pouring the contents into a suitable, small amount (1 teaspoon maximum) of sweetened food product to mask the bitter taste. The mixture should be stirred and the entire contents given to the patient immediately after preparation.

Alternatively, licensed product information provides guidelines for a pharmacist to compound a solution (final concentration 15 mg/mL for children more than 1 year of age) from oseltamivir capsules using either water containing 0.1% w/v sodium benzoate, cherry syrup (*Humco*), or *Ora-Sweet SF*, as a vehicle. UK licensed product information also provides guidelines for compounding a 10 mg/mL solution for use in children less than 1 year of age.

Administration in children. Oseltamivir is given orally in the treatment and prophylaxis of influenza A and B in children aged 1 year and over. In addition, during the 2009 H1N1 pandemic, dosing recommendations for oseltamivir for treatment and postexposure prophylaxis in children less than 1 year of age were also developed.

Doses for children 1 year of age and over are determined by body-weight and may be given twice daily for 5 days for treatment, or once daily for 10 days for prophylaxis, of influenza A and B as follows:

- children over 40 kg: 75 mg
- more than 23 kg to 40 kg: 60 mg
- more than 15 kg to 23 kg: 45 mg
- 15 kg or less: 30 mg

Doses for use in children less than 1 year of age are determined by age and body-weight, and are given twice daily for 5 days for treatment, or once daily for 10 days for prophylaxis. The following doses are recommended:

- infants 0 to 1 month of age: 2 mg/kg
- those from 1 to 3 months of age: 2.5 mg/kg
- those from 3 to 12 months of age: 3 mg/kg

In the USA the recommended treatment dose of oseltamivir in children less than 1 year of age is 3 mg/kg twice daily.[1,2] Although it is not licensed for postexposure prophylaxis in children under 1 year of age, the CDC[1] recommends a dose of 3 mg/kg once daily; for those aged less than 3 months prophylaxis is not recommended unless considered to be essential. For the treatment of infants aged 14 days or less WHO recommends a dose of 2.5 to 3 mg/kg once daily and in those aged 15 days to 12 months a dose of 3 mg/kg twice daily.[3] *Premature infants* might have a slower clearance of oseltamivir as a result of an immature renal system and therefore the weight-based dosing recommendations for full-term infants are probably not appropriate, furthermore there are insufficient data to recommend a specific dose for them.[1]

Therapy should begin within 48 hours of exposure or the onset of symptoms. During a community outbreak, prophylaxis may be continued for up to 6 weeks.

The *BNFC* advises the following adjustments of normal doses in children with **renal impairment** according to the estimated glomerular filtration rate (eGFR):

For *treatment of influenza*:
- eGFR > 30 to 60 mL/minute per 1.73m²: 40% of normal dose twice daily
- eGFR > 10 to 30 mL/minute per 1.73m²: 40% of normal dose once daily
- eGFR ⩽ 10 mL/minute per 1.73m²: use not recommended

For *prevention of influenza*:
- eGFR > 30 to 60 mL/minute per 1.73m²: 40% of normal dose once daily
- eGFR > 10 to 30 mL/minute per 1.73m²: 40% of normal dose every 48 hours
- eGFR ⩽ 10 mL/minute per 1.73m²: use not recommended

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Administration in renal impairment. Oral doses of oseltamivir should be reduced in patients with renal impairment, according to creatinine clearance (CC).

Licensing authorities differ in their recommendations. UK licensed product information gives the following guidance for **adults**:

For *treatment of influenza*:
- CC > 30 to 60 mL/minute: 30 mg twice daily
- CC > 10 to 30 mL/minute: 30 mg once daily
- CC ⩽ 10 mL/minute: use not recommended
- haemodialysis patients: 30 mg after each dialysis session
- peritoneal dialysis patients: 30 mg single dose

For *prevention of influenza*:
- CC > 30 to 60 mL/minute: 30 mg once daily
- CC > 10 to 30 mL/minute: 30 mg every second day
- CC ⩽ 10 mL/minute: use not recommended
- haemodialysis patients: 30 mg after every second dialysis session
- peritoneal dialysis patients: 30 mg once weekly

US licensed product information advises that the dose of oseltamivir be reduced in adults with CC between 10 and 30 mL/minute; 75 mg daily is recommended for *treatment of influenza*, and 75 mg every other day *or* 30 mg daily is recommended for *prophylaxis of influenza*. No recommendations are given for patients with end-stage renal disease, including those who are dialysis-dependent.

For details of dose adjustments in children with renal impairment, see p. 1006.3.

Influenza. Reviews[1-11] of oseltamivir and other neuraminidase inhibitors in the treatment and prophylaxis of influenza (p. 960.2). There is some evidence[12] that zanamivir is more effective than oseltamivir for influenza B. However, a study[13] in Japanese children found oseltamivir and zanamivir to be equally effective in reducing the febrile period in those with influenza A (H1N1), influenza A (H3N2), and influenza B virus infection. A systematic review and quantitative analysis[14] to evaluate the safety and efficacy of extended-duration (more than 4 weeks) use of neuraminidase inhibitors for prophylaxis against seasonal influenza, reported that there was no statistically significant difference between oseltamivir and zanamivir prophylaxis for preventing symptomatic influenza among immunocompetent white and Japanese adults, although nausea and vomiting were more common among those who took oseltamivir.

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2. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. *Drugs* 2001; **61:** 263–83.
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4. Cooper NJ, *et al.* Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003; **326:** 1235–9.
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13. Sugaya N, *et al.* Comparison of the clinical effectiveness of oseltamivir and zanamivir against influenza virus infection in children. *Clin Infect Dis* 2008; **47:** 339–45.
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Adverse Effects

The most commonly reported adverse effects associated with oseltamivir treatment or prophylaxis in adults are nausea and vomiting, abdominal pain, bronchitis, insomnia, and vertigo. Diarrhoea, dizziness, headache, cough, and fatigue may occur, but many adverse effects may be difficult to distinguish from the symptoms of influenza. Other adverse effects occurring less commonly or for which the frequency of occurrence is unknown have included unstable angina, anaemia, arrhythmias, gastrointestinal bleeding, haemorrhagic or pseudomembranous colitis, pneumonia, pyrexia, and peritonsillar abscess. There have been occasional reports of anaphylaxis and skin rashes, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Elevated liver enzymes and hepatitis, including cases of fatal fulminant hepatitis or hepatic failure, have been reported rarely. Prophylaxis in adults has also been associated with aches and pains, dyspepsia, rhinorrhoea, and upper respiratory-tract infections.

The most commonly reported adverse effects in children receiving treatment or prophylaxis with oseltamivir are vomiting and other gastrointestinal problems. Other commonly occurring adverse events include asthma, bronchitis, conjunctivitis, dermatitis, epistaxis, ear disorders and otitis media, lymphadenopathy, pneumonia, and sinusitis.

There have been postmarketing reports (mainly in Japanese children and adolescents) of neuropsychiatric adverse effects (see below).

Incidence of adverse effects. A cross-sectional online survey[1] reporting on schoolchildren taking prophylactic oseltamivir for the pandemic (H1N1) 2009 influenza found that less than half (48%) of those in primary school completed a full course, compared with about three-quarters (76%) of secondary school pupils. More than half (53%) of all the children reported one or more adverse effects. Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, stomach pain or cramps were reported by 40% of children, while 18% reported a mild neuropsychiatric adverse effect such as poor concentration, inability to think clearly, problems in sleeping, feeling dazed or confused, bad dreams or nightmares, or behaving strangely. Neuropsychiatric adverse effects were more commonly reported by secondary (20%) than primary (13%) schoolchildren.

The MHRA (UK) reported[2] that between 23rd July 2009 and 6th October 2009, 628 351 treatment courses of oseltamivir had been issued (for management of the pandemic (H1N1) 2009 influenza via the National Pandemic Flu Service) and 1365 suspected adverse effects to oseltamivir had been voluntarily submitted to them between 1st April 2009 and 8th October 2009. The most commonly reported suspected adverse effects were consistent with the recognised adverse effects of oseltamivir, such as mild allergic reactions, gastrointestinal effects, headache, and dizziness, all of which can be caused by a flu-like illness; no new safety concerns were identified. However, they also received 6 reports in which the patient died, as well as some reports of liver reactions, including two reports of liver failure, but there is no evidence to confirm that oseltamivir was directly responsible for any of these events.

1. Kitching A, *et al.* Oseltamivir adherence and side effects among children in three London schools affected by influenza A(H1N1)v, May 2009–an internet-based cross-sectional survey. *Eur Surveill.* 2009; **14** (30th Jul.) 2–5. Available at: http://www.eurosurveillance.org/images/dynamic/EE/V14N30/art19287.pdf (accessed 22/10/09)
2. MHRA. UK suspected adverse drug reaction (ADR) analysis influenza antivirals - oseltamivir (Tamiflu) and zanamivir (Relenza), (issued 15 October 2009). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con059973.pdf (accessed 22/10/09)

Neuropsychiatric effects. An FDA review of the Adverse Event Reporting System (AERS) database from March 2004 to April 2005 reported 75 cases of serious adverse effects linked to the use of oseltamivir in children; 69 from Japan, 5 from USA, and 1 from Canada. Thirty-two cases of neuropsychiatric adverse effects including cases of delirium, abnormal behaviour, hallucinations, convulsions, and encephalitis, were reported, with 31 of these cases being reported from Japan. Twelve deaths were reported; 4 from sudden death, 4 due to cardiopulmonary arrest, and others due to disturbance of consciousness (without falling), pneumonia, asphyxiation, and acute pancreatitis with cardiopulmonary arrest. All deaths were reported from Japan.[1] The Japanese Ministry of Health Labour and Welfare reported that from 2001 to May 2007 they received 1377 adverse effects reports associated with the use of oseltamivir, including 567 reports of serious neuropsychiatric adverse effects and 211 cases of abnormal behaviour. Death was reported in 71 cases.[2] After the suicides of 2 adolescents, the Japanese authorities advised against the use of oseltamivir in adolescents aged 10 to 19 years.[3] However, given that influenza itself may have neuropsychiatric sequelae, any causal relationship with the drug remains unproven.[1,3]

A manufacturer-initiated comprehensive assessment[4] identified 3051 spontaneous reports of neuropsychiatric adverse effects in influenza patients treated with oseltamivir between 1999 and 15 September 2007; 2772 (90.9%) events were from Japan, 190 (6.2%) from the USA, and 89 (2.9%) from other countries. During this period oseltamivir was prescribed to around 48 million people worldwide. Neuropsychiatric adverse effects were more common in children (2218 events in 1808 children aged 16 years and younger versus 833 events in 658 adults) and more frequently reported in males. They generally occurred within 48 hours of starting treatment and the onset of influenza illness, with the most commonly reported neuropsychiatric adverse effects being abnormal behaviour, delusions, perceptual disturbances, and delirium or delirium-like events. Most of the reported neuropsychiatric adverse effects resolved spontaneously, but in rare cases resulted in injury or death. The available data indicated that the incidence of neuropsychiatric adverse effects in those who took oseltamivir was not higher than in those who did not. Furthermore, no clinically relevant differences in plasma pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate were noted between Japanese and Caucasian patients.

See also Incidence of Adverse Effects, above

1. FDA, Center for Drug Evaluation and Research. Pediatric safety update for Tamiflu: Pediatric Advisory Committee meeting (issued 18 November 2005). Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_06_06_summary.pdf (accessed 13/06/08)
2. Hama R. Oseltamivir's adverse reactions: Fifty sudden deaths may be related to central suppression. *BMJ* 2007; **335:** 59.
3. Maxwell SRJ. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007; **334:** 1232–3.
4. Toovey S, *et al.* Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Safety* 2008; **31:** 1097–114.

Precautions

Oseltamivir is not recommended in patients with creatinine clearance of 10 mL/minute or less and it should be given with caution and dosage should be reduced in patients with a creatinine clearance of 10 to 30 mL/minute.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Breast feeding. Oseltamivir and its active metabolite are distributed into breast milk in *rodents*. Licensed product information recommends that it should only be given to breast-feeding mothers if the potential benefit justifies the potential risk.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oseltamivir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Studies in *rodents* given high doses of oseltamivir have not found it to be fetotoxic or embryotoxic. Data on the use of oseltamivir in pregnant women are limited and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk; prescribing guidance from local health authorities should also be taken into consideration.

Pregnant women with influenza have an increased risk of morbidity, particularly due to respiratory complications, and high excess mortality rates have been seen in previous influenza pandemics.[1] Healthcare authorities[2,3] therefore supported the use of a neuramidase inhibitor such as oseltamivir in pregnant women during the pandemic (H1N1) 2009 influenza virus outbreak.

Reviews[4-6] of medical records for pregnant women treated with a neuramidase inhibitor during the 2009 influenza pandemic indicated that treatment within 48

hours of onset of symptoms was associated with better outcomes.[5] A review[1] of the use of oseltamivir in pregnancy reported that adverse pregnancy outcomes were not found to be higher than background incidence rates, and that oseltamivir did not appear to be causally related to adverse pregnancy or fetal outcomes.

1. Donner B, *et al.* Safety of oseltamivir in pregnancy: a review of preclinical and clinical data. *Drug Safety* 2010; **33:** 631–42.
2. CDC. Updated interim recommendations for obstetric health care providers related to use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available at: http://www.cdc.gov/H1N1flu/pregnancy/antiviral_messages.htm (accessed 22/05/13)
3. WHO. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance (issued November 2009). Available at: http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf (accessed 22/05/13)
4. Louie JK, *et al.* Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010; **362:** 27–35.
5. Siston AM, *et al.* Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA* 2010; **303:** 1517–25.
6. CDC. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)—United States, April 2009–August 2010. *MMWR* 2011; **60:** 1193–6.

Interactions

Oseltamivir may potentially inhibit replication of the influenza virus in live influenza virus vaccines. Therefore, US licensed product information states that live influenza virus vaccines should not be given until 48 hours after stopping oseltamivir and that oseltamivir should not be given for 2 weeks after live influenza virus vaccines have been given. Inactivated (split virion or surface antigen) vaccines are not expected to be affected by oseltamivir.

Antiviral Action

Oseltamivir has antiviral activity similar to that of zanamivir (p. 1024.2). Its active metabolite, oseltamivir carboxylate, selectively blocks the viral surface enzyme neuraminidase, thereby preventing the release of virus particles from infected cells. Oseltamivir is active against influenza A and B viral neuraminidase.

Resistance. Oseltamivir-resistant type A virus, including H5N1 subtypes, have been reported in patients being treated for influenza.[1-3] A study[1] in Japan found that 9 of 50 (18%) children with influenza A (H3N2) virus infection who had been treated with oseltamivir had a virus with a drug-resistance mutation in the neuraminidase gene (mainly R292K). Another study[4] in Japan reported resistant influenza A (H1N1) viruses with the H274Y mutation in 7 of 43 (16%) oseltamivir-treated children. In both these studies the children were given an oral dose of 2 mg/kg twice daily. However, a larger study[5] in the US reported no resistance in children who received age- and weight-tailored (and therefore sometimes substantially higher) doses than those used in the Japanese studies. A small study[6] in the UK, during the 2005-2007 influenza season, in children treated with a tiered weight-based oseltamivir dosing regimen recovered antiviral resistant viruses from 3 of 11 children with influenza A (H1N1), 1 of 34 with influenza A (H3N2), and from none of the 19 children with influenza B virus. Transmission of oseltamivir-resistant influenza was not very common during the 2006-2007 influenza season, but by the winter of 2007-2008 H274Y mutations were frequently identified among influenza A (H1N1) isolates in many areas of Europe[7,8] and in December 2008 the CDC reported that 24 out of 25 influenza A (H1N1) isolates tested were resistant to oseltamivir but remained susceptible to zanamivir.[9] A study[10] in the USA reported that 98.5% of 268 influenza A (H1N1) isolates from the 2008 to 2009 season were resistant to oseltamivir and that they carried the neuraminidase H274Y mutation. Other N1-containing strains, including avian influenza A (H5N1), which have the same H274Y mutation are therefore also likely to develop oseltamivir resistance during treatment, but not zanamivir resistance.[7,8] Influenza A (H3N2) remains susceptible to both oseltamivir and zanamivir.[7]

Systematic surveillance conducted during the 2009 (H1N1) influenza pandemic, by the Global Influenza Surveillance Network has detected sporadic and infrequent incidents of oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, but there is no evidence of person-to-person transmission or that these resistant viruses are circulating within communities or worldwide. As of the 25th September 2009, 28 resistant viruses had been detected and characterised worldwide. All of these viruses had the same H275Y mutation that confers resistance to oseltamivir, but not to zanamivir. Twelve of these drug-resistant viruses were associated with the use of oseltamivir for postexposure prophylaxis, and 10 were isolated from patients receiving oseltamivir treatment, 6 of whom had severe immunosuppression; 2 were isolated from patients who were not taking oseltamivir for either treatment or prophylaxis.[11]

Resistance to influenza B virus does not occur as often as to influenza A viruses. A study[12] in 74 Japanese children infected with influenza B virus and given oseltamivir reported 1 case of reduced sensitivity to neuraminidase inhibitors; reduced sensitivity was also identified in 7 of 422 viruses from untreated patients, indicating that resistant influenza B viruses appear to be transmitted within communities and families.

No viruses resistant to zanamivir have been isolated from immunocompetent people,[13] although resistance occurred in an immunocompromised child infected with influenza B.[14]

1. Kiso M, *et al.* Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004; **364:** 759–65.
2. de Jong MD, *et al.* Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; **353:** 2667–72.
3. Le QM, *et al.* Avian flu: isolation of drug-resistant H5N1 virus. *Nature* 2005; **437:** 1108. Correction. *ibid.*; **438:** 754.
4. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; **55** (suppl 1): i5–i21.
5. Hayden FG, *et al.* Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004; **189:** 440–9.
6. Stephenson I, *et al.* Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis* 2009; **48:** 389–96.
7. Monto AS. Implications of antiviral resistance of influenza viruses. *Clin Infect Dis* 2009; **48:** 397–9.
8. Weinstock DM, Zuccotti G. The evolution of influenza resistance and treatment. *JAMA* 2009; **301:** 1066–9.
9. CDC. Update: Influenza Activity—United States, September 28–November 29, 2008. *MMWR* 2008; **57:** 1329–32. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5749.pdf (accessed 26/10/09)
10. Dharan NJ, *et al.* Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA* 2009; **301:** 1034–41.
11. WHO. Antiviral use and the risk of drug resistance pandemic (H1N1) 2009 briefing note 12 (issued 25th September 2009). Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_antiviral_use_20090925/en/index.html (accessed 19/10/09)
12. Hatakeyama S, *et al.* Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. *JAMA* 2007; **297:** 1435–42.
13. Moscona A. Oseltamivir-resistant influenza? *Lancet* 2004; **364:** 733–4.
14. Gubareva LV, *et al.* Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998; **178:** 1257–62.

Pharmacokinetics

Oseltamivir is readily absorbed from the gastrointestinal tract after oral doses and is extensively metabolised in the liver to the active entity, oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as the carboxylate. Binding to plasma proteins is about 3% for the carboxylate and 42% for the parent drug. Oseltamivir has a plasma half-life of 1 to 3 hours and the carboxylate a plasma half-life of 6 to 10 hours. The carboxylate is not metabolised further and is eliminated in the urine.

Reviews.

1. Abe M, *et al.* Pharmacokinetics of oseltamivir in young and very elderly subjects. *Ann Pharmacother* 2006; **40:** 1724–30.
2. Rayner CR, *et al.* Population pharmacokinetics of oseltamivir when coadministered with probenecid. *J Clin Pharmacol* 2008; **48:** 935–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agripan; Agucort; Tamiflu; Veltamir; ***Austral.***: Tamiflu; ***Austria***: Tamiflu; ***Belg.***: Tamiflu; ***Braz.***: Tamiflu; ***Canad.***: Tamiflu; ***Chile***: Euvirax; Rimivat; Tamiflu; Virobin; ***China***: Ao Er Fei (奥尔菲); Ke Wei (可威); Ou Rui Si (欧瑞斯); Tamiflu (达菲); ***Cz.***: Tamiflu; ***Denm.***: Tamiflu; ***Fin.***: Tamiflu; ***Fr.***: Tamiflu; ***Ger.***: Tamiflu; ***Gr.***: Tamiflu; ***Hong Kong***: Tamiflu; ***Hung.***: Tamiflu; ***India***: Fluvir; ***Irl.***: Tamiflu; ***Israel***: Tamiflu; ***Ital.***: Tamiflu; ***Jpn***: Tamiflu; ***Malaysia***: Fluhalt; Omiflu; Tamiflu; ***Mex.***: Tamiflu; ***Neth.***: Tamiflu; ***Norw.***: Tamiflu; ***NZ***: Tamiflu; ***Philipp.***: Tamiflu; ***Pol.***: Tamiflu; ***Port.***: Tamiflu; ***Rus.***: Tamiflu (Тамифлю); ***S.Afr.***: Tamiflu; ***Singapore***: Tamiflu; ***Spain***: Tamiflu; ***Swed.***: Tamiflu; ***Switz.***: Tamiflu; ***Thai.***: GPO-A-Flu; Tamiflu; ***Turk.***: Enfluvir; Tamiflu; ***UAE***: FluFly; ***UK***: Tamiflu; ***Ukr.***: Tamiflu (Тамифлю); ***USA***: Tamiflu.

Pharmacopoeial Preparations
BP 2014: Paediatric Oseltamivir Oral Solution;
USP 36: Oseltamivir Phosphate Capsules.

Penciclovir *(BAN, USAN, rINN)*

BRL-39123; BRL-39123-D (penciclovir sodium); Penciclovirum; Penciklovir; Pensikloviiri; Pensiklovir; Пенцикловир.

9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine.

$C_{10}H_{15}N_5O_3$=253.3

CAS — 39809-25-1 (penciclovir); 97845-62-0 (penciclovir sodium).

ATC — D06BB06; J05AB13.

ATC Vet — QD06BB06; QJ05AB13.

UNII — 359HUE8FJC.

Uses and Administration

Penciclovir is a nucleoside analogue structurally related to guanine, which is active against herpesviruses. It is applied topically as a 1% cream every 2 hours during waking hours for 4 days in the treatment of herpes labialis (see Herpes Simplex Infections, p. 955.2).

For systemic use, penciclovir is given orally as the prodrug famciclovir (see p. 979.1). Intravenous dosage of penciclovir has been investigated.

References.

1. Spruance SL, *et al.* Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. *JAMA* 1997; **277:** 1374–9.
2. Lazarus HM, *et al.* Intravenous penciclovir for treatment of herpes simplex infections in immunocompromised patients: results of a multicenter, acyclovir-controlled trial. *Antimicrob Agents Chemother* 1999; **43:** 1192–7.
3. Boon R, *et al.* Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2000; **22:** 76–90.
4. Raborn GW, *et al.* Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc* 2002; **133:** 303–9.
5. Lin L, *et al.* Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. *J Dermatol Treat* 2002; **13:** 67–72.

Adverse Effects and Precautions

Penciclovir applied topically may cause transient stinging, burning, and numbness.

For adverse effects of penciclovir after systemic use of famciclovir, see p. 979.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies penciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Antiviral Action

Penciclovir has antiviral activity similar to that of aciclovir (p. 966.1). It is active *in vitro* and *in vivo* against herpes simplex virus types 1 and 2 and against varicella-zoster virus. This activity is due to intracellular conversion by virus-induced thymidine kinase into penciclovir triphosphate, which inhibits replication of viral DNA and persists in infected cells for more than 12 hours. It also has activity against Epstein-Barr virus and hepatitis B virus.

References.

1. Vere-Hodge RA. Famciclovir and penciclovir: the mode of action of famciclovir including its conversion to penciclovir. *Antiviral Chem Chemother* 1993; **4:** 67–84.
2. Boyd MR, *et al.* Penciclovir: a review of its spectrum of activity, selectivity, and cross-resistance pattern. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 3–11.
3. Bacon TH, Boyd MR. Activity o f penciclovir against Epstein-Barr virus. *Antimicrob Agents Chemother* 1995; **39:** 1599–1602.
4. Sarisky RT, *et al.* Profiling penciclovir susceptibility and prevalence of resistance of herpes simplex virus isolates across eleven clinical trials. *Arch Virol* 2003; **148:** 1757–69.

Pharmacokinetics

Penciclovir is poorly absorbed from the gastrointestinal tract. For systemic use it is usually given orally as the prodrug famciclovir, which is rapidly converted to penciclovir. Peak plasma concentrations proportional to the dose (over the range 125 to 750 mg) occur after 45 minutes to 1 hour. The plasma elimination half-life is about 2 hours. The intracellular half-life of the active triphosphate metabolite is longer. Penciclovir is less than 20% bound to plasma proteins. Penciclovir is mainly excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pentavir; ***Austral.***: Vectavir; ***Austria***: Famvir; Fenivir; ***Belg.***: Vectavir; ***Braz.***: Penvir Labia; Vectavir†; ***Canad.***: Denavir; ***China***: Danpule (丹普乐); Fu Tan (夫坦); Heng Ao Pu Kang (恒奥普康); Keyou (可由); Li Ke Shuang (丽科爽); Li Zhu Jun Le (丽珠君乐); ***Cz.***: Vectavir; ***Denm.***: Vectavir; ***Fin.***: Vectavir; ***Ger.***: Fenistil Pencivir†; ***Gr.***: Fenivir; Vectavir; ***Hung.***: Fenivir; ***Irl.***: Vectavir; ***Israel***: Fenlips; ***Ital.***: Vectavir; Zilip; ***Neth.***: Fenistil Penciclovir; Vectavir†; ***Norw.***: Vectavir; ***Port.***: Denovir†; Fenivir; ***Rus.***: Fenistil Pencivir (Фенистил Пенцивир); ***S.Afr.***: Fenivir†; ***Singapore***: Vectavir; ***Spain***: Fenivir; Vectavir†; ***Swed.***: Vectavir; ***Switz.***: Famvir†; Fenivir; ***Turk.***: Vectavir; ***UK***: Fenistil; Vectavir; ***Ukr.***: Fenistil Pencivir (Фенистил Пенцивир); ***USA***: Denavir.

Peptide T

D-Ala-peptide-T-amide; Péptido T; Пептид Т.

Profile

Peptide T is an octapeptide segment of the envelope glycoprotein of HIV. It has been investigated for the treatment of HIV infection and HIV-associated neurological

disorders. Peptide T has also been tried in the treatment of psoriasis.

Peramivir *(USAN, rINN)*

BCX-1812; Péramivir; Peramivirum; RWJ-270201; Перамивир.
(1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-Acetylamino-2-ethylbutyl]-4-[(aminoiminomethyl)amino]-2-hydroxycyclopentanecarboxylic acid trihydrate.
$C_{15}H_{28}N_4O_4,3H_2O$=382.5
CAS — 229614-55-5 (peramivir monohydrate).
UNII — QW7Y7ZR15U.

Uses and Administration

Peramivir is a neuraminidase inhibitor that is given intravenously; it is being evaluated in phase 3 clinical studies for the treatment of influenza (see p. 960.2). Although it has not yet been approved for marketing, the FDA has authorised the emergency use of peramivir in the USA to treat certain adult and paediatric patients with suspected or laboratory-confirmed pandemic (H1N1) 2009 influenza, or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology.

The recommended dose for patients from 18 years of age is 600 mg given intravenously over 30 minutes once daily for 5 to 10 days. Dose adjustments are needed in patients with renal impairment, see below.

For details of doses in children, see below.

Administration in children. Peramivir may be given to children in the treatment of pandemic (H1N1) 2009 influenza, similarly to adults (see above). Doses may be given intravenously over 60 minutes once daily for 5 to 10 days according to age as follows:

- birth to 30 days old: 6 mg/kg
- 31 to 90 days old: 8 mg/kg
- 91 to 180 days old: 10 mg/kg
- 181 days old to 5 years of age: 12 mg/kg
- 6 to 17 years of age: 10 mg/kg

The maximum daily dose is 600 mg. For details of dose adjustments in children with renal impairment, see below.

Administration in renal impairment. Intravenous doses of peramivir should be reduced in patients with renal impairment, according to creatinine clearance (CC):

Adults from 18 years of age.

- CC 31 to 49 mL/minute: 150 mg daily
- CC 10 to 30 mL/minute: 100 mg daily
- CC less than 10 mL/minute: 100 mg on day 1, then 15 mg daily thereafter
- Intermittent haemodialysis: 100 mg on day 1, and 2 hours after the end of each dialysis session

Infants and children.

- CC 31 to 49 mL/minute per 1.73 m^2:
  - 1.5 mg/kg daily in those from birth to 30 days old
  - 2 mg/kg daily in those from 31 to 90 days old
  - 2.5 mg/kg daily in those from 91 to 180 days old
  - 3 mg/kg daily in those from 181 days old to 5 years of age
  - 2.5 mg/kg daily in those from 6 to 17 years of age
- CC 10 to 30 mL/minute per 1.73 m^2:
  - 1 mg/kg daily in those from birth to 30 days old
  - 1.3 mg/kg daily in those from 31 to 90 days old
  - 1.6 mg/kg daily in those from 91 to 180 days old
  - 1.9 mg/kg daily in those from 181 days old to 5 years of age
  - 1.6 mg/kg daily in those from 6 to 17 years of age
- CC less than 10 mL/minute per 1.73 m^2:
  - 1 mg/kg on day 1, then 0.15 mg/kg daily in those from birth to 30 days old
  - 1.3 mg/kg on day 1, then 0.2 mg/kg daily in those from 31 to 90 days old
  - 1.6 mg/kg on day 1, then 0.25 mg/kg daily in those from 91 to 180 days old
  - 1.9 mg/kg on day 1, then 0.3 mg/kg daily in those from 181 days to 5 years of age
  - 1.6 mg/kg on day 1, then 0.25 mg/kg daily in those from 6 to 17 years of age
- For children on intermittent haemodialysis, the following doses, based on age and weight, are given on day 1, and then 2 hours after each dialysis session:
  - 1 mg/kg for those from birth to 30 days old
  - 1.3 mg/kg for those from 31 to 90 days old
  - 1.6 mg/kg for those from 91 to 180 days old
  - 1.9 mg/kg for those from 181 days to 5 years of age
  - 1.6 mg/kg for those from 6 to 17 years of age

Adverse Effects

Safety and efficacy data for peramivir are limited. The most commonly reported adverse events have been diarrhoea, nausea, vomiting, and neutropenia. Although not seen in clinical studies to date the FDA considers that it may rarely cause anaphylaxis or serious skin reactions. As with other neuraminidase inhibitors, neurologic and behavioral symptoms have been infrequently reported. For further information on neurological and other adverse effects associated with neuraminidase inhibitors, see under Oseltamivir, p. 1007.2.

Patients with known or suspected renal insufficiency should have a baseline creatinine clearance measurement before taking peramivir. Dosage adjustments may be necessary in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Rapiacta.

Pleconaril *(USAN, rINN)*

Pléconaril; Pleconarilo; Pleconarilum; VP-63843; Win-63843; Плеконарил.
3-{4-[3-(3-Methyl-5-isoxazolyl)propoxy]-3,5-xylyl}-5-(trifluoromethyl)-1,2,4-oxadizole.
$C_{18}H_{18}F_3N_3O_3$=381.4
CAS — 153168-05-9.
ATC — J05AX06.
ATC Vet — QJ05AX06.
UNII — 9H4570Q89D.

Profile

Pleconaril is an antiviral with activity against a range of picornaviruses. It has been investigated for the oral treatment of viral meningitis and encephalitis, upper respiratory-tract viral infections, and other enteroviral infections. However, there have been concerns over efficacy, viral resistance, and interactions with oral contraceptives. Development of an intranasal formulation for the common cold has also been investigated.

References.

1. Nowak-Wegrzyn A, *et al.* Successful treatment of enterovirus infection with the use of pleconaril in 2 infants with severe combined immunodeficiency. *Clin Infect Dis* 2001; **32:** E13–E14.
2. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001; **32:** 228–35.
3. Aradottir E, *et al.* Severe neonatal enteroviral hepatitis treated with pleconaril. *Pediatr Infect Dis J* 2001; **20:** 457–9.
4. Starlin R, *et al.* Acute flaccid paralysis syndrome associated with echovirus 19, managed with pleconaril and intravenous immunoglobulin. *Clin Infect Dis* 2001; **33:** 730–2.
5. Hayden FG, *et al.* Oral pleconaril treatment of picornavirus-associated viral respiratory illness in adults: efficacy and tolerability in phase II clinical trials. *Antivir Ther* 2002; **7:** 53–65.
6. Abzug MJ, *et al.* Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Pediatr Infect Dis J* 2003; **22:** 335–41.
7. Hayden FG, *et al.* Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. *Clin Infect Dis* 2003; **36:** 1523–32.
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Poly I.poly C12U

Poli(I)^{2}poli(C_{12}U); Poly(I):poly(C_{12},U); Поли I.Поли C12U.

Profile

Poly I.poly C12U is a synthetic mismatched polymer of double-stranded RNA with antiviral and immunomodulatory activity (see also Poly I. Poly C, p. 2594.1). It is under investigation in the treatment of HIV infection, and also in renal cell carcinoma, chronic fatigue syndrome, invasive melanoma, and hepatitis B and C.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ampligen.

Propagermanium *(rINN)*

Propagermanio; Пропагерманий.
A polymer obtained from 3-(trihydroxygermyl)propionic acid.
$(C_3H_5GeO_{3.5})_n$
CAS — 12758-40-6.

Profile

Propagermanium is an immunomodulator that has been used in chronic hepatitis B infections. Acute exacerbation of hepatitis, including some fatalities, has been reported in patients receiving propagermanium.

References.

1. Hirayama C, *et al.* Propagermanium: a nonspecific immune modulator for chronic hepatitis B. *J Gastroenterol* 2003; **38:** 525–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Serocion.

Raltegravir *(BAN, USAN, rINN)*

Raltégravir; Raltegravirum; Raltegrawir; Ральтегравир.
N-{2-[4-(4-Fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl}-5-methyl-1,3,4-oxadiazole-2-carboxamide.
$C_{20}H_{21}FN_6O_5$=444.4
CAS — 518048-05-0.
ATC — J05AX08.
ATC Vet — QJ05AX08.
UNII — 22VKV8053U.

Raltegravir Potassium *(BANM, USAN, rINNM)*

Kalii Raltegravirum; MK-0518; Raltegravir potásico; Raltégravir Potassique; Калия Ральтегравир.
Potassium 4-{[4-fluorobenzyl)carbamoyl]-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidin-5-olate.
$C_{20}H_{20}FKN_6O_5$=482.5
CAS — 871038-72-1.
UNII — 43Y000U234.

Uses and Administration

Raltegravir is an inhibitor of HIV integrase, an enzyme essential for insertion of viral DNA into the host genome, and thus for replication. It is used with other antiretrovirals for treatment of HIV infection and AIDS (p. 957.2) and is licensed for use in both treatment-naive and treatment-experienced patients.

It is given orally as the potassium salt but doses are expressed in terms of the base; 434 mg of raltegravir potassium is equivalent to about 400 mg of raltegravir. The usual dose is the equivalent of 400 mg of raltegravir twice daily, with or without food. For details of doses in children and adolescents, see below.

Doses of raltegravir may need to be amended when given with rifampicin: a dose of 800 mg twice daily has been suggested.

References.

1. Iwamoto M, *et al.* Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. *Clin Pharmacol Ther* 2008; **83:** 293–9.
2. Croxtall JD, *et al.* Raltegravir. *Drugs* 2008; **68:** 131–8.
3. Croxtall JD, Keam SJ. Raltegravir: a review of its use in the management of HIV infection in treatment-experienced patients. *Drugs* 2009; **69:** 1059–75.
4. Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clin Infect Dis* 2009; **48:** 931–9.
5. Lennox JL, *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374:** 796–806. Correction. *ibid.*; 786.
6. Croxtall JD, Scott LJ. Raltegravir: in treatment-naive patients with HIV-1 infection. *Drugs* 2010; **70:** 631–42.
7. Steigbigel RT, *et al.* BENCHMRK Study Teams. Long-term efficacy and safety of raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 phase III trials. *Clin Infect Dis* 2010; **50:** 605–12.
8. Ramkumar K, Neamati N. Raltegravir: the evidence of its therapeutic value in HIV-1 infection. *Core Evid* 2010; **4:** 131–47.
9. Skiest DJ, *et al.* Similar efficacy of raltegravir when used with or without a protease inhibitor in treatment-experienced patients. *HIV Clin Trials* 2011; **12:** 131–40.
10. Brainard DM, *et al.* Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J Clin Pharmacol* 2011; **51:** 1376–1402.
11. Rokas KEE, *et al.* Role of raltegravir in HIV-1 management. *Ann Pharmacother* 2012; **46:** 578–89.

Administration in children. For the treatment of HIV infection in children from 2 years of age and adolescents raltegravir is given with other antiretroviral drugs. In the USA, oral *film-coated* or *chewable* tablets are available; the two formulations are not interchangeable as the chewable tablet has a higher bioavailability compared with the film-coated tablets. Doses are based on body-weight.

In children from 2 years (and weighing at least 10 kg) to less than 12 years of age, the following dose recommendations are made for *chewable tablets*:

- 10 to less than 14 kg: 75 mg twice daily
- 14 to less than 20 kg: 100 mg twice daily
- 20 to less than 28 kg: 150 mg twice daily
- 28 to less than 40 kg: 200 mg twice daily
- at least 40 kg: 300 mg twice daily (maximum dose)

Film-coated tablets may be given to children from 6 years of age (and weighing at least 25 kg) and adolescents; the usual oral dose is 400 mg twice daily.

Adverse Effects and Precautions

On the basis of limited data, raltegravir appears to be well tolerated; non-specific adverse effects associated with raltegravir-based regimens include rash, insomnia, abnormal dreams, headache, abdominal pain, diarrhoea, nausea, vomiting, asthenia, fatigue, dizziness, and vertigo. Rarely, more serious adverse effects such as immune reconstitution syndrome, gastritis, hepatitis, renal failure, neutropenia, thrombocytopenia, and hypersensitivity and severe skin reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis have occurred. Psychiatric disturbances, including anxiety, depression, paranoia, and suicidal ideation have also been reported, particularly in those with a pre-existing history of mental illness. Abnormal creatine phosphokinase values may occur and myopathy and rhabdomyolysis have been reported although a causal relationship has not been established; nonetheless, caution is advised in patients at increased risk of these conditions. Increased liver transaminases and serum triglyceride concentrations may also occur.

Interactions

Raltegravir is not a substrate for cytochrome P450 isoenzymes, and does not appear to interact with drugs metabolised by this mechanism. However, rifampicin induces the glucuronidase responsible for raltegravir metabolism (UGT1A1) and reduces plasma concentrations of raltegravir; if use with rifampicin cannot be avoided, increasing the dose of raltegravir may be considered (see Uses and Administration, p. 1009.3).

Antivirals. Plasma concentrations of raltegravir were modestly increased by *atazanavir* and ritonavir-boosted atazanavir in healthy subjects; this increase is not considered to be clinically significant.[1]

In a pharmacokinetic study, use of raltegravir and *maraviroc* together resulted in decreased plasma concentrations of both drugs, although these changes were also not thought to be clinically significant.[2]

1. Iwamoto M, *et al.* Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *Clin Infect Dis* 2008; **47:** 137–40.
2. Andrews E, *et al.* Assessment of the pharmacokinetics of co-administered maraviroc and raltegravir. *Br J Clin Pharmacol* 2010; **69:** 51–7.

Gastrointestinal drugs. The solubility of raltegravir is pH-dependent, and use of *omeprazole* has been noted to increase plasma concentrations of raltegravir in healthy subjects.[1] However, some HIV-infected patients (and particularly those with AIDS) have increased gastric pH relating to their illness, and data from HIV-infected patients suggests acceptable safety and only modest pharmacokinetic interaction when gastric-acid reducing drugs are used with raltegravir.[1] US licensed product information for raltegravir therefore suggests that no dose adjustment is needed when raltegravir is used with gastric-acid reducing drugs, although UK licensed information has advised that such combinations should be avoided unless considered essential.

1. Iwamoto M, *et al.* Effects of omeprazole on plasma levels of raltegravir. *Clin Infect Dis* 2009; **48:** 489–92.

Pharmacokinetics

Raltegravir is absorbed on oral dosage and peak concentrations occur after 3 hours. There is considerable interindividual variation in the pharmacokinetics. It is metabolised via glucuronidation, catalysed by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and excreted in both urine and faeces as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Isentress; ***Austria***: Isentress; ***Belg.***: Isentress; ***Braz.***: Isentress; ***Canad.***: Isentress; ***Chile***: Isentress; ***China***: Isentress (艾生特); ***Cz.***: Isentress; ***Denm.***: Isentress; ***Fr.***: Isentress; ***Ger.***: Isentress; ***Gr.***: Isentress; ***Hong Kong***: Isentress; ***Hung.***: Isentress; ***Irl.***: Isentress; ***Israel***: Isentress; ***Ital.***: Isentress; ***Malaysia***: Isentress; ***Neth.***: Isentress; ***Norw.***: Isentress; ***NZ***: Isentress; ***Pol.***: Isentress; ***Port.***: Isentress; ***Rus.***: Isentress (Исентресс); ***Singapore***: Isentress; ***Spain***: Isentress; ***Swed.***: Isentress; ***Switz.***: Isentress; ***Thai.***: Isentress; ***UK***: Isentress; ***Ukr.***: Isentress (Исентресс); ***USA***: Isentress.

Resiquimod *(rINN)*

R-848; Résiquimod; Resiquimodum; S-28463; VML-600; Резихимод.

4-Amino-2-(ethoxymethyl)-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

$C_{17}H_{22}N_4O_2$=314.4

CAS — 144875-48-9.

UNII — V3DMU7PVXF.

Profile

Resiquimod is an immune response modifier that has been investigated for the topical treatment of genital herpes, common warts, and actinic keratosis. It is also being studied as a potential adjunct therapy for improving the immune response to certain vaccines.

References.

1. Spruance SL, *et al.* Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. *J Infect Dis* 2001; **184:** 196–200.
2. Mark KE, *et al.* Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: a randomized, controlled trial. *J Infect Dis* 2007; **195:** 1324–31.
3. Szeimies RM, *et al.* A phase II dose-ranging study of topical resiquimod to treat actinic keratosis. *Br J Dermatol* 2008; **159:** 205–10.
4. Igartua M, Pedraz JL. Topical resiquimod: a promising adjuvant for vaccine development? *Expert Rev Vaccines* 2010; **9:** 23–7.

Ribavirin *(BAN, USAN, rINN)*

ICN-1229; Ribaviriini; Ribavirina; Ribavirinas; Ribavirine; Ribavirinum; RTCA; Tribavirin; Рибавирин.

1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

$C_8H_{12}N_4O_5$=244.2

CAS — 36791-04-5.

ATC — J05AB04.

ATC Vet — QJ05AB04.

UNII — 49717AWG6K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Ribavirin). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; slightly soluble or very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.5. Protect from light.

USP 36: (Ribavirin). A white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. Store in airtight containers.

Uses and Administration

Ribavirin is a synthetic nucleoside analogue structurally related to guanine. It is given by aerosol in the treatment of RSV infections (p. 961.3); this route appears to give better results than the oral route although its efficacy is questionable. It is used orally with an interferon alfa or peginterferon alfa in the treatment of chronic hepatitis C (p. 990.3), including HIV co-infection. Ribavirin has been tried in haemorrhagic fevers, such as haemorrhagic fever with renal syndrome and Lassa fever (p. 1011.1), and in SARS (p. 962.2).

For details of doses in children, see below.

Ribavirin is used, with an interferon alfa or peginterferon alfa, for the treatment of chronic **hepatitis C**. For information on the dose of interferon alfa used in the treatment of chronic hepatitis C see under Interferon Alfa, p. 989.2. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In those with hepatitis C infection alone (*mono-infection*), patients with viral genotype 1, and probably genotype 4, should generally be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks; data on genotypes 5 or 6 are insufficient to make recommendations. In *co-infection* with HIV, treatment should generally be given for 48 weeks regardless of genotype.

Rebetol (*Schering-Plough*) is used, with interferon alfa-2b or peginterferon alfa-2b for hepatitis C.

The following doses are recommended in the UK:

- adults up to 65 kg: 400 mg both in the morning and in the evening
- 65 to 80 kg: 400 mg in the morning and 600 mg in the evening
- from 81 to 105 kg: 600 mg both in the morning and in the evening
- over 105 kg: 600 mg in the morning and 800 mg in the evening

In the USA, the dose of ribavirin given with interferon alfa-2b is:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

The following doses are used with peginterferon alfa-2b:

- adults up to 65 kg: 400 mg both in the morning and in the evening
- from 66 to 80 kg: 400 mg in the morning and 600 mg in the evening
- from 81 to 105 kg: 600 mg both in the morning and in the evening
- from 105 kg: 600 mg in the morning and 800 mg in the evening

Copegus (*Roche*) is used in the UK with interferon alfa-2a or peginterferon alfa-2a and in the USA with peginterferon alfa-2a.

The following doses are used with peginterferon alfa-2a for mono-infection in genotype 1 or 4:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For mono-infection in genotype 2 or 3 (with peginterferon alfa-2a):

- all adults: 400 mg both in the morning and in the evening

The following doses are used with interferon alfa-2a for mono-infection in genotype 1 to 4:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For co-infection with HIV:

- all adults: 800 mg daily, irrespective of genotype

Dose reductions of ribavirin may be necessary in patients who develop low haemoglobin concentrations. Ribavirin is contra-indicated in patients with a creatinine clearance less than 50 mL/minute.

Reviews.

1. Gish RG. Treating HCV with ribavirin analogues and ribavirin-like molecules. *J Antimicrob Chemother* 2006; **57:** 8–13.
2. Gambarin-Gelwan M, Jacobson IM. Optimal dose of peginterferon and ribavirin for treatment of chronic hepatitis C. *J Viral Hepatitis* 2008; **15:** 623–33.
3. Reddy KR, *et al.* Ribavirin: current role in the optimal clinical management of chronic hepatitis C. *J Hepatol* 2009; **50:** 402–11.
4. Shiffman ML. What future for ribavirin? *Liver Int* 2009; **29** (suppl 1): 68–73.
5. Brok J, *et al.* Ribavirin monotherapy for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 22/01/10).
6. Aghemo A, *et al.* Pegylated IFN-α 2a and ribavirin in the treatment of hepatitis C. *Expert Rev Anti Infect Ther* 2009; **7:** 925–35.
7. Gluud LL, *et al.* Peginterferon plus ribavirin for chronic hepatitis C in patients with human immunodeficiency virus. *Am J Gastroenterol* 2009; **104:** 2335–41.
8. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children [withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 18/08/10).

Administration. Reference[1] to the intravenous use of ribavirin.

1. Riner A, *et al.* Intravenous ribavirin—review of the FDA's Emergency Investigational New Drug Database (1997-2008) and literature review. *Postgrad Med* 2009; **121:** 139–46.

Administration in children. Preparations of ribavirin are available for aerosol administration to infants and children with severe **RSV** infection via a small particle aerosol generator. Solutions containing 20 mg/mL are used; 300 mL, representing 6 g of ribavirin, is delivered over a 12-to 18-hour period by aerosol at an average concentration of 190 micrograms/litre of air. Treatment is given for 3 to 7 days.

Ribavirin is used, with an interferon alfa or peginterferon alfa, for the treatment of chronic **hepatitis C**. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In hepatitis C mono-infection, patients with viral genotype 1 should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks.

Rebetol (Schering-Plough) is used, with interferon alfa-2b or peginterferon alfa-2b, for hepatitis C.

The following doses are recommended in the UK for children 3 years of age and older:

- less than 47 kg: 15 mg/kg daily in 2 divided doses
- 47 to 49 kg: 200 mg in the morning and 400 mg in the evening
- 50 to 65 kg: 400 mg both in the morning and in the evening
- over 65 kg: the adult dose (above)

In the USA, ribavirin is licensed for use with interferon alfa-2b and peginterferon alfa-2b, for the treatment of children from 3 to 17 years of age. The recommended doses of ribavirin are:

- less than 47 kg: 15 mg/kg daily
- 47 to 59 kg: 400 mg both in the morning and in the evening
- 60 to 73 kg: 400 mg in the morning and 600 mg in the evening
- over 73 kg: 600 mg both in the morning and in the evening

Copegus (Roche) is not licensed for use in those less than 18 years of age.

For information on the dose of interferon alfa used in the treatment of chronic hepatitis C in children see under Interferon Alfa, p. 990.1.

Encephalitis. A beneficial response to ribavirin was reported in a child with severe La Crosse encephalitis.[1]

Ribavirin was given intravenously in a dose of 25 mg/kg over the first 24 hours and then reduced to 15 mg/kg daily for a further 9 days. A small open-label study[2] suggested that ribavirin might also be able to reduce mortality and neurological deficits in acute Nipah encephalitis. However, oral ribavirin was not effective in reducing mortality in children with Japanese encephalitis.[3]

Intraventricular ribavirin (plus intraventricular interferon and oral isoprinosine) was found to be effective in 4 of 5 patients with subacute sclerosing panencephalitis.[4] A concentration of ribavirin in the CSF of 50 to 200 micrograms/mL completely inhibited viral replication; doses of ribavirin given to achieve this concentration ranged from 1 to 9 mg/kg daily.

1. McJunkin JE, *et al.* Treatment of severe La Crosse encephalitis with intravenous ribavirin following diagnosis by brain biopsy. *Pediatrics* 1997; **99:** 261–7.
2. Chong HT, *et al.* Treatment of acute Nipah encephalitis with ribavirin. *Ann Neurol* 2001; **49:** 810–13.
3. Kumar R, *et al.* Randomized, controlled trial of oral ribavirin for Japanese encephalitis in children in Uttar Pradesh, India. *Clin Infect Dis* 2009; **48:** 400–6.
4. Hosoya M, *et al.* Pharmacokinetics and effects of ribavirin following intraventricular administration for treatment of subacute sclerosing panencephalitis. *Antimicrob Agents Chemother* 2004; **48:** 4631–5.

Haemorrhagic fevers. The treatment of haemorrhagic fevers (p. 952.1) is mainly symptomatic. However, ribavirin has been reported to reduce mortality in patients with Lassa fever,[1] haemorrhagic fever with renal syndrome,[2] and possibly Crimean-Congo haemorrhagic fever[3-5] and Bolivian haemorrhagic fever.[6] Intravenous ribavirin has also been tried in the related hantavirus pulmonary syndrome,[7,8] but a small randomised, double-blind, placebo-controlled study[9] with intravenous ribavirin reported no significant difference in survival between the 2 groups.

For treatment of *Lassa fever*, ribavirin has been given intravenously in a dose of 2 g initially, then 1 g every 6 hours for 4 days, then 500 mg every 8 hours for 6 days.[1] Treatment is most effective if started within 6 days of the onset of fever. Experience has shown that rigors may occur if the drug is given as a bolus injection, but that this can be overcome by giving it as an infusion over 30 minutes.[10] For prophylaxis, an oral dose of ribavirin 600 mg 4 times daily for 10 days has been suggested for adults,[11] although this was considered to be excessive by other commentators[12] who suggested that oral doses of 1 g daily (after an intravenous loading dose for those in whom the start of prophylaxis is delayed) might be suitable.

1. McCormick JB, *et al.* Lassa fever: effective therapy with ribavirin. *N Engl J Med* 1986; **314:** 20–6.
2. Huggins JW, *et al.* Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis* 1991; **164:** 1119–27.
3. Fisher-Hoch SP, *et al.* Crimean Congo-haemorrhagic fever treated with oral ribavirin. *Lancet* 1995; **346:** 472–5.
4. Mardani M, *et al.* The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. *Clin Infect Dis* 2003; **36:** 1613–18.
5. Soares-Weiser K, *et al.* Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis. *BMC Infect Dis* 2010; **10:** 207.
6. Kilgore PE, *et al.* Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 1997; **24:** 718–22.
7. Anonymous. Hantavirus pulmonary syndrome—northeastern United States, 1994. *JAMA* 1994; **272:** 997–8.
8. Prochoda K, *et al.* Hantavirus-associated acute respiratory failure. *N Engl J Med* 1993; **329:** 1744.
9. Mertz GJ, *et al.* Collaborative Antiviral Study Group. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis* 2004; **39:** 1307–13.
10. Fisher-Hoch SP, *et al.* Unexpected adverse reactions during a clinical trial in rural West Africa. *Antiviral Res* 1992; **19:** 139–47.
11. Holmes GP, *et al.* Lassa fever in the United States: investigation of a case and new guidelines for management. *N Engl J Med* 1990; **323:** 1120–23.
12. Johnson KM, Monath TP. Imported Lassa fever—reexamining the algorithms. *N Engl J Med* 1990; **323:** 1139–41.

Adverse Effects

When given *by inhalation*, ribavirin has sometimes led to worsening of lung function, bacterial pneumonia, and pneumothorax, to cardiovascular effects (including a fall in blood pressure and cardiac arrest), and, rarely, to anaemia, haemolysis, and reticulocytosis. Conjunctivitis and skin rash have also occurred. Precipitation of inhaled ribavirin and consequent accumulation of fluid has occurred in the tubing of ventilating equipment.

The most common adverse effects reported by patients taking *oral* ribavirin, with either interferon alfa or peginterferon alfa, are psychiatric reactions (such as anxiety, depression, insomnia, and irritability) and flu-like symptoms. Life-threatening or fatal adverse effects include severe depression, suicidal ideation, relapse of drug abuse or overdose, and bacterial infection. Severe adverse effects include haemolytic anaemia, leucopenia, thrombocytopenia, aplastic anaemia, diabetes mellitus, auto-immune disorders, gastrointestinal symptoms, pancreatitis, pulmonary embolism, chest pain, liver dysfunction, and interstitial pneumonitis. Lupus erythematosus, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), and photosensitivity have also been reported. Growth retardation (including decrease in height and weight) has been reported in children. Many varied adverse effects may occur as a result of the use of ribavirin with interferon alfa (see under Adverse Effects in Interferon Alfa, p. 992.2).

Incidence of adverse effects. A review[1] of adverse effects reported in 110 patients with suspected or probable SARS who were treated with ribavirin found that 61% of the patients had evidence of haemolytic anaemia. In a smaller cohort of 76 patients hypocalcaemia and hypomagnesaemia were reported in 58% and 46% of patients, respectively, while 29% had evidence of both hypocalcaemia and hypomagnesaemia. A retrospective cohort study[2] found that the adverse effects strongly associated with the use of ribavirin (mostly high-dose) in 306 patients with confirmed or probable SARS, were progressive anaemia, hypomagnesaemia, and bradycardia.

1. Knowles SR, *et al.* Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis* 2003; **37:** 1139–42.
2. Muller MP, *et al.* Canadian SARS Research Network. Adverse events associated with high-dose ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome. *Pharmacotherapy* 2007; **27:** 494–503.

Precautions

SPECIFIC CAUTIONS FOR INHALED TREATMENT. Standard supportive respiratory and fluid management should be maintained during aerosol treatment with ribavirin and electrolytes should be monitored closely. Equipment should be monitored for precipitation of ribavirin. Precautions should be taken to minimise atmospheric pollution with ribavirin during aerosol inhalation.

SPECIFIC CAUTIONS FOR ORAL TREATMENT. Ribavirin should not be given orally to patients with pre-existing medical conditions that could be exacerbated by ribavirin-induced haemolysis, including significant or unstable cardiac disease or haemoglobinopathies (thalassaemia or sickle-cell anaemia). Blood cell counts and chemistry should be measured at the start of treatment, after 2 and 4 weeks of treatment, and periodically thereafter. Patients with renal impairment and a creatinine clearance of less than 50 mL/minute should not receive oral ribavirin. It should be avoided in patients with severe hepatic impairment or decompensated cirrhosis of the liver (Child-Pugh 6 or more). The potential for development of gout should be considered in predisposed patients. Patients should be monitored for signs and symptoms of psychiatric disorders. Ribavirin therapy is contra-indicated in children and adolescents with a history of, or existing, psychiatric disorders. The growth of children should be monitored and thyroid function should be tested every 3 months. Patients infected with hepatitis C virus and HIV should be carefully monitored for signs of mitochondrial toxicity and lactic acidosis. Dental and periodontal disorders have been reported and regular dental examinations and good oral hygiene are advised.

Contact lenses. Report of damage to a nurse's soft contact lenses after intermittent occupational exposure to aerosolised ribavirin over a period of 1 month.[1]

1. Diamond SA, Dupuis LL. Contact lens damage due to ribavirin exposure. *DICP Ann Pharmacother* 1989; **23:** 428–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ribavirin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Oral ribavirin has been reported to be teratogenic and embryocidal in *rodents* and is contra-indicated in pregnancy or in those who may become pregnant. Ribavirin was not found to be teratogenic in *baboons*. Although there are no case reports of teratogenicity after exposure to aerosolised ribavirin during pregnancy, licensed product information advises that pregnant women and those planning pregnancy should avoid exposure to the aerosol. Pregnancy should also be avoided in partners of male patients taking ribavirin orally. Effective contraception should be used during treatment and for 6 months after the end of treatment. Male patients whose partners are pregnant should use a condom to minimise vaginal exposure to ribavirin.

Interactions

Use of ribavirin with zidovudine is not recommended as patients are at increased risk of anaemia. Increased toxicity has also been seen with didanosine, and the combination should be avoided. Ribavirin inhibits the phosphorylation of NRTIs such as zidovudine, lamivudine, and stavudine, but although UK licensed product information suggests this may reduce their activity against HIV, US product information indicates that no such reduction has been seen in practice.

Anticoagulants. For reference to the effect of ribavirin on the activity of *warfarin*, see under Antivirals, p. 1533.1.

Antiviral Action

Ribavirin inhibits many viruses *in vitro* and in *animal* models. However, this activity has not necessarily correlated with activity against human infections. Ribavirin is phosphorylated but its mode of action is still unclear; it may act at several sites, including cellular enzymes, to interfere with viral nucleic acid synthesis. The mono- and triphosphate derivatives are believed to be responsible for its antiviral activity. Susceptible DNA viruses include herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae group, influenza, parainfluenza, measles, mumps, and RSV, and HIV.

Pharmacokinetics

Aerosolised ribavirin is absorbed systemically, but local concentrations in the respiratory tract secretions are much higher than plasma concentrations. Plasma half-life is about 9.5 hours. The bioavailability of aerosolised ribavirin is unknown and may depend on the mode of delivery.

Ribavirin is rapidly absorbed after oral doses and peak plasma concentrations occur within 1 to 2 hours. Absorption is extensive but oral bioavailability is about 45 to 65% as a result of first-pass metabolism. Steady state plasma concentrations occur after about 4 weeks with twice-daily oral doses resulting in peak plasma concentrations 6 times higher than that after single doses. On stopping dosing the plasma half-life is about 300 hours as a result of slow elimination from non-plasma compartments. Ribavirin does not bind to plasma proteins. Ribavirin is not metabolised by the cytochrome P450 system; it is metabolised by reversible phosphorylation and degradation involving deribosylation and amide hydrolysis to give a triazole carboxyacid metabolite. After a single oral dose the terminal half-life is about 120 to 170 hours. Ribavirin is mainly excreted in the urine as unchanged drug and metabolites. Insignificant amounts of the drug are removed by haemodialysis.

References.

1. Kramer TH, *et al.* Hemodialysis clearance of intravenously administered ribavirin. *Antimicrob Agents Chemother* 1990; **34:** 489–90.
2. Glue P, *et al.* The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. *Br J Clin Pharmacol* 2000; **49:** 417–21.
3. Tsubota A, *et al.* Pharmacokinetics of ribavirin in combined interferon-alpha 2b and ribavirin therapy for chronic hepatitis C virus infection. *Br J Clin Pharmacol* 2003; **55:** 360–7.
4. Kamar N, *et al.* Ribavirin pharmacokinetics in renal and liver transplant patients: evidence that it depends on renal function. *Am J Kidney Dis* 2004; **43:** 140–6.
5. Uchida M, *et al.* Assessment of adverse reactions and pharmacokinetics of ribavirin in combination with interferon alpha-2b in patients with chronic hepatitis C. *Drug Metab Pharmacokinet* 2004; **19:** 438–43.
6. Wade JR, *et al.* Pharmacokinetics of ribavirin in patients with hepatitis C virus. *Br J Clin Pharmacol* 2006; **62:** 710–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Copegus; Laztie†; Ribavirol; Vibuzol; Xilopar; ***Austral.***: Rebetol; Virazide†; ***Austria***: Copegus; Rebetol; ***Belg.***: Copegus; Rebetol; Virazole; ***Braz.***: Ribav; Viramid; Virazole; ***Canad.***: Virazole; ***Chile***: Rebetol; ***China***: Altissum (奥得清); Ao Jia (奥佳); Bang Qing (邦庆); Da Chang (达畅); Hua Le Sha (华乐沙); Jun Da Tan (均达坦); Li Li De (利力德); Li Li Ning (利力宁†); Li Mai Xin (利迈欣); Nai De (奈德); Nanyuan (南元); Qi Li Qing (奇力青); Rui Di (锐迪); Tong Xin (同欣); Wei La Ke (维拉克); Wei Li Ning (威利宁); Wei Lin (威林); WeiRuiKe (威锐克); Weilexing (威乐星); Xinweiling (信韦灵); ***Cz.***: Copegus; Rebetol; ***Denm.***: Copegus; Rebetol; ***Fin.***: Copegus; Rebetol; ***Fr.***: Copegus; Rebetol; ***Ger.***: Copegus; Rebetol; Virazole; ***Gr.***: Copegus; Rebetol; Virazole; ***Hong Kong***: Copegus; Rebetol; Virazole; ***Hung.***: Copegus; Rebetol; ***India***: Ribavin; ***Indon.***: Hepaviral; Rebetol; Virazide; ***Irl.***: Copegus; Rebetol; ***Israel***: Copegus; Rebetol; ***Ital.***: Copegus; Rebetol; Virazole; ***Jpn***: Copegus; Rebetol; ***Malaysia***: Copegus; Rebetol; ***Mex.***: Copegus; Desiken; Trivorin; Varinar; Vilona; Virazide; ***Neth.***: Copegus; Rebetol; Vilarib; Virazole; ***Norw.***: Copegus; Rebetol; ***NZ***: Copegus; Rebetol; ***Philipp.***: Rebetol; Ribazole; ***Pol.***: Copegus; Rebetol; ***Port.***: Copegus; Rebetol; ***Rus.***: Arviron (Арвирон)†; Rebetol (Ребетол); Ribamidil (Рибамидил); Ribapeg (Рибапег); Ribavin (Рибавин); Trivorin (Триворин); Virazole (Виразол); ***S.Afr.***: Copegus; ***Singapore***: Copegus; Rebetol; Virazole; ***Spain***: Copegus; Rebetol; Virazole; ***Swed.***: Copegus; Rebetol; Virazole; ***Switz.***: Copegus; Rebetol; ***Thai.***: Copegus; Rebetol; ***Turk.***: Copegus; Rebetol; Ribasphere; Viron; ***UK***: Copegus; Rebetol; Virazole; ***Ukr.***: Copegus (Копегус); Livel (Ливел); Rebetol (Ребетол); ***USA***: Copegus; Rebetol; RibaPak†; Ribasphere; Ribaspheres; Ribatab†; Virazole; ***Venez.***: Rebetol.

Multi-ingredient Preparations. ***Arg.***: Bioferon Hepakit; ***Austral.***: Pegasys RBV; Pegatron; Rebetron†; ***Canad.***: Pegasys RBV; Pegetron; ***Hong Kong***: Rebetron†; ***Mex.***: Hepatron C†; Pegtron

Cotronak Kit; ***NZ***: Pegasys RBV; Pegatron; Rebetron†; Roferon-A RBV; ***Philipp.***: Pegasys RBV.

Pharmacopoeial Preparations
BP 2014: Ribavirin Powder for Nebuliser Solution;
USP 36: Ribavirin Capsules; Ribavirin for Inhalation Solution; Ribavirin Tablets.

Rilpivirine *(USAN, rINN)*

R-278474; Rilpivirin; Rilpivirina; Rilpivirinum; TMC-278; Рильпивирин.
4-{[4-({4-[(1*E*)-2-Cyanoethenyl]-2,6-dimethylphenyl}amino)pyrimidin-2-yl]amino}benzonitrile.
$C_{22}H_{18}N_6$=366.4
CAS — 500287-72-9.
ATC — J05AG05.
ATC Vet — QJ05AG05.
UNII — FI96A8X663.

Rilpivirine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de rilpivirina; Rilpivirine, Chlorhydrate de; Rilpivirini Hydrochloridum; Рильпивирина Гидрохлорид.
$C_{22}H_{18}N_6$,HCl=402.9
CAS — 700361-47-3.
ATC — J05AG05.
ATC Vet — QJ05AG05.
UNII — 212WAX8KDD.

Uses and Administration

Rilpivirine is a second-generation, diarylpyrimidine NNRTI with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when rilpivirine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

Rilpivirine is given orally as the hydrochloride, but doses are expressed in terms of rilpivirine; 27.5 mg of rilpivirine hydrochloride is equivalent to about 25 mg of rilpivirine. It is given with food in a dose of 25 mg daily with a once-daily NRTI regimen.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. A co-formulated tablet containing rilpivirine, emtricitabine, and tenofovir (sometimes referred to as 'Btripla') is available in some countries. A slow-release, parenteral formulation is also under investigation for extended-interval intramuscular or subcutaneous use.

References.

1. Pozniak AL, *et al.* Efficacy and safety of TMC278 in antiretroviral-naive HIV-1 patients: week 96 results of a phase IIb randomized trial. *AIDS* 2010; **24:** 55–65.
2. Azijn H, *et al.* TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTI-resistant HIV-1. *Antimicrob Agents Chemother* 2010; **54:** 718–27.
3. Macarthur RD. Clinical Trial Report: TMC278 (Rilpivirine) versus efavirenz as initial therapy in treatment-naïve, HIV-1-infected patients. *Curr Infect Dis Rep* 2011; **13:** 1–3.
4. Miller CD, *et al.* Rilpivirine: a new addition to the anti-HIV-1 armamentarium. *Drugs Today* 2011; **47:** 5–15.
5. Molina JM, *et al.* Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; **378:** 238–46.
6. Cohen CJ, *et al.* Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; **378:** 229–37.

Adverse Effects

The most common adverse effects of moderate intensity associated with antiretroviral regimens containing rilpivirine are depressive disorders, insomnia, headache, and rashes. Depressive disorders include depressed mood, altered mood, dysphoria, and negative thoughts, and more serious psychiatric adverse effects such as severe depression, and suicidal ideation and suicide attempts. Other adverse effects of moderate intensity include abdominal pain, dry mouth, nausea and vomiting, fatigue, somnolence, abnormal dreams, and dizziness.

Raised liver enzyme values of more than 2.5 times the upper limit of normal were reported in 3 to 4% of patients. Raised total bilirubin and serum creatinine values and raised serum-cholesterol (total and low-density lipoprotein) concentrations have been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including rilpivirine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including rilpivirine.

Precautions

Rilpivirine is not recommended in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution in patients with moderate liver disease. It should also be used with caution in patients with severe renal impairment or end-stage renal disease.

Interactions

Rilpivirine is metabolised mainly by cytochrome P450 isoenzyme CYP3A4. Consequently, it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Clarithromycin, erythromycin, and troleandomycin may increase the plasma concentration of rilpivirine due to enzyme inhibition; an alternative to these macrolides (such as azithromycin) should be considered whenever possible. Alternatively, enzyme inducers may decrease plasma concentrations of rilpivirine. Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, systemic corticosteroids (except for single doses), and St John's wort may significantly decrease the concentration of rilpivirine due to CYP3A enzyme induction. Use of these drugs with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Drugs that increase the gastric pH may also decrease plasma concentrations of rilpivirine and result in possible loss of antiviral activity and development of resistance. Use of rilpivirine plus a proton pump inhibitor is contra-indicated, while antacids or histamine H_2-receptor antagonists should be used with caution and only histamine H_2-receptor antagonists that can be given once daily should be used. When given concomitantly, histamine H_2-receptor antagonists should be given at least 12 hours before or at least 4 hours after rilpivirine, while antacids should be given at least 2 hours before or at least 4 hours after rilpivirine.

Rilpivirine inhibits p-glycoprotein *in vitro* and plasma concentrations of drugs transported by this mechanism (such as digoxin and dabigatran) may be increased.

Supratherapeutic doses of rilpivirine prolong the QTc interval; consequently, caution is advised when rilpivirine is given with drugs with a known risk of torsade de pointes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Edurant; ***Canad.***: Edurant; ***Denm.***: Edurant; Eviplera; ***Irl.***: Edurant; ***Israel***: Edurant; ***Jpn***: Edurant; ***Neth.***: Edurant; ***Norw.***: Edurant; ***Spain***: Edurant; ***Swed.***: Edurant; ***Switz.***: Edurant; ***UK***: Edurant; ***USA***: Edurant.

Multi-ingredient Preparations. ***Ger.***: Eviplera; ***Israel***: Eviplera; ***Norw.***: Eviplera; ***Swed.***: Eviplera; ***Switz.***: Eviplera; ***UK***: Eviplera; ***USA***: Complera.

Rimantadine Hydrochloride

(BANM, USAN, rINNM)

EXP-126; Hidrocloruro de rimantadina; Rimantadina, hidrocloruro de; Rimantadine, Chlorhydrate de; Rimantadini Hydrochloridum; Римантадина Гидрохлорид.
(*RS*)-1-(Adamantan-1-yl)ethylamine hydrochloride; α-Methyl-1-adamantanemethylamine hydrochloride.
$C_{12}H_{21}N$,HCl=215.8
CAS — 13392-28-4 (rimantadine); 1501-84-4 (rimantadine hydrochloride).
ATC — J05AC02.
ATC Vet — QJ05AC02.
UNII — JE107OOS8Y.

Pharmacopoeias. In *US*.

USP 36: (Rimantadine Hydrochloride). Store at a temperature of 15 degrees to 30 degrees.

Uses and Administration

Rimantadine hydrochloride is used similarly to amantadine hydrochloride (p. 890.3) in the prophylaxis and treatment of susceptible influenza A infections (p. 960.2). It is given orally in usual adult doses of 200 mg daily in divided doses. In elderly patients the usual daily dose is 100 mg. A dosage reduction is also necessary in patients with severe renal or severe hepatic impairment (see below).

For details of doses in children, see below.

Reviews.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/06/08).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 21/10/09).

Administration in children. For the prophylaxis of influenza A in children from 1 year of age, an oral dose of 5 mg/kg daily in 1 or 2 divided doses, up to a maximum daily dose of 150 mg, may be given. Children 10 years of age and older may be given 100 mg twice daily; those weighing less than 40 kg should be given a dose of 5 mg/kg daily, regardless of their age. Although not licensed for the treatment of influenza A some experts consider that it may be given to children from 1 year of age.

Administration in hepatic or renal impairment. The usual oral dose of rimantadine in patients with severe renal or severe hepatic impairment and in elderly nursing home patients is 100 mg daily.

Adverse Effects and Precautions

The incidence and severity of adverse effects associated with rimantadine appear to be low. Those most commonly reported are gastrointestinal disturbances such as nausea, vomiting, abdominal pain, dry mouth, and anorexia, CNS effects such as headache, insomnia, nervousness, and dizziness, and asthenia. Other less frequently reported adverse effects include ataxia, agitation, concentration difficulties, diarrhoea, dyspepsia, depression, dyspnoea, skin rash, somnolence, and tinnitus.

There have been reports of convulsions, including grand mal convulsions, and rimantadine should be given with caution to patients with epilepsy. Doses are reduced in severe renal or hepatic impairment; reduced doses are also used in the elderly.

A review[1] of clinical studies in adults concluded that rimantadine and amantadine were equally effective for prevention and treatment of influenza A, but rimantadine was significantly better tolerated than amantadine at usual doses. Another systematic review[2] evaluating the safety and efficacy of amantadine and rimantadine in children and the elderly with influenza A concluded that although rimantadine was safe in these groups, its efficacy was unproven and therefore its use could not be recommended.

In a study[3] to evaluate the safety of long-term rimantadine for elderly, chronically ill individuals during an influenza A epidemic, a significantly greater proportion of patients taking rimantadine developed anxiety and/or nausea compared with those taking placebo. There was also a significantly greater number of days in which anxiety, nausea, confusion, depression, or vomiting were reported. Most of these adverse effects lasted less than 9 days and were seldom severe except in 2 patients who withdrew from the study because of insomnia, anxiety, or both and a third who suffered a generalised convulsion. In a larger study[4] the incidence of these symptoms was similar in treatment and placebo groups.

Observations of seizures in 2 patients receiving influenza prophylaxis with rimantadine hydrochloride emphasised that chronically ill and elderly patients prone to seizures (especially those who may have had antiepileptic therapy withdrawn) may be at greater risk of developing seizures.[5] A precautionary measure of reducing the rimantadine hydrochloride dosage to 100 mg daily and temporary re-introduction of antiepileptics was suggested.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 3/10/07).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/02/08).
3. Patriarca PA, *et al.* Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A virus infections in nursing homes. *Antimicrob Agents Chemother* 1984; **26:** 101–3.
4. Monto AS, *et al.* Safety and efficacy of long-term use of rimantadine for prophylaxis of type A influenza in nursing homes. *Antimicrob Agents Chemother* 1995; **39:** 2224–8.
5. Bentley DW, *et al.* Rimantadine and seizures. *Ann Intern Med* 1989; **110:** 323–4.

Breast feeding. Rimantadine is distributed into breast milk in *animals* in concentrations about twice those measured in the serum. US licensed product information states that rimantadine should be avoided in breast-feeding mothers.

Pregnancy. Although there are no data available on the use of rimantadine in pregnant women, US licensed product information states that it should only be used if potential benefit justifies the risk to the fetus as embryotoxicity has been reported in *rats* given high doses of rimantadine.

Antiviral Action

Rimantadine is an M2 ion channel inhibitor that inhibits influenza A virus replication mainly by blocking the M2-protein ion channel, thereby preventing fusion of the virus and the host-cell membranes and the release of viral RNA into the cytoplasm of infected cells.

Resistance to rimantadine can occur rapidly and resistant virus may be transmitted to close contacts of patients treated with rimantadine and cause influenza. Rimantadine and amantadine show complete cross-resistance.

Resistance. Resistance of influenza A viruses to the adamantane M2 ion channel inhibitors amantadine and rimantadine can occur spontaneously or emerge rapidly during treatment. A single point mutation in the code sequence for the amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross-resistance to both amantadine and rimantadine. The resistant viruses can still replicate and be transmitted.[1-3] A report[4] describing the global prevalence of adamantane-resistant influenza A viruses over a 10 year period shows an increase in drug resistance from 0.4% during the 1994/5 influenza season to 12.3% during the 2003/4 season. During the 2005/6 influenza season, WHO and the National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories in the United States reported tests on 120 influenza viruses of which 109 (91%) were found to have substitutions in the M2 protein that would confer resistance to amantadine and rimantadine.[3] In the USA, the reported adamantane resistance rate for influenza A increased from 11% for the 2004/5 influenza season to 92% for the 2005/6 influenza season.[5] On the basis of this information, the CDC no longer recommends amantadine or rimantadine for the treatment or prophylaxis of influenza A infections.[3,6]

1. Belshe RB, *et al*. Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. *J Virol* 1988; **62:** 1508–12.
2. Hayden FG, *et al*. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med* 1989; **321:** 1696–1702.
3. CDC. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005–06 influenza season. *MMWR* 2006; **55:** 44–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5502a7.htm (accessed 13/06/08)
4. Bright RA, *et al*. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.
5. Bright RA, *et al*. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. *JAMA* 2006; **295:** 891–4.
6. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-6): 1–54. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf (accessed 13/06/08)

Pharmacokinetics

Rimantadine hydrochloride is well, but slowly, absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 6 hours. It has a large volume of distribution and long elimination half-life; reported figures for half-life in healthy adults range from 13 to 65 hours (mean 25.4 hours) and from 20 to 65 hours (mean 32 hours) in those over 70 years of age. Protein binding of rimantadine is about 40%. It is extensively metabolised in the liver with less than 25% of a dose being excreted unchanged in the urine; about 75% is excreted as hydroxylated metabolites over 72 hours. In severe renal or hepatic impairment the elimination half-life is about double, necessitating a dosage reduction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jin Di Na (金迪钠); Jin-Tong (津彤); Li An (立安); Tai Zhi Ao (太之奥); ***Cz.***: Maridin†; ***Mex.***: Gabirol; ***Pol.***: Rimantin; ***Rus.***: Algirem (Альгирем)†; Orvirem (Орвирем); ***Ukr.***: Remavir (Ремавир); ***USA***: Flumadine.

Multi-ingredient Preparations. ***Rus.***: Antigrippin-Maximum (Антигриппин-Максимум); Antigrippin-Maximum (Антигриппин-Максимум).

Pharmacopoeial Preparations
USP 36: Rimantadine Hydrochloride Tablets.

Ritonavir *(BAN, USAN, rINN)*

A-84538; Abbott-84538; ABT-538; Ritonaviiri; Ritonavirum; Ритонавир.

5-Thiazolylmethyl {(αS)-α-[(1S,3S)-1-hydroxy-3-((2S)-2-{3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido}-3-methylbutyramido)-4-phenylbutyl]phenethyl}carbamate; *N*[1]-[(1S,3S,4S)-1-Benzyl-3-hydroxy-5-phenyl-4-(1,3-thiazol-5-ylmethoxycarbonylamino)pentyl]-*N*[2]-{[(2-isopropyl-1,3-thiazol-4-yl)methyl](methyl)carbamoyl}-L-valinamide.

$C_{37}H_{48}N_6O_5S_2$=720.9

CAS — 155213-67-5.

ATC — J05AE03.

ATC Vet — QJ05AE03.

UNII — O3J8G9O825.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Ritonavir). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane; very slightly soluble in acetonitrile. It exhibits polymorphism. Protect from light.

USP 36: (Ritonavir). A white to light tan powder. Practically insoluble in water; very soluble in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature between 5 degrees and 30 degrees. Protect from light.

Uses and Administration

Ritonavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when ritonavir is used alone, and it is therefore given with other antiretrovirals. It is also widely used as a pharmacokinetic enhancer of other HIV-protease inhibitors (ritonavir-boosted therapy).

For treatment, ritonavir is given orally in an adult dose of 600 mg twice daily with food. In order to minimise nausea, ritonavir may be started at a dose of 300 mg twice daily and gradually increased over a period of up to 14 days by 100 mg twice daily to a total of 600 mg twice daily. For details of doses in children, see below.

When used as a pharmacokinetic enhancer ritonavir is given in doses of 100 to 200 mg once or twice daily.

Reviews.

1. Lea AP, Faulds D. Ritonavir. *Drugs* 1996; **52:** 541–6.
2. Cooper CL, *et al*. A review of low-dose ritonavir in protease inhibitor combination therapy. *Clin Infect Dis* 2003; **36:** 1585–92.
3. Wilkins E. The current role of ritonavir-boosted protease inhibitors in the management of HIV infection. *J HIV Ther* 2008; **13:** 9–18.
4. Bierman WF, *et al*. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS* 2009; **23:** 279–91.

Administration. Adjusting the dosage of ritonavir from 600 mg twice daily to 300 mg every 6 hours improved tolerability in 2 patients who would otherwise have stopped the drug.[1]

1. Merry C, *et al*. Improved tolerability of ritonavir derived from pharmacokinetic principles. *Br J Clin Pharmacol* 1996; **42:** 787.

Administration in children. For the treatment of HIV infection in children, ritonavir is given daily with other antiretroviral drugs. US licensed product information permits the use of oral ritonavir in infants over 1 month of age, whereas in the UK it is recommended from 2 years of age. The dose given should not exceed the maximum adult dose of 600 mg twice daily.

The recommended dose regimen is an initial dose of 250 mg/m^2 twice daily increasing by 50 mg/m^2 twice daily at 2- or 3-day intervals up to 350 to 400 mg/m^2 twice daily.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing ritonavir are asthenia, gastrointestinal effects (abdominal pain, anorexia, nausea, vomiting, and particularly diarrhoea), headache, taste disorder, and numbness or tingling around the mouth or in the extremities. One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Other commonly reported adverse effects include anxiety, dizziness, insomnia, fever, other gastrointestinal effects (dry mouth, dyspepsia, flatulence, local throat irritation, mouth ulcer), hyperaesthesia, malaise, pharyngitis, pruritus, rash, sweating, vasodilatation, and weight loss. Allergic reactions include urticaria, mild skin eruptions, bronchospasm, angioedema, and rarely anaphylaxis. A possible association with Stevens-Johnson syndrome has been reported with ritonavir. Reported abnormal laboratory results are decreased haemoglobin levels and potassium concentrations, increased eosinophil counts, raised liver enzymes, amylase, and uric acid concentrations, and decreased free and total thyroxine concentrations; white blood cell and neutrophil counts may be reduced or increased.

Adverse effects associated with the use of ritonavir as a pharmacokinetic booster are dependent on the other HIV-protease inhibitor.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including ritonavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy including ritonavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Ritonavir (as an antiviral agent or as a pharmacokinetic enhancer) should not be used in patients with decompensated liver disease. Caution is advised in patients with severe hepatic impairment (Child-Pugh Grade C) without decompensation, when ritonavir is used as a pharmacokinetic booster with another HIV-protease inhibitor, although specific recommendations depend on the other drug. Patients with pre-existing liver disease or co-infection with chronic hepatitis B or C who are treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Patients should be monitored for signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, and increased serum lipase or amylase levels) and ritonavir treatment should be stopped in patients developing pancreatitis. Ritonavir may prolong the PR interval in some patients, in rare cases leading to second- or third-degree AV block; it should therefore be used with caution in those at increased risk, including patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischaemic heart disease, or cardiomyopathy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ritonavir as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

The interaction of ritonavir with the cytochrome P450 isoenzyme system is complex. Ritonavir is metabolised mainly by CYP3A4 (and to a lesser extent 2D6), and it also strongly **inhibits** these and other isoenzymes in the following rank order:

CYP3A > CYP2D6 > CYP2C9 > CYP2C19 > CYP2A6, CYP2E1

Conversely, ritonavir also **induces** the activity of some isoenzymes, including CYP1A2, CYP2C9, and CYP2C19.

Consequently, use with ritonavir may lead to altered serum concentrations of drugs metabolised by these enzymes. The enzyme-inhibiting properties of ritonavir are exploited in its use as a pharmacokinetic enhancer to boost other HIV-protease inhibitors.

In addition to its effects on the cytochrome P450 isoenzyme system, ritonavir has a high affinity for P-glycoprotein, of which it is both a substrate, and a strong inhibitor. Ritonavir also induces the activity of glucuronosyltransferases (UGT).

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir with drugs for which elevated plasma concentrations caused by ritonavir-mediated enzyme inhibition may lead to serious or life-threatening events. In the USA, such drugs include:

- the alpha$_1$-adrenergic antagonist alfuzosin
- antiarrhythmics (amiodarone, bepridil, flecainide, propafenone, and quinidine)
- antipsychotics (clozapine and pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (lovastatin and simvastatin)

For similar reasons, UK licensed product information also contra-indicates the use of ritonavir with the analgesics pethidine, piroxicam, and dextropropoxyphene, the antiarrhythmic encainide, the antihistamines astemizole and terfenadine, the antibacterial fusidic acid, and some other sedatives and hypnotics (clorazepate, diazepam, estazolam, and flurazepam). Use of rifabutin is also contra-indicated in the UK when ritonavir is being used in antiretroviral doses of 600 mg twice daily, although it may be used in adjusted doses when low-dose ritonavir is used to boost selected HIV-protease inhibitors (see under Uses and Administration of Rifabutin, p. 349.1).

Owing to the potential for increased serum concentrations of sildenafil, licensing authorities contra-indicate ritonavir with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir may increase serum concentrations of inhaled fluticasone or salmeterol and combination with either is not

recommended. Ritonavir is not recommended for use with voriconazole as substantially reduced plasma concentrations of the latter drug may occur; when ritonavir doses of 400 mg twice daily or higher are used co-administration is contra-indicated. St John's wort decreases the concentration of ritonavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Ritonavir should be used with caution with other drugs that can cause PR-interval prolongation (such as calcium-channel blockers, beta blockers, digoxin, and atazanavir), particularly where those drugs are also metabolised by CYP3A4.

Oral liquid formulations of ritonavir currently contain alcohol and use with disulfiram or metronidazole should be avoided.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

References.
1. Foisy MM, *et al.* Induction effects of ritonavir: implications for drug interactions. *Ann Pharmacother* 2008; **42:** 1048–59.

Antiviral Action

Ritonavir is a selective, competitive, reversible inhibitor of HIV protease. It is active against HIV-1 and, to a lesser extent, HIV-2. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Ritonavir is also a potent inhibitor of the cytochrome P450 subfamily CYP3A (chiefly the isoenzyme CYP3A4), and low-dose ritonavir is used with other HIV-protease inhibitors to decrease their metabolism and thus increase plasma concentrations of the other HIV-protease inhibitor; such use is referred to as ritonavir pharmacokinetic enhancement or ritonavir-boosted therapy. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur; in general the greater the number of mutations, the higher the level of resistance. Cross-resistance between HIV-protease inhibitors and NRTIs or NNRTIs is considered unlikely.

Pharmacokinetics

Ritonavir is absorbed after oral doses and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food, and is dose-related. Protein binding is reported to be about 98% and penetration into the CNS is minimal. Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Five metabolites have been identified and the major metabolite has antiviral activity, but concentrations in plasma are low. Studies in HIV-infected children 2 to 14 years of age indicate that ritonavir clearance is 1.5 to 1.7 times greater than in adults. About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine (3.5% as unchanged drug). The elimination half-life is 3 to 5 hours.

References.
1. Hsu A, *et al.* Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* 1997; **41:** 898–905.
2. Hsu A, *et al.* Ritonavir: clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; **35:** 275–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Busvir; Rifaxi†; ***Austral.***: Norvir; ***Austria***: Norvir; ***Belg.***: Norvir; ***Braz.***: Norvir; Ritovir; ***Canad.***: Norvir; ***Chile***: Norvir; ***China***: Norvir (爱治威); ***Cz.***: Norvir; ***Denm.***: Norvir; ***Fin.***: Norvir; ***Fr.***: Norvir; ***Ger.***: Norvir; ***Gr.***: Norvir; ***Hong Kong***: Norvir; ***Hung.***: Norvir; ***India***: Empetus; Ritomune; ***Indon.***: Norvir; ***Irl.***: Norvir; ***Israel***: Norvir; ***Ital.***: Norvir; ***Jpn***: Norvir; ***Malaysia***: Norvir; ***Mex.***: Norvir; ***Neth.***: Norvir; ***Norw.***: Norvir; ***NZ***: Norvir; ***Pol.***: Norvir; ***Port.***: Norvir; ***Rus.***: Norvir (Норвир); ***S.Afr.***: Norvir; ***Singapore***: Norvir; ***Spain***: Norvir; ***Swed.***: Norvir; ***Switz.***: Norvir; ***Thai.***: Norvir; Rinavir†; ***Turk.***: Norvir; ***UK***: Norvir; ***USA***: Norvir; ***Venez.***: Norvir.

Multi-ingredient Preparations. ***Arg.***: Kaletra; ***Austral.***: Kaletra; ***Austria***: Kaletra; ***Belg.***: Kaletra; ***Braz.***: Kaletra; ***Canad.***: Kaletra; ***Chile***: Kaletra; ***China***: Aluvia (克力芝); ***Cz.***: Kaletra; ***Denm.***: Kaletra; ***Fin.***: Kaletra; ***Fr.***: Kaletra; ***Ger.***: Kaletra; ***Gr.***: Kaletra; ***Hong Kong***: Kaletra; ***Hung.***: Kaletra; ***India***: Emletra; Lopimune; Ritomax-L; ***Irl.***: Kaletra; ***Israel***: Kaletra; ***Ital.***: Kaletra; ***Malaysia***: Kaletra; ***Mex.***: Kaletra; ***Neth.***: Kaletra; ***Norw.***: Kaletra; ***NZ***: Kaletra; ***Pol.***: Kaletra; ***Port.***: Kaletra; ***Rus.***: Kaletra (Калетра); ***S. Afr.***: Aluvia; Kaletra; ***Singapore***: Kaletra; ***Spain***: Kaletra; ***Swed.***: Kaletra; ***Switz.***: Kaletra; ***Thai.***: Aluvia; Kaletra; ***Turk.***: Kaletra; ***UK***: Kaletra; ***USA***: Kaletra; ***Venez.***: Kaletra.

Pharmacopoeial Preparations

USP 36: Lopinavir and Ritonavir Tablets; Ritonavir Capsules; Ritonavir Oral Solution; Ritonavir Tablets.

Saquinavir *(BAN, USAN, rINN)*

Ro-31-8959; Sakinavir; Saquinavirum; Саквинавир.

N^1-[(1*S*,2*R*)-1-Benzyl-3-[(3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)perhydroisoquinolin-2-yl]-2-hydroxypropyl]-N^2-(2-quinolylcarbonyl)-L-asparta mide; (*S*)-*N*-[(α*S*)-α-[(1*R*)-2-[(3*S*,4a*S*,8a*S*)-3-(*tert*-Butylcarbamoyl)octahydro-2(1*H*)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamidosuccinamide.

$C_{38}H_{50}N_6O_5$=670.9

CAS — 127779-20-8.

ATC — J05AE01.

ATC Vet — QJ05AE01.

UNII — L3JE09KZ2F.

Pharmacopoeias. In *Int.*

Saquinavir Mesilate *(BANM, rINNM)*

Mesilato de saquinavir; Ro-31-8959/003; Sakinaviirimesilaatti; Sakinavirmesilat; Saquinavir, Mésilate de; Saquinavir, mesilato de; Saquinavir Mesylate (USAN); Saquinaviri Mesilas; Saquinavirmesilat; Саквинавира Мезилат.

Saquinavir methanesulfonate.

$C_{38}H_{50}N_6O_5,CH_4O_3S$=767.0

CAS — 149845-06-7.

ATC — J05AE01.

ATC Vet — QJ05AE01.

UNII — UHB9Z3841A.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Saquinavir Mesilate). A white or almost white, slightly hygroscopic powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Saquinavir Mesylate). Store in airtight containers.

Uses and Administration

Saquinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when saquinavir is used alone, and it is therefore used with other antiretrovirals, including low-dose ritonavir which is given as a pharmacokinetic enhancer (ritonavir-boosted saquinavir).

Saquinavir is given orally as the mesilate but doses are expressed in terms of the base; 229 mg of saquinavir mesilate is equivalent to about 200 mg of saquinavir. The dose is 1 g twice daily given with ritonavir 100 mg twice daily with or after food.

To reduce the risk of cardiac conduction disturbances (see below), UK licensed product information advises that treatment-naive patients be given a reduced dose of 500 mg twice daily (with ritonavir 100 mg twice daily) for the first 7 days of treatment. Patients switching immediately (without a wash-out period) from another ritonavir-boosted HIV-protease inhibitor or a NNRTI-based regimen, however, should start saquinavir at the standard recommended dose.

Reviews.
1. Vella S, Floridia M. Saquinavir: clinical pharmacology and efficacy. *Clin Pharmacokinet* 1998; **34:** 189–201.
2. Figgitt DP, Plosker GL. Saquinavir soft-gel capsule: an updated review of its use in the management of HIV infection. *Drugs* 2000; **60:** 481–516.
3. Plosker GL, Scott LJ. Saquinavir: a review of its use in boosted regimens for treating HIV infection. *Drugs* 2003; **63:** 1299–1324.
4. la Porte CJ. Saquinavir, the pioneer antiretroviral protease inhibitor. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1313–22.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing saquinavir are gastrointestinal disorders (abdominal pain, diarrhoea, flatulence, nausea, vomiting) and fatigue. Other commonly reported adverse effects include alopecia, anaemia, anorexia, increased appetite, asthenia, constipation, dizziness, dry lips, mouth and skin, dyspepsia, dyspnoea, eczema, headache, hypersensitivity, decreased libido, malaise, muscle spasm, paraesthesia, peripheral neuropathy, pruritus, rash, sleep disturbances, and taste disorders. Commonly reported laboratory abnormalities include raised liver enzyme values, increased blood amylase, bilirubin, and creatinine, and lowered haemoglobin and platelet, lymphocyte, and white blood cell count. Rare but serious adverse effects that may be associated with saquinavir include acute myeloid leukaemia, haemolytic anaemia, allergic reactions, ascites, bullous skin eruptions, intestinal obstruction, jaundice, nephrolithiasis, pancreatitis, polyarthritis, portal hypertension, seizures, Stevens-Johnson syndrome, attempted suicide, and thrombocytopenia (occasionally fatal). Ritonavir-boosted saquinavir may cause dose-dependent prolongation of both the PR and QT intervals; cases of second- or third-degree AV block and torsade de pointes have been reported rarely.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including saquinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including saquinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Ritonavir-boosted saquinavir should not be used in patients with decompensated liver disease and should be used with caution in patients with moderate hepatic or severe renal impairment. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Ritonavir-boosted saquinavir may cause cardiac conduction abnormalities and is therefore best avoided in patients at increased risk, such as those with underlying structural heart disease (including congestive heart failure and other cardiomyopathies), pre-existing cardiac conduction abnormalities (including QT-interval prolongation, clinically significant bradycardia, or AV block), ischaemic heart disease, or uncorrected electrolyte disturbances (particularly hypokalaemia). Baseline and follow-up electrocardiograms should be considered for patients starting ritonavir-boosted saquinavir, particularly when use cannot be avoided in those at high risk for conduction disturbances, or where hepatic impairment or drug interactions (see below) may increase exposure to saquinavir; treatment should be stopped if arrhythmia, or prolongation of the PR or QT intervals occur. Treatment-naive patients are considered to be at particular risk of QT-and PR-interval prolongation, with the highest risk occurring in the first week of therapy; UK licensed product information therefore recommends a lower initial dose for the first week of treatment in these patients (see above).

For information on the use of HIV-protease inhibitors in pregnancy, see under Indinavir, p. 987.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies saquinavir as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Saquinavir is reported to be metabolised by the cytochrome P450 system, with the specific isoenzyme CYP3A4 responsible for more than 90% of the hepatic metabolism. Saquinavir is also a substrate and an inhibitor of P-glycoprotein. Drugs that affect this isoenzyme and/or P-glycoprotein may modify saquinavir plasma concentrations. Saquinavir may alter the pharmacokinetics of other drugs that are metabolised by this enzyme system or that are substrates for P-glycoprotein.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted saquinavir with drugs that are highly dependent on CYP3A4 or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. In the UK, these drugs may include

- antiarrhythmics (amiodarone, bepridil, dofetilide, disopyramide, flecainide, hydroquinidine, systemic lidocaine, propafenone, and quinidine)
- antidepressants (amitriptyline, imipramine, and trazodone)
- antihistamines (astemizole, mizolastine, and terfenadine)
- the antimalarial quinine
- antimycobacterials (dapsone and rifampicin)
- antipsychotics (pimozide)
- macrolide antibacterials (erythromycin and clarithromycin)

- opioid analgesics (alfentanil, fentanyl, and methadone)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated.

Although UK licensed product information contra-indicates the use of phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil) with ritonavir-boosted saquinavir, other authorities consider that these combinations may be used with caution, with adjusted doses, in certain clinical situations (see Uses and Administration of Sildenafil, p. 2364.2, Tadalafil, p. 2368.2, and Vardenafil, p. 2372.1). Ritonavir-boosted saquinavir may also increase serum concentrations of inhaled fluticasone or salmeterol and combination with either is not recommended. Both Garlic and St John's wort decrease the concentration of saquinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Use of ritonavir-boosted saquinavir is best avoided with drugs known to prolong the QT or PR interval (such as ibutilide, sotalol, halofantrine, pentamidine, sparfloxacin, clozapine, haloperidol, the phenothiazines, sertindole, sultopride, ziprasidone, atazanavir, ritonavir-boosted lopinavir, digoxin, the calcium-channel blockers, and the beta-adrenergic blockers). Where such combinations cannot be avoided, US licensed product information advises that they may be used with caution and ECG monitoring. Use with drugs that both prolong the QT interval and increase serum concentrations of saquinavir is contra-indicated.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Saquinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. HIV isolates resistant to saquinavir have been reported and variable cross-resistance with other HIV-protease inhibitors has been seen. Cross-resistance between saquinavir and NRTIs or NNRTIs is unlikely because these drugs have different target enzymes.

Pharmacokinetics

Saquinavir is absorbed to a limited extent (about 30%) after oral doses of the mesilate and undergoes extensive first-pass hepatic metabolism, resulting in a bioavailability of 4% when taken with food. Bioavailability was found to be greater from a soft gelatin capsule formulation of saquinavir base in a suitable vehicle (*Fortovase, Roche*) than from a hard capsule formulation (*Invirase, Roche*). Bioavailability is substantially less when saquinavir is taken in the fasting state. Plasma concentrations are reported to be higher in HIV-infected patients than in healthy subjects. Saquinavir is about 98% bound to plasma proteins and extensively distributed into the tissues, although CSF concentrations are reported to be negligible. It is rapidly metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to several inactive monohydroxylated and dihydroxylated compounds. It is excreted mainly in the faeces with a reported terminal elimination half-life of 13.2 hours.

References.

1. Regazzi MB, *et al.* Pharmacokinetic variability and strategy for therapeutic drug monitoring of saquinavir (SQV) in HIV-1 infected individuals. *Br J Clin Pharmacol* 1999; **47:** 379–82.
2. Grub S, *et al.* Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2002; **71:** 122–30.
3. Acosta EP, *et al.* Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; **48:** 430–6.
4. Dickinson L, *et al.* Population pharmacokinetics of ritonavir-boosted saquinavir regimens in HIV-infected individuals. *J Antimicrob Chemother* 2008; **62:** 1344–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fortovase; Proteovir; ***Austral.***: Fortovase†; Invirase; ***Austria***: Invirase; ***Belg.***: Invirase; ***Braz.***: Fortovase; Invirase; Svir; ***Canad.***: Invirase; ***Chile***: Invirase; ***China***: Fortovase (复得维); Invirase (因服雷); ***Cz.***: Invirase; ***Denm.***: Invirase; ***Fin.***: Invirase; ***Fr.***: Invirase; ***Ger.***: Invirase; ***Gr.***: Fortovase; Invirase; ***Hong Kong***: Invirase; ***Hung.***: Invirase; ***Irl.***: Invirase; ***Israel***: Invirase; ***Ital.***: Invirase; ***Jpn***: Fortovase†; Invirase; ***Malaysia***: Invirase; ***Mex.***: Fortovase; Invirase; ***Neth.***: Fortovase†; Invirase; ***Norw.***: Invirase; ***NZ***: Fortovase†; Invirase†; ***Philipp.***: Invirase; ***Pol.***: Invirase; ***Port.***: Invirase; ***Rus.***: Fortovase (Фортоваза); Invirase (Инвираза); ***S.Afr.***: Invirase; ***Singapore***: Fortovase; Invirase; ***Spain***: Invirase; ***Swed.***: Invirase; ***Switz.***: Invirase; ***Thai.***: Fortovase†; Invirase; ***UK***: Invirase; ***USA***: Invirase; ***Venez.***: Fortovase.

Pharmacopoeial Preparations

USP 36: Saquinavir Capsules.

Simeprevir *(USAN, pINN)*

Siméprévir; Simeprevirum; TMC-435; TMC-435350; Симепревир.

(2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(Cyclopropylsulfonyl)-2-({7-methoxy-8-methyl-2-[4-(1-methylethyl)thiazol-2-yl]quinolin-4-yl}oxy)-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide.

$C_{38}H_{47}N_5O_7S_2$=749.9

CAS — 923604-59-5.

UNII — 9WS5RD66HZ.

Profile

Simeprevir is an oral HCV-protease inhibitor effective against hepatitis C virus (HCV) serine protease NS3/4A. It is used in the treatment of chronic hepatitis C (p. 952.1) genotype 1 infection in adults with compensated liver disease, including cirrhosis. Doses are given as the sodium salt but expressed as the base; simeprevir 150 mg is equivalent to about 154 mg of simeprevir sodium. An oral dose equivalent to simeprevir 150 mg once daily with food is given as part of a combined regimen with peginterferon alfa and ribavirin (tri-therapy) for 12 weeks. This is followed by 12 or 36 weeks of treatment with peginterferon alfa and ribavirin (bi-therapy) depending on patient history and hepatitis C-RNA (HCV-RNA) levels.

References.

1. Vaidya A, Perry CM. Simeprevir: first global approval. *Drugs* 2013; **73:** 2093–2106.
2. You DM, Pockros PJ. Simeprevir for the treatment of chronic hepatitis C. *Expert Opin Pharmacother* 2013; **14:** 2581–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Galexos; ***Jpn***: Sovriad; ***USA***: Olysio.

Sofosbuvir *(USAN, rINN)*

PSI-7977; Sofosbuvirum; Софосбувир.

1-Methylethyl *N*-[(*S*)-{[(2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl]methoxy}phenoxyphosphoryl]-L-alaninate.

$C_{22}H_{29}FN_3O_9P$=529.5

CAS — 1190307-88-0.

UNII — WJ6CA3ZU8B.

Profile

Sofosbuvir is an oral nucleotide analogue inhibitor effective against hepatitis C virus (HCV) polymerase NS5B. It is used in the treatment of chronic hepatitis C (p. 952.1) genotypes 1, 2, 3, or 4. Sofosbuvir is given in an oral dose of 400 mg once daily in a combined regimen according to genotype:

- 1 or 4: sofosbuvir with ribavirin and peginterferon alfa for 12 weeks. Sofosbuvir with ribavirin for 24 weeks may be used in patients with genotype 1 infection who are unable to take peginterferon alfa
- 2: sofosbuvir with ribavirin for 12 weeks
- 3: sofosbuvir with ribavirin for 24 weeks

It has also been tried in combination with daclatasvir (p. 971.1).

References.

1. Herbst DA, Reddy KR. Sofosbuvir, a nucleotide polymerase inhibitor, for the treatment of chronic hepatitis C virus infection. *Expert Opin Invest Drugs* 2013; **22:** 527–36.
2. Asselah T. Sofosbuvir for the treatment of hepatitis C virus. *Expert Opin Pharmacother* 2014; **15:** 121–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Sovaldi.

Sorivudine *(BAN, USAN, rINN)*

Bravavir; Bromovinylarauracil; Brovavir; BV-araU; BVAU; Sorivudin; Sorivudina; Sorivudinum; SQ-32756; YN-72; Соривудин.

(*E*)-1-β-D-Arabinofuranosyl-5-(2-bromovinyl)uracil.

$C_{11}H_{13}BrN_2O_6$=349.1

CAS — 77181-69-2.

UNII — C7VOZ162LV.

Profile

Sorivudine is a synthetic thymidine derivative with antiviral activity against varicella-zoster virus. An oral preparation has been given for the treatment of herpes zoster but was withdrawn from the market in Japan after deaths in patients also given fluorouracil. A topical preparation is now being studied.

References.

1. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342:** 1166.
2. Diasio RB. Sorivudine and 5-fluorouracil: a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; **46:** 1–4.

Stavudine *(BAN, USAN, pINN)*

BMY-27857; d4T; Estavudina; Sanilvudine; Stavudiini; Stavudin; Stavudinas; Stavudinum; Ставудин.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine.

$C_{10}H_{12}N_2O_4$=224.2

CAS — 3056-17-5.

ATC — J05AF04.

ATC Vet — QJ05AF04.

UNII — BO9LE4QFZF.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Stavudine). A white or almost white powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. Protect from light and humidity.

USP 36: (Stavudine). A white to off-white, crystalline powder. Soluble in water, in dimethylacetamide, and in dimethyl sulfoxide; sparingly soluble in alcohol, in acetonitrile, and in methyl alcohol; slightly soluble in dichloromethane; insoluble in petroleum spirit. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Stavudine is a nucleoside reverse transcriptase inhibitor related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when stavudine is used alone, and it is therefore used with other antiretrovirals. Stavudine is given orally, usually as a capsule or solution. Usual adult doses of stavudine are 40 mg every 12 hours for patients weighing 60 kg or more or 30 mg every 12 hours for patients weighing less than 60 kg.

For details of doses in infants, children, and adolescents, see below.

For details of reduced doses of stavudine to be used in patients with renal impairment, see below.

Reviews.

1. Hurst M, Noble S. Stavudine: an update of its use in the treatment of HIV infection. *Drugs* 1999; **58:** 919–49.
2. Cheer SM, Goa KL. Stavudine once daily. *Drugs* 2002; **62:** 2667–74.
3. Hill A, *et al.* Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. *Expert Opin Pharmacother* 2007; **8:** 679–88.
4. Makinson A, *et al.* Safety of stavudine in the treatment of HIV infection with a special focus on resource-limited settings. *Expert Opin Drug Safety* 2008; **7:** 283–93.
5. Martin JC, *et al.* Early nucleoside reverse transcriptase inhibitors for the treatment of HIV: a brief history of stavudine (D4T) and its comparison with other dideoxynucleosides. *Antiviral Res* 2010; **85:** 34–8.
6. Spaulding A, *et al.* Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naïve individuals. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 10/08/10).

Administration in children. For the treatment of HIV infection in infants, children, and adolescents stavudine is given orally with other antiretroviral drugs. Doses are based on age and body-weight:

- in neonates from birth to 13 days old a dose of 500 micrograms/kg every 12 hours may be given
- in infants at least 14 days old and those weighing less than 30 kg the dose is 1 mg/kg every 12 hours
- in children and adolescents weighing 30 kg or more, the adult dose is given (see above)

Administration in renal impairment. Dosage reduction according to creatinine clearance (CC) is recommended for patients receiving oral stavudine who have renal impairment:

- CC 26 to 50 mL/minute: 20 mg every 12 hours (those weighing 60 kg or more) or 15 mg every 12 hours (those weighing less than 60 kg)
- CC below 26 mL/minute: 20 mg every 24 hours (those weighing 60 kg or more) or 15 mg every 24 hours (those weighing less than 60 kg)

Adverse Effects

The most common adverse effect reported with stavudine either as monotherapy or with other antiretrovirals is

peripheral neuropathy; risk generally relates to cumulative dose and it is also increased in patients taking stavudine with didanosine and hydroxycarbamide. Other common adverse effects include abnormal dreams, abdominal pain, nausea, diarrhoea, drowsiness, dyspepsia, fatigue, dizziness, depression, headache, insomnia, pruritus, and rash. Abnormal liver function tests may occur and hepatitis, hepatic failure, and pancreatitis have been reported rarely; fatalities have occurred and were reported most often in patients taking stavudine with didanosine and hydroxycarbamide. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs, and particularly with stavudine. There have been reports of motor weakness associated with stavudine, occurring particularly with lactic acidosis; the presentation may mimic that of Guillain-Barré syndrome (including respiratory failure), and symptoms may continue or worsen even after stavudine is stopped.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including stavudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including stavudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported; effects on blood lipids and fat distribution, in particular, are generally thought to occur more frequently with stavudine than with other NRTIs. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the nervous system. Peripheral neuropathy is a well recognised adverse effect of stavudine and has been the subject of a review.[1] A cross-sectional study[2] of 294 HIV-infected patients using stavudine, found increased age and height to be independently associated with development of neuropathy; the authors suggested that, where possible, patients aged at least 40 years or those who are at least 170 cm tall (and particularly those meeting both criteria) should not be treated with stavudine-based regimen.

1. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998; **19:** 481–94.
2. Cherry CL, *et al*. Age and height predict neuropathy risk in patients with HIV prescribed stavudine. *Neurology* 2009; **73:** 315–20.

Gynaecomastia. Bilateral gynaecomastia was associated with stavudine use in a patient with HIV infection who was also receiving lamivudine and co-trimoxazole.[1] Symptoms resolved when stavudine was stopped. Four other cases of gynaecomastia were reported in HIV-infected patients given HAART regimens containing stavudine.[2]

1. Melbourne KM, *et al*. Gynecomastia with stavudine treatment in an HIV-positive patient. *Ann Pharmacother* 1998; **32:** 1108.
2. Manfredi R, *et al*. Gynecomastia associated with highly active antiretroviral therapy. *Ann Pharmacother* 2001; **35:** 438–9.

Precautions

Stavudine should be used with caution in patients with a history of peripheral neuropathy; if it develops during stavudine use, the patient should be switched to an alternative treatment regimen. Treatment with stavudine may be associated with lactic acidosis and should also be stopped if there is a rapid increase in aminotransferase concentrations, pronounced hepatotoxicity (which may include progressive hepatomegaly or steatosis), or metabolic or lactic acidosis of unknown aetiology. Stavudine should be given with caution to patients (particularly obese women) with hepatomegaly, hepatitis, or other risk factors for liver disease. If liver enzymes increase to >5 times the upper limit of normal during treatment then stavudine should be stopped. Patients co-infected with chronic hepatitis B or C who are being treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. Patients with a history of, or risk factors for, pancreatitis should also be observed carefully for signs of pancreatitis during stavudine treatment. Use with other drugs likely to cause peripheral neuropathy or pancreatitis should be avoided if possible. Stavudine should be used with caution and doses reduced in patients with renal impairment.

After a 2010 regulatory review of stavudine where its benefit-risk ratio was scrutinised, the European Medicines Agency recommended that its use be strictly limited. It advised that, due to the toxicity of stavudine, the drug should only be used when no other appropriate treatments were available; patients using stavudine should be assessed frequently and switched to an appropriate alternative as soon as possible.[1]

1. EMEA. Questions and answers on the review of Zerit (stavudine): outcome of a renewal procedure (issued 17 Feb 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/human/000110/WC500102227.pdf (accessed 06/04/11)

Gender. In a prospective study[1] in a cohort of 559 Ugandan patients starting antiretroviral therapy, about a quarter changed their treatment regimen at least once over 3 years. The cause of treatment substitution was drug toxicity in 91 patients and in 76 this was due to stavudine. Analysis indicated that stavudine toxicity leading to change of regimen was almost twice as likely in women as in men, suggesting that long-term stavudine use was less well tolerated in women, and should be avoided if possible.

1. Castelnuovo B, *et al*. Stavudine toxicity in women is the main reason for treatment change in a 3-year prospective cohort of adult patients started on first-line antiretroviral treatment in Uganda. *J Acquir Immune Defic Syndr* 2011; **56:** 59–63.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies stavudine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

The intracellular activation of stavudine and hence its antiviral effect may be inhibited by zidovudine, doxorubicin, and ribavirin.

Use of stavudine with other drugs known to cause pancreatitis or peripheral neuropathy should be avoided if possible. The combination of hydroxycarbamide and didanosine if given with stavudine, may carry a higher risk of adverse effects including hepatotoxicity, peripheral neuropathy, and pancreatitis (fatal and non-fatal).

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al*. A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Phenylpropanolamine. Hypertensive crisis associated with use of phenylpropanolamine and clemastine occurred in a patient receiving HIV prophylaxis with indinavir, lamivudine, and stavudine.[1] The most likely cause was an interaction between phenylpropanolamine and stavudine, although interactions with the other antiretrovirals could not be ruled out.

1. Khurana V, *et al*. Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106:** 118–19.

Antiviral Action

Stavudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Stavudine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Stavudine is absorbed rapidly after oral doses and peak plasma concentrations occur within 1 hour. It has a reported bioavailability of about 86%. Food delays but does not reduce absorption. Stavudine crosses the blood-brain barrier producing a CSF to plasma ratio of about 0.4 after 4 hours. Binding to plasma proteins is negligible. Stavudine is metabolised intracellularly to the active antiviral triphosphate. The elimination half-life is reported to be about 1 to 1.5 hours after single or multiple doses. The intracellular half-life of stavudine triphosphate has been estimated to be 3.5 hours *in vitro*. About 40% of a dose is excreted in the urine by active tubular secretion and glomerular filtration. Stavudine is removed by haemodialysis.

References.

1. Rana KZ, Dudley MN. Clinical pharmacokinetics of stavudine. *Clin Pharmacokinet* 1997; **33:** 276–84.
2. Kaul S, *et al*. Effect of food on bioavailability of stavudine in subjects with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1998; **42:** 2295–8.
3. Grasela DM, *et al*. Pharmacokinetics of single-dose oral stavudine in subjects with renal impairment and in subjects requiring hemodialysis. *Antimicrob Agents Chemother* 2000; **44:** 2149–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lion; Stamar; Stavubergen; STV; Tonavir; Zerit; ***Austral.***: Zerit; ***Austria***: Zerit; ***Belg.***: Zerit; ***Braz.***: Svudin; Zeritavir†; ***Canad.***: Zerit; ***Chile***: Zerit; ***China***: Ai Fu Ding (艾复定); Sazi (沙之); Xin Fu Da (欣复达); Zerit (赛瑞特); ***Cz.***: Zerit; ***Denm.***: Zerit; ***Fin.***: Zerit; ***Fr.***: Zerit; ***Ger.***: Zerit; ***Gr.***: Zerit; ***Hong Kong***: Zerit; ***Hung.***: Zerit; ***India***: Stavir; ***Indon.***: Zerit†; ***Irl.***: Zerit; ***Ital.***: Zerit; ***Jpn***: Zerit; ***Malaysia***: Virostav; ***Mex.***: Landstav†; Pravidine†; Ranstar†; Zerit; ***Neth.***: Zerit; ***Norw.***: Zerit†; ***NZ***: Zerit; ***Pol.***: Zerit; ***Port.***: Zerit; ***Rus.***: Actastav (Актастав); Zerit (Зерит); ***S.Afr.***: Stavir; Vanra; Zerit; ***Singapore***: Zerit; ***Spain***: Zerit; ***Swed.***: Zerit; ***Switz.***: Zerit; ***Thai.***: Stavir; Zerit†; ***Turk.***: Zerit; ***UK***: Zerit; ***USA***: Zerit; ***Venez.***: Stavir; Zerit.

Multi-ingredient Preparations. ***India***: Emduo-E; Emduo-N; Emduo; Emtri; Lamivir S; Lamostad-N; Lamostad; Triomune; ***S. Afr.***: Sonke-LamiNevStav; Triomune; Virtrium; ***Thai.***: GPO-Vir S; La-Stavir; ***Venez.***: Triomune.

Pharmacopoeial Preparations
USP 36: Stavudine Capsules; Stavudine for Oral Solution.

Telaprevir *(USAN, rINN)*

LY-570310; MP-424; Télaprévir; Telaprevirum; VRT-111950; VX-950; Телапревир.

(1*S*,3a*R*,6a*S*)-2-{(2*S*)-2-[(2*S*)-Cyclohexyl[(pyrazin-2-ylcarbonyl)amino]acetamido]-3,3-dimethylbutanoyl}-*N*-[(3*S*)-1-cyclopropylamino-1,2-dioxohexan-3-yl]octahydrocyclopenta[*c*]pyrrole-1-carboxamide.

$C_{36}H_{53}N_7O_6$=679.9

CAS — 402957-28-2.

UNII — 655M5O3W0U.

Uses and Administration

Telaprevir is an oral peptidomimetic HCV-protease inhibitor effective against hepatitis C virus (HCV) serine protease NS3/4A. It is used in the treatment of chronic hepatitis C (p. 952.1) genotype 1 infection in adults with compensated liver disease, including cirrhosis. Telaprevir is given in an oral dose of 750 mg three times daily (once every 7 to 9 hours) with food in a combined regimen with peginterferon alfa and ribavirin (tri-therapy) for 12 weeks. This is followed by 12 or 36 weeks of treatment with peginterferon alfa and ribavirin (bi-therapy) depending on patient history and hepatitis C-RNA (HCV-RNA) levels; UK and US licensed product information gives the following guidance:

For *previously untreated patients* and those who have *relapsed after interferon-based therapy*

- where HCV-RNA is undetectable at weeks 4 and 12: 12 weeks of bi-therapy (total 24 weeks of treatment)
  US licensed product information advises that treatment-naive patients with *cirrhosis* may benefit from 36 weeks of bi-therapy (total 48 weeks of treatment); in the UK, this approach is advocated for all patients with cirrhosis, irrespective of HCV-RNA levels at weeks 4 and 12
- where HCV-RNA is detectable but 1000 units/mL or less at weeks 4 and/or 12: 36 weeks of bi-therapy (total 48 weeks of treatment)

For *prior partial- and nonresponders to interferon-based therapy*

- 36 weeks of bi-therapy (total 48 weeks of treatment)

For all patients, HCV-RNA levels >1000 units/mL at week 4 or 12 or detectable HCV-RNA levels at week 24 are an indication of treatment futility, in which case therapy should be abandoned.

The dose of telaprevir may occasionally need to be adjusted to compensate for the effect of an interacting drug. UK-licensed product information for telaprevir recommends a dose of 1.125 g three times daily when telaprevir is to be given with *efavirenz*.

References.

1. Hézode C, *et al*. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; **360:** 1839–50.
2. McHutchison JG, *et al*. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; **360:** 1827–38. Correction. *ibid.*; **361:** 1516.
3. McHutchison JG, *et al*. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; **362:** 1292–303. Correction. *ibid.*; 1647. [dose]

Adverse Effects

The addition of an HCV-protease inhibitor to a regimen of peginterferon alfa and ribavirin can result in significant additional toxicity, particularly dermatological, gastrointestinal, and haematological. In particular, telaprevir increases the risk of rash, which can include serious skin reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome.

Adverse effects associated with the use of telaprevir with peginterferon alfa and ribavirin are wide ranging, but the most common adverse effects reported in clinical studies were anaemia, rash, itch, nausea, and diarrhoea. Other common effects that have been reported include oral candidiasis, blood dyscrasias (including lymphopenia and thrombocytopenia), hypothyroidism, metabolic disorders (such as hyperuricaemia and hypokalaemia), taste disturbances, syncope, gastrointestinal and anorectal disorders (including anal itch and fissure, haemorrhoids, rectal haemorrhage, and proctalgia), hyperbilirubinaemia, eczema, facial swelling, and peripheral oedema.

Precautions

Telaprevir must not be used as monotherapy as there is a high likelihood of viral resistance developing; because it must always be given with peginterferon alfa and ribavirin, precautions with respect to the use of these medications must be observed (see p. 995.1 and p. 1011.2, respectively).

Telaprevir-containing regimens generally increase the incidence and degree of anaemia compared with peginterferon alfa and ribavirin alone; consequently haemoglobin should be monitored before, and at least every 4 weeks during, telaprevir use. Telaprevir-containing regimens have also been associated with a high incidence of rash, and in rare cases, serious skin reactions such as drug rash with eosinophilia and systemic symptoms and Stevens-Johnson syndrome. If a serious skin reaction occurs, the telaprevir-containing regimen should be permanently and immediately stopped and the patient referred for medical care. Patients who develop mild to moderate rashes should be monitored for progression of rash or development of systemic symptoms, in which case telaprevir should be stopped (although peginterferon alfa and ribavirin may be continued in certain circumstances). Telaprevir is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh class B or C, score ≥7) or in those with decompensated liver disease. Telaprevir may cause modest prolongation of the QT interval, and should be used with caution in patients already at risk for QT-interval prolongation.

Interactions

Telaprevir is an inhibitor of the CYP3A family of cytochrome P450 isoenzymes and is expected to increase exposure to drugs that are metabolised by these enzymes; telaprevir in combination with peginterferon alfa and ribavirin is contra-indicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. Although specific guidance may vary between licensing authorities, these drugs may include:

- the alpha$_1$-adrenoreceptor antagonist alfuzosin
- antiarrhythmics (amiodarone and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- calcium-channel blockers (bepridil)
- ergot derivatives (dihydroergotamine, ergonovine, ergotamine, and methylergonovine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (atorvastatin, lovastatin, and simvastatin)

Owing to the potential for increased serum concentrations of phosphodiesterase type-5 inhibitors (such as sildenafil and tadalafil), telaprevir should be avoided with these drugs when they are given at the doses needed for the treatment of pulmonary hypertension. Similarly, telaprevir may increase serum concentrations of inhaled budesonide, fluticasone, or salmeterol; combination with any of these is not recommended.

Telaprevir is a substrate of the CYP3A group of cytochrome P450 isoenzymes; as a result, drugs that induce or inhibit these enzymes might be expected to decrease or increase exposure to telaprevir. In particular, use with potent inducers of these enzymes (such as carbamazepine, phenobarbital, phenytoin, rifampicin, or St John's wort) should be avoided. Similarly, use with ritonavir-boosted darunavir, fosamprenavir, or lopinavir is not advised; for telaprevir dosing recommendations for co-administration with efavirenz, see Uses and Administration, p. 1016.3. Co-administration with mild or moderate inducers of CYP3A should also be avoided if possible, particularly in patients who are prior nonresponders to peginterferon alfa and ribavirin.

Telaprevir is also an inhibitor and substrate of P-glycoprotein (P-gp). Its use with drugs that are substrates for P-gp transport might be expected to lead to their prolonged therapeutic action or adverse effects; similarly, use with drugs that induce or inhibit P-gp could cause decreased or increased exposure to telaprevir, respectively.

Due to the risk of arrhythmia, telaprevir should not be given with class Ia or III antiarrhythmics (except intravenous lidocaine); it should be used with caution with the class Ic antiarrhythmics propafenone and flecainide. Care is also advised when telaprevir must be used with drugs known to prolong the QT interval.

Hormonal contraception may not be reliable during use of telaprevir, and for up to 2 months after it is stopped. During this time, women of child-bearing potential should use two effective forms of non-hormonal contraception.

Antiviral Action

Telaprevir is an inhibitor of the NS3/4A protease of hepatitis C virus (HCV), a protein involved in the post-translational processing of HCV polyproteins that is required for viral replication. It must always be given with peginterferon alfa and ribavirin to minimise the risk of viral resistance. Although telaprevir was developed to target HCV genotype 1, it also appears to have some activity against genotype 2.

Pharmacokinetics

Telaprevir is absorbed orally, and peak plasma concentrations generally occur about 4 to 5 hours after a dose. Bioavailability is significantly affected by food; compared with a standard meal, telaprevir exposure is increased by 20% when the drug is taken with a high-fat caloric meal, and decreased by 73% when taken on an empty stomach. Telaprevir exposure is also increased by co-administration with peginterferon alfa and ribavirin. It is about 59 to 76% bound to plasma proteins (mainly albumin and alpha 1-acid glycoprotein) and widely distributed to tissues, with a volume of distribution estimated to be in the order of 252 litres (although interindividual variation is about 72%).

Telaprevir is extensively metabolised by the liver via hydrolysis, oxidation, and reduction to produce multiple metabolites; the most prominent are a 30-fold less active *R*-diastereomer of telaprevir (VRT-127394), pyrazinoic acid, and an inactive ketone-reduced metabolite. *In-vitro* studies indicate that CYP3A4 is the main cytochrome P450 isoenzyme responsible for the metabolism of telaprevir, although non-CYP-mediated metabolism likely plays a role as well.

About 90% of a radiolabelled 750-mg dose of telaprevir is recovered within 96 hours of being given, 80% in the faeces (about half of this as unchanged drug or its diastereoisomer), and the remainder in expired air with traces in urine. The steady-state half-life is about 9 to 11 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Incivo; ***Canad.***: Incivek; ***Denm.***: Incivo; ***Fr.***: Incivo; ***Ger.***: Incivo; ***Irl.***: Incivo; ***Israel***: Incivo; ***Jpn***: Telavic; ***Neth.***: Incivo; ***Norw.***: Incivo; ***Spain***: Incivo; ***Swed.***: Incivo; ***Switz.***: Incivo; ***UK***: Incivo; ***USA***: Incivek.

Telbivudine *(BAN, USAN, rINN)*

L-dT; Epavudine; LDT-600; NV-02B; Telbivudina; Telbivudinum; Тельбивудин.

2′-Deoxy-L-thymidine; 1-(2-Deoxy-β-L-*erythro*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione.

$C_{10}H_{14}N_2O_5$=242.2

CAS — 3424-98-4.

ATC — J05AF11.

ATC Vet — QJ05AF11.

UNII — 2OC4HKD3SF.

Uses and Administration

Telbivudine is a L-nucleoside analogue with specific activity against the hepatitis B virus. It is given orally for the treatment of chronic hepatitis B (p. 952.1) in patients with compensated liver disease and evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of telbivudine is 600 mg once daily. For details of dosage modification in patients with renal impairment, see below.

References.

1. Kim JW, *et al.* Telbivudine: a novel nucleoside analog for chronic hepatitis B. *Ann Pharmacother* 2006; **40:** 472–8.
2. Jones R, Nelson M. Novel anti-hepatitis B agents: a focus on telbivudine. *Int J Clin Pract* 2006; **60:** 1295–9.
3. Keam SJ. Telbivudine. *Drugs* 2007; **67:** 1917–29.
4. Hadziyannis SJ, Vassilopoulos D. Telbivudine in the treatment of chronic hepatitis B. *Expert Rev Gastroenterol Hepatol* 2008; **2:** 13–22.
5. Osborn MK. Safety and efficacy of telbivudine for the treatment of chronic hepatitis B. *Ther Clin Risk Manag* 2009; **5:** 789–98.
6. Milazzo L, *et al.* Telbivudine in the treatment of chronic hepatitis B: experience in HIV type-1-infected patients naive for antiretroviral therapy. *Antivir Ther* 2009; **14:** 869–72.
7. Liaw YF, *et al.* 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136:** 486–95.
8. Lui YY, Chan HL. Treatment of chronic hepatitis B: focus on telbivudine. *Expert Rev Anti Infect Ther* 2009; **7:** 259–68.

Administration in renal impairment. Oral doses of telbivudine should be reduced in patients with renal impairment by modifying the dosing interval according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: 600 mg once daily
- CC 30 to 49 mL/minute: 600 mg every 48 hours
- CC less than 30 mL/minute (and not on dialysis): 600 mg every 72 hours
- end stage renal disease: 600 mg every 96 hours

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Adverse Effects

The most common adverse effects reported for telbivudine are cough, dizziness, fatigue, gastrointestinal effects including abdominal pain, diarrhoea, and nausea, and rash. There have also been reports of arthralgia, myalgia, myopathy including myositis, and malaise. Serum amylase, lipase and creatine phosphokinase levels may be increased. Raised serum alanine aminotransferase concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with telbivudine. There have been occasional reports of peripheral neuropathy, particularly when given with peginterferon alfa-2a.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues (see Zidovudine, p. 1024.3).

Precautions

Telbivudine should be given with caution to patients with cirrhosis, hepatomegaly, or other risk factors for liver disease and should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Exacerbation of hepatitis B has been reported both during and after stopping treatment with telbivudine. Liver function should be monitored closely during treatment and for several months after treatment is stopped. Patients taking telbivudine should be monitored for peripheral neuropathy and treatment should be stopped if myopathy or peripheral neuropathy is diagnosed. Dosage reduction may be necessary in patients with renal impairment.

Interactions

Caution should be exercised when telbivudine is given with other drugs that alter renal function; serum concentrations of either drug may be affected. Telbivudine should be given with caution to patients taking other drugs associated with myopathy (such as azole antifungals, ciclosporin, corticosteroids, erythromycin, fibrates, HMG-CoA reductase inhibitors, penicillamine, and zidovudine).

Interferons. For mention of an increased risk of peripheral neuropathy in patients given both telbivudine and *peginterferon alfa-2a*, see Adverse Effects, above.

Antiviral Action

Telbivudine is phosphorylated intracellularly to the active triphosphate form, which competes with thymidine 5′-triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby causing DNA chain termination and inhibiting hepatitis B viral replication.

Telbivudine has no activity against HIV.

Pharmacokinetics

Telbivudine is absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur after about 3 hours. Absorption is not affected when given with food. Binding of telbivudine to plasma proteins is about 3.3% *in vitro*. Telbivudine is not metabolised by the cytochrome P450 system. It is mainly excreted renally by glomerular filtration as unchanged drug, with a terminal elimination half-life of 30 to 53.6 hours. Telbivudine is partially removed by haemodialysis.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sebivo; ***Austral.***: Sebivo; ***Austria***: Sebivo; ***Braz.***: Sebivo; ***Canad.***: Sebivo; ***China***: Sebivo (素比伏); ***Cz.***: Sebivo; ***Denm.***: Sebivo†; ***Fr.***: Sebivo; ***Ger.***: Sebivo; ***Gr.***: Sebivo; ***Hong Kong***: Sebivo; ***Indon.***: Sebivo; ***Irl.***: Sebivo; ***Israel***: Sebivo; ***Ital.***: Sebivo; ***Malaysia***: Sebivo; ***Neth.***: Sebivo; ***Norw.***: Sebivo; ***NZ***: Sebivo; ***Philipp.***: Sebivo; ***Pol.***: Sebivo; ***Port.***: Sebivo; ***Rus.***: Sebivo (Себиво); ***Singapore***: Sebivo†; ***Spain***: Sebivo; ***Swed.***: Sebivo; ***Switz.***: Sebivo; ***Thai.***: Sebivo; ***Turk.***: Sebivo; ***UK***: Sebivo; ***Ukr.***: Sebivo (Себиво); ***USA***: Tyzeka.

Tenofovir *(BAN, USAN, rINN)*

GS-1278; PMPA; (*R*)-PMPA; Ténofovir; Tenofovirum; Тенофовир.

9-[(*R*)-2-(Phosphonomethoxy)propyl]adenine monohydrate; {[(*R*)-2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl} phosphonic acid monohydrate.

$C_9H_{14}N_5O_4P,H_2O$=305.2

CAS — 147127-20-6 (anhydrous tenofovir); 206184-49-8 (tenofovir monohydrate).

UNII — 99YXE507IL.

Tenofovir Disoproxil Fumarate

(BANM, USAN, rINNM)

Bis(POC)PMPA Fumarate; Fumarato de disoproxilo de tenofovir; GS-4331/05; Ténofovir Disoproxil. Fumarate de; Tenofovir, fumarato del disoproxilo de; Tenofovirum Disoproxilum Fumaras; Тенофовир Дизопроксил Фумарат.

9-{(*R*)-2-[(Bis[[(isopropoxycarbonyl)oxy]methoxy}phosphinyl) methoxy]propyl}adenine fumarate (1:1).

$C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$=635.5

CAS — 202138-50-9.

ATC — J05AF07.

ATC Vet — QJ05AF07.

UNII — OTT9J7900I.

Uses and Administration

Tenofovir is a nucleotide reverse transcriptase inhibitor with antiviral activity against HIV-1 and hepatitis B. It is used in the treatment of HIV infection and AIDS (p. 957.2) and chronic hepatitis B infection (see below). It may also have a role in reducing the transmission of HIV infection (see below). Viral resistance emerges rapidly when tenofovir is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

It is given orally as the disoproxil fumarate ester. Tenofovir disoproxil fumarate 300 mg is equivalent to about 245 mg of tenofovir disoproxil and to about 136 mg of tenofovir. For the treatment of either **HIV** or **chronic hepatitis B** infection the usual dose is 300 mg of the disoproxil fumarate ester once daily with food. For details of doses in children and adolescents for the treatment of HIV infection, see below.

For details of doses of tenofovir disoproxil fumarate to be used in adult patients with renal impairment, see below.

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing tenofovir disoproxil fumarate in combination with emtricitabine, and with efavirenz plus emtricitabine are available in some countries. It is also a component of a four-drug, fixed-dose combination product with elvitegravir and emtricitabine and the pharmacokinetic enhancer cobicistat (p. 2482.3).

A gel containing tenofovir 1% is under investigation as a topical microbicide in the prevention of HIV infection. For further information see below. A lipid-conjugated formulation, hexadecyloxypropyl tenofovir (CMX-157), thought to have improved antiviral activity due to better intracellular uptake, is also under investigation for the treatment of HIV and AIDS.

References.

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Administration in children. For the treatment of **HIV infection** in children from 2 years of age and adolescents, tenofovir disoproxil fumarate is given daily with other antiretroviral drugs. The dose is based on body-weight, which should be monitored periodically and the dose adjusted if necessary.

In the USA, an oral *powder* or *film-coated tablets* are available for use; the film-coated tablets may be given to children weighing 17 kg or more and who are able to swallow intact tablets. The recommended dose for both formulations is 8 mg/kg once daily; doses should not exceed the adult dose (see above).

Administration in renal impairment. Doses of tenofovir disoproxil fumarate should be modified by adjustment of the dosing interval in adult patients with renal impairment according to their creatinine clearance (CC):

- CC 50 mL/minute or more: usual once-daily dosage (see Uses and Administration, above)
- CC 30 to 49 mL/minute: every 48 hours
- CC 10 to 29 mL/minute: every 72 to 96 hours
- haemodialysis patients: a dose every 7 days or after a cumulative total of 12 hours of dialysis

There is a lack of data to make dosage recommendations for children and adolescents with renal impairment.

Hepatitis B. In a meta-analysis evaluating the efficacy of various licensed therapies for chronic hepatitis B in treatment-naive patients,[1] tenofovir was found to be the most effective oral antiviral agent during the first year of treatment in hepatitis B e antigen (HBeAg)-negative patients. In HBeAg-positive patients, tenofovir and entecavir were found to be the most effective treatments.

Much of the data confirming tenofovir's potent effect on hepatitis B viral (HBV) suppression comes from large phase 3 studies involving mainly treatment-naive patients, and whether tenofovir is effective as monotherapy in treatment-experienced patients has been an area of some debate. However, treatment with tenofovir (alone or with emtricitabine) led to complete HBV suppression (at 48 weeks) in 81% of patients who had previously had inadequate response to treatment with adefovir; response was not influenced by the presence of pre-existing antiviral resistance mutations to adefovir or lamivudine.[2] In a similar study in patients who had lamivudine-resistant virus and failed to respond adequately to adefovir therapy, use of tenofovir led to HBV suppression in 46% and 64% of patients at 48 and 96 weeks respectively; the authors noted, however, that efficacy in this heavily pretreated population was inferior to that reported for treatment-naive patients.[3]

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3. Patterson SJ, *et al*. Tenofovir disoproxil fumarate rescue therapy following failure of both lamivudine and adefovir dipivoxil in chronic hepatitis B. *Gut* 2011; **60:** 247–54.

Prevention of HIV transmission. Use of **oral** tenofovir may also have a role in reducing the transmission of HIV infection. In a study involving homosexual men,[1] use of a once-daily, combined oral preparation of tenofovir and emtricitabine led to a 44% lower incidence of HIV infection over and above standard preventative interventions and services (over a median 1.2 years of follow-up). As a result of these data, the CDC has issued guidance[2] on the use of pre-exposure prophylaxis to prevent HIV infection in men who have sex with men. However, one arm of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was reportedly terminated early when interim analysis suggested oral tenofovir was of no value in African women at high risk of infection (FEM-PrEP).[3] Another arm of the study examining oral tenofovir with or without oral emtricitabine in at-risk women was reported to be ongoing.[4] However, more recently[5] it has been reported that 2 studies, whose results remain to be published, have shown that pre-exposure prophylaxis using oral tenofovir with or without emtricitabine is effective.

Tenofovir is being investigated[6-11] as a topical gel for its potential as a microbicide in the prevention of HIV transmission. In a double-blind, placebo-controlled study,[10] use of a tenofovir 1% vaginal gel before and after sexual intercourse reduced the incidence of HIV infection by an estimated 39% overall, and by 54% among women with > 80% adherence to the gel regimen. However, contradictory effectiveness outcomes were reported following an interim review of the VOICE study.[11] A 6% rate of HIV infection was reported for both the group receiving the 1% tenofovir vaginal gel and for the placebo group; this arm of the VOICE study was also stopped.

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7. Carballo-Diéguez A, *et al*. Acceptability of tenofovir gel as a vaginal microbicide by US male participants in a Phase I clinical trial (HPTN 050). *AIDS Care* 2007; **19:** 1026–31.
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9. Schwartz JL, *et al*. Safety evaluation of 1% tenofovir gel in healthy men. *Int J STD AIDS* 2009; **20:** 384–6.
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Adverse Effects

Adverse effects commonly associated with tenofovir either as monotherapy for the treatment of chronic hepatitis B or with other antiretrovirals for the treatment of HIV are mild to moderate gastrointestinal events such as anorexia, abdominal pain and distention, diarrhoea, dyspepsia, flatulence, nausea, and vomiting. Other commonly reported adverse effects are asthenia, dizziness, fatigue, and headache. Rashes may occur. Hypophosphataemia is also common. Serum-amylase concentrations may be raised and pancreatitis has been reported rarely. There have also been reports of raised liver enzymes and hepatitis.

Renal effects, including nephritis, nephrogenic diabetes insipidus, proximal renal tubulopathy (including Fanconi syndrome), and renal failure have been associated with the use of tenofovir, and may occur weeks to months after the start of therapy. Bone pain and osteomalacia, sometimes contributing to fractures, may result from proximal renal tubulopathy; muscle weakness, myopathy, and rarely rhabdomyolysis may also occur.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs; the risk is thought to be low for tenofovir, but cannot be excluded given its structural similarity to the NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including tenofovir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including tenofovir disoproxil fumarate, although tenofovir itself has not been clearly implicated as a causative factor in these effects and has generally been associated with a favourable lipid profile. Tenofovir also appears less likely than the NRTIs to be associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the kidneys. Use of tenofovir in patients with HIV infection has been associated with renal toxicity,[1] including Fanconi syndrome,[2] interstitial nephritis,[3] and acute renal failure.[4,5] The mechanism of acute renal failure appears to be tubular necrosis, which may not resolve on withdrawal of the drug.[6] Some studies have indicated that glomerular filtration rate or creatinine clearance was consistently decreased in patients given tenofovir-containing regimens;[7,8] it has been reported that this is greater if combined with HIV-protease inhibitors than NNRTIs.[8] Other studies have not found renal toxicity to be a significant problem.[9,10] A systematic review[11] of 17 studies concluded that although use of tenofovir was associated with loss of renal function, the clinical magnitude of the effect was modest; it was concluded that use need not be restricted in areas where facilities for regular monitoring of renal function were not readily available.

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2. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *AIDS Patient Care STDS* 2008; **22:** 99–103.
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4. Hynes P, *et al.* Acute renal failure after initiation of tenofovir disoproxil fumarate. *Ren Fail* 2007; **29:** 1063–6.
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11. Cooper RD, *et al.* Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010; **51:** 496–505.

Precautions

Due to the risk of development of HIV resistance, tenofovir must not be used in patients with hepatitis B who are co-infected with HIV, unless it is as part of an appropriate antiretroviral combination regimen. Treatment with tenofovir should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. It should be given with caution to patients with hepatomegaly or other risk factors for liver disease. In particular, extreme caution should be exercised in patients with co-existing hepatitis C infection who are receiving interferon alfa and ribavirin. In patients co-infected with hepatitis B, there is a risk of severe acute exacerbation of hepatitis when tenofovir is stopped, and liver function should be monitored closely in such patients for at least several months.

Renal function and serum phosphate concentrations should be monitored before treatment is started, every 4 weeks during the first year of therapy, and then every 3 months (but see also Effects on the Kidney, p. 1018.3); in patients with a history of renal impairment or who are particularly at risk, more frequent monitoring may be needed; particular risk factors for renal impairment with tenofovir include older age, hypertension, hepatitis C co-infection, lower baseline creatinine clearance, low CD4+ count, and concomitant use of a HIV-protease inhibitor. Tenofovir should be used with caution, and doses modified, in patients with renal impairment. If serum-phosphate concentrations fall markedly or if creatinine clearance is below 50 mL/minute, renal function should be evaluated within a week, and the dose interval may need to be adjusted or treatment interrupted. Tenofovir may be associated with reduction in bone density and patients should be observed for evidence of bone abnormalities; bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia; supplementation with calcium and vitamin D may be beneficial.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tenofovir disoproxil fumarate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Use of tenofovir with nephrotoxic drugs or with other drugs eliminated by active tubular secretion is not recommended; if such use is unavoidable, renal function should be monitored weekly. Tenofovir should not be used with adefovir. Once daily triple drug regimens of tenofovir and lamivudine with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should also be avoided. Tenofovir increases the plasma concentrations of didanosine (see p. 974.1). Decreased plasma concentrations of atazanavir and increased plasma concentrations of tenofovir occur when tenofovir is given with atazanavir; the effect is significantly reduced when ritonavir is added as a booster. Use of ritonavir-boosted lopinavir with tenofovir modestly increases the plasma concentrations of tenofovir.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antiviral Action

Tenofovir is converted intracellularly to the diphosphate. This diphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase and incorporation into viral DNA. It also inhibits hepatitis B virus polymerase, resulting in inhibition of viral replication. Tenofovir-resistant strains of HIV have been identified and cross-resistance to other reverse transcriptase inhibitors may occur.

Pharmacokinetics

Tenofovir disoproxil fumarate, a prodrug, is rapidly absorbed and converted to tenofovir after oral doses and peak plasma concentrations occur after 1 to 2 hours. Bioavailability in fasting patients is about 25%, but this is enhanced when tenofovir disoproxil fumarate is taken with a high fat meal. Tenofovir is widely distributed into body tissues, particularly the kidneys and liver. Binding to plasma proteins is less than 1% and that to serum proteins about 7%. The terminal elimination half-life of tenofovir is 12 to 18 hours. Tenofovir is excreted mainly in the urine by both active tubular secretion and glomerular filtration. It is removed by haemodialysis.

References.
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2. Kearney BP, *et al.* Pharmacokinetics and dosing recommendations of tenofovir disoproxil fumarate in hepatic or renal impairment. *Clin Pharmacokinet* 2006; **45:** 1115–24.
3. Gagnieu MC, *et al.* Population pharmacokinetics of tenofovir in AIDS patients. *J Clin Pharmacol* 2008; **48:** 1282–8.
4. Benaboud S, *et al.* Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother* 2011; **55:** 1315–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Leuzan; Virakam; Viread; ***Austral.***: Viread; ***Austria***: Viread; ***Belg.***: Viread; ***Canad.***: Viread; ***Chile***: Viread; ***China***: Viread (韦瑞德); ***Cz.***: Viread; ***Denm.***: Eviplera; Viread; ***Fin.***: Viread; ***Fr.***: Viread; ***Ger.***: Viread; ***Gr.***: Viread; ***Hong Kong***: Viread; ***Hung.***: Viread; ***Irl.***: Viread; ***Israel***: Viread; ***Ital.***: Viread; ***Mex.***: Viread; ***Neth.***: Viread; ***Norw.***: Viread; ***NZ***: Viread; ***Pol.***: Viread; ***Port.***: Viread; ***S.Afr.***: Viread; Zefin; ***Singapore***: Viread; ***Spain***: Viread; ***Swed.***: Viread; ***Switz.***: Viread; ***Thai.***: Ricovir; Viread; ***UK***: Viread; ***USA***: Viread.

Multi-ingredient Preparations. ***Arg.***: Truvada; ***Austral.***: Atripla; Truvada; ***Austria***: Atripla; Truvada; ***Belg.***: Atripla; Truvada; ***Canad.***: Atripla; Truvada; ***Chile***: Truvada; ***Cz.***: Atripla; Truvada; ***Denm.***: Atripla; Truvada; ***Fin.***: Truvada; ***Fr.***: Atripla; Truvada; ***Ger.***: Atripla; Eviplera; Truvada; ***Gr.***: Atripla; Truvada; ***Hong Kong***: Atripla; Truvada; ***Irl.***: Atripla; Truvada; ***Israel***: Atripla; Eviplera; Truvada; ***Ital.***: Atripla; Truvada; ***Jpn***: Stribild; ***Mex.***: Truvada; ***Neth.***: Atripla; Truvada; ***Norw.***: Atripla; Eviplera; Truvada; ***NZ***: Atripla; Truvada; ***Pol.***: Atripla; Truvada; ***Port.***: Atripla; Truvada; ***S.Afr.***: Adco Emtevir; Didivir; Truvada; Tyricten; ***Spain***: Atripla; Truvada; ***Swed.***: Atripla; Eviplera; Truvada; ***Switz.***: Atripla; Eviplera; Truvada; ***Thai.***: Atripla; Ricovir-Em; Truvada; ***UK***: Atripla; Eviplera; Stribild; Truvada; ***USA***: Atripla; Complera; Stribild; Truvada.

Tilorone Hydrochloride *(USAN, rINNM)*

Hidrocloruro de tilorona; NSC-143969; Tilorone, Chlorhydrate de; Tiloroni Hydrochloridum; Тилорона Гидрохлорид.

2,7-Bis(2-diethylaminoethoxy)fluoren-9-one dihydrochloride.

$C_{25}H_{34}N_2O_3,2HCl$=483.5

CAS — 27591-69-1.

UNII — BJ507J4LKY.

Profile

Tilorone is reported to be an interferon inducer with antiviral and immunomodulatory properties and has been used in the treatment of viral infections; the hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Amixin (Амиксин); Lavomax (Лавомакс); ***Ukr.***: Amixin (Амикси); Lavomax (Лавомакс).

Tipranavir *(rINN)*

PNU-140690; Tipranavirum; Typranawir; U-140690; Типранавир.

3′-[(1*R*)-1-[(6*R*)-5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl]propyl]-5-(trifluoromethyl)-2-pyridinesulfonanilide.

$C_{31}H_{33}F_3N_2O_5S$=602.7

CAS — 174484-41-4.

ATC — J05AE09.

ATC Vet — QJ05AE09.

UNII — ZZT404XD09.

Tipranavir Sodium *(BANM, rINNM)*

Natrii Tipranavirum; PNU-140690E; Tipranavir Disodium (USAN); Tipranavir sodico; Tipranavir Sodique; Натрий Типранавир.

$C_{31}H_{31}F_3N_2Na_2O_5S$=646.6

CAS — 191150-83-1.

ATC — J05AE09.

ATC Vet — QJ05AE09.

UNII — 9BAN2XG1ZW.

Uses and Administration

Tipranavir is a non-peptide HIV-protease inhibitor with antiviral activity against HIV. It is used for the treatment of HIV infection and AIDS (p. 957.2) in treatment-experienced patients or in those with multidrug-resistant HIV infection. Viral resistance emerges rapidly when tipranavir is used alone, and it is therefore used with other antiretrovirals.

It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer (ritonavir-boosted tipranavir). The dose is tipranavir 500 mg (with ritonavir 200 mg) given orally twice daily with food.

For details of doses in children see below.

No dose adjustment is required for patients with renal impairment or mild liver disease. Tipranavir should not be given to patients with moderate to severe liver disease.

Reviews.
1. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. *Drugs* 2005; **65:** 1669–77.
2. Dong BJ, Cocohoba JM. Tipranavir: a protease inhibitor for HIV salvage therapy. *Ann Pharmacother* 2006; **40:** 1311–21.
3. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. *Clin Pharmacokinet* 2006; **45:** 665–82.
4. Temesgen Z, Feinberg J. Tipranavir: a new option for the treatment of drug-resistant HIV infection. *Clin Infect Dis* 2007; **45:** 761–9.
5. Orman JS, Perry CM. Tipranavir: a review of its use in the management of HIV infection. *Drugs* 2008; **68:** 1435–63.
6. Courter JD, *et al.* Tipranavir: a new protease inhibitor for the pediatric population. *Expert Rev Anti Infect Ther* 2008; **6:** 797–803.

Administration in children. For the treatment of HIV infection in children from 2 years of age, tipranavir is given orally with other antiretroviral drugs. It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer. Doses are based on body-weight or body-surface and should not exceed the maximum adult dose (see above).

- The usual recommended dose in children is: tipranavir 14 mg/kg (with ritonavir 6 mg/kg) twice daily *or* tipranavir 375 mg/m² (with ritonavir 150 mg/m²) twice daily
- US licensed product information suggests that children who are intolerant or develop toxicities to the usual dose may take a reduced dose, provided that their virus is not resistant to multiple HIV-protease inhibitors: tipranavir 12 mg/kg (with ritonavir 5 mg/kg) twice daily *or* tipranavir 290 mg/m² (with ritonavir 115 mg/m²) twice daily

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing tipranavir are gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, and vomiting), fatigue, and headache. Serious adverse effects reported include increased risk of bleeding and intracranial haemorrhage including some fatalities. Severe hepatotoxicity (hepatitis and hepatic decompensation, including some fatalities) has also occurred; ritonavir-boosted tipranavir appears to be more likely to cause adverse hepatic events than other HIV-protease inhibitors. Rashes, generally occurring after about 2 months of treatment and lasting about 3 weeks have been reported; rashes are sometimes accompanied by joint pain, stiffness, throat tightness, or generalised pruritus.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including tipranavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement

(buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including tipranavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Intracranial haemorrhage. In June 2006, the manufacturer (*Boehringer Ingelheim, USA*) reported that there had been 14 reports of intracranial haemorrhage (ICH) linked to the use of ritonavir-boosted tipranavir, including 8 fatalities, among about 7000 HIV-1 infected patients in clinical trials.[1] The median time to onset of an ICH event was 525 days. It was noted that many of these patients had other risk factors for ICH, such as CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or use of anticoagulants or antiplatelet drugs. The FDA and EMEA subsequently advised that ritonavir-boosted tipranavir should be used with caution in patients at risk of bleeding; it should be noted that routine monitoring of coagulation parameters is not indicated as no pattern of abnormal coagulation parameters has been seen in patients taking tipranavir, or before the development of tipranavir-associated ICH. However, a cohort study[2] estimating the background rate of ICH, and comparing it to that in tipranavir users estimated that 455 to 5000 HIV-infected patients would need to be given tipranavir for 1 year to cause 1 extra case of ICH over the background rate.

There has also been a report of ICH in a patient using tipranavir whose only apparent predisposing factor was cryptococcal meningitis.[3]

1. Boehringer Ingelheim, USA. Important safety information: intracranial hemorrhage in patients receiving Aptivus (tipranavir) capsules (issued 30th June 2006). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153070.pdf (accessed 16/03/11)
2. Justice AC, *et al.* Drug toxicity, HIV progression, o r comorbidity of aging: does tipranavir use increase the risk of intracranial hemorrhage? *Clin Infect Dis* 2008; **47:** 1226–30.
3. Chrysos G, *et al.* Intracranial haemorrhage possibly related to tipranavir in an HIV-1 patient with cryptococcal meningitis. *J Infect* 2008; **57:** 85–7.

Precautions

Tipranavir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh class B or C), and should be used with caution in those with mild impairment (Child-Pugh A). Treatment should not be started in patients with pretreatment liver enzyme values more than 5 times the upper limit of normal. Patients should be closely monitored for clinical signs and symptoms of hepatitis; monitoring of liver enzymes is recommended before and during treatment with tipranavir. In patients with mild hepatic impairment, chronic hepatitis, or other underlying liver disease more frequent monitoring is recommended. Treatment should be interrupted or stopped if liver function deteriorates and should be permanently stopped if liver enzyme values increase to more than 10 times the upper limit of normal or if signs or symptoms of clinical hepatitis develop. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients who are at increased risk of bleeding, due to trauma, surgery, or certain medical conditions (such as haemophilia A or B) or who are taking antiplatelet drugs or anticoagulants, as reports of spontaneous bleeding and intracranial haemorrhage have been associated with the use of tipranavir. Tipranavir oral solution contains vitamin E and patients given the oral solution should not take high doses of supplemental vitamin E.

Tipranavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy.

Interactions

Tipranavir is both an inducer and an inhibitor of the cytochrome P450 isoenzyme CYP3A4 although when given with low-dose ritonavir there is a net inhibition of CYP3A4; there is therefore the potential for complex interactions with other drugs metabolised by this enzyme. Ritonavir-boosted tipranavir is also a net inducer of P-glycoprotein.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted tipranavir with drugs that are highly dependent on CYP3A4 or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. In the UK, these drugs include

- antiarrhythmics (amiodarone, bepridil, flecainide, metoprolol in doses used for heart failure, propafenone, and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

Use with halofantrine, lumefantrine, or tolterodine is also not recommended. In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated. Owing to the potential for increased serum concentrations of sildenafil, ritonavir-boosted tipranavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir-boosted tipranavir may increase serum concentrations of inhaled fluticasone and salmeterol and combination is not recommended. Rifampicin and St John's wort decrease the concentration of tipranavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Tipranavir is a non-peptide HIV-protease inhibitor. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. HIV isolates resistant to tipranavir have been reported and viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Tipranavir is absorbed to a limited extent after oral doses. Food improves the tolerability and bioavailability is increased with a high fat meal. Peak plasma concentrations occur within 1 to 5 hours and steady state is usually reached after 7 to 10 days of treatment. Tipranavir is about 99.9% bound to plasma proteins. It is metabolised by the cytochrome P450 system (mainly the isoenzyme CYP3A4), although when given with ritonavir metabolism is minimal with the majority of tipranavir being excreted unchanged in the faeces. The mean elimination half-life of tipranavir is 4.8 to 6 hours.

References.

1. Weizsaecker K, *et al.* Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS* 2011; **22:** 294–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aptivus; ***Austral.***: Aptivus; ***Austria***: Aptivus; ***Belg.***: Aptivus; ***Braz.***: Elodius; ***Canad.***: Aptivus; ***Cz.***: Aptivus; ***Denm.***: Aptivus; ***Fin.***: Aptivus†; ***Fr.***: Aptivus; ***Ger.***: Aptivus; ***Gr.***: Aptivus; ***Hung.***: Aptivus; ***Irl.***: Aptivus; ***Ital.***: Aptivus; ***Mex.***: Aptivus; ***Neth.***: Aptivus; ***Norw.***: Aptivus†; ***Pol.***: Aptivus; ***Port.***: Aptivus; ***Spain***: Aptivus; ***Swed.***: Aptivus; ***Switz.***: Aptivus; ***UK***: Aptivus; ***USA***: Aptivus.

Trichosanthin

Compound Q; GLQ-223 (a purified form of trichosanthin); Tricosantina.

CAS — 60318-52-7 (trichosanthins); 116899-30-0 (Trichosanthes kirilowii); 160185-58-0 (Trichosanthes kirilowii root); 120947-28-6 (GLQ-223).

Profile

Trichosanthin is a polypeptide extracted from the tuber of the Chinese cucumber, *Trichosanthes kirilowii* (Cucurbitaceae). It has been investigated in the treatment of HIV infection and is used in China as an abortifacient.

HIV infection and AIDS. Trichosanthin has been given to patients with AIDS, AIDS-related complex, or HIV infection.[1,2] It has generally been given by intravenous injection, the use of the intramuscular route having been abandoned due to the occurrence of pain and necrosis at the injection site.[1] A common adverse effect with intravenous use was a flu-like syndrome with headache, myalgias, fever, and arthralgia and was generally mild to moderate,[3] although neurological effects progressing to coma with fatalities have been reported.[1,2] Improvements in surrogate markers for HIV infection have been reported including increases in CD4+ T lymphocyte counts in patients with moderate disease[3] and in patients failing to respond to reverse transcriptase inhibitors.[4]

1. Byers VS, *et al.* A phase I/II study of trichosanthin treatment of HIV disease. *AIDS* 1990; **4:** 1189–96.
2. Kahn JO, *et al.* The safety and pharmacokinetics of GLQ223 in subjects with AIDS and AIDS-related complex: a phase I study. *AIDS* 1990; **4:** 1197–1204.
3. Kahn JO, *et al.* Safety, activity, and pharmacokinetics of GLQ223 in patients with AIDS and AIDS-related complex. *Antimicrob Agents Chemother* 1994; **38:** 260–7.
4. Byers VS, *et al.* A phase II study of effect of addition of trichosanthin to zidovudine in patients with HIV disease and failing antiretroviral agents. *AIDS Res Hum Retroviruses* 1994; **10:** 413–20.

Trifluridine *(USAN, rINN)*

F_3T; F_3TDR; NSC-75520; Trifluorothymidine; Trifluorothymidinum; Trifluorotymidiini; Trifluorotymidin; Trifluridiini; Trifluridin; Trifluridina; Trifluridinum; Трифлуридин.

ααα-Trifluorothymidine; 2′-Deoxy-5-trifluoromethyluridine.

$C_{10}H_{11}F_3N_2O_5$=296.2

CAS — 70-00-8.

ATC — S01AD02.

ATC Vet — QS01AD02.

UNII — RMW9V5RW38.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Trifluridine). A white, crystalline powder. Soluble in water. Protect from light.

USP 36: (Trifluridine). A white, odourless powder, appearing under the microscope as rod-like crystals. Store in airtight containers. Protect from light.

Uses and Administration

Trifluridine is a pyrimidine nucleoside structurally related to thymidine. It is used in the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex viruses (p. 955.2). One drop of a 1% ophthalmic solution is instilled into the eye every 2 hours up to a maximum of 9 times daily until complete re-epithelialisation has occurred. Treatment is then reduced to one drop every 4 hours to a minimum of 5 drops daily for a further 7 days. Treatment should not be continued for more than a total of 21 days.

Trifluridine, alone or as a combined formulation with a thymidine phosphorylase inhibitor to reduce its metabolism (TAS-102), has been investigated in the treatment of malignant neoplasms.

Reviews.

1. Heidelberger C, King DH. Trifluorothymidine. *Pharmacol Ther* 1979; **6:** 427–42.
2. Carmine AA, *et al.* Trifluridine: a review of its antiviral activity and therapeutic use in the topical treatment of viral eye infections. *Drugs* 1982; **23:** 329–53.
3. Temmink OH, *et al.* Therapeutic potential of the dual-targeted TAS-102 formulation in the treatment of gastrointestinal malignancies. *Cancer Sci* 2007; **98:** 779–89.
4. Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 15/03/11).

Adverse Effects

Adverse effects occurring after the use of trifluridine in the eyes are similar to those for idoxuridine (p. 985.1) but have been reported to occur less frequently.

References.

1. Udell IJ. Trifluridine-associated conjunctival cicatrization. *Am J Ophthalmol* 1985; **99:** 363–4.

Antiviral Action

Trifluridine acts similarly to idoxuridine to interfere with viral DNA synthesis after phosphorylation. It is reported to be active against herpes simplex viruses, some adenoviruses, vaccinia viruses, and CMV. Like idoxuridine it is incorporated into mammalian DNA.

Pharmacokinetics

Trifluridine is absorbed through the cornea after application to the eye and penetration may be increased in the presence of damage or inflammation. Systemic absorption does not appear to follow ocular administration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Viroptic; ***Fr.***: Virophta; ***Ger.***: Triflumann; ***Gr.***: Thilol; Triherpine; Viromidin; ***Ital.***: Triherpine†; ***Neth.***: TFT Ophtiole†; ***Port.***: Viridin†; ***S.Afr.***: TFT; ***Thai.***: Triherpine†; ***Turk.***: TFT-Thilo; ***USA***: Viroptic.

Pharmacopoeial Preparations

BP 2014: Trifluridine Eye Drops.

Tromantadine Hydrochloride *(rINNM)*

D-41; Hidrocloruro de tromantadina; Tromantadina, hidrocloruro de; Tromantadine, Chlorhydrate de; Tromantadinhydrochlorid; Tromantadini Hydrochloridum; Тромантадина Гидрохлорид.

N-1-Adamantyl-2-(2-dimethylaminoethoxy)acetamide hydrochloride; 2-(2-Dimethylaminoethoxy)-*N*-(tricyclo [3.3.1.1^{3,7}]dec-1-yl)acetamide hydrochloride.

$C_{16}H_{28}N_2O_2$,HCl=316.9

CAS — 53783-83-8 (tromantadine); 41544-24-5 (tromantadine hydrochloride).

ATC — D06BB02; J05AC03.

ATC Vet — QD06BB02; QJ05AC03.

UNII — H09LUS437B.

Profile

Tromantadine hydrochloride is a derivative of amantadine (p. 890.3) used for its antiviral activity. It is applied topically at a concentration of 1% in the treatment of herpes simplex infections of the skin and mucous membranes (p. 955.2).

Contact dermatitis has been reported after the topical use of tromantadine hydrochloride.

Effects on the skin. References to contact dermatitis associated with the use of tromantadine.

1. Fanta D, Mischer P. Contact dermatitis from tromantadine hydrochloride. *Contact Dermatitis* 1976; **2:** 282–4.
2. Lembo G, *et al.* Allergic dermatitis from Viruserol ointment probably due to tromantadine hydrochloride. *Contact Dermatitis* 1984; **10:** 317.
3. Jauregui I, *et al.* Allergic contact dermatitis from tromantadine. *J Investig Allergol Clin Immunol* 1997; **7:** 260–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Viru-Merz Serol; ***Braz.***: Herpex; ***Cz.***: Viru-Merz; ***Ger.***: Viru-Merz Serol; ***Gr.***: Viru-Merz Serol; ***Hong Kong***: Viru-Merz; ***Hung.***: Viru-Merz; ***Indon.***: Viru-Merz; ***Israel***: Viru-Merz; ***Ital.***: Drolanin; ***Malaysia***: Viru-Merz; ***Mex.***: Viru-Serol; ***Philipp.***: Viru-Merz†; ***Pol.***: Viru-Merz; ***Port.***: Viru-Merz; ***Rus.***: Viru-Merz Serol (Виру-Мерц Серол); ***Singapore***: Viru-Merz; ***Spain***: Viru-Serol†; ***Switz.***: Viru-Merz Serol†.

Valaciclovir Hydrochloride

(BANM, rINNM)

256U87 (valaciclovir); Hidrocloruro de valaciclovir; Valaciclovir, Chlorhydrate de; Valaciclovir, hidrocloruro de; Valacicloviri hydrochloridum; Valacyclovir Hydrochloride (USAN); Валацикловира Гидрохлорид.

L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine hydrochloride.

$C_{13}H_{20}N_6O_4$,HCl=360.8

CAS — 124832-26-4 (valaciclovir); 124832-27-5 (valaciclovir hydrochloride).

ATC — J05AB11.

ATC Vet — QJ05AB11.

UNII — G447S0T1VC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Valaciclovir Hydrochloride, Anhydrous). A white or almost white powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in anhydrous alcohol.

USP 36: (Valacyclovir Hydrochloride). A white to off-white powder. Soluble in water; insoluble in dichloromethane. Store in airtight containers at a temperature below 30 degrees.

Uses and Administration

Valaciclovir is a prodrug of the antiviral aciclovir (p. 964.1). It is used in the treatment of herpes zoster (p. 956.2) and herpes simplex infections (p. 955.2) of the skin and mucous membranes, including genital herpes. Treatment should be started as soon as symptoms occur; ideally within 48 to 72 hours. In immunocompromised patients treatment for herpes zoster may be given to patients who present within one week of vesicle formation or at any time before full crusting of lesions. Valaciclovir is also used for the suppression of recurrent herpes simplex infections and can reduce the risk of transmission of genital herpes to susceptible partners when used as suppressive therapy and as part of safer sex practices. It is also used for the prophylaxis of CMV infection after solid organ transplantation.

Valaciclovir is given orally as the hydrochloride; doses are expressed in terms of the base. Valaciclovir hydrochloride 1.11 g is equivalent to about 1 g of valaciclovir.

For **herpes zoster**, the dose is 1 g three times daily for 7 days in immunocompetent patients; in immunocompromised patients treatment should be continued for a further 2 days after crusting of lesions.

For treatment of **herpes simplex infections** in immunocompetent patients, 500 mg is given twice daily for 3 to 5 days for recurrent episodes or for up to 10 days for a first episode; in the USA, the recommended dose for a first episode of genital herpes is 1 g twice daily for 10 days. For treatment of herpes simplex infections in immunocompromised patients the recommended dose is 1 g twice daily for at least 5 days for recurrent episodes or for up to 10 days for initial episodes.

For the *suppression* of herpes simplex infection in immunocompetent patients, a dose of 500 mg daily (as a single dose, or in two divided doses in those with very frequent recurrences), is recommended; in the USA, a dose of 1 g once daily is recommended for suppression of recurrent genital herpes, although for those with a history of 9 or fewer recurrences per year, a dose of 500 mg once daily is also considered sufficient. A dose of 500 mg twice daily may be used in immunocompromised patients. To *reduce transmission* of genital herpes in those with a history of 9 or fewer recurrences per year a dose of 500 mg once daily is taken by the infected partner.

For the treatment of herpes labialis, a total daily dose of 4g given in two divided doses 12 hours apart (but not less than 6 hours apart) is suggested as an alternative regimen for immunocompetent persons.

A dose of 2 g four times daily is recommended for prophylaxis of **CMV infection** in solid organ transplant recipients; prophylaxis should begin as soon as possible post-transplant and is usually continued for 90 days.

For doses used in children or in patients with renal impairment, see below.

References.

1. Ormrod D, *et al.* Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000; **59:** 839–63.
2. Ormrod D, Goa K. Valaciclovir: a review of its use in the management of herpes zoster. *Drugs* 2000; **59:** 1317–40.
3. Tyring SK, *et al.* Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. *J Infect Dis* 2002; **186** (suppl 1): S40–S46.
4. Corey L, *et al.* Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350:** 11–20.
5. Brantley JS, *et al.* Valacyclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006; **4:** 367–76.
6. Fife KH, *et al.* Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81:** 1321–7.
7. Vigil KJ, Chemaly RF. Valacyclovir: approved and off-label uses for the treatment of herpes virus infections in immunocompetent and immunocompromised adults. *Expert Opin Pharmacother* 2010; **11:** 1901–13.

Administration in children. Although not licensed for this use in the UK, in the USA valaciclovir is indicated for the treatment of chickenpox (varicella) in immunocompetent children from 2 up to 18 years of age. An oral dose of 20 mg/kg (to a maximum of 1 g) 3 times daily for 5 days is recommended; treatment should begin within 24 hours of the onset of rash. Valaciclovir is available in the USA as a solid oral dosage form (*Valtrex Caplets; GSK, USA*). Licensed product information includes specifications for extemporaneous preparation of an oral suspension containing 25 or 50 mg/mL to facilitate appropriate dosing in children, by grinding the caplets and suspending in Suspension Structured Vehicle *USNF* with a suitable flavouring agent. The resultant suspension is stored at 2 to 8 degrees and used within 28 days of preparation.

In the UK, valaciclovir is licensed for use in the prophylaxis of CMV infection after renal transplantation in children from 12 years of age; doses are the same as those in adults (above). The *BNFC* considers that valaciclovir may also be given, if necessary, to children 12 years and over for herpes zoster (in immunocompromised children) and treatment and suppression of herpes simplex, in doses equivalent to those in adults.

Administration in renal impairment. Oral doses of valaciclovir may need to be reduced in patients with renal impairment. The following adjusted doses are suggested according to creatinine clearance (CC):

Immunocompetent patients:

Herpes zoster.

- CC 30 to 49 mL/minute: 1 g every 12 hours
- CC 10 to 29 mL/minute: 1 g every 24 hours
- CC less than 10 mL/minute: 500 mg every 24 hours

Acute episodes of herpes simplex infection (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 500 mg every 12 hours
- CC less than 30 mL/minute: 500 mg every 24 hours

US licensed product information recommends:

- CC 10 to 29 mL/minute: 1 g every 24 hours for initial episodes of genital herpes; 500 mg every 24 hours for recurrence
- CC less than 10 mL/minute: 500 mg every 24 hours for both initial and recurrent episodes of genital herpes

Suppression of recurrent herpes simplex (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 500 mg every 24 hours; those with 10 or more relapses a year: 250 mg every 12 hours
- CC less than 30 mL/minute: 250 mg every 24 hours

US licensed product information recommends:

- CC less than 30 mL/minute: 500 mg every 24 hours; those with 9 or fewer relapses a year: 500 mg every 48 hours

Reduction of transmission of genital herpes.

- CC less than 15 mL/minute: 250 mg every 24 hours

Alternative regimen for herpes labialis.

- CC 30 to 49 mL/minute: 1 g every 12 hours for 2 doses
- CC 10 to 29 mL/minute: 500 mg every 12 hours for 2 doses
- CC less than 10 mL/minute: 500 mg as a single dose

Immunocompromised patients:

Herpes zoster

- CC 30 to 49 mL/minute: 1 g every 12 hours
- CC 10 to 29 mL/minute: 1 g every 24 hours
- CC less than 10 mL/minute: 500 mg every 24 hours

Acute episodes of herpes simplex infection (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 1 g every 12 hours
- CC less than 30 mL/minute: 1 g every 24 hours

Suppression of recurrent herpes simplex (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 500 mg every 12 hours
- CC less than 30 mL/minute: 500 mg every 24 hours

US licensed product information recommends:

- CC less than 30 mL/minute: 500 mg every 24 hours

Prophylaxis of CMV.

- CC 50 to 74 mL/minute: 1.5 g every 6 hours
- CC 25 to 49 mL/minute: 1.5 g every 8 hours
- CC 10 to 24 mL/minute: 1.5 g every 12 hours
- CC less than 10 mL/minute: 1.5 g every 24 hours

Patients requiring haemodialysis should receive the lowest recommended dose after the dialysis run. Supplementary doses are not needed after chronic ambulatory peritoneal dialysis or continuous arteriovenous haemofiltration/dialysis.

HIV infection. For information on the use of valaciclovir in the treatment of patients co-infected with herpes simplex virus type 2 and HIV-1 see under Aciclovir, p. 964.3.

Sickle-cell disease. A preliminary study[1] of the use of valaciclovir as an antisickling agent in the management of sickle-cell disease (p. 1123.2).

1. Ender KL, *et al.* Safety of short-term valacyclovir as an anti-sickling agent in sickle-cell anemia. *Pediatr Blood Cancer* 2011; **56:** 843–5.

Adverse Effects and Precautions

As for Aciclovir, p. 965.1.

Breast feeding. In a study in 5 women who took oral valaciclovir 500 mg twice daily for 7 days, concentrations of the active metabolite aciclovir in breast milk were 3.4 times those in maternal serum at 4 hours after the initial dose, although the ratio declined to 1.85 at steady-state concentrations. Nonetheless, it was calculated that the amount ingested by an infant would be negligible (about 2% of a standard neonatal dose of intravenous aciclovir, with exposure further reduced by the poor oral bioavailability of the drug), and valaciclovir was thus considered compatible with breast feeding.[1]

1. Sheffield JS, *et al.* Acyclovir concentrations in human breast milk after valaciclovir administration. *Am J Obstet Gynecol* 2002; **186:** 100–102.

Effects on the nervous system. Mononeuritis multiplex due to vasculitis has been reported[1] in a woman a week after a one-day course of valaciclovir for the treatment of herpes labialis. Symptoms improved within 10 days of treatment with oral prednisolone but reoccurred upon rechallenge with valaciclovir.

1. Pary LF, *et al.* Vasculitic mononeuritis multiplex induced by valacyclovir. *Neurology* 2004; **62:** 1906–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valaciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Pregnancy. For information on the use of valaciclovir in pregnancy see under Precautions of Aciclovir, p. 965.3.

Interactions

As for Aciclovir, p. 966.1.

Antiviral Action

As for Aciclovir, p. 966.1.

Pharmacokinetics

As for Aciclovir, p. 966.2.

Valaciclovir is readily absorbed from the gastrointestinal tract after oral doses, and is rapidly and almost completely converted to aciclovir and valine by first-pass intestinal or hepatic metabolism. After a 1-g oral dose of valaciclovir, bioavailability of aciclovir is about 54% with peak plasma concentrations occurring after 1 to 2 hours. Valaciclovir is eliminated mainly as aciclovir and its metabolite 9-carboxymethoxymethylguanine; less than 1% of a dose of valaciclovir is excreted unchanged in the urine.

References.
1. Steingrimsdottir H, *et al.* Bioavailability of aciclovir after oral administration of aciclovir and its prodrug valaciclovir to patients with leukopenia after chemotherapy. *Antimicrob Agents Chemother* 2000; **44:** 207–9.
2. Höglund M, *et al.* Comparable aciclovir exposures produced by oral valaciclovir and intravenous aciclovir in immunocompromised cancer patients. *J Antimicrob Chemother* 2001; **47:** 855–61.
3. Bras AP, *et al.* Comparative bioavailability of acyclovir from oral valacyclovir and acyclovir in patients treated for recurrent genital herpes simplex virus infection. *Can J Clin Pharmacol* 2001; **8:** 207–11.
4. Nadal D, *et al.* An investigation of the steady-state pharmacokinetics of oral valacyclovir in immunocompromised children. *J Infect Dis* 2002; **186** (suppl 1): S123–S130.
5. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. *J Antimicrob Chemother* 2004; **53:** 899–901.
6. Kimberlin DW, *et al.* Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. *Clin Infect Dis* 2010; **50:** 221–8.
7. Smith JP, *et al.* Pharmacokinetics of acyclovir and its metabolites in cerebrospinal fluid and systemic circulation after administration of high-dose valacyclovir in subjects with normal and impaired renal function. *Antimicrob Agents Chemother* 2010; **54:** 1146–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Valtrex; Viramixal; Viranet; ***Austral.***: Vaclovir; Valacor; Valnir; Valnir; Valtrex; Valvala; Zelitrex; ***Austria***: Valtrex; Viropel; ***Belg.***: Zelitrex; ***Braz.***: Valtrex; ***Canad.***: Valtrex; ***Chile***: Pervioral; Vacper; Vadiral; Valtrex; ***China***: A Mai Xin (阿迈新); Kenong (科侬); Li Ke Fen (丽科分); Lizhuwei (丽珠威); Ming Zhu Xin (明竹欣); Valtrex (维德思); ***Cz.***: Valtrex; ***Denm.***: Zelitrex; ***Fin.***: Valavir; Valtrex; ***Fr.***: Zelitrex; ***Ger.***: Valtrex; ***Gr.***: Valtrex; Vociflon; ***Hong Kong***: Valtrex; ***India***: Valcivir; ***Indon.***: Herclov; Inclovir; Valtrex; Valvir; ***Irl.***: Myval; Valotix; Valtrex; ***Israel***: Valtrex; ***Ital.***: Talavir; Zelitrex; ***Malaysia***: Valtrex; ***Mex.***: Rapivir; Valinir; ***Neth.***: Zelitrex; ***Norw.***: Valtrex; ***NZ***: Valtrex; ***Philipp.***: Valtrex; ***Pol.***: Valtrex; ***Port.***: Crotax; Sades; Ticofarma; Valavir; Valtrex; ***Rus.***: Vacirex (Вацирекс); Valtrex (Валтрекс); ***S.Afr.***: Anviro; Zelitrex; Zelivire; ***Singapore***: Valtrex; ***Spain***: Tridiavir; Valherpes†; Valtrex; Virval†; ***Swed.***: Valtrex; ***Switz.***: Valtrex; ***Thai.***: Valtrex; ***Turk.***: Valtrex; ***UK***: Valtrex; ***Ukr.***: Gerpeval (Герпевал); Valavir (Валавир); Valmax (Вальмакс); Valtrex (Вальтрекс); Valtrovir (Вальтровир); ***USA***: Valtrex; ***Venez.***: Valtrex.

Pharmacopoeial Preparations
USP 36: Valacyclovir Oral Suspension; Valacyclovir Tablets.

Valganciclovir Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de valganciclovir; Ro-107-9070/194; RS-079070-194; Valganciclovir, Chlorhydrate de; Valganciclovir, hidrocloruro de; Valgancicloviri Hydrochloridum; Вальганцикловира Гидрохлорид.

L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy] methyl] guanine hydrochloride .

$C_{14}H_{22}N_6O_5$,HCl=390.8

CAS — 175865-60-8 (valganciclovir); 175865-59-5 (valganciclovir hydrochloride).

ATC — J05AB14.

ATC Vet — QJ05AB14.

UNII — 4P3T9QF9NZ.

Pharmacopoeias. In *US.*

USP 36: (Valganciclovir Hydrochloride). A white to off-white powder. Very slightly soluble in alcohol; practically insoluble in isopropyl alcohol, in acetone, in hexane, and in ethyl acetate. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. References.
1. Anaizi NH, *et al.* Stability of valganciclovir in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; **59:** 1267–70.
2. Henkin CC, *et al.* Stability of valganciclovir in extemporaneously compounded liquid formulations. *Am J Health-Syst Pharm* 2003; **60:** 687–90.

Uses and Administration

Valganciclovir is a prodrug of the antiviral ganciclovir (p. 982.3) that is used for the treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in transplant recipients who have received an organ from a CMV-positive donor (see below).

Valganciclovir is given orally with food as the hydrochloride; doses are expressed in terms of the base. Valganciclovir hydrochloride 1.1 g is equivalent to about 1 g of valganciclovir.

For *induction* in patients with active **CMV retinitis**, the dose is 900 mg twice daily for 21 days. For *maintenance* after induction, or in patients with inactive CMV retinitis, the dose is 900 mg once daily. Patients whose retinitis deteriorates during maintenance may repeat induction but the possibility of viral resistance should be considered. For *prevention* of CMV disease in **organ transplant** recipients, the dose is 900 mg daily starting within 10 days and continuing until 100 days after transplantation. Prophylaxis for kidney transplant patients may be given daily for 200 days after transplantation, but the possible risk of developing leucopenia and neutropenia should be considered.

For valganciclovir doses used in children or patients with renal impairment, see below.

Reviews.
1. Freeman RB. Valganciclovir: oral prevention and treatment of cytomegalovirus in the immunocompromised host. *Expert Opin Pharmacother* 2004; **5:** 2007–16.
2. Cvetković RS, Wellington K. Valganciclovir: a review of its use in the management of CMV infection and disease in immunocompromised patients. *Drugs* 2005; **65:** 859–78.
3. Pescovitz MD. Valganciclovir: recent progress. *Am J Transplant* 2010; **10:** 1359–64.
4. Asberg A, *et al.* Valganciclovir for the prevention and treatment of CMV in solid organ transplant recipients. *Expert Opin Pharmacother* 2010; **11:** 1159–66.

Administration in children. Although not recommended in the UK for patients younger than 18 years, in the USA valganciclovir is licensed for use in the prevention of CMV disease in children aged 4 months to 16 years who have received a heart or kidney transplant. The oral solution is the preferred formulation for children since it allows for more accurate dosing; however, tablets can be used if the dose required is a multiple of 450 mg (the available strength) or within 10% of this. The recommended oral daily dose is calculated with a formula based on body-surface and creatinine clearance (to a maximum of 900 mg) and rounded to the nearest 25-mg increment. Licensed product information (*Valcyte; Roche, USA*)[1] should be consulted for details of the formula. Dosing should begin within 10 days of transplantation, and be continued until 100 days post-transplantation.

1. Roche USA. Valcyte Full Prescribing Information (issued August 2010). Available at: http://www.gene.com/gene/products/information/valcyte/pdf/pi.pdf (accessed 15/10/10)

Administration in renal impairment. Doses of oral valganciclovir should be reduced in renal impairment according to creatinine clearance (CC). Licensed product information recommends the following doses:
- CC 40 to 59 mL/minute: 450 mg twice daily for *induction* and 450 mg once daily for *maintenance* or *prevention*
- CC 25 to 39 mL/minute: 450 mg once daily for *induction* and 450 mg every two days (or 225 mg once daily) for *maintenance* or *prevention*
- CC 10 to 24 mL/minute: 450 mg every two days (or 225 mg once daily) for *induction* and 450 mg twice weekly (or 125 mg once daily) for *maintenance* or *prevention*
- haemodialysis patients: 200 mg 3 times a week for *induction* and 100 mg 3 times a week for *maintenance* or *prevention*; doses should be given after the dialysis session

Cytomegalovirus infections. Valganciclovir produces high systemic concentrations of ganciclovir after oral doses; exposure may be higher than with intravenous ganciclovir regimens.[1] It is therefore active against CMV infections (p. 954.2). It has been shown to be of benefit for both induction therapy and maintenance treatment of CMV retinitis in patients with AIDS,[2-4] and although this has become less widespread in the developed world with the advent of HAART, it continues to be a problem in resource-poor settings in particular; there have been calls for valganciclovir to be made more widely available for treatment in preference to less effective and convenient drugs.[3]

Valganciclovir is also used in the prophylaxis and preemptive treatment of CMV infections in transplant recipients,[5-10] and many centres consider it to be the standard of care for this indication (including in liver transplantation although it is not licensed for such use in the USA—see Adverse Effects, Treatment, and Precautions, below).[11] Late-onset disease (occurring after the drug is stopped) may be a problem with prophylactic regimens (particularly in CMV-negative patients given a CMV-positive graft) and extended prophylactic regimens after kidney[12,13] and lung[14] transplantation have therefore been investigated;[12,14] for kidney transplant patients licensed product information indicates that prophylaxis may be continued until 200 days after transplantation. The problem of late-onset disease is negligible with pre-emptive treatment.[15]

1. Einsele H, *et al.* Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood* 2006; **107:** 3002–8.
2. Martin DF, *et al.* Valganciclovir Study Group. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med* 2002; **346:** 1119–26. Correction. *ibid.*; **347:** 862.
3. Heiden D, *et al.* Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. *PLoS Med* 2007; **4:** e334. Available at: http://medicine.plosjournals.org/archive/1549-1676/4/12/pdf/10.1371_journal.pmed.0040334-S.pdf (accessed 28/08/08)
4. Patil AJ, *et al.* Valganciclovir in the treatment of cytomegalovirus retinitis in HIV-infected patients. *Clin Ophthalmol* 2010; **4:** 111–19.
5. Paya C, *et al.* Valganciclovir Solid Organ Transplant Study Group. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4:** 611–20.
6. Khoury JA, *et al.* Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *Am J Transplant* 2006; **6:** 2134–43.
7. Said T, *et al.* Oral valgancyclovir versus intravenous gancyclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transplant Proc* 2007; **39:** 997–9.
8. Asberg A, *et al.* VICTOR Study Group. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007; **7:** 2106–13.
9. Len O, *et al.* RESITRA. Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; **46:** 20–7.
10. Asberg A, *et al.* Valganciclovir for the prevention and treatment of CMV in solid organ transplant recipients. *Expert Opin Pharmacother* 2010; **11:** 1159–66.
11. Snydman DR. Use of valganciclovir for prevention and treatment of cytomegalovirus disease. *Clin Infect Dis* 2008; **46:** 28–9.
12. Humar A, *et al.* The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant* 2010; **10:** 1228–37.
13. Humar A, *et al.* Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study. *Transplantation* 2010; **90:** 1427–31.
14. Palmer SM, *et al.* Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. *Ann Intern Med* 2010; **152:** 761–9.
15. Sun H-Y, *et al.* Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. *Am J Transplant* 2008; **8:** 2111–18.

Human herpesvirus-8. Human herpesvirus-8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), causes Kaposi sarcoma (p. 718.1), primary effusion lymphoma (see under AIDS-related Lymphomas, p. 697.2), and some types of multicentric Castleman disease (see under Uses and Administration of Rituximab, p. 853.1). A small randomised, double-blind, placebo-controlled, crossover study[1] in 26 (HIV-infected and non-infected) men with HHV-8 infection found that oral valganciclovir 900 mg daily for 8 weeks significantly reduced HHV-8 oropharyngeal mucosal replication; the frequency with which HHV-8 was detected in the saliva was reduced as was the quantity of HHV-8 detected. However, replication resumed after treatment was stopped. Some have suggested that valganciclovir may have a role in chronic maintenance treatment of Castleman disease.[2]

1. Casper C, *et al.* Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis* 2008; **198:** 23–30.
2. Bower M. How I treat HIV-associated multicentric Castleman disease. *Blood* 2010; **116:** 4415–21.

Adverse Effects, Treatment, and Precautions

As for Ganciclovir, p. 983.3.

In the USA, valganciclovir is not indicated for use in liver transplant recipients, because of reports of a higher incidence of tissue-invasive CMV infection compared with patients treated with ganciclovir (although see Cytomegalovirus Infections, above). In the UK, valganciclovir is licensed for use in the prevention of CMV disease in all solid organ graft recipients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valganciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Interactions

As for Ganciclovir, p. 984.1.

Antiviral Action

As for Ganciclovir, p. 984.2.

Pharmacokinetics

Valganciclovir is well absorbed from the gastrointestinal tract after oral doses and is rapidly converted to ganciclovir

by first-pass intestinal or hepatic metabolism. The bioavailability of ganciclovir after an oral dose with food is reported to be about 60% and peak plasma concentrations of ganciclovir occur after 1 to 3 hours. Valganciclovir is eliminated in the urine as ganciclovir (see p. 984.2).

References.
1. Brown F, *et al*. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. *Clin Pharmacokinet* 1999; **37:** 167–76.
2. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. *J Clin Pharmacol* 1999; **39:** 800–4.
3. Pescovitz MD, *et al*. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. *Antimicrob Agents Chemother* 2000; **44:** 2811–15.
4. Wiltshire H, *et al*. Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; **44:** 495–507.
5. Winston DJ, *et al*. Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. *Biol Blood Marrow Transplant* 2006; **12:** 635–40.
6. Zhao W, *et al*. Population pharmacokinetics of ganciclovir following administration of valganciclovir in paediatric renal transplant patients. *Clin Pharmacokinet* 2009; **48:** 321–8.
7. Caldés A, *et al*. Population pharmacokinetics of ganciclovir after intravenous ganciclovir and oral valganciclovir administration in solid organ transplant patients infected with cytomegalovirus. *Antimicrob Agents Chemother* 2009; **53:** 4816–24.
8. Perrottet N, *et al*. Valganciclovir in adult solid organ transplant recipients: pharmacokinetic and pharmacodynamic characteristics and clinical interpretation of plasma concentration measurements. *Clin Pharmacokinet* 2009; **48:** 399–418.
9. Pescovitz MD, *et al*. Pharmacokinetics of oral valganciclovir solution and intravenous ganciclovir in pediatric renal and liver transplant recipients. *Transpl Infect Dis* 2010; **12:** 195–203.
10. Welker H, *et al*. Ganciclovir pharmacokinetic parameters do not change when extending valganciclovir cytomegalovirus prophylaxis from 100 to 200 days. *Transplantation* 2010; **90:** 1414–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Valixa; ***Austral.***: Valcyte; ***Austria***: Valcyte; ***Belg.***: Valcyte; ***Braz.***: Valcyte; ***Canad.***: Valcyte; ***Chile***: Valixa; ***China***: Valcyte (万赛维); ***Cz.***: Valcyte; ***Denm.***: Valcyte; ***Fin.***: Valcyte; ***Fr.***: Rovalcyte; ***Ger.***: Valcyte; ***Gr.***: Valcyte; ***Hong Kong***: Valcyte; ***Hung.***: Valcyte; ***Indon.***: Valcyte; ***Irl.***: Valcyte; ***Israel***: Valcyte; ***Ital.***: Darilin; Valcyte; ***Malaysia***: Valcyte; ***Mex.***: Valcyte; ***Neth.***: Valcyte; Valixa; ***Norw.***: Valcyte; ***NZ***: Valcyte; ***Philipp.***: Valcyte; ***Pol.***: Valcyte; ***Port.***: Rovalcyte; ***Rus.***: Valcyte (Вальцит); ***S.Afr.***: Valcyte; ***Singapore***: Valcyte; ***Spain***: Valcyte; ***Swed.***: Valcyte; ***Switz.***: Valcyte; ***Thai.***: Valcyte; ***Turk.***: Valcyte; ***UK***: Valcyte; ***Ukr.***: Valcyte (Вальцит); ***USA***: Valcyte; ***Venez.***: Valixa.

Pharmacopoeial Preparations
USP 36: Valganciclovir Tablets.

Vidarabine *(BAN, USAN, rINN)*

Adenine Arabinoside; Ara-A; CI-673; Vidarabiini; Vidarabin; Vidarabina; Vidarabinum; Видарабин.

9-β-D-Arabinofuranosyladenine monohydrate.

$C_{10}H_{13}N_5O_4,H_2O$=285.3

CAS — 5536-17-4 (anhydrous vidarabine); 24356-66-9 (vidarabine monohydrate).

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

UNII — FA2DM6879K (vidarabine); 3XQD2MEW34 (anhydrous vidarabine).

Pharmacopoeias. In *US*.

USP 36: (Vidarabine). A white to off-white powder. Very slightly soluble in water; slightly soluble in dimethylformamide. Store in airtight containers.

Vidarabine Phosphate *(BANM, USAN, rINNM)*

Ara-AMP; Arabinosyladenine Monophosphate; CI-808; Fosfato de vidarabina; Vidarabina, fosfato de; Vidarabine 5′-Monophosphate; Vidarabine, Phosphate de; Vidarabini Phosphas; Видарабина Фосфат.

9-β-D-Arabinofuranosyladenine 5′-(dihydrogen phosphate).

$C_{10}H_{14}N_5O_7P$=347.2

CAS — 29984-33-6.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

UNII — 106XV160TZ.

Vidarabine Sodium Phosphate

(BANM, USAN, rINNM)

CI-808 Sodium; Fosfato sódico de vidarabina; Natrii Vidarabini Phosphas; Vidarabina, fosfato sódico de; Vidarabine, Phosphate Sodique de; Натрия Видарабина Фосфат.

9-β-D-Arabinofuranosyladenine 5′-(dihydrogen phosphate) disodium.

$C_{10}H_{12}N_5Na_2O_7P$=391.2

CAS — 71002-10-3.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

UNII — ZEC0WCC7UA.

Uses and Administration

Vidarabine is a purine nucleoside obtained from *Streptomyces antibioticus*. It has been used in the treatment of herpes simplex and varicella-zoster infections (p. 955.2 and p. 956.2), although aciclovir and related drugs are generally preferred.

Vidarabine has been used topically in the treatment of herpes simplex keratitis and keratoconjunctivitis as a 3% ophthalmic ointment.

It has also been used as the sodium phosphate as a 10% gel for the treatment of genital herpes.

Vidarabine was formerly used intravenously in the treatment of severe and disseminated herpes simplex infections and herpes zoster but aciclovir is preferred.

Adverse Effects

Adverse effects that may occur when vidarabine is applied to the eyes include irritation, pain, superficial punctate keratitis, photophobia, lachrymation, and occlusion of the lachrymal duct.

Pharmacokinetics

Systemic absorption does not occur after application of vidarabine to the eye; trace amounts of its principal metabolite hypoxanthine arabinoside (arabinosyl hypoxanthine), and vidarabine, if the cornea is damaged, may be found in the aqueous humour.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Hansikang (汉司康); ***Gr.***: Erpimycin; Tekarin; Virerpin; ***Jpn***: Arasena-A.

Pharmacopoeial Preparations
USP 36: Vidarabine Ophthalmic Ointment.

Zalcitabine *(BAN, USAN, rINN)*

ddC; ddCyd; Dideoxycytidine; NSC-606170; Ro-24-2027; Ro-24-2027/000; Tsalsitabiini; Zalcitabin; Zalcitabina; Zalcitabinum; Zalsitabin; Зальцитабин.

2′,3′-Dideoxycytidine.

$C_9H_{13}N_3O_3$=211.2

CAS — 7481-89-2.

ATC — J05AF03.

ATC Vet — QJ05AF03.

UNII — 6L3XT8CB3I.

NOTE. The code DDC has also been used as a synonym for Ditiocarb, p. 1550.2.

Pharmacopoeias. In *US*.

USP 36: (Zalcitabine). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol, in acetonitrile, in chloroform, and in dichloromethane; slightly soluble in cyclohexane. Store in airtight containers. Protect from light.

Uses and Administration

Zalcitabine is a nucleoside reverse transcriptase inhibitor derived from cytidine with antiviral activity against HIV. It has been used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when zalcitabine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

Zalcitabine is given orally in a dose of 750 micrograms every 8 hours. Doses should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Doses of zalcitabine should be reduced for patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 40 mL/minute: 750 micrograms every 12 hours
- CC less than 10 mL/minute: 750 micrograms every 24 hours

Adverse Effects

The most serious adverse effects of zalcitabine are peripheral neuropathy, which can affect up to one-third of patients, and pancreatitis which is rare, affecting up to about 1% of patients, but which can be fatal. Other severe adverse effects include oral and oesophageal ulceration, hypersensitivity reactions including anaphylaxis, cardiomyopathy and heart failure, lactic acidosis and severe hepatomegaly with steatosis (both potentially life-threatening), and hepatic failure.

Precautions

Zalcitabine should be interrupted or stopped if peripheral neuropathy develops. Neuropathy is usually slowly reversible if treatment is stopped promptly but may be irreversible if treatment is continued after symptoms develop. Zalcitabine should be avoided in patients who already have peripheral neuropathy and used with caution in patients at risk of developing it (especially those with a low CD4+ cell count) or taking other drugs that may cause it (see Interactions, below).

Treatment should be interrupted in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded. Zalcitabine should be permanently withdrawn if pancreatitis develops. Patients with a history of pancreatitis or of raised serum amylase should be monitored closely. Zalcitabine should not be used with other drugs known to cause pancreatitis (see Interactions, below).

Zalcitabine should be used with caution in patients with hepatic impairment and treatment interrupted or stopped if hepatic function deteriorates or there are signs of hepatic damage or lactic acidosis. It should be used with caution in patients with renal impairment, and dosage reductions may be necessary. It should also be used with caution in patients with cardiomyopathy or heart failure.

Complete blood count and biochemical tests should be carried out before treatment starts and at regular intervals throughout therapy.

Handling. Exposure of the skin to zalcitabine and inhalation of zalcitabine powder should be avoided.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zalcitabine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Zalcitabine should not be used with other drugs known to cause pancreatitis (for example intravenous pentamidine). Caution is necessary when zalcitabine is given with other drugs that may cause peripheral neuropathy, such as other nucleoside reverse transcriptase inhibitors, chloramphenicol, dapsone, ethionamide, isoniazid (the clearance of which may also be affected—see p. 313.2), metronidazole, nitrofurantoin, ribavirin, and vincristine. Use of zalcitabine with didanosine is not recommended.

The absorption of zalcitabine is reduced by about 25% when given with aluminium- or magnesium-containing antacids.

Cimetidine, probenecid, or trimethoprim can reduce the renal excretion of zalcitabine, resulting in elevated plasma concentrations. Renal excretion of zalcitabine may also be reduced by amphotericin B, aminoglycosides, or foscarnet, potentially increasing its toxicity.

The antiviral action of zalcitabine may be antagonised by lamivudine and the two drugs should not be used together.

Antiviral Action

Zalcitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

The emergence of zalcitabine-resistant strains of HIV has been reported.

References.
1. Jeffries DJ. The antiviral activity of dideoxycytidine. *J Antimicrob Chemother* 1989; **23** (suppl A): 29–34.

Pharmacokinetics

Zalcitabine is absorbed from the gastrointestinal tract with a bioavailability of greater than 80%. The rate of absorption is reduced if given with food. Peak plasma concentrations in the fasting state occur within about 1 hour. Zalcitabine crosses the blood-brain barrier producing CSF concentrations ranging from 9 to 37% of those in plasma. Binding to plasma proteins is negligible. The plasma elimination half-life is about 2 hours.

Zalcitabine is metabolised intracellularly to the active antiviral triphosphate. It does not appear to undergo any substantial hepatic metabolism and is excreted mainly in the urine, in part by active tubular secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hivid†; ***Gr.***: Hivid; ***Jpn***: Hivid†; ***Mex.***: Arlevid; Hivid; ***Rus.***: Hivid (Хивид); ***Singapore***: Hivid; ***Thai.***: Hivid†; ***Turk.***: Hivid; ***Venez.***: Hivid.

Pharmacopoeial Preparations
USP 36: Zalcitabine Tablets.

Zanamivir *(BAN, USAN, rINN)*

GG-167; GR-121167X; 4-Guanidino-2,4-dideoxy-2,3-dehydro-*N*-acetylneuraminic Acid; Tsanamiviiri; Zanamivirum; Занамивир.

5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-*glycero*-D-*galacto*-non-2-enonic acid.

$C_{12}H_{20}N_4O_7$=332.3

CAS — 139110-80-8.

ATC — J05AH01.

ATC Vet — QJ05AH01.

UNII — L6O3XI777I.

Uses and Administration

Zanamivir is a neuraminidase inhibitor used by inhalation for the treatment and prophylaxis (postexposure and seasonal) of influenza A and B (p. 960.2). For *treatment*, it is given in a dose of 10 mg twice daily for 5 days, starting as soon as possible (within 48 hours) after the onset of symptoms.

Zanamivir is given by inhalation for *postexposure prophylaxis* of influenza A and B in household or close contacts and should be started within 36 hours of exposure. The dose is 10 mg once daily for 10 days. For *seasonal prophylaxis* in a community setting 10 mg once daily may be given for up to 28 days and treatment should start within 5 days of an outbreak.

For details of doses in children, see below.

Administration. Although normally given by inhalation, zanamivir has occasionally been given intravenously[1-3] in doses of 600 mg twice daily to seriously ill patients.

1. Kidd IM, *et al.* H1N1 pneumonitis treated with intravenous zanamivir. *Lancet* 2009; **374:** 1036.
2. Gaur AH, *et al.* Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. *N Engl J Med* 2010; **362:** 88–9.
3. Härter G, *et al.* Intravenous zanamivir for patients with pneumonitis due to pandemic (H1N1) 2009 influenza virus. *Clin Infect Dis* 2010; **50:** 1249–51.

Administration in children. Zanamivir is given by inhalation for the treatment and postexposure prophylaxis of influenza A and B. For *treatment*, children may be given the same dose as adults (10 mg twice daily for 5 days), starting within 36 to 48 hours after the onset of symptoms. In the USA it is approved for those from 7 years of age whereas UK licensed product information permits use from 5 years of age.

Postexposure prophylaxis after close contact with infected patients should be started within 36 hours of exposure. Children from 5 years of age may be given the same dose as adults (10 mg once daily for 10 days). Zanamivir is also used for seasonal prophylaxis in a community setting, and the *BNFC* suggests that during an epidemic this dose may be given for up to 28 days.

Influenza. Reviews.[1-3] For further information on neuraminidase inhibitors (including zanamivir), see Influenza, under Oseltamivir, p. 1007.1.

1. Cheer SM, Wagstaff AJ. Zanamivir: an update of its use in influenza. *Drugs* 2002; **62:** 71–106.
2. Fleming DM. Zanamivir in the treatment of influenza. *Expert Opin Pharmacother* 2003; **4:** 799–805.
3. Tappenden P, *et al.* Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation. *Health Technol Assess* 2009; **13:** 1–246.

Adverse Effects

Inhaled zanamivir has generally been well tolerated. Acute bronchospasm or decline in respiratory function, with some fatalities, has been reported rarely in patients with a history of respiratory disease and very rarely in those with no such history. Other effects that have been noted include nasal symptoms, headache, gastrointestinal symptoms, cough, and bronchitis, but they may be difficult to distinguish from the symptoms of influenza. There have also been rare reports of hypersensitivity reactions, including oropharyngeal oedema and severe skin rashes.

There have been postmarketing reports (mostly from Japan) of neuropsychiatric adverse effects, such as delirium and abnormal behaviour, in patients taking neuraminidase inhibitors such as zanamivir.

Reviews.

1. Freund B, *et al.* Zanamivir: a review of clinical safety. *Drug Safety* 1999; **21:** 267–81.
2. Gravenstein S, *et al.* Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Safety* 2001; **24:** 1113–25.

Precautions

Zanamivir should be used with caution in patients with chronic respiratory diseases as they may be at increased risk of bronchospasm; if zanamivir use is considered appropriate, patients with asthma or chronic obstructive pulmonary disease should have a fast-acting bronchodilator available during treatment. Patients on maintenance therapy with inhaled bronchodilators should inhale the bronchodilator before zanamivir. Patients experiencing bronchospasm should be advised to stop zanamivir and seek medical attention.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Zanamivir inhalation powder should only be given via the diskhaler device provided by the manufacturer; it should not be given in a nebuliser or mechanical ventilator. Death has occurred when the inhalation powder was dissolved in a solution and given by mechanical ventilation.

Pregnancy. For information on the use of neuramidase inhibitors such as Zanamivir in pregnancy, see Oseltamivir, p. 1007.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zanamivir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Antiviral Action

Zanamivir inhibits the viral surface enzyme neuraminidase (sialidase) which is essential for the release of newly formed viral particles from infected cells, and may facilitate access of virus through mucus to the cell surface. Zanamivir is active against influenza A and B virus replication.

Resistance. For information on the development of resistance to zanamivir and other neuraminidase inhibitors, see under Oseltamivir, p. 1008.1.

Pharmacokinetics

Zanamivir is poorly absorbed after oral doses with a bioavailability of about 2%. Inhaled doses produce high local concentrations in the respiratory tract. About 4 to 20% of the inhaled dose is absorbed producing peak serum concentrations at about 1 to 2 hours. Zanamivir is less than 10% bound to plasma protein. It is not metabolized and the absorbed portion is excreted unchanged in the urine with a serum half-life of 2.6 to 5 hours; unabsorbed drug is excreted in the faeces.

References.

1. Aoki FY, Hayden FG (eds. The pharmacokinetics of zanamivir: a new inhaled antiviral for influenza. *Clin Pharmacokinet* 1999; **36** (suppl 1): 1–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Relenza; ***Austral.***: Relenza; ***Austria***: Relenza; ***Belg.***: Relenza; ***Braz.***: Relenza; ***Canad.***: Relenza; ***China***: Relenza (依乐韦); ***Cz.***: Relenza; ***Denm.***: Relenza; ***Fin.***: Relenza; ***Fr.***: Relenza; ***Ger.***: Relenza; ***Gr.***: Relenza; ***Hong Kong***: Relenza; ***Hung.***: Relenza; ***Irl.***: Relenza; ***Israel***: Relenza; ***Ital.***: Relenza; ***Malaysia***: Relenza; ***Mex.***: Relenza; ***Neth.***: Relenza; ***Norw.***: Relenza; ***NZ***: Relenza; ***Philipp.***: Relenza; ***Pol.***: Relenza; ***Port.***: Relenza; ***Rus.***: Relenza (Реленза); ***S. Afr.***: Relenza; ***Singapore***: Relenza; ***Spain***: Relenza; ***Swed.***: Relenza; ***Switz.***: Relenza; ***Thai.***: Relenza; ***Turk.***: Relenza; ***UK***: Relenza; ***Ukr.***: Relenza (Реленца); ***USA***: Relenza.

Zidovudine *(BAN, USAN, rINN)*

Atsidotymidiini; Azidodeoxythymidine; Azidothymidine; Azidotimidina; AZT; Azydotymidyna; BW-509U; BW-A509U; Compound-S; Tsidovudiini; Zidovudin; Zidovudina; Zidovudinas; Zidovudinum; Zydowudyna; Зидовудин.

3′-Azido-3′-deoxythymidine.

$C_{10}H_{13}N_5O_4$=267.2

CAS — 30516-87-1.

ATC — J05AF01.

ATC Vet — QJ05AF01.

UNII — 4B9XT59T7S.

NOTE. The abbreviation AZT has also been used for azathioprine.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Zidovudine). A white or brownish powder. It shows polymorphism. Sparingly soluble in water; soluble in dehydrated alcohol. Protect from light.

USP 36: (Zidovudine). A white to yellowish powder. Exhibits polymorphism. Sparingly soluble in water; soluble in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Zidovudine is a nucleoside reverse transcriptase inhibitor structurally related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when zidovudine is used alone, and it is therefore usually used with other antiretrovirals. It may be used alone to prevent vertical transmission from mother to infant if combination antiretroviral therapy is not available.

Zidovudine is given orally in combination with other antiretrovirals for **treatment** in doses of 250 or 300 mg twice daily. Zidovudine may be given by intravenous infusion of a solution containing 2 or 4 mg/mL over 1 hour for short-term management of patients unable to take it orally. The dose is 1 or 2 mg/kg every 4 hours (equivalent to an oral dose of 1.5 or 3 mg/kg every 4 hours).

For the **prevention** of maternal-fetal HIV transmission (p. 959.1), zidovudine may be given orally to *mothers* after the fourteenth week of pregnancy until the beginning of labour in a dose of 100 mg five times daily. During labour and delivery, zidovudine is given by intravenous infusion in a dose of 2 mg/kg over 1 hour, then 1 mg/kg per hour by continuous infusion until the umbilical cord is clamped. When a caesarean section is planned the intravenous infusion is started 4 hours before the operation.

For details of doses in *infants and children*, including the prevention of maternal-fetal HIV transmission, see below.

Blood tests should be carried out regularly as described under Precautions, p. 1026.1. If the white cell count or haemoglobin level fall significantly, the dose should be reduced or, alternatively, treatment interrupted briefly, until there is evidence of recovery. Treatment should be stopped if toxicity is severe and cautiously reintroduced once the bone marrow has recovered. Dosage adjustments may also be necessary in patients with renal (see below) or hepatic impairment.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing zidovudine in combination with lamivudine or with abacavir plus lamivudine are available in some countries.

Administration in children. For the **treatment of HIV infection** in infants and children zidovudine is given orally or intravenously with other antiretroviral drugs. UK licensed product information recommends the following *oral* doses based on body-weight; doses should not exceed the maximum adult dose:

For the oral solution:

- 4 kg up to 9 kg: 12 mg/kg twice daily
- 9 to 30 kg: 9 mg/kg twice daily
- 30 kg or more: 250 or 300 mg twice daily

For the oral capsule:

- 8 to 14 kg: 100 mg twice daily
- 14 to 21 kg: 100 mg in the morning, and 200 mg in the evening
- 22 to 30 kg: 200 mg twice daily
- 30 kg or more: 250 or 300 mg twice daily

In the USA, oral zidovudine is licensed for use in children from 4 weeks of age. Based on body-weight, the same daily mg/kg doses listed above are recommended, given in 2 or 3 divided doses. Alternatively, dosing may be based on body-surface area; a daily dose of 480 mg/m^2 (in 2 or 3 divided doses) is recommended.

Zidovudine may also be given by *intravenous infusion* in a dose of 80 to 160 mg/m^2 every 6 hours. An intravenous dose of 120 mg/m^2 every 6 hours is equivalent to an oral dose of about 180 mg/m^2 every 6 hours

For the **prevention of maternal-fetal HIV transmission** the newborn infant is given zidovudine 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing for 6 weeks. Neonates unable to receive oral doses are given 1.5 mg/kg by intravenous infusion over 30 minutes every 6 hours. (For doses to be given to the mother for the prevention of maternal-fetal transmission see above.)

Administration in renal impairment. Oral doses of zidovudine should be reduced in patients with severe renal impairment (creatinine clearance less than 10 to 15 mL/minute) and in those on haemodialysis or peritoneal dialysis. Licensed product information gives the following guidance:

- *oral* administration: 100 mg every 6 to 8 hours
- *intravenous* administration: 1 mg/kg every 6 to 8 hours

Adverse Effects

The commonest serious adverse effects reported with zidovudine are haematological toxicities such as anaemia, leucopenia, and neutropenia. They occur most often when higher doses are used (1.2 to 1.5 g daily) and in patients with advanced HIV disease and a low CD4+ cell count (less than

100 cells/mm^3). These haematological toxicities are usually reversed by interrupting treatment or reducing dosage but the anaemia may be severe enough to require blood transfusion. Aplastic anaemia, pure red cell aplasia, pancytopenia, and thrombocytopenia have been rarely reported.

Other commonly reported adverse effects include dizziness, headache, malaise, myalgia, and gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea, and vomiting. Long-term use of zidovudine has been associated with symptomatic myopathy. Raised liver enzymes, hyperbilirubinaemia, lactic acidosis, and severe hepatomegaly with steatosis have been reported as rare, but potentially fatal, occurrences in patients taking zidovudine alone or with other antiretrovirals. Other rare but potentially serious adverse effects include cardiomyopathy, convulsions, and pancreatitis.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including zidovudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including zidovudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the blood. Bone marrow suppression (in particular anaemia) was the major dose-limiting adverse effect seen in early clinical studies of zidovudine, where the drug was used in total daily doses of 1 to 1.5 g. In these studies, up to 50% of patients developed anaemia or leucopenia[1] sometimes requiring multiple blood transfusions for management.[2] It should be noted, however, that the doses used in modern HAART regimens are typically much lower, and haematological adverse effects consequently occur at a much lower frequency than in these early reports.. Those with more advanced HIV disease, lower CD4+ counts, decreased serum-vitamin B_{12} or -folinic acid concentrations, or baseline anaemia or neutropenia may be at greater risk.[1]

Recombinant erythropoietin has been used in an attempt to reduce the need for blood transfusion in zidovudine-induced anaemia, and measurement of baseline serum-erythropoietin concentrations may help determine which patients will benefit; pooled data from 4 studies[3] suggested that recombinant erythropoietin was effective in reducing the mean transfusion requirement only in patients with endogenous serum-erythropoietin concentrations of 500 units/litre or less. Similarly, use of granulocyte colony-stimulating factor may be of benefit in reducing zidovudine-induced neutropenia (for further information, see under Uses and Administration of Pegfilgrastim, p. 1152.3).

1. McLeod GX, Hammer SM. Zidovudine: five years later. *Ann Intern Med* 1992; **117:** 487–501.
2. Richman DD, *et al*. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. *N Engl J Med* 1987; **317:** 192–7.
3. Henry DH, *et al*. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. *Ann Intern Med* 1992; **117:** 739–48.

Effects on the CNS. Reports of adverse effects on the CNS associated with zidovudine include mania,[1,2] seizures[3,4] (following an overdose in one patient[5]), psychogenic panic,[6] and Wernicke's encephalopathy,[7] mostly involving one or two patients in each case. CNS toxicity, thought to be zidovudine-related, contributed to the death of an AIDS patient.[8]

For reports of neurological symptoms associated with mitochondrial dysfunction in infants whose mothers received perinatal zidovudine, see Effects on Mitochondria, below.

1. Maxwell S, *et al*. Manic syndrome associated with zidovudine treatment. *JAMA* 1988; **259:** 3406–7.
2. Wright JM, *et al*. Zidovudine-related mania. *Med J Aust* 1989; **150:** 339–40.
3. Harris PJ, Caceres CA. Azidothymidine in the treatment of AIDS. *N Engl J Med* 1988; **318:** 250.
4. D'Silva M, *et al*. Seizure associated with zidovudine. *Lancet* 1995; **346:** 452.
5. Routy JP, *et al*. Seizure after zidovudine overdose. *Lancet* 1989; **i:** 384–5.
6. Levitt AJ, Lippert GP. Psychogenic panic after zidovudine therapy—the therapeutic benefit of an N of 1 trial. *Can Med Assoc J* 1990; **142:** 341–2.
7. Davtyan DG, Vinters HV. Wernicke's encephalopathy in AIDS patient treated with zidovudine. *Lancet* 1987; **i:** 919–20.
8. Hagler DN, Frame PT. Azidothymidine neurotoxicity. *Lancet* 1986; **ii:** 1392–3.

Effects on the heart. An observational study[1] evaluated whether NRTIs increase the risk of myocardial infarction in HIV-infected individuals. Of 33 347 patients enrolled in the D:A:D study, myocardial infarction was reported in 517. Recent use of abacavir or didanosine (but not cumulative use) was associated with an increased rate of myocardial infarction (relative risk 1.90 and 1.49 respectively) compared with those with no recent use of the drugs. The excess risk could not be explained by underlying established cardiovascular risk factors and was not present beyond 6 months after stopping the drug. No associations were found between the rate of myocardial infarction and use of zidovudine, stavudine, or lamivudine.

Subsequent studies exploring the reproducibility of these findings have shown conflicting results. In an analysis of data from 2752 patients enrolled in the SMART study,[2] current use of abacavir was associated with increased risk of cardiovascular disease compared with other NRTIs, including a significantly increased risk of myocardial infarction (hazard ratio of 4.3); didanosine, however, was not found to be associated with increased cardiovascular risk. In contrast, a pooled, post-hoc analysis[3] of 52 manufacturer-sponsored studies (14 174 patients) found no excess risk of myocardial infarction with antiretroviral regimens containing abacavir compared with regimens not containing the drug.

Based on available data, and the lack of an established, biological mechanism explaining the reported risk, the EMEA have concluded that a causal relationship between treatment with abacavir and the risk of myocardial infarction can neither be confirmed nor refuted.[4] However, a subsequent meta-analysis conducted by the FDA did not show any increased risk of myocardial infarction with the use of abacavir.[5]

1. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; **371:** 1417–26. Correction. *ibid*.; **372:** 292.
2. SMART/INSIGHT and DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008; **22:** F17–F24.
3. Brothers CH, *et al*. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr* 2009; **51:** 20–8.
4. MHRA/CHM. Abacavir: risk of myocardial infarction—update from epidemiological studies. *Drug Safety Update* 2009; **2** (12): 4–5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON051771&RevisionSelectionMethod=LatestReleased (accessed 24/11/09)
5. FDA. FDA drug safety communication: safety review update of abacavir and possible increased risk of heart attack (issued 1 March 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245164.htm (accessed 23/03/11)

Effects on the liver. Severe hepatomegaly with steatosis and lactic acidosis has been reported with most NRTIs, but is most commonly seen with didanosine, stavudine, and zidovudine;[1] for further information, see Effects on the Metabolism, below. Zidovudine has also been associated with rare cases of severe, acute hepatitis;[2-4] reversible increases in liver enzymes and rashes were also reported in 2 patients receiving prophylaxis with zidovudine and zalcitabine after exposure to HIV.[5]

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 10 January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 29/03/11)
2. Dubin G, Braffman MN. Zidovudine-induced hepatotoxicity. *Ann Intern Med* 1989; **110:** 85–6.
3. Shintaku M, *et al*. Fulminant hepatic failure in an AIDS patient: possible zidovudine-induced hepatotoxicity. *Am J Gastroenterol* 1993; **88:** 464–6.
4. Pai VB, *et al*. Acute hepatitis and bleeding possibly induced by zidovudine and ritonavir in an infant with HIV infection. *Pharmacotherapy* 2000; **20:** 1135–40.
5. Henry K, *et al*. Hepatotoxicity and rash associated with zidovudine and zalcitabine chemoprophylaxis. *Ann Intern Med* 1996; **124:** 855.

Effects on the metabolism. NRTIs, including zidovudine, are known to interfere with lactate production and clearance in the body, leading to a spectrum of possible hyperlactataemia syndromes ranging from asymptomatic, non-acidotic hyperlactataemia, to potentially fatal lactic acidosis with associated hepatic steatosis. The time to onset of toxicity is generally prolonged; in published studies, the median duration of NRTI exposure before diagnosis of lactic acidosis was 9 months (range 3 to 20 months).[1] Effects on lactate metabolism are thought to occur as a consequence of mitochondrial toxicity (see below).[1,2]

In cohort studies, the incidence of lactic acidosis has been reported to range from 1.3 to 3.9 cases per 1000 person-years on antiretroviral therapy,[1] although the incidence may be higher among women and obese patients;[1,3,4] mortality rates of up to 50% have been reported in some case series, particularly where serum-lactate concentrations exceed 10 mmol/litre.[4] In HIV-infected patients, didanosine and stavudine exposure are thought to produce the highest risk of hyperlactataemia, whereas lamivudine,[1] zidovudine,[5] abacavir,[1,6] and tenofovir[1,6] are considered to be safer. There is some evidence that switching to a zidovudine-based antiretroviral regimen may be a safe option for patients who have recovered from stavudine-induced lactic acidosis;[3] relapse is possible, however,[6] and close monitoring is advised.[5]

1. Ogedegbe A-EO, *et al*. Hyperlactataemia syndromes associated with HIV therapy. *Lancet Infect Dis* 2003; **3:** 329–37.
2. Arenas-Pinto A, *et al*. Lactic acidosis in HIV infected patients: a systematic review of published cases. *Sex Transm Infect* 2003; **79:** 340–3.
3. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis* 2007; **45:** 254–60.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 10 January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 29/03/11)
5. Boubaker K, *et al*. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis* 2001; **33:** 1931–7.
6. Castelnuovo B, *et al*. Is it safe to switch from stavudine to zidovudine after developing symptomatic hyperlactatemia? *Afr Health Sci* 2008; **8:** 133–4.

Effects on mitochondria. Concern has been expressed[1] over the effects of NRTIs on mitochondria after reports in France[2] of mitochondrial dysfunction in 8 infants whose mothers had received zidovudine alone, or with lamivudine, to prevent vertical transmission of HIV infection during pregnancy. The effects manifested themselves as severe demyelinating neurological disorder in 2 of the 8, both of whom died after about one year of life. Three other infants had seizures, 1 with severe cardiomyopathy and 1 with spastic diplegia, while the remaining 3 were asymptomatic. None were infected with HIV. A study[3] involving echocardiograms performed from birth to 5 years of age in 382 infants without HIV infection (36 with zidovudine exposure) and 58 infants with HIV infection (12 with zidovudine exposure), all of whom were born to HIV-infected women, found, however, that there was no evidence of abnormality in left ventricular structure or function associated with perinatal zidovudine. While it was considered that further assessment of this toxicity was required, it was emphasised that recommendations for zidovudine use during pregnancy should be maintained.[1,2]

The effects of NRTIs on mitochondria have since been extensively reviewed,[4-14] and many of their established adverse effects such as myopathy, neuropathy, hepatotoxicity, lipodystrophy, and the lactic acidosis-hepatic steatosis syndrome have been hypothesised to result from their ability to inhibit mitochondrial DNA polymerase γ, although other mechanisms may also be involved. Zalcitabine, didanosine, and stavudine are thought to have the highest potential for mitochondrial toxicity and lamivudine and abacavir the least.[4]

1. CSM. Antiretroviral drugs in pregnancy and mitochondrial cytopathy in infants. *Current Problems* 1999; **25:** 15. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 22/05/06)
2. Blanche S, *et al*. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999; **354:** 1084–9.
3. Lipshultz SE, *et al*. Absence of cardiac toxicity of zidovudine in infants. *N Engl J Med* 2000; **343:** 759–66.
4. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* 2000; **22:** 685–708.
5. Loubeyre-Unique C, *et al*. Antirétroviraux et grossesse: cytopathie mitochondriale et analogues nucléosidiques. *Therapie* 2001; **56:** 261–6.
6. White AJ. Mitochondrial toxicity and HIV therapy. *Sex Transm Infect* 2001; **77:** 158–73.
7. Walker UA, Brinkman K. NRTI induced mitochondrial toxicity as a mechanism for HAART related lipodystrophy: fact or fiction? *HIV Med* 2001; **2:** 163–5.
8. Lewis W. Mitochondrial dysfunction and nucleoside reverse transcriptase inhibitor therapy: experimental clarifications and persistent clinical questions. *Antiviral Res* 2003; **58:** 189–97.
9. Walker UA. Update on mitochondrial toxicity: where are we now? *J HIV Ther* 2003; **8:** 32–5.
10. Lewis W, *et al*. Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. *Nat Rev Drug Discov* 2003; **2:** 812–22.
11. Lewis W. Nucleoside reverse transcriptase inhibitors, mitochondrial DNA and AIDS therapy. *Antivir Ther* 2005; **10** (suppl 2): M13–M27.
12. Moyle G. Mechanisms of HIV and nucleoside reverse transcriptase inhibitor injury to mitochondria. *Antivir Ther* 2005; **10** (suppl 2): M47–M52.
13. Cherry CL, *et al*. Mitochondrial toxicity of nucleoside analogues: mechanism, monitoring and management. *Sex Health* 2005; **2:** 1–11.
14. Kohler JJ, Lewis W. A brief overview of mechanisms of mitochondrial toxicity from NRTIs. *Environ Mol Mutagen* 2007; **48:** 166–72.

Effects on the musculoskeletal system. Myalgia and other adverse effects on the muscle can occur in patients taking zidovudine, although it has sometimes been difficult to determine whether the effects were caused by the drug or by the underlying HIV infection.[1-4] Zidovudine-induced myopathy has been considered to be a distinct condition characterised by the presence of abnormal mitochondria in muscle-biopsy specimens;[2] this view is supported by the fact that the myopathy readily responds to the withdrawal

of zidovudine or to treatment with corticosteroids or other anti-inflammatory drugs.[1-3] For further discussion of the effects of zidovudine on mitochondria, see p. 1025.3.

Arthralgia involving the knees, elbows, ankles, and wrists has been reported in a patient receiving zidovudine.[5]

1. Gertner E, *et al.* Zidovudine-associated myopathy. *Am J Med* 1989; **86:** 814–18.
2. Dalakas MC, *et al.* Mitochondrial myopathy caused by long-term zidovudine therapy. *N Engl J Med* 1990; **322:** 1098–1105.
3. Till M, MacDonell KB. Myopathy with human immunodeficiency virus type 1 (HIV-1) infection: HIV-1 or zidovudine? *Ann Intern Med* 1990; **113:** 492–4.
4. Simpson DM, *et al.* Myopathies associated with human immunodeficiency virus and zidovudine: can their effects be distinguished? *Neurology* 1993; **43:** 971–6.
5. Murphy D, *et al.* Zidovudine related arthropathy. *BMJ* 1994; **309:** 97.

Effects on the nails. Bluish or brownish discoloration of fingernails and/or toenails has been reported in several patients receiving zidovudine.[1-5] Dark-skinned patients appear to be most commonly affected.[2,4] Occasionally the abnormal pigmentation also involves the skin.[3,5] It has been pointed out that discoloration of nails has occurred in HIV-infected patients without exposure to zidovudine.[6] Painless periungual pyogenic granulomata has been reported in a patient 3 months after starting treatment with a combined antiretroviral regimen of zidovudine, lamivudine, plus efavirenz; one month after the zidovudine and the lamivudine was stopped the lesions had nearly resolved.[7] Paronychia was reported in 12 HIV-infected patients taking lamivudine.[8] In a further report, 6 patients developed paronychia while taking lamivudine with indinavir.[9]

1. Furth PA, Kazakis AM. Nail pigmentation changes associated with azidothymidine (zidovudine). *N Engl J Med* 1987; **107:** 350.
2. Vaiopoulos G, *et al.* Nail pigmentation and azidothymidine. *Ann Intern Med* 1988; **108:** 777.
3. Merenich JA, *et al.* Azidothymidine-induced hyperpigmentation mimicking primary adrenal insufficiency. *Am J Med* 1989; **86:** 469–70.
4. Don PC, *et al.* Nail dyschromia associated with zidovudine. *Ann Intern Med* 1990; **112:** 145–6.
5. Bendick C, *et al.* Azidothymidine-induced hyperpigmentation of skin and nails. *Arch Dermatol* 1989; **125:** 1285–6.
6. Chandrasekar PH. Nail discoloration and human immunodeficiency virus infection. *Am J Med* 1989; **86:** 506–7.
7. Williams LH, Fleckman P. Painless periungual pyogenic granulomata associated with reverse transcriptase inhibitor therapy in a patient with human immunodeficiency virus infection. *Br J Dermatol* 2007; **156:** 163–4.
8. Zerboni R, *et al.* Lamivudine-induced paronychia. *Lancet* 1998; **351:** 1256.
9. Tosti A, *et al.* Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; **140:** 1165–8.

Precautions

Zidovudine should be used with care in patients with anaemia or bone-marrow suppression. Dosage adjustments or treatment interruptions may be necessary and it has been recommended that zidovudine should not be used if the neutrophil count or haemoglobin value is abnormally low. In patients with advanced symptomatic HIV disease taking oral zidovudine, blood tests should be carried out at least every 2 weeks for the first 3 months of treatment and at least monthly thereafter; blood tests should be performed at least every week in those receiving intravenous zidovudine. In patients with early HIV infection blood tests may be performed less frequently (e.g. every 1 to 3 months).

Care is also required in the elderly and in patients with reduced renal or hepatic function who may require reductions in dose. Patients with risk factors for liver disease should be monitored during treatment. Zidovudine is not recommended in patients with moderate to severe liver disease (Child-Pugh scores 7 to 15). Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Patients with hepatitis C receiving interferon alfa and ribavirin may be at special risk and particular care may be necessary in obese patients and in women. Treatment with zidovudine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology.

Zidovudine should not be given to neonates with hyperbilirubinaemia severe enough to need treatment other than phototherapy or with markedly increased aminotransferase concentrations.

Interference with laboratory tests. Raised urinary thymine concentrations in neonates, due to maternal zidovudine treatment, could produce erroneous results in screening tests for inborn errors of metabolism.[1]

1. Sewell AC. Zidovudine and confusion in urinary metabolic screening. *Lancet* 1998; **352:** 1227.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zidovudine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Giving zidovudine to pregnant women with HIV infection from 14 weeks of gestation until delivery, and subsequently to the neonate, has been shown to reduce vertical transmission of the infection (see Uses and Administration, p. 1024.3). Studies have shown that zidovudine can be fetotoxic in *animals* when given early in pregnancy; however, limited studies in human pregnancy have revealed no evidence of human teratogenicity[1] and no adverse effects were seen in a group of infants followed for up to 5.6 years.[2] Although licensed product information recommends that zidovudine should not generally be given before 14 weeks of gestation, it is considered by some experts[1] to be the preferred NRTI for use in antiretroviral regimens during pregnancy.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)
2. Culnane M, *et al.* Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA* 1999; **281:** 151–7.

Interactions

Care should be taken when using zidovudine with drugs that are myelosuppressive (such as amphotericin B, cotrimoxazole, dapsone, doxorubicin, flucytosine, ganciclovir, interferon, systemic pentamidine, pyrimethamine, and vinca alkaloids) or nephrotoxic. Drugs that undergo glucuronidation may delay the metabolism of zidovudine but few of these appear to produce clinically important increases in zidovudine plasma concentrations. Increased toxicity and decreased antiretroviral activity has been reported when zidovudine is given with some other antiviral drugs, and pharmacokinetic interactions have been reported with some of anti-infective drugs often used in patients with HIV infection.

Analgesics. There may be an increased risk of haematotoxicity during use of zidovudine with *NSAIDs*.

Decreased zidovudine clearance[1] and increased area under the zidovudine plasma concentration-time curve[2] has been seen in patients receiving *methadone*.

Severe hepatotoxicity has occurred after use of *paracetamol* in a patient taking zidovudine and co-trimoxazole.[3] However, neither short-term[4] nor long-term[5] studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol.

1. Burger DM, *et al.* Pharmacokinetic variability of zidovudine in HIV-infected individuals: subgroup analysis and drug interactions. *AIDS* 1994; **8:** 1683–9.
2. Schwartz EL, *et al.* Pharmacokinetic interactions of zidovudine and methadone in intravenous drug-using patients with HIV infection. *J Acquir Immune Defic Syndr* 1992; **5:** 619–26.
3. Shriner K, Goetz MB. Severe hepatotoxicity in a patient receiving both acetaminophen and zidovudine. *Am J Med* 1992; **93:** 94–6.
4. Sattler FR, *et al.* Acetaminophen does not impair clearance of zidovudine. *Ann Intern Med* 1991; **114:** 937–40.
5. Burger DM, *et al.* Pharmacokinetics of zidovudine and acetaminophen in a patient on chronic acetaminophen therapy. *Ann Pharmacother* 1994; **28:** 327–30.

Antibacterials. Studies have indicated that the absorption of zidovudine could be reduced by *clarithromycin*.[1] Licensed product information recommends giving zidovudine and clarithromycin at least 2 hours apart since this has been shown to have no overall effect on the bioavailability of zidovudine.[2] Use of *rifampicin* by patients taking zidovudine has been reported to reduce exposure to zidovudine, probably by inducing glucuronidation and amination. Licensed product information for zidovudine has warned that this may result in a partial, or total, loss of efficacy of the drug.[3,4] *Rifabutin* has not been shown to have a marked effect on zidovudine clearance.[5] *Trimethoprim* has been reported[6,7] to decrease the renal clearance of zidovudine by up to 60% with a consequent increase in plasma concentrations, although it was only thought likely to be of clinical significance in patients with hepatic impairment.[7]

For a report of reduced *pyrazinamide* concentrations in patients receiving zidovudine, see p. 346.2.

1. Polis MA, *et al.* Clarithromycin lowers plasma zidovudine levels in persons with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 1709–14.
2. Vance E, *et al.* Pharmacokinetics of clarithromycin and zidovudine in patients with AIDS. *Antimicrob Agents Chemother* 1995; **39:** 1355–60.
3. Burger DM, *et al.* Pharmacokinetic interaction between rifampin and zidovudine. *Antimicrob Agents Chemother* 1993; **37:** 1426–31.
4. Gallicano KD, *et al.* Induction of zidovudine glucuronidation and amination pathways by rifampicin in HIV-infected patients. *Br J Clin Pharmacol* 1999; **48:** 168–79.
5. Gallicano K, *et al.* Effect of rifabutin on the pharmacokinetics of zidovudine in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1995; **21:** 1008–11.
6. Chatton JY, *et al.* Trimethoprim, alone or in combination with sulphamethoxazole, decreases the renal excretion of zidovudine and its glucuronide. *Br J Clin Pharmacol* 1992; **34:** 551–4.
7. Lee BL, *et al.* Zidovudine, trimethoprim, and dapsone pharmacokinetic interactions in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1996; **40:** 1231–6.

Antiepileptics. Giving *valproic acid* to 6 patients taking zidovudine produced increases in plasma-zidovudine concentrations and the area under the plasma concentration-time curve.[1] The evidence suggested that this was due to reduced glucuronidation of zidovudine. Zidovudine may possibly reduce or increase plasma concentrations of *phenytoin*.

1. Lertora JJL, *et al.* Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. *Clin Pharmacol Ther* 1994; **56:** 272–8.

Antifungals. Use of *fluconazole* with zidovudine produced higher serum-zidovudine concentrations, increased the area under the serum concentration-time curve, and prolonged terminal half-life compared with zidovudine alone in a study in 12 patients.[1] Studies *in vitro* suggested that fluconazole could inhibit the glucuronidation of zidovudine; inhibition was also seen with *amphotericin B*, *ketoconazole*, and *miconazole*, but not with *flucytosine* or *itraconazole*.[2]

1. Sahai J, *et al.* Effect of fluconazole on zidovudine pharmacokinetics in patients infected with human immunodeficiency virus. *J Infect Dis* 1994; **169:** 103–7.
2. Sampol E, *et al.* Comparative effects of antifungal agents on zidovudine glucuronidation by human liver microsomes. *Br J Clin Pharmacol* 1995; **40:** 83–6.

Antigout drugs. Use of *probenecid* with zidovudine results in increased plasma concentrations and area under the plasma concentration-time curve of zidovudine, probably due to inhibition of glucuronidation;[1] tubular secretion of the glucuronide metabolite is also reduced. A high incidence of adverse effects has been reported in some patients receiving this combination.[2]

1. de Miranda P, *et al.* Alteration of zidovudine pharmacokinetics by probenecid in patients with AIDS or AIDS-related complex. *Clin Pharmacol Ther* 1989; **46:** 494–500.
2. Petty BG, *et al.* Zidovudine with probenecid: a warning. *Lancet* 1990; **335:** 1044–5.

Antiprotozoals. Use of *atovaquone* with zidovudine produced moderate increases in the zidovudine plasma concentration and area under the plasma concentration-time curve, probably by inhibition of glucuronidation.[1]

1. Lee BL, *et al.* Atovaquone inhibits the glucuronidation and increases the plasma concentrations of zidovudine. *Clin Pharmacol Ther* 1996; **59:** 14–21.

Antivirals. Although there is some evidence from studies *in vitro* that *ribavirin* inhibits phosphorylation of zidovudine, and might therefore reduce its antiviral activity, it is unclear whether an interaction of clinical significance occurs; licensed product information for zidovudine does not recommend the combination, but product information for ribavirin varies, with the US product indicating that no clinical effect was seen. However, the combination may increase the risk of anaemia. Zidovudine product information also recommends that the use of zidovudine with *stavudine* be avoided since similar antagonism has been shown *in vitro*.[1] *Interferon alfa* and zidovudine had a synergistic cytotoxicity to bone-marrow progenitor cells.[2] Severe haematological toxicity occurred when zidovudine was added to *ganciclovir* therapy in AIDS patients with CMV retinitis, necessitating substantial dosage reductions or withdrawal of zidovudine in the majority of patients;[3,4] this additive toxicity with ganciclovir may be one reason why patients given zidovudine and ganciclovir do less well than those given zidovudine and foscarnet. Combined therapy with zidovudine and *aciclovir* is not generally associated with additional toxicity[5] but severe fatigue and lethargy were reported in a patient given aciclovir with zidovudine; this did not occur when either drug was given alone.[6] Evidence of a pharmacokinetic interaction between zidovudine and *didanosine* has been conflicting, with reports of no effect,[7] increased,[8] and decreased[9] plasma concentrations of zidovudine. Small reductions in didanosine plasma concentrations have been reported in patients also receiving zidovudine.[10] However, all changes have generally been small and are likely to be of limited clinical significance. Exposure to zidovudine (as measured by peak plasma concentrations and area under the concentration-time curve) was reduced in HIV patients also given *ritonavir*, whereas the pharmacokinetics of ritonavir were not affected by zidovudine;[11] the clinical relevance of this was not known. Modest increases in plasma-zidovudine concentrations occur on use with *lamivudine*. Although this interaction is usually clinically insignificant, profound anaemia has been reported rarely in patients given this combination.[12,13]

1. Havlir DV, *et al.* In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000; **182:** 321–5.

2. Berman E, *et al*. Synergistic cytotoxic effect of azidothymidine and recombinant interferon alpha on normal human bone marrow progenitor cells. *Blood* 1989; **74:** 1281–6.
3. Millar AB, *et al*. Treatment of cytomegalovirus retinitis with zidovudine and ganciclovir in patients with AIDS: outcome and toxicity. *Genitourin Med* 1990; **66:** 156–8.
4. Hochster H, *et al*. Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS: an AIDS Clinical Trials Group study. *Ann Intern Med* 1990; **113:** 111–17.
5. Tartaglione TA, *et al*. Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; **35:** 2225–31.
6. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; **316:** 547.
7. Collier AC, *et al*. Combination therapy with zidovudine and didanosine compared with zidovudine alone in HIV-1 infection. *Ann Intern Med* 1993; **119:** 786–93.
8. Barry M, *et al*. Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in patients with the acquired immunodeficiency syndrome. *Br J Clin Pharmacol* 1994; **37:** 421–6.
9. Burger DM, *et al*. Pharmacokinetic interaction study of zidovudine and didanosine. *J Drug Dev* 1994; **6:** 187–94.
10. Gibb D, *et al*. Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in children with HIV infection. *Br J Clin Pharmacol* 1995; **39:** 527–30.
11. Cato A, *et al*. Multidose pharmacokinetics of ritonavir and zidovudine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1998; **42:** 1788–93.
12. Hester EK, Peacock JE. Profound and unanticipated anemia with lamivudine-zidovudine combination therapy in zidovudine-experienced patients with HIV infection. *AIDS* 1998; **12:** 439–40.
13. Tseng A, *et al*. Precipitous declines in hemoglobin levels associated with combination zidovudine and lamivudine therapy. *Clin Infect Dis* 1998; **27:** 908–9.

Antiviral Action

Zidovudine is converted intracellularly in stages to the triphosphate via thymidine kinase and other kinases. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. It has also been shown to possess activity against Epstein-Barr virus and Gram-negative bacteria *in vitro*.

Zidovudine-resistant strains of HIV emerge rapidly during zidovudine therapy and are responsible for the lack of benefit with long-term monotherapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. The emergence of zidovudine-resistant HIV strains in patients receiving long-term therapy with zidovudine has been recognised since 1989.[1,2] The emergence of drug resistance is associated with the duration[3] of treatment with zidovudine, but not the dose,[4] and is attributed to a high frequency of mutations in the HIV reverse transcriptase gene.[3,5] Development of high-level resistance to zidovudine in patients with advanced HIV infection has been associated with rapid disease progression and death.[6] Primary infection with zidovudine-resistant HIV strains has been recorded,[7] as has zidovudine resistance in patients receiving other nucleoside reverse transcriptase inhibitors,[8,9] although it is possible that these patients had unrecorded exposure to zidovudine.[8] **Cross-resistance** with other reverse transcriptase inhibitors has been recorded and, although the use of zidovudine with lamivudine has been reported to delay or reverse the emergence of some mutations conferring zidovudine resistance, dual resistance to zidovudine and lamivudine has occurred.[10] Analysis of the Delta study[11] found no delay in the emergence of zidovudine resistance when used with didanosine or zalcitabine, although circulating concentrations of resistant virus were lower during combination therapy and antiviral activity was apparently not impaired. Nevertheless, it could be anticipated that the use of zidovudine with other antiretrovirals, and particularly the highly active regimens which suppress viral replication to a high degree, could delay the emergence of resistance. The clinical response of patients with previous exposure to multiple regimens could be compromised by the presence of multidrug resistance.[12,13]

1. Larder BA, *et al*. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 1989; **243:** 1731–4.
2. Rooke R, *et al*. Isolation of drug-resistant variants of HIV-1 from patients on long-term zidovudine therapy. *AIDS* 1989; **3:** 411–15.
3. Japour AJ, *et al*. Prevalence and clinical significance of zidovudine resistance mutations in human immunodeficiency virus isolated from patients after long-term zidovudine treatment. *J Infect Dis* 1995; **171:** 1172–9.
4. Richman DD, *et al*. Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1990; **3:** 743–6.
5. Loveday C, *et al*. HIV-1 RNA serum-load and resistant viral genotypes during early zidovudine therapy. *Lancet* 1995; **345:** 820–4.
6. D'Aquila RT, *et al*. Zidovudine resistance and HIV-1 disease progression during antiretroviral therapy. *Ann Intern Med* 1995; **122:** 401–8.
7. Erice A, *et al*. Brief report: primary infection with zidovudine-resistant human immunodeficiency virus type 1. *N Engl J Med* 1993; **328:** 1163–5.
8. Lin P-F, *et al*. Genotypic and phenotypic analysis of human immunodeficiency virus type 1 isolates from patients on prolonged stavudine therapy. *J Infect Dis* 1994; **170:** 1157–64.
9. Demeter LM, *et al*. Development of zidovudine resistance mutations in patients receiving prolonged didanosine monotherapy. *J Infect Dis* 1995; **172:** 1480–5.
10. Miller V, *et al*. Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapy failure. *J Infect Dis* 1998; **177:** 1521–32.
11. Brun-Vézinet F, *et al*. HIV-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the Delta trial. *Lancet* 1997; **350:** 983–90.
12. Kavlick MF, *et al*. Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; **177:** 1506–13.
13. Shafer RW, *et al*. Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients. *Ann Intern Med* 1998; **128:** 906–11.

Pharmacokinetics

Zidovudine is rapidly absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism with a bioavailability of about 60 to 70%. Peak plasma concentrations occur after about 1 hour. Absorption is delayed when given with food, but bioavailability is probably unaffected. Zidovudine crosses the blood-brain barrier producing CSF to plasma ratios of about 0.5. It crosses the placenta and is distributed into breast milk. It has been detected in semen. Plasma protein binding is reported to be 34 to 38%. The plasma half-life is about 1 hour.

Zidovudine is metabolised intracellularly to the antiviral triphosphate. It is also metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine as unchanged drug and metabolite.

Reviews.

1. Acosta EP, *et al*. Clinical pharmacokinetics of zidovudine: an update. *Clin Pharmacokinet* 1996; **30:** 251–62.

Neonates. The pharmacokinetics of zidovudine in infants more than 14 days old are reported to be similar to those in adults. After maternal doses the half-life of zidovudine in 7 neonates has been reported to be extended to a mean of 13 hours.[1] In infants given zidovudine, those under 14 days of age had lower total clearance, longer terminal half-life (about 3 hours), and higher bioavailability than older infants.[2] Zidovudine clearance was low and the half-life prolonged to about 7 hours in premature infants.[3]

1. O'Sullivan MJ, *et al*. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase 1 Acquired Immunodeficiency Syndrome Clinical Trials Group Study (protocol 082). *Am J Obstet Gynecol* 1993; **168:** 1510–16.
2. Boucher FD, *et al*. Phase 1 evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr* 1993; **122:** 137–44.
3. Mirochnick M, *et al*. Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. *Antimicrob Agents Chemother* 1998; **42:** 808–12.

Pregnancy. In a study in 3 pregnant women with HIV infection,[1] the area under the concentration-time curve for zidovudine was reduced and the clearance of an oral dose increased during pregnancy when compared with up to 4 weeks postpartum. These results differed from those reported from another study which reported no differences during or after pregnancy.[2] This latter study, however, used values obtained no later than 48 hours postpartum for comparison, at which time it is unlikely that physiological functions would have returned to the non-pregnant state. Zidovudine and its glucuronide metabolite cross the placenta reaching concentrations in the fetal blood similar to those in maternal blood.[3,4] However, concentrations of zidovudine in the fetal CNS have been reported to be below those required to exert an anti-HIV effect.[5]

1. Watts DH, *et al*. Pharmacokinetic disposition of zidovudine during pregnancy. *J Infect Dis* 1991; **163:** 226–32.
2. O'Sullivan MJ, *et al*. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase 1 Acquired Immunodeficiency Syndrome Clinical Trials Group Study (protocol 082). *Am J Obstet Gynecol* 1993; **168:** 1510–16.
3. Gillet JY, *et al*. Fetoplacental passage of zidovudine. *Lancet* 1989; **ii:** 269–70.
4. Chavanet P, *et al*. Perinatal pharmacokinetics of zidovudine. *N Engl J Med* 1989; **321:** 1548–9.
5. Lyman WD, *et al*. Zidovudine concentrations in human fetal tissue: implications for perinatal AIDS. *Lancet* 1990; **335:** 1280–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisazet; Enper†; Retrovir; Zetrotax; ***Austral.***: Retrovir; ***Austria***: Retrovir; ***Belg.***: Retrovir; ***Braz.***: Produvir†; Retrovir; Revirax; Zidovir; ***Canad.***: Novo-AZT; Retrovir; ***Chile***: Retrovir; ***China***: Ai Jian (艾健); Ding Te (鼎特); FeiTe (费特); He Pu Ren (荷普仁); JiuLi (久利); Ke Ai Si (克艾斯); Kedu (克度); Na Xin De (纳信得); Pu Xi Ding (浦希丁); Qi Luo Ke (奇洛克); Retrovir (立妥威); Wei Nuo (伟诺); Zorpex (佐平斯); ***Cz.***: Retrovir; ***Denm.***: Retrovir; ***Fin.***: Retrovir; ***Fr.***: Retrovir; ***Ger.***: Retrovir; ***Gr.***: Apo; Retrovir; Viroclon; Zidrevir; ***Hong Kong***: Retrovir; ***Hung.***: Retrovir†; ***India***: Lazid; Retrovir; Zidovir; Zilion; Zydowin; ***Indon.***: Retrovir; ***Irl.***: Retrovir; ***Israel***: Retrovir; ***Ital.***: Retrovir; ***Malaysia***: Retrovir; ***Mex.***: Azetavir; Novavir; Pranadox†; Retrovir; Timivudin†; Zidic-C†; Zynaraam; ***Neth.***: Retrovir; ***Norw.***: Retrovir; ***NZ***: Retrovir; ***Philipp.***: Retrovir; ***Pol.***: Azovir†; Retrovir; ***Port.***: Ambrodil†; Retrovir; ***Rus.***: Retrovir (Ретровир); Thymazide (Тимазид); Viro-Z (Виро-ЗЕТ); Zido-H (Зидо-ЭЙЧ); Zidovirine (Зидовирин); ***S.Afr.***: Dozra; Retrovir; ***Singapore***: Retrovir; ***Spain***: Retrovir; ***Swed.***: Retrovir; ***Switz.***: Retrovir; ***Thai.***: Antivir; Retrovir; T-ZA†; TO Vir; ***Turk.***: Retrovir; ***UK***: Retrovir; ***USA***: Retrovir; ***Venez.***: Retrovir; Zidovir.

Multi-ingredient Preparations. ***Arg.***: 3TC Complex; 3TC/AZT†; Ganvirel Duo; Imunoxa Complex†; Kess Complex; Lazinevir; Muvidina; Tricivir; Trilaxis; Trivudin; Ultraviral Duo†; Zetavudin; Zidomuv; ***Austral.***: Combivir; Trizivir; ***Austria***: Combivir; Trizivir; ***Belg.***: Combivir; Trizivir; ***Braz.***: Biovir; Zidolam; ***Canad.***: Combivir; Trizivir; ***Chile***: Combivir; Tricivir; ***China***: Combivir (双汰芝); Trizivir (三协唯); ***Cz.***: Combivir; Trizivir; ***Denm.***: Combivir; Trizivir; ***Fin.***: Combivir; Trizivir; ***Fr.***: Combivir; Trizivir; ***Ger.***: Combivir; Trizivir; ***Gr.***: Combivir; Trizivir; ***Hong Kong***: Combivir; Trizivir; ***Hung.***: Combivir; Trizivir; ***India***: Combivir; Cytocom-E; Cytocom-N; Cytocom; Duovir N; Duovir-E; Duovir; Lamda-Z; Lami Plus; Lamsyn-Z; Lamuzid; Lazid-E; Lazid-N; ***Irl.***: Combivir; Trizivir; ***Israel***: Combivir; Trizivir; ***Ital.***: Combivir; Trizivir; ***Malaysia***: Combivir; ***Mex.***: Combivir; Trizivir; ***Neth.***: Combivir; Trizivir; ***Norw.***: Combivir; Trizivir; ***NZ***: Combivir; Trizivir; ***Philipp.***: Combivir; ***Pol.***: Combivir; Trizivir; ***Port.***: Combivir; Trizivir; ***Rus.***: Combivir (Комбивир); Trizivir (Тризивир); ***S.Afr.***: Cipla-Duovir; Colamziv; Combivir; Combozil; Lamzid; Lodiz; Retrovir/3TC Post-HIV Exposure; Sonke Abaclamizid; Trizivar; ***Singapore***: Combivir; Trizivir; ***Spain***: Combivir; Trizivir; ***Swed.***: Combivir; Trizivir; ***Switz.***: Combivir; Trizivir; ***Thai.***: Combid; GPO-Vir Z; Zilavir; Zovilam; ***Turk.***: Combivir; Trizivir; ***UK***: Combivir; Trizivir; ***USA***: Combivir; Trizivir; ***Venez.***: Combivir; Duovir; Trizivir.

Pharmacopoeial Preparations

BP 2014: Zidovudine and Lamivudine Tablets; Zidovudine Capsules; Zidovudine Tablets;

USP 36: Lamivudine and Zidovudine Tablets; Zidovudine Capsules; Zidovudine Injection; Zidovudine Oral Solution; Zidovudine Tablets.

Anxiolytic Sedatives Hypnotics and Antipsychotics

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The drugs in this chapter include:
- anxiolytic sedatives, formerly called minor tranquillisers, which have been used in the management of anxiety disorders
- drugs used to produce sleep (hypnotics)
- drugs used in the treatment of psychoses (antipsychotics, formerly called major tranquillisers). The term neuroleptic is sometimes used to describe those antipsychotics that have effects on the extrapyramidal system

The difference in action between anxiolytics and hypnotics is mainly one of degree and the same drug or group of drugs can have both effects, larger doses being necessary to produce a state of sleep.

The benzodiazepines (typified by Diazepam, p. 1063.2) replaced the barbiturates (typified by Amobarbital, p. 1037.2) and related sedatives as the major group of drugs used as anxiolytics and hypnotics. Some benzodiazepines are also used for their muscle relaxant and anticonvulsant properties. Newer anxiolytics include buspirone (p. 1042.1), a drug that affects serotonin neurotransmission.

The classical antipsychotics (typified by Chlorpromazine, p. 1045.2) include the butyrophenones, the diphenylbutylpiperidines, the indole derivatives, the phenothiazines, and the thioxanthenes. Some newer antipsychotics such as clozapine (p. 1057.3), risperidone (p. 1103.2), olanzapine (p. 1089.3), quetiapine (p. 1101.1), and amisulpride (p. 1036.3) are often referred to as atypical antipsychotics because of their reduced tendency to cause the extrapyramidal effects typical of classical antipsychotics.

Anxiety disorders

Anxiety is an emotional condition characterised by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating, and tremor. It can be a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are difficult to define and various classifications exist:
- in **acute stress disorder** anxiety is associated with a recent extremely stressful event such as bereavement, and is likely to resolve within a few weeks
- in **generalised anxiety disorder** there is persistent pervasive anxiety and worry, usually lasting 6 months or more, resulting in distress or marked difficulty in performing daily tasks. Symptoms include fatigue and disturbed sleep, motor tension, autonomic hyperactivity, irritability, and loss of concentration

The first step in the **management** of anxiety that cannot be attributed to an underlying disease is the use of psychological treatments such as cognitive therapy. Such therapy can be effective in most types of anxiety. If unsuccessful, short-term treatment with a benzodiazepine may be considered.[1] Benzodiazepines exert an effect very rapidly, possibly even after the first dose, and this makes them suitable for treating an acute reaction.[2] However, their use in chronic conditions such as generalised anxiety disorder is limited by serious problems of dependence (see under Diazepam, p. 1065.1). Tolerance may develop to the anxiolytic effects of benzodiazepines although this appears to be less likely than tolerance to the psychomotor effects. No one benzodiazepine appears more effective than the others in the treatment of anxiety disorders.[3] However, adverse effects and pharmacokinetic parameters may influence choice.

Buspirone, an azaspirodecanedione, appears to have broadly similar efficacy to the benzodiazepines but a slower onset of action; it may cause less sedation and dependence. It is reported to lack euphoriant effect. Its efficacy is reduced in patients who have had previous extensive use of benzodiazepines.[4,5]

Increasingly, antidepressants are considered preferable to benzodiazepines for the treatment of generalised anxiety disorder;[1,2,4,6-12] they are particularly appropriate when medium or long-term therapy is necessary or when depression is also present. They may take several weeks to have an effect, so combined therapy with benzodiazepines may be required initially. Tricyclic antidepressants such as imipramine have a proven benefit in the treatment of generalised anxiety disorder.[2-4,6-8] SSRIs are an alternative;[3,12-14] escitalopram and paroxetine are often used. The noradrenaline and serotonin reuptake inhibitor venlafaxine may also be used.[1,8,12] These relatively newer drugs are safer in overdose and are associated with less severe adverse effects than the tricyclics and in the UK NICE[1] and others[9,11] consider SSRIs to be the antidepressants of choice in generalised anxiety disorder.

Beta blockers may be useful for the control of the physical symptoms of anxiety.[14] There is little evidence to support the efficacy of antihistamines such as hydroxyzine in anxious patients,[2] and the *BNF* considers the use of antihistamines solely for their sedative effect in anxiety to be inappropriate. Antipsychotics have been used by some in severe anxiety for their sedative effects; long-term use should be avoided because of the risk of tardive dyskinesia. Antiepileptics such as pregabalin and tiagabine have been found to be effective for the treatment of generalised anxiety disorder.[15]

Anxiety may be present with other disorders such as depression in **mixed anxiety and depressive disorders**, the management of which is discussed under Depression on p. 398.1.

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Obsessive-compulsive disorder. Obsessive-compulsive disorder is associated with intrusive, recurrent, obsessional thoughts and/or repetitive compulsive behaviour (e.g. hand washing) performed in a ritualistic manner. A combination of pharmacological, behavioural, and psychosocial methods appears to have the most successful long-term outcome in its treatment. **Drug therapy** is based on antidepressants that inhibit reuptake of serotonin.[1-12] These include clomipramine, the SSRIs, and the serotonin and noradrenaline reuptake inhibitor venlafaxine. There is some evidence that clomipramine is more effective than the SSRIs but its adverse effects are more problematic.[3,5,13] In the UK NICE considers SSRIs to be the antidepressants of choice in obsessive-compulsive disorder;[8] similar recommendations are also made in some US[10] and international[11] guidelines. It may take 4 to 6 weeks before any response is obtained and up to about 12 weeks to achieve an optimal effect.[2,10,14] If one serotonin reuptake inhibitor fails then another can be tried;[2-5,8,10] for example, it has been suggested that patients who fail to respond to trials with two SSRIs might then try switching to a drug from a different class (e.g. clomipramine or venlafaxine).[6] Treatment should be continued for at least 12 months in those who respond.[8] However, about 40 to 60% of patients do not respond to these drugs and of those who do, many do not achieve complete remission.[3] Also of those who do respond, many relapse when drug therapy is withdrawn and prolonged or even life-long therapy may be necessary;[7,14] however, long-term efficacy and tolerability of serotonin reuptake inhibitors in obsessive-compulsive disorder has yet to be established.[15] It has been suggested that patients may be maintained on reduced dosage[16] but the optimum dosage remains uncertain.[7] Gradual withdrawal over several months may be more successful if patients are also receiving behavioural therapy.[5]

Drugs such as buspirone, lithium, pindolol, and some antipsychotics including the atypicals have been tried as **adjuncts** when patients are refractory to serotonin reuptake inhibitors and behavioural therapy but results of such augmentation therapy have been variable.[2-7] NICE recommends adding an antipsychotic to an SSRI or clomipramine, or using clomipramine with citalopram in such patients.[8] Intravenous clomipramine has been tried in patients refractory to augmentation therapy.[6]

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Panic disorder. Panic disorder is characterised by severe, sudden, unexpected, recurrent exacerbations of anxiety (panic attacks). During an attack there is a feeling of fear, terror, and impending doom or even death accompanied by autonomic symptoms. Attacks are followed by persistent worry (for at least 1 month) about further attacks and their consequences.

If behavioural or cognitive therapy fails in the management of panic disorder, drug therapy can then be tried but it may need to be prolonged as there is a high rate of relapse on withdrawal.[1] Antidepressants are the drugs of choice in the treatment of panic disorder. While some also consider the combination of psychotherapy with antidepressant therapy to be first-line treatment for panic disorder[2] others consider that a clear benefit of using cognitive behavioural therapy with drug treatment has not yet been shown.[3] Tricyclic antidepressants or SSRIs can reduce the frequency of panic attacks and can often prevent them completely.[4-7] Efficacy is broadly comparable, although SSRIs may be associated with a lower incidence of serious adverse effects.[3,7-11] In the UK NICE considers SSRIs to be the drugs of first choice in panic disorder;[12] US guidelines[3] consider SSRIs and the serotonin and noradrenaline reuptake inhibitor venlafaxine to be the drugs of first choice. Clomipramine or imipramine may be tried as second-line treatments.[12] MAOIs such as phenelzine are also effective but dietary restrictions and serious adverse effects limit their use to patients unresponsive to tricyclics and SSRIs.[3,6]

It may take several weeks before the effects of antidepressants are seen and initially there may be an increase in anxiety and the frequency of panic attacks. Benzodiazepines are sometimes used as adjuncts until antidepressants exert their full effect.[3,6-9,11] Short courses of benzodiazepines may also be of use in patients who cannot tolerate, or who are refractory to, antidepressants.[4] However, any benefit may be outweighed by the risk of dependence[5] and NICE does not recommend their use in the treatment of panic disorder.[12] There is little evidence to support the use of beta blockers, but they may control physical symptoms. Other drugs that may produce beneficial effects in some patients include valproate[4,6,8,13] and possibly clonidine.[14]

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Phobic disorders. Phobic disorders consist of an irrational or exaggerated fear of, and a wish to avoid, specific objects, activities, or situations. As there is a strong link between **agoraphobia** and panic disorder (see above) it is treated similarly. Simple or specific phobias are usually unresponsive to pharmacotherapy and respond better to behavioural therapy, although paroxetine or benzodiazepines may be considered for disabling phobias unresponsive to such measures.[1]

SSRIs, particularly paroxetine, are considered to be the drugs of choice for the treatment of **social anxiety disorder** (social phobia).[1-6] The serotonin and noradrenaline reuptake inhibitor venlafaxine is also used.[1] A systematic review and meta-analysis[7] found evidence to support the efficacy of escitalopram, fluvoxamine, paroxetine, sertraline, and venlafaxine in the treatment of social anxiety disorder; efficacy was found to be similar between these drugs although adverse reaction profiles are known to be different. MAOIs such as phenelzine are effective in social anxiety disorder and can improve anticipatory anxiety and functional disability;[8,9] however, a systematic review found them to be less consistently effective than the SSRIs,[10] and their use is limited by dietary restrictions and serious adverse effects. Results with the reversible inhibitor of monoamine oxidase moclobemide have been variable.[2-5,10] The benzodiazepines bromazepam and clonazepam have been reported to be of some benefit,[1,2,4,5,8,11] although benzodiazepines should be used with caution because of the risk of dependence and abuse. Other drugs being investigated for the treatment of social anxiety disorder include gabapentin and pregabalin.[1,12]

Beta blockers may help to reduce the physical symptoms in **performance-related anxiety**.[4,8,11]

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Post-traumatic stress disorder. In post-traumatic stress disorder (PTSD), anxiety is precipitated by persistent recall of a traumatic experience that was exceptionally threatening or catastrophic in nature. Patients may also suffer from negative symptoms such as avoidance, alienation, emotional numbness, and social withdrawal. The main treatment is psychotherapy.[1-6] Drug therapy is largely aimed at accompanying symptoms of anxiety or depression.[7] The combination of both methods of therapy is preferred for severe cases.[8] Negative symptoms are usually resistant to pharmacotherapy. Some 8 to 12 weeks of treatment is generally thought necessary to judge the efficacy of treatment.[2,3]

SSRIs are the drugs of choice for most of the symptoms of PTSD.[1-3,6,8-13] Tricyclic antidepressants or, in refractory patients, MAOIs, may be used as alternatives to SSRIs to help reduce traumatic recollections and nightmares, and to repress flashbacks.[1-3,9] The newer antidepressants nefazodone and venlafaxine have also been tried,[1-3,9] generally in patients refractory to SSRIs, and some consider these drugs to be more suitable alternatives than tricyclics or MAOIs, which may have serious adverse effects.[10] Atypical antipsychotics have been studied as monotherapy and as adjuncts when patients are refractory to SSRIs; they may also be considered where paranoia or flashbacks are prominent.[10]

In the UK NICE[5] recommends the use of paroxetine, mirtazapine, amitriptyline, or phenelzine in patients who refuse psychotherapy, where psychotherapy is inappropriate or ineffective, or as adjunctive therapy in those with significant comorbid depression or severe hyperarousal. In patients who do not respond, further drug therapy may be considered with a different class of antidepressant or adjunctive olanzapine. Drug therapy should be continued for at least 12 months in responders before gradual withdrawal.

It has been suggested that antiepileptics should be considered in those with comorbid bipolar disorder, and where impulsivity and anger predominate.[10] Carbamazepine and valproate appear to improve symptoms of hyperreactivity, violent behaviour, and angry outbursts but only a small number of patients have been studied.[9,10,14] Lamotrigine may also relieve avoidance and intrusive symptoms although, again, patient numbers are small.[9,14]

Benzodiazepines may be helpful for short-term management of anxiety and sleep disturbances (although some studies have failed to show benefit[7]) but they must be used with caution because of the risk of dependence and abuse,[1,10,11] and the possibility of worsening PTSD;[11] some do not favour their use, even short-term.[3,6] In several small studies, prazosin has been found to be a promising and fairly well-tolerated drug in the management of sleep-related symptoms.[13,15]

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Extrapyramidal disorders

Extrapyramidal disorders are movement disorders involving the brain's motor systems outside the pyramidal tract. They are usually characterised by akinesia (a loss of movement) or bradykinesia (abnormal slowness of movement) accompanied by an increase in muscle tone (typified by parkinsonism, p. 889.1); or by dyskinesias (abnormal involuntary movements), often accompanied by a reduction in muscle tone (see below for some examples). Drug-induced extrapyramidal disorders are discussed under Chlorpromazine, p. 1049.2.

Ballism. Ballism, sometimes called hemiballism or hemiballismus because it is usually unilateral, consists of involuntary flinging movements of the extremities and most often results from acute vascular infarction or haemorrhage of the subthalamic nucleus. It often improves spontaneously but dopamine-blocking antipsychotics such as haloperidol or dopamine-depleting drugs such as tetrabenazine may be needed to control severe symptoms. Surgery may be necessary in severe cases.

Chorea. Chorea is characterised by brief involuntary muscle contractions and an inability to sustain voluntary contractions. It may be related to neurological abnormalities in the caudate nucleus and putamen of the striatum as well as other basal ganglia structures. Overactivity of dopaminergic nigrostriatal pathways and depletion of gamma-aminobutyric acid (GABA) and acetylcholine may also play a part. Chorea may be an adverse effect of some drugs, including antipsychotics, levodopa, and oral contraceptives; it may also be a symptom of an underlying disorder such as SLE.

Huntington's chorea (Huntington's disease, progressive hereditary chorea) is a hereditary autosomal dominant disease characterised by chorea, behavioural disturbances, and a progressive decline in cognitive function culminating in dementia and death. The identification of a gene marker for Huntington's chorea now makes it possible to identify carriers of the abnormal gene.[1-4] Symptoms usually appear in mid-life, with death following after about 15 years, although there are also juvenile-onset forms. Westphal variant, a form commonest in children, tends to be characterised more by rigidity than by chorea.[1]

Sydenham's chorea (St Vitus' dance; chorea minor) is an acute, usually self-limiting, disorder with an autoimmune basis, characterised by chorea and behavioural disturbances. It commonly occurs about 6 months after rheumatic fever but is now rare since the incidence of

rheumatic fever has declined. It may also arise during pregnancy (chorea gravidarum).

Treatment of chorea is symptomatic only and does not alter the progressive decline of Huntington's chorea;[1-7] Sydenham's chorea resolves spontaneously within weeks or months but antibacterial prophylaxis to prevent recurrence of rheumatic fever (p. 202.3) has been recommended. Other forms of chorea may resolve with treatment of the underlying disorder or withdrawal of any causative drug.

Tetrabenazine has been used effectively in chorea, although not all patients respond, and it may produce depression.[1-3,7] Nevertheless, tetrabenazine was found to be the drug with the best available clinical evidence in the symptomatic treatment of Huntington's chorea.[4,6] The mode of action is thought to involve depletion of striatal dopamine.[2] Reserpine, which has a similar action and effects, has also been used but is limited by its adverse effects.[2]

Phenothiazines such as fluphenazine[2] have dopamine-receptor blocking activity and have also been used to treat chorea. Other antipsychotics with a similar mode of action that have been used include haloperidol,[1,2,4] pimozide,[2] and sulpiride.[1,2,4] Some atypical antipsychotics[2,4,7] such as olanzapine, quetiapine, risperidone, and zotepine have also been tried. Adverse effects such as tardive dyskinesias may limit the use of antipsychotics,[1,2] and doses should be kept as low as possible;[2] attempts to control choreiform movements completely are not recommended. In addition to improving chorea, antipsychotics may also be of value in controlling the behavioural symptoms associated with Huntington's chorea; anxiolytics and antidepressants may also be of use.[1,2]

Carbamazepine[1] has been tried with some degree of success in a limited number of patients. The use of drugs to increase GABA activity has been of little value.[2] Other drugs being investigated include amantadine,[3] minocycline,[2,3] and ubidecarenone.[1-3] Implantation of human and porcine fetal neural cells is being studied,[1] as are various forms of gene therapy.

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Tics. Tics may manifest as sudden, involuntary, brief, isolated, repetitive movements, both simple (e.g. eye blinking, nose twitching, or head jerking) and complex (e.g. touching, jumping, or kicking); they may also be sensory in nature or may present in a vocal or phonic way and can range from simple clearing of the throat to more complex symptoms such as echolalia (involuntary repetition of others speech) or coprolalia (involuntary and inappropriate swearing). Symptoms can usually be suppressed voluntarily and may increase with stress and decrease with distraction.[1-3] Some tics persist during sleep.[2,3] The most common cause is **Tourette's syndrome** (Gilles de la Tourette's syndrome), in which behavioural disturbances usually accompany the tics.[1-5] It is a genetic disorder with an onset during childhood and is characterised by recurrent multiple motor and vocal tics that are not due to the direct physiological effects of a substance or a medical condition, with a duration of at least 1 year.

Most patients' symptoms wax and wane and behavioural therapy and reassurance may be sufficient to resolve mild tics.[1,5] Drug treatment may be necessary if tics are severe enough to cause discomfort or embarrassment.[1,2,4,6] Clonidine[1,5-7] or guanfacine[1,5-7] are increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects. For more severe cases the classical antipsychotics pimozide or haloperidol have been widely tried[3,8] to decrease the frequency and severity of tics, and may improve any accompanying behavioural disturbances; however, the risk of developing serious adverse effects such as tardive dyskinesia should be balanced against the perceived benefits of treatment.[8] Pimozide may be slightly less effective than haloperidol, but adverse effects are less frequent.[9] Other antipsychotics such as fluphenazine, sulpiride, or tiapride have also been tried;[4,6,8] increasingly, atypical antipsychotics, notably risperidone but also including olanzapine, quetiapine, and ziprasidone, are preferred because their adverse effect profile is seen as more acceptable.[7] Doses should be as low as possible, bearing in mind that optimum treatment does not necessarily lead to the complete control of symptoms.[2,4]

Other drugs[1-4,6,8] that may be used in the management of tics and/or behavioural aspects of Tourette's syndrome include baclofen, botulinum toxin, clonazepam, levodopa, pergolide, and tetrabenazine. Nicotine has been reported to produce benefit when used alone or with haloperidol in patients whose symptoms were not satisfactorily controlled with haloperidol alone.[7,10]

For drugs used in the treatment of comorbid disorders commonly associated with Tourette's syndrome, such as obsessive-compulsive disorder and attention deficit hyperactivity disorder, see p. 1028.2 and p. 2314.1, respectively.

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Hypochondriasis

Hypochondriasis (hypochondriacal neurosis) is a morbid preoccupation with one's health characterised by a fear or belief that normal bodily sensations are indicative of serious disease. It persists despite medical reassurance and management is difficult. If hypochondriasis is secondary to a psychiatric disorder, particularly depression and some anxiety disorders, treatment aimed at the primary condition may also lead to resolution of the hypochondriacal symptoms.[1-3]

Cognitive and behavioural therapies may be useful in the treatment of hypochondriasis; drug treatment of primary hypochondriasis has been less well studied although antidepressants such as the SSRIs may be effective.[1-4] Pimozide is used in the management of hypochondriacal psychoses such as delusions of parasitic infestation.[5] Atypical antipsychotics such as quetiapine and risperidone have been used as alternatives to pimozide in the treatment of delusional parasitosis.[6-8] A systematic review[7] did not find any randomised controlled studies on the use of classical or atypical antipsychotics in the treatment of delusional parasitosis but tentatively concluded that, based on weak evidence, antipsychotics are effective in treating primary delusional parasitosis. Pimozide had the best evidence of efficacy but its use is limited by its more problematic adverse effects.

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Psychoses

Psychoses and psychotic disorders are terms that have been used to describe a collection of severe psychiatric disorders in which the patient has disordered thinking and loses contact with reality due to delusions and/or hallucinations. There may be accompanying mood or behavioural disturbances. *Organic psychoses* arise from organic brain disease produced by toxic insults, metabolic disturbances, infections, or structural abnormalities and may be acute (delirium) or chronic (dementia) in nature.

Disturbed behaviour. Drug therapy is sometimes indicated for the immediate control of severely disturbed, agitated, or violent behaviour associated with a variety of conditions such as toxic delirium, brain damage, mania (see Bipolar Disorder, p. 397.2), or other psychotic disorders. In the UK NICE has issued guidelines on the short-term management of disturbed or violent behaviour in adults.[1] Antipsychotics and benzodiazepines, either alone or in combination, are commonly used for disturbed behaviour. There is little agreement on the best antipsychotic for these indications, selection depending mainly on the condition of the patient and the adverse effect profile of the drug.[2-9] Oral therapy should be tried first and parenteral therapy only given if this is ineffective or refused. The high-potency butyrophenone haloperidol is commonly used for **acutely disturbed behaviour** although it lacks any sedative effects and may be associated with severe extrapyramidal adverse effects. The atypical antipsychotics such as olanzapine and risperidone are increasingly used in acute situations. A systematic review,[10] albeit of 3 small studies, concluded tentatively that there was no difference in efficacy and incidence of adverse effects between low-dose haloperidol and olanzapine or risperidone in the management of delirium; high-dose haloperidol was associated with a greater incidence of extrapyramidal effects. Benzodiazepines such as diazepam and lorazepam are valuable sedatives for the disturbed or delirious patient. A combination of an antipsychotic and a benzodiazepine allows the use of lower doses of each drug. However, a systematic review[11] considered that there were insufficient data to support or refute the use of benzodiazepines, either alone or with an antipsychotic, in the treatment of acute psychosis. Another systematic review[12] found the combination of haloperidol and the antihistamine promethazine, both given intramuscularly, to be effective.

Other drugs that have had some success in the control of symptoms such as agitation, aggression, rage, or violent behaviour include beta blockers, lithium, carbamazepine, and valproate. Buspirone and antidepressants such as the SSRIs and trazodone may also be useful.

Antipsychotics appear to be modestly effective for the control of disturbed behaviour associated with the **dementia** of chronic conditions such as Alzheimer's disease (p. 388.1).[13-18] However, antipsychotics can themselves precipitate confusion or exacerbate dementia and may hasten cognitive decline, increase the risk of falls, incontinence, and drowsiness, and interfere with the performance of motor skills.[19] Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotics and the reaction can be life-threatening. In 2005, the FDA[20] was aware of placebo-controlled studies that showed an increased risk of mortality with the use of the atypical antipsychotics aripiprazole, olanzapine, quetiapine, and risperidone in elderly patients with dementia; most of the deaths appeared to be due to cardiovascular events or infection. The FDA considered it likely that the atypicals as a group were associated with an increased risk of death in such patients (for further details, see the Elderly, under Risperidone, p. 1105.1). After a further review, in 2008, of 2 observational studies in elderly patients, the FDA[21] concluded that both classical and atypical antipsychotics were associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis (for more details, see the Elderly, under Chlorpromazine, p. 1051.1). Methodological limitations precluded any conclusion that classical antipsychotics have a greater mortality risk than atypical antipsychotics.

Antipsychotics are used only after careful consideration of the causes of disturbed behaviour and the benefits and risks of antipsychotic treatment. Very low doses are given at first and increased gradually according to clinical response and development of adverse effects; the necessity for continued use is reviewed periodically. Again, there is no agreement over the choice of antipsychotic. A systematic review noted that while there was limited evidence to support the routine use of haloperidol for agitation in dementia, it appeared to reduce aggression.[22] Atypical antipsychotics such as olanzapine, quetiapine, and risperidone may be less likely to produce extrapyramidal effects, but cerebrovascular adverse effects are a problem. The UK CSM recommended[23] in 2004 that risperidone and olanzapine should not be used to treat behavioural problems in elderly patients with dementia after analysis of placebo-controlled clinical studies revealed an increased risk of stroke with these 2 atypical antipsychotics (but see below). Guidelines for the management of behavioural and psychiatric symptoms in patients with dementia and a history of stroke or transient ischaemic attacks issued in the UK[24] state that consideration should be given to the withdrawal of existing olanzapine and risperidone therapy, and starting treatment with a classical antipsychotic or an atypical that has not been associated with an increased risk of cerebrovascular adverse effects. A large multicentre study[25] concluded that adverse effects of atypical antipsychotics (olanzapine, quetiapine, and risperidone) outweigh their benefits in treating behavioural disturbances in patients with Alzheimer's disease. A long-term placebo-controlled study[26] in patients with Alzheimer's disease given antipsychotics (chlorpromazine, haloperidol, risperidone, thioridazine, or trifluoperazine) also concluded that, for most patients, stopping antipsychotic therapy had no overall detrimental effect on functional and cognitive status. The authors suggested that although antipsychotics may have some value in the maintenance treatment of more severe behavioural disturbances, any potential benefits must be weighed against the risk of serious adverse effects. During follow-up[27] a higher mortality rate was found in the patients who continued to receive antipsychotics compared with those who stopped antipsychotic therapy; most patients were taking risperidone or haloperidol. The authors

noted that antipsychotics should only be used for short periods in the treatment of severe neuropsychiatric symptoms, particularly aggression, in this patient group. In 2009, the UK CHM[28] stated that analysis of 3 randomised studies showed a clear benefit for the short-term use of risperidone in the treatment of aggression in elderly patients with dementia; risperidone is now licensed for such use in the UK.

The sedative drug, clomethiazole, may be a useful alternative to antipsychotics for the control of agitated behaviour in elderly patients, generally causing fewer adverse effects; respiratory depression, excessive sedation, and dependence may, however, be a problem. Benzodiazepines are not generally indicated for the management of elderly demented patients because of the risks of dependence with continued use, disinhibiting effects, and the particular problems of these drugs in old people (see the Elderly, under Diazepam, p. 1067.2). They are not as effective as antipsychotics in reducing behavioural problems, but may be useful in short courses for the management of severe anxiety disorders, or given as required for patients who only have rare episodes of agitation.

The use of antipsychotics in the control of **disturbed behaviour in children** is controversial and can probably be justified only in severe cases resistant to non-pharmacological therapy.[29-31] Aggression in children (with autism, conduct disorder, and mental retardation) has been treated with antipsychotics on a short-term basis. High-potency classical antipsychotics such as haloperidol may be less likely to cause sedation or impair arousal, cognitive function, and learning. Atypical antipsychotics such as olanzapine and risperidone have been used for the control of aggression in children with autism and conduct disorder but are associated with weight gain.[30-32] Nonetheless, in some countries, including the USA, aripiprazole and risperidone are licensed for the treatment of irritability associated with autistic disorder in children and adolescents; in the UK, risperidone is licensed for the short-term treatment of persistent aggression in conduct disorder in children and adolescents with subaverage intellectual functioning or mental retardation. Quetiapine and ziprasidone have also been tried in the treatment of behavioural disturbances associated with autistic disorder.[32,33] The tendency of antipsychotics to lower the seizure threshold is an important consideration in autistic children who are at an increased risk of seizure disorders. Other drugs that have been tried include clonidine, lithium, and the SSRIs.[30,31] Guidance on the management of autism spectrum disorders has been issued by the American Academy of Pediatrics.[34]

Antipsychotics have been used to control the symptoms of **drug-induced psychosis** in patients with Parkinson's disease.[35-37] Initially, other possible causes such as infections or metabolic and endocrine changes should be eliminated.[36] If psychotic symptoms persist, antiparkinsonian drugs should be gradually stopped or used at the lowest effective dose. Treatment of sleep disturbances in these patients may reduce psychosis; low doses of sedating antidepressants, such as mirtazapine, nortriptyline, or trazodone, are preferable to benzodiazepines or antihistamines which may contribute to confusion and psychosis.[37] Psychosis may be particularly difficult to treat, since the extrapyramidal effects of classical antipsychotics can exacerbate the movement disorder. Benefit has been reported with the atypical antipsychotic clozapine (which must be used with caution because of the risk of agranulocytosis) but results with other atypical antipsychotics such as risperidone and olanzapine have been mixed; quetiapine appears to be reasonably well tolerated. Other drugs that have been tried include anticholinesterases such as donepezil and rivastigmine; ECT may be considered in patients refractory to drug treatment.[36,37]

Antipsychotics have been used for palliative treatment of agitation and restlessness in patients with **terminal restlessness**.[38-40] Although antipsychotics may exacerbate the existing tendency to myoclonus and convulsions in these patients and may not produce adequate sedation in the terminal phase, haloperidol can be used where sedation is not required. Some[38-40] even consider haloperidol to be the drug of choice; chlorpromazine[38-40] and olanzapine have been used as alternatives. Benzodiazepines (such as lorazepam or midazolam), levomepromazine, and propofol have also been used.[38,40]

Paraphilias and other **deviant sexual behaviour** are rare in women so treatment is focused largely towards men; it consists mainly of psychotherapy and the use of libido-suppressing drugs such as the anti-androgens.[41-44] The use of such pharmacotherapy is controversial and involves not only medical but legal issues. Drugs used for their anti-androgenic action include cyproterone and medroxyprogesterone. Gonadorelin analogues have also been tried for suppression of libido.[42] Medroxyprogesterone has also been used for the control of intrusive disinhibited sexual behaviour in elderly men with dementia. SSRIs may be used in less severe cases, especially in the control of fantasies associated with various paraphilias; they may also be used with an antihormonal drug if the latter provides inadequate improvement alone.[43,44] The antipsychotic benperidol is used in some countries for the management of sexual deviations but its value is not established. In general, few well-controlled blinded studies have been conducted into the pharmacological treatment of sexual offenders and there is no evidence that drug treatment reduces the rate of re-offending.

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Mania. Mania usually occurs as part of bipolar disorder. The treatment of acute attacks of mania including mention of the role of antipsychotics is described under Bipolar Disorder, p. 397.2.

Schizophrenia. Schizophrenia is a complex disorder associated with a high morbidity; it may be a group of related syndromes rather than a single disorder. Schizophrenia begins most commonly in late adolescence to the early twenties and many patients develop a chronic illness with repeated relapses. The estimated prevalence is between 0.2 to 1% in the general population. The main clinical features of acute schizophrenia syndrome can be divided into psychotic features such as delusions and hallucinations, and disorganised features involving speech, thought, and behaviour (together often known as 'positive' symptoms). The main features of the chronic syndrome are apathy, lack of drive, and social withdrawal (so-called 'negative' symptoms). Positive symptoms tend to respond better to drug therapy than negative symptoms. The pathophysiological mechanism of schizophrenia is unclear. Since classical antipsychotics used in the treatment of schizophrenia block dopamine D_2 receptors in the midbrain it has been suggested that dopaminergic system overactivity may be involved. However, the efficacy of atypical antipsychotics such as clozapine (see below), which is a relatively weak dopamine D_2 inhibitor, has raised the possibility that an imbalance of other neurotransmitters such as serotonin and adenosine may also be involved (see also Action, under Chlorpromazine, p. 1046.1).

The **treatment** of schizophrenia consists mainly of a combination of psychosocial therapy and antipsychotics.[1-16] Drug treatment must be started as soon as possible for best outcome. There is little difference in the efficacy of classical antipsychotics such as chlorpromazine and haloperidol. The atypical antipsychotic clozapine appears to be more effective than classical antipsychotics in the management of both positive and negative symptoms, but its use is restricted because it can cause potentially fatal agranulocytosis. Comparative studies have shown that other atypical antipsychotics are at least as effective on positive symptoms as the classical antipsychotics, although claims of greater effects on negative symptoms remain to be proven.

Choice of therapy depends on the risk of adverse effects (which vary between the different groups of antipsychotics), any past treatment, and, unfortunately, cost. The atypical antipsychotics may be better tolerated than classical antipsychotics and, in particular, extrapyramidal symptoms may be less frequent. However, classical antipsychotics are still widely used, since the diversity of their preparations (tablets, oral liquids, injections, and depot injections) and lower cost offer advantages over the atypicals. Because the atypical antipsychotics risperidone and olanzapine have been associated with an increased risk of stroke when used in elderly patients with dementia (see the Elderly, under Risperidone, p. 1105.1), some UK guidelines[17] have recommended that other antipsychotics should be considered for patients with a history of stroke, transient ischaemic attacks, or other cerebrovascular disease even in the absence of dementia. However, there is little evidence to guide prescribing in older patients.[18]

There is great interindividual variation in response to antipsychotics, and choosing the most appropriate one may require a trial of antipsychotics from different chemical groups and careful adjustment of dosage. The Royal College of Psychiatrists in the UK has issued advice for those considering the use of higher than normally recommended doses of antipsychotics (see under Administration in the Uses and Administration of Chlorpromazine, p. 1046.1).

However, in recent years there has been a trend in favour of lower doses of antipsychotics, often with adjunctive benzodiazepines (see below). The use of more than one antipsychotic at the same time is not usually recommended.

About 30% of patients may have little or no response to classical antipsychotics while many others have only a partial response. Such **resistant schizophrenia** may be due to poor patient compliance, which is a major problem in schizophrenic patients; lack of compliance may be a result of adverse effects (see below for possible treatments) or because the patient has a relapse while on medication and is unable to maintain treatment.[19] A patient should not be considered resistant to therapy until at least 2 different antipsychotics (NICE also recommends that at least one of these should have been an atypical[13]) have each been given for an adequate trial period (at least 6 to 8 weeks). If other drugs are still ineffective, clozapine may be tried; it should be given for at least 3 months before resorting to measures such as ECT or the use of adjunctive drugs (see below).

After the initial control of schizophrenia with antipsychotics, relapse rates are high in those who stop treatment, therefore **maintenance** therapy is probably warranted. Some recommend the use of lower doses of antipsychotics during maintenance to reduce adverse effects, although this may increase the risk of relapse. The decision to withdraw an antipsychotic completely in a stabilised patient is complex and depends on the number of previous psychotic episodes. In some cases maintenance therapy may need to be indefinite. Regular injections of long-acting depot antipsychotics are sometimes used for maintenance therapy especially if compliance is a problem.[13,20] They are particularly useful for patients living in the community, and may also be advantageous for those who respond poorly to therapy because of increased first-pass metabolism or intestinal malabsorption. Concern over the possibility of increased extrapyramidal effects and other adverse effects with depot antipsychotics has not been substantiated.

Adjunctive drugs have been used in schizophrenia either to augment antipsychotics or reduce their adverse effects.[21] The short-term addition of a *benzodiazepine* to the initial treatment of acute episodes of schizophrenia can provide a useful extra sedative and anxiolytic effect. It may also allow a smaller dose of antipsychotic to be used and thereby reduce the likelihood of extrapyramidal effects. However, a systematic review[22] concluded that the available evidence for such use is poor and inconclusive.

The use of *antimuscarinic antiparkinsonian drugs* for the treatment or prophylaxis of antipsychotic-induced extrapyramidal adverse effects is controversial (see Extrapyramidal Disorders on p. 1049.2). They are particularly effective in the management of acute dystonic reactions but efficacy in drug-induced parkinsonism itself may be minimal and little benefit has been found in akathisia. Fears that the long-term use of antimuscarinics increases the risk of tardive dyskinesia appear to be unfounded, although they may worsen the condition and should be stopped if it develops. However, the adverse effects of antimuscarinics can be troublesome and may compound the antimuscarinic actions of the antipsychotic. Antimuscarinics also have euphoric effects. Routine use of prophylactic antimuscarinics is therefore not indicated with the possible exception of short-term use in patients at high risk of developing dystonias, or in patients with a history of drug-induced dystonias. Antimuscarinics may be given on a short-term basis to treat dystonias.

Addition of *lithium* to antipsychotic treatment may be worthwhile in some patients who fail to respond to an antipsychotic alone, although there is the danger of an interaction (see p. 431.3).

The value of treatment of depressive symptoms of schizophrenia with *antidepressants* is not established but the addition of antidepressants such as the tricyclics is considered worth a trial for depression occurring during the recovery phase after an acute episode of psychosis.

Carbamazepine has produced modest benefit in some patients with refractory schizophrenia, the main effect being a reduction in accompanying symptoms such as excitement, impulsivity, and aggression, but use of carbamazepine with haloperidol has also resulted in reduced haloperidol concentrations and clinical deterioration in a few patients. A systematic review[23] found no significant benefit of adjunctive carbamazepine therapy. *Valproate* has also been tried; however, a systematic review[24] found no data to support or refute the use of valproate, either alone or in combination with antipsychotics, in the treatment of schizophrenia.

Propranolol in high doses has been reported to be beneficial in refractory schizophrenia but several controlled studies of adjunctive use have found slight or no benefit. However, it may be of use as an adjunct in patients who develop akathisia unresponsive to antimuscarinics.

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Sedation

Since sedatives reduce excitement and anxiety, they may be used before or during various medical procedures to alleviate fear and produce a state of calmness in the patient. A practical aim for situations requiring **conscious sedation**, for example in *dentistry* or during investigative procedures such as *endoscopy*, may be the reduction or abolition of physiological and psychological responses to the stress without loss of consciousness, cooperation, or protective reflexes. A greater degree of sedation may be required for patients in *intensive care* and some consider that patients should be maintained asleep but easily rousable. The difference between sedatives and hypnotics is mainly dose related. The same drug or group of drugs can have both effects, larger doses being necessary for a hypnotic effect, that is to produce a state of sleep.

Some specific situations where sedation may be required are discussed below. The use of sedatives in premedication for anaesthesia is discussed on p. 1899.1.

Dental sedation. Intravenous midazolam has largely superseded diazepam for sedation in dental procedures. However, midazolam needs to be given slowly in small increments as its sedative end-point is reached much more abruptly than with diazepam. Midazolam has a more rapid onset of action and recovery, and produces a greater degree of amnesia than diazepam, but it can cause hallucinations in children.[1] There is insufficient evidence to support the routine use of intravenous sedation for dental procedures in children under the age of 16 years and it is recommended that such use, along with the use of general anaesthetics, combination regimens, and non-standard routes, should be restricted to specialist centres or hospital settings.[2]

Inhaled nitrous oxide (usually 20 to 40% with oxygen[3]) is a widely used analgesic and sedative for conscious sedation of patients with mild to moderate anxiety about dental procedures.[3,4] It is relatively safe and simple to use although there is some concern over its long-term effect on dental staff.[3,4] Nitrous oxide inhalation is well tolerated by children and remains the preferred technique in the management of anxiety in such patients although a certain amount of patient cooperation is required[1,2,5] and supplementary local analgesia is recommended in potentially painful procedures.[2]

Oral sedatives may also be used to provide conscious sedation[4] and are particularly useful to ensure that the patient has a restful night before the procedure; hypnotics may be used for 1 to 3 nights before. Those drugs used include the benzodiazepines diazepam, nitrazepam, and temazepam; temazepam is preferred when it is important to minimise any residual effects. The antihistamines hydroxyzine and promethazine have been used in children.[1,4,5] Oral sedatives have no analgesic effects and appropriate analgesia should be given.[5] It has been suggested that the efficacy of the oral sedative in adult patients can be enhanced by the careful addition of inhaled nitrous oxide; the depth of sedation can be changed as necessary by varying the titration of the latter.[4]

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Endoscopy. The practice of giving sedation routinely before endoscopy varies widely between and within countries.[1-3] It is unclear whether sedation improves patient comfort and the ease of performing the procedure;[1] there may be a failure to distinguish between the need for sedation and the need for analgesia in such procedures. Ultimately the acceptability of unsedated endoscopy differs from patient to patient and procedure to procedure,[2] and it may be appropriate to offer patients the choice.[4]

Intravenous benzodiazepines are commonly used for sedation during endoscopy.[1,2,5,6] Midazolam is generally preferred to diazepam because of its shorter duration of action and greater amnestic effects.[6] Since hypoventilation and oxygen desaturation may occur with benzodiazepines and the procedure itself can lower oxygen saturation, some recommend the use of prophylactic nasal oxygen with oxygen saturation monitoring.[2,3,5,6]

Intravenous opioid analgesics such as morphine and pethidine have also been given but they have largely been replaced by the newer shorter-acting opioids, for example fentanyl, which have faster recovery times.[3,6] Benzodiazepines have often been given with opioids, including pethidine, since such combinations may reduce gagging and increase patient tolerance.[2] They can be used together to achieve deep sedation at higher doses than those used for conscious sedation. However, there is an increased risk of cardiorespiratory effects and, possibly, fatalities with such combinations.[2,5] Therefore, the use of the lowest effective doses has been recommended[3,5] and opioids should be given before benzodiazepines, where possible, and their effects monitored before proceeding.[5] The addition of intravenous diphenhydramine, droperidol (but see also Adverse Effects, Treatment, and Precautions of Droperidol, p. 1072.2), or promethazine to such combinations may result in deeper sedation and may be used in patients who are inadequately sedated.[6]

Low-dose intravenous propofol has also been used for conscious sedation as an alternative to, or with, midazolam and opioids.[4] It potentiates the effects of benzodiazepines and opioids, thus reducing the doses required for sedation and analgesia.[6] Propofol has been used alone for deep sedation especially in prolonged or complex procedures; benefit has not been shown conclusively for shorter procedures.[6] The risk of adverse effects may limit its use[6] and the presence of an anaesthetist is usually required.[5] Fospropofol, a prodrug of propofol, is available in some countries for sedation.

Continuous monitoring of the sedated patient's haemodynamic and ventilatory status, and level of consciousness is recommended.[2-10]

The use of topical anaesthetics such as lidocaine should probably be reserved for those who prefer to undergo endoscopy without sedation as topical anaesthesia appears to serve little useful function in patients premedicated with benzodiazepines or opioids.[4,11] There appears to be no practical difference between individual topical anaesthetics. Sprays are safer and may be more effective than lozenges,

but even when using a spray it is difficult to anaesthetise the oropharyngeal region effectively.

There is great variation in the methods of sedation and analgesia used for **children** undergoing endoscopy.[7-10] The choice between general anaesthesia and sedation in these patients is subject to debate.[7] Many of the regimens used appear to be similar to those used in adults; drugs commonly used include midazolam, opioids such as fentanyl or pethidine, and propofol.[7,10] However, the use of propofol is generally not recommended in children (see Incidence of Adverse Effects, under Propofol, p. 1913.3). In the UK, general anaesthesia is the favoured method for younger children; premedication with oral midazolam has also been used.[8]

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Intensive care. Not all patients in intensive care units require sedatives if sufficient analgesia is achieved, particularly after the first 24 to 48 hours, but most will require a balanced combination of analgesics and sedatives to relieve pain and anxiety.[1-9] It is inappropriate to use high doses of analgesics to achieve deep sedation and it is also inappropriate to use sedatives alone for patients who are in pain. Adequate analgesia is recommended before giving sedatives in order to avoid over-sedation.[6,7] The required level of sedation may vary but, in general, many consider patients should be maintained asleep but easily rousable.

Most sedatives and analgesics are given parenterally. Continuous intravenous infusion avoids the peaks and troughs of analgesia and sedation associated with intermittent intramuscular or intravenous dosage, but to what extent it improves patient outcomes is unclear: sedation produced in this way may prolong the need for mechanical ventilation and increase pulmonary complications.

Opioid analgesics have both sedative and analgesic properties and are appropriate for sedation when pain is anticipated, although special care is required in those not artificially ventilated. The antitussive action of the opioids may also help ventilated patients to tolerate a tracheal tube. The choice of opioid may vary between centres, as well as with patient characteristics. Morphine is a suitable opioid in many situations in intensive care[6] but has a slow onset of action. If prolonged sedation is required, analgesia can be obtained by a loading dose followed by a continuous infusion. Many centres now favour the use of one of the phenylpiperidine derivatives, fentanyl, alfentanil, sufentanil, or remifentanil.[5-9]

Propofol is widely used for short-term sedation (up to 72 hours) in intensive care units,[4-9] although concerns have been raised about its safety, particularly in children (in whom use is generally not recommended), or with prolonged use or higher rates of infusion (see also Incidence of Adverse Effects, under Propofol, p. 1913.3). It may be particularly useful in neurosurgical patients to reduce raised intracranial pressure,[6,8] or when rapid awakening is important.[6]

Benzodiazepines induce sleep and reduce anxiety and muscle tone as well as providing profound amnesia; however, they do not provide analgesia. Midazolam has a rapid onset and short duration of action following single doses, and has largely replaced diazepam as the benzodiazepine of choice for sedation. It is particularly favoured for longer-term sedation (more than 72 hours).[5,9] The half-life of midazolam can be substantially increased when given as a continuous intravenous infusion for long-term sedation in patients in intensive care. Lorazepam has also been used[1,6] particularly in the USA,[6] and may be associated with less variability in awakening times, although onset of action may be slower than midazolam. All benzodiazepines tend to produce cardiovascular and respiratory depression and care is required if they are used with opioids as is usually the case in this setting.

Flumazenil is a specific benzodiazepine antagonist and some suggest that it may be of use to assist the return of spontaneous respiration and consciousness in patients receiving benzodiazepines. Multiple doses may be required as it has a short duration of action.[1] However, its routine use after prolonged benzodiazepine treatment is not usually recommended because of the risk of inducing withdrawal symptoms.[6]

Dexmedetomidine is also approved for use in intensive care as a sedative; it is stated to have analgesic-sparing properties.[6]

Ketamine has been investigated for sedation in the intensive care setting[4] and appears to be effective; it may be used as an adjuvant.[8,9] Clonidine is also used as an adjuvant to other drugs.[3,6,8,9] In agitated or delirious patients haloperidol may be used.[4,6]

Stopping treatment with sedatives such as benzodiazepines, opioids, and propofol too rapidly may lead to withdrawal symptoms,[6,7] especially after high doses or prolonged sedation (more than 1 week). Doses should be tapered to prevent such symptoms. Tolerance to benzodiazepines can develop and may be related to long-term sedation (2 days or more); tolerance to opioids has also been reported.[7]

Methods of sedation and analgesia for **children** in intensive care are subject to debate. Many of the regimens used appear to be similar to those used in adults or modifications of existing regimens for paediatric sedation. Drugs commonly used include midazolam and opioids such as fentanyl or, in particular, morphine.[3] However, there has been some concern over a report of encephalopathy associated with the prolonged use of midazolam with fentanyl for sedation in infants under intensive care (see Encephalopathy, under Effects on the Nervous System, p. 1066.2). As mentioned above, propofol is not recommended for children in intensive care.

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Sleep disorders

The exact function of sleep is uncertain but it is believed to be involved in energy conservation, total body restoration and recuperation, and development and growth. There are two states of sleep: non-rapid-eye-movement (non-REM) sleep, which is subdivided into 4 stages, and rapid-eye-movement (REM) sleep, sometimes called stage 5. Initially there is a period of light sleep (stages 1 and 2) followed by deep sleep (stages 3 and 4); this latter period is also known as slow-wave sleep. After stage 4, which occurs about 90 minutes after first falling asleep, there is a period of REM sleep (stage 5) during which most dreams occur and EEG traces show high-frequency waves. During a period of sleep there are several cycles of stages 1 to 4 followed by REM sleep, with periods of non-REM sleep becoming shorter and periods of REM sleep longer. It is the slow-wave sleep that is considered to be the more restorative. Most healthy adults sleep for single periods of between 7 to 8 hours a day, although there is a wide range of normal sleeping time (from 4 to 11 hours). In old age there is less slow-wave sleep and sleep becomes more fragmented.

Sleep disorders include insomnia (see below), hypersomnia such as narcolepsy, p. 2314.3, in which the timing, length, and quality of sleep is altered, and the parasomnias (see Sleep-associated Movement Disorders, p. 1034.2) in which abnormal events occur during sleep.

Insomnia. Insomnia is the inability to achieve or maintain sleep and is the most common of the sleep disorders.[1-20] It often leaves sufferers feeling unrefreshed by sleep and may lead to impaired daytime performance.

- Transient insomnia may occur in those who normally sleep well and may be due to an alteration in the conditions that surround sleep, for example noise, or to an unusual pattern of rest as in shift work or travelling between time zones (jet lag). It may also be associated with acute disorders.
- Short-term insomnia is often related to an emotional problem or more serious medical illness such as acute pain. It may last for a few weeks and may recur.
- Chronic insomnia may be attributed to an underlying psychiatric disorder, especially depression or anxiety, to alcohol or drug abuse, to certain drug treatments, to excessive caffeine intake, to daytime napping, or to physical causes such as pain, pruritus, or dyspnoea.

Management of insomnia requires resolution of any stressful precipitant or identification and treatment of any underlying causes, with an emphasis on non-pharmacological measures such as counselling, behavioural therapy, development of relaxation techniques, and avoidance of stimulant substances. Hypnotic drugs should ideally be reserved for short courses in the acutely distressed patient; they should be avoided in the elderly, and their use is rarely justified in children. Generally, hypnotics should be given at the lowest effective dose for as short a period as possible. In transient insomnia one or two doses of a short-acting hypnotic may be indicated, whereas in short-term insomnia intermittent doses of a short-acting hypnotic given for no more than 3 weeks (preferably only 1 week) may be appropriate. Chronic insomnia rarely benefits from hypnotics and routine use of hypnotics is undesirable. Tolerance can develop rapidly (in 3 to 14 days with continuous use) and withdrawal after long-term use can lead to rebound insomnia and a withdrawal syndrome.

Benzodiazepines are generally regarded as the hypnotics of choice. They hasten sleep onset, decrease nocturnal awakenings, increase total sleeping time, and often impart a sense of deep and refreshing sleep. Slow-wave sleep and REM sleep are, however, reduced and the extra sleeping time is largely made up of relatively light sleep. A short-acting benzodiazepine such as temazepam is generally used when residual sedation is undesirable, if falling asleep is a problem, or, when necessary, in elderly patients. However, a withdrawal syndrome is more common with the short-acting benzodiazepines. Longer-acting benzodiazepines such as nitrazepam are indicated when early waking is a problem and possibly when an anxiolytic effect is needed during the day or when some impairment of psychomotor function is acceptable.

Because of the hazard of dependence with benzodiazepines (see p. 1065.1), the UK CSM[21] has issued certain recommendations:

- they should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress
- they should be given in the lowest dose which controls symptoms (if possible, intermittently)
- they should not be continued beyond 4 weeks
- they should be withdrawn by gradual tapering of the dose to zero

Subsequently, the EU Committee on Proprietary Medicinal Products (CPMP) has recommended that the treatment period should be limited to 2 weeks when brotizolam, midazolam, or triazolam are used.[22]

Tolerance to the hypnotic effects of benzodiazepines develops rapidly, with sleep latency and pattern returning to pretreatment levels within a few weeks of starting treatment.

Several other drugs have been used as alternatives to the benzodiazepines. Zaleplon, zopiclone, and zolpidem act on the same receptors or receptor subtypes as the benzodiazepines although structurally they are unrelated. Their short duration of action makes them more suitable for patients who have trouble falling asleep. The CPMP has recommended that treatment with zolpidem should be limited to a maximum of 4 weeks.[22] It remains to be proven whether these drugs offer any advantages over the benzodiazepines. Indeed, the CSM considers that zopiclone has the same potential for adverse psychiatric reactions, including dependence, as benzodiazepines.[23] NICE[24] in the UK found no compelling evidence of any clinically useful differences between these drugs and the shorter-acting benzodiazepines in terms of efficacy, adverse effects, or potential for dependence or abuse, and recommends that patients who do not respond to zaleplon, zopiclone, zolpidem, or benzodiazepines should not be switched between these hypnotics; patients may be switched if adverse effects directly related to a specific drug occur.

The tricyclic antidepressant, doxepin, may be used in the management of insomnia characterised by difficulty in sleep maintenance.[25] It is given in lower doses than those used for depression.

The use of cloral hydrate and its derivatives as hypnotics is now very limited. They have been used as alternatives to benzodiazepines in the elderly, although there is no convincing evidence of any special value in these patients. They used to be considered useful hypnotics for children but such use is rarely justified.

Clomethiazole has also been used as an alternative to benzodiazepines in the elderly. Nasal and conjunctival

irritation may be troublesome, and the danger of overdosage and risk of dependence should be considered.

Some antihistamines have hypnotic properties and a number, including alimemazine, diphenhydramine, doxylamine, and promethazine, are marketed for insomnia. They may cause troublesome antimuscarinic effects and those with longer half-lives may cause hangover effects. Promethazine is also popular for use in children, but such use is not usually justified (see Sudden Infant Death Syndrome under Adverse Effects of Promethazine, p. 639.1, for further details).

Barbiturates are no longer recommended as hypnotics because of their adverse effects. The CSM[26] has advised that barbiturates should only be used for insomnia that is severe and intractable when there are compelling reasons to, and then only in patients already taking barbiturates. It was also advised that attempts should be made to wean patients off barbiturate hypnotics. Similarly, compounds such as ethchlorvynol, and methaqualone are not recommended.

Alcohol is not recommended because it has a short weak hypnotic action, and rebound excitation can result in early morning insomnia. Its diuretic effects can interrupt sleep and chronic use can lead to rapid development of tolerance and addiction.

Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity in the treatment of insomnia. Its efficacy is difficult to substantiate and, since the publication of reports linking tryptophan with the eosinophilic-myalgia syndrome, preparations indicated for insomnia have been withdrawn from the market in many countries.

Melatonin, a hormone believed to be involved in the maintenance of circadian rhythms, may be useful in the treatment of insomnias such as those due to **jet lag**[27] or other disorders (where it might act by resetting the body clock), and in the elderly. However, its benefits have been questioned,[28] and certainly evidence for a direct hypnotic effect is less conclusive; its sleep-inducing properties are usually only seen after very high, supraphysiological concentrations have been attained.[5,6] Ramelteon, a melatonin receptor agonist, is used as a hypnotic in some countries.

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28. Buscemi N, *et al*. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006; **332:** 385–8.

Sleep-associated movement disorders. Parasomnias are motor disorders, with or without autonomic features, that occur during sleep or are exaggerated by sleep. Some of the main parasomnias include nightmares, night terrors, sleepwalking (somnambulism), nocturnal enuresis (p. 2349.1), bruxism (teeth grinding), head banging, and aggression during sleep. Other common movement disorders associated with sleep are restless legs syndrome and periodic limb movements in sleep. Parasomnias are common but rarely require treatment with drugs other than the symptomatic treatment of sleep-related medical problems. The management of some of these conditions is discussed briefly below.

The **restless legs syndrome** is characterised by an unpleasant creeping sensation deep in the legs with an irresistible urge to move them. Symptoms begin during relaxation in the evenings and in bed, and interfere with the ability to fall asleep. The aetiology of this condition is obscure and treatment has been largely empirical.[1-11] Drug treatment may not always be necessary and non-pharmacological methods such as good sleep hygiene should be tried initially.[1,3,7,8,12] There have been reports of efficacy with a wide range of treatments, although few have been well studied. Dopaminergic therapy has emerged as a common first-line treatment, a long-acting agonist, such as cabergoline, pergolide, pramipexole, or ropinirole, being preferred in order to avoid the complications associated with levodopa.[5,6,8-12] Anticonvulsants, such as carbamazepine, clonazepam, and gabapentin may be of use in those intolerant of dopamine agonists or in those who require additional medication.[5,8-11] Other drugs that have been reported to be of benefit include some opioids, clonidine, and the benzodiazepines.[5,7-12] Iron supplementation may be effective if the syndrome is associated with iron deficiency.[2-4,7-12] Many patients with restless legs syndrome exhibit **periodic limb movements in sleep**,[2,3] characterised by repetitive periodic leg and foot jerking during sleep. Treatments tried are similar to those for the restless legs syndrome; clonazepam and levodopa are amongst the drugs shown to be of benefit.

Some **parasomnias** have responded to treatment with benzodiazepines.[13-15] These include bruxism, head banging, aggression during sleep, night terrors, and sleepwalking.

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6. Hening WA, *et al*. American Academy of Sleep Medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 2004; **27:** 560–83. Also available at: http://journalsleep.org/Articles/270329.pdf (accessed 15/08/08)
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14. Wills L, Garcia J. Parasomnias: epidemiology and management. *CNS Drugs* 2002; **16:** 803–10.
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Acamprosate Calcium

(BANM, USAN, rINNM)

Acamprosat-Calcium; Acamprosate calcique; Acamprosate de Calcium; Acamprosato de calcio; Acamprosatum calcicum; Akamprosaattikalsium; Akamprosát vápenatá sůl; Akamprosatkalcium; Akamprosato kalcio druska; Akamprozát-kalcium; Calcii Acamprosatum; Calcium Acetylhomotaurinate; Кальций Акампрозат.

Calcium 3-acetamido-1-propanesulphate.

$C_{10}H_{20}CaN_2O_8S_2$=400.5

CAS — 77337-76-9 (acamprosate); 77337-73-6 (acamprosate calcium).

ATC — N07BB03.

UNII — 59375N1D0U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Acamprosate Calcium). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 5.5 to 7.0.

Uses and Administration

Acamprosate has a chemical structure similar to that of the endogenous amino acid, homotaurine, which is a structural analogue of gamma-aminobutyric acid (GABA—p. 2509.2) and taurine (p. 2626.2). It is given as the calcium salt to prevent relapse in alcoholics who have been weaned off alcohol (below). The usual oral dose is 666 mg of acamprosate calcium given three times daily. In patients weighing less than 60 kg a suitable dose is 666 mg at breakfast followed by 333 mg at midday and 333 mg at night. For doses in patients with renal impairment, see below. Treatment should be started as soon as possible after alcohol withdrawal and maintained, even if the patient relapses, for the recommended period of 1 year.

Administration in renal impairment. It is considered[1] likely that accumulation of acamprosate would occur with prolonged use of therapeutic doses in patients with renal impairment. It has been reported that the mean maximum concentration of acamprosate after a single 666-mg oral dose was 813 nanograms/mL in 12 patients with moderate or severe renal impairment compared with 198 nanograms/mL in 6 healthy subjects; values for the plasma elimination half-life were 47 and 18 hours, respectively.

Licensed product information in the UK contra-indicates the use of acamprosate in patients with renal impairment (serum creatinine greater than 120 micromoles/litre). US licensed product information also contra-indicates the use of acamprosate in those with severe renal impairment (creatinine clearance (CC) less than 30 mL/minute). However, in those with moderate impairment (CC 30 to 50 mL/minute), an initial oral dose of 333 mg three times daily may be given.

1. Wilde MI, Wagstaff AJ. Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 1997; **53:** 1038–53.

Alcohol dependence. Acamprosate is considered to be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p. 1735.1). A systematic review[1] of 24 randomised, placebo-controlled studies involving 6915 patients concluded that acamprosate helps to prevent relapse and increase the number of drink-free days during treatment and possibly for up to one year thereafter. However, other outcomes such as preventing a return to heavy drinking were not statistically significant with acamprosate treatment; in addition, its use with naltrexone did not produce any additional benefit.

Several mechanisms have been proposed to account for acamprosate's action including inhibition of neuronal hyperexcitability by antagonising excitatory amino acids such as glutamate.

1. Rösner S, *et al*. Acamprosate for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2010 (accessed 01/02/11).

Gambling. A case report of a patient who noticed that she was able to avoid excessive gambling while receiving treatment with acamprosate for alcoholism.[1]

1. Raj YP. Gambling on acamprosate: a case report. *J Clin Psychiatry* 2010; **71:** 1245–6.

Tinnitus. Acamprosate has been tried[1] in the management of tinnitus (p. 1994.1) with some beneficial results.

1. Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: double-blind study. *Braz J Otorhinolaryngol* 2005; **71:** 618–23.

Adverse Effects

The main adverse effect of acamprosate is dose-related diarrhoea; nausea, vomiting, and abdominal pain occur less frequently. Other adverse effects have included pruritus, and occasionally a maculopapular rash; bullous skin reactions have occurred rarely. Depression and fluctuations in libido have also been reported. Hypersensitivity reactions including urticaria, angioedema, and anaphylaxis have been reported very rarely.

Effects on the skin. A case of erythema multiforme in a woman with cirrhosis of the liver has been attributed to use of acamprosate[1] although both the diagnosis and any association with acamprosate have been seriously challenged.[2]

1. Fortier-Beaulieu M, *et al*. Possible association of erythema multiforme with acamprosate. *Lancet* 1992; **339:** 991.
2. Potgieter AS, Opsomer L. Acamprosate as cause of erythema multiforme contested. *Lancet* 1992; **340:** 856–7.

Precautions

Acamprosate is not metabolised via the liver and its pharmacokinetics are not altered in patients with mild to moderate hepatic impairment (Child-Pugh Classes A and B); no change in dose is required in such patients. In patients with severe hepatic impairment (Child-Pugh Class C), UK licensed product information contra-indicates the

use of acamprosate although no advice is provided in US licensed information. For precautions regarding the use of acamprosate in patients with renal impairment, see under Uses and Administration, p. 1034.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acamprosate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/07/11)

Pharmacokinetics

Absorption of acamprosate from the gastrointestinal tract is slow but sustained and is subject to considerable interindividual variation. Steady-state concentrations occur after dosage for 7 days. Bioavailability is reduced if given with food. Acamprosate is not protein bound and although it is hydrophilic it is reported to cross the blood-brain barrier. Acamprosate does not appear to be metabolised and is excreted unchanged in the urine. The elimination half-life after oral doses has been reported to be about 33 hours.

References.

1. Saivin S, *et al.* Clinical pharmacokinetics of acamprosate. *Clin Pharmacokinet* 1998; **35**: 331–45.
2. Xu F, *et al.* Pharmacokinetics of acamprosate calcium in healthy Chinese subjects after oral administration of three dosage levels. *Arzneimittelforschung* 2009; **59**: 631–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Campral; ***Austral.***: Campral; ***Austria***: Campral; ***Belg.***: Campral; ***Canad.***: Campral; ***Chile***: Campral; ***Cz.***: Campral; ***Denm.***: Campral; ***Fr.***: Aotal; ***Ger.***: Campral; ***Hung.***: Campral†; ***India***: Acamprol; ***Irl.***: Campral; ***Jpn***: Regtect; ***Mex.***: Campral†; ***Neth.***: Campral; ***Norw.***: Campral; ***Pol.***: Campral; ***Port.***: Campral; ***S.Afr.***: Besobrial; ***Singapore***: Campral; ***Spain***: Campral; Zulex†; ***Swed.***: Campral; ***Switz.***: Campral; ***Turk.***: Campral; ***UK***: Campral; ***USA***: Campral.

Acecarbromal *(rINN)*

Acécarbromal; Acecarbromalum; Acetcarbromal; Acetylcarbromal; Ацекарбромал.

N-Acetyl-*N*′-(2-bromo-2-ethylbutyryl)urea.

$C_9H_{15}BrN_2O_3$=279.1

CAS — 77-66-7.

UNII — E47C56IGOY.

Profile

Acecarbromal is a bromureide with similar actions to those of carbromal (p. 1044.1). It has been used for its sedative properties but the use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Afrodor†; ***Rus.***: Afrodor (Афродор)†.

Acepromazine *(BAN, rINN)*

Acepromazin; Acepromazina; Acépromazine; Acepromazinum; Asepromatsiini; Ацепромазин.

10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

$C_{19}H_{22}N_2OS$=326.5

CAS — 61-00-7.

ATC — N05AA04.

ATC Vet — QN05AA04.

UNII — 54EJ303F0R.

Acepromazine Maleate *(BANM, USAN, rINNM)*

Acepromazina, maleato de; Acépromazine, Maléate d'; Acepromazini Maleas; Acetylpromazine Maleate; Asepromazin Maleat; Maleato de acepromazina; Ацепромазина Малеат.

10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone hydrogen maleate.

$C_{19}H_{22}N_2OS,C_4H_4O_4$=442.5

CAS — 3598-37-6.

ATC — N05AA04.

ATC Vet — QN05AA04.

UNII — 37862HP2OM.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet)*.

BP(Vet) 2014: (Acepromazine Maleate). A yellow crystalline powder. Soluble in water and in alcohol; freely soluble in chloroform; slightly soluble in ether. A 1% solution in water has a pH of 4.0 to 4.5.

USP 36: (Acepromazine Maleate). pH of a 1% solution is between 4.0 and 5.5. Protect from light.

Profile

Acepromazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has been given orally as the maleate in the treatment of anxiety disorders, hiccups, and nausea and vomiting. Doses equivalent to 10 to 20 mg of the base may be given as a single dose or up to three times daily for anxiety disorders; lower doses have been given for hiccups, and nausea and vomiting.

Acepromazine, as the base, has also been given in preparations for the management of insomnia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Plegicil; ***Turk.***: Plegicil.

Multi-ingredient Preparations. ***Fr.***: Noctran†.

Aceprometazine *(rINN)*

16-64 CB; Aceprometazina; Acéprométazine; Aceprometazinum; Ацепрометазин.

10-(2-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

$C_{19}H_{22}N_2OS$=326.5

CAS — 13461-01-3.

UNII — 984N9YTM4Y.

Profile

Aceprometazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It is available usually as the maleate in preparations for the management of insomnia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Mepronizine†; Noctran†.

Allobarbital *(USAN, rINN)*

Allobarbitaali; Allobarbitalum; Alfobarbitone; Alobarbital; Diallylbarbitone; Diallylbarbituric Acid; Diallylmalonylurea; Diallymalum; NSC-9324; Аллобарбитал.

5,5-Diallylbarbituric acid.

$C_{10}H_{12}N_2O_3$=208.2

CAS — 52-43-7.

ATC — N05CA21.

ATC Vet — QN05CA21.

UNII — 8NT43GG2HA.

Profile

Allobarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used in combination preparations for the treatment of sleep disorders and pain but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Demalgonil†; ***Pol.***: Krople Zoladkowe†; Pabialgin P†; ***Turk.***: Spasmo-Panalgine.

Alprazolam *(BAN, USAN, rINN)*

Alpratsolaami; Alprazolám; Alprazolamas; Alprazolamum; U-31889; Алпразолам.

8-Chloro-1-methyl-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine.

$C_{17}H_{13}ClN_4$=308.8

CAS — 28981-97-7 (alprazolam).

ATC — N05BA12.

ATC Vet — QN05BA12.

UNII — YU55MQ3IZY.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of alprazolam:

Bars; Benzo; Coffins; Dogbones; Fo' Bars; Fo's; Footballs; Forgetful Pills; Four Bars; French Fries; Gold Bars; Green Bars; Quad bar; School Buses; Sticks; Totem Poles; White Bars; X-Boxes; Xan-Bars; Xannies; Xanny; Xany Bars; Zanny; Zan-Bars; Zannies; Zanny-Bars; Zany bar; Zbars; Z-Bars.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Alprazolam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Alprazolam). A white to off-white crystalline powder. Insoluble in water; soluble in alcohol; sparingly soluble in acetone; freely soluble in chloroform; slightly soluble in ethyl acetate.

Uses and Administration

Alprazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term treatment of anxiety disorders (below) in oral doses of 250 to 500 micrograms three times daily, increased where necessary every 3 to 4 days to a total daily dose of 3 or 4 mg.

In the treatment of panic disorder, with or without agoraphobia, initial oral doses of 500 micrograms may be given three times daily, increased where necessary in steps of no more than 1 mg every 3 to 4 days; doses of up to 10 mg daily have been used.

In elderly or debilitated patients, an initial dose of 250 micrograms two or three times daily has been suggested. For doses in patients with hepatic or renal impairment, see below.

A modified-release preparation of alprazolam is also available for once-daily dosing.

Reviews.

1. Verster JC, Volkerts ER. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. *CNS Drug Rev* 2004; **10**: 45–76.

Administration in hepatic or renal impairment. UK licensed product information advises caution when using alprazolam in patients with hepatic or renal impairment; it is contra-indicated in those with severe hepatic impairment. In the USA, licensed product information states that patients with advanced liver disease may be given an initial oral dose of 250 micrograms two or three times daily.

Anxiety disorders. Alprazolam has been tried in the management of anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1).

References.

1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160**: 191–202.
2. Lepola UM, *et al.* Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; **8**: 115–18.
3. Pollack MH, *et al.* Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol* 1993; **13**: 257–63.
4. Spiegel DA. Efficacy studies of alprazolam in panic disorder. *Psychopharmacol Bull* 1998; **34**: 191–5.
5. Rickels K. Alprazolam extended-release in panic disorder. *Expert Opin Pharmacother* 2004; **5**: 1599–1611.
6. Uhlenhuth EH, *et al.* Cognitive style, alprazolam plasma levels, and treatment response in panic disorder. *Depress Anxiety* 2008; **25**: E18–E26.

Depression. Although they may be useful for associated anxiety, benzodiazepines are not usually considered appropriate for treatment of depression (p. 398.1); however, some drugs such as alprazolam have been tried for this indication.[1]

1. Kravitz HM, *et al.* Alprazolam and depression: a review of risks and benefits. *J Clin Psychiatry* 1993; **54:** (suppl): 78–84.

Premenstrual syndrome. Alprazolam has been reported[1-3] to produce a marginal to good response in the premenstrual syndrome (p. 2272.3) but others have not found it to be of benefit,[4] and the role of benzodiazepines is limited by their adverse effects. If benzodiazepines are selected it is recommended that in order to reduce the risk of dependence and withdrawal symptoms they should be carefully restricted to the luteal phase in selected patients.[5] Withdrawal symptoms may be more severe after short-acting drugs such as alprazolam. Antidepressant drugs such as SSRIs may be preferred.

1. Smith S, *et al.* Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol* 1987; **70**: 37–43.
2. Harrison WM, *et al.* Treatment of premenstrual dysphoria with alprazolam: a controlled study. *Arch Gen Psychiatry* 1990; **47**: 270–5.
3. Freeman EW, *et al.* A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995; **274**: 51–7.
4. Evans SM, *et al.* Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. *Neuropsychopharmacology* 1998; **19**: 499–516.
5. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. *Drug Safety* 1994; **10**: 160–9.

Tinnitus. Alprazolam has been tried[1-4] in the management of tinnitus (p. 1994.1) although adverse effects can limit usefulness.

1. Johnson RM, *et al.* Use of alprazolam for relief of tinnitus: a double-blind study. *Arch Otolaryngol Head Neck Surg* 1993; **119:** 842–5.
2. Huynh L, Fields S. Alprazolam for tinnitus. *Ann Pharmacother* 1995; **29:** 311–12.
3. Vernon JA, Meikle MB. Masking devices and alprazolam treatment for tinnitus. *Otolaryngol Clin North Am* 2003; **36:** 307–20.
4. Jalali MM, *et al.* The effects of alprazolam on tinnitus: a cross-over randomized clinical trial. *Med Sci Monit* 2009; **15:** PI55–PI60.

Dependence and Withdrawal

As for Diazepam, p. 1065.1. Dependence may be a particular problem at the high doses used in the treatment of panic disorder.

For the purpose of withdrawal regimens, 250 micrograms of alprazolam may be considered equivalent to about 5 mg of diazepam.

Withdrawal symptoms. Nonconvulsive status epilepticus was reported[1] in a 64-year-old man with renal insufficiency who had stopped taking alprazolam 1 mg nightly after having taken it for several years; the authors noted that this symptom has also been reported with the withdrawal of diazepam and lorazepam.

1. Olnes MJ, *et al.* Nonconvulsive status epilepticus resulting from benzodiazepine withdrawal. *Ann Intern Med* 2003; **139:** 956–8.

Adverse Effects and Treatment

As for Diazepam, p. 1065.3.

Effects on the liver. A patient receiving phenelzine for depression developed abnormal liver enzyme values on 2 occasions when alprazolam was added to the treatment.[1] It was not possible to say if this was due to alprazolam alone or a synergistic effect with phenelzine.

1. Roy-Byrne P, *et al.* Alprazolam-related hepatotoxicity. *Lancet* 1983; **ii:** 786–7.

Effects on the skin. There have been some reports of alprazolam-induced photosensitivity.[1,2]

1. Kanwar AJ, *et al.* Photosensitivity due to alprazolam. *Dermatologica* 1990; **181:** 75.
2. Watanabe Y, *et al.* Photosensitivity due to alprazolam with positive oral photochallenge test after 17 days administration. *J Am Acad Dermatol* 1999; **40:** 832–3.

Overdosage. A retrospective analysis[1] of 2063 hospital admissions for benzodiazepine overdosage in one region of Australia between January 1987 and October 2002 found that patients who took an overdose of alprazolam were about twice as likely to require admission to intensive care as those taking other benzodiazepines. Flumazenil was required in 14% of the 131 alprazolam overdoses, and ventilation in 16%, which was also significantly more than for other benzodiazepines. Given the apparently greater toxicity of alprazolam in overdosage, its increasing prescription to groups at risk of self-poisoning was of concern.

1. Isbister GK, *et al.* Alprazolam is relatively more toxic than other benzodiazepines in overdose. *Br J Clin Pharmacol* 2004; **58:** 88–95.

Precautions

As for Diazepam, p. 1066.3.

Abuse. High doses of alprazolam taken after maintenance doses of methadone produced a 'high' without pronounced sedation; the drug was also misused by nonopioid-drug abusers.[1] The usual urine toxicology screens for benzodiazepines often give false-negative results for alprazolam because of the extremely low concentrations of metabolites excreted, making abuse difficult to detect. A subsequent review[2] considered that the literature did not support the widely held belief that alprazolam had a greater liability for abuse than other benzodiazepines, but the possibility could not be discounted.

1. Weddington WW, Carney AC. Alprazolam abuse during methadone maintenance therapy. *JAMA* 1987; **257:** 3363.
2. Rush CR, *et al.* Abuse liability of alprazolam relative to other commonly used benzodiazepines: a review. *Neurosci Biobehav Rev* 1993; **17:** 277–85.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of alprazolam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

From a study[2] of the distribution of alprazolam into breast milk in 8 women it was estimated that the average daily dose of alprazolam ingested by a breast-fed infant would range from 0.3 to 5 micrograms/kg or about 3% of a maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Oo CY, *et al.* Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk. *Br J Clin Pharmacol* 1995; **40:** 231–6.

Handling. Care should be taken to prevent inhaling particles of alprazolam and exposing the skin to it.

Hepatic impairment. Oral alprazolam 1 mg was absorbed more slowly in 17 patients with alcoholic cirrhosis with no ascites than in 17 healthy subjects.[1] Mean peak alprazolam concentrations occurred after 3.34 hours in the cirrhotic patients and 1.47 hours in the healthy subjects. Mean elimination half-life for cirrhotic patients was 19.7 hours compared with 11.4 hours for healthy subjects. However, there were no significant differences in the maximum plasma concentrations achieved. The results indicate that alprazolam, in common with other benzodiazepines that undergo oxidative metabolism, would accumulate to a greater extent in patients with alcoholic liver disease than in healthy subjects; the daily dose of alprazolam may need to be reduced by half in this population. See also Administration in Hepatic or Renal Impairment, p. 1035.3.

1. Juhl RP, *et al.* Alprazolam pharmacokinetics in alcoholic liver disease. *J Clin Pharmacol* 1984; **24:** 113–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alprazolam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Alprazolam is well absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations occurring within 1 to 2 hours of a dose. The mean plasma half-life is 11 to 15 hours. Alprazolam is 70 to 80% bound to plasma proteins, mainly albumin. It is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4. Metabolites include α-hydroxyalprazolam, which is reported to be about half as active as the parent compound, 4-hydroxyalprazolam, and an inactive benzophenone. Plasma concentrations of metabolites are very low. Alprazolam is excreted in the urine as unchanged drug and metabolites.

References.

1. Greenblatt DJ, Wright CE. Clinical pharmacokinetics of alprazolam: therapeutic implications. *Clin Pharmacokinet* 1993; **24:** 453–71.
2. Wright CE, *et al.* Pharmacokinetics and psychomotor performance of alprazolam: concentration-effect relationship. *J Clin Pharmacol* 1997; **37:** 321–9.
3. Kaplan GB, *et al.* Single-dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. *J Clin Pharmacol* 1998; **38:** 14–21.
4. Park J-Y, *et al.* Effect of CYP3A5*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. *Clin Pharmacol Ther* 2006; **79:** 590–9.
5. Glue P, *et al.* Pharmacokinetics of an extended release formulation of alprazolam (Xanax XR) in healthy normal adolescent and adult volunteers. *Am J Ther* 2006; **13:** 418–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alplax; Alprazol; Amziax; Ansielix; Aplacaina†; Bayzolam; Becede; Bestrol; Calmol; Droxol; Emeral; Isoproxal; Krama; Medronal†; Nivelan N; Novazolam; Pirval; Plasedan†; Prenadona†; Prinox; Psicosedol†; PTA; Razolam; Relaxten; Rilow; Rospaz; Silarten†; Tensium; Thiprasolan; Tranquinal; Xanax; ***Austral.***: Alprax; Kalma; Ralozam; Xanax; ***Austria***: Alprastad; Xanor; ***Belg.***: Alpraz; Alprazomed; Docalprazo†; Topazolam†; Xanax; ***Braz.***: Alfron; Altrox; Apraz; Constante; Frontal; Neozolam; Teufron; Tranquinal; Zoldac; ***Canad.***: Apo-Alpraz; Novo-Alprazol†; Nu-Alpraz; Xanax; ***Chile***: Adax; Grifoalpram†; Prazam; Sanerva; Tricalma; Zotran; ***Cz.***: Frontin; Helex; Neurol; Xanax; ***Denm.***: Alprox; Tafil; ***Fin.***: Alprox; Xanor; ***Fr.***: Xanax; ***Ger.***: Cassadan†; Tafil; ***Gr.***: Antanax; Saturnil; Xanax; ***Hong Kong***: Alprax; Kalma†; Nalion†; Renax†; Xanax; ***Hung.***: Frontin; Helex; Xanax; ***India***: Alap; Aleez; Alep; Alltop; Alp; Alpam; Alparazole; Alpkair; Alpose; Alpra; Alpradol-MD; Alpraquil; Alprax; Alprocontin†; Alprose; Alprosym; Alrif; Alzex; Alzoact; Alzocum; Alzokam; Alzolam; Alzomax; Alzopax; Alzot; Alzy; Anax; Anxicalm; Anxico; Anxit; Anxorel; Anxyl; Anzal; Anzi; Anzilum; Atam; Ateez; Atrest; Balmusa; Berest; Besquil; Bio Zolam; Bliz MD; Calmtec; Dalp; Eurelax; Eurolam; FAD; Finezol; Hiprazole; Indolam; Jolistar; Kaprolam; L-Peez; Lamcin; Loral; Luzarn; Manorest; Morecalm; Nitril; Norex; Notence; Onapract; Pacyl; Restyl; Tranax; Xycalm; Zolam; ***Indon.***: Actazolam; Alganax; Alviz; Apazol; Atarax; Calmlet†; Feprax; Frixitas; Grazolam; Soxietas†; Xanax; Zolastin; Zypraz; ***Irl.***: Alprol; Alprox†; Calmax; Gerax; Xanax; ***Israel***: Alpralid; Alprox; Xanagis; Xanax; ***Ital.***: Alpravecs; Alprazig; Frontal; Mialin; Valeans; Xanax; ***Malaysia***: Alpraline; Alpranax; Apo-Alpraz; Asolan; Besquil; Prazovex; Xanax; ***Mex.***: Alzam; Farmapram; Irizz; Neupax; Noxeprom; Pisalpra; Tafil; Tazun; ***Neth.***: Xanax; ***Norw.***: Xanor; ***NZ***: Xanax; ***Philipp.***: Altrox; Xanor; ***Pol.***: Afobam; Alprazomerck; Alprox; Neurol; Xanax; Zomiren; ***Port.***: Pazolam; Prazam; Unilan; Xanax; ***Rus.***: Alzolam (Алзолам); Helex (Хелекс); Neurol (Неурол); Xanax (Ксанакс); Zolomaks (Золомакс); ***S.Afr.***: Adco-Alzam; Azor; Xanor; Zopax; ***Singapore***: Alzolam; Apo-Alpraz; Dizolam; Xanax; Zacetin; ***Spain***: Trankimazin; ***Swed.***: Xanor; ***Switz.***: Xanax; ***Thai.***: Alcelam; Allam; Alnax; Alpazam; Alpralan; Alpramed; Alprax†; Anax†; Anpress; Dizolam†; Farzolam; Inzolam; Manex†; Marzolam; Mitranax; Moxinax; Pharnax; Prazol; Siampraxol; Sunax; Xalam; Xanacine; Xanax; Xiemed; Zolam; ***Turk.***: Xanax; ***UK***: Xanax; ***USA***: Niravam; Xanax; ***Venez.***: Abaxon; Alpram; Ansilan; Tafil.

Multi-ingredient Preparations. ***Arg.***: Alplax Digest; Alplax Net; Ansielix Digest; Euciton Stress; Sidomal; Tensium Gastric; Tranquinal Soma; ***India***: Alamflu; Alltop-P; Alltop-S; Alp-FT; Alp-FTD; Alprax Forte; Alprax Plus; Alprax Z; Alprine Plus; Alprine-H; Altalin; Altin; Alzex Forte; Alzex Plus; Ambulax-HD; Ambulax-M; Ambulax; Anxit Forte; Anxit Plus; Anzi-P; Ateez-F; Azo-F; Azo-O; Azo-S; Balmusa Plus; Calmtec-P; Cam Plus; Cardilax; Censir Forte; Cooltime; Coral-F; Depten-AZ; Depwell; Destres; Exiten Plus; Faa Plus; Faxtin-A; Fiden-AZ; Fludep Plus; Fludep-AZ; Flumusa; Fluwel; Fluxin-AL; Fluzolam; Kurelam-F; L-Peez F; L-Peez S; Manorest Forte; Manorest Plus; MCalm; Mebasap-AL; Mebrin-AZ; Meloprax; Mentolift-Plus; Restyl Forte; Restyl Plus; Stresnil; Zopax Plus; ***Mex.***: Neupax Duo-S.

Pharmacopoeial Preparations

USP 36: Alprazolam Extended-release Tablets; Alprazolam Oral Suspension; Alprazolam Orally Disintegrating Tablets; Alprazolam Tablets.

Amisulpride *(BAN, rINN)*

Amisülprid; Amisulprid; Amisulprida; Amisulpridas; Amisulpridi; Amisulpridum; Amiszulprid; DAN-216; Амисульприд.

4-Amino-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulphonyl)-2-methoxybenzamide; (*RS*)-4-Amino-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-(ethylsulfonyl)-*o*-anisamide.

$C_{17}H_{27}N_3O_4S$=369.5

CAS — 71675-85-9.

ATC — N05AL05.

ATC Vet — QN05AL05.

UNII — 8110R61I4U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. & (Amisulpride). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane.

Uses and Administration

Amisulpride is a substituted benzamide atypical antipsychotic. It is reported to have a high affinity for dopamine D_2 and D_3 receptors. Amisulpride is used mainly in the management of psychoses such as schizophrenia (below) but in some countries it has also been tried in depression (p. 398.1).

For acute psychotic episodes, a daily dosage of between 400 and 800 mg may be given orally in 2 divided doses, increased if necessary to 1.2 g daily. For patients with mainly negative symptoms, daily doses between 50 and 300 mg are recommended. Daily doses of up to 300 mg may be given as a single dose. Amisulpride has also been given by intramuscular injection in doses of 400 mg daily.

Reduced doses are recommended in patients with renal impairment, see below.

Although unlicensed in the UK for use in children and adolescents aged under 18 years, the *BNFC* suggests that those aged from 15 to 18 years may be given the usual oral adult dose of amisulpride for the same indications (see above).

Administration in children. For details of uses and associated doses in adolescents, see Uses and Administration, above.

Administration in renal impairment. For patients with renal impairment, the oral dose of amisulpride should be reduced according to creatinine clearance (CC):

- CC between 30 and 60 mL/minute: half the usual dose (see Uses and Administration, above)
- CC between 10 and 30 mL/minute: one-third the usual dose

Similar reductions are also recommended when amisulpride is given intramuscularly.

Schizophrenia. Reviews[1-3] of amisulpride indicate that it may be more effective than classical antipsychotics against general and negative symptoms of schizophrenia (p. 1031.3), and has fewer extrapyramidal adverse effects.

1. Leucht S, *et al.* Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002; **159:** 180–90.

2. Mota Neto JIS, *et al.* Amisulpride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 24/05/05).
3. Pani L, *et al.* Practical issues with amisulpride in the management of patients with schizophrenia. *Clin Drug Investig* 2008; **28:** 465–77.

Adverse Effects, Treatment, and Precautions

Although amisulpride may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Insomnia, anxiety, and agitation are common adverse effects with amisulpride. Other less common effects include drowsiness and gastrointestinal disorders such as constipation, nausea, vomiting, and dry mouth. Allergic reactions, abnormal liver function tests, and seizures have been reported rarely.

Hyperprolactinaemia, which may result in galactorrhoea, amenorrhoea, impaired fertility, gynaecomastia, breast pain, and sexual dysfunction, has occurred with amisulpride use. Weight gain has also been noted. Dose-related extrapyramidal dysfunction may occur, but symptoms such as acute dystonia, parkinsonism, and akathisia are generally mild at licensed doses. Tardive dyskinesia has been reported after long-term use and there have been rare cases of neuroleptic malignant syndrome. Hypotension and bradycardia have been reported occasionally; QT prolongation, in rare cases leading to torsade de pointes, has also been noted. The risk of QT prolongation is increased by pre-existing conditions such as bradycardia, hypokalaemia, and congenital or acquired QT prolongation; patients should be reviewed for these conditions before starting amisulpride treatment. Certain medications may also increase the risk (see Interactions, below).

Amisulpride should not be given to patients with phaeochromocytoma or prolactin-dependent tumours. It should be used with caution in patients with severe renal impairment, or a history of epilepsy or Parkinson's disease. The risk of hypotension and sedation is increased in elderly patients.

Amisulpride may affect the performance of skilled tasks including driving.

Withdrawal symptoms have occurred rarely when amisulpride has been stopped abruptly; a gradual dose reduction may be appropriate when stopping amisulpride.

Effects on body-weight. A review[1] has suggested that the risk of weight gain with amisulpride treatment is less than with olanzapine or risperidone, although cases have been reported.[2] The increased risk of weight gain with some atypical antipsychotics is also discussed under Adverse Effects of Clozapine, p. 1059.1.

1. McKeage K, Plosker GL. Amisulpride: a review of its use in the management of schizophrenia. *CNS Drugs* 2004; **18:** 933–56.
2. Papadimitriou GN, *et al.* Acute weight gain induced by amisulpride monotherapy in a first-episode schizophrenic patient. *Int Clin Psychopharmacol* 2006; **21:** 181–4.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Overdosage. The effects of overdosage of amisulpride in 2 patients have been reported.[1] The first patient had taken about 3 g of amisulpride and an unknown amount of dosulepin and was found to have had a blood-amisulpride concentration of 9.63 micrograms/mL. Generalised convulsions, which resolved spontaneously, were followed by coma, motor restlessness, tachycardia, and slight prolongation of the QT interval. The patient was treated with gastric lavage and had recovered within 48 hours. The second patient, who had been found dead, had a blood-amisulpride concentration of 41.7 micrograms/mL. Severe cardiotoxicity occurred in 4 further cases of amisulpride overdoses of between about 4 and 32 g reported to Australian poisons information centres;[2] all 4 had marked QT prolongation, with bundle branch block or torsade de pointes, and one, who was thought to have ingested between 16 and 24 g, died after cardiac arrest.

1. Tracqui A, *et al.* Amisulpride poisoning: a report on two cases. *Hum Exp Toxicol* 1995; **14:** 294–8.
2. Isbister GK, *et al.* Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsades de pointes. *Med J Aust* 2006; **184:** 354–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amisulpride as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

Amisulpride should not be given with drugs that may induce arrhythmias (including torsade de pointes); such drugs include some antiarrhythmics, cisapride, thioridazine, erythromycin, and halofantrine. The risk of arrhythmias is also increased with drugs that prolong the QT interval, such as pimozide, haloperidol, and tricyclic antidepressants, and with drugs that produce bradycardia or hypokalaemia, including beta blockers, some calcium-channel blockers, clonidine, digoxin, guanfacine, potassium-depleting diuretics, and lithium; use of these drugs with amisulpride requires caution.

The central effects of other CNS depressants including alcohol may be enhanced by amisulpride. Amisulpride may also enhance the effects of antihypertensive drugs. The dopamine-blocking activity of amisulpride may antagonise the actions of dopaminergics such as levodopa and they should not be given together.

In 7 patients receiving amisulpride, introduction of *lithium* resulted in an average increase of 32% of the dose-corrected plasma concentration of amisulpride.[1] An earlier study had noted that plasma concentrations of amisulpride were raised in patients also taking *clozapine*.[2]

1. Bergemann N, *et al.* Increase in plasma concentrations of amisulpride after receiving co-medication with lithium. *Pharmacopsychiatry* 2005; **38:** 44.
2. Bergemann N, *et al.* Plasma amisulpride levels in schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol* 2004; **14:** 245–50.

Pharmacokinetics

Amisulpride is absorbed from the gastrointestinal tract but bioavailability is reported to be only about 48%. An initial peak in plasma concentration has been reported to occur 1 hour after oral doses and a second higher peak after 3 to 4 hours. Plasma protein binding is reported to be only about 16%. Metabolism is limited, with most of a dose appearing in the urine as unchanged drug. The terminal elimination half-life is about 12 hours.

References.

1. Rosenzweig P, *et al.* A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol* 2002; **17:** 1–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Enorden; ***Austral.***: Amipride; Solian; Sulprix; ***Austria***: Solian; ***Belg.***: Solian; ***Braz.***: Socian; ***Chile***: Socian; ***China***: Solian (索里昂); ***Cz.***: Amilia; Deniban; Solian; ***Denm.***: Amitrex†; Solian; ***Fr.***: Solian; ***Ger.***: Amisulid†; Solian; ***Gr.***: Goldalian; Isofredil; Matil; Nodasic; Prilarem; Solamid; Solian; Sulpisal; Zoloser; ***Hong Kong***: Solian; ***Hung.***: Amiprid; Amitrex; Asulpan; ***India***: Amgrace; Amigold; Goldpride; ***Irl.***: Solian; ***Israel***: Solian; ***Ital.***: Deniban; Solian; Sulamid; ***Malaysia***: Solian; ***Mex.***: Solian; ***Norw.***: Solian; ***NZ***: Solian; ***Philipp.***: Solian; ***Pol.***: Amisan; Solian; ***Port.***: Amitrex; Socian; ***Rus.***: Lymipranil (Лимипранил); Solian (Солиан); ***S.Afr.***: Solian; ***Singapore***: Solian; ***Spain***: Aracalm; Misulmylan†; Solian; ***Switz.***: Solian; ***Turk.***: Paxiprid; Solian; ***UK***: Solian; ***Ukr.***: Soleron (Солерон); Solian (Солиан).

Pharmacopoeial Preparations
BP 2014: Amisulpride Oral Solution; Amisulpride Tablets.

Amobarbital *(BAN, rINN)*

Amobarbitaali; Amobarbitál; Amobarbitalis; Amobarbitalum; Amylobarbitone; Pentymalum; Амобарбитал.

5-Ethyl-5-isopentylbarbituric acid.

$C_{11}H_{18}N_2O_3$=226.3

CAS — 57-43-2.

ATC — N05CA02.

ATC Vet — QN05CA02.

UNII — GWH6IJ239E.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of amobarbital:

Amys; Birds; Blue; Blue angels; Blue birds; Blue bullets; Blue clouds; Blue devils; Blue dolls; Blue heaven; Blue heavens; Blues.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Amobarbital). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol; soluble in dichloromethane. Forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Amobarbital Sodium *(BANM, rINNM)*

Amobarbitaalinatrium; Amobarbital-Natrium; Amobarbital sódico; Amobarbital sodique; Amobarbital sodná sůl; Amobarbitalio natrio druska; Amobarbitalnatrium; Amobarbitál-nátrium; Amobarbitalum Natricum; Amylobarbitone Sodium; Barbamylum; Natrii Amobarbitalum; Pentymalnatrium; Sodium Amobarbital; Soluble Amylobarbitone; Натрий Амобарбитал.

Sodium 5-ethyl-5-isopentylbarbiturate.

$C_{11}H_{17}N_2NaO_3$=248.3

CAS — 64-43-7.

ATC — N05CA02.

ATC Vet — QN05CA02.

UNII — G0313KNC7D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Jpn includes Amobarbital Sodium for Injection.

Ph. Eur. 8: (Amobarbital Sodium). A white or almost white, hygroscopic, granular powder. Very soluble in carbon dioxide-free water (a small fraction may be insoluble); freely soluble in alcohol. A 10% solution in water has a pH of not more than 11.0. Store in airtight containers.

USP 36: (Amobarbital Sodium). A white, odourless, hygroscopic, friable, granular powder. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. Solutions decompose on standing; decomposition is accelerated by heat. pH of a 10% solution in water is not more than 11.0. Store in airtight containers.

Incompatibility. Amobarbital may be precipitated from preparations containing amobarbital sodium, depending on the concentration and pH. Amobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Uses and Administration

Amobarbital is a barbiturate that has been used as a hypnotic and sedative. Its use can no longer be recommended because of its adverse effects and risk of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p. 1033.2) in patients already taking it. Amobarbital sodium has been used parenterally for premedication in anaesthetic procedures (p. 1899.1) although barbiturates for pre-operative sedation have generally been replaced by other drugs. It has also been used to control refractory tonic-clonic status epilepticus (p. 510.2) although the short-acting barbiturate thiopental is preferred.

The usual oral dose of amobarbital for insomnia was 100 to 200 mg of the base or 60 to 200 mg of the sodium salt, taken at bedtime. A more rapid onset of effect was obtained with the sodium salt.

Barbiturates with a longer action such as phenobarbital (p. 535.2) are still used in epilepsy and those with a shorter action such as methohexital (p. 1909.3) or thiopental (p. 1918.2) for anaesthesia.

General references.

1. López-Muñoz F, *et al.* The history of barbiturates a century after their clinical introduction. *Neuropsychiatr Dis Treat* 2005; **1:** 329–43.

Cerebrovascular disorders. For mention of the use of barbiturate-induced coma in the management of patients with cerebral ischaemia or raised intracranial pressure, see under Pentobarbital, p. 1095.1.

Wada test. The Wada test, also known as the intracarotid amobarbital procedure, in which amobarbital sodium is injected into one internal carotid artery, has been used to assess brain function associated with one cerebral hemisphere and has typically been used for pre-operative screening of candidates for epilepsy surgery. However, with the advent of safer non-invasive techniques, its continued use has been questioned.[1,2]

1. Baxendale SA, *et al.* Evidence-based practice: a reevaluation of the intracarotid amobarbital procedure (Wada test). *Arch Neurol* 2008; **65:** 841–5.
2. Baxendale S. The Wada test. *Curr Opin Neurol* 2009; **22:** 185–9.

Dependence and Withdrawal of Barbiturates

The development of dependence is a high risk with amobarbital and other barbiturates and may occur after regular use even in therapeutic doses for short periods. Barbiturates should not therefore be stopped abruptly, but should be withdrawn by gradual reduction of the dose over a period of days or weeks. A long-acting barbiturate such as phenobarbital may be substituted for a short- or intermediate-acting one, followed by gradual reduction of the phenobarbital dose.

Withdrawal symptoms are similar to those of alcohol withdrawal but can be more severe. Minor symptoms may appear 8 to 12 hours after the last dose, usually in the following order: anxiety, muscle twitching, tremors of hands and fingers, progressive weakness, dizziness, distortion in visual perception, nausea, vomiting, insomnia, and orthostatic hypotension. Convulsions, hallucinations, and delirium may occur within 16 hours and last up to 5 days after stopping barbiturates abruptly. The intensity of withdrawal symptoms gradually declines over about 15 days. Fatalities due to cardiovascular collapse have occurred.

References.
1. Loder E, Biondi D. Oral phenobarbital loading: a safe and effective method of withdrawing patients with headache from butalbital compounds. *Headache* 2003; **43:** 904–9.
2. Mauskop A. Simplified butalbital withdrawal protocol. *Headache* 2004; **44:** 290–1.

Adverse Effects

Drowsiness and sedation are the most frequent adverse effects of amobarbital and other barbiturates and are a consequence of dose-related CNS depression. Other adverse effects include respiratory depression, headache, gastrointestinal disturbances, ataxia, agitation, confusion, and abnormal thinking. Paradoxical excitement and irritability may occur, particularly in children, the elderly, and patients in acute pain. Hypersensitivity reactions occur rarely and include rashes (erythema multiforme and exfoliative dermatitis, sometimes fatal, have been reported), hepatitis and cholestasis, and photosensitivity. Blood disorders, including megaloblastic anaemia after chronic use of barbiturates, have also occurred occasionally.

Neonatal intoxication, drug dependence, and symptoms resembling vitamin-K deficiency have been reported in infants born to mothers who received barbiturates during pregnancy. Congenital malformations have been reported in children of women who took barbiturates during pregnancy, but the causal role has been debated.

Nystagmus, miosis, hyporeflexia or areflexia, dysarthria, and ataxia may occur with excessive doses of barbiturates. The toxic effects of overdosage result from profound CNS depression and include coma, respiratory and cardiovascular depression, with hypotension and shock leading to renal failure and death. Hypothermia may occur with subsequent pyrexia on recovery. Erythematous or haemorrhagic blisters reportedly occur in about 6% of patients, but are not characteristic solely of barbiturate poisoning.

Solutions of the sodium salts of barbiturates are extremely alkaline, and tissue necrosis has followed accidental intra-arterial injection or extravasation. Thrombophlebitis, pain, and injury to adjacent nerves can occur at the site of injection. Intravenous injection may be hazardous; hypotension, shock, severe respiratory depression, laryngospasm, and apnoea have occurred particularly after rapid injection.

Overdosage. A detailed review of drug-induced stupor and coma, including that caused by barbiturates.[1]

1. Ashton CH, *et al.* Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; **8:** 1–59.

Treatment of Adverse Effects

After an overdose of a barbiturate, endotracheal intubation may be necessary if the patient is unconscious. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with barbiturates to be uncertain. However, it is suggested that oral activated charcoal may be considered in adults and children if this is given within 1 hour of ingestion and the quantity of barbiturate exceeds the following amount:

- amobarbital: 4 mg/kg
- barbital: 4 mg/kg
- butobarbital: 6 mg/kg
- cyclobarbital: 8 mg/kg
- methylphenobarbital: 7 mg/kg
- phenobarbital: 4 mg/kg

Activated charcoal is also recommended in children and treatment-naive adults who have ingested any amount of pentobarbital or secobarbital, and in those adults who are taking the drugs, if the usual daily dose or 5 mg/kg has been exceeded. Patients who have ingested any amount of thiopental or veterinary preparations of pentobarbital or secobarbital should be given activated charcoal. Repeat doses of activated charcoal are useful in enhancing the elimination of phenobarbital and should be considered in patients who are experiencing severe symptoms following an overdose, such as coma or cardiovascular or respiratory collapse; care should be taken to protect the airway. Repeat doses may also be warranted in overdoses involving drugs such as methylphenobarbital and primidone that are metabolised to phenobarbital. In addition, patients should be managed with intensive supportive therapy, with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions, and to the maintenance of the electrolyte balance. Charcoal haemoperfusion or haemodialysis should be considered in severe cases.

Precautions

Because of their adverse effects and risk of dependence the use of barbiturates as hypnotics and sedatives can no longer be recommended (but see Uses and Administration, p. 1037.3).

Amobarbital and other barbiturates are best avoided in elderly and debilitated patients, in young adults, in children, and in those with depression or a history of drug or alcohol addiction or abuse.

Amobarbital is contra-indicated in patients with pulmonary insufficiency, sleep apnoea, pre-existing CNS depression or coma, and severe hepatic impairment, and should be given with caution to those with renal impairment. Barbiturates given to patients in pain may provoke a paradoxical excitatory reaction, unless an analgesic is also given. With continued use, tolerance develops to the sedative or hypnotic effects of the barbiturates to a greater extent than to their lethal effects. Barbiturates may cause drowsiness which may persist the next day; affected patients should not drive or operate machinery.

See Adverse Effects, above, for the hazards of giving barbiturates during pregnancy and Breast Feeding, below, for cautions on their use in nursing mothers.

Dependence readily develops after use of barbiturates with a **withdrawal syndrome** if stopped abruptly (see Dependence and Withdrawal, above).

Barbiturates are abused for their euphoriant effects.

Breast feeding. Small amounts of barbiturates are distributed into breast milk, and most authorities, such as the *BNF*, consider that they should not be taken while breast feeding. The last available guidance from the American Academy of Pediatrics noted[1] that the long-acting antiepileptic barbiturate, phenobarbital, has been associated with significant effects on some nursing infants, although it suggests that some other barbiturates may be compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Interactions

Sedation or respiratory depression with barbiturates may be enhanced by drugs with CNS-depressant properties; in particular alcohol should be avoided. Barbiturates generally induce liver microsomal enzymes, and thus increase the rate of metabolism (and decrease the activity) of many other drugs as well as endogenous substances. Continued use may result in induction of their own metabolism. MAOIs may prolong the CNS depressant effects of some barbiturates, probably by inhibition of their metabolism. However, MAOIs, like other antidepressants, also reduce the convulsive threshold and thereby antagonise the anticonvulsant action of barbiturates.

For some further interactions involving barbiturates, see under Phenobarbital, p. 537.2.

Pharmacokinetics

Amobarbital is readily absorbed from the gastrointestinal tract and is rapidly distributed to all tissues and fluids. It is about 60% bound to plasma proteins. It has a half-life of about 20 to 25 hours, which is considerably extended in neonates. It crosses the placenta and small amounts are distributed into breast milk. Amobarbital is metabolised in the liver; up to about 50% is excreted in the urine as 3′-hydroxyamylobarbital and up to about 30% as *N*-hydroxyamylobarbital, with less than 1% appearing unchanged. Up to about 5% is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Amytal; ***Jpn***: Isomytal; ***Thai.***: Amytal; ***UK***: Amytal; ***USA***: Amytal†.

Multi-ingredient Preparations. ***Arg.***: Cuait N†; ***Hong Kong***: Alubar†; Alutal†; Amiton†; ***S.Afr.***: Repasma†; ***Thai.***: Ama; ***UK***: Tuinal; ***USA***: Tuinal.

Pharmacopoeial Preparations

USP 36: Amobarbital Sodium for Injection; Secobarbital Sodium and Amobarbital Sodium Capsules.

Amperozide *(BAN, rINN)*

Amperozida; Ampérozide; Amperozidum; FG-5606; Амперозид.

4-[4,4-Bis(4-fluorophenyl)butyl]-*N*-ethylpiperazine-1-carboxamide.

$C_{23}H_{29}F_2N_3O$=401.5

CAS — 75558-90-6 (amperozide); 75529-73-6 (amperozide hydrochloride).

ATC Vet — QN05AX90.

UNII — 0M2W3TAG39.

Profile

Amperozide is an antipsychotic that has been used in veterinary medicine.

Aripiprazole *(BAN, USAN, rINN)*

Aripiprazol; Aripiprazolum; OPC-31; OPC-14597; Арипипразол.

7-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1*H*)-one.

$C_{23}H_{27}Cl_2N_3O_2$=448.4

CAS — 129722-12-9.

ATC — N05AX12.

ATC Vet — QN05AX12.

UNII — 82VFR53I78.

Pharmacopoeias. In *US.*

USP 36: (Aripiprazole). A white to off-white, crystalline powder. Insoluble in water and in methyl alcohol; freely soluble in dichloromethane; sparingly soluble in toluene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Aripiprazole is an atypical antipsychotic that has serotonin 5-HT_{1A}-receptor partial agonist and 5-HT_{2A}-receptor antagonist properties as well as being a partial agonist at dopamine D_2 receptors. It is used in the management of schizophrenia and of bipolar disorder. Aripiprazole is also used as an adjunct in the treatment of depression. (See Psychiatric Disorders, p. 1039.1.) Aripiprazole is usually given orally or by intramuscular injection as the anhydrous substance. The longer-acting monohydrate polymorphous form is given by intramuscular injection. For all routes, doses are expressed in terms of the equivalent amount of the anhydrous substance; aripiprazole monohydrate 104 mg is equivalent to about 100 mg of anhydrous aripiprazole.

For the treatment of **schizophrenia**, aripiprazole is given in an initial oral dose of 10 or 15 mg once daily. The usual maintenance dose is 15 mg once daily although the dose may be adjusted at intervals of not less than 2 weeks up to a maximum of 30 mg daily.

For the treatment of *acute manic or mixed episodes* in **bipolar disorder**, a recommended initial oral dose is 15 mg once daily as monotherapy, or 10 or 15 mg if given as an adjunct to lithium or valproate; this may subsequently be increased to 30 mg once daily according to response. For the *maintenance treatment* of bipolar disorder, patients should be continued on the same dose on which they were stabilised.

Aripiprazole (as the anhydrous substance) may be given by deep intramuscular injection for acute agitation in patients with schizophrenia or bipolar mania. The recommended initial dose is 9.75 mg although some patients may only need 5.25 mg and others up to 15 mg. If necessary, further doses may be given after at least 2 hours, up to a maximum total daily dose of 30 mg. Patients should be switched to oral therapy as soon as possible if ongoing treatment is required. The long-acting depot preparation (aripiprazole monohydrate) may also be given by deep intramuscular gluteal injection once every month for maintenance therapy of schizophrenia. Patients with no history of aripiprazole use should initially be treated with aripiprazole orally to assess tolerability and response. The recommended initial and maintenance dose is a single monthly injection of 400 mg (no sooner than 26 days after the previous injection). Oral antipsychotic therapy should be continued for the first 14 days after the first injection. The dose may be reduced to 300 mg monthly if adverse effects occur.

As adjunctive therapy in **depression**, US licensed product information recommends an initial oral dose of 2 to 5 mg once daily; the dose may be adjusted in increments of

up to 5 mg at intervals of not less than 1 week to a maximum of 15 mg daily. The usual recommended dose is 5 to 10 mg once daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, below for further details. Adjustments may also be needed in those who are poor CYP2D6 metabolisers (see Administration in Genetic Variation, below).

For details of uses and associated doses in children and adolescents, see below.

Administration in children. In the USA, aripiprazole is licensed for the treatment of:
- schizophrenia in adolescents aged 13 to 17 years
- bipolar disorder in those aged 10 to 17 years
- irritability associated with autistic disorder in those aged 6 to 17 years

In the UK, aripiprazole is licensed for the treatment of:
- schizophrenia in adolescents aged 15 years and older
- acute manic episodes associated with bipolar disorder in those aged 13 years and older

NICE recommends aripiprazole as an option for the treatment of schizophrenia in 15- to 17-year-olds who are intolerant of, or have an inadequate response or contra-indications to risperidone.[1] (It was noted that risperidone is considered the most widely used first-line atypical antipsychotic in the UK for adolescents with schizophrenia although such use is unlicensed.)

For **schizophrenia** or *acute manic or mixed episodes* in **bipolar disorder**, the recommended initial oral dose is 2 mg daily increased to 5 mg daily after 2 days and then to the target dose of 10 mg daily after another 2 days; any subsequent dose increases should be made in 5-mg increments up to a total maximum dose of 30 mg daily. For the *maintenance treatment* of bipolar disorder, patients should be continued on the same dose on which they were stabilised. Aripiprazole may be given as monotherapy, or as an adjunct to lithium or valproate, in bipolar disorder.

For the treatment of **irritability associated with autistic disorder**, the recommended initial oral dose is 2 mg daily increased to 5 mg daily; if necessary, the dose may be adjusted in increments of up to 5 mg at intervals of not less than 1 week to a maximum of 15 mg daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, below for further details. Adjustments may also be needed in those who are poor CYP2D6 metabolisers (see Administration in Genetic Variation, below).

1. NICE. Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years: Technology Appraisal Guidance 213 (issued January 2011). Available at: http://www.nice.org.uk/nicemedia/live/13317/52608/52608.pdf (accessed 28/03/13)

Administration in genetic variation. The dose of oral and intramuscular aripiprazole (anhydrous) should be reduced to half the usual dose (see Uses and Administration, p. 1038.3) in patients who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2D6; a quarter of the usual dose should be given to those who are also taking potent CYP3A4 inhibitors.

The monthly dose of the long-acting intramuscular preparation (aripiprazole monohydrate) should be reduced to 300 mg in poor CYP2D6 metabolisers; those who are also taking CYP3A4 inhibitors for longer than 14 days should be given 200 mg.

Psychiatric disorders. Aripiprazole is used in the management of *schizophrenia* (p. 1031.3).[1-7] Although data are scanty, systematic reviews[1-3] have concluded that aripiprazole does not have significant advantages over other atypical and classical antipsychotics in the treatment of schizophrenia. However, it was found to be better tolerated, including a lower risk for hyperprolactinaemia and QT interval prolongation compared with other atypical antipsychotics.

Aripiprazole is also used in patients with *bipolar disorder* (p. 397.2)[7-9] and as an adjunct in the treatment of *depression* (p. 398.1).[10] It is used for the treatment of irritability associated with *autistic disorder* in children and adolescents.[11,12]

1. El-Sayeh HGG, Morganti C. Aripiprazole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 15/05/06).
2. Bhattacharjee J, El-Sayeh HGG. Aripiprazole versus typical antipsychotic drugs for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 29/05/09).
3. Khanna P, *et al*. Aripiprazole versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2013 (accessed 06/06/13).
4. Belgamwar RB, El-Sayeh HGG. Aripiprazole versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2011 (accessed 06/06/13).
5. NICE. Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years: Technology Appraisal Guidance 213 (issued January 2011). Available at: http://www.nice.org.uk/nicemedia/live/13317/52608/52608.pdf (accessed 07/06/13)
6. Croxtall JD. Aripiprazole: a review of its use in the management of schizophrenia in adults. *CNS Drugs* 2012; **26:** 155–83.
7. Doey T. Aripiprazole in pediatric psychosis and bipolar disorder: a clinical review. *J Affect Disord* 2012; **138** (suppl): S15–S21.
8. Dhillon S. Aripiprazole: a review of its use in the management of mania in adults with bipolar I disorder. *Drugs* 2012; **72:** 133–62.
9. NICE. Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder: Technology Appraisal Guidance 292 (issued July 2013). Available at: http://www.nice.org.uk/nicemedia/live/14225/64565/64565.pdf (accessed 29/11/13)
10. Pae CU, *et al*. Aripiprazole as adjunctive therapy for patients with major depressive disorder: overview and implications of clinical trial data. *CNS Drugs* 2011; **25:** 109–27.
11. Curran MP. Aripiprazole: in the treatment of irritability associated with autistic disorder in pediatric patients. *Paediatr Drugs* 2011; **13:** 197–204.
12. Ching H, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2012 (accessed 06/06/13).

Adverse Effects, Treatment, and Precautions

Although aripiprazole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Common adverse effects with aripiprazole include gastrointestinal disorders such as constipation, dyspepsia, nausea, and vomiting, headache, anxiety, insomnia, lightheadedness, and drowsiness. Weight gain has been reported; however, this appears to be slight. Blood dyscrasias including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia may occur. The incidence of extrapyramidal effects with aripiprazole is low with akathisia being most commonly reported. Tardive dyskinesia has been reported infrequently and there have been a few cases of neuroleptic malignant syndrome. Pathological gambling has also been reported.

Tachycardia and orthostatic hypotension are uncommon with aripiprazole treatment; bradycardia, ventricular arrhythmias, cardiac arrest, and sudden unexplained death have been reported very rarely as have QT prolongation and torsade de pointes. Nonetheless aripiprazole should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension.

Seizures are rare with aripiprazole but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

When aripiprazole is used as an adjunct in depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1.

Aripiprazole may affect the performance of skilled tasks including driving.

References.
1. Pae CU. A review of the safety and tolerability of aripiprazole. *Expert Opin Drug Safety* 2009; **8:** 373–86.
2. Kirino E. Efficacy and safety of aripiprazole in child and adolescent patients. *Eur Child Adolesc Psychiatry* 2012; **21:** 361–8.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.
1. McQuade RD, *et al*. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004; **65** (suppl 18): 47–56.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Licensed product information for aripiprazole also includes a warning about evidence of a dose-response relationship between cerebrovascular adverse events and the use of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease.

Overdosage. The manufacturer has reported that patients have taken estimated overdoses of up to 1080 mg of aripiprazole with no fatalities. Signs and symptoms have included nausea, vomiting, asthenia, diarrhoea, and somnolence. In one report a 27-year-old woman who ingested 330 mg of aripiprazole with cyclobenzaprine 10 mg and quetiapine 25 mg was found to be drowsy but easily rousable 50 minutes later.[1] Initial treatment consisted of oral activated charcoal; recovery was subsequently uneventful. Serum concentrations of aripiprazole and its main metabolite dehydro-aripiprazole, measured 195 minutes after ingestion, were 596 nanograms/mL and 120 nanograms/mL, respectively. In another report[2] a 2½-year-old child vomited and became lethargic within 1 hour of taking 195 mg of aripiprazole (17.1 mg/kg). Activated charcoal was given 3 hours after ingestion but she subsequently became unconscious. However, respiratory support was not required and the child gradually regained consciousness over the next 24 hours. Symptoms of somnolence, ataxia, and tremulousness resolved over 7 days. The serum concentration of aripiprazole plus dehydro-aripiprazole was 1873 nanograms/mL 10 hours after ingestion.

1. Carstairs SD, Williams SR. Overdose of aripiprazole, a new type of antipsychotic. *J Emerg Med* 2005; **28:** 311–13.
2. Seifert SA. Aripiprazole (Abilify®) overdose in a 2.5 year-old. *J Toxicol Clin Toxicol* 2003; **41:** 647–8.

Pregnancy. For comments on the use of some atypical antipsychotics, including aripiprazole, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Licensed product information states that aripiprazole showed possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Aripiprazole should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

The central effects of other CNS depressants including alcohol may be enhanced by aripiprazole. Aripiprazole may also enhance the effects of antihypertensive drugs. It should be used with caution in patients also receiving drugs that prolong the QT interval or cause electrolyte imbalance.

Aripiprazole is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Potent inhibitors of CYP3A4, such as ketoconazole, or of CYP2D6, such as quinidine, can increase aripiprazole plasma concentrations. Conversely, potent CYP3A4 inducers, such as carbamazepine, can reduce plasma concentrations of aripiprazole. Dose adjustment of aripiprazole (anhydrous) is usually recommended when it is given with such drugs:
- potent inhibitors of CYP2D6: reduce to half the usual dose (see Uses and Administration, p. 1038.3); however, dose reduction is not necessary when aripiprazole is used for adjunctive treatment of depression
- potent inhibitors of CYP3A4: reduce to half the usual dose
- a combination of potent, moderate, or weak inhibitors of CYP2D6 and of CYP3A4: reduce to a quarter of the usual dose
- potent inducers of CYP3A4: increase to double the usual dose

The monthly dose of the long-acting preparation (aripiprazole monohydrate) should only be reduced in patients taking these isoenzyme inhibitors for longer than 14 days, as follows:
- patients receiving 400 mg monthly of aripiprazole and also taking:
  - potent CYP2D6 *or* CYP3A4 inhibitors: reduce to 300 mg
  - CYP2D6 *and* CYP3A4 inhibitors: reduce to 200 mg
- patients receiving 300 mg monthly of aripiprazole and also taking:
  - potent CYP2D6 *or* CYP3A4 inhibitors: reduce to 200 mg
  - CYP2D6 *and* CYP3A4 inhibitors: reduce to 160 mg

The use of CYP3A4 inducers for longer than 14 days should be avoided.

Antiepileptics. For a report of Stevens-Johnson syndrome occurring on use of aripiprazole with *lamotrigine*, see p. 530.2.

Pharmacokinetics

Aripiprazole is well absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur in about 3 to 5 hours. After intramuscular injection, peak plasma concentrations occur between 1 to 3 hours. Bioavailability is reported to be 87% with oral tablets and 100% with the intramuscular injection; it is widely distributed. Aripiprazole is metabolised mainly in the liver and pathways involved include dehydrogenation and hydroxylation, via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and *N*-dealkylation, via CYP3A4. The major metabolite, dehydro-aripiprazole, is also active and represents about 40% of the plasma levels of aripiprazole. The mean elimination half-lives of aripiprazole

and dehydro-aripiprazole are about 75 and 95 hours, respectively; in a minority of poor metabolisers the half-life of aripiprazole may be extended to about 146 hours. Protein binding of aripiprazole and its major metabolite is about 99%, mainly to albumin. Elimination is mostly in the faeces (about 55%), with about 25% of a dose appearing in the urine, mainly in the form of metabolites.

It is distributed into breast milk.

References.
1. Mallikaarjun S, *et al.* Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *J Clin Pharmacol* 2004; **44:** 179–87.
2. Boulton DW, *et al.* Pharmacokinetics and tolerability of intramuscular, oral and intravenous aripiprazole in healthy subjects and in patients with schizophrenia. *Clin Pharmacokinet* 2008; **47:** 475–85.
3. Mallikaarjun S, *et al.* Effects of hepatic or renal impairment on the pharmacokinetics of aripiprazole. *Clin Pharmacokinet* 2008; **47:** 533–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arixind; Arlemide; Groven†; Irazem; Lemidal; Siblix; ***Austral.***: Abilify; ***Austria***: Abilify; ***Belg.***: Abilify; ***Braz.***: Abilify; ***Canad.***: Abilify; ***Chile***: Abilify; Arilex; Azymol; Ilimit; Labosol; Viza; ***China***: Abilify (安律凡); An Lv Fan (安律凡)†; Ao Pai (奥派); Brisking (博思清); ***Cz.***: Abilify; ***Denm.***: Abilify; ***Fin.***: Abilify; ***Fr.***: Abilify; ***Ger.***: Abilify; ***Gr.***: Abilify; ***Hong Kong***: Abilify; ***Hung.***: Abilify; ***India***: Arena; Aria; Aridus; Arilan; Arip-MT; Aripat-MD; Aripra-MT; Arive; Arpicin; Arpizol; Arza; Arzu; Asprito; Elrip; Real One; ***Indon.***: Abilify; ***Irl.***: Abilify; ***Israel***: Abilify; Ariply; ***Ital.***: Abilify; ***Jpn***: Abilify; ***Malaysia***: Abilify; ***Mex.***: Abilify; ***Neth.***: Abilify; ***Norw.***: Abilify; ***NZ***: Abilify; ***Philipp.***: Abilify; ***Pol.***: Abilify; ***Port.***: Abilify; ***Rus.***: Abilify (Абилифай); ***S.Afr.***: Abilify; ***Singapore***: Abilify; ***Spain***: Abilify; ***Swed.***: Abilify; ***Switz.***: Abilify; ***Thai.***: Abilify; ***Turk.***: Abilify; Abizol; Ignis; ***UK***: Abilify; ***USA***: Abilify; ***Venez.***: Abilify.

Asenapine Maleate *(BANM, USAN, rINNM)*

Asénapine, Maléate d'; Asenapini Maleas; Maleato de asenapina; Org-5222; Азенапина Малеат.

(3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-c]pyrrole (2*Z*)-2-butenedioate (1:1).

$C_{17}H_{16}ClNO,C_4H_4O_4$=401.8

CAS — 65576-45-6 (asenapine); 85650-56-2 (asenapine maleate).

ATC — N05AH05.

ATC Vet — QN05AH05.

UNII — CU9463U2E2.

Uses and Administration

Asenapine maleate is an atypical antipsychotic reported to be an antagonist at various serotonin and dopamine receptors, as well as at adrenergic (α_1 and α_2) and histamine (H_1 and H_2) receptors. It is used in the management of schizophrenia (p. 1031.3) and of bipolar disorder (p. 397.2).

Asenapine is given sublingually as the maleate although doses are expressed in terms of the base; 7 mg of asenapine maleate is equivalent to about 5 mg of asenapine. Eating and drinking should be avoided for 10 minutes after taking asenapine.

The usual initial and target dose for the *acute* treatment of **schizophrenia** is the equivalent of 5 mg of the base twice daily. This dose may also be used for *maintenance treatment* although a dose of 10 mg twice daily may be required by some patients if tolerated.

When used as monotherapy in the *acute treatment of mixed or manic episodes* associated with **bipolar disorder**, the initial and maintenance dose is 10 mg twice daily; this may be reduced to 5 mg twice daily if adverse effects occur. The initial dose when used as adjunctive therapy with either lithium or valproate, is 5 mg twice daily; this may be increased to 10 mg twice daily depending on the clinical response and tolerability.

References.
1. Potkin SG, *et al.* Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 2007; **68:** 1492–1500.
2. Weber J, McCormack PL. Asenapine. *CNS Drugs* 2009; **23:** 781–92.
3. McIntyre RS, *et al.* Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 2010; **122:** 27–38.
4. Schoemaker J, *et al.* Long-term assessment of asenapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry* 2010; **43:** 138–46.
5. Kane JM, *et al.* A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry* 2011; **72:** 349–55.

Adverse Effects, Treatment, and Precautions

Although asenapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with asenapine include somnolence, dizziness, and oral hypoaesthesia. Other common adverse effects include gastrointestinal disorders, fatigue, irritability, anxiety, and weight increase. Neuroleptic malignant syndrome and extrapyramidal symptoms such as tardive dyskinesia and akathisia have also been reported. Local reactions associated with its sublingual use include mucosal ulceration, blistering, and inflammation, which may be severe enough to stop therapy. Systemic hypersensitivity reactions have also occurred.

Hyperprolactinaemia, which may result in galactorrhoea, amenorrhoea, gynaecomastia, and impotence, has occurred with asenapine. Blood dyscrasias including leucopenia, neutropenia, and thrombocytopenia may occur.

Orthostatic hypotension and syncope have been reported with asenapine, particularly in early treatment; QT prolongation, which in rare cases can lead to torsade de pointes, has also been noted. Asenapine should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension; in addition, it should be avoided in those with a history of arrhythmias or other conditions that may increase the risk of QT prolongation including bradycardia or hypokalaemia. Certain medications may also increase the risk (see Interactions, below).

Seizures may occasionally occur with asenapine and it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold. Asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh class C).

Asenapine may affect the performance of skilled tasks including driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Hypersensitivity. An FDA review[1] of its Adverse Event Reporting System (AERS) database from approval in August 2009 up to September 2010 identified 52 cases of type I hypersensitivity reactions associated with asenapine; 8 cases had reported after the first dose. Symptoms reported included anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnoea, wheezing, and rash.

1. FDA. Drug safety communication: serious allergic reactions reported with the use of Saphris (asenapine maleate) (issued 1st September, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm270243.htm (accessed 17/01/12)

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants including alcohol may be enhanced by asenapine. Asenapine is also an α_1-adrenergic antagonist and may enhance the effects of certain antihypertensive drugs. There may be a risk of QT prolongation when asenapine is given with other drugs that are known to cause this effect. Asenapine can antagonise the effects of dopaminergics.

The metabolism of asenapine is mediated mainly by uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) and the cytochrome P450 isoenzymes (in particular CYP1A2). Use with drugs that inhibit, induce, or act as a substrate to these enzyme pathways may affect plasma concentrations of asenapine: fluvoxamine, a CYP1A2 inhibitor, may significantly increase the plasma levels of asenapine. Asenapine, itself, is a weak inhibitor of CYP2D6, and should be given cautiously with drugs such as paroxetine that are both substrates and inhibitors of CYP2D6.

Pharmacokinetics

Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. Its bioavailability is reduced by food and drink. Plasma protein binding is high (95%). Metabolism of asenapine is mainly through direct glucuronidation by uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) and oxidation by cytochrome P450 isoenzymes (mainly CYP1A2). The mean terminal half-life is about 24 hours. Asenapine is excreted in the urine (about 50%) and faeces (about 40%); only a small amount is excreted unchanged.

Asenapine is thought to be distributed into breast milk on the basis of studies in *rats*.

References.
1. Peeters P, *et al.* Asenapine pharmacokinetics in hepatic and renal impairment. *Clin Pharmacokinet* 2011; **50:** 471–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Saphris; ***Belg.***: Sycrest; ***Braz.***: Saphris; ***Canad.***: Saphris; ***Cz.***: Sycrest; ***Denm.***: Sycrest; ***Fr.***: Sycrest; ***Ger.***: Sycrest; ***Israel***: Saphris; ***Neth.***: Sycrest; ***Norw.***: Sycrest; ***Pol.***: Sycrest; ***Port.***: Sycrest; ***Singapore***: Saphris; ***Spain***: Sycrest; ***Switz.***: Sycrest; ***UK***: Sycrest; ***USA***: Saphris.

Avizafone *(BAN, rINN)*

Avizafona; Avizafonum; Prodiazepam; Ro-03-7355; Ro-03-7355/000; Ro-03-7355/002 (avizafone hydrochloride); Авизафон.

L-Lysyl-(2′-benzoyl-4′-chloro-*N*′-methyl)glycinanilide.

$C_{22}H_{27}ClN_4O_3$=430.9

CAS — 65617-86-9 (avizafone); 60067-16-5 (avizafone hydrochloride).

UNII — 65NK71K78P.

Profile

Avizafone is rapidly metabolised in the body to diazepam (p. 1063.2) and is included as the anticonvulsant component of an intramuscular injection used by military personnel as an antidote to nerve agents. The usual dose of avizafone given in this preparation is 10 mg, repeated every 15 minutes if necessary up to a total dose of 30 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Nerve Agent Antidote L4A1.

Azaperone *(BAN, USAN, rINN)*

Atsaperoni; Azaperon; Azaperona; Azapérone; Azaperonum; R-1929; Азаперон.

4′-Fluoro-4-[4-(2-pyridyl)piperazin-1-yl]butyrophenone.

$C_{19}H_{22}FN_3O$=327.4

CAS — 1649-18-9.

ATC Vet — QN01AX91; QN05AD90.

UNII — 19BV78AK7W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Azaperone for Veterinary Use; Azaperone BP (Vet) 2014). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Azaperone). M.p. 92 degrees to 95 degrees. Protect from light.

Profile

Azaperone is a butyrophenone antipsychotic used as a tranquilliser in veterinary medicine.

Barbital *(BAN, rINN)*

Barbitaali; Barbitál; Barbitalis; Barbitalum; Barbitone; Diemalum; Diethylmalonylurea; Барбитал.

5,5-Diethylbarbituric acid.

$C_8H_{12}N_2O_3$=184.2

CAS — 57-44-3.

ATC — N05CA04.

ATC Vet — QN05CA04.

UNII — 5WZ53ENE2P.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Barbital). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; soluble in boiling water and in alcohol. It forms water-

soluble compounds with alkali hydroxides and carbonates and with ammonia.

Barbital Sodium *(BANM, rINN)*

Barbital de sodio; Barbital sódico; Barbital sodique; Barbital sodowy; Barbitalum Natricum; Barbitone Sodium; Diemalnatrium; Soluble Barbitone; Барбитал Натрий.

Sodium 5,5-diethylbarbiturate.

$C_8H_{11}N_2NaO_3$=206.2

CAS — 144-02-5.

ATC — N05CA04.

ATC Vet — QN05CA04.

UNII — 275L5M93QS.

Profile

Barbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It was formerly used for its hypnotic and sedative properties but barbiturates are no longer considered appropriate for such purposes.

Benperidol *(BAN, USAN, rINN)*

Benpéridol; Benperidoli; Benperidolis; Benperidolum; Benzperidol; CB-8089; McN-JR-4584; R-4584; Беннеридол.

1-[1-[3-(4-Fluorobenzoyl)propyl]-4-piperidyl]benzimidazolin-2-one.

$C_{22}H_{24}FN_3O_2$=381.5

CAS — 2062-84-2.

ATC — N05AD07.

ATC Vet — QN05AD07.

UNII — 97O6X78C53.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Benperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Benperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). Doses of 0.25 to 1.5 mg daily in divided doses are given orally in the management of deviant sexual behaviour (below). Elderly or debilitated patients may require reduced doses and half the usual dose may be sufficient.

In some countries benperidol is given orally or parenterally for the treatment of psychotic conditions (p. 1030.2).

Deviant sexual behaviour. Results of a double-blind placebo-controlled crossover study found no difference between the effect of benperidol 1.25 mg daily, chlorpromazine 125 mg daily, or placebo on sexual drive and arousal in 12 paedophilic sexual offenders, except for a lower frequency of sexual thoughts with benperidol.[1] The effects of benperidol are unlikely to be sufficient to control severe forms of antisocial sexually deviant behaviour. The management of deviant sexual behaviour is discussed under Disturbed Behaviour on p. 1030.2.

1. Tennent G, *et al.* The control of deviant sexual behaviour by drugs: a double-blind controlled study of benperidol, chlorpromazine, and placebo. *Arch Sex Behav* 1974; **3:** 261–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Frenactil; ***Ger.***: Glianimon; ***Gr.***: Glianimon; ***Neth.***: Frenactil†; ***UK***: Anquil.

Bentazepam *(USAN, rINN)*

Bentazépam; Bentazepamum; CI-718; QM-6008; Бентазепам.

1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*]-1,4-diazepin-2-one.

$C_{17}H_{16}N_2OS$=296.4

CAS — 29462-18-8.

UNII — 66JKK43S1Z.

Profile

Bentazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given, in usual oral doses of 25 mg every 8 hours, in the short-term treatment of anxiety disorders (p. 1028.1); it has also been used in insomnia.

Effects on the liver. Severe chronic active hepatitis has been reported in a 65-year-old man who had received long-term treatment with bentazepam.[1]

1. Andrade RJ, *et al.* Bentazepam-associated chronic liver disease. *Lancet* 1994; **343:** 860.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Tiadipona.

Blonanserin *(rINN)*

AD-5423; Blonanserina; Blonansérine; Blonanserinum; Блонансерин.

2-(4-Ethyl-1-piperazinyl)-4-(*p*-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclo-octa[*b*]pyridine.

$C_{23}H_{30}FN_3$=367.5

CAS — 132810-10-7.

UNII — AQ316B4F8C.

Profile

Blonanserin is an atypical antipsychotic reported to be an antagonist at dopamine D_2 and serotonin ($5\text{-}HT_2$) receptors. It is given orally for the treatment of schizophrenia (p. 1031.3) in an initial dose of 4 mg twice daily, increased gradually according to response thereafter. The usual maintenance dose is 8 to 16 mg daily; the maximum daily dose is 24 mg.

References.

1. Garcia E, *et al.* The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia: a randomized, double-blind, placebo-controlled, multicentre study. *CNS Drugs* 2009; **23:** 615–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Lonasen.

Bromazepam *(BAN, USAN, rINN)*

Bromatsepaami; Brómazepám; Bromazépam; Bromazepamas; Bromazepamum; Ro-5-3350; Бромазепам.

7-Bromo-1,3-dihydro-5-(2-pyridyl)-1,4-benzodiazepin-2-one.

$C_{14}H_{10}BrN_3O$=316.2

CAS — 1812-30-2.

ATC — N05BA08.

ATC Vet — QN05BA08.

UNII — X015L14V0O.

NOTE. The name Seniran has been used as a trade mark for bromazepam.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bromazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble or sparingly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Bromazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been used in the short-term treatment of anxiety disorders (p. 1028.1) occurring alone or associated with insomnia. A usual initial oral dose for anxiety is 6 to 18 mg daily in divided doses. Doses up to 60 mg daily have occasionally been given. Initial doses for elderly and debilitated patients should not exceed 3 mg daily in divided doses.

References.

1. Kaplan SA, *et al.* Biopharmaceutical and clinical pharmacokinetic profile of bromazepam. *J Pharmacokinet Biopharm* 1976; **4:** 1–16.
2. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
3. Erb T, *et al.* Preoperative anxiolysis with minimal sedation in elderly patients: bromazepam or clorazepate-dipotassium? *Acta Anaesthesiol Scand* 1998; **42:** 97–101.
4. Lakhal K, *et al.* Protracted deep coma after bromazepam poisoning. *Int J Clin Pharmacol Ther* 2010; **48:** 79–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atemperator; Balamol†; Benedorm†; Bromatanil†; Butecam†; Creosedin; Equisedin; Estomina; Fabozepam; Finaten; Gasmol; Lexotanil; Neurozepam; Nulastres; Octanyl; Sipcar; Tritopam; ***Austral.***: Lexotan; ***Austria***: Lexotanil; ***Belg.***: Bromatop; Bromidem; Docbromaze†; Lexotan; ***Braz.***: Bromalex; Bromoxon; Fluxtar; Lexfast; Lexotan; Lezepan; Nervium†; Neurilan; Relaxil†; Somalium; Uni Bromazepax; ***Canad.***: Lectopam; ***Chile***: Lexotanil; Totasedan†; ***Cz.***: Lexaurin; ***Denm.***: Bromam; Lexotan; ***Fr.***: Anxyrex†; Lexomil; Quietiline; ***Ger.***: Bromazanil†; Bromazep†; Gityl; Lexostad†; Lexotanil; neo OPT†; Normoc†; ***Gr.***: Anconevron; Evagelin; Lexotanil; Libronil-R; Notorium; Pascalium; ***Hong Kong***: Akamon; Lexilium†; Lexotan; ***Indon.***: Lexotan; Lexzepam; ***Irl.***: Lexotan; ***Israel***: Lenitin†; ***Ital.***: Brixopan; Compendium; Lexotan; ***Malaysia***: Akamon; Lexotan; ***Mex.***: Hatmmony; Lexotan; Otedram; ***Philipp.***: Lexotan; ***Pol.***: Lexotan; Sedam; ***Port.***: Bromalex; Lexotan; Ultramidol; ***Rus.***: Lexotan (Лексотан); ***S.Afr.***: Brazepam; Bromaze; Lexotan; ***Singapore***: Lexotan; ***Spain***: Lexatin; ***Switz.***: Lexotanil; ***Thai.***: Lexotan; ***Venez.***: Lexotanil; Nervan.

Multi-ingredient Preparations. ***Arg.***: Biorgan B; Colixane B; Debridat B; Eudon; Eumotil-T; Faradil Novo; Fenatrop-A†; Miopropan-T; Somasedan; Vegestabil Digest; Veralipral T; ***Braz.***: Bromopirin; Sulpan; ***Ital.***: Lexil.

Bromisoval *(rINN)*

Bromisovaali; Bromisovalerylurea; Bromisovalum; Bromovalerylurea; Bromsoval; Bromvalerylurea; Bromvaletone; Bromylum; Бромизовал.

N-(2-Bromo-3-methylbutyryl)urea.

$C_6H_{11}BrN_2O_2$=223.1

CAS — 496-67-3.

ATC — N05CM03.

ATC Vet — QN05CM03.

UNII — 469GW8R486.

Pharmacopoeias. In *Jpn.*

Profile

Bromisoval has actions and uses similar to those of carbromal (p. 1044.1) but the use of bromides is generally deprecated.

References.

1. Wang Y-T, *et al.* Pseudohyperchloraemia due to bromvalerylurea abuse. *Nephrol Dial Transplant* 2005; **20:** 1767–8.
2. Kowa H, *et al.* A case of acute bromvalerylurea intoxication: clinical course and alteration in serum bromvalerylurea concentration. *No To Shinkei* 2006; **58:** 323–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Pol.***: Milocardin; ***Rus.***: Pagluferal (Паглюферал).

Bromperidol *(BAN, USAN, rINN)*

Bromiperidoli; Brómperidol; Brompéridol; Bromperidoli; Bromperidolis; Bromperidolum; R-11333; Бромперидол.

4-[4-(*p*-Bromophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

$C_{21}H_{23}BrFNO_2$=420.3

CAS — 10457-90-6.

ATC — N05AD06.

ATC Vet — QN05AD06.

UNII — LYH6F7I22E.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bromperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

Bromperidol Decanoate *(BANM, USAN, rINNM)*

Brompéridol, décanoate de; Bromperidol, decanoato de; Bromperidoldecanoat; Brómperidol-dekanoát; Bromperidol-dekanoat; Bromperidol-dekanoát; Bromperidoli Decanoas; Bromperidolidekanoaatti; Bromperidolio dekanoatas; Decanoato de bromperidol; R-46541; Бромперидола деканоат.

$C_{31}H_{41}BrFNO_3$=574.6

CAS — 75067-66-2.

UNII — 73LG72M4LV.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bromperidol Decanoate). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane. It melts at about 60 degrees. Store at a temperature below 25 degrees. Protect from light.

Profile

Bromperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given in the treatment of schizophrenia (p. 1042.1) and other psychoses (p. 1030.2). Some bromperidol preparations are prepared with the aid of lactic acid and may be stated to contain bromperidol lactate. However, doses are expressed in terms of the equivalent amount of bromperidol. A usual oral dose is 1 to 15 mg daily, although up to 50 mg daily has been given. Elderly patients may require reduced doses of bromperidol. Bromperidol has also been given by intramuscular or intravenous injection.

The long-acting decanoate ester may be used for patients requiring long-term therapy with bromperidol. Doses are expressed in terms of the base; bromperidol decanoate 68.4 mg is equivalent to about 50 mg of bromperidol. Doses equivalent to up to 300 mg of bromperidol every 4 weeks have been given by deep intramuscular injection.

References.
1. Benfield P, *et al.* Bromperidol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in psychoses. *Drugs* 1988; **35:** 670–84.

Schizophrenia. A systematic review[1] suggested that depot bromperidol had some benefits in schizophrenia (p. 1031.3) but was less effective than depot haloperidol or fluphenazine.

1. Adams CE, *et al.* Depot bromperidol decanoate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bromodol; Erodium; ***Belg.***: Impromen; ***Ger.***: Impromen; Tesoprel†; ***Gr.***: Bromodol; ***Ital.***: Impromen; ***Neth.***: Impromen; ***Thai.***: Brofed†.

Brotizolam *(BAN, USAN, rINN)*

Brotitsolaami; Brotizolamum; Brotyzolam; We-941-BS; We-941; Бротизолам.

2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine.

$C_{15}H_{10}BrClN_4S$=393.7

CAS — 57801-81-7.

ATC — N05CD09.

ATC Vet — QN05CD09.

UNII — 5XZM1R3DKF.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Brotizolam). A white or yellowish powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble or slightly soluble in methyl alcohol.

Profile

Brotizolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given for the short-term (up to 2 weeks) management of insomnia (p. 1033.2) in usual oral doses of 250 micrograms at night. The suggested dose for elderly and debilitated patients is 125 micrograms.

Abuse. Reference to abuse of brotizolam in Germany and Hong Kong.[1]

1. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_856.pdf (accessed 28/07/09)

Pharmacokinetics. References.

1. Bechtel WD. Pharmacokinetics and metabolism of brotizolam in humans. *Br J Clin Pharmacol* 1983; **16:** 279S–283S.
2. Jochemsen R, *et al.* Pharmacokinetics of brotizolam in healthy subjects following intravenous and oral administration. *Br J Clin Pharmacol* 1983; **16:** 285S–290S.
3. Tokairin T, *et al.* Inhibition of the metabolism of brotizolam by erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in brotizolam metabolism. *Br J Clin Pharmacol* 2005; **60:** 172–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lendorm; ***Belg.***: Lendormin; ***Chile***: Dormex; Noctilan; ***Ger.***: Lendormin; ***Gr.***: Lendormin; ***Hung.***: Lendormin; ***Israel***: Bondormin; ***Ital.***: Lendormin; Nimbisan†; ***Jpn***: Lendormin; ***Mex.***: Lindormin; ***Neth.***: Lendormin; ***Port.***: Lendormin; ***S.Afr.***: Lendormin; ***Spain***: Sintonal; ***Venez.***: Lendormin.

Buspirone Hydrochloride

(BANM, USAN, rINNM)

Buspiron Hidroklorür; Buspirona, hidrocloruro de; Buspirone, chlorhydrate de; Buspironhydrochlorid; Buspiron-hydrochlorid; Buspironhydroklorid; Buspironi hydrochloridum; Buspironihydrokloridi; Buspironu chlorowodorek; Hidrocloruro de buspirona; MJ-9022-1; Буспирона Гидрохлорид.

8-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride.

$C_{21}H_{31}N_5O_2$,HCl=422.0

CAS — 36505-84-7 (buspirone); 33386-08-2 (buspirone hydrochloride).

ATC — N05BE01.

ATC Vet — QN05BE01.

UNII — 207LT9J9OC.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Buspirone Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 36: (Buspirone Hydrochloride). A white crystalline powder. Very soluble in water; sparingly soluble in alcohol and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol; very slightly soluble in ethyl acetate; practically insoluble in hexanes. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Buspirone hydrochloride is an azaspirodecanedione (azapirone) anxiolytic. It is reported to be largely lacking in sedative, anticonvulsant, and muscle relaxant actions.

In the short-term management of anxiety disorders (below), buspirone hydrochloride is given in initial oral doses of 5 mg two or three times daily. The dose may be increased in steps of 5 mg at 2- to 3-day intervals, if required, to a usual range of 15 to 30 mg daily given in divided doses. The recommended maximum daily dose, to be given in divided doses, is 45 mg in the UK and 60 mg in the USA.

Dose adjustments of buspirone may be necessary in patients also taking potent inhibitors or inducers of the cytochrome P450 isoenzyme CYP3A4. See Interactions, p. 1043.2, for further details.

Action. Buspirone has dopaminergic, noradrenergic, and serotonin-modulating properties[1] and its anxiolytic effects appear to be related to its action on serotonin (5-hydroxytryptamine, 5-HT) neurotransmission. Buspirone, and the related drugs gepirone (p. 1076.3) and tandospirone (p. 1109.1), are partial agonists at 5-HT_{1A} receptors.[1,2] While such drugs may inhibit serotonin neurotransmission (most likely via 5-HT_{1A} autoreceptor stimulation), they may also have postsynaptic 5-HT_{1A} agonist activity and thus facilitate serotonin neurotransmission.[1] To complicate matters further, 5-HT_{1A} partial agonists have shown both anxiolytic and anxiogenic properties in *animal* models of anxiety. Clinical studies have, however, shown that buspirone is effective in the treatment of generalised anxiety (see below).

Clinical studies with buspirone and gepirone suggest that 5-HT_{1A} partial agonists may have an antidepressant effect (see Depression, below), possibly by downregulation of either 5-HT_{1A} or 5-HT_2 receptors or both.[1] There is some suggestion that buspirone has an anti-aggressive action in humans (see Disturbed Behaviour, below); it is unclear whether this is mediated via dopaminergic or serotonergic mechanisms.[1]

Buspirone also has characteristics of both a dopamine agonist and antagonist; this may result in stimulation of both growth hormone and prolactin secretion.[3]

1. Glitz DA, Pohl R. 5-HT_{1A} partial agonists: what is their future? *Drugs* 1991; **41:** 11–18.
2. Marsden CA. The pharmacology of new anxiolytics acting on 5-HT neurones. *Postgrad Med J* 1990; **66** (suppl 2): S2–S6.
3. Meltzer HY, *et al.* The effect of buspirone on prolactin and growth hormone secretion in man. *Arch Gen Psychiatry* 1983; **40:** 1099–1102.

Anxiety disorders. Buspirone has been shown to be as effective as the benzodiazepines in the short-term treatment of generalised anxiety disorder (p. 1028.1) and to be less likely to cause sedation or psychomotor and cognitive impairment. It also appears to have a lower propensity for interaction with alcohol and a lower risk of abuse and dependence. However, its usefulness may be limited by a relatively slow response to treatment, which may take up to 2 to 4 weeks to appear. Its efficacy may be reduced in patients who have recently taken benzodiazepines. It appears to be ineffective in panic disorder and convincing evidence of efficacy in other anxiety disorders is lacking.

References.
1. Deakin JFW. A review of clinical efficacy of 5-HT_{1A} agonists in anxiety and depression. *J Psychopharmacol* 1993; **7:** 283–9.
2. Pecknold JC. A risk-benefit assessment of buspirone in the treatment of anxiety disorders. *Drug Safety* 1997; **16:** 118–32.
3. Fulton B, Brogden RN. Buspirone: an updated review of its clinical pharmacology and therapeutic applications. *CNS Drugs* 1997; **7:** 68–88.
4. Chessick CA, *et al.* Azapirones for generalized anxiety disorder. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/04/08).
5. Mokhber N, *et al.* Randomized, single-blind, trial of sertraline and buspirone for treatment of elderly patients with generalized anxiety disorder. *Psychiatry Clin Neurosci* 2010; **64:** 128–33.

Bruxism. SSRI-induced bruxism has been successfully controlled by adjunctive therapy with buspirone[1,2] and the related drug tandospirone (p. 1109.1).[3] However, such use has been questioned by the authors of another report[4] who suggested reducing the dosage of the SSRI first before giving buspirone.

1. Romanelli F, *et al.* Possible paroxetine-induced bruxism. *Ann Pharmacother* 1996; **30:** 1246–7.
2. Bostwick JM, Jaffee MS. Buspirone as an antidote to SSRI-induced bruxism in 4 cases. *J Clin Psychiatry* 1999; **60:** 857–60.
3. Kishi Y. Paroxetine-induced bruxism effectively treated with tandospirone. *J Neuropsychiatr Clin Neurosci* 2007; **19:** 90–1.
4. Ranjan S, *et al.* Antidepressant-induced bruxism: need for buspirone? *Int J Neuropsychopharmacol* 2006; **9:** 485–7.

Cerebellar ataxias. In general, the management of cerebellar ataxias is mainly supportive. Although buspirone improved some symptoms of ataxia in a small preliminary study[1] of patients with cerebellar cortical activity, a more recent small study[2] found that it was not superior to placebo in patients with spinocerebellar ataxia.

1. Trouillas P, *et al.* Buspirone, a 5-hydroxytryptamine$_{1A}$ agonist, is active in cerebellar ataxia: results of a double-blind drug placebo study in patients with cerebellar cortical atrophy. *Arch Neurol* 1997; **54:** 749–52.
2. Assadi M, *et al.* Treatment of spinocerebellar ataxia with buspirone. *J Neurol Sci* 2007; **260:** 143–6.

Depression. Buspirone has been investigated for augmentation of therapy with antidepressants with serotonin reuptake inhibiting activity in patients with refractory depression (p. 398.1), but results have been variable.

References.
1. Fischer P, *et al.* Weak antidepressant response after buspirone augmentation of serotonin reuptake inhibitors in refractory severe depression. *Int Clin Psychopharmacol* 1998; **13:** 83–6.
2. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol* 1998; **18:** 465–9.
3. Landen M, *et al.* A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry* 1998; **59:** 664–8.
4. Appelberg BG, *et al.* Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry* 2001; **62:** 448–52.
5. Önder E, Tural Ü. Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. *J Affect Disord* 2003; **76:** 223–7.
6. Trivedi MH, *et al.* STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006; **354:** 1243–52.

Disturbed behaviour. Buspirone has been tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (p. 1030.2) but evidence of efficacy is limited. Nonetheless, in the management of dementia, some[1] consider that it might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant or unresponsive to antipsychotics.

1. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)

Extrapyramidal disorders. Although there have been reports[1,2] that buspirone may improve symptoms of drug-induced dyskinesia (p. 1049.2), drugs with dopaminergic actions have mostly exacerbated symptoms and there are a few reports of extrapyramidal disorders with buspirone (see under Adverse Effects, p. 1043.1).

1. Moss LE, *et al.* Buspirone in the treatment of tardive dyskinesia. *J Clin Psychopharmacol* 1993; **13:** 204–9.
2. Bonifati V, *et al.* Buspirone in levodopa-induced dyskinesias. *Clin Neuropharmacol* 1994; **17:** 73–82.

Substance dependence. *ALCOHOL.* Despite an early study[1] suggesting that buspirone could reduce alcohol craving in alcohol dependent patients, later studies[2-4] have overall failed to confirm that buspirone improves abstinence or reduces alcohol consumption. Some studies[4,5] have also found that buspirone may improve certain psychopathological symptoms in these patients, although others[2] have found no such benefit; a meta-analysis[6] of 5 studies favoured the former interpretation.

The management of alcohol withdrawal and abstinence is discussed on p. 1735.1.

1. Bruno F. Buspirone in the treatment of alcoholic patients. *Psychopathology* 1989; **22** (suppl 1): 49–59.
2. Malcolm R, *et al.* A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcohol Clin Exp Res* 1992; **16:** 1007–13.
3. George DT, *et al.* Buspirone does not promote long term abstinence in alcoholics. *Clin Pharmacol Ther* 1995; **57:** 161.
4. Malec E, *et al.* Buspirone in the treatment of alcohol dependence: a placebo-controlled trial. *Alcohol Clin Exp Res* 1996; **20:** 307–12.
5. Kranzler HR, *et al.* Buspirone treatment of anxious alcoholics: a placebo-controlled trial. *Arch Gen Psychiatry* 1994; **51:** 720–31.
6. Malec TS, *et al.* Efficacy of buspirone in alcohol dependence: a review. *Alcohol Clin Exp Res* 1996; **20:** 853–8.

CANNABIS. Buspirone has been investigated in the treatment of cannabis dependence; 2 small studies[1,2] have shown some positive results.

1. McRae AL, *et al.* Buspirone for treatment of marijuana dependence: a pilot study. *Am J Addict* 2006; **15:** 404.
2. McRae-Clark AL, *et al.* A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend* 2009; **105:** 132–8.

NICOTINE. A systematic review[1] noted that buspirone has produced conflicting results in the management of smoking cessation (p. 2570.2); however, its possible benefit cannot be ruled out based on evidence available at that time.

1. Hughes JR, *et al.* Anxiolytics for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/01/09).

OPIOIDS. Buspirone has been investigated in the management of opioid withdrawal (p. 109.2) in dependent

patients; 2 small studies[1,2] have produced encouraging results.

1. Rose JS, *et al.* Effects of buspirone in withdrawal from opiates. *Am J Addict* 2003; **12:** 253–9.
2. Buydens-Branchey L, *et al.* Efficacy of buspirone in the treatment of opioid withdrawal. *J Clin Psychopharmacol* 2005; **25:** 230–6.

Dependence and Adverse Effects

If adverse effects occur with buspirone hydrochloride, they are usually at the start of treatment and generally subside with continued treatment or decreased dosage. Dizziness, nausea, headache, nervousness, light-headedness, and excitement are amongst the most frequent adverse effects reported. Other adverse effects have included tachycardia, palpitations, non-specific chest pain, drowsiness, paraesthesias, sleep disturbances, confusion, seizures, dry mouth, tinnitus, sore throat, nasal congestion, fatigue, and sweating. A syndrome of restlessness appearing shortly after the start of treatment has been reported in a small number of patients given buspirone. Buspirone is reported to produce less sedation, and to have a lower potential for abuse and dependence, than the benzodiazepines.

Effects on the nervous system. Mild acute hypertension and panic were reported on two occasions after the addition of single 10-mg doses of buspirone to therapy with tricyclic antidepressants in a 40-year-old man with panic disorder. Adrenergic or serotonin dysfunction were postulated as possible mechanisms for the reaction.[1,2] Psychotic reactions associated with buspirone treatment have also been reported in a few patients.[3] There have also been isolated reports of mania,[4] and seizures have been reported, mainly in overdosage.[5]

1. Chignon JM, Lepine JP. Panic and hypertension associated with single dose of buspirone. *Lancet* 1989; **ii:** 46–7.
2. Norman TR, Judd FK. Panic attacks, buspirone, and serotonin function. *Lancet* 1989; **ii:** 615.
3. Friedman R. Possible induction of psychosis by buspirone. *Am J Psychiatry* 1991; **148:** 1606.
4. Price WA, Bielefeld M. Buspirone-induced mania. *J Clin Psychopharmacol* 1989; **9:** 150–1.
5. Catalano G, *et al.* Seizures associated with buspirone overdose: case report and literature review. *Clin Neuropharmacol* 1998; **21:** 347–50.

EXTRAPYRAMIDAL DISORDERS. There have been isolated reports of exacerbation or precipitation of movement disorders[1-4] associated with the use of buspirone. However, buspirone has also been reported to have been of benefit in some patients with tardive dyskinesia (see Extrapyramidal Disorders under Uses and Administration, p. 1042.3).

1. Hammerstad JP, *et al.* Buspirone in Parkinson's disease. *Clin Neuropharmacol* 1986; **9:** 556–60.
2. Ritchie EC, *et al.* Acute generalized myoclonus following buspirone administration. *J Clin Psychiatry* 1988; **49:** 242–3.
3. Strauss A. Oral dyskinesia associated with buspirone use in an elderly woman. *J Clin Psychiatry* 1988; **49:** 322–3.
4. LeWitt PA, *et al.* Persistent movement disorders induced by buspirone. *Mov Disord* 1993; **8:** 331–4.

Precautions

Buspirone hydrochloride should be used with caution in patients with renal or hepatic impairment and is contra-indicated if the impairment is severe. It should not be used in patients with epilepsy or a history of such disorders. It does not show cross-tolerance with benzodiazepines or other common sedatives or hypnotics and will not block symptoms of their withdrawal; they should, therefore, be gradually withdrawn before starting treatment with buspirone. Buspirone may impair the patient's ability to drive or operate machinery.

Diagnosis and testing. Buspirone may interfere with diagnostic assays of urinary catecholamines.[1]

1. Cook FJ, *et al.* Effect of buspirone on urinary catecholamine assays. *N Engl J Med* 1995; **332:** 401.

Hepatic impairment. Caution has been advised when using buspirone in patients with liver disease. The mean peak plasma-buspirone concentration after an oral dose was about 16 times higher in cirrhotic patients than in controls[1] and the elimination half-life was prolonged about twofold. A secondary peak concentration was seen in some subjects, occurring between 4 and 24 hours after a dose in the cirrhotics and after between 2 and 8 hours in controls. Data from a multiple-dose study[2] suggested that there was accumulation of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine in hepatic impairment, but that plasma concentrations appeared to reach steady state after 3 days regardless of the state of liver function. The AUC and mean peak concentration for buspirone were both higher in patients with hepatic impairment than in healthy subjects, but there were no significant differences for its metabolites. Specific dosing recommendations could not be made for patients with hepatic impairment because of the high intra- and inter-subject variations in plasma-buspirone concentrations.

1. Dalhoff K, *et al.* Buspirone pharmacokinetics in patients with cirrhosis. *Br J Clin Pharmacol* 1987; **24:** 547–50.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; **46:** 41–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies buspirone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/07/11)

Pregnancy and breast feeding. In some *animal* studies, large doses of buspirone during pregnancy had adverse effects on survival and on birth and weanling weight. Distribution into milk has been found in studies in *rats*. Recommendations in licensed product information for use during pregnancy or breast feeding vary from avoid, if possible, to contra-indicated.

Renal impairment. Caution has been advised when giving buspirone to patients with renal impairment.[1,2] There is evidence of accumulation of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine after repeated doses but plasma concentrations appeared to reach steady state after 3 days regardless of the degree of renal function. At steady state both the AUC and maximum concentrations for buspirone and its metabolite were greater in patients with renal failure than in healthy subjects. The metabolite, but not the parent drug, was removed by haemodialysis. Specific dosing recommendations could not be made for patients with renal impairment because of the high intra- and inter-subject variations in buspirone plasma concentrations on repeated dosage.

1. Caccia S, *et al.* Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. *Clin Pharmacokinet* 1988; **14:** 171–7.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; **46:** 41–7.

Interactions

The sedative effects of buspirone may be enhanced if taken with alcohol or other CNS depressants. Because of reports of increased blood pressure in patients receiving buspirone hydrochloride with an MAOI, licensed product information for buspirone recommends that it should not be given with an MAOI.

The metabolism of buspirone is mediated by the cytochrome P450 isoenzyme CYP3A4 and therefore there is the potential for interactions between buspirone and other drugs that inhibit, induce, or act as a substrate for this isoenzyme. The dose of buspirone may need to be reduced if given at the same time as potent inhibitors of CYP3A4 such as diltiazem, erythromycin, itraconazole, nefazodone, ritonavir, and verapamil; licensed product information suggests giving 2.5 mg of buspirone orally once or twice daily when used with such drugs. Grapefruit juice may also increase plasma concentrations of buspirone and should be avoided. Conversely, plasma concentrations of buspirone may be reduced by enzyme-inducing drugs such as rifampicin and the dosage of buspirone may need adjusting with such use.

Antidepressants. Serotonin syndrome (p. 443.2) has been reported with the use of buspirone with *citalopram*,[1] with *fluoxetine*,[2] and with *St John's wort*.[3]

1. Spigset O, Adielsson G. Combined serotonin syndrome and hyponatraemia caused by a citalopram-buspirone interaction. *Int Clin Psychopharmacol* 1997; **12:** 61–3.
2. Manos GH. Possible serotonin syndrome associated with buspirone added to fluoxetine. *Ann Pharmacother* 2000; **34:** 871–4.
3. Dannawi M. Possible serotonin syndrome after combination of buspirone and St John's Wort. *J Psychopharmacol* 2002; **16:** 401.

Antipsychotics. For the effect of buspirone on serum concentrations of *haloperidol*, see under Chlorpromazine, p. 1053.1. For a report of potentially fatal gastrointestinal bleeding and marked hyperglycaemia after use of buspirone with *clozapine*, see under Clozapine, p. 1062.1.

Antivirals. Parkinson-like symptoms developed in a 54-year-old man taking a drug regimen that included buspirone, *indinavir*, and *ritonavir*.[1] It was suspected that ritonavir, a more potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 than indinavir, was mainly responsible for causing increased plasma-buspirone concentrations. Symptoms resolved after a change in antiviral regimen and reduction in the dose of buspirone.

1. Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. *Ann Pharmacother* 2003; **37:** 202–5.

Pharmacokinetics

Buspirone hydrochloride is rapidly absorbed from the gastrointestinal tract reaching peak plasma concentrations within 40 to 90 minutes after an oral dose. Systemic bioavailability is low because of extensive first-pass metabolism, but may be increased if given with food as this delays absorption from the gastrointestinal tract and thereby reduces presystemic clearance. Buspirone is about 95% bound to plasma proteins. Metabolism in the liver is extensive via the cytochrome P450 isoenzyme CYP3A4; hydroxylation yields several inactive metabolites and oxidative dealkylation produces 1-(2-pyrimidinyl)-piperazine, which is reported to be about 25% as potent as the parent drug in one model of anxiolytic activity. The elimination half-life of buspirone is usually about 2 to 4 hours but half-lives of up to 11 hours have been reported. Buspirone is excreted mainly as metabolites in the urine, and also in the faeces. Distribution of buspirone and its metabolites into milk has been found in studies in *rats*.

References.

1. Mahmood I, Sahajwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet* 1999; **36:** 277–87.
2. Edwards DJ, *et al.* Pharmacokinetics of buspirone in autistic children. *J Clin Pharmacol* 2006; **46:** 508–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ansial; Aristopiron†; ***Austral.***: Buspar; ***Austria***: Buspar; ***Belg.***: Buspar†; ***Braz.***: Ansitec; Buspar; ***Canad.***: Buspar†; Bustab; ***Chile***: Paxon; ***China***: Qibite (奇比特); Suxin (苏新); Yi Shu (一舒); ***Denm.***: Buspar†; ***Fin.***: Anksilon; Buspar†; ***Fr.***: Buspar†; ***Ger.***: Anxut; Bespar†; Busp†; ***Gr.***: Abivax; Anchocalm; Antipsichos; Bergamol; Bespar; Boronex; Epsilat; Hiremon; Hobatstress; Komasin; Lanamont; Lebilon; Ledion; Lostress; Loxapin; Nadrifor; Nervostal; Nevrorestol; Norbal; Pendium; Stressigal; Svitalark; Tendan; Tensispes; Trafuril; Umolit; Vulbefer; ***Hong Kong***: Buspar†; Kalmiren†; ***Hung.***: Anxiron; Spitomin; ***India***: Buscalm; Buson; Buspidac; Buspin; ***Indon.***: Tran-Q†; Xiety; ***Irl.***: Buspar†; ***Israel***: Sorbon; ***Ital.***: Buspar†; ***Mex.***: Buspar; ***Norw.***: Buspar†; ***NZ***: Biron; Buspar; ***Pol.***: Mabuson†; Spamilan; ***Port.***: Ansiten; Busansil; Buscalma; Buspar†; Buspium†; Itagil; Psibeter†; ***Rus.***: Spitomin (Спитомин); ***S.Afr.***: Buspar; Pasrin; ***Spain***: Buspar†; ***Swed.***: Buspar†; ***Switz.***: Buspar†; ***Thai.***: Anxiolan; ***Turk.***: Buspon; ***UK***: Buspar†; ***USA***: Buspar†; ***Venez.***: Dalpas.

Pharmacopoeial Preparations

USP 36: Buspirone Hydrochloride Tablets.

Butalbital *(USAN, rINN)*

Alisobumalum; Allylbarbital; Allylbarbituric Acid; Butalbitaali; Butalbitalum; Itobarbital; Tetrallobarbital; Буталбитал.

5-Allyl-5-isobutylbarbituric acid.

$C_{11}H_{16}N_2O_3$=224.3

CAS — 77-26-9.

UNII — KHS0AZ4JVK.

NOTE. The name Butalbital has also been applied to talbutal, the *S*-butyl analogue, which was formerly used as a hypnotic and sedative.

Compounded preparations of butalbital may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine

Pharmacopoeias. In *US*.

USP 36: (Butalbital). A white odourless crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in alcohol, in chloroform, and in ether; soluble in solutions of fixed alkalis and alkali carbonates. A saturated solution is acid to litmus.

Profile

Butalbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used mainly in combination preparations with analgesics in the treatment of occasional tension-type headaches, but other treatments are generally preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Fiorinal C; Fiorinal; Pronal-C; Pronal; ratio-Tecnal C; ratio-Tecnal; Trianal C; Trianal; ***Ital.***: Optalidon; ***Switz.***: Cafergot-PB†; ***USA***: Alagesic LQ; Amaphen with Codeine; Americet; Anolor; Ascomp with Codeine; Bupap; Butex; Capacet; Cephadyn; Dolgic LQ; Dolgic Plus; Dolgic; Endolor; Esgic-Plus; Esgic; Fioricet with Codeine; Fioricet; Fiorinal with Codeine; Fiorinal; Margesic; Marten-Tab; Medigesic†; Orbivan CF; Orbivan; Pacaps; PhenazoForte Plus; Phrenilin w Caffeine and Codeine; Phrenilin; Promacet; Prominol; Pyridium Plus; Repan; Sedapap; Tencet; Tencon; Trellium Plus†; Triad; Zebutal.

Pharmacopoeial Preparations

USP 36: Butalbital and Aspirin Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules.

Butobarbital (BAN)

Butethal; Butobarbitaali; Butobarbitalum; Butobarbitone; Бутобарбитал.

5-Butyl-5-ethylbarbituric acid.

$C_{10}H_{16}N_2O_3$=212.2

CAS — 77-28-1.

ATC — N05CA03.

ATC Vet — QN05CA03.

UNII — OHZ8QAW6YC.

NOTE. Care should be taken to avoid confusion between barbiturates with similar names: Butobarbital should be distinguished from Butabarbital, a synonym for Secbutabarbital (p. 1106.2), and Secbutabarbital should be distinguished from Secobarbital (p. 1106.3).

Profile

Butobarbital is a barbiturate that has been used as a hypnotic. It has general properties similar to those of amobarbital (p. 1037.2). Its use can no longer be recommended because of the risk of its adverse effects and of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p. 1033.2) in patients already taking it. It was given in usual oral doses of 100 to 200 mg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Soneryl.

Calcium Bromolactobionate

Bromolactobionato de calcio; Calcium Galactogluconate Bromide.

Calcium bromide lactobionate hexahydrate.

$Ca(C_{12}H_{21}O_{12})_2,CaBr_2,6H_2O$=1062.6

CAS — 33659-28-8 (anhydrous calcium bromolactobionate).

UNII — 46EGF47S9V.

Profile

Calcium bromolactobionate has sedative properties and has been given orally in the treatment of insomnia and anxiety disorders. The use of bromides is generally deprecated.

Overdosage. Bromide intoxication has been reported[1] in a patient after overdosage with calcium bromolactobionate tablets.

1. Danel VC, *et al.* Bromide intoxication and pseudohyperchloremia. *Ann Pharmacother* 2001; **35:** 386–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Bromocalcio†; Nervolta†; Sedofantil; ***Ital.***: Calcibronat; ***Mon.***: Calcibronat.

Captodiame Hydrochloride (BANM, pINNM)

Captodiame, Chlorhydrate de; Captodiami Hydrochloridum; Captodiamine Hidrochloride; Captodiamine Hydrochloride; Captodiamo, hidrocloruro de; Hidrocloruro de captodiamo; Каптодиама Гидрохлорид.

2-(4-Butylthiobenzhydrylthio)ethyldimethylamine hydrochloride.

$C_{21}H_{29}NS_2$,HCl=396.0

CAS — 486-17-9 (captodiame); 904-04-1 (captodiame hydrochloride).

ATC — N05BB02.

ATC Vet — QN05BB02.

UNII — 9I7N9PR9J2.

Profile

Captodiame hydrochloride is given in oral doses of 50 mg three times daily for the treatment of anxiety disorders (p. 1028.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Covatine.

Carbromal (BAN, rINN)

Bromodiethylacetylurea; Carbromalum; Karbromaali; Karbromal; Карбромал.

N-(2-Bromo-2-ethylbutyryl)urea.

$C_7H_{13}BrN_2O_2$=237.1

CAS — 77-65-6.

ATC — N05CM04.

ATC Vet — QN05CM04.

UNII — 0Y299JY9V3.

Profile

Carbromal is a bromureide with general properties similar to those of the barbiturates (see Amobarbital, p. 1037.2). It was formerly used for its hypnotic and sedative properties. Chronic use of carbromal could result in bromide accumulation and symptoms resembling bromism (see Bromides, p. 2461.1). The use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Demalgon.

Carpipramine Hydrochloride (rINNM)

Carpipramina, hidrocloruro de; Carpipramine, Chlorhydrate de; Carpipramine Dihydrochloride; Carpipramini Hydrochloridum; Hidrocloruro de carpipramina; PZ-1511; Карпипрамина Гидрохлорид.

1-[3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl]-4-piperidinopiperidine-4-carboxamide dihydrochloride monohydrate.

$C_{28}H_{38}N_4O$,2HCl,H_2O=537.6

CAS — 5942-95-0 (carpipramine); 7075-03-8 (anhydrous carpipramine hydrochloride); 100482-23-3 (carpipramine maleate).

UNII — 53X71X3I1W.

Profile

Carpipramine is structurally related both to imipramine (p. 426.2) and to butyrophenones such as haloperidol (p. 1077.1). It has been used in the management of anxiety disorders (p. 1028.1) and psychoses such as schizophrenia (p. 1031.3). Carpipramine is given as the hydrochloride although doses are expressed in terms of the base; carpipramine hydrochloride 60.2 mg is equivalent to about 50 mg of carpipramine. A usual oral dose is equivalent to 150 mg of the base daily in 2 or 3 divided doses, with a range of 50 to 400 mg daily. The maleate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Prazinil; ***Jpn***: Defekton.

Chlordiazepoxide (BAN, rINN)

Chlordiazepoksidas; Chlordiazepoxid; Chlordiazépoxide; Chlordiazepoxidum; Chlorodiazepoksyd; Clordiazepossido; Clordiazepóxido; Klooridiatsepoksidi; Klordiazepoksit; Klordiazepoxid; Klórdiazepoxid; Methaminodiazepoxide; Хлордиазепоксид.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide.

$C_{16}H_{14}ClN_3O$=299.8

CAS — 58-25-3.

ATC — N05BA02.

ATC Vet — QN05BA02.

UNII — 6RZ6XEZ3CR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of chlordiazepoxide:

Green apples; Green and blacks; Lib.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Chlordiazepoxide). An almost white or light yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Chlordiazepoxide). A yellow, practically odourless, crystalline powder. Insoluble in water; soluble 1 in 50 of alcohol, 1 in 6250 of chloroform, and 1 in 130 of ether. Store in airtight containers. Protect from light.

Chlordiazepoxide Hydrochloride

(BANM, USAN, rINNM)

Chlordiazepoksido hidrochloridas; Chlordiazepoksydu chlorowodorek; Chlordiazépoxide, chlorhydrate de; Chlordiazepoxidhydrochlorid; Chlordiazepoxid-hydrochlorid; Chlordiazepoxidi Hydrochloridum; Clordiazepóxido, hidrocloruro de; Hidrocloruro de clordiazepóxido; Klooridiatsepoksidihydrokloridi; Klordiazepoksit Hidroklorür; Klórdiazepoxid-hidroklorid; Klordiazepoxidhydroklorid; Methaminodiazepoxide Hydrochloride; NSC-115748; Ro-5-0690; Хлордиазепоксида Гидрохлорид.

$C_{16}H_{14}ClN_3O$,HCl=336.2

CAS — 438-41-5.

ATC — N05BA02.

ATC Vet — QN05BA02.

UNII — MFM6K1XWDK.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Chlordiazepoxide Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Chlordiazepoxide Hydrochloride). A white or practically white, odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; insoluble in petroleum spirit. Store in airtight containers. Protect from light.

Uses and Administration

Chlordiazepoxide is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term treatment of anxiety disorders (p. 1028.1) occurring alone or associated with insomnia. Chlordiazepoxide is also used in muscle spasm (p. 2014.1) and in alcohol withdrawal syndrome (p. 1735.1); it has been given for premedication.

Chlordiazepoxide is given orally as the hydrochloride or the base; the doses given apply equally to both. It has also been given by deep intramuscular or slow intravenous injection as the hydrochloride.

Elderly and debilitated patients should be given one-half or less of the usual dose.

The usual oral dose for the treatment of **anxiety** is up to 30 mg daily in divided doses; in severe conditions up to 100 mg daily has been given. For insomnia associated with anxiety, 10 to 30 mg may be given orally before bedtime. Oral doses of 5 to 10 mg may be given 3 or 4 times daily on the days preceding surgery for pre-operative apprehension and anxiety.

For relief of **muscle spasm** a dose of 10 to 30 mg daily given orally in divided doses is recommended.

For the control of the acute symptoms of **alcohol withdrawal** chlordiazepoxide or chlordiazepoxide hydrochloride may be given in an oral dose of 25 to 100 mg repeated as needed after 2 to 4 hours, up to a maximum of 300 mg daily.

For details of doses in children, see below.

Administration in children. In the USA, chlordiazepoxide hydrochloride is licensed for use in children aged 6 years or over for the short-term treatment of anxiety disorders and for pre-operative apprehension and anxiety. An oral dose of 5 mg may be given 2 to 4 times daily; in some children this may be increased to 10 mg 2 or 3 times daily.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 12.5 mg of chlordiazepoxide is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Hepatic impairment. Progressive drowsiness began after 20 days of treatment with chlordiazepoxide in a woman with cirrhosis and hepatitis.[1] One week after stopping the drug the patient could not be roused, and full consciousness was not regained for another week. Accumulation of active metabolites of chlordiazepoxide may have been responsible for the prolonged stupor.

1. Barton K, *et al.* Chlordiazepoxide metabolite accumulation in liver disease. *Med Toxicol* 1989; **4:** 73–6.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Absorption of chlordiazepoxide is almost complete after oral doses; peak plasma concentrations occur after 1 to 2 hours. Absorption after intramuscular injection may be slow and erratic depending on the site of injection. Chlordiazepoxide is about 96% bound to plasma proteins. Reported values for the elimination half-life of chlordiazepoxide have ranged from about 5 to 30 hours, but its main active metabolite desmethyldiazepam (nordazepam, p. 1089.3) has a half-life of several days. Other pharmacologically active metabolites of chlordiazepoxide include desmethylchlordiazepoxide, demoxepam, and oxazepam (p. 1092.2). Chlordiazepoxide passes into the CSF and breast milk, and crosses the

placenta. Unchanged drug and metabolites are excreted in the urine, mainly as conjugated metabolites.

References.
1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of chlordiazepoxide. *Clin Pharmacokinet* 1978; **3**: 381–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: OCM; ***Braz.***: Psicosedin; ***Cz.***: Elenium; ***Denm.***: Klopoxid; Risolid†; ***Fin.***: Risolid; ***Ger.***: Librium; Multum†; Radepur; ***Gr.***: Oasil; ***Hong Kong***: Corlium†; Librium; Litamin; ***Hung.***: Elenium; Librium; ***India***: Anxizide; Cebrum; Cloxide; Ebrium; Equilibrium; Lib-CT; Librium; ***Indon.***: Cetabrium†; Librium; ***Irl.***: Librium; Rima†; ***Ital.***: Librium; ***Malaysia***: Benpine; ***NZ***: Novapam; ***Pol.***: Elenium; ***Port.***: Paxium; ***Rus.***: Elenium (Элениум); ***S.Afr.***: Librium†; ***Singapore***: Benpine; Klorpo; ***Spain***: Huberplex; Omnalio†; ***Thai.***: Benpine; Chlordibrax; Chlordixide; Chlorzep; Comoben; Cozep; Epoxide; Med-Zepoxide; Metaxide; Minoxide; Zepoxide; Zepoxin; ***UK***: Librium; Tropium; ***USA***: Librium; ***Venez.***: Eposal.

Multi-ingredient Preparations. ***Arg.***: Libraxin; ***Austria***: Limbitrol; ***Braz.***: Limbitrol; Menotensil; ***Canad.***: Apo-Chlorax; Librax; Pro Chlorax†; ***Chile***: Aero Itan; Aerogastrol; Antalin; Garceptol; Gastrolen; Lerogin; Libraxin; Limbatrilin; Morelin; No-Ref; Profisin; Tensoliv; Tiperin; ***China***: Fufang Dan An Pian (复方胆氨片); ***Fin.***: Klotriptyl; Librax; Limbitrol; ***Fr.***: Librax; ***Gr.***: Librax; Pro-Alusin-L; ***Hong Kong***: Epilon; Librax; Syntabrax†; ***India***: Acirex; Alspas Forte; Amichlor; Amixide H; Amize; Amizep; Amrea-C; Amypres-C; Anxitab; Cebrex Forte; Cebrex; Chlotrip; Cibis; Clidox; Cloxide Plus; Colinorm; Cynosleep; Depsodep; Dorpep; Emotrip; Equicalm; Equirex; Febl; Fit; Gentrip Forte; Gentrip Plus; IBS; Libotryp; Librax; Librodep; Librospas; Librosym; Librotop; Limbitrol; Limbival; Meva-C; Mirip; Mitryp; Neurospas-CD; Normaline Plus; Normaline-H; Normaxin-RT; Normaxin; Normozin; Orlidox-D; Orlidox; Parazin-C; Spasrax; ***Indon.***: Braxidin; Cliad; Klidibrax; Librax; Limbitrol; Melidox; Neurogen†; Renagas; Sanmag; Spasmium; ***Israel***: Nirvaxal†; ***Ital.***: Diapatol; Librax; Limbitryl; Sedans; ***Malaysia***: Liblan; ***Port.***: Librax; ***Rus.***: Amixide (Амиксид); ***S.Afr.***: Librax†; Limbitrol†; ***Singapore***: Apo-Chlorax; Chlobax; Librax†; Medocalum†; Syntabrax; ***Spain***: Psico Blocan†; ***Switz.***: Librax; Librocol; Limbitrol; ***Thai.***: Cebarax†; Dirax; Kenspa; Librax; Licon; Modurax; Pobrax; Radibrax; Tumax; Utorax; ***Turk.***: Klipaks; Libkol; Librax; ***USA***: Clindex; Librax; Limbitrol; ***Venez.***: Librax.

Pharmacopoeial Preparations
BP 2014: Chlordiazepoxide Capsules; Chlordiazepoxide Hydrochloride Tablets;
USP 36: Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules; Chlordiazepoxide Hydrochloride Capsules; Chlordiazepoxide Hydrochloride for Injection; Chlordiazepoxide Tablets.

Chlormezanone *(BAN, rINN)*

Chlormethazanone; Chlormézanone; Chlormezanonum; Clormezanona; Kloorimetsanoni; Klormezanon; Хлормезанон.

2-(4-Chlorophenyl)-3-methylperhydro-1,3-thiazin-4-one 1,1-dioxide.

$C_{11}H_{12}ClNO_3S$=273.7

CAS — 80-77-3.

ATC — M03BB02.

ATC Vet — QM03BB02.

UNII — GP568V9G19.

Profile

Chlormezanone has been used in the treatment of anxiety disorders and insomnia. It was also used in conditions associated with painful muscle spasm, often in compound preparations with analgesics; its mechanism of action is not clear but is probably related to its sedative effect. Chlormezanone was withdrawn from use in many countries after reports of serious skin reactions (see below).

Effects on the skin. Chlormezanone was responsible for 5 of 86 cases of fixed drug eruption detected in a Finnish hospital from 1971 to 1980.[1] In the period from 1981 to 1985 chlormezanone was responsible for 1 out of 77 such eruptions.[2] In a case control study[3] comparing drug use in 245 patients hospitalised because of toxic epidermal necrolysis or Stevens-Johnson syndrome and 1147 controls, 13 patients and one control were found to have taken chlormezanone. From these figures a high crude relative risk of 62 was calculated; the excess risk was estimated to be 1.7 cases per million users per week.

1. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Dermatol* 1985; **112:** 575–8.
2. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.
3. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Ansioval; Calmosedan; Cardiosedantol; Diapam; Dolnix; Dolonase; Fibrorelax; Multisedil; Neo Butartrol; Precenid; Promidan; Sedantol; Sedilit; Sin-Algin; ***Hong Kong***: Parazone; ***India***: Dilofen-MR; Dolobak; Ontact Forte; ***S.Afr.***: Myoflex†.

Chlorpromazine *(BAN, rINN)*

Chlorpromazinum; Clorpromazina; Klooripromatsiini; Klorpromazin; Хлорпромазин.

3-(2-Chlorophenothiazin-10-yl)propyldimethylamine.

$C_{17}H_{19}ClN_2S$=318.9

CAS — 50-53-3.

ATC — N05AA01.

ATC Vet — QN05AA01.

UNII — U42B7VYA4P.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Chlorpromazine). A white or creamy-white powder or waxy solid; odourless or almost odourless. M.p. 56 degrees to 58 degrees. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform. Protect from light.

USP 36: (Chlorpromazine). A white crystalline solid with an amine-like odour. It darkens on prolonged exposure to light. Practically insoluble in water; soluble 1 in 3 of alcohol, 1 in 2 of chloroform, 1 in 3 of ether, and 1 in 2 of benzene; freely soluble in dilute mineral acids; practically insoluble in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Chlorpromazine Embonate *(BANM, rINNM)*

Chlorpromazine, Embonate de; Chlorpromazine Pamoate; Chlorpromazini Embonas; Clorpromazina, embonato de; Embonato de clorpromazina; Хлорпромазина Эмбонат.

$(C_{17}H_{19}ClN_2S)_2C_{23}H_{16}O_6$=1026.1

ATC — N05AA01.

ATC Vet — QN05AA01.

UNII — 85RG9X8ZHE.

Chlorpromazine Hydrochloride

(BANM, rINNM)

Aminazine; Chloropromazyny chlorowodorek; Chlorpromazin hydrochlorid; Chlorpromazine, Chlorhydrate de; Chlorpromazinhydrochlorid; Chlorpromazini Hydrochloridum; Chlorpromazino hidrochloridas; Clorpromazina, hidrocloruro de; Hidrocloruro de clorpromazina; Klooripromatsiinihydrokloridi; Klorpromazin Hidroklorür; Klórpromazin-hidroklorid; Klorpromazinhydroklorid; Хлорпромазина Гидрохлорид.

$C_{17}H_{19}ClN_2S$,HCl=355.3

CAS — 69-09-0.

ATC — N05AA01.

ATC Vet — QN05AA01.

UNII — 9WP59609J6.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chlorpromazine Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. It decomposes on exposure to air and light. Very soluble in water; freely soluble in alcohol. A freshly prepared 10% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Chlorpromazine Hydrochloride). A white or slightly creamy-white odourless crystalline powder. It darkens on prolonged exposure to light. Soluble 1 in 1 of water, 1 in 1.5 of alcohol, and 1 in 1.5 of chloroform; insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Dilution. Solutions containing 2.5% of chlorpromazine hydrochloride may be diluted to 100 mL with 0.9% sodium chloride solution provided that the pH of the dilution does not exceed the critical range of pH 6.7 to 6.8.[1] Using saline of pH 7.0 or 7.2, the final solution had a pH of 6.4.

1. D'Arcy PF, Thompson KM. Stability of chlorpromazine hydrochloride added to intravenous infusion fluids. *Pharm J* 1973; **210:** 28.

Incompatibility. Incompatibility has been reported between chlorpromazine hydrochloride injection and several other compounds; precipitation of chlorpromazine base from solution is particularly likely if the final pH is increased. Compounds reported to be incompatible with chlorpromazine hydrochloride include aminophylline, amphotericin B, aztreonam, some barbiturates, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, morphine sulfate (when preserved with chlorocresol), some penicillins, and remifentanil.

For a warning about incompatibility between chlorpromazine solution (*Thorazine; GSK, USA*) and carbamazepine suspension (*Tegretol; Novartis, USA*), see p. 512.2.

Sorption. There was a 41% loss of chlorpromazine hydrochloride from solution when infused for 7 hours via a plastic infusion set (cellulose propionate burette with PVC tubing), and a 79% loss after infusion for 1 hour from a glass syringe through silastic tubing.[1] Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.

Uses and Administration

Chlorpromazine is a phenothiazine antipsychotic. It has a wide range of activity arising from its depressant actions on the CNS and its alpha-adrenergic blocking and antimuscarinic activities. Chlorpromazine is a dopamine inhibitor; the turnover of dopamine in the brain is also increased. There is some evidence that the antagonism of central dopaminergic function, especially at the D_2-dopaminergic receptor, is related to therapeutic effect in psychotic conditions. Chlorpromazine possesses sedative properties but patients usually develop tolerance rapidly to the sedation. It has antiemetic, serotonin-blocking, and weak antihistaminic properties and slight ganglion-blocking activity. It inhibits the heat-regulating centre so that the patient tends to acquire the temperature of the surroundings (poikilothermy). Chlorpromazine can relax skeletal muscle.

Chlorpromazine is widely used in the management of psychotic conditions as well as in some non-psychotic disorders, such as:

- acute and chronic schizophrenia (p. 1047.1)
- to reduce acute mania, as in bipolar disorder (p. 1046.2)
- control of severely disturbed, agitated, or violent behaviour (p. 1030.2) and sometimes other psychiatric conditions
- as an adjunct for the short-term treatment of severe anxiety (but see also p. 1028.1), and to reduce preoperative anxiety
- as an antiemetic in some forms of nausea and vomiting (p. 1047.1); it is ineffective in motion sickness
- in the alleviation of intractable hiccup (p. 1046.3)
- as an adjunct in the treatment of tetanus (p. 209.2 and p. 2029.2) and to control symptoms in acute intermittent porphyria (p. 1556.1)
- for induction of hypothermia

Chlorpromazine is given orally as the hydrochloride and the embonate. For both salts, the doses are expressed as the hydrochloride; chlorpromazine embonate 144 mg is equivalent to about 100 mg of chlorpromazine hydrochloride. The phenolphthalinate has also been used orally. Chlorpromazine is also given by injection as the hydrochloride and doses are expressed in terms of this salt. The base is given rectally as suppositories; doses are in terms of the base.

Dosage varies both with the individual and with the purpose for which the drug is being used. In most patients with **psychiatric conditions** *oral treatment* may be used from the start, typically commencing with a dosage of 25 mg of the hydrochloride, or its equivalent as the embonate, three times daily and increasing as necessary; daily doses of 75 mg may be given as a single dose at night. In some patients doses of 10 mg three times daily may be adequate. Maintenance doses, when required, usually range from 25 to 100 mg three times daily, although psychotic patients may require daily doses of up to 1 g or more.

For *parenteral use*, deep intramuscular injection is preferable for psychiatric and most **other indications**, but diluted solutions have sometimes been given by slow intravenous infusion for indications such as tetanus, severe intractable hiccup, or nausea and vomiting associated with surgery. Subcutaneous injection is contra-indicated. After injection of chlorpromazine, patients should remain in the supine position for at least 30 minutes; blood pressure should be monitored. The usual dose by intramuscular injection is 25 to 50 mg repeated every 6 to 8 hours if required, although oral therapy should be substituted as soon as possible.

If the oral and parenteral routes are not suitable chlorpromazine may be given *rectally* as suppositories containing 100 mg of chlorpromazine base; this is stated to have an effect comparable with 40 to 50 mg of the hydrochloride orally or 20 to 25 mg intramuscularly. The usual rectal dose is 100 mg every 6 to 8 hours.

Initial oral doses of chlorpromazine of one-third to one-half the usual adult dose have been recommended for *elderly* or *debilitated patients*; doses should be increased more gradually. Intramuscular doses in the elderly may need to be reduced to up to one-quarter of the usual dose.

Doses of 10 to 25 mg every 4 to 6 hours orally are recommended for control of **nausea and vomiting**. If necessary, an initial dose of 25 mg may be given by intramuscular injection, followed by 25 to 50 mg every 3 to 4 hours until vomiting stops.

If **intractable hiccup** does not respond to an oral dose of 25 to 50 mg three or four times daily for 2 to 3 days then 25 to 50 mg may be given intramuscularly; if this fails 25 to 50 mg in 500 to 1000 mL of 0.9% sodium chloride should be given by slow intravenous infusion, with the patient supine, and careful monitoring of the blood pressure.

For details of doses in *children*, see below.

Action. The therapeutic effects of antipsychotics appear to be mediated, at least in part, by interference with dopamine transmission in the brain. Chlorpromazine, thioridazine, and thioxanthene derivatives have relatively equal affinity for D_1 or D_2 receptors, although their metabolites tend to be more potent as D_2 blockers.[1] Butyrophenones (such as haloperidol) and diphenylbutylpiperidines (such as pimozide) are relatively selective for D_2 receptors, and the substituted benzamides (such as sulpiride) are highly D_2-specific. Clozapine has complex actions: it is a relatively weak inhibitor of D_2 receptors but has a high affinity for several other receptors including D_1, D_4, and serotonin$_2$ ($5\text{-}HT_2$) receptors.[2] Other atypicals mostly share this profile of greater $5\text{-}HT_2$ than D_2 antagonism.[2]

The traditional hypothesis of the action of antipsychotics has been that blockade of D_2 receptors in the limbic and cortical regions is responsible for the antipsychotic effects, and that adverse extrapyramidal motor effects result from blockade of D_2 receptors in the striatum (a typical motor region of the basal ganglia).[3] Modification of prolactin secretion results from blockade of D_2 receptors in the anterior pituitary. However, this hypothesis cannot satisfactorily account for the pharmacological profiles of atypical antipsychotics and the debate concerning their mechanism of action continues. It has been suggested that the balance between $5\text{-}HT_2$ and D_2 antagonism is important in determining 'atypicality' (but the atypical antipsychotic amisulpride lacks marked $5\text{-}HT_2$ antagonism), or that rapid dissociation from the D_2 receptor may be the determining factor (but it is not clear that some atypicals such as risperidone meet this criterion).[2] Other systems, such as glutamate, may play a role in modulating efficacy against negative versus positive symptoms;[2] it has been suggested that the calcium antagonist actions of the diphenylbutylpiperidines may also be important in this respect.[4]

Division of antipsychotics into low- and high-potency drugs is discussed in Administration, below. For reference to the actions of antipsychotics on neuroendocrine function, see Effects on Endocrine Function under Adverse Effects, p. 1048.2.

1. Ereshefsky L, *et al*. Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9:** 682–707.
2. Remington G. Understanding antipsychotic 'atypicality': a clinical and pharmacological moving target. *J Psychiatry Neurosci* 2003; **28:** 275–84.
3. Anonymous. Now we understand antipsychotics? *Lancet* 1990; **336:** 1222–3.
4. Snyder SH. Drug and neurotransmitter receptors: new perspectives with clinical relevance. *JAMA* 1989; **261:** 3126–9.

Administration. The classical antipsychotics are often divided into:

- **low-potency** drugs (phenothiazines with an aliphatic or piperidine side-chain or thioxanthenes with an aliphatic side-chain)
- **high-potency** drugs (butyrophenones, diphenylbutylpiperidines, and phenothiazines or thioxanthenes with a piperazine side-chain)

At doses with equipotent antipsychotic activity, the low-potency drugs are more prone to cause sedation and antimuscarinic or α-adrenergic-blocking effects than the high-potency drugs. However, they are associated with a lower incidence of extrapyramidal effects, with the exception of tardive dyskinesia which is likely to occur to the same extent with all classical antipsychotics.

Equivalent doses of antipsychotics quoted in the literature have varied considerably. In the UK the following daily doses of oral antipsychotics have been suggested to have approximately equipotent antipsychotic activity for doses up to the maximum licensed doses:

- chlorpromazine hydrochloride 100 mg
- clozapine 50 mg
- haloperidol 2 to 3 mg
- pimozide 2 mg
- risperidone 0.5 to 1 mg
- sulpiride 200 mg
- thioridazine 100 mg
- trifluoperazine 5 mg

It should be noted that all patients receiving pimozide require an ECG before, and periodically during, treatment (see p. 1097.2). Droperidol and thioridazine also require specialist supervision (see p. 1072.1 and p. 1110.3, respectively).

Suggested equipotent doses of intramuscular depot antipsychotics are:

- flupentixol decanoate 40 mg every 2 weeks
- fluphenazine decanoate 25 mg every 2 weeks
- haloperidol (as the decanoate) 100 mg every 4 weeks
- pipotiazine palmitate 50 mg every 4 weeks
- zuclopenthixol decanoate 200 mg every 2 weeks

It has been noted[1] that *high doses* of antipsychotics (greater than the equivalent of 600 mg of chlorpromazine daily) are generally not necessary for the treatment (both initial and maintenance) of psychotic disorders, and may be associated with an increased risk of adverse effects as well as with a diminished clinical response. However, if high doses of antipsychotics have to be used, then doses should be increased gradually with caution and under the supervision of a specialist with facilities for emergency resuscitation available. The Royal College of Psychiatrists in the UK (which defines high-dose therapy as that involving a total daily dose greater than the upper limit recommended in the *BNF*) has issued recommendations concerning the use of high-dose antipsychotic medication.[2] It considers:

- current evidence does not justify the routine use of high-dose therapy with antipsychotics
- if high-dose therapy is used, this should only be after evidence-based strategies have failed, and as a carefully-monitored therapeutic trial
- the decision to use high-dose therapy, and the expected outcome, should be fully documented, after expert assessment of the patient
- the possible contra-indications to therapy, and the risk of drug interactions, should be assessed beforehand
- an ECG should be carried out before starting high-dose therapy and should be repeated after a few days, and then every 1 to 3 months in the early stages of treatment, or as clinically indicated
- doses should be increased in relatively small increments, with time to assess response before a further increase
- the use of 'as-required' antipsychotic medication, and of drug combinations, should be carefully monitored to avoid the inadvertent increase of total doses above high-dose thresholds

The existence of a *therapeutic range* (or therapeutic window) has not been found for most antipsychotics (with the possible exception of haloperidol[3]), and plasma concentrations of these drugs must be interpreted with caution.[1,3] Many factors make it difficult to establish a meaningful correlation between dose, plasma concentrations, and clinical improvement. These include incomplete absorption, first-pass effect, enzyme induction, the presence of active and inactive metabolites, ethnicity, smoking, and factors occurring at the receptor level.[3]

1. Baldessarini RJ, *et al*. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988; **45:** 77–91.
2. The Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. *Council Report CR138*; London: Royal College of Psychiatrists, May 2006. Available at: http://www.rcpsych.ac.uk/files/pdfversion/CR138.pdf (accessed 30/05/06)
3. Sramek JJ, *et al*. Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22:** 373–80.

Administration in children. Chlorpromazine is used in children for the management of acute and chronic schizophrenia, control of severely disturbed, agitated, or violent behaviour, autism, to reduce pre-operative anxiety, and as an antiemetic in some forms of nausea and vomiting. It has also been used for induction of hypothermia.

Chlorpromazine hydrochloride may be given to children aged 1 to 12 years in a dose of 500 micrograms/kg every 4 to 6 hours orally or every 6 to 8 hours by intramuscular injection. However, for psychiatric indications the oral dose for children aged 6 to 12 years is usually one-third to one-half the usual adult dose (see p. 1045.3); alternatively, the *BNFC* suggests an oral dose of 10 mg 3 times daily. To reduce pre-operative anxiety a single oral dose is given 2 to 3 hours before the procedure. For all indications, daily doses should not normally exceed 40 mg of chlorpromazine hydrochloride in children aged 1 to 5 years or 75 mg in those aged 6 to 12 years. Chlorpromazine may be given to infants under 1 year of age if considered to be life-saving. Children and adolescents aged 12 years and over may be given usual adult doses, see p. 1045.3.

For reference to the use of lytic cocktails containing chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see Lytic Cocktails, under Sedation, p. 122.2.

Bipolar disorder. Patients with bipolar disorder (p. 397.2) suffering from acute mania with coexisting psychotic features, agitation, or disruptive behaviour are usually treated with antipsychotics as they produce rapid control of symptoms. Classical antipsychotics such as chlorpromazine or haloperidol have been widely used, although use of atypical antipsychotics, such as clozapine or olanzapine, is growing.

Chorea. For a discussion of the management of various choreas, including mention of the use of phenothiazines such as chlorpromazine, see p. 1029.3.

Dyspnoea. It has been shown that in healthy subjects an oral dose of 25 mg of chlorpromazine hydrochloride can reduce exercise-induced breathlessness without affecting ventilation or causing sedation.[1] Although other drugs may be preferred in patients with advanced cancer and dyspnoea (p. 108.3), chlorpromazine may relieve air hunger unresponsive to usual measures,[2] and, if required, can be used to sedate dying patients who have unrelieved distress. It is recommended that initial doses should be small: 12.5 mg by slow intravenous injection or 25 mg by suppository may be given.

1. O'Neill PA, *et al*. Chlorpromazine—a specific effect on breathlessness? *Br J Clin Pharmacol* 1985; **19:** 793–7.
2. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to other drugs.[1] However, they often act non-specifically, damping down excessive movements by causing a degree of drug-induced parkinsonism and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders, under Adverse Effects, p. 1049.2).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.

Eclampsia and pre-eclampsia. Drug combinations known as lytic cocktails have been used in many countries for the management of pre-eclampsia and imminent eclampsia. The cocktail has usually consisted of a combination of chlorpromazine, pethidine, and/or promethazine. In general, however, phenothiazines are not recommended in late pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p. 1251.1); the management of eclampsia, which is the convulsive phase, is discussed on p. 511.1.

Headache. Some phenothiazines such as chlorpromazine, levomepromazine, and prochlorperazine have been used in migraine to control severe nausea and vomiting unresponsive to antiemetics such as metoclopramide and domperidone (see p. 670.3), and to relieve the pain of severe migraine attacks unresponsive to parenteral dihydroergotamine or sumatriptan.

References.

1. Stiell IG, *et al*. Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20:** 1201–5.
2. Jones EB, *et al*. Safety and efficacy of rectal prochlorperazine for the treatment of migraine in the emergency department. *Ann Emerg Med* 1994; **24:** 237–41.
3. Coppola M, *et al*. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26:** 541–6.
4. Jones J, *et al*. Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14:** 262–4.
5. Kelly AM, *et al*. Intravenous chlorpromazine versus intramuscular sumatriptan for acute migraine. *J Accid Emerg Med* 1997; **14:** 209–11.
6. Bigal ME, *et al*. Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med* 2002; **23:** 141–8.

Hiccup. A hiccup is an involuntary spasmodic contraction of the diaphragm that causes a sudden inspiration of air which is then checked abruptly by closure of the glottis. Hiccups often have a simple cause such as gastric distension and usually resolve spontaneously or respond to simple measures. Intractable hiccups may stem from a serious underlying cause such as brain disorders, metabolic or endocrine disturbances, CNS infections, and oesophageal or other gastrointestinal disorders. Other precipitants include anaesthesia or drug therapy.

Treatment of intractable hiccups should initially be aimed at controlling or removing the underlying cause including the relief of gastric distension or oesophageal obstruction.[1-5] Measures that raise carbon dioxide pressure such as breath holding, rebreathing, or alteration of normal respiratory rhythm can be effective. Stimulation of the pharynx can also interrupt hiccups and may explain the action of a host of remedies such as sipping iced water, gargling, and swallowing granulated sugar. Many drugs have been tried in the treatment of hiccups but evidence of efficacy is largely from anecdotal reports or uncontrolled studies. An early treatment protocol[6] for intractable hiccups (based on a review of the literature and the authors' experience) suggested stepwise management until an effective measure was found, as follows:

- correction of any metabolic abnormality
- swallowing dry granulated sugar
- decompressing the stomach via nasogastric tube, then irritation of the pharynx
- intravenous chlorpromazine 25 to 50 mg, repeated up to 3 times if necessary; if parenteral therapy is effective maintain on oral chlorpromazine for 10 days (licensed

information recommends the use of oral therapy first — see Uses and Administration, p. 1045.3)
- metoclopramide 10 mg intravenously; if successful maintain on oral metoclopramide for 10 days
- oral quinidine 200 mg 4 times daily
- if this fails, consider left phrenic nerve block and crush

In later discussions,[1,3] chlorpromazine still emerged as the most consistently effective drug treatment; metoclopramide appeared to be an acceptable second choice and nifedipine an appropriate third choice,[3] although haloperidol was also considered to be of value.[1,4] Other phenothiazines that have been used for intractable hiccup include perphenazine and promazine. It was also considered that clonazepam, carbamazepine, phenytoin, and valproic acid might be of value, especially in neuropathic hiccups.[1] Some beneficial results have been reported with amitriptyline and amantadine; other drugs being tried in the treatment of hiccups include baclofen and gabapentin. The *BNF* recommends that in palliative care patients, a preparation combining an antacid with an antiflatulent be given for hiccups due to gastric distension. If this fails, metoclopramide (orally or by subcutaneous or intramuscular injection) should be added; baclofen, nifedipine, or chlorpromazine should be reserved for those patients in whom metoclopramide is also ineffective.

1. Howard RS. Persistent hiccups: if excluding or treating any underlying pathology fails try chlorpromazine. *BMJ* 1992; **305:** 1237–8.
2. Rousseau P. Hiccups. *South Med J* 1995; **88:** 175–81.
3. Friedman NL. Hiccups: a treatment review. *Pharmacotherapy* 1996; **16:** 986–95.
4. WHO. Hiccup. In: *Symptom relief in terminal illness*. Geneva: WHO, 1998.
5. Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. *Am J Hosp Palliat Care* 2003; **20:** 149–54.
6. Williamson BWA, Macintyre IMC. Management of intractable hiccup. *BMJ* 1977; **2:** 501–3.

Lesch-Nyhan syndrome. The Lesch-Nyhan syndrome is an inherited disorder caused by a complete deficiency of hypoxanthine-guanine phosphoribosyl transferase, an enzyme involved in purine metabolism. It is characterised by hyperuricaemia, spasticity, choreoathetosis, self-mutilation, and mental retardation. The hyperuricaemia (see p. 600.1) can be controlled by drugs such as allopurinol but there appears to be no effective treatment for the neurological deficits. It has been suggested that the behavioural problems might be associated with alterations in the brain's dopamine system. There have been rare reports of improvement in self-mutilation in patients given antipsychotics or antiepileptics such as carbamazepine and gabapentin.

References.
1. Nyhan WL, Wong DF. New approaches to understanding Lesch-Nyhan disease. *N Engl J Med* 1996; **334:** 1602–4.

Migraine. See under Headache, p. 1046.3.

Nausea and vomiting. Many antipsychotics, with the notable exception of thioridazine, have antiemetic properties and have been used in the prevention and treatment of nausea and vomiting (p. 1814.3) arising from a variety of causes such as radiation sickness, malignancy, and emesis caused by drugs, including antineoplastics and opioid analgesics. Reference to the risk to the fetus of therapy with phenothiazines during pregnancy can be found under Precautions, p. 1051.3 and on p. 614.2.

Schizophrenia. Classical antipsychotics such as chlorpromazine, haloperidol, and thioridazine have been the traditional drug treatment of choice for patients with schizophrenia (p. 1031.3); however, atypical antipsychotics may now be preferred as first-line therapy. There is little difference in efficacy between the classical antipsychotics, but the use of thioridazine is now restricted in the treatment of schizophrenia because of the risk of cardiotoxicity.

Substance dependence. *ALCOHOL* For advice against the use of antipsychotics for alcohol withdrawal, see p. 1735.1.

OPIOIDS. In a discussion of neonatal abstinence syndrome (p. 110.1), it was noted in 1986 that, although opioids, diazepam, and phenobarbital were widely used in the USA for the management of this condition, chlorpromazine had tended to be the preferred treatment in the UK.[1] This was still true as late as the mid-1990s, although practice varied widely.[2] However, a systematic review[3] found insufficient evidence to support the use of chlorpromazine in the management of neonatal abstinence syndrome. The following dosage schedule has been suggested:[1] chlorpromazine is begun with a loading dose of 3 mg/kg, followed by a total oral maintenance dose of 3 mg/kg daily, divided into 4 or 6 doses. The authors suggested that this dose might be increased by 3 mg/kg daily if withdrawal symptoms were particularly severe. Once stabilised a reduction in the dose of chlorpromazine by 2 mg/kg every third day is attempted.[1] Complications of phenothiazine usage have been notably absent, although rarely seizures may occur.

1. Rivers RPA. Neonatal opiate withdrawal. *Arch Dis Child* 1986; **61:** 1236–9.
2. Morrison CL, Siney C. A survey of the management of neonatal opiate withdrawal in England and Wales. *Eur J Pediatr* 1996; **155:** 323–6.
3. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 02/10/07).

Taste disorders. Disturbances of the sense of taste may be broadly divided into either loss or distortion of taste. Loss of taste may be either complete (ageusia) or partial (hypogeusia). Distortion of taste (dysgeusia) may occur as aliageusia in which stimuli such as food or drink produce an inappropriate taste or as phantogeusia in which an unpleasant taste is not associated with an external stimuli and is sometimes referred to as a gustatory hallucination. Taste disturbances have many causes including infections, metabolic or nutritional disturbances, radiation, CNS disorders, neoplasms, drug therapy, or may occur as a consequence of normal ageing.[1] Management mainly consists of treatment of any underlying disorder. Withdrawal of offending drug therapy is commonly associated with resolution but occasionally effects persist and may require treatment.[2] Zinc or vitamin therapy has been used but there is insufficient evidence to indicate efficacy[1,3] for taste disturbances secondary to drug therapy or medical conditions that do not involve low zinc or vitamin concentrations. Phantogeusia might be linked to excessive activity of dopaminergic receptors as it has been reported[4] to respond to short-term treatment with small doses of antipsychotic drugs such as haloperidol or pimozide.

1. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA* 1997; **278:** 1357–62.
2. Henkin RI. Drug-induced taste and smell disorders: incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Safety* 1994; **11:** 318–77.
3. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; **30:** 186–7.
4. Henkin RI. Salty and bitter taste. *JAMA* 1991; **265:** 2253.

Adverse Effects

Chlorpromazine generally produces less central depression than the barbiturates or benzodiazepines, and tolerance to its initial sedative effects develops fairly quickly in most patients. It has antimuscarinic properties and may cause adverse effects such as dry mouth, constipation, difficulty with micturition, blurred vision, and mydriasis. Tachycardia, ECG changes (particularly Q-and T-wave abnormalities), and, rarely, cardiac arrhythmias may occur; hypotension (usually orthostatic) is common. Other adverse effects include delirium, agitation and, rarely, catatonic-like states, insomnia or drowsiness, nightmares, depression, miosis, EEG changes and convulsions, nasal congestion, precipitation of glaucoma, minor abnormalities in liver function tests, inhibition of ejaculation, impotence, and priapism.

Hypersensitivity reactions include urticaria, exfoliative dermatitis, erythema multiforme, and contact sensitivity. A syndrome resembling SLE has been reported. Jaundice has occurred, and probably has an immunological origin. Prolonged therapy may lead to deposition of pigment in the skin, or more frequently the eyes; corneal and lens opacities have occurred. Pigmentary retinopathy has occurred only rarely with chlorpromazine. Photosensitivity reactions are more common with chlorpromazine than with other antipsychotics.

Haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, and a potentially fatal agranulocytosis have occasionally been reported; they may be manifestations of a hypersensitivity reaction. Most cases of agranulocytosis have occurred within 4 to 10 weeks of starting treatment, and symptoms such as sore throat or fever should be watched for and white cell counts instituted should they appear. Mild leucopenia has been stated to occur in up to 30% of patients on prolonged high dosage.

Extrapyramidal dysfunction and resultant disorders include acute dystonia, a parkinsonism-like syndrome, and akathisia; late effects include tardive dyskinesia and perioral tremor. The neuroleptic malignant syndrome may also occur.

Chlorpromazine alters endocrine and metabolic functions. Patients have developed amenorrhoea, galactorrhoea, and gynaecomastia due to hyperprolactinaemia, weight gain, and hyperglycaemia and altered glucose tolerance. Body temperature regulation is impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

There have been isolated reports of sudden death with chlorpromazine; possible causes include cardiac arrhythmias or aspiration and asphyxia due to suppression of the cough and gag reflexes.

Pain and irritation at the injection site may occur on injection. Nodule formation may occur after intramuscular injection.

Phenothiazines do not cause dependence of the type encountered with barbiturates or benzodiazepines. However, withdrawal symptoms have been seen on abrupt withdrawal in patients receiving prolonged and/or high-dose maintenance therapy.

Although the adverse effects of **other phenothiazines** are broadly similar in nature to those of chlorpromazine, their frequency and pattern tend to fall into 3 groups:
- group 1 (e.g. chlorpromazine, levomepromazine, and promazine) are generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal effects
- group 2 (e.g. pericyazine, pipotiazine, and thioridazine) are generally characterised by moderate sedative effects, marked antimuscarinic effects, and fewer extrapyramidal effects than groups 1 or 3
- group 3 (e.g. fluphenazine, perphenazine, prochlorperazine, and trifluoperazine) are generally characterised by fewer sedative and antimuscarinic effects but more pronounced extrapyramidal effects than groups 1 or 2

Classical antipsychotics of **other chemical groups** tend to resemble the phenothiazines of group 3. They include the butyrophenones (e.g. benperidol and haloperidol); diphenylbutylpiperidines (e.g. pimozide); thioxanthenes (flupentixol and zuclopenthixol); substituted benzamides (e.g. sulpiride); oxypertine; and loxapine.

Carcinogenicity. See Effects on Endocrine Function, p. 1048.2.

Convulsions. Treatment with antipsychotics can result in EEG abnormalities and lowered seizure threshold.[1] Seizures can be induced particularly in patients with a history of epilepsy or drug-induced seizures, abnormal EEG, previous electroconvulsive therapy, or pre-existing CNS abnormalities. The risk appears to be greatest at the start of antipsychotic therapy, or with high doses, or abrupt increases of dose, or with the use of more than one antipsychotic. The incidence of antipsychotic-induced convulsions is, however, probably less than 1%.

In general, the epileptic potential has been correlated with the propensity of the antipsychotic to cause sedation. Phenothiazines with marked sedative effects [group 1] such as chlorpromazine appear to present a higher risk than those with strong extrapyramidal effects [group 3]. Haloperidol appears to carry a relatively low risk of seizures. The following drugs have been suggested when classical antipsychotic therapy is considered necessary in patients at risk of seizures or being treated for epilepsy: fluphenazine, haloperidol, pimozide, or trifluoperazine. Antipsychotic dosage should be increased slowly and the possibility of interactions with antiepileptic therapy considered (see under Interactions, p. 1052.2).

The atypical antipsychotic clozapine appears to be associated with a particularly high risk of seizures (see Effects on the Nervous System, under Clozapine, p. 1060.1). Risperidone may be preferred if an atypical antipsychotic is to be used in patients at risk of seizures.

1. Pisani F, *et al.* Effects of psychotropic drugs on seizure threshold. *Drug Safety* 2002; **25:** 91–110.

Effects on the blood. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them phenothiazines for which there were 87 reports of agranulocytosis (42 fatal) and 33 of neutropenia (22 fatal). The most frequently implicated phenothiazines were chlorpromazine with 51 reports of agranulocytosis (26 fatal) and 12 of neutropenia (2 fatal) and thioridazine with 20 reports of agranulocytosis (9 fatal) and 10 of neutropenia (none fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 18/07/08)

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. For further details, see Effects on Body-weight, in Clozapine, p. 1059.1.

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.

Effects on the cardiovascular system. Orthostatic hypotension is a common problem in patients taking psychotropic drugs and is particularly pronounced with low-potency antipsychotics.[1]

Various **ECG changes** or frank **arrhythmias** have occurred in patients receiving antipsychotics. T-wave changes have been reported with low-potency antipsychotics; they are usually benign and reversible, and subject to diurnal fluctuations. Low-potency antipsychotics, particularly *thioridazine* and *mesoridazine*, and the high-potency drug *pimozide*, prolong the QT interval in a similar manner to class I antiarrhythmics such as quinidine or procainamide; their use is therefore contra-indicated in patients taking such antiarrhythmics. *Droperidol*, another high-potency drug, has also been reported to prolong the QT interval.[2] Thioridazine is most frequently discussed in case reports of psychotropic drug-induced torsade de pointes;[2] *chlorpromazine* and *pimozide* have also been implicated. The increased risk of QT prolongation with droperidol, mesoridazine, and thioridazine have led to restrictions on their use; for further details see individual monographs. Torsade de pointes has also been reported after overdosage[3-5] with, or high intravenous[6] doses of, the high-potency antipsychotic *haloperidol*. There are also isolated reports of cardiac arrhythmias after attempts at rapid control with high doses of haloperidol.[7,8] *Melperone*, a butyrophenone antipsychotic related to haloperidol, has been reported to have class III electrophysiologic and antiarrhythmic activity.[9,10]

In the UK, the risk of arrhythmias with antipsychotic treatment has been considered by an expert working group of the CSM;[11] the following recommendations were made regarding ECG monitoring:

- the need for an ECG should be based on a patient's relevant medical history, family history, and clinical examination; the elderly and those with a personal or family history of heart disease or any cardiac abnormalities would benefit the most from a baseline ECG (Licensed product information for both pimozide and thioridazine recommend that an ECG should be performed in all patients before starting treatment with either of these drugs.)
- during treatment an ECG should be performed in patients who have palpitations or other symptoms suggestive of cardiac disease; if the QT interval is prolonged then a reduction in dose may be required, if it exceeds 500 milliseconds treatment may need to be stopped
- an ECG should be considered during dose increases
- potassium levels should be monitored before and during treatment and in particular during periods of acute illnesses

Sudden unexpected deaths have been reported in patients receiving classical or atypical antipsychotics.[12] Whether this is due to the disease being treated or to the treatment is still unclear. However, in a retrospective cohort study[13] involving about 482 000 patients, analysis of 1487 sudden cardiac deaths indicated that patients receiving classical antipsychotics in doses of more than 100 mg of thioridazine or its equivalent had a 2.4-fold increase in the rate of sudden cardiac death, rising to a 3.53-fold increase in those patients with pre-existing severe cardiovascular disease. A later case-control study[14] in 5 UK psychiatric hospitals found that sudden unexplained death in psychiatric patients was associated with hypertension, ischaemic heart disease, and current treatment with thioridazine. Although several mechanisms have been suggested for the effect, prolongation of the QT interval has been implicated in a proportion of the cases.[12] More recently, in a retrospective cohort study,[15] involving 93 300 antipsychotic users (44 218 used classical antipsychotics and 46 089 used atypicals) and 186 600 matched controls of non-users, analyses of 1870 sudden cardiac deaths that occurred during the approximately 1 million patient-years of follow-up concluded that current users of classical or atypical antipsychotics had a similar dose-related increased risk of sudden cardiac death when compared with non-users; former users had no significantly increased risk. The excess mortality may also in part be due to the poor health outcomes of some patients with schizophrenia because of lack of appropriate health care. An 11-year follow-up cohort study[16] in schizophrenics concluded that all-cause mortality was decreased with the long-term use of classical or atypical antipsychotics when compared with no antipsychotic use. In addition, the study also found that current use of clozapine was associated with the lowest mortality rate when compared with current use of perphenazine; quetiapine, haloperidol, and risperidone had the highest rates.

Results from a case-control study[17] have suggested that use of classical antipsychotics may be associated with an increased risk of idiopathic **venous thromboembolism.** The risk was most pronounced during the first 3 months of treatment, and was higher for low-potency than high-potency antipsychotics; this study did not examine the risk of venous thromboembolism with atypical antipsychotics. A more recent analysis[18] of the WHO database of adverse drug reactions found no association between venous thromboembolism and the use of low-potency or high-potency classical antipsychotics when considered as 2 groups; however, a statistically significant association was found with the use of zuclopenthixol, a high-potency drug, when considered on its own. A robust association was also found with the use of atypical antipsychotics—see also under Clozapine, p. 1059.3. Nevertheless, the authors acknowledged the limitations of this study such as reporting bias and incomplete clinical data, and further investigation was considered warranted.

1. DiGiacomo J. Cardiovascular effects of psychotropic drugs. *Cardiovasc Rev Rep* 1989; **10:** 31–2, 39–41, and 47.
2. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355:** 1048–52.
3. Zee-Cheng C-S, *et al.* Haloperidol and torsades de pointes. *Ann Intern Med* 1985; **102:** 418.
4. Henderson RA, *et al.* Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. *Hum Exp Toxicol* 1991; **10:** 59–62.
5. Wilt JL, *et al.* Torsade de pointes associated with the use of intravenous haloperidol. *Ann Intern Med* 1993; **119:** 391–4.
6. O'Brien JM, *et al.* Haloperidol-induced torsade de pointes. *Ann Pharmacother* 1999; **33:** 1046–50.
7. Mehta D, *et al.* Cardiac arrhythmia and haloperidol. *Am J Psychiatry* 1979; **136:** 1468–9.
8. Bett JHN, Holt GW. Malignant ventricular tachyarrhythmia and haloperidol. *BMJ* 1983; **287:** 1264.
9. Møgelvang JC, *et al.* Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; **208:** 61–4.
10. Hui WKK, *et al.* Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; **15:** 144–9.
11. CSM/MHRA. Cardiac arrhythmias associated with antipsychotic drugs. *Current Problems* 2006; **31:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
12. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 2002; **62:** 1649–71.
13. Ray WA, *et al.* Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; **58:** 1161–7.
14. Reilly JG, *et al.* Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry* 2002; **180:** 515–22.
15. Ray WA, *et al.* Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; **360:** 225–35. Correction. *ibid.*; **361:** 1814.
16. Tiihonen J, *et al.* 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; **374:** 620–7.
17. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000; **356:** 1219–23.
18. Hägg S, *et al.* Associations between venous thromboembolism and antipsychotics: a study of the WHO database of adverse drug reactions. *Drug Safety* 2008; **31:** 685–94.

Effects on endocrine function. Antipsychotics can alter the secretion of prolactin, growth hormone, and thyrotrophin from the anterior pituitary via their ability to block central dopamine-D_2 receptors. Therapeutic doses of classical antipsychotics (and some atypical antipsychotics such as amisulpride and risperidone) increase serum-prolactin concentrations; this effect occurs at lower doses and after shorter latent periods than the antipsychotic effects. However, partial tolerance to the hyperprolactinaemic effect may develop on long-term use.[1] Serum prolactin declines to normal values within 3 weeks of stopping oral antipsychotic therapy but may remain raised for 6 months after an intramuscular depot injection.[1]

The long-term consequences of gonadal hormone deficiency, secondary to raised prolactin concentrations, have caused concern. There is evidence[2] that patients taking long-term prolactin-raising antipsychotics are at high risk of osteoporosis associated with hypogonadism. Long-term antipsychotic treatment has also been shown to increase the incidence of mammary tumours in the *rat*. Although early studies[3,4] found little or no evidence that chronic use in humans alters the risk of breast cancer among women with schizophrenia, a later retrospective cohort study[5] found a modest dose-related increase in the risk of breast cancer in women using antipsychotic dopamine antagonists. A similar increase was seen in women receiving antiemetic dopamine antagonists. Fears that pituitary abnormalities, including pituitary tumours,[6] might develop in patients on long-term phenothiazine therapy have not been confirmed.[7,8]

Antipsychotics can in some circumstances reduce both basal and stimulated growth-hormone secretion but attempts to use them to treat dysfunctions in growth-hormone regulation have not been successful.[9] Although some clinical studies show that acute dosage of antipsychotics increased both basal and stimulated thyrotrophin secretion, the majority of studies find either no change or only a small increase in thyrotrophin secretion following long-term use.

A small study[10] has suggested that thioridazine may be more likely than other antipsychotics to decrease serum concentrations of testosterone or luteinising hormone in men. However, concentrations were within the normal range in most patients taking antipsychotics.

See also Effects on Fluid and Electrolyte Homoeostasis, below and Effects on Sexual Function, p. 1049.1.

1. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; **64:** 2291–2314.
2. Meaney AM, *et al.* Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *Br J Psychiatry* 2004; **184:** 503–8.
3. Mortensen PB. The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health* 1989; **43:** 43–7.
4. Mortensen PB. The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res* 1994; **12:** 185–94.
5. Wang PS, *et al.* Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry* 2002; **59:** 1147–54.
6. Asplund K, *et al.* Phenothiazine drugs and pituitary tumors. *Ann Intern Med* 1982; **96:** 533.
7. Rosenblatt S, *et al.* Chronic phenothiazine therapy does not increase sellar size. *Lancet* 1978; **ii:** 319–20.
8. Lilford VA, *et al.* Long-term phenothiazine treatment does not cause pituitary tumours. *Br J Psychiatry* 1984; **144:** 421–4.
9. Gunnet JW, Moore KE. Neuroleptics and neuroendocrine function. *Ann Rev Pharmacol Toxicol* 1988; **28:** 347–66.
10. Brown WA, *et al.* Differential effects of neuroleptic agents on the pituitary-gonadal axis in men. *Arch Gen Psychiatry* 1981; **38:** 1270–2.

Effects on the eyes. Phenothiazines may induce a pigmentary retinopathy that is dependent on both the dose and the duration of treatment.[1] Those phenothiazine derivatives with piperidine side-chains such as thioridazine have a higher risk of inducing retinal toxicity than other phenothiazine derivatives, with relatively few cases reported for those with aliphatic side-chains such as chlorpromazine; the piperazine group does not appear to exert direct ocular toxicity.[2] The retinopathy may present either acutely, (sudden loss of vision associated with retinal oedema and hyperaemia of the optic disc), or chronically, (a fine pigment scatter appearing in the central area of the fundus, extending peripherally but sparing the macula). Chronic paracentral and pericentral scotomas may be found. Although pigmentary disturbances may progress after withdrawal of thioridazine, they are not always paralleled by deterioration in visual function; nonetheless, some cases have led to progressive chorioretinopathy.[3] The critical ocular toxic dose of thioridazine is reported to be 800 mg daily[1] and UK licensed product information has recommended that a daily dose of 600 mg should not usually be exceeded. However, there is a report[4] of pigmentary retinopathy in a patient who received long-term thioridazine in daily doses not exceeding 400 mg; the total dose was 752 g.

Pigmentation may also occur in the cornea, lens, and conjunctiva following use of phenothiazines. It may occur in association with pigmentary changes in the skin and is dose-related. In a study of 100 Malaysian patients, ocular pigmentation occurred in slightly more than half of those who had received a total dose of chlorpromazine of 100 to 299 g and in 13 of 15 who had received 300 to 599 g.[5] All those who had received more than 600 g of chlorpromazine or thioridazine had ocular pigmentation. Cataract formation, mainly of an anterior polar variety, has been seen rarely, mainly in patients on chlorpromazine. It does not appear to be dose-related.[2]

A patient who had received fortnightly injections of fluphenazine 12.5 mg for 10 years (total dose 3.25 g) developed bilateral maculopathy after unprotected exposure of less than 2-minute's duration to a welding arc.[6] It was postulated that accumulation of phenothiazine in the retinal epithelium sensitised the patient to photic damage. However, another patient who had received fortnightly injections of fluphenazine 25 mg for 25 years (total dose 16.25 g) developed bilateral maculopathy without exposure to any extreme photochemical sources.[7] The authors concluded that this was due to a direct effect of fluphenazine secondary to its accumulation in the retinal epithelium.

1. Spiteri MA, James DG. Adverse ocular reactions to drugs. *Postgrad Med J* 1983; **59:** 343–9.
2. Crombie AL. Drugs causing eye problems. *Prescribers' J* 1981; **21:** 222–7.
3. Marmor MF. Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function. *Br J Ophthalmol* 1990; **74:** 739–42.
4. Lam RW, Remick RA. Pigmentary retinopathy associated with low-dose thioridazine treatment. *Can Med Assoc J* 1985; **132:** 737.
5. Ngen CC, Singh P. Long-term phenothiazine administration and the eye in 100 Malaysians. *Br J Psychiatry* 1988; **152:** 278–81.
6. Power WJ, *et al.* Welding arc maculopathy and fluphenazine. *Br J Ophthalmol* 1991; **75:** 433–5.
7. Lee MS, Fern AI. Fluphenazine and its toxic maculopathy. *Ophthalmic Res* 2004; **36:** 237–9.

Effects on fluid and electrolyte homoeostasis. There have been occasional reports of water intoxication in patients taking antipsychotics. A review[1] of hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion associated with psychotropics summarised 20 such reports for antipsychotics in the literature. The drugs implicated were thioridazine (8 reports), haloperidol (3 reports), chlorpromazine, trifluoperazine, and fluphenazine (2 reports each), and flupentixol, tiotixene, and clozapine (1 report each). The majority of reports did not permit clear conclusions and, particularly in the cases of prolonged treatment, the role of the medication was unclear. However, at least 3 of the cases were well documented and supported the view that antipsychotics could cause hyponatraemia. A more recent review[2] has also concluded that both classical and atypical antipsychotics may induce hyponatraemia.

A report not considered by the above review described water retention and peripheral oedema associated with chlorpromazine.[3] A small controlled study[4] found that 5 of

10 evaluated patients receiving haloperidol decanoate had impaired fluid homoeostasis.

1. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
2. Meulendijks D, *et al*. Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. *Drug Safety* 2010; **33:** 101–14.
3. Witz L, *et al*. Chlorpromazine induced fluid retention masquerading as idiopathic oedema. *BMJ* 1987; **294:** 807–8.
4. Rider JM, *et al*. Water handling in patients receiving haloperidol decanoate. *Ann Pharmacother* 1995; **29:** 663–6.

Effects on lipid metabolism. Most antipsychotics are associated with hyperlipidaemia. A review[1] found evidence of a higher risk of hyperlipidaemia in patients receiving low-potency classical antipsychotics, such as chlorpromazine and thioridazine, or the atypical antipsychotics, clozapine, olanzapine, and quetiapine. High-potency classical antipsychotics, such as haloperidol, and the atypical antipsychotics aripiprazole, risperidone, and ziprasidone, appeared to be associated with a lower risk of hyperlipidaemia. Possible mechanisms for dyslipidaemia associated with antipsychotic therapy include the development of glucose intolerance, weight gain, and dietary changes. For further details, see Effects on Body-weight under Adverse Effects of Clozapine, p. 1059.1 and Effects on Body-weight, p. 1047.3.

1. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res* 2004; **70:** 1–17.

Effects on the liver. Chlorpromazine and other phenothiazines may cause hepatocanalicular cholestasis often with hepatocyte damage suggestive of immunological liver injury.[1] Only a small number of patients taking the drug are affected and the onset is usually in the first 4 weeks of therapy. The drug or one of its metabolites may induce alteration in the liver-cell membrane so that it becomes antigenic; there is also good evidence for direct hepatotoxicity related to the production of free drug radical. There may be an individual idiosyncrasy in the metabolism of chlorpromazine and in the production of these radicals. A study has suggested that patients who have poor sulfoxidation status combined with unimpaired hydroxylation capacity may be most likely to develop jaundice with chlorpromazine.[2]

A preliminary study[3] showing a high incidence of gallstones in psychiatric inpatients in Japan found a correlation between the presence of gallstones and the duration of illness and use of antipsychotics. It was speculated that gallstones could be a consequence of phenothiazine-induced cholestasis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Watson RGP, *et al*. A proposed mechanism for chlorpromazine jaundice—defective hepatic sulphoxidation combined with rapid hydroxylation. *J Hepatol* 1988; **7:** 72–8.
3. Fukuzako H, *et al*. Ultrasonography detected a higher incidence of gallstones in psychiatric inpatients. *Acta Psychiatr Scand* 1991; **84:** 83–5.

Effects on sexual function. The phenothiazines can cause both impotence and ejaculatory dysfunction.[1] Thioridazine has been frequently implicated, and in an early report 60% of 57 male patients taking the drug reported sexual dysfunction compared with 25% of 64 men taking other antipsychotics.[2] There are also several reports of priapism with phenothiazines;[1,3-5] alpha-adrenoceptor blocking properties of these compounds may be partly responsible. Male sexual dysfunction, including priapism, has been reported only rarely with other classical antipsychotics such as the butyrophenones, diphenylbutylpiperidines, and thioxanthenes.[6] Priapism has also been reported with clozapine[7] and other atypical antipsychotics. The effects of antipsychotics on female sexual function are less well studied. Orgasmic dysfunction has been reported with thioridazine, trifluoperazine, and fluphenazine.[8]

The effects of hyperprolactinaemia (see Effects on Endocrine Function, p. 1048.2) on sexual function are described on p. 2252.2.

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Kotin J, *et al*. Thioridazine and sexual dysfunction. *Am J Psychiatry* 1976; **133:** 82–5.
3. Baños JE, *et al*. Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
4. Chan J, *et al*. Perphenazine-induced priapism. *DICP Ann Pharmacother* 1990; **24:** 246–9.
5. Salado J, *et al*. Priapism associated with zuclopenthixol. *Ann Pharmacother* 2002; **36:** 1016–18.
6. Fabian J-L. Psychotropic medications and priapism. *Am J Psychiatry* 1993, **150:** 349–50.
7. Patel AG, *et al*. Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
8. Segraves RT. Psychiatric drugs and inhibited female orgasm. *J Sex Marital Ther* 1988; **14:** 202–7.

Effects on the skin. *DEPOT INJECTION.* Of 217 patients given a combined total of 2354 depot antipsychotic injections 42 (19.4%) had local problems at the site of injection; 18 (8.3%) had chronic complications and 30 (13.8%) acute reactions.[1] Acute problems reported included 31 episodes of unusual pain, 21 of bleeding or haematoma, 19 of clinically important leakage of drug from injection site, 11 of acute inflammatory indurations, and 2 of transient nodules. Complications were more common in patients receiving concentrated preparations, higher doses, weekly injections, haloperidol decanoate or zuclopenthixol decanoate, and injection volumes greater than 1 mL and in those treated for more than 5 years. Chronic reactions were more common in patients aged over 50 years.

1. Hay J. Complications at site of injection of depot neuroleptics. *BMJ* 1995; **311:** 421.

PHOTOSENSITIVITY. Testing in 7 subjects taking chlorpromazine revealed that photosensitivity reactions manifested mainly as immediate erythema and that sensitivity was primarily to light in the long ultraviolet (UVA) and visible wavebands. Sensitivity to UVB was normal.[1]

The incidence of photosensitivity reactions to chlorpromazine has been given as 3%. However, a higher incidence of 16 to 25% has also been reported.[2]

See also Effects on the Eyes, p. 1048.3.

1. Ferguson J, *et al*. Further clinical and investigative studies of chlorpromazine phototoxicity. *Br J Dermatol* 1986; **115** (suppl 30): 35.
2. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; **14:** 252–9.

PIGMENTATION. The pigment found in the skin of patients treated with chlorpromazine was considered[1] to be a chlorpromazine-melanin polymer formed in a light-catalysed anaerobic reaction. Hydrogen chloride liberated during the reaction could account for the skin irritation. Intracutaneous injection of a preparation of the polymer into 2 subjects produced a bluish-purple discoloration which faded in 3 days.

1. Huang CL, Sands FL. Effect of ultraviolet irradiation on chlorpromazine II: anaerobic condition. *J Pharm Sci* 1967; **56:** 259–64.

Extrapyramidal disorders. Antipsychotics and several other drugs, including antiemetics such as metoclopramide and some antidepressants, can produce a range of dyskinesias or involuntary movement disorders involving the extrapyramidal motor system, including parkinsonism, akathisia, acute dystonia, and chronic tardive dyskinesia.[1-4] Such reactions are a major problem in the clinical management of patients receiving antipsychotics. Reactions of this type can occur with any antipsychotic, but (excluding tardive dyskinesia) are particularly prominent during treatment with high-potency drugs such as the tricyclic piperazines and butyrophenones. Antipsychotics such as clozapine carry a low risk of extrapyramidal effects and are therefore described as atypical antipsychotics. The incidence of tardive dyskinesia does appear to be minimal with clozapine, although there is less evidence for other atypical antipsychotics (p. 1060.2; but see also below).

Of 2811 patients studied[5] in the first few months of therapy with prochlorperazine (a drug with a high propensity to cause extrapyramidal reactions), 57 reported adverse effects, 16 of which involved the extrapyramidal system. There were 4 dystonic-dyskinesic reactions (an incidence of 1 in 464 and 1 in 707 for patients aged under and over 30 years respectively), 9 reports of parkinsonism (under 60 years, 1 in 1555; over 60 years, 1 in 159), and 3 reports of akathisia (1 in 562).

One explanation of extrapyramidal disorders is an imbalance between dopaminergic and cholinergic systems in the brain. However, this simple model fails to explain the co-existence of a variety of extrapyramidal effects, and several alternative mechanisms have been proposed.[2,6] Hypotheses based on interactions between different dopamine receptor types may help to explain the decreased tendency of some antipsychotics to induce these reactions (see Action under Uses and Administration, p. 1046.1).

1. CSM/MCA. Drug-induced extrapyramidal reactions. *Current Problems* 1994; **20:** 15–16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
2. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; **47:** 575–604.
3. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *Am J Health-Syst Pharm* 1997; **54:** 2461–77.
4. Jiménez-Jiménez FJ, *et al*. Drug-induced movement disorders. *Drug Safety* 1997; **16:** 180–204.
5. Bateman DN, *et al*. Extrapyramidal reactions to metoclopramide and prochlorperazine. *Q J Med* 1989; **71:** 307–11.
6. Ereshefsky L, *et al*. Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9:** 682–707.

AKATHISIA. Akathisia is a condition of mental and motor restlessness in which there is an urge to move about constantly and an inability to sit or stand still. It is the most common motor adverse effect of treatment with antipsychotics.[1] Acute akathisia is dose-dependent, usually develops within a few days of beginning treatment or after a rapid increase in dose, and usually improves if the drug is stopped or the dose reduced. *Antimuscarinic antiparkinsonian drugs* appear to provide only limited benefit, although success may be more likely in patients with concomitant parkinsonism. A low dose of a *beta blocker* such as *propranolol* (although good evidence is lacking[2]) or a *benzodiazepine*[3] may be helpful. Improvement has also been reported with *clonidine* and *amantadine* but the usefulness of these drugs may be limited by adverse effects or development of tolerance, respectively. The tardive form, like tardive dyskinesia (see below), which appears after several months of treatment, does not respond to antimuscarinics and is difficult to treat.

1. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Safety* 2000; **22:** 73–81.
2. Barnes TRE, *et al*. Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).
3. Resende Lima A *et al*. Benzodiazepines for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 15/05/09).

DYSTONIA. Acute dystonic reactions, which mainly affect the muscles of the face, neck, and trunk and include jaw clenching (trismus), torticollis, and oculogyric crisis are reported to occur in up to 10% of patients taking antipsychotics. Laryngeal dystonia is rare, but potentially fatal.[1] Dystonias usually occur within the first few days of treatment or after a dosage increase but may also develop on withdrawal. They are transitory, and are most common in children and young adults. Dystonic reactions may be controlled by *antimuscarinics* such as *biperiden* or *procyclidine*, or by *antihistamines* such as *diphenhydramine* or *promethazine*.[2] *Benzodiazepines* such as *diazepam* can also be used. Prophylactic antimuscarinics can prevent the development of dystonias, but routine use is not recommended as not all patients require them and tardive dyskinesia may be unmasked or worsened (see below); such a strategy should probably be reserved for short-term use in those at high risk of developing dystonic reactions, such as young adults starting treatment with high-potency antipsychotics or in patients with a history of drug-induced dystonias.[3,4] Some patients may develop tardive dystonia. A range of drugs has been tried in this condition but without consistent benefit.[5]

1. Koek RJ, Pi EH. Acute laryngeal dystonic reactions to neuroleptics. *Psychosomatics* 1989; **30:** 359–64.
2. van Harten PN, *et al*. Acute dystonia induced by drug treatment. *BMJ* 1999; **319:** 623–6.
3. WHO. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment: a consensus statement. *Br J Psychiatry* 1990; **156:** 412.
4. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; **156:** 413–14.
5. Raja M. Managing antipsychotic-induced acute and tardive dystonia. *Drug Safety* 1998; **19:** 57–72.

PARKINSONISM. Parkinsonism, often indistinguishable from idiopathic Parkinson's disease (p. 889.1), may develop during therapy with antipsychotics, usually after the first few weeks or months of treatment. It is generally stated to be more common in adults and the elderly, although a retrospective study with haloperidol found an inverse relationship between drug-induced parkinsonism and age.[1] This parkinsonism is generally reversible on drug withdrawal or dose reduction, and may sometimes disappear gradually despite continued drug therapy. *Antimuscarinic antiparkinsonian* drugs are used to suppress the symptoms of parkinsonism.[2] However, they are often minimally effective and commonly cause adverse effects. Routine use for prophylaxis is not recommended because of the risk of unmasking or exacerbating tardive dyskinesia (see below). *Amantadine* is an alternative to the antimuscarinics.[2]

1. Moleman P, *et al*. Relationship between age and incidence of parkinsonism in psychiatric patients treated with haloperidol. *Am J Psychiatry* 1986; **143:** 232–4.
2. Marno DC, *et al*. Managing antipsychotic-induced parkinsonism. *Drug Safety* 1999; **20:** 269–75.

TARDIVE DYSKINESIA. The central feature of tardive dyskinesia is orofacial dyskinesia characterised by protrusion of the tongue ('fly catching'), lipsmacking, sucking, lateral chewing, and pouting of the lips and cheeks. The trunk and limbs also become involved with choreiform movements such as repetitive 'piano-playing' hand movements, shoulder shrugging, foot tapping, or rocking movements. The prevalence of tardive dyskinesia among those receiving antipsychotics varies widely but up to 60% of patients may develop symptoms. In most cases the condition is mild and not progressive and tends to wax and wane. Although tardive dyskinesia usually develops after many years of antipsychotic therapy no clear correlation has been shown between development of the condition and the length of drug treatment or the type and class of drug. However, *clozapine* does not appear to be associated with the condition (but see below) and in some cases use has resulted in improvement of established tardive dyskinesia (see Schizophrenia under Clozapine, p. 1058.2). Whether other atypical antipsychotics also have a lower incidence of tardive dyskinesia is unknown. Early data suggested that this may be the case;[1-3] a more recent cohort study[4] concluded that the risk with atypical antipsychotics (excluding clozapine) is more than half that with classical antipsychotics. Perhaps surprisingly, this study also found that there was a non-significant increase in the risk of tardive dyskinesia with clozapine when compared with clas-

sical antipsychotics. However, it was not clear whether this was an actual increase in risk with clozapine or if clozapine-treated patients were at a greater risk of illness-related dyskinesia. Symptoms of tardive dyskinesia often develop after stopping the antipsychotic or after dose reduction. Risk factors include old age, female sex, affective disorder, schizophrenia characterised by negative symptoms, and organic brain damage.

Suggested causes of tardive dyskinesia include dopaminergic overactivity, imbalance between dopaminergic and cholinergic activity, supersensitivity of postsynaptic dopamine receptors, presynaptic catecholaminergic hyperfunction, and alterations of the gamma-aminobutyric acid (GABA) system.

Options in the management of tardive dyskinesia include attempts at treatment while maintaining antipsychotic therapy, or withdrawal of antimuscarinic therapy, and either withdrawal of the antipsychotic or reduction of the dosage to the minimum required or transfer to an atypical antipsychotic.

Although many drugs have been tried in the **treatment** of tardive dyskinesia there have been relatively few double-blind studies. Reviews of tardive dyskinesia[1,5-7] have concluded that there appeared to be no reliable or safe treatment. Overall, classical antipsychotics appeared to be the most effective in masking symptoms of tardive dyskinesia but tolerance may develop and a worsening of the underlying pathophysiology by antipsychotics had to be assumed on theoretical grounds. Other drugs with antidopaminergic actions that were probably of comparable efficacy included *reserpine, oxypertine, tetrabenazine,* and *metirosine.* The next most effective drugs were considered to be noradrenergic antagonists such as *clonidine.* Some encouraging results had also been obtained with GABAergic drugs such as the *benzodiazepines, baclofen, valproate,* and *vigabatrin,* although systematic reviews of studies of some GABAergic drugs[8] including benzodiazepines[9] found the evidence inconclusive and/or unconvincing. The efficacy of cholinergics could not be confirmed.[10,11] Dopaminergics and antimuscarinics mostly exacerbated symptoms but others[12] had commented that there was no convincing evidence that long-term use of antimuscarinics increased the risk of developing the condition. Other drugs whose value is unclear include *vitamin E*[13] and some calcium-channel blockers.[14]

Withdrawal of the causative drug usually worsens the condition although symptoms often diminish or disappear over a period of weeks or sometimes a year or so. Success is most likely in younger patients. During withdrawal, drugs such as *diazepam* or *clonazepam* may be given to alleviate symptoms. Although classical antipsychotics are effective, their routine use to suppress symptoms is not recommended but they may be required for acute distressing or life-threatening reactions or in chronic tardive dyskinesia unresponsive to other treatment. In extremely severe resistant cases some have used an antipsychotic with *valproate* or *carbamazepine* or *reserpine* with *metirosine.*

In view of the unsatisfactory management of tardive dyskinesia, emphasis is placed on its **prevention**. Antipsychotics should be prescribed only when clearly indicated, should be given in the minimum dose, and continued only when there is evidence of benefit. Although drug holidays have been suggested for reducing the risk of tardive dyskinesia, the limited evidence indicates that interruptions in drug treatment may increase the risk of both persistent dyskinesia and psychotic relapse.[15] Increasing the dose of antipsychotic generally improves the condition, but only temporarily.

1. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res* 1999; **35** (suppl): S61–S66.
2. Kane JM. Tardive dyskinesia in affective disorders. *J Clin Psychiatry* 1999; **60** (suppl 5): 43–7.
3. Llorca P-M, *et al*. Tardive dyskinesias and antipsychotics: a review. *Eur Psychiatry* 2002; **17:** 129–38.
4. Woods SW, *et al*. Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study. *J Clin Psychiatry* 2010; **71:** 463–74.
5. Haag H, *et al*. , eds. Tardive Dyskinesia. *WHO Expert Series on Biological Psychiatry Volume I.* Seattle: Hogrefe & Huber, 1992.
6. Egan MF, *et al*. Treatment of tardive dyskinesia. *Schizophr Bull* 1997; **23:** 583–609.
7. Najib J. Tardive dyskinesia: a review and current treatment options. *Am J Ther* 1999; **6:** 51–60.
8. Rathbone J, *et al*. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 12/08/08).
9. Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).
10. Tammenmaa I, *et al*. Cholinergic medication for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/08/08).
11. Tammenmaa IA, *et al*. Systematic review of cholinergic drugs for neuroleptic-induced tardive dyskinesia: a meta-analysis of randomized controlled trials. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28:** 1099–1107.
12. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; **156:** 413–14.
13. McGrath J, Soares-Weiser K. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 21/08/08).
14. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/05).
15. Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 12/05/06).

Neuroleptic malignant syndrome. The neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to some drugs including antipsychotics and other dopamine antagonists such as metoclopramide. The clinical **features** of the classic syndrome are usually considered to include hyperthermia, severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction, and altered levels of consciousness. Skeletal muscle damage may occur and the resulting myoglobinuria may lead to renal failure. However, there appear to be no universal criteria for diagnosis. Some believe the classic syndrome to be the extreme of a range of effects associated with antipsychotics and have introduced the concept of milder variants or incomplete forms. Others consider it to be a rare idiosyncratic reaction and suggest that the term neuroleptic malignant syndrome should be reserved for the full-blown reaction. Consequently, estimates of the **incidence** vary greatly and recent estimates have ranged from 0.02 to 2.5%. The mortality rate has been substantial; although it has decreased over the years with improved diagnosis and management, this may also be due to the detection and inclusion of the milder or incomplete variants. Possible risk factors include dehydration, pre-existing organic brain disease, and a history of a previous episode; young males have also been reported to be particularly susceptible.

The **pathogenesis** of NMS is still unclear. Blockade of dopaminergic receptors in the corpus striatum is thought to cause muscular contraction and rigidity generating heat while blockade of dopaminergic receptors in the hypothalamus leads to impaired heat dissipation. Peripheral mechanisms such as vasomotor paralysis may also play a role. Also a syndrome resembling NMS has been seen after withdrawal of treatment with dopamine agonists such as levodopa (see p. 906.2). Symptoms develop rapidly over 24 to 72 hours and may occur days to months after starting antipsychotic medication or increase in dosage, but no consistent correlation with dosage or length of therapy has been found. Symptoms may last for up to 14 days after stopping oral antipsychotics, or for up to 4 weeks after stopping depot preparations. All antipsychotics are capable of inducing NMS; depot preparations may, however, be associated with prolonged recovery once it develops, and hence a higher mortality rate. Use with lithium carbonate or antimuscarinics may increase the likelihood of developing the syndrome.

Antipsychotic medication should be withdrawn immediately once the diagnosis of the classic syndrome is made; this should be followed by symptomatic and supportive **therapy** including cooling measures, correction of dehydration, and treatment of cardiovascular, respiratory, and renal complications. Whether antipsychotics should be withdrawn from patients with mild attacks and how they should be managed is a matter of debate.

The efficacy of specific drug therapy remains to be proven, and justification for use is based mainly on case reports.

- *Dantrolene* was first used because of its efficacy in malignant hyperthermia. It has a direct action on skeletal muscle and may be particularly effective for the reversal of hyperthermia of muscle origin.
- In contrast, dopaminergic agonists may resolve hyperthermia of central origin, restoring dopaminergic transmission and hence alleviating extrapyramidal symptoms. There have been isolated reports of success with *amantadine* and *levodopa* but *bromocriptine* is generally preferred. Any underlying psychosis may, however, be aggravated by dopaminergic drugs.
- Since dantrolene and dopaminergics act in different ways a combination of the two might be useful, but any advantage is unproven.
- *Antimuscarinics* are generally considered to be of little use and may aggravate the associated hyperthermia.
- *Benzodiazepines* may be used for sedation in agitated patients and may be of use against concomitant catatonia. ECT may be an alternative in refractory cases of NMS or when catatonic symptoms are present.

Re-introduction of antipsychotic therapy may be possible but is not always successful and extreme caution is advised. It has been recommended that a gap of at least 5 to 14 days should be left after resolution of the symptoms before attempting re-introduction.

References.

1. Wells AJ, *et al*. Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. *Drug Intell Clin Pharm* 1988; **22:** 475–80.
2. Bristow MF, Kohen D. How "malignant" is the neuroleptic malignant syndrome? *BMJ* 1993; **307:** 1223–4.
3. Kornhuber J, Weller M. Neuroleptic malignant syndrome. *Curr Opin Neurol* 1994; **7:** 353–7.
4. Velamoor VR, *et al*. Management of suspected neuroleptic malignant syndrome. *Can J Psychiatry* 1995; **40:** 545–50.
5. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; **47:** 575–604.
6. Bristow MF, Kohen D. Neuroleptic malignant syndrome. *Br J Hosp Med* 1996; **55:** 517–20.
7. Velamoor VR. Neuroleptic malignant syndrome: recognition, prevention and management. *Drug Safety* 1998; **19:** 73–82.
8. Adnet P, *et al*. Neuroleptic malignant syndrome. *Br J Anaesth* 2000; **85:** 129–35.
9. Strawn JR, *et al*. Neuroleptic malignant syndrome. *Am J Psychiatry* 2007; **164:** 870–6.

Withdrawal. Stopping treatment with an antipsychotic abruptly may produce withdrawal symptoms, the most common of which are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation.[1] Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days. They are more severe and frequent when antimuscarinics are stopped simultaneously.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.

Treatment of Adverse Effects

After an overdose of chlorpromazine or other phenothiazines, patients should be managed with intensive symptomatic and supportive therapy. Activated charcoal should be given orally if a potentially toxic amount of the phenothiazine has been ingested within 1 hour of presentation, provided that the airway can be protected; the benefit of gastric decontamination is uncertain. Dialysis is of little or no value in poisoning by phenothiazines.

Hypotension should be corrected by raising the patient's legs and by giving intravenous fluids. Drugs with pronounced alpha-adrenergic activity, such as noradrenaline, or high-dose dopamine may be beneficial where hypotension is thought to be mainly due to decreased systemic vascular resistance. Central venous pressure monitoring should be considered in refractory cases. If a vasoconstrictor is considered necessary in the management of phenothiazine-induced hypotension the use of adrenaline or other sympathomimetics with high beta-adrenergic agonist properties should be avoided since the alpha-blocking effects of phenothiazines may impair the usual alpha-mediated vasoconstriction of these drugs, resulting in unopposed beta-adrenergic stimulation and increased hypotension.

The treatment of neuroleptic malignant syndrome and the difficulties of treating extrapyramidal adverse effects, especially tardive dyskinesia, are discussed above and on p. 1049.2, respectively.

Precautions

Chlorpromazine and other phenothiazines are contra-indicated in patients with pre-existing CNS depression or coma, bone-marrow suppression, phaeochromocytoma, or prolactin-dependent tumours. They should be used with caution or not at all in patients with impaired liver, kidney, cardiovascular, cerebrovascular, and respiratory function and in those with angle-closure glaucoma, a history of jaundice, parkinsonism, diabetes mellitus, hypothyroidism, myasthenia gravis, paralytic ileus, prostatic hyperplasia, or urinary retention. Care is required in patients with epilepsy or a history of seizures as phenothiazines may lower the seizure threshold. Debilitated patients may be more prone to the adverse effects of phenothiazines as may the elderly, especially those with dementia. For precautions of phenothiazines in pregnancy, see p. 1051.3.

The sedative effects of phenothiazines are most marked in the first few days of treatment; affected patients should not drive or operate machinery.

The effects of phenothiazines on the vomiting centre may mask the symptoms of overdosage of other drugs, or of disorders such as gastrointestinal obstruction. Use at extremes of temperature may be hazardous since body temperature regulation is impaired by phenothiazines.

Regular eye examinations are advisable for patients receiving long-term phenothiazine therapy and avoidance of undue exposure to direct sunlight is recommended. Phenothiazines should be used with caution in the presence of acute infection or leucopenia. Blood counts are advised if the patient develops an unexplained infection or fever.

Patients should remain supine for at least 30 minutes after parenteral doses of chlorpromazine; blood pressure should be monitored.

Abrupt withdrawal of phenothiazine therapy is best avoided.

AIDS. Isolated reports[1,2] have suggested that patients with AIDS may be particularly susceptible to antipsychotic-induced extrapyramidal effects.

1. Hollander H, *et al.* Extrapyramidal symptoms in AIDS patients given low-dose metoclopramide or chlorpromazine. *Lancet* 1985; **ii:** 1186.
2. Edelstein H, Knight RT. Severe parkinsonism in two AIDS patients taking prochlorperazine. *Lancet* 1987; **ii:** 341–2.

Asthma. Findings of a retrospective case-control study[1] appeared to indicate that asthmatic patients given antipsychotics were at an increased risk of death or near death from asthma.

1. Joseph KS, *et al.* Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ* 1996; **312:** 79–82.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of chlorpromazine by mothers during breast feeding may be of concern, since there have been reports of galactorrhoea in the mother and of drowsiness, lethargy, and declines in developmental scores in the infant. The *BNF* considers that the use of antipsychotics such as chlorpromazine should be avoided by breast-feeding mothers unless absolutely necessary.

Chlorpromazine was detected[2] in all milk samples from 4 women at concentrations ranging from 7 to 98 nanograms/mL. Two of the women breastfed their infants, but one infant showed no effects while the other was noted to be drowsy and lethargic; milk-chlorpromazine concentrations were 7 and 92 nanograms/mL, respectively.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/10/04)
2. Wiles DH, *et al.* Chlorpromazine levels in plasma and milk of nursing mothers. *Br J Clin Pharmacol* 1978; **5:** 272–3.

Children. Few phenothiazines are recommended for use in children; in particular there have been concerns about the use of phenothiazine derivatives in infants (see Sudden Infant Death Syndrome, p. 639.1). For reference to the use of chlorpromazine in infants suffering neonatal abstinence syndrome see Substance Dependence, Opioids, under Uses and Administration, p. 1047.1. For other uses in children see also Administration in Children, p. 1046.2.

References.

1. Dyer KS, Woolf AD. Use of phenothiazines as sedatives in children: what are the risks? *Drug Safety* 1999; **21:** 81–90.

Contact sensitisation. The *BNF* warns that because of the risk of contact sensitisation, health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

Driving. While psychotic disorders probably adversely affect driving skill, treatment with antipsychotics can also be hazardous, although patients may be safer drivers with medication than without. Impairment of performance is largely related to sedative and extrapyramidal effects. In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. During an acute psychotic illness, or an episode of mania or hypomania, driving should cease. After an isolated episode, re-licensing can be considered provided the patient has remained well and stable for at least 3 months, is compliant with treatment, and has regained insight; in addition, the patient should be free from any adverse effects of medication that would impair driving. If there have been 4 or more episodes of mood swing within the previous 12 months, at least 6 months of stability will be required before re-licensing can be considered. Drivers of heavy goods and public service vehicles are normally required to be well and stable for 3 years before driving can resume.[1]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 25/11/13)

The elderly. The risk of *hip fracture* has been reported to be increased in elderly patients given antipsychotics. A large case-control study in patients over 65 found that current users of antipsychotics had a twofold increase in the risk of hip fractures.[1] The effect was dose-related and the increased risk was similar for chlorpromazine, haloperidol, and thioridazine. It was suggested that antipsychotic-induced sedation or orthostatic hypotension could increase the risk of falls in elderly persons. A study in 12 schizophrenic patients receiving antipsychotics plus other drugs such as antimuscarinics or benzodiazepines has suggested that long-term treatment with antipsychotics may decrease bone mineralisation.[2] A later study suggested that any increased risk of falls might be due to an effect of antipsychotics on balance as thioridazine was found to increase sway in elderly but not young subjects.[3] A meta-analysis of 98 studies[4] concluded that there was a moderate and clinically significant increase in the risk of fractures with the use of most classes of psychotropic drugs, including antipsychotics. However, the evidence from these studies was based solely on observational data, with minimal adjustment for confounders, and potential for publication bias.

A large case-control study[5] found the risk of community-acquired *pneumonia* to be increased in patients aged 65 years and over who were current users of either classical or atypical antipsychotics. The risk was dose-dependent and occurred soon after beginning treatment.

The use of antipsychotics to manage behavioural complications of *dementia* may increase the rate of cognitive decline.[6,7] Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotic drugs,[8,9] and the reaction can be extremely serious, even fatal. If these drugs are to be used in elderly patients with dementia, then very low doses should be used, and special care should be taken if the dementia is suspected to be of the Lewy-body type since sudden life-threatening deterioration may occur.[10] Depot preparations should not be used and, since dopamine D_2 receptors may be involved, it has been suggested that consideration could be given to using an antipsychotic such as clozapine that does not principally antagonise those receptors;[9] however, the use of atypical antipsychotics in such patients is not without its risk and there is evidence of an increased death rate with their use (see under Risperidone, p. 1105.1).

An *increased risk of death* has also been noted in elderly patients given classical antipsychotics. Retrospective cohort studies,[11,12] involving around 60 000 patients given atypical or classical antipsychotics, found that classical antipsychotics were at least as likely as the atypicals to increase the risk of death in the elderly. The authors also suggested that the greatest increase in risk occurred soon after starting therapy and with higher doses of classical antipsychotics. A similar risk of death with use of classical antipsychotics was also seen in a large retrospective population-based study[13] in elderly patients with dementia when compared with that seen with use of atypicals in this patient group. On review of 2 of these studies,[12,13] the FDA concluded that both classical and atypical antipsychotics were associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.[14] However, methodological limitations precluded any conclusion that classical antipsychotics have a greater mortality risk than atypical antipsychotics.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p. 1030.2.

1. Ray WA, *et al.* Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987; **316:** 363–9.
2. Higuchi T, *et al.* Certain neuroleptics reduce bone mineralization in schizophrenic patients. *Neuropsychobiology* 1987; **18:** 185–8.
3. Liu Y, *et al.* Comparative clinical effects of thioridazine (THD) on fall risk on young and elderly subjects. *Clin Pharmacol Ther* 1995; **57:** 200.
4. Takkouche B, *et al.* Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Safety* 2007; **30:** 171–84.
5. Trifirò G, *et al.* Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med* 2010; **152:** 418–25.
6. McShane R, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ* 1997; **314:** 266–70.
7. Holmes C, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Carriers of apolipoprotein E ε4 allele seem particularly susceptible to their effects. *BMJ* 1997; **314:** 1411.
8. McKeith I, *et al.* Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* 1992; **305:** 673–8.
9. Piggott MA, *et al.* DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* 1994; **343:** 1044–5. Correction. *ibid.;* 1170. [Title: Dopamine D2 receptors in demented patients with severe neuroleptic sensitivity.]
10. CSM/MCA. Neuroleptic sensitivity in patients with dementia. *Current Problems* 1994; **20:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 30/05/06)
11. Wang PS, *et al.* Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; **353:** 2335–41.
12. Schneeweiss S, *et al.* Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *Can Med Assoc J* 2007; **176:** 627–32. Correction. *ibid.;* 1613.
13. Gill SS, *et al.* Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; **146:** 775–86.
14. FDA. Information for healthcare professionals: conventional antipsychotics (issued 16th June, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm (accessed 26/07/10)

Epilepsy. See Convulsions under Adverse Effects, p. 1047.3.

Folic acid deficiency. Concentrations of folate in serum and erythrocytes were reduced in 15 patients receiving long-term treatment with chlorpromazine or thioridazine.[1] All the patients had significant induction of hepatic microsomal enzymes. It was suggested that folate deficiency due to the induction of microsomal enzymes might subsequently limit enzyme induction and hence reduce drug metabolism, which could lead to symptoms of toxicity in patients apparently stabilised for several years. The dietary intake of patients on long-term treatment with enzyme-inducing drugs might be inadequate.

1. Labadarios D, *et al.* The effects of chronic drug administration on hepatic enzyme induction and folate metabolism. *Br J Clin Pharmacol* 1978; **5:** 167–73.

Hypoparathyroidism. There have been rare reports[1,2] of acute dystonic reactions associated with the use of phenothiazines in patients with untreated hypoparathyroidism. Caution was recommended in giving phenothiazine derivatives to patients with hypoparathyroidism and it was suggested that any acute reaction to such a drug should prompt investigation for some form of latent tetany.

1. Schaaf M, Payne CA. Dystonic reactions to prochlorperazine in hypoparathyroidism. *N Engl J Med* 1966; **275:** 991–5.
2. Gur H, *et al.* Acute dystonic reaction to methotrimeprazine in hypoparathyroidism. *Ann Pharmacother* 1996; **30:** 957–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorpromazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pregnancy. Licensed product information generally does not recommend the use of phenothiazines in late pregnancy; such use may be associated with intoxication of the neonate. Chlorpromazine may prolong labour and should be withheld until the cervix is dilated 3 to 4 cm. Overall, however, it has been suggested[1] that the criteria for the selection of an antipsychotic for use in pregnant women do not differ from those used in nonpregnant women. It was also concluded that the benefits of continuing antipsychotic treatment at the minimum effective dose would usually outweigh any risks to the fetus.

A review[2] of the use of phenothiazines in pregnancy concluded that there was no clear evidence that these drugs caused a significant increase in fetal malformations. Nevertheless it was considered advisable that if pregnant patients required such treatment, then a single phenothiazine should be used and that it should be one of the established drugs.

A subsequent review[3] of the literature reported that women with schizophrenia are generally at increased risk for poor obstetric outcomes including preterm delivery, low birth-weight, and neonates who are small for their gestational age. It was also considered that there was an increased risk of congenital malformation when the fetus was exposed to phenothiazines during weeks 4 to 10 of gestation but this conclusion and the methods used to select the data to review have been criticised.[4]

See also p. 614.2 for the use of phenothiazines as antiemetics during pregnancy.

1. Trixler M, Tényi T. Antipsychotic use in pregnancy: what are the best treatment options? *Drug Safety* 1997; **16:** 403–10.
2. McElhatton PR. The use of phenothiazines during pregnancy and lactation. *Reprod Toxicol* 1992; **6:** 475–90.
3. Patton SW, *et al.* Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can J Psychiatry* 2002; **47:** 959–65.
4. Levinson A. Review: women with schizophrenia have poorer pregnancy outcomes than other women, but it is unclear whether antipsychotic medications affect their infants. *Evid Based Ment Health* 2003; **6:** 89.

Renal impairment. Although there do not seem to be specific indications for dosage adjustment of phenothiazines in renal impairment, the *BNF* considers that cerebral sensitivity to antipsychotics may be increased in severe impairment. Phenothiazine-induced toxic psychosis occurred in 4 patients with chronic renal failure who had been given chlorpromazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; **10:** 191–5.

Interactions

The most common interactions encountered with phenothiazines such as chlorpromazine result from use with drugs that have similar pharmacological actions. Symptoms of CNS depression may be enhanced by other drugs with CNS-depressant properties including alcohol, general anaesthetics, hypnotics, anxiolytics, and opioids. When given with other drugs that produce orthostatic hypotension, dosage adjustments may be necessary. However, it should be noted that phenothiazines have been reported to reduce the antihypertensive action of guanethidine and other adrenergic neurone blockers. As many phenothiazines possess antimuscarinic actions they can potentiate the adverse effects of other drugs with antimuscarinic actions, including tricyclic antidepressants and the antimuscarinic antiparkinsonian drugs that may be given to treat phenothiazine-induced extrapyramidal effects. In theory, antipsychotics with dopamine-blocking activity and dopaminergic drugs such as those used to treat parkinson-

ism may be mutually antagonistic. Use with metoclopramide may increase the risk of antipsychotic-induced extrapyramidal effects.

There is an increased risk of arrhythmias when antipsychotics are used with drugs that prolong the QT interval, including certain antiarrhythmics, other antipsychotics, some non-sedating antihistamines, antimalarials, and cisapride; use with diuretics that cause electrolyte imbalance (particularly hypokalaemia) may also have the same effect. There is also an increased risk of arrhythmias when tricyclic antidepressants are used with antipsychotics that prolong the QT interval.

Because of an increased risk of seizures US licensed product information for chlorpromazine recommends withdrawal before the use of metrizamide for radiographic procedures.

Most interactions with antipsychotics are as a result of additive pharmacological effects.[1] Since tolerance develops to many of these adverse effects, interactions are likely to be most important in the early stages of combination therapy.

1. Livingston MG. Interactions that matter: 11 antipsychotic drugs. *Prescribers' J* 1987; **27**(Dec): 26–9.

Alcohol. Phenothiazines may increase the CNS depressant effects of alcohol. There has been a report of akathisia and dystonia after consumption of alcohol by patients taking antipsychotics;[1] alcohol might lower the threshold of resistance to neurotoxic adverse effects.

1. Lutz EG. Neuroleptic-induced akathisia and dystonia triggered by alcohol. *JAMA* 1976; **236:** 2422–3.

Antacids. Studies in 6 patients showed that chlorpromazine plasma concentrations were significantly lower after giving chlorpromazine with an *aluminium hydroxide* and *magnesium trisilicate* antacid gel (*Gelusil*) than after chlorpromazine alone.[1] *In-vitro* studies indicated that chlorpromazine was highly bound to the gel.

1. Fann WE, *et al*. Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J Clin Pharmacol* 1973; **13:** 388–90.

Antiarrhythmics. There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with antiarrhythmics (especially *amiodarone*, *disopyramide*, *procainamide*, and *quinidine*) should be avoided. Use of haloperidol with amiodarone is also not recommended. A study[1] in healthy subjects has suggested that quinidine might increase plasma concentrations of haloperidol.

1. Young D, *et al*. Effect of quinidine on the interconversion kinetics between haloperidol and reduced haloperidol in humans: implications for the involvement of cytochrome P450IID6. *Eur J Clin Pharmacol* 1993; **44:** 433–8.

Antibacterials. Seven schizophrenic patients whose antitubercular therapy included *rifampicin* (in addition to isoniazid, and in some cases also ethambutol) had lower serum concentrations of haloperidol compared with tuberculotic schizophrenic patients receiving no antimycobacterials and with non-tuberculotic schizophrenics.[1] Pharmacokinetic studies involving some of these patients indicated accelerated haloperidol clearance in the presence of rifampicin. Abnormally high serum-haloperidol concentrations occurred in 3 of 18 patients treated with *isoniazid* alone.

Black galactorrhoea occurred in a patient receiving *minocycline*, perphenazine, amitriptyline hydrochloride, and diphenhydramine hydrochloride.[2] Simultaneous occurrence of phenothiazine-induced galactorrhoea and tetracycline-induced pigmentation was considered responsible.

Sudden cardiac deaths have been reported[3] in patients given *clarithromycin* and pimozide. Elevated pimozide plasma concentrations were recorded after pretreatment with clarithromycin.[4] The manufacturer of pimozide has recommended that pimozide should not be used with macrolide antibacterials.

1. Takeda M, *et al*. Serum haloperidol levels of schizophrenics receiving treatment for tuberculosis. *Clin Neuropharmacol* 1986; **9:** 386–97.
2. Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; **121:** 417–18.
3. Flockhart DA, *et al*. A metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity. *Clin Pharmacol Ther* 1996; **59:** 189.
4. Desta Z, *et al*. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolisers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; **65:** 10–20.

Anticoagulants. For reference to the effects of some antipsychotics on the activity of anticoagulants, see under Warfarin, p. 1533.1.

Antidepressants. Interactions between antipsychotics and *tricyclic antidepressants* are generally of two forms: additive pharmacological effects such as antimuscarinic effects or hypotension; or pharmacokinetic interactions. Although not commonly reported in the literature, additive antimuscarinic activity may be a significant risk especially in the elderly. Careful drug selection might help to prevent the development of serious adverse effects. Mutual inhibition of liver enzymes involved in the metabolism of both the antipsychotic and the tricyclic antidepressant might result in increased plasma concentrations of either drug. In one study,[1] addition of *nortriptyline* to chlorpromazine therapy produced an increase in plasma concentrations of chlorpromazine but this resulted in a paradoxical increase in agitation and tension.

There is an increased risk of arrhythmias when tricyclic antidepressants are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with tricyclic antidepressants should be avoided.

Increased serum concentrations of haloperidol have occurred when patients were also given *fluoxetine*,[2] *fluvoxamine*,[3] or *nefazodone*. Isolated reports[4-9] of extrapyramidal symptoms, psychoneuromotor syndrome, stupor, bradycardia, and urinary retention associated with use of fluoxetine with antipsychotics suggest that fluoxetine might exacerbate the adverse effects of antipsychotics or produce additive toxicity. Similar CNS effects have been noted in subjects given perphenazine and *paroxetine*.[10] There has also been an isolated report of a patient who complained of amenorrhoea and galactorrhoea after fluvoxamine was added to loxapine therapy.[11] Significant increases in the plasma concentrations of thioridazine have occurred after use with fluvoxamine.[12] Paroxetine may also inhibit the metabolism of thioridazine, resulting in increased thioridazine plasma concentrations; UK licensed product information for paroxetine contra-indicates their concomitant use. The US licensed product information for paroxetine states that giving paroxetine with pimozide was associated with a mean increase of 151% in the area under the concentration-time curve of pimozide and 62% in its mean peak plasma concentration. Due to the narrow therapeutic index of pimozide concomitant use of these 2 drugs is contra-indicated.

Combinations of antipsychotics and *lithium* should be used with care. Lithium can reduce plasma-chlorpromazine concentrations and there is a report of ventricular fibrillation on withdrawal of lithium from a patient also taking chlorpromazine. Chlorpromazine has also been reported to enhance the excretion of lithium. Neurotoxic or extrapyramidal symptoms have been reported rarely in patients taking antipsychotics and lithium; these may be atypical cases of lithium toxicity or neuroleptic malignant syndrome. The above issues are discussed in detail, and references given, on p. 431.3.

A patient on long-term trifluoperazine treatment developed neuroleptic malignant syndrome after a single dose of *venlafaxine*.[13] The authors noted that the manufacturers of venlafaxine have received a small number of similar reports after introduction of venlafaxine in patients receiving antipsychotics including molindone.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with phenothiazines.

1. Loga S, *et al*. Interaction of chlorpromazine and nortriptyline in patients with schizophrenia. *Clin Pharmacokinet* 1981; **6:** 454–62.
2. Goff DC, *et al*. Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. *Am J Psychiatry* 1991; **148:** 790–2.
3. Daniel DG, *et al*. Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* 1994; **14:** 340–3.
4. Tate JL. Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine. *Am J Psychiatry* 1989; **146:** 399–400.
5. Ahmed I, *et al*. Possible interaction between fluoxetine and pimozide causing sinus bradycardia. *Can J Psychiatry* 1993; **38:** 62–3.
6. Ketai R. Interaction between fluoxetine and neuroleptics. *Am J Psychiatry* 1993; **150:** 836–7.
7. Hansen-Grant S, *et al*. Fluoxetine-pimozide interaction. *Am J Psychiatry* 1993; **150:** 1751–2.
8. D'Souza DC, *et al*. Precipitation of a psychoneuromotor syndrome by fluoxetine in a haloperidol-treated schizophrenic patient. *J Clin Psychopharmacol* 1994; **14:** 361–3.
9. Benazzi F. Urinary retention with fluoxetine-haloperidol combination in a young patient. *Can J Psychiatry* 1996; **41:** 606–7.
10. Özdemir V, *et al*. Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin Pharmacol Ther* 1997; **62:** 334–47.
11. Jeffries J, *et al*. Amenorrhea and galactorrhea associated with fluvoxamine in a loxapine-treated patient. *J Clin Psychopharmacol* 1992; **12:** 296–7.
12. Carrillo JA, *et al*. Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. *J Clin Psychopharmacol* 1999; **19:** 494–9.
13. Nimmagadda SR, *et al*. Neuroleptic malignant syndrome after venlafaxine. *Lancet* 2000; **354:** 289–90.

Antidiabetic drugs. Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance the dose of *oral hypoglycaemics* or of *insulin* may need to be increased in diabetics.

Antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* are potent enzyme inducers and may decrease plasma concentrations of antipsychotics or their active metabolites when used together.[1-5] The clinical effect of any interaction has not been consistent; worsening, improvement, or no change in psychotic symptoms have all been noted. Delirium has been reported in a patient given haloperidol and carbamazepine.[6] Phenytoin might also exacerbate antipsychotic-induced dyskinesia.[7] Care should be taken when withdrawing enzyme-inducing antiepileptics as this may result in a rise in antipsychotic serum concentrations.[8]

The effect of antipsychotics on antiepileptic concentrations is discussed on p. 517.2 (carbamazepine) and p. 544.1 (phenytoin). It should also be remembered that antipsychotics may lower the seizure threshold.

1. Loga S, *et al*. Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; **2:** 197–208.
2. Linnoila M, *et al*. Effect of anticonvulsants on plasma haloperidol and thioridazine levels. *Am J Psychiatry* 1980; **137:** 819–21.
3. Jann MW, *et al*. Effects of carbamazepine on plasma haloperidol levels. *J Clin Psychopharmacol* 1985; **5:** 106–9.
4. Arana GW, *et al*. Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? *Am J Psychiatry* 1986; **143:** 650–1.
5. Ereshefsky L, *et al*. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; **11:** 296–301.
6. Kanter GL, *et al*. Case report of a possible interaction between neuroleptics and carbamazepine. *Am J Psychiatry* 1984; **141:** 1101–2.
7. DeVeaugh-Geiss J. Aggravation of tardive dyskinesia by phenytoin. *N Engl J Med* 1978; **298:** 457–8.
8. Jann MW, *et al*. Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* 1989; **28:** 153–9.

Antihistamines. For the effect of a preparation containing *chlorphenamine maleate* and phenylpropanolamine hydrochloride on thioridazine, see Sympathomimetics (p. 1053.2). There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with antihistamines such as *astemizole* or *terfenadine* should be avoided.

Antihypertensives. For discussion of the interaction between phenothiazines and drugs with hypotensive properties, see Interactions, p. 1051.3. For a report of chlorpromazine enhancing the hyperglycaemic effect of *diazoxide*, see p. 1352.2. For reports of hypertension or dementia in patients given *methyldopa* and antipsychotics, see p. 1432.3.

Antimalarials. Pretreatment with single doses of *chloroquine sulfate*, *amodiaquine hydrochloride*, or *sulfadoxine with pyrimethamine* increased the plasma concentrations of chlorpromazine and 7-hydroxychlorpromazine, but not of chlorpromazine sulfoxide, in schizophrenic patients maintained on chlorpromazine.[1] The raised plasma concentrations appeared to be associated with a greater level of sedation.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of antipsychotics, and pimozide in particular, with antimalarials such as *halofantrine*, *mefloquine*, or *quinine* should be avoided. For the possible effects of the use of *quinidine* with antipsychotics see Antiarrhythmics, above.

1. Makanjuola ROA, *et al*. Effects of antimalarial agents on plasma levels of chlorpromazine and its metabolites in schizophrenic patients. *Trop Geogr Med* 1988; **40:** 31–3.

Antimigraine drugs. A report[1] of a patient receiving loxapine who had a dystonic reaction within 15 minutes of subcutaneous *sumatriptan* suggests that these two drugs might interact or potentiate each other's adverse effects. However, the patient had a history of dystonic reactions associated with haloperidol and was receiving benzatropine prophylactically. Furthermore, the dose of loxapine had been increased 2 days before the event and this may have predisposed the patient to dystonia.

1. Garcia G, *et al*. Dystonic reaction associated with sumatriptan. *Ann Pharmacother* 1994; **28:** 1199.

Antiparkinsonian drugs. Antiparkinsonian drugs are sometimes given with antipsychotics for the management of antipsychotic-induced adverse effects including extrapyramidal disorders (see under Adverse Effects, p. 1049.2). Theoretically, dopaminergics such as *levodopa* and *bromocriptine* might induce or exacerbate psychotic symptoms. A study in 18 subjects and review of the literature suggested that bromocriptine can be used safely in patients at risk of psychotic illness provided they are clinically stable and maintained on antipsychotics.[1] Conversely, antipsychotics might antagonise the effects of dopaminergics; diminished therapeutic effects of levodopa have been noted with several antipsychotics (see p. 907.3) and thioridazine has been reported to oppose the prolactin-lowering action of bromocriptine (see p. 899.1).

Additive antimuscarinic adverse effects are obviously a risk when antimuscarinic antiparkinsonian drugs are given with antipsychotics. Although these are generally mild, serious reactions have occurred. *Trihexyphenidyl*[2] and *orphenadrine*[3] have both been reported to decrease plasma concentrations of chlorpromazine, possibly by interfering

with absorption from the gastrointestinal tract. Reports suggesting that antimuscarinics may antagonise the antipsychotic effects of antipsychotics at the neurotransmitter level require substantiating.

1. Perovich RM, *et al.* The behavioral toxicity of bromocriptine in patients with psychiatric illness. *J Clin Psychopharmacol* 1989; **9:** 417–22.
2. Rivera-Calimlim L, *et al.* Effects of mode of management on plasma chlorpromazine in psychiatric patients. *Clin Pharmacol Ther* 1973; **14:** 978–86.
3. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; **2:** 197–208.

Antipsychotics. Elevated plasma levels of haloperidol were reported[1] in a patient being treated for schizophrenia when *chlorpromazine* or *clozapine* were also given.

1. Allen SA. Effect of chlorpromazine and clozapine on plasma concentrations of haloperidol in a patient with schizophrenia. *J Clin Pharmacol* 2000; **40:** 1296–7.

Antivirals. *Ritonavir* may increase the plasma concentration of some antipsychotics. The increases expected for pimozide were considered in licensed product information for ritonavir to be large enough to recommend that these drugs should not be used together. Other classical antipsychotics predicted to have increases include haloperidol, perphenazine, and thioridazine; it was recommended that monitoring of drug concentrations and/or adverse effects were required when used with ritonavir.

Beta blockers. Chlorpromazine and *propranolol* may mutually inhibit each other's hepatic metabolism. Propranolol has been reported to increase plasma concentrations of chlorpromazine[1] and thioridazine,[2,3] and *pindolol* to increase plasma-thioridazine concentrations.[4] Neither beta blocker tested had a significant effect on haloperidol concentrations,[3,4] although there is a report of severe hypotension or cardiopulmonary arrest occurring on 3 occasions in a schizophrenic patient given haloperidol with propranolol.[5] The clinical significance of antipsychotic-beta blocker interactions is unclear.

For the effect of chlorpromazine on propranolol, see Anxiolytics and Antipsychotics, under Interactions of Beta Blockers, p. 1322.1.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. The use of antipsychotics, and pimozide in particular, with *sotalol* should be avoided.

1. Peet M, *et al.* Pharmacokinetic interaction between propranolol and chlorpromazine in schizophrenic patients. *Lancet* 1980; **ii:** 978.
2. Silver JM, *et al.* Elevation of thioridazine plasma levels by propranolol. *Am J Psychiatry* 1986; **143:** 1290–2.
3. Greendyke RM, Kanter DR. Plasma propranolol levels and their effect on plasma thioridazine and haloperidol concentrations. *J Clin Psychopharmacol* 1987; **7:** 178–82.
4. Greendyke RM, Gulya A. Effect of pindolol administration on serum levels of thioridazine, haloperidol, phenytoin, and phenobarbital. *J Clin Psychiatry* 1988; **49:** 105–7.
5. Alexander HE, *et al.* Hypotension and cardiopulmonary arrest associated with concurrent haloperidol and propranolol therapy. *JAMA* 1984; **252:** 87–8.

Buspirone. The use of haloperidol with buspirone has resulted in increased serum haloperidol concentrations. However, while some[1] found the mean rise in serum-haloperidol concentrations to be 26%, that seen by others[2] was not statistically significant.

1. Goff DC, *et al.* An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* 1991; **11:** 193–7.
2. Huang HF, *et al.* Lack of pharmacokinetic interaction between buspirone and haloperidol in patients with schizophrenia. *J Clin Pharmacol* 1996; **36:** 963–9.

Cimetidine. Despite expectations that cimetidine might reduce the metabolism of chlorpromazine, mean steady-state plasma concentrations of chlorpromazine fell rather than rose in 8 patients given cimetidine for 7 days in addition to regular chlorpromazine therapy.[1] The explanation was probably that cimetidine interfered with chlorpromazine absorption. Excessive sedation, necessitating a reduction in chlorpromazine dosage, has been reported[2] after addition of cimetidine to the drug therapy of 2 chronic schizophrenics.

1. Howes CA, *et al.* Reduced steady-state plasma concentrations of chlorpromazine and indomethacin in patients receiving cimetidine. *Eur J Clin Pharmacol* 1983; **24:** 99–102.
2. Byrne A, O'Shea B. Adverse interaction between cimetidine and chlorpromazine in two cases of chronic schizophrenia. *Br J Psychiatry* 1989; **155:** 413–15.

Cocaine. The risk of antipsychotic-induced dystonic reactions may be increased in cocaine abusers. Dystonia occurred in 6 of 7 cocaine abusers treated with haloperidol.[1]

1. Kumor K, *et al.* Haloperidol-induced dystonia in cocaine addicts. *Lancet* 1986; **ii:** 1341–2.

Desferrioxamine. Loss of consciousness lasting 48 to 72 hours occurred in 2 patients given prochlorperazine during desferrioxamine therapy.[1] Prochlorperazine may enhance the removal of transition metals from brain cells by desferrioxamine.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; **56:** 345–55.

Disulfiram. A psychotic patient, previously maintained with plasma-perphenazine concentrations of 2 to 3 nanomol/mL on an oral dose of 8 mg twice daily, was readmitted with subtherapeutic plasma-perphenazine concentrations of less than 1 nanomol/mL, despite unchanged dosage, after disulfiram therapy.[1] The concentration of the sulfoxide metabolite of perphenazine was much increased. After a change from oral to intramuscular perphenazine therapy there was a substantial clinical improvement associated with a return to therapeutic plasma concentrations of perphenazine and a fall in concentration of the metabolite. Disulfiram appears to greatly enhance biotransformation of oral perphenazine to inactive metabolites, but parenteral administration avoids the 'first-pass' effect in the liver.

1. Hansen LB, Larsen N-E. Metabolic interaction between perphenazine and disulfiram. *Lancet* 1982; **ii:** 1472.

General anaesthetics. A schizophrenic patient without a history of epilepsy who was receiving oral chlorpromazine and flupentixol depot injection had a convulsive seizure when given *enflurane* anaesthesia.[1]

1. Vohra SB. Convulsions after enflurane in a schizophrenic patient receiving neuroleptics. *Can J Anaesth* 1994; **41:** 420–2.

Naltrexone. Two patients maintained on thioridazine experienced intense sleepiness and lethargy after receiving 2 doses of naltrexone.[1]

1. Maany I, *et al.* Interaction between thioridazine and naltrexone. *Am J Psychiatry* 1987; **144:** 966.

NSAIDs. A report of severe drowsiness and confusion in patients given haloperidol with *indometacin*.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; **i:** 830–1.

Opioid analgesics. For reference to the effects of phenothiazines on *pethidine*, see p. 123.3.

Piperazine. There has been an isolated report[1] of convulsions associated with the use of chlorpromazine in a child who had received piperazine several days earlier. Subsequent *animal*[1-3] studies produced conflicting evidence for an interaction and it was suggested[3] that an interaction would only be clinically significant when high concentrations of piperazine were reached in the body.

1. Boulos BM, Davis LE. Hazard of simultaneous administration of phenothiazine and piperazine. *N Engl J Med* 1969; **280:** 1245–6.
2. Armbrecht BH. Reaction between piperazine and chlorpromazine. *N Engl J Med* 1970; **282:** 1490–1.
3. Sturman G. Interaction between piperazine and chlorpromazine. *Br J Pharmacol* 1974; **50:** 153–5.

Sympathomimetics. For reference to the possible interaction between phenothiazines and *adrenaline*, see Treatment of Adverse Effects, p. 1050.3.

A 27-year-old woman with schizophrenia and T-wave abnormality of the heart,[1] receiving thioridazine 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of also taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with *phenylpropanolamine hydrochloride* 50 mg (*Contac C*).

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; **119:** 729–31.

Tobacco smoking. Smoking has been shown to decrease the incidence of chlorpromazine-induced sedation[1,2] and orthostatic hypotension.[2] Studies indicate that the clearance of chlorpromazine,[3] fluphenazine,[4] tiotixene,[5] haloperidol,[6] and thioridazine[7] may be increased in patients who smoke. It has been suggested that some of the components of smoke may act as liver-enzyme inducers. The clinical significance of this effect is unclear but the possible need to use increased doses in smokers should be borne in mind.

1. Swett C. Drowsiness due to chlorpromazine in relation to cigarette smoking: a report from the Boston Collaborative Drug Surveillance Program. *Arch Gen Psychiatry* 1974; **31:** 211–13.
2. Pantuck EJ, *et al.* Cigarette smoking and chlorpromazine disposition and actions. *Clin Pharmacol Ther* 1982; **31:** 533–8.
3. Chetty M, *et al.* Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol* 1994; **46:** 523–6.
4. Ereshefsky L, *et al.* Effects of smoking on fluphenazine clearance in psychiatric inpatients. *Biol Psychiatry* 1985; **20:** 329–32.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; **11:** 296–301.
6. Jann MW, *et al.* Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology (Berl)* 1986; **90:** 468–70.
7. Berecz R, *et al.* Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype. *Eur J Clin Pharmacol* 2003; **59:** 45–50.

Vitamins. Giving *ascorbic acid*, for vitamin C deficiency, to a patient receiving fluphenazine for bipolar disorder was associated with a fall in serum concentrations of fluphenazine and a deterioration of behaviour.[1]

1. Dysken MW, *et al.* Drug interaction between ascorbic acid and fluphenazine. *JAMA* 1979; **241:** 2008.

Xanthine-containing beverages. Studies *in vitro* have shown precipitation of some antipsychotics from solution by addition of *coffee* and *tea*.[1,2] However, in a study of 16 patients taking antipsychotics no correlation could be found between plasma-antipsychotic concentrations or behaviour and tea or coffee consumption.[3]

1. Kulhanek F, *et al.* Precipitation of antipsychotic drugs in interaction with coffee or tea. *Lancet* 1979; **ii:** 1130.
2. Lasswell WL, *et al.* In vitro interaction of neuroleptics and tricyclic antidepressants with coffee, tea, and gallotannic acid. *J Pharm Sci* 1984; **73:** 1056–8.
3. Bowen S, *et al.* Effect of coffee and tea on blood levels and efficacy of antipsychotic drugs. *Lancet* 1981; **i:** 1217–18.

Pharmacokinetics

Chlorpromazine is readily, although sometimes erratically, absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after ingestion. It is subject to considerable first-pass metabolism in the gut wall and is also extensively metabolised in the liver and is excreted in the urine and bile in the form of many active and inactive metabolites; there is some evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after intramuscular doses. Moreover, there is very wide intersubject variation in plasma concentrations of chlorpromazine; no simple correlation has been found between plasma concentrations of chlorpromazine and its metabolites, and their therapeutic effect (see Administration under Uses and Administration, p. 1046.1). Paths of metabolism of chlorpromazine include hydroxylation and conjugation with glucuronic acid, *N*-oxidation, oxidation of a sulfur atom, and dealkylation. Although the plasma half-life of chlorpromazine itself has been reported to be about 30 hours, elimination of the metabolites may be very prolonged. There is limited evidence that chlorpromazine induces its own metabolism.

Chlorpromazine is about 95 to 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ampliactil; Conrax; ***Austral.***: Largactil; ***Braz.***: Amplictil; Clopsina; Clorpromaz; Longactil; ***Chile***: Largactil; ***Cz.***: Plegomazin; ***Fin.***: Klorpromaz; ***Fr.***: Largactil; ***Gr.***: Largactil; Solidon; Zuledin; ***Hung.***: Hibernal; ***India***: Cain; Clozine; Emetil; Megatil; ***Indon.***: Cepezet; Meprosetil; Promactil; ***Irl.***: Clonactil; Clonazine†; ***Israel***: Taroctyl; ***Ital.***: Largactil; Prozin; ***Jpn***: Wintermin; ***Malaysia***: Matcine; ***Mex.***: Largactil; ***NZ***: Largactil; ***Philipp.***: Globazine; Laractyl; Proma; Promazine; Psynor; Thorazine; ***Pol.***: Fenactil; ***Port.***: Largactil; Largatrex†; ***Rus.***: Aminazin (Аминазин); ***S.Afr.***: Largactil; ***Singapore***: Largo; Matcine; ***Spain***: Largactil; ***Switz.***: Chlorazin; ***Thai.***: Chlopazine; Chlorpromasit†; Chlorpromed; Duncan†; Matcine; Plegomazine; Pogetol; Prozine; ***Turk.***: Largactil; ***UK***: Largactil; ***Ukr.***: Aminazin (Аминазин).

Multi-ingredient Preparations. ***Arg.***: 6-Copin†; 6-Copin; ***India***: Chlorectil Plus; Clozine Forte; Clozine Plus; Emetil DS; Emetil Plus; Lacalm; Manocalm Forte; Neocalm Forte; Trinicalm Forte; ***Thai.***: Ama.

Pharmacopoeial Preparations

BP 2014: Chlorpromazine Injection; Chlorpromazine Oral Solution; Chlorpromazine Suppositories; Chlorpromazine Tablets;

USP 36: Chlorpromazine Hydrochloride Injection; Chlorpromazine Hydrochloride Oral Concentrate; Chlorpromazine Hydrochloride Syrup; Chlorpromazine Hydrochloride Tablets; Chlorpromazine Suppositories.

Chlorprothixene *(BAN, USAN, rINN)*

Chlorprothixène; Chlorprothixenum; Clorprotixeno; Kloriprotikseeni; Klorprotixen; N-714; Ro-4-0403; Хлорпротиксен.

(*Z*)-3-(2-Chlorothioxanthen-9-ylidene)-*NN*-dimethylpropylamine.

$C_{18}H_{18}ClNS$=315.9

CAS — *113-59-7.*

ATC — *N05AF03.*

ATC Vet — *QN05AF03.*

UNII — *9S7OD60EWP.*

Pharmacopoeias. In *Chin.*

Chlorprothixene Hydrochloride

(BANM, rINNM)

Chloroprotyksenu chlorowodorek; Chlorprothixène, Chlorhydrate de; Chlorprothixenhydrochlorid; Chlorprothixenhydrochlorid; Chlorprothixeni Hydrochloridum; Chlorprotikseno hidrochloridas; Clorprotixeno, hidrocloruro de; Hidrocloruro de clorprotixeno; Klooriprotikseenihydrokloridi; Klórprotixen-hidroklorid; Klorprotixenhydroklorid; Хлорпротиксена Гидрохлорид.

$C_{18}H_{19}Cl_2NS$=352.3

ATC — N05AF03.

ATC Vet — QN05AF03.

UNII — 268KCR965N.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Chlorprothixene Hydrochloride). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.4 to 5.2. Protect from light.

Profile

Chlorprothixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.2). It is used mainly in the treatment of psychoses (p. 1030.2). Chlorprothixene is given as the hydrochloride. Preparations of chlorprothixene prepared with the aid of lactic acid have been stated to contain chlorprothixene lactate. The acetate, citrate, and the mesilate have also been used.

Chlorprothixene is usually given orally as the hydrochloride and doses are expressed in terms of this salt. A usual oral initial dose for the treatment of psychoses is 15 to 50 mg three or four times daily, increased according to response; doses of up to 600 mg or more daily have been given in severe or resistant cases. Chlorprothixene should be used in reduced dosage for elderly or debilitated patients.

Adverse effects. A 59-year-old man receiving chlorprothixene (for the second time) for acute mania developed severe obstructive jaundice within a few days; he was also taking chlorpropamide, digoxin, and diuretics.[1] Chlorprothixene was considered the most likely cause of the jaundice, though chlorpropamide could not be excluded.

1. Ruddock DGS, Hoenig J. Chlorprothixene and obstructive jaundice. *BMJ* 1973; **1:** 231.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of chlorprothixene on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Chlorprothixene and its sulfoxide metabolite were concentrated in the breast milk of 2 mothers given chlorprothixene 200 mg daily but it was calculated that the amount ingested by the nursing infant was only 0.1% of the maternal dose per kg body-weight.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Presence of chlorprothixene and its metabolites in breast milk. *Eur J Clin Pharmacol* 1984; **27:** 611–13.

Metabolism. Results from studies on the metabolism of chlorprothixene in *animals* and man[1] indicated that in addition to the major metabolite chlorprothixene-sulfoxide, 2 further urinary metabolites were identified, namely *N*-desmethylchlorprothixene-sulfoxide and chlorprothixene-sulfoxide-*N*-oxide.

1. Raaflaub J. Zum Metabolismus des Chlorprothixen. *Arzneimittelforschung* 1967; **17:** 1393–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorprothixene as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Truxal; ***Denm.***: Truxal; ***Fin.***: Truxal; ***Ger.***: Truxal; ***Gr.***: Truxal; ***Hung.***: Truxal; ***Neth.***: Truxal; ***Norw.***: Truxal; ***Rus.***: Truxal (Труксал); ***Swed.***: Truxal; ***Switz.***: Truxal; Truxaletten†; ***Ukr.***: Truxal (Труксал).

Cinolazepam *(rINN)*

Cinolazépam; Cinolazepamum; OX-373; Цинолазепам.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-3-hydroxy-2-oxo-1*H*-1,4-benzodiazepine-1-propionitrile.

$C_{18}H_{13}ClFN_3O_2$=357.8

CAS — 75696-02-5.

ATC — N05CD13.

ATC Vet — QN05CD13.

UNII — 68P0556B0U.

Profile

Cinolazepam is a benzodiazepine derivative with general properties similar to those of diazepam (p. 1063.2) that has been used in the short-term management of sleep disorders in usual oral doses of 40 mg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Gerodorm; ***Cz.***: Gerodorm; ***Hung.***: Gerodorm.

Clocapramine Hydrochloride *(rINNM)*

Chlorcarpipramine Hydrochloride; Clocapramina, hidrocloruro de; Clocapramine, Chlorhydrate de; Clocapramini Hydrochloridum; Hidrocloruro de clocapramina; Y-4153; Клокапрамина Гидрохлорид.

1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl][1,4′-bipiperidine]-4′-carboxamide dihydrochloride monohydrate.

$C_{28}H_{37}ClN_4O,2HCl,H_2O$=572.0

CAS — 47739-98-0 (clocapramine); 28058-62-0 (clocapramine hydrochloride).

UNII — 9NLU6H3LRD.

Pharmacopoeias. In *Jpn.*

Profile

Clocapramine is a chlorinated derivative of carpipramine (p. 1044.2). The hydrochloride is given orally in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Clofekton; Padrasen.

Clomethiazole *(BAN, rINN)*

Chlormethiazole; Clométhiazole; Clomethiazolum; Clometiazol; Klometiatsoli; Klometiazol; Клометиазол.

5-(2-Chloroethyl)-4-methyl-1,3-thiazole.

C_6H_8ClNS=161.6

CAS — 533-45-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

UNII — 0C5DBZ19HV.

Pharmacopoeias. In *Br.*

BP 2014: (Clomethiazole). A colourless to slightly yellowish-brown liquid with a characteristic odour. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. A 0.5% solution in water has a pH of 5.5 to 7.0. Store at a temperature of 2 degrees to 8 degrees.

Clomethiazole Edisilate *(BANM, rINNM)*

Chlormethiazole Edisylate; Chlormethiazole Ethanedisulphonate; Clométhiazole, Edisilate de; Clomethiazole Edisylate (USAN); Clomethiazoli Edisilas; Clometiazol, edisilato de; Edisilato de clometiazol; Klometiazolu edysylan; NEX-002; Клометиазола Эдизилат.

5-(2-Chloroethyl)-4-methylthiazole ethane-1,2-disulphonate.

$(C_6H_8ClNS)_2,C_2H_6O_6S_2$=513.5

CAS — 1867-58-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

UNII — 22NJI0W1D2.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Clomethiazole Edisilate). A white crystalline powder with a characteristic odour. Freely soluble in water; soluble in alcohol; practically insoluble in ether.

Incompatibility. Several studies have shown that clomethiazole edisilate may permeate through or be sorbed onto plastics used in intravenous infusion bags or giving sets.[1-4] The drug may also react with and soften the plastic.[1] Licensed product information has suggested that thrombophlebitis, fever, and headache reported in young children during prolonged infusions may have been due to reaction with plastic giving sets and silastic cannulae. Recommendations for intravenous use have therefore included the use of a motor-driven glass syringe in preference to a plastic drip set in small children, changing plastic drip sets at least every 24 hours when used in older patients, and use of teflon intravenous cannulas.

1. Lingam S, *et al.* Problems with intravenous chlormethiazole (Heminevrin) in status epilepticus. *BMJ* 1980; **280:** 155–6.
2. Tsuei SE, *et al.* Sorption of chlormethiazole by intravenous infusion giving sets. *Eur J Clin Pharmacol* 1980; **18:** 333–8.
3. Kowaluk EA, *et al.* Dynamics of clomethiazole edisylate interaction with plastic infusion systems. *J Pharm Sci* 1984; **73:** 43–7.
4. Lee MG. Sorption of four drugs to polyvinyl chloride and polybutadiene intravenous administration sets. *Am J Hosp Pharm* 1986; **43:** 1945–50.

Uses and Administration

Clomethiazole is a hypnotic and sedative with anticonvulsant effects. It is used orally in the treatment of agitation and restlessness (see Disturbed Behaviour, p. 1030.2) in elderly patients, in the short-term management of severe insomnia (p. 1033.2) in the elderly, and in the treatment of acute alcohol withdrawal symptoms (p. 1735.1). It was also given as an intravenous infusion in the management of status epilepticus and impending or actual eclampsia; however, a parenteral formulation of clomethiazole no longer appears to be available.

In the UK, clomethiazole is available as capsules containing 192 mg of clomethiazole base and as syrup containing 250 mg of the edisilate in 5 mL. As a result of differences in the bioavailability of these preparations, 192 mg of the base in the capsules is considered therapeutically equivalent to 250 mg (5 mL) of the edisilate in the syrup, i.e. one capsule or 5 mL of syrup are equivalent in their effects.

The usual hypnotic dose of clomethiazole for **insomnia** is 1 or 2 capsules (192 or 384 mg of the base) or the equivalent before bedtime. For **restlessness and agitation** 1 capsule (192 mg of the base), or the equivalent, may be given 3 times daily.

Various clomethiazole regimens have been suggested for the treatment of **alcohol withdrawal**, usually starting with 2 to 4 capsules, or the equivalent, which may be repeated after some hours if necessary. In the first 24 hours, 9 to 12 capsules, or the equivalent, divided into 3 or 4 doses, can be given; the dose is then gradually reduced over the next 5 days. Treatment should be carried out in hospital or in specialist centres, and use for longer than 9 days is not recommended because of the risk of dependence (see below).

Porphyria. Clomethiazole is one of the drugs that has been used for seizure prophylaxis in patients with porphyria who continue to have convulsions while in remission. However, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clomethiazole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Stroke. Clomethiazole has been studied[1,2] as a neuroprotective drug in the acute management of patients with stroke, but no beneficial effect on long-term outcome was found.

1. Wahlgren NG, *et al.* CLASS Study Group. Clomethiazole Acute Stroke Study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. *Stroke* 1999; **30:** 21–8.
2. Lyden P, *et al.* Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. *Stroke* 2002; **33:** 122–8.

Substance dependence. For a discussion of the management of *opioid* withdrawal symptoms, including mention of the use of clomethiazole, see p. 109.2.

Dependence and Withdrawal

Dependence may develop, particularly with prolonged use of higher than recommended doses of clomethiazole. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects, Treatment, and Precautions

Clomethiazole may produce nasal congestion and irritation, sneezing, and conjunctival irritation sometimes associated with a headache. Nasopharyngeal or bronchial secretions may be increased. Skin rashes and urticaria have also occurred and in rare cases bullous eruptions have been reported. Gastrointestinal disturbances including nausea and vomiting, have been reported after oral doses. Reversible increases in liver enzyme values and blood-bilirubin concentrations have also been noted. Clomethiazole can cause excessive drowsiness, particularly in high

doses; drowsiness may persist the next day, and patients affected should not drive or operate machinery. Paradoxical excitation or confusion may occur rarely. Anaphylaxis has also been reported rarely.

Excessive doses may produce coma, respiratory depression, hypotension, and hypothermia; pneumonia may follow increased respiratory secretion. Treatment is as for barbiturate overdose (see Amobarbital, p. 1038.1).

Clomethiazole is contra-indicated in patients with acute pulmonary insufficiency, and should be given with care to patients with sleep apnoea syndrome, chronic pulmonary insufficiency, or renal, liver, cerebral, or cardiac disease. Clomethiazole should be given with caution to elderly patients as there may be increased bioavailability and delayed elimination. Paradoxical worsening of epilepsy may occur in the Lennox Gastaut syndrome.

Administration by intravenous infusion. Severe adverse effects have followed the intravenous use of clomethiazole, and intravenous preparations are no longer generally available. Facilities for intubation and resuscitation were required when clomethiazole was given intravenously, with care taken to ensure that the patient's airway was maintained since there is a risk of mechanical obstruction during deep sedation. At too high a rate of infusion, sleep induced with clomethiazole could lapse into deep unconsciousness and patients required close and constant observation. Rapid infusion has also caused transient apnoea and hypotension, and special care was needed in patients susceptible to cerebral or cardiac complications, including the elderly. With prolonged infusion there was also a risk of electrolyte imbalance due to the water load involved with the glucose vehicle. Recovery has been considerably delayed after prolonged infusion.

Effects on the heart. Cardiac arrest in 2 chronic alcoholics might have been associated with clomethiazole infusion.[1]

1. McInnes GT, *et al*. Cardiac arrest following chlormethiazole infusion in chronic alcoholics. *Postgrad Med J* 1980; **56:** 742–3.

Overdosage. A report of clomethiazole poisoning on 16 occasions in 13 patients, some of whom had also taken other drugs and alcohol.[1] There was increased salivation on 7 occasions; otherwise the clinical features were those of barbiturate poisoning (see Adverse Effects of Amobarbital, p. 1038.1). The highest plasma-clomethiazole concentration was 36 micrograms/mL, with the highest value in a conscious patient 11.5 micrograms/mL. All the patients survived following intensive supportive treatment as for barbiturate poisoning.

1. Illingworth RN, *et al*. Severe poisoning with chlormethiazole. *BMJ* 1979; **2:** 902–3.

Parotitis. Acute bilateral parotitis has been reported in a patient given clomethiazole.[1] The swelling disappeared after withdrawal of clomethiazole and recurred on rechallenge.

1. Bosch X, *et al*. Parotitis induced by chlormethiazole. *BMJ* 1994; **309:** 1620.

Pregnancy. There have been reports of neonates being adversely affected by clomethiazole given to their mothers for pre-eclampsia or eclampsia;[1,2] effects included sedation, hypotonia, and apnoea. It was suggested that the effects might have been due to a synergistic interaction between clomethiazole and diazoxide as these drugs were given to most of the mothers with affected infants.[1]

1. Johnson RA. Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide. *BMJ* 1976; **1:** 943.
2. Wood C, Renou P. Sleepy and hypotonic neonates. *Med J Aust* 1978; **2:** 73.

Interactions

The sedative effects of clomethiazole are enhanced by CNS depressants such as alcohol, barbiturates, other hypnotics and sedatives, and antipsychotics.

Alcohol. Although clomethiazole has been a popular choice for the treatment of alcohol withdrawal symptoms (p. 1735.1), if it is given long-term, patients readily transfer dependency to it; if they also continue to abuse alcohol this may lead to severe self-poisoning with deep coma and potentially fatal respiratory depression.[1]

1. McInnes GT. Chlormethiazole and alcohol: a lethal cocktail. *BMJ* 1987; **294:** 592.

Beta blockers. Sinus bradycardia developed in an 84-year-old woman taking *propranolol* for hypertension 3 hours after she took a second dose of clomethiazole 192 mg.[1] Her pulse rate increased on stopping propranolol and clomethiazole and later stabilised when she took propranolol with haloperidol.

1. Adverse Drug Reactions Advisory Committee (Australia). *Med J Aust* 1979; **2:** 553.

Diazoxide. For a report of adverse reactions in neonates born to mothers given clomethiazole and diazoxide, see Pregnancy under Adverse Effects, Treatment, and Precautions, above.

Histamine H_2-antagonists. Use of *cimetidine* 1 g daily for 1 week increased sleep time induced by a 1-g oral dose of clomethiazole edisilate in most of 8 healthy subjects from between 30 to 60 minutes to at least 2 hours.[1] This was associated with a 31% reduction in the mean clearance of clomethiazole, a 69% rise in the mean peak plasma concentration of the hypnotic, and an increase in its mean elimination half-life from 2.33 to 3.63 hours.

Ranitidine did not significantly affect the pharmacokinetics of clomethiazole in a study in 7 healthy subjects.[2]

1. Shaw G, *et al*. Cimetidine impairs the elimination of chlormethiazole. *Eur J Clin Pharmacol* 1981; **21:** 83–5.
2. Mashford ML, *et al*. Ranitidine does not affect chlormethiazole or indocyanine green disposition. *Clin Pharmacol Ther* 1983; **34:** 231–3.

Pharmacokinetics

Clomethiazole is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 15 to 90 minutes after oral doses depending on the formulation used. It is widely distributed in the body and is reported to be 65% bound to plasma proteins. Clomethiazole is extensively metabolised, probably by first-pass metabolism in the liver with only small amounts appearing unchanged in the urine. The elimination half-life has been reported to be about 4 hours but this may be increased to 8 hours or longer in the elderly or in patients with hepatic impairment. Clomethiazole crosses the placenta and is distributed into breast milk.

Hepatic impairment. Studies in 8 patients with advanced cirrhosis of the liver and in 6 healthy men showed that the amount of unmetabolised clomethiazole reaching the circulation after an oral dose was about 10 times higher in the patients than in the controls.[1] Low concentrations in the controls were related to extensive first-pass metabolism in the liver.

1. Pentikäinen PJ, *et al*. Pharmacokinetics of chlormethiazole in healthy volunteers and patients with cirrhosis of the liver. *Eur J Clin Pharmacol* 1980; **17:** 275–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hemineurin†; ***Cz.***: Heminevrin; ***Ger.***: Distraneurin; ***Gr.***: Distaneurin; Distraneurine; Heminevrin; ***Hung.***: Heminevrin; ***Irl.***: Heminevrin†; ***Norw.***: Heminevrin; ***Pol.***: Heminevrin; ***Spain***: Distraneurine; ***Swed.***: Heminevrin; ***Switz.***: Distraneurin; ***UK***: Heminevrin†.

Pharmacopoeial Preparations
BP 2014: Clomethiazole Capsules; Clomethiazole Infusion; Clomethiazole Oral Solution.

Cloral Betaine *(BAN, rINN)*

Chloral Betaine (USAN); Cloral betaína; Cloral Bétaïne; Cloralum Betainum; Compound 5107; Хлораль Бетаин.

An adduct of cloral hydrate and betaine.

$C_7H_{12}Cl_3NO_3,H_2O$=282.5

CAS — 2218-68-0.

UNII — 8680278NRH.

Profile

Cloral betaine rapidly dissociates in the stomach to release cloral hydrate and has actions and uses similar to those of cloral hydrate (below). It is given orally in the short-term management of insomnia (p. 1033.2), as tablets containing 707 mg (equivalent to about 414 mg of cloral hydrate). The usual hypnotic dose is one or two tablets taken at night with water or milk. The maximum daily dose is five tablets (equivalent to about 2 g of cloral hydrate). A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Somnwell†; Welldorm.

Cloral Hydrate

Chloral Hydrate (BAN); Chloral, hydrate de; Chloralhydrat; Chloralhydrát; Chlorali Hydras; Chloralio hidratas; Chloralu wodzian; Cloral, hidrato de; Kloraalihydraatti; Kloral Hidrat; Klorál-hidrát; Kloralhydrat; Хлоралгидрат.

2,2,2-Trichloroethane-1,1-diol.

$C_2H_3Cl_3O_2$=165.4

CAS — 302-17-0.

ATC — N05CC01.

ATC Vet — QN05CC01.

UNII — 418M5916WG.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of cloral hydrate:

Jellies; Jelly beans; Joy Juice; Knockout Drops; Knock out drops; Mickey; Mickeys; Mickey Finn; Mickey Finns; Peter; Torpedo.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chloral Hydrate). Colourless, transparent crystals. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Chloral Hydrate). Colourless, transparent, or white crystals having an aromatic, penetrating, and slightly acrid odour. It volatilises slowly on exposure to air and melts at about 55 degrees. Soluble 1 in 0.25 of water, 1 in 1.3 of alcohol, 1 in 2 of chloroform, and 1 in 1.5 of ether; very soluble in olive oil. Store in airtight containers.

Incompatibility. Cloral hydrate is reported to be incompatible with alkalis, alkaline earths, alkali carbonates, soluble barbiturates, borax, tannin, iodides, oxidising agents, permanganates, and alcohol (cloral alcoholate may crystallise out). It forms a liquid mixture when triturated with many organic compounds, such as camphor, menthol, phenazone, phenol, thymol, and quinine salts.

Uses and Administration

Cloral hydrate is a hypnotic and sedative with properties similar to those of the barbiturates. It is used in the short-term management of insomnia (p. 1033.2) and has been used for sedation and as a premedicant (see Anaesthesia, p. 1899.1); its use as a hypnotic, particularly in children, is now limited. It has also been used in the management of acute alcohol withdrawal symptoms (p. 1735.1).

Externally, cloral hydrate has a rubefacient action and has been used as a counter-irritant.

Cloral hydrate is given orally as a liquid or dissolved in a suitable vehicle within gelatin capsules. It has also been dissolved in a bland fixed oil and given by enema or as suppositories.

It should not be given as tablets because of the risk of damage to the mucous membrane of the alimentary tract.

The usual oral hypnotic dose is 0.5 to 1 g given as a single dose at night; as a sedative 250 mg can be given three times daily. The maximum daily dose for both indications is 2 g. Oral dosage forms should be taken well diluted or with plenty of water or milk.

A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment. For doses in children, see below.

Derivatives of cloral hydrate, such as acetylglycinamide-cloral hydrate, cloral betaine (above), chloralose (p. 2150.2), chloralodol, and dichloralphenazone (p. 1071.3), which break down in the body to yield cloral hydrate, have been used similarly.

Administration in children. Cloral hydrate has been used in the short-term management of insomnia and for sedation and as a premedicant in children; however, carcinogenicity was once a cause for concern (see Carcinogenicity p. 1056.1) and such use is now limited.

Children aged 2 to 11 years may be given cloral hydrate 30 to 50 mg/kg (maximum single dose of 1 g) orally at night as a hypnotic; those aged 12 years and older may be given the usual adult dose for this indication (see Uses and Administration, above).

Although not licensed in the UK for sedation of children before a painless procedure, the *BNFC* suggests the following oral doses, given 45 to 60 minutes beforehand: neonates and children up to 12 years of age, 30 to 50 mg/kg, although up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring; 12 to 18 years, 1 to 2 g. Doses may be given rectally if the oral route cannot be used.

Dependence and Withdrawal, Adverse Effects, and Treatment

Cloral hydrate has an unpleasant taste and is corrosive to skin and mucous membranes unless well diluted. The most frequent adverse effect is gastric irritation; abdominal distension and flatulence may also occur. CNS effects such as drowsiness, light-headedness, ataxia, headache, paradoxical excitement, hallucinations, nightmares, delirium, and confusion (sometimes with paranoia) occur occasionally. Hypersensitivity reactions include rashes (erythema multiforme and Stevens-Johnson syndrome have been reported with the related compound triclofos). Ketonuria may occur.

The effects of acute overdosage resemble acute barbiturate intoxication (see Amobarbital, p. 1038.1 and

Overdosage below), and are managed similarly. In addition the irritant effect may cause initial vomiting, and gastric necrosis leading to strictures. Cardiac arrhythmias have been reported. Jaundice may follow liver damage, and albuminuria may follow kidney damage.

Tolerance may develop and dependence may occur. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p. 1038.1).

Incidence of adverse effects. In a drug surveillance programme,[1] adverse effects of cloral hydrate, which were reversible, occurred in 2.3% of 1130 patients evaluated and included gastrointestinal symptoms (10 patients), CNS depression (20), and rash (5). In 1 patient the prothrombin time was increased; in another hepatic encephalopathy seemed to worsen; and bradycardia developed in a further patient. In another such programme, adverse effects occurred in about 2% of 5435 patients given cloral hydrate.[2] Three reactions were described as life-threatening.

1. Shapiro S, *et al.* Clinical effects of hypnotics II: an epidemiologic study. *JAMA* 1969; **209:** 2016–20.
2. Miller RR, Greenblatt DJ. Clinical effects of chloral hydrate in hospitalized medical patients. *J Clin Pharmacol* 1979; **19:** 669–74.

Carcinogenicity. Cloral hydrate has been widely used as a sedative, especially in children. Concern over warnings that cloral hydrate was carcinogenic in *rodents*[1] has prompted some experts, including the American Academy of Pediatrics, to review the relative risks of the medical use of this drug.[2,3] The original warnings appear to have been based, in part, on the assumption that cloral hydrate was a reactive metabolite of trichloroethylene and was responsible for its carcinogenicity, but there is evidence to suggest that the carcinogenicity of trichloroethylene is due to a reactive intermediate epoxide metabolite. Studies *in vitro* indicate that cloral hydrate can damage chromosomes in some mammalian test systems but there have been no studies of the carcinogenicity of cloral hydrate in humans. Some long-term studies in *mice* have linked cloral hydrate with the development of hepatic adenomas or carcinomas. However, it was noted that cloral hydrate was not the only sedative that had been shown to be a carcinogen in experimental *animals*. The American Academy of Pediatrics considered cloral hydrate to be an effective sedative with a low incidence of acute toxicity when given short-term as recommended and, although the information on carcinogenicity was of concern, it was not sufficient to justify the risk associated with the use of less familiar sedatives. There was no evidence in infants or children showing that any of the available alternatives were safer or more effective. However, the use of repetitive dosing with cloral hydrate to maintain prolonged sedation in neonates and other children was of concern because of the potential for accumulation of drug metabolites and resultant toxicity.

A more recent cohort study[4] found no persuasive evidence to support a relationship between the use of cloral hydrate and the development of cancer. However, the statistical power was low for weak associations, particularly for some individual cancer sites.

1. Smith MT. Chloral hydrate warning. *Science* 1990; **250:** 359.
2. Steinberg AD. Should chloral hydrate be banned? *Pediatrics* 1993; **92:** 442–6.
3. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. *Pediatrics* 1993; **92:** 471–3.
4. Haselkorn T, *et al.* Short-term chloral hydrate administration and cancer in humans. *Drug Safety* 2006; **29:** 67–77.

Effects on the CNS. A 2-year-old child[1] had the first of 2 seizures 60 minutes after receiving cloral hydrate 70 mg/kg for sedation.

1. Muñoz M, *et al.* Seizures caused by chloral hydrate sedative doses. *J Pediatr* 1997; **131:** 787–8.

Hyperbilirubinaemia. Small retrospective studies[1] have suggested that prolonged use of cloral hydrate in neonates may be associated with the development of hyperbilirubinaemia. This may possibly be related to the prolonged half-life of the metabolite trichloroethanol in neonates.

1. Lambert GH, *et al.* Direct hyperbilirubinemia associated with chloral hydrate administration in the newborn. *Pediatrics* 1990; **86:** 277–81.

Overdosage. The general management of poisoning with cloral hydrate resembles that for barbiturates (see Treatment of Adverse Effects, under Amobarbital, p. 1038.1). Activated charcoal may be given orally to drug-naive adults and children within 1 hour of ingestion of more than 50 mg/kg, provided that the airway can be protected; for those already receiving cloral hydrate, consider giving activated charcoal if double the therapeutic dose has been taken. However, the value of gastric decontamination for overdose is uncertain. Of 76 cases of cloral hydrate poisoning reported to the UK National Poisons Information Service (NPIS), 47 were severe.[1] Of 39 adults, 12 had cardiac arrhythmias including 5 with cardiac arrest. Antiarrhythmic drugs were recommended unless obviously contra-indicated. Haemoperfusion through charcoal or haemodialysis was recommended for patients in prolonged coma. Cardiac arrhythmias and CNS depression were also major features of 12 cases of cloral hydrate overdosage reported from Australia.[2] Lidocaine was not always successful in controlling arrhythmias, but propranolol was successful in all 7 patients in whom it was used. It was noted that resistant arrhythmias, particularly ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, were the usual cause of death in patients who had taken an overdosage of cloral hydrate. Although there had been no controlled studies of antiarrhythmic therapy in overdosage with cloral hydrate, the successful use of beta blockers appeared to be a recurring feature in reports in the literature. Indeed, the UK NPIS notes that tachyarrhythmias usually respond readily to an intravenous beta blocker such as esmolol or metoprolol.

Giving flumazenil produced an increased level of consciousness, pupillary dilatation, and return of respiratory rate and blood pressure towards normal in a patient who had taken an overdosage of cloral hydrate.[3]

1. Wiseman HM, Hampel G. Cardiac arrhythmias due to chloral hydrate poisoning. *BMJ* 1978; **2:** 960.
2. Graham SR, *et al.* Overdose with chloral hydrate: a pharmacological and therapeutic review. *Med J Aust* 1988; **149:** 686–8.
3. Donovan KL, Fisher DJ. Reversal of chloral hydrate overdose with flumazenil. *BMJ* 1989; **298:** 1253.

Precautions

Cloral hydrate should not be used in patients with marked hepatic or renal impairment or severe cardiac disease, and oral dosage is best avoided in the presence of gastritis. As with all sedatives, it should be used with caution in those with respiratory insufficiency.

Cloral hydrate can cause drowsiness that may persist the next day; affected patients should not drive or operate machinery. Prolonged use and abrupt withdrawal of cloral hydrate should be avoided to prevent precipitation of withdrawal symptoms. Repeated doses in infants and children may lead to accumulation of metabolites and thereby increase the risk of adverse effects. Use is best avoided during pregnancy.

Cloral hydrate may interfere with some tests for urinary glucose or 17-hydroxycorticosteroids.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, use of cloral hydrate by breast-feeding mothers has been reported to cause sleepiness in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Neonates. The half-life of trichloroethanol, an active metabolite of cloral hydrate, is prolonged in neonates;[1] values of up to 66 hours have been reported in some studies. Short-term sedation in the neonate with single oral doses of 25 to 50 mg/kg of cloral hydrate is considered[1] to be probably relatively safe, but repeated dosage carries the risk of accumulation of metabolites which may result in serious toxicity. Toxic reactions may occur even after the drug has been stopped since the metabolites may accumulate for several days.

1. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.

Obstructive sleep apnoea. Children with obstructive sleep apnoea could be at risk from life-threatening respiratory obstruction if cloral hydrate is used for sedation. Details of 2 such children who suffered respiratory failure after sedation with cloral hydrate for lung function studies have been reported.[1]

1. Biban P, *et al.* Adverse effect of chloral hydrate in two young children with obstructive sleep apnea. *Pediatrics* 1993; **92:** 461–3.

Porphyria. Although cloral hydrate has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] UK licensed product information recommends that it should not be used in patients susceptible to acute attacks of porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The sedative effects of cloral hydrate are enhanced by other CNS depressants such as alcohol (the 'Mickey Finn' of detective fiction), barbiturates, and other sedatives.

Cloral hydrate may alter the effects of coumarin anticoagulants (see Warfarin, p. 1533.1). A hypermetabolic state, apparently due to displacement of thyroid hormones from their binding proteins, has been reported in patients given an intravenous dose of furosemide subsequent to cloral hydrate.

Pharmacokinetics

Cloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral doses. It is widely distributed throughout the body. It is rapidly metabolised to trichloroethanol and trichloroacetic acid (p. 1727.2) in the erythrocytes, liver, and other tissues. It is excreted partly in the urine as trichloroethanol and its glucuronide (urochloralic acid) and as trichloroacetic acid. Some is also excreted in the bile.

Trichloroethanol is the active metabolite, and passes into the CSF, into breast milk, and across the placenta. The half-life of trichloroethanol in plasma is reported to range from about 7 to 11 hours but is considerably prolonged in the neonate. Trichloroacetic acid has a plasma half-life of several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Kloral; ***Ger.***: Chloraldurat†; ***Singapore***: Little's Chloral Syrup Paed; ***Switz.***: Chloraldurat†; Nervifene; ***UK***: Welldorm; ***USA***: Aquachloral†; Somnote†.

Multi-ingredient Preparations. ***Belg.***: Dentophar†; Sedemol; Sulfa-Sedemol; ***Rus.***: Efcamon (Эфкамон); ***Turk.***: Dilan†.

Pharmacopoeial Preparations
BP 2014: Cloral Hydrate Oral Solution;
USP 36: Chloral Hydrate Capsules; Cloral Hydrate Syrup.

Clorazepic Acid *(BAN)*

Clorazépico, ácido.
7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid.
$C_{16}H_{11}ClN_2O_3$=314.7
CAS — 23887-31-2; 20432-69-3.
UNII — D51WO0G0L4.

Clorazepate Monopotassium *(USAN)*

Abbott-39083; 4311-CB; Clorazepato monopotásico; Моно-калий Клоразепата.
Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate.
$C_{16}H_{10}ClKN_2O_3$=352.8
CAS — 5991-71-9.
UNII — MS63G8NQUI.

Dipotassium Clorazepate *(BANM, rINN)*

Abbott-35616; AH-3232; 4306-CB; Clorazépate Dipotassique; Clorazepate Dipotassium (USAN); Clorazepato de dipotasio; Dikalii Clorazepas; Dikalio klorazepatas; Dikaliumclorazepat; Dikaliumkloratsepaatti; Dikaliumklorazepat; Dikálium-klórazepát; Kalii Clorazepas; Kaliumkloratsepaatti; Klaiumklorazepat; Klorazepát didraselná sůl; Klorazepat Dipotasyum; Potassium Clorazepate; Дикалия Клоразепат.
Compound of Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate with potassium hydroxide.
$C_{16}H_{11}ClK_2N_2O_4$=408.9
CAS — 57109-90-7.
ATC — N05BA05.
ATC Vet — QN05BA05.
UNII — 63FN7G03XY.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dipotassium Clorazepate). A white or light yellow, crystalline powder. Solutions in water and in alcohol are unstable and should be used immediately. Freely soluble or very soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Clorazepate Dipotassium). A light yellow, crystalline powder which darkens on exposure to light. Soluble in water but, upon standing, may precipitate from the solution; slightly soluble in alcohol and in isopropyl alcohol; practically insoluble in acetone, in chloroform, in dichloromethane, in ether, and in benzene. Store under nitrogen in airtight containers. Protect from light.

Uses and Administration

Clorazepate is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is mainly used in the short-term treatment of anxiety disorders (p. 1028.1), as an adjunct in the management of epilepsy (p. 506.1), and in the alcohol withdrawal syndrome (p. 1735.1).

Dipotassium clorazepate is usually given orally but preparations for intravenous or intramuscular use are also available in some countries. Modified-release preparations given once daily are available in some countries for maintenance therapy.

For the treatment of **anxiety** a usual oral dose of 30 mg of dipotassium clorazepate daily is given in divided doses, adjusted according to response to within the range of 15 to 60 mg daily. It may also be given as a single dose at night, initially in a dose of 15 mg.

Up to 90 mg has been given daily in divided doses in the management of **epilepsy** or the **alcohol withdrawal syndrome**.

Reduced doses should be given to elderly or debilitated patients; initial doses of 7.5 to 15 mg daily have been suggested for the treatment of anxiety.

For details of doses in children, see below.

Administration in children. As an adjunct in the management of epilepsy, children aged between 9 and 12 years may be given dipotassium clorazepate orally in a maximum initial dose of 7.5 mg twice daily, increased by no more than 7.5 mg every week to a maximum of 60 mg daily; older children may be given the usual adult dose (see p. 1056.3).

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Effects on the liver. Jaundice and hepatic necrosis has been associated with clorazepate.[1]

1. Parker JLW. Potassium clorazepate (Tranxene)-induced jaundice. *Postgrad Med J* 1979; **55:** 908–910.

Effects on the nervous system. For reference to extrapyramidal disorders associated with the use of benzodiazepines, including clorazepate, see Diazepam, p. 1066.1.

Hypersensitivity. Pruritus and erythematous rash developed in a patient after taking oral dipotassium clorazepate;[1] although intradermal and patch testing gave negative results, symptoms recurred on rechallenge. Cross-sensitivity to diazepam was seen but not to bentazepam.

1. Aznar RC, *et al.* Hypersensitivity to chlorazepate dipotassium. *Allergy* 2005; **60:** 264–5.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Clorazepate is decarboxylated rapidly at the low pH in the stomach to form desmethyldiazepam (nordazepam, p. 1089.3), which is quickly absorbed.

References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; **24:** 446–51.
2. Bertler Å, *et al.* Intramuscular bioavailability of chlorazepate as compared to diazepam. *Eur J Clin Pharmacol* 1985; **28:** 229–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Justum; Tencilan; Tranxilium; ***Austria***: Tranxilium; ***Belg.***: Tranxene; Uni-Tranxene; ***Braz.***: Tranxilene; ***Canad.***: Novo-Clopate; ***Chile***: Calner; Tranxilium; ***Fr.***: Tranxene; ***Ger.***: Tranxilium; ***Gr.***: Tranxene; ***Hong Kong***: Tranxene; ***Israel***: Tranxal; ***Ital.***: Transene; ***Mex.***: Tranxene; ***Neth.***: Tranxene; Tranxilium†; ***Philipp.***: Tranxene; ***Pol.***: Cloranxen; Tranxene; ***Port.***: Medipax; Tranxene; ***S.Afr.***: Tranxene; ***Singapore***: Tranxene; ***Spain***: Tranxilium; ***Switz.***: Tranxilium; ***Thai.***: Anxene; Anxielax†; Cexene; Cloramed†; Cloraxene†; Cloraze; Clozepate; Deda; Dipot; Dopam; Flulium; Frexene; Gaxene; Manotran†; Polizep; Pomadom†; Posene†; Sanor; Serene; T-Five; Tenmed; Tranadon-S; Trancap; Tranclor†; Trancon; Tranmed; Tranpate†; Tranpon; Transpon; Tranxene; Tranzep; Uptran; Upzene; Zetran†; ***Turk.***: Anksen; Tranxilene; ***USA***: Tranxene; ***Venez.***: Tranxen.

Multi-ingredient Preparations. ***Arg.***: Euciton Complex; Maxitratobes†; Tranxilium Digest; Vegestabil; ***Fr.***: Noctran†; ***Spain***: Dorken†.

Pharmacopoeial Preparations

USP 36: Clorazepate Dipotassium Tablets.

Clotiapine *(BAN, rINN)*

Clothiapine (USAN); Clotiapina; Clotiapinum; HF-2159; Клотиапин.

2-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine.

$C_{18}H_{18}ClN_3S$=343.9

CAS — 2058-52-8.

ATC — N05AH06.

ATC Vet — QN05AH06.

UNII — Z05HCY0X1T.

Profile

Clotiapine is a dibenzothiazepine antipsychotic with general properties similar to those of the phenothiazines (see Chlorpromazine, p. 1045.2). It is used in a variety of psychiatric disorders including schizophrenia (p. 1031.3), mania (see Bipolar Disorder, p. 397.2), and anxiety (p. 1028.1). It is given orally in doses ranging from 10 to 200 mg daily in divided doses; up to 360 mg daily has been given in severe or resistant psychoses. It may also be given by slow intravenous or deep intramuscular injection.

Psychoses. A systematic review[1] found that good evidence to support the use of clotiapine over other treatments in acute psychotic illness was lacking.

1. Berk M, *et al.* Clotiapine for acute psychotic illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Etumina; ***Belg.***: Etumine; ***Israel***: Entumin; ***Ital.***: Entumin; ***S.Afr.***: Etomine; ***Spain***: Etumina; ***Switz.***: Entumine.

Clotiazepam *(rINN)*

Clotiazépam; Clotiazepamum; Y-6047; Клотиазепам.

5-(2-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one.

$C_{16}H_{15}ClN_2OS$=318.8

CAS — 33671-46-4.

ATC — N05BA21.

ATC Vet — QN05BA21.

UNII — ZCN055599V.

Pharmacopoeias. In *Jpn.*

Profile

Clotiazepam is a short-acting thienodiazepine with general properties similar to those of diazepam (p. 1063.2). A usual oral dose for the short-term management of anxiety disorders (p. 1028.1) is 5 to 15 mg daily given in divided doses but up to 60 mg daily has been used. For insomnia (p. 1033.2) 10 mg has been given as a single dose at night. An oral dose of 10 to 15 mg has been given for premedication (see Anaesthesia, p. 1899.1). Reduced doses may be required in elderly or debilitated patients.

Effects on the liver. Development of hepatitis in a 65-year-old woman was attributed to clotiazepam begun 7 months earlier.[1] The patient took triazolam and lorazepam without any apparent effect on the liver, and it was speculated that the hepatotoxic effect of clotiazepam was related to the thiophene ring present in the chemical structure.

1. Habersetzer F, *et al.* Clotiazepam-induced acute hepatitis. *J Hepatol* 1989; **9:** 256–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Clozan; ***Chile***: Rize; ***Fr.***: Veratran; ***Ital.***: Rizen; Tienor; ***Jpn***: Rize; ***Spain***: Distensan.

Cloxazolam *(rINN)*

Cloxazolamum; CS-370; Kloksatsolaami; Kloxazolam; Клоксазолам.

10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

$C_{17}H_{14}Cl_2N_2O_2$=349.2

CAS — 24166-13-0.

ATC — N05BA22.

ATC Vet — QN05BA22.

UNII — GYL649Z0HY.

Pharmacopoeias. In *Jpn.*

Profile

Cloxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). A usual oral dose of 2 to 4 mg daily is given in divided doses for the short-term treatment of anxiety disorders (p. 1028.1); higher doses of up to 12 mg daily may be needed in some patients. A dose of 100 micrograms/kg may be used for premedication (see Anaesthesia, p. 1899.1).

References.

1. Ito M, *et al.* Cloxazolam treatment for patients with intractable epilepsy. *Pediatr Neurol* 2004; **30:** 111–14.
2. Kimura N, *et al.* Initial and long-term effects of cloxazolam with intractable epilepsy. *Pediatr Neurol* 2010; **43:** 403–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tolestan; ***Belg.***: Akton; ***Braz.***: Anoxolan; Cloxadil; Clozal; Elum; Eutonis; Olcadil; ***Jpn***: Sepazon; ***Port.***: Cloxam; Olcadil.

Clozapine *(BAN, USAN, rINN)*

Clozapin; Clozapina; Clozapinum; HF-1854; Klotsapiini; Klozapin; Klozapina; Klozapinas; Клозапин.

8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepine.

$C_{18}H_{19}ClN_4$=326.8

CAS — 5786-21-0.

ATC — N05AH02.

ATC Vet — QN05AH02.

UNII — J60AR2IKIC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Clozapine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. It dissolves in dilute acetic acid.

USP 36: (Clozapine). A yellow crystalline powder. Insoluble in water; soluble in alcohol, in acetone, and in chloroform; sparingly soluble in acetonitrile.

Stability. A suspension of clozapine 100 mg in 5 mL, made by crushing clozapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for at least 18 days after preparation.[1]

1. Ramuth S, *et al.* A liquid clozapine preparation for oral administration in hospital. *Pharm J* 1996; **257:** 190–1.

Uses and Administration

Clozapine is a dibenzodiazepine derivative and the prototype of the atypical antipsychotics. It has relatively weak dopamine receptor-blocking activity at D_1, D_2, D_3, and D_5 receptors but has a high affinity for the D_4 receptor. Clozapine possesses alpha-adrenergic blocking, antimuscarinic, antihistaminic, antiserotonergic, and sedative properties.

Clozapine is used for the management of schizophrenia (p. 1058.2); however, because of the risk of agranulocytosis, it is reserved for patients who fail to respond to other antipsychotics, including other atypicals, or who have severe neurological effects with such drugs. In the USA, it may also be used for reducing the risk of recurrent suicidal behaviour in those with schizophrenia or schizoaffective disorder who are at chronic risk for suicidal behaviour. In the UK, it is also used in the management of treatment-resistant psychoses associated with Parkinson's disease (p. 1058.1).

Clozapine use must be accompanied by strict procedures for the monitoring of white blood cell counts (see Precautions, p. 1060.3). To minimise the incidence of adverse effects, clozapine therapy should be introduced gradually, beginning with low doses and increasing according to response.

In the treatment of **schizophrenia**, including reducing the risk of suicidal behaviour, the usual oral dose is 12.5 mg once or twice on the first day followed by 25 mg once or twice on the second day. Thereafter the daily dosage may be increased gradually in steps of 25 to 50 mg to achieve a daily dose of up to 300 mg within 14 to 21 days (US licensed product information permits up to 450 mg daily by the end of 2 weeks). Subsequent increases in steps of 50 to 100 mg may be made once or twice weekly; a daily dosage of 900 mg should not be exceeded. Once a therapeutic response has been obtained (most patients respond to 200 to 450 mg daily), a gradual reduction of dosage to a suitable maintenance dose is recommended. The total daily dose is given in divided doses; a larger portion may be given at night. Daily maintenance doses of 200 mg or less may be given as a single dose in the evening. Although unlicensed in the UK for children and adolescents aged under 16 years, the *BNFC* suggests that those aged 12 years and over may be given the usual adult doses.

Elderly patients may require lower doses of clozapine and it is recommended that treatment should start with a dose of 12.5 mg on the first day and that subsequent dose increments should be restricted to 25 mg.

If clozapine is to be withdrawn, this should be done gradually over a 1- to 2-week period. However, immediate withdrawal with careful observation is essential if

neutropenia develops or if myocarditis or cardiomyopathy is suspected (see Precautions, p. 1060.3).

For patients who are restarting treatment after an interval of more than 2 days, 12.5 mg may be given once or twice on the first day. If this dose is well tolerated it may be possible to increase the dosage more quickly than when first starting. However, patients who have had respiratory or cardiac arrest with initial dosing, but were then successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after a break of even 24 hours. Additional monitoring of blood cell counts may also be required if treatment is interrupted, see Treatment Break, under Monitoring, p. 1061.2.

It is recommended that oral therapy with other antipsychotics should be withdrawn gradually before treatment with clozapine is started.

Clozapine has also been given by intramuscular injection.

In the management of treatment-resistant **psychoses in Parkinson's disease**, the initial oral dose of clozapine is no more than 12.5 mg once daily in the evening. Thereafter, the daily dosage may be increased in steps of 12.5 mg up to twice a week; a dose of 50 mg daily should not be reached before the end of the second week. The usual dose ranges from 25 to 37.5 mg daily. Increases in the daily dose above 50 mg should only be made in exceptional cases in steps of 12.5 mg at weekly intervals up to a maximum of 100 mg daily. The total daily dose should preferably be given as a single dose in the evening. Dosage of antiparkinsonian drugs may be increased when there has been complete remission of psychotic symptoms for at least 2 weeks with clozapine therapy. If psychotic symptoms recur after increases in antiparkinsonian therapy, the dose of clozapine may need to be increased in line with the above guidance. As in patients with schizophrenia, planned withdrawal of clozapine in patients with Parkinson's disease should also be gradual in steps of 12.5 mg over 1 to 2 weeks.

Action. Antipsychotics are thought to work through inhibition of dopamine D_2-receptors (see p. 1046.1), but this hypothesis fails to explain the activity of the atypical antipsychotics such as clozapine. How clozapine produces its antipsychotic activity is not clear; it has a high affinity for several different receptors.[1]

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; **164:** 141–8.

Administration. There has been controversy over the bioequivalence or otherwise of different brands of clozapine. Although some reports indicate that it is perfectly possible to switch from branded to generic clozapine,[1-5] the need for monitoring and concerns about any requirement for retitration of doses (because of potential lack of bioequivalence[6]) have to be taken into account. There have been a few reports of exacerbation of psychotic symptoms in patients who were switched to a generic formulation.[7,8]

1. Sajbel TA, *et al*. Converting patients from brand-name clozapine to generic clozapine. *Ann Pharmacother* 2001; **35:** 281–4.
2. Makela EH, *et al*. Branded versus generic clozapine for treatment of schizophrenia. *Ann Pharmacother* 2003; **37:** 350–3.
3. Stoner SC, *et al*. A program to convert patients from trade-name to generic clozapine. *Pharmacotherapy* 2003; **23:** 806–10.
4. Bazire S, Burton V. Generic clozapine in schizophrenia: what is all the fuss about? *Pharm J* 2004; **273:** 720–1.
5. Oluboka O, *et al*. Does therapeutic equivalence follow bioequivalence? A randomized trial to assess clinical effects after switching from Clozaril to generic clozapine (Gen-Clozapine). *J Clin Pharmacol* 2010; **50:** 531–5.
6. Lam YW, *et al*. Branded versus generic clozapine: bioavailability comparison and interchangeability issues. *J Clin Psychiatry* 2001; **62** (suppl 5): 18–22.
7. Kluznik JC, *et al*. Clinical effects of a randomized switch of patients from clozaril to generic clozapine. *J Clin Psychiatry* 2001; **62** (suppl 5): 14–17.
8. Mofsen R, Balter J. Case reports of the reemergence of psychotic symptoms after conversion from brand-name clozapine to a generic formulation. *Clin Ther* 2001; **23:** 1720–31.

Administration in children. For details of uses and associated doses of clozapine in children and adolescents, see p. 1057.3.

Bipolar disorder. Clozapine is of benefit for the treatment of mania in patients with bipolar disorder (p. 397.2), and the use of atypical antipsychotics in the management of such patients is increasing. However, the adverse effects of clozapine may restrict its use.

Dementia. Although atypical antipsychotics such as clozapine have been tried in elderly patients with dementia, their use is associated with an increased risk of mortality in such patients; for further details, see under Risperidone, p. 1105.1. For further discussion of the management of disturbed behaviour, see p. 1030.2.

Parkinsonism. Clozapine is used as an alternative to classical antipsychotics in the management of **treatment-resistant psychoses** in patients with Parkinson's disease (p. 889.1). Some neurologists even consider clozapine to be the antipsychotic of choice in these patients,[1] although this remains to be determined. A review[2] in 1994 considered that there was little evidence to support clozapine as first choice given the quality of the available studies and the need for extensive monitoring. However, a subsequent double-blind, placebo-controlled study[3] showed that low-dose clozapine treatment (up to 50 mg daily) significantly improved drug-induced psychosis without worsening parkinsonism. Adverse effects noted in this study were generally mild, although in the clozapine group of 30 patients, there was 1 report of leucopenia. A similar study also reported benefit,[4] although 7 of 32 patients noted some aggravation of parkinsonism, usually mild and transient, while receiving clozapine. Adverse effects reported from other individuals have also included a patient with parkinsonism who had worsening of psychotic symptoms when her dose of clozapine was increased,[5] and the sudden return of psychosis in another patient with parkinsonism whose psychosis was successfully treated with clozapine for 5 years.[6]

Low-dose clozapine (about 40 mg daily) also appears to be of benefit in the management of **levodopa-induced dyskinesias** in patients with severe Parkinson's disease.[7]

1. Klein C, *et al*. Clozapine in Parkinson's disease psychosis: 5-year follow-up review. *Clin Neuropharmacol* 2003; **26:** 8–11.
2. Pfeiffer C, Wagner ML. Clozapine therapy for Parkinson's disease and other movement disorders. *Am J Hosp Pharm* 1994; **51:** 3047–53.
3. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; **340:** 757–63.
4. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 1999; **353:** 2041–2.
5. Auzou P, *et al*. Worsening of psychotic symptoms by clozapine in Parkinson's disease. *Lancet* 1994; **344:** 955.
6. Greene P. Clozapine therapeutic plunge in patient with Parkinson's disease. *Lancet* 1995; **345:** 1172–3.
7. Durif F, *et al*. Clozapine improves dyskinesias in Parkinson disease: a double-blind, placebo-controlled study. *Neurology* 2004; **62:** 381–8.

Schizophrenia. Clozapine is an effective antipsychotic for the management of schizophrenia (p. 1031.3) but its use is limited by its haematotoxicity. Its efficacy and superiority over classical antipsychotics was shown in a multicentre study.[1] Patients refractory to at least 3 different antipsychotics and who failed to improve after a single-blind trial of haloperidol, were randomised, double-blind, to treatment for 6 weeks with either clozapine up to 900 mg daily, or chlorpromazine hydrochloride up to 1800 mg daily with benzatropine mesilate up to 6 mg daily. Of the 267 patients included in the evaluation, 5 of 141 (4%) improved with chlorpromazine and benzatropine, and 38 of 126 (30%) improved with clozapine. Clozapine was superior to chlorpromazine in the treatment of negative as well as positive symptoms. Reviews[2,3] of clozapine indicate that these findings have been replicated both in subsequent studies and in clinical practice; nevertheless, the authors of the later review[3] considered the data from the included studies to be weak and prone to bias. It is unclear for how long clozapine should be tried: although 1 study[4] identified new responses up to 12 months after starting therapy, others have indicated that if improvement was not seen within the first 6 to 24 weeks, it was unlikely to occur.[2,5]

Clozapine is also used to reduce suicide risk in patients with refractory chronic schizophrenia.[6] The reported suicide rate of 0.05% per year in 6300 patients in the UK given clozapine since 1990 was considered to be tenfold less than expected.[7] A subsequent study[8] found it to be more effective than olanzapine in preventing suicide attempts in patients with schizophrenia or schizoaffective disorder at high risk.

Clozapine has shown consistent clinical benefit in schizophrenic patients with persistent aggressive or violent behaviour.[2,9] Whether this is due to a sedative effect, a specific antiaggressive action, or just reflects an overall improvement in psychosis is unknown.

Clozapine has been advocated for use in schizophrenic patients with moderate to severe tardive dyskinesia. It is still unclear whether clozapine can itself cause tardive dyskinesia but some patients with established tardive dyskinesia have had improvement in their symptoms when using clozapine.[10,11]

1. Kane J, *et al*. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45:** 789–96.
2. Buckley PF. New dimensions in the pharmacologic treatment of schizophrenia and related psychoses. *J Clin Pharmacol* 1997; **37:** 363–78. Correction. *ibid*. 1998; **38:** 27.
3. Essali A, *et al*. Clozapine versus typical neuroleptic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 04/06/09).
4. Meltzer HY, *et al*. A prospective study of clozapine in treatment-resistant schizophrenic patients I: preliminary report. *Psychopharmacology (Berl)* 1989; **99:** S68–S72.
5. Conley RR, *et al*. Time to clozapine response in a standardized trial. *Am J Psychiatry* 1997; **154:** 1243–7.
6. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry* 1995; **152:** 183–90.
7. Kerwin RW. Clozapine: back to the future for schizophrenia research. *Lancet* 1995; **345:** 1063–4.
8. Meltzer HY, *et al*. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; **60:** 82–91. Correction. *ibid*. 735.
9. Volavka J, *et al*. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol* 2004; **24:** 225–8.
10. Tamminga CA, *et al*. Clozapine in tardive dyskinesia: observations from human and animal model studies. *J Clin Psychiatry* 1994; **55** (suppl B): 102–6.
11. Nair C, *et al*. Dose-related effects of clozapine on tardive dyskinesia among "treatment-refractory" patients with schizophrenia. *Biol Psychiatry* 1996; **39:** 529–30.

Adverse Effects and Treatment

Although clozapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary; antimuscarinic effects with clozapine may be more pronounced. Sedation and weight gain may also be more prominent. Clozapine can cause reversible neutropenia which may progress to a potentially fatal agranulocytosis; strict monitoring of white blood cell counts is essential (see Precautions, p. 1060.3). Eosinophilia may also occur. Anaemia, thrombocytopenia, and thrombocythaemia have been reported rarely.

Extrapyramidal disorders, including tardive dyskinesia, appear to be rare with clozapine. Clozapine has little effect on prolactin secretion. Clozapine appears to have a greater epileptic potential than chlorpromazine but a comparable risk of cardiovascular effects such as tachycardia and orthostatic hypotension. In rare cases, circulatory collapse with cardiac and respiratory arrest has occurred, and hypertension has also been reported. Clozapine is also associated with an increased risk of developing myocarditis that may, in rare cases, be fatal; cardiomyopathy and pericarditis have also been reported.

Additional adverse effects of clozapine include dizziness, hypersalivation (particularly at night), headache, nausea, vomiting, constipation (which, in a few cases, has led to gastrointestinal obstruction, faecal impaction, and paralytic ileus), urinary incontinence and retention, fatigue, and transient fever which must be distinguished from the signs of impending agranulocytosis. There have also been rare reports of dysphagia, parotid gland enlargement, confusion, delirium, thromboembolism, acute pancreatitis, hepatitis and cholestatic jaundice, and very rarely fulminant hepatic necrosis. Isolated cases of acute interstitial nephritis have been reported. Abnormalities of glucose homoeostasis and the onset of diabetes mellitus occur uncommonly; severe hyperglycaemia, sometimes leading to ketoacidosis or hyperosmolar coma, has been reported very rarely. There have also been rare reports of hypercholesterolaemia and hypertriglyceridaemia. Many of the adverse effects of clozapine are most common at the start of therapy and may be minimised by gradual increase in dosage.

Effects on the blood. Clozapine can cause reversible neutropenia which, if the drug is not withdrawn immediately, may progress to a potentially fatal **agranulocytosis**. Particular concern over this adverse effect dates from 1975 when 17 cases of neutropenia or agranulocytosis, 8 of them fatal, were reported in Finland;[1] the calculated incidence[2] of agranulocytosis or severe granulocytopenia during this Finnish epidemic was 7.1 per 1000. These reports led to the withdrawal of clozapine in some countries or to restrictions in its use and intense haematological monitoring in others. After studies showing the efficacy of clozapine in severely ill schizophrenic patients unresponsive to adequate therapy with classical antipsychotics, the drug became available in the UK and USA in 1990 with strict procedures for monitoring of white blood cell counts. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[3] Clozapine was one of the individual drugs most frequently implicated, with 14 reports of agranulocytosis (1 fatal) and 119 of neutropenia (none fatal). Various estimates of the **incidence** of clozapine-associated agranulocytosis have been made; analysis of data from 11 555 patients given clozapine in the USA[4] showed a cumulative incidence of agranulocytosis of 8.0 per 1000 at 1 year and 9.1 per 1000 at 1½ years with the risk being increased in elderly patients. The majority of cases of agranulocytosis occurred within 3 months of the start of treatment with the risk peaking in the third month. The manufacturers reported a lower incidence of agranulocytosis of 4.8 per 1000 patients for the first 6 months[5] and an annual rate of 0.8 per 1000 patients during the next 2½ years. These figures were based on data on 56 000 patients in the USA given clozapine up to the end of March 1993. Analysis of data[6] on 6316 patients registered in the UK and Ireland between January 1990 and July 1994 to receive (although not necessarily given) clozapine produced a cumulative incidence of agranulocytosis of 0.7% during the first year and 0.8% over the whole study period. Most cases of agranulocytosis and neutropenia occurred during the first 6 to 18 weeks of treatment. The incidence of agranulocytosis (0.07%) and neutropenia (0.7%) seen during the second year of ther-

apy was of the same order of magnitude noted for some phenothiazine antipsychotics.

These data[6] and comparable data from the USA[7] were considered to indicate that mandatory haematological monitoring (see Precautions, p. 1060.3) helped to reduce the risks of clozapine-induced neutropenia and agranulocytosis and associated deaths.

The mechanism for clozapine-induced agranulocytosis is unclear and may be the result of direct toxicity or an immune response.[8,9] **Predisposing factors** for development of agranulocytosis have not been identified, apart from a possible excess of cases in female patients and an increased risk with increasing age. Furthermore, both agranulocytosis and neutropenia do not appear to be dose-related effects with clozapine. A postulated higher incidence of agranulocytosis in patients of Jewish background may be related to genetic factors.[10] Africans and Afro-Caribbeans appear to be at increased risk of developing neutropenia[6] and it has been noted[11] that many patients from these ethnic groups are currently already excluded from treatment with clozapine because their normal white blood cell and neutrophil counts are below the recommended range for treatment (see Monitoring under Precautions, p. 1061.1). However, UK licensed product information recommends that patients who have low white blood cell counts due to benign ethnic neutropenia may begin clozapine treatment with the agreement of a haematologist.

Evidence would suggest that development of clozapine-induced leucopenia or granulocytopenia precludes **retreatment** with clozapine at any future date; in a series of 9 retreated patients, all developed leucopenia or agranulocytosis again.[12] In the USA, patients who have had clozapine withdrawn because of moderate leucopenia (judged to be when counts fall to 2000 to 3000 cells/mm^3) are considered eligible for a return to clozapine treatment when this count returns to normal; such patients are considered to have a five- or sixfold greater risk of agranulocytosis.[5]

1. Idänpään-Heikkilä J, *et al.* Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; **11:** 193–8.
2. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharmacol* 1977; **11:** 199–201.
3. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Alvir JMJ, *et al.* Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993; **329:** 162–7.
5. Finkel MJ, Arellano F. White-blood-cell monitoring and clozapine. *Lancet* 1995; **346:** 849.
6. Atkin K, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169:** 483–8.
7. Honigfeld G, *et al.* Reducing clozapine-related morbidity and mortality: 5 years experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; **59** (suppl 3): 3–7.
8. Gerson SL, *et al.* Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* 1991; **338:** 262–3.
9. Hoffbrand AV, *et al.* Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; **7** (suppl 1): 1–60.
10. Leiberman JA, *et al.* HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990; **47:** 945–8.
11. Fisher N, Baigent B. Treatment with clozapine: black patients' low white cell counts currently mean that they cannot be treated. *BMJ* 1996; **313:** 1262.
12. Safferman AZ, *et al.* Rechallenge in clozapine-induced agranulocytosis. *Lancet* 1992; **339:** 1296–7.

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. However, a later review considered that there was overwhelming evidence that atypical antipsychotics induced more weight gain than classical antipsychotics.[2]

A separate review[3] calculated the average monthly weight gain associated with atypical antipsychotics to be:

- olanzapine (2.28 kg)
- zotepine (2.28 kg)
- quetiapine (1.76 kg)
- clozapine (1.72 kg)
- risperidone (0.96 kg)
- ziprasidone (0.80 kg)

A more recent review[4] of both short- (14 weeks or less) and long-term (6 months or more) studies noted that, out of all the atypicals considered, weight gain was greatest with olanzapine and clozapine, and the least with aripiprazole and ziprasidone. A review[5] of long-term (1 year or more) studies noted that although clozapine was associated with the highest risk of weight gain, and ziprasidone the lowest, the differences in risk with other atypicals were less intense when compared with findings from short-term studies which suggested the following decreasing order of weight-gain potential: clozapine, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, and ziprasidone.

Weight gain occurred most frequently during the first 6 to 12 months of treatment. It was recommended that if weight gain was more than 2 kg during the first 2 weeks, a strict dietary regimen should be started immediately. However, more recent opinion is that a change of antipsychotic may be necessary (see Effects on Carbohydrate Metabolism, below). Anti-obesity drugs have been tried although their routine use is not generally recommended.[2,6]

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.
2. Ananth J, *et al.* Atypical antipsychotic induced weight gain: pathophysiology and management. *Ann Clin Psychiatry* 2004; **16:** 75–85.
3. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Safety* 2001; **24:** 59–73.
4. Haddad P. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol* 2005; **19** (suppl): 16–27.
5. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. *Drug Safety* 2006; **29:** 303–19.
6. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; **62** (suppl 7): 22–31.

Effects on carbohydrate metabolism. Treatment with clozapine may be associated with an increased risk of glucose intolerance and diabetes mellitus; a similar association has also been noted for some other atypical antipsychotics.[1]

Data received by WHO indicated that up to December 2000, there had been 480 reports of glucose intolerance with clozapine, 253 with olanzapine, and 138 with risperidone.[2] In some cases weight gain was also reported, which may predispose to development of glucose intolerance. Other risk factors identified included an underlying diabetic condition, male gender, and use with some other medications including valproate, SSRIs, and buspirone. Regular monitoring of weight, blood glucose, and blood lipids was recommended in patients receiving clozapine, olanzapine, and risperidone.

Glucose intolerance has also been reported for the atypical antipsychotic quetiapine.[3,4]

Other reviewers have also found similar evidence of an increased risk of diabetes with atypical antipsychotics.[5,6] In September 2003 the FDA therefore requested labelling changes for all atypical antipsychotics to include the following recommendations and warnings:

- patients with diabetes mellitus receiving atypical antipsychotics should be monitored regularly for worsening glucose control
- patients with risk factors for diabetes mellitus should undergo fasting blood glucose testing at the start of, and during, treatment with atypical antipsychotics
- all patients given atypical antipsychotics should be monitored during treatment and those who develop hyperglycaemia should undergo fasting blood glucose testing
- in some cases hyperglycaemia resolved on withdrawal of the atypical antipsychotic but some patients needed antidiabetic therapy despite withdrawal

However, the American Diabetes Association and several other American medical associations[7] consider that the risks vary between atypical antipsychotics and have recommended that this should be taken into account when prescribing. The risk of weight gain, diabetes, and dyslipidaemia was considered to be greatest for clozapine and olanzapine, with risperidone and quetiapine having intermediate effects, and aripiprazole and ziprasidone having little effect (see also Effects on Body-Weight, above). They recommended that *baseline monitoring* should include:

- personal and family history of obesity, diabetes, dyslipidaemia, hypertension, or cardiovascular disease
- weight, height, and waist circumference
- blood pressure
- fasting blood glucose
- fasting lipid profile

Patients at risk for diabetes should receive an atypical drug with a lower propensity for weight gain and glucose intolerance. *Follow-up monitoring* should consist of reassessment of weight at 4, 8, and 12 weeks, and it was recommended that a change of antipsychotic should be considered for any patient who gained more than 5% of their original weight during treatment. Fasting plasma glucose and blood pressure should be assessed at 3 months and annually or more frequently thereafter according to risk. Lipid levels should also be assessed after 3 months and, if normal, at 5-year intervals thereafter. Any patient with worsening glycaemia or dyslipidaemia should be changed to an antipsychotic that has not been associated with significant weight gain or diabetes.

1. Melkersson K, Dahl M-L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs* 2004; **64:** 701–23.
2. Hedenmalm K, *et al.* Glucose intolerance with atypical antipsychotics. *Drug Safety* 2002; **25:** 1107–16.
3. Griffiths J, Springuel P. Atypical antipsychotics: impaired glucose metabolism. *Can Adverse Drug React News* 2001; **11** (4): 3–6. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v11n4-eng.pdf (accessed 21/08/08)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Atypical antipsychotics and hyperglycaemia. *Aust Adverse Drug React Bull* 2004; **23:** 11–12. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0406.htm (accessed 25/05/05)
5. Citrome LL, Jaffe AB. Relationship of atypical antipsychotics with development of diabetes mellitus. *Ann Pharmacother* 2003; **37:** 1849–57.
6. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005; **19** (suppl 1): 1–93.
7. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; **27:** 596–601. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/2/596.pdf (accessed 24/05/05)

Effects on the cardiovascular system. The UK CSM[1] issued a warning in November 1993 of the risk of **myocarditis** with clozapine. Three patients who died while taking clozapine had evidence of myocarditis. The CSM had also received one other report of myocarditis and one of cardiomyopathy associated with clozapine. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) subsequently reported[2] another 5 cases of clozapine-associated myocarditis in November 1994. A later report[3] from Australia identified 15 cases of myocarditis, including 5 fatalities, between January 1993 and March 1999 (these figures were established using both data from ADRAC and the Australian manufacturers). Between September 1989 and December 1999 the FDA had received reports of 28 cases of myocarditis (18 fatal) and 41 of cardiomyopathy (10 fatal) temporally associated with clozapine use.[4] A review[5] by the pharmacovigilance authorities in New Zealand stated that by November 1999 the manufacturers (*Novartis*) had analysed 125 reports of myocarditis received worldwide including 35 fatalities; 53% had occurred during the first month of treatment but about 5% occurred more than 2 years after starting treatment. A more recent review[6] of reports submitted to ADRAC between 1993 and 2003 identified 116 cases of myocarditis; of these, 60 patients were known to have recovered and 12 died. Myocarditis developed within a median of 17 days of starting clozapine therapy. In a reminder article,[7] the CSM has also commented that myocarditis occurs most commonly in the first 2 months whereas cardiomyopathy generally develops later in therapy. Pericarditis and pericardial effusions have also been reported. As myocarditis can be difficult to diagnose and confirmation is not always possible, the CSM recommended that if there was a high clinical suspicion of myocarditis, antipsychotic medication should be stopped. Presenting features might include persistent tachycardia at rest, heart failure, arrhythmia, or symptoms mimicking myocardial infarction or pericarditis. Patients who have developed clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

There is also evidence[8] that clozapine may be associated with fatal **thromboembolism**. Between February 1990 and December 1999, the FDA[9] had received 99 reports of venous thromboembolism associated with clozapine treatment. Of these reports, 83 mentioned pulmonary embolism with or without deep-vein thrombosis and 16 mentioned deep-vein thrombosis alone; 63 deaths were due to pulmonary embolism. The Swedish Adverse Reactions Advisory Committee had received reports[10] on 6 cases (5 fatal) of pulmonary embolism and 6 of venous thrombosis associated with clozapine treatment as of March 2000. The effect seemed to occur mainly in the first 3 months of treatment, and the majority of the cases involved men. However, analysis of data[11] from Germany and Switzerland suggests that the incidence of clozapine-associated thromboembolism is no different from that in psychiatric patients treated with classical antipsychotics or no antipsychotics at all.

For a discussion of **sudden unexpected deaths** associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

There have been isolated reports[12,13] of **paradoxical hypertension** in patients receiving clozapine. Use with atenolol has controlled the hypertension and allowed clozapine therapy to be continued.

Some studies[14] have suggested that serious cardiovascular effects might occur more frequently and might be more severe in healthy subjects given clozapine than in patients with schizophrenia. The manufacturers had therefore requested that pharmacokinetic studies of clozapine should be performed in patients with treatment-resistant schizophrenia rather than in healthy subjects.

For further details of effects of clozapine on the cardiovascular system, see Benzodiazepines under Interactions, p. 1062.1.

1. CSM/MCA. Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). *Current Problems* 1993; **19:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

2. Adverse Drug Reactions Advisory Committee (ADRAC). Clozapine and myocarditis. *Aust Adverse Drug React Bull* 1994; **13** (Nov): 14–15.
3. Kilian JG, *et al*. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999; **354:** 1841–5.
4. La Grenade L, *et al*. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med* 2001; **345:** 224–5.
5. New Zealand Medicines and Medical Devices Safety Authority. Potentially fatal complications of clozapine therapy: myocarditis, venous thromboembolism and constipation. Available at: http://www.medsafe.govt.nz/profs/puarticles/clozl.htm (accessed 24/05/05)
6. Haas SJ, *et al*. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Safety* 2007; **30:** 47–57.
7. CSM/MCA. Clozapine and cardiac safety: updated advice for prescribers. *Current Problems* 2002; **28:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
8. Paciullo CA. Evaluating the association between clozapine and venous thromboembolism. *Am J Health-Syst Pharm* 2008; **65:** 1825–9.
9. Knudson JF, *et al*. Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; **356:** 252–3.
10. Hägg S, *et al*. Association of venous thromboembolism and clozapine. *Lancet* 2000; **355:** 1155–6.
11. Wolstein J, *et al*. Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; **356:** 252.
12. Gupta S. Paradoxical hypertension associated with clozapine. *Am J Psychiatry* 1994; **151:** 148.
13. Ennis LM, Parker RM. Paradoxical hypertension associated with clozapine. *Med J Aust* 1997; **166:** 278.
14. Pokorny R, *et al*. Normal volunteers should not be used for bioavailability or bioequivalence studies of clozapine. *Pharm Res* 1994; **11:** 1221.

Effects on fluid and electrolyte homoeostasis. Hyponatraemia has been reported to be associated with clozapine,[1] as with other antipsychotics (p. 1048.3). It was emphasised that hyponatraemia should be excluded as a possible trigger when considering the epileptogenic potential of clozapine.

1. Ogilvie AD, Croy MF. Clozapine and hyponatraemia. *Lancet* 1992; **340:** 672.

Effects on the gastrointestinal tract. The UK CSM had received 20 reports of serious gastrointestinal reactions resembling obstruction associated with clozapine treatment as of March 1999, of which 3 were fatal.[1] These reactions were thought to be due to the antimuscarinic actions of clozapine and, therefore, more likely to occur when clozapine was taken with other drugs with antimuscarinic actions such as tricyclic antidepressants, some antiparkinsonian drugs, and other antipsychotics; care was also warranted in those patients with a history of colonic disease or previous bowel surgery. It was also important to recognise and treat constipation in patients receiving clozapine to prevent the development of more serious complications such as obstruction and paralytic ileus. Subsequently, there have been continuing reports of serious gastrointestinal effects associated with clozapine-induced hypomotility, including bowel obstruction, ischaemia, and perforation.[2-5]

1. CSM/MCA. Clozapine (Clozaril) and gastrointestinal obstruction. *Current Problems* 1999; **25:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
2. Palmer SE, *et al*. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. *J Clin Psychiatry* 2008; **69:** 759–68.
3. Leung JSY, *et al*. Rapidly fatal clozapine-induced intestinal obstruction without prior warning signs. *Aust N Z J Psychiatry* 2008; **42:** 1073–4.
4. Hibbard KR, *et al*. Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. *Psychosomatics* 2009; **50:** 416–19.
5. Martínez Díaz-Caneja C, *et al*. Severe bowel ischemia due to clozapine with complete remission after withdrawal. *J Clin Psychopharmacol* 2010; **30:** 463–5.

Effects on the kidneys. Acute interstitial nephritis has been associated with clozapine treatment.[1-3] All 3 patients had acute renal failure which resolved when the drug was stopped. The authors of 1 report noted that the UK CSM had received 7 reports of acute renal failure associated with clozapine treatment, including 1 death, between December 1989 and February 1999.[2]

1. Elias TJ, *et al*. Clozapine-induced acute interstitial nephritis. *Lancet* 1999; **354:** 1180–1.
2. Fraser D, Jibani M. An unexpected and serious complication of treatment with the atypical antipsychotic drug clozapine. *Clin Nephrol* 2000; **54:** 78–80.
3. Au AF, *et al*. Clozapine-induced acute interstitial nephritis. *Am J Psychiatry* 2004; **161:** 1501.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism, p. 1059.2.

Effects on the nervous system. As with other antipsychotics (see Convulsions, p. 1047.3), clozapine can lower the seizure threshold and cause EEG abnormalities, although treatment with clozapine appears to be associated with a higher frequency of seizures. A review[1] of 1418 patients treated with clozapine in the USA between 1972 and 1988 found that 41 had had generalised tonic-clonic seizures. It was considered that the risk of clozapine-induced seizures was dose-related. The seizure frequency was calculated to be:

- 1% at a dosage less than 300 mg daily
- 2.7% at 300 to 599 mg daily
- 4.4% with a dosage of 600 mg or more daily

Six of the patients had been taking other drugs reported to lower the seizure threshold. Therapy with clozapine was continued in 31 of the 41 patients by reducing the total daily dose of clozapine; antiepileptic drug therapy was begun in about half of the patients.

The UK CSM[2] considered that, although the epileptogenic effect of clozapine was claimed to be dose-related, the metabolism and plasma concentrations of clozapine were highly variable, and data from 8 cases reported to the CSM suggested that convulsions might possibly be related to high plasma concentrations in susceptible individuals. A low initial dosage followed by careful increases according to response and downward titration thereafter to a maintenance dose was recommended to avoid convulsions in susceptible individuals.

1. Devinsky O, *et al*. Clozapine-related seizures. *Neurology* 1991; **41:** 369–71.
2. CSM. Convulsions may occur in patients receiving clozapine (Clozaril, Sandoz). *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

Effects on the pancreas. There have been isolated reports of pancreatitis associated with clozapine therapy[1-3] and overdosage.[4] A systematic review[5] of the FDA's surveillance database and published case reports up to February 2002 found 192 patients who had pancreatitis (22 fatalities) after treatment with one or more antipsychotics. This included monotherapy with clozapine (72 patients), olanzapine (62 patients), risperidone (31 patients), and haloperidol (12 patients). Most cases occurred within 6 months of starting therapy.

1. Martin A. Acute pancreatitis associated with clozapine use. *Am J Psychiatry* 1992; **149:** 714.
2. Frankenburg FR, Kando J. Eosinophilia, clozapine, and pancreatitis. *Lancet* 1992; **340:** 251.
3. Garlipp P, *et al*. The development of a clinical syndrome of asymptomatic pancreatitis and eosinophilia after treatment with clozapine in schizophrenia: implications for clinical care, recognition and management. *J Psychopharmacol* 2002; **16:** 399–400.
4. Jubert P, *et al*. Clozapine-related pancreatitis. *Ann Intern Med* 1994; **121:** 722–3.
5. Koller EA, *et al*. Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. *Pharmacotherapy* 2003; **23:** 1123–30.

Extrapyramidal disorders. Clozapine retains a place in therapy, despite its propensity to cause agranulocytosis, because, in part, of its reduced rate of extrapyramidal effects (see also p. 1049.2). Other drugs in the class have since been developed. However, although atypical antipsychotics carry a lower risk of causing extrapyramidal disorders, the risk is not zero; acute effects and tardive syndromes have been reported with these drugs, and the developing tendency to use them for high-dose therapy may perhaps narrow the margin of advantage.[1]

1. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. *Drug Safety* 2005; **28:** 191–208.

Hypersalivation. Hypersalivation has been reported[1,2] to occur in up to 54% of patients receiving clozapine. The pathophysiology for this effect is unclear, but proposed mechanisms include action at muscarinic (M_3 and M_4) receptors, blockade of α_2-adrenoceptors, or distortion of the swallowing reflex. Management strategies have included chewing gum to increase frequency of swallowing or reduction of clozapine dosage in stabilised patients; antimuscarinics, including intranasal ipratropium, or α_2-agonists have been tried when other methods have failed. However, systemic antimuscarinics could potentially exacerbate the antimuscarinic adverse effects of clozapine. A recent systematic review[3] concluded that there are currently insufficient data to make any recommendations for treatment; the included studies had various limitations and a high risk of bias.

1. Davydov L, Botts SR. Clozapine-induced hypersalivation. *Ann Pharmacother* 2000; **34:** 662–5.
2. Sockalingam S, *et al*. Clozapine-induced hypersalivation: a review of treatment strategies. *Can J Psychiatry* 2007; **52:** 377–84.
3. Syed R, *et al*. Pharmacological interventions for clozapine-induced hypersalivation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 03/06/09).

Neuroleptic malignant syndrome. A review of the literature[1] suggested that clozapine may produce fewer extrapyramidal effects and a lower rise in creatine kinase concentrations than classical antipsychotics. The incidence of neuroleptic malignant syndrome (NMS—p. 1050.2) with clozapine appeared to be similar to that with classical antipsychotics;[1] however, its presentation may differ, with fever and rigidity less frequent, and possibly less severe, but diaphoresis more common.[2] Nevertheless, a later review[3] concluded that manifestations of NMS associated with the atypical antipsychotics clozapine, olanzapine, quetiapine, and risperidone were of similar nature and severity to those associated with classical antipsychotics. NMS has also been reported[4] with the use of amisulpride and aripiprazole.

Use of the atypical antipsychotics aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone has been associated with case reports of NMS in children and adolescents aged 11 to 18 years; symptoms were consistent with those seen in adults.[5]

1. Sachdev P, *et al*. Clozapine-induced neuroleptic malignant syndrome: a review and report of new cases. *J Clin Psychopharmacol* 1995; **15:** 365–71.
2. Karagianis JL, *et al*. Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. *Ann Pharmacother* 1999; **33:** 623–30. Correction. *ibid.*; 1011.
3. Ananth J, *et al*. Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004; **65:** 464–70.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Aripiprazole and neuroleptic malignant syndrome. *Aust Adverse Drug React Bull* 2007; **26:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0704.pdf (accessed 03/04/08)
5. Croarkin PE, *et al*. Neuroleptic malignant syndrome associated with atypical antipsychotics in pediatric patients: a review of published cases. *J Clin Psychiatry* 2008; **69:** 1157–65.

Withdrawal. Abrupt withdrawal of clozapine may be associated with symptoms that have been described as 'cholinergic rebound' although the manifestations, which may include headache, profuse sweating, hypersalivation, bronchoconstriction, agitation, enuresis, and diarrhoea also have some common features with the serotonin syndrome (p. 443.2); motor disorders and exacerbation of extrapyramidal disorders have also occurred. In addition, as with other antipsychotics, abrupt withdrawal of clozapine may be associated with rapid relapse of the original psychosis. In a retrospective case-note study of 29 schizophrenic patients whose clozapine treatment was withdrawn, abrupt withdrawal in 20 resulted in a marked, immediate deterioration in their mental state.[1] Of 3 further patients who had delirium with psychotic symptoms shortly after stopping clozapine, symptoms developed in 1 within 24 hours despite gradual withdrawal of clozapine over a 2-week period.[2] All the patients responded rapidly to resumption of low doses of clozapine.

1. Baker M, White T. Life after clozapine. *Med Sci Law* 2004; **44:** 217–21.
2. Stanilla JK, *et al*. Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin Psychiatry* 1997; **58:** 252–5.

Precautions

Clozapine should not be given to patients with uncontrolled epilepsy, alcoholic or toxic psychoses, drug intoxication, or a history of circulatory collapse. It should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. It is contra-indicated in patients with bone-marrow suppression, myeloproliferative disorders, or any abnormalities of white blood cell count or differential blood count. It is also contra-indicated in patients with a history of drug-induced neutropenia or agranulocytosis with the exception of that due to chemotherapy. It should not be used with drugs that carry a high risk of bone-marrow suppression (see Interactions, p. 1061.2).

Clozapine is contra-indicated in patients with severe renal impairment; caution is required in mild to moderate renal impairment. It should be used with caution in hepatic impairment and avoided in symptomatic or progressive liver disease or hepatic failure. Patients with a history of cardiac impairment or abnormal cardiac findings on examination should be referred to a specialist for further evaluation, which may include an ECG; treatment with clozapine should only then be started if the potential benefits clearly outweigh any risk. Clozapine should not be used in severe heart failure.

Clozapine possesses antimuscarinic properties and consequently it is contra-indicated in patients with paralytic ileus; it should also be used with caution in benign prostatic hyperplasia and angle-closure glaucoma.

Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes (see Effects on Carbohydrate Metabolism, p. 1059.2).

Monitoring the white blood cell and absolute neutrophil counts is mandatory during clozapine treatment and should be carried out in accordance with official recommendations; these may vary between countries (see Monitoring, p. 1061.1 for further details). Patients or their carers should report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.

Patients who develop tachycardia at rest, dyspnoea, arrhythmias, chest pain, or other signs and symptoms of heart failure should be investigated immediately and clozapine treatment stopped if a diagnosis of myocarditis or cardiomyopathy is suspected.

Because of an increased risk of collapse due to orthostatic hypotension associated with rapid dose escalation during initial titration of clozapine dosage, it is recommended that treatment should be begun under close medical supervision. In addition, patients with Parkinson's disease should have

their blood pressure monitored for the first weeks of treatment.

On planned withdrawal, the dose of clozapine should be reduced gradually over at least a 1- to 2-week period in order to avoid the risk of rebound psychosis and other withdrawal symptoms (see p. 1060.3). If abrupt withdrawal is necessary then patients should be observed carefully.

Clozapine may affect the performance of skilled tasks such as driving.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of clozapine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Clozapine appears to be distributed into breast milk in relatively high concentrations.[2] Concentrations in a patient given 50 mg daily were 63.5 nanograms/mL in breast milk and 14.7 nanograms/mL in plasma; at 100 mg daily they were 115.6 nanograms/mL and 41.4 nanograms/mL, respectively.

The manufacturers have also stated that studies in *animals* suggest that clozapine is excreted into breast milk and has an effect on nursing infants; they recommend that mothers receiving clozapine should not breast feed.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/05)
2. Barnas C, *et al*. Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. *Am J Psychiatry* 1994; **151:** 945.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Monitoring. *WHITE CELL COUNTS.* A white blood cell count and a differential blood count must be performed before the start of, and during, clozapine therapy. Treatment should not be started if the white blood cell count is less than 3500 cells/mm^3 and the absolute neutrophil count (ANC) is less than 2000 cells/mm^3, or if there is an abnormal differential count. Monitoring should continue throughout therapy and for 4 weeks after withdrawal.

In the EU, including the UK, monitoring is performed at weekly intervals for the first 18 weeks and then at least every 2 weeks between weeks 18 and 52; after 1 year of treatment with stable neutrophil counts, patients may be monitored at least every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 or the ANC falls to between 1500 and 2000 cells/mm^3 then monitoring should be performed at least **twice weekly** until values stabilise or increase.
- Clozapine should be **withdrawn** immediately if the white blood cell count falls below 3000 cells/mm^3 or the ANC drops below 1500 cells/mm^3; counts should be monitored daily until they return to normal. Clozapine should not be restarted in these patients.

In the USA, white blood cell and ANC are monitored weekly for the first 6 months and then every 2 weeks thereafter; after 1 year of therapy, patients may be monitored every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 and the ANC is above 1500 cells/mm^3 then monitoring should be performed **twice weekly**.
- If the white blood cell count falls below 3000 cells/mm^3 or the ANC is below 1500 cells/mm^3 then clozapine treatment should be **interrupted** and counts performed daily initially. Clozapine may be restarted if the white blood cell count recovers to above 3500 cells/mm^3 and the ANC to above 2000 cells/mm^3. After recovery, weekly monitoring is recommended for the next 12 months before reducing to every 2 weeks for 6 months, and then every 4 weeks thereafter.
- Clozapine should be **withdrawn** if the white blood cell count falls below 2000 cells/mm^3 or the ANC drops below 1000 cells/mm^3; counts should be monitored daily, initially, until they return to normal. Clozapine should not be restarted in these patients.

In patients with decreased white blood cell or ANC it is especially important that they or their carers report the development of any infection or signs such as fever, sore throat, or flu-like symptoms that suggest infection.

EOSINOPHIL COUNT. In the EU, clozapine should be withdrawn if the eosinophil count is greater than 3000 cells/mm^3; it should only be restarted once the count has fallen to below 1000 cells/mm^3.

Similar advice is given in US licensed product information although the values differ: clozapine should be withdrawn if the eosinophil count is above 4000 cells/mm^3 and restarted once the count has fallen to below 3000 cells/mm^3.

PLATELET COUNT. European licensing information states that clozapine should be stopped if the platelet count falls below 50 000 cells/mm^3.

TREATMENT BREAK. If treatment with clozapine is interrupted for reasons other than abnormal haematological values then more frequent monitoring may be required following resumption of therapy.

In the EU, patients who have taken clozapine for at least 18 weeks and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 4 weeks if the counts are stable; a break of 4 weeks or more would require weekly monitoring for the next 18 weeks.

US licensed product information recommends resuming weekly monitoring for 6 months in all patients whose therapy has been interrupted for more than 1 month; frequency of monitoring is then reduced as described in White Cell Counts, see above. Those who have taken clozapine for at least 6 months and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 2 weeks for 6 months if the counts are stable; those on clozapine for over 1 year may be monitored every 4 weeks after initial weekly monitoring for 6 weeks.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clozapine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. A review of the literature[1] between 1993 and April 2004 suggested that clozapine and olanzapine do not appear to increase the risk of fetal teratogenicity; literature regarding aripiprazole, quetiapine, risperidone, and ziprasidone was incomplete or not available. The rate of spontaneous abortions in pregnant women exposed to clozapine or olanzapine was not found to be higher than that of the general population; however, these 2 drugs increased the risk of hyperglycaemia in pregnant women. A prospective comparative study[2] of pregnancy outcomes in women taking clozapine, olanzapine, quetiapine, and risperidone also concluded that atypicals do not appear to be associated with an increased risk for major malformations when compared with the baseline risk in the general population. The authors recommended that benefits and risks be weighed carefully in each case and optimal control of the psychiatric disorder be maintained throughout pregnancy and postpartum together with careful monitoring.

1. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. *Ann Pharmacother* 2004; **38:** 1265–71.
2. McKenna K, *et al*. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 2005; **66:** 444–9.

Interactions

Clozapine may enhance the central effects of MAOIs and CNS depressants including alcohol, antihistamines, benzodiazepines, and opioid analgesics.

Clozapine should not be used with drugs that carry a high risk of bone-marrow suppression including carbamazepine, co-trimoxazole, chloramphenicol, penicillamine, sulfonamides, antineoplastics, or pyrazolone analgesics such as azapropazone. Long-acting depot antipsychotics have myelosuppressive potential and should not be used with clozapine as they cannot be withdrawn rapidly should neutropenia occur. Additive effects may occur when clozapine is given with drugs that possess antimuscarinic, hypotensive, or respiratory depressant effects. Clozapine may reduce the effects of alpha-adrenoceptor agonists such as noradrenaline.

The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit or act as a substrate to this isoenzyme may affect plasma concentrations of clozapine and the dose of clozapine may need to be altered. Increased plasma-clozapine concentrations, with an increased risk of adverse effects, may be seen in patients who suddenly stop smoking. Use with phenytoin or other enzyme-inducing drugs may accelerate the metabolism of clozapine and reduce its plasma concentrations.

References.

1. Taylor D. Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 1997; **171:** 109–12.

Antibacterials. A patient with schizophrenia controlled with clozapine therapy had a tonic-clonic seizure 7 days after starting treatment with *erythromycin*.[1] It appeared that erythromycin had inhibited the metabolism of clozapine and raised its serum concentrations. Increased drowsiness and hypersalivation have been seen in a patient receiving clozapine and *ampicillin*; he recovered when ampicillin was replaced with doxycycline.[2]

Giving clozapine with *rifampicin* has resulted in decreased clozapine concentrations with consequent return of paranoid thoughts in a patient with a complicated history of schizophrenia.[3] An improvement was seen after rifampicin was replaced with ciprofloxacin. The interaction was thought to be due to the induction of cytochrome P450 isoenzymes, particularly CYP1A2, by rifampicin, resulting in the accelerated metabolism of clozapine.

1. Funderburg LG, *et al*. Seizure following addition of erythromycin to clozapine treatment. *Am J Psychiatry* 1994; **151:** 1840–1.
2. Csík V, Molnár J. Possible adverse interaction between clozapine and ampicillin in an adolescent with schizophrenia. *J Child Adolesc Psychopharmacol* 1994; **4:** 123–8.
3. Joos AAB, *et al*. Pharmacokinetic interaction of clozapine and rifampicin in a forensic patient with atypical mycobacterial infection. *J Clin Psychopharmacol* 1998; **18:** 83–5.

Antidepressants. Rises in serum concentrations of clozapine have been found in patients receiving clozapine after addition of *fluoxetine*[1] or *fluvoxamine*[2] to therapy. Increased serum concentrations of clozapine have also been reported when *paroxetine* or *sertraline* was added to therapy.[3] A possible serotonin syndrome (p. 443.2) has been reported[4] in a patient receiving *clomipramine* after clozapine was gradually withdrawn from the treatment regimen, although the symptoms were also similar to those of clozapine withdrawal (see p. 1060.3). There has been an isolated report[5] of a patient who developed myoclonic jerks 79 days after fluoxetine was added to treatment with clozapine and lorazepam, although some[6] doubt whether the effects were entirely due to an interaction. Giving clozapine with *lithium* may increase the risk of neuroleptic malignant syndrome. For reference to neurological reactions in patients receiving lithium with clozapine, see p. 431.3.

1. Centorrino F, *et al*. Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151:** 123–5.
2. Jerling M, *et al*. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994; **16:** 368–74.
3. Centorrino F, *et al*. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996; **153:** 820–2.
4. Zerjav-Lacombe S, Dewan V. Possible serotonin syndrome associated with clomipramine after withdrawal of clozapine. *Ann Pharmacother* 2001; **35:** 180–2.
5. Kingsbury SJ, Puckett KM. Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152:** 473.
6. Baldessarini RJ, *et al*. Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152:** 473–4.

Antiepileptics. Use of *phenytoin* or other *enzyme-inducing antiepileptics* may accelerate the metabolism of clozapine and reduce its plasma concentrations. Studies have found that addition of *sodium valproate* to clozapine therapy may increase[1] or decrease[2] plasma concentrations of clozapine. Although no increase in clozapine-related adverse effects or loss of control of psychotic symptoms were reported in these studies, there has been a report[3] of a patient who developed sedation, confusion, slurring of speech and other functional impairment after valproate was given with clozapine.

See also under Benzodiazepines, p. 1062.1.

1. Centorrino F, *et al*. Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151:** 123–5.
2. Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. *Biol Psychiatry* 1994; **36:** 487–8.
3. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol* 1995; **15:** 139–41.

Antipsychotics. Giving *risperidone* to a patient with schizoaffective disorder partially controlled by clozapine produced clinical improvement but was associated with a 74% rise in serum-clozapine concentrations over a 2-week period.[1] Although no adverse effects occurred in this patient, the potential for serious adverse effects requires caution if these drugs are used together. Neuroleptic malignant syndrome associated with use of clozapine with *haloperidol* has been reported.[2]

See also under Chlorpromazine, p. 1053.1.

1. Tyson SC, *et al*. Pharmacokinetic interaction between risperidone and clozapine. *Am J Psychiatry* 1995; **152:** 1401–2.
2. Garcia G, *et al*. Neuroleptic malignant syndrome with antidepressant/antipsychotic drug combination. *Ann Pharmacother* 2001; **35:** 784–5.

Antivirals. Although UK licensed product information for *ritonavir* states that it may increase plasma concentrations of clozapine with a resultant increase in the risk of toxicity, there is evidence to suggest that, in fact, ritonavir may decrease the plasma concentrations of clozapine.[1] Ritonavir has been noted to induce the cytochrome P450 isoenzyme CYP1A2 and hence, as clozapine is mainly

metabolised via this isoenzyme, an acceleration of the metabolism of clozapine would be expected.

1. Penzak SR, *et al.* Comment: significant interactions with new antiretrovirals and psychotropic drugs. *Ann Pharmacother* 1999; **33:** 1372–3.

Benzodiazepines. Concern has been expressed over reports of cardiorespiratory collapse in patients taking both clozapine and benzodiazepines.[1,2] In response, the manufacturers of clozapine outlined[3] similar cases reported to them in the USA. Of 7 cases of respiratory arrest or depression only 2 involved recent use of a benzodiazepine; among 26 cases of orthostatic hypotension with syncope reported during the first year the drug was marketed, only 8 included recent benzodiazepine use. The manufacturers concluded that an increased risk of such reactions in patients taking both drugs simultaneously was possible but not established, and advised caution when starting clozapine therapy in patients taking benzodiazepines.

Hypersalivation associated with clozapine and benzodiazepines may be exacerbated when these drugs are used together. A patient[4] had increased hypersalivation, salivary thickening, and distension of the parotid glands when *clonazepam* was added to treatment with clozapine. Adverse effects reported in 5 other patients given clozapine with benzodiazepines included hypersalivation, sedation, ataxia, and symptoms of delirium.[5,6]

1. Sassim N, Grohmann R. Adverse drug reactions with clozapine and simultaneous application of benzodiazepines. *Pharmacopsychiatry* 1988; **21:** 306–7.
2. Friedman LJ, *et al.* Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; **325:** 518.
3. Finkel MJ, Schwimmer JL. Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; **325:** 518–19.
4. Martin SD. Drug-induced parotid swelling. *Br J Hosp Med* 1993; **50:** 426.
5. Cobb CD, *et al.* Possible interaction between clozapine and lorazepam. *Am J Psychiatry* 1991; **148:** 1606–7.
6. Jackson CW, *et al.* Delirium associated with clozapine and benzodiazepine combinations. *Ann Clin Psychiatry* 1995; **7:** 139–41.

Buspirone. Potentially fatal gastrointestinal bleeding, accompanied by severe acidosis and hyperglycaemia, developed in a patient given buspirone with clozapine.[1] The patient had previously been taking clozapine for over a year without adverse effect, and was subsequently maintained on clozapine alone without a recurrence of symptoms.

1. Good MI. Lethal interaction of clozapine and buspirone? *Am J Psychiatry* 1997; **154:** 1472–3.

Gastrointestinal drugs. A patient stabilised on clozapine developed increased serum clozapine concentrations and signs of clozapine toxicity after starting treatment with *cimetidine*.[1] Cimetidine was withdrawn and ranitidine substituted without recurrence of toxicity.

A marked reduction in plasma-clozapine concentrations was seen in 2 smokers stabilised on the antipsychotic who began treatment with *omeprazole*,[2] a known inducer of the cytochrome P450 isoenzyme CYP1A2. However, a small retrospective analysis of the effect of stopping omeprazole in 13 patients taking both drugs suggested that the effect of omeprazole was only significant in non-smokers, and the clozapine dose did not need to be adjusted in any of these patients.[3]

1. Szymanski S, *et al.* A case report of cimetidine-induced clozapine toxicity. *J Clin Psychiatry* 1991; **52:** 21–2.
2. Frick A, *et al.* Omeprazole reduces clozapine plasma concentrations: a case report. *Pharmacopsychiatry* 2003; **36:** 121–3.
3. Mookhoek EJ, Loonen AJ. Retrospective evaluation of the effect of omeprazole on clozapine metabolism. *Pharm World Sci* 2004; **26:** 180–2.

Xanthines. *Caffeine* may inhibit the metabolism of clozapine.[1,2] Care should be taken before stopping or starting caffeine-containing beverages in patients stabilised on clozapine treatment.

1. Carrillo JA, *et al.* Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* 1998; **18:** 311–16.
2. Hägg S, *et al.* Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2000; **49:** 59–63.

Pharmacokinetics

Although clozapine is well absorbed from the gastrointestinal tract, its bioavailability is limited to about 50% by first-pass metabolism. Peak plasma concentrations occur, on average, about 2.5 hours after oral doses. Clozapine is about 95% bound to plasma proteins and has a mean terminal elimination half-life of about 12 hours at steady state. It is almost completely metabolised and routes of metabolism include *N*-demethylation, hydroxylation, and *N*-oxidation; the desmethyl metabolite (norclozapine) has limited activity. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the faeces. There is wide interindividual variation in plasma concentrations of clozapine and no simple correlation has been found between plasma concentrations and therapeutic effect. It is distributed into breast milk.

References.

1. Jann MW, *et al.* Pharmacokinetics and pharmacodynamics of clozapine. *Clin Pharmacokinet* 1993; **24:** 161–76.
2. Lin S-K, *et al.* Disposition of clozapine and desmethylclozapine in schizophrenic patients. *J Clin Pharmacol* 1994; **34:** 318–24.
3. Freeman DJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in clozapine therapy? *Clin Pharmacokinet* 1997; **32:** 93–100.
4. Olesen OV. Therapeutic drug monitoring of clozapine treatment: therapeutic threshold value for serum clozapine concentrations. *Clin Pharmacokinet* 1998; **34:** 497–502.
5. Guitton C, *et al.* Clozapine and metabolite concentrations during treatment of patients with chronic schizophrenia. *J Clin Pharmacol* 1999; **39:** 721–8.
6. Dettling M, *et al.* Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. *Psychopharmacology (Berl)* 2000; **152:** 80–6.
7. Renwick AC, *et al.* Monitoring of clozapine and norclozapine plasma concentration-time curves in acute overdose. *J Toxicol Clin Toxicol* 2000; **38:** 325–8.
8. Frazier JA, *et al.* Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. *J Clin Psychopharmacol* 2003; **23:** 87–91.
9. Tang Y-L, *et al.* Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. *Br J Clin Pharmacol* 2007; **64:** 49–56.

Bioavailability. Mean plasma concentration of clozapine increased from 329 to 629 nanograms/mL in 10 patients when switched from an extemporaneous liquid formulation to conventional tablets.[1]

1. Coker-Adeyemi F, Taylor D. Clozapine plasma levels in patients switched from clozapine liquid to tablets. *Pharm J* 2002; **269:** 650–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lapenax; Sequax; ***Austral.***: Clopine; Clozaril; ***Austria***: Lanolept; Leponex; ***Belg.***: Leponex; ***Braz.***: Leponex; Pinazan; ***Canad.***: Clozaril; ***Chile***: Dicomex; Leponex; ***Cz.***: Leponex; ***Denm.***: Cloment†; Leponex; ***Fin.***: Froidir; Leponex; ***Fr.***: Leponex; ***Ger.***: Elcrit; Leponex; ***Gr.***: Leponex; ***Hong Kong***: Clozaril; ***Hung.***: Leponex; ***India***: Chrozap; Clomach; Clopaz; Cozacin; Lozapin; Lozaril; Sizopin; ***Indon.***: Clopine; Clorilex; Clozaril; Luften; Sizoril; ***Irl.***: Clozalux; Clozaril; Denzapine; ***Israel***: Leponex; Lozapine; ***Ital.***: Leponex; ***Jpn***: Clozaril; ***Malaysia***: Anzapine; Clozarem; Clozaril; Zapine; ***Mex.***: Clopsine; Leponex; ***Neth.***: FazaClo†; Leponex; ***Norw.***: Leponex; ***NZ***: Clopine; Clozaril; ***Philipp.***: Ihope; Leponex; Syclop; Ziproc; ***Pol.***: Klozapol; Leponex; ***Port.***: Leponex; Ozapim; ***Rus.***: Azaleptin (Азалептин); Closastene (Клозастен); Leponex (Лепонекс); ***S. Afr.***: Cloment; Leponex; ***Singapore***: Clozaril; ***Spain***: Leponex; Nemea; ***Swed.***: Leponex; ***Switz.***: Clopin; Leponex; ***Thai.***: Cloril; Clozamed; Clozaril; ***Turk.***: Clonex; Leponex; ***UK***: Clozaril; Denzapine; Zaponex; ***Ukr.***: Azapin (Азапин); Leponex (Лепонекс); ***USA***: Clozaril; FazaClo; Versacloz; ***Venez.***: Leponex.

Pharmacopoeial Preparations
BP 2014: Clozapine Oral Suspension;
USP 36: Clozapine Tablets.

Cyamemazine *(rINN)*

Ciamemazina; Cyamémazine; Cyamemazinum; Cyamepromazine; RP-7204; Циамемазин.
10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile.
$C_{19}H_{21}N_3S$=323.5
CAS — 3546-03-0 (cyamemazine); 93841-82-8 (cyamemazine tartrate).
ATC — N05AA06.
ATC Vet — QN05AA06.
UNII — A2JGV5CNU4.

Profile

Cyamemazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It is used in the management of a variety of psychiatric disorders including anxiety disorders (p. 1028.1) and aggressive behaviour (p. 1030.2).

Cyamemazine has been given orally as the base or the tartrate and by injection as the base. Doses are expressed in terms of the base; cyamemazine tartrate 36.6 mg is equivalent to about 25 mg of cyamemazine. Oral doses have ranged from 25 to 300 mg daily, depending on the individual and the condition being treated; the daily dosage is given in 2 or 3 divided doses. Up to 600 mg daily has been given orally in severe or resistant psychoses. Doses given by intramuscular injection have ranged from 25 to 200 mg daily.

Cyamemazine should be given in reduced dosage to elderly patients; the parenteral route is not recommended for the elderly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Tercian; ***Port.***: Tercian.

Cyclobarbital *(BAN, rINN)*

Ciclobarbital; Cyclobarbitalum; Cyclobarbitone; Cyklobarbital; Ethylhexabital; Hexemalum; Syklobarbitaali; Циклобарбитал.
5-(Cyclohex-1-enyl)-5-ethylbarbituric acid.
$C_{12}H_{16}N_2O_3$=236.3
CAS — 52-31-3.
ATC — N05CA10.
ATC Vet — QN05CA10.
UNII — 0M8A98AD9H.

NOTE. The name ciclobarbital has sometimes been applied to hexobarbital.

Cyclobarbital Calcium *(BANM, rINNM)*

Calcii Cyclobarbitalum; Ciclobarbital cálcico; Ciclobarbital Calcium; Cyclobarbital Calcique; Cyclobarbitalum Calcicum; Cyclobarbitone Calcium; Cyklobarbital wapniowy; Hexemalcalcium; Кальций Циклобарбитал.
Calcium 5-(cyclohex-1-enyl)-5-ethylbarbiturate.
$(C_{12}H_{15}N_2O_3)_2Ca$=510.6
CAS — 5897-20-1.
ATC — N05CA10.
ATC Vet — QN05CA10.
UNII — 0HZN7FV25R.

Pharmacopoeias. In *Pol.*

Profile

Cyclobarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). The calcium salt has been used as a hypnotic but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Reladorm (Реладорм).

Delorazepam *(pINN)*

Chlordesmethyldiazepam; Clordesmethyldiazepam; Délorazépam; Delorazepamum; Делоразепам.
7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.
$C_{15}H_{10}Cl_2N_2O$=305.2
CAS — 2894-67-9.
UNII — O91W32476G.

Profile

Delorazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been used in the short-term treatment of anxiety disorders (p. 1028.1) in oral doses of 0.5 to 2 mg given 2 or 3 times daily. An oral dose of 0.5 to 2 mg has also been given at night for insomnia (p. 1033.2). The drug has also been given parenterally.

Administration in hepatic or renal impairment. The pharmacokinetics of total delorazepam were unchanged in patients with renal failure undergoing haemodialysis compared with controls.[1] However, the apparent volume of distribution of unbound drug was smaller and the clearance slower. The volume of distribution and clearance of unchanged drug was also reduced in patients with liver disease.[2]

1. Sennesael J, *et al.* Pharmacokinetics of intravenous and oral chlordesmethyldiazepam in patients on regular haemodialysis. *Eur J Clin Pharmacol* 1991; **41:** 65–8.
2. Bareggi SR, *et al.* Effects of liver disease on the pharmacokinetics of intravenous and oral chlordesmethyldiazepam. *Eur J Clin Pharmacol* 1995; **48:** 265–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Dadumir; En.

Detomidine Hydrochloride

(BANM, USAN, rINNM)

Demotidini Hydrochloridum; Detomidiinihydrokloridi; Detomidin hydrochlorid; Detomidina, hidrocloruro de; Détomidine, chlorhydrate de; Detomidin-hidroklorid; Detomidinhydroklorid; Detomidini Hydrochloridum; Hidrocloruro de detomidina; MPV-253-Alf; Детомидина Гидрохлорид.
4-(2,3-Dimethylbenzyl)imidazole hydrochloride.
$C_{12}H_{14}N_2$,HCl=222.7

CAS — 76631-46-4 (detomidine); 90038-01-0 (detomidine hydrochloride).
UNII — 95K4LKB6QE.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Detomidine Hydrochloride for Veterinary Use; Detomide Hydrochloride BP(Vet) 2014). A white or almost white, hygroscopic, crystalline powder. Soluble in water; freely soluble in alcohol; practically insoluble in acetone; very slightly soluble in dichloromethane. Protect from moisture.

Profile

Detomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Dexmedetomidine Hydrochloride *(BANM, USAN, rINNM)*

Deksmedetomidin Hidroklorür; Dexmedetomidina, hidrocloruro de; Dexmédétomidine, Chlorhydrate de; Dexmedetomidini Hydrochloridum; Hidrocloruro de dexmedetomidina; MPV-1440 (dexmedetomidine); Дексмедетомидина Гидрохлорид.

(*S*)-4-[1-(2,3-Xylyl)ethyl]imidazole hydrochloride.

$C_{13}H_{16}N_2$,HCl=236.7

CAS — 113775-47-6 (dexmedetomidine); 145108-58-3 (dexmedetomidine hydrochloride).
ATC — N05CM18.
ATC Vet — QN05CM18.
UNII — 1018WH7F9I.

Uses and Administration

Dexmedetomidine is a selective alpha$_2$-adrenergic receptor agonist with anxiolytic, analgesic, and sedative properties. It is used for the sedation (p. 1032.2) of mechanically ventilated patients in intensive care and of non-intubated patients in surgical and medical procedures. Dexmedetomidine is given as the hydrochloride, but doses are expressed in terms of the base. Dexmedetomidine hydrochloride 118 micrograms is equivalent to about 100 micrograms of dexmedetomidine.

It is diluted to a concentration of 4 micrograms/mL in sodium chloride 0.9% before use and is given by intravenous infusion in a loading dose equivalent to 1 microgram/kg of dexmedetomidine over 10 minutes. This is followed by a maintenance infusion of 200 to 700 nanograms/kg per hour for up to 24 hours when used in intensive care settings. For use in procedural sedation, the loading dose is followed by a maintenance infusion of 0.2 to 1 micrograms/kg per hour; lower loading doses may be required for less invasive procedures. Reduced doses may be necessary in patients with hepatic impairment or in the elderly.

The racemate, medetomidine (p. 1083.2), is used as the hydrochloride in veterinary medicine.

References.
1. Venn RM, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999; **54:** 1136–42.
2. Bhana N, *et al.* Dexmedetomidine. *Drugs* 2000; **59:** 263–8.
3. Coursin DB, *et al.* Dexmedetomidine. *Curr Opin Crit Care* 2001; **7:** 221–6.
4. Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. *Neurosurgery* 2005; **57** (suppl): 1–10.
5. Szumita PM, *et al.* Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. *Am J Health-Syst Pharm* 2007; **64:** 37–44.
6. Pandharipande PP, *et al.* Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; **298:** 2644–53.
7. Riker RR, *et al.* SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301:** 489–99.
8. Gerlach AT, *et al.* An updated focused review of dexmedetomidine in adults. *Ann Pharmacother* 2009; **43:** 2064–74.
9. Farag E. Dexmedetomidine in the neurointensive care unit. *Discov Med* 2010; **9:** 42–5.

Adverse Effects and Precautions

The most common adverse effect of dexmedetomidine is hypotension. Other common adverse effects include hypertension, nausea and vomiting, bradycardia, tachycardia, fever, hypoxia, and anaemia. Patients should be continuously monitored during use. Dexmedetomidine should be used with caution in patients with advanced heart block, or hepatic impairment, or in the elderly.

Interactions

The effects of other CNS depressants may be enhanced by dexmedetomidine. Dexmedetomidine may also increase the effects of other vasodilators or drugs such as cardiac glycosides, that have negative chronotropic effects.

Pharmacokinetics

Dexmedetomidine is about 94% protein bound, but this has been reported to be significantly decreased in patients with hepatic impairment. Dexmedetomidine is almost completely metabolised by direct glucuronidation or by cytochrome P450 isoenzymes. It is excreted mainly as metabolites in the urine and faeces. The terminal elimination half-life is about 2 hours.

References.
1. De Wolf AM, *et al.* The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001; **93:** 1205–9.
2. Anttila M, *et al.* Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 691–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Precedex; ***Austral.***: Precedex; ***Braz.***: Precedex; ***Canad.***: Precedex; ***Cz.***: Precedex†; ***Denm.***: Dexdor; ***Hong Kong***: Precedex; ***Indon.***: Precedex; ***Irl.***: Dexdor; ***Jpn***: Precedex; ***Malaysia***: Precedex; ***Mex.***: Precedex†; ***Norw.***: Dexdor; ***NZ***: Precedex; ***Philipp.***: Precedex; ***Pol.***: Precedex†; ***S. Afr.***: Precedex; ***Singapore***: Precedex; ***Spain***: Dexdor; ***Swed.***: Dexdor; ***Switz.***: Dexdor; ***Thai.***: Precedex; ***Turk.***: Precedex†; ***UK***: Dexdor; ***Ukr.***: Dexdor (Дексдор); ***USA***: Precedex.

Diazepam *(BAN, USAN, rINN)*

Diatsepaami; Diazepám; Diazépam; Diazepamas; Diazepamum; LA-III; NSC-77518; Ro-5-2807; Wy-3467; Диазепам.

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{16}H_{13}ClN_2O$=284.7

CAS — 439-14-5.
ATC — N05BA01.
ATC Vet — QN05BA01.
UNII — Q3JTX2Q7TU.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of diazepam:

Benzo; Black pearl; Blue; Blue bombers; Blue boys; Blue magoo's; Blue thunder; Blues; Drunk pills; La Roche; Ludes; Mother's little helper; Mother's little helpers; Pami; Roaches; Roachies; Roche; V; V's blues; Valleys; Vallies; Vals.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Diazepam). A white or almost white, crystalline powder. Very slightly soluble in water; soluble in alcohol. Protect from light.

USP 36: (Diazepam). An off-white to yellow, practically odourless, crystalline powder. Soluble 1 in 333 of water, 1 in 16 of alcohol, 1 in 2 of chloroform, and 1 in 39 of ether. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between diazepam and several other drugs. Licensed product information for diazepam injection advises against its admixture with other drugs.

Sorption. Substantial adsorption of diazepam onto some plastics may cause problems when giving the drug by continuous intravenous infusion. More than 50% of diazepam in solution may be adsorbed onto the walls of PVC infusion bags and their use should, therefore, be avoided. Giving sets should contain the minimum amount of PVC tubing and should not contain a cellulose propionate volume-control chamber. Suitable materials for infusion containers, syringes, and giving sets for diazepam include glass, polyolefin, polypropylene, and polyethylene.

References.
1. Cloyd JC, *et al.* Availability of diazepam from plastic containers. *Am J Hosp Pharm* 1980; **37:** 492–6.
2. Parker WA, MacCara ME. Compatibility of diazepam with intravenous fluid containers and administration sets. *Am J Hosp Pharm* 1980; **37:** 496–500.
3. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
4. Kowaluk EA, *et al.* Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am J Hosp Pharm* 1983; **40:** 417–23.
5. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Stability. Care should be observed when diluting diazepam injections for infusion because of problems of precipitation. Directions in the licensed product information should be followed regarding diluent and concentration of diazepam and all solutions should be freshly prepared.

Uses and Administration

Diazepam is a long-acting benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnestic properties. Its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. Diazepam is used in the short-term treatment of severe anxiety disorders (p. 1028.1), as a hypnotic in the short-term management of insomnia (p. 1033.2), as a sedative (p. 1032.2) and premedicant (see Anaesthesia, p. 1899.1), as an anticonvulsant (particularly in the management of status epilepticus and febrile convulsions), in the control of muscle spasm of various aetiologies, and in the management of withdrawal symptoms (see also the references on p. 1064.3 and p. 1065.1).

Diazepam is **administered** orally, rectally, and parenterally with the risk of dependence very much influencing the dose and duration of treatment. Doses should be the lowest that can control symptoms and courses of treatment should be short, not normally exceeding 4 weeks, with diazepam being withdrawn gradually (see under Dependence and Withdrawal, p. 1065.1). Elderly and debilitated patients should be given not more than one-half the usual adult dose. Dosage reduction may also be required in patients with hepatic or renal impairment.

Oral use is appropriate for many indications and modified-release formulations are available in some countries. *Rectal* use may be by rectal solution or gel; it has been given as a suppository. Diazepam is also given by deep intramuscular or slow intravenous injection, although absorption after *intramuscular injection* may be erratic and provides lower blood concentrations than those after oral doses. The intramuscular route is usually only used when oral or intravenous dosage is not possible. *Intravenous injection* should be carried out slowly into a large vein of the antecubital fossa at a recommended rate of no more than 1 mL of a 0.5% solution (5 mg) per minute. It is advisable to keep the patient in the supine position and under medical supervision for at least an hour after the dose. Diazepam may be given by continuous *intravenous infusion*; because of the risk of precipitation of diazepam, solutions should be freshly prepared following directions regarding diluent and concentration of diazepam as stated in the licensed product information. Diazepam is substantially adsorbed onto some plastics (see Sorption, above). Facilities for resuscitation should always be available when diazepam is given intravenously.

Diazepam may be given for **severe anxiety** in usual *oral* doses of 2 mg three times daily to a maximum of 30 mg daily; a wider dose range of 4 to 40 mg daily in divided doses is licensed in the USA. Diazepam may be given as a *rectal solution* in a dose of 500 micrograms/kg repeated after 12 hours if necessary. Diazepam may sometimes have to be given by *intramuscular* or *intravenous injection* when a dose of up to 10 mg may be used, repeated if necessary after 4 hours. The *BNF* states that this dose has also been given intravenously for the control of acute panic attacks but should only be used when other measures have failed.

The benzodiazepines have a limited role in **insomnia** and diazepam is used for the short-term management of insomnia associated with anxiety. The *BNF* recommends an *oral* dose of 5 to 15 mg at bedtime, although doses of up to 30 mg are licensed.

Diazepam may be given for **premedication** before general anaesthesia or for **sedation** during minor surgical or investigative procedures. *Oral* doses for premedication are in the range of 5 to 20 mg. When given by *intravenous injection* for premedication or sedation the dose is usually 100 to 200 micrograms/kg or 10 to 20 mg. Diazepam 500 micrograms/kg may also be given as a *rectal* solution.

Diazepam is used in a variety of **seizures**. It is given *orally* as an adjunct in some types of epilepsy; for this purpose, 2 to 60 mg may be given daily in divided doses. A *rectal gel* formulation is also available for adjunctive use in the management of episodes of increased seizure activity in patients with refractory epilepsy; a usual dose of 200 micrograms/kg may be given, and repeated after 4 to 12 hours if necessary. No more than 5 episodes a month and no more than 1 episode every 5 days should be treated with this formulation. For febrile convulsions, status epilepticus, and convulsions due to poisoning, giving a *rectal solution* may be appropriate. Licensed doses for the rectal solution differ but a typical dose is 500 micrograms/kg (maximum of 30 mg); the *BNF* suggests doses of 10 to 20 mg. If convulsions are not controlled by the first dose the use of other anticonvulsive measures is recommended in the licensed product information, however, the *BNF* suggests that the dose may be repeated once after 10 to 15 minutes if seizures are not controlled. Alternatively, diazepam may be given by *intravenous* injection in a dose of 150 to 250 micrograms/kg, repeated after 30 to 60 minutes (the *BNF* suggests a dose of 10 mg which may be repeated once after 10 minutes) if necessary. Other schedules involve giving smaller amounts more frequently or giving diazepam

intramuscularly, though again absorption may be too slow. Once the seizures have been controlled, a slow intravenous infusion providing up to 3 mg/kg over 24 hours has been used to protect against recurrence.

Diazepam 2 to 15 mg daily may be given *orally* in divided doses to alleviate **muscle spasm**. The dose may be increased in severe spastic disorders, such as cerebral palsy, to up to 60 mg daily. If given by intramuscular or slow intravenous *injection* the dose is 10 mg repeated if necessary after 4 hours. When used to control acute drug-induced dystonic reactions, the *BNF* suggests a dose of 5 to 10 mg by *intravenous* injection, repeated as necessary after a minimum of 10 minutes. Larger doses are used in tetanus with 100 to 300 micrograms/kg being given every 1 to 4 hours by intravenous injection. Alternatively 3 to 10 mg/kg may be given over 24 hours by continuous intravenous infusion or by nasoduodenal tube using a suitable liquid oral dose form. Diazepam may also be given as a *rectal solution* in a dose of 500 micrograms/kg, repeated every 12 hours if necessary.

For details of doses in children, see below.

Symptoms of the **alcohol withdrawal syndrome** may be controlled by diazepam given *orally* in a dose of 5 to 20 mg, repeated if necessary after 2 to 4 hours; another approach is to give 10 mg three or four times on the first day reducing to 5 mg three or four times daily as required. Diazepam may need to be given by *injection* if the symptoms are severe and if delirium tremens has developed; 10 to 20 mg by intramuscular or intravenous injection, repeated after 4 hours if necessary, may be adequate, although some patients may require higher doses.

Reviews.
1. Ashton H. Guidelines for the rational use of benzodiazepines: when and what to use. *Drugs* 1994; **48:** 25–40.
2. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry* 2004; **65** (suppl 5): 7–12.
3. Stevens JC, Pollack MH. Benzodiazepines in clinical practice: consideration of their long-term use and alternative agents. *J Clin Psychiatry* 2005; **66** (suppl 2): 21–7.
4. Witek MW, *et al*. Review of benzodiazepine use in children and adolescents. *Psychiatr Q* 2005; **76:** 283–96.
5. Cloos JM, Ferreira V. Current use of benzodiazepines in anxiety disorders. *Curr Opin Psychiatry* 2009; **22:** 90–5.

Administration in children. Diazepam has been given for **premedication** before general anaesthesia or for **sedation** during minor surgical or investigative procedures in children. UK licensed product information suggests the following doses:

orally
- 2 to 10 mg

intravenously (preferably as the emulsion preparation; injection formulations containing benzyl alcohol should be avoided in neonates, see p. 1067.2)
- 100 to 200 micrograms/kg

rectally (as a rectal solution in children aged 1 year and older)
- 250 to 500 micrograms/kg (usually, for practical reasons, a dose of 5 or 10 mg)

The *BNFC* considers that perioperative use of diazepam is not recommended in children as onset and magnitude of response are unreliable, and paradoxical effects may occur.

Diazepam is used in a variety of **seizures**. In some countries a *rectal gel* formulation is available for adjunctive use in the management of episodes of increased seizure activity in children aged 2 years and older with refractory epilepsy; the following doses, repeated once after 4 to 12 hours if necessary, may be given according to age:
- 2 to 5 years: 500 micrograms/kg
- 6 to 11 years: 300 micrograms/kg
- 12 years and older: 200 micrograms/kg

For febrile convulsions, status epilepticus, and convulsions due to poisoning, giving a *rectal solution* may be appropriate. A dose of 500 micrograms/kg of a rectal solution, repeated every 12 hours if necessary, has been recommended in licensed product information for children aged 1 year and over. Alternatively, the *BNFC* suggests giving the following doses, repeated once after 10 minutes if necessary, according to age:
- neonates: 1.25 to 2.5 mg
- 1 month to 2 years: 5 mg
- 2 to 12 years: 5 to 10 mg
- 12 to 18 years: 10 to 20 mg

Doses by *intravenous* injection, given at a rate of not more than 5 mg/minute and repeated if necessary after 30 to 60 minutes, are within the range of 200 to 300 micrograms/kg; alternatively, 1 mg may be given for each year of age. The *BNFC* suggests giving the following doses over 3 to 5 minutes, repeated once after 10 minutes if necessary:
- neonates to 12 years: 300 to 400 micrograms/kg
- 12 to 18 years: 10 mg

Diazepam 2 to 40 mg daily may be given *orally* in divided doses to alleviate **muscle spasm** of various aetiologies. For muscle spasm in cerebral spasticity or postoperative skeletal muscle spasm, the *BNFC* suggests initial oral doses based on age and given twice daily, as follows:
- 1 to 12 months: 250 micrograms/kg
- 1 to 5 years: 2.5 mg
- 5 to 12 years: 5 mg
- 12 to 18 years: 10 mg (maximum of 40 mg daily)

For life-threatening acute drug-induced dystonic reactions, the *BNFC* suggests giving the following doses based on age by *intravenous* injection over 3 to 5 minutes:
- 1 month to 12 years: 100 micrograms/kg
- 12 to 18 years: 5 to 10 mg

The dose may be repeated as necessary after at least 10 minutes.

For muscle spasm in tetanus, the *BNFC* suggests that children aged from 1 month to 18 years may be given 100 to 300 micrograms/kg every 1 to 4 hours by intravenous injection; alternatively, 3 to 10 mg/kg may be given over 24 hours by continuous intravenous infusion or by nasoduodenal tube using a suitable liquid oral dose form.

Diazepam may also be given as a *rectal* solution in a dose of 500 micrograms/kg to children aged 1 year and older, repeated every 12 hours if necessary.

Administration in hepatic impairment. Oxidative metabolism of diazepam is apparently reduced in patients with hepatic impairment, resulting in a prolonged half-life and reduced clearance.[1-3] A reduction in dosage was generally required in these studies, but no specific advice is given in licensed product information for the UK or USA.

1. Branch RA, *et al*. Intravenous administration of diazepam in patients with chronic liver disease. *Gut* 1976; **17:** 975–83.
2. Klotz U, *et al*. Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. *Clin Pharmacol Ther* 1977; **21:** 430–6.
3. Ochs HR, *et al*. Repeated diazepam dosing in cirrhotic patients: cumulation and sedation. *Clin Pharmacol Ther* 1983; **33:** 471–6.

Administration in renal impairment. Diazepam and its metabolites are excreted in urine, and UK licensed product information suggests that dosage reduction may be required in patients with renal impairment, but gives no specific advice on how to do this.

Cardiac arrhythmias. Although not considered to be an antiarrhythmic, diazepam has been tried with good effect in treating the cardiotoxicity of chloroquine poisoning (see p. 652.3). However, diazepam has been reported to possess both antiarrhythmic and pro-arrhythmic properties, possibly depending on the dose.[1]

1. Kumagai K, *et al*. Antiarrhythmic and proarrhythmic properties of diazepam demonstrated by electrophysiological study in humans. *Clin Cardiol* 1991; **14:** 397–401.

Chloroquine poisoning. For reference to the possible use of diazepam to decrease the cardiotoxic effects of chloroquine, see p. 652.3.

Conversion and dissociative disorders. Conversion and dissociative disorders (formerly known as hysteria) are characterised by physical symptoms that occur in the absence of organic disease.[1] Medication has no part to play in the treatment of these disorders unless they are secondary to conditions such as depression or anxiety disorders requiring treatment in their own right.

There have been suggestions that sedatives such as diazepam or midazolam may be used to confirm the diagnosis of hysterical paralysis.[2,3] The test tends to exacerbate organic disease while psychiatric dysfunction may improve.

1. Kihlstrom JF. Dissociative disorders. *Annu Rev Clin Psychol* 2005; **1:** 227–53.
2. Ellis SJ. Diazepam as a truth drug. *Lancet* 1990; **336:** 752–3.
3. Keating JJ, *et al*. Hysterical paralysis. *Lancet* 1990; **336:** 1506–7.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders, and the value of benzodiazepines, see p. 1030.2. Benzodiazepines may also be useful in palliative care for the relief of terminal restlessness and confusion; however, benzodiazepine use alone has been associated with an exacerbation of symptoms. Those that have been tried include diazepam, clonazepam, lorazepam, and midazolam. Parenteral midazolam, given with the antipsychotic haloperidol, is often the treatment of choice in an imminently dying patient with delirium.

Dyspnoea. Despite the hazards of use in patients with any form of respiratory depression or pulmonary insufficiency (see Respiratory System Disorders under Precautions, p. 1068.1) benzodiazepines such as diazepam have been tried in the treatment of dyspnoea (p. 108.3), in the belief that reduction of an elevated respiratory drive may alleviate respiratory distress. However, benefits have not been confirmed. Benzodiazepines may be of use in patients with advanced cancer who have rapid shallow respiration. Some[1] recommend trying a low dose of a benzodiazepine, given either regularly or as required, in palliative care only if anxiety appears to be a major component or trigger of breathlessness and is not relieved by non-pharmacological measures. The *BNF* suggests that 5 to 10 mg daily of diazepam may be helpful.

1. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.

Eclampsia and pre-eclampsia. Diazepam has been used for the initial control of impending or actual eclampsia (p. 511.1), but magnesium sulfate is now generally the preferred treatment.

Epilepsy and other convulsive disorders. Some benzodiazepines such as diazepam are used for the control of status epilepticus (p. 510.2), including status epilepticus in patients with porphyria (but see also Porphyria under Precautions, p. 1067.3), and for febrile convulsions (p. 511.2) and seizures associated with alcohol withdrawal (p. 1735.1); diazepam has also been used in eclampsia (see above) and for neonatal seizures (p. 511.3). Benzodiazepines such as clobazam and clonazepam may be used in the management of epilepsy (p. 506.1), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Diazepam has been used as an adjunct in the management of some types of epilepsy including myoclonus.

References.
1. Rosman NP, *et al*. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993; **329:** 79–84.
2. Somerville ER, Antony JH. Position statement on the use of rectal diazepam in epilepsy. *Med J Aust* 1995; **163:** 268–9.
3. Uhari M, *et al*. Effect of acetaminophen and low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126:** 991–5.
4. Akinbi MS, Welty TE. Benzodiazepines in the home treatment of acute seizures. *Ann Pharmacother* 1999; **33:** 99–102.
5. Rey E, *et al*. Pharmacokinetic optimisation of benzodiazepine therapy for acute seizures: focus on delivery routes. *Clin Pharmacokinet* 1999; **36:** 409–24.
6. Ogutu BR, *et al*. Pharmacokinetics and anticonvulsant effects of diazepam in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol* 2002; **53:** 49–57.
7. Riss J, *et al*. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurol Scand* 2008; **118:** 69–86.
8. Anderson M. Benzodiazepines for prolonged seizures. *Arch Dis Child Educ Pract Ed* 2010; **95:** 183–9.

Extrapyramidal disorders. For reference to the use of benzodiazepines in the treatment of antipsychotic-induced extrapyramidal disorders, see Chlorpromazine, p. 1049.2.

Irritable bowel syndrome. Although some benzodiazepines have been used in the management of irritable bowel syndrome (p. 1813.3) there is no evidence to support their use in this condition. The related compound dextofisopam (see Tofisopam, p. 1112.2) is under investigation.

Mania. Benzodiazepines have been used as short-term adjuncts in the initial control of manic episodes in patients with bipolar disorder (p. 397.2) until lithium has achieved its full effect.

Muscle spasm. Diazepam and other benzodiazepines may be used for the relief of muscle spasm (p. 2014.1) of various aetiologies including that secondary to muscle or joint inflammation or trauma, such as in acute **low back pain** (p. 9.2), or resulting from **spasticity** (p. 2014.2), **dystonias** (p. 903.3), **stiff-man syndrome** (see below), **cerebral palsy**, **poisoning**, or **tetanus** (p. 2029.2). High doses are often required and treatment may be limited by adverse effects or by risk of dependence.

STIFF-MAN SYNDROME. Stiff-man syndrome is a rare condition characterised by painful intermittent spasms and rigidity of the axial and limb muscles. Its exact cause is unknown but there is some evidence to implicate autoantibodies against one of the enzymes involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). It is frequently associated with auto-immune diseases and type 1 diabetes mellitus. Patients typically respond to benzodiazepines and this may be of use in the differential diagnosis of the syndrome. Diazepam has been the mainstay of treatment but clonazepam may also be of use, especially in familial startle disease, a rare congenital form of stiff-man syndrome. Although rigidity and spasms in stiff-man syndrome are not completely resolved by diazepam the degree of improvement can be sufficient to restore the functional level to near normal. However, large doses are often required and sedation might be a limiting factor in some patients. Other drugs that have been used when diazepam is ineffective or poorly tolerated include baclofen or sodium valproate but benefit may be less evident. There have been isolated anecdotal reports of improvement with vigabatrin, tiagabine, gabapentin, and levetiracetam; botulinum A toxin has also been tried. Antiepileptics or baclofen may sometimes be combined with benzodiazepines. Corticosteroids may be of benefit, although any response may take several weeks, and the chronic nature of the disorder and the high incidence of

type 1 diabetes mellitus may make their use problematic. Other attempts at immunomodulation such as plasmapheresis have yielded variable results; there is some evidence of the efficacy of immunoglobulins but repeated infusions are required to maintain response.

References.
1. Stayer C, Meinck H-M. Stiff-man syndrome: an overview. *Neurologia* 1998; **13:** 83–8.
2. Levy LM, *et al.* The stiff-person syndrome - an autoimmune disorder affecting neurotransmission of γ-aminobutyric acid. *Ann Intern Med* 1999; **131:** 522–30.
3. Meinck H-M. Stiff man syndrome. *CNS Drugs* 2001; **15:** 515–26.
4. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345:** 1870–6.
5. Vasconcelos OM, Dalakas MC. Stiff-person syndrome. *Curr Treat Options Neurol* 2003; **5:** 79–90.
6. Murinson BB. Stiff-person syndrome. *Neurologist* 2004; **10:** 131–7.
7. Dalakas MC. Advances in the pathogenesis and treatment of patients with stiff person syndrome. *Curr Neurol Neurosci Rep* 2008; **8:** 48–55.

Nausea and vomiting. Benzodiazepines, particularly lorazepam, are used as adjuncts in the management of nausea and vomiting (p. 1814.3) induced by cancer chemotherapy, particularly anticipatory emesis. Midazolam has been tried for the prophylaxis of postoperative nausea and vomiting; for references, see p. 1086.3.

Premenstrual syndrome. For mention of the limited role of benzodiazepines in the management of premenstrual syndrome, see p. 2272.3.

Schizophrenia. Benzodiazepines may be useful adjuncts to antipsychotics in the initial management of schizophrenia (p. 1031.3).

Sleep-associated movement disorders. Sleep-associated movement disorders (p. 1034.2) rarely require treatment other than the symptomatic treatment of sleep-related medical problems. Some of these conditions, including restless legs syndrome, sleepwalking, and night terrors, have been reported to respond to benzodiazepines. Although the muscle relaxant and anxiolytic action of a benzodiazepine can be helpful in bruxism (teeth grinding) it has been recommended that they should only be prescribed on a short-term basis during the acute phase.

References.
1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100:** 333–7.

Substance dependence. The benzodiazepines are used in the symptomatic management of *alcohol* withdrawal (p. 1735.1), of *opioid* withdrawal (p. 109.2), and of *cocaine* withdrawal (p. 1990.1).

Vertigo. Although intravenous diazepam has been used to abort acute attacks of vertigo of peripheral origin (p. 612.3), it can prolong compensation and recovery from vestibular lesions.[1]

1. Rascol O, *et al.* Antivertigo medications and drug-induced vertigo: a pharmacological review. *Drugs* 1995; **50:** 777–91.

Dependence and Withdrawal

The development of dependence is common after regular use of benzodiazepines, even in therapeutic doses for short periods. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in those with marked personality disorders. Benzodiazepines should therefore be withdrawn by gradual reduction of the dose after regular use for even a few weeks; the time needed for withdrawal can vary from about 4 weeks to a year or more. The extent to which tolerance occurs has been debated but appears to involve psychomotor performance more often than anxiolytic effects. Drug-seeking behaviour is uncommon with therapeutic doses of benzodiazepines. High doses of diazepam and other benzodiazepines, injected intravenously, have been abused for their euphoriant effects.

Benzodiazepine withdrawal syndrome. Development of dependence to benzodiazepines cannot be predicted but risk factors include high dosage, regular continuous use, the use of benzodiazepines with a short half-life, use in patients with dependent personality characteristics or a history of drug or alcohol dependence, and the development of tolerance. The mechanism of dependence is unclear but may involve reduced gamma-aminobutyric acid (GABA) activity resulting from down-regulation of GABA receptors.

Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension. Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

Symptoms typical of withdrawal have occurred despite continued use of benzodiazepines and have been attributed either to the development of tolerance or, as in the case of very short-acting drugs such as triazolam, to rapid benzodiazepine elimination. Pseudowithdrawal has been reported in patients who believed incorrectly that their dose of benzodiazepine was being reduced. Benzodiazepine withdrawal syndrome can theoretically be distinguished from these reactions and from rebound phenomena (return of original symptoms at greater than pretreatment severity) by the differing **time course**. A withdrawal syndrome is characterised by its onset, by the development of new symptoms, and by a peak in intensity followed by resolution. Onset of withdrawal symptoms depends on the half-life of the drug and its active metabolites. Symptoms can begin within a few hours after withdrawal of a short-acting benzodiazepine, but may not develop for up to 3 weeks after stopping a longer-acting benzodiazepine. Resolution of symptoms may take several days or months. The dependence induced by short- and long-acting benzodiazepines appears to be qualitatively similar although withdrawal symptoms may be more severe with short-acting benzodiazepines. Rebound effects are also more likely with short-acting benzodiazepines. Rebound and withdrawal symptoms develop particularly rapidly with the very short-acting drug triazolam.

With increased awareness of the problems of benzodiazepine dependence, emphasis has been placed on **prevention** by proper use and careful patient selection. For example, the UK CSM has recommended that benzodiazepines should be reserved for the short-term relief (2 to 4 weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress and is occurring alone or with insomnia or short-term psychosomatic, organic, or psychotic illness.

Withdrawal from long-term benzodiazepine use should generally be encouraged. Established dependence can be difficult to treat; the patient should have professional and family support and behavioural therapy may be helpful. Withdrawal in a specialist centre may be required for some patients. Abrupt withdrawal of benzodiazepines has resulted in severe withdrawal symptoms, so benzodiazepine withdrawal should be flexible and carried out at a tolerable reduction rate that is dependent on the initial dose, duration of use, and clinical response. Short-term users (2 to 4 weeks only) can usually taper off within 2 to 4 weeks; however, long-term users should be withdrawn over several months or more. Clinicians often favour transferring long-term benzodiazepine users stepwise, one dose at a time over about a week, to an equivalent dose of diazepam given at night; the following rough dosage equivalents to *diazepam 5 mg* have been recommended in the UK:

- alprazolam 250 micrograms
- chlordiazepoxide 12.5 mg
- clobazam 10 mg
- clonazepam 250 micrograms
- flurazepam 7.5 to 15 mg
- loprazolam 0.5 to 1 mg
- lorazepam 500 micrograms
- lormetazepam 0.5 to 1 mg
- nitrazepam 5 mg
- oxazepam 10 mg
- temazepam 10 mg

The daily dosage of diazepam can then be reduced in steps of 1 to 2 mg every 2 to 4 weeks. In patients taking high doses of benzodiazepines, it may be appropriate initially to reduce in steps of up to one-tenth of the daily dose every 1 to 2 weeks. If troublesome abstinence effects occur the dose should be held level for a longer period before further reduction; increased dosage should be avoided if possible. Smaller steps of 500 micrograms may be appropriate towards the end of withdrawal. For long-term patients, the time required for complete withdrawal can vary from several months to a year or longer. In many cases the rate of withdrawal is best decided by the patient. Adjuvant therapy with beta blockers, antidepressants, and antipsychotic drugs should be avoided where possible.

Symptoms gradually improve after withdrawal but postwithdrawal syndromes lasting for several weeks or months have been described. Withdrawal symptoms in long-term users usually resolve within 6 to 18 months of the last dose. Continued support may be required for the first year after withdrawal to prevent relapse.

References.
1. CSM. Benzodiazepines, dependence and withdrawal symptoms. *Current Problems 21* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
2. Marriott S, Tyrer P. Benzodiazepine dependence: avoidance and withdrawal. *Drug Safety* 1993; **9:** 93–103.
3. Pétursson H. The benzodiazepine withdrawal syndrome. *Addiction* 1994; **89:** 1455–59.
4. Ashton H. The treatment ofbenzodiazepine dependence. *Addiction* 1994; **89:** 1535–41.
5. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry* 2005; **66** (suppl 2): 28–33.
6. Denis C, *et al.* Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).
7. Oude Voshaar RC, *et al.* Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry* 2006; **189:** 213–20.
8. DoH (England) and the devolved administrations (2007). *Drug misuse and dependence: UK guidelines on clinical management* (updated September 2007). London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive. Also available at: http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf (accessed 26/07/10)
9. Lader M, *et al.* Withdrawing benzodiazepines in primary care. *CNS Drugs* 2009; **23:** 19–34.

Adverse Effects

Drowsiness, sedation, muscle weakness, and ataxia are the most frequent adverse effects of diazepam use. They generally decrease on continued dosage and are a consequence of CNS depression. Less frequent effects include vertigo, headache, confusion, depression (but see Effects on Mental Function, p. 1066.1), slurred speech or dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may have a paradoxical excitation which may lead to hostility, aggression, and disinhibition. Jaundice, blood disorders, and hypersensitivity reactions have been reported rarely; raised liver enzyme values have occurred. Respiratory depression and hypotension occasionally occur with high dosage and parenteral use.

Pain and thrombophlebitis may occur with some intravenous formulations of diazepam.

Overdosage can produce CNS depression and coma or paradoxical excitation. However, fatalities are rare when taken alone.

Use of diazepam in the first trimester of pregnancy has occasionally been associated with congenital malformations in the infant but no clear relationship has been established. This topic is reviewed under Pregnancy p. 1067.3. Use of diazepam in late pregnancy has been associated with intoxication of the neonate.

Carcinogenicity. The International Agency for Research on Cancer concluded[1] that there was sufficient evidence from human studies that diazepam did not produce breast cancer, and that there were inadequate data to support its potential carcinogenicity at other sites. For most other benzodiazepines the lack of human studies meant that the carcinogenic risk to humans was not classifiable. However, there appeared to be sufficient evidence of carcinogenicity in *animal* studies for oxazepam to be classified as possibly carcinogenic in humans.

1. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 66* 1996. Also available at: http://monographs.iarc.fr/ENG/Monographs/vol66/volume66.pdf (accessed 15/05/06)

Effects on body temperature. Studies in healthy subjects[1,2] indicate that benzodiazepines can reduce body temperature. After a single oral dose of diazepam 10 mg in 11 subjects, body temperature on exposure to cold fell to a mean of 36.93 degrees compared with 37.08 degrees on exposure without the drug.[1] An 86-year-old woman developed hypothermia[3] after being given nitrazepam 5 mg. After recovery she was mistakenly given another 5-mg dose of nitrazepam and again developed hypothermia. Midazolam (given as anaesthetic premedication) also produces modest decreases in core body temperature, which can be abolished by atropine,[4] but its effects are negligible compared with other elements of the anaesthetic regimen.[5]

Hypothermia has been reported in the neonates of mothers given benzodiazepines during the late stages of pregnancy.

1. Martin SM. The effect of diazepam on body temperature change in humans during cold exposure. *J Clin Pharmacol* 1985; **25:** 611–13.
2. Matsukawa T, *et al.* I.M. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. *Br J Anaesth* 1997; **78:** 396–9.
3. Impallomeni M, Ezzat R. Hypothermia associated with nitrazepam administration. *BMJ* 1976; **1:** 223–4.
4. Matsukawa T, *et al.* Atropine prevents midazolam-induced core hypothermia in elderly patients. *J Clin Anesth* 2001; **13:** 504–8.
5. Kurz A, *et al.* Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; **81:** 393–8.

Effects on endocrine function. Galactorrhoea with normal serum-prolactin concentrations has been noted in 4 women taking benzodiazepines.[1] Gynaecomastia has been reported in men taking diazepam;[2-4] doses ranged from up to 30 mg daily to up to 140 mg daily. Serum-oestradiol concentrations were raised in some patients. However, raised plasma-testosterone concentrations have also

occurred in men taking diazepam 10 to 20 mg daily for 2 weeks.[5]

1. Kleinberg DL, *et al*. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977; **296:** 589–600.
2. Moerck HJ, Magelund G. Gynaecomastia and diazepam abuse. *Lancet* 1979; **i:** 1344–5.
3. Bergman D, *et al*. Increased oestradiol in diazepam related gynaecomastia. *Lancet* 1981; **ii:** 1225–6.
4. Jelenkovic AV, Macukanovic-Golubovic LD. Diazepam-associated gynecomastia. *Ann Pharmacother* 2005; **39:** 201.
5. Argüelles AE, Rosner J. Diazepam and plasma-testosterone levels. *Lancet* 1975; **ii:** 607.

Effects on the eyes. Brown opacification of the lens occurred in 2 patients who took oral diazepam 5 mg or more daily over several years.[1] Severe visual field loss associated with very high doses (100 mg) of diazepam has also been described.[2]

1. Pau H. Braune scheibenförmige Einlagerungen in die Linse nach Langzeitgabe von Diazepam (Valium). *Klin Monatsbl Augenheilkd* 1985; **187:** 219–20.
2. Elder MJ. Diazepam and its effects on visual fields. *Aust N Z J Ophthalmol* 1992; **20:** 267–70.

Effects on the liver. Cholestatic jaundice[1] and focal hepatic necrosis with intracellular cholestasis[2] have been associated with the use of diazepam.

1. Jick H, *et al*. Drug-induced liver disease. *J Clin Pharmacol* 1981; **21:** 359–64.
2. Tedesco FJ, Mills LR. Diazepam (Valium) hepatitis. *Dig Dis Sci* 1982; **27:** 470–2.

Effects on mental function. The effects of benzodiazepines on psychomotor performance in laboratory tests[1] are not easily extrapolated to the clinical situation. For example postoperative cognitive dysfunction in the elderly does not seem to be related to benzodiazepine concentration in the blood.[2]

A meta-analysis[3] of 13 studies found that long-term benzodiazepine use is associated with cognitive dysfunction such as impairments in visual-spatial ability, concentration and attention, motor skills, verbal and non-verbal memory, reaction time, and general intellectual ability. A further meta-analysis[4] using some of the above studies suggested that although cognitive function improved after benzodiazepine withdrawal, there remains significant impairment, at least for the first 6 months, when compared with control subjects or normative data and that some impairment may be permanent.

Paradoxical reactions characterised by increased talkativeness, excitement, insomnia, excessive movement, hostility, and rage have been reported[5] with benzodiazepines. These reactions occur in less than 1% of patients and there is some evidence that young or advanced age, genetic predisposition, alcoholism, and psychiatric or personality disorders are risk factors.

Sexual fantasies have been reported in women sedated with intravenous diazepam or midazolam.[6] These appear to be dose-related.[7]

The view that benzodiazepines can cause depression, albeit infrequently, has been queried.[8]

Some benzodiazepines such as clorazepate, are used as antiepileptics. For a review of the effects of antiepileptic therapy on cognition and mood and, in particular, the increased risk of suicidal ideation or behaviour, see p. 508.3.

Adverse effects of alprazolam on behaviour have also been reviewed.[9]

1. Woods JH, *et al*. Abuse liability of benzodiazepines. *Pharmacol Rev* 1987; **39:** 251–413.
2. Rasmussen LS, *et al*. Benzodiazepines and postoperative cognitive dysfunction in the elderly. *Br J Anaesth* 1999; **83:** 585–9.
3. Barker MJ, *et al*. Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs* 2004; **18:** 37–48.
4. Barker MJ, *et al*. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Arch Clin Neuropsychol* 2004; **19:** 437–54.
5. Mancuso CE, *et al*. Paradoxical reactions to benzodiazepines: literature review and treatment options. *Pharmacotherapy* 2004; **24:** 1177–85.
6. Dundee JW. Fantasies during sedation with intravenous midazolam or diazepam. *Med Leg J* 1990; **58:** 29–34.
7. Brahams D. Benzodiazepine sedation and allegations of sexual assault. *Lancet* 1989; **i:** 1339–40.
8. Patten SB, Love EJ. Drug-induced depression: incidence, avoidance and management. *Drug Safety* 1994; **10:** 203–19.
9. Cole JO, Kando JC. Adverse behavioral events reported in patients taking alprazolam and other benzodiazepines. *J Clin Psychiatry* 1993; **54** (suppl): 49–61.

Effects on the nervous system. There are a few isolated reports of extrapyramidal symptoms in patients taking benzodiazepines.[1-4] Benzodiazepines have been used to treat such symptoms induced by antipsychotics (see Extrapyramidal Disorders under Chlorpromazine, p. 1049.2).

1. Rosenbaum AH, De La Fuente JR. Benzodiazepines and tardive dyskinesia. *Lancet* 1979; **ii:** 900.
2. Sandyk R. Orofacial dyskinesias associated with lorazepam therapy. *Clin Pharm* 1986; **5:** 419–21.
3. Stolarek IH, Ford MJ. Acute dystonia induced by midazolam and abolished by flumazenil. *BMJ* 1990; **300:** 614.
4. Joseph AB, Wroblewski BA. Paradoxical akathisia caused by clonazepam, clorazepate and lorazepam in patients with traumatic encephalopathy and seizure disorders: a subtype of benzodiazepine-induced disinhibition? *Behav Neurol* 1993; **6:** 221–3.

ENCEPHALOPATHY. Prolonged use of midazolam with fentanyl has been associated with encephalopathy in infants sedated under intensive care.[1]

1. Bergman I, *et al*. Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr* 1991; **119:** 644–9.

Effects on sexual function. The sedative effects of benzodiazepines may reduce sexual arousal and lead to impotence in some patients. Conversely sexual performance may be improved by therapy if it was previously impaired by anxiety.

Increased libido and orgasmic function has been reported in 2 women after withdrawal of long-term benzodiazepine use.[1]

1. Nutt D, *et al*. Increased sexual function in benzodiazepine withdrawal. *Lancet* 1986; **ii:** 1101–2.

Effects on skeletal muscle. In a report[1] of 2 patients who developed rhabdomyolysis secondary to hyponatraemia it was suggested that the use of benzodiazepines might have contributed to the rhabdomyolysis. Of 8 reported cases of rhabdomyolysis associated with hyponatraemia, 5 had received benzodiazepines. Rhabdomyolysis associated with intravenous drug abuse of oral temazepam formulations has also been reported.[2]

1. Fernández-Real JM, *et al*. Hyponatremia and benzodiazepines result in rhabdomyolysis. *Ann Pharmacother* 1994; **28:** 1200–1.
2. Deighan CJ, *et al*. Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. *Q J Med* 2000; **93:** 29–33.

Effects on the skin. There have been rare reports of cutaneous reactions to benzodiazepines, including contact dermatitis, fixed drug eruptions, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 2 allergic skin reactions attributed to diazepam among 4707 recipients of the drug[1] giving a reaction rate of 0.4 per 1000 recipients.

1. Bigby M, *et al*. Drug-induced cutaneous reactions. *JAMA* 1986; **256:** 3358–63.

Hypersensitivity. Hypersensitivity reactions including anaphylaxis are very rare after use of diazepam. Reactions have been attributed to the polyoxyl castor oil (p. 2202.3) vehicle used for some parenteral formulations.[1] There is also a report of a type I hypersensitivity reaction to a lipid emulsion formulation of diazepam.[2]

See also Effects on the Skin, above, and Local Reactions, below.

1. Hüttel MS, *et al*. Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid MR). *Br J Anaesth* 1980; **52:** 77–9.
2. Deardon DJ, Bird GLA. Acute (type 1) hypersensitivity to iv Diazemuls. *Br J Anaesth* 1987; **59:** 391.

Local reactions. Ischaemia and gangrene have been reported after accidental intra-arterial injection of diazepam.[1,2] Clinical signs may not occur until several days after the event. Pain and thrombophlebitis after intravenous use may be similarly delayed. Local reactions after intravenous injection have been attributed to the vehicle, and have been seen more often when diazepam is given as a solution in propylene glycol than in polyoxyl castor oil.[3] An emulsion of diazepam in soya oil and water has been associated with a lower incidence of local reactions.[3] Pain and phlebitis may also be caused by precipitation of diazepam at the site of infusion.[4] Arterial spasm in a patient given diazepam intravenously was probably due to pressure from a cuff on the arm being inflated causing extravasation of diazepam out of the vein and into the radial artery.[5]

Local irritation has also occurred after rectal use of diazepam.[6]

For a report of the exacerbation of diazepam-induced thrombophlebitis by penicillamine, see p. 1070.3.

1. Gould JDM, Lingam S. Hazards of intra-arterial diazepam. *BMJ* 1977; **2:** 298–9.
2. Rees M, Dormandy J. Accidental intra-arterial injection of diazepam. *BMJ* 1980; **281:** 289–90.
3. Olesen AS, Hüttel MS. Local reactions to iv diazepam in three different formulations. *Br J Anaesth* 1980; **52:** 609–11.
4. Hussey EK, *et al*. Correlation of delayed peak concentration with infusion-site irritation following diazepam administration. *DICP Ann Pharmacother* 1990; **24:** 678–80.
5. Tin LNW, *et al*. Arterial spasm after administration of diazepam. *Br J Anaesth* 1994; **72:** 139.
6. Hansen HC, *et al*. Local irritation after administration of diazepam in a rectal solution. *Br J Anaesth* 1989; **63:** 287–9.

Overdosage. Impairment of consciousness is fairly rapid in poisoning by benzodiazepines.[1] Deep coma or other manifestations of severe depression of brainstem vital functions are rare; more common is a sleep-like state from which the patient can be temporarily roused by appropriate stimuli. There is usually little or no respiratory depression, and cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension. Since tolerance to benzodiazepines develops rapidly, consciousness is often regained while concentrations of drug in the blood are higher than those which induced coma. Anxiety and insomnia can occur during recovery from acute overdosage, while a full-blown withdrawal syndrome, possibly with major convulsions, can occur in patients who have previously been chronic users.

During the years 1980 to 1989, 1576 fatal poisonings in Britain were attributed to benzodiazepines.[2] Of these, 891 were linked to overdosage with benzodiazepines alone and another 591 to overdosage combined with alcohol. A comparison of these mortality statistics with prescribing data for the same period, to calculate a toxicity index of deaths per million prescriptions, suggested that there were differences between the relative toxicities of individual benzodiazepines in overdosage; flurazepam and temazepam were found to be the most toxic in overdosage. A later study of another 303 cases of benzodiazepine poisoning[3] supported these differences in toxicity as well as pointing to the relative safety of the benzodiazepines in overdosage. See also under Alprazolam, p. 1036.1.

1. Ashton CH, *et al*. Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; **8:** 1–59.
2. Serfaty M, Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry* 1993; **163:** 386–93.
3. Buckley NA, *et al*. Relative toxicity of benzodiazepines in overdose. *BMJ* 1995; **310:** 219–21.

Treatment of Adverse Effects

The treatment of benzodiazepine overdosage is generally symptomatic and supportive. Patients who are asymptomatic after 4 hours are unlikely to develop severe toxicity. Activated charcoal may be given orally if the amount ingested was large (see below) and treatment is within one hour of ingestion. The specific benzodiazepine antagonist, flumazenil (p. 1551.3), is rarely required, and can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients (see p. 1552.1); the UK Poisons Information Service, contra-indicates its use in mixed overdoses. However, use of flumazenil may sometimes provide an alternative to ventilation, particularly in patients with severe respiratory disorders, or in children who are naive to benzodiazepines.

For a discussion of the general principles of the management of acute poisoning, see p. 1537.1.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with benzodiazepines to be uncertain. However, it is suggested that oral activated charcoal may be considered in adults and children if this is given within 1 hour of ingestion and the quantity of benzodiazepine exceeds the following amount, provided that the airway can be protected:

- alprazolam: 100 micrograms/kg
- bromazepam: 1 mg/kg
- chlordiazepoxide: 1.5 mg/kg
- clobazam: 1 mg/kg
- clonazepam: 500 micrograms/kg
- diazepam: 500 micrograms/kg
- flunitrazepam: 100 micrograms/kg
- flurazepam: 2 mg/kg
- loprazolam: 100 micrograms/kg
- lorazepam: 100 micrograms/kg
- lormetazepam: 70 micrograms/kg
- midazolam: 1 mg/kg
- nitrazepam: 400 micrograms/kg
- oxazepam: 3 mg/kg
- prazepam: 1 mg/kg
- temazepam: 2 mg/kg
- triazolam: 50 micrograms/kg

Elderly patients or those with severe hepatic disease may require intervention at a lower amount.

Precautions

Diazepam should be avoided in patients with pre-existing CNS depression or coma, respiratory depression, acute pulmonary insufficiency, myasthenia gravis, or sleep apnoea, and used with care in those with chronic pulmonary insufficiency. Diazepam should be given with care to elderly or debilitated patients who may be more prone to adverse effects. Caution is required in patients with muscle weakness, or those with hepatic or renal impairment, who may require reduced doses; its use should be avoided in severe hepatic impairment. The sedative effects of diazepam are most marked during the first few days of use; affected patients should not drive or operate machinery (see also Driving, p. 1067.1). Monitoring of cardiorespiratory function is generally recommended when benzodiazepines are used for deep sedation.

Diazepam is not appropriate for the treatment of chronic psychosis or for phobic or obsessional states. Diazepam-induced disinhibition may precipitate suicide or aggressive behaviour and it should not, therefore, be used alone to treat depression or anxiety associated with depression; it

should also be used with care in patients with personality disorders. Caution is required in patients with organic brain changes particularly arteriosclerosis. In cases of bereavement, psychological adjustment may be inhibited by diazepam.

Licensed product information for diazepam and other benzodiazepines may advise against their use in patients with glaucoma, but the rationale for this contra-indication is unclear.

For warnings on the use of benzodiazepines during pregnancy and breast feeding, see below.

Dependence characterised by a withdrawal syndrome may develop after regular use of diazepam, even in therapeutic doses for short periods (see p. 1065.1); because of the risk of dependence, diazepam should be used with caution in patients with a history of alcohol or drug abuse.

Since hypotension and apnoea may occur when benzodiazepines are given intravenously it has been recommended that this route should only be used when facilities for reversing respiratory depression with mechanical ventilation are available. Patients should remain supine and under medical supervision for at least one hour after intravenous injection. Intravenous infusion is best undertaken in specialist centres with intensive care facilities where close and constant supervision can be undertaken.

Breast feeding. The last available guidance from the American Academy of Pediatrics considered that benzodiazepine use by nursing mothers for long periods was a cause for concern; anxiolytic drugs appear in breast milk and could conceivably alter CNS function in the infant both in the short and long term.[1] Similarly, in the UK the CSM has recommended[2] that benzodiazepines should not be given to breast-feeding mothers. In one reviewer's opinion[3] the limited distribution into breast milk did not constitute a hazard to the breast-fed infant but the infant should be monitored for sedation and the inability to suckle. Another group has also reported a low incidence of toxicity and adverse effects in the breast-fed infants of mothers taking psychotropic drugs including benzodiazepines.[4] It has been suggested[5] that if a benzodiazepine must be used during breast feeding it would be preferable to use a short-acting drug with minimal distribution into breast milk and inactive metabolites; oxazepam, lorazepam, alprazolam, or midazolam might be suitable.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. CSM/MCA. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=-CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
3. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8:** 461–75.
4. Birnbaum CS, *et al*. Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Abstract: *Pediatrics* 1999; **104:** 104. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e11 (accessed 28/04/04)
5. Chisholm CA, Kuller JA. A guide to the safety of CNS-active agents during breastfeeding. *Drug Safety* 1997; **17:** 127–42.

Cardiovascular disorders. See under Respiratory System Disorders, p. 1068.1.

Driving. Patients affected by drowsiness while taking benzodiazepines should not drive or operate machinery. In the UK, it is an offence to drive while unfit due to the influence of any drug, and benzodiazepines are considered to be the most likely psychotropic medication to impair driving performance, particularly the long-acting compounds.[1] However, it is also noted that drivers with psychiatric illnesses may be safer when well controlled with regular medication than when ill. In addition there are restrictions on holding a driving licence for those who persistently misuse or have a dependency on benzodiazepines.

A meta-analysis[2] of 11 epidemiological studies of the effect of benzodiazepines on driving abilities found that patients taking benzodiazepines had a significantly increased risk of motor vehicle collisions when compared with non-users. Older adults were found to have a risk of collision similar to that in mixed-age groups, despite their increased susceptibility to some effects of benzodiazepines such as daytime fatigue and adverse cognitive effects; this paradox may be explained by less frequent or less risky driving patterns of older adults. The meta-analysis also examined 16 experimental studies of benzodiazepine use (in both healthy subjects and in patients) and performance in driving simulators or on-road tests. No delay or slowing of brake reaction time was found although maintaining road position was more difficult with benzodiazepine use.

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)
2. Rapoport MJ, *et al*. Benzodiazepine use and driving: a meta-analysis. *J Clin Psychiatry* 2009; **70:** 663–73.

The elderly. Old age may alter the distribution, elimination, and clearance of benzodiazepines.[1,2] Metabolic clearance of benzodiazepines metabolised mainly by oxidation appears to be reduced but not clearance of those biotransformed by glucuronide conjugation or nitroreduction. Prolonged half-life in the elderly may be a result of such a decrease in clearance or of an increase in the volume of distribution. The clinical consequence of these changes depends on factors such as dosage schedule and extent of first-pass extraction by the liver.

Irrespective of pharmacokinetic changes, the elderly may have increased sensitivity to acute doses of benzodiazepines.[1-3] Impairment of memory, cognitive function, and psychomotor performance and behaviour disinhibition may be more common than with younger patients.[4] Long-term use commonly exacerbates underlying dementia in elderly patients.[4]

There is evidence to suggest an increased rate of hip fracture due to falls among elderly patients taking benzodiazepines.[5,6] A review[5] of 11 epidemiological studies suggested that benzodiazepine use in the elderly increased the risk of hip fracture; however, results were equivocal with some hospital-based studies finding no significant increase in risk. More consistent results were seen when such studies were excluded: the risk of fracture was increased by about 50% with benzodiazepine use. There was little evidence to suggest that the risk differed between short- and long-acting benzodiazepines although the correlation between hip fracture and benzodiazepine half-life remains controversial. Patients using higher doses and those who had recently started therapy were found to have the highest risk of hip fracture. A later cohort study[6] suggested that the risk is highest during the first 2 weeks of starting therapy and declines thereafter.

The upshot of the pharmacokinetic and pharmacodynamic changes of benzodiazepines in the elderly is that adverse effects may be more frequent in these patients and lower doses are commonly required. If use of a benzodiazepine is considered necessary in elderly patients, a short-acting drug is to be preferred. It should also be remembered that the elderly are at increased risk of sleep-related breathing disorders, such as sleep apnoea and the use of hypnotics such as benzodiazepines should be avoided in these patients (see Respiratory System Disorders, p. 1068.1).

1. Greenblatt DJ, *et al*. Implications of altered drug disposition i n elderly: studies of benzodiazepines. *J Clin Pharmacol* 1989; **29:** 866–72.
2. Greenblatt DJ, *et al*. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly: therapeutic considerations. *Clin Pharmacokinet* 1991; **21:** 165–77 and 262–73.
3. Swift CG. Pharmacodynamics: changes in homeostatic mechanisms, receptor and target organ sensitivity in the elderly. *Br Med Bull* 1990; **46:** 36–52.
4. Juergens SM. Problems with benzodiazepines in elderly patients. *Mayo Clin Proc* 1993; **68:** 818–20.
5. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. *CNS Drugs* 2003; **17:** 825–37.
6. Wagner AK, *et al*. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med* 2004; **164:** 1567–72.

Formulation. Parenteral formulations of diazepam may contain the excipient benzyl alcohol, which has been associated with a fatal toxic syndrome in neonates (see p. 1741.1). Licensed product information recommends that such formulations should not be used in premature babies or neonates. Benzyl alcohol poisoning has also been reported with prolonged use of high-dose intravenous infusions of diazepam.[1]

The excipients polyethylene glycol and propylene glycol are included in some benzodiazepine preparations including those of diazepam and lorazepam and toxicity due to these excipients have also been reported (see Toxicity, under Propylene Glycol, p. 2205.3).

1. López-Herce J, *et al*. Benzyl alcohol poisoning following diazepam intravenous infusion. *Ann Pharmacother* 1995; **29:** 632.

Hangover effects. Long-acting benzodiazepines accumulate in the body to a greater extent than ones with a shorter half-life. Although this might be expected to increase the frequency of daytime sedation and impairment of performance (so-called hangover effects) after a hypnotic dose, such a straightforward relationship has not always occurred in practice.[1]

Anterograde amnesia is more common with short-acting drugs such as triazolam; 'traveller's amnesia' has been used to describe amnesia in persons taking benzodiazepines for sleep disturbances resulting from jet lag.[2]

1. Greenblatt DJ, *et al*. Neurochemical and pharmacokinetic correlates of the clinical action of benzodiazepine hypnotic drugs. *Am J Med* 1990; **88** (suppl 3A): 18S–24S.
2. Meyboom RHB. Benzodiazepines and pilot error. *BMJ* 1991; **302:** 1274–5.

High-altitude disorders. Sleep may be impaired at high altitude due to frequent arousals associated with pronounced oxygen desaturation and periodic breathing. Traditional advice has been that sedatives should not be given at high altitude.[1] Caution may also be warranted at moderate altitudes especially in non-acclimatised climbers.[2] It has been argued that since diazepam, and possibly other sedatives, blunt the hypoxic ventilatory response, sleep hypoxaemia might be exacerbated (see also Respiratory System Disorders, p. 1068.1). A small study[3] has suggested that small doses of a short-acting benzodiazepine, such as 10 mg of temazepam, might actually improve the subjective quality of sleep and reduce episodes of arterial desaturation without changing mean oxygen saturation. Another small study[4] also found that 10-mg doses of temazepam were effective in reducing periodic breathing; daytime performance at altitude was not found to be impaired. However, the possibility of an interaction between acetazolamide taken for prophylaxis or treatment of acute mountain sickness and the benzodiazepine should be borne in mind; ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of triazolam by acetazolamide.[5]

1. Sutton JR, *et al*. Insomnia, sedation, and high altitude cerebral oedema. *Lancet* 1979; **i:** 165.
2. Röggla G, *et al*. Effect of temazepam on ventilatory response at moderate altitude. *BMJ* 2000; **320:** 56.
3. Dubowitz G. Effect of temazepam on oxygen saturation and sleep quality at high altitude: randomised placebo controlled crossover trial. *BMJ* 1998; **316:** 587–9.
4. Nickol AH, *et al*. Temazepam at high altitude reduces periodic breathing without impairing next-day performance: a randomized cross-over double-blind study. *J Sleep Res* 2006; **15:** 445–54.
5. Masuyama S, *et al*. Ondine's curse': side effect of acetazolamide? *Am J Med* 1989; **86:** 637.

Neonates. A retrospective review of records from 63 infants given lorazepam or midazolam in a neonatal intensive-care unit indicated that there were 14 cases of adverse effects associated with benzodiazepine use (seizures in 6 cases, hypotension in 5, and respiratory depression in 3).[1] Seven of these were associated with intravenous bolus doses of lorazepam and the remainder with continuous midazolam infusions. Despite the limitations of the study, the incidence of adverse effects in this group seemed high, and the authors recommended that benzodiazepine use in neonates be accompanied by close monitoring. See also Formulation, above.

1. Ng E, *et al*. Safety of benzodiazepines in newborns. *Ann Pharmacother* 2002; **36:** 1150–5.

Nervous system disorders. Benzodiazepines can reduce cerebral perfusion pressure and blood oxygenation to an extent that results in irreversible neurological damage in patients with head injuries. Consequently, they should be given with great care to such patients.[1,2] Their use should be avoided for the control of seizures in patients with head injuries or other acute neurological lesions as these patients can be managed effectively with phenytoin.

1. Eldridge PR, Punt JAG. Risks associated with giving benzodiazepines to patients with acute neurological injuries. *BMJ* 1990; **300:** 1189–90.
2. Papazian L, *et al*. Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. *Br J Anaesth* 1993; **71:** 267–71.

EPILEPSY. As with other antiepileptic drugs,[1] there have been rare reports of benzodiazepines producing paradoxical exacerbation of seizures in patients with epilepsy.[2-5]

1. Guerrini R, *et al*. Antiepileptic drug-induced worsening of seizures in children. *Epilepsia* 1998; **39** (suppl 3): S2–S10.
2. Prior PF, *et al*. Intravenous diazepam. *Lancet* 1971; **2:** 434–5.
3. Tassinari CA, *et al*. A paradoxical effect: status epilepticus induced by benzodiazepines (Valium and Mogadon). *Electroencephalogr Clin Neurophysiol* 1971; **31:** 182.
4. Di Mario FJ, Clancy RR. Paradoxical precipitation of tonic seizures by lorazepam in a child with atypical absence seizures. *Pediatr Neurol* 1988; **4:** 249–51.
5. Borusiak P, *et al*. Seizure-inducing paradoxical reaction to antiepileptic drugs. *Brain Dev* 2000; **22:** 243–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diazepam as probably porphyrinogenic; it should be prescribed only for compelling indications and precautions should be considered in all patients.[1]

Intravenous diazepam has been used successfully, however, to control status epilepticus occurring after the acute porphyric attack.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Pregnancy. Benzodiazepines have been widely used in pregnant patients.[1] Use of benzodiazepines in the *third trimester* and during *labour* seems to be associated in some infants with neonatal withdrawal symptoms or the floppy infant syndrome. Also a small number exposed *in utero* to benzodiazepines have shown slow development in the early years but by 4 years of age most had developed normally, and for those that had not it was not possible to prove a cause-effect relationship with benzodiazepine

exposure. In a meta-analysis[2] of live births after benzodiazepine use during the *first trimester* of pregnancy, pooled data from cohort studies showed no apparent association between benzodiazepine use and the risk of major malformations or oral cleft alone. There was, however, a small but significantly increased risk of oral cleft according to data from case-control studies. Although benzodiazepines did not appear to be a major human teratogen, use of ultrasonography was advised to rule out visible forms of cleft lip. A more recent study[3] of exposure to benzodiazepines and/or the hypnotics zaleplon, zolpidem, and zopiclone during early pregnancy in 1979 infants and during late pregnancy in 401 infants found an increased risk of premature birth and low birth-weight but no significant effect on intra-uterine growth for each group of infants; the risk of premature birth appeared to be higher in the latter group. Although no increased risk of oral cleft was found in exposed infants, there was a tentative association with the occurrence of pyloric stenosis and small intestinal atresia. A study[4] of 112 infants born to women who attempted suicide with large doses of diazepam (range: 25 to 800mg) did not find an increase in the rate of congenital abnormalities; findings were similar in 10 other pregnant women who took between 60 and 500 mg of medazepam in suicide attempts.[5] Nevertheless, the UK CSM has recommended[6] that women of child-bearing potential prescribed benzodiazepines should be advised to contact the physician about stopping the drug if they intend to become, or suspect that they are, pregnant.

1. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8:** 461–75.
2. Dolovich LR, *et al*. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998; **317:** 839–43.
3. Wikner BN, *et al*. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Safety* 2007; **16:** 1203–10.
4. Gidai J, *et al*. No association found between use of very large doses of diazepam by 112 pregnant women for a suicide attempt and congenital abnormalities in their offspring. *Toxicol Ind Health* 2008; **24:** 29–39.
5. Gidai J, *et al*. A study of the effects of large doses of medazepam used for self-poisoning in 10 pregnant women on fetal development. *Toxicol Ind Health* 2008; **24:** 61–8.
6. CSM/MCA. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)

Respiratory system disorders. Benzodiazepines may affect the control of ventilation during sleep and may worsen sleep apnoea or other sleep-related breathing disorders especially in patients with chronic obstructive pulmonary disease or cardiac failure.[1] Risk factors for sleep apnoea, which often goes undiagnosed, include old age, obesity, male gender, postmenopausal status in women, and a history of heavy snoring. Although benzodiazepines may reduce sleep fragmentation, their long-term use may result in conversion from partial to complete obstructive sleep apnoea in heavy snorers or in short repetitive central sleep apnoea in patients with recent myocardial infarction.

For concerns about the use of benzodiazepines in patients with sleep hypoxaemia due to high altitude see High-altitude Disorders, p. 1067.3.

1. Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990; **88** (suppl 3A): 25S–28S.

Interactions

Enhanced sedation or respiratory and cardiovascular depression may occur if diazepam or other benzodiazepines are given with other drugs that have CNS-depressant properties; these include alcohol, antidepressants, sedative antihistamines, antipsychotics, general anaesthetics, other hypnotics or sedatives, and opioid analgesics. The metabolism of most benzodiazepines is mediated mainly by the cytochrome P450 system, particularly the isoenzymes CYP2C19 and CYP3A4. Hence, adverse effects may also be produced by use with drugs that inhibit or induce or are metabolised by these isoenzymes. Drugs that have been reported to alter the pharmacokinetics of benzodiazepines are discussed in detail below but few of these interactions are likely to be of clinical significance. Benzodiazepines such as alprazolam, diazepam, and midazolam that are metabolised mainly by hepatic microsomal oxidation may be more susceptible to pharmacokinetic changes than those eliminated mainly by glucuronide conjugation such as lorazepam, oxazepam, and temazepam.

Analgesics. The peak plasma concentration of oxazepam was significantly decreased when *diflunisal* was given to 6 healthy subjects, while the renal clearance of the glucuronide metabolite was reduced and its mean elimination half-life increased from 10 to 13 hours.[1] Diflunisal also displaced oxazepam from plasma protein binding sites *in vitro*. *Aspirin* shortened the time to induce anaesthesia with midazolam in 78 patients also possibly due to competition for plasma protein binding sites.[2] *Paracetamol* produced no significant change in plasma concentrations of diazepam or its major metabolite and only marginal changes in urine concentrations in 4 healthy subjects.[3]

Benzodiazepines such as diazepam, lorazepam, and midazolam may be used with opioid analgesics in anaesthetic or analgesic regimens. An additive sedative effect is to be expected[4] but there are also reports of severe respiratory depression with midazolam and *fentanyl*[5] or sudden hypotension with midazolam and fentanyl[6] or *sufentanil*.[7] The clearance of midazolam appears to be reduced by fentanyl,[8] possibly as a result of competitive inhibition of metabolism by the cytochrome P450 isoenzyme CYP3A. Careful monitoring is therefore required during use of midazolam with these opioids and the dose of both drugs may need to be reduced. Synergistic potentiation of the induction of anaesthesia has been reported between midazolam and fentanyl,[9] but one study has suggested that midazolam can reduce the analgesic effects of sufentanil.[10] Pretreatment with *morphine* or *pethidine* has decreased the rate of oral absorption of diazepam. This has been attributed to the effect of opioid analgesics on gastrointestinal motility.[11]

Dextropropoxyphene prolonged the half-life and reduced the clearance of alprazolam but not diazepam or lorazepam in healthy subjects.[12]

Hallucinations have been reported[13] after oral sedation with triazolam in a patient suspected of taking large quantities of *oxycodone* tablets.

1. Van Hecken AM, *et al*. The influence of diflunisal on the pharmacokinetics of oxazepam. *Br J Clin Pharmacol* 1985; **20:** 225–34.
2. Dundee JW, *et al*. Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Mulley BA, *et al*. Interactions between diazepam and paracetamol. *J Clin Pharm* 1978; **3:** 25–35.
4. Tverskoy M, *et al*. Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; **68:** 282–5.
5. Yaster M, *et al*. Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86:** 463–7.
6. Burtin P, *et al*. Hypotension with midazolam and fentanyl in the newborn. *Lancet* 1991; **337:** 1545–6.
7. West JM, *et al*. Sudden hypotension associated with midazolam and sufentanil. *Anesth Analg* 1987; **66:** 693–4.
8. Hase I, *et al*. I.V. fentanyl decreases the clearance of midazolam. *Br J Anaesth* 1997; **79:** 740–3.
9. Ben-Shlomo I, *et al*. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth* 1990; **64:** 45–7.
10. Luger TJ, Morawetz RF. Clinical evidence for a midazolam-sufentanil interaction in patients with major trauma. *Clin Pharmacol Ther* 1991; **49:** 133.
11. Gamble JAS, *et al*. Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
12. Abernethy DR, *et al*. Interaction of propoxyphene with diazepam, alprazolam and lorazepam. *Br J Clin Pharmacol* 1985; **19:** 51–7.
13. Goodchild JH, Donaldson M. Hallucinations and delirium in the dental office following triazolam administration. *Anesth Prog* 2005; **52:** 17–20.

Antiarrhythmics. An interaction between clonazepam and existing therapy with *amiodarone* was suspected in a 78-year-old man who had symptoms of benzodiazepine toxicity 2 months after starting with clonazepam 500 micrograms given at bedtime for restless leg syndrome;[1] symptoms resolved on withdrawal of clonazepam.

1. Witt DM, *et al*. Amiodarone-clonazepam interaction. *Ann Pharmacother* 1993; **27:** 1463–4.

Antibacterials. Both *erythromycin*[1] and *troleandomycin*[2] have been reported to inhibit the hepatic metabolism of triazolam in healthy subjects. Peak plasma-triazolam concentrations were increased, half-life prolonged, and clearance reduced. Troleandomycin prolonged the psychomotor impairment and amnesia produced by triazolam.[2] Loss of consciousness after erythromycin infusion in a child premedicated with midazolam was attributed to a similar interaction,[3] and increases in peak plasma concentrations of midazolam with profound and prolonged sedation have been reported after use of erythromycin.[4] Use of midazolam with erythromycin should be avoided or the dose of midazolam reduced by 50 to 75%. The clearance of midazolam is also reduced by *clarithromycin*, with an approximate doubling of the benzodiazepine's oral bioavailability.[5,6] Licensed product information for *quinupristin/dalfopristin* states that it too may increase plasma concentrations of midazolam. *Roxithromycin* has been reported[7] to have some effects on the pharmacokinetics and pharmacodynamics of midazolam but these changes were not thought clinically relevant. However, it was recommended that as a precaution the lowest possible effective dose of midazolam should be used when given with roxithromycin. In another study[8] *azithromycin* did not appear to have any effect on the metabolism or psychomotor effects of midazolam.

There is an isolated report of significant rises in steady-state blood-midazolam concentration coinciding with dosage of *ciprofloxacin*.[9] Also ciprofloxacin has been reported to reduce diazepam clearance and prolong its terminal half-life,[10] although psychometric tests did not show any changes in diazepam's pharmacodynamics. Ciprofloxacin appears to have no effect on the pharmacokinetics or pharmacodynamics of temazepam.[11]

Isoniazid has been reported to increase the half-life of a single dose of diazepam[12] and triazolam[13] but not of oxazepam[13] in healthy subjects. In contrast, *rifampicin* has decreased the half-life of alprazolam,[14] diazepam,[15] and nitrazepam[16] and more or less abolishes the effects of midazolam[17] and triazolam,[18] while *ethambutol* has no effect on diazepam pharmacokinetics.[12] In patients receiving therapy for tuberculosis with isoniazid, rifampicin, and ethambutol the half-life of a single diazepam dose was shortened and its clearance increased.[12] Thus the enzyme-inducing effect of rifampicin appears to predominate over the enzyme-inhibiting effect of isoniazid.

1. Phillips JP, *et al*. A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol* 1986; **6:** 297–9.
2. Warot D, *et al*. Troleandomycin-triazolam interaction in healthy volunteers: pharmacokinetic and psychometric evaluation. *Eur J Clin Pharmacol* 1987; **32:** 389–93.
3. Hiller A, *et al*. Unconsciousness associated with midazolam and erythromycin. *Br J Anaesth* 1990; **65:** 826–8.
4. Olkkola KT, *et al*. A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; **53:** 298–305.
5. Gorski JC, *et al*. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther* 1998; **64:** 133–43.
6. Quinney SK, *et al*. Interaction between midazolam and clarithromycin in the elderly. *Br J Clin Pharmacol* 2008; **65:** 98–109.
7. Backman JT, *et al*. A pharmacokinetic interaction between roxithromycin and midazolam. *Eur J Clin Pharmacol* 1994; **46:** 551–5.
8. Mattila MJ, *et al*. Azithromycin does not alter the effects of oral midazolam on human performance. *Eur J Clin Pharmacol* 1994; **47:** 49–52.
9. Orko R, *et al*. Intravenous infusion of midazolam, propofol and vecuronium in a patient with severe tetanus. *Acta Anaesthesiol Scand* 1988; **32:** 590–2.
10. Kamali F, *et al*. The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 365–7.
11. Kamali F, *et al*. The influence of ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of temazepam in the young and elderly. *J Clin Pharm Ther* 1994; **19:** 105–9.
12. Ochs HR, *et al*. Diazepam interaction with antituberculous drugs. *Clin Pharmacol Ther* 1981; **29:** 671–8.
13. Ochs HR, *et al*. Differential effect of isoniazid on triazolam oxidation and oxazepam conjugation. *Br J Clin Pharmacol* 1983; **16:** 743–6.
14. Schmider J, *et al*. Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; **9:** 725–34.
15. Ohnhaus EE, *et al*. The effect of antipyrine and rifampin on the metabolism of diazepam. *Clin Pharmacol Ther* 1987; **42:** 148–56.
16. Brockmeyer NH, *et al*. Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.
17. Backman JT, *et al*. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin Pharmacol Ther* 1996; **59:** 7–13.
18. Villikka K, *et al*. Triazolam is ineffective in patients taking rifampicin. *Clin Pharmacol Ther* 1997; **61:** 8–14.

Anticoagulants. Plasma binding of diazepam and desmethyldiazepam (nordazepam) was reduced, and free concentrations increased, immediately after intravenous *heparin*.[1]

Benzodiazepines do not usually interact with oral anticoagulants although there have been rare reports of altered anticoagulant activity.

1. Routledge PA, *et al*. Diazepam and N-desmethyldiazepam redistribution after heparin. *Clin Pharmacol Ther* 1980; **27:** 528–32.

Antidepressants. It has been recommended that the dosage of alprazolam should be reduced when given with *fluvoxamine*, as concomitant use has resulted in doubling of plasma-alprazolam concentrations.[1] Since plasma concentrations of bromazepam[2] and of diazepam[3] also appear to be affected by fluvoxamine, it has been suggested that patients taking fluvoxamine who require a benzodiazepine should preferentially receive one such as lorazepam, which has a different metabolic pathway.[3] Small studies suggest that *fluoxetine* can also increase plasma concentrations of alprazolam.[4,5] Fluoxetine appears to have a similar effect on diazepam but plasma concentrations of diazepam's active metabolite desmethyldiazepam (nordazepam) are reduced and it is considered that the overall effect is likely to be minor.[6] The potential for a clinically significant interaction with *sertraline*, *paroxetine*, or *citalopram* is considered to be less.[7]

The US manufacturers have reported that alprazolam may increase the steady-state plasma concentrations of *imipramine* and *desipramine*, although the clinical significance of such changes is unknown. For a suggestion that benzodiazepines may increase the oxidation of *amineptine* to a toxic metabolite, see Effects on the Liver under Adverse Effects of Amitriptyline, p. 403.3.

Nefazodone has been reported to raise concentrations of alprazolam and triazolam, resulting in increased sedation, and impairment of psychomotor performance.[8,9] Nefazodone may inhibit the oxidative metabolism of alprazolam and triazolam. Raised concentrations of midazolam have similarly been seen when given orally with nefazodone.[10] No interaction was reported with lorazepam, which is mainly eliminated by conjugation.

For reference to an isolated report of hypothermia after administration of diazepam and *lithium*, see p. 431.3.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with benzodiazepines.

1. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994; **46:** 35–9.
2. Van Harten J, *et al.* Influence of multiple-dose administration of fluvoxamine on the pharmacokinetics of the benzodiazepines bromazepam and lorazepam: a randomized crossover study. *Eur Neuropsychopharmacol* 1992; **2:** 381.
3. Perucca E, *et al.* Inhibition of diazepam metabolism by fluvoxamine: a pharmacokinetic study in normal volunteers. *Clin Pharmacol Ther* 1994; **56:** 471–6.
4. Lasher TA, *et al.* Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology (Berl)* 1991; **104:** 323–7.
5. Greenblatt DJ, *et al.* Fluoxetine impairs clearance of alprazolam but not of clonazepam. *Clin Pharmacol Ther* 1992; **52:** 479–86.
6. Lemberger L, *et al.* The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. *Clin Pharmacol Ther* 1988; **43:** 412–19.
7. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33:** 454–71.
8. Greene DS, *et al.* Coadministration of nefazodone (NEF) and benzodiazepines I: pharmacokinetic assessment. *Clin Pharmacol Ther* 1994; **55:** 141.
9. Kroboth P, *et al.* Coadministration of nefazodone and benzodiazepines II: pharmacodynamic assessment. *Clin Pharmacol Ther* 1994; **55:** 142.
10. Lam YWF, *et al.* Effect of antidepressants and ketoconazole on oral midazolam pharmacokinetics. *Clin Pharmacol Ther* 1998; **63:** 229.

Antiepileptics. *Carbamazepine, phenobarbital,* and *phenytoin* are all inducers of hepatic drug-metabolising enzymes. Therefore, in patients receiving long-term therapy with these drugs the metabolism of benzodiazepines may be enhanced. For oral midazolam the effects of carbamazepine or phenytoin may be sufficient to virtually abolish the effects of a standard dose, with a more than 90% reduction in peak serum concentrations of the benzodiazepine.[1] Interactions between benzodiazepines and these antiepileptics are further discussed on p. 517.2 (carbamazepine) and p. 544.2 (phenytoin).

Results from a study[2] involving 66 children and adults given clobazam showed a significant increase in clobazam clearance, leading to accumulation of its principal active metabolite *N*-desmethylclobazam, in the 16 patients also taking *felbamate*. The metabolism of clobazam and *N*-desmethylclobazam was reduced by *stiripentol*, a potent hepatic enzyme inhibitor, resulting in a threefold increase in the plasma concentrations of this metabolite.[3]

Serum-clonazepam concentrations fell markedly in 4 of 8 children who had *lamotrigine* added to their therapy.[4]

Sodium valproate has been reported to displace diazepam from plasma-protein binding sites.[5] Sporadic reports exist of adverse effects when valproate is given with clonazepam[6,7] with the development of drowsiness and, more seriously, absence status epilepticus, but the existence of an interaction is considered to be unproven.[8] Drowsiness has also been reported when valproate was given with nitrazepam.[9] Use of valproate semisodium with lorazepam has resulted in raised concentrations of lorazepam due to inhibition of glucuronidation of lorazepam.[10]

1. Backman JT, *et al.* Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. *Epilepsia* 1996; **37:** 253–7.
2. Contin M, *et al.* Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. *Ther Drug Monit* 1999; **21:** 604–8.
3. Giraud C, *et al.* In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. *Drug Metab Dispos* 2006; **34:** 608–11.
4. Eriksson A-S, *et al.* Pharmacokinetic interactions between lamotrigine and other antiepileptic drugs in children with intractable epilepsy. *Epilepsia* 1996; **37:** 769–73.
5. Dhillon S, Richens A. Valproic acid and diazepam interaction in vivo. *Br J Clin Pharmacol* 1982; **13:** 553–60.
6. Watson WA. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; **300:** 678.
7. Browne TR. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; **300:** 679.
8. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
9. Jeavons PM, *et al.* Treatment of generalized epilepsies of childhood and adolescence with sodium valproate (Epilim). *Dev Med Child Neurol* 1977; **19:** 9–25.
10. Samara EE, *et al.* Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. *J Clin Pharmacol* 1997; **37:** 442–50.

Antifungals. Both a single dose and multiple doses of *ketoconazole* decreased the clearance of a single intravenous injection of chlordiazepoxide.[1] Studies[2-4] have shown that ketoconazole and *itraconazole* can have marked pharmacokinetic interactions with midazolam or triazolam and greatly increase the intensity and duration of action of these benzodiazepines. The AUC for oral midazolam was 15 times greater with ketoconazole and 10 times greater with itraconazole while peak plasma concentrations of midazolam were increased fourfold and threefold, respectively.[2] *Voriconazole* has also been reported[5] to have a similar effect on oral midazolam, increasing its AUC by about tenfold and peak plasma concentration by about fourfold. The AUC for triazolam was 22 times greater with ketoconazole and 27 times with itraconazole;[3] peak plasma concentrations of triazolam were increased about threefold by both antifungals. Ketoconazole has also been reported to have a similar but less pronounced effect on alprazolam,[6] as have itraconazole on brotizolam[7] and etizolam.[8] One study[9] indicated that the risk of interaction persists for several days after cessation of itraconazole therapy. It is recommended that the use of these antifungals with benzodiazepines should be avoided or that the dose of the benzodiazepine should be greatly reduced. A similar but less pronounced interaction occurs between *fluconazole* and oral midazolam[10] or triazolam;[11] nonetheless, the dosage of the benzodiazepine should be reduced during use together. There has also been a suggestion that oral *clotrimazole* lozenges may increase the bioavailability of oral midazolam.[12]

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; **37:** 290–7.
2. Olkkola KT, *et al.* Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **55:** 481–5.
3. Varhe A, *et al.* Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **56:** 601–7.
4. Greenblatt DJ, *et al.* Interaction of triazolam and ketoconazole. *Lancet* 1995; **345:** 191.
5. Saari TI, *et al.* Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Clin Pharmacol Ther* 2006; **79:** 362–70.
6. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; **9:** 725–34.
7. Osanai T, *et al.* Effect of itraconazole on the pharmacokinetics and pharmacodynamics of a single oral dose of brotizolam. *Br J Clin Pharmacol* 2004; **58:** 476–81.
8. Araki K, *et al.* Inhibition of the metabolism of etizolam by itraconazole in humans: evidence for the involvement of CYP3A4 in etizolam metabolism. *Eur J Clin Pharmacol* 2004; **60:** 427–30.
9. Neuvonen PJ, *et al.* The effect of ingestion time interval on the interaction between itraconazole and triazolam. *Clin Pharmacol Ther* 1996; **60:** 326–31.
10. Ahonen J, *et al.* Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. *Eur J Clin Pharmacol* 1997; **51:** 415–19.
11. Varhe A, *et al.* Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. *Br J Clin Pharmacol* 1996; **42:** 465–70.
12. Shord SS, *et al.* Effects of oral clotrimazole troches on the pharmacokinetics of oral and intravenous midazolam. *Br J Clin Pharmacol* 2010; **69:** 160–6.

Antihistamines. A reduction in temazepam metabolism by *diphenhydramine* may have contributed to perinatal death after ingestion of these drugs by the mother.[1]

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; **313:** 1417–18.

Antivirals. The NNRTIs *delavirdine* and *efavirenz*,[1] and HIV-protease inhibitors such as *indinavir, nelfinavir, ritonavir*,[1-4] and *saquinavir*[1,5] may inhibit the hepatic microsomal systems involved in the metabolism of some benzodiazepines. Prolonged use of protease inhibitors may also *induce* these metabolic systems; interactions may therefore be complex and difficult to predict. Monitoring and dosage adjustments for the benzodiazepine may be needed, or the combination should be avoided. Benzodiazepines which should **not** be used with HIV-protease inhibitors include alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, and triazolam.

1. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; **36:** 1598–1613.
2. Greenblatt DJ, *et al.* Extensive impairment of triazolam and alprazolam clearance by short-term low-dose ritonavir: the clinical dilemma of concurrent inhibition and induction. *J Clin Psychopharmacol* 1999; **19:** 293–6.
3. Greenblatt DJ, *et al.* Alprazolam-ritonavir interaction: implications for product labeling. *Clin Pharmacol Ther* 2000; **67:** 335–41.
4. Greenblatt DJ, *et al.* Differential impairment of triazolam and zolpidem clearance by ritonavir. *J Acquir Immune Defic Syndr* 2000; **24:** 129–36.
5. Palkama VJ, *et al.* Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam. *Clin Pharmacol Ther* 1999; **66:** 33–9.

Beta blockers. A clear pattern of interactions between benzodiazepines and beta blockers has not emerged. *Propranolol* may inhibit the metabolism of diazepam[1,2] and bromazepam,[3] and *metoprolol* may inhibit the metabolism of diazepam[1,4] or bromazepam[5] to some extent, although in many cases the effect on pharmacokinetics and pharmacodynamics is unlikely to be of clinical significance. No significant pharmacokinetic interaction has been seen between propranolol and alprazolam,[2] lorazepam,[2] or oxazepam,[6] although the rate of alprazolam absorption may be decreased.[2] Similarly no pharmacokinetic interaction has been seen between *atenolol* and diazepam,[1] *labetalol* and oxazepam,[6] or metoprolol and lorazepam.[5]

1. Hawksworth G, *et al.* Diazepam/β-adrenoceptor antagonist interactions. *Br J Clin Pharmacol* 1984; **17:** 69S–76S.
2. Ochs HR, *et al.* Propranolol interactions with diazepam, lorazepam, and alprazolam. *Clin Pharmacol Ther* 1984; **36:** 451–5.
3. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
4. Klotz U, Reimann IW. Pharmacokinetic and pharmacodynamic interaction study of diazepam and metoprolol. *Eur J Clin Pharmacol* 1984; **26:** 223–6.
5. Scott AK, *et al.* Interaction of metoprolol with lorazepam and bromazepam. *Eur J Clin Pharmacol* 1991; **40:** 405–9.
6. Sonne J, *et al.* Single dose pharmacokinetics and pharmacodynamics of oral oxazepam during concomitant administration of propranolol and labetalol. *Br J Clin Pharmacol* 1990; **29:** 33–7.

Calcium-channel blockers. Peak plasma concentrations of midazolam were doubled and the elimination half-life of midazolam prolonged when given to healthy subjects receiving *diltiazem* or *verapamil*.[1] A similar interaction has been found between diltiazem and triazolam.[2,3] Concomitant use should be avoided or the dose of these benzodiazepines reduced.

1. Backman JT, *et al.* Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br J Clin Pharmacol* 1994; **37:** 221–5.
2. Varhe A, *et al.* Diltiazem enhances the effects of triazolam by inhibiting its metabolism. *Clin Pharmacol Ther* 1996; **59:** 369–75.
3. Kosuge K, *et al.* Enhanced effect of triazolam with diltiazem. *Br J Clin Pharmacol* 1997; **43:** 367–72.

Ciclosporin. *In-vitro* studies suggested that ciclosporin could inhibit the metabolism of midazolam.[1] However, blood-ciclosporin concentrations in patients given ciclosporin to prevent graft rejection were considered too low to result in such an interaction.

1. Li G, *et al.* Is cyclosporin A an inhibitor of drug metabolism? *Br J Clin Pharmacol* 1990; **30:** 71–7.

Clonidine. Anxiety was reduced and sedation was enhanced when clonidine was given with flunitrazepam for premedication.[1]

1. Kulka PJ, *et al.* Sedative and anxiolytic interactions of clonidine and benzodiazepines. *Br J Anaesth* 1994; **72** (suppl 1): 81.

Clozapine. For reports of cardiorespiratory collapse and other adverse effects in patients taking benzodiazepines and clozapine, see p. 1062.1.

Corticosteroids. The metabolism of midazolam was increased in chronic users of *glucocorticoids*,[1] perhaps due to the induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. The changes were not considered clinically relevant if midazolam was given intravenously, but might be so if it was given orally.

1. Nakajima M, *et al.* Effects of chronic administration of glucocorticoid on midazolam pharmacokinetics in humans. *Ther Drug Monit* 1999; **21:** 507–13.

Digoxin. For the effects of alprazolam and diazepam on digoxin pharmacokinetics, see p. 1357.1.

Disulfiram. Evidence from healthy and alcoholic subjects suggests that chronic use of disulfiram can inhibit the metabolism of chlordiazepoxide and diazepam leading to a prolonged half-life and reduced clearance; there was little effect on the disposition of oxazepam.[1] No significant pharmacokinetic interaction occurred between disulfiram and alprazolam in alcoholic patients.[2] Temazepam toxicity, attributed to use of disulfiram with temazepam, has been reported.[3]

See also under Disulfiram, p. 2496.3.

1. MacLeod SM, *et al.* Interaction of disulfiram with benzodiazepines. *Clin Pharmacol Ther* 1978; **24:** 583–9.
2. Diquet B, *et al.* Lack of interaction between disulfiram and alprazolam in alcoholic patients. *Eur J Clin Pharmacol* 1990; **38:** 157–60.
3. Hardman M, *et al.* Temazepam toxicity precipitated by disulfiram. *Lancet* 1994; **344:** 1231–2.

Gastrointestinal drugs. *Antacids* have variable effects on the absorption of benzodiazepines[1-6] but any resulting interaction is unlikely to be of major clinical significance.

Several studies, usually involving single doses of diazepam given to healthy subjects, have shown that *cimetidine* can inhibit the hepatic metabolism of diazepam.[7-10] The clearance of diazepam has generally been decreased and the half-life prolonged. Some studies have also shown impaired metabolic clearance of the major metabolite, desmethyldiazepam (nordazepam). Cimetidine has also been reported to inhibit the metabolism of other benzodiazepines (generally those metabolised by oxidation) including alprazolam,[11,12] bromazepam,[13] chlordiazepoxide,[14] clobazam,[15,16] flurazepam,[17] midazolam,[18] nitrazepam,[19] and triazolam.[11,12] Cimetidine does not appear to inhibit the hepatic metabolism of lorazepam,[17] oxazepam,[17] or temazepam.[20] The clinical significance of these interactions between cimetidine and benzodiazepines remains dubious, and little effect on cognitive function or degree of sedation has been shown.

Most studies have failed to find an effect of *ranitidine* on the hepatic metabolism of diazepam,[21-24] although one study[25] reported an increase in the bioavailability of a single oral dose of midazolam, and considered that an effect on hepatic clearance was more likely than an effect on absorption. These results were consistent with those of another study which showed an enhanced sedative effect of midazolam in patients pretreated with ranitidine.[26] The bioavailability of triazolam has also been increased by ranitidine.[27] Ranitidine has been reported to have no effect on the pharmacokinetics of lorazepam[22] or on the sedative effect of temazepam.[26]

Famotidine[10] or *nizatidine*[24] do not appear to inhibit the hepatic metabolism of diazepam.

Oral diazepam was absorbed more rapidly after intravenous *metoclopramide*.[28] Enhanced motility of the gastrointestinal tract was implicated. *Cisapride* may also accelerate the absorption of diazepam.[29]

Studies of continuous *omeprazole* dosage on the pharmacokinetics of a single intravenous dose of diazepam in healthy subjects indicate inhibition of diazepam metabolism in a similar manner to cimetidine.[30,31] Omeprazole decreases the clearance and prolongs the elimination half-life of diazepam; in addition both the formation and elimination of desmethyldiazepam appear to be decreased. The effects may be greater in rapid than in slow metabolisers of omeprazole[32] and vary between ethnic groups.[33] Licensed product information for *esomeprazole* states that it too may decrease diazepam clearance. The clinical significance of these interactions is unknown; however, product information for omeprazole and esomeprazole suggests that dosage reduction of diazepam may be necessary. *Lansoprazole*[34] and *pantoprazole*[35] have been reported not to affect the pharmacokinetics of diazepam.

1. Nair SG, *et al*. The influence of three antacids on the absorption and clinical action of oral diazepam. *Br J Anaesth* 1976; **48:** 1175–80.
2. Greenblatt DJ, *et al*. Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. *Clin Pharmacol Ther* 1976; **19:** 234–9.
3. Chun AHC, *et al*. Effect of antacids on absorption of clorazepate. *Clin Pharmacol Ther* 1977; **22:** 329–35.
4. Shader RI, *et al*. Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* 1978; **24:** 308–15.
5. Greenblatt DJ, *et al*. Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther* 1978; **24:** 600–9.
6. Shader RI, *et al*. Steady-state plasma desmethyldiazepam during long-term clorazepate use: effect of antacids. *Clin Pharmacol Ther* 1982; **31:** 180–3.
7. Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. *N Engl J Med* 1980; **302:** 1012–14.
8. Gough PA, *et al*. Influence of cimetidine on oral diazepam elimination with measurement of subsequent cognitive change. *Br J Clin Pharmacol* 1982; **14:** 739–42.
9. Greenblatt DJ, *et al*. Clinical importance of the interaction of diazepam and cimetidine. *N Engl J Med* 1984; **310:** 1639–43.
10. Locniskar A, *et al*. Interaction of diazepam with famotidine and cimetidine, two H_2-receptor antagonists. *J Clin Pharmacol* 1986; **26:** 299–303.
11. Abernethy DR, *et al*. Interaction of cimetidine with the triazolobenzodiazepines alprazolam and triazolam. *Psychopharmacology (Berl)* 1983; **80:** 275–8.
12. Pourbaix S, *et al*. Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1985; **23:** 447–51.
13. Ochs HR, *et al*. Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
14. Desmond PV, *et al*. Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann Intern Med* 1980; **93:** 266–8.
15. Grigoleit H-G, *et al*. Pharmacokinetic aspects of the interaction between clobazam and cimetidine. *Eur J Clin Pharmacol* 1983; **25:** 139–42.
16. Pullar T, *et al*. The effect of cimetidine on the single dose pharmacokinetics of oral clobazam and N-desmethylclobazam. *Br J Clin Pharmacol* 1987; **23:** 317–21.
17. Greenblatt DJ, *et al*. Interaction of cimetidine with oxazepam, lorazepam, and flurazepam. *J Clin Pharmacol* 1984; **24:** 187–93.
18. Sanders LD, *et al*. Interaction of H2-receptor antagonists and benzodiazepine sedation: a double-blind placebo-controlled investigation of the effects of cimetidine and ranitidine on recovery after intravenous midazolam. *Anaesthesia* 1993; **48:** 286–92.
19. Ochs HR, *et al*. Cimetidine impairs nitrazepam clearance. *Clin Pharmacol Ther* 1983; **34:** 227–30.
20. Greenblatt DJ, *et al*. Noninteraction of temazepam and cimetidine. *J Pharm Sci* 1984; **73:** 399–401.
21. Klotz U, *et al*. Effect of ranitidine on the steady state pharmacokinetics of diazepam. *Eur J Clin Pharmacol* 1983; **24:** 357–60.
22. Abernethy DR, *et al*. Ranitidine does not impair oxidative or conjugative metabolism: noninteraction with antipyrine, diazepam, and lorazepam. *Clin Pharmacol Ther* 1984; **35:** 188–92.
23. Fee JPH, *et al*. Diazepam disposition following cimetidine or ranitidine. *Br J Clin Pharmacol* 1984; **17:** 617P–18P.
24. Klotz U, *et al*. Nocturnal doses of ranitidine and nizatidine do not affect the disposition of diazepam. *J Clin Pharmacol* 1987; **27:** 210–12.
25. Fee JPH, *et al*. Cimetidine and ranitidine increase midazolam bioavailability. *Clin Pharmacol Ther* 1987; **41:** 80–4.
26. Wilson CM, *et al*. Effect of pretreatment with ranitidine on the hypnotic action of single doses of midazolam, temazepam and zopiclone. *Br J Anaesth* 1986; **58:** 483–6.
27. Vanderveen RP, *et al*. Effect of ranitidine on the disposition of orally and intravenously administered triazolam. *Clin Pharm* 1991; **10:** 539–43.
28. Gamble JAS, *et al*. Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
29. Bateman DN. The action of cisapride on gastric emptying and the pharmacokinetics of oral diazepam. *Eur J Clin Pharmacol* 1986; **30:** 205–8.
30. Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. *Lancet* 1984; **i:** 969.
31. Andersson T, *et al*. Effect of omeprazole and cimetidine on plasma diazepam levels. *Eur J Clin Pharmacol* 1990; **39:** 51–4.
32. Andersson T, *et al*. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin Pharmacol Ther* 1990; **47:** 79–85.
33. Caraco Y, *et al*. Interethnic difference in omeprazole's inhibition of diazepam metabolism. *Clin Pharmacol Ther* 1995; **58:** 62–72.
34. Lefebvre RA, *et al*. Influence of lansoprazole treatment on diazepam plasma concentrations. *Clin Pharmacol Ther* 1992; **52:** 458–63.
35. Gugler R, *et al*. Lack of pharmacokinetic interaction of pantoprazole with diazepam in man. *Br J Clin Pharmacol* 1996; **42:** 249–52.

General anaesthetics. A synergistic interaction has been found for the hypnotic effects of midazolam and *thiopental*.[1] Although midazolam failed to produce anaesthesia at the doses used, the drug caused a twofold increase in the anaesthetic potency of thiopental. Similar synergistic interactions have been seen between midazolam and both *methohexital*[2] and *propofol*.[3,4] The interaction between midazolam and propofol could not be explained solely by alteration in free-plasma concentration of either drug,[5] although a later study[6] does suggest that propofol reduces the clearance of midazolam via its inhibitory effects on the metabolism of midazolam by the cytochrome P450 isoenzyme CYP3A4. It has been reported that midazolam can produce a marked reduction in the concentration of *halothane* required for anaesthesia.[7]

1. Short TG, *et al*. Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; **66:** 13–19.
2. Tverskoy M, *et al*. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth* 1989; **63:** 109–12.
3. McClune S, *et al*. Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
4. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
5. Teh J, *et al*. Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.
6. Hamaoka N, *et al*. Propofol decreases the clearance of midazolam by inhibiting CYP3A4: an in vivo and in vitro study. *Clin Pharmacol Ther* 1999; **66:** 110–7.
7. Inagaki Y, *et al*. Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–7.

Grapefruit juice. Grapefruit juice has been reported to be able to increase the bioavailability of oral diazepam,[1] midazolam,[2,3] quazepam,[4] and triazolam[3-5] and to raise peak plasma concentrations. Repeated ingestion of grapefruit juice increased the concentration and half-life of triazolam to a greater extent than a single ingestion.[6] The clinical significance of such interactions may be of little or no practical importance.

1. Ozdemir M, *et al*. Interaction between grapefruit juice and diazepam in humans. *Eur J Drug Metab Pharmacokinet* 1998; **23:** 55–9.
2. Kupferschmidt HHT, *et al*. Interaction between grapefruit juice and midazolam in humans. *Clin Pharmacol Ther* 1995; **58:** 20–8.
3. Vanakoski J, *et al*. Grapefruit juice does not enhance the effects of midazolam and triazolam in man. *Eur J Clin Pharmacol* 1996; **50:** 501–8.
4. Sugimoto K, *et al*. Interaction between grapefruit juice and hypnotic drugs: comparison of triazolam and quazepam. *Eur J Clin Pharmacol* 2006; **62:** 209–15.
5. Hukkinen SK, *et al*. Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. *Clin Pharmacol Ther* 1995; **58:** 127–31.
6. Lilja JJ, *et al*. Effect of grapefruit juice dose on grapefruit juice-triazolam interaction: repeated consumption prolongs triazolam half-life. *Eur J Clin Pharmacol* 2000; **56:** 411–15.

Kava. A patient whose medication included alprazolam, cimetidine, and terazosin became lethargic and disoriented after starting to take kava.[1] An interaction between kava and the benzodiazepine was suspected.

1. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; **125:** 940–1.

Levodopa. For reference to the effects of benzodiazepines on levodopa, see Anxiolytics, p. 907.3.

Neuromuscular blockers. For reference to the effect of diazepam on neuromuscular blockade, see Benzodiazepines, under the Interactions of Atracurium, p. 2032.2.

Oral contraceptives. Some studies with alprazolam,[1] chlordiazepoxide,[2] and diazepam[3] have supported suggestions that oral contraceptives may inhibit the biotransformation of benzodiazepines metabolised by oxidation, although no significant pharmacokinetic alterations have occurred with clotiazepam[4] or triazolam.[1] The biotransformation of benzodiazepines metabolised by conjugation, such as lorazepam, oxazepam, or temazepam, may be enhanced[1,2] or unchanged.[5] No consistent correlation has been seen between the above pharmacokinetic changes and clinical effects. It has been noted[6] that psychomotor impairment due to oral diazepam was greater during the menstrual pause than during the 21-daily oral contraceptive cycle. This may have been due to an effect of oral contraceptives on diazepam absorption. Another study[7] noted that women taking oral contraceptives appeared to be more sensitive to psychomotor impairment after single oral doses of alprazolam, lorazepam, or triazolam, than controls. The effects of temazepam were minimal in both groups. Alterations in sedative or amnesic effect could not be established with any certainty.

1. Stoehr GP, *et al*. Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; **36:** 683–90.
2. Patwardhan RV, *et al*. Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. *Hepatology* 1983; **3:** 248–53.
3. Abernethy DR, *et al*. Impairment of diazepam metabolism by low-dose estrogen-containing oral-contraceptive steroids. *N Engl J Med* 1982; **306:** 791–2.
4. Ochs HR, *et al*. Disposition of clotiazepam: influence of age, sex, oral contraceptives, cimetidine, isoniazid and ethanol. *Eur J Clin Pharmacol* 1984; **26:** 55–9.
5. Abernethy DR, *et al*. Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther* 1983; **33:** 628–32.
6. Ellinwood EH, *et al*. Effects of oral contraceptives on diazepam-induced psychomotor impairment. *Clin Pharmacol Ther* 1984; **35:** 360–6.
7. Kroboth PD, *et al*. Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. *Clin Pharmacol Ther* 1985; **38:** 525–32.

Penicillamine. Phlebitis associated with intravenous diazepam resolved with local heat but recurred on two separate occasions after oral penicillamine.[1]

1. Brandstetter RD, *et al*. Exacerbation of intravenous diazepam-induced phlebitis by oral penicillamine. *BMJ* 1981; **283:** 525.

Probenecid. Probenecid increased the half-life of intravenous lorazepam in 9 healthy subjects.[1] Probenecid was considered to impair glucuronide formation selectively and thus the clearance of drugs like lorazepam. Probenecid has also shortened the time to induce anaesthesia with midazolam in 46 patients.[2] The effect was considered to be due to competition for plasma protein binding sites. Probenecid has also been reported[3] to reduce the clearance of nitrazepam but not of temazepam.

1. Abernethy DR, *et al*. Probenecid inhibition of acetaminophen and lorazepam glucuronidation. *Clin Pharmacol Ther* 1984; **35:** 224.
2. Dundee JW, *et al*. Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Brockmeyer NH, *et al*. Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.

Smooth muscle relaxants. Intracavernosal *papaverine* produced prolonged erection in 2 patients who had been given intravenous diazepam as an anxiolytic before the papaverine.[1]

1. Vale JA, *et al*. Papaverine, benzodiazepines, and prolonged erections. *Lancet* 1991; **337:** 1552.

Tobacco smoking. The Boston Collaborative Drug Surveillance Program reported drowsiness as an adverse effect of diazepam or chlordiazepoxide less frequently in smokers than non-smokers.[1] Pharmacokinetic studies have, however, been divided between those indicating that smoking induces the hepatic metabolism of benzodiazepines and those showing no effect on benzodiazepine pharmacokinetics.[2] Hence, diminished end-organ responsiveness may in part account for the clinical effects seen. Taking large amounts of xanthine-containing beverages as well may decrease any enzyme-inducing effects of smoking.[3]

1. Boston Collaborative Drug Surveillance Program, Boston University Medical Center. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* 1973; **288:** 277–80.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
3. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.

Xanthines. There are reports of *aminophylline* given intravenously reversing the sedation from intravenous diazepam,[1-3] although not always completely[2] nor as effectively as flumazenil.[4] Blockade of adenosine receptors by aminophylline has been postulated as the mechanism of this interaction.[3,5]

Xanthine-containing beverages may be expected to decrease the incidence of benzodiazepine-induced drowsiness because of their CNS-stimulating effects and their ability to induce hepatic drug-metabolising enzymes. However, decreased drowsiness has only sometimes been seen and the actions of xanthines may themselves be decreased by heavy tobacco smoking.[6,7]

1. Arvidsson SB, *et al*. Aminophylline antagonises diazepam sedation. *Lancet* 1982; **ii:** 1467.
2. Kleindienst G, Usinger P. Diazepam sedation is not antagonised completely by aminophylline. *Lancet* 1984; **i:** 113.
3. Niemand D, *et al*. Aminophylline inhibition of diazepam sedation: is adenosine blockade of GABA-receptors the mechanism? *Lancet* 1984: **i:** 463–4.
4. Sibai AN, *et al*. Comparison of flumazenil with aminophylline to antagonise midazolam in elderly patients. *Br J Anaesth* 1991; **66:** 591–5.
5. Henauer SA, *et al*. Theophylline antagonises diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol* 1983; **25:** 743–7.
6. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.
7. Ghoneim MM, *et al*. Pharmacokinetic and pharmacodynamic interactions between caffeine and diazepam. *J Clin Psychopharmacol* 1986; **6:** 75–80.

Pharmacokinetics

Diazepam is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30 to 90 minutes of oral doses. Diazepam is rapidly absorbed when given as a rectal solution; peak plasma concentrations occur after about 10 to 30 minutes. Absorption may be erratic after intramuscular injection and lower peak plasma concentrations may be obtained compared with those after oral doses. Diazepam is highly lipid soluble and crosses the blood-brain barrier; it acts promptly on the brain, and its initial effects decrease rapidly as it is redistributed into fat depots and tissues.

Diazepam has a biphasic half-life with an initial rapid distribution phase and a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2 to 5 days of its principal active metabolite, desmethyldiazepam (nordazepam, p. 1089.3). Diazepam and desmethyldiazepam accumulate on repeated

dosage and the relative proportion of desmethyldiazepam in the body increases with long-term use. No simple correlation has been found between plasma concentrations of diazepam or its metabolites and their therapeutic effect.

Diazepam is extensively metabolised in the liver, notably via the cytochrome P450 isoenzymes CYP2C19 and CYP3A4; in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. It is excreted in the urine, mainly in the form of free or conjugated metabolites. Diazepam is 98 to 99% bound to plasma proteins.

The plasma elimination half-life of diazepam and/or its metabolites is prolonged in neonates, in the elderly, and in patients with hepatic or renal impairment. In addition to crossing the blood-brain barrier, diazepam and its metabolites also cross the placental barrier and are distributed into breast milk.

Reviews.

1. Bailey L, *et al.* Clinical pharmacokinetics of benzodiazepines. *J Clin Pharmacol* 1994; **34:** 804–11.
2. Fukasawa T, *et al.* Effects of genetic polymorphism of cytochrome P450 enzymes on the pharmacokinetics of benzodiazepines. *J Clin Pharm Ther* 2007; **32:** 333–41.

Absorption and plasma concentrations. *CHRONIC ORAL ADMINISTRATION.* In 36 patients given diazepam 2 to 30 mg daily for periods from one month to 10 years, plasma-diazepam concentrations were directly related to dose and inversely related to age.[1] There was a close association between the plasma concentrations of diazepam and its metabolite desmethyldiazepam and both concentrations were independent of the duration of therapy. Plasma-diazepam concentration ranges were 20 nanograms/mL to 1.01 micrograms/mL, and plasma-desmethyldiazepam concentration ranges were 55 nanograms/mL to 1.765 micrograms/mL. A similar study[2] reached the same general conclusions.

1. Rutherford DM, *et al.* Plasma concentrations of diazepam and desmethyldiazepam during chronic diazepam therapy. *Br J Clin Pharmacol* 1978; **6:** 69–73.
2. Greenblatt DJ, *et al.* Plasma diazepam and desmethyldiazepam concentrations during long-term diazepam therapy. *Br J Clin Pharmacol* 1981; **1:** 35–40.

RECTAL. In 6 *adults* given diazepam 10 mg orally or as a solution (*Valium injection; Roche, UK*) by rectum, mean bioavailability was 76 and 81%, respectively compared with the same dose by intravenous injection.[1] In a second study by the same group, bioavailability was considered to be lower with diazepam suppositories than with the solution given rectally.[1] Studies support the use of rectal solution rather than suppositories in children.[2,3]

1. Dhillon S, *et al.* Bioavailability of diazepam after intravenous, oral and rectal administration in adult epileptic patients. *Br J Clin Pharmacol* 1982; **13:** 427–32.
2. Dhillon S, *et al.* Rectal absorption of diazepam in epileptic children. *Arch Dis Child* 1982; **57:** 264–7.
3. Sonander H, *et al.* Effects of the rectal administration of diazepam. *Br J Anaesth* 1985; **57:** 578–80.

Distribution into breast milk. Concentrations of diazepam and desmethyldiazepam transferred from mother to infant via breast milk have been measured.[1,2]

See also under Precautions, p. 1067.1.

1. Erkkola R, Kanto J. Diazepam and breast-feeding. *Lancet* 1972; **i:** 1235–6.
2. Brandt R. Passage of diazepam and desmethyldiazepam into breast milk. *Arzneimittelforschung* 1976; **26:** 454–7.

The elderly. For mention of pharmacokinetics in the elderly, see under Precautions, p. 1067.2.

Hepatic impairment. For reference to the altered pharmacokinetics of diazepam in patients with hepatic impairment, see Administration in Hepatic Impairment, p. 1064.2.

Metabolism. Most benzodiazepines are highly lipophilic compounds requiring biotransformation before excretion from the body, and many form active metabolites that affect the duration of action. The benzodiazepines may be classified as long-, intermediate-, or short-acting compounds.[1]

- **Long-acting** benzodiazepines are either N_1-desalkyl derivatives (*delorazepam* and *nordazepam*) or are oxidised in the liver to N_1-desalkyl derivatives (benzodiazepines so oxidised include *chlordiazepoxide, clobazam, clorazepate, cloxazolam, diazepam, flurazepam, halazepam, ketazolam, medazepam, oxazolam, pinazepam, prazepam,* and *quazepam*). Clorazepate and prazepam may be considered as prodrugs since the metabolite is the expected active principle. Both parent drug and metabolites contribute to the activity of the other long-acting drugs. Further biotransformation of N_1-desalkylated metabolites proceeds much more slowly than for the parent drug, and they therefore accumulate in the body after a few days of treatment. The rate-limiting step of their metabolism (with the exception of the 1,5-derivatives) is C3-hydroxylation to the pharmacologically active oxazepam or its 2′-halogenated analogues.
- **Intermediate-acting** benzodiazepines are 7-nitrobenzodiazepines such as *clonazepam, flunitrazepam,* and *nitrazepam* which are metabolised by nitroreduction with no important known active metabolites.

The metabolites of long- and intermediate-acting benzodiazepines require conjugation before excretion in the urine.

- **Short-acting** benzodiazepines include the C3-hydroxylated benzodiazepines such as *lorazepam, lormetazepam, oxazepam,* and *temazepam* which undergo rapid conjugation with glucuronic acid to water-soluble inactive metabolites that are excreted in the urine, and drugs such as *alprazolam, brotizolam, estazolam, etizolam, midazolam, tofisopam,* and *triazolam* which require oxidation involving aliphatic hydroxylation before subsequent conjugation. Although these hydroxylated metabolites may retain pharmacological activity, they are unlikely to contribute significantly to clinical activity because of their negligible plasma concentrations and rapid inactivation by glucuronidation.

Drug-metabolising capacity is influenced by many factors including genetics, age, gender, endocrine and nutritional status, smoking, disease, and concurrent drug therapy. This results in wide interindividual variation in both parent drug concentrations and metabolite-to-parent drug ratios.

1. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; **18:** 434–59.

Pregnancy. The passage of diazepam across the placenta depends in part on the relative degrees of protein binding in mother and fetus. This in turn is influenced by factors such as stage of pregnancy and plasma concentrations of free fatty acids in mother and fetus.[1-6] Adverse effects may persist in the neonate for several days after birth because of immature drug-metabolising enzymes. Competition between diazepam and bilirubin for protein binding sites could result in hyperbilirubinaemia in the neonate.[7]

For further adverse effects associated with the use of benzodiazepines during pregnancy, see under Precautions, p. 1067.3.

1. Idänpään-Heikkilä J, *et al.* Placental transfer and fetal metabolism of diazepam-Cl^{14} in early human pregnancy. *Clin Pharmacol Ther* 1971; **12:** 293.
2. Kanto J, *et al.* Accumulation of diazepam and N-demethyldiazepam in the fetal blood during the labour. *Ann Clin Res* 1973; **5:** 375–9.
3. Lee JN, *et al.* Serum protein binding of diazepam in maternal and foetal serum during pregnancy. *Br J Clin Pharmacol* 1982; **14:** 551–4.
4. Kuhnz W, Nau H. Differences in in vitro binding of diazepam and N-desmethyldiazepam to maternal and fetal plasma proteins at birth: relation to free fatty acid concentration and other parameters. *Clin Pharmacol Ther* 1983; **34:** 220–6.
5. Nau H, *et al.* Decreased serum protein binding of diazepam and its major metabolite in the neonate during the first postnatal week related to increased free fatty acid levels. *Br J Clin Pharmacol* 1984; **17:** 92–8.
6. Ridd MJ, *et al.* The disposition and placental transfer of diazepam in cesarean section. *Clin Pharmacol Ther* 1989; **45:** 506–12.
7. Notarianni LJ. Plasma protein binding of drugs in pregnancy and in neonates. *Clin Pharmacokinet* 1990; **18:** 20–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cuadel; Daiv; Dezepan; Diactal; Dipezona; Fabotranil†; Lembrol; Plidan; Plidex T; Psicotop; Rupediz; Saromet; Valium; ***Austral.***: Antenex; Ducene†; Ranzepam; Valium; Valpam; ***Austria***: Gewacalm; Psychopax; Stesolid; Valium; ***Belg.***: Valium; ***Braz.***: Ansilive; Calmociteno; Compaz; Diazefast; Dienpax; Dienzepax; Kiatrium; Letansil†; Menostress; Noan; Pazolini†; Relapax; Santiazepam; Somaplus; Uni Diazepax; Valium; Vetansil†; ***Canad.***: Diastat; Diazemuls; Novo-Dipam; Valium; Vivol†; ***Chile***: Pacinax†; ***Cz.***: Apaurin; Stesolid†; ***Denm.***: Apozepam; Hexalid; Stesolid; Valaxona†; ***Fin.***: Diapam; Medipam; Stesolid; ***Fr.***: Valium; ***Ger.***: Diazep†; Faustan; Stesolid†; Valiquid; Valium; Valocordin-Diazepam; ***Gr.***: Apollonset; Atarviton; Mozepam; Nivalen; Reval; Stedon; Stesolid; ***Hong Kong***: Antenex†; Diazemuls; Kratium; Stesolid; Synium†; Valpam; ***Hung.***: Seduxen; Stesolid†; ***India***: Alzepam; Anxol; Calmod; Calmpose; Camrelease-TR; Diaclam; Diaze; Diazecalm; Dipax; Direc-2; Dizep-P; Dizep; Elcion; Juniz; Lakpam; Lori; Paciquil; Paxum; Placidox; Rec-DZ; Valium; Zepose; ***Indon.***: Mentalium†; Stesolid; Trazep; Valdimex; Valisanbe; Valium; ***Irl.***: Anxicalm; Diazemuls; Rimapam†; Stesolid; Valium; ***Israel***: Assival; Diaz†; Stesolid†; ***Ital.***: Ansiolin; Diazemuls; Micronoan; Noan; Tranquirit; Valium; Vatran; ***Malaysia***: Diapine; Diapo; Valium; ***Mex.***: Alboral; Arzepam; Benzyme†; Ifa-Fonal; Laxyl†; Onapan†; Ortopsique; Relazepam; Sunzepan; Valium; Zepan†; ***Neth.***: Diazemuls; Stesolid; ***Norw.***: Stesolid; Valium; Vival; ***NZ***: D-Pam; Diazemuls†; Propam†; Stesolid; ***Philipp.***: Anxiol; Nixtensyn; Pamizep; Trankil; Valium; Valzepam; ***Pol.***: Neorelium; Relanium; Relsed; ***Port.***: Bialzepam; Metamidol; Stesolid; Unisedil; Valium; ***Rus.***: Apaurin (Апаурин); Relanium (Реланиум); Relium (Релиум); Seduxen (Седуксен); Sibazon (Сибазон); ***S.Afr.***: Benzopin†; Betapam; Calmpose†; Doval; Pax; Scripto-Pam; Tranject; Valium; ***Singapore***: Diapine; Diapo; Stesolid; ***Spain***: Aneurol; Gobanal†; Pacium†; Stesolid; Valium; Vincosedan; ***Swed.***: Stesolid; ***Switz.***: Paceum; Psychopax; Stesolid; Valium; ***Thai.***: A-Zerax; Azepam†; Calmipam; Diadon; Diamed; Diano; Diapam; Diapine; Diaz; Diazepion; Dilium; Dimed; Dipam; Ditran; Divopan; Dizan†; Dizep; Dizepam; Dizzepam; DZP2; Manodiazo; Manolium; Med-Zepam; Monozide; Pam; Popam; Ropam; Sipam; Tranolan; V Day Zepam; Valax; Valenium; Valium†; Vason†; Vescopam; Vispam; Vomed; Vorapam; Winopam; Zam; Zepam; Zepaxid; Zopam; ***Turk.***: Diapam; Diazem; Lizan; Nervium; ***UK***: Dialar; Diazemuls; Rimapam; Stesolid; Tensium; ***Ukr.***: Relanium (Реланиум); Seduxen (Седуксен)†; ***USA***: Diastat; Valium; ***Venez.***: Talema; Telsomet.

Multi-ingredient Preparations. ***Arg.***: Arnol; Dafne; Faradil; Pasminox Somatico; Spasmoctyl Somatico; Tratobes; ***Austria***: Betamed; Harmomed; ***Braz.***: Dialudon; ***Chile***: Ansioval; Calmosedan; Cardiosedantol; Diapam; Multisedil; Promidan; Sedantol; Sedilit; ***Fin.***: Relapamil†; Vertipam†; ***Gr.***: Distedon; ***India***: Depik Forte; Depik Plus; Depranil Plus; Depsol Forte; Depsol Plus; Depsonil-DZ; Dericip Plus; Diamin Plus; Diaze-P; Dizepax; Eldep Forte; Eldep-M; Eldep-Plus; Imipam; ***Indon.***: Analsik; Cetalgin; Danalgin; Hedix; Metaneuron; Neurindo; Neurodial; Neuroval; Opineuron; Potensik; Proneuron; ***Ital.***: Gamibetal Plus; Spasen Somatico; Spasmeridan†; Spasmomen Somatico; Valpinax; Valtrax; ***Mex.***: Adepsique; Esbelcaps; Numencial; Qual; Redotex; ***Rus.***: Reladorm (Реладорм); ***Spain***: Ansium; Tepazepan; Tropargal; ***Turk.***: Spazmo-Valibrin; ***USA***: Emergent-Ez.

Pharmacopoeial Preparations

BP 2014: Diazepam Injection; Diazepam Oral Solution; Diazepam Rectal Solution; Diazepam Tablets;

USP 36: Diazepam Capsules; Diazepam Extended-release Capsules; Diazepam Injection; Diazepam Tablets.

Dichloralphenazone *(BAN)*

Dicloralfenazona; Dikloraalifenatsoni; Dikloralfenazon; Дихлоралфеназон.

$C_{15}H_{18}Cl_6N_2O_5$=519.0

CAS — 480-30-8.

ATC — N05CC04.

ATC Vet — QN05CC04.

UNII — YYX637R279.

Pharmacopoeias. In *US.*

USP 36: (Dichloralphenazone). A white microcrystalline powder with a slight odour characteristic of cloral hydrate. Freely soluble in water, in alcohol, and in chloroform; soluble in dilute acids. It is decomposed by dilute alkalis liberating chloroform.

Profile

Dichloralphenazone dissociates when given, to form cloral hydrate and phenazone. It has the general properties of cloral hydrate (p. 1055.2), although it is less likely to cause gastric irritation after oral doses. Phenazone-induced skin eruptions may, however, occur (see p. 124.2). Dichloralphenazone is used in some countries in combination preparations mainly for the treatment of tension and vascular headaches.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Acudrin; ***USA***: Epidrin; Midrin; Migragesic IDA; Migrazone; Nodolor.

Pharmacopoeial Preparations

USP 36: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Dixyrazine

Diksyratsiini; Dixirazina; Dixyrazin; Dixyrazinum; UCB-3412; Диксиразин.

2-(2-[4-[2-Methyl-3-(phenothiazin-10-yl)propyl]piperazin-1-yl]ethoxy)ethanol.

$C_{24}H_{33}N_3O_2S$=427.6

CAS — 2470-73-7.

ATC — N05AB01.

ATC Vet — QN05AB01.

UNII — 7H368W3AYC.

Profile

Dixyrazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has a piperazine side-chain. It is given for its antipsychotic, antiemetic, and sedative properties in oral doses ranging from 20 to 75 mg daily. Dixyrazine has also been given by injection.

References.

1. Larsson S, *et al.* Premedication with intramuscular dixyrazine (Esucos): a controlled double-blind comparison with morphine-scopolamine and placebo. *Acta Anaesthesiol Scand* 1988; **32:** 131–4.
2. Karlsson E, *et al.* The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiol Scand* 1993; **37:** 45–8.
3. Oikkonen M, *et al.* Dixyrazine premedication for cataract surgery: a comparison with diazepam. *Acta Anaesthesiol Scand* 1994; **38:** 214–17.

4. Feet PO, Götestam KG. Increased antipanic efficacy in combined treatment with clomipramine and dixyrazine. *Acta Psychiatr Scand* 1994; **89:** 230–4.
5. Kokinsky E, *et al.* Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. *Acta Anaesthesiol Scand* 1999; **43:** 191–5.
6. Glaser C, *et al.* Dixyrazine for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2004; **48:** 1287–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dixyrazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Esucos†; ***Fin.***: Esucos†; ***Ital.***: Esucos.

Droperidol *(BAN, USAN, rINN)*

Dropéridol; Droperidoli; Droperidolis; Droperidolum; McN-JR-4749; R-4749; Дроперидол.

1-{1-[3-(4-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl}-benzimidazolin-2-one.

$C_{22}H_{22}FN_3O_2$=379.4

CAS — 548-73-2.

ATC — N05AD08.

ATC Vet — QN05AD08.

UNII — O9U0F09D5X.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Droperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dimethylformamide. Protect from light.

USP 36: (Droperidol). A white to light tan amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 140 of alcohol, 1 in 4 of chloroform, and 1 in 500 of ether. Store under nitrogen in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Uses and Administration

Droperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.2). The duration of action of droperidol has been reported to last about 2 to 4 hours although alteration of alertness may last for up to 12 hours.

One manufacturer of droperidol (*Janssen-Cilag*) voluntarily withdrew it from the market worldwide in March 2001 after reports of QT prolongation, serious ventricular arrhythmias, or sudden death in association with its use. However, in the USA, droperidol remained available from other manufacturers although its use was restricted to the management of nausea and vomiting after surgical or diagnostic procedures (p. 1814.3) in patients who fail to show an adequate response to other treatments. Droperidol subsequently returned to the UK market in 2008 from another manufacturer and its use was similarly restricted. It is also available, in some other countries, for use as a premedicant, as an adjunct in anaesthesia, and for the control of agitated patients in acute psychoses and in mania. Droperidol has been used in the management of chemotherapy-induced nausea and vomiting. It has also been used with an opioid analgesic such as fentanyl citrate to maintain patients in a state of neuroleptanalgesia in which they are calm and indifferent to the surroundings and able to cooperate with the surgeon. The longer duration of action of droperidol must be kept in mind when using it with such opioid analgesics.

For the prevention and treatment of postoperative **nausea and vomiting** a maximum initial dose of 2.5 mg intramuscularly or intravenously has been given in the USA; additional doses of 1.25 mg may be given if necessary. In the UK, an intravenous dose ranging from 625 micrograms to 1.25 mg is recommended. Doses may be given 30 minutes before the anticipated end of surgery and repeated every 6 hours as required. Elderly patients should be given doses of 625 micrograms. Lower doses are also recommended for those with hepatic or renal impairment (see below). In the UK, droperidol may also be given for the prevention of nausea and vomiting induced by morphine and its derivatives during postoperative patient-controlled analgesia: 15 to 50 micrograms of droperidol per mg of morphine, up to a maximum of 5 mg daily of droperidol, may be given intravenously.

For details of doses in children, see below.

References.
1. McKeage K, *et al.* Intravenous droperidol: a review of its use in the management of postoperative nausea and vomiting. *Drugs* 2006; **66:** 2123–47.
2. Jackson CW, *et al.* Evidence-based review of the black-box warning for droperidol. *Am J Health-Syst Pharm* 2007; **64:** 1174–86.

Administration in children. Droperidol may be used for the prevention and treatment of postoperative nausea and vomiting in children who fail to show an adequate response to other treatments. In the USA, those aged 2 to 12 years have been given a maximum initial dose of 100 micrograms/kg intramuscularly or intravenously. In the UK, children aged over 2 years and adolescents may be given an intravenous dose of 20 to 50 micrograms/kg, up to a maximum of 1.25 mg. Doses may be given 30 minutes before the anticipated end of surgery and repeated every 6 hours as required.

Administration in hepatic or renal impairment. UK licensed product information recommends that patients with hepatic or renal impairment should be given droperidol in doses of 625 micrograms by intravenous injection.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. There is an increased risk of cardiotoxicity and prolongation of the QT interval (see p. 1047.3) with droperidol. Droperidol should not be used in patients with known or suspected QT prolongation; it should also be used with extreme caution, if at all, in patients at risk of arrhythmias, including those with impairment of cardiac function, hypokalaemia, or other electrolyte imbalance. It is recommended that a baseline ECG is performed in all patients before use of droperidol.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies droperidol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3. The risk of arrhythmias with droperidol may be increased by other drugs that prolong the QT interval or cause electrolyte disturbances (see also under Pimozide, p. 1097.2, for further details).

Droperidol is metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4; use with inhibitors of these isoenzymes may reduce the metabolism of droperidol and prolong its action.

Pharmacokinetics

Plasma concentrations of droperidol fall rapidly after intravenous dosage and the mean elimination half-life is 134 minutes. Droperidol is 85 to 90% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP1A2 and CYP3A4, and to a lesser extent by CYP2C19, to inactive metabolites. About 75% of a dose is excreted in the urine, with 1% being excreted unchanged; 11% appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Droleptan; ***Austria***: Xomolix; ***Belg.***: Dehydrobenzperidol; ***Braz.***: Droperdal; ***Cz.***: Xomolix; ***Denm.***: Dehydrobenzperidol; ***Fin.***: Dehydrobenzperidol; ***Fr.***: Droleptan; ***Ger.***: Xomolix; ***Gr.***: Dehydrobenzperidol; Droleptan; Xomolix; ***Hung.***: Xomolix; ***India***: Droperol; ***Irl.***: Xomolix; ***Neth.***: Dehydrobenzperidol; ***Norw.***: Dridol; ***NZ***: Droleptan; ***Port.***: Dehidrobenzperidol†; Xomolix; ***S.Afr.***: Inapsin; Paxical†; ***Spain***: Xomolix; ***Swed.***: Dridol; ***UK***: Xomolix; ***USA***: Inapsine†.

Multi-ingredient Preparations. ***Arg.***: Disifelit; ***Braz.***: Nilperidol; ***Gr.***: Thalamonal.

Pharmacopoeial Preparations
BP 2014: Droperidol Injection; Droperidol Tablets;
USP 36: Droperidol Injection.

Estazolam *(USAN, rINN)*

Abbott-47631; D-40TA; Estatsolaami; Estazolamum; Эстазолам.

8-Chloro-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*]-1,4-benzodiazepine.

$C_{16}H_{11}ClN_4$=294.7

CAS — 29975-16-4.

ATC — N05CD04.

ATC Vet — QN05CD04.

UNII — 3653EQV54C.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Estazolam). A white to pale yellowish-white crystal. Practically insoluble in water and in ether; sparingly soluble in alcohol; soluble in methyl alcohol and in acetic anhydride. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Estazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given as a hypnotic in the short-term management of insomnia (p. 1033.2) in usual oral doses of 0.5 to 2 mg at night; doses of up to 4 mg may be needed in some patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Noctal; ***Fr.***: Nuctalon; ***Indon.***: Esilgan; ***Ital.***: Esilgan; ***Jpn***: Eurodin; ***Mex.***: Tasedan; ***Philipp.***: Esilgan; ***Port.***: Kainever.

Pharmacopoeial Preparations
USP 36: Estazolam Tablets.

Eszopiclone *(USAN, rINN)*

Eszopiclona; Eszopiclonum; Эзопикльон; (*S*)-Zopiclone; (+)-Zopiclone.

(+)-(5*S*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

$C_{17}H_{17}ClN_6O_3$=388.8

CAS — 138729-47-2.

ATC — N05CF04.

ATC Vet — QN05CF04.

UNII — UZX80K71OE.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of eszopiclone:

Sleepeasy.

Profile

Eszopiclone is the (+)-isomer of zopiclone (p. 1118.1) and is used similarly as a hypnotic in the short-term management of insomnia (p. 1033.2).

The usual oral dose is 2 mg immediately before bedtime; if appropriate, the dose may be started at or increased to 3 mg. In elderly patients who have difficulty falling asleep, the initial dose is 1 mg; this may be increased to 2 mg. For elderly patients who have difficulty staying asleep, the starting dose is 2 mg.

The dose should be reduced in patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4; a starting dose not exceeding 1 mg is recommended which may then be increased to 2 mg. For doses in patients with hepatic impairment, see below.

Reviews.
1. Melton ST, *et al.* Eszopiclone for insomnia. *Ann Pharmacother* 2005; **39:** 1659–66.
2. Halas CJ. Eszopiclone. *Am J Health-Syst Pharm* 2006; **63:** 41–8.
3. Hair PI, *et al.* Eszopiclone: a review of its use in the treatment of insomnia. *Drugs* 2008; **68:** 1415–34.
4. Morin AK, Willett K. The role of eszopiclone in the treatment of insomnia. *Adv Therapy* 2009; **26:** 500–18.

Administration in hepatic impairment. The starting oral dose of eszopiclone should be reduced to 1 mg at bedtime in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild to moderate impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: 8 Horas; Inductal; Miapax; Novo Insomnium; ***Chile***: Eszop; Noptic; Plessir; Valnoc; Zopinon; ***China***: Wen Fei (文飞); Yi Tan Ning (伊坦宁); ***India***: Fulnite; ***Jpn***: Lunesta; ***USA***: Lunesta.

Ethchlorvynol *(BAN, rINN)*

β-Chlorovinyl Ethyl Ethynyl Carbinol; Etclorvinol; *E*-Ethchlorvynol; Éthchlorvynol; Ethchlorvynolum; Etkloorivinoli; Etklorvinol; Этхлорвинол.

1-Chloro-3-ethylpent-1-en-4-yn-3-ol.

C_7H_9ClO=144.6

CAS — 113-18-8.

ATC — N05CM08.

ATC Vet — QN05CM08.

UNII — 6EIM3851UZ.

Pharmacopoeias. In *US*.

USP 36: (Ethchlorvynol). A colourless to yellow, slightly viscous liquid having a characteristic pungent odour. It

darkens on exposure to air and light. Immiscible with water; miscible with most organic solvents. Store in airtight containers of glass or polyethylene, using polyethylene-lined closures. Protect from light.

Profile

Ethchlorvynol is a hypnotic and sedative with effects broadly similar to those of the barbiturates (see Amobarbital, p. 1037.2). It also has some anticonvulsant and muscle relaxant properties. It has been given for the short-term management of insomnia but has been largely superseded by other drugs.

Preparations

Pharmacopoeial Preparations
USP 36: Ethchlorvynol Capsules.

Ethyl Alpha-bromoisovalerate

Ethyl 2-Bromoisovalerate; Ethyl 2-Bromo-3-methylbutanoate; Ethyl 2-Bromo-3-methylbutyrate.
Alpha-bromoisovaleric Acid Ethyl Ester.
$C_7H_{13}BrO_2$=209.1
CAS — 609-12-1.

Profile

Ethyl alpha-bromoisovalerate has actions and uses similar to those of carbromal (p. 1044.1) but the use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.:*** Barboval (Барбовал); Valoserdin (Валосердин); ***Ukr.:*** Barboval (Барбовал); Corvaldinum (Корвалдин); Corvaltab (Корвалтаб).

Ethyl Loflazepate *(rINN)*

CM-6912; Éthyle, Loflazépate d'; Ethylis Loflazepas; Loflazepato de etilo; Этил Лофлазепат.
Ethyl 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylate.
$C_{18}H_{14}ClFN_2O_3$=360.8
CAS — 29177-84-2.
ATC — N05BA18.
ATC Vet — QN05BA18.
UNII — VJB5FW9W9J.

Profile

Ethyl loflazepate is a long-acting benzodiazepine derivative with general properties similar to those of diazepam (p. 1063.2). It is used in the short-term treatment of anxiety disorders (p. 1028.1) in usual oral doses of 1 to 3 mg daily as a single dose or in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.:*** Victan; ***China:*** Meilax (美乐适); ***Fr.:*** Victan; ***Jpn:*** Meilax; ***Mex.:*** Victan; ***Port.:*** Victan; ***Thai.:*** Victan†.

Etifoxine Hydrochloride *(BANM, rINNM)*

Etifoxin Hydrochloride; Etifoxina, hidrocloruro de; Étifoxine, Chlorhydrate d'; Etifoxini Hydrochloridum; Hidrocloruro de etifoxina; Hoe-36801; Этифоксина Гидрохлорид.
6-Chloro-4-methyl-4-phenyl-3,1-benzoxazin-2-yl(ethyl) amine hydrochloride.
$C_{17}H_{17}ClN_2O$,HCl=337.2
CAS — 21715-46-8 (etifoxine); 56776-32-0 (etifoxine hydrochloride).
ATC — N05BX03.
ATC Vet — QN05BX03.
UNII — NBL8010WH5.

Profile

Etifoxine hydrochloride is an anxiolytic used for the short-term treatment of anxiety (p. 1028.1). It is given in usual oral doses of 150 or 200 mg daily in 2 or 3 divided doses.

References.

1. Nguyen N, *et al.* Efficacy of etifoxine compared to lorazepam monotherapy in the treatment of patients with adjustment disorders with anxiety: a double-blind controlled study in general practice. *Hum Psychopharmacol* 2006; **21:** 139–49. Correction. *ibid.*; 562.
2. Zeilhofer HU. Etifoxine (Stresam) for chemotherapy-induced pain? *Pain* 2009; **147:** 9–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.:*** Stresam; ***Rus.:*** Strezam (Стрезам); ***S.Afr.:*** Stresam; ***Ukr.:*** Stresam (Стрезам).

Etizolam *(rINN)*

AHR-3219; Étizolam; Etizolamum; Y-7131; Этизолам.
4-(2-Chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine.
$C_{17}H_{15}ClN_4S$=342.8
CAS — 40054-69-1.
ATC — N05BA19.
ATC Vet — QN05BA19.
UNII — A76XI0HL37.

Pharmacopoeias. In *Jpn.*

Profile

Etizolam is a short-acting benzodiazepine derivative with general properties similar to those of diazepam (p. 1063.2). It is given for the short-term treatment of insomnia (p. 1033.2) and anxiety disorders (p. 1028.1) in oral doses of up to 3 mg daily in divided doses or as a single dose at night.

References.

1. Fukasawa T, *et al.* Pharmacokinetics and pharmacodynamics of etizolam are influenced by polymorphic CYP2C19 activity. *Eur J Clin Pharmacol* 2005; **61:** 791–5.
2. Kato Z, *et al.* Accidental etizolam ingestion in a child. *Pediatr Emerg Care* 2007; **23:** 472–3.
3. De Candia MP, *et al.* Effects of treatment with etizolam 0.5 mg BID on cognitive performance: a 3-week, multicenter, randomized, double-blind, placebo-controlled, two-treatment, three-period, noninferiority crossover study in patients with anxiety disorder. *Clin Ther* 2009; **31:** 2851–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India:*** Etizola; ***Ital.:*** Depas; Pasaden; ***Jpn:*** Depas.

Fabomotizole Hydrochloride *(pINNM)*

Afobazol; Afobazole; Aphobazole; CM-346; Fabomotizole, Chlorhydrate d'; Fabomotizoli Hydrochloridum; Hidrocloruro de fabomotizol; Obenoxazine Hydrochloride; SM-346; Афобазола Гидрохлорид; Фабомотизола Гидрохлорид.
5-Ethoxy-2-{[2-(4-morpholinyl)ethyl]thio}-1*H*-benzimidazole Monohydrochloride.
$C_{15}H_{21}N_3O_2S$,HCl=343.9
CAS — 173352-21-1 (fabomotizole); 173352-39-1 (fabomotizole monohydrochloride).
UNII — HDO6HX6NZU.

NOTE. Afobazol is a registered trade mark in some countries and may be used to describe the dihydrochloride.

Profile

Fabomotizole is a non-benzodiazepine anxiolytic used in the treatment of anxiety disorders (p. 1028.1). It has been given orally as the dihydrochloride in a usual dose of 10 mg three times daily. A maximum of 60 mg may be given daily.

References.

1. Neznamov GG, *et al.* Aphobazol—new selective anxyolytic drug. *Zh Nevrol Psikhiatr Im S S Korsakova* 2005; **105:** 35–40.
2. Medvedev VE, *et al.* Psychopharmacotherapy of anxiety disorders in patients with cardio-vascular diseases: the use of aphobazole. *Zh Nevrol Psikhiatr Im S S Korsakova* 2007; **107:** 25–9.

Fluanisone *(BAN, rINN)*

Fluanison; Fluanisona; Fluanisoni; Fluanisonum; Haloanisone; MD-2028; R-2028; R-2167; Флуанизон.
4′-Fluoro-4-[4-(2-methoxyphenyl)piperazin-1-yl]butyrophenone.
$C_{21}H_{25}FN_2O_2$=356.4
CAS — 1480-19-9.
ATC — N05AD09.
ATC Vet — QN05AD09.
UNII — 1D0W98U1I4.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Fluanisone). White or almost white to buff-coloured, odourless or almost odourless crystals or powder. It exhibits polymorphism. M.p. 72 degrees to 76 degrees. Practically insoluble in water; freely soluble in alcohol, in chloroform, in ether, and in dilute solutions of organic acids. Protect from light.

Profile

Fluanisone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It has been used in the management of agitated states in psychiatric patients and as anaesthetic premedication.

Fluanisone is used in veterinary medicine for neuroleptanalgesia.

Fludiazepam *(rINN)*

Fludiazépam; Fludiazepamum; ID-540; Флудиазепам.
7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.
$C_{16}H_{12}ClFN_2O$=302.7
CAS — 3900-31-0.
ATC — N05BA17.
ATC Vet — QN05BA17.
UNII — 7F64A2K16Z.

Pharmacopoeias. In *Jpn.*

Profile

Fludiazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given in the short-term treatment of anxiety disorders (p. 1028.1) in a usual oral dose of 250 micrograms three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn:*** Erispan.

Flunitrazepam *(BAN, USAN, rINN)*

Flunitratsepaami; Flunitrazepám; Flunitrazépam; Flunitrazepamas; Flunitrazepamum; Ro-5-4200; Флунитразепам.
5-(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-1,4-benzodiazepin-2-one.
$C_{16}H_{12}FN_3O_3$=313.3
CAS — 1622-62-4.
ATC — N05CD03.
ATC Vet — QN05CD03.
UNII — 620X0222FQ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of flunitrazepam:

Benzo; Circles; Date rape drug; Forget me drug; Forget pill; Forget-me pill; Forget-Me-Pill; Getting roached; La Rocha; La Roche; Lunch money drug; Mexican valium; Pingus; R2; R-2; Reynolds; Rib; Rick James Biatch; Roach; Roach 2; Roach-2; Roaches; Roachies; Roapies; Robutal; Rochas dos; Roche; Roches; Rolpes; Roofie; Roofies; Roopies; Rope; Rophies; Rophy; Ropies; Roples; Ropples; Row-shay; Ruffies; Ruffles; Sedexes; Wolfies.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Flunitrazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone. Protect from light.

Uses and Administration

Flunitrazepam is an intermediate- or short-acting benzodiazepine (depending on dose) with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term management of insomnia (p. 1033.2), as a premedicant in surgical procedures, and for induction of anaesthesia (p. 1899.1).

A usual oral dose for **insomnia** is 0.5 to 1 mg at night; up to 2 mg may be given if necessary. In elderly or debilitated patients the initial dose should not exceed 500 micrograms at night; up to 1 mg may be given if necessary.

A dose of 1 to 2 mg (15 to 30 micrograms/kg) has been given intramuscularly or orally for **premedication** or by slow intravenous injection for **induction** of general anaesthesia.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Abuse. A WHO review[1] concluded that flunitrazepam had a moderate abuse potential that might be higher than that of other benzodiazepines. It was reported that there was current evidence of widespread abuse of flunitrazepam among drug abusers, particularly among those who used opioids or cocaine. Flunitrazepam has also been abused at social gatherings where it is taken orally or intranasally.[2,3]

Flunitrazepam is tasteless and odourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[2-4] A 1-

mg dose may produce impairment for 8 to 12 hours.[2] Some manufacturers have incorporated a blue dye into flunitrazepam tablets to increase visibility when placed into drinks[4] but caution is still necessary as it has been reported that blue tropical drinks and punches are being used to overcome this.

1. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_856.pdf (accessed 21/08/08)
2. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
3. National Institute on Drug Abuse. Club drugs (GHB, Ketamine, and Rohypnol) (updated July 2010). Available at: http://www.drugabuse.gov/pdf/infofacts/ClubDrugs10.pdf (accessed 12/11/10)
4. Simmons MM, Cupp MJ. Use and abuse of flunitrazepam. *Ann Pharmacother* 1998; **32:** 117–19.

Breast feeding. Concentrations in breast milk the morning after a single evening 2-mg dose of flunitrazepam were considered to be too low to produce clinical effects in breast-fed infants, although accumulation in the milk might occur after repeated use.[1]

1. Kanto J, *et al.* Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26:** 539–46.

Local reactions. Of 43 patients given a single intravenous dose of flunitrazepam 1 to 2 mg, two had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution]. However, there was little difference in the incidence of local reactions after intravenous use of flunitrazepam and diazepam in another study.[2]

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; **2:** 1384–5.
2. Mikkelsen H, *et al.* Local reactions after iv injections of diazepam, flunitrazepam and isotonic saline. *Br J Anaesth* 1980; **52:** 817–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flunitrazepam as probably porphyrinogenic; it should be prescribed only for compelling indications and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Flunitrazepam is readily absorbed from the gastrointestinal tract after oral doses. It is about 77 to 80% bound to plasma proteins. Flunitrazepam is extensively metabolised in the liver and excreted mainly in the urine as metabolites (free or conjugated). Its principal metabolites are 7-aminoflunitrazepam and *N*-desmethylflunitrazepam; *N*-desmethylflunitrazepam is reported to be pharmacologically active but less so than the parent compound. The elimination half-life of flunitrazepam is reported to be between 16 and 35 hours. Flunitrazepam crosses the placental barrier and is distributed into breast milk.

References.
1. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11:** 18–35.
2. Pariente-Khayat A, *et al.* Pharmacokinetics and tolerance of flunitrazepam in neonates and in infants. *Clin Pharmacol Ther* 1999; **66:** 136–9.

Pregnancy. Concentrations of flunitrazepam in umbilical-vein and umbilical-artery plasma were lower than those in maternal venous plasma about 11 to 15 hours after a dose of flunitrazepam 1 mg in 14 pregnant women; concentrations in amniotic fluid were lower still.[1]

1. Kanto J, *et al.* Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26:** 539–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nervocuril; Primum; Rohypnol; ***Austral.***: Hypnodorm; ***Austria***: Guttanotte; Rohypnol; Somnubene; ***Belg.***: Rohypnol; ***Braz.***: Rohydorm; Rohypnol; ***Chile***: Ipnopen; ***Denm.***: Flunipam; ***Fr.***: Narcozep; Rohypnol; ***Ger.***: Fluninoc†; Rohypnol; ***Gr.***: Hipnosedon; Ilman; Neo Nifalium; Nilium; Stedonil; Vulbegal; ***Hong Kong***: Flunita; Rohypnol; ***Irl.***: Rohypnol; ***Israel***: Hypnodorm; ***Ital.***: Roipnol; Valsera; ***Mex.***: Rohypnol; ***Norw.***: Flunipam†; ***Pol.***: Rohypnol†; ***Port.***: Rohypnol†; ***Rus.***: Rohypnol (Рогипнол); ***S.Afr.***: Hypnor; Insom†; Rohypnol; ***Spain***: Rohipnol†; ***Swed.***: Fluscand†; ***Switz.***: Rohypnol; ***Thai.***: Rohypnol†.

Flupentixol *(BAN, rINN)*

Flupenthixol; Flupentiksoli; Flupentixolum; LC-44; N-7009; Флупентиксол.

(*Z*)-2-{4-[3-(2-Trifluoromethylthioxanthen-9-ylidene)propyl]piperazin-1-yl}ethanol.

$C_{23}H_{25}F_3N_2OS$=434.5

CAS — 2709-56-0.

ATC — N05AF01.

ATC Vet — QN05AF01.

UNII — FA0UYH6QUO.

Flupentixol Decanoate *(BANM, rINNM)*

cis-Flupenthixol Decanoate; Decanoato de flupentixol; Flupenthixol Decanoate; (*Z*)-Flupenthixol Decanoate; Flupentiksol Dekanoat; Flupentixol, Décanoate de; Flupentixol, decanoato de; Flupentixoli Decanoas; Флупентиксола Деканоат.

$C_{33}H_{43}F_3N_2O_2S$=588.8

CAS — 30909-51-4.

ATC — N05AF01.

ATC Vet — QN05AF01.

UNII — 3B2FE28C1W.

Pharmacopoeias. In *Br.*

BP 2014: (Flupentixol Decanoate). A yellow viscous oil. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Store at a temperature below -15 degrees and protect from light.

Flupentixol Hydrochloride *(BANM, rINNM)*

Flupenthixol Dihydrochloride; Flupenthixol Hydrochloride; Flupentiksol Dihidroklorür; Flupentiksolidihydrokloridi; Flupentiksolio dihidrochloridas; Flupentixol, Chlorhydrate de; Flupentixol, dichlorhydrate de; Flupentixol, hidrocloruro de; Flupentixol-dihidroklorid; Flupentixol-dihydrochlorid; Flupentixoldihydroklorid; Flupentixoli dihydrochloridum; Flupentixoli Hydrochloridum; Hidrocloruro de flupentixol; Флупентиксола Гидрохлорид.

$C_{23}H_{25}F_3N_2OS.2HCl$=507.4

CAS — 2413-38-9.

ATC — N05AF01.

ATC Vet — QN05AF01.

UNII — 96L0Z069N1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flupentixol Dihydrochloride; Flupentixol Hydrochloride BP 2014). A white or almost white powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Enever RP, *et al.* Fluenthixol dihydrochloride decomposition in aqueous solution. *J Pharm Sci* 1979; **68:** 169–71.
2. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32:** 25–9.

Uses and Administration

Flupentixol is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain. Flupentixol is used mainly in the treatment of schizophrenia (p. 1031.3) and other psychoses. Unlike chlorpromazine, an activating effect has been ascribed to flupentixol, and it is not indicated in overactive or manic patients. Flupentixol has also been used for its antidepressant properties.

Flupentixol is given orally as the hydrochloride although doses are expressed in terms of the base; flupentixol hydrochloride 3.5 mg is equivalent to about 3 mg of flupentixol. Flupentixol is also given as the longer-acting decanoate ester by deep intramuscular injection. The long-acting preparation available in the UK contains flupentixol decanoate as the *cis(Z)*-isomer (see Action, below) and doses are expressed in terms of the amount of *cis(Z)*-flupentixol decanoate.

The usual initial *oral* dose for the treatment of **psychoses** is the equivalent of 3 to 9 mg of flupentixol twice daily adjusted according to response; the maximum recommended daily dose is 18 mg. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If given by *deep intramuscular* injection, an initial test dose of 20 mg of the decanoate, as 1 mL of a 2% oily solution, is used. Then, after at least 7 days and according to response, this may be followed by doses of 20 to 40 mg every 2 to 4 weeks. Shorter dosage intervals or greater amounts may be required according to the patient's response. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If doses greater than 40 mg (2 mL) are considered necessary they should be divided between 2 separate injection sites. Another means of reducing the volume of fluid to be injected in patients requiring high-dose therapy is to give an injection containing 100 or 200 mg/mL of the decanoate (10 or 20%). The usual maintenance dose is between 50 mg every 4 weeks and 300 mg every 2 weeks but doses of up to 400 mg weekly have been given in severe or resistant cases.

Flupentixol has also been given as the hydrochloride for the treatment of mild to moderate **depression**, with or without anxiety (p. 398.1). The usual initial *oral* dose, expressed in terms of the equivalent amount of flupentixol, is 1 mg (0.5 mg in the elderly) daily, increased after 1 week to 2 mg (1 mg in the elderly) and then to a maximum of 3 mg (1.5 mg in the elderly) daily. Doses above 2 mg (1 mg in the elderly) should be given in 2 divided doses. The last dose of the day should be given no later than 4 p.m. and if no effect has been noted within 1 week of reaching the maximum dose, treatment should be withdrawn.

Action. Patients with acute schizophrenic illnesses taking α-flupentixol[(*Z*)-flupentixol or *cis*-flupentixol] improved more after 3 weeks than patients who were taking equal doses of β-flupentixol[(*E*)-flupentixol or *trans*-flupentixol] or a placebo.[1] The α-isomer had more effect on the positive symptoms of the disease; this difference was less apparent for the negative symptoms. The difference in activity between the isomers was attributed to the greater dopamine-receptor blocking activity of the α-isomer rather than to differences in distribution.[2]

1. Johnstone EC, *et al.* Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet* 1978; **i:** 848–51.
2. Crow TJ, Johnstone EC. Mechanism of action of neuroleptic drugs. *Lancet* 1978; **i:** 1050.

Adverse Effects and Treatment

As for Chlorpromazine, p. 1047.2. Flupentixol is less likely to cause sedation, but extrapyramidal effects are more frequent.

Sudden death. Sudden death has been reported in 3 patients given depot injections of flupentixol decanoate.[1]

1. Turbott J, Smeeton WMI. Sudden death and flupenthixol decanoate. *Aust N Z J Psychiatry* 1984; **18:** 91–4.

Precautions

As for Chlorpromazine, p. 1050.3. Flupentixol is not recommended in states of excitement or overactivity, including mania.

When flupentixol is used in the management of depression, patients should be closely monitored during early therapy until significant improvement in depression is seen because suicide is an inherent risk in depressed patients. For further details, see Depression, p. 398.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flupentixol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Flupentixol is readily absorbed from the gastrointestinal tract after oral use and is probably subject to first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous metabolites; there is evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after estimated equivalent doses of the intramuscular depot preparation. Moreover, there is very wide intersubject variation in plasma concentrations of flupentixol, but, in practice, no simple correlation has been found between the therapeutic effect and plasma concentrations of flupentixol and its metabolites. After oral doses, peak plasma concentrations occur in about 4 hours and the biological half-life is about 35 hours. Paths of metabolism of flupentixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. Flupentixol is more than 95% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Flupentixol crosses the placental barrier and small amounts have been detected in breast milk.

The decanoate ester of flupentixol is very slowly absorbed from the site of intramuscular injection and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to flupentixol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fluanxol; ***Austria***: Fluanxol; ***Belg.***: Fluanxol; ***Canad.***: Fluanxol; ***Chile***: Fluanxol; ***China***: Fluanxol (孚岚素); ***Cz.***: Fluanxol; ***Denm.***: Fluanxol; ***Fin.***: Fluanxol; ***Fr.***: Fluanxol; ***Ger.***: Fluanxol; ***Gr.***: Fluanxol; ***Hong Kong***: Fluanxol; ***Hung.***: Fluanxol; ***India***: Fluanxol; Flupen; Novoxit; ***Irl.***: Depixol; Fluanxol; ***Israel***: Fluanxol; ***Malaysia***: Fluanxol; ***Mex.***: Fluanxol; ***Neth.***: Fluanxol; ***Norw.***: Fluanxol; ***NZ***: Fluanxol; ***Philipp.***: Fluanxol; ***Pol.***: Fluanxol; ***Port.***: Fluanxol; ***Rus.***: Fluanxol (Флюанксол); ***S.Afr.***: Fluanxol; ***Singapore***: Fluanxol; ***Swed.***: Fluanxol; ***Switz.***: Fluanxol; ***Thai.***: Fluanxol; ***Turk.***: Fluanxol; ***UK***: Depixol; Fluanxol; ***Ukr.***: Fluanxol (Флюанксол).

Multi-ingredient Preparations. ***Austria***: Deanxit; ***Belg.***: Deanxit; ***China***: Deanxit (黛力新); ***Hong Kong***: Anfree; Danxipress; Deanxit; Quali-Xit; ***India***: Ambulax-FM; Deanxit; Delewal; Denxol; Flupen-M; Forcalm; Franxit; Fycida-M; Melicen-FP; Meliyos; Melthix; Metflu; ***Singapore***: Deanxit; ***Spain***: Deanxit; ***Switz.***: Deanxit; ***Thai.***: Deanxit.

Pharmacopoeial Preparations
BP 2014: Flupentixol Injection.

Fluphenazine *(BAN, rINN)*

Flufenatsiini; Flufenazin; Flufenazina; Fluphénazine; Fluphenazinum; Флуфеназин.

2-{4-[3-(2-Trifluoromethylphenothiazin-10-yl)propyl]piperazin-1-yl}ethanol.

$C_{22}H_{26}F_3N_3OS$=437.5

CAS — 69-23-8.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — S79426A41Z.

Fluphenazine Decanoate *(BANM, rINNM)*

Decanoato de flufenazina; Flufenatsiinidekanoaatti; Flufenazin Dekanoat; Flufenazina, decanoato de; Flufenazindekanoat; Flufenazin-dekanoát; Flufenazine-dekanoát; Flufenazino dekanoatas; Fluphenazindecanoat; Fluphénazine, Décanoate de; Fluphenazini Decanoas; Флуфеназина деканоат.

$C_{32}H_{44}F_3N_3O_2S$=591.8

CAS — 5002-47-1.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — FMU62K1L3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Fluphenazine Decanoate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Fluphenazine Decanoate). Store in airtight containers. Protect from light.

Fluphenazine Enantate *(BANM, rINNM)*

Enantato de flufenazina; Flufenatsiinienantaatti; Flufenazina, enantato de; Flufenazinenantat; Flufenazin-enantát; Flufenazino enantatas; Fluphénazine, Enantate de; Fluphenazine Enanthate; Fluphenazine Heptanoate; Fluphenazinenantat; Fluphenazini Enantas; Флуфеназина Энантат.

$C_{29}H_{38}F_3N_3O_2S$=549.7

CAS — 2746-81-8.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — QSB34YF0W9.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Fluphenazine Enantate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Fluphenazine Enanthate). A pale yellow to yellow-orange, clear to slightly turbid, viscous liquid having a characteristic odour. Insoluble in water; soluble 1 in less than 1 of alcohol and of chloroform and 1 in 2 of ether. Stable in air at room temperature but unstable in strong light. Store in airtight containers. Protect from light.

Fluphenazine Hydrochloride *(BANM, rINNM)*

Flufenatsiinihydrokloridi; Flufenazina, hidrocloruro de; Flufenazin-dihydrochlorid; Flufenazin-hidroklorid; Flufenazinhydroklorid; Flufenazino hidrochloridas; Flufenazyny chlorowodorek; Fluphenazindihydrochlorid; Fluphénazine, Chlorhydrate de; Fluphenazine Dihydrochloride; Fluphenazini Dihydrochloridum; Fluphenazini Hydrochloridum; Hidrocloruro de flufenazina; Флуфеназина Гидрохлорид.

$C_{22}H_{26}F_3N_3OS,2HCl$=510.4

CAS — 146-56-5.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — ZOU145W1XL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Fluphenazine Dihydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 1.9 to 2.4. Protect from light.

USP 36: (Fluphenazine Hydrochloride). A white or nearly white, odourless crystalline powder. Soluble 1 in 1.4 of water and 1 in 6.7 of alcohol; slightly soluble in acetone and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Fluphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain. Fluphenazine is used in the treatment of psychiatric disorders including schizophrenia (below) and mania (see Bipolar Disorder, p. 397.2). It has also been used for severe anxiety and behavioural disturbances. Fluphenazine is given orally or sometimes by intramuscular injection as the hydrochloride; for both routes, doses are expressed in terms of fluphenazine hydrochloride. It is also given orally as the maleate, doses being expressed in terms of fluphenazine. The longer-acting decanoate or enantate esters of fluphenazine are given by intramuscular or sometimes subcutaneous injection; for both esters, doses are expressed in terms of the ester.

The usual initial *oral* dose of the hydrochloride for the treatment of schizophrenia, mania, and other **psychoses** is 2.5 to 10 mg daily given in divided doses every 6 to 8 hours; the dose is then increased according to response up to a usual maximum of 20 mg daily, although higher doses have occasionally been given. Dosage may subsequently be reduced to a usual maintenance dose of 1 to 5 mg daily which may be given as a single dose. A lower initial dose of 1 to 2.5 mg daily, increased according to response, is recommended in the elderly. Treatment is sometimes started with an initial *intramuscular* injection of 1.25 mg of the hydrochloride adjusted thereafter according to response. The usual initial intramuscular dose is 2.5 to 10 mg daily given in divided doses every 6 to 8 hours. In general the required parenteral doses of fluphenazine hydrochloride have been found to be about one-third to one-half of those given orally. When symptoms are controlled, oral maintenance therapy may be substituted.

The long-acting decanoate or enantate esters of fluphenazine are usually given by deep intramuscular injection and are used mainly for the *maintenance* treatment of patients with schizophrenia or other chronic psychoses. The onset of action is usually within 1 to 3 days of injection and significant effects on psychosis are usually evident within 2 to 4 days. An initial dose of fluphenazine decanoate 12.5 mg (6.25 mg in the elderly) is given intramuscularly. Subsequent adjustments in the amounts and the dosage interval should be made according to the patient's response; the amounts required may range from 12.5 to 100 mg and the intervals required may range from 2 weeks to 5 or 6 weeks. Lower doses may be possible in some patients (see Schizophrenia, below). If doses greater than 50 mg are considered necessary, cautious increments should be made in steps of 12.5 mg. The enantate ester of fluphenazine has been given in a similar dose range at intervals of 1 to 3 weeks.

Schizophrenia. References[1-3] to fluphenazine decanoate in schizophrenia (p. 1031.3) indicating that low doses (10 mg or less every 2 weeks) may be effective in some patients. Use of standard doses at greater intervals (6 weeks) has also been tried.[4] A systematic review of the use of depot fluphenazine in schizophrenia found little advantage over oral use in terms of compliance.[5] Another systematic review[6] considered that although oral fluphenazine is inexpensive and widely available, other drugs may be preferable because of its adverse effects.

1. Kane JM, *et al.* Low-dose neuroleptic treatment of outpatient schizophrenics: I preliminary results for relapse rates. *Arch Gen Psychiatry* 1983; **40:** 893–6.
2. Marder SR, *et al.* Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. *Arch Gen Psychiatry* 1987; **44:** 581–21.
3. Hogarty GE, *et al.* Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia: results of a two-year controlled study. *Arch Gen Psychiatry* 1988; **45:** 797–805.
4. Carpenter WT, *et al.* Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry* 1999; **156:** 412–18.
5. David A, *et al.* Depot fluphenazine decanoate and enanthate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/04/05).
6. Matar HE, AlMerie MQ. Oral fluphenazine versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Tourette's syndrome. Fluphenazine has been tried as an alternative to standard dopamine antagonists such as haloperidol or pimozide in the symptomatic management of Tourette's syndrome (p. 1030.1).

Adverse Effects and Treatment

As for Chlorpromazine, p. 1047.2. Fluphenazine is less likely to cause sedation, hypotension, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects.

Convulsions. For mention of fluphenazine as one of the antipsychotics suitable for patients at risk of seizures, see p. 1047.3.

Effects on the liver. A patient developed jaundice 17 days after the first of 3 injections of a depot antipsychotic containing fluphenazine decanoate given over a 2-week period.[1] Indicators of severe liver toxicity, with extreme hyperbilirubinaemia and raised liver enzyme values, were noted and he remained very ill for the next 4 months. The patient showed cross-sensitivity to haloperidol but not to flupentixol.

See also under Chlorpromazine, p. 1049.1.

1. Kennedy P. Liver cross-sensitivity to antipsychotic drugs. *Br J Psychiatry* 1983; **143:** 312.

Overdosage. A patient who took about 30 fluphenazine hydrochloride 2.5-mg tablets was treated with gastric lavage.[1] Twenty hours after hospital admission he had difficulty in breathing due to spasm of the respiratory muscles; other very severe extrapyramidal adverse effects were also present. Muscle spasm was controlled by diazepam.

There were few adverse effects in a patient given intramuscular fluphenazine decanoate 50 mg every 4 hours, instead of the intended 4 weeks, to a total of 1050 mg.[2] About 3 weeks after the period of overdosage the patient had some degree of hypothermia and tachycardia, and after a further week parkinsonian signs appeared. No specific treatment was given.

1. Ladhani FM. Severe extrapyramidal manifestations following fluphenazine overdose. *Med J Aust* 1974; **2:** 26.
2. Cheung HK, Yu ECS. Effect of 1050 mg fluphenazine decanoate given intramuscularly over six days. *BMJ* 1983; **286:** 1016–17.

Precautions

As for Chlorpromazine, p. 1050.3. Fluphenazine may exacerbate depression and therefore it is contra-indicated in severely depressed patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluphenazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pregnancy. A neonate delivered to a mother who had received fluphenazine hydrochloride 10 to 20 mg daily throughout pregnancy had nasal congestion with severe rhinorrhoea, respiratory distress, vomiting, and extrapyramidal symptoms. Respiratory symptoms appeared to respond to pseudoephedrine.

1. Nath SP, *et al.* Severe rhinorrhea and respiratory distress in a neonate exposed to fluphenazine hydrochloride prenatally. *Ann Pharmacother* 1996; **30:** 35–7.

Interactions

As for Chlorpromazine, p. 1051.3. Fluphenazine is metabolised by the cytochrome P450 isoenzyme CYP2D6 and is itself an inhibitor of this enzyme; other substrates or inhibitors of CYP2D6 may increase plasma concentrations and prolong the effects of fluphenazine.

Pharmacokinetics

Fluphenazine hydrochloride is absorbed after oral doses, and has a reported plasma half-life of 14.7 hours. Fluphenazine decanoate and fluphenazine enantate are very slowly absorbed from the site of subcutaneous or intramuscular injection. They both gradually release fluphenazine into the body and are therefore suitable for use as depot injections. The cytochrome P450 isoenzyme CYP2D6 is involved in fluphenazine metabolism. The plasma half-life of fluphenazine decanoate has been reported to be 6 to 9 days after intramuscular injection.

References[1-4] to the pharmacokinetics of fluphenazine.

The plasma half-life of fluphenazine after a single dose was 14.7 hours in 1 patient given the hydrochloride orally and 14.9 and 15.3 hours in 2 patients given the

hydrochloride by intramuscular injection.[1] The half-life was 3.6 and 3.7 days in 2 patients given the enantate intramuscularly and 9.6 and 6.8 days in 2 patients given the decanoate intramuscularly. Peak plasma-fluphenazine concentrations occurred earlier in patients given fluphenazine decanoate compared with those who received the enantate. Fluphenazine sulfoxide and 7-hydroxyfluphenazine were identified in the urine and faeces.

1. Curry SH, *et al.* Kinetics of fluphenazine after fluphenazine dihydrochloride, enanthate and decanoate administration to man. *Br J Clin Pharmacol* 1979; **7:** 325–31.
2. Wistedt B, *et al.* Slow decline of plasma drug and prolactin levels after discontinuation of chronic treatment with depot neuroleptics. *Lancet* 1981; **i:** 1163.
3. Midha KK, *et al.* Kinetics of oral fluphenazine disposition in humans by GC-MS. *Eur J Clin Pharmacol* 1983; **25:** 709–11.
4. Marder SR, *et al.* Plasma levels of parent drug and metabolites in patients receiving oral and depot fluphenazine. *Psychopharmacol Bull* 1989; **25:** 479–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Modecate; ***Austria***: Dapotum†; ***Braz.***: Flufenan; ***Canad.***: Modecate; ***Chile***: Modecate; ***China***: Deca (滴加); ***Cz.***: Afluditen; Moditen; ***Denm.***: Siqualone†; ***Fin.***: Siqualone; ***Fr.***: Modecate; Moditen†; ***Ger.***: Dapotum†; Lyogen; ***Hong Kong***: Modecate†; ***Hung.***: Moditen; ***India***: Anatensol; Fludecan; FPZ; ***Indon.***: Anatensol†; Modecate†; ***Irl.***: Modecate; ***Israel***: Fludecate; ***Ital.***: Moditen; ***Jpn***: Flumezin; ***Malaysia***: Deca; Monasan; ***Mex.***: Siqualine; ***Neth.***: Anatensol; ***NZ***: Anatensol; Modecate; ***Philipp.***: Fluxim; Modezine; Shrizine†; Sydepres†; ***Port.***: Anatensol; Phenazin†; ***Rus.***: Moditen (Модитен); ***S.Afr.***: Fludecate†; Modecate; ***Spain***: Modecate; ***Swed.***: Siqualone; ***Switz.***: Dapotum†; ***Thai.***: Deca; Fluzine; Pharnazine; ***Turk.***: Prolixin; ***UK***: Modecate; ***Ukr.***: Moditen (Модитен); ***Venez.***: Moditen.

Multi-ingredient Preparations. ***Braz.***: Diserim; ***Chile***: Motitrel†; ***Indon.***: Motival†; ***Irl.***: Motival†; ***Ital.***: Dominans; ***Mex.***: Motival; ***S.Afr.***: Motival†; ***Thai.***: Cetavol.

Pharmacopoeial Preparations
BP 2014: Fluphenazine Decanoate Injection; Fluphenazine Tablets;
USP 36: Fluphenazine Decanoate Injection; Fluphenazine Enanthate Injection; Fluphenazine Hydrochloride Elixir; Fluphenazine Hydrochloride Injection; Fluphenazine Hydrochloride Oral Solution; Fluphenazine Hydrochloride Tablets.

Flurazepam *(BAN, rINN)*

Fluratsepaami; Flurazépam; Flurazepamum; Флуразепам.
7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one.
$C_{21}H_{23}ClFN_3O$=387.9
CAS — 17617-23-1.
ATC — N05CD01.
ATC Vet — QN05CD01.
UNII — IHP475989U.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of flurazepam:
Downs.

Pharmacopoeias. In *Jpn*.

Flurazepam Monohydrochloride

(BANM, rINNM)

Fluratsepaamimonohydrokloridi; Flurazepam hydrochlorid; Flurazépam, Monochlorhydrate de; Flurazepam, monohidrocloruro de; Flurazepami Hydrochloridum; Flurazepami Monohydrochloridum; Flurazepám-monohidroklorid; Flurazepammonohydroklorid; Flurazepamo monohidrochloridas; Monochidrocloruro de flurazepam; Флуразепама Моногидрохлорид.
$C_{21}H_{23}ClFN_3O$,HCl=424.3
CAS — 36105-20-1.
ATC — N05CD01.
ATC Vet — QN05CD01.
UNII — 7C4JH842IJ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Flurazepam Monohydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.0. Protect from light.

Flurazepam Dihydrochloride *(BANM, rINNM)*

Dihidrocloruro de flurazepam; Flurazépam, Dichlorhydrate de; Flurazepam, dihidrocloruro de; Flurazepam Hydrochloride (USAN); Flurazepamhydrochlorid; Flurazepami Dihydrochloridum; NSC-78559; Ro-5-6901; Флуразепама Дигидрохлорид.
$C_{21}H_{23}ClFN_3O$,2HCl=460.8
CAS — 1172-18-5.
ATC — N05CD01.
ATC Vet — QN05CD01.
UNII — 756RDM536M.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Flurazepam Hydrochloride). An off-white to yellow crystalline powder. Is odourless or has a slight odour. Soluble 1 in 2 of water, 1 in 4 of alcohol, 1 in 90 of chloroform, 1 in 3 of methyl alcohol, 1 in 69 of isopropyl alcohol, 1 in 5000 of ether and of petroleum spirit, and 1 in 2500 of benzene. A solution in water is acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Flurazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (p. 1033.2).

In the USA flurazepam is given as the dihydrochloride and doses are expressed in terms of this salt; flurazepam dihydrochloride 30 mg is equivalent to about 25.3 mg of flurazepam. Doses of 15 to 30 mg orally at night are given. In the UK flurazepam is given as the monohydrochloride although doses are expressed in terms of the base; flurazepam monohydrochloride 32.8 mg is equivalent to about 30 mg of flurazepam. Oral doses equivalent to 15 to 30 mg of flurazepam at night are given.

A maximum initial dose of 15 mg has been suggested for elderly or debilitated patients.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 7.5 to 15 mg of flurazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Effects on the liver. Reports of cholestatic jaundice after the use of flurazepam.[1,2]

1. Fang MH, *et al.* Cholestatic jaundice associated with flurazepam hydrochloride. *Ann Intern Med* 1978; **89:** 363–4.
2. Reynolds R, *et al.* Cholestatic jaundice induced by flurazepam hydrochloride. *Can Med Assoc J* 1981; **124:** 893–4.

Effects on taste. Flurazepam had been reported to cause dysgeusia.[1]

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983 (June): 368–71.

Renal impairment. Five patients on maintenance haemodialysis developed encephalopathy attributed to flurazepam and diazepam.[1]

1. Taclob L, Needle M. Drug-induced encephalopathy in patients on maintenance haemodialysis. *Lancet* 1976; **ii:** 704–5.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Flurazepam is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 30 to 60 minutes of oral doses. It undergoes extensive first-pass metabolism and is excreted in the urine, mainly as conjugated metabolites. The major active metabolite, *N*-desalkylflurazepam, is reported to have a half-life ranging from 47 to 100 hours or more and to cross the placental barrier.

Metabolism. The metabolism of flurazepam was studied in 4 healthy male subjects given 30 mg daily for 2 weeks.[1] A hydroxyethyl metabolite was present in the blood shortly after a dose. The *N*-desalkyl metabolite, the major metabolite in the blood, had a half-life ranging from 47 to 100 hours. Steady-state concentrations were reached after 7 to 10 days and were about 5 to 6 times greater than those seen on day 1. Results from a study in 3 patients indicated that some metabolism of flurazepam may occur in the small bowel mucosa.[2]

1. Kaplan SA, *et al.* Blood level profile in man following chronic oral administration of flurazepam hydrochloride. *J Pharm Sci* 1973; **62:** 1932–5.
2. Mahon WA, *et al.* Metabolism of flurazepam by the small intestine. *Clin Pharmacol Ther* 1977; **22:** 228–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Staurodorm; ***Braz.***: Dalmadorm; ***Canad.***: Dalmane; Novo-Flupam†; Som Pam; Somnol†; ***Ger.***: Dalmadorm; Staurodorm Neu; ***Gr.***: Dalmadorm; ***Hong Kong***: Dalmadorm; ***India***: Fluracap; Fluraz; Nindral; ***Indon.***: Dalmadorm; ***Irl.***: Dalmane; Dalmapam; ***Ital.***: Dalmadorm; Felison; Flunox; Remdue; Valdorm; ***Jpn***: Benozil; ***Neth.***: Dalmadorm; ***Port.***: Dalmadorm; Morfex; ***S.Afr.***: Dalmadorm†; ***Singapore***: Dalmadorm†; ***Spain***: Dormodor; ***Switz.***: Dalmadorm; ***Thai.***: Dalmadorm†; ***UK***: Dalmane; ***USA***: Dalmane†; ***Venez.***: Fluralema.

Pharmacopoeial Preparations
BP 2014: Flurazepam Capsules;
USP 36: Flurazepam Hydrochloride Capsules.

Fluspirilene *(BAN, USAN, rINN)*

Fluspirileeni; Fluspirilen; Fluspirilenas; Fluspirilène; Fluspirileno; Fluspirilenum; McN-JR-6218; R-6218; Флуспирилен.
8-[4,4-Bis(4-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.
$C_{29}H_{31}F_2N_3O$=475.6
CAS — 1841-19-6.
ATC — N05AG01.
ATC Vet — QN05AG01.
UNII — C5QA4GLR9M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fluspirilene). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. Protect from light.

Profile

Fluspirilene is a diphenylbutylpiperidine antipsychotic and has general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.2). It is less likely to cause sedation. Fluspirilene has been given by deep intramuscular injection for the treatment of psychoses including schizophrenia (below). A usual initial dose is up to 2 mg weekly by deep intramuscular injection, increased according to response. Usual maintenance doses have ranged from 1 to 10 mg weekly although higher doses have been used in exceptional cases.

Adverse effects. References.

1. McCreadie RG, *et al.* Probable toxic necrosis after prolonged fluspirilene administration. *BMJ* 1979; **1:** 523–4.

Schizophrenia. A systematic review[1] found that evidence to support the use of depot fluspirilene over oral chlorpromazine or other depot antipsychotics in the treatment of schizophrenia (p. 1031.3) was lacking.

1. Abhijnhan A, *et al.* Depot fluspirilene for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Imap; ***Belg.***: Imap; ***Ger.***: Fluspi†; Imap; ***Neth.***: Imap.

Flutoprazepam *(rINN)*

Flutoprazépam; Flutoprazepamum; KB-509; Флутопразепам.
7-Chloro-1-(cyclopropylmethyl)-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.
$C_{19}H_{16}ClFN_2O$=342.8
CAS — 25967-29-7.
UNII — 2GHY1101MM.

Profile

Flutoprazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given for the short-term treatment of anxiety disorders (p. 1028.1) and insomnia (p. 1033.2). Typical oral doses are 2 to 4 mg once or twice daily; in the elderly, the maximum daily dose should be 4 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Restas.

Gepirone Hydrochloride *(USAN, rINNM)*

BMY-13805-1; Gepirona, hidrocloruro de; Gépirone, Chlorhydrate de; Gepironi Hydrochloridum; Hidrocloruro de gepirona; MJ-13805-1; Org-33062 (gepirone); Гепирона Гидрохлорид.
3,3-Dimethyl-*N*-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}glutarimide hydrochloride.
$C_{19}H_{29}N_5O_2$,HCl=395.9
CAS — 83928-76-1 (gepirone); 83928-66-9 (gepirone hydrochloride).

ATC — N06AX19.
ATC Vet — QN06AX19.
UNII — 80C9L8EP6V.

NOTE. The names Ariza and Variza have been used as trade marks for gepirone.

Profile

Gepirone is structurally related to buspirone (p. 1042.1). It has been investigated as the hydrochloride for the treatment of depression and anxiety disorders.

Action. Gepirone is a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the 5-HT_{1A} subtype. For reference to the actions and potential uses of such drugs, see Buspirone, p. 1042.2.

References.
1. Feiger AD, *et al.* Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. *J Clin Psychiatry* 2003; **64:** 243–9.
2. Robinson DS, *et al.* A review of the efficacy and tolerability of immediate-release and extended-release formulations of gepirone. *Clin Ther* 2003; **25:** 1618–33.
3. Amsterdam JD, *et al.* Sustained efficacy of gepirone-IR in major depressive disorder: a double-blind placebo substitution trial. *J Psychiatr Res* 2004; **38:** 259–65.
4. Alpert JE, *et al.* Gepirone extended-release treatment of anxious depression: evidence from a retrospective subgroup analysis in patients with major depressive disorder. *J Clin Psychiatry* 2004; **65:** 1069–75.
5. Keller MB, *et al.* Relapse prevention with gepirone ER in outpatients with major depression. *J Clin Psychopharmacol* 2005; **25:** 79–84.
6. Bielski RJ, *et al.* Gepirone extended-release in the treatment of adult outpatients with major depressive disorder: a double-blind, randomized, placebo-controlled, parallel-group study. *J Clin Psychiatry* 2008; **69:** 571–7.

Halazepam *(BAN, USAN, rINN)*

Halatsepaami; Halazépam; Halazepamum; Sch-12041; Галазепам.

7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepin-2-one.

$C_{17}H_{12}ClF_3N_2O$=352.7

CAS — 23092-17-3.
ATC — N05BA13.
ATC Vet — QN05BA13.
UNII — 320YC168LF.

Profile

Halazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given for the short-term treatment of anxiety disorders (p. 1028.1) in usual oral doses of 20 to 40 mg every 6 to 8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Pacinone; ***Spain***: Alapryl.

Haloperidol *(BAN, USAN, rINN)*

Aloperidolo; Halopéridol; Haloperidoli; Haloperidolis; Haloperidolum; McN-JR-1625; R-1625; Галоперидол.

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

$C_{21}H_{23}ClFNO_2$=375.9

CAS — 52-86-8.
ATC — N05AD01.
ATC Vet — QN05AD01.
UNII — J6292F8L3D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Haloperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol, in dichloromethane, and in methyl alcohol. Protect from light.

USP 36: (Haloperidol). A white to faintly yellowish amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 15 of chloroform, and 1 in 200 of ether. A saturated solution is neutral to litmus. Store in airtight containers. Protect from light.

Dilution. See Incompatibility, below.

Incompatibility. A precipitate formed after dilution of haloperidol (as the lactate) in sodium chloride 0.9% injection when the final haloperidol concentration was 1 mg/mL or higher.[1]

Undiluted haloperidol (5 mg/mL) injection has been reported to be incompatible with heparin sodium (diluted in sodium chloride 0.9% or glucose 5% injection),[2] sodium nitroprusside (diluted in glucose 5%),[1] cefmetazole sodium,[3] and diphenhydramine.[4] A mixture of equal volumes of sargramostim 10 micrograms/mL and haloperidol (as the lactate) 200 micrograms/mL resulted in a precipitate at 4 hours.[5]

1. Outman WR, Monolakis J. Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 1539–41.
2. Solomon DA, Nasimnyk KK. Compatibility of haloperidol lactate and heparin sodium. *Am J Hosp Pharm* 1982; **39:** 843–4.
3. Hutchings SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
4. Ukhun IA. Compatibility of haloperidol and diphenhydramine in a hypodermic syringe. *Ann Pharmacother* 1995; **29:** 1168–9.
5. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; **49:** 402–6.

Stability. A combination of the stabilisers benzyl alcohol and vanillin could protect haloperidol from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilisation of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Haloperidol Decanoate *(BANM, USAN, rINNM)*

Decanoato de haloperidol; Halopéridol, Décanoate d'; Haloperidol, decanoato de; Haloperidoldecanoat; Haloperidoldekanoat; Haloperidol-dekanoát; Haloperidoli Decanoas; Haloperidolidekanoaatti; Haloperidolio dekanoatas; R-13672; Галоперидола Деканоат.

$C_{31}H_{41}ClFNO_3$=530.1

CAS — 74050-97-8.
ATC — N05AD01.
ATC Vet — QN05AD01.
UNII — AC20PJ4101.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Haloperidol Decanoate). A white or almost white powder. It melts at about 42 degrees. Practically insoluble in water; very soluble in alcohol, in dichloromethane, and in methyl alcohol. Store at a temperature below 25 degrees. Protect from light.

USP 36: (Haloperidol Decanoate). A white or almost white powder. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Haloperidol is a butyrophenone with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It is an antipsychotic with actions most closely resembling those of phenothiazines with a piperazine side-chain.

Haloperidol is used in the treatment of various psychoses including schizophrenia (below) and mania (see Bipolar Disorder, p. 397.2), and in behaviour disturbances (p. 1030.2), in Tourette's syndrome and severe tics (p. 1078.1), in intractable hiccups (p. 1046.3), and in severe anxiety (p. 1028.1), including for the sedation of patients in intensive care (p. 1033.1) or palliative care. Haloperidol has also been used for its antiemetic effect in the management of nausea and vomiting of various causes (p. 1814.3).

Haloperidol is usually given orally or by injection as the base or intramuscularly as the long-acting decanoate ester. Some haloperidol preparations are prepared with the aid of lactic acid and may be stated to contain haloperidol lactate. Doses are expressed in terms of the equivalent amount of haloperidol. Haloperidol decanoate 141 mg is equivalent to about 100 mg of haloperidol. Dosages should be reduced in elderly or debilitated patients; a usual starting dose is half the normal adult dose. Doses at the lower end of the scale are also advised for adolescents; for details of doses in children, see below.

The usual initial *oral* dose for the treatment of **psychoses** and associated behavioural disorders is 0.5 to 5 mg two or three times daily. In severe or resistant psychoses up to 30 mg daily is recommended in the UK, whereas in the USA doses of up to 100 mg daily are allowed; doses above 100 mg daily have rarely been used. The dose should be reduced gradually according to response. Maintenance doses as low as 3 to 10 mg daily may be sufficient.

For the control of acute psychotic conditions, haloperidol may be given *intramuscularly* in doses of 2 to 10 mg; subsequent doses may be given hourly, until symptoms are controlled, although dosage intervals of 4 to 8 hours may be adequate, up to a maximum of 18 mg daily. For the emergency control of very severely disturbed patients, an initial intramuscular dose of no more than 18 mg is recommended. The *intravenous* route has also been used.

In patients already stabilised on an oral dose of haloperidol and requiring long-term therapy the long-acting decanoate ester may be given by *deep intramuscular* injection. The usual initial dose is the equivalent of 10 to 20 times the total daily oral dose of haloperidol, up to a maximum of 100 mg; if more than 100 mg is required for an initial dose the excess should be given after 3 to 7 days. Subsequent doses, usually given every 4 weeks, may be increased in steps of 50 mg to up to 300 mg or more, according to the patient's requirements, both dose and dose interval being adjusted as required.

In the management of **nausea and vomiting** haloperidol has been given in a dose of 1 to 2 mg by *intramuscular* injection. In palliative care haloperidol 1.5 mg may be given orally once or twice daily, increased if necessary to 5 to 10 mg daily given in divided doses; alternatively, it may be given by *subcutaneous* infusion (via a syringe driver) in doses of 2.5 to 10 mg over 24 hours. The *intravenous* route has also been used.

A starting *oral* dose of 0.5 to 1.5 mg three times daily has been suggested for the management of **Tourette's syndrome** and severe **tics**. Up to about 30 mg daily may be needed in Tourette's syndrome, although requirements vary considerably and the dose must be very carefully adjusted to obtain the optimum response; a maintenance dose of 4 mg daily is effective for most patients.

For intractable **hiccups** a suggested *oral* dose is 1.5 mg given 3 times daily adjusted according to response.

An *oral* dose of 500 micrograms twice daily has been used as adjunctive treatment in the short-term management of severe **anxiety disorders**.

In palliative care, haloperidol has been given in a dose of 2 mg *orally* or 2.5 mg by *subcutaneous* injection, repeated every 2 hours if required, for the treatment of **restlessness and confusion**. It may also be given as a subcutaneous infusion in a dose of 5 to 15 mg over 24 hours.

Administration in children. In the UK, for the treatment of **schizophrenia** and **behavioural disorders** in children, a total daily maintenance oral dose of haloperidol 25 to 50 micrograms/kg is given in 2 divided doses. In the USA, a higher dose range of 50 to 150 micrograms/kg daily is given orally to those aged 3 to 12 years and weighing between 15 to 40 kg. A maximum daily dose of 10 mg has been recommended in the UK but US licensed product information states that there is little evidence of behaviour improvement with daily doses of more than 6 mg.

Although unlicensed for the management of **nausea and vomiting** in palliative care, the *BNFC* suggests that infants and children aged 1 month to 12 years may be given 25 to 85 micrograms/kg of haloperidol over 24 hours by continuous subcutaneous infusion; older children may be given 1.5 to 5 mg over 24 hours or an oral dose of 1.5 mg at night increased to 1.5 mg (maximum of 5 mg) twice daily if necessary. The intravenous route has also been used.

In the UK, for the management of **Tourette's syndrome** and severe **tics**, children may be given oral maintenance doses of up to 10 mg daily of haloperidol. Alternatively, the *BNFC* suggests that those aged 5 to 12 years may be given a n oral dose o f 12.5 to 25 micrograms/kg twice daily, adjusted according to response; older children may be given 1.5 mg three times daily. In the USA, oral doses of 50 to 75 micrograms/kg daily are given to those aged 3 to 12 years and weighing between 15 to 40 kg.

In palliative care, the *BNFC* suggests an oral dose of haloperidol 10 to 20 micrograms/kg every 8 to 12 hours for the treatment of **restlessness and confusion**.

Ballism. Dopamine-blocking antipsychotics such as haloperidol may sometimes be needed for the management of patients with ballism (p. 1029.3) when symptoms are severe.

Chorea. For a discussion of the management of various choreas, including mention of the use of haloperidol, see p. 1029.3.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to other drugs. However, they often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p. 1049.2).

Schizophrenia. Systematic reviews[1,2] of the use of haloperidol for schizophrenia (p. 1031.3) concluded that it appears to be of similar efficacy to chlorpromazine although it is associated with a high incidence of extrapyramidal adverse effects. An earlier systematic review[3] considered that the limited evidence did not indicate any advantages of giving haloperidol in doses greater than 7.5 mg daily to patients with uncomplicated acute schizophrenia.

1. Joy CB, *et al.* Haloperidol versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 19/03/08).
2. Leucht C, *et al.* Haloperidol versus chlorpromazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).

3. Waraich PS, *et al*. Haloperidol dose for the acute phase of schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 19/03/08).

Sneezing. Intractable sneezing in a patient was controlled by haloperidol given in doses of up to 5 mg twice daily.[1] Symptoms recurred when treatment was stopped after 5 weeks but responded again to 5 mg three times daily. On gradual reduction of dosage over 6 months the patient had no recurrence and had remained symptom-free after 6 months without medication.

1. Davison K. Pharmacological treatment for intractable sneezing. *BMJ* 1982; **284:** 1163–4.

Stuttering. Stuttering (stammering) is a disorder that affects the fluency of speech. Developmental stuttering usually occurs in early childhood and is more common in boys than girls. While stuttering may cease in some children after only a few months, it may become a chronic condition in others. Stuttering that starts during adulthood is rarer and may be the result of a neurological insult. It should also be remembered that stuttering may be drug induced. While stuttering may be greatly improved with intensive speech training the efficacy of other forms of management such as hypnosis, psychotherapy, counselling, and drug therapy has been largely unconvincing.[1] Many drugs have been used to treat stuttering; however, a review of the literature[2] indicated that there were few adequate studies of their efficacy. Haloperidol was considered to be the most well studied drug and its efficacy had been shown by several double-blind placebo-controlled studies. Most patients needed to continue taking haloperidol to maintain improvement but few did so because of its adverse effects. Double-blind studies have on the whole failed to confirm reports of benefit for drugs such as beta blockers and calcium-channel blockers although isolated patients may have marked improvement. Other drugs that have been studied and which might be of benefit include clomipramine,[3] SSRIs,[4] and atypical antipsychotics[4] such as olanzapine and risperidone; formoterol, local anaesthetics, and injections of botulinum toxin have also been tried.

1. Andrews G, *et al*. Stuttering. *JAMA* 1988; **260:** 1445.
2. Brady JP, *et al*. The pharmacology of stuttering: a critical review. *Am J Psychiatry* 1991; **148:** 1309–16.
3. Gordon CT, *et al*. A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56:** 238–42.
4. Costa D, Kroll R. Stuttering: an update for physicians. *Can Med Assoc J* 2000; **162:** 1849–55.

Taste disorders. For reference to the use of haloperidol in the treatment of taste disorders, see Chlorpromazine, p. 1047.2.

Tourette's syndrome. Many patients with Tourette's syndrome (p. 1030.1) do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide are most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. However, superiority of either drug in terms of efficacy or adverse effects has not been clearly shown.[1,2] Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to be as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al*. Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; **46:** 722–30.
2. Sallee FR, *et al*. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; **154:** 1057–62.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Haloperidol is less likely to cause sedation, hypotension, or antimuscarinic effects, but is associated with a higher incidence of extrapyramidal effects. Haloperidol should be used with great care in children and adolescents as they may be at increased risk of severe dystonic reactions; patients with hyperthyroidism may also be at increased risk. The risk of QT prolongation and/or ventricular arrhythmias may be increased with high doses or with parenteral use of haloperidol, particularly intravenous administration.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of haloperidol by mothers during breast feeding may be of concern, since there have been reports of decline in developmental scores in breast-fed infants. Licensed product information also reports that there have been isolated cases of extrapyramidal effects in breast-fed infants.

The concentration of haloperidol in breast milk of one mother given a mean daily dose of about 30 mg for 6 days was reported to be 5 nanograms/mL; on day 12 the concentration 9 hours after a 12-mg dose was 2 nanograms/mL.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Stewart RB, *et al*. Haloperidol excretion in human milk. *Am J Psychiatry* 1980; **137:** 849–50.

Convulsions. For mention of haloperidol as one of the antipsychotics suitable for patients at risk of seizures, see p. 1047.3.

Effects on the liver. Liver dysfunction with jaundice and eosinophilia developed in a 15-year-old male 4 weeks after starting haloperidol and benzatropine mesilate.[1] The drugs were stopped 2 weeks later but some symptoms lasted for 28 months. The reaction was suggestive of a drug-induced hypersensitivity reaction and haloperidol was the most likely cause. Haloperidol-induced liver injury was considered to be rare.

1. Dincsoy HP, Saelinger DA. Haloperidol-induced chronic cholestatic liver disease. *Gastroenterology* 1982; **83:** 694–700.

Overdosage. Symptoms of haloperidol overdosage in children have ranged from the expected, such as drowsiness, restlessness, confusion, marked extrapyramidal symptoms, and hypothermia,[1,2] to unexpected reactions such as bradycardia (possibly secondary to hypothermia)[1] and an episode of severe, delayed hypertension.[3]

Torsade de pointes has followed overdosage in adults (for references, see Effects on the Cardiovascular System under Chlorpromazine, p. 1047.3).

1. Scialli JVK, Thornton WE. Toxic reactions from a haloperidol overdose in two children: thermal and cardiac manifestations. *JAMA* 1978; **239:** 48–9.
2. Sinaniotis CA, *et al*. Acute haloperidol poisoning in children. *J Pediatr* 1978; **93:** 1038–9.
3. Cummingham DG, Challapalli M. Hypertension in acute haloperidol poisoning. *J Pediatr* 1979; **95:** 489–90.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies haloperidol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Retroperitoneal fibrosis. Obstructive uropathy was noted in a 45-year-old woman given haloperidol 5 to 15 mg daily for 8 years.[1] Benzatropine was also taken during that time, and in the previous 5 years she had taken chlorpromazine and fluphenazine. Retroperitoneal fibrosis was diagnosed and was tentatively associated with long-term antipsychotic therapy.

1. Jeffries JJ, *et al*. Retroperitoneal fibrosis and haloperidol. *Am J Psychiatry* 1982; **139:** 1524–5.

Toxic encephalopathy. Possible toxic encephalopathy after use of high intravenous doses of haloperidol has been reported.[1] The patient, who had a history of bipolar disorder and cerebrovascular accident, had been given increasing intravenous doses of haloperidol (up to 270 mg daily) to control post-surgical agitation. The encephalopathy had resolved 8 days after stopping haloperidol.

1. Maxa JL, *et al*. Possible toxic encephalopathy following high-dose intravenous haloperidol. *Ann Pharmacother* 1997; **31:** 736–7.

Interactions

As for Chlorpromazine, p. 1051.3. The metabolism of haloperidol is mediated by several routes including the cytochrome P450 system, particularly the isoenzymes CYP3A4 and CYP2D6. Therefore, there is the potential for interactions between haloperidol and other drugs that induce, inhibit, or act as a substrate for these isoenzymes, resulting in altered haloperidol concentrations; it may be necessary to amend the dosage of haloperidol when given with such drugs. Haloperidol itself is also an inhibitor of CYP2D6 and may increase the plasma concentrations of tricyclic antidepressants by inhibiting their metabolism.

Haloperidol must be used with extreme caution in patients receiving lithium; an encephalopathic syndrome has been reported after their use together (see p. 431.3).

Pharmacokinetics

Haloperidol is readily absorbed from the gastrointestinal tract after oral use. It is metabolised in the liver and is excreted in the urine and, via the bile, in the faeces; there is evidence of enterohepatic recycling. Owing to first-pass metabolism in the liver, plasma concentrations after oral doses are lower than those after intramuscular injection. Moreover, there is wide intersubject variation in plasma concentrations of haloperidol. In practice, however, no strong correlation has been found between plasma concentrations of haloperidol and its therapeutic effect. Routes of metabolism of haloperidol include oxidative *N*-dealkylation, particularly via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, glucuronidation, and reduction of the ketone group to form an alcohol known as reduced haloperidol. Metabolites are ultimately conjugated with glycine. Haloperidol has been reported to have a plasma elimination half-life ranging from about 12 to 38 hours after oral doses. Haloperidol is about 92% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Haloperidol is distributed into breast milk.

The decanoate ester of haloperidol is very slowly absorbed from the injection site and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to haloperidol.

References.

1. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. *Clin Pharmacokinet* 1999 **37:** 435–56.

Metabolites. The clinical significance of the reduced metabolite of haloperidol has been much debated.[1,2] Its activity appears to be substantially less than that of the parent drug but there is some evidence for re-oxidation of reduced haloperidol to haloperidol.[1-3] Some studies suggest that nonresponders to haloperidol have elevated ratios of reduced haloperidol to haloperidol in the plasma, although other workers have reported contrary findings.[2] Pyridinium metabolites resulting from oxidation of haloperidol have been detected in the urine and there is concern that they may be neurotoxic in a manner similar to MPTP (see Parkinsonism, p. 889.1), a compound which can induce irreversible parkinsonism.[4]

1. Sramek JJ, *et al*. Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22:** 373–80.
2. Froemming JS, *et al*. Pharmacokinetics of haloperidol. *Clin Pharmacokinet* 1989; **17:** 396–423.
3. Chakraborty BS, *et al*. Interconversion between haloperidol and reduced haloperidol in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 45–8.
4. Eyles DW, *et al*. Quantitative analysis of two pyridinium metabolites of haloperidol in patients with schizophrenia. *Clin Pharmacol Ther* 1994; **56:** 512–20.

Therapeutic drug monitoring. Measurement of concentrations of haloperidol or reduced haloperidol in scalp hair has been suggested as a useful means of monitoring compliance.[1,2] Evidence for the existence of any relationship between plasma concentrations of haloperidol and therapeutic effect in schizophrenia has been discussed.[3]

1. Uematsu T, *et al*. Human scalp hair as evidence of individual dosage history of haloperidol: method and retrospective study. *Eur J Clin Pharmacol* 1989; **37:** 239–44.
2. Matsuno H, *et al*. The measurement of haloperidol and reduced haloperidol in hair as an index of dosage history. *Br J Clin Pharmacol* 1990; **29:** 187–94.
3. Ulrich S, *et al*. The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. *Clin Pharmacokinet* 1998; **34:** 227–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Enabran†; Halopidol; Halozen; Limerix; Neupram; ***Austral.***: Haldol; Serenace; ***Austria***: Haldol; ***Belg.***: Haldol; ***Braz.***: Decan Haloper; Haldol; Halo; Haloper; Loperidol†; Uni Haloper; ***Canad.***: Novo-Peridol; ***Chile***: Alternus; Haldol; ***China***: Haridol-D (哈力多-D); ***Denm.***: Serenase; ***Fin.***: Serenase; ***Fr.***: Haldol; ***Ger.***: Haldol; Haloper; ***Gr.***: Alased; Aloperidin; Ovocterol; Sevium; ***Hong Kong***: Haldol; Serenace; ***India***: Benzydol-P; Brain-Rest; Cizoren; Depidol; Dolcin; Gendol; Haldol; Halidace; Halidol; Halobid; Halopace; Halopidol; Haloton; Hexidol; Larenase; Lodol; Mindol; Oprex; Serenace; ***Indon.***: Dores; Govotil; Haldol; Lodomer; Serenace; ***Irl.***: Haldol; Serenace; ***Israel***: Haldol; Haloper; Pericate; Peridor†; ***Ital.***: Haldol; Serenase; ***Malaysia***: Manace; Mapress; ***Mex.***: Haldol; Haloperil; Hispadol; Kepsidol; Pulsit; Trenpe; ***Neth.***: Haldol; ***Norw.***: Haldol; ***NZ***: Haldol; Serenace; ***Philipp.***: Haldol; Seredol; Serenace; ***Pol.***: Decaldol; ***Port.***: Haldol; ***Rus.***: Haloper (Галопер)†; Senorm (Сенорм); ***S.Afr.***: Serenace; ***Singapore***: Haloxen; Manace; Serenace; ***Swed.***: Haldol; ***Switz.***: Haldol; ***Thai.***: H-Tab; Haldol†; Halo-P; Halomed; Halopol; Haricon; Haridol; Perida†; Polyhadon; ***Turk.***: Leptol; Norodol; Sedaperidol; ***UK***: Dozic; Haldol; Serenace; ***USA***: Haldol; ***Venez.***: Haldol; Tiplac.

Multi-ingredient Preparations. ***India***: Cizoren Plus; Combidol; Halotex; Hexidol Forte; Hexidol Kit; Hexidol Plus; Manodol; Mindol Forte; Mindol Plus.

Pharmacopoeial Preparations

BP 2014: Haloperidol Capsules; Haloperidol Injection; Haloperidol Oral Solution; Haloperidol Tablets; Strong Haloperidol Oral Solution;

USP 36: Haloperidol Injection; Haloperidol Oral Solution; Haloperidol Tablets.

Haloxazolam *(rINN)*

Haloxazolamum; Галоксазолам.

10-Bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

$C_{17}H_{14}BrFN_2O_2$=377.2
CAS — 59128-97-1.
UNII — M448L2V8XP.

Pharmacopoeias. In *Jpn*.

Profile

Haloxazolam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given as a hypnotic in the short-term management of insomnia (p. 1033.2) in usual oral doses of 5 or 10 mg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Somelin.

Iloperidone *(BAN, USAN, rINN)*

HP-873; ILO-522; Iloperidona; Iloperidone; Iloperidonum; Илоперидон.
4′-{3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy}-3′-methoxyacetophenone.
$C_{24}H_{27}FN_2O_4$=426.5
CAS — 133454-47-4.
UNII — VPO7KJ050N.

Uses and Administration

Iloperidone is a benzisoxazole atypical antipsychotic reported to be an antagonist at dopamine D_2, serotonin (5-HT_2), and adrenergic (α_1 and α_2) receptors. It is given orally for the treatment of schizophrenia (p. 1031.3) in an initial dose of 1 mg twice daily, increased to 2, 4, 6, 8, 10, and 12 mg twice daily on days 2 to 7, respectively, to the target dose range of 6 to 12 mg twice daily. If therapy has been interrupted for more than 3 days, the dose of iloperidone should be re-titrated.

The usual dose should be reduced by one-half in those who are also taking potent inhibitors of the cytochrome P450 isoenzymes CYP2D6 (such as fluoxetine or paroxetine) or CYP3A4 (such as clarithromycin or ketoconazole), and in poor metabolisers of CYP2D6 substrates.

References.
1. Potkin SG, *et al.* Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. *J Clin Psychopharmacol* 2008; **28** (suppl 1): S4–S11.
2. Kane JM, *et al.* Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol* 2008; **28** (suppl 1): S29–S35.
3. Scott LJ. Iloperidone: in schizophrenia. *CNS Drugs* 2009; **23:** 867–80.
4. Caccia S, *et al.* New atypical antipsychotics for schizophrenia: iloperidone. *Drug Des Devel Ther* 2010; **4:** 33–48.
5. Citrome L. Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. *Expert Opin Drug Metab Toxicol* 2010; **6:** 1551–64.
6. Arif SA, Mitchell MM. Iloperidone: a new drug for the treatment of schizophrenia. *Am J Health-Syst Pharm* 2011; **68:** 301–8.

Adverse Effects, Treatment, and Precautions

Although iloperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with iloperidone are dizziness, somnolence, fatigue, dry mouth, nasal congestion, and weight gain. Other common adverse effects include nausea, diarrhoea, extrapyramidal effects, and arthralgia. Priapism, leucopenia, and hyperprolactinaemia resulting in gynaecomastia and galactorrhoea occur rarely.

Iloperidone has been associated with QT prolongation; it should be stopped in those with persistent QT_c measurements of more than 500 milliseconds. Orthostatic hypotension associated with dizziness, tachycardia, and syncope has also been frequently reported. Iloperidone should be used with caution in patients with cardiovascular or cerebrovascular disease, or with conditions that may predispose to hypotension; in addition, it should be avoided in those with a history of arrhythmias or other conditions that may increase the risk of QT prolongation including bradycardia, recent myocardial infarction, or electrolyte disturbances such as hypokalaemia and hypomagnesaemia. Certain drugs may also increase the risk (see Interactions, below). Baseline serum potassium and magnesium screening should be performed before starting iloperidone therapy in patients who are at risk of significant electrolyte disturbances and periodically monitored thereafter.

Seizures have been noted with iloperidone and it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

Use in patients with hepatic impairment is not recommended due to a lack of data.

Iloperidone may affect the performance of skilled tasks such as driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics and recommendations for monitoring are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by iloperidone. Iloperidone is also an α_1-adrenergic antagonist and may enhance the effects of some antihypertensives. There may be an increased risk of QT prolongation when iloperidone is given with other drugs that are known to cause this effect.

The metabolism of iloperidone is mediated by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Use with drugs that inhibit these isoenzymes can increase plasma concentrations of iloperidone and a dose reduction of iloperidone is recommended.

Pharmacokinetics

Iloperidone is well absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within 2 to 4 hours. It is about 95% bound to serum proteins. Iloperidone is metabolised in the liver mainly by carbonyl reduction, hydroxylation (mediated by the cytochrome P450 isoenzyme CYP2D6 and subject to genetic polymorphism), and *O*-demethylation (mediated by CYP3A4). Excretion is mainly in the urine and, to a lesser extent, in the faeces.

Distribution into milk has been found in studies in *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Fanapt; ***USA***: Fanapt.

Ketazolam *(BAN, USAN, rINN)*

Ketatsolaami; Kétazolam; Ketazolamum; U-28774; Кетазолам.
11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-*d*][1,4]benzodiazepine-4,7(6*H*)-dione.
$C_{20}H_{17}ClN_2O_3$=368.8
CAS — 27223-35-4.
ATC — N05BA10.
ATC Vet — QN05BA10.
UNII — 92A214MD7Y.

Profile

Ketazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given in the short-term treatment of anxiety (p. 1028.1) in usual oral doses of 15 to 60 mg daily, either in divided doses or as a single dose at night. Reduced doses may be required in elderly or debilitated patients.

References.
1. Angelini G, *et al.* Ketazolam, a new long-acting benzodiazepine, in the treatment of anxious patients: a multicenter study of 2,056 patients. *Curr Ther Res* 1989; **45:** 294–304.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ansieten; ***Chile***: Ansietil; Sedatival; ***Ital.***: Anseren; ***Port.***: Unakalm; ***S.Afr.***: Solatran†; ***Spain***: Marcen†; Sedotime; ***Switz.***: Solatran.

Levomepromazine *(BAN, USAN, rINN)*

CL-36467; CL-39743; Levomepromatsiini; Levomepromazin; Levomepromazina; Lévomépromazine; Levomepromazinum; Methotrimeprazine; RP-7044; SKF-S116; XP-03; Левомепромазин.
(-)-*NN*-Dimethyl-3-(2-methoxyphenothiazin-10-yl)-2-methylpropylamine; 3-(2-Methoxyphenothiazin-10-yl)-2-methylpropyldimethylamine.
$C_{19}H_{24}N_2OS$=328.5
CAS — 60-99-1.
ATC — N05AA02.
ATC Vet — QN05AA02.
UNII — 9G0LAW7ATQ.

Pharmacopoeias. In *US*.

USP 36: (Methotrimeprazine). A fine white, practically odourless, crystalline powder. Soluble 1 in 10 of water, of alcohol, and of methyl alcohol, and 1 in 2 of chloroform; freely soluble in ether; sparingly soluble in alcohol at 25 degrees but freely soluble in boiling alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Levomepromazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levomepromazina; Levomepromatsiinihydrokloridi; Levomepromazin hydrochlorid; Levomepromazina, hidrocloruro de; Lévomépromazine, chlorhydrate de; Levomepromazin-hidroklorid; Levomepromazinhydrochlorid; Levomepromazinhydroklorid; Levomepromazini Hydrochloridum; Levomepromazino hidrochloridas; Lewomepromazyny chlorowodorek; Methotrimeprazine Hydrochloride; Левомепромазина Гидрохлорид.
$C_{19}H_{24}N_2OS$,HCl=364.9
CAS — 4185-80-2; 1236-99-3.
ATC — N05AA02.
ATC Vet — QN05AA02.
UNII — 42BB1Y2586.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Levomepromazine Hydrochloride). A white or very slightly yellow, slightly hygroscopic crystalline powder. It deteriorates on exposure to air and light. Freely soluble in water and in alcohol. Store in airtight containers. Protect from light.

Incompatibility. Levomepromazine hydrochloride is reported to be incompatible with alkaline solutions.

Levomepromazine Maleate

(BANM, USAN, rINNM)

Levomepromatsiinimaleaatti; Levomepromazin maleinát; Levomepromazina, maleato de; Lévomépromazine, Maléate de; Levomepromazini maleas; Levomepromazinmaleat; Levomepromazin-maleát; Levomepromazino maleatas; Lewomepromazyny maleinian; Maleato de levomepromazina; Methotrimeprazine Hydrogen Maleate; Methotrimeprazine Maleate; Левомепромазина Малеат.
$C_{19}H_{24}N_2OS$,$C_4H_4O_4$=444.5
CAS — 7104-38-3.
ATC — N05AA02.
ATC Vet — QN05AA02.
UNII — 5KN5Y9V01K.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Levomepromazine Maleate). A white or slightly yellowish crystalline powder. It deteriorates when exposed to air and light. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. The supernatant of a 2% dispersion in water has a pH of 3.5 to 5.5. Protect from light.

Uses and Administration

Levomepromazine is a phenothiazine with pharmacological activity similar to that of both chlorpromazine (p. 1045.3) and promethazine (p. 638.3). It has antihistaminic actions (p. 610.1) as well as CNS effects resembling those of chlorpromazine. It is also reported to have analgesic and antiemetic activity. It is used in the treatment of various psychoses including schizophrenia (p. 1031.3), as an analgesic for moderate to severe pain, and for premedication (see Anaesthesia, p. 1899.1). It is also used in palliative care for the control of symptoms such as restlessness, agitation, pain (p. 1080.1), and nausea and vomiting (p. 1814.3).

Levomepromazine is also used in veterinary medicine.

Levomepromazine is given orally as the maleate or the hydrochloride, or by injection as the hydrochloride. In the UK, doses such as those given below are expressed in terms of the appropriate salt. However, in some countries, the dose of levomepromazine may be expressed in terms of the

base. The embonate has also been used. Care is required in elderly patients because of the risk of severe hypotension; if levomepromazine is given to such patients reduced doses may be necessary.

The usual initial oral dose of levomepromazine maleate for the treatment of **schizophrenia** is 25 to 50 mg daily; the daily dosage is usually divided into 3 portions with a larger portion taken at night. Doses of 100 to 200 mg have been given to non-ambulant patients increased gradually to 1 g daily if necessary.

When used in **palliative care** for the management of severe terminal **pain** and associated **restlessness and agitation**, levomepromazine hydrochloride 12.5 to 25 mg may be given intramuscularly, or by intravenous injection after dilution with an equal volume of sodium chloride 0.9% injection; in cases of severe agitation, up to 50 mg may be given every 6 to 8 hours. Alternatively it may be given, suitably diluted with sodium chloride 0.9% injection, by continuous subcutaneous infusion via a syringe driver; doses range from a total of 25 to 200 mg daily. Patients given large initial doses should remain in bed. If oral therapy is more convenient, levomepromazine maleate may be given orally in a dose of 12.5 to 50 mg every 4 to 8 hours. Although it is licensed for such use either as monotherapy or adjunctive therapy, the *BNF* recommends that it should be reserved as an adjunct to opioid analgesia in patients with severe pain unresponsive to other measures. The *BNF* also suggests an oral dose of levomepromazine maleate 6 to 50 mg daily given as a single dose or in 2 divided doses for the management of **nausea and vomiting** where first-line antiemetics have proved inadequate. Alternatively, it may be given by continuous subcutaneous infusion (as above) in doses ranging from a total of 5 to 25 mg daily; however, sedation can limit the dose.

For details of doses in children, see below.

Levomepromazine hydrochloride given parenterally has been used in some countries for the control of acute pain, as a **premedicant**, and for postoperative analgesia. In some countries levomepromazine is also licensed for use as an **anxiolytic** and **sedative**, and in the management of other types of pain, including **labour pain**.

Administration in children. Levomepromazine may be used in children for the treatment of various psychoses including schizophrenia although they are very susceptible to its hypotensive and sedative effects: licensed product information suggests giving a 10-year-old an oral dose of 12.5 to 25 mg of the maleate daily in divided doses; a dose of 37.5 mg daily should not be exceeded.

Experience with parenteral use of levomepromazine hydrochloride in children is limited but the *BNFC* suggests a dose of 100 to 400 micrograms/kg given over 24 hours by continuous intravenous or subcutaneous infusion for those aged 1 month to 12 years in the management of nausea and vomiting in palliative care; older children may be given the usual adult dose (see p. 1079.3). It has also been used in the treatment of pain and associated restlessness and confusion in palliative care in a dose of 0.35 to 3 mg/kg given over 24 hours by continuous subcutaneous infusion for those aged 1 to 12 years; older children may be given the usual adult dose (see above).

Pain. As levomepromazine appears to possess intrinsic analgesic activity in addition to its antiemetic and antipsychotic actions it has been used for the symptomatic control of restlessness and vomiting and as an adjunct to opioid analgesics in pain control (see Choice of Analgesic, p. 4.2) in terminally ill patients.

References.

1. Oliver DJ. The use of methotrimeprazine in terminal care. *Br J Clin Pract* 1985; **39**: 339–40.
2. Patt RB, *et al*. The neuroleptics as adjuvant analgesics. *J Pain Symptom Manage* 1994; **9**: 446–53.
3. O'Neill J, Fountain A. Levomepromazine (methotrimeprazine) and the last 48 hours. *Hosp Med* 1999; **60**: 564–7.
4. Skinner J, Skinner A. Levomepromazine for nausea and vomiting in advanced cancer. *Hosp Med* 1999; **60**: 568–70.

HEADACHE. Levomepromazine is one of those phenothiazines (see p. 1046.3) that has been effective[1] in relieving the pain of severe migraine attacks.

1. Stiell IG, *et al*. Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20**: 1201–5.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2, although it may be more sedating. See also Adverse Effects of Antihistamines, p. 613.1.

Levomepromazine may cause severe orthostatic hypotension, and patients taking large initial doses, patients over 50 years of age, or those given injections, should be lying down. Children are very susceptible to the hypotensive and sedative effects of levomepromazine.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levomepromazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Antidepressants. Although *MAOIs* have been used with phenothiazines without untoward effects, the use of levomepromazine with MAOIs should probably be avoided as this combination has been implicated in 2 fatalities.[1,2]

1. Barsa JA, Saunders JC. A comparative study of tranylcypromine and pargyline. *Psychopharmacologia* 1964; **6**: 295–8.
2. McQueen EG. New Zealand committee on adverse drug reactions: fourteenth annual report 1979. *N Z Med J* 1980; **91**: 226–9.

Pharmacokinetics

In a study involving 5 psychiatric patients peak plasma concentrations of levomepromazine were noted 1 to 4 hours after oral doses and 30 to 90 minutes after injection into the gluteal muscle.[1] About 50% of an oral dose reached the systemic circulation. Although the metabolite levomepromazine sulfoxide could not be detected after a single intramuscular injection, it was found in concentrations higher than unmetabolised levomepromazine after single and multiple oral dosage, both substances reaching a steady state in the plasma within 7 days of starting multiple-dose oral therapy. Fluctuations in plasma concentration during multiple-dose oral therapy indicated that until the correlation between acute adverse effects and peak plasma concentration of levomepromazine had been further studied the total daily dose should be divided into 2 or 3 portions when larger oral doses of levomepromazine are used.

1. Dahl SG. Pharmacokinetics of methotrimeprazine after single and multiple doses. *Clin Pharmacol Ther* 1976; **19**: 435–42.

Half-life. In 8 psychiatric patients given levomepromazine 50 to 350 mg daily the plasma half-life showed wide variation, from 16.5 to 77.8 hours, and did not correlate with the dose given.[1]

1. Dahl SG, *et al*. Pharmacokinetics and relative bioavailability of levomepromazine after repeated administration of tablets and syrup. *Eur J Clin Pharmacol* 1977; **11**: 305–310.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Detenler; Levolam; Nozinan; Sunonix; Togrel; ***Austria***: Nozinan; ***Belg.***: Nozinan; ***Braz.***: Levozine; Meprozin; Neozine; ***Canad.***: Apo-Methoprazine; Novo Meprazine; Nozinan; ***Chile***: Sinogan; ***Cz.***: Tisercin; ***Denm.***: Nozinan; ***Fin.***: Levozin; Nozinan†; ***Fr.***: Nozinan; ***Ger.***: Levium†; Neurocil; ***Gr.***: No-Calm; Nozinan; Sinogan; ***Hung.***: Tisercin; ***Irl.***: Nozinan; ***Israel***: Methozane†; Nozinan; Ronexine; ***Ital.***: Nozinan; ***Mex.***: Levocina; Sinogan; ***Neth.***: Nozinan; ***Norw.***: Nozinan; ***NZ***: Nozinan; ***Philipp.***: Nozinan; ***Pol.***: Tisercin; ***Port.***: Nozinan; ***Rus.***: Tisercin (Тизерцин); ***Spain***: Sinogan; ***Swed.***: Nozinan; ***Switz.***: Nozinan; ***UK***: Levinan; Nozinan; ***Ukr.***: Tisercin (Тизерцин); ***Venez.***: Sinogan.

Pharmacopoeial Preparations

BP 2014: Levomepromazine Injection; Levomepromazine Tablets;

USP 36: Methotrimeprazine Injection.

Loprazolam Mesilate *(BANM, rINNM)*

HR-158; Loprazolam, Mésilate de; Loprazolam, mesilato de; Loprazolam Mesylate; Loprazolam Methanesulphonate; Loprazolami Mesilas; Mesilato de loprazolam; RU-31158; Лопразолама Мезилат.

6-(2-Chlorophenyl)-2,4-dihydro-2-(4-methylpiperazin-1-ylmethylene)-8-nitroimidazo[1,2-*a*][1,4]benzodiazepin-1-one methanesulphonate monohydrate.

$C_{23}H_{21}ClN_6O_3,CH_4O_3S,H_2O$=579.0

CAS — 61197-73-7 (loprazolam); 70111-54-5 (anhydrous loprazolam mesilate).

ATC — N05CD11.

ATC Vet — QN05CD11.

UNII — VKF8383J65.

Pharmacopoeias. In *Br.*

BP 2014: (Loprazolam Mesilate). A yellow crystalline powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether.

Uses and Administration

Loprazolam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is usually used as a hypnotic in the short-term management of insomnia (p. 1033.2). Loprazolam is given as the mesilate but doses are expressed in terms of the base; loprazolam mesilate 1.25 mg is equivalent to about 1 mg of loprazolam. Usual oral doses are equivalent to 1 mg of loprazolam at night; this may be increased to up to 2 mg if necessary. A starting dose of 500 micrograms increased to a maximum of 1 mg may be appropriate for elderly or debilitated patients.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 0.5 to 1 mg of loprazolam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16**: 337–64.
2. Dorling MC, Hindmarch I. Pharmacokinetic profile of loprazolam in 12 young and 12 elderly healthy volunteers. *Drugs Exp Clin Res* 2001; **27**: 151–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dormonoct; ***Belg.***: Dormonoct; ***Fr.***: Havlane; ***Neth.***: Dormonoct; ***Port.***: Dormonoct; ***S.Afr.***: Dormonoct; ***Spain***: Somnovit.

Pharmacopoeial Preparations

BP 2014: Loprazolam Tablets.

Lorazepam *(BAN, USAN, rINN)*

Loratsepaami; Lorazepám; Lorazépam; Lorazepamas; Lorazepamum; Wy-4036; Лоразепам.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1,4-benzodiazepin-2-one.

$C_{15}H_{10}Cl_2N_2O_2$=321.2

CAS — 846-49-1.

ATC — N05BA06.

ATC Vet — QN05BA06.

UNII — O26FZP769L.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of lorazepam:

Benzo; Somnios.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Lorazepam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; sparingly or slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Lorazepam). A white or practically white, practically odourless powder. Insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Visual incompatibility has been noted with lorazepam and sargramostim[1] or aztreonam.[2]

1. Trissel LA, *et al*. Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; **49**: 402–6.
2. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52**: 1086–90.

Solubility. The solubility of lorazepam in fluids for intravenous use (water, glucose injection, lactated Ringer's injection, and sodium chloride injection) was greatest in glucose injection 5% at 62 micrograms/mL and lowest in sodium chloride injection 0.9% at 27 micrograms/mL;[1] these differences in solubility appeared to be pH related. Commercial injections are reported to contain polyethylene glycol in propylene glycol to overcome this poor solubility. However, precipitation has been noted[2] in solutions prepared by dilution of lorazepam injection with sodium chloride injection 0.9% to a concentration of 500 micrograms/mL. One group of workers[3] have reported that they had overcome such problems of precipitation by using glucose injection 5% as a diluent and by avoiding final concentrations of lorazepam between 80 micrograms/mL and 1 mg/mL. It was suggested that the propylene glycol in the mixture might account for the unusual concentration effect. Such recommendations have been adopted by another group[4] although they saw that precipitation occurred if a formulation of lorazepam containing

4 mg/mL was used to prepare the injection; no precipitation was noted when a formulation containing 2 mg/mL was used. The group also commented that a US manufacturer of lorazepam injection advised that admixtures should be prepared with the 2 mg/mL formulation only.

1. Newton DW, *et al.* Lorazepam solubility in and sorption from intravenous admixture solutions. *Am J Hosp Pharm* 1983; **40:** 424–7.
2. Boullata JI, *et al.* Precipitation of lorazepam infusion. *Ann Pharmacother* 1996; **30:** 1037–8.
3. Volles DF, *et al.* More on usability of lorazepam admixtures for continuous infusion. *Am J Health-Syst Pharm* 1996; **53:** 2753–4.
4. Levanda M. Noticeable difference in admixtures prepared from lorazepam 2 and 4 mg/ml. *Am J Health-Syst Pharm* 1998; **55:** 2305.

Sorption. Significant loss of lorazepam has been reported from solutions stored in PVC[1] or polypropylene[2] giving equipment; polyolefin[3-5] or glass[6] equipment appears to be more suitable.

1. Hoey LL, *et al.* Lorazepam stability in parenteral solutions for continuous intravenous administration. *Ann Pharmacother* 1996; **30:** 343–6.
2. Stiles ML, *et al.* Stability of deferoxamine mesylate, floxuridine, fluorouracil, hydromorphone hydrochloride, lorazepam, and midazolam hydrochloride in polypropylene infusion-pump syringes. *Am J Health-Syst Pharm* 1996; **53:** 1583–8.
3. Trissel LA, Pearson SD. Storage of lorazepam in three injectable solutions in polyvinyl chloride and polyolefin bags. *Am J Hosp Pharm* 1994; **51:** 368–72.
4. Norenberg JP, *et al.* Stability of lorazepam in 0.9% sodium chloride stored in polyolefin bags. *Am J Health-Syst Pharm* 2004; **61:** 1039–41.
5. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
6. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Uses and Administration

Lorazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term treatment of anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1), as a hypnotic in the short-term management of insomnia (p. 1033.2), and as an anticonvulsant particularly in the management of status epilepticus (p. 510.2). Lorazepam has a prolonged antiepileptic action and may be the preferred initial treatment in status epilepticus if intravenous access is available. It is also used for its sedative and amnestic properties in premedication and as an adjunct in regimens for the control of nausea and vomiting associated with cancer chemotherapy (below).

Lorazepam is usually given orally or by injection as the base although the pivalate is available for oral use in some countries. Sublingual tablets are used in some countries in doses similar to those for standard tablets. The intramuscular route is usually only used when oral or intravenous dosage is not possible. Injections should usually be diluted before use; intravenous injections should be given at a rate of not more than 2 mg/minute into a large vein. Lorazepam should be given in reduced dosage to elderly or debilitated patients; half the usual adult dose, or less, may be sufficient.

The usual oral dose of lorazepam for the treatment of **anxiety disorders** is 1 to 6 mg daily in 2 or 3 divided doses with the largest dose taken at night; up to 10 mg daily has been given. A dose of 25 to 30 micrograms/kg may be given by injection every 6 hours for acute anxiety. Lorazepam has also been used for **panic disorder**. A suggested oral dose in the *BNF* is 3 to 5 mg daily. For acute attacks, parenteral lorazepam may be given; the *BNF* suggests a dose of 25 to 30 micrograms/kg (usual range 1.5 to 2.5 mg) repeated every 6 hours if necessary. A single oral dose of 1 to 4 mg at bedtime may be given for **insomnia** associated with anxiety. However, the MHRA in the UK advises against the use of oral daily doses of lorazepam above 4 mg for anxiety and phobia, and 2 mg for insomnia.

For **premedication** an oral dose of 2 to 3 mg may be given the night before the operation followed by a further dose of 2 to 4 mg given 1 to 2 hours before the operation. Lorazepam may also be given parenterally for premedication; UK licensed product information recommends that a dose of 50 micrograms/kg may be given 30 to 45 minutes before the operation if given intravenously or 1 to 1½ hours before if given intramuscularly. Similar regimens are also used in other countries; US licensed product information suggests a maximum dose of 4 mg when given intravenously or intramuscularly.

In the management of **status epilepticus** 4 mg may be given as a single intravenous dose; this may be repeated once after 10 to 15 minutes if seizures continue or recur. The *BNF* suggests that this dose may also be given for febrile **convulsions** and convulsions due to poisoning.

For details of doses in children, see below.

In patients receiving modestly emetogenic chemotherapy, lorazepam 1 to 2 mg orally may be added to antiemetic therapy with domperidone or metoclopramide, for the prophylaxis of **nausea and vomiting**. The addition of lorazepam may be helpful in the prevention of anticipatory symptoms because of its anxiolytic, sedative, and amnestic effects.

Administration in children. For **premedication** in children, the *BNFC* suggests that 50 to 100 micrograms/kg (maximum of 4 mg) of lorazepam may be given orally at least 1 hour before surgery to those aged 1 month to 12 years; older children may be given 1 to 4 mg. The same dose may be given the night before in addition to, or to replace, the dose before the operation. The *BNFC* also suggests that 50 to 100 micrograms/kg (maximum of 4 mg) may be given by slow intravenous injection, over 3 to 5 minutes (maximum rate of 50 micrograms/kg over 3 minutes), 30 to 45 minutes before the operation to those aged 1 month to 18 years. In the UK, oral lorazepam is licensed for use in children aged 5 years and over and parenteral preparations are licensed in those aged 12 years and over *when used as a premedicant*.

In the management of **status epilepticus** UK licensed product information recommends a single intravenous dose of 2 mg. Alternatively, the *BNFC* suggests that neonates and children up to 12 years old may be given 100 micrograms/kg (maximum of 4 mg) as a single dose by slow intravenous injection; this may be repeated once after 10 minutes if necessary. Older children may be given the usual adult dose (see above). The *BNFC* also recommends these doses for febrile convulsions and convulsions due to poisoning.

Catatonia. Lorazepam has been tried[1,2] with some success in the treatment of catatonia.

1. Manjunatha N, *et al.* Idiopathic recurrent catatonia needs maintenance lorazepam: case report and review. *Aust N Z J Psychiatry* 2007; **41:** 625–7.
2. Seethalakshmi R, *et al.* Catatonic syndrome: importance of detection and treatment with lorazepam. *Ann Clin Psychiatry* 2008; **20:** 5–8.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders and the value of benzodiazepines, see p. 1030.2.

References.

1. Bieniek SA, *et al.* A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; **18:** 57–62.
2. Alexander J, *et al.* Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting: pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. *Br J Psychiatry* 2004; **185:** 63–9.

Nausea and vomiting. Lorazepam is used as an adjunct[1,2] for the control of nausea and vomiting associated with cancer chemotherapy (p. 1814.3).

1. Malik IA, *et al.* Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin: a prospective randomized trial. *Am J Clin Oncol* 1995; **18:** 170–5.
2. Bleicher J, *et al.* Lorazepam, diphenhydramine, and haloperidol transdermal gel for rescue from chemotherapy-induced nausea/vomiting: results of two pilot trials. *J Support Oncol* 2008; **6:** 27–32.

Premedication and sedation. Lorazepam is used as a premedicant (see Anaesthesia, p. 1899.1) and as a sedative for therapeutic and investigative procedures such as dental treatment (p. 1032.2) and endoscopy (p. 1032.3), and also in intensive care (p. 1033.1).

References.

1. Maltais F, *et al.* A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest* 1996; **109:** 1195–8.

Substance dependence. Lorazepam has been used in the management of symptoms of alcohol withdrawal (p. 1735.1).

References.

1. D'Onofrio G, *et al.* Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; **340:** 915–19.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 500 micrograms of lorazepam may be considered equivalent to about 5 mg of diazepam.

Withdrawal symptoms. In a prospective open-label study[1] of 29 children, withdrawal symptoms occurred in 7 after stopping lorazepam, which had been used for sedation during mechanical ventilation; the dose of lorazepam had been tapered over 6 days before stopping treatment.

1. Dominguez KD, *et al.* Withdrawal from lorazepam in critically ill children. *Ann Pharmacother* 2006; **40:** 1035–9.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. Pain and a sensation of burning have occurred after injection of lorazepam.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of lorazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Free lorazepam concentrations in the breast milk of 4 mothers ranged from 8 to 9 nanograms/mL four hours after receiving a 3.5-mg oral dose.[2] This represented about 15 to 26% of the concentration in plasma, and was probably sufficiently low to cause no adverse effects in breast-fed infants.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth* 1985; **57:** 1042–3.

Effects on the blood. A case of pancytopenia associated with oral lorazepam was reported[1] in 1988; only 5 instances of thrombocytopenia and none of leucopenia had been reported to the UK CSM or the UK manufacturers over the previous 13 years.

1. El-Sayed S, Symonds RP. Lorazepam induced pancytopenia. *BMJ* 1988; **296:** 1332.

Effects on fluid and electrolyte homoeostasis. Inappropriate secretion of antidiuretic hormone related to ingestion of lorazepam was considered to be the cause of hyponatraemia in an 81-year-old woman.[1]

1. Engel WR, Grau A. Inappropriate secretion of antidiuretic hormone associated with lorazepam. *BMJ* 1988; **297:** 858.

Effects on the nervous system. For reference to extrapyramidal disorders associated with use of lorazepam, see Diazepam, p. 1066.1.

The elderly. For discussion of the need for reduced dosage of benzodiazepines in elderly patients, see Diazepam, p. 1067.2.

Formulation. Some parenteral formulations of lorazepam contain benzyl alcohol, polyethylene glycol, and propylene glycol. Benzyl alcohol may cause 'gasping syndrome' in neonates (see p. 1741.1) and should be avoided in infants and children up to 3 years old. Polyethylene glycol and propylene glycol have also been reported to cause toxicity (see p. 2205.3) particularly in patients with renal or hepatic impairment and in children.

Hepatic impairment. Lorazepam is contra-indicated in severe hepatic impairment; patients with mild to moderate impairment may require reduced doses. Although the elimination half-life of lorazepam was increased in 13 patients with alcoholic cirrhosis compared with 11 control subjects, this was not associated with an impairment in systemic plasma clearance.[1] With the exception of a modest decrease in the extent of plasma protein binding, acute viral hepatitis had no effect on the disposition kinetics of lorazepam.

1. Kraus JW, *et al.* Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; **24:** 411–19.

Local reactions. Of 40 patients given a single intravenous dose of lorazepam 4 mg three had local thrombosis 2 to 3 days later and 6 had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution].

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; **2:** 1384–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lorazepam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Lorazepam is readily absorbed from the gastrointestinal tract after oral doses, with a bioavailability of about 90%; peak plasma concentrations occur about 2 hours after an oral dose. The absorption profile after intramuscular injection is similar to that after oral dosage.

Lorazepam is about 85% bound to plasma proteins. It crosses the blood-brain barrier and the placenta; it is also distributed into breast milk. Lorazepam is metabolised in the liver to the inactive glucuronide, and excreted in the urine. The elimination half-life has been reported to range from about 10 to 20 hours.

References.

1. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; **6:** 89–105.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; **57:** 135–45.

3. Swart EL, *et al*. Population pharmacokinetics of lorazepam and midazolam and their metabolites in intensive care patients on continuous venovenous hemofiltration. *Am J Kidney Dis* 2005; **45:** 360–71.
4. Chung JY, *et al*. Effect of the UGT2B15 genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. *Clin Pharmacol Ther* 2005; **77:** 486–94.
5. de Wit M, *et al*. Lorazepam concentrations, pharmacokinetics and pharmacodynamics in a cohort of mechanically ventilated ICU patients. *Int J Clin Pharmacol Ther* 2006; **44:** 466–73.

Children. References[1,2] to the pharmacokinetics of lorazepam in children.

1. Relling MV, *et al*. Lorazepam pharmacodynamics and pharmacokinetics in children. *J Pediatr* 1989; **114:** 641–6.
2. Muchohi SN, *et al*. Pharmacokinetics and clinical efficacy of lorazepam in children with severe malaria and convulsions. *Br J Clin Pharmacol* 2008; **65:** 12–21.

NEONATES. References[1-3] to slow elimination of lorazepam by neonates.

1. Cummings AJ, Whitelaw AGL. A study of conjugation and drug elimination in the human neonate. *Br J Clin Pharmacol* 1981; **12:** 511–15.
2. McDermott CA, *et al*. Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992; **120:** 479–83.
3. Reiter PD, Stiles AD. Lorazepam toxicity in a premature infant. *Ann Pharmacother* 1993; **27:** 727–9.

Distribution. Evidence suggests that lorazepam undergoes enterohepatic recirculation with possible first-pass metabolism.[1]

1. Herman RJ, *et al*. Disposition of lorazepam in human beings: enterohepatic recirculation and first-pass effect. *Clin Pharmacol Ther* 1989; **46:** 18–25.

CNS. In a study involving 6 healthy subjects, peak plasma-lorazepam concentrations were reached 5 minutes after the end of a one-minute intravenous injection.[1] CNS effects, as measured by EEG activity, were not maximal until 30 minutes after injection; they declined to baseline values slowly over 5 to 8 hours in a similar manner to plasma concentrations. In contrast, CNS effects of diazepam were maximal immediately after the injection. They also declined more rapidly than lorazepam, but again in a similar way to plasma concentrations. Studies in *mice* suggested that the slow onset of action of lorazepam that has been reported by some is at least partly explained by a delay in passage from systemic blood into brain tissue.

1. Greenblatt DJ, *et al*. Kinetic and dynamic study of intravenous lorazepam; comparison with intravenous diazepam. *J Pharmacol Exp Ther* 1989; **250:** 134–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aplacasse; Calmatron; Emotival; Kalmalin; Lorezan; Lyovial; Microzepam; Nervistop; Sidenar; Trapax; ***Austral.***: Ativan; ***Austria***: Merlit; Temesta; ***Belg.***: Docloraze†; Lauracalm†; Lorazemed†; Lorazetop; Loridem; Optisedine; Serenase; Temesta; ***Braz.***: Ansirax; Lorapan; Lorax; Lorazefast; Max-Pax; Mesmerin; ***Canad.***: Ativan; Novo-Lorazem; Nu-Loraz; ***Chile***: Abinol; Amparax; ***China***: Jia Pu Le (佳普乐); Le La An (乐拉安); Lora (罗拉); ***Denm.***: Orfidal; Temesta; ***Fin.***: Temesta; ***Fr.***: Temesta; ***Ger.***: Tavor; Tolid; ***Gr.***: Aripax; Ativan; Cicletan; Dorm; Modium; Nevrogamma; Nifalin; Novhepar; Proneurit; Tavor; Titus; Trankilium; ***Hong Kong***: LAtiwen†; Lorans; Lorivan; Silence; ***India***: Almazine; Anxipose; Atipam; Ativan; C-Van; Calmese; L-Pam; L-Zepam; Larpose; Lopez; Lora; Loracalm; Loraz; Lorcin; Lorel; Loripam; Lorivan; Lorpik; Lorvan; Oratric; Orazep; ***Indon.***: Ativan†; Merlopam; Renaquil; ***Irl.***: Ativan; ***Israel***: Lorivan; ***Ital.***: Control; Loralin; Lorans; Slipirem†; Tavor; Zeloram; ***Malaysia***: Ativan†; Lorans; ***Mex.***: Ativan; Sinestron; ***Neth.***: Temesta; ***NZ***: Ativan; ***Pol.***: Lorafen; ***Port.***: Ansilor; Lorenin; Lorsedal; Rialam; ***Rus.***: Lorafen (Лорафен); ***S.Afr.***: Ativan; Tranqipam; ***Singapore***: Ativan†; Lorans; ***Spain***: Donix; Idalprem†; Orfidal; Placinoral; ***Swed.***: Temesta; ***Switz.***: Lorasifar; Sedazin; Temesta; ***Thai.***: Anta; Anxira; Hawkcopax; Kemora; Lizavan; Lonza; Lora-P; Lora; Loramed; Lorapam†; Lorapine; Loravan; Lorazep; Lorazin; Lozepam; Ora; Razepam; Tranavan; Vemed; Zora; ***Turk.***: Ativan; ***UK***: Ativan; ***USA***: Ativan; ***Venez.***: Ativan.

Multi-ingredient Preparations. ***Switz.***: Somnium.

Pharmacopoeial Preparations
BP 2014: Lorazepam Injection; Lorazepam Tablets;
USP 36: Lorazepam Injection; Lorazepam Oral Concentrate; Lorazepam Tablets.

Lormetazepam *(BAN, USAN, rINN)*

Lormetatsepaami; Lormétazépam; Lormetazepamum; Wy-4082; Лорметазепам.
(*RS*)-7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-1,4-benzodiazepin-2-one.
$C_{16}H_{12}Cl_2N_2O_2$=335.2
CAS — 848-75-9.
ATC — N05CD06.
ATC Vet — QN05CD06.
UNII — GU56C842ZA.

Pharmacopoeias. In *Br.*

BP 2014: (Lormetazepam). A white crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

Uses and Administration

Lormetazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is mainly used as a hypnotic in the short-term management of insomnia (p. 1033.2) in usual oral doses of 0.5 to 1.5 mg at night. A dose of 500 micrograms is recommended for elderly or debilitated patients. Lormetazepam is also used in some countries for premedication.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 0.5 to 1 mg of lormetazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Lormetazepam is rapidly absorbed from the gastrointestinal tract after oral doses, with a bioavailability of about 80%; peak plasma concentrations are reported to occur about 1.5 hours after an oral dose. Binding to plasma proteins is extensive. It is metabolised in the liver to the inactive glucuronide, and excreted in the urine. The terminal half-life is reported to be about 11 hours.

A brief review of the pharmacokinetics of lormetazepam.[1]

1. Greenblatt DJ, *et al*. Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; **8:** 233–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Noctamid; ***Belg.***: Doclormeta†; Loramet; Loranka; Lormetamed†; Metatop; Noctacalm†; Noctamid; Octonox†; Sedaben; Stilaze; ***Chile***: Nocton; ***Denm.***: Pronoctan; ***Fr.***: Noctamide; ***Ger.***: Ergocalm; Loretam; Noctamid; ***Gr.***: Loramet; Noctamid; ***Irl.***: Noctamid; ***Ital.***: Axilium; Ipnolor; Luzul; Mexylor; Minias; ***Neth.***: Noctamid; ***NZ***: Noctamid; ***Pol.***: Noctofer; ***S.Afr.***: Loramet; Noctamid; ***Spain***: Aldosomnil; Loramet; Noctamid; ***Switz.***: Loramet; Noctamid; ***Thai.***: Loramet.

Pharmacopoeial Preparations
BP 2014: Lormetazepam Tablets.

Loxapine *(BAN, USAN, rINN)*

CL-62362; Loksapiini; Loxapin; Loxapina; Loxapinum; Oxilapine; SUM-3170; Локсапин.
2-Chloro-11-(4-methylpiperazin-1-yl)dibenz[*b,f*][1,4]oxazepine.
$C_{18}H_{18}ClN_3O$=327.8
CAS — 1977-10-2.
ATC — N05AH01.
ATC Vet — QN05AH01.
UNII — LER583670J.

Loxapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de loxapina; Loxapina, hidrocloruro de; Loxapine, Chlorhydrate de; Loxapini Hydrochloridum; Локсапина Гидрохлорид.
$C_{18}H_{18}ClN_3O,HCl$=364.3
ATC — N05AH01.
ATC Vet — QN05AH01.
UNII — 376MYL4MAL.

Loxapine Succinate *(BANM, USAN, rINNM)*

CL-71563; Loxapina, succinato de; Loxapine, Succinate de; Loxapini Succinas; Succinato de loxapina; Локсапина Суксинат.
$C_{18}H_{18}ClN_3O,C_4H_6O_4$=446.0
CAS — 27833-64-3.
ATC — N05AH01.
ATC Vet — QN05AH01.
UNII — X595G0MRYU.

Pharmacopoeias. In *US.*

USP 36: (Loxapine Succinate). A white to yellowish, odourless, crystalline powder. Store in airtight containers.

Uses and Administration

Loxapine is a dibenzoxazepine with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It is used for the treatment of psychoses including schizophrenia (below) and for acute agitation associated with bipolar disorder (p. 397.2) or schizophrenia.

In the treatment of psychoses including schizophrenia, loxapine is given orally as the succinate and by intramuscular injection as the base. Doses are expressed in terms of the base; loxapine succinate 34 mg is equivalent to about 25 mg of loxapine. The usual oral dose is 20 to 50 mg daily initially, in 2 divided doses, increased according to response over the next 7 to 10 days to 60 to 100 mg daily or more, in 2 to 4 divided doses; the maximum recommended dose is 250 mg daily. Maintenance doses are usually in the range of 20 to 60 mg daily, in divided doses. For the control of acute conditions it is given by intramuscular injection in daily doses of up to 300 mg in 2 or 3 divided doses. Reduced dosage may be required in elderly patients.

Loxapine is also given by oral inhalation (as the base) in the treatment of acute agitation associated with bipolar disorder or schizophrenia; the usual dose is 10 mg once in a 24-hour period.

Loxapine has also been given orally and by intramuscular injection as the hydrochloride.

Disturbed behaviour. The use of inhaled loxapine in the treatment of acute agitation in patients with bipolar disorder[1] or schizophrenia[2,3] has been studied.

For a discussion of the use and limitations of antipsychotics such as loxapine in patients with disturbed behaviour, see p. 1030.2.

1. Kwentus J, *et al*. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipolar Disord* 2012; **14:** 31–40.
2. Lesem MD, *et al*. Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. *Br J Psychiatry* 2011; **198:** 51–8.
3. Allen MH, *et al*. Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2011; **72:** 1313–21.

Schizophrenia. A brief review of loxapine[1] found no conclusive evidence that it was particularly effective in patients with paranoid schizophrenia (p. 1031.3). A subsequent systematic review considered that the limited evidence did not indicate a clear difference in its effects from other antipsychotics.[2]

1. Anonymous. Clozapine and loxapine for schizophrenia. *Drug Ther Bull* 1991; **29:** 41–2.
2. Chakrabarti A, *et al*. Loxapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 19/03/08).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Other adverse effects reported include nausea and vomiting, seborrhoea, dyspnoea, ptosis, headache, paraesthesia, facial flush, weight gain or loss, and polydipsia. Dysgeusia and throat irritation have been reported following the oral inhalation of loxapine.

Loxapine oral inhalation can cause bronchospasm which could lead to respiratory distress and respiratory arrest. It is contra-indicated in patients with a history of asthma, bronchospasm, or acute respiratory symptoms. All patients should be monitored for breathing difficulties at least every 15 minutes for a minimum of one hour following an oral inhalation of loxapine.

Abuse. There has been a report of 3 cases of loxapine succinate abuse.[1]

1. Sperry L, *et al*. Loxapine abuse. *N Engl J Med* 1984; **310:** 598.

Effects on carbohydrate metabolism. Reversible nonketotic hyperglycaemia, coma, and delirium developed in a patient receiving loxapine 150 mg daily in addition to lithium therapy.[1] Symptoms improved on stopping loxapine, but subsequently recurred when the patient was given amoxapine. The causative agent may have been 7-hydroxyamoxapine, a common metabolite of both amoxapine and loxapine.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Mania. A patient, initially diagnosed as having schizophrenia, developed manic symptoms after receiving loxapine.[1] The diagnosis was revised to schizoaffective disorder but it was suspected that loxapine had a role in the emergence of the affective symptoms. As loxapine shares common metabolites with the antidepressant amoxapine it was suggested that an antidepressant effect might have precipitated the manic symptoms.

1. Gojer JAC. Possible manic side-effects of loxapine. *Can J Psychiatry* 1992; **37:** 669–70.

Overdosage. An 8-year-old child was treated with activated charcoal within 30 minutes of being given 375 mg of loxapine by accident.[1] The child became drowsy and was asleep but arousable 1 hour after ingestion. The degree of sedation appeared to peak after 3.75 hours and the child was discharged about 20 hours after ingestion.

1. Tarricone NW. Loxitane overdose. *Pediatrics* 1998; **101:** 496.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Loxapine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 2 hours. It is rapidly absorbed following oral inhalation with peak plasma concentrations occurring within 2 minutes. It is very rapidly and extensively metabolised and there is evidence for a first-pass effect. It is mainly excreted in the urine, in the form of its conjugated metabolites, with smaller amounts appearing in the faeces as unconjugated metabolites; a substantial proportion of a dose is excreted in the first 24 hours. The terminal elimination half-life ranges from 6 to 8 hours. The major metabolites of loxapine are the active 7- and 8-hydroxyloxapine, which are conjugated to the glucuronide or sulfate; other metabolites include hydroxyloxapine-*N*-oxide, loxapine-*N*-oxide, and hydroxydesmethylloxapine (hydroxyamoxapine). Loxapine is widely distributed and is 96.6% bound to plasma proteins. It is thought, on the basis of *animal* studies, to cross the placenta and be distributed into breast milk.

References.

1. Spyker DA, *et al.* Pharmacokinetics of loxapine following inhalation of a thermally generated aerosol in healthy volunteers. *J Clin Pharmacol* 2010; **50:** 169–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Loxapac; ***Fr.***: Loxapac; ***Gr.***: Loxapac; ***India***: Loxapac; ***USA***: Adasuve; Loxitane.

Pharmacopoeial Preparations
USP 36: Loxapine Capsules.

Lurasidone Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lurasidona; Lurasidone, Chlorhydrate de; Lurasidoni Hydrochloridum; SM-13496 (lurasidone or lurasidone hydrochloride); SMP-13496 (lurasidone); Луразидона Гидрохлорид.

(3a*R*,4*S*,7*R*,7*S*)-2-{(1*R*,2*R*)-2-[(1,2-Benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride.

$C_{28}H_{36}N_4O_2S$,HCl=529.1

CAS — 367514-87-2 (lurasidone); 367514-88-3 (lurasidone hydrochloride).
ATC — N05AE05.
ATC Vet — QN05AE05.
UNII — O0P4I5851I.

Profile

Lurasidone hydrochloride is an atypical antipsychotic reported to be an antagonist at dopamine D_2, serotonin 5-HT_{2A} and 5-HT_7, and adrenergic α_{2A} and α_{2C} receptors, and a partial agonist at serotonin 5-HT_{1A} receptors. It may be given orally for the treatment of schizophrenia (p. 1031.3) in an initial dose of 40 mg once daily with food; the maximum recommended daily dose is 160 mg.

Lurasidone hydrochloride is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and those who are also taking moderate CYP3A4 inhibitors (such as diltiazem) should be given an initial dose of 20 mg daily; the maximum recommended daily dose is 80 mg. Use with potent CYP3A4 inhibitors (such as ketoconazole) or inducers (such as rifampicin) is not recommended.

Reduced doses are recommended in patients with hepatic or renal impairment, see Administration in Hepatic and Renal Impairment, below.

References.

1. Nakamura M, *et al.* Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70:** 829–36.
2. Meyer JM, *et al.* Lurasidone: a new drug in development for schizophrenia. *Expert Opin Invest Drugs* 2009; **18:** 1715–26.

Administration in hepatic impairment. An initial oral dose of 20 mg daily of lurasidone is recommended for patients with moderate (Child-Pugh score of 7 to 9) or severe (Child-Pugh score of 10 to 15) hepatic impairment. The maximum recommended daily dose is 40 mg for those with severe impairment and 80 mg for moderate impairment.

Administration in renal impairment. An initial oral dose of 20 mg daily of lurasidone is recommended for patients with moderate (creatinine clearance [CC] of 30 to < 50 mL/min) or severe (CC of < 30 mL/min) renal impairment; the maximum recommended daily dose is 80 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Latuda; ***Switz.***: Latuda; ***USA***: Latuda.

Medazepam *(BAN, rINN)*

Medatsepaami; Médazépam; Medazepamum; Медазепам.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine.

$C_{16}H_{15}ClN_2$=270.8

CAS — 2898-12-6.
ATC — N05BA03.
ATC Vet — QN05BA03.
UNII — P0J3387W3S.

Pharmacopoeias. In *Jpn*.

Medazepam Hydrochloride *(USAN)*

Medazepam, hidrocloruro de; Ro-5-4556.

$C_{16}H_{15}ClN_2$,HCl=307.2

CAS — 2898-11-5.
ATC — N05BA03.
ATC Vet — QN05BA03.
UNII — ETM878JC9K.

Profile

Medazepam is a long-acting benzodiazepine with properties similar to those of diazepam (p. 1063.2). It has been given for the short-term treatment of anxiety disorders (p. 1028.1). A usual oral dose is 10 to 30 mg daily given in 2 or 3 divided doses, or as a single dose at night; a maximum of 60 mg daily may be given in severe conditions. Reduced doses should be given to elderly or debilitated patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Ansilan; ***Ger.***: Rudotel; Rusedal; ***Hung.***: Nobrium†; Rudotel; Rusedal†; ***Pol.***: Rudotel; ***Rus.***: Mezapam (Мезапам); Rudotel (Рудотель); ***Thai.***: Celium; Medazine.

Multi-ingredient Preparations. ***Ital.***: Debrum; ***Spain***: Nobritol; ***Turk.***: Tanko-Buskas†; Tranko-Buskas.

Medetomidine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de medetomidina; Medetomidiinihydrokloridi; Medetomidina, hidrocloruro de; Médétomidine, Chlorhydrate de; Medetomidinhydroklorid; Medetomidini Hydrochloridum; MPV-785; Медетомидина Гидрохлорид.

(±)-4-[1-(2,3-Xylyl)ethyl]imidazole monohydrochloride.

$C_{13}H_{16}N_2$,HCl=236.7

CAS — 86347-15-1 (medetomidine hydrochloride); 86347-14-0 (medetomidine).
ATC Vet — QN05CM91.
UNII — BH210P244U.

Profile

Medetomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Its *S*-enantiomer dexmedetomidine (p. 1063.1) is used as the hydrochloride for sedation in intensive care and in surgical and medical procedures.

Melperone Hydrochloride *(BANM, rINNM)*

FG-5111; Flubuperone Hydrochloride; Hidrocloruro de melperona; Melperon Hidroklorür; Melperona, hidrocloruro de; Melpérone, Chlorhydrate de; Melperoni Hydrochloridum; Methylperone Hydrochloride; Мелперона Гидрохлорид.

4′-Fluoro-4-(4-methylpiperidino)butyrophenone hydrochloride.

$C_{16}H_{22}FNO$,HCl=299.8

CAS — 3575-80-2 (melperone); 1622-79-3 (melperone hydrochloride).
ATC — N05AD03.
ATC Vet — QN05AD03.
UNII — 88G640374K.

Profile

Melperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given orally as the hydrochloride for the management of psychoses such as schizophrenia (below) and in disturbed behaviour (p. 1030.2); doses are expressed as the hydrochloride. A usual oral dose is up to 400 mg daily in divided doses. It has also been given intramuscularly in acute conditions.

Cardiac arrhythmias. Melperone has been reported to have class III electrophysiologic and antiarrhythmic activity[1,2] but its clinical use as an antiarrhythmic would be limited by a high incidence of adverse effects.[2] For a discussion of the cardiovascular effects of antipsychotics in general, see under Chlorpromazine, p. 1047.3.

1. Møgelvang JC, *et al.* Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; **208:** 61–4.
2. Hui WKK, *et al.* Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; **15:** 144–9.

Pharmacokinetics. References.

1. Köppel C, *et al.* Gas chromatographic-mass spectrometric study of urinary metabolism of melperone. *J Chromatogr Biomed Appl* 1988; **427:** 144–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies melperone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Schizophrenia. References[1-3] to the use of melperone in schizophrenia (p. 1031.3). It has been suggested that melperone should be considered as an atypical antipsychotic in view of the low incidence of extrapyramidal effects associated with its use.

1. Meltzer HY, *et al.* Melperone in the treatment of neuroleptic-resistant schizophrenia. *Psychiatry Res* 2001; **105:** 201–9.
2. Sumiyoshi T, *et al.* The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. *Schizophr Res* 2003; **59:** 7–16.
3. Sumiyoshi T, *et al.* A comparison of two doses of melperone, an atypical antipsychotic drug, in the treatment of schizophrenia. *Schizophr Res* 2003; **62:** 65–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Buronil; ***Belg.***: Buronil; ***Cz.***: Buronil; ***Denm.***: Buronil; ***Fin.***: Melpax†; ***Ger.***: Eunerpan†; Mel-Puren†; Melneurin†; ***Port.***: Bunil; ***Swed.***: Buronil; ***Turk.***: Buronon†.

Meprobamate *(BAN, rINN)*

Meprobamaatti; Meprobamat; Meprobamát; Meprobamatas; Méprobamate; Meprobamato; Meprobamatum; Meprotanum; Мепробамат.

2-Methyl-2-propyltrimethylene dicarbamate.

$C_9H_{18}N_2O_4$=218.3

CAS — 57-53-4.
ATC — N05BC01.
ATC Vet — QN05BC01.
UNII — 9I7LNY769Q.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of meprobamate:

Miltown; Mother's little helper; Uncle Miltie.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Meprobamate). A white or almost white, crystalline or amorphous powder. Slightly soluble in water; freely soluble in alcohol.

USP 36: (Meprobamate). A white powder having a characteristic odour. Slightly soluble in water; freely soluble in alcohol and in acetone; practically insoluble or insoluble in ether. Store in airtight containers.

Uses and Administration

Meprobamate is a carbamate with hypnotic, sedative, and some muscle relaxant properties, although in therapeutic doses its sedative effect rather than a direct action may be responsible for muscle relaxation. It has been used in the short-term treatment of anxiety disorders (p. 1028.1) and also for the short-term management of insomnia (p. 1033.2) but has largely been superseded by other drugs (see also under Adverse Effects and Treatment, p. 1084.1). Meprobamate has sometimes been used, alone or with an analgesic, in the management of muscle spasm (p. 2014.1) and painful musculoskeletal disorders but such use is no longer considered appropriate.

The usual anxiolytic dose is 400 mg orally three or four times daily to a maximum of 2.4 g daily. In elderly patients, no more than half the usual adult dose has been suggested.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects and Treatment

Drowsiness is the most frequent adverse effect of meprobamate. Other effects include nausea, vomiting, diarrhoea, paraesthesia, weakness, and CNS effects such as headache, paradoxical excitement, dizziness, ataxia, and disturbances of vision. There may be hypotension, tachycardia, and cardiac arrhythmias. Hypersensitivity reactions occur occasionally. These may be limited to rashes, urticaria, and purpura or may be more severe with angioedema, bronchospasm, or anuria. Erythema multiforme or Stevens-Johnson syndrome, and exfoliative or bullous dermatitis have been reported.

Blood disorders including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and aplastic anaemia have occasionally been reported.

Overdosage with meprobamate produces symptoms similar to those of barbiturate overdosage (see Amobarbital, p. 1038.1), and is managed similarly; activated charcoal, given orally or by nasogastric tube, may be considered in patients who present within 1 hour of ingesting a toxic dose (more than 60 mg/kg in adults) or after any amount in a child.

In 2012, the European Medicines Agency reviewed[1,2] available data on the safety and efficacy of oral meprobamate-containing preparations and concluded that the risks, particularly of serious CNS adverse effects, outweigh any benefits. The gradual withdrawal of such preparations from the EU market was recommended, although they amy remain available in other countries.

1. EMEA. Press release: European Medicines Agency recommends suspension of marketing authorisations for meprobamate-containing medicines in the European Union—gradual withdrawal period of 15 months recommended (issued 20th January, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/01/WC500120728.pdf (accessed 08/08/13)
2. EMEA. Questions and answers on the suspension of the marketing authorisations for oral meprobamate-containing medicines (issued 30th March, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/meprobamate_107/WC500120737.pdf (accessed 08/08/13)

Overdosage. Two children aged 2 and 2.5 years recovered with conservative management alone after overdosage of meprobamate with bendroflumethiazide despite measured plasma-meprobamate concentrations of 170 and 158 micrograms/mL, respectively.[1] Although it had been recommended that haemoperfusion should be considered at plasma-meprobamate concentrations above 100 micrograms/mL, the authors considered that experience with adults suggested haemoperfusion should normally only be considered at plasma concentrations above 200 micrograms/mL.

A retrospective study[2] of 74 patients admitted to an intensive care unit for meprobamate poisoning found that 29 developed hypotension (mean meprobamate plasma concentration 106 micrograms/mL); no predictive factor for the development of hypotension was identified. However, in another study[3] of 59 cases of meprobamate poisoning, mean plasma concentrations of meprobamate measured on admittance were found to be correlated with the resulting coma according to the Glasgow Coma Scale (GCS):

- GCS group A: 111.05 micrograms/mL
- GCS group B: 80.77 micrograms/mL
- GCS group C: 62.6 micrograms/mL

The authors considered that the determination of meprobamate concentrations was essential to ensure the use of appropriate care.

1. Dennison J, *et al.* Meprobamate overdosage. *Hum Toxicol* 1985; **4:** 215–17.
2. Charron C, *et al.* Incidence, causes and prognosis of hypotension related to meprobamate poisoning. *Intensive Care Med* 2005; **31:** 1582–6.
3. Buire A-C, *et al.* Overdose of meprobamate: plasma concentration and Glasgow Coma Scale. *Br J Clin Pharmacol* 2009; **68:** 126–7.

Precautions

Meprobamate is contra-indicated in patients with acute pulmonary insufficiency or respiratory depression. Meprobamate should be used with caution in patients with hepatic or renal impairment, depression, muscle weakness, and, as with all sedatives, in those with respiratory disease. Meprobamate should be given with care to elderly or debilitated patients. Meprobamate may induce seizures in those with a history of epilepsy.

Meprobamate may cause drowsiness; affected patients should not drive or operate machinery.

Breast feeding. Licensed product information states that the use of meprobamate should be avoided in breast feeding mothers as concentrations in milk may be up to four times those in maternal plasma and may cause drowsiness in the infant.

Pregnancy. Licensed product information states that meprobamate should be avoided during pregnancy, particularly during the first trimester, as some studies,[1] but not all,[2] have suggested an increased risk of congenital malformations associated with the use of anxiolytics (including meprobamate).

In a group of 107 women who had attempted suicide using large doses of meprobamate, there were 42 live births, 39 pregnancy terminations, and 24 miscarriages or early fetal losses;[3] 2 women were lost to follow up. Of the 42 live births, 34 mothers used other drugs in their suicide attempts, in particular, the benzodiazepine diazepam; the dose of meprobamate used for the suicide attempt by this group ranged from 1 g to 26 g, with a mean of 3.69 g. Congenital abnormalities were noted in 7 of the exposed children, but the incidence of abnormalities was not significantly different when compared with sibling controls. Neurological development was also comparable with sibling controls.

1. Milkovich L, van den Berg BJ. Effects of prenatal meprobamate and chlordiazepoxide hydrochloride on human embryonic and fetal development. *N Engl J Med* 1974; **291:** 1268–71.
2. Hartz SC, *et al.* Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. *N Engl J Med* 1975; **292:** 726–8.
3. Timmermann G, *et al.* A study of teratogenic and fetotoxic effects of large doses of meprobamate used for a suicide attempt by 42 pregnant women. *Toxicol Ind Health* 2008; **24:** 97–107.

Interactions

The sedative effects of meprobamate are enhanced by CNS depressants including alcohol. Meprobamate is capable of inducing hepatic microsomal enzyme systems involved in drug metabolism: the metabolism of other drugs may be enhanced if given concurrently.

Pharmacokinetics

Meprobamate is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after ingestion. Meprobamate is widely distributed; plasma protein binding is about 20%. It is extensively metabolised in the liver and is excreted in the urine mainly as an inactive hydroxylated metabolite and its glucuronide conjugate. About 10% of a dose is excreted unchanged. Meprobamate has a half-life reported to range from about 6 to 17 hours, although this may be prolonged after chronic use.

It diffuses across the placenta and appears in breast milk at concentrations of up to 4 times those in the maternal plasma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Microbamat†; Miltaunt†; ***Fr.***: Equanil†; ***Gr.***: Praol†; ***Hung.***: Andaxin†; ***Israel***: Mepro; ***Ital.***: Quanil†; ***S.Afr.***: Equanil; ***Switz.***: Meprodil†; ***Thai.***: Reinbamate.

Multi-ingredient Preparations. ***Canad.***: 282 MEP†; ***Chile***: Butartrol; ***Fin.***: Anervan†; Crampiton; ***Fr.***: Kaologeais†; Mepronizine†; Precyclan†; ***Indon.***: Deparon†; ***Mex.***: Artrilan†; ***Norw.***: Anervan†; ***S.Afr.***: Adco-Payne; Adco-Synaleve; Antipyn Forte; Ban Pain†; Briscopyn†; Dynapayne; Equagesic†; Fevapar; Go-Pain; Medipyn; Megapyn; Meprogesic; Mepromol; Micro-Gesic†; Painagon; Painrite†; Pynmed; Salterpyn; Spectrapain Forte; Stilpane†; Stilpane; Stopayne; Supragesic; Tenston†; Tenston; Trinagesic; Vacudol Forte†; ***Turk.***: Danitrin Fort; ***UK***: Paxidal†; ***USA***: Equagesic.

Pharmacopoeial Preparations

USP 36: Meprobamate Oral Suspension; Meprobamate Tablets.

Mesoridazine *(BAN, USAN, rINN)*

Mesoridatsiini; Mesoridazin; Mesoridazina; Mésoridazine; Mesoridazinum; Mesuridazine; Mezoridazin; NC-123; TPS-23; Мезоридазин.

10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylsulphinyl)phenothiazine.

$C_{21}H_{26}N_2OS_2$=386.6

CAS — 5588-33-0.

ATC — N05AC03.

ATC Vet — QN05AC03.

UNII — 5XE4NWM740.

Mesoridazine Besilate *(BANM, rINNM)*

Bencenosulfonato de mesoridazina; Besilato de mesoridazina; Mesoridazina, besilato de; Mesoridazine Benzenesulphonate; Mésoridazine, Bésilate de; Mesoridazine Besylate; Mesoridazini Besilas; Mesuridazine Benzenesulphonate; Мезоридазина безилат.

$C_{21}H_{26}N_2OS_2.C_6H_6O_3S$=544.7

CAS — 32672-69-8 (mesoridazine besilate).

ATC — N05AC03.

ATC Vet — QN05AC03.

UNII — T4G2I958J2.

Pharmacopoeias. In *US.*

USP 36: (Mesoridazine Besylate). A white to pale yellowish powder having not more than a faint odour. Soluble 1 in 1 of water, 1 in 11 of alcohol, 1 in 3 of chloroform, and 1 in 6300 of ether; freely soluble in methyl alcohol. pH of a freshly prepared 1 in 100 solution is between 4.2 and 5.7. Store in airtight containers. Protect from light.

Profile

Mesoridazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain and is a metabolite of thioridazine (p. 1110.2). Mesoridazine was usually given as the besilate, orally or by intramuscular injection.

Mesoridazine has been shown to prolong the QT interval in a dose-related manner which increases the risk of life-threatening arrhythmias such as torsade de pointes and sudden death; consequently its use in schizophrenia was restricted. (For further details see under Precautions of Thioridazine, p. 1111.1). Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential, and it is no longer available in many countries.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of mesoridazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Lidanil.

Pharmacopoeial Preparations

USP 36: Mesoridazine Besylate Injection; Mesoridazine Besylate Oral Solution; Mesoridazine Besylate Tablets.

Methaqualone *(BAN, USAN, rINN)*

Cl-705; CN-38703; Metacualona; Metakvalon; Metakvalonas; Metakvaloni; Methachalonum; Methakvalon; Methaqualon; Méthaqualone; Methaqualonum; QZ-2; R-148; TR-495; Метахалон.

2-Methyl-3-*o*-tolylquinazolin-4-(3*H*)-one.

$C_{16}H_{14}N_2O$=250.3

CAS — 72-44-6 (methaqualone); 340-56-7 (methaqualone hydrochloride).

ATC — N05CM01.

ATC Vet — QN05CM01.

UNII — 7ZKH8MQW6T.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methaqualone:

300's; 712; 714; 714s; Bandits; Beiruts; Blou Bulle; Blue Balls; Blue bulls; Disco biscuits; Down and dirtys; Drunfos; Drunken Monkey; Ewings; Flamingos; Flowers; Fourstrokes; Fuckers; Genuines; Germans; Golfsticks; Gorilla Biscuits; Humbles; Joe Fridays; Knoppies; Lemmon 714; Lemmons; Lemons; Lennons; Lewds; Lizards; Loss-of-memory; Love drug; Lovers; Ludes; Luds; Lula; Magwheels; Mandies; No. 714; Pressouts; Pupumala; Q; Qua; Quaa; Quaalude; Quaaludes; Quaas; Quack; Quacks; Quad; Quads; Quas; Quay; Roar; Seven fourteen; Seven fourteens; Shiny Tops; Soaper; Soapers; Sopes; Sopor; Sopors; Sporos; Strawberries; Super Sopors; Supers; Supper; The love drug; Three hundreds; Vitamin Q; Wagon Wheels; Wallbangers; Whore pills.

Profile

Methaqualone is a quinazoline derivative with hypnotic and sedative properties. It has been given orally in the short-term management of insomnia but the use of methaqualone for this purpose is no longer considered appropriate. It has also been given with diphenhydramine for an enhanced effect.

Methaqualone has been withdrawn from the market in many countries because of problems with abuse.

Adverse effects and symptoms of overdosage are similar to those of barbiturates (see Amobarbital, p. 1038.1) although cardiac and respiratory depression reportedly occur less frequently.

Abuse. Although oral abuse of methaqualone has greatly declined in developed countries after the widespread withdrawal of the tablets, smoking of (usually illicitly manufactured) methaqualone, generally with cannabis and tobacco, is a major public health problem in South Africa, and some other parts of Africa and India. Although diazepam has been used to manage dependence, controlled studies to assess treatment efficacy are lacking.[1]

1. McCarthy G, *et al.* Treatment for methaqualone dependence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 11/05/06).

Mexazolam *(rINN)*

CS-386; Methylcloxazolam; Mexazolamum; Мексазолам.
10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-3-methyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.
$C_{18}H_{16}Cl_2N_2O_2$=363.2
CAS — 31868-18-5.
UNII — 55969B6237.

Profile

Mexazolam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given for its anxiolytic and sedative properties in usual oral doses of 0.5 to 1 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Melex; ***Port.***: Sedoxil.

Midazolam *(BAN, rINN)*

Midatsolaami; Midazolám; Midazolamas; Midazolamum; Ro-21-3971; Мидазолам.
8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine.
$C_{18}H_{13}ClFN_3$=325.8
CAS — 59467-70-8.
ATC — N05CD08.
ATC Vet — QN05CD08.
UNII — R60L0SM58C.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Midazolam). A white or yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in methyl alcohol.

USP 36: (Midazolam). A white or yellowish powder. Insoluble in water. Store in airtight containers. Protect from light. The hydrochloride salt of midazolam is soluble in aqueous solutions.

Midazolam Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de midazolam; Midazolam, Chlorhydrate de; Midazolam, hidrocloruro de; Midazolami Hydrochloridum; Ro-21-3981/003; Мидазолама Гидрохлорид.
$C_{18}H_{13}ClFN_3$,HCl=362.2
CAS — 59467-96-8.
ATC — N05CD08.
ATC Vet — QN05CD08.
UNII — W7TTW573JJ.

Incompatibility. The visual compatibility of midazolam hydrochloride with a range of drugs was studied over a period of 4 hours.[1] A white precipitate was formed immediately with dimenhydrinate, pentobarbital sodium, perphenazine, prochlorperazine edisilate, and ranitidine hydrochloride. Similar incompatibility has been reported[2,3] with furosemide, thiopental, and parenteral nutrition solutions. Visual incompatibility of midazolam hydrochloride may be seen if the resultant mixture has a pH of 5 or more;[4,5] however, significant loss of midazolam has also been noted in solutions that remained clear despite an increase in pH.

1. Forman JK, Souney PF. Visual compatibility of midazolam hydrochloride with common preoperative injectable medications. *Am J Hosp Pharm* 1987; **44:** 2298–9.
2. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
3. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1295–300.
4. Swart EL, *et al.* Compatibility of midazolam hydrochloride and lorazepam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2020–2.
5. Good PD, *et al.* The compatibility and stability of midazolam and dexamethasone in infusion solutions. *J Pain Symptom Manage* 2004; **27:** 471–5.

Stability. Licensed product information states that solutions of midazolam hydrochloride in sodium chloride 0.9%, glucose 5%, or glucose 4% with sodium chloride 0.18% are stable at room temperature for up to 24 hours, and similar solutions containing the equivalent of 500 micrograms/mL of the base were stable for 36 days[1] when stored in glass bottles at temperatures of 4 degrees to 6 degrees, 24 degrees to 26 degrees, and 39 degrees to 41 degrees. Other workers[2] found that a solution containing midazolam hydrochloride equivalent to 1 mg/mL of the base in sodium chloride 0.9% was stable for at least 10 days when stored in PVC bags. The product information advises against admixture with Compound Sodium Lactate Intravenous Infusion (Hartmann's solution) as the potency of midazolam is reduced.

1. Pramar YV, *et al.* Stability of midazolam hydrochloride in syringes and i. v. fluids. *Am J Health-Syst Pharm* 1997; **54:** 913–15.
2. McMullin ST, *et al.* Stability of midazolam hydrochloride in polyvinyl chloride bags under fluorescent light. *Am J Health-Syst Pharm* 1995; **52:** 2018–20.

Midazolam Maleate *(BANM, USAN, rINNM)*

Maleato de midazolam; Midazolam, Maléate de; Midazolam, maleato de; Midazolami Maleas; Ro-21-3981/001; Мидазолама Малеат.
$C_{18}H_{13}ClFN_3.C_4H_4O_4$=441.8
CAS — 59467-94-6.
ATC — N05CD08.
ATC Vet — QN05CD08.
UNII — 77520S18SE.

Uses and Administration

Midazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3), except that it has a more potent amnestic action. It is mainly used for sedation (p. 1087.1) in minor surgical or investigative procedures and in intensive care, for premedication, and for induction of general anaesthesia. It is also used as a hypnotic in the short-term (up to 2 weeks) management of insomnia (p. 1086.3) and as an anticonvulsant (for further details, see p. 1086.2). When midazolam is used as a premedicant or for conscious sedation, onset of sedation occurs at about 15 minutes after intramuscular injection reaching a peak at 30 to 60 minutes, and within about 3 to 5 minutes after intravenous injection. When given intravenously as an anaesthetic induction agent, anaesthesia is induced in about 2 to 2.5 minutes; onset of action is more rapid when premedication with an opioid analgesic has been given.

Since the sedative end-point is reached abruptly with midazolam, dosage must be titrated carefully against the response of the patient; lower doses of midazolam are required when it is used with opioid analgesics. Respiratory and cardiac function should be monitored continuously, and facilities for resuscitation should always be available. It is advisable to keep the patient supine during intravenous use and throughout the procedure. Midazolam should be given in reduced doses to **elderly** or **debilitated patients** (see p. 1086.2).

Midazolam is used as the hydrochloride for oral, parenteral, and rectal dosage; the maleate may also be given orally. All doses are given in terms of the base; midazolam hydrochloride 8.3 mg or midazolam maleate 10.2 mg are both equivalent to about 7.5 mg of midazolam.

Total **sedative** doses for dental and minor surgical and other procedures may range from 2.5 to 7.5 mg (about 70 micrograms/kg) *intravenously* although a total dose greater than 5 mg is not usually needed; an initial dose of 2 to 2.5 mg given at a rate of 2 mg/minute 5 to 10 minutes before the start of the procedure has been suggested, with further increments of 0.5 to 1 mg at intervals of at least 2 minutes if required until the desired end-point is reached.

Patients in **intensive care** who require continuous sedation can be given midazolam by *intravenous infusion.* In the UK, an initial intravenous loading dose of 30 to 300 micrograms/kg may be given in increments to induce sedation; each increment of 1 to 2.5 mg should be injected slowly over 20 to 30 seconds, allowing 2 minutes between each dose. In the USA a lower dose of 10 to 50 micrograms/kg (typically about 0.5 to 4 mg) is recommended. The maintenance dose, given by intravenous infusion, varies considerably but a dose of between 20 and 200 micrograms/kg per hour has been suggested. The loading dose should be reduced or omitted, and the maintenance dose reduced, for patients with hypovolaemia, vasoconstriction, or hypothermia. The need for continuous infusion should be reassessed on a daily basis to reduce the risk of accumulation and prolonged recovery. Abrupt withdrawal should be avoided after prolonged use.

Midazolam is given *intramuscularly* as a **premedicant** about 20 to 60 minutes before surgery. The usual dose is about 5 mg; doses range from 70 to 100 micrograms/kg. Alternatively, *intravenous* doses of 1 to 2 mg, repeated if required, may be given 5 to 30 minutes before the procedure.

The usual total dose of midazolam for **induction of anaesthesia** is about 150 to 250 micrograms/kg by slow *intravenous injection* in premedicated patients and 300 to 350 micrograms/kg in those who have not received a premedicant. The desired level of anaesthesia is achieved by stepwise titration; each increment of not more than 5 mg should be injected over 20 to 30 seconds at intervals of 2 minutes. Additional doses may be needed to complete induction; up to 600 micrograms/kg has been used in resistant cases. Further incremental doses of midazolam of about 25% of the induction dose have also been given as a component of the regimens used for the **maintenance of anaesthesia** during short surgical procedures.

Midazolam is also given for sedation in **combined anaesthesia** by *intravenous injection* in a dose of 30 to 100 micrograms/kg repeated as required or by *intravenous infusion* in a dose of 30 to 100 micrograms/kg every hour.

For details of doses in children, see below.

Midazolam maleate is also given *orally* for the short-term management of **insomnia**; the usual dose is the equivalent of midazolam 7.5 to 15 mg at night.

Administration. The rectal,[1] intranasal,[1-5] buccal,[6-11] and sublingual[1,12] routes have all been proposed as alternatives to parenteral use of midazolam.

Intranasal midazolam has caused intense burning, irritation, and lachrymation on instillation, and use of a lidocaine nasal spray has been advocated before giving midazolam to children.[13,14] Alternatively, intranasal delivery of atomised midazolam may cause less discomfort.[15,16] The use of midazolam spray intranasally in adults would be impractical and uncomfortable because of the large volume required. It has therefore been tried as a nebulised solution in adults.[17,18]

1. Wong L, McQueen KD. Midazolam routes of administration. *DICP Ann Pharmacother* 1991; **25:** 476–7.
2. Theroux MC, *et al.* Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department. *Pediatrics* 1993; **91:** 624–7.
3. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; **77:** 529–30.
4. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; **24:** 646–51.
5. Ljungman G, *et al.* Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics* 2000; **105:** 73–8.
6. Body R, Ijaz M. Buccal midazolam as an alternative to rectal diazepam for prolonged seizures in childhood and adolescence. *Emerg Med J* 2005; **22:** 364–5.
7. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366:** 205–10.
8. Baysun S, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005; **44:** 771–6.
9. Bailie RK, *et al.* Premedication with buccal midazolam in children and in adults with learning disabilities. *Anaesthesia* 2007; **62:** 535–6.
10. Wilson KE, *et al.* Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children: a randomized, cross-over, clinical trial. *Acta Anaesthesiol Scand* 2007; **51:** 1062–7.
11. Mpimbaza A, *et al.* Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008; **121:** 165–6. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/1/e58 (accessed 23/04/09)
12. Karl HW, *et al.* Transmucosal administration of midazolam for premedication of pediatric patients: comparison of the nasal and sublingual routes. *Anesthesiology* 1993; **78:** 885–91.
13. Lugo RA, *et al.* Complication of intranasal midazolam. *Pediatrics* 1993; **92:** 638.
14. Chiaretti A, *et al.* Intranasal lidocaine and midazolam for procedural sedation in children. *Arch Dis Child* 2011; **96:** 160–3.
15. Gilchrist F, *et al.* The use of intranasal midazolam in the treatment of paediatric dental patients. *Anaesthesia* 2007; **62:** 1262–5.
16. Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care* 2008; **24:** 300–3.
17. Hodgson PE, *et al.* Administration of nebulized intranasal midazolam to healthy adult volunteers: a pilot study. *Br J Anaesth* 1994; **73:** 719P.
18. McCormick ASM, *et al.* Plasma concentrations and sedation scores after nebulized and intranasal midazolam in healthy volunteers. *Br J Anaesth* 2008; **100:** 631–6.

INTRATHECAL. See Pain, p. 1086.3.

Administration in children. Midazolam may be used in children for **sedation** in minor surgical or investigative procedures. In the UK, the oral and buccal routes are not licensed for this use; however, these routes may be used in children and the following doses, according to age, have been suggested in the *BNFC*:

orally

- 1 month to 18 years: 500 micrograms/kg (maximum of 20 mg) 30 to 60 minutes before the procedure

An oral liquid is available from specialist manufacturers in the UK; alternatively, the injection solution may be diluted with apple or black currant juice, chocolate sauce, or cola.

buccally

- 6 months to 10 years: 200 to 300 micrograms/kg (maximum of 5 mg)

- 10 to 18 years: 6 to 7 mg (maximum of 8 mg if weighing 70 kg or over)

Solutions for buccal use are available from specialist manufacturers in the UK; half the dose should be given between the upper lip and gum on each side of the mouth using an oral syringe and retained for at least 5 minutes before swallowing. [A licensed preparation for buccal use is also available in the UK, however, it is not authorised for use in sedation.]

In the USA, a single oral dose of 250 to 500 micrograms/kg (maximum of 20 mg) is licensed in children aged 6 months and over, although those under 6 years or less cooperative patients may require up to 1 mg/kg.

If the *intravenous* route is more suitable, the following licensed doses may be given according to age:

- 6 months to 5 years: 50 to 100 micrograms/kg up to a total dose of 600 micrograms/kg (but not exceeding 6 mg)
- 6 to 12 years: 25 to 50 micrograms/kg up to a total dose of 400 micrograms/kg (or a maximum of 10 mg)
- older children should be given usual adult doses (see p. 1085.2)

Initial doses should be given over 2 to 3 minutes and an additional interval of 2 to 5 minutes is recommended before giving further doses. Although unlicensed, the *BNFC* suggests that initial doses of midazolam 25 to 50 micrograms/kg may be given intravenously to those aged 1 month and over.

In some countries including the UK, the injection solution may be used *rectally* for sedation in children aged 6 months and over; doses range from 300 to 500 micrograms/kg as a single dose. The injection solution may be diluted with Water for Injections up to a total volume of 10 mL if the volume is too small.

The *intramuscular* route should only be used in children in exceptional cases as such injections are painful; usual doses ranging from 50 to 150 micrograms/kg have been suggested for children aged 1 to 15 years.

Midazolam is also used in children in **intensive care** who require sedation; the following *intravenous* doses are given according to age and adjusted according to response:

- neonates with a gestational age of less than 32 weeks: 60 micrograms/kg per hour by continuous intravenous infusion, reduced after 24 hours to 30 micrograms/kg per hour; treatment duration should not exceed 4 days
- neonates with a gestational age of greater than 32 weeks and infants aged up to 6 months: 60 micrograms/kg per hour by continuous intravenous infusion; treatment duration should not exceed 4 days in neonates
- over 6 months to 12 years: an initial loading dose of 50 to 200 micrograms/kg by intravenous injection over at least 3 minutes; maintenance doses are given as a continuous intravenous infusion and range from 30 to 120 micrograms/kg per hour
- older children should be given usual adult doses (see above)

Loading doses are not recommended in infants aged under 6 months.

A small retrospective observational study[1] of children on prolonged mechanical ventilation (at least 5 days) found that those aged between 1 and 4 years needed higher maintenance doses of midazolam (up to 300 micrograms/kg per hour) when compared with those who were older and younger. The authors also noted that midazolam alone was a poor sedative for all age groups with most children needing additional drugs to maintain adequate sedation.

Midazolam is also used as a **premedicant** and may be given 15 to 30 minutes before the procedure. *Oral* doses are similar to those used for sedation (see above). The *rectal* route is used for premedication in some countries; total doses recommended in the UK in children aged over 6 months range from 300 to 500 micrograms/kg. The *intramuscular* route is also licensed in those aged 1 to 15 years in doses of 80 to 200 micrograms/kg; however, as before, this route should only be used in exceptional circumstances.

For **induction of anaesthesia**, a dose of 150 micrograms/kg by *slow intravenous injection* has been recommended in children over 7 years of age. However, the *BNFC* notes that such use is rare and suggests giving increments of 50 micrograms/kg (maximum of 2.5 mg) over 2 to 5 minutes; after waiting 2 to 5 minutes, additional doses may then be given every 2 minutes, if required, to a maximum total dose of 500 micrograms/kg (not exceeding 25 mg) in those aged up to 18 years.

For the use of midazolam in the management of **status epilepticus**, see Convulsions, below.

Some general references to the use of midazolam in children.[2,3]

1. de Gast-Bakker D-AH, *et al*. Age is of influence on midazolam requirements in a paediatric intensive care unit. *Acta Paediatr* 2007; **96:** 414–17.
2. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998; **35:** 37–47.
3. Marshall J, *et al*. Pediatric pharmacodynamics of midazolam oral syrup. *J Clin Pharmacol* 2000; **40:** 578–89.

Administration in the elderly. Midazolam should be used with caution in patients aged 60 years and over, and those who are debilitated or chronically ill; lower doses should be given and these patients should be continuously monitored for early alterations in vital functions. Peak effects may be reached more slowly in elderly patients than in younger subjects.

For **sedation** in dental and minor surgical and other procedures, an initial dose of 0.5 to 1.5 mg given *intravenously* at a maximum rate of 2 mg/minute 5 to 10 minutes beforehand has been suggested, with further increments of 0.5 to 1 mg if required to a usual maximum total dose of 3.5 mg or until the desired end-point is reached.

For continuous sedation in **intensive care**, the usual adult dose (see p. 1085.2) may be given.

Midazolam is given *intramuscularly* as a **premedicant** about 20 to 60 minutes before surgery. The usual dose is 2 to 3 mg (doses range from 20 to 50 micrograms/kg). Alternatively, an initial *intravenous* dose of 500 micrograms, repeated slowly if required, may be given 5 to 30 minutes before the procedure.

The usual total dose for **induction of anaesthesia** is 50 to 150 micrograms/kg by slow *intravenous injection* in premedicated patients and 150 to 300 micrograms/kg in those who have not received a premedicant. Lower doses (up to 250 micrograms/kg) may be sufficient in severely ill or debilitated patients who have not received a premedicant. The desired level of anaesthesia is achieved by stepwise titration. Further incremental doses of midazolam of about 25% of the induction dose have also been given as a component of the regimens used for the **maintenance of anaesthesia** during short surgical procedures.

For sedation in **combined anaesthesia**, lower maintenance doses will be required (see above for the usual adult dose).

Midazolam maleate is also given *orally* for the short-term management of **insomnia**; the usual dose is the equivalent of midazolam 7.5 mg at night.

Conversion and dissociative disorders. For reference to the use of midazolam in the diagnosis of conversion disorders, such as hysterical paralysis, see p. 1064.2.

Convulsions. Benzodiazepines such as diazepam or lorazepam given parenterally are often tried first to control status epilepticus (p. 510.2). Midazolam has been used as an alternative.[1] It may be of value when intravenous access is difficult as effective concentrations of midazolam can be obtained after intramuscular injection.[2,3] The *BNF* considers it to be the benzodiazepine of choice when a continuous subcutaneous infusion is required for the control of convulsions, such as in palliative care, and states that it may be given in an initial dose of 20 to 40 mg every 24 hours. Intravenous midazolam has been used in some centres[4] for status epilepticus refractory to diazepam, lorazepam, or phenytoin but reviews of the literature[5] reveal that evidence of efficacy is limited mainly to uncontrolled studies and anecdotal reports. The *BNFC* states that for the treatment of status epilepticus or febrile convulsions, a dose of midazolam of 1 microgram/kg per minute by continuous intravenous infusion may be given to neonates, children, and adolescents up to 18 years of age after an initial loading dose of 150 to 200 micrograms/kg. The infusion rate may be increased by 1 microgram/kg per minute every 15 minutes until the seizure is controlled or until a maximum of 5 micrograms/kg per minute is reached. Higher intravenous doses of midazolam have been advocated by some[6] for children with refractory status epilepticus.

The intranasal[7,8] and buccal[9] routes have also been used for the management of seizures, and UK guidelines[10] consider buccal midazolam an alternative to rectal diazepam for initial management of status epilepticus in the home setting or where intravenous access is not possible. In addition, studies[11-13] found that buccal midazolam was more effective than rectal diazepam for treatment of children with seizures in the hospital setting and did not appear to increase the risk of respiratory depression. Results from another study[14] also suggested that buccal midazolam can be used as an alternative to intravenous diazepam, particularly where intravenous access is difficult to establish. The *BNF* states that a dose of midazolam 10 mg, repeated once after 10 minutes if necessary, may be given by the buccal route to adults aged 18 years and over. The *BNFC* suggests giving the following buccal doses, which may be repeated once after 10 minutes if necessary, according to age:

- neonate to 3 months: 300 micrograms/kg (maximum of 2.5 mg)
- 3 months to 1 year: 2.5 mg
- 1 to 5 years: 5 mg
- 5 to 10 years: 7.5 mg
- 10 to 18 years: 10 mg

A proprietary buccal solution is licensed in the EU for use in children aged from 3 months to under 18 years and is given in similar doses; product information advises that those aged between 3 and 6 months should be treated in a hospital setting.

Midazolam has also been tried[15] in the management of acute convulsions associated with severe malaria in children.

1. Hanley DF, *et al*. Use of midazolam in the treatment of refractory status epilepticus. *Clin Ther* 1998; **20:** 1093–1105.
2. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
3. Towne AR, DeLorenzo RJ. Use of intramuscular midazolam for status epilepticus. *J Emerg Med* 1999; **17:** 323–8.
4. Bebin M, Bleck TP. New anticonvulsant drugs: focus on flunarizine, fosphenytoin, midazolam and stiripentol. *Drugs* 1994; **48:** 153–71.
5. Denzel D, Burstein AH. Midazolam in refractory status epilepticus. *Ann Pharmacother* 1996; **30:** 1481–3.
6. Morrison G, *et al*. High-dose midazolam therapy for refractory status epilepticus in children. *Intensive Care Med* 2006; **32:** 2070–6.
7. Wallace SJ. Nasal benzodiazepines for management of acute childhood seizures? *Lancet* 1997; **349:** 222.
8. Lahat E, *et al*. Intranasal midazolam for childhood seizures. *Lancet* 1998; **352:** 620.
9. Scott RC, *et al*. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999; **353:** 623–6.
10. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020NICEguideline.pdf (accessed 21/08/08)
11. McIntyre J, *et al*. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366:** 205–10.
12. Baysun S, *et al*. A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005; **44:** 771–6.
13. Mpimbaza A, *et al*. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008; **121:** 165–6. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/1/e58 (accessed 23/04/09)
14. Talukdar B, Chakrabarty B. Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. *Brain Dev* 2009; **31:** 744–9.
15. Muchohi SN, *et al*. Pharmacokinetics and clinical efficacy of midazolam in children with severe malaria and convulsions. *Br J Clin Pharmacol* 2008; **66:** 529–38.

Disturbed behaviour. For a discussion of the palliative treatment of terminal restlessness with benzodiazepines such as midazolam, see p. 1030.2.

Dyspnoea. Benzodiazepines such as midazolam may relieve dyspnoea in patients with advanced cancer, especially when this is associated with anxiety (see also Diazepam, p. 1064.2). Subcutaneous doses of midazolam of 5 mg every 4 hours have been combined successfully with morphine.[1] Midazolam has also been suggested[2] as an alternative to chlorpromazine in patients with advanced cancer and intractable dyspnoea to relieve air hunger and to sedate dying patients who have unrelieved distress.

1. Navigante AH, *et al*. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage* 2006; **31:** 38–47.
2. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Midazolam given intravenously or subcutaneously has been reported[1,2] to have been effective in 3 patients with metastatic cancer who had hiccups unresponsive to conventional treatment. However, it has been noted[1,3] that benzodiazepines such as midazolam may exacerbate or precipitate hiccups.

1. Wilcock A, Twycross R. Midazolam for intractable hiccup. *J Pain Symptom Manage* 1996; **12:** 59–61.
2. Moro C, *et al*. Midazolam for long-term treatment of intractable hiccup. *J Pain Symptom Manage* 2005; **29:** 221–3.
3. Rousseau P. Hiccups. *South Med J* 1995; **88:** 175–81.

Insomnia. For discussion of the management of insomnia including limitations on the use of benzodiazepines and a recommendation that the period of treatment with midazolam should be limited to 2 weeks, see p. 1033.2.

References.

1. Monti JM, *et al*. The effect of midazolam on transient insomnia. *Eur J Clin Pharmacol* 1993; **44:** 525–7.

Nausea and vomiting. Midazolam has been tried[1-5] for the prophylaxis of postoperative nausea and vomiting.

1. Rodolà F. Midazolam as an anti-emetic. *Eur Rev Med Pharmacol Sci* 2006; **10:** 121–6.
2. Lee Y, *et al*. Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomised controlled trial. *Anaesthesia* 2007; **62:** 18–22.
3. Riad W, *et al*. Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children. *Eur J Anaesthesiol* 2007; **24:** 697–701.
4. Jung JS, *et al*. Prophylactic antiemetic effect of midazolam after middle ear surgery. *Otolaryngol Head Neck Surg* 2007; **137:** 753–6.
5. Tarhan Ö, *et al*. Subhypnotic doses of midazolam prevent nausea and vomiting during spinal anesthesia for cesarean section. *Minerva Anestesiol* 2007; **73:** 629–33.

Pain. The conventional use of benzodiazepines in pain management is as muscle relaxants to relieve pain associated with skeletal muscle spasm (see under Choice of Analgesic, p. 4.2). Midazolam has been studied[1-7] for use

as an intrathecal analgesic but, because of some uncertainty about its risk and benefits, its use has been uncommon. A meta-analysis[8] of 13 studies found that the use of intrathecal midazolam as an adjunct to spinal anaesthesia improved perioperative or peripartum analgesia and reduced the incidence of postoperative nausea and vomiting, particularly when used for caesarean section; the authors considered that further study of its safety was warranted although neurological symptoms were rare and not significantly increased when compared with placebo.

1. Cripps TP, Goodchild CS. Intrathecal midazolam and the stress response to upper abdominal surgery. *Clin J Pain* 1988; **4:** 125–8.
2. Serrao JM, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. *Pain* 1992; **48:** 5–12.
3. Baaijens PFJ, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a randomized double-blind placebo-controlled study. *Br J Anaesth* 1995; **74** (suppl 1): 143.
4. Valentine JMJ, *et al.* The effect of intrathecal midazolam on postoperative pain. *Eur J Anaesthesiol* 1996; **13:** 589–93.
5. Batra YK, *et al.* Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. *Int J Clin Pharmacol Ther* 1999; **37:** 519–23.
6. Duncan MA, *et al.* Prospective audit comparing intrathecal analgesia (incorporating midazolam) with epidural and intravenous analgesia after major open abdominal surgery. *Anaesth Intensive Care* 2007; **35:** 558–62.
7. Murali Krishna T, *et al.* Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. *Eur J Anaesthesiol* 2008; **25:** 299–306.
8. Ho KM, Ismail H. Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. *Anaesth Intensive Care* 2008; **36:** 365–73.

Premedication and sedation. Midazolam is used as a premedicant (see Anaesthesia, p. 1899.1) and as a sedative (p. 1032.2) for therapeutic and investigative procedures such as dental treatment (p. 1032.2) and endoscopy (see below). It is also used to provide continuous sedation in patients in intensive care (p. 1033.1) although a systematic review has raised concerns about such use in neonates (see also Children under Precautions, below).

References.

1. Sandler ES, *et al.* Midazolam versus fentanyl as premedication for painful procedures in children with cancer. *Pediatrics* 1992; **89:** 631–4.
2. Jacqz-Aigrain E, *et al.* Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet* 1994; **344:** 646–50.
3. McErlean M, *et al.* Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion. *J Pediatr* 2003; **142:** 429–30.
4. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003; **327:** 708–11.
5. Ng E, *et al.* Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/03/06).
6. Averley PA, *et al.* An RCT pilot study to test the effects of intravenous midazolam as a conscious sedation technique for anxious children requiring dental treatment: an alternative to general anaesthesia. *Br Dent J* 2004; **197:** 553–8.
7. Lam C, *et al.* Midazolam premedication in children: a pilot study comparing intramuscular and intranasal administration. *Anesth Prog* 2005; **52:** 56–61.
8. Wilson KE, *et al.* A comparison of oral midazolam and nitrous oxide sedation for dental extractions in children. *Anaesthesia* 2006; **61:** 1138–44.

ENDOSCOPY. Intravenous benzodiazepines such as diazepam or midazolam are often the preferred drugs for sedation in patients undergoing endoscopy (p. 1032.3). They are sometimes used with opioid analgesics for sedation.[1]

A reduced dose of midazolam was required for endoscopy when it was given as a bolus intravenous injection rather than as a slow intravenous titration. A study in 788 patients undergoing endoscopy found that a mean dose of 4.65 mg of midazolam given as a bolus intravenous injection was safe and effective in patients under 70 years of age whereas a mean dose of 1.89 mg was sufficient for patients over 70 years of age.[2] Furthermore, topical pharyngeal anaesthesia was not required with these doses of midazolam. Intravenous boluses were also easier to give and associated with less oxygen desaturation than titrating the dose.[3] Another study found that even lower doses of midazolam (35 micrograms/kg) were effective as premedication before gastroscopy, and were associated with fewer complications than higher doses (70 micrograms/kg).[4]

Intranasal[5] and oral[6,7] midazolam have also been tried for sedation before endoscopy, particularly in children.[5,6]

1. Mamula P, *et al.* Safety of intravenous midazolam and fentanyl for pediatric GI endoscopy: prospective study of 1578 endoscopies. *Gastrointest Endosc* 2007; **65:** 203–10.
2. Smith MR, *et al.* Small bolus injections of intravenous midazolam for upper gastrointestinal endoscopy: a study of 788 consecutive cases. *Br J Clin Pharmacol* 1993; **36:** 573–8.
3. Morrow JB, *et al.* Sedation for colonoscopy using a single bolus is safe, effective, and efficient: a prospective, randomized, double-blind trial. *Am J Gastroenterol* 2000; **95:** 2242–7.
4. Campo R, *et al.* Efficacy of low and standard midazolam doses for gastroscopy: a randomized, double-blind study. *Eur J Gastroenterol Hepatol* 2000; **12:** 187–90.
5. Fishbein M, *et al.* Evaluation of intranasal midazolam in children undergoing esophagogastroduodenoscopy. *J Pediatr Gastroenterol Nutr* 1997; **25:** 261–6.
6. Martinez JL, *et al.* A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy. *J Pediatr Gastroenterol Nutr* 2002; **35:** 51–8.
7. Mui LM, *et al.* Premedication with orally administered midazolam in adults undergoing diagnostic upper endoscopy: a double-blind placebo-controlled randomized trial. *Gastrointest Endosc* 2005; **61:** 195–200.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Withdrawal symptoms have been reported[1,2] in children after stopping midazolam, which had been used for sedation during mechanical ventilation; in the majority of cases, midazolam had been given with an opioid which can confound symptoms of benzodiazepine withdrawal.[2]

1. van Engelen BGM, *et al.* Benzodiazepine withdrawal reaction in two children following discontinuation of sedation with midazolam. *Ann Pharmacother* 1993; **27:** 579–81.
2. Ista E, *et al.* Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. *Crit Care Med* 2008; **36:** 2427–32.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. There have been reports of life-threatening adverse respiratory and cardiovascular events occurring after use of midazolam; when giving midazolam the precautions given under Incidence of Adverse Effects, below should be observed to lessen the risk of such reactions. Pain, tenderness, and thrombophlebitis have occurred after injection of midazolam. Hiccups have been reported.

Incidence of adverse effects. Death due to respiratory depression, hypotension, or cardiac arrest has been reported in patients given intravenous midazolam for conscious sedation.[1] Within about 6 months of its introduction in the USA in May 1986, 13 fatalities due to cardiorespiratory depression had been reported (higher doses were used initially in the USA than those in the UK). By January 1988, 66 deaths had been reported, although in November 1987 the adult dosage recommendation had been reduced to 70 micrograms/kg and to 50 micrograms/kg for elderly patients. Fatalities have also occurred in the UK [where the dose is 70 micrograms/kg, reduced in the elderly] with 4 deaths reported to the UK CSM by November 1987.

While it appears that midazolam and diazepam produce very similar degrees of hypoventilation and oxygen desaturation when used in equivalent doses,[2] the sedative end-point does appear to be reached more abruptly with midazolam.[3] Licensed product information recommends that the following precautions should therefore be taken:

- facilities for resuscitation should always be available when intravenous midazolam is used
- respiratory and cardiac function should be monitored continuously
- the dose of midazolam should be carefully titrated against the response of the patient and the product recommendations concerning dosage rate be observed
- particular care, including a reduction in midazolam dosage, is required in patients also receiving opioid analgesics, in the elderly and children, and in debilitated or chronically ill patients such as those with compromised cardiorespiratory function, chronic renal failure, or hepatic impairment
- similar warnings apply to the use of oral midazolam where it is available

The National Patient Safety Agency[4] in the UK has also issued guidelines on the use of midazolam for conscious sedation after it had received 498 reports (3 fatalities) of inappropriate dosage, particularly with high-strength preparations, for such use between November 2004 and November 2008.

The availability of the benzodiazepine antagonist, flumazenil, should not be an encouragement to use larger doses of midazolam.[1]

Since endoscopy of the upper gastrointestinal tract can itself reduce oxygen saturation, some workers have advocated the prophylactic use of nasal oxygen during this procedure for those patients at particular risk as outlined above.

1. Anonymous. Midazolam—is antagonism justified? *Lancet* 1988; **ii:** 140–2.
2. Bell GD. Review article: premedication and intravenous sedation for upper gastrointestinal endoscopy. *Aliment Pharmacol Ther* 1990; **4:** 103–22.
3. Ryder W, Wright PA. Dental sedation: a review. *Br Dent J* 1988; **165:** 207–16.
4. National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR011: reducing risk of overdose with midazolam injection in adults (issued 9th December, 2008). Available at: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59896 (accessed 11/11/10)

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of midazolam on breast-fed infants was unknown its use by mothers during breast feeding might be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Midazolam could not be detected in breast milk from 11 mothers the morning after either the first or the fifth nightly 15-mg oral dose.[2] Additional study of 2 mothers found that midazolam and its hydroxy-metabolite disappeared rapidly from milk with undetectable concentrations at 4 hours. The mean milk to plasma ratio for midazolam was 0.15 in 6 paired samples. Another study[3] using midazolam 2 mg intravenously for pre-operative sedation in 5 mothers concluded that the amount of midazolam excreted into breast milk within 24 hours after administration was less than 0.1% of the maternal dose, and hence unlikely to affect a healthy full-term breast-feeding infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30:** 787–93.
3. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.

Children. An intravenous bolus injection of midazolam in children already receiving intravenous morphine after cardiac surgery produced an undesirable transient fall in cardiac output.[1] It was suggested that for patients already receiving other drugs that provide sedation the use of midazolam in the early postoperative period should be limited to a continuous infusion. Similarly, it has been recommended[2] that bolus intravenous doses of midazolam should be avoided in neonates due to the occurrence of hypotension.

The initial dosage of midazolam used for continuous intravenous sedation may need to be reduced in critically ill children under 3 years of age since the plasma clearance of midazolam appears to be reduced in these patients.[3]

1. Shekerdemian L, *et al.* Cardiovascular effects of intravenous midazolam after open heart surgery. *Arch Dis Child* 1997; **76:** 57–61.
2. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.
3. Hughes J, *et al.* Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996; **30:** 27–30.

Effects on mental function. For discussion of the adverse effects of benzodiazepines on mental function, including reports of sexual fantasies in women sedated with intravenous midazolam, see Diazepam, p. 1066.1.

Effects on the nervous system. For reference to acute dystonia associated with use of midazolam, see Diazepam, p. 1066.1.

ENCEPHALOPATHY. For a report of prolonged use of midazolam with fentanyl being associated with encephalopathy in infants sedated under intensive care, see Diazepam, p. 1066.2.

MYOCLONUS. Myoclonic twitching of all four limbs was noted[1] in 6 of 102 neonates who received a continuous intravenous infusion of midazolam at a rate of 30 to 60 micrograms/kg per hour. Myoclonus ceased a few hours after stopping the infusion and never recurred. No ictal activity was detected in EEGs recorded during the myoclonus.

1. Magny JF, *et al.* Midazolam and myoclonus in neonate. *Eur J Pediatr* 1994; **153:** 389–90.

The elderly. Sedation with midazolam in elderly subjects needed only about half the dose necessary to produce comparable effects in younger subjects.[1] Pharmacodynamic differences due to age suggested an increase in sensitivity of the CNS to midazolam in the elderly subjects.

1. Albrecht S, *et al.* The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther* 1999; **65:** 630–9.

Hepatic impairment. For the precautions to be observed in patients with impaired liver function, see under Pharmacokinetics, p. 1088.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies midazolam as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Renal impairment. Five patients with severe renal impairment had prolonged sedation when given midazolam; this was attributed to accumulation of conjugated metabolites.[1]

1. Bauer TM. *et al.* Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; **346:** 145–7.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Absorption of midazolam is rapid, peak plasma concentrations occurring within 20 to 60 minutes of a dose, depending on the route. Extensive first-pass metabolism results in a low systemic bioavailability after oral doses. Bioavailability is higher, but variable, after intramuscular injection; figures of more than 90% are often cited.

Midazolam is lipophilic at physiological pH. It crosses the placenta and is distributed into breast milk (but see p. 1087.2). Midazolam is about 96 to 98% bound to plasma proteins, mainly albumin.

Midazolam usually has a short elimination half-life of about 1.5 to 2.5 hours although half-lives up to 6 times longer have been reported in critically ill patients. The half-life of midazolam is also prolonged in neonates, in the elderly, and in patients with liver disorders or cardiac insufficiency.

Midazolam is metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4. The major metabolite, 1-hydroxymidazolam (alpha-hydroxymidazolam) has some activity; its half-life is less than 1 hour. Midazolam metabolites are excreted in the urine, mainly as glucuronide conjugates.

References.
1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Swart EL, *et al*. Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; **57:** 135–45.

Children. In a study[1] of the pharmacokinetics of midazolam in children the bioavailability of a dose of 150 micrograms/kg was 100, 87, 27, and 18% when given by the intravenous, intramuscular, oral, and rectal routes, respectively. The oral bioavailability was reduced to 16 and 15% after increasing the dose to 450 micrograms/kg and 1 mg/kg, respectively. There was bioequivalence between the 150 micrograms/kg intramuscular dose and the 450 micrograms/kg oral dose from 45 to 120 minutes after dosage. Absorption from the rectal route gave lower serum-midazolam concentrations than the oral route at the 150 micrograms/kg dose.

Midazolam appears to be absorbed rapidly when given intranasally to children with mean peak plasma concentrations being achieved within about 12 minutes;[2-4] values of 30 and 55% have been reported for the bioavailability[3,4] but methods to optimise nasal delivery have resulted in higher bioavailability in studies in adults (see below). A study comparing intranasal, intravenous, and rectal dosage of midazolam in children found that plasma concentrations from 45 minutes after intranasal and intravenous doses were similar; those after rectal doses were consistently less than after these other 2 routes.[2] Possible reasons suggested by the authors for this included the effect that the wide interindividual variations in rectal pH may have had on the absorption of midazolam.

Another study has investigated the relationship between intravenous dose and plasma-midazolam concentrations in children.[5]

See also under Precautions, p. 1087.3.

1. Payne K, *et al*. The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989; **37:** 267–72.
2. Malinovsky J-M, *et al*. Plasma concentrations of midazolam after iv, nasal or rectal administration in children. *Br J Anaesth* 1993; **70:** 617–20.
3. Rey E, *et al*. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol* 1991; **41:** 355–7.
4. Kauffman RE, *et al*. Intranasal absorption of midazolam. *Clin Pharmacol Ther* 1995; **57:** 209.
5. Tolia V, *et al*. Pharmacokinetic and pharmacodynamic study of midazolam in children during esophagogastroduodenoscopy. *J Pediatr* 1991; **119:** 467–71.

NEONATES. References[1-7] to the pharmacokinetics of midazolam in neonates.

1. Jacqz-Aigrain E, *et al*. Pharmacokinetics of midazolam in critically ill neonates. *Eur J Clin Pharmacol* 1990; **39:** 191–2.
2. Jacqz-Aigrain E, *et al*. Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *Eur J Clin Pharmacol* 1992; **42:** 329–32.
3. Burtin P, *et al*. Population pharmacokinetics of midazolam in neonates. *Clin Pharmacol Ther* 1994; **56:** 615–25.
4. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.
5. Harte GJ, *et al*. Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997**33:** 335–8.
6. Lee TC, *et al*. Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. *Anesthesiology* 1999; **90:** 451–7.
7. de Wildt SN, *et al*. Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther* 2001; **70:** 525–31.

Half-life. Data collected from 7 studies involving 90 subjects have suggested that the prolonged midazolam half-lives reported in a small number of patients are secondary to increases in the volume of distribution and not a result of alterations in clearance and metabolism.[1] Prolongation of the half-life of midazolam has been reported[2] in 2 patients after sustained infusion for status epilepticus.

1. Wills RJ, *et al*. Increased volume of distribution prolongs midazolam half-life. *Br J Clin Pharmacol* 1990; **29:** 269–72.
2. Narituku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology* 2000 **54:** 1366–8.

Intranasal administration. Plasma concentrations of midazolam sufficient to induce conscious sedation are rapidly attained after intranasal doses.[1] Although bioavailability of up to 55% had previously been obtained in children after intranasal use (see above), slow administration and other methods to optimise nasal delivery have resulted in higher bioavailability in adults; a mean ranging from 72.5 to 92% has been reported in some studies.[2-5]

1. Burstein AH, *et al*. Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. *J Clin Pharmacol* 1997; **37:** 711–18.
2. Björkman S, *et al*. Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. *Br J Anaesth* 1997; **79:** 575–80.
3. Knoester PD, *et al*. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray: a study in healthy volunteers. *Br J Clin Pharmacol* 2002; **53:** 501–7.
4. Wermeling DP, *et al*. Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. *Anesth Analg* 2006; **103:** 344–9.
5. Haschke M, *et al*. Pharmacokinetics and pharmacodynamics of nasally delivered midazolam. *Br J Clin Pharmacol* 2010; **69:** 607–16.

Liver disorders. The pharmacokinetics of midazolam in patients with advanced cirrhosis of the liver were characterised by an increase in oral systemic bioavailability[1] and by a decrease in clearance with consequent prolongation of elimination half-life.[1,2] Dosage may need to be reduced. However, metabolism of midazolam has been found in the anhepatic period of liver transplantation indicating extrahepatic metabolism (see below).

1. Pentikäinen PJ, *et al*. Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989; **29:** 272–7.
2. MacGilchrist AJ, *et al*. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. *Gut* 1986; **27:** 190–5.

Metabolism. For a discussion of the metabolism of benzodiazepines, see Diazepam, p. 1071.1. Midazolam appears to be metabolised by at least 3 different cytochrome P450 isoenzymes found in the liver and in the kidney.[1] Variations in the activity of these enzymes might account for some of the interindividual differences in pharmacokinetics and pharmacodynamics seen with midazolam.[2] However, a study[3] in patients undergoing liver transplantation has indicated that the small intestine is a significant site for the first-pass metabolism of midazolam, metabolism presumably being catalysed by the cytochrome P450 isoenzyme CYP3A4 found in intestinal mucosa.

1. Wandel C, *et al*. Midazolam is metabolized by at least three different cytochrome P450 enzymes. *Br J Anaesth* 1994; **73:** 658–61.
2. Lown KS, *et al*. The erythromycin breath test predicts the clearance of midazolam. *Clin Pharmacol Ther* 1995; **57:** 16–24.
3. Paine MF, *et al*. First-pass metabolism of midazolam by the human intestine. *Clin Pharmacol Ther* 1996; **60:** 14–24.

Sublingual administration. High bioavailability (about 75%) and reliable plasma concentrations have been achieved after sublingual doses of midazolam.[1]

1. Schwagmeier R, *et al*. Midazolam pharmacokinetics following intravenous and buccal administration. *Br J Clin Pharmacol* 1998; **46:** 203–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dalam; Dormicum; Dormid; Drimnorth; Gobbizolam; Rem; Ukel†; ***Austral.***: Hypnovel; ***Austria***: Dormicum; ***Belg.***: Dormicum; ***Braz.***: Dormant; Dormire; Dormium; Dormonid; Hipnazolam; Midadorm; ***Chile***: Dormonid; Noctura; Terap; Zolmid; ***China***: Dormicum (多美康); Fulsed (弗赛得); Li Yue Xi (力月西); ***Cz.***: Dormicum; Fulsed†; ***Denm.***: Dormicum†; ***Fin.***: Dormicum; ***Fr.***: Hypnovel; Versed; ***Ger.***: Buccolam; Dormicum; ***Gr.***: Damizol; Dormicum; Dormixal; Epistatus; ***Hong Kong***: Dormicum; ***Hung.***: Dormicum; ***India***: Benzosed; Fulsed; Mezolam; Miben; Midapic; Midaz; Midosed; Midzee; Midzol; ***Indon.***: Anesfar; Dormicum; Fortanest; Hipnoz; Miloz; Sedacum; Sezolam; ***Irl.***: Buccolam; Hypnovel; ***Israel***: Midazol†; Midolam; ***Ital.***: Ipnovel; ***Malaysia***: Domi; Dormicum; Fulsed; Mizolam; ***Mex.***: Dormicum; Midozor; Relacum; Zomsol†; ***Neth.***: Dormicum; ***Norw.***: Dormicum†; ***NZ***: Hypnovel; ***Philipp.***: Dormicum; Dormizol; Sedoz; ***Pol.***: Dormicum; Midanium; Sopodorm; ***Port.***: Dormicum; Zolamid; ***Rus.***: Dormicum (Дормикум); Fulsed (Фулсед); ***S.Afr.***: Dormicum; Midacum; Midanium†; Midazoject; ***Singapore***: Domi; Dormicum; Fulsed; ***Spain***: Dormicum; ***Swed.***: Dormicum; ***Switz.***: Dormicum; ***Thai.***: Dormicum†; ***Turk.***: Demizolam; Dormicum; ***UK***: Buccolam; Hypnovel; ***Ukr.***: Fulsed (Фульсед); ***Venez.***: Benzosed; Doricum; Midazepin.

Pharmacopoeial Preparations
BP 2014: Midazolam Injection; Midazolam Oral Solution; Midazolam Oromucosal Solution;
USP 36: Midazolam Injection.

Molindone Hydrochloride *(BANM, USAN, rINNM)*

EN-1733A; Hidrocloruro de molindona; Molindona, hidrocloruro de; Molindone, Chlorhydrate de; Molindoni Hydrochloridum; Молиндона Гидрохлорид.

3-Ethyl-1,5,6,7-tetrahydro-2-methyl-5-(morpholinomethyl) indol-4-one hydrochloride.

$C_{16}H_{24}N_2O_2$,HCl=312.8

CAS — 7416-34-4 (molindone); 15622-65-8 (molindone hydrochloride).

ATC — N05AE02.

ATC Vet — QN05AE02.

UNII — 1DWS68PNE6.

Pharmacopoeias. In *US.*

USP 36: (Molindone Hydrochloride). pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Profile

Molindone is an indole derivative with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.2). It has been given orally as the hydrochloride for the treatment of psychoses including schizophrenia.

Psychiatric disorders. A systematic review[1] found that, based on limited data, molindone appeared to be effective in schizophrenia (p. 1031.3) and other severe psychoses but evidence of differences from other classical antipsychotics was lacking. However, weight loss appears to be more prominent (see p. 1047.3).

1. Bagnall A-M, *et al*. Molindone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 04/09/13).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Moban†.

Pharmacopoeial Preparations
USP 36: Molindone Hydrochloride Tablets.

Moperone Hydrochloride *(rINNM)*

Hidrocloruro de moperona; Methylperidol Hydrochloride; Moperona, hidrocloruro de; Mopérone, Chlorhydrate de; Moperoni Hydrochloridum; R-1658 (moperone); Моперона Гидрохлорид.

4′-Fluoro-4-(4-hydroxy-4-*p*-tolylpiperidino)butyrophenone hydrochloride.

$C_{22}H_{26}FNO_2$,HCl=391.9

CAS — 1050-79-9 (moperone); 3871-82-7 (moperone hydrochloride).

ATC — N05AD04.

ATC Vet — QN05AD04.

Profile

Moperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It has been given orally for the treatment of psychoses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Luvatren†.

Mosapramine *(rINN)*

Clospipramine; Mosapramina; Mosapraminum; Y-516; Мозапрамин.

(±)-1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl) propyl]hexahydrospiro[imidazo[1,2-*a*]pyridine-3(2*H*),4′-piperidin]-2-one.

$C_{28}H_{35}ClN_4O$=479.1

CAS — 89419-40-9 (mosapramine); 98043-60-8 (mosapramine hydrochloride).

ATC — N05AX10.

ATC Vet — QN05AX10.

UNII — 04UZQ7O9SJ.

Profile

Mosapramine is an antipsychotic that is used as the hydrochloride in the treatment of schizophrenia.

References.
1. Ishigooka J, *et al*. Pilotstudy of plasma concentrations of mosapramine, a new iminodibenzyl antipsychotic agent, after multiple oral administration in schizophrenic patients. *Curr Ther Res* 1994; **55:** 331–42.
2. Takahashi N, *et al*. Comparison of risperidone and mosapramine addition to neuroleptic treatment in chronic schizophrenia. *Neuropsychobiology* 1999; **39:** 81–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cremin.

Nemonapride *(rINN)*

Emonapride; Nemonaprida; Némonapride; Nemonapridum; YM-09151-2; Немонаприд.

(±)-*cis*-*N*-(1-Benzyl-2-methyl-3-pyrrolidinyl)-5-chloro-4-(methylamino)-*o*-anisamide.

$C_{21}H_{26}ClN_3O_2$=387.9

CAS — 93664-94-9.

UNII — Q88T5P3444.

Profile

Nemonapride is a substituted benzamide antipsychotic with general properties similar to those of sulpiride (p. 1107.3). It is given orally in the treatment of schizophrenia (p. 1031.3) in usual doses of 9 to 36 mg daily in divided doses; up to 60 mg daily may be given if necessary.

References.

1. Satoh K, *et al.* Effects of nemonapride on positive and negative symptoms of schizophrenia. *Int Clin Psychopharmacol* 1996; **11:** 279–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Emilace (艾敏斯); ***Jpn***: Emilace.

Nimetazepam *(rINN)*

Menifazepam; Nimétazépam; Nimetazepamum; S-1530; Нуметазепам.

1,3-Dihydro-1-methyl-7-nitro-5-phenyl-1,4-benzodiazepin-2-one.

$C_{16}H_{13}N_3O_3$=295.3

CAS — 2011-67-8.

UNII — 4532264KW6.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nimetazepam:

Happy 5

Profile

Nimetazepam is a benzodiazepine with the general properties of diazepam (p. 1063.2). It has been given for the short-term management of insomnia (p. 1033.2) in a usual oral dose of 3 or 5 mg at night. It appears to have been subject to abuse, especially in South East Asia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Erimin.

Nitrazepam *(BAN, USAN, rINN)*

Nitratsepaami; Nitrazepám; Nitrazépam; Nitrazepamas; Nitrazepamum; NSC-58775; Ro-5-3059; Ro-4-5360; Нитразепам.

1,3-Dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{11}N_3O_3$=281.3

CAS — 146-22-5.

ATC — N05CD02.

ATC Vet — QN05CD02.

UNII — 9CLV70W7HS.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nitrazepam:

Don; Moggies; Moogles; Nitro's; The Don.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn*.

Ph. Eur. 8: (Nitrazepam). A white or yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

Uses and Administration

Nitrazepam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (p. 1033.2) and is reported to act in 30 to 60 minutes to produce sleep lasting for 6 to 8 hours. Nitrazepam has also been used in epilepsy, notably for infantile spasms (below).

The usual oral dose for insomnia is 5 mg at night, although 10 mg may be required in some patients. Elderly or debilitated patients should not be given more than half of the usual adult dose.

Administration in children. For details of doses of nitrazepam in children, see Epilepsy, below.

Epilepsy. Benzodiazepines are sometimes employed in the management of epilepsy (p. 506.1), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Nitrazepam has perhaps been most useful in the treatment of infantile spasms (as for example in West's syndrome) and the so-called infantile myoclonic seizures. The *BNFC* suggests that those aged from 1 month to 2 years may be given initial oral doses of 125 micrograms/kg twice daily, adjusted according to response over 2 to 3 weeks to 250 micrograms/kg twice daily (maximum of 500 micrograms/kg, but not exceeding 5 mg, twice daily); the same total daily dose may also be given in 3 divided doses. There has been concern, however, over swallowing difficulties with subsequent aspiration and reports of unexpected death associated with the use of nitrazepam in young children (see Effects on the Digestive System under Adverse Effects, below).

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 5 mg of nitrazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Effects on the digestive system. Two children given nitrazepam as part of their antiepileptic therapy developed drooling, eating difficulty, and aspiration pneumonia; symptoms improved in one patient when the dosage of nitrazepam was reduced.[1] Manometric studies indicated that the onset of normal cricopharyngeal relaxation in swallowing was delayed in these patients until after hypopharyngeal contraction, resulting in impaired swallowing and spillover of material into the trachea. Other workers[2] have found similar effects on swallowing and cricopharyngeal relaxation in children given nitrazepam. The deaths of 6 epileptic children under 5 years of age who were treated with nitrazepam have been reported.[3] Three of the deaths were unexpected, and in view of the previous reports of swallowing difficulties and aspiration, it was recommended that the use of nitrazepam in young children be restricted to those in whom seizure control fails to improve with other antiepileptics. Another study[4] also found an apparently increased risk of death, especially in young patients with intractable epilepsy, associated with nitrazepam therapy.

1. Wyllie E, *et al.* The mechanism of nitrazepam-induced drooling and aspiration. *N Engl J Med* 1986; **314:** 35–8.
2. Lim HCN, *et al.* Nitrazepam-induced cricopharyngeal dysphagia, abnormal esophageal peristalsis and associated bronchospasm: probable cause of nitrazepam-related sudden death. *Brain Dev* 1992; **14:** 309–14.
3. Murphy JV, *et al.* Deaths in young children receiving nitrazepam. *J Pediatr* 1987; **111:** 145–7.
4. Rintahaka PJ, *et al.* Incidence of death in patients with intractable epilepsy during nitrazepam treatment. *Epilepsia* 1999; **40:** 492–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nitrazepam as probably porphyrinogenic; it should be prescribed only for compelling indications and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Nitrazepam is fairly readily absorbed from the gastrointestinal tract, although there is some individual variation. Peak plasma concentrations occur 2 to 3 hours after ingestion. It is about 87% bound to plasma proteins. It crosses the blood-brain and the placental barriers and traces are found in breast milk. Nitrazepam is metabolised in the liver, mainly by nitroreduction followed by acetylation; none of the metabolites possess significant activity. It is excreted in the urine in the form of its metabolites (free or conjugated) with only small amounts of a dose appearing unchanged. Up to about 20% of an oral dose is found in the faeces. Mean elimination half-lives of 24 to 30 hours have been reported.

Distribution into breast milk. A mean milk-to-plasma ratio of 0.27 was obtained after giving nitrazepam 5 mg orally for 5 nights to 9 puerperal women.[1] The accumulation of nitrazepam in milk over the study period was similar to that in plasma.

1. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30:** 787–93.

Hepatic impairment. The pharmacokinetics of intravenous nitrazepam in 12 patients with cirrhosis of the liver has been compared with 9 healthy subjects aged 22 to 49 years and 8 healthy elderly subjects aged 67 to 76 years.[1] The mean elimination half-life of nitrazepam was 26 hours in young and 38 hours in elderly subjects, the difference, which was not significant, being chiefly due to the greater volume of distribution in elderly subjects. Although there was also no significant difference between young and elderly subjects in percentage of unbound nitrazepam (13.0 and 13.9% respectively) there was a substantially higher unbound fraction in the patients with cirrhosis, the mean value being 18.9%, and clearance of unbound nitrazepam was reduced relative to healthy subjects.

1. Jochemsen R, *et al.* Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. *Br J Clin Pharmacol* 1983; **15:** 295–302.

Metabolism. Although the acetylation of the reduced metabolite of nitrazepam has been reported to be controlled by acetylator phenotype,[1] no significant differences between either half-life or residual effects of nitrazepam were seen in slow and fast acetylators.[2]

1. Karim AKMB, Price Evans DA. Polymorphic acetylation ofnitrazepam. *J Med Genet* 1976; **13:** 17–19.
2. Swift CG, *et al.* Acetylator phenotype, nitrazepam plasma concentrations and residual effects. *Br J Clin Pharmacol* 1980; **9:** 312P–313P.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Alodorm; Mogadon; ***Austria***: Mogadon; ***Belg.***: Mogadon; ***Braz.***: Nitrapan; Nitrazepol; Sonebon; ***Canad.***: Mogadon; Nitrazadon; ***Denm.***: Apodorm; Mogadon†; Pacisyn; ***Fin.***: Insomin; ***Fr.***: Mogadon; ***Ger.***: Dormo-Puren†; Imeson; Mogadan; Novanox; Radedorm†; ***Hong Kong***: Alodorm†; Mogadon; ***Hung.***: Eunoctin; ***India***: Baronite; Dormin; Gentravit; Hypnoril; Hypnotex; Insomin; Nigap; Nipam; Nitavan; Nithra; Nitravet; Nitraz; Nitrocalm; Nitrosun; Nitrosym; ***Indon.***: Dumolid; ***Irl.***: Mogadon; ***Israel***: Numbon; ***Ital.***: Mogadon; ***Neth.***: Mogadon; ***Norw.***: Apodorm; Mogadon; ***NZ***: Insoma†; Nitrados; ***Philipp.***: Mozepam; ***Rus.***: Eunoctin (Эуноктин); Nitrosun (Нитросан); Radedorm (Радедорм); ***S.Afr.***: Arem; Mogadon; Ormodon†; Paxadorm; ***Singapore***: Dima†; Nitrados; ***Swed.***: Apodorm†; Mogadon; ***Switz.***: Mogadon; ***Thai.***: Nitrados; ***UK***: Mogadon; Remnos; Somnite†; ***Venez.***: Onirema.

Multi-ingredient Preparations. ***China***: Xi Li Shu (希力舒).

Pharmacopoeial Preparations

BP 2014: Nitrazepam Oral Suspension; Nitrazepam Tablets.

Nordazepam *(rINN)*

A-101; Demethyldiazepam; Desmethyldiazepam; *N*-Desmethyldiazepam; Nordazépam; Nordazepamum; Nordiazepam; Ro-5-2180; Нордазепам.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{11}ClN_2O$=270.7

CAS — 1088-11-5.

ATC — N05BA16.

ATC Vet — QN05BA16.

UNII — 67220MCM01.

Profile

Nordazepam is a long-acting benzodiazepine with the general properties of diazepam (p. 1063.2). It is the principal active metabolite of several benzodiazepines and has a half-life of 2 to 5 days. It is given in oral doses of up to 15 mg daily for the short-term treatment of anxiety disorders (p. 1028.1) and insomnia (p. 1033.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Calmday; ***Fr.***: Nordaz; ***Ger.***: Tranxilium N†; ***Gr.***: Lomax; ***Ital.***: Madar; ***Singapore***: Nordaz.

Olanzapine *(BAN, USAN, rINN)*

LY-170053; Olantsapiini; Olanzapin; Olanzapina; Olanzapinum; Оланзапин.

2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine.

$C_{17}H_{20}N_4S$=312.4

CAS — 132539-06-1.

ATC — N05AH03.

ATC Vet — QN05AH03.
UNII — N7U69T4SZR.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Olanzapine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. It shows polymorphism.

USP 36: (Olanzapine). A yellow crystalline solid. Practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; soluble in propyl alcohol; sparingly soluble in acetonitrile.

Stability. A suspension of olanzapine 1 mg/mL, made by crushing olanzapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for 2 weeks when stored in a refrigerator.[1]

1. Harvey EJ, *et al.* The preparation and stability of a liquid olanzapine preparation for oral administration in hospitals. *Pharm J* 2000; **265:** 275–6.

Olanzapine Embonate *(BANM, rINNM)*

Embonato de olanzapina; Olanzapine, Embonate d'; Olanzapine Pamoate (USAN); Olanzapini Embonas; Оланзапина Эмбонат.

$C_{23}H_{16}O_6.C_{17}H_{20}N_4S,H_2O$=718.8
CAS — 221373-18-8.
ATC — N05AH03.
ATC Vet — QN05AH03.
UNII — X7S6Q4MHCB.

Uses and Administration

Olanzapine is a thienobenzodiazepine atypical antipsychotic. It has affinity for serotonin, muscarinic, histamine (H_1), and adrenergic (α_1) receptors as well as various dopamine receptors.

Olanzapine is used for the management of schizophrenia (below) and for the treatment of moderate to severe mania associated with bipolar disorder (below). It is also given with fluoxetine for the treatment of the depressive phase of bipolar disorder (below) and for treatment-resistant unipolar depression (p. 398.1). Olanzapine is usually given orally or by intramuscular injection as the base. The longer-acting embonate salt is given by intramuscular injection. For all routes, doses are expressed in terms of the equivalent amount of olanzapine; olanzapine embonate 230.1 mg is equivalent to about 100 mg of olanzapine.

UK licensed product information states that the usual initial oral dose for **schizophrenia** is 10 mg daily as a single dose; thereafter dosage adjustments may be made according to response at intervals of not less than 24 hours to within the range of 5 to 20 mg daily. The licensed starting dose in the USA is 5 to 10 mg daily and it is recommended that dosage adjustments beyond 10 mg daily are made at intervals of not less than 1 week; the daily dosage should be adjusted in steps of 5 mg.

The long-acting depot preparation may also be given by deep intramuscular injection every 2 or 4 weeks for maintenance therapy of schizophrenia. Patients with no history of olanzapine use should initially be treated with olanzapine orally to assess tolerability and response. Treatment may then be started as follows, according to target oral olanzapine dose:

- 10 mg daily: 210 mg every 2 weeks or 405 mg every 4 weeks, then 150 mg every 2 weeks or 300 mg every 4 weeks after 2 months of therapy
- 15 mg daily: 300 mg every 2 weeks, then 210 mg every 2 weeks or 405 mg every 4 weeks after 2 months of therapy
- 20 mg daily: 300 mg every 2 weeks, then 300 mg every 2 weeks after 2 months of therapy

Patients should be monitored for signs of relapse during the first 1 or 2 months of treatment. If oral olanzapine supplementation is required, then the combined total dose of both formulations should not exceed the corresponding maximum oral dose of 20 mg daily.

For the treatment of *acute mixed or manic episodes* in **bipolar disorder**, a recommended initial oral dose is 10 or 15 mg daily as monotherapy or 10 mg if given as an adjunct to lithium or valproate; the daily dosage may be adjusted in steps of 5 mg if necessary, at intervals of not less than 24 hours to a dose of between 5 and 20 mg daily. If a response is achieved, therapy may continue at the same dosage to prevent recurrence. For *maintenance treatment* in patients whose manic episodes have responded previously to olanzapine, the recommended starting dose is 10 mg daily.

For the treatment of the **depressive phase** of bipolar disorder and for treatment-resistant **unipolar depression**, a recommended initial oral dose of olanzapine is 5 mg once daily; dosage adjustments may be made according to efficacy and tolerance to within the range of olanzapine 5 to 12.5 mg daily for bipolar disorder or 5 to 20 mg daily for unipolar depression. In some countries olanzapine is available as a fixed-dose combination with fluoxetine for these indications.

For the **rapid control of agitation and disturbed behaviour** in patients with schizophrenia or mania, olanzapine may be given intramuscularly in an initial dose of 5 to 10 mg followed by 5 to 10 mg as required after 2 hours. Not more than 3 injections should be given in any 24-hour period and the maximum daily dose, including olanzapine given orally, should not exceed 20 mg. Injections may be given for a maximum of 3 days but transfer to oral therapy should be started as soon as possible.

The metabolism of olanzapine might be slower in female, elderly, or non-smoking patients; if more than one of these factors is present, a lower initial dose (e.g. 5 mg daily if given orally) and a more gradual dose escalation should be considered. The intramuscular dose should be reduced by half in the elderly. A lower starting dose of 150 mg every 4 weeks of the long-acting depot preparation is not routinely indicated but should be considered in patients aged over 65 years; treatment should not be started in those aged over 75 years due to lack of data. See Administration in Hepatic or Renal Impairment, below for doses in patients with hepatic or renal impairment.

For details of uses and associated doses in adolescents, see Administration in Children, below.

The benzoate and tartrate salts are used similarly in some countries.

Administration in children. In the USA, olanzapine is licensed for the treatment of schizophrenia and as monotherapy for acute manic or mixed episodes associated with bipolar disorder in adolescents aged 13 to 17 years. For both indications, the recommended initial oral dose is 2.5 or 5 mg once daily, increased to the target dose of 10 mg daily. Efficacy has been shown with doses ranging from 2.5 to 20 mg daily. Dosage adjustments, if necessary, should be made in steps of 2.5 or 5 mg.

Although unlicensed in the UK for use in children and adolescents aged under 18 years, the *BNFC* suggests that olanzapine may be given to those aged 12 years and over. For the management of schizophrenia and the treatment of mania as part of combination therapy, an initial oral dose of 5 to 10 mg daily, adjusted to the usual range of 5 to 20 mg daily, may be given; for the treatment of mania as monotherapy, an initial oral dose of 15 mg daily, adjusted to the usual range of 5 to 20 mg daily, is suggested.

Administration in hepatic or renal impairment. A starting dose of 5 mg daily of olanzapine orally or by intramuscular injection, or 150 mg every 4 weeks of the long-acting depot preparation, may be necessary for patients with renal or hepatic impairment; for patients with moderate hepatic insufficiency (Child-Pugh classes A and B), the starting dose should only be increased with caution.

Bipolar disorder. Olanzapine is of benefit for the treatment, and prevention, of mania, with or without psychosis, in patients with bipolar disorder (p. 397.2), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of olanzapine-induced mania (see p. 1091.3).

There is also increasing interest in the use of olanzapine for the depressive phase of bipolar disorder, and for other forms of resistant depression. In some countries olanzapine is available as a fixed-dose combination with fluoxetine.

References.

1. Shelton RC, *et al.* A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001; **158:** 131–4.
2. Rendell JM, *et al.* Olanzapine alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/05/05).
3. McCormack PL, Wiseman LR. Olanzapine: a review of its use in the management of bipolar I disorder. *Drugs* 2004; **64:** 2709–26.
4. Shelton RC. Olanzapine/fluoxetine combination for bipolar depression. *Expert Rev Neurother* 2006; **6:** 33–9.
5. Tohen M, *et al.* Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry* 2007; **164:** 1547–56.
6. Strawn JR, Delbello MP. Olanzapine for the treatment of bipolar disorder in children and adolescents. *Expert Opin Pharmacother* 2008; **9:** 467–74.
7. Deeks ED, Keating GM. Olanzapine/fluoxetine: a review of its use in the treatment of acute bipolar depression. *Drugs* 2008; **68:** 1115–37.
8. Cipriani A, *et al.* Olanzapine in long-term treatment for bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 01/06/09).
9. Trivedi MH, *et al.* An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry* 2009; **70:** 387–96.

Nausea and vomiting. For mention of the use of olanzapine as a second-line drug to control nausea and vomiting in palliative care see p. 1814.3.

Parkinsonism. Olanzapine is associated with a relatively low incidence of extrapyramidal disorders and has been studied[1] for use in the treatment of psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p. 1030.2). However, there have been several reports of adverse effects including exacerbation of the movement disorder (see Parkinsonism, under Precautions, p. 1092.1).

1. Wolters EC, *et al.* Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. *Neurology* 1996; **47:** 1085–7.

Psychiatric disorders. The main treatment for *post-traumatic stress disorder* (p. 1029.2) is psychotherapy but adjunctive olanzapine may be used in patients refractory to psychotherapy and/or drug treatment with antidepressants. Olanzapine has also been tried for the control of *aggression* in children with autism and conduct disorder (see Disturbed Behaviour, p. 1030.2).

Schizophrenia. Studies suggest that olanzapine is as effective as haloperidol against positive symptoms of schizophrenia (p. 1031.3) and more effective against negative symptoms in the short-term and possibly in the long-term,[1-5] although a systematic review considered the evidence equivocal.[6] Quality of life has also been judged to be greater in patients treated with olanzapine.[7] In comparative studies, extrapyramidal adverse effects have been less frequent with olanzapine than haloperidol and fewer patients have discontinued treatment with olanzapine. There are relatively few published comparisons with other atypical antipsychotics, but one systematic review[8] concluded that there was little to differentiate between olanzapine and risperidone apart from their adverse effects; risperidone was particularly associated with movement disorders and sexual dysfunction while olanzapine induced rapid weight gain. Another study has suggested that olanzapine is not inferior to clozapine.[9] A more recent systematic review[10] found that olanzapine may be slightly more effective than aripiprazole, quetiapine, risperidone, and ziprasidone, whereas no difference in efficacy was found when compared with amisulpride and clozapine. Olanzapine was also found to be associated with more weight gain than most other atypical antipsychotics except for clozapine. Olanzapine's efficacy in the treatment of patients with refractory schizophrenia remains to be determined; a small, randomised study found it to be no more effective than haloperidol.[11]

Olanzapine has also been studied[12-14] for the treatment of schizophrenia in children and adolescents, and is licensed for such use in some countries.

1. Beasley CM, *et al.* Olanzapine HGAD Study Group. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996; **14:** 111–23.
2. Beasley C, *et al.* Olanzapine versus haloperidol: long-term results of the multi-center international trial. *Eur Neuropsychopharmacol* 1996; **6** (suppl 3): 59.
3. Beasley CM, *et al.* Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* 1997; **7:** 125–37.
4. Tollefson GD, *et al.* Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997; **154:** 457–65.
5. Bhana N, *et al.* Olanzapine: an updated review of its use in the management of schizophrenia. *Drugs* 2001; **61:** 111–61.
6. Duggan L, *et al.* Olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 24/05/05).
7. Hamilton SH, *et al.* Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology* 1998; **18:** 41–9.
8. Jayaram MB, *et al.* Risperidone versus olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 16/01/07).
9. Naber D, *et al.* Randomized double blind comparison of olanzapine vs clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatr Scand* 2005; **111:** 106–15.
10. Komossa K, *et al.* Olanzapine versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 24/03/10).
11. Buchanan RW, *et al.* Olanzapine treatment of residual positive and negative symptoms. *Am J Psychiatry* 2005; **162:** 124–9.
12. Quintana H, *et al.* An open-label study of olanzapine in children and adolescents with schizophrenia. *J Psychiatr Pract* 2007; **13:** 86–96.
13. Dittmann RW, *et al.* Effectiveness and tolerability of olanzapine in the treatment of adolescents with schizophrenia and related psychotic disorders: results from a large, prospective, open-label study. *J Child Adolesc Psychopharmacol* 2008; **18:** 54–69.
14. Kryzhanovskaya L, *et al.* Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2009; **48:** 60–70.

Stuttering. Although olanzapine may be of benefit in the treatment of stuttering (p. 1078.1),[1,2] it has been associated with reports of stuttering in 6 adult patients with schizophrenia or depression.[3]

1. Lavid N, *et al.* Management of child and adolescent stuttering with olanzapine: three case reports. *Ann Clin Psychiatry* 1999; **11:** 233–6.
2. Maguire GA, *et al.* Olanzapine in the treatment of developmental stuttering: a double-blind, placebo-controlled trial. *Ann Clin Psychiatry* 2004; **16:** 63–7.
3. Bär KJ, *et al.* Olanzapine- and clozapine-induced stuttering: a case series. *Pharmacopsychiatry* 2004; **37:** 131–4.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) haloperidol or pimozide are com-

monly used but atypical antipsychotics, including olanzapine, are increasingly being tried.[1-5]

1. Stamenkovic M, *et al*. Effective open-label treatment of tourette's disorder with olanzapine. *Int Clin Psychopharmacol* 2000; **15:** 23–8.
2. Onofrj M, *et al*. Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. *J Neurol* 2000; **247:** 443–6.
3. Budman CL, *et al*. An open-label study of the treatment efficacy of olanzapine for Tourette's disorder. *J Clin Psychiatry* 2001; **62:** 290–4.
4. Stephens RJ, *et al*. Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome: a pilot study. *J Child Adolesc Psychopharmacol* 2004; **14:** 255–66.
5. McCracken JT, *et al*. Effectiveness and tolerability of open label olanzapine in children and adolescents with Tourette syndrome. *J Child Adolesc Psychopharmacol* 2008; **18:** 501–8.

Adverse Effects, Treatment, and Precautions

Although olanzapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with olanzapine are somnolence and weight gain; hyperprolactinaemia is also common, but usually asymptomatic. Increased appetite, dizziness, fatigue, elevated plasma glucose, triglyceride, and liver enzyme values, oedema, orthostatic hypotension, and mild transient antimuscarinic effects such as constipation and dry mouth are also relatively common. Blood dyscrasias including agranulocytosis, eosinophilia, leucopenia, neutropenia, and thrombocytopenia have also been reported. Weight gain, sedation, and liver enzyme values, lipid, and prolactin alterations may be greater in adolescents than in adults. More severe abnormalities of glucose homoeostasis are uncommon; severe hyperglycaemia, or exacerbation of pre-existing diabetes, sometimes leading to ketoacidosis, coma, or death, has occurred. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Clinical monitoring of plasma lipids and weight have also been recommended.

Olanzapine is associated with a low incidence of extrapyramidal effects, including tardive dyskinesia, although these effects may be more likely at high doses and in the elderly; the risk of tardive dyskinesia also increases with long-term use. Neuroleptic malignant syndrome has been reported rarely.

Patients receiving olanzapine intramuscularly should be closely observed for 2 to 4 hours for hypotension, bradyarrhythmia, and hypoventilation. Olanzapine should not be given intramuscularly to patients with a history of cardiovascular disease or after heart surgery; caution is recommended when giving olanzapine orally to such patients and to those with cerebrovascular disease or conditions predisposing to hypotension. It is recommended that blood pressure is periodically assessed in elderly patients.

The antimuscarinic effects of olanzapine contra-indicate its use in patients with angle-closure glaucoma; caution is also advised in those with conditions such as benign prostatic hyperplasia or paralytic ileus. Olanzapine is also not recommended in Parkinson's disease since its use has commonly been associated with an increase in parkinsonian symptoms and hallucinations. It should be used with caution in patients with hepatic impairment, or a history of blood dyscrasias, bone marrow depression, or myeloproliferative disease. Seizures are rare with olanzapine but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

When olanzapine is used for the depressive phase in bipolar disorder or for unipolar depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see Bipolar Disorder, p. 397.2 and Depression, p. 398.1.

Olanzapine may affect the performance of skilled tasks such as driving.

Withdrawal symptoms, including sweating, tremor, anxiety, and nausea and vomiting, have occurred rarely when olanzapine has been stopped abruptly; a gradual dose reduction may be appropriate when stopping olanzapine.

References.

1. Beasley CM, *et al*. Safety of olanzapine. *J Clin Psychiatry* 1997; **58** (suppl 10): 13–17.
2. Biswasl PN, *et al*. The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. *J Psychopharmacol* 2001; **15:** 265–71.
3. Kryzhanovskaya LA, *et al*. The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials. *J Clin Psychiatry* 2009; **70:** 247–58. Correction. *ibid.;* 1729.
4. Marder SR, *et al*. Case reports of postmarketing adverse event experiences with olanzapine intramuscular treatment in patients with agitation. *J Clin Psychiatry* 2010; **71:** 433–41.

Breast feeding. From a study[1] of the distribution of olanzapine into breast milk in 7 breast feeding women taking a median dose of 7.5 mg daily, it was estimated that the weight-adjusted median dose ingested by the breast-fed infants was 1.02% of the maternal dose. Olanzapine was not detected in the plasma of the 6 infants from whom a sample was taken; no adverse effects were seen in any of the 7 infants. However, UK licensed product information states that at steady state the estimated mean exposure of breast-fed infants of mothers taking olanzapine would be 1.8% of the maternal dose and recommends that patients should not breast feed if they are taking olanzapine.

1. Gardiner SJ, *et al*. Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. *Am J Psychiatry* 2003; **160:** 1428–31.

Effects on the blood. A review[1] has described 11 reports of olanzapine-associated haematotoxicity that included 3 cases of agranulocytosis, 6 of neutropenia, and 2 of leucopenia. In most cases, the haematotoxicity developed within the first month of treatment and patients recovered after olanzapine withdrawal. There was a history of clozapine-associated haematotoxicity in 5 patients. It was suggested that white blood cell counts should be monitored periodically during olanzapine treatment.

Olanzapine has also apparently delayed recovery of granulocyte counts in patients with clozapine-induced granulocytopenia who were switched to olanzapine before blood counts had returned to the normal range.[2]

There have been case reports[3,4] of thrombocytopenia associated with olanzapine treatment. In one report,[3] the patient improved on stopping olanzapine but subsequently had a similar episode associated with benzatropine therapy. In another report,[4] an elderly patient with pre-existing immune thrombocytopenia died from bleeding complications due to thrombocytopenia associated with olanzapine treatment; the patient's plasma concentration of olanzapine was reported to be 10 times the usual mean therapeutic value.

1. Tolosa-Vilella C, *et al*. Olanzapine-induced agranulocytosis: a case report and review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26:** 411–4.
2. Flynn SW, *et al*. Prolongation of clozapine-induced granulocytopenia associated with olanzapine. *J Clin Psychopharmacol* 1997; **17:** 494–5.
3. Bogunovic O, Viswanathan R. Thrombocytopenia possibly associated with olanzapine and subsequently with benztropine mesylate. *Psychosomatics* 2000; **41:** 277–88.
4. Carrillo JA, *et al*. Thrombocytopenia and fatality associated with olanzapine. *Eur J Clin Pharmacol* 2004; **60:** 295–6.

Effects on body temperature. Olanzapine has been associated with occasional reports of hypothermia. In one report[1] body temperature fell as low as 33.4 degrees over several days in a woman receiving olanzapine for bipolar disorder. The patient, who also had subclinical hypothyroidism, was asymptomatic, and body temperature returned to normal once olanzapine was stopped; it was unclear whether the endocrine abnormalities had contributed to the condition.

1. Blass DM, Chuen M. Olanzapine-associated hypothermia. *Psychosomatics* 2004; **45:** 135–9.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.

1. Haberfellner EM, Rittmannsberger H. Weight gain during long-term treatment with olanzapine: a case series. *Int Clin Psychopharmacol* 2004; **19:** 251–3.
2. Hennen J, *et al*. Weight gain during treatment of bipolar I patients with olanzapine. *J Clin Psychiatry* 2004; **65:** 1679–87.
3. Hester EK, Thrower MR. Current options in the management of olanzapine-associated weight gain. *Ann Pharmacother* 2005; **39:** 302–10.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Further references for such effects associated with olanzapine use are given below; in some cases the outcome was fatal.

1. Bettinger TL, *et al*. Olanzapine-induced glucose dysregulation. *Ann Pharmacother* 2000; **34:** 865–7.
2. Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycemic nonketonic coma. *Ann Pharmacother* 2001:**35:** 300–302.
3. Bonanno DG, *et al*. Olanzapine-induced diabetes mellitus. *Ann Pharmacother* 2001; **35:** 563–5.
4. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother* 2001; **35:** 1556–8.
5. Koller E, *et al*. Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA* 2001; **286:** 2547–8.
6. CSM. Olanzapine (Zyprexa) and diabetes. *Current Problems* 2002; **28:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
7. Koro CE, *et al*. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002; **325:** 243–5.
8. Ramaswamy K, *et al*. Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; **30:** 589–99.

Effects on the cardiovascular system. Two of 3 elderly patients who developed venous thromboembolism shortly after starting treatment with olanzapine also had symptoms of pulmonary embolism.[1] There have been 2 further isolated cases[2,3] of pulmonary embolism associated with olanzapine therapy; it had been reported in a 28-year-old man[2] and in a 22-year-old man[3] after 10 weeks and after 6 months of olanzapine therapy, respectively. Both patients recovered and were switched to another atypical antipsychotic.

For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

1. Hägg S, *et al*. Olanzapine and venous thromboembolism. *Int Clin Psychopharmacol* 2003; **18:** 299–300.
2. Waage IM, Gedde-Dahl A. Pulmonary embolism possibly associated with olanzapine treatment. *BMJ* 2003; **327:** 1384.
3. Health Canada. Olanzapine (Zyprexa): suspected association with pulmonary embolism. *Can Adverse React News* 2005; **15** (1): 5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n1-eng.pdf (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

Further references.

1. Osser DN, *et al*. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry* 1999; **60:** 767–70.

Effects on the liver. Acute hepatocellular cholestatic jaundice developed in a 78-year-old woman 13 days after starting treatment with olanzapine.[1]

1. Jadallah KA, *et al*. Acute hepatocellular-cholestatic liver injury after olanzapine therapy. *Ann Intern Med* 2003; **138:** 357–8.

Effects on the nervous system. A 31-year-old woman with a complicated medical history suffered three generalised tonic-clonic seizures after 13 days of therapy with olanzapine.[1] She recovered after treatment with phenytoin. Another patient with Huntington's disease also suffered a severe generalised tonic-clonic seizure after treatment with olanzapine 30 mg daily for 1 month.[2] Olanzapine was continued but carbamazepine was added; there was no recurrence of the seizure.

1. Lee JW, *et al*. Seizure associated with olanzapine. *Ann Pharmacother* 1999; **33:** 554–6.
2. Bonelli RM. Olanzapine-associated seizure. *Ann Pharmacother* 2003; **37:** 149–50.

Effects on the pancreas. There have been reports of pancreatitis associated with olanzapine.[1-3] See also under Clozapine, p. 1060.2.

1. Doucette DE, *et al*. Olanzapine-induced acute pancreatitis. *Ann Pharmacother* 2000; **34:** 1128–31.
2. Hagger R, *et al*. Olanzapine and pancreatitis. *Br J Psychiatry* 2000; **177:** 567.
3. Waage C, *et al*. Olanzapine-induced pancreatitis: a case report. *JOP* 2004; **5:** 388–91.

Effects on sexual function. Priapism has been reported[1,2] in 2 patients receiving olanzapine.

1. Deirmenjian JM, *et al*. Olanzapine-induced reversible priapism: a case report. *J Clin Psychopharmacol* 1998; **18:** 351–3.
2. Songer DA, Barclay JC. Olanzapine-induced priapism. *Am J Psychiatry* 2001; **158:** 2087–8.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Extrapyramidal disorders. There have been isolated reports[1,2] of tardive dyskinesia associated with olanzapine treatment. However, the incidence of extrapyramidal effects (p. 1049.2) is generally lower with atypical than classical antipsychotics.

1. Herrán A, Vázquez-Barquero JL. Tardive dyskinesia associated with olanzapine. *Ann Intern Med* 1999; **131:** 72.
2. Bella VL, Piccoli F. Olanzepine-induced tardive dyskinesia. *Br J Psychiatry* 2003; **182:** 81–2.

Mania. Although olanzapine is used in the treatment of bipolar disorder, it has been associated with reports of mania in both schizophrenic and bipolar patients.[1-4] A report sponsored by the manufacturers noted that no association was seen in pooled data from 2 placebo-controlled studies involving 254 bipolar patients.[5]

1. Lindenmayer J-P, Klebanov R. Olanzapine-induced manic-like syndrome. *J Clin Psychiatry* 1998; **59:** 318–19.
2. Fitz-Gerald MJ, *et al*. Olanzapine-induced mania. *Am J Psychiatry* 1999; **156:** 1114.
3. Aubry J-M, *et al*. Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; **61:** 649–55.
4. Henry C, Demotes-Mainard J. Olanzapine-induced mania in bipolar disorders. *J Psychiatry Neurosci* 2002; **27:** 200–201.
5. Baker RW, *et al*. Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *J Affect Disord* 2003; **73:** 147–53.

Neuroleptic malignant syndrome. Cases of neuroleptic malignant syndrome (p. 1050.2) have been associated with olanzapine therapy.[1-4]

1. Filice GA, *et al*. Neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 1998; **32:** 1158–9.

2. Nyfort-Hansen K, Alderman CP. Possible neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 2000; **34:** 667.
3. Suh H, *et al.* Neuroleptic malignant syndrome and low-dose olanzapine. *Am J Psychiatry* 2003; **160:** 796.
4. Kogoj A, Velikonja I. Olanzapine induced neuroleptic malignant syndrome--a case review. *Hum Psychopharmacol* 2003; **18:** 301–9.

Overdosage. A 2½-year-old boy was found sleeping and difficult to arouse after taking one or two 7.5-mg olanzapine tablets.[1] His reported symptoms included agitation, aggressive behaviour, miosis, hypersalivation, tachycardia, and ataxia; he recovered after 24 hours. Symptoms suggestive of diabetes insipidus, together with mild CNS depression, have also been reported,[2] in an adolescent who took 75 mg of olanzapine with a small quantity of prazepam. The polyuria responded to desmopressin. A review[3] identified 29 fatalities associated with olanzapine overdose, but evidence of a direct causative relationship was limited.

1. Yip L, *et al.* Olanzapine toxicity in a toddler. *Pediatrics* 1998; **102:** 1494.
2. Etienne L, *etal.* Polyuria after olanzapine overdose. *Am J Psychiatry* 2004; **161:** 1130.
3. Chue P, Singer P. A review of olanzapine-associated toxicity and fatality in overdose. *J Psychiatry Neurosci* 2003; **28:** 253–61.

Parkinsonism. Worsening of motor function has been reported[1-4] in patients with parkinsonism after use of olanzapine.

1. Graham JM, *et al.* Olanzapine in the treatment of hallucinosis in idiopathic Parkinson's disease: a cautionary note. *J Neurol Neurosurg Psychiatry* 1998 **65:** 774--7.
2. Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine. *Mov Disord* 1999; **14:** 1014–16.
3. Goetz CG, *et al.* Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* 2000; **55:** 789–94.
4. Manson AJ, *et al.* Low-dose olanzapine for levodopa induced dyskinesias. *Neurology* 2000; **55:** 795–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies olanzapine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The manufacturer has reviewed both prospective and retrospective cases of pregnancies that have been exposed to olanzapine treatment.[1] Of the 37 prospective pregnancies, there were 14 therapeutic abortions (with no reported abnormality in the fetus), 3 spontaneous abortions (again with no reported abnormality in the fetus), and 1 still-birth. The remaining 19 pregnancies included 16 normal births without complications and 1 premature birth; the 2 other births were complicated by post-term deliveries. Eleven retrospective cases were also identified and included 2 cases of major malformation (dysplastic kidney and Down's syndrome), 1 case of fetal death after a maternal overdose, and 1 case each of neonatal convulsion and sudden infant death. For comments on the use of some atypical antipsychotics, including olanzapine, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

1. Goldstein DJ, *et al.* Olanzapine-exposed pregnancies and lactation: early experience. *J Clin Psychopharmacol* 2000; **20:** 399–403.

Speech disorders. Although olanzapine may be used in the treatment of stuttering, it has also been associated with reports of the development of the disorder, see under Uses and Administration, p. 1090.3.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by olanzapine. Olanzapine may antagonise the effects of dopaminergics. Neutropenia may be more common when olanzapine is given with valproate. Use with valproate or lithium has also been associated with an increased incidence of tremor, dry mouth, increased appetite, and weight gain. There may be a risk of QT prolongation when olanzapine is given with other drugs that are known to cause this effect.

Drugs that induce hypotension, bradycardia, or respiratory depression should be used with caution in patients given intramuscular olanzapine. Parenteral benzodiazepine treatment should be given at least 1 hour after intramuscular olanzapine as it is recommended that they are not given together.

The metabolism of olanzapine is mediated to some extent by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit, induce, or act as a substrate to this isoenzyme may affect plasma concentrations of olanzapine and a dose adjustment of olanzapine may be required. The CYP1A2 inhibitor fluvoxamine significantly inhibits the metabolism of olanzapine. The clearance of olanzapine is increased by tobacco smoking and carbamazepine.

Valproate. In a study of 4 patients, valproate reduced plasma concentrations of olanzapine by 32.3 to 78.8% (mean 53.6%).[1]

1. Bergemann N, *et al.* Valproate lowers plasma concentrations of olanzapine. *Pharmacopsychiatry* 2005; **38:** 44.

Pharmacokinetics

Olanzapine is well absorbed from the gastrointestinal tract after oral doses but undergoes considerable first-pass metabolism. Peak plasma concentrations occur about 5 to 8 hours after oral doses and about 15 to 45 minutes after an intramuscular dose. Olanzapine is about 93% bound to plasma proteins. It is extensively metabolised in the liver, mainly by direct glucuronidation and by oxidation mediated through the cytochrome P450 isoenzymes CYP1A2, and, to a lesser extent, CYP2D6. The 2 major metabolites, 10-*N*-glucuronide and 4′-*N*-desmethyl olanzapine, appear to be inactive. About 57% of a dose is excreted in the urine, mainly as metabolites, and about 30% appears in the faeces. The mean plasma elimination half-life has been variously reported to be about 30 to 38 hours; half-lives tend to be longer in female than in male patients. Olanzapine is distributed into breast milk.

References.

1. CallaghanJT, *et al.* Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999; **37:** 177–93.
2. Markowitz JS, *et al.* Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol* 2006; **46:** 164–71.
3. Bigos KL, *et al.* Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol* 2008; **48:** 157–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Apsico; Midax; Sartina; Simina; Zyprexa; ***Austral.***: Lanzek; Lanzek; Zylap; Zypine; Zyprexa; ***Austria***: Zypadhera; Zyprexa; ***Belg.***: Zypadhera; Zyprexa; ***Braz.***: Lanzamed; Olazofren; Zopix; Zyprexa; ***Canad.***: Zyprexa; ***Chile***: Amulsin; Oleanz; Olivin; Sincris; Tanssel; Zapinex; Zyprexa; ***China***: Ou Lan Ning (欧兰宁); Ximin (悉敏); Zyprexa (再普乐); ***Cz.***: Aedon; Arkolamyl; Clingozan; Lapozan; Nykob; Olazax; Olipazix; Olpinat; Parnassan; Stygapon; Zalasta; Zolafren; Zypadhera; Zyprexa; ***Denm.***: Arkolamyl; Asterilon†; Kynapine; Lazapix; Nykob; Nylsanuc; Olzamed†; Zalasta; Zamil; Zynilmed†; Zypadhera; Zyprexa; ***Fin.***: Solazin†; Zyprexa; ***Fr.***: Arkolamyl; Zypadhera; Zyprexa; ***Ger.***: Zalasta; Zypadhera; Zyprexa; ***Gr.***: Bloonis; Caprilon; Lapenza; Lapozan; Lazap; Niolib; Norpen Oro; Nyzol; Olanzalet; Olapine; Olenxa; Olmyzem; Ozapex; Xoltiva; Zalasta; Zalepin; Zonapin; Zoxil; Zypadhera; Zypefar; Zyprexa; ***Hong Kong***: Zyprexa; ***Hung.***: Bloonis; Mitab; Olanzep; Olpinat; Parnassan; Zypadhera; Zyprexa; ***India***: Cinol; Dopin; Jolyon-MD; Joyzol; Lano; Lanopin; M-Olan; Manza; Meltolan; Olace; Oladay; Olan; Olandus; Olanex; Olanzapik; Olapax; Olapin; Oleanz; Oles; Olexar; Olima; Oliza; Olpin; Oltal; Olzap; Onza; Opin; Opirap; Ozace; Ozap; Ozapin; Psycholanz; ***Indon.***: Olandoz; Remital; Zyprexa; ***Irl.***: Arkolamyl; Kozylex; Olazax; Rolyprexa; Zalasta; Zypadhera; Zyprexa; ***Israel***: Zappa; Zypadhera; Zyprexa; ***Ital.***: Arkolamyl; Olafid; Zyprexa; ***Jpn***: Zyprexa; ***Malaysia***: Zyprexa; ***Mex.***: Zyprexa; ***Neth.***: Arkolamyl; Clingozan†; Kozylex†; Lansyn; Lazapix†; Olanzaran; Olasyn; Olazax; Olstadryn†; Ozapex; Sanza; Synza; Zalasta; Zypadhera; Zyprexa; ***Norw.***: Zypadhera; Zyprexa; ***NZ***: Olanzine; Zyprexa; ***Philipp.***: Olan; Olanzapro; Zanprex; Zyprexa; ***Pol.***: Anzorin; Arkolamyl; Asterilon; Clingozan; Lanzapin; Nykob; Olanzin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Parnassan; Ranofren; Sanza; Synza; Zalasta; Zapilux; Zolafren; Zolaxa; Zypadhera; Zyprexa; ***Port.***: Decolan; Fordep†; Lernup; Nakozap†; Nolian†; Olan; Olapin†; Olasyn; Olazax; Synza; Tizina; Xapritx†; Zalasta; Ziprodec; Zolafren†; Zonapir†; Zypadhera; Zyprexa; ***Rus.***: Zalasta (Заласта); Zyprexa (Зипрекса); ***S.Afr.***: Oleanz; Olexar; Redilanz; Zyprexa; ***Singapore***: Onzapin; Zyprexa; ***Spain***: Arenbil; Zalasta; Zapris; Zolafren; Zypadhera; Zyprexa; ***Swed.***: Arkolamyl; Zalasta; Zypadhera; Zyprexa; ***Switz.***: Zyprexa; ***Thai.***: Olapin; Zyprexa; ***Turk.***: Apzet; Elynza; Oferta; Olfrex; Ollafax; Ozaprin; Rexapin; Zeprola; Zophix; Zyprexa; Zyzapin; ***UK***: Zypadhera; Zyprexa; ***Ukr.***: Zyprexa (Зипрекса); ***USA***: Zyprexa; ***Venez.***: Zyprexa.

Multi-ingredient Preparations. ***Chile***: Symbyax; ***India***: Cinol Forte; Cinol Plus; Depten-OZ; M-Olan Plus; Oladay-F; Olanex-F; Olapin Forte; Olapin Plus; Olorest-F; ***Mex.***: Symbyax; ***USA***: Symbyax.

Pharmacopoeial Preparations

USP 36: Olanzapine and Fluoxetine Capsules; Olanzapine Tablets.

Oxazepam *(BAN, USAN, rINN)*

Oksatsepaami; Oksazeoam; Oksazepam; Oksazepamas; Oxazepám; Oxazépam; Oxazepamum; Wy-3498; Оксазепам.

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one.

$C_{15}H_{11}ClN_2O_2$=286.7

CAS — 604-75-1.

ATC — N05BA04.

ATC Vet — QN05BA04.

UNII — 6GOW6DWN2A.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Oxazepam). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Oxazepam). A creamy-white to pale yellow, practically odourless powder. Practically insoluble in water; soluble 1 in 220 of alcohol, 1 in 270 of chloroform, and 1 in 2200 of ether. pH of a 2% suspension in water is between 4.8 and 7.0.

Uses and Administration

Oxazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term management of anxiety disorders (p. 1028.1) and insomnia (p. 1033.2) associated with anxiety. Oxazepam is also used for the control of symptoms associated with alcohol withdrawal (p. 1735.1). Oxazepam is usually given as the base but the hemisuccinate has been used in some multi-ingredient preparations.

The usual oral dose of oxazepam for the treatment of anxiety or for control of symptoms of alcohol withdrawal is 15 to 30 mg three or four times daily. Lower doses of 7.5 to 15 mg three or four times daily may be tried for mild to moderate anxiety. A suggested initial dose for elderly or debilitated patients is 10 mg three times daily increased if necessary up to 10 to 20 mg three or four times daily. For the treatment of insomnia associated with anxiety oxazepam 15 to 25 mg may be given one hour before retiring; up to 50 mg may occasionally be necessary.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 10 mg of oxazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, but short-acting ones such as oxazepam may be preferred.

Seven patients with acute viral hepatitis, 6 with cirrhosis of the liver, and 16 age-matched healthy control subjects took a single dose of oxazepam 15 or 45 mg orally.[1] Urinary excretion rates and plasma elimination patterns were unaltered in patients with acute and chronic parenchymal liver disease. Oxazepam 15 mg orally was also given three times daily for 2 weeks to 2 healthy subjects and to 2 patients with cirrhosis and did not appear to accumulate in any of the four.

1. Shull HJ, *et al.* Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; **84:** 420–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxazepam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Renal impairment. Pharmacokinetic studies suggest that, in general, the dosage of oxazepam does not need adjusting in patients with renal impairment.[1-3]

1. Murray TG, *et al.* Renal disease, age, and oxazepam kinetics. *Clin Pharmacol Ther* 1981; **30:** 805–9.
2. Busch U, *et al.* Pharmacokinetics of oxazepam following multiple administration in volunteers and patients with chronic renal disease. *Arzneimittelforschung* 1981; **31:** 1507–11.
3. Greenblatt DJ, *et al.* Multiple-dose kinetics and dialyzability of oxazepam in renal insufficiency. *Nephron* 1983; **34:** 234–8.

Thyroid disorders. There was a reduction in half-life and an increase in the apparent oral clearance of oxazepam in 7 hyperthyroid patients.[1] In 6 hypothyroid patients there was no overall change in oxazepam elimination, although 5 of the 6 complained of drowsiness despite a relatively low dose (15 mg).

1. Scott AK, *et al.* Oxazepam pharmacokinetics in thyroid disease. *Br J Clin Pharmacol* 1984; **17:** 49–53.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Oxazepam is well absorbed from the gastrointestinal tract; peak plasma concentrations occur about 2 to 3 hours after ingestion. It crosses the placenta and has been detected in breast milk. Oxazepam is about 97% bound to plasma

proteins and has been reported to have an elimination half-life ranging from about 4 to 15 hours. It is largely metabolised to the inactive glucuronide which is excreted in the urine.

Pregnancy. The placental passage of oxazepam and its metabolism in 12 women given a single dose of oxazepam 25 mg during labour has been studied.[1] Oxazepam was readily absorbed and peak plasma concentrations were in the same range as those reported in healthy males and non-pregnant females given the same dose, although the plasma half-life (range 5.3 to 7.8 hours in 8 subjects studied) was shorter than that reported for non-pregnant subjects. Oxazepam was detected in the umbilical vein of all 12 patients with the ratio between umbilical to maternal vein concentration of oxazepam reaching a value of about 1.35 and remaining constant beyond a dose-delivery time of 3 hours. All of the babies had a normal Apgar score value. The oxazepam plasma half-life in the newborns was about 3 to 4 times that of the mothers, although in 3 the plasma concentration of oxazepam conjugate rose during the first 6 to 10 hours after delivery indicating the ability of the neonate to conjugate oxazepam.

1. Tomson G, *et al.* Placental passage of oxazepam and its metabolism in mother and newborn. *Clin Pharmacol Ther* 1979; **25:** 74–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pausafren T; ***Austral.***: Alepam; Murelax; Serepax; ***Austria***: Adumbran; Anxiolit; Praxiten; ***Belg.***: Seresta; Tranquo; ***Canad.***: Novoxapam; ***China***: Youfei (优菲); ***Denm.***: Alopam; Oxabenz; Oxapax; ***Fin.***: Opamox; Oxamin; ***Fr.***: Seresta; ***Ger.***: Adumbran†; Oxa; Praxiten; ***Gr.***: Adumbran; ***India***: Serepax; ***Israel***: Vaben; ***Ital.***: Limbial; Serpax; ***Neth.***: Seresta; ***Norw.***: Alopam; Sobril; ***NZ***: Ox-Pam; ***Pol.***: Oxam†; ***Port.***: Serenal; ***Rus.***: Nozepam (НОЗЕПАМ); Tazepam (Тазепам); ***S.Afr.***: Medopam†; Noripam†; Purata; Serepax; ***Swed.***: Oxascand; Sobril; ***Switz.***: Anxiolit; Seresta; ***USA***: Serax†.

Multi-ingredient Preparations. ***Austria***: Anxiolit plus; ***Chile***: Novalona; ***Spain***: Suxidina; ***Venez.***: Vuscobras.

Pharmacopoeial Preparations
BP 2014: Oxazepam Tablets;
USP 36: Oxazepam Capsules; Oxazepam Tablets.

Oxazolam *(rINN)*

Oxazolamum; Oxazolazepam; Оксазолам.
10-Chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.
$C_{18}H_{17}ClN_2O_2$=328.8
CAS — 24143-17-7.
UNII — 1V2WI2NA1C.

Pharmacopoeias. In *Jpn*.

Profile

Oxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given orally in doses of 10 to 20 mg up to three times daily for the short-term treatment of anxiety disorders (p. 1028.1).

Oxazolam has also been given orally as a premedicant in general anaesthesia (p. 1899.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Nebusun†; Pelusarl; Serenal; Toccata†.

Paliperidone *(BAN, USAN, rINN)*

9-Hydroxyrisperidone; Paliperidona; Palipéridone; Paliperidonum; RO-76477; Палиперидон.
(±)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.
$C_{23}H_{27}FN_4O_3$=426.5
CAS — 144598-75-4.
ATC — N05AX13.
ATC Vet — QN05AX13.
UNII — 838F01T721.

Paliperidone Palmitate *(BANM, USAN, rINNM)*

Palipéridone, Palmitate de; Paliperidoni Palmitas; Palmitato de paliperidona; RO-92670; Палиперидона Палмитат.
(9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate.
$C_{39}H_{57}FN_4O_4$=664.9
CAS — 199739-10-1.
UNII — R8P8USM8FR.

Uses and Administration

Paliperidone is a benzisoxazole derivative and is the major active metabolite of the atypical antipsychotic risperidone (p. 1103.2). It is reported to be an antagonist at dopamine (D_2, serotonin (5-HT_2), adrenergic (α_1 and α_2), and histamine (H_1) receptors. It is used in the treatment of schizophrenia (p. 1031.3) and schizoaffective disorder. Paliperidone is given orally as the base and doses are expressed in terms of the base. It is also given intramuscularly as the long-acting palmitate ester; these doses are expressed in terms of either the ester or the base. Paliperidone palmitate 156 mg is equivalent to about 100 mg of paliperidone.

For the treatment of **schizophrenia**, the recommended oral dose of paliperidone is 6 mg once daily as a modified-release preparation; doses may range from 3 to 12 mg daily; dose increases should be made in steps of 3 mg at intervals of more than 5 days.

Intramuscular injection of paliperidone may be given into the deltoid or gluteal regions although the first 2 injections should be made into the deltoid muscle. Patients with no history of paliperidone or risperidone use should be given oral paliperidone or risperidone initially to assess tolerability. Intramuscular paliperidone may be given in an initial dose of 150 mg followed by 100 mg one week later. Thereafter, the recommended monthly maintenance dose is 75 mg with a range of 25 to 150 mg; further dose adjustments should be made at monthly intervals.

For the treatment of **schizoaffective disorder** as monotherapy or as an adjunct to mood stabilisers and/or antidepressants, paliperidone is given orally in doses similar to those used for schizophrenia except dose increases should be made at intervals of more than 4 days.

For details of dose reductions in patients with renal impairment, see below.

For details of uses and associated doses in children and adolescents, see Administration in Children, below.

References.
1. Dolder C, *et al.* Paliperidone for schizophrenia. *Am J Health-Syst Pharm* 2008; **65:** 403–13.
2. Nussbaum AM, Stroup TS. Paliperidone for the treatment of adults with schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 01/06/09).
3. Meltzer HY, *et al.* Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. *J Clin Psychiatry* 2008; **69:** 817–29.
4. Marino J, Caballero J. Paliperidone extended-release for the treatment of schizophrenia. *Pharmacotherapy* 2008; **28:** 1283–98.
5. Chwieduk CM, Keating GM. Paliperidone extended release: a review of its use in the management of schizophrenia. *Drugs* 2010; **70:** 1295–1317.
6. Owen RT. Paliperidone palmitate injection: its efficacy, safety and tolerability in schizophrenia. *Drugs Today* 2010; **46:** 463–71.
7. Canuso CM, *et al.* Role of paliperidone extended-release in treatment of schizoaffective disorder. *Neuropsychiatr Dis Treat* 2010; **6:** 667–79.
8. Gahr M, *et al.* Paliperidone extended-release: does it have a place in antipsychotic therapy? *Drug Des Devel Ther* 2011; **5:** 125–46.
9. Bossie CA, *et al.* Onset of efficacy and tolerability following the initiation dosing of long-acting paliperidone palmitate: post-hoc analyses of a randomized, double-blind clinical trial. *BMC Psychiatry* 2011; **11:** 79. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-11-79.pdf (accessed 13/10/11)
10. Yang LP. Oral paliperidone: a review of its use in the management of schizoaffective disorder. *CNS Drugs* 2011; **25:** 523–38.
11. Carter NJ. Extended-release intramuscular paliperidone palmitate: a review of its use in the treatment of schizophrenia. *Drugs* 2012; **72:** 1137–60.

Administration in children. In the USA, an oral modified-release preparation of paliperidone is licensed for the treatment of schizophrenia in adolescents aged 12 to 17 years. The recommended initial dose is 3 mg once daily; when necessary, dose increases should be made in steps of 3 mg at intervals of more than 5 days. Doses may range from 3 to 6 mg daily in those who weigh less than 51 kg or up to 12 mg daily in those weighing 51 kg or more.

References.
1. Singh J, *et al.* A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biol Psychiatry* 2011; **70:** 1179–87.

Administration in renal impairment. The plasma concentrations of paliperidone are increased in patients with renal impairment. The usual oral daily dosage (see above) should therefore be adjusted according to creatinine clearance (CC) as follows:

- CC 50 to 80 mL/minute: initially 3 mg once daily, may be increased thereafter to 6 mg once daily, according to response and tolerance
- CC 10 to 50 mL/minute: initially 1.5 mg once daily, may be increased thereafter to 3 mg once daily

Paliperidone, when given orally, has not been studied in patients with a CC of less than 10 mL/minute; use in such patients is not recommended.

The intramuscular dose should also be reduced as follows:

- CC 50 to 80 mL/minute: initially 100 mg followed, one week later, by 75 mg; thereafter, the recommended monthly maintenance dose is 50 mg with a range of 25 to 100 mg

Intramuscular use is not recommended in patients with a CC of less than 50 mL/minute.

Adverse Effects, Treatment, and Precautions

Although paliperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with paliperidone are headache, dizziness, somnolence, sedation, agitation, fatigue, gastrointestinal effects such as constipation, dyspepsia, dry mouth, and nausea and vomiting, weight gain, extrapyramidal effects such as akathisia, dystonia, hypertonia, and tremor, tachycardia including sinus tachycardia, and nasopharyngitis. Other common adverse effects include blurred vision, orthostatic hypotension, arthralgia, back pain, and pain in the extremities. Tardive dyskinesia, small intestinal obstruction, and hyperprolactinaemia resulting in gynaecomastia, menstrual disturbances, amenorrhoea, and galactorrhoea occur rarely. Priapism has also been reported, as have neuroleptic malignant syndrome, agranulocytosis, leucopenia, and neutropenia.

Paliperidone has been associated with QT prolongation rarely and it should be used with caution in patients with cardiovascular disease, or with a family history of QT prolongation; certain drugs may also increase the risk (see Interactions, below).

Paliperidone should be used with caution in patients with renal or severe hepatic (Child-Pugh class C) impairment, with cardiovascular disease or other conditions predisposing to hypotension, with cerebrovascular disease, or with a history of seizures or conditions that lower the seizure threshold.

Paliperidone may affect the performance of skilled tasks such as driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics and recommendations for monitoring are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Formulation. As an oral modified-release preparation, paliperidone is contained within a non-absorbable tablet shell that releases the drug at a controlled rate. This biologically inert shell is eliminated intact in the faeces, along with other insoluble components of the tablet core.

Hypersensitivity. An anaphylactoid reaction to long-acting paliperidone palmitate injection has been reported[1] in a patient with established tolerance of oral risperidone; symptoms resolved with supportive treatment and oral risperidone was restarted without sequelae. An excipient, polyethylene glycol 4000, within the formulation was considered to be a possible causative agent.

1. Perry R, *et al.* Anaphylactoid reaction to paliperidone palmitate extended-release injectable suspension in a patient tolerant of oral risperidone. *Am J Health-Syst Pharm* 2012; **69:** 40–3.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by paliperidone. Additive effects may occur when paliperidone is given with drugs that can cause orthostatic hypotension. There may be an increased risk of QT prolongation when paliperidone is given with other drugs that are known to cause this effect. Paliperidone

may antagonise the actions of levodopa and other dopaminergics.

Paliperidone is a substrate of P-glycoprotein, and P-glycoprotein inducers such as carbamazepine may decrease paliperidone concentrations. The dose of paliperidone may need to be increased when given with such drugs and decreased when such drugs are stopped; full induction is achieved in 2 to 3 weeks and wears off over a similar period upon stopping the inducer.

Valproate may increase paliperidone concentrations and dose reduction of oral paliperidone may be required; however, this interaction is not expected to be clinically significant with intramuscular paliperidone.

Drugs that affect gastrointestinal transit time, such as metoclopramide, may affect the absorption of oral paliperidone.

Pharmacokinetics

Peak plasma-paliperidone concentrations occur about 24 hours after an oral dose and about 13 days after an intramuscular dose. Paliperidone is 74% bound to plasma proteins, mainly to α_1-acid glycoprotein and albumin. It is not extensively metabolised in the liver but undergoes dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. About 59% of a dose is excreted unchanged in the urine. The elimination half-life has been reported to be about 23 hours after oral dosage and ranging from 25 to 49 days after intramuscular dosage.

Paliperidone is distributed into breast milk.

References.

1. Boom S, *et al.* Single- and multiple-dose pharmacokinetics and dose proportionality of the psychotropic agent paliperidone extended release. *J Clin Pharmacol* 2009; **49:** 1318–30.
2. Samtani MN, *et al.* Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. *Clin Pharmacokinet* 2009; **48:** 585–600.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Invega; ***Austral.***: Invega; ***Austria***: Invega; ***Belg.***: Invega; Xeplion; ***Braz.***: Invega; ***Canad.***: Invega; ***China***: Invega (芮达); ***Cz.***: Invega; Xeplion; ***Denm.***: Invega; Xeplion; ***Fr.***: Invega†; Xeplion; ***Ger.***: Invega†; Xeplion; ***Gr.***: Invega; ***Hong Kong***: Invega; ***Hung.***: Invega; ***India***: Paliris; ***Indon.***: Invega; ***Irl.***: Invega; Xeplion; ***Israel***: Invega; Xeplion; ***Ital.***: Invega; ***Jpn***: Invega; ***Malaysia***: Invega; ***Mex.***: Inveda; ***Neth.***: Invega; Xeplion; ***Norw.***: Xeplion; ***NZ***: Invega; ***Philipp.***: Invega; ***Pol.***: Invega; ***Port.***: Invega; ***Rus.***: Invega (Инвега); ***Singapore***: Invega; ***Spain***: Invega; Xeplion; ***Swed.***: Invega; Xeplion; ***Switz.***: Invega; Xeplion; ***Thai.***: Invega; ***UK***: Invega; Xeplion; ***USA***: Invega.

Paraldehyde

Paracetaldehído; Paracetaldehyde; Paraldehid; Paraldehidas; Paraldehído; Paraldehit; Paraldehyd; Paraldéhyde; Paraldehydi; Paraldehydum; Паральдегид.

The trimer of acetaldehyde; 2,4,6-Trimethyl-1,3,5-trioxane.

$(C_2H_4O)_3$=132.2

CAS — 123-63-7.

ATC — N05CC05.

ATC Vet — QN05CC05.

UNII — S6M3YBG8QA.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Paraldehyde). A colourless or slightly yellow, transparent liquid. It solidifies on cooling to form a crystalline mass. It may contain a suitable amount of an antoxidant. Relative density 0.991 to 0.996. F.p. is 10 degrees to 13 degrees; not more than 10% distils below 123 degrees and not less than 95% below 126 degrees. Soluble in water but less soluble in boiling water; miscible with alcohol and with volatile oils. Store in small well-filled airtight containers. Protect from light.

USP 36: (Paraldehyde). A colourless transparent liquid with a strong characteristic, but not unpleasant or pungent, odour. It is subject to oxidation to form acetic acid. It may contain a suitable stabiliser. Specific gravity is about 0.99. It has a congealing temperature of not lower than 11 degrees and distils completely between 120 degrees and 126 degrees. Soluble 1 in 10 of water v/v, but only 1 in 17 of boiling water v/v; miscible with alcohol, with chloroform, with ether, and with volatile oils. Store in well-filled airtight containers of not more than 30 mL at a temperature not exceeding 25 degrees. Protect from light. It must not be used more than 24 hours after opening the container.

Incompatibility. Paraldehyde exerts a solvent action upon rubber, polystyrene, and styrene-acrylonitrile copolymer and should not be given in plastic syringes made with these materials.

An evaluation of the compatibility of paraldehyde with plastic syringes and needle hubs concluded that, if possible, all-glass syringes should be used with paraldehyde.[1] Needles with plastic hubs could be used. Polypropylene syringes with rubber-tipped plastic plungers (*Plastipak*), or glass syringes with natural rubber-tipped plastic plungers (*Glaspak*) were acceptable only for the immediate administration or measurement of paraldehyde doses.

1. Johnson CE, Vigoreaux JA. Compatibility of paraldehyde with plastic syringes and needle hubs. *Am J Hosp Pharm* 1984; **41:** 306–8.

Stability. Paraldehyde decomposes on storage, particularly after the container has been opened. Partly decomposed paraldehyde is **dangerous** if given. It must not be used if it has a brownish colour or a sharp penetrating odour of acetic acid.

Uses and Administration

Paraldehyde is a hypnotic and sedative with antiepileptic effects. However, because of the hazards associated with its use, its tendency to react with plastic, and the risks associated with its deterioration, it has largely been superseded by other drugs. It is still occasionally used to control status epilepticus (p. 510.2) resistant to conventional treatment. Given rectally or intramuscularly it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

At low temperature it solidifies to form a crystalline mass. If it solidifies, the whole should be liquefied before use.

A dose (expressed as undiluted paraldehyde) of 20 mL has been given rectally. Paraldehyde should be diluted before it is given; prediluted enemas of 8 to 50% are available in some countries, such as the UK.

The usual intramuscular dose is 5 to 10 mL. Doses should be given by deep injection into the buttocks and not more than 5 mL should be administered at each injection site.

For doses in children, see below.

Paraldehyde has been given by slow intravenous infusion in specialist centres with intensive care facilities but this route is not usually recommended; it must be diluted in sodium chloride 0.9% before use.

Paraldehyde has been given orally; it should always be well diluted to avoid gastric irritation.

References.

1. Rowland AG, *et al.* Review of the efficacy of rectal paraldehyde in the management of acute and prolonged tonic-clonic convulsions. *Arch Dis Child* 2009; **94:** 720–3.

Administration in children. Paraldehyde may be used in children to control status epilepticus resistant to conventional treatment. Although unlicensed, the *BNFC* suggests that a single rectal dose (expressed as undiluted paraldehyde) of 0.4 mL/kg (maximum of 10 mL) may be given to neonates and children up to 18 years of age. Paraldehyde should be diluted before use. In some countries, it is also licensed for use by deep intramuscular injection; a dose of 0.1 to 0.15 mL/kg may be given every 4 to 8 hours. No more than 5 mL should be administered at each injection site.

Dependence and Withdrawal

Prolonged use of paraldehyde may lead to dependence, especially in alcoholics. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects and Treatment

Paraldehyde decomposes on storage and deaths from corrosive poisoning have followed the use of such material. Paraldehyde has an unpleasant taste and imparts a smell to the breath; it may cause skin rashes.

Oral or rectal use of paraldehyde may cause gastric or rectal irritation. Intramuscular injection is painful and associated with tissue necrosis, sterile abscesses, and nerve damage. Intravenous use is extremely hazardous since it may cause pulmonary oedema and haemorrhage, hypotension and cardiac dilatation, and circulatory collapse; thrombophlebitis is also associated with intravenous use.

Overdosage results in rapid laboured breathing owing to damage to the lungs and to acidosis. Nausea and vomiting may follow oral overdoses. Respiratory depression and coma as well as hepatic and renal damage may occur. Treatment is as for barbiturate overdose (see Amobarbital, p. 1038.1).

Precautions

Paraldehyde should not be given to patients with gastric disorders and it should be used with caution, if at all, in patients with bronchopulmonary disease or hepatic impairment. It should not be given rectally in the presence of colitis. Old paraldehyde must never be used.

Paraldehyde must be well diluted before oral or rectal use; if it is deemed essential to give paraldehyde intravenously it must be well diluted and given very slowly with extreme caution (see also Adverse Effects, above and Uses, above). Intramuscular injections may be given undiluted but care should be taken to avoid nerve damage. Plastic syringes should be avoided (see Incompatibility, above).

Interactions

The sedative effects of paraldehyde are enhanced by CNS depressants such as alcohol, barbiturates, and other sedatives. A few case reports suggest that disulfiram may enhance the toxicity of paraldehyde; use together is not recommended.

Pharmacokinetics

Paraldehyde is generally absorbed readily, although absorption is reported to be slower after rectal than after oral or intramuscular doses. It is widely distributed and has a reported half-life of 4 to 10 hours. About 80% of a dose is metabolised in the liver probably to acetaldehyde, which is oxidised by aldehyde dehydrogenase to acetic acid. Unmetabolised drug is largely excreted unchanged through the lungs; only small amounts appear in the urine. It crosses the placental barrier and is distributed into breast milk.

Preparations

Pharmacopoeial Preparations

BP 2014: Paraldehyde Injection.

Penfluridol *(BAN, USAN, rINN)*

McN-JR-16341; Penfluridoli; Penfluridolum; R-16341; Пенфлуридол.

4-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(*p,p'*-difluorobenzhydryl)propyl]piperidin-4-ol.

$C_{28}H_{27}ClF_5NO$=524.0

CAS — 26864-56-2.

ATC — N05AG03.

ATC Vet — QN05AG03.

UNII — 25TLU22Q8H.

Pharmacopoeias. In *Chin.*

Profile

Penfluridol is a diphenylbutylpiperidine antipsychotic and shares the general properties of the phenothiazine, chlorpromazine (p. 1045.2). After oral doses it has a prolonged duration of action that lasts for about a week. It is used in the treatment of psychoses including schizophrenia (below).

The usual oral dose of penfluridol for the treatment of chronic psychoses is 20 to 60 mg once a week. Doses of up to 250 mg once a week may be required in severe or resistant conditions.

Schizophrenia. A systematic review[1] concluded that penfluridol appears to have a similar efficacy and adverse effects profile to other classical antipsychotics used in the treatment of schizophrenia (p. 1031.3). The authors also suggested that penfluridol, in a weekly oral dose of 40 to 80 mg, is a suitable alternative, particularly for patients who do not respond to daily oral medication or adapt well to depot drugs.

1. Soares BGO, Lima MS. Penfluridol for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/03/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Semap; ***Braz.***: Semap; ***Denm.***: Semap†; ***Gr.***: Flupidol; Semap; ***India***: Flump; ***Israel***: Semap†; ***Mex.***: Semap; ***Neth.***: Semap; ***Switz.***: Semap†.

Pentobarbital *(BAN, rINN)*

Aethaminalum; Mebubarbital; Mebumal; Pentobarbitaali; Pentobarbitál; Pentobarbitalis; Pentobarbitalum; Pentobarbitone; Пентобарбитал.

5-Ethyl-5-(1-methylbutyl)barbituric acid.

$C_{11}H_{18}N_2O_3$=226.3

CAS — 76-74-4.

ATC — N05CA01.

ATC Vet — QN05CA01; QN51AA01.

UNII — I4744080IR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of pentobarbital:

Blockbuster; Menish; Nebbies; Nembies; Nemish; Nemmies; Nimbies; Nimby; Yellow; Yellow bullets; Yellow dolls; Yellow jackets; Yellow submarines; Yellows.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pentobarbital). Colourless crystals or a white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 36: (Pentobarbital). A white or practically white, practically odourless, fine powder. Very slightly soluble in water and in carbon tetrachloride; soluble 1 in 4.5 of alcohol, 1 in 4 of chloroform, and 1 in 10 of ether; very soluble in acetone and in methyl alcohol; soluble in benzene. Store in airtight containers.

Pentobarbital Calcium *(BANM, rINNM)*

Calcii Pentobarbitalum; Pentobarbital cálcico; Pentobarbital Calcique; Pentobarbitone Calcium; Кальций Пентобарбитал.

Calcium 5-ethyl-5-(1-methylbutyl)barbiturate.

$(C_{11}H_{17}N_2O_3)_2Ca$=490.6

ATC — N05CA01.

ATC Vet — QN05CA01.

Pharmacopoeias. In *Jpn.*

Pentobarbital Sodium *(BANM, rINNM)*

Aethaminalum-Natrium; Ethaminal Sodium; Mebumalnatrium; Natrii Pentobarbitalum; Pentobarbitaalinatrium; Pentobarbital-Natrium; Pentobarbital sódico; Pentobarbital Sodique; Pentobarbital sodná sůl; Pentobarbitalio natrio druska; Pentobarbitalnatrium; Pentobarbitál-nátrium; Pentobarbitalum natricum; Pentobarbitone Sodium; Sodium Pentobarbital; Soluble Pentobarbitone; Натрий Пентобарбитал.

Sodium 5-ethyl-5-(1-methylbutyl)barbiturate.

$C_{11}H_{17}N_2NaO_3$=248.3

CAS — 57-33-0.

ATC — N05CA01.

ATC Vet — QN05CA01.

UNII — NJJ0475N0S.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pentobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Very soluble in water. A 10% solution in water has a pH of 9.6 to 11.0 when freshly prepared. Store in airtight containers.

USP 36: (Pentobarbital Sodium). White, crystalline granules or white powder. Is odourless or has a slight characteristic odour. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. pH of a 10% solution in water is between 9.8 and 11.0. Solutions decompose on standing, the decomposition being accelerated at higher temperatures. Store in airtight containers.

Incompatibility. Pentobarbital may be precipitated from preparations containing pentobarbital sodium, depending on the concentration and pH. Pentobarbital sodium has, therefore, been reported to be incompatible with many other drugs particularly acids and acidic salts.

Uses and Administration

Pentobarbital is a barbiturate that has been used as a hypnotic and sedative. It has general properties and uses similar to those of amobarbital (p. 1037.3). It has been used as a sedative and in the short-term management of insomnia (p. 1033.2) but barbiturates are not considered appropriate for such purposes. Pentobarbital sodium has also been used for premedication in anaesthetic procedures (p. 1899.1), but barbiturates for pre-operative sedation have been replaced by other drugs. It has been given parenterally as part of the emergency management of acute seizures including status epilepticus (p. 510.2) although the short-acting barbiturate thiopental is usually used. Pentobarbital is usually given as the sodium salt, although pentobarbital itself and its calcium salt have both been used.

A usual oral dose of pentobarbital sodium for insomnia was 100 to 200 mg, given at bedtime. Usual parenteral doses for other indications were 150 to 200 mg as a single intramuscular dose or 100 mg by slow intravenous injection.

Cerebrovascular disorders. Barbiturate-induced coma (commonly with pentobarbital or thiopental) has been used, both therapeutically and prophylactically, to protect the brain from ischaemia (see under Thiopental, p. 1919.1), and for raised intracranial pressure (p. 1271.3) refractory to conventional therapies, although there has been debate as to efficacy and safety.

References.

1. Marshall GT, *et al.* Pentobarbital coma for refractory intra-cranial hypertension after severe traumatic brain injury: mortality predictions and one-year outcomes in 55 patients. *J Trauma* 2010; **69:** 275–83.

Dependence and Withdrawal

As for Amobarbital, p. 1038.1.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p. 1038.1.

Formulation. For a report of lactic acidosis associated with intravenous infusion of a parenteral formulation of pentobarbital containing propylene glycol, see Toxicity under Propylene Glycol, p. 2205.3.

Interactions

As for Amobarbital, p. 1038.2.

Pharmacokinetics

Pentobarbital is well absorbed from the gastrointestinal tract after oral or rectal doses, and is reported to be about 60 to 70% bound to plasma proteins. The elimination half-life appears to be dose-dependent and reported values have ranged from 15 to 50 hours. Pentobarbital is metabolised in the liver, mainly by hydroxylation, and excreted in the urine mainly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Mebumal; ***Jpn***: Ravona; ***S.Afr.***: Sopental†; ***USA***: Nembutal.

Multi-ingredient Preparations. ***Arg.***: Dimaval; ***USA***: Cafatine-PB.

Pharmacopoeial Preparations

BP 2014: Pentobarbital Tablets;
USP 36: Pentobarbital Sodium Injection.

Perazine Dimalonate

P-725 (perazine); Pemazine Dimalonate; Perazina, dimalonato de.

10-[3-(4-Methylpiperazin-1-yl)propyl]phenothiazine dimalonate.

$C_{20}H_{25}N_3S,2C_3H_4O_4$=547.6

CAS — 84-97-9 (perazine); 14777-25-4 (perazine dimalonate).

ATC — N05AB10.

ATC Vet — QN05AB10.

Pharmacopoeias. *Pol.* includes only an injection of the dimalonate. It also includes a monograph for Perazine Dimaleate.

Profile

Perazine dimalonate is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2) and is used for the treatment of psychotic conditions. It has a piperazine side-chain. It is given orally as the dimalonate although doses are expressed in terms of the base; perazine dimalonate 40.3 mg is equivalent to about 25 mg of perazine. Usual doses are the equivalent of 50 to 600 mg of the base daily; up to 1 g daily has been given in resistant cases. It has also been given intramuscularly.

Perazine dimaleate given orally has been used similarly.

Adverse effects. Acute axonal neuropathies of superficial nerve fibres developed in 5 patients receiving perazine dimalonate after exposure to sunlight.[1]

1. Roelcke U, *et al.* Acute neuropathy in perazine-treated patients after sun exposure. *Lancet* 1992; **340:** 729–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Taxilan; ***Pol.***: Peragal; Perazin; Perazyna†; Pernazinum.

Pericyazine *(BAN)*

Periciazin; Periciazina; Periciazine (pINN); Péricyazine; Periciazinum; Perisiatsiini; Propericiazine; RP-8909; SKF-20716; Перициазин.

10-[3-(4-Hydroxypiperidino)propyl]phenothiazine-2-carbonitrile; 1-[3-(2-Cyanophenothiazin-10-yl)propyl]piperidin-4-ol.

$C_{21}H_{23}N_3OS$=365.5

CAS — 2622-26-6.

ATC — N05AC01.

ATC Vet — QN05AC01.

UNII — 3405M6FD73.

Uses and Administration

Pericyazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain. It is used in the treatment of psychoses including schizophrenia (p. 1031.3) and disturbed behaviour (p. 1030.2), and in the short-term management of severe anxiety (p. 1028.1).

Pericyazine is usually given as the base but the mesilate and tartrate have also been used.

The usual oral dose for the treatment of severe anxiety, agitation, aggression, or impulsive behaviour is 15 to 30 mg daily given in 2 divided doses, the larger amount in the evening. In schizophrenia and severe psychoses initial doses of 75 mg daily may be given in divided doses, increased if necessary, at weekly intervals by increments of 25 mg, to a maximum of 300 mg daily.

Elderly patients should be given reduced doses: a recommended initial dose is 5 to 10 mg daily for anxiety or disturbed behaviour and 15 to 30 mg daily for schizophrenia or psychosis, both in divided doses.

For details of doses in children, see below.

Administration in children. For the treatment of behavioural disorders and schizophrenia in children, a recommended initial oral dose of pericyazine in those aged 1 year and over is 500 micrograms daily for a child weighing 10 kg; for heavier children this initial dose may be increased by 1 mg for each additional 5 kg, to a maximum total of 10 mg daily. Doses may be gradually increased according to response but the daily maintenance dose should not exceed twice the initial dose. Children aged 12 years and over may be given the usual adult dose (see above).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Sedation and orthostatic hypotension may be marked.

Interactions

As for Chlorpromazine, p. 1051.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Neuleptil; ***Austral.***: Neulactil; ***Braz.***: Neuleptil; ***Canad.***: Neuleptil; ***Chile***: Neuleptil; ***Denm.***: Neulactil; ***Fin.***: Neulactil; ***Fr.***: Neuleptil; ***Gr.***: Nemactil; Neuleptil; ***Hong Kong***: Neulactil; ***Israel***: Neuleptil; ***Ital.***: Neuleptil; ***Neth.***: Neuleptil; ***NZ***: Neulactil; ***Rus.***: Neuleptil (Неулептил); ***Spain***: Nemactil; ***UK***: Neulactil; ***Venez.***: Neuleptil.

Perospirone Hydrochloride *(rINNM)*

Hidrocloruro de perospirona; Perospirona, hidrocloruro de; Pérospirone, Chlorhydrate de; Perospironi Hydrochloridum; SM-9018; Перospирона Гидрохлорид.

cis-N-{4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl}-1,2-cyclohexanedicarboximide hydrochloride.

$C_{23}H_{30}N_4O_2S$,HCl=463.0

CAS — 150915-41-6 (perospirone); 129273-38-7 (perospirone hydrochloride).

UNII — T884I76TMN (perospirone hydrochloride); 503S4466IP (perospirone hydrochloride dihydrate).

Profile

Perospirone is an antipsychotic used in the treatment of schizophrenia (p. 1031.3). Although it has been described as an atypical antipsychotic, the incidence of extrapyramidal effects may be rather higher than is usually seen with atypical drugs such as clozapine (p. 1057.3). Perospirone hydrochloride is given in usual oral doses of 12 to 48 mg daily in 3 divided doses.

References.

1. Onrust SV, McClellan K. Perospirone. *CNS Drugs.* 2001; **15:** 329–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kang Er Ting (康尔汀); ***Jpn***: Lullan.

Perphenazine *(BAN, rINN)*

Perfenatsiini; Perfenazin; Perfenazina; Perfenazinas; Perfenazyna; Perphenazin; Perphénazine; Perphenazinum; Перфеназин.

2-{4-[3-(2-Chlorophenothiazin-10-yl)propyl]piperazin-1-yl}ethanol.

$C_{21}H_{26}ClN_3OS$=404.0

CAS — 58-39-9.

ATC — N05AB03.

ATC Vet — QN05AB03.
UNII — FTA7XXY4EZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Jpn also includes the maleate.

Ph. Eur. 8: (Perphenazine). A white or yellowish-white crystalline powder. M.p. 96 degrees to 100 degrees. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute solutions of hydrochloric acid. Protect from light.

USP 36: (Perphenazine). A white to creamy-white odourless powder. M.p. 94 degrees to 100 degrees. Practically insoluble in water; soluble 1 in 7 of alcohol and 1 in 13 of acetone; freely soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Perphenazine has been reported to be incompatible with cefoperazone sodium[1] and with midazolam hydrochloride (see p. 1085.1).

1. Gasca M, *et al.* Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.

Perphenazine Decanoate *(BANM, rINNM)*

Decanoato de perfenazina; Perfenazina, decanoato de; Perphénazine, Décanoate de; Perphenazini Decanoas; Перфеназина деканоат.

$C_{31}H_{44}ClN_3O_2S$=558.2
ATC — N05AB03.
ATC Vet — QN05AB03.

Perphenazine Enantate *(BANM, rINNM)*

Enantato de perfenazina; Perfenazina, enantato de; Perphénazine, Enantate de; Perphenazine Enanthate; Perphenazine Heptanoate; Perphenazini Enantas; Перфеназина энантат.

$C_{28}H_{38}ClN_3O_2S$=516.1
CAS — 17528-28-8.
ATC — N05AB03.
ATC Vet — QN05AB03.
UNII — Z6RS3DKN8J.

Uses and Administration

Perphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain. It is used in the treatment of various psychoses including schizophrenia (p. 1031.3) and mania (see Bipolar Disorder, p. 397.2) as well as disturbed behaviour (p. 1030.2) and in the short-term, adjunctive management of severe anxiety (p. 1028.1). Perphenazine is also used for the management of postoperative or chemotherapy-induced nausea and vomiting (p. 1814.3) and for the treatment of intractable hiccup (p. 1046.3).

Perphenazine is usually given orally as the base; it has also been given by intramuscular or intravenous injection. The fendizoate derivative has also been given orally. Long-acting decanoate or enantate esters of perphenazine, given by intramuscular injection, are available in some countries.

The usual initial oral dose for the treatment of **schizophrenia, mania, and other psychoses** is 4 mg three times daily. The dose is adjusted according to response up to a usual maximum of 24 mg daily, although up to 64 mg daily has occasionally been used in hospitalised patients. Similar doses have been used for the management of **severe agitated or violent behaviour** or in **severe anxiety**. Perphenazine has sometimes been used in preparations with tricyclic antidepressants such as amitriptyline in the treatment of anxiety with depression.

For the **control of nausea and vomiting** the usual oral dose is 4 mg three times daily but up to 8 mg three times daily may be required.

The long-acting decanoate or enantate esters of perphenazine are given by deep intramuscular injection in doses ranging from about 50 to 300 mg of ester given at intervals of 2 to 4 weeks.

Perphenazine and its esters should be given in reduced doses to the elderly but it should be noted that they are not indicated for the management of agitation and restlessness in these patients.

References.

1. Hartung B, *et al.* Perphenazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 14/04/05).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Perphenazine has been associated with a lower frequency of sedation, but a higher incidence of extrapyramidal effects.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of perphenazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The distribution of perphenazine into breast milk was studied[2] in a mother who was receiving oral perphenazine 24 mg daily, later reduced to 16 mg daily. Breast feeding was started after it was estimated that a breast-fed infant would ingest about 0.1% of a maternal dose. Treatment with perphenazine lasted for 3.5 months and during this period the child thrived normally and no drug-induced symptoms were seen.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Olesen OV, *et al.* Perphenazine in breast milk and serum. *Am J Psychiatry* 1990; **147:** 1378–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies perphenazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Perphenazine is well absorbed after oral doses and undergoes some first-pass metabolism, resulting in a relative bioavailability of about 60 to 80%. Peak plasma concentrations occur between 1 to 3 hours after ingestion. It is widely distributed and crosses the placenta. Perphenazine is extensively metabolised; up to 70% is excreted in the urine mainly as metabolites, with about 5% being excreted in the faeces. The plasma elimination half-life of perphenazine is between 9 and 12 hours. Perphenazine decanoate and perphenazine enantate are slowly absorbed from the site of intramuscular injection. They gradually release perphenazine into the body and are therefore suitable for use as depot injections.

Perphenazine 5 or 6 mg given intravenously had a plasma half-life from 8.4 to 12.3 hours in a study of 4 schizophrenic patients and 4 healthy subjects.[1] Plasma-perphenazine concentrations varied considerably 3 to 5 hours after dosing; this was followed by an exponential elimination phase. Plasma concentrations were undetectable after a 6-mg oral dose in 4 healthy subjects and only low plasma concentrations of its sulfoxide metabolite could be detected; this was attributed to a marked first-pass effect. Systemic availability was also variable and poor in 4 schizophrenic patients given perphenazine 12 mg three times daily. However, it was considered that oral therapy should be given at 8-hour intervals. Intramuscular injection of perphenazine enantate 50 or 100 mg every 2 weeks gave plasma-perphenazine concentrations similar to those after continuous oral dosage, but high initial absorption in the first 2 to 3 days was associated with serious CNS adverse effects.

1. Hansen CE, *et al.* Clinical pharmacokinetic studies of perphenazine. *Br J Clin Pharmacol* 1976; **3:** 915–23.

Metabolism. In 12 healthy subjects there was a clear difference in the disposition of a single oral dose of perphenazine between poor and extensive hydroxylators of debrisoquine.[1]

1. Dahl-Puustinen M-L, *et al.* Disposition of perphenazine is related to polymorphic debrisoquin hydroxylation in human beings. *Clin Pharmacol Ther* 1989; **46:** 78–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Decentan†; ***Denm.***: Trilafon; ***Fin.***: Peratsin; ***Fr.***: Trilifan†; ***Ger.***: Decentan; ***Hong Kong***: Synazin†; ***Indon.***: Trilafon; ***Irl.***: Fentazin; ***Israel***: Perphenan; ***Ital.***: Trilafon; ***Jpn***: PZC; ***Mex.***: Leptopsique; ***Norw.***: Trilafon; ***Philipp.***: Trilafon†; ***Pol.***: Trilafon; ***Rus.***: Etaperazin (Этаперазин); ***Spain***: Decentan; ***Swed.***: Trilafon; ***Switz.***: Trilafon; ***Thai.***: Conazine; Pernamed; Pernazine; Perzine; Porazine; ***UK***: Fentazin.

Multi-ingredient Preparations. ***Arg.***: Karile; ***Canad.***: Apo-Peram†; PMS-Levazine; ***Fin.***: Pertriptyl; ***Gr.***: Minitran; Triphenaze; ***Indon.***: Mutabon-D; Mutabon-M; ***Ital.***: Mutabon; ***Mex.***: Adepsique; ***Port.***: Mutabon; ***Spain***: Mutabase; ***Thai.***: Neuragon†; Polybon; ***UK***: Triptafen; ***USA***: Etrafon†.

Pharmacopoeial Preparations

BP 2014: Perphenazine Tablets;

USP 36: Perphenazine and Amitriptyline Hydrochloride Tablets; Perphenazine Injection; Perphenazine Oral Solution; Perphenazine Syrup; Perphenazine Tablets.

Phenazepam

Fenazepam; Феназепам.

7-Bromo-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{10}BrClN_2O$=349.6
CAS — 51753-57-2.
UNII — 3DSB43090Z.

Profile

Phenazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is used in the short-term treatment of anxiety disorders and as an anticonvulsant. There have been concerns about abuse (see Overdosage, below).

Overdosage. Severe intoxication resulting from abuse of a 400- to 600-mg dose of phenazepam (usual single dose up to 1 mg) has been reported in a patient in Sweden. The authors reported that the half-life of phenazepam was about 60 hours and in other cases patients had still shown symptoms more than 14 days after ingestion.[1]

Abuse of phenazepam has been reported in several other countries, including Finland, the UK, and the USA; screening of post-mortem blood samples in Scotland between January and July 2011 identified 9 deaths where phenazepam was present, in all cases in persons with a history of drug misuse.[2]

1. Mrozkowska J, *et al.* Missbruk av fenazepam—ny företeelse i Sverige. Bensodiazepinderivat från Ryssland gav svår intoxikation. *Lakartidningen* 2009; **106:** 516–17.
2. Maskell PD, *et al.* Phenazepam is currently being misused in the UK. *BMJ* 2011; **343:** 59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Elzepam (Элзепам); Phenorelaxan (Фенорелаксан); Phezipam (Фезипам); Trankvezipam (Транквезипам).

Phenprobamate *(BAN, rINN)*

Fenprobamaatti; Fenprobamat; Fenprobamato; MH-532; Phenprobamatum; Proformiphen; Фенпробамат.

3-Phenylpropyl carbamate.

$C_{10}H_{13}NO_2$=179.2
CAS — 673-31-4.
ATC — M03BA01.
ATC Vet — QM03BA01.
UNII — UJZ473TPS0.

Profile

Phenprobamate is a carbamate with general properties similar to those of meprobamate (p. 1083.3). It has been used for its anxiolytic and muscle relaxant actions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Gamaflex; Gamakuil.

Multi-ingredient Preparations. ***Turk.***: Kuiflex; Kuilil.

Pimozide *(BAN, USAN, rINN)*

McN-JR-6238; Pimotsidi; Pimozid; Pimozida; Pimozidas; Pimozidum; Pimozyd; R-6238; Пимозид.

1-{1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidyl}benzimidazolin-2-one; 1-{1-[3-(4,4′-Difluorobenzhydryl)propyl]-4-piperidyl}benzimidazolin-2-one.

$C_{28}H_{29}F_2N_3O$=461.6
CAS — 2062-78-4.
ATC — N05AG02.
ATC Vet — QN05AG02.
UNII — 1HIZ4DL86F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pimozide). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Pimozide). A white crystalline powder. Insoluble in water; soluble 1 in 1000 of alcohol, of ether, and of methyl alcohol, 1 in 100 of acetone, 1 in 10 of chloroform, and 1 in more than 1000 of 0.1N hydrochloric acid. Store in airtight containers. Protect from light.

Uses and Administration

Pimozide is a diphenylbutylpiperidine antipsychotic and is structurally similar to the butyrophenones. It is a long-

acting antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3), although it also has some calcium-blocking activity. Pimozide is given orally in the management of psychoses including schizophrenia (below), paranoid states, and monosymptomatic hypochondria (p. 1030.2) and in Tourette's syndrome (below). An ECG should be performed in all patients before starting treatment with pimozide (see Adverse Effects, Treatment, and Precautions, below).

In **schizophrenia**, treatment is usually begun with a dose of 2 mg daily (the *BNFC* suggests 1 mg in those aged 12 to 18 years), adjusted thereafter according to response in increments of 2 to 4 mg at intervals of not less than 1 week. The usual dose range is 2 to 20 mg daily. It is generally given as a single daily dose.

In **monosymptomatic hypochondria** and **paranoid psychoses**, the initial dose is 4 mg daily adjusted as above to a maximum daily dose of 16 mg.

Pimozide treatment should start at half the usual initial dosage in elderly patients.

In the USA, pimozide is only licensed for the treatment of **Tourette's syndrome**; initial doses are 1 to 2 mg daily in divided doses, increased thereafter every other day to a maximum of 10 mg daily or 200 micrograms/kg daily. Dose adjustment has been suggested for patients who are poor CYP2D6 metabolisers; see Administration in Genetic Variation, below. For details of doses in children, see below.

Administration in children. In the USA, pimozide is licensed for the treatment of children with Tourette's syndrome; initial oral doses are 50 micrograms/kg once daily at bedtime, increased thereafter every third day to a maximum of 200 micrograms/kg (not exceeding 10 mg) daily. US licensed product information also suggests that genotyping for cytochrome P450 isoenzyme CYP2D6 should be performed when the dose is increased above 50 micrograms/kg daily, that this is the maximum recommended dose in CYP2D6 poor metabolisers, and that the interval between dose increases should be at least 14 days in these patients.

Although not licensed in the UK, the *BNFC* suggests that children aged 2 to 12 years may be given oral doses of 1 to 4 mg daily and those aged 12 to 18 years, 2 to 10 mg daily.

For doses in adolescents with schizophrenia, see Uses and Administration, p. 1096.3.

Administration in genetic variation. US licensed product information for pimozide suggests that genotyping for cytochrome P450 isoenzyme CYP2D6 should be performed when the oral dose is increased above 4 mg daily, that this is the maximum recommended dose in CYP2D6 poor metabolisers, and that the interval between dose increases should be at least 14 days in these patients. (In the USA, pimozide is only licensed for the treatment of Tourette's syndrome.)

For dosage adjustment in children, see above.

Chorea. Antipsychotics such as pimozide have some action against choreiform movements (p. 1029.3) as well as being of use to control the behavioural disturbances of Huntington's chorea.

References.

1. Shannon KM, Fenichel GM. Pimozide treatment of Sydenham's chorea. *Neurology* 1990; **40:** 186.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to other drugs.[1] In very severe dystonia combination therapy may be required. Pimozide in gradually increasing doses up to 12 mg daily with tetrabenazine and trihexyphenidyl is sometimes effective. However, antipsychotics often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p. 1049.2).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.

Schizophrenia. A systematic review[1] concluded that pimozide appears to be of similar efficacy to other classical antipsychotics in the treatment of schizophrenia (p. 1031.3). There was no evidence that it was particularly useful for those with delusional disorders or with mainly negative symptoms.

1. Rathbone J, McMonagle T. Pimozide for schizophrenia or related psychoses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 20/03/08).

Taste disorders. For reference to the use of pimozide in the treatment of taste disorders, see under Chlorpromazine, p. 1047.2.

Tourette's syndrome. Tourette's syndrome (see Tics, p. 1030.1) is a disorder characterised by motor and vocal tics and behavioural disturbances. Many patients with Tourette's syndrome do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide[1-3] have been most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. Pimozide may be slightly less effective than haloperidol, but adverse effects are also less frequent.[3] Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al*. Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; **46:** 722–30.
2. Sallee FR, *et al*. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; **154:** 1057–62.
3. Pringsheim T, Marras C. Pimozide for tics in Tourette's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 28/09/09).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Extrapyramidal effects may be more common than with chlorpromazine but pimozide may be less likely to cause sedation, hypotension, or antimuscarinic effects.

Ventricular arrhythmias and other ECG abnormalities, such as prolongation of the QT interval and T-wave changes, have been associated with the use of pimozide; an ECG should therefore be performed before, and repeated periodically during, treatment. If repolarisation changes appear or arrhythmias develop, the need for continuing treatment should be reviewed; the dose of pimozide should be reduced or, if the QT interval exceeds 500 milliseconds, therapy should be withdrawn. Pimozide is contra-indicated in patients with pre-existing prolongation of the QT interval, or a family history of congenital QT prolongation, and in patients with a history of cardiac arrhythmias. Electrolyte disturbances such as hypokalaemia or hypomagnesaemia in patients receiving pimozide may lead to cardiotoxicity.

Effects on the cardiovascular system. The UK CSM has received reports of ventricular arrhythmias and other ECG abnormalities such as prolongation of the QT interval and T-wave changes associated with the use of pimozide.[1,2] In August 1990 they had received 13 reports of sudden unexpected death since 1971; many of these patients had no evidence of pre-existing cardiac disease, and 7 were under 30 years of age. Five of the 13 were also taking other antipsychotics. Most cases were associated with doses greater than 20 mg daily and many had had the dose increased rapidly, possibly resulting in substantial tissue accumulation. By February 1995 the CSM had received a total of 40 reports (16 fatal) of serious cardiac reactions most of which involved arrhythmias.

See also under Chlorpromazine, p. 1047.3.

1. CSM. Cardiotoxic effects of pimozide. *Current Problems 29* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024447&RevisionSelectionMethod=LatestReleased (accessed 07/08/08)
2. CSM/MCA. Cardiac arrhythmias with pimozide (Orap). *Current Problems* 1995; **21:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Genetic factors. The metabolism of pimozide is mediated to some extent by the cytochrome P450 isoenzyme CYP2D6. Patients who are poor CYP2D6 metabolisers may have higher concentrations of pimozide than those who are extensive metabolisers, and their dosage of pimozide may need to be amended; for further details, see Administration in Genetic Variation, above.

Interactions

As for Chlorpromazine, p. 1051.3. The risk of arrhythmias with pimozide may be increased by other drugs that prolong the QT interval including some antiarrhythmics, other antipsychotics (including depot preparations), tricyclic antidepressants, the antihistamines terfenadine and astemizole, antimalarials, and cisapride; use together should be avoided. Use with drugs that induce electrolyte disturbances, such as diuretics, should also be avoided.

The use of pimozide with drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 is contra-indicated; the resultant decrease in the metabolism of pimozide may lead to increased plasma concentrations and hence greater risk of cardiac arrhythmias. CYP3A4 inhibitors include the macrolide antibacterials such as clarithromycin, erythromycin, and troleandomycin; the azole antifungals including itraconazole and ketoconazole; the HIV-protease inhibitors; the NNRTIs; nefazodone, and zileuton. The metabolism of pimozide may also be inhibited by grapefruit juice and use together should be avoided.

Pimozide is also metabolised by CYP2D6, albeit to a lesser extent, and *in vitro* data indicate that the CYP2D6 inhibitor quinidine may reduce the metabolism of pimozide; UK licensed product information contra-indicates the use of such inhibitors with pimozide. The isoenzyme CYP1A2 may also be involved in the metabolism of pimozide and consequently there is a theoretical possibility of interactions with CYP1A2 inhibitors.

Pimozide should also not be used with SSRIs such as citalopram, escitalopram, paroxetine, and sertraline. Paroxetine and sertraline have been reported to increase the plasma concentrations of pimozide, and hence there may be a greater risk of QT prolongation. Citalopram and escitalopram have been reported to prolong the QT interval when used with pimozide; the mechanism of this interaction is unknown. Use of pimozide with SSRIs has also been reported to cause extrapyramidal effects, oculogyric crises, and sedation.

Antibacterials. Sudden deaths have occurred in patients given pimozide and *clarithromycin*, see p. 1052.1.

Pharmacokinetics

More than half of an oral dose of pimozide is reported to be absorbed. It undergoes significant first-pass metabolism. Peak plasma concentrations have been reported after 4 to 12 hours and there is a considerable interindividual variation in the concentrations achieved. Pimozide is metabolised in the liver mainly by *N*-dealkylation and excreted in the urine and faeces in the form of metabolites and unchanged drug. Metabolism is mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP2D6; CYP1A2 may also be involved. Pimozide has a mean elimination half-life of about 55 hours, although half-lives of up to 150 hours have been noted in some patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Orap; ***Austral.***: Orap†; ***Austria***: Orap; ***Belg.***: Orap; ***Braz.***: Orap; ***Canad.***: Orap; ***Chile***: Orap; ***Denm.***: Orap; ***Fr.***: Orap; ***Ger.***: Orap; ***Gr.***: Pirium; ***Hong Kong***: Orap; ***India***: Larap; Neurap; Orap; ***Indon.***: Orap; ***Irl.***: Orap; ***Israel***: Orap; ***Ital.***: Orap; ***Jpn***: Orap; ***Neth.***: Orap; ***NZ***: Orap†; ***Port.***: Orap; ***S.Afr.***: Orap; ***Singapore***: Orap; ***Spain***: Orap; ***Thai.***: Orap†; Pizide; ***Turk.***: Norofren; ***UK***: Orap; ***USA***: Orap; ***Venez.***: Orap.

Pharmacopoeial Preparations
BP 2014: Pimozide Tablets;
USP 36: Pimozide Tablets.

Pinazepam *(rINN)*

Pinazépam; Pinazepamum; Пиназепам.
7-Chloro-1,3-dihydro-5-phenyl-1-(prop-2-ynyl)-2*H*-1,4-benzodiazepin-2-one.
$C_{18}H_{13}ClN_2O$=308.8
CAS — 52463-83-9.
ATC — N05BA14.
ATC Vet — QN05BA14.
UNII — 5286RBZ882.

Profile

Pinazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given in usual oral doses of 5 to 20 mg daily in divided doses for the short-term treatment of anxiety disorders (p. 1028.1). Doses of 2.5 to 5 mg at night have been used in the treatment of insomnia (p. 1033.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Domar; ***Ital.***: Domar; ***Mex.***: Yunir; ***Singapore***: Domar; ***Spain***: Duna; ***Thai.***: Domar.

Pipamperone *(BAN, USAN, rINN)*

Floropipamide; McN-JR-3345; Pipamperon; Pipamperona; Pipampérone; Pipamperoni; Pipamperonum; R-3345; Пипамперон.
1-[3-(4-Fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide.
$C_{21}H_{30}FN_3O_2$=375.5
CAS — 1893-33-0.
ATC — N05AD05.
ATC Vet — QN05AD05.
UNII — 5402501F0W.

Pipamperone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipamperona; Pipamperona, hidrocloruro de; Pipampérone, Chlorhydrate de; Pipamperoni Hydrochloridum; Пипамперона Гидрохлорид.

$C_{21}H_{30}FN_3O_2,2HCl$=448.4

CAS — 2448-68-2.
ATC — N05AD05.
ATC Vet — QN05AD05.
UNII — IT085U64JB.

Profile

Pipamperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given orally as the hydrochloride for the treatment of psychoses. Doses are expressed in terms of the base; pipamperone hydrochloride 47.8 mg is equivalent to about 40 mg of pipamperone. Usual initial doses, equivalent to 40 mg of the base, have been given 2 or 3 times daily, increased gradually thereafter according to response; doses of 360 mg or more have been given daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Dipiperon; ***Denm.***: Dipiperon; ***Fr.***: Dipiperon; ***Ger.***: Dipiperon; ***Gr.***: Dipiperon; ***Neth.***: Dipiperon; ***Switz.***: Dipiperon.

Pipotiazine *(BAN, rINN)*

Pipothiazine; Pipotiatsiini; Pipotiazin; Pipotiazina; Pipotiazinum; RP-19366; Пипотиазин.

10-[3-[4-(2-Hydroxyethyl)piperidino]propyl]-*NN*-dimethylphenothiazine-2-sulphonamide; 2-[4-[3-(2-Dimethylsulphamoylphenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

$C_{24}H_{33}N_3O_3S_2$=475.7

CAS — 39860-99-6.
ATC — N05AC04.
ATC Vet — QN05AC04.
UNII — L903J9JPYV.

Pipotiazine Palmitate *(BANM, USAN, rINNM)*

IL-19552; Palmitato de pipotiazina; Pipothiazine Palmitate; Pipotiazina, palmitato de; Pipotiazine, Palmitate de; Pipotiazini Palmitas; RP-19552; Пипотиазина Палмитат.

$C_{40}H_{63}N_3O_4S_2$=714.1

CAS — 37517-26-3.
ATC — N05AC04.
ATC Vet — QN05AC04.
UNII — 4Q3H01QRMI.

Uses and Administration

Pipotiazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain. It is used in the treatment of schizophrenia (below) and other psychoses. Pipotiazine is given orally as the base and by deep intramuscular injection as the palmitate ester; oral doses are expressed as the base and parenteral doses are expressed as the ester.

A usual oral dose of pipotiazine for the treatment of psychoses is 5 to 20 mg daily; in severe psychoses up to 30 mg daily has been given for brief periods.

The long-acting palmitate ester of pipotiazine is given by deep intramuscular injection. An initial test dose of 25 mg is followed by a further 25 to 50 mg after 4 to 7 days. The dosage is then adjusted in increments of 25 to 50 mg according to response every 4 weeks. Usual maintenance doses of 50 to 100 mg are given at average intervals of 4 weeks; the maximum recommended dose in the UK is 200 mg every 4 weeks.

Pipotiazine should be given in reduced dosage to elderly patients; a starting dose of 5 to 10 mg has been suggested for pipotiazine palmitate intramuscular injections.

Schizophrenia. A systematic review[1] concluded that depot pipotiazine palmitate appeared to be no different in terms of efficacy or adverse effects to other antipsychotics given orally or by depot injection in the treatment of schizophrenia (p. 1031.3).

1. Dinesh M, *et al.* Depot pipotiazine palmitate and undecylenate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Effects on mental function. Manic symptoms developed in a schizophrenic patient given pipotiazine palmitate. Symptoms recurred on rechallenge.[1]

1. Singh AN, Maguire J. Pipothiazine palmitate induced mania. *BMJ* 1984; **289:** 734.

Pharmacokinetics

Pipotiazine palmitate is very slowly absorbed from the site of intramuscular injection. It gradually releases pipotiazine into the body and is therefore suitable for use as a depot injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Piportil L4; ***Braz.***: Piportil; ***Canad.***: Piportil L4; ***Chile***: Piportyl; ***China***: Ni Meng Shu (尼蒙舒); ***Fr.***: Piportil; ***Hung.***: Piportil†; ***Irl.***: Piportil†; ***Mex.***: Piportil L4; ***NZ***: Piportil; ***Rus.***: Piportil (Пипортил)†; ***Singapore***: Piportil; ***Spain***: Lonseren; ***UK***: Piportil.

Prazepam *(BAN, USAN, rINN)*

Pratsepaami; Prazepám; Prazépam; Prazepamas; Prazepamum; W-4020; Празепам.

7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{19}H_{17}ClN_2O$=324.8

CAS — 2955-38-6.
ATC — N05BA11.
ATC Vet — QN05BA11.
UNII — Q30VCC064M.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Prazepam). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

Profile

Prazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). After oral doses, prazepam undergoes extensive first-pass metabolism in the liver to oxazepam (p. 1092.2) and desmethyldiazepam (nordazepam, p. 1089.3). Desmethyldiazepam is largely responsible for the pharmacological activity of prazepam. The usual oral dose for the short-term treatment of anxiety disorders (p. 1028.1) is 30 mg daily as a single nightly dose or in divided doses; in severe conditions up to 60 mg daily has been given. In elderly or debilitated patients, treatment should start with a daily dose of no more than 15 mg.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of prazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The ratio of desmethyldiazepam in plasma to that in breast milk of 5 women given prazepam 20 mg three times daily for 3 days was 9.6 from measurements 12 hours after the last dose.[2] It was estimated that a breast-fed infant of a mother on continuous prazepam therapy would ingest the equivalent of about 4% of the daily maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Brodie RR, *et al.* Concentrations of N-descyclopropylmethylprazepam in whole-blood, plasma, and milk after administration of prazepam to humans. *Biopharm Drug Dispos* 1981; **2:** 59–68.

Pharmacokinetics. References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; **24:** 446–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Demetrin; ***Belg.***: Lysanxia; ***Fr.***: Lysanxia; ***Ger.***: Demetrin; Mono Demetrin; ***Gr.***: Centrac; Demetonevrin; ***Irl.***: Centrax; ***Ital.***: Prazene; Trepidan; ***Neth.***: Reapam; ***Port.***: Demetrin; ***S.Afr.***: Demetrin; ***Switz.***: Demetrin; ***Thai.***: Pozapam; Prasepine†.

Prochlorperazine *(BAN, rINN)*

Chlormeprazine; Prochlorpemazine; Prochlorpérazine; Prochlorperazinum; Proclorperazina; Proklooriperatsiini; Proklorperazin; Прохлорперазин.

2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine.

$C_{20}H_{24}ClN_3S$=373.9

CAS — 58-38-8.
ATC — N05AB04.
ATC Vet — QN05AB04.
UNII — YHP6YLT61T.

Pharmacopoeias. In *US.*

USP 36: (Prochlorperazine). A clear, pale yellow, viscous liquid, sensitive to light. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in ether. Store in airtight containers. Protect from light.

Prochlorperazine Edisilate *(BANM, rINNM)*

Chlormeprazine Edisylate; Edisilato de proclorperazina; Prochlorpemazine Edisylate; Prochlorpérazine, Edisilate de; Prochlorperazine Edisylate; Prochlorperazine Ethanedisulphonate; Prochlorperazini Edisilas; Proclorperazina, edisilato de; Прохлорперазина Эдизилат.

$C_{20}H_{24}ClN_3S,C_2H_6O_6S_2$=564.1

CAS — 1257-78-9.
ATC — N05AB04.
ATC Vet — QN05AB04.
UNII — PG20W5VQZS.

Pharmacopoeias. In *US.*

USP 36: (Prochlorperazine Edisylate). A white to very light yellow odourless crystalline powder. Soluble 1 in 2 of water and 1 in 1500 of alcohol; insoluble in chloroform and in ether. Solutions in water are acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. See under Prochlorperazine Mesilate, below.

Prochlorperazine Maleate *(BANM, rINNM)*

Chlormeprazine Maleate; Maleato de proclorperazina; Prochloroperazyny maleinian; Prochlorpemazine Maleate; Prochlorperazine Dihydrogen Maleate; Prochlorperazine Dimaleate; Prochlorpérazine, Maléate de; Prochlorperazin-hydrogenmaleat; Prochlorperazini Maleas; Prochlorperazin-maleinát; Prochlorperazino maleatas; Proclorperazina, maleato de; Proklooriperatsiinimaleaatti; Proklorperazinmaleat; Proklórperazin-maleát; Прохлорперазина Малеат.

$C_{20}H_{24}ClN_3S,2C_4H_4O_4$=606.1

CAS — 84-02-6.
ATC — N05AB04.
ATC Vet — QN05AB04.
UNII — I1T8O1JTL6.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Prochlorperazine Maleate). A white or pale yellow, crystalline powder. Very slightly soluble in water and in alcohol. A freshly prepared saturated solution in water has a pH of 3.0 to 4.0. Protect from light.

USP 36: (Prochlorperazine Maleate). A white or pale yellow, practically odourless, crystalline powder. Practically insoluble in water; soluble 1 in 1200 of alcohol; slightly soluble in warm chloroform. Its saturated solution is acid to litmus. Store in airtight containers. Protect from light.

Prochlorperazine Mesilate *(BANM, rINNM)*

Chlormeprazine Mesylate; Mesilato de proclorperazina; Prochlorpemazine Mesylate; Prochlorperazine Dimethanesulphonate; Prochlorpérazine, Mésilate de; Prochlorperazine Mesylate; Prochlorperazine Methanesulphonate; Prochlorperazini mesilas; Prochlorperazini Mesylas; Proclorperazina, mesilato de; Прохлорперазина Мезилат.

$C_{20}H_{24}ClN_3S,2CH_3SO_3H$=566.1

CAS — 5132-55-8.
ATC — N05AB04.
ATC Vet — QN05AB04.
UNII — 531SH87H9N.

Pharmacopoeias. In *Br.*

BP 2014: (Prochlorperazine Mesilate). A white or almost white, odourless or almost odourless powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 2.0 to 3.0. Protect from light.

Incompatibility. Incompatibility has been reported between the edisilate or mesilate salts of prochlorperazine and several other compounds: these include aminophylline, amphotericin B, ampicillin sodium, aztreonam, some barbiturates, benzylpenicillin salts, calcium gluconate, cefalotin sodium, cefmetazole sodium, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, midazolam hydrochloride, and some sulfonamides. Incompat-

ibility between prochlorperazine edisilate and morphine sulfate has been attributed to phenol present in some formulations of the opioid.[1,2] Incompatibility has been reported on dilution of prochlorperazine edisilate injection with sodium chloride injection containing methyl hydroxybenzoate and propyl hydroxybenzoate as preservatives.[3] The problem did not occur with unpreserved sodium chloride or when benzyl alcohol was used as preservative. Prochlorperazine mesilate syrup has been reported to be incompatible with magnesium trisilicate mixture.[4]

1. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; **42:** 2651.
2. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; **44:** 67.
3. Jett S, *et al*. Prochlorperazine edisylate incompatibility. *Am J Hosp Pharm* 1983; **40:** 210.
4. Greig JR. Stemetil syrup and magnesium trisilicate. *Pharm J* 1986; **237:** 504.

Uses and Administration

Prochlorperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain. Prochlorperazine and its salts are widely used in the prevention and treatment of nausea and vomiting (p. 1814.3) including that associated with migraine (see Headache, below) or drug-induced emesis. They are also used for the short-term symptomatic relief of vertigo (p. 612.3) as occurs in Ménière's disease (p. 611.2) or labyrinthitis, and in the management of schizophrenia (p. 1031.3), mania (see Bipolar Disorder, p. 397.2), and other psychoses. Prochlorperazine has been used as an adjunct in the short-term management of severe anxiety (p. 1028.1).

Prochlorperazine as one of its salts may be given by various routes:

- orally as the maleate or the mesilate; the edisilate has also been given by this route
- buccally as the maleate
- parenterally as the edisilate or the mesilate

It may also be given rectally as the base.

Depending on the country or the manufacturer, doses of prochlorperazine are expressed either as the base or the salt. Prochlorperazine edisilate 7.5 mg, prochlorperazine maleate 8.1 mg, or prochlorperazine mesilate 7.6 mg are each equivalent to about 5 mg of prochlorperazine. Most doses in the UK are expressed in terms of the maleate or mesilate, while most doses in the USA are expressed in terms of the base. As a result there is a disparity in the dosage recommendations for these countries, with the doses in the USA tending to be higher.

Reduced dosage may be required in elderly patients.

For **nausea and vomiting** doses are as follows:

- in the UK, the usual *oral* dose for prevention is 5 to 10 mg of the maleate or mesilate (roughly equivalent to about 3 to 6.5 mg of the base) 2 or 3 times daily
- for the treatment of nausea and vomiting, recommended UK doses are 20 mg of the maleate or mesilate *orally* or 12.5 mg of the mesilate by deep *intramuscular* injection followed if necessary by a further dose of 10 mg given 2 hours after an oral dose or 6 hours after an intramuscular dose. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily
- in the USA, the *oral* dose for the control of nausea and vomiting is the equivalent of 5 or 10 mg of the base (as the maleate) given 3 or 4 times daily. The recommended *intramuscular* dosage is the equivalent of 5 to 10 mg of the base (as the edisilate) given every 3 to 4 hours if necessary, up to a total of 40 mg of the base daily. The *rectal* dose is 25 mg of the base given twice daily. In the management of severe nausea and vomiting the equivalent of 2.5 to 10 mg of prochlorperazine (as the edisilate) may be given by slow *intravenous* injection or infusion at a rate not exceeding 5 mg/minute; doses should not exceed 40 mg daily

For treatment of **psychoses** the following doses have been given:

- in the UK, prochlorperazine maleate or mesilate may be given in an *oral* dose of 12.5 mg twice daily for 7 days adjusted gradually to 75 to 100 mg daily according to response; some patients may be maintained on doses of 25 to 50 mg daily. The equivalent of prochlorperazine mesilate 12.5 to 25 mg two or three times daily may be given by deep *intramuscular* injection
- in the USA, prochlorperazine is given as the maleate in usual initial *oral* doses equivalent to 5 or 10 mg of the base 3 or 4 times daily adjusted according to response up to a maximum of 150 mg of base daily. In acute disturbances it may be given by deep *intramuscular* injection as the edisilate in usual doses equivalent to 10 to 20 mg of the base and repeated every 2 to 4 hours if necessary

For details of doses in children, see below.

Oral doses of 5 to 10 mg of the maleate or mesilate (or, in the USA, the equivalent of 5 mg of the base) up to 3 or 4 times daily have been used for short-term adjunctive management of **severe anxiety disorders**.

Prochlorperazine is also licensed in the UK for the treatment of **vertigo** including that due to Ménière's disease. It is given *orally* in doses of 15 to 30 mg of the maleate or mesilate daily in divided doses; after several weeks the dose may be gradually reduced to 5 to 10 mg daily. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily.

Administration in children. Owing to the risk of severe extrapyramidal reactions, prochlorperazine should be used with extreme caution in children; it is not recommended for very young children or those weighing less than 10 kg.

There are similar discrepancies with children's doses of prochlorperazine to those of adult doses, see Uses and Administration, above. The following doses are suggested in the treatment of **nausea and vomiting**:

- Where use in children is unavoidable, UK licensed product information has suggested that 250 micrograms/kg of the maleate or mesilate may be given orally 2 or 3 times daily to those aged 1 year and over for the prevention and treatment of nausea and vomiting; the intramuscular route is considered unsuitable. However, the *BNFC* suggests giving intramuscular doses, repeated up to 3 times daily if necessary, according to age as follows: 2 to 5 years, 1.25 to 2.5 mg; 5 to 12 years, 5 to 6.25 mg.
- In the USA oral and intramuscular routes are advocated for children aged 2 years and over. The usual oral antiemetic dose, given in divided doses, ranges up to 7.5 mg of the base or its equivalent daily in children weighing about 10 to 13 kg; in children 14 to 17 kg, up to 10 mg daily; from 18 to 39 kg, up to 15 mg daily. More than one day of oral antiemetic therapy is seldom necessary. The suggested intramuscular dose is the equivalent of 132 micrograms/kg of the base given as a single deep intramuscular injection of the edisilate.

In the USA, prochlorperazine is also licensed for the treatment of **schizophrenia**. The usual oral dose, given in divided doses, ranges up to 20 mg of the base or its equivalent daily in those aged 2 to 5 years, and up to 25 mg daily in children aged 6 to 12 years. It may also be given intramuscularly in similar doses to those used for nausea and vomiting.

Headache. Some phenothiazines such as prochlorperazine have been used in the control of the symptoms of severe migraine (see p. 1046.3). In comparative studies[1,2] prochlorperazine appears to have been more effective in relieving migraine headache and nausea and vomiting than metoclopramide when these drugs were given parenterally. Intravenous prochlorperazine was shown to be effective in aborting intractable migraine in children in a small uncontrolled study.[3]

1. Coppola M, *et al*. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26:** 541–6.
2. Jones J, *et al*. Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14:** 262–4.
3. Kabbouche MA, *et al*. Tolerability and effectiveness of prochlorperazine for intractable migraine in children. *Pediatrics* 2001; **107:** 767. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e62 (accessed 28/04/04)

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Prochlorperazine may cause less sedation and fewer antimuscarinic effects but extrapyramidal effects may be more frequent.

Severe dystonic reactions have followed the use of prochlorperazine, particularly in children and adolescents. It should therefore be used with extreme care in children. In addition, in the UK, parenteral use in children is not recommended.

Local irritation has occurred after the use of buccal tablets of prochlorperazine maleate.

Effects on the cardiovascular system. Hypertension has been reported[1] in a few patients given prochlorperazine intravenously for prophylaxis of cisplatin-induced nausea and vomiting.

See also under Chlorpromazine, p. 1047.3.

1. Roche H, *et al*. Hypertension and intravenous antidopaminergic drugs. *N Engl J Med* 1985; **312:** 1125–6.

Effects on the mouth. Reports of ulceration and soreness of the lip and tongue have been associated with use of prochlorperazine maleate oral tablets.[1,2] The erosive cheilitis resolved after withdrawal of prochlorperazine and recurred on rechallenge.

1. Duxbury AJ, *et al*. Erosive cheilitis related to prochlorperazine maleate. *Br Dent J* 1982; **153:** 271–2.
2. Reilly GD, Wood ML. Prochlorperazine-—an unusual cause of lip ulceration. *Acta Derm Venereol (Stockh)* 1984; **64:** 270–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prochlorperazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

The pharmacokinetics of prochlorperazine were studied in 8 healthy subjects after doses of 6.25 and 12.5 mg intravenously, and 25 mg orally.[1] There was a marked interindividual variation in pharmacokinetics after intravenous doses but no evidence of dose-dependent pharmacokinetics; mean terminal half-lives were 6.8 hours for the higher and 6.9 hours for the lower dose. The apparent volume of distribution was very high and plasma clearance values were apparently greater than liver plasma flow, suggesting that the liver may not be the only site of metabolism. After oral doses, prochlorperazine concentrations were detectable in only 4 of the 8 subjects, due in part to a low bioavailability but also to the lack of sensitivity of the high-pressure liquid chromatographic assay used. The time to peak plasma concentration varied from 1.5 to 5 hours, and the peak concentrations varied from 1.6 to 7.6 nanograms/mL. Bioavailability was estimated to range from 0 to 16%. A low bioavailability due to high first-pass metabolism would be expected because of the high plasma clearance of prochlorperazine.

1. Taylor WB, Bateman DN. Preliminary studies of the pharmacokinetics and pharmacodynamics of prochlorperazine in healthy volunteers. *Br J Clin Pharmacol* 1987; **23:** 137–42.

Buccal route. Both single- and multiple-dose studies indicated that bioavailability of prochlorperazine maleate was greater after buccal doses than when given orally.[1,2] Doses of 3 mg twice daily by the buccal route and 5 mg three times daily by mouth produced similar steady-state plasma-prochlorperazine concentrations.[1]

1. Hessell PG, *et al*. A comparison of the availability of prochlorperazine following im buccal and oral administration. *Int J Pharmaceutics* 1989; **52:** 159–64.
2. Finn A, *et al*. Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. *J Clin Pharmacol* 2005; **45:** 1383–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nausetil; Procalm; Prozine; Stemetil; Stemzine; ***Canad.***: Apo-Prochlorazine; Nu-Prochlor; ***Denm.***: Stemetil; ***Fin.***: Stemetil; ***Hong Kong***: Antinaus†; Dhaperazine; Metil†; PCP†; Peratil†; Seratil; Stemetil; ***India***: Bukatel; Comptil; Emex; Emidoxyn; Emikind; Ingametil; Meditil; Nausetil; Stemetil; Vometil; ***Irl.***: Buccastem; Stemetil; ***Ital.***: Stemetil; ***Malaysia***: Dhaperazine; Lartil; Nautisol; Prochlor; Protazine; ***Neth.***: Stemetil†; ***Norw.***: Stemetil; ***NZ***: Antinaus; Buccastem; Stemetil; ***Pol.***: Chloropernazinum; ***S.Afr.***: Mitil; Scripto-Metic; Stemetil; ***Singapore***: Dhaperazine; PCP; Peratil; Prochlor; Properazine; Stemetil; ***Swed.***: Stemetil†; ***Thai.***: Proclozine; Stabil; Stemetil; ***UK***: Buccastem; Stemetil; ***USA***: Compazine†; Compro.

Multi-ingredient Preparations. ***India***: Emidoxyn Forte; Ghoom; Mizeco; Motion Plus; Neuromol; Nuroflow; ***Ital.***: Difmetre.

Pharmacopoeial Preparations

BP 2014: Prochlorperazine Buccal Tablets; Prochlorperazine Injection; Prochlorperazine Oral Solution; Prochlorperazine Tablets;

USP 36: Prochlorperazine Edisylate Injection; Prochlorperazine Maleate Tablets; Prochlorperazine Oral Solution; Prochlorperazine Suppositories.

Promazine *(BAN, rINN)*

A-145; NSC-31447; Promatsiini; Promazin; Promazina; Promazinum; Propazinum; 3276-RP; RP-3276; WY-1094; Промазин.

NN-Dimethyl-3-phenothiazin-10-ylpropylamine.

$C_{17}H_{20}N_2S$=284.4

CAS — 58-40-2.

ATC — N05AA03.

ATC Vet — QN05AA03.

UNII — O9M39HTM5W.

NOTE. The code A-145 has also been used for *N*-ethylcarbaminomethyl-*L*-isoleucine, a compound investigated as an antineoplastic

Promazine Embonate *(BANM, rINNM)*

Embonato de promazina; Promazina, embonato de; Promazine, Embonate de; Promazine Pamoate; Promazini Embonas; Промазина Эмбонат.

$(C_{17}H_{20}N_2S)_2,C_{23}H_{16}O_6$=957.2

ATC — N05AA03.

ATC Vet — QN05AA03.

Promazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de promazina; Promatsiinihydrokloridi; Promazina, hidrocloruro de; Promazine, Chlorhydrate de; Promazinhidroklorid; Promazinhydrochlorid; Promazin-hydrochlorid; Promazinhydroklorid; Promazini hydrochloridum; Promazino hidrochloridas; Promazyny chlorowodorek; Промазина Гидрохлорид.

$C_{17}H_{20}N_2S$,HCl=320.9

CAS — 53-60-1.

ATC — N05AA03.

ATC Vet — QN05AA03.

UNII — U16EOR79U4.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Promazine Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Very soluble in water, in alcohol, and in dichloromethane. A freshly prepared 5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Promazine Hydrochloride). A white or slightly yellow, practically odourless, crystalline powder. It oxidises upon prolonged exposure to air and acquires a pink or blue colour. Soluble 1 in 3 of water; freely soluble in chloroform. pH of a 1 in 20 solution is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between promazine hydrochloride and several other compounds: these include aminophylline, some barbiturates, benzylpenicillin potassium, chlortetracycline, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, phenytoin sodium, prednisolone sodium phosphate, and sodium bicarbonate.

Sorption. A study[1] of drug loss from intravenous delivery systems reported an 11% loss of promazine hydrochloride from solution when infused for 7 hours via a plastic infusion set, and a 59% loss after infusion for one hour from a glass syringe through silastic tubing. Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.

Stability. A study of the stability of promazine diluted to a 0.1% infusion in sodium chloride 0.9% or glucose 5% found that solutions in glucose 5% remained stable for up to 6 days at 4 degrees, and at room temperature, provided they were stored in the dark.[1] However, with sodium chloride 0.9% as the diluent, deterioration of promazine was seen 24 hours after preparation, even when stored in the dark, and after 8 hours when exposed to light. Temperature had no effect on degradation rate.

1. Tebbett IR, *et al.* Stability of promazine as an intravenous infusion. *Pharm J* 1986; **237:** 172–4.

Uses and Administration

Promazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has relatively weak antipsychotic activity and is not generally used for the management of psychoses. It is mainly used for the short-term management of agitated or disturbed behaviour (p. 1030.2). It has also been given for the alleviation of nausea and vomiting (p. 1814.3). Promazine is given as the hydrochloride orally, buccally, intramuscularly, or by slow intravenous injection. Promazine has also been given orally as the embonate.

For the treatment of **agitated behaviour**, promazine hydrochloride is given in oral doses of 100 to 200 mg four times daily. It has also been given by intramuscular or slow intravenous injection in a dose of 50 mg.

A dose of 25 to 50 mg every 4 to 6 hours has been given buccally for the control of **nausea and vomiting**; it has also been given parenterally for this indication.

Promazine should be given in reduced dosage to elderly or debilitated patients; 25 mg orally of the hydrochloride initially, increasing, if necessary, to 50 mg four times daily has been suggested for the control of agitation and restlessness.

Hiccup. Promazine hydrochloride has been used in some countries for the treatment of intractable hiccup. A protocol for the management of intractable hiccups may be found under Chlorpromazine, p. 1046.3.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Pregnancy. An increased incidence of neonatal jaundice coincided with the increased use of promazine.[1] A decrease in the incidence of jaundice was noted 3 months after the total withdrawal of the drug from the hospital although restriction of its use during labour had no impact.

1. John E. Promazine and neonatal hyperbilirubinaemia. *Med J Aust* 1975; **2:** 342–4.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

The pharmacokinetics of promazine appear to be generally similar to those of chlorpromazine (p. 1053.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Prazine; Sinophenin; Sparine; ***Ital.***: Talofen; ***Rus.***: Propazine (Пропазин); ***S.Afr.***: Sparine†; ***Switz.***: Prazine; ***USA***: Prozine.

Pharmacopoeial Preparations

BP 2014: Promazine Injection; Promazine Tablets;

USP 36: Promazine Hydrochloride Injection; Promazine Hydrochloride Oral Solution; Promazine Hydrochloride Syrup; Promazine Hydrochloride Tablets.

Propionylpromazine

Dipropimazine; Propionilpromazina; Propiopromazine.

CAS — 3568-24-9.

UNII — Y1BCT3341I.

Profile

Propionylpromazine is a phenothiazine antipsychotic that has been used for sedation and premedication in veterinary medicine.

Prothipendyl Hydrochloride *(BANM, rINNM)*

D-206; Hidrocloruro de protipendilo; Phrenotropin; Prothipendyl, Chlorhydrate de; Prothipendyli Hydrochloridum; Protipendilo, hidrocloruro de; Протипендила Гидрохлорид.

NN-Dimethyl-3-(pyrido[3,2-*b*][1,4]benzothiazin-10-yl)propylamine hydrochloride monohydrate.

$C_{16}H_{19}N_3S$,HCl,H_2O=339.9

CAS — 303-69-5 (prothipendyl); 1225-65-6 (anhydrous prothipendyl hydrochloride).

ATC — N05AX07.

ATC Vet — QN05AX07.

UNII — 7610629RVH.

Profile

Prothipendyl is an azaphenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It is given as the hydrochloride in oral doses of 40 to 80 mg two to four times daily for the treatment of psychoses (p. 1030.2) and agitation. Prothipendyl hydrochloride may also be given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dominal; ***Belg.***: Dominal; ***Ger.***: Dominal.

Proxibarbal *(rINN)*

HH-184; Proksybarbal; Proxibarbalum; Proxibarbital; Проксибарбал.

5-Allyl-5-(2-hydroxypropyl)barbituric acid.

$C_{10}H_{14}N_2O_4$=226.2

CAS — 2537-29-3.

ATC — N05CA22.

ATC Vet — QN05CA22.

UNII — F97OMS297F.

Pharmacopoeias. In *Pol.*

Profile

Proxibarbal is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used as a sedative in the management of anxiety disorders. It has also been used in the treatment of headache. However, barbiturates are not considered appropriate in the management of these conditions. Proxibarbal has been associated with severe hypersensitivity-induced thrombocytopenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Axeen; ***Hung.***: Vasalgin†.

Quazepam *(BAN, USAN, rINN)*

Kvatsepaami; Kvazepam; Quazépam; Quazepamum; Sch-16134; Квазепам.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepine-2-thione.

$C_{17}H_{11}ClF_3N_2S$=386.8

CAS — 36735-22-5.

ATC — N05CD10.

ATC Vet — QN05CD10.

UNII — JF8V0828ZI.

Pharmacopoeias. In *US.*

USP 36: (Quazepam). Off-white to yellowish powder.

Uses and Administration

Quazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is given as a hypnotic in the short-term management of insomnia (p. 1033.2), in an initial oral dose of 15 mg at night; in elderly or debilitated patients and some other patients this can be reduced to 7.5 mg.

References.

1. Nishiyama T, *et al.* Effects of quazepam as a preoperative night hypnotic: comparison with brotizolam. *J Anesth* 2007; **21:** 7–12.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of quazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

However, a study in 4 women given a single 15-mg dose of quazepam found that only about 0.1% of the dose was excreted over 48 hours in breast milk, as quazepam and its 2 major metabolites.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Hilbert JM, *et al.* Excretion of quazepam into human breast milk. *J Clin Pharmacol* 1984; **24:** 457–62.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Quazepam is readily absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being reached in about 2 hours. It is metabolised extensively in the liver. The principal active metabolites are 2-oxoquazepam and *N*-desalkyl-2-oxoquazepam (*N*-desalkylflurazepam) which have elimination half-lives of about 39 and 73 hours, respectively, compared with a half-life of 39 hours for quazepam. Further hydroxylation occurs and quazepam is excreted in the urine and faeces mainly as conjugated metabolites.

Quazepam and its two active metabolites are more than 95% bound to plasma proteins. Quazepam and its metabolites are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Dormyl; ***Jpn***: Doral; ***Spain***: Quiedorm; ***USA***: Doral.

Pharmacopoeial Preparations

USP 36: Quazepam Tablets.

Quetiapine Fumarate

(BANM, USAN, pINNM)

Fumarato de quetiapina; ICI-204636; Quetiapina, fumarato de; Quétiapine, Fumarate de; Quetiapini Fumaras; ZD-5077; ZM-204636; Кветиапина Фумарат.

2-[2-(4-Dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy] ethanol fumarate (2:1) salt.

$(C_{21}H_{25}N_3O_2S)_2, C_4H_4O_4$=883.1

CAS — 111974-69-7 (quetiapine); 111974-72-2 (quetiapine fumarate).

ATC — N05AH04.

ATC Vet — QN05AH04.

UNII — 2S3PL1B6UJ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of quetiapine fumarate:

Baby heroin; Susie-Q; Quell.

Uses and Administration

Quetiapine fumarate is a dibenzothiazepine atypical antipsychotic. It is reported to have affinity for serotonin ($5\text{-}HT_2$), histamine (H_1), and adrenergic (α_1 and α_2) receptors as well as dopamine D_1 and D_2 receptors. Quetiapine is used in the treatment of schizophrenia (below) and of bipolar disorder (below). It is also used for the symptomatic relief of unipolar depression (below) in patients who are refractory to, or intolerant of, antidepressants.

Quetiapine is given orally as the fumarate although doses are expressed in terms of the base; 28.8 mg of quetiapine fumarate is equivalent to about 25 mg of quetiapine.

The usual initial daily dose in **schizophrenia** is the equivalent of 50 mg of the base on day one given in 2 divided doses. UK licensed product information recommends to give 100 mg on day two, 200 mg on day three, and 300 mg on day four; daily doses are given in 2 divided doses. The dosage is then adjusted, according to response and tolerance, to a usual range of 300 to 450 mg daily, although 150 mg daily may be adequate for some patients; the maximum recommended dose is 750 mg daily. US product information states that the usual initial daily dose is increased on days two and three in steps of 50 to 150 mg, as tolerated, to a target of 300 to 400 mg daily by day four. The daily dose on the first day is given in 2 divided doses, but may be given in 3 divided doses thereafter according to tolerance. The daily dosage may be further adjusted as necessary in steps of 50 to 100 mg at intervals of not less than 2 days to a usual range similar to that licensed in the UK.

In the treatment of *acute manic episodes* associated with **bipolar disorder**, the initial dose is 100 mg on day one, 200 mg on day two, 300 mg on day three, and 400 mg on day four; daily doses are given in 2 divided doses. Further dose increases to 800 mg daily by day six should be made in steps of no greater than 200 mg daily. The dose may then be adjusted according to response and tolerance to a usual range of 400 to 800 mg daily, although, in some patients, 200 mg daily may be adequate. Quetiapine is also used for the *depressive phase* of bipolar disorder. The initial dose is 50 mg once daily at bedtime increased to 100 mg on day two, 200 mg on day three, and 300 mg on day four. The dose may be further increased to 400 mg on day five and 600 mg on day eight, if necessary. For the *maintenance treatment* of bipolar disorder, patients should be continued on the same dose on which they were stabilised.

A modified-release preparation of quetiapine is available in some countries for once-daily dosing in the treatment of schizophrenia and of bipolar disorder.

The modified-release preparation is also used as an adjunct to antidepressants in the management of **unipolar depression**. The initial dose is 50 mg once daily on days one and two, increased to the usual dose of 150 mg once daily on day three; thereafter, the dose may be increased to a maximum of 300 mg daily as necessary.

Quetiapine should be given in reduced doses to the elderly; a recommended starting dose of the immediate-release tablets is 25 mg daily, which may be increased every day in increments of 25 to 50 mg according to response. Similarly, elderly patients should be started on the lowest available dose of the modified-release preparation and titrated at a slower rate. The effective dose range is likely to be lower than in younger adults. Reduced doses are also recommended in patients with hepatic impairment, see Administration in Hepatic Impairment, below.

For details of uses and associated doses in children and adolescents, see Administration in Children, below.

Administration in children. In the USA, quetiapine is licensed for the treatment of schizophrenia in adolescents aged 13 to 17 years and, as monotherapy, for the treatment of acute manic or mixed episodes associated with bipolar disorder in those aged 10 to 17 years. For both indications, the recommended initial oral dose is the equivalent of 50 mg of the base on day one, followed by 100 mg on day two, 200 mg on day three, 300 mg on day four, and 400 mg on day five; daily doses are usually given in 2 divided doses, or if necessary in 3 divided doses according to response and tolerance. The dosage is then adjusted in steps of no greater than 100 mg, according to response and tolerance, to a usual range of 400 to 800 mg daily for schizophrenia, or 400 to 600 mg daily for bipolar disorder.

Although unlicensed in the UK for use in children and adolescents aged under 18 years, the *BNFC* suggests that quetiapine may be given, under specialist supervision, to those aged 12 years and over. For the treatment of schizophrenia, usual oral adult doses (see Use and Administration, above) may be given; a modified-release preparation may also be used for once-daily dosing. For the treatment of acute manic episodes associated with bipolar disorder, doses are similar to those licensed in the USA for this indication (see above).

Administration in hepatic impairment. Quetiapine should be given in reduced doses to patients with hepatic impairment; a recommended initial oral dose of the immediate-release tablets is 25 mg daily, increased in steps of 25 to 50 mg daily according to response. Similarly, those with hepatic impairment should be started on the lowest available dose of the modified-release preparation.

Bipolar disorder. Quetiapine is of benefit for the treatment of mania in patients with bipolar disorder (p. 397.2) and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of quetiapine-induced mania (see p. 1102.2). Quetiapine is also used in the depressive phase of bipolar disorder, and for other forms of resistant depression (below).

References.

1. Vieta E, *et al.* Quetiapine in the treatment of rapid cycling bipolar disorder. *Bipolar Disord* 2002; **4:** 335–40.
2. Delbello MP, *et al.* A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1216–23.
3. Yatham LN, *et al.* Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol* 2004; **24:** 599–606. Correction. *ibid.* 2005; **25:** 103.
4. Bowden CL, *et al.* A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 2005; **66:** 111–21.
5. Dando TM, Keating GM. Quetiapine: a review of its use in acute mania and depression associated with bipolar disorder. *Drugs* 2005; **65:** 2533–51.
6. Calabrese JR, *et al.* BOLDER Study Group. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 2005; **162:** 1351–60.
7. Thase ME, *et al.* BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 2006; **26:** 600–9. Correction. *ibid.* 2007; **27:** 51.
8. Pini S, *et al.* The role of quetiapine in the treatment of bipolar disorder. *Expert Opin Pharmacother* 2006; **7:** 929–40.
9. Khouzam HR, Singh F. Bipolar disorder: historic perspective, current pharmacologic treatment options and a review of quetiapine. *Expert Rev Neurother* 2006; **6:** 131–44.
10. Keating GM, Robinson DM. Quetiapine: a review of its use in the treatment of bipolar depression. *Drugs* 2007; **67:** 1077–94.
11. Brahm NC, *et al.* Quetiapine for acute mania in bipolar disorder. *Am J Health-Syst Pharm* 2007; **64:** 1045–53.
12. Weisler RH, *et al.* Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. *J Clin Psychiatry* 2008; **69:** 769–82.
13. DelBello MP, *et al.* A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord* 2009; **11:** 483–93.
14. Young AH, *et al.* EMBOLDEN I (Trial 001) Investigators. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 2010; **71:** 150–62.
15. McElroy SL, *et al.* EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 2010; **71:** 163–74.

Depression. A modified-release preparation of quetiapine is used in some countries for the management of resistant depression (p. 398.1).

References.

1. Cutler AJ, *et al.* Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. *J Clin Psychiatry* 2009; **70:** 526–39. Correction. *ibid.*; 1729.
2. Bauer M, *et al.* Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *J Clin Psychiatry* 2009; **70:** 540–9.
3. Weisler R, *et al.* Moonstone Study Group. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. *CNS Spectr* 2009; **14:** 299–313.

Parkinsonism. Quetiapine has been tried as an antipsychotic[1-4] in patients with parkinsonism (p. 889.1).

1. Fernandez HH, *et al.* Long-term outcome of quetiapine use for psychosis among Parkinsonian patients. *Mov Disord* 2003; **18:** 510–14.
2. Juncos JL, *et al.* Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. *Mov Disord* 2004; **19:** 29–35.
3. Morgante L, *et al.* Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol* 2004; **27:** 153–6. Correction. *ibid.*; 256.
4. Kurlan R, *et al.* Alzheimer's Disease Cooperative Study Group. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* 2007; **68:** 1356–63.

Schizophrenia. A systematic review[1] noted that, although quetiapine is effective for the treatment of schizophrenia (p. 1031.3), it appeared comparable with classical antipsychotics and risperidone. The incidence of extrapyramidal effects was lower with quetiapine therapy but the risk of dry mouth and somnolence was higher. Quetiapine was not found to benefit negative symptoms.

1. Srisurapanont M, *et al.* Quetiapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 30/05/05).

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) haloperidol or pimozide are commonly used but atypical antipsychotics, including quetiapine, are increasingly being tried.[1-3]

1. Mukaddes NM, Abali O. Quetiapine treatment of children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 2003; **13:** 295–9.
2. Little AE, *et al.* Quetiapine in the treatment of tic disorder. *Ann Pharmacother* 2006; **40:** 1472.
3. de Jonge JL, *et al.* Quetiapine in patients with Tourette's disorder: an open-label, flexible-dose study. *J Clin Psychiatry* 2007; **68:** 1148–50.

Adverse Effects, Treatment, and Precautions

Although quetiapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Quetiapine has been associated with a low incidence of extrapyramidal symptoms but tardive dyskinesia may occur after long-term treatment. Rises in prolactin concentrations may be less than with chlorpromazine.

The most frequent adverse effects with quetiapine are somnolence, headache, and dizziness. Other common adverse effects include weight gain, particularly during early treatment, and rises in plasma-triglyceride and total cholesterol concentrations. Mild asthenia, anxiety, irritability, fever, rhinitis, peripheral oedema, increased appetite, constipation, dyspepsia, dry mouth, and raised liver enzyme values are also relatively common. Orthostatic hypotension associated with dizziness, tachycardia, and syncope has been reported, particularly during initial dose-titration. Prolongation of QT interval is rarely significant with quetiapine. Venous thromboembolism has been reported rarely. Hyperglycaemia and exacerbation of pre-existing diabetes have been reported rarely. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of developing, diabetes. Neuroleptic malignant syndrome is rare with quetiapine. Leucopenia, neutropenia, thrombocytopenia, and eosinophilia have also been reported, as have reduced plasma-thyroid hormone concentrations. There have been rare reports of seizures, hypersensitivity reactions including angioedema, and priapism.

Asymptomatic changes in the lens of the eye have occurred in patients during long-term treatment with quetiapine; cataracts have developed in *dogs* during chronic dosing studies. In the USA, it is recommended that patients should have an eye examination to detect cataract formation when starting therapy with quetiapine and every 6 months during treatment.

Adverse effects such as increased appetite, extrapyramidal symptoms, and rises in prolactin concentrations may occur at a higher frequency in children and adolescents than in adults. Increases in blood pressure have been reported in children and adolescents, and blood pressure should be measured at the beginning of, and periodically during, treatment with quetiapine.

Quetiapine should be used with caution in patients with hepatic or renal impairment, with cardiovascular disease or other conditions predisposing to hypotension, with cerebrovascular disease, or with a history of seizures or conditions that lower the seizure threshold.

When quetiapine is used for the depressive phase in bipolar disorder or for unipolar depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see Bipolar Disorder, p. 397.2 and Depression, p. 398.1.

Quetiapine may affect the performance of skilled tasks including driving.

Gradual withdrawal of quetiapine is recommended because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses, with abrupt cessation.

Abuse. References to the abuse of quetiapine.

1. Pierre JM, *et al.* Intranasal quetiapine abuse. *Am J Psychiatry* 2004; **161:** 1718.
2. Hussain MZ, *et al.* Intravenous quetiapine abuse. *Am J Psychiatry* 2005; **162:** 1755–6.
3. Waters BM, Joshi KG. Intravenous quetiapine-cocaine use ("Q-ball"). *Am J Psychiatry* 2007; **164:** 173–4.
4. Morin AK. Possible intranasal quetiapine misuse. *Am J Health-Syst Pharm* 2007; **64:** 723–5.
5. Reeves RR, Brister JC. Additional evidence of the abuse potential of quetiapine. *South Med J* 2007; **100:** 834–6.
6. Paparrigopoulos T, *et al.* Quetiapine: another drug with potential for misuse? A case report. *J Clin Psychiatry* 2008; **69:** 162–3.
7. Murphy D, *et al.* Addictive potential of quetiapine. *Am J Psychiatry* 2008; **165:** 918.
8. Tcheremissine OV. Is quetiapine a drug of abuse? Reexamining the issue of addiction. *Expert Opin Drug Safety* 2008; **7:** 739–48.

Breast feeding. In a case report[1] of a mother receiving oral quetiapine 200 mg daily, the maximum concentration of the drug in breast milk an hour after the dose was reported to be 62 micrograms/litre; the mean concentration over 6 hours was 13 micrograms/litre. The authors concluded that the breast-fed infant would ingest, at maximum, the daily equivalent of 0.43% of the weight-adjusted maternal dose. Follow-up at 4.5 months reported no adverse effects in the infant, who had been breast fed from 8 weeks of age.

Licensed product information recommends that patients receiving quetiapine should not breast feed.

1. Lee A, *et al.* Excretion of quetiapine in breast milk. *Am J Psychiatry* 2004; **161:** 1715–16.

Effects on the blood. There have been reports of leucopenia,[1] neutropenia,[2] and pancytopenia[3] associated with quetiapine therapy; all 3 patients improved when the drug was stopped. Thrombotic thrombocytopenic purpura has also been reported in a patient who received quetiapine on 2 separate occasions 2 years apart.[4] From December 1997 to October 2006, Health Canada[5] had received 11 reports of thrombocytopenia associated with quetiapine, 6 of which were associated with quetiapine alone. In one of these 6 cases, thrombocytopenia recurred 3 months after restarting quetiapine, which had stopped for 1 month.

1. Clark N, *et al.* Quetiapine and leukopenia. *Am J Psychiatry* 2001; **158:** 817–18.
2. Croarkin P, Rayner T. Acute neutropenia in a patient treated with quetiapine. *Psychosomatics* 2001; **42:** 368.
3. Iraqi A. A case report of pancytopenia with quetiapine use. *Am J Geriatr Psychiatry* 2003; **11:** 694.
4. Huynh M, *et al.* Thrombotic thrombocytopenic purpura associated with quetiapine. *Ann Pharmacother* 2005; **39:** 1346–8.
5. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; **17** (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2_e.pdf (accessed 09/04/08)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.

1. Brecher M, *et al.* Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry* 2007; **68:** 597–603.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including quetiapine, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Further references for such effects associated with quetiapine use are given below.

1. Koller EA, *et al.* A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. *J Clin Psychiatry* 2004; **65:** 857–63.
2. Takahashi M, *et al.* Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. *Pharmacopsychiatry* 2005; **38:** 183–4.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

Effects on the pancreas. From December 1997 to October 2006, Health Canada[1] had received 9 reports of pancreatitis associated with quetiapine, 5 of which were associated with quetiapine alone. One patient was reported to have developed severe haemorrhagic pancreatitis, and another, necrotising pancreatitis. One report described pancreatitis occurring on two separate occasions in the patient.

1. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; **17** (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 26/07/10)

Effects on the respiratory system. Hyperventilation and respiratory alkalosis have been reported with quetiapine use.[1] Acute respiratory failure developed[2] in a 92-year-old woman with a history of chronic obstructive pulmonary disease who was given a single 50-mg dose of quetiapine.

1. Shelton PS, *et al.* Hyperventilation associated with quetiapine. *Ann Pharmacother* 2000; **34:** 335–7.
2. Jabeen S, *et al.* Acute respiratory failure with a single dose of quetiapine fumarate. *Ann Pharmacother* 2006; **40:** 559–62.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Mania. Although it is used in the treatment of bipolar disorder, quetiapine has been associated with mania. In one report, a 26-year-old man with schizophrenia developed manic symptoms after starting treatment with quetiapine; the symptoms resolved when quetiapine was withdrawn.[1]

1. Lykouras L, *et al.* Manic symptoms associated with quetiapine treatment. *Eur Neuropsychopharmacol* 2003; **13:** 135–6.

Overdosage. Hypotension, tachycardia, and somnolence were the main clinical events seen in a patient who had taken an overdose of 3 g of quetiapine.[1] Tachycardia of an unexpectedly long duration was also noted. Management was symptomatic, including maintenance of fluids. Asymptomatic prolongation of the QT interval was seen in another patient who had taken a 2-g overdose of quetiapine.[2] Her treatment regimen also included risperidone, and the authors warned that considerable QT interval prolongation may occur when patients overdose on quetiapine while taking therapeutic doses of risperidone.

A subsequent report[3] has described a case series of 18 patients who took from 500 mg to 24 g of quetiapine either alone (6 patients) or with other drugs (12). Quetiapine overdosage was mainly associated with CNS and respiratory depression and sinus tachycardia. Four of the 18 patients required mechanical ventilation but no deaths occurred. The corrected QT interval, but not the QT interval, was prolonged, but apart from sinus tachycardia no patient had a dysrhythmia. Seizures occurred in 2 patients and delirium in 3. The patient who took 24 g of quetiapine was found to have had a peak blood concentration of 20.48 micrograms/mL. She had presented 1.5 hours after ingestion and was intubated and treated with gastric lavage followed by activated charcoal. About 2.5 hours later she had a generalised tonic-clonic seizure. The patient was discharged after 40 hours without sequelae. Another analysis[4] considered 14 cases of overdose, the amounts varying from 1.2 to 18 g; there appeared to be no correlation between the amount taken and the serum concentration, nor was severity of intoxication necessarily correlated with greater intake. Toxicity was generally mild, with tachycardia and somnolence as the main presenting symptoms; there were no fatalities.

1. Beelen AP, *et al.* Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. *Hum Exp Toxicol* 2001; **20:** 215–19.
2. Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. *Clin Pharmacol Ther* 2000; **68:** 92–7.
3. Balit CR, *et al.* Quetiapine poisoning: a case series. *Ann Emerg Med* 2003; **42:** 751–8.
4. Hunfeld NG, *et al.* Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. *Ther Drug Monit* 2006; **28:** 185–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quetiapine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics, including quetiapine, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by quetiapine. Quetiapine should be used with caution in patients also receiving antihypertensives or drugs that prolong the QT interval. Quetiapine may antagonise the actions of dopaminergics such as levodopa.

CYP3A4 is the main isoenzyme responsible for cytochrome P450-mediated metabolism of quetiapine and it should be used with caution, if at all, with potent inhibitors of CYP3A4 such as erythromycin, fluconazole, itraconazole, and ketoconazole; lower doses of quetiapine are recommended when given with such drugs. Conversely, enzyme inducers such as carbamazepine and phenytoin may decrease the plasma concentrations of quetiapine, and higher doses of quetiapine may be necessary. Thioridazine has also been reported to increase the clearance of quetiapine.

Antibacterials. In a study involving 19 Chinese patients with schizophrenia taking quetiapine 200 mg twice daily, adding *erythromycin* 500 mg three times daily increased the peak plasma concentration, area under the concentration-time curve, and terminal elimination half-life of quetiapine by 68, 129, and 92%, respectively. Reductions in plasma concentrations of the metabolites of quetiapine suggested that erythromycin had probably inhibited quetiapine's metabolism by the cytochrome P450 isoenzyme CYP3A4. Modification of dosage was recommended in this patient group taking these two drugs together.[1]

1. Li K-Y, *et al.* Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005; **60:** 791–5.

Antipsychotics. For a report of asymptomatic QT prolongation associated with quetiapine in a patient also receiving *risperidone*, see under Overdosage, above.

Pharmacokinetics

Quetiapine is well absorbed after oral doses and widely distributed throughout the body. Peak plasma concentrations occur in about 1.5 hours. It is about 83% bound to plasma proteins. Quetiapine is extensively metabolised in the liver by sulfoxidation mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and by oxidation. It is excreted mainly as inactive metabolites with about 73% of a dose appearing in the urine and about 20% in the faeces. The elimination half-life has been reported to be about 6 to 7 hours.

It is distributed into breast milk.

References.

1. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 2001; **40:** 509–22.
2. Jaskiw GE, *et al.* Pharmacokinetics of quetiapine in elderly patients with selected psychotic disorders. *Clin Pharmacokinet* 2004; **43:** 1025–35. Correction. *ibid.*; 1178.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atipina; Biatrix; Dominium; Etiasel; Inquetia; Kemoter; Quepaz; Quetiaros; Quetiazic; Rostrum; Seroquel; Vesparax; ***Austral.***: Sequase; Seronia; Seroquel; Syquet; ***Austria***: Quetialan; Seroquel; ***Belg.***: Seroquel; ***Braz.***: Kitapen; Neotiapim; Querok; Queropax; Quetipin; Quetros; Seroquel; ***Canad.***: Seroquel; ***Chile***: Asicot; Gofyl; Norsic; Quetiazic; Quetidin; Qutipin; Seroquel; ***China***: QiWei (启维); Seroquel (思瑞康); Shu Si (舒思); ***Cz.***: Derin; Equeta; Geldoren; Hedonin; Ketilept; Kventiax; Nantarid; Quepita†; Quepsan; Questax; Quetifi†; Quetin†; Quetrop; Resirentin; Seratio; Seroquel; Stadaquel; Taiqutabs; ***Denm.***: Alzen; Generiapin†; Lobarr†; Loplive†; Loquen†; Mylaquel†; Nantarid; Quelan; Quemed; Quemyl†; Quetastad; Queteper; Quetilis; Quetiratio†; Seresano; Seroquel; Setinin; Stadaquel; Symquel; Tiaquin; ***Fin.***: Ketipinor; Seroquel; ***Fr.***: Xeroquel; ***Ger.***: Seroquel; ***Gr.***: Quepin; Seroquel; ***Hong Kong***: Seroquel; ***Hung.***: Equepin; Ketilept; Kventiax; Lantiapin†; Nantarid; Resirentin; Seroquel; Setinin; ***India***: Quel; Seroquin; Socalm; ***Indon.***: Seroquel; ***Irl.***: Notiabolfen; Quelor†; Quetex; Seropia; Seroquel; Seroquin†; Setinin; Tevaquel; ***Israel***: Seroquel; ***Ital.***: Queteper; Seroquel; ***Jpn***: Seroquel; ***Malaysia***: Ketipinor; Seroquel; ***Mex.***: Seroquel; ***Neth.***: Derin†; Gentiapin; Kefrenex†; Kwetaplex; Quentapil; Quetex; Quetiafair; Quetrop; Seroquel; ***Norw.***: Seroquel; ***NZ***: Quetapel; Seroquel; ***Philipp.***: Ketilept; Q-win; Seroquel; ***Pol.***: Bonogren; Etiagen; Geldoren; Gentiapin; Kefrenex; Ketilept; Ketipinor; Ketrel; Kventiax; Kwetaplex; Kwetinor; Loquen; Nantarid; Poetra; Quentapil; Quetiser; Seroquel; Setinin; Symquel; Vorta; ***Port.***: Alzen; Ketiron†; Neuroracet†; Pinapaz†; Raikar†; Seroquel; Viketo†; ***Rus.***: Ketilept (Кетилепт); Kventiax (Квентиакс); Lacvel (Лаквель); Nantarid (Нантарид); Seroquel (Сероквель); ***S. Afr.***: Dopaquel; Quetoser; Serez; Seroquel; Truvalin; ***Singapore***: Ketipinor; Seroquel; ***Spain***: Ilufren; Psicotric; Qudix; Quentiax; Quetiamylan; Rocoz; Seroquel; ***Swed.***: Seroquel; ***Switz.***: Sequase; Seroquel; ***Thai.***: Neutapin; Quantia; Seroquel; ***Turk.***: Cedrina; Gyrex; Ketya; Piquet; Serex; Seroquel; ***UK***: Seotiapim; Seroquel; Sondate; ***Ukr.***: Ketilept (Кетилепт); Quetiron (Кветирон); Seroquel (Сероквель); ***USA***: Seroquel; ***Venez.***: Seroquel.

Raclopride *(BAN, rINN)*

A-40664 (raclopride tartrate); FLA-870; Racloprida; Raclopridium; Raclopridum; Rakloprid; Raklopridi; Раклоприд.

(*S*)-3,5-Dichloro-*N*-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide.

$C_{15}H_{20}Cl_2N_2O_3$=347.2

CAS — 84225-95-6 (raclopride); 98185-20-7 (raclopride tartrate).

UNII — 430K3SOZ7G.

Profile

Raclopride is a substituted benzamide related to sulpiride (p. 1107.3). It has been investigated for the treatment of psychoses. Since it binds selectively and with high affinity to D_2 dopaminergic receptors, raclopride labelled with carbon-11 has been tried as a tracer in computerised tomographic studies of neurological disorders associated with dysfunction of brain D_2 dopaminergic receptors.

Ramelteon *(BAN, USAN, rINN)*

Ramelteón; Ramelteon; Ramelteonum; TAK-375; Рамельтеон.

(-)-*N*-{2-[(8*S*)-1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl]ethyl}propanamide.

$C_{16}H_{21}NO_2$=259.3

CAS — 196597-26-9.

ATC — N05CH02.

ATC Vet — QN05CH02.

UNII — 901AS54I69.

Profile

Ramelteon is a melatonin receptor agonist used as a hypnotic in the management of insomnia (p. 1033.2), particularly in patients who have difficulty falling asleep. The usual oral dose is 8 mg taken within 30 minutes of bedtime; it should not be taken with, or immediately after, a high-fat meal.

Ramelteon is not recommended for patients with severe hepatic impairment; it should be used with caution in those with moderate impairment.

Ramelteon is metabolised mainly via the cytochrome P450 isoenzyme CYP1A2 and therefore it should not be used with fluvoxamine, a potent inhibitor of this isoenzyme; it should also be used with caution in patients taking other drugs that inhibit this isoenzyme.

Severe anaphylactic or anaphylactoid reactions have been reported rarely. Hallucinations and behavioural changes such as bizarre behaviour, agitation, and mania have also been reported; amnesia and anxiety may occur unpredictably. Complex sleep-related behaviours, such as eating or driving while asleep, have been associated with ramelteon therapy; the risk of such behaviour is increased when taken with alcohol or other CNS depressants.

Reviews.

1. Reynoldson JN, *et al.* Ramelteon: a novel approach in the treatment of insomnia. *Ann Pharmacother* 2008; **42:** 1262–70.
2. Simpson D, Curran MP. Ramelteon: a review of its use in insomnia. *Drugs* 2008; **68:** 1901–19.
3. Pandi-Perumal SR, *et al.* Ramelteon: a review of its therapeutic potential in sleep disorders. *Adv Therapy* 2009; **26:** 613–26.
4. Miyamoto M. Pharmacology of ramelteon, a selective MT_1/MT_2 receptor agonist: a novel therapeutic drug for sleep disorders. *CNS Neurosci Ther* 2009; **15:** 32–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Rozerem; ***Jpn***: Rozerem; ***Philipp.***: Rozerem; ***USA***: Rozerem.

Rilmazafone Hydrochloride *(rINNM)*

Hidrocloruro de rilmazafona; Rilmazafone, Chlorhydrate de; Rilmazafoni Hydrochloridum; 450191-S; Рильмазафона Гидрохлорид.

5-[(2-Aminoacetamido)methyl]-1-[4-chloro-2-(*o*-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide hydrochloride dihydrate.

$C_{21}H_{20}Cl_2N_6O_3$,HCl,$2H_2O$=547.8

CAS — 99593-25-6 (rilmazafone); 85815-37-8 (anhydrous rilmazafone hydrochloride).

UNII — 25T258X8BV.

Profile

Rilmazafone hydrochloride is a hypnotic and sedative used in the short-term treatment of insomnia (p. 1033.2) in usual oral doses of 1 to 2 mg at bedtime; it is also used in similar doses as a premedicant (see Anaesthesia, p. 1899.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Rhythmy.

Risperidone *(BAN, USAN, rINN)*

R-64766; Risperidon; Risperidona; Risperidonas; Rispéridone; Risperidoni; Risperidonum; Riszperidon; Rysperydon; Рисперидон.

3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl}-6,7,8,9-tetrahydro-2-methylpyrido[1,2-*a*]pyrimidin-4-one.

$C_{23}H_{27}FN_4O_2$=410.5

CAS — 106266-06-2.

ATC — N05AX08.

ATC Vet — QN05AX08.

UNII — L6UH7ZF8HC.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Risperidone). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute acid solutions. Protect from light.

USP 36: (Risperidone). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in dichloromethane.

Uses and Administration

Risperidone is a benzisoxazole atypical antipsychotic, reported to be an antagonist at dopamine D_2, serotonin ($5\text{-}HT_2$), adrenergic (α_1 and α_2), and histamine (H_1) receptors. It is given orally for the treatment of schizophrenia (p. 1104.2) and in the short-term treatment of acute manic or mixed episodes associated with bipolar disorder (p. 1104.1). It is also given orally for the short-term (up to 6 weeks) treatment of persistent aggression (see Disturbed Behaviour, p. 1104.1) in patients with moderate to severe Alzheimer's disease unresponsive to non-pharmacological therapies and when there is risk of harm to self or others. Risperidone may be given by deep intramuscular injection for maintenance therapy in patients with schizophrenia tolerant to oral antipsychotics, or with bipolar disorder.

For **schizophrenia**, the usual initial oral dose of risperidone is 2 mg daily; this may be increased to 4 mg daily on the second day, and subsequently adjusted as required in steps of 1 or 2 mg according to tolerance, at intervals of not less than 24 hours. Most patients benefit from doses of 4 to 6 mg daily. Risperidone may be given once daily or in 2 divided doses. Extrapyramidal symptoms may be more likely with doses above 10 mg daily; US licensed product information does not recommend daily doses above 6 mg if divided into 2 doses, although higher doses are permitted if given as a single dose. The maximum recommended dose is 16 mg daily.

An initial oral dose of 500 micrograms twice daily slowly increased in steps of 500 micrograms twice daily, if necessary, to a dose of 1 to 2 mg twice daily is recommended for elderly patients with schizophrenia.

The long-acting formulation of risperidone should be given by deep intramuscular injection every 2 weeks. Patients with no history of risperidone use should be given risperidone orally for several days to assess tolerability. Treatment may then be started as follows:

- patients not stabilised on oral risperidone: 25 mg every 2 weeks
- patients stabilised on oral risperidone for at least 2 weeks in doses of 4 mg daily or less: 25 mg every 2 weeks
- patients stabilised on oral risperidone for at least 2 weeks in doses above 4 mg daily: 37.5 mg every 2 weeks

Oral risperidone should be continued for the first 3 weeks after the first injection.

Dose increases of 12.5 mg may be considered at least 4 weeks after the previous adjustment up to a maximum of 50 mg every 2 weeks; the clinical effects of a dose adjustment may not be seen for at least 3 weeks after the change.

For the treatment of *mania* in **bipolar disorder**, a recommended initial oral dose is 2 to 3 mg once daily. Dosage adjustments of 1 mg daily may be made at intervals of not less than 24 hours up to a total of 6 mg daily. The initial dosage regimen in elderly patients should be reduced as for schizophrenia (see above). In the USA, the long-acting injection may be given by deep intramuscular injection for *maintenance therapy* in a dose of 25 mg every 2 weeks; some patients may benefit from a higher dose of 37.5 or 50 mg.

For the treatment of **persistent aggression** in Alzheimer's disease, the usual initial oral dose is 250 micrograms twice daily. Dosage adjustments of 250 micrograms twice daily may be made no more frequently than every other day if required. The optimum dose for most patients is 500 micrograms twice daily although some may need up to 1 mg twice daily.

Reduced doses are recommended in patients with hepatic or renal impairment, see Administration in Hepatic or Renal Impairment, p. 1104.1.

For details of uses and associated doses in children and adolescents, see Administration in Children and Disturbed Behaviour, below and p. 1104.1, respectively.

Action. Risperidone is described as an atypical antipsychotic; although it has a lower propensity to produce parkinsonism, dystonias and akathisias have been reported.[1] (See also Extrapyramidal Disorders, p. 1105.2.) The traditional hypothesis is that antipsychotics work through inhibition of dopamine D_2 receptors and that extrapyramidal adverse effects result from blockade of D_2 receptors in the striatum (see p. 1046.1). Like clozapine, risperidone has a high affinity for $5\text{-}HT_2$ receptors and, like haloperidol, it has a high affinity for dopamine D_2 receptors. Risperidone also binds to alpha-adrenergic and histamine H_1 sites. It is unclear whether risperidone's antipsychotic effect is due to activity at dopamine D_2 receptors or at another site. It has been suggested[1] that other potent effects of risperidone may be counterbalancing the D_2 activity to produce its atypicality.

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; **164:** 141–8.

Administration in children. In the USA, risperidone is licensed for the treatment of schizophrenia in adolescents aged 13 to 17 years, acute manic or mixed episodes associated with bipolar disorder in children and adolescents aged 10 to 17 years, and irritability associated with autistic disorder in those aged 5 to 17 years. In the UK, risperidone is licensed for the short-term (up to 6 weeks) treatment of persistent aggression in conduct disorder in children and adolescents aged 5 to 18 years with subaverage intellectual functioning or mental retardation; specialist supervision is recommended.

For **schizophrenia** or **mania**, an initial oral dose of 500 micrograms is given once daily in the morning or in the evening. This may be increased in steps of 0.5 or 1 mg according to tolerance, at intervals of not less than 24 hours, to a dose of 3 mg daily for schizophrenia or 2.5 mg daily for mania. The maximum recommended dose for both indications is 6 mg daily. The total daily dose may be given in 2 divided doses to those who have persistent somnolence. Although unlicensed in the UK, the *BNFC* suggests that it may be used in those aged 12 years and over for the oral treatment of acute and chronic psychoses in doses similar to those used in the treatment of schizophrenia in adults (see Uses and Administration, above); for the short-term treatment of acute manic episodes associated with bipolar disorder, the *BNFC* recommends doses similar to those licensed for this indication in the USA (see above).

For the treatment of **irritability associated with autistic disorder**, the following oral doses are given once daily or in 2 divided doses according to body-weight:

- 15 to < 20 kg: the usual initial daily dose is 250 micrograms; this may be increased to 500 micrograms daily after at least 4 days and subsequently adjusted as required in steps of 250 micrograms, generally at intervals of no less than 2 weeks
- 20 kg and over: the usual initial daily dose is 500 micrograms; this may be increased to 1 mg daily after at least 4 days and subsequently adjusted as required in steps of 500 micrograms, generally at intervals of no less than 2 weeks
- The maximum recommended dose, regardless of body-weight, is 3 mg daily
- For those who have persistent somnolence, the total daily dose may be given as a single dose at bedtime, or in 2 divided doses, or in a reduced dose

The *BNFC* suggests that risperidone may be used in children over 5 years old for the short-term treatment of severe aggression in autism. Doses are similar to those licensed for autistic disorders in the USA (see above) although the maximum daily dose may differ, those recommended by the *BNFC* are: 1 mg in those weighing 15 to 20 kg, 2.5 mg in those under 45 kg, and 3 mg in those over 45 kg.

For further details on the use of risperidone in children with autism see Disturbed Behaviour, p. 1104.1.

In the treatment of **persistent aggression in conduct disorder**, the following oral doses are given once daily according to body-weight:

- under 50 kg: the usual initial dose is 250 micrograms daily, subsequently adjusted in steps of 250 micrograms no more frequently than every other day if required; the optimum dose for most patients is 500 micrograms daily although some may benefit from 250 micrograms daily whilst others may need 750 micrograms daily
- 50 kg and over: the usual initial dose is 500 micrograms daily, subsequently adjusted in steps of 500 micrograms no more frequently than every other day if required; the optimum dose for most patients is 1 mg daily although some may benefit from 500 micrograms daily whilst others may need 1.5 mg daily

Administration in hepatic or renal impairment. UK licensed product information recommends that initial and consecutive oral doses of risperidone should be halved in patients with hepatic or renal impairment irrespective of the indication. In the USA, licensed information recommends, for those with severe impairment, an initial oral dose of 500 micrograms twice daily, slowly increased thereafter in steps of 500 micrograms (or less) twice daily, if necessary; above doses of 1.5 mg twice daily, increases should be made at intervals of at least 1 week.

Patients who tolerate an oral dose of risperidone of at least 2 mg daily may be switched to the long-acting formulation of risperidone; a dose of 25 mg by deep intramuscular injection every 2 weeks is recommended. Alternatively, an initial dose of 12.5 mg by deep intramuscular injection may be given.

AIDS. Risperidone was used successfully to control HIV- or AIDS-related psychosis in 21 patients, some of whom also had manic symptoms.[1] No extrapyramidal symptoms were reported during treatment. However, for reports suggesting that risperidone can induce or exacerbate manic symptoms in patients with schizoaffective disorders, see under Mania in Adverse Effects, p. 1105.3. For an interaction between risperidone and antiretroviral therapy in a patient with AIDS, see under Interactions, p. 1106.1.

1. Singh AN, *et al.* Treatment of HIV-related psychotic disorders with risperidone: a series of 21 cases. *J Psychosom Res* 1997; **42:** 489–93.

Anxiety disorders. Although there have been anecdotal reports[1,2] of improvement after the addition of risperidone to treatment in patients with obsessive-compulsive disorder refractory to conventional treatment, there has also been a report[3] of a patient whose obsessive-compulsive behaviour recurred when he was treated with risperidone for tardive dyskinesia.

1. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry* 1995; **56:** 423–9.
2. McDougle CJ, *et al.* Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. *J Clin Psychiatry* 1995; **56:** 526–8.
3. Remington G, Adams M. Risperidone and obsessive-compulsive symptoms. *J Clin Psychopharmacol* 1994; **14:** 358–9.

Bipolar disorder. Risperidone is of benefit for the treatment of mania, including in patients with bipolar disorder (p. 397.2), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of risperidone-induced mania (see p. 1105.3).

References.

1. Segal J, *et al.* Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clin Neuropharmacol* 1998; **21:** 176–80.
2. Sachs GS, *et al.* Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* 2002; **159:** 1146–54.
3. Yatham LN, *et al.* Mood stabilisers plus risperidone or placebo in the treatment of acute mania: international, double-blind, randomised controlled trial. *Br J Psychiatry* 2003; **182:** 141–7. Correction. *ibid.*; 369.
4. Hirschfeld RM, *et al.* Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry* 2004; **161:** 1057–65.
5. Nguyen LN, Guthrie SK. Risperidone treatment of bipolar mania. *Ann Pharmacother* 2006; **40:** 674–82.
6. Rendell JM, *et al.* Risperidone alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
7. Deeks ED. Risperidone long-acting injection: in bipolar I disorder. *Drugs* 2010; **70:** 1001–12.

Disturbed behaviour. Risperidone has been tried[1-4] in the management of behavioural disturbances in **elderly patients with dementia** (p. 1030.2); however, such use has been associated with an increased risk of death (see the Elderly, under Adverse Effects, p. 1105.1). Furthermore, despite anecdotal reports[5] of efficacy in patients with Lewy-body dementia, other reports[6] suggest that these patients are likely to be just as sensitive to risperidone as to classical antipsychotics (see the Elderly in Precautions for Chlorpromazine, p. 1051.1). Nevertheless, risperidone is licensed in the UK for the short-term treatment of persistent aggression in patients with moderate to severe Alzheimer's disease unresponsive to non-pharmacological therapies and when there is risk of harm to self or others; for details of doses see Uses and Administration, p. 1103.2.

There is evidence[7-12] that risperidone may be effective in reducing behavioural disturbances in **children with autism** (see Disturbed Behaviour, p. 1030.2), but it appears to have little effect on core symptoms, and it has been pointed out that the marked hyperprolactinaemia induced by risperidone could lead to hypogonadism, and deleterious effects on adolescent bones.[13] A systematic review[14] concluded that risperidone may be of some benefit for symptoms such as hyperactivity, irritability, repetition, and social withdrawal although this must be weighed against the risk of adverse effects, notably weight gain. The authors noted that only 3 studies were analysed, including 1 that was carried out in adults, and the data available were limited; further studies were considered warranted. Nonetheless, in some countries, including the USA, risperidone is licensed for the treatment of irritability associated with autistic disorder in children and adolescents aged 5 to 16 years; for details of doses see Administration in Children, p. 1103.3.

Risperidone may also be effective in reducing aggressive symptoms in children of subaverage intellect with **conduct disorder**;[15] for details of doses, see above.

1. De Deyn PP, *et al.* A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 1999; **53:** 946–55.
2. Falsetti AE. Risperidone for control of agitation in dementia patients. *Am J Health-Syst Pharm* 2000; **57:** 862–70.
3. Katz IR, *et al.* Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. *J Clin Psychiatry* 1999; **60:** 107–15.
4. Brodaty H, *et al.* A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* 2003; **64:** 134–43.
5. Allen RL, *et al.* Risperidone for psychotic and behavioural symptoms in Lewy body dementia. *Lancet* 1995; **346:** 185.
6. McKeith IG, *et al.* Neuroleptic sensitivity to risperidone in Lewy body dementia. *Lancet* 1995; **346:** 699.
7. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347:** 314–21.
8. Shea S, *et al.* Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Abstract: *Pediatrics* 2004; **114:** 1329. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/5/e634 (accessed 15/01/07)
9. Reyes M, *et al.* A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry* 2006; **163:** 402–10.
10. Reyes M, *et al.* Long-term safety and efficacy of risperidone in children with disruptive behaviour disorders: results of a 2-year extension study. *Eur Child Adolesc Psychiatry* 2006; **15:** 97–104.
11. Chavez B, *et al.* Role of risperidone in children with autism spectrum disorder. *Ann Pharmacother* 2006; **40:** 909–16.
12. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Pediatr Drugs* 2007; **9:** 343–54.
13. Valiquette G. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347:** 1890–1.
14. Jesner OS, *et al.* Risperidone for autism spectrum disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 10/04/08).
15. LeBlanc JC, *et al.* Risperidone reduces aggression in boys with a disruptive behaviour disorder and below average intelligence quotient: analysis of two placebo-controlled randomized trials. *Int Clin Psychopharmacol* 2005; **20:** 275–83.

Dystonias. Antipsychotics are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to treatment with levodopa or antimuscarinics, but, as with classical antipsychotics, there is the risk of adding drug-induced extrapyramidal effects to the dystonia. Risperidone has been reported to be of benefit in a few patients with idiopathic segmental dystonia partly insensitive to haloperidol.[1]

1. Zuddas A, Cianchetti C. Efficacy of risperidone in idiopathic segmental dystonia. *Lancet* 1996; **347:** 127–8.

Parkinsonism. There have been conflicting reports of the use of risperidone as an antipsychotic in a small number of patients with Parkinson's disease (see also Disturbed Behaviour, p. 1030.2). While some patients found that risperidone ameliorated levodopa-induced hallucinations without worsening extrapyramidal symptoms,[1,2] others reported that risperidone produced a substantial worsening of symptoms.[2,3]

1. Meco G, *et al.* Risperidone for hallucinations in levodopa-treated Parkinson's disease patients. *Lancet* 1994; **343:** 1370–1.
2. Leopold NA. Risperidone treatment of drug-related psychosis in patients with parkinsonism. *Mov Disord* 2000; **15:** 301–4.
3. Ford B, *et al.* Risperidone in Parkinson's disease. *Lancet* 1994; **344:** 681.

Schizophrenia. Risperidone is claimed to produce a relatively low incidence of extrapyramidal effects and to have efficacy against both positive and negative symptoms of schizophrenia (p. 1031.3). Most of the earlier studies compared risperidone with haloperidol but, of these, some of the major studies[1-3] were criticised for potential methodological flaws[4,5] and it was difficult to determine any difference in efficacy including effect on negative symptoms. A later systematic review[6] suggested that risperidone's benefits over haloperidol or other classical antipsychotics were marginal; although it did appear to reduce the risk of extrapyramidal effects compared with haloperidol, the latter produces a relatively high incidence of such effects. Furthermore, the risk of extrapyramidal effects with risperidone appears to be dose-dependent:[7] although similar to that for placebo overall, at doses of more than 10 mg the risk appears to approach that associated with haloperidol. In a more recent double-blind randomised study[8] the relapse rate after at least 2 years of treatment in patients with first-episode psychosis, who had initially responded to relatively small daily doses of risperidone (mean modal 3.3 mg) or haloperidol (2.9 mg), was 42% (82 of 197 patients) and 55% (111 of 203), respectively. The median time to relapse was also longer for risperidone (466 days) when compared with haloperidol (205 days). A recent review[9] concluded that there was still a lack of strong evidence for an optimal dose for risperidone but considered that doses of 4 to 6 mg daily did appear to be optimal for clinical response and adverse effects; there was also weaker evidence that 2 to 4 mg daily was of value for first episodes. In the few comparative studies with other atypical antipsychotics, risperidone has appeared to be of similar efficacy to clozapine.[10] However, another systematic review[11] concluded that such equivalence with clozapine cannot be assumed. For a systematic review of studies comparing risperidone with olanzapine, see p. 1090.3. There is insufficient evidence to indicate whether risperidone is effective for treatment-resistant or poorly responsive patients but there is some evidence that patients stabilised on risperidone may be less likely to relapse.[12] A systematic review[13] of the use of the long-acting injectable formulation of risperidone in schizophrenia considered that, although it might offer the advantage of better compliance, there was little evidence of benefit over oral use.

1. Chouinard G, *et al.* A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993; **13:** 25–40.
2. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994; **151:** 825–35.
3. Peuskens J, *et al.* Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995; **166:** 712–26.
4. Livingston MG. Risperidone. *Lancet* 1994; **343:** 457–60.
5. Musser WS, Kirisci L. Critique of the Canadian multicenter placebo-controlled study of risperidone and haloperidol. *J Clin Psychopharmacol* 1995; **15:** 226–8.
6. Hunter RH, *et al.* Risperidone versus typical antipsychotic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 30/05/05).
7. Owens DGC. Extrapyramidal side effects and tolerability of risperidone: a review. *J Clin Psychiatry* 1994; **55** (suppl 5): 29–35.
8. Schooler N, *et al.* Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 2005; **162:** 947–53.
9. Li C, *et al.* Risperidone dose for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 23/11/09).
10. Klieser E, *et al.* Randomized, double-blind, controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. *J Clin Psychopharmacol* 1995; **15** (suppl 1): 45S–51S.
11. Gilbody SM, *et al.* Risperidone versus other atypical antipsychotic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 30/05/05).
12. Csernansky JG, *et al.* A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002; **346:** 16–22.
13. Hosalli P, Davis JM. Depot risperidone for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 30/05/05).

Stuttering. Risperidone 0.5 to 2 mg daily was found to be of benefit in the management of stuttering (p. 1078.1) in a placebo-controlled study[1] involving 16 patients but there has also been a case report[2] of a patient whose stuttering returned during treatment with risperidone.

1. Maguire GA, *et al.* Risperidone for the treatment of stuttering. *J Clin Psychopharmacol* 2000; **20:** 479–82.
2. Lee H-J, *et al.* A case of risperidone-induced stuttering. *J Clin Psychopharmacol* 2001; **21:** 115–16.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) haloperidol or pimozide are commonly used but atypical antipsychotics, especially risperidone, are being increasingly tried.[1-3]

1. Bruun RD, Budman CL. Risperidone as a treatment for Tourette's syndrome. *J Clin Psychiatry* 1996; **57:** 29–31.
2. Bruggeman R, *et al.* Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry* 2001; **62:** 50–6.
3. Scahill L, *et al.* A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 2003; **60:** 1130–5.

Adverse Effects, Treatment, and Precautions

Although risperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Risperidone is reported to be less likely to cause sedation or extrapyramidal effects (see also Uses and Administration, p. 1103.2) but agitation may occur more frequently. Other common adverse effects include insomnia, anxiety, and headache. Dyspepsia, nausea and vomiting, abdominal pain, constipation, blurred vision, sexual dysfunction including priapism, urinary incontinence, rash and other allergic reactions, drowsiness, concentration difficulties, dizziness, fatigue, and rhinitis have been reported less commonly. In addition to orthostatic hypotension, hypertension has been reported infrequently. Other adverse effects with risperidone include cerebrovascular accidents, tachycardia, weight gain, oedema, and increased liver enzyme values. Risperidone may cause dose-dependent increases in prolactin levels. In rare cases, hyperglycaemia and exacerbation of pre-existing diabetes mellitus have also been reported. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes.

Other rare effects include blood dyscrasias including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia, seizures, body temperature dysregulation, hyponatraemia, neuroleptic malignant syndrome, and tardive dyskinesia.

Risperidone should be used with caution in patients with cardiovascular disease, including conditions associated with QT prolongation, or conditions predisposing to hypotension. Caution is also recommended in patients with a history of or at risk of developing cerebrovascular disease, in patients with Parkinson's disease or epilepsy, and in patients with hepatic or renal impairment.

Risperidone may affect the performance of skilled tasks such as driving.

Gradual withdrawal of risperidone is recommended because of the risk of withdrawal symptoms, including sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Breast feeding. From the study of concentrations of oral risperidone and its active metabolite, 9-hydroxyrisperidone, in the breast milk of a mother receiving 6 mg daily, it was estimated that a breast-fed infant would ingest the daily equivalent of 4.3% (as risperidone equivalents) of the weight-adjusted maternal dose.[1] Later case reports[2] of 3 women receiving oral risperidone 3 mg daily, 4 mg daily, and 1.5 mg daily estimated that a breast-fed infant would receive the daily equivalent of 2.3%, 2.8%, and 4.7%, respectively, of the weight-adjusted maternal dose. Where breast feeding occurred, in the latter 2 cases, no adverse effects were reported in the breast-fed infants; risperidone and 9-hydroxyrisperidone were not detected in the plasma of either infant.

Licensed product information states that patients receiving risperidone should not breast feed; the US information also recommends that patients should not breast feed for at least 12 weeks after intramuscular injection.

1. Hill RC, *et al.* Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol* 2000; **20:** 285–6.
2. Ilett KF, *et al.* Transfer of risperidone and 9-hydroxyrisperidone into human milk. *Ann Pharmacother* 2004; **38:** 273–6.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.

1. Safer DJ. A comparison of risperidone-induced weight gain across the age span. *J Clin Psychopharmacol* 2004; **24:** 429–36.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including risperidone, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Further references.

1. Koller EA, *et al.* Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy* 2003; **23:** 735–44.
2. Ramaswamy K, *et al.* Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; **30:** 589–99.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

Effects on the liver. There has been a report of 2 cases of hepatotoxicity associated with risperidone.[1] An idiosyncratic reaction to risperidone was suspected in another patient who developed hepatotoxicity after receiving only 2 doses of risperidone.[2]

1. Fuller MA, *et al.* Risperidone-associated hepatotoxicity. *J Clin Psychopharmacol* 1996; **16:** 84–5.
2. Phillips EJ, *et al.* Rapid onset of risperidone-induced hepatotoxicity. *Ann Pharmacother* 1998; **32:** 843.

Effects on the skin. A patient developed facial and periorbital oedema 2 weeks after her dose of risperidone reached 6 mg daily.[1] The oedema subsided when the dose was halved but recurred shortly after it was again increased to 6 mg. She had previously had a similar reaction to lithium and there was also a family history of angioedema.

1. Cooney C, Nagy A. Angio-oedema associated with risperidone. *BMJ* 1995; **311:** 1204.

The elderly. After analysis of data from controlled studies there was evidence that the use of risperidone in elderly patients with **dementia** appeared to be associated with an increased risk of cerebrovascular adverse effects such as stroke and transient ischaemic attacks. In 4 studies, involving 764 such patients treated with risperidone, there were 29 cases of cerebrovascular adverse events (4 fatal) versus 7 cases (1 fatal) in 466 patients given placebo. Post-marketing data for elderly dementia patients, representing over 2.4 million patient-years of exposure, included 37 cases, of which 16 were fatal.[1]

The UK CSM[2] therefore recommended at the time that risperidone should not be used to treat behavioural problems in elderly patients with dementia (but see below). Similarly, the CSM[2] recommended that olanzapine should not be used to treat behavioural problems or dementia-related psychosis in elderly patients with dementia after analysis of placebo-controlled studies revealed a threefold increase in cerebrovascular adverse effects including stroke and a twofold increase in all-cause mortality. It was considered[2] that the risk may not be confined to use in dementia and should be considered relevant to any patient with a history of stroke or transient ischaemic attack or other risk factors for cerebrovascular disease, including hypertension, diabetes, current smoking, or atrial fibrillation.

The FDA[3] has also advised about an increased risk of death with the use of atypical antipsychotics as a group in the treatment of behavioural problems in elderly patients with dementia. Their advice was based on an unpublished analysis of 17 placebo-controlled studies involving aripiprazole, olanzapine, quetiapine, or risperidone use in elderly demented patients with behavioral disorders: the analysis found that 15 studies showed an increase in the mortality rate in the drug-treated group compared with the placebo-treated patients. A total of 5106 patients were included in these studies, and a 1.6- to 1.7-fold increase in mortality was seen; most of the deaths appeared due to cardiovascular events or infection. Another published meta-analysis[4] of placebo-controlled studies also had similar findings.

However, 3 large retrospective population-based studies in the elderly (1 involving 10 385 patients given atypicals and 1015 given classical antipsychotics,[5] another involving 17 845 given atypicals and 14 865 given classical antipsychotics,[6] and the third involving 24 359 given atypicals and 12 882 given classical antipsychotics[7]), suggested that use of atypical antipsychotics was not associated with a statistically significant increased risk of stroke compared with the classical drugs. Furthermore, UK licensed product information states that a higher incidence of mortality was seen in elderly patients with dementia who were taking risperidone and furosemide when compared with those taking either drug alone; use of risperidone with other diuretics (mainly low-dose thiazides) was not associated with such findings.

More recently, the UK CHM[8] (formerly the CSM) stated that analysis of 3 randomised studies showed a clear benefit for the short-term use of risperidone in the treatment of aggression in elderly patients with dementia. Indeed, risperidone is now licensed for such use in the UK but the balance of risks and benefits should be carefully assessed for every patient; for further details and doses see Uses and Administration, p. 1103.2.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p. 1030.2 and under Precautions of Chlorpromazine, p. 1051.1.

1. Janssen-Ortho Inc. Health Canada. Important drug safety information: Risperdal (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials (issued 11th October, 2002). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/risperdal_hpc-cps-eng.pdf (accessed 21/08/08)
2. Duff G. Atypical antipsychotic drugs and stroke: message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 9th March, 2004). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019488.pdf (accessed 21/08/08)
3. FDA. Public Health Advisory: deaths with antipsychotics in elderly patients with behavioral disturbances (issued 11th April, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm053171.htm (accessed 26/07/10)
4. Schneider LS, *et al.* Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; **294:** 1934–43.
5. Herrmann N, *et al.* Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004; **161:** 1113–15.
6. Gill SS, *et al.* Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ* 2005; **330:** 445–8.
7. Schneeweiss S, *et al.* Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *Can Med Assoc J* 2007; **176:** 627–32. Correction. *ibid.*; 1613.
8. MHRA/CHM. Antipsychotics: use in elderly people with dementia. *Drug Safety Update* 2009; **2** (8): 5–6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON041211 (accessed 03/06/09)

Extrapyramidal disorders. In reports of 3 cases of tardive dystonia associated with oral risperidone therapy,[1,2] onset ranged from 3 to 8 months after starting the drug. Dyskinesia has also been reported 5 days after the withdrawal of oral risperidone and citalopram therapy.[3] In another report,[4] three patients receiving risperidone orally developed early-onset tardive dyskinesia despite the addition of antimuscarinic therapy with biperiden or trihexyphenidyl. Extrapyramidal adverse effects have also been reported within 24 hours of intramuscular risperidone injection.[5] However, the incidence of extrapyramidal effects (p. 1049.2) is generally lower with atypical than classical antipsychotics.

1. Vercueil L, Foucher J. Risperidone-induced tardive dystonia and psychosis. *Lancet* 1999; **353:** 981.
2. Krebs MO, Olie JP. Tardive dystonia induced by risperidone. *Can J Psychiatry* 1999; **44:** 507–508.
3. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; **34:** 269.
4. Suzuki E, *et al.* Tardive dyskinesia with risperidone and anticholinergics. *Am J Psychiatry* 2002; **159:** 1948.
5. Adamou M, Hale AS. Extrapyramidal syndrome and long-acting injectable risperidone. *Am J Psychiatry* 2004; **161:** 756–7.

Mania. Although it is used in the treatment of bipolar disorder, risperidone has been associated with reports of mania in both schizophrenic and bipolar patients.[1-3]

1. Dwight MM, *et al.* Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. *Lancet* 1994; **344:** 554–5.
2. Zolezzi M, Badr MG. Risperidone-induced mania. *Ann Pharmacother* 1999; **33:** 380–1.
3. Aubry J-M, *et al.* Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; **61:** 649–55.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (p. 1050.2) has occasionally been associated with risperidone.[1-5]

1. Sharma R, *et al.* Risperidone-induced neuroleptic malignant syndrome. *Ann Pharmacother* 1996; **30:** 775–8.
2. Tarsy D. Risperidone and neuroleptic malignant syndrome. *JAMA* 1996; **275:** 446.
3. Reeves RR, *et al.* Neuroleptic malignant syndrome during a change from haloperidol to risperidone. *Ann Pharmacother* 2001; **35:** 698–701.
4. Gerritsen AA, *et al.* Het maligne neurolepticasyndroom bij gebruik van risperidon. *Ned Tijdschr Geneeskd* 2004; **148:** 1801–4.
5. Norris B, *et al.* Neuroleptic malignant syndrome with delayed onset of fever following risperidone administration. *Ann Pharmacother* 2006; **40:** 2260–4.

Overdosage. A 3½-year-old child developed extrapyramidal symptoms after accidental ingestion of a single 4-mg tablet of risperidone.[1] The child was initially treated with gastric lavage, activated charcoal, and sorbitol; extrapyramidal symptoms responded to treatment with diphenhydramine and the child recovered completely. The need to monitor for and treat hypotension after overdosage with risperidone was highlighted in a report[2] of a 15-year-old girl who took 40 mg of risperidone. A 72-year-old woman receiving risperidone 6 mg daily was found unconscious, hypotensive, and hypothermic.[3] Other reported symptoms include first-degree heart block, prolonged QT interval, and respiratory arrest; she recovered after supportive treatment.

1. Cheslik TA, Erramouspe J. Extrapyramidal symptoms following accidental ingestion of risperidone in a child. *Ann Pharmacother* 1996; **30:** 360–3.
2. Himstreet JE, Daya M. Hypotension and orthostasis following a risperidone overdose. *Ann Pharmacother* 1998; **32:** 267.
3. Rassam S, Srinivasa R. Respiratory depression after accidental risperidone overdose. *Am J Emerg Med* 2002; **20:** 570.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies risperidone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics, including risperidone, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Further references.

1. Coppola D, *et al.* Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. *Drug Safety* 2007; **30:** 247–64.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by risperidone. Risperidone may also enhance the effects of antihypertensives. There may be an increased risk of QT prolongation when risperidone is given with other drugs that are known to cause this effect. Risperidone may antagonise the actions of levodopa and other dopaminergics.

Carbamazepine has been shown to decrease the antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) of risperidone and a similar effect may be seen with other enzyme inducers. Fluoxetine may increase the plasma concentrations of the antipsychotic fraction by raising the concentration of risperidone. Dose adjustment of risperidone may be necessary in such situations.

Increased mortality has been reported in elderly patients with dementia who are given risperidone and furosemide (see the Elderly, above). Caution is advised when using risperidone with furosemide or other potent diuretics.

Antiepileptics. For the effect of risperidone on *valproate*, see p. 557.3.

Antipsychotics. For a report suggesting that risperidone might increase plasma concentrations of *clozapine*, see p. 1061.3. For a report of asymptomatic QT prolongation associated with *quetiapine* in a patient also receiving risperidone, see under Overdosage of Quetiapine, p. 1102.2.

Antivirals. Dystonia and worsening of tremors were reported 1 week after adding *indinavir* and *ritonavir* to treatment with risperidone in a patient with AIDS;[1] he recovered once all 3 drugs were withdrawn and after treatment with clonazepam. An early exposure to risperidone, indinavir, and ritonavir had not resulted in any extrapyramidal adverse effects. The authors considered this to reflect the patient's relatively short exposure to risperidone at the time.

1. Kelly DV, *et al.* Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. *Ann Pharmacother* 2002; **36:** 827–30.

Pharmacokinetics

Risperidone is readily absorbed after oral doses and peak plasma concentrations occur within 1 to 2 hours. It is extensively metabolised in the liver by hydroxylation to its main active metabolite, 9-hydroxyrisperidone (paliperidone, p. 1093.1); oxidative *N*-dealkylation is a minor metabolic pathway. Hydroxylation is mediated by the cytochrome P450 isoenzyme CYP2D6 and is subject to genetic polymorphism. Excretion is mainly in the urine and, to a lesser extent, in the faeces. Risperidone and 9-hydroxyrisperidone are about 90% and 77% bound to plasma proteins, respectively. Both are distributed into breast milk.

Metabolism. Although the hydroxylation of risperidone is subject to genetic polymorphism, the pharmacokinetics and effects of the active antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) have been reported to vary little between extensive and poor metabolisers.[1] A mean value of 19.5 hours has been reported for the terminal elimination half-life of the active fraction following oral doses of risperidone.[1]

1. Huang M-L, *et al.* Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. *Clin Pharmacol Ther* 1993; **54:** 257–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dozic; Dropicine; Edalen; Restelea; Riatul; Risper; Risperdal; Risperin; Rispex; Roxodyn; Sequinan; ***Austral.***: Ozidal; Resdone; Rispa; Risperdal; Rixadone; ***Austria***: Aleptan; Risperdal; Rispolin†; ***Belg.***: Risperdal; ***Braz.***: Esquidon; Respidon; Ripevil; Risleptic; Risperdal; Risperix; Riss; Viverdal; Zargus; ***Canad.***: Risperdal; ***Chile***: Dagotil; Goval; Radigen; Risperdal; Spiron; ***China***: Dan Ke (单克); Jing Ping (敬平); Ke Tong (可同); Risperdal (维思通); Si Li Shu (思利舒); Suo Le (索乐); Zhuo Fei (卓菲); Zhuo Fu (卓夫); ***Cz.***: Apo-Risper; Medorisper; Ridoner; Rigenin†; Rileptid; Ripetomar†; Risepro; Rispadim†; Rispedep†; Rispedolet†; Rispedospes†; Rispemar†; Rispen; Rispera; Risperdal; Risperigamma†; Risperinin†; Risperit†; Risperstad†; Rispimed†; Rispolux; Risset†; Rorendo; Unispera†; ***Denm.***: Ripexal; Risperanne; Risperdal; Rispolept; ***Fin.***: Rispazin†; Risperdal; ***Fr.***: Risperdal; Risperdalconsta; Risperdaloro; ***Ger.***: Risocon; Rispe-Q†; Risperdal; Risperdoc†; Risperigamma; ***Gr.***: Adovia; Axelabron; Belasperdal-S; Capulton; Depolan; Depredon; Deteron; Dixine; Evitrat; Helposper; Isipredon; Lassen; Leterzin; Linipon; Lucipral; Muistin; Natibo; Nerve; Novoris; Orotral; Preridon; Psychordal; Ribex; Ridoron; Rifocus; Ripepral; Risenar; Risgal; Risidral; Rispalm; Rispefar; Rispelen; Rispen; Rispenet†; Risperascol; Risperdal; Risperom; Risperoprol; Rispersan; Rispogen; Rubrum; Sperelax; Wisperdon; Zafitral; ***Hong Kong***: Rileptid; Risperdal; Risperigamma; ***Hung.***: Hunperdal; Perdox; Rileptid; Ripedon; Rispe; Risperdal; Rispolux; Rispons; Ronkal†; Rosipin; Torendo; Ziperid; ***India***: Cinris; Genrest; Respidon; Risnia; Risperdal; Rispid; Rozidal; ***Indon.***: Neripros; Nodiril; Persidal; Risperdal; Rizodal; Zofredal; ***Irl.***: Perdamel; Resdal†; Rispal; Rispatal; Risperdal; Risperger; Rispeva; Rispone; ***Israel***: Rispefar; Risperdal; Risperidex; Rispond; Speridone; ***Ital.***: Belivon; Risperdal; ***Jpn***: Risperdal; ***Malaysia***: Risperdal; Rozidal; ***Mex.***: Limbik; Reskizof; Risperdal; Rispolux; Silderec; Upmotev; ***Neth.***: Belivon†; Rispenon†; Risperdal; Rispimed†; Rispimedica†; Torendo†; ***Norw.***: Risperdal; Rispolept; ***NZ***: Ridal; Risperdal; Risperon; ***Philipp.***: Aspidon; Renuvie; Rileptid; Risdin; Rispedin; Risperdal; Rispond; ***Pol.***: Apo-Risperid; Disaperid; Doresol; Galperinon; Lioxam†; Mepharis†; Nodir; Orizon; Ranperidon; Rispen; Risperatio†; Risperiwin†; Risperon; Rispofren†; Rispolept; Rispolux; Risset; Ryspolit; Speridan; Torendo; Ziperid; ***Port.***: Itraxel; Lergitec; Lotin; Neclav; Perdin; Ripax; Risperdal; Smissen†; Zoridal; ***Rus.***: Leptinorm (Лептинорм); Neipilept (Нейпилепт); Ridonex (Ридонекс); Rileptid (Рилептид); Risdonal (Рисдонал); Rispaksole (Риспаксол); Rispen (Риспен); Rispolept (Рисполепт); Rispolux (Рисполюкс); Risset (Риссет); Sizodon (Сизодон); Speridan (Спередан); Torendo (Торендо); ***S.Afr.***: Perizal; Rispacor; Rispacor; Risperdal; Risperlet; Risponz; Rutra; Schizorol; Zoxadon; ***Singapore***: Ridal; Risperdal; ***Spain***: Arketin; Atornil†; Calmapride; Diaforin; Risfarmal†; Rispemylan; Risperdal; ***Swed.***: Risperdal; ***Switz.***: Risperdal; ***Thai.***: Neuris; Risperdal; ***Turk.***: Nodirep; Perilife; Restela; Ricus; Ricus; Ripesil; Risperdal; Rixol; Rixper; ***UK***: Risperdal; ***Ukr.***: Neirispin (Нейриспин); Ridonex (Ридонекс); Rileptid (Рилептид); Rispaxol (Риспаксол); Risperon (Рисперон); Rispond (Риспонд); Risset (Риссет); ***USA***: Risperdal; ***Venez.***: Ridal; Risperdal; Risperid.

Multi-ingredient Preparations. ***India***: Cinris Forte; Don Forte; Don Plus; Don-LS; Etores-TR; Genrest Plus; Genrest-LS.

Pharmacopoeial Preparations

USP 36: Risperidone Oral Solution; Risperidone Orally Disintegrating Tablets; Risperidone Tablets.

Romifidine *(BAN, rINN)*

Romifidiini; Romifidin; Romifidina; Romifidinum; STH-2130; Ромифидин.

2-Bromo-6-fluoro-*N*-(1-imidazolin-2-yl)aniline.

$C_9H_9BrFN_3$=258.1

CAS — 65896-16-4.

ATC Vet — QN05CM93.

UNII — 876351L05K.

Profile

Romifidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties and is used in veterinary medicine.

Secbutabarbital *(rINN)*

Butabarbital; Butabarbitone; Secbutabarbitalum; Secbutobarbital (BAN); Secbutobarbitone; Секбутабарбитал.

5-*sec*-Butyl-5-ethylbarbituric acid.

$C_{10}H_{16}N_2O_3$=212.2

CAS — 125-40-6.

UNII — P0078O25A9.

NOTE. Care should be taken to avoid confusion between barbiturates with similar names: Butabarbital, a synonym for Secbutabarbital, should be distinguished from Butobarbital (p. 1044.1), and Secbutabarbital should be distinguished from Secobarbital (below).

Pharmacopoeias. In *US*.

USP 36: (Butabarbital). A white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol, in chloroform, in ether, and in aqueous solutions of alkali hydroxides and carbonates. Store in airtight containers.

Secbutabarbital Sodium *(rINNM)*

Butabarbital Sodium; Natrii Secbutabarbitalum; Secbutabarbital sódico; Secbutabarbital Sodique; Secbutobarbital Sodium (BANM); Secbutobarbitone Sodium; Secumalnatrium; Sodium Butabarbital; Натрий Секбутабарбитал.

Sodium 5-*sec*-butyl-5-ethylbarbiturate.

$C_{10}H_{15}N_2NaO_3$=234.2

CAS — 143-81-7.

UNII — 9WTD50I91B.

Pharmacopoeias. In *US*.

USP 36: (Butabarbital Sodium). A white powder. Soluble 1 in 2 of water, 1 in 7 of alcohol, and 1 in 7000 of chloroform; practically insoluble in absolute ether. pH of a 10% solution in water is between 10.0 and 11.2. Store in airtight containers.

Profile

Secbutabarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used as a hypnotic and sedative although barbiturates are no longer considered appropriate for such purposes. For the short-term management of insomnia (p. 1033.2) it was usually given as the sodium salt in oral doses of 50 to 100 mg at night; as a sedative 15 to 30 mg has been given 3 or 4 times daily. Secbutabarbital base has also been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Butisol.

Multi-ingredient Preparations. ***USA***: Butibel; Phenazopyridine Plus; Pyrelle HB†; Urelief Plus; ***Venez.***: Butropina; Eumidral.

Pharmacopoeial Preparations

USP 36: Butabarbital Sodium Elixir; Butabarbital Sodium Tablets.

Secobarbital *(rINN)*

Meballymal; Quinalbarbitone; Sécobarbital; Secobarbitalum; Secobarbitone; Sekobarbitaali; Секобарбитал.

5-Allyl-5-(1-methylbutyl)barbituric acid.

$C_{12}H_{18}N_2O_3$=238.3

CAS — 76-73-3.

ATC — N05CA06.

ATC Vet — QN05CA06; QN51AA02.

UNII — 1P7H87IN75.

NOTE. Care should be taken to avoid confusion between barbiturates with similar names: Secobarbital should be distinguished from Secbutabarbital (above).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of secobarbital:

F-40s; Marshmallow reds; M&Ms; Mexican reds; Pink ladies; Pink lady; Pinks; RDs; Red birds; Red bullets; Red devil; Red devils; Red dolls; Red lillies; Reds; Seccies; Seccy; Seco; Seggy.

Pharmacopoeias. In *US*.

USP 36: (Secobarbital). A white amorphous or crystalline odourless powder. Very slightly soluble in water; freely soluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates; soluble in chloroform; soluble 1 in 8.5 of 0.5N sodium hydroxide. A saturated solution in water has a pH of about 5.6. Store in airtight containers.

Secobarbital Sodium *(BAN, rINNM)*

Meballymalnatrium; Natrii Secobarbitalum; Quinalbarbitone Sodium; Secobarbital sódico; Sécobarbital Sodique; Secobarbitalum Natricum; Secobarbitone Sodium; Натрий Секобарбитал.

Sodium 5-allyl-5-(1-methylbutyl)barbiturate.

$C_{12}H_{17}N_2NaO_3$=260.3

CAS — 309-43-3.

ATC — N05CA06.

ATC Vet — QN05CA06.

UNII — XBP604F6UM.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Secobarbital Sodium). A white odourless hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in ether. pH of a 10% solution in water is between 9.7 and 10.5. Solutions decompose on standing, heat accelerating the decomposition. Store in airtight containers.

Incompatibility. Secobarbital may be precipitated from preparations containing secobarbital sodium depending on the concentration and pH. Secobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Uses and Administration

Secobarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.3). It has been used as a hypnotic and sedative but can no longer be recommended because of its adverse effects and risk of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p. 1033.2) in patients already taking it. It was usually given in an oral dose of 100 mg of the sodium salt at night. For premedication in anaesthetic procedures (p. 1899.1) the sodium salt has been given orally or by intramuscular or intravenous injection although barbiturates for preoperative sedation have generally been replaced by other drugs.

Dependence and Withdrawal

As for Amobarbital, p. 1038.1.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p. 1038.1.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving secobarbital, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding. However, for the view that barbiturates should not be used in women who are breast feeding, see under Amobarbital, p. 1038.2.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Industrial exposure. Exposure to secobarbital sodium among 6 workers in the pharmaceutical industry resulted in absorption of substantial amounts of the drug, with

blood concentrations approaching those expected after a therapeutic dose.[1] There continued to be evidence of absorption, despite protective masks to reduce inhalation, and it appeared that substantial absorption was taking place through the skin.

1. Baxter PJ, *et al.* Exposure to quinalbarbitone sodium in pharmaceutical workers. *BMJ* 1986; **292:** 660–1.

Interactions

As for Amobarbital, p. 1038.2.

Pharmacokinetics

Secobarbital is well absorbed from the gastrointestinal tract after oral doses and is reported to be about 46 to 70% bound to plasma proteins. The mean elimination half-life is reported to be 28 hours, with a range of 15 to 40 hours. It is metabolised in the liver, mainly by hydroxylation, and excreted in the urine as metabolites and a small amount of unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Ional; ***UK***: Seconal; ***USA***: Seconal.

Multi-ingredient Preparations. ***UK***: Tuinal; ***USA***: Tuinal.

Pharmacopoeial Preparations
USP 36: Secobarbital Sodium and Amobarbital Sodium Capsules; Secobarbital Sodium Capsules; Secobarbital Sodium for Injection; Secobarbital Sodium Injection.

Sertindole *(BAN, USAN, rINN)*

Lu-23-174; Sertindol; Sertindoli; Sertindolum; Сертиндол.
1-(2-{4-[5-Chloro-1-(*p*-fluorophenyl)indol-3-yl]piperidino}ethyl)-2-imidazolidinone.
$C_{24}H_{26}ClFN_4O$=440.9
CAS — 106516-24-9.
ATC — N05AE03.
ATC Vet — QN05AE03.
UNII — GW4Z8795P.

Uses and Administration

Sertindole is an atypical antipsychotic that is an antagonist at central dopamine (D_2), serotonin ($5\text{-}HT_2$), and adrenergic (α_1) receptors. It is used in the treatment of schizophrenia (p. 1031.3) in patients who are unable to tolerate at least one other antipsychotic. In addition, sertindole should only be prescribed to patients enrolled in clinical studies to ensure adequate monitoring, especially regular ECG measurements (see Adverse Effects, below).

Sertindole is given in an initial oral dose of 4 mg once daily, increased gradually in steps of 4 mg every 4 or 5 days to a usual maintenance dose of 12 to 20 mg once daily. The maximum dose is 24 mg daily. Slower dose titration and lower maintenance doses are advisable for the elderly and patients with mild to moderate hepatic impairment.

If therapy is interrupted for 1 week or more, the dose of sertindole should be re-titrated. An ECG should also be undertaken before re-starting sertindole.

References.
1. Lewis R. *et al.* Sertindole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/05/06).

Adverse Effects, Treatment, and Precautions

Although sertindole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Sertindole is associated with a low incidence of extrapyramidal adverse effects and does not appear to cause sedation. Prolactin elevation may be less frequent. The most common adverse effects with sertindole are peripheral oedema, rhinitis, dyspnoea, sexual dysfunction, dizziness, dry mouth, orthostatic hypotension, weight gain, and paraesthesia. Hyperglycaemia, convulsions, and tardive dyskinesia are uncommon.

Marketing of sertindole has been restricted because of cardiac arrhythmias and sudden cardiac deaths associated with its use (see below). Since sertindole has been associated with prolongation of the QT interval, usually during the first 3 to 6 weeks of treatment, it is recommended that patients should have an ECG before the start of therapy and periodically during treatment. Patients with pre-existing prolongation of the QT interval or a family history of congenital QT prolongation should not be given sertindole and sertindole should be stopped if such prolongation occurs during treatment. In addition, sertindole is contra-indicated in patients with a history of cardiovascular disease, heart failure, cardiac hypertrophy, arrhythmias, or bradycardia. Certain medications may also increase the risk (see Interactions, below).

Sertindole should not be given to patients with uncorrected hypokalaemia or hypomagnesaemia. Baseline serum potassium and magnesium screening should be performed before starting sertindole therapy in patients who are at risk of significant electrolyte disturbances. Serum potassium should be monitored in patients with electrolyte disturbances, vomiting or diarrhoea, or receiving diuretics during sertindole treatment. It is also recommended that blood pressure should be monitored during dose titration and in early maintenance therapy.

Sertindole is contra-indicated in patients with severe hepatic impairment. It should be used with caution in the elderly and in patients with Parkinson's disease, mild to moderate hepatic impairment, or a history of seizures.

Sertindole may affect the performance of skilled tasks including driving.

Gradual withdrawal of sertindole is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. Prolongation of the QT interval is said by the manufacturer to be common in patients given sertindole, with the effect being greater at the upper end of the dose range. In addition, the QT interval is prolonged to a greater extent than that seen with some other antipsychotics. QT interval prolongation is a known risk factor for the development of serious arrhythmias such as torsade de pointes although such arrhythmias are uncommon with sertindole.

In evidence presented to the FDA it was reported that as of 1st June 1996 there had been 27 deaths, 16 due to adverse cardiac events, among the 2194 patients given sertindole in clinical studies.[1] By the end of November 1998, the UK CSM was aware of 36 suspected adverse drug reactions with a fatal outcome, 9 of which originated in the UK.[2] There had also been 13 reports of serious but non-fatal cardiac arrhythmias in the UK. Although not all the fatalities were related to sudden cardiac events, at the time the CSM considered that, given the number of serious arrhythmias and sudden cardiac deaths, the risk-benefit ratio of sertindole was no longer favourable. The drug was withdrawn from the market in the UK and subsequently in some other countries, although it remained available on a named-patient basis. However, in 2001, the issue was re-evaluated by the CSM and the European advisory body, the Committee on Proprietary Medicinal Products, and it was recommended that sertindole could be reintroduced in Europe under certain restrictions.[3] Initially sertindole should only be prescribed to patients enrolled in clinical studies to ensure that they are carefully selected and monitored. In the UK, sertindole was remarketed in September 2002.

The risk of sudden unexpected deaths associated with antipsychotic use in general is discussed under Adverse Effects of Chlorpromazine, p. 1047.3.

1. Barnett AA. Safety concerns over antipsychotic drug, sertindole. *Lancet* 1996; **348:** 256.
2. CSM/MCA. Suspension of availability of sertindole (Serdolect). *Current Problems* 1999; **25:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
3. CSM/MCA. Restricted re-introduction of the atypical antipsychotic sertindole (Serdolect) (issued 10th September, 2002). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019523 (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The risk of arrhythmias with sertindole may be increased by other drugs that prolong the QT interval and use together should be avoided. Sertindole should be given with caution with drugs that produce electrolyte disturbances; monitoring of serum potassium is recommended if given with potassium-depleting diuretics.

Sertindole may antagonise the effects of dopaminergics.

Sertindole is extensively metabolised by the cytochrome P450 isoenzymes of the group CYP3A and by CYP2D6. The use of potent inhibitors of CYP3A such as indinavir, itraconazole, and ketoconazole with sertindole is contra-indicated. Minor increases in sertindole plasma concentrations have been noted in patients given macrolide antibacterials or calcium-channel blockers which also inhibit CYP3A; the use of these CYP3A4 inhibitors with sertindole is not recommended despite the small increase. Fluoxetine and paroxetine, potent inhibitors of CYP2D6, have increased plasma concentrations of sertindole by a factor of 2 to 3 and lower maintenance doses of sertindole may be required. In contrast, enzyme inducers such as rifampicin, carbamazepine, phenytoin, and phenobarbital may decrease sertindole plasma levels by a factor of 2 to 3; in such cases, higher doses of sertindole may be required.

Pharmacokinetics

Sertindole is slowly absorbed and peak concentrations occur about 10 hours after oral doses. It is about 99.5% bound to plasma proteins and readily crosses the placenta. Sertindole is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A. There is moderate interindividual variation in the pharmacokinetics of sertindole due to polymorphism in the isoenzyme CYP2D6. Poor metabolisers, deficient in this isoenzyme, may have plasma concentrations of sertindole 2 to 3 times higher than other patients. The two major metabolites, dehydrosertindole and norsertindole, appear to be inactive. Sertindole and its metabolites are excreted slowly, mainly in the faeces with a minor amount appearing in the urine. The mean terminal half-life is about 3 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Serdolect; ***Austral.***: Serdolect; ***Austria***: Serdolect; ***Belg.***: Serdolect; ***Cz.***: Serdolect; ***Denm.***: Serdolect; ***Fin.***: Serdolect; ***Ger.***: Serdolect; ***Gr.***: Serdolect; ***Hung.***: Serdolect; ***Irl.***: Serdolect; ***Israel***: Serdolect; ***Malaysia***: Serdolect; ***Mex.***: Serlect; ***Neth.***: Serdolect; ***Norw.***: Serdolect; ***NZ***: Serdolect; ***Philipp.***: Serdolect; ***Pol.***: Serdolect; ***Port.***: Serdolect; ***Rus.***: Serdolect (Сердолект); ***Spain***: Serdolect; ***Swed.***: Serdolect; ***Switz.***: Serdolect; ***Turk.***: Serdolect; ***UK***: Serdolect†; ***Ukr.***: Serdolect (Сердолект).

Spiperone *(BAN, USAN, rINN)*

Espiperona; R-5147; Spipérone; Spiperonum; Spiroperidol; Спиперон.
8-[3-(4-Fluorobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.
$C_{23}H_{26}FN_3O_2$=395.5
CAS — 749-02-0.
UNII — 4X6E73CJ0Q.

Profile

Spiperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It has been given orally in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Spiropitan.

Sulpiride *(BAN, USAN, rINN)*

Sulpirid; Sulpirida; Sulpiridas; Sulpiridi; Sulpiridum; Sülprid; Szulpirid; Сульпирид.
N-(1-Ethylpyrrolidin-2-ylmethyl)-2-methoxy-5-sulphamoylbenzamide.
$C_{15}H_{23}N_3O_4S$=341.4
CAS — 15676-16-1 (sulpiride).
ATC — N05AL01.
ATC Vet — QN05AL01.
UNII — 7MNE9M8287.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8 (Sulpiride). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in

methyl alcohol. It dissolves in dilute solutions of mineral acids and in alkali hydroxides.

Levosulpiride *(rINN)*

Levosulpirida; Lévosulpiride; Levosulpiridum; Levosulpride; L-Sulpiride; Левосульпирид.

$C_{15}H_{23}N_3O_4S$=341.4

CAS — 23672-07-3.

ATC — N05AL07.

ATC Vet — QN05AL07.

UNII — JTG7R315LK.

Uses and Administration

Sulpiride is a substituted benzamide antipsychotic that is reported to be a selective antagonist of central dopamine (D_2, D_3, and D_4) receptors. It is also claimed to have mood elevating properties.

Sulpiride is mainly used in the treatment of psychoses such as schizophrenia (below). It has also been given in the management of Tourette's syndrome (below), anxiety disorders, depression, vertigo, and benign peptic ulceration (see Gastrointestinal Disorders, below). Levosulpiride, the L-isomer of sulpiride, has been used similarly to sulpiride.

In the treatment of **schizophrenia** in adults and children aged 14 years and over, initial oral doses of 200 to 400 mg of sulpiride are given twice daily, increased if necessary up to a maximum of 1.2 g twice daily in patients with mainly positive symptoms or up to a total of 800 mg daily in patients with mainly negative symptoms. Patients with mixed positive and negative symptoms, with neither predominating, are given usual doses of 400 to 600 mg twice daily. Lower initial doses have been recommended in elderly patients, subsequently adjusted as required.

Sulpiride is also given in some countries by intramuscular injection, in usual doses ranging from 200 to 800 mg daily.

Dosage adjustment is advised in patients with renal impairment (see below).

Administration in children. For details of doses in the treatment of Tourette's syndrome in children, see below. For details of adolescent doses in the treatment of schizophrenia, see above.

Administration in renal impairment. A single intravenous dose of sulpiride 100 mg was given to 6 healthy subjects with normal renal function (creatinine clearance greater than 90 mL/minute) and to 3 groups of 6 patients each with creatinine clearances (CC) in the ranges of 30 to 60, 10 to 30, and less than 10 mL/minute.[1] There was a progressive diminution in the rate of elimination and an increase in half-life with decreasing renal function. The mean plasma elimination half-lives were 5.90, 11.02, 19.27, and 25.96 hours in the 4 groups, respectively.

Licensed product information suggests that dosage reduction or longer dosage interval may be required in patients with renal impairment, but gives no specific advice on how to do this.

1. Bressolle F, *et al.* Pharmacokinetics of sulpiride after intravenous administration in patients with impaired renal function. *Clin Pharmacokinet* 1989; **17:** 367–73.

Chorea. Antipsychotics have some action against choreiform movements (p. 1029.3) as well as being of use to control the behavioural disturbances of Huntington's chorea. Although sulpiride was found to have produced an overall reduction in abnormal movements in 11 patients with Huntington's chorea when compared with placebo in a double-blind study[1] there was generally no accompanying functional improvement and patients with mild disease tended to worsen when taking sulpiride.

1. Quinn N, Marsden CD. A double blind trial of sulpiride in Huntington's disease and tardive dyskinesia. *J Neurol Neurosurg Psychiatry* 1984; **47:** 844–7.

Gastrointestinal disorders. Although sulpiride is used in some countries as an adjunct in the treatment of peptic ulcer disease (p. 1816.2) it is not among the more usual drugs used for this indication. Efficacy has also been claimed for sulpiride or levosulpiride in a variety of other gastrointestinal disorders, including irritable bowel disease (p. 1813.3), decreased gastrointestinal motility (p. 1808.2), and nausea and vomiting (p. 1814.3), but again they are not among the drugs usually considered for use in these conditions.

Lactation induction. Drug therapy has been used occasionally to stimulate lactation in breast-feeding mothers, although good maternal education and support in techniques that promote physiological lactation remain the most important methods. Dopamine antagonists such as sulpiride can produce modest increases in breast milk production[1-3] although metoclopramide has been more widely used (see p. 2130.1). However, there is concern about the adverse effects of these drugs. As sulpiride appears in breast milk and may be associated with adverse effects in the infant it has been recommended that it should not be used to enhance milk production.[4,5]

1. Aono T, *et al.* Effect of sulpiride on poor puerperal lactation. *Am J Obstet Gynecol* 1982; **143:** 927–32.
2. Ylikorkala O, *et al.* Sulpiride improves inadequate lactation. *BMJ* 1982; **285:** 249–51.
3. Ylikorkala O, *et al.* Treatment of inadequate lactation with oral sulpiride and buccal oxytocin. *Obstet Gynecol* 1984; **63:** 57–60.
4. Pons G, *et al.* Excretion of psychoactive drugs into breast milk: pharmacokinetic principles and recommendations. *Clin Pharmacokinet* 1994; **27:** 270–89.
5. Lasich AJ. Sulpiride and breastfeeding. *S Afr Med J* 2005; **95:** 624–6.

Schizophrenia. A systematic review[1] of the use of sulpiride for schizophrenia (p. 1031.3) or serious mental illness concluded that while sulpiride might be as effective as the classical antipsychotics for schizophrenia and appeared to produce few adverse effects, evidence of its value for treating negative symptoms was lacking. Comparisons with the atypical antipsychotic drugs were also lacking.

1. Soares B, *et al.* Sulpiride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 21/08/08).

Tourette's syndrome. When drug treatment is needed for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) dopamine antagonists such as the antipsychotics haloperidol or pimozide are most commonly used but sulpiride has also been tried.[1] Although unlicensed in the UK for the treatment of Tourette's syndrome, the *BNFC* has suggested that oral doses of sulpiride 50 to 400 mg twice daily may be given to children aged from 2 to 12 years, and 100 to 400 mg twice daily to adolescents aged from 12 to 18 years.

1. Robertson MM, *et al.* Management of Gilles de la Tourette syndrome using sulpiride. *Clin Neuropharmacol* 1990; **13:** 229–35.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Sleep disturbances, overstimulation, and agitation may occur. Extrapyramidal effects appear to be as frequent as with chlorpromazine but have usually been mild. It has been suggested that sulpiride is less likely to cause tardive dyskinesia but good evidence of any important difference is lacking. Sulpiride is less likely to cause sedation than chlorpromazine and antimuscarinic effects are minimal. Cardiovascular effects such as hypotension are generally rare although they may occur with overdosage.

Sulpiride should be given with care to manic or hypomanic patients in whom it may exacerbate symptoms.

Breast feeding. Sulpiride may be distributed into breast milk and the *BNF* recommends that its use should be avoided in mothers wishing to breast feed.

On the fifth day after starting D-sulpiride, DL-sulpiride, or L-sulpiride in a dose of 50 mg twice daily, mean concentrations of sulpiride in breast milk from 45 women were 840, 850, and 810 nanograms/mL respectively.[1]

1. Polatti F. Sulpiride isomers and milk secretion in puerperium. *Clin Exp Obstet Gynecol* 1982; **9:** 144–7.

Effects on the cardiovascular system. Sulpiride 100 mg orally caused an attack of hypertension in 6 of 26 hypertensive patients; in 4 it induced a rise in urinary excretion of vanillylmandelic acid and catecholamines.[1] A transient rise in blood pressure and catecholamines after sulpiride occurred in 3 patients who were found to have a phaeochromocytoma; another patient probably had a phaeochromocytoma. The means by which sulpiride provoked hypertension were not known but appeared to be due to a noradrenergic effect. Sulpiride should be avoided during the treatment of phaeochromocytoma, and prescribed with great care in hypertensive patients.

1. Corvol P, *et al.* Poussées hypertensives déclenchées par le sulpiride. *Sem Hop Paris* 1974; **50:** 1265–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulpiride as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] However UK licensed product information contra-indicates sulpiride use in porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Renal impairment. For the precautions to be observed in patients with impaired renal function, see under Uses and Administration, above.

Interactions

As for Chlorpromazine, p. 1051.3

Gastrointestinal drugs. Giving sulpiride with therapeutic doses of *sucralfate* or an *antacid* containing aluminium and magnesium hydroxides to 6 healthy subjects reduced the mean oral bioavailability of sulpiride by 40 and 32%, respectively.[1] When sulpiride was given 2 hours after the antacid or sucralfate (each in 2 subjects), bioavailability was reduced by about 25%. This interaction was expected to be clinically significant, and it was recommended that sulpiride should be given before, rather than with or after, sucralfate or antacids.

1. Gouda MW, *et al.* Effect of sucralfate and antacids on the bioavailability of sulpiride in humans. *Int J Pharmaceutics* 1984; **22:** 257–63.

Pharmacokinetics

Sulpiride is slowly absorbed from the gastrointestinal tract; peak plasma concentrations are attained 3 to 6 hours after ingestion. Bioavailability is low and subject to interindividual variation. It is rapidly distributed to the tissues but passage across the blood-brain barrier is poor. Sulpiride is about 40% bound to plasma proteins and is reported to have a plasma half-life of about 8 to 9 hours. It is excreted in the urine and faeces, mainly as unchanged drug. Sulpiride is distributed into breast milk.

References.

1. Wiesel F-A, *et al.* The pharmacokinetics of intravenous and oral sulpiride in healthy human subjects. *Eur J Clin Pharmacol* 1980; **17:** 385–91.
2. Bressolle F, *et al.* Sulpiride pharmacokinetics in humans after intramuscular administration at three dose levels. *J Pharm Sci* 1984; **73:** 1128–36.
3. Bressolle F, *et al.* Absolute bioavailability, rate of absorption, and dose proportionality of sulpiride in humans. *J Pharm Sci* 1992; **81:** 26–32.
4. Mauri MC, *et al.* L-sulpiride in young and elderly negative schizophrenics: clinical and pharmacokinetic variables. *Prog Neuropsychopharmacol Biol Psychiatry* 1994; **18:** 355–6.
5. Muller MJ, *et al.* Serum levels of sulpiride enantiomers after oral treatment with racemic sulpiride in psychiatric patients: a pilot study. *Pharmacopsychiatry* 2001; **34:** 27–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dislep; Vipral; ***Austria***: Dogmatil; Meresa†; Meresasul; ***Belg.***: Docsulpiri†; Dogmatil; Levopraid; ***Braz.***: Dogmatil; Equilid; ***Chile***: Aplacid; Dislep; Endacine; Istefral; Sanblex; Sedusen; Sulpilan; Sulpivol; ***Cz.***: Dogmatil; Prosulpin; Sulpirol; ***Denm.***: Dogmatil; Dolmatil; ***Fin.***: Suprium; ***Fr.***: Dogmatil; Synedil; ***Ger.***: Arminol†; Dogmatil†; Meresa; Meresasul; neogama†; Sulpivert; Vertigo-Meresa; vertigo-neogama; ***Gr.***: Calmoflorine; Darleton; Desmenat; Dogmatyl; Eclorion; Esalfon; Fardalan; Fidelan; Mariastel; Noneston; Nufarol; Nylipark; Omaha; Omiryl; Ozoderpin; Restful; Silavidon; Stamonevrol; Valirem; Zymocomb; ***Hong Kong***: Dogmatil; Spanomid†; ***Hung.***: Depral; ***India***: Lesuride; Levoride; Nexipride; ***Indon.***: Dogmatil; ***Irl.***: Dolmatil; ***Israel***: Modal; ***Ital.***: Championyl; Dobren; Equilid; Levobren; Levopraid; ***Jpn***: Dogmatyl; ***Malaysia***: Dogmatil; Sulpin; ***Mex.***: Dislep; Ekilid; Pontiride; Rimastine; ***Neth.***: Dogmatil; ***Philipp.***: Dogmatil†; ***Port.***: Dogmatil; ***Rus.***: Betamax (Бетамакс); Eglek (Эглек); Eglonil (Эвитол); Prosulpin (Просульпин); ***S.Afr.***: Eglonyl; Espiride; ***Singapore***: Devodil; Dogmatil; Sulris; ***Spain***: Digton†; Dogmatil; Guastil; Leboprideł; Levogastrol; Pausedal; Psicocen; Tepavil; ***Switz.***: Dogmatil; ***Turk.***: Dogmatil; Meresa; Sulpir; Zeprid; ***UK***: Dolmatil; Sulpor; ***Ukr.***: Betamax (Бетамакс); Eglonil (Эглонил); ***Venez.***: Dislep.

Multi-ingredient Preparations. ***Arg.***: Alplax Digest; Tranquinal Soma; Tranxilium Digest; Vegestabil; ***Braz.***: Bromopirin; Sulpan; ***Mex.***: Neupax Duo-S; Numencial; ***Spain***: Ansium; Tepazepan.

Pharmacopoeial Preparations

BP 2014: Sulpiride Tablets.

Sultopride Hydrochloride *(rINNM)*

Hidrocloruro de sultoprida; LIN-1418; Sultoprida, hidrocloruro de; Sultopride, Chlorhydrate de; Sultopridi Hydrochloridum; Сультоприда Гидрохлорид.

N-(1-Ethylpyrrolidin-2-ylmethyl)-5-ethylsulphonyl-2-methoxybenzamide hydrochloride.

$C_{17}H_{26}N_2O_4S,HCl$=390.9

CAS — 53583-79-2 (sultopride); 23694-17-9 (sultopride hydrochloride).

ATC — N05AL02.

ATC Vet — QN05AL02.

Profile

Sultopride is a substituted benzamide with general properties similar to those of sulpiride (p. 1107.3). It has been used in psychoses such as schizophrenia (p. 1031.3). It has also been used in the emergency management of agitation in psychotic or aggressive patients.

Ventricular arrhythmias, including torsade de pointes, have been reported. It has been recommended that sultopride should not be used in patients with bradycardia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Barnetil; ***Rus.***: Topral (Топрал).

Tandospirone Citrate *(BANM, USAN, rINNM)*

Citrato de tandospirona; Metanopirone Citrate; SM-3997 (tandospirone or tandospirone citrate); Tandospirona, citrato de; Tandospirone, Citrate de; Tandospironi Citras; Тандоспирона Цитрат.

(1R*,2S*,3R*,4S*)-*N*-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-2,3-norbornanedicarboximide citrate.

$C_{21}H_{29}N_5O_2,C_6H_8O_7$=575.6

CAS — 87760-53-0 (tandospirone); 112457-95-1 (tandospirone citrate).

UNII — 0R8E9BWM4J.

Profile

Tandospirone, a partial agonist at serotonin (5-HT) receptors of the 5-HT_{1A} subtype, is an anxiolytic structurally related to buspirone (p. 1042.1). It also has antidepressant actions. Tandospirone citrate is given in usual oral doses of 30 mg daily in 3 divided doses up to a maximum of 60 mg daily.

References.

1. Sumiyoshi T, *et al.* The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. *Biol Psychiatry* 2001; **49:** 861–8.
2. Yamada K, *et al.* Clinical efficacy of tandospirone augmentation in patients with major depressive disorder: a randomized controlled trial. *Psychiatry Clin Neurosci* 2003; **57:** 183–7.
3. Takei A, *et al.* Treatment of cerebellar ataxia with 5-HT1A agonist. *Cerebellum* 2005; **4:** 211–15.
4. Miwa H, *et al.* Efficacy of the 5-HT1A agonist tandospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. *Am J Gastroenterol* 2009; **104:** 2779–87.

Bruxism. Tandospirone has been tried in the management of bruxism; for further details, see under Buspirone, p. 1042.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Lv Kang (律康); Sediel (希德); ***Jpn***: Sediel.

Tasimelteon *(USAN, rINN)*

BMS-214778; Tasimelteón; Tasimeltéon; Tasimelteonum; VEC-162; Тасимелтеон.

N-{[(1*R*,2*R*)-2-(2,3-Dihydro-1-benzofuran-4-yl)cyclopropyl]methyl}propanamide.

$C_{15}H_{19}NO_2$=245.3

CAS — 609799-22-6.

UNII — SHS4PU80D9.

Profile

Tasimelteon is a melatonin receptor agonist that is being investigated for the treatment of transient insomnia associated with circadian rhythm disturbances such as those caused by shift work or jet lag.

References.

1. Rajaratnam SMW, *et al.* Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 2009; **373:** 482–91.
2. Hardeland R. Tasimelteon, a melatonin agonist for the treatment of insomnia and circadian rhythm sleep disorders. *Curr Opin Investig Drugs* 2009; **10:** 691–701.

Temazepam *(BAN, USAN, rINN)*

ER-115; 3-Hydroxydiazepam; K-3917; Ro-5-5345; Tematsepaami; Temazepám; Témazépam; Temazepamas; Temazepamum; Wy-3917; Темазепам.

7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-1,4-benzodiazepin-2-one.

$C_{16}H_{13}ClN_2O_2$=300.7

CAS — 846-50-4.

ATC — N05CD07.

ATC Vet — QN05CD07.

UNII — CHB1QD2QSS.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of temazepam:

Beans; Egg; Eggs; Jellies; Jelly babies; Knockout Pills; Mazzies; Oranges; Rugby Balls; Temazies; Temmies; Terms; Wobbly jellies; Yellow eggs.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Temazepam). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Temazepam). A white or nearly white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from light.

Uses and Administration

Temazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (p. 1033.2) and for premedication before surgical or investigative procedures (see Anaesthesia, p. 1899.1).

A usual oral dose for insomnia is 10 to 20 mg at night; exceptionally, doses up to 40 mg may be required. For premedication the usual oral dose is 20 to 40 mg given half to one hour beforehand.

Temazepam should be given in reduced dosage to elderly or debilitated patients; half of the usual adult dose, or less, may be sufficient (see also Administration in the Elderly, below).

For details of doses in children, see Administration in Children, below.

Administration. For reference to the various formulations of oral temazepam that have been used, see Abuse under Adverse Effects, Treatment, and Precautions, below.

Administration in children. Temazepam may be given to children for premedication before surgical or investigative procedures. In the UK, licensed product information recommends a dose of 1 mg/kg as an oral solution 1 hour beforehand; the *BNFC* only recommends use in older children, and suggests that those aged 12 to 18 years may be given an oral dose of 10 to 20 mg.

Administration in the elderly. In a small study[1] a 7.5-mg dose of temazepam was found to be adequate for the short-term management of insomnia in elderly patients.

1. Vgontzas AN, *et al.* Temazepam 7.5 mg: effects on sleep in elderly insomniacs. *Eur J Clin Pharmacol* 1994; **46:** 209–13.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 10 mg of temazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Abuse. Liquid-filled temazepam *capsules* were widely abused on the illicit drugs market, the liquid gel lending itself to intravenous injection.[1] This formulation was, therefore, replaced in some countries by tablets or by semi-solid gel-filled capsules, which were intended to be difficult to inject even after heating or diluting the gel in various solvents.[2] In spite of this there is evidence of intravenous or intra-arterial abuse of these capsules,[3-5] and there are reports of ischaemia, in some cases necessitating amputation.[6-8] The *tablets* may also be liable to abuse; there has been a report of death after intravenous injection of a solution containing crushed temazepam tablets.[9] The manufacturers of a temazepam *elixir* considered that, because of its viscosity and its low strength relative to the liquid in the capsules, it had a low potential for intravenous abuse.[10] Nonetheless, there have been reports[3] of some drug abusers injecting large quantities of diluted elixir.

For mention of rhabdomyolysis associated with abuse of temazepam, see Effects on Skeletal Muscle, under Diazepam, p. 1066.2.

1. Farrell M, Strang J. Misuse of temazepam. *BMJ* 1988; **297:** 1402.
2. Launchbury AP. Temazepam abuse. *Pharm J* 1990; **244:** 749.
3. Ruben SM, Morrison CL. Temazepam misuse in a group of injecting drug users. *Br J Addict* 1992; **87:** 1387–92.
4. Scott RN, *et al.* Intra-arterial temazepam. *BMJ* 1992; **304:** 1630.
5. Adiseshiah M, *et al.* Intra-arterial temazepam. *BMJ* 1992; **304:** 1630.
6. Blair SD, *et al.* Leg ischaemia secondary to non-medical injection of temazepam. *Lancet* 1991; **338:** 1393–4.
7. Fox R, *et al.* Misuse of temazepam. *BMJ* 1992; **305:** 253.
8. Feeney GFX, Gibbs HH. Digit loss following misuse of temazepam. *Med J Aust* 2002; **176:** 380.
9. Vella EJ, Edwards CW. Death from pulmonary microembolization after intravenous injection of temazepam. *BMJ* 1993; **307:** 26.
10. Drake J, Ballard R. Misuse of temazepam. *BMJ* 1988; **297:** 1402.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of temazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Temazepam was detected in breast milk in only one of 10 mothers given temazepam as a bedtime sedative;[2] temazepam was given in a dose of 10 to 20 mg and milk concentrations were measured about 15 hours after a dose. The authors considered that breast-fed neonates would ingest negligible amounts of temazepam.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Lebedevs TH, *et al.* Excretion of temazepam in breast milk. *Br J Clin Pharmacol* 1992; **33:** 204–6.

Effects on the skin. Generalised lichenoid drug eruption that had persisted for 5 months in an elderly patient receiving therapy including temazepam resolved within 10 days of stopping the benzodiazepine.[1] Bullous eruptions associated with temazepam overdose have also been reported.[2]

1. Norris P, Sounex TS. Generalised lichenoid drug eruption associated with temazepam. *BMJ* 1986; **293:** 510.
2. Verghese J, Merino J. Temazepam overdose associated with bullous eruptions. *Acad Emerg Med* 1999; **6:** 1071.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, and UK licensed product information advises that temazepam should be avoided in severe cases. However, short-acting benzodiazepines such as temazepam may pose less risk in patients with hepatic impairment; in a study of 15 patients with cirrhosis and 16 healthy subjects, liver disease had no significant effect on the pharmacokinetic parameters or pattern of elimination of temazepam.[1]

1. Ghabrial H, *et al.* The effects of age and chronic liver disease on the elimination of temazepam. *Eur J Clin Pharmacol* 1986; **30:** 93–7.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Temazepam is fairly readily absorbed from the gastrointestinal tract, although the exact rate of absorption depends on the formulation. It is about 96% bound to plasma proteins. Temazepam is metabolised mainly in the liver; mean elimination half-lives of about 8 to 15 hours or longer have been reported. It is excreted mainly in the urine in the form of its inactive glucuronide conjugate together with small amounts of the demethylated derivative, oxazepam, also in conjugated form. Temazepam is distributed into breast milk.

Absorption and plasma concentration. Various oral temazepam formulations have been available worldwide. These included powder-filled hard gelatin capsules, liquid-filled soft gelatin capsules, semi-solid gel-filled soft gelatin capsules, and an elixir. There has been considerable debate over the comparative absorption profiles of temazepam from these formulations which have, in some cases, been modified over the years. It should be noted that pharmacokinetic studies of temazepam do not always clearly state the formulation used.

Temazepam 30 mg was given as a premedicant to 80 patients undergoing surgery in the form of capsules [type not stated] or elixir.[1] Mean peak plasma concentrations of about 800 nanograms/mL occurred 30 minutes after a dose of either formulation although there was wide interindividual variation in plasma concentrations. The evidence corresponded with previous suggestions that a plasma concentration of about 250 nanograms/mL or more was required to ensure sedation. The presence or absence of anxiety did not influence the absorption of the preparations.

1. Hosie HE, Nimmo WS. Temazepam absorption in patients before surgery. *Br J Anaesth* 1991; **66:** 20–4.

Distribution into CSF. A study in 13 male patients showed a correlation between the unbound concentration of temazepam in plasma and the amount of temazepam detected in CSF.[1] The mean CSF to total plasma temazepam concentration ratio was 5.2.

1. Badcock NR. Plasma and cerebrospinal fluid concentrations of temazepam following oral drug administration. *Eur J Clin Pharmacol* 1990; **38:** 153–5.

Metabolism. References.

1. Locniskar A, Greenblatt DJ. Oxidative versus conjugative biotransformation of temazepam. *Biopharm Drug Dispos* 1990; **11:** 499–506.

Sex differences. The elimination half-life was significantly longer at 16.8 hours among 17 women given temazepam 30 mg compared with 12.3 hours among 15 men.[1] The total clearance was also lower among women. After correction for differences in protein binding, unbound clearance was still lower in women than men but there was no significant effect of age on this parameter. Time to peak

plasma concentration and volume of distribution were not affected by the age or sex of the subjects.

1. Divoll M, *et al.* Effect of age and gender on disposition of temazepam. *J Pharm Sci* 1981; **70:** 1104–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Normison; Temaze; Temtabs; ***Canad.***: Restoril; ***Fin.***: Tenox; ***Fr.***: Normison; ***Ger.***: Planum; Pronervon T†; Remestan; Temazep†; ***Gr.***: Euhypnos; Normison; Reposium; Tonirem; ***Hung.***: Signopam; ***Irl.***: Insomniger; Nortem; Tenox; ***Ital.***: Euipnos†; Normison; ***Neth.***: Normison; ***NZ***: Euhypnos; Normison; ***Pol.***: Signopam; ***Port.***: Normison; ***Rus.***: Signopam (Сигнопам); ***S.Afr.***: Normison; ***Switz.***: Normison; ***Thai.***: Euhypnos; ***USA***: Restoril.

Pharmacopoeial Preparations
BP 2014: Temazepam Oral Solution; Temazepam Tablets;
USP 36: Temazepam Capsules.

Tetrazepam *(BAN, pINN)*

CB-4261; Tetratsepaami; Tetrazepám; Tétrazépam; Tetrazepamas; Tetrazepamum; Тетразепам.
7-Chloro-5-(cyclohex-1-enyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.
$C_{16}H_{17}ClN_2O$=288.8
CAS — 10379-14-3.
ATC — M03BX07.
ATC Vet — QM03BX07.
UNII — FO92091VP8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tetrazepam). A light yellow or yellow crystalline powder. Practically insoluble in water; soluble in acetonitrile; freely soluble in dichloromethane. Protect from light.

Profile

Tetrazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been used for its muscle relaxant properties in the treatment of muscle spasm; however, serious cutaneous reactions have been reported and this has led to the suspension of tetrazepam in the EU (see below for further details).

Effects on the skin. There have been case reports of cutaneous reactions to tetrazepam, including contact dermatitis,[1-4] erythema multiforme,[5] acute generalised exanthematous pustulosis,[6] and toxic epidermal necrolysis.[7] Of 9 patients who had had cutaneous reactions to tetrazepam none had reactions to diazepam, bromazepam, or lorazepam and in 5 cases where oral provocation tests were performed there were also no reactions.[8]

In April 2013, the European Pharmacovigilance Risk Assessment Committee (PRAC) reviewed[9] all available data on the risk of cutaneous reactions with tetrazepam, and its efficacy in licensed indications. It was found that half of all reported reactions were cutaneous; some of which were serious, life-threatening, or fatal, and included Stevens-Johnson syndrome and DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. These reactions were unpredictable and occurred at any stage during treatment, including after short-term therapy and at recommended doses. Moreover, the risk of cutaneous reactions was found to be higher with tetrazepam than with other benzodiazepines and the data on its efficacy were not sufficiently robust to support its use. Consequently, the European Medicines Agency suspended the marketing authorisation of tetrazepam in the EU.

1. Lepp U, *et al.* Occupational airborne contact allergy to tetrazepam. *Contact Dermatitis* 2003; **49:** 260–1.
2. Ferran M, *et al.* Occupational airborne contact dermatitis from sporadic exposure to tetrazepam during machine maintenance. *Contact Dermatitis* 2005; **52:** 173–4.
3. Breuer K, *et al.* Occupational airborne contact allergy to tetrazepam in a geriatric nurse. *J Dtsch Dermatol Ges* 2009; **7:** 896–8.
4. Vander Hulst K, *et al.* Occupational allergic contact dermatitis from tetrazepam in nurses. *Contact Dermatitis* 2010; **62:** 303–8.
5. Cabrerizo Ballesteros S, *et al.* Erythema multiforme to tetrazepam. *J Investig Allergol Clin Immunol* 2007; **17:** 205–6.
6. Thomas E, *et al.* Acute generalized exanthematous pustulosis due to tetrazepam. *J Investig Allergol Clin Immunol* 2008; **18:** 119–22.
7. Delesalle F, *et al.* Toxic epidermal necrolysis caused by tetrazepam. *Int J Dermatol* 2006; **45:** 480.
8. Barbaud A, *et al.* No cross-reactions between tetrazepam and other benzodiazepines: a possible chemical explanation. *Contact Dermatitis* 2009; **61:** 53–6.
9. EMEA. Tetrazepam-containing medicines (issued 24th April, 2013). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Tetrazepam_containing_medicinal_products/human_referral_prac_000015.jsp&mid=WC0b01ac05805c516f (accessed 04/12/13)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Myolastan†; ***Belg.***: Epsipam†; Myolastan†; ***Cz.***: Myolastan†; ***Fr.***: Myolastan†; Panos†; ***Ger.***: Musapam†; Musaril†; Myospasmal†; Rilex†; Tetra-saar†; Tetrazep†; ***Mex.***: Miolastan; ***Pol.***: Miozepam†; Myolastan†; Myopam†; Tetraratio†; ***Spain***: Myolastan†.

Thioproperazine Mesilate *(BANM, rINNM)*

Mesilato de tioproperazina; RP-7843; SKF-5883; Thioproperazine Dimethanesulphonate; Thiopropérazine, Mésilate de; Thioproperazine Mesylate; Thioproperazine Methanesulphonate; Thioproperazini Mesilas; Tioproperazina, mesilato de; Тиопроперазина Мезилат.
NN-Dimethyl-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine-2-sulphonamide dimethanesulphonate.
$C_{22}H_{30}N_4O_2S_2.2CH_4O_3S$=638.8
CAS — 316-81-4 (thioproperazine); 2347-80-0 (thioproperazine mesilate).
ATC — N05AB08.
ATC Vet — QN05AB08.
UNII — 71P630M192.

Pharmacopoeias. In *Fr.*

Profile

Thioproperazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has a piperazine side-chain. It is used in the treatment of schizophrenia (p. 1031.3), mania (see Bipolar Disorder, p. 397.2), and other psychoses. Thioproperazine is given as the mesilate although doses are expressed in terms of the base; thioproperazine mesilate 7.2 mg is equivalent to about 5 mg of thioproperazine. Initial daily doses of 5 mg are given orally, increased as necessary; the usual effective dosage is 30 to 40 mg daily. In severe or resistant cases daily doses of 90 mg or more have been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Majeptil; ***Gr.***: Majeptil; ***Rus.***: Majeptil (Мажептил).

Thioridazine *(BAN, USAN, rINN)*

Thioridazin; Thioridazinum; Tioridatsiini; Tioridazin; Tioridazina; Tioridazinas; TP-21; Тиоридазин.
10-[2-(1-Methyl-2-piperidyl)ethyl]-2-methylthiophenothiazine.
$C_{21}H_{26}N_2S_2$=370.6
CAS — 50-52-2.
ATC — N05AC02.
ATC Vet — QN05AC02.
UNII — N3D6TG58NI.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Thioridazine). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Thioridazine). A white to slightly yellow crystalline or micronised powder; odourless or having a faint odour. Practically insoluble in water; freely soluble in dehydrated alcohol and in ether; very soluble in chloroform. Protect from light.

Thioridazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tioridazina; Thioridazin hydrochlorid; Thioridazine, chlorhydrate de; Thioridazinhydrochlorid; Thioridazini Hydrochloridum; Tioridatsiinihydrokloridi; Tioridazina, hidrocloruro de; Tioridazinhidroklorid; Tioridazinhydroklorid; Tioridazino hidrochloridas; Tiorydazny chlorowodorek; Tiorydazyny chlorowodorek; Тиоридазина Гидрохлорид.
$C_{21}H_{26}N_2S_2$,HCl=407.0
CAS — 130-61-0.
ATC — N05AC02.
ATC Vet — QN05AC02.
UNII — 4WCI67NK8M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Thioridazine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Thioridazine Hydrochloride). A white to slightly yellow granular powder having a slight odour. Freely soluble in water, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. For a warning about incompatibility between thioridazine hydrochloride solution (*Mellaril; Novartis, USA*) and carbamazepine suspension (*Tegretol; Novartis, USA*), see p. 512.2.

Uses and Administration

Thioridazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain and, unlike chlorpromazine, has little antiemetic activity.

The use of thioridazine has been restricted to the treatment of schizophrenia (p. 1031.3) in patients who fail to show an adequate response to treatment with other antipsychotics. Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential; it has been withdrawn in some countries, including the UK.

For all patients starting thioridazine it is recommended that ECG and electrolyte screening are performed periodically (see Precautions, p. 1111.1 for details).

Thioridazine is given orally as the hydrochloride or the base, and doses may be expressed in terms of either. In some countries, doses of oral liquid preparations have been given in terms of the base, whereas those of the tablets have been given as the hydrochloride. In the USA, all doses are given in terms of the hydrochloride. Thioridazine 22.8 mg is equivalent to about 25 mg of thioridazine hydrochloride.

In the treatment of schizophrenia thioridazine hydrochloride should be started at the usual dose of 50 to 100 mg three times daily and slowly titrated upwards to a maximum of 800 mg daily if necessary; doses should be reduced once effective control is achieved. The daily dosage range is 200 to 800 mg, which may be given in 2 to 4 divided doses. It has been recommended that increases in doses should be no more than 100 mg weekly.

Thioridazine should be given in lower initial doses to patients with a low body-mass or those with hepatic or renal impairment; dosage increases should also be more gradual.

In those patients who require withdrawal of thioridazine, the dose should be gradually reduced over 1 to 2 weeks to avoid symptoms such as gastrointestinal disorders, dizziness, anxiety, and insomnia that are sometimes seen after abruptly stopping high-dose or long-term treatment.

References.

1. Fenton M, *et al.* Thioridazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/03/08).

Adverse Effects and Treatment

As for Chlorpromazine, p. 1047.2.

Thioridazine has been associated with a higher incidence of antimuscarinic effects, but lower incidence of extrapyramidal effects than chlorpromazine. It may also be less sedating. However, it is more likely to induce hypotension and there is an increased risk of cardiotoxicity and dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use has been restricted (see Precautions, and Uses and Administration, p. 1111.1 and above, respectively). Sexual dysfunction also appears to be more frequent with thioridazine.

Pigmentary retinopathy characterised by reduced visual acuity, brownish colouring of vision, and impairment of night vision has been seen particularly in patients taking large doses.

Effects on the cardiovascular system. Between 1964 and 2001, the UK CSM received 42 reports of suspected heart rate and rhythm disorders associated with thioridazine.[1] There were 21 fatalities reported out of 39 cases where the outcome was known.

See also under Chlorpromazine, p. 1047.3.

1. CSM/MCA. QT interval prolongation with antipsychotics. *Current Problems* 2001; **27:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 12/05/06)

Hypersensitivity. Pruritus and erythematous rash on the genitals of a woman after sexual intercourse were found to be due to thioridazine present in the seminal fluid of her husband, who was taking 100 mg daily at night.[1]

1. Sell MB. Sensitization to thioridazine through sexual intercourse. *Am J Psychiatry* 1985; **142:** 271–2.

Overdosage. Rhabdomyolysis has been reported in a patient after overdosage with thioridazine.[1] Twenty-four hours after taking 9.4 g of thioridazine the patient presented with difficulty in moving and speaking. On examination he had swelling and tenderness over his upper arms, thighs, and calves. Ataxia and transient dysarthria were attributed to generalised muscle weakness. Other

effects were consistent with antimuscarinic effects of thioridazine. He had no signs of neuroleptic malignant syndrome but his urine contained myoglobin. The patient was treated with gastric lavage, activated charcoal, and rehydration. Serum biochemistry returned to normal over 1 week and the muscle tenderness and weakness disappeared.

1. Nankivell BJ, *et al*. Rhabdomyolysis induced by thioridazine. *BMJ* 1994; **309:** 378.

Precautions

As for Chlorpromazine, p. 1050.3. Thioridazine should not be used in patients with clinically significant cardiac disorders, uncorrected hypokalaemia or other electrolyte imbalance, with known or suspected QT prolongation or a family history of QT prolongation, or with a history of ventricular arrhythmias including torsade de pointes. Use is also contra-indicated in patients known to have reduced activity of the cytochrome P450 isoenzyme CYP2D6, which is responsible for thioridazine metabolism. Use with drugs liable to interfere with the metabolism of thioridazine, with other drugs known to prolong the QT interval, and with drugs likely to cause electrolyte imbalance should also be avoided (see under Interactions, below).

For all patients starting thioridazine it is recommended that a baseline ECG and electrolyte screening are performed. An ECG should also be repeated before each dose increase, 1 week after the maximum therapeutic dose has been reached, and at 6-monthly intervals in those who continue treatment. Serum electrolyte concentrations should also be monitored periodically during treatment and any imbalance corrected.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thioridazine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3. The metabolism of thioridazine is mediated by the cytochrome P450 isoenzyme CYP2D6; thioridazine itself is also an inhibitor of CYP2D6. Therefore, there is the potential for interactions between thioridazine and other drugs that inhibit or act as a substrate for this enzyme; such drugs should not be given with thioridazine. Some examples include antiarrhythmics, certain antidepressants including the SSRIs and tricyclics, certain antipsychotics, beta blockers, HIV-protease inhibitors, and opioids.

Use with other drugs known to prolong the QT interval such as class IA and class III antiarrhythmics, tricyclic antidepressants, and some other antipsychotics should also be avoided, as should use with those drugs known to cause electrolyte imbalance.

Pharmacokinetics

The pharmacokinetics of thioridazine appear to be generally similar to those of chlorpromazine (p. 1053.3). Thioridazine is metabolised by the cytochrome P450 isoenzyme CYP2D6. Its main active metabolite is mesoridazine (p. 1084.2); another metabolite, sulforidazine, also has some activity. Thioridazine and its active metabolites are reported to be highly bound to plasma proteins (more than 95%). The plasma half-life of thioridazine has been estimated to be about 4 to 10 hours. It also crosses the placenta and is distributed into breast milk.

References.

1. Mårtensson E, Roos B-E. Serum levels of thioridazine in psychiatric patients and healthy volunteers. *Eur J Clin Pharmacol* 1973; **6:** 181–6.
2. Axelsson R, Mårtensson E. Serum concentration and elimination from serum of thioridazine in psychiatric patients. *Curr Ther Res* 1976; **19:** 242–65.

Metabolism. In 10 psychiatric patients stabilised on thioridazine, therapy was replaced by equipotent doses of the side-chain sulfoxide (mesoridazine) and side-chain sulfone (sulforidazine) metabolites of thioridazine.[1] Both metabolites were shown to have an antipsychotic effect, the dose of each required being about two-thirds that of thioridazine. The serum half-lives were thioridazine 21 hours, mesoridazine 16 hours, and sulforidazine 13 hours. Apathy, depression, and restlessness gradually developed during treatment with the 2 metabolites and they could not be used for any length of time. Extrapyramidal symptoms, hypersalivation, and drowsiness were more common with the metabolites; 2 patients had epileptic seizures, and 1 receiving sulforidazine developed probable cholestatic jaundice.

There is some evidence that the metabolism of thioridazine is influenced by debrisoquine hydroxylation phenotype.[2] A single-dose study in 19 healthy male subjects found slower formation of mesoridazine, and hence higher serum-thioridazine concentrations in poor debrisoquine hydroxylators compared with extensive hydroxylators. Formation of thioridazine ring-sulfoxide appeared to be compensatorily increased in slow hydroxylators.

1. Axelsson R. On the serum concentrations and antipsychotic effects of thioridazine, thioridazine side-chain sulfoxide and thioridazine side-chain sulfone, in chronic psychotic patients. *Curr Ther Res* 1977; **21:** 587–605.
2. von Bahr C, *et al*. Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. *Clin Pharmacol Ther* 1991; **49:** 234–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Meleril; ***Austral.***: Aldazine†; ***Braz.***: Melleril; Unitidazin; ***Chile***: Simultan; ***China***: Ridazine (利达新); ***Ger.***: Melleril; ***Gr.***: Detril; Elperil; Melleril; ***India***: Melleril; Melozine; Thioril; ***Indon.***: Melleril†; ***Israel***: Ridazin; ***Mex.***: Dazithin; Melleril; ***NZ***: Aldazine†; ***Philipp.***: Thiozine; ***Rus.***: Sonapax (Сонапакс); Thiodazine (Тиодазин); Thioril (Тиорил); Tison (Тисон); ***Thai.***: Dazine-P; Ridazine; Thiomed; Thiosia; ***Turk.***: Mellerettes; Melleril; ***Ukr.***: Ridazine (Ридазин)†; Sonapax (Сонапакс).

Pharmacopoeial Preparations

USP 36: Thioridazine Hydrochloride Oral Solution; Thioridazine Hydrochloride Tablets; Thioridazine Oral Suspension.

Tiapride Hydrochloride *(BANM, rINNM)*

FLO-1347; Hidrocloruro de tiaprida; Tiaprida, hidrocloruro de; Tiapride, Chlorhydrate de; Tiaprid-hidroklorid; Tiapridhydrochlorid; Tiaprid-hydrochlorid; Tiapridhydroklorid; Tiapridi hydrochloridum; Tiapridihydrokloridi; Tiaprido hidrochloridas; Тиаприда Гидрохлорид.

N-(2-Diethylaminoethyl)-2-methoxy-5-methylsulphonylbenzamide hydrochloride.

$C_{15}H_{24}N_2O_4S,HCl$=364.9

CAS — 51012-32-9 (tiapride); 51012-33-0 (tiapride hydrochloride).

ATC — N05AL03.

ATC Vet — QN05AL03.

UNII — 25N106WEDO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tiapride Hydrochloride). A white or almost white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. A 5% solution in water has a pH of 4.0 to 6.0.

Uses and Administration

Tiapride is a substituted benzamide with general properties similar to those of sulpiride (p. 1107.3).

It is usually given as the hydrochloride in the management of behavioural disorders (below), to treat dyskinesias (see Extrapyramidal Disorders, below), and as an analgesic. Doses are expressed in terms of the equivalent amount of base; tiapride hydrochloride 222.2 mg is equivalent to about 200 mg of tiapride. Oral doses of 100 to 300 mg daily are usually given for behavioural disorders; higher daily doses have been used in the management of dyskinesias. Oral doses of 200 to 400 mg daily may be given for severe intractable pain. Tiapride hydrochloride has also been given by intramuscular or intravenous injection.

Disturbed behaviour. For a discussion of the management of disturbed behaviour including limitations on the use of antipsychotics, see p. 1030.2.

References.

1. Gutzmann H, *et al*. Measuring the efficacy of psychopharmacological treatment of psychomotoric restlessness in dementia: clinical evaluation of tiapride. *Pharmacopsychiatry* 1997; **30:** 6–11.
2. Allain H, *et al*. Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. *Psychopharmacology (Berl)* 2000; **148:** 361–6.

Extrapyramidal disorders. Tiapride has been tried in the treatment of antipsychotic-induced tardive dyskinesia (p. 1049.3), but, as with all antipsychotics, improvement may only be short-term.

Tiapride has also been tried in the treatment of Tourette's syndrome (see Tics, p. 1030.1).

For reference to the use of tiapride in suppressing the adverse effects of levodopa on respiration, see p. 905.3.

CHOREA. Antipsychotics have some action against choreiform movements as well as being of use to control the behavioural disturbances of Huntington's chorea, and tiapride has been quite widely used for this purpose. For a discussion of the management of various choreas, see p. 1029.3.

References.

1. Roos RAC, *et al*. Tiapride in the treatment of Huntington's chorea. *Acta Neurol Scand* 1982; **65:** 45–50.
2. Deroover J, *et al*. Tiapride versus placebo: a double-blind comparative study in the management of Huntington's chorea. *Curr Med Res Opin* 1984; **9:** 329–38.

Substance dependence. An early review[1] concluded that the role of tiapride in acute *alcohol* withdrawal (p. 1735.1) was likely to be limited as patients at risk of severe reactions would still require adjunctive therapy for the control of hallucinations and seizures. In one study,[2] following detoxification, tiapride appeared to help, to some degree, to alleviate distress, improve abstinence and drinking behaviour, and facilitate reintegration within society but a subsequent study[3] failed to find any advantage over placebo. Interest in its use with carbamazepine continues.[4-6]

1. Peters DH, Faulds D. Tiapride: a review of its pharmacology and therapeutic potential in the management of alcohol dependence syndrome. *Drugs* 1994; **47:** 1010–32.
2. Shaw GK, *et al*. Tiapride in the prevention of relapse in recently detoxified alcoholics. *Br J Psychiatry* 1994; **165:** 515–23.
3. Bender S, *et al*. The efficacy of the dopamine D_2/D_3 antagonist tiapride in maintaining abstinence: a randomized, double-blind, placebo-controlled trial in 299 alcohol-dependent patients. *Int J Neuropsychopharmacol* 2007; **10:** 653–60.
4. Franz M, *et al*. Treatment of alcohol withdrawal: tiapride and carbamazepine versus clomethiazole: a pilot study. *Eur Arch Psychiatry Clin Neurosci* 2001; **251:** 185–92.
5. Lucht M, *et al*. Alcohol withdrawal treatment in intoxicated vs non-intoxicated patients: a controlled open-label study with tiapride/carbamazepine, clomethiazole and diazepam. *Alcohol Alcohol* 2003; **38:** 168–75.
6. Soyka M, *et al*. Efficacy and safety of outpatient alcohol detoxification with a combination of tiapride/carbamazepine: additional evidence. *Pharmacopsychiatry* 2006; **39:** 30–4.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Effects on the cardiovascular system. Torsade de pointes developed after a single dose of tiapride in an elderly patient with cardiac disease, a known risk factor for such arrhythmias.[1]

1. Iglesias E, *et al*. Tiapride-induced torsade de pointes. *Am J Med* 2000; **109:** 509.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Tiapride is rapidly absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is excreted largely unchanged in the urine. The plasma half-life is reported to range from 3 to 4 hours. It is thought to be distributed into breast milk on the basis of *animal* studies.

The steady-state pharmacokinetics of tiapride have been studied in 5 elderly patients with tardive dyskinesia, and in 2 patients with Huntington's chorea.[1] All patients received oral tiapride 100 mg three times daily for 7 days. The mean peak plasma concentration of tiapride was 1.47 micrograms/mL, achieved a mean of 1.4 hours after dosing, and the mean elimination half-life was 3.8 hours. These values did not differ significantly from those previously reported in younger healthy subjects, although renal clearance was slightly lower in these patients. About half of the dose of tiapride was excreted unchanged by the kidneys; a metabolite, probably *N*-monodesethyltiapride was detected in the urine but its identity was not confirmed.

1. Roos RAC, *et al*. Pharmacokinetics of tiapride in patients with tardive dyskinesia and Huntington's disease. *Eur J Clin Pharmacol* 1986; **31:** 191–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Delpral; ***Belg.***: Tiapridal; ***Braz.***: Tiapridal; ***Chile***: Sereprid; ***China***: Luo Yi (罗逸); Shang Yan (尚岩); Wei Qi (维奇); ***Cz.***: Tiapra; Tiapralan; Tiapridal; ***Fr.***: Tiapridal; ***Ger.***: Tiapridex†; ***Gr.***: Tiapridal; ***Hung.***: Tiager; Tiapridal; ***Ital.***: Italprid; Sereprile; ***Jpn***: Gramalil; ***Neth.***: Elbaprid†; Tiacob†; Tiapridal; Tiazet; ***Pol.***: Tiapridal; ***Port.***: Tiapridal; ***Rus.***: Tiapridal (Тиапридал); ***Singapore***: Tiapridal; ***Spain***: Tiaprizal; ***Switz.***: Tiapridal.

Timiperone *(rINN)*

DD-3480; Timiperona; Timipérone; Timiperonum; Тимиперон.

4′-Fluoro-4-[4-(2-thioxo-1-benzimidazolinyl)piperidino] butyrophenone.

$C_{22}H_{24}FN_3OS$=397.5

CAS — 57648-21-2.

UNII — 626DQ7N19L.

Profile

Timiperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given orally or by intravenous or intramuscular injection in the treatment of schizophrenia. Timiperone has also been given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Celmanil; Tolopelon.

Tiotixene *(BAN, rINN)*

NSC-108165; P-4657B; Thiothixene (USAN); Thiothixene; Tiotikseeni; Tiotixen; Tiotixène; Tiotixeno; Tiotixenum; Тиотиксен.

(*Z*)-*NN*-Dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulphonamide.

$C_{23}H_{29}N_3O_2S_2$=443.6

CAS — 5591-45-7; 3313-26-6 (tiotixene Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

UNII — 7318FJ13YJ.

Pharmacopoeias. In *US*.

USP 36: (Thiothixene). White to tan, practically odourless, crystals. Practically insoluble in water; soluble 1 in 110 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 120 of ether; slightly soluble in acetone and in methyl alcohol. Store in airtight containers. Protect from light.

Tiotixene Hydrochloride *(BANM, rINNM)*

CP-12252-1; Hidrocloruro de tiotixeno; Thiothixene Hydrochloride (USAN); Tiotixène, Chlorhydrate de; Tiotixeni Hydrochloridum; Tiotixeno, hidrocloruro de; Тиотиксена Гидрохлорид.

$C_{23}H_{29}N_3O_2S_2,2HCl,2H_2O$=552.6

CAS — 58513-59-0 (anhydrous tiotixene hydrochloride); 49746-04-5 (anhydrous tiotixene hydrochloride, Z-isomer); 22189-31-7 (tiotixene hydrochloride dihydrate); 49746-09-0 (tiotixene hydrochloride dihydrate, Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

UNII — B3CRJ1EWJU.

Pharmacopoeias. In *US*, which permits both the dihydrate and the anhydrous form.

USP 36: (Thiothixene Hydrochloride). It is anhydrous ($C_{23}H_{29}N_3O_2S_2,2HCl$ = 516.5) or contains two molecules of water of hydration. A white or practically white crystalline powder having a slight odour. Soluble 1 in 8 of water, 1 in 270 of dehydrated alcohol, and 1 in 280 of chloroform; practically insoluble in acetone, in ether, and in benzene. Store in airtight containers. Protect from light.

Stability. A combination of the stabilisers hydroxyquinoline sulfate and vanillin could protect tiotixene from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Uses and Administration

Tiotixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain. It is used in the treatment of psychoses including schizophrenia (p. 1031.3). Tiotixene is given orally as the base or hydrochloride; it has also been given by intramuscular injection as the hydrochloride. Doses are expressed in terms of the base. Tiotixene 1 mg is equivalent to about 1.2 mg of tiotixene hydrochloride.

The usual initial oral dose is 2 mg three times daily (or 5 mg twice daily in more severe conditions) gradually increasing to 20 to 30 mg daily if necessary; once-daily dosage may be adequate. In severe or resistant psychoses doses of up to 60 mg daily may be given. A dose of 4 mg two to four times daily increased if necessary to a maximum of 30 mg daily has been given intramuscularly.

Tiotixene should be given in reduced dosage to elderly or debilitated patients.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Tiotixene is less likely to cause sedation but extrapyramidal effects are more frequent.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

In 15 adequately controlled schizophrenic patients receiving oral tiotixene 15 to 60 mg daily in 2, 3, or 4 divided doses, plasma concentrations were found to be in the relatively narrow range of 10 to 22.5 nanograms/mL 126 to 150 minutes after the last daily dose despite the fourfold difference in dosage.[1] Investigations in a further 5 patients indicated that peak plasma concentrations were obtained about 1 to 3 hours after a dose, indicating rapid absorption with an absorption half-time of about 30 minutes. There was an early plasma half-life of about 210 minutes and a late half-life of about 34 hours; resurgence of drug concentrations in some subjects might have been due to enterohepatic recycling.

1. Hobbs DC, *et al.* Pharmacokinetics of thiothixene in man. *Clin Pharmacol Ther* 1974; **16:** 473–8.

Metabolism. There has been a study[1] indicating that tiotixene may induce its own metabolism.

1. Bergling R, *et al.* Plasma levels and clinical effects of thioridazine and thiothixene. *J Clin Pharmacol* 1975; **15:** 178–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Navane†; ***Canad.***: Navane; ***Hong Kong***: Navane†; ***NZ***: Thixit†; ***USA***: Navane.

Pharmacopoeial Preparations

USP 36: Thiothixene Capsules; Thiothixene Hydrochloride for Injection; Thiothixene Hydrochloride Injection; Thiothixene Hydrochloride Oral Solution.

Tofisopam *(rINN)*

EGYT-341; Tofisopaami; Tofisopamum; Tofizopam; Тофизопам.

1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine.

$C_{22}H_{26}N_2O_4$=382.5

CAS — 22345-47-7.

ATC — N05BA23.

ATC Vet — QN05BA23.

UNII — UZC80HAU42.

Pharmacopoeias. In *Jpn*.

Profile

Tofisopam is a short-acting 2,3-benzodiazepine related structurally to the 1,4-benzodiazepines such as diazepam (p. 1063.2) and sharing some of the same actions. It is reported, however, to be largely lacking in the sedative, anticonvulsant, and muscle relaxant properties of the conventional benzodiazepines. Tofisopam has been given orally in the short-term treatment of anxiety disorders. The *R*-(+)-isomer, dextofisopam, is under investigation in the treatment of irritable bowel syndrome.

References.

1. Leventer SM, *et al.* Clinical trial: dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. *Aliment Pharmacol Ther* 2008; **27:** 197–206.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Grandaxin; ***Hung.***: Grandaxin; ***Jpn***: Bydaxin; Clasopan†; Cobandaxin; Emandaxin†; Grandaxin; Granpam; Hymidin; Myronin; Tofiel; Tofilsin; Tofis; Tolbanasin; Tronheim; Tsurubel; ***Rus.***: Grandaxin (Грандаксин); ***Thai.***: Grandaxin.

Triacetonamine Tosilate

Tempidon; Триацетонамина Тозилат.

2,2,6,6-Tetramethyl-4-piperidone toluene-4-sulfonate.

$C_{16}H_{25}NO_4S$=327.4

CAS — 826-36-8 (triacetonamine); 29334-13-2 (triacetonamine tosilate).

Profile

Triacetonamine tosilate has anxiolytic actions and is used in combination preparations with analgesics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Tempalgin (Темпалгин); Tempanginol (Темпангинол); ***Ukr.***: Tempalgin (Темпалгин); Tempanal (Темпанал).

Triazolam *(BAN, USAN, rINN)*

Clorazolam; Triatsolaami; Triazolamum; U-33030; Триазолам.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine.

$C_{17}H_{12}Cl_2N_4$=343.2

CAS — 28911-01-5.

ATC — N05CD05.

ATC Vet — QN05CD05.

UNII — 1HM943223R.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Triazolam). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 1000 of alcohol, 1 in 25 of chloroform, and 1 in 600 of 0.1N hydrochloric acid.

Uses and Administration

Triazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term (up to 2 weeks) management of insomnia (p. 1033.2) in oral doses of 125 to 250 micrograms at night; doses of up to 500 micrograms at night have been used for resistant cases but these may be associated with an increased risk of severe adverse effects (see Effects on Mental Function, below). Initial doses of 125 micrograms at night have been suggested for elderly or debilitated patients, increased up to a maximum of 250 micrograms only if necessary.

Administration in hepatic or renal impairment. See under Precautions, p. 1113.1.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects and Treatment

As for Diazepam, p. 1065.3.

Effects on the liver. A 44-year-old man developed severe pruritus with jaundice which subsequently proved fatal. Liver histology showed intense cholestasis. Triazolam was considered to be the most likely cause.[1]

1. Cobden I, *et al.* Fatal intrahepatic cholestasis associated with triazolam. *Postgrad Med J* 1981; **57:** 730–1.

Effects on mental function. The effects of triazolam on mental function have been controversial since van der Kroef first described in 1979 a range of symptoms including anxiety, amnesia, depersonalisation and derealisation, depression, paranoia, and severe suicidal tendencies that he had seen in 25 patients and attributed to triazolam.[1] This led to suspension of triazolam in the Netherlands (reapproved in 1990) and removal of the 1-mg tablet from other markets. Continued reporting of similar symptoms of cognitive impairment with triazolam resulted in withdrawal of the 500-microgram dosage form in several countries in 1987 and 1988 and in a gradual reduction of recommended dosage from 1 mg at night down to 125 to 250 micrograms at night. Subsequently, all strengths of triazolam were withdrawn from the UK[2] and some other markets in 1991. Opinion remained divided over the adverse effects of triazolam, the main issues being its propensity to cause adverse effects relative to other benzodiazepines and whether its risk-benefit ratio is acceptable to justify its continued use.[3,4]

Others[5] have reviewed spontaneous adverse effects reported to the FDA for triazolam, temazepam, and flurazepam. Daytime sedation was noted with all three, but triazolam caused more agitation, confusion, hallucinations, and amnesia. Such effects occurred frequently with the 250-microgram dose as well as with the 500-microgram dose. Similar results were obtained after analysis of reports for triazolam and temazepam in the first 7 years of marketing, although the possibility that selection factors were producing higher reporting rates for triazolam could not be entirely excluded.[6] When triazolam 500 micrograms, lormetazepam 2 mg, or placebo, was given to groups of 40 patients for 25 nights the greatest frequency of daytime anxiety, panic, derealisation, and paranoia was noted with triazolam.[7] Another study[8] found a greater total number of reports of memory impairment or amnesia after nightly doses of triazolam 500 micrograms compared with temazepam 30 mg. Triazolam also impaired delayed, but not immediate, memory recall. Similar cases of memory impairment occurring with triazolam at doses of 125 and 250 micrograms have reportedly been submitted to the UK CSM.[2] The emergence of daytime symptoms after more than a few days' treatment with triazolam could be attributed to rebound or withdrawal phenomena occurring as a result of rapid elimination of the drug.

As regards the risk-benefit ratio of triazolam some have questioned the hypnotic efficacy of the drug at a dose of

250 micrograms and consider that reduction of the dose has decreased efficacy more than adverse effects.[3]

In defence of triazolam, the FDA and the manufacturers (*Upjohn*) have considered epidemiological studies which, unlike the FDA spontaneous reporting scheme, have been unable to find a substantial difference in its adverse effects compared with other benzodiazepines except, perhaps, in the incidence of amnesia.[9] Retrospective studies[10,11] claiming similar findings have been the subject of criticism.[12-14] Other workers have cited studies indicating benefit of triazolam 250 micrograms for the treatment of insomnia.[15] A review by the US Institute of Medicine found that triazolam was safe when given in a dose of 250 micrograms daily for 7 to 10 days but called for studies of lower doses and of long-term use.[16]

1. Van der Kroef C. Reactions to triazolam. *Lancet* 1979; **ii:** 526.
2. Anonymous. The sudden withdrawal of triazolam—reasons and consequences. *Drug Ther Bull* 1991; **29:** 89–90.
3. O'Donovan MC, McGuffin P. Short acting benzodiazepines. *BMJ* 1993; **306:** 945–6.
4. Ghaeli P, *et al*. Triazolam treatment controversy. *Ann Pharmacother* 1994; **28:** 1038–40.
5. Bixler EO, *et al*. Adverse reactions to benzodiazepine hypnotics: spontaneous reporting system. *Pharmacology* 1987; **35:** 286–300.
6. Wysowski DK, Barash D. Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's spontaneous reporting system. *Arch Intern Med* 1991; **151:** 2003–8.
7. Adam K, Oswald I. Can a rapidly-eliminated hypnotic cause daytime anxiety? *Pharmacopsychiatry* 1989; **22:** 115–19.
8. Bixler EO, *et al*. Next-day memory impairment with triazolam use. *Lancet* 1991; **337:** 827–31.
9. Drucker RF, MacLeod N. Benzodiazepines. *Pharm J* 1989; **243:** 508.
10. Hindmarch I, *et al*. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 55.
11. Rothschild AJ, *et al*. Triazolam and disinhibition. *Lancet* 1993; **341:** 186.
12. Hawley CJ, *et al*. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567.
13. Vela-Bueno A. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567.
14. Kales A, *et al*. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567–8.
15. Gillin JC, Byerley WF. Diagnosis and management of insomnia. *N Engl J Med* 1990; **323:** 487.
16. Ault A. FDA advisers find no major Halcion dangers. *Lancet* 1997; **350:** 1760.

Precautions

As for Diazepam, p. 1066.3.

Hepatic impairment. Cirrhosis decreased the apparent oral clearance of triazolam to an extent depending on the severity of the liver disease.[1] An initial dose of 125 micrograms was suggested for patients with severe liver dysfunction. It was suggested that the relative lack of effect that mild to moderate cirrhosis had on the metabolism of oral triazolam might be due to some first-pass metabolism occurring in the intestinal wall.[2]

1. Kroboth PD, *et al*. Nighttime dosing of triazolam in patients with liver disease and normal subjects: kinetics and daytime effects. *J Clin Pharmacol* 1987; **27:** 555–60.
2. Robin DW, *et al*. Triazolam in cirrhosis: pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1993; **54:** 630–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies triazolam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Renal impairment. Peak plasma-triazolam concentrations were lower in 11 dialysis patients compared with 11 controls.[1] It was postulated that a relatively high basal gastric acid secretion in dialysis patients could result in hydrolysis and opening of the ring structure of triazolam effectively reducing its systemic availability. Giving an antacid could reverse this effect. Renal failure had no other effect on the pharmacokinetics of triazolam which could probably be given in usual doses.

1. Kroboth PD, *et al*. Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics. *Br J Clin Pharmacol* 1985; **19:** 839–42.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Triazolam is rapidly and nearly completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within 2 hours of an oral dose. Triazolam has a plasma elimination half-life ranging from 1.5 to 5.5 hours. It is reported to be about 89% bound to plasma proteins. Hydroxylation of triazolam in the liver is mediated by the cytochrome P450 isoenzyme CYP3A4. Triazolam is excreted in the urine mainly in the form of its conjugated metabolites with only small amounts appearing unchanged. Distribution of triazolam and its metabolites into milk has been found in studies in *rats*.

References.
1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Greenblatt DJ, *et al*. Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin Pharmacol Ther* 2004; **76:** 467–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Halcion; ***Austria***: Halcion; ***Belg.***: Halcion; ***Canad.***: Apo-Triazo; ***Chile***: Balidon; Somese; ***China***: Hanlexin (酣乐欣); ***Denm.***: Halcion; ***Fin.***: Halcion; ***Gr.***: Halcion; ***Hong Kong***: Halcion; ***Irl.***: Halcion; Trilam†; ***Israel***: Halcion†; ***Ital.***: Halcion; Songar; Zotrilax†; ***Malaysia***: Inzolam; Somese; ***Mex.***: Halcion; ***NZ***: Halcion; Hypam; ***Port.***: Halcion; ***Rus.***: Halcion (Хальцион); ***S.Afr.***: Halcion; ***Spain***: Halcion; ***Swed.***: Halcion; ***Switz.***: Halcion; ***Thai.***: Halcion; Trialam; Trycam; ***USA***: Halcion; ***Venez.***: Somese.

Pharmacopoeial Preparations
USP 36: Triazolam Tablets.

Triclofos Sodium *(BANM, USAN, rINNM)*

Natrii Triclofosum; Sch-10159; Sodium Triclofos; Triclofós sódico; Triclofos Sodique; Натрий Триклофос.

Sodium 2,2,2-trichloroethyl hydrogen orthophosphate.

$C_2H_3Cl_3NaO_4P$=251.4

CAS — 306-52-5 (triclofos); 7246-20-0 (triclofos sodium).

ATC — N05CM07.

ATC Vet — QN05CM07.

UNII — 9F90KA5Q8U.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2014: (Triclofos Sodium). A white or almost white, odourless or almost odourless, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 3.0 to 4.5.

Profile

Triclofos sodium has hypnotic and sedative actions similar to those of cloral hydrate (p. 1055.2) but it causes less gastric irritation; also, it is not corrosive to skin and mucous membranes. It has been used similarly in the short-term management of insomnia and for sedation of children before painless procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Tricloryl; ***Israel***: Triclonam.

Pharmacopoeial Preparations
BP 2014: Triclofos Oral Solution.

Trifluoperazine Hydrochloride

(BANM, rINNM)

Hidrocloruro de trifluoperazina; Trifluoperazin Hidroklorür; Trifluoperazin hydrochlorid; Trifluoperazina, hidrocloruro de; Trifluoperazindihydrochlorid; Trifluopérazine, Chlorhydrate de; Trifluoperazinhidroklorid; Trifluoperazinhydroklorid; Trifluoperazini Hydrochloridum; Trifluoperazino hidrochloridas; Trifluoperazyny chlorowodorek; Trifluoriperatsiinihydrokloridi; Triphthazinum; Трифлуоперазина Гидрохлорид.

10-[3-(4-Methylpiperazin-1-yl)propyl]-2-trifluoromethylphenothiazine dihydrochloride.

$C_{21}H_{24}F_3N_3S,2HCl$=480.4

CAS — 117-89-5 (trifluoperazine); 440-17-5 (trifluoperazine hydrochloride).

ATC — N05AB06.

ATC Vet — QN05AB06.

UNII — 6P1Y2SNF5V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Trifluoperazine Hydrochloride). A white to pale yellow, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in ether. A 10% solution in water has a pH of 1.6 to 2.5. Protect from light.

USP 36: (Trifluoperazine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. Soluble 1 in 3.5 of water, 1 in 11 of alcohol, and 1 in 100 of chloroform; insoluble in ether and in benzene. pH of a 1 in 20 solution is between 1.7 and 2.6. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Trifluoperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain.

Trifluoperazine is used in the treatment of a variety of psychiatric disorders including schizophrenia (below), severe anxiety (p. 1028.1), and disturbed behaviour (p. 1030.2). It is also used for the control of nausea and vomiting (p. 1814.3).

Trifluoperazine is given orally as the hydrochloride but doses are expressed in terms of the base. Trifluoperazine 1 mg is equivalent to about 1.2 mg of trifluoperazine hydrochloride. A modified-release preparation is available in some countries. It has also been given by intramuscular injection. Trifluoperazine should be given in reduced dosage to elderly or debilitated patients.

The usual initial oral dose for the treatment of schizophrenia and other **psychoses** is 2 to 5 mg twice daily, gradually increased to a usual range of 15 to 20 mg daily; in severe or resistant psychoses daily doses of 40 mg or more have been given.

For the control of **nausea and vomiting** the usual oral dose is 1 or 2 mg twice daily; up to 6 mg daily may be given in divided doses.

When used as an adjunct in the short-term management of **severe anxiety disorders** doses are similar to those used for the control of nausea and vomiting.

For details of doses in children, see below.

Administration in children. The initial oral dose of trifluoperazine for the treatment of schizophrenia and other psychoses in children under 12 years old is up to 5 mg daily given in divided doses. Thereafter, the dose may be adjusted according to age, body-weight, and response, at intervals of not less than 3 days; US licensed product information suggests a usual maximum of 15 mg daily in children aged 6 to 12 years.

For the control of nausea and vomiting children aged 3 to 5 years may be given up to 1 mg daily in divided doses; this may be increased to a maximum of 4 mg daily in those aged 6 to 12 years.

When used as an adjunct in the short-term management of severe anxiety disorders doses are similar to those used for the control of nausea and vomiting.

Children and adolescents aged 12 years and over may be given usual adult doses, see above.

Schizophrenia. A systematic review[1] of the use of trifluoperazine for schizophrenia (p. 1031.3) concluded that it appeared to be of similar efficacy to other commonly used classical antipsychotics with a similar profile of adverse effects. However, there did not appear to be good evidence for claims that it was effective for schizophrenia at low doses.

1. Marques LO, *et al*. Trifluoperazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 17/05/05).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Trifluoperazine is less likely to cause sedation, hypotension, hypothermia, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects particularly when the daily dose exceeds 6 mg.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trifluoperazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Trifluoperazine hydrochloride is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1.5 to 6 hours after oral doses. Bioavailability is subject to interindividual variation. It is highly bound to plasma proteins. The elimination of trifluoperazine is multiphasic and the terminal half-life is about 22 hours. The major metabolite is the possibly active *N*-oxide. Other metabolites include the sulfoxide and the 7-hydroxy derivative. Trifluoperazine is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cuait Trifluoperazina; Stelazine; ***Austral.***: Stelazine; ***Braz.***: Stelazine; ***Canad.***: Terfluzine†; ***Gr.***: Oxyperazine; Stelazine; Stelium; ***Hong Kong***: Stelazine; ***India***: Gencalm; Neocalm; Trinicalm; ***Indon.***: Stelazine; Stelosi; ***Irl.***: Stelazine; ***Ital.***: Modalina; ***Mex.***: Flupazine; Stelazine; ***NZ***: Stelazine; ***Rus.***: Triphtazine (Трифтазин); ***S. Afr.***: Stelazine; Terflurazine†; ***Spain***: Eskazine†; ***Thai.***: Psyrazine; Triflumed; Triozine; Triplex†; ***Turk.***: Stilizan; ***UK***: Stelazine; ***Venez.***: Leptazine; Taclorpil.

Multi-ingredient Preparations. ***Arg.***: Cuait D; Cuait N†; Stelapar; ***India***: Benzyzine; Cloxide Plus; Cynosleep; Equicalm; F Plus; Fit; Gastabid; Gencalm Plus; Kaytrix-C; Lacalm Plus; Lacalm; Librosym; Librotop; Manocalm Forte; Manocalm Plus; Neocalm Forte; Neocalm Plus; Normozin; Parazin-C; Sycot; Trinicalm Forte; Trinicalm Plus; ***Ital.***: Parmodalin; ***Mex.***: Stelabid.

Pharmacopoeial Preparations
BP 2014: Trifluoperazine Tablets;
USP 36: Trifluoperazine Hydrochloride Injection; Trifluoperazine Hydrochloride Syrup; Trifluoperazine Hydrochloride Tablets.

Trifluperidol *(BAN, USAN, rINN)*

McN-JR-2498; R-2498; Triflupéridol; Trifluperidoli; Trifluperidolum; Трифлуперидол.
4′-Fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone.
$C_{22}H_{23}F_4NO_2$=409.4
CAS — 749-13-3.
ATC — N05AD02.
ATC Vet — QN05AD02.
UNII — R8869Q7R8I.

Trifluperidol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trifluperidol; Triflupéridol, Chlorhydrate de; Trifluperidol, hidrocloruro de; Trifluperidoli Hydrochloridum; Трифлуперидола Гидрохлорид.
$C_{22}H_{23}F_4NO_2$,HCl=445.9
CAS — 2062-77-3.
ATC — N05AD02.
ATC Vet — QN05AD02.
UNII — UIC8RB6P81.

Profile

Trifluperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1), and has been used as the hydrochloride in the treatment of psychoses including schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Triperidol.

Triflupromazine *(BAN, rINN)*

Fluopromazine; Triflupromazina; Triflupromazinum; Трифлупромазин.
NN-Dimethyl-3-(2-trifluoromethylphenothiazin-10-yl)propylamine.
$C_{18}H_{19}F_3N_2S$=352.4
CAS — 146-54-3.
ATC — N05AA05.
ATC Vet — QN05AA05.
UNII — RO16TQF95Y.

Pharmacopoeias. In *US.*

USP 36: (Triflupromazine). A light amber viscous oily liquid that crystallises into large irregular crystals during prolonged storage. Practically insoluble in water. Store in airtight containers. Protect from light.

Triflupromazine Hydrochloride *(BANM, rINNM)*

Fluopromazine Hydrochloride; Hidrocloruro de triflupromazina; Triflupromazina, hidrocloruro de; Triflupromazine, Chlorhydrate de; Triflupromazini Hydrochloridum; Трифлупромазина Гидрохлорид.
$C_{18}H_{19}F_3N_2S$,HCl=388.9
CAS — 1098-60-8.
ATC — N05AA05.
ATC Vet — QN05AA05.
UNII — 9E75N4A5HM.

Pharmacopoeias. In *US.*

USP 36: (Triflupromazine Hydrochloride). A white to pale tan crystalline powder having a slight characteristic odour. Soluble 1 in less than 1 of water and of alcohol and 1 in 1.7 of chloroform; soluble in acetone; insoluble in ether. Store in glass containers. Protect from light.

Profile

Triflupromazine hydrochloride is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has been used mainly in the management of psychoses and the control of nausea and vomiting. Triflupromazine hydrochloride has usually been given by injection but in some countries oral preparations may have been available.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Siquil.

Pharmacopoeial Preparations
USP 36: Triflupromazine Hydrochloride Injection; Triflupromazine Hydrochloride Tablets; Triflupromazine Oral Solution.

Trimetozine *(USAN, rINN)*

Abbott-22370; NSC-62939; PS-2383; Trimetozina; Trimétozine; Trimetozinum; Триметоцин.
4-(3,4,5-Trimethoxybenzoyl)morpholine.
$C_{14}H_{19}NO_5$=281.3
CAS — 635-41-6.
UNII — 31EPT7G9PL.

Profile

Trimetozine has been used for its sedative properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Trioxazin†.

Valnoctamide *(USAN, rINN)*

McN-X-181; NSC-32363; Valnoctamida; Valnoctamidum; Вальноктамид.
2-Ethyl-3-methylvaleramide.
$C_8H_{17}NO$=143.2
CAS — 4171-13-5.
ATC — N05CM13.
ATC Vet — QN05CM13.
UNII — 3O25NRX9YG.

Profile

Valnoctamide, an isomer of valpromide (p. 553.2), has been given orally in the treatment of anxiety disorders.

References.

1. Bialer M, *et al.* Pharmacokinetics of a valpromide isomer, valnoctamide, in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 289–91.
2. Barel S, *et al.* Stereoselective pharmacokinetic analysis of valnoctamide in healthy subjects and in patients with epilepsy. *Clin Pharmacol Ther* 1997; **61:** 442–9.
3. Bersudsky Y, *et al.* Valnoctamide as a valproate substitute with low teratogenic potential in mania: a double-blind, controlled, add-on clinical trial. *Bipolar Disord* 2010; **12:** 376–82.

Interactions. For a discussion of the potential interaction between carbamazepine and valnoctamide, see Antiepileptics, p. 516.3.

Veralipride *(rINN)*

Veraliprida; Véralipride; Veralipridum; Вералиприд.
N-[(1-Allyl-2-pyrrolidinyl)methyl]-5-sulphamoyl-2-veratramide.
$C_{17}H_{25}N_3O_5S$=383.5
CAS — 66644-81-3.
ATC — N05AL06.
ATC Vet — QN05AL06.
UNII — S7064109UD.

Profile

Veralipride is a substituted benzamide antipsychotic that has been used in the treatment of cardiovascular and psychological symptoms associated with the menopause. Preparations of veralipride have now been withdrawn from the market in some countries because of the opinion that there is an unacceptable balance of risks and benefits; adverse effects such as anxiety, depression, and tardive dyskinesia have been associated with veralipride, both during and after treatment.

Menopausal disorders. HRT with oestrogens is the mainstay of treatment for acute symptoms associated with the menopause (see p. 2245.1) but when it is considered to be unsuitable a variety of other drugs including veralipride have been tried.[1] It has also been tried with raloxifene in postmenopausal women.[2] However, treatment with veralipride has been associated with extrapyramidal adverse effects[3,4] and it has since been withdrawn from the market in some countries (see also above).

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40:** 220–30.
2. Morgante G, *et al.* Veralipride administered in combination with raloxifene decreases hot flushes and improves bone density in early postmenopausal women. *Gynecol Endocrinol* 2004; **18:** 194–8.
3. Masmoudi K, *et al.* Troubles extrapyramidaux sous véralipride (Agréal), traitement symptomatique des bouffées de chaleur: à propos de 17 cas. *Rev Med Interne* 2005; **26:** 453–7.
4. Raja M, Azzoni A. Tardive dyskinesia after long-term veralipride treatment. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 252–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Veralipral; ***Braz.***: Agreal; ***Chile***: Agreal†; ***Gr.***: Phyllan; ***Mex.***: Aclimafel; Veraligral†.

Multi-ingredient Preparations. ***Arg.***: Veralipral T.

Zaleplon *(BAN, USAN, rINN)*

CL-284846; L-846; LJC-10846; Tsaleploni; ZAL-846; Zaleplón; Zaléplone; Zaleplonum; Залеплон.
3′-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetanilide.
$C_{17}H_{15}N_5O$=305.3
CAS — 151319-34-5.
ATC — N05CF03.
ATC Vet — QN05CF03.
UNII — S62U433RMH.

Pharmacopoeias. In *US.*

USP 36: (Zaleplon). A white to off-white powder. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in propylene glycol. Protect from light.

Uses and Administration

Zaleplon is a pyrazolopyrimidine with similar sedative properties to the benzodiazepines (see Diazepam, p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (below). Zaleplon has a rapid onset and short duration of action. The usual oral dose is 10 mg at bedtime although US licensed product information notes that some patients may require 20 mg. Elderly or debilitated patients or those also taking cimetidine should be given 5 mg. For dosages in patients with hepatic impairment, see below.

Administration in hepatic impairment. The oral dose of zaleplon should be reduced to 5 mg at bedtime in patients with mild to moderate hepatic impairment; it should not be given to those with severe impairment.

Insomnia. Zaleplon is a pyrazolopyrimidine hypnotic. Although not related structurally to the benzodiazepines it appears to act by binding selectively to the benzodiazepine type I receptor (BZ1- or ω_1-receptors) on the GABA subtype A complex. Zaleplon reduces sleep latency but has little effect on sleep duration; it is rapidly absorbed and eliminated and consequently residual effects the next day are said to be minimal. These characteristics make it best suited for the treatment of patients with insomnia (p. 1033.2) who have difficulty falling asleep; zaleplon can either be taken at bedtime or during the night if a patient has trouble falling back to sleep, provided they are assured of at least 4 hours uninterrupted sleep.

References.

1. Anonymous. Zaleplon for insomnia. *Med Lett Drugs Ther* 1999; **41:** 93–4.
2. Danjou P, *et al.* A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. *Br J Clin Pharmacol* 1999; **48:** 367–74.
3. Elie R, *et al.* Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry* 1999; **60:** 536–44.
4. Dooley M, Plosker GL. Zaleplon: a review of its use in the treatment of insomnia. *Drugs* 2000; **60:** 413–45.
5. George CFP. Pyrazolopyrimidines. *Lancet* 2001; **358:** 1623–6.
6. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.
7. Barbera J, Shaprio [sic] C. Benefit-risk assessment of zaleplon in the treatment of insomnia. *Drug Safety* 2005; **28:** 301–18.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. Zaleplon should be used with caution and in reduced doses in patients with hepatic impairment, and should be avoided where this is severe.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to patients who present within one hour of ingestion of more than 50 mg zaleplon by adults, or 1 mg/kg by children, provided that the airway can be protected. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zaleplon toxicity.

References.
1. Israel AG, Kramer JA. Safety of zaleplon in the treatment of insomnia. *Ann Pharmacother* 2002; **36:** 852–9.

Abuse. In a controlled study in healthy patients with a history of drug abuse, zaleplon was shown to have a comparable abuse potential to that of the benzodiazepine, triazolam.[1]

1. Rush CR, *et al*. Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. *Psychopharmacology (Berl)* 1999; **145:** 39–51.

Breast feeding. Licensed product information for zaleplon advises that it should not be given to breast-feeding mothers since, although only a small amount is excreted into breast milk, the effect on the nursing infant is not known.

Zaleplon was detected in the breast milk of 5 women who had been given a 10-mg dose.[1] The milk-to-plasma concentration ratio for zaleplon was about 0.5. No infants were breast fed during the study.

1. Darwish M, *et al*. Rapid disappearance of zaleplon from breast milk after oral administration to lactating women. *J Clin Pharmacol* 1999; **39:** 670–4.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zaleplon, see under Zolpidem, p. 1117.2.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zaleplon, see under Zolpidem, p. 1117.2.

Overdosage. A report of overdose with zaleplon noted for the blue-green discoloration of the patient's mouth and lips, urine, and emesis, which was attributed to the dye used in the zaleplon capsules ingested.[1]

1. Louis CJ, *et al*. A case of zaleplon overdose. *Clin Toxicol* 2008; **46:** 782.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zaleplon as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1. Zaleplon is primarily metabolised by aldehyde oxidase and use with inhibitors of this enzyme, such as cimetidine, may result in increased plasma concentrations of zaleplon (see Uses and Administration, p. 1114.3). Zaleplon is also partly metabolised by the cytochrome P450 isoenzyme CYP3A4 and, consequently, caution is advised when zaleplon is given with drugs that are substrates for, or potent inhibitors of, this isoenzyme. Cimetidine is also an inhibitor of CYP3A4 and thus inhibits both the primary and secondary metabolic pathways of zaleplon.

Use with rifampicin or other potent enzyme-inducing drugs may accelerate the metabolism of zaleplon and reduce its plasma concentrations.

Pharmacokinetics

Zaleplon is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in about one hour after oral dosage. A heavy meal or one with a high-fat content delays absorption and reduces peak concentrations. Bioavailability is about 30% due to significant first-pass hepatic metabolism. Zaleplon is metabolised primarily by aldehyde oxidase to form 5-oxo-zaleplon and, to a lesser extent, by the cytochrome P450 isoenzyme CYP3A4 to desethylzaleplon, which is further metabolised by aldehyde oxidase to 5-oxo-desethylzaleplon. The plasma-elimination half-life of zaleplon is about 1 hour. About 70% of a dose is excreted in the urine as these inactive metabolites or their glucuronides; less than 1% is excreted unchanged. About 17% of a dose is eliminated in the faeces, mainly as 5-oxo-zaleplon. Zaleplon is distributed into breast milk.

References.
1. Greenblatt DJ, *et al*. Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. *Clin Pharmacol Ther* 1998; **64:** 553–61.
2. Drover D, *et al*. Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; **22:** 1443–61.
3. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hegon; Hipnodem; ***Belg.***: Sonata; ***Braz.***: Sonata; ***Chile***: Plenidon; Sedartryl; ***China***: An Ji Xin (安己辛); An Wei De (安维得); An Yun (安云); Bai Jie Min (百介民); En Nuo Xin (恩诺欣); He Bang Li An (禾邦立安); Hui Ning (惠宁); Hui Te Ning (惠特宁); Qu Ning (曲宁); Rui Chen (瑞晨); Si Mei (思每); Si Te Chang Jia (斯特长佳); Siweitan (思威坦); Tong An Qi (通安其); ***Cz.***: Sonata; Zerene; ***Denm.***: Sonata; ***Fin.***: Sonata†; ***Ger.***: Sonata; ***Gr.***: Sonata; ***Hung.***: Sonata; ***India***: Zalep; Zaplon; Zaso; ***Irl.***: Sonata; Zerene; ***Ital.***: Sonata; Zerene†; ***Neth.***: Sonata; Zerene†; ***Pol.***: Selofen; Sonata; Zerene; ***Port.***: Sonata; Zerene; ***Rus.***: Andante (Андante); ***Spain***: Sonata†; ***Swed.***: Sonata; ***Switz.***: Sonata; ***UK***: Sonata; ***Ukr.***: Andante (Андante); Selofen (Селофен); ***USA***: Sonata.

Pharmacopoeial Preparations
USP 36: Zaleplon Capsules.

Ziprasidone *(BAN, rINN)*

Ziprasidona; Ziprasidonum; Зипрасидон.
5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-2-indolinone.
$C_{21}H_{21}ClN_4OS$=412.9
CAS — 146939-27-7 (ziprasidone).
ATC — N05AE04.
ATC Vet — QN05AE04.
UNII — 6UKA5VEJ6X.

Ziprasidone Hydrochloride

(BANM, USAN, rINNM)

CP-88059-1; CP-88059; Hidrocloruro de ziprasidona; Ziprasidona, hidrocloruro de; Ziprasidone, Chlorhydrate de; Ziprasidoni hydrochloridum; Зипрасидона Гидрохлорид.
$C_{21}H_{21}ClN_4OS,HCl,H_2O$=467.4
CAS — 122883-93-6 (anhydrous ziprasidone hydrochloride); 138982-67-9 (ziprasidone hydrochloride monohydrate).
ATC — N05AE04.
ATC Vet — QN05AE04.
UNII — 216X081ORU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ziprasidone Hydrochloride Monohydrate). A white or slightly pink powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in methyl alcohol and in dichloromethane. Protect from light.

USP 36: (Ziprasidone Hydrochloride). A white to slightly pink powder. Practically insoluble in water; very soluble in methyl alcohol; slightly soluble in isopropyl alcohol and in hot tetrahydrofuran. Store in airtight containers. Protect from light.

Ziprasidone Mesilate *(BANM, rINNM)*

CP-88059/27; Mesilato de ziprasidona; Ziprasidona, mesilato de; Ziprasidone, Mésilate de; Ziprasidone Mesylate; Ziprasidone Mesylate (USAN); Ziprasidoni Mesilas; Зипрасидона Мезилат.
$C_{21}H_{21}ClN_4OS,CH_4O_3S,3H_2O$=563.1
CAS — 199191-69-0.
ATC — N05AE04.
ATC Vet — QN05AE04.
UNII — 3X6SAX83JZ.

Uses and Administration

Ziprasidone is an atypical antipsychotic reported to have affinity for adrenergic (α_1), histamine (H_1), and serotonin (5-HT_2) receptors as well as dopamine (D_2) receptors. It is used for the treatment of schizophrenia (below) and in acute manic or mixed episodes associated with bipolar disorder (below). Ziprasidone is given orally, usually as the hydrochloride; it is also given parenterally as the mesilate. Ziprasidone bisulfate has also been used. Doses are expressed in terms of the base; ziprasidone hydrochloride 11.3 mg or ziprasidone mesilate 13.6 mg are each equivalent to about 10 mg of ziprasidone.

For the treatment of **schizophrenia**, ziprasidone hydrochloride is given in an initial oral dose equivalent to 20 mg twice daily with food. Doses may be increased if necessary at intervals of not less than 2 days up to 80 mg twice daily. For maintenance, doses as low as 20 mg twice daily may be effective.

For acute agitation in patients with schizophrenia, ziprasidone may be given as the mesilate by intramuscular injection. The recommended dose is equivalent to 10 to 20 mg as required, to a maximum of 40 mg daily for 3 consecutive days. Doses of 10 mg may be given every 2 hours and doses of 20 mg may be given every 4 hours. Patients should be switched to oral therapy as soon as possible.

For the treatment of *acute mixed or manic episodes* in **bipolar disorder**, ziprasidone hydrochloride is given in an initial oral dose equivalent to 40 mg twice daily with food. The dose should be increased to 60 or 80 mg twice daily on the second day of treatment and subsequently adjusted according to tolerance. It is also used for the *maintenance treatment* of bipolar disorder as an adjunct to lithium or valproate; patients should be continued on the same dose on which they were stabilised, within a range of 40 to 80 mg twice daily.

Bipolar disorder. Ziprasidone is effective in the management of acute mania in patients with bipolar disorder[1,2] (p. 397.2) but it may be associated with the induction of mania or hypomania in such patients.[3] It is also used as an adjunct in maintenance treatment.[4]

1. Keck PE, *et al*. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003; **160:** 741–8.
2. Keck PE, *et al*. Long-term safety and efficacy of ziprasidone in subpopulations of patients with bipolar mania. *J Clin Psychiatry* 2009; **70:** 844–51.
3. Baldassano CF, *et al*. Ziprasidone-associated mania: a case series and review of the mechanism. *Bipolar Disord* 2003; **5:** 72–5.
4. Bowden CL, *et al*. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 2010; **71:** 130–7.

Schizophrenia. A systematic review[1] of the efficacy and safety of ziprasidone in patients with schizophrenia (p. 1031.3) found that from the limited data available ziprasidone was as effective as haloperidol; it was less likely to provoke extrapyramidal disorders but appeared to cause more nausea and vomiting, and pain at the site of injection. A comparative study[2] of intramuscular ziprasidone with intramuscular haloperidol also found a favourable outcome in patients with acute psychoses. At the time comparisons with other atypical antipsychotics were lacking. However, a more recent review,[3] concluded that, based on limited data, ziprasidone may be slightly less effective than amisulpride, olanzapine, and risperidone but had a lower propensity to induce weight gain and associated adverse effects.

1. Bagnall A, *et al*. Ziprasidone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 20/10/05).
2. Brook S, *et al*. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; **61:** 933–41.
3. Komossa K, *et al*. Ziprasidone versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 23/11/09).

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1), haloperidol or pimozide are commonly used but atypical antipsychotics such as ziprasidone are increasingly being tried.[1]

1. Sallee FR, *et al*. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000; **39:** 292–9.

Adverse Effects, Treatment, and Precautions

Although ziprasidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Frequent adverse effects with ziprasidone include somnolence, rash or urticaria, gastrointestinal disturbances, dizziness, flu-like symptoms, hypertension, headache, agitation, confusion, and dyspnoea. Orthostatic hypotension may be a problem, particularly when starting treatment. Ziprasidone may increase prolactin levels and weight gain has also been noted. Sexual dysfunction has been reported infrequently. Extrapyramidal symptoms may occur, and tardive dyskinesia may develop with prolonged use. There have also been infrequent or rare cases of cholestatic jaundice, hepatitis, seizures, blood dyscrasias including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia, and hyperlipidaemia. Hyperglycaemia occurs uncommonly with ziprasidone. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of, developing diabetes.

Ziprasidone has been associated with dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use is contra-indicated in patients with a history of QT prolongation or cardiac arrhythmias, with recent acute myocardial infarction, or with decompensated heart failure. Certain medications may also increase the risk (see Interactions, p. 1116.1). Baseline serum potassium and magnesium screening should be performed in patients who are at risk of significant electrolyte disturbances and hypokalaemia or hypomagnesaemia should be corrected before starting ziprasidone therapy. Serum electrolytes should be monitored in patients who start diuretic therapy during ziprasidone treatment. Patients receiving ziprasidone who have symptoms that might indicate torsade de pointes

(e.g. dizziness, palpitations, or syncope) should be further evaluated.

Ziprasidone should be used with caution in patients with a history of seizures or in conditions that lower the seizure threshold, cardiovascular or cerebrovascular disease, or conditions which predispose to hypotension. Since intramuscular injections are formulated with cyclodextrin, which is cleared by renal filtration, licensed product information recommends caution in patients with renal impairment.

Ziprasidone may affect the performance of skilled tasks including driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Extrapyramidal disorders. Tardive dyskinesia has been associated with ziprasidone therapy;[1-3] onset ranged from 2 to 34 months after starting the drug. Acute dystonia has also been reported[4,5] with ziprasidone. However, the incidence of extrapyramidal adverse effects (p. 1049.2) is generally lower with atypical than classical antipsychotics.

1. Rosenquist KJ, *et al*. Tardive dyskinesia and ziprasidone. *Am J Psychiatry* 2002; **159:** 1436.
2. Keck ME, *et al*. Ziprasidone-related tardive dyskinesia. *Am J Psychiatry* 2004; **161:** 175–6.
3. Ananth J, *et al*. Tardive dyskinesia in 2 patients treated with ziprasidone. *J Psychiatry Neurosci* 2004; **29:** 467–9.
4. Ziegenbein M, *et al*. Ziprasidone-induced Pisa syndrome after clozapine treatment. *J Neuropsychiatr Clin Neurosci* 2003; **15:** 458–9.
5. Mason MN, *et al*. Ziprasidone-induced acute dystonia. *Am J Psychiatry* 2005; **162:** 625–6.

Mania. Although it is used in the treatment of bipolar disorder, ziprasidone has been associated with reports of mania in bipolar patients, see under Uses and Administration, p. 1115.3.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS—p. 1050.2) has been associated with ziprasidone;[1] however, the patient had also received lithium, a drug that has been associated with NMS.

1. Borovicka MC, *et al*. Ziprasidone- and lithium-induced neuroleptic malignant syndrome. *Ann Pharmacother* 2006; **40:** 139–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ziprasidone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics, including ziprasidone, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

US licensed product information states that ziprasidone showed possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Ziprasidone should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

Use of ziprasidone with other drugs known to prolong the QT interval is contra-indicated because of the increased risk of arrhythmias. Monitoring of serum electrolytes is recommended if ziprasidone is given with diuretics.

The metabolism of ziprasidone is mediated by the cytochrome P450 isoenzyme CYP3A4. Therefore, there is the potential for interactions between ziprasidone and other drugs that induce, inhibit, or act as a substrate for this enzyme.

Ziprasidone may enhance the effects of other CNS depressants and certain antihypertensives; it may antagonise the effects of levodopa and dopaminergics.

Pharmacokinetics

Ziprasidone is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 6 to 8 hours after oral doses. The presence of food may double the absorption. After intramuscular injection, peak plasma concentrations occur within 1 hour. Plasma protein binding is about 99%. Ziprasidone is extensively metabolised by aldehyde oxidase (about 66% of a dose) and by the cytochrome P450 isoenzyme CYP3A4. The mean terminal elimination half-life has been reported to be about 7 hours after oral dosage and about 2 to 5 hours after intramuscular dosage. Ziprasidone is excreted mainly as metabolites in the faeces (about 66%) and urine (about 20%); less than 5% of a dose appears as unchanged drug.

References.

1. Various. The pharmacokinetics of ziprasidone. *Br J Clin Pharmacol* 2000; **49** (suppl 1): 1S–76S.
2. Miceli JJ, *et al*. Pharmacokinetics, safety, and tolerability of intramuscular ziprasidone in healthy volunteers. *J Clin Pharmacol* 2005; **45:** 620–30.
3. Preskorn SH. Pharmacokinetics and therapeutics of acute intramuscular ziprasidone. *Clin Pharmacokinet* 2005; **44:** 1117–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zeldox; ***Austral.***: Zeldox; ***Austria***: Zeldox; ***Braz.***: Geodon; ***Canad.***: Zeldox; ***Chile***: Zeldox; ***China***: Li Fu Jun An (力复君安); Si Bei Ge (思贝格); Zeldox (卓乐定); ***Cz.***: Zeldox; Zipsi; Zypsila; ***Denm.***: Geodon; Zeldox; ***Fin.***: Zeldox; ***Ger.***: Zeldox; ***Gr.***: Geodon; ***Hong Kong***: Zeldox; ***Hung.***: Ypsila; Zeldox; ***India***: Azona; Zipsydon; ***Irl.***: Geodon; ***Israel***: Geodon; ***Ital.***: Zeldox; ***Malaysia***: Zeldox; ***Mex.***: Geodon; ***Norw.***: Zeldox; ***NZ***: Zeldox; ***Philipp.***: Zeldox†; ***Pol.***: Pramaxima; Zeldox; Zipragen; Zipwell; Zypsila; ***Port.***: Zeldox; ***Rus.***: Zeldox (Зелдокс); ***S.Afr.***: Geodon; ***Singapore***: Zeldox; ***Spain***: Geodon; Zeldox; Zypsilan; ***Swed.***: Zeldox; ***Thai.***: Zeldox; ***Turk.***: Zeldox; ***Ukr.***: Zeldox (Зелдокс); ***USA***: Geodon; ***Venez.***: Geodon.

Zolazepam Hydrochloride

(BANM, USAN, rINNM)

CI-716; Hidrocloruro de zolazepam; Zolazépam, Chlorhydrate de; Zolazepam, hidrocloruro de; Zolazepami Hydrochloridum; Золазепама Гидрохлорид.

4-(*o*-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpirazole[3,4-*e*][1,4]diazepin-7(1*H*)-one monohydrochloride.

$C_{15}H_{15}FN_4O,HCl$=322.8

CAS — 31352-82-6 (zolazepam); 33754-49-3 (zolazepam hydrochloride).

UNII — 45SJ093Q1N.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Zolazepam Hydrochloride). A white to off-white crystalline powder. Freely soluble in water and in 0.1N hydrochloric acid; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. pH of a 10% solution in water is between 1.5 and 3.5. Store in airtight containers.

Profile

Zolazepam hydrochloride is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is used with tiletamine (p. 1920.1) for general anaesthesia in veterinary medicine.

Zolpidem Tartrate *(BANM, USAN, rINNM)*

SL-80.0750-23N; SL-80.0750 (zolpidem); Tartrato de zolpidem; Tsolpideemitartraatti; Zolpidem Hemitartrate; Zolpidem, tartrate de; Zolpidem, tartrato de; Zolpidemi Tartras; Zolpidemo tartratas; Zolpidem-tartarát; Zolpidemtartrat; Zolpidemu winian; Золпидема Тартрат.

N,N-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide hemitartrate.

$(C_{19}H_{21}N_3O)_2,C_4H_6O_6$=764.9

CAS — 82626-48-0 (zolpidem); 99294-93-6 (zolpidem tartrate).

ATC — N05CF02.

ATC Vet — QN05CF02.

UNII — WY6W63843K.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of zolpidem tartrate:

Sleepeasy; Tic-Tacs.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Zolpidem Tartrate). A white or almost white hygroscopic crystalline powder. Slightly soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Zolpidem Tartrate). White to off-white, hygroscopic powder. Slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines (see Diazepam, p. 1063.3), but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and is used as a hypnotic in the short-term management of insomnia (below), including when waking in the middle of the night is followed by difficulty returning to sleep.

The usual oral or sublingual dose in patients who have difficulty in falling to sleep is 10 mg taken immediately before retiring; however, some licensed product information recommend an initial dose of 5 mg, particularly for women because of reduced zolpidem clearance (for details, see Pharmacokinetics, p. 1117.3). In elderly or debilitated patients, treatment should be limited to a dose of 5 mg at night.

In the treatment of difficulty returning to sleep after waking in the middle of the night, zolpidem tartrate may be taken sublingually provided there are more than 4 hours of planned sleep remaining. The usual dose is 1.75 mg for women and 3.5 mg for men; elderly patients should be given 1.75 mg regardless of gender.

Doses should also be reduced in patients with hepatic impairment, see below.

Modified-release and oral spray formulations of zolpidem tartrate are also available.

Administration in hepatic impairment. For the treatment of insomnia in patients with hepatic impairment who have difficulty in falling asleep, zolpidem tartrate should be started at an oral or sublingual dose of 5 mg at bedtime regardless of gender; this may be increased to 10 mg, if necessary, in those aged under 65 years. UK licensed product information contra-indicates the use of zolpidem in patients with severe impairment.

In the treatment of difficulty returning to sleep after waking in the middle of the night, zolpidem tartrate may be given sublingually at a dose of 1.75 mg regardless of gender provided there are more than 4 hours of planned sleep remaining.

Catatonia. Anecdotal reports[1,2] suggesting that zolpidem may be a useful test in the diagnosis of catatonia.

1. Thomas P, *et al*. Test for catatonia with zolpidem. *Lancet* 1997; **349:** 702.
2. Zaw ZF, Bates GDL. Replication of zolpidem test for catatonia in an adolescent. *Lancet* 1997; **349:** 1914.

Insomnia. Zolpidem is an imidazopyridine with strong sedative actions, but only minor anxiolytic, muscle relaxant, or anticonvulsant properties. Some degree of amnesia has been reported. Zolpidem appears to act by binding to the benzodiazepine receptor component of the GABA receptor complex. It has, however, a selective affinity for the subtype of benzodiazepine receptors prevalent in the cerebellum (BZ1-or ω_1-receptors) as opposed to those more commonly found in the spinal cord (BZ2- or ω_2-receptors) or in the peripheral tissues (BZ3-or ω_3-receptors). Zolpidem has a rapid onset and short duration of hypnotic action and at usual doses decreases time to sleep onset and increases duration of sleep with little apparent effect on sleep stages (see Insomnia, p. 1033.2). Reviews agree that clinical studies have shown zolpidem to have hypnotic activity superior to placebo and generally similar to comparative benzodiazepines. Although it does not appear to produce rebound insomnia to any great extent, there appears to be little evidence that zolpidem offers any advantage over short-acting benzodiazepines in terms of residual effects the next day, or its potential to induce tolerance or withdrawal symptoms or dependence (see also under Dependence and Withdrawal, p. 1117.1).

References.

1. Langtry HD, Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 1990; **40:** 291–313.
2. Lobo BL, Greene WL. Zolpidem: distinct from triazolam? *Ann Pharmacother* 1997; **31:** 625–32.
3. Nowell PD, *et al*. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA* 1997; **278:** 2170–7.
4. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000; **59:** 865–89.
5. Terzano MG, *et al*. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.

6. Harrison TS, Keating GM. Zolpidem: a review of its use in the management of insomnia. *CNS Drugs* 2005; **19:** 65–89.
7. Moen MD, Plosker GL. Zolpidem extended-release. *CNS Drugs* 2006; **20:** 419–26.
8. Barkin RL. Zolpidem extended-release: a single insomnia treatment option for sleep induction and sleep maintenance symptoms. *Am J Ther* 2007; **14:** 299–305.
9. Yang LP, Deeks ED. Sublingual zolpidem (Edluar®; Sublinox®). *CNS Drugs* 2012; **26:** 1003–10.
10. Roth T, *et al*. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. *Sleep* 2013; **36:** 189–96.

Parkinsonism. Although preliminary findings[1] in 10 patients suggested that zolpidem might improve symptoms of Parkinson's disease concern has been expressed[2] over the risk of falls associated with zolpidem-induced drowsiness and the serious consequences for these patients. Benefit has also been reported[3] in the treatment of antipsychotic-induced parkinsonism in one patient with symptoms of repetitive persistent gross tremors of the hands.

1. Daniele A, *et al*. Zolpidem in Parkinson's disease. *Lancet* 1997; **349:** 1222–3.
2. Lavoisy J, Marsac J. Zolpidem in Parkinson's disease. *Lancet* 1997; **350:** 74.
3. Farver DK, Khan MH. Zolpidem for antipsychotic-induced parkinsonism. *Ann Pharmacother* 2001; **35:** 435–7.

Permanent vegetative state. Zolpidem in a single dose of 10 mg has produced temporary arousal in 3 patients thought to be in permanent vegetative state.[1] Effects lasted for about 4 hours.

1. Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation* 2006; **21:** 23–8.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Withdrawal symptoms. A 37-year-old man, who increased his dose from 10 mg to 130 mg daily over 2 months, had a generalised tonic-clonic seizure after zolpidem was abruptly stopped.[1] The patient recovered after being started on a benzodiazepine dosage tapering programme. Symptoms attributed to daytime abstinence after excessive night-time doses have been reported[2] in 2 patients and included anxiety, tremor, sweating, nausea, gastric and abdominal pain, swallowing difficulties, tachycardia, and tachypnoea. The patients had increased their doses because of the development of tolerance to the hypnotic effect but had begun to have muscle twitches and myoclonic jerks.

1. Gilbert DL, Staats PS. Seizure after withdrawal from supratherapeutic doses of zolpidem tartrate, a selective omega I benzodiazepine receptor agonist. *J Pain Symptom Manage* 1997; **14:** 118–20.
2. Cavallaro R, *et al*. Tolerance and withdrawal with zolpidem. *Lancet* 1993; **342:** 374–5.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to adults or children who present within one hour of ingesting more than 1 mg/kg of zolpidem. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zolpidem toxicity (but see also Overdosage, below).

Reviews.

1. Darcourt G, *et al*. The safety and tolerability of zolpidem—an update. *J Psychopharmacol* 1999; **13:** 81–93.

Abuse. Zolpidem abuse has been reported;[1,2] effects noted include a paradoxical stimulant effect when taking large doses. Tolerance may also develop. Intravenous abuse has also been reported.[3]

See also Withdrawal Symptoms, above.

1. Gericke CA, Ludolph AC. Chronic abuse of zolpidem. *JAMA* 1994; **272:** 1721–2.
2. Victorri-Vigneau C, *et al*. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol* 2007; **64:** 198–209.
3. Brunelle E, *et al*. Zolpidem: intravenous misuse in drug abusers. *Addiction* 2005; **100:** 1377–8.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving zolpidem, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In 5 women given a 20-mg dose of zolpidem, the amount of drug excreted in breast milk after 3 hours ranged between 0.76 and 3.88 micrograms, which represented 0.004 to 0.019% of the dose.[2] No detectable (below 0.5 nanograms/mL) zolpidem was found in subsequent milk samples.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)
2. Pons G, *et al*. Zolpidem excretion in breast milk. *Eur J Clin Pharmacol* 1989; **37:** 245–8.

Effects on the liver. Hepatitis developed on 2 separate occasions in a 53-year-old woman after the use of zolpidem for insomnia.[1]

1. Karsenti D, *et al*. Hepatotoxicity associated with zolpidem treatment. *BMJ* 1999; **318:** 1179.

Effects on mental function. Psychotic reactions, which may not subsequently be recalled, have been reported in patients taking therapeutic doses of zolpidem.[1-4] Somnambulism has also been reported with zolpidem.[5,6] Other complex sleep-related behaviours, such as eating or driving while asleep, have been reported with zaleplon,[7] zolpidem,[6,7] and zopiclone. Such behaviour is more likely to occur when these drugs are taken with alcohol or other CNS depressants, or when taken in doses exceeding the recommended maximum. It is not clear if there are differences in risk with individual drugs; however, as a precautionary measure, the FDA[8] had requested for labelling changes that highlight these adverse effects to be made to all hypnotics marketed in the USA. There has also been a report of a patient who took 40 mg of zolpidem orally and stabbed himself after being commanded by the resulting auditory hallucinations to do so.[9]

1. Ansseau M, *et al*. Psychotic reactions to zolpidem. *Lancet* 1992; **339:** 809.
2. Iruela LM, *et al*. Zolpidem-induced macropsia in anorexic woman. *Lancet* 1993; **342:** 443–4.
3. Brodeur MR, Stirling AL. Delirium associated with zolpidem. *Ann Pharmacother* 2001; **35:** 1562–4.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Seeing things with zolpidem. *Aust Adverse Drug React Bull* 2002; **21:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0202.pdf (accessed 21/08/08)
5. Yang W, *et al*. One rare side effect of zolpidem—sleepwalking: a case report. *Arch Phys Med Rehabil* 2005; **86:** 1265–6.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Zolpidem and bizarre sleep related effects. *Aust Adverse Drug React Bull* 2007; **26:** 2–3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0702.pdf (accessed 10/03/08)
7. Southworth MR, *et al*. FDA. Nonbenzodiazepine hypnotic use and cases of "sleep driving". *Ann Intern Med* 2008; **148:** 486–7.
8. FDA. FDA news: FDA requests label change for all sleep disorder drug products (issued 14th March, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108868.htm (accessed 26/07/10)
9. Manfredi G, *et al*. Command hallucinations with self-stabbing associated with zolpidem overdose. *J Clin Psychiatry* 2010; **71:** 92–3.

Hypersensitivity. Rare cases of angioedema involving the tongue, glottis, or larynx have been reported after the first or subsequent doses of hypnotics such as eszopiclone, zaleplon, zolpidem, and zopiclone; additional symptoms suggestive of anaphylaxis have also developed in some patients.

Overdosage. A retrospective analysis of 344 cases of acute overdosage with zolpidem reported to the Paris Poison Center and the manufacturers *Synthelabo* has been published.[1] The ingested dose, where known, ranged from 10 to 1400 mg, and the most common adverse effect was drowsiness (in 89 patients). Other adverse effects probably associated with the overdosage included coma in 4 patients and vomiting in 7. Recovery was usually rapid when overdosage involved only zolpidem. The authors recommended that patients who had ingested more than 100 mg of zolpidem should undergo gastric lavage and should be monitored for at least 12 hours (but see Adverse Effects, Treatment, and Precautions, above). Although flumazenil (p. 1552.2) may be used to reverse the effects of zolpidem toxicity, the authors of this analysis[1] found that in general it was not required.

1. Garnier R, *et al*. Acute zolpidem poisoning—analysis of 344 cases. *J Toxicol Clin Toxicol* 1994; **32:** 391–404.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zolpidem as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1.

Antidepressants. A 16-year-old girl who had been taking *paroxetine* 20 mg daily for 3 days began to hallucinate and became disorientated one hour after taking zolpidem 10 mg at night. The delirium cleared spontaneously 4 hours later without treatment.[1] When questioned, at least one other of the author's patients given this combination reported transient visual hallucinations. Other isolated cases of visual hallucinations have been reported in patients taking zolpidem with antidepressants including *bupropion, desipramine, fluoxetine, sertraline*, and *venlafaxine*.[2]

1. Katz SE. Possible paroxetine-zolpidem interaction. *Am J Psychiatry* 1995; **152:** 1689.
2. Elko CJ, *et al*. Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *J Toxicol Clin Toxicol* 1998; **36:** 195–203.

Antiepileptics. A 47-year-old man with a history of bipolar disorder, who was receiving citalopram and zolpidem, had episodes of somnambulism after he was also given *valproic acid* for treatment of manic symptoms.[1] The episodes stopped on withdrawal of valproic acid and returned on rechallenge. An interaction between zolpidem and valproic acid was suspected (but somnambulism has also been associated with zolpidem alone, see Effects on Mental Function, above).

For the suggestion that *carbamazepine* and *phenytoin* may interact with zolpidem, see Rifampicin, below.

1. Sattar SP, *et al*. Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* 2003; **37:** 1429–33.

Antifungals. Use of *ketoconazole* with zolpidem has resulted in increased plasma concentrations, and an enhanced sedative effect, of zolpidem, albeit only modest.[1] The use of zolpidem with *fluconazole*[1] or *itraconazole*[1,2] has resulted in small, non-significant changes in the pharmacokinetics and sedative effects of zolpidem.

1. Greenblatt DJ, *et al*. Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. *Clin Pharmacol Ther* 1998; **64:** 661–71.
2. Luurila H, *et al*. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. *Eur J Clin Pharmacol* 1998; **54:** 163–6.

Antivirals. HIV-protease inhibitors such as *ritonavir* may increase plasma concentrations of zolpidem with a risk of extreme sedation and respiratory depression; use together is possible provided the patient is carefully monitored for excessive sedative effects.

Rifampicin. Rifampicin reduced the hypnotic effect of zolpidem in a study in 8 healthy female subjects.[1] The area under the curve for zolpidem was reduced by 73% after rifampicin and the peak plasma concentration by 58%. The elimination half-life of zolpidem was reduced from 2.5 to 1.6 hours. Similar effects could be expected with other potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as carbamazepine and phenytoin.

1. Villikka K, *et al*. Rifampin reduces plasma concentrations and effects of zolpidem. *Clin Pharmacol Ther* 1997; **62:** 629–34.

Pharmacokinetics

Zolpidem is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur within 3 hours and are about 45% higher in women than in men given the same oral dose because of lower clearance rate in women. Zolpidem undergoes first-pass metabolism and an absolute bioavailability of about 70% has been reported. Zolpidem has an elimination half-life of about 2.5 hours and is about 92% bound to plasma proteins. It is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4; the inactive metabolites of zolpidem are excreted in the urine and faeces. Zolpidem is distributed into breast milk.

References.

1. Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. *Clin Pharmacokinet* 1995; **29:** 142–53.
2. von Moltke LL, *et al*. Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and in vivo correlations. *Br J Clin Pharmacol* 1999; **48:** 89–97.
3. Drover D, *et al*. Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; **22:** 1443–61.
4. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.
5. Greenblatt DJ, *et al*. Dynamics and kinetics of a modified-release formulation of zolpidem: comparison with immediate-release standard zolpidem and placebo. *J Clin Pharmacol* 2006; **46:** 1469–80.
6. Greenblatt DJ, *et al*. Comparison of pharmacokinetic profiles of zolpidem buffered sublingual tablet and zolpidem oral immediate-release tablet: results from a single-center, single-dose, randomized, open-label crossover study in healthy adults. *Clin Ther* 2013; **35:** 604–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ambien; Dormilan; Durnit; Nocte; Somit; Somnipax; Sumenan; Zolodorm; ***Austral.***: Dormizol; Somidem; Stildem; Stilnox; Zolpibell†; ***Austria***: Ivadal; Mondeal; Zoldem; ***Belg.***: Stilnoct; Zolpitop; ***Braz.***: Lioram; Noctiden; Stilnox; Zylinox; ***Canad.***: Sublinox; ***Chile***: Adormix†; Damixan; Dormilam; Dormosol; Somnil; Somnipron; Somno; Stilnox; Sucedal; ***China***: Le Tan (乐坦); Nuo Bin (诺宾); Stilnox (思诺思); ***Cz.***: Eanox; Hypnogen; Insom; Stilnoct†; Stilnox; Zolpimerck†; Zolpinox; Zolsana; Zonadin†; ***Denm.***: Nimadorm†; Stilnoct; Zonoct; ***Fin.***: Somnor; Stella; Stilnoct; ***Fr.***: Stilnox; ***Ger.***: Bikalm†; Stilnox; Zoldem†; Zolpi-Lich†; Zolpi-Q†; Zolpinox; ***Gr.***: Alespan; Hypnoforin; Hypnonorm; Stilnox; ***Hong Kong***: Stilnox; Stildem; Vicknox; ***Hung.***: Ambien†; Hypnogen; Pidezol; Sanval; Somnogen; Stilnox; ***India***: Ambiz†; Ambulax-Z; Dactive; Dem; Inzofresh; Isodem; Nidra; Nitrest; Olpitric; Sove; Zleep; Zoldem; ***Indon.***: Stilnox; Zolmia; ***Irl.***: Nytamel; Stilnoct; Zoldem; Zolnod; ***Israel***: Ambien; Stilnox; Zodorm; ***Ital.***: Nottem; Stilnox; ***Jpn***: Myslee; ***Malaysia***: Sobrium; Somidem; Stilnox; Zopim; ***Mex.***: Nitrest; Nocte; Stil-

nox; ***Neth.***: Stilnoct; ***Norw.***: Stilnoct; ***Philipp.***: Stilnox; Ziohex; Zoldem; Zolpid; ***Pol.***: Apo-Zolpin; Hypnogen; Nasen; Onirex; Polsen; Sanval; Stilnox; Xentic; Zolpic; ZolpiGen; Zolsana; Zoratio; ***Port.***: Cymerion; Stilnox; ***Rus.***: Hypnogen (Гипногeн); Ivadal (Ивадал); Nitrest (Нитрест); Sanval (Санвал); Snovitel (Сновител); Zolsana (Зольсана); Zonadine (Зонадин); ***S.Afr.***: Ivedal; Noxidem; Stilnox; Zolnoxs; Zolpihexal; ***Singapore***: Stilnox; ***Spain***: Dalparan; Stilnox; ***Swed.***: Stilnoct; ***Switz.***: Dorlotil; Stilnox; Zoldorm; ***Thai.***: Stilnox; ***UK***: Stilnoct; ***USA***: Ambien; Edluar; Intermezzo; Tovalt†; Zolpimist; ***Venez.***: Atrimon; Stilnox; Zolpidex.

Pharmacopoeial Preparations

USP 36: Zolpidem Tartrate Extended-Release Tablets; Zolpidem Tartrate Tablets.

Zopiclone *(BAN, rINN)*

27267-RP; Tsopikloni; Zopiclon; Zopiclona; Zopiclonum; Zopiklon; Zopiklonas; Зопиклон.

6-(5-Chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

$C_{17}H_{17}ClN_6O_3$=388.8

CAS — 43200-80-2.

ATC — N05CF01.

ATC Vet — QN05CF01.

UNII — 03A5ORL08Q.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of zopiclone: Zoppies.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Zopiclone). A white or slightly yellowish powder. Practically insoluble in water and in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Uses and Administration

Zopiclone is a cyclopyrrolone with similar sedative, anxiolytic, muscle relaxant, amnestic, and anticonvulsant properties to those of the benzodiazepines (see Diazepam, p. 1063.3). Like diazepam, its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA) in the brain. Zopiclone is reported to bind to the benzodiazepine receptor component of the GABA receptor complex but at a different site to the benzodiazepines. It has a short duration of action.

Zopiclone is used as a hypnotic in the short-term management of insomnia (below). The usual oral dose is 7.5 mg taken shortly before retiring. Treatment should start with a dose of 3.75 mg in elderly patients. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Eszopiclone, the (+)-isomer of zopiclone, is used similarly (see p. 1072.3).

Administration in hepatic or renal impairment. In those with renal impairment or mild to moderate hepatic impairment, treatment with zopiclone should start with an oral dose of 3.75 mg taken shortly before retiring. It should not be given to patients with severe hepatic impairment.

Insomnia. Zopiclone has a similar pharmacological and pharmacokinetic profile to the short-acting benzodiazepines. It is claimed to initiate sleep rapidly, without reduction of total rapid-eye-movement (REM) sleep, and then sustain it with preservation of normal slow-wave sleep (see Insomnia, p. 1033.2). It is generally considered to be as effective as a hypnotic as the benzodiazepines. Rebound insomnia has occurred but does not appear to be common. Residual effects the next day may be less pronounced after zopiclone than after short-acting benzodiazepines but there appears to be little evidence that zopiclone offers any clinical advantage in terms of its potential to induce tolerance, withdrawal symptoms, or dependence. For recommendations of the UK CSM concerning its use as a hypnotic, see Incidence of Adverse Effects, below.

References.

1. Noble S, *et al.* Zopiclone: an update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 1998; **55:** 277–302.
2. Hajak G. A comparative assessment of the risks and benefits of zopiclone: a review of 15 years' clinical experience. *Drug Safety* 1999; **21:** 457–69.
3. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

There have been reports[1,2] of zopiclone dependence and associated withdrawal symptoms on dosage reduction or cessation of use. However, a 67-year-old man who increased his dosage of zopiclone up to 337.5 mg daily to treat insomnia without apparent adverse effects, had his zopiclone withdrawn without severe complications over 4 weeks using drug and cognitive therapy.[3] A WHO expert committee[4] considered in 2006 that the likelihood of zopiclone abuse was low and not great enough to warrant international control.

1. Jones IR, Sullivan G. Physical dependence on zopiclone: case reports. *BMJ* 1998; **316:** 117.
2. Sikdar S. Physical dependence on zopiclone. *BMJ* 1998; **317:** 146.
3. Kuntze MF, *et al.* Excessive use of zopiclone: a case report. *Swiss Med Wkly* 2002; **132:** 523.
4. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. A bitter or metallic taste in the mouth has been the most frequently reported adverse effect with zopiclone.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to adults or children who present within one hour of ingesting more than 1 mg/kg of zopiclone. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zopiclone toxicity. (See also Overdosage, below).

Incidence of adverse effects. In a French postmarketing survey[1] of 20 513 patients treated with zopiclone, the most commonly reported adverse events were bitter taste (3.6%), dry mouth (1.6%), difficulty arising in the morning (1.3%), sleepiness (0.5%), nausea (0.5%), and nightmares (0.5%). The UK CSM[2] had received 122 reports of adverse reactions to zopiclone over a period of about one year since the product's introduction in November 1989. A fifth of these were neuropsychiatric reactions, a proportion similar to that found with other hypnotics. Many of these reactions were potentially serious and involved hallucinations (3 auditory and 2 visual), amnesia (4 cases), and behavioural disturbances (10, including 3 cases of aggression). Most reactions started immediately or shortly after the first dose and improved rapidly on stopping the drug. Three patients had difficulty in stopping treatment, 2 because of withdrawal symptoms and one due to repeated rebound insomnia. The CSM considered that, although differing structurally from the benzodiazepines, zopiclone has the same potential for adverse psychiatric reactions, including dependence. As with the benzodiazepines it should be reserved for patients with severe sleep disturbance and its duration of use limited to 28 days; care should also be taken in the elderly, those who have a history of previous psychiatric illness, or who are prone to drug abuse.

1. Allain H, *et al.* Postmarketing surveillance of zopiclone in insomnia: analysis of 20,513 cases. *Sleep* 1991; **14:** 408–13.
2. CSM. Zopiclone (Zimovane) and neuro-psychiatric reactions. *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024448&RevisionSelectionMethod=LatestReleased (accessed 20/07/09)

Abuse. For a report of zopiclone abuse see under Dependence and Withdrawal, above.

Administration. Results in 9 healthy subjects given zopiclone indicated a significant delay in onset of action when the drug was taken in the supine, as opposed to the standing, position; this was associated with a prolongation of more than 20 minutes in the lag time before absorption began.[1] In order to obtain a rapid and complete hypnotic effect from zopiclone the tablet should be swallowed in the standing position.

1. Channer KS, *et al.* The effect of posture at the time of administration on the central depressant effects of the new hypnotic zopiclone. *Br J Clin Pharmacol* 1984; **18:** 879–86.

Driving. For reference to the increased risk of road-traffic accidents for drivers taking benzodiazepines, see p. 1067.1.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zopiclone, see under Zolpidem, p. 1117.2.

Hepatic impairment. Zopiclone was given in a dose of 7.5 mg to 7 cirrhotic patients and 8 healthy subjects; a further 2 cirrhotic patients received 3.75 mg.[1] Mean peak plasma concentrations were similar in healthy subjects and those with hepatic impairment following equivalent doses but time to peak plasma concentration was 4 hours in the latter as compared with 2 hours in the healthy subjects. Elimination was greatly prolonged in cirrhotic patients, in whom the mean plasma half-life was 8.53 hours compared with 3.5 hours. The CNS-depressant effects of zopiclone were delayed in the cirrhotic patients in a way consistent with the pharmacokinetic changes. There was also some evidence of an increased response in these patients.

1. Parker G, Roberts CJC. Plasma concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; **16:** 259–65.

For precautions and doses recommended in licensed product information, see under Uses and Administration, above.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zopiclone, see under Zolpidem, p. 1117.2.

Overdosage. Fatalities have been reported after zopiclone overdose.[1,2] Methaemoglobinaemia and renal failure have been reported in a patient who took 2.25 g of zopiclone in a suicide attempt.[3]

Flumazenil may rarely be used to reverse the effects of severe zopiclone toxicity. see Non-benzodiazepine Antagonism under Flumazenil, p. 1552.2.

1. Boniface PJ, Russell SGG. Two cases of fatal zopiclone overdose. *J Anal Toxicol* 1996; **20:** 131–3.
2. Meatherall RC. Zopiclone fatality in a hospitalized patient. *J Forensic Sci* 1997; **42:** 340–3.
3. Kung SW, *et al.* Zopiclone-associated methemoglobinemia and renal impairment. *Clin Toxicol* 2008; **46:** 1099–1100.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zopiclone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1. Use with rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4, such as carbamazepine or phenytoin, is likely to reduce the effects of zopiclone.

Antibacterials. In a study in healthy subjects *erythromycin* increased the rate of absorption of zopiclone and prolonged its elimination.[1] In another study[2] in 8 healthy subjects *rifampicin* was associated with an 82% reduction in the area under the curve for zopiclone. The peak plasma concentration of zopiclone was reduced from 76.9 to 22.5 nanograms/mL and the elimination half-life from 3.8 to 2.3 hours.

1. Aranko K, *et al.* The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; **38:** 363–7.
2. Villikka K, *et al.* Concentrations and effects of zopiclone are greatly reduced by rifampicin. *Br J Clin Pharmacol* 1997; **43:** 471–4.

Pharmacokinetics

Zopiclone is rapidly absorbed and widely distributed after oral doses. It has an elimination half-life of 3.5 to 6.5 hours and is reported to be about 45 to 80% bound to plasma proteins. Zopiclone is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4 and, to a lesser extent, CYP2C8; the 2 major metabolites, the less active zopiclone *N*-oxide and the inactive *N*-desmethylzopiclone, are excreted mainly in the urine. About 50% of a dose is converted by decarboxylation to inactive metabolites, which are partly eliminated via the lungs as carbon dioxide. Only about 5% of a dose appears unchanged in the urine and about 16% appears in the faeces. Excretion of zopiclone in the saliva may explain reports of a bitter taste. It is also distributed into breast milk.

Reviews.

1. Fernandez C, *et al.* Clinical pharmacokinetics of zopiclone. *Clin Pharmacokinet* 1995; **29:** 431–41.
2. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.

Distribution into breast milk. Zopiclone was distributed into breast milk in 12 women in concentrations about half those in plasma.[1] The calculated dose that would be received by a neonate was 1.5 micrograms/kg, corresponding to 1.2% of the maternal dose.

1. Matheson I, *et al.* The excretion of zopiclone into breast milk. *Br J Clin Pharmacol* 1990; **30:** 267–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Foltran; Imovane; Insomnium; ***Austral.***: Imovane; Imrest; ***Austria***: Somnal; ***Belg.***: Imovane; ***Braz.***: Imovane; ***Canad.***: Imovane; Rhovane; ***Chile***: Alpaz; Imovane; Losopil; Zetix; Zometic; Zonix; ***China***: Imovane (忆梦返); Jin Meng (金盟); Qing Er Qi (青尔齐); San Chen (三辰); ***Cz.***: Zopitin; ***Denm.***: Imoclone; Imovane; Imozop; ***Fin.***: Imovane; Zopinox; Zopitin; ***Fr.***: Imovane; ***Ger.***: Optidorm; Somnosan; Ximovan; Zop†; Zopi-Puren†; ***Gr.***: Imovane; ***Hong Kong***: Dopareel; Eurovan; Imolone†; Imovane; Zolief; Zomni; ***Hung.***: Imovane; Somnol; Zopigen; ***India***: Lyzop; Zopicon; ***Irl.***: Zileze; Zimoclone; Zimovane; Zopitan; Zorclone; ***Israel***: Imovane; Nocturno; ***Ital.***: Imovane; ***Malaysia***: Imovane; Insopin; Zolon; ***Mex.***: Imovane; ***Neth.***: Imovane; ***Norw.***: Imovane; ***NZ***:

Imovane; ***Pol.***: Dobroson; Imovane; Senzop; Zopiratio; ***Rus.***: Imovane (Имован); Milovan (Милован); Piclodorm (Пиклодорм); Relaxon (Релаксон); Slipvell (Слипвэлл); Somnol (Сомнол); Torson (Торсон); Zolinox (Золинокс); ***S.Afr.***: Adco-Zopimed; Alchera; Imovane; Z-Dorm; Zopigen; Zopivane; ***Singapore***: Imovane; ***Spain***: Datolan; Limovan; Siaten; Zopicalma; ***Swed.***: Imovane; ***Switz.***: Imovane; ***Turk.***: Imovane; ***UK***: Zimovane; ***Ukr.***: Imovane (Имован); Normason (Нормасон); Piklon (Піклон); Sonnat (Соннат).

Pharmacopoeial Preparations
BP 2014: Zopiclone Tablets.

Zotepine *(BAN, rINN)*

Zotepina; Zotépine; Zotepinum; Зотепин.
2-[(8-Chlorodibenzo[*b,f*]-thiepin-10-yl)oxy]-*N,N*-dimethylethylamine.
$C_{18}H_{18}ClNOS$=331.9
CAS — 26615-21-4.
ATC — N05AX11.
ATC Vet — QN05AX11.
UNII — U29O83JAZW.

Profile

Zotepine is an atypical antipsychotic that, in addition to its antagonist action at central dopamine (D_1 and D_2) receptors, binds to serotonin ($5\text{-}HT_2$), adrenergic (α_1), and histamine (H_1) receptors and also inhibits noradrenaline reuptake. It has been given in the treatment of schizophrenia (below) in an initial oral dose of 25 mg three times daily, increased according to response, at intervals of 4 days, to a maximum of 100 mg three times daily. There is an appreciable increase in the incidence of seizures at doses above 300 mg daily. For elderly patients, a starting dose of 25 mg has been given twice daily, increased gradually up to a maximum of 75 mg twice daily. Doses should also be reduced in patients with hepatic or renal impairment, see below.

Zotepine has uricosuric properties and should not be given to patients with acute gout or a history of nephrolithiasis; it should be used with caution in patients with a history of gout or hyperuricaemia.

Administration in hepatic or renal impairment. For patients with renal or hepatic impairment, an initial oral dose of zotepine 25 mg has been given twice daily, increased gradually up to a maximum of 75 mg twice daily.

Schizophrenia. A systematic review[1] of short-term studies of zotepine for schizophrenia (p. 1031.3) concluded tentatively that it was as effective as classical antipsychotics and might be of benefit in patients with negative symptoms; in addition, it seemed less likely to provoke extrapyramidal disorders. A later systematic review[2] that compared zotepine with other atypical antipsychotics found insufficient evidence for a meaningful comparison to be drawn.

1. DeSilva P, *et al.* Zotepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/04/08).
2. Subramanian S, *et al.* Zotepine versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 03/06/13).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nipolept†; ***Cz.***: Zoleptil; ***Ger.***: Nipolept†; ***Indon.***: Lodopin; ***Jpn***: Lodopin; Losizopilon; Majorpin; Setous; ***Port.***: Zoleptil; ***Turk.***: Zoleptil; ***UK***: Zoleptil†.

Zuclopenthixol *(BAN, rINN)*

AY-62021 (clopenthixol or clopenthixol hydrochloride); *cis*-Clopenthixol; α-Clopenthixol; *Z*-Clopenthixol; N-746 (clopenthixol or clopenthixol hydrochloride); NSC-64087 (clopenthixol); Tsuklopentiksoli; Zuclopenthixolum; Zuclopentixol; Zuklopentixol; Зуклопентиксол.
(*Z*)-2-{4-[3-(2-Chloro-10*H*-dibenzo[*b,e*]thiin-10-ylidene)propyl]piperazin-1-yl}ethanol.
$C_{22}H_{25}ClN_2OS$=401.0
CAS — 53772-83-1 (zuclopenthixol); 982-24-1 (clopenthixol).
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 47ISU063SG.

NOTE. Clopenthixol (*BAN, INN, USAN*) is a mixture of the *Z* and *E* isomers.

Zuclopenthixol Acetate *(BANM, rINNM)*

Acetato de zuclopentixol; Zuclopenthixol, Acétate de; Zuclopenthixoli Acetas; Zuclopentixol, acetato de; Zuklopentiksol Asetat; Зуклопентиксола Ацетат.

$C_{24}H_{27}ClN_2O_2S$=443.0
CAS — 85721-05-7.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 349S2ZHF05.

Pharmacopoeias. In *Br.*

BP 2014: (Zuclopenthixol Acetate). A yellowish, viscous oil. Very slightly soluble in water; very soluble in alcohol, in dichloromethane, and in ether. Store at a temperature not exceeding -20 degrees. Protect from light.

Zuclopenthixol Decanoate *(BANM, rINNM)*

Decanoato de zuclopentixol; Tsuklopentiksolidekanoaatti; Zuclopenthixol, Décanoate de; Zuclopenthixoldecanoat; Zuclopenthixoli decanoas; Zuclopentixol, decanoato de; Zuklopenthixol-dekanoát; Zuklopentiksol Dekanoat; Zuklopentiksolio dekanoatas; Zuklopentixoldekanoat; Zuklopentyksolu dekanonian; Зуклопентиксола Деканоат.
$C_{32}H_{43}ClN_2O_2S$=555.2
CAS — 64053-00-5.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — TSS9KIZ5OG.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Zuclopenthixol Decanoate). A yellow viscous oily liquid. Very slightly soluble in water; very soluble in alcohol and in dichloromethane. Store under an inert gas in airtight containers at a temperature not exceeding -20 degrees. Protect from light.

Zuclopenthixol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de zuclopentixol; Zuclopenthixol, Chlorhydrate de; Zuclopenthixol Dihydrochloride; Zuclopenthixoli Hydrochloridum; Zuclopentixol, hidrocloruro de; Zuklopentiksol Dihidroklorür; Зуклопентиксола Гидрохлорид.
$C_{22}H_{25}ClN_2OS,2HCl$=473.9
CAS — 58045-23-1.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 7042692VYN.

Pharmacopoeias. In *Br.*

BP 2014: (Zuclopenthixol Hydrochloride). An off-white granular powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.
1. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32:** 25–9.

Uses and Administration

Zuclopenthixol is a thioxanthene of high potency with general properties similar to the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain.

Zuclopenthixol is used for the treatment of schizophrenia (below), mania (see Bipolar Disorder, p. 397.2), and other psychoses. It may be particularly suitable for agitated or aggressive patients who may become over-excited with flupentixol. Zuclopenthixol hydrochloride is usually given orally with doses expressed in terms of the base; zuclopenthixol hydrochloride 11.8 mg is equivalent to about 10 mg of zuclopenthixol. Zuclopenthixol hydrochloride has also been given intramuscularly. Zuclopenthixol acetate and zuclopenthixol decanoate are given by deep intramuscular injection; doses are expressed in terms of the ester. The acetate ester has a rapid onset of action and a duration of action of 2 to 3 days; it is used as a 5% oily solution for the initial treatment of acute psychoses and for exacerbations of chronic psychoses. The longer-acting decanoate ester is used as a 20% oily solution for the maintenance treatment of chronic psychoses; a 50% solution is available for those requiring high doses.

- The usual initial *oral* dose of the hydrochloride for the treatment of **psychoses** is the equivalent of 20 to 30 mg of the base daily in divided doses; in severe or resistant cases up to 150 mg daily has been given. The recommended maximum single dose is 40 mg. The usual maintenance dose is 20 to 50 mg daily.
- The usual dose of zuclopenthixol acetate is 50 to 150 mg by deep *intramuscular* injection repeated, if necessary, after 2 or 3 days. Some patients may need an additional injection between 1 and 2 days after the first dose. Zuclopenthixol acetate is not intended for maintenance treatment; no more than 4 injections should be given in a maximum course of 2 weeks and the total dose should not exceed 400 mg. When maintenance treatment is required, *oral* zuclopenthixol hydrochloride may be introduced 2 to 3 days after the last injection of zuclopenthixol acetate, or *intramuscular* injections of the decanoate (see below) begun with the last injection of the acetate.
- The long-acting decanoate should be given by deep *intramuscular* injection; treatment is usually started with a test dose of 100 mg. This may be followed after at least 1 week by a dose of 200 to 500 mg or more, every 1 to 4 weeks, adjusted according to response. Injection volumes greater than 2 mL should be divided between 2 separate injection sites. The maximum recommended dose of zuclopenthixol decanoate is 600 mg weekly.

Elderly or debilitated patients should be given reduced doses of zuclopenthixol. Licensed product information states that the dose of the hydrochloride or the decanoate may need to be reduced to one-quarter or one-half of the usual initial dose; in addition, the maximum single dose of the acetate should be limited to 100 mg.

Dosage adjustment is also advised in patients with hepatic or renal impairment (see below).

Administration in hepatic or renal impairment. Licensed product information recommends that for both zuclopenthixol acetate and hydrochloride, half the usual recommended intramuscular and oral dose, respectively, should be used for patients with hepatic impairment; a dosage reduction is considered to be unnecessary in patients with renal impairment but where there is renal failure half the usual dosage is recommended.

Schizophrenia. A systematic review[1] comparing zuclopenthixol decanoate with other depot antipsychotics considered that although it may induce more adverse effects, limited data suggested it might offer advantages such as lower relapse rates and increased acceptability in the treatment of schizophrenia (p. 1031.3) and similar serious mental illnesses. Similar reviews of the use of the acetate[2] or hydrochloride[3] found, however, that evidence of additional benefit over other antipsychotics was lacking.

1. Coutinho E, *et al.* Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 14/04/05).
2. Gibson RC, *et al.* Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).
3. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 12/05/06).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Zuclopenthixol is less likely to cause sedation but extrapyramidal effects are more frequent.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zuclopenthixol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Zuclopenthixol is absorbed after oral doses and peak plasma concentrations occur 3 to 6 hours later. The biological half-life after oral doses is reported to be about 1 day. Paths of metabolism of zuclopenthixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. It is mainly excreted in the faeces as unchanged drug and its *N*-dealkylated metabolite. Zuclopenthixol is about 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Small amounts of drug or metabolites cross the placenta and are distributed into breast milk.

On intramuscular injection the acetate and decanoate esters of zuclopenthixol are hydrolysed to release zuclopenthixol. Zuclopenthixol acetate has a relatively quick onset of action after injection and a duration of action of 2 to 3 days. It is therefore useful for the control of acute psychotic symptoms while avoiding repeated injections. The decanoate has a much longer duration of action and is a suitable depot preparation for maintenance treatment.

Metabolism. Determination of metaboliser phenotype with regard to cytochrome P450 isoenzyme CYP2D6 appeared to be of limited value in patients receiving zuclopenthixol as interindividual variation appeared to be

the main factor affecting dose to serum concentration ratios.[1]

1. Linnet K, Wiborg O. Influence of Cyp2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopenthixol. *Ther Drug Monit* 1996; **18:** 629–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clopixol; ***Austral.***: Clopixol; ***Austria***: Cisordinol; ***Belg.***: Clopixol; ***Braz.***: Clopixol; ***Canad.***: Clopixol; ***Chile***: Cisordinol; ***China***: Clopixol (高抗素); ***Cz.***: Cisordinol; ***Denm.***: Cisordinol; Clopixol; ***Fin.***: Cisordinol; ***Fr.***: Clopixol; ***Ger.***: Ciatyl-Z; ***Gr.***: Clopixol; ***Hong Kong***: Clopixol; ***Hung.***: Cisordinol; ***India***: Clopixol; ***Irl.***: Clopixol; ***Israel***: Clopixol; ***Ital.***: Clopixol; ***Malaysia***: Clopixol; ***Mex.***: Clopixol; ***Neth.***: Cisordinol; Clopixol; ***Norw.***: Cisordinol; ***NZ***: Clopixol; ***Philipp.***: Clopixol†; ***Pol.***: Clopixol; ***Port.***: Cisordinol; ***Rus.***: Clopixol (Клопиксол); ***S.Afr.***: Clopixol; Colpixol†; ***Singapore***: Clopixol; ***Spain***: Clopixol; ***Swed.***: Cisordinol; ***Switz.***: Clopixol; ***Thai.***: Clopixol; ***Turk.***: Clopixol; ***UK***: Clopixol; ***Ukr.***: Clopixol (Клопиксол).

Pharmacopoeial Preparations

BP 2014: Zuclopenthixol Acetate Injection; Zuclopenthixol Decanoate Injection; Zuclopenthixol Tablets.

Blood Products Plasma Expanders and Haemostatics

Haematopoiesis, p. 1121
Anaemias, p. 1121
Aplastic anaemia, p. 1121
Haemolytic anaemia, p. 1122
Iron-deficiency anaemia, p. 1123
Megaloblastic anaemia, p. 1123
Normocytic-normochromic anaemia, p. 1123
Sideroblastic anaemia, p. 1123
Haemoglobinopathies, p. 1123
Sickle-cell disease, p. 1123
β-Thalassaemia, p. 1124
Haemostasis and Fibrinolysis, p. 1124
Acquired haemorrhagic disorders, p. 1125
Disseminated intravascular coagulation, p. 1126
Haemaphilias, p. 1126
Inherited haemorrhagic disorders, p. 1128
Neonatal intraventricular haemorrhage, p. 1128
Thrombocytopenia, p. 1129
von Willebrand's disease, p. 1129
Neutropenia, p. 1130

This chapter describes the management of blood disorders including some anaemias, haemorrhagic disorders, and neutropenia. It covers blood, blood products and substitutes, and colloid plasma expanders; crystalloid plasma expanders are generally solutions of sodium chloride (p. 1797.3) or glucose (p. 2068.3) or both. Also included in the chapter are haemostatic drugs and erythropoietin and other colony-stimulating factors. The management of haematological malignancies is covered in the Antineoplastics chapter, p. 691.1.

Haematopoiesis

In the embryo and fetus, the formation and development of blood cells occurs at various sites including the liver, spleen, thymus, lymph nodes, and bone marrow; from birth throughout the rest of life it occurs mainly in the bone marrow with a small amount occurring in the lymph nodes. The bone marrow contains pluripotent stem cells that differentiate into different types of progenitor cells (committed stem cells); these then mature into various types of blood cells under the influence of growth factors and hormones. The main cellular components of blood are red blood cells (erythrocytes), white blood cells (leucocytes), and platelets.

Erythrocyte production is stimulated by erythropoietin, a hormone released by the kidney in response to anaemia or hypoxia.

The leucocytes are classified according to their morphological appearance into granulocytes, lymphocytes, and monocytes. The granulocytes are further classified as neutrophils, eosinophils, and basophils, according to the characteristics of their cytoplasmic granules. The term polymorphonuclear leucocytes can be applied to granulocytes in general but applies in particular to neutrophils. Most lymphocytes are matured in the lymph nodes, thymus, and spleen, from bone marrow lymphocyte precursors. Lymphocytes enter the bloodstream via the lymphatics, but only a small proportion are present in the blood. Monocytes are released into the blood but then enter the tissues to become fixed tissue macrophages. The maturation of leucocytes is stimulated by granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF).

Platelet maturation is stimulated by thrombopoietin.

Other growth factors involved at various stages of blood cell development include stem cell factor and interleukins-1, -3, -4, -5, -6, and -11.

The average blood cell counts in adults are:

- erythrocytes (men): 5.0×10^{12} cells/litre
- erythrocytes (women): 4.3×10^{12} cells/litre
- leucocytes: 7.0×10^{9} cells/litre (7000 cells/mm^3) but the value can vary markedly, even in the same individual at different times, from 4 to 11×10^{9} cells/litre. This total is made up of:
  neutrophils (40 to 80%)
  lymphocytes (20 to 40%)
  monocytes (2 to 10%)
  eosinophils (1 to 6%)
  basophils (< 1 to 2%)
- platelets: 150 to 450×10^{9} cells/litre (150 000 to 450 000 cells/mm^3)

Anaemias

Anaemia is usually understood to mean a lowering of haemoglobin concentration, red cell count, or packed cell volume to below 'normal' values, but the criteria for normality are difficult to establish. WHO's suggested definition of anaemia in populations living at around sea level is a haemoglobin concentration below:

- 13 g per 100 mL in men
- 12 g per 100 mL in women
- 11 g per 100 mL in pregnant women
- 12 g per 100 mL in children aged 12 to 14 years
- 11.5 g per 100 mL in children aged 5 to 11 years
- 11 g per 100 mL in children aged 6 to 59 months

However, because of individual variation, some apparently normal individuals have blood haemoglobin concentrations below these values, while others may be above these values and still be effectively anaemic.

Reduction in overall haemoglobin concentrations may be due to fewer red cells, with the cells retaining normal amounts of haemoglobin (normochromic anaemia), or the amount of haemoglobin in the cells may be reduced (hypochromic anaemia). Red cells themselves may be reduced in size (microcytic), enlarged (macrocytic), or normal in size (normocytic).

The immediate cause of anaemia may be decreased red cell production (due to defective proliferation and/or maturation of red cells from their precursors in bone marrow), increased red cell destruction (i.e. haemolysis), or loss of red cells from the circulation due to haemorrhage, either occult or overt. These conditions may occur due to underlying disease, nutritional deficiency, congenital disorders, or toxicity due to drugs or other substances and the cause must always be sought before an appropriate treatment can be determined.

The symptoms of anaemia are as variable as its causes but may include fatigue, pallor, dyspnoea, palpitations, headache, faintness or lightheadedness, tinnitus, anorexia and gastrointestinal disturbances, and loss of libido; tachycardia, heart failure, and retinal haemorrhage may occur in severe anaemia.

The treatment of anaemia depends upon its type and cause. Some of the principal types are classified in Table 1, below, and their management is discussed in more detail under the relevant headings. Sickle-cell disease and β-thalassaemia are discussed under Haemoglobinopathies, p. 1123.2.

Table 1. Types of anaemias.

Classification	Anaemia	Mean cell volume	Haemoglobin	Associated with
Microcytic	Iron-deficiency anaemia	Decreased (or normal in early stages)	Hypochromic	Blood loss, malabsorption, inadequate iron intake
	Hereditary sideroblastic anaemia	Decreased	Hypochromic	
	Thalassaemias	Decreased	Hypochromic	
Macrocytic	Megaloblastic anaemia	Increased	Normochromic	Vitamin B_{12} deficiency, folate deficiency (including drug induced)
	Acquired sideroblastic anaemia	Increased	Hypochromic	Alcoholism, drug or other toxicity
Normocytic	Normocytic-normochromic anaemia	Normal	Normochromic	Anaemia of chronic disorders, bone-marrow disorders (including aplastic anaemia), malignancy, renal failure, endocrine disorders, prematurity
Haemolytic	Haemolytic anaemia	Increased		Immune disorders, drug toxicity, hereditary disorders
	Sickle-cell anaemia			

Reviews.
1. Spivak JL. The blood in systemic disorders. *Lancet* 2000; **355:** 1707–12.
2. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. *Mayo Clin Proc* 2003; **78:** 1274–80.
3. Tefferi A. Practical algorithms in anemia diagnosis. *Mayo Clin Proc* 2004; **79:** 955–6.

Aplastic anaemia

Aplastic anaemia is characterised by pancytopenia (a deficiency of all cellular elements of the blood) and hypoplasia of the bone marrow, with less than 25% of the marrow occupied by haematopoietic cells but without evident fibrosis or malignant infiltration. It is relatively rare, although it may be somewhat more common in the Far East, and is mainly seen in younger adults. Some forms, such as Fanconi's anaemia, are inherited but most are induced, for example by the effects of cytotoxic drugs or radiation, idiosyncratic reactions to other drugs, seronegative fulminant hepatitis, or auto-immune reactions. Since all cell lines are affected patients develop thrombocytopenia and neutropenia as well as anaemia, and symptoms include bleeding syndromes and infections as well as typical symptoms of anaemia. Paroxysmal nocturnal haemoglobinuria (see Haemolytic Anaemia, p. 1122.2), in which genetic mutation causes the production of abnormal blood cells and results in haemolysis, can be associated with aplastic anaemia.

Although spontaneous recovery has occurred, untreated aplastic anaemia is usually fatal. Management may be divided into supportive care and attempts to restore bone-marrow function with bone marrow transplantation or immunosuppression, and has been the subject of guidelines and reviews.[1-4]

Supportive care involves the prevention and treatment of infection (see Infections in Immunocompromised Patients, p. 186.3), the control of haemorrhage with platelet concentrates, and where necessary, infusions of red

blood cells (with platelets to prevent haemorrhage) for anaemia. The risk of developing alloimmunisation, which can result in platelet refractoriness and increase the risk of graft rejection after allogeneic bone marrow transplantation, may be reduced by the use of leucocyte-depleted red cells and platelets. Some guidelines[4] also recommend the use of irradiated blood products in patients receiving antilymphocyte immunoglobulin, although evidence to support this is lacking and practice varies worldwide.

In patients aged under 40 years with ***severe disease*** and with a suitable HLA-identical sibling donor, **bone marrow transplantation** offers the prospect of long-term cure, and is considered the treatment of choice.[1,2,4,5] Ideally this should be performed early before the patient has received too many transfusions, which increase the risk of rejection, and before infection develops. Bone marrow stem cells are recommended because chronic graft-versus-host disease and overall survival may be worse when peripheral blood stem cells are used.[2,4] Umbilical cord blood is an alternative source of stem cells and may be associated with less acute and chronic graft-versus-host disease than bone marrow transplantation.[4] However, the use of cord blood is limited by the low number of cells that can be obtained.

In patients unsuitable for bone marrow transplantation, or where a suitable sibling donor is not available, treatment with **immunosuppressants** may be tried. About 50% of patients are reported to respond to a course of antilymphocyte immunoglobulin, and the addition of ciclosporin further improves response rates to between 60 and 80% and 5-year survival to between 75 and 90%.[1,4] However, one long-term study[6] providing follow-up data for 11 years has found no significant difference in survival between regimens of antilymphocyte immunoglobulin with or without ciclosporin.[6] Response to treatment is usually delayed, and starts after about 3 to 4 months.[4] Ciclosporin has been used alone but is less effective than antilymphocyte immunoglobulin.[1,2]

Despite these good rates of response with the addition of ciclosporin, relapse is not uncommon.[7] A second course of antilymphocyte immunoglobulin is recommended if there is no response, or there is relapse, after 3 months.[4] Ciclosporin is continued after a response has occurred and until the blood count has been stable for at least 12 months; it may then be slowly withdrawn, usually over many months and depending on blood counts.[4] Some patients may require continued therapy.[2,3]

In patients with severe aplastic anaemia who have failed at least 1 course of antilymphocyte immunoglobulin and ciclosporin, and who are less than 50 years old, a matched unrelated bone marrow transplantation using a fludarabine-based regimen without irradiation may be considered.[4]

Good response rates have been reported from combined regimens including a granulocyte colony-stimulating factor.[8] However, there are concerns about long-term use and the role of these factors is still under investigation.[2,4,9] There has been interest in the use of other haematopoietic growth factors including granulocyte-macrophage colony-stimulating factor, ancestim (stem cell factor), epoetin, interleukin-1, interleukin-3, and interleukin-6, either alone or with immunosuppression, but results have generally been poor or studies stopped because of toxicity, and so the use of these factors is not recommended.[4,9] However, short courses of granulocyte colony-stimulating factor may be considered for supportive therapy in neutropenic patients with severe systemic infections that are not responding to antibacterial or antifungal therapy.[4] Neutrophil responses are usually seen in patients with non-severe aplastic anaemia who have residual marrow granulocytopenic activity.

Oxymetholone was used extensively before the availability of antilymphocyte immunoglobulin and ciclosporin. It can increase the response to antilymphocyte immunoglobulin alone, but it can be hepatotoxic and causes virilisation, and is generally used for patients who have failed several courses of antilymphocyte immunoglobulin with ciclosporin, or where this regimen cannot be used.[4] Cyclophosphamide is commonly used in preparation for bone marrow transplantation and complete remission has also been reported with high-dose cyclophosphamide alone.[10,11] However, a randomised study[12] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those receiving cyclophosphamide. Further follow-up[13] also found that relapse rates were no different. Nonetheless, cyclophosphamide continues to be of investigational interest.[3]

Responses to immunosuppressants are often partial, but this may be sufficient to free the patient from dependency on transfusions and intensive antibacterial cover, and is considered well worth achieving.[1] Nevertheless, the procedure is not curative; patients appear to retain some underlying defect in marrow function, and in the long term about 15% of them develop leukaemias or myelodysplasias.[1]

Children with severe aplastic anaemia are treated similarly to adults.[14,15] Although some reports have suggested that the response to immunosuppressant therapy may be lower in children under 5 years of age, others have shown the opposite.[14] The choice of treatment in children may also need to take into account the potential long-term adverse effects of treatment, particularly with immunosuppressants or irradiation, on endocrine function, growth, fertility, and the development of secondary malignancies.

Older patients tend to be treated with immunosuppressant therapy rather than bone marrow transplantation.[4] A retrospective cohort study[16] that compared patients older than 50 years with younger patients found that more older patients had received ciclosporin alone, that the response to immunosuppression was independent of age at the time of treatment, and that although survival decreased with age deaths were similar to those in a general population and were not related to the type of treatment or the number of courses of treatment.

The outcome of **pregnancy** in women who had previously been treated for aplastic anaemia with an immunosuppressant regimen has been described.[17] Of 36 pregnancies, 22 were uncomplicated and 7 were complicated by relapse of aplastic anaemia; complications appeared to be more likely in women with low platelet counts and paroxysmal nocturnal haemoglobinuria. Rarely, aplastic anaemia can develop during pregnancy, and although the disease may remit spontaneously after termination or delivery, this does not occur in all cases.[18,19] Supportive care is the mainstay for management of aplastic anaemia during pregnancy, although the use of ciclosporin may be considered if transfusions are required.[4]

Patients with ***non-severe aplastic anaemia*** may require supportive therapy only. However, those who are transfusion-dependent,[4,20] or who have significant neutropenia with an associated risk of infection,[4] may be candidates for immunosuppressive therapy. For children, bone marrow transplantation from an HLA-identical sibling may be considered in those with non-severe disease who are transfusion-dependent, particularly if the blood count is falling.[4]

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Haemolytic anaemia

The normal life span of an erythrocyte is about 120 days; a haemolytic state is defined as a reduction in this mean life span due to premature destruction of red cells, either intravascularly, or more commonly after sequestration by the spleen or liver. Healthy bone marrow can compensate for even quite severe haemolysis by increased erythropoiesis; however, if the red cell survival-time is less than 15 days, or if the bone marrow is abnormal, or there is a deficiency of folate, iron, or other necessary nutrients, then compensation will be inadequate and haemolytic anaemia will result. In addition to typical symptoms of anaemia (p. 1121.2) patients frequently have jaundice and splenomegaly, while the increased erythropoiesis results in reticulocytosis (elevated counts of immature red cells).

Haemolytic anaemias may be either congenital or acquired. The **congenital** disorders include:

- those due to membrane defects in the erythrocyte, such as spherocytosis or elliptocytosis
- those due to enzyme defects (including the various forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency)
- those due to haemoglobin defects (haemoglobinopathies), including sickle-cell disease (p. 1123.2) and β-thalassaemia (p. 1124.1)

The **acquired** haemolytic anaemias arise from many causes but may be divided into immune and non-immune types. The immune types include:

- some drug-induced haemolytic anaemias (including those produced by penicillins, rifampicin, and methyldopa)
- auto-immune haemolytic anaemia (further classified into warm or cold depending on the temperature at which the red cell antibodies are most active)
- paroxysmal nocturnal haemoglobinuria, resulting from complement-mediated red cell lysis
- haemolytic disease of the newborn (see p. 2377.2)

The non-immune types include:

- haemolysis due to infections such as malaria
- chemically-induced haemolysis (due to a direct effect on the red cell rather than an immunologically-mediated one, and including the effects of toxins such as copper and arsenic as well as some snake venoms, and drugs such as amphotericin B, dapsone, and sulfasalazine)
- the effects of mechanical trauma

Treatment of haemolytic anaemia depends on the underlying cause, although general supportive measures (bed rest, transfusion if haemodynamic abnormalities make it necessary, and supplementation with folate) will be similar in all poorly-compensated patients. Well compensated haemolysis may require no treatment at all, although clearly elucidation and, where possible, removal of the cause is desirable.

Hereditary haemolytic disorders such as spherocytosis[1] mostly respond well to splenectomy, although milder forms may not require treatment. In patients with G6PD deficiency, treatment consists essentially of avoidance of drugs or foodstuffs likely to provoke haemolysis.

Acquired haemolytic anaemia is best treated by identification and where possible elimination of any underlying cause. Most drug-induced haemolytic anaemias respond rapidly to withdrawal of the offending substance.

Auto-immune haemolytic anaemias require treatment aimed at maintaining the patient and controlling haemolysis. Although treatment may need to be prolonged, in many patients with idiopathic disease antibodies eventually disappear or decrease to insignificant titres after months or years. The auto-immune haemolytic anaemias may be secondary to other disorders including leukaemias, lymphomas, and SLE; correction of the underlying disease often results in marked improvement of accompanying haemolysis.

In patients with warm auto-immune haemolytic anaemia treatment starts with corticosteroids.[2] A typical initial dose is oral prednisone or prednisolone 1 to 1.5 mg/kg daily. The onset of response is usually rapid and most patients benefit within 10 to 14 days. The initial effective dose of corticosteroid should be continued until a satisfactory response has been obtained, and once there is haematologic stabilisation the dose may be gradually reduced. Many patients will require low-dose maintenance therapy. If symptoms do not respond to tolerable doses of corticosteroids splenectomy should be considered. Immunosuppressants such as azathioprine or cyclophosphamide may be considered in patients refractory to other therapy; responses are reportedly variable, but they sometimes permit reduction of corticosteroid maintenance doses. There are some reports of benefit from the use of danazol and some cases have responded to rituximab. High-dose intravenous normal immunoglobulin may be used in some patients if the adverse effects of long-term corticosteroid or immunosuppressant therapy are severe. Plasma exchange may be useful for acute management of severe haemolysis while other therapies are taking effect.[2] Transfusion is problematic in these patients because of the difficulty in establishing compatibility between patient and donor.[3] Nonetheless, transfusion may be life-saving in acute disease, and the least incompatible blood should be used.

In patients with cold auto-immune haemolytic anaemias such as cold haemagglutinin disease it is additionally important to keep the patient warm.[2] Corticosteroids and splenectomy are generally of no benefit in these patients (although there may be a responsive subgroup), but treatment with oral chlorambucil 2 to 4 mg daily may produce a response. Blood transfusion should be avoided if

possible, and if given it should be preferably via a warming coil and infused slowly. Rituximab has also been tried with some success in cold auto-immune haemolytic anaemia.

In paroxysmal nocturnal haemoglobinuria, red cells are more sensitive to complement-mediated lysis because of a deficiency in protective membrane proteins on the cell surface. Haemolysis may be accompanied by neutropenia, thrombocytopenia, and venous thrombosis, and in some patients there may be some overlap with aplastic anaemia, see p. 1121.3. Curative therapy for paroxysmal nocturnal haemoglobinuria is possible with allogeneic haematopoietic stem cell transplantation. More recently, eculizumab has become available; a monoclonal antibody directed at the complement protein C5, it inhibits terminal complement activation to reduce haemolysis and transfusion requirements.[4,5]

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Iron-deficiency anaemia

For a discussion of iron deficiency anaemia and its management, see under Iron, p. 2073.2.

Megaloblastic anaemia

For a discussion of megaloblastic anaemia and its management, see under Vitamin B_{12}, p. 2109.1.

Normocytic-normochromic anaemia

Anaemias in which red cell size and cellular haemoglobin are not significantly different from normal (normocytic-normochromic anaemias) form a substantial proportion of all cases. Such anaemias are usually secondary to another disease and include:

- anaemia of chronic disorders (associated with chronic infection such as tuberculosis, malignancy, inflammatory disorders such as inflammatory bowel disease, polymyalgia rheumatica, rheumatoid arthritis, and SLE)
- anaemia of renal failure
- anaemia of prematurity
- anaemia associated with endocrine disorders such as hypothyroidism or hypopituitarism
- anaemias associated with primary bone-marrow failure (including aplastic anaemia, p. 1121.3, pure red cell aplasia, marrow fibrosis or infiltration as in myelodysplasia or leukaemia, and marrow failure associated with AIDS).

Iron-deficiency anaemia (p. 2073.2), which is usually classified as microcytic and hypochromic may in fact be neither, particularly in the early stages, and should be differentiated from anaemia of chronic disease. The latter is also accompanied by changes in iron metabolism, notably sequestration of iron in reticuloendothelial cells: plasma iron is low but in contrast to iron deficiency the total iron binding capacity is reduced and serum ferritin is often increased.

The **treatment** of most of these anaemias is essentially that of the underlying disease. Blood transfusion has been given when anaemia is severe. In patients with anaemia of renal failure, which is due at least in part to decreased erythropoietin production by the damaged kidney, regular subcutaneous or intravenous injection of recombinant human erythropoietins (epoetins) can completely reverse the anaemia; darbepoetin alfa and peginesatide acetate are used similarly. Epoetins may also have a role in anaemia of prematurity and some drug-induced anaemias, and have been investigated in patients with the anaemia of chronic disease and some other normocytic-normochromic anaemias.

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Sideroblastic anaemia

The sideroblastic anaemias are characterised by a population of hypochromic red cells in the presence of increased serum-iron concentrations, and abnormal erythroid precursors, known as ring sideroblasts, in the bone marrow. They are associated with abnormalities in porphyrin biosynthesis leading to diminished production of haem, and increased mitochondrial iron uptake. Sideroblastic anaemias may be of various types, and are classified as acquired or hereditary.

Acquired sideroblastic anaemia. Acquired sideroblastic anaemia may either be idiopathic, or secondary to either a drug or toxin (such as alcohol, isoniazid, chloramphenicol, or lead) or to a disease (including hypothyroidism, rheumatoid arthritis, haemolytic or megaloblastic anaemias, leukaemias, and lymphomas). The treatment of the secondary forms is essentially the treatment of the underlying disease or removal of the precipitating cause. The anaemia is usually mild and often macrocytic.

Patients with idiopathic disease usually have only mild anaemia, and most require no treatment. Although rarely suffering from vitamin B_6 deficiency a few patients will respond at least partially to high oral doses of pyridoxine, up to 400 mg daily, and a trial is considered worthwhile in all patients. If patients become symptomatic, transfusion may be required, but should be kept to a minimum because of the problems of iron overload. All patients with sideroblastic anaemia must have their serum-iron and -ferritin concentrations regularly monitored, and be given desferrioxamine by regular bolus injection when there is evidence of iron overload. The use of epoetins and granulocyte colony-stimulating factor is under investigation.

Hereditary sideroblastic anaemia. The hereditary forms of the disease appear to be sex-linked, and almost always manifest themselves in males. The anaemia may be more severe than in acquired sideroblastic anaemia, and is usually microcytic.

A trial of pyridoxine is considered worthwhile as some forms are responsive, but in many cases there is no benefit. Some patients develop gradually increasing iron loads, and may eventually develop haemosiderosis; to prevent this, regular venesection or the use of desferrioxamine are indicated if there is evidence of iron accumulation. Allogeneic bone marrow or haematopoietic stem cell transplantation is under investigation.

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Haemoglobinopathies

Haemoglobinopathies are clinical abnormalities due to altered structure, function, or production of haemoglobin. Human haemoglobins are tetramers, constructed of 4 globin chains each enfolding an iron-containing haem moiety: two of these globins are of the 'α-like' types (globins α or ζ) and two are 'non-α' (types β, γ, δ, or ε). The normal major adult haemoglobin, haemoglobin A, comprises two α and two β chains, while the predominant fetal haemoglobin, haemoglobin F (also present in minute amounts in normal adults), is composed of two α and two γ globins. The erythroblast inherits two genes for the production of α globin and one for β globin production from each parent, and a mutation in a single α gene will therefore affect only 25% of the haemoglobin produced, whereas a single β mutation will affect 50%: the β-haemoglobinopathies, due to defective β globin production, are therefore more likely to produce symptoms, and the most widespread forms are the β-thalassaemias (p. 1124.1) and sickle-cell disease (below).

Sickle-cell disease

Sickle-cell disease is a haemoglobinopathy (see above) in which a structural abnormality in the β globin chain results in the formation of an abnormal haemoglobin, haemoglobin S. In the deoxygenated state haemoglobin S is less soluble and polymerises into rod-like fibres, and cells containing high concentrations of haemoglobin S subsequently become deformed into a sickle shape. Normal haemoglobins can be incorporated into the polymer but some, such as fetal haemoglobin (haemoglobin F), are not; increasing concentrations of these in the red cell reduce the rate of sickling.

The heterozygous form, sickle-cell trait, is generally asymptomatic except in conditions of extreme anoxia, although characteristic abnormalities of renal function (inadequate concentration of the urine) may be present. As with thalassaemia trait (see p. 1124.1) it is more common in populations of tropical origin, and has been postulated to offer a degree of protection against malaria. In the homozygous form a varying degree of haemolytic anaemia is present, accompanied by increased erythropoiesis. In addition to shortened survival, the decreased flexibility of the deformed erythrocytes can lead to occlusion of the microvasculature, and sickle-cell crisis. The latter may manifest as excruciating pain due to infarction of the blood supply to the bones, or infarction of other organs including lung, liver, kidney, penis (leading to priapism), and brain (stroke). An acute chest syndrome occurs in many patients, and may be fatal. It is a form of acute lung injury associated with infarction, fat embolism, and infection, and may progress to acute respiratory distress syndrome. Occasionally a large proportion of red cell mass may become trapped in the spleen or liver (sequestration crisis) with death due to gross anaemia. Chronic complications include skin ulceration, renal failure, retinal detachment, and increased susceptibility to infection.

Treatment of sickle-cell disease is essentially symptomatic.[1-7] Young children should receive prophylactic penicillin and pneumococcal vaccine, to reduce the risk of infection (see Spleen Disorders, p. 207.3). Infection should be treated early, and folate supplementation given if necessary since the increased erythropoiesis resulting from chronic haemolysis may increase folate requirements.

Sickle-cell crisis requires hospitalisation, with the use of large volumes of intravenous fluids for dehydration, analgesia including opioids for pain (see p. 11.1), and treatment of any concurrent infection. Oxygen should be given if the patient is hypoxaemic. Where crisis affects a vital organ with life-threatening or potentially disabling consequences partial exchange transfusion should be carried out promptly, as no other therapy exists. Where rapid enlargement of spleen or liver indicates a sequestration crisis, transfusion is also important to avoid fatal anaemia.

Maintenance transfusion is rarely indicated, although it may be given to patients who have already had a stroke; measures to avoid iron overload such as phlebotomy or desferrioxamine chelation are necessary in patients receiving regular transfusions. Prophylactic transfusions in children at high risk have been reported[8] to reduce the incidence of first stroke but the risks and benefits of treatment must be carefully considered. A further study[9] investigated whether prophylactic transfusions could be safely stopped after 30 months in children who had not had an overt stroke and who had reverted to low stroke risk. The study was stopped early when it was found that in those who stopped transfusions there was a significant return to high risk and that some patients had subsequently suffered a stroke. Splenectomy may be recommended in the management of recurrent splenic sequestration.

Research into specific therapy for sickling has produced some promising results. Because haemoglobin F is known to protect against sickling, considerable interest has centred on attempts to stimulate fetal haemoglobin production. Most studies have used hydroxycarbamide. Initial results showed some elevation in mean fetal haemoglobin concentrations, but responses were very variable. However, a subsequent randomised controlled study in 299 patients[10] reported that therapy with hydroxycarbamide caused a 44% reduction in the median annual rate of painful crises. The beneficial effects did not become evident for several months. Observational follow-up of 233 patients in this group,[11] for up to 9 years, suggested that hydroxycarbamide also reduced mortality. Beneficial effects have also been reported in initial studies in children[12-14] and sustained benefits have been reported in longer-term cohort studies.[15,16] Results from a small study[17] in children suggested that hydroxycarbamide, with serial phlebotomy to reduce iron overload, may be an effective replacement for secondary stroke prophylaxis in patients who are unable to continue with long-term maintenance transfusions. Although one study,[16] in which some children had received hydroxycarbamide for up to 8 years, found no evidence of mutagenic changes or cases of malignancy, the potential toxicity of long-term therapy remains a concern. A short-chain fatty acid, butyric acid, which has a low order of toxicity, has been reported to stimulate fetal haemoglobin in patients with sickle-cell disease when given by infusion as arginine butyrate.[18] Promising results have also been reported in small studies[19] using oral sodium phenylbutyrate. Other drugs under investigation include clotrimazole, decitabine, inhaled nitric oxide, and the nonionic surfactant poloxamer 188. There is also some investigation into gene therapy.

As in thalassaemia (see p. 1124.1), bone marrow transplantation is potentially curative in a small minority of patients, but the indications for transplantation are much less well established.[20]

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β -Thalassaemia

β-Thalassaemia is a haemoglobinopathy (p. 1123.2) that is due to a deficiency in β globin production accompanied by normal production of α globin chains that, in the absence of sufficient partner chains, are insoluble and precipitate out in erythrocytes and erythroid precursors as large cellular inclusions. These interfere with red cell maturation resulting in ineffective haematopoiesis, retard the passage of red cells from the bone marrow, and create a tendency for those red cells that do mature to be trapped and destroyed in the spleen. The condition is therefore characterised by a hypochromic, microcytic anaemia accompanied by haemolysis. In the heterozygous form, where only one of the β globin genes is affected (known as thalassaemia trait or thalassaemia minor) the anaemia is mild and clinically insignificant. There is some evidence that patients with this form of the disease have a degree of protection from malaria, which may account for the more frequent distribution of the trait in the populations of areas such as the Mediterranean, parts of Africa, and Asia.

The more severe forms of the disease (known as thalassaemia intermedia if haemoglobin levels are high enough not to require regular transfusion, or thalassaemia major in transfusion-dependent patients) occur in homozygous patients who inherit a defective β globin gene from both parents. Severe anaemia develops in the first year of life as fetal haemoglobin production (which does not involve a β globin) is replaced by the production of adult haemoglobin. The anaemia stimulates erythropoietin production, and if not corrected massive proliferation of red cell precursors develops within, and eventually beyond, the bone marrow, resulting in recurrent bone fractures, deformity of the skull due to expansion of the marrow spaces, and compression of vital structures such as the spinal cord with consequent paresis. Other symptoms include splenomegaly and hypersplenism (resulting in neutropenia and thrombocytopenia), increased susceptibility to infection, and hypermetabolism which may lead to folate deficiency because of the increased folate requirement. If untreated, death in patients with thalassaemia major usually occurs by the 2nd or 3rd year.

Treatment. The mainstay of treatment for severe β-thalassaemia is regular blood transfusion to correct the anaemia. Transfusions should be started as early as possible in life once it is clear that anaemia is severe enough to warrant them. Various transfusion regimens have been used based on different pretransfusion haemoglobin concentrations.[1] The Thalassaemia International Federation[2] recommends regular blood transfusions, usually every 2 to 5 weeks, to maintain the pretransfusion haemoglobin concentration above 9 to 10.5 g per 100 mL. A higher target of 11 to 12 g per 100 mL may be appropriate for patients with heart disease. The post-transfusion concentration should not exceed 14 to 15 g per 100 mL. It is also recommended that patients should receive leucocyte-depleted packed red cells in order to minimise adverse reactions and platelet allo-immunisation (an immune response to donor platelets). Washed red cells may be used in patients who have repeated severe allergic transfusion reactions. The use of leucocyte-depleted red cells is also desirable in patients who are candidates for haematopoietic stem cell transplantation to reduce the risk of graft rejection and CMV reactivation.[1] An increase in transfusion requirements is a sign of hypersplenism, and splenectomy may be indicated depending on the state of iron overload. However, splenectomy should be avoided if possible below the age of 5 years because of the increased risk of overwhelming sepsis.[2] For a discussion of antibacterial prophylaxis in splenectomised patients, see Spleen Disorders, p. 207.3.

If anaemia is corrected by transfusion, growth and development proceed fairly normally in thalassaemic children. However, because the body lacks a mechanism for the excretion of excess iron, repeated transfusion invariably results in iron overload (p. 1545.2), leading eventually to haemochromatosis. The consequences of haemochromatosis include liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and particularly heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up usually leads to death (mainly through heart failure or arrhythmia) by the time patients reach their mid-20s. The accumulation of iron can be retarded by the chelator desferrioxamine and regular systemic use has been shown to improve survival in thalassaemic children,[2,3] and to protect against the cardiac complications of iron overload.[2-4] Ideally, continuous administration of iron chelation therapy optimises iron excretion. Desferrioxamine is usually given by subcutaneous infusion over 8 to 12 hours, several times a week. Alternatively, twice daily subcutaneous boluses may be considered if an infusion pump is not available or prolonged infusion is not tolerated in patients who are not at high risk of heart disease. Continuous 24-hour intravenous infusion may be considered in patients with severe iron overload or significant cardiac complications, or when rapid reversal of iron loading is desirable before pregnancy or bone marrow transplantation.[2] There is some suggestion that intensive desferrioxamine therapy can improve impaired organ function,[3] but it is considered preferable to begin chelation therapy as early as possible to try to prevent organ damage developing in the first place. In practice, desferrioxamine therapy is started after the first 10 to 20 transfusions or when the ferritin concentration rises above 1 mg/litre, usually at about 3 years of age.[2,5] If therapy is started before this age, careful monitoring of growth and bone development is recommended[2] and liver biopsy has been advocated.[3] Better iron excretion is achieved if patients are given oral ascorbic acid supplements in addition to desferrioxamine (but see under Interactions for Desferrioxamine, p. 1547.3). Patients with thalassaemia may have increased folate requirements and folate supplementation may also be necessary. Although it is not yet certain how much chelation therapy will prolong survival the fact that a nearly normal iron balance can be achieved long term seems hopeful. Deferiprone has been used as an oral alternative to desferrioxamine,[6] but there are conflicting reports regarding its efficacy and safety in the longer term.[7,8] It may have a role in patients for whom desferrioxamine therapy is unsuitable.[2] Combination therapy using desferrioxamine with deferiprone is under investigation,[5] and may be considered when monotherapy is insufficient to control levels of iron or when there is significant heart disease.[2] Deferasirox is another oral chelator that has become available more recently.[2]

In addition to the essentially symptomatic treatment of thalassaemia there is growing experience with the use of bone marrow transplantation where suitable facilities and compatible donors exist;[2] if transplantation is carried out before organ damage is marked, successfully transplanted patients are apparently cured and can lead a normal life.[9,10] Gene therapy is also under investigation.

An alternative approach using hydroxycarbamide in an attempt to stimulate fetal haemoglobin production and 'mop up' some of the excess α globin chains has been tried experimentally but results have been mixed. Results of an initial study in patients given butyric acid (as an arginine butyrate infusion) for the same purpose appeared more promising[11] although a subsequent study failed to show any benefit.[12] Mixed results have also been reported with the use of oral butyrate derivatives such as sodium phenylbutyrate[13] and isobutyramide.[14]

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Haemostasis and Fibrinolysis

Haemostasis is the physiological response that occurs when blood vessels are damaged. It results in coagulation (formation of a blood clot) and thus stops bleeding. The initial response is the formation of a plug of platelets, which adhere both to the injured tissue and to each other. The vessel injury, with factors released by the platelets, trigger a series of reactions (the coagulation 'cascade') mediated by proteins circulating in the plasma (blood clotting factors). This results in formation of an insoluble fibrin clot that reinforces the initial platelet plug. Regulatory mechanisms come into operation to prevent widespread coagulation. Lysis of the clot (fibrinolysis) then occurs when wound healing and tissue repair are underway.

Platelet aggregation. Platelets usually circulate in plasma in an inactive form. Contact with damaged endothelium causes them to become activated and to adhere to the site of injury. This adhesion is partly mediated by binding of von Willebrand factor (factor VIII-related antigen; vWF), a plasma protein that also acts as a carrier for factor VIII, to a glycoprotein (termed GPIb) on the platelet membrane surface. Substances are secreted by the activated platelets which cause further platelet aggregation (adenosine diphosphate and thromboxane A_2) and vasoconstriction (serotonin and thromboxane A_2). Thromboxane A_2 secreted by platelets is derived from arachidonic acid.

- Adenosine diphosphate stimulates platelet activation and aggregation by its effect at $P2Y_{12}$ receptors on the platelet surface. This effect is inhibited by **antiplatelet drugs** such as clopidogrel, prasugrel, and ticlopidine, that are $P2Y_{12}$ receptor antagonists.
- The enzyme cyclo-oxygenase is required for the synthesis of thromboxane A_2 and this enzyme is inhibited by the antiplatelet drugs aspirin and sulfinpyrazone. Aspirin binds irreversibly to the enzyme and therefore the antiplatelet effect lasts for the lifetime of the platelet. Sulfinpyrazone is a reversible inhibitor of the enzyme.

Platelet aggregation involves interaction of fibrinogen with a receptor, glycoprotein IIb/IIIa, on the platelet surface.

- Antiplatelet drugs such as abciximab act by blocking this receptor.

In addition to their action in forming the initial haemostatic plug, platelets are also involved in coagulation by providing a surface on which interactions between clotting factors take place, resulting in more efficient coagulation.

Coagulation. The series of reactions that results in formation of a fibrin clot may be conveniently considered as two pathways, the *intrinsic* pathway (triggered within the blood) and the *extrinsic* pathway (triggered by substances extraneous to the blood). While this distinction is useful for understanding *in-vitro* coagulation and is the basis for tests that are specific for each pathway (see below), the mechanism of *in-vivo* coagulation is not so segregated and factors appearing in one pathway are also necessary for reactions in the other pathway. The intrinsic and extrinsic pathways of coagulation and the *in-vivo* pathways are discussed further below and are represented in summary form in Figure 1, p. 1126 and Figure 2, p. 1127, respectively. Factors circulate in the blood in an inactive form and are activated by cleavage of peptide bonds. The numerals attached to the factors reflect the order in which they were discovered and not their importance or position in the chain of reaction. The letter 'a' after a factor name or number denotes the activated form. Factors involved in blood coagulation are listed in Table 2, p. 1125. Once the coagulation cascade is started, activated factors act in positive feedback mechanisms to amplify the activation steps thus producing rapid coagulation. Cofactors are necessary as they increase the speed of the reactions. Other components necessary for coagulation are calcium ions and a membrane surface. Calcium ions are required for nearly all the reactions. Many of the activation steps, notably those involving factors VII, IX, and X, take place on a membrane surface expressing tissue factor, or platelets. Factors bind to phospholipids on the membrane surface.

The *extrinsic* pathway begins when *tissue factor* (factor III; tissue thromboplastin) is released from damaged tissue. This forms a complex with *factor VII* (proconvertin; SPCA; stable factor) and factor VIIa and directly activates *factor X* (Stuart factor; Stuart-Prower factor). The *intrinsic* pathway begins when blood comes into contact with a negatively charged surface. *Factor XII* (Hageman factor) interacts with high molecular weight kininogen (HMWK; Fitzgerald factor) and prekallikrein (Fletcher factor) to produce *kallikrein*, which activates factor XII. The active factor XIIa then activates *factor XI* (plasma thromboplastin antecedent; PTA), which in turn activates *factor IX* (Christmas factor; plasma thromboplastin component; PTC). *Factor VIII* (antihaemophilic factor; AHF) is activated by thrombin to factor VIIIa to act as a cofactor for factor IXa, which converts *factor X* to factor Xa. The extrinsic and intrinsic pathways therefore converge with the activation of factor X. *Factor V* (Ac-

globulin; labile factor; proaccelerin) is activated by thrombin to factor Va to be a cofactor for factor Xa, which converts prothrombin (*factor II*) to thrombin with the subsequent formation of a *fibrin* gel. *Factor XIII* (fibrin stabilising factor; FSF) is also activated by thrombin to factor XIIIa, which stabilises the fibrin gel to form a stable clot.

The dependence of many steps in the coagulation cascade on calcium ions (know as *factor IV*) allows coagulation *in vitro* to be blocked by the addition of calcium chelators, such as sodium citrate, to collected blood. When collected blood is tested for coagulation function, addition of calcium ions allows clotting to proceed. Tests of coagulation function include activated partial thromboplastin time (APTT), which is a measure of the activity of the intrinsic system, prothrombin time (PT), a measure of the activity of the extrinsic system, and thrombin clotting time, which measures the conversion of fibrinogen (*factor I*) to fibrin.

The factors involved in triggering the *in-vitro intrinsic* pathway, that is prekallikrein, factor XII, and possibly factor XI, are probably not important in *in-vivo* blood coagulation as deficiency of any of these factors is not associated with a serious bleeding disorder. The important step in the clotting cascade *in vivo* is release of *tissue factor* (factor III) from damaged tissue. As has already been mentioned, tissue factor forms a complex with *factor VII* and factor VIIa that activates *factor X*. Factor Xa activates *prothrombin* resulting in formation of a *fibrin clot* which occurs as described above under the *in-vitro* systems. To enhance coagulation, various positive feedback mechanisms and other clotting factors operate to increase production of activated factors VII and X. For example, formation of factor VIIa is amplified by factor VIIa itself and by factor Xa. Formation of factor Xa is amplified by factor IXa produced by the action of thrombin on factor XI.

Regulation of coagulation. The process of blood coagulation is regulated to ensure that it remains localised at the site of injury and does not result in more widespread clotting. This is achieved by dilution of clotting factors in flowing blood, by rapid hepatic clearance of many activated factors or products, and by natural anticoagulant mechanisms, which include antithrombin III, protein C, and protein S (see Figure 2, p. 1127). *Antithrombin III* (major antithrombin; AT-III; heparin cofactor) inhibits the serine protease clotting factors, that is, thrombin, IXa, Xa, XIa, and XIIa. Antithrombin III is activated by binding to glycosaminoglycans, such as heparan glycosaminoglycan and dermatan sulfate, present in vascular endothelium.

- Heparin and low-molecular-weight heparins act as **anticoagulants** by binding antithrombin III at a specific binding site and enhancing its inhibitory effect on the serine protease clotting factors. At therapeutic doses of heparin the factors inhibited are thrombin and factor Xa. Low-dose heparin, such as that given for the prophylaxis of thromboembolism, inhibits factor Xa. Very high doses of heparin have a direct inhibitory effect on antithrombin III. Heparinoids which lack the specific binding site for antithrombin III do not have the anticoagulant properties of heparin. Low-molecular-weight heparins have a higher ratio of anti-factor-Xa to antithrombin activity than heparin and therefore mainly inhibit factor Xa.

Proteins C and S are both vitamin K-dependent plasma proteins. Protein C (autoprothrombin IIA; factor XIV) circulates in plasma in an inactive form. It is activated by contact with thrombin that is bound to thrombomodulin, a receptor located on the surface of endothelial cells. Activated protein C inhibits factors Va and VIIIa and therefore slows blood clotting. Protein S acts as a cofactor in this inhibition.

Vitamin K is essential for the activities of factors II, VII, IX, and X. It is also essential for the activity of proteins C and S. These factors contain glutamic acid residues that undergo carboxylation in the liver, a reaction requiring reduced vitamin K as a cofactor. This carboxylation step allows the factors to bind calcium, a reaction necessary for their function in the clotting cascade.

- Deficiency of vitamin K or the use of **oral anticoagulants** (which are vitamin K antagonists) therefore impairs the function of these clotting factors. Oral anticoagulants have no effect on circulating clotting factors and thus the time required before the anticoagulant effect is seen depends on the individual clearance rate of the factor.

Fibrinolysis is the mechanism of clot dissolution. It is mediated by *plasminogen*, which circulates in plasma in an inactive form; conversion to its active form, *plasmin*, occurs when plasminogen binds to fibrin in the presence of a *plasminogen activator* (see Figure 2, p. 1127). Plasmin, a *proteolytic enzyme*, digests fibrin clots and hydrolyses other proteins, including factors II, V, VIII, and XII. As fibrin is lysed, plasmin is released which is inhibited by α_2-antiplasmin to prevent a systemic lytic state developing. There are two types of plasminogen activator, *tissue plasminogen activator* (tPA), which originates from the endothelium, and *urokinase*, which is activated from prourokinase. Activators of prourokinase include plasmin. Tissue plasminogen activator binds to fibrin and thus activates plasminogen bound to fibrin much more rapidly than circulating plasminogen; therefore the fibrinolytic action of tissue plasminogen activator is fibrin specific. Urokinase does not bind to fibrin, and therefore its fibrinolytic action is not fibrin specific, although it is activated by plasmin that is bound to fibrin. *In vivo*, fibrinolysis is almost entirely due to the activity of tissue plasminogen activator.

- The two types of plasminogen activator with their different modes of action provide the basis for the specificity of **thrombolytics** (the so-called 'clot specific' effect), which act by promoting the conversion of plasminogen to plasmin. The tissue plasminogen activators alteplase and tenecteplase are fibrin-specific thrombolytics, and streptokinase and urokinase are fibrin-nonspecific.
- The **antifibrinolytic drugs** aminocaproic acid and tranexamic acid act mainly by blocking the binding of plasminogen and plasmin to fibrin, thereby preventing the breakdown of fibrin clots.
- Aprotinin, an inhibitor of proteolytic enzymes, acts as a **haemostatic** by inhibiting the action of plasmin and therefore preventing the breakdown of fibrin clots. Other drugs acting as haemostatics include batroxobin, which is reported to promote the production of fibrin from fibrinogen, and etamsylate, which has a stabilising effect on the capillary wall. Drugs such as oxidised cellulose, calcium alginate, collagen, and gelatin act by providing a physical meshwork within which clotting can occur. Adrenaline, adrenalone, and noradrenaline produce haemostasis by causing vasoconstriction. Drugs with astringent properties such as alum and ferric chloride are also used for haemostasis.

The use of haemostatics may be considered when bleeding cannot be controlled by direct measures such as the application of pressure, suture or ligation, or electrocoagulation.

Dysfunction of the haemostatic mechanisms or the systems regulating haemostasis produces haemorrhagic disorders (acquired, below, and inherited p. 1128.2) or thromboembolic (p. 1273.2) disorders.

Table 2. Proteins involved in blood coagulation and in fibrinolysis.

	Proteins	Synonyms
Blood coagulation	Factor I	Fibrinogen
	Factor II*	Prothrombin
	Factor III	Tissue thromboplastin; tissue factor
	Factor IV	Calcium ion
	Factor V	Ac-globulin; labile factor; proaccelerin
	Factor VI (unassigned)	
	Factor VII*	Proconvertin; SPCA; stable factor
	Factor VIII	Antihaemophilic factor; AHF
	Factor IX*	Christmas factor; plasma thromboplastin component; PTC
	Factor X*	Stuart factor; Stuart-Prower factor
	Factor XI	Plasma thromboplastin antecedent; PTA
	Factor XII	Hageman factor
	Factor XIII	Fibrin stabilising factor; FSF
	von Willebrand factor	Factor VIII-related antigen; vWF
	High molecular weight kininogen	HMWK; Fitzgerald factor
	Prekallikrein	Fletcher factor
Fibrinolysis	Plasminogen	
	Prourokinase	
	Tissue plasminogen activator	tPA
	Antithrombin III	Major antithrombin; AT-III; Heparin cofactor
	Protein C*	Autoprothrombin IIA; Factor XIV
	Protein S*	
	α_2-Antiplasmin	

* denotes vitamin K-dependent factor

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Acquired haemorrhagic disorders

Bleeding disorders sometimes arise due to disturbances in either clotting factors or platelets, or to vascular wall defects occurring as a result of a disease or a medical or surgical procedure. Disturbances and defects may also be drug-induced. In some conditions, including renal and liver disease, cardiopulmonary bypass procedures, or following massive blood transfusion, disturbances in many of the homoeostatic mechanisms occur simultaneously producing complex haemorrhagic disorders, sometimes referred to as complex acquired coagulopathies.

One of the commoner causes of haemorrhagic disorder caused by *disturbance of clotting factors* is overdose with heparin, oral anticoagulants, or thrombolytics. Different approaches are used in the management of overdose with these drugs, as discussed in Treatment of Adverse Effects under Heparin (p. 1399.3), Warfarin Sodium (p. 1529.1), and Streptokinase (p. 1506.3).

Deficiencies in clotting factors may occur in several diseases. Vitamin K is essential for the activity of several clotting factors and plasma proteins (see Haemostasis and Fibrinolysis, p. 1124.3), and disorders that cause a deficiency of vitamin K can lead to impairment of these. Diseases of the small bowel and biliary tract can impair absorption of vitamin K, and liver disease reduces the production of clotting factors. Deficiency is generally treated by giving vitamin K, although this is not always effective in patients with liver diseases. Vitamin K is widely used for the prevention and treatment of neonatal vitamin K deficiency bleeding (p. 2123.2). Examples of other acquired disorders that affect clotting factors but occur rarely include acquired haemophilia affecting factor VIII (see Haemophilias, p. 1126.3) and von Willebrand syndrome (see von Willebrand's Disease, p. 1129.3).

Low platelet concentrations can be associated with many other illnesses and increase the risk of bleeding; management is discussed in Thrombocytopenia, p. 1129.2.

Various drugs are used, or are under investigation, for their effect on *perioperative blood loss*.[1-4] Topical treatments such as fibrin glue, gelatin-based films and sponges, oxidised cellulose, and thrombin are used for a local haemostatic effect in surgical procedures. The antifibrinolytic drugs aprotinin, aminocaproic acid, and tranexamic acid are used to reduce bleeding and transfusion requirements in procedures such as liver transplantation and cardiac surgery involving cardiopulmonary bypass. Desmopressin is used in surgical patients with some congenital and acquired bleeding disorders, but in patients without pre-existing bleeding disorders it has not consistently been shown to be of benefit. Recombinant activated factor VII (eptacog alfa) is used in the management of bleeding in patients with

Figure 1. Simplified representation of *in-vitro* coagulation.

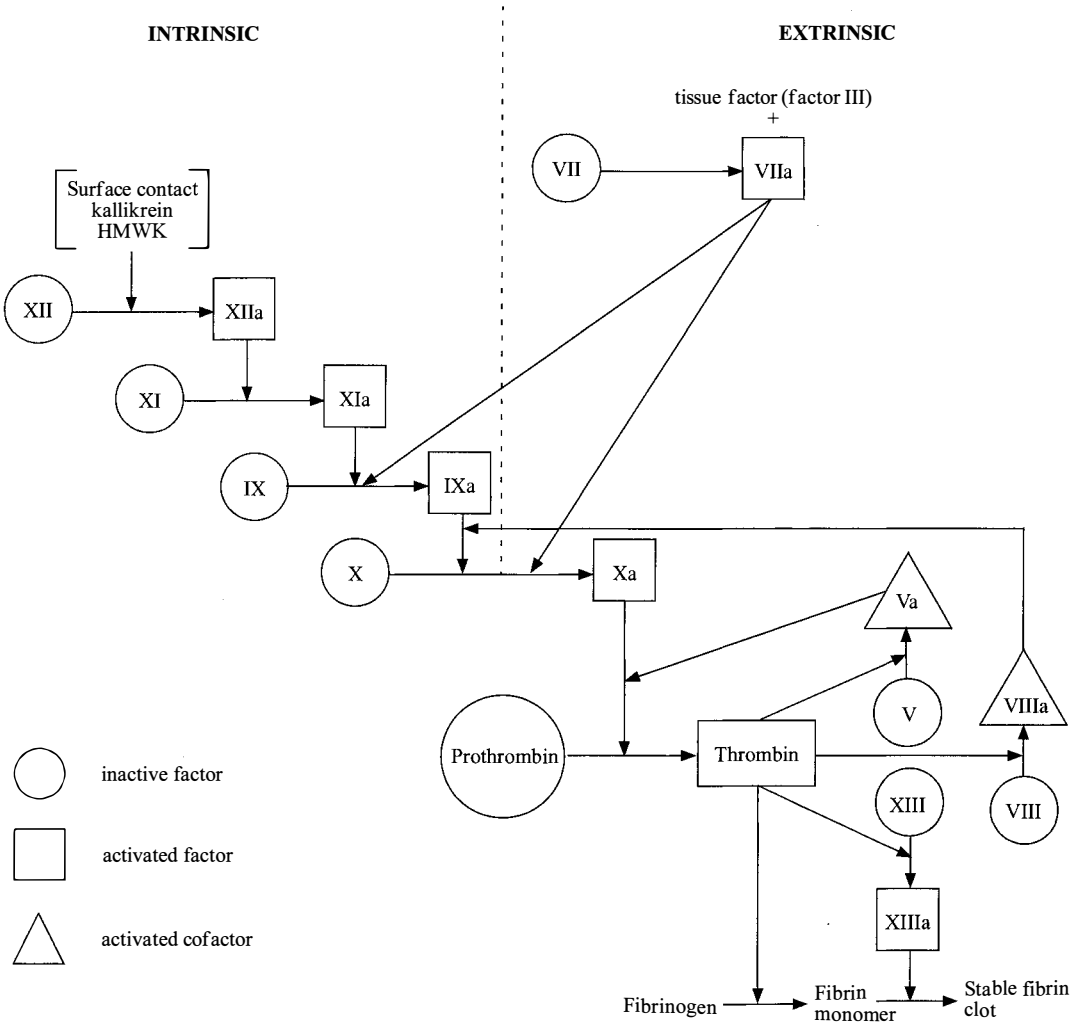

haemophilia, but it is also under investigation in surgical patients with normal haemostasis.

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Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is an acute or chronic syndrome resulting from an underlying condition that causes pathological stimulation of coagulation at some point in the coagulation pathway (see Haemostasis and Fibrinolysis, p. 1124.3); thrombin generation triggered by uncontrolled tissue factor is probably the main factor in most cases. Causes include obstetric emergencies (placental abruption, amniotic fluid embolism), infection (bacterial septicaemia, viraemia), neoplasms, trauma (head injury, burns), venomous snake bites, transfusion of incompatible blood, liver disease, and various vascular causes.

Stimulation of coagulation leads to microvascular thrombosis that produces widespread tissue ischaemia and may lead to ischaemia of major organs. Simultaneously, secondary activation of the fibrinolytic system and consumption of coagulation factors produces bleeding, which is often the predominant manifestation. Symptoms are therefore very variable and include those of bleeding, such as spontaneous bruising, prolonged bleeding from intravenous puncture sites, and gastrointestinal and pulmonary haemorrhage, and those of thrombosis, such as acute renal failure, venous thromboembolism, skin necrosis, liver failure, cerebral infarction, acute respiratory distress, and coma. Some cases may be asymptomatic.

Treatment of DIC is aimed mainly at the underlying cause since the condition will not resolve until the underlying trigger is removed. Recovery is often fairly rapid once treatment is started. Supportive therapy to ensure adequate hydration and tissue oxygenation is also vital. These measures may be sufficient in patients with asymptomatic DIC. Most patients with symptomatic DIC also require therapy with plasma and platelets to replace coagulation factors and arrest bleeding. Coagulation factor concentrates such as fibrinogen concentrate or cryoprecipitate are not favoured, as they do not contain all coagulation factors and they may be contaminated with traces of activated coagulation factors, which can exacerbate the coagulation disorder in these patients. Nevertheless, they may be considered in patients with fluid overload because they are available in smaller volumes, and may be useful in severe hypofibrinogenaemia that persists despite plasma replacement. Heparin has been used in the management of DIC with the aim of switching off the coagulatory mechanisms. Although benefit has been shown with some underlying causes, heparin may worsen bleeding and its use in DIC is considered by some to be controversial. Where the risk of bleeding is relatively minor and thrombosis predominates, heparin may be appropriate. Other measures that have been tried in limited numbers of patients include use of a low-molecular-weight heparin. Prophylactic doses of heparin or low-molecular-weight heparin may be used to prevent venous thromboembolism in critically ill patients who are not bleeding. Concentrates of activated protein C have been used in DIC associated with severe sepsis and have improved coagulation abnormalities and mortality. The recombinant form, drotrecogin alfa (activated), has also been used, but provided no survival benefit in patients with severe sepsis and septic shock. Antithrombin III has also been used, but despite beneficial reports of use in sepsis-related DIC a large study found no benefit.

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Haemophilias

The haemophilias are bleeding disorders caused by low concentrations of specific coagulation factors. Acquired haemophilia is rare and most patients have inherited forms. The most well known are haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency). Factor XI deficiency, originally called haemophilia C, is mentioned under Inherited Haemorrhagic Disorders, p. 1128.2.

Haemophilia A (classical haemophilia, factor VIII deficiency) is the most common of the serious hereditary bleeding disorders.[1] It is an X-linked recessive disorder and therefore, with rare exceptions, males are affected and females are carriers. The condition is due to deficiency of factor VIII and severity of bleeding is related to the residual factor level. The condition is severe when there is less than 1% of normal factor VIII activity, moderate when the factor VIII concentration is 1 to 5% of normal, and mild when the factor concentration is greater than 5%. Clots are slow to form and break up easily, and bleeding after trauma or surgery may be prolonged. In moderate and severe haemophilia A bleeding may occur into major joints producing long-term joint destruction, a major cause of morbidity in haemophilia. Other frequent sites of bleeding are large muscles, and renal and intestinal tracts. CNS haemorrhage may also occur, especially after trauma.

All cross-references refer to entries in Volume A

Figure 2. Simplified representation of *in-vivo* coagulation and fibrinolysis.

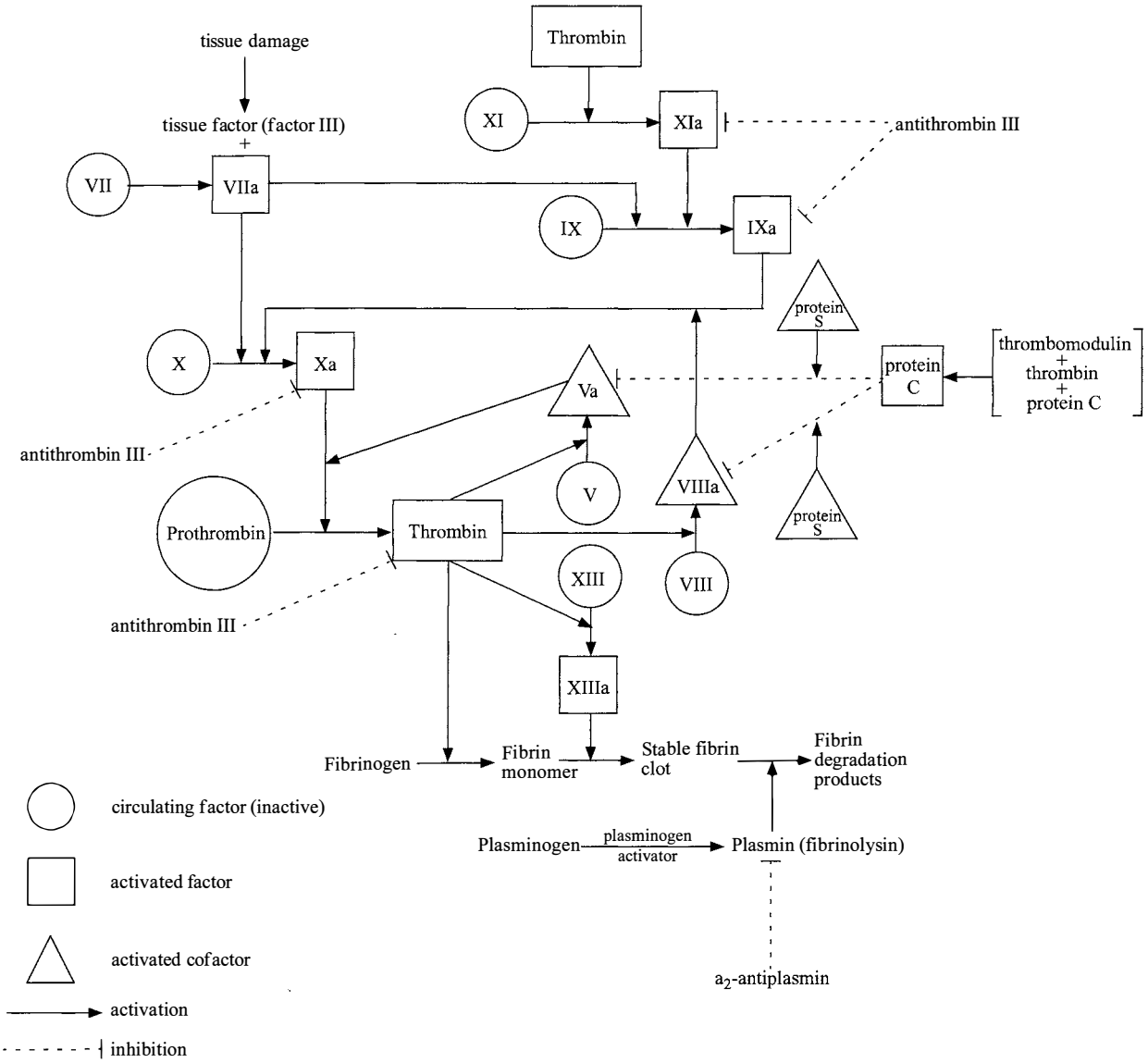

Treatment of bleeding episodes depends on the severity of the haemophilia.[1-4] Patients with moderate to mild haemophilia A can be satisfactorily treated with desmopressin,[5,6] which produces an increase in factor VIII and von Willebrand factor, and increases platelet adhesion and expression of tissue factor. Desmopressin also transiently stimulates plasma fibrinolytic activity, and it has been suggested that use with an antifibrinolytic, such as tranexamic acid, may inhibit this effect. However, there is no evidence for haemostatic improvement with this combination, although tranexamic acid itself is effective in the management of mucosal bleeding and during dental surgery.[5] Desmopressin is usually given intravenously. The subcutaneous route is an alternative but the maximum effect is slower. It can also be given intranasally, and this route is used by patients to treat themselves outside hospital. In patients with more severe haemophilia A, desmopressin is ineffective and treatment of bleeding episodes requires replacement of factor VIII. The amount given depends on the severity of bleeding.

Desmopressin and factor VIII preparations are also used for the *prevention of bleeding episodes* in situations where haemorrhage may be anticipated, for example before surgery or dental treatment;[7,8] patients with haemophilia A should also not be given intramuscular injections (because of potential muscle damage and bleeding into muscle) unless they are given during a period when the patient is covered by replacement factor. Prophylactic cover with an antifibrinolytic, such as tranexamic acid given orally (or, in dentistry, also topically as a mouthwash), may also be used and should be continued for 5 to 7 days after the procedure. Fibrin glue can also be useful in the control of local bleeding.[8]

An alternative method of management has been practised in Sweden since 1958 where *continuous prophylaxis* with factor VIII is given to patients with severe haemophilia A with the aim of preventing arthropathy. Therapy is started at 1 to 2 years of age and the factor VIII concentration is maintained at a level of at least 1% of normal. Patients who began receiving prophylaxis before the age of 2 have had almost no bleeding episodes and joints have remained normal for up to 16 years of follow-up.[9,10] This approach has subsequently been adopted in other countries, but regimens have varied in terms of the threshold specified for the introduction of prophylaxis, the dose of factor VIII used, and outcome measures.[11,12] Information has been mainly provided by observational studies, but a randomised controlled study[13] found less joint damage and fewer joint and other haemorrhages at 6 years of age in boys who had been given regular factor VIII prophylaxis compared with episodic treatment given only for clinically recognised joint haemorrhage. Prophylaxis is generally continued through adolescence to adulthood; about 30% of young adults are able to stop regular prophylaxis and can be adequately managed with intermittent prophylaxis tailored to specific activities, such as sports and other potentially traumatic events.[12]

There are various factor VIII preparations available that vary in activity and source.[4] Most products were previously derived from pooled donor plasma and were associated with transmission of viruses including HIV (leading to the subsequent development of AIDS), hepatitis B, and other hepatitis viruses. The introduction of products treated with heat or chemicals, and efforts to screen the donor material from which factor VIII is obtained, seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses such as human parvovirus B19 and hepatitis A may still be transmitted. It is recommended that patients not already immune should be vaccinated against hepatitis A and B. There is some concern that variant Creutzfeldt-Jakob disease (vCJD) may be transmitted by plasma-derived clotting factor products, but there is no proof as yet that this has occurred. Factor VIII produced by recombinant DNA technology may avoid the dangers of possible viral transmission and is therefore the factor VIII preparation of choice (but see also Transmission of Infections under Factor VIII, p. 1149.1). It has been suggested that high-purity plasma-derived factor VIII preparations slow the decline in CD4 count in haemophiliac patients who are HIV-positive, but this was based on the measurement of surrogate markers and the purity of clotting factor preparations has been found not to affect the development of AIDS. Factor VIII preparations are usually given by bolus injection, but there is increasing interest in the use of continuous infusion[2,11] because it can maintain a steady state of clotting factor concentrations and reduce the amount of concentrate used. Evidence from controlled studies is needed to confirm the perceived benefits of this method.

A serious complication of replacement therapy in haemophilia A is the development of *antibodies to factor VIII* (often called inhibitors). The reported incidence varies widely, up to about 30%. Antibodies are more likely to develop in young patients with severe haemophilia who receive continuous prophylaxis, but can also arise in patients with mild haemophilia, typically after intensive replacement therapy; some patients appear to have a genetic predisposition.[14] Antibody concentrations can be measured and may be classified as either low-titre or high-

titre; patients are further described as low or high responders according to the increase in antibody production when given factor VIII.[15]

The management of acute bleeding episodes can be problematic in these patients, and depends on the characteristics of the antibodies.[14-16] Patients with low-titre low-responding antibodies are generally treated with high-dose factor VIII. Porcine factor VIII may be useful in high-titre or highly-responding patients at least in the short term, although with longer use antibodies to the porcine material can develop in turn. (The manufacture of porcine factor VIII was discontinued in 2004, but a recombinant product is in development.) Otherwise, when high-titre highly-responding antibodies are present, bleeding episodes are managed with factor VIII inhibitor bypassing fraction, or recombinant factor VIIa, which bypass the factor VIII-dependent step in the coagulation cascade. The removal of antibodies by plasmapheresis, with or without extracorporeal immunoadsorption, followed by high-dose factor VIII, has been used in high-titre patients when other measures have failed.[16]

Attempts have been made to induce tolerance and eradicate the antibodies.[14,15,17] Regimens have used regular doses of factor VIII over prolonged periods, sometimes with immunosuppression by cyclophosphamide, immunomodulation by normal immunoglobulin, or extracorporeal immunoadsorption. The treatment of bleeding episodes during immune tolerance induction therapy can be difficult, requiring the use of factor VIII inhibitor bypassing fraction or recombinant factor VIIa.

A future development that may provide a clinical cure for haemophilia is *gene therapy*.[1,18,19] However, despite successful treatment in *animal* models, initial human studies for haemophilia A and B have shown no sustained responses.

Haemophilia B (factor IX deficiency; Christmas disease) is less common than haemophilia A. The classification and clinical features of this form are the same as for haemophilia A, but are related to a deficiency of factor IX. Treatment follows the same principles as for haemophilia A,[1-4] except that desmopressin does not affect factor IX concentrations and is therefore ineffective in haemophilia B. Bleeding episodes are treated with factor IX replacement, preferably using recombinant factor IX or plasma-derived highly purified factor IX preparations that do not contain other clotting factors. Low-purity factor IX preparations derived from plasma that contain other clotting factors in addition to factor IX (prothrombin complex concentrates) are associated with thromboembolic complications, particularly in patients with liver disease and others at increased risk of thromboembolism or disseminated intravascular coagulation. Fresh frozen plasma may be used in emergencies if specific factor IX products are unavailable. Antifibrinolytic drugs may be used in patients treated with purified factor IX preparations,[3] but should be avoided in those given prothrombin complex concentrates because of the increased risk of thrombosis. Continuous prophylaxis using factor IX preparations has also been used in haemophilia B.[9,10] As in patients with haemophilia A, vaccination against hepatitis A and hepatitis B is recommended for all haemophiliacs not already immune.

Antibody inhibitors of factor IX can be produced although the incidence of antibody formation is lower than that seen in haemophilia A. Acute bleeding episodes in these patients may be managed using recombinant factor VIIa.[1] Induction of tolerance has also been used for antibodies in haemophilia B, but the response is not as good as for haemophilia A and these patients appear to be at risk of anaphylaxis and nephrotic syndrome.[1,14]

As mentioned under haemophilia A, gene therapy is under investigation as a possible clinical cure.

Acquired haemophilia is a rare disease in which autoantibodies form against factor VIII.[20,21] In about 50% of cases, factor VIII autoantibodies are idiopathic; the rest are associated with other conditions including the postpartum period, malignancies, auto-immune diseases, and adverse drug reactions. The bleeding pattern is different to congenital haemophilia and usually occurs as bleeding in the skin or muscles, haematuria, haematemesis or melaena, and prolonged postpartum or postoperative bleeding; haemarthroses are relatively uncommon.

Treatment for acute episodes depends on the severity of bleeding and the antibody titre. Desmopressin is only effective in patients with low inhibitor titres. Large doses of plasma-derived or recombinant factor VIII may be effective, but the dose required to saturate the autoantibodies can be difficult to predict and therapy must be closely monitored to adjust dosage according to factor VIII concentrations. The use of porcine factor VIII concentrate is an alternative. Increasingly, patients are being managed with factor VIII inhibitor bypassing fraction or recombinant factor VIIa, and these may be used when the titre is very high or bleeding persists despite the use of factor VIII concentrates.

Up to a third of patients with acquired haemophilia have a spontaneous resolution of their autoantibodies. For other patients, treatment to eradicate or suppress the autoantibodies is often based on a corticosteroid, such as prednisone, given alone or combined with cyclophosphamide; evidence for the efficacy of such treatment is largely anecdotal however. Other combinations that have also been tried include a corticosteroid with azathioprine, or a corticosteroid with cyclophosphamide plus vincristine. Ciclosporin, alone or with a corticosteroid, has been used as a salvage therapy. Rituximab has produced durable responses, when used alone or with immunosuppressive therapy, in a small number of patients. Intravenous immunoglobulin has been tried, but any benefit is questionable. Similarly, plasmapheresis and immunoadsorption have been used, but their contribution to the success of treatment is difficult to assess because they are usually combined with immunosuppressive drug therapy. Factor VIII immune tolerance regimens are rarely, if ever, used in acquired haemophilia.

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Inherited haemorrhagic disorders

Inherited disorders that lead to abnormal bleeding include platelet disorders and disturbances in clotting factors.

Inherited platelet disorders can affect platelet function, size, and number. Platelet function disorders include abnormalities in platelet receptors (such as Glanzmann's thrombasthenia), platelet granules (storage pool deficiencies), signal transduction pathways and granule release, and membrane phospholipids.[1,2] Treatment depends on the disorder, but in some conditions desmopressin or platelet transfusions are useful in the management of bleeding.[2] Inherited thrombocytopenias are discussed under Thrombocytopenia, p. 1129.2.

Inherited disorders that result in deficiencies or abnormalities of clotting factors can cause variable degrees of bleeding. The most common inherited disorders of clotting factors are haemophilias A and B (p. 1126.3) and von Willebrand disease (p. 1129.3). Other inherited disorders are rare[3] but include abnormalities of fibrinogen, deficiencies of the individual factors II, V, VII, X, XI (haemophilia C), XIII, and combined deficiencies of factors V and VIII, or of factors II, VII, IX, and X. Management depends on the clotting factors affected and the degree or risk of bleeding. In general, antifibrinolytics such as tranexamic acid may be adequate for control of mucosal bleeding and menorrhagia, and fibrin glue may be useful for local haemostasis. Severe bleeding requires the replacement of clotting factors, preferably using specific factor concentrates or recombinant factor products; fresh frozen plasma may be a suitable alternative when more specific products are not available. Vitamin K treatment may be considered in patients with deficiencies of vitamin K-dependent clotting factors (II, VII, IX, and X).

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Neonatal intraventricular haemorrhage

Intraventricular haemorrhage, also referred to as periventricular or periventricular-intraventricular haemorrhage, is bleeding from vessels in or around the ventricles of the brain. It is the major cause of death in very low birth-weight neonates and can affect up to 60% of neonates weighing less than 1500 g. Intraventricular haemorrhage is rare in neonates over 32 weeks of gestation, since the vessels that bleed involute early in the third trimester. Intraventricular haemorrhage usually develops within the first 3 days of life. The haemorrhage may be graded from 1 to 4 according to severity, the higher numbered grades being the most severe and most likely to produce the long-term consequences of impaired motor and mental function. The aetiology is probably multifactorial and may include fluctuations in cerebral blood flow due to failure of autoregulatory mechanisms and tissue damage caused by oxygen free-radicals.

Once intraventricular haemorrhage has occurred **treatment** is supportive and includes correction of anaemia, hypotension, and acidaemia, and management of raised intracranial pressure.

As intraventricular haemorrhage is a major risk factor for impaired motor and mental development **prevention** is very important. Many interventions aim to reduce its incidence and include prevention of premature births, avoidance of hypercapnia, correction of major haemodynamic disturbances, and correction of coagulation abnormalities. Various drugs have also been tried including corticosteroids, etamsylate, indometacin, pancuronium, phenobarbital, vitamin E, and vitamin K. Some of these drugs have been given to the mother antenatally since the development of intraventricular haemorrhage may be related to perinatal events.

- Giving corticosteroids to pregnant women at risk of preterm delivery is recommended to prevent neonatal respiratory distress syndrome (p. 1608.3) and may also reduce the incidence of intraventricular haemorrhage.[1] A review of data from 12 controlled studies involving antenatal corticosteroid use (mainly to prevent respiratory distress syndrome)[2] suggested that the risk of intraventricular haemorrhage was also reduced but this was based on limited data. Further studies[3-6] have supported this finding, although few have involved randomised doses of corticosteroids. The mechanism for the beneficial effect of corticosteroids is not clear but avoidance of neonatal hypotension has been suggested.[3]
- Etamsylate limits capillary bleeding through its action on hyaluronic acid and initial studies showed a reduction in intraventricular haemorrhage. A subsequent study[7] showed little evidence of benefit on short-term follow-up, although confidence intervals were wide. Follow-up[8] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Follow-up of another study[9] also found that despite a reported reduction in intraventricular haemorrhage with etamsylate, developmental outcome assessments at about 4 years of age showed that it had not reduced cerebral palsy compared with the control group.
- Indometacin may reduce cerebral blood flow as a result of vasoconstriction, reduce oxygen free-radical damage, and accelerate maturation of blood vessels around the ventricles. Early studies produced conflicting results but a later larger multicentre study[10] showed a reduction in both incidence and severity although there was an unusually large number of neonates with severe intraventricular haemorrhage in the control group.[11] A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps.[11] However, follow-up of the infants included in the multicentre study at the ages of 3 years,[12] 4.5 years,[13] and 8 years,[14] reported no adverse effects on cognitive or motor development. Further

analysis of the data from this cohort has suggested that indometacin may reduce intraventricular haemorrhage in boys but have little effect in girls;[15] a true difference in effect between the sexes remains to be confirmed however. Another large multicentre study[16] also found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[17] concluded that although indometacin prophylaxis reduced the rate of severe intraventricular haemorrhage, it did not improve the rate of survival free of neurosensory disability.

- Neuromuscular blockers, such as pancuronium, abolish non-synchronous respiration and therefore stabilise both cerebral and arterial blood flow velocity and some studies have shown a reduction in intraventricular haemorrhage in mechanically ventilated neonates (see Intensive Care, p. 2028.3). However, other studies have produced conflicting results and routine use in all ventilated neonates is not recommended.
- Phenobarbital was also suggested to act by stabilising fluctuations in cerebral blood flow, and studies of use in neonates show similarly inconsistent results with many showing no benefit. A meta-analysis[18] concluded that postnatal phenobarbital could not be recommended as prophylaxis, and was associated with an increased need for mechanical ventilation. Initial studies of antenatal phenobarbital were more promising with a decrease in severity of haemorrhage being reported.[19] However, a larger randomised study[20] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants who could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[21] A concern with the use of phenobarbital in the perinatal period is that it may lower Apgar scores and produce respiratory depression. A meta-analysis[22] did not support the maternal use of phenobarbital.
- Vitamin E protects polyunsaturated fatty acids, and thus membranes, from oxidation. As oxygen free-radical damage may contribute to the development of intraventricular haemorrhage, vitamin E may have a role in its prevention. Results have been conflicting. A systematic review[23] of studies in preterm infants (gestational age less than 37 weeks or birth-weight less than 2500g) found that vitamin E reduced the risk of intraventricular haemorrhage overall, but only reduced the risk of severe haemorrhage in surviving very low birth-weight infants (less than 1000 g). There was also a suggestion that intravenous vitamin E may have no effect compared with other dosage routes. However, the strength of these findings is limited and there was an increased risk of sepsis associated with vitamin E use, such that the role of supplementation with this vitamin has not been established in preterm infants.
- The activity of vitamin K-dependent coagulation factors is reduced in neonates and antenatal vitamin K in mothers has been tried as a means of preventing intraventricular haemorrhage. However, results of studies have not been promising. Most studies have been too small to produce conclusive results and a larger randomised controlled study[24] in 139 mothers failed to find any benefit from vitamin K prophylaxis. A subsequent systematic review[25] of 7 studies, including this one, also concluded that antenatal vitamin K use did not prevent intraventricular haemorrhage in preterm infants.

Plasma volume expansion using fresh frozen plasma or a plasma substitute has also been thought to reduce intraventricular haemorrhage by stabilising the circulation, but a prospective multicentre study found no evidence of reduction in haemorrhage[26] or subsequent death and disability[27] after the use of plasma or gelatin as volume expanders.

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Thrombocytopenia

Platelet concentrations in healthy individuals range from 150×10^9 cells/litre to 450×10^9 cells/litre, and thrombocytopenia is often **defined** as a reduction in the number of circulating platelets to less than 150×10^9 cells/litre (150 000 cells/mm^3). As the platelet count falls the risk of bleeding increases, although spontaneous bleeding is uncommon unless the count falls below 10×10^9 cells/litre to 20×10^9 cells/litre, or there is an abnormality in platelet function. Thrombocytopenia can result from decreased production, increased destruction, or abnormal splenic sequestration of platelets.

There are several **congenital forms** of thrombocytopenia that can affect platelet size, number, and function. They range across a wide clinical spectrum from mild forms, which may only be discovered incidentally and do not require specific treatment, to severe forms that are associated with a high risk of bleeding and may ultimately require haematopoietic stem cell transplantation.[1]

Secondary thrombocytopenia can be associated with many other illnesses.[2] Decreased platelet production may occur in bone marrow diseases such as leukaemias and aplastic anaemia, some viral illnesses, chronic alcohol toxicity, and liver disease. Increased destruction of platelets occurs in many disorders including immune thrombocytopenia (p. 1606.1), sepsis, disseminated intravascular coagulation (p. 1126.1), and thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p. 1159.1). Gestational thrombocytopenia[3] is a mild form that usually occurs in late pregnancy, in which platelet concentrations return to normal within 12 weeks after delivery. More severe thrombocytopenia may be caused by obstetric conditions including pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. Neonatal thrombocytopenia[4] that is mild and of early onset (in the first 72 hours of life) may be secondary to placental insufficiency and reduced platelet production. More severe thrombocytopenia of later onset may result from platelet destruction associated with sepsis or necrotising enterocolitis. In neonatal allo-immune thrombocytopenia, maternal antibodies against fetal platelet antigens cross the placenta to cause disease ranging from mild self-limiting thrombocytopenia to neonatal intracranial haemorrhage. In neonatal auto-immune thrombocytopenia there is placental transfer of maternal platelet autoantibodies in mothers with conditions such as idiopathic thrombocytopenic purpura or SLE.

Drug-induced thrombocytopenia has been reported with many drugs.[5-9] Decreased platelet production can be caused by drugs that have a toxic effect on bone marrow, including many antineoplastics. Drugs that are often implicated in immune-mediated platelet destruction include anticonvulsants, cinchona alkaloid derivatives (quinine, quinidine), diuretics, disease-modifying antirheumatic drugs (penicillamine, gold salts), NSAIDs, and sulfonamides. The 2 types of heparin-induced thrombocytopenia have been well documented (see p. 1399.1).

Treatment of thrombocytopenia is based on management of the underlying disorder where appropriate, or stopping the offending drug. Platelet infusions are used in the treatment of active bleeding or in thrombocytopenic patients who are at risk of bleeding. They should not be used when there is a thrombotic process such as in thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia. The platelet count at which infusion may be considered depends on various factors including the cause of thrombocytopenia, the presence of additional risk factors such as sepsis, the degree of bleeding, and whether the risk is related to surgery. For example, if there is active bleeding or invasive procedures are contemplated, platelet infusion may be used when the count is less than 50×10^9 cells/litre. In patients with no bleeding and no additional risk factors, a lower threshold of 5×10^9 cells/litre may be adequate.[2,10] Patients requiring long-term treatment may develop antibodies to HLA with repeated transfusions from random donors, which results in impaired responsiveness to subsequent transfusion; these patients should receive platelets obtained from a single donor for each transfusion, preferably HLA-matched.[2,10] In platelet refractoriness, when thrombocytopenia is a result of non-immune platelet destruction, treatment is problematic and although prophylactic platelet infusions may be given, it is unknown whether this is effective.[10]

Oprelvekin (recombinant human interleukin-11) is a platelet growth factor that has recently been introduced for the prevention of severe antineoplastic-induced thrombocytopenia. Romiplostim and eltrombopag, both thrombopoietin receptor agonists, have been developed for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia. Recombinant human thrombopoietin is also under investigation.

1. Drachman JG. Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood* 2004; **103:** 390–8.
2. Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. *Am J Respir Crit Care Med* 2000; **162:** 347–51.
3. Kam PCA, *et al*. Thrombocytopenia in the parturient. *Anaesthesia* 2004; **59:** 255–64.
4. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F359–F364.
5. George JN, *et al*. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998; **129:** 886–90.
6. Rizvi MA, *et al*. Drug-induced thrombocytopenia: an updated systematic review. *Ann Intern Med* 2001; **134:** 346.
7. Hibbard AB, *et al*. Reports of drug-induced thrombocytopenia. *Ann Intern Med* 2003; **138:** 239.
8. van den Bemt PMLA, *et al*. Drug-induced immune thrombocytopenia. *Drug Safety* 2004; **27:** 1243–52.
9. Li X, *et al*. Drug-induced thrombocytopenia: an updated systematic review. *Ann Intern Med* 2005; **142:** 474–5.
10. Murphy MF, *et al*. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; **122:** 10–23. Also available at: http://www.bcshguidelines.com/pdf/platelettrans040703.pdf (accessed 27/10/05)

von Willebrand's disease

von Willebrand's disease (vWD)[1-3] is a congenital bleeding disorder caused by a deficiency or dysfunction of von Willebrand factor (vWF), a plasma protein that stimulates platelet aggregation and acts as a carrier for factor VIII to protect it from premature destruction. There is also a secondary deficiency of factor VIII, because of its dependence on vWF. There are 3 main phenotypes of vWD:

- type 1 is the most common and is characterised by mild to moderate deficiencies of vWF and factor VIII
- type 2 results in qualitative abnormalities of vWF, and is further divided into subtypes according to the defect
- type 3 is rare but is a severe bleeding disorder due to very low or undetectable plasma levels of vWF, with low but usually detectable concentrations of factor VIII.

The clinical presentation of vWD includes easy bruising and bleeding from mucosal surfaces, such as epistaxis; severely affected patients may have spontaneous soft-tissue bleeding resulting in haematomas and haemarthroses. Excessive and prolonged bleeding can occur after surgery, and women may have excessive bleeding during menstruation and childbirth.[1-3]

Patients are usually only treated at the time of spontaneous bleeding or given prophylaxis before invasive procedures. Desmopressin transiently increases both vWF and factor VIII levels and is used in patients with type 1 disease. It is less likely to be effective in type 2 disease where vWF is dysfunctional. It is generally contra-indicated in type

2B disease because the abnormal vWF that is released may induce platelet aggregation and thrombocytopenia, although this is usually transient and often not associated with bleeding or thrombosis. Type 3 disease does not respond to desmopressin because of the lack of vWF stores.[1-3]

Plasma concentrates that contain both vWF and factor VIII are used when desmopressin is not suitable. A concentrate that contains highly purified vWF, with very little factor VIII, is available in some countries. Very highly purified factor VIII preparations, or recombinant forms, should not be used; they do not contain appreciable amounts of vWF so the factor VIII therefore has a very short half-life, making it ineffective (but see also below, about the management of patients with alloantibodies). When haemorrhage is not controlled despite adequate factor VIII levels, platelet concentrates may be required.[1-3] Cryoprecipitate may be used as a source of clotting factors and vWF when other measures have failed, or in serious situations when vWF concentrates are not available, but it does not consistently correct bleeding time and has a higher risk of transfusion-transmitted infection.[2,3]

Some patients with type 3 disease who have received multiple transfusions develop alloantibodies that inactivate vWF and form circulating immune complexes. Further use of concentrates that contain vWF is contra-indicated because of the risk of anaphylaxis. There are a few reports of successful control of surgical bleeding in such patients by continuous infusion of recombinant forms of factor VIII and activated factor VII, which contain no vWF.[1,2]

Antifibrinolytic drugs, such as tranexamic acid or aminocaproic acid, may be sufficient in the management of less severe forms of mucosal bleeding, and are used as adjuncts to desmopressin or plasma concentrates in patients undergoing surgery.[1-3] Fibrin glue or bovine thrombin may also be used as topical adjuncts for oral surgery.[3] Hormonal contraceptives can reduce bleeding in women with vWD and menorrhagia.[1-3]

Acquired von Willebrand syndrome is rare, and is usually associated with conditions such as lymphoproliferative and myeloproliferative diseases, cancers, auto-immune diseases, and hypothyroidism. Some drugs have been reported to cause an acquired von Willebrand syndrome, including ciprofloxacin and valproic acid. Depending on the underlying cause, vWF activity may be affected by accelerated clearance, reduced synthesis, or an inhibition of function. Management is based on treatment of the underlying cause, but specific options for treatment of bleeding include desmopressin, factor concentrates, and intravenous immunoglobulin.[1-4] Plasma exchange and extracorporeal immunoadsorption have also been used successfully.[2,4]

1. Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med* 2004; **351:** 683–94.
2. Pasi KJ, *et al.* Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004; **10:** 218–31.
3. Nichols WL, *et al.* von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia* 2008; **14:** 171–232. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2007.01643.x/pdf (accessed 13/08/10)
4. Kumar S, *et al.* Acquired von Willebrand disease. *Mayo Clin Proc* 2002; **77:** 181–7.

Neutropenia

A circulating neutrophil count below 1.5×10^9 cells/litre (1500 cells/mm^3) is usually regarded as abnormal and neutrophil counts below 0.5×10^9 cells/litre are associated with increased risk of infections. Neutropenia may be a result of reduced production, increased peripheral destruction, or increased peripheral pooling of neutrophils, and can be inherited or acquired.

Inherited forms of neutropenia are rare and include congenital agranulocytosis (Kostmann's syndrome: severe persistent neutropenia with frequent and severe infections that start in infancy) and cyclic neutropenia (fluctuating periods of neutropenia accompanied by fever, mouth ulceration, and serious infection).

Granulocyte colony-stimulating factors have been shown to reduce the incidence of severe infections and have improved substantially the quality of life of patients with congenital neutropenias although there are some concerns over their safety. As patients survive longer with such treatment they show an increased risk of developing myelodysplastic syndrome and leukaemia. However, it is unclear whether prolonged survival unmasks the natural course of the disease or whether granulocyte colony-stimulating factor further increases the risk of leukaemic transformation. Haematopoietic stem cell transplantation may be indicated for patients whose disease is refractory to colony-stimulating therapy or has transformed into myelodysplastic syndrome or leukaemia. Cyclic neutropenia is also managed with granulocyte colony-stimulating factor, but leukaemic transformation does not seem to occur in these patients.

There are many causes of **acquired** neutropenia. Drugs are a common cause, either by direct toxicity to the bone marrow, or by immune-mediated marrow suppression or peripheral destruction. Drugs that cause dose-related direct toxicity include cytotoxic and immunosuppressive drugs, flucytosine, ganciclovir, and zidovudine. Drugs that appear to cause neutropenia by immune-mediated mechanisms include sulfur-containing drugs (such as captopril, co-trimoxazole, and some antithyroid drugs), clozapine, penicillins, and cephalosporins. Patients with drug-induced neutropenia usually present with fever of sudden onset, sore throat, mouth ulcers, headache, and malaise. This condition is also known as **agranulocytosis**. Other causes of acquired neutropenia include serious bacterial and viral infections, radiotherapy, neoplasms that invade bone marrow, and some auto-immune disorders.

The management of acquired neutropenia includes the treatment of any contributory condition. Drug-induced neutropenia is usually managed by withdrawal of the offending drug. After an idiosyncratic reaction the implicated drug should not be given again, since abrupt neutropenia will usually be precipitated. Colony-stimulating factors can be used to manage drug-induced neutropenia.

In all neutropenic patients onset of fever is indicative of serious infection and is treated immediately with empirical antibacterial therapy, as described under Infections in Immunocompromised Patients, p. 186.3.

General references.

1. Zeidler C, *et al.* Congenital neutropenias. *Rev Clin Exp Hematol* 2003; **7:** 72–83.
2. Bhatt V, Saleem A. Drug-induced neutropenia—pathophysiology, clinical features, and management. *Ann Clin Lab Sci* 2004; **34:** 131–7.
3. James RM, Kinsey SE. The investigation and management of chronic neutropenia in children. *Arch Dis Child* 2006; **91:** 852–8.

Albumin ⊗

Albümin; Albúmina; Albumine; Albuminlösung vom Menschen; Albuminum.

ATC — B05AA01.

ATC Vet — QB05AA01; QV08DA01 (microspheres of human albumin).

UNII — 27432CM55Q (bovine albumin); B05Y6V2CZS (egg albumin); ZIF514RVZR (human albumin).

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii) and *US.*

USNF includes a solution of a recombinant human albumin.

Ph. Eur. 8: (Human Albumin Solution; Albumini Humani Solutio). A sterile liquid preparation of a plasma protein fraction containing human albumin obtained from the plasma of healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. It is prepared as a concentrated solution containing 15 to 25% of total protein or as an isotonic solution containing 3.5 to 5% of total protein; not less than 95% of the total protein is albumin. A suitable stabiliser, such as sodium octanoate or *N*-acetyltryptophan or a combination of the two, may be added but no antimicrobial preservative or antibiotic is added. It contains not more than 160 mmol of sodium per litre and not more than 200 micrograms of aluminium per litre. The solution is sterilised by filtration and distributed aseptically into containers which are sealed to prevent contamination and maintained at 59 degrees to 61 degrees for not less than 10 hours. Finally, the containers are incubated for not less than 14 days at 30 degrees to 32 degrees or for not less than 4 weeks at 20 degrees to 25 degrees and examined visually for signs of microbial contamination. It should be stored in a colourless glass container and protected from light.

A clear, almost colourless, yellow, amber, or green slightly viscous liquid. A solution in sodium chloride 0.9% containing 1% protein has a pH of 6.7 to 7.3.

The BP 2014 gives Albumin and Human Albumin as approved synonyms.

USP 36: (Albumin Human). A sterile, nonpyrogenic, preparation of serum albumin obtained by fractionating material (blood, plasma, serum, or placentas) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It is made by a process that yields a product that is safe for intravenous use. It contains 4, 5, 20, or 25% of serum albumin and not less than 96% of the total protein is albumin. It may contain sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent; it contains no added antimicrobial agent. It contains 130 to 160 mmol of sodium per litre. It is a practically odourless, moderately viscous, clear, brownish fluid. It should be stored in airtight containers.

USNF 31: (rAlbumin Human). Recombinant Albumin Human (rHA) is produced by recombinant DNA expression in *Saccharomyces cerevisiae*. Structural equivalence (primary, secondary, and tertiary) between rHA and human serum albumin (HSA) has been demonstrated. It is presented as a sterile and nonpyrogenic aqueous liquid consisting of a 10% or 20% solution in Water for Injection. It contains no added antimicrobial agents, but it may contain appropriate stabilising agents. Clear, slightly viscous, and colourless to yellow amber in colour. Store in airtight glass containers at a temperature of 2 degrees to 8 degrees. Do not allow to freeze.

Uses and Administration

Albumin is the major protein involved in maintaining colloid osmotic pressure in the blood. It also binds several endogenous and exogenous substances including bilirubin, steroid hormones, and many, mainly acidic, drugs.

Albumin solutions are used for plasma volume replacement and to restore colloid osmotic pressure. They have been used in conditions such as burns, severe acute albumin loss, and acute hypovolaemic shock (p. 1279.3). They are also used as an exchange fluid in therapeutic plasmapheresis. Concentrated albumin solutions are used in neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn (p. 2377.2). They have also been suggested for short-term management of hypoproteinaemia in hepatic disease and in diuretic-resistant patients with nephrotic syndrome but are of little value in chronic hypoproteinaemias.

Albumin may be included in diagnostic preparations such as those labelled with technetium-99m (p. 2228.1) for use as radiopharmaceuticals in scanning of the heart, lung, liver, spleen, bone marrow, veins, and lymphatic system. Albumin labelled with iodine-125 (p. 2225.2) is used to measure blood and plasma volumes, blood circulation, and cardiac output. A suspension of albumin microspheres with perflutren (p. 1595.2) is available for enhancing cardiac ultrasound imaging.

Recombinant forms of human albumin have been developed as excipients for vaccines and other drug products, and for the treatment of hypoalbuminaemia and hypovolaemic shock.

Albumin solutions are usually available as 4.5% or 5% solutions, which are iso-osmotic with plasma, and as 20% or 25% solutions which are hyperosmotic with respect to plasma, and cause a movement of fluid from the extravascular to the intravascular compartment. These concentrated solutions may be used undiluted or may be diluted with a suitable solution, commonly sodium chloride 0.9% or glucose 5%. Adequate hydration should be maintained and electrolytes monitored in patients receiving hyperosmotic solutions of albumin.

The amount of albumin solution given will depend upon the clinical condition of the patient and the response to treatment. The following doses have been suggested:

- acute hypovolaemic shock: an initial dose of 25 g (for example, 500 mL of a 5% solution or 100 mL of a 25% solution)
- hypoproteinaemia: a maximum of 2 g/kg daily

The rate of intravenous infusion should be adjusted according to the indication and patient response, but in general, suggested rates of infusion are up to 5 mL/minute (5% solution) or 1 to 2 mL/minute (20% solution). In plasmapheresis the albumin infusion rate should be adjusted according to the rate of removal.

For the use of albumin in children, see below.

Albumin solutions should not be used for parenteral nutrition.

References.

1. Nicholson JP, *et al.* The role of albumin in critical illness. *Br J Anaesth* 2000; **85:** 599–610.
2. Matejtschuk P, *et al.* Production of human albumin solution: a continually developing colloid. *Br J Anaesth* 2000; **85:** 887–95.
3. Haynes GR, *et al.* Albumin administration–what is the evidence of clinical benefit? A systematic review of randomized controlled trials. *Eur J Anaesthesiol* 2003; **20:** 771–93.
4. Mendez CM, *et al.* Albumin therapy in clinical practice. *Nutr Clin Pract* 2005; **20:** 314–20.
5. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; **19:** 157–67.
6. Kobayashi K. Summary of recombinant human serum albumin development. *Biologicals* 2006; **34:** 55–9.

Administration in children. The amount and concentration of albumin solution given will depend upon the clinical condition of the patient and the response to treatment. When used in children the following doses, given by intravenous infusion, have been suggested:

- acute hypovolaemic shock: an initial dose of about 1 g/kg
- hypoproteinaemia: a maximum of 2 g/kg daily
- neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn: 1 g/kg before or during exchange transfusion (using a concentrated solution such as 25% albumin)

Adverse Effects and Precautions

Adverse reactions to albumin infusion occur rarely and include nausea and vomiting, increased salivation, flushing, urticaria, hypotension, tachycardia, and febrile reactions. These effects usually respond to slowing or stopping the infusion. Allergic reactions, including severe anaphylactic shock, are possible. Rapid increases in circulatory volume can cause vascular overload, hypertension, haemodilution, and pulmonary oedema. Solutions containing albumin 20 or 25% are hyperosmotic and draw fluid from the extravascular compartment.

Infusion of albumin solutions is contra-indicated in patients with severe anaemia or heart failure. They should be given with caution to patients with hypertension or low cardiac reserve. Dehydrated patients may require additional fluids. Injured or postoperative patients should be observed carefully when given albumin as the rise in blood pressure may result in bleeding from previously undetected sites.

Human albumin preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60 degrees, have reduced the risk of transmitting some viral infections.

Aluminium toxicity. Albumin solutions may contain appreciable amounts of aluminium. Marked increases in plasma-aluminium concentrations have been found in patients receiving large volumes by infusion and accumulation of aluminium may occur in patients with renal impairment.[1-3] In the UK albumin solutions with an aluminium content of less than 200 micrograms/litre are available for use in premature infants and patients undergoing dialysis.

1. Milliner DS, *et al.* Inadvertent aluminum administration during plasma exchange due to aluminum contamination of albumin-replacement solutions. *N Engl J Med* 1985; **312:** 165–7.
2. Maher ER, *et al.* Accumulation of aluminium in chronic renal failure due to administration of albumin replacement solutions. *BMJ* 1986; **292:** 306.
3. Maharaj D, *et al.* Aluminium bone disease in patients receiving plasma exchange with contaminated albumin. *BMJ* 1987; **295:** 693–6.

Critically ill patients. Volume expansion with albumin (a colloid) has been widely used in critically ill patients, although its use had never been formally tested in large controlled studies. A systematic review based on available studies up to March 1998 (relatively small, old studies that recorded only a small number of deaths) suggested that albumin was of no benefit in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia, and that it might be linked to increased mortality.[1] The authors of the review stressed that these results should be treated with caution but nevertheless called for an urgent reconsideration of the use of albumin in critically ill patients.

The review was severely criticised[2] and while it was recognised that albumin had probably been overused in the past it was considered that more studies were required to define the effect of albumin on mortality.[3-5] Another review[6] found that the use of albumin did not significantly affect mortality; this meta-analysis had broader criteria and included studies that were considered to be relevant but that had been excluded by the other review.

In response to this debate, albumin 4% was compared with sodium chloride 0.9% for resuscitation in a study of 6997 hypovolaemic patients in intensive care (the SAFE study).[7] This large, randomised, double-blind study found equivalent rates of death from any cause during the 28-day study period. Survival-time during the 28 days, length of stay in the intensive care unit and in hospital, time on mechanical inhalation or renal replacement therapy, and development of organ failure were also similar. Although these two fluids seem clinically equivalent in a heterogeneous population of patients in intensive care, further study of selected groups, such as those with trauma or severe sepsis, is required.

An update to the original 1998 review included the results of SAFE. The authors maintained that patients with burns (a group excluded from the large study) or hypoproteinaemia might still be at risk of increased mortality, and although no longer suggesting a generally increased risk, concluded that there was no evidence that albumin reduced mortality in patients with hypovolaemia. Whether highly selected groups of critically ill patients might benefit is as yet unclear.[8]

Pharmacovigilance data reported to albumin suppliers over 3 years (1998 to 2000) have also been analysed.[9] During this period of heightened awareness about possible adverse effects of albumin, due to the publication of the 1998 review, a total of 1.62×10^7 doses of 40 g had been distributed. Serious adverse effects possibly or probably related to albumin were found to be rare, and no death was classified as probably related to albumin use.

On a broader level, debate continues about the relative merits and risks of such colloid solutions, compared with those of crystalloids such as glucose or sodium chloride solutions, in the management of hypovolaemia and shock (p. 1279.3).

1. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; **317:** 235–40.
2. Various. Human albumin administration in critically ill patients. *BMJ* 1998; **317:** 882–6. [Letters.]
3. Tomlin M. Albumin usage in the critically ill. *Pharm J* 1998; **261:** 193.
4. McClelland B. Albumin: don't confuse us with the facts. *BMJ* 1998; **317:** 829–30.
5. CSM/MCA. The safety of human albumin. *Current Problems* 1999; **25:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
6. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; **135:** 149–64.
7. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350:** 2247–56.
8. The Albumin Reviewers. Human albumin solution for resuscitation and volume expansion in critically ill patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 27/10/05).
9. Vincent J-L, *et al.* Safety of human albumin—serious adverse events reported worldwide in 1998–2000. *Br J Anaesth* 2003; **91:** 625–30.

Dilution. If concentrated albumin solutions are to be diluted before use, a suitable solution such as sodium chloride 0.9% or glucose 5% must be used. Albumin 25% that was erroneously diluted with water to produce a hypo-osmolar albumin 5% solution has produced severe haemolysis and renal failure in patients undergoing plasmapheresis,[1,2] including one fatality.[3]

1. Steinmuller DR. A dangerous error in the dilution of 25 percent albumin. *N Engl J Med* 1998; **338:** 1226.
2. Pierce LR, *et al.* Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. *Am J Health-Syst Pharm* 1998; **55:** 1057,1062, 1070.
3. Anonymous. Hemolysis associated with 25% human albumin diluted with sterile water—United States, 1994–1998. *MMWR* 1999; **48:** 157–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies albumin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Transmission of infections. There has been concern that albumin preparations may carry a potential risk of transmission of viral and subviral particles, notably Creutzfeldt-Jakob disease. In 1993, *Pasteur-Mérieux* (one of the largest producers of blood products) withdrew all products containing albumin derived from placental blood[1] due to uncertainty regarding the adequacy of screening procedures for placentas as a source. It was considered that the agent responsible for Creutzfeldt-Jakob disease might be contained in placentas from women who have been treated with growth hormone derived from cadaver pituitaries. More recently, the production of blood products (including albumin) using plasma from UK donors has been phased out due to the possible risk of transmission of new variant Creutzfeldt-Jakob disease.

1. Anonymous. Placental-derived albumin preparations withdrawn. *WHO Drug Inf* 1994; **8:** 29–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Albuminar; Buminate; Flexbumin; Zenalb; ***Austral.***: Albumex; ***Austria***: Albunorm; ***Belg.***: Albunorm; Alburex; Flexbumin; Octalbine; ***Braz.***: Albuminar; Alburex; Beribumin; Blaubimax; Octalbin; Plasbumin; ***Canad.***: Alburex; Albutein; Buminate; Plasbumin; ***Chile***: Plasbumin†; ***China***: Albuminar (亚玛); AlbuRx (安博灵); Albutein; Anpu Laishi (安普莱士); Buminate; Octapharma (奥达); Plasbumin (拜斯明); ***Cz.***: Albunorm; Alburex; Flexbumin; ***Denm.***: Albuminativ†; Flexbumin; Maasol; Nanocoll; Octalbin†; Venticoll; ***Fin.***: Albuman; Albuminativ; Albunorm; Flexbumin; Octalbin; ***Fr.***: Albunorm; Flexbumin; Octalbine†; Vialebex; ***Ger.***: Albiomin; Albunorm; Alburex; Humanalbin; Plasbumin; ***Gr.***: Albiomin; Albuman; Albuminar; Albuminativ; Alburex; Flexbumin; Hibumine; Nialbumin; Plasbumin; Zenalb; ***Hong Kong***: Albumex; Albutein; Biseko; Buminate; Kamapharm†; NSA†; Plasbumin; ***India***: Alba; Albudac; Albumed; Albumeon; Alburel; Albutein; Biseko; Humin; ***Indon.***: Albapure; Albuminar; Alburaas; Albutein; Cealb; Farmin; Fimalbumin; Octalbin; Plasbumin; Robumin; Zenalb; ***Irl.***: Albuminativ†; Albunorm; Flexbumin; ***Israel***: Albiomin; Albuminativ; Egg Plus; Frosstimage Kit (MAA); Zenalb; ***Ital.***: Albital; Alburex; Albutein; Nanocoll; Octalbin; Plasbumin; ***Jpn***: Medway; ***Malaysia***: Albutein; Buminate†; Zenalb; ***Mex.***: Albunate; Octalbin; Vanderbumin†; ***Neth.***: Albuman; Albunorm; Alburex; Cealb; Flexbumin; Octalbine; ***Norw.***: Albuminativ†; Flexbumin; ***NZ***: Albumex; Octalbin; ***Philipp.***: Albumax; Albuminar; Alburel; Albutein; Kedrialb; Plasbumin; Plasbutein; Zenalb; ***Pol.***: Biseko; ***Port.***: Albiomin; Albuminativ†; Albunorm; Alburex; Flexbumin; ***Rus.***: Plasbumin (Плазбумин); Zenalb (Зенальб); ***S.Afr.***: Albusol; ***Singapore***: Albutein; Buminate; NSA; Zenalb; ***Spain***: Albiomin; Albunorm; Alburex; Albutein; Flexbumin; Octalbin†; Plasbumin; ***Swed.***: Albuminativ; Albunorm; Flexbumin; ***Switz.***: Flexbumin; ***Thai.***: Albiomin; Alburaas; Albutein; Buminate; Flexbumin; Zenalb; ***Turk.***: Alba; Albuman; Albuminar; Biotest; Cealb; Plasbumin; Vialebex; Zenalb; ***UK***: Albunorm; Alburex; Albutein; Flexbumin; Obruman; Zenalb; ***USA***: Albumarc; Albuminar; AlbuRx; Albutein; Buminate†; Kedbumin; Plasbumin.

Multi-ingredient Preparations. ***Denm.***: Pharmalgen Albumin; ***Rus.***: Ferrohematogen (Феррогематоген); Hematogen C (Гематоген С); Hematogen C Vita (Гематоген С Вита); Hematogen Nova (Гематоген Новый); ***Swed.***: Tisseel Duo Quick; ***Ukr.***: Lactoprotein-C (Лактопротеин-С).

Pharmacopoeial Preparations
Ph. Eur.: Human Albumin Solution;
USP 36: Albumin Human.

Aminaphthone

Aminaftona; Aminaftone; Aminaphtone; Aminonaphthone. 2-Hydroxy-3-methylnaphtho-1,4-hydroquinone 2-(4-aminobenzoate); 3-Methylnaphthalene-1,2,4-triol 2-(4-aminobenzoate).

$C_{18}H_{15}NO_4$=309.3

CAS — 14748-94-8.

UNII — 03JLX11PE9.

Profile

Aminaphthone is a haemostatic. Daily doses of 150 to 225 mg orally have been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Capilarema; ***Ital.***: Capillarema; ***Port.***: Capilarema.

Aminocaproic Acid *(BAN, USAN, rINN)*

Acide Aminocaproïque; Ácido aminocapróico; Ácido aminocaproico; Acidum Aminocaproicum; Aminocaproico, ácido; Aminocapronsäure; Aminokaproniappo; Aminokaprono rūgštis; Aminokapronsav; Aminokapronsyra; CL-10304; CY-116; EACA; Epsilon Aminocaproic Acid; JD-177; Kwas ε-aminokapronowy; Kyselina aminokapronová; NSC-26154; Аминокапроновая Кислота.

6-Aminohexanoic acid.

$C_6H_{13}NO_2$=131.2

CAS — 60-32-2.

ATC — B02AA01.

ATC Vet — QB02AA01.

UNII — U6F3787206.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Aminocaproic Acid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 20% solution in water has a pH of 7.5 to 8.0.

USP 36: (Aminocaproic Acid). A fine, white, odourless or practically odourless, crystalline powder. Soluble 1 in 3 of water and 1 in 450 of methyl alcohol; slightly soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in acids and in alkalis. Its solutions are neutral to litmus. Store in airtight containers.

Uses and Administration

Aminocaproic acid is an antifibrinolytic used similarly to tranexamic acid (p. 1164.2) in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It has also been used in the prophylaxis of hereditary angioedema (p. 1132.1).

A plasma concentration of about 130 micrograms/mL is considered to be necessary for effective inhibition of fibrinolysis and the recommended dosage schedules are aimed at producing and maintaining this concentration for as long as is necessary. For the treatment of **haemorrhage**, aminocaproic acid may be given orally in an initial dose of 5 g, followed by 1 or 1.25 g every hour. Alternatively, similar doses may be given intravenously as a 2% solution; the initial dose (4 to 5 g) should be given over one hour followed by a continuous infusion of 1 g/hour. Up to 8 hours of treatment is often sufficient. Should treatment need to be extended, then the maximum dose over 24 hours should not normally exceed 24 g.

Aminocaproic acid may be given, usually with factor VIII or IX products, as prophylaxis or treatment in patients with **haemophilia** (p. 1126.3) who undergo dental extraction. Oral doses of 50 to 100 mg/kg (up to 6 g) may be given every 4 to 6 hours (maximum 24 g per 24 hours). Treatment may be started before the procedure, and is usually given for a total of 7 to 10 days.

Care is required when aminocaproic acid is used in patients with renal impairment and dosage should be reduced.

Hereditary angioedema. In the management of hereditary angioedema (p. 2485.2), antifibrinolytic drugs may be used as an alternative to androgens for the prophylaxis of attacks. The usual oral dose of aminocaproic acid in such patients is 1 g three or four times daily. It has also been used intravenously for acute attacks, and anecdotal reports suggest it may be modestly helpful, but there is no published evidence suggesting significant benefit.[1]

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.

Adverse Effects

Adverse effects associated with aminocaproic acid include dose-related gastrointestinal disturbances, dizziness, tinnitus, headache, nasal and conjunctival congestion, and rashes. Aminocaproic acid may cause muscle damage. This has usually occurred with high doses given for prolonged periods; renal failure may develop. Thrombotic complications have been reported, although they are usually a consequence of inappropriate use. If aminocaproic acid is given by rapid intravenous injection it can produce hypotension, bradycardia, and arrhythmias. There have been reports of a few patients suffering from convulsions, dry ejaculation, or cardiac and hepatic damage.

Effects on the blood. Very high doses of aminocaproic acid (36 g or more daily) have been given intravenously in the management of subarachnoid haemorrhage (see Stroke, p. 1269.2). One study[1] reported rebleeding and excessive intra-operative bleeding and suggested that this was due to an antiplatelet effect of the aminocaproic acid. However, a comment on this report[2] pointed out that any antiplatelet effect was independent of its antifibrinolytic action and that this effect could only aggravate rebleeding, if it occurs, rather than causing it. However, early surgical intervention is now used to manage subarachnoid haemorrhage, and in a series of 307 patients treated with high-dose short-term aminocaproic acid before early surgery it was found that, compared with older reports in the literature, there was a low rate of rebleeding without an apparent increase in adverse effects.[3]

1. Glick R, *et al.* High dose ε-aminocaproic acid prolongs the bleeding time and increases rebleeding and intraoperative hemorrhage in patients with subarachnoid hemorrhage. *Neurosurgery* 1981; **9:** 398–401.
2. Kassell NF. Comment. *Neurosurgery* 1981; **9:** 401.
3. Leipzig TJ, *et al.* Reducing the risk of rebleeding before early aneurysm surgery: a possible role for antifibrinolytic therapy. *J Neurosurg* 1997; **86:** 220–5.

Effects on the kidneys. Adverse renal effects of aminocaproic acid are rare but have included renal arterial thrombosis, glomerular capillary thrombosis, and renal pelvic or ureteral obstruction caused by upper urinary tract thrombosis.[1] Cases of acute renal failure associated with myopathy are described under Effects on the Muscles, below.

1. Manjunath G, *et al.* Epsilon-aminocaproic acid and renal complications: case report and review of the literature. *Clin Nephrol* 2002; **58:** 63–7.

Effects on the muscles. There have been cases of reversible myopathy,[1-4] associated with daily doses of aminocaproic acid ranging from 10 to 49 g and treatment durations of about 1 to 3 months. In some patients myoglobinuria or acute tubular necrosis also occurred. Suggested mechanisms for the reaction have included a direct dose-related effect on the muscle fibre[2] or a defect in aerobic energy provision induced by aminocaproic acid.[3]

1. Brown JA, *et al.* Myopathy induced by epsilon-aminocaproic acid. *J Neurosurg* 1982; **57:** 130–4.
2. Vanneste JAL, van Wijngaarden GK. Epsilon-aminocaproic acid myopathy. *Eur Neurol* 1982; **21:** 242–8.
3. Van Renterghem D, *et al.* Epsilon amino caproic acid myopathy: additional features. *Clin Neurol Neurosurg* 1984; **86:** 153–7.
4. Seymour BD, Rubinger M. Rhabdomyolysis induced by epsilon-aminocaproic acid. *Ann Pharmacother* 1997; **31:** 56–8.

Precautions

As for Tranexamic Acid, p. 1165.2.

The range of adverse effects that have been noted with aminocaproic acid indicates that caution is required in patients with renal or cardiac disorders. Should treatment be prolonged, it is advisable to monitor creatine phosphokinase values for signs of muscle damage.

Renal impairment. High anion gap metabolic acidosis developed in a 65-year-old woman with sepsis and acute renal failure who received aminocaproic acid for a haemorrhagic coagulopathy.[1] The acidosis improved temporarily after haemodialysis and resolved on withdrawal of aminocaproic acid and systemic alkalinisation. Although the dose of aminocaproic acid had been reduced because of renal impairment, it was suggested that more conservative dosing and close monitoring may be indicated in such patients. Hyperkalaemia has been attributed to the use of aminocaproic acid in a few patients with chronic renal failure.[2]

1. Budris WA, *et al.* High anion gap metabolic acidosis associated with aminocaproic acid. *Ann Pharmacother* 1999; **33:** 308–11.
2. Nzerue CM, Falana B. Refractory hyperkalaemia associated with use of epsilon-aminocaproic acid during coronary bypass in a dialysis patient. *Nephrol Dial Transplant* 2002; **17:** 1150–1.

Interactions

Retinoids. Aminocaproic acid should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p. 1727.1).

Pharmacokinetics

Aminocaproic acid is readily absorbed when given orally and peak plasma concentrations occur within 2 hours. It is widely distributed and is rapidly excreted in the urine, mainly unchanged, with a terminal elimination half-life of about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Caprocat; Ipsilon; ***Braz.***: Ipsilon; ***China***: Kai Nai Yin (凯乃银); ***Fr.***: Hexalense†; ***Hung.***: Acepramin; ***India***: Hamostat; Hemocid; ***Port.***: Epsicaprom; ***Rus.***: Polycapran (Поликапран); ***Spain***: Caproamin†; ***Ukr.***: AKK (AKK); ***USA***: Amicar; ***Venez.***: Caproamin.

Multi-ingredient Preparations. ***Braz.***: Eaca Balsamico; ***Rus.***: Polygemostat (Полигемостат).

Pharmacopoeial Preparations

USP 36: Aminocaproic Acid Injection; Aminocaproic Acid Syrup; Aminocaproic Acid Tablets.

Aminomethylbenzoic Acid

Aminometilbenzoico, ácido; PAMBA; Аминометилбензойная Кислота.

4-Aminomethylbenzoic acid.

$C_8H_9NO_2$=151.2

CAS — 56-91-7.

ATC — B02AA03.

ATC Vet — QB02AA03.

UNII — 68WG9JKC7L.

Profile

Aminomethylbenzoic acid is an antifibrinolytic with actions and uses similar to those of tranexamic acid (p. 1164.2). It is given orally in typical doses of 300 mg to 1 g daily, in 3 or 4 divided doses; it is also given by intramuscular injection, or intravenously by slow injection or infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Ben (艾本); Ao Rui Ai (奥瑞艾); Fu Fen (弗芬); He Er Kang (赫尔康); Hong Yu Shu (虹雨舒); Ji Xiang Hong (吉祥红); Shuai Zhi (帅郅); Wei Ka (唯卡); ***Cz.***: Pamba; ***Ger.***: Pamba.

Multi-ingredient Preparations. ***Ukr.***: Revalid (Ревалид).

Ancestim *(USAN, rINN)*

Ancestimum; r-metHuSCF; SCF; Stem Cell Factor; Анцестим.

N-L-Methionyl-1–165-haematopoietic cell growth factor KL (human clone V19.8:hSCF162), dimer.

CAS — 163545-26-4.

ATC — L03AA12.

ATC Vet — QL03AA12.

UNII — PYB4Q6JG41.

Uses and Administration

Ancestim is a recombinant human stem cell factor. It is used with filgrastim (p. 1151.3) to mobilise peripheral blood progenitor cells that are to be collected by apheresis harvest and used for autologous transplantation. The dose of ancestim is 20 micrograms/kg daily by subcutaneous injection; the injections of ancestim and filgrastim must be given at separate sites.

References.

1. Chin-Yee IH, *et al.* Optimising parameters for peripheral blood leukapheresis after r-metHuG-CSF (filgrastim) and r-metHuSCF (ancestim) in patients with multiple myeloma: a temporal analysis of CD34(+) absolute counts and subsets. *Bone Marrow Transplant* 2002; **30:** 851–60.
2. Prosper F, *et al.* Mobilization of peripheral blood progenitor cells with a combination of cyclophosphamide, r-metHuSCF and filgrastim in patients with breast cancer previously treated with chemotherapy. *Leukemia* 2003; **17:** 437–41.
3. To LB, *et al.* Successful mobilization of peripheral blood stem cells after addition of ancestim (stem cell factor) in patients who had failed a prior mobilization with filgrastim (granulocyte colony-stimulating factor) alone or with chemotherapy plus filgrastim. *Bone Marrow Transplant* 2003; **31:** 371–8.
4. da Silva MG, *et al.* Ancestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior insufficient PBPC collection. *Bone Marrow Transplant* 2004; **34:** 683–91.

Adverse Effects and Precautions

Injection site reactions commonly occur with the use of ancestim. Other skin reactions, including pruritus, rash, and urticaria, are less frequent. Systemic hypersensitivity reactions are also common and may be life-threatening. Premedication with antihistamines (both H_1- and H_2-antagonists) and an inhaled beta$_2$ agonist bronchodilator should be used, and the patient observed for at least an hour after ancestim is given. Tachycardia and respiratory symptoms including pharyngitis, dyspnoea, and cough, have also been reported.

Ancestim should not be given in the period from 24 hours before to 24 hours after a dose of cytotoxic chemotherapy or radiotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Stemgen; ***Canad.***: Stemgen; ***NZ***: Stemgen.

Antithrombin III *(BAN, rINN)*

Antithrombin III Human; Antithrombine III; Antithrombinum III; Antitrombiini III; Antitrombin III; Antitrombina III; Antitrombina III humana; Antytrombina III; AT-III; Cofactor I de la heparina; Heparin Cofactor; Heparin Cofactor I; Major Antithrombin; Антитромбин III.

CAS — 52014-67-2.

ATC — B01AB02.

ATC Vet — QB01AB02.

UNII — T0LTO7L82X.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Human Antithrombin III Concentrate; Antithrombinum III Humanum Densatum). A preparation of a glycoprotein fraction obtained from human plasma that inactivates thrombin in the presence of an excess of heparin. The plasma is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, distributed into sterile containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or in an atmosphere of inert gas. No antimicrobial preservative is added but a suitable stabiliser (such as albumin) is permitted. When reconstituted in the volume of solvent stated on the label, the resulting solution contains not less than 25 international units of antithrombin III per mL.

A white or almost white, hygroscopic, friable solid or powder. Store in airtight containers. Protect from light.

USP 36: (Antithrombin III Human). A glycoprotein, which is the major inhibitor of thrombin and other activated clotting factors, including factors IX, X, XI, and XII, and the cofactor through which heparin exerts its effect. It is obtained from human plasma of healthy donors who must, as far as can be ascertained, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. The method of manufacturing includes steps that have been shown to remove or inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, filled aseptically into its final, sterile containers, and immediately frozen. It is then freeze-dried, and the containers are closed under vacuum. No antimicrobial preservative is added at any stage of production. When reconstituted in the recommended volume of diluent, the pH is between 6.0 and 7.5, and the potency is not less than 25 USP units of antithrombin III per mL.

Store at a temperature of 2 degrees to 8 degrees, excursions permitted up to 25 degrees. Protect from light.

Antithrombin Alfa *(USAN, rINN)*

Antithrombine Alfa; Antithrombinum Alfa; Antitrombina alfa; Human Antithrombin III from the milk of transgenic goats (glycoform alfa); Recombinant Human Antithrombin; Антитромбин Альфа.

CAS — 84720-88-7.
UNII — AWV6I5L6H2.

Units

The potency of antithrombin III is expressed in international units and preparations may be assayed using the second International Standard for antithrombin concentrate (1997); each ampoule contains 4.7 international units of functional activity and 5.1 international units of antigenic activity.

One USP unit is described as the amount of antithrombin III that forms a complex with 1 unit of thrombin at 25 degrees in the presence of heparin at a pH of 8.4. Since assays of antithrombin III are carried out at 37 degrees, it is unclear whether USP units and international units are precisely equivalent, but in practice US preparations, like those elsewhere, appear to have their potency defined in international units.

The potency of antithrombin alfa is also expressed in international units.

Uses and Administration

Antithrombin III is a protein in plasma; it is the major endogenous inhibitor of thrombin and other activated clotting factors including factors IX, X, XI, and XII (p. 1124.3), and is the cofactor through which heparin (p. 1397.1) exerts its effect. Genetic and acquired deficiency of antithrombin III occurs and is associated with susceptibility to thromboembolic disorders.

Human plasma-derived antithrombin III is given intravenously to patients with antithrombin III deficiency in the treatment of thromboembolism and for prophylaxis associated with surgical and obstetric procedures. The aim of therapy is to restore plasma-antithrombin III concentrations to normal levels; the initial loading dose may be calculated to achieve 120% of normal, with maintenance doses aimed at concentrations between 80 and 120%. The dose, frequency, and duration of therapy are individualised for each patient taking into account the patient's pretreatment concentration and presence of active coagulation.

Antithrombin alfa is used similarly in the prophylaxis of venous thromboembolism in surgical and obstetric patients with congenital antithrombin III deficiency.

References.
1. Bucur SZ, *et al*. Uses of antithrombin III concentrate in congenital and acquired deficiency states. *Transfusion* 1998; **38:** 481–98.
2. Roemisch J, *et al*. Antithrombin: a new look at the actions of a serine protease inhibitor. *Blood Coag Fibrinol* 2002; **13:** 657–70.
3. Konkle BA, *et al*. Use of recombinant human antithrombin in patients with congenital antithrombin deficiency undergoing surgical procedures. *Transfusion* 2003; **43:** 390–4.

Septicaemia. Antithrombin III has been used in septicaemia (p. 203.2) in an attempt to manage the pro-coagulant state that occurs. Initial small studies reported a reduction in mortality[1] but a large controlled study[2] (KyberSept) found that treatment with antithrombin III had no effect on 28-day mortality. A further small observational study and meta-analysis also found no benefit from the use of antithrombin III in septicaemia.[3] These studies had used antithrombin III for less than 7 days, and a small study[4] in surgical patients with septicaemia found that 14 days of treatment with antithrombin III did improve measures of coagulation and fibrinolysis, the changes being most evident in the second week of therapy. However, the study was not large enough to test effects on mortality. Subsequent analysis of data from the KyberSept study appeared to show that 28-day mortality was in fact reduced in patients who had not been given heparin as well as antithrombin III;[5] combined use increased the risk of bleeding and apparently decreased the benefits of treatment with antithrombin III.

1. Eisele B, *et al*. Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 1998; **24:** 663–72.
2. Warren BL, *et al*. KyberSept Trial Study Group. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286:** 1869–78. Correction. *ibid.* 2002; **287:** 192.
3. Messori A, *et al*. Antithrombin III in patients admitted to intensive care units: a multicenter observational study. *Crit Care* 2002; **6:** 447–51.
4. Hoffmann JN, *et al*. Effect of long-term and high-dose antithrombin supplementation on coagulation and fibrinolysis in patients with severe sepsis. *Crit Care Med* 2004; **32:** 1851–9.
5. Hoffmann JN, *et al*. The KyberSept Investigators. Benefit/risk profile of high-dose antithrombin in patients with severe sepsis treated with and without concomitant heparin. *Thromb Haemost* 2006; **95:** 850–6.

Veno-occlusive disease. There is some evidence[1] from case reports and small studies that antithrombin III may have a beneficial effect on veno-occlusive disease associated with haematopoietic stem cell transplantation (p. 1937.1).

1. Ibrahim RB, *et al*. Anti-thrombin III in the management of hematopoietic stem-cell transplantation–associated toxicity. *Ann Pharmacother* 2004; **38:** 1053–9.

Adverse Effects and Precautions

Adverse effects of antithrombin III include flushing, headache, dizziness, chest tightness, nausea, a foul taste in the mouth, chills, and cramps. These can be controlled by slowing or stopping the infusion. Allergic reactions occur rarely. Injection site oozing and haematoma formation can occur, and haemorrhage (intra-abdominal, haemarthrosis, haematuria, and postprocedural) has been reported with the use of antithrombin alfa.

Human plasma-derived antithrombin III preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60 degrees, have reduced the risk of transmitting some viral infections. Antithrombin alfa is produced in the milk of transgenic goats, and should not be used in patients who are hypersensitive to goat proteins or goat milk components.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies antithrombin III as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Concomitant use of heparin and antithrombin III increases the risk of bleeding. Clinical effect and coagulation tests must be monitored and the dose of heparin adjusted as appropriate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anbinex; Kybernin P; ***Austral.***: Thrombotrol-VF; ***Austria***: Atenativ; Kybernin P; Thrombhibin†; ***Braz.***: Kybernin P; ***Canad.***: Thrombate; ***Cz.***: Anbinex; Atenativ; ATryn; Kybernin P; ***Denm.***: Atenativ; ATryn†; ***Fin.***: Atenativ; ***Fr.***: Aclotine; ***Ger.***: Anbinex; AT III; Atenativ; Kybernin; ***Gr.***: Atenativ; Atryn; Kybernin P; ***Hung.***: Atenativ; Kybernin P; ***Indon.***: Kybernin P; ***Israel***: Anbinex; ***Ital.***: Anbinex; Atenativ; Kybernin P; ***Jpn***: Neuart; ***Mex.***: Atend; Octati; ***Neth.***: Atenativ; ATryn; ***Norw.***: Atenativ; ***NZ***: Thrombotrol-VF; ***Pol.***: ATryn; ***Port.***: Anbinex; Atenativ; ATryn; Kybernin P; ***Singapore***: Anbinex; ***Spain***: Anbinex; Atenativ; Kybernin P; ***Swed.***: Atenativ; ATryn†; ***Switz.***: Atenativ; Kybernin; ***Turk.***: Anbin; Kybernin P; ***UK***: ATryn; ***USA***: ATryn; Thrombate III.

Pharmacopoeial Preparations
Ph. Eur.: Human Antithrombin III Concentrate;
USP 36: Antithrombin III Human.

Aprotinin *(BAN, USAN, rINN)*

Aprotiniini; Aprotinina; Aprotininas; Aprotinine; Aprotininum; Aprotynina; Bayer A-128; Riker 52G; RP-9921; Апротинин.
CAS — 9087-70-1.
ATC — B02AB01.
ATC Vet — QB02AB01.
UNII — 04XPW8C0FL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Aprotinin). A polypeptide consisting of 58 amino acids that inhibits the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It contains not less than 3 Ph. Eur. units/mg calculated with reference to the dried substance. An almost white, hygroscopic powder. Soluble in water and in isotonic solutions; practically insoluble in organic solvents. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Aprotinin Concentrated Solution). A solution of aprotinin containing not less than 15 Ph. Eur. units/mL. A clear colourless solution. Store in airtight containers. Protect from light.

USP 36: (Aprotinin). A polypeptide consisting of a chain of 58 amino acid residues, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It is obtained from bovine tissues and purified by a suitable process, and is stored as a bulk solution or lyophilised powder. Its potency is not less than 3 USP units/mg calculated with reference to the dried substance.

The lyophilised powder should be stored in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light. The bulk solution should be stored in airtight containers at a temperature not exceeding 25 degrees. Do not allow to freeze.

Incompatibility. Aprotinin is reported to be incompatible with corticosteroids, heparin, tetracyclines, and nutrient solutions containing amino acids or fat emulsions.

Units

The potency of aprotinin is expressed in terms of kallikrein (kallidinogenase) inactivator units (KIU) or of trypsin inactivation (Ph. Eur. units). One KIU is contained in 140 nanograms of aprotinin. One Ph. Eur. and one USP unit is equivalent to about 1800 KIU.

Potency has also been expressed in terms of plasmin inactivation (antiplasmin units).

Uses and Administration

Aprotinin is a haemostatic. It is an inhibitor of proteolytic enzymes including chymotrypsin, kallikrein (kallidinogenase), plasmin, and trypsin.

Aprotinin has been used to reduce blood loss and transfusion requirements in patients at increased risk of major blood loss during coronary artery bypass graft surgery with cardiopulmonary bypass. The marketing of aprotinin injection was suspended worldwide because of a possible increased risk of death associated with its use in cardiac surgery (see Haemorrhagic Disorders, below). However, in some countries, such as Canada, the resumption of marketing has been permitted, and it may be available in other countries, such as the USA, for investigational use using a special access protocol. It has also been used in the treatment of hyperfibrinolytic haemorrhage associated with raised plasma concentrations of plasmin. Aprotinin is applied topically as a component of fibrin glues (p. 1151.2).

It is recommended that because of the risk of hypersensitivity reactions an intravenous test dose of 10 000 KIU should be given to all patients at least 10 minutes before the therapeutic dose. All intravenous doses of aprotinin should be given through a central venous line.

In **coronary artery bypass graft surgery**, the test dose is followed by a loading dose given with the patient in a supine position, after induction of anaesthesia but before incision; 2 000 000 KIU is given intravenously over 20 to 30 minutes. The loading dose is followed by a continuous infusion of 500 000 KIU/hour until the end of the operation. An additional dose of 2 000 000 KIU is added to the prime volume of the extracorporeal circuit. The total amount of aprotinin used is usually no more than 7 000 000 KIU. A regimen using half the dose for loading, maintenance, and to prime the circuit, has been used in low-risk patients.

Haemorrhagic disorders. Aprotinin has been used in the treatment of life-threatening haemorrhage caused by raised plasma concentrations of plasmin. It has also been used in the treatment of severe bleeding arising from overdosage with thrombolytics (see Treatment of Adverse Effects under Streptokinase, p. 1506.3).

Aprotinin has been used to reduce blood loss in patients undergoing surgery, particularly cardiac surgery involving cardiopulmonary bypass. This bypass procedure is complicated by a postperfusion syndrome that includes impairment of haemostasis and pulmonary dysfunction. Contributing factors include ischaemia reperfusion, surgical trauma, endotoxaemia, and blood contact with the artificial surfaces of the bypass apparatus. This syndrome has been interpreted as a 'whole body inflammatory response', and the beneficial effect of aprotinin has been attributed to an attenuation of this response. As well as its inhibitory effect on fibrinolysis, aprotinin is thought to have effects on the complement system, cytokines, neutrophil activation, and platelet function.[1,2] Aprotinin has reduced blood loss and transfusion requirements in patients undergoing both primary and repeat cardiac surgery.[1,3-6] The usual dosage regimen (as given in Uses and Administration, above) and low-dosage regimens (50% of the usual dose) appear to be equally effective, but regimens that use aprotinin only as a pump prime dose appear to be less effective.[1,6]

The safety of aprotinin in cardiac surgery has been questioned, however, because of the results of two observational studies. One analysis[7] of patient outcome after the use of aminocaproic acid, aprotinin, tranexamic acid, or no treatment, found that although the three drugs had reduced blood loss to a similar extent, aprotinin was associated with an increased risk of cardiovascular and cerebrovascular events (myocardial infarction, heart failure, stroke, or encephalopathy) and renal failure. Observational follow-up also found that aprotinin, but not aminocaproic acid or tranexamic acid, was associated with an increased risk of death in the 5 years after surgery.[8] In another study[9] that compared data from patients who had received either aprotinin or tranexamic acid, there was an increased risk of renal dysfunction associated with aprotinin, particularly in patients with abnormal pre-operative renal function. In response to these studies, the FDA recommended[10] that patients receiving aprotinin should be carefully monitored, and that physicians should consider limiting its use to situations where the clinical benefit of reduced blood loss is essential and outweighs the potential risks.

The concerns raised by these studies and the FDA's recommendation prompted further analysis of data relating

to the effects of aprotinin. A meta-analysis[11] that included studies in different types of surgery, although the majority were in cardiac surgery, found no increased risk of death, cardiovascular events, or renal failure. However, because the reporting of renal function was lacking for many studies, and therefore a potential for bias, the authors were not confident that a modest increase in risk could be ruled out. Another meta-analysis[12] that was limited to studies in cardiac surgery also found no increased risk of death or cardiovascular events with aprotinin. There was also no increase in the risk of dialysis-dependent renal failure, but high-dose aprotinin did increase the risk of renal dysfunction, compared with placebo. Two large retrospective studies, which attempted to account for confounding variables, were also undertaken in cohorts of patients who had undergone coronary artery bypass graft surgery. One study found that, compared with aminocaproic acid, aprotinin increased the risk of in-hospital death.[13] The other found increased inpatient renal dysfunction, and death at 30 days and 1 year, in patients given aprotinin compared with aminocaproic acid or no antifibrinolytic therapy. Survival estimates also found an association between aprotinin use and reduced survival for up to 10 years after surgery.[14]

Preliminary data analysis from a randomised study (BART) also found an increased risk of death with aprotinin, compared with aminocaproic acid or tranexamic acid, and in November 2007, authorities such as the FDA[15] and EMEA[16] recommended that marketing of aprotinin injection be suspended. The BART study,[17] which was stopped early, included different types of high-risk cardiac surgery patients requiring cardiopulmonary bypass. Despite evidence of a modest reduction in the risk of massive bleeding, there was a strong and consistently negative mortality trend associated with aprotinin. The rate of death from any cause at 30 days was 6% in the aprotinin group, which equated to a relative risk of 1.53 (95% confidence interval, 1.06 to 2.22) compared with the combined results from patients given aminocaproic acid or tranexamic acid. In May 2008 the FDA confirmed that, in the USA, aprotinin injection would only be available for investigational use according to a special treatment protocol, for patients undergoing coronary artery bypass graft surgery requiring cardiopulmonary bypass.[18]

One of the meta-analyses[11] was updated in 2011 to include the results of subsequent studies including BART. This review[6] of randomised controlled studies concluded that although aprotinin was more effective than aminocaproic acid and tranexamic acid at minimising blood loss in cardiac surgery, it was associated with an increased risk of death. However, most of the data contributing to this risk was from the BART study. There was no significant increase in risk of myocardial infarction, stroke, other thrombotic events, or renal dysfunction. Around the same time, Canadian[19] and European[20] regulatory authorities also reviewed aprotinin information, concluding that the BART results were unreliable[20] and could not confirm an association between aprotinin and increased mortality.[19] Marketing suspension in Canada was lifted in 2011,[19] and a similar recommendation to resume marketing was made in Europe in 2012;[20] however, it was limited to patients at risk of major blood loss during isolated cardiopulmonary bypass surgery. Both regulatory authorities also advised on the importance of adequate anticoagulation with heparin during aprotinin treatment.

Aprotinin has been used to reduce transfusion requirements during liver transplantation, by its effect on intra-operative hyperfibrinolysis.[21,22] However, concerns about an increased risk of thromboembolism in these patients has been raised.[23] A systematic review[24] of 23 studies using antifibrinolytic drugs, 18 of which used aprotinin, found no evidence of an increased risk of thromboembolic complications in liver transplant patients, but noted that the studies were underpowered and that identification of subgroups of patients at risk may have been missed. Aprotinin has also been used to reduce transfusion requirements during orthopaedic surgery.[25]

1. Peters DC, Noble S. Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. *Drugs* 1999; **57** 233–60.
2. Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg* 2001; **71:** 745–54.
3. Bidstrup BP, *et al.* Aprotinin therapy in cardiac operations: a report on use in 41 cardiac centers in the United Kingdom. *Ann Thorac Surg* 1993; **55:** 971–6.
4. Laupacis A, Fergusson D. Drugs to minimize perioperative bloodloss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anesth Analg* 1997; **85:** 1258–67.
5. Sedrakyan A, *et al.* Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004; **128:** 442–8.
6. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 02/10/13).
7. Mangano DT, *et al.* The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; **354:** 353–65.
8. Mangano DT, *et al.* Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007; **297:** 471–9.
9. Karkouti K, *et al.* A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; **46:** 327–38.
10. FDA. FDA issues Public Health Advisory for Trasylol (issued 8th February, 2006). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108592.htm (accessed 13/08/10)
11. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).
12. Brown JR, *et al.* Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; **115:** 2801–13.
13. Schneeweiss S, *et al.* Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med* 2008; **358:** 771–83.
14. Shaw AD, *et al.* The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med* 2008; **358:** 784–93.
15. FDA. FDA requests marketing suspension of Trasylol (issued 5th November, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109021.htm (accessed 13/08/10)
16. EMEA. European Medicines Agency recommends suspension of marketing authorisation of aprotinin-containing medicines for systemic use (issued 21st November, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015517.pdf (accessed 13/08/10)
17. Fergusson DA, *et al.* The BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358:** 2319–31. Correction. *ibid.* 2010; **363:** 1290.
18. FDA. Manufacturer removes remaining stocks of Trasylol: access limited to investigational use (issued 14th May, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116895.htm (accessed 13/08/10)
19. Bayer Healthcare. Notice to hospitals: Health Canada endorsed important safety information on Trasylol (aprotinin) (issued 19 September, 2011). Available at: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/14666a-eng.php (accessed 02/10/13)
20. EMA. European Medicines Agency recommends lifting suspension of aprotinin: review finds that benefits of all antifibrinolytic medicines outweigh risks in restricted range of indications (issued 17 February, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/02/WC500122914.pdf (accessed 02/10/13)
21. Porte RJ, *et al.* Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. *Lancet* 2000; **355:** 1303–9.
22. Rentoul TM, *et al.* The effect of aprotinin on transfusion requirements in pediatric orthotopic liver transplantation. *Pediatr Transplant* 2003; **7:** 142–8.
23. Lentschener C, *et al.* A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005; **100:** 1248–55.
24. Molenaar IQ, *et al.* Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant* 2007; **7:** 185–94.
25. Kokoszka A, *et al.* Evidence-based review of the role of aprotinin in blood conservation during orthopaedic surgery. *J Bone Joint Surg Am* 2005; **87-A:** 1129–36.

Pancreatitis. Aprotinin has been tried in the management of pancreatitis (p. 2580.2) because of the postulated role of proteolytic enzymes in this condition. However, results have been largely disappointing.

Adverse Effects and Precautions

Aprotinin is usually well tolerated. Local thrombophlebitis can occur. Adverse effects including bronchospasm, hypotension, cardiac arrhythmias, gastrointestinal disturbances, and rashes are considered to be hypersensitivity reactions; anaphylaxis, including fatalities, has occurred. The use of aprotinin is contra-indicated for 12 months after a previous exposure because of the increased risk of anaphylaxis during that time. A test dose is recommended for all patients and the use of prophylactic histamine antagonists may be considered; a hypersensitivity reaction to the therapeutic dose of aprotinin can still occur even after an uneventful test dose. There have been reports of renal dysfunction and reversible renal failure in patients given aprotinin during open-heart surgery with extracorporeal circulation; the risk may be increased in patients with pre-existing renal impairment or risk factors for altered renal function. For further details of an increased risk of cardiovascular and cerebrovascular events, renal failure, and death in patients undergoing surgery, and suspension of the marketing of aprotinin, see Haemorrhagic Disorders under Uses and Administration, p. 1133.3.

Disseminated intravascular coagulation. Fatal disseminated intravascular coagulation has been reported in a patient after the use of intraoperative autotransfusion and aprotinin during surgery.[1] Activation of the clotting system occurs during autotransfusion although this usually causes no systemic adverse effects. While there were other possible causes, it was suggested that aprotinin could have contributed to deposition of fibrin microthrombi in the microvasculature and prevented subsequent fibrinolysis.

1. Milne AA, *et al.* Disseminated intravascular coagulation after aortic aneurysm repair, intraoperative salvage autotransfusion, and aprotinin. *Lancet* 1994; **344:** 470–1.

Effects on coagulation tests. Aprotinin prolongs both the activated partial thromboplastin time (APTT) and activated clotting time (ACT), depending on the ACT activation method used. However, aprotinin is not a heparin-sparing drug, and its effects on these tests may result in an overestimation in the degree of anticoagulation and subsequent underdosing of heparin. In patients undergoing cardiopulmonary bypass surgery, APTT should not be used alone to monitor coagulation parameters. ACT should also be used, taking into consideration the effect of aprotinin on the test in use; for example, a minimal celite-ACT of 750 seconds, or kaolin-ACT of 480 seconds, independent of the effects of haemodilution and hypothermia, have been recommended. Also, a fixed-dose heparin regimen or heparin-protamine titration method are suggested. Patients may require additional heparin during extended extracorporeal circulation, and protamine reversal of heparin should be based on a fixed ratio to the amount of heparin given, or be guided by protamine titration.

It should also be noted that aprotinin injection and heparin injection are pharmaceutically incompatible.

Effects on the respiratory system. Acute respiratory distress syndrome developed in a 24-year-old male 2 hours after the start of an intravenous infusion of aprotinin for bleeding after tonsillectomy.[1] Mechanical ventilation was required for 4 days.

1. Vucicevic Z, Suskovic T. Acute respiratory distress syndrome after aprotinin infusion. *Ann Pharmacother* 1997; **31:** 429–32.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, can occur with the use of aprotinin both on primary and secondary exposure. In a study[1] of 248 re-exposures to aprotinin in 240 patients undergoing cardiac surgery, there were 7 cases of anaphylactic reactions ranging from mild to severe with a higher incidence of reactions occurring in those patients re-exposed within 6 months of the previous dose. A review[2] of 124 reported reactions in 122 patients also found that reactions ranged from mild to severe, and that about half were life-threatening and 11 were fatal. The risk of reaction was greatest with re-exposure to aprotinin as this had been the situation in 80% of the cases, although there were 19 cases associated with the first use of aprotinin. The average risk of anaphylaxis was estimated to be 2.8% in re-exposed patients. Most reactions occurred within 6 months of previous exposure, and the risk was greatest in the first 3 months. Various diagnostic tests have been tried in an attempt to predict hypersensitivity risk. Aprotinin-specific serum-IgG was reported to be detectable in about 50% of patients who had received only one aprotinin treatment, but other tests such as pre-operative skin testing were not found to be reliable.

Several measures have been suggested in order to reduce the risk of hypersensitivity reactions to aprotinin, including the use of an intravenous test dose in all patients, but it must be noted that these also have the potential to trigger a reaction.[1] For patients who have previously received aprotinin it has been recommended that re-exposure should be avoided for at least 6 months,[1,2] that aprotinin-specific antibody screening should be done,[2] and that prophylactic histamine H_1- and H_2-antagonists should be given to ameliorate severe anaphylactic reactions[1] although there are reports of reactions occurring despite antihistamine and corticosteroid prophylaxis.[2] It has also been suggested that in cardiac surgery, aprotinin should only be given when cardiopulmonary bypass is available to assist resuscitation.[1,2]

There have also been rare reports of hypersensitivity reactions on re-exposure to aprotinin used locally as a component of fibrin sealant.[3-5] In one fatal case[4] the previous exposure to fibrin sealant had been 5 years before.

1. Dietrich W, *et al.* Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997;**113:** 194–201.
2. Beierlein W, *et al.* Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; **79:** 741–8.
3. Beierlein W, *et al.* An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000; **40:** 302–5.
4. Oswald A-M, *et al.* Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; **99:** 762–3.
5. Schievink WI, *et al.* Anaphylactic reactions to fibrin sealant injection for spontaneous spinal CSF leaks. *Neurology* 2008; **70:** 885–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aprotinin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Heparin. For comment on the use of aprotinin with heparin, see Effects on Coagulation Tests, above.

Neuromuscular blockers. For reports of apnoea when aprotinin was used with neuromuscular blockers, see p. 2032.2.

Retinoids. Aprotinin should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p. 1727.1).

Pharmacokinetics

Aprotinin, being a polypeptide, is inactivated in the gastrointestinal tract. After intravenous use, it is excreted in the urine as inactive degradation products. The terminal elimination half-life is about 5 to 10 hours.

Renal impairment. The terminal elimination half-life of aprotinin was reported as 13.3 and 14.9 hours, respectively, in two patients with chronic renal impairment given aprotinin by intravenous infusion over 30 minutes.[1] A study[2] of cardiac surgical patients undergoing cardiopulmonary bypass also found that aprotinin clearance was reduced in those with renal impairment. The elimination half-life was about 20 hours in patients with end stage renal disease compared with about 8 hours in those with creatinine clearance greater than 50 mL/min.

1. Müller FO, *et al.* Pharmacokinetics of aprotinin in two patients with chronic renal impairment. *Br J Clin Pharmacol* 1996; **41:** 619–20.
2. O'Connor CJ, *et al.* The impact of renal dysfunction on aprotinin pharmacokinetics during cardiopulmonary bypass. *Anesth Analg* 1999; **89:** 1101–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Quagu-Test; Rivilina; ***Belg.***: Trasylol†; ***Braz.***: Trasylol†; ***Canad.***: Trasylol; ***China***: Hetailin (赫泰林); Yi Mei Tai (壹枚泰); ***Denm.***: Trasylol; ***India***: Aprogen; Apronin; Aprostat; Aprotec; Aprotin; Haemaprot; Haemoprot; Kallistat; ***Indon.***: Trasylol†; ***Israel***: Protosol; ***Philipp.***: Trasylol; ***Pol.***: Trasylol; ***Rus.***: Aprotex (Апротекс); Contrykal (Контрикал); Gordox (Гордокс); Ingitril (Ингитрил); Vero-Narcap (Веронаркап); ***S.Afr.***: Trasylol; ***Singapore***: Trasylol; ***Switz.***: Trasylol; ***Turk.***: Trasylol; ***Ukr.***: Contriven (Контривен); Contrycal (Контрикал); Gordox (Гордокс); Trasylol (Трасилол)†; ***Venez.***: Trasylol.

Multi-ingredient Preparations. ***Arg.***: Beriplast P; Lacrimax†; Maxus; Optilac; Tissucol; ***Austral.***: Tisseel Duo†; ***Austria***: Beriplast; Tisseel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Artiss; Tissucol Duo; Tissucol Kit; ***Braz.***: Beriplast P; ***Canad.***: Artiss; Tisseel; ***Chile***: Beriplast P†; ***Cz.***: Artiss; Tisseel; Tissucol; ***Denm.***: Artiss; Tisseel Duo Quick; ***Fin.***: Artiss; Tisseel Duo Quick; Tisseel; ***Fr.***: Artiss; Beriplast; Tissucol; ***Ger.***: Artiss; Beriplast; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Beriplast; Tisseel; ***Hong Kong***: Beriplast P; TachoComb; Tisseel; ***Hung.***: Beriplast P; Tissucol-Kit; ***Indon.***: Beriplast; ***Irl.***: Artiss; Tisseel; ***Israel***: Beriplast†; Tisseel†; ***Ital.***: Beriplast; Tissucol; ***Jpn***: Bolheal; ***Mex.***: Beriplast P; ***Neth.***: Artiss; Beriplast P; Tisseel; Tissucol Duo; Tissucol; ***Norw.***: Artiss; Tisseel; ***NZ***: Tisseel Duo; ***Pol.***: Beriplast; ***Port.***: Tissucol Duo†; ***Rus.***: TachoComb (ТахоКомб); Tissucol Kit (Тиссукол Кит); ***Singapore***: TachoComb; ***Spain***: Artiss; Beriplast P Combi; Tissucol Duo; ***Swed.***: Artiss; Tisseel Duo Quick; ***Switz.***: Artiss; Beriplast P; Tisseel; Tissucol Duo S†; Tissucol†; ***Thai.***: Tisseel; ***Turk.***: Beriplast P; Tisseel VH; ***UK***: Tisseel; ***USA***: Artiss; Tisseel.

Pharmacopoeial Preparations
USP 36: Aprotinin Injection.

Batroxobin *(rINN)*

Batroxobina; Batroxobine; Batroxobinum; Батроксобин.
CAS — 9039-61-6 (batroxobin); 9001-13-2 (haemocoagulase).
ATC — B02BX03.
ATC Vet — QB02BX03.
UNII — 47RYF40GA9.

Profile

Batroxobin is an enzyme obtained from the venom of the viper *Bothrops atrox*. It has also been obtained from *Bothrops moojeni* and a similar preparation is derived from *Bothrops jararaca*.

Batroxobin is reported to act on fibrinogen to produce a fibrin monomer that can be converted by thrombin to a fibrin clot. It is used both as a haemostatic and, in larger doses, to induce a hypofibrinogen state in the management of thromboembolic disorders. When used as a haemostatic it is usually given with a factor-X activator; such a combined preparation is known as haemocoagulase (hemocoagulase). Batroxobin has been given parenterally or by local application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bang Ting (邦亭); Reptilase (立芷雪); Su Le Juan (速乐涓); Su Ling (苏灵); ***India***: Botroclot; Botropase; Colase; Reptilase.

Blood ⊗

Blod; Bloed; Blut; Sang; Sangre; Sangue; Sanguis; Vér; Veri; Кровь.
UNII — 43MX67MYM9.

Uses and Administration

Blood is a complex fluid with many functions including the maintenance of hydration of the tissues, maintenance of body temperature, and the transport within the body of gases, ions, nutrients, hormones, enzymes, antibodies, waste products of metabolism, and drugs.

The main components of blood are plasma, red blood cells (erythrocytes), white blood cells (leucocytes), and platelets (for further information on different blood cells and their formation, and average counts in adults, see Haematopoiesis, p. 1121.1). Serum is the fluid which remains once blood or plasma has clotted; it is, in effect, plasma with fibrinogen removed.

Whole blood is used as a source of red cell concentrates, clotting factors, platelets, plasma and plasma fractions, and immunoglobulins, each of which has specific indications for use. Because of the risks involved in transfusing whole blood and the need for economy in its use, the appropriate blood component should be used whenever possible.

Whole blood may be used where replacement of plasma proteins as well as red blood cells is needed, for example after acute blood loss during surgery or severe haemorrhage. It may also be used to supplement the circulation during cardiac bypass surgery.

The amount of whole blood transfused and the rate at which it is given depend upon the patient's age and general condition, upon the state of their circulatory system, and upon the therapeutic indication for transfusion.

The expression 'unit of blood' generally represents a volume of about 510 mL, including anticoagulant. For blood preparations a unit generally refers to the quantity of a blood component obtained from 1 unit of whole blood. Specific units of activity are used for some blood components.

The haemoglobin concentration of the blood of the average adult is raised by about 1 g per 100 mL by the transfusion of 1 unit of whole blood.

Reviews and guidelines for the use of blood and blood components.

1. Goodnough LT, *et al.* Transfusion medicine: blood transfusion. *N Engl J Med* 1999; **340:** 438–47.
2. WHO. *The clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns.* Geneva: WHO, 2001. Also available as *The clinical use of blood handbook* at: http://whqlibdoc.who.int/publications/2001/9241545399.pdf (accessed 27/10/5)
3. Australian Red Cross Blood Service. *Transfusion medicine manual.* Available at: http://www.manual.transfusion.com.au/Home.aspx (accessed 29/08/08)
4. British Committee for Standards in Haematology Transfusion Task Force. Transfusion guidelines for neonates and older children. *Br J Haematol* 2004; **124:** 433–53. Correction. *ibid.* 2007; **136:** 514–16. Also available at: http://www.bcshguidelines.com/pdf/Neonates_124_4_2004.pdf (accessed 27/10/05)
5. British Committee for Standards in Haematology. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; **135:** 634–41.
6. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/index.aspx?Publication=HTM (accessed 30/11/09)
7. American Red Cross. Practice guidelines for blood transfusion: a compilation from recent peer-reviewed literature, second edition (issued April 2007). Available at: http://www.redcross.org/www-files/Documents/WorkingWiththeRedCross/practiceguidelinesforbloodtrans.pdf (accessed 13/08/10)
8. Council of Europe. *Guide to the preparation, use and quality assurance of blood components.* 14th ed. Strasbourg: Council of Europe Publishing, 2008.
9. ContrerasM, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009.

Autologous blood transfusion. Reviews and guidelines have been published on autologous blood transfusion, a procedure where a patient acts as their own blood donor, the blood usually being collected shortly before elective surgery or salvaged during the surgical procedure.[1-6]

1. British Committee for Standards in Haematology Blood Transfusion Task Force. Guidelines for autologous transfusion II: perioperative haemodilution and cell salvage. *Br J Anaesth* 1997; **78:** 768–71. Also available at: http://www.bcshguidelines.com/pdf/bja768.pdf (accessed 27/10/05)
2. Goodnough LT, *et al.* Transfusion medicine: blood conservation. *N Engl J Med* 1999; **340:** 525–33.
3. Vanderlinde ES, *et al.* Autologous transfusion. *BMJ* 2002; **324:** 772–5.
4. Carless P, *et al.* Autologous transfusion techniques: a systematic review of their efficacy. *Transfus Med* 2004; **14:** 123–44.
5. British Committee for Standards in Haematology, Transfusion Task Force. Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion. *Transfus Med* 2007; **17:** 354–65. Also available at: http://www.bcshguidelines.com/pdf/alt_allogeneic_blood_transfusion.pdf (accessed 09/06/08)
6. Thomas D, Hunt B. Alternatives to allogeneic blood transfusion. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 89–94.

Adverse Effects

The rapid transfusion of large volumes of whole blood may overload the circulation and cause pulmonary oedema. Transfusion of very large volumes of citrated blood can lead to hypocalcaemia, although this is not usually a problem unless there is hepatic impairment or hypothermia. Hyperkalaemia may occur but on its own is rarely clinically significant. Hypothermia may result from rapid transfusion of large volumes of cooled blood and may, combined with hypocalcaemia, hyperkalaemia, and resultant acidosis, lead to cardiotoxicity. Disseminated intravascular coagulation may also occur in patients receiving large-volume transfusions. Repeated transfusions of blood, as in thalassaemia, may lead to iron overload.

The transfusion of incompatible blood causes haemolysis, possibly with renal failure. Pyrexia, rigors, and urticaria may be due to antibodies towards blood components. Severe allergic reactions and anaphylaxis can occur. Delayed reactions may occur more than 24 hours after transfusion in patients in whom previous transfusion or pregnancy has induced sensitisation; these reactions are usually mild and manifest as fever, chills, fall in haemoglobin concentration, and haemoglobinuria.

Transmission of infections. The use of blood, blood components, or blood products has been associated with the transmission of viruses, most notably hepatitis B virus and HIV; other reports of transmission include CMV, hepatitis C and possibly other hepatitis viruses, HTLV-I and -II, and the prion causing variant Creutzfeldt-Jakob disease. Transmission of bacterial and parasitic diseases is also possible including syphilis, Chagas' disease, and malaria.

The main methods of minimising the risk of transmission of infection are by rigorous selection of blood donors and by microbiological screening tests. Contamination during collection and processing is minimised by using closed systems and by strict aseptic technique. Treatment of blood products with heat or chemicals can inactivate some organisms including some viruses, in particular HIV-1, but blood and blood components cannot be treated in either of these ways. Patients receiving multiple transfusions of pooled plasma products are at increased risk of contracting infections and can be offered immunological protection, for example hepatitis B vaccine.

Reviews.

1. Regan F, Taylor C. Blood transfusion medicine. *BMJ* 2002; **325:** 143–7.
2. Goodnough LT. Risks of blood transfusion. *Crit Care Med* 2003; **31** (suppl): S678–S686.
3. Pomper GJ, *et al.* Risks of transfusion-transmitted infections: 2003. *Curr Opin Hematol* 2003; **10:** 412–18.
4. Hardy J-F, *et al.* Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anesth* 2004; **51:** 293–310.
5. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/index.aspx?Publication=HTM (accessed 30/11/09)
6. Kitchen AD, Barbara JAJ. Current information on the infectious risks of allogeneic blood transfusion. *Transfus Altern Transfus Med* 2008; **10:** 102–11.
7. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; **113:** 3406–17.
8. Contreras M, Navarrete C. Immunological complications of blood transfusion. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 61–8.
9. Barbara J, Contreras M. Infectious complications of blood transfusion: bacteria and parasites. In: Contreras M. ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 69–73.
10. Barbara J, Contreras M. Infectious complications of blood transfusion: viruses. In: Contreras M. ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 74–8.

Creutzfeldt-Jakob disease. While there is no proof that transmission of classical sporadic Creutzfeldt-Jakob disease by blood or blood products has occurred,[1-3] 4 cases have been reported of highly probable transmission of variant Creutzfeldt-Jakob disease (vCJD) by non-leucodepleted blood transfusion.[3-7] It is recognised that there is a need for further assessment of the potential risk of transmission of vCJD by such products.

Precautionary measures have been implemented in the UK to minimise transmission of vCJD by blood or tissues:[8]

- plasma is imported from outside the UK for fractionation to manufacture plasma derivatives
- leucocytes are removed from donated blood (leucodepletion) as it was thought that this would remove infectivity (however, *animal* studies have shown that this is not the case and that prion concentration in the blood is likely to be reduced by only about 40%[9])
- plasma is imported for clinical use in patients born after January 1996 (this date was chosen because it was considered that foods infected with bovine spongiform encephalopathy had been largely eliminated from the diet by this time[9]) and by July 2005 this had been extended to all patients under the age of 16
- donations of blood, platelets, and live bone are not accepted from donors who themselves have received blood components since 1 January 1980, or from any donors who have received intravenous immunoglobulin

prepared from UK plasma or who have undergone plasma exchange anywhere in the world

Concern at the risk of transmitting Creutzfeldt-Jakob disease by albumin prepared from placental blood has led to restriction on this source of albumin (see Transmission of Infections under Albumin, p. 1131.2).

1. Wilson K, *et al.* Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies. *BMJ* 2000; **321:** 17–19.
2. Dorsey K, *et al.* Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. *Transfusion* 2009; **49:** 977–84.
3. Hewitt P, *et al.* Variant Creutzfeldt-Jakob disease and its impact on the UK blood supply. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 79–82.
4. Llewelyn CA, *et al.* Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004; **363:** 417–21.
5. Peden AH, *et al.* Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; **364:** 527–9.
6. Wroe SJ, *et al.* Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006; **368:** 2061–7.
7. Turner ML, Ludlam CA. An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products. *Br J Haematol* 2009; **144:** 14–23.
8. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/index.aspx?Publication=HTM (accessed 30/11/09)
9. Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products. *Br J Haematol* 2005; **132:** 13–24.

Effects on leucocytes. A study of 50 patients in an intensive care unit found that 45 of them developed leucocytosis after transfusion of packed red blood cells.[1] The leucocytosis, which was accounted for by neutrophils, occurred immediately after transfusion and persisted for 12 hours. A further study[2] of 96 critically ill patients found that leucocytosis commonly occurred in those who were not septic and had received unfiltered packed red cells. Mean white cell counts were increased significantly 2 hours after infusion, remained elevated for about 12 hours, and returned to baseline by 24 hours. In 11 patients who required more than one transfusion, the use of filtered packed red cells was not associated with leucocytosis. Concentrations of interleukin-8 were found to be raised in unfiltered blood after 4 weeks of storage, and were higher in the transfused blood that caused leucocytosis. The authors suggested that cytokines produced by leucocytes in stored blood might be responsible for leucocytosis in recipients of unfiltered packed red cells.

1. Fenwick JC, *et al.* Blood transfusion as a cause of leucocytosis in critically ill patients. *Lancet* 1994; **344:** 855–6.
2. Izbicki G, *et al.* Transfusion-related leukocytosis in critically ill patients. *Crit Care Med* 2004; **32:** 439–42.

Effects on the lungs. A rare but life-threatening complication of transfusion of blood or other plasma-containing products is acute lung injury, often termed transfusion-related acute lung injury (TRALI). Symptoms develop during or within 6 hours of infusion and are those of acute respiratory distress syndrome[1-3] (p. 1599.3). Treatment is the same as for acute respiratory distress of any cause but oxygen exchange usually begins to improve between 24 and 48 hours; if the patient survives there appear to be no long-term sequelae.[1] The presence of HLA-specific antileucocyte antibodies in plasma from multiparous female donors appears to play a role in starting the reaction;[1,3] such antibodies have also been identified in some implicated male donors.[2] Another mechanism, the neutrophil priming hypothesis, proposes that TRALI results from 2 independent events. The first event causes the recipient's neutrophils to be primed and is related to the recipient's condition; in the second event the infused blood product activates the primed neutrophils in the lung, which causes endothelial damage.[2,3]

1. Wallis JP. Transfusion-related acute lung injury (TRALI)—under-diagnosed and under-reported. *Br J Anaesth* 2003; **90:** 573–6.
2. Holness L, *et al.* Fatalities caused by TRALI. *Transfus Med Rev* 2004; **18:** 184–8.
3. Kleinman S, *et al.* Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004; **44:** 1774–89.

Graft-versus-host disease. Acute graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1937.1) has been reported in both immunocompromised and immunocompetent patients after blood transfusion.[1] Symptoms include fever, rash, abnormal liver function tests, diarrhoea, and pronounced leucopenia and pancytopenia. The reaction can be severe and fatal.

High-risk immunocompromised groups include bone marrow transplant recipients, patients with congenital immunodeficiencies, fetuses receiving intra-uterine transfusions, patients with Hodgkin's disease, and patients treated with purine analogue drugs such as fludarabine. Patients at less risk include those with acute leukaemia, non-Hodgkin's lymphoma, solid tumours treated with intensive chemotherapy or radiotherapy, premature infants and those undergoing exchange transfusion, and solid organ transplant recipients.

Immunocompetent patients who share an HLA haplotype with HLA-homozygous blood donors also appear to be at increased risk. Such cases have been reported particularly in Japan, where practices have included the use of transfusions from blood relatives. There is also a high incidence of shared haplotype in the population.

Infusion of products containing viable lymphocytes appears to be responsible. Treatment of graft-versus-host disease associated with transfusion is largely ineffective and patients considered to be at risk should be given products depleted of viable lymphocytes by irradiation. Blood products depleted of leucocytes by filtration still contain a small percentage of viable leucocytes, and this should not be used as the sole method to prevent graft-versus-host disease.

1. Schroeder ML. Transfusion-associated graft-versus-host disease. *Br J Haematol* 2002; **117:** 275–87.

Malignant neoplasms. Perioperative allogeneic blood transfusion may be associated with an increase in the risk of recurrence, and decreased long-term survival, after resection of malignancy. This suggestion was based on retrospective observational studies, and was attributed to immunosuppressant effects of allogeneic blood. Randomised controlled studies have produced conflicting results, but a 1996 review[1] did not find a detrimental effect on the risk of cancer recurrence, and suggested that the findings of the observational studies probably resulted from the confounding effect of factors associated with the need for transfusion. A later meta-analysis[2] of 32 studies of perioperative transfusion in patients undergoing colorectal surgery concluded that the cancer recurrence rate was increased (odds ratio 1.68) in patients given transfusions. Risk factors associated with this increase were rectal disease, more advanced disease, and an increased number of transfused units. However, many of the included studies had small sample sizes, there was significant heterogeneity, and other possible surgery-related risk factors could not be evaluated, such that a causal association between the increased risk of cancer recurrence and transfusion could not be established. Other systematic reviews have come to different conclusions. A meta-analysis[3] of studies in patients undergoing resection of any type of solid tumour included only studies that used an active comparator (leucocyte-depleted or autologous blood). Only 8 studies met the inclusion criteria and the analysis provided no evidence of an increased risk of death or cancer recurrence in patients given allogeneic blood. The proposed detrimental immunosuppressive effect of perioperative allogeneic blood transfusion was studied in colorectal cancer patients given either allogeneic packed red cells (buffy coat removed) or leucocyte-depleted red cells.[4] Although the leucocyte count is reduced when the buffy coat is removed, more leucocytes are removed from leucocyte-depleted red cells, which should reduce any immunosuppressive effect. However, after 5 years there was no difference in survival or recurrence rates between the two groups. Survival was better for a third group of non-transfused patients, but this may be explained by a higher incidence of rectal cancer in the transfused groups, and the better clinical status of patients not requiring transfusion. A review[5] of individual studies and meta-analyses concluded that a causal relationship between allogeneic blood transfusion and solid cancer recurrence had not been proven. There was some evidence for transfusion-associated immunomodulation, but the mechanisms of effect and the specific constituents of allogeneic blood that mediate the effect remain unclear.

Epidemiological studies have reported an increase in the incidence of non-Hodgkin's lymphoma coinciding with the increase in the use of allogeneic blood transfusions since the 1950s. Proposed mechanisms have included transfusion-associated immunosuppression, transmission of oncogenic viruses, and blood donation by prelymphomatous donors.[6,7] Although some case-control studies have reported no association between blood transfusion and the development of non-Hodgkin's lymphoma,[8,9] others have reported a positive association, particularly for some subtypes of lymphoma.[10] Reviews[6,7] of these and other studies have found considerable disagreement between reports. This may result from biases in study design, confounding factors such as HIV infection, and lack of consensus on lymphoma classification.

1. Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. *Transfusion* 1996; **36:** 175–86.
2. Amato AC, Pescatori M. Effect of perioperative blood transfusions on recurrence of colorectal cancer: meta-analysis stratified on risk factors. *Dis Colon Rectum* 1998; **41:** 570–85.
3. McAlister FA, *et al.* Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies. *Br J Surg* 1998; **85:** 171–8.
4. van de Watering LMG, *et al.* Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence. *Br J Surg* 2001; **88:** 267–72.
5. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? *Blood* 2001; **97:** 1180–95.
6. Vamvakas EC. Allogeneic blood transfusion as a risk factor for the subsequent development of non-Hodgkin's lymphoma. *Transfus Med Rev* 2000; **14:** 258–68.
7. Chow EJ, Holly EA. Blood transfusions and non-Hodgkin's lymphoma. *Epidemiol Rev* 2002; **24:** 269–79.
8. Maguire-Boston EK, *et al.* Blood transfusion and risk of non-Hodgkin's lymphoma. *Am J Epidemiol* 1999; **149:** 1113–18.
9. Chow EJ, Holly EA. Blood transfusions as a risk factorfor non-Hodgkin's lymphoma in the San Francisco Bay Area: a population-based study. *Am J Epidemiol* 2002; **155:** 725–31.
10. Cerhan JR, *et al.* Blood transfusions and risk of non-Hodgkin's lymphoma subtypes and chronic lymphocytic leukemia. *Cancer Epidemiol Biomarkers Prev* 2001; **10:** 361–8.

Precautions

Whole blood should generally not be transfused unless the ABO and Rh groups of the patient's and the donor's blood have been verified and a compatibility check made between the patient's serum and the donor's red cells (see under Blood Groups, below).

The Rh group of the recipient should always be determined and ideally all patients should be transfused with blood of homologous Rh groups.

To reduce the possibility of cardiac arrest from cardiac hypothermia when large volumes are used or the blood is transfused rapidly, and to minimise postoperative shivering, stored blood should be carefully warmed to about 37 degrees before transfusion.

Whole blood should not be given to patients with chronic anaemia who have a normal or elevated plasma volume.

Drugs should *not* be added to blood.

Transfusion of blood from donors who have recently been receiving drug treatment may be hazardous to the recipient.

Guidelines[1-4] for accepting blood from donors who have been receiving drugs have been published.

1. Ferner RE, *et al.* Drugs in donated blood. *Lancet* 1989; **ii:** 93–4.
2. Stichtenoth DO, *et al.* Blood donors on medication: are deferral periods necessary? *Eur J Clin Pharmacol* 2001; **57:** 433–40.
3. UK Blood Transfusion Services. Whole blood and components donor selection guidelines: drug index (revised 23rd April, 2008). Available at: http://www.transfusionguidelines.org.uk/index.asp?Publication=DI&Section=4 (accessed 29/08/08)
4. American Red Cross. Eligibility criteria by topic. Available at: http://www.redcrossblood.org/donating-blood/eligibility-requirements/eligibility-criteria-topic (accessed 13/08/10)

Abuse. References to the infusion of whole blood or packed red blood cells to enhance athletic performance.[1,2]

1. Ekblom BT. Blood boosting and sport. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000; **14:** 89–98.
2. Leigh-Smith S. Blood boosting. *Br J Sports Med* 2004; **38:** 99–101.

Blood groups. The chief blood group systems are the ABO system and the Rhesus system.

In simple terms red blood cells carry on their surface genetically determined antigens. A person with antigen A, B, A plus B, or neither is classified as group A, B, AB, or O respectively. Such persons will have, in their serum, antibodies to B, A, neither, or both respectively—anti-B (β), anti-A (α), or anti-B plus anti-A (α + β). Giving blood containing red cells from a person of group A to a person with anti-A results in agglutination or possibly haemolysis. For the determination of the ABO group the agglutinogens of the red cells and the agglutinins of the serum are determined by testing against known standards.

In the Rhesus system many persons carry an antigen (Rh-positive) which stimulates antibody formation in Rh-negative persons; subsequent exposure to Rh-positive blood causes haemolysis.

Many variants of these and other systems, are recognised.

Calcium Alginate

Alginato cálcico; E404; Кальция Альгинат.

CAS — 9005-35-0.

ATC — B02BC08.

ATC Vet — QB02BC08.

UNII — 8P20S56HZI.

Profile

Calcium alginate is the calcium salt of alginic acid (p. 2167.2), a polyuronic acid composed of residues of D-mannuronic and L-guluronic acids. It may be obtained from seaweeds, mainly species of *Laminaria*. Calcium alginate is used as an absorbable haemostatic and for the promotion of wound healing (p. 1690.1); it is also used in the form of a mixed calcium-sodium salt of alginic acid as a fibre made into a dressing or packing material. Calcium ions in the calcium alginate fibres are exchanged for sodium ions in the blood and exudate to form a hydrophilic gel.

Alginic acid and its calcium and sodium salts are widely used in the food industry.

References.

1. Thomas S. Alginate dressings in surgery and wound management–part 1. *J Wound Care* 2000; **9:** 56–60.

2. Thomas S. Alginate dressings in surgery and wound management: part 2. *J Wound Care* 2000; **9:** 115–19.
3. Thomas S. Alginate dressings in surgery and wound management: part 3. *J Wound Care* 2000; **9:** 163–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kaltostat; Nu-Derm Alginato; ***Austral.***: Algisite M; Melgisorb; Sorbsan; ***Belg.***: Algisite M; Algosteril; Askina Sorb; Kaltostat; Melgisorb; SeaSorb Soft; Sorbalgon; Suprasorb A; Tegaderm Alginate; Urgosorb; ***Canad.***: Kaltostat; Melgisorb; Restore CalciCare; Tegaderm Alginate; ***Fr.***: Algosteril; Coalgan; Stop Hemo; Suprasorb A; Tegaderm Alginate; ***Ger.***: Urgosorb; ***Gr.***: Stop Hemo; ***India***: Calkariaa; ***Indon.***: Bioplacenton Tulle; ***Irl.***: Kaltostat†; Sorbsan†; ***Ital.***: Algosteril; Kaltostat; Melgisorb; Suprasorb A; ***S.Afr.***: Kaltostat; ***UK***: Algosteril; Comfeel SeaSorb; Kaltostat; Sorbsan; ***USA***: Calalgin.

Multi-ingredient Preparations. ***Arg.***: Comfeel Purilon; Comfeel SeaSorb; Fibracol Plus; Mylanta Reflux; Purilon†; SeaSorb†; ***Austral.***: Flaminal; ***Canad.***: Carboflex; ***Fr.***: Clip Hemo†; Melgisorb; Purilon; SeaSorb; Sorbalgon Plus; Urgosorb; ***Ger.***: Comfeel Plus; DracoAlgin; InfectoHoney Alginat†; Melgisorb Ag; Purilon; SeaSorb Soft; SeaSorb-Ag; Urgosorb Silver; ***Israel***: Kaltocarb; Kaltostat; ***Port.***: Kaltostat; ***Rus.***: Polygemostat (Полигемостат); ***UK***: Comfeel Plus; SeaSorb Soft.

Carbazochrome *(rINN)*

AC-17; Adrenochrome Monosemicarbazone; Carbazochromum; Carbazocromo; Monosemicarbazona de adrenocromo; Карбазохром.

3-Hydroxy-1-methyl-5,6-indolinedione semicarbazone.

$C_{10}H_{12}N_4O_3$=236.2

CAS — 69-81-8 (carbazochrome); 13051-01-9 (carbazochrome salicylate); 51460-26-5 (carbazochrome sodium sulfonate).

ATC — B02BX02.

ATC Vet — QB02BX02.

UNII — 81F061RQS4.

Pharmacopoeias. *Jpn* includes Carbazochrome Sodium Sulfonate ($C_{10}H_{11}N_4NaO_5S,3H_2O$ = 376.3).

Profile

Carbazochrome, an oxidation product of adrenaline, has been given as a haemostatic. Carbazochrome sodium sulfonate may be given orally in doses ranging from 30 to 150 mg daily, in at least 3 divided doses. Parenteral doses of 10 mg may be given subcutaneously or intramuscularly, and up to 100 mg may be given intravenously. It has also been given as the dihydrate and as the salicylate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Di Ka Ning (迪卡咛); Le Zhi Na (乐止纳); Luoye (洛叶); Na Neng (纳能); Su Bo Te (苏孛特); Tai Si Neng (太司能); Xue Yi Ting (雪益亭); ***Hong Kong***: Adona†; ***India***: Klog; Sigmachrome; Siochrome†; Styptocid; ***Indon.***: Adona; Adrome; Chromazol; Crome; ***Ital.***: Adona; ***Jpn***: Adona; ***Port.***: Adrenoxil†; ***Thai.***: Neo-Hesna†.

Multi-ingredient Preparations. ***India***: Cadisper C; CKP†; Siochrome; Styptocid; Styptocip; ***Ital.***: Fleboside; ***Jpn***: Behyd-RA; ***Mex.***: Hemosin-K; ***Spain***: Perfus Multivitaminico†.

Darbepoetin Alfa *(BAN, USAN, rINN)* ⊗

Darbepoetiinialfa; Darbepoetina alfa; Darbépoétine Alfa; Darbepoetinum Alfa; Darbepoyetina alfa; NESP; Novel Erythropoiesis Stimulating Protein; Дарбепоетин Альфа.

30-L-Asparagine-32-L-threonine-87-L-valine-88-L-asparagine-90-L-threonineerythropoietin (human).

CAS — 209810-58-2.

ATC — B03XA02.

ATC Vet — QB03XA02.

UNII — 15UQ94PT4P.

Uses and Administration

Darbepoetin alfa is an analogue of the endogenous protein hormone erythropoietin with similar properties to the epoetins (p. 1141.2). It is used in the management of anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p. 1123.1) and for anaemia caused by chemotherapy in patients with non-myeloid malignancies.

For **anaemia of chronic renal failure**, the aim of treatment is to use the lowest dose necessary to reduce the need for blood transfusion. A target haemoglobin range of 10 to 12 g per 100 mL has been used, but US licensed product information now recommends that darbepoetin alfa therapy may be considered when the haemoglobin concentration is less than 10 g per 100 mL, and to reduce the dose or stop therapy if the concentration exceeds 10 g per 100 mL in patients not on dialysis or when it approaches or exceeds 11 g per 100 mL in patients on dialysis (see also Haematocrit and Haemoglobin, under Precautions of Epoetins, p. 1144.3). The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 1 g per 100 mL in any 2-week period, or 2 g per 100 mL per month, is suggested.

Darbepoetin alfa is given by subcutaneous or intravenous injection. In patients on haemodialysis, the intravenous route is recommended to reduce the risk of developing neutralising antibodies and pure red cell aplasia (see Effects on the Blood under Epoetins, p. 1143.3); the subcutaneous route is preferable in those not receiving haemodialysis to avoid puncture of the peripheral veins. Various dosage regimens can be found in licensed product information. Initial doses for patients on haemodialysis include:

- 450 nanograms/kg once weekly
- 750 nanograms/kg once every 2 weeks

For patients not on dialysis, recommendations include:

- 450 nanograms/kg once weekly
- 450 nanograms/kg once every 4 weeks
- 750 nanograms/kg once every 2 weeks
- 1.5 micrograms/kg once every month

The dose may be increased at intervals of not less than 4 weeks, according to response, until the target haemoglobin concentration is achieved. In general, adjustments are made by increasing or decreasing the dose by about 25%. For maintenance therapy patients may be converted from weekly doses to once every 2 weeks, and should receive a dose that is equal to twice the dose that had been given once weekly. Those given an initial dose once every 2 weeks may be converted to a maintenance dose given once a month; this is equal to twice the dose that had been given once every 2 weeks.

Darbepoetin alfa may be used for treating symptomatic chemotherapy-associated anaemia in patients with **non-myeloid malignant disease**. However, US licensed product information cautions that it is not indicated when the anticipated outcome is cure, as the impact of darbepoetin alfa therapy on progression-free and overall survival has not been adequately studied. See also Anaemias (under Epoetins, p. 1142.3) for FDA restrictions on the prescribing of darbepoetin alfa for patients with cancer, and advice from the MHRA on when blood transfusion may be the preferred therapy.

Darbepoetin alfa is given subcutaneously in an initial dose of 500 micrograms (6.75 micrograms/kg) once every 3 weeks; if the response is inadequate after 9 weeks, further therapy with darbepoetin alfa may not be effective. Alternatively, it may be given in an initial dose of 2.25 micrograms/kg once weekly. If the response is inadequate after 6 weeks, the dose may be increased to 4.5 micrograms/kg once weekly. Darbepoetin alfa should be stopped after the course of chemotherapy has finished, but UK licensed product information states that it may be continued for up to 4 weeks. The rate of rise in haemoglobin should be gradual; a rate not exceeding 2 g per 100 mL per month, and a target haemoglobin of not more than 12 g per 100 mL, are suggested. Once the desired haemoglobin target has been reached, the dose should be reduced by 25 to 50% to maintain that level.

Darbepoetin alfa is under investigation in the management of patients with anaemia and heart failure.

Reviews.

1. Ibbotson T, Goa KL. Darbepoetin alfa. *Drugs* 2001; **61:** 2097–2104.
2. The NESP Usage Guidelines Group. Practical guidelines for the use of NESP in treating renal anaemia. *Nephrol Dial Transplant* 2001; **16** (suppl 3): 22–8.
3. Overbay DK, Manley HJ. Darbepoetin-α : a review of the literature. *Pharmacotherapy* 2002; **22:** 889–97.
4. Joy MS. Darbepoetin alfa: a novel erythropoiesis-stimulating protein. *Ann Pharmacother* 2002; **36:** 1183–92.
5. Cvetkovic RS, Goa KL. Darbepoetin alfa in patients with chemotherapy-related anaemia. *Drugs* 2003; **63:** 1067–74.
6. Siddiqui MAA, Keating GM. Darbepoetin alfa: a review of its use in the treatment of anaemia in patients with cancer receiving chemotherapy. *Drugs* 2006; **66:** 997–1012.

Administration in children. Darbepoetin alfa therapy may be used in children for the treatment of anaemia associated with chronic renal failure. It may be started in children aged 11 years and older in doses similar to those used in adults (see above).

Adverse Effects and Precautions

As for Epoetins, p. 1143.3 and p. 1144.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies darbepoetin alfa as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

On subcutaneous injection the bioavailability of darbepoetin alfa is about 37% and absorption is slow. A terminal half-life of about 21 hours has been found after intravenous use in patients with chronic renal failure who were receiving dialysis. After subcutaneous use a half-life of about 46 hours has been found in patients receiving dialysis, while it was about 70 hours in those with chronic renal failure but not receiving dialysis, and about 74 hours in patients with cancer.

References.

1. Heatherington AC, *et al.* Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) in cancer patients: preliminary report. *Br J Cancer* 2001; **84** (suppl): 11–16.
2. Allon M, *et al.* Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. *Clin Pharmacol Ther* 2002; **72:** 546–55.
3. Lerner G, *et al.* Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. *Pediatr Nephrol* 2002; **17:** 933–7.
4. Heatherington AC, *et al.* Pharmacokinetics of darbepoetin alfa after intravenous or subcutaneous administration in patients with non-myeloid malignancies undergoing chemotherapy. *Clin Pharmacokinet* 2006; **45:** 199–211.
5. Padhi D, *et al.* An extended terminal half-life for darbepoetin alfa: results from a single-dose pharmacokinetic study in patients with chronic kidney disease not receiving dialysis. *Clin Pharmacokinet* 2006; **45:** 503–10.
6. Takama H, *et al.* Population pharmacokinetics of darbepoetin alfa in haemodialysis and peritoneal dialysis patients after intravenous administration. *Br J Clin Pharmacol* 2007; **63:** 300–309.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aranesp; ***Austria***: Aranesp; ***Belg.***: Aranesp; ***Canad.***: Aranesp; ***Cz.***: Aranesp; Nespo†; ***Denm.***: Aranesp; ***Fin.***: Aranesp; ***Fr.***: Aranesp; ***Ger.***: Aranesp; ***Gr.***: Aranesp; ***Hong Kong***: Aranesp; ***Hung.***: Aranesp; ***Irl.***: Aranesp; ***Israel***: Aranesp; ***Ital.***: Aranesp; Nespo†; ***Neth.***: Aranesp; ***Norw.***: Aranesp; ***NZ***: Aranesp; ***Pol.***: Aranesp; ***Port.***: Aranesp; ***Rus.***: Aranesp (Аранесп); ***Singapore***: Aranesp†; Nesp; ***Spain***: Aranesp; ***Swed.***: Aranesp; ***Switz.***: Aranesp; ***Thai.***: Nesp; ***Turk.***: Aranesp; ***UK***: Aranesp; ***USA***: Aranesp.

Dextran 1 *(BAN, rINN)* ⊗

Dekstraani 1; Dekstranas 1; Dextrán 1; Dextrano 1; Dextranum 1; Декстран 1.

CAS — 9004-54-0 (dextran).

ATC — B05AA05.

ATC Vet — QB05AA05.

UNII — I8LHQ0D645.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dextran 1 for Injection). A low-molecular-weight fraction of dextran, consisting of a mixture of isomalto-oligosaccharides. It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 1000.

A white or almost white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol.

USP 36: (Dextran 1). A low-molecular-weight fraction of dextran, consisting of a mixture of isomalto-oligosaccharides. It is obtained by controlled hydrolysis and fractionation of dextrans produced by fermentation of certain strains of *Leuconostoc mesenteroides*, in the presence of sucrose. It is a glucose polymer in which the linkages between glucose units are almost exclusively α-1,6. Its weight average molecular weight is about 1000.

A white to off-white, hygroscopic powder. Very soluble in water; sparingly soluble in alcohol. pH of a 15% solution in water is between 4.5 and 7.0. Store at a temperature between 4 degrees and 30 degrees.

Profile

Dextran 1 is used to prevent severe anaphylactic reactions to infusions of dextran. It is reported to occupy the binding sites of dextran-reactive antibodies and so prevent the formation of large immune complexes with higher molecular weight dextrans.

Dextran 1 is given in usual doses of 20 mL of a solution containing 150 mg/mL by intravenous injection about 1 to 2 minutes before the infusion of the higher molecular weight dextran; the interval should not exceed 15 minutes. The dose of dextran 1 should be repeated if further infusions of dextran are required more than 48 hours after the initial dose. For doses used in children, see below.

Administration in children. A suggested intravenous dose of dextran 1 for children is 0.3 mL/kg of a solution containing 150 mg/mL.

Use. Two large multicentre studies (involving about 29 200 and 34 950 patients) have suggested that dextran 1

prevented anaphylactic reactions by hapten inhibition in a dose-dependent way.[1,2] It did not reduce the incidence of mild reactions, which are not generally mediated by antibodies. Another large study[3] comparing the effects of giving dextran 1 either 2 minutes before injection of dextran 40 or 70 or mixed with the injection, was stopped after the occurrence of 2 severe reactions in the admixture group. A comparison[4] of severe anaphylactic reactions to dextran infusion during the period 1983 to 1992 (when prophylaxis with dextran 1 was used) with reactions reported during the period 1975 to 1979 (no prophylaxis) found that the use of dextran 1 was associated with a 35-fold reduction in severe anaphylactic reactions to dextran infusion.

There were 21, 20, and 2 adverse reactions to dextran 1 in the first 3 studies respectively, including nausea, skin reactions, bradycardia, and hypotension. Apart from one patient, reactions to dextran 1 were mild and were considered to be of minor clinical importance. In the fourth study, adverse effects to dextran 1 were reported in about one case per 100 000 doses.

1. Ljungström K-G, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition I: a Scandinavian multicenter study on the effects of 10 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983; **149:** 341–8.
2. Renck H, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition III: Scandinavian multicenter study on the effects of 20 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983; **149:** 355–60.
3. Renck H, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition II: a comparison of the effects of 20 mL dextran 1, 15% administered either admixed to or before dextran 70 or dextran 40. *Acta Chir Scand* 1983; **149:** 349–53.
4. Ljungström K-G. Safety of dextran in relation to other colloids - ten years experience with hapten inhibition. *Infusionsther Transfusionsmed* 1993; **20:** 206–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Promit; ***Denm.***: Promiten; ***Hung.***: Promiten; ***Norw.***: Promiten; ***S.Afr.***: Promit†; ***Swed.***: Promiten; ***USA***: Promit†.

Dextran 40 *(BAN, USAN, rINN)* ⊗

Dekstraani 40; Dekstran 40; Dekstranas 40; Dextrán 40; Dextrano 40; Dextranum 40; LMD; LMWD; Low-molecular-weight Dextran; LVD; Декстран 40.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — K3R6ZDH4DU.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

Eur. (see p. vii) and *Jpn* describe Dextran 40 for Injection.

Ph. Eur. 8: (Dextran 40 for Injection). A mixture of polysaccharides, mainly of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 40 000.

A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

USP 36: (Dextran 40). It is derived by controlled hydrolysis and fractionation of polysaccharides elaborated by the fermentative action of certain strains of *Leuconostoc mesenteroides* on a sucrose substrate. It is a glucose polymer in which the linkages between glucose units are almost entirely of the α-1:6 type. Its weight average molecular weight is in the 35 000 to 45 000 range. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 40 preparations.

Uses and Administration

Dextran 40 is a plasma volume expander used in the management of hypovolaemic shock (p. 1279.3). As a 10% solution, dextran 40 exerts a slightly higher colloidal osmotic pressure than plasma proteins and thus produces a greater expansion of plasma volume than dextrans of a higher molecular weight, although the expansion may have a shorter duration because of more rapid renal excretion. Dextran 40 also reduces blood viscosity and inhibits sludging or aggregation of red blood cells. It is used in the prophylaxis and treatment of postoperative thromboembolic disorders, in conditions where improved circulatory flow is required, and as a priming solution during extracorporeal circulation.

Dextran 40 is given by intravenous infusion as a 10% solution in sodium chloride 0.9% or glucose 5%. Doses depend on the clinical condition of the patient.

In **shock**, a maximum of 20 mL/kg during the first 24 hours has been recommended; the first 10 mL/kg may be given by rapid intravenous infusion. Doses of up to 10 mL/kg may be given daily thereafter for up to 5 days. Dehydration should preferably be corrected before dextran 40 is given.

In the treatment of **thromboembolic disorders** a suggested regimen is 500 to 1000 mL over 4 to 6 hours on the first day, then 500 mL over 4 to 6 hours on the next and subsequent alternate days for not more than 10 days.

For prophylaxis of postoperative thromboembolic disorders, 500 mL over 4 to 6 hours may be given during or at the end of surgery and the dose repeated on the next day; treatment may be continued in high risk patients on alternate days for up to 10 days.

A dose of 10 to 20 mL/kg has been added to extracorporeal perfusion fluids.

Dextran 40 is also an ingredient of artificial tears.

Post-dural puncture headache. Dextran 40 has been used in the treatment of post-dural puncture headache (p. 1983.1) when other measures, including epidural autologous blood patch, have been ineffective. Reports[1-3] have described dextran 40 given in an epidural bolus dose of 20 mL. Sometimes this has been followed by a continuous epidural infusion of 3 to 4 mL/hour, and in these cases headache was relieved within 20 hours of starting the infusion.[1,2]

1. Aldrete JA. Persistent post-dural-puncture headache treated with epidural infusion of dextran. *Headache* 1994; **34:** 265–7.
2. Reynvoet MEJ, *et al.* Epidural dextran 40 patch for postdural puncture headache. *Anaesthesia* 1997; **52:** 886–8.
3. Souron V, Hamza J. Treatment of postdural puncture headaches with colloid solutions: an alternative to epidural blood patch. *Anesth Analg* 1999; **89:** 1333–4.

Thromboembolic disorders. Dextran 40 is only one of a variety of drugs that have been used for the prophylaxis of venous thromboembolism (p. 1274.1) resulting from surgical operations such as hip replacement surgery. Dextran 40 may be used to prevent thromboembolic complications in some types of vascular surgery including carotid endarterectomy.[1]

1. Abir F, *et al.* Efficacy of dextran solutions in vascular surgery. *Vasc Endovascular Surg* 2004; **38:** 483–91.

Adverse Effects, Treatment, and Precautions

As for Dextran 70, p. 1139.1.

Rapid renal excretion of dextran 40 in patients with reduced urine flow can result in high urinary concentrations which increase urinary viscosity and may cause oliguria or acute renal failure. Therefore, infusions of dextran 40 are contra-indicated in renal disease with oliguria; should anuria or oliguria occur during treatment dextran 40 should be withdrawn. Dehydration should preferably be corrected before giving dextran 40. Dextran 40 can cause capillary oozing of wound surfaces.

Effects on the kidneys. Acute renal failure has been associated with dextran 40[1-4] and less frequently with dextran 70.[1] The mechanism of the effect is unclear but suggestions include an increase in plasma oncotic pressure that decreases filtration pressure in the glomerulus and hence decreases glomerular filtration rate,[2] obstruction within the tubules,[2,4] or a direct toxic effect on renal cells.[4] Plasmapheresis has been used successfully to remove dextran from the circulation.[2-4]

1. Feest TG. Low molecular weight dextran: a continuing cause of acute renal failure. *BMJ* 1976; **2:** 1300.
2. Tsang RKY, *et al.* Acute renal failure in a healthy young adult after dextran 40 infusion for external-ear reattachment surgery. *Br J Plast Surg* 2000; **53:** 701–3.
3. Kato A, *et al.* Complication of oliguric acute renal failure in patients treated with low-molecular weight dextran. *Ren Fail* 2001; **23:** 679–84.
4. Vos SCB, *et al.* Acute renal failure during dextran-40 antithrombotic prophylaxis: report of two microsurgical cases. *Ann Plast Surg* 2002; **48:** 193–6.

Hypersensitivity. For reports of anaphylactic reactions associated with use of dextran 40, see Dextran 70, p. 1139.1, and Dextran 1, p. 1137.3.

Pharmacokinetics

After intravenous infusion dextran 40 is slowly metabolised to glucose. About 70% of a dose is excreted unchanged in the urine within 24 hours. A small amount is excreted into the gastrointestinal tract and eliminated in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fu Ta Le (福他乐); Shen Shui Qing (绅水清); Xin Run Luo (欣润络); ***Denm.***: Rheomacrodex; ***Gr.***: Deltadex; Gentran; Neodextril; ***Hung.***: Rheomacrodex; ***India***: Microspan-40; ***Indon.***: Otsutran; ***Ital.***: Eudextran; Plander R; ***Jpn***: Saviosol; ***Mex.***: Rheomacrodex†; ***Norw.***: Rheomacrodex; ***Philipp.***: LM Dextran; ***Port.***: Bas-Dextrano†; Neodextril 40; ***Rus.***: Haemostabil (Гемостабил); Rheomacrodex (Реомакродекс)†; Rheopolydex (Реополидекс); Rheopolyglukin (Реополиглюкин); ***S.Afr.***: Rheomacrodex; ***Singapore***: Onkovertin; ***Spain***: Rheomacrodex; ***Swed.***: Perfadex; Rheomacrodex; ***Thai.***: Onkovertin†; ***Turk.***: Rheomacrodex; ***UK***: Gentran 40; ***USA***: Gentran 40; Rheomacrodex.

Multi-ingredient Preparations. ***Rus.***: Rheogluman (Реоглюман).

Pharmacopoeial Preparations
BP 2014: Dextran 40 Infusion;
USP 36: Dextran 40 in Dextrose Injection; Dextran 40 in Sodium Chloride Injection.

Dextran 60 *(BAN, rINN)* ⊗

Dekstraani 60; Dekstranas 60; Dextrán 60; Dextrano 60; Dextranum 60; Декстран 60.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — ZNJ8R2417Z.

Pharmacopoeias. *Eur.* (see p. vii) describes Dextran 60 for Injection.

Ph. Eur. 8: (Dextran 60 for Injection). A mixture of polysaccharides, mainly of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 60 000.

A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 60 preparations.

Profile

Dextran 60 is a plasma volume expander with actions and uses similar to those of dextran 70 (below). It is given by intravenous infusion as a 3 or 6% solution in sodium chloride 0.9% or a mixture of electrolytes.

Dextran 60 is also used topically for dry eyes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Macrodex; ***Norw.***: Plasmodex; ***Swed.***: Plasmodex.

Dextran 70 *(BAN, USAN, rINN)* ⊗

Dekstraani 70; Dekstran 70; Dekstranas 70; Dextrán 70; Dextrano 70; Dextranum 70; Polyglucin (dextran); Декстран 70.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — 7SA290YK68.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

Eur. (see p. vii) describes Dextran 70 for Injection.

Ph. Eur. 8: (Dextran 70 for Injection). A mixture of polysaccharides, mainly of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 70 000.

A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

USP 36: (Dextran 70). It is derived by controlled hydrolysis and fractionation of polysaccharides elaborated by the fermentative action of certain appropriate strains of *Leuconostoc mesenteroides* on a sucrose substrate. It is a glucose polymer in which the linkages between glucose units are almost entirely of the α-1:6 type. Its weight average molecular weight is in the 63 000 to 77 000 range. A 6% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 70 preparations.

Storage. Crystals may form in solutions of dextran if they are stored at low temperatures. These may be redissolved by warming for a short time.

Uses and Administration

Dextran 70 is a plasma volume expander used in the management of hypovolaemic shock (p. 1279.3). As a 6% solution dextran 70 exerts a colloidal osmotic pressure similar to that of plasma proteins and thus produces less

expansion of plasma volume than dextrans of a lower molecular weight, although the expansion may have a longer duration because of less rapid renal excretion. Dextran 70 also reduces blood viscosity, interferes with fibrin polymerisation, has an antiplatelet effect, and inhibits sludging or aggregation of red blood cells. It may be used in the prophylaxis of postoperative thromboembolic disorders (p. 1274.1).

Dextran 70 is given by intravenous infusion as a 6% solution, usually in sodium chloride 0.9% or glucose 5%.

Doses depend on the severity of the plasma loss and on the degree of haemoconcentration.

In **shock**, the usual initial dose for rapid expansion of plasma volume is 500 to 1000 mL infused at a rate of 20 to 40 mL/minute. A suggested maximum dose is 20 mL/kg during the first 24-hour period and 10 mL/kg per day thereafter; treatment should not continue for longer than 3 days. Patients may also require blood, coagulation factors, and electrolytes. A hypertonic solution of 6% dextran 70 in sodium chloride 7.5% is also available for use as a plasma expander, given in a single intravenous dose of 250 mL over 2 to 5 minutes, followed by isotonic fluids as required.

For the prophylaxis of pulmonary embolism or venous **thrombosis** in moderate- to high-risk patients undergoing surgery, a dose of 500 to 1000 mL may be given over 4 to 6 hours either during or immediately after surgery. A dose of 500 mL should be given on the next day and in high-risk patients on subsequent alternate days for up to 2 weeks after the operation.

A 32% solution of dextran 70 has been instilled into the uterus in a dose of 50 to 100 mL as a rinsing and dilatation fluid to aid **hysteroscopy**.

Dextran 70 is also an ingredient of artificial tears.

Hypertonic solutions. There is some evidence to suggest that hypertonic solutions of dextran 70 in sodium chloride 7.5% may be an effective treatment option for hypovolaemic shock resulting from trauma.[1,2]

1. Wade CE, *et al.* Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. *Surgery* 1997; **122:** 609–16.
2. Alpar EK, Killampalli VV. Effects of hypertonic dextran in hypovolaemic shock: a prospective clinical trial. *Injury* 2004; **35:** 500–506.

Adverse Effects and Treatment

Infusions of dextrans may occasionally produce hypersensitivity reactions such as fever, nasal congestion, joint pains, urticaria, hypotension, and bronchospasm. Severe anaphylactic reactions occur rarely and may be fatal. Dextran-reactive antibodies have been detected in patients who have not previously received dextran. This may possibly be in response to dietary or bacterial polysaccharides. Nausea and vomiting have also been reported. These reactions are treated symptomatically after withdrawal of the dextran.

Dextran 1 (p. 1137.3) may be used to block the formation of dextran-reactive antibodies and hence the hypersensitivity reactions.

Effects on the blood. A syndrome of acute hypotension, pulmonary oedema, coagulopathy, and anaemia, has occurred after the intra-uterine instillation of 32% solution of dextran 70 for hysteroscopy.[1] The volumes of solution that were used in 10 reported cases ranged from 300 to 1200 mL, and these large volumes may have contributed to the intravascular absorption of dextran. The pathogenesis and role of dextran in this syndrome are unclear but suggestions have included acute volume overload, direct alveolar endothelial damage, and release of tissue factors that promote fibrinolysis and a consumptive coagulopathy.

1. Ellingson TL, Aboulafia DM. Dextran syndrome: acute hypotension, noncardiogenic pulmonary edema, anemia, and coagulopathy following hysteroscopic surgery using 32% dextran 70. *Chest* 1997; **111:** 513–18.

Effects on the kidneys. For a report of acute renal failure associated with use of dextran 70, see Dextran 40, p. 1138.2.

Hypersensitivity. In a retrospective study of allergic reactions to dextran 40 and dextran 70 reported in Sweden from 1970 to 1979,[1] there were 478 reports of reactions, 458 of which were considered to be due to dextran, out of 1 365 266 infusions given. There was a male to female ratio of 1.5 to 1 for all reactions and a ratio of 3 to 1 for the most severe reactions. The mean age of the patients was higher in those with severe reactions. Of the 28 fatal reactions, 27 occurred within 5 minutes of the start of the infusion and 25 when less than 25 mL had been infused. Three of the fatal reactions occurred after a test dose of only 0.5 to 1 mL and it was strongly recommended that such test doses should not be used.

An anaphylactic reaction has also been reported[2] more than 75 minutes after intraperitoneal instillation. After successful symptomatic treatment symptoms recurred 20 minutes later, due to slow absorption of dextran from the peritoneal cavity. No further reaction occurred after removal of 200 mL of intraperitoneal fluid by culdocentesis.

Anaphylactoid reactions after BCG vaccination have been attributed to hypersensitivity to dextran in the formulation.[3]

The use of dextran 1 for the prevention of hypersensitivity reactions is discussed under that monograph (p. 1137.3).

1. Ljungström K-G, *et al.* Adverse reactions to dextran in Sweden 1970–1979. *Acta Chir Scand* 1983; **149:** 253–62.
2. Borten M, *et al.* Recurrent anaphylactic reaction to intraperitoneal dextran 75 used for prevention of postsurgical adhesions. *Obstet Gynecol* 1983; **61:** 755–7.
3. Rudin C, *et al.* Anaphylactoid reaction to BCG vaccine containing high molecular weight dextran. *Eur J Pediatr* 1995; **154:** 941–2.

Precautions

Dextran infusions produce a progressive dilution of oxygen-carrying capacity, coagulation factors, and plasma proteins and may overload the circulation. They are therefore contra-indicated in patients with severe heart failure, bleeding disorders such as hypofibrinogenaemia or thrombocytopenia, or renal failure and should be used with caution in patients with renal impairment, haemorrhage, chronic liver disease, or those at risk of developing pulmonary oedema or heart failure. Central venous pressure should be monitored during the initial period of infusion to detect fluid overload. Also patients should be watched closely during the early part of the infusion period, and the infusion stopped immediately if signs of anaphylactic reactions appear. Infusions should also be stopped if there are signs of oliguria or renal failure. The haematocrit should not be allowed to fall below 30% and all patients should be observed for early signs of bleeding complications. The bleeding time may be increased especially in patients receiving large volumes of dextrans. Deficiency of coagulation factors should be corrected and fluid and electrolyte balance maintained. Dehydration should be corrected before or at least during dextran infusions, in order to maintain an adequate urine flow.

The anticoagulant effect of heparin may be enhanced by dextran.

The higher molecular weight dextrans may interfere with blood grouping and cross-matching of blood, while the lower molecular weight dextrans may interfere with some methods. Therefore, whenever possible, a sample of blood should be collected before giving the dextran infusion and kept frozen in case such tests become necessary.

The presence of dextran may interfere with the determination of glucose, bilirubin, or protein in blood.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dextrans as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

After intravenous infusion dextrans with a molecular weight of less than 50 000 are excreted unchanged by the kidney. Dextrans with a molecular weight greater than 50 000 are slowly metabolised to glucose. Small amounts of dextrans are excreted into the gastrointestinal tract and eliminated in the faeces.

About 50% of dextran 70 is excreted unchanged in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hyskon†; ***Canad.***: LMD; ***China***: Run Qi (润齐); ***Denm.***: Macrodex; RescueFlow; ***Fin.***: RescueFlow; ***Fr.***: RescueFlow†; ***Ital.***: Plander; ***Neth.***: RescueFlow†; ***Norw.***: Macrodex; RescueFlow; ***Port.***: Neodextril 70; ***S. Afr.***: Macrodex†; RescueFlow; ***Swed.***: Macrodex; RescueFlow; ***Switz.***: Dialens†; ***Turk.***: Macrodex; RescueFlow; ***UK***: Gentran 70; RescueFlow; ***USA***: Gentran 70†; Hyskon; Macrodex†; ***Venez.***: Lacridos; Lacrimart; Lagrimas Artificiales.

Multi-ingredient Preparations. ***Arg.***: Alcon Lagrimas; Kalopsis Lagrimas; Phoenix Lagrimas; Tears Naturale Forte; Tears Naturale†; Visine Plus; ***Austral.***: Bion Tears; Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Belg.***: Alcon Adequad; Lacrystat; Tears Naturale; ***Braz.***: Lacribell; Lacrima Plus; Opti-Tears; Trisorb; ***Canad.***: Artificial Tears†; Bion Tears; Tears Naturale Forte; Tears Naturale; Visine Advance Triple Action; ***Chile***: Kliner; Lagrimas Artificiales; Naphtears; Nico Drops; Nicotears; Novo-Tears; Tears Naturale; ***China***: Bion Tears (倍然); Tears Naturale Forte (新泪然); Tears Naturale II (泪然II); ***Cz.***: Tears Naturale; ***Denm.***: Dacriosol; ***Gr.***: Tearprol; Tears Naturale; ***Hong Kong***: Bion Tears; Tears Naturale Forte; Tears Naturale; ***Hung.***: Dacrolux; Tears Naturale; ***Indon.***: Isotic Tearin; Tears Naturale II; Tears; ***Irl.***: Physiotears†; Tears Naturale; ***Israel***: Tears Natural; ***Ital.***: Dacriosol; ***Malaysia***: Bion Tears; Dacrolux; Tears Naturale; ***Mex.***: Lacrima Plus; Naphtears; Naturalag; Tears Naturale; Visine Extra; ***Neth.***: Duratears; Tears Naturale; ***Norw.***: Tears Naturale; ***NZ***: Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Philipp.***: Gentle Tears; Tears Naturale; ***Pol.***: Tears Naturale; ***Rus.***: Tears Naturale (Слеза Натуральная); ***S. Afr.***: Tears Naturale; ***Singapore***: Bion Tears; Tears Naturale; ***Spain***: Dacrolux; Tears Humectante; ***Swed.***: Bion Tears; ***Switz.***: Tears Naturale; ***Thai.***: Bion Tears†; Opsar Tears; Tears Naturale; ***Turk.***: Dacrolux; Tears Naturale; ***UK***: Tears Naturale; ***Ukr.***: Tears Naturale (Штучні Сльози)†; ***USA***: Advanced Relief Visine; Bion Tears; Lacri-Tears; LubriTears; Moisture Drops; Nature's Tears; Ocucoat†; Tears Naturale; Tears Renewed†; ***Venez.***: Opti-Fresh.

Pharmacopoeial Preparations
BP 2014: Dextran 70 Infusion;
USP 36: Dextran 70 in Dextrose Injection; Dextran 70 in Sodium Chloride Injection.

Dextran 75 *(BAN, USAN, rINN)* ⊗

Dextrán 75; Dextrano 75; Dextranum 75; Декстран 75.
CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — JY83SHX053.

Profile

Dextran 75 consists of dextrans (glucose polymers) of weight average molecular weight about 75 000 that are derived from the dextrans produced by the fermentation of sucrose by means of a certain strain of *Leuconostoc mesenteroides*.

Dextran 75 is a plasma volume expander with actions and uses similar to dextran 70 (p. 1138.3). It is given by intravenous infusion as a 6% solution in sodium chloride 0.9% or glucose 5%.

Ecallantide *(USAN, rINN)*

DX-88; Ecalantida; Écallantide; Ecallantidum; Экальнантид.
Human plasma kallikrein-inhibitor (synthetic protein).
CAS — 460738-38-9.
ATC — B06AC03.
ATC Vet — QB06AC03.
UNII — 5Q6TZN2HNM.

Uses and Administration

Ecallantide is a recombinant inhibitor of human plasma kallikrein. It reduces the conversion of high molecular weight kininogen to bradykinin and is used in the treatment of acute attacks of hereditary angioedema (p. 2485.2). Three subcutaneous doses of 10 mg are given as a single treatment; the 3 injection sites may be in the same or different anatomical areas (abdomen, thigh, or upper arm), but should be separated by at least 5 cm and away from the site of the attack. If the attack persists, a second dose of three 10-mg injections may be given within 24 hours.

Reviews.

1. Levy JH, O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Invest Drugs* 2006; **15:** 1077–90.
2. Schneider L, *et al.* Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol* 2007; **120:** 416–22.
3. Lehmann A. Ecallantide (DX-88), a plasma kallikrein inhibitor for the treatment of hereditary angioedema and the prevention of blood loss in on-pump cardiothoracic surgery. *Expert Opin Biol Ther* 2008; **8:** 1187–99.

Adverse Effects and Precautions

Hypersensitivity reactions, including pruritus, rash, and urticaria, have occurred in patients given ecallantide. Anaphylaxis has also been reported, usually within 1 hour of dosing, and must be distinguished from hereditary angioedema, which has similar symptoms. Other adverse effects include headache, nausea, diarrhoea, and pyrexia. Injection site reactions such as pruritus, erythema, pain, irritation, urticaria, and bruising have also occurred.

Antibodies to ecallantide have been found in some patients, which may increase the risk of hypersensitivity reactions; the long-term effects of antibody formation are unknown.

References.

1. Caballero T, López-Serrano C. Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J Allergy Clin Immunol* 2006; **117:** 476–7.

Pharmacokinetics

Peak plasma concentrations of ecallantide occur about 2 to 3 hours after a subcutaneous dose. It is excreted in the urine, and has an elimination half-life of about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel*: Kalbitor; *USA*: Kalbitor.

Eltrombopag *(rINN)*

Eltrombopagum; SB-497115; Элтромбопаг.
3′-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl}-2′-hydroxybiphenyl-3-carboxylic acid.
$C_{25}H_{22}N_4O_4$=442.5
CAS — 496775-61-2.
ATC — B02BX05.
ATC Vet — QB02BX05.
UNII — S56D65XJ9G.

Eltrombopag Olamine *(USAN, rINNM)*

Eltrombopag olamina; Eltrombopagum Olaminum; SB-497115-GR; Элтромбопаг Оламин.
3′-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl}-2′-hydroxybiphenyl-3-carboxylic acid compound with 2-aminoethanol (1:2).
$C_{25}H_{22}N_4O_4.2(C_2H_7NO)$=564.6
CAS — 496775-62-3.
ATC — B02BX05.
ATC Vet — QB02BX05.
UNII — 4U07F515LG.

Uses and Administration

Eltrombopag is a non-peptide thrombopoietin receptor agonist. It interacts with the receptor to produce an increase in platelet production. Eltrombopag is used to treat thrombocytopenia in patients with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura; p. 1606.1), who have not responded sufficiently to treatment with corticosteroids, immunoglobulins, or splenectomy and are at increased risk of bleeding. It is also used for thrombocytopenia in patients with chronic hepatitis C (p. 952.1) to allow the use of interferon-based therapy. Eltrombopag should not be used in an attempt to normalise platelet counts.

Eltrombopag is given as the olamine salt, but doses are expressed in terms of the free acid; 12.8 mg of eltrombopag olamine is equivalent to about 10 mg of eltrombopag.

In patients with chronic immune thrombocytopenia, the usual initial oral dose is equivalent to 50 mg of eltrombopag once daily, given on an empty stomach. A reduced dose of 25 mg once daily is recommended for patients of East Asian origin (e.g. Chinese). The dose may need to be reduced in patients with hepatic impairment (see below). The dose of eltrombopag should be adjusted to achieve and maintain a platelet count of at least 50×10^9 cells/litre, as necessary, to reduce the risk of bleeding. The effect of a dose change should be monitored for at least 2 weeks. The daily dose should not exceed 75 mg.

In patients with hepatitis C, an initial oral dose of eltrombopag 25 mg once daily is used; no dose reduction is needed for those of East Asian origin or with hepatic impairment (but see also Adverse Effects and Precautions, below, regarding hepatotoxicity risks in these patients). The dose may be adjusted in steps of 25 mg every 2 weeks until the platelet count allows antiviral therapy to be started, and then to avoid reductions of the interferon dose. The maximum recommended daily dose of eltrombopag is 100 mg. If antiviral therapy is stopped then eltrombopag treatment should also cease.

US licensed product information advises the following adjustments based on platelet counts.

- If the platelet count is *lower than* 50×10^9 *cells/litre* for at least 2 weeks, the daily dose should be increased by 25 mg. In patients with chronic immune thrombocytopenia eltrombopag should be discontinued if, after 4 weeks of treatment at the maximum dose, the platelet count has not risen to a level sufficient to avoid clinically important bleeding. (UK licensed information also suggests that in patients with hepatitis C, treatment should be stopped if there has been insufficient response after 2 weeks at the maximum dose.)
- If the count is *higher than* 200×10^9 *cells/litre* at any time, then the daily dose should be reduced by 25 mg. The effects of this and any subsequent dose adjustment, should be assessed after waiting 2 weeks.
- If the count is *higher than* 400×10^9 *cells/litre*, then eltrombopag should be withheld and platelet counts measured twice a week. Treatment may be restarted at the previous daily dose reduced by 25 mg, when the count has fallen below 150×10^9 cells/litre; for patients already taking 25 mg daily, treatment may be restarted at 12.5 mg once daily. If the count is higher than 400×10^9 cells/litre after 2 weeks at the lowest dose of eltrombopag, treatment should be permanently stopped.

Licensed product information in other countries may differ regarding the platelet count threshold at which dose adjustments should be made. For example, UK information advises that the dose should be reduced when the platelet count is higher than 100×10^9 cells/litre in patients with hepatitis C or 150×10^9 cells/litre in those with immune thrombocytopenia; and treatment withheld if the count is higher than 150×10^9 cells/litre in hepatitis C or 250×10^9 cells/litre in immune thrombocytopenia.

Liver function tests and full blood counts (including platelet counts and peripheral blood smears) must be monitored frequently during eltrombopag therapy. Blood tests should also be routinely monitored after stopping the drug. For further details on monitoring, see below.

Eltrombopag is also under investigation as a platelet growth factor for the management of oncology-related thrombocytopenia and in aplastic anaemia.

References.
1. McHutchison JG, *et al.* Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; **357:** 2227–36.
2. Bussel JB, *et al.* Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; **357:** 2237–47.
3. Tillmann HL, *et al.* Role of growth factors and thrombopoietic agents in the treatment of chronic hepatitis C. *Curr Gastroenterol Rep* 2009; **11:** 5–14.
4. Bussel JB, *et al.* Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **373:** 641–8.
5. Cheng G, *et al.* Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; **377:** 393–402. Correction. *ibid.*; 640.
6. Garnock-Jones KP. Eltrombopag: a review of its use in treatment-refractory chronic primary immune thrombocytopenia. *Drugs* 2011; **71:** 1333–53.
7. Zhang Y, Kolesar JM. Eltrombopag: an oral thrombopoietin receptor agonist for the treatment of idiopathic thrombocytopenic purpura. *Clin Ther* 2011; **33:** 1560–76.
8. Olnes MJ, *et al.* Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *N Engl J Med* 2012; **367:** 11–19. Correction. *ibid.*; 284.

Administration in hepatic impairment. Patients with chronic immune thrombocytopenia and hepatic impairment should start eltrombopag treatment at an oral dose of 25 mg once daily. Dose increases should only be made at intervals of at least 3 weeks. For patients of East Asian origin (e.g. Chinese) an initial dose of 12.5 or 25 mg once daily may be used; if it is then necessary to increase the dose, the lower dose of 12.5 mg should be increased to 25 mg daily before any further increases of 25 mg.

No dose adjustment is considered necessary in patients being treated for thrombocytopenia associated with hepatitis C who have hepatic impairment.

Adverse Effects and Precautions

The most common serious adverse effect of eltrombopag is haemorrhage, which usually occurs after stopping the drug. Bleeding problems such as epistaxis, gingival bleeding, and ecchymosis may also occur. Other common adverse effects include headache, insomnia, fatigue, arthralgia, myalgia, paraesthesia, peripheral oedema, rash, pruritus, alopecia, dry eye, and cataracts. Gastrointestinal disturbances have included dyspepsia, nausea, vomiting, diarrhoea, and constipation.

Eltrombopag may cause hepatotoxicity. Raised liver function tests including bilirubin have been reported, and should therefore be monitored carefully (see below). Caution is advised in patients with liver disease and a reduced initial dose is recommended for those with chronic immune thrombocytopenia. Most patients with chronic hepatitis C who are also receiving an interferon and ribavirin will develop indirect hyperbilirubinaemia; those with cirrhosis may also be at increased risk of hepatic decompensation and death.

Excessive increases in platelet counts with eltrombopag treatment may lead to thrombosis or thromboembolic complications. The drug should be used with caution in patients with known risk factors for thromboembolism. Patients with chronic liver disease are at increased risk of portal venous thrombosis in particular. Eltrombopag increases the risk for the development or progression of reticulin fibre deposition in the bone marrow, and a risk of bone marrow fibrosis with cytopenias has not been excluded. Monitoring of full blood count and peripheral blood smears is essential (see below).

Due to the way eltrombopag acts on haematopoietic cells, it may possibly increase the risk of haematological malignancies.

Effects on the cardiovascular system. A study[1] of eltrombopag in the treatment of thrombocytopenia due to chronic liver disease of various causes was stopped early because of an excessive number of cases of portal venous thrombosis in patients given the drug (patients had been given eltrombopag or placebo for 14 days before elective invasive surgery). Five of the 6 patients who developed thrombosis had platelet counts above 200×10^9 cells/litre. The manufacturer (*GSK, USA*) and the FDA issued a reminder that eltrombopag should be used with caution in patients with known risk factors for thromboembolism.[2]

1. Afdhal NH, *et al.* ELEVATE Study Group. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med* 2012; **367:** 716–24.
2. FDA. Promacta (eltrombopag): portal venous system thromboses in study of patients with chronic liver disease (issued 12th May, 2010). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211796.htm (accessed 02/06/10)

Effects on the skin. Severe skin reactions, including maculopapular rash, erythroderma, and pruritus, have been described in 2 patients given eltrombopag. The reactions occurred 9 weeks and 3 months after starting the drug; the patients were managed symptomatically and eltrombopag was replaced by romiplostim. A third patient with mild rash and pruritus was treated with antihistamines and eltrombopag therapy continued.[1]

1. Meyer SC, *et al.* Severe cutaneous toxicity related to eltrombopag. *Br J Haematol* 2013; **160:** 412–14.

Monitoring. *BLOOD.* A full blood count, including the platelet count and peripheral blood smears, must be assessed before starting eltrombopag, then monitored weekly during dose adjustment and monthly during stable therapy. The level of cellular morphologic abnormalities must be established before starting treatment, and eltrombopag should be stopped if new or worsening abnormalities or cytopenias develop. After stopping treatment, thrombocytopenia is likely to recur. As this may increase the risk of bleeding, full blood counts (including platelet counts) should be monitored every week for at least 4 weeks after eltrombopag is stopped.

EYES. Licensed product information recommends that an eye examination should be performed before starting eltrombopag and then regularly during treatment, for signs and symptoms of cataract formation.

LIVER. Liver function including bilirubin levels should be measured before starting eltrombopag and then every 2 weeks while the dose is adjusted; once the dose is established, monthly monitoring is recommended. Tests should be repeated within 3 to 5 days if found to be abnormal and, if this is confirmed, liver function should be monitored every week. Eltrombopag should be stopped if alanine aminotransferase levels increase to ≥ 3 times above the upper limit of normal, or to ≥ 3 times above baseline for patients with pre-existing elevations, and these increases are:

- progressive or
- persistent for 4 weeks or longer or
- accompanied by increased direct bilirubin or by signs and symptoms of hepatic injury or decompensation

Interactions

The absorption of eltrombopag is reduced by polyvalent cations such as aluminium, calcium, iron, magnesium, selenium, and zinc. To avoid subtherapeutic serum concentrations, eltrombopag should not be taken within 4 hours of some foods such as milk and dairy products, mineral supplements, antacids or other preparations containing such cations. The use of lopinavir-ritonavir can reduce plasma concentrations of eltrombopag, and platelet counts should be closely monitored when lopinavir-ritonavir therapy is started or stopped.

Eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and breast cancer resistance protein (BCRP), and may increase exposure to drugs that are substrates of these; it has been reported to increase plasma concentrations of rosuvastatin.

References.
1. Williams DD, *et al.* Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies. *Clin Ther* 2009; **31:** 764–76.
2. Wire MB, *et al.* Assessment of the pharmacokinetic interaction between eltrombopag and lopinavir-ritonavir in healthy adult subjects. *Antimicrob Agents Chemother* 2012; **56:** 2846–51.

Pharmacokinetics

Eltrombopag is absorbed from the gastrointestinal tract and peak plasma concentration occur 2 to 6 hours after a dose. The concentration of eltrombopag in red blood cells is about 50 to 79% of the plasma concentration. It is highly bound to plasma proteins. Eltrombopag is extensively metabolised, undergoing oxidative metabolism by the cytochrome P450 isoenzymes CYP1A2 and CYP 2C8, and glucuronidation by the UDP-glucuronosyltransferases UGT1A1 and UGT1A3. About 31% of a dose is eliminated in the urine as metabolites, and about 59% in the faeces; 20% of a dose is eliminated unchanged in the faeces. The elimination half-life is about 26 to 35 hours in patients with immune thrombocytopenia.

After adjustment for body-weight, plasma-eltrombopag exposure is found to be about 50% higher in some patients

of East Asian origin (e.g. Japanese, Chinese, Taiwanese, and Korean) compared with Caucasian patients.

References.
1. Bauman JW, *et al.* Effect of hepatic or renal impairment on eltrombopag pharmacokinetics. *J Clin Pharmacol* 2011; **51:** 739–50.
2. Gibiansky E, *et al.* Population pharmacokinetics of eltrombopag in healthy subjects and patients with chronic idiopathic thrombocytopenic purpura. *J Clin Pharmacol* 2011; **51:** 842–56.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Revolade; ***Austria***: Revolade; ***Belg.***: Revolade; ***Braz.***: Revolade; ***Cz.***: Revolade; ***Denm.***: Revolade; ***Fr.***: Revolade; ***Ger.***: Revolade; ***Gr.***: Revolade; ***Irl.***: Revolade; ***Israel***: Revolade; ***Jpn***: Revolade; ***Norw.***: Revolade; ***NZ***: Revolade; ***Pol.***: Revolade; ***Port.***: Revolade; ***Rus.***: Revolade (Революйд); ***Spain***: Revolade; ***Swed.***: Revolade; ***Switz.***: Revolade; ***Thai.***: Revolade; ***Turk.***: Revolade; ***UK***: Revolade; ***Ukr.***: Revolade (Революд); ***USA***: Promacta.

Epoetins ⊗

Epoetinas; Эпоэтины.
ATC — B03XA01.
ATC Vet — QB03XA01.

Description. Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor produced mainly in the kidneys.

Erythropoietin for clinical use is produced by recombinant DNA technology and the name epoetin is often applied to such material. Epoetin alfa, epoetin beta, epoetin gamma, epoetin lambda, epoetin omega, epoetin theta, and epoetin zeta are recombinant human erythropoietins derived from a cloned human erythropoietin gene. All have the same 165 amino acid sequence but differ in the glycosylation pattern. Epoetin delta is a recombinant human erythropoietin derived from a genetically engineered continuous human cell line. It has the same amino acid sequence and glycosylation pattern as human erythropoietin.

Pharmacopoeias. *Eur.* (see p. vii) includes Erythropoietin Concentrated Solution.

Ph. Eur. 8: (Erythropoietin Concentrated Solution). A clear or slightly turbid colourless solution, containing 0.05 to 1% of glycoproteins indistinguishable from naturally occurring human erythropoietin in terms of amino acid sequence and glycosylation pattern. It has a potency of not less than 100 000 units per mg of active substance. Store in airtight containers below -20 degrees and avoid repeated freezing and thawing.

Epoetin Alfa *(BAN, USAN, rINN)* ⊗

EPO; Epoetina alfa; Époétine Alfa; Epoetinum Alfa; Эпоэтин Альфа.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α.
CAS — 113427-24-0.
ATC — B03XA01.
ATC Vet — QB03XA01.
UNII — 64FS3BFH5W.

NOTE. The name epoetin alfa has been permitted in some commercial preparations containing epoetin lambda, and some literature may use the term epoetin alfa to represent epoetin lambda (see below).

Epoetin Beta *(BAN, USAN, rINN)* ⊗

BM-06.019; EPOCH; Epoetina beta; Époétine Bêta; Epoetinum Beta; Эпоэтин Бета.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β.
CAS — 122312-54-3.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Delta *(BAN, USAN, rINN)* ⊗

Epoetina delta; Époétine Delta; Epoetinum Delta; GA-EPO; HMR-4396; Эпоэтин Дельта.
1–165-Erythropoietin (human HMR4396), glycoform δ.
CAS — 261356-80-3.
ATC — B03XA01.
ATC Vet — QB03XA01.
UNII — 474EI5756Y.

Epoetin Gamma *(BAN, rINN)* ⊗

BI-71.052; Epoetina gamma; Époétine Gamma; Epoetinum Gamma; Эпоэтин Гамма.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform γ.
CAS — 130455-76-4.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Kappa *(rINN)* ⊗

Epoetina Kappa; Époétine Kappa; Epoetinum Kappa; JR-013; Эпоэтин Каппа.
1–165-Erythropoietin (human JR-013), glycoform κ.
CAS — 879555-13-2.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Lambda ⊗

HX-575.
ATC — B03XA01.
ATC Vet — QB03XA01.

NOTE. Epoetin lambda was developed as a biosimilar product to epoetin alfa, but glycosylation patterns differ between the two forms. The name epoetin alfa has been permitted in some commercial preparations containing epoetin lambda, and some literature may use the term epoetin alfa to represent epoetin lambda.

Epoetin Omega *(rINN)* ⊗

Epoetina omega; Époétine Oméga; Epoetinum Omega; Эпоэтин Омега.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform ω.
CAS — 148363-16-0.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Theta *(BAN, rINN)* ⊗

Epoetina Zeta; Époétine Thêta; Epoetinum Theta; Эпоэтин Тета.
Human erythropoietin-(1–165)-peptide, glycoform θ.
CAS — 762263-14-9.
ATC — B03XA01.
ATC Vet — QB03XA01.

NOTE. In Spanish, epoetin theta is given the name Epoetina Zeta (*rINN*), which should not be confused with Epoetin Zeta (below).

Epoetin Zeta *(rINN)* ⊗

Epoetina dseta; Époétine Zêta; Epoetinum Zeta; Эпоэтин Дзета.
1–165-Erythropoietin (human clone B03XA01), glycoform ζ.
CAS — 604802-70-2.
ATC — B03XA01.
ATC Vet — QB03XA01.

NOTE. In Spanish, the name Epoetina Dseta (*rINN*) is used for epoetin zeta. These terms should not be confused with the Spanish name Epoetina Zeta (*rINN*), which is used for Epoetin Theta (above).

Stability. Proprietary preparations of recombinant human erythropoietin may contain albumin or amino acids for stability. Use in neonates may necessitate making very dilute solutions. A study of the stability of epoetin alfa in various intravenous fluids[1] found that a minimum of 0.05% protein was required to prevent loss of drug from solutions containing epoetin alfa 0.1 units/mL. In another study,[2] 0.0125% albumin was sufficient to prevent loss of drug from a solution containing epoetin alfa 100 units/mL. Epoetin alfa was stable for up to 24 hours in a solution for enteral use in neonates, formulated to mimic amniotic fluid, which also contained filgrastim and electrolytes.[3] Epoetin alfa and filgrastim were stable for at least 24 hours when refrigerated and for at least 3 weeks when frozen. At room temperature epoetin alfa was stable for 24 hours and filgrastim was stable for 18 hours. Lowered epoetin alfa concentrations were thought to be due to adsorption to the plastic infusion bag or tubing, and this was overcome by priming the tubing.

1. Ohls RK, Christensen RD. Stability of human recombinant epoetin alfa in commonly used neonatal intravenous solutions. *Ann Pharmacother* 1996; **30:** 466–8.
2. Widness JA, Schmidt RL. Comment: epoetin alfa loss with NaCl 0.9% dilution. *Ann Pharmacother* 1996; **30:** 1501–2.
3. Calhoun DA, *et al.* Stability of filgrastim and epoetin alfa in a system designed for enteral administration in neonates. *Ann Pharmacother* 2000; **34:** 1257–61.

Uses and Administration

Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor. It is secreted mainly by the kidneys, although a small amount is produced in extrarenal sites such as the liver. Erythropoietin regulates erythropoiesis by stimulating the differentiation and proliferation of erythroid precursors, the release of reticulocytes into the circulation, and the synthesis of cellular haemoglobin. The release of erythropoietin is promoted by hypoxia or anaemia, and up to 1000 times the normal serum-erythropoietin concentration may be reached under these conditions; this response may be impaired in some disease states such as chronic renal failure. The haematological response to erythropoietin is reduced if there is an inadequate supply of iron. For an outline of blood cell formation in general and average cell counts in adults see Haematopoiesis, p. 1121.1.

Epoetins alfa, beta, lambda, theta, and zeta are recombinant human erythropoietins available for clinical use that have the same pharmacological actions as endogenous erythropoietin. They are used in the management of symptomatic anaemia associated with chronic renal failure in dialysis and predialysis patients; they may reduce or obviate the need for blood transfusions in these patients. Epoetins alfa, beta, lambda, theta, and zeta are also used in the management of chemotherapy-induced anaemia in patients with non-myeloid malignant disease. Epoetin alfa is used in zidovudine-related anaemia in HIV-positive patients. Epoetin beta is used in the prevention of anaemia of prematurity. Epoetins are also being evaluated in the management of normocytic-normochromic anaemias of various other causes (see p. 1142.3). In all patients, iron status should be monitored and supplementation provided if necessary.

Epoetins alfa, beta, lambda, and zeta may also be used in patients with moderate anaemia (but no iron deficiency) before elective surgery to increase the yield of blood collected for autologous blood transfusion. Epoetin alfa and lambda may also be used in such patients to reduce the need for allogeneic blood transfusion.

In the management of **anaemia of chronic renal failure** epoetins may be given intravenously or subcutaneously. For haemodialysis patients the dose of epoetin should be given intravenously because of the risk of pure red cell aplasia reported with subcutaneous use (see Effects on the Blood, p. 1143.3); it is usually given during or at the end of the dialysis session using the dialysis vascular access, although licensed product information for epoetin lambda recommends that it should always be administered after completion of dialysis. For predialysis and peritoneal dialysis patients, in whom intravenous access is not readily available, doses should be given subcutaneously. The aim of treatment is to use the lowest dose necessary to reduce the need for blood transfusion. A target haemoglobin range of 10 to 12 g per 100 mL, or to increase the haematocrit to 30 to 36%, has been used, but US licensed product information now recommends that epoetin therapy may be considered when the haemoglobin concentration is less than 10 g per 100 mL, and to reduce the dose or stop therapy if the concentration exceeds 10 g per 100 mL in patients not on dialysis or when it approaches or exceeds 11 g per 100 mL in patients on dialysis (see also Haematocrit and Haemoglobin, under Precautions, p. 1144.3). The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 1 g per 100 mL in any 2-week period, or 2 g per 100 mL over 4 weeks, is suggested.

Epoetin alfa, lambda, or ***zeta*** may be given by intravenous injection over at least 1 to 5 minutes; a slower intravenous injection is preferred in patients who have flu-like symptoms as adverse effects. Epoetin alfa or zeta may also be given subcutaneously.

- In predialysis and haemodialysis patients, a recommended initial dose of epoetin alfa, lambda, or zeta is 50 international units/kg three times weekly. For epoetin alfa, a higher initial dose of 50 to 100 units/kg three times weekly has been suggested in the US licensed product information.
- Doses may be increased at 4-week intervals in increments of 25 units/kg until the target is reached.
- In patients on peritoneal dialysis an initial dose of epoetin alfa or zeta 50 units/kg given twice weekly may be used.

Once the target haemoglobin is reached, doses of epoetin alfa, lambda, or zeta may need to be adjusted for maintenance therapy.

- In predialysis patients the usual total weekly dose of epoetin alfa or zeta is 50 to 100 units/kg given in three divided doses. A total weekly dose of 600 units/kg should not be exceeded.
- In haemodialysis patients the usual weekly dose of epoetin alfa, lambda, or zeta is between 75 and 300 units/kg given in three divided doses.
- In patients on peritoneal dialysis, the usual weekly dose of epoetin alfa or zeta is 50 to 100 units/kg given in two divided doses.

Epoetin beta is used similarly in the management of anaemia of chronic renal failure in dialysis and predialysis patients. It may be given subcutaneously or by intravenous injection over 2 minutes. The following dosages may be used in adults and children.

- For subcutaneous injection the initial dose is 60 units/kg weekly for 4 weeks; the total weekly dose may be divided to be given in daily doses or three times a week.
- For intravenous injection the initial dose is 40 units/kg three times weekly for 4 weeks; the dose may then be increased to 80 units/kg three times weekly.
- Thereafter the dose of epoetin beta may be increased at 4-week intervals, for both subcutaneous and intravenous injection; the increment should be equivalent to 60 units/kg weekly given in divided doses as outlined above, until the target haemoglobin concentration or haematocrit is reached. A total weekly dose of 720 units/kg of epoetin beta should not be exceeded.

For maintenance, the dose is halved initially and then adjusted every 1 to 2 weeks according to response. The weekly subcutaneous maintenance dose may be divided into 1, 3, or 7 doses; in patients stabilised on a once-weekly dose, it may be possible to adjust to a single dose every 2 weeks.

Epoetin theta is also given intravenously or subcutaneously in the management of anaemia of chronic renal failure.

- For subcutaneous injection the initial dose is 20 units/kg three times weekly for 4 weeks; the dose may then be increased, if necessary, to 40 units/kg three times weekly.
- For intravenous injection the initial dose is 40 units/kg three times weekly for 4 weeks; the dose may then be increased, if necessary, to 80 units/kg three times weekly.
- Thereafter the dose of epoetin theta, for both subcutaneous and intravenous injection, may be increased in steps of 25% of the previous dose at monthly intervals until the target haemoglobin concentration is reached. A total weekly dose of 700 units/kg should not be exceeded.

For maintenance, the dose should be adjusted as required. The weekly subcutaneous maintenance dose may be given in a single weekly dose or 3 divided doses. For intravenous dosing, the total weekly dose may be given in 2 or 3 divided doses.

Epoetins may be used for treating symptomatic chemotherapy-associated anaemia in patients with **non-myeloid malignant disease**. However, US licensed product information for epoetin alfa cautions that it is not indicated when the anticipated outcome is cure, because of the potential impact of epoetin therapy on progression-free and overall survival. See also Anaemias, below, for restrictions on the prescribing of epoetins in the USA for patients with cancer. Epoetin alfa, beta, lambda, theta, or zeta may be given by subcutaneous injection, usually when the haemoglobin concentration has fallen to 10 g or lower per 100 mL. The rise in haemoglobin should be gradual; a rate not exceeding 1 g per 100 mL in any 2-week period, or 2 g per 100 mL over 4 weeks, and a target haemoglobin concentration of 10 to 12 g per 100 mL, are suggested.

- ***Epoetin alfa, lambda***, or ***zeta*** may be given in an initial dose of 150 units/kg three times weekly; epoetin alfa or zeta may also be given in a dose of 450 units/kg once weekly. The dose may be increased after 4 weeks, if necessary, to 300 units/kg three times weekly. Alternatively, epoetin alfa may be given in a once-weekly dose of 40 000 units, which may be increased to 60 000 units after 4 weeks if necessary. If the response is still inadequate after 4 weeks at the higher dose, treatment should be stopped.
- ***Epoetin beta*** may be given in an initial dose of 30 000 units (about 450 units/kg) weekly, as a single dose or divided into 3 to 7 doses. The dose may be doubled after 4 weeks if necessary, but treatment should be stopped if the response is still inadequate after 4 weeks at the higher dose. The total weekly dose should not exceed 60 000 units.
- ***Epoetin theta*** may be given in an initial dose of 20 000 units once weekly. The dose may be increased after 4 weeks, if necessary, to 40 000 units weekly. If the response is still inadequate after 4 weeks at this dose, it may be increased to a maximum weekly dose of 60 000 units. However, treatment should be stopped if the response is still inadequate after 12 weeks of therapy.

Once the desired haemoglobin concentration has been reached, the dose of epoetin alfa may be reduced by 25% for maintenance therapy, and adjusted as necessary; the dose of epoetin beta or zeta may be reduced by 25 to 50%. Epoetins should be stopped after the end of chemotherapy, but may be continued for up to one month in the UK.

In **HIV-positive patients** on zidovudine therapy, epoetin alfa may be beneficial if the endogenous serum-erythropoietin concentration is 500 milliunits/mL or less. Epoetin alfa is given by subcutaneous or intravenous injection in an initial dose of 100 units/kg three times weekly for 8 weeks. The dose may then be increased every 4 to 8 weeks by 50 to 100 units/kg according to response. However, patients are unlikely to benefit from doses above 300 units/kg three times weekly if this dose has failed to elicit a satisfactory response. The haemoglobin concentration should not be allowed to exceed 12 g per 100 mL.

To increase the yield of **autologous blood** for transfusion, epoetin alfa, beta, or zeta may be used with iron supplementation in patients with mild to moderate anaemia (haemoglobin 10 to 13 g per 100 mL or haematocrit 33 to 39%). Epoetin lambda may be used similarly. The dose depends on the volume of blood required for collection and on factors such as the patient's whole blood volume and haematocrit. At the time of donating blood, the epoetin should be given after the donation procedure. Suggested regimens are:

- ***epoetin alfa*** or ***zeta*** 600 units/kg given intravenously twice weekly starting 3 weeks before surgery
- ***epoetin lambda*** 300 to 600 units/kg given intravenously twice weekly starting 3 weeks before surgery
- 200 to 800 units/kg of ***epoetin beta*** intravenously, or 150 to 600 units/kg subcutaneously, twice weekly for 4 weeks before surgery

To reduce the need for **allogeneic blood transfusion**, epoetin alfa or lambda may be given in a dose of 600 units/kg subcutaneously once weekly starting 3 weeks before surgery, with a fourth dose given on the day of surgery. Alternatively, when the time before surgery is short, 300 units/kg subcutaneously daily may be given for 10 days before surgery, on the day of surgery, and for 4 days after. All patients should be given adequate iron supplementation, and epoetin treatment should be stopped if the haemoglobin concentration reaches 15 g per 100 mL or higher.

For the use of epoetins in **children**, see below.

Reviews.

1. Markham A, Bryson HM. Epoetin alfa: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in nonrenal applications. *Drugs* 1995; **49:** 232–54.
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Administration in children. Epoetins are used in children for the management of anaemia associated with chronic renal failure and chemotherapy, and general advice about the rates of administration and rise in haemoglobin, and stopping epoetin therapy after chemotherapy, is similar to that given for adults (see p. 1141.2). However, some licensed product information suggests a lower haemoglobin target range for children than for adults, as described below. Epoetin beta may also be used for the prevention of anaemia of prematurity (see also Anaemias, below).

In the management of **anaemia of chronic renal failure**, epoetins are generally given intravenously to children on haemodialysis.

- The initial dose of epoetin alfa or zeta is 50 units/kg three times weekly. The dose may be increased at 4-week intervals in increments of 25 units/kg until a target haemoglobin concentration of 9.5 to 11 g per 100 mL is reached.

The usual total weekly maintenance dose given in three divided doses is:

- 225 to 450 units/kg for those weighing less than 10 kg
- 180 to 450 units/kg for those weighing 10 to 30 kg
- 90 to 300 units/kg for those weighing over 30 kg

Epoetin beta is given in similar unit/kg doses to those used for adults (see p. 1141.2).

In the management of symptomatic chemotherapy-associated anaemia in children with **non-myeloid malignant disease**, epoetin alfa may be given intravenously in a single weekly dose of 600 units/kg (to a maximum of 40 000 units). The dose may be increased if necessary after 4 weeks to 900 units/kg (maximum 60 000 units).

In the prevention of **anaemia of prematurity**, epoetin beta is given to neonates with a birth-weight of 750 to 1500 g and a gestational age of less than 34 weeks. A subcutaneous dose of 250 units/kg is given three times weekly. Treatment should be started as early as possible (preferably within 3 days of birth) and continued for 6 weeks.

Results from small studies suggest that once-weekly epoetin dosing regimens might be as effective as three times weekly dosing in premature infants, and that further investigation is warranted.[1,2] Although epoetin is generally given subcutaneously for anaemia of prematurity, other routes have been tried. Intravenous infusion in total parenteral nutrition solutions produced satisfactory results in a group of 20 neonates.[3] Enteral dosage in one small study[4] increased plasma-erythropoietin concentrations and peak reticulocyte counts, but in another larger study[5] it had no effect. For a warning about diluting epoetin solutions for use in neonates, see Stability, p. 1141.2.

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Anaemias. Epoetins are used in normocytic-normochromic anaemias (p. 1123.1) associated with low endogenous erythropoietin concentrations.

Anaemia associated with *chronic renal disease* is mainly a result of inadequate production of erythropoietin in the kidney. Other factors that can contribute to the anaemia include iron deficiency, blood loss associated with dialysis, and severe hyperparathyroidism. The use of epoetins in the management of renal anaemia became well established,[1,2] based on consistently good results for correction of anaemia and reports of improvement in quality of life.[1,3] In predialysis patients, epoetins were also reported to correct anaemia, reduce the requirement for blood transfusions, and improve quality of life and exercise capacity, but there may be increased hypertension[2,4] and it is unknown whether the need for dialysis is delayed.[4] However, the optimum haemoglobin range has not been established and higher targets have been associated with increased cardiovascular risks[5] (see also Haematocrit and Haemoglobin, under Precautions, p. 1144.3). An assessment of studies reporting effects on quality of life also concluded that there were high risks for bias because of selective reporting of outcomes.[5] Over 90% of patients with renal anaemia respond to treatment with epoetins.[1] Many factors can contribute to a poor response (see Precautions, p. 1144.2) and the patient should always be investigated and the cause corrected where possible. Common causes of inadequate response are iron deficiency, inflammatory disorders, chronic blood loss, hyperparathyroidism, and aluminium toxicity.[1,6]

Epoetins may be given intravenously or subcutaneously. Epoetin given subcutaneously produces lower but more sustained plasma concentrations and total weekly maintenance doses are reduced.[1,2,7] The subcutaneous route is generally used in predialysis patients and those on peritoneal dialysis,[1,2] partly because of the need to avoid venepuncture of veins that are likely to be needed for future haemodialysis access. While subcutaneous injection can also be used for haemodialysis patients, the intravenous route is preferred because of the rare risk of pure red cell aplasia reported with subcutaneous use[1] (see Effects on the Blood, p. 1143.3) and the ready availability of intravenous access. The dosage frequency may also be important in maximising the response to treatment, but may be influenced by the epoetin being used, route of administration, treatment phase, and patient preference. For example, giving epoetins 2 or 3 times a week may allow for a lower total weekly dose than once weekly, and may be more effective, but dosing once weekly may be more convenient for maintenance therapy.[1,2] A systematic review[8] concluded that there was no evidence to support one frequency over another in terms of maintaining target haemoglobin. See Uses and Administration, p. 1141.2, for examples of licensed doses, routes, and dose frequency for epoetins. Darbepoetin alfa (p. 1137.1) is given at longer dosage intervals than epoetins and there is no difference in weekly dosage requirements between subcutaneous and intravenous routes.[2,7]

Intraperitoneal use of epoetins has also been proposed and investigated.[9,10] However, this route is rarely used because the doses must be given into a dry abdomen,[1] dose requirements are generally higher than those for intravenous or subcutaneous use, and there is the potential for more frequent episodes of peritonitis.[1,2]

Blood transfusions are often used to treat *anaemia of prematurity*, and epoetins have been investigated as a means of reducing transfusion requirements. A systematic review[11] found that although epoetin reduced transfusion needs, the effect was only modest and there was considerable variation between studies. More selective reviews of very-low-birth-weight infants (less than 1500 g) also found modest reductions in transfusion requirements, whether epoetin was started within the first week of life[12] or after one week,[13] although transfusion requirements were unlikely to be eliminated completely. Response to the late use of epoetin was also found to be dose-dependent.[13] Another review[14] found evidence of an increase in the risk of retinopathy of prematurity in neonates treated with epoetins in the first week after birth. For most studies, this was a secondary study outcome and the effect could have been a chance finding; it was also considered possible that

high iron supplementation could have been a contributing factor.

Factors contributing to *cancer-related anaemia* include chemotherapy, radiotherapy, and the malignancy itself. Epoetin therapy can reduce the need for blood transfusions in cancer patients[15] and may improve quality of life.[16] Guidelines for the use of epoetins in chemotherapy-induced anaemia have been issued (see Anaemia, under Bone-marrow Depression, p. 731.1). There has, however, been some concern raised about the effect of epoetin therapy on patient survival. A placebo-controlled study of epoetin alfa to maintain normal haemoglobin concentrations (12 to 14 g per 100 mL) in patients receiving chemotherapy for metastatic breast cancer was terminated early when an increase in death was found in the epoetin group.[17] In another placebo-controlled study[18] of patients with head and neck cancer undergoing radiotherapy, epoetin beta was associated with correction of anaemia but poorer locoregional progression-free survival. In contrast, analysis of a study[19] in patients with lymphoproliferative malignancies found no effect of epoetin beta on patient survival. Subsequently, a study of the quality of life in anaemic patients with advanced non-small cell lung cancer was stopped early, when an unplanned safety analysis suggested a reduced overall survival in patients given epoetin alfa.[20] However, few epoetin studies were designed to assess their effects on tumour response and survival, although two later studies did aim to investigate these outcomes. One study in women treated with radiochemotherapy for advanced cervical cancer reported no positive correlation between haemoglobin increase and improvement in clinical outcomes, and could not draw a definite conclusion as to whether epoetin beta had an effect on disease progression or survival.[21] Another study, in women given chemotherapy for metastatic breast cancer, found that epoetin beta had no significant effect on overall survival.[22] Meta-analyses, which included these and other studies in cancer patients, found that epoetin or darbepoetin alfa therapy was associated with increased risks of venous thromboembolism[23] and death.[23,24] Studies to date have generally used haemoglobin targets of 12 g and above per 100 mL, and further information is needed on the benefits and risks associated with the lower targets now advised (see Uses and Administration, p. 1141.2). In response to these concerns, authorities have strengthened warnings in licensed product information regarding the use of epoetins and related products in patients with cancer. The FDA has directed[25] that epoetins and darbepoetin alfa can be prescribed for patients with cancer only by healthcare professionals who have completed specified training in the ESA APPRISE oncology program; in addition, they must only be dispensed by hospitals that are enrolled in the program. The MHRA has advised[26] that blood transfusion should be the preferred option for the management of anaemia in patients with cancer, particularly in those receiving adjuvant chemotherapy or who are being treated with curative intent. They also suggest that transfusion may be preferable in patients with advanced or metastatic cancer who have a good survival prognosis.

Epoetins are sometimes used to treat *anaemias from other causes*. Potential applications include zidovudine-induced anaemia in AIDS patients (see Effects on the Blood under Zidovudine, p. 1025.1), postpartum anaemia,[27,28] and anaemia of chronic diseases such as rheumatoid arthritis,[29,30] inflammatory bowel disease,[31-33] and chronic heart failure.[34] Epoetin treatment is also being investigated in critically ill patients,[35,36] but firm evidence of clinical benefit is lacking and routine use is not recommended.[37,38]

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Cardiovascular diseases. There is some interest[1] in the non-haematopoietic effects of erythropoietin, including protection from apoptosis, antioxidant activity, and pro-angiogenic effects. A possible role in the management of ischaemic stroke and myocardial infarction has been investigated.[2]

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Perinatal brain injury. There is interest in the potential neuroprotective effects of epoetins,[1] particularly when given to neonates at risk of perinatal brain injury. A small study[2] showed that premature extremely low birth-weight infants with an elevated erythropoietin level due to epoetin use had higher mental development index scores at 18 to 22 months corrected age follow-up than those with lower erythropoietin concentrations, although psychomotor developmental index was not significantly different. Furthermore, it has also been seen that the neurodevelopmental outcomes, at age 10 to 13 years, of extremely preterm infants were significantly better in those who had received epoetin for the management of anaemia in the first weeks of life but only in those who had neonatal intraventricular haemorrhage.[3] Other studies[4,5] showed safety and tolerability of short-term therapy using doses higher than those generally used for anaemia of prematurity. Epoetin treatment might also reduce the risk of disability and improve neurodevelopmental outcomes in full-term neonates with mild to moderate hypoxic-ischaemic encephalopathy.[6,7]

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Surgery. Concern over the safety of blood transfusions and the need to conserve blood supplies has led to interest in methods of reducing blood use in surgery. Recombinant human erythropoietin has been used to increase the number of units harvested for autologous transfusion[1] and to reduce transfusion requirements.[2-4] It has also been used as an alternative to blood transfusions in Jehovah's Witnesses.[5-8]

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Adverse Effects and Treatment

Adverse effects of epoetins include flu-like symptoms such as fever, chills, headache, arthralgias, myalgias, asthenia, dizziness, and tiredness, which occur especially at the start of treatment. Other effects include rashes, urticaria, nausea and vomiting, diarrhoea, hyperkalaemia, and reactions at the injection site. Severe hypersensitivity reactions have been reported rarely. Pure red cell aplasia associated with neutralising antibodies has been reported rarely in patients with chronic renal failure. It has also been rarely reported in patients with hepatitis C treated with ribavirin and interferon when also given epoetins. Epoetins are not approved for the management of anaemia associated with hepatitis C treatment. Modest increases in the platelet count within the normal range may occur during epoetin therapy.

Hypertension is common with the use of epoetins, particularly in patients with renal failure, and is associated with a rapid rise in haematocrit. Hypertensive crisis with encephalopathy and seizures has been reported, even in patients with initially normal or low blood pressure.

Reports of thromboembolism include myocardial ischaemia and infarction, transient ischaemic attacks and cerebrovascular accidents, deep-vein thrombosis, and pulmonary embolism. Shunt thromboses may occur in the arteriovenous fistulae of dialysis patients, and occlusion of the dialysis system is possible, due to an increased haematocrit.

General references.

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Effects on the blood. The use of recombinant human erythropoietin has been associated with an increase in **thrombotic events**, including vascular access thrombosis in haemodialysis patients. Several mechanisms have been proposed for this increase such as increased blood viscosity, effects on proteins involved in coagulation, activation

of platelets and the endothelium, and a vasoconstrictor effect on vascular smooth muscle.[1]

Pure red cell aplasia has been reported rarely, in patients with chronic renal failure, after months to years of treatment with epoetin alfa; most patients have been found to have antibodies to epoetins.[2] There have also been a few cases in patients treated with epoetin beta.[3-5] A review[5] of cases reported between January 1988 and April 2004 found that the number peaked in 2001 and 2002, and decreased rapidly when changes were made to recommendations for storage, handling, and use of epoetin alfa preparations. The effect appeared to be brand specific[6-8] and associated particularly with the subcutaneous use of preparations containing polysorbate 80 as a stabiliser.[9] Other possible causes have been proposed including contamination with silicone lubricant used in pre-filled syringes or release of organic compounds from rubber plungers.[10] Subsequently, manufacturers have reported that cases of red cell aplasia with neutralising antibodies have also occurred in chronic renal failure patients treated with subcutaneous darbepoetin alfa.[11] They also warn that because of cross-reactivity, patients who develop antibody-mediated anaemia with either an epoetin or darbepoetin alfa should not be swapped to another erythropoietic protein.

Epoetin-induced red cell aplasia has been managed with withdrawal of the epoetin and treatment with immunosuppressants including corticosteroids, cyclophosphamide, and ciclosporin. Intravenous normal immunoglobulin has also been used. Kidney transplantation is reported to bring about a rapid recovery.[10,12]

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Effects on electrolytes. Hyperkalaemia and hyperphosphataemia may occur in patients receiving recombinant human erythropoietin. However, hypophosphataemia has also been reported in cirrhotic patients given erythropoietin before autologous blood donation.[1]

1. Kajikawa M, *et al*. Recombinant human erythropoietin and hypophosphatemia in patients with cirrhosis. *Lancet* 1993; **341:** 503–4.

Effects on mental function. Visual hallucinations occurred in 4 patients during treatment with recombinant human erythropoietin, stopped when treatment was withdrawn, and recurred in 2 patients when erythropoietin was reinstituted.[1] Commenting on these and a further 7 cases,[2] the manufacturers considered the reaction to be extremely rare and that the contribution of concurrent medication could not be discounted. In two groups of dialysis patients treated with recombinant human erythropoietin, 15 of 134 and 2 of 103 had visual hallucinations.[3] Increasing age appeared to be a risk factor. Hallucination, associated with hypertension, has occurred during epoetin therapy in a patient with a history of bone marrow transplantation.[4]

1. Steinberg H. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325:** 285.
2. Stead RB. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325:** 285.
3. Steinberg H, *et al*. Erythropoietin and visual hallucinations in patients on dialysis. *Psychosomatics* 1996; **37:** 556–63.
4. van den Bent MJ, *et al*. Erythropoietin induced visual hallucinations after bone marrow transplantation. *J Neurol* 1999; **246:** 614–16.

Effects on the skin. Rashes may occur during treatment with recombinant human erythropoietin.

Pseudoporphyria cutanea tarda, a photosensitivity disorder, has been reported in 2 children undergoing peritoneal dialysis and receiving erythropoietin.[1] However, it was pointed out that this disorder has occurred in adults undergoing dialysis and the children were also receiving other potential photosensitisers.

A fatal case of erythema multiforme has been attributed to a single dose of epoetin alfa. The patient also had eosinophilia and systemic symptoms suggestive of DRESS syndrome.[2]

1. Harvey E, *et al*. Pseudoporphyria cutanea tarda: two case reports on children receiving peritoneal dialysis and erythropoietin therapy. *J Pediatr* 1992; **121:** 749–52.
2. Norgard N, Wall GC. Possible drug rash with eosinophilia and systemic symptoms syndrome after exposure to epoetin alfa. *Am J Health-Syst Pharm* 2005; **62:** 2524–6.

Effects on the spleen. Aggravation of splenomegaly was reported in 2 patients with myeloproliferative disorders after use of recombinant human erythropoietin.[1] Splenic infarction has been reported in a patient with aplastic anaemia given erythropoietin,[2] and peliosis of the spleen was discovered at autopsy in a patient with end-stage renal failure who had been receiving erythropoietin.[3]

1. Iki S, *et al*. Adverse effect of erythropoietin in myeloproliferative disorders. *Lancet* 1991; **337:** 187–8.
2. Imashuku S, *et al*. Splenic infarction after erythropoietin therapy. *Lancet* 1993; **342:** 182–3.
3. Lam KY, *et al*. Peliosis of the spleen: possible association with chronic renal failure and erythropoietin therapy. *Postgrad Med J* 1995; **71:** 493–6.

Effects of subcutaneous injection. Localised pain can occur on subcutaneous injection of human recombinant erythropoietin. In comparisons of preparations it has been suggested that different excipients may affect this.[1-5] It has generally been reported that epoetin alfa preparations containing citrate buffer are more painful than those with phosphate buffer, and that epoetin beta preparations are less painful than epoetin alfa preparations.

1. Frenken LAM, *et al*. Assessment of pain after subcutaneous injection of erythropoietin in patients receiving haemodialysis. *BMJ* 1991; **303:** 288.
2. Lui SF, *et al*. Pain after subcutaneous injection of erythropoietin. *BMJ* 1991; **303:** 856.
3. Yu AW, *et al*. Pain perception following subcutaneous injections of citrate-buffered and phosphate-buffered epoetin alfa. *Int J Artif Organs* 1998; **21:** 341–3.
4. Veys N, *et al*. Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. *Clin Nephrol* 1998; **49:** 41–4.
5. Cumming MN, *et al*. Subcutaneous erythropoietin alpha (Eprex) is more painful than erythropoietin beta (Recormon). *Nephrol Dial Transplant* 1998; **13:** 817.

Treatment of adverse effects. Venesection[1] and erythropheresis[2] have been used to treat raised haematocrit and haemoglobin concentrations caused by recombinant human erythropoietin overdose. Venesection also successfully reduced the blood pressure in 4 patients with life-threatening hypertension associated with recombinant human erythropoietin treatment.[3] None of the patients had a raised haematocrit and the hypertension had been unresponsive to antihypertensive therapy.

1. Brown KR, *et al*. Recombinant erythropoietin overdose. *Am J Emerg Med* 1993; **11:** 619–21.
2. Hoffman RS, *et al*. Erythropoietin overdose treated with emergent erythropheresis. *Vet Hum Toxicol* 2002; **44:** 157–9.
3. Fahal IH, *et al*. Phlebotomy for erythropoietin-associated malignant hypertension. *Lancet* 1991; **337:** 1227.

Precautions

Epoetins should be used with caution in patients with hypertension, a history of seizures, thrombocytosis, chronic hepatic impairment, ischaemic vascular disease, or in patients with malignant tumours. Hypertension should be well controlled before treatment is started and blood pressure monitored during treatment.

Response to epoetins may be diminished by iron deficiency, infection or inflammatory disorders, haemolysis, or aluminium intoxication. Anaemia due to folic acid and vitamin B_{12} deficiencies should also be excluded, since these may also reduce the response. Patients developing sudden lack of efficacy should be investigated. If pure red cell aplasia is diagnosed treatment should be stopped and testing for epoetin antibodies considered; patients should not be transferred to another epoetin.

Patients undergoing dialysis may require increased doses of heparin in view of the increase in packed cell volume.

Platelet counts, haemoglobin concentrations, and serum-potassium concentrations should be monitored regularly.

Dosage must be carefully controlled to avoid too fast an increase in haematocrit and haemoglobin, and recommended values should not be exceeded because of the increased risks of hypertension and thrombotic events.

For reference to the potential effect of epoetins on tumour progression and progression-free survival when used in patients with cancer, see under Anaemias in Uses and Administration, p. 1142.3.

Abuse. The potential dangers from abuse of recombinant human erythropoietin by athletes have been reviewed.[1] Normally, optimal athletic conditioning leads to little change in red cell volume but a significant increase in plasma volume and total blood volume. In contrast, the artificial increase in the red cell mass induced by epoetin is usually accompanied by a decrease in plasma volume and no change in total blood volume. Lack of medical supervision and fluid loss during endurance events increase the risk of serious adverse consequences of these changes in blood viscosity produced by such misuse of epoetin. In one case,[2] cerebral sinus thrombosis in a cyclist was attributed to the combined use of epoetin, human growth hormone, and high doses of vitamins A and E.

1. Spivak JL. Erythropoietin use and abuse: when physiology and pharmacology collide. *Adv Exp Med Biol* 2001; **502:** 207–24.
2. Lage JMM, *et al*. Cyclist's doping associated with cerebral sinus thrombosis. *Neurology* 2002; **58:** 665.

Haematocrit and haemoglobin. A study[1] involving 1233 patients undergoing haemodialysis and suffering from heart failure or ischaemic heart disease found that erythropoietin in doses sufficient to increase haematocrit to 42% (within the normal range) was associated with lack of benefit and a trend towards increased mortality when compared with doses sufficient to maintain a lower haematocrit of around 30%. However, these results are difficult to interpret, since within each group, increased haematocrit was associated with lower mortality, despite the between-group differences. The possibility that intravenous iron supplementation might have contributed to these adverse results was considered, but commentators suggested that until further data were available aiming for a haematocrit of 33 to 36%, and using intravenous iron supplementation where necessary, was still appropriate.[2]

Two studies have looked at the effects of adjusting haemoglobin to different concentrations in patients with chronic renal impairment who did not yet need dialysis. In the CHOIR study[3] of 1432 patients, epoetin alfa was used to adjust haemoglobin to either 11.3 or 13.5 g per 100 mL. The risk of cardiovascular complications, particularly death and hospitalisation for congestive heart failure, was increased in the group with the higher haemoglobin target, without any additional improvement in quality of life. The CREATE study[4] included 603 patients who were treated with epoetin beta to adjust haemoglobin to either 13.0 to 15.0 g per 100 mL or 10.5 to 11.5 g per 100 mL. Although the measures for quality of life were better in the group adjusted to the higher target and there was no statistically significant difference between the groups in the risk of cardiovascular complications, there was a trend towards a more favourable outcome in the low-target group. The FDA subsequently issued a reminder[5] that in patients receiving epoetins or darbepoetin alfa, a target haemoglobin range of 10 to 12 g per 100 mL was recommended, and that haemoglobin concentrations and blood pressure should be monitored. Further information on cardiovascular effects was generated by the placebo-controlled TREAT study[6] of 4038 patients with type 2 diabetes and chronic renal disease, but not needing dialysis, in which darbepoetin alfa was used to target a maintenance haemoglobin of 13.0 g per 100 mL (a median of 12.5 was achieved), compared with about 10.6 g per 100 mL in the placebo group. Although there were no significant differences in death or overall cardiovascular events, stroke was significantly more likely to occur in patients given darbepoetin alfa. A meta-analysis[7] of 27 studies, including these 3, concluded that targeting higher haemoglobin concentrations increased the risk for stroke, hypertension, and vascular access thrombosis, and probably increased the risk for death, serious cardiovascular events, and end-stage renal disease. Subsequent to the TREAT study the FDA[8] amended its recommendations for patients with chronic renal disease: consider starting epoetin or darbepoetin alfa when the haemoglobin level is less than 10 g per 100 mL, use the lowest dose necessary to reduce the need for blood transfusion, and reduce the dose or stop therapy if the haemoglobin exceeds 10 g per 100 mL in patients not on dialysis or when it approaches or exceeds 11 g per 100 mL in patients on dialysis.

1. Besarab A, *et al*. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584–90.
2. Adamson JW, Eschbach JW. Erythropoietin for end-stage renal disease. *N Engl J Med* 1998; **339:** 625–7.
3. Singh AK, *et al*. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085–98.
4. Drüeke TB, *et al*. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355:** 2071–84.
5. FDA. Information for healthcare professionals: erythropoiesis stimulating agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)] (issued 16th November, 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126488.htm (accessed 13/08/10)
6. Pfeffer MA, *et al*. TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361:** 2019–32.
7. Palmer SC, *et al*. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010; **153:** 23–33.
8. FDA. Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease (issued 24th June, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm (accessed 02/08/11)

Resistance. Many factors may contribute to a poor response to recombinant human erythropoietin (see Precautions, above). A study in patients with anaemia of end-stage renal disease[1] found that inadequate dialysis was associated with a reduced response to erythropoietin treatment. The dialysis time and mode of dialysis may also influence response to erythropoietin therapy.[2] Antibodies to recombinant human erythropoietin have also been

reported.[3,4] Delayed clinical response to recombinant human erythropoietin in a patient[5] could have been due to an inherited subclinical pyruvate kinase deficiency.

1. Ifudu O, *et al.* The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 1996; **334:** 420–5.
2. Locatelli F, *et al.* The modality of dialysis treatment: does it influence the response to erythropoietin treatment? *Nephrol Dial Transplant* 2001; **16:** 1971–4.
3. Peces R, *et al.* Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; **335:** 523–4.
4. Viron B, *et al.* Anticorps anti-érythropoïétine humaine recombinante: une cause exceptionnelle de résistance à l'érythropoïétine. *Nephrologie* 2002; **23:** 19–22.
5. Zachée P, *et al.* Pyruvate kinase deficiency and delayed clinical response to recombinant human erythropoietin treatment. *Lancet* 1989; **i:** 1327–8.

Pharmacokinetics

Epoetins show some differences in their pharmacokinetics, possibly due to differences in glycosylation and in the formulation of the commercial preparations.

Epoetin alfa is slowly and incompletely absorbed after subcutaneous injection, and a relative bioavailability of about 10 to 20% has been reported. Peak concentrations after epoetin alfa intravenously are attained within 15 minutes, and within 5 to 24 hours after subcutaneous injection.

The elimination half-life of epoetin alfa after intravenous doses has been reported to be 4 to 13 hours in patients with chronic renal failure; the half-life is generally less in patients with normal renal function. An estimated elimination half-life of about 24 hours has been reported for epoetin alfa given subcutaneously.

Epoetin beta is similarly slowly and incompletely absorbed after subcutaneous injection, and its absolute bioavailability has been reported to be 23 to 42%. Peak serum concentrations are attained within 12 to 28 hours of subcutaneous doses. An elimination half-life of 4 to 12 hours has been reported after intravenous doses and a terminal half-life of 13 to 28 hours after subcutaneous doses.

Epoetin lambda is slowly and incompletely absorbed after subcutaneous injection, with peak serum concentrations occurring between 6 and 24 hours, and a bioavailability of 20 to 30%. After intravenous administration the mean half-life in healthy subjects ranges from 2.5 to 6.7 hours. The estimated half-life following subcutaneous use is 24 hours.

Epoetin theta is slowly and incompletely absorbed after subcutaneous injection, with peak serum concentrations occurring after about 10 to 14 hours and a bioavailability of about 31%. Elimination half-lives of 6 and 4 hours have been reported after single and repeated intravenous doses in patients with chronic renal failure undergoing haemodialysis. Half-lives ranging from 22 to 41 hours have been reported after subcutaneous injection in healthy subjects and other patient groups.

Epoetin zeta has a bioavailability of about 20% after subcutaneous injection, and peak serum concentrations occur after about 12 to 18 hours. The half-life after subcutaneous injection has been estimated to be about 24 hours. After intravenous injection, a half-life of about 4 hours has been measured in healthy subjects, and about 5 hours in patients with chronic renal failure; the half-life in children is about 6 hours.

References.
1. Macdougall IC, *et al.* Clinical pharmacokinetics of epoetin (recombinant human erythropoietin). *Clin Pharmacokinet* 1991; **20:** 99–113.
2. Halstenson CE, *et al.* Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 1991; **50:** 702–12.
3. Gladziwa U, *et al.* Pharmacokinetics of epoetin (recombinant human erythropoietin) after long term therapy in patients undergoing haemodialysis and haemofiltration. *Clin Pharmacokinet* 1993; **25:** 145–53.
4. Montini G, *et al.* Pharmacokinetics and hematologic response to subcutaneous administration of recombinant human erythropoietin in children undergoing long-term peritoneal dialysis: a multicenter study. *J Pediatr* 1993; **122:** 297–302.
5. Brown MS, *et al.* Single-dose pharmacokinetics of recombinant human erythropoietin in preterm infants after intravenous and subcutaneous administration. *J Pediatr* 1993; **122:** 655–7.
6. Reddingius RE, *et al.* Pharmacokinetics of recombinant human erythropoietin in children treated with continuous ambulatory peritoneal dialysis. *Eur J Pediatr* 1994; **153:** 850–4.
7. Chakraborty A, *et al.* Population pharmacokinetics of erythropoietin in critically ill subjects. *J Clin Pharmacol* 2005; **45:** 193–202.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Epogen; Eprex; Eritrogen; Hemax; Hypercrit; Pronivel; Recormon; ***Austral.***: Eprex; NeoRecormon; Novicrit; ***Austria***: Abseamed; Binocrit; Eporatio; Erypo; NeoRecormon; Retacrit; ***Belg.***: Binocrit; Eprex; NeoRecormon; ***Braz.***: Eprex; Eritina†; Eritromax; Hemax-Eritron; Hemoprex; Ior Epocim; Recormon; Tinax; ***Canad.***: Eprex; ***Chile***: Epokine; Eprex†; Hepta; Hypercrit; Recormon; ***China***: Epiao (益比奥); Espo (利血宝); Espogen (阿司伯根); Hemax (弘能); Huan Er Bo (环尔博); Jia Lin Hao (佳林豪); Jimaixin (济脉欣); Ninghongxin (宁红欣); Nuo Zhi Su (诺之素); Recormon (罗可曼); Sai Bo Er (赛博尔); Xue Da Sheng (雪达升); Yi Bei (依倍); Yi Pu Ding (依普定); Yi Pu Li (怡普利); Yibao (怡宝); ***Cz.***: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; ***Denm.***: Eprex; NeoRecormon; Retacrit; ***Fin.***: Eprex; NeoRecormon; ***Fr.***: Binocrit; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; ***Ger.***: Abseamed; Binocrit†; Biopoin; Dynepo†; Eporatio; Erypo; NeoRecormon; Retacrit; Silapo; ***Gr.***: Abseamed; Binocrit; Dynepo; Eprex; NeoRecormon; Recormon; Retacrit; ***Hong Kong***: Eprex; Recormon; ***Hung.***: Binocrit; Eporatio; Eprex; NeoRecormon; Retacrit; ***India***: Ceriton; Epofer; Eponis 2K; Eposis; Epotin; Epotop; Epox; Eprex; Erypro; Espogen; Hemax; LG Espogen; NeoRecormon; Wepox; ***Indon.***: Epoglobin; Epotrex-NP; Eprex; Hemapo; Recormon; ***Irl.***: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; ***Israel***: Binocrit; Eporatio; Eprex; Recormon; ***Ital.***: Abseamed; Binocrit; Dynepo†; Eprex; NeoRecormon; Retacrit; ***Jpn***: Epogin; Espo; ***Malaysia***: Eprex; Recormon; ***Mex.***: Alveritin; Bioyetin; Epomax; Eprex; Erlan; Exetin-A; Hypercrit†; Negortire; Recormon; Yepotin†; ***Neth.***: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; ***Norw.***: Eprex; NeoRecormon; Retacrit; ***NZ***: Eprex; NeoRecormon; Recormon†; ***Philipp.***: Efotin; Epogen; Epokine; Eposino; Epotin; Eprex; Recormon; Renogen; Shanpoietin; Wepox; ***Pol.***: Abseamed; Binocrit; Biopoin; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; ***Port.***: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; ***Rus.***: Epocomb (Эпокомб); Epocrin (Эпокрин); Epostim (Эпостим); Eprex (Эпрекс); Eralfon (Эральфон); Erythrostim (Эритростим); Recormon (Рекормон); ***S.Afr.***: Eprex; Recormon; Repotin; ***Singapore***: Eprex; Recormon; ***Spain***: Binocrit; Dynepo†; Epopen†; Eporatio; Eprex; NeoRecormon; Retacrit; ***Swed.***: Binocrit; Eporatio; Eprex; NeoRecormon; Retacrit; ***Switz.***: Abseamed; Binocrit; EpoTheta; Eprex; Recormon; ***Thai.***: EPIAO; Epokine; EPOO†; Eporon†; Eposis; Eprex; Eritine; Eritrogen; Espogen; Hemapo; Hemax; Recormon; Renogen; ***Turk.***: Epobel; Eprex; NeoRecormon; Recormon; ***UAE***: Epotin; ***UK***: Binocrit; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; ***Ukr.***: Epobiokrin (Эпобиокрин); Epovitan (Эповитан); Erythroetin (Эритроэтин); Recormon (Рекормон); Wepox (Вепокс)†; ***USA***: Epogen; Procrit; ***Venez.***: Eprex; Hypercrit; Recormon.

Pharmacopoeial Preparations
BP 2014: Erythropoietin Injection.

Etamsylate *(BAN, rINN)*

Ciclonamina; Cyclonamine; E-141; Etamsilat; Etamsilatas; Etamsilato; Etamsylaatti; Etamsylat; Etamsylát; Étamsylate; Etamsylatum; Etamszilát; Ethamsylate (USAN); Ethamsylate; MD-141; Этамзилат.

Diethylammonium 2,5-dihydroxybenzenesulphonate.

$C_{10}H_{17}NO_5S$=263.3

CAS — 2624-44-4.

ATC — B02BX01.

ATC Vet — QB02BX01.

UNII — 24YL531VOH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Etamsylate). A white or almost white, crystalline powder. It shows polymorphism. Very soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 10% solution in water has a pH of 4.5 to 5.6. Store in airtight containers. Protect from light.

Uses and Administration

Etamsylate is a haemostatic that appears to maintain the stability of the capillary wall and correct abnormal platelet adhesion. It is given for the prophylaxis and control of haemorrhages from small blood vessels.

For short-term treatment of blood loss in menorrhagia (below) a dose of 500 mg is given orally four times daily during menstruation. For the control of haemorrhage after surgery etamsylate may be given orally or by intramuscular or intravenous injection in a dose of 250 to 500 mg. A dose may be given 1 hour before surgery, and further doses given after surgery and repeated every 4 to 6 hours as necessary. Intravenous doses may be given during surgery if necessary. For etamsylate use in prophylaxis of neonatal intraventricular haemorrhage, see below.

Administration in children. For information on etamsylate prophylaxis of intraventricular haemorrhage in premature neonates, see below.

Menorrhagia. When given during menstruation to women with idiopathic menorrhagia (p. 2300.3), etamsylate was as effective as mefenamic acid in reducing uterine blood loss in 1 study,[1] but was ineffective in another.[2] A review, which included published and unpublished results from these and 2 earlier studies, reported that etamsylate produced about a 10 to 15% reduction in menstrual blood loss.[3] Etamsylate is now considered to be less effective than other treatments for menorrhagia, and is no longer recommended.[4]

1. Chamberlain G, *et al.* A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. *Br J Obstet Gynaecol* 1991; **98:** 707–11.
2. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313:** 579–82.
3. Coulter A, *et al.* Treating menorrhagia in primary care: an overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care* 1995; **11:** 456–71.
4. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 06/03/08)

Neonatal intraventricular haemorrhage. Etamsylate is one of several drugs that have been tried in the prevention of intraventricular haemorrhage in very low birthweight infants (p. 1128.3). In some countries it is licensed for intramuscular use in doses of 10 mg/kg. The first dose is given within the first 2 hours after birth, and repeated every 6 hours for 4 days.

Some studies have used mainly the intravenous route. In a multicentre, placebo-controlled, double-blind study,[1] etamsylate was given in an initial dose of 12.5 mg/kg intravenously or intramuscularly within 1 hour of delivery, followed by the same dose intravenously every 6 hours for 4 days to a total dose of 200 mg/kg. Of 330 infants who had had no evidence of haemorrhage soon after delivery, the subsequent incidence of haemorrhage in the 162 who received etamsylate was reduced, particularly the more extensive grades when compared with the 168 who received placebo. Of a further 30 infants with evidence of periventricular haemorrhage before treatment, 21 were given etamsylate and 9 placebo; treatment with etamsylate limited the extension of bleeding. There was also a reduction in patent ductus arteriosus in the treated infants. However, a subsequent study using the same dosage regimen,[2] showed little benefit on short-term follow-up. It was considered that the study size may have been too small and the drug given too late; the initial dose was given within 4 hours of birth whereas, in the previous study, treatment was started within 1 hour of birth. Follow-up[3] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Developmental outcome assessments at about 4 years of age in patients from the first study[4] also found that despite the original reduction in intraventricular haemorrhage with etamsylate, it had not reduced cerebral palsy compared with the control group.

1. Benson JWT, *et al.* Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet* 1986; **ii:** 1297–1300.
2. The EC Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates: early mortality and morbidity. *Arch Dis Child* 1994; **70:** F201–F205.
3. Elbourne D, *et al.* Randomised controlled trial of prophylactic etamsylate: follow up at 2 years of age. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F183–F187.
4. Schulte J, *et al.* Developmental outcome of the use of etamsylate for prevention of periventricular haemorrhage in a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F31–F35.

Adverse Effects and Precautions

Nausea, vomiting, diarrhoea, fever, headache, and rashes have occurred after use of etamsylate. Headache and rashes may disappear on reduced dosage, and gastrointestinal disturbances are reduced by giving etamsylate after food. Transient hypotension has been reported after intravenous injection.

Pharmacokinetics

Etamsylate is absorbed from the gastrointestinal tract. It is excreted unchanged, mainly in the urine. Etamsylate is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Impedil; ***Belg.***: Dicynone; ***Braz.***: Dicinone; ***Chile***: Dicynone; ***China***: Ai Fen (艾分); An Di Xin (安迪欣); Heng Zhi (恒智); Ka Le (卡乐); Lizhining (力制凝); Ni Ji (尼基); Tian Yi Shu (天亦舒); Xun Di (迅迪); Zhuo Xun (卓迅); ***Cz.***: Dicynone; ***Fr.***: Dicynone; ***Hung.***: Dicynone; ***India***: Alstat; Amilate; Bloc; Botrostat; C-Sylate; Capilyte; Clotawin; Cosklot; Cotham; Culoc; Dicynene; Disylate; Eith; Eklot; Elyte; Emsulate; Ensulate; Eselin; Ethacid; Ethafy; Ethaklot; Ethamcip; Ethams; Ethamstat; Ethariv; Ethasyl; Etholate; Ethver; Ethylate; Eustal; Floban; H-Stat; Hamodam; Hemklot; Hemoclot; Hemolate; Hemostat; Hemsyl; Himolan; Kelate; Kloty; Late; Masyla; Mazo; Medistat; Noflo; Revici-E; ***Indon.***: Dicynone; ***Irl.***: Dicynene; ***Ital.***: Dicynone; Eselin; ***Mex.***: Dicynone; ***Rus.***: Dicynone (Дицинон); ***Singapore***: Dicynone; ***Spain***: Dicinone†; Hemo 141; ***Switz.***: Dicynone; ***UK***: Dicynene; ***Ukr.***: Dicynone (Дицинон); ***Venez.***: Dicynone.

Multi-ingredient Preparations. ***India***: C-Sylate Plus; Capihem; Capitrax Plus; Clotawin-T; Clotem Plus; Coag; Coastat Plus; Cosklot Plus; Eklot-MF; Etam; Etex-T; Ethatol; ETM-T; Etosys;

Fetran-ES; Fibran Plus; Hamodam-T; Hemocrat; Klotinex; Menoguard; Menostat; No Blos For.

Etherified Starches ⊗

Almidón, éteres de; HES; Hydroxyethyl Starch; Hydroxyéthylamidon; Hydroxyethylamylum.
2-Hydroxyethyl ether starch.
CAS — 9005-27-0.
ATC — B05AA07.
ATC Vet — QB05AA07.
UNII — 875Y4127EA (hetastarch).

Description. Etherified starches are starches that are composed of more than 90% of amylopectin and that have been etherified to varying extents.

- hetastarch (*BAN*, *USAN*): an average of 7 or 8 of the hydroxy groups in each 10 D-glucopyranose units of starch polymer have been converted into OCH_2CH_2OH groups
- hydroxyethyl starch 130/0.4 (*USAN*): an average of 3.8 to 4.5 of the hydroxy groups in each 10 D-glucopyranose units of starch polymer have been converted into OCH_2CH_2OH groups
- pentastarch (*BAN*, *USAN*): an average of 4 or 5 of the hydroxy groups in each 10 D-glucopyranose units of the starch polymer have been converted to OCH_2CH_2OH groups

Etherified starches also vary in terms of average molecular weight and the position of etherification within the glucopyranose unit.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Starches, Hydroxyethyl; Amyla Hydroxyethyla). Hydroxyethyl starches are partially substituted poly(2-hydroxyethyl)ethers of waxy maize starch or potato starch, which primarily consist of amylopectin. The type of hydroxyethyl starch is defined by 2 numbers: the mean molecular weight and the number of hydroxyethyl groups per anhydroglucose unit expressed as the molar substitution. Hydroxyethyl starch is also characterised by the number of hydroxyethyl groups located at the C2 group over the number of hydroxyethyl groups located at C6, expressed as the C2/C6 ratio. White or almost white powders. Hygroscopic until a water content of about 12 to 15% is reached. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in anhydrous ethanol.

Incompatibility. Hetastarch is incompatible with many compounds including some injectable antibacterials.

References.

1. Wohlford JG, Fowler MD. Visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1989; **46:** 995–6.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.

Uses and Administration

Etherified starches are plasma volume expanders used in the management of hypovolaemic shock (p. 1279.3). Those most commonly used include high-molecular-weight hetastarch (weight average molecular weight 450 000 to 480 000) and medium-molecular-weight pentastarch (weight average molecular weight 200 000 to 250 000). Other etherified starches that are used include low-molecular-weight tetrastarch (hydroxyethyl starch 130/0.4), low-molecular-weight pentastarch, and medium-molecular-weight hexastarch, which has a degree of etherification between that of pentastarch and hetastarch. A higher molecular weight hetastarch is also available. Isooncotic solutions of etherified starches, for example, 6% hetastarch or 6% medium-molecular-weight pentastarch, exert a similar colloidal osmotic pressure to human albumin, and when given by intravenous infusion produce an expansion of plasma volume slightly in excess of the infused volume. Hyperoncotic solutions, for example 10% medium-molecular-weight pentastarch, produce an expansion of plasma volume of about 1.5 times the infused volume. The duration of effect depends on the characteristics of the starch used; for 6% hetastarch the effect lasts for 24 to 36 hours.

Etherified starches are given intravenously as solutions in sodium chloride 0.9% or other electrolytes; concentrations used are usually 6 or 10%, although 3% solutions are also available for some. The dose and rate of infusion depend on the amount of fluid lost and degree of haemoconcentration; usual doses are in the range of 500 to 2500 mL daily, depending on the preparation used, and the infusion rate may be up to about 20 mL/kg per hour if necessary.

Hetastarch and pentastarch increase the erythrocyte sedimentation rate when added to whole blood. They are therefore used in leucapheresis procedures to increase the yield of granulocytes. Doses of 250 to 700 mL may be added to venous blood in the ratio 1 part to at least 8 parts of whole blood in such procedures. Up to 2 such procedures per week and a total of 7 to 10 have been reported to be safe.

Hetastarch and hexastarch have also been used in extracorporeal perfusion fluids.

References.

1. Treib J, *et al.* An international view of hydroxyethyl starches. *Intensive Care Med* 1999; **25:** 258–68.

Administration in children. Etherified starches of various degrees of substitution and molecular weights have been used as plasma expanders in children.[1-3]

1. Brutocao D, *et al.* Comparison of hetastarch with albumin for postoperative volume expansion in children after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1996; **10:** 348–51.
2. Paul M, *et al.* A randomized, controlled study of fluid management in infants and toddlers during surgery: hydroxyethyl starch 6% (HES 70/0.5) vs lactated Ringer's solution. *Paediatr Anaesth* 2003; **13:** 603–8.
3. Liet J-M, *et al.* Plasma volume expansion by medium molecular weight hydroxyethyl starch in neonates: a pilot study. *Pediatr Crit Care Med* 2003; **4:** 305–7.

Stroke. Haemodilution with pentastarch has been tried in patients with acute ischaemic stroke (p. 1269.2) in an attempt to improve reperfusion of the brain by lowering blood viscosity. However, one study was terminated early when an excess mortality was noted in the haemodilution group.[1] The early fatalities occurred almost exclusively in patients with severe strokes; cerebral oedema was the main cause of death within one week of the onset of symptoms. Among the survivors neurological recovery was better among those who received haemodilution. A systematic review[2] of 18 haemodilution studies, which included 5 using etherified starches, found no benefit in terms of fatality or functional outcome with haemodilution. See also Effects on the Blood, below

1. Hemodilution in Stroke Study Group. Hypervolemic hemodilution treatment of stroke: results of a randomized multicenter trial using pentastarch. *Stroke* 1989; **20:** 317–23.
2. Asplund K. Haemodilution for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 27/10/05).

Adverse Effects and Precautions

Hypersensitivity reactions including anaphylactic reactions have occurred after infusion of etherified starches. Pruritus can occur after long-term use of high doses of etherified starches; the onset may be delayed until weeks after the last infusion. Serum-amylase concentrations may appear to increase during infusion of etherified starches due to formation of an enzyme-substrate complex that is only eliminated slowly.

Precautions that should be observed with plasma expanders are described under Dextran 70, p. 1139.2, and these should be considered when etherified starches are used. There may be some interference with blood grouping and cross-matching of blood.

Reviews.

1. Wiedermann CJ. Hydroxyethyl starch - can the safety problems be ignored? *Wien Klin Wochenschr* 2004; **116:** 583–94.

Effects on the blood. Use of plasma expanders causes dilution of clotting factors and may also have direct effects on coagulation. Effects of etherified starches on the coagulation system include[1,2] a decrease in clotting factor VIII and von Willebrand factor that results in an acquired type I von Willebrand disease (see p. 1129.3), a prolongation of the activated partial thromboplastin time, and a reduction in platelet volume. The extent of these effects appears to depend on the molecular weight and the rate of degradation *in vivo* of the starch. Etherified starches of high molecular weight that are more slowly degraded (due to a high degree of substitution or a high ratio of hydroxyethylation at the C2:C6 positions) have a greater effect on blood coagulation than medium and low molecular weight, easily degraded, etherified starches. Coagulopathy and haemorrhage have been reported with the use of solutions of etherified starches.[1,3] Serious complications such as intracranial bleeding and cerebral oedema have been reported in studies of patients with ischaemic stroke and other brain injuries who have been treated with etherified starches of various molecular weights and degrees of substitution, and several studies have been stopped prematurely as a result.[4]

1. Treib J, *et al.* Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78:** 974–83.
2. de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; **29:** 1261–7.
3. Jonville-Béra A-P, *et al.* Acquired type I von Willebrand's disease associated with highly substituted hydroxyethyl starch. *N Engl J Med* 2001; **345:** 622–3.
4. Wiedermann CJ. Complications of hydroxyethyl starch in acute ischemic stroke and other brain injuries. *Pathophysiol Haemost Thromb* 2003; **33:** 225–8.

Effects on the kidneys. Osmotic-nephrosis-like lesions found at biopsy in some transplanted kidneys have been attributed to use of solutions of etherified starches in the donor patient.[1] Such use has also been reported to impair immediate graft function.[2] However, another study[3] found no association between the use of these solutions in the donor patient and osmotic-nephrosis-like lesions or delayed graft function. Oliguric acute renal failure and osmotic-nephrosis-like lesions occurred in a patient who was given an etherified starch infusion during surgery for carcinoma of the tonsils.[4]

Etherified starches should be used with caution in patients with renal impairment.

1. Legendre CH, *et al.* Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; **342:** 248–9.
2. Cittanova ML, *et al.* Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **348:** 1620–22.
3. Coronel B, *et al.* Hydroxyethylstarch and renal function in kidney transplant recipients. *Lancet* 1997; **349:** 884.
4. De Labarthe A, *et al.* Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient. *Am J Med* 2001; **111:** 417–18.

Effects on the skin. Pruritus has been reported after infusion of etherified starches.[1] It appears to be associated with tissue deposition of the starch although the actual mechanism by which this provokes pruritus is unresolved. The effect appears to be dose-related, which may explain the differences in reported incidences that have ranged from less than 10% to more than 60% of patients being affected. The molecular weight and degree of substitution of the etherified starch do not appear to be risk factors. The pruritus is usually generalised, but there are reports of localised pruritus affecting the trunk, extremities, anogenital area, and head and neck. It is frequently severe, persistent, and refractory to treatment, causing sleep disturbances and adversely affecting quality of life. Attacks of pruritus may be precipitated by heat, sweating, exercise, bathing, mechanical pressure, and mental stress. It typically has a delayed onset of 1 to 6 weeks after exposure to the etherified starch. Average durations of 9 to 15 weeks have been reported, but in some cases pruritus has continued for up to 2 years. The condition is generally unresponsive to treatment, although there have been reports of relief with topical capsaicin, ultraviolet therapy, or oral naltrexone.

Marked and persistent periocular swelling developed in a patient after 15 daily infusions of hetastarch.[2] Abnormal accumulation of hetastarch was found in the periocular tissues.

1. Bork K. Pruritus precipitated by hydroxyethyl starch: a review. *Br J Dermatol* 2005; **152:** 3–12.
2. Kiehl P, *et al.* Decreased activity of acid α -glucosidase in a patient with persistent periocular swelling after infusions of hydroxyethyl starch. *Br J Dermatol* 1998; **138:** 672–77.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etherified starches (hydroxyethylstarch) as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

Etherified starches consist of mixtures of molecules with a range of molecular weights and with varying degrees of etherification. After intravenous infusion the molecules with a molecular weight of less than 50 000 are readily excreted unchanged by the kidney; larger molecules are metabolised and eliminated more slowly. The rate of metabolism depends upon the size of the molecule and the degree and position of etherification, with a high molecular weight, high degree of etherification, and etherification mainly at the C2 position leading to a slower rate of metabolism and hence a longer duration of action. About 33% of a dose of high-molecular-weight hetastarch (weight average molecular weight 450 000) and about 70% of a dose of medium-molecular-weight pentastarch (weight average molecular weight 250 000) is excreted in the urine in 24 hours. Etherified starches may be distributed to various tissues; a small proportion of the dose may persist in the body for several years.

References.

1. Mishler JM, *et al.* Changes in the molecular composition of circulating hydroxyethyl starch following consecutive daily infusions in man. *Br J Clin Pharmacol* 1979; **7:** 505–9.
2. Mishler JM, *et al.* Post-transfusion survival of hydroxyethyl starch 450/0.70 in man: a long-term study. *J Clin Pathol* 1980; **33:** 155–9.
3. Yacobi A, *et al.* Pharmacokinetics of hydroxyethyl starch in normal subjects. *J Clin Pharmacol* 1982; **22:** 206–12.
4. Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinet* 2005; **44:** 681–99.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hemohes; Hessico; Infukoll HES; Lorihess; Venofundin; Voluven; ***Austral.***: Voluven; ***Austria***: HAES-steril; Hemohes†; HyperHAES; PlasmaHES; Tetraspan; Venofundin; Volulyte; Voluven; ***Belg.***: Venohes; ***Canad.***: Hextend; Pentaspan; Volulyte; Voluven; ***Chile***: HAES-steril; Hemohes; Voluven; ***China***: HAES-steril (贺斯); Hemohes (海

斯); Huo Mu (霍姆); HyperHAES (贺苏); Venofundin (文诺方汀); Voluven (万汶); Ying Yuan (盈源); ***Cz.***: HAES-steril; Hemohes†; HyperHAES; Plasma Volume; Serag-HAES†; Tetraspan; Volulyte; Voluven; ***Denm.***: HAES-steril; Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; ***Fin.***: HAES-steril†; Hemohes†; Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; ***Fr.***: Heafusine; Hyperhes; PlasmaVolume; Plasmohes; Restorvol; Voluven; ***Ger.***: HAES-Rheopond†; HAES-steril; Hemohes; HyperHAES; Infukoll HES; PlasmaVolume; Rheohes†; Serag-HAES†; Tetraspan; Venofundin; Vitafusal; VitaHES; Volulyte; Voluven; ***Gr.***: HAES-steril; Hemohes; Hespan; PlasmaVolume; Tetraspan; Venofundin; Volulyte; Voluven; ***Hong Kong***: Tetraspan; Volulyte; Voluven; ***Hung.***: HAES-steril; Hesra; HyperHAES; Tetraspan; Volulyte; Voluven; ***India***: Expan; HAES-steril; Hestar; ***Indon.***: Expafusin; Fima HES; HAES-steril; Hemohes†; TetraHES; Voluven; WIDAHES; ***Irl.***: HyperHAES; Plasma Volume; Venofundin†; Volulyte; ***Israel***: HAES-sterile; Hemohes; Voluven; ***Ital.***: Amidolite; HAES-steril; HyperHAES; PlasmaVolume; Tetraspan; Volulyte; Voluven; ***Jpn***: Hespander; ***Malaysia***: Voluven; ***Mex.***: HAES-steril; Hestar; Voluven; ***Neth.***: Elohaes; HAES-steril†; Hemohes†; HyperHAES; PlasmaVolume; Tetraspan; Venofundin; Volulyte; Voluven; ***Norw.***: Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; ***NZ***: Hemohes†; Venofundin; Voluven; ***Philipp.***: HAES-steril; Volulyte; Voluven; Xpand; ***Pol.***: HAES-steril; Hemohes; HyperHAES; Tetraspan; Volulyte; Voluven; ***Port.***: HAES-steril; Hemohes†; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; ***Rus.***: HAES-steril (ХАЕС-стерил); Hemohes (Гемохес); HyperHAES (ГиперХАЕС); Infukoll HES (Инфукол ГЭК); Plasmaline (Плазмалин); PolyHES (ПолиХЭС); Refortan (Рефортан); ReoHES (РеоХЕС); Stabisol (Стабизол); Tetraspan (Тетраспан); Volecam (Волекам); Volemcor (Волемкор); Voluven (Волювен); ***S.Afr.***: HAES-steril; Venofundin; Vitahes; Voluven; ***Singapore***: HAES-steril†; Hemohes; Volulyte; Voluven; ***Spain***: Hemohes; Hes Grifols†; PlasmaVolume; Volulyte; Voluven; ***Swed.***: HAES-steril†; Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; ***Switz.***: HAES-steril; Hemohes†; HyperHAES; Tetraspan; Venofundin; Voluven; ***Thai.***: HAES-steril†; Hemohes; Hestar†; TetraHes; Tetraspan; Volulyte; Voluven; ***Turk.***: Biohes; Bioplazma†; Expahes; HAES-steril; Hemohes†; HyperHAES; Isohes; Plasmasteril†; Varihes; Voluven; ***UK***: HAES-steril†; Hemohes†; HyperHAES†; Infukoll†; Tetraspan†; Venofundin†; Volulyte†; Voluven†; ***Ukr.***: Gecodes (Гекодез); Haecodes (Гекодез); HAES-steril (Хаэс-Стерил); Hetasorb (Хетасорб); HyperHAES (ГиперХАЕС); Refortan (Рефортан); Stabizol (Стабизол); Venofundin (Венофундин); Voluven (Волювен); ***USA***: Hespan; Pentaspan; Voluven.

Multi-ingredient Preparations. ***Belg.***: Tetraspan; ***Irl.***: EquiHes; Voluven; ***Spain***: Isohes; ***Thai.***: Infukoll HES†.

Factor VII

Facteur VII; Factor estable; Proconvertin; Proconvertina; SPCA; Stable Factor; Фактор VII.

ATC — B02BD05.

ATC Vet — QB02BD05.

UNII — 4156XVB4QD (human factor VII); 15FH07392N (human factor VIIa).

Description. Factor VII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Eptacog Alfa (Activated) is in use for a recombinant factor VIIa.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Coagulation Factor VII; Factor VII Coagulationis Humanus; Dried Factor VII Fraction BP 2014). A sterile, liquid or freeze-dried preparation of a plasma protein fraction that contains the single-chain glycoprotein factor VII and may also contain small amounts of the activated form, the two-chain derivative factor VIIa, as well as coagulation factors II, IX, and X, and protein C and protein S. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VII fraction is dissolved in a suitable liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. No antimicrobial preservative or antibiotic is added. The specific activity is not less than 2 international units of factor VII per mg of protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 15 international units/mL.

A white or almost white, pale yellow, green, or blue hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Eptacog Alfa (Activated) *(BAN, rINN)*

Eptacog alfa (activado); Eptacog Alfa (activé); Eptacogum Alfa (activatum); Эптаког Альфа (Активированный).

Blood-coagulation factor VII (human clone λHVII2463 protein moiety).

CAS — 102786-52-7; 102786-61-8.

ATC — B02BD08.

ATC Vet — QB02BD08.

UNII — AC71R787OV.

Units

The potency of factor VII is expressed in international units and preparations may be assayed using the International Standard for blood coagulation factor VII concentrate, human (1998).

The potency of factor VIIa (activated factor VII) is expressed in international units and preparations may be assayed using the first International Standard for blood coagulation factor VIIa concentrate (1993).

Uses and Administration

Factor VII may be used as replacement therapy in patients with rare genetic deficiencies of factor VII.

Factor VIIa (activated factor VII) is used to treat bleeding episodes and to prevent bleeding associated with surgery in patients with haemophilia A or haemophilia B who have developed antibodies to factor VIII or factor IX, respectively, and in acquired haemophilia (see Haemophilias, p. 1126.3). It may also be used in congenital factor VII deficiency and Glanzmann's thrombasthenia (see Inherited Haemorrhagic Disorders, p. 1128.2). Factor VIIa may also be useful in patients with von Willebrand's disease (p. 1129.3). Factor VIIa is given as the recombinant form, eptacog alfa (activated). Eptacog alfa (activated) 100 micrograms is equivalent to 5000 international units.

In the treatment of bleeding episodes in patients with **haemophilia**, an initial dose of eptacog alfa (activated) 90 micrograms/kg is given by intravenous bolus injection over 2 to 5 minutes. Further doses may be given as required to achieve and maintain haemostasis, initially every 2 to 3 hours. The dose may then be adjusted (effective doses have ranged from 35 to 120 micrograms/kg), or the dosing interval increased, according to response. Treatment may need to be continued for up to 3 weeks or more following serious bleeding episodes. A similar regimen may be used in patients with haemophilia when they undergo an invasive procedure or surgery, in which case the initial dose should be given immediately before the intervention. Mild to moderate episodes of joint, muscle, or mucocutaneous bleeding may be adequately managed with 2 or 3 doses of 90 micrograms/kg given at 3-hour intervals, with 1 additional dose if required; alternatively, a single dose of 270 micrograms/kg may be given. When these regimens for mild to moderate bleeding are used as home therapy, treatment should not exceed 24 hours.

In **factor VII deficiency**, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 15 to 30 micrograms/kg every 4 to 6 hours until haemostasis is achieved.

In **Glanzmann's thrombasthenia** that is refractory to platelet transfusions, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 90 micrograms/kg every 2 hours; at least 3 doses should be given.

Eptacog alfa pegol (activated), a long-acting pegylated form of the drug, is under investigation in patients with haemophilias A and B who have developed antibodies.

Reviews.

1. Poon M-C. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol* 2001; **8:** 312–18.
2. Midathada MV, *et al.* Recombinant factor VIIa in the treatment of bleeding. *Am J Clin Pathol* 2004; **121:** 124–37.
3. Anonymous. Novoseven for non-hemophilia hemostasis. *Med Lett Drugs Ther* 2004; **46:** 33–4.
4. Parameswaran R, *et al.* Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; **11:** 100–106.
5. Siddiqui MAA, Scott LJ. Recombinant factor VIIa (eptacog alfa): a review of its use in congenital or acquired haemophilia and other congenital bleeding disorders. *Drugs* 2005; **65:** 1161–77.
6. Mariani G, *et al.* Congenital factor VII deficiency: therapy with recombinant activated factor VII—a critical appraisal. *Haemophilia* 2006; **12:** 19–27.
7. Sumner MJ, *et al.* Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. *Haemophilia* 2007; **13:** 451–61.
8. Obergfell A, *et al.* Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature. *Haemophilia* 2008; **14:** 233–41.

Administration. Recombinant factor VIIa is usually given by bolus intravenous injection. The successful use of continuous infusion has been described in a few small studies and case reports.[1]

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; **36:** 882–91.

Administration in children. Children are generally given similar microgram/kg doses of eptacog alfa (activated) to those used in adults for bleeding in haemophilia (see above). However, children clear the drug faster than adults and may need higher doses to achieve similar plasma concentrations.

The use of eptacog alfa (activated) in children for bleeding of various causes has been reviewed.[1,2]

1. Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders–a 2006 review. *Haemophilia* 2006; **12:** 457–72.
2. Goldstein B, *et al.* Evidence-based use of recombinant FVIIa (NovoSeven, NiaStase) for the treatment of hemophilia with inhibitors in children and adolescents. *Transfus Apher Sci* 2008; **38:** 25–32.

Haemorrhagic disorders. As well as being used in patients with haemophilia, recombinant factor VIIa has been tried or investigated in patients with bleeding of various other causes.[1,2] There have been reports of recombinant factor VIIa used to manage or prevent bleeding associated with oral[3-5] or parenteral[6] anticoagulants. There are also a few reports of it successfully controlling bleeding associated with diffuse alveolar haemorrhage[7-9] or dengue haemorrhagic fever;[10] it has also been studied in the management of acute variceal bleeding (p. 2563.1). In the management of massive postpartum haemorrhage (p. 2130.2), recombinant factor VIIa is increasingly being used when standard medical and surgical therapies are inadequate. There are suggestions that it may reduce the need for blood products, control bleeding sufficiently to allow transfer of the patient to a facility where angiography and embolisation can be performed, and reduce the need for hysterectomy.[11] However, evidence consists largely of case reports and case series. Although advice has been published, based on this evidence and expert opinion,[12] the place of recombinant factor VIIa in the treatment of postpartum haemorrhage remains to be confirmed. Initial investigation of recombinant factor VIIa in the acute management of intracerebral haemorrhage was promising,[13] but a phase 3 study found that it did not reduce the rates of death or severe disability, compared with placebo.[14] Recombinant factor VIIa is also under investigation in the management of serious bleeding after surgery or trauma.[15,16]

1. Lam MSH, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. *Ann Pharmacother* 2005; **39:** 885–91.
2. Mallarkey G, *et al.* An evaluation of eptacog alfa in nonhaemophiliac conditions. *Drugs* 2008; **68:** 1665–89.
3. Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002; **137:** 884–8.
4. Freeman WD, *et al.* Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clin Proc* 2004; **79:** 1495–1500.
5. Talkad A, *et al.* Reversal of warfarin-induced anticoagulation with factor VIIa prior to rt-PA in acute stroke. *Neurology* 2005; **64:** 1480–1.
6. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; **44:** 718–26.
7. Betensley AD, Yankaskas JR. Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. *Am J Respir Crit Care Med* 2002; **166:** 1291–2.
8. Pastores SM, *et al.* Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. *Chest* 2003; **124:** 2400–2403.
9. Henke D, *et al.* Successful treatment of diffuse alveolar hemorrhage with activated factor VII. *Ann Intern Med* 2004; **140:** 493–4.
10. Chuansumrit A, *et al.* The use of recombinant activated factor VII for controlling life-threatening bleeding in dengue shock syndrome. *Blood Coag Fibrinol* 2004; **15:** 335–42.
11. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. *Int J Obstet Anesth* 2007; **16:** 29–34.
12. Welsh A, *et al.* Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. *Aust N Z J Obstet Gynaecol* 2008; **48:** 12–16.
13. Mayer SA, *et al.* Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352:** 777–85.
14. Mayer SA, *et al.* FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; **358:** 2127–37.
15. Dutton RP, *et al.* Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; **57:** 709–18.
16. Levi M, *et al.* Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med* 2005; **33:** 883–90.

Adverse Effects and Precautions

Use of eptacog alfa (activated) may be associated with nausea, vomiting, skin reactions, fever, headache, and changes in blood pressure. Reports of hypersensitivity including anaphylaxis are rare, but eptacog alfa (activated) should be avoided or used with caution in patients who are known to be hypersensitive to *mouse*, *hamster*, or *bovine* proteins. Eptacog alfa (activated) should be used with caution in patients with conditions associated with circulating tissue factor, such as advanced atherosclerosis, crush injury, or septicaemia, since there is a risk of precipitating thrombosis or disseminated intravascular coagulation.

Effects on the cardiovascular system. Reports of 185 serious thromboembolic events associated with eptacog alfa (activated), that had been received by the FDA up to the end of 2004, have been reviewed.[1] Data were collected from both clinical studies and spontaneous reports. Various forms of arterial and venous thrombosis had been described, and most events were found to have occurred after its use for unlicensed indications in patients without haemophilia. Thromboembolism in haemophiliacs treated with eptacog alfa (activated) between May 2003 and December 2006 has also been reviewed.[2] The average risk of a thromboembolic event was about 3.75 per 100 000 infusions.

1. O'Connell KA, *et al.* Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; **295:** 293–8.
2. Abshire T, Kenet G. Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors. *Haemophilia* 2008; **14:** 898–902.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eptacog alfa as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Eptacog alfa (activated) should not be used with activated or nonactivated prothrombin complex concentrates because of an increased risk of thromboembolism.

Pharmacokinetics

The mean terminal half-life of eptacog alfa (activated) is about 3 hours. However, clearance appears to be related to age, and may be increased by more than 50% in children.

References.
1. Klitgaard T, Nielsen TG. Overview of the human pharmacokinetics of recombinant activated factor VII. *Br J Clin Pharmacol* 2008; **65:** 3–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: NovoSeven; ***Austral.***: NovoSeven; ***Austria***: NovoSeven; ***Belg.***: NovoSeven; ***Braz.***: NovoSeven; ***Canad.***: NiaStase; ***Chile***: NovoSeven; ***China***: NovoSeven (诺其); ***Cz.***: NovoSeven; ***Denm.***: NovoSeven; ***Fin.***: NovoSeven; ***Fr.***: NovoSeven; ***Ger.***: Immuseven; NovoSeven; ***Gr.***: NovoSeven; ***Hong Kong***: NovoSeven; ***Hung.***: NovoSeven; ***India***: NovoSeven; ***Irl.***: NovoSeven; ***Israel***: NovoSeven; ***Ital.***: NovoSeven; Provertin-UM TIM 3; ***Jpn***: NovoSeven; ***Malaysia***: NovoSeven; ***Mex.***: NovoSeven; ***Neth.***: NovoSeven; ***Norw.***: NovoSeven; ***NZ***: NovoSeven; ***Philipp.***: NovoSeven; ***Pol.***: NovoSeven; ***Port.***: NovoSeven; ***Rus.***: Coagil-VII (Коагил-VII); NovoSeven (НовоСэвен); ***S.Afr.***: NovoSeven; ***Singapore***: NovoSeven; ***Spain***: NovoSeven; ***Swed.***: NovoSeven; ***Switz.***: NovoSeven; ***Thai.***: NovoSeven; ***Turk.***: NovoSeven; ***UK***: NovoSeven; ***Ukr.***: NovoSeven (Новосевен); ***USA***: NovoSeven.

Pharmacopoeial Preparations
Ph. Eur.: Human Coagulation Factor VII.

Factor VIII

AHF; Antihaemophilic Factor; Facteur VIII; Factor antihemofílico A; Антигемофилический Фактор; Фактор VIII.
ATC — B02BD02.
ATC Vet — QB02BD02.
UNII — 839MOZ74GK (human factor VIII); P89DR4NY54 (recombinant human factor VIII).

Description. Factor VIII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The names Moroctocog Alfa (see below), Octocog Alfa (see below), and Rurioctocog Alfa are in use for recombinant factor VIII.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Coagulation Factor VIII; Factor VIII Coagulationis Humanus; Dried Factor VIII Fraction BP 2014). A sterile freeze-dried preparation of a plasma protein fraction that contains the glycoprotein coagulation factor VIII with varying amounts of von Willebrand factor, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VIII fraction is dissolved in an appropriate liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Auxiliary substances such as a stabiliser may be added. No antimicrobial preservative or antibiotic is added. The specific activity is not less than 1 international unit of factor VIII:C per mg of total protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 20 international units of factor VIII:C per mL.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Human Coagulation Factor VIII (rDNA); Factor VIII Coagulationis Humanus (ADNr)Dried Factor VIII (rDNA) BP 2014). A freeze-dried preparation of glycoproteins having the same activity as coagulation factor VIII in human plasma. It is prepared as full-length factor VIII (octocog alfa), or as a shortened two-chain structure (relative molecular mass 90 000 and 80 000), in which the B-domain has been deleted from the heavy chain (moroctocog alfa). Full-length human rDNA coagulation factor VIII contains 25 potential *N*-glycosylation sites, 19 in the B-domain of the heavy chain, 3 in the remaining part of the heavy chain (relative molecular mass 90 000) and 3 in the light chain (relative molecular mass 80 000).

Human coagulation factor VIII (rDNA) is produced by recombinant DNA technology in mammalian cell culture. Auxiliary substances such as a stabiliser may be added. A white or slightly yellow powder or friable mass. pH of the reconstituted preparation is 6.5 to 7.5. Protect from light.

Moroctocog Alfa *(BAN, rINN)*

Moroctocogum Alfa; Moroktokog Alfa; Moroktokogialfa; Мороктоког Альфа.
(1—742)–(1637—1648)-Blood-coagulation factor VIII (human reduced) complex with 1649—2332-blood-coagulation factor VIII (human reduced).
CAS — 284036-24-4.
UNII — 113E3Z3CJJ.

Pharmacopoeias. *Eur.* (see p. vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Octocog Alfa *(BAN, rINN)*

Bay-w-6240; Factor VIII (rDNA); Octocogum Alfa; Октоког Альфа.
Blood-coagulation factor VIII (human), glycoform α.
CAS — 139076-62-3.

Pharmacopoeias. *Eur.* (see p. vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Units

The potency of factor VIII is expressed in international units and preparations may be assayed using the sixth International Standard for blood coagulation factor VIII concentrate, human (1998).

Uses and Administration

Factor VIII is used as replacement therapy in patients with haemophilia A, a genetic deficiency of factor VIII; it may also be used in acquired haemophilia (see Haemophilias, p. 1126.3).

Preparations of factor VIII may be derived from human plasma or recombinant sources. They are used to control bleeding episodes in the treatment of patients with haemophilia A and to prevent bleeding episodes in such patients undergoing dental and surgical procedures. They may also be used for long-term prophylaxis in patients with severe haemophilia A.

Preparations of factor VIII are given by slow intravenous injection or short infusion, and some octocog alfa preparations may also be given by continuous infusion. The dosage of factor VIII should be determined for each patient and will vary with the circumstances involving bleeding or type of surgery to be performed. In adults, a dose of 1 international unit/kg has been reported to raise the plasma concentration of factor VIII by about 2% (of normal). The response may be lower in children. A suggested formula to calculate, approximately, the dose required for a given effect is:

$$\text{units} = \text{wt (kg)} \times 0.5 \times \%\ \text{desired increase (of normal)}$$

Recommended doses vary depending on the preparation used, but the following increments in plasma concentration of factor VIII have been suggested:

- for mild to moderate haemorrhage an increase to 20 to 30% of normal, usually with a single dose of 10 to 15 units/kg
- for more serious haemorrhage or minor surgery an increase to 30 to 50% of normal, by a usual initial dose of 15 to 25 units/kg followed by 10 to 15 units/kg every 8 to 12 hours if required
- for severe haemorrhage or major surgery an increase to 80 to 100% of normal may be necessary, the usual initial dose being 40 to 50 units/kg followed by 20 to 25 units/kg every 8 to 12 hours. Some octocog alfa preparations may also be given for major surgery as an initial pre-operative bolus followed by a continuous infusion, adjusted postoperatively to daily clearance and desired factor VIII concentrations

For long-term prophylaxis in severe haemophilia A, doses of 10 to 50 units/kg every 2 or 3 days, as required, may be used.

In patients with inhibitory antibodies to human factor VIII, a porcine factor VIII preparation has been used. Its manufacture was discontinued in 2004, but a recombinant product (OBI-1) is in development.

Some factor VIII concentrates also contain von Willebrand factor and these preparations may be used in the management of von Willebrand's disease (p. 1129.3). Commercial very highly purified and recombinant factor VIII preparations do not contain appreciable amounts of von Willebrand factor and are thus ineffective.

Cryoprecipitate is an alternative source of clotting factors and contains factor VIII, factor XIII, von Willebrand factor, fibrinogen, and fibronectin. It has been used in the treatment of haemophilia A and von Willebrand's disease but safer more specific clotting factor alternatives are now available and preferred.

Reviews.
1. McCormack PL, Plosker GL. Octocog alfa, plasma/albumin-free method. *Drugs* 2005; **65:** 2613–20.
2. Frampton JE, Wagstaff AJ. Sucrose-formulated octocog alfa: a review of its use in patients with haemophilia A. *Drugs* 2008; **68:** 839–53.

Administration. Surgical prophylaxis or significant haemorrhage in patients with haemophilia A is usually managed with injections of factor VIII given intravenously every 8 to 12 hours. However, continuous intravenous infusion has been used as an alternative.[1,2] It prevents wide fluctuations in factor VIII plasma concentrations and there is a progressive decrease in clearance associated with steady state. Studies have suggested that continuous infusion is as effective as bolus injection, but with a lower concentrate requirement. Concerns about continuous infusion include factor VIII stability, bacterial contamination, local irritation and thrombophlebitis, and inhibitor formation.

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; **36:** 882–91.
2. Schulman S. Continuous infusion. *Haemophilia* 2003; **9:** 368–75.

Adverse Effects and Precautions

Allergic reactions may sometimes follow the use of factor VIII preparations; the chills, urticaria, and headache experienced by some patients may be allergic manifestations. There is the possibility of intravascular haemolysis in patients with blood groups A, B, or AB receiving high doses or frequently repeated doses of factor VIII preparations due to the content of blood group isoagglutinins; also massive doses of some preparations may produce hyperfibrinogenaemia. Such risks should be reduced with more highly purified preparations.

Factor VIII preparations have been associated with the transmission of some viral infections, including hepatitis B and C, and more notably transmission of HIV. Strenuous efforts are now undertaken to screen the donor material from which factor VIII material is obtained and new methods of manufacture have also been introduced with the aim of inactivating any viruses present. Vaccination against hepatitis A and B is recommended for patients not already immune. Recombinant preparations are also available.

Some patients develop antibodies to factor VIII (see Resistance, p. 1149.1).

Effects on blood platelets. There have been case reports of thrombocytopenia associated with use of porcine factor VIII.[1] A retrospective study[2] of patients treated with porcine factor VIII found that the platelet count fell in 61% of 175 infusions given to 57 patients. The fall was generally clinically insignificant and platelet count appeared to recover within an hour. The effect was, however, dose-related, and larger reductions in platelet count were usually associated with intensive replacement over several days for surgery or trauma.

1. Green D, Tuite GF. Declining platelet counts and platelet aggregation during porcine VIII:C infusions. *Am J Med* 1989; **86:** 222–4.
2. Hay CRM, *et al.* Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost* 1996; **75:** 25–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies factor VIII as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Resistance. Some patients with haemophilia A develop inhibitory antibodies to factor VIII (see Haemophilias, p. 1126.3). The risk is highest within the first 20 to 100 treatments. Low-titre antibodies are usually transient and overcome by increased or continuing treatment with factor VIII. With high-titre highly responding antibodies, however, bleeding episodes may need to be managed with factor VIII inhibitor bypassing fraction (activated prothrombin complex concentrate), or recombinant factor VIIa. Highly responding antibodies can be eradicated by immune tolerance regimens, using regular infusion of factor concentrates over long periods, with additional immunosuppression and immuno-adsorption in some cases.[1] Postmarketing monitoring in Europe has revealed a higher number of cases of inhibitory antibodies associated with recombinant factor VIII preparations than would be expected from experience with plasma-derived products.[2] However, a review[3] by the EMEA found that, on the basis of available data, it was not possible to estimate and compare the incidence of inhibitors between different recombinant factor VIII products. They warned that recurrence of low-titre antibodies had occurred after switching from one product to another in previously treated patients with more than 100 exposure days who had a history of inhibitor development. They also requested that further investigation be undertaken by companies that market recombinant factor VIII products.

There have also been reports of lack of effect with the use of the recombinant factor VIII, moroctocog alfa, for prophylaxis, in patients who have no evidence of antibodies to factor VIII.[4]

1. Bolton-Maggs PHB, Pasi KJ. Haemophilias A and B. *Lancet* 2003; **361:** 1801–9.
2. EMEA. EMEA public statement: review of recombinant factor VIII (FVIII) products and inhibitor development: Advate, Kogenate Bayer/Helixate NexGen, Kogenate/Helixate, Recombinate, ReFacto (issued 18th October, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/02/WC500074387.pdf (accessed 13/08/10)
3. EMEA. Public statement: EMEA completes the review of recombinant factor VIII products and inhibitor development (issued 31st July, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500011389.pdf (accessed 13/08/10)
4. Wyeth Canada. Important safety information about Refacto (moroctocog alfa), antihemophilic factor (recombinant) [BDDrFVIII] (issued 15th September, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/refacto_hpc-cps-eng.pdf (accessed 29/08/08)

Transmission of infections. Treatment with heat or chemicals and efforts to screen the donor material from which factor VIII and other clotting factors are obtained seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses, such as human parvovirus B19 and hepatitis A, may still be transmitted. Vaccination against hepatitis A and B has been recommended for all patients who receive or may require blood products. Plasma-derived clotting factor preparations, or recombinant preparations containing added albumin, may carry a risk of transmission of variant Creutzfeldt-Jakob disease (see under Blood, p. 1135.3). There has also been some concern about the use of human and animal products in the culture media used to manufacture recombinant clotting factor preparations, because of the theoretical risk of viral transmission from infected cell lines. Recombinant manufacturing techniques and formulations have changed over time and human and animal products are no longer used in some preparations.[1]

1. Keeling D, *et al.* United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO). Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2008; **14:** 671–84. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2008.01695.x/pdf (accessed 13/08/10)

Pharmacokinetics

In patients with haemophilia A, factor VIII preparations have a terminal half-life of about 12 hours, whether human-derived or of recombinant origin.

References.
1. Messori A, *et al.* Clinical pharmacokinetics of factor VIII in patients with classic haemophilia. *Clin Pharmacokinet* 1987; **13:** 365–80.
2. Björkman S, *et al.* Pharmacokinetics of factor VIII in humans: obtaining clinically relevant data from comparative studies. *Clin Pharmacokinet* 1992; **22:** 385–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Advate; Beriate P; Emoclot; Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Immunate; Koate-DVI; Kogenate; Monoclate-P; Octanate; Optivate; Recombinate; ***Austral.***: Biostate; Kogenate; Recombinate; ReFacto†; Xyntha; ***Austria***: Advate; Beriate; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate†; ReFacto; Wilate; ***Belg.***: Advate; Factane; Haemate; Helixate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Braz.***: Beriate P†; Haemate; Hemofil; Immunate; Koate; Kogenate; Monoclate-P†; Recombinate; ***Canad.***: Advate; Helixate; Humate-P; Kogenate; Recombinate†; ReFacto†; Wilate; Xyntha; ***Chile***: Emoclot; Fanhdi; Koate-DVI†; Kogenate; ***China***: Haimo Laishi (海莫莱士); Kang Si Ping (康斯平); Kogenate (拜科奇); ***Cz.***: Advate; Fanhdi; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Denm.***: Advate; Haemate; Helixate; Kogenate; Octanate; ReFacto; Wilnativ; ***Fin.***: Advate; Amofil; Haemate; Immunate; Kogenate; Octafil; Recombinate; ReFacto; Wilate; ***Fr.***: Advate; Factane; Helixate; Hemofil M†; Kogenate; Monoclate-P†; Octanate; Recombinate†; ReFacto; ***Ger.***: Advate; Beriate; Fanhdi; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Gr.***: 8 Y; Advate; Fanhdi; Haemate; Haemoctin; Helixate; Hemofil M; Hyate:C†; Immunate; Koate-HP; Kogenate; Monoclate-P; Octanate; Recombinate; ReFacto; ***Hong Kong***: Aleviate; Alphanate; Biostate; Haemate†; Hemofil M; Koate-DVI; Kogenate; Recombinate; ***Hung.***: Advate; Beriate P; Fanhdi†; Haemate; Haemoctin SDH; Helixate; Humafactor-8; Immunate; Kogenate; Octanate; Recombinate; ReFacto; ***India***: Emoclot; Fanhdi; Haemoctin SDH; Hemofil M; Iort3; Monoclate P; ***Indon.***: Koate; Kogenate; ***Irl.***: Advate; Fanhdi; Helixate; Kogenate; Octanate; ReFacto; Wilate; ***Israel***: Fanhdi; Haemate; Haemoctin SDH; Helixate; Hemofil M; Immunate; Koate; Kogenate; Monarc-M†; Monoclate-P†; Octanate; Optivate; Recombinate; ReFacto†; Wilate; Xyntha; ***Ital.***: Advate; Alphanate; Beriate P; Emoclot; Fanhdi; Haemate; Haemoctin; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Talate; ***Jpn***: Advate; Recombinate; ***Malaysia***: Advate; Aleviate; Alphanate; Fanhdi†; Hemofil†; Kogenate; ***Mex.***: Beriate P; Kogenate; Monoclate-P†; Octanate; Optivate; ***Neth.***: Aafact; Advate; Alphanate; Bioclate†; Haemate; Haemoctin; Helixate; Hemofil†; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Norw.***: Advate; Haemate; Helixate; Kogenate; Octanate; ReFacto; Wilate; ***NZ***: Advate; AHF†; Biostate; Kogenate; Octanate; Recombinate; ReFacto†; Wilate; Xyntha; ***Philipp.***: Alphanate; Hemofil M; Koate-DVI; ***Pol.***: Czynnik VIII (Metoda M)†; Haemoctin†; Helixate; Hemofil; Immunate; Kogenate; ReFacto; ***Port.***: Advate; Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH†; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Rus.***: Beriate (Бериате); Emoclot (Эмоклот); Fanhdi (Фанди); Haemoctin (Гемоктин); Hemofil (Гемофил); Immunate (Иммунат); Koate (Коэйт-ДВИ); Kogenate (Когенэйт); LongEight (ЛонгЭйт); Octanate (Октанат); Wilate (Вилате); ***S.Afr.***: Haemosolvate; ***Singapore***: Alphanate; Biostate; Fanhdi; Haemoctin SDH; Hemofil M; Kogenate; Optivate; ***Spain***: Advate; Beriate P; Fanhdi; Haemate; Haemoctin; Helixate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Swed.***: Advate; Haemate; Helixate; Immunate; Kogenate; Octanate; Octonativ-M†; Recombinate; ReFacto; Wilate; ***Switz.***: Advate; Beriate; Haemate; Haemoctin; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Thai.***: Alphanate; Emoclot; Fanhdi†; Haemoctin SDH; Hemofil M; Hemoraas; Immunate; Kogenate; Method M; Octanate; Recombinate; ***Turk.***: Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH; Haemoetin†; Hemofil M; Immunate; Koate-DVI; Kogenate; Liberate; Monarc-M†; Octanate; Octavi; Recombinate; ***UK***: Advate; Alphanate; Beriate P; Fanhdi; Haemate; Helixate; Hyate:C†; Kogenate; Monoclate-P; Octanate; Optivate; Recombinate; ReFacto; Replenate; Wilate; ***Ukr.***: BioKlot (БиоКлот); ReFacto (РеФакто); ***USA***: Advate; Alphanate; Helixate; Hemofil M; Humate-P; Koate-DVI; Kogenate; Monarc-M†; Monoclate-P; Recombinate; ReFacto; Wilate; Xyntha; ***Venez.***: Fandhi.

Multi-ingredient Preparations. ***Arg.***: Eluage; Wilate.

Pharmacopoeial Preparations

Ph. Eur.: Human Coagulation Factor VIII (rDNA); Human Coagulation Factor VIII.

Factor VIII Inhibitor Bypassing Fraction

Activated Prothrombin Complex Concentrate; Anti-inhibitor Coagulant Complex; Complejo coagulante antiinhibidor del factor VIII; Faktör VIII Inhibitör Baypaslayan Fraksiyonu; Антиингибиторный Коагулянтный Комплекс.

ATC — B02BD03.
ATC Vet — QB02BD03.
UNII — CS849DUN3M.

Uses and Administration

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma and contain factors II, IX, and X, and activated factor VII; small amounts of factor VIII and factors of the kallikrein-kinin system are also present. They are used in patients with haemophilia A who have antibodies to factor VIII and in patients with acquired antibodies to factor VIII (see Haemophilias, p. 1126.3). The dose is given intravenously and depends on the preparation used.

References.
1. White GC. Seventeen years' experience with Autoplex/Autoplex T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at a major haemophilia centre. *Haemophilia* 2000; **6:** 508–12.
2. Wilde JT. Evidence for the use of activated prothrombin complex concentrates (aPCCs) in the treatment of patients with haemophilia and inhibitors. *Pathophysiol Haemost Thromb* 2002; **32** (suppl): 9–12.
3. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia* 2004; **10:** 169–73.
4. Perry D, *et al.* FEIBA prophylaxis in haemophilia patients: a clinical update and treatment recommendations. *Haemophilia* 2010; **16:** 80–9.

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of preparations with factor VIII inhibitor bypassing activity. Rapid infusion may cause headache, flushing, and changes in blood pressure and pulse rate.

It should not be given if disseminated intravascular coagulation is suspected or if there are signs of fibrinolysis. It should be used with caution in patients with liver disease. The risk of thromboembolism may be increased with the use of high doses or in patients with thrombotic risk factors.

As with other plasma-derived products, there is a risk of transmission of infection.

References.
1. Ehrlich HJ, *et al.* Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. *Haemophilia* 2002; **8:** 83–90.
2. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. *Haemophilia* 2004; **10** (suppl): 10–16.
3. Aledort LM. Factor VIII inhibitor bypassing activity (FEIBA) – addressing safety issues. *Haemophilia* 2008; **14:** 39–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies factor VIII inhibitor bypassing fraction as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Feiba; ***Austria***: Feiba; ***Belg.***: Confidex; Feiba; ***Braz.***: Feiba; ***Canad.***: Feiba; ***Chile***: Feiba; ***Cz.***: Feiba; Ocplex; ***Denm.***: Feiba; ***Fin.***: Confidex; Feiba; ***Fr.***: Feiba; ***Ger.***: Feiba; ***Gr.***: Feiba; ***Hung.***: Feiba; ***Israel***: Feiba; ***Ital.***: Feiba; ***Malaysia***: Feiba†; ***Neth.***: Feiba; ***Norw.***: Confidex; Feiba; ***NZ***: Feiba; ***Pol.***: Feiba; ***Port.***: Feiba; ***Rus.***: Feiba (Фейба); ***S.Afr.***: Feiba; ***Spain***: Feiba; ***Swed.***: Confidex; Feiba; Ocplex; ***Switz.***: Feiba; ***Thai.***: Feiba; ***Turk.***: Feiba; ***UK***: Feiba; ***USA***: Feiba.

Factor IX

Christmas Factor; Facteur IX; Factor antihemofílico B; Factor Christmas; Plasma Thromboplastin Component; PTC; Фактор IX.

ATC — B02BD04.
ATC Vet — QB02BD04.
UNII — 6U90Y1795T (human factor IX); FW411QXD5M (factor IX complex).

Description. Factor IX is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Nonacog Alfa is in use for recombinant factor IX.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Human Coagulation Factor IX; Factor IX Coagulationis Humanus; Dried Factor IX Fraction BP 2014). A sterile freeze-dried preparation of a plasma protein fraction containing coagulation factor IX, prepared by a method that effectively separates it from other prothrombin complex factors (factors II, VII, and X). It is prepared from human plasma obtained from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed to maintain functional integrity of factor IX, to minimise activation of any coagulation factor, and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor IX fraction is dissolved in a suitable liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. Heparin, antithrombin, or other auxiliary substances such as a stabiliser may be included. No antimicrobial preservative or antibiotic is added. The specific activity is not less than 50 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

Ph. Eur. 8: (Human Prothrombin Complex; Prothrombinum Multiplex Humanum; Dried Prothrombin Complex BP 2014). A sterile plasma protein fraction containing human coagulation factor IX with variable amounts of coagulation factors II, VII, and X. It is prepared by fractionation of human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface

antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed in particular to minimise thrombogenicity and includes a step or steps that have been shown to remove or inactivate known agents of infection. The prothrombin complex fraction is dissolved in a suitable liquid, sterilised by filtration, distributed aseptically into final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. No antimicrobial preservative or antibiotic is added. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. The potency of the preparation is not less than 0.6 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or slightly coloured, very hygroscopic, powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

USP 36: (Factor IX Complex). A sterile freeze-dried powder consisting of partially purified factor IX fraction, as well as concentrated factor II, VII, and X fractions of venous plasma obtained from healthy human donors. It contains no preservatives. It should be stored at 2 degrees to 8 degrees in hermetically-sealed containers. It should be used within 4 hours after reconstitution and administered with equipment that includes a filter.

Nonacog Alfa *(BAN, USAN, rINN)*

Nonacogum Alfa; Nonakog Alfa; Nonakogialfa; Нонаког Альфа.

Blood-coagulation factor IX (human), glycoform α; Blood-coagulation factor IX (synthetic human).

CAS — 113478-33-4; 181054-95-5.

ATC — B02BD09.

ATC Vet — QB02BD09.

UNII — 382L14738L.

Units

The activity of factor IX is expressed in terms of international units and preparations may be assayed using the third International Standard for blood coagulation factor IX concentrate, human (1996).

Uses and Administration

Factor IX is used as replacement therapy in patients with haemophilia B (Christmas disease), a genetic deficiency of factor IX (see Haemophilias, p. 1126.3).

There are two forms of factor IX preparation derived from plasma; one is of high purity, the other is rich in other clotting factors (prothrombin complex concentrates). A recombinant factor IX preparation, nonacog alfa, is also available. Preparations that contain other factors as well as factor IX may sometimes be useful for the treatment of bleeding due to deficiencies of factors II, VII, and X, as well as IX, and in the preparation of such patients for surgery; they may also be used for immediate reversal of coumarin anticoagulants and in the management of patients with haemophilia A who have antibodies to factor VIII.

Factor IX is given by slow intravenous infusion. In patients with factor IX deficiency the dosage should be determined for each patient and will vary with the preparation used and the circumstances of bleeding or type of surgery to be performed. Suggested target factor IX concentrations for patients with haemophilia B vary, but the following have been suggested:

- for mild to moderate haemorrhage the plasma concentration of factor IX should be raised to 20 to 30% of normal
- for more serious haemorrhage or minor surgery it should be raised to 30 to 60% of normal
- for severe haemorrhage or major surgery an increase to 60 to 100% of normal may be necessary

Calculation of the appropriate dose varies according to the manufacturers' recommendations.

For long-term prophylaxis in severe haemophilia B, doses of 20 to 40 international units/kg every 3 or 4 days, as required, may be used.

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of factor IX preparations and there may be chills and urticaria. Other adverse effects include nausea and vomiting, headache, and flushing particularly after rapid infusion. Intravascular coagulation and thrombosis have been reported, mainly in patients with liver disease, and factor IX should be used with care in patients at risk of thromboembolism or disseminated intravascular coagulation. The risk should be less with more highly purified preparations.

As with other plasma derivatives there is a possibility of transmitting viral infection, although selection of donors and heat or chemical treatments of products are used to minimise the risk. Vaccination against hepatitis A and B is recommended for patients not already immune.

Antibodies to factor IX may develop rarely.

Effects on the cardiovascular system. Some factor IX preparations derived from plasma contain other clotting factors in addition to factor IX (prothrombin complex concentrates), and some preparations have also contained activated clotting factors. Such preparations have the potential to produce thromboembolic complications.[1,2] Reported complications include arterial and venous thrombosis, pulmonary embolism, acute myocardial infarction, and disseminated intravascular coagulation. Risk factors in haemophiliacs include liver disease, severe muscle haemorrhages, crush injuries, immobilisation, and orthopaedic surgery. Rapid infusion of factor IX concentrates, or repeated large doses, may also increase the risk of thromboembolism. The risks of thromboembolism have been reduced with the development of more purified prothrombin complex concentrates, and highly purified factor IX preparations that do not contain other clotting factors.[1,3]

1. Köhler M. Thrombogenicity of prothrombin complex concentrates. *Thromb Res* 1999; **95** (suppl): S13–S17.
2. Najaf SM, *et al*. Myocardial infarction during factor IX infusion in hemophilia B: case report and review of the literature. *Ann Hematol* 2004; **83:** 604–7.
3. Santagostino E, *et al*. Markers of hypercoagulability in patients with hemophilia B given repeated, large doses of factor IX concentrates during and after surgery. *Thromb Haemost* 1994; **71:** 737–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies factor IX as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] NAPOS has not yet classified nonacog alfa or prothrombin complex concentrates.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aimafix; Benefix; Berinin P; Beriplex PN; Immunine; Mononine; Octanine; Protromplex; Replenine-VF; ***Austral.***: Benefix; Monofix-VF; ***Austria***: Benefix; Beriplex PN; Cofact; Haemonine; Immunine; Mononine; Octanine; Octaplex; Prothromplex Partiell; Prothromplex S-TIM 4†; Prothromplex TOTAL; ***Belg.***: Benefix; Mononine; Nonafact; Octanine; Octaplex; PPSB Conc SD; ***Braz.***: Berinin†; Beriplex PN; Immunine; Mononine†; Octaplex; Prothromplex-T; ***Canad.***: Benefix; Beriplex PN; Immunine; Mononine†; Octaplex; ***Chile***: Aimafix; ***China***: Pushu Laishi (普舒莱士); ***Cz.***: Benefix; Immunine; Mononine; Nonafact; Octanine; Protromplex; ***Denm.***: Benefix; Nanofix; Nanotiv†; Octaplex; ***Fin.***: Benefix; Cofact; Nonafact; Octanine; Octaplex; ***Fr.***: Benefix; Betafact; Kanokad; Kaskadil†; Mononine; Octafix; Octaplex; ***Ger.***: Alphanine; Benefix; Berinin; Beriplex PN; Cofact; Haemonine; Immunine; Mononine; Octanine; Octaplex; PPSB Konzentrat S-TIM†; PPSB-human; ***Gr.***: Benefix; Beriplex PN; Betafact; Haemonine; Immunine; Mononine; Replenine; ***Hong Kong***: Alphanine; Benefix; Monofix-VF; Profilnine; Proplex T†; Prothrombinex; ***Hung.***: Benefix; Berinin P; Beriplex PN; Humafactor-9; Immunine†; Octanine F; Prothromplex; ***India***: Immunine; ***Indon.***: Cofact; ***Irl.***: Benefix; Immunine; Nanofix; Nanotiv†; Nonafact; Octaplex; ***Israel***: Benefix; Beriplex; Betafact; Mononine; Nanotiv†; Octaplex; Proplex†; Replenine; ***Ital.***: Aimafix; Alphanine†; Benefix; Immunine; Mononine; Protromplex TIM 3; Uman-Complex DI; ***Malaysia***: Alphanine; Profilnine; Replenine; ***Mex.***: Berinin P; Octanine F; Replenine†; ***Neth.***: Alphanine; Benefix; Beriplex PN; Betafact; Cofact; Immunine; Mononine; Nanotiv†; Nonafact; Octaplex; ***Norw.***: Benefix; Immunine; Nanotiv†; Octanine; Octaplex; Prothromplex; ***NZ***: Benefix; Monofix; Pronativ; Prothrombinex; ***Philipp.***: Alphanine†; Profilnine; ***Pol.***: Benefix; Immunine; Nonafact; Prothromplex; ***Port.***: Aimafix; Benefix; Beriplex; Betafact; Immunine; Mononine; Nanotiv; Nonafact; Octaninef; Octaplex; ***Rus.***: Aimafix (Аимафикс); Immunine (Иммунин); Octanine (Октанайн); Protromplex (Протромплекс); Replenin-VF (Репленина-ВФ); ***S.Afr.***: Haemosolvex; Prothromplex-T TIM 4†; ***Singapore***: Alphanine; Monofix-VF; Profilnine; Replenine; ***Spain***: Benefix; Berinin P; Beriplex; Immunine; Mononine; Nanotiv†; Novix; Octanine; Octaplex; Prothromplex; ***Swed.***: Benefix; Immunine; Mononine; Nanofix; Nanotiv†; ***Switz.***: Benefix; Berinin; Beriplex; Immunine; Octanine F; Octaplex; Prothromplex; ***Thai.***: Aimafix; Alphanine; Immunine; Octanine; Profilnine; ***Turk.***: Aimafix; Berinin P; Betafact; Cofact; Immunine; Kaskadil; Konyne†; Nonafact; Octanine F; Octanyne; Reblenine; Replenine; ***UK***: Alphanine; Benefix; Beriplex PN; Mononine; Octaplex; Replenine; ***Ukr.***: Benefix (БенеФикс); ***USA***: Alphanine; Bebulin VH; Benefix; Kcentra; Mononine; Profilnine; Proplex T†; Rixubis.

Multi-ingredient Preparations. ***Rus.***: Uman-Complex DI (Уман-Комплекс ДИ).

Pharmacopoeial Preparations

Ph. Eur.: Human Coagulation Factor IX; Human Prothrombin Complex;

USP 36: Factor IX Complex.

Factor XI

Facteur XI; Plasma Thromboplastin Antecedent; PTA; Фактор XI.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Human Coagulation Factor XI; Factor XI Coagulationis Humanus; Dried Factor XI Fraction BP 2014). A plasma protein fraction that contains coagulation factor XI. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor XI fraction is dissolved in a suitable liquid, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under nitrogen. Heparin, C_1-esterase inhibitor, and antithrombin III, may be added. No antimicrobial preservative is added. When reconstituted as stated on the label the resulting solution contains not less than 50 units/mL.

A white or almost white powder or friable solid. pH of the reconstituted preparation is 6.8 to 7.4. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Factor XI is used as replacement therapy in patients with congenital factor XI deficiency (haemophilia C; see Inherited Haemorrhagic Disorders, p. 1128.2) for the prevention and treatment of haemorrhage. The dose is based on the degree of factor XI deficiency and the condition of the patient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hemoleven; ***Gr.***: Hemoleven.

Factor XIII

Fibrin-stabilising Factor; FSF; Фактор XIII.

ATC — B02BD07.

ATC Vet — QB02BD07.

UNII — F7R0FBC1XD.

Description. Factor XIII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Catridecacog is in use for recombinant factor XIII A-subunit.

Catridecacog *(rINN)*

Catridécacog; Catridecacogum; NN-1841; Катридекаког.

Human factor XIII $[A_2]$ homodimer (allele F13A*1B), recombinant DNA origin.

CAS — 606138-08-3.

ATC — B02BD11.

ATC Vet — QB02BD11.

UNII — NU23Q531G1.

Uses and Administration

Factor XIII is used as replacement therapy in patients with a genetic deficiency of factor XIII (see Inherited Haemorrhagic Disorders, p. 1128.2). It may also be used in patients with acquired deficiency of factor XIII, and for supportive therapy in postoperative wound healing.

Factor XIII derived from human plasma is given by slow intravenous injection or infusion. Licensed dosage recommendations for prophylaxis of haemorrhage in patients with genetic deficiency vary between countries, but are based on the degree of deficiency and the condition of the patient. In Europe, about 10 units/kg may be given once a month. The interval between doses may be shortened if spontaneous haemorrhage occurs. In the USA, an initial dose of 40 units/kg is given once every 4 weeks, and adjusted in steps of 5 units/kg to maintain a trough factor XIII activity level of between 5 and 20%. Factor XIII is also licensed in some European countries for pre-operative prophylaxis and for treatment of bleeding episodes. For pre-operative use, a dose of up to 35 units/kg may be given immediately before the operation and followed by adequate doses to maintain efficacy until the wound is healed. For the treatment of severe bleeding episodes and extensive haematomas 10 to 20 units/kg should be given daily, until bleeding stops. In acute bleeding, especially intracranial

bleeding, doses of up to 50 units/kg may be needed to raise factor XIII to normal levels. Doses of at least 15 to 20 units/kg daily may be required for the treatment of haemorrhage in acquired factor XIII deficiency.

In the promotion of postoperative wound healing, a dose of 10 units/kg may be given on the day of the operation and on each of the next 3 days; in some cases a dose of up to 20 units/kg may be used.

Cryoprecipitate is also used as a source of factor XIII.

Factor XIII is also a component of fibrin glues (see Fibrin, below).

Catridecacog is a recombinant factor XIII A-subunit. It is structurally identical to human factor XIII A subunit [A_2] and is used in the prophylactic treatment of bleeding in patients, aged 6 years or more, with congenital factor XIII A-subunit deficiency. The recommended dose of 35 units/kg is given once each month by slow intravenous bolus injection. Dose adjustment may be made based on factor XIII activity levels.

References.
1. Lim W, *et al*. Prophylactic and perioperative replacement therapy for acquired factor XIII deficiency. *J Thromb Haemost* 2004; **2:** 1017–19.
2. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia* 2008; **14:** 1190–1200.
3. Inbal A, *et al*. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012; **119:** 5111–17.

Inflammatory bowel disease. Some patients with inflammatory bowel disease (p. 1811.3) may be deficient in factor XIII, possibly due to increased intestinal blood loss seen in severe ulcerative colitis or increased mucosal deposition of factor XIII in Crohn's disease. Factor XIII concentrate given intravenously has produced beneficial results in 12 patients with active ulcerative colitis resistant to conventional therapy with corticosteroids and mesalazine[1] and has also been associated with healing of intractable fistulae in 3 of 4 patients with Crohn's disease.[2] However, a controlled study[3] found no benefit from factor XIII in active corticosteroid-refractory ulcerative colitis.

1. Lorenz R, *et al*. Factor XIII substitution in ulcerative colitis. *Lancet* 1995; **345:** 449–50.
2. Oshitani N, *et al*. Treatment of Crohn's disease fistulas with coagulation factor XIII. *Lancet* 1996: **347:** 119–20.
3. Bregenzer N, *et al*. Lack of clinical efficacy of additional factor XIII treatment in patients with steroid refractory colitis. *Z Gastroenterol* 1999; **37:** 999–1004.

Wounds and ulcers. Topical factor XIII has been reported to promote wound healing in patients with refractory leg ulcers.[1-3]

1. Wozniak G, *et al*. Factor XIII in ulcerative leg disease: background and preliminary clinical results. *Semin Thromb Hemost* 1996; **22:** 445–50.
2. Herouy Y, *et al*. Factor XIII-mediated inhibition of fibrinolysis and venous leg ulcers. *Lancet* 2000; **355:** 1970–1.
3. Hildenbrand T, *et al*. Treatment of nonhealing leg ulcers with fibrin-stabilizing factor XIII: a case report. *Dermatol Surg* 2002; **28:** 1098–9.

Adverse Effects and Precautions

Like other clotting factor preparations (see Factor VIII, p. 1148.3), the use of plasma-derived factor XIII may be associated with risks of hypersensitivity reactions, thrombosis, and viral infection transmission. Inhibitors of factor XIII may occur very rarely.

Headache has been reported as a common adverse effect of catridecacog. Risks of hypersensitivity and thrombosis also exist. Catridecacog should not be given to patients who have developed neutralising antibodies to factor XIII without close monitoring.

Catridecacog is not effective for prophylaxis in patients with factor XIII B-subunit deficiency.

Pharmacokinetics

In patients with congenital factor XIII deficiency, catridecacog has an estimated half-life of 11.8 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fibrogammin P; ***Austria***: Fibrogammin; ***Belg.***: Fibrogammin; ***Braz.***: Fibrogammin; ***Denm.***: Novothirteen; ***Fr.***: Fibrogammin; ***Ger.***: Fibrogammin; ***Gr.***: Fibrogammin; ***Hong Kong***: Fibrogammin P†; ***Israel***: Fibrogammin; ***Switz.***: Fibrogammin; Novothirteen; ***UK***: Fibrogammin P; ***USA***: Corifact.

Multi-ingredient Preparations. ***Arg.***: Beriplast P; Tissucol; ***Austral.***: Tisseel Duo†; ***Austria***: Beriplast; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Tissucol Duo; Tissucol Kit; ***Braz.***: Beriplast P; ***Canad.***: Tisseel; ***Chile***: Beriplast P†; ***Cz.***: Tissucol; ***Denm.***: Tisseel Duo Quick; ***Fin.***: Tisseel Duo Quick; ***Fr.***: Beriplast; Tissucol; ***Ger.***: Beriplast; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Beriplast; ***Hong Kong***: Beriplast P; Tisseel; ***Hung.***: Beriplast P; Tissucol-Kit; ***Indon.***: Beriplast; ***Irl.***: Tisseel; ***Israel***: Beriplast†; Tisseel†; ***Ital.***: Beriplast; ***Jpn***: Bolheal; ***Mex.***: Beriplast P; ***Neth.***: Beriplast P; Tisseel; Tissucol Duo; Tissucol; ***Norw.***: Tisseel; ***NZ***: Tisseel Duo; ***Pol.***: Beriplast; ***Port.***: Tissucol Duo†; ***Rus.***: Tissucol Kit (Тиссукол Кит); ***Spain***: Beriplast P Combi; Tissucol Duo; ***Swed.***: Tisseel Duo Quick; ***Switz.***: Beriplast P; Tisseel; Tissucol Duo S†; Tissucol†; ***Turk.***: Beriplast P; ***UK***: Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit.

Fibrin *(rINN)*

Fibrina; Fibrine; Fibrinum; Фибрин.

Pharmacopoeias. Many pharmacopoeias have monographs for fibrin preparations, including *Eur.* (see p. vii).

Ph. Eur. 8: (Fibrin Sealant Kit; Fibrini Glutinum). It is composed of two components, a fibrinogen concentrate containing human fibrinogen (component 1), and a human thrombin preparation (component 2). The kit may also contain other ingredients, such as human factor XIII, a fibrinolysis inhibitor, or calcium ions. Stabilisers such as human albumin may be added. The human constituents are obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The constituents are passed through a bacteria-retentive filter and distributed aseptically into sterile containers. Containers of freeze-dried constituents are sealed under vacuum or filled with oxygen-free nitrogen or other suitable inert gas before sealing. No antimicrobial preservative is added. When thawed or reconstituted as stated on the label, the fibrinogen concentrate contains not less than 40 g/litre of clottable protein; the activity of the thrombin preparation varies over a wide range (about 4 to 1000 international units/mL). Protect from light.

Profile

Fibrin glue is prepared by mixing solutions containing fibrinogen, thrombin, and calcium ions, with the addition of aprotinin to inhibit fibrinolysis. It may also include factor XIII and other clotting components. Fibrin glue is used as a haemostatic to control haemorrhage during surgical procedures or as a spray to bleeding surfaces. Some preparations are used for autologous skin-graft adhesion in the management of burns.

A dry artificial sponge of human fibrin, known as human fibrin foam, has been used similarly as a haemostatic; it is prepared by clotting human thrombin with a foam of human fibrinogen solution. A collagen sponge coated with thrombin and fibrinogen is also available to promote haemostasis and tissue sealing, and to provide suture support in vascular surgery.

Adverse effects. Fatal neurotoxicity has been reported[1] after the use of a fibrin sealant during neurosurgical procedures. The toxicity may have been due to the presence of tranexamic acid as a stabiliser in the formulation, and such formulations should not be used in surgical operations where contact with the CSF or dura mater could occur.[2]

For rare reports of hypersensitivity reactions to aprotinin used locally as a component of fibrin sealant, see p. 1134.3.

1. CSM/MCA. Quixil human surgical sealant: reports of fatal reactions. *Current Problems* 1999; **25:** 19. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)
2. CSM/MCA. Quixil human surgical sealant: update on fatal neurotoxic reactions. *Current Problems* 2000; **26:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074606&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)

Use. Reviews.

1. Dunn CJ, Goa KL. Fibrin sealant: a review of its use in surgery and endoscopy. *Drugs* 1999; **58:** 863–86.
2. Carless PA, *et al*. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 03/06/05).
3. MacGillivray TE. Fibrin sealants and glues. *J Card Surg* 2003; **18:** 480–5.
4. Fattahi T, *et al*. Clinical applications of fibrin sealants. *J Oral Maxillofac Surg* 2004; **62:** 218–24.
5. Schexneider KI. Fibrin sealants in surgical or traumatic hemorrhage. *Curr Opin Hematol* 2004; **11:** 323–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kang Pu Xin (康普欣).

Multi-ingredient Preparations. ***Arg.***: Beriplast P; Tissucol; ***Austral.***: Tisseel Duo†; ***Austria***: Beriplast; Evicel; TachoSil; Tisseel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Artiss; TachoSil; Tissucol Duo; Tissucol Kit; ***Braz.***: Beriplast P; TachoSil; ***Canad.***: Artiss; Tisseel; ***Chile***: Beriplast P†; ***Cz.***: Artiss; Evicel; TachoSil; Tisseel; Tissucol; ***Denm.***: Artiss; Evicel; TachoSil; Tisseel Duo Quick; ***Fin.***: Artiss; TachoSil; Tisseel Duo Quick; Tisseel; ***Fr.***: Artiss; Beriplast; Evicel; TachoSil; Tissucol; ***Ger.***: Artiss; Beriplast; Evicel; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Beriplast; Evicel; TachoSil; Tisseel; ***Hong Kong***: Beriplast P; Tisseel; ***Hung.***: Beriplast P; TachoSil; Tissucol-Kit; ***Indon.***: Beriplast; ***Irl.***: Artiss; Evicel; TachoSil; Tisseel; ***Israel***: Beriplast†; Evicel; TachoSil; Tisseel†; ***Ital.***: Beriplast; TachoSil; Tissucol; ***Jpn***: TachoSil; ***Mex.***: Beriplast P; ***Neth.***: Artiss; Beriplast P; TachoSil; Tisseel; Tissucol Duo; Tissucol; ***Norw.***: Artiss; Evicel; TachoSil; Tisseel; ***NZ***: Tisseel Duo; ***Pol.***: Beriplast; Evicel; TachoSil; ***Port.***: Evicel; TachoSil; Tissucol Duo†; ***Rus.***: Tissucol Kit (Тиссукол Кит); ***Spain***: Artiss; Beriplast P Combi; Evicel; TachoSil; Tissucol Duo; ***Swed.***: Artiss; Evicel; TachoSil; Tisseel Duo Quick; ***Switz.***: Artiss; Beriplast P; Evicel; TachoSil; Tisseel; Tissucol Duo S†; Tissucol†; ***Thai.***: Tisseel; ***Turk.***: Beriplast P; ***UK***: TachoSil; Tisseel; ***USA***: Artiss; Evicel; TachoSil; Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit.

Fibrinogen

Factor I; Fibrinogène; Fibrinógeno; Fibrinogenum; Fibrinojen; Fibrynogen.
ATC — B02BB01; B02BC10.
ATC Vet — QB02BB01.
UNII — N94833051K (human fibrinogen).

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Fibrinogen; Fibrinogenum Humanum). A sterile freeze-dried preparation of a plasma protein fraction containing the soluble constituent of human plasma that is transformed to fibrin on addition of thrombin. It is obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Stabilisers, including protein such as human albumin, salts, and buffers may be added. No antimicrobial preservative or antibiotic is added. When dissolved in the volume of solvent stated on the label, the solution contains not less than 10 g/litre of fibrinogen.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

Fibrinogen has been used to control haemorrhage associated with low blood-fibrinogen concentration in afibrinogenaemia or hypofibrinogenaemia although plasma or cryoprecipitate is usually preferred. Fibrinogen has also been used in disseminated intravascular coagulation (p. 1126.1). It is a component of fibrin glue (see Fibrin, above). Recombinant human fibrinogen is under investigation.

Fibrinogen labelled with radionuclides has also been used in diagnostic procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: RiaSTAP; ***Austria***: Haemocomplettan; ***Belg.***: Riastap; ***Braz.***: Haemocomplettan; ***China***: Fabu Laishi (法布莱士); ***Cz.***: Haemocomplettan; ***Denm.***: Riastap; ***Fin.***: Riastap; ***Fr.***: Clottafact; Clottagen†; Haemocomplettan†; Riastap; ***Ger.***: Haemocomplettan; ***Gr.***: Haemocomplettan; ***Hung.***: Haemocomplettan; ***India***: Fibroraas; ***Irl.***: Riastap; ***Israel***: Haemocomplettan; ***Neth.***: Haemocomplettan; ***Norw.***: Riastap; ***Port.***: Haemocomplettan; ***Spain***: RiaSTAP; ***Swed.***: Riastap; ***Switz.***: Haemocomplettan; ***Thai.***: Fibroraas; ***Turk.***: Haemocomplettan; ***UK***: Riastap; ***USA***: RiaSTAP.

Multi-ingredient Preparations. ***Arg.***: Beriplast P; Tissucol; ***Austral.***: Tisseel Duo†; ***Austria***: Beriplast; Evicel; TachoSil; Tisseel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Artiss; Quixil†; TachoSil; Tissucol Duo; Tissucol Kit; ***Braz.***: Beriplast P; TachoSil; ***Canad.***: Artiss; Tisseel; ***Chile***: Beriplast P†; ***China***: FibinGluRAAS (护固莱士); ***Cz.***: Artiss; Evicel; TachoSil; Tisseel; Tissucol; ***Denm.***: Artiss; Evicel; Quixil; TachoSil; Tisseel Duo Quick; ***Fin.***: Artiss; Quixil; TachoSil; Tisseel Duo Quick; Tisseel; ***Fr.***: Artiss; Beriplast; Evicel; TachoSil; Tissucol; ***Ger.***: Artiss; Beriplast; Evicel; Quixil†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Beriplast; Evicel; TachoSil; Tisseel; ***Hong Kong***: Beriplast P; TachoComb; Tisseel; ***Hung.***: Beriplast P; TachoSil; Tissucol-Kit; ***Indon.***: Beriplast; ***Irl.***: Artiss; Evicel; TachoSil; ***Israel***: Beriplast†; TachoSil; Tisseel†; ***Ital.***: Beriplast; Quixil; TachoSil; ***Jpn***: Bolheal; TachoSil; ***Mex.***: Beriplast P; ***Neth.***: Artiss; Beriplast P; Quixil†; TachoSil; Tisseel; Tissucol Duo; Tissucol; ***Norw.***: Artiss; Evicel; TachoSil; Tisseel; ***NZ***: Tisseel Duo; ***Pol.***: Beriplast; Evicel; TachoSil; ***Port.***: Evicel; TachoSil; Tissucol Duo†; ***Rus.***: TachoComb (ТахоКомб); Tissucol Kit (Тиссукол Кит); ***Singapore***: TachoComb; ***Spain***: Artiss; Beriplast P Combi; Evicel; TachoSil; Tissucol Duo; ***Swed.***: Artiss; Evicel; Quixil†; TachoSil; Tisseel Duo Quick; ***Switz.***: Artiss; Beriplast P; Evicel; Quixil; TachoSil; Tisseel; Tissucol Duo S†; Tissucol†; ***Thai.***: Fibingluraas; Tisseel; ***Turk.***: Beriplast P; Tisseel VH; ***UK***: TachoSil; Tisseel; ***Ukr.***: TachoComb (Тахокомб); ***USA***: Artiss; Evarrest; Evicel; TachoSil; Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit; Human Fibrinogen.

Filgrastim *(BAN, USAN, rINN)*

Filgrastiimi; Filgrastimum; r-metHuG-CSF; XM-02 (filgrastim or tbo-filgrastim); Филграстим.

A recombinant human granulocyte colony-stimulating factor.
CAS — 121181-53-1.
ATC — L03AA02.
ATC Vet — QL03AA02.
UNII — PVI5M0M1GW.

NOTE. The FDA approved the name tbo-filgrastim to describe the contents of *Granix (Teva, USA)*. However, in Europe this substance was granted marketing authorisation as a biosimilar filgrastim and marketed as *Tevagrastim (Teva, Europe)*.

Pharmacopoeias. In *US. Eur.* (see p. vii) includes a concentrated solution.

Ph. Eur. 8: (Filgrastim Concentrated Solution). A solution of a protein having the primary structure of the granulocyte colony-stimulating factor (G-CSF) plus 1 additional amino acid, an *N*-terminal methionine. In contrast to its natural counterpart, the protein is not glycosylated. It is produced by a method based on recombinant DNA technology, using bacteria as host cells. It contains a minimum 900 micrograms of protein per mL and has a minimum potency of 1.0×10^8 units per mg of protein. A clear, colourless, or slightly yellowish liquid.

USP 36: (Filgrastim). It is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains not less than 0.9 mg/mL of filgrastim. Store in airtight containers at a temperature between 2 degrees and 8 degrees. Protect from light during long-term storage.

Lipegfilgrastim *(USAN, rINN)*

Lipegfilgrastimum; XM-22; Липэгфилграстим.
Filgrastim conjugated with methoxy polyethylene glycol via a carbohydrate linker consisting of glycine, *N*-acetylneuraminic acid, and *N*-acetylgalactosamine.
CAS — 1117844-87-7.
ATC — L03AA14.
ATC Vet — QL03AA14.
UNII — 4AWF0N6QV3.

NOTE. The name Lonquex has been used as a trade mark for lipegfilgrastim.

Pegfilgrastim *(BAN, rINN)*

Pegfilgrastiimi; Pegfilgrastimum; Pegfilgrastimun; Пегфильграстим.
Filgrastim conjugated with monomethoxy polyethylene glycol.
CAS — 208265-92-3.
ATC — L03AA13.
ATC Vet — QL03AA13.
UNII — 3A58010674.

Incompatibility. References.
1. Trissel LA, Martinez JF. Compatibility of filgrastim with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51:** 1907–13.

Stability. Solutions of filgrastim must not be diluted with sodium chloride solutions as precipitation will occur. Glucose 5% solution may be used if dilution is necessary. However, filgrastim in diluted solution may be adsorbed onto glass or plastic materials and so it should not be diluted below the recommended minimum concentration (2 micrograms/mL). Also, to protect from adsorption, solutions that are diluted to concentrations of filgrastim below 15 micrograms/mL must have albumin added to give a final concentration of 2 mg/mL. For mention of the stability of filgrastim in a solution intended for enteral use in neonates, see Stability under Epoetins, p. 1141.2.

Uses and Administration

Filgrastim is a granulocyte colony-stimulating factor (G-CSF), a haematopoietic growth factor that stimulates the development of granulocytes (see Haematopoiesis, p. 1121.1). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation. It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation. Filgrastim is also used in the management of chronic neutropenia (congenital, cyclic, or idiopathic), and for persistent neutropenia in patients with advanced HIV infection.

Filgrastim may be given intravenously or subcutaneously. Doses may be expressed in micrograms or in units; 10 micrograms is equivalent to 1 million units.

As an **adjunct to antineoplastic therapy**, filgrastim is given in a dose of 5 micrograms/kg daily starting not less than 24 hours after the last dose of antineoplastic. It can be given as a single daily subcutaneous injection, as a continuous intravenous or subcutaneous infusion, or as a daily intravenous infusion over 15 to 30 minutes. Treatment is continued until the neutrophil count has stabilised within the normal range which may take up to 14 days or more. A formulation of filgrastim conjugated with monomethoxy polyethylene glycol (pegfilgrastim) may also be used to reduce the incidence of neutropenia associated with antineoplastic therapy; it is given by subcutaneous injection in a single dose of 6 mg, given not less than 24 hours after the last dose of antineoplastic. Lipegfilgrastim, described as a glycopegylated filgrastim, is also in development for this indication; a single dose of 6 mg is given subcutaneously about 24 hours after chemotherapy.

The initial dose of filgrastim following **bone marrow transplantation** is 10 micrograms/kg daily, adjusted according to response. This may be given by intravenous infusion over 30 minutes or 4 hours, or by continuous intravenous or subcutaneous infusion over 24 hours.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 10 micrograms/kg daily of filgrastim may be given subcutaneously as a single daily injection or by continuous infusion for 4 to 7 days until the last leucapheresis procedure (usually performed on days 5 to 7 as required). If filgrastim is given after myelosuppressive chemotherapy, the dose is halved to 5 micrograms/kg daily by subcutaneous injection. It is given from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, so that leucapheresis can be performed. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 4 or 5 days until leucapheresis (usually started on day 5).

In patients with **congenital neutropenia** the initial dose is 12 micrograms/kg daily and in patients with idiopathic or cyclic neutropenia the initial dose is 5 micrograms/kg daily. In these forms of neutropenia the dose is given subcutaneously in single or divided doses and should be adjusted according to response.

In patients with **HIV infection** and persistent neutropenia the initial dose is 1 microgram/kg daily by subcutaneous injection. The dose may be titrated up to a maximum of 4 micrograms/kg daily until a normal neutrophil count is achieved and then adjusted for maintenance according to response. Maintenance doses of 300 micrograms daily on 1 to 7 days a week have been used.

The filgrastim doses described above for patients receiving antineoplastic therapy and for chronic neutropenias may also be given to **children**. The use of pegfilgrastim in children is limited and its safety and efficacy have not been adequately established.

References and reviews.
1. Dale DC, ed. Filgrastim anniversary supplement: reviewing 10 years of clinical experience, a seminar-in-print. *Drugs* 2002; **62** (suppl 1): 1–98.
2. Curran MP, Goa KL. Pegfilgrastim. *Drugs* 2002; **62:** 1207–13.
3. Renwick W, *et al.* Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs* 2009; **23:** 175–86.
4. Bondarenko I, *et al.* Efficacy and safety of lipegfilgrastim versus pegfilgrastim: a randomized, multicenter, active-control phase 3 trial in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy. *BMC Cancer* 2013; **13:** 386.

Aplastic anaemia. Colony-stimulating factors, including granulocyte colony-stimulating factors, have been tried in patients with aplastic anaemia (p. 1121.3).

Infections. As well as stimulating the development and maturation of haematopoietic precursors, granulocyte and granulocyte-macrophage colony-stimulating factors have been found to enhance neutrophil chemotaxis and phagocytosis, enhance oxidative activity, increase microbicidal activity and antibody-mediated cellular cytotoxicity, and delay neutrophil apoptosis. Granulocyte-macrophage colony-stimulating factor also modifies macrophage and monocyte functions in inflammation and cellular immune response.[1] It has therefore been suggested that colony-stimulating factors might be useful adjuncts in the treatment of infections in non-neutropenic patients, but their clinical role is yet to be established.

The use of granulocyte colony-stimulating factor was reported[2] to reduce mortality rates in patients with septic shock due to the bacterial infection melioidosis (p. 190.2). In small placebo-controlled studies of patients with the protozoal infection cutaneous leishmaniasis (p. 922.1), ulcers healed faster in those treated with granulocyte-macrophage colony-stimulating factor, as an adjunct to antimony therapy, by intralesional injection[3] and topical application.[4]

However, granulocyte colony-stimulating factor does not appear to be of benefit as an adjunct in the management of pneumonia[5] (p. 200.1). In diabetic foot infections (see Diabetic Foot Disease, p. 464.2) granulocyte colony-stimulating factor does not appear to affect wound healing, although there is some suggestion that it may reduce the likelihood of surgical intervention.[6]

In HIV infection (p. 957.2), granulocyte-macrophage colony-stimulating factor has been reported to improve CD4 + cell counts.[7]

Granulocyte-macrophage colony-stimulating factor has been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[8]

1. Root RK, Dale DC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in nonneutropenic patients. *J Infect Dis* 1999; **179** (suppl): S342–S352.
2. Cheng AC, *et al.* Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis* 2004; **38:** 32–7.
3. Almeida R, *et al.* Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony-stimulating factor versus stibogluconate alone in the treatment of cutaneous leishmaniasis. *J Infect Dis* 1999; **180:** 1735–7.
4. Santos JB, *et al.* Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. *J Infect Dis* 2004; **190:** 1793–6.
5. Cheng AC, *et al.* Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 16/06/08).
6. Cruciani M, *et al.* Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care* 2005; **28:** 454–60.
7. Deresinski SC. Granulocyte-macrophage colony-stimulating factor: potential therapeutic, immunological and antiretroviral effects in HIV infection. *AIDS* 1999; **13:** 633–43.
8. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; **25:** 709–18.

Ischaemia. Colony-stimulating factors have been investigated for their ability to mobilise stem cells and modulate inflammation in cardiovascular disorders characterised by ischaemia. Granulocyte colony-stimulating factor (G-CSF) has been tried in atherosclerotic coronary artery disease and particularly after myocardial infarction (p. 1257.1). However, studies have been small, and reviews have concluded that although there was mobilisation of stem cells that might be of benefit in myocardial regeneration, G-CSF provided no additional benefit to reperfusion therapy after myocardial infarction.[1,2] A systematic review also concluded that the use of G-CSF did not increase the risk of coronary restenosis or cardiovascular events after reperfusion therapy for myocardial infarction.[3] Benefit has been reported in 7 patients with acute ischaemic stroke (p. 1269.2) given filgrastim 15 micrograms/kg subcutaneously daily for 5 days in addition to the usual care given to 3 controls.[4] There was a greater improvement in neurological function in filgrastim-treated patients on 12 months of follow-up, but larger studies are required to confirm the benefit.

1. Kastrup J, *et al.* Myocardial regeneration induced by granulocyte-colony-stimulating factor mobilization of stem cells in patients with acute or chronic ischaemic heart disease: a non-invasive alternative for clinical stem cell therapy? *Eur Heart J* 2006; **27:** 2748–54.
2. Zohlnhöfer D, *et al.* Stem cell mobilization by granulocyte colony-stimulating factor for myocardial recovery after acute myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 2008; **51:** 1429–37.
3. Ince H, *et al.* Cardiovascular events and re-stenosis following administration of G-CSF in acute myocardial infarction: systematic review and meta-analysis. *Heart* 2008; **94:** 610–16.
4. Shyu W-C, *et al.* Granulocyte colony-stimulating factor for acute ischemic stroke: a randomized controlled trial. *Can Med Assoc J* 2006; **174:** 927–33.

Neutropenia. Granulocyte colony-stimulating factors are used in the management of neutropenia. They may be used[1] long-term in the management of inherited forms of neutropenia (p. 1130.1). They are used short-term[2-5] to treat or prevent antineoplastic-induced neutropenia (p. 731.1) and have also been used in patients with neutropenia induced by other drugs.[6-11] Colony-stimulating factors are also used[12] in the management of neutropenia in patients with HIV-associated infection (p. 958.3) including that due to myelosuppressive therapies such as cotrimoxazole, pyrimethamine, and zidovudine. A controlled study[13] in 258 patients with advanced HIV infection found that prophylactic use of granulocyte colony-stimulating factor reduced the incidence of severe neutropenia and also suggested that the incidence and duration of bacterial infections was reduced.

Due to immature neutrophil production and function, neonates are susceptible to infection and preterm neonates are at particular risk. The use of colony-stimulating factors for prophylaxis or as adjuncts in the treatment of septicaemia (p. 203.2) in neonates has been investigated in a few small studies but there is insufficient evidence of benefit to recommend the use of granulocyte or granulocyte-macrophage colony-stimulating factors in these patients. There is also limited evidence to suggest that they may reduce mortality as adjuncts to treatment in

patients with sepsis and severe neutropenia.[14,15] Granulocyte colony-stimulating factors have also been tried with mixed results in neonates with the rare condition of alloimmune neutropenia.[16,17]

1. Zeidler C, *et al*. Management of Kostmann syndrome in the G-CSF era. *Br J Haematol* 2000; **109:** 490–5.
2. Repetto L, *et al*. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* 2003; **39:** 2264–72.
3. Sung L, *et al*. Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22:** 3350–6.
4. Clark OAC, *et al*. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2005; **23:** 4198–4214.
5. Smith TJ, *et al*. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://jco.ascopubs.org/cgi/reprint/24/19/3187 (accessed 13/08/10)
6. Wickramanayake PD, *et al*. Use of granulocyte colony-stimulating factor (filgrastim) in the treatment of non-cytotoxic drug-induced agranulocytosis. *Eur J Med Res* 1995; **1:** 153–6.
7. Murphy PT, Casey MC. Sulphasalazine induced agranulocytosis revisited. *Ir Med J* 1998; **91:** 216.
8. Bhidayasiri R, *et al*. Correction of mesalazine-induced neutropenia with high dose G-CSF. *Am J Gastroenterol* 2000; **95:** 3321–2.
9. Andrès E, *et al*. Nonchemotherapy drug-induced agranulocytosis in elderly patients: the effects of granulocyte colony-stimulating factor. *Am J Med* 2002; **112:** 460–4.
10. Andrès E, *et al*. Modern management of non-chemotherapy drug-induced agranulocytosis: a monocentric cohort study of 90 cases and review of the literature. *Eur J Intern Med* 2002; **13:** 324–8.
11. Hägg S, *et al*. Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol* 2003; **18:** 173–4.
12. Kuritzkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin Infect Dis* 2000; **30:** 256–60.
13. Kuritzkes DP, *et al*. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. *AIDS* 1998; **12:** 65–74.
14. Banerjea MC, Speer CP. The current role of colony-stimulating factors in prevention and treatment of neonatal sepsis. *Semin Neonatol* 2002; **7:** 335–49.
15. Carr R, *et al*. G-CSF and GM-CSF for treating or preventing neonatal infections. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 27/10/05).
16. Felix JK, Calhoun DA. Neonatal alloimmune neutropenia in premature monozygous twins. *Pediatrics* 2000; **106:** 340–2.
17. Maheshwari A, *et al*. Resistance to recombinant human granulocyte colony-stimulating factor in neonatal alloimmune neutropenia associated with anti-human neutrophil antigen-2a (NB1) antibodies. Abstract: *Pediatrics* 2002; **109:** 698. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/4/e64 (accessed 27/10/05)

Adverse Effects

The main adverse effects of granulocyte colony-stimulating factors such as filgrastim during short-term treatment are musculoskeletal pain and dysuria. Hypersensitivity reactions have been reported rarely. In patients receiving long-term treatment the most frequent adverse effects are bone pain and musculoskeletal pain. Other adverse effects include splenic enlargement, thrombocytopenia, anaemia, epistaxis, headache, diarrhoea, and cutaneous vasculitis. There have been reports of pulmonary infiltrates leading to respiratory failure or acute respiratory distress syndrome, and rare reports of splenic rupture. Rises in lactate dehydrogenase, alkaline phosphatase, and uric acid, are usually mild to moderate, dose-dependent, and reversible.

Colony-stimulating factors are fetotoxic in *animal* studies.

General references.

1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; **13:** 371–406.
2. Gutierrez-Delgado F, Bensinger W. Safety of granulocyte colony-stimulating factor in normal donors. *Curr Opin Hematol* 2001; **8:** 155–60.
3. Cottle TE, *et al*. Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. *Semin Hematol* 2002; **39:** 134–40.
4. Crawford J. Safety and efficacy of pegfilgrastim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2003; **23** (suppl): 15S–19S.
5. Pulsipher MA, *et al*. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood* 2009; **113:** 3604–11.

Disseminated intravascular coagulation. Long-term treatment with granulocyte colony-stimulating factor in a 7-year-old boy with HIV infection and zidovudine-induced neutropenia produced evidence of disseminated intravascular coagulation on 2 occasions.[1]

1. Mueller BU, *et al*. Disseminated intravascular coagulation associated with granulocyte colony-stimulating factor therapy in a child with human immunodeficiency virus infection. *J Pediatr* 1995; **126:** 749–52.

Effects on the bones. Bone mineral loss and osteoporosis have been reported in children with severe congenital neutropenia receiving granulocyte colony-stimulating factor for long periods.[1-3] However, the role of granulocyte colony-stimulating factor in producing this effect is uncertain since bone mineral loss may be a feature of the underlying disease.

1. Bishop NJ, *et al*. Osteoporosis in severe congenital neutropenia treated with granulocyte colony-stimulating factor. *Br J Haematol* 1995; **89:** 927–8.
2. Yakisan E, *et al*. High incidence of significant bone loss in patients with severe congenital neutropenia (Kostmann's syndrome). *J Pediatr* 1997; **131:** 592–7.
3. Sekhar RV, *et al*. Severe osteopenia in a young boy with Kostmann's congenital neutropenia treated with granulocyte colony-stimulating factor: suggested therapeutic approach. Abstract: *Pediatrics* 2001; **108:** 756–7. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e54 (accessed 27/10/05)

Effects on the eyes. Subretinal haemorrhage resulting in irreversible loss of vision in one eye occurred in a 4-year-old girl who received filgrastim and nartograstim for chemotherapy-induced neutropenia and for mobilising peripheral blood stem cells.[1] It was postulated that the colony-stimulating factor reactivated a primary ocular inflammation probably caused by an infection. Bilateral peripapillary and macular retinal haemorrhage occurred in an adult being treated for mantle cell lymphoma.[2] It was attributed to retinal leucostasis secondary to hyperleucocytosis resulting from the use of filgrastim for stem cell mobilisation. Vision improved after cessation of filgrastim and the use of leucapheresis.

1. Matsumura T, *et al*. Subretinal haemorrhage after granulocyte colony-stimulating factor. *Lancet* 1997; **350:** 336. Correction. *ibid.*; 1406.
2. Salloum E, *et al*. Hyperleukocytosis and retinal hemorrhages after chemotherapy and filgrastim administration for peripheral blood progenitor cell mobilization. *Bone Marrow Transplant* 1998; **21:** 835–7.

Effects on the lungs. There have been reports of exacerbation of chemotherapy-induced pulmonary toxicity in patients receiving granulocyte colony-stimulating factor (G-CSF) with bleomycin, cyclophosphamide, or methotrexate. A systematic review[1] of 73 cases noted that the doses of the antineoplastics were below the usual toxic cumulative dose, suggesting that G-CSF may have lowered the threshold for pulmonary toxicity of these drugs. It has been proposed that G-CSF has an activating effect on neutrophils that makes them toxic to the alveolar capillary wall. The review also included 2 cases of pulmonary toxicity in non-neutropenic patients treated with G-CSF alone. The circumstances of 9 other cases suggested that neutropenic patients with a recent history of pulmonary infiltrates may be at increased risk of acute respiratory distress syndrome during neutropenia recovery. The true role of G-CSF in these cases of pulmonary toxicity remains unclear, however.

1. Azoulay E, *et al*. Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. *Chest* 2001; **120:** 1695–1701.

Effects on the skin. Skin reactions may occur in patients given colony-stimulating factors. In a study in women with inflammatory breast cancer, a pruritic skin reaction developed at the subcutaneous injection site in all 7 given granulocyte-macrophage colony-stimulating factor.[1] A review[2] of 8 cases of generalised pruritic maculopapular rash associated with granulocyte or granulocyte-macrophage colony-stimulating factor found that in 6 of them the rash resolved in 4 to 17 days even though therapy was continued and half the patients did not receive any treatment for the rash. A localised lichenoid reaction has been described for granulocyte colony-stimulating factor.[3] Exacerbation of psoriasis[4] and precipitation or exacerbation of neutrophilic dermatoses including Sweet's syndrome,[5-7] pyoderma gangrenosum,[8] and neutrophilic eccrine hidradenitis[9] have been reported following use of granulocyte colony-stimulating factor.

1. Steger GG, *et al*. Cutaneous reactions to GM-CSF in inflammatory breast cancer. *N Engl J Med* 1992; **327:** 286.
2. Álvarez-Ruiz S, *et al*. Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. *J Eur Acad Dermatol Venereol* 2004; **18:** 310–13.
3. Viallard AM, *et al*. Lichenoid cutaneous drug reaction a t injection sites of granulocyte colony-stimulating factor (filgrastim). *Dermatology* 1999; **198:** 301–3.
4. Kavanaugh A. Flare of psoriasis and psoriatic arthritis following treatment with granulocyte colony-stimulating factor. *Am J Med* 1996; **101:** 567.
5. Petit T, *et al*. Lymphoedema-area-restricted Sweet syndrome during G-CSF treatment. *Lancet* 1996; **347:** 690.
6. Garty BZ, *et al*. Sweet syndrome associated with G-CSF treatment in a child with glycogen storage disease type Ib. *Pediatrics* 1996; **97:** 401–3.
7. Hasegawa M, *et al*. Sweet's syndrome associated with granulocyte colony-stimulating factor. *Eur J Dermatol* 1998; **8:** 503–5.
8. Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors: a review of associated neutrophilic dermatoses and vasculitides. *Arch Dermatol* 1994; **130:** 77–81.
9. Bachmeyer C, *et al*. Neutrophilic eccrine hidradenitis induced by granulocyte colony-stimulating factor. *Br J Dermatol* 1998; **139:** 354–5.

Effects on the thyroid. Reversible thyroid dysfunction has been reported in patients with pre-existing thyroid antibodies during treatment with granulocyte-macrophage colony-stimulating factor,[1] but not with granulocyte colony-stimulating factor.[2] However, clinical hypothyroidism has been reported in a patient with no history of thyroid dysfunction or thyroid antibodies during treatment with granulocyte colony-stimulating factor.[3]

1. Hoekman K, *et al*. Reversible thyroid dysfunction during treatment with GM-CSF. *Lancet* 1991; **338:** 541–2.
2. van Hoef MEHM, Howell A. Risk of thyroid dysfunction during treatment with G-CSF. *Lancet* 1992; **340:** 1169–70.
3. de Luis DA, Romero E. Reversible thyroid dysfunction with filgrastim. *Lancet* 1996; **348:** 1595–6.

Inflammatory disorders. Reactivation of various inflammatory disorders including rheumatoid arthritis[1] and pseudogout[2,3] has been reported after use of granulocyte colony-stimulating factors. For further reports of reactivation of sites of inflammation, see under Effects on the Eyes and Effects on the Skin, above.

1. Vildarsson B, *et al*. Reactivation of rheumatoid arthritis and development of leukocytoclastic vasculitis in a patient receiving granulocyte colony-stimulating factor for Felty's syndrome. *Am J Med* 1995; **98:** 589–91.
2. Sandor V, *et al*. Exacerbation of pseudogout by granulocyte colony-stimulating factor. *Ann Intern Med* 1996; **125:** 781.
3. Teramoto S, *et al*. Increased synovial interleukin-8 and interleukin-6 levels in pseudogout associated with granulocyte colony-stimulating factor. *Ann Intern Med* 1998; **129:** 424–5.

Precautions

Since granulocyte colony-stimulating factors such as filgrastim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although more recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. Filgrastim and lenograstim should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy because of the sensitivity of rapidly dividing myeloid cells. Pegfilgrastim should not be used from 14 days before until 24 hours after chemotherapy. The safety and efficacy of granulocyte colony-stimulating factor therapy has not been established in patients receiving chemoradiotherapy, and concomitant use is generally avoided.

Transient cytogenetic modifications have occurred in healthy donors given filgrastim for the mobilisation of peripheral blood progenitor cells. The significance of these changes is not known, and long-term safety follow-up of donors is ongoing. Until more is known, licensed product information recommends that donors should be monitored for at least 10 years.

Granulocyte colony-stimulating factors should be used with caution in patients with sickle-cell disease. Preparations of filgrastim may contain sorbitol as an excipient; care is advisable in patients with hereditary fructose intolerance.

The complete blood count should be monitored regularly during therapy with granulocyte colony-stimulating factors. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Transient positive changes in bone imaging findings have occurred with growth factor therapy, and should be considered when interpreting results. Bone density should be monitored in patients with osteoporosis who are receiving long-term treatment with filgrastim.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies filgrastim and pegfilgrastim as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Sickle-cell disease. Granulocytosis occurs during sickle-cell crisis (p. 1123.2) although the role of granulocytes in vaso-occlusion has not been established. Sickle-cell crisis has occurred in patients with sickle-cell disease who have been given granulocyte colony-stimulating factor.[1-3]

1. Abboud M, *et al*. Granulocytosis causing sickle-cell crisis. *Lancet* 1998; **351:** 959.
2. Adler BK, *et al*. Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. *Blood* 2001; **97:** 3313–14.
3. Wei A, Grigg A. Granulocyte colony-stimulating factor–induced sickle cell crisis and multiorgan dysfunction in a patient with compound heterozygous sickle cell/ β^+ thalassemia. *Blood* 2001; **97:** 3998–9.

Pharmacokinetics

After subcutaneous injection, peak serum concentrations of filgrastim occur within about 8 hours. The serum elimination half-life of filgrastim after intravenous or subcutaneous injection is about 3.5 hours. Pegfilgrastim peak concentrations occur later, at 16 to 120 hours after subcutaneous doses. Elimination of pegfilgrastim is non-linear and clearance becomes saturated and decreases with increasing dose. It is mainly eliminated by neutrophil-mediated clearance, such that the serum concentration of pegfilgrastim declines rapidly with neutrophil recovery. It has a half-life of 15 to 80 hours after subcutaneous injection.

Reviews.

1. Zamboni WC. Pharmacokinetics of pegfilgrastim. *Pharmacotherapy* 2003; **23** (suppl): 9S–14S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: FI-GCF; Filgen; Filgramega; Neulastim; Neupogen; Neutrofil; Neutromax; ***Austral.***: Neulas-

The symbol † denotes a preparation no longer actively marketed

ta; Neupogen; Nivestim; Tevagrastim; ***Austria***: Neulasta; Neupogen; Nivestim; Ratiograstim; Zarzio; ***Belg.***: Neulasta; Neupogen; Tevagrastim; Zarzio; ***Braz.***: Filgrastine; Granulen; Granulokine; Leucin; Leukocim; Myograf; Neulastim; Tevagrastim; ***Canad.***: Neulasta; Neupogen; ***Chile***: Foltran; Neulastim; Neupogen; Neutromax; ***China***: Baolijin (保力津); Gran (惠尔血); Jilifen (吉粒芬); ***Cz.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Denm.***: Granulokine†; Neulasta; Neupogen; Nivestim; Ratiograstim†; Zarzio; ***Fin.***: Neulasta; Neupogen; ***Fr.***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Ger.***: Biograstim†; Neulasta; Neupogen; Nivestim; Ratiograstim; ***Gr.***: Granulokine; Neulasta; Nivestim; Tevagrastim†; Zarzio; ***Hong Kong***: Neulastim; Neupogen; Scimax; ***Hung.***: Neulasta; Neupogen; Ratiograstim; Tevagrastim; Zarzio; ***India***: Filgen; Grafeel; Grastim; Neukine; Neulastim; Neumax; Neupeg; Neupogen; NFil; Nufil-Safe; ***Indon.***: Leucogen; Leukokine; Neulastim; Neupogen; ***Irl.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Israel***: Neulastim; Neupogen; Tevagrastim; ***Ital.***: Granulokine; Neulasta; Neupogen†; Neupopeg†; Ratiograstim; ***Jpn***: Gran; ***Malaysia***: Gran; Neupogen; Peglasta; ***Mex.***: Biofilgran; Filatil; Inmunef†; Ior LC; Neukine; Neulastim; Neupogen; ***Neth.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Norw.***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***NZ***: Neulastim; Neupogen; ***Philipp.***: Granulokine; Macroleuco; Neulastyl; Peglasta; Recombicyte; SciLocyte; White-C; ***Pol.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Port.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Rus.***: Filergim (Филергим); Granogen (Граноген); Grasalva (Грасальва); Leicita (Лейцита); Leucostim (Лейкостим); Mielastra (Миеластра); Neitrostim (Нейтростим); Neulastim (Неуластим); Neupogen (Нейпоген); Neupomax (Нейпомакс); Tevagrastim (Теваграстим); ***S.Afr.***: Neupogen; ***Singapore***: Gran; Neulastim; Neupogen; Peglasta; ***Spain***: Neulasta; Neupogen; Nivestim; Ratiograstim; Zarzio; ***Swed.***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Switz.***: Neulasta; Neupogen; TevaGrastim; Zarzio; ***Thai.***: Filgen; Gran; Jilifen†; Neukine; Neulastim; Neupogen; Neutromax; Peglasta; ***Turk.***: Leucostim; Neupogen; ***UK***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Ukr.***: Filstim (Филстим); Grastim (Граστим); Neulastim (Неуластим); Neupogen (Нейпоген); TevaGrastim (ТеваГрастим); ***USA***: Granix; Neulasta; Neupogen; ***Venez.***: Neupogen.

Gelatin ⊗

Gelatina; Gelatine; Gélatine; Liivate; Modifiye Jelatin; Želatyna; Želatina; Zselatin; Желатин.

ATC — B02BC01 (absorbable gelatin sponge); B05AA06 (gelatin).

ATC Vet — QB02BC01 (absorbable gelatin sponge); QB05AA06 (gelatin).

UNII — 2G86QN327L.

Grades. Gelling grades of gelatin are usually graded by gel strength, expressed as 'Bloom value', 'Bloom strength', or 'Bloom rating'.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.* Also in *USNF*.

The gelatin described in some pharmacopoeias is not necessarily suitable for preparations for parenteral use or for other special purposes.

Ph. Eur. 8: (Gelatin). A purified protein obtained either by partial acid hydrolysis (type A), by partial alkaline hydrolysis (type B), or by enzymatic hydrolysis of collagen from animals (including fish and poultry); it may also be a mixture of different types. The hydrolysis leads to gelling and non-gelling product grades. Gelling grades are characterised by the gel strength (Bloom value). It is not suitable for parenteral use or for other special purposes.

A faintly yellow or light yellowish-brown solid, usually occurring as translucent sheets, shreds, powder, or granules.

Gelling grades of gelatin swell in cold water and on heating give a colloidal solution which on subsequent cooling forms a more or less firm gel. Gelatin is practically insoluble in common organic solvents. Different gelatins form aqueous solutions that vary in clarity and colour. A 1% solution in water at about 55 degrees has a pH of 3.8 to 7.6. Protect from heat and moisture.

USNF 31: (Gelatin). It is obtained from collagen of animals (including fish and poultry) by partial alkaline and/or acid hydrolysis, by enzymatic hydrolysis, or by thermal hydrolysis. The hydrolysis leads to gelling or non-gelling grades.

Faintly yellow or amber sheets, flakes, or shreds, or a coarse to fine powder, the colour varying in depth according to the particle size. A solution has a slight, characteristic, bouillon-like odour. It is stable in air when dry, but is subject to microbial decomposition when moist or in solution. Gelatin swells and softens when immersed in cold water, gradually absorbing 5 to 10 times its weight of water. Soluble in hot water, in 6N acetic acid, and in a hot mixture of glycerol and water; insoluble in alcohol, in chloroform, in ether, and in fixed and volatile oils. Protect from heat and moisture.

Incompatibility. A white precipitate was formed immediately when vancomycin injection was infused through a giving set containing modified fluid gelatin solution.[1]

1. Taylor A, Hornbrey P. Incompatibility of vancomycin and gelatin plasma expanders. *Pharm J* 1991; **246:** 466.

Uses and Administration

Gelatin is a protein that has both clinical and pharmaceutical uses.

Gelatin is used as a haemostatic in surgical procedures as an absorbable film or sponge and can absorb many times its weight of blood. It is also employed as a plasma volume expander similarly to the dextrans in hypovolaemic shock (p. 1279.3). A 4% solution of a modified fluid gelatin (succinylated gelatin) has been infused in doses of 500 to 1000 mL. It may also be used in the form of a gelatin-derived polymer, see Polygeline, p. 1160.3.

Gelatin rods may be employed to temporarily block tear outflow in the diagnosis of dry eye (p. 2190.1).

Gelatin is used in the preparation of pastes, pastilles, suppositories, tablets, and hard and soft capsule shells. It is also used for the microencapsulation of drugs and other industrial materials. It has been used as a vehicle for injections: Pitkin's Menstruum, which consists of gelatin, glucose, and acetic acid, has been used in a modified form for heparin while hydrolysed gelatin has been used for corticotropin. Gelatin is an ingredient of preparations used for the protection of stomas and lesions.

Haemostasis. Gelatin acts as a haemostatic (p. 1124.3) by providing a physical meshwork within which clotting can occur.

Gelatin powder may be applied dry to wound beds and may be most useful when mixed with saline or thrombin and applied to bone. Gelatin sponge can be applied dry or soaked in saline or thrombin solutions. When applied to skin wounds the gelatin liquefies within 2 to 5 days; when implanted into tissues it is absorbed within 4 to 6 weeks. Adverse reactions include an increased incidence of infection, compression of surrounding tissue due to fluid absorption, granuloma formation, and fibrosis. Generally, gelatin sponges cause little tissue reaction and can be applied to bone, dura, and pleural tissue (but see also Hypersensitivity, below).

References.

1. Larson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; **14:** 623–32.
2. Schonauer C, *et al.* The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. *Eur Spine J* 2004; **13** (suppl): S89–S96.
3. Gabay M. Absorbable hemostatic agents. *Am J Health-Syst Pharm* 2006; **63:** 1244–53.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p. 1128.3). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155:** 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348:** 229–32.

Adverse Effects

Hypersensitivity reactions including anaphylactic reactions have occurred after the infusion of gelatin or its derivatives. Rapid infusion of gelatin derivatives may directly stimulate the release of histamine and other vasoactive substances.

For adverse reactions associated with the topical use of gelatin, see Haemostasis under Uses and Administration, above.

Hypersensitivity. Severe anaphylactoid reactions have been reported with infusion of modified fluid gelatin solutions.[1,2] As of June 2006, the Australian Adverse Drug Reactions Advisory Committee[3] had also received 70 reports of hypotension or hypersensitivity reactions associated with succinylated gelatin. Although severe hypersensitivity reactions to gelatin-based plasma expanders appear to be rare, they may be under-reported and fatalities have occurred.[2] The possibility of cross reactivity between succinylated gelatin and polygeline has also been considered; there are a few reports of patients who, after a reaction during clinical use with one plasma expander, have shown a positive skin test result to the other.[4,5] Some hypersensitivity reactions have been attributed to the use of gelatin as an excipient in vaccines[6-8] and other injectable drug products.[9] A haemostatic gelatin sponge put into place at the end of spinal surgery for a disc hernia was thought to be responsible for a delayed hypersensitivity reaction that caused oedema of the soft tissues and subsequent tingling and paresis of the lower limbs; removal of the sponge produced improvement.[10]

For reports of fatal reactions in asthmatic patients given gelatin derivatives, see Polygeline, p. 1160.3.

1. Blanloeil Y, *et al.* Accidents anaphylactoïdes sévères après perfusion d'une gélatine fluide modifiée en solution équilibrée. *Therapie* 1983; **38:** 539–46.
2. Walker SR, MacSweeney ST. Plasma expanders used to treat or prevent hypotension can themselves cause hypotension. *Postgrad Med J* 1998; **74:** 492–4.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Problems with colloids in fluid resuscitation. *Aust Adverse Drug React Bull* 2006; **25:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0606.pdf (accessed 07/12/06)
4. Russell WJ, Fenwick DG. Anaphylaxis to Haemaccel and cross reactivity to Gelofusin. *Anaesth Intensive Care* 2002; **30:** 481–3.
5. Russell WJ, Fenwick DG. Cross-reactivity between Gelofusin and Haemaccel. *Anaesth Intensive Care* 2003; **31:** 121–2.
6. Kelso JM. The gelatin story. *J Allergy Clin Immunol* 1999; **103:** 200–202.
7. Patja A, *et al.* Allergic reactions to measles-mumps-rubella vaccination. Abstract: *Pediatrics* 2001; **107:** 398. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/2/e27 (accessed 27/10/05)
8. Pool V, *et al.* Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. Abstract: *Pediatrics* 2002; **110:** 1241. Full version: http://pediatrics.aappublications.org/cgi/content/full/110/6/e71 (accessed 27/10/05)
9. Sakaguchi M, *et al.* A case of anaphylaxis to gelatin included in erythropoietin products. *J Allergy Clin Immunol* 1999; **103:** 349–50.
10. Purello-D'Ambrosio F, *et al.* Allergy to gelatin. *Allergy* 2000; **55:** 414–15.

Precautions

When gelatin or its derivatives are used as plasma expanders the precautions under Dextran 70 (p. 1139.2) should be considered. There does not appear to be any interference with blood grouping and cross-matching of blood.

When gelatin is used as an absorbable haemostatic the precautions under Oxidised Cellulose (p. 1157.3) should be considered.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gelatin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

After infusion of modified fluid gelatin (succinylated gelatin), 75% of the dose is excreted in the urine in 24 hours. The half-life is about 4 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gelafundin; Geloplasma†; Infukoll; ***Austral.***: Gelfoam; Gelofusine; ***Austria***: Gelofusin; Geloplasma; ***Belg.***: Gelofusine; ***Braz.***: Colagenan†; Gelfoam; ***Canad.***: Gelfoam; ***Chile***: Gelfoam; Gelofusine; Geloplasma; ***China***: Gelofusine (佳乐施); Xue An (雪安); ***Cz.***: Gelofusine; Geloplasma; ***Denm.***: Gelofusine; ***Fin.***: Gelofusine; ***Fr.***: Bloxang†; Gel-Phan†; Gelodiet; Gelofusine; Plasmion; ***Ger.***: Gelafundin; Gelafusal; Gelaspon; Gelastypt; Spongostan; stypro; ***Gr.***: Gelofusine; ***Hong Kong***: Gelofusine; ***Hung.***: Gelofusine; ***India***: Seraccel; ***Indon.***: Gelafundin; ***Irl.***: Gelaspan; Gelofusine; Geloplasma; ***Israel***: Gelfoam†; ***Ital.***: Cutanplast†; Eufusin; Gelofusine; Infuplas; Spongostan; Surgiflo; ***Malaysia***: Gelfoam; ***Mex.***: Gelafundin; ***Neth.***: Gelaspan; Gelofusine; Geloplasma; ***Norw.***: Gelaspan; ***NZ***: Gelafusal; Gelfilm†; Gelfoam†; Gelofusine†; ***Philipp.***: Gelfoam; ***Pol.***: Gelofusine; Geloplasma; ***Port.***: Gelafundina†; Gelofusine; Geloplasma; ***Rus.***: Gelatinol (Желатиноль); Gelofusin (Гелофузин); Geloplasma (Гелоплазма); ***S.Afr.***: Gelofusine; ***Singapore***: Gelfoam; Gelofusine; ***Spain***: Gelafundina; Geloplasma; ***Swed.***: Gelaspan; Gelofusine; ***Switz.***: Physiogel; ***Thai.***: Gelafundin†; Gelofusine; ***Turk.***: Gelofusin; ***UK***: Gelaspan; Gelofusine; Geloplasma; Isoplex; Volplex; ***Ukr.***: Gelofusine (Гелофузин); ***USA***: Gelfilm; Gelfoam; ***Venez.***: Gelfoam; Gelofusine.

Multi-ingredient Preparations. ***Arg.***: Aminoterapia; Cistimax; Megaplus; Mucobase; Valcatil Plus; Valcatil; ***Austral.***: Orabase; Stomahesive; ***Canad.***: Orabase; Orahesive; Tegasorb†; ***Fr.***: Rectopanbiline; ***Gr.***: Geloplasma; ***India***: Gelofusine; ***Indon.***: Nutrasendi; ***Irl.***: Orabase†; ***Ital.***: Eavit Plus; Eavit; Solecin†; Vitalux Plus; ***Jpn***: Choreito; Choreitogoshimotsuto; Kyukikyogaito; Shakanzoto; Unkeito; ***NZ***: Orabase; Stomahesive; ***Philipp.***: Thinber Fiber Complex†; ***Port.***: Dagragel; Efluvium Saquetas†; ***Rus.***: Gelplastan (Желпластан); ***S.Afr.***: Granuflex; Orabase†; ***Singapore***: Androlistica; ***UK***: Orabase; Orahesive; Stomahesive; ***USA***: Dome-Paste.

Pharmacopoeial Preparations

USP 36: Absorbable Gelatin Film; Absorbable Gelatin Sponge.

Haemoglobin ⊗

Emoglobina; Hämoglobin; Hemoglobiini; Hemoglobin; Hemoglobina; Hemoglobine; Hæmoglobin; Гемоглобин.

Hemoglobin Glutamer (rINN) ⊗

Haemoglobin Glutamer; Hemoglobina glutámero; Hémoglobine Glutamère; Hemoglobinum Glutamerum; Гемоглобин Глутамер.

ATC — B05AA10 (bovine).

ATC Vet — QB05AA10 (bovine); QB05AA90.

NOTE. The species of origin and average molecular mass should be indicated (e.g. hemoglobin glutamer-250 (bovine) indicates a polymerised haemoglobin of bovine origin with an average mass of 250 kD).

Profile

Haemoglobin has the property of reversible oxygenation and is the respiratory pigment of blood. Solutions of haemoglobin or modified haemoglobin are being investigated as blood substitutes.

Hemoglobin glutamer-250 (bovine) (HBOC-201; haemoglobin-based oxygen carrier-201) is a polymerised bovine haemoglobin that is used for the treatment of anaemia in surgical patients.

Hemoglobin glutamer-200 (bovine) (HBOC-301) is used in veterinary medicine for the treatment of anaemia in *dogs*.

Pyridoxalated haemoglobin polyoxyethylene (hemoximer) is reported to have nitric oxide scavenging effects. It is under investigation in shock.

Use. The structure of haemoglobin gives a non-linear oxygen dissociation curve; almost maximum oxygen saturation occurs in normal arterial blood without the need for oxygen-enriched air. Thus the use of haemoglobin solutions for emergencies appears logical. Initial *animal* experiments with haemoglobin from haemolysed erythrocytes resulted in serious renal damage but haemoglobin is not itself nephrotoxic and the development of stroma-free haemoglobin solutions reduced this toxicity. However, once released from the erythrocytes, haemoglobin loses its ability to hold 2,3-diphosphoglycerate, which is essential for the delivery of oxygen, and haemoglobin, being a small molecule, is rapidly excreted by the kidneys. Various methods have been tried to overcome these problems; formation of crosslinked haemoglobin restores the oxygen affinity to that of whole blood and conjugation, polymerisation, or microencapsulation in a lipid membrane extend the half-life. Although there is ongoing development of these preparations there are reservations concerning haemoglobin solutions as blood substitutes. Bovine blood is one source used for production but there are concerns about potential antigenicity or disease transmission; the use of outdated donated human blood is limited by availability. There is also concern about impairment of immune mechanisms. The development of recombinant human haemoglobin may overcome these problems and may allow further modification of the haemoglobin molecule.

References.

1. Farrar D, Grocott M. Intravenous artificial oxygen carriers. *Hosp Med* 2003; **64:** 352–6.
2. Creteur J, Vincent J-L. Hemoglobin solutions. *Crit Care Med* 2003; **31** (suppl): S698–S707.
3. Chang TMS. Hemoglobin-based red blood cell substitutes. *Artif Organs* 2004; **28:** 789–94.
4. Mackenzie CF, Bucci C. Artificial oxygen carriers for trauma: myth or reality. *Hosp Med* 2004; **65:** 582–8.
5. Awasthi V. Pharmaceutical aspects of hemoglobin-based oxygen carriers. *Curr Drug Deliv* 2005; **2:** 133–42.
6. Stowell CP. What happened to blood substitutes? *Transfus Clin Biol* 2005; **12:** 374–9.
7. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; **11:** 4099–4114.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Hemopure.

Multi-ingredient Preparations. ***Gr.***: Hemovital†; ***India***: Globifex; Haem Up; Haem-Up Gems; HB Rich; Hemfast; Hemfer; Hepp Forte.

Human Haematopoietic Stem Cells

Stammzellen vom Menschen, Hämatopoetische.

Pharmacopoeias. In *Eur* (see p. vii).

Ph. Eur. 8: (Human Haematopoietic Stem Cells; Cellulae Stirpes Haematopoieticae Humanae). Primitive multipotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages. They are found in small numbers in bone marrow, in the mononuclear cell fraction of circulating blood and in umbilical cord blood. The preparation also contains haematopoietic progenitor cells, which are capable of differentiation but not self-renewal. The numbers of haematopoietic stem cells and haematopoietic progenitor cells are correlated.

Profile

Haematopoietic stem cells and progenitor cells are produced during haematopoiesis (p. 1121.1). They may be collected directly from bone marrow, from peripheral blood after mobilisation, or from umbilical cord blood. These preparations are used in haematopoietic stem cell transplantation (p. 1937.1).

Infusion-related reactions to haematopoietic stem cell preparations may be caused by excipients. Patients given allogeneic haematopoietic stem cells are at risk of graft-versus-host disease and should receive appropriate immunosuppressive therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Hemacord.

Interleukin-3

IL-3; Interleucina 3; Interleukina 3; Interleuquina 3; Интерлейкин 3.

UNII — A802907MI4.

Profile

Interleukin-3 is a cytokine that acts as a colony-stimulating factor. It is under investigation in the management of myelosuppression associated with cancer chemotherapy and after bone marrow transplantation. A fusion molecule with granulocyte-macrophage colony-stimulating factor, known as milodistim (PIXY-321), has also been investigated but results have been disappointing.

Lenograstim (BAN, USAN, rINN)

Lenograstiimi; Lénograstim; Lenograstimum; rG-CSF; Ленограстим.

A recombinant human granulocyte colony-stimulating factor.

CAS — 135968-09-1.

ATC — L03AA10.

ATC Vet — QL03AA10.

UNII — 6WS4C399GB.

Stability. Solutions of colony-stimulating factors may be adsorbed onto glass or plastic materials. Solutions of lenograstim should not be diluted below the minimum recommended concentration for the formulation used.

Uses and Administration

Lenograstim is a granulocyte colony-stimulating factor with actions and uses similar to those of filgrastim (p. 1152.1). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p. 731.1). It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation. Lenograstim is also used in the treatment of severe congenital neutropenia (p. 1130.1).

When used as an **adjunct to antineoplastic therapy** and after **bone marrow transplantation**, lenograstim may be given in a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily. In patients receiving antineoplastics it is given subcutaneously, and in post-transplant patients it is given by intravenous infusion over 30 minutes or by subcutaneous injection. Lenograstim is started not less than 24 hours after the last dose of antineoplastic or the infusion of bone marrow or peripheral blood stem-cells. Treatment is given until the expected nadir has passed and the neutrophil count has stabilised at a level at which treatment can be stopped; the maximum recommended treatment period is 28 consecutive days.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily may be given by subcutaneous injection. It is started within 1 to 5 days after completion of chemotherapy and given until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leucapheresis is performed when the post-nadir leucocyte count is rising or after assessment of CD34+ cells in the blood. When used alone, a lenograstim dose of 10 micrograms/kg (1.28 million international units/kg) daily is given subcutaneously for 4 to 6 days, with leucapheresis usually performed between days 5 and 7. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 5 or 6 days before leucapheresis.

In patients with severe **congenital neutropenia** the initial dose of lenograstim is 150 micrograms/m^2 (equivalent to 5 micrograms/kg) daily by subcutaneous injection. Neutrophil recovery should be assessed over 7 to 14 days, and the dose may need to be adjusted up to 20 micrograms/kg daily. Maintenance therapy should be adjusted according to response, and a reduced dose or alternate day dosing may be possible in some patients.

References.

1. Frampton JE, *et al.* Lenograstim: a review of its pharmacological properties and therapeutic efficacy in neutropenia and related clinical settings. *Drugs* 1995; **49:** 767–93.
2. Dunn CJ, Goa KL. Lenograstim: an update of its pharmacological properties and use in chemotherapy-induced neutropenia and related clinical settings. *Drugs* 2000; **59:** 681–717.
3. Martino M, *et al.* Harvesting peripheral blood progenitor cells from healthy donors: retrospective comparison of filgrastim and lenograstim. *J Clin Apher* 2005; **20:** 129–36.

Adverse Effects and Precautions

As for Filgrastim, p. 1153.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lenograstim as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lenobio; ***Austral.***: Granocyte; ***Austria***: Granocyte; ***Belg.***: Granocyte; ***Braz.***: Granocyte; ***Chile***: Granocyte; ***China***: Granocyte (格拉诺赛特); ***Denm.***: Granocyte; ***Fin.***: Granocyte; ***Fr.***: Granocyte; ***Ger.***: Granocyte; ***Gr.***: Granocyte; ***Hung.***: Granocyte; ***India***: Granocyte; ***Indon.***: Granocyte; ***Irl.***: Granocyte; ***Israel***: Granocyte; ***Ital.***: Granocyte; Myelostim; ***Jpn***: Neutrogin; ***Malaysia***: Granocyte; ***Neth.***: Granocyte; ***Norw.***: Granocyte†; ***NZ***: Granocyte; ***Philipp.***: Granocyte; ***Pol.***: Granocyte; ***Port.***: Granocyte; ***Rus.***: Granocyte (Граноцит); ***S.Afr.***: Granocyte; ***Singapore***: Granocyte; ***Spain***: Euprotin†; Granocyte; ***Swed.***: Granocyte; ***Switz.***: Granocyte; ***Thai.***: Granocyte; ***Turk.***: Granocyte; ***UK***: Granocyte; ***Ukr.***: Granocyte (Граноцит); ***Venez.***: Granocyte.

Leucocytes

Leucociti; Leucócitos; Leucocitos; Leucocyti; Leukocitak; Leukocyten; Leukocyter; Leukocyty; Leukosyytit; Leukozyten; Лейкоциты.

Description. Preparations of leucocytes contain granulocytes with a variable content of red blood cells, lymphocytes, and platelets. Depending on the method of collection they may also contain dextran or hetastarch.

Uses and Administration

Transfusion of leucocytes has been used in patients with severe granulocytopenia and infection which has not been controlled by treatment with appropriate antimicrobials. A dose of granulocyte concentrate typically transfused for adults contains about 1×10^{10} neutrophils. Hydrocortisone and chlorphenamine have been given intravenously before transfusion to reduce the severity of adverse reactions.

References.

1. Yeghen T, Devereux S. Granulocyte transfusion: a review. *Vox Sang* 2001; **81:** 87–92.
2. Hubel K, Engert A. Granulocyte transfusion therapy for treatment of infections after cytotoxic chemotherapy. *Onkologie* 2003; **26:** 73–9.
3. Briones MA, *et al.* Granulocyte transfusion: revisited. *Curr Hematol Rep* 2003; **2:** 522–7.
4. Elebute M, *et al.* Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 22–6.

Adverse Effects and Precautions

Leucocyte transfusions may cause severe transfusion reactions and fever. As with other blood products, there is a risk of transmission of infection. Severe lung reactions, including fluid overload with pulmonary oedema, are a particular problem in patients with active pulmonary infections.

Red blood cell compatibility testing is necessary because of the content of red blood cells. Graft-versus-host disease may occur in immunosuppressed recipients, and can be avoided by irradiating the product before it is given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Immodin; ***Ger.***: Leuko-Norm†.

Methoxy Polyethylene Glycol-Epoetin Beta ⊗

Pegserepoetin Alfa; Pegzerepoetin Alfa; R-744; Ro-50-3821; Метоксиполиэтиленгликоль Эпоэтин Бета.
1-165-Erythropoietin (human) monoamide with α-(3-carboxypropyl)-ω-methoxypoly(oxy-1,2-ethanediyl).
CAS — 677324-53-7.
ATC — B03XA03.
ATC Vet — QB03XA03.
UNII — LR3UXN0193.

Uses and Administration

Methoxy polyethylene glycol-epoetin beta is described as a continuous erythropoietin receptor activator (CERA), with similar properties to the epoetins (p. 1141.2) but a longer duration of action. It is used in the treatment of symptomatic anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p. 1123.1). A starting dose of 600 nanograms/kg is given once every 2 weeks as a single intravenous or subcutaneous injection. Alternatively, for patients who are not on dialysis, a starting dose of 1.2 micrograms/kg once every month by subcutaneous injection may be given. For patients being switched from another erythropoiesis-stimulating agent such as an epoetin or darbepoetin alfa, the starting dose of methoxy polyethylene glycol-epoetin beta should be based on previous doses of these agents; high starting doses may be appropriate in some patients. The dose may be adjusted by about 25%, at monthly intervals, so that the rate of rise of haemoglobin is between 1 and 2 g per 100 mL each month. When the target haemoglobin concentration of between 10 and 12 g per 100 mL has been achieved, a maintenance dose may be given once monthly; this is equal to twice the dose that had been given once every 2 weeks.

Methoxy polyethylene glycol-epoetin beta is also under investigation in the treatment of anaemia in patients with non-myeloid malignant disease receiving chemotherapy.

References.
1. Sulowicz W, *et al.* PROTOS Study Investigators. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol* 2007; **2:** 637–46.
2. Levin NW, *et al.* MAXIMA study investigators. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet* 2007; **370:** 1415–21.
3. Österborg A, *et al.* Phase II study of three dose levels of continuous erythropoietin receptor activator (C.E.R.A.) in anaemic patients with aggressive non-Hodgkin's lymphoma receiving combination chemotherapy. *Br J Haematol* 2007; **136:** 736–44.
4. Klinger M, *et al.* Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomized trial. *Am J Kidney Dis* 2007; **50:** 989–1000.
5. Spinowitz B, *et al.* RUBRA Study Investigators. C.E.R.A. maintains stable control of hemoglobin in patients with chronic kidney disease on dialysis when administered once every two weeks. *Am J Nephrol* 2008; **28:** 280–9.
6. Macdougall IC, *et al.* ARCTOS Study Investigators. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol* 2008; **3:** 337--47.
7. Canaud B, *et al.* STRIATA Study Investigators. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. *Nephrol Dial Transplant* 2008; **23:** 3654–61.
8. Curran MP, McCormack PL. Methoxy polyethylene glycol-epoetin beta: a review of its use in the management of anaemia associated with chronic kidney disease. *Drugs* 2008; **68:** 1139–56.

Adverse Effects and Precautions

As for Epoetins, p. 1143.3 and p. 1144.2.

Pharmacokinetics

In patients with chronic renal impairment, methoxy polyethylene glycol-epoetin beta is absorbed after subcutaneous injection with an absolute bioavailability of about 60%. It has a terminal elimination half-life of about 134 hours after intravenous injection and about 140 hours when given subcutaneously. Haemodialysis does not affect its pharmacokinetics.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mircera; ***Austral.***: Mircera; ***Belg.***: Mircera; ***Braz.***: Mircera; ***Chile***: Mircera; ***Cz.***: Mircera; ***Denm.***: Mircera; ***Fr.***: Mircera; ***Ger.***: Mircera; ***Gr.***: Mircera; ***Hong Kong***: Mircera; ***Hung.***: Mircera; ***India***: Mircera; ***Indon.***: Mircera; ***Irl.***: Mircera; ***Israel***: Mircera; ***Ital.***: Mircera; ***Jpn***: Mircera; ***Malaysia***: Mircera; ***Mex.***: Mircera; ***Neth.***: Mircera; ***Norw.***: Mircera; ***Philipp.***: Mircera; ***Pol.***: Mircera; ***Port.***: Mircera; ***Rus.***: Mircera (Мирцера); ***S.Afr.***: Mircera; ***Spain***: Mircera; ***Swed.***: Mircera; ***Switz.***: Mircera; ***Thai.***: Mircera; ***Turk.***: Mircera; ***UK***: Mircera; ***Ukr.***: Mircera (Мирцера).

Mirimostim *(rINN)*

Mirimostimum; Миримостим.
1–214-Colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced), homodimer.
CAS — 121547-04-4.

Profile

Mirimostim is a macrophage colony-stimulating factor (M-CSF). It promotes the differentiation and proliferation of monocytes and macrophage precursors, and stimulates secretion of granulocyte and granulocyte-macrophage colony-stimulating factors (see Haematopoiesis, p. 1121.1). Mirimostim is used in the management of neutropenia in patients receiving myelosuppressive cancer chemotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Leukoprol.

Molgramostim *(BAN, USAN, rINN)*

Molgramostiimi; Molgramostimum; Sch-39300; Молграмостим.
A recombinant human granulocyte-macrophage colony-stimulating factor; Colony-stimulating factor 2 (human clone pHG_{25} protein moiety reduced).
CAS — 99283-10-0.
ATC — L03AA03.
ATC Vet — QL03AA03.
UNII — B321AL142J.

Pharmacopoeias. *Eur.* (see p. vii) includes a concentrated solution.

Ph. Eur. 8: (Molgramostim Concentrated Solution; Molgramostimi Solutio Concentrata). A solution of a protein having the structure of the granulocyte-macrophage colony-stimulating factor which is produced and secreted by various human blood cell types. It contains not less than 2.0 mg of protein per mL. A clear, colourless liquid. Store in airtight containers at a temperature below -65 degrees. Protect from light.

Stability. Solutions of molgramostim may be adsorbed onto glass and plastic materials and therefore should not be diluted below the recommended minimum concentration of 7 micrograms/mL.

Uses and Administration

Molgramostim is a granulocyte-macrophage colony-stimulating factor (GM-CSF), a haematopoietic growth factor that stimulates the development of white blood cells, particularly granulocytes, macrophages, and monocytes (see Haematopoiesis, p. 1121.1). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p. 731.1). It has also been used to reduce ganciclovir-induced neutropenia (see Effects on the Blood, p. 983.3).

As an **adjunct to antineoplastic therapy**, molgramostim is given by subcutaneous injection, starting 24 hours after the last dose of antineoplastic, in a dose of 5 to 10 micrograms/kg (60 000 to 110 000 international units/kg) daily. Treatment should be continued for 7 to 10 days.

Following **bone marrow transplantation**, molgramostim may be given by intravenous infusion over 4 to 6 hours in a dose of 10 micrograms/kg (110 000 international units/kg) daily. Treatment should be begun the day after bone marrow transplantation and continued for up to 30 days depending on the neutrophil count.

For the management of **ganciclovir-induced neutropenia**, molgramostim has been given by subcutaneous injection in a dose of 5 micrograms/kg (60 000 international units/kg) daily. After 5 doses have been given the dose of molgramostim should be adjusted according to the neutrophil count.

The maximum dose for any indication should not exceed 10 micrograms/kg (110 000 international units/kg) daily.

General references.
1. Armitage JO. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1998; **92:** 4491–4508.
2. Mangi MH, Newland AC. Febrile neutropenia: prophylactic and therapeutic use of GM-CSF. *Eur J Cancer* 1999; **35** (suppl): S4–S7.
3. Croockewit S. GM-CSF in haematopoietic stem cell transplantation. *Eur J Cancer* 1999; **35** (suppl): S11–S13.
4. Sung L, *et al.* Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22:** 3350–6.
5. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://jco.ascopubs.org/cgi/reprint/24/19/3187 (accessed 13/08/10)

Infections. See under Filgrastim, p. 1152.2, and under HIV Infection and AIDS in Sargramostim, p. 1163.1.

Respiratory disorders. Pulmonary alveolar proteinosis is a rare diffuse lung disease that may result from impaired alveolar macrophage function caused by neutralising autoantibodies. It is characterised by excessive surfactant accumulation, and is usually managed with whole-lung lavage. Several months of therapy with subcutaneous granulocyte-macrophage colony-stimulating factor, typically in doses of 5 or 6 micrograms/kg daily, has been reported to induce remission in some patients.[1-7] Both molgramostim and sargramostim have been tried, but some reports are unclear as to which was used. There has also been a case report[8] of the effective use of inhaled granulocyte-macrophage colony-stimulating factor.

1. Barraclough RM, Gillies AJ. Pulmonary alveolar proteinosis: a complete response to GM-CSF therapy. *Thorax* 2001; **56:** 664–5.
2. Seymour JF, *et al.* Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. *Am J Respir Crit Care Med* 2001; **163:** 524–31.
3. Schoch OD, *et al.* BAL findings in a patient with pulmonary alveolar proteinosis successfully treated with GM-CSF. *Thorax* 2002; **57:** 277–80.
4. Romero A, *et al.* GM-CSF therapy in pulmonary alveolar proteinosis. *Thorax* 2002; **57:** 837.
5. Khanjari F, *et al.* GM-CSF and proteinosis. *Thorax* 2003; **58:** 645.
6. Abdul Rahman JA, *et al.* Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: successful treatment with granulocyte-macrophage colony stimulating factor after a partial response to whole lung lavage. *Respirology* 2004; **9:** 419–22.
7. Venkateshiah SB, *et al.* An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. *Chest* 2006; **130:** 227–37.
8. Arai T, *et al.* Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. *Respir Med* 2004; **98:** 1227–30.

Wounds and ulcers. Macrophages and granulocyte-macrophage colony-stimulating factors play important roles in several mechanisms essential to wound healing.[1] Recombinant granulocyte-macrophage colony-stimulating factors are being tried in non-healing wounds and ulcers (p. 1690.1), particularly chronic venous leg ulcers. They have been given by perilesional subcutaneous injection and topical application in a few small studies and case reports with apparent promotion of wound healing.[1] In a study[2] of patients with pressure ulcers, healing was better during a 35-day period of treatment with granulocyte-macrophage colony-stimulating factor compared with placebo. However, a year after the treatment period there was no difference.[3] In a group of 3 patients with inherited disorders of neutrophil function, topical sargramostim was reported to be of benefit in wound healing.[4] In 1 case sargramostim was also given by continuous subcutaneous infusion for 72 hours into the surgical site of a gastrostomy closure. Topical molgramostim has also been used to promote healing of sickle-cell leg ulcers.[5] Molgramostim has been used as a mouthwash to relieve severe recurrent aphthous mouth ulcers in a small number of patients with AIDS.[6] There has also been some investigation of the use of granulocyte-macrophage colony-stimulating factor for oral mucositis in cancer patients, particularly those undergoing radiotherapy for head and neck cancers. Small studies of subcutaneous injection or topical application as a mouthwash have provided some optimistic results.[7,8] Comparative studies, however, have found molgramostim to be no better than hydrocortisone mouthwash[9] and perhaps only slightly better than sucralfate mouthwash.[10]

1. Groves RW, Schmidt-Lucke JA. Recombinant human GM-CSF in the treatment of poorly healing wounds. *Adv Skin Wound Care* 2000; **13:** 107–12.
2. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231:** 600–611.
3. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181:** 81–6.
4. De Ugarte DA, *et al.* Treatment of chronic wounds by local delivery of granulocyte-macrophage colony-stimulating factor in patients with neutrophil dysfunction. *Pediatr Surg Int* 2002; **18:** 517–20.
5. Méry L, *et al.* Topical effectiveness of molgramostim (GM-CSF) in sickle cell leg ulcers. *Dermatology* 2004; **208:** 135–7.
6. Herranz P, *et al.* Successful treatment of aphthous ulcerations in AIDS patients using topical granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2000; **142:** 171–6.
7. Fung SM, Ferrill MJ. Granulocyte macrophage-colony stimulating factor and oral mucositis. *Ann Pharmacother* 2002; **36:** 517–20.
8. Mantovani G, *et al.* Phase II clinical trial of local use of GM-CSF for prevention and treatment of chemotherapy- and concomitant chemoradiotherapy-induced severe oral mucositis in advanced head and neck cancer patients: an evaluation of effectiveness, safety and costs. *Oncol Rep* 2003; **10:** 197–206.
9. Sprinzl GM, *et al.* Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. *Eur J Cancer* 2001; **37:** 2003–9.
10. Saarilahti K, *et al.* Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. *Int J Radiat Oncol Biol Phys* 2002; **54:** 479–85.

Adverse Effects

Granulocyte-macrophage colony-stimulating factors such as molgramostim may cause transient hypotension and

flushing, bone pain and musculoskeletal pain, fever and chills, dyspnoea, rash, fatigue, and gastrointestinal effects. Antibodies have been detected. Anaphylactic reactions, pleural and pericardial effusion, and cardiac arrhythmias have been reported rarely.

Colony-stimulating factors are fetotoxic in *animal* studies.

General references.
1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; **13:** 371–406.
2. Moleski RJ. Comparison of G-CSF and GM-CSF adverse event profiles in office-based practices: preliminary study results. *Pharmacotherapy* 2000; **20** (suppl): 112S–117S.
3. Milkovich G, *et al*. Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2000; **20:** 1432–40.

Antibodies. Antibodies can develop in patients given recombinant granulocyte-macrophage colony-stimulating factors. The antibodies have been reported to occur more commonly, and in higher titres, in patients who are not immunocompromised compared with those who are.[1,2] Although some binding antibodies are non-neutralising and have no apparent clinical effect,[3] neutralising antibodies can reduce the efficacy of the colony-stimulating factor in repeated treatment cycles.[1,2] However, antibodies have been reported to become undetectable after several weeks[2] and do not appear to have long-term effects.[1] Cross-reactivity between different granulocyte-macrophage colony-stimulating factors has been reported,[1-3] and antibody formation may also be product dependent.[2]

1. Ragnhammar P, *et al*. Induction of anti-recombinant human granulocyte-macrophage colony-stimulating factor (Escherichia coli-derived) antibodies and clinical effects in nonimmunocompromised patients. *Blood* 1994; **84:** 4078–87.
2. Wadhwa M, *et al*. Immunogenicity of granulocyte-macrophage colony-stimulating factor (GM-CSF) products in patients undergoing combination therapy with GM-CSF. *Clin Cancer Res* 1999; **5:** 1353–61.
3. Ullenhag G, *et al*. Incidence of GM-CSF antibodies in cancer patients receiving GM-CSF for immunostimulation. *Clin Immunol* 2001; **99:** 65–74.

Effects on the skin. See under Filgrastim, p. 1153.2.

Effects on the thyroid. See under Filgrastim, p. 1153.2.

Precautions

Since granulocyte-macrophage colony-stimulating factors such as molgramostim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although more recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. They should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy or radiotherapy because of the sensitivity of rapidly dividing myeloid cells.

Granulocyte-macrophage colony-stimulating factors should be used with caution in patients with pulmonary disease as they may be predisposed to dyspnoea. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Caution is also necessary in patients with fluid retention or heart failure as fluid retention may be aggravated.

The complete blood count should be monitored regularly during therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies molgramostim as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Growgen-GM; Molcass; ***Braz.***: Leucocitim; ***Gr.***: Leucomax; Mielogen; ***India***: Leucomax†; ***Irl.***: Leucomax†; ***Mex.***: Bagomol†; Gramal; ***NZ***: Leucomax; ***Rus.***: Neustim (Неостим); ***Thai.***: Leucomax; ***Turk.***: Leucomax.

Naftazone *(BAN, rINN)*

Naftazona; Naftazonum; Нафтазон.
1,2-Naphthoquinone 2-semicarbazone.
$C_{11}H_9N_3O_2$=215.2
CAS — 15687-37-3.
ATC — C05CX02.
ATC Vet — QC05CX02.
UNII — 15B0523P5L.

Profile

Naftazone is a haemostatic, and is reported to increase venous tone and have a capillary stabilising effect. It has been used in venous insufficiency of the lower limbs and diabetic retinopathy, in oral doses of 30 mg daily. It was formerly given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Mediaven; ***Fr.***: Etioven; ***Switz.***: Mediaven; ***Turk.***: Mediaven.

Nartograstim *(rINN)*

Nartograstimum; Нартограстим.
A recombinant human granulocyte colony-stimulating factor; *N*-L-Methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine colony-stimulating factor (human clone 1034).
CAS — 134088-74-7.

Profile

Nartograstim is a granulocyte colony-stimulating factor with properties similar to those of filgrastim (p. 1151.3). It has been given by intravenous or subcutaneous injection in the management of neutropenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Neu-Up.

Oprelvekin *(USAN, rINN)*

Oprelvekina; Oprelvékine; Oprelvekinum; rhIL-11; YM-294; Опрельвекин.
2-178-Interleukin 11 (human clone pXM/IL-11).
$C_{854}H_{1411}N_{253}O_{235}S_2$=19047.3
CAS — 145941-26-0.
ATC — L03AC02.
ATC Vet — QL03AC02.
UNII — HM5641GA6F.

Uses and Administration

Oprelvekin, a recombinant human interleukin-11, is a platelet growth factor that stimulates the proliferation and maturation of megakaryocytes and thus increases the production of platelets. Oprelvekin is given by subcutaneous injection in a dose of 50 micrograms/kg daily to prevent severe thrombocytopenia and reduce the need for platelet transfusions in high-risk patients after myelosuppressive, but not myeloablative, chemotherapy for non-myeloid malignancies (see Thrombocytopenia under Treatment of Adverse Effects in Antineoplastics, p. 731.2). The dose should be reduced in severe renal impairment (see below). The initial dose should be given 6 to 24 hours after the last dose of antineoplastic, and continued up to a maximum of 21 days. Treatment with oprelvekin should be stopped at least 2 days before starting the next planned cycle of chemotherapy.

Oprelvekin has been investigated for the treatment of Crohn's disease, rheumatoid arthritis, and chronic hepatitis C.

Administration in renal impairment. In severe renal impairment (creatinine clearance less than 30 mL/min) the recommended dose of oprelvekin is 25 micrograms/kg daily by subcutaneous injection.

Thrombocytopenia. References.
1. Tepler I, *et al*. A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood* 1996; **87:** 3607–14.
2. Isaacs C, *et al*. Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *J Clin Oncol* 1997; **15:** 3368–77.
3. Reynolds CH. Clinical efficacy of rhIL-11. *Oncology (Huntingt)* 2000; **14** (suppl 8): 32–40.

Adverse Effects and Precautions

Fluid retention may occur and lead to peripheral oedema, dyspnoea and pulmonary oedema, capillary leak syndrome, and exacerbation of pre-existing pleural effusions; caution is required when giving oprelvekin to patients with a history or signs of heart failure. Dilutional anaemia may occur. Fluid balance and electrolytes should be monitored in patients receiving long-term diuretic therapy. Transient atrial arrhythmias commonly occur; there have also been some reports of ventricular arrhythmias occurring within 2 to 7 days of starting oprelvekin. Other adverse effects include exfoliative dermatitis, blurred vision, and conjunctival injection. Hypersensitivity reactions, including anaphylaxis, have been reported with the use of oprelvekin. Papilloedema has been reported, and oprelvekin should be used with caution in patients with pre-existing papilloedema or tumours involving the CNS.

Use of oprelvekin after myeloablative chemotherapy and bone marrow transplantation is considered to be contra-indicated because of an increased incidence of adverse effects.

Fetotoxicity has been reported in *animals*.

Reviews.
1. Smith JW. Tolerability and side-effect profile of rhIL-11. *Oncology (Huntingt)* 2000; **14** (suppl 8): 41–7.

Effects on the eyes. Papilloedema has been reported in patients treated with oprelvekin,[1] and was found to be a dose-limiting adverse effect in a study of safety and pharmacokinetics in children.[2]

1. Peterson DC, *et al*. Oprelvekin-associated bilateral optic disk edema. *Am J Ophthalmol* 2005; **139:** 367–8.
2. Cairo MS, *et al*. Phase I/II dose escalation study of recombinant human interleukin-11 following ifosfamide, carboplatin and etoposide in children, adolescents and young adults with solid tumours or lymphoma: a clinical, haematological and biological study. *Br J Haematol* 2005; **128:** 49–58.

Pharmacokinetics

The bioavailability of oprelvekin after subcutaneous injection is about 80%, peak serum concentrations occur after about 3 hours, and it has a terminal half-life of about 7 hours. Oprelvekin is metabolised before excretion by the kidneys, and its clearance is reduced in renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Neumega; Plaquemax; ***China***: Jijufen (吉巨芬); ***Israel***: Neumega†; ***Rus.***: Neumega (Неумега); ***USA***: Neumega; ***Venez.***: Neumega.

Oxidised Cellulose

Ácido celulósico; Cellulosic Acid; Celulosa oxidada; Oxidized Cellulose; Целлюлоза Окисленная.
CAS — 9032-53-5.
ATC — B02BC02.
ATC Vet — QB02BC02.

Description. Oxidised cellulose is a sterile polyanhydroglucuronic acid, prepared by the oxidation of a suitable form of cellulose.

Pharmacopoeias. In *US* which also includes Oxidized Regenerated Cellulose.

USP 36: (Oxidized Cellulose). It contains not less than 16% and not more than 24% of carboxyl groups, calculated on the dried basis. It is a slightly off-white gauze or lint with a slight, charred odour. Insoluble in water and in acids; soluble in dilute alkalis. Store at a temperature not exceeding 8 degrees. Protect from direct sunlight.

USP 36: (Oxidized Regenerated Cellulose). It contains 18 to 24% of carboxyl groups calculated on the dried basis. It is a slightly off-white knit fabric, with a slight odour. Insoluble in water and in dilute acids; soluble in dilute alkalis. Store at a temperature between 15 degrees and 30 degrees. Protect from direct sunlight.

Uses and Administration

Oxidised cellulose and oxidised regenerated cellulose are absorbable haemostatics (p. 1124.3). When applied to a bleeding surface, they swell to form a gelatinous mass which aids in the formation of a clot. It is gradually absorbed by the tissues, usually within 7 to 14 days. These materials also have a weak bactericidal action. They are used in surgery as adjuncts in the control of moderate bleeding where suturing or ligation is impracticable or ineffective; they should not be used to control haemorrhage from large arteries. The gauze, lint, or knitted material should be laid on the bleeding surface or held firmly against the tissues until haemostasis is achieved; removal should then be considered (see Adverse Effects and Precautions, below). Oxidised cellulose should be used as the dry material as moistening will reduce its ability to absorb blood.

Adverse Effects and Precautions

Foreign body reactions may occur after the use of oxidised cellulose or oxidised regenerated cellulose. Headache, burning, and stinging have been reported and sneezing has been noted after use in epistaxis. Oxidised cellulose swells on contact with a bleeding surface; this could result in tissue necrosis, nerve damage, obstruction, or vascular stenosis if packed closely, especially into bony cavities, or if wrapped tightly around blood vessels. To minimise such complica-

tions the removal of excess material should be considered after haemostasis is achieved, and oxidised cellulose should always be removed after use near the spinal cord or optic nerve. Oxidised cellulose should not be used in packing or implantation for fractures since it may interfere with bone regeneration or cause cyst formation. It should not be used as a surface dressing, except for immediate control of haemorrhage, as it inhibits epithelialisation.

Oxidised cellulose should be used as the dry material since moistening will reduce its ability to absorb blood. Silver nitrate or other escharotic chemicals should not be applied before use as cauterisation might inhibit absorption of oxidised cellulose. Thrombin is inactivated by the low pH of oxidised cellulose; it is recommended that oxidised cellulose should not be impregnated with other haemostatics or antibacterials.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Surgicel†; ***Ger.***: Tabotamp; ***Hong Kong***: Stop Bleed; ***Irl.***: Seal-On†; Traumacel P†; ***Ital.***: Tabotamp; ***UK***: Oxycel; StopBleed; ***USA***: Oxycel; Surgicel.

Multi-ingredient Preparations. ***Ital.***: Promogran Prisma; Promogran; ***UK***: Seal-On.

Oxypolygelatin ⊗

Oxipoligelatina.

Profile

Oxypolygelatin is a polymer derived from gelatin (p. 1154.1). It has been used as a 5.5% solution as a plasma volume expander. There have been reports of anaphylaxis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Gelifundol†.

Peginesatide *(USAN, rINN)* ⊗

AF-37702 (peginesatide or peginesatide acetate); Peginesatida; Péginésatide; Peginesatidum; Пэгинесатид.

$N^{6,21}$,$N^{6,21'}$-{[(N^2,N^6-bis{[ω-Methoxypoly(oxyethylene)]carbonyl}-DL-lysyl-β-alanyl)imino]bis(methylenecarbonyl)}bis[acetylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(naphthalen-1-yl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminyl-L-prolyl-L-leucyl-L-arginyl-*N*-methylglycyl-L-lysinamide] cyclic (6→15:6′→15′)-bisdisulfide.

$C_{231}H_{350}N_{62}O_{58}S_6(C_2H_4O)_n$

CAS — 913976-27-9; 1350810-60-4.

ATC — B03XA04.

ATC Vet — QB03XA04.

UNII — JX56W9N61Q.

NOTE. The name Hematide has been used as a trade mark for peginesatide.

Peginesatide Acetate *(USAN, rINNM)* ⊗

Acetato de peginesatida; AF-37702 (peginesatide or peginesatide acetate); Péginésatide, Acétate de; Peginesatidi Acetas; Пэгинесатида Ацетат.

$C_{231}H_{350}N_{62}O_{58}S_6(C_2H_4O)_nxC_2H_4O$

CAS — 1185870-58-9; 1350810-83-1.

ATC — B03XA04.

ATC Vet — QB03XA04.

UNII — 44STI720CW.

Uses and Administration

Peginesatide is a synthetic pegylated peptide-based erythropoiesis-stimulating agent; it has no amino acid sequence homology with endogenous erythropoietin. It is used for the treatment of anaemia due to chronic kidney disease (see Normocytic-normochromic Anaemia, p. 1123.1) in patients on dialysis (but see Adverse Effects and Precautions, below). For an outline of blood cell formation in general and average cell counts in adults see Haematopoiesis, p. 1121.1. Peginesatide is given as the acetate although doses are expressed in terms of the base.

The aim of treatment is to use the lowest dose necessary to reduce the need for blood transfusion. Peginesatide may be started in patients with a haemoglobin concentration of less than 10 g per 100 mL; the dose should be reduced or therapy stopped when the concentration approaches or exceeds 11 g per 100 mL (for details see Haematocrit and Haemoglobin, under Precautions of Epoetins, p. 1144.3). The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension and the dose should be reduced if it exceeds 1 g per 100 mL in any 2-week period, or 2 g per 100 mL per month. The recommended initial dose of peginesatide for those who are not currently receiving erythropoiesis-stimulating agents is 40 micrograms/kg as an intravenous or subcutaneous injection given once monthly. In patients who have previously received such agents, the initial monthly dose of peginesatide should be based on the weekly dose of the erythropoiesis-stimulating agent at the time of switching. The dose may be increased at intervals of not less than 4 weeks, according to response, until the target haemoglobin concentration is achieved. Haemoglobin concentrations should be monitored at least every 2 weeks until stable, then at least monthly. In general, adjustments are made by increasing or decreasing the dose by about 25%. Treatment should be stopped if the response is inadequate after a 12-week escalation period.

References.

1. Stead RB, *et al.* Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. *Blood* 2006; **108:** 1830–4.
2. Macdougall IC. Hematide, a novel peptide-based erythropoiesis-stimulating agent for the treatment of anemia. *Curr Opin Investig Drugs* 2008; **9:** 1034–47.
3. Macdougall IC, *et al.* A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N Engl J Med* 2009; **361:** 1848–55.
4. Macdougall IC, *et al.* Dose-finding study of peginesatide for anemia correction in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2011; **6:** 2579–86.
5. Mikhail A. Profile of peginesatide and its potential for the treatment of anemia in adults with chronic kidney disease who are on dialysis. *J Blood Med* 2012; **3:** 25–31.
6. Graul AI. Peginesatide for the treatment of anemia in the nephrology setting. *Drugs Today* 2012; **48:** 395–403.

Adverse Effects and Precautions

As for Epoetins, p. 1143.3 and p. 1144.2. Serious, and sometimes fatal, hypersensitivity reactions have been reported with peginesatide; these have occurred within 30 minutes following its first intravenous use. In February 2013 the FDA instructed dialysis organisations to discontinue use of peginesatide pending investigation.

Pharmacokinetics

After subcutaneous injection, maximum plasma concentrations of peginesatide are reached in about 48 hours, and the bioavailability is about 46%. The mean half-life of peginesatide in healthy subjects is about 25 hours after intravenous injection and about 53 hours after subcutaneous injection. The mean half-life after intravenous use in dialysis patients is about 48 hours, and mean volume of distribution is about 35 mL/kg. Peginesatide is not metabolised and is excreted mainly in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Omontys.

Plasma

Blodplasma; Bloedplasma; Blutplasma; Osocze krwi; Plasma sanguíneo; Veriplasma; Плазма Крови.

ATC — B05AX03.

ATC Vet — QB05AX03.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Plasma for Fractionation; Plasma Humanum ad Separationem). The liquid part of human blood remaining after separation of the cellular elements from whole blood or collected in an apheresis procedure; it is intended for the manufacture of plasma-derived products. It is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

A light yellow to green, clear or slightly turbid liquid, without visible signs of haemolysis. Frozen plasma should be stored at or below -20 degrees; it may still be used for fractionation if the temperature is between -20 degrees and -15 degrees for not more than a total of 72 hours without exceeding -15 degrees on more than one occasion as long as the temperature is at all times -5 degrees or lower.

Ph. Eur. 8: (Human Plasma (Pooled and Treated for Virus Inactivation); Plasma Humanum Coagumentum Conditumque ad Exstinguendum Virum). A frozen or freeze-dried, sterile, non-pyrogenic preparation obtained from human plasma derived from donors belonging to the same ABO blood group. The plasma used complies with the requirements for Human Plasma for Fractionation (above). The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to inactivate known agents of infection.

The frozen preparation, after thawing, is a clear or slightly opalescent liquid free from solid and gelatinous particles. The freeze-dried preparation is an almost white or slightly yellow powder or friable solid.

Uses and Administration

Fresh frozen plasma contains useful amounts of clotting factors. It should be reserved for patients with proven abnormalities in blood coagulation. Indications include congenital deficiencies in clotting factors for which specific concentrates are unavailable, severe multiple clotting factor deficiencies (for example in patients with liver disease), rapid reversal of the action of coumarin anticoagulants, and disseminated intravascular coagulation. It may be used after massive blood transfusion when there is evidence of coagulation deficiency but its value for routine prophylaxis against abnormal bleeding tendencies in patients receiving massive blood transfusions is contentious except where clotting abnormalities have been confirmed. It has also been used in the treatment of thrombotic thrombocytopenic purpura and as a source of plasma proteins.

The amount of fresh frozen plasma transfused depends on the required level of clotting factors. A unit of fresh frozen plasma refers to the quantity of plasma obtained from 1 unit of whole blood; this generally represents a volume of about 250 mL, including anticoagulant.

Fresh frozen plasma should not be used as a volume expander or as a nutritional source.

Therapeutic plasma exchange or plasmapheresis (see below) are used in a wide variety of disorders.

Plasma is used to prepare blood products including albumin, antithrombin III, blood clotting factors, immunoglobulins, and platelets. Other preparations include cryoprecipitate depleted plasma, which is deficient in fibrinogen, factor VIII, von Willebrand factor, cryoglobulin, and fibronectin, and single donor plasma, which is not frozen. A solvent-detergent-treated plasma preparation is available.

Guidelines and reviews. General references to the use of plasma.

1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.
2. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; **126:** 11–28. Also available at: http://www.bcshguidelines.com/pdf/freshfrozen_280604.pdf (accessed 27/10/05) Addenda, amendments, and corrections (4 sets) at http://www.bcshguidelines.com/pdf/Amendments_FFP_091205.pdf (issued 07/12/05),*ibid.* 2007; **136:** 514–16, at http://www.bcshguidelines.com/pdf/FFPAmendment_1_17_Oct_2007.pdf (issued 17/10/07), at http://www.bcshguidelines.com/pdf/FFPAmendment_2_17_Oct_2007.pdf (issued 17/10/07) (accessed 19/06/08)
3. Stanworth SJ, *et al.* Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; **126:** 139–52.
4. Cohen H, Baglin T. Plasma products and indications for their use. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 40–47.

Hereditary angioedema. For a mention of fresh frozen plasma being used in hereditary angioedema, see p. 2485.2.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p. 1128.3). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155:** 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348:** 229–32.

Plasma exchange. Therapeutic plasma exchange or plasmapheresis are procedures in which plasma is selectively removed from the body while the cellular constituents of blood are retained. Although the two terms are commonly used synonymously, plasmapheresis generally involves the removal of small volumes of plasma, whereas plasma exchange removes larger volumes which must be replaced with a suitable fluid.

They have been tried in a number of disorders, including many with an immunological basis, when conventional treatment has not been successful. The aim is removal or reduction of those constituents of plasma causing or aggravating a disease or replacement of deficient plasma factors if the deficiency is the cause of the disorder.

Volume and frequency of plasma exchange is determined by the pathophysiology of the undesirable plasma constituent. For example, removal of antibody usually requires exchange of 1.5 times the estimated plasma volume

(3 to 4 litres) repeated daily or on alternate days until the desired reduction is obtained. The replacement fluid used depends on the volume and the condition being treated; albumin solutions, plasma expanders, or sodium chloride 0.9% are frequently used, whereas in conditions where there is deficiency of a plasma factor replacement of blood components such as immunoglobulins may be required. Fresh frozen plasma has been used as a replacement fluid but is associated with a high incidence of adverse effects and is generally reserved for the management of thrombotic thrombocytopenic purpura.

Technological developments, such as the use of specific adsorbents and the use of multiple filters with different pore sizes, may enable removal of only the desired constituent and avoid removal and subsequent replacement of total plasma.

References.
1. Michaud D, *et al*. Therapeutic plasma exchange. *Dynamics* 2001; **12:** 18–24.
2. Madore F. Plasmapheresis: technical aspects and indications. *Crit Care Clin* 2002; **18:** 375–92.
3. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; **19:** 157–67.

Thrombotic microangiopathies. Thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome are both syndromes characterised by intravascular platelet clumping.[1-6] Thrombocytopenia also occurs and fragmentation of erythrocytes, partly caused by the red cells passing through areas of the microvasculature occluded by the platelet aggregation, leads to microvascular haemolytic anaemia. In **thrombotic thrombocytopenic purpura** (TTP) the platelet aggregation is extensive and obstructs the vessels of various organs producing ischaemia or even infarction. The CNS, notably the brain, is often the area mainly affected although some degree of renal involvement may occur. It is an uncommon disorder; adult women, in whom the condition presents as a chronic relapsing illness, are slightly more frequently affected. It may be associated with abnormalities of von Willebrand factor due to deficiency or impaired activity of a protease, ADAMTS-13,[5,6] a recombinant form of which is under investigation for treatment.

In **haemolytic-uraemic syndrome** (HUS) the platelet aggregation is relatively less widespread and less severe and mainly affects the renal microvasculature although extra-renal manifestations may also occur. The primary consequences are hypertension and acute renal insufficiency or ultimately, if untreated, renal failure. Most cases of HUS occur in early childhood and follow a diarrhoeal illness caused by *Shigella dysenteriae* or *Escherichia coli*. However, the condition is becoming increasingly recognised in adults, particularly the elderly. Some cases may be drug induced. With appropriate symptomatic therapy HUS is typically a self-limiting disease with spontaneous recovery although fatalities have been known. Atypical HUS[7] is a rare form of disordered complement regulation often associated with genetic mutations; the prognosis for these patients is poor.

The supportive **management** of both syndromes follows similar lines.[1,3,4] In HUS, or TTP with renal symptoms, special attention needs to be directed towards the prevention of renal failure. Hypovolaemia should be corrected, with careful control of fluid and electrolyte balance and hypertension. Haemodialysis will be needed if renal failure develops. Severe anaemia requires blood transfusion, but platelet transfusion should be avoided.

Plasma exchange (see p. 1158.3) is considered to be the mainstay of therapy for TTP.[1-6] The optimal regimen has not been determined, but it is usually performed daily. There is also some debate about the preferred fluid replacement; plasma exchange using cryosupernatant (the plasma remaining after cryoprecipitate is prepared, and which is depleted of von Willebrand factor) may be more efficacious than fresh frozen plasma.[3] When plasma exchange is not available, infusion of fresh frozen plasma may be used.[1,3] In HUS, there is some debate over the use of plasma exchange or infusion. Some consider that these have no proven benefit in HUS[2,3] but others[1] have challenged this belief. Plasma exchange or infusion are also used in atypical HUS, although evidence for which is most appropriate is limited.[7]

Antiplatelet therapy and corticosteroids are often given, although neither has been adequately investigated and antiplatelets such as ticlopidine and clopidogrel have been reported to cause TTP (see p. 1512.3). Aspirin and dipyridamole have been used, but are not recommended when profound thrombocytopenia is present because of the potential bleeding risk, without proven benefit. However, low-dose aspirin may be used when platelet counts have recovered after plasma exchange in TTP.[1,3] Some reports have described improved outcome in both syndromes with corticosteroids.[8] They are often used with plasma exchange in TTP.[1,3,4] However, a randomised, double-blind study[9] in children with HUS failed to show any difference between oral corticosteroids and placebo in terms of haematological or neurological recovery, although renal function appeared to improve more rapidly in those receiving corticosteroids. Eculizumab, a complement pathway blocker, may be used in atypical HUS.[10]

Other drugs may also be tried, particularly in refractory TTP. Some treatments that have been reported to be beneficial in case reports or small series include normal immunoglobulin,[1,4] azathioprine,[1] ciclosporin,[1,3] cyclophosphamide,[3] and vincristine.[1-4] The monoclonal antibody, rituximab, has also been investigated.[2] The use of a protein-A immuno-adsorption column may be considered in the management of TTP associated with malignancy or bone marrow transplantation.[3] Epoprostenol may be tried in order to inhibit platelet-endothelial interactions but again has not been subject to controlled studies; anecdotal evidence presents both favourable and negative results.[11] Alteplase has been used successfully in one patient with HUS.[12] Splenectomy may also be considered.[1,3,4]

1. Elliott MA, Nichols WL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Mayo Clin Proc* 2001; **76:** 1154–62.
2. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; **347:** 589–600.
3. British Society for Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003; **120:** 556–73.
4. Nabhan C, Kwaan HC. Current concepts in the diagnosis and management of thrombotic thrombocytopenic purpura. *Hematol Oncol Clin North Am* 2003; **17:** 177–99.
5. Mayer SA, Aledort LM. Thrombotic microangiopathy: differential diagnosis, pathophysiology and therapeutic strategies. *Mt Sinai J Med* 2005; **72:** 166–75.
6. George JN. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006; **354:** 1927–35.
7. Taylor CM, *et al*. Working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. *Br J Haematol* 2010; **148:** 37–47.
8. Bell WR, *et al*. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med* 1991; **325:** 398–403.
9. Perez N, *et al*. Steroids in the hemolytic uremic syndrome. *Pediatr Nephrol* 1998; **12:** 101–4.
10. Hodgkins KS, *et al*. Clinical grand rounds: atypical hemolytic uremic syndrome. *Am J Nephrol* 2012; **35:** 394–400.
11. Bobbio-Pallavicini E, *et al*. Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79:** 429–37.
12. Kruez W, *et al*. Successful treatment of haemolytic-uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; **341:** 1665–6.

Adverse Effects and Precautions

As for Blood, p. 1135.3, though with a low risk of transmitting cell-associated viruses. However, the production of blood products using plasma from UK donors has been phased out due to the possible risk of transmission of variant Creutzfeldt-Jakob disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Octaplas; ***Belg.***: Octaplas; ***Cz.***: Octaplas; ***Fin.***: Octaplas; ***Ger.***: Octaplas; ***Hung.***: Octaplas; ***Irl.***: Octaplas; ***Ital.***: Octaplas; Plasmasafe; ***Mex.***: Octaplas; ***Neth.***: Octaplas†; Omniplasma; ***Norw.***: Octaplas; ***NZ***: Octaplas; ***Port.***: Novoplas; Octaplas; ***Swed.***: Octaplas; ***Switz.***: Octaplas; ***UK***: Octaplas; ***USA***: Octaplas.

Multi-ingredient Preparations. ***Port.***: Quixil†; ***Rus.***: Gelplastan (Желпластан).

Plasma Protein Fraction ⊗

Fracción proteica del plasma; Белковые Фракции Плазмы.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US*.

USP 36: (Plasma Protein Fraction). A sterile preparation of serum albumin and globulin obtained by fractionating material (blood, plasma, or serum) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It contains 5% of protein; not less than 83% of the total protein is albumin; not more than 17% is alpha and beta globulins; not more than 1% has the electrophoretic properties of gamma globulin. It contains sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent but no antimicrobial preservative. It contains 130 to 160 mmol/litre of sodium, and not more than 2 mmol/litre of potassium. A solution in 0.15M sodium chloride containing 1% protein has a pH between 6.7 and 7.3. It should be used within 4 hours of opening the container.

Profile

Plasma protein fraction consists mainly of albumin with a small proportion of globulins; it does not contain blood-clotting factors. It has properties and uses similar to those of other albumin solutions (p. 1130.3). It is given intravenously as a solution containing 5% of total protein. The amount of plasma protein fraction given will depend upon the clinical condition of the patient. For hypovolaemic shock an initial infusion of 250 to 500 mL has been suggested at a rate not normally exceeding 10 mL/minute. For doses used in children, see below. In hypoproteinaemia, 1 to 1.5 litres of a 5% solution will provide 50 to 75 g of protein. Patients with normal blood volume may require slow infusion to prevent excessive volume expansion.

As with other albumin solutions, plasma protein fraction should not be used for parenteral nutrition.

Administration in children. A 5% solution of plasma protein fraction may be given to infants and young children in the management of hypovolaemic shock. An initial dose of up to 33 mL/kg may be given by intravenous infusion, at a rate of up to 10 mL/minute. Doses should be adjusted according to the condition of the patient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Biseko; ***Ger.***: Biseko; ***Gr.***: Plasmanate†; ***Hong Kong***: Plasmanate†; ***Hung.***: Biseko; ***Indon.***: Plasmanate; ***Israel***: Plasmanate; ***Ital.***: PPS; Uman-Serum; ***Philipp.***: Plasmanate†; ***S.Afr.***: Bioplasma FDP; ***Singapore***: Plasmanate; ***Thai.***: Biseko†; ***Turk.***: Biseko; ***USA***: Plasma-Plex; Plasmanate; Protenate.

Multi-ingredient Preparations. ***Fin.***: Tisseel Duo Quick; ***Ger.***: Tissucol Duo S; Tissucol-Kit; ***Hung.***: Tissucol-Kit; ***Ital.***: Tissucol; ***Swed.***: Tisseel Duo Quick; ***Switz.***: Tissucol Duo S†.

Pharmacopoeial Preparations
USP 36: Plasma Protein Fraction.

Platelets

Blodplader; Blodplater; Blodplättar; Bloedplaatjes; Blutplättchen; Piastrine; Plaquetas; Plaquettes; Płytek Krwi; Thrombocytes; Verihiutale; Тромбоциты.

Uses and Administration

Blood platelets assist in the haemostatic process (p. 1124.3) by aggregating to form a platelet thrombus, and by releasing factors involved in initiating coagulation.

Transfusions of platelet concentrates are given to patients with thrombocytopenic haemorrhage (see p. 1129.2). They are also given prophylactically to reduce the frequency of haemorrhage in thrombocytopenia associated with the chemotherapy of neoplastic disease (see p. 731.2).

References.
1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.
2. Schiffer CA, *et al*. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1519–38. Also available at: http://jco.ascopubs.org/cgi/reprint/19/5/1519.pdf (accessed 13/08/10)
3. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; **122:** 10–23. Also available at: http://www.bcshguidelines.com/pdf/platelettrans040703.pdf (accessed 27/10/05)
4. Heal JM, Blumberg N. Optimizing platelet transfusion therapy. *Blood Rev* 2004; **18:** 149–65.
5. Stroncek DF, Rebulla P. Platelet transfusions. *Lancet* 2007; **370:** 427–38.
6. Elebute M, *et al*. Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion*. 4th ed. Chichester: Wiley-Blackwell, 2009: 22–6.

Adverse Effects and Precautions

Transmission of infection has been associated with the transfusion of blood products including platelets (see Blood, p. 1135.3). Since platelets are stored at room temperature there is increased risk of bacterial infection after transfusion. Transfusion reactions including fever and urticaria are not uncommon. Recipients of multiple transfusions of platelet concentrates from random donors may develop antibodies to HLA which result in impaired responsiveness to subsequent transfusions. Use of leucocyte-depleted platelet concentrates reduces the incidence of transfusion reactions and of HLA sensitisation. Platelet concentrates prepared from Rh(D)-positive donors should generally not be given to Rh(D)-negative women of child-bearing potential. Ideally platelet concentrates should also be ABO-compatible with the recipient.

ABO compatibility. Platelets express the ABO blood group antigens and the plasma component of platelet concentrates may contain alloantibodies from the donor (see Blood Groups, p. 1136.3). Ideally, ABO-identical platelet concentrates should be used, but ABO-compatible concentrates are often used and incompatible concentrates may be used in an emergency. However, the use of ABO-mismatched platelets can reduce the efficacy of the platelet transfusion. Also, acute haemolytic reactions can occur after infusion of mismatched platelets if the infused

plasma contains high antibody titres or the volume of plasma infused is large. Some have suggested that screening donors for high antibody titres should be routine in order to avoid this, but there is no consensus as to the definition of critical titre. There have been mixed reports on whether the use of ABO-mismatched platelets has an effect on the recipient's long-term clinical course.

Reviews.
1. Lozano M, Cid J. The clinical implications of platelet transfusions associated with ABO or Rh(D) incompatibility. *Transfus Med Rev* 2003; **17:** 57–68.

HLA antibodies. Platelets obtained from single donors have been used in patients receiving multiple transfusions of platelet concentrates to reduce the formation of antibodies to HLA. Some practitioners suggest[1] that patients who are likely to need long-term platelet support should be typed for HLA A and B antigens and screened for HLA antibodies. Leucocyte-depleted platelets and UVB-irradiated platelets have also been tried. A study[2] in 530 patients found that the incidence of platelet refractoriness was reduced from 13% of those patients receiving pooled platelet concentrates to 3% and 5% of those receiving leucocyte-depleted and UVB-irradiated platelets, respectively. A meta-analysis[3] of this and earlier small studies also concluded that leucocyte depletion reduced the risk of alloimmunisation and platelet refractoriness. Some guidelines[4] have nonetheless considered that there is no convincing evidence of clinical benefit from routine use.

1. Dan ME, Schiffer CA. Strategies for managing refractoriness to platelet transfusions. *Curr Hematol Rep* 2003; **2:** 158–64.
2. The Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med* 1997; **337:** 1861–9.
3. Vamvakas EC. Meta-analysis of randomized controlled trials of the efficacy of white cell reduction in preventing HLA-alloimmunization and refractoriness to random-donor platelet transfusions. *Transfus Med Rev* 1998; **12:** 258–70.
4. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; **8:** 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)

Plerixafor *(USAN, rINN)*

AMD-3100; JM-3100; Plérixafor; Plerixaforum; SDZ-SID-791; SID-791; Плериксафор.

1,1′-(1,4-Phenylenebismethylene)bis(1,4,8,11-tetraazacyclotetradecane).

$C_{28}H_{54}N_8$=502.8

CAS — 110078-46-1 (plerixafor); 155148-31-5 (plerixafor hydrochloride).

ATC — L03AX16.

ATC Vet — QL03AX16.

UNII — S915P5499N.

Uses and Administration

Plerixafor is a CXCR4 chemokine receptor antagonist that blocks the binding of stromal cell-derived factor 1α. It inhibits the retention of haematopoietic stem cells in bone marrow, and increases their number in peripheral blood. In patients with non-Hodgkin's lymphoma or multiple myeloma, plerixafor is used, with granulocyte colony-stimulating factor (G-CSF), to mobilise stem cells for collection and subsequent autologous transplantation (see Haematopoietic Stem Cell Transplantation, p. 1937.1). G-CSF is given for 4 days before the first dose of plerixafor, and on each morning before apheresis. A dose of plerixafor 240 micrograms/kg is given by subcutaneous injection 6 to 11 hours before starting apheresis, usually for up to 4 consecutive days. The dose should not exceed 40 mg daily. For reduced doses to be used in renal impairment, see below.

References.
1. Holtan SG, *et al.* AMD3100 affects autograft lymphocyte collection and progression-free survival after autologous stem cell transplantation in non-Hodgkin lymphoma. *Clin Lymphoma Myeloma* 2007; **7:** 315–18.
2. Gazitt Y, *et al.* Improved mobilization of peripheral blood CD34+ cells and dendritic cells by AMD3100 plus granulocyte-colony-stimulating factor in non-Hodgkin's lymphoma patients. *Stem Cells Dev* 2007; **16:** 657–66.
3. Calandra G, *et al.* AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data. *Bone Marrow Transplant* 2008; **41:** 331–8.
4. Cashen A, *et al.* A phase II study of plerixafor (AMD3100) plus G-CSF for autologous hematopoietic progenitor cell mobilization in patients with Hodgkin lymphoma. *Biol Blood Marrow Transplant* 2008; **14:** 1253–61.
5. Wagstaff AJ. Plerixafor: in patients with non-Hodgkin's lymphoma or multiple myeloma. *Drugs* 2009; **69:** 319–26.
6. DiPersio JF, *et al.* 3102 Investigators. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood* 2009; **113:** 5720–6.
7. DiPersio JF, *et al.* 3101 Investigators. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol* 2009; **27:** 4767–73.

Administration in renal impairment. In moderate and severe renal impairment (creatinine clearance 50 mL/min or less) the dose of plerixafor should be reduced to 160 micrograms/kg, given by subcutaneous injection 6 to 11 hours before apheresis, usually for up to 4 consecutive days. The daily dose should not exceed 27 mg. There is insufficient information to recommend doses for patients on haemodialysis.

Adverse Effects and Precautions

Adverse gastrointestinal effects are common with the use of plerixafor and include diarrhoea, nausea, vomiting, flatulence, abdominal distention or pain, dyspepsia, and dry mouth. Other common effects include fatigue, arthralgia, headache, dizziness, insomnia, hyperhidrosis, and erythema. Injection site reactions also occur frequently. Systemic reactions occurring within about 30 minutes of injection have been reported in a small number of patients, and include urticaria, periorbital swelling, dyspnoea, and hypoxia. Some cases of vasovagal reactions, orthostatic hypotension, and syncope, within 1 hour of injection, have also been reported. Based on studies showing splenic enlargement after plerixafor administration in *rats*, it is recommended that patients with left upper abdominal pain and/or scapular or shoulder pain should be investigated for splenic integrity.

As the use of plerixafor with granulocyte colony-stimulating factor increases circulating leucocytes, white blood cell counts should be monitored. Plerixafor should be used with caution when the neutrophil count is above 50 000 cells/microlitre. Thrombocytopenia has also occurred and platelet counts should be monitored. Plerixafor should not be used for stem cell mobilisation and collection in patients with leukaemia, as there is a risk of mobilising leukaemic cells which could contaminate the apheresis product.

Based on its mechanism of action, plerixafor has the potential to cause congenital malformations when given to pregnant women. Teratogenicity has been shown in *animal* studies.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies plerixafor as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

Peak plasma concentrations of plerixafor occur about 30 to 60 minutes after a subcutaneous dose. It is about 58% bound to plasma proteins and largely confined to the extravascular fluid space. Plerixafor is not metabolised. About 70% of a dose is eliminated in the urine within 24 hours after a dose, and the terminal plasma half-life is about 3 to 5 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mozobil; ***Austria***: Mozobil; ***Belg.***: Mozobil; ***Canad.***: Mozobil; ***Cz.***: Mozobil; ***Denm.***: Mozobil; ***Fr.***: Mozobil; ***Ger.***: Mozobil; ***Gr.***: Mozobil; ***Irl.***: Mozobil; ***Israel***: Mozobil; ***Neth.***: Mozobil; ***Norw.***: Mozobil; ***Pol.***: Mozobil; ***Port.***: Mozobil; ***Singapore***: Mozobil; ***Spain***: Mozobil; ***Swed.***: Mozobil; ***UK***: Mozobil; ***USA***: Mozobil.

Policresulen *(rINN)*

Acidum Metacresolsulfonicum c. Formaldehydo; *m*-Cresolsulphonic acid-formaldehyde condensation product; Dicresulene polymer; Dihydroxydimethyldiphenylmethanedisulphonic acid polymer; Formaldehydhaltig Metakresolsulfonsyra; Formaldehydipitoinen Metakresolisulfonihappo; Metacresolsulfonic Acid-Formaldehyde; Metacresolsulphonic Acid-Formaldehyde; Methylenebis(hydroxytoluenesulphonic acid) polymer; Policrésulène; Policresuleno; Policresulenum; Polikresuleeni; Polikresulen; Polímero de dicresuleno; Polycresolsulfonate; Поликрезулен.

α-(4-Hydroxy-2-methyl-5-sulfobenzyl)-ω-(4-hydroxy-5-sulfo-*o*-tolyl)poly[(4-hydroxy-2-methyl-5-sulfo-*m*-phenylene) methylene]; 2-Hydroxy-*p*-toluenesulfonic acid, polymer with formaldehyde.

$(C_8H_9O_4S)(C_8H_8O_4S)_n(C_7H_7O_4S)$

CAS — 9011-02-3; 101418-00-2.

ATC — D08AE02; G01AX03.

ATC Vet — QD08AE02; QG01AX03; QG51AD02.

Profile

Policresulen is used as a topical haemostatic and antiseptic. It is also used similarly in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Albocresil; ***Braz.***: Albocresil; ***China***: Albothyl (爱宝疗); ***Cz.***: Vagothyl†; ***Ger.***: Albothyl; ***Hong Kong***: Albothyl; ***Hung.***: Vagothyl; ***Indon.***: Albothyl; ***Ital.***: Emaftol; Negatol; ***Malaysia***: Albothyl; ***Mex.***: Albothyl; ***Philipp.***: Albothyl; ***Pol.***: Albothyl; Vagothyl; ***Port.***: Nelex; ***Rus.***: Vagothyl (Ваготил); ***Singapore***: Albothyl; ***Switz.***: Negatol Dental.

Multi-ingredient Preparations. ***Arg.***: Proctyl; ***Braz.***: Proctox-H; Proctyl; ***Cz.***: Faktu; ***Ger.***: Faktu†; ***Hong Kong***: Faktu; ***India***: Faktu; ***Indon.***: Faktu; ***Mex.***: Proctoacid; ***Philipp.***: Faktu; ***Port.***: Faktu; ***Singapore***: Faktu; ***Switz.***: Faktu.

Polygeline *(BAN, pINN)* ⊗

Poligelina; Polygéline; Polygelinum; Полигелин.

CAS — 9015-56-9.

ATC — B05AA10.

Description. Polygeline is a polymer prepared by cross-linking polypeptides derived from denatured gelatin with a di-isocyanate to form urea bridges.

Incompatibility. Intravenous preparations of polygeline contain calcium ions and are incompatible with citrated blood.

Uses and Administration

Polygeline is a plasma volume expander used as a 3.5% solution with electrolytes in the management of hypovolaemic shock (p. 1279.3). The rate of infusion depends on the condition of the patient and does not normally exceed 500 mL in 60 minutes although it may be greater in emergencies. Initial doses for hypovolaemic shock usually consist of 500 to 1000 mL; up to 1500 mL of blood loss can be replaced by polygeline alone. Patients losing greater volumes of blood will require blood transfusion as well as plasma expanders.

Polygeline is also used in extracorporeal perfusion fluids, as a perfusion fluid for isolated organs, as fluid replacement in plasma exchange, and as a carrier solution for insulin. For plasma exchange, up to 2 litres of polygeline may be given as sole replacement fluid.

Adverse Effects

As for Gelatin, p. 1154.2.

Hypersensitivity. Fatal reactions after polygeline infusion have been reported in 2 patients with bronchial asthma.[1,2] Both patients were undergoing epidural analgesia with bupivacaine and polygeline was given to correct hypotension that had not responded to infusion of crystalloids. One patient developed focal seizures.[2] Both patients developed refractory bronchospasm and cardiac arrhythmias and died despite intensive resuscitation attempts.

Licensed product information recommends that prophylaxis with histamine H_1- and H_2-antagonists should be given to patients with known allergic conditions such as asthma. Similar advice has been offered[3] for patients undergoing anaesthesia and receiving polygeline following findings of an increased incidence of severe histamine-related reactions in such patients. Nevertheless, severe respiratory distress developed in an asthmatic patient given polygeline under spinal anaesthesia despite premedication with bronchodilators and antihistamines.[4]

There is a possibility of cross reactivity between polygeline and succinylated gelatin (see Gelatin, p. 1154.2).

1. Freeman MK. Fatal reaction t o haemaccel. *Anaesthesia* 1979; **34:** 341–3.
2. Barratt S, Purcell GJ. Refractory bronchospasm following "Haemaccel" infusion and bupivacaine epidural anaesthesia. *Anaesth Intensive Care* 1988; **16:** 208–11.
3. Lorenz W, *et al.* Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. *Lancet* 1994; **343:** 933–40.
4. Kathirvel S, *et al.* Severe life threatening reaction to Haemaccel in a patient with bronchial asthma. *Eur J Anaesthesiol* 2001; **18:** 122–3.

Precautions

Precautions that should be observed with plasma expanders are described under Dextran 70, p. 1139.2, and should be considered when polygeline is used for this purpose.

Polygeline preparations contain calcium ions and therefore should be used with caution in patients being treated with cardiac glycosides.

Pharmacokinetics

Like gelatin, polygeline is excreted mainly in the urine. The half-life is about 5 to 8 hours.

Renal impairment. In a study[1] in 52 patients with normal or impaired renal function given 500 mL of polygeline 3.5% about 50% of the dose was excreted in the urine within 48 hours in those with normal renal function. Excretion of polygeline in those with renal impairment, based on the patient's glomerular filtration rate (GFR), was found to be:

- GFR 31 to 90 mL/minute: unimpaired
- GFR 11 to 30 mL/minute: slightly reduced
- GFR 2 to 10 mL/minute: reduced to 27% in 48 hours
- GFR 0.5 to 2 mL/minute: reduced to 9.3% in 48 hours

The mean half-life of the elimination phase was 505 minutes in those with adequate renal function, increasing to 985 minutes in those with end-stage renal failure. Polygeline 500 mL of 3.5% solution could be given twice weekly for 1 to 2 months even in patients with total anuria.

1. Köhler H, *et al*. Elimination of hexamethylene diisocyanate cross-linked polypeptides in patients with normal or impaired renal function. *Eur J Clin Pharmacol* 1978; **14:** 405–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Haemaccel; ***Austral.***: Haemaccel; ***Austria***: Haemaccel†; ***Braz.***: Haemaccel; ***Chile***: Elcel†; ***Denm.***: Haemaccel; ***Ger.***: Haemaccel†; ***Gr.***: Haemaccel; ***India***: Haemaccel; ***Indon.***: Haemaccel; ***Irl.***: Haemaccel; ***Ital.***: Emagel; Gelplex; ***Mex.***: Haemaccel; Phygelin†; ***Neth.***: Haemaccel; ***Norw.***: Haemaccel; ***NZ***: Haemaccel; ***Philipp.***: Plasmax; ***Port.***: Haemaccel; ***S.Afr.***: Haemaccel; ***Singapore***: Haemaccel; ***Thai.***: Haemaccel; Plasmax†; ***UK***: Haemaccel†.

Protein C

Autoprothrombin IIA; Factor XIV; Proteína C; Протеин С.
ATC — B01AD12.
ATC Vet — QB01AD12.
UNII — 3Z6589TXPW.

Drotrecogin Alfa (Activated) *(BAN, USAN, rINN)*

Drotrecogina alfa (activada); Drotrécogine Alfa (activé); Drotrecoginum Alfa; Drotrecoginum Alfa (activatum); Drotrekogiinialfa; Drotrekogin Alfa; LY-203638; Дротрекогин Альфа (activated).
Recombinant human activated protein C (rh-APC).
CAS — 98530-76-8.
ATC — B01AD10.
ATC Vet — QB01AD10.
UNII — JGH8MYC891.

Incompatibility. In a simulated Y-site study,[1] only 6 of 34 drugs were found to be both physically and chemically compatible with drotrecogin alfa (activated); these were ceftriaxone, cisatracurium, fluconazole, glyceryl trinitrate, potassium chloride, and vasopressin. Drugs found to be incompatible were adrenaline hydrochloride, albumin, amiodarone hydrochloride, ampicillin with sulbactam, ceftazidime, ciclosporin, ciprofloxacin, clindamycin, dobutamine hydrochloride, dopamine hydrochloride, fosphenytoin, furosemide, gentamicin sulfate, heparin sodium, imipenem with cilastatin, insulin, levofloxacin, magnesium sulfate, metronidazole, midazolam hydrochloride, nitroprusside sodium, noradrenaline acid tartrate, piperacillin with tazobactam, potassium phosphate, ranitidine hydrochloride, ticarcillin with clavulanic acid, tobramycin sulfate, and vancomycin hydrochloride.

1. Mann HJ, *et al*. Physical and chemical compatibility of drotrecogin alfa (activated) with 34 drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; **61:** 2664–71. Correction. *ibid.* 2005; **62:** 1134.

Uses and Administration

Protein C is an endogenous inhibitor of blood coagulation (see Haemostasis and Fibrinolysis, p. 1124.3). A preparation of protein C purified from human plasma is used in the management of thromboembolic disorders, including coumarin-induced skin necrosis, in patients with congenital deficiency of protein C. The dose should be adjusted according to response in protein C activity; 100% activity should be targeted initially for acute therapy, then adjusted to be more than 25% for the duration of treatment. Licensed UK product information suggests an initial dose of 60 to 80 international units/kg. In the USA, an initial dose of 100 to 120 international units/kg is suggested for acute episodes and short-term prophylaxis of thromboembolism, followed by 3 doses of 60 to 80 units/kg every 6 hours, then maintenance doses of 45 to 60 units/kg every 6 or 12 hours. Doses of 45 to 60 units/kg every 12 hours are suggested for long-term prophylaxis. As a solution of 100 international units/mL it is given by intravenous injection at a maximum rate of 2 mL/minute.

For the use of protein C in children, see below.

Drotrecogin alfa (activated) is a recombinant activated protein C that has been used in the management of severe sepsis in high-risk patients with multiple organ failure. It is under investigation in the treatment of acute respiratory distress syndrome.

Administration in children. Dosage regimens of protein C used for children and neonates with protein C deficiency are the same as those used in adults (see above). However, for children weighing less than 10 kg the rate of injection should not exceed 0.2 mL/kg per minute.

Severe sepsis. Severe sepsis (sepsis associated with acute organ dysfunction; see Septicaemia, p. 203.2) involves a systemic inflammatory response, inappropriate coagulation, and impaired fibrinolysis. These contribute to the development of disseminated intravascular coagulation (DIC) and microvascular thrombosis (p. 1126.1). Endogenous protein C becomes depleted as it is activated in an attempt to restore homoeostasis. In the small number of cases that have been reported,[1-3] protein C replacement appeared to improve rate of survival and clinical outcome in the management of purpura fulminans and DIC in severe meningococcaemia. Protein C has also been used in a few patients with purpura fulminans associated with sepsis caused by other organisms such as *Streptococcus pneumoniae*.[4]

Drotrecogin alfa (activated) was studied in the management of severe sepsis and found to reduce morbidity and mortality, but with an increased risk of serious bleeding events[5-9] (see also Effects on the Blood, below). Pooled study data suggested that earlier treatment (within 24 hours of first organ dysfunction) was associated with more benefit than later treatment,[10] and subgroup analysis suggested that the benefits were greatest in those at greater risk of death.[11] A subsequent large, multicentre randomised study[12] (the ADDRESS trial) examined the effects of drotrecogin alfa (activated) in patients with severe sepsis but a low risk of death (APACHE II score less than 25, or single organ failure). The study was terminated early, as interim analysis indicated that there was no benefit from active therapy, and in the subgroup of patients with single organ failure who had undergone surgery within the last 30 days, those given the drug appeared to have a higher mortality rate than those assigned to placebo. Various regulatory bodies issued guidance restricting the use of drotrecogin alfa (activated) to high-risk patients under specialist care.[13-15] The PROWESS-SHOCK study subsequently found no survival benefit for patients with severe sepsis and septic shock, and drotrecogin alfa (activated) was voluntarily withdrawn in October 2011.[16]

Similar results to those in adults were reported in initial studies of drotrecogin alfa (activated) in children.[17,18] However, a large placebo-controlled study was stopped early when an interim analysis found that drotrecogin alfa (activated) was highly unlikely to show an improvement over placebo in the primary end-point of composite time to complete organ failure resolution over 14 days.[19] The analysis also found an increase in the rate of CNS bleeding in the drotrecogin alfa (activated) group.

1. Rintala E, *et al*. Protein C in the treatment of coagulopathy in meningococcal disease. *Lancet* 1996; **347:** 1767.
2. Smith OP, *et al*. Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. *Lancet* 1997; **350:** 1590–3.
3. Alberio L, *et al*. Protein C replacement in severe meningococcemia: rationale and clinical experience. *Clin Infect Dis* 2001; **32:** 1338–46. Correction. *ibid.*; 1803.
4. Rintala E, *et al*. Protein C substitution in sepsis-associated purpura fulminans. *Crit Care Med* 2000; **28:** 2373–8.
5. Bernard GR, *et al*. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344:** 699–709.
6. Lyseng-Williamson KA, Perry CM. Drotrecogin alfa (activated). *Drugs* 2002; **62:** 617–30.
7. Vincent J-L, *et al*. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med* 2003; **31:** 834–40.
8. Bernard GR, *et al*. Extended evaluation of recombinant human activated protein C United States Trial (ENHANCE US): a single-arm, phase 3B, multicenter study of drotrecogin alfa (activated) in severe sepsis. *Chest* 2004; **125:** 2206–16.
9. Vincent J-L, *et al*. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; **33:** 2266–77.
10. Vincent J-L, *et al*. Use of an integrated clinical trial database to evaluate the effect of timing of drotrecogin alfa (activated) treatment in severe sepsis. *Crit Care* 2006; **10:** R74.
11. Ely EW, *et al*. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003; **31:** 12–19.
12. Abraham E, *et al*. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; **353:** 1332–41.
13. NICE. Drotrecogin alfa (activated) for severe sepsis: Technology Appraisal 84 (September 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/TA084guidance.pdf (accessed 01/09/08)
14. EMEA Committee for Medicinal Products for Human Use. Press release (issued 21st April, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/12/WC500017772.pdf (accessed 16/08/10)
15. CHM/MHRA. Drotrecogin alfa (activated) (Xigris): risk-benefit in the management of sepsis. *Current Problems* 2006; **31:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023866&RevisionSelectionMethod=LatestReleased (accessed 23/05/07)
16. Lilly. Lilly announces withdrawal of Xigris following recent clinical trial results (issued 25th October, 2011). Available at: https://investor.lilly.com/releasedetail2.cfm?ReleaseID=617602 (accessed 28/10/11)
17. Barton P, *et al*. Safety, pharmacokinetics, and pharmacodynamics of drotrecogin alfa (activated) in children with severe sepsis. *Pediatrics* 2004; **113:** 7–17.
18. Goldstein B, *et al*. ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. *Pediatr Crit Care Med* 2006; **7:** 200–211.
19. Nadel S, *et al*. REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007; **369:** 836–43.

Adverse Effects and Precautions

As with other plasma-derived products, protein C preparations carry a risk of transmission of infection. Hypersensitivity reactions are possible. There have also been postmarketing reports of haemothorax, hypotension, hyperhidrosis, fever, and restlessness. Antibodies to protein C may develop in patients treated for congenital protein C deficiency.

Drotrecogin alfa (activated) may increase the risk of severe bleeding episodes. When used in patients with severe sepsis, it is therefore contra-indicated in those who are at low risk for death, such as those with single-organ failure, especially after surgery. It is also contra-indicated in patients with active internal bleeding and in those in which bleeding could be associated with a high risk of death or significant morbidity. Drotrecogin alfa (activated) should be used with caution when there is any other increased risk of bleeding. Drotrecogin alfa (activated) should be stopped 2 hours before any invasive surgery or procedure with an inherent risk of bleeding; it may be restarted 12 hours after major invasive procedures or surgery, or immediately after uncomplicated less invasive procedures, if adequate haemostasis has been achieved.

Effects on the blood. The safety data from early clinical studies and spontaneous reports during clinical use of drotrecogin alfa (activated) have been reviewed.[1] The overall rate of serious bleeding events was 5.3% during the 28-day study period. Serious bleeding events that were considered to be probably related to the use of drotrecogin alfa (activated) occurred in between 2.1% and 2.8% of patients, and often during the infusion period. Risks associated with serious bleeding events were invasive procedures and severe thrombocytopenia; meningitis may also be a risk factor for intracranial haemorrhage. It was recommended that drotrecogin alfa (activated) should not be used when the platelet count is less than 30 000/mm^3.

A subsequent large, multicentre, randomised study of drotrecogin alfa (activated) in patients with severe sepsis, but a low risk of death (the ADDRESS study), confirmed the increased incidence of bleeding in patients with single organ failure who had undergone recent surgery (within 30 days); these patients also had an increased death rate (see Severe Sepsis, above).

1. Bernard GR, *et al*. Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis. *Crit Care* 2003; **7:** 155–63.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies protein C and drotrecogin alfa (activated) as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

When oral anticoagulants such as warfarin are started in patients receiving protein C replacement therapy, a transient hypercoagulable state may occur because of the rapid suppression of vitamin K-dependent protein C activity. An initial low dose of the oral anticoagulant should be increased gradually, and protein C replacement continued, until anticoagulation is stabilised. The risk of bleeding may be increased if tissue plasminogen activator and protein C are used together.

The risk of bleeding with drotrecogin alfa (activated) may be increased if it is used with other drugs that affect haemostasis, such as thrombolytics, oral anticoagulants, antiplatelet drugs, glycoprotein IIb/IIIa-receptor antagonists, and prostacyclins. Low doses of heparin for venous thromboembolism prophylaxis may be used with drotrecogin alfa (activated) without increased risk of serious bleeding. However, in a study of patients with severe sepsis who were already receiving prophylactic heparin, the risks of death and serious adverse events were increased if heparin was stopped when drotrecogin alfa (activated) was started; the reason for this was unclear.

Pharmacokinetics

In patients with protein C deficiency, the terminal half-life of administered protein C may range from about 5 to 15

hours. The half-life may be considerably reduced in patients with acute thrombosis. Systemic exposure may also be reduced in very young children.

During continuous infusion for the management of severe sepsis, steady-state plasma concentrations of drotrecogin alfa (activated) occur in about 2 hours. It is inactivated by plasma protease inhibitors and rapidly cleared from the circulation, falling to below measurable limits within about 2 hours of stopping the infusion.

References.
1. Macias WL, *et al.* Pharmacokinetic-pharmacodynamic analysis of drotrecogin alfa (activated) in patients with severe sepsis. *Clin Pharmacol Ther* 2002; **72:** 391–402.
2. Levy H, *et al.* Obesity does not alter the pharmacokinetics of drotrecogin alfa (activated) in severe sepsis. *Ann Pharmacother* 2005; **39:** 262–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Xigris†; ***Austral.***: Xigris†; ***Austria***: Ceprotin; Xigris†; ***Belg.***: Ceprotin; Xigris†; ***Braz.***: Xigris†; ***Canad.***: Xigris†; ***Chile***: Xigris†; ***Cz.***: Ceprotin; Xigris†; ***Denm.***: Xigris†; ***Fin.***: Ceprotin; Xigris†; ***Fr.***: Protexel; Xigris†; ***Ger.***: Ceprotin; Xigris†; ***Gr.***: Ceprotin; Xigris; ***Hong Kong***: Xigris†; ***Hung.***: Xigris†; ***India***: Xigris†; ***Irl.***: Ceprotin; Xigris†; ***Israel***: Xigris†; ***Ital.***: Ceprotin; Xigris†; ***Jpn***: Anact C; ***Malaysia***: Xigris†; ***Mex.***: Xigris†; ***Neth.***: Ceprotin; Xigris†; ***Norw.***: Ceprotin†; Xigris†; ***NZ***: Xigris†; ***Pol.***: Ceprotin; Xigris†; ***Port.***: Ceprotin; Xigris†; ***Rus.***: Ceprotin (Сепротин); Xigris (Зигрис)†; ***S.Afr.***: Xigris†; ***Singapore***: Xigris†; ***Spain***: Ceprotin; Xigris†; ***Swed.***: Ceprotin; Xigris†; ***Switz.***: Ceprotin; Xigris†; ***Turk.***: Xigris†; ***UK***: Ceprotin; Xigris†; ***USA***: Ceprotin; Xigris†; ***Venez.***: Xigris†.

Red Blood Cells ⊗

Eritrociták; Eritrociti; Eritrócitos; Eritrocitos; Erythrocytes; Érythrocytes; Erythrocyti; Erythrozyten; Erytrocyten; Erytrocyter; Erytrocytów; Erytrocytter; Globules Rouges; Globuli Rossi; Glóbulos rojos; Glóbulos Vermelhos; Røde Blodceller; Röda Blodkroppar; Rode Bloedcel; Roten Blutkörperchen; Vörösvértestek; Эритроциты.

ATC — B05AX01.
UNII — 2K524Y8G0J.

Uses and Administration

Transfusions of red blood cells are given for the treatment of severe anaemia without hypovolaemia (p. 1121.2).

Red blood cells are also used for exchange transfusion in babies with haemolytic disease of the newborn (p. 2377.2). Red cells may be used with volume expanders for acute blood loss of less than half of the blood volume; if more than half of the blood volume has been lost, whole blood should be used.

Other red blood cell products are available. Concentrated red cells in an optimal additive solution containing sodium chloride, adenine, glucose, and mannitol has reduced viscosity and an extended shelf-life. Leucocyte-depleted red cells may be used in patients who have developed antibodies to previous transfusions or in whom development of antibodies is undesirable. Frozen, thawed, and washed red cell concentrates in which plasma proteins are removed in addition to leucocytes and platelets may be used in patients with rare antibodies.

Reviews and guidelines.

1. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; **8:** 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)
2. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; **113:** 24–31. Also available at: http://www.bcshguidelines.com/pdf/bjh2701.pdf (accessed 27/10/05)
3. Hill SR, *et al.* Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 16/06/05).
4. Klein HG, *et al.* Red blood cell transfusion in clinical practice. *Lancet* 2007; **370:** 415–26.
5. Morley SL. Red blood cell transfusions in acute paediatrics. *Arch Dis Child Educ Pract Ed* 2009; **94:** 65–73.
6. Murphy M, Wallis J. Red cell transfusion. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 15–21.

Adverse Effects and Precautions

As for Blood, p. 1135.3.

Antibody formation. Patients with sickle-cell anaemia frequently require repeated transfusions of red blood cells. Alloimmunisation is a common problem in these patients, and has the potential to cause haemolytic transfusion reactions.[1] Alloantibodies were detected in 32 of 107 black patients with sickle-cell anaemia who had received red cell transfusions compared with 1 of 19 non-black patients who had received transfusions for other chronic anaemias.[2] The incidence of antibody formation was related to the number of transfusions received. An analysis of the red cell phenotypes suggested that the high rate of alloimmunisation among patients with sickle-cell anaemia could be due to racial differences between donors and recipients. Alloimmunisation can also occur in thalassaemia patients who are given transfusions,[3] and the incidence in these patients may also be affected by racial differences between donors and recipients.[4] Erythrocyte autoantibody formation has also been reported.[1,3]

1. Aygun B, *et al.* Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion* 2002; **42:** 37–43.
2. Vichinsky EP, *et al.* Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *N Engl J Med* 1990; **322:** 1617–21.
3. Singer ST, *et al.* Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. *Blood* 2000; **96:** 3369–73.
4. Ho H-K, *et al.* Alloimmunization in Hong Kong southern Chinese transfusion-dependent thalassemia patients. *Blood* 2001; **97:** 3999--4000.

Romiplostim *(BAN, USAN, rINN)*

AMG-531; Romiplostimum; Ромиплостим.

L-Methionyl[human immunoglobulin heavy constant gamma 1-(227 *C*-terminal residues)-peptide (Fc fragment)] fusion protein with 41 amino acids peptide, (7-7′:10,10′)-bisdisulfide dimer.

CAS — 267639-76-9.
ATC — B02BX04.
ATC Vet — QB02BX04.
UNII — GN5XU2DXKV.

Uses and Administration

Romiplostim is an Fc-peptide fusion protein that acts as an agonist at the thrombopoietin receptor to stimulate platelet production; it has no amino acid sequence homology with endogenous thrombopoietin. Romiplostim is used to treat thrombocytopenia in patients with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura; p. 1606.1). It should only be used when the response to treatment with corticosteroids, immunoglobulins, or splenectomy has been insufficient, and the patient is at increased risk of bleeding. Romiplostim should not be used in an attempt to normalise platelet counts. The safety and efficacy of romiplostim have not been established for patients younger than 18 years old, but see below for some references to use in children.

The initial dose of romiplostim is 1 microgram/kg given by subcutaneous injection. This is repeated once weekly, and adjusted by increments of 1 microgram/kg to raise the platelet count to at least 50×10^9 cells/litre as necessary to reduce the risk of bleeding. The weekly dose should not exceed 10 micrograms/kg. All doses should be calculated using the patient's actual body-weight at the start of treatment.

- UK licensed product information recommends that the dose should be reduced by 1 microgram/kg if the count is higher than 150×10^9 cells/litre for 2 consecutive weeks (US information suggests a threshold of 200×10^9 cells/litre).
- Romiplostim should be withheld and platelet counts measured weekly if the count is higher than 250×10^9 cells/litre (US threshold 400×10^9 cells/litre); treatment may be restarted at a dose reduced by 1 microgram/kg when the count has fallen below 150×10^9 cells/litre (200×10^9 cells/litre in the USA).
- Romiplostim should be stopped if the platelet count is not raised sufficiently to avoid clinically important bleeding after 4 weeks of treatment at the maximum weekly dose of 10 micrograms/kg.

Complete blood counts, including platelet counts and peripheral blood smears, should be assessed weekly during dosage adjustment, and monthly during stable romiplostim therapy. Complete blood counts, including platelet counts, should be monitored weekly for at least 2 weeks after stopping romiplostim (see also below).

References.
1. Bussel JB, *et al.* AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006; **355:** 1672–81. Correction. *ibid.*; 2054.
2. Kuter DJ, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; **371:** 395–403.
3. Frampton JE, Lyseng-Williamson KA. Romiplostim. *Drugs* 2009; **69:** 307–17.
4. Bussel JB, *et al.* Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood* 2009; **113:** 2161–71. Correction. *ibid.*; 4822.
5. Ipema HJ, *et al.* Romiplostim management of immune thrombocytopenic purpura. *Ann Pharmacother* 2009; **43:** 914–19.
6. Kuter DJ, *et al.* Romiplostim or standard of care in patients with immune thrombocytopenia. *N Engl J Med* 2010; **363:** 1889–99.
7. NICE. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (issued April 2011). Available at: http://www.nice.org.uk/nicemedia/live/13467/54219/54219.pdf (accessed 19/10/11)
8. Zeng Y, *et al.* TPO receptor agonist for chronic idiopathic thrombocytopenic purpura. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2011 (accessed 19/10/11).

Administration in children. Romiplostim has been studied in the treatment of thrombocytopenia in children with chronic immune thrombocytopenia, using similar dosage regimens to those used in adults (see Uses and Administration, above).[1,2]

1. Elalfy MS, *et al.* Romiplostim in children with chronic refractory ITP: randomized placebo controlled study. *Ann Hematol* 2011; **90:** 1341–4.
2. Bussel JB, *et al.* A randomized, double-blind study of romiplostim to determine its safety and efficacy in children with immune thrombocytopenia. *Blood* 2011; **118:** 28–36.

Adverse Effects and Precautions

Adverse effects of romiplostim include headache, arthralgia, myalgia, pain in the extremities, abdomen, back, or shoulder, dizziness, insomnia, gastrointestinal disturbances, and paraesthesia. Skin reactions have included pruritus, ecchymosis, and rash, as well as injection-site reactions and haemorrhage.

Excessive increases in platelet counts may lead to thrombosis or thromboembolism. Cases of thromboembolism, including portal vein thrombosis, have been reported in patients with chronic liver disease, and romiplostim should only be used in patients with moderate to severe hepatic impairment (Child-Pugh score of 7 or more) when the expected benefit outweighs this risk.

Romiplostim increases the risk for the development or progression of reticulin fibre deposition in the bone marrow, and a risk of bone marrow fibrosis with cytopenias has not been excluded. The level of cellular morphological abnormalities should be established before starting romiplostim and monitored monthly during stable therapy. Romiplostim should be stopped if new or worsening abnormalities or cytopenias develop.

Romiplostim should not be used to treat thrombocytopenia due to myelodysplastic syndrome because of the risks of transient increases in peripheral blast cell counts and progression to acute myeloid leukaemia, which have been reported in studies of romiplostim.

When romiplostim is stopped, thrombocytopenia may become worse than before treatment was started. As this may increase the risk of bleeding, complete blood counts (including platelet counts) should be monitored weekly for at least 2 weeks after romiplostim is stopped.

Neutralising antibodies may reduce the efficacy of romiplostim.

Effects on the peripheral circulation. Erythromelalgia of the hands and feet occurred within 48 hours after an initial dose of romiplostim in a 59-year-old man.[1] The condition recurred after each weekly dose, and subsided within a few days.

1. Kluger N, *et al.* Romiplostim-induced erythromelalgia in a patient with idiopathic thrombocytopenic purpura. *Br J Dermatol* 2009; **161:** 482–4.

Pharmacokinetics

During weekly subcutaneous treatment, peak serum-romiplostim concentrations occur about 7 to 50 hours after a dose (median 14 hours), and the half-life has ranged from 1 to 34 days (median 3.5 days). Serum concentration varies and is, in part, dependent on binding to the thrombopoietin receptor on platelets, such that higher platelet counts are associated with lower serum concentrations of romiplostim, and vice versa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nplate; ***Austria***: Nplate; ***Belg.***: Nplate; ***Canad.***: Nplate; ***Cz.***: Nplate; ***Denm.***: Nplate; ***Fr.***: Nplate; ***Ger.***: Nplate; ***Gr.***: Nplate; ***Hung.***: Nplate; ***Irl.***: Nplate; ***Israel***: Nplate; ***Jpn***: Romiplate; ***Neth.***: Nplate; ***Norw.***: Nplate; ***Pol.***: Nplate; ***Port.***: Nplate; ***Spain***: Nplate; ***Swed.***: Nplate; ***UK***: Nplate; ***USA***: Nplate.

Sargramostim *(BAN, USAN, rINN)*

BI-61.012; rhu GM-CSF; Sargramostimum; Сарграмостим.

A recombinant human granulocyte-macrophage colony-stimulating factor; 23-L-Leucinecolony-stimulating factor 2 (human clone pHG_{25} protein moiety).

CAS — 123774-72-1.
ATC — L03AA09.
ATC Vet — QL03AA09.
UNII — 5TAA004E22.

Pharmacopoeias. In *US.*

USP 36: (Sargramostim). A single chain, glycosylated polypeptide of 127 amino acid residues expressed from *Saccharomyces cerevisiae.* The glycoprotein mainly consists of 3 molecular species having relative molecular weights of about 19 500, 16 800, and 15 500 due to different levels of glycosylation. Sargramostim has the property of generating granulocyte, macrophage, and mixed granulocyte macrophage colonies from haematopoietic progenitor cells found

in bone marrow. Store in sealed containers at a temperature of -20 degrees or below.

Stability. Solutions of sargramostim may be adsorbed onto glass or plastic materials and so albumin must be added to give a final concentration of 1 mg/mL to solutions that are diluted to concentrations of sargramostim below 10 micrograms/mL.

Uses and Administration

Sargramostim is a granulocyte-macrophage colony-stimulating factor with actions and uses similar to those of molgramostim (p. 1156.2). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p. 731.1). It is also used after bone marrow transplantation when engraftment is delayed or has failed. Sargramostim may be used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous peripheral blood stem cell transplantation, as well as after transplantation to improve engraftment.

As an **adjunct to antineoplastic therapy**, sargramostim is given by intravenous infusion over 4 hours in a dose of 250 micrograms/m^2 daily for up to 42 days as required.

After **bone marrow transplantation**, sargramostim may be given in a dose of 250 micrograms/m^2 daily by intravenous infusion over 2 hours. When engraftment is delayed or has failed, a course of sargramostim 250 micrograms/m^2 daily for 14 days may be used. The dose can be repeated after a 7-day interval if engraftment has not occurred. A third course of 500 micrograms/m^2 daily for 14 days may be tried after another 7-day interval if needed, but further dose escalation is unlikely to be of benefit.

For **mobilisation** of peripheral blood progenitor cells a dose of 250 micrograms/m^2 daily is given by continuous intravenous infusion over 24 hours or by subcutaneous injection, with leucapheresis usually starting on day 5. The same dosing regimen may be used after peripheral blood stem cell transplantation, until neutrophil recovery.

HIV infection and AIDS. Sargramostim has been evaluated in the management of HIV infection (p. 957.2). There is some evidence to suggest that it might help to decrease and suppress viral load, and increase CD4+ cell counts, by enhancing the activity of antiretroviral drugs and increasing the resistance of monocytes to HIV infection.[1-3] However, in a study[4] of patients who were medically stable but had incompletely controlled HIV replication, sargramostim did not have a significant antiviral effect and there was only a trend towards increased CD4+ counts. A small study[5] found that molgramostim blunted viral rebound after interruption of HAART.

1. Skowron G, *et al*. The safety and efficacy of granulocyte-macrophage colony-stimulating factor (sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. *J Infect Dis* 1999; **180:** 1064–71.
2. Brites C, *et al*. A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and nucleoside analogue therapy in AIDS. *J Infect Dis* 2000; **182:** 1531–5.
3. Angel JB, *et al*. Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. *AIDS* 2000; **14:** 387–95.
4. Jacobson JM, *et al*. Granulocyte-macrophage colony-stimulating factor induces modest increases in plasma human immunodeficiency virus (HIV) type 1 RNA levels and CD4+ lymphocyte counts in patients with uncontrolled HIV infection. *J Infect Dis* 2003; **188:** 1804–14.
5. Fagard C, *et al*. A controlled trial of granulocyte macrophage-colony stimulating factor during interruption of HAART. *AIDS* 2003; **17:** 1487–92.

Inflammatory bowel disease. A small dose-escalating study[1] reported a beneficial effect from the use of sargramostim in Crohn's disease (see Inflammatory Bowel Disease, p. 1811.3). A subsequent larger placebo-controlled study[2] in moderate to severe active disease found that the rate of response to sargramostim was not significantly different from that of placebo. Although disease severity and quality of life improved in the sargramostim group, later unpublished study results were said to be disappointing, and in June 2007 the manufacturer declared that it would not be investigating sargramostim any further in Crohn's disease.

1. Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; **360:** 1478–80.
2. Korzenik JR, *et al*. Sargramostim for active Crohn's disease. *N Engl J Med* 2005; **352:** 2193–2201.

Malignant neoplasms. It has been suggested that granulocyte-macrophage colony-stimulating factor may be able to increase antitumour immune activity. Sargramostim, given by nebuliser to stimulate a local response, has been investigated in patients with lung metastases.[1,2]

1. Anderson PM, *et al*. Aerosol granulocyte macrophage-colony stimulating factor: a low toxicity, lung-specific biological therapy in patients with lung metastases. *Clin Cancer Res* 1999; **5:** 2316–23.
2. Rao RD, *et al*. Aerosolized granulocyte macrophage colony-stimulating factor (GM-CSF) therapy in metastatic cancer. *Am J Clin Oncol* 2003; **26:** 493–8.

Respiratory disorders. See under Molgramostim (p. 1156.3) for mention of the use of sargramostim in pulmonary alveolar proteinosis.

Wounds and ulcers. See under Molgramostim (p. 1156.3) for mention of the use of sargramostim in the promotion of wound healing.

Adverse Effects and Precautions

As for Molgramostim, p. 1156.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Leukine.

Pharmacopoeial Preparations
USP 36: Sargramostim for Injection.

Thrombin *(rINN)*

Factor IIa; Thrombine; Thrombinum; Trombin; Trombina; Тромбин.
CAS — 9002-04-4.
ATC — B02BC06; B02BD30.
ATC Vet — QB02BC06; QB02BD30.
UNII — 25ADE2236L.

Thrombin Alfa *(USAN, rINN)*

Human thrombin (recombinant, glycosylated); Thrombine Alfa; Thrombinum Alfa; Trombina alfa; Тромбин Альфа.
Human thrombin (recombinant, glycofrom α).
CAS — 869858-13-9.
UNII — SCK81AMR7R.

Uses and Administration

Thrombin is a protein substance produced *in vivo* from prothrombin that converts soluble fibrinogen into insoluble fibrin thus producing coagulation.

Thrombin of either human or bovine origin is applied topically to control bleeding from capillaries and small venules. It is applied directly to the bleeding surface either as a solution or dry powder. It may also be used with absorbable gelatin sponge during surgical procedures. Thrombin alfa, a recombinant human thrombin, is used similarly.

Thrombin is a component of fibrin glue (p. 1151.2).

General references. Reviews.
1. Lundblad RL, *et al*. A review of the therapeutic uses of thrombin. *Thromb Haemost* 2004; **91:** 851–60.

Pseudoaneurysm. An acute pseudoaneurysm is an arterial rupture, contained by fibromuscular tissue, that communicates with the artery via a narrow neck. Insertion-site femoral pseudoaneurysm can occur as a result of procedures such as cardiac catheterisation and peripheral angiography. It is usually treated with ultrasound-guided compression, but this time-consuming technique causes discomfort for both the patient and the staff carrying out the procedure, and may be of limited success for large pseudoaneurysms and patients receiving anticoagulation. Surgical repair may be required in some patients. As an alternative to pressure or surgery, thrombin has been given by ultrasound-guided percutaneous injection. In reported series,[1-4] complete thrombosis of the pseudoaneurysm sac occurred in more than 90% of patients with one injection of bovine thrombin. Bovine thrombin has also been used when compression has failed,[4,5] and a comparative study[6] in 30 patients found thrombin to be more successful than compression. Human thrombin has also been used successfully.[7] A retrospective review[8] concluded that bovine and human thrombin were equally effective. The successful use of autologous thrombin in a few patients has also been described.[9]

1. La Perna L, *et al*. Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. *Circulation* 2000; **102:** 2391–5.
2. Mohler ER, *et al*. Therapeutic thrombin injection of pseudoaneurysms: a multicenter experience. *Vasc Med* 2001; **6:** 241–4.
3. Olsen DM, *et al*. A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 2002; **36:** 779–82.
4. Stone P, *et al*. Iatrogenic pseudoaneurysms: comparison of treatment modalities, including duplex-guided thrombin injection. *W V Med J* 2003; **99:** 230–2.
5. Lönn L, *et al*. Treatment of femoral pseudoaneurysms: percutaneous US-guided thrombin injection versus US-guided compression. *Acta Radiol* 2002; **43:** 396–400.
6. Lönn L, *et al*. Prospective randomized study comparing ultrasound-guided thrombin injection to compression in the treatment of femoral pseudoaneurysms. *J Endovasc Ther* 2004; **11:** 570–6.
7. Maleux G, *et al*. Percutaneous injection of human thrombin to treat iatrogenic femoral pseudoaneurysms: short- and midterm ultrasound follow-up. *Eur Radiol* 2003; **13:** 209–12.
8. Vázquez V, *et al*. Human thrombin for treatment of pseudoaneurysms: comparison of bovine and human thrombin sonogram-guided injection. *Am J Roentg* 2005; **184:** 1665–71.
9. Quarmby JW, *et al*. Autologous thrombin for treatment of pseudoaneurysms. *Lancet* 2002; **359:** 946–7.

Adverse Effects and Precautions

Hypersensitivity reactions, including anaphylaxis, have occurred rarely. Thrombin solutions must not be injected into blood vessels.

Antibody formation. Exposure to thrombin preparations of bovine origin has led to the development of antibodies to bovine thrombin and factor V with cross-reactivity, in some cases, to human factors. The presence of inhibitors to human factors may produce bleeding abnormalities and interfere with clotting measurements. Platelet infusions, fresh frozen plasma, and activated prothrombin complex concentrates have been used in the management of acute haemorrhagic complications, though often with limited success. Treatments that have been tried, in order to reduce the antibody titre, have included corticosteroids, ciclosporin, antineoplastics, intravenous immunoglobulin, and plasmapheresis.[1,2] Despite the availability of preparations containing virus-inactivated human fibrinogen the use of bovine thrombin is reported to be widespread and cases of acquired factor V inhibitor continue to occur.[3]

1. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. *J Lab Clin Med* 1999; **133:** 326–34.
2. Streiff MB, Ness PM. Acquired FV inhibitors: a needless iatrogenic complication of bovine thrombin exposure. *Transfusion* 2002; **42:** 18–26.
3. Kirkeby KM, Aronowitz P. Acquired factor V inhibitor: a common and avoidable complication of topical bovine thrombin application. *Am J Med* 2005; **118:** 805.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Recothrom; ***China***: Kang Li Ning (康立宁); ShuPing LaiShi (舒平莱士); Siduopu (斯多普); ***NZ***: Thrombostat†; ***Pol.***: BioTrombina; Gastrotrombina; ***S.Afr.***: Tisseel†; ***Singapore***: Thrombostat; ***USA***: Evithrom; Recothrom; Thrombi-Gel; Thrombi-Pad; Thrombinar; Thrombostat.

Multi-ingredient Preparations. ***Arg.***: Beriplast P; Tissucol; ***Austral.***: Tisseel Duo†; ***Austria***: Beriplast; Evicel; TachoSil; Tisseel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Artiss; Quixil†; TachoSil; Tissucol Duo; Tissucol Kit; ***Braz.***: Beriplast P; TachoSil; ***Canad.***: Artiss; Tisseel; ***Chile***: Beriplast P†; ***China***: FibinGluRAAS (护固莱士); ***Cz.***: Artiss; Evicel; TachoSil; Tisseel; Tissucol; ***Denm.***: Artiss; Evicel; Quixil; TachoSil; Tisseel Duo Quick; ***Fin.***: Artiss; Quixil; TachoSil; Tisseel Duo Quick; Tisseel; ***Fr.***: Artiss; Beriplast; Evicel; Quixil†; TachoSil; Tissucol; ***Ger.***: Artiss; Beriplast; Evicel; Quixil†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Beriplast; Evicel; TachoSil; Tisseel; ***Hong Kong***: Beriplast P; TachoComb; Tisseel; ***Hung.***: Beriplast P; TachoSil; Tissucol-Kit; ***Indon.***: Beriplast; ***Irl.***: Artiss; Evicel; TachoSil; Tisseel; ***Israel***: Beriplast†; Evicel; Quixil†; TachoSil; Thrombixil; Tisseel†; ***Ital.***: Beriplast; Quixil; TachoSil; Tissucol; ***Jpn***: Bolheal; TachoSil; ***Mex.***: Beriplast P; ***Neth.***: Artiss; Beriplast P; Quixil†; TachoSil; Tisseel; Tissucol Duo; Tissucol; ***Norw.***: Artiss; Evicel; TachoSil; Tisseel; ***NZ***: Tisseel Duo; ***Pol.***: Beriplast; Evicel; TachoSil; ***Port.***: Evicel; Quixil†; TachoSil; Tissucol Duo†; ***Rus.***: TachoComb (ТахоКомб); Tissucol Kit (Тиссукол Кит); ***Singapore***: TachoComb; ***Spain***: Artiss; Beriplast P Combi; Evicel; TachoSil; Tissucol Duo; ***Swed.***: Artiss; Evicel; Quixil†; TachoSil; Tisseel Duo Quick; ***Switz.***: Artiss; Beriplast P; Evicel; Quixil; TachoSil; Tisseel; Tissucol Duo S†; Tissucol†; ***Thai.***: Fibingluraas; Tisseel; ***Turk.***: Beriplast P; Tisseel VH; ***UK***: TachoSil; Tisseel; ***Ukr.***: TachoComb (Тахокомб); ***USA***: Artiss; Evarrest; Evicel; TachoSil; Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit.

Thrombomodulin Alfa *(rINN)*

ART-123; Thrombomoduline Alfa; Thrombomodulinum Alfa; Trombomodulina alfa; Тромбомодулин Альфа.
1–498-Thrombomodulin (human clone TMP26/TMJ1 protein moiety reduced).
CAS — 120313-91-9.

NOTE. The name Recomodulin has been used as a trade mark for thrombomodulin alfa.

Profile

Endogenous thrombomodulin is a transmembrane protein found on the surface of endothelial cells, which acts as a thrombin receptor. Thrombomodulin-bound thrombin activates protein C, which then inactivates clotting factors and so limits coagulation.

Thrombomodulin alfa, a recombinant form of thrombomodulin, is under investigation in the prophylaxis of venous thromboembolism and is used in the treatment of disseminated intravascular coagulation.

References.
1. Kearon C, *et al.* Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2005; **3:** 962–8.
2. Saito H, *et al.* Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 2007; **5:** 31–41.
3. Ogawa E, *et al.* Successful treatment of disseminated intravascular coagulation in a child with acute myelogenous leukaemia using recombinant thrombomodulin. *Br J Haematol* 2010; **149:** 911–12.

Thromboplastin

Citozima; Cytozyme; Thrombokinase; Trombocinasa; Tromboplastina; Tromboplastyna; Tromboquinasa; Тромбопластин.

UNII — 1U5PI2DLU1.

Profile

Tissue thromboplastin (tissue factor; factor III) is a membrane glycoprotein that is released from damaged tissue and initiates coagulation. The term thromboplastin may also be applied to other related substances with similar activity. Commercial preparations may contain tissue extracts comprising a variety of such substances.

Preparations of thromboplastin have been used as haemostatics.

A preparation of thromboplastin derived from rabbit brain is used in the determination of the prothrombin time for the control of anticoagulant therapy (for further details see Uses and Administration of Warfarin Sodium, p. 1527.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Clauden.

Multi-ingredient Preparations. ***Braz.***: Claudemor.

Thrombopoietin

Trombopoietina; Trombopoyetina; Тромбопоэтин.

Profile

Thrombopoietin is a naturally occurring colony-stimulating factor that regulates thrombopoiesis (see Haematopoiesis, p. 1121.1). Recombinant thrombopoietin, and a form of recombinant thrombopoietin conjugated with polyethylene glycol (pegacaristim, PEG-megakaryocyte growth and development factor, PEG-rHuMGDF), are under investigation. They have been studied in the management of thrombocytopenia (p. 1129.2) in patients receiving myelosuppressive or myeloablative chemotherapy, and in patients with myelodysplastic syndrome or HIV-associated thrombocytopenia. There is also some interest in the use of recombinant forms of thrombopoietin in stem cell mobilisation regimens and to increase platelet counts in healthy apheresis donors. However, some results have been disappointing and there are reports of neutralising antibody development.

General references. Studies and reviews.

1. Vadhan-Raj S, *et al.* Safety and efficacy of transfusions of autologous cryopreserved platelets derived from recombinant human thrombopoietin to support chemotherapy-associated severe thrombocytopenia: a randomised cross-over study. *Lancet* 2002; **359:** 2145–52.
2. Nomura S, *et al.* Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. *Blood* 2002; **100:** 728–30.
3. Schuster MW, *et al.* The effects of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet recovery in breast cancer patients undergoing autologous bone marrow transplantation. *Exp Hematol* 2002; **30:** 1044–50.
4. Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. *Blood* 2002; **100:** 3457–69.
5. Linker C, *et al.* Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplantation. *Biol Blood Marrow Transplant* 2003; **9:** 405–13.
6. Vadhan-Raj S, *et al.* Importance of predosing of recombinant human thrombopoietin to reduce chemotherapy-induced early thrombocytopenia. *J Clin Oncol* 2003; **21:** 3158–67.
7. Geissler K, *et al.* Prior and concurrent administration of recombinant human megakaryocyte growth and development factor in patients receiving consolidation chemotherapy for de novo acute myeloid leukemia—a randomized, placebo-controlled, double-blind safety and efficacy study. *Ann Hematol* 2003; **82:** 677–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Te Bi Ao (特比澳); ***Philipp.***: Tpiao.

Tranexamic Acid *(BAN, USAN, rINN)*

Acide Tranexamique; Ácido tranexámico; Acidum Tranexamicum; AMCA; *trans*-AMCHA; CL-65336; Kyselina tranexamová; Traneksaamihappo; Traneksamik Asit; Traneksamo rūgštis; Tranexámico, ácido; Tranexamsäure; Tranexámsav; Tranexamsyra; Транексамовая Кислота.

trans-4-(Aminomethyl)cyclohexanecarboxylic acid.

$C_8H_{15}NO_2$=157.2

CAS — 1197-18-8.

ATC — B02AA02.

ATC Vet — QB02AA02.

UNII — 6T84R30KC1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tranexamic Acid). A white or almost white, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 7.0 to 8.0.

USP 36: (Tranexamic Acid). White, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. Store in airtight containers at a temperature not exceeding 30 degrees.

Incompatibility. Solutions of tranexamic acid are incompatible with benzylpenicillin, and should not be added to blood for transfusion.

Uses and Administration

Tranexamic acid is an antifibrinolytic drug that inhibits breakdown of fibrin clots. It acts mainly by blocking the binding of plasminogen and plasmin to fibrin; direct inhibition of plasmin occurs only to a limited degree. Tranexamic acid is used in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It is also used in the prophylaxis of hereditary angioedema.

Tranexamic acid is given orally and by slow intravenous injection or continuous infusion. Parenteral dosage is usually changed to oral after a few days. Alternatively, an initial intravenous injection may be followed by continuous infusion.

For short-term use in localised **haemorrhage** (below), usual oral doses are 1 to 1.5 g (or 15 to 25 mg/kg) 2 or 3 times daily. For slow intravenous injection, doses of 0.5 to 1 g are given 3 times daily (or 10 mg/kg is given 3 or 4 times daily). An administration rate of 100 mg/min should be used. Tranexamic acid is given by continuous infusion at a rate of 25 to 50 mg/kg daily.

When used in menorrhagia (p. 1165.1), a maximum dose of 4 g daily is given orally for up to 5 days during menstruation.

Tranexamic acid may also be given by slow intravenous injection in some cases of generalised bleeding. A dose of 10 mg/kg has been used for neutralisation of thrombolytic therapy. In disseminated intravascular coagulation, a single dose of 1 g may be sufficient to control bleeding (but see Precautions, p. 1165.2, regarding the safe use of tranexamic acid in this condition).

Tranexamic acid is used for prolonged periods in **hereditary angioedema** (p. 1165.1) in doses of 1 to 1.5 g given orally 2 or 3 times daily. It may be given intermittently or continuously, and the dose may be reduced to 500 mg once or twice daily as the attacks diminish. When used for short-term prophylaxis to prevent attacks related to surgery or dental work, a dose of 1 g may be given 4 times daily, for 48 hours before and after the procedure.

For doses used in children, see below.

Reduced doses are recommended for patients with renal impairment (see below).

Solutions of tranexamic acid have been applied topically, for example as a bladder irrigation or mouthwash.

Administration in children. Children may be given tranexamic acid in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. Usual doses of 15 to 25 mg/kg orally to a maximum of 1.5 g, or 10 mg/kg intravenously to a maximum of 1 g, are given 2 or 3 times daily. The *BNFC* also suggests that a dose of 45 mg/kg may be given by continuous intravenous infusion over 24 hours.

Similar doses have been used in the prophylaxis of hereditary angioedema. A consensus document[1] has recommended, as a general guide, an oral dose of 50 mg/kg daily (or 1 to 2 g daily) for long-term prophylaxis, but advised that the lowest effective maintenance dose should be used, and that alternate-day or twice-weekly regimens should be considered. For short-term prophylaxis, it suggested a dose of 500 mg given 4 times daily for 48 hours before and after surgery or dental procedures. A review[2] of paediatric treatment suggested an oral regimen of 20 to 40 mg/kg daily, to a maximum of 3 g, given in 2 or 3 divided doses, for long-term prophylaxis. This dose was also suggested for short-term prophylaxis before surgery, starting 5 days before the procedure and continuing for 2 days after. Prophylaxis for 2 or 3 days could be considered during infections, or when other precipitating factors are present.

1. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]
2. Farkas H, *et al.* Management of hereditary angioedema in pediatric patients. Abstract: *Pediatrics* 2007; **120:** 635. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/3/e713 (accessed 21/12/09)

Administration in renal impairment. Licensed product information recommends reduced doses of tranexamic acid for patients with renal impairment, based on the serum-creatinine concentration (SCC):

- SCC 120 to 250 micromoles/litre: 15 mg/kg twice daily orally, or 10 mg/kg twice daily intravenously
- SCC 250 to 500 micromoles/litre: 15 mg/kg once daily orally, or 10 mg/kg once daily intravenously
- SCC higher than 500 micromoles/litre: 7.5 mg/kg once daily or 15 mg/kg once every 48 hours orally, or 5 mg/kg once daily or 10 mg/kg once every 48 hours intravenously (some products contra-indicate use in severe renal impairment)

Haemorrhagic disorders. Tranexamic acid and aminocaproic acid are structurally related synthetic antifibrinolytic drugs that block the binding of plasminogen and plasmin to fibrin, thereby preventing dissolution of the haemostatic plug.[1,2] A plasma concentration of tranexamic acid of 5 to 10 micrograms/mL has been considered necessary for effective inhibition of fibrinolysis.[2]

Antifibrinolytics are used to control haemorrhage that is considered to be caused by excessive fibrinolysis. Antifibrinolytic therapy may also be indicated in the prevention of rebleeding in some haemorrhagic conditions, the rationale being to retard dissolution of the haemostatic plug formed in response to vascular injury.

In haemorrhage caused by a congenital or acquired deficiency of blood coagulation factors, haemostatic drugs have a secondary role and may be useful in reducing requirements of factor concentrates. In patients with haemophilias (p. 1126.3) antifibrinolytics may be added to coagulation factor replacement before dental surgery, and used in the prevention and treatment of mucosal bleeding after the procedure. The route depends on the severity of the coagulation factor deficiency and the procedure to be undertaken; for example, tooth extraction will probably require more prophylactic cover than dental scaling. Regimens therefore vary,[3-7] but an initial oral or intravenous dose of tranexamic acid may be followed by oral use, or topical 5% mouthwash continued for up to 7 days after dental procedures. Tranexamic acid has been used similarly in patients with von Willebrand's disease[4] (p. 1129.3). An approach using tranexamic acid mouthwashes has also been used to reduce the risk of bleeding after oral surgery in patients on anticoagulant therapy.[8,9] Tranexamic acid may prove beneficial in patients with other congenital bleeding disorders such as α_2-antiplasmin deficiency.[10] Aminocaproic acid has been tried in a few patients with hereditary haemorrhagic telangiectasia with mixed results.[11] Tranexamic acid has been reported to be effective in the control of epistaxis in these patients; reports generally describe oral use,[12,13] but tranexamic acid has also been applied directly as nasal drops.[14]

Tranexamic acid or aminocaproic acid have been suggested to control bleeding in many other conditions. These include haemorrhage after surgical or other procedures including prostatectomy, bladder surgery, and cervical conisation. They may be used to reduce perioperative blood loss and allogeneic transfusion requirements.[15-19] They may also be effective in other conditions associated with excessive fibrinolysis such as menorrhagia (see p. 1165.1), epistaxis, and placental abruption. Tranexamic acid has also been found to reduce the risk of death in bleeding trauma patients, when given within 8 hours of injury.[20]

Tranexamic acid and aminocaproic acid have each been used in an attempt to prevent rebleeding in patients with subarachnoid haemorrhage (see Stroke, p. 1269.2), particularly if surgery is to be delayed. However, while rebleeding may be reduced, there can be an increase in the incidence of cerebral ischaemic complications resulting in little overall improvement in outcome.[21] Paradoxically, rebleeding has been noted in patients given high doses of aminocaproic acid after subarachnoid haemorrhage (see Effects on the Blood under Aminocaproic Acid, p. 1132.1).

Tranexamic acid has been used to control gastrointestinal haemorrhage, e.g. due to peptic ulcer disease (p. 1816.2) or oesophageal varices (see Variceal Haemorrhage under Monoethanolamine, p. 2563.1). In a meta-analysis[22] of 7 studies in patients with upper gastrointestinal haemorrhage, mortality was lower in those treated with tranexamic acid compared with placebo. However, there were no significant

differences in bleeding-related death, rebleeding or continued bleeding, surgery, or transfusion requirements. The management of upper gastrointestinal haemorrhage has changed significantly since some of the studies were undertaken, and tranexamic acid is not recommended for routine use in these patients.

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3. Zanon E, *et al*. Proposal of a standard approach to dental extraction in haemophilia patients: a case-control study with good results. *Haemophilia* 2000; **6:** 533–6.
4. Stubbs M, Lloyd J. A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B. *Aust Dent J* 2001; **46:** 37–40.
5. Villar A, *et al*. The use of haemostatic drugs in haemophilia: desmopressin and antifibrinolytic agents. *Haemophilia* 2002; **8:** 189–93.
6. Lee APH, *et al*. Effectiveness in controlling haemorrhage after dental scaling in people with haemophilia by using tranexamic acid mouthwash. *Br Dent J* 2005; **198:** 33–8.
7. Scully C, *et al*. Oral care for people with hemophilia or a hereditary bleeding tendency, second edition (World Federation of Hemophilia, Treatment of Hemophilia series, April 2008, No 27). Available at: http://www.wfh.org/2/docs/Publications/Dental_Care/TOH-27_Oral-Care-Revised2008.pdf (accessed 09/12/09)
8. Carter G, Goss A. Tranexamic acid mouthwash—a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg* 2003; **32:** 504–7.
9. Carter G, *et al*. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg* 2003; **61:** 1432–5.
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11. Annichino-Bizzacchi JM, *et al*. Hereditary hemorrhagic telangiectasia response to aminocaproic acid treatment. *Thromb Res* 1999; **96:** 73–6.
12. Sabbà C, *et al*. Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001; **345:** 926.
13. Sabbà C, *et al*. Rendu-Osler-Weber disease: experience with 56 patients. *Ann Ital Med Int* 2002; **17:** 173–9.
14. Klepfish A, *et al*. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med* 200 1; **161:** 767.
15. Levi M, *et al*. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; **354:** 1940–7.
16. Schmarts. Antifibrinolytics. *Acta Anaesthesiol Belg* 2003; **54:** 319–22.
17. Ho KM, Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesth Intensive Care* 2003; **31:** 529–37.
18. Brown JR, *et al*. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; **115:** 2801–13.
19. Henry DA, *et al*. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
20. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376:** 23–32.
21. Roos YB, *et al*. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 27/10/05).
22. Gluud LL, *et al*. Systematic review: tranexamic acid for upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2008; **27:** 752–8.

Hereditary angioedema. Tranexamic acid is used as prophylactic therapy in the management of hereditary angioedema (p. 2485.2).

Menorrhagia. Tranexamic acid is used in women with menorrhagia (p. 2300.3) who do not require contraception or hormonal therapy. It reduces uterine blood loss in such women when used during menstruation.[1-3] A comparative study[1] found oral tranexamic acid 1 g every 6 hours to be more effective than the NSAID mefenamic acid, a commonly used treatment for the condition, and etamsylate. It is also more effective than cyclical norethisterone[2] (although less so than a progesterone-releasing intrauterine device[3]). A review,[4] which included these and some other studies, reported that tranexamic acid reduces menstrual blood loss by about 34 to 59% over 2 to 3 cycles.

1. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313:** 579–82.
2. Preston JT, *et al*. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; **102:** 401–406.
3. Milsom I, *et al*. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991; **164:** 879–83.
4. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs* 2003; **63:** 1417–33.

Adverse Effects

Tranexamic acid appears to be well tolerated. It can produce dose-related gastrointestinal disturbances. Hypotension and dizziness have occurred, particularly after rapid intravenous dosage. Thrombotic complications (including cerebral thrombosis and central retinal venous and arterial occlusion) have been reported in patients receiving tranexamic acid, but these are usually a consequence of its inappropriate use (see Precautions, below). Ocular and visual disturbances, including disturbance of colour vision, have been associated with use of tranexamic acid; in such cases the drug should be stopped. Other adverse effects that have been reported include hypersensitivity reactions, skin reactions, musculoskeletal pain, and convulsions.

Effects on the eyes. Tranexamic acid has been associated with retinopathy[1] and visual impairment.[2] A haemodialysis patient developed almost total loss of vision within 2 weeks of starting daily tranexamic acid injections after emergency surgery for a bleeding peptic ulcer. Vision was largely restored within a few days of stopping tranexamic acid,[2] although some impairment persisted in conditions of poor light. The patient had experienced visual impairment previously when given tranexamic acid. The authors noted that doses of tranexamic acid should be reduced in patients with renal impairment undergoing dialysis.

A patient undergoing regular peritoneal dialysis for Epstein's syndrome developed ligneous conjunctivitis, gingival hyperplasia, and peritoneal protein loss associated with the use of tranexamic acid.[3]

1. Snir M, *et al*. Central venous stasis retinopathy following the use of tranexamic acid. *Retina* 1990; **10:** 181–4.
2. Kitamura H, *et al*. Tranexamic acid-induced visual impairment in a hemodialysis patient. *Clin Exp Nephrol* 2003; **7:** 311–14.
3. Diamond JP, *et al*. Tranexamic acid-associated ligneous conjunctivitis with gingival and peritoneal lesions. *Br J Ophthalmol* 1991; **75:** 753–4.

Effects on the skin. A widespread, patchy rash with associated blisters, considered on skin biopsy to be a fixed-drug eruption, occurred in a 33-year-old woman.[1] Tranexamic acid, which she had taken for 8 years and which had been well tolerated, was identified as the cause. Desensitisation was unsuccessful. Tranexamic acid was also suspected as being the cause of a fixed-drug eruption in a 36-year-old woman.[2] Pruritic, vesicle-bullous lesions appeared within a few hours of starting tranexamic acid and the lesions resolved completely 3 days after stopping therapy even though other drug treatment was continued.

1. Kavanagh GM, *et al*. Tranexamic acid (Cyklokapron)-induced fixed-drug eruption. *Br J Dermatol* 1993; **128:** 229–30.
2. Carrión-Carrión C, *et al*. Bullous eruption induced by tranexamic acid. *Ann Pharmacother* 1994; **28:** 1305–6.

Precautions

Tranexamic acid should not be used in patients with active intravascular clotting because of the risk of thrombosis. Patients with a history of, or predisposition to, thromboembolism are also at risk if given antifibrinolytic therapy. Haemorrhage due to disseminated intravascular coagulation should therefore not be treated with antifibrinolytic compounds unless the condition is mainly due to disturbances in fibrinolytic mechanisms; tranexamic acid has been used when the latter conditions are met, but with careful monitoring and anticoagulant cover.

Lysis of existing extravascular clots may be inhibited in patients receiving tranexamic acid. Patients with massive haematuria from the upper urinary tract may be at increased risk of ureteric obstruction. Doses of tranexamic acid should be reduced in patients with renal impairment. Licensed product information recommends that regular eye examinations and liver function tests should be performed if tranexamic acid is used long term.

Some studies have suggested that tranexamic acid when given to patients after a subarachnoid haemorrhage increases the incidence of cerebral ischaemic complications (see Haemorrhagic Disorders under Uses, p. 1164.3).

Rapid intravenous dosage may be associated with adverse effects (see above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tranexamic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Drugs with actions on haemostasis should be given with caution to patients on antifibrinolytic therapy. The risk of thrombosis may be increased if tranexamic acid is given with factor IX complex concentrates or factor VIII inhibitor bypassing fraction, and such combinations are not recommended. Antifibrinolytics and thrombolytics have antagonistic effects, and concomitant use may reduce the efficacy of both. The potential for thrombus formation may be increased by oestrogens.

Retinoids. Antifibrinolytics should be used with caution in patients receiving oral *tretinoin* as thrombotic events have been reported in patients being treated with tranexamic acid and tretinoin (see Antifibrinolytics, p. 1727.1).

Pharmacokinetics

Tranexamic acid is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 3 hours. Bioavailability is about 45%. Tranexamic acid is widely distributed throughout the body and has very low protein binding. It diffuses across the placenta and is distributed into breast milk. Tranexamic acid has a plasma elimination half-life of about 2 hours. It is excreted in the urine mainly as unchanged drug.

References.

1. Andersson L, *et al*. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann N Y Acad Sci* 1968; **146:** 642–56.
2. Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynecol Scand* 1970; **49:** 241–2.
3. Pilbrant Å, *et al*. Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol* 1981; **20:** 65–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tranexal; ***Austral.***: Cyklokapron; ***Austria***: Cyklokapron; ***Belg.***: Exacyl; ***Braz.***: Hemoblock; Transamin; Trexacont; ***Canad.***: Cyklokapron; ***Chile***: Espercil; ***China***: Bei Rui Ning (贝瑞宁); Feimin (菲敏); He Mo Sai (荷莫塞); JieNing (捷凝); Jiening (捷宁); Ka Wei An (卡维安); Li Da Fei (力达非); Ta Jiu Shu (他久舒); Transamin (妥塞敏); ***Cz.***: Exacyl; ***Denm.***: Cyklokapron; Cyklonova; ***Fin.***: Caprilon; Cyklokapron; ***Fr.***: Exacyl; Spotof; ***Ger.***: Cyklokapron; ***Gr.***: Transamin; ***Hong Kong***: CP-Tran; Cyklokapron†; Qualixamin; Tosano; Transamin; ***Hung.***: Exacyl; ***India***: Bio-Stat; Capitrax; Clip; Clotawin-T; Coastat; Cyklokapron; Cymin; Dubatran; Examic; Fegan; Gynae-Pil; Menogia; Mouzex; Nexim; Tranarest; Tranfib; ***Indon.***: Asamnex; Clonex; Ditranex†; Ethinex; Intermic; Kalnex; Lunex; Nexa; Nexitra; Plasminex; Pytramic; Ronex; Theranex†; Tranec; Tranexid; Transamin; Tranxa; ***Irl.***: Cyklokapron; ***Israel***: Hexakapron; ***Ital.***: Tranex; Ugurol; ***Jpn***: Transamin; ***Malaysia***: Transamin; Tren; ***Neth.***: Cyklokapron; ***Norw.***: Cyklokapron; ***NZ***: Cyklokapron; ***Philipp.***: Cyclotrax; Cyklokapron†; Dostan; Fibrinon; Fimoplas; Hemoclot; Hemostan; Hemostop; Hemotrex; Micranex; Pantrex; Proklot; Tarnex; Trenaxin; ***Pol.***: Exacyl; ***Rus.***: Tranexam (Транексам); ***S.Afr.***: Cyklokapron; Tranic; ***Singapore***: Cyklokapron; ***Spain***: Amchafibrin; ***Swed.***: Cyklo-F; Cyklokapron; Cyklonova; Tranon; ***Switz.***: Cyklokapron; ***Thai.***: Axamin; Falete; Tramic; Transamin; Transic; Tranxamax; Tranxic; ***Turk.***: Transamine; ***UK***: Cyklo-F; Cyklokapron; Femstrual; ***Ukr.***: Tranexam (Транексам); ***USA***: Cyklokapron; Lysteda; ***Venez.***: Ciclokapron.

Multi-ingredient Preparations. ***Belg.***: Quixil†; ***Denm.***: Quixil; ***Fin.***: Quixil; ***Fr.***: Quixil†; ***Ger.***: Quixil†; ***India***: Bio-Stat-MF; C-Sylate Plus; Capihem; Capitrax Plus; Chromostat; Clip-MF; Clotawin-T; Clotem Plus; Coag; Coastat Plus; Coastat-Gyne; Cosklot Plus; Cyclocos-TX; Cyclosym-TX; Dubatran-MF; Etam; Etex-T; Ethatol; ETM-T; Etosys-MF; Etosys; Examic-MF; Fenamic; Fetran-ES; Fetran-MF; Fibran Plus; Fibran-M; Florasyl-MF; Gynae-Pil Forte; Hamodam-M; Hamodam-T; Hemocrat; HMT; Klotinex; Meffnex; Mefitrax; Meflam; Mefnex; Mefsyn-TX; Meftal-TX; Meftrax; Menogia-MF; Menoguard; Menospan-MF; Menostat; Menotran; Mouzex-MF; No Blos For; Noblifen; Tranfib MF; ***Ital.***: Quixil; ***Jpn***: Sin Colgen Kowa Kaze†; ***Neth.***: Quixil†; ***Port.***: Quixil†; ***Swed.***: Quixil†; ***Switz.***: Quixil.

Pharmacopoeial Preparations
BP 2014: Tranexamic Acid Injection; Tranexamic Acid Mouthwash; Tranexamic Acid Tablets.

von Willebrand Factor

Facteur Willebrand humain (human von Willebrand factor); Factor humanus von Willebrandi (human von Willebrand factor); Factor VIII-related Antigen; vWF; Фактор фон Виллебранда.

UNII — ZE22NE22F1 (von Willebrand factor human); 5T6B772R4Q (human coagulation factor viii/von Willebrand factor complex).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Human von Willebrand Factor). A sterile freeze-dried preparation of a plasma protein fraction that contains the glycoprotein von Willebrand factor with varying amounts of coagulation factor VIII, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors: the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

When reconstituted as stated on the label, the potency is not less than 20 international units of von Willebrand factor per mL. It is a white or pale yellow, hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

von Willebrand factor is used in the treatment and prophylaxis of bleeding in von Willebrand's disease (p. 1129.3), usually when desmopressin is ineffective or contra-indicated. It is generally contained in plasma concentrate preparations with factor VIII (p. 1148.1), but

highly purified preparations that contain very little factor VIII are also available in some countries. Dosage depends on the extent and source of bleeding. Hypersensitivity reactions may occur rarely, and as for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

References.
1. Smith MP, *et al.* Continuous infusion therapy with very high purity von Willebrand factor concentrate in patients with severe von Willebrand disease. *Blood Coag Fibrinol* 1997; **8:** 6–12.
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1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Wilfactin; ***Cz.***: Willfact; ***Denm.***: Willfact; ***Fin.***: Wilfactin; ***Fr.***: Wilfactin; Wilstart; ***Ger.***: Willfact; ***Gr.***: Wilfactin; ***Neth.***: Wilfactin; ***Norw.***: Willfact; ***Switz.***: Willfact.

Bone Modulating Drugs

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The processes of bone turnover, and the regulation of body calcium, are intimately connected. The concentration of calcium in plasma is normally kept within a narrow range (p. 1777.3). It is regulated by the absorption and excretion of calcium, and also by modulation of the normal resorption and formation of bone and hence the movement of calcium to and from the skeletal reservoir. The endogenous substances parathyroid hormone, calcitonin, and vitamin D, are involved in the regulation of calcium homoeostasis.

Drugs described in this chapter affect bone resorption or formation, with effects on serum calcium. They include:
- bisphosphonates
- bone morphogenetic proteins
- calcitonins
- cinacalcet hydrochloride
- gallium nitrate
- parathyroid hormone
- strontium ranelate
- teriparatide

The inorganic fluoride salts, which can promote bone formation when given in appropriate doses, are discussed in the chapter on Nutritional Agents (see Sodium Fluoride, p. 2089.2).

Bone and Bone Disease

The skeleton acts as mechanical support and protection to softer tissues and organs. It is also important in electrolyte homoeostasis, acting as a reservoir of certain ions and minerals such as calcium, phosphorus, and magnesium.

Bone has two components: an organic matrix, called **osteoid**, consisting mainly of collagen, and a mineral phase deposited through that matrix; the latter, comprising about 70% of the skeletal mass, is composed chiefly of **hydroxyapatite** (a complex crystalline salt of calcium and phosphate). There are two structural forms known in mature bone:
- cortical (lamellar) bone, which has a dense, continuous structure
- trabecular (cancellous) bone, which has a 'spongy' structure of linked plates and is associated with high bone turnover and growth.

The peripheral or appendicular parts of the skeleton are mainly cortical bone, while the axial or central parts, such as the spine and pelvis, contain substantial amounts of trabecular bone.

Bone is a dynamic tissue: once new bone has been laid down it is subject to a continual process of formation and resorption called **remodelling**. Remodelling takes place along bone surfaces and is carried out by bone cells (osteoclasts and osteoblasts) that originate in the marrow and share common origins with blood cells. Stimulated by physical or chemical signals, **osteoclasts** dig a cavity into the bone (bone resorption); they are then replaced by **osteoblasts** that synthesise new osteoid to fill the cavity (bone formation) and may help to promote its subsequent mineralisation. The actions of these two types of bone cell are closely linked, and agents that suppress resorption ultimately decrease bone formation too. However, at any given time there is a deficit in potential bone mass, the **remodelling space**, which represents sites of bone resorption that have not yet been filled in. Any stimulus that affects bone turnover by altering the recruitment of osteoblasts and osteoclasts to remodelling will result in an increase or decrease in the remodelling space, until a new steady state is achieved, and this will be seen as a decrease or increase in bone mass. Lifelong accumulation of remodelling deficits leads to age-related bone loss.

Bone also contains **osteocytes**, which are cells derived from osteoblasts thought to be involved in the movement of minerals.

Bone cells are controlled by systemic hormones including parathyroid hormone, 1,25-dihydroxycholecalciferol (calcitriol), calcitonin, and local regulators such as bone morphogenetic proteins and cytokines. A local signalling system involving the protein RANKL (receptor activator of nuclear factor-kappa B ligand), which induces osteoclast differentiation and activation and promotes bone resorption, and the protein osteoprotegerin, which inhibits osteoclast formation and prevents bone resorption, is mediated via the receptor RANK found on osteoclasts and their precursors.

Bone diseases may be due to defects in the production of osteoid or its mineralisation, or to an imbalance in resorption and formation of bone. Bone balance can be affected by diverse stimuli such as dietary insufficiency, hormones, including sex hormones, and drugs such as corticosteroids.

Hypercalcaemia of malignancy

About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive.[1,2] The condition is thought to be mediated usually by parathyroid hormone-related protein released from tumour tissue, which acts both locally and systemically to enhance osteoclastic bone resorption and increase renal tubular calcium reabsorption. Increased levels of parathyroid hormone-related protein have been found in hypercalcaemic patients, especially those with solid tumours, regardless of the existence of bone metastases.[3,4] Other causes of hypercalcaemia of malignancy include the activation of osteoclasts by the local release of bone-resorbing cytokines such as interleukin-1, interleukin-6, tumour necrosis factors, and growth factors;[3,4] this mechanism occurs particularly in those with myeloma.[4] The RANKL signalling system may play an important role.[5] Some lymphomas secrete active vitamin D, enhancing osteoclastic bone resorption and intestinal calcium absorption. Rarely, ectopic secretion of parathyroid hormone may cause hypercalcaemia.[6]

Bisphosphonates are the preferred drugs for **treating** hypercalcaemia once the patient has been adequately rehydrated with intravenous sodium chloride 0.9% (see Hypercalcaemia, p. 1778.1). It has been recommended[6] that therapy be begun as soon as possible, since a response is only seen after 2 to 4 days; in about 60 to 90% of patients serum calcium concentrations normalise within 4 to 7 days, and responses last for up to 3 weeks.[6] There is some evidence that bisphosphonates may be less effective in patients with high initial levels of parathyroid hormone-related protein; in addition, they have no effect on the renal tubular resorption of calcium.[2] There is no consensus as to the best bisphosphonate to choose. Pamidronate has been widely used and is considered by many to be the drug of choice.[7] A systematic review,[2] which noted that aminobisphosphonates were most effective in this condition, considered low-dose clodronate less effective than pamidronate although no difference was seen at higher doses. Others have queried the existence of a dose response for clodronate;[1] the fact it can be given subcutaneously, or orally (after intravenous therapy) may be useful.[1,4] Etidronate, which can also be given orally, is also less effective than pamidronate,[7,8] and prolonged therapy may cause osteomalacia. Alendronate has been found to be as effective as clodronate, and superior to etidronate.[2] Studies with neridronate and risedronate have been more limited;[1] incadronate has also been used.[2] However, newer aminobisphosphonates such as ibandronate and zoledronate may be the most effective option, with longer durations of response and more convenient dosage than pamidronate.[1,4] In patients unresponsive to low initial doses of bisphosphonates, some recommend larger doses;[6] alternatively, other drugs may be considered.

Calcitonin has a rapid onset of action, and is particularly useful in life-threatening hypercalcaemia.[1,7] This effect, however, is short-lived, and calcitonin is generally used as adjunctive therapy.[1] When given with bisphosphonates, calcitonin reduces serum calcium more rapidly than bisphosphonates given alone.[4]

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, has been used to obtain a rapid (within 24 hours) and sustained reduction in plasma-calcium concentrations in severe hypercalcaemia. However, it is highly toxic and its use no longer recommended.[1,5] *Gallium nitrate* also inhibits bone resorption; initial studies in patients with hypercalcaemia associated with malignancy have indicated beneficial effects,[3] but bisphosphonates are still likely to be preferred.[4,5]

Corticosteroids are useful in hypercalcaemia associated with corticosteroid-sensitive haematological malignancies such as lymphoma or myeloma.[1,4,6] In addition they may be useful to overcome renal tubular resistance to calcitonin[9] but otherwise are not usually effective.[10] There have been individual reports of beneficial results using somatostatin analogues such as *octreotide* for the treatment of hypercalcaemia of malignancy.

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Malignant neoplasms

The bisphosphonates and calcitonins are used to control the hypercalcaemia that often accompanies malignant disease (see above). Bisphosphonates are also used in metastatic bone disease (p. 700.3) to control bone pain and to reduce skeletal complications such as fractures. Evidence of the ability of bisphosphonates to prevent the development of bone metastases is conflicting. Bisphosphonates have been found to be effective in reducing the skeletal complications of multiple myeloma (p. 699.2) and are recommended in those patients with bone disease. Denosumab is also under investigation in the prevention of the development of bone metastases.

Osteogenesis imperfecta

Osteogenesis imperfecta (brittle bone syndrome) is a heterogeneous inherited disorder of connective tissue characterised by bone fragility, osteopenia, short stature, joint laxity, teeth defects, and hearing abnormalities.[1,2] It is often classified into 4 forms, I-IV, which vary in clinical severity, and radiological and genetic aspects;[1] some distinguish 3 further forms, V, VI, and VII.[2]

Orthopaedic treatment and physical activity programmes form the basis of **therapy**: at present there is no curative drug therapy.[1-3] *Calcitonins* were commonly used in management, but their use has declined.[1] Beneficial effects have been reported with growth hormone, especially in moderate forms of the disease.[1] *Bisphosphonates* have been found useful in osteogenesis imperfecta,[3,4] particularly in severe disease.[1] It is generally agreed that they improve bone mineral density,[3-5] and commentators have suggested that this is associated with improvements in chronic pain, fracture rate, and mobility,[3,4] although a systematic review considered that these benefits, as well as long-term safety (particularly in children) had not yet been adequately demonstrated.[5] Cyclic intravenous pamidronate has been the most widely used bisphosphonate, but benefit has also been reported with intermittent intravenous neridronate,[6,7] as well as daily oral clodronate.[8] Alendronate and zoledronate are under investigation.[4] Bisphosphonates may also be useful for associated immobilisation hypercalcaemia.[9] Immobilisation can also result in calcium and vitamin D deficiency, and prophylactic supplementation may be useful.[3] Bone marrow transplantation and the potential of antisense gene therapy are being investigated.[1,2]

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Osteomalacia and rickets

Osteomalacia occurs in adults when there is impaired mineralisation of the bone matrix, and rickets occurs in children due to defective mineralisation of the cartilaginous growth plate.[1-3] Generally the inadequate bone mineralisation results from deficiency or abnormal metabolism of vitamin D,[1,2,4] calcium deficiency,[1,5] or phosphate deficiency or depletion.[1-3] Several hereditary disorders are associated with the development of rickets including vitamin D-pseudodeficiency rickets (vitamin D-dependent rickets), in which there is impaired synthesis of 1,25-dihydroxycholecalciferol (Type I) or receptor resistance to 1,25-dihydroxycholecalciferol (Type II), and X-linked hypophosphataemic rickets.[2,6] Osteomalacia also occurs in renal osteodystrophy[2] associated with chronic renal failure (see p. 1170.1). Oncogenic osteomalacia is a rare form characterised by hypophosphataemia and renal phosphate wasting caused by a tumour, usually mesenchymal.[2,3] Some drugs including various antiepileptics (p. 540.2), etidronate, and aluminium salts, can interfere with bone mineralisation and cause osteomalacia. Osteomalacia may present with generalised or local bone pain, polyarthralgias, or muscle weakness.[2] Rickets characteristically causes skeletal deformities, epiphyseal enlargement, muscle hypotonia, and teeth defects.[1-4,6]

Treatment of osteomalacia and rickets is mainly aimed at correcting any underlying deficiency.[2] Vitamin D substances, calcium, or phosphate supplements can be given orally as appropriate but doses require careful individual adjustment to maintain calcium and phosphate concentrations within normal limits.[2,5] Vitamin D requirements are probably greater in those with reduced calcium intake, and calcium requirements greater in those with limited sunlight exposure and dietary vitamin D intake.[5]

A variety of forms or analogues of vitamin D are available (see p. 2112.3). For the treatment of simple vitamin D deficiency colecalciferol or ergocalciferol are generally preferred.[4] If malabsorption is suspected, larger doses or parenteral use may be necessary, but where large doses are required it may be preferable to use one of the more potent forms of vitamin D such as calcitriol.[2]

Simple calcium deficiency may be a more important cause of rickets than vitamin D deficiency in some populations. A study in African children with rickets found that their calcium intake was low and that they responded better to calcium supplementation, with or without vitamin D, than to vitamin D alone.[5]

Type I vitamin D-pseudodeficiency rickets requires replacement therapy with calcitriol. In Type II disease, resistance to calcitriol treatment may be so extreme that only very large supplements of calcium may be effective. X-linked hypophosphataemic rickets is considered to be best treated with combined phosphate supplementation and calcitriol.[3] There has also been some interest in the use of growth hormone in children with hypophosphataemic rickets.[7] A form of hypophosphataemic rickets, rickets of prematurity (see under Osteomalacia, p. 1794.1), may occur in small, premature infants fed exclusively on breast milk, and phosphate supplementation plus calcium and vitamin D has been suggested in such cases. Prophylaxis of calcium or vitamin D deficiencies through adequate dietary intake or supplementation is controversial given difficulties in deciding definitive requirements (see Human Requirements under Calcium, p. 1788.2, and Human Requirements, p. 2118.1, and Osteomalacia, p. 2116.2, under vitamin D).

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Osteoporosis

Osteoporosis is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and risk of fracture, particularly of the long bones (distal forearm and neck of the femur) and the vertebrae.[1-9] Although bone formation outstrips resorption in youth, accumulated small deficits from remodelling (see Bone and Bone Disease, p. 1167.1) result in a gradual loss of bone mass after the third or fourth decades.[2-4,6,10] Primary osteoporosis is therefore usually an age-related disease. It can affect both sexes, though women are at greater risk because bone loss is accelerated, to a variable degree, after the menopause.[1-3,5,6,10,11] Osteoporosis can also be secondary to chronic endocrine or metabolic conditions[1,5,6,10-12] such as hyperparathyroidism (p. 1170.3), hyperthyroidism (p. 2332.2), diabetes mellitus (p. 458.2), Cushing's syndrome (p. 2559.1), malabsorption syndromes, anorexia nervosa, or inflammatory bowel disease (p. 1811.3) affecting calcium and vitamin D absorption. Other conditions associated with bone loss and osteoporosis include osteogenesis imperfecta (p. 1167.3), rheumatoid arthritis (p. 13.2), complex regional pain syndrome (p. 8.1), chronic renal disease, multiple myeloma (p. 699.2), and HIV (p. 958.3); osteoporosis may also follow organ and tissue transplantation or prolonged immobilisation. Other secondary causes include the use of drugs[1,5,6,10,11,13,14] such as corticosteroids (p. 1616.2), thyroid hormones, anticonvulsants, gonadorelin analogues (p. 2282.1), aromatase inhibitors, and heparin (p. 1399.2).

Risk factors for osteoporosis include non-modifiable predictors of low bone mineral density (BMD), such as female sex, increased age, Caucasian or Asian race, while other factors are potentially modifiable but may be independent of BMD, such as cigarette smoking, alcohol consumption, low body-weight, and physical inactivity. Other factors include early menopause, hypogonadism, including prolonged amenorrhoea in women, high caffeine intake, and nutritional deficiencies such as low calcium intake and vitamin D deficiency.[1,3,6,10,13,15,16] The most important risk factors for osteoporosis-related fracture are a history of low-trauma fracture as an adult (40 years of age or older) and low BMD.[1,3,4] For men, important risk factors include increasing age (over 70 years) and low body-weight (BMI of less than 20 kg/m^2).[16]

Patients are usually asymptomatic until fractures occur,[6,15] and up to two-thirds of vertebral fractures may also be asymptomatic.[1,6] Fractures can result in pain, deformity (kyphosis, loss of height), and disability.[1] Currently, the most reliable method of **assessment** for osteoporosis and fracture risk is measurement of BMD, usually by dual energy X-ray absorptiometry.[1,3,4,6,17] WHO have defined osteoporosis as a BMD 2.5 standard deviations or more below the young adult mean, and severe or established osteoporosis as this BMD in the presence of one or more fragility fractures.[3] There is no universally agreed policy on screening for osteoporosis, but measurement of BMD should be considered in those thought to be at risk of osteoporosis if the result is likely to affect treatment decisions.[2,3,7,10,18,19]

Since osteoporosis is defined in terms of BMD, the distinction between clinical consequences, such as fractures, and risk, is blurred. Thus, differences between prevention and treatment are increasingly difficult to define; objectives are similar and interventions the same.[3] Goals in **management** are to prevent fractures, optimise skeletal development to maximise peak BMD at skeletal maturity, stabilise BMD and prevent bone loss, preserve structural skeletal integrity, decrease morbidity and mortality from fractures, and to relieve symptoms of fractures and skeletal deformity.[1,4] Secondary causes of osteoporosis should be identified and treated as appropriate.[4]

General **non-pharmacological** measures include:

- ensuring adequate dietary calcium and vitamin D intake (see under Human Requirements, p. 1788.2 and p. 2118.1), especially during growth.[1,3,4,20,21] Supplementation may be necessary, see below.
- regular weight-bearing exercise; during growth this optimises peak bone mass,[3,4,19-21] but is also beneficial in pre-and postmenopausal women in terms of increasing BMD and reducing the risk of fractures.[1,4,19,22] However, exercise does not appear to prevent fractures in postmenopausal women during the first 2 years of exercise.[23]
- lifestyle modifications such as smoking cessation (p. 2570.2) and moderation of caffeine and alcohol intake.[1,3,4,9,21,22]
- interventions to reduce or prevent falls and injuries; measures to protect the patient should falls occur may also be considered.[1,4,19,21,22]
- Supportive therapy in the acute phase of a fracture, including pain relief, surgery or appropriate orthopaedic management.[20]

Pharmacological treatment aims to increase bone mass, either by inhibiting bone resorption, or by stimulating bone formation through anabolic effects.[1,24] While many drugs are used, not all have been well evaluated for their effect on fracture rates, and there are few comparisons.[25] Furthermore, many studies have been conducted in postmenopausal osteoporotic women, and evaluation in postmenopausal women with normal BMD, osteopenic women with no fracture, or men, is limited.[3,19]

- Calcium and vitamin D supplementation is accepted baseline adjunctive treatment for osteoporosis and may also be used as a prophylactic measure.[4,7,20,24] Calcium supplementation has a small but positive effect on BMD and tends to reduce the incidence of vertebral fractures. Low vitamin D status has been associated with reduced BMD, and increased risk of falls and hip fracture in elderly people; however, differences in baseline vitamin D concentrations make comparison of studies difficult.[8] Vitamin D supplementation appears to reduce the risk of hip and non-vertebral fractures,[7,8] especially in those with vitamin D deficiency. Excessive vitamin D should be avoided, as this may decrease BMD.[2] Studies of supplementation with calcium plus vitamin D show equivocal results on fracture rates.[8] However, daily calcium with vitamin D supplementation is recommended for elderly institutionalised people with limited exposure to sunlight.[18,19,22]
- Bisphosphonates are antiresorptive drugs that are used first-line for the treatment and prevention of osteoporosis.[4,18,19,21] While aminobisphosphonates and non-nitrogen-containing bisphosphonates differ in their effect on BMD,[17,26] no comparative studies have been done and BMD changes do not necessarily correlate with fracture reduction;[26] some consider effect on fracture rates to be similar.[17]
  There is good evidence that alendronate, risedronate, or zoledronate can prevent bone loss,[4,11] improve BMD,[1,4,6] and reduce the risk of both vertebral and non-vertebral fractures.[1,2,4,8,9,15,24] These effects are seen within 1 year of starting treatment,[27] and effects on BMD persist for some while after stopping the drug, particularly with alendronate.[17] Evidence for other bisphosphonates is more patchy: oral or intravenous ibandronate,[11] and intravenous pamidronate[6] have been shown to increase BMD at the spine and hip. Oral ibandronate has been shown to decrease vertebral fracture risk in women with osteoporosis, as well as non-vertebral fracture risk in those with severe disease.[11,28] Intravenous ibandronate has been associated with a reduction in the incidence of new fractures.[11] Oral cyclical etidronate has been shown to decrease the risk of vertebral fractures,[1,3] (as has oral clodronate[20]), but evidence for an effect on non-vertebral fractures is less clear.[20] In the UK, NICE recommends[29] alendronate for the primary prevention of osteoporotic fragility fractures in postmenopausal women with confirmed osteoporosis; those below 65 years must have an independent clinical risk factor for fracture and at least one additional indicator of low BMD, women aged 65 to 69 years must have an independent clinical risk factor for fracture, and women aged 70 years or older must have an independent clinical risk factor for fracture or an indicator of low BMD. Risedronate and etidronate are recommended as alternatives in high-risk women unable to take alendronate. NICE also recommends[30] alendronate for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with confirmed osteoporosis who have sustained a clinically apparent fracture; risedronate and etidronate are alternatives in high-risk women unable to take alendronate.
- In postmenopausal women, HRT (p. 2245.1) was initially considered first-line,[31] as its antiresorptive action has been shown to preserve BMD and decrease hip and vertebral fracture risk.[1,2,24] However, results from the Women's Health Initiative and Million Women studies suggested that long-term use of HRT could increase the risk of breast and some other cancers (see p. 2246.3), while not reducing cardiovascular risk or improving cognitive function. The UK CSM has thus recommended that HRT no longer be considered as a first-line therapy for the prevention of osteoporosis in women aged over 50 years and at increased risk of fractures;[32] it remains an option for those intolerant of or refractory to other therapies, and for prevention of osteoporosis in women with premature menopause until the age of 50. It has been suggested that treatment not exceed 5 years,[24] although others suggest treatment of 7 to 10 years in order to maximise effect in those women considered at greater benefit than risk with HRT.[2] A large study found that women who had stopped using HRT more than 5 years previously had similar hip fracture risk to those who had never used HRT. However, those who had stopped using HRT within the previous 5 years had a higher risk of hip fracture than in those who had never taken HRT.[33]
- Raloxifene is a selective oestrogen receptor modulator (SERM) that partially mimics the effects of oestrogen in bone and the cardiovascular system, but without the stimulatory effects on the endometrium and breast.[3] Raloxifene significantly increases BMD in postmenopausal women and reduces vertebral fracture risk in those women with osteoporosis,[4,21,34] although it may exacerbate cardiovascular problems.[11,18] Risk of non-vertebral fracture is not affected,[3,18] and some consider SERMs less effective than the bisphosphonates.[6] NICE recommends[30] raloxifene for the secondary prevention of osteoporotic fragility fractures in high-risk women unable to take bisphosphonates. It is not recommended for primary prevention in postmenopausal women.[29]
- Combination therapy of HRT or raloxifene with bisphosphonates has increased BMD but with no effects on fracture reduction.[20]
- Strontium ranelate has both anabolic and resorptive properties.[20] It has been found to increase BMD at the spine and hip, and reduce new vertebral, non-vertebral, and hip fractures in postmenopausal women with

osteoporosis.[9,11] NICE recommends strontium ranelate for the primary[29] and secondary[30] prevention of osteoporotic fragility fractures in high-risk postmenopausal women unable to take bisphosphonates.

- Parathyroid hormone and its analogue teriparatide also have anabolic effects on bone, and increase BMD at the spine.[21,24] Daily subcutaneous injections of teriparatide reduced the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis.[4,35] Teriparatide has also been shown to increase lumbar and femoral BMD, and reduce non-vertebral fractures to a greater extent than alendronate.[5] The response to parathyroid hormone may be modified by previous or concurrent treatment with antiresorptive drugs.[8] NICE recommends[30] teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women who have had an unsatisfactory response to bisphosphonates or who are unable to take bisphosphonates or strontium ranelate; women aged 65 years or older must have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3.5 standard deviations or more below the mean) plus more than 2 fractures, and women aged 55 to 64 must have an extremely low BMD plus more than 2 fractures.
- Calcitonins are antiresorptive agents with an adjunctive or second-line role in the treatment of osteoporosis; calcitonin (salmon) is given by subcutaneous injection or intranasally as a spray. Both routes have been found to increase spinal BMD;[1,4,5] decreases in vertebral[4,31] fracture risk have been seen with the nasal spray, although the beneficial effect on nonvertebral fracture may be less than with bisphosphonates.[36] A review by the EMEA found an increased risk of cancer with long-term use of calcitonins and subsequently recommended against their use in postmenopausal osteoporosis (for further details see Carcinogenicity, under Adverse Effects, Treatment, and Precautions of Calcitonins, p. 1179.2); however, such use may still be permitted in other countries. It has been suggested that the analgesic effects of calcitonins may be valuable in patients with acute pain due to osteoporotic fractures,[2,3,18,24] the analgesia being achieved within 2 weeks,[6] although some would only recommend it for pain from acute vertebral compression fractures.[21]
- Denosumab is a monoclonal antibody that reversibly inhibits osteoclast-mediated bone resorption. It has been shown to improve bone mineral density and reduce the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis,[4] and may be considered first-line therapy for women who cannot take bisphosphonates.[37] It is also used for osteoporosis in men and bone loss associated with some hormonal treatments for cancer.
- Tibolone is a synthetic steroid with combined oestrogenic, progestogenic, and androgenic properties, that increases BMD comparably to HRT, relieves vasomotor symptoms, and does not cause endometrial proliferation.[3] However, there are limited data on fracture prevention, and some do not recommend its use for treatment of osteoporosis.[24] A large study[38] of the treatment of osteoporosis in postmenopausal women aged between 60 and 85 years was stopped early when it was found that although tibolone reduced the risk of fracture, breast cancer, and possibly colon cancer, there was an increased risk of stroke. The authors therefore concluded that tibolone should not be used in elderly women and women with risk factors for stroke.
- Anabolic steroids such as nandrolone have been found to increase BMD similarly to HRT, but adverse effects and limited data on fracture reduction efficacy have limited their use.[3,19]
- Fluoride has a direct anabolic effect on the osteoblast, stimulating bone formation; it has been given as sodium fluoride or sodium monofluorophosphate in the treatment of osteoporosis.[3] However, increases in lumbar BMD with fluoride have not resulted in decreased vertebral fracture rate, and may even be associated with increased bone fragility and an increase in non-vertebral fractures.[3,39] Thus fluoride is not widely recommended for osteoporosis management; fluoride water concentrations should be taken into account if it is used.[3]
- There is some suggestion that HMG-CoA reductase inhibitors (statins) can stimulate bone formation and have the potential to reduce fracture risk, but data are conflicting, and further studies are needed.[40,41]
- Thiazide diuretics reduce urinary calcium excretion and observational studies have found patients to have a higher BMD and fewer hip fractures;[3] however, effects are small and therapy is likely to be restricted to an adjunctive preventative role.[1,3,5]
- Ipriflavone is a synthetic isoflavone that may inhibit bone resorption; results on BMD from trials are conflicting, and data on fracture reduction lacking.[1,3]
- Vitamin K plays a role in bone metabolism, and is licensed in some countries in the management of osteoporosis; it has been suggested that vitamin K substances should be given to patients at risk of reduced bone mineralisation.[42] A systematic review and meta-analysis found that vitamin K supplementation was associated with increased BMD and a reduced fracture incidence, especially of the hip;[43] however, routine supplementation is not considered justified until these results are confirmed in a large randomised study with fractures as primary outcome.
- Potential anabolic agents in the management of osteoporosis include growth hormone and insulin-like growth factor I.[5,35] Novel antiresorptive agents under investigation include cathepsin K inhibitors,[44] cytokine inhibitors,[5,24] and osteoprotegerin.[5,45]

There is less evidence to guide decisions on the management of osteoporosis in **men**[3,46] than in postmenopausal women. Calcium and vitamin D intake or supplementation, nutritional and lifestyle advice are similar to that for women.[46-48] In hypogonadal men with osteoporosis, testosterone replacement therapy should be used.[3,46,47] In eugonadal men, there are concerns regarding the potential long-term adverse effects of exogenous testosterone.[46,48] Therefore, in men with idiopathic osteoporosis, bisphosphonates may be the treatment of choice.[47] Alendronate has been found to increase BMD at all sites and decrease vertebral fracture rates in men with osteoporosis,[47] and there have been some reports of beneficial effects on lumbar BMD have been reported with cyclical etidronate. Preliminary results with risedronate indicate favourable increases in lumbar BMD and a decrease in vertebral fracture risk.[46]

Beneficial effects on both lumbar and femoral BMD have been reported with teriparatide; its effect on BMD when used alone was found to be greater than when used with alendronate, or that of alendronate alone.[47] After teriparatide is stopped, treatment with a bisphosphonate is recommended to further increase BMD.[13] While efficacy in fracture prevention is lacking, teriparatide may be considered second-line for patients unable to take bisphosphonates.[46] Nasal calcitonin (salmon) has been found to increase lumbar BMD in men with idiopathic osteoporosis,[47] but most similarly reserve its use for those who cannot tolerate bisphosphonates.[46,48]

Of the other available drugs, fluoride has increased BMD and decreased vertebral but not non-vertebral fractures.[47] Thiazide diuretics have been reported to be of benefit, but data on BMD and fracture risk are conflicting; they may be given as adjunctive therapy in men with hypercalciuria.[46] Use of growth hormone in men with idiopathic osteoporosis led to gains in BMD in a small uncontrolled study.[48]

In **children**, calcium and vitamin D supplements are considered appropriate for low BMD.[49] Although there are only limited data in children, bisphosphonates (particularly pamidronate) have been used for both prevention and treatment. In children who have osteoporotic fractures, increases in BMD, reductions in fracture frequency, and relief of pain have been reported after bisphosphonate use.

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Paget's disease of bone

Paget's disease of bone (osteitis deformans) is a progressive bone disease of unknown aetiology, characterised by excessive and disorganised bone resorption and formation.[1-4] It may affect single (monostotic) or multiple bones (polyostotic);[1,2,5] the most commonly affected bones include the pelvis, femur, lumbar spine, skull, and tibia.[1,2,4,5] It affects 1 to 2% of white adults older than 55 years[1] and its frequency increases with age,[1,2] although there are large ethnic and geographical differences in incidence.[1] Patients may be asymptomatic, but some present with musculoskeletal and bone pain, or with bone weakness and deformity that can result in fractures.[2-4,6] Other complications include hearing loss, osteoarthritis, spinal stenosis, nerve compression (especially of the spinal cord), cranial nerve palsies, and rarely, hydrocephalus or brainstem compression. Cardiac output increases due to increased skeletal vascularity, but high-output heart failure is rare, as is malignant transformation to osteosarcoma.[2-4]

Patients who are asymptomatic may require no **treatment**;[5,7] however treatment is warranted, in those patients with biochemical markers of active disease or in whom the sites of disease are associated with a risk of progression and future complications.[4,7] Drug therapy is guided by monitoring biochemical improvement in disease activity.[2,8]

Bone pain may be treated with *analgesics* or *NSAIDs*, or with drugs that reduce bone resorption, such as the calcitonins and bisphosphonates.[2,4,5]

Bisphosphonates are indicated for persistent bone pain, or to prevent further progression of the disease, especially if

complications such as spinal-cord compression are present or there is a risk of such complications.[3,7] Disease activity may be reduced for several months, or years, after bisphosphonate therapy has ceased.[7] However, while bone turnover is suppressed, and osteolytic lesions may be healed, the underlying disorder is not cured; data on long-term effects of bisphosphonates on fractures, bone deformity, or osteoarthritis are limited and they may theoretically exacerbate hearing loss.[2]

Initial experience was with etidronate,[7,8] but it is less effective than the newer drugs, and with high doses or prolonged treatment can affect bone mineralisation;[4,7,8] while some still consider it effective,[7] others consider it to have little place in the management of Paget's disease.[3,8,9] Clodronate appears to provide a higher and more sustained response than etidronate.[7] Pamidronate, more effective at healing lesions than etidronate, also gives a prolonged response, although its effects may diminish due to resistance.[7] Alendronate or risedronate both reduce biochemical markers of disease activity with sustained remission,[4,7,9] are more effective than etidronate,[9] and overcome resistance to pamidronate;[3] risedronate may be useful after incomplete response to etidronate.[7] Tiludronate is also more effective than etidronate, with no effect on bone mineralisation, no reported resistance,[7] and may be a viable option for those patients unable to tolerate other bisphosphonates.[4] Neridronate has been reported to be beneficial in those patients with resistance to etidronate and clodronate.[7] Preliminary studies indicate suppression of disease activity with ibandronate.[8] Zoledronate has shown benefit in refractory disease, and some suggest that it should be a first-line option.[6]

Bisphosphonates have superseded *calcitonins*,[3,5,7,8] which have a short-lived effect and which generally are less effective in suppressing bone turnover and improving bone pain.[2] Calcitonins may still have a role in those patients for whom bisphosphonates are intolerable or ineffective;[5,8] however, resistance to both bisphosphonates and calcitonins may occur,[4] and long-term use of calcitonins has been associated with an increased risk of cancer (for details see Carcinogenicity, under Adverse Effects, Treatment, and Precautions of Calcitonins, p. 1179.2).

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, is highly effective in the treatment of Paget's disease of bone.[7] However, it is associated with severe toxicity and is therefore now avoided or reserved for patients refractory to other drugs.[4,7,8]

Studies with *gallium nitrate*, another inhibitor of bone resorption, have indicated beneficial effects in the treatment of Paget's disease of bone, but long-term haematological safety has not been established,[7] and routine use is not recommended.[8] *Ipriflavone* has also been reported to be of benefit, but remains investigational for Paget's disease.[7]

In selected patients, orthopaedic *surgery* for a fracture, knee or hip replacement, spinal stenosis, or correction of a bone deformity may be appropriate.[4,7,8] A calcitonin or bisphosphonate may be given for up to 3 months before surgery in order to reduce bone vascularity and minimise blood loss during the operation,[2,4,7] although this effect has not been verified in studies.[8] Such treatment also helps to prevent development of hypercalcaemia due to prolonged immobilisation.[4]

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Renal osteodystrophy

Patients with chronic renal failure (p. 1781.1) may develop complex changes to bone known as renal osteodystrophy[1-6] as part of the wider metabolic derangement known as chronic kidney disease-mineral and bone disorder (CKD-MBD).[7,8] These are often classified according to the state of bone turnover[1,3,5] and bone biopsy is the gold standard for diagnosis and classification.[2-6] Progressive renal failure is associated with hypocalcaemia, hyperphosphataemia, and some decrease in vitamin D metabolism, which increase the production of parathyroid hormone. This leads to secondary hyperparathyroidism (see below) and **high bone turnover** disease.[1,3-5] This manifests as *osteitis fibrosa*,[1,3-5] a condition characterised by increased osteoclastic and osteoblastic activity, woven and irregular osteoid, and bone marrow fibrosis.[2-6] **Low bone turnover** disease includes *osteomalacia* (see p. 1168.1) and *adynamic bone disease*.[1-5] These are characterised by defective mineralisation, decreased bone formation, and an absence of osteoclasts and osteoblasts; osteoid seams are wider or increased in osteomalacia, but normal or decreased in adynamic bone disease.[1-4,9] Osteomalacia, associated with vitamin D deficiency or aluminium toxicity (which has adverse effects on bone, see p. 1820.3), is decreasing in incidence with the removal of aluminium from dialysate solutions and decreasing use of aluminium-containing phosphate binders.[1-3,5,10] The pathogenesis of adynamic bone disease is not fully understood; its increasing incidence is thought to be due to suppression of parathyroid hormone secretion caused by increased exposure to calcium salts, as phosphate binders or in dialysate fluid, and vitamin D analogues.[1-6,9,10] Risk factors for its development include elderly age, diabetes mellitus, and peritoneal dialysis.[1-3,5,9] **Mixed uraemic osteodystrophy** has features of both high bone turnover with hyperparathyroidism, and defective bone mineralisation or osteomalacia.[1-6]

Patients with renal osteodystrophy may develop **osteopenia** or **osteoporosis**.[11]

Treatment is aimed at preventing bone disease by controlling the plasma concentrations of phosphate, calcium, parathyroid hormone, and correcting vitamin D deficiency; it should therefore be begun early in the course of renal impairment.[1,2,4,5]

- ***Hyperphosphataemia*** (p. 1778.3) is initially controlled with a low-phosphate diet but many patients, especially those on dialysis, also need an oral phosphate binder to complex with dietary phosphate in the gastrointestinal tract and reduce its absorption.[1,4]
  Calcium salts such as the carbonate or acetate are effective phosphate binders and have been found to suppress parathyroid hormone concentrations.[1,2,4,12] Calcium citrate is not recommended, because it increases intestinal aluminium absorption.[3,4,12] Calcium salts also raise plasma-calcium concentrations but hypercalcaemia can occur.[4,9] The use of dialysis fluids with a lower calcium content has been suggested for these patients.[4] Use of calcium can also contribute to the development of adynamic bone disease[1,9] and precipitate exogenous calcium deposition in the soft tissues;[1,9,12] coronary artery calcification is a particular problem contributing to cardiac mortality in patients with chronic renal failure.[2-4,13] Hyperphosphataemia or use of vitamin D can exacerbate calcification.[4,12,13]
  Aluminium-based phosphate binders have been given but relatively large doses are required and, as mentioned above, aluminium accumulation can lead to osteomalacia and adynamic bone disease in patients with impaired renal function; their use is no longer generally recommended.[2,3,12] Magnesium carbonate also binds phosphate, but may cause hypermagnesaemia and interfere with bone mineralisation.[2] Dialysate magnesium content may need to be reduced.[4]
  Other phosphate binders that do not contain calcium or aluminium have been tried. Sevelamer is a cationic polymer capable of binding phosphate[2,3] without affecting serum calcium.[4] It has been shown to be equivalent to calcium-based binders,[2,3,12] and is effective in dialysis patients.[1] It has been reported to reduce calcium scores in the coronary artery when compared with calcium salts.[4] Lanthanum carbonate is a cation with a high affinity for phosphate and similar efficacy to calcium carbonate.[3] It has been used effectively in dialysis patients but long-term potential toxic effects are as yet undetermined.[4]
- *Vitamin D* compounds that do not require renal hydroxylation, such as calcitriol or its synthetic analogue, alfacalcidol, are used to correct ***hypocalcaemia*** and to contribute to the control of ***secondary hyperparathyroidism***;[1,4] *calcium supplements* may also occasionally be required. Oversuppression of parathyroid hormone concentration should be avoided to deter the development of adynamic bone disease.[1] Calcitriol is given orally at first, but may also be given intravenously or intraperitoneally to patients on dialysis;[2,4-6] doses are adjusted according to response but the effect should be carefully monitored as hypercalcaemia and hyperphosphataemia may develop.[1,4,5] Use of alfacalcidol in the early stages of renal failure, before dialysis is required, has been reported to improve subclinical bone disease.[1] Newer vitamin D analogues suppress parathyroid activity but with potentially less effect on serum calcium and phosphate;[2-4,13] these include doxercalciferol, maxacalcitol, paricalcitol, and falecalcitriol (see Hyperparathyroidism, p. 2115.2).
  Calcimimetics increase the sensitivity of the calcium-sensing receptor of the parathyroid cells.[3] *Cinacalcet* has reduced parathyroid hormone concentrations[2] without inducing hypercalcaemia or hyperphosphataemia[13] in dialysis patients.

  Patients with hyperparathyroidism unresponsive to drug therapy, or who develop hypercalcaemia (which may itself further aggravate the decline in renal function), may require sub-total or total parathyroidectomy.[2-4] There is a risk of inducing a low turnover bone state; hyperparathyroidism can also recur after surgery.[4] Bone mineral density improves after surgery.[2]
  Bisphosphonates can be used in the acute management of hypercalcaemia,[2] but seem to be of little use in the long-term treatment of hyperparathyroidism. They may be effective in increasing bone mineral density in haemodialysis patients.[3] Some, however, consider their use is unjustified, even in those with documented osteopenia or osteoporosis, and that they may exacerbate adynamic bone disease due to their effects on bone mineralisation.[11]
- ***Adynamic bone disease*** is treated by stimulating parathyroid hormone-driven bone turnover and mineralisation.[2,3] Calcium and vitamin D supplementation may need to be reduced or stopped, and dialysate calcium concentrations reduced.[2,9] Aluminium deposition needs to be excluded; the use of aluminium-based phosphate binders is clearly undesirable in these patients.[2,9] On bone biopsy, if aluminium accumulation is evident, chelation with *desferrioxamine* may be considered.[2,4]
- ***Osteomalacia*** may respond to vitamin D treatment.[2]
- Treatment of ***mixed uraemic osteodystrophy*** involves management of both hyperparathyroidism and mineralisation defects.[2]

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Rickets

See Osteomalacia and Rickets, p. 1168.1.

Parathyroid Disorders

Parathyroid hormone, secreted by the parathyroid gland, maintains concentrations of ionised calcium in extracellular fluid within normal limits. It acts directly on the kidney to enhance renal reabsorption of calcium, to increase phosphate excretion, and to promote the conversion of vitamin D to its active metabolite, 1,25-dihydroxycholecalciferol, which in turn, enhances calcium absorption from the gastrointestinal tract. Parathyroid hormone also acts on bone, to accelerate bone resorption and the release of calcium and phosphate into the extracellular fluid. Secretion of parathyroid hormone is primarily regulated by the extracellular concentration of ionised calcium; hypocalcaemia stimulates secretion whereas hypercalcaemia has an inhibitory effect. 1,25-Dihydroxycholecalciferol can also suppress parathyroid hormone secretion.

Disorders of parathyroid hormone secretion cause a disruption of calcium homoeostasis and in the long-term, may result in bone disease.

Hyperparathyroidism

Primary hyperparathyroidism is a disorder of parathyroid hormone hypersecretion usually caused by adenomas or hyperplasia of the parathyroid glands; parathyroid carcinoma is a rare cause.[1-4] Patients are often asymptomatic, or have non-specific constitutional symptoms such as fatigue, weakness, anorexia, or bone pain.[3-6] About 20% of patients present with nephrolithiasis, overt bone disease, or neuromuscular weakness.[5] Symptoms and signs of hypercalcaemia (p. 1778.1) may occur;[3,5] hypercalcaemia is usually mild or even intermittent, and severe hypercalcaemia is rare.[7]

Secondary hyperparathyroidism is common in chronic renal failure (p. 1781.1). Other causes of hypocalcaemia or vitamin D deficiency resulting in increased parathyroid hormone secretion include dietary

deficiencies or malabsorption, or lack of exposure to sunlight.[1,3] While patients may also be asymptomatic, manifestations can include arthritis, bone pain, myopathy, tendon rupture, or complications such as coronary artery calcification and calciphylaxis; symptoms of the underlying cause can occur.[3]

Tertiary hyperparathyroidism results from autonomous hypersecretion by the parathyroid gland in patients with long-standing secondary hyperparathyroidism, and often occurs after kidney transplantation.[1,3]

Surgical parathyroidectomy is the **treatment** of choice for symptomatic ***primary hyperparathyroidism.***[1-4,6,8] In patients with asymptomatic primary hyperparathyroidism, no treatment may be necessary, and patients are monitored for serum calcium, serum creatinine, and bone mineral density;[3,5,6,9] the timing of any surgical intervention has been subject to debate.[1,2,4]

In patients for whom surgery is not an option, hypercalcaemia must be controlled. Restriction of dietary calcium is not generally recommended, as this may raise parathyroid hormone levels further.[3,5,6,9,10] While *vitamin D* supplementation may be reasonable in patients with low concentrations of 1,25-dihydroxycholecalciferol, high doses can worsen hypercalcaemia and cause hypercalciuria.[5] Oral *phosphate* supplements have been given in the short-term to alleviate hypercalciuria and hypercalcaemia; intravenous use is no longer recommended.[9] The more potent *bisphosphonates* can be used in the acute management of hypercalcaemia,[9] but seem to be of little benefit in the long-term treatment of hyperparathyroidism.[1,9] However, bisphosphonates such as alendronate may be of use in those patients with low bone mineral density.[3,5,8-12] Although *calcitonins* have a rapid hypocalcaemic effect it is usually short-lived;[9] they are therefore generally given as adjunctive therapy with a bisphosphonate.[2] *Oestrogens* have been reported to increase bone mineral density in postmenopausal women with primary hyperparathyroidism, and to have a small effect on calcium concentrations;[5] however, the high doses needed, and the risks associated with HRT, generally preclude their use.[3,5,6] *Raloxifene*, a selective oestrogen receptor modulator, may be an alternative, having been found to decrease serum calcium and bone turnover in a small, short-term study.[13] Calcium receptor agonists (calcimimetics) may be of benefit in primary hyperparathyroidism by increasing the sensitivity of the calcium-sensing receptor.[5,8-10] In a small dose-finding study,[14] *cinacalcet* decreased serum calcium and lowered parathyroid hormone concentrations without increasing urinary calcium excretion in all dose groups. A larger, placebo-controlled study by the same group found that cinacalcet rapidly normalised serum calcium and modestly decreased parathyroid hormone concentrations; this effect was sustained over 52 weeks.[15] Use of parathyroid hormone peptides to induce autoantibodies against parathyroid hormone resulted in improvement in hypercalcaemia in a woman with parathyroid carcinoma.[16]

Treatment of ***secondary hyperparathyroidism*** is usually aimed at the underlying cause of the hypocalcaemia;[1] early treatment of patients with chronic renal failure can prevent or delay its onset. Treatment is based on appropriate vitamin D replacement and reduction of hyperphosphataemia.[1,3] Oral phosphate binders bind dietary phosphate in the gastrointestinal tract reducing its absorption.[1,3] These have included *calcium salts* such as the carbonate and acetate, which raise serum calcium but carry the risk of inducing hypercalcaemia. *Aluminium hydroxide* also binds phosphate, but can cause osteomalacia (p. 1168.1) and adynamic bone disease (see Renal Osteodystrophy, p. 1170.1). *Sevelamer* is a polymer that does not contain calcium or aluminium, and is capable of binding phosphate.[3] *Vitamin D* compounds that do not require renal hydroxylation for activation, such as calcitriol or its analogue alfacalcidol, are used to lower parathyroid hormone, but the high doses required can induce hypercalcaemia and hyperphosphataemia;[3] newer analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol (see p. 2115.2). *Cinacalcet* is also given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and on haemodialysis. A systematic review[17] of 8 placebo-controlled studies in this patient group concluded that cinacalcet was effective in decreasing concentrations of parathyroid hormone, and serum calcium and phosphorus. However, further studies were needed to ascertain the benefits of calcimimetics over standard therapy and to confirm improvements in patient-based outcomes such as parathyroidectomy rates, fracture, renal osteodystrophy, cardiovascular disease, and mortality.

In patients refractory to medical therapy for secondary hyperparathyroidism, parathyroidectomy may be an option; percutaneous ethanol injection has been used as an alternative.[3,10] Kidney transplantation (p. 1939.2) may cause regression of secondary hyperparathyroidism in some patients, but the condition recurs in about a third of renal graft recipients.[1]

Tertiary hyperparathyroidism is usually treated with surgery.[1,3]

1. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000; **343:** 1863–75. Correction. *ibid.*; **344:** 696.
2. Kearns AE, Thompson GB. Medical and surgical management of hyperparathyroidism. *Mayo Clin Proc* 2002; **77:** 87–91. Correction. *ibid.*; 298.
3. Ahmad R, Hammond JM. Primary, secondary, and tertiary hyperparathyroidism. *Otolaryngol Clin North Am* 2004; **37:** 701–13.
4. AACE/AAES Task Force on Primary Hyperparathyroidism. The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism. *Endocr Pract* 2005; **11:** 49–54. Also available at: http://www.aace.com/pub/pdf/guidelines/HyperparathyroidPS.pdf (accessed 19/06/06)
5. Bilezikian JP, Silverberg SJ. Asymptomatic primary hyperparathyroidism. *N Engl J Med* 2004; **350:** 1746–51.
6. Bilezikian JP, *et al.* Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Miner Res* 2002; **17** (suppl): N2–N11.
7. Al Zahrani A, Levine MA. Primary hyperparathyroidism. *Lancet* 1997; **349:** 1233–8.
8. Vestergaard P. Current pharmacological options for the management of primary hyperparathyroidism. *Drugs* 2006; **66:** 2189–2211.
9. Marcus R. Diagnosis and treatment of hyperparathyroidism. *Rev Endocr Metab Disord* 2000; **1:** 247–52.
10. Farford B, *et al.* Nonsurgical management of primary hyperparathyroidism. *Mayo Clin Proc* 2007; **82:** 351–5. Correction. *ibid.*; 890.
11. Hershman JM, *et al.* Bisphosphonate therapy in primary hyperparathyroidism. *J Bone Miner Res* 2003; **18:** 1889.
12. Khan AA, *et al.* Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3319–25.
13. Rubin MR, *et al.* Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 1174–8.
14. Shoback DM, *et al.* The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 5644–9.
15. Peacock M, *et al.* Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90:** 135–41.
16. Bradwell AR, *et al.* Control o f hypercalcaemia o f parathyroid carcinoma by immunisation. *Lancet* 1999; **353:** 370–3.
17. Strippoli GFM, *et al.* Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 06/01/09).

Hypoparathyroidism

Hypoparathyroidism occurs when there is a deficiency of parathyroid hormone secretion. This may be due to damage or destruction of the glands, e.g. by surgery[1] or disease.[2] Hypoparathyroidism can also arise from auto-immune disease, agenesis of the parathyroid glands (DiGeorge syndrome), defective synthesis of parathyroid hormone (familial hypoparathyroidism), or mutations of the parathyroid and renal calcium-sensing receptors (autosomal dominant hypocalcaemic hypercalciuria) leading to defective regulation of parathyroid hormone secretion.[1,2] Other factors that may lead to a deficiency in parathyroid hormone include hypomagnesaemia and parathyroid adenomas. Where the deficiency results from resistance to parathyroid hormone the condition is termed **pseudohypoparathyroidism**.[1] Parathyroid hormone, as teriparatide, is used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism leads to hypocalcaemia and hyperphosphataemia,[1,3] although in some patients these may not become significant until there is an increased calcium demand, as in pregnancy. Vitamin D deficiency also develops.[1,3] Clinical features reflect the underlying cause of the hypoparathyroidism, but if it occurs rapidly, hypocalcaemia can be acute, with consequent paraesthesia, tetany, and seizures.[1] In chronic hypoparathyroidism, chronic hypocalcaemia may cause cataracts and visual impairment.[1] Hypomagnesaemia and metabolic alkalosis may also occur.[3]

Treatment is aimed at correcting the hypocalcaemia (p. 1778.2) that results mainly from decreased renal tubular calcium resorption.[3] In patients with acute hypocalcaemic tetany parenteral doses of *calcium salts*, along with either oral or parenteral *calcitriol*, may be necessary.[1,3] In those with chronic hypocalcaemia treatment is usually with oral calcium, such as calcium carbonate (which has the advantage of binding phosphate), and vitamin D compounds such as calcitriol (which increase the intestinal absorption of calcium).[1,3] Calcium concentrations and renal function require careful monitoring as resultant hypercalcaemia can cause hypercalciuria, nephrolithiasis, and renal damage.[1] *Thiazide diuretics* may also minimise renal calcium losses.[3] Efficacy of treatment may vary depending on the underlying cause.[1,2]

Teriparatide has been shown to be effective in the treatment of chronic hypoparathyroidism. In 2 studies comparing it with calcium and calcitriol treatment,[4,5] teriparatide maintained serum calcium in the normal range, and decreased urine calcium excretion.

Parathyroid tissue *transplantation* is rarely possible as allografts require immunosuppression. Autografting may result in recurrence of pre-parathyroidectomy hyperparathyroidism.[1] However, good results have been reported after transplantation of parathyroid cells, depleted of antigen-bearing cells, in a few patients with postsurgical hypoparathyroidism.[6,7]

1. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000; **343:** 1863–75. Correction. *ibid.*; **344:** 696.
2. Thakker RV. Genetic developments in hypoparathyroidism. *Lancet* 2001; **357:** 974–6.
3. Pallotti F, *et al.* Diagnostic and therapeutic aspects of iatrogenic hypoparathyroidism. *Tumori* 2003; **89:** 547–9.
4. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism: results of a short-term randomized crossover trial. *JAMA* 1996; **276:** 631–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.
6. Decker GAG, *et al.* Allotransplantation of parathyroid cells. *Lancet* 1995; **345:** 124. Correction. *ibid.*; 464.
7. Hasse C, *et al.* Parathyroid allotransplantation without immunosuppression. *Lancet* 1997; **350:** 1296–7.

Alendronate

ATC — M05BA04.
ATC Vet — QM05BA04.
UNII — X1J18R4W8P.

Alendronic Acid *(BAN, rINN)*

Acide Alendronique; Ácido alendrónico; Acidum Alendronicum; AHButBP; Alendrónico, ácido; Alendronihappo; Alendronik Asit; Alendronsyra; Aminohydroxybutylidene Diphosphonic Acid; Алендроновая Кислота.

4-Amino-1-hydroxybutane-1,1-diylbis(phosphonic acid).

$C_4H_{13}NO_7P_2$=249.1

CAS — 66376-36-1.
ATC — M05BA04.
ATC Vet — QM05BA04.

Alendronate Sodium *(USAN, rINNM)*

Alendronat Sodyum; Alendronate de Sodium; Alendronato sódico; G-704650; L-670452; MK-0217; MK-217; Monosodium alendronate; Natrii Alendronas; Natrii Alendronas Trihydricus; Natrio alendronatas; Natriumalendronaatti; Natriumalendronat; Nátrium-alendronát; Natrium-alendronát trihydrát; Sodium Alendronate (BANM); Sodium, alendronate de; Натрий Алендронат.

Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate trihydrate.

$C_4H_{12}NNaO_7P_2.3H_2O$=325.1

CAS — 121268-17-5.
ATC — M05BA04.
ATC Vet — QM05BA04.
UNII — 2UY4M2U3RA (alendronate sodium trihydrate); 4988K7X26P (anhydrous alendronate sodium).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sodium Alendronate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dichloromethane; very slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0.

USP 36: (Alendronate Sodium). A white, free-flowing powder. Soluble in water; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in isopropyl alcohol; very slightly soluble in dimethyl sulfoxide, in methyl alcohol, and in propylene glycol.

Uses and Administration

Alendronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It is a potent inhibitor of bone resorption and is given in the management of osteoporosis either alone or with vitamin D. Alendronate is used for the treatment of Paget's disease of bone. It has also been given in the treatment of bone metastases and hypercalcaemia of malignancy.

Alendronate is given orally as the sodium salt, but doses are expressed in terms of alendronic acid; alendronate sodium 1.3 mg is equivalent to about 1 mg of alendronic acid. The specific instructions given in Adverse Effects and Precautions, p. 1172.3 should be followed to minimise adverse effects and permit adequate absorption.

The usual dosage for the treatment of **osteoporosis** in men and postmenopausal women is 10 mg daily. Postmenopausal women may be given 5 mg daily for prophylaxis. It may also be given once weekly to postmenopausal women in a dose of 70 mg for treatment of osteoporosis, or 35 mg for prophylaxis. Men with osteoporosis may be treated with 70 mg once weekly.

For the treatment of corticosteroid-induced osteoporosis a dose of 5 mg daily is given; postmenopausal women who do not take HRT should be given 10 mg daily for treatment or prevention.

In adults with **Paget's disease** of bone the usual dose is 40 mg daily for 6 months; treatment may be repeated if necessary after an interval of a further 6 months.

For details of administration in renal impairment, see below.

Alendronate has also been given by intravenous infusion.

Administration. Alendronate once-weekly was considered to be therapeutically equivalent to once-daily dosing in both the treatment[1,2] and prevention[3] of osteoporosis, although the treatment study[1] was considered[4,5] to lack information about other drugs being taken and reasons for withdrawal, and studied bone mineral density, not fracture. Tolerability of a once-weekly regimen was comparable to placebo in one study[6] and to once-daily dosing in another;[7] a review[5] concluded that weekly dosage carried a lower risk of upper gastrointestinal symptoms.

1. Schnitzer T, *et al.* Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)* 2000; **12:** 1–12.
2. The Alendronate Once-Weekly Study Group. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002; **17:** 1988–96.
3. Luckey MM, *et al.* Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. *Obstet Gynecol* 2003; **101:** 711–21.
4. Tsun EC, Heck AM. Intermittent dosing of alendronate. *Ann Pharmacother* 2001; **35:** 1471–5.
5. Sambrook P. Once weekly alendronate. *Drugs Today* 2003; **39:** 339–46.
6. Greenspan S, *et al.* Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2002; **77:** 1044–52.
7. Simon JA, *et al.* Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. *Clin Ther* 2002; **24:** 1871–86.

Administration in renal impairment. Elimination of alendronate is reduced in *rats* with kidney failure and is likely to be reduced in patients with renal impairment. Licensed product information makes the following recommendations for oral dosage based on creatinine clearance (CC):

- mild to moderate renal impairment (CC greater than 35 mL/minute): no dose adjustment needed
- severe renal impairment (CC less than 35 mL/minute): use is not recommended due to lack of experience with alendronate in this population

Charcot neuroarthropathy. Bisphosphonates, including alendronate, have been tried for Charcot neuroarthropathy, see under Bisphosphonates, p. 1174.1.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous alendronate 7.5 mg daily for 3 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Adami S, *et al.* Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; **56:** 201–4.

Gaucher disease. In a placebo-controlled study of patients with Gaucher disease (p. 2433.3), the addition of oral alendronate 40 mg daily to enzyme therapy increased lumbar bone mineral density, but had no effect on focal lesions;[1] the authors concluded that alendronate may be useful adjunctive therapy especially in those patients at risk of osteopenic fracture.

1. Wenstrup RJ, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004; **104:** 1253–7.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. A randomised dose-response study[1] found that single intravenous doses of alendronate 5 mg or more effectively lowered serum-calcium concentrations in patients with tumour-induced hypercalcaemia. Alendronate has also been used to treat hypercalcaemia associated with vitamin D intoxication in children.[2,3]

1. Nussbaum SR, *et al.* Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. *J Clin Oncol* 1993; **11:** 1618–23.
2. Orbak Z, *et al.* Vitamin D intoxication and therapy with alendronate (case report and review of literature). *Eur J Pediatr* 2006; **165:** 583–4.
3. Doneray H, *et al.* Intragastric alendronate therapy in two infants with vitamin D intoxication: a new method. *Clin Toxicol* 2008; **46:** 300–2.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p. 1170.3), but seem to be of little benefit for long-term treatment. In patients with primary hyperparathyroidism, oral alendronate significantly increased bone mineral density, especially at the lumbar spine; virtually all of this gain appeared to occur within the first year of treatment. Alendronate is considered to be useful in those patients for whom parathyroidectomy is not possible.[1-4]

1. Rossini M, *et al.* Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 113–19.
2. Parker CR, *et al.* Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. *J Clin Endocrinol Metab* 2002; **87:** 4482–9.
3. Chow CC, *et al.* Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 581–7.
4. Khan AA, *et al.* Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3319–25.

Malignant neoplasms of the bone. For information on the use of bisphosphonates for metastatic bone disease, see Malignant Neoplasms of the Bone, under Bisphosphonates, p. 1174.1.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including alendronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Alendronate significantly increases bone mineral density (BMD) of the lumbar spine and femoral neck in **postmenopausal women** with osteoporosis;[1,2] it increases vertebral BMD in postmenopausal women without osteoporosis, but not quite to the same extent as HRT.[1]

Continuous long-term therapy appears to be more effective than short-term treatment in terms of skeletal benefits,[1-4] but a residual effect on BMD remains for several years after stopping treatment,[3-5] despite resumption of bone loss after withdrawal of alendronate.[4-6] Studies[7,8] in early postmenopausal women suggested that a *higher initial dosage* might be more effective in terms of BMD gain and residual effect.

The effect of alendronate on fracture risk may depend on *baseline bone mineral density*.[2] Treatment reduced the incidence of new vertebral and nonvertebral fractures in women with prior fractures; in women without prior fractures, alendronate reduced the incidence of clinical fractures in those with osteoporosis,[9] but not in those with higher BMD.[10] A systematic review[11] found that alendronate showed a clinically important benefit in the secondary prevention of all osteoporotic fractures; statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were seen. No significant reductions were found for primary prevention of osteoporotic fractures, but the reduction in vertebral fractures with alendronate was deemed to be clinically important.

Alendronate is also used in **men** with osteoporosis; in a 2-year randomised study, an oral dose of 10 mg daily increased vertebral and nonvertebral BMD and helped prevent vertebral fractures.[12] Oral alendronate 70 mg weekly also increased BMD significantly in osteoporotic men after 1 year when compared to placebo; fracture incidence, not a primary end-point, was similar in both groups.[13]

Alendronate also increases bone mass density in men and women receiving oral **corticosteroids** at doses equivalent to at least 7.5 mg prednisone daily,[14,15] and may be of some benefit in reducing bone loss after heart[16] and liver[17] **transplantation**.

In men with prostate cancer given androgen deprivation therapy, BMD of the spine and hip significantly improved in those given once-weekly alendronate for 1 year compared with those given calcium and vitamin D supplementation alone.[18] A second year of once-weekly alendronate gave continued improvements in BMD, whereas stopping resulted in bone loss and increased bone turnover. A 1-year delay in starting bisphosphonate treatment resulted in smaller gains in BMD compared with those who were given early treatment.[19]

Limited available data suggest that alendronate may be safe and effective for patients with HIV who have decreased BMD.[20]

1. Sharpe M, *et al.* Alendronate: an update of its use in osteoporosis. *Drugs* 2001; **61:** 999–1039.
2. Pérez-López FR. Postmenopausal osteoporosis and alendronate. *Maturitas* 2004; **48:** 179–92.
3. Tonino RP, *et al.* Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000; **85:** 3109–15.
4. Bone HG, *et al.* Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; **350:** 1189–99.
5. Black DM, *et al.* FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; **296:** 2927–38.
6. Ravn P, *et al.* Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. *J Clin Endocrinol Metab* 2000; **85:** 1492–7.
7. Sambrook PN, *et al.* Alendronate in the prevention of osteoporosis: 7-year follow-up. *Osteoporosis Int* 2004; **15:** 483–8.
8. McClung MR, *et al.* Early Postmenopausal Intervention Cohort (EPIC) Group Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab* 2004; **89:** 4879–85.
9. Black DM, *et al.* Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. *J Clin Endocrinol Metab* 2000; **85:** 4118–24.
10. Cummings SR, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:** 2077–82.
11. Wells GA, *et al.* Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
12. Orwoll E, *et al.* Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000; **343:** 604–10.
13. Miller PD, *et al.* Weekly oral alendronic acid in male osteoporosis. *Clin Drug Invest* 2004; **24:** 333–41.
14. Saag KG, *et al.* Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med* 1998; **339:** 292–9.
15. de Nijs RNJ, *et al.* STOP Investigators. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. *N Engl J Med* 2006; **355:** 675–84.
16. Shane E, *et al.* Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. *N Engl J Med* 2004; **350:** 767–76.
17. Atamaz F, *et al.* The prevention of bone fractures after liver transplantation: experience with alendronate treatment. *Transplant Proc* 2006; **38:** 1448–52.
18. Greenspan SL, *et al.* Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 2007; **146:** 416–24.
19. Greenspan SL, *et al.* Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. *J Clin Oncol* 2008; **26:** 4426–34.
20. Lin D, Rieder MJ. Interventions for the treatment of decreased bone mineral density associated with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 15/04/08).

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Oral alendronate 40 mg daily for 6 months was more effective than etidronate or placebo in the treatment of Paget's disease,[1] although an earlier study[2] found a more sustained reduction in biochemical markers with an oral dose of 80 mg daily. Alendronate has also been shown to be as effective as pamidronate in previously untreated patients, but in those who had previously been treated with pamidronate alendronate was markedly more effective in producing biochemical remission.[3]

1. Reid IR, Siris E. Alendronate in the treatment of Paget's disease of bone. *Int J Clin Pract* 1999; **101** (suppl): 62–6.
2. Khan SA, *et al.* Alendronate in the treatment of Paget's disease of bone. *Bone* 1997; **20:** 263–71.
3. Walsh JP, *et al.* A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. *Bone* 2004; **34:** 747–54.

Polymyositis and dermatomyositis. Alendronate has been reported to be effective in the treatment of calcinosis[1] associated with juvenile dermatomyositis (p. 1611.1).

1. Mukamel M, *et al.* New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment. *J Pediatr* 2001; **138:** 763–6.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Gastrointestinal symptoms such as abdominal pain, dyspepsia, diarrhoea or constipation are the most frequent adverse effects with alendronate. Severe oesophageal reactions such as oesophagitis, erosions, ulceration, and stricture have occurred (see p. 1173.1); patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as dysphagia, new or worsening heartburn, pain on swallowing, or retrosternal pain. Peptic ulceration has also been reported.

Alendronate should not be given to patients with abnormalities of the oesophagus or other factors that might delay oesophageal emptying, or those unable to stand or sit upright for at least 30 minutes. It should be used with caution in patients with upper gastrointestinal abnormalities. To minimise the risk of oesophageal reactions:

- patients should be instructed to swallow alendronate tablets whole with plenty of water (not less than 200 mL), in an upright position (standing or sitting). Mineral water with a high concentration of calcium should be avoided
- tablets should be taken on rising for the day, on an empty stomach, at least 30 minutes before breakfast and any other oral medication
- patients should remain upright for at least 30 minutes after taking the tablets, and should not lie down before eating the first meal of the day
- alendronate should not be taken at bedtime, or before getting up for the day

Hypocalcaemia should be corrected before starting alendronate therapy, and other disorders affecting mineral metabolism such as vitamin D deficiency or hypoparathyroidism should also be treated; serum calcium in these patients should be monitored during therapy.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, including alendronate, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including alendronate, see under Bisphosphonates, p. 1175.2.

Effects on the heart. For discussion of a possible increased risk of serious atrial fibrillation with bisphosphonates, including alendronate, see Effects on the Heart, under Bisphosphonates, p. 1175.3.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including alendronate, see under Bisphosphonates, p. 1176.1.

Effects on the liver. Hepatitis[1,2] and hepatocellular damage with raised liver enzyme concentrations[3,4] have been reported after therapy with alendronate.

1. Lieversé RJ. Hepatitis after alendronate. *Neth J Med* 1998; **53:** 271–2.
2. Carrère C, *et al*. Hépatite aiguë sévère imputable á l'alendronate. *Gastroenterol Clin Biol* 2002; **26:** 179–80.
3. Halabe A, *et al*. Liver damage due to alendronate. *N Engl J Med* 2000; **343:** 365.
4. de la Serna Higuera C, *et al*. Lesión hepatocelular inducida por alendronato. *Gastroenterol Hepatol* 2001; **24:** 244–6.

Effects on mental state. Auditory hallucinations and red-coloured visual disturbances were reported[1] in a patient taking alendronate for osteoporosis.

1. Coleman CI, *et al*. Alendronate-induced auditory hallucinations and visual disturbances. *Pharmacotherapy* 2004; **24:** 799–802.

Effects on the musculoskeletal system. A 63-year old woman given alendronate 70 mg once weekly for osteoporosis developed diffuse severe myalgia and transient acute symmetrical polyarthritis 12 hours after ingestion. Symptoms did not recur after stopping the drug.[1] From the initial marketing of alendronate up until November 2002, the FDA had received reports of severe bone, joint, and/or muscle pain in 118 patients, including a child given the drug in error. Of 83 patients for whom information was available, 55 improved after stopping alendronate; in most of these improvement was gradual, although some experienced immediate relief. Nine of these 83 patients had recurrence of pain when given alendronate again. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[2] As of May 2006, 7 cases of synovitis linked to alendronate use had been reported in New Zealand; in one case, severe synovitis caused carpal tunnel syndrome that required urgent decompression.[3]

Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

1. Gerster JC, Nicole F. Acute polyarthritis related to once-weekly alendronate in a woman with osteoporosis. *J Rheumatol* 2004; **31:** 829–30.
2. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; **165:** 346–7.
3. Savage R. Alendronate and inflammatory adverse reactions (issued May 2006). Available at: http://www.medsafe.govt.nz/profs/puarticles/alendinflam.htm#Myalgia (accessed 15/04/08)

Effects on the oesophagus. Between September 1995 and March 1996 the UK CSM had received 10 reports of adverse effects on the oesophagus in patients receiving alendronate sodium.[1] Of these, 4 were of oesophageal reflux, 4 of oesophagitis, and 2 of oesophageal ulceration. As of March 1996, worldwide an estimated 475 000 patients had received alendronate and 199 patients had oesophageal reactions reported to the manufacturer, of which 51 were serious or severe.[2] Endoscopic findings included erosions, ulcerations, exudative inflammation, and thickening of the oesophagus. Bleeding was rare, and oesophageal perforation was not reported. Most oesophageal reactions occurred within 1 week to 2 months of starting alendronate therapy. Recovery occurred when alendronate was stopped; however, it was considered important that patients be followed up for the possible development of strictures.[2] In about 60% of the cases where the information was available, alendronate had not been taken in accordance with the precautions for use (see p. 1172.3).

The CSM subsequently noted[3] that it had continued to receive reports of reactions; by July 1998 there had been 97 reports in the UK, in 1 case associated with a fatality. It was estimated that 1 to 2% of patients might experience oesophageal reactions even when following the precautions for use. Some have reported a much higher incidence of unacceptable upper gastrointestinal symptoms in clinical practice.[4] However, a large placebo-controlled trial of alendronate did not find any increase in upper gastrointestinal events in patients taking alendronate.[5]

1. CSM/MCA. Oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1996; **22:** 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. de Groen PC, *et al*. Esophagitis associated with the use of alendronate. *N Engl J Med* 1996; **335:** 1016–21.
3. CSM/MCA. Reminder: severe oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)
4. Kelly R, Taggart H. Incidence of gastrointestinal side effects due to alendronate is high in clinical practice. *BMJ* 1997; **315:** 1235.
5. Bauer DC, *et al*. Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med* 2000; **160:** 517–25.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare, see p. 1177.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alendronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Like other bisphosphonates, alendronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is about 0.4% when taken half an hour before food, reduced from 0.7% in the fasting state; absorption is negligible when taken up to 2 hours after a meal. Plasma protein binding is about 78%. Bisphosphonates do not appear to be metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

References.

1. Gertz BJ, *et al*. Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther* 1995; **58:** 288–98.
2. Cocquyt V, *et al*. Pharmacokinetics of intravenous alendronate. *J Clin Pharmacol* 1999; **39:** 385–93.
3. Porras AG, *et al*. Pharmacokinetics of alendronate. *Clin Pharmacokinet* 1999; **36:** 315–28.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actimax; Alenato; Arendal; Berlex; Brek; Carmotin†; Dronat; Filxine; Findeclin Combi; Findeclin; Fosamax; Lendronal; Marvil; Oseotenk; Osteobon; Osteofene; Osteonate; Pamoseo; Regenesis; Reyoin†; Rixofem; Silidral; Tilios; ***Austral.***: Adronat; Alendro; Alendrobell; Fosamax; Ossmax; ***Austria***: Alendronstad; Fosamax; ***Belg.***: Beenos; Fosamax; ***Braz.***: Alendil; Alendosseo; Bonalen; Cleveron; Endronax; Endrostan; Fosamax; Minusorb; Ostenan; Osteofar; Osteoform; Osteoral; Terost; ***Canad.***: Fosamax; ***Chile***: Aldrox; Arendal; Fosamax Plus; Fosamax; Fosval; Holadren; Leodrin; Osdren; Oseotal; Oseum; Osteosan†; Pasodron; ***China***: Anlun (安仑); Fosamax (福善美); Gubang (固邦); Tian Ke (天可); ***Cz.***: Aldrion†; Alendrogen; Alenwin; Bonalen†; Fosamax; Fosteofos; Gendron; Lindron†; Ralenost†; Siranin; ***Denm.***: Bonasol; Fosamax; ***Fin.***: Bonasol; Fosamax; ***Fr.***: Fosamax; ***Ger.***: Alendro-Q†; Alendromed; Alendron; Fosamax; Tevabone; Tevanate†; ***Gr.***: Aldromax; Aledrolet; Alefos; Alendo; Alendral; Ampine; Arthroplus; Aurodren; Bestalen; Bonedron; Caltera; Dargol; Debenal; Delfoza; Deparex; Difonate; Discozal; Drofaz; Dronalent; Eldinir; En-Por; Enimon; Farmemax; Forosa; Fosalen; Fosamax; Fosandron; Fosazom; Jamax-S; Ledronin; Lozostun; Meldoz; Moralen; Mosmass; Osaston; Ostalert; Ostaven; Osteonat; Osteos; Ostomax; Porocalm; Promax†; Ridon; Riledron; Tevanate; Tivarun; Zakondronate†; Zemaros; Zulgar; ***Hong Kong***: Allentop; Fosamax; Osteofos; ***Hung.***: Alendis; Alendromax; Alendron; Epolar; Fortimax; Fosamax; Massidron; Sedron; Trabecan; ***India***: Alenost; Bifosa; Denfos; Dronal; Osteofos; ***Indon.***: Alexonal†; Alovell; Fosamax†; Nichospor; Osteofar; Voroste; ***Irl.***: Alendromax; Bonasol; Fosalen; Fosamax; Fostepor; Fostolin; Osteomel; Romax; Steovess; Tevanate; ***Israel***: Alendrovenir; Fosalan; Maxibone; Tevanate; ***Ital.***: Adronat; Alendros; Alenic; Bonasol; Doryx; Dronal; Fosamax; Genalen; Glamor; Loss; Nofrattil; Porodron; Realen; Tevabone; ***Jpn***: Bonalon; Teiroc; ***Malaysia***: Fosamax; ***Mex.***: Alxis; Apodrolen; Blindafe; Dronadil; Drovitan; Fosamax; Fosfacid†; Landrolen†; Lenadrin; Leodrin; Nafadren; Osso; Sinfract; Synostep; Tonadron†; Zondra; ***Neth.***: Alendratol†; Alendris†; Alendronax; Alendronorm†; Bonasol; Dronatex†; Dronatifer†; Fosamax; Ostadil; Ostaham†; Osteonorm; Randronate; Steovess; ***Norw.***: Fosamax; ***NZ***: Fosamax; ***Philipp.***: Forosa; Fosamax; Tevanate; ***Pol.***: Alenato; Alendran; Alendrogen; AlendroLEK†; Densidron; Fosamax; Lindron†; Osalen†; Ostemax; Ostenil; Ostodronic; Ostolek; Rekostin; Sedron; ***Port.***: Adronat; Alehelm; Aleostito; Bifosal; Blocan; Caldronate; Flamisul; Fosamax; Lendral†; Nozat; ***Rus.***: Forosa (Фороза); Fosamax (Фосамакс); Lindron (Линдрон); Ostalon (Осталон); Osterepar (Остерепар); Strongos (Стронгос); Tevanate (Теванат); ***S.Afr.***: Aldren; Boniran; Fosagen; Fosamax; Ostena; Osteobon; Osteonate; ***Singapore***: Fosamax; ***Spain***: Adelan; Alendrocare; Alendrofarm; Alendrogyn†; Alenvir; Bifoal Semanal; Calbion; Fosamax; Lefosan; Semandrol; ***Swed.***: Alenat; Fosamax; ***Switz.***: Alendron; Fosamax; ***Thai.***: Aldren; Bonmax; Fosamax; Ralenost; ***Turk.***: Alemaks; Andante; Bonacton; Bonemax; Fosamax; Osalen; Osteomax; Vegabon; ***UK***: Fosamax; ***Ukr.***: Alendros (Алендрос)†; Ostalon (Осталон); Ostemax (Остемакс); Osteofos (Остеофос); Ralenost (Раленост)†; ***USA***: Fosamax; ***Venez.***: Aldronac; Aliot; Defixal; Fixopan; Fosamax; Osteodur; OsteoMax; Porosal.

Multi-ingredient Preparations. ***Arg.***: Fosamax Plus; Marvil D; Regenesis Max; Silidral Plus; ***Austral.***: Adronat Plus D-Cal; Adronat Plus; Dronalen Plus D-Cal; Dronalen Plus; Fosamax Plus; ***Austria***: Fosavance; ***Belg.***: Fosavance; ***Braz.***: Alendil Calcio D; Fosamax D; ***Canad.***: Fosavance; ***Chile***: Aldrox-D; Arendal D3; Leodrin Plus; ***China***: Fosamax Plus (福美加); ***Cz.***: Adrovance; Fosavance; Vantavo; ***Denm.***: Fosavance; ***Fin.***: Fosavance; ***Fr.***: Adrovance; Fosavance; ***Ger.***: Fosavance; ***Gr.***: Adrovance; Fosavance; ***Hong Kong***: Fosamax Plus; ***Hung.***: Calcisedron-D; Epolar Trio; Fosavance; ***Indon.***: Fosamax Plus; ***Irl.***: Adrovance; Fosavance; Vantavo; ***Israel***: Fosavance; ***Ital.***: Adrovance; Fosavance; ***Malaysia***: Fosamax Plus; ***Mex.***: Fosamax Plus; ***Neth.***: Adrovance; Alenca D3; Alendromed; Bonendro; Fosavance; Vantavo; ***Norw.***: Fosavance; ***NZ***: Fosamax Plus; ***Philipp.***: Fosavance; ***Pol.***: Adrovance; ***Port.***: Adrovance; Fosavance; Vantavo; ***Rus.***: Fosavance (Фосаванс); Ostalon Calcium-D (Осталон Кальций-Д); Tevabone (Тевабон); ***S.Afr.***: Fosavance; ***Singapore***: Fosamax Plus; ***Spain***: Adrovance; Fosavance; ***Swed.***: Fosavance; ***Switz.***: Fosavance; ***Thai.***: Fosamax Plus; Maxmarvil; ***Turk.***: Fosavance; Vegabon Plus D; ***UK***: Fosavance; ***Ukr.***: Ostalon Calcium-D (Осталон Кальций-Д); ***USA***: Fosamax Plus.

Pharmacopoeial Preparations

BP 2014: Alendronic Acid Tablets;
USP 36: Alendronate Sodium Tablets.

Arzoxifene *(rINN)* ⊗

Arzoxifène; Arzoxifeno; Arzoxifenum; LY-353381; Арзоксифен.

2-(*p*-Methoxyphenyl)-3-[*p*-(2-piperidinoethoxy)phenoxy]benzo[*b*]thiophene-6-ol.

$C_{28}H_{29}NO_4S$=475.6

CAS — 182133-25-1.

UNII — E569WG6E60.

Arzoxifene Hydrochloride *(USAN, rINNM)* ⊗

Arzoxifène, Chlorhydrate d'; Arzoxifeni Hydrochloridum; Hidrocloruro de arzoxifeno; SERM-3; Арзоксифена Гидрохлорид.

2-(*p*-Methoxyphenyl)-3-[*p*-(2-piperidinoethoxy)phenoxy]benzo[*b*]thiophene-6-ol hydrochloride.

$C_{28}H_{29}NO_4S,HCl$=512.1

CAS — 182133-27-3.

UNII — FU88PI0433.

Profile

Arzoxifene, like raloxifene (p. 2303.1), is a selective oestrogen receptor modulator; it has been investigated for the prevention and treatment of postmenopausal osteoporosis and to reduce the risk of breast cancer, but results in osteoporosis were disappointing.

References.

1. Deshmane V, *et al*. Phase III double-blind trial of arzoxifene compared with tamoxifen for locally advanced or metastatic breast cancer. *J Clin Oncol* 2007; **25:** 4967–73.

Bisphosphonates

Bifosfonaten; Bifosfonati; Bifosfonatos; Biphosphonates; Bisfosfonater; Bisfosfoniany; Difosfonaten; Difosfonati; Difosfonatos; Diphosphonates; Бифосфонаты.

Bisphosphonates are analogues of pyrophosphate, in which the central oxygen atom is replaced by a carbon atom with two further substituents—see Figure 1, p. 1175. Like pyrophosphate they have a strong affinity for bone. The bisphosphonates are used chiefly for their antiresorptive and hypocalcaemic properties (see Uses and Administration, below).

Uses and Administration

The bisphosphonates inhibit bone resorption and thus have a hypocalcaemic effect. They are pyrophosphate analogues that have a high affinity for the hydroxyapatite of bone, and that inhibit bone resorption by osteoclasts; because of the coupling of resorption and formation this results in an overall reduction in remodelling and bone turnover (see Bone and Bone Disease, p. 1167.1). Their antiresorptive potency varies widely. The bisphosphonates also inhibit the formation and dissolution of hydroxyapatite crystals and thus have the potential to interfere with bone mineralisation. The degree to which the bisphosphonates inhibit mineralisation in clinical practice varies; etidronate is the most potent inhibitor of those now in general clinical use.

Because bone resorption increases plasma-calcium concentrations, the bisphosphonates are used as adjuncts to the treatment of severe hypercalcaemia, especially when associated with malignancy. They are also used in disorders associated with excessive bone resorption and turnover, such as Paget's disease of bone and osteoporosis, as well as in the management of bone metastases. Etidronate has been used in the prevention and treatment of ectopic ossification.

The affinity of bisphosphonates for bone allows complexes labelled with radioactive technetium-99m (see p. 2228.1) to be used diagnostically as bone scanning agents.

Bisphosphonates have been given by intravenous infusion or orally. In the latter case food should be avoided for a suitable period before and after a dose, especially foods with a high calcium content such as milk.

References.
1. Brown DL, Robbins R. Developments in the therapeutic applications of bisphosphonates. *J Clin Pharmacol* 1999; **39:** 651–60.
2. Shoemaker LR. Expanding role of bisphosphonate therapy in children. *J Pediatr* 1999; **134:** 264–7.
3. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* 2003; **9:** 2643–58.
4. Cohen SB. An update on bisphosphonates. *Curr Rheumatol Rep* 2004; **6:** 59–65.
5. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005; **39:** 668–77.
6. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics* 2007; **119** (suppl 2): S150–S162.
7. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. *J Dent Res* 2007; **86:** 1022–33.
8. Russell RG, *et al*. Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci* 2007; **1117:** 209–57.
9. Drake MT, *et al*. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; **83:** 1032–45.

Charcot neuroarthropathy. Six months of treatment with once-weekly alendronate has been reported[1] to improve signs and symptoms of Charcot neuroarthropathy (a sometimes painful deformity in limbs that have lost sensory innervation). Zoledronic acid has also been tried, but was not found to be effective.[2]

1. Pitocco D, *et al*. Six-month treatment with alendronate in acute Charcot neuroarthropathy: a randomized controlled trial. *Diabetes Care* 2005; **28:** 1214–15.
2. Pakarinen T-K, *et al*. The effect of zoledronic acid on the clinical resolution of Charcot neuroarthropathy: a pilot randomized controlled trial. *Diabetes Care* 2011; **34:** 1514–16.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients.

Ectopic ossification. Bisphosphonates that are potent inhibitors of mineralisation such as etidronate have been advocated for prevention of ectopic ossification (p. 103.2), but they do not prevent the formation of the osteoid matrix, and delayed mineralisation may occur once they are withdrawn.

Hypercalcaemia. In patients with severe symptomatic hypercalcaemia restoration and maintenance of adequate hydration and urine flow is essential, and helps to reduce plasma-calcium concentrations by promoting calcium diuresis. In hypercalcaemia of malignancy (p. 1167.2) therapy with inhibitors of bone resorption such as the bisphosphonates is used. Although sustained, the action of bisphosphonates is not particularly rapid; they may be used with a calcitonin where both rapid and prolonged diminution of plasma-calcium concentration is desired.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p. 1170.3), but seem to be of little benefit for long-term treatment.

Juvenile idiopathic arthritis. Bisphosphonates may have a role[1] in preventing low bone mineral density and fragility fractures in children with juvenile idiopathic arthritis (p. 12.1).

1. Thornton J, *et al*. Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child* 2006; **91:** 753–61.

Malignant neoplasms of the bone. There is good evidence that some bisphosphonates are of benefit in **treatment** of patients with metastatic bone disease (see p. 700.3).

Due to the high cumulative doses of bisphosphonates used in cancer patients, there is a higher risk of osteonecrosis of the jaw, see p. 1176.3. Treatment strategies have been suggested to limit the risk of adverse effects while maintaining efficacy. In multiple myeloma (see p. 699.2), some have recommended[1,2] that monthly intravenous bisphosphonate therapy continue for 2 years. After 2 years, therapy can be stopped in those who have achieved a complete response or who are in a stable plateau phase. If disease is still active, frequency of infusion can be decreased to once every 3 months. However, others recommend stopping therapy after 1 year in those with a complete response or very good partial response. For those with a poorer response and ongoing active bone disease, bisphosphonates may be continued for up to 2 years.[3] In newly diagnosed patients, pamidronate is favoured over zoledronate as data suggest the risk of osteonecrosis may be higher with the latter.[1-3] However, routinely switching patients from zoledronate to pamidronate is not recommended, as no data suggest that this will prevent osteonecrosis. Multiple myeloma patients without evidence of skeletal involvement should not routinely be given bisphosphonates.[1]

There is also much interest in the use of bisphosphonates to **prevent** the development of bone metastases; however, preliminary evidence of their efficacy is conflicting. Specific references for the management of bone metastases may be found under the individual drugs.

1. Lacy MQ, *et al*. Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. *Mayo Clin Proc* 2006; **81:** 1047–53.
2. Kyle RA, *et al*. American Society of Clinical Oncology. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; **25:** 2464–72. Also available at: http://jco.ascopubs.org/cgi/reprint/JCO.2007.12.1269v1.pdf (accessed 12/02/09)
3. Durie BGM, *et al*. International Myeloma Working Group. Use of bisphosphonates in multiple myeloma: IMWG response to Mayo Clinic consensus statement. *Mayo Clin Proc* 2007; **82:** 516–7; author reply 517–18.

Malignant neoplasms of the breast. Preliminary data suggested that zoledronate might have antitumour effects that could reduce the risk of breast cancer progression.[1] An analysis[2] of interim results from 2 studies in postmenopausal women treated with letrozole for early breast cancer reported that patients who were also treated with zoledronate from the start had a lower 12-month rate of breast cancer recurrence compared with those who had treatment delayed until bone loss became clinically significant or a fragility fracture occurred. A subsequent study[3] in premenopausal women with oestrogen receptor-positive early breast cancer found that addition of zoledronate to adjuvant endocrine therapy improved disease-free survival at about 4 years, compared with endocrine therapy alone. Epidemiological data have suggested that this may be a class effect. Treatment with oral bisphosphonates for longer than 1 year was found to be associated with a reduced risk of postmenopausal breast cancer in one case-control study.[4] Additionally, a cohort study[5] found a lower incidence of invasive breast cancer in postmenopausal women treated with the oral bisphosphonates alendronate, etidronate, pamidronate, and tiludronate. Fewer oestrogen-positive breast cancers were diagnosed in the bisphosphonate group, and there was a trend towards fewer oestrogen-negative breast cancers; however, the incidence of ductal carcinoma *in situ* was increased, and the authors suggested that bisphosphonates may prevent *in-situ* carcinomas from progressing to invasive cancer. The AZURE study, where 5 years of intravenous zoledronic acid was added to standard chemotherapy or hormonal therapy for premenopausal or postmenopausal women with breast cancer, reported no improvement in overall survival or recurrence with zoledronic acid treatment, although a subgroup of 1100 women who were at least 60 years of age or postmenopausal for more than 5 years had a 29% reduced risk of dying from breast cancer.[6]

1. Lyseng-Williamson KA. Zoledronic acid: a review of its use in breast cancer. *Drugs* 2008; **68:** 2661–82.
2. Brufsky A, *et al*. Z-FAST and ZO-FAST Study Groups. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008; **13:** 503–14.
3. Gnant M, *et al*. ABCSG-12 Trial Investigators. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; **360:** 679–91.
4. Rennert G, *et al*. Use of bisphosphonates and risk of postmenopausal breast cancer. *J Clin Oncol* 2010; **28:** 3577–81.
5. Chlebowski RT, *et al*. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. *J Clin Oncol* 2010; **28:** 3582–90.
6. Voelker R. "Disappointing" trial results offer hope for older women with breast cancer. *JAMA* 2011; **305:** 765–6.

Multiple myeloma. In addition to the beneficial effects of bisphosphonates on skeletal complications from bone metastases in multiple myeloma patients (see also Malignant Neoplasms of the Bone, p. 1193.2), zoledronate was reported to improve overall survival in newly diagnosed patients compared with clodronate.[1]

1. Morgan GJ, *et al*. National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 2010; **376:** 1989–99.

Osteogenesis imperfecta. Bisphosphonates have been tried in osteogenesis imperfecta (p. 1167.3), but orthopaedic treatment and physical activity programmes form the basis of therapy.

Osteoporosis. Bisphosphonates are used first-line in the prevention and treatment of osteoporosis (p. 1168.1). Alendronate, risedronate and cyclical etidronate are used orally; clodronate and ibandronate have been used both orally and parenterally, and ibandronate, pamidronate, and zoledronate by intermittent intravenous infusion. Generally, in the management of **postmenopausal** osteoporosis, bisphosphonates increase bone mineral density (BMD) at both the spine and hip and reduce vertebral fractures; effect on non-vertebral fractures varies.[1,2] Treatment in women at highest risk, with prevalent fractures or low BMD, is considered most effective.[2] In the UK, NICE[3] recommends alendronate for the *primary* prevention of osteoporotic fragility fractures in women with confirmed osteoporosis; postmenopausal women below 65 years must have an independent clinical risk factor for fracture and at least one additional indicator of low BMD, women aged 65 to 69 years must have an independent clinical risk factor for fracture, and women aged 70 years or older must have an independent clinical risk factor for fracture or an indicator of low BMD. Risedronate and etidronate are recommended as alternatives in high-risk women unable to take alendronate. NICE[4] also recommends alendronate for the *secondary* prevention of osteoporotic fragility fractures in postmenopausal women with confirmed osteoporosis who have sustained a clinically apparent fracture; risedronate and etidronate are alternatives in high-risk women unable to take alendronate. Data also suggest that the more severe the osteoporosis, the greater the benefit, and since bone density continues to decline with age, and vertebral fracture incidence rises after age 75, some consider treatment more beneficial in older women.[5] However, others have expressed concern about a possible increase in brittleness of bones with long-term bisphosphonate treatment.[6]

Although there is less evidence for the efficacy of bisphosphonates for the treatment of idiopathic osteoporosis in **men**, some consider them the treatment of choice. A systematic review[7] stated that, while further evaluation of bisphosphonate therapy in **children** with secondary osteoporosis is warranted, evidence does not support their use as standard therapy.

Bisphosphonates are also considered effective at prevention and treatment of **corticosteroid-induced** osteoporosis.[8] Fracture risk (see p. 1616.2) may also be reduced although a systematic review was inconclusive in this respect.[8]

A meta-analysis of bisphosphonate use in the early **post-transplant** period found that they were effective in reducing BMD decline at the lumbar spine; however, prolonged and more intensive treatment may increase the risk of adynamic or low bone turnover disease.[9]

Bisphosphonates are also effective at increasing the BMD at the lumbar spine and hip in patients with **cystic fibrosis**, although the effect on the rate of fractures is not yet clear.[10]

1. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med* 2003; **19:** 395–414.
2. Masud T, Giannini S. Preventing osteoporotic fractures with bisphosphonates: a review of the efficacy and tolerability. *Aging Clin Exp Res* 2003; **15:** 89–98.
3. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 160 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA160guidance.pdf (accessed 12/01/09)
4. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 161 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA161guidance.pdf (accessed 12/01/09)
5. Dhesi JK, *et al*. The implications of a growing evidence base for drug use in elderly patients. Part 4: vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; **61:** 521–8.
6. Ott S. New treatments for brittle bones. *Ann Intern Med* 2004; **141:** 406–7.
7. Ward L, *et al*. Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/04/08).
8. Homik J, *et al*. Bisphosphonates for steroid induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 22/02/05).
9. Mitterbauer C, *et al*. Effects of bisphosphonates on bone loss in the first year after renal transplantation—a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21:** 2275–81.
10. Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 22/10/10).

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease.

Adverse Effects, Treatment, and Precautions

Bisphosphonates may cause gastrointestinal disturbances including abdominal pain, nausea and vomiting, and diarrhoea or constipation. Peptic ulceration has been reported. Existing gastrointestinal problems may be exacerbated, and oral bisphosphonates should generally be given with care or avoided if acute upper gastrointestinal inflammation is present. Gastrointestinal disturbances may be more frequent with aminobisphosphonates such as alendronate, ibandronate, and risedronate; oesophagitis has also occurred. General precautions to minimise the risk of oesophageal reactions, (see under Alendronate, p. 1172.3) should be observed.

Disturbances in serum electrolytes may occur, most commonly hypocalcaemia and hypophosphataemia. Existing hypocalcaemia or other disturbances of bone and mineral metabolism should be effectively treated before starting bisphosphonate therapy. Adequate intake of calcium and vitamin D is important, and supplementation may be needed if dietary intake is insufficient. Bisphos-

Figure 1. Comparative structures of the bisphosphonates.

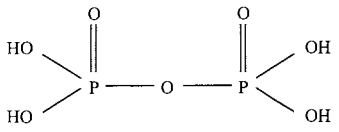

Pyrophosphate

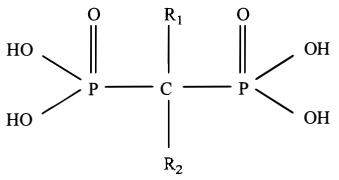

Generic structure of a bisphosphonate

R_1	R_2	Name
$C_3H_6.NH_2$	OH	Alendronic Acid
Cl	Cl	Clodronic Acid
CH_3	OH	Etidronic Acid
$C_2H_4.NCH_3.C_5H_{11}$	OH	Ibandronic Acid
$C_7H_{13}.NH$	H	Incadronic Acid
H	H	Medronic Acid
$CH_2.C_7H_5N_2$	OH	Minodronic Acid
$C_5H_{10}.NH_2$	OH	Neridronic Acid
H	OH	Oxidronic Acid
$C_2H_4.NH_2$	OH	Pamidronic Acid
$CH_2.C_5H_4N$	OH	Risedronic Acid
$S.C_6H_4Cl$	H	Tiludronic Acid
$CH_2.C_3H_3N_2$	OH	Zoledronic Acid

phonates may cause musculoskeletal pain (which can be severe and incapacitating), osteonecrosis of the jaw (see also Dental Care, below), ocular disturbances, and headache. Hypersensitivity reactions have occurred rarely; angioedema, rashes, urticaria, and pruritus have been reported. Other rare adverse effects include blood disorders such as anaemia, thrombocytopenia, leucopenia and disturbances in liver enzyme values.

Transient fever and flu-like symptoms have been reported, usually at the start of treatment, and are common with infusions of ibandronate, pamidronate, and zoledronate. There may be local reactions, including thrombophlebitis, after parenteral doses. Dizziness, vertigo, asthenia, peripheral oedema, paraesthesia, taste disturbances, and joint disorders have also occurred.

Impairment of renal function has been reported with bisphosphonates, particularly when given parenterally. As a result their use should generally be avoided in patients with moderate to severe renal impairment and they should be used with care in those with lesser degrees of renal impairment.

Etidronate interferes with bone mineralisation, especially at higher doses, which can result in osteomalacia and an increased incidence of fracture. Etidronate should be stopped if a fracture occurs, until healing is complete. It has also been associated with a flare in bone pain in some patients with Paget's disease. Impaired mineralisation is much less marked at usual doses of other bisphosphonates.

Overdosage with bisphosphonates would be likely to result in symptoms of hypocalcaemia; if necessary, parenteral infusion of a calcium salt could be given. Giving milk or antacids, to bind the bisphosphonate and minimise absorption, has been suggested for oral overdosage.

There is little clinical experience with bisphosphonates in pregnancy and they are generally contra-indicated; bisphosphonates have been associated with skeletal abnormalities in the fetus when given to pregnant *animals*.

Reviews.

1. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol* 2006; **17:** 897–907.
2. Bobba RS, *et al*. Tolerability of different dosing regimens of bisphosphonates for the treatment of osteoporosis and malignant bone disease. *Drug Safety* 2006; **29:** 1133–52.
3. Strampel W, *et al*. Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Safety* 2007; **30:** 755–63.
4. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc* 2009; **84:** 632–7.

Carcinogenicity. There have been infrequent reports of oesophageal cancer in patients who had taken oral bisphosphonates, particularly alendronate.[1] Some also had Barrett's oesophagus, and it has been suggested that oral bisphosphonates are contra-indicated in such patients (oral bisphosphonates should generally be used with care or avoided where acute upper gastrointestinal inflammation is present, see p. 1174.3).

Further investigation has produced conflicting results. A nested case-control study[2] using data from the UK General Practice Research Database found an increased risk of oesophageal cancer in those taking oral bisphosphonates (alendronate, etidronate, and risedronate) over an average of 7.5 years of follow-up. This increased risk was mainly restricted to those with 10 or more prescriptions or those who were treated for 3 years or more, and did not vary between the different bisphosphonates. In contrast, a cohort study[3] using the same database did not find any association between oral bisphosphonates and oesophageal cancer over 4.5 years of follow-up, although differences in design may explain the discrepancies between the 2 studies.[4]

An increased incidence of ductal carcinoma *in situ* has been reported with bisphosphonate use, see Malignant Neoplasms of the Breast, under Uses and Administration, p. 1174.2.

1. Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 2009; **360:** 89–90.
2. Green J, *et al*. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. *BMJ* 2010; **341:** c4444.
3. Cardwell CR, *et al*. Exposure to oral bisphosphonates and risk of esophageal cancer. *JAMA* 2010; **304:** 657–63.
4. Wysowski DK. Oral bisphosphonates and oesophageal cancer. *BMJ* 2010; **341:** 516–17.

Dental care. Osteonecrosis of the jaw has been reported in patients given bisphosphonates (see p. 1176.3). Of the published cases most were associated with intravenous therapy in cancer patients, although some have followed oral therapy in patients with osteoporosis. In many cases the effect followed dental surgery. The Adverse Drug Reactions Advisory Committee in Australia has recommended that all patients scheduled to receive intravenous bisphosphonates should have a dental review,[1] and that any dental procedures be completed before beginning the drug.[1,2] Furthermore, health professionals should be aware of the presenting clinical features of osteonecrosis.[2] In the UK, the MHRA has recommended a dental review before bisphosphonate treatment in patients with cancer; other patients only require a dental review if they have poor dental status. During treatment, patients should maintain good oral hygiene, have regular check-ups, and report any oral symptoms.[3] Licensed information for some bisphosphonates has been amended in several countries to include warnings that all patients with potential risk factors for osteonecrosis of the jaw have a dental review before treatment.[4]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and osteonecrosis of the jaw. *Aust Adverse Drug React Bull* 2005; **24:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.pdf (accessed 30/11/06)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Osteonecrosis of the jaw (ONJ) with bisphosphonates. *Aust Adverse Drug React Bull* 2006; **25:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 30/11/06)
3. MHRA/CHM. Bisphosphonates: osteonecrosis of the jaw. *Drug Safety Update* 2009; **3** (4): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON062549&RevisionSelectionMethod=LatestReleased (accessed 19/02/10)
4. Tarassoff P, Hei Y-J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; **353:** 101–102. Correction. *ibid.*; 2728.

Effects on the ears. For mention of ototoxicity associated with the use of etidronate in 2 patients with pre-existing otosclerosis, and a recommendation that such patients be monitored when given bisphosphonates, see p. 1183.3. For similar effects with pamidronate, see p. 1188.1.

Effects on the eyes. Ocular effects have been associated with bisphosphonates and although reactions to pamidronate appeared to be rare, the manufacturers were aware of 23 cases up to September 1993 that were possibly associated with the drug.[1] The reactions included anterior uveitis in 7 patients and unilateral episcleritis or scleritis in 3. In one previously reported case,[2] bilateral iritis was associated with risedronate and subsequently pamidronate in a patient who had earlier received etidronate without ill-effect. There have been subsequent reports of unilateral and bilateral scleritis with pamidronate, requiring the drug to be stopped.[3] Anterior[3,4] and posterior[5] uveitis have continued to be reported, and more recently, diplopia with conjunctival swelling and eyelid oedema.[6,7] Similarly, alendronate[8-11] and zoledronate[12] have been associated with scleritis and anterior uveitis. Zoledronic acid has also been associated with orbital pain and swelling.[13] Scleritis,[14] episcleritis,[15] and uveitis[16] have also been reported with risedronate, and bilateral anterior uveitis with clodronate.[17] Non-specific conjunctivitis and abnormal or blurred vision have occurred with most of the bisphosphonates, including etidronate.[14] Dry eye, sore eye, and conjunctivitis were the most frequently reported ophthalmological events assessed as related to risedronate therapy in a prescription-event monitoring study in England.[18] The Australian Adverse Drug Reactions Advisory Committee was aware of 38 reports of serious ocular reactions to bisphosphonates as of April 2004; these were associated with pamidronate or alendronate in 18 cases each, and risedronate or zoledronate in 1 case each.[16] Most reports were of inflammatory reactions such as uveitis, iritis, scleritis, episcleritis, or optic neuritis, and occurred a median of 3 weeks after starting therapy. The risk might be higher with intravenous bisphosphonates, but the frequency of reports was thought to relate mostly to usage.[16] Acute retinal pigment epitheliitis has been reported after an intravenous infusion of zoledronate.[19] Patients who have ocular pain or vision loss while taking bisphosphonates should have the drug stopped and be referred to an ophthalmologist.[14]

1. Macarol V, Fraunfelder FT. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol* 1994; **118:** 220–4.
2. Siris ES. Bisphosphonates and iritis. *Lancet* 1993; **341:** 436–7.
3. Fraunfelder FW, *et al*. Scleritis and other ocular side effects associated with pamidronate disodium. *Am J Ophthalmol* 2003; **135:** 219–22.
4. Rey J, *et al*. Uveitis, an under-recognized adverse effect of pamidronate: case report and literature review. *Joint Bone Spine* 2000; **67:** 337–40.
5. Haverbeke G, *et al*. Posterior uveitis: an under-recognized adverse effect of pamidronate: 2 case reports. *Bull Soc Belge Ophtalmol* 2003; **290:** 71–6.
6. Meaney TPJ, *et al*. Diplopia following intravenous administration of pamidronate. *Eye* 2004; **18:** 103–4.
7. Ryan PJ, Sampath R. Idiopathic orbital inflammation following intravenous pamidronate. *Rheumatology (Oxford)* 2001; **40:** 956–7.
8. Mbekeani JN, *et al*. Ocular inflammation associated with alendronate therapy. *Arch Ophthalmol* 1999; **117:** 837–8.
9. Malik AR, *et al*. Bilateral acute anterior uveitis after alendronate. *Br J Ophthalmol* 2002; **86:** 1443.
10. Salmen S, *et al*. Nongranulomatous anterior uveitis associated with alendronate therapy. *Invest Clin* 2002; **43:** 49–52.
11. Asensio Sánchez VM, *et al*. Bifosfonatos e inflamación intraocular. *Arch Soc Esp Oftalmol* 2004; **79:** 85–8.
12. Moore MM, Beith JM. Acute unilateral anterior uveitis and scleritis following a single infusion of zoledronate for metastatic breast cancer. *Med J Aust* 2008; **188:** 370–1.
13. Sharma NS, *et al*. Zoledronic acid infusion and orbital inflammatory disease. *N Engl J Med* 2008; **359:** 1410–11.
14. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. *N Engl J Med* 2003; **348:** 1187–8.
15. Viñas G, *et al*. Episcleritis secundaria a risedronato. *Med Clin (Barc)* 2002; **118:** 598–9.
16. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and ocular inflammation. *Aust Adverse Drug React Bull* 2004; **23:** 7–8. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0404.htm (accessed 22/02/05)
17. Fietta P, *et al*. Clodronate induced uveitis. *Ann Rheum Dis* 2003; **62:** 378.
18. Aurich-Barrera B, *et al*. Ophthalmological events in patients receiving risedronate: summary of information gained through follow-up in a prescription-event monitoring study in England. *Drug Safety* 2006; **29:** 151–60.
19. Gilhotra JS, *et al*. Acute retinal pigment epitheliitis associated with intravenous bisphosphonate. *Br J Ophthalmol* 2006; **90:** 798–9.

Effects on the heart. In a study of once-yearly zoledronate for the treatment of postmenopausal osteoporosis, the number of patients who had arrhythmia in the zoledronate group was significantly higher than that in the placebo group.[1] An increased incidence of serious atrial fibrillation was also seen in the zoledronate group. Fifty patients in the zoledronate group had serious atrial fibrillation, compared with 20 patients in the placebo group. Among the 50 patients, the events occurred more than 30 days after infusion in 47 patients, by which time zoledronate would be undetectable in the circulation. The mechanism by which bisphosphonates might cause arrhythmia or atrial fibrillation is unclear; little or no effect on serum calcium concentrations was seen when measured 9 to 11 days after zoledronate infusion.

In an analysis[2] of a randomised study of alendronate in postmenopausal women with osteoporosis, 47 serious atrial fibrillation adverse events were reported in the alendronate group, compared with 31 events among those receiving placebo. There was no increased risk of all atrial fibrillation adverse events.

Although the observed association might have been due to chance,[1] it was felt that the possibility of an increased risk of atrial fibrillation with bisphosphonates should be explored.[2] Two case-control studies examining the association[3,4] came to opposite conclusions as to whether bisphosphonate treatment increased the risk of atrial fibrillation. A systematic review[5] did not find an association between bisphosphonate use (alendronate, risedronate, and zoledronate) and all atrial fibrillation events, stroke, or cardiovascular mortality; however, serious atrial fibrillation events were more common with bisphosphonates than placebo. In the UK, the MHRA stated in July 2008 that any risk appeared low and the balance of risk and benefit for bisphosphonates remained favourable.[6] The FDA in the USA examined study data for 38 045 patients who were treated with either bisphosphonates or placebo,[7] and found that atrial fibrillation was rare. Although one large study showed a significant increase in the rate of serious atrial fibrillation events, across all studies no clear association

between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was seen. Increasing dose or duration of therapy was also not associated with an increased rate of atrial fibrillation.

1. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.
2. Cummings SR, *et al.* Alendronate and atrial fibrillation. *N Engl J Med* 2007; **356:** 1895–6.
3. Heckbert SR, *et al.* Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med* 2008; **168:** 826–31.
4. Sørensen HT, *et al.* Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ* 2008; **336:** 813–16.
5. Loke YK, *et al.* Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. *Drug Safety* 2009; **32:** 219–28.
6. MHRA/CHM. Bisphosphonates: atrial fibrillation. *Drug Safety Update* 2008; **1** (12): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased (accessed 16/07/08)
7. FDA. Update of safety review follow-up to the October 1, 2007 early communication about the ongoing safety review of bisphosphonates: (bisphosphonates: alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel W/Calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa)) (issued 12th November 2008). Available at: http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm (accessed 07/01/09)

Effects on the kidneys. Renal failure was associated with the intravenous use of etidronate in 2 patients with hypercalcaemia of malignancy.[1] One had been given a high dose (1 g) by short intravenous infusion on two successive days and the other had an elevated serum-creatinine concentration before treatment. A third patient given clodronate, who also developed renal failure, also had a slightly raised serum-creatinine concentration beforehand. Others[2] commented that with smaller doses of etidronate or clodronate (up to 300 mg daily) by intravenous infusion over 2 to 3 hours, renal impairment had not been seen in more than 40 patients treated. They noted a trend towards raised creatinine concentrations which was reversed when etidronate infusions were stopped. Another group[3] found increased serum-creatinine concentrations after the first infusion of etidronate when compared with placebo, but not after subsequent infusions. An overdose of parenteral etidronate led to acute renal failure in one patient.[4] Pamidronate has been associated with nephrotoxicity,[5] proteinuria,[6] acute tubular necrosis,[7,8] and collapsing focal segmental glomerulosclerosis.[9] Zoledronic acid has been associated with reports of renal impairment, occasionally after a single dose. Acute renal failure requiring dialysis or with a fatal outcome has occurred, particularly in patients with pre-existing renal impairment or other risk factors including advanced age, dehydration, or use of other nephrotoxic drugs or diuretics.[10-12] Health Canada reported that as of April 2010, Novartis had received 265 reports of renal impairment after use of one zoledronic acid preparation (*Aclasta*) corresponding to a reporting rate of about 20 cases per 100 000 patient-years of exposure.[10] Six cases of acute tubular necrosis have been reported with zoledronate;[13] all patients had received pamidronate on previous occasions, and most had mildly raised baseline serum creatinine. While pamidronate may have potentiated the renal toxicity seen with zoledronate, the authors noted that the patterns of nephrotoxicity differ between the 2 drugs. Reports to the Australian Adverse Drug Reactions Advisory Committee have suggested that renal failure or renal impairment may occur more often with zoledronate than with other bisphosphonates.[14] There has also been a report of acute renal failure with alendronate treatment in a patient with myeloma,[15] and with tiludronate in a patient treated for hypercalcaemia of malignancy.[16]

1. Bounameaux HM, *et al.* Renal failure associated with intravenous diphosphonates. *Lancet* 1983; **i:** 471.
2. Kanis JA, *et al.* Effects of intravenous diphosphonates on renal function. *Lancet* 1983; **i:** 1328.
3. Hasling C, *et al.* Etidronate disodium for treating hypercalcaemia of malignancy: a double blind placebo-controlled study. *Eur J Clin Invest* 1986; **16:** 433–7.
4. O'Sullivan TL, *et al.* Acute renal failure associated with the administration of parenteral etidronate. *Ren Fail* 1994; **16:** 767–73.
5. Lockridge L, *et al.* Pamidronate-associated nephrotoxicity in a patient with Langerhans' histiocytosis. *Am J Kidney Dis* 2002; **40:** E2.
6. Desikan R, *et al.* Nephrotic proteinuria associated with high-dose pamidronate in multiple myeloma. *Br J Haematol* 2002; **119:** 496–9.
7. Banerjee D, *et al.* Short-term, high-dose pamidronate-induced acute tubular necrosis: the postulated mechanisms of bisphosphonate nephrotoxicity. *Am J Kidney Dis* 2003; **41:** E18.
8. Smetana S, *et al.* Pamidronate-induced nephrotoxic tubular necrosis—a case report. *Clin Nephrol* 2004; **61:** 63–7.
9. Markowitz GS, *et al.* Nephrotic syndrome after treatment with pamidronate. *Am J Kidney Dis* 2002; **39:** 1118–22.
10. Novartis. Health Canada endorsed important safety information on Aclasta (zoledronic acid) (issued 12th October, 2010). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2010/aclasta_hpc-cps-eng.pdf (accessed 23/09/11)
11. MHRA. Intravenous zoledronic acid: adverse effects on renal function. *Drug Safety Update* 2010; **3**(9): 6–7. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con076503.pdf (accessed 23/09/11)
12. FDA. Zoledronic acid for osteoporosis (marketed as Reclast): renal impairment and acute renal failure. *Drug Safety Newsletter* 2009; **2** (2): 13–15. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/UCM168579.pdf (accessed 23/09/11)
13. Markowitz GS, *et al.* Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 2003; **64:** 281–9.
14. Adverse Drug Reactions Advisory Committee (ADRAC). Renal impairment with zoledronic acid. *Aust Adverse Drug React Bull* 2007; **26:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0710.htm (accessed 06/11/07)
15. Zazgornik J, *et al.* Acute renal failure and alendronate. *Nephrol Dial Transplant* 1997; **12:** 2797–8.
16. Dumon JC, *et al.* Efficacy and safety of the bisphosphonate tiludronate for the treatment of tumor-associated hypercalcemia. *Bone Miner* 1991; **15:** 257–66.

Effects on the musculoskeletal system. Two types of musculoskeletal reactions have been reported with bisphosphonates. The FDA[1] has highlighted the possibility of severe and sometimes incapacitating bone, joint, and/or muscle **pain** that can occur within days, months, or years of starting bisphosphonate treatment. Symptoms may resolve quickly, slowly, or not at all after stopping the bisphosphonate. This is in contrast to the **acute phase response** that can occur after the first dose of an aminobisphosphonate;[2-5] arthralgia, myalgia, and bone pain are accompanied by fever, chills, fatigue, and malaise. A study to characterise the acute phase response occurring up to 3 days after zoledronate infusion found inflammatory changes in many body systems, including the joints, gastrointestinal tract, eyes, upper-respiratory tract, and possibly the skin, as well as the more non-specific symptoms of headache, fever, and fatigue.[5] Symptoms are transient and self-limiting, usually lasting 1 to 3 days, and either do not recur[2] or lessen with further doses.[4,5] Reactions were more common in younger patients, those taking NSAIDs, and those with pre-existing back pain, and less common in smokers, diabetics, those also on calcitonin, and those with previous exposure to bisphosphonates.[5] Acute phase responses are usually associated with intravenous administration, but have also occurred with oral bisphosphonates. The nitrogen-containing aminobisphosphonates seem to cause this reaction by inhibiting the mevalonate pathway, inducing the release of proinflammatory cytokines such as tumour necrosis factor α and interleukin-6.[2]

1. FDA. Information for healthcare professionals: Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) (issued 07/01/08). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/bisphosphonatesHCP.htm (accessed 19/01/09)
2. Strampel W, *et al.* Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Safety* 2007; **30:** 755–63.
3. Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. *J Oncol Pharm Pract* 2007; **13:** 223–9.
4. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol* 2006; **17:** 897–907.
5. Reid IR, *et al.* Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab* 2010; **95:** 4380–7.

ATYPICAL FRACTURES. A link has been suggested between prolonged alendronate treatment (usually between 1 and 10 years) and low-impact or spontaneous, non-spinal, atypical fractures.[1-6] Although most of the reported cases of such fractures have occurred in women taking alendronate, the most commonly prescribed bisphosphonate, such fractures have also been reported with ibandronate, risedronate, and zoledronate.[7] These fractures have been defined as atypical by their location in the subtrochanteric region and femoral shaft, transverse or oblique orientation, minimal or no associated trauma, and absence of comminution (breakage into several pieces). Other associated features include cortical thickening and a tendency to be bilateral.[8] Prodromal symptoms such as thigh pain, vague discomfort, and subjective weakness have been reported.[3,8] Although the oversuppression of bone turnover by the drug could explain these fractures,[1,2,9] non-adherence to bisphosphonate therapy has also been suggested as a possible cause,[9] and factors such as chronic corticosteroid use, oestrogen therapy, or parathyroid insufficiency could also contribute.[1]

In contrast to a case-control study[5] which found that prolonged bisphosphonate use for more than 5 years was associated with atypical fractures of the femoral shaft, a cohort study[10] found that patients with atypical fractures were no more likely to be on alendronate than patients with more typical osteoporotic hip fractures, and the pattern of occurrence was similar for all fracture types. Furthermore, the risk of fracture was reduced by high adherence to alendronate treatment, suggesting that the cause of atypical fractures was more likely to be osteoporosis than bisphosphonates therapy. Epidemiological studies have also shown no increased incidence of atypical fractures since bisphosphonates were approved for osteoporosis,[11] and a secondary analysis of 3 large studies found no increased risk associated with bisphosphonates even after 10 years of treatment, although the occurrence of such fractures was very rare which prevented definitive conclusions from being drawn.[7] Nonetheless, in the USA the FDA has recommended[12] that all bisphosphonates used in the treatment of osteoporosis should carry a warning of the potential risk of atypical fracture of the femur.

The management of atypical fractures thought to be associated with bisphosphonate therapy is not established. Drug holidays, once initial bisphosphonate therapy has lowered the osteoporotic fracture risk, have been considered as a possible way to reduce the risk of atypical fractures.[8,13] The positive effect bisphosphonates have on fracture risk appears to be sustained for a period after stopping treatment, and a drug holiday of between 2 to 5 years after an initial treatment period of 2 to 3 years has been suggested.[13] Although fracture healing has been reported during continued alendronate treatment,[9] some recommend stopping bisphosphonates if atypical fracture occurs.[8] Patients may have delayed or absent healing even once alendronate is stopped,[1] and the associated morbidity can be high. Surgical intervention may be required.[8] Alternative treatment with the anabolic agent teriparatide may be considered,[8,14] particularly if there is little evidence of healing 4 to 6 weeks post-surgery.[8]

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4. Ing-Lorenzini K, *et al.* Low-energy femoral fractures associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. *Drug Safety* 2009; **32:** 775–85.
5. Lenart BA, *et al.* Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int* 2009; **20:** 1353–62.
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7. Black DM, *et al.* HORIZON Pivotal Fracture Trial Steering Committee. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med* 2010; **362:** 1761–71.
8. Shane E, *et al.* Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2010; **25:** 2267–94. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf (accessed 21/10/10)
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10. Abrahamsen B, *et al.* Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res* 2009; **24:** 1095–1102.
11. Shane E. Evolving data about subtrochanteric fractures and bisphosphonates. *N Engl J Med* 2010; **362:** 1825–7.
12. FDA. FDA Drug Safety Communication: safety update for osteoporosis drugs, bisphosphonates, and atypical fractures (issued 13/10/2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm (accessed 16/11/10)
13. Schmidt GA, *et al.* Risks and benefits of long-term bisphosphonate therapy. *Am J Health-Syst Pharm* 2010; **67:** 994–1001.
14. Lenart BA, *et al.* More on atypical fractures of the femoral diaphysis. *N Engl J Med* 2008; **359:** 317–18.

OSTEONECROSIS. Osteonecrosis of the jaw has been reported with the use of some bisphosphonates.[1-4] The majority of reports have been in cancer patients treated with intravenous bisphosphonates who were also receiving chemotherapy and corticosteroids. However, osteonecrosis has also been reported in patients receiving oral bisphosphonates for osteoporosis or Paget's disease although the risk appears to be low.[5,6] Most cases have been associated with dental procedures such as tooth extraction, and many patients had local infection including osteomyelitis.[2,3] Presenting features may include altered local sensation, maxillofacial pain, toothache, denture sore spots, loose teeth, exposed bone or impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour.[3] Osteonecrosis occurs more frequently in the mandible than the maxilla;[5,6] avascular necrosis of the hip[7] and osteonecrosis of the auditory canal has also been reported.[8]

Bisphosphonate-associated osteonecrosis of the jaw has since been defined as exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks in those treated with a bisphosphonate who have not received radiotherapy to the jaw.[5,6,9] A history of dental problems, such as infection, invasive dental procedures, periodontal disease or poor dental hygiene, or the presence of dental implants or dentures may exacerbate the problem. Other possible *risk* factors include oral trauma, tobacco use, increasing age, or comorbid conditions such as diabetes or obesity.[5,6] Anti-angiogenic agents such as bevacizumab and sunitinib (see p. 748.2 and p. 859.2, respectively) may contribute to oral mucosal breakdown and subsequent development of osteonecrosis of the jaw. For recommendations on dental care in patients prescribed bisphosphonates see p. 1175.2. However, the most important risk factor for the development of osteonecrosis is considered to be bisphosphonate exposure.

Osteonecrosis occurs more frequently in patients treated with intravenous bisphosphonates than with oral. The cumulative dose is also considered to be significant, and the risk of osteonecrosis increases with the dose and duration of intravenous therapy.[5] Furthermore, the type of bisphosphonate used may affect the risk; higher potency nitrogen-containing bisphosphonates appear to present the highest risk,[5,10] and there is some suggestion that the risk may be higher with zoledronate than with pamidronate.[5] Although certain cancers, such as breast cancer and multiple myeloma, have been associated with a higher incidence of osteonecrosis,[11] the potency of the bisphosphonate, the

route used, and the cumulative dose appear to be of greater importance than the indication for treatment, and the increased risk of osteonecrosis in cancer patients is thought to be related to the higher cumulative doses given.[5,11]

Proposed *mechanisms* by which bisphosphonates induce osteonecrosis include excessive reduction of bone turnover, immunomodulation, infection, and impairment of angiogenesis.[5]

Measures for *prevention* include a pre-treatment dental exam and good dental hygiene during treatment, see Dental Care, p. 1175.2. Once osteonecrosis has developed, however, no effective treatment is known and *management* is conservative and according to severity. Control of pain and infection is important, and surgical debridement or resection of necrotic bone is used for advanced lesions.[6,9] Stopping bisphosphonate therapy does not necessarily promote healing of the necrotic process[4,10] and recovery of normal osteoclast function and bone turnover may be gradual.[12] However, some have suggested that long-term stoppage of intravenous treatment may allow lesions to stabilise and reduce symptoms, and breaks of 6 to 12 months in oral therapy may allow better resolution after debridement.[6] In 97 multiple myeloma patients who were observed for at least 3.2 years after bisphosphonate-related osteonecrosis of the jaw, osteonecrosis resolved in 62%, resolved and then recurred in 12%, and did not resolve over a follow-up period of at least 9 months in 26%.[13] Recurrence was precipitated by restarting bisphosphonate treatment or by dental procedures and could be at the same or a different site. The authors of the study suggested that multiple myeloma patients who develop osteonecrosis of the jaw after dental procedures can restart bisphosphonate therapy if skeletal-related events develop; however, patients with spontaneous osteonecrosis had a higher risk of recurrence and permanent interruption of bisphosphonate treatment may be justified. For further recommendations regarding bisphosphonate use in multiple myeloma, see Malignant Neoplasms of the Bone, under Uses and Administration, p. 1174.1.

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12. Woo S-B, *et al.* Narrative review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; **144:** 753–61. Correction. *ibid.*; **145:** 235. [title]
13. Badros A, *et al.* Natural history of osteonecrosis of the jaw in patients with multiple myeloma. *J Clin Oncol* 2008; **26:** 5904–9.

Effects on the respiratory system. Bronchospasm induced by bisphosphonates has been reported in 2 patients who were aspirin-sensitive asthmatics. The first patient complained of shortness of breath and wheezing 10 minutes after the start of an infusion of clodronate while the second developed similar symptoms 2 days after the start of cyclical therapy with oral etidronate. Oral rechallenge in both patients resulted in a fall in the forced expiratory values at 1 second.[1] The reaction in these 2 patients was not considered to be immune-mediated. Risedronate reportedly induced bronchiolitis obliterans organising pneumonia in a patient with sarcoidosis.[2]

For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, under Etidronate, p. 1183.3.

1. Rolla G, *et al.* Bisphosphonate-induced bronchoconstriction in aspirin-sensitive asthma. *Lancet* 1994; **343:** 426–7.
2. Arai T, *et al.* Risedronate induced BOOP complicated with sarcoidosis. *Thorax* 2005; **60:** 613–14.

Hypersensitivity. Bisphosphonates may rarely cause hypersensitivity reactions such as angioedema, urticaria, and pruritus. Reports include a severe allergic reaction to medronate disodium when given as a radiopharmaceutical,[1] and mild skin rashes in 2 patients given oral pamidronate.[2] There has also been a report of erythroderma with lesions of the mucous membranes associated with use of clodronate in one patient,[3] and severe epidermal necrosis may have been associated with tiludronate in another.[4] A possibly drug-related rash has also been reported in a patient receiving alendronate.[5] Other cutaneous reactions reported with alendronate include urticaria,[6] erythematous papules and petechiae,[7] gyrate erythema,[8] and drug-induced lichen planus;[9] licensed product information states that Stevens-Johnson syndrome has been reported. Two patients with cutaneous reactions to pamidronate or clodronate were able to continue oral clodronate after desensitisation.[10] Licensed product information states that zoledronate has been associated with rare reports of hypersensitivity, including angioedema and bronchoconstriction, and very rarely, with anaphylaxis.

1. Elliott AT, *et al.* Severe reaction to diphosphonate: implications for treatment of Paget's disease. *BMJ* 1988; **297:** 592–3.
2. Mautalen CA, *et al.* Side effects of disodium aminohydroxypropylidenediphosphonate (APD) during treatment of bone diseases. *BMJ* 1984; **288:** 828–9.
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4. Roux C, *et al.* Long-lasting dermatological lesions after tiludronate therapy. *Calcif Tissue Int* 1992; **50:** 378–80.
5. Chesnut CH, *et al.* Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995; **99:** 144–52.
6. Kontoleon P, *et al.* Urticaria after administration of alendronate. *Acta Derm Venereol* 2000; **80:** 398.
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9. Lazarov A, *et al.* Alendronate-induced lichen planus. *Isr Med Assoc J* 2002; **4:** 389–90.
10. Phillips EJ, *et al.* Allergic reactions to bisphosphonates: a report of three cases and an approach to management. *J Clin Pharmacol* 1998; **38:** 842–86.

Interactions

The bisphosphonates are not well absorbed from the gastrointestinal tract, and dosage with food further impairs their absorption.

Compounds containing aluminium, calcium, iron, or magnesium, including antacids and mineral supplements and some osmotic laxatives, can also impair the absorption of bisphosphonates given orally.

It has been suggested that the use of certain bisphosphonates with NSAIDs may result in an increased incidence of gastrointestinal or renal adverse effects.

There may be additive hypocalcaemic effects with aminoglycosides.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*,[1] or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

1. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* 1993; **4:** 432–3.
2. Pedersen-Bjergaard U, Myhre J. Severe hypocalcaemia after treatment with diphosphonate and aminoglycoside. *BMJ* 1991; **302:** 295. Correction. *ibid.*; 791.

Pharmacokinetics

The bisphosphonates are poorly absorbed after oral doses, with bioavailabilities in the fasting state ranging from about 0.7% (alendronate; risedronate) to up to 6% (etidronate; tiludronate). Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. They have a high affinity for bone, with about 50% of an absorbed dose sequestered to ossified tissues and retained in the body for prolonged periods. Excretion is in the urine, as unchanged drug; they do not appear to be metabolised.

References.
1. Cremers SCLM, *et al.* Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet* 2005; **44:** 551–70.

Bone Morphogenetic Proteins

BMP; Proteínas morfogenéticamente óseas; Костные Морфогенетические Белки.

ATC — M05BC01 (BMP-2); M05BC02 (BMP-7).

Dibotermin Alfa *(BAN, USAN, rINN)*

Dibotermina alfa; Dibotermine Alfa; Diboterminum Alfa; hrBMP-2; rhBMP-2; Диботермин Альфа.

Human recombinant bone morphogenetic protein 2.

CAS — 246539-15-1.

ATC Vet — QM05BC01.

UNII — T472P45MG6.

Eptotermin Alfa *(BAN, rINN)*

Eptotermina alfa; Eptotermine Alfa; Eptoterminum Alfa; hrBMP-7; OP-1; Osteogenic Protein-1; Эптотермин Альфа.

Human recombinant bone morphogenetic protein 7.

CAS — 129805-33-0.

ATC Vet — QM05BC02.

UNII — IT063R5MY0.

Profile

Bone morphogenetic proteins (BMPs) are growth factors that promote ectopic bone formation and can be extracted from demineralised bone matrix. Several have been identified and developed for use in orthopaedic and reconstructive surgery; some have been produced by recombinant technology.

Eptotermin alfa is a recombinant form used in adults for the treatment of non-union of tibia of at least 9 months duration in cases where bone grafting has failed or is unfeasible. Up to a maximum of 6.6 mg eptotermin alfa may be used, the amount depending on the size of the defect. It is also used in adults with spondylolisthesis for posterolateral lumbar spine fusion where bone grafting has failed or is contra-indicated. To fuse a single level of the lumbar spine, 3.3 mg eptotermin alfa is used on each side of the spine. Dibotermin alfa, another recombinant form, is used as an adjunct to standard care for the treatment of acute tibia fractures in adults, as an implant containing up to a maximum of 24 mg. The implant is also indicated for anterior lumbar spine fusion, as a substitute for bone grafting, in adults with degenerative disc disease who have had at least 6 months of non-operative treatment. Dibotermin alfa is also used as an alternative to bone grafting for sinus augmentation, and for localised alveolar ridge augmentations for defects associated with extraction sockets. Osteogenin (BMP-3) is under investigation.

References.
1. Westerhuis RJ, *et al.* Use of bone morphogenetic proteins in traumatology. *Injury* 2005; **36:** 1405–12.
2. Giannoudis PV, Tzioupis C. Clinical applications of BMP-7: the UK perspective. *Injury* 2005; **36** (suppl 3): S47–S50.
3. Wikesjö UM, *et al.* Tissue engineering with recombinant human bone morphogenetic protein-2 for alveolar augmentation and oral implant osseointegration; experimental observations and clinical perspectives. *Clin Implant Dent Relat Res* 2005; **7:** 112–19.
4. Granjeiro JM, *et al.* Bone morphogenetic proteins: from structure to clinical use. *Braz J Med Biol Res* 2005; **38:** 1463–73.
5. Garrison KR, *et al.* Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess* 2007; **11:** 1–150.
6. Mussano F, *et al.* Bone morphogenetic proteins and bone defects: a systematic review. *Spine* 2007; **32:** 824–30.

Adverse effects. The FDA issued a warning in July 2008 that use of recombinant human bone morphogenetic protein products in cervical spine fusion had been associated with at least 38 reports of swelling of neck and throat tissue, with resultant compression of the airway or vulnerable neurological structures. Complications were often life-threatening, and had required respiratory support and/or tracheotomy in some cases. The use of alternative treatments or enrollment in approved clinical studies was recommended when treating cervical spine problems.[1]

1. FDA. FDA Public Health Notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. Available at: http://www.fda.gov/cdrh/safety/070108-rhbmp.html (accessed 17/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: InductOs; ***Belg.***: InductOs; ***Cz.***: InductOs; Opgenra; Osigraft; ***Denm.***: InductOs; Opgenra; Osigraft; ***Fin.***: InductOs; ***Fr.***: InductOs; Osigraft; ***Ger.***: Opgenra; Osigraft; ***Gr.***: InductOs; Osigraft; ***Irl.***: InductOs; Opgenra; Osigraft; ***Ital.***: Osigraft; ***Neth.***: InductOs; Opgenra; Osigraft; ***Norw.***: InductOs; ***Pol.***: InductOs; Opgenra; Osigraft; ***Port.***: InductOs; Opgenra; Osigraft; ***Spain***: InductOs; Osigraft; ***Swed.***: InductOs; Osigraft; ***Switz.***: InductOs; Osigraft; ***UK***: InductOs; ***USA***: Infuse Bone Graft.

Calcitonins

Calcitoninas.

ATC — H05BA01 (salmon synthetic); H05BA02 (pork natural); H05BA03 (human synthetic).

ATC Vet — QH05BA01 (salmon synthetic); QH05BA02 (pork natural); QH05BA03 (human synthetic).

Calcitonin (Human)

Calcitonina (humana); Calcitonin-human; Human Calcitonin.
$C_{151}H_{226}N_{40}O_{45}S_3$=3417.9
CAS — 21215-62-3.
ATC — H05BA03 (human synthetic).
ATC Vet — QH05BA03 (human synthetic).
UNII — I0IO929019.

Description. Calcitonin (human) is a synthetic polypeptide comprising 32 amino acids in the same linear sequence as in naturally occurring human calcitonin.

Calcitonin (Pork) *(BANM)*

Calcitonina (cerdo); Calcitonina porcina.
CAS — 12321-44-7.
ATC — H05BA02 (pork natural).
ATC Vet — QH05BA02 (pork natural).
UNII — A385N5VGB4.

NOTE. The synonym thyrocalcitonin and the CAS number 9007-12-9 have been used for calcitonin that is often of pork origin.

Description. Calcitonin (pork) is a polypeptide hormone obtained from pork thyroid.

Calcitonin (Salmon) *(BAN)*

Calcitonin (Lachs); Calcitonina (salmón); Calcitonin-salmon; Calcitoninum salmonis; Kalcitonin lososí; Kalcytonina Łososiowa; Kalsitoniini (lohi); Kalsitonin (Somon); Lašišų kalcitoninas; Laxkalcitonin; Lazac-kalcitonin; Salcatonin; Salcatonina; Salkatonin; Salmon Calcitonin; SCT-1; SMC-20-051.
$C_{145}H_{240}N_{44}O_{48}S_2$=3431.9
CAS — 47931-85-1.
ATC — H05BA01 (salmon synthetic).
ATC Vet — QH05BA01 (salmon synthetic).
UNII — 7SFC6U2VI5.

Nomenclature. There may be some confusion between the terms Salcatonin and Calcitonin (Salmon) (Salmon Calcitonin; Calcitonin-salmon) although in practice these names appear to be used for the same substance.

- The Ph. Eur. 8 defines Calcitonin (Salmon) as a polypeptide having the structure determined for salmon calcitonin I. It is available as an acetate.
- Calcitonin (Salmon)/Salcatonin (*BAN*) is defined as a *component* of natural salmon calcitonin. The BP 2014 defines Calcitonin (Salmon)/Salcatonin as a synthetic polypeptide having the structure determined for salmon calcitonin I.
- In the USA, Calcitonin (*USAN*) includes calcitonin (human) and calcitonin (salmon) and there Salcatonin is understood to be a synthetic polypeptide structurally similar to natural salmon calcitonin (Calcitonin Salmon (Synthesis)). The US manufacturers use Calcitonin-salmon for a synthetic polypeptide with the same structure as calcitonin of salmon origin.

The names Ostora and Capsitonin have been used as trade marks for oral calcitonin (salmon).

Pharmacopoeias. In *Chin*, *Eur.* (see p. vii), and *US.*.

Ph. Eur. 8: (Calcitonin (Salmon)). A white or almost white powder. It is obtained by chemical synthesis or by a method based on recombinant DNA (rDNA) technology. Freely soluble in water. Store at 2 degrees to 8 degrees. If the substance is sterile store in a sterile, airtight, tamper-proof container. Protect from light.

USP 36: (Calcitonin Salmon). It is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. 1 mg of acetic acid-free, anhydrous calcitonin salmon is equivalent to 6000 USP units. Store in airtight containers at a temperature of 2 degrees to 8 degrees, or maintain in a frozen state. Protect from light.

Elcatonin *(rINN)*

Carbocalcitonin; Elcatonina; Elcatonine; Elcatoninum; [Aminosuberic Acid 1,7]-eel Calcitonin; [Asu^{1,7}]-E-CT; Элькатонин.
1-Butyric acid-7-L-2-aminobutyric acid)-26-L-aspartic acid-27-L-valine-29-L-alaninecalcitonin (salmon).
$C_{148}H_{244}N_{42}O_{47}$=3363.8
CAS — 60731-46-6.
ATC — H05BA04.
ATC Vet — QH05BA04.
UNII — W0CMS474JK.

Description. Elcatonin is a synthetic analogue of eel calcitonin.

Pharmacopoeias. In *Jpn*.

Incompatibility. Like some other peptide drugs, calcitonin may be adsorbed onto the plastic of intravenous giving sets; it has been suggested that solutions for intravenous infusion should contain some protein to prevent the sorption and consequent loss of potency (see under Administration, below).

Units

0.8 units of calcitonin, porcine, are contained in one ampoule of the second International Standard Preparation (1991).

128 units of calcitonin, salmon, are contained in approximately 20 micrograms of freeze-dried purified synthetic salmon calcitonin, with mannitol 2 mg in one ampoule of the second International Standard Preparation (1989).

17.5 units of calcitonin, human, are contained in one ampoule of the second International Standard Preparation (1991).

88 units of calcitonin, eel, are contained in one ampoule of the first International Standard Preparation (1989).

Potency of calcitonins is estimated by comparing the hypocalcaemic effect, in *rats*, with that of the standard preparation, and is expressed in international or MRC units which are considered to be equivalent. One manufacturer states that 100 international units by this assay is equivalent to 1 mg of porcine or human calcitonin, and to 25 micrograms of salmon calcitonin although other, slightly different, equivalencies have been cited for other preparations. However, although 1 unit of pork calcitonin, 1 unit of salmon calcitonin, and 1 unit of human calcitonin should give the same response in humans this is not necessarily the case. Doses of calcitonin that have been considered approximately equivalent in practice are:

- 80 units of pork calcitonin
- 50 units of salmon calcitonin
- 500 micrograms of human calcitonin

Clinically, doses of pork and salmon calcitonin are expressed in units whereas those of human calcitonin can be expressed by weight, probably a reflection of its purity.

Uses and Administration

Calcitonin is a hormone produced by mammalian thyroid parafollicular cells or the ultimobranchial gland in non-mammalian vertebrates. In man its secretion and biosynthesis are regulated by the plasma-calcium concentration. It has a hypocalcaemic action that is due primarily to inhibition of osteoclastic bone resorption; of less importance is a direct effect on the kidneys resulting in increased urinary excretion of calcium and phosphorus. Calcitonin contains 32 amino acids; the sequence varies according to the species. Synthetic calcitonin (salmon) is most commonly used in practice; it is the most potent and has the longest duration of action. Naturally occurring calcitonin (pork) has been used, and synthetic calcitonin (human) and elcatonin (a synthetic derivative of eel calcitonin) are available in some countries.

Calcitonins are used in the treatment of diseases characterised by high bone turnover such as Paget's disease of bone. They are also given as an adjunct in the treatment of severe hypercalcaemia, especially that associated with malignancy, and in the prevention of acute bone loss due to sudden immobilisation such as in osteoporotic fractures. In some countries calcitonins are used in the management of postmenopausal osteoporosis; however, the EMEA recommended against such use due to the increased risk of cancer with long-term treatment (see Carcinogenicity, p. 1179.2) and restricted their use in other conditions (see below).

Calcitonins are generally given by subcutaneous or intramuscular injection; some have been given intranasally, rectally, or by intravenous infusion or slow intravenous injection.

In **Paget's disease of bone** the usual dose range for calcitonin (salmon) is 50 units three times weekly to 100 units daily by subcutaneous or intramuscular injection. Calcitonin (human) is usually given by subcutaneous or intramuscular injection; doses range from 500 micrograms two to three times weekly, to 250 or 500 micrograms daily; severe cases may require up to 1 mg daily in 2 divided doses. In the EU, such use of calcitonin is restricted to patients who do not respond to, or are intolerant of, other therapy and duration of treatment is limited to 3 months (or 6 months in exceptional circumstances).

As an adjunct to the treatment of **hypercalcaemia**, calcitonins have a rapid effect which is greatest in patients with an increased bone turnover. Calcitonin (salmon) may be given by subcutaneous or intramuscular injection in a dose of 4 units/kg every 12 hours, increased if necessary after one or two days to 8 units/kg every 12 hours, up to a maximum of 8 units/kg every 6 hours after a further two days. Alternatively, 100 units every 6 to 8 hours may be given, increased after one or two days to a maximum of 400 units every 6 to 8 hours. In the emergency treatment of hypercalcaemic crisis, calcitonin (salmon) has also been given intravenously: a suggested dose is up to 10 units/kg diluted in 500 mL of sodium chloride 0.9% and given by slow intravenous infusion over at least 6 hours (see also Administration below for the problems of intravenous dosage). Calcitonin (human) 500 micrograms every 6 hours has also been given by slow intravenous injection for hypercalcaemia of malignancy.

Calcitonin (salmon) is also used for the **prevention of acute bone loss** due to sudden immobilisation such as in patients with recent osteoporotic fractures. The recommended dose is 100 units once daily (or 50 units twice daily) by subcutaneous or intramuscular injection, for 2 to 4 weeks only; the dose may be reduced to 50 units daily at the start of remobilisation.

In the USA, calcitonin (salmon) is used in the treatment of **postmenopausal osteoporosis** in a dose of 200 units daily intranasally by nasal spray, alternating nostrils each day. A subcutaneous or intramuscular dose of 100 units every other day has been suggested. Supplementary calcium (equivalent to at least 600 mg of elemental calcium daily) and vitamin D (400 units daily) should also be given.

For details of administration in renal impairment, see below.

Calcitonin (salmon) has also been used for the control of **bone pain due to malignant neoplasms** although in the EU such use is no longer considered appropriate.

Oral formulations of calcitonin (salmon) are being studied.

Administration. Calcitonins have poor oral bioavailability and are usually given by subcutaneous or intramuscular injection. To improve patient acceptability, especially in diseases requiring long-term drug therapy, alternative routes have been investigated:[1]

- calcitonin (salmon) has proved effective when given **intranasally** in usual doses of 50 to 200 units daily (for references, see Osteoporosis p. 1179.1), and intranasal products for osteoporosis are available in some countries.
- suppositories containing 300 units of calcitonin (salmon) have been used **rectally** in the management of hypercalcaemia; one suppository being given three times daily (total daily dose of 900 units).[2,3] Daily doses of 100 units of calcitonin (salmon) by suppository have been tried in postmenopausal osteoporosis[4] and in patients with bone pain.[5]
- calcitonins have been given by **intravenous infusion**, but this is rarely necessary and may cause more adverse effects. If intravenous use is essential, it has been suggested[6] that some protein must be present in the solution to prevent adsorption onto the plastic of the giving set. However, in practice this does not seem to be the case; in the UK, manufacturer's recommendations are for dilution with normal saline, while acknowledging that such dilution results in a loss of potency, and dosage is adjusted accordingly. Presumably dilution with a protein-containing solution would allow lower doses to be used. The manufacturers do specify that solutions for infusion should be prepared immediately before use and that glass or hard plastic containers should not be used.

Novel formulations of an orally active calcitonin have been investigated; one such formulation using a low-molecular-weight carrier, was considered effective and well-tolerated in early studies.[7,8]

1. Inzerillo AM, *et al.* Calcitonin: physiological actions and clinical applications. *J Pediatr Endocrinol Metab* 2004; **17:** 931–40.
2. Thiébaud D, *et al.* Effectiveness of salmon calcitonin administered as suppositories in tumor-induced hypercalcemia. *Am J Med* 1987; **82:** 745–50.
3. Thiébaud D, *et al.* Fast and effective treatment of malignant hypercalcemia: combination of suppositories of calcitonin and a single infusion of 3-amino 1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990; **150:** 2125–8.
4. Gonnelli S, *et al.* Effect of rectal salmon calcitonin treatment on bone mass and bone turnover in patients with established postmenopausal osteoporosis: a 1-year crossover study. *Curr Ther Res* 1993; **54:** 458–65.
5. Mannarini M, *et al.* Analgesic effect of salmon calcitonin suppositories in patients with bone pain. *Curr Ther Res* 1994; **55:** 1079–83.
6. Stevenson JC. Current management of malignant hypercalcaemia. *Drugs* 1988; **36:** 229–38.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17:** 1478–85.
8. Tankó LB, *et al.* Safety and efficacy of a novel salmon calcitonin (sCT) technology-based oral formulation in healthy postmenopausal women: acute and 3-month effects on biomarkers of bone turnover. *J Bone Miner Res* 2004; **19:** 1531–8.

Administration in renal impairment. Calcitonins are metabolised mainly in the kidneys and pharmacokinetic studies (see p. 1179.3) have indicated that the dosage of calcitonins may need to be reduced in patients with renal insufficiency, but there have been no specific guidelines.

Charcot neuroarthropathy. In a small study in patients with acute Charcot neuroarthropathy, intranasal calcitonin with calcium supplementation significantly reduced

bone turnover compared with calcium supplementation alone.[1]

1. Bem R, *et al.* Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. *Diabetes Care* 2006; **29:** 1392–4.

Hypercalcaemia. Calcitonins can be used in addition to rehydration and diuresis in the management of moderate to severe symptomatic hypercalcaemia (p. 1778.1), including that of malignancy (p. 1167.2). Because of their rapid effect, they may be particularly useful in life-threatening hypercalcaemia. However, although they have a rapid effect it is usually short-lived; calcitonins are therefore generally given as an adjunct with other therapy such as a bisphosphonate.

Malignant neoplasms of the bone. Calcitonins may be useful adjuvants in the treatment of malignant disease involving the bone, not only to correct hypercalcaemia of malignancy (p. 1167.2), but perhaps to relieve bone pain and osteolysis. A systematic review[1] concluded however that available evidence did not support the use of calcitonin for metastatic bone pain; the review was limited to only a few studies. Other therapeutic measures were recommended until further studies are done. In the EU, the use of injectable calcitonins for metastatic bone pain is no longer recommended.

1. Martinez-Zapata MJ, *et al.* Calcitonin for metastatic bone pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/04/08).

Osteogenesis imperfecta. There have been reports[1,2] of beneficial effects with calcitonins in the treatment of osteogenesis imperfecta (p. 1167.3), but their use has declined in favour of bisphosphonates.

1. Castells S, *et al.* Therapy of osteogenesis imperfecta with synthetic salmon calcitonin. *J Pediatr* 1979; **95:** 807–11.
2. Nishi Y, *et al.* Effect of long-term calcitonin therapy by injection and nasal spray on the incidence of fractures in osteogenesis imperfecta. *J Pediatr* 1992; **121:** 477–80.

Osteoporosis. Calcitonins may be used in the treatment of **postmenopausal** osteoporosis (p. 1168.1). Long-term use of calcitonins has been associated with an increased risk of cancer and they are not recommended for postmenopausal osteoporosis in the EU (for further details see Carcinogenicity, under Adverse Effects, below); however, such use may still be permitted in other countries. They are usually second-line agents; however, because of their analgesic effect, they may be useful for the initial treatment of those with bone pain due to vertebral crush fractures.[1] Calcitonin (salmon) nasal spray has been shown to significantly reduce the risk of vertebral fractures in women with established osteoporosis,[2] although the study has been criticised[3] for a high drop-out rate. Any effect on hip fracture is unestablished.[1,2]

Calcitonins have also been tried in the prevention and treatment of other types of osteoporosis. In the management of **corticosteroid**-induced osteoporosis, they appear to maintain bone mineral density (BMD) at the lumbar spine, but not at the femoral neck. Effects on prevention of fractures have not been established.[1,4] Nasal calcitonin (salmon) has been found to increase lumbar spine BMD in **men** with idiopathic osteoporosis.[1]

1. Silverman SL. Calcitonin. *Endocrinol Metab Clin North Am* 2003; **32:** 273–84.
2. Chesnut CH, *et al.* A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med* 2000; **109:** 267–76.
3. Cummings SR, Chapurlat RD. What PROOF proves about calcitonin and clinical trials. *Am J Med* 2000; **109:** 330–1.
4. Cranney A, *et al.* Calcitonin for preventing and treating corticosteroid-induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 22/02/05).

Paget's disease of bone. Calcitonins may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. However, the bisphosphonates have largely superseded the calcitonins in this role.

Pain. In addition to bone pain associated with malignancy and with bone disorders such as Paget's disease, calcitonins may also have other analgesic properties. Beneficial results have been seen in various painful conditions, including complex regional pain syndrome (p. 8.1), and particularly with intranasal salmon calcitonin.[1] Salmon calcitonin 100 or 200 units intravenously has also provided relief[2] from phantom limb pain (p. 10.3) after amputation. A small double-blind crossover study of intravenous calcitonin in amputee patients with phantom limb pain found it was ineffective, however, in contrast to ketamine.[3] Intranasal calcitonin at a dose of 200 units also provided only transient relief of phantom limb sensation after spinal cord injury in a patient refractory to clomipramine;[4] the authors speculated that optimal dosage may not have been used and noted that all previous studies were in amputees.

For a discussion on pain and its management, see p. 4.1.

1. Appelboom T. Calcitonin in reflex sympathetic dystrophy syndrome and other painful conditions. *Bone* 2002; **30** (suppl): 84S–86S.
2. Wall GC, Heyneman CA. Calcitonin in phantom limb pain. *Ann Pharmacother* 1999; **33:** 499–501.
3. Eichenberger U, *et al.* Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* 2008; **106:** 1265–73.
4. Shapiro S, *et al.* Calcitonin treatment for phantom limb pain. *Can J Psychiatry* 2004; **49:** 499.

Adverse Effects, Treatment, and Precautions

Calcitonins may cause nausea, vomiting, diarrhoea, dizziness, flushing, and tingling of the hands. These reactions are dose dependent, usually transient, and occur more often with intravenous doses. Nausea and vomiting may be reduced by giving doses at bedtime and after meals, or by giving an antiemetic beforehand. Other adverse effects have included rash, an unpleasant taste, abdominal pain, urinary frequency, tremor, oedema, headache, flu-like symptoms, visual disturbances, pruritus, musculoskeletal pain including arthralgia, hypertension, and fatigue. A diabetogenic effect has been reported rarely. Inflammatory reactions at the injection site have been reported with some calcitonins. Transient hypocalcaemia may occur after injections of calcitonin, and use is contra-indicated in patients with hypocalcaemia. The most commonly reported adverse effects associated with intranasal calcitonin are nasal discomfort, rhinitis, sinusitis, and epistaxis. Nasal ulcers may develop and intranasal calcitonin should be withheld until small ulcers heal, or withdrawn for severe ulceration.

Calcitonins should be given with care to patients with renal impairment or heart failure. If children receive calcitonin it should preferably be for short periods and bone growth should be monitored.

Circulating antibodies may develop after several months of use but resistance does not necessarily follow (see also Antibody Formation, below). Serious hypersensitivity reactions have occurred rarely and include bronchospasm, swelling of the tongue and throat, and anaphylactic shock which has occasionally been fatal. Allergic reactions should be differentiated from non-allergic flushing and hypotension. A skin test is advised before use if hypersensitivity is suspected.

Long-term use of calcitonin has been associated with an increased risk of cancer, see Carcinogenicity, below.

Calcitonin has inhibited lactation in *animals*.

Calcitonin (pork) may contain trace amounts of thyroid hormones, but clinical effects are unlikely in most patients.

Antibody formation. Long-term treatment with heterologous calcitonins may lead to the formation of neutralising antibodies. This appears to be common in patients given calcitonin (pork) or, to a lesser extent, calcitonin (salmon). Calcitonin (human) is less immunogenic than pork or salmon, but a study[1] has also detected antibodies to human calcitonin in 1 of 33 women with postmenopausal osteoporosis after 6 months of therapy.

The degree to which such antibodies affect therapeutic activity is uncertain. Some studies have suggested a significant loss of therapeutic activity in patients who developed neutralising antibodies to calcitonin (salmon),[2] or a restoration in activity after a switch from salmon to human calcitonin in such patients;[3] equally, others have presented evidence that the activity of calcitonin (salmon) was not reduced by the development of antibodies to the drug.[4]

1. Grauer A, *et al.* Formation of neutralizing antibodies after treatment with human calcitonin. *Am J Med* 1993; **95:** 439–42.
2. Grauer A, *et al.* In vitro detection of neutralizing antibodies after treatment of Paget's disease of bone with nasal salmon calcitonin. *J Bone Miner Res* 1990; **5:** 387–91.
3. Muff R, *et al.* Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990; **89:** 181–4.
4. Reginster JY, *et al.* Influence of specific anti-salmon calcitonin antibodies on biological effectiveness of nasal salmon calcitonin in Paget's disease of bone. *Scand J Rheumatol* 1990; **19:** 83–6.

Carcinogenicity. In 2012, an EMEA review[1,2] of all available data on calcitonin found an increased risk of cancer of various types with long-term use that varied between 0.7% in studies using an unlicensed oral formulation to 2.4% in studies using intranasal formulations. It was recommended that all formulations of calcitonin should no longer be used for the treatment of postmenopausal osteoporosis and that intranasal formulations be withdrawn in the EU; treatment of other conditions should be limited to the shortest possible time using the smallest effective dose, see Uses and Administration, p. 1178.2.

1. EMEA. Press release: European Medicines Agency recommends limiting long-term use of calcitonin medicines (issued 20th July, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/07/WC500130122.pdf (accessed 30/10/12)
2. EMEA. Questions and answers on the review of calcitonin-containing medicines (issued 19th July, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Calcitonin_31/WC500130149.pdf (accessed 30/10/12)

Effect on glucose metabolism. A single subcutaneous injection of calcitonin (salmon) has been reported to increase blood-glucose concentrations,[1] but long-term treatment with calcitonins was considered unlikely to cause diabetes.[2] Nevertheless, deterioration in diabetic control has been noted in a patient given calcitonin (pork)[3] and postprandial release of insulin was abolished by intravenous salmon calcitonin in 8 patients with duodenal ulcers.[4]

1. Gattereau A, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1977; **ii:** 1076–7.
2. Evans IMA, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1978; **i:** 280.
3. Thomas DW, *et al.* Deterioration in diabetic control during calcitonin therapy. *Med J Aust* 1979; **2:** 699–70.
4. Jonderko K. Effect of calcitonin on gastric emptying in patients with an active duodenal ulcer. *Gut* 1989; **30:** 430–5.

Gynaecomastia. A 62-year-old man developed painful gynaecomastia on two occasions after treatment with calcitonin (salmon) given by subcutaneous injection.[1]

1. Vankrunkelsven PJ, Thijs MM. Salcatonin and gynaecomastia. *Lancet* 1994; **344:** 482.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcitonin (salmon) as probably not porphyrinogenic based on a report of uneventful use in one patient with acute porphyria; it may be used as a drug of first choice and no precautions are needed. Calcitonin (pork), calcitonin (human), and elcatonin are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

There is a theoretical possibility that dosage adjustments of cardiac glycosides or calcium-channel blockers may be required in patients who are given injections of calcitonin, because of the effects of the latter on serum calcium.

Pharmacokinetics

Calcitonins are rapidly inactivated when given orally. After injection, calcitonins are quickly metabolised, primarily in the kidneys but also in blood and peripheral tissues. Bioavailability has been reported to be about 70%; plasma protein binding is about 30 to 40%. The inactive metabolites and a small proportion of unchanged drug are excreted in the urine. The elimination half-life after injection of calcitonin (human) is stated to be 60 minutes and that of calcitonin (salmon) about 70 to 90 minutes.

Calcitonins are also absorbed through the nasal and rectal mucosa. Although figures have varied widely, about 3% of an intranasal dose of calcitonin (salmon) is reported to be bioavailable compared with the same dose given by intramuscular injection, with peak plasma concentrations occurring after about 30 to 40 minutes compared with 15 to 25 minutes after the parenteral dose. Elimination half-life has been reported to be about 16 to 43 minutes.

After the *subcutaneous injection* of 19.9 micrograms of synthetic calcitonin (salmon) in 16 healthy subjects,[1] absorption was rapid with an absorption half-life of 23.4 minutes. The maximum mean plasma concentration was 384 picograms/mL at 60 minutes after which excretion was fairly rapid with an elimination half-life of 87 minutes. These results and those from previously reported investigations of salmon, human, and porcine calcitonin could not easily be compared, especially since different assay methods had been used. Nevertheless it was concluded that bioavailability from subcutaneous and intramuscular injection sites was good; that dosage may need to be adjusted in renal insufficiency because of low metabolic clearance rate; and that the higher potency of calcitonin (salmon) is due to higher intrinsic activity at the receptor site rather than to pharmacokinetic differences. The US manufacturers have cited a half-life of 1.02 hours after a single subcutaneous injection of calcitonin (human) 500 micrograms. The plasma elimination half-life of elcatonin was about 4.8 hours after *intramuscular injection* in healthy subjects.[2]

Calcitonins are absorbed on *intranasal* or *rectal* dosage. Peak plasma concentrations of calcitonin (salmon) were achieved after 20 to 60 minutes when given by nasal spray in doses ranging from 200 to 400 units.[3] In another study[4] calcitonin (salmon) 200 units, repeated once after 3 hours, was given by nasal spray or suppository to healthy subjects. Absorption was prompt and the total amount absorbed was similar with either route. However, whereas intranasal dosage produced low peaks with calcitonin (salmon) still detectable in the blood after 3 to 5 hours, rectal dosage produced peak plasma concentrations about 6 to 8 times higher but the drug was undetectable within 2 hours; plasma concentrations were lower than those found after injection. Another group[5] found calcitonin (human) to be poorly absorbed when given intranasally to healthy

subjects. Absorption from nasal powder or spray solutions was improved by the presence of the surfactants dihydrofusinate or glycocholate.

Investigations carried out in 4 osteoporotic patients[6] suggested that the rectal calcitonin (salmon) could provide 65% of the bioavailability of intramuscular doses.

A study of an *oral* formulation of calcitonin (salmon) in healthy subjects evaluated different oral doses in comparison to intravenous dosing, and found 1.2 mg orally to be comparable to 10 micrograms intravenously, in terms of bioavailability and efficacy.[7]

1. Nüesch E, Schmidt R. Comparative pharmacokinetics of calcitonins. In: Pecile A, ed. *Calcitonin international congress series no. 540*. Amsterdam: Excerpta Medica, 1980: 352–64.
2. Segre G, *et al*. Pharmacokinetics of carbocalcitonin in humans. *Clin Trials J* 1986; **23** (suppl 1): 23–8.
3. Kurose H, *et al*. Intranasal absorption of salmon calcitonin. *Calcif Tissue Int* 1987; **41:** 249–51.
4. Buclin T, *et al*. The effect of rectal and nasal administration of salmon calcitonin in normal subjects. *Calcif Tissue Int* 1987; **41:** 252–8.
5. Pontiroli AE, *et al*. Nasal administration of glucagon and human calcitonin to healthy subjects: a comparison of powders and spray solutions and of different enhancing agents. *Eur J Clin Pharmacol* 1989; **37:** 427–30.
6. Gennari C, *et al*. Pharmacodynamic activity of synthetic salmon calcitonin in osteoporotic patients: comparison between rectal and intramuscular administration: pilot study. *Curr Ther Res* 1993; **53:** 301–8.
7. Buclin T, *et al*. Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17:** 1478–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Miacalcic; ***Austria***: Ucecal; ***Belg.***: Calsynar†; Miacalcic; Steocalcin†; ***Braz.***: Acticalcin; Calsynar; Miacalcic; Seacalcit; Serocalcin†; ***Canad.***: Calcimar; Caltine; Miacalcin; ***Chile***: Calnisan†; Miacalcic; ***China***: Bang Rui De (邦瑞得); Calco (考克); Da Fen Gai (达芬盖); Elcitonin (益盖宁); Gai Rui Ning (盖瑞宁); Gu Tai Ning (固泰宁); Han Xin (翰欣); Jin Er Li (金尔力); Miacalcic (密盖息); Si Di Nuo (斯迪诺); ***Cz.***: Miacalcic; Osteodon†; Tonocalcin; ***Denm.***: Miacalcic; ***Fin.***: Miacalcic; ***Fr.***: Cadens; Calsyn; Cibacalcine†; Miacalcic; ***Ger.***: Calci†; Karil†; ***Gr.***: Alciton; Alfaton; Alicitonin; Arsipor; Assocals; Aurocalcin; Brosidon; Calc-Up; Calci-10; Calcicontrol; Calcideron; Calciphar; Calciplus; Calcispren; Calcitherapy; Calciton; Calco; Calcytonil; Caloston; Calsal; Calsaton; Calsynar; Caltec; Cibacalcin; Crocalcin; Doctadryle; Farmicalcine; Galcin; Genecalcin; Iamacalcin; Iricalcin; Latonina; Lixocam; Miacalcic; Miadenil; Mioser; Myocal; Neostesin; Nopremin; Norcalcin; Nylex; Osanit; Osivan; Osteonorm; Osticalcin; Ostifix; Ostoplus; Ostosalm; Pluston; Rafacalcin; Redicalcin; Rothrin; Sal-Cal; Salcatol; Salmocalcin; Salmofar; Salmoten; Sanopor; Steocin; Tendolon; Tonocalcin; Tosicalcin; Transcalcium; Ucecal; Velkacalcin; Zyoston; ***Hong Kong***: Miacalcic; ***Hung.***: Biostin†; Calco; Miacalcic; ***India***: Biocalcin; Calcinase; Calsynar; Miacalcic; Ostospray; Zycalcit; ***Indon.***: Miacalcic; Tonocalcin; ***Irl.***: Miacalcic; Miakaril; Ostulex; ***Israel***: Fortical; Miacalcic; Salco; ***Ital.***: Calcitonina; Salmofar†; ***Jpn***: Calcitoran; Elcitonin; ***Malaysia***: Miacalcic; Tendolon; ***Mex.***: Miacalcic; Oseum; ***Neth.***: Forcaltonin†; ***Norw.***: Miacalcic; ***NZ***: Miacalcic; ***Philipp.***: Miacalcic; ***Pol.***: Calcihexal†; Calcitonin; Miacalcic; Tonocalcin; ***Port.***: Calcitar†; Calsyn; Miacalcic; Osseocalcina; Osteodon; Ostinate; Salcat; Tonocaltin; ***Rus.***: Alostin (Алостин); Miacalcic (Миакальцик); Osteover (Остеовер); ***S.Afr.***: Miacalcic; ***Singapore***: Miacalcic; ***Spain***: Calogen†; Calsynar; Carbicalcin; Diatin†; Fosatur†; Miacalcic; Oseototal†; Ospor†; Osteobion†; Ostetan†; Tonocaltin†; ***Swed.***: Miacalcic; ***Switz.***: Miacalcic; ***Thai.***: Cadotin; Calci-10; Calco; Miacalcic; Mycalcin; Salmocin; Tonocalcin; ***Turk.***: Biocalcin; Calcitonina; Calsynar; Miacalcic; Salmocalcin; Strabone; Tonocalcin; Ucecal; ***UK***: Miacalcic; ***Ukr.***: Miacalcic (Миакальцик); ***USA***: Calcimar; Fortical; Miacalcin; Osteocalcin.

Pharmacopoeial Preparations
BP 2014: Calcitonin (Salmon) Injection;
USP 36: Calcitonin Salmon Injection; Calcitonin Salmon Nasal Solution.

Cinacalcet Hydrochloride

(BANM, USAN, rINNM)

AMG-073 (cinacalcet); Cinacalcet, Chlorhydrate de; Cinacalcet, hidrocloruro de; Cinacalceti Hydrochloridum; Hidrocloruro de cinacalcet; KRN-1493; Цинакальцета Гидрохлорид.

N-[(1*R*)-1-(Naphthalen-1-yl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine hydrochloride.

$C_{22}H_{22}F_3N,HCl$=393.9

CAS — 364782-34-3.
ATC — H05BX01.
ATC Vet — QH05BX01.
UNII — 1K860WSG25.

Uses and Administration

Cinacalcet is a calcimimetic agent that increases the sensitivity to extracellular calcium of the calcium-sensing receptors of the parathyroid gland, which regulate parathyroid hormone secretion; this results in a reduction in parathyroid hormone secretion as well as a decrease in serum calcium. Cinacalcet hydrochloride is given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, as well as for the reduction of hypercalcaemia in patients with parathyroid carcinoma or primary hyperparathyroidism (where parathyroidectomy is not an option). Doses are expressed in terms of the base; cinacalcet hydrochloride 33 mg is equivalent to about 30 mg of cinacalcet.

In the treatment of **secondary hyperparathyroidism**, the initial dose is 30 mg once daily, increased at intervals of 2 to 4 weeks by 30 mg to a maximum of 180 mg daily.

For the treatment of **hypercalcaemia** in patients with parathyroid carcinoma or primary hyperparathyroidism, cinacalcet is given in an initial dose of 30 mg twice daily, increased sequentially at intervals of 2 to 4 weeks to a maximum of 90 mg three or four times daily.

References.
1. Franceschini N, *et al*. Cinacalcet HCl: a calcimimetic agent for the management of primary and secondary hyperparathyroidism. *Expert Opin Invest Drugs* 2003; **12:** 1413–21.
2. Shoback DM, *et al*. The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 5644–9.
3. Block GA, *et al*. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; **350:** 1516–25.
4. Joy MS, *et al*. Calcimimetics and the treatment of primary and secondary hyperparathyroidism. *Ann Pharmacother* 2004; **38:** 1871–80.
5. Peacock M, *et al*. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90:** 135–41.
6. Barman Balfour JA, Scott LJ. Cinacalcet hydrochloride. *Drugs* 2005; **65:** 271–81.
7. Cunningham J, *et al*. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68:** 1793–1800.
8. Dong BJ. Cinacalcet: an oral calcimimetic agent for the management of hyperparathyroidism. *Clin Ther* 2005; **27:** 1725–51.
9. NICE. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy: Technology Appraisal Guidance 117 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA117guidance.pdf (accessed 18/04/08)
10. Drüeke TB, Ritz E. Treatment of secondary hyperparathyroidism in CKD patients with cinacalcet and/or vitamin D derivatives. *Clin J Am Soc Nephrol* 2009; **4:** 234–41.

Administration in hepatic impairment. For precautions when using cinacalcet in those with hepatic impairment, see below.

Adverse Effects and Precautions

Hypocalcaemia and adynamic bone disease can occur; serum calcium and intact parathyroid hormone concentrations should be monitored regularly, especially in patients with a history of seizure disorders or hepatic impairment. A reduction in free testosterone concentrations has also been reported during treatment. Other adverse effects of cinacalcet include gastrointestinal disturbances, myalgia, dizziness, paraesthesia, seizures, hypertension, asthenia, anorexia, rashes, and non-cardiac chest pain. There have been isolated reports of hypotension, worsening heart failure, or both, in patients with impaired cardiac function. Hypersensitivity reactions including angioedema and urticaria have been reported. Plasma concentrations of cinacalcet may be increased in patients with moderate to severe hepatic impairment, and caution and close monitoring are advised.

Interactions

Cinacalcet is partly metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Concentrations of cinacalcet have almost doubled when given with the CYP3A4 inhibitor ketoconazole. Dose adjustments of cinacalcet may be required if therapy with strong inhibitors or inducers of CYP3A4 is started, or stopped. Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism, and dose adjustments may be necessary if patients start or stop smoking. Cinacalcet is a strong inhibitor of cytochrome P450 isoenzyme CYP2D6; exposure to amitriptyline, desipramine, and nortriptyline has been increased when given with cinacalcet.

Pharmacokinetics

Peak plasma concentrations occur 2 to 6 hours after an oral dose of cinacalcet, and are substantially increased if given with food. Clearance from plasma is biphasic, with a terminal half-life of about 30 to 40 hours. Cinacalcet is approximately 93 to 97% bound to plasma proteins. It is rapidly and extensively metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Metabolites are renally excreted, with 80% of the dose recovered in the urine, and 15% in the faeces.

References.
1. Kumar GN, *et al*. Metabolism and disposition of calcimimetic agent cinacalcet HCl in humans and animal models. *Drug Metab Dispos* 2004; **32:** 1491–1500.
2. Padhi D, *et al*. No effect of renal function or dialysis on pharmacokinetics of cinacalcet (Sensipar/Mimpara). *Clin Pharmacokinet* 2005; **44:** 509–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Sensipar; ***Austria***: Mimpara; ***Belg.***: Mimpara; ***Braz.***: Mimpara; ***Canad.***: Sensipar; ***Cz.***: Mimpara; Parareg†; ***Denm.***: Mimpara; ***Fin.***: Mimpara; ***Fr.***: Mimpara; ***Ger.***: Mimpara; ***Gr.***: Mimpara; Sensipar; ***Hong Kong***: Regpara; ***Hung.***: Mimpara; ***Irl.***: Mimpara; ***Israel***: Mimpara; ***Ital.***: Mimpara; Parareg†; ***Jpn***: Regpara; ***Neth.***: Mimpara; ***Norw.***: Mimpara; ***NZ***: Sensipar; ***Pol.***: Mimpara; ***Port.***: Mimpara; ***Rus.***: Mimpara (Мимпара); ***Spain***: Mimpara; ***Swed.***: Mimpara; ***Switz.***: Mimpara; ***Turk.***: Mimpara; ***UK***: Mimpara; ***USA***: Sensipar.

Clodronate

ATC — M05BA02.
ATC Vet — QM05BA02.

Clodronic Acid *(BAN, USAN, rINN)*

Acide Clodronique; Ácido clodrónico; Acidum Clodronicum; Cl_2MBP; Cl_2MDP; Clodrónico, ácido; DkhMDF; Klodronihappo; Klodronsyra; Клодроновая Кислота.

(Dichloromethylene)diphosphonic acid.

$CH_4Cl_2O_6P_2$=244.9

CAS — 10596-23-3.
ATC — M05BA02.
ATC Vet — QM05BA02.
UNII — 0813BZ6866.

Clodronate Disodium *(USAN, rINNM)*

177501; BM-06.011; Clodronas Dinatricum; Clodronate disodique; Clodronate Sodium; Clodronato disódico; Dichloromethane Diphosphonate Disodium; Dichloromethylene Diphosphonate Disodium; Dinatrii Clodronas; Dinatriumklodronaatti; Dinatriumklodronat; Disodium Clodronate; Sodium Clodronate (BANM); Sodyum Klodronat; ZK-00091106; Динатрий Клодронат.

Disodium (dichloromethylene)diphosphonate tetrahydrate.

$CH_2Cl_2Na_2O_6P_2.4H_2O$=360.9

CAS — 22560-50-5.
ATC — M05BA02.
ATC Vet — QM05BA02.
UNII — N030400H8J (clodronate disodium tetrahydrate); Y05R4GCQ1H (anhydrous clodronate disodium).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clodronate Disodium Tetrahydrate). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. A 5% solution in water has a pH of 3.0 to 4.5.

Uses and Administration

Clodronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses. Clodronate is used, generally as the disodium salt, as an adjunct in the treatment of severe hypercalcaemia associated with malignancy. In addition, it is used in the management of osteolytic lesions and bone pain associated with skeletal metastases. Doses are expressed in terms of anhydrous clodronate disodium; 125 mg of clodronate disodium tetrahydrate is equivalent to about 100 mg of anhydrous substance.

Clodronate is given by slow intravenous infusion, diluted in sodium chloride 0.9% or glucose 5%, or orally, as a single daily dose or in 2 divided doses; food should be avoided for at least 1 hour before or 1 hour after an oral dose. Clodronate disodium is available in capsules of 400 mg and standard tablets of 800 mg. Tablets of clodronate disodium 520 mg are also available in some countries, and have a greater bioavailability than the capsules or standard tablets; one such tablet of clodronate disodium 520 mg is considered equivalent to about two capsules each containing clodronate disodium 400 mg or one 800-mg standard tablet (but see Bioavailability, p. 1182.1).

In the management of osteolytic lesions, hypercalcaemia, and bone pain associated with **skeletal metastases** in patients with breast cancer or multiple myeloma, clodronate disodium 1.6 g daily (4 capsules or 2 standard tablets) is given orally, and may be increased if necessary to a maximum of 3.2 g daily. Alternatively a dose of 1.04 g (2 tablets) daily, increased if necessary up to 2.08 g daily, may be given as enhanced bioavailability tablets.

In **hypercalcaemia of malignancy** clodronate disodium is given by intravenous infusion over not less than 2 hours in a dose of 300 mg in 500 mL of infusion solution daily on successive days until normocalcaemia is achieved (usually within 5 days); duration of treatment

should not exceed 7 days. Alternatively, it may be given as a single intravenous infusion of 1.5 g in 500 mL of infusion solution over a period of at least 4 hours. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy may be given orally in similar doses to those used for initial oral treatment of metastases. If hypercalcaemia recurs, the intravenous dose may be repeated.

For details of administration in renal impairment, see below.

General references.

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; **47:** 945–82.
2. Kanis JA, McCloskey EV. Clodronate. *Cancer* 1997; **80** (suppl): 1691–5.
3. Brandi ML. Impiego del clodronato nei disordini del metabolismo minerale: stato dell'arte nell'anno 2000. *Minerva Med* 2001; **92:** 251–68.
4. Dando TM, Wiseman LR. Clodronate: a review of its use in the prevention of bone metastases and the management of skeletal complications associated with bone metastases in patients with breast cancer. *Drugs Aging* 2004; **21:** 949–62.

Administration. In Italy, clodronate is also used *intramuscularly*.[1,2] The usual dose for maintenance therapy of hypercalcaemia is 100 mg daily for 2 to 3 weeks; in the prevention and treatment of postmenopausal osteoporosis, 100 mg is given every 7 to 14 days. However, injection into the gluteal muscle caused local hardening; severe pain at the injection site may limit prolonged use of this route.[1] In Canada, clodronate has been given *subcutaneously* in doses of 1500 mg in 50 to 250 mL of infusion solution over 2 to 3 hours, to treat hypercalcaemia associated with malignancy. The chest and abdomen were the sites most frequently used; pain was the most common adverse effect.[3]

1. Rossini M, *et al*. Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; **24:** 125–9.
2. Filipponi P, *et al*. Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; **26:** 269–74.
3. Roemer-Bécuwe C, *et al*. Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; **26:** 843–8.

Administration in renal impairment. A pharmacokinetic study[1] found that renal clearance of *intravenous* clodronate was highly dependent on renal function. While recommending caution in interpreting these results for patients with malignancy or severe bone disease, the authors recommended the following dose adjustments based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: up to 25% reduction in dose
- CC 12 to 49 mL/minute: 25 to 50% dose reduction
- CC less than 12 mL/minute: 50% dose reduction

Licensed product information recommends similar dose adjustments for intravenous use. In dialysis patients, it is suggested that the daily dose of clodronate disodium 300 mg is infused before haemodialysis sessions, and the dose reduced by 50% on dialysis-free days; duration of treatment should not exceed 5 days. Clodronate is partially removed from the circulation by peritoneal dialysis.

Dose recommendations for *oral* clodronate in renal impairment vary between countries. In the UK the following adjustments are made:

- CC between 10 and 30 mL/minute: 50% dose reduction
- CC below 10 mL/minute: contra-indicated

Alternatively, some other countries such as Canada suggest the following dose adjustments:

- CC 50 to 80 mL/minute: no dose reduction required
- CC 30 to 50 mL/minute: 25% reduction in dose
- CC less than 30 mL/minute: 50% reduction in dose

1. Saha H, *et al*. Pharmacokinetics of clodronate in renal failure. *J Bone Miner Res* 1994; **9:** 1953–8.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous clodronate 300 mg daily for 10 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Varenna M, *et al*. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome: a randomized, double blind, placebo controlled study. *J Rheumatol* 2000; **27:** 1477–83.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. Clodronate has been shown to be effective[1-4] in the treatment of malignant hypercalcaemia. A small dose-response study[3] found low-dose clodronate for mild cases to be as effective as high-dose clodronate for moderate to severe cases of tumour-induced hypercalcaemia.

1. O'Rourke NP, *et al*. Effective treatment of malignant hypercalcaemia with a single intravenous infusion of clodronate. *Br J Cancer* 1993; **67:** 560–3.
2. Elomaa I, Blomqvist C. Clodronate and other bisphosphonates as supportive therapy in osteolysis due to malignancy. *Acta Oncol* 1995; **34:** 629–36.
3. Shah S, *et al*. Is there a dose response relationship for clodronate in the treatment of tumour induced hypercalcaemia? *Br J Cancer* 2002; **86:** 1235–7.
4. Roemer-Bécuwe C, *et al*. Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; **26:** 843–8.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Clodronate is licensed for such use in many countries. Studies in breast cancer patients with bone metastases found that clodronate reduced the incidence of fractures,[1,2] and delayed the time to onset of new bone events.[2,3] (For mention of the use of clodronate to prevent treatment-related osteoporosis in breast cancer patients see Osteoporosis, below.) A meta-analysis[4] confirmed the benefits of the bisphosphonate in reducing skeletal events and hence morbidity, but not mortality; however, no clear advantage could be shown versus pamidronate or zoledronate, which were also of benefit.

Whether bisphosphonates can prevent the development of new skeletal metastases is unclear. Results of studies using clodronate to reduce skeletal metastases in women with breast cancer have been conflicting,[1,5-7] and one study in women with node-positive disease actually suggested an increase in concomitant visceral metastases.[6] Overall, the studies appeared limited by duration, and further data are needed.[8] In a trial of patients with multiple myeloma,[9] oral clodronate was found to slow the progression of skeletal disease, especially in those patients with less overt disease at diagnosis; the authors suggested starting clodronate early in the course of the disease.

1. Kanis JA, *et al*. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* 1996; **19:** 663–7.
2. Kristensen B, *et al*. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999; **246:** 67–74.
3. Tubiana-Hulin M, *et al*. Essai comparatif randomisé en double aveugle clodronate oral 1600 mg/j versus placebo chez des patientes avec métastases osseuses de cancer du sein: double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. *Bull Cancer* 2001; **88:** 701–7.
4. Machado M, *et al*. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009; **31:** 962–79.
5. Diel IJ, *et al*. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; **339:** 357–63.
6. Saarto T, *et al*. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001; **19:** 10–17.
7. Powles T, *et al*. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002; **20:** 3219–24.
8. Hurst M, Noble S. Clodronate: a review of its use in breast cancer. *Drugs Aging* 1999; **15:** 143–67.
9. McCloskey EV, *et al*. A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. *Br J Haematol* 1998; **100:** 317–25.

Multiple myeloma. For the effect of bisphosphonates, including clodronic acid, on survival in multiple myeloma, see under Bisphosphonates, p. 1174.2.

Osteogenesis imperfecta. Clodronate has been reported to be of benefit in a boy with osteogenesis imperfecta (p. 1167.3) type I. Starting at 13½ years old he was given oral clodronate 400 mg daily for 5 years, and sustained no new low-trauma fractures during this time. Treatment was stopped for 8 months, but bone mineral density remained below normal limits. Clodronate was restarted at 800 mg daily and given with no untoward effects, until the patient was 22 years old, 8 years after initial referral.[1]

1. Ashford RU, *et al*. Oral clodronate as treatment of osteogenesis imperfecta. *Arch Dis Child* 2003; **88:** 945.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Clodronate is licensed for this use in some countries. Studies of its use in daily oral doses, or intermittent intravenous infusions,[1] or intramuscular injections (at 7-, 10- or 14-day intervals)[1,2] found increases in bone mineral density at various sites in postmenopausal women with osteoporosis or low bone mass. A large study[3] in postmenopausal women with vertebral osteopenia found that oral clodronate 800 mg daily prevented bone loss in the lumbar spine and femoral trochanter, but not the femoral neck; this dose has been shown to reduce vertebral fracture risk in women with postmenopausal or secondary osteoporosis.[4] The risk of vertebral fractures was also reduced in patients with arthritis receiving corticosteroids, who were given intramuscular clodronate once weekly.[5] Three years of oral clodronate treatment significantly reduced the incidence of spinal osteoporosis in patients with breast cancer who received adjuvant chemotherapy or anti-oestrogens, and this reduction was still evident 7 years after stopping clodronate.[6] Oral clodronate may also be of benefit in reducing bone loss after heart transplantation,[7] but the benefits of intravenous clodronate in a small prospective study in patients receiving parenteral nutrition (who are at high risk of osteoporosis) were uncertain.[8]

1. Filipponi P, *et al*. Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; **26:** 269–74.
2. Rossini M, *et al*. Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; **24:** 125–9.
3. Välimäki MJ, *et al*. Prevention of bone loss by clodronate in early postmenopausal women with vertebral osteopenia: a dose-finding study. *Osteoporosis Int* 2002; **13:** 937–47.
4. McCloskey E, *et al*. Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004; **19:** 728–36.
5. Frediani B, *et al*. Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. *Bone* 2003; **33:** 575–81.
6. Saarto T, *et al*. Ten-year follow-up of 3 years of oral adjuvant clodronate therapy shows significant prevention of osteoporosis in early-stage breast cancer. *J Clin Oncol* 2008; **26:** 4289–95.
7. Ippoliti G, *et al*. Clodronate treatment of established bone loss in cardiac recipients: a randomized study. *Transplantation* 2003; **75:** 330–4.
8. Haderslev KV, *et al*. Effect of cyclical intravenous clodronate therapy on bone mineral density and markers of bone turnover in patients receiving home parenteral nutrition. *Am J Clin Nutr* 2002; **76:** 482–8.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. A review[1] of clodronate stated that oral doses of 800 to 1600 mg daily were effective in reducing bone turnover in patients with Paget's disease, and that remission after stopping was longer with the higher dose. Duration of therapy also appears to affect response;[1] longer treatment was associated with a longer time to relapse.[2] Short-term intravenous clodronate (300 mg daily for 5 to 10 days) has also been found to reduce biochemical markers of bone turnover, and sustain remission for up to 1 year.[1,3]

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; **47:** 945–82.
2. Khan SA, *et al*. Duration of response with oral clodronate in Paget's disease of bone. *Bone* 1996; **18:** 185–90.
3. Broggini M, *et al*. Short courses of intravenous clodronate in the treatment of Paget's disease of bone: a long-term follow-up trial. *Int J Clin Pharmacol Res* 1993; **13:** 301–4.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Gastrointestinal symptoms with oral clodronate may be reduced by giving it in divided doses rather than as a single daily dose. Reversible increases in liver enzyme values and serum parathyroid hormone have occurred; transient moderate leucopenia has been reported. Monitoring of hepatic and renal function, white cell counts, and serum calcium and phosphate is advised. Clodronate has precipitated bronchospasm, even in patients with no history of asthma. Transient proteinuria has been reported immediately after intravenous infusion.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including clodronate, see under Bisphosphonates, p. 1175.2.

Effects on the kidneys. For mention of renal failure developing in a patient with slightly raised serum-creatinine concentrations who subsequently received an intravenous infusion of clodronate, see under Bisphosphonates, p. 1176.1.

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including clodronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p. 1176.2).

Effects on the respiratory system. For a report of bronchospasm in an aspirin-sensitive asthmatic, induced by an infusion of clodronate, see p. 1177.1.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. For published reports of cutaneous reactions associated with clodronate, see p. 1177.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clodronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*,[1] or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

1. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* 1993; **4:** 432–3.
2. Pedersen-Bjergaard U, Myhre J. Severe hypocalcaemia after treatment with diphosphonate and aminoglycoside. *BMJ* 1991; **302:** 295. Correction. *ibid.*; 791.

Pharmacokinetics

Like other bisphosphonates, clodronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is only 1 to 4%, and may differ appreciably between different oral formulations. On absorption or intravenous dosage it is cleared rapidly from the blood with a reported plasma half-life of only about 2 hours, but has a high affinity for bone. Binding to serum plasma proteins is low. Clodronate is not metabolised. Over 70% of an intravenous dose is excreted unchanged in the urine within 24 hours, the remainder being sequestered to bone tissue.

References.

1. Conrad KA, Lee SM. Clodronate kinetics and dynamics. *Clin Pharmacol Ther* 1981; **30:** 114–20.
2. Yakatan GJ, *et al*. Clodronate kinetics and bioavailability. *Clin Pharmacol Ther* 1982; **31:** 402–10.
3. Ylitalo P, *et al*. Comparison of pharmacokinetics of clodronate after single and repeated doses. *Int J Clin Pharmacol Ther* 1999; **37:** 294–300.

Bioavailability. Enhanced bioavailability tablets of clodronate disodium are available in some countries, the licensed dose of which is less than the dose of the standard formulations (see Uses and Administration, p. 1180.3). However, an open, randomised, crossover study in 88 subjects found that a 1040-mg dose of an enhanced tablet formulation provided only 52% of the bioavailable dose of 1600 mg of a standard capsule formulation.[1]

1. Lapham G, *et al*. Bioavailability of two clodronate formulations. *Br J Hosp Med* 1996; **56:** 231–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bonefos; ***Austria***: Bonefos; Lodronat; ***Belg.***: Bonefos; ***Braz.***: Bonefos; Ostac†; ***Canad.***: Bonefos; Clasteon; ***China***: Bonefos (固令); De Wei (德维); Di Gai Na (迪盖纳); Ya Kun Yu (雅坤宇); ***Cz.***: Bonefos; Lodronat; ***Denm.***: Bonefos; ***Fin.***: Bonefos; Clodrobon; ***Fr.***: Clastoban; Lytos; ***Ger.***: Bonefos; Clodron beta; Clodron†; Ostac; ***Gr.***: Bonefos; Ostac; ***Hong Kong***: Bonefos; Ostac†; ***Hung.***: Bonefos; ***Indon.***: Bonefos; ***Irl.***: Bonefos; Clasteon; Loron†; ***Israel***: Bonefos; ***Ital.***: Clasteon; Climaclod; Clodeosten; Clodron; Clody; Difosfonal; Moticlod; Niklod; Osteonorm; Osteostab; Soclonat†; ***Malaysia***: Bonefos; ***Mex.***: Bonefos; ***Neth.***: Bonefos; Ostac; ***Norw.***: Bonefos; ***Philipp.***: Bonefos; ***Pol.***: Bonefos; Sindronat; ***Port.***: Bonefos; Ostac; ***Rus.***: Bonefos (Бонефос); Clobir (Клобир); ***S.Afr.***: Bonephos; ***Singapore***: Bonefos; Ostac; ***Spain***: Bonefos; ***Swed.***: Bonefos; Ostac†; ***Switz.***: Bonefos; Ostac†; ***Thai.***: Bonefos; ***Turk.***: Bonefos; Froximun; ***UK***: Bonefos; Clasteon; Loron; ***Ukr.***: ClodronSandoz (КлодронСандоз).

Denosumab *(BAN, USAN, rINN)*

AMG-162; Dénosumab; Denosumabum; Денозумаб.

Immunoglobulin G2, anti-(human RANK ligand) (human monoclonal AMG162 heavy chain), disulfide with human monoclonal AMG162 light chain, dimer.

CAS — 615258-40-7.
ATC — M05BX04.
ATC Vet — QM05BX04.
UNII — 4EQZ6YO2HI.

Uses and Administration

Denosumab is a human monoclonal antibody (p. 2561.1) that specifically targets the receptor activator of nuclear factor-kappa B ligand (RANKL), a mediator of the resorptive phase of bone remodelling. It is used in the treatment of osteoporosis (p. 1168.1) in postmenopausal women or men who are at increased risk of fractures. It is also used in the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and bone loss associated with adjuvant aromatase inhibitor therapy in women with breast cancer at increased risk of fractures. Additionally, denosumab is used for the prevention of skeletal events associated with bone metastases from solid tumours (see Malignant Neoplasms of the Bone, p. 700.3). In the treatment of giant cell tumour of bone, denosumab may be used where the tumour is unresectable or where resection is likely to result in severe morbidity. It is given as a subcutaneous injection into the thigh, abdomen, or upper arm.

For osteoporosis and for bone loss associated with hormone ablation in men with prostate cancer or aromatase inhibitor therapy in women with breast cancer, the recommended dose is denosumab 60 mg once every 6 months.

For prevention of skeletal events associated with bone metastases from solid tumours, denosumab 120 mg is given every 4 weeks.

For giant cell tumour of bone the recommended dose is 120 mg given every 4 weeks with an additional dose of 120 mg given on days 8 and 15 of the first month of therapy.

Calcium and vitamin D supplementation is suggested to prevent hypocalcaemia.

Denosumab is also under investigation for other conditions, including rheumatoid arthritis and multiple myeloma; it is also being studied in the prevention of bone metastases. A few patients with Paget's disease of bone have been treated with denosumab.

References.

1. Stopeck AT, *et al*. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010; **28:** 5132–9.
2. Thomas D, *et al*. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010; **11:** 275–80.
3. Chitre M, *et al*. Denosumab for treatment of postmenopausal osteoporosis. *Am J Health-Syst Pharm* 2011; **68:** 1409–18. Correction. *ibid.*; 1676.
4. Scott LJ, Muir VJ. Denosumab: in the prevention of skeletal-related events in patients with bone metastases from solid tumours. *Drugs* 2011; **71:** 1059–69.
5. Sutton EE, Riche DM. Denosumab, a RANK ligand inhibitor, for postmenopausal women with osteoporosis. *Ann Pharmacother* 2012; **46:** 1000–9.
6. Anonymous. Denosumab for postmenopausal osteoporosis? *Drug Ther Bull* 2012; **50:** 6–8.
7. Lipton A, Balakumaran A. Denosumab for the treatment of cancer therapy-induced bone loss and prevention of skeletal-related events in patients with solid tumors. *Expert Rev Clin Pharmacol* 2012; **5:** 359–71.
8. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. *Curr Opin Oncol* 2012; **24:** 397–403.
9. Smith MR, *et al*. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012; **379:** 39–46.
10. Hageman K, *et al*. The role of denosumab for prevention of skeletal-related complications in multiple myeloma. *Ann Pharmacother* 2013; **47:** 1069–74.
11. Ford J, *et al*. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. *Health Technol Assess* 2013; **17:** 1–386. Also available at: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0020/76016/FullReport-hta17290.pdf (accessed 20/08/13)

Adverse Effects and Precautions

The most common adverse effects reported with denosumab include back pain, musculoskeletal pain, hypercholesterolaemia, and cystitis. Other common adverse effects include sciatica, gastrointestinal disturbances such as constipation anaemia, peripheral oedema, asthenia, vertigo, insomnia, pruritus, cardiac disorders such as angina and atrial fibrillation, and other musculoskeletal disorders such as bone pain and myalgia. Skin reactions such as eczema or rash have occurred, and therapy may be stopped if symptoms are severe. Pancreatitis, occasionally fatal, has been reported.

Infections reported during denosumab treatment include upper respiratory-tract infections, cystitis, pharyngitis, and herpes zoster. A higher incidence of serious infections has also been reported, including cellulitis, endocarditis, erysipelas, and infections affecting the abdomen, urinary-tract, and ear. Caution is required in patients also taking immunosuppressive drugs or with an impaired immune system.

Osteonecrosis of the jaw has been reported rarely in patients taking denosumab, as with bisphosphonates (see p. 1176.3). A dental examination should be carried out before starting treatment, and any necessary preventative treatment carried out for those patients with risk factors for osteonecrosis. Good oral hygiene should be maintained during treatment.

Denosumab can cause severe hypocalcaemia and fatalities have occurred. Pre-existing hypocalcaemia should be corrected before treatment begins and calcium and vitamin D supplements should be taken during therapy. Calcium, phosphorus, and magnesium concentrations should be monitored in patients predisposed to hypocalcaemia such as those with severe renal impairment or hypoparathyroidism.

A slightly higher incidence of new malignancies has been reported with denosumab, including breast, reproductive, and gastrointestinal-tract cancers, although a causal link has not been established. In patients with prostate cancer receiving androgen-deprivation therapy, a higher incidence of cataracts and diverticulitis was seen.

Denosumab treatment can suppress bone remodelling and patients should be monitored for adverse outcomes such as delayed fracture healing, atypical fractures, and osteonecrosis of the jaw.

Pharmacokinetics

Peak plasma concentrations of denosumab occur a median of 10 days after a single subcutaneous dose in a fasting patient. Serum-denosumab concentrations then decline over 3 to 5 months with a mean half-life of about 26 days. No accumulation was seen with repeated dosing once every 6 months. Denosumab is expected to be eliminated via immunoglobulin clearance pathways, resulting in degradation to small peptides and amino acids.

References.

1. Gibiansky L, *et al*. Population pharmacokinetic analysis of denosumab in patients with bone metastases from solid tumours. *Clin Pharmacokinet* 2012; **51:** 247–60.
2. Sutjandra L, *et al*. Population pharmacokinetic meta-analysis of denosumab in healthy subjects and postmenopausal women with osteopenia or osteoporosis. *Clin Pharmacokinet* 2011; **50:** 793–807.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Prolia; Xgeva; ***Austria***: Prolia; ***Belg.***: Prolia; Xgeva; ***Canad.***: Prolia; Xgeva; ***Cz.***: Prolia; ***Denm.***: Prolia; Xgeva; ***Fr.***: Prolia; Xgeva; ***Ger.***: Prolia; Xgeva; ***Gr.***: Prolia; ***Hung.***: Prolia; ***Irl.***: Prolia; Xgeva; ***Israel***: Prolia; Xgeva; ***Jpn***: Pralia; Ranmark; ***Neth.***: Prolia; Xgeva; ***Norw.***: Prolia; Xgeva; ***Pol.***: Prolia; ***Singapore***: Prolia; ***Spain***: Prolia; Xgeva; ***Swed.***: Prolia; Xgeva; ***Switz.***: Prolia; ***UK***: Prolia; Xgeva; ***Ukr.***: Prolia (Пролиа); ***USA***: Prolia; Xgeva.

Eldecalcitol *(rINN)*

ED-71; Eldécalcitol; Eldecalcitolum; Эльдекальцитол.

(5*Z*,7*E*)-2β-(3-Hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol.

$C_{30}H_{50}O_5$=490.7

CAS — 104121-92-8.
UNII — I2JP8UE90H.

NOTE. Do not confuse with elocalcitol (p. 2357.3).

Profile

Eldecalcitol is a derivative of vitamin D (p. 2112.3) that is used for the management of osteoporosis (p. 1168.1). The usual oral dose is 750 nanograms daily, although this may be reduced to 500 nanograms in patients unable to tolerate the higher dosage. The main adverse effects are hypercalcaemia and its associated effects such as hypercalciuria.

Reviews.

1. Sanford M, McCormack PL. Eldecalcitol: a review of its use in the treatment of osteoporosis. *Drugs* 2011; **71:** 1755–70. Correction. *ibid.*; 2390.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Edirol.

Etidronate

ATC — M05BA01.
ATC Vet — QM05BA01.

Etidronic Acid *(BAN, USAN, rINN)*

Acide Étidronique; Ácido etidrónico; Acidum Etidronicum; Etidrónico, ácido; Etidronihappo; Etidronsyra; Этидроновая Кислота.

1-Hydroxyethylidenedi(phosphonic acid).

$C_2H_8O_7P_2$=206.0

CAS — 2809-21-4.
ATC — M05BA01.
ATC Vet — QM05BA01.
UNII — M2F465ROXU.

Etidronate Disodium *(USAN, rINNM)*

Dinatrii etidronas; Dinatriumetidronaatti; Dinatriumetidronat; Dinatrium-etidronát; Disodium Etidronate (BANM); Disodu etydronian; Disodyum Etidronat; EHDP; Etidronas Dinatricum; Etidronat-Dinatrium; Etidronate Disodique; Étidronate disodique; Etidronato disódico; Динатрий Этидронат.

Disodium dihydrogen (1-hydroxyethylidene)diphosphonate.

$C_2H_6Na_2O_7P_2$=250.0

CAS — 7414-83-7.
ATC — M05BA01.
ATC Vet — QM05BA01.
UNII — M16PXG993G.

NOTE. Other etidronic acid sodium salts are designated as etidronate monosodium, etidronate trisodium, and etidronate tetrasodium. The name etidronate sodium is used only in *Martindale* where the salt cannot be identified more precisely.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Etidronate Disodium). A white or yellowish, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.2 to 5.2. Store in airtight containers.

USP 36: (Etidronate Disodium). A white powder that may contain lumps. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. pH of a 1% solution in water is between 4.2 and 5.2.

Uses and Administration

Etidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It inhibits the growth and dissolution of hydroxyapatite crystals in bone and may also directly impair osteoclast activity. It diminishes bone resorption and thus reduces bone turnover.

Etidronate is given in bone disorders in which excessive bone resorption is a problem, such as Paget's disease of bone and osteoporosis. In addition, it may be used for the prevention and treatment of ectopic (heterotopic) ossification. Etidronate may also be given orally after a course of intravenous bisphosphonate in the management of hypercalcaemia of malignancy. A chelate of etidronate with radioactive technetium-99m (p. 2228.1) is used diagnostically as a bone scanning agent and a similar compound with rhenium-186 for the palliation of bone metastases in prostate cancer (see below).

Etidronate is given orally as the disodium salt, usually as a single daily dose. Food should be avoided for 2 hours before and after oral doses. Etidronate disodium has also been given by slow intravenous infusion.

In the treatment of **Paget's disease**, etidronate disodium is given orally in a usual initial dose of 5 mg/kg daily for not more than 6 months. Doses above 10 mg/kg daily should be reserved for severe disease and should not be given for more than 3 months at a time. The maximum dose is 20 mg/kg daily. The response to etidronate may be slow in onset and may continue for several months after stopping therapy. Therefore, further treatment should only be given after a drug-free interval of at least 3 months and after evidence of relapse; it should not be given for longer than the initial treatment.

For the treatment of **osteoporosis**, the prevention of bone loss in postmenopausal women, and the prevention and treatment of corticosteroid-induced osteoporosis, etidronate is given in an intermittent or cyclical regimen with a calcium salt; oral etidronate disodium 400 mg is given daily for 14 days followed by the equivalent of 500 mg of elemental calcium orally for 76 days. Treatment has continued for 3 years in most patients; a small number of patients have been successfully treated for up to 7 years. The optimum duration of treatment has not been established.

For the prevention and treatment of **ectopic ossification** complicating hip replacement etidronate disodium has been given orally in a dose of 20 mg/kg daily for 1 month before and 3 months after the operation. For ectopic ossification due to spinal cord injury it has been given in a dose of 20 mg/kg daily for 2 weeks followed by 10 mg/kg daily for 10 weeks.

Etidronate may be given in the management of **hypercalcaemia of malignancy**, to maintain serum-calcium concentrations at an acceptable level after initial treatment with an intravenous bisphosphonate. Etidronate disodium 20 mg/kg daily is given orally for 30 days, starting on the day after the last intravenous bisphosphonate dose. If effective, etidronate treatment may be extended to a maximum of 90 days.

For details of administration in renal impairment, see below.

Administration in renal impairment. The *BNF* has recommended that the oral dose of etidronate should be reduced in patients with mild renal impairment, and that its use should be avoided when impairment is more severe.

Ectopic ossification. Bisphosphonates that inhibit bone mineralisation such as etidronate have been used to prevent ectopic ossification (p. 103.2). Some studies, using higher and more prolonged oral doses (20 mg/kg daily for 6 months) than are generally recommended for treatment after spinal cord injury, have suggested that this may improve effectiveness.[1,2] Etidronate has also been used to treat calciphylaxis and vascular and soft-tissue calcification associated with haemodialysis.[3-5]

1. Banovac K, *et al.* Treatment of heterotopic ossification after spinal cord injury. *J Spinal Cord Med* 1997; **20:** 60–65.
2. Banovac K. The effect of etidronate on late development of heterotopic ossification after spinal cord injury. *J Spinal Cord Med* 2000; **23:** 40–4.
3. Hashiba H, *et al.* Inhibition of the progression of aortic calcification by etidronate treatment in hemodialysis patients: long-term effects. *Ther Apher Dial* 2006; **10:** 59–64.
4. Shiraishi N, *et al.* Successful treatment of a patient with severe calcific uremic arteriolopathy (calciphylaxis) by etidronate disodium. *Am J Kidney Dis* 2006; **48:** 151–4.
5. Mori H, *et al.* Etidronate for the treatment of progressive tumoral calcinosis in hemodialysis patients. *Intern Med* 2007; **46:** 1485–6.

Hypercalcaemia. Bisphosphonates (including etidronate although other bisphosphonates may be more suitable) are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated.

There are reports of response[1-3] to oral etidronate 5 mg/kg twice daily in the treatment of hypercalcaemia associated with subcutaneous fat necrosis of the newborn refractory to standard treatment.

1. Rice AM, Rivkees SA. Etidronate therapy for hypercalcemia in subcutaneous fat necrosis of the newborn. *J Pediatr* 1999; **134:** 349–51.
2. Wiadrowski TP, Marshman G. Subcutaneous fat necrosis of the newborn following hypothermia and complicated by pain and hypercalcaemia. *Australas J Dermatol* 2001; **42:** 207–10.
3. Trullemans B, *et al.* Etidronate per os dans le cadre d'une hypercalcémie secondaire à une cytostéatonécrose compliquée de néphrocalcinose. *Arch Pediatr* 2007; **14:** 170–2.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3). Etidronate, labelled with rhenium-186 or its isotope rhenium-188, is used for the palliation of painful bone metastases of prostate,[1,2] breast,[3,4] lung,[4,5] and various other cancers.[4]

1. Han SH, *et al.* The Placorhen study: a double-blind, placebo-controlled, randomized radionuclide study with ^{186}Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. *J Nucl Med* 2002; **43:** 1150–6.
2. Liepe K, *et al.* Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases. *Br J Cancer* 2003; **89:** 625–9.
3. Sciuto R, *et al.* Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. *Breast Cancer Res Treat* 2001; **66:** 101–9.
4. Li S, *et al.* Rhenium-188 HEDP to treat painful bone metastases. *Clin Nucl Med* 2001; **26:** 919–22.
5. Zhang H, *et al.* Rhenium-188-HEDP therapy for the palliation of pain due to osseous metastases in lung cancer patients. *Cancer Biother Radiopharm* 2003; **18:** 719–26.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including etidronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p. 1168.1). Etidronate is used in a cyclical regimen for both the treatment and prevention of **postmenopausal** osteoporosis. It increases bone mineral density (BMD), largely in the lumbar spine and femoral neck, and reduces the risk of vertebral fractures,[1,2] but not non-vertebral fractures.[2] Additive effects on BMD have been found when etidronate was used with oestrogen.[1] Etidronate also prevents bone loss and maintains or increases BMD in **corticosteroid-induced** osteoporosis,[1,3] and has shown some benefit in reducing bone loss after organ transplantation.[1] In an uncontrolled study[4] in **men** with idiopathic vertebral osteoporosis, cyclical etidronate increased BMD at the lumbar spine.

1. Hanley DA, *et al.* Etidronate therapy in the treatment and prevention of osteoporosis. *J Clin Densitom* 2000; **3:** 79–95.
2. Wells GA, *et al.* Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
3. Adachi JD, *et al.* A pooled data analysis on the use of intermittent cyclical etidronate therapy for the prevention and treatment of corticosteroid induced bone loss. *J Rheumatol* 2000; **27:** 2424–31.
4. Anderson FH, *et al.* Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures. *Age Ageing* 1997; **26:** 359–65.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Initial experience was with etidronate, but bisphosphonates that have less effect on bone mineralisation may be preferred. In studies, alendronate[1] and risedronate[2] were found to be more effective than etidronate.

1. Siris E, *et al.* Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab* 1996; **81:** 961–7.
2. Miller PD, *et al.* A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; **106:** 513–20.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Unlike the newer bisphosphonates etidronate produces marked impairment of bone mineralisation at high therapeutic doses. An increase in bone pain may occur in patients with Paget's disease. Impairment of bone mineralisation may result in osteomalacia, and fractures have been reported. If a fracture occurs etidronate should be stopped until healing is complete. Hyperphosphataemia may occur, usually at high doses, but generally resolves 2 to 4 weeks after the end of therapy. There have been reports of paraesthesias, peripheral neuropathy, and confusion. Burning of the tongue, alopecia, erythema multiforme, and exacerbation of asthma have occurred rarely. Transient loss or alteration of taste has been reported mainly during and after intravenous infusion.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, including etidronate, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the blood. For a report of pancytopenia caused by etidronate therapy, see Effects on the Skin, below.

Effects on the ears. Ototoxicity, manifest as tinnitus and hearing loss, has been reported[1] in 2 patients given etidronate for osteoporosis; both patients had pre-existing otosclerosis and the authors recommended that those with ear pathology be monitored audiometrically when given bisphosphonates.

1. Yeşil S, *et al.* Further hearing loss during osteoporosis treatment with etidronate. *Postgrad Med J* 1998; **74:** 363–4.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including etidronate, see under Bisphosphonates, p. 1175.2.

Effects on the gastrointestinal tract. Oral etidronate was not associated with an increased incidence of upper gastrointestinal problems in a retrospective cohort study.[1] There was also no evidence of an increased incidence of gastrointestinal effects when given with NSAIDs or corticosteroids. Similarly, another large cohort study found no increased risk of peptic ulcer disease associated with the use of cyclical etidronate.[2] However, oesophageal ulceration has been reported with daily etidronate;[3,4] in one case possibly associated with incorrect use,[3] and in another, complicated by prior use of diclofenac, and a history of gastro-oesophageal reflux disease.[4]

1. van Staa T, *et al.* Upper gastrointestinal adverse events and cyclical etidronate. *Am J Med* 1997; **103:** 462–7.
2. Burger H, *et al.* Cyclical etidronate use is not associated with symptoms of peptic ulcer disease. *Eur J Clin Pharmacol* 2000; **56:** 319–22.
3. Macedo G, *et al.* Ulcerative esophagitis caused by etidronate. *Gastrointest Endosc* 2001; **53:** 250–1.
4. Maroy B. Ulcère géant de l'oesophage probablement dû à la prise d'étidronate. *Gastroenterol Clin Biol* 2001; **25:** 917–18.

Effects on the kidneys. Bisphosphonates are excreted by the kidneys, thus caution is advised in patients with renal impairment. When given by intravenous infusion for the treatment of hypercalcaemia of malignancy they have been reported to affect renal function adversely; hypercalcaemia or malignancy may also have contributed. For reports of renal failure associated with etidronate see under Bisphosphonates, p. 1176.1.

Effects on the musculoskeletal system. Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

Effects on mental state. Sensory hallucinations and confusion were reported in an elderly woman given daily etidronate for a week. Symptoms resolved on stopping the drug and recurred on rechallenge.[1] Mood disturbances, lack of concentration, and memory impairment were also reported in 3 patients receiving longer-term cyclical treatment; symptoms again diminished on stopping etidronate and reappeared after rechallenge.[2]

1. Burnet SP, Petrie JP. Wake up and smell the roses'—a drug reaction to etidronate. *Aust N Z J Med* 1999; **29:** 93.
2. Wolffenbuttel BHR, van der Klauw MM. Psychische bijwerkingen van behandeling met bisfosfonaten. *Ned Tijdschr Geneeskd* 2003; **147:** 35–7.

Effects on the respiratory system. For a report of bronchospasm induced by etidronate in an aspirin-sensitive asthmatic, see p. 1177.1. For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, below.

Effects on the skin. A 47-year old woman with a history of auto-immune rheumatic disease developed toxic epidermal necrolysis, pancytopenia, and acute respiratory distress syndrome 7 days after starting etidronate for osteoporosis; she died of cardiorespiratory failure, secondary to the acute respiratory distress syndrome, despite aggressive supportive measures.[1]

1. Coakley G, Isenberg DA. Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. *Br J Rheumatol* 1995; **34:** 798.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare (see p. 1177.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies etidronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Anti-inflammatory drugs. For a lack of apparent interaction between cyclical etidronate and corticosteroids or NSAIDs see under Effects on the Gastrointestinal Tract, p. 1183.3.

Pharmacokinetics

After oral doses of etidronate, absorption is variable and appears to be dose dependent. At usual doses about 1 to 6% of a dose is absorbed. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. Etidronate is rapidly cleared from the blood and has been reported to have a plasma half-life of 1 to 6 hours. It is not metabolised. About 50% is excreted in the urine within 24 hours, the remainder being sequestered to bone and slowly eliminated. The half-life of etidronate in bone exceeds 90 days. Unabsorbed etidronate appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Difosfen; ***Austral.***: Didronel; ***Austria***: Didronel†; ***Belg.***: Osteodidronel; ***Canad.***: Didronel†; ***China***: Bang Te Lin (邦特林); Gende (根德); Luodi (洛迪); Yilin (依膦); ***Denm.***: Didronate†; Didronel; ***Fin.***: Didronate†; ***Fr.***: Didronel; ***Ger.***: Didronel†; Diphos†; Etidron†; ***Gr.***: Anfozan; Biotredine; Dralen; Eopon; Etidron; Etiplus; Feminoflex; Maxibral; Oflocin; Osfo; Ostedron; Osteodrug; Osteoton; Ostogene; Ostopor; Somaflex; Sterodome; Sviroxit; Tilferan; ***India***: Disonate; Dronate-OS†; Etifem; ***Irl.***: Didronel†; ***Israel***: Didronel; ***Ital.***: Etidron; ***Jpn***: Didronel; ***Neth.***: Didronel†; ***Norw.***: Didronate; ***NZ***: Didronel; Etidrate†; ***Pol.***: Ostedron†; ***Rus.***: Xydifon (Ксидифон); ***Singapore***: Difosfen; ***Spain***: Difosfen†; Osteum; ***Swed.***: Didronate†; ***Switz.***: Didronel†; ***Thai.***: Difosfen; ***Turk.***: Didronat; ***UK***: Didronel; ***USA***: Didronel.

Multi-ingredient Preparations. ***Arg.***: Emoform Total; Squam; Squam; ***Austral.***: Didrocal; ***Canad.***: Didrocal; Etidrocal; Gen-Eti-Cal†; Novo-Etidronatecal; ***Denm.***: Didronate Calcium†; ***Fin.***: Didronate + Calcium†; ***Ger.***: Didronel Kit; ***Irl.***: Didronel PMO†; ***Neth.***: Didrokit; ***Norw.***: Didronate + Calsium†; ***Swed.***: Didronate + Calcium; ***UK***: Didronel PMO†; Tiloetca Combi.

Pharmacopoeial Preparations
BP 2014: Etidronate Tablets;
USP 36: Etidronate Disodium Tablets.

Gallium Nitrate *(USAN)*

Galio, nitrato de; NSC-15200; WR-135675.
$Ga(NO_3)_3,9H_2O$=417.9
CAS — 13494-90-1 (anhydrous gallium nitrate); 135886-70-3 (gallium nitrate nonahydrate).
UNII — VRA0C6810N (gallium nitrate); Y2V2R4W9TQ (anhydrous gallium nitrate).

Uses and Administration

Gallium nitrate is an inorganic metallic salt with hypocalcaemic properties. It acts to decrease bone resorption by osteoclasts, with a lesser and probably indirect increase in bone formation, and a consequent decline in serum calcium.

Gallium nitrate is used in the treatment of hypercalcaemia associated with malignant neoplasms. It has been investigated in other disorders associated with abnormally enhanced bone turnover, such as Paget's disease of bone, and is under investigation in refractory non-Hodgkin's lymphoma. For the treatment of hypercalcaemia of malignancy doses of 100 to 200 mg/m^2 may be given daily for up to 5 days, diluted in 1 litre of sodium chloride 0.9% or glucose 5% and infused intravenously over 24 hours. Adequate hydration before and during treatment is essential: a urinary output of at least 2 litres daily should be maintained, and renal function should be regularly monitored.

Hypercalcaemia. Gallium nitrate is used in the treatment of hypercalcaemia of malignancy (p. 1167.2). It appears to be effective in patients with solid tumours and increased levels of parathyroid-related protein.[1,2]

1. Chitambar CR. Gallium nitrate revisited. *Semin Oncol* 2003; **30** (suppl): 1–4.
2. Leyland-Jones B. Treatment of cancer-related hypercalcemia: the role of gallium nitrate. *Semin Oncol* 2003; **30** (suppl); 13–19.

Paget's disease of bone. Beneficial results[1] were reported when gallium nitrate was given subcutaneously in doses of 250 or 500 micrograms/kg daily for 14 days to patients with advanced Paget's disease of bone (p. 1169.3). In this pilot multicentre study 14 days of gallium nitrate injections were followed by 4 weeks off medication and the cycle repeated once.

1. Bockman RS, *et al.* A multicenter trial of low dose gallium nitrate in patients with advanced Paget's disease of bone. *J Clin Endocrinol Metab* 1995; **80:** 595–602.

Adverse Effects, Treatment, and Precautions

Gallium nitrate may produce serious nephrotoxicity, especially when given as a brief intravenous infusion; continuous infusion, with adequate hydration, may reduce the incidence of renal damage. Serum creatinine should be monitored during therapy and treatment stopped if it exceeds 25 mg/litre. Gallium nitrate should be given with great care and in reduced doses, if at all, to patients with existing renal impairment.

Gastrointestinal disturbances, rashes, metallic taste, visual and auditory disturbances, anaemia, hypophosphataemia, and hypocalcaemia have also been reported.

Effects on the nervous system. Although it has been suggested, given the chemical similarity of gallium to aluminium, that repeated doses, particularly in the presence of renal impairment, might lead to severe neurotoxicity,[1] studies in *rats* do not provide any evidence of central neurological abnormalities.[2]

1. Altmann P, Cunningham J. Hazards of gallium for the treatment of Paget's disease of bone. *Lancet* 1990; **335:** 477.
2. Matkovic V, *et al.* Hazards of gallium for Paget's disease of bone. *Lancet* 1990; **335:** 1099. Correction. *ibid.*; 1352.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Ganite.

Ibandronate

ATC — M05BA06.
ATC Vet — QM05BA06.

Ibandronic Acid *(BAN, rINN)*

Acide Ibandronique; Ácido ibandrónico; Acidum Ibandronicum; BM-21.0955; Ibandrónico, ácido; Ibandronik Asit; Ибандроновая Кислота.
[1-Hydroxy-3-(methylpentylamino)propylidene]diphosphonic acid.
$C_9H_{23}NO_7P_2$=319.2
CAS — 114084-78-5.
ATC — M05BA06.
ATC Vet — QM05BA06.
UNII — UMD7G2653W.

Ibandronate Sodium *(USAN)*

Ibandronate de Sodium; Ibandronato sódico; Natrii Ibandronas; Natriumibandronaatti; Natriumibandronat; Sodium Ibandronate (rINNM); Sodium Ibandronate (BANM); Натрий Ибандронат.
$C_9H_{22}NNaO_7P_2,H_2O$=359.2
CAS — 138926-19-9.
ATC — M05BA06.
ATC Vet — QM05BA06.
UNII — J12U072QL0.

Uses and Administration

Ibandronate is an aminobisphosphonate (p. 1173.3) that is a potent inhibitor of bone resorption. It is used as the sodium salt in hypercalcaemia of malignancy, for the prevention of fracture and bone complications in patients with breast cancer and bone metastases, and for the treatment and prevention of postmenopausal osteoporosis.

Ibandronate sodium is given by intravenous infusion or orally, the dose being expressed in terms of ibandronic acid; ibandronate sodium 1.13 mg is equivalent to about 1 mg of ibandronic acid. Specific instructions for oral use (see Precautions in Alendronate, p. 1172.3) should be followed to minimise adverse effects and permit adequate absorption.

For **hypercalcaemia of malignancy**, a single intravenous dose of the equivalent of 2 to 4 mg ibandronic acid is given, up to a maximum of 6 mg; it is diluted in 500 mL of sodium chloride 0.9% or glucose 5%, and infused over 2 hours.

For the prevention of skeletal events in patients with breast cancer and **bone metastases**, the equivalent of 6 mg ibandronic acid is given intravenously, diluted in 100 mL of sodium chloride 0.9% or glucose 5%, and infused over at least 15 minutes. The dose is repeated every 3 to 4 weeks. Alternatively, ibandronic acid 50 mg daily may be given orally.

For the prevention and treatment of postmenopausal **osteoporosis**, ibandronate is given orally in a usual dose equivalent to 150 mg of ibandronic acid once monthly on the same date each month; alternatively, 2.5 mg daily may be given. If the once-monthly dose is missed, and the next scheduled dose is more than 7 days away, the dose should be taken the next morning, and the patient should then return to the original schedule. However, if the next dose is less than 7 days away, then the patient should wait until that next scheduled dose; 2 tablets must not be taken within the same week. Alternatively, treatment may be given intravenously, in a dose equivalent to 3 mg of ibandronic acid once every 3 months; the injection is given over 15 to 30 seconds. If the dose is missed, the injection should be given as soon as possible; the next injection should then be rescheduled 3 months from this injection, as it should not be given more frequently than once every 3 months.

For details of doses in renal impairment, see below.

General references.

1. Dooley M, Balfour JA. Ibandronate. *Drugs* 1999; **57:** 101–108.
2. Barrett J, *et al.* Ibandronate: a clinical pharmacological and pharmacokinetic update. *J Clin Pharmacol* 2004; **44:** 951–65.
3. Anonymous. Ibandronate (Boniva): a new oral bisphosphonate. *Med Lett Drugs Ther* 2005; **47:** 35.
4. Guay DR. Ibandronate, an experimental intravenous bisphosphonate for osteoporosis, bone metastases, and hypercalcemia of malignancy. *Pharmacotherapy* 2006; **26:** 655–73.
5. Zaidi M, *et al.* Progression of efficacy with ibandronate: a paradigm for the development of new bisphosphonates. *Ann N Y Acad Sci* 2007; **1117:** 273–82.
6. Reginster JY, *et al.* Ibandronate in profile: drug characteristics and clinical efficacy. *Expert Opin Drug Metab Toxicol* 2008; **4:** 941–51.

Administration in renal impairment. UK and US licensed product information for ibandronate states that the dose should be adjusted on the basis of creatinine clearance (CC).

When used for the prevention of skeletal events in patients with breast cancer and **bone metastases**, the following *oral* doses are recommended:

- CC equal to or greater than 50 mL/minute: no adjustment necessary
- CC less than 50 mL/minute but equal to or greater than 30 mL/minute: 50 mg every other day
- CC below 30 mL/minute: 50 mg once weekly

Since a 15-minute infusion time has not been studied in cancer patients with a CC less than 50 mL/minute, the following *intravenous* doses are recommended, to be given every 3 to 4 weeks in a solution of sodium chloride 0.9% or glucose 5%:

- CC equal to or greater than 50 mL/minute: no adjustment necessary
- CC less than 50 mL/minute, but equal to or greater than 30 mL/minute: 4 mg in 500 mL of infusion solution, infused over 1 hour
- CC less than 30 mL/minute: 2 mg in 500 mL of infusion solution, infused over 1 hour

In patients with **osteoporosis**, the following recommendations are given, for *oral* or *intravenous* use:

- mild or moderate renal impairment (CC equal to or greater than 30 mL/minute): no adjustment necessary
- CC below 30 mL/minute: not recommended

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. In a dose-response study,[1] 2 mg of ibandronate was found to be significantly less effective than 4 or 6 mg in correcting hypercalcaemia, and response was better in those patients with breast cancer or haematological tumours. In comparison to pamidronate,[2] ibandronate was reported to be more effective in those patients with higher initial baseline serum calcium; duration of response was also longer with ibandronate. In a series of case reports, intravenous ibandronate rapidly corrected hypercalcaemia and restored renal function in multiple myeloma patients. The authors suggested that, although unlicensed for this use, ibandronate should be considered in this patient population.[3]

1. Ralston SH, *et al.* Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. *Br J Cancer* 1997; **75:** 295–300.
2. Pecherstorfer M, *et al.* Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer* 2003; **11:** 539–47.
3. Henrich D, *et al.* Ibandronate for the treatment of hypercalcemia or nephrocalcinosis in patients with multiple myeloma and acute renal failure: case reports. *Acta Haematol (Basel)* 2006; **116:** 165–72.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Ibandronate is licensed for such use in many countries. In patients with bone metastases from breast cancer, both oral[1] and intravenous[2] ibandronate reduced the skeletal morbidity period rate (the number of 12-week periods with new bone complications). A pilot study[3] in

18 patients with skeletal metastases from various tumours, and with bone pain insufficiently controlled with opioid analgesics, found short-term intensive intravenous ibandronate (4 mg for 4 consecutive days) to significantly reduce bone pain scores; this analgesic effect was obtained within 7 days, and sustained for a further 5 weeks. A review[4] concluded that once-monthly intravenous dosing could aid compliance, since it can be given simultaneously with cancer therapy; the absence of any apparent renal toxicity associated with ibandronate was a further advantage in its use in cancer patients.

Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Tripathy D, *et al.* Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* 2004; **15:** 743–50.
2. Body J-J, *et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003; **14:** 1399–1405.
3. Mancini I, *et al.* Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. *J Clin Oncol* 2004; **22:** 3587–92.
4. McCormack PL, Plosker GL. Ibandronic acid: a review of its use in the treatment of bone metastases of breast cancer. *Drugs* 2006; **66:** 711–28.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). In the treatment of **postmenopausal** osteoporosis, *oral* ibandronate in intermittent regimens of 20 mg every alternate day,[1] or 20 mg weekly[2] has been found to have equivalent effects on bone mineral density (BMD) to 2.5 mg daily. Intermittent oral ibandronate (20 mg every alternate day for 12 doses every 3 months) was also as effective as the lower daily dose in reducing the incidence of osteoporotic fractures in postmenopausal women.[3] In the prevention of postmenopausal osteoporosis, both 2.5 mg daily[4] and 20 mg weekly[5] prevented bone loss at the spine and hip. A large study comparing three different monthly regimens with the 2.5 mg daily regimen found them to be of similar efficacy in terms of improvement in lumbar BMD after 1 year; 150 mg given once monthly was considered to be superior to the low-dose daily regimen.[6] A review[7] concluded that this unique once-monthly regime could benefit patients by improving compliance.

Intravenous ibandronate 2 mg given every 3 months has also proven effective in increasing BMD in the treatment[8] and prevention[9] of postmenopausal osteoporosis. A large, randomised, double-blind study compared 2 intravenous regimens (2 mg every 2 months and 3 mg every 3 months) with oral ibandronate 2.5 mg daily in postmenopausal women with osteoporosis. After 1 year, both intravenous regimens increased lumbar BMD scores significantly more than the oral regimen. Similar results were obtained for proximal femoral BMD scores, except that for femoral neck BMD, the 2-monthly regimen and daily oral regimen were not significantly different.[10] After 2 years, these results were reported to have been maintained.[11] In **corticosteroid-induced** osteoporosis, intravenous ibandronate 2 mg every 3 months was better than daily oral alfacalcidol at reducing vertebral fractures.[12,13] Intravenous ibandronate has also shown to be of benefit in reducing bone loss after kidney **transplantation**.[14] A pilot study[15] of intermittent ibandronate given intravenously to **men** with severe osteoporosis significantly increased BMD at the lumbar spine, trochanter, and femoral neck.

1. Riis BJ, *et al.* Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. *J Bone Miner Res* 2001; **16:** 1871–8.
2. Cooper C, *et al.* Efficacy and safety of oral weekly ibandronate in the treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88:** 4609–15.
3. Chesnut CH, *et al.* Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004; **19:** 1241–9.
4. McClung MR, *et al.* Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res* 2004; **19:** 11–18.
5. Tankó LB, *et al.* Oral weekly ibandronate prevents bone loss in postmenopausal women. *J Intern Med* 2003; **254:** 159–67.
6. Miller PD, *et al.* Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* 2005; **20:** 1315–22.
7. Chesnut CH. Treating osteoporosis with bisphosphonates and addressing adherence: a review of oral ibandronate. *Drugs* 2006; **66:** 1351–9.
8. Adami S, *et al.* Efficacy and safety of ibandronate given by intravenous injection once every 3 months. *Bone* 2004; **34:** 881–9.
9. Stakkestad JA, *et al.* Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. *Ann Rheum Dis* 2003; **62:** 969–75.
10. Delmas PD, *et al.* Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006; **54:** 1838–46.
11. Croom KF, Scott LJ. Intravenous ibandronate: in the treatment of osteoporosis. *Drugs* 2006; **66:** 1593–1601.
12. Ringe JD, *et al.* Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. *Osteoporosis Int* 2003; **14:** 801–7.
13. Ringe JD, *et al.* Three-month ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis. *Rheumatology (Oxford)* 2003; **42:** 743–9.
14. Grotz W, *et al.* Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001; **12:** 1530–7.
15. Lamy O, *et al.* Intravenous ibandronate in men with osteoporosis: an open pilot study over 2 years. *J Endocrinol Invest* 2003; **26:** 728–32.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Gastrointestinal symptoms such as abdominal pain, dyspepsia, and nausea are the most frequent adverse effects with oral ibandronate. Severe oesophageal reactions such as oesophagitis, and ulceration have occurred; patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn. Gastric ulceration has been reported. To minimise the risk of oesophageal reactions, precautions similar to those for alendronate (see p. 1172.3) should be observed. Anaemia and bronchospasm have occurred rarely, as has taste disturbance, paraesthesia, and uraemia. Serum calcium, magnesium, and phosphate should be monitored. Hypocalcaemia should be corrected before starting ibandronate therapy; adequate intake of calcium and vitamin D is important. Transient fever after parenteral use is common. Flu-like symptoms have been reported after both parenteral and intermittent oral use, typically after the first dose.

Effects on the musculoskeletal system. Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, including ibandronate, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibandronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Like other bisphosphonates, ibandronate is poorly absorbed after oral doses; absolute bioavailability is less than 1%. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is reduced by about 90% when given with food, by about 30% when given half an hour before food, and by about 75% when given 2 hours after food. About half of the absorbed portion is sequestered to bone; the remainder is excreted in urine. Plasma protein binding is about 87%. Bisphosphonates do not appear to be metabolised, and the unabsorbed fraction of ibandronate is excreted unchanged in the faeces.

References.
1. Bergner R, *et al.* Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. *J Clin Pharmacol* 2007; **47:** 942–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adromux; Bandrobon; Bantuc; Bonviva; Brexell Plus; Deltrox; Elasterin; Femorel; Ibanleg; Idena; Mesel; Modifical; Silidral Uno; ***Austral.***: Bondronat; ***Austria***: Bondronat; Bonviva; ***Belg.***: Bondronat; Bonviva; ***Braz.***: Bonviva; ***Chile***: Bondronat; Bonviva; Darmas; Dronaval; Ibadrox; Ibames; Idena; Recaxin; ***China***: Ai Ben (艾本); Bondronat (邦罗力); Jia Nuo Shun (佳诺顺); ***Cz.***: Baxogar; Bondenza†; Bondronat; Bonviva; Etanorden; Gerousia; Iasibon; Mirdezel; Ossica; Quodixor; ***Denm.***: Bondronat; Bonviva; Etanorden; Iasibon; ***Fin.***: Bondronat; Bonviva; Clastec; Ibamyl; ***Fr.***: Bondronat; Bonviva; ***Ger.***: Bondronat; Bonviva; ***Gr.***: Bondronat; Bonviva; ***Hong Kong***: Bondronat; Bonviva; ***Hung.***: Bondronat; Bonviva; Ossica; ***India***: Bandrone; Bondronat; Bonviva; Idrofos; ***Indon.***: Bondronat; Bonviva; ***Irl.***: Bondenza†; Bondronat; Bonefurbit; Bonviva; Iasibon; Kefort; Osbonelle; ***Israel***: Bonat; ***Ital.***: Bondronat; Bonviva; Etanorden; Licobondrat; ***Jpn***: Bonviva; ***Malaysia***: Bonviva; ***Mex.***: Bondronat†; Bonviva; ***Neth.***: Baxogar; Bondenza†; Bondronat; Bonefurbit; Bonviva; Destara†; Etanorden; Iasibon; Ibagenit; IbandroMylan; Ikametin; Licobondrat; Osbonelle; Phacebonate; Quodixor; Ribobandron; ***Norw.***: Bondronat; Bonviva; ***Philipp.***: Bondronat; Bonviva; ***Pol.***: Bondenza†; Bondronat; Bonviva; Iasibon; Ossica; ***Port.***: Bondenza†; Bondronat; Bonviva; Destara†; ***Rus.***: Bondronat (Бондронат); Bonviva (Бонвива); ***S.Afr.***: Bondronat; ***Singapore***: Bondronat; Bonviva; ***Spain***: Abrion; Bondenza†; Bondronat; Bonviva; ***Swed.***: Bondronat; Bonviva; ***Switz.***: Bondronat; Bonviva; ***Thai.***: Bondronat†; Bonviva; ***Turk.***: Bondronat; Bonviva; Osiban; ***UK***: Bondronat; Bonviva; ***Ukr.***: Bondronat (Бондронат); Bonviva (Бонвива); ***USA***: Boniva.

Multi-ingredient Preparations. ***Arg.***: Femorel Max; Modifical Duo.

Incadronate

Incadronic Acid *(rINN)*

Acide Incadronique; Ácido incadrónico; Acidum Incadronicum; Cimadronic Acid; Incadrónico, ácido; YM-175; Инкадроновая Кислота.

[(Cycloheptylamino)methylene]diphosphonic acid.

$C_8H_{19}NO_6P_2$=287.2

CAS — 124351-85-5.

UNII — G5C4M8847E.

Incadronate Disodium

Disodium Incadronate (rINNM); Incadronas Dinatricum; Incadronate Disodique; Incadronato disódico; Динатрий Инкадронат.

Disodium [(cycloheptylamino)methylene]diphosphonate.

$C_8H_{17}NNa_2O_6P_2$=331.2

CAS — 138330-18-4.

Profile

Incadronate is an aminobisphosphonate (p. 1173.3) that is a potent inhibitor of bone resorption. It is given by intravenous infusion as incadronate disodium for hypercalcaemia of malignancy in a dose of 10 mg over 2 to 4 hours; if necessary this dose may be repeated at intervals of no less than 1 week. Hypocalcaemia and hypotension may occur. Incadronate is under investigation for the treatment of bone metastases in patients with breast cancer.

References.
1. Usui T, *et al.* Pharmacokinetics of incadronate, a new bisphosphonate, in healthy volunteers and patients with malignancy-associated hypercalcemia. *Int J Clin Pharmacol Ther* 1997; **35:** 239–44.
2. Matsumoto T, *et al.* Comparative study of incadronate and elcatonin in patients with malignancy-associated hypercalcaemia. *J Int Med Res* 2002; **30:** 230–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Yin Fu (茵福); ***Jpn***: Bisphonal†; ***Philipp.***: Bisphonal; ***Thai.***: Bisphonal.

Ipriflavone *(rINN)*

FL-113; Ipriflavona; Ipriflavonum; Иприфлавон.

7-Isopropoxyisoflavone.

$C_{18}H_{16}O_3$=280.3

CAS — 35212-22-7.

ATC — M05BX01.

ATC Vet — QM05BX01.

UNII — 80BJ7WN25Z.

Profile

Ipriflavone is a synthetic isoflavonoid that inhibits resorption of bone and is available in some countries for the treatment of osteoporosis (p. 1168.1). It is given orally in a dose of 200 mg three times daily.

Osteoporosis. Despite an earlier favourable report,[1] a prospective randomised controlled study in postmenopausal women with low bone mass failed to show prevention of bone loss or improvements in markers of bone metabolism with ipriflavone.[2] There was also a significant incidence of lymphopenia with the drug.

1. Agnusdei D, *et al.* Effects of ipriflavone on bone mass and bone remodeling in patients with established postmenopausal osteoporosis. *Curr Ther Res* 1992; **51:** 82–91.
2. Alexandersen P, *et al.* Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001; **285:** 1482–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Osteoplus; Rebone; ***China***: An Ti Fen (安体芬); Gu Su An (固苏桉); Li La (力拉); Xin Yi Sheng (信依生); ***Ital.***: Osteofix; ***Jpn***: Osten.

Multi-ingredient Preparations. ***Arg.***: Copelia; ***India***: Calflavone; Ipridol; ***Indon.***: Vosteon; ***UK***: Osteopro.

Lasofoxifene *(BAN, rINN)* ⊗

Lasofoxifène; Lasofoxifeno; Lasofoxifenum; Лазофоксифен.

(-)-*cis*-5,6,7,8-Tetrahydro-6-phenyl-5-{*p*-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2-naphthol.

$C_{28}H_{31}NO_2$=413.6

CAS — 180916-16-9.

ATC — G03XC03.

ATC Vet — QG03XC03.

UNII — 337G83N988.

Lasofoxifene Tartrate *(BANM, USAN, rINNM)* ⊗

CP-336156CB; Lasofoxifene, Tartrate de; Lasofoxifeni Tartras; Tartrato de lasofoxifeno; Лазофоксифена Тартрат.
(-)-*cis*-5,6,7,8-Tetrahydro-6-phenyl-5-{*p*-[2-(1-pyrrolidinyl) ethoxy]phenyl}-2-naphthol D-tartrate (1:1).
$C_{28}H_{31}NO_3.C_4H_6O_6$=563.6
CAS — 190791-29-8.
ATC — G03XC03.
ATC Vet — QG03XC03.
UNII — 85X09V2GSO.

NOTE. The name Fablyn has been used as a trade mark for lasofoxifene tartrate.

Profile

Lasofoxifene is a selective oestrogen receptor modulator similar to raloxifene (p. 2303.1), that was developed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

References.

1. Gennari L. Lasofoxifene, a new selective estrogen receptor modulator for the treatment of osteoporosis and vaginal atrophy. *Expert Opin Pharmacother* 2009; **10:** 2209–20.
2. Cummings SR, *et al.* PEARL Study Investigators. Lasofoxifene in postmenopausal women with osteoporosis. *N Engl J Med* 2010; **362:** 686–96.
3. LaCroix AZ, *et al.* PEARL Investigators. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. *J Natl Cancer Inst* 2010; **102:** 1706–15.
4. Ensrud K, *et al.* Lasofoxifene and cardiovascular events in postmenopausal women with osteoporosis: five-year results from the postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial. *Circulation* 2010; **122:** 1716–24.
5. Goldstein SR, *et al.* Postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial: 5-year gynecological outcomes. *Menopause* 2011; **18:** 17–22.
6. Peterson GM, *et al.* Lasofoxifene: selective estrogen receptor modulator for the prevention and treatment of postmenopausal osteoporosis. *Ann Pharmacother* 2011; **45:** 499–509.

Medronate

Medronic Acid *(BAN, USAN, pINN)*

Acid medronique; Acide Médronique; Ácido medrónico; Acidum medronicum; Medrónico, ácido; Медроновая Кислота.
Methylenebis(phosphonic acid).
$CH_6O_6P_2$=176.0
CAS — 1984-15-2.
UNII — 73OS0QIN3O.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Medronic Acid for Radiopharmaceutical Preparations). A white or almost white, amorphous or crystalline, hygroscopic powder. Very soluble in water; very slightly soluble in absolute alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Medronate Disodium *(USAN, pINNM)*

Disodium Medronate (BANM); Disodium Methylene Diphosphonate; MDP; Medronas Dinatricum; Médronate Disodique; Medronato disódico; Динатрий Медронат.
Disodium dihydrogen methylenediphosphonate.
$CH_4Na_2O_6P_2$=220.0
CAS — 25681-89-4.
UNII — HAY5MT18L3.

Profile

Medronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It has a strong affinity for bone. Complexes of medronate disodium and stannous chloride or fluoride, or medronic acid, stannous chloride dihydrate, and ascorbic acid, are labelled with radioactive technetium-99m (p. 2228.1) and used diagnostically as bone scanning agents; they are given intravenously.

Hypersensitivity. For reference to a severe allergic reaction attributed to the medronate component of a radiopharmaceutical, see under Adverse Effects and Precautions of Bisphosphonates, p. 1177.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Amerscan Medronate†; ***Irl.***: Medronate Draximage†; ***Israel***: Frosstimage Kit (MDP).

Multi-ingredient Preparations. ***Denm.***: Amerscan Stannous†.

Minodronate

Minodronic Acid *(rINN)*

Acide Minodronique; Ácido minodrónico; Acidum minodronicum; Ono-5920; YH-529; YM-529; Минодроновая Кислота.
(1-Hydroxy-2-imidazo[1,2-*a*]pyridin-3-ylethylidene)diphosphonic acid.
$C_9H_{12}N_2O_7P_2$=322.1
CAS — 127657-42-5.
UNII — 40SGR63TGL.

Profile

Minodronate is a bisphosphonate that inhibits bone resorption. It is given as minodronic acid hydrate for the treatment of osteoporosis; 1 mg is given orally once daily, usually in the morning. Specific instructions for oral use (see Precautions in Alendronate, p. 1172.3) should be followed to minimise adverse effects and permit adequate absorption.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn.***: Bonoteo; Recalbon.

Neridronate

Neridronic Acid *(rINN)*

Acide Néridronique; Ácido neridrónico; Acidum neridronicum; AHDP; AHHexBP; Aminohexane Diphosphonate; Neridrónico, ácido; Неридроновая Кислота.
(6-Amino-1-hydroxyhexylidene)diphosphonic acid.
$C_6H_{17}NO_7P_2$=277.1
CAS — 79778-41-9.
UNII — 8U27U3RIN4.

Neridronate Sodium *(rINNM)*

Natrii Neridronas; Néridronate de Sodium; Neridronato sódico; Натрий Неридронат.
UNII — H6JVB49Q0F.

Profile

Neridronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p. 1173.3). It inhibits bone resorption and is given intravenously as the sodium salt in the management of osteogenesis imperfecta (p. 1167.3); it has been used in the treatment of malignant hypercalcaemia (p. 1167.2) and diseases associated with excessive bone turnover such as Paget's disease of bone (p. 1169.3) and osteoporosis (p. 1168.1). The intramuscular route has also been used.

References.

1. O'Rourke NP, *et al.* Treatment of malignant hypercalcaemia with aminohexane bisphosphonate (neridronate). *Br J Cancer* 1994; **69:** 914–17.
2. Filipponi P, *et al.* Paget's disease of bone: benefits of neridronate as a first treatment and in cases of relapse after clodronate. *Bone* 1998; **23:** 543–8.
3. Adami S, *et al.* Short-term intravenous therapy with neridronate in Paget's disease. *Clin Exp Rheumatol* 2002; **20:** 55–8.
4. Adami S, *et al.* Intravenous neridronate in adults with osteogenesis imperfecta. *J Bone Miner Res* 2003; **18:** 126–30.
5. Braga V, *et al.* Intravenous intermittent neridronate in the treatment of postmenopausal osteoporosis. *Bone* 2003; **33:** 342–5.
6. Cascella T, *et al.* Effects of neridronate treatment in elderly women with osteoporosis. *J Endocrinol Invest* 2005; **28:** 202–8.
7. Gatti D, *et al.* Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled study. *J Bone Miner Res* 2005; **20:** 758–63.
8. Adami S, *et al.* Intramuscular neridronate in postmenopausal women with low bone mineral density. *Calcif Tissue Int* 2008; **83:** 301–7.
9. Benucci M, *et al.* Effects of monthly intramuscular neridronate in rheumatic patients in chronic treatment with low-dose glucocorticoids. *Clin Exp Rheumatol* 2009; **27:** 567–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Nerixia.

Odanacatib *(USAN, rINN)*

Odanacatibum; Оданакатиб.
(2*S*)-*N*-(1-Cyanocyclopropyl)-4-fluoro-4-methyl-2-{[(1*S*)-2,2,2-trifluoro-1-[4′-(methylsulfonyl)(1,1′-biphenyl)-4-yl]ethyl} amino)pentanamide.
$C_{25}H_{27}F_4N_3O_3S$=525.6
CAS — 603139-19-1.
UNII — N673F6W2VH.

Profile

Odanacatib is a cathepsin-K inhibitor that reduces bone resorption. It is being investigated for the treatment of osteoporosis.

References.

1. Bone HG, *et al.* Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. *J Bone Miner Res* 2009; **25:** 937–47.
2. Lewiecki EM. Odanacatib, a cathepsin K inhibitor for the treatment of osteoporosis and other skeletal disorders associated with excessive bone remodeling. *IDrugs* 2009; **12:** 799–809.

Oxidronate

Oxidronic Acid *(BAN, USAN, pINN)*

Acide Oxidronique; Ácido oxidrónico; Acidum Oxidronicum; Oxidrónico, ácido; Оксидроновая Кислота.
(Hydroxymethylene)diphosphonic acid.
$CH_6O_7P_2$=192.0
CAS — 15468-10-7.
UNII — 71MR4V32TI.

Oxidronate Disodium *(pINNM)*

Disodium Oxidronate; HMDP; Oxidronas Dinatricum; Oxidronate Disodique; Oxidronate Sodium; Oxidronato disódico; Sodium Oxidronate (BANM); Динатрий Оксидронат.
Disodium (hydroxymethylene)diphosphonate.
$CH_4Na_2O_7P_2$=236.0
CAS — 14255-61-9.
UNII — H852YK87WP.

Profile

Oxidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It has a strong affinity for bone. A chelate of oxidronate disodium with radioactive technetium-99m (p. 2228.1) is used diagnostically as a bone scanning agent; it is given intravenously.

Pamidronate

ATC — M05BA03.
ATC Vet — QM05BA03.
UNII — OYY3447OMC.

Pamidronic Acid *(BAN, rINN)*

Acide Pamidronique; Ácido pamidrónico; Acidum Pamidronicum; Aminohydroxypropylidenebisphosphonate; APD; Pamidrónico, ácido; Pamidronihappo; Pamidronsyra; Памидроновая Кислота.
3-Amino-1-hydroxypropylidenebis(phosphonic acid).
$C_3H_{11}NO_7P_2$=235.1
CAS — 40391-99-9.
ATC — M05BA03.
ATC Vet — QM05BA03.

Pamidronate Disodium *(USAN, rINNM)*

Aminohydroxypropylidenebisphosphonate Disodium; CGP-23339A; CGP-23339AE; Dinatrii Pamidronas Pentahydricus; Dinatriumpamidronaattipentahydraatti; Dinatrium-pamidronát pentahydrát; Disodium Aminohydroxypropylidenediphosphonate; Disodium Pamidronate (BANM); Disodu pamidronian pięciowodny; Disodyum Pamidronat; Pamidronaattidinatrium; Pamidronas Dinatricum; Pamidronatdinatrium; Pamidronatdinatriumpentahydrat; Pamidronate Disodique; Pamidronate disodique pentahydraté; Pamidronato disódico; Pamidronatum Dinatricum; Динатрий Памидронат.
Disodium 3-amino-1-hydroxypropylidenebisphosphonate pentahydrate.
$C_3H_9NNa_2O_7P_2.5H_2O$=369.1
CAS — 109552-15-0 (pamidronate disodium pentahydrate); 57248-88-1 (anhydrous pamidronate disodium).
ATC — M05BA03.
ATC Vet — QM05BA03.
UNII — 8742T8ZQZA (pamidronate disodium pentahydrate); C7S8VWP5DH (anhydrous pamidronate disodium).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Pamidronate Disodium Pentahydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in dichloromethane. It is sparingly soluble in dilute mineral acids and dissolves in dilute alkaline solutions. A 1.0% solution in water has a pH of 7.8 to 8.8.

USP 36: (Pamidronate Disodium). A white crystalline powder. Soluble in water and in 2N sodium hydroxide; sparingly soluble 0.1N acetic acid and in 0.1N hydrochloric acid; practically insoluble in organic solvents. pH of a 1% solution in water is between 7.8 and 8.8. Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Pamidronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses.

Pamidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also used in the treatment of osteolytic lesions and bone pain in multiple myeloma or bone metastases associated with breast cancer. It may also be of benefit in bone disorders associated with excessive bone resorption, including Paget's disease of bone.

Pamidronate disodium is given by slow intravenous infusion. UK licensed product information recommends infusion at a rate not exceeding 60 mg/hour (or not exceeding 20 mg/hour in patients with established or suspected renal impairment) and at a concentration not exceeding 60 mg per 250 mL of infusion solution (sodium chloride 0.9% or glucose 5%). In the USA, the recommended concentration of infusion and rate vary depending on the indication.

In **hypercalcaemia of malignancy** pamidronate disodium is given by slow intravenous infusion in a total dose of 15 to 90 mg according to the initial plasma-calcium concentration. In the UK, the total dose is given as a single infusion or in divided doses over 2 to 4 days. In the USA, the total dose is given as a single infusion, doses of 60 mg to 90 mg being given over 2 to 24 hours. Plasma-calcium concentrations generally start declining 24 to 48 hours after a dose of pamidronate with normalisation within 3 to 7 days. Treatment may be repeated if normocalcaemia is not achieved within this time or if hypercalcaemia recurs.

In patients with **osteolytic lesions and bone pain** of multiple myeloma or bone metastases associated with breast cancer, pamidronate disodium may be given in doses of 90 mg by intravenous infusion every 3 to 4 weeks.

In the treatment of **Paget's disease** the dosage regimen in the UK is 30 mg by slow infusion once a week for 6 weeks (total dose 180 mg), or 30 mg in the first week then 60 mg every other week for 6 weeks (total dose 210 mg). These courses may be repeated every 6 months, and the total dose increased if necessary up to a maximum of 360 mg. Alternatively, the dose used in the USA is 30 mg by infusion over 4 hours, repeated on consecutive days to a total dose of 90 mg. This course is repeated when clinically indicated.

For details of administration in renal impairment, see below.

Pamidronate has also been given orally.

General references.

1. Coukell AJ, Markham A. Pamidronate: a review of its use in the management of osteolytic bone metastases, tumour-induced hypercalcaemia and Paget's disease of bone. *Drugs Aging* 1998; **12:** 149–68.

Administration in renal impairment. Pharmacokinetic studies suggest that no dosage reduction of pamidronate disodium is required in patients with any degree of renal impairment.[1] However, UK product information currently recommends that the rate of infusion be reduced to a maximum of 20 mg/hour for patients with established or suspected renal impairment; use in those with severe renal impairment (creatinine clearance less than 30 mL/minute) is not advised as clinical experience is limited.

1. Berenson JR, *et al.* Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol* 1997; **37:** 285–90.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients. In small studies, intravenous pamidronate 30 mg daily for 3 days, or at 1 mg/kg daily for 1 or 3 days,[1] or 60 mg daily for 3 days,[2] significantly improved pain and range of movement in cases refractory to previous treatment.

1. Maillefert JF, *et al.* Pooled results from 2 trials evaluating bisphosphonates in reflex sympathetic dystrophy. *J Rheumatol* 1999; **26:** 1856–7.
2. Kubalek I, *et al.* Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases. *Rheumatology (Oxford)* 2001; **40:** 1394–7.

Gaucher disease. Treatment with oral pamidronate disodium in doses of 600 mg daily in adults,[1] and 150 to 300 mg daily in children,[2] or intravenous pamidronate disodium in doses of 45 mg every 3 weeks,[3] has been reported to improve bone lesions of Gaucher disease (p. 2433.3) in a few patients.

1. Harinck HIJ, *et al.* Regression of bone lesions in Gaucher's disease during treatment with aminohydroxypropylidene bisphosphonate. *Lancet* 1984; **ii:** 513.
2. Samuel R, *et al.* Aminohydroxy propylidine bisphosphonate (APD) treatment improves the clinical skeletal manifestations of Gaucher's disease. *Pediatrics* 1994; **94:** 385–9.
3. Ciana G, *et al.* Short-term effects of pamidronate in patients with Gaucher's disease and severe skeletal involvement. *N Engl J Med* 1997; **337:** 712.

Hypercalcaemia. Bisphosphonates, of which pamidronate is one of the most effective, are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Pamidronate is licensed for such use in many countries. A literature review[1] of phase II and III studies concluded that pamidronate was effective in the treatment of pain and skeletal complications from metastatic disease, particularly in patients with breast cancer or multiple myeloma, but that its efficacy in those with other neoplasms needed confirmation. A long-term follow-up[2] of 2 randomised trials of pamidronate in women with breast cancer confirmed its efficacy over placebo. However, a pooled analysis[3] of its use for palliation of bone pain in men with metastatic prostate cancer found no treatment benefit with pamidronate over placebo. A meta-analysis[4] confirmed the benefits of the bisphosphonate in reducing skeletal events, and hence morbidity, in patients with cancer, but not mortality; however, no clear advantage could be shown versus clodronate or zoledronate, which were also of benefit. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Ripamonti C, *et al.* Role of pamidronate disodium in the treatment of metastatic bone disease. *Tumori* 1998; **84:** 442–55.
2. Lipton A, *et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; **88:** 1082–90.
3. Small EJ, *et al.* Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003; **21:** 4277–84.
4. Machado M, *et al.* Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009; **31:** 962–79.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including pamidronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Osteogenesis imperfecta. Pamidronate has produced benefit in patients with osteogenesis imperfecta (p. 1167.3). Although the dosage and timing varied between centres and age groups, all patients were given cyclical intravenous pamidronate;[1-6] bone mineral density increased, fracture incidence decreased, and patients reported improvements in mobility, pain and chronic fatigue. Treated infants achieved motor milestones earlier than untreated controls; vertebral height was also improved.[5] While bone size and density also increased in patients given pamidronate, especially in those with larger baseline deficits in bone mass,[7] serum calcium decreased markedly, and bone turnover was suppressed;[8] clinical problems were not evident if calcium intake was sufficient, but consequences of a chronically low bone turnover are unknown. A study in young patients found that bone metabolism is still suppressed, and that bone mass gains continue, for 2 years after stopping therapy.[9]

1. Glorieux FH, *et al.* Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998; **339:** 947–52.
2. Plotkin H, *et al.* Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab* 2000; **85:** 1846–50.
3. Åström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002; **86:** 356–64.
4. Falk MJ, *et al.* Intravenous bisphosphonate therapy in children with osteogenesis imperfecta. *Pediatrics* 2003; **111:** 573–8.
5. Åström E, *et al.* Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. *Arch Dis Child* 2007; **92:** 332–8.
6. Senthilnathan S, *et al.* Two doses of pamidronate in infants with osteogenesis imperfecta. *Arch Dis Child* 2008; **93:** 398–400.
7. Rauch F, *et al.* Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. *J Bone Miner Res* 2003; **18:** 610–14.
8. Rauch F, *et al.* Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. *J Clin Endocrinol Metab* 2003; **88:** 986–92.
9. Rauch F, *et al.* Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J Clin Endocrinol Metab* 2006; **91:** 1268–74.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p. 1168.1). A placebo-controlled trial of oral pamidronate 150 mg daily found it to be effective in increasing bone mineral density (BMD) of the lumbar spine and femoral neck in both **men** and **women**.[1] Intravenous pamidronate at 30 mg every 3 months, or 60 mg every 6 months, also increased BMD in the lumbar spine, femoral neck, and trochanter in an observational, retrospective study.[2] Single intravenous infusions of pamidronate given every 3 months have also been reported to increase BMD and reduce fracture rates in **children** with osteoporosis;[3,4] annual doses were in the region of 4 mg/kg.

An open study[5] in men with prostate cancer (but no bone metastases) and receiving leuprorelin, found that addition of pamidronate 60 mg intravenously every 12 weeks prevented **therapy-induced** bone loss in the hip and lumbar spine. Acute bone loss from the femur and pelvis after hip arthroplasty was also reduced by a single infusion of 90 mg pamidronate in a small prospective study.[6] Similarly, in premenopausal women with chemotherapy-induced bone loss, pamidronate 60 mg intravenously every 3 months prevented bone loss at the spine and hip compared with placebo.[7]

In a small study[8] of patients receiving **corticosteroids**, pamidronate given intravenously either as a single infusion of 90 mg, or as 90 mg followed by 30 mg every 3 months for 1 year, significantly increased BMD at the lumbar spine, femoral neck, and total hip. In lymphoma patients receiving corticosteroids as part of chemotherapy regimens, pamidronate 30 mg intravenously every 3 months reduced bone loss when compared with placebo.[9] Pamidronate has shown beneficial increases in or preservation of BMD in patients after heart,[10,11] liver,[11] lung,[12] or stem cell[13] transplantation.

1. Brumsen C, *et al.* Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. *J Bone Miner Res* 2002; **17:** 1057–64.
2. Chan SSY, *et al.* Intravenous pamidronate in the treatment and prevention of osteoporosis. *Intern Med J* 2004; **34:** 162–6.
3. Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. *J Pediatr* 2003; **142:** 417–23.
4. Gandrud LM, *et al.* Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. *J Pediatr Endocrinol Metab* 2003; **16:** 887–92.
5. Smith MR, *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; **345:** 948–55.
6. Wilkinson JM, *et al.* Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial. *J Bone Miner Res* 2001; **16:** 556–64.
7. Fuleihan GE-H, *et al.* Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90:** 3209–14.
8. Boutsen Y, *et al.* Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001; **16:** 104–12.
9. Kim SH, *et al.* Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. *Am J Med* 2004; **116:** 524–8.
10. Krieg MA, *et al.* Intravenous pamidronate as treatment for osteoporosis after heart transplantation: a prospective study. *Osteoporosis Int* 2001; **12:** 112–16.
11. Dodidou P, *et al.* Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. *Osteoporosis Int* 2003; **14:** 82–9.
12. Cahill BC, *et al.* Prevention of bone loss and fracture after lung transplantation: a pilot study. *Transplantation* 2001; **72:** 1251–5.
13. Grigg AP, *et al.* Pamidronate reduces bone loss after allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2006; **91:** 3835–43.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Pamidronate was initially used orally for Paget's disease, but intravenous therapy has been preferred because of a lower incidence of adverse effects.[1,2] With the usual total dose of 180 mg, remission is considered likely in most patients with mild to moderate disease, but unlikely if disease is severe.[2] However, higher doses (about 340 mg) were found to be effective in those with very active disease, and also associated with a longer remission.[1] In a 2-year study[3] of 3 different doses, pamidronate increased bone mineral density in pagetic bone of the lumbar spine, femoral neck, and total hip, but lacked this effect on non-pagetic bone in the same areas; loss of density was apparent in non-pagetic forearm bone in the group given the highest dose (240 mg). Patients with coexistent osteoarthritis or arthropathy responded less well to pamidronate in terms of pain perception, than those patients without joint disease.[4] While hearing loss may or may not improve with pamidronate,[5,6] there has been a report of successful treatment of optic neuropathy due to Paget's disease with pamidronate and dexamethasone.[7] Bisphosphonates have also been given in other bone diseases with a similar pathology, particularly increased osteoclastic resorption. For example, pamidronate has had beneficial effects in patients with fibrous dysplasia of bone, a rare congenital disease leading to osteolytic lesions.[8-10]

1. Selby PL. Pamidronate in the treatment of Paget's disease. *Bone* 1999; **24:** 57S–58S.
2. Tucci JR, Bontha S. Intravenously administered pamidronate in the treatment of Paget's disease of bone. *Endocr Pract* 2001; **7:** 423–9. Correction. *ibid.* 2002; **8:** 78.
3. Gutteridge DH, *et al.* Bone density changes in Paget's disease 2 years after iv pamidronate: profound, sustained increases in pagetic bone with

severity-related loss in forearm nonpagetic cortical bone. *Bone* 2003; **32:** 56–61.
4. Vasireddy S, *et al.* Patterns of pain in Paget's disease of bone and their outcomes on treatment with pamidronate. *Clin Rheumatol* 2003; **22:** 376–80.
5. Donáth J, *et al.* Effect of bisphosphonate treatment in patients with Paget's disease of the skull. *Rheumatology (Oxford)* 2004; **43:** 89–94.
6. Murdin L, Yeoh LH. Hearing loss treated with pamidronate. *J R Soc Med* 2005; **98:** 272–4.
7. Isasi C, *et al.* Successful treatment of optic neuropathy in osteitis deformans. *Rheumatology (Oxford)* 2002; **41:** 948–50.
8. Liens D, *et al.* Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet* 1994; **343:** 953–4.
9. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. *J Pediatr* 2000; **137:** 403–9.
10. Plotkin H, *et al.* Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *J Clin Endocrinol Metab* 2003; **88:** 4569–75.

Rheumatoid arthritis and spondyloarthropathies. Intravenous[1] and oral[2] use of pamidronate has reportedly produced some modification of disease in a few patients with rheumatoid arthritis (p. 13.2). Continuous oral pamidronate therapy was shown to be effective in preserving and increasing bone mass in a 3-year randomised controlled trial involving 105 patients with rheumatoid arthritis.[3] In contrast, a small controlled study[4] in 26 patients found no significant effect on rheumatoid arthritis disease activity with intravenous pamidronate. There are reports of an analgesic response to pamidronate in patients with acute rheumatic pain of various aetiologies, including arthritis and ankylosing spondylitis, and a trial[5] in patients with ankylosing spondylitis found a dose-dependent therapeutic effect with pamidronate.[6] Use of intravenous pamidronate and methylprednisolone has also been investigated as part of the management of patients with NSAID-unresponsive ankylosing spondylitis.[7]

1. Eggelmeijer F, *et al.* Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. *J Rheumatol* 1994;**21:** 2016–20.
2. Maccagno A, *et al.* Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand J Rheumatol* 1994; **23:** 211–14.
3. Eggelmeijer F, *et al.* Increased bone mass with pamidronate treatment in rheumatoid arthritis: results of a three-year randomized, double-blind trial. *Arthritis Rheum* 1996; **39:** 396–402.
4. Lodder MC, *et al.* Effects of high dose intravenous pamidronate on disease activity and bone metabolism in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2003; **30:** 2080–1.
5. El-Shafei A, *et al.* Is pamidronate effective for acute rheumatic pain? *Ann Rheum Dis* 2002; **61:** 183.
6. Maksymowych WP, *et al.* A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; **46:** 766–73.
7. Malaviya AN, *et al.* A new strategy of drug treatment in NSAID-unresponsive ankylosing spondylitis: combination of pamidronate and methylprednisolone monthly intravenous infusions on the background of a combination of disease modifying drugs sulfasalazine and methotrexate. *J Assoc Physicians India* 2007; **55:** 193–7.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3.

Fever and flu-like symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes) are common during intravenous infusion of pamidronate but generally resolve spontaneously. Pamidronate should not be given by bolus injection, as severe local reactions and thrombophlebitis have occurred. CNS effects include agitation, confusion, dizziness, lethargy, insomnia, and somnolence. There have been isolated cases of seizures, and visual hallucinations. In addition to hypocalcaemia and hypophosphataemia, which are common, hypomagnesaemia or hypokalaemia may occur, and rarely, hypernatraemia, or hyperkalaemia. Both hypotension and hypertension have been reported. Anaemia, thrombocytopenia, and lymphocytopenia may occur. Bronchospasm and interstitial pneumonitis have occurred rarely.

Pamidronate should be used with caution in those with cardiac disease, because of the potential for fluid overload, and in those who have had thyroid surgery, because of the increased risk of hypocalcaemia due to relative hypoparathyroidism. Serum electrolytes, calcium and phosphate should be monitored during therapy, along with renal function. Patients should be warned against driving or operating machinery after treatment if somnolence or dizziness occur.

Effects on the ears. Ototoxicity, manifest as tinnitus and sudden hearing loss, has been reported[1] in 2 patients given both intravenous and oral pamidronate for pre-existing otosclerosis.[1] A patient given 5 pamidronate infusions for Paget's disease developed tinnitus, vertigo, and hearing loss; the latter two symptoms resolved over 9 months, but tinnitus persisted.[2]

1. Boumans LJJM, Poublon RML. The detrimental effect of aminohydroxypropylidene bisphosphonate (APD) in otospongiosis. *Eur Arch Otorhinolaryngol* 1991; **248:** 218–21.
2. Reid IR, *et al.* Ototoxicity associated with intravenous bisphosphonate administration. *Calcif Tissue Int* 1995; **56:** 584–5.

Effect on electrolytes. Pamidronate has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in 2 patients. In each case, other conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328:** 335–6.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including pamidronate, see under Bisphosphonates, p. 1175.2.

Effects on the gastrointestinal tract. The tolerability of pamidronate given *orally* may depend to some extent on the particular formulation. Gastrointestinal disturbances (in 21.8%) and haematological abnormalities (in 9.4%) were the main adverse effects associated with oral pamidronate in an open study of elderly patients.[1] Oesophagitis, noted earlier[2] in 4 of 49 patients given a different formulation, was not reported in this study.[1]

1. Spivacow FR, *et al.* Tolerability of oral pamidronate in elderly patients with osteoporosis and other metabolic bone diseases. *Curr Ther Res* 1996; **57:** 123–30.
2. Lufkin EG, *et al.* Pamidronate: an unrecognised problem in gastrointestinal tolerability. *Osteoporosis Int* 1994; **4:** 320–2.

Effects on the kidneys. Like other bisphosphonates (see p. 1176.1), pamidronate may cause adverse renal effects. UK licensed product information notes that there have been isolated cases of haematuria, acute renal failure, and deterioration of pre-existing renal disease. Renal function should be monitored during long-term pamidronate therapy, especially in patients with pre-existing renal disease or a predisposition to renal impairment. Longer infusion times may reduce the risk of renal toxicity, and various infusion rates have been recommended, see Uses and Administration, p. 1187.1.

Effects on mental state. Palpitations, followed by visual hallucinations, suicidal ideation, and clinical depression were reported in an elderly man after a single infusion of pamidronate for Paget's disease; he had no previous psychiatric history. Treatment with thioridazine reduced the frequency and effect of the hallucinations.[1]

1. Foley-Nolan D, *et al.* Pamidronate associated hallucinations. *Ann Rheum Dis* 1992; **51:** 927–8.

Effects on the musculoskeletal system. Although pamidronate appears to be a less potent inhibitor of bone mineralisation than etidronate, mineralisation defects have been reported in patients with Paget's disease of bone receiving pamidronate.[1] The resultant osteomalacia was not associated with any adverse clinical effects. Pamidronate-induced osteopetrosis has also been reported.[2] Acute pseudogout arthritis in a woman treated with pamidronate for acute hypercalcaemia was possibly due to deposition of calcium in the joints.[3] Severe bone pain occurred in more patients than expected when pamidronate was used for treatment of low bone density in cystic fibrosis;[4] an increase in proinflammatory cytokines was postulated as a mechanism for this effect.[5]

Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

1. Adamson BB, *et al.* Mineralisation defects with pamidronate therapy for Paget's disease. *Lancet* 1993; **342:** 1459–60.
2. Whyte MP, *et al.* Bisphosphonate-induced osteopetrosis. *N Engl J Med* 2003; **349:** 457–63.
3. Malnick SDH *et al.* Acute pseudogout as a complication of pamidronate. *Ann Pharmacother* 1997; **31:** 499–500.
4. Haworth CS, *et al.* Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. *Lancet* 1998; **352:** 1753–4.
5. Teramoto S, *et al.* Increased cytokines and pamidronate-induced bone pain in adults with cystic fibrosis. *Lancet* 1999; **353:** 750.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. Rash and pruritus occasionally follow pamidronate infusion. Mild skin rashes have also been reported in some patients taking oral pamidronate (see also under Bisphosphonates, p. 1177.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pamidronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Bisphosphonates cross the placenta in animals and humans. These drugs also persist in mineralised bone for many years. Thus, in theory, even if use were to be avoided during pregnancy, the fetus might still be exposed to bisphosphonates from prior therapy released from the maternal skeleton. Furthermore, suppressed bone turnover caused by residual bisphosphonate might cause maternal complications during pregnancy.[1] However, no adverse effects were seen during pregnancy in 2 women with osteogenesis imperfecta given intravenous pamidronate before conception. One infant had transient asymptomatic hypocalcaemia, and one had bilateral talipes equinovarus (a congenital deformity in which the foot turns downwards and inwards). No other skeletal abnormalities were noted. The authors advised monitoring of neonatal calcium concentrations in infants born to mothers treated with pamidronate.[1] In another report of 3 women given long-term pamidronate before conception, 4 healthy infants were born with no evidence of biochemical or skeletal abnormalities.[2]

1. Munns CFJ, *et al.* Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. *J Bone Miner Res* 2004; **19:** 1742–5.
2. Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. *J Clin Endocrinol Metab* 2006; **91:** 2017–20.

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Plasma concentrations of pamidronate rise rapidly after the start of an intravenous infusion; the apparent plasma half-life is 0.8 hours. Plasma protein binding is about 54%. Pamidronate is not metabolised, and about 20 to 55% of the dose is excreted in the urine unchanged within 72 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment and infusion rates may need to be reduced (see p. 1187.1).

Like all bisphosphonates, oral pamidronate is poorly absorbed from the gastrointestinal tract; bioavailability is about 1 to 3%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aminomux; Pamdosa; Pandrat; ***Austral.***: Aredia; Pamisol; ***Austria***: Aredia; Ebedronat; Pamidro-Cell†; Pamitor; ***Belg.***: Aredia; Pamidrin; ***Braz.***: Aredia; Fauldpami; Pamidrom; Pamired; ***Canad.***: Aredia; ***Chile***: Aminomux†; Pamifos; ***China***: Aredia (阿可达); Boning (博宁); Ren Yi (仁怡); ***Cz.***: Aredia†; Pamitor; ***Denm.***: Aredia†; Pamifos; ***Fin.***: Aredia†; Pamifos; ***Fr.***: Aredia†; Ostepam; Paminject†; ***Ger.***: Aredia; Axidronat; Novapam; Pamidro-cell; Pamidron†; Pamifos; Ribodronat; ***Gr.***: Aredia; Pamerit; Pamidrone; ***Hong Kong***: Aredia; Pamisol; ***Hung.***: Aredia; Pamifos; Pamitor; ***India***: Aredia; Aredronet; Bonapam; Pamidria; Pamidro; Pamifos; ***Indon.***: Aredia†; Pamired; ***Irl.***: Aredia; ***Israel***: Aredia; ***Ital.***: Amidrox†; Aredia; Texpami†; ***Jpn***: Aredia; ***Malaysia***: Aredia; Pamired; Pamisol; ***Mex.***: Aredia; Pamisol; ***Neth.***: Pamipro; ***NZ***: Pamisol; ***Philipp.***: Aredia; ***Pol.***: Aredia; Pamidia; Pamifos; Pamisol; Pamitor; ***Port.***: Pamidran; ***Rus.***: Aredia (Аредиа); Pomegara (Помегара); ***S.Afr.***: Aredia; ***Singapore***: Aredia; Pamired; Pamisol; ***Spain***: Aredia; Linoten†; Pamifos†; ***Swed.***: Aredia†; Pamifos; ***Switz.***: Aredia; Pamidron†; Pamifos†; ***Thai.***: Aredia; Pamisol; ***Turk.***: Aredia; Pamex; Pamidem; ***UK***: Aredia; ***Ukr.***: Aredia (Аредиа); Pamired (Памиред); ***USA***: Aredia†; ***Venez.***: Aminomux.

Pharmacopoeial Preparations
BP 2014: Pamidronate Disodium Infusion;
USP 36: Pamidronate Disodium for Injection.

Parathyroid Hormone *(BAN, USAN, rINN)*

1-84 Parathormone; ALX1-11 (human recombinant parathyroid hormone); Hormona paratiroidea; Hormone Parathyroïde; Hormonum Parathyroidum; Parathormone; Parathyrin; Parathyroid hormone (1-84); Paratirina; PTH; PTH (1-84); Паратироид Гормон.

CAS — 9002-64-6; 68893-82-3 (human parathyroid hormone); 345663-45-8 (human recombinant parathyroid hormone).
ATC — H05AA03.
ATC Vet — QH05AA03.
UNII — N19A0T0E5J.

Uses and Administration

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first (N-terminal) 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Endogenous parathyroid hormone is involved in the maintenance of plasma-calcium concentrations through its actions on bone, kidney, and indirectly on the gastrointestinal tract (see also under Parathyroid Disorders, p. 1170.3).

Exogenous parathyroid hormone was formerly used in acute hypoparathyroidism with tetany. It has also been used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism. A human recombinant form is

under investigation for the treatment of hypoparathyroidism.

The human recombinant form is used for the treatment of osteoporosis in postmenopausal women at high risk of fractures. The recommended dose is 100 micrograms once daily, given by subcutaneous injection into the abdomen; treatment may be continued for up to 24 months. Supplemental calcium and vitamin D may be needed if dietary intake is inadequate. However, if serum calcium becomes persistently raised, and there is no underlying disease, calcium and vitamin D should be withdrawn, and parathyroid hormone dosing changed to 100 micrograms on every other day. If elevated concentrations persist, parathyroid hormone therapy should be stopped until values return to normal.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones are now used for diagnostic purposes, and for the treatment of osteoporosis (see Teriparatide, p. 1191.2).

References.
1. Rittmaster RS, *et al.* Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 2000; **85:** 2129–34.
2. Hodsman AB, *et al.* Efficacy and safety of human parathyroid hormone-(1–84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88:** 5212–20.
3. Anonymous. ALX 111: ALX1-11, parathyroid hormone (1-84)–NPS Allelix, PREOS, PTH, recombinant human parathyroid hormone, rhPTH (1-84). *Drugs R D* 2003; **4:** 231–5.
4. White H, Ahmad A. PREOS NPS (Allelix/Nycomed). *Curr Opin Investig Drugs* 2005; **6:** 1057–66.
5. Shrader SP, Ragucci KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother* 2005; **39:** 1511–16.
6. Moen MD, Scott LJ. Recombinant full-length parathyroid hormone (1-84). *Drugs* 2006; **66:** 2371–81; discussion 2382–5.
7. Greenspan SL, *et al.* Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med* 2007; **146:** 326–39.

Administration in renal or hepatic impairment. UK licensed product information states that no dose adjustment is necessary for parathyroid hormone when it is used in patients with mild to moderate renal or hepatic impairment, defined as those with a creatinine clearance of 30 to 80 mL/minute, and a total score of 7 to 9 on the Child-Pugh scale, respectively. Use in severe renal or hepatic impairment is not recommended due to lack of data.

Adverse Effects, Treatment, and Precautions

Transient hypercalcaemia and hypercalciuria are very common with parathyroid hormone treatment; persistent hypercalcaemia may necessitate dose reduction or withdrawal of therapy (see Uses and Administration, p. 1188.3). Patients should be monitored at months 1, 3, and 6 for elevated concentrations of serum or urinary calcium; monitoring beyond 6 months is not considered necessary for those whose serum calcium is within normal limits at 6 months. On injection, serum calcium concentrations reach a maximum after 6 to 8 hours, returning to baseline after 20 to 24 hours; blood samples for monitoring should thus be taken at least 20 hours after the most recent dose. Gastrointestinal disturbances, especially nausea, also occur commonly, as do headache, dizziness, fatigue, palpitations, muscle cramps, extremity or back pain, and injection site erythema. Hyperuricaemia has also been reported.

Pharmacokinetics

Subcutaneous parathyroid hormone produces peak plasma concentrations 1 to 2 hours after injection. The average half-life is about 1.5 hours and the absolute bioavailability is about 55%. Parathyroid hormone is removed from the blood by a receptor-mediated process in the liver and broken down into smaller peptide fragments, which either undergo further degradation within the cell or are released back into the blood and renally cleared.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Preotact; ***Cz.***: Preotact; ***Denm.***: Preotact†; ***Fr.***: Preotact†; ***Ger.***: Preotact; ***Gr.***: Preotact; ***Irl.***: Preotact; ***Ital.***: Preotact; ***Neth.***: Preotact; ***Norw.***: Preotact; ***Pol.***: Preotact; ***Port.***: Preotact; ***Spain***: Preotact; ***Swed.***: Preotact†; ***UK***: Preotact.

Plicamycin *(BAN, USAN, rINN)*

A-2371; Aureolic Acid; Mithramycin; Mithramycinum; Mitramycin; Mitramysiini; NSC-24559; PA-144; Plicamicina; Plicamycine; Plicamycinum; Пликамицин.

$C_{52}H_{76}O_{24}$=1085.2

CAS — 18378-89-7.

ATC — L01DC02.

ATC Vet — QL01DC02.

UNII — NIJ123W41V.

Description. Plicamycin is an antineoplastic antibiotic produced by the growth of *Streptomyces argillaceus, S. plicatus* and *S. tanashiensis.*

Pharmacopoeias. In *US.*

USP 36: (Plicamycin). A yellow, odourless, hygroscopic, crystalline powder, with a potency of not less than 900 micrograms/mg, calculated on the dry basis. It loses not more than 8% of its weight when dried. Slightly soluble in water and in methyl alcohol; very slightly soluble in alcohol; freely soluble in ethyl acetate. A 0.05% solution in water has a pH of 4.5 to 5.5. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Profile

Plicamycin is a highly toxic antibiotic with antineoplastic and hypocalcaemic properties. It may act by complexing with DNA in the presence of divalent cations and inhibiting synthesis of ribonucleic acid. Lowering of serum calcium concentrations has been suggested to result from antagonism of the effects of vitamin D and parathyroid hormone on osteoclasts.

Plicamycin has been used in the symptomatic management of hypercalcaemia and hypercalciuria associated with malignancy if it cannot be managed by other means (see below). It has also been used in the treatment of malignant neoplasms of the testis not susceptible to surgery or radiotherapy; however, other agents are preferred (p. 715.1).

The major adverse effect of plicamycin is a dose-related bleeding syndrome, manifest initially as epistaxis, which may progress to haematemesis and potentially fatal haemorrhage. Severe thrombocytopenia may also occur due to bone-marrow depression. Gastrointestinal effects are common and other adverse effects include fever, malaise, drowsiness, lethargy and weakness, headache, depression, skin rashes, facial flushing, and reduced serum concentrations of calcium, phosphorus, and potassium. There may also be reversible impairment of renal and hepatic function.

Extravasation of plicamycin solutions may cause local irritation, cellulitis, and phlebitis.

Hypercalcaemia. Where treatment is required for hypercalcaemia it is aimed at increasing urinary excretion of calcium and maintaining adequate hydration. Drugs that inhibit bone resorption may also be used if hypercalcaemia is severe, particularly when it is associated with malignancy (see p. 1167.2). Plicamycin is highly toxic, and the bisphosphonates and calcitonins are generally preferred; however, it has been given in a dose of 25 micrograms/kg intravenously over 4 to 6 hours.[1,2] Although a single dose might be sufficient to normalise the serum calcium concentration, the dose can be repeated several times at intervals of 24 to 72 hours.

1. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326:** 1196–1203.
2. Hall TG, Schaiff RAB. Update on the medical treatment of hypercalcemia of malignancy. *Clin Pharm* 1993; **12:** 117–25.

Paget's disease of bone. Plicamycin has been used as a second- or third-line drug in the therapy of Paget's disease of bone (p. 1169.3), reserved for patients refractory to other treatment. Nonetheless, occasional successes are reported: one patient with refractory Paget's disease had apparent cure of her symptoms after treatment with plicamycin 25 micrograms/kg daily for 15 doses, followed by 1500 micrograms weekly for about 2 months and every 2 weeks for 6 weeks.[1] She had remained asymptomatic for 18 years after treatment. However, similar regimens have been used in other patients without this degree of success.[1] Another patient, who was refractory to calcitonin and pamidronate therapy, showed a considerable improvement in pain relief and biochemical parameters when treated with 30 micrograms/kg plicamycin daily for 3 days.[2]

1. Ryan WG, *et al.* Apparent cure of Paget's disease of bone. *Am J Med* 1990; **89:** 825–6.
2. Wimalawansa SJ. Dramatic response to plicamycin in a patient with severe Paget's disease refractory to calcitonin and pamidronate. *Semin Arthritis Rheum* 1994; **23:** 267.

Preparations

Pharmacopoeial Preparations
USP 36: Plicamycin for Injection.

Risedronate

Risedronaatti; Risedronat; Risedronatum.

ATC — M05BA07.

ATC Vet — QM05BA07.

Risedronic Acid *(BAN, rINN)*

Acide Risédronique; Ácido risedrónico; Acidum Risedronicum; Risedrónico, ácido; Ризедроновая Кислота.

[1-Hydroxy-2-(3-pyridinyl)ethylidene]diphosphonic acid.

$C_7H_{11}NO_7P_2$=283.1

CAS — 105462-24-6.

ATC — M05BA07.

ATC Vet — QM05BA07.

UNII — KM2Z91756Z.

Risedronate Sodium *(BANM, USAN, rINNM)*

Monosodium Risedronate; Natrii Risedronas; NE-58095; Risedronat Sodyum; Risédronate de Sodium; Risedronato sódico; Sodium Risedronate; Натрий Ризедронат.

Sodium trihydrogen [1-hydroxy-2-(3-pyridyl)ethylidene] diphosphonate.

$C_7H_{10}NNaO_7P_2$=305.1

CAS — 115436-72-1.

ATC — M05BA07.

ATC Vet — QM05BA07.

UNII — OFG5EXG60L.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Risedronate Sodium 2.5-Hydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides and mineral acids. pH of a 1% solution in water is 4.0 to 5.0.

USP 36: (Risedronate Sodium). A white to off-white powder. Soluble in water and in aqueous solutions; insoluble in common organic solvents.

Uses and Administration

Risedronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p. 1173.3). It inhibits bone resorption and is used either alone or with calcium, or with calcium and vitamin D for the prevention and treatment of postmenopausal osteoporosis. It is also used for the treatment of osteoporosis in men. Risedronate is also used for prevention and treatment of corticosteroid-induced osteoporosis, and for the treatment of Paget's disease of bone.

Risedronate is given orally as the sodium salt. The specific instructions given in Adverse Effects and Precautions, p. 1190.1 should be followed to minimise gastrointestinal adverse effects and permit adequate absorption. The recommended dosage for **Paget's disease** of bone is 30 mg of risedronate sodium once daily for 2 months. Treatment may be repeated once if necessary after an interval of a further 2 months. The recommended dosage for the treatment or prevention of postmenopausal or corticosteroid-induced **osteoporosis** is 5 mg daily. Alternatively, for postmenopausal osteoporosis, 35 mg may be taken once weekly, 75 mg may be taken on 2 consecutive days of each month, or 150 mg may be taken once a month. For men with osteoporosis, the recommended dose is 35 mg once weekly.

For details of administration in renal impairment, see below.

General references.
1. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161:** 353–60.
2. Dunn CJ, Goa KL. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* 2001; **61:** 685–712.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23:** 1409–21.
4. White NJ, Perry CM. Risedronate once a week. *Treat Endocrinol* 2003; **2:** 415–20.

Administration. A procedure for the extemporaneous preparation of an oral solution from risedronate tablets has been proposed,[1] for use in patients who cannot swallow whole tablets or require feeding tubes.

1. Dansereau RJ, Crail DJ. Extemporaneous procedures for dissolving risedronate tablets for oral administration and for feeding tubes. *Ann Pharmacother* 2005; **39:** 63–7.

Administration in renal impairment. Renal clearance of risedronate significantly correlated to renal function in a pharmacokinetic study,[1] although the authors concluded that generally no dosage adjustment appears necessary for patients with mild to moderate renal impairment (creatinine clearance (CC) greater than 20 mL/minute). Licensed product information states that no dosage adjustment is necessary when CC is greater than 30 mL/minute; however, use of risedronate is contra-indicated in patients with severe renal impairment (CC less than 30 mL/minute), due to a lack of clinical data.

1. Mitchell DY, *et al.* Effect of renal function on risedronate pharmacokinetics after a single oral dose. *Br J Clin Pharmacol* 2000; **49:** 215–22.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Risedronate improves bone mineral density (BMD) and reduces the risk of both vertebral and non-vertebral fractures in **postmenopausal** osteoporosis;[1-4] effects are maintained for at least 5 years.[5] In **corticosteroid-induced** osteoporosis, risedronate increases BMD at the lumbar spine, femoral neck, and trochanter.[3,6] Risedronate is also used to treat **men** with osteoporosis. In a controlled study in elderly men after a stroke, those given risedronate had increased BMD and a decreased risk of hip fracture.[7] In a prospective controlled study, 12 months of daily risedronate significantly increased BMD at the lumbar spine, femoral neck, and hip, and significantly reduced the incidence of new vertebral fractures in men with primary or secondary osteoporosis.[8]

A once-monthly regimen of risedronate was found to be similar in efficacy and safety to the once-daily regimen.[9]

1. Sickels JM, Nip C-S. Risedronate for the prevention of fractures in postmenopausal osteoporosis. *Ann Pharmacother* 2002; **36:** 664–70.
2. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161:** 353–60.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23:** 1409–21.
4. Wells G, *et al*. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/04/08).
5. Sorensen OH, *et al*. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003; **32:** 120–6.
6. Dougherty JA. Risedronate for the prevention and treatment of corticosteroid-induced osteoporosis. *Ann Pharmacother* 2002; **36:** 512–16.
7. Sato Y, *et al*. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med* 2005; **165:** 1743–8.
8. Ringe JD, *et al*. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 2006; **26:** 427–31.
9. Delmas PD, *et al*. Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. *Bone* 2008; **42:** 36–42.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Risedronate has been found to improve pagetic bone lesions,[1] and to be more effective than etidronate.[2]

1. Brown JP, *et al*. Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. *Bone* 2000; **26:** 263–7.
2. Miller PD, *et al*. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; **106:** 513–20.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. The most frequent adverse effects during risedronate therapy are arthralgia and gastrointestinal disturbances. To minimise the risk of gastrointestinal effects precautions similar to those for alendronate should be observed (see p. 1172.3), although UK licensed product information allows for the tablets to be taken other than on rising (but not at bedtime or within 2 hours of food or drink). Hypocalcaemia should be corrected before beginning risedronate therapy.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, including risedronate, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including risedronate, see under Bisphosphonates, p. 1175.2.

Effects on the gastrointestinal tract. Although, like other oral bisphosphonates, it is recommended that risedronate be taken with care (see above) to avoid gastrointestinal effects, pooled analysis of 9 studies involving 10 068 patients receiving risedronate 5 mg daily indicated that the drug was not associated with an increased frequency of upper gastrointestinal effects, even among patients at increased risk due to active gastrointestinal disease or treatment with aspirin or NSAIDs as well.[1] However, it was noted that comprehensive postmarketing data would be required to see how these results would be reflected in clinical practice. Studies in women previously intolerant to alendronate found that risedronate 5 mg daily[2] and 30 mg once weekly[3] were well tolerated.

In 2 large trials, male and female patients with mild to moderate osteoarthritis of the knee were given risedronate 5 mg once daily, 15 mg once daily, 35 mg once weekly, 50 mg once weekly, or placebo. Patients were allowed continued use of aspirin or NSAIDs. Again, pooled analysis found no increased frequency of upper gastrointestinal adverse events in those given risedronate, even in those patients considered at increased risk for such events.[4]

1. Taggart H, *et al*. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* 2002; **77:** 262–70. Correction. *ibid.*; 601.
2. Adachi JD, *et al*. Tolerability of risedronate in postmenopausal women intolerant of alendronate. *Aging (Milano)* 2001; **13:** 347–54.
3. Delaney MF, *et al*. Bone density changes with once weekly risedronate in postmenopausal women. *J Clin Densitom* 2003; **6:** 45–50.
4. Adami S, *et al*. Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 1278–85.

Effects on the heart. For discussion of a possible increased risk of serious atrial fibrillation with bisphosphonates, including risedronate, see Effects on the Heart, under Bisphosphonates, p. 1175.3.

Effects on the musculoskeletal system. From the initial marketing of risedronate until June 2003, the FDA had received 6 reports of severe bone, joint, or muscle pain. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[1]

Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, including risedronate, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

1. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; **165:** 346–7.

Effects on the respiratory system. For a report of bronchiolitis obliterans organising pneumonia induced by risedronate, see p. 1177.1.

Hypersensitivity. Allergic reactions to bisphosphonates are rare, see p. 1177.1. Angioedema, generalised rashes, and bullous skin reactions, some severe, have been reported with risedronate.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies risedronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Like other bisphosphonates, risedronate is poorly absorbed orally. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The mean bioavailability is 0.63% in the fasting state, and is reduced by 30% when given 1 hour before breakfast, and by 55% when given half an hour before breakfast. Plasma protein binding is about 24%. Risedronate is not metabolised. About half of the absorbed portion is excreted in the urine within 24 hours; the remainder is sequestered to bone for a prolonged period. Unabsorbed drug is eliminated unchanged in the faeces.

Absorption. Absorption of a single dose of risedronate was comparable when given 0.5 to 1 hour before breakfast or 2 hours after an evening meal in a study in healthy subjects.[1] The pharmacokinetics of risedronate are dose-proportional after a single oral dose.[2]

1. Mitchell DY, *et al*. The effect of dosing regimen on the pharmacokinetics of risedronate. *Br J Clin Pharmacol* 1999; **48:** 536–42.
2. Mitchell DY, *et al*. Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. *J Clin Pharmacol* 2000; **40:** 258–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actonel; Ductonar; Rentop; Ribastamin; Ridron; Risedon; ***Austral.***: Acris; Actonel; Risedro; ***Austria***: Actonel; ***Belg.***: Actonel; ***Braz.***: Actonel; Risedronel; Risedross; Risonato; ***Canad.***: Actonel; ***Chile***: Actonel; ***China***: Gusong (???? (Sue Ho?)); Ji Wei (吉威); Wei Shan (唯善); ***Cz.***: Actonel†; Juverital; Norifaz; Norsed†; Nurrid†; Rigat; Risendros; Tevanel; ***Denm.***: Juverital; Nurrid; Optinate; Racidrix; Riseratio; Risostad; Vionate; ***Fin.***: Optinate; Riseos†; Riseratio; Vionate†; ***Fr.***: Actonel; ***Ger.***: Actonel; ***Gr.***: Actonel; Bondapen; Bonmate; Difosfon-S; Motivus; Riselib; ***Hong Kong***: Actonel; ***Hung.***: Actonel; Boneact; ***India***: Actonel; Fossical; Gemfos; Risofos; ***Indon.***: Actonel; Osteonate; Retonel; ***Irl.***: Actonel; Ridate; Risonate; Risontel; ***Israel***: Actonel; Ribone; ***Ital.***: Actonel; Avestra; Optinate; ***Jpn***: Actonel; Benet; ***Malaysia***: Actonel; ***Mex.***: Actonel; Alesone; Misodron; Reosvec; Seralis; Tecnodron; Teonav†; ***Neth.***: Actonel; Melenor; Varibona; ***Norw.***: Optinate; ***Philipp.***: Actonel; ***Pol.***: Actonel; Norifaz; Resorpate; Rigat; Risendros; ***Port.***: Actonel; Norifaz; Norsed; Rizat; ***Rus.***: Actonel (Актонель); Risendros (Ризендрос); ***S.Afr.***: Actamax; Actonel; ***Singapore***: Actonel; ***Spain***: Acrel; Actonel; Miosen; Risemyl†; ***Swed.***: Optinate; ***Switz.***: Actonel; ***Thai.***: Actonel; ***Turk.***: Actonel; Arilex; ***UK***: Actonel; ***Ukr.***: Risendros (Ризендрос)†; ***USA***: Actonel; Atelvia; ***Venez.***: Actonel.

Multi-ingredient Preparations. ***Arg.***: Ribastamin Duo; Ridron Pack; ***Austral.***: Actonel Combi D; Actonel Combi; ***Belg.***: Actonel Combi D; ***Canad.***: Actonel plus Calcium†; ***Denm.***: Optinate Combi; ***Fin.***: Optinate Combi D†; ***Fr.***: Actonelcombi; ***Ger.***: Actonel plus Calcium D; Actonel plus Calcium; ***Hong Kong***: Actonel plus Calcium D; ***Hung.***: Actonel Trio; Norifaz Trio; ***Irl.***: Actonel Combi; Actonel Plus Ca & D; ***Mex.***: Actonel Trio; Seralis VIP; ***Neth.***: ActoCalD†; Actokit D; Actokit; Actonel plus Calcium†; ***Swed.***: Optinate Combi†; ***UK***: Actonel Combi; ***USA***: Actonel with Calcium†.

Pharmacopoeial Preparations
USP 36: Risedronate Sodium Tablets.

Strontium Ranelate *(rINNM)*

FK-481; Ranelate de Strontium; Ranelato de estroncio; S-12911; Strontii Ranelas; Стронций Ранелат.
2-(2-Carboxy-4-cyano-5-[*N*,*N*-di(carboxymethyl)amino]thiophen-3-yl) acetic acid distrontium salt.
$C_{12}H_6N_2O_8SSr_2$=513.5
CAS — 135459-87-9.
ATC — M05BX03.
ATC Vet — QM05BX03.
UNII — 04NQ160FRU (strontium ranelate); 8PD4806E06 (strontium ranelate octahydrate).

Uses and Administration

Strontium ranelate is claimed to stimulate bone formation as well as reduce bone resorption. It is used to treat severe osteoporosis (below) in postmenopausal women at high risk of fracture and in men at increased risk of fracture. The recommended oral dose is 2 g daily, given at night and preferably at least 2 hours after food.

For details of administration in renal impairment, see below.

References.

1. Marie PJ. Strontium ranelate: new insights into its dual mode of action. *Bone* 2007; **40** (suppl 1): S5–S8.
2. Fonseca JE. Rebalancing bone turnover in favour of formation with strontium ranelate: implications for bone strength. *Rheumatology (Oxford)* 2008; **47** (suppl 4): iv17–iv19.

Administration in renal impairment. Strontium excretion occurs via the kidneys and clearance decreases as creatinine clearance (CC) decreases. UK licensed product information states that no dosage adjustment of strontium ranelate is required in patients with mild to moderate renal impairment (CC 30 to 70 mL/minute). However, it is not recommended for those with severe renal impairment (CC below 30 mL/minute) because of a lack of pharmacokinetic data in these patients; continuation of treatment in patients developing severe renal impairment should be considered on an individual basis.

Osteoporosis. Strontium ranelate, given orally with calcium and vitamin D supplements, has been found to reduce the risk of vertebral[1] and non-vertebral[2] fractures in postmenopausal women with osteoporosis (p. 1168.1). A pooled analysis of data from these 2 studies concluded that strontium ranelate reduced both vertebral and non-vertebral fractures in patients aged 80 years or older.[3] Protection against fractures was detected within 12 months, and sustained throughout 3 years of treatment. Hip fractures were also reduced over 3 years, but this did not reach statistical significance; the authors concluded that the analysis may not have been sufficiently powered in this respect. A systematic review[4] concluded that while strontium ranelate reduces vertebral fractures, there is less of a reduction with non-vertebral fractures, and the effect on hip fracture remains unclear. Some have cautioned about the interpretation of bone mineral density (BMD) changes with strontium ranelate, since stronger X-ray attenuation by strontium compared with calcium must be corrected for to avoid overestimating the effect. However, increases in BMD could be useful clinically in gauging long-term compliance.[5]

NICE considers strontium ranelate an alternative treatment option for both primary[6] and secondary[7] prevention of osteoporotic fragility fractures in high-risk postmenopausal women who are unable to take a bisphosphonate. A review[8] of the place of strontium ranelate in therapy considered that although it might be an alternative in patients who could not tolerate a bisphosphonate there was no convincing published evidence to support claims that it stimulated bone formation as well as reducing resorption. Further reviews[4,9] concluded that additional research to confirm its mechanism of action is required and that long-term fracture data are needed, along with comparative studies evaluating the efficacy of strontium ranelate relative to other therapies such as bisphosphonates. A subsequent review[10] reported that strontium ranelate reduced the risk of vertebral and nonvertebral fractures in two studies lasting 5 years and continued to provide protection against new fractures during the 3-year extensions of these studies.

Strontium ranelate has also been reported to have beneficial effects on measure of bone mineral density and markers of bone resorption in men with osteoporosis.[11]

1. Meunier PJ, *et al.* The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004; **350:** 459–68.
2. Reginster JY, *et al.* Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005; **90:** 2816–22.
3. Seeman E, *et al.* Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006; **21:** 1113–20.
4. O'Donnell S, *et al.* Strontium ranelate for preventing and treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Fogelman I, Blake GM. Strontium ranelate for the treatment of osteoporosis: is useful, but changes in bone mineral density need careful interpretation. *BMJ* 2005; **330:** 1400–1.
6. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women amended: Technology Appraisal 160 (issued January 2011). Available at: http://guidance.nice.org.uk/nicemedia/live/11746/47176/47176.pdf (accessed 24/06/13)
7. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women amended: Technology Appraisal 161 (issued January 2011). Available at: http://guidance.nice.org.uk/nicemedia/live/11748/42447/42447.pdf (accessed 24/06/13)
8. Anonymous. Strontium ranelate for osteoporosis? *Drug Ther Bull* 2006; **44:** 29–32.
9. Stevenson M, *et al.* The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007; **11:** 1–134.
10. Deeks ED, Dhillon S. Strontium ranelate: a review of its use in the treatment of postmenopausal osteoporosis. *Drugs* 2010; **70:** 733–59.
11. Kaufman JM, *et al.* Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. *J Clin Endocrinol Metab* 2013; **98:** 592–601.

Adverse Effects and Precautions

Common adverse effects of strontium ranelate include gastrointestinal disturbances, headache, dermatitis, and eczema. Disturbances in consciousness, memory loss, and seizures may occur and there have been reports of alopecia, pyrexia, confusion, peripheral oedema, and bronchial hyperreactivity.

Treatment with strontium ranelate has been associated with an increased incidence in venous thromboembolism including pulmonary embolism, and its use is contra-indicated in patients considered at risk or with a history of thromboembolic disorders. A higher risk of myocardial infarction has also been reported, and the use of strontium ranelate is contra-indicated in patients with a history of ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, or uncontrolled hypertension. It should be used with caution in patients with other significant risk factors for cardiovascular events. Transient reversible increases in creatine kinase activity have been reported. Hypersensitivity reactions, including rash, pruritus, urticaria, angioedema, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred. Drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, has also been reported.

Strontium may interfere with certain methods used for the determination of serum and urinary calcium.

Strontium ranelate should not be given with food or antacids—see Interactions, below.

Alopecia. Between May 2005 and January 2008, the Spanish pharmacovigilance system received 5 reports of alopecia associated with strontium ranelate treatment.[1] A causal association was suspected due to the temporal relationship between the start of treatment and the onset of alopecia, the improvement of most cases on drug withdrawal, and the exclusion of other causes. Inorganic strontium has also traditionally been a component of depilatory creams. One of the reported cases also had some features of Stevens-Johnson syndrome, and the authors suggested that alopecia may be one symptom of a more complex and severe hypersensitivity syndrome.

1. Sainz M, *et al.* Strontium ranelate may cause alopecia. *BMJ* 2009; **338:** b1494.

Effects on the cardiovascular system. In a cohort analysis of strontium ranelate used in general practice, mainly for postmenopausal osteoporosis, there was a crude annual incidence of venous thromboembolism of 6.24 cases per 1000 patient-years exposed. This was similar to estimates in populations of similar age and in populations treated for osteoporosis. However, a history of venous thromboembolism was identified as a significant risk factor.[1]

1. Osborne V, *et al.* Incidence of venous thromboembolism in users of strontium ranelate: an analysis of data from a prescription-event monitoring study in England. *Drug Safety* 2010; **33:** 579–91.

Hypersensitivity. As of November 2007, the EMEA had received reports of 16 cases of drug rash with eosinophilia and systemic symptoms (DRESS), a serious and life-threatening condition, in patients treated with strontium ranelate. Two fatalities were reported. Reactions appeared within 3 to 6 weeks of starting therapy, with skin rash, accompanied by fever, swollen glands, eosinophilia, and effects on the liver, kidneys, and lungs. Patients are advised to stop treatment with strontium ranelate if a rash occurs and to seek medical advice; treatment should not be restarted.[1] Similar advice, and a reminder that the drug should also be used with caution in patients with risk factors for venous thromboembolism, was issued in June 2008 by the Australian regulatory authorities; although there had been no fatalities, they had seen 16 reports of rash, one accompanied by fever and one by eosinophilia.[2]

1. EMEA. EMEA recommends changes in the product information for Protelos/Osseor due to the risk of severe hypersensitivity reactions (issued 16th November 2007). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease_Protelos_41745807en.pdf (accessed 21/01/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Severe skin reactions and venous thromboembolism with strontium ranelate (Protos). *Aust Adverse Drug React Bull* 2008; **27:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0806.pdf (accessed 17/07/08)

Interactions

Food, milk, and calcium-containing compounds may reduce the bioavailability of strontium ranelate; antacids containing aluminium or magnesium may reduce its absorption. Such products should be given at least 2 hours apart from, and, in the case of antacids, preferably after, strontium ranelate. Because of possible complex formation, strontium ranelate should not be given with oral tetracyclines or quinolones.

Pharmacokinetics

Strontium ranelate has an absolute bioavailability of about 25% after an oral dose; calcium or food reduces the bioavailability by about 60 to 70%. Peak plasma concentrations are achieved 3 to 5 hours after an oral dose. Plasma protein binding is low. Strontium ranelate has a high affinity for bone tissue. It is not metabolised, and has a half-life of about 60 hours. Excretion occurs via the kidneys and gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Osteovital; Prodinam; Protos; Troncel; ***Austral.***: Protos; ***Austria***: Protelos; ***Belg.***: Protelos; ***Braz.***: Protos; ***Chile***: Protelos; ***China***: Osseor (欧思美); ***Cz.***: Osseor; Protelos; ***Denm.***: Protelos; ***Fr.***: Protelos; ***Ger.***: Protelos; ***Gr.***: Protelos; ***Hong Kong***: Protos; ***Hung.***: Protelos; ***Indon.***: Protos; ***Irl.***: Osseor; Protelos; ***Israel***: Protelos; ***Ital.***: Osseor; Protelos; ***Malaysia***: Protaxos; ***Neth.***: Osseor; Protelos; ***NZ***: Protos; ***Philipp.***: Protos; ***Pol.***: Osseor; Protelos; ***Port.***: Osseor; Protelos; ***Rus.***: Bivalos (Бивалос); ***S.Afr.***: Protos; ***Singapore***: Protos; ***Spain***: Osseor; Protelos; ***Swed.***: Protelos; ***Thai.***: Protaxos; ***Turk.***: Protelos; ***UK***: Protelos; ***Ukr.***: Bivalos (Бивалос).

Multi-ingredient Preparations. ***Arg.***: Osteovital Plus.

Teriparatide *(BAN, USAN, rINN)*

(1-34) Human parathormone; (1-34) Human parathyroid hormone; 1-34 Parathormone (human); hPTH 1-34; Human parathormone (1-34); Human parathyroid hormone (1-34); Human PTH (1-34); LY-333334; Parathyroid hormone peptide (1-34); Teriparatid; Teriparatida; Tériparatide; Teriparatidum; Терипаратид.

$C_{181}H_{291}N_{55}O_{51}S_2$=4117.8

CAS — 52232-67-4.

ATC — H05AA02.

ATC Vet — QH05AA02.

UNII — 10T9C5U89I.

Teriparatide Acetate *(BANM, USAN, rINNM)*

Acetato de teriparatida; Teriparatida, acetato de; Tériparatide, Acétate de; Teriparatidi Acetas; Терипаратида Ацетат.

$C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.yC_2H_4O_2$

CAS — 99294-94-7 (teriparatide acetate).

ATC — H05AA02.

ATC Vet — QH05AA02.

UNII — 9959P4V12N.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid biologically active N-terminal region of human parathyroid hormone (p. 1188.3). It is used in the treatment of established postmenopausal osteoporosis, especially in those with a high fracture risk, and in men with primary or hypogonadal osteoporosis who are at increased risk of fracture. Teriparatide may also be used to treat osteoporosis associated with prolonged corticosteroid therapy in women and men at increased risk of fracture.

The usual dose of teriparatide is 20 micrograms subcutaneously daily into the thigh or abdominal wall. Treatment is limited to a maximum of 2 years in total. A transdermal formulation is also under investigation.

Teriparatide acetate has been given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism. Hypoparathyroidism is characterised by a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism is characterised by resistance to the effects of parathyroid hormone (see p. 1171.2). Teriparatide acetate is used *diagnostically* to distinguish between these 2 conditions.[1] A synthetic 1-38 fragment of human parathyroid hormone (hPTH 1-38) has been used similarly.[2] Teriparatide has also been used to *treat* hypoparathyroidism.[3-5]

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; **109:** 800–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; **146:** 373–7.
3. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* 1996; **276:** 631–6.
4. Winer KK, *et al.* A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998; **83:** 3480–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.

Osteoporosis. Parathyroid hormone is capable of stimulating both formation and resorption of bone. Continuous infusion of teriparatide leads to a persistent elevation of parathyroid hormone and greater bone resorption by stimulating osteoclasts, with a net decrease in bone volume, and resultant hypercalcaemia; in contrast, daily (intermittent) injections increase bone volume by increasing osteoblastic proliferation.[1-3] Teriparatide appears to have less effect on cortical than trabecular bone,[3] suggesting that, although it may be helpful in preventing vertebral fractures, its impact on fractures of the proximal femur may be more limited. However, while treatment with teriparatide substantially increases lumbar spine bone mineral density (BMD), beneficial increases are also seen at the hip,[1] and in a pivotal study (the Fracture Prevention Trial)[4] in **postmenopausal** women with osteoporosis (p. 1168.1), it decreased the risk of both vertebral and non-vertebral fracture. In a follow-up study, the reduction in vertebral fracture risk in patients treated with teriparatide for a mean of 19 months persisted for at least an additional 18 months after daily treatment was stopped.[5] Teriparatide appears to improve bone geometry, with no detrimental effect on cortical bone.[6] In the UK, NICE[7] recommends teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women who have had an unsatisfactory response to bisphosphonates or who are unable to take bisphosphonates or strontium ranelate; women aged 65 years or older must have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3.5 standard deviations or more below the mean) plus more than 2 fractures, and women aged 55 to 64 should have an extremely low BMD plus more than 2 fractures. It has been pointed out that evidence of reduction in teriparatide's effect with current or recent alendronate therapy (see below) might make its use as a second-line agent problematic.[8]

Data on combination therapy are limited, but some studies suggest that teriparatide with HRT is more effective than HRT alone.[9] Previous HRT treatment, however, may attenuate the BMD increases seen with teriparatide alone.[10] Increases in BMD have been reported in patients taking teriparatide with or after raloxifene.[10] The effect of teriparatide with the antiresorptive bisphosphonates has yet to be determined.[2,6,9,11] Although there is some suggestion that teriparatide still increases bone formation after treatment with alendronate,[9] a study in men found that, when given together, alendronate impaired the anabolic effects of teriparatide.[12] For this reason, some consider that teriparatide be started immediately after stopping bisphosphonates.[11]

It has been suggested that the degree of suppression of bone turnover before treatment[6] or the bisphosphonate used previously[13] may influence the response to teriparatide. A study of daily or cyclical teriparatide in women with osteoporosis found that although the teriparatide-induced increase in BMD may be slightly lower in women who had previously taken alendronate than in those who had never received it, the increase in spinal BMD was still impressive. Intermittent cyclical treatment with teriparatide had similar effects on BMD to daily dosage.[14] Bisphosphonate therapy has been recommended to maintain BMD improvements after teriparatide treatment.[10]

In postmenopausal women with osteoporosis taking HRT and **corticosteroids**,[15] the addition of teriparatide significantly increased BMD of the lumbar spine; modest changes in hip bone mass were not significant.

In **men** with osteoporosis, teriparatide increased BMD in the lumbar spine and at the femoral neck;[9] risk of fracture was also reduced.[1]

1. Cappuzzo KA, Delafuente JC. Teriparatide for severe osteoporosis. *Ann Pharmacother* 2004; **38:** 294–302.
2. Madore GR, *et al.* Parathyroid hormone. *J Am Acad Orthop Surg* 2004; **12:** 67–71.
3. Brixen KT, *et al.* Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. *Basic Clin Pharmacol Toxicol* 2004; **94:** 260–70.
4. Neer RM, *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344:** 1434–41.
5. Lindsay R,*et al.* Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med* 2004; **164:** 2024–30.
6. Rubin MR, Bilezikian JP. Parathyroid hormone as an anabolic skeletal therapy. *Drugs* 2005; **65:** 2481–98.
7. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 161 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA161guidance.pdf (accessed 12/01/09)
8. Anonymous. Teriparatide for postmenopausal osteoporosis. *Drug Ther Bull* 2004; **42:** 93–5.
9. Quattrocchi E, Kourlas H. Teriparatide: a review. *Clin Ther* 2004; **26:** 841–54.
10. Stroup J, *et al.* Teriparatide in the treatment of osteoporosis. *Am J Health-Syst Pharm* 2008; **65:** 532–9.
11. Deal C. The use of intermittent human parathyroid hormone as a treatment for osteoporosis. *Curr Rheumatol Rep* 2004; **6:** 49–58.
12. Finkelstein JS, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; **349:** 1216–26.
13. Miller PD, *et al.* Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J Clin Endocrinol Metab* 2008; **93:** 3785–93.
14. Cosman F, *et al.* Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; **353:** 566–75.
15. Lane NE, *et al.* Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. *J Clin Invest* 1998; **102:** 1627–33.

Adverse Effects and Precautions

Gastrointestinal disturbances, pain in the limb of injection, headache, and dizziness are the most common adverse effects in patients treated with subcutaneous teriparatide. Dizziness, vertigo, and syncope may be associated with transient orthostatic hypotension in some patients, particularly when beginning treatment. Those so affected should not drive or operate potentially hazardous machinery. Asthenia, arthralgia, anaemia, tachycardia, emphysema, and rhinitis may occur. Angina pectoris, depression, dyspnoea, leg cramps, pneumonia, urinary disorders, and sciatica have also been reported. Muscle spasms have been commonly reported, sometimes after the first dose; serious back spasms may occur very rarely. A metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate. It is a peptide and the possibility of systemic hypersensitivity reactions should be borne in mind. Renal impairment has been reported. Hypercalcaemia may develop with teriparatide or the acetate and it is therefore contra-indicated in patients with pre-existing hypercalcaemia. Transient increases in serum calcium concentrations have been noted after teriparatide injection in normocalcaemic patients; any blood monitoring should be carried out at least 16 hours after the most recent dose. Hypercholesterolaemia and hyperuricaemia have also been reported. Caution is advised in patients with active or recent renal calculi.

Teriparatide is contra-indicated in patients with severe renal impairment and should be used with caution with those with moderate impairment. Teriparatide is also contra-indicated in pregnancy as studies in *animals* have shown reproductive toxicity.

There was an increased incidence of osteosarcoma in *rats* and rare reports in humans given teriparatide; it should not be used in patients who may be at increased risk, including those with a history of skeletal metastases or previous radiotherapy to the skeleton, those with metabolic bone disease such as Paget's disease and hyperparathyroidism, those with unexplained elevations of serum alkaline phosphatase, or children and young adults with open epiphyses.

Pharmacokinetics

Teriparatide is extensively absorbed after subcutaneous injection; peak plasma concentrations are reached after about 30 minutes. Absolute bioavailability is reported to be about 95%. The serum half-life is 5 minutes after intravenous use, and approximately 1 hour after subcutaneous injection (reflecting time needed for absorption from the injection site). No studies have been done on the metabolism or excretion of teriparatide; parathyroid hormone is believed to be enzymatically metabolised in the liver and excreted by the kidneys.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Forteo; ***Austral.***: Forteo; ***Austria***: Forsteo; ***Belg.***: Forsteo; ***Braz.***: Forteo; ***Canad.***: Forteo; ***Chile***: Forteo; ***China***: Forsteo (复泰奥); ***Cz.***: Forsteo; ***Denm.***: Forsteo; ***Fin.***: Forsteo; ***Fr.***: Forsteo; ***Ger.***: Forsteo; ***Gr.***: Forsteo; ***Hong Kong***: Forteo; ***Hung.***: Forsteo; ***India***: Forteo; ***Irl.***: Forsteo; ***Israel***: Forteo; ***Ital.***: Forsteo; ***Jpn***: Teribone; ***Malaysia***: Forteo; ***Mex.***: Forteo; ***Neth.***: Forsteo; ***Norw.***: Forsteo; ***NZ***: Forteo; ***Philipp.***: Forteo; ***Pol.***: Forsteo; ***Port.***: Forsteo; ***Rus.***: Forsteo (Форстео); ***S.Afr.***: Forteo; ***Singapore***: Forteo; ***Spain***: Forsteo; ***Swed.***: Forsteo; ***Switz.***: Forsteo; ***Thai.***: Forteo; ***Turk.***: Forsteo; ***UK***: Forsteo; ***USA***: Forteo; ***Venez.***: Forteo.

Tiludronate

ATC — M05BA05.
ATC Vet — QM05BA05.

Tiludronic Acid *(BAN, rINN)*

Acide Tiludronique; Ácido tiludrónico; Acidum Tiludronicum; ME-3737; SR-41319; Tiludrónico, ácido; Tiludronihappo; Tiludronik Asit; Tiludronsyra; Тилудроновая Кислота.
{[(*p*-Chlorophenyl)thio]methylene}diphosphonic acid.
$C_7H_9ClO_6P_2S$=318.6
CAS — 89987-06-4.
ATC — M05BA05.
ATC Vet — QM05BA05.
UNII — 6PN559HP4Y.

Tiludronate Disodium *(USAN)*

Disodium Tiludronate; Natrii Tiludronas; Sodium Tiludronate; SR-41319B; Tiludronate de Sodium; Tiludronate Sodium (BANM); Tiludronate Sodium (rINNM); Tiludronato sódico; Натрий Тилудронат.
Disodium dihydrogen {[(*p*-chlorophenyl)thio]methylene} diphosphonate hemihydrate.
$C_7H_7ClNa_2O_6P_2S,½H_2O$=371.6
CAS — 149845-07-8 (anhydrous disodium tiludronate); 155453-10-4 (tiludronate disodium hemihydrate).
ATC — M05BA05.
ATC Vet — QM05BA05.
UNII — BH6M93CIA0.

Uses and Administration

Tiludronate is a bisphosphonate with similar properties to those of the bisphosphonates in general (p. 1173.3). It inhibits bone resorption and is used for Paget's disease of bone.

It is given orally as tiludronate disodium, but doses are expressed in terms of the equivalent amount of tiludronic acid; 117 mg of tiludronate disodium is equivalent to about 100 mg of tiludronic acid. To ensure adequate absorption doses should be taken with plenty of water (at least 200 mL), at least 2 hours before or after meals. In Paget's disease of bone the usual dose is 400 mg once daily for 3 months, and this may be repeated if necessary after an interval of at least 3 to 6 months.

Tiludronate has been tried in postmenopausal osteoporosis, but results were disappointing.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including tiludronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Asthenia and dizziness have been reported rarely.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including tiludronate, see under Bisphosphonates, p. 1176.1.

Effects on the musculoskeletal system. Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

Effects on the skin. As with other bisphosphonates, tiludronate has been associated with rash and pruritus. For reference to a case of massive epidermal necrosis possibly associated with tiludronate, see Hypersensitivity, under Bisphosphonates, p. 1177.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tiludronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2. Indometacin may increase the bioavailability of tiludronate two to fourfold; diclofenac does not appear to have this effect. Aspirin may decrease the bioavailability of tiludronate by 50%.

Pharmacokinetics

Like other bisphosphonates tiludronate is poorly absorbed after oral doses. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The oral bioavailability of tiludronate is about 6% in the fasting state, and is reduced by about 90% when given within 2 hours of food. Plasma protein binding is about 90%, mostly to albumin. Tiludronate is not metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Skelid; ***Belg.***: Skelid; ***Fr.***: Skelid; ***Ger.***: Skelid†; ***Hung.***: Skelid†; ***Neth.***: Skelid†; ***Port.***: Skelid†; ***Spain***: Skelid; ***Switz.***: Skelid†; ***UK***: Skelid†; ***USA***: Skelid.

Zoledronate

ATC — M05BA08.
ATC Vet — QM05BA08.

Zoledronic Acid *(BAN, USAN, rINN)*

Acide Zolédronique; Ácido zoledrónico; Acidum Zoledronicum; CGP-42446; Tsoledronihappo; Zoledrónico, ácido; Zoledronik Asit; Zoledronsyra; Золедроновая Кислота.
(1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid.
$C_5H_{10}N_2O_7P_2$=272.1
CAS — 118072-93-8 (anhydrous zoledronic acid); 165800-06-6 (zoledronic acid monohydrate).
ATC — M05BA08.
ATC Vet — QM05BA08.
UNII — 70HZ18PH24 (anhydrous zoledronic acid); 6XC1PAD3KF (zoledronic acid monohydrate).

Incompatibility. Zoledronic acid should not be mixed with calcium or other infusion solutions such as lactated Ringer's solution that contain divalent cations.

Stability. Zoledronic acid infusion is physically stable for 24 hours at 2 degrees to 8 degrees once diluted to 100mL in sodium chloride 0.9% or glucose 5% as per licensed product information.

Zoledronate Disodium *(BANM, USAN, rINNM)*

CGP-42446A; ZOL-446; Zoledronas Dinatricum; Zolédronate Disodique; Zoledronato disódico; Динатрий Золедронат.
Disodium dihydrogen (1-hydroxy-2-imidazol-1-ylethylidene) diphosphonate tetrahydrate.
$C_5H_8N_2Na_2O_7P_2,4H_2O$=388.1
CAS — 165800-07-7.
ATC — M05BA08.
ATC Vet — QM05BA08.
UNII — 7D7G51SA24.

Zoledronate Trisodium *(BANM, USAN, rINNM)*

CGP-42446B; Zoledronas Trinatricum; Zolédronate Trisodique; Zoledronato trisódico; Тринатрий Золедронат.
Trisodium hydrogen (1-hydroxy-2-imidazol-1-ylethylidene) diphosphonate hydrate (5:2).
$C_5H_7N_2Na_3O_7P_2,2½H_2O$=383.1
CAS — 165800-08-8.
ATC — M05BA08.
ATC Vet — QM05BA08.
UNII — ARL915IH66.

Uses and Administration

Zoledronate is an aminobisphosphonate (p. 1173.3) that is a potent inhibitor of bone resorption. It is used for the treatment of hypercalcaemia of malignancy, and Paget's disease of bone, as well as for prevention of skeletal events in patients with advanced bone malignancies. It is also used for the treatment and prevention of glucocorticoid-induced osteoporosis and osteoporosis in postmenopausal women,

and for the treatment of osteoporosis in men. Zoledronic acid is given as an intravenous infusion over not less than 15 minutes.

For **hypercalcaemia of malignancy** a single dose of 4 mg is used, diluted with 100 mL of sodium chloride 0.9% or glucose 5%. The treatment may be repeated if necessary after at least 7 days, at a dose of 4 mg. Individual doses should not exceed 4 mg, as there is an increased risk of adverse renal effects, including renal failure.

Zoledronic acid is given for the prevention of skeletal events in patients with advanced **bone malignancies** (p. 700.3) at a dose of 4 mg, diluted as above, every 3 to 4 weeks.

For the treatment of **Paget's disease** of bone, zoledronic acid is given as a single intravenous infusion of 5 mg. Patients who relapse can be re-treated with zoledronic acid; an additional intravenous infusion of 5 mg may be given after an interval of at least 1 year from the initial dose.

For the treatment of postmenopausal **osteoporosis**, osteoporosis in men, and glucocorticoid-induced osteoporosis, the recommended dose is a single intravenous infusion of zoledronic acid 5 mg given once a year. In patients with a recent low-trauma hip fracture, it is recommended that zoledronic acid should be started 2 or more weeks after hip fracture repair. In the USA, the same dose is also given annually for the prevention of glucocorticoid-induced osteoporosis; for the prevention of postmenopausal osteoporosis, a single dose of 5 mg zoledronic acid is given once every 2 years.

For doses in renal impairment, see below.

Calcium and vitamin D supplements are recommended for patients with advanced bone malignancies, Paget's disease, and osteoporosis treated with zoledronic acid.

Reviews.

1. Cheer SM, Noble S. Zoledronic acid. *Drugs* 2001; **61:** 799–805.
2. Theriault RL. Zoledronic acid (Zometa) use in bone disease. *Expert Rev Anticancer Ther* 2003; **3:** 157–66.
3. Neville-Webbe H, Coleman RE. The use of zoledronic acid in the management of metastatic bone disease and hypercalcaemia. *Palliat Med* 2003; **17:** 539–53.
4. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther* 2003; **25:** 2669–2708.
5. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
6. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.
7. Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. *Cancer Treat Rev* 2008; **34:** 183–92.
8. Lyseng-Williamson KA. Zoledronic acid: a review of its use in breast cancer. *Drugs* 2008; **68:** 2661–82.
9. Anonymous. Annual zoledronic acid for osteoporosis. *Drug Ther Bull* 2008; **46:** 93–6.

Administration in renal impairment. Despite the fact that renal clearance of zoledronic acid correlates to renal function, a pharmacokinetic study[1] concluded that no dosage adjustment appeared necessary in patients with mild to moderate renal impairment (creatinine clearance 50 to 80 mL/minute, and 10 to 50 mL/minute, respectively).

Licensed product information also states that no adjustment is necessary in mild to moderate renal impairment for patients with **hypercalcaemia of malignancy**, but defines this degree of impairment in terms of serum creatinine less than 400 micromoles/litre or less than 4.5 mg per 100 mL; the risks and benefits of therapy should be considered before treating those with more severe impairment.

However, for patients with advanced **bone malignancies**, the intravenous dose of zoledronic acid should be adjusted on the basis of creatinine clearance (CC) as follows:

- CC greater than 60 mL/minute: 4 mg (no adjustment necessary)
- CC 50 to 60 mL/minute: 3.5 mg
- CC 40 to 49 mL/minute: 3.3 mg
- CC 30 to 39 mL/minute: 3 mg
- CC below 30 mL/minute: treatment not recommended

Serum creatinine should be measured before each dose and treatment withheld if renal function has deteriorated. Renal deterioration is defined as an increase of 44 micromoles/litre or 500 micrograms per 100 mL for those patients with normal baseline creatinine, and an increase of 88 micromoles/litre or 1 mg per 100 mL for those with abnormal baseline creatinine. Treatment may be restarted at the dose used before treatment interruption once the creatinine returns to within 10% of the baseline value.

For patients with **Paget's disease** or **osteoporosis**, licensed product information states that no dose adjustment is considered necessary for those with CC of 35 mL/minute or more; treatment is contra-indicated in those with CC of less than 35 mL/minute or evidence of acute renal impairment due to an increased risk of renal failure.

1. Skerjanec A, *et al.* The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003; **43:** 154–62.

Charcot neuroarthropathy. Bisphosphonates, including zoledronic acid, have been tried for Charcot neuroarthropathy, see under Bisphosphonates, p. 1174.1.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. Zoledronate has been shown to have a faster onset, higher response rate, and longer duration of action than pamidronate.[1] It also has a shorter infusion time than pamidronate,[1] and some consider it the treatment of choice for hypercalcaemia of malignancy.[2-4] However, zoledronate has caused severe hypocalcaemia in some patients, see Effects on Electrolytes, below.

1. Major P, *et al.* Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; **19:** 558–67.
2. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. *Oncologist* 2002; **7:** 481–91.
3. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
4. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Zoledronate is licensed for such use in many countries.[1]

In the treatment of skeletal complications from bone metastases secondary to multiple myeloma or breast cancer, zoledronate was more effective than pamidronate in reducing the risk of complications from breast cancer; it was of similar efficacy in those with multiple myeloma.[2] In a placebo-controlled study in patients with prostate cancer,[3] zoledronate reduced the number of skeletal-related events, and increased the median time to events. In patients with bone metastases arising from lung cancer and other solid tumours (excluding breast or prostate cancer), zoledronate reduced skeletal morbidity; the primary end-point, which excluded hypercalcaemia as a skeletal-related event, did not reach statistical significance.[4] However, the authors noted that the patient groups had a shorter-than-expected survival-time. A longer term follow-up of this study[5] confirmed a sustained reduction in risk of developing skeletal events with zoledronate. A later meta-analysis[6] confirmed the benefits of the bisphosphonate in reducing skeletal events, and hence morbidity, in patients with cancer, but not mortality; however, no clear advantage could be shown versus clodronate or pamidronate, which were also of benefit. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear. For the suggestion that zoledronate may have wider benefits against non-skeletal malignancy, see below.

1. Dhillon S, Lyseng-Williamson KA. Zoledronic Acid: a review of its use in the management of bone metastases of malignancy. *Drugs* 2008; **68:** 507–34.
2. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003; **98:** 1735–44.
3. Saad F, *et al.* Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004; **96:** 879–82.
4. Rosen LS, *et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003; **21:** 3150–7.
5. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer* 2004; **100:** 2613–21.
6. Machado M, *et al.* Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009; **31:** 962–79.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including zoledronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Multiple myeloma. For the effect of bisphosphonates, including zoledronic acid, on survival in multiple myeloma, see under Bisphosphonates, p. 1174.2.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Five different dosage regimens of zoledronate all increased bone mineral density (BMD) in **postmenopausal** women when given intermittently over the course of 1 year in a placebo-controlled study.[1] Compared with placebo, a once-yearly infusion of zoledronate over a 3-year period significantly reduced the risk of vertebral, hip, and other fractures in postmenopausal women with osteoporosis.[2] BMD was also significantly increased. Adverse events were similar in both groups, including renal function changes; however, serious atrial fibrillation occurred more frequently in the zoledronate group (see Effects on the Heart, under Bisphosphonates, p. 1175.3). Once-yearly infusion of zoledronate beginning within 90 days after surgical repair of a low-trauma hip fracture was associated with a reduction in the rate of new vertebral and non-vertebral fractures, although the reduction in the risk of new hip fractures was non-significant.[3] Further studies comparing once-yearly zoledronic acid with oral bisphosphonates are needed to determine their place in the management of osteoporosis.[4] The use of zoledronate for osteoporosis in **men** has also been reviewed.[5]

An integrated analysis of interim (12 month) results from 2 studies evaluating zoledronate for the prevention of cancer **treatment-induced** bone loss, in postmenopausal women with early breast cancer treated with letrozole, suggested that adding zoledronate to the regimen from the start was more effective than delaying treatment until there was evidence of bone loss.[6] Zoledronic acid has also been shown to prevent bone loss in premenopausal women undergoing chemotherapy for early breast cancer.[7,8]

In a small study,[9] zoledronate improved the calcium content of cancellous bone, maintained femoral neck BMD, and increased lumbar spine BMD after kidney transplantation. In a similar study of liver transplant recipients, zoledronate also had favourable effects on BMD. This effect tended to diminish at 12 months when compared with placebo; the authors considered this to be due to improved general health, mobility, muscle mass, and nutrition as a consequence of improved liver function.[10]

1. Reid IR, *et al.* Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002; **346:** 653–61.
2. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.
3. Lyles KW, *et al.* HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; **357:** 1799–1809.
4. Woodis CB. Once-yearly administered intravenous zoledronic acid for postmenopausal osteoporosis. *Ann Pharmacother* 2008; **42:** 1085–9.
5. Maricic M. Intravenous zoledronic acid: what are the indications for male osteoporosis? *Curr Osteoporos Rep* 2010; **8:** 4–9.
6. Brufsky A, *et al.* Z-FAST and ZO-FAST Study Groups. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008; **13:** 503–14.
7. Hershman DL, *et al.* Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2008; **26:** 4739–45.
8. Gnant M, *et al.* Austrian Breast and Colorectal Cancer Study Group (ABCSG). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol* 2008; **9:** 840–9.
9. Haas M, *et al.* Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 2003; **63:** 1130–6.
10. Crawford BAL, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; **144:** 239–48.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Zoledronate is highly effective in Paget's disease. Single infusions of up to 400 micrograms have been shown to inhibit bone resorption in patients with active Paget's disease.[1,2] In a patient[3] with disease refractory to other bisphosphonates, a single infusion of 4 mg improved symptoms and improved biochemical markers of disease activity. A placebo-controlled study compared a single infusion of 5 mg zoledronic acid with a 60-day course of oral risedronate 30 mg daily. Patients receiving zoledronic acid had significantly more rapid and marked reduction in serum alkaline phosphatase concentrations, higher response rates, and shorter median times to response than those on risedronate. During an open extension study, patients on risedronate had a significantly larger loss of therapeutic response than those given zoledronic acid.[4] A review[5] concluded that zoledronic acid was an important first-line treatment for Paget's disease.

1. Arden-Cordone M, *et al.* Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int* 1997; **60:** 415–18.
2. Buckler H, *et al.* Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone* 1999; **24** (suppl): 81S–85S.
3. Chung G, Keen RW. Zoledronate treatment in active Paget's disease. *Ann Rheum Dis* 2003; **62:** 275–6.
4. Reid IR, *et al.* Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005; **353:** 898–908.
5. Keating GM, Scott LJ. Zoledronic acid: a review of its use in the treatment of Paget's disease of bone. *Drugs* 2007; **67:** 793–804.

Adverse Effects and Precautions

As for the bisphosphonates in general, p. 1174.3.

Other adverse effects that have been reported with zoledronic acid include alopecia and hyperhidrosis.

Effect on electrolytes. Zoledronate has more potent effects on calcium than some of the other bisphosphonates, and has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in some patients.[1,2] In most cases, pre-existing conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1] Vit-

amin D deficiency should be treated before starting zoledronate.[1,2]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328:** 335–6.
2. Breen TL, Shane E. Prolonged hypocalcemia after treatment with zoledronic acid in a patient with prostate cancer and vitamin D deficiency. *J Clin Oncol* 2004; **22:** 1531–2.

Effects on the eyes. For reports of ocular effects with bisphosphonates, including zoledronate, see p. 1175.2.

Effects on the heart. For discussion of a possible increased risk of serious atrial fibrillation with bisphosphonates, including zoledronate, see Effects on the Heart, under Bisphosphonates, p. 1175.3.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, see under Bisphosphonates, p. 1176.1. It is important to ensure adequate hydration before and after doses of zoledronic acid as dehydration predisposes to deterioration in renal function. Treatment may need to be modified in some patients with renal impairment (see Administration in Renal Impairment, p. 1193.1).

Effects on the musculoskeletal system. Musculoskeletal reactions, atypical fractures, and osteonecrosis of the jaw have been reported after the use of bisphosphonates, including zoledronate, see under Adverse Effects of Bisphosphonates, p. 1176.2 *et seq.*

Effects on the nervous system. Seizures have been reported after intravenous infusion of zoledronic acid.[1]

1. Tsourdi E, *et al.* Seizures associated with zoledronic acid for osteoporosis. *J Clin Endocrinol Metab* 2011; **96:** 1955–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zoledronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Plasma concentrations of zoledronate rise rapidly after the start of an intravenous infusion. Plasma protein binding is low; it has been reported to range between 28 and 56%. Zoledronate is not metabolised, and about 23 to 55% of the dose is excreted in the urine unchanged within 24 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Terminal elimination half-life is about 146 hours. Renal clearance is slower in patients with severe renal impairment (see Administration in Renal Impairment, p. 1193.1).

References.

1. Chen T, *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; **42:** 1228–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aclasta; Dreico; Eriophos; Ledron; Rionit; Simpla; Sinresor; Varidronico; Xedron†; Zometa; ***Austral.***: Aclasta; Zometa; ***Austria***: Aclasta; Zometa; ***Belg.***: Aclasta; Zometa; ***Braz.***: Aclasta; Blaztere; Zometa; ***Canad.***: Aclasta; Zometa; ***Chile***: Aclasta; Zometa; ***China***: Aclasta (密固达); Ai Lang (艾朗); Bo Lai Ning (博来宁); Gai Ning (盖柠); Su Qi (苏奇); Yin Li Da (因力达); YiTai (依泰); Zhen Da (震达); Zhuo Lai (卓莱); Zometa (择泰); Zuorui (佐锐); ***Cz.***: Aclasta; Zometa; ***Denm.***: Aclasta; Zometa; ***Fin.***: Aclasta; Zometa; ***Fr.***: Aclasta; Zometa; ***Ger.***: Aclasta; Zometa; ***Gr.***: Aclasta; Zometa; ***Hong Kong***: Aclasta; Zometa; ***Hung.***: Aclasta; Zometa; ***India***: Blaztere; Cytozol; Zoldria; Zometa; ***Indon.***: Aclasta; Zometa; ***Irl.***: Aclasta; Zometa; ***Israel***: Aclasta; Zomera; ***Ital.***: Aclasta; Zometa; ***Jpn***: Zometa; ***Malaysia***: Aclasta; Zometa; ***Mex.***: Zometa; ***Neth.***: Aclasta; Desinobon; Fayton; Symblasta; Zacidate; Zalit; Zoledreenos; Zolenia; Zometa; ***Norw.***: Aclasta; Zometa; ***NZ***: Aclasta; Zometa; ***Philipp.***: Aclasta; Zometa; ***Pol.***: Aclasta; Zometa; ***Port.***: Aclasta; Zometa; ***Rus.***: Aclasta (Акласта); Blaztere (Блазтера); Resorba (Резорба); Rezoklastin (Резокластин); Veroklast (Верокласт); Zolerix (Золерикс); Zometa (Зомета); ***S. Afr.***: Aclasta; Zobone; Zomedron; Zometa; ***Singapore***: Aclasta; Zometa; ***Spain***: Aclasta; Zometa; ***Swed.***: Aclasta; Zometa; ***Switz.***: Aclasta; Zolacin; Zometa; ***Thai.***: Aclasta; Leuzotev; Zinvel; Zolennic; Zometa; ***Turk.***: Aclasta; Ostezolen; Zoledrin; Zolenat; Zomebon; Zometa; ***UK***: Aclasta; Zometa; ***Ukr.***: Aclasta (Акласта); Blazter (Блазтер); Zometa (Зомета); ***USA***: Reclast; Zometa; ***Venez.***: Zoldria; Zometa.

Bronchodilators and Anti-asthma Drugs

Anti-asthma Drug Groups, p. 1195
Antimuscarinics, p. 1195
Beta agonists, p. 1195
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Management of Reversible Airways Obstruction, p. 1195
Asthma, p. 1195
Chronic abstructive pulmonary disease, p. 1199

This chapter includes many of those drugs used for their bronchodilator or anti-inflammatory properties in the management of reversible airways obstruction, such as asthma and chronic obstructive pulmonary disease.

The main bronchodilators discussed in this chapter are the sympathomimetic beta agonists (stimulants of beta-adrenoceptors), and the xanthines (mainly theophylline). The antimuscarinic bronchodilators ipratropium, oxitropium, and tiotropium are also included. The major class of anti-inflammatory drugs, the corticosteroids, are discussed separately, on p. 1597.1; other drugs considered to act on the processes of airway inflammation and which are included in this section include sodium cromoglicate and its analogues, and the various drugs that act on leukotriene synthesis and receptor binding, on platelet-activating factor (PAF), or on other aspects of the inflammatory cascade.

Anti-asthma Drug Groups

Antimuscarinics

The parasympathetic nervous system plays a role in the regulation of bronchomotor tone, and antimuscarinic drugs have bronchodilator properties. The quaternary ammonium compounds aclidinium bromide, glycopyrronium bromide, ipratropium bromide, oxitropium bromide, and tiotropium bromide are the antimuscarinic (anticholinergic) bronchodilators in current use; as well as reduced CNS effects they have less effect on mucociliary clearance than drugs such as atropine, which can produce accumulation of viscid lower airway secretions and a risk of mucus plugging in these patients. An antimuscarinic may be the bronchodilator of choice in the management of chronic obstructive pulmonary disease. In patients with asthma they are usually reserved for use in life-threatening acute asthma exacerbations.

Described in this chapter are

- Aclidinium, p. 1201.1
- Ipratropium, p. 1211.3
- Oxitropium, p. 1218.1
- Tiotropium, p. 1238.1

Beta agonists

The sympathetic nervous system plays a role in the regulation of bronchomotor tone and $beta_2$-adrenoceptors in bronchial smooth muscle produce bronchodilatation when stimulated. Short-acting selective agonists of $beta_2$-adrenoceptors ($beta_2$ agonists; $beta_2$ stimulants), of which salbutamol is the paradigmatic example, are therefore first-line drugs for the relief of asthma symptoms. They are also widely used in the management of chronic obstructive pulmonary disease, although antimuscarinic bronchodilators may be preferred or used in addition. Long-acting $beta_2$ agonists are used in asthma in patients also requiring anti-inflammatory therapy. They may also be used in some patients with chronic obstructive pulmonary disease.

Described in this chapter are

- Arformoterol, p. 1202.3
- Bambuterol, p. 1203.1
- Bitolterol, p. 1203.2
- Carmoterol, p. 1207.1
- Clenbuterol, p. 1207.2
- Fenoterol, p. 1208.2
- Formoterol, p. 1209.2
- Hexoprenaline, p. 1211.1
- Indacaterol, p. 1211.2
- Isoetarine, p. 1213.2
- Levosalbutamol, p. 1213.3
- Orciprenaline, p. 1217.3
- Pirbuterol, p. 1218.3
- Procaterol, p. 1219.1
- Reproterol, p. 1219.2
- Salbutamol, p. 1220.2
- Salmeterol, p. 1224.1
- Terbutaline, p. 1228.1
- Tretoquinol, p. 1239.1
- Tulobuterol, p. 1239.2
- Vilanterol, p. 1239.3

Corticosteroids

Corticosteroids are widely used for their anti-inflammatory (glucocorticoid) properties in the management of asthma, and may be beneficial in some patients with chronic obstructive pulmonary disease. Because of the potential adverse effects associated with prolonged systemic corticosteroid therapy, inhalation of corticosteroids with reduced systemic activity is preferred; oral corticosteroids are generally only used in short courses, and at relatively low doses, to gain control of the disease. The actions and uses of the corticosteroids are discussed in much greater detail in the section beginning on p. 1597.1.

Leukotriene inhibitors and antagonists

Leukotrienes appear to play an important role in the inflammatory process of asthma, and some drugs may modify or inhibit this action. Leukotriene synthesis may be prevented by blockade of the enzyme 5-lipoxygenase with inhibitors such as zileuton. Alternatively, leukotriene receptor antagonists such as zafirlukast may be used to block specific receptors (usually those of leukotriene D_4) and prevent their activation. These anti-leukotriene drugs have a role in the prophylactic management of asthma as an alternative when inhaled corticosteroids cannot be used in mild asthma, and as add-on therapy in more severe asthma.

Described in this chapter are

- Amlexanox, p. 1202.2
- Ibudilast, p. 1211.2
- Montelukast, p. 1214.3
- Pemirolast, p. 1218.2
- Pranlukast, p. 1218.3
- Tipelukast, p. 1239.1
- Zafirlukast, p. 1239.3
- Zileuton, p. 1240.3

Mast cell stabilisers

The role of the mast cell in starting an inflammatory cascade has long been recognised as important, and the best established of the mast cell stabilisers are sodium cromoglicate and nedocromil sodium. These compounds inhibit mast cell degranulation in response to antigens or other stimuli, and hence prevent the release of histamine, leukotrienes, and other inflammatory mediators. They are usually well tolerated and guidelines for the treatment of asthma mention their use for prophylactic therapy as an alternative, or a supplement, to corticosteroids, particularly in children. However, it is generally considered that the corticosteroids are more effective.

Described in this chapter are

- Amlexanox, p. 1202.2
- Nedocromil, p. 1216.2
- Pemirolast, p. 1218.2
- Repirinast, p. 1219.2
- Sodium Cromoglicate, p. 1225.3
- Tranilast, p. 1239.1

Xanthines

Xanthines are drugs with complex actions that include, in varying degrees, relaxation of bronchial smooth muscle and relief of bronchospasm, stimulant effects on respiration, and anti-inflammatory effects. Theophylline and its derivatives have long been used for their bronchodilator properties in the management of asthma and chronic obstructive pulmonary disease, but the narrow therapeutic range and the propensity for interactions with other drugs make theophylline a difficult drug to use, and it tends to be reserved for combination therapy in patients who cannot be managed with other bronchodilators (such as the $beta_2$ agonists) plus inhaled corticosteroids.

Described in this chapter are

- Acefylline piperazine, p. 1200.3
- Ambroxol acefyllinate, p. 1201.2
- Aminophylline, p. 1201.2
- Bamifylline, p. 1203.2
- Bufylline, p. 1203.3
- Caffeine, p. 1203.3
- Choline Theophyllinate, p. 1207.1
- Diprophylline, p. 1207.3
- Doxofylline, p. 1208.1
- Etamiphylline Camsilate, p. 1208.2
- Etofylline, p. 1208.2
- Heptaminol Acefyllinate, p. 1210.3
- Proxyphylline, p. 1219.2
- Theobromine, p. 1229.2
- Theophylline, p. 1229.3

Management of Reversible Airways Obstruction

Asthma

Asthma is a chronic inflammatory disease in which the patient has episodes of reversible airways obstruction due to bronchial hyperresponsiveness. It is a common disorder, the prevalence of which has increased sharply over the last 40 years, particularly in children, with prevalence greater than 30% in some areas. More than 10% of the population in developed countries are affected. Rates are increasing in developing countries as they become more westernised,[1] and global differences in prevalence appear to be lessening.[2] It has been suggested that asthma is probably not one illness, but a collection of different phenotypes which meet the criteria for clinical diagnosis of asthma.[3,4] Although there is no clear definition of the asthma phenotype, 3 categories have been suggested: clinical phenotypes such as severity-defined or defined by age at onset, trigger-related phenotypes such as allergy-or aspirin-induced asthma, and inflammatory phenotypes such as eosinophilic asthma.[4] Current guidelines classify by severity according to the clinical features present before treatment.[5-7] Asthma may be described as extrinsic when it is associated with exposure to a specific allergen such as pollen or house-dust mite, or to a non-specific stimulus such as a chemical irritant or exercise. It may be described as intrinsic when no external precipitating factor is identifiable.

The aetiology of asthma is poorly understood, but both genetic and environmental factors are believed to contribute to development and progression of the disease.[1,8,9]

Resistance to airflow in asthma is increased by a number of abnormalities, including contraction of the airway smooth muscle, the presence of excessive secretions within the airway lumen, and inflammatory cell infiltration. The inflammation in chronic asthma causes remodelling, found as shedding and thickening of the airway epithelium, and hypertrophy and hyperplasia of smooth muscle.[8,9] Airway remodelling or thickening may be important in more severe disease and can result in relatively irreversible narrowing of the airways.[7]

The principal symptoms of asthma are wheezing, dyspnoea (breathlessness), chest tightness, and cough, and these symptoms tend to be variable, intermittent, worse at night or early morning, and provoked by particular triggers. In an acute attack, the respiratory rate is rapid and tachycardia is common.[5-7] The peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV_1) are decreased in asthma, and in a severe asthmatic attack the PEF is generally less than 50% of predicted values. Life-threatening features include exhaustion, cyanosis, bradycardia, hypotension, confusion, and coma.[5-7]

Management of asthma. As asthma is a chronic disease, management involves prophylactic measures to reduce inflammation and airway resistance and to maintain airflow, as well as specific regimens for the treatment of acute attacks. **Measurements** of lung function play an important part in determining treatment and patients are encouraged to monitor their own disease by using a simple peak flow meter to measure PEF;[5-7] spirometry is used to measure airflow limitation and reversibility in hospitals and surgeries.[5-7] Use of exhaled nitric oxide has been investigated to monitor disease control with corticosteroids;[10] however, an asthma treatment strategy using exhaled nitric oxide did not result in a large reduction in exacerbations or less use of inhaled corticosteroids.[11]

Drug therapy is preferably given by **inhalation** to deliver the drugs directly to the desired site of action. This produces higher local concentrations and permits smaller doses than would be required orally, with a consequent reduction in adverse effects. Systematic reviews[12-14] have found that hand-held inhaler devices including pressurised metered-dose inhalers (MDIs), dry powder inhalers, and breath actuated pressurised MDIs, are generally equally effective for the delivery of short-acting $beta_2$ agonists and corticosteroids in stable asthma. Choice of inhaler should be individualised, especially in children, taking into account ease of use, safety, and convenience.[6,7,14] Differences in drug delivery exist between inhaler devices and this should be considered when substituting one device for another.[7]

Spacer devices can be fitted to some MDIs to act as reservoirs for the drug to make it easier for the patient to inhale each dose correctly. Use of MDIs with spacer devices produce outcomes which are at least equivalent to nebuliser therapy.[14,15] Nebulisers tend to be reserved for patients who are unable or unwilling to use these devices, although the choice of spacer and method of use may substantially affect drug delivery.[5,16] Use of a spacer device for the inhalation of high doses of corticosteroids reduces oropharyngeal deposition, systemic absorption, and adverse effects.[5-7] Specially adapted or modified inhalation devices, as well as spacer devices, are also available to enable children to achieve a correct technique when using inhaled drug therapy, but alternative routes of delivery such as oral dosage or nebulisation may be necessary for some infants and small children.[16] Frequent intermittent or continuous nebulisation of short-acting $beta_2$ agonists are both effective in patients with severe bronchoconstriction.[14]

The standard **drugs** used in the management of asthma are the $beta_2$ agonists and corticosteroids.[5-7]

$Beta_2$ agonists relax the bronchial smooth muscle to produce bronchodilatation by selectively stimulating $beta_2$-

adrenergic receptors. Short-acting selective beta$_2$ agonists such as salbutamol or terbutaline are the initial drugs of choice for use as required to relieve acute bronchospasm; if inhaled, they can have an almost immediate bronchodilating effect. Regular use of beta$_2$ agonists is mainly restricted to long-acting beta$_2$ agonists such as salmeterol xinafoate in patients also requiring anti-inflammatory prophylactic treatment; a short-acting beta$_2$ agonist should still be used as required.[5-7]

Corticosteroids are the most effective preventer therapy available for the management of asthma.[17] They are used for their anti-inflammatory properties and to reduce bronchial hyperresponsiveness; they must be taken regularly to achieve maximum benefit. Corticosteroid therapy is recommended both for acute attacks and chronic asthma prophylaxis. Meta-analysis suggests that systemic corticosteroids speed the resolution of exacerbations and reduce the rate of relapse.[18,19] It has also been suggested that inhaled corticosteroids may be of benefit in acute asthma if multiple doses are inhaled at intervals of less than 30 minutes, over a 90 to 120 minute period.[20] In chronic asthma, regular inhaled corticosteroids are one of the cornerstones of management. Combining inhaled corticosteroids with long-acting beta$_2$ agonists may have synergistic benefits;[17,21,22] such a combination is more effective than combining inhaled corticosteroids with anti-leukotriene drugs.[23] The use of an inhaled corticosteroid, budesonide, and a rapid and long-acting beta$_2$ agonist, formoterol, in a combined inhaler as both regular maintenance therapy and as a reliever when required, has been studied.[24] Giving additional corticosteroid with each reliever inhalation in response to symptoms could be expected to provide improved control of airway inflammation,[25] and reductions in the rate of exacerbations have been reported[26,27] with relatively lower doses of inhaled corticosteroid in patients with uncontrolled persistent asthma, compared with more conventional treatment regimens using a beta$_2$ agonist as a reliever. While the place of budesonide/formoterol maintenance and reliever therapy in the management of asthma is not yet clearly defined,[25] some guidelines[6,7] include this regimen (referred to by the manufacturer, *AstraZeneca*, as Symbicort Maintenance and Reliever Therapy, or SMART) as an option for adults at Step 3 (see below).

Exercise-induced bronchoconstriction is also reduced in both adults and children by regular use of inhaled corticosteroids.[28]

Various studies have examined the role that inhaled corticosteroids might play in modifying the development of asthma in symptomatic children.[29-31] Although the short-term therapeutic efficacy varied between studies, possibly due to the differing lengths of treatment and study populations used, in all 3 studies the long-term clinical and functional outcomes did not differ in children treated with inhaled corticosteroids compared with placebo.

Xanthines such as aminophylline or theophylline may be given for their bronchodilating properties although there is evidence that the long-acting beta$_2$ agonist salmeterol produces a greater improvement in lung function, reduces the need for rescue short-acting beta$_2$ agonists, and has fewer adverse effects compared with theophylline.[32] There is disagreement about adding xanthine treatment to beta$_2$ agonists for the management of acute severe asthma (see below).

Inhaled *antimuscarinics* such as ipratropium bromide or oxitropium bromide, used with beta$_2$ agonists, are given in acute asthma; a systematic review[33] found that inhaled multiple doses of antimuscarinic reduced hospital admissions and improved lung function tests compared with beta$_2$ agonists alone.

Cromoglicate or nedocromil may be used as an alternative to corticosteroids for the prophylaxis of less severe asthma or combined with other therapy. *Anti-leukotrienes* such as the leukotriene receptor antagonist zafirlukast and the leukotriene inhibitor zileuton are another alternative or adjunct to inhaled corticosteroids. When used with inhaled corticosteroids, anti-leukotrienes bring modest improvements in lung function compared with inhaled corticosteroids alone.[34] They may also be useful in exercise-induced bronchoconstriction.[5-7] The anti-IgE monoclonal antibody *omalizumab*[17,35] is available for use in selected patients with allergen-induced asthma. A systematic review of omalizumab,[36] as adjunctive therapy to corticosteroids, found that treatment led to a reduction, and in some cases, withdrawal of regular inhaled corticosteroid, as well as a reduction in asthma exacerbations; longer term evaluation of adverse effects, direct comparison with inhaled corticosteroids, and assessment in children is needed.

CHRONIC ASTHMA

Advice for patients with chronic asthma includes avoidance of smoking, of allergens such as pollen, and of bronchoconstricting drugs such as beta blockers. Patients who have had asthma induced by aspirin and NSAIDs should also avoid these drugs. Skin testing to determine allergen sensitivity may be advisable.[5-7] US guidelines[5] suggest consideration of immunotherapy to desensitise patients with poorly controlled disease unavoidably exposed to a precipitating allergen. Although there is increasing evidence of benefit from such treatment[37] the size of the benefit overall remains somewhat uncertain, and the potential adverse effects make it controversial (see under Allergen Immunotherapy, p. 2435.1). UK guidelines[6] consider that although there is evidence of benefit from immunotherapy when compared with placebo, comparative studies with other asthma treatments are needed.

Gastro-oesophageal reflux has been suggested as another exacerbating factor;[38] symptoms of gastro-oesophageal reflux disease are about one and a half times more common among individuals with asthma than the general population,[39] although the exact nature of the association remains unclear. A 2003 systematic review of acid suppressive therapy concluded that it did not benefit asthma in most patients;[40] more recent studies on the subject support this view,[41,42] although one did note reduced exacerbations and an improvement in the asthma quality of life in patients given lansoprazole compared with placebo.[42]

Guidelines for drug therapy of chronic asthma have been issued in many countries including Australia,[43] Canada,[44,45] the UK,[6] and the USA,[5] and by the Global Initiative for Asthma (GINA).[7] Guidelines specifically for the management of childhood asthma have been issued by The European Pediatric Asthma Group.[46] In general, guidelines advocate a stepwise approach to treatment. Initial control is achieved with the early use of anti-inflammatory drugs at doses most appropriate for the severity of disease. In mild to moderate asthma, starting inhaled corticosteroids at very high doses and stepping down confers no benefit,[47,48] and relatively low initial doses are recommended.[5-7]

Guidelines vary slightly in their definition of low, moderate and high inhaled **corticosteroid doses**—for the definitions of these terms in UK, US, and global asthma guidelines see Asthma, under Choice of Corticosteroid, p. 1600.3.

In adults and older children

The ***UK*** recommendations for adults and children over 5 years of age with chronic asthma are as follows:

- Step 1; mild intermittent asthma
  Patients requiring only occasional relief from symptoms may be adequately managed with an inhaled short-acting beta$_2$ agonist such as salbutamol or terbutaline taken when needed.
- Step 2; regular preventer therapy
  Regular inhaled corticosteroids may be added at an appropriate starting dose for the severity of the disease if symptoms are present or an inhaled beta$_2$agonist is required three times a week or more, or if symptoms wake the patient from sleep one night a week. Patients who have had an exacerbation of asthma requiring oral corticosteroids in the last 2 years should also be considered for regular inhaled corticosteroids. *Alternatives* are cromoglicate or nedocromil, leukotriene receptor antagonists, or modified-release oral theophylline, but these are less effective.
- Step 3; initial add-on therapy
  If adequate control is not achieved, the preferred treatment is to supplement low-dose inhaled corticosteroids with a long-acting inhaled beta$_2$ agonist such as salmeterol xinafoate. If there is only suboptimal response, the long-acting beta$_2$ agonist is continued and inhaled corticosteroid increased to a moderate dose. If there is no response to a long-acting beta$_2$ agonist, it should be stopped and inhaled corticosteroid increased to a moderate dose; if control is still inadequate addition of another drug such as a leukotriene receptor antagonist or modified-release oral theophylline should be considered.
- Step 4; persistent poor control
  For patients with persistent poor control of asthma despite use of inhaled moderate-dose corticosteroids and an additional drug (usually a long-acting inhaled beta$_2$ agonist), increasing the inhaled corticosteroid to a high dose should be considered. Patients over 12 years of age may alternatively benefit from addition of either a leukotriene receptor antagonist, modified-release oral theophylline, or an oral modified-release beta$_2$ agonist. If a trial of a particular treatment option is ineffective, the drug is stopped (or in the case of an increased dose of inhaled corticosteroid, reduced).
- Step 5; continuous or frequent use of oral corticosteroids
  If further control is needed, then an oral corticosteroid such as prednisolone may also be given in single daily doses at the lowest dose providing adequate control. High-dose inhaled corticosteroids should also be maintained. Other treatments may be considered to minimise the use of corticosteroid tablets, such as a 6-week trial of treatment with long-acting beta$_2$ agonists, leukotriene receptor antagonists, or theophylline. If a trial of a particular treatment option is not effective, the drug is stopped. When other treatments have proved unsuccessful in patients over 12 years of age, a 3-month trial of immunomodulators such as methotrexate, ciclosporin, and oral gold may be considered for their anti-inflammatory, immunosuppressant, and corticosteroid-sparing properties: their use must be balanced against their potentially serious adverse effects. Referral for specialist care is advised for all patients at this step.

The ***US*** recommendations for chronic asthma management in adults and children over 5 years are:

- Step 1
  A short-acting inhaled beta$_2$ agonist is recommended, taken as required to relieve symptoms.
- Step 2
  As in UK guidelines, if regular controller therapy is needed, then a low-dose inhaled corticosteroid is the preferred treatment. Other alternatives include cromoglicate, nedocromil, a leukotriene receptor antagonist, and theophylline.
- Step 3
  The preferred treatment for patients over 12 years who are not controlled with low-dose inhaled corticosteroids, is either addition of a long-acting inhaled beta$_2$ agonist or increasing the inhaled corticosteroid to a moderate dose. In children aged 5 to 12 years either a leukotriene receptor antagonist or modified-release oral theophylline are equally acceptable treatment options in place of a long-acting inhaled beta$_2$ agonist; however, they are secondary options for patients 12 years and over, along with the leukotriene inhibitor zileuton.
- Step 4
  An increase in the inhaled corticosteroid to a moderate dose is recommended in patients not controlled by Step 3. A long-acting inhaled beta$_2$ agonist is the preferred addition to this; alternatives include either a leukotriene receptor antagonist or modified-release theophylline, or in patients 12 years and over, the leukotriene inhibitor zileuton.
- Step 5
  High-dose inhaled corticosteroid in addition to a long-acting inhaled beta$_2$ agonist is the preferred treatment for patients on Step 5. Alternatively, children aged 5 to 11 years may benefit from either a leukotriene receptor antagonist or modified-release theophylline in place of a long-acting inhaled beta$_2$ agonist. Omalizumab may be considered for patients 12 years and over who have allergies.
- Step 6
  As in Step 5 of the UK guidelines above, an oral corticosteroid may be added to the inhaled high-dose corticosteroid and long-acting beta$_2$ agonist. Alternatively, children aged 5 to 11 years may benefit from either a leukotriene receptor antagonist or modified-release theophylline in place of a long-acting beta$_2$ agonist. Omalizumab may be considered for patients 12 years and over who have allergies.

Consultation with an asthma specialist is recommended from Step 4.

Global guidelines for the management of asthma in adults and children aged over 5 years recommend:

- Step 1, as for UK guidelines, a short-acting inhaled beta$_2$ agonist is the recommended reliever treatment. An inhaled antimuscarinic such as ipratropium, a short-acting oral beta$_2$ agonist, or immediate-release theophylline may be considered as alternatives.
- Step 2; reliever medication plus single controller
  As in UK guidelines a low-dose inhaled corticosteroid is the preferred treatment; anti-leukotrienes are considered an appropriate alternative.
- Step 3; reliever medication plus one or two controllers
  A low-dose inhaled corticosteroid with a long-acting inhaled beta$_2$ agonist (the preferred option in adolescents and adults), or else increasing the inhaled corticosteroid to a moderate (the preferred option in children over 5 years) or high dose should be considered. Alternative treatment options for all ages are a combination of low-dose inhaled corticosteroid with either an anti-leukotriene or modified-release theophylline.
- Step 4; reliever medication plus two or more controllers
  The preferred treatment at Step 4 is to combine a moderate or high dose of an inhaled corticosteroid with a long-acting inhaled beta$_2$ agonist. Addition of either an anti-leukotriene or modified-release theophylline may also provide benefit. High-dose inhaled corticosteroids should be reserved for patients who are not controlled by moderate doses combined with a long-acting inhaled beta$_2$ agonist and/or an additional controller; they are recommended only on a trial basis for 3 to 6 months.
- Step 5
  As in Step 5 of UK guidelines and Step 6 of US guidelines, an oral corticosteroid may be considered in addition to another controller medication. Omalizumab is an option for patients with allergic asthma who remain uncontrolled on combinations of other controllers including a high dose of inhaled or oral corticosteroids.

Referral to an asthma specialist is recommended from Step 4.

A short 'rescue' course of oral prednisolone may also be needed at any time and at any step for an acute exacerbation.

In children under 5 years of age

Recommendations for the management of chronic asthma in children under 5 years of age have also been issued in the UK[6] and USA,[5] and by GINA.[49] There is limited information available for this age group, however, and some recommendations are based on extrapolations from studies in older children and adults. These guidelines also provide a stepwise approach to management. UK recommendations for management of chronic asthma in children under 5 years of age are as follows:

- Step 1; mild intermittent asthma
  Inhaled short-acting $beta_2$ agonist as required.
- Step 2; regular preventer therapy
  A low-dose inhaled corticosteroid may be added if control is poor. If a corticosteroid cannot be used, an alternative to be considered is a leukotriene receptor antagonist.
- Step 3; initial add-on therapy
  Addition of a leukotriene receptor antagonist may be considered if control is poor in those already taking inhaled corticosteroids. In those taking a leukotriene receptor antagonist alone, addition of a low-dose inhaled corticosteroid should be reconsidered. Children under 2 years and those who have persistent poor control on Step 3, may be referred to a respiratory paediatrician (Step 4).

Global guidelines are similar to those in the UK.

The US makes the following recommendations for the management of chronic asthma in children under 5 years of age:

- Step 1, as for UK guidelines above.
- Step 2
  As in UK guidelines, addition of a low-dose inhaled corticosteroid is recommended. Alternative, but less preferable, treatments include the leukotriene receptor antagonist montelukast, and cromoglicate.
- Step 3
  An increase in the inhaled corticosteroid to moderate-dose should be considered.
- Step 4
  In addition to moderate-dose inhaled corticosteroid, consider either a long-acting inhaled $beta_2$ agonist or montelukast.
- Step 5
  The inhaled corticosteroid is increased to high-dose, in addition to either a long-acting $beta_2$ agonist or montelukast.
- Step 6
  In patients who remain uncontrolled, an oral corticosteroid may be added.

Consultation with an asthma specialist is recommended from step 4 onwards.

A short course of oral prednisolone may also be needed for acute exacerbations of asthma.

For all ages, treatment should be regularly **reviewed** and **reduced** in a stepwise manner if asthma is well controlled. Patients should be maintained on the lowest possible dose of inhaled corticosteroid; a reduction in dose every 3 months should be considered, decreasing the dose by about 25 to 50% each time.[6,7]

ACUTE SEVERE ASTHMA

An acute attack of severe asthma (status asthmaticus) is potentially life-threatening and treatment should be instituted as soon as possible. UK guidelines[6] provide guidance on the assessment and initial treatment of exacerbations of asthma in general practice and in the accident and emergency department. Patients with any features of a life-threatening attack, or a severe attack persisting after initial treatment with high-dose short-acting $beta_2$ agonist and an oral corticosteroid, require admission to hospital.

In adults.

Guidelines suggest the following regimen for the hospital management of adults:[6]

- Initially, oxygen should be given to all hypoxaemic patients with acute severe or life-threatening asthma to maintain an oxygen saturation of 94 to 98%.
- High doses of inhaled short-acting $beta_2$ agonists (salbutamol 5 mg or terbutaline 10 mg) and antimuscarinic (ipratropium bromide 500 micrograms) should be given via a nebuliser with oxygen, or compressed air if oxygen is not available; if neither of these is available, multiple actuations of a MDI into a large volume spacer device may be used.
- High doses of systemic corticosteroids are also required: for example, oral prednisolone 40 to 50 mg daily or intravenous hydrocortisone 100 mg every 6 hours. Alternatively, intramuscular methylprednisolone 160 mg may be given instead of a course of oral prednisolone.
- A single intravenous dose of magnesium sulfate (1.2 to 2 g infused over 20 minutes) may be considered at this stage if life-threatening features are still present. The role of magnesium sulfate has not been fully established, although there is some evidence that it has bronchodilator effects in adults. A meta-analysis concluded that its routine use was not justified, but that it appears to be safe and beneficial in some patients with severe exacerbations.[50]
- Subsequently, oxygen therapy should be continued, as should corticosteroid treatment with oral prednisolone or intravenous hydrocortisone.
- Nebulised $beta_2$ agonists and ipratropium bromide may be given every 4 to 6 hours. If the patient's condition has not improved after 15 to 30 minutes, the nebulised $beta_2$ agonist should be given more frequently (up to every 15 minutes, or in a continuous regimen such as salbutamol 10 mg hourly).
- If progress is still unsatisfactory, then an infusion of aminophylline (5 mg/kg over 20 minutes then 500 to 700 micrograms/kg per hour, monitoring blood concentrations if continued for more than 24 hours; the loading dose should not be given to patients already on maintenance oral therapy), or a parenteral $beta_2$ agonist may be considered, although there is limited evidence to support the routine use of either of these drugs.
- Patients who deteriorate further with drowsiness, unconsciousness, or respiratory arrest need transferral to an intensive care unit and intermittent positive-pressure ventilation.

Oral prednisolone treatment is continued for at least 5 days or until recovery. Once lung function is stabilised the patient can be discharged taking inhaled corticosteroids and bronchodilators.

In children.

UK guidelines suggest the following regimen for acute asthma in **children aged 2 years and over**:[6]

- Severe acute attacks in children are initially treated with oxygen, given via either a face mask or nasal cannula, to maintain an oxygen saturation of 94 to 98%. High-dose short-acting $beta_2$ agonists are also given, either via a nebuliser (salbutamol 2.5 mg or terbutaline 5 mg in children aged 2 to 5 years; up to 5 mg of salbutamol and up to 10 mg of terbutaline may be given in children over 5 years) using oxygen as the driving gas, or as multiple actuations of a MDI into a large volume spacer device. There is some evidence that in children with acute asthma, use of spacers rather than nebulisers improves oxygenation, and reduces adverse effects and time spent in the emergency department.[15]
- A systemic corticosteroid at a high dose is also required, either oral prednisolone (20 mg daily in children aged 2 to 5 years, and 30 to 40 mg daily in those over 5 years of age: children already receiving maintenance oral corticosteroids should receive 2 mg/kg up to a maximum of 60 mg daily), or intravenous hydrocortisone (4 mg/kg every 4 hours in more severely affected children).
- If life-threatening features are present, or response to $beta_2$ agonists is poor, nebulised ipratropium bromide (250 micrograms) may be added. Bronchodilators may be repeated every 20 to 30 minutes initially, and then weaned according to response.
- If no improvement is seen, transfer to a paediatric intensive care unit is recommended. Further treatment options to consider are intravenous salbutamol (15 micrograms/kg over 10 minutes followed by an infusion of 1 to 5 micrograms/kg per minute of a 200 microgram/mL solution); intravenous aminophylline (5 mg/kg over 20 minutes then 1 mg/kg per hour; the loading dose should not be given in children already receiving oral theophylline); and, for children over 5 years of age, a single intravenous dose of magnesium sulfate (40 mg/kg to a maximum of 2 g over 20 minutes).

Subsequent management follows a similar routine to that in adults.

For **children under 2 years of age** with acute asthma UK guidelines recommend beginning with oxygen and a trial of short-acting $beta_2$ agonist given by multiple actuations of an MDI into a large volume spacer or via a nebuliser (salbutamol 2.5 mg or terbutaline 5 mg). The $beta_2$ agonist is repeated every 1 to 4 hours if responding; if response is poor nebulised ipratropium (250 micrograms) is added. A short course of a high-dose oral corticosteroid (prednisolone 10 mg daily for up to 3 days) may be considered.

Global guidelines[7,49] for acute severe asthma are similar to those in the UK, except parenteral $beta_2$ agonists are not recommended for routine use in severe asthma exacerbations, although they are included as a treatment option for critically-ill patients. US guidelines also suggest that the parenteral use of $beta_2$ agonists is of unproven value. Also in contrast to the UK, the intravenous use of xanthines is not recommended in the USA. In compiling the UK guidelines the British Thoracic Society has taken the view that although most patients on maximal doses of nebulised $beta_2$ agonists and corticosteroids derive no additional benefit from intravenous aminophylline, some could obtain additional bronchodilatation; intravenous aminophylline was therefore recommended for patients with life-threatening unresponsive acute asthma attacks;[6] some evidence in children,[51] although not in adults,[52] supports this. In contrast, the most recent US guidelines issued by the National Asthma Education and Prevention Program do not recommend the use of xanthines as they are considered to offer no benefit over the optimal use of inhaled short-acting $beta_2$ agonists and increase the frequency of adverse effects.[5] In consequence, in the US guidelines, adult patients whose asthma cannot be managed with oxygen, inhaled short-acting $beta_2$ agonists and antimuscarinics, and systemic corticosteroids may be considered for treatment with intravenous magnesium sulfate or nebulisation with a mixture of helium and oxygen (heliox) in order to avoid intubation and mechanical ventilation. UK guidelines consider there is no evidence to support the use of heliox; a meta-analysis[53] concluded that the existing evidence on heliox failed to show a clear benefit, and although lung function might be improved in the most severe acute asthma patients, the number and size of studies available for analysis was small and the quality variable.

OTHER ASPECTS OF ASTHMA MANAGEMENT

Other therapeutic approaches for the management of asthma are currently under investigation.[54] Ultra-long-acting $beta_2$ agonists under development such as carmoterol, milveterol (GSK-159797; TD-3327), and indacaterol are suitable for once daily use, leading to increased convenience for patients.[55] Carbamazepine has shown potential as a treatment for asthma in addition to regular asthma therapy;[56] improved lung function and fewer exacerbations have been reported. The recombinant human B-type natriuretic peptide (BNP), nesiritide, has been reported to be an effective bronchodilator when given intravenously;[57] its clinical role, if any, remains to be determined. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases. However, a systematic review[1] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further studies were warranted. Ketolides also appear to have immunomodulatory effects: a 10-day course of oral telithromycin started with standard treatment for acute asthma in adults was reported to improve asthma symptoms, regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[58] The mechanism of this effect is unclear, however, and further studies are needed.[59]

Interestingly, furosemide given by inhalation has been found to protect against bronchoconstriction induced by exercise[60] and external stimuli,[61,62] but was not effective in improving bronchial hyperresponsiveness in a 4-week study,[63] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[64] Any clinical application has yet to be determined.[65] There has been some interest in heparin given by inhalation,[65-67] and nebulised lidocaine may be of some benefit;[65,68,69] intravenous lidocaine or oral mexiletine have been shown to block reflex bronchoconstriction.[70] Inhaled magnesium sulfate may also be of some adjunctive benefit to $beta_2$ agonists in the management of acute episodes.[71]

There is increasing study of the cellular mechanisms of inflammation in asthma and ways of controlling them.[72] Phosphodiesterase type-4 is an enzyme that hydrolyses cyclic adenosine monophosphate (cyclic AMP), stimulating the release of acute inflammatory mediators and immune responses; it is found in airways smooth muscle, pulmonary nerves, and inflammatory and immune cells relevant to the pathogenesis of asthma. Phosphodiesterase type-4 inhibitors such as roflumilast are under investigation for their anti-inflammatory and bronchodilator activity.[72,73] The thromboxane A_2 antagonist, seratrodast, is being tried for its effects on pulmonary function and mucus secretion. Asthma-relevant cytokines or chemokines have been targeted in several ways. Interleukin-4 (IL-4) stimulates a range of inflammatory processes in asthma, and soluble recombinant interleukin-4 receptor (IL-4R; rhuIL-4R) is being investigated[74,75] as an antagonist to bind and neutralise interleukin-4. Investigation into the recombinant human IL-4 variant, pitrakinra, is showing promising results in late phase asthmatic responses to allergen challenge.[76] The anti-CD25 interleukin-2 antagonist daclizumab has also been investigated with some reported benefit. An anti-interleukin-5 antibody, mepolizumab, has also been investigated;[72,75] although airway and bone-marrow eosinophils were reduced, no clinical benefits were noted. Cytokines which have a potential anti-inflammatory effect are interleukin-10,[72] interleukin-12, and interferon gamma.[72,75] TNF-α may also play a role in severe asthma. The anti-TNF antibody infliximab, and the TNF receptor blocker etanercept have been shown to be effective in other inflammatory diseases.[72] Small studies using parenteral etanercept have shown some benefit on lung function and

symptoms;[77,78] promising results have also been reported with intravenous infliximab.[79]

The effects of diet and dietary supplements on asthma have also been of interest. Modification of dietary fatty acids in the first 5 years of life,[80] did not reduce the risk of asthma or allergic disease in children considered to be at high risk for developing asthma. Dietary ascorbic acid supplementation has been investigated, and although an improvement in post-exercise lung function and symptoms were noted in one small placebo-controlled study in adults with asthma and exercise-induced bronchoconstriction,[81] a systematic review including this study and 4 others considered that there was insufficient evidence to recommend a specific role for vitamin C in the treatment of asthma.[82] Maternal diet during pregnancy has also been examined; Vitamin D deficiency has been suggested as playing a possible role in immune-mediated disorders such as asthma.[83]

Exercise-induced asthma. For most patients exercise-induced asthma is an expression of poorly controlled asthma and regular treatment with inhaled corticosteroids should be reviewed.[6] Immediately before exercise, inhaled short-acting $beta_2$ agonists are the drugs of choice.[6,7] If exercise is a specific problem in patients taking inhaled corticosteroids, consideration may be given to leukotriene receptor antagonists, long-acting $beta_2$ agonists (although some tolerance may occur), cromoglicate, oral $beta_2$ agonists or theophylline.[6]

Pregnancy. It is particularly important that asthma should be well controlled during pregnancy; where this is achieved asthma has no important effects on pregnancy, labour, or the fetus.[5-7,84-87] A prospective case-control study[88] found no increase in the risk of major congenital malformations in children born to mothers being treated for asthma.

Inhalation has particular advantages as a means of giving drugs during pregnancy because the therapeutic action can be achieved without the need for plasma drug concentrations liable to have a pharmacological effect on the fetus. Systemic treatment should not be withheld if indicated, although there is insufficient information to support the use of anti-leukotrienes, except as continued treatment in women who were taking these before pregnancy for asthma not controlled by other medications.[6,85,86]

Severe exacerbations can have an adverse effect on pregnancy and should be treated promptly with conventional therapy, including oral or parenteral corticosteroids, oxygen, and nebulisation of a $beta_2$ agonist.[6,86] Prednisolone is a suitable corticosteroid for oral use since very little of the drug reaches the fetus.[85]

Occupational asthma. More than 10% of adult-onset asthma cases can be attributed to occupational exposure to pulmonary irritants.[89] Reduction or avoidance of exposure to the trigger is ideally an important component of management.[6,7,89,90] Symptoms may still persist; however, the prognosis for workers with occupational asthma is worse for those who remain exposed for more than one year after symptoms develop, compared with those removed earlier.[6]

Rhinitis and asthma. There is a significant association between allergic rhinitis and asthma.[7,91] It has been proposed that they are both manifestations of a single inflammatory process within the respiratory tract.[92] Asthma outcomes may be improved by following a combined therapeutic approach to comorbid allergic rhinitis and asthma.[91] Intranasal corticosteroids, an effective treatment for allergic rhinitis, have produced conflicting results in studies which assessed their effects on asthma symptoms.[91] Leukotriene receptor antagonists have produced benefits for patients with both allergic rhinitis and asthma and the anti-IgE antibody omalizumab may have a role in more severe cases.[91,93]

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Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD, chronic obstructive lung disease, chronic obstructive airways disease) is a common disorder characterised by airflow obstruction which is more or less continuous and not fully reversible, unlike asthma. The airflow limitation is usually progressive and is associated with chronic inflammation which is mainly caused by cigarette smoking;[1,2] passive smoking exposure[3] genetic factors, infections, environmental pollution, and occupational dust and chemical exposure[4] may also have an aetiological role. Symptoms of COPD include chronic and progressive dyspnoea, wheeze, frequent respiratory-tract infections, cough, and sputum production.[1,2] COPD may affect central or proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature to varying degrees in individuals with the disease[1,5]

- **Central airways.** Hypertrophy of the mucous glands and an increase in the number of goblet cells within the bronchial mucosa leads to an increase in mucus production (*chronic bronchitis*). Patients suffer from a chronic productive cough with excessive sputum production, and have been described as 'blue bloaters'. Airway wall changes include squamous metaplasia of the airway epithelium, loss of cilia and ciliary dysfunction, and increased smooth muscle and connective tissue.
- **Peripheral airways.** *Bronchiolitis* is present in the small airways. Goblet cell hyperplasia, squamous cell metaplasia, inflammatory cell infiltration, and fibrosis are all seen, leading to irreversible narrowing of the airways.
- **Lung parenchyma.** *Emphysema* occurs in the lung parenchyma in COPD. An abnormal permanent enlargement of air spaces distal to the terminal bronchioles is accompanied by destruction of the alveolar wall without obvious fibrosis. There is excessive airway collapse upon expiration and irreversible airways obstruction. Dyspnoea is a prominent symptom; a marked loss of weight may also be noted. Patients may hyperventilate to maintain oxygen levels in the blood and have been called 'pink puffers' in contrast to the 'blue bloaters' of the classic bronchitic presentation. Emphysema can sometimes be caused by a hereditary deficiency of $alpha_1$-proteinase inhibitor ($alpha_1$ antitrypsin), see p. 2438.2. Microscopic lesions can progress to form bullae, which are defined as an emphysematous space greater than 1 cm in diameter.
- **Pulmonary vasculature.** Initially these changes are characterised by thickening of the vessel wall and endothelial dysfunction. These are followed by increased vascular smooth muscle and inflammatory cell infiltration. In advanced stages of the disease there is collagen deposition and emphysematous destruction of the capillary bed.
- **Extrapulmonary changes.** Patients with severe COPD with hypoxaemia and hypercapnia can develop *cor pulmonale* (heart disease secondary to disease of the lungs and respiratory system) marked by pulmonary hypertension, right ventricular hypertrophy, and right heart failure.[5,6] COPD is also associated with systemic inflammation and skeletal muscle wasting.[5]

Management of COPD. Although there is less consensus than for asthma, guidelines for the treatment of COPD have been issued in several countries,[1,2,5,7-9] and some clinicians have developed clinical algorithms for management.[10] The most important therapeutic intervention is encouraging those patients who smoke to stop; this is the most effective intervention to reduce disease progression.[1,2,11] Psychological support and adjunctive drug therapy may be required (see Smoking Cessation, p. 2570.2). Prevention of respiratory infection should be considered; influenza vaccination is recommended[1,2,5,7,8] and can reduce serious illness and death in patients with COPD by about 50%.[1,5,7,8] Compared with influenza vaccination, there is less well-defined benefit from pneumococcal vaccination in patients with COPD.[8] It is generally recommended however,[1,2,7,8] and a study found most benefit in younger patients and those with more severe disease.[12]

Drug treatment is mainly symptomatic and palliative using bronchodilators, corticosteroids, and oxygen therapy.

First-line drug therapy for the treatment of COPD consists of bronchodilators to alleviate bronchospasm and any reversible component of the airways obstruction. Either an inhaled short-acting *antimuscarinic*, such as ipratropium bromide, or a short-acting *$beta_2$ agonist*, is suggested as the initial bronchodilator.[1,2,7] Individual responses to the different classes of bronchodilators are variable.[8] In mild disease inhaled bronchodilators can be used on an as-needed basis.[1,2,7,8] In moderate and more severe disease, therapeutic options include the regular use of these bronchodilators either alone[7] or in combination,[7,8] or the addition of long-acting bronchodilators such as the $beta_2$ agonists salmeterol and formoterol or the antimuscarinic tiotropium.[1,2,5,7,8] A review[13] of the role of long-acting bronchodilators in COPD found that they effectively improved lung function; however, they differed in their effects on other outcomes. Only tiotropium had consistent superiority to the short-acting bronchodilator ipratropium. A reduction in COPD exacerbations and related hospitalisations and improved symptoms and quality of life have been reported in two systematic reviews[14,15] of tiotropium compared with either placebo or ipratropium; improvements in lung function compared with either placebo, ipratropium, or a long-acting $beta_2$ agonist were also noted. Regular treatment with long-acting bronchodilators is more effective and convenient than with shorter acting drugs.[1,2] Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilatation while avoiding the need for high doses and the associated adverse effects.[1,2,7] Ipratropium given with salmeterol has been associated with beneficial effects on quality of life and lung function compared with salmeterol alone.[16] Beneficial effects on lung function have also been reported with tiotropium plus formoterol compared with either treatment alone.[17,18] A *xanthine* such as an oral modified-release preparation of theophylline may also be considered, usually where short and long-acting bronchodilators are ineffective, or in patients unable to use inhaled therapy, as there is an increased risk of adverse effects and drug interactions as well as a need for monitoring.[1,2,7,8,19] Theophylline has been reported to reduce exacerbations compared with a long-acting $beta_2$ agonist,[20] but is less effective than inhaled corticosteroids. Theophylline may also have positive cardiac inotropic effects, see under Chronic Obstructive Pulmonary Disease, p. 1231.1, which could be of value in cor pulmonale. Roflumilast is an oral *phosphodiesterase inhibitor* that can be used for maintenance treatment in those with severe disease; its place in therapy is not yet established.

Inhaled corticosteroids have been reported to reduce the rate of exacerbations,[21-23] and guidelines recommend regular treatment with an *inhaled corticosteroid* combined with a long-acting $beta_2$ agonist for symptomatic patients with moderate to severe COPD and repeated exacerbations.[1,2,5] UK guidelines[2] include recommendations on the selection of bronchodilators and corticosteroids for regular inhaled maintenance treatment according to predicted FEV_1 for those who remain breathless or have exacerbations despite using short-acting $beta_2$ agonists or short-acting antimuscarinics.

Although some guidelines[7] still recommend trying oral prednisolone in selected patients with stable COPD to assess response to continued inhaled corticosteroid therapy, a large study[24] found that the response to a course of oral prednisolone was unrelated to the change in FEV_1 and health status over the next 3 years of treatment with either inhaled fluticasone or placebo. Other guidelines[2] have therefore concluded that a short course of oral corticosteroid is a poor predictor of long-term response to inhaled therapy, and do not recommend this assessment. A systematic review[23] also found that bronchodilator reversibility and bronchial hyper-responsiveness did not predict response to inhaled corticosteroids.

Whether inhaled corticosteroids improve the long-term outcomes of COPD is less clear. There has been some suggestion that inhaled corticosteroids reduce mortality,[25,26] although subsequent systematic reviews[23,27] did not find any significant effect. A study[28] designed to assess the effect of a combination inhaler containing an inhaled corticosteroid (fluticasone) and the long-acting $beta_2$ agonist salmeterol on survival in COPD patients did not show a significant reduction in all-cause mortality, but benefits were seen in the rate of exacerbations, lung function, and health status compared with placebo. Unexpectedly, the study investigators also reported a higher probability of pneumonia amongst patients given medications containing fluticasone. A later systematic review[27] also found an excess risk of pneumonia in patients with COPD, and a case-control study suggested the risk increased with higher doses of inhaled corticosteroids.[29] Other meta-analyses compared combined inhaled corticosteroid and long-acting $beta_2$ agonist in one inhaler with either placebo,[30] long-acting $beta_2$ agonist,[31] or inhaled corticosteroid.[32] Combination therapy led to a significant reduction in exacerbation rates compared with placebo, long-acting $beta_2$ agonist, and inhaled corticosteroid. However, another systematic review considered that the relative efficacy and safety of such a combination versus the antimuscarinic tiotropium was uncertain.[33] All-cause mortality was reduced with combination therapy compared with either placebo or inhaled corticosteroid, but no impact was seen in comparison with long-acting $beta_2$ agonists.[30-32] Again, the increased incidence of pneumonia in the inhaled corticosteroid groups was a cause of concern. The UK MHRA has warned[34] of the need to be vigilant for the development of pneumonia and other infections in patients with COPD who are using inhaled corticosteroids, as the symptoms of infection often overlap with those of exacerbation of COPD; the use of corticosteroids should be reconsidered if such infections develop. The MHRA also warned[35] that since the benefit of adding an inhaled corticosteroid to a long-acting $beta_2$ agonist was limited, such combination therapy should only be used when COPD progresses to severe disease, and that inhaled corticosteroids should not be used alone.

The effect that inhaled corticosteroids have on the rate of decline in lung function seen in COPD patients has also been studied. A pooled analysis[36] found that, although small but significant improvements in FEV_1 were recorded in the first 6 months of treatment with inhaled corticosteroid compared with placebo (particularly in ex-smokers and women), the rate of decline was not affected after the first 6 months. A systematic review[23] came to similar conclusions regarding lung function decline, but reported a slowing in the rate of decline in quality of life. A later 3-year placebo-controlled study did demonstrate a reduction in the yearly rate of decline in lung function with a combination of fluticasone and salmeterol, or either component alone.[37]

Long-term maintenance use of *oral* corticosteroids is not generally recommended,[1,2,5,7,8] although they have a place in the short-term management of exacerbations (see below), and withdrawal after an exacerbation may be difficult in some patients with advanced disease.[2]

In patients with severe COPD and persistent hypoxaemia, supplemental *oxygen* provided on an almost continuous long-term basis at home has been found to improve survival and alleviate complications such as cor pulmonale, polycythaemia and neuropsychological impairment.[38,39] Guidelines recommend starting oxygen therapy in patients whose resting PaO_2 is less than 55 mmHg (about 7.3 kPa), or whose arterial-oxygen saturation is less than about 88%.[1,2,5,7,8] It may also be considered when PaO_2 is between 55 and 60 mmHg (7.3 to 8 kPa) or arterial-oxygen saturation is less than about 90%, and if there is evidence of polycythaemia, pulmonary hypertension, or right heart failure.[1,2,5,7,8] Nocturnal oxygen therapy may benefit some patients who suffer from nocturnal hypoxaemia,[5,7] but not all guidelines recommend it, as evidence for clinical benefits and improvement in survival is lacking.[5] Evidence of benefit from short-term, 'as-needed' oxygen inhalation after exertion is lacking,[40] although a review of studies using ambulatory oxygen during an exercise test reported an improvement in exercise performance versus placebo;[41] selected patients might gain some benefits.[2,42]

A meta-analysis[43] of the use of *mucolytics* suggested a small reduction in exacerbations and in the total number of days of disability; benefit may be greater in patients with frequent or prolonged exacerbations. Although most guidelines do not recommend widespread use,[1,2] patients with chronic productive cough may be considered for treatment;[2] a reduction in exacerbations has been reported.[1,7] Patients who are not prescribed inhaled corticosteroids may also gain some benefit.[1,43] Improved pulmonary function has been reported in patients given aerosolised surfactant.[44]

There is some evidence that treatment with *cardiovascular drugs* can produce improvements in some pulmonary measures. Cohort and case control studies have reported a reduced COPD and pneumonia/influenza mortality risk with the use of statins.[45] Another case control study[46] also reported a reduction in pulmonary as well as cardiovascular outcomes with statins, ACE inhibitors, and angiotensin II receptor inhibitors, the largest benefits occurring with the combination of statins and either ACE inhibitors or angiotensin II receptor inhibitors. This combination was associated with a reduction in COPD hospitalisations, total mortality in both high- and low-risk groups, and myocardial infarction in the high-risk group.

A systematic review[47] to assess the effects of cardioselective beta blockers on respiratory function of patients with COPD found no adverse effects on lung function or respiratory symptoms compared with placebo, and concluded that they should not be routinely withheld from patients with COPD and cor pulmonale. Additionally, a retrospective study[48] noted a reduced mortality associated with beta blocker use in patients hospitalised for acute exacerbations of COPD.

Surgery may be used in selected patients with end-stage disease who remain symptomatic despite optimal medical treatment. Bullectomy may be used to remove a large bulla that does not contribute to gas exchange.[1,2,5,7,49] Lung transplantation (p. 1941.3) may be used in very advanced COPD,[1,2,5,7] particularly in patients with idiopathic emphysema or $alpha_1$ antitrypsin deficiency.[49] In severe COPD with hyperinflation and obvious target areas, lung volume reduction surgery may be considered; it may be a better option than medical therapy to reduce mortality in patients

with mainly upper-lobe emphysema and low exercise capacity.[1,2,5,7,50]

Much *investigational therapy* has focused, with variable results, on three key processes in COPD: oxidative tissue damage, protease-mediated tissue destruction, and leucocyte-driven chronic inflammation.[51,52] Oxidative stress has been targeted with antoxidants, particularly acetylcysteine.[53] Various mediators of the inflammatory processes have also been targeted, for example, inhibitors of interleukin-8[53,54] and phosphodiesterase type 4.[53,55,56] Other therapies which have been considered include inhibitors of cell signalling, TNF, and adhesion molecules and chemokines.[53] Retinoids have been studied in emphysema for potential positive effects on lung repair.[57] Small studies have reported improvements in dyspnoea[58,59] and exercise capacity[59] with inhaled furosemide. Inhaled formulations of trospium chloride and the long-acting antimuscarinic glycopyrronium bromide are under development for the treatment of COPD. There is also evidence that oral therapy with polyunsaturated fatty acids (including omega-3 and omega-6 fatty acids) may improve exercise capacity.[60] As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases; however, their role in COPD remains to be determined.

Exacerbations. Patients with COPD frequently suffer acute exacerbations of their symptoms, and may require hospitalisation. They are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase inflammation.[61] Treatment options include maximal bronchodilators, antibacterials, systemic corticosteroids, and oxygen as necessary, with appropriate management of any associated cardiovascular disorder.[1,2,5,7,8,62]

For *bronchodilator* therapy a short-acting $beta_2$ agonist may be combined with a short-acting antimuscarinic such as ipratropium,[1,5,7,8] although evidence for the efficacy of this combination is lacking.[63] Some guidelines[1,2] further advocate use of a xanthine such as intravenous theophylline in unresponsive patients, although evidence of a clear benefit with systemic xanthines is inconsistent.[64]

Systemic *corticosteroids* are beneficial in acute exacerbations of COPD.[1,2,5,7,8] Studies[65,66] of severe acute exacerbation requiring hospitalisation have found systemic corticosteroids to improve lung function and reduce the length of hospital stay, and a later meta-analysis confirmed that early treatment with oral or parenteral corticosteroids reduced treatment failure and the need for additional treatment, although it was also associated with an increased risk of adverse effects.[67] Some consider that the most effective dose and duration of treatment is yet to be established,[67,68] although one study[65] found that a 2-week course was as effective as a longer course of 8 weeks. Guidelines suggest oral doses of prednisolone 25 to 50 mg daily, or equivalent, for 7 to 14 days.[1,2,5,7,8] There is also no evidence of long-term benefit.[65,66] Inhaled budesonide may be an alternative to oral corticosteroids in the treatment of exacerbations.[1]

The use of *antibacterials* for acute exacerbations has long been controversial. Meta-analysis[69] has suggested a decrease in mortality, treatment failure, and sputum purulence compared with placebo in moderately to severely ill patients, although the analysis included only a small number of studies, with important differences in design (see also Bronchitis, p. 175.3). Guidelines recommend their use on an empirical basis where signs of infection are present[1,2,5,7,8] but do not support prophylactic antibacterial cover for those with recurrent acute exacerbations.[1,2,5,7] Short courses of antibacterial therapy (5 days or less) are as effective as longer courses in mild to moderate exacerbations.[70]

Oxygen therapy is required in patients with hypoxia; the goal is to maintain oxygen saturation above 90% but prevent increasing CO_2 retention.[1,5,7] Uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis, and respiratory arrest; in hospital, arterial blood gases should be used to guide treatment.[2] Some guidelines[7] suggest low initial oxygen concentrations of 24 to 28%. A 2006 systematic review[71] found a lack of evidence on the safest way to provide initial oxygen treatment in COPD exacerbations.

Respiratory stimulants such as doxapram[72] are of limited use but may be considered when non-invasive ventilation is unavailable or inappropriate.[1,2]

Despite intensive therapy, some patients progress to respiratory muscle fatigue and require ventilatory support.

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Acefylline Piperazine *(BAN, rINN)*

Acefilina piperazina; Acéfylline Pipérazine; Acefyllinum Piperazinum; Acepifylline; Piperazine Theophylline Ethanoate; Ацефиллин Пиперазин.

Piperazine bis(theophyllin-7-ylacetate) (1:1).

$(C_9H_{10}N_4O_4)_2.C_4H_{10}N_2$=562.5

CAS — 18833-13-1; 18428-63-2.

ATC — R03DA09.

ATC Vet — QR03DA09.

UNII — 121911OS6Z.

Profile

Acefylline piperazine is a derivative of theophylline (p. 1229.3) that has been used for its bronchodilator effects. It is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Cadiphylate; Etophylate; ***Indon.***: Etaphylline.

Multi-ingredient Preparations. ***India***: Cadiphylate.

Aclidinium Bromide *(USAN, rINN)*

14115700; Aclidinii Bromidum; Bromure d'Aclidinium; Bromuro de aclidinio; LAS-34273; LAS-W-330; Аклидиний Бромид.

(3*R*)-3-{[Hydroxydi(thiophen-2-yl)acetyl]oxy}-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide.

$C_{26}H_{30}BrNO_4S_2$=564.6

CAS — 320345-99-1.

ATC — R03BB05.

ATC Vet — QR03BB05.

UNII — UQW7UF9N91.

Uses and Administration

Aclidinium bromide is a quaternary ammonium antimuscarinic used similarly to ipratropium (p. 1211.3) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (p. 1199.1); it is not suitable for the initial treatment of acute bronchospasm. Aclidinium is given by inhalation, via a dry powder inhaler, as the bromide, although doses may be expressed as either the base or the salt; aclidinium bromide 375 micrograms is equivalent to about 322 micrograms of aclidinium.

Metered doses from the inhaler device may be expressed as the amount delivered *into* the mouthpiece (400 micrograms of aclidinium bromide per actuation) or the amount delivered *from* the mouthpiece (corresponding to 375 micrograms of aclidinium bromide per inhalation). The usual dose is one metered dose inhaled twice daily.

References.

1. Frampton JE. Aclidinium: in chronic obstructive pulmonary disease. *Drugs* 2012; **72:** 1999–2011.
2. Fuhr R, *et al.* Efficacy of aclidinium bromide 400 µg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. *Chest* 2012; **141:** 745–52.
3. Jones PW, *et al.* Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J* 2012; **40:** 830–6.
4. Kerwin EM, *et al.* Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD* 2012; **9:** 90–101.

Adverse Effects and Precautions

As for Ipratropium Bromide (p. 1212.2).

The most frequently reported adverse effects of inhaled aclidinium bromide are headache and nasopharyngitis. Other adverse effects include cough, dysphonia, rhinitis, sinusitis, and diarrhoea.

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p. 1312.3. However, these interactions are not usually seen with antimuscarinics, such as aclidinium bromide, given by inhalation.

Pharmacokinetics

Aclidinium bromide is rapidly absorbed from the lung, with peak plasma concentrations occurring within 5 minutes of inhalation in healthy subjects and within 15 minutes in patients with chronic obstructive pulmonary disease. Whole lung deposition of inhaled aclidinium bromide is about 30% of the metered dose; less than 5% reaches the systemic circulation as unchanged aclidinium. Aclidinium bromide is rapidly hydrolysed in plasma.

Aclidinium bromide is rapidly and extensively metabolised by chemical and enzymatic hydrolysis (mainly by butyrylcholinesterase) to inactive metabolites. After intravenous dosing, about 1% is excreted as unchanged drug in the urine; 54 to 65% of the dose is excreted as metabolites in the urine and 20 to 33% as metabolites in the faeces. After inhalation, about 0.1% is excreted as unchanged drug in the urine; the estimated effective half-life is reported to be 5 to 8 hours, and the terminal elimination half-life about 2 to 3 hours.

References.

1. Jansat JM, *et al.* Safety and pharmacokinetics of single doses of aclidinium bromide, a novel long-acting, inhaled antimuscarinic, in healthy subjects. *Int J Clin Pharmacol Ther* 2009; **47:** 460–8.
2. Jansat JM, *et al.* Safety and pharmacokinetics of multiple doses of aclidinium bromide, a novel long-acting muscarinic antagonist for the treatment of chronic obstructive pulmonary disease, in healthy participants. *J Clin Pharmacol* 2009; **49:** 1239–46.
3. Ortiz S, *et al.* Safety and tolerability of aclidinium administered intravenously and absolute bioavailability of inhaled aclidinium in healthy male participants. *J Clin Pharmacol* 2012; **52:** 819–27.
4. de la Motte S, *et al.* Pharmacokinetics and safety of aclidinium bromide in younger and elderly patients with chronic obstructive pulmonary disease. *Int J Clin Pharmacol Ther* 2012; **50:** 403–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Eklira Genuair; ***Neth.***: Eklira Genuair; ***Norw.***: Eklira Genuair; ***Spain***: Bretaris; Eklira Genuair; ***UK***: Eklira Genuair; ***USA***: Tudorza.

Ambroxol Acefyllinate *(BANM, rINNM)*

Acebrofylline; Acebrophylline; Acefilinato de ambroxol; Ambroxol Acéfylline; Ambroxoli Acefyllinas; Амброксола Ацефиллинат.

$C_{13}H_{18}Br_2N_2O_2C_9H_{10}N_4O_4$=616.3

CAS — 96989-76-3.

UNII — 0HM1E174TN.

Profile

Ambroxol has mucolytic properties (see Ambroxol Hydrochloride, p. 1654.3) but theophylline derivatives such as the acefyllinate are used as bronchodilators. Ambroxol acefyllinate is given in an oral dose of 100 mg twice daily. For doses in children see below.

Administration in children. Ambroxol acefyllinate can be used as a bronchodilator in children. Children from 1 to 6 years of age may be given an oral dose of 25 mg twice daily, and children from 6 to 12 years, 50 mg twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Brismucol†; Brondilat; Brondyneo; Bronfilil; Brontek; Cebronfilina†; Expecdilat; Filinar; Hiflux; Teomuc; ***India***: A-Xanthin; Ab-Phylline; Bestofyline-A; Mucoreg; ***Ital.***: Ambromucil; Broncomnes; Surfolase; ***Mex.***: Brismucol; Kasmucol; ***Venez.***: Brixilon; Bronilis; Klas.

Multi-ingredient Preparations. ***India***: Acedril.

Aminophylline *(BAN, pINN)*

Aminofilin; Aminofilina; Aminofylin; Aminofylliini; Aminofyllin; Aminophyllinum; Euphyllinum; Metaphyllin; Teofilina y etilenodiamina, mezcla de; Teofilinas-etilendiaminas; Teofillinetiléndiamin; Teofylliinietyleenidiamiini; Teofyllinetylendiamin; Theophyllaminum; Theophylline and Ethylenediamine; Theophylline Ethylenediamine Compound; Théophylline-éthylènediamine; Theophyllinum Et Ethylenediaminum; Аминофиллин.

A mixture of theophylline and ethylenediamine (2:1), its composition approximately corresponding to the formula below.

$(C_7H_8N_4O_2)_2,C_2H_4(NH_2)_2$=420.4

CAS — 317-34-0 (anhydrous aminophylline).

ATC — R03DA05.

ATC Vet — QR03DA05.

UNII — 27Y3KJK423.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 8: (Theophylline-Ethylenediamine, Anhydrous; Aminophylline BP 2014). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish hygroscopic powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 36: (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Aminophylline Hydrate *(BANM, pINNM)*

Aminofilina dwuwodna; Aminofilina hidratada; Aminofylin hydratovaný; Aminophylline, Hydrate d'; Aminophyllini Hydratum; Aminophyllinum Dihydricum; Aminophyllinum Hydricum; Teofylliinietyleenidiamiinihydraatti; Teofyllinetylendiaminhydrat; Théophylline-éthylènediamine hydratée; Theophyllinum et ethylenediaminum hydricum; Аминофиллина Гидрат.

$(C_7H_8N_4O_2)_2,C_2H_4(NH_2)_2,2H_2O$=456.5

CAS — 49746-06-7; 5897-66-5 (aminophylline dihydrate); 76970-41-7 (aminophylline monohydrate).

ATC — R03DA05.

ATC Vet — QR03DA05.

UNII — C229N9DX94 (aminophylline dihydrate); Y7E0LU9ZM5 (aminophylline monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 8: (Theophylline-ethylenediamine Hydrate; Aminophylline Hydrate BP 2014). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in well-filled airtight containers. Protect from light.

USP 36: (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Incompatibility. Aminophylline solutions should not be allowed to come into contact with metals.

Solutions of aminophylline are alkaline and if the pH falls below 8, crystals of theophylline will deposit.[1] Drugs known to be unstable in alkaline solutions, or that would lower the pH below the critical value, should not be mixed with aminophylline.

1. Edward M. pH—an important factor in the compatibility of additives in intravenous therapy. *Am J Hosp Pharm* 1967; **24:** 440–9.

Uses and Administration

Aminophylline has the actions and uses of theophylline (see p. 1229.3) and is used similarly as a bronchodilator in the management of asthma (p. 1195.2) and chronic obstructive pulmonary disease (p. 1199.1). Aminophylline has also been used to relieve neonatal apnoea (p. 1204.3). It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease. Aminophylline is usually preferred to theophylline when greater solubility in water is required, particularly in intravenous formulations.

Aminophylline may be given in the anhydrous form or as the hydrate, and doses may be expressed as either; aminophylline hydrate 1.09 mg is equivalent to about 1 mg of aminophylline. The USP 36 specifies that aminophylline preparations should be labelled with respect to their anhydrous *theophylline* content; aminophylline 1 mg and aminophylline hydrate 1.09 mg are equivalent to about 0.86 mg theophylline. As the pharmacokinetics of theophylline are affected by several factors including age, smoking, disease, diet, and drug interactions, the dose of aminophylline must be carefully individualised and serum-theophylline concentrations monitored (see Uses and Administration of Theophylline, p. 1229.3).

In the management of **acute severe bronchospasm**, aminophylline may be given intravenously by slow injection or infusion. To reduce adverse effects, intravenous aminophylline should not be given at a rate greater than 25 mg/minute. In adults who have not been taking aminophylline, theophylline, or other xanthine-containing medication, a loading dose of 5 mg/kg ideal (lean) bodyweight or 250 to 500 mg of aminophylline may be given intravenously over 20 to 30 minutes by slow injection or infusion, followed by a maintenance infusion dose of 500 micrograms/kg per hour. Older patients and those with cor pulmonale, heart failure, or liver disease may require lower maintenance doses; smokers often need higher maintenance doses. A loading dose may not be considered necessary unless the patient's condition is deteriorating.

Intravenous aminophylline is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, the serum-theophylline concentration should first be assessed and the initial loading dose should be calculated on the basis that each 600 micrograms/kg of aminophylline (equivalent to about 500 micrograms/kg theophylline) will increase serum-theophylline concentration by 1 microgram/mL.

In the management of **chronic bronchospasm** aminophylline may be given orally as modified-release preparations; a usual dose is aminophylline hydrate 225 to 450 mg twice daily. Therapy should start with the lower dose and be increased as appropriate. Retitration of the dosage is required if the patient is changed from one modified-release preparation to another as the bioavailability of modified-release aminophylline preparations may vary.

For doses of aminophylline used in children, see Administration in Children, below.

Intramuscular injection of aminophylline causes intense local pain and is not recommended.

Aminophylline has also been used as the hydrochloride.

Administration. *RECTAL ADMINISTRATION.* Absorption from aminophylline suppositories is erratic and this dose form has been associated with toxicity, hence the warnings that suppositories should not be used, especially in children. In the UK suppositories are no longer readily available; one hospital wishing to use the rectal route for apnoea in premature infants (see Neonatal Apnoea, p. 1204.3) achieved therapeutic plasma-theophylline concentrations with a specially formulated rectal gel.[1]

1. Cooney S, *et al.* Rectal aminophylline gel in treatment of apnoea in premature newborn babies. *Lancet* 1991; **337:** 1351.

Administration in children. Aminophylline may be given intravenously, by slow injection or infusion, to manage **acute severe bronchospasm** in children. Doses should be calculated using ideal or lean body-weight. In children who have not been taking aminophylline, theophylline or other xanthine-containing medicine, UK licensed product information recommends a loading dose of 5 mg/kg given by slow injection or infusion over 20 to 30 minutes. Initial maintenance dose ranges are:

- 6 months up to 10 years of age: 1 mg/kg per hour
- 10 to 16 years of age: 800 micrograms/kg per hour

Although unlicensed in the UK for use in children under 6 months, the *BNFC* suggests that these doses may be used from 1 month of age. Children aged from 12 to 18 years may be given 500 to 700 micrograms/kg per hour. Serum-theophylline concentrations should be used to guide further dose adjustments.

Children who are already receiving theophylline, aminophylline or other xanthine-containing medicines, should not normally receive a loading dose of intravenous aminophylline unless serum-theophylline concentration is available to guide dosage. Loading doses are based on the expectation that each 600 micrograms/kg lean body-weight of aminophylline will result in a 1-microgram/mL increase in serum-theophylline concentration.

Oral modified-release preparations are given to children with a body-weight over 40 kg in the long-term management of **chronic bronchospasm**. An initial dose of aminophylline hydrate 225 mg twice daily may be given if the child has not previously taken xanthine preparations, increased after 1 week to 450 mg twice daily according to serum-theophylline concentrations. Different modified-release preparations are not considered interchangeable.

Aminophylline has also been used in the management of **neonatal apnoea** (see p. 1204.3). For further information on the dosage of theophylline itself in neonates, see Administration in Infants, p. 1230.2.

Cardiac arrhythmias. For mention of the use of aminophylline for bradyarrhythmias, see Theophylline, p. 1231.1.

Erectile dysfunction. For reference to the use of a cream containing aminophylline, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p. 1392.2.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p. 827.1.

Motor neurone disease. A study[1] in 25 patients with amyotrophic lateral sclerosis (see p. 2605.2) found that aminophylline improved the endurance of respiratory muscles and increased the handgrip strength of skeletal muscles; it may have some potential therapeutic benefit in such patients.

1. Berto MC, *et al.* Acute action of aminophylline in patients with amyotrophic lateral sclerosis. *Acta Neurol Scand* 2007; **115:** 301–5.

Reduction of body fat. Cosmetic aminophylline cream has been promoted for its supposed ability to remove fat ('cellulite') from the thighs.[1] Concern has been raised about the potential for topical sensitisation.[2] Cosmetic use of aminophylline is banned in some countries.

1. Dickinson BI, Gora-Harper ML. Aminophylline for cellulite removal. *Ann Pharmacother* 1996; **30:** 292–3.
2. Simon PA. Comment: aminophylline-containing cream. *Ann Pharmacother* 1996; **30:** 1341.

Renal colic. Aminophylline has been studied[1] for its potential value as an adjunct in the management of the pain associated with renal calculi (p. 6.3).

1. Djaladat H, *et al.* The effect of aminophylline on renal colic: a randomized double blind controlled trial. *South Med J* 2007; **100:** 1081–4.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p. 1231.2, p. 1232.3, and p. 1233.1. Hypersensitivity has been associated with the ethylenediamine content.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aminophylline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Theophylline, p. 1233.3.

Pharmacokinetics

Aminophylline, a complex of theophylline with ethylenediamine, readily liberates theophylline in the body. The pharmacokinetics of theophylline are discussed on p. 1236.3.

Studies in healthy subjects suggested that ethylenediamine does not affect the pharmacokinetics of theophylline after oral or intravenous dosage.[1,2]

1. Aslaksen A, *et al.* Comparative pharmacokinetics of theophylline and aminophylline in man. *Br J Clin Pharmacol* 1981; **11:** 269–73.
2. Caldwell J, *et al.* Theophylline pharmacokinetics after intravenous infusion with ethylenediamine or sodium glycinate. *Br J Clin Pharmacol* 1986; **22:** 351–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cardirenal; Fadafilina; Larjanfilina; ***Braz.***: Aminoima†; Aminoliv; Asmafin; Asmapen; Asmodrin; Asmoquinol; Minoton; Pulmodilat†; Unifilin; ***Canad.***: Phyllocontin†; ***Chile***: Cardiomin; ***China***: Xing You Shan (星尤善); ***Cz.***: Syntophyllin; ***Denm.***: Teofylamin; ***Fin.***: Aminocont; ***Gr.***: Euphyllin†; Phyllotemp; ***Hung.***: Diaphyllin; ***India***: Minophyl; ***Indon.***: Phyllocontin; ***Irl.***: Phyllocontin; ***Ital.***: Aminomal; Tefamin; ***Jpn***: Neophyllin; ***Mex.***: Amofilin†; Drafilyn-Z; ***Philipp.***: Theofil; ***Port.***: Filotempo; ***S.Afr.***: Phyllocontin; ***Spain***: Eufilina†; ***Swed.***: Teofyllamin; ***Thai.***: Amino; Asmalia†; ***Turk.***: Aminocardol; Asmafilin; Carena; Filinsel; ***UK***: Phyllocontin; ***Venez.***: Broncophilina.

Multi-ingredient Preparations. ***Braz.***: Alergo Filinal; Dispneitrat†; ***China***: Asmeton (阿斯美); Cha Xin Na Min (茶新那敏); Fufang Dan An Pian (复方胆氨片); Ke Zhi (克之); ***Hong Kong***: Amiton†; Asmeton; ***India***: Broncofree; Cortasthma; ***Mex.***: Paliatil; ***Port.***: Anti-Asmatico†; ***S.Afr.***: Genasma†; Natrophylline Compound†; Repasma†; ***USA***: Emergent-Ez.

Pharmacopoeial Preparations

BP 2014: Aminophylline Injection; Aminophylline Tablets; Prolonged-release Aminophylline Tablets;

USP 36: Aminophylline Delayed-release Tablets; Aminophylline Injection; Aminophylline Oral Solution; Aminophylline Rectal Solution; Aminophylline Suppositories; Aminophylline Tablets.

Amlexanox *(BAN, USAN, rINN)*

AA-673; Amlexanoxo; Amlexanoxum; Amoxanox; CHX-3673; Амлексанокс.

2-Amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acid.

$C_{16}H_{14}N_2O_4$=298.3

CAS — 68302-57-8.

ATC — A01AD07; R03DX01.

ATC Vet — QA01AD07; QR03DX01.

UNII — 8RL1C2459K.

NOTE. The name Elics has been used as a trade mark for amlexanox.

Pharmacopoeias. In *Jpn*.

Profile

Amlexanox has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1225.3) and also acts as a leukotriene inhibitor. It is given orally in the management of asthma (p. 1195.2) and for allergic rhinitis (p. 612.1); a dose of 25 or 50 mg three times daily has been suggested. Amlexanox is also given as a metered-dose nasal spray for allergic rhinitis, and as 0.25% eye drops for allergic conjunctivitis.

Amlexanox is also applied in the management of aphthous ulcers (see Mouth Ulceration, p. 1814.2); a 5% oral paste may be used 4 times daily. Other formulations include a 2-mg biodegradable oral disc designed to deliver amlexanox locally.

References.

1. Khandwala A, *et al.* 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **83:** 222–30.
2. Khandwala A, *et al.* 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: II. Pharmacokinetics and demonstration of clinical safety. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **83:** 231–8.
3. Bell J. Amlexanox for the treatment of recurrent aphthous ulcers. *Clin Drug Investig* 2005; **25:** 555–66.
4. Murray B, *et al.* The efficacy of amlexanox OraDisc on the prevention of recurrent minor aphthous ulceration. *J Oral Pathol Med* 2006; **35:** 117–22.
5. Liu J, *et al.* An evaluation on the efficacy and safety of amlexanox oral adhesive tablets in the treatment of recurrent minor aphthous ulceration in a Chinese cohort: a randomized, double-blind, vehicle-controlled, unparallel multicenter clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102:** 475–81.
6. Meng W, *et al.* A clinical evaluation o f amlexanox oral adhesive pellicles in the treatment of recurrent aphthous stomatitis and comparison with amlexanox oral tablets: a randomized, placebo controlled, blinded, multicenter clinical trial. *Trials* 2009; **10:** 30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An He (安呵); Fu Rui Si (福瑞斯); Li Ke Bang (立克邦); Xishumai (西扑迈); ***Fin.***: Aftasol†; ***Irl.***: Aphtheal; ***Jpn***: Solfa; ***Neth.***: Miraftil; ***Port.***: Aftaid; ***USA***: Aphthasol†.

Arformoterol Tartrate *(USAN, rINNM)* ⊗

Arformotérol, Tartrate d'; Arformoteroli Tartras; *R,R*-Formoterol Tartrate; Tartrato de arformoterol; Арформотерола Тартрат.

(-)-*N*-[2-Hydroxy-5-{(1*R*)-1-hydroxy-2-{[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino}ethyl}phenyl]formamide hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

$C_{19}H_{24}N_2O_4.C_4H_6O_6$=494.5

CAS — 67346-49-0 (arformoterol); 200815-49-2 (arformoterol tartrate).

UNII — 5P8VJ21235.

Profile

Arformoterol is the *R,R*-enantiomer of the $beta_2$-adrenoceptor agonist formoterol (p. 1209.2) and has similar properties. Arformoterol is a long-acting selective $beta_2$ agonist that is used as a bronchodilator in the management of chronic obstructive pulmonary disease (p. 1199.1). It is given as the tartrate, but doses are described in terms of the base; 22 micrograms of arformoterol tartrate is equivalent to about 15 micrograms of arformoterol. Given as a nebulised solution, a usual inhaled dose of arformoterol is 15 micrograms given every 12 hours.

References.

1. Lötvall J, *et al.* The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
2. Anonymous. Arformoterol (Brovana) for COPD. *Med Lett Drugs Ther* 2007; **49:** 53–5.
3. Baumgartner RA, *et al.* Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther* 2007; **29:** 261–78.
4. Matera MG, Cazzola M. Ultra-long-acting β_2-adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? *Drugs* 2007; **67:** 503–15.
5. King P. Role of arformoterol in the management of COPD. *Int J Chron Obstruct Pulmon Dis* 2008; **3:** 385–91.
6. Donohue JF, *et al.* Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: a one year evaluation of safety and tolerance. *Ther Adv Respir Dis* 2008; **2:** 37–48.
7. Madaan A. Arformoterol tartrate in the treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease. *Drugs Today* 2009; **45:** 3–9.
8. Panettieri RA, *et al.* Comparison of the efficacy and safety of arformoterol 15 µg twice daily and arformoterol 30 µg once daily in COPD: a single-dose, multicenter, randomized, modified-blind, two-way crossover study. *Clin Ther* 2009; **31:** 1716–23.
9. Hanania NA, *et al.* The safety and efficacy of arformoterol and formoterol in COPD. *COPD* 2010; **7:** 17–31.
10. Cazzola M, *et al.* Arformoterol tartrate in the treatment of COPD. *Expert Rev Respir Med* 2010; **4:** 155–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Brovana.

Bambuterol Hydrochloride

(BANM, rINNM) ⊗

Bambutérol, Chlorhydrate de; Bambuterol, hidrocloruro de; Bambuterol-hidroklorid; Bambuterolhydrochlorid; Bambuterol-hydrochlorid; Bambuterolhydroklorid; Bambuteroli hydrochloridum; Bambuterolihydrokloridi; Bambuterolio hidrochloridas; Hidrocloruro de bambuterol; KWD-2183; Бамбутерола Гидрохлорид.

(*RS*)-5-(2-*tert*-Butylamino-1-hydroxyethyl)-*m*-phenylene bis (dimethylcarbamate) hydrochloride.

$C_{18}H_{29}N_3O_5$,HCl=403.9

CAS — 81732-65-2 (bambuterol); 81732-46-9 (bambuterol monohydrochloride).

ATC — R03CC12.

ATC Vet — QR03CC12.

UNII — 786Q84QZ3F.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bambuterol Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol.

Uses and Administration

Bambuterol is an inactive prodrug of terbutaline (p. 1228.1), a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has similar actions to those of salbutamol (p. 1220.2) except that it has a more prolonged duration of action (at least 24 hours). Bambuterol hydrochloride is used as a long-acting bronchodilator for persistent reversible airways obstruction in conditions such as asthma (p. 1195.2). The usual dose is 10 to 20 mg orally once daily at bedtime. Doses may need to be reduced in renal impairment (see below).

Administration in renal impairment. Licensed product information recommends that the initial dose of bambuterol hydrochloride should be halved in patients with renal impairment (glomerular filtration rate less than 50 mL/minute). Further doses should be adjusted according to response.

Asthma. References.

1. Fugleholm AM, *et al.* Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma. *Eur Respir J* 1993; **6:** 1474–8.
2. Gunn SD, *et al.* Comparison of the efficacy, tolerability and patient acceptability of once-daily bambuterol tablets against twice-daily controlled release salbutamol in nocturnal asthma. *Eur J Clin Pharmacol* 1995; **48:** 23–8.
3. Zarkovic JP, *et al.* The Bambuterol Multicentre Study Group. One-year safety study with bambuterol once daily and terbutaline three times daily in 2-12-year-old children with asthma. *Pediatr Pulmonol* 2000; **29:** 424–9.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3. Bambuterol is not recommended for patients with severe hepatic impairment as its metabolism would be unpredictable. The dose of bambuterol should be reduced in renal impairment (see above). It is unsuitable for the relief of acute bronchospasm or in patients with unstable respiratory disease.

Effects on the heart. A prescription event monitoring study found an excess risk of non-fatal heart failure in elderly patients receiving bambuterol, particularly in the first month of treatment.[1] See also under Salbutamol, p. 1222.1.

1. Martin RM, *et al.* Risk of non-fatal cardiac failure and ischaemic heart disease with long acting β$_2$ agonists. *Thorax* 1998; **53:** 558–62.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bambuterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Salbutamol, p. 1223.1. Bambuterol inhibits plasma cholinesterases and can prolong the action of drugs such as suxamethonium (see Sympathomimetics, under Suxamethonium, p. 2040.1) that are inactivated by these enzymes.

Pharmacokinetics

Nearly 20% of a dose of bambuterol is absorbed from the gastrointestinal tract after oral doses. It is slowly metabolised in the body to its active metabolite, terbutaline; peak terbutaline concentrations are reported to occur about 4 to 7 hours after a dose of bambuterol as tablets. The slow rate at which metabolism occurs determines the prolonged duration of action of bambuterol of at least 24 hours. Hydrolysis of bambuterol is catalysed by plasma cholinesterase; however, bambuterol also inhibits plasma cholinesterase and therefore partly inhibits its own metabolism. For the metabolism and excretion of terbutaline, see p. 1229.1.

References.

1. Sitar DS. Clinical pharmacokinetics of bambuterol. *Clin Pharmacokinet* 1996; **31:** 246–56.
2. Nyberg L, *et al.* Pharmacokinetics of bambuterol in healthy subjects. *Br J Clin Pharmacol* 1998; **45:** 471–8.
3. Bang U, *et al.* Pharmacokinetics of bambuterol in subjects homozygous for the atypical gene for plasma cholinesterase. *Br J Clin Pharmacol* 1998; **45:** 479–84.
4. Ahlström H, *et al.* Pharmacokinetics of bambuterol during oral administration to asthmatic children. *Br J Clin Pharmacol* 1999; **48:** 299–308.
5. Rosenborg J, *et al.* Pharmacokinetics of bambuterol during oral administration of plain tablets and solution to healthy adults. *Br J Clin Pharmacol* 2000; **49:** 199–206.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bambec; ***Braz.***: Bambair; Bambec; ***China***: Ao Duo Li (奥多利); Bambec (帮备); BangShun (邦顺); Bei He Jian (贝合健); Hui Jie (汇杰); Li Ke Fei (立可菲); Luo Xi (洛希); LuoLi (罗利); Zhu Long (祝龙); ***Denm.***: Bambec; Oxeol; ***Fr.***: Oxeol; ***Ger.***: Bambec; ***India***: Abel; Asthafree; Bambudil; Bemlo; Betaday; ***Norw.***: Bambec; ***NZ***: Bambec; ***Philipp.***: Bambec; Bambutec; Pulmitac; ***Singapore***: Bambec; ***Spain***: Bambec; ***Swed.***: Bambec; ***Thai.***: Bambec; ***UK***: Bambec.

Multi-ingredient Preparations. ***India***: Montair Plus; Monway Plus; Odimont Plus.

Bamifylline Hydrochloride

(BANM, USAN, rINNM)

AC-3810; Bamifilina, hidrocloruro de; Bamifylline, Chlorhydrate de; Bamifyllini Hydrochloridum; BAX-2739Z; 8102-CB; CB-8102; Hidrocloruro de bamifilina; Бамифиллина Гидрохлорид.

8-Benzyl-7-[2-(*N*-ethyl-*N*-2-hydroxyethylamino)ethyl]theophylline hydrochloride.

$C_{20}H_{27}N_5O_3$,HCl=421.9

CAS — 2016-63-9 (bamifylline); 20684-06-4 (bamifylline hydrochloride).

ATC — R03DA08.

ATC Vet — QR03DA08.

UNII — 66466QLM3S.

Profile

Bamifylline hydrochloride is a theophylline derivative (p. 1229.3) that is used for its bronchodilator properties in reversible airways obstruction. It is not converted to theophylline in the body. It is given in usual oral doses of 600 or 900 mg daily in 2 or 3 divided doses. It is also given rectally as suppositories, and by slow intravenous infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Bamifix; ***Fr.***: Trentadil; ***Ital.***: Bamifix; Briofil.

Bitolterol Mesilate *(BANM, rINNM)* ⊗

Bitoltérol, Mésilate de; Bitolterol, mesilato de; Bitolterol Mesylate (USAN); Bitolteroli Mesilas; Mesilato de bitolterol; Win-32784; Битолтерола Мезилат.

4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-o-phenylene di-*p*-toluate methanesulphonate.

$C_{28}H_{31}NO_5$,CH_4O_3S=557.7

CAS — 30392-40-6 (bitolterol); 30392-41-7 (bitolterol mesilate).

ATC — R03AC17.

ATC Vet — QR03AC17.

UNII — 4E53T3611U.

Profile

Bitolterol is an inactive prodrug that is hydrolysed in the body to colterol, a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has similar properties to those of salbutamol (p. 1220.2), and has been used as a bronchodilator in the management of diseases with reversible airways obstruction such as asthma (p. 1195.2) or in some patients with chronic obstructive pulmonary disease (p. 1199.1); inhalation results in the rapid onset of bronchodilatation (2 to 4 minutes) with a duration of action of 5 or more hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Tornalate†.

Bufylline *(BAN)*

Ambuphylline (USAN); Bufilina; Theophylline-aminoisobutanol; Буфиллин.

2-Amino-2-methylpropan-1-ol theophyllinate.

$C_{11}H_{19}N_5O_3$=269.3

CAS — 5634-34-4.

ATC — R03DA10.

ATC Vet — QR03DA10.

UNII — VOU5V0B772.

Profile

Bufylline is a theophylline derivative (p. 1229.3) that has been used for its bronchodilator effects as an ingredient of preparations promoted for coughs and other respiratory-tract disorders. The ethiodide has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: EMS Expectorante; Revenil Dospan; Revenil Expectorante; Revenil; Xpe Expectorante; ***S. Afr.***: Nethaprin Dospan†; Nethaprin Expectorant†.

Caffeine *(BAN)*

Anhydrous Caffeine; Cafeína; Cafeína anhidra; Caféine; Coffein; Coffeinum; Guaranina; Guaranine; Kofeiini; Kofein; Kofeina; Kofeinas; Koffein; Methyltheobromine; Metilteobromina; Teína; Théine; Кофеин.

1,3,7-Trimethylpurine-2,6(3*H*,1*H*)-dione; 1,3,7-Trimethylxanthine; 7-Methyltheophylline.

$C_8H_{10}N_4O_2$=194.2

CAS — 58-08-2.

ATC — N06BC01.

ATC Vet — QN06BC01.

UNII — 3G6A5W338E.

NOTE. Compounded preparations of caffeine may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 8: (Caffeine). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 36: (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Caffeine Citrate *(BANM)*

Cafeína, citrato de; Citrated Caffeine; Coffeinum Citricum; Кофеина Цитрат.

$C_8H_{10}N_4O_2$,$C_6H_8O_7$=386.3

CAS — 69-22-7.

ATC — N06BC01.

ATC Vet — QN06BC01.

UNII — U26EO4675Q.

Caffeine Hydrate *(BANM)*

Cafeína monohidrato; Caféine monohydratée; Caffeine Monohydrate; Coffein-Monohydrat; Coffeinum Monohydricum; Kofeiinimonohydraatti; Kofein monohydrát; Kofeinas monohidratas; Koffein-monohidrát; Kofeiinmonohydraat; Кофеин Моногидрат.

$C_8H_{10}N_4O_2$,H_2O=212.2

CAS — 5743-12-4.

ATC — N06BC01.

ATC Vet — QN06BC01.

UNII — 9T65I06326.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 8: (Caffeine Monohydrate; Caffeine Hydrate BP 2014). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly

soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 36: (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Stability. References to the stability of caffeine and caffeine citrate.

1. Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984; **41:** 2405–6.
2. Nahata MC, *et al.* Stability of caffeine injection in intravenous admixtures and parenteral nutrition solutions. *DICP Ann Pharmacother* 1989; **23:** 466–7.
3. Hopkin C, *et al.* Stability study of caffeine citrate. *Br J Pharm Pract* 1990; **12:** 133.
4. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. *Am J Hosp Pharm* 1994; **51:** 512–14.
5. Fraser BD. Stability of caffeine citrate injection in polypropylene syringes at room temperature. *Am J Health-Syst Pharm* 1997; **54:** 1106, 1108.

Uses and Administration

Caffeine is a methylxanthine that, like theophylline (p. 1229.3), inhibits the enzyme phosphodiesterase and has an antagonistic effect at central adenosine receptors. It is a stimulant of the CNS, particularly the higher centres, and it can produce a condition of wakefulness and increased mental activity. It may also stimulate the respiratory centre, increasing the rate and depth of respiration. Its bronchodilating properties are weaker than those of theophylline. Caffeine facilitates the performance of muscular work and increases the total work that can be performed by a muscle. The diuretic action of caffeine is weaker than that of theophylline.

Caffeine is used as a mild CNS stimulant in usual oral doses of 50 to 100 mg, although doses of up to 200 mg may be used. Doses should not be taken more often than every 3 hours. It is also frequently included in oral analgesic preparations with aspirin, paracetamol, or codeine in unit doses of about 15 to 65 mg but its clinical benefit is debated (see Pain, p. 1205.1). Caffeine is sometimes given with ergotamine in preparations for the treatment of migraine, usually in unit doses of 100 mg. Caffeine citrate has been used similarly. For details of doses in children, see Administration in Children, below.

Caffeine and sodium benzoate and caffeine and sodium salicylate are readily soluble in water and have been used when caffeine is to be given by injection.

Beverages of coffee, tea, and cola provide active doses of caffeine (see p. 2648.2).

General references.

1. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.
2. Keisler BD, Armsey TD. Caffeine as an ergogenic aid. *Curr Sports Med Rep* 2006; **5:** 215–9.
3. Jones G. Caffeine and other sympathomimetic stimulants: modes of action and effects on sports performance. *Essays Biochem* 2008; **44:** 109–23.
4. Ferré S. An update on the mechanisms of the psychostimulant effects of caffeine. *J Neurochem* 2008; **105:** 1067–79.

Administration in children. Caffeine is used in the short-term treatment of neonatal apnoea of prematurity (below).

- An initial loading dose of caffeine citrate 20 mg/kg (equivalent to 10 mg/kg caffeine) is given orally or by intravenous infusion over 30 minutes. If there is inadequate response to the first loading dose, a second loading dose may be given. Licensed product information recommendations for timing of the second dose vary; redosing after either 4 hours or 24 hours have been suggested. If there is continued inadequate response, serum-caffeine concentrations should be measured before further doses are given.
- Beginning 24 hours after the loading dose, a maintenance dose of caffeine citrate 5 to 10 mg/kg (2.5 to 5 mg/kg caffeine) daily is given either orally or by intravenous infusion over 10 minutes.

Serum concentrations of caffeine should be measured before starting treatment in infants who have already been treated with theophylline (which is metabolised to caffeine in infants) or whose mothers consumed caffeine before delivery. Infants with impaired renal or hepatic function should also have serum concentrations of caffeine monitored, and doses reduced if necessary. Serious toxicity has been associated with serum concentrations greater than 50 micrograms/mL.

Optimal duration of treatment has not been established, however therapy is usually continued until the neonate has reached 37 weeks of gestational age when apnoea of prematurity usually resolves spontaneously. It is recommended that caffeine should be stopped when the patient has 5 to 7 days without a significant apnoeic attack.

Asthma. Caffeine's bronchodilating activity is about 40% that of theophylline[1] and oral doses of 5 or 10 mg/kg have been shown to produce an effect.[2,3] Because of its weak action other xanthines are generally recommended in asthma (p. 1195.2), but it may need to be avoided before tests of lung function.[4]

1. Gong H, *et al.* Bronchodilator effects of caffeine in coffee: a dose-response study of asthmatic subjects. *Chest* 1986; **89:** 335–42.
2. Becker AB, *et al.* The bronchodilator effects and pharmacokinetics of caffeine in asthma. *N Engl J Med* 1984; **310:** 743–6.
3. Bukowskyj M, Nakatsu K. The bronchodilator effect of caffeine in adult asthmatics. *Am Rev Respir Dis* 1987; **135:** 173–5.
4. Welsh EJ, *et al.* Caffeine for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 13/07/10).

Dementia. A cohort study in 7017 patients aged 65 years and over examined the association between caffeine intake, cognitive decline, and incident dementia.[1] Caffeine consumption itself was found to be significantly associated with many variables also associated with cognitive decline, such as age, gender, depressive symptoms, and cardiovascular disease. Although no relationship was found between baseline caffeine intake and incident dementia in a 4-year follow-up period, caffeine consumption appeared to reduce cognitive decline in women without dementia. The authors concluded that further studies are required to ascertain whether caffeine may be of value in prolonging the period of mild cognitive impairment in women before a diagnosis of dementia.

1. Ritchie K, *et al.* The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology* 2007; **69:** 536–45.

Diabetes mellitus. A single dose of caffeine 250 mg proved beneficial in augmenting warning symptoms and physiological responses to experimentally-induced hypoglycaemia in diabetic patients,[1] and was suggested as a potentially useful adjunct for diabetics who have difficulty in recognising the onset of hypoglycaemia (see Diabetic Emergencies, p. 465.3). In a subsequent placebo-controlled crossover study oral caffeine 200 mg twice daily appeared to enhance the intensity of hypoglycaemic warning symptoms in patients with type 1 diabetes on a low-caffeine diet.[2] A later study[3] reported an association between caffeine and a reduction in the frequency of nocturnal hypoglycaemia in patients with type 1 diabetes, which the authors suggested may explain the increase in warning symptoms and hormonal responses previously reported in daytime hypoglycaemia. Caffeine has also been seen to impair postprandial glucose metabolism in patients with type 2 diabetes,[4] raising concern about the potential hazards of caffeine in these patients for whom decreases in insulin sensitivity might increase average glucose levels and the risk of diabetic complications.

1. Debrah K, *et al.* Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet* 1996; **347:** 19–24.
2. Watson JM, *et al.* Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 2000; **23:** 455–9.
3. Richardson T, *et al.* Influence of caffeine on frequency of hypoglycaemia detected by continuous interstitial glucose monitoring system in patients with long-standing type 1 diabetes. *Diabetes Care* 2005; **28:** 1316–20.
4. Lane JD, *et al.* Caffeine impairs glucose metabolism in type 2 diabetes. *Diabetes Care* 2004; **27:** 2047–8.

Diagnosis and testing. Caffeine excretion assessed by measuring its urinary metabolites or by the exhalation of labelled CO_2 in breath after doses of ^{13}C- or ^{14}C-labelled caffeine has been used to develop liver function tests and to determine the activity of specific enzymes such as xanthine oxidase, P450 cytochromes, and polymorphic *N*-acetyltransferase.[1]

Caffeine given orally has been used to assess acetylator status by determining the metabolic ratio of the metabolites 5-acetylamino-6-formylamino-1-methyluracil (AFMU) to 1-methylxanthine in urine,[2] but some have questioned its value.[3]

Caffeine has also been investigated in the diagnosis of susceptibility to malignant hyperthermia.[4] Intramuscular injection induced a temporary hypermetabolic reaction in subjects susceptible to malignant hyperthermia, but not in non-susceptible subjects or healthy controls. The authors suggested that monitoring of carbon dioxide, produced by hypermetabolism, might offer a minimally invasive test for such susceptibility.

1. Kalow W, Tang B-K. The use of caffeine for enzyme assays: a critical appraisal. *Clin Pharmacol Ther* 1993; **53:** 503–14.
2. Hildebrand M, Seifert W. Determination of acetylator phenotype in caucasians with caffeine. *Eur J Clin Pharmacol* 1989; **37:** 525–6.
3. Notarianni LJ, *et al.* Caffeine as a metabolic probe: NAT2 phenotyping. *Br J Clin Pharmacol* 1996; **41:** 169–73.
4. Anetseder M, *et al.* Diagnosis of susceptibility to malignant hyperthermia by use of a metabolic test. *Lancet* 2002; **359:** 1579–80.

ECT. In patients whose seizure duration is declining despite maximal ECT stimulation, pretreatment with high-dose intravenous caffeine increases seizure duration without affecting seizure threshold. Theophylline has been used similarly, see p. 1233.2.

References.

1. Hinkle PE, *et al.* Use of caffeine to lengthen seizures in ECT. *Am J Psychiatry* 1987; **144:** 1143–8.
2. Coffey CE, *et al.* Caffeine augmentation of ECT. *Am J Psychiatry* 1990; **147:** 579–85.
3. Kelsey MC, Grossberg GT. Safety and efficacy of caffeine-augmented ECT in elderly depressives: a retrospective study. *J Geriatr Psychiatry Neurol* 1995; **8:** 168–72.

Neonatal apnoea. Apnoea of infancy has been defined as cessation of breathing either lasting 20 seconds or more or associated with bradycardia, cyanosis, pallor, and marked hypotonia, for which no specific cause can be identified.[1] Premature infants (less than 37 weeks of gestation) can exhibit periodic breathing with pathological apnoea (apnoea of prematurity); this usually resolves as the infant approaches term and the neurological systems controlling ventilation mature.[1,2]

The management of neonatal apnoea for which no underlying disorder can be found may involve supportive measures such as cardiorespiratory monitoring;[1] continuous positive airways pressure and drug therapy may be required.[3]

The methylxanthines, aminophylline, theophylline, and caffeine, reduce the frequency of apnoea and the need for mechanical ventilation in preterm infants during the first seven days of therapy.[4] In preterm infants given intermittent positive airway pressure, prophylactic methylxanthine treatment increases the chances of successful extubation within one week.[5] There is evidence to suggest that this benefit might be more helpful in infants of extremely low birth-weight extubated in the first week. High doses of caffeine, 20 mg/kg daily, have been used around the time of extubation in neonates born at less than 30 weeks of gestation. Short term benefits were noted,[6] and no evidence of harm in the first year of life. A review of the use of prophylactic methylxanthines found no evidence to show that caffeine prevents apnoea in at-risk preterm infants, or that it reduces the severity of apnoea or its symptoms; prophylactic methylxanthines might, however, reduce the duration of need for positive pressure ventilation and the rate of patent ductus arteriosus ligation.[7] Caffeine has also been reported to reduce the incidence of bronchopulmonary dysplasia in infants with very low birth-weight,[3] so that positive airways pressure could be stopped earlier in infants given caffeine compared with those given placebo. A later evaluation of these infants found that caffeine therapy improved the rate of survival without neurodevelopmental disability at 18 to 21 months.[8] The incidence of cerebral palsy and cognitive delay were also reduced. Earlier stopping of positive airway pressure in the infants assigned to caffeine explained almost half of the beneficial long-term effect of caffeine, but further studies are required to ascertain other potential mechanisms of action. When assessed at 5 years, neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in these children.[9] Rates of cognitive impairment were much lower at 5 years than at 18 months, and similar in the 2 groups, suggesting that cognitive delay may not be a lasting outcome after preterm birth.

Caffeine has a wider therapeutic index, fewer peripheral adverse effects than theophylline, and a longer half-life enabling once-daily dosage, and is therefore preferred.[4,10] Caffeine is given as the citrate salt, and is well absorbed when given orally. For details of doses, see Administration in Children, above. The *BNFC* considers appropriate serum concentrations in neonatal apnoea to be 10 to 20 mg/litre (50 to 100 micromol/litre). Higher concentrations of 25 to 35 mg/litre (130 to 180 micromol/litre) may sometimes be required. Previous treatment with theophylline, infants born to mothers who consumed caffeine before delivery, infants showing signs of toxicity, or infants who require higher doses will require monitoring of plasma caffeine concentrations; however, routine monitoring of plasma concentrations is not always considered necessary.[11] During the first year of life, the elimination half-life of both caffeine and theophylline decreases significantly as the infant matures; regular monitoring of serum concentrations and constant dosage adjustments are therefore required if therapy is prolonged.[1]

For details of the adverse effects on the cardiovascular system associated with caffeine during treatment of neonatal apnoea, see Effects on the Cardiovascular System, p. 1205.2.

Use of doxapram has been tried for apnoea that does not respond to xanthine therapy;[1,2,12] its effects were similar to the methylxanthines.[13,14] Doxapram is poorly absorbed orally and adverse effects such as hypertension, CNS stimulation, and heart block have been reported.[15]

1. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
2. Ruggins NR. Pathophysiology of apnoea in preterm infants. *Arch Dis Child* 1991; **66:** 70–73.
3. Schmidt B, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354:** 2112–21.
4. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Available in The Cochrane Database of

Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 03/07/12).
5. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 03/07/12).
6. Steer P, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F499–F503.
7. Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 03/07/12).
8. Schmidt B, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; **357:** 1893–1902.
9. Schmidt B, *et al.* Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012; **307:** 275–82.
10. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 03/07/12).
11. Natarajan G, *et al.* Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007; **119:** 936–40.
12. Hascoet J-M, *et al.* Risks and benefits of therapies for apnoea in premature infants. *Drug Safety* 2000; **23:** 363–79.
13. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
14. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
15. Henderson-Smart DJ, Steer P. Doxapram versus methylxanthine for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Obesity. A 1999 review[1] of non-prescription weight loss supplements concluded that controlled studies have not shown fat loss in overweight individuals using caffeine without an energy-restricted diet. A later study[2] examined a herbal combination product, containing amongst its active ingredients caffeine (from kola nut) and ephedrine (from ephedra), in the treatment of overweight and obesity without other lifestyle modifications. Some beneficial effects on body-weight were reported after 12 weeks of treatment compared with placebo; however, although no serious adverse effects were seen in the healthy subjects enrolled in this study, the herbal product used contained relatively low amounts of active ingredients compared with preparations used in other similar studies. The FDA has since banned the sale of dietary supplements containing ephedra as they present an unreasonable risk to health (see Ephedra, p. 1663.1), and concerns have been raised about potential additive stimulant effects of preparations containing both caffeine and ephedrine, see Sympathomimetics under Interactions, p. 1206.2.

1. Egger G, *et al.* The effectiveness of popular, non-prescription weight loss supplements. *Med J Aust* 1999; **171:** 604–8.
2. Coffey CS, *et al.* A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. *Int J Obes Relat Metab Disord* 2004; **28:** 1411–19.

Orthostatic hypotension. Caffeine has been of benefit in the treatment of orthostatic hypotension (p. 1634.3) due to autonomic failure in some patients, especially for postprandial hypotension.[1-3] However, efficacy has only been shown in mild cases and it is usually ineffective in severe cases.[4]

1. Onrot J, *et al.* Hemodynamic and humoral effects of caffeine in autonomic failure. *N Engl J Med* 1985; **313:** 549–54.
2. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with dihydroergotamine and caffeine. *Ann Intern Med* 1986; **105:** 168–73.
3. Tonkin AL. Postural hypotension. *Med J Aust* 1995; **162:** 436–8.
4. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; **35:** 124–32.

Pain. Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics but is of debatable benefit (see under Choice of Analgesic, p. 4.2). Some investigators have failed to show that caffeine offers any benefit[1,2] but others have shown that the adjuvant use of caffeine can increase analgesic activity.[3-8] A meta-analysis of 10 studies comparing paracetamol plus caffeine with paracetamol alone in women with postpartum uterine cramp found any benefit of the combination to be minimal.[9] A literature review[10] concluded that there was some evidence that caffeine may be useful as an analgesic adjuvant in relieving headache, but that the dose may need to be at least 65 mg and that these higher doses increase the risk of nervousness and dizziness. Evidence for the effects of caffeine in other types of pain, such as postpartum, postoperative, dental, rheumatic, and cancer pain, was inconclusive.

In the UK it is generally recommended that caffeine-containing analgesic preparations should not be used not only because of doubts about caffeine enhancing the analgesic effect but because it can add to gastrointestinal adverse effects and in large doses can itself cause headache.

Whether caffeine enhances the gastrointestinal absorption of ergotamine in preparations for the relief of migraine is not clear.

1. Winter L, *et al.* A double-blind, comparative evaluation of acetaminophen, caffeine, and the combination of acetaminophen and caffeine in outpatients with post-operative oral surgery pain. *Curr Ther Res* 1983; **33:** 115–22.
2. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.
3. Laska EM, *et al.* Caffeine as an analgesic adjuvant. *JAMA* 1984; **251:** 1711–18.
4. Rubin A, Winter L. A double-blind randomized study of an aspirin/caffeine combination versus acetaminophen/aspirin combination versus acetaminophen versus placebo in patients with moderate to severe postpartum pain. *J Int Med Res* 1984; **12:** 338–45.
5. Schachtel BP, *et al.* Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* 1991; **151:** 733–7.
6. Migliardi JR, *et al.* Caffeine as an analgesic adjuvant in tension headache. *Clin Pharmacol Ther* 1994; **56:** 576–86.
7. Kraetsch HG, *et al.* Analgesic effects of propyphenazone in comparison to its combination with caffeine. *Eur J Clin Pharmacol* 1996; **49:** 377–82.
8. Diener HC, *et al.* The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; **25:** 776–87.
9. Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain—a meta-analysis. *J Clin Pharm Ther* 1996; **21:** 261–82.
10. Zhang W-Y. A benefit-risk assessment of caffeine as an analgesic adjuvant. *Drug Safety* 2001; **24:** 1127–42.

POST-DURAL PUNCTURE HEADACHE. Intravenous caffeine sodium benzoate may relieve post-dural puncture headache (p. 1983.1) that persists despite conservative therapy. However, the evidence for such use has been questioned.[1]

1. Halker RB, *et al.* Caffeine for the prevention and treatment of postdural puncture headache: debunking the myth. *Neurologist* 2007; **13:** 323–7.

Psoriasis. The efficacy of a 10% formulation of topical caffeine in the treatment of psoriasis has been investigated in a group of 39 patients with stable plaque psoriasis.[1] Improvements were seen at each 2-week follow-up stage, but the difference only became significant after 8 weeks. The only adverse effect noted during the study was mild itching, reported by 2 of the caffeine recipients.

1. Vali A, *et al.* Evaluation of the efficacy of topical caffeine in the treatment of psoriasis vulgaris. *J Dermatol Treat* 2005; **16:** 234–7.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p. 1231.2, p. 1232.3, and p. 1233.1.

Tolerance occurs rapidly to the stimulating effects of caffeine; physical signs of withdrawal including irritability, restlessness, lethargy, and headache may occur if intake is stopped abruptly.

General references.

1. Wills S. Drugs and substance misuse: caffeine. *Pharm J* 1994; **252:** 822–4.
2. Fredholm BB, *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999; **51:** 83–133.

Breast feeding. The American Academy of Pediatrics[1] states that caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no effects occur with moderate intake of caffeinated beverages (2 or 3 cups daily) and caffeine is usually compatible with breast feeding. Furthermore, a prospective cohort study of over 800 infants showed no significant consequences of maternal caffeine consumption on sleep patterns at the age of 3 months, even in those whose mothers consumed ≥ 300 mg daily during pregnancy and while breast feeding.[2]

Studies examining the transfer of caffeine into breast milk after oral doses of 35 to 336 mg of caffeine have recorded peak maternal plasma concentrations of 2.4 to 4.7 micrograms/mL, peak maternal saliva concentrations of 1.2 to 9.2 micrograms/mL, and peak breast-milk concentrations of 1.4 to 7.2 micrograms/mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a hazard, although irritability and a poor sleeping pattern were reported.[3-6]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)
2. Santos IS, *et al.* Maternal caffeine consumption and infant nighttime waking: prospective cohort study. *Pediatrics* 2012; **129:** 860–8.
3. Tyrala EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979; **54:** 787–800.
4. Hildebrandt R, *et al.* Transfer of caffeine to breast milk. *Br J Clin Pharmacol* 1983; **15:** 612P.
5. Sagraves R, *et al.* Pharmacokinetics of caffeine in human breast milk after a single oral dose of caffeine. *Drug Intell Clin Pharm* 1984; **18:** 507.
6. Berlin CM, *et al.* Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics* 1984; **73:** 59–63.

Effects on the cardiovascular system. An increased caffeine intake has been associated with an increase in daytime blood pressure.[1] The study, in 82 healthy, normotensive adolescents, suggested that caffeine use may be a factor contributing to essential hypertension in young people.

High dose caffeine (25 mg/kg) used as a loading dose in the prevention and treatment of neonatal apnoea (see p. 1204.3) resulted in a marked reduction of cerebral and intestinal blood flow velocity in preterm infants;[2] no changes were noted in left ventricular output, blood pressure, or heart rate. The authors attributed the effect on blood flow velocity to vasoconstriction, and suggested a smaller caffeine loading dose, repeated several hours later. A later study, also in preterm infants, which examined the effect of a divided loading dose of caffeine (12.5 mg/kg repeated after 4 hours), found that cerebral blood flow velocity was decreased after the second dose; intestinal blood flow velocity and left ventricular output remained unchanged.[3] The authors concluded that the 20% reduction in cerebral blood flow velocity seen was probably not meaningful for infants with adequate cerebral oxygen supply; however, an infant's ability to respond to hypoxaemia by vasodilatation may be compromised.

For a discussion of the effects of caffeine-containing beverages on cardiovascular risk factors, see p. 2648.3.

1. Savoca MR, *et al.* Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005; **18:** 116–20.
2. Hoecker C, *et al.* Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. *Pediatrics* 2002; **109:** 784–7.
3. Hoecker C, *et al.* Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F61–F64.

Effects on mental function. The effects of caffeine on sleep, including its potential to cause sleep disturbances and excessive daytime sleepiness, have been reviewed.[1,2]

1. James JE, Keane MA. Caffeine, sleep and wakefulness: implications of new understanding about withdrawal reversal. *Hum Psychopharmacol* 2007; **22:** 549–58.
2. Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. *Sleep Med Rev* 2008; **12:** 153–62.

Headache. The association of caffeine with headache has been reviewed.[1] Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand.[2] It has also been suggested that postoperative headache could be attributed to caffeine withdrawal as fasting patients are required to abstain from drinking tea or coffee before surgical procedures. Several studies[3-5] have found a positive association between postoperative headache and daily caffeine consumption, although there have also been negative findings.[6] A prospective study suggested that a prophylactic intravenous dose of caffeine on the day of surgery reduced the likelihood of postoperative headache in patients at risk of caffeine withdrawal.[7]

In a case-control study,[8] investigating the possible association of dietary and medicinal caffeine use with chronic daily headache (CDH), caffeine was found to be a modest risk factor for CDH onset, regardless of headache type. Patients suffering from CDH were more likely overall to have been high caffeine consumers before the onset of CDH; no association was found with current caffeine consumption.

1. Shapiro RE. Caffeine and headaches. *Curr Pain Headache Rep* 2008; **12:** 311–5.
2. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *BMJ* 1990; **300:** 1558–9.
3. Galletly DC, *et al.* Does caffeine withdrawal contribute to postanaesthetic morbidity? *Lancet* 1989; **i:** 1335.
4. Weber JG, *et al.* Perioperative ingestion of caffeine and postoperative headache. *Mayo Clin Proc* 1993; **68:** 842–5.
5. Nikolajsen L, *et al.* Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. *Br J Anaesth* 1994; **72:** 295–7.
6. Verhoeff FH, Millar JM. Does caffeine contribute to postoperative morbidity? *Lancet* 1990; **336:** 632.
7. Weber JG, *et al.* Prophylactic intravenous administration of caffeine and recovery after ambulatory surgical procedures. *Mayo Clin Proc* 1997; **72:** 621–6.
8. Scher AI, *et al.* Caffeine as a risk factor for chronic daily headache: a population-based study. *Neurology* 2004; **63:** 2022–7.

Overdosage. Reports and reviews of caffeine toxicity.

1. Zimmerman PM, *et al.* Caffeine intoxication: a near fatality. *Ann Emerg Med* 1985; **14:** 1227–9.
2. Dalvi RR. Acute and chronic toxicity of caffeine: a review. *Vet Hum Toxicol* 1986; **28:** 144–50.
3. Rivenes SM, *et al.* Intentional caffeine poisoning in an infant. *Pediatrics* 1997; **99:** 736–8.
4. Anderson BJ, *et al.* Caffeine overdose in a premature infaot: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999; **27:** 307–11.
5. Ergenekon E, *et al.* Caffeine intoxication in a premature neonate. *Paediatr Anaesth* 2001; **11:** 737–9.
6. Holstege CP, *et al.* Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol* 2003; **41:** 1003–7.
7. de Wijkerslooth LRH, *et al.* Life-threatening hypokalaemia and lactate accumulation after autointoxication with Stacker 2, a 'powerful slimming agent'. *Br J Clin Pharmacol* 2008; **66:** 728–31.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies caffeine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Pregnancy. Studies of maternal caffeine intake on pregnancy outcomes have had mixed results. Although some prospective studies have found that maternal caffeine intake was associated with reduced fetal growth,[1,2] another study did not support this conclusion,[3] and a moderate reduction in caffeine intake in the second half of pregnancy was reported to have no effect on birth-weight or length of gestation.[4] Similarly, conflicting results have been reported for the effect of caffeine on miscarriage[5-8] and the risk of sudden infant death syndrome.[9,10] A report evaluating the reproductive effects of caffeine for the Food Standards Agency in the UK,[11] concluded that maternal caffeine intake during pregnancy is associated with an increased risk of fetal growth restriction. It seemed likely that the risk was increased with a caffeine intake of about 200 mg daily, but a lower threshold below which there was no increase in risk was not identified. It was also not possible to ascertain causality, although it was considered prudent to assume this. Although the literature suggested a positive association between caffeine intake and miscarriage, limitations in study design did not allow a firm conclusion to be drawn and data on other adverse effects such as preterm birth and congenital malformations were also inconclusive.

1. Cook DG, *et al.* Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. *BMJ* 1996; **313:** 1358–62.
2. CARE Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. Abridged version: *BMJ* 2008; **337:** 1334–8. Full version: http://www.bmj.com/cgi/reprint/337/nov03_2/a2332 (accessed 25/08/09)
3. Clausson B, *et al.* Effect of caffeine exposure during pregnancy on birth weight and gestational age. *Am J Epidemiol* 2002; **155:** 429–36.
4. Bech BH, *et al.* Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial. Abridged version: *BMJ* 2007; **334:** 409. Full version: http://www.bmj.com/cgi/reprint/334/7590/409 (accessed 25/08/09)
5. Mills JL, *et al.* Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993; **269:** 593–7.
6. Klebanoff MA, *et al.* Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med* 1999; **341:** 1639–44.
7. Infante-Rivard C, *et al.* Fetal loss associated with caffeine intake before and during pregnancy. *JAMA* 1993; **270:** 2940–3.
8. Cnattingius S, *et al.* Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000; **343:** 1839–45.
9. Ford RPK, *et al.* Heavy caffeine intake in pregnancy and sudden infant death syndrome. *Arch Dis Child* 1998; **78:** 9–13.
10. Alm B, *et al.* Caffeine and alcohol as risk factors for sudden infant death syndrome. *Arch Dis Child* 1999; **81:** 107–11.
11. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Statement on the reproductive effects of caffeine. Available at: http://cot.food.gov.uk/pdfs/cotstatementcaffeine200804.pdf (accessed 25/08/09)

Interactions

Like theophylline (see p. 1233.3) caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to many interactions with other drugs and substances that enhance or reduce its metabolic clearance.

Reviews.

1. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet* 2000; **39:** 127–53.

Alcohol. In a study of 8 healthy subjects given an oral dose of alcohol of 2.2 mL/kg, caffeine 150 mg by mouth did not antagonise the central effects of alcohol and, instead, a synergistic interaction occurred which further increased reaction time. The common practice of drinking coffee after drinking alcohol in order to sober up is not supported by these results.[1] Another study[2] found that some antagonism of the central effects of alcohol was produced by caffeine, although there was no reversal of subjective sensations of drunkenness; however the dose of caffeine in this study (400 mg) was considerably higher.

1. Oborne DJ, Rogers Y. Interactions of alcohol and caffeine on human reaction time. *Aviat Space Environ Med* 1983; **54:** 528–34.
2. Azcona O, *et al.* Evaluation of the central effects of alcohol and caffeine interaction. *Br J Clin Pharmacol* 1995; **40:** 393–400.

Antiarrhythmics. In 7 healthy subjects and 5 patients with cardiac arrhythmias, *mexiletine* in a single dose of 200 mg and a dose of 600 mg daily respectively, reduced the elimination of caffeine by 30 to 50%.[1] *Lidocaine*, *flecainide*, and *tocainide* had no effect on caffeine elimination in healthy subjects.[1]

1. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* 1987; **317:** 117.

Antibacterials. Caffeine elimination half-life has been reported to be increased and clearance decreased when given with *ciprofloxacin*,[1-3] *enoxacin*,[2,3] and *pipemidic acid*,[2,3] whereas *lomefloxacin*,[4] *norfloxacin*,[2,3] and *ofloxacin*[2,3] had little or no effect on these parameters. Enoxacin had the greatest inhibitory effect on caffeine clearance.[2,3]

1. Healy DP, *et al.* Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; **33:** 474–8.
2. Harder S, *et al.* Ciprofloxacin-caffeine: a drug interaction established using in vivo and in vitro investigations. *Am J Med* 1989; **87** (suppl 5A): 89–91S.
3. Barnett G, *et al.* Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* 1990; **39:** 63–9.
4. Healy DP, *et al.* Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1991; **35:** 660–4.

Antidepressants. Fluvoxamine has been reported to significantly reduce the clearance and prolong the elimination half-life of caffeine.[1] The clinical importance of this interaction, attributed to inhibition of cytochrome P450 isoenzyme CYP1A2 by fluvoxamine, is unknown.

1. Culm-Merdek KE, *et al.* Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol* 2005; **60:** 486–93.

Antiepileptics. The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking *phenytoin* compared with healthy controls, resulting in lower plasma-caffeine concentrations. Treatment with *carbamazepine* or *valproic acid* had no effect on the pharmacokinetics of caffeine.[1]

1. Wietholtz H, *et al.* Effects of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 1989; **36:** 401–6.

Antifungals. In a single-dose study in healthy subjects, *terbinafine* 500 mg by mouth decreased the clearance and increased the elimination half-life of caffeine 3 mg/kg given intravenously. *Ketoconazole* 400 mg by mouth did not prolong the elimination of caffeine to a significant extent.[1]

1. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 279–83.

Antigout drugs. In a study in 2 healthy subjects, the plasma half-life of caffeine was essentially unchanged by 7 days of oral treatment with *allopurinol* 300 mg or 600 mg daily. However, allopurinol caused a specific, dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.[1]

1. Grant DM, *et al.* Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986; **21:** 454–8.

Gastrointestinal drugs. Oral *cimetidine* 1 g daily reduced the systemic clearance of caffeine and prolonged its elimination half-life in 5 healthy subjects. Although the steady-state plasma-caffeine concentration would increase by about 70%, it was thought unlikely that this would produce adverse clinical effects.[1] However, in contrast a study in 11 children given cimetidine in doses of 11 to 36 mg/kg daily for gastritis found no evidence that it altered the metabolism of a dose of ^{13}C-labelled caffeine.[2]

1. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. *Br J Clin Pharmacol* 1981; **12:** 155–9.
2. Parker AC, *et al.* Lack of inhibitory effect of cimetidine on caffeine metabolism in children using the caffeine breath test. *Br J Clin Pharmacol* 1997; **43:** 467–70.

Lithium. For mention of the effect of caffeine on serum-lithium concentrations, see Xanthines, p. 432.3.

Methoxsalen. Single oral doses of 1.2 mg/kg methoxsalen have reduced the clearance of caffeine in patients with psoriasis,[1,2] consistent with a cytochrome P450 isoenzyme CYP1A2-dependent inhibition of caffeine demethylation.[2]

1. Mays DC, *et al.* Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. *Clin Pharmacol Ther* 1987; **42:** 621–6.
2. Bendriss EK, *et al.* Inhibition of caffeine metabolism by 5-methoxypsoralen in patients with psoriasis. *Br J Clin Pharmacol* 1996; **41:** 421–4.

Sex hormones. The clearance of caffeine has been reported to be reduced and its elimination half-life increased in women taking *oral contraceptives*.[1-3] This interaction was thought to be due to impairment of hepatic metabolism of caffeine by sex hormones and could result in increased accumulation of caffeine. Similar results have been reported[4] in a study of postmenopausal women given oestrogens for *hormone replacement therapy* and caffeine.

1. Patwardhan RV, *et al.* Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med* 1980; **95:** 603–8.
2. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* 1985; **28:** 425–8.
3. Balogh A, *et al.* Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination. *Eur J Clin Pharmacol* 1995; **48:** 161–6.
4. Pollock BG, *et al.* Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women. *J Clin Pharmacol* 1999; **39:** 936–40.

Sympathomimetics. Use of caffeine 400 mg with *phenylpropanolamine* 75 mg, both given orally as modified-release preparations, produced greater plasma-caffeine concentrations in healthy subjects than caffeine alone. Greater increases in blood pressure and more reports of physical adverse effects occurred after the combination than after either drug alone.[1]

Giving caffeine with *ephedrine* has been reported to produce significant cardiovascular, metabolic, and hormonal responses, including increased systolic blood pressure and heart rate, and raised fasting glucose and insulin.[2] These enhanced effects appear to be the result of a pharmacodynamic rather than a pharmacokinetic interaction, and led to the issue of a warning by Health Canada in 2006 not to use weight loss products containing both caffeine and ephedrine, since the combination had caused reported adverse effects ranging from dizziness, tremors, headaches, and irregularities in heart rate to seizures, psychosis, heart attacks, and stroke.[3] Those particularly at risk include individuals suffering from ischaemic heart disease, hypertension, and diabetes.[2,3]

1. Lake CR, *et al.* Phenylpropanolamine increases plasma caffeine levels. *Clin Pharmacol Ther* 1990; **47:** 675–85.
2. Haller CA, *et al.* Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. *Clin Pharmacol Ther* 2004; **75:** 259–73.
3. Health Canada. Health Canada advises consumers not to use weight loss products containing ephedrine and caffeine (issued 23rd May 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_33-eng.php (accessed 09/07/08)

Theophylline. For the effect of caffeine on the metabolism and elimination of theophylline, see p. 1235.3.

Pharmacokinetics

Caffeine is absorbed readily after oral doses and is widely distributed throughout the body. It is also absorbed through the skin. Absorption when given rectally by suppository may be slow and erratic. Absorption after intramuscular injection may be slower than after oral doses. Caffeine passes readily into the CNS and into saliva; low concentrations are also present in breast milk. Caffeine crosses the placenta.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged. Hepatic cytochrome P450 isoenzyme CYP1A2 is involved in caffeine enzymatic metabolism. Neonates have a greatly reduced capacity to metabolise caffeine, due to their immature hepatic enzyme systems, and it is largely excreted unchanged in the urine. By 9 months of age, urinary excretion is similar to that seen in adults. Elimination half-lives are about 3 to 7 hours in adults but may be about 3 to 4 days in neonates.

Metabolism and excretion. The metabolism of caffeine has been shown to be dose dependent[1,2] with clearance decreasing as the dose is increased suggesting saturable metabolism. Four- to fivefold differences in plasma half-lives of caffeine are common among healthy people. The plasma half-life of caffeine is decreased by smoking[3] and by exercise,[4] and is increased by liver disease such as cirrhosis and viral hepatitis,[3,5] and in pregnancy.[3] The plasma half-life of caffeine is not affected by old age[6] or obesity.[7] Drug interactions also affect the pharmacokinetics of caffeine (see above).

1. Cheng WSC, *et al.* Dose-dependent pharmacokinetics of caffeine in humans: relevance as a test of quantitative liver function. *Clin Pharmacol Ther* 1990; **47:** 516–24.
2. Denaro CP, *et al.* Dose-dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther* 1990; **48:** 277–85.
3. Kalow W. Variability of caffeine metabolism in humans. *Arzneimittelforschung* 1985; **35:** 319–24.
4. Collomp K, *et al.* Effects of moderate exercise on the pharmacokinetics of caffeine. *Eur J Clin Pharmacol* 1991; **40:** 279–82.
5. Scott NR, *et al.* The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease. *Br J Clin Pharmacol* 1989; **27:** 205–13.
6. Blanchard J, Sawers SJA. Comparative pharmacokinetics of caffeine in young and elderly men. *J Pharmacokinet Biopharm* 1983; **11:** 109–26.
7. Abernethy DR, *et al.* Caffeine disposition in obesity. *Br J Clin Pharmacol* 1985; **20:** 61–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Guarana†; Percutafeine; ***Austral.***: Cafnea; No Doz; ***Austria***: Coffekapton; ***Canad.***: Alert Aid†; Pep-Back; Wake Ups; Water Joe†; ***Chile***: Jaquedryl; Percutafeine; ***China***: Kang Yu Deng Tong (康裕登通); ***Cz.***: Kinedryl; Peyona; ***Fin.***: Cofi-Tabs†; ***Fr.***: Lipofeine; Percutafeine; ***Gr.***: Cafcit; Peyona; ***Indon.***: Panadol Extra; ***Irl.***: Peyona; Pro-Plus†; ***Neth.***: Peyona; ***Pol.***: Kofex†; Peyona; ***Port.***: Peyona; ***Rus.***: Vasobral (Вазобрал); ***Spain***: Durvitan; Peyona; ***UK***: Peyona; Pro-Plus; ***Ukr.***: Cefecon N (Цефекон Н); Glycodin (Глікодин)†; ***USA***: Cafcit; Caffedrine; Enerjets; Keep Alert; Lucidex; NoDoz; Stay Alert; Vivarin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Aspirin and Caffeine Tablets; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Paracetamol and Caffeine Tablets; Paracetamol, Codeine Phosphate and Caffeine Capsules; Paracetamol, Codeine Phosphate and Caffeine Tablets; Soluble Paracetamol and Caffeine Tablets;

USP 36: Acetaminophen and Caffeine Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Butalbital, Acetaminophen, and

Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Caffeine and Sodium Benzoate Injection; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Orphenadrine Citrate, Aspirin, and Caffeine Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules.

Carmoterol *(rINN)* ⊗

Carmotérol; Carmoterolum; CHF-4226; Quinoterol; TA-2005; Кармотерол.

8-Hydroxy-5-{(1*R*)-1-hydroxy-2-{[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino}ethyl}quinolin-2(1*H*)-one.

$C_{21}H_{24}N_2O_4$=368.4

CAS — 147568-66-9.

UNII — 9810NUL4D1.

Profile

Carmoterol is a beta$_2$ agonist under investigation in asthma and chronic obstructive pulmonary disease.

Choline Theophyllinate *(BAN, rINN)*

Choline, Théophyllinate de; Cholini Theophyllinas; Koliiniteofyllinaatti; Kolinteofyllinat; Oxtrifilina; Oxtriphylline; Teocinato de colina; Teofilinato de colina; Theophylline Cholinate; Холина Теофиллинат.

$C_{12}H_{21}N_5O_3$=283.3

CAS — 4499-40-5.

ATC — R03DA02.

ATC Vet — QR03DA02.

UNII — 3K045XR58X.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Choline Theophyllinate). A white crystalline powder, odourless or with a faint amine-like odour. It contains between 41.9% and 43.6% of choline and between 61.7% and 65.5% of theophylline, each calculated with reference to the dried substance. Very soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. Store at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Oxtriphylline). A white crystalline powder, having an amine-like odour. It contains not less than 61.7% and not more than 65.5% of anhydrous theophylline. Soluble 1 in 1 of water; freely soluble in alcohol; very slightly soluble in chloroform. A 1% solution in water has a pH of about 10.3. Store in airtight containers.

Profile

Choline theophyllinate is a theophylline salt that liberates theophylline (p. 1229.3) in the body; choline theophyllinate 1.57 mg is equivalent in theophylline content to about 1 mg of anhydrous theophylline. It is used as a bronchodilator for reversible airways obstruction. The usual initial oral dose for adults is 800 mg daily, in 4 divided doses. The daily dose should be adjusted according to clinical response and serum-theophylline concentrations (see Uses and Administration of Theophylline, p. 1229.3). For details of doses in children see Administration in children, below.

Administration in children. Choline theophyllinate can be given to children aged from 10 years in an initial oral dose of 100 to 200 mg; further doses are guided by symptoms and serum-theophylline concentrations. An average daily dose of 10 to 20 mg/kg is usually required.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies choline theophyllinate as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Brondecon Elixir†; ***Canad.***: Choledyl; ***Gr.***: Choledyl; ***Swed.***: Teovent.

Multi-ingredient Preparations. ***Austral.***: Brondecon Expectorant†; ***Canad.***: Choledyl Expectorant; ***India***: Airomol; Alkarex-PD; Efelin-PD; ***NZ***: Broncelix†; Brondecon†.

Pharmacopoeial Preparations

BP 2014: Choline Theophyllinate Tablets;

USP 36: Oxtriphylline Delayed-release Tablets; Oxtriphylline Extended-release Tablets; Oxtriphylline Oral Solution; Oxtriphylline Tablets.

Clenbuterol Hydrochloride *(BANM, rINNM)* ⊗

Clenbutérol, Chlorhydrate de; Clenbuterol, hidrocloruro de; Clenbuterolhydrochlorid; Clenbuteroli hydrochloridum; Hidrocloruro de clenbuterol; Klenbuterol hydrochlorid; Klenbuterol-hidroklorid; Klenbuterolhydrokloridi; Klenbuterolio hidrochloridas; NAB-365 (clenbuterol); Кленбутерола Гидрохлорид.

1-(4-Amino-3,5-dichlorophenyl)-2-*tert*-butylaminoethanol hydrochloride.

$C_{12}H_{18}Cl_2N_2O$,HCl=313.6

CAS — 37148-27-9 (clenbuterol); 21898-19-1 (clenbuterol hydrochloride).

ATC — R03AC14; R03CC13.

ATC Vet — QR03AC14; QR03CC13.

UNII — GOR5747GWU.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of clenbuterol:

Angel Dust; Clen.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

In *US* for veterinary use only.

Ph. Eur. 8: (Clenbuterol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 7.0.

USP 36: (Clenbuterol Hydrochloride). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 7.0. Protect from light.

Profile

Clenbuterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2). It is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in certain patients with chronic obstructive pulmonary disease (p. 1199.1). A usual oral dose is 20 micrograms twice daily. Clenbuterol hydrochloride has also been given by inhalation. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, clenbuterol indicates deterioration of asthma control and the need for review of therapy.

Abuse. Clenbuterol has been used illicitly in animal feeds in an attempt to promote weight gain and to increase muscle to lipid mass. Adverse effects typical of sympathomimetic activity have been attributed to such misuse both in farmers perpetrating such acts[1] and in innocent persons consuming meat products from affected animals.[2-5] Clenbuterol has been abused by sportsmen for its anabolic effects,[6] although it is doubtful as to whether it enhances performance.[7] Myocardial infarction was described in an otherwise healthy 17-year-old bodybuilder after abuse of clenbuterol.[8] Coronary artery spasm and/or temporary thrombosis were suggested as possible explanations for this adverse effect. A case of overdosage in a bodybuilder who took 108.75 mg of clenbuterol hydrochloride has been reported.[9] He presented after about 30 minutes with anxiety, palpitations, and shortness of breath. His supraventricular tachycardia was eventually controlled with esmolol after adenosine and then diltiazem had proved ineffective, but subsequent atrial fibrillation required cardioversion. Contamination of illicit heroin with clenbuterol has also been reported.[10-13]

1. Dawson J. β Agonists put meat in the limelight again. *BMJ* 1990; **301:** 1238–9.
2. Martínez-Navarro JF. Food poisoning related to consumption of illicit β -agonist in liver. *Lancet* 1990; **336:** 1311.
3. Maistro S, *et al.* Beta blockers to prevent clenbuterol poisoning. *Lancet* 1995; **346:** 180.
4. Brambilla G, *et al.* Food poisoning following consumption of clenbuterol-treated veal in Italy. *JAMA* 1997; **278:** 635.
5. Ramos F, *et al.* Proposed guidelines for clenbuterol food poisoning. *Am J Med* 2004; **117:** 362.
6. Anonymous. Muscling in on clenbuterol. *Lancet* 1992; **340:** 403.
7. Spann C, Winter ME. Effect of clenbuterol on athletic performance. *Ann Pharmacother* 1995; **29:** 75–7.
8. Kierzkowska B, *et al.* Myocardial infarction in a 17-year-old body builder using clenbuterol. *Circ J* 2005; **69:** 1144–6.
9. Daubert GP, *et al.* Acute clenbuterol overdose resulting in supraventricular tachycardia and atrial fibrillation. *J Med Toxicol* 2007; **3:** 56–60.
10. CDC. Atypical reactions associated with heroin use: five states, January-April 2005. *MMWR* 2005; **54:** 793–6. Correction. *ibid.*; 852.
11. Hoffman RS, *et al.* A descriptive study of an outbreak of clenbuterol-containing heroin. *Ann Emerg Med* 2008; **52:** 548–53.
12. Manini A, *et al.* A novel neuromuscular syndrome associated with clenbuterol-tainted heroin. *Clin Toxicol* 2008; **46:** 1088–92.
13. Dimaano JQ, *et al.* Street drugs possibly tainted with clenbuterol. *J Emerg Nurs* 2008; **34:** 582–3.

Urinary incontinence. A systematic review of the use of adrenergic agonists, including clenbuterol, in urinary incontinence, found that there was weak evidence to suggest that their use was better than placebo.[1] Although only minor adverse effects were reported, the authors noted that there was still potential for rare but serious adverse effects reported elsewhere in the literature.

1. Alhasso A, *et al.* Adrenergic drugs for urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 15/01/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bronq-C; Clembumar; Oxibron; ***Austria***: Spiropent; ***Chile***: Airum; Asmeren; ***Cz.***: Spiropent; ***Ger.***: Spiropent; ***Gr.***: Spiropent; ***Hung.***: Spiropent; ***Indon.***: Spiropent; ***Ital.***: Monores; ***Jpn***: Spiropent; ***Malaysia***: Mavilex; ***Mex.***: Novegam; Oxyflux; Spiropent; ***Philipp.***: Spiropent; ***Port.***: Broncoterol†; Cesbron†; ***Spain***: Ventolase†; ***Venez.***: Brodilan; Brodilin; Buclen; Clenbunal; Risopent.

Multi-ingredient Preparations. ***Arg.***: Mucosolvon Compositum; Oxibron NF; ***Austria***: Mucospas; ***China***: Ambrocol (易坦静); ***Ger.***: Spasmo-Mucosolvan; ***Mex.***: Ambodil-C; Balsibron-C; Brogal Compositum; Bronolban-M; Brosolan C†; Broxofar Compuesto; Broxol Plus; Broxolim-C; Ebromin P; Fludexol-CL; Loxorol; Mucosolvan Compositum; Mucovibrol C; Sekretovit Ex; Septacin Ex; Seraxol; Serbol; ***Port.***: Clembroxol; Mucospas; Ventoliber; ***Venez.***: Ambromuco Compositum; Arbixil; Clenbuxol; Litusix Compositum; Mucolin; Mucosolvan Compositum.

Diprophylline *(BAN, rINN)*

Difilina; Dihydroxypropyltheophyllinum; Diprofilina; Diprofilinas; Diprofillin; Diprofylin; Diprofylliini; Diprofyllin; Diprophyllin; Diprophyllinum; Dyphylline; Glyphyllinum; Hyphylline; Дипрофиллин.

7-(2,3-Dihydroxypropyl)-1,3-dimethylxanthine; 7-(2,3-Dihydroxypropyl)theophylline.

$C_{10}H_{14}N_4O_4$=254.2

CAS — 479-18-5.

ATC — R03DA01.

ATC Vet — QR03DA01.

UNII — 263T0E9RR9.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Diprophylline). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Dyphylline). A white, odourless, amorphous or crystalline solid. Freely soluble in water; sparingly soluble in alcohol and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Uses and Administration

Diprophylline is a theophylline derivative which is used similarly to theophylline (p. 1229.3) as a bronchodilator in reversible airways obstruction.

The usual oral dose of diprophylline is up to 15 mg/kg every 6 hours. It has also been given intramuscularly. Diprophylline is also an ingredient of preparations that have been promoted for coughs.

Action. Improvements in measurements of lung function after diprophylline in oral doses of 15 and 20 mg/kg were only one-third to one-half those obtained after oral theophylline 6 mg/kg.[1]

1. Furukawa CT, *et al.* Diphylline versus theophylline: a double-blind comparative evaluation. *J Clin Pharmacol* 1983; **23:** 414–18.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p. 1231.2, p. 1232.3, and p. 1233.1. Diprophylline is mainly excreted unchanged in the urine and should therefore be used with caution in patients with renal impairment; dose adjustments may be required. However, unlike theophylline, plasma concentrations of diprophylline are not greatly affected by changes in liver function or hepatic enzyme activity such as those produced by smoking or age.

Breast feeding. In a study of 20 women given diprophylline by intramuscular injection,[1] diprophylline was found to concentrate in breast milk, with a milk to serum concentration ratio of about 2. However, it was considered that the quantity of diprophylline a breast-fed infant would ingest was unlikely to produce any pharmacological action unless the child was very sensitive. The American Academy of Pediatrics[2] also considers that the use of diprophylline is usually compatible with breast feeeding.

1. Jarboe CH, *et al.* Dyphylline elimination kinetics in lactating women: blood to milk transfer. *J Clin Pharmacol* 1981; **21:** 405–10.

2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

Interactions

Since diprophylline does not undergo metabolism by hepatic microsomal cytochrome P450 it does not exhibit the many interactions seen with theophylline (p. 1233.3). However, the possibility of synergistic effects should be borne in mind if it is used with other xanthines.

Probenecid. Probenecid has been reported to decrease the clearance of diprophylline thus prolonging its half-life.[1-3]

1. May DC, Jarboe CH. Inhibition of clearance of dyphylline by probenecid. *N Engl J Med* 1981; **304:** 791.
2. May DC, Jarboe CH. Effect of probenecid on dyphylline elimination. *Clin Pharmacol Ther* 1983; **33:** 822–5.
3. Acara M, *et al*. Probenecid inhibition of the renal excretion of dyphylline in chicken, rat and man. *J Pharm Pharmacol* 1987; **39:** 526–30.

Pharmacokinetics

Diprophylline is rapidly absorbed from the gastrointestinal tract and from the site of intramuscular injections. Diprophylline is not converted to theophylline in the body. It is largely excreted unchanged in the urine with an elimination half-life of about 2 hours. Diprophylline is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: A Shen Nuo Qi (阿圣诺奇); Ruo Chang (若畅); Tian Quan Xi Ning (天泉息宁); ***Gr.***: Silbephylline; ***Hong Kong***: Diproline†; Syneophylline†; Uni-Dyphine†; ***Ital.***: Katasma; ***Port.***: Neufil; ***Turk.***: Astmadin; Difilin; ***USA***: Dylix; Lufyllin.

Multi-ingredient Preparations. ***Fr.***: Ozothine a la Diprophylline; ***Hong Kong***: Broncholax†; ***Israel***: Philinal†; Philinet†; ***Ital.***: Cort-Inal; ***Spain***: Alergical Expectorante; Bronsal; ***Turk.***: Broksin; ***UK***: Noradran; ***USA***: Difil-G; Dilex-G; Dy-G†; Dyflex-G; Dyphylline-GG†; Jay-Phyl; Lufyllin-GG; Panfil G.

Pharmacopoeial Preparations

USP 36: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Dyphylline Elixir; Dyphylline Injection; Dyphylline Tablets.

Doxofylline *(USAN, rINN)*

ABC 12/3; Doxofilina; Doxofyllinum; Доксофиллин.

7-(1,3-Dioxolan-2-ylmethyl)theophylline.

$C_{11}H_{14}N_4O_4$=266.3

CAS — 69975-86-6.

ATC — R03DA11.

ATC Vet — QR03DA11.

UNII — MPM23GMO7Z.

Profile

Doxofylline is a theophylline derivative (p. 1229.3) which is used as a bronchodilator in reversible airways obstruction. It is given in oral doses of up to 1.2 g daily. It may also be given by slow intravenous injection.

References.
1. Dini FL, Cogo R. Doxofylline: a new generation xanthine bronchodilator devoid of major cardiovascular adverse effects. *Curr Med Res Opin* 2001; **16:** 258–68.
2. Sankar J, *et al*. Doxofylline: the next generation methylxanthine. *Indian J Pediatr* 2008; **75:** 251–4.
3. Shukla D, *et al*. Doxofylline: a promising methylxanthine derivative for the treatment of asthma and chronic obstructive pulmonary disease. *Expert Opin Pharmacother* 2009; **10:** 2343–56.
4. Page CP. Doxofylline: a "novofylline". *Pulm Pharmacol Ther* 2010; **23:** 231–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Li Nuo Er (安利诺尔); An Sai Ma (安赛玛); Chuan Ning (川苧); Fei Te Ai Si (菲特艾斯); Jian Fang Neng (健方能); Lang Ming (朗铭); Lv Meng (绿萌); Na De Lai (纳德来); Shu Zhi (舒志); Shuai An (帅安); Shuweixin (枢维新); Suo Di (索迪); Suo Ji (索霁); Suo Li An (索利安); Xi Si Nuo (喜思诺); Xin Qian Ping (新茜平); Xin Xi Ping (新西平); Yi Suo (益索); YiLi (奕利); ***India***: Bestofyline; Coxylate; D-Xanthin; Doxfil; Doxfree; Doxiba; Doxma; Doxobid; Doxobron; Doxosafe; Doxovent; Efin-CR; Everdox; Filodox; Fyline; Fyly; Lunair; Monofin; Mucosma; Oxowin; Oxypur; ***Ital.***: Ansimar; ***Mex.***: Axofin†; ***Phi'lipp.***: Ansimar; Dilatair; Maxivent; Puroxan; ***Thai.***: Puroxan; ***Ukr.***: Aerofillin (Аэрофиллин).

Multi-ingredient Preparations. ***India***: Mucosma-T.

Etamiphylline Camsilate *(BANM, rINNM)*

Camsilato de dietamifilina; Camsilato de etamifilina; Camsilato de parafilina; Diétamiphylline Camphosulfonate; Etamifilina, camsilato de; Étamiphylline, Camsilate d'; Etamiphylline Camsylate; Etamiphyllini Camsilas; Etamphyllin Camsylate; Этамифиллина Камзилат.

7-(2-Diethylaminoethyl)-1,3-dimethylxanthine camphor-10-sulphonate; 7-(2-Diethylaminoethyl)theophylline camphor-10-sulphonate.

$C_{23}H_{37}N_5O_6S$=511.6

CAS — 314-35-2 (etamiphylline); 19326-29-5 (etamiphylline camsilate).

ATC — R03DA06.

ATC Vet — QR03DA06.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Etamiphylline Camsilate). A white or almost white powder. Very soluble in water; soluble in alcohol and in chloroform; very slightly soluble in ether. A 10% solution in water has a pH of 3.9 to 5.4.

Profile

Etamiphylline camsilate is a derivative of theophylline (p. 1229.3) and has been used as a bronchodilator in reversible airways obstruction. Etamiphylline does not liberate theophylline in the body. Etamiphylline camsilate is used in veterinary medicine.

The hydrochloride salt has also been used.

Etofylline *(BAN, rINN)*

Aethophyllinum; Etofilina; Etofilinas; Etofillin; Etofylin; Etofylliini; Etofyllin; Étofylline; Etofyllinum; Hydroxyaethyltheophyllinum; Hydroxyéthylthéophylline; Oxyetophylline; Этофиллин.

7-(2-Hydroxyethyl)-1,3-dimethylxanthine; 3,7-Dihydro-7-(2-hydroxyethyl)-1,3-dimethyl-1*H*-purine-2,6-dione; 7-(2-Hydroxyethyl)theophylline.

$C_9H_{12}N_4O_3$=224.2

CAS — 519-37-9.

ATC — C04AD04.

ATC Vet — QC04AD04.

UNII — L164909TBI.

Profile

Etofylline is a derivative of theophylline (p. 1229.3) that is an ingredient of preparations promoted for respiratory and cardiovascular disorders. It is not converted to theophylline in the body.

Etofylline nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Oxyphyllin.

Multi-ingredient Preparations. ***Cz.***: Ersilan; Oxantil; ***Hong Kong***: Instenon; ***India***: Agrophyllin; Albutamol; Asthos; Bronchilet; Delin; Dericip; Deriphyllin; Deripil; Efelin; Eto-Salbetol; Glophyllin; Terphylin; ***Rus.***: Instenon (Инстенон); ***S.Afr.***: Actophlem; Alcophyllex; Dilinct; Solphyllex; Solphyllin; Theophen Comp; ***Ukr.***: Instenon (Инстенон).

Fenoterol *(BAN, USAN, rINN)* ⊗

Fénotérol; Fenoteroli; Fenoterolum; Фенотерол.

1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol.

$C_{17}H_{21}NO_4$=303.4

CAS — 13392-18-2.

ATC — G02CA03; R03AC04; R03CC04.

ATC Vet — QG02CA03; QR03AC04; QR03CC04.

UNII — 22M9P70OQ9.

Fenoterol Hydrobromide *(BANM, rINNM)* ⊗

Fénotérol, Bromhydrate de; Fenoterol, hidrobromuro de; Fenaterol-hidrobromid; Fenoterolhydrobromid; Fenoterol-hydrobromid; Fenoteroli Hydrobromidum; Fenoterolihydrobromidi; Fenoterolio hidrobromidas; Fenoterolu bromowodorek; Hidrobromuro de fenoterol; TH-1165a; Фенотерола Гидробромид.

1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol hydrobromide.

$C_{17}H_{21}NO_4$,HBr=384.3

CAS — 1944-12-3.

ATC — G02CA03; R03AC04; R03CC04.

ATC Vet — QG02CA03; QR03AC04; QR03CC04.

UNII — RLI45Z99RB.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fenoterol Hydrobromide). A white or almost white, crystalline powder. Soluble in water and in alcohol. A 4% solution in water has a pH of 4.2 to 5.2. Protect from light.

Uses and Administration

Fenoterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity largely selective for $beta_2$ receptors (a $beta_2$ agonist). It has actions and uses similar to those of salbutamol (p. 1220.2) and is used as a bronchodilator in the management of reversible airways obstruction, as occurs in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). On inhalation, fenoterol acts within a few minutes and has a duration of action of about 3 to 5 hours.

In the management of **reversible airways obstruction,** fenoterol hydrobromide may be given from a *metered-dose aerosol* in a dose of 1 or 2 inhalations of 100 micrograms up to 4 times daily, with at least 3 hours between doses; a maximum daily dose of 800 micrograms is recommended Current asthma guidelines recommend that inhaled short-acting $beta_2$ agonists such as fenoterol be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of fenoterol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, fenoterol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

Fenoterol hydrobromide is available as a *dry powder* inhaler in some countries; 1 inhalation of 200 micrograms, repeated once after 10 minutes if necessary, is given 3 or 4 times daily.

Fenoterol may be inhaled as a *nebulised solution* for acute attacks of bronchospasm; it may be given with the antimuscarinic ipratropium, in a dose of fenoterol hydrobromide 1.25 mg, up to a maximum of 4 times daily. Fenoterol hydrobromide is also given alone in a dose of 0.5 to 1.25 mg depending on severity, increased to a total daily dose of 2 mg in severe cases.

Fenoterol hydrobromide may also be given *orally* for the relief of bronchospasm at a dose of 2.5 to 5 mg three times daily.

For doses in children, see Administration in Children, below.

Fenoterol hydrobromide has also been used similarly to salbutamol, in the management of **premature labour** (see p. 2131.1). A suggested dose, by intravenous infusion, has been 0.5 to 3 micrograms/minute, up to a maximum of 4 micrograms/minute. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3).

Oral or *rectal* $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, fenoterol hydrobromide could be given orally in a dose of 5 mg every 3 to 6 hours, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

Administration in children. In some countries fenoterol has been given via a metered-dose inhaler to children over 6 years of age, at the same doses used in adults (see Uses and Administration, above).

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3.

Increased mortality. Since the introduction of metered-dose aerosols of beta agonists there have been two reported epidemics of increased morbidity and mortality in asthmatic patients associated with their use. The first occurred in the 1960s and was linked with the use of high-dose isoprenaline inhalers.[1] The use of isoprenaline was subsequently largely stopped in favour of more selective $beta_2$ agonists.

The second epidemic occurred in New Zealand in the late 1970s and 1980s and was associated with the use of fenoterol.[1-5] When use of fenoterol fell in New Zealand, so too did the asthma mortality rate.[5] Heavy or regular use of fenoterol was implicated.[6,7] Fenoterol was also implicated in increased asthma morbidity and mortality in a study in Canada,[7] as was salbutamol, and results from Japan also suggested a relation between asthma deaths and excessive use of beta agonists, particularly fenoterol.[8] However, an analysis of the New Zealand deaths could not identify such a risk with beta agonists other than fenoterol.[5]

There is still debate about this second epidemic. The individual case control studies, including the one from Canada,[7] showed an increased morbidity and mortality in patients taking fenoterol, but a meta-analysis of the accumulated data to 1992 suggested that the increase in mortality in the patients taking $beta_2$ agonists was slight and

only significant when they were given by nebulisation.[9] Also a working party of the UK CSM considered[10] that a causal link between asthma mortality and beta-agonist use could neither be confirmed nor refuted.

Not surprisingly there are different views on the cause of the increased asthma mortality. The cardiotoxicity of the beta agonist might have to be considered, although evidence for such an effect is considered by some to be slight.[11] The severity of the asthma might have been a factor in two different ways. One hypothesis is that patients used more fenoterol because they had severe asthma and were already at increased risk of dying.[12] Another proposes that heavy beta-agonist use led to an increase in asthma severity[13] which could be explained by a down regulation of beta receptors.[14]

This may appear to be only of historical interest since mortality rates have fallen and current recommendations for the use of short-acting beta$_2$ agonists, which are generally more selective than fenoterol, are for them to be taken as required rather than on a regular basis; indeed increasing use of such drugs is seen as an indication to amend the treatment schedule. Moreover, the dose of fenoterol has been reduced in recent years. However, controversy over regular use of short-acting beta$_2$ agonists continues to be fed by conflicting studies of their benefit. More recently 2 further observational studies have reported an association between use of short-acting beta$_2$ agonists and adverse effects on mortality.[15,16] A cohort study,[15] designed to evaluate the effect of respiratory medications on asthma death, found an association between the excessive use of short-acting beta$_2$ agonists and an increased risk of asthma death; no additional risk was found with fenoterol beyond the risk associated with beta$_2$ agonists as a class. It was unknown whether excessive use was a symptom or a cause of worsening asthma. A case-control study[16] similarly found a modestly increased risk of mortality associated with use of short-acting beta$_2$ agonists in the previous 1 to 5 years. However, the study had insufficient power to come to any conclusions regarding the effects of fenoterol, which was rarely prescribed alone, and concluded that evidence for a direct adverse effect of beta$_2$ agonists was inconclusive; other explanations might include lack of more appropriate asthma care, more severe disease or increasing severity of disease, or a tendency for patients whose disease was not responding to receive a wider range of treatments.

For discussion of similar concerns about the use of *long-acting* beta$_2$ agonists in asthma, see Salmeterol, p. 1224.3.

1. Pearce N, *et al*. Beta agonists and asthma mortality: déjà vu. *Clin Exp Allergy* 1991; **21:** 401–10.
2. Crane J, *et al*. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet* 1989; **i:** 917–22.
3. Pearce N, *et al*. Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81. *Thorax* 1990; **45:** 170–5.
4. Grainger J, *et al*. Prescribed fenoterol and death from asthma in New Zealand, 1981–7: a further case-control study. *Thorax* 1991; **46:** 105–111.
5. Pearce N, *et al*. End of the New Zealand asthma mortality epidemic. *Lancet* 1995; **345:** 41–4.
6. Sears MR, *et al*. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; **336:** 1391–6.
7. Spitzer WO, *et al*. The use of β -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; **326:** 501–6.
8. Beasley R, *et al*. β -agonist therapy and asthma mortality in Japan. *Lancet* 1998; **351:** 1406–7.
9. Mullen M, *et al*. The association between β -agonist use and death from asthma: a meta-analytic integration of case control studies. *JAMA* 1993; **270:** 1842–5.
10. CSM. Beta-agonist use in asthma: report from the CSM Working Party. *Current Problems 33* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)
11. Sears MR, Taylor DR. The β$_2$-agonist controversy: observations, explanations and relationship to asthma epidemiology. *Drug Safety* 1994; **11:** 259–83.
12. Fuller RW. Use of β$_2$ agonists in asthma: much ado about nothing? *BMJ* 1994; **309:** 795–6.
13. Sears MR. Asthma deaths in New Zealand. *Lancet* 1995; **345:** 655–6.
14. Tattersfield AE. Use of β$_2$ agonists in asthma: much ado about nothing? *BMJ* 1994; **309:** 794–5.
15. Lanes SF, *et al*. Respiratory medications and risk of asthma death. *Thorax* 2002; **57:** 683–6.
16. Anderson HR, *et al*. Bronchodilator treatment and deaths from asthma: case-control study. Abridged version: *BMJ* 2005; **330:** 117. Full version: http://www.bmj.com/cgi/reprint/330/7483/117 (accessed 15/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fenoterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pulmonary oedema. Pulmonary oedema has occurred in women given beta agonists, including fenoterol,[1] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, on p. 1222.3.

1. Hawker F. Pulmonary oedema associated with β$_2$-sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

Fenoterol is incompletely absorbed from the gastrointestinal tract and is also subject to extensive first-pass metabolism by sulfate conjugation. It is excreted in the urine and bile almost entirely as the inactive sulfate conjugate. Fenoterol is distributed into breast milk.

References.

1. Warnke K, *et al*. The pharmacokinetics of the beta 2-adrenoceptor agonist fenoterol in healthy women. *Eur J Clin Pharmacol* 1992; **43:** 663–5.
2. Hochhaus G, Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the beta-2-agonists terbutaline, salbutamol and fenoterol. *Int J Clin Pharmacol Ther Toxicol* 1992; **30:** 342–62.
3. Hildebrandt R, *et al*. Pharmacokinetics of fenoterol in pregnant and nonpregnant women. *Eur J Clin Pharmacol* 1993; **45:** 275–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alveofen; Asmopul; Berotec; ***Austria***: Berotec; ***Belg.***: Berotec†; ***Braz.***: Berotec; Bromifen; Bromotec; Fenatec; Fenozan†; ***Cz.***: Berotec; ***Denm.***: Berotec†; ***Ger.***: Berotec; Partusisten; ***Gr.***: Berotec; Ftagirol; ***Hung.***: Berotec†; ***Indon.***: Berotec; ***Irl.***: Berotec†; ***Ital.***: Dosberotec; ***Jpn***: Berotec; ***Malaysia***: Berotec; Feno; ***Mex.***: Partusisten; ***Neth.***: Berotec†; Partusisten; ***Philipp.***: Berotec†; ***Pol.***: Berotec; ***Port.***: Berotec†; ***Rus.***: Berotec (Беротек); Partusisten (Партусистен); ***S.Afr.***: Berotec; ***Singapore***: Berotec; ***Switz.***: Berotec; ***Thai.***: Berotec†; Iperol; ***Ukr.***: Berotec (Беротек); ***Venez.***: Segamol.

Multi-ingredient Preparations. ***Arg.***: Berodual; Ipradual; ***Austria***: Berodual; Berodualin; ***Belg.***: Duovent; ***Braz.***: Duovent; ***Canad.***: Duovent; ***Chile***: Berodual; ***Cz.***: Berodual; ***Denm.***: Berodual; Duovent; ***Fin.***: Atrovent Comp; ***Fr.***: Bronchodual; ***Ger.***: Berodual; ***Gr.***: Berodual; ***Hung.***: Berodual; ***India***: Fenovent; ***Indon.***: Berodual; ***Irl.***: Duovent†; ***Ital.***: Duovent; ***Malaysia***: Berodual; Duovent; ***Mex.***: Berodual; Berosolvon; ***Neth.***: Berodual; ***Philipp.***: Berodual; ***Pol.***: Berodual; ***Port.***: Berodual; ***Rus.***: Berodual (Бородуал); Ditec (Дитек)†; ***S.Afr.***: Atrovent Beta; Berodual†; Duovent; Sabax Nebrafen; ***Singapore***: Berodual; Duovent; ***Switz.***: Berodual; ***Thai.***: Aeroduol; Berodual; Inhalex; Ipratteral; Punol; ***UK***: Duovent†; ***Ukr.***: Berodual (Бородуал); ***Venez.***: Berodual; Duovent; Respidual.

Pharmacopoeial Preparations

BP 2014: Fenoterol Pressurised Inhalation.

Fenspiride Hydrochloride *(USAN, rINNM)*

Decaspiride; Fenspirida, hidrocloruro de; Fenspiride, Chlorhydrate de; Fenspiridi Hydrochloridum; Hidrocloruro de fenspirida; JP-428; NAT-333; NDR-5998A; Фенспирида Гидрохлорид.

8-Phenethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride.

$C_{13}H_{18}N_2O_2$,HCl=296.8

CAS — 5053-06-5 (fenspiride); 5053-08-7 (fenspiride hydrochloride).

ATC — R03BX01; R03DX03.

ATC Vet — QR03BX01; QR03DX03.

UNII — 832NBX878V.

Profile

Fenspiride is reported to have bronchodilator and anti-inflammatory properties. It is given as the hydrochloride in asthma (p. 1195.2) and other respiratory disorders in usual oral doses of 160 to 240 mg daily in divided doses before meals. It has also been given rectally and by intramuscular or intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Pneumorel; ***Hong Kong***: Pneumorel†; ***Ital.***: Pneumorel; ***Pol.***: Elofen; Eurespal; Fenspogal; Pulneo; ***Port.***: Pneumorel; ***Rus.***: Eurespal (Эреспал); ***Ukr.***: Erespal (Эреспал); Inspiron (Инспирон).

Formoterol Fumarate

(BANM, USAN, rINNM) ⊗

BD-40A; CGP-25827A; Eformoterol Fumarat; Eformoterol Fumarate; Formoterol Fumarat; Formotérol, Fumarate de; Formoterol, fumarato de; Formoterolfumarat; Formoterolfumarát; Formoteroli fumaras; Formoterolifumaaatti; Formoterolio fumaratas; Formoterolu fumaran; Fumarato de eformoterol; Fumarato de formoterol; YM-08316; Формотерола Фумарат.

(±)-2′-Hydroxy-5′-[(*RS*)-1-hydroxy-2-{[(*RS*)-*p*-methoxy-α-methylphenethyl]amino}ethyl]formanilide fumarate.

$(C_{19}H_{24}N_2O_4)_2,C_4H_4O_4$=804.9

CAS — 73573-87-2 (formoterol); 43229-80-7 (formoterol fumarate).

ATC — R03AC13.

ATC Vet — QR03AC13.

UNII — P3T5QA5J9N (formoterol fumarate); W34SHF8J2K (formoterol fumarate dihydrate).

Pharmacopoeias. *Eur.* (see p. vii), *Jpn*, and *US* include the dihydrate, $(C_{19}H_{24}N_2O_4)_2,C_4H_4O_4,2H_2O$ = 840.9.

Ph. Eur. 8: (Formoterol Fumarate Dihydrate; Formoteroli Fumaras Dihydricus). A white or almost white or slightly yellow powder. Slightly soluble in water and in isopropyl alcohol; practically insoluble in acetonitrile; soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 36: (Formoterol Fumarate). A white or almost white or slightly yellow powder. Slightly soluble in water and in isopropyl alcohol; soluble in methyl alcohol; freely soluble in acetic acid and in dimethyl sulfoxide; practically insoluble in acetonitrile and in ether. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

Stability. Nebuliser solution containing formoterol fumarate 10 micrograms/mL was found to be physically and chemically stable when mixed with the following solutions:[1]

- budesonide inhalation suspension 250 micrograms/mL
- acetylcysteine solution 100 mg/mL
- ipratropium bromide inhalation solution 200 micrograms/mL
- sodium cromoglicate inhalation solution 10 mg/mL

The authors of this study noted that when these solutions were mixed and nebulised, or given sequentially, the amount of drug delivered *in vitro* was increased compared with single-drug nebulisation. Additionally, sequential nebulisation led to higher delivery of the first drug given. The clinical implications of these results were unclear.

1. Akapo S, *et al*. Compatibility and aerosol characteristics of formoterol fumarate mixed with other nebulizing solutions. *Ann Pharmacother* 2008; **42:** 1416–24.

Uses and Administration

Formoterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity specific to beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2), but like salmeterol (p. 1224.1) it has a prolonged duration of action of up to 12 hours; it is therefore not considered suitable for the symptomatic relief of acute attacks of bronchospasm. It is used with regular inhaled corticosteroid when a regular long-acting beta$_2$ agonist is needed for management of chronic asthma (p. 1195.2), or for prevention of exercise-induced asthma. It is also used in chronic obstructive pulmonary disease (p. 1199.1).

Formoterol is given by inhalation as the fumarate but how the dose is expressed may depend on the formulation.

- A usual dose for **asthma** is 1 inhalational capsule of formoterol fumarate 12 micrograms twice daily. In the UK, this may be increased to 2 inhalational capsules (24 micrograms) twice daily if necessary for severe disease. In the USA, 1 inhalational capsule of 12 micrograms may be taken when required, at least 15 minutes before exercise, to prevent exercise-induced bronchoconstriction in those patients not taking regular doses; additional doses should not be taken within 12 hours.
- Metered doses from a dry powder inhaler may be expressed as the amount delivered *into* the mouthpiece (multiples of 6 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to multiples of 4.5 micrograms per inhalation). Usual doses, expressed as the amount delivered *into* the mouthpiece, are 6 or 12 micrograms once or twice daily, increased if necessary in severe disease to 24 micrograms twice daily. (In the UK, a dose of 12 micrograms may be taken before exercise to prevent exercise-induced bronchoconstriction.) No more than 36 micrograms should be inhaled as a single dose, with a maximum daily dose of 72 micrograms.
- Metered doses from an aerosol inhaler may also be expressed as the amount delivered *into* the mouthpiece (12 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to 10.1 micrograms per inhalation). Usual doses are 1 or 2 inhalations twice daily.

Treatment should be reassessed if this proves inadequate; in the UK, some preparations are licensed for additional short-term symptom relief, but such use is contrary to current asthma guidelines (see p. 1195.2).

In **chronic obstructive pulmonary disease**, a usual dose from inhalation capsules is formoterol fumarate 12 micrograms twice daily.

Metered doses from a dry powder inhaler, expressed as the amount delivered *into* the mouthpiece, are 12 micrograms once or twice daily while those from an aerosol

inhaler are 12 micrograms twice daily; if required, additional doses may be used for relief of symptoms. A maximum of 24 micrograms may be inhaled as a single dose, with a total maximum daily dose of 48 micrograms.

Formoterol fumarate may also be inhaled via a nebuliser in a dose of 20 micrograms twice daily.

An oral formulation of formoterol fumarate is available in some countries for reversible airways obstruction; doses of 80 micrograms have been given twice daily.

For doses of formoterol fumarate used in children, see Administration in Children, below.

Reviews.

1. Faulds D, *et al.* Formoterol: a review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991; **42:** 115–37.
2. Bartow RA, Brogden RN. Formoterol: an update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs* 1998; **55:** 303–22.
3. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting β$_2$-agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; **27:** 689–715.

Administration in children. Doses of formoterol fumarate inhaled from inhalational capsules in children aged 5 years or older are the same as those for adults, see Uses and Administration, p. 1209.3.

Formoterol fumarate may be given by metered-dose dry powder inhaler to children 6 years of age and over. The usual dose, expressed as the amount delivered *into* the mouthpiece, is 6 to 12 micrograms once or twice daily. Occasionally up to 48 micrograms daily may be required (maximum single dose should not exceed 12 micrograms).

In some countries, such as Japan, formoterol fumarate has been given orally to children from the age of 6 months at a dose of 4 micrograms/kg daily, in 2 or 3 divided doses.

Asthma. Formoterol is a long-acting beta$_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p. 1195.2, generally recommend that the use of long-acting beta$_2$ agonists be reserved for patients with chronic asthma who have already progressed to inhaled corticosteroids; they are not a substitute for corticosteroids. Combinations of formoterol with an inhaled corticosteroid, used as both maintenance and reliever therapy, have been studied. Results are seemingly encouraging, although what role such combinations should play in therapy is not yet clearly defined. Formoterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, protection against bronchoconstriction is reduced (see Tolerance, below), and high-dose therapy may be associated with an increased rate of severe exacerbations (see Asthma under Adverse Effects and Precautions, below). Although long-acting bronchodilators should not be used for acute relief of asthma, formoterol has reportedly been used successfully as part of the management of acute severe asthma in hospital.

References.

1. van der Molen T, *et al.* Effects of the long acting β agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. *Thorax* 1996; **52:** 535–9.
2. Pauwels RA, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997; **337:** 1405–11. Correction. *ibid.*; 1998; **338:** 139.
3. O'Byrne PM, *et al.* Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001; **164:** 1392–7.
4. Goldsmith DR, Keating GM. Budesonide/formoterol: a review of its use in asthma. *Drugs* 2004; **64:** 1597–1618.
5. Pedersen S. Budesonide plus formoterol for reliever therapy in asthma. *Lancet* 2006; **368:** 707–8.
6. Pohunek P, *et al.* Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. *Pediatr Allergy Immunol* 2006; **17:** 458–65. Correction. *ibid.*; 551.
7. Berger WE. The use of inhaled formoterol in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; **97:** 24–33. Correction. *ibid.*; 562. [dosage error in text]
8. Hermansen MN, *et al.* Acute relief of exercise-induced bronchoconstriction by inhaled formoterol in children with persistent asthma. *Chest* 2006; **129:** 1203–9.
9. Bateman ED, *et al.* Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. *Respir Res* 2006; **7:** 13.
10. O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006; **368:** 794–803.
11. Cates CJ, Lasserson TJ. Combination formoterol and budesonide as maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 11/08/09).
12. Cates CJ, Lasserson TJ. Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 11/08/09).
13. Rodrigo GJ, *et al.* Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2010; **104:** 247–52.

Stuttering. Inhaled formoterol 12 micrograms daily was reported to improve stuttering (p. 1078.1) in 3 children between 14 and 20 years old. In 2 males, the onset of effect was about 6 weeks, but long-term follow-up was not possible. In the female patient there was early improvement that persisted during 45 weeks of treatment.[1]

1. Pešák J. Preliminary experience with formoterol for the treatment of stuttering. *Ann Pharmacother* 2004; **38:** 1323.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3. Inhalation of formoterol may be associated with paradoxical bronchospasm, and high doses have been associated with an increase in severe exacerbations of asthma. It should not be used in patients who are not also receiving an inhaled corticosteroid.

Long-acting beta$_2$ agonists such as formoterol are not appropriate for the treatment of acute bronchospasm.

Conjunctival irritation and eyelid oedema have been reported in isolated cases.

References.

1. Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. *Drug Safety* 2002; **25:** 213–23.
2. Pauwels RA, *et al.* Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003; **22:** 787–94.

Asthma. A review of 3 controlled studies comparing inhaled formoterol with placebo, concluded that regular use of high-dose formoterol (48 micrograms daily) may be associated with more frequent serious asthma exacerbations.[1] The concomitant use of inhaled corticosteroids was allowed but not mandatory, and was not reported in the review, which led to debate on whether the results of the study would be applicable when current prescribing guidelines for asthma were followed.[2,3]

In contrast to this, a subsequent study,[4] designed to test the hypothesis of a dose-related increase in serious asthma exacerbations with formoterol therapy, did not show any increase in serious asthma exacerbations between different formoterol doses and placebo. Again, inhaled corticosteroid use was allowed but not mandatory, with 62.4% of patients reported as receiving regular anti-inflammatory therapy.

A systematic review[5] firmly concluded that the addition of a long-acting beta$_2$ agonist (such as formoterol) to low or high doses of inhaled corticosteroids reduced the risk of asthma exacerbations compared with ongoing treatment with similar doses of inhaled corticosteroids alone. The addition of a long-acting beta$_2$ agonist reduced by 23% the relative risk of patients requiring systemic corticosteroids for an asthma exacerbation, over 4 to 54 weeks. There is no evidence of a difference in safety between treatment with formoterol plus a corticosteroid (typically budesonide) and salmeterol plus a corticosteroid (fluticasone).[6] However, for concerns about serious adverse effects associated with long-acting beta$_2$ agonists in asthma, including systematic reviews of largely asthma-related events with formoterol, see Increased Mortality, under Salmeterol p. 1224.3.

1. Mann M, *et al.* Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003; **124:** 70–4.
2. Rissmiller RW, *et al.* Asthma exacerbations and formoterol. *Chest* 2004; **125:** 1590–1.
3. van der Molen T. Formoterol and asthma exacerbations. *Chest* 2004; **125:** 1591.
4. Wolfe J, *et al.* Formoterol, 24 µg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 µg bid, with and without extra doses taken on demand, and placebo. *Chest* 2006; **129:** 27–38.
5. Ducharme FM, *et al.* Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 03/08/10).
6. Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 13/07/10).

Effects on skeletal muscle. Myalgia and muscle weakness associated with elevated creatine kinase has been reported during formoterol therapy.[1] Subsequent muscle biopsy suggested mitochondrial dysfunction. No inflammatory changes were seen and symptoms resolved on withdrawal of formoterol.

1. Kiernan MC, *et al.* Mitochondrial dysfunction and rod-like lesions associated with administration of β 2 adrenoceptor agonist formoterol. *Neuromuscul Disord* 2004; **14:** 375–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies formoterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Tolerance. Regular use of formoterol produced bronchodilator desensitisation,[1-3] and tachyphylaxis to bronchoprotection against methacholine, effects that have been noted with other long-acting beta$_2$ agonists (see Salmeterol, p. 1225.2) and short-acting beta$_2$ agonists (see Salbutamol, p. 1222.3).

1. van der Woude HJ, *et al.* Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting β$_2$ agonists. *Thorax* 2001; **56:** 529–35.
2. Jones SL, *et al.* Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol. *Eur Respir J* 2001; **17:** 368–73.
3. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. *Respir Res* 2005; **6:** 107. Also available at: http://respiratory-research.com/content/pdf/1465-9921-6-107.pdf (accessed 15/01/08)

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

Inhaled formoterol is rapidly absorbed. It is largely metabolised by glucuronidation and *O*-demethylation, with about 10% being excreted in the urine as unchanged drug. The mean terminal elimination half-life after inhalation is estimated to be 10 hours.

Stereoselectivity. Formoterol occurs as a racemic mixture, in which arformoterol (p. 1202.3), the *R,R*-enantiomer, is the active form.[1,2] It has been suggested that stereoselective metabolism and excretion may account for the individual variation in duration of effect seen with formoterol, although the exact mechanism remains unclear.[1,3]

1. Zhang M, *et al.* Stereoselective glucuronidation of formoterol by human liver microsomes. *Br J Clin Pharmacol* 2000; **49:** 152–7.
2. Lötvall J, *et al.* The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
3. Zhang M, *et al.* Stereoselective urinary excretion of formoterol and its glucuronide conjugate in human. *Br J Clin Pharmacol* 2002; **54:** 246–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fordilen; Oxis; Xanol; ***Austral.***: Foradile; Oxis; ***Austria***: Foradil; Oxis; ***Belg.***: Foradil; Formagal; Formoair; Oxis; ***Braz.***: Fluir; Foradil; Formare; Formocaps; Oxis; ***Canad.***: Foradil; Oxeze; ***China***: Atock (安通克); Oxis (奥克斯); Pan De Xin (盼得欣); ***Cz.***: Atimos; Foradil; Forair†; Formano; Formovent; Oxis†; ***Denm.***: Delnil; Eformax†; Foradil; Formo; Fostair; Oxez; Oxis; ***Fin.***: Cycloterol; Fomeda; Foradil; Formaxa; Oxis; ***Fr.***: Asmelor; Atimos; Foradil; Formoair; ***Ger.***: Foradil; Forair; Formatris; FormoLich; Formotop; Oxis; ***Gr.***: Broncoteril; Edufil; Foradil; Forair; Forcap; Formaxa; Formopen; Formotil; Imotec; Kinitron; Oxez; ***Hong Kong***: Oxis; ***Hung.***: Atimos; Diffumax†; Foradil; Fortofan†; Oxis; ***India***: Deriform; Foratec; ***Irl.***: Foradil; Oxis; ***Israel***: Foradil; Oxis; ***Ital.***: Aliterol; Atimos; Eolus; Evervent; Feronal; Foradil; Forotan; Fortasint; Kurovent; Levovent; Liferol; Oxis; ***Jpn***: Atock; Oxis; ***Malaysia***: Oxis; ***Mex.***: Foradil; Oxis; ***Neth.***: Atimos; Foradil; Formocaps†; Oxis; ***Norw.***: Foradil†; Oxis; ***NZ***: Foradil; Oxis; ***Phil.***: Atock; Foradil; Oxis†; ***Pol.***: Atimos; Diffumax; Foradil; Forastmin; Oxis; Oxodil; Zafiron; Zomexil; ***Port.***: Asmatec; Atimos; Eformax†; Foradil; Forair; Formaxa†; Oxis; ***Rus.***: Atimos (Атимос); Foradil (Форадил); Oxis (Оксис); ***S.Afr.***: Foradil; Foratec; Oxis; ***Singapore***: Foradil; Oxis†; ***Spain***: Broncoral; Foradil; Formatris; Neblik; Oxis; ***Swed.***: Foradil; Formatris; Oxis; ***Switz.***: Foradil; Oxis; ***Thai.***: Oxis; ***Turk.***: Atimos; Foradil; Forast; Foryxa; Oxis; Ventofor; ***UK***: Atimos Modulite; Foradil; Oxis; ***Ukr.***: Fortix (Фортикс); Zafiron (Зафирон); ***USA***: Foradil; Perforomist; ***Venez.***: Fluir; Foradil; Formotec.

Multi-ingredient Preparations. ***Arg.***: Frevia; Neumoterol; Symbicort; ***Austral.***: Symbicort; ***Austria***: Formodual; Foster; Symbicort; ***Belg.***: Flutiform; Inuvair; Symbicort; ***Braz.***: Alenia; Foraseq; Fostair; Symbicort; Vannair; ***Canad.***: Symbicort; Zenhale; ***Chile***: Symbicort; Vannair; ***China***: Symbicort (信必可); ***Cz.***: Budfor; Combair; Edoflo; Formodual†; Symbicort; ***Denm.***: Assieme; Innovair; Rilast; Sinestic; Symbicort; ***Fin.***: Flutiform; Innovair; Symbicort; ***Fr.***: Formodual; Innovair; Symbicort; ***Ger.***: Foster; Inuvair; Symbicort; ***Gr.***: Foster; Inuvair; Symbicort; ***Hong Kong***: Symbicort; ***Hung.***: Foster; Symbicort; ***India***: Avessa; Budamate; Combihale-FF; Duova; Fomtide; Foracort; Formonide; ***Indon.***: Symbicort; ***Irl.***: Budfor; Edoflo; Symbicort; ***Israel***: Symbicort; ***Ital.***: Assieme; Assiememite; Formodual; Foster; Inuver; Sinestic; Sinesticmite†; Symbicort; ***Jpn***: Symbicort; ***Malaysia***: Foracort; Symbicort; ***Mex.***: Symbicort; ***Neth.***: Assieme; Budfor; Edoflo†; Flutiform; Formodual; Foster; Iffeza; Sinestic; Symbicort; ***Norw.***: Flutiform; Inuxair; Symbicort; ***NZ***: Symbicort; Vannair; ***Philipp.***: Symbicort; ***Pol.***: Fostex; Symbicort; ***Port.***: Assieme; Formodual; Foster; Symbicort; ***Rus.***: Foradil Combi (Форадил Комби); Foster (Фостер); Simbicort (Симбикорт)†; Symbicort (Симбикорт); ***S.Afr.***: Symbicord; ***Singapore***: Symbicort; ***Spain***: Formodual; Foster; Rilast; Symbicort; ***Swed.***: Innovair; Symbicort; ***Switz.***: Symbicort; Vannair; ***Thai.***: Symbicort; ***Turk.***: Combipack; Foradil Combi; Foster; Innovair; Symbicort; Ventofor-Combi; ***UK***: flutiform; Fostair; Symbicort; ***Ukr.***: Simbicort (Симбикорт); ***USA***: Dulera; Symbicort; ***Venez.***: Foraseq; Symbicort.

Heptaminol Acefyllinate *(rINNM)*

Acefilinato de heptaminol; Acéfyllinate d'Heptaminol; Acefyllinum Heptaminolum; Heptaminol, acefilinato de; Heptaminol Acéfylline; Heptaminol Acephyllinate; Heptaminol Theophylline Ethanoate; Heptaminol Theophylline-7-

acetate; Heptaminoli Acefyllinas; Гептаминола Ацефиллинат.
The 6-amino-2-methylheptan-2-ol salt of theophyllin-7-ylacetic acid .
$C_8H_{19}NO.C_9H_{10}N_4O_4$=383.4
CAS — 5152-72-7; 10075-18-0.
ATC — C01DX08.
ATC Vet — QC01DX08.
UNII — WL6JNI78OE.

Profile

Heptaminol acefyllinate is a derivative of theophylline (p. 1229.3) that has been used for its bronchodilator and cardiovascular effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Cariamyl.

Multi-ingredient Preparations. ***Braz.***: Sureptil; ***Spain***: Diclamina†.

Hexoprenaline Hydrochloride

(BANM, rINNM) ⊗

Hexoprenalina, hidrocloruro de; Hexoprénaline, Chlorhydrate d'; Hexoprenalini Hydrochloridum; Hidrocloruro de hexoprenalina; ST-1512; Гексопреналина Гидрохлорид.
N,N'-Hexamethylenebis[4-(2-amino-1-hydroxyethyl)pyrocatechol] dihydrochloride; *N,N'*-Hexamethylenebis[2-amino-1-(3,4-dihydroxyphenyl)ethanol] dihydrochloride.
$C_{22}H_{32}N_2O_6.2HCl$=493.4
CAS — 3215-70-1 (hexoprenaline); 4323-43-7 (hexoprenaline dihydrochloride).
ATC — R03AC06; R03CC05.
ATC Vet — QR03AC06; QR03CC05.

Hexoprenaline Sulfate *(BANM, USAN, rINNM)* ⊗

Hexoprenalina, sulfato de; Hexoprénaline, Sulfate d'; Hexoprenaline Sulphate; Hexoprenalini Sulfas; Sulfato de hexoprenalina; Гексопреналина Сульфат.
(±)-α,α'-[Hexamethylenebis(iminomethylene)]-bis[3,4-dihydroxybenzyl alcohol] sulfate (1:1).
$C_{22}H_{32}N_2O_6.H_2SO_4$=518.6
CAS — 32266-10-7.
ATC — R03AC06; R03CC05.
ATC Vet — QR03AC06; QR03CC05.
UNII — U8159102C.

Profile

Hexoprenaline is a direct-acting sympathomimetic with mainly beta-adrenergic activity selective to $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2) and has been used as a bronchodilator in the treatment of reversible airways obstruction as occurs with asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). It has sometimes been used similarly to salbutamol in the management of premature labour (p. 2131.1).

Hexoprenaline is usually given as the hydrochloride or sulfate.

For the relief of **bronchoconstriction**, a typical adult oral dose of the salts has been 0.5 to 1 mg three times daily. The salts were also formerly given by inhalation. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, hexoprenaline indicates deterioration of asthma control and the need for review of therapy.

In the management of **premature labour** an intravenous infusion of hexoprenaline sulfate, diluted in glucose 5% or sodium chloride 0.9%, can be given at an initial rate of about 300 nanograms/minute. Infusion may be preceded by slow intravenous injection of 10 micrograms as a loading dose over 5 to 10 minutes. $Beta_2$ agonist therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3). Oral or rectal therapy is no longer recommended in premature labour because of a lack of evidence of benefit from treatment given by these routes of administration. A lower dose prolonged infusion of 75 nanograms/minute has been used for support during cervical cerclage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Argocian; ***Austria***: Gynipral; ***Cz.***: Gynipral; ***Hong Kong***: Ipradol; ***Rus.***: Gynipral (Гинипрал); ***S.Afr.***: Ipradol†; ***Switz.***: Gynipral; ***Ukr.***: Gynipral (Гинипрал).

Ibudilast *(rINN)*

AV-411; Ibudilastum; KC-404; MN-166; Ибудиласт.
1-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-2-methyl-1-propanone.
$C_{14}H_{18}N_2O$=230.3
CAS — 50847-11-5.
ATC — R03DC04.
ATC Vet — QR03DC04.
UNII — M0TTH61XC5.

Pharmacopoeias. In *Jpn.*

Profile

Ibudilast is an orally active leukotriene antagonist (p. 1195.2), phosphodiesterase inhibitor, and platelet-activating factor antagonist. It is given orally in the management of asthma (p. 1195.2) in a dose of 10 mg twice daily.

Ibudilast is also promoted for the management of dizziness secondary to impaired cerebral circulation following cerebral infarction, in doses of 10 mg three times daily.

Ibudilast is also under investigation for the treatment of multiple sclerosis and for chronic neuropathic pain.

References.

1. Kishi Y, *et al.* Ibudilast: a non-selective PDE inhibitor with multiple actions on blood cells and the vascular wall. *Cardiovasc Drug Rev* 2001; **19:** 215–25.
2. Ledeboer A, *et al.* Ibudilast (AV-411): a new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. *Expert Opin Invest Drugs* 2007; **16:** 935–50.
3. Rolan P, *et al.* Ibudilast in healthy volunteers: safety, tolerability and pharmacokinetics with single and multiple doses. *Br J Clin Pharmacol* 2008; **66:** 792–801.
4. Rolan P, *et al.* Ibudilast: a review of its pharmacology, efficacy and safety in respiratory and neurological disease. *Expert Opin Pharmacother* 2009; **10:** 2897–2904.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Si Yi Ke (司易可); Wei Chang (维畅); ***Jpn***: Ketas.

Indacaterol *(BAN, USAN, rINN)* ⊗

Indacatérol; Indacaterolum; QAB-149; Индакатерол.
5-{(1*R*)-2-[(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)amino]-1-hydroxyethyl}-8-hydroxyquinolin-2(1*H*)-one.
$C_{24}H_{28}N_2O_3$=392.5
CAS — 312753-06-3.
ATC — R03AC18.
ATC Vet — QR03AC18.
UNII — 8OR09251MQ.

Indacaterol Maleate *(BANM, USAN, rINNM)* ⊗

Indacatérol, Maléate d'; Indacaterolí Maleas; Maleato de indacaterol; QAB-149-AFA; Индакатерола Малеат.
5-{(1*R*)-2-[(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)amino]-1-hydroxyethyl}-8-hydroxyquinolin-2(1*H*)-one hydrogen (2*Z*)-2-butenedioate (salt).
$C_{24}H_{28}N_2O_3.C_4H_4O_4$=508.6
CAS — 753498-25-8.
ATC — R03AC18.
ATC Vet — QR03AC18.
UNII — 2JEC1ITX7R.

Uses and Administration

Indacaterol is a long-acting $beta_2$ agonist used as a bronchodilator in the maintenance treatment of chronic obstructive pulmonary disease; it is not indicated for the relief of acute bronchospasm. It is given as the maleate but doses are expressed as the base; indacaterol maleate 1.3 mg is equivalent to about 1 mg of indacaterol. Inhalation results in a rapid onset (within 5 minutes) of bronchodilatation, which lasts for up to 24 hours.

In the UK indacaterol maleate is given as inhalation powder in capsules containing the equivalent of indacaterol 150 micrograms or 300 micrograms, and supplying indacaterol 120 micrograms or 240 micrograms, respectively, from the mouthpiece of the device. The contents of one capsule are inhaled daily, at the same time each day. In the USA a lower dose of one 75-microgram capsule daily, supplying indacaterol 57 micrograms from the mouthpiece, is licensed.

Indacaterol has also been investigated in the treatment of asthma.

References.

1. Roig J, *et al.* Indacaterol, a novel once daily inhaled β 2-adrenoreceptor agonist. *Open Respir Med J* 2009; **3:** 27–30.
2. Beeh KM, Beier J. Indacaterol, a novel inhaled, once-daily, long-acting $beta_2$-agonist for the treatment of obstructive airways diseases. *Adv Therapy* 2009; **26:** 691–9. Correction. *ibid.*; 812. [dose]
3. Dahl R, *et al.* INVOLVE Study Investigators. Efficacy of a new once-daily long-acting inhaled β 2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010; **65:** 473–9.
4. Moen MD. Indacaterol: in chronic obstructive pulmonary disease. *Drugs* 2010; **70:** 2269–80.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3 and p. 1222.3. Nasopharyngitis, cough, and upper respiratory-tract infections are common.

Interactions

As for Salbutamol, p. 1223.1.

Indacaterol is metabolised by the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein and inhibitors of these substances may increase systemic exposure to indacaterol, although this did not affect safety in clinical studies.

Pharmacokinetics

Peak concentrations of indacaterol occur about 15 minutes after inhalation, and absolute bioavailability was on average 43%. Indacaterol is metabolised by cytochrome P450 isoenzymes, particularly CYP3A4. Uridine diphosphate glucuronosyltransferase 1A1 (UGT 1A1) also contributes to metabolism and indacaterol is a low-affinity substrate for P-glycoprotein. When indacaterol was given orally, about 90% was excreted in the faeces; renal clearance plays a minor role in excretion via the urine. The average terminal half-life was 45.5 to 126 hours, but a half-life of 40 to 52 hours was calculated after repeated dosing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Onbrize; ***Austral.***: Onbrez; ***Austria***: Onbrez; ***Belg.***: Onbrez; ***Canad.***: Onbrez; ***Cz.***: Hirobriz; Onbrez; Oslif; ***Denm.***: Onbrez; ***Fr.***: Onbrez; Oslif; ***Ger.***: Onbrez; ***Gr.***: Onbrez; ***Hung.***: Onbrez; ***Irl.***: Hirobriz; Onbrez; Oslif; ***Israel***: Onbrez; ***Jpn***: Onbrez; ***Neth.***: Hirobriz; Onbrez; Oslif; ***Norw.***: Onbrez; ***Philipp.***: Onbrez; ***Pol.***: Hirobriz; Onbrez; Oslif; ***Port.***: Hirobriz; Onbrez; Oslif; ***Singapore***: Onbrez; ***Spain***: Hirobriz; Onbrez; Oslif; ***Swed.***: Onbrez; ***Switz.***: Onbrez; ***Thai.***: Onbrez; ***Turk.***: Onbrez; ***UK***: Onbrez; ***Ukr.***: Onbrez (Онбрез); ***USA***: Arcapta.

Ipratropium Bromide *(BAN, USAN, rINN)*

Bromuro de ipratropio; Ipratropii Bromidum; Ipratropii Bromidum Monohydricum; Ipratropio bromidas; Ipratropio, bromuro de; Ipratropiowy bromek; Ipratropium bromid monohydrát; Ipratropium, Bromure d'; Ipratropiumbromid; Ipratropium-bromid; Ipratropiumbromidi; Ipratropyum Bromür; Sch-1000-Br-monohydrate; Sch-1000; Ипратропия Бромид.
(1*R*,3*r*,5*S*,8*r*)-8-Isopropyl-3-[(±)-tropoyloxy]tropanium bromide monohydrate.
$C_{20}H_{30}BrNO_3.H_2O$=430.4
CAS — 22254-24-6 (anhydrous ipratropium bromide); 66985-17-9 (ipratropium bromide monohydrate).
ATC — R01AX03; R03BB01.
ATC Vet — QR01AX03; QR03BB01.
UNII — J697UZ2A9J.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Ipratropium Bromide). White or almost white crystalline powder. Soluble in water; slightly soluble in alcohol; freely soluble in methyl alcohol. The pH of a 1% solution in water is 5.0 to 7.5.

USP 36: (Ipratropium Bromide). A white to off-white, crystalline powder. Soluble in water; slightly soluble in alcohol; freely soluble in methyl alcohol. A 10% solution has a pH of 5 to 7. Store in airtight containers.

Stability. In a study[1] of the stability of admixtures of ipratropium and salbutamol nebuliser solutions equal ratio mixtures were found to retain more than 90% of their initial concentrations after storage for 5 days at 4 degrees or 22 degrees in the dark or at 22 degrees under continuous fluorescent lighting.

1. Jacobson GA, Peterson GM. Stability of ipratropium bromide and salbutamol nebuliser admixtures. *Int J Pharm Pract* 1995; **3:** 169–73.

Uses and Administration

Ipratropium bromide is a quaternary ammonium antimuscarinic (p. 1195.1). It is used by inhalation as a bronchodilator in the treatment of reversible airways

obstruction, as in asthma and chronic obstructive pulmonary disease (see below).

In the UK the dose of ipratropium bromide from the metered-dose aerosol is expressed in terms of the amount of drug released from the valve into the mouthpiece (20 micrograms) whereas in the USA it is expressed in terms of the dose emitted from the mouthpiece (17 micrograms, equivalent to 21 micrograms released from the valve); recommended doses may therefore appear lower in the USA. For **reversible airways obstruction**, the usual UK dose from a metered-dose aerosol is 1 or 2 inhalations (20 or 40 micrograms) three or four times daily; single doses of up to 4 inhalations may be required. Comparable doses are used in the USA, but it is recommended that the daily dose should not exceed 12 inhalations. Ipratropium bromide may also be given by inhalation as a nebulised solution in doses of 250 to 500 micrograms up to 4 times daily. Dry powder inhalation capsules have been used.

Ipratropium bromide, given intranasally, is also used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms is given into each nostril by metered-dose nasal spray 2 or 3 times daily. US licensing also permits higher doses of 84 micrograms into each nostril 3 or 4 times daily, for up to 4 days when rhinorrhoea is associated with the common cold; doses of 84 micrograms may be given into each nostril 4 times daily, for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis.

For details of doses in children, see Administration in Children, below.

Administration in children. Children may be given ipratropium bromide via a metered dose aerosol in the treatment of **reversible airways obstruction**. UK licensed product information recommends doses by age as follows:

- under 6 years: 1 inhalation of 20 micrograms three times daily
- 6 to 12 years: 1 or 2 inhalations of 20 micrograms three times daily
- 12 years and over: adult doses, see p. 1211.3

Ipratropium bromide may also be given by inhalation as a nebulised solution. UK licensed product information recommends the following doses:

- under 6 years, for the treatment of acute asthma only: 125 to 250 micrograms, given no more often than every 6 hours up to a total daily dose of 1 mg
- 6 to 12 years, for the treatment of acute or chronic asthma: 250 micrograms, repeated if necessary up to a total daily dose of 1 mg
- 12 years and over: adult doses, see p. 1211.3.

Ipratropium bromide is used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms may be given into both nostrils two or three times daily. In the UK this dose may be given to children from 12 years of age, but in the USA this dose is licensed in children from 6 years of age.

US licensing also permits higher doses for up to 4 days when rhinorrhoea is associated with the common cold:

- 5 to 11 years: 84 micrograms into each nostril three times daily
- 12 years and over: adult doses, see p. 1211.3

Higher doses are also permitted in the USA for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis. Children 5 years of age and over may be given the same dose as adults, see p. 1211.3.

Asthma. Ipratropium bromide is currently recommended as an adjunct to $beta_2$ agonists in the management of acute severe asthma, see p. 1195.2. Antimuscarinic drugs, mainly ipratropium but also including oxitropium (p. 1218.1), glycopyrronium and atropine, have been reviewed in the treatment of both acute and chronic asthma. A systematic review and meta-analysis[1] of the efficacy of antimuscarinics in the treatment of acute asthma in children and adults, found they produced significant reductions in hospital admissions. Combined treatment with an inhaled $beta_2$ agonist also produced a significant increase in respiratory function.

Systematic reviews of antimuscarinic drugs have concluded that there is currently insufficient evidence to justify their routine use in adults[2] or children[3] with chronic asthma.

1. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; **60:** 740–6.
2. Westby M, *et al.* Anticholinergic agents for chronic asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 18/02/08).
3. McDonald NJ, *et al.* Anticholinergic therapy for chronic asthma in children over 2 years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 07/05/10).

Chronic obstructive pulmonary disease. Inhaled antimuscarinics, such as ipratropium bromide, are currently recommended as bronchodilators in chronic obstructive pulmonary disease (COPD) guidelines, see p. 1199.1. A systematic review compared regular treatment with ipratropium (given for at least 4 weeks) with treatment using regular short-acting $beta_2$ agonists in stable COPD;[1] it found small benefits on lung function outcomes and quality of life with ipratropium compared with a short-acting $beta_2$ agonist; a reduction in the requirements for oral corticosteroids was also seen. Combination therapy with ipratropium and a short-acting $beta_2$ agonist was associated with some clinically meaningful lung function outcomes compared with the $beta_2$ agonist alone, but these were not reflected in subjective improvements or symptom scores.

A systematic review comparing ipratropium with a long-acting $beta_2$ agonist in stable COPD,[2] found that salmeterol had more effect than ipratropium on lung function, but no major differences were seen between symptom responses to ipratropium and salmeterol. Combination treatment with these two drugs was better than salmeterol alone in terms of quality of life.

1. Appleton S, *et al.* Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
2. Appleton S, *et al.* Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/02/08).

Hypersalivation. Ipratropium has been tried for its antimuscarinic properties in the management of sialorrhoea and hypersalivation of various causes,[1-4] but studies have suggested that it is of little value in reducing saliva production in patients with parkinsonism[3] or hypersalivation induced by clozapine.[4]

1. Kunwar AR, *et al.* Ipratropium bromide for treatment of bethanechol-induced sialorrhea. *Ann Pharmacother* 2003; **37:** 1343.
2. Freudenreich O, *et al.* Clozapine-induced sialorrhea treated with sublingual ipratropium spray: a case series. *J Clin Psychopharmacol* 2004; **24:** 98–100.
3. Thomsen TR, *et al.* Ipratropium bromide spray as treatment for sialorrhea in Parkinson's disease. *Mov Disord* 2007; **22:** 2268–73.
4. Sockalingam S, *et al.* Treatment of clozapine-induced hypersalivation with ipratropium bromide: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2009; **70:** 1114–19.

Rhinitis. Ipratropium bromide is used intranasally for the treatment of rhinorrhoea in allergic and non-allergic rhinitis (p. 612.1). It has also relieved rhinorrhoea and sneezing associated with the common cold, alone or with intranasal corticosteroids or xylometazoline.

References.

1. Georgitis JW, *et al.* Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. *Clin Exp Allergy* 1994; **24:** 1049–55.
2. Hayden FG, *et al.* Effectiveness and safety of intranasal ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 89–97.
3. Dockhorn R, *et al.* Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol* 1999; **82:** 349–59.
4. Bonadonna P, *et al.* Cold-induced rhinitis in skiers—clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. *Am J Rhinol* 2001; **15:** 297–301.
5. Kim KT, *et al.* Pediatric Atrovent Nasal Spray Study Group. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005; **94:** 73–9.
6. Eccles R, *et al.* Effects of intranasal xylometazoline, alone or in combination with ipratropium, in patients with common cold. *Curr Med Res Opin* 2010; **26:** 889–99.

Adverse Effects and Precautions

Ipratropium and other inhaled antimuscarinic bronchodilators commonly cause dry mouth and constipation, and rarely, urinary retention. They should be used with care in prostatic hyperplasia. Acute angle-closure glaucoma has been reported; the mist or solution should not be allowed to enter the eyes, particularly in patients susceptible to glaucoma. As with other bronchodilators, paradoxical bronchospasm has occurred. Tachycardia, palpitations, and arrhythmias have been reported with ipratropium. Hypersensitivity reactions, including urticaria, angioedema, rash, and anaphylaxis have occurred rarely. Nausea and vomiting, dyspepsia, headaches, and dizziness have also been reported.

Intranasal ipratropium has been associated with nasal dryness, irritation, and epistaxis.

For details of the adverse effects of, and precautions for, antimuscarinics in general, see Atropine, p. 1312.1 and p. 1312.2.

Buccal ulceration. A report[1] of inflammation and ulceration of the buccal mucosa associated with the use of an ipratropium bromide inhaler.

1. Spencer PA. Buccal ulceration with ipratropium bromide. *BMJ* 1986; **292:** 380.

Effects on the cardiovascular system. A large systematic review[1] found that use of the inhaled antimuscarinics ipratropium and tiotropium for more than 30 days increased the risk of myocardial infarction and cardiovascular death in patients with chronic obstructive pulmonary disease (COPD) compared with placebo or an active control (an inhaled $beta_2$ agonist with or without an inhaled corticosteroid). The magnitude of the risk was difficult to discern as many of the studies included were small and short-term, resulting in few events. An increased risk of cardiovascular death with the use of ipratropium has also been reported in a case-control study[2] in COPD patients, and a cohort study involving 82 717 US veterans with COPD also found that exposure to ipratropium within the last 6 months was associated with an increased risk of cardiovascular events (heart failure, acute coronary syndrome, or arrhythmias).[3] However, these findings are contrary to results from other studies. A cohort study[4] comparing the safety of tiotropium to long-acting $beta_2$ agonists suggested users had a similar risk of cardiovascular events and a 4-year placebo-controlled study[5] of tiotropium in about 6000 patients with COPD reported a reduction in cardiac morbidity, although the study was not designed to assess cardiovascular events. Other analyses[6,7] of pooled data from studies in patients with obstructive lung disease suggested serious cardiovascular events did not occur more often in patients taking tiotropium than in those taking placebo or salmeterol. Further studies are considered necessary in order to confirm the cardiovascular safety of inhaled antimuscarinics.[8]

For further discussion of a possible increased risk of mortality associated with ipratropium use, see p. 1213.1.

For further information on the risk to the cardiovascular system associated with tiotropium, see Effects on the Cerebrovascular System, p. 1238.2.

1. Singh S, *et al.* Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; **300:** 1439–50. Correction. *ibid.* 2009; **301:** 1227–30.
2. Lee TA, *et al.* Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008; **149:** 380–90.
3. Ogale SS, *et al.* Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010; **137:** 13–19.
4. Jara M, *et al.* Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. *Drug Safety* 2007; **30:** 1151–60.
5. Tashkin DP, *et al.* UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359:** 1543–54.
6. Kesten S, *et al.* Pooled clinical trial analysis of tiotropium safety. *Chest* 2006; **130:** 1695–1703. Also available at: http://www.chestjournal.org/content/130/6/1695.full.pdf+html (accessed 07/08/09)
7. Rodrigo GJ, *et al.* Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. *Respir Med* 2009; **103:** 1421–9.
8. Salpeter SR. Do inhaled anticholinergics increase or decrease the risk of major cardiovascular events? A synthesis of the available evidence. *Drugs* 2009; **69:** 2025–33.

Effects on the eyes. Ocular complications have been reported with the use of aerosolised ipratropium. A patient with a history of glaucoma developed angle-closure glaucoma after use of ipratropium from a metered dose inhaler (MDI) with nebulised salbutamol.[1] Pupillary dilatation[2] and blurred vision[3] have been reported in association with ipratropium given through a spacer device in patients also given salbutamol therapy, and a 4-year-old child who attempted to self-administer an ipratropium MDI developed anisocoria (unequal dilatation of the pupils) and ataxia.[4] Angle-closure glaucoma,[5-7] pupillary dilatation,[7-10] and anisocoria[11,12] have been reported in patients given *nebulised* ipratropium, usually with salbutamol, through a poorly fitting face mask. The antimuscarinic effects of ipratropium can lead to impaired drainage of aqueous humour in the eyes of patients predisposed to angle-closure glaucoma; use with salbutamol may intensify this problem by increasing the production of aqueous humour.[6] Studies[13,14] suggest that patients with a history of angle-closure glaucoma might be at an increased risk of developing glaucoma when nebulised ipratropium and salbutamol are used together.

1. Hall SK. Acute angle-closure glaucoma as a complication of combined β-agonist and ipratropium bromide therapy in the emergency department. *Ann Emerg Med* 1994; **23:** 884–7.
2. Weir REP, *et al.* Pupil blown by a puffer. *Lancet* 2004; **363:** 1853.
3. Kizer KM, *et al.* Blurred vision from ipratropium bromide inhalation. *Am J Health-Syst Pharm* 2000; **57:** 996–7.
4. Bond DW, *et al.* Mydriasis due to self-administered inhaled ipratropium bromide. *Eur J Pediatr* 2002; **161:** 178.
5. Packe GE, *et al.* Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. *Lancet* 1984; **ii:** 691.
6. Shah P, *et al.* Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol. *BMJ* 1992; **304:** 40–1.
7. Mulpeter KM, *et al.* Ocular hazards of nebulized bronchodilators. *Postgrad Med J* 1992; **68:** 132–3.
8. Roberts TE, Pearson DJ. Wide eyed and breathless. *BMJ* 1989; **299:** 1348.
9. Woelfle J, *et al.* Unilateral fixed dilated pupil in an infant after inhalation of nebulized ipratropium bromide. *J Pediatr* 2000; **136:** 423–4.
10. Openshaw H. Unilateral mydriasis from ipratropium in transplant patients. *Neurology* 2006; **67:** 914–15.
11. Lust K, Livingstone I. Nebulizer-induced anisocoria. *Ann Intern Med* 1998; **128:** 327.
12. Iosson N. Nebulizer-associated anisocoria. *N Engl J Med* 2006; **354:** e8.
13. Watson WTA, *et al.* Effect of nebulized ipratropium bromide on intraocular pressures in children. *Chest* 1994; **105:** 1439–41.
14. Kalra L, Bone MF. The effect of nebulized bronchodilator therapy on intraocular pressures in patients with glaucoma. *Chest* 1988; **93:** 739–41.

Effects on the gastrointestinal tract. Paralytic ileus developed shortly after starting ipratropium therapy in 2 patients, apparently due to the inadvertent swallowing of the drug during inhalation.[1,2] Both patients also had other predisposing factors for paralytic ileus (cystic fibrosis,[1] spastic diplegia[2]).

1. Mulherin D, FitzGerald MX. Meconium ileus equivalent in association with nebulised ipratropium bromide in cystic fibrosis. *Lancet* 1990; **355:** 552.
2. Markus HS. Paralytic ileus associated with ipratropium. *Lancet* 1990; **355:** 1224.

Effects on the respiratory tract. Antimuscarinics typically inhibit mucociliary clearance and inhibit secretions of the nose, mouth, pharynx, and bronchi. However, inhaled ipratropium bromide has virtually no effect on sputum viscosity or volume and, in contrast to atropine, it does not affect mucociliary function in the respiratory tract.[1,2]

1. Gross NJ. Ipratropium bromide. *N Engl J Med* 1988; **319:** 486–94.
2. Mann KV, *et al.* Use of ipratropium bromide in obstructive lung disease. *Clin Pharm* 1988; **7:** 670–80.

BRONCHOSPASM. Paradoxical bronchoconstriction occurring after the use of ipratropium was reported in 3 patients.[1] A further report[2] of paradoxical bronchoconstriction after nebulised salbutamol and ipratropium suggested that this adverse effect might have been caused by benzalkonium chloride present in the nebuliser solutions. Nebuliser solutions of ipratropium in some countries contain benzalkonium chloride as a preservative. Solutions available in the UK are preservative-free but licensed product information still recommends that the first doses of ipratropium nebuliser solution should be inhaled under medical supervision.

1. Connolly CK. Adverse reaction to ipratropium bromide. *BMJ* 1982; **285:** 934–5.
2. Boucher M, *et al.* Possible associations of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; **26:** 772–4.

Effects on the urinary tract. Treatment with nebulised ipratropium bromide has resulted in urinary retention in elderly men especially those with prostatic hyperplasia.[1,2] Micturition difficulties associated with use of ipratropium and salbutamol in a child have also been reported.[3]

1. Lozewicz S. Bladder outflow obstruction induced by ipratropium bromide. *Postgrad Med J* 1989; **65:** 260–1.
2. Pras E, *et al.* Urinary retention associated with ipratropium bromide. *DICP Ann Pharmacother* 1991; **25:** 939–40.
3. Hooimeijer HL, *et al.* Bemoeilijkte mictie bij een kind toegeschreven aan het gebruik van ipratropium en salbutamol. *Ned Tijdschr Geneeskd* 2007; **151:** 2726–8.

Increased mortality. A case-control study found an unexpected association between death from asthma and treatment with ipratropium, which was not explained by comorbidity due to chronic obstructive pulmonary disease (COPD).[1] A retrospective cohort study[2] of elderly patients also found a slight increase in the risk of death in asthma patients using ipratropium, although this may have been due to the confounding effect of disease severity. No increase in all-cause mortality was seen in patients with COPD using ipratropium. In contrast, another case-control study reported an increased risk of death associated with use of ipratropium for COPD.[3] A longitudinal cohort study of 1100 patients with obstructive lung disease found an increased risk of premature death associated with ipratropium in both asthma and COPD patients.[4] After adjusting for confounding factors such as forced expiratory volume, smoking status, BMI, and presence of cor pulmonale, ipratropium was associated with a mortality risk ratio (RR) of 2.4 in asthmatic patients and 1.6 in COPD patients. Again, residual confounding by disease severity could not be ruled out.

For a suggestion that inhaled ipratropium can increase the risk of cardiovascular death, see Effects on the Cardiovascular System, p. 1212.2.

1. Guite HF, *et al.* Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999; **54:** 301–7.
2. Sin DD, Tu JV. Lack of association between ipratropium bromide and mortality in elderly patients with chronic obstructive airway disease. *Thorax* 2000; **55:** 194–7.
3. Lee TA, *et al.* Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008; **149:** 380–90.
4. Ringbæk T, Viskum K. Is there any association between inhaled ipratropium and mortality in patients with COPD and asthma? *Respir Med* 2003; **97:** 264–72.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ipratropium bromide as probably not porphyrinogenic when used by inhalation; it may be used as a drug of first choice and no precautions are needed. It is classified as not porphyrinogenic when used intranasally.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p. 1312.3. However, these interactions are not usually seen with antimuscarinics, such as ipratropium, given by inhalation.

Salbutamol. For reference to nebulised salbutamol exacerbating the adverse effects of nebulised ipratropium in patients predisposed to angle-closure glaucoma, see under Effects on the Eyes, p. 1212.3.

Pharmacokinetics

After inhalation, around 10 to 30% of a dose is deposited in the lungs where it exerts its therapeutic effect. Only a small amount of ipratropium reaches the systemic circulation. The majority of a dose is swallowed but is poorly absorbed from the gastrointestinal tract. Ipratropium and its metabolites are eliminated in the urine and faeces.

References.

1. Ensing K, *et al.* Pharmacokinetics of ipratropium bromide after single dose inhalation and oral and intravenous administration. *Eur J Clin Pharmacol* 1989; **36:** 189–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerotrop; Akitropio; Atrovent; Iprabron; ***Austral.***: Aeron; Apoven†; Atrovent; Ipratrin; Ipravent; ***Austria***: Atrovent; Itrop; ***Belg.***: Atronase; Atrovent; Nebu-Trop; ***Braz.***: Alvent; Ares; Atrovent; Bromovent; Iprabon†; Ipraneo; ***Canad.***: Apo-Ipravent; Atrovent; Novo-Ipramide; ***Chile***: Aerotrop; Atrovent; ***China***: Atrovent (爱全乐); ***Cz.***: Atrovent; ***Denm.***: Atrovent; ***Fin.***: Atrovent; Ipraxa; ***Fr.***: Atrovent; Ipratrogen; ***Ger.***: Atrovent; Itrop; ***Gr.***: Atrovent; Tyrolen; ***Hong Kong***: Atrovent; Cyclovent†; Steri-Neb†; ***Hung.***: Atrovent; ***India***: Ipneb; Ipramist; Ipranase; Ipratop; Ipravent; ***Indon.***: Atrovent; ***Irl.***: Atrovent; Ipravent; Rinatec; ***Israel***: Aerovent; Apovent†; Atrovent; ***Ital.***: Atem; Rinovagos; ***Jpn***: Atrovent; ***Malaysia***: Atrovent; ***Mex.***: Atrovent; ***Neth.***: Atrovent; Ipraxa; ***Norw.***: Atrovent; Ipraxa; ***NZ***: Apo-Ipravent; Atrovent; Univent; ***Philipp.***: Atrovent; Broncho-vent; ***Pol.***: Atrovent; ***Port.***: Atrovent; Ipraxa; ***Rus.***: Atrovent (Атровент); Ipravent (Иправент); ***S.Afr.***: Atrovent; Ipvent; ***Singapore***: Atrovent; Steri-Neb Ipratropium; ***Spain***: Atroaldo; Atrovent; ***Swed.***: Atrovent; Ipraxa; ***Switz.***: Atropair; Atrovent; Rhinovent; ***Thai.***: Atrovent†; Iperol; ***Turk.***: Atrovent; ***UAE***: Atropulm; ***UK***: Atrovent; Respontin; Rinatec; ***USA***: Atrovent; ***Venez.***: Alovent.

Multi-ingredient Preparations. ***Arg.***: Berodual; Combivent; Ipradual; Iprasalb; Salbutral AC; ***Austral.***: Combivent; ***Austria***: Berodual; Berodualin; Combivent; ***Belg.***: Combivent; Duovent; Nebu-Iprasal; Otrivine Duo; ***Braz.***: Combivent; Duovent; ***Canad.***: Combivent; Duovent; Gen-Combo†; Mylan-Combo; ratio-Ipra Sal; ***Chile***: Berodual; Combivent; Salbutral AC; ***China***: Combivent (可必特); Ren Shu (仁舒); ***Cz.***: Berodual; ***Denm.***: Berodual; Combipramol†; Combivent; Duovent; Ipramol; Sapimol; Zymelin Plus; ***Fin.***: Atrodual; Atrovent Comp; Ipramol; Otrivin Comp; Salipra†; ***Fr.***: Bronchodual; ***Ger.***: Berodual; ***Gr.***: Berodual; Berovent; Demoren; Ipramol; Otrivin Advance; ***Hong Kong***: Combivent; Ipramol; ***Hung.***: Berodual; Otrivin Duo; ***India***: Aeromist; Combimist; Duolin; Fenovent; ***Indon.***: Berodual; Combivent; ***Irl.***: Combineb; Combivent; Duovent†; Ipramol; ***Israel***: Otrivin Complete; ***Ital.***: Almeida; Biwind; Breva; Duovent; Naos; ***Malaysia***: Berodual; Combivent; Duolin; Duovent; Ipramol; ***Mex.***: Berodual; Combivent; ***Neth.***: Berodual; Combipramol†; Combivent; Ipramol; Otrivin Duo; ***Norw.***: Otrivin Comp; Zycomb; ***NZ***: Combivent; Duolin; ***Philipp.***: Adsal Plus; Berodual; Combipul; Combivent; Duavent; Pulmodual; ***Pol.***: Berodual; Otrivin Duo; ***Port.***: Berodual; Combivent; Ipramol; Otrifar; ***Rus.***: Berodual (Бородуал); Ipramol (Ипрамол); Xymelin Extra (Ксимелин Экстра); ***S.Afr.***: Adco-Combineb; Atrovent Beta; Berodual†; Combivent; Duolin; Duovent; Sabax Nebrafen; ***Singapore***: Berodual; Combivent; Duovent; ***Spain***: Combiprasal; Otriduo; ***Swed.***: Combivent; Ipramol; Otrivin Comp; Sapimol; ZyComb†; ***Switz.***: Berodual; Dospir; Ipramol; ***Thai.***: Aeroduol; Berodual; Combivent; Inhalex; Iprateral; Punol; ***Turk.***: Combivent; ***UK***: Combivent; Duovent†; Ipramol; ***Ukr.***: Berodual (Бородуал); Xymelin Extra (Ксимелин Экстра); Zycomb (Зикомб)†; ***USA***: Combivent; Duo-Neb; ***Venez.***: Berodual; Combivent; Duolin; Duovent; Ipralin; Respidual.

Pharmacopoeial Preparations

BP 2014: Ipratropium Inhalation Powder, hard capsule; Ipratropium Nebuliser Solution; Ipratropium Pressurised Inhalation.

Isoetarine *(BAN, rINN)* ⊗

Isoetariini; Isoetarin; Isoetarina; Isoétarine; Isoetarinum; Isoetharine (USAN); Win-3406; Изоэтарин.

1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutan-1-ol.

$C_{13}H_{21}NO_3$=239.3

CAS — 530-08-5.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

UNII — YV0SN3276Q.

Isoetarine Hydrochloride *(BANM, rINNM)* ⊗

Etyprenaline Hydrochloride; Hidrocloruro de isoetarina; Isoetarina, hidrocloruro de; Isoétarine, Chlorhydrate d'; Isoetarini Hydrochloridum; Isoetharine Hydrochloride; *N*-Isopropylethylnoradrenaline Hydrochloride; Изоэтарина Гидрохлорид.

$C_{13}H_{21}NO_3$,HCl=275.8

CAS — 50-96-4; 2576-92-3.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

UNII — 51V8U784H3.

Pharmacopoeias. In *US.*

USP 36: (Isoetharine Hydrochloride). A white to off-white, odourless, crystalline solid. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 4.0 to 5.6. Store in airtight containers.

Isoetarine Mesilate *(BANM, rINNM)* ⊗

Isoetarina, mesilato de; Isoétarine, Mésilate d'; Isoetarini Mesilas; Isoetharine Mesylate; Isoetharine Methanesulphonate; *N*-Isopropylethylnoradrenaline Mesylate; Mesilato de isoetarina; Изоэтарина Мезилат.

$C_{13}H_{21}NO_3,CH_4O_3S$=335.4

CAS — 7279-75-6.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

UNII — DV74WJ5PJB.

Pharmacopoeias. In *US.*

USP 36: (Isoetharine Mesylate). White or practically white, odourless, crystals. Freely soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 5.5. Store in airtight containers.

Profile

Isoetarine is a sympathomimetic with mainly beta-adrenergic activity. It has actions similar to those of salbutamol (p. 1220.2) but is less selective for $beta_2$ adrenoceptors. Isoetarine has been used by inhalation as a bronchodilator in the management of reversible airways obstruction.

Preparations

Pharmacopoeial Preparations

USP 36: Isoetharine Inhalation Solution; Isoetharine Mesylate Inhalation Aerosol.

Levosalbutamol *(rINN)* ⊗

Levalbuterol; Lévosalbutamol; Levosalbutamolum; Левосальбутамол.

(*R*)-α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol.

$C_{13}H_{21}NO_3$=239.3

CAS — 34391-04-3.

UNII — EDN2NBH5SS.

Levosalbutamol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levosalbutamol; Levalbuterol Hydrochloride (USAN); Lévosalbutamol, Chlorhydrate de; Levosalbutamol, hidrocloruro de; Levosalbutamoli Hydrochloridum; Левосальбутамола Гидрохлорид.

(*R*)-α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol hydrochloride.

$C_{13}H_{21}NO_3$,HCl=275.8

CAS — 50293-90-8.

UNII — WDQ1526QJM.

Pharmacopoeias. In *US.*

USP 36: (Levalbuterol Hydrochloride). A 1% solution has a pH of 4.5 to 5.5. Store in airtight containers at 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Levosalbutamol Sulfate *(rINNM)* ⊗

Levalbuterol Sulfate (USAN); Lévosalbutamol, Sulfate de; Levosalbutamol Sulphate; Levosalbutamoli Sulfas; Sulfato de levosalbutamol; Левосальбутамола Сульфат.

(*R*)-α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-αα′-diol sulfate (2:1).

$(C_{13}H_{21}NO_3)_2,H_2SO_4$=576.7

CAS — 148563-16-0.

UNII — 71TH42O2CQ.

Levosalbutamol Tartrate (rINNM) ⊗

Levalbuterol Tartrate (USAN); Lévosalbutamol, Tartrate de; Levosalbutamoli Tartras; Tartrato de levosalbutamol; Левосальбутамола Тартрат.

(α[1]*R*)-α[1]-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1).

$2(C_{13}H_{21}NO_3),C_4H_6O_6$=628.7

CAS — 661464-94-4.

UNII — ADS413E22M.

Uses and Administration

Levosalbutamol, the *R* (-)-enantiomer of salbutamol (p. 1220.2), may be used as an alternative to racemic salbutamol for the management of asthma (p. 1195.2). It is given as the hydrochloride, sulfate, or tartrate but doses are usually expressed in terms of the base; 1.15 mg of levosalbutamol hydrochloride, 2.4 mg of levosalbutamol sulfate, and 2.63 mg of levosalbutamol tartrate are equivalent to about 1 mg of levosalbutamol. For the relief of acute bronchospasm, 1 or 2 inhalations of the equivalent of 45 micrograms of levosalbutamol can be given from a metered-dose aerosol, repeated every 4 to 6 hours as required.

Levosalbutamol may also be inhaled via a nebuliser; usual doses equivalent to levosalbutamol 630 micrograms are inhaled three times daily, increased if necessary to 1.25 mg three times daily. For children's doses, see Administration in Children below. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, levosalbutamol indicates deterioration of asthma control and the need for review of therapy.

Levosalbutamol is also under investigation in a topical formulation for the treatment of cutaneous lupus erythematosus.

General reviews.

1. Jenne JW. The debate on S-enantiomers of β-agonists: tempest in a teapot or gathering storm? *J Allergy Clin Immunol* 1998; **102:** 893–5.
2. Nowak R. Single-isomer levalbuterol: a review of the acute data. *Curr Allergy Asthma Rep* 2003; **3:** 172–8.
3. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol* 2003; **90:** 583–91.
4. Datta D, *et al.* A n evaluation o f nebulized levalbuterol i n stable COPD. *Chest* 2003; **124:** 844–9.
5. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; **7:** 310–14.

Action. *In vitro,* levosalbutamol had slightly higher affinity than racemic salbutamol for beta$_1$ and beta$_2$ adrenoceptors.[1] The *S*(+)-enantiomer had low affinity for these receptors. All 3 were mildly selective for beta$_2$ adrenoceptors.

1. Penn RB, *et al.* Comparison of R-, S-, and RS-albuterol interaction with human β$_1$- and β$_2$-adrenergic receptors. *Clin Rev Allergy Immunol* 1996; **14:** 37–45.

Administration in children. Children aged 4 years and older may be given levosalbutamol via a metered-dose aerosol at the same dose as that used for adults, see Uses and Administration, above.

Children aged from 6 to 11 years of age may be given levosalbutamol via a nebuliser in doses from 310 to 630 micrograms three times daily.

Asthma. Controlled studies comparing levosalbutamol with racemic salbutamol for the treatment of asthma have produced variable results. Levosalbutamol provided greater bronchodilatation than the equivalent amount of the racemate in some studies.[1,2] A decrease in hospital admissions and an increase in patient-discharge rates have also been reported.[3-5] Controlled studies comparing levosalbutamol with racemic salbutamol in children with acute asthma have generally failed to show any clinical benefit over the racemate.[6-8] A review concluded that, although current studies did not provide evidence of a substantial advantage for levosalbutamol over racemic salbutamol, the data were insufficient to determine whether subsets of the patient population might benefit from single isomer therapy.[9]

1. Pleskow WW, *et al.* Pairwise comparison of levalbuterol versus racemic albuterol in the treatment of moderate-to-severe asthma. *Allergy Asthma Proc* 2004; **25:** 429–36.
2. Nowak R, *et al.* A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. *Am J Emerg Med* 2006; **24:** 259–67.
3. Carl JC, *et al.* Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. *J Pediatr* 2003; **143:** 731–6.
4. Schreck DM, Babin S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED. *Am J Emerg Med* 2005; **23:** 842–7.
5. Truitt T, *et al.* Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest* 2003; **123:** 128–35.
6. Qureshi F, *et al.* Clinical efficacy o f racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005; **46:** 29–36.
7. Hardasmalani MD, *et al.* Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care* 2005; **21:** 415–19.
8. Andrews T, *et al.* High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: a randomized trial. *J Pediatr* 2009; **155:** 205–10.
9. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; **7:** 310–14.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3.

Incidence of adverse effects. Some studies have reported that beta-adrenergic adverse effects (e.g. nervousness and increased heart rate) are less frequent with inhaled levosalbutamol than with racemic salbutamol.[1-4] In general, however, little difference has been seen in clinical practice.[5] Despite preliminary evidence that the increased airway hyperresponsiveness occasionally seen with long-term racemic salbutamol (see Tolerance, p. 1222.3) may be due to the *S*(+)-enantiomer, and therefore might not occur with levosalbutamol,[6] a small study was unable to find any favourable protective effect.[7]

1. Nelson HS, *et al.* Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998; **102:** 943–52.
2. Milgrom H, *et al.* Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol* 2001; **108:** 938–45.
3. Handley DA, *et al.* Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. *J Asthma* 2000; **37:** 319–27.
4. Tripp K, *et al.* A cumulative dose study of levalbuterol and racemic albuterol administered by hydrofluoroalkane-134a metered-dose inhaler in asthmatic subjects. *J Allergy Clin Immunol* 2008; **122:** 544–9.
5. Ameredes BT, Calhoun WJ. Levalbuterol versus albuterol. *Curr Allergy Asthma Rep* 2009; **9:** 401–9.
6. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; **346:** 1101.
7. Sjöswärd KN, *et al.* Single-isomer R-salbutamol is not superior to racemate regarding protection for bronchial hyperresponsiveness. *Respir Med* 2004; **98:** 990–9.

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

There is some systemic absorption of inhaled levosalbutamol. After a single dose levosalbutamol has a half-life of 3.3 hours. For details of the metabolism and excretion of salbutamol enantiomers, see Stereoselectivity, under Salbutamol p. 1223.2.

Metabolism. There is evidence that levosalbutamol is metabolised faster than *S*(+)-salbutamol.

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; **41:** 35–40.
2. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β$_2$ adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; **52:** 849–52.
3. Gumbhir-Shah K, *et al.* Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 1096–1106.
4. Boulton DW, Fawcett JP. The pharmacokinetics of levosalbutamol: what are the clinical implications? *Clin Pharmacokinet* 2001; **40:** 23–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Albulair; Ventoplus; ***India***: Levolin; ***USA***: Xopenex.

Pharmacopoeial Preparations

USP 36: Levalbuterol Inhalation Solution.

Mepolizumab (USAN, rINN)

Mépolizumab; Mepolizumabum; SB-240563; Меполизумаб. Immunoglobulin G1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563 γ1-chain), disulfide with human-mouse monoclonal SB-240563 κ-chain, dimer.

CAS — 196078-29-2.

ATC — L04AC05.

ATC Vet — QL04AC06.

Profile

Mepolizumab is a humanised anti-interleukin-5 monoclonal antibody. It is under investigation in the management of asthma, as well as the treatment of hypereosinophilic syndrome (chronic eosinophilic leukaemia), and eosinophilic oesophagitis (p. 1810.1).

References.

1. Leckie MJ, *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; **356:** 2144–8.
2. Plötz S-G, *et al.* Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003; **349:** 2334–9.
3. Braun-Falco M, *et al.* Angiolymphoid hyperplasia with eosinophilia treated with anti-interleukin-5 antibody (mepolizumab). *Br J Dermatol* 2004; **151:** 1103–4.
4. Garrett JK, *et al.* Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004; **113:** 115–19.
5. Rothenberg ME, *et al.* Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358:** 1215–28. Correction. *ibid.*; 2530.
6. Haldar P, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; **360:** 973–84.
7. Nair P, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; **360:** 985–93.
8. Straumann A, *et al.* Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010; **59:** 21–30.

Montelukast Sodium

(BANM, USAN, rINNM)

L-706631; MK-476; Montelukast sódico; Montélukast Sodique; Natrii Montelukastum; Натрий Монтелукаст.

Sodium 1-[[[(*R*)-*m*-[(*E*)-2-(7-chloro-2-quinolyl)-vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]-benzyl]thio]methyl] cyclopropaneacetate.

$C_{35}H_{35}ClNNaO_3S$=608.2

CAS — 158966-92-8 (montelukast); 151767-02-1 (montelukast sodium).

ATC — R03DC03.

ATC Vet — QR03DC03.

UNII — U1O3J18SFL.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Montelukast Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in dichloromethane; freely soluble to very soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Montelukast Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in dichloromethane; freely soluble to very soluble in alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Montelukast is a selective leukotriene receptor antagonist with actions and uses similar to those of zafirlukast (p. 1240.1) although it is reported to have a longer duration of action. It is used as the sodium salt, but doses are expressed in terms of the base; montelukast sodium 10.38 mg is equivalent to about 10 mg of montelukast.

Montelukast sodium is used in the management of asthma (see p. 1215.1) and allergic rhinitis (see p. 1215.3). It is given orally in doses equivalent to 10 mg of montelukast once daily. In chronic asthma, the dose is given in the evening. For acute prevention of exercise-induced bronchoconstriction, the dose should be given at least 2 hours before exercise and not repeated within 24 hours. Patients already taking montelukast daily for another indication, including chronic asthma, should not take additional doses for exercise-induced bronchoconstriction. Montelukast is not used to treat an acute asthma attack. In the treatment of seasonal or perennial allergic rhinitis (without asthma), the dose may be taken in either the morning or evening.

For details of doses in children, see below.

Administration in children. Montelukast sodium has been widely used in children,[1] for whom it is available as oral granules and chewable tablets. Chewable tablets are suitable for those aged 2 years and older; oral granules are suitable for infants from 6 months of age as they may be given directly into the mouth or mixed with a small amount of soft food. Oral daily doses, expressed as montelukast, are based on age:

- 6 months up to 2 years: 4 mg (as granules)
- 2 to 5 years: 4 mg (as granules or chewable tablets)
- 6 to 14 years: 5 mg (as chewable tablets)
- 15 years and over: use the adult dose, see above

In the UK, the above doses are licensed for the management of chronic asthma and from 2 years of age for the prophylaxis of exercise-induced asthma; in asthmatic children with concomitant seasonal allergic rhinitis, it is only licensed from age 15. Doses should be taken in the evening.

In the USA these doses are licensed from 1 year of age in chronic asthma, to be given as a single daily dose in the evening. In the prevention of exercise-induced bronchoconstriction in children aged 6 years and older, a dose may be given at least 2 hours before exercise, and not repeated within 24 hours. Patients already being treated with daily therapy for another indication, including chronic asthma, should not be given additional doses for exercise-induced bronchoconstriction. Montelukast is also licensed for use in allergic rhinitis (without asthma) in the USA. The above daily doses can be given either in the morning or the

evening from 2 years of age in seasonal allergic rhinitis and from 6 months of age in perennial allergic rhinitis.

1. Bisgaard H, *et al*. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. *Pediatr Pulmonol* 2009; **44:** 568–79.

Asthma. Use of montelukast in asthma (p. 1195.2) has been reviewed,[1-4] (further general references for leukotriene antagonists can be found under Zafirlukast, p. 1240.1). Montelukast produced modest improvements compared with placebo in chronic asthma and exercise-induced asthma in both adults[5,6] and children.[7-9] In a systematic review[10] of studies in adults and children comparing leukotriene receptor antagonists with inhaled corticosteroids for monotherapy in mild to moderate persistent asthma, in which more than half of the studies used montelukast, leukotriene antagonists were found to be less effective in maintaining asthma control. The difference was particularly marked in patients with moderate disease. Addition of montelukast to an inhaled corticosteroid has significantly improved asthma control in adults and adolescents,[11] and in children,[12,13] with mild to moderate asthma. However, in adults and adolescents the addition of an inhaled long-acting beta$_2$ agonist, such as salmeterol, is more effective;[11,14] comparative studies in children are limited.[14]

Montelukast may be used for prophylaxis in patients with chronic exercise-induced asthma.[15,16] However, it may only be effective in 50 to 80% of patients.[16] There is some evidence that montelukast may be more effective than inhaled salmeterol for the chronic treatment of exercise-induced asthma,[17,18] and although a later study[19] found similar effects on lung function with the two drugs, a more favourable effect was seen on gas exchange during moderate exercise with the use of montelukast.

Montelukast has also been studied in adults and children for the treatment of acute asthma, using either oral therapy or an investigational injectable form. However, despite some evidence of improvement in lung function, the addition of montelukast to standard therapy did not significantly affect rates of hospital admission.[20]

1. Jarvis B, Markham A. Montelukast: a review of its therapeutic potential in persistent asthma. *Drugs* 2000; **59:** 891–928.
2. Nayak A. A review of montelukast in the treatment of asthma and allergic rhinitis. *Expert Opin Pharmacother* 2004; **5:** 679–86.
3. Storms W. Update on montelukast and its role in the treatment of asthma, allergic rhinitis and exercise-induced bronchoconstriction. *Expert Opin Pharmacother* 2007; **8:** 2173–87.
4. Amlani S, *et al*. Montelukast for the treatment of asthma in the adult population. *Expert Opin Pharmacother* 2011; **12:** 2119–28.
5. Leff JA, *et al*. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998; **339:** 147–52.
6. Reiss TF, *et al*. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. *Arch Intern Med* 1998; **158:** 1213–20.
7. Knorr B, *et al*. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *JAMA* 1998; **279:** 1181–6.
8. Kemp JP, *et al*. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; **133:** 424–8.
9. Knorr B, *et al*. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Abstract: *Pediatrics* 2001; **108:** 754–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e48 (accessed 14/04/08)
10. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2012 (accessed 17/06/13).
11. Joos S, *et al*. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. *Thorax* 2008; **63:** 453–62.
12. Phipatanakul W, *et al*. Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2003; **91:** 49–54.
13. Johnston NW, *et al*. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007; **120:** e702–e712.
14. Ducharme FM, *et al*. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2011 (accessed 17/06/13).
15. Grzelewski T, Stelmach I. Exercise-induced bronchoconstriction in asthmatic children: a comparative systematic review of the available treatment options. *Drugs* 2009; **69:** 1533–53.
16. Carver TW. Exercise-induced asthma: critical analysis of the protective role of montelukast. *J Asthma Allergy* 2009; **2:** 93–103.
17. Villaran C, *et al*. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 1999; **104:** 547–53.
18. Edelman JM, *et al*. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction: a randomized, double-blind trial. *Ann Intern Med* 2000; **132:** 97–104.
19. Steinshamn S, *et al*. Effects of montelukast and salmeterol on physical performance and exercise economy in adult asthmatics with exercise-induced bronchoconstriction. *Chest* 2004; **126:** 1154–60.
20. Watts K, Chavasse RJPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2012 (accessed 17/06/13).

Bronchiolitis. Bronchiolitis due to RSV infection is often followed by post-bronchiolitic reactive airways disease, characterised by asthma-like wheeze and other symptoms. Results from a placebo-controlled pilot study in infants with acute bronchiolitis suggested a reduction in symptoms after the first 2 weeks of montelukast treatment,[1] generating some interest in whether montelukast could prevent or modify more persistent asthma that has been associated with RSV.[2] However, a further similar study found no benefit with montelukast treatment compared with placebo,[3] and did not support the use of montelukast in infants with acute bronchiolitis.

1. Bisgaard H. Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med* 2003; **167:** 379–83.
2. Szefler SJ, Simoes EAF. Montelukast for respiratory syncytial virus bronchiolitis: significant effect or provocative findings? *Am J Respir Crit Care Med* 2003; **167:** 290–1.
3. Amirav I, *et al*. A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. Abstract: *Pediatrics* 2008; **122:** 1361. Full version: http://pediatrics.aappublications.org/cgi/reprint/122/6/e1249 (accessed 17/08/09)

Cystic fibrosis. A small study in children with cystic fibrosis (p. 177.2) found that montelukast reduced eosinophilic inflammation.[1] A later study,[2] reported improved lung function and a reduction in coughing and wheezing, and concluded that montelukast may have measurable anti-inflammatory activity in patients with cystic fibrosis. In a small group of adult patients with cystic fibrosis[3] montelukast improved symptoms, in particular exercise tolerance and peak expiratory flow rates. The patients who benefited the most had positive *Aspergillus* serology, and the authors suggested that colonisation of the airways in cystic fibrosis by *Aspergillus* stimulates T helper cell inflammation and leukotriene synthesis. A review of leukotriene receptor antagonists in cystic fibrosis[4] concluded that clinical benefit seemed likely in a subset of patients with bronchial hyperresponsiveness similar to that seen in asthma.

A study into the pharmacokinetics of montelukast in cystic fibrosis[5] found that the dose of montelukast and the dosing interval do not need to be modified if the goal of therapy is to achieve similar serum concentrations as for asthma treatment; however the efficacy of these concentrations for the inflammatory lung disease of patients with cystic fibrosis was unknown.

1. Schmitt-Grohé S, *et al*. Anti-inflammatory effects of montelukast in mild cystic fibrosis. *Ann Allergy Asthma Immunol* 2002; **89:** 599–605.
2. Stelmach I, *et al*. Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. *Ann Allergy Asthma Immunol* 2005; **95:** 372–80.
3. Morice AH, *et al*. Montelukast sodium in cystic fibrosis. *Thorax* 2001; **56:** 244–5.
4. Schmitt-Grohé S, Zielen S. Leukotriene receptor antagonists in children with cystic fibrosis lung disease: anti-inflammatory and clinical effects. *Pediatr Drugs* 2005; **7:** 353–63.
5. Graff GR, *et al*. Montelukast pharmacokinetics in cystic fibrosis. *J Pediatr* 2003; **142:** 53–6.

Eczema. Despite early indications from some small clinical studies and case reports[1-3] that montelukast might be of benefit in eczema (p. 1684.1) larger, more recent studies have failed to show any improvement compared with placebo.[4,5]

1. Capella GL, *et al*. A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11:** 209–13.
2. Hon KLE, *et al*. Brief case series: montelukast, at doses recommended for asthma treatment, reduces disease severity and increases soluble CD14 in children with atopic dermatitis. *J Dermatolog Treat* 2005; **16:** 15–18.
3. Angelova-Fischer I, Tsankov N. Successful treatment of severe atopic dermatitis with cysteinyl leukotriene receptor antagonist montelukast. *Acta Dermatovenerol Alp Panonica Adriat* 2005; **14:** 115–19.
4. Veien NK, *et al*. Montelukast treatment of moderate to severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2005; **53:** 147–9.
5. Friedmann PS, *et al*. A double-blind, placebo-controlled trial of montelukast in adult atopic eczema. *Clin Exp Allergy* 2007; **37:** 1536–40.

Gastrointestinal disorders. Benefit has been reported[1] with the use of montelukast in patients with eosinophilic oesophagitis (see p. 1810.1). A systematic review with recommendations for the diagnosis and treatment of eosinophilic oesophagitis[2] concluded that although leukotriene receptor antagonists had been shown to induce symptomatic relief at high doses, no significant improvements in histology were noted and their use for the treatment of eosinophilic oesophagitis is not supported by the current literature.

1. Attwood SEA, *et al*. Eosinophilic oesophagitis: a novel treatment using montelukast. *Gut* 2003; **52:** 181–5.
2. Furuta GT, *et al*. American Gastroenterological Association; North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133:** 1342–63. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508507014746.pdf (accessed 14/04/08)

Graft-versus-host disease. A pilot study in refractory, chronic graft-versus-host disease (GVHD) after allogeneic haematopoietic stem cell transplantation (p. 1937.1),[1] saw an improvement in 15 of 19 patients after montelukast was added to their standard immunosuppressive regimens; in 4 patients signs of chronic GVHD were resolved, 2 showed significant improvement, and 9 showed moderate improvement.

1. Or R, *et al*. Sparing effect by montelukast treatment for chronic graft versus host disease: a pilot study. *Transplantation* 2007; **83:** 577–81.

Mastocytosis. Montelukast has been tried, with some success, in the treatment of systemic mastocytosis (p. 1226.3) in an infant.[1]

1. Tolar J, *et al*. Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med* 2004; **350:** 735–6.

Rhinitis. Montelukast is used in allergic rhinitis (p. 612.1), where large placebo-controlled studies have shown it to relieve symptoms in both seasonal allergic rhinitis,[1,2] and perennial allergic rhinitis.[3] However, a meta-analysis[4] of leukotriene antagonists (mainly montelukast) for management of allergic rhinitis concluded that while leukotriene antagonists were modestly more effective than placebo and of similar efficacy to antihistamines, in reducing nasal symptoms and improving rhinoconjunctivitis, they were less effective than corticosteroids even when used with antihistamines. A later systematic review[5] commented that some studies in allergic rhinitis using a combination of montelukast and an antihistamine had produced results comparable with intranasal corticosteroids. Also, in patients with both allergic rhinitis and asthma, montelukast had resulted in significant improvements in both when compared with placebo.

1. Philip G, *et al*. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002; **32:** 1020–8.
2. van Adelsberg J, *et al*. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **90:** 214–22.
3. Patel P, *et al*. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **95:** 551–7.
4. Wilson AM, *et al*. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; **116:** 338–44.
5. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. *Drugs* 2007; **67:** 887–901.

Sleep-disordered breathing. Montelukast with an intranasal corticosteroid has been reported to be beneficial in a small study in children with residual sleep-disordered breathing after tonsillectomy and adenoidectomy.[1]

1. Kheirandish L, *et al*. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics* 2006; **117:** e61–e66.

Urticaria. Montelukast has been investigated in the treatment of urticaria (p. 1689.2) with variable results.[1] However, urticaria has also been described as a suspected adverse effect of montelukast therapy.

Montelukast has been reported to be more effective than placebo when used with the antihistamine desloratadine in the treatment of delayed pressure urticaria.[2]

1. McBayne TO, Siddall OM. Montelukast treatment of urticaria. *Ann Pharmacother* 2006; **40:** 939–42.
2. Nettis E, *et al*. Desloratadine in combination with montelukast suppresses the dermagraphometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **155:** 1279–82.

Adverse Effects and Precautions

As for Zafirlukast, p. 1240.1.

Additionally, palpitations and seizures have been reported with montelukast use. In children, eczema and infections such as varicella, gastroenteritis, and upper respiratory-tract infections have occurred.

Churg-Strauss syndrome. For discussion of the possible role of leukotriene antagonists in Churg-Strauss syndrome see under Zafirlukast, p. 1240.2.

Effects on the CNS. For information on the CNS adverse effects associated with use of anti-leukotrienes, see under Zafirlukast, p. 1240.2.

Hepatic impairment. Although there is evidence of effects on the liver in patients receiving montelukast, and although it is largely eliminated by hepatic metabolism, montelukast (unlike zafirlukast) is not considered by licensed product information to be contra-indicated in hepatic impairment, and no dose adjustment is considered necessary in mild to moderate hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies montelukast as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Licensed product information recommends caution when potent inducers of cytochrome P450 isoenzymes, such as phenytoin, phenobarbital, or rifampicin are given with montelukast.

Corticosteroids. For a report of peripheral oedema in a patient given montelukast and *prednisone*, see Leukotriene Antagonists, p. 1620.2.

Phenobarbital. Peak serum concentrations after a single dose of montelukast 10 mg were reduced by 20% in 14 healthy subjects who took phenobarbital 100 mg daily for 14 days, and area under the serum concentration-time curve was reduced by 38%. However, it was not thought that montelukast doses would need adjustment if given with phenobarbital.[1]

1. Holland S, *et al.* Metabolism of montelukast (M) is increased by multiple doses of phenobarbital (P). *Clin Pharmacol Ther* 1998; **63:** 231.

Pharmacokinetics

Peak plasma concentrations of montelukast occur 2 to 4 hours after oral doses. The mean oral bioavailability is about 64 to 73%. Montelukast is more than 99% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes, mainly by CYP2C8 and to a lesser extent by CYP3A4 and CYP2C9. The plasma half-life ranges from 2.7 to 5.5 hours. Montelukast and its metabolites are excreted principally in the faeces via the bile.

References.

1. Knorr B, *et al.* Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999; **39:** 786–93.
2. Knorr B, *et al.* Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol* 1999; **41:** 612–19.
3. Migoya E, *et al.* Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol* 2004; **44:** 487–94.
4. Knorr B, *et al.* Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol* 2006; **46:** 620–7.
5. Kearns GL, *et al.* Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* 2008; **48:** 502–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Inspirol; Montrate; Rolast; Singulair; ***Austral.***: Singulair; ***Austria***: Singulair; ***Belg.***: Rhinosingulair; Singulair; ***Braz.***: Montelair; Singulair; ***Canad.***: Singulair; ***Chile***: Asventol; Brondilat; Montecross; Singulair; ***China***: Singulair (顺尔宁†); ***Cz.***: Brogalas; Castispir; Elukan; Eonic; Miralust; Monkasta; Monlucare; Montecon; Montel; Montelar; Monteratio; Montexal; Montulind; Singulair; Telumantes; ***Denm.***: Asthmont†; Elukan; Kemtelo; Kestilumar; Lukair; Metiprego; Miralust; Monspes†; Montegen; Montetrinas; Monthan; Montisartas; Montulind; Olekast†; Otelus†; Singulair; ***Fin.***: Airathon; Astecon; Singulair; ***Fr.***: Singulair; ***Ger.***: Montelubronch; Singulair; ***Gr.***: Montast; Pneumo-Kast; Singulair; Telukast; ***Hong Kong***: Singulair; ***Hung.***: Singulair; ***India***: Airway; Astham; Breathezy; Emlucast; Kast; MK; Molly; Montair; Montal; Montasma; Montek; Montelast; Monti; Odimont; ***Irl.***: Molat; Montelair; Singulair; ***Israel***: Singulair; Take Air; ***Ital.***: Asthmont; Kemtelo; Lukasm; Mintalos; Monstonol; Montegen; Monthan; Moolpas; Otelus; Singulair; Xigenast; ***Jpn***: Kipres; ***Malaysia***: Singulair; ***Mex.***: Singulair; ***Neth.***: Airathon; Kastlutemon; Lukastang; Montefranc; Monthan; Singulair; Spirokast; ***Norw.***: Singulair; ***NZ***: Singulair; ***Philipp.***: Brecare; Kastair; Kastorion; Leukast; Montair; Montecad; Montekast; Montemax; Montiget; Singulair; ***Pol.***: Airathon; Asmenol; Astmirex; Drimon; Eonic; Hardic; Milukante; Monkasta; Montelak; Montenorm; Montessan; Montest; Promonta; Singulair; Symlukast; Vizendo; ***Port.***: Deprivet†; Dilocea; Lukair; Singulair; Singulergy; Synglarin†; ***Rus.***: Monkasta (Монкаста); Singulair (Сингуляр); ***S.Afr.***: Lumont; Singulair; Sintrine; Topraz; ***Singapore***: Singulair; ***Spain***: Monkasta; Pluralais; Singulair; ***Swed.***: Singulair; ***Switz.***: Lukair; Singulair; ***Thai.***: Montek; Singulair; ***Turk.***: Airlast; Clast; Luxat; Monax; N-Fess; Notta; Onceair; Respair; Singulair; Zespira; ***UK***: Singulair; ***Ukr.***: Lucast (Лукаст); Milukant (Милукант); Montel (Монтел); Singlon (Синглон); Singulair (Сингуляр); ***USA***: Singulair; ***Venez.***: Airon; Inuvic; Monukast; Singulair.

Multi-ingredient Preparations. ***India***: Airway-L; Alnacet-M; Arokast; Breathezy-L; Dilevocet-M; Folcet-MT; Hiskast; Kurecet-M; L-Montus; Largy-M; Lazine-M; LCRal Plus; Le-Zyncet-M; Lemont-LC; Lepit-MK; Leverest-MK; Levocet-M; Levoclic-M; Levoriz-MK; Levotin Plus; Levotra-M; Levotrin-M; Levoz-M; Levzed-MK; Luka; Luzei-M; Luzer-M; Lycit-M; M-Kast-L; Molly-Plus; Moncet; Mondeo-LC; Mondeslor; Montair Plus; Montair-LC; Montasma Plus; Montbre; Montegen-L; Montek-LC; Montilife; Montlu-L; Montral; Monty; Monway Plus; Mosha-L; Mucopen; Nislevo-MK; Noal-LM; Nukast; Odimont Plus; Okasma; Ontelio-L; ***Philipp.***: Co-Altria; Zykast.

Nedocromil Sodium *(BANM, USAN, rINNM)*

FPL-59002 (nedocromil); FPL-59002KC (nedocromil calcium); FPL-59002KP (nedocromil sodium); Natrii Nedocromilum; Nédocromil Sodique; Nedocromilo sódico; Nedocromilum Natricum; Nedokromiilinatrium; Nedokromil Sodyum; Nedokromilnatrium; Натрий Недокромил.

Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate.

$C_{19}H_{15}NNa_2O_7$=415.3

CAS — 69049-73-6 (nedocromil); 69049-74-7 (nedocromil sodium); 101626-68-0 (nedocromil calcium).

ATC — R01AC07; R03BC03; S01GX04.

ATC Vet — QR01AC07; QR03BC03; QS01GX04.

UNII — ET8IF4KS1T.

NOTE. Nedocromil Calcium is also *USAN*.

Uses and Administration

Nedocromil sodium has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1226.1) and is used similarly in the management of chronic asthma. It should not be used to treat an acute attack of asthma.

For **asthma**, nedocromil sodium is inhaled from a metered-dose aerosol. The usual dose for adults and children from 6 years of age is 4 mg inhaled four times daily which may be decreased to 4 mg twice daily after control of symptoms is achieved. Clinical improvement may not be obtained for 1 week or longer after beginning therapy.

Nedocromil sodium is also used topically in the treatment of **allergic conjunctivitis** and allergic **rhinitis**. For seasonal and perennial allergic conjunctivitis it is given as a 2% solution, instilled into each eye twice daily. This may be increased to 4 times daily if necessary, which is the usual dose in vernal keratoconjunctivitis. In seasonal allergic conjunctivitis, treatment is usually given for no more than 12 weeks. In allergic rhinitis nedocromil sodium is used as a 1% nasal spray: one spray is given into each nostril 2 to 4 times daily for up to 8 weeks. For details of doses in children, see Administration in Children, below.

General references.

1. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993; **45:** 693–715.
2. Parish RC, Miller LJ. Nedocromil sodium. *Ann Pharmacother* 1993; **27:** 599–606.

Administration in children. Nedocromil sodium is given by metered-dose aerosol inhalation in the management of asthma in children from 6 years of age at the adult dose, see above. Although unlicensed in the UK for younger children, the *BNFC* recommends the same dose from 5 years of age.

Similarly, for the topical treatment of seasonal allergic conjunctivitis and vernal keratoconjunctivitis, the adult dose may be given to children from 6 years of age, see above. Treatment of perennial allergic conjunctivitis with nedocromil sodium is not licensed in children in the UK, but the *BNFC* recommends adult doses from 6 years of age.

Asthma. Nedocromil sodium is generally considered to be an alternative to sodium cromoglicate in the management of asthma (p. 1195.2). Nedocromil has been shown to improve symptoms and reduce bronchodilator intake in adults[1] and children[2] with chronic asthma. However, a systematic review[3] of nedocromil for chronic asthma in children subsequently found that although a number of small studies have shown that nedocromil improves airflow limitation, reduces symptoms, and reduces bronchial hyperresponsiveness, this has not been confirmed in a larger long-term study of children with milder asthma. Its place in relation to other asthma therapies for children is also unclear. It may be used before exercise to reduce exercise-induced bronchoconstriction,[4] and appears to be as effective as sodium cromoglicate for this indication.[5]

1. Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. *Eur Respir J* 1993; **6:** 35–41.
2. Armenio L, *et al.* Double blind, placebo controlled study of nedocromil sodium in asthma. *Arch Dis Child* 1993; **68:** 193–7.
3. Sridhar AV, McKean M. Nedocromil sodium for chronic asthma in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/04/08).
4. Spooner CH, *et al.* Nedocromil sodium for preventing exercise-induced bronchoconstriction. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 14/04/08).
5. Kelly KD, *et al.* Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconstriction. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 14/04/08).

Cough. For references indicating a positive response to sodium cromoglicate but not to nedocromil sodium in the management of cough induced by ACE inhibitor therapy, see Cough, p. 1226.3.

Rhinitis and conjunctivitis. Nedocromil has been used in the management of allergic rhinitis (p. 612.1) and conjunctivitis (p. 611.1). In the management of seasonal allergic rhinitis, there is some evidence that prophylactic mometasone furoate (p. 1644.1) reduces symptoms more effectively than nedocromil.[1] In vernal keratoconjunctivitis nedocromil may be more effective than cromoglicate (see p. 1227.1), but is less effective than fluorometholone.[2]

1. Pitsios C, *et al.* Efficacy and safety of mometasone furoate vs nedocromil sodium as prophylactic treatment for moderate/severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006; **96:** 673–8.
2. Tabbara KF, Al-Kharashi SA. Efficacy of nedocromil 2% versus fluorometholone 0.1%: a randomised, double masked trial comparing the effects on severe vernal keratoconjunctivitis. *Br J Ophthalmol* 1999; **83:** 180–4.

Adverse Effects and Precautions

Inhaled nedocromil sodium may cause headache, gastrointestinal disturbances (nausea, vomiting, dyspepsia, and abdominal discomfort). An unusual or unpleasant taste is reported rarely. Paradoxical bronchospasm may occur. Eye drops may cause transient burning and stinging.

It should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (see p. 1227.2) also apply.

Incidence of adverse effects. A review[1] of nedocromil sodium noted that adverse effects were infrequent, mild, and short-lived. The most common effect appeared to be an unpleasant or bitter taste, which occurred in 12 to 13% of patients, although less than 1% of patients stopped treatment because of it. Other adverse effects included cough (in 7%), headache (6%), sore throat (5.7%), nausea (4%), and vomiting (1.7%).

1. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993; **45:** 693–715.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nedocromil as not porphyrinogenic when used ophthalmically; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11) NC for intranasal use and for obstructive airway diseases.

Pregnancy. For discussion of the safety of nedocromil when used during pregnancy, see Sodium Cromoglicate, p. 1227.2.

Pharmacokinetics

Nedocromil sodium is poorly absorbed from the gastrointestinal tract; about 10% of the inhaled dose is absorbed from the lungs. Absorption is also poor after topical ophthalmic use, and occurs mainly through the nasal mucosa. Nedocromil sodium is excreted unchanged in the urine and faeces. The half-life is stated to range from about 1 to 3.3 hours.

The extent of absorption or bioavailability of nedocromil sodium after inhalation in healthy subjects was 7 to 9% of the dose, including 2 to 3% oral absorption and 5 to 6% absorption from the respiratory tract.[1] After inhalation of nedocromil sodium 4 mg the mean peak plasma concentration was 3.3 nanograms/mL in healthy subjects and 2.8 nanograms/mL in asthmatic patients, after about 20 and 40 minutes respectively. The mean total urinary excretion 24 hours after a single dose was 5.4% of the dose in healthy subjects and 2.3% in asthmatics.

1. Neale MG, *et al.* The pharmacokinetics of nedocromil sodium, a new drug for the treatment of reversible obstructive airways disease, in human volunteers and patients with reversible obstructive airways disease. *Br J Clin Pharmacol* 1987; **24:** 493–501.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tilade; ***Austria***: Tilade; Tilarin†; Tilavist; ***Braz.***: Tilade; ***Canad.***: Alocril; ***Cz.***: Tilade; ***Denm.***: Tilade†; Tilavist; ***Fin.***: Tilade; ***Fr.***: Tilavist; ***Ger.***: Irtan; ***Gr.***: Tilade; ***Irl.***: Tilade; ***Israel***: Tilavist; ***Ital.***: Kovilen; Kovinal; Tilade; Tilarin; Tilavist; ***Mex.***: Irtan; ***Neth.***: Tilade; Tilavist; ***Norw.***: Tilavist; ***NZ***: Tilade; ***Port.***: Tilavist; ***Rus.***: Tilade (Тайлед); ***Singapore***: Tilade; ***Spain***: Tilad; Tilavist; ***Swed.***: Tilavist; ***Switz.***: Tilavist†; ***Turk.***: Tilade†; ***UK***: Rapitil; Tilade; ***USA***: Alocril.

Omalizumab *(BAN, USAN, rINN)*

CGP-51901; E-25; IGE-025; Olizumab; Omalizumabum; rhuMAb-E25; Омализумаб.

Immunoglobulin G, anti-(human immunoglobulin E Fc region)(human-mouse monoclonal E25 clone pSVIE26 γ-chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 κ-chain, dimer.

CAS — 242138-07-4.

ATC — R03DX05.

ATC Vet — QR03DX05.
UNII — 2P471X1Z11.

Uses and Administration

Omalizumab is a recombinant humanised monoclonal antibody that selectively binds to IgE. It inhibits the binding of IgE to mast cells and basophils, thus reducing the release of mediators of the allergic response. Omalizumab is used in the prophylactic management of moderate to severe, persistent allergic asthma (p. 1195.2). The dose depends on the patient's weight and pre-treatment serum-IgE concentrations; in the UK, dosage regimens range from 225 to 600 mg given every 2 weeks or 75 to 600 mg every 4 weeks, whereas in the USA regimens range from 225 to 375 mg every 2 weeks or 150 to 300 mg every 4 weeks. Omalizumab is given by subcutaneous injection, and not more than 150 mg should be given at one injection site. Total IgE concentrations rise during treatment (see Pharmacokinetics, below), remaining elevated for up to 1 year after withdrawal, and cannot be used to determine continued dosage. Dose determination after treatment interruptions lasting up to 1 year should be based on pre-treatment serum-IgE concentrations.

Omalizumab is under investigation in the prophylactic management of seasonal allergic rhinitis.

References.

1. Ådelroth E, *et al.* Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; **106:** 253–9.
2. Easthope S, Jarvis B. Omalizumab. *Drugs* 2001; **61:** 253–60.
3. Casale TB, *et al.* Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; **286:** 2956–67.
4. Chervinsky P, *et al.* Omalizumab, an anti-IgE antibody, in treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **91:** 160–7.
5. Hanf G, *et al.* Omalizumab inhibits allergen challenge-induced nasal response. *Eur Respir J* 2004; **23:** 414–18.
6. Vignola AM, *et al.* Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; **59:** 709–17.
7. Ben-Shoshan M. Omalizumab: not only for asthma. *Recent Pat Inflamm Allergy Drug Discov* 2008; **2:** 191–201.
8. Morjaria JB, Polosa R. Off-label use of omalizumab in non-asthma conditions: new opportunities. *Expert Rev Respir Med* 2009; **3:** 299–308.

Administration in children. Omalizumab is used for the prophylactic management of severe persistent allergic asthma in children from 6 years of age. The dose depends on the child's weight and pre-treatment serum-IgE concentrations; dose ranges are the same as those in adults, see above.

Aspergillosis. Successful treatment of allergic bronchopulmonary aspergillosis with omalizumab has been reported in children with cystic fibrosis.[1,2] In one such report,[1] repeated improvement in symptoms and normalisation in lung function within 2 to 4 hours of giving omalizumab led to complete withdrawal of corticosteroid treatment in a 12 year old girl. Others[2] have reported similar benefits.

1. van der Ent CK, *et al.* Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax* 2007; **62:** 276–7.
2. Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. *Pediatr Pulmonol* 2008; **43:** 607–10.

Asthma. Omalizumab may be used for the treatment of severe persistent allergic (IgE mediated) asthma as an add-on therapy to optimised standard therapy in adults (see Asthma, p. 1195.2). It has been shown to reduce exacerbations and corticosteroid requirement compared with placebo in adults with moderate-to-severe allergic asthma.[1] It also reduced exacerbation rates in patients with inadequately controlled, severe persistent asthma,[2] and is considered to be an effective therapy in difficult-to-treat, high-risk adult patients.[3,4]

A systematic review[5] of omalizumab therapy for chronic asthma found that omalizumab was more effective than placebo at reducing exacerbations and improving quality of life. Although omalizumab had an *inhaled*-corticosteroid-sparing effect, the clinical significance of the magnitude of reduction remains open to interpretation, and other factors such as cost-effectiveness and comparative efficacy compared with other add-on therapy should be considered. In patients on *oral* corticosteroids, no significant impact was seen on either exacerbations or oral corticosteroid dose.

Omalizumab has been investigated in the treatment of childhood asthma with encouraging results.[6,7]

1. Solèr M, *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; **18:** 254–61.
2. Humbert M, *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; **60:** 309–16.
3. Hendeles L, Sorkness CA. Anti-immunoglobulin E therapy with omalizumab for asthma. *Ann Pharmacother* 2007; **41:** 1397–1410.
4. Price D. The use of omalizumab in asthma. *Prim Care Respir J* 2008; **17:** 62–72.
5. Walker S, *et al.* Anti-IgE for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
6. Berger W, *et al.* Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003; **91:** 182–8.
7. Milgrom H, *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; **108:** E36. Full version: http://pediatrics.aappublications.org/cgi/reprint/108/2/e36.pdf (accessed 14/04/08)

Churg-Strauss syndrome. A response to omalizumab has been reported[1] in 2 refractory cases of Churg-Strauss syndrome (p. 1603.1) which had previously been masked by corticosteroid therapy. However, Churg-Strauss syndrome has also been reported as an adverse effect of omalizumab (see below).

1. Pabst S, *et al.* Apparent response to anti-IgE therapy in two patients with refractory "forme fruste" of Churg-Strauss syndrome. *Thorax* 2008; **63:** 747–8.

Adverse Effects and Precautions

Injection site reactions are common with the use of omalizumab. Other adverse effects that have been reported include generalised pain, fatigue, arthralgia, myalgia, dizziness, earache, gastrointestinal disturbances, headache, fractures, pruritus, dermatitis, and alopecia. An increased incidence of parasitic infection has been reported in patients at high risk for helminthic infections. Viral infections, upper respiratory-tract infections, sinusitis, pharyngitis, and flu-like illness can also occur. Systemic eosinophilia such as Churg-Strauss syndrome has also been reported.

Potentially life-threatening anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, cough, or chest tightness has been seen after omalizumab treatment. Anaphylactic reactions may occur up to 4 days after a dose, and as early as the first dose or more than 1 year after beginning regular treatment. Serum sickness reactions have also been reported rarely with omalizumab use; symptoms usually appear 1 to 5 days after an injection and include arthritis or arthralgia, rash, urticaria, fever, and lymphadenopathy.

Severe thrombocytopenia has been reported with use of omalizumab.

Licensed product information notes an increased incidence of malignancies in patients given omalizumab.

In children, pyrexia and upper abdominal pain are commonly reported after omalizumab treatment.

Omalizumab should not be used for the treatment of acute asthma attacks, and inhaled corticosteroids should not be abruptly withdrawn on starting omalizumab therapy.

References.

1. Deniz YM, Gupta N. Safety and tolerability of omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody. *Clin Rev Allergy Immunol* 2005; **29:** 31–48.
2. Limb SL, *et al.* Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007; **120:** 1378–81. Correction. *ibid.* 2008; **121:** 178.
3. Cox L, *et al.* American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007; **120:** 1373–7.
4. Corren J, *et al.* Safety and tolerability of omalizumab. *Clin Exp Allergy* 2009; **39:** 788–97.

Effects on the cardiovascular system. Interim findings from a study to assess the long-term safety of omalizumab have suggested a disproportionate increase in cardiovascular and cerebrovascular problems among patients treated with omalizumab compared with an untreated control group. Reported problems included cardiomyopathy, myocardial infarction, arrhythmias, heart failure, syncope, transient ischaemic attacks, pulmonary hypertension, and thrombosis. Further data are required before a causal relationship can be ascertained; regulatory bodies in both Canada and the USA are carrying out reviews.[1,2]

1. Health Canada. Health Canada reviewing possible association of asthma drug Xolair (omalizumab) with increased risk of cardiovascular problems (issued 13th August 2009). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_129-eng.php (accessed 16/03/10)
2. FDA. Omalizumab (marketed as Xolair) - early communication about an ongoing safety review (issued 16th July 2009). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172406.htm (accessed 16/03/10)

Effects on the cerebrovascular system. For a possible association between omalizumab treatment and an increase in cerebrovascular adverse effects, see above.

Pharmacokinetics

Omalizumab is absorbed after subcutaneous injection with a bioavailability of about 62%, reaching peak serum concentrations after 7 to 8 days. It is removed by IgG and IgE clearance processes in the liver, with a serum elimination half-life of about 26 days. During treatment with omalizumab, the serum concentration of free IgE decreases but that of total IgE increases because the omalizumab-IgE complex has a slower elimination rate than free IgE.

References.

1. Hayashi N, *et al.* A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007; **63:** 548–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Xolair; ***Austral.***: Xolair; ***Austria***: Xolair; ***Belg.***: Xolair; ***Braz.***: Xolair; ***Canad.***: Xolair; ***Chile***: Xolair; ***Cz.***: Xolair; ***Denm.***: Xolair; ***Fr.***: Xolair; ***Ger.***: Xolair; ***Gr.***: Xolair; ***Hong Kong***: Xolair; ***Hung.***: Xolair; ***Irl.***: Xolair; ***Israel***: Xolair; ***Ital.***: Xolair; ***Jpn***: Xolair; ***Malaysia***: Xolair; ***Neth.***: Xolair; ***Norw.***: Xolair; ***NZ***: Xolair; ***Philipp.***: Xolair; ***Pol.***: Xolair; ***Port.***: Xolair; ***Rus.***: Xolair (Ксолар); ***Singapore***: Xolair; ***Spain***: Xolair; ***Swed.***: Xolair; ***Switz.***: Xolair; ***Thai.***: Xolair; ***Turk.***: Xolair; ***UK***: Xolair; ***Ukr.***: Xolair (Ксолар); ***USA***: Xolair; ***Venez.***: Xolair.

Orciprenaline Sulfate *(BANM, rINNM)* ⊗

Metaproterenol Sulfate (USAN); Metaproterenol Sulphate; Orciprenalin sulfát; Orciprenalina, sulfato de; Orciprénaline, Sulfate d'; Orciprenaline Sulphate; Orciprenalini Sulfas; Orciprenalino sulfatas; Orciprenalinsulfat; Orciprenalin-szulfát; Orcyprenaliny siarczan; Orsiprenaliinisulfaatti; Orsiprenalin Sülfat; Sulfato de metaproterenol; Sulfato de orciprenalina; Th-152; Орципреналина Сульфат.

1-(3,5-Dihydroxyphenyl)-2-isopropylaminoethanol sulphate; *N*-Isopropyl-*N* (β,3,5-trihydroxyphenethyl)ammonium sulphate.

$(C_{11}H_{17}NO_3)_2,H_2SO_4$=520.6

CAS — 586-06-1 (orciprenaline); 5874-97-5 (orciprenaline sulfate).

ATC — R03AB03; R03CB03.

ATC Vet — QR03AB03; QR03CB03.

UNII — GJ20H50YF0.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Orciprenaline Sulfate). A white, slightly hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Metaproterenol Sulfate). A white to off-white crystalline powder. Freely soluble in water. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Uses and Administration

Orciprenaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity. It has actions and uses similar to those of salbutamol (p. 1220.2) but is less selective for beta$_2$ receptors.

Orciprenaline sulfate is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). However, more selective beta$_2$ agonists such as salbutamol or terbutaline are now preferred. On inhalation, the onset of action is usually within 30 minutes and can last from 1 to 5 hours.

Orciprenaline sulfate may be inhaled as a 0.4 or 0.6% *nebulised solution* from unit-dose vials containing 10 or 15 mg, respectively. For relief of acute **bronchospasm**, one vial is inhaled up to every 4 hours; in the management of chronic disease, one vial has been given 3 or 4 times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, orciprenaline indicates deterioration of asthma control and the need for review of therapy.

In the chronic management of reversible airways obstruction, orciprenaline sulfate has been given *orally* in a usual adult dose of 20 mg three or four times daily.

In acute bronchospasm orciprenaline sulfate has been given *parenterally*. A dose of 250 to 500 micrograms has been given by slow intravenous injection, or 5 to 10 micrograms/minute by intravenous infusion. Alternatively, an intramuscular or subcutaneous injection of 0.5 to 1 mg has been used.

Orciprenaline sulfate has also been used similarly to isoprenaline (see p. 1412.1) for its cardiovascular effects in the treatment of **bradycardia** of various types, notably in AV heart block and sinus bradycardia. In such cases oral doses of up to 240 mg daily in divided doses, have been used. For doses of orciprenaline used in children, see Administration in Children, below.

Administration in children. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use, and chronic treatment with orciprenaline would generally be regarded as inappropriate in children. Nonetheless, an oral preparation is licensed for such use in some countries; in the USA, children aged from 6 to 9 years may be given

orciprenaline sulfate 10 mg three or four times daily for reversible bronchospasm. Children aged over 9 years, or over about 25 kg, may be given adult doses, see p. 1217.3.

Asthma. Orciprenaline sulfate is considered less suitable for the relief of reversible airways obstruction than the selective beta$_2$ agonists. The UK MHRA considers that study data show substantial therapeutic advantages for salbutamol over orciprenaline with respect to improvements in pulmonary function, dosing frequency, and adverse effects.[1,2]

1. MHRA. MHRA public assessment report. Orciprenaline sulphate (Alupent): planned withdrawal from the UK market following a risk-benefit analysis (issued November 2009). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con062531.pd (accessed 17/03/10)
2. MHRA/CHM. Orciprenaline sulphate (Alupent): withdrawal due to unfavourable benefit-risk profile. *Drug Safety Update* 2009; **3** (4): 6. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON062549&RevisionSelectionMethod=LatestReleased (accessed 03/09/10)

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3 and p. 1222.3. Adverse effects are more common because of the non-selective beta agonist effect of orciprenaline, and in particular, tachycardia and palpitations can occur before maximum bronchodilatation. For the adverse effects and precautions pertaining to non-selective beta agonists see under Sympathomimetics, p. 1508.2 and p. 1508.3.

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

After oral doses orciprenaline is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver; about 40% of an oral dose is reported to reach the circulation unchanged. It is excreted in the urine mainly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Alupent†; ***Ger.***: Alupent; ***Gr.***: Alupent; ***India***: Alupent; ***Indon.***: Alupent; ***Irl.***: Alupent†; ***Ital.***: Alupent†; ***Jpn***: Alotec†; ***Mex.***: Alupent; ***Pol.***: Astmopent†; ***Rus.***: Astmopent (Астмопент)†; ***UK***: Alupent†; ***USA***: Alupent†.

Multi-ingredient Preparations. ***Chile***: Broncodual Compuesto; Cloval Compuesto; Pulbronc; Solvanol; Tusabron†; Vapoflu; ***Gr.***: Silomat Compositum; ***Indon.***: Silomat Compositum†; ***Irl.***: Alupent Expectorant†; ***Mex.***: Bisolpent Ex; ***Philipp.***: Bisolpent; ***S.Afr.***: Adco-Linctopent; Benylin Chesty; Bisolvon Linctus DA; Bronkese Compound; Flemeze; ***UAE***: Orcinol†.

Pharmacopoeial Preparations
BP 2014: Orciprenaline Tablets;
USP 36: Metaproterenol Sulfate Inhalation Aerosol; Metaproterenol Sulfate Inhalation Solution; Metaproterenol Sulfate Syrup; Metaproterenol Sulfate Tablets.

Oxitropium Bromide *(BAN, rINN)*

Ba-253; Bromuro de oxitropio; Oksitropiumbromidi; Oxitropii Bromidum; Oxitropio, bromuro de; Oxitropium, Bromure d'; Oxitropiumbromid; Окситропия Бромид.
6,7-Epoxy-8-ethyl-3-[(*S*)-tropoyloxy]tropanium bromide; (3*s*,6*R*,7*S*,8*r*)-8-Ethyl-3-[(*S*)-tropoyloxy]-6,7-epoxytropanium bromide.
$C_{19}H_{26}BrNO_4$=412.3
CAS — 30286-75-0.
ATC — R03BB02.
ATC Vet — QR03BB02.
UNII — SF4NW7NH7C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oxitropium Bromide). A white or almost white, crystalline powder. It exhibits polymorphism. Very soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol; practically insoluble in dichloromethane.

Profile

Oxitropium bromide is a quaternary ammonium antimuscarinic with actions similar to those of ipratropium bromide (p. 1211.3), to which it is structurally related. It is used as a bronchodilator in the treatment of reversible airways obstruction, as in asthma (p. 1195.2) and chronic obstructive pulmonary disease (p. 1199.1). Doses of 100 or 200 micrograms by inhalation from a metered-dose aerosol have been given 2 or 3 times daily. Oxitropium bromide may also be given as a nebulised solution in doses of 1.5 mg inhaled 2 or 3 times daily. *Animal* studies have shown reproductive toxicity with high doses of oxitropium, hence the recommendation that it should not be used during pregnancy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Oxivent; ***Ital.***: Oxivent; ***Jpn***: Tersigan.

Pemirolast Potassium *(USAN, rINNM)*

BL-5617; BMY-26517; Kalii Pemirolastum; Pemirolast potásico; Pémirolast Potassique; Калия Пемироласт.
Potassium 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.
$C_{10}H_7KN_6O$=266.3
CAS — 69372-19-6 (pemirolast); 100299-08-9 (pemirolast potassium).
UNII — 497A17OUUE.

Profile

Pemirolast potassium has mast cell stabilising properties like sodium cromoglicate (p. 1225.3) and may also be a leukotriene inhibitor. It has been used in the treatment of chronic asthma (p. 1195.2) and in the prophylaxis of allergic rhinitis (p. 612.1) and conjunctivitis (p. 611.1). Pemirolast potassium has no bronchodilator properties and should not be used for the treatment of acute asthma attacks.

For asthma, the usual dose is 10 mg orally twice daily after food. For allergic rhinitis the dose is halved. Pemirolast potassium 0.1% eye drops are instilled 4 times daily in the prophylactic management of allergic conjunctivitis. For details of doses in children, see below.

Pemirolast has also been investigated for the prevention of restenosis after coronary artery stent placement.

References.
1. Hasegawa T, *et al.* Kinetic interaction between theophylline and a newly developed anti-allergic drug, pemirolast potassium. *Eur J Clin Pharmacol* 1994; **46:** 55–8.
2. Anonymous. New drugs for allergic conjunctivitis. *Med Lett Drugs Ther* 2000; **42:** 39–40.
3. Abelson MB, *et al.* Pemirolast potassium 0.1% ophthalmic solution is an effective treatment for allergic conjunctivitis: a pooled analysis of two prospective, randomized, double-masked, placebo-controlled, phase III studies. *J Ocul Pharmacol Ther* 2002; **18:** 475–88.
4. Shulman DG. Two mast cell stabilizers, pemirolast potassium 0.1% and nedocromil sodium 2%, in the treatment of seasonal allergic conjunctivitis: a comparative study. *Adv Therapy* 2003; **20:** 31–40.
5. Ohsawa H, *et al.* Preventive effect of an antiallergic drug, pemirolast potassium, on restenosis after stent placement: quantitative coronary angiography and intravascular ultrasound studies. *J Cardiol* 2003; **42:** 13–22.
6. Gous P, Ropo A. A comparative trial of the safety and efficacy of 0.1 percent pemirolast potassium ophthalmic solution dosed twice or four times a day in patients with seasonal allergic conjunctivitis. *J Ocul Pharmacol Ther* 2004; **20:** 139–50.
7. Yahata H, *et al.* Prophylactic effect of pemirolast, an antiallergic agent, against hypersensitivity reactions to paclitaxel in patients with ovarian cancer. *Int J Cancer* 2006; **118:** 2636–8.

Administration in children. Pemirolast potassium may be used in the management of asthma in children in the following oral doses:
- 1 to 4 years: 2.5 mg twice daily after food
- 5 to 10 years: 5 mg twice daily after food
- 11 years and above: use adult doses, see above

For allergic rhinitis, the above doses are halved.

Pemirolast potassium 0.1% eye drops can be used four times daily in children over 3 years with allergic conjunctivitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ai Xin Yi Le (艾欣益乐); Alegysal (研立双); Min Si Tong (珉思通); Ni Er Ping (尼尔平); PuLiMin (普利敏); Ze Er Sheng (泽而生); ***Hong Kong***: Pemirox; ***Indon.***: Alegysal; ***Jpn***: Alegysal; ***Philipp.***: Alegysal; ***Thai.***: Pemirox; ***USA***: Alamast.

Pirbuterol *(BAN, rINN)* ⊗

Pirbutérol; Pirbuteroli; Pirbuterolum; Pyrbuterol; Пирбутерол.
2-*tert*-Butylamino-1-(5-hydroxy-6-hydroxymethyl-2-pyridyl) ethanol.
$C_{12}H_{20}N_2O_3$=240.3
CAS — 38677-81-5.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.
UNII — OG645J8RVW.

Pirbuterol Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de pirbuterol; CP-24314-14; Pirbutérol, Acétate de; Pirbuterol, acetato de; Pirbuteroli Acetas; Pyrbuterol Acetate; Пирбутерола Ацетат.
$C_{12}H_{20}N_2O_3,C_2H_4O_2$=300.4
CAS — 65652-44-0.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.
UNII — 1EH73XKR9N.

Pirbuterol Hydrochloride

(BANM, USAN, rINNM) ⊗

CP-24314-1; Hidrocloruro de pirbuterol; Pirbutérol, Chlorhydrate de; Pirbuterol, hidrocloruro de; Pirbuteroli Hydrochloridum; Pyrbuterol Hydrochloride; Пирбутерола Гидрохлорид.
$C_{12}H_{20}N_2O_3,2HCl$=313.2
CAS — 38029-10-6.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.
UNII — J6793T658K.

Profile

Pirbuterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2).

Pirbuterol is used for its bronchodilating properties. It is given as the acetate in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). On inhalation, pirbuterol exerts an effect within 10 minutes, which is reported to last at least 5 hours.

Pirbuterol is given by inhalation as the acetate but doses are expressed in terms of the base: pirbuterol acetate 250 micrograms is equivalent to about 200 micrograms of pirbuterol. It is given via a metered-dose aerosol in a usual dose equivalent to pirbuterol 200 to 400 micrograms (1 to 2 inhalations) as required but not more often than every four hours. A total daily dose of 2.4 mg (12 inhalations) should not be exceeded. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, pirbuterol indicates deterioration of asthma control and the need for review of therapy.

Pirbuterol has also been given orally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Maxair†; ***USA***: Maxair.

Pitrakinra *(rINN)*

AER-001; Bay-16-9996; Pitrakinrum; Питракинра.
L-Methionyl-[121-aspartic acid,124-aspartic acid]interleukin-4.

NOTE. The name Aerovant has been used as a trade mark for pitrakinra.

Profile

Pitrakinra is a dual interleukin-4 and -13 receptor antagonist that is under investigation in the treatment of asthma.

References.
1. Wenzel S, *et al.* Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet* 2007; **370:** 1422–31.
2. Burmeister Getz E, *et al.* Human pharmacokinetics/pharmacodynamics of an interleukin-4 and interleukin-13 dual antagonist in asthma. *J Clin Pharmacol* 2009; **49:** 1025–36.

Pranlukast *(BAN, rINN)*

ONO-1078; Pranlukastum; Пранлукаст.
N-[4-Oxo-2-(1*H*-tetrazol-5-yl)-4*H*-1-benzopyran-8-yl]-*p*-(4-phenylbutoxy)benzamide.
$C_{27}H_{23}N_5O_4$=481.5
CAS — 103177-37-3.
ATC — R03DC02.
ATC Vet — QR03DC02.
UNII — TB8Z891092.

Profile

Pranlukast is a selective antagonist of the leukotriene C_4, D_4, and E_4 receptors with similar properties to zafirlukast (p. 1239.3). It is used in the management of asthma

(p. 1195.2) and allergic rhinitis (p. 612.1), at a usual oral dose of pranlukast hydrate 225 mg twice daily.

For details of doses in children, see below.

References.
1. Tamaoki J, *et al.* Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. *Am J Respir Crit Care Med* 1997; **155:** 1235–40.
2. Barnes NC, *et al.* Pranlukast, a novel leukotriene receptor antagonist: results of the first European, placebo-controlled, multicentre clinical study in asthma. *Thorax* 1997; **52:** 523–7.
3. Grossman J, *et al.* Results of the first US double-blind, placebo-controlled, multicenter clinical study in asthma with pranlukast, a novel leukotriene receptor antagonist. *J Asthma* 1997; **34:** 321–8.
4. Keam SJ, *et al.* Pranlukast: a review of its use in the management of asthma. *Drugs* 2003; **63:** 991–1019.
5. Niitsuma T, *et al.* Clinical evaluation of response to long-term treatment with Pranlukast in patients with bronchial asthma. *J Investig Allergol Clin Immunol* 2004; **14:** 284–91.
6. Horiguchi T, *et al.* Comparative evaluation of the leukotriene receptor antagonist pranlukast versus the steroid inhalant fluticasone in the therapy of aged patients with mild bronchial asthma. *Arzneimittelforschung* 2007; **57:** 87–91.
7. Asano K, *et al.* Impact of pharmacokinetics and pharmacogenetics on the efficacy of pranlukast in Japanese asthmatics. *Respirology* 2009; **14:** 822–7.

Administration in children. Children with asthma may be given 3.5 mg/kg of pranlukast hydrate orally twice daily. The maximum daily dose is 10 mg/kg, not to exceed the usual adult daily dose of 450 mg (see p. 1218.3).

Churg-Strauss syndrome. For discussion of the potential causative role of leukotriene antagonists in Churg-Strauss syndrome, see under Zafirlukast, p. 1240.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Onon; ***Mex.***: Azlaire; ***Venez.***: Azlaire.

Procaterol Hydrochloride

(BANM, USAN, rINNM) ⊗

CI-888; Hidrocloruro de procaterol; OPC-2009; Procatérol, Chlorhydrate de; Procaterol, hidrocloruro de; Procateroli Hydrochloridum; Prokaterolhydroklorid; Prokaterolihydroklorid; Прокатерола Гидрохлорид.

(±)-*erythro*-8-Hydroxy-5-(1-hydroxy-2-isopropylaminobutyl) quinolin-2(1*H*)-one hydrochloride; (±)-8-Hydroxy-5-[(1*R**,2*S**)-1-hydroxy-2-isopropylaminobutyl]-2-quinolone hydrochloride.

$C_{16}H_{22}N_2O_3$,HCl=326.8

CAS — 72332-33-3 (procaterol); 59828-07-8 (procaterol hydrochloride).

ATC — R03AC16; R03CC08.

ATC Vet — QR03AC16; QR03CC08.

UNII — 4VD1BRT7T8.

NOTE. Commercial procaterol hydrochloride is the hemihydrate ($C_{16}H_{22}N_2O_3$,HCl,½H_2O = 335.8).

Pharmacopoeias. *Chin.* and *Jpn* include the hemihydrate.

Profile

Procaterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity selective to beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2) and it is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) or in some patients with chronic obstructive pulmonary disease (p. 1199.1). On inhalation it produces an effect within 5 minutes and the effect can last up to 8 hours.

To relieve acute bronchospasm, a usual dose of 20 micrograms of procaterol hydrochloride is given by inhalation from a metered-dose aerosol or dry powder inhaler up to 4 times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, procaterol indicates deterioration of asthma control and the need for review of therapy. An inhalation solution containing 100 micrograms/mL has been given via a nebuliser in usual doses of 30 to 50 micrograms. Procaterol hydrochloride can also be given orally in doses of 50 micrograms once or twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bai Da Tu (佰达图); Chuan Di (川迪); Meptin (美普清); Xi Si Ning (希思宁); ***Cz.***: Lontermin; ***Hong Kong***: Meptin; ***Indon.***: Ataroc; Meptin; Vactiv; ***Jpn***: Meptin; ***Malaysia***: Meptin; ***Philipp.***: Meptin; ***Port.***: Onsudil; ***Singapore***: Meptin; ***Thai.***: Caterol; Meptin.

Proxyphylline

(BAN, rINN)

Proksifilinas; Proksifylliini; Proxifilina; Proxifillin; Proxifyllin; Proxyfylin; Proxyphyllin; Proxyphyllinum; Проксифиллин.

7-(2-Hydroxypropyl)-1,3-dimethylxanthine; (*RS*)-1,3-Dimethyl-7-(2-hydroxypropyl)purine-2,6(3*H*,1*H*)-dione; 7-(2-Hydroxypropyl)theophylline.

$C_{10}H_{14}N_4O_3$=238.2

CAS — 603-00-9.

ATC — R03DA03.

ATC Vet — QR03DA03.

UNII — 13G1DMN4P0.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Proxyphylline). A white or almost white, crystalline powder. Very soluble in water; soluble in alcohol. Protect from light.

Profile

Proxyphylline is a derivative of theophylline (p. 1229.3) which is used as a bronchodilator and for its cardiovascular properties. Proxyphylline is readily absorbed from the gastrointestinal tract and it is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Santussal; ***Ger.***: Antihypertonicum S; ***Mex.***: Gadital.

Repirinast

(USAN, rINN)

MY-5116; Répirinast; Repirinastum; Репиринаст.

Isopentyl 5,6-dihydro-7,8-dimethyl-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-2-carboxylate.

$C_{20}H_{21}NO_5$=355.4

CAS — 73080-51-0.

UNII — 4K8KA8B61G.

Profile

Repirinast is an orally active anti-allergic with a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1225.3). It has been given orally in the management of asthma (p. 1195.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Romet.

Reproterol Hydrochloride

(BANM, USAN, rINNM) ⊗

D-1959 (reproterol); Hidrocloruro de reproterol; Réprotérol, Chlorhydrate de; Reproterol, hidrocloruro de; Reproteroli Hydrochloridum; W-2946M; Репротерола Гидрохлорид.

7-{3-[(3,5,β-Trihydroxyphenethyl)amino]propyl}theophylline hydrochloride.

$C_{18}H_{23}N_3O_5$,HCl=425.9

CAS — 54063-54-6 (reproterol); 13055-82-8 (reproterol hydrochloride).

ATC — R03AC15; R03CC14.

ATC Vet — QR03AC15; QR03CC14.

UNII — Y4I1COJ8W8.

Profile

Reproterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2).

Reproterol hydrochloride is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1).

For the relief of bronchospasm, reproterol is given with sodium cromoglicate via a metered-dose aerosol, in a usual dose of 2 inhalations of reproterol hydrochloride 500 micrograms four times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, reproterol indicates deterioration of asthma control and the need for review of therapy. A slow intravenous injection of reproterol hydrochloride 90 micrograms, repeated after 10 minutes if necessary, has been used in the treatment of status asthmaticus. Reproterol has also been given orally.

Administration in children. For the relief of bronchospasm in children, reproterol hydrochloride is given with sodium cromoglicate via a metered-dose aerosol at the same dose used in adults (see above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Bronchospasmin; ***Gr.***: Bronchospasmin.

Multi-ingredient Preparations. ***Ger.***: Aarane N; Allergospasmin.

Roflumilast

(USAN, rINN)

APTA-2217; B-9302-107; BY-217; BYK-20869; Roflumilastum; Рофлумиласт.

3-(Cyclopropylmethoxy)-*N*-(3,5-dichloro-4-pyridyl)-4-(difluoromethoxy)benzamide.

$C_{17}H_{14}Cl_2F_2N_2O_3$=403.2

CAS — 162401-32-3.

ATC — R03DX07.

ATC Vet — QR03DX07.

UNII — 0P6C6ZOP5U.

Uses and Administration

Roflumilast is a phosphodiesterase type-4 inhibitor that is used for maintenance treatment of severe chronic obstructive pulmonary disease as an adjunct to bronchodilators. An oral dose of 500 micrograms is taken once daily. It should not be used to treat acute bronchospasm.

Roflumilast is also under investigation in the treatment of asthma.

References.
1. Bateman ED, *et al.* Efficacy and safety of roflumilast in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 679–86.
2. Calverley PM, *et al.* Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **176:** 154–61.
3. Field SK. Roflumilast: an oral, once-daily selective PDE-4 inhibitor for the management of COPD and asthma. *Expert Opin Invest Drugs* 2008; **17:** 811–18.
4. Calverley PMA, *et al.* M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; **374:** 685–94.
5. Fabbri LM, *et al.* M2-127 and M2-128 study groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009; **374:** 695–703.
6. Cazzola M, *et al.* Roflumilast in chronic obstructive pulmonary disease: evidence from large trials. *Expert Opin Pharmacother* 2010; **11:** 441–9.
7. Gross NJ, *et al.* Treatment of chronic obstructive pulmonary disease with roflumilast, a new phosphodiesterase 4 inhibitor. *COPD* 2010; **7:** 141–53.
8. Sanford M. Roflumilast: in chronic obstructive pulmonary disease. *Drugs* 2010; **70:** 1615–27.

Adverse Effects and Precautions

The most commonly reported adverse effects with roflumilast are gastrointestinal disturbances such as diarrhoea and nausea, abdominal pain, headache, and a decrease in appetite and body-weight. These adverse effects mostly occur within the first weeks of therapy and resolve on continued treatment. Weight should be checked regularly, particularly in those who are underweight, and treatment stopped if a significant weight decrease occurs. Other less common adverse effects include hypersensitivity, rash, palpitations, tremor, dizziness, gastritis, muscle spasms and weakness, myalgia, back pain, and fatigue. Gynaecomastia, dysgeusia, urticaria, respiratory-tract infections, haematochezia (blood in the stools), and increases in liver enzymes and creatine phosphokinase have been reported rarely.

An increased risk of psychiatric disorders such as insomnia, anxiety, and depression have been reported with roflumilast, and suicidal ideation and behaviour, including successful suicide attempts, have occurred rarely. Roflumilast is not recommended in patients with a history of depression and suicidal ideation or behaviour, and caution is advised in patients who report previous or existing psychiatric symptoms or those on other drugs likely to cause psychiatric events.

Roflumilast is extensively metabolised in the liver and should be used with caution in patients with mild hepatic impairment (defined as Child-Pugh class A); it is not recommended in those with moderate or severe impairment (Child-Pugh class B or C). Due to a lack of data, roflumilast is not recommended in patients taking immunosuppressive drugs, or those with severe immunological disease, severe infectious disease, cancer, or severe heart failure (NYHA grades 3 or 4).

Roflumilast should not be used for the treatment of acute asthma attacks.

Interactions

The active *N*-oxide metabolite of roflumilast has similar potency to roflumilast and is the main contributor to overall phosphodiesterase type-4 inhibition. Roflumilast is metabolised via the cytochrome P450 isoenzymes CYP3A4 and

CYP1A2, and inhibitors or inducers of these enzymes may affect exposure to roflumilast and its *N*-oxide metabolite.

Use of roflumilast with theophylline or with an oral contraceptive containing gestodene and ethinylestradiol has resulted in increased inhibition of phosphodiesterase type-4.

Roflumilast has not been shown to inhibit or induce any cytochrome P450 isoenzymes, aside from a weak induction of CYP2B6.

Fluvoxamine. Repeated doses of fluvoxamine (an inhibitor of the cytochrome P450 isoenzymes CYP1A2 and CYP2C19) increased exposure to roflumilast in a pharmacokinetic study.[1] Although the rate of formation of the active *N*-oxide metabolite was decreased, clearance was also decreased, resulting in increased exposure to the metabolite. The authors of the study suggested that this increase could have been due to CYP2C19 inhibition of *N*-oxide metabolism by fluvoxamine, as CYP1A2 was not involved in the metabolism of roflumilast *N*-oxide. Total phosphodiesterase-4 inhibition was increased by about 60%.

1. von Richter O, *et al.* Effect of fluvoxamine on the pharmacokinetics of roflumilast and roflumilast N-oxide. *Clin Pharmacokinet* 2007; **46:** 613–22.

Ketoconazole. Exposure to roflumilast was increased after single and repeated doses of ketoconazole, a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4. Formation of the active *N*-oxide metabolite was delayed and exposure was slightly decreased after a single ketoconazole dose, but unchanged after repeated dosing. The authors stated that both roflumilast and its *N*-oxide are metabolised by CYP3A4 but to different degrees. Overall phosphodiesterase type-4 inhibition was unaffected and it was considered unnecessary to adjust the roflumilast dose when giving with ketoconazole.[1]

1. Lahu G, *et al.* Effect of single and repeated doses of ketoconazole on the pharmacokinetics of roflumilast and roflumilast N-oxide. *J Clin Pharmacol* 2008; **48:** 1339–49.

Rifampicin. Exposure to roflumilast decreased when it was given with rifampicin, a potent inducer of the cytochrome P450 isoenzyme CYP3A4. Exposure to the active *N*-oxide metabolite was also reduced despite increased formation, and the authors of the study suggested that rifampicin could mediate these effects by induction of CYP3A4 and CYP2C19 as both are involved in metabolism of the *N*-oxide. Overall phosphodiesterase type-4 inhibition was reduced by about 60%.[1]

1. Nassr N, *et al.* Effects of rifampicin on the pharmacokinetics of roflumilast and roflumilast N-oxide in healthy subjects. *Br J Clin Pharmacol* 2009; **68:** 580–7.

Pharmacokinetics

Following an oral dose on an empty stomach, peak plasma concentrations of roflumilast occur after about 0.5 to 2 hours, and after about 4 to 13 hours for the active metabolite roflumilast *N*-oxide. Food delays the time taken to reach maximum concentration but does not affect total exposure to the active compounds. The absolute bioavailability is about 80%. Plasma-protein binding of roflumilast and roflumilast *N*-oxide is about 99% and 97%, respectively. Studies in *animals* indicate that roflumilast is readily distributed to organs and tissues without evidence of accumulation; penetration of the blood-brain barrier is low. Steady-state plasma concentrations are reached after about 4 days for roflumilast, and 6 days for the *N*-oxide. Total exposure to both compounds is increased in females, elderly patients, and in non-Caucasians, and slightly decreased in smokers.

Roflumilast is extensively metabolised in the liver both via conjugation and via cytochrome P450 isoenzymes. The main metabolite is roflumilast *N*-oxide the formation of which is mediated by CYP3A4 and CYP1A2. Roflumilast and its *N*-oxide have similar potency; however, exposure to the metabolite is about tenfold greater and it is the main contributor to overall activity. The *N*-oxide is further metabolised via CYP3A4, CYP2C19, and extra-hepatic CYP1A1.

After an oral dose, the median plasma effective half-lives of roflumilast and roflumilast N-oxide are about 17 and 30 hours, respectively. About 20% of an oral or intravenous dose is recovered in the faeces, and 70% in the urine as inactive metabolites.

References.
1. Hermann R, *et al.* Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. *Clin Pharmacokinet* 2007; **46:** 403–16.
2. Bethke TD, *et al.* Dose-proportional intraindividual single- and repeated-dose pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor. *J Clin Pharmacol* 2007; **47:** 26–36.
3. Neville KA, *et al.* Single-dose pharmacokinetics of roflumilast in children and adolescents. *J Clin Pharmacol* 2008; **48:** 978–85.

All cross-references refer to entries in Volume A

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Daxas; ***Cz.***: Daliresp; Daxas; Libertek; ***Denm.***: Daxas; ***Fr.***: Daxas; ***Ger.***: Daxas; ***Gr.***: Daxas; ***Irl.***: Daliresp; Libertek; ***Israel***: Daliresp; ***Neth.***: Daliresp; Daxas; Libertek; ***Norw.***: Daxas; ***Pol.***: Daxas; ***Port.***: Daxas; ***Spain***: Daxas; Libertek; ***Swed.***: Daxas; ***Switz.***: Daxas; ***UK***: Daxas; ***Ukr.***: Daxas (Даксас); ***USA***: Daliresp.

Salbutamol *(BAN, rINN)* ⊗

AH-3365; Albuterol (USAN); Salbutamoli; Salbutamolis; Salbutamolum; Sch-13949W; Szalbutamol; Сальбутамол.

2-*tert*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl) ethanol.

$C_{13}H_{21}NO_3$=239.3

CAS — 18559-94-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.

UNII — QF8SVZ843E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Salbutamol). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.

USP 36: (Albuterol). A white crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.

Salbutamol Sulfate *(BANM, rINNM)* ⊗

Albuterol Sulfate (USAN); Salbutamol Hemisulphate; Salbutamol, sulfate de; Salbutamol, sulfato de; Salbutamol Sulphate; Salbutamoli Sulfas; Salbutamolio sulfatas; Salbutamolisulfaatti; Salbutamolsulfat; Salbutamol-sulfát; Salbutamolu siarczan; Sulfato de albuterol; Sulfato de salbutamol; Szalbutamol-szulfát; Сальбутамола Сульфат.

$(C_{13}H_{21}NO_3)_2,H_2SO_4$=576.7

CAS — 51022-70-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.

UNII — 021SEF3731.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Salbutamol Sulfate). A white or almost white crystalline powder. It shows Polymorphism. Freely soluble in water; practically insoluble or very slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Albuterol Sulfate). A white or practically white powder. Freely soluble in water; slightly soluble in alcohol, in chloroform, and in ether. Protect from light.

Stability. For mention of the stability of a 1:1 mixture of salbutamol and ipratropium nebuliser solutions, see under Ipratropium, p. 1211.3.

Uses and Administration

Salbutamol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist—p. 1195.1). This results in its bronchodilating action being more prominent than its effect on the heart.

Salbutamol and salbutamol sulfate are used as bronchodilators in the management of reversible airways obstruction, as in asthma and in some patients with chronic obstructive pulmonary disease. Salbutamol also decreases uterine contractility and may be given as the sulfate to arrest premature labour (p. 2131.1).

Inhalation results in the rapid onset (within 5 minutes) of bronchodilatation, which lasts for about 3 to 6 hours. After oral doses, the onset of action is within 30 minutes, with a peak effect between 2 to 3 hours after the dose, and a duration of action of up to 6 hours; modified-release preparations that have a longer duration of action are available.

Salbutamol is used as the base or sulfate in aerosol inhalers and as the sulfate in other preparations. The dosage is expressed in terms of salbutamol base; salbutamol sulfate 1.2 mg is equivalent to about 1 mg of salbutamol.

For the relief of **acute bronchospasm**, 1 or 2 inhalations of salbutamol 100 micrograms may be given from a conventional *metered-dose aerosol* as required, up to 4 times daily. Two inhalations may also be given just before exertion for the prophylaxis of exercise-induced bronchospasm. (In the USA these inhalations may be expressed as supplying 100 micrograms, the amount delivered *into* the mouthpiece, or 90 micrograms, the amount delivered *from* the mouthpiece.) Current asthma guidelines (see p. 1195.2) recommend that inhaled short-acting $beta_2$ agonists such as salbutamol be used on an as-required, not regular, basis. In those patients requiring more than occasional use of salbutamol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, salbutamol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy. Salbutamol sulfate is now available in chlorofluorocarbon (CFC)-free aerosols. Doses for these aerosols (expressed in terms of salbutamol) are the same as for conventional aerosols.

Salbutamol may also be inhaled as the sulfate from dry powder *inhalers* or *discs*, particularly by patients who have difficulty using aerosol formulations. Doses are similar to those given by metered-dose aerosols, although not all dry powder formulations are bioequivalent.

When inhalation is ineffective, *oral* salbutamol may be given in a dose of 2 to 4 mg three or four times daily as the sulfate; some patients may require doses of up to 8 mg three or four times daily, but such increased doses are unlikely to be tolerated or to provide much extra benefit. Elderly patients should be given the lower doses initially. Modified-release preparations are also available; a usual adult dose is 8 mg twice daily.

In more severe or unresponsive bronchospasm salbutamol sulfate may be given intermittently via a *nebuliser* in adults and children. Licensed doses are 2.5 to 5 mg of salbutamol repeated up to 4 times daily; continuous use is also possible, usually at a rate of 1 to 2 mg/hour. However, guidelines allow for more frequent use or continuous use at a higher rate in acute severe asthma (see under Asthma, p. 1195.2). Single-dose units of 0.1% or 0.2%, or a concentrated solution of salbutamol 0.5%, are available for nebulisation. Continuous use is usually as a 0.005 to 0.01% solution in sodium chloride 0.9%. Patients with acute severe asthma may require supplemental oxygen.

Alternatively, salbutamol can be given via a spacer device for acute severe asthma. Four inhalations of 100 micrograms from a metered-dose inhaler are given initially, then a further 2 inhalations are given every 2 minutes according to response, up to a maximum of 10 inhalations.

In the management of a severe attack of bronchospasm a slow *intravenous injection* of salbutamol 250 micrograms as a solution containing 50 micrograms/mL as the sulfate may be required; alternatively salbutamol may be given by intravenous infusion of a solution containing 5 mg in 500 mL (10 micrograms/mL) at a usual rate of 3 to 20 micrograms/minute according to the patient's need; higher dosages have been used in patients with respiratory failure.

Salbutamol sulfate can also be given for bronchospasm by *subcutaneous* or *intramuscular* injection in doses of salbutamol 500 micrograms every 4 hours as required.

For the arrest of uncomplicated **premature labour** between 22 and 37 weeks of gestation salbutamol sulfate is given by *intravenous infusion*, preferably with the aid of a syringe pump at a concentration of 200 micrograms/mL of salbutamol in glucose 5%. If no syringe pump is available then the infusion should be with a more dilute solution of 20 micrograms/mL in glucose 5%. The same dose is used as with the syringe pump. The recommended initial rate of infusion is 10 micrograms/minute increased at intervals of 10 minutes until there is a response; the rate is then increased slowly until contractions cease. The usual effective dose is 10 to 45 micrograms/minute. The infusion should be maintained at the rate at which contractions cease for 1 hour, then reduced by decrements of 50% at intervals of 6 hours. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions, p. 1222.3).

The maternal pulse should be monitored throughout the infusion and the infusion rate adjusted to avoid a maternal heart rate of more than 120 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema.

Oral or *rectal* $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, salbutamol could be given orally in doses of 4 mg three or four times daily, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

For doses of salbutamol used in children, see Administration in Children p. 1221.1.

Administration. $Beta_2$ agonists are used extensively in the management of reversible airways obstruction. A common, effective, and convenient method of dosage is by a pressurised aerosol inhaler. With this route relief is provided rapidly and fewer systemic adverse effects are likely to occur than with oral use. It is important that patients using conventional inhalers employ the correct technique, which involves coordinating actuation of the aerosol with inhalation; if patients have difficulty with this, alternatives are available. Spacer devices may be used with inhalers. These are added on to the inhaler and reduce the velocity of the aerosol; also more propellant may evaporate before inhalation allowing a greater proportion of the drug to

reach the lungs, and coordination of actuation of the aerosol and inhalation is less important. Breath-actuated aerosol inhalers and dry powder inhalers are also available and are actuated by the patient's inspiration and thus avoid entirely the need for coordination of actuation and inhalation; however, inhalation of the dry powder has occasionally caused irritation of the throat or coughing.

The oral route can be used although generally a form of inhaled therapy as described above is preferable. Formulations intended for oral use are commercially available, including modified-release formulations. Nebulisation is an alternative method of delivery and this may be used in the management of severe acute attacks as may parenteral therapy.

Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Conventional and breath-actuated HFA preparations are available. HFA aerosols may feel and taste different to CFC aerosols.

Administration in children. For the treatment of reversible airways obstruction, including nocturnal asthma, and prevention of allergen- or exercise-induced **bronchospasm** in children, the *BNFC* suggests the following usual doses of salbutamol:

by aerosol inhalation

- 1 month to 18 years of age, 100 or 200 micrograms (1 or 2 inhalations) up to four times daily, for occasional use only

by inhalation of dry powder from inhalers or discs doses vary between preparations, although they are used in children from about 5 years of age in doses similar to those given by metered-dose aerosols

Inhaled therapy is generally considered first-line treatment, but oral therapy may be necessary if an inhaler device cannot be used. In the UK salbutamol syrup is licensed for children from 2 years of age and modified-release oral preparations from 3 years of age:

orally using an immediate-release preparation

- 1 month to 2 years of age, 100 micrograms/kg (up to a maximum dose of 2 mg) three or four times daily
- 2 to 6 years of age, 1 to 2 mg three or four times daily
- 6 to 12 years of age, 2 mg three or four times daily
- over 12 years of age, doses as for adults, see Uses and Administration, p. 1220.2

orally using a modified-release preparation

- 3 to 12 years of age, 4 mg twice daily
- over 12 years of age, as for adults, see p. 1220.2

In the management of acute mild to moderate **exacerbations** of asthma, salbutamol may be given using a metered-dose aerosol inhaler via a spacer device. For children of all ages, 1 inhalation (100 micrograms) may be given every 15 to 30 seconds up to a maximum of 10 inhalations. The dose may be repeated after 10 to 20 minutes if required. In more severe exacerbations, salbutamol can be given intermittently via a nebuliser. A dose of 2.5 mg, which can be increased to 5 mg in children over 5 years of age, can be repeated every 20 to 30 minutes or as necessary. Immediate transfer to hospital and inhalation of oxygen is also required. Children under 18 months of age often respond poorly to bronchodilators; nebulised $beta_2$ agonists have been associated with mild paradoxical bronchospasm and transient worsening of oxygen saturation.

Although parenteral salbutamol is not licensed in the UK for use in children, the *BNFC* recommends the following doses in the management of **acute severe** or life-threatening acute asthma:

by intravenous injection over 5 minutes

- 1 month to 2 years of age, 5 micrograms/kg as a single dose
- 2 to 18 years of age, 15 micrograms/kg (to a maximum of 250 micrograms) as a single dose

by continuous intravenous infusion

- 1 month to 18 years of age, 1 to 2 micrograms/kg per minute, adjusted according to response and heart rate up to 5 micrograms/kg per minute. Doses above 2 micrograms/kg per minute require close monitoring

Salbutamol can be used to treat severe **hyperkalaemia** in children (see Hyperkalaemia below). The *BNFC* recommends:

by intravenous injection over 5 minutes

- children of all ages, 4 micrograms/kg as a single dose; repeated if necessary

by inhalation of nebulised solution (although intravenous injection is preferred)

- children of all ages, 2.5 or 5 mg as a single dose; repeated if necessary

Asthma. Short-acting $beta_2$ agonists such as salbutamol are used for short-term relief in all patients with symptomatic asthma (p. 1195.2). High doses are used in acute asthma, but current recommendations for chronic asthma are for low doses to be inhaled as required rather than regularly. When patients with mild asthma find that symptomatic relief is needed more than 3 times a week, then that should be a sign for additional treatment with anti-inflammatory drugs. Increasing need for, or decreased effect of, short-acting $beta_2$ agonists indicates deteriorating asthma and the requirement for stepping up therapy. In one placebo-controlled study,[1] patients with stable asthma receiving regular high doses of a short-acting inhaled $beta_2$ agonist were able to reduce the dose considerably with no change in asthma control, lending further support to the recommendation for 'as-required' rather than regular use of these drugs. The discussion under Fenoterol on p. 1208.3 on the increased mortality that has been seen in asthma patients and the connection with asthma therapy includes a view that regular use might have contributed to the increased mortality. However, a systematic review[2] of studies of short-acting $beta_2$ agonists, most of which used salbutamol, found no clear clinical advantage or detriment from regular use compared with taking them as required.

1. Harrison TW, *et al.* Randomised placebo controlled trial of β agonist dose reduction in asthma. *Thorax* 1999; **54:** 98–102.
2. Walters EH, *et al.* Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/01/08).

Bronchiolitis. Acute bronchiolitis (inflammation of the bronchioles associated with viral respiratory-tract infection, usually due to RSV—see p. 961.3) is a poorly defined respiratory condition seen in infants and young children. The diagnostic criteria, and the usual management, vary considerably from country to country. $Beta_2$ agonists such as salbutamol are widely prescribed in the USA, but not in the UK, and attempts to establish their benefits have produced conflicting results.[1] Modest benefit (but no difference in hospital admission rate) has been reported from a meta-analysis of bronchodilator therapy in general,[2] but a meta-analysis of $beta_2$-agonist therapy in bronchiolitis did not show it to be effective.[3] Some comparative studies have suggested that nebulised adrenaline is more effective than salbutamol.[4,5] However, one study in hospitalised children found no benefit from nebulised salbutamol in terms of improved oxygenation or length of hospital stay,[6] and another[7] found no difference in efficacy between nebulised adrenaline, salbutamol, and sodium chloride 0.9%.

The use of oral salbutamol in infants with acute viral bronchiolitis has been found to be no more effective than placebo and so is not recommended.[8]

1. Everard ML. Acute bronchiolitis—a perennial problem. *Lancet* 1996; **348:** 279–80.
2. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 25/01/08).
3. Flores G, Horwitz RI. Efficacy of β2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997; **100:** 233–9.
4. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–92.
5. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–7.
6. Dobson JV, *et al.* The use of albuterol in hospitalized infants with bronchiolitis. *Pediatrics* 1998; **101:** 361–8.
7. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141:** 818–24.
8. Patel H, *et al.* Randomized, double-blind, placebo-controlled trial of oral albuterol in infants with mild-to-moderate acute viral bronchiolitis. *J Pediatr* 2003; **142:** 509–14.

Chronic obstructive pulmonary disease. Salbutamol and other $beta_2$ agonist bronchodilators form part of the first-line treatment of chronic obstructive pulmonary disease (p. 1199.1).

Cough. For studies of inhaled salbutamol in the treatment of cough, see under Beclometasone, p. 1622.1.

Hyperkalaemia. Salbutamol can lower plasma-potassium concentrations by promoting intracellular uptake,[1,2] and this effect has been used in treating mild hyperkalaemia (p. 1779.1) associated with chronic disorders such as renal failure[3,4] and hyperkalaemic periodic paralysis.[5] However, such use is controversial: the effects of salbutamol may be inconsistent[6] and some clinicians prefer to avoid the use of $beta_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7]

Salbutamol has been used to lower plasma-potassium concentrations in children[8] and premature neonates[9] with some success. For doses of salbutamol used to treat severe hyperkalaemia in children, see Administration in Children above.

1. Bushe C. Salbutamol for hyperkalaemia. *Lancet* 1983; **ii:** 797.
2. Anonymous. Hyperkalaemia—silent and deadly. *Lancet* 1989; **i:** 1240.
3. Allon M, *et al.* Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; **110:** 426–9.
4. McClure RJ, *et al.* Treatment of hyperkalaemia using intravenous and nebulised salbutamol. *Arch Dis Child* 1994; **70:** 126–8.
5. Wang P, Clausen T. Treatment of attacks in hyperkalaemic familial periodic paralysis by inhalation of salbutamol. *Lancet* 1976; **i:** 221–3.
6. Wong S-L, Maltz HC. Albuterol for the treatment of hyperkalemia. *Ann Pharmacother* 1999; **33:** 103–6.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352:** 135–40.
8. Helfrich E, *et al.* Salbutamol for hyperkalaemia in children. *Acta Paediatr* 2001; **90:** 1213–16.
9. Singh BS, *et al.* Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. *J Pediatr* 2002; **141:** 16–20.

Lymphangioleiomyomatosis. Inhaled $beta_2$ agonists are often helpful in treating the reversible component of airway obstruction in women with pulmonary lymphangioleiomyomatosis, and a trial of treatment is warranted.[1,2] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p. 2288.3.

1. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
2. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.

Muscular dystrophies. There is some evidence that $beta_2$ agonists affect muscle strength and have an anabolic effect, although whether this applies when given by inhalation has been queried—see Abuse, under Precautions, p. 1223.1. Salbutamol has therefore been investigated in a small number of patients in the management of muscular dystrophies (p. 1608.1). Oral doses of modified-release salbutamol up to 12 mg daily have been used in boys aged between 5 and 11 years with Duchenne or Becker muscular dystrophies,[1,2] and doses of 8 or 16 mg twice daily have been given to adults with facioscapulohumeral dystrophy.[3,4] Although some improvements in muscle strength and muscle mass have been reported, not all muscle groups respond and the long-term effects of treatment are not known.

1. Fowler EG, *et al.* Pilot trial of albuterol in Duchenne and Becker muscular dystrophy. *Neurology* 2004; **62:** 1006–8.
2. Skura CL, *et al.* Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. *Neurology* 2008; **70:** 137–43.
3. Kissel JT, *et al.* Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. *Neurology* 2001; **57:** 1434–40.
4. van der Kooi EL, *et al.* Strength training and albuterol in facioscapulohumeral muscular dystrophy. *Neurology* 2004; **63:** 702–8.

Premature labour. $Beta_2$ agonists such as salbutamol have been used as tocolytics in the management of premature labour (p. 2131.1), and can postpone labour for a few days, but the risk of adverse cardiovascular and metabolic events including pulmonary oedema (see p. 1222.3) means that great care and appropriate monitoring of the patient's heart rate and state of hydration are needed.

Proctalgia fugax. Inhalation of salbutamol from a metered-dose inhaler at the beginning of an attack has been shown to reduce the duration of pain in patients with proctalgia fugax.[1]

1. Eckardt VF, *et al.* Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol* 1996; **91:** 686–9.

Adverse Effects

As for Sympathomimetics, p. 1508.2. Salbutamol has mainly beta-agonist effects and, like other beta agonists, may cause fine tremor of skeletal muscle (particularly the hands), palpitations, tachycardia, nervous tension, headaches, peripheral vasodilatation, and rarely muscle cramps. Inhalation causes fewer adverse effects than systemic dosage, and the more selective $beta_2$ agonists cause fewer adverse effects than less selective beta agonists. Potentially serious hypokalaemia has been reported after large doses. Myocardial ischaemia has also been reported. Hypersensitivity reactions have occurred, including paradoxical bronchospasm, angioedema, urticaria, hypotension, and collapse.

The high doses of salbutamol used intravenously to delay premature labour have additionally been associated with nausea and vomiting, and with severe adverse cardiac and metabolic effects and pulmonary oedema.

Effects on the CNS. Visual hallucinations lasting for an hour have been reported[1] after use of nebulised salbutamol in an elderly patient. At the time of the report the manufacturers were aware of 3 cases of hallucinations in children given oral salbutamol but no such reaction had been previously reported in adults given recommended doses.

Hyperactivity and restlessness have been reported with the use of salbutamol; however, a small placebo-controlled study of 19 children,[2] failed to show a statistically significant difference in activity levels after a nebulised dose of salbutamol.

1. Khanna PB, Davies R. Hallucinations associated with the administration of salbutamol via a nebuliser. *BMJ* 1986; **292:** 1430.
2. Hadjikoumi I, *et al.* Bronchodilator therapy and hyperactivity in preschool children. *Arch Dis Child* 2002; **86:** 202–4. Also available at: http://adc.bmj.com/cgi/reprint/86/3/202 (accessed 15/01/08)

Effects on electrolytes and metabolism. Salbutamol, in common with other $beta_2$-agonists, may cause *hypokalaemia* and *hyperglycaemia*. These effects are related to the dose and route of salbutamol used; hypokalaemia is more common after parenteral and nebulised use. Hypokal-

aemia may be potentiated by therapy with corticosteroids, diuretics, or xanthines, and by hypoxia; potassium concentrations should therefore be monitored in severe asthma.

Effects on the eyes. It has been suggested that salbutamol and to a greater extent ritodrine may contribute to retinopathy in the premature infant when used for premature labour.[1]

A case of acute angle-closure glaucoma was attributed to dilatation of the pupil by stimulation of the sympathetic nervous system secondary to local absorption of nebulised salbutamol in the eye; the patient also had other risk factors for developing glaucoma.[2] For reports of glaucoma precipitated by the combined use of ipratropium bromide and salbutamol via a nebuliser, see Ipratropium Bromide, p. 1212.3.

1. Michie CA, *et al.* Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; **71:** F149.
2. Rho DS. Acute angle-closure glaucoma after albuterol nebulizer treatment. *Am J Ophthalmol* 2000; **130:** 123–4.

Effects on the heart. The main adverse cardiac effect of salbutamol is **tachycardia** due to increased sympathetic effects on the cardiovascular system. Such tachycardia is dose dependent and is more common after systemic than inhaled therapy. A meta-analysis[1] of randomised, placebo-controlled studies in patients with asthma or chronic obstructive pulmonary disease (COPD) confirmed that single doses of $beta_2$ agonists can cause an increase in heart rate and a reduction in potassium concentrations (see also Effects on Electrolytes and Metabolism, p. 1221.3). The **longer-term effects** of $beta_2$ agonists on the cardiovascular system were also assessed and an increased risk of adverse cardiovascular events due to sinus tachycardia was found. There was also a trend towards an increase in major adverse events including ventricular tachycardia, atrial fibrillation, syncope, heart failure, myocardial infarction, cardiac arrest, and sudden death. **Myocardial ischaemia** has been reported with salbutamol when used to delay premature labour.[2] Eleven of 17 reports were considered serious, including one fatality. Most of these reports involved the use of parenteral formulations; none involved the use of inhaled salbutamol formulations for the relief of bronchospasm. However, there is some evidence that high doses of inhaled salbutamol can decrease coronary flow reserve, and might exacerbate ischaemia in patients with coronary artery disease.[3] Observational studies into the association between $beta_2$ agonist use and the risk of **myocardial infarction** have produced conflicting results. Some have reported an increased risk,[4,5] whereas others have reported that this risk is increased only in patients with asthma[6] but not in those with COPD.[6,7] In patients with asthma and long QT syndrome, treatment with $beta_2$ agonists (salbutamol, salmeterol, and orciprenaline) increased the risk of cardiac events such as syncope, myocardial infarction, and sudden cardiac death. The risk was higher in the first year of $beta_2$ agonist treatment but was reduced in patients also receiving beta blockers.[8] Similarly, a case-control study[9] in hypertensive patients reported that the risk of myocardial infarction was only increased in patients with ischaemic heart disease who had recently started treatment with $beta_2$ agonists. The authors of this study felt that this increased risk was likely to have been due to latent cardiovascular disease rather than a direct effect of the $beta_2$ agonists. Case-control and cohort studies have also suggested that patients with pre-existing **heart failure** may be at increased risk of hospitalisation from arrhythmias[10] or exacerbation of heart failure[11,12] with the use of $beta_2$ agonists.

However, a causal relationship cannot necessarily be established from these case-control and cohort studies, because of confounding factors such as comorbidity, and because the extent of $beta_2$ agonist use could only be estimated from prescription record systems.

See also Pregnancy, below.

1. Salpeter SR, *et al.* Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; **125:** 2309–21.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Kochiadakis GE, *et al.* Effect of inhaled salbutamol on coronary circulation in humans. *Int J Cardiol* 2007; **117:** 408–10.
4. Au DH, *et al.* The risk of myocardial infarction associated with inhaled β-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000; **161:** 827–30.
5. Au DH, *et al.* Association between inhaled β-agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002; **121:** 846–51.
6. Lemaitre RN, *et al.* Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 2002; **113:** 711–16.
7. Suissa S, *et al.* Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003; **58:** 43–6.
8. Thottathil P, *et al.* International Long QT Syndrome Investigative Group. Risk of cardiac events in patients with asthma and long-QT syndrome treated with $beta_2$ agonists. *Am J Cardiol* 2008; **102:** 871–4.
9. de Vries F, *et al.* Use of $beta_2$ agonists and risk of acute myocardial infarction in patients with hypertension. *Br J Clin Pharmacol* 2008; **65:** 580–6.
10. Bouvy ML, *et al.* Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med* 2000; **160:** 2477–80.
11. Au DH, *et al.* Risk of mortality and heart failure exacerbations associated with inhaled β-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003; **123:** 1964–9.
12. Au DH, *et al.* Association between chronic heart failure and inhaled β-2-adrenoceptor agonists. *Am Heart J* 2004; **148:** 915–20.

Effects on the respiratory system. Paradoxical bronchoconstriction has occasionally been reported after bronchodilating therapy. With nebuliser solutions, it has been suggested that the preservatives present could be responsible (see also under Ipratropium, p. 1213.1), or that the pH may contribute if non-neutral. In addition, regular use of $beta_2$ agonists such as salbutamol (as opposed to use on an as-needed basis) has been shown to increase airway hyperresponsiveness to various stimuli and to lead to the possible development of tolerance to the bronchoprotective effect (see below).

The increased risk of pulmonary oedema associated with salbutamol is mentioned under Pulmonary Oedema, below.

Increased mortality. The increased incidence of morbidity and mortality that occurred in asthmatic patients mainly involved fenoterol, but salbutamol has been implicated. The debate on the relevance of beta agonist therapy to this increased morbidity and mortality is discussed under Fenoterol on p. 1208.3.

Overdosage. Reports of overdosage with salbutamol[1-6] have generally only described the features that may be expected with $beta_2$ agonists such as tachycardia, CNS stimulation, tremor, hypokalaemia, and hyperglycaemia. The plasma-potassium concentration and pulse rate have been found to correlate with the plasma concentration of salbutamol.[7] Symptomatic treatment of the adverse effects has proved successful although it is unlikely to be required after repeated inhalation. In the UK, the *National Poisons Information Service* notes that activated charcoal may be considered after oral overdose in patients who have taken a potentially toxic amount and present within 1 hour. Further management is mainly supportive. Tachycardia with adequate cardiac output is best left untreated, but in extreme cases beta blockers such as metoprolol or esmolol may be used (caution is required in patients with a history of bronchospasm, see p. 1320.3). Persistent hypertension may respond to an intravenous infusion of glyceryl trinitrate or another nitrate; calcium-channel blockers are an alternative. Beta blockers should be avoided because of the risk of paradoxical hypertension and coronary vasoconstriction from unopposed alpha effects.

1. Morrison GW, Farebrother MJB. Overdose of salbutamol. *Lancet* 1973; **ii:** 681.
2. O'Brien IAD, *et al.* Hypokalaemia due to salbutamol overdosage. *BMJ* 1981; **282:** 1515–16.
3. Prior JG, *et al.* Self-poisoning with oral salbutamol. *BMJ* 1981; **282:** 1932.
4. Connell JMC, *et al.* Metabolic consequences of salbutamol poisoning reversed by propranolol. *BMJ* 1982; **285:** 779.
5. Spiller HA, *et al.* A two-year retrospective study of accidental pediatric albuterol ingestions. *Pediatr Emerg Care* 1993; **9:** 338–40.
6. Leikin JB, *et al.* Hypokalemia after pediatric albuterol overdose: a case series. *Am J Emerg Med* 1994; **12:** 64–6.
7. Lewis LD, *et al.* A study of self poisoning with oral salbutamol—laboratory and clinical features. *Hum Exp Toxicol* 1993; **12:** 397–401. Correction. *ibid.* 1994; **13:** 371.

Pregnancy. Most adverse effects associated with salbutamol in pregnancy relate to the cardiovascular and metabolic effects of the very high doses given by intravenous infusion in attempts to delay premature labour (see also under Pulmonary Oedema, below). Maternal effects include myocardial ischaemia,[1,2] unifocal ventricular ectopics associated with the hypokalaemic response to intravenous salbutamol,[3] and heart failure in a hypertensive woman.[4] Similarly, serious fetal and neonatal cardiovascular complications have also been associated with tocolytic salbutamol.[5]

Metabolic acidosis after salbutamol infusions in diabetic women has also been reported.[6,7]

For reports of retinopathy in the premature infant see Effects on the Eyes above.

1. Whitehead MI, *et al.* Myocardial ischaemia after withdrawal of salbutamol for pre-term labour. *Lancet* 1979; **ii:** 904.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Chew WC, Lew LC. Ventricular ectopics after salbutamol infusion for preterm labour. *Lancet* 1979; **ii:** 1383–4.
4. Whitehead MI, *et al.* Acute congestive cardiac failure in a hypertensive woman receiving salbutamol for premature labour. *BMJ* 1980; **280:** 1221–2.
5. Katz VL, Seeds JW. Fetal and neonatal cardiovascular complications from β-sympathomimetic therapy for tocolysis. *Am J Obstet Gynecol* 1989; **161:** 1–4.
6. Chapman MG. Salbutamol-induced acidosis in pregnant diabetics. *BMJ* 1977; **1:** 639–40.
7. Thomas DJB, *et al.* Salbutamol-induced diabetic ketoacidosis. *BMJ* 1977; **2:** 438.

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including salbutamol,[1-4] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions, below.

1. Hawker F. Pulmonary oedema associated with $beta_2$-sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; **110:** 714–18.
3. Hamel H, *et al.* Œdème pulmonaire et tocolyse par bêta-mimétiques. *Rev Mal Respir* 2002; **19:** 241–4.
4. Chapuis C, *et al.* Œdème aigu du poumon au décours d'une tocolyse par nicardipine et salbutamol lors d'une menace d'accouchement prématuré sur grossesse gémellaire. *J Gynecol Obstet Biol Reprod (Paris)* 2005; **34:** 493–6.

Tolerance. Some studies suggest that regular inhalation of a short-acting $beta_2$ agonist, although it continues to produce bronchodilatation, increases airway hyperresponsiveness and may reduce the protective effect against bronchoconstriction provoked by stimuli such as bradykinin, methacholine, or allergen.[1-6] Such tolerance is considered another argument against regular use of short-acting drugs.[1] Reduced bronchoprotective effects have also been found with long-acting $beta_2$ agonists (see Salmeterol, p. 1225.2).

It has been suggested that reduced benefit with salbutamol may be due to the *S*(+)-enantiomer,[7,8] which unlike the *R* (-)-enantiomer (levosalbutamol, p. 1213.3) does not possess bronchodilating activity. Stereoselective metabolism (see under Pharmacokinetics, p. 1223.2) means that regular use of the racemate could lead to accumulation of the *S*-enantiomer, which provides a possible mechanism for the effect. Genetic polymorphism of the $beta_2$-adrenoceptor has also been proposed as another possible mechanism.[9,10]

1. Cockcroft DW, *et al.* Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993; **342:** 833–7.
2. O'Connor BJ, *et al.* Tolerance to the nonbronchodilator effects of inhaled β$_2$-agonists in asthma. *N Engl J Med* 1992; **327:** 1204–8.
3. Cockcroft DW, *et al.* Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995; **96:** 44–9.
4. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; **153:** 65–9.
5. Crowther SD, *et al.* Varied effects of regular salbutamol on airway responsiveness to inhaled spasmogens. *Lancet* 1997; **350:** 1450.
6. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; **14:** 283–7.
7. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; **346:** 1101.
8. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of β agonists. *J Allergy Clin Immunol* 1999; **104** (suppl): S69–S76.
9. Israel E, *et al.* Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004; **364:** 1505–12.
10. Broadley KJ. β-Adrenoceptor responses of the airways: for better or worse? *Eur J Pharmacol* 2006; **533:** 15–27.

Precautions

Salbutamol and other beta agonists should be given with caution in hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, and diabetes mellitus (especially on intravenous use—blood glucose should be monitored since ketoacidosis has been reported).

In *severe asthma* particular caution is also required to avoid inducing hypokalaemia as this effect may be potentiated by hypoxia or by the effect of other anti-asthma drugs on potassium (see Interactions, p. 1223.1); plasma-potassium concentrations should be monitored.

$Beta_2$ agonists such as salbutamol are not appropriate for use alone in the treatment of more than mild asthma (see Asthma, p. 1195.2). Increasing need for, or decreased duration of effect of, inhaled salbutamol and other short-acting $beta_2$ agonists indicates deterioration of asthma control and the likely requirement for increased anti-inflammatory therapy.

In *women being treated for premature labour* the risk of pulmonary oedema means that the patient's state of hydration and cardiac and respiratory function should be monitored very carefully; the volume of infusion fluid should be kept to the minimum (normally using glucose 5% as the diluent), and $beta_2$-agonist therapy should be stopped immediately and diuretic therapy started if signs of pulmonary oedema develop. Other risk factors for pulmonary oedema include multiple pregnancy and heart disease. Ischaemic heart disease or significant risk factors for ischaemic heart disease are specific contra-indications; where heart disease is suspected assessment by a physician experienced in cardiology is needed. Eclampsia and severe pre-eclampsia are also contra-indications, with special care needed in mild to moderate pre-eclampsia. Other contra-indications include intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage (which requires immediate delivery), placenta praevia, and cord compression; $beta_2$ agonists should not be used for threatened miscarriage. See also Uses and Administration, p. 1220.2.

For details of the precautions to be observed with sympathomimetics in general, see p. 1508.3.

Abuse. Salbutamol inhalers have been subject to abuse, particularly by children and young adults.[1-7] This has occurred in both asthmatic and non-asthmatic individuals and has been thought to be for the effect of sympathetic stimulation and for the effect of the fluorocarbon propellants. The introduction of fluorocarbon-free inhalers should reduce the latter motivation, although not the former.

The *World Anti-Doping Agency* prohibits the use of all beta$_2$ agonists in athletes, in and out of competition,[8] on the basis of their supposed ergogenic effect. Although a therapeutic use exemption may be granted for the use of inhaled salbutamol or salmeterol, e.g. in the management of asthma, the presence of salbutamol in urine at concentrations above 1 microgram/mL is considered an adverse analytical finding, unless pharmacokinetic studies show that such concentrations are being produced after inhalation of the drug at therapeutic doses up to a maximum of 1.6 mg daily; this has been shown to be a possibility.[9] The idea that abuse of inhaled beta$_2$ agonists can improve performance in non-asthmatic individuals has been questioned.[10]

1. Brennan PO. Inhaled salbutamol: a new form of drug abuse? *Lancet* 1983; **ii:** 1030–1.
2. Thompson PJ, *et al.* Addiction to aerosol treatment: the asthmatic alternative to glue sniffing. *BMJ* 1983; **287:** 1515–16.
3. Brennan PO. Addiction to aerosol treatment. *BMJ* 1983; **287:** 1877.
4. Wickramasinghe H, Liebeschuetz HJ. Addiction to aerosol treatment. *BMJ* 1983; **287:** 1877.
5. O'Callaghan C, Milner AD. Aerosol treatment abuse. *Arch Dis Child* 1988; **63:** 70.
6. Rakhmanina NY, *et al.* Hypokalemia in an asthmatic child from abuse of albuterol metered dose inhaler. *Pediatr Emerg Care* 1998; **14:** 145–7.
7. Boland B, *et al.* Salbutamol inhaler misuse: a persisting problem? *Addiction* 2008; **103:** 1907.
8. World Anti-Doping Agency. The world anti-doping code: the 2010 prohibited list international standard. Available at: http://www.wada-ama.org/rtecontent/document/2010_Prohibited_List_Final_EN_Web.pdf (accessed 14/10/09)
9. Schweizer C, *et al.* Doping test reveals high concentrations of salbutamol in a Swiss track and field athlete. *Clin J Sport Med* 2004; **14:** 312–5.
10. Kindermann W, Meyer T. Inhaled β_2 agonists and performance in competitive athletes. *Br J Sports Med* 2006; **40** (suppl 1): i43–i47.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies salbutamol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Use of salbutamol and other beta$_2$ agonists with corticosteroids, diuretics, or xanthines increases the risk of hypokalaemia, and monitoring of potassium concentrations is recommended in severe asthma, where such combination therapy is common (see also Effects on Electrolytes and Metabolism, p. 1221.3). For an outline of interactions associated with sympathomimetics in general, see p. 1508.3.

Beta$_2$ agonists. Patients receiving *salmeterol* may require salbutamol to control an acute attack of bronchospasm. One study indicated that the effects might be additive,[1] but another showed that patients receiving salmeterol had reduced sensitivity to salbutamol and might need higher doses of the latter for acute relief.[2] However, a study in asthmatics admitted to a hospital emergency department with acute exacerbations of their illness, found that previous salmeterol therapy did not reduce the efficacy of standard doses of salbutamol.[3] Others have also noted attenuation of the bronchoprotective effects of a beta$_2$ agonist (in this case, *fenoterol*) by salmeterol.[4]

1. Smyth ET, *et al.* Interaction and dose equivalence of salbutamol and salmeterol in patients with asthma. *BMJ* 1993; **306:** 543–5.
2. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995; **346:** 201–6.
3. Korosec M, *et al.* Salmeterol does not compromise the bronchodilator response to albuterol during acute episodes of asthma. *Am J Med* 1999; **107:** 209–13.
4. van Veen A, *et al.* Regular use of long-acting β_2-adrenoceptor agonists attenuates the bronchoprotective efficacy of short-acting β_2-adrenoceptor agonists in asthma. *Br J Clin Pharmacol* 2000; **50:** 499P.

Beta blockers. Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators and are contra-indicated in asthmatic patients as they may cause serious bronchoconstriction, even if given as eye drops. No adverse interaction normally occurs between beta-agonist bronchodilators and cardioselective beta blockers; however, bronchospasm can sometimes occur in asthmatic patients, particularly if high doses are used. In a case-control study in postoperative coronary artery bypass graft patients, use of sotalol with salbutamol led to an increased risk for postoperative atrial fibrillation.[1]

1. Vader C, *et al.* Interaction between sotalol and albuterol after CABG: influence on postoperative arrhythmias and length of stay at an intensive care unit. *Br J Clin Pharmacol* 2002; **53:** 555P–556P.

Cardiac glycosides. Hypokalaemia produced by beta$_2$ agonists may result in an increased susceptibility to digitalis-induced arrhythmias although salbutamol intravenously and orally can also decrease serum concentrations of *digoxin* (see Beta$_2$ Agonists, p. 1357.1).

Corticosteroids. Corticosteroids and beta$_2$ agonists may both produce falls in plasma potassium concentrations; there is evidence that such falls can be exacerbated by use together.[1] The possibility of enhanced hyperglycaemic effects from such a combination should also be borne in mind.

It has been suggested that in acute severe asthma, corticosteroids may modify beta receptors, reversing the beta receptor desensitisation and downregulation caused by beta$_2$ agonists and enhancing the bronchodilator response.[2] In chronic asthma there is little evidence to support this theory; however, combination therapy with corticosteroids and beta$_2$ agonists has been found to have beneficial effects on asthma control; the exact mechanism for this remains unclear.

1. Taylor DR, *et al.* Interaction between corticosteroid and beta-agonist drugs: biochemical and cardiovascular effects in normal subjects. *Chest* 1992; **102:** 519–24.
2. Taylor DR, Hancox RJ. Interactions between corticosteroids and β agonists. *Thorax* 2000; **55:** 595–602.

Diuretics. Hypokalaemia is known to be a possible adverse effect during treatment with beta$_2$ agonists such as salbutamol or terbutaline, and this may be enhanced if diuretics are also given;[1,2] in addition the arrhythmogenic potential of this interaction may be clinically important in patients with ischaemic heart disease.[1]

1. Lipworth BJ, *et al.* Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. *Am J Med* 1989; **86:** 653–7.
2. Newnham DM, *et al.* The effects of frusemide and triamterene on the hypokalaemic and electrocardiographic responses to inhaled terbutaline. *Br J Clin Pharmacol* 1991; **32:** 630–2.

Neuromuscular blockers. Salbutamol given intravenously has been reported to enhance the neuromuscular blockade produced by *pancuronium* and by *vecuronium* (see Sympathomimetics, p. 2033.2).

Xanthines. An enhanced hypokalaemic effect may occur when salbutamol is given with *theophylline*.[1,2] See also under Terbutaline, p. 1229.1 and Sympathomimetics, under Theophylline, p. 1236.3 for the potentiation of other effects.

1. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; **25:** 571–8.
2. Kolski GB, *et al.* Hypokalemia and respiratory arrest in an infant with status asthmaticus. *J Pediatr* 1988; **112:** 304–7.

Pharmacokinetics

Salbutamol is readily absorbed from the gastrointestinal tract. When given by inhalation, 10 to 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is swallowed and absorbed from the gut.

Salbutamol is subject to first-pass metabolism in the liver and possibly in the gut wall but does not appear to be metabolised in the lung; the main metabolite is the inactive sulfate conjugate.

Salbutamol is rapidly excreted, mainly in the urine, as metabolites and unchanged drug; a smaller proportion is excreted in the faeces.

The plasma half-life of salbutamol has been estimated to range from 4 to 6 hours.

General references.

1. Walker SR, *et al.* The clinical pharmacology of oral and inhaled salbutamol. *Clin Pharmacol Ther* 1972; **13:** 861–7.
2. Hetzel MR, Clark TJH. Comparison of intravenous and aerosol salbutamol. *BMJ* 1976; **2:** 919.
3. Lin C, *et al.* Isolation and identification of the major metabolite of albuterol in human urine. *Drug Metab Dispos* 1977; **5:** 234–8.
4. Morgan DJ, *et al.* Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986; **22:** 587–93.
5. Lipworth BJ, *et al.* Single dose and steady-state pharmacokinetics of 4 mg and 8 mg oral salbutamol controlled-release in patients with bronchial asthma. *Eur J Clin Pharmacol* 1989; **37:** 49–52.
6. Rey E, *et al.* Pharmacokinetics of intravenous salbutamol in renal insufficiency and its biological effects. *Eur J Clin Pharmacol* 1989; **37:** 387–9.
7. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; **34:** 311–15.
8. Milliez JM, *et al.* Pharmacokinetics of salbutamol in the pregnant woman after subcutaneous administration with a portable pump. *Obstet Gynecol* 1992; **80:** 182–5.
9. Narasimha Murthy S, Hiremath SR. Clinical pharmacokinetic and pharmacodynamic evaluation of transdermal drug delivery systems of salbutamol sulfate. *Int J Pharm* 2004; **287:** 47–53.
10. Bonnelykke K, *et al.* Age dependent systemic exposure to inhaled salbutamol. *Br J Clin Pharmacol* 2007; **64:** 241–4.

Stereoselectivity. The *R* (-)-enantiomer of salbutamol (levosalbutamol—p. 1213.3) is preferentially metabolised and is therefore cleared from the body more rapidly than the *S*(+)-enantiomer, which lacks bronchodilator activity but may be implicated in some of the adverse effects of salbutamol (see Tolerance, under Adverse Effects, p. 1222.3).

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; **41:** 35–40.
2. Boulton DW, *et al.* Transplacental distribution of salbutamol enantiomers at Caesarian section. *Br J Clin Pharmacol* 1997; **44:** 587–90.
3. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β_2 adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; **52:** 849–52.
4. Ward JK, *et al.* Enantiomeric disposition of inhaled, intravenous and oral racemic-salbutamol in man — no evidence of enantioselective lung metabolism. *Br J Clin Pharmacol* 2000; **49:** 15–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aircosalm; Airsalbu; Amocasin; Asmatol; Butamol; Cercini†; Duopack; Microterol; Nebutrax; Niblet; Respiret; Salbuden; Salbulin; Salbutol; Salbutral + Aeromed; Salbutral; Venticil; Ventimol; Ventolin; Yontal; Zoom; ***Austral.***: Airomir; Asmol; Butamol; Epaq†; Respax†; Ventolin; ***Austria***: Buventol†; Sultanol; ***Belg.***: Airomir; Docsalbuta†; Ventolin; ***Braz.***: Aerodini; Aerogold; Aerogreen; Aerojet; Aerolin; Aerotrat; Asmakil†; Asmaliv; Broncofedrin; Bronconal; Butovent; Dilamol; Neutoss; Prodotamol†; Pulmoflux; Salbutam; Salbutamax†; Tussiliv; ***Canad.***: Airomir; Apo-Salvent; Ventolin; ***Chile***: Aerolin; Agrilin; Airomir†; Asmavent; Bropil; Butotal; Fesema; Respolin†; Salbutral; Sinasmal; ***China***: Da Fen Ke Chuang (达芬科闯); Etinoline (爱纳灵); Hui Bai Shi (惠百释); Kang Er Shu Ning (伉尔纾宁); Lv Ke (律克); Pin Chuan (品川); Sai Bi Shu (赛比舒); Sha Bo Te (沙博特); Ventolin (万托林); Xi Bei Ta (西倍他); ***Cz.***: Buventol; Ecosal; Ventilastin; Ventolin; ***Denm.***: Airomir; Buventol; Salamol; Salbuvent; Ventolin; Ventoline; Volmax†; ***Fin.***: Airomir; Buventol; Ventilastin; Ventoline; ***Fr.***: Airomir; Asmasal; Buventol†; Salbumol; Ventexxair†; Ventilastin; Ventoline; ***Ger.***: Apsomol†; Broncho Fertiginhalat†; Broncho Inhalat; Bronchospray; Epaq†; Padiamol†; Pentamol; Salbu; Salbubronch; Salbuhexal†; Salbulair; SalbuSandoz†; Sultanol; Ventilastin; ***Gr.***: Aerolin; Asthmotrat; Brocofrin; Buventol; Comer; Normobron; Novahaler; Salbumol; Salbunova; Salomol; ***Hong Kong***: Asmaliv†; Asmol†; Asthalin; Cybutol; Etinoline; Respolin†; Salamol; Salmol; Syntalin†; Uni-Butamol†; Vantin†; Ventamol†; Ventodisks†; Ventolin; Ventomol†; Volmax†; Zenmolin; ***Hung.***: Buventol; Ecosal; Ventolin; ***India***: Aerotaz; Asmanil; Asthalin; Bronko; Bronkonat; Brosol; Derihaler; Durasal; Salbetol; Salmaplon; Salsol; ***Indon.***: Asmacare; Azmacon; Bronchosal; Brondisal; Buventol†; Fartolin; Glisend†; Hivent; Lasal; Librentin†; Pritasma; Salbron; Salbuven; Suprasma; Ventolin; Volmax†; ***Irl.***: Aerolin†; Airomir†; Asmasal; Gerivent; Salamol Steri-Neb; Salamol; Salbuvent; Ventamol; Ventolin; ***Israel***: Salbutrim; Ventolin; ***Ital.***: Broncovaleas; Ventmax; Ventolin; Volmax†; ***Malaysia***: Airomir†; Asthalin; Beatolin; Bonair; Butavent; Buventol; Salamol; Salmax; Ventolin; Volmax; ***Mex.***: Apo-Salvent; Assal; Avedox-FC; Azyrol†; Biorenyn; Bonair†; Capacit; Cobamol; Dicoterol†; Exafil; Farmarest; Oladin†; Quinfaval; Salamol†; Salbutalan; Salcomed; Tunxin; Unibron; Ventolin; Volmax†; Zibil; ***Neth.***: Airomir; Salamol; Ventolin; ***Norw.***: Airomir; Buventol; Ventoline; ***NZ***: Airomir; Apo-Salvent†; Asmigen†; Asthalin; Buventol; Respigen; Respolin; Salamol; Salapin; Ventolin; Volmax; ***Philipp.***: Activent; Adsal; Aero-Vent; Airomir; Amoltex; Asbunyl; Asfrenon; Asmacaire; Asmalin; Astagen; Asvimol; Axmaxolv; Bioneb; Brytolin; Cletal†; Efamed; Emplusal; Hivent; Librentin†; Meventil; Provexel NS; Prox-S; Resdil; Rhinol; SAL; Salbuflo; Salbumed; Salvex; Sedalin; Venalax XPT; Venalax; Ventar; Vento-Broncho; Ventolin; Ventosal†; Vimonzil; ***Pol.***: Buventol; Steri-Neb Salamol†; Velaspir; Ventodisk†; Ventolin; ***Port.***: Airomir; Salbulair; Ventilan; ***Rus.***: Asthalin (Астралин); Salamol (Саламол); Salben (Сальбен); Salgim (Сальгим); Saltos (Сальтос); Ventolin (Вентолин); ***S.Afr.***: Airomir†; Asthavent; Cybutol; Venteze; Ventolin; Volmax; ***Singapore***: Apo-Salvent; Asmol; Asthma Formula; Azmasol; Brethmol; Butahale; Buventol; Medolin; Salbuair; Salmol; Venderol; Ventamol; Ventolin; Volmax; Zenmolin; ***Spain***: Aldobronquial; Buto Asma†; Buto-Air; Respiroma†; Salbuair; Ventilastin†; Ventoaldo; Ventolin; ***Swed.***: Airomir; Buventol; Sabufarm; Ventilastin; Ventoline; ***Switz.***: Ecovent; Salamol; Ventolin; ***Thai.***: Aeromol; Antomol; Asmasal; Asmol; Asthalin; Asthamol; Asthmolin; Bronchosol; Butamol†; Buto Asma; Butovent†; Buventol; Durasal; Naso; Sabumol; Salbusian; Salbutac; Salda†; Saldol; Salmol; Salvent; Solia; Sulbuta-N; Venterol; Ventolin; Violin; Zalbu; Zebu†; ***Turk.***: Asthavent; Butovent; Salbulin; Salbutam; Salbutol; Vent-o-sal; Ventodisk; Ventolin; Volmax; ***UAE***: Butalin; ***UK***: Airomir; Asmasal; Pulvinal Salbutamol; Salamol; Salapin; Salbulin; Ventmax; Ventolin; ***Ukr.***: Salamol-Eko (Саламол-Эко); Ventolin (Вентолин); ***USA***: Accuneb; ProAir; Proventil; Ventolin; VoSpire; ***Venez.***: Asthalin; Butoas; Salbulis; Salbumed; Salburol; Salbutan.

Multi-ingredient Preparations. ***Arg.***: Beclasma; Butocort; Butosol†; Combivent; Iprasalb; Salbutol Beclo; Salbutral AC; Ventide; ***Austral.***: Combivent; ***Austria***: Combivent; ***Belg.***: Combivent; Nebu-Iprasal; ***Braz.***: Aerocort S; Aeroflux; Aerotide; Broncocilin; Clenil Compositum; Combivent; ***Canad.***: Combivent; Gen-Combo†; Mylan-Combo; ratio-Ipra Sal; ***Chile***: Aero-Plus; Aerosoma†; Asmavent-B; Belomet; Butocort; Butotal B; Combivent; Herolan Aerosol; Salbutral AC; Ventide; ***China***: Combivent (可必特); Ren Shu (仁舒); Shun Qi (顺奇); Yi Xi Qing (易息晴); ***Denm.***: Combipramol†; Combivent; Ipramol; Sapimol; ***Fin.***: Atrodual; Ipramol; Redol Comp; Salipra†; ***Gr.***: Berovent; Demoren; Ipramol; ***Hong Kong***: Combivent; Ipramol;

Uni-Butamol Expectorant†; Ventide†; Ventolin Expectorant†; ***India***: Aerocort; Aeromist; Aerotide; Aerovent; Airomol; Albutamol; Alernyl-B; Alkarex-PD; Amborex-GS; Ambrex; Ambril-S; Ambril-SG; Ambro PD; Ambro S; Ambro TS; Ambrodil-S; Ambrogen-S; Ambrolax-PD; Ambrolite-S; Ambrolite-ST; Ambros-GM; Ambrosol; Amcare; Amcof; Amrolite 2S; Asmatide-BR; Ast-Ex; Asthacrom†; Asthalin AX; Asthalin Expectorant; Asthavent-BR; Asthos; Axalin-AX†; Axalin; Axol Plus; Benylin E; Brex-S; Brodil; Bronchilet; Broncophyl Plus; Broncordil P; Bronko Plus; Bronkosyrup-EX; Bronmix; Brox; Budesal; C-Cold; Carbasma; Combimist; Coriminic X; Derisone; Duolin; Durabec; Durasalyn; Eascof; Efelin-PD; Efelin; Elkof; Elkuf; Elsol-S; Eto-Salbetol; Exituss; Exol; Expectus; Instaryl-P; Instaryl; Kofarest; LCF; Mastifen-S; Mexol-G; Mituss-AX; Mituss-BR; Muco Asthalin; Mucobar-S; Mucolinc; Mucoresp; Neorex; Okaril; Pulmo-Rest Expectorant†; Pulmo-Rest; Theo-Asthalin; Ventorlin Exp; ***Indon.***: Combivent; Fartolin Expectorant; Lasal Expectorant; Proventol Expectorant; Salbron Expectorant; Salbuven Expectorant; Teosal; Ventide†; Ventolin Expectorant; ***Irl.***: Combineb; Combivent; Ipramol; ***Ital.***: Almeida; Biwind; Breva; Clenil Compositum; Naos; Plenaer; ***Malaysia***: Aerocort; Combivent; Duolin; Ipramol; Salbutamol Expectorant; Ventolin Expectorant†; ***Mex.***: Aeroflux; Apomuxol; Broxol Air; Combivent; Dinolan; Flamebin; Fluvicil; Fluxol; Fultac; Mucoflux; Musaldox; Neumyn-AS; Removil; Salamflux; Sibilex; Solbotex; Ulax-C; Ventide; ***Neth.***: Combipramol†; Combivent; Ipramol; ***NZ***: Combivent; Duolin; ***Philipp.***: Adsal Plus; Asbunyl Plus; Asfrenon GF; Asmalin Broncho; Broncaire Expectorant; Bronchospec; Brytolin; Clarituss Plus; Combipul; Combivent; Duavent; Efamed Plus; Hicaryl; Histaril; Neovent†; Pecof; Pediavent; Pulmodual; Pulmovent; Rhinol Plus; Salbumed Plus; Salvex XP; SGX; Solmux-Broncho (Reformulated); Ventar EXP; Vento-Broncho G; Ventolin Expectorant; Venzadril; ***Port.***: Combivent; Ipramol; Propavente; ***Rus.***: Ascoril Expectorant (Аскорил Экспекторант); Biasten (Биастен); Ipramol (Ипрамол); Jocet (Джосет); Kasnol (Кашнол); ***S.Afr.***: Adco-Combineb; Combivent; Duolin; Duro-Tuss†; ***Singapore***: Combivent; ***Spain***: Butosol; Combiprasal; ***Swed.***: Combivent; Ipramol; Sapimol; ***Switz.***: Dospir; Ipramol; ***Thai.***: Almasal; Asmol Expectorant; Beclosal; Biovent†; Clenil Compositum†; Combivent; Royalin; Sabumol Ex; Salmol Expectorant; Ventolin Expectorant†; ***Turk.***: Clenil Kompoze; Combivent; Ventide; ***UK***: Combivent; Ipramol; ***Ukr.***: Ascoril Expectorant (Аскорил Экспекторант)†; Joset (Джосет); Salbroxol (Сальброксол); ***USA***: Combivent; DuoNeb; ***Venez.***: Aerocort; Aeroflux; Beclosal; Broxodin; Butosol; Combivent; Duolin; Ipralin; Venticort; Ventide.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Salbutamol Capsules; Prolonged-release Salbutamol Tablets; Salbutamol Inhalation Powder, predispensed; Salbutamol Inhalation Powder; Salbutamol Injection; Salbutamol Nebuliser Solution; Salbutamol Oral Solution; Salbutamol Pressurised Inhalation; Salbutamol Tablets;
USP 36: Albuterol Tablets.

Salmeterol Xinafoate

(BANM, USAN, rINNM) ⊗

GR-33343G; Salmaterol Xinafoate; Salmeterol 1-Hydroxy-2-naphthoate; Salmeterol Ksinafoat; Salmétérol, Xinafoate de; Salmeterol, xinafoato de; Salmeterolii Xinafoas; Salmeteroliksinafoaatti; Salmeterolio ksinafoatas; Salmeterolxinafoat; Salmeterol-xinafoát; Sameterolxinafoat; Xinafoato de Salmeterol; Салметерола Ксинафоат.

(*RS*)-5-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl} salicyl alcohol 1-hydroxy-2-naphthoate.

$C_{25}H_{37}NO_4,C_{11}H_8O_3$=603.8

CAS — 89365-50-4 (salmeterol); 94749-08-3 (salmeterol xinafoate).

ATC — R03AC12.

ATC Vet — QR03AC12.

UNII — 6EW8Q962A5.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Salmeterol Xinafoate). A white or almost white powder. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. Protect from light.

USP 36: (Salmeterol Xinafoate). A white or off-white powder. Practically insoluble in water (pH 8.0) and in saline solution (0.9% w/w); slightly soluble in alcohol, in isopropyl alcohol, and in chloroform; soluble in methyl alcohol. Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Salmeterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). When given by inhalation, salmeterol acts as a bronchodilator. The onset of action is about 10 to 20 minutes but the full effect may not be apparent until after several doses. Unlike short-acting $beta_2$ agonists (see Salbutamol, p. 1220.2), salmeterol is therefore not suitable for the symptomatic relief of an acute attack of bronchospasm. However, it is long-acting with a duration of action of about 12 hours and is indicated where the regular use of a long-acting $beta_2$ agonist is required for persistent reversible airways obstruction, as in chronic asthma or in some patients with chronic obstructive pulmonary disease. It may be useful in protecting against nocturnal and exercise-induced asthma attacks. Short-acting $beta_2$ agonists (on an as-required basis) and regular anti-inflammatory therapy should continue to be used.

Salmeterol is used in the form of the xinafoate; doses are expressed in terms of the equivalent amount of salmeterol; salmeterol xinafoate 1.45 micrograms is equivalent to about 1 microgram of salmeterol.

The usual dose is 50 micrograms of salmeterol twice daily from a metered-dose aerosol or dry powder inhaler; if necessary, up to 100 micrograms may be inhaled twice daily. For doses of salmeterol used in children, see Administration in Children, below.

Reviews.

1. Meyer JM, *et al.* Salmeterol: a novel, long-acting $beta_2$-agonist. *Ann Pharmacother* 1993; **27:** 1478–87.
2. Bennett J, Tattersfield A. Drugs in focus: 15. Salmeterol. *Prescribers' J* 1995; **35:** 84–8.
3. Adkins JC, McTavish D. Salmeterol: a review of its pharmacological properties and clinical efficacy in the management of children with asthma. *Drugs* 1997; **54:** 331–54.
4. Jackson CM, Lipworth B. Benefit-risk assessment of long-acting β_2-agonists in asthma. *Drug Safety* 2004; **27:** 243–70.
5. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting β_2-agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; **27:** 689–715.

Administration in children. For persistent reversible airways obstruction that requires regular bronchodilatation, including nocturnal asthma and prevention of exercise-induced asthma, children aged 4 to 12 years may be given 50 micrograms of salmeterol twice daily by inhalation.

Asthma. Salmeterol is a long-acting $beta_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p. 1195.2, generally recommend that salmeterol should be reserved for use in patients with chronic asthma who have already progressed to inhaled corticosteroids; it is not a substitute for corticosteroids. Most evidence suggests that, apart from in severe exacerbations, adding a long-acting $beta_2$ agonist to standard dose inhaled corticosteroid therapy may be more effective than increasing the dose of corticosteroid, or than combining a corticosteroid and an anti-leukotriene drug. Salmeterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, duration of protection against exercise-induced bronchoconstriction is reduced (see Tolerance, p. 1225.2).

References.

1. Lockey RF, *et al.* Nocturnal asthma: effect of salmeterol on quality of life and clinical outcomes. *Chest* 1999; **115:** 666–73.
2. Shrewsbury S, *et al.* Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000; **320:** 1368–73.
3. Holimon TD, *et al.* Nocturnal asthma uncontrolled by inhaled corticosteroids: theophylline or long-acting beta2 agonists. *Drugs* 2001; **61:** 391–418.
4. Johansson G, *et al.* Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. *Clin Drug Invest* 2001; **21:** 633–42.
5. Heyneman CA, *et al.* Fluticasone versus salmeterol/low-dose fluticasone for long-term asthma control. *Ann Pharmacother* 2002; **36:** 1944–9.
6. Bateman ED, *et al.* Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004; **170:** 836–44.
7. Weiler JM, *et al.* Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005; **94:** 65–72.
8. Gibson PG, *et al.* Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).
9. Masoli M, *et al.* Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005; **60:** 730–4.
10. Ducharme FM, *et al.* Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 15/01/08).
11. Walters EH, *et al.* Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
12. The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007; **356:** 2027–39.
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14. Ni Chroinin M, *et al.* Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 17/03/10).
15. Ducharme FM, *et al.* Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 03/08/10).

Chronic obstructive pulmonary disease. Guidelines indicate that long-acting $beta_2$ agonists such as salmeterol may be used for maintenance therapy in moderate and severe chronic obstructive pulmonary disease (see p. 1199.1). Improvement in lung function and symptoms has been seen in such patients after regular treatment with inhaled salmeterol;[1-3] a reduction in exacerbations has also been seen.[4] Additional benefit has been reported from the use of salmeterol with inhaled corticosteroids.[5-7]

1. Boyd G, *et al.* An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; **10:** 815–21.
2. Mahler DA, *et al.* Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999; **115:** 957–65.
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4. Appleton S, *et al.* Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 15/01/08).
5. Calverley P, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; **361:** 449–56. Correction. *ibid.*; 1660.
6. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; **67:** 2383–2405.
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Adverse Effects and Precautions

As for Salbutamol, p. 1221.3. Inhalation of salmeterol may be associated with paradoxical bronchospasm, and it should not be used in patients who are not also receiving an inhaled corticosteroid. Very rarely, arthralgia has been reported with salmeterol use.

Salmeterol is not appropriate for the treatment of acute bronchospasm or for patients whose asthma is deteriorating.

Effects on the cardiovascular system. A pooled analysis[1] of safety data from 7 studies of salmeterol in chronic obstructive pulmonary disease found no evidence of an increased risk of cardiovascular adverse effects. The duration of these studies had ranged from 12 weeks to 1 year. For further discussion of $beta_2$ agonist use (including salmeterol) and the risk of cardiac events such as myocardial infarction, see Effects on the Heart, under Salbutamol, p. 1222.1

1. Ferguson GT, *et al.* Cardiovascular safety of salmeterol in COPD. *Chest* 2003; **123:** 1817–24.

Effects on the respiratory system. Transient paradoxical bronchoconstriction with breathlessness, wheeze, or cough has been reported in 6 asthmatic patients after inhalation of salmeterol from a metered-dose aerosol but not after inhalation of the dry powder formulation by diskhaler.[1] The fluorocarbon propellants in the metered-dose aerosol were suspected as the irritants causing bronchoconstriction.

1. Wilkinson JRW, *et al.* Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler. *BMJ* 1992; **305:** 931–2.

Effects on the skin. Urticarial rash associated with inhaled salmeterol, of which the propellant was not the cause, has been reported. Although many urticarial reactions and a variety of rashes had been attributed to beta-agonist therapy their reproducibility had not always been documented.[1]

1. Hatton MQF, *et al.* Salmeterol rash. *Lancet* 1991; **337:** 1169–70.

Increased mortality. Interim results from a large controlled study (SMART)[1] designed to evaluate the safety of salmeterol in patients with *asthma*, found a small but statistically significant increase in respiratory-related and asthma-related deaths or life-threatening episodes in the total population receiving salmeterol compared with placebo. This imbalance occurred mainly in the African-American subpopulation, and combined with difficulties in enrolment, led to early termination of the study. Various factors may have influenced the differences in outcomes seen with salmeterol; greater disease severity was noted at baseline in the African-American subgroup compared with Caucasian subjects, and nearly half of all participants were not receiving inhaled corticosteroids.

A subsequent meta-analysis[2] of 19 placebo-controlled studies of patients with asthma who were taking the long-acting $beta_2$ agonists salmeterol or formoterol (see p. 1209.2), reported an increased risk of hospitalisation for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo. A subgroup analysis that examined studies in which more than 75% of patients were also receiving inhaled corticosteroids also found an increased risk of hospital admission. The applicability of this review to therapy as recommended by current guidelines has been questioned,[3] as many of the studies included in the primary analysis did not require inhaled corticosteroids to be used, and studies which compared different asthma maintenance regimens were excluded because they were not placebo-controlled.

Systematic reviews of regular treatment with salmeterol[4] or formoterol[5] for chronic asthma found an increased risk of

serious non-fatal adverse effects compared with placebo. In contrast, subsequent reviews of regular treatment with salmeterol[6] or formoterol[7] plus inhaled corticosteroids found no difference in serious adverse effects when compared with inhaled corticosteroids although results were not sufficient to conclude that there was no increased risk. Additionally, the number of deaths was too small to allow a firm conclusion to be reached on the effect of long-acting $beta_2$ agonists on mortality. A direct toxic effect of $beta_2$ agonists,[7] concomitant asthma treatments and adherence to treatment,[8,9] differences in baseline disease severity,[1,8] racial or genetic factors,[1] polymorphism,[10] tolerance,[10,11] and masking of underlying airway inflammation by long-acting $beta_2$ agonists[10] have all been proposed as possible explanations for the increased risk of adverse outcomes reported with long-acting $beta_2$ agonists.

In contrast to the above studies, a meta-analysis[12] of 66 manufacturer-sponsored studies involving 20 966 patients with persistent asthma, suggested that the addition of salmeterol to inhaled corticosteroids did not alter the risk for asthma-related hospitalisation compared with inhaled corticosteroids alone, although asthma-related intubation or death was too infrequent to draw conclusions. In addition, a case-control study[13] that included 532 patients under age 65 who had died from asthma, matched with 532 controls with a hospital admission for asthma, found no evidence of adverse effects on mortality with medium to long-term use of inhaled long-acting $beta_2$ agonists. An earlier observational cohort study also found no evidence that salmeterol contributed to deaths reported from asthma.[14]

Current asthma guidelines advocate use of a long-acting $beta_2$ agonist in addition to inhaled corticosteroids, and not as monotherapy, see Management of Asthma, p. 1195.2. A review[15] by the UK MHRA concluded that:

- epidemiological data indicated that since the introduction of long-acting beta agonists there had been a reduction in asthma-related hospitalisations in adolescents and a decrease in asthma-related mortality in all ages.
- data from controlled clinical study did not reflect the safety concern from postmarketing studies, possibly due to more consistent use of corticosteroids in controlled settings
- the data supported the use of long-acting beta agonists with inhaled corticosteroids consistent with the UK guidelines on the management of asthma and that to aid compliance in the concomitant use of a corticosteroid, a combination inhaler should be used when appropriate

A systematic review in patients with stable, moderate-to-severe *chronic obstructive pulmonary disease* found that the use of long-acting $beta_2$ agonists was not associated with a higher rate of respiratory-related mortality compared with placebo.[16]

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2. Salpeter SR, *et al.* Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006; **144:** 904–12.
3. Ernst P, *et al.* Safety and effectiveness of long-acting inhaled β-agonist bronchodilators when taken with inhaled corticosteroids. *Ann Intern Med* 2006; **145:** 692–4.
4. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 12/08/09).
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9. Nelson HS, Dorinsky PM. Safety of long-acting β-agonists. *Ann Intern Med* 2006; **145:** 706.
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14. Mann RD, *et al.* Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996; **49:** 247–50.
15. MHRA/CHM. Long-acting $beta_2$ agonists for asthma: review. *Drug Safety Update* 2008; **1** (6): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033510&RevisionSelectionMethod=LatestReleased (accessed 22/05/08)
16. Rodrigo GJ, *et al.* Safety of long-acting β-agonists in stable COPD: a systematic review. *Chest* 2008; **133:** 1079–87.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies salmeterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Tolerance. As with short-acting $beta_2$ agonists (see Salbutamol, p. 1222.3), there is evidence that regular use of long-acting $beta_2$ agonists such as salmeterol produces tachyphylaxis to their protective effect against bronchoconstriction, as provoked by stimuli such as allergen, methacholine, or exercise.[1-4] The authors of a study of the long-term effect of salmeterol on exercise-induced asthma concluded that the decreased bronchoprotective effect over time was due to a decrease in duration of action (to less than 9 hours) rather than tachyphylaxis,[5] but this interpretation was criticised.[6,7]

There is also some evidence to suggest that symptomatic relief by short-acting $beta_2$ agonists is significantly reduced by regular use of long-acting $beta_2$ agonists.[8,9] Receptor downregulation, induced by regular use of a long-acting $beta_2$ agonist, has been suggested as the mechanism for this reduction in response and may lead to patients requiring higher doses of $beta_2$ agonists to attain relief from an acute asthma attack.[9,10] One study suggested that the greater tachyphylaxis to short-acting $beta_2$ agonists seen with salmeterol compared with formoterol might represent the expression of partial antagonism by salmeterol at $beta_2$ receptors.[8] Whatever the mechanism, the reduced bronchoprotective effect is perhaps more of a concern with long-acting $beta_2$ agonists, since, unlike the short-acting $beta_2$ agonists, their use on a regular basis is recommended.[11] See also $Beta_2$ Agonists, under Interactions of Salbutamol, p. 1223.1.

1. Cheung D, *et al.* Long-term effects of a long-acting $beta_2$-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; **327:** 1198–1203.
2. Bhagat R, *et al.* Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1995; **108:** 1235–9.
3. Booth H, *et al.* Salmeterol tachyphylaxis in steroid treated asthmatic subjects. *Thorax* 1996; **51:** 1100–4.
4. Simons FER, *et al.* Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997; **99:** 655–9.
5. Nelson JA, *et al.* Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998; **339:** 141–6.
6. Aziz I, Lipworth BJ. Exercise-induced asthma. *N Engl J Med* 1998; **339:** 1783.
7. Dickey BF, Adachi R. Exercise-induced asthma. *N Engl J Med* 1998; **339:** 1783–4.
8. van Veen A, *et al.* A comparison of salmeterol and formoterol in attenuating airway responses to short-acting $beta_2$-agonists. *Pulm Pharmacol Ther* 2003; **16:** 153–61.
9. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. Abridged version: *Respir Res* 2005; **6:** 107. Full version: http://respiratory-research.com/content/6/1/107 (accessed 15/01/08)
10. Lipworth BJ. Airway subsensitivity with long-acting $beta_2$-agonists: is there cause for concern? *Drug Safety* 1997; **16:** 295–308.
11. Abisheganaden J, Bonshey HA. Long-acting inhaled $beta_2$-agonists and the loss of "bronchoprotective" efficacy. *Am J Med* 1998; **104:** 494–7.

Interactions

As for Salbutamol, p. 1223.1.

Salmeterol is metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with oral ketoconazole has resulted in an increased systemic exposure to inhaled salmeterol with the potential to increase adverse effects; similar interactions could occur with other potent inhibitors of CYP3A4. Licensed product information suggests that salmeterol and ketoconazole should not be used together. Use of salmeterol with erythromycin, a moderate inhibitor of CYP3A4, did not have a significant effect on exposure to salmeterol.

For a study suggesting a decreased effect of salbutamol in patients receiving salmeterol, as well as a report of additive effects, see $Beta_2$ Agonists under Interactions of Salbutamol, p. 1223.1.

Pharmacokinetics

After inhalation of therapeutic doses of salmeterol, only low concentrations occur in the plasma. Salmeterol is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 to α-hydroxy-salmeterol, which is eliminated mainly in the faeces.

Reviews.

1. Cazzola M, *et al.* Clinical pharmacokinetics of salmeterol. *Clin Pharmacokinet* 2002; **41:** 19–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Serevent; ***Austral.***: Serevent; ***Austria***: Serevent; ***Belg.***: Serevent; ***Braz.***: Serevent; ***Canad.***: Serevent; ***Chile***: Serevent; Xemos; ***China***: Ping Te (平特); Qitai (祺泰); Serevent (施立稳); Si Duo Mi (司多米); ***Cz.***: Serevent; ***Denm.***: Serevent; ***Fin.***: Serevent; ***Fr.***: Serevent; ***Ger.***: Aeromax†; Serevent; ***Gr.***: Salment; Serevent; ***Hong Kong***: Serevent; ***Hung.***: Serevent; ***India***: Azrol; Salmeter; Serobid; ***Indon.***: Serevent†; ***Irl.***: Serevent; ***Israel***: Serevent; ***Ital.***: Arial; Salmetedur; Serevent; ***Jpn***: Serevent; ***Malaysia***: Serevent†; ***Mex.***: Serevent; ***Neth.***: Serevent; ***Norw.***: Serevent; ***NZ***: Serevent; ***Philipp.***: Serevent†; ***Pol.***: Pulmoterol; Serevent; ***Port.***: Dilamax; Serevent; Ultrabeta; ***Rus.***: Serevent (Серевент); ***S.Afr.***: Serevent; ***Singapore***: Serevent; ***Spain***: Beglan; Betamican; Inaspir; Serevent; ***Swed.***: Serevent; ***Switz.***: Serevent; ***Thai.***: Serevent; ***Turk.***: Astmerole; Serevent; ***UK***: Neovent; Serevent; ***USA***: Serevent; ***Venez.***: Salspray; Serevent.

Multi-ingredient Preparations. ***Arg.***: Crivanil Plus; Flutivent; Lirtodac Plus; Neumotide; Proair Bronquial; Seretide; ***Austral.***: Seretide; ***Austria***: Seretide; Viani; ***Belg.***: Seretide; Viani†; ***Braz.***: Seretide; ***Canad.***: Advair; ***Chile***: Aerometrol Plus; Aurituss; Brexotide; Flunacross-S; Fluxamol; Seretide; ***China***: Seretide (舒利迭); ***Cz.***: Duaspir†; Seretide; ***Denm.***: Aliflus†; Seretaide; Seretide; ***Fin.***: Seretide; Viani; ***Fr.***: Seretide; ***Ger.***: Atmadisc; Viani; ***Gr.***: Byany; Rolenium; Seretide; Viani; ***Hong Kong***: Seretide; ***Hung.***: Seretide; Thoreus; ***India***: Combitide; Esiflo; Forair; Seretide; Seroflo; ***Indon.***: Seretide; ***Irl.***: Seretide; Viani; ***Israel***: Seretide; ***Ital.***: Aliflus; Seretide; ***Malaysia***: Seretide; ***Mex.***: Flixovent; Seretide; ***Neth.***: Aliflus; Brisair†; Seretide; ***Norw.***: Seretide; ***NZ***: Seretide; ***Philipp.***: Salmeflo; Seretide; ***Pol.***: Seretide; ***Port.***: Brisomax; Maizar; Seretaide; Veraspir; ***Rus.***: Seretide (Серетид); Tevacomb (Тевакомб); ***S.Afr.***: Foxair; Sereflo; Seretide; ***Singapore***: Seretide; ***Spain***: Anasma; Brisair; Inaladuo; Plusvent; Seretide; ***Swed.***: Seretide; ***Switz.***: Seretide; ***Thai.***: Seretide; Seroflo; ***Turk.***: Respiro; Seretide; ***UK***: Seretide; ***Ukr.***: Seretide (Серетид); ***USA***: Advair; ***Venez.***: Seretide.

Seratrodast *(USAN, rINN)*

A-73001; AA-2414; Abbott-73001; ABT-001; Sératrodast; Seratrodastum; Сератродаст.

(±)-2,4,5-Trimethyl-3,6-dioxo-ζ-phenyl-1,4-cyclohexadiene-1-heptanoic acid.

$C_{22}H_{26}O_4$=354.4

CAS — 112665-43-7; 103186-19-2.

ATC — R03DX06.

ATC Vet — QR03DX06.

UNII — 4U58JM421N.

Profile

Seratrodast is a thromboxane A_2 antagonist that is reported to reduce airway hyperresponsiveness. It is given orally in the prophylactic management of asthma (p. 1195.2), in single doses of 80 mg in the evening after food.

Adverse effects include gastrointestinal disturbances, drowsiness, headache, palpitations, and hepatitis. Hepatic function should be monitored and the drug should be withdrawn if hypersensitivity reactions such as rashes and pruritus occur, or if there is elevation of liver enzyme values. Seratrodast should be used with care in patients with pre-existing hepatic impairment. It is not suitable for the treatment of an acute asthmatic attack.

References.

1. Tamaoki J, *et al.* Effect of a thromboxane A_2 antagonist on sputum production and its physicochemical properties in patients with mild to moderate asthma. *Chest* 2000; **118:** 73–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Changnuo (畅诺); Quan Kang Nuo (荃康诺); ***Jpn***: Bronica.

Sodium Cromoglicate *(BANM, rINNM)*

Cromoglicate de Sodium; Cromoglicato de sodio; Cromoglicato disódico; Cromolyn Sodium (USAN); Dinatrii Cromoglicas; Dinatrium-chromoglykát; Disodium Cromoglycate; FPL-670; Natrii Cromoglicas; Natrio kromoglikatas; Natriumchromoglicat; Natriumcromoglicat; Natriumkromoglikaatti; Natriumkromoglikat; Nátrium-kromoglikát; Sodium, cromoglicate de; Sodium Cromoglycate; Sodyum Kromoglikat; Натрий Кромоглицият.

Disodium 4,4′-dioxo-5,5′-(2-hydroxytrimethylenedioxy)di(4*H*-chromene-2-carboxylate).

$C_{23}H_{14}Na_2O_{11}$=512.3

CAS — 16110-51-3 (cromoglicic acid); 15826-37-6 (sodium cromoglicate).

ATC — A07EB01; D11AX17, R01AC01; R03BC01; S01GX01.

ATC Vet — QA07EB01; QD11AH03; QR01AC01; QR03BC01; QS01GX01.

UNII — Q2WXR1I0PK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Sodium Cromoglicate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Cromolyn Sodium). A white, odourless, hygroscopic, crystalline powder. Soluble in water; insoluble in alcohol and in chloroform. Store in airtight containers.

Uses and Administration

Sodium cromoglicate is used for the prevention of allergic reactions. Although its precise mode of action remains uncertain, it is believed to act mainly by preventing release of mediators of inflammation from sensitised mast cells through stabilisation of mast-cell membranes. It has no direct antihistamine or anti-inflammatory action.

Sodium cromoglicate can prevent the asthmatic response to a variety of allergic and non-allergic stimuli. It is used in the management of chronic asthma that cannot be managed with inhaled $beta_2$ agonists alone; it is not used for acute attacks of asthma.

Sodium cromoglicate is also used in the prophylaxis and treatment of seasonal and perennial allergic rhinitis and allergic conditions of the eye including acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis. It has been given orally, with dietary restriction, for the prevention of food allergies, and is also used in the treatment of mastocytosis.

It is important that the regular use of sodium cromoglicate is maintained, both in the prophylactic control of asthma and in the management of other allergic conditions. Beneficial effects may take several weeks to become established.

In the prophylaxis of **asthma**, sodium cromoglicate is given by inhalation as a nebulised solution or from a metered-dose aerosol. The usual dose as nebulised solution is 20 mg by inhalation 4 times daily increased, if necessary, to 6 or 8 times daily. Once the asthma has been stabilised it may be possible to reduce the dosage. In some countries, sodium cromoglicate is available in different strengths of metered-dose aerosol. Using a metered-dose aerosol providing 5 mg per inhalation, the usual dose is 10 mg four times daily, increased to 6 to 8 times daily if necessary; it may be possible to reduce the dosage to 5 mg four times daily once the asthma has been stabilised. Additional doses may be taken before exercise. Metered-dose aerosols providing 1 mg per inhalation are also available. The usual dose is 2 mg four times daily, which can be doubled if necessary. The adequacy of the lower dosage has been questioned (see under Administration, below).

Inhalation of sodium cromoglicate may cause bronchospasm; separate inhalation of a $beta_2$ agonist such as salbutamol a few minutes beforehand should prevent this. Use of a combination product containing a $beta_2$ agonist is not recommended as this is liable to be used inappropriately for relief of bronchospasm rather than for its prophylactic effect.

For the prophylaxis of **allergic rhinitis**, sodium cromoglicate solution can be given as a nasal spray. A 4% spray that delivers about 5 mg per actuation may be given as one spray into each nostril 2 to 4 times daily. Prophylactic treatment for seasonal allergic rhinitis should begin 2 to 3 weeks before exposure to the offending allergen and should continue throughout the season. In **allergic conjunctivitis** and **vernal keratoconjunctivitis**, sodium cromoglicate is used as drops of 2 or 4%, applied 4 to 6 times daily.

In **food allergy** and in **mastocytosis**, sodium cromoglicate may be given in oral doses of 200 mg four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled, but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled.

For details of doses in children, see Administration in Children below.

Action. Sodium cromoglicate has a range of actions at cellular level that may be important for its protective effect in asthma. It is known as a mast cell stabiliser that inhibits the release of histamine and other inflammatory mediators from sensitised mast cells. Other reported actions include a direct effect on airway nerves[1,2] and antagonism[3] of substance P, which ties up with its inhibition of the effects of platelet activating factor (PAF).[4,5]

There have been a few reports[6-8] of sodium cromoglicate producing bronchodilatation. However, in practice other drugs with accepted bronchodilating activity are used for this effect in asthma treatment schedules, see p. 1195.2.

1. Barnes PJ. Asthma as an axon reflex. *Lancet* 1986; **i:** 242–5.
2. Dixon M, *et al.* The effects of sodium cromoglycate on lung irritant receptors and left ventricular cardiac receptors in the anaesthetized dog. *Br J Pharmacol* 1979; **67:** 569–74.
3. Page C. Sodium cromoglycate, a tachykinin antagonist? *Lancet* 1994; **343:** 70.
4. Morley J, *et al.* The platelet in asthma. *Lancet* 1984; **ii:** 1142–4.
5. Morley J. PAF and airway hyperreactivity: prospects for novel prophylactic anti-asthma drugs. In: *PAF, Platelets, and Asthma*, Basel, Birkhäuser Verlag, 1987: 87–95.
6. Horn CR, *et al.* Bronchodilator effect of disodium cromoglycate administered as a dry powder in exercise induced asthma. *Br J Clin Pharmacol* 1984; **18:** 798–801.
7. Weiner P, *et al.* Bronchodilating effect of cromolyn sodium in asthmatic patients at rest and following exercise. *Ann Allergy* 1984; **53:** 186–8.
8. Yuksel B, Greenough A. Bronchodilator effect of nebulized sodium cromoglycate in children born prematurely. *Eur Respir J* 1993; **6:** 387–90.

Administration. The efficacy of sodium cromoglicate 2 mg four times daily by metered-dose aerosol inhaler has been shown by controlled studies in adults and children with asthma.[1-5] However, although sodium cromoglicate 2 mg by inhalation from a metered-dose aerosol was reported[6] to be as effective as 20 mg inhaled as powder, the tenfold difference in dosage has been questioned,[7] and others have reported contrary results.[8,9] It has been suggested that an aerosol supplying 5 mg per metered dose (see Uses and Administration, above) would be preferable.[10] In a comparison of single-dose pretreatment from metered-dose inhalers, sodium cromoglicate 10 mg (2 X 5 mg puffs) was as effective as beclometasone dipropionate 200 micrograms in inhibiting bronchial responsiveness to histamine.[11]

Care is required if inhaled sodium cromoglicate is given via a spacer device; evidence suggests that these may greatly influence the amount of drug delivered, reducing it to one-third of the dose delivered by inhaler actuation in some cases.[12]

1. Geller-Bernstein C, Levin S. Sodium cromoglycate pressurised aerosol in childhood asthma. *Curr Ther Res* 1983; **34:** 345–9.
2. Wheatley D. Sodium cromoglycate in aerosol form in regular users of bronchodilator drugs. *Curr Med Res Opin* 1983; **8:** 333–7.
3. Rubin AE, *et al.* The treatment of asthma in adults using sodium cromoglycate pressurized aerosol: a double-blind controlled trial. *Curr Med Res Opin* 1983; **8:** 553–8.
4. Blumenthal MN, *et al.* A multicenter evaluation of the clinical benefits of cromolyn sodium aerosol by metered-dose inhaler in the treatment of asthma. *J Allergy Clin Immunol* 1988; **81:** 681–7.
5. Selcow JE, *et al.* Clinical benefits of cromolyn sodium aerosol (MDI) in the treatment of asthma in children. *Ann Allergy* 1989; **62:** 195–9.
6. Latimer KM, *et al.* Inhibition by sodium cromoglycate of bronchoconstriction stimulated by respiratory heat loss: comparison of pressurised aerosol and powder. *Thorax* 1984; **39:** 277–81.
7. Anonymous. Sodium cromoglycate aerosol. *Drug Ther Bull* 1982; **20:** 27.
8. Robson RA, *et al.* Sodium cromoglycate: spincaps or metered dose aerosol. *Br J Clin Pharmacol* 1981; **11:** 383–4.
9. Bar-Yishay E, *et al.* Duration of action of sodium cromoglycate on exercise induced asthma: comparison of 2 formulations. *Arch Dis Child* 1983; **58:** 624–7.
10. Tullett WM, *et al.* Dose-response effect of sodium cromoglycate pressurised aerosol in exercise induced asthma. *Thorax* 1985; **40:** 41–4.
11. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987; **79:** 734–40.
12. Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996; **51:** 835–40.

Administration in children. Children may be given sodium cromoglicate for prophylactic management of asthma and allergic rhinitis, and in the prophylaxis and treatment of acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis, using adult doses, see Uses and Administration, above. Different countries may have different licensed lower age limits and some inhalation dosage forms are unsuitable in very young children.

In food allergy and in mastocytosis, sodium cromoglicate may be given orally to children from 2 years of age. A dose of 100 mg is given four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled. For food allergy, adult doses may be given to children from 14 years of age, and from 13 years for mastocytosis, see above.

Asthma. Sodium cromoglicate is used as a prophylactic agent in the management of chronic asthma (p. 1195.2), but in practice inhaled corticosteroids are preferred if regular prophylactic treatment is indicated, i.e. if the condition cannot be managed with occasional use of an inhaled short-acting $beta_2$ agonist alone. Even in children, in whom cromoglicate has tended to be more widely used, inhaled corticosteroids are considered first-line preventers. A systematic review[1] comparing sodium cromoglicate with inhaled corticosteroids found that inhaled corticosteroids were superior in terms of asthma control and lung function for both children and adults with chronic asthma. However, guidelines still specify the use of cromoglicate or nedocromil as a valid alternative to inhaled corticosteroids in some circumstances. Another systematic review[2] found insufficient evidence to conclude that sodium cromoglicate was more effective than placebo for maintenance treatment of chronic asthma in children, although the results favoured treatment for some outcomes such as symptom scores and bronchodilator use.

Response to treatment with nebulised sodium cromoglicate was found to be age-related in a study of children under 2 years of age with recurrent or persistent wheezy bronchitis and a history of allergic symptoms.[3] It was effective in children of 12 to 24 months of age but not in those below 12 months. Similarly, nebulised sodium cromoglicate was no more effective than placebo in the treatment of a group of 31 infants with persistent wheezing aged under 1 year.[4]

1. Guevara JP, *et al.* Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
2. van der Wouden JC, *et al.* Inhaled sodium cromoglycate for asthma in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 14/08/09).
3. Geller-Bernstein C, Levin S. Nebulised sodium cromoglycate in the treatment of wheezy bronchitis in infants and young children. *Respiration* 1982; **43:** 294–8.
4. Furfaro S, *et al.* Efficacy of cromoglycate in persistently wheezing infants. *Arch Dis Child* 1994; **71:** 331–4.

Cogan's syndrome. Sodium cromoglicate eye drops improved blurred vision in a patient who had had Cogan's syndrome (p. 1603.2) for 18 years.[1] Sodium cromoglicate capsules [orally] also reduced the frequency of fever attacks in this patient.

1. Carter F, Nabarro J. Cromoglycate for Cogan's syndrome. *Lancet* 1987; **i:** 858.

Cough. Sodium cromoglicate has been used with modest success by aerosol inhalation to suppress the cough associated with ACE inhibitor therapy (p. 1285.3) in some patients.[1,2] However, inhalation of nedocromil sodium was not helpful in the treatment of ACE inhibitor induced cough in 6 diabetic patients.[3] A systematic review[4] considered that there was no good evidence to support the use of inhaled cromoglicate or nedocromil in the treatment of non-specific cough in children.

1. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; **341:** 560.
2. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; **345:** 13–16.
3. Puolijoki H, Rekiaro M. Lack of effect of nedocromil sodium in ACE-inhibitor-induced cough. *Lancet* 1995; **345:** 394.
4. Chang A, *et al.* Inhaled cromones for prolonged non-specific cough in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).

Eczema. A 4% sodium cromoglicate lotion was found to be of benefit in improving symptoms and reducing topical corticosteroid use in a study[1] in children with moderately severe atopic dermatitis (p. 1684.1).

1. Stainer R, *et al.* Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2–12 years: a double-blind, randomized, placebo-controlled trial. *Br J Dermatol* 2005; **152:** 334–41.

Food allergy. Oral sodium cromoglicate has been used in the prophylaxis of food allergy reactions (p. 611.2). However, efficacy has not been unequivocally established.

Mastocytosis. Mastocytosis is a rare condition characterised by abnormal proliferation of mast cells and their accumulation in body tissues.[1-3] Signs and symptoms of the disease result from the spontaneous or induced release of mast cell mediators. Mastocytosis occurs in cutaneous or systemic forms, which are further subdivided based on clinical presentation and prognosis. Clinical algorithms and recommendations for diagnosis, treatment, and response criteria have been developed.[4-6]

- *Cutaneous mastocytosis* most often manifests as urticaria pigmentosa (disseminated red-brown macules, papules, or plaques); other symptoms include flushing, pruritus, urticaria, blistering, and dermatographism. Mastocytomas may occur as brownish solitary or multiple nodular accumulations of mast cells. In children with cutaneous mastocytosis, symptoms will resolve in about half by adolescence.
- *Systemic mastocytosis* can involve diverse organs and tissues including the bones, liver, spleen, lymph nodes, haematopoietic system, gastrointestinal tract, and also the skin. General symptoms include fatigue, weight loss, fever, and sweats. Gastrointestinal complaints such as abdominal pain and diarrhoea are common, and some patients have malabsorption, steatorrhoea, or peptic ulcer disease. Bone marrow involvement may result in bone pain, osteoporosis, fractures, bone marrow fibrosis, and myeloproliferative and myelodysplastic diseases. Other systemic effects include lymphadenopathy, hepatosplenomegaly, headache and other neuropsychiatric symptoms, syncope, and anaphylactoid reactions.

Avoidance of trigger factors is an important measure in the management of mastocytosis. Such factors include exposure to extremes of cold or heat (hot bath or sunbathing), emotional stress, mechanical irritation (vigorous towel rubbing, massage), infections, alcohol, some drugs (e.g. aspirin, NSAIDs, opioid analgesics, sympathomimetics, polymyxin B, dextran, radiographic dyes), and animal venoms.[1,2,5,7]

Treatment is aimed at relieving symptoms and does not alter the course of the disease.[1,2,4,5,7,8] H_1-antagonist antihistamines such as hydroxyzine and cyproheptadine are used to provide relief of flushing, pruritus, urticaria, blistering, and abdominal pain. Patients at risk of anaphylactoid reactions should carry adrenaline for self-

injection, and those who have repeated reactions should be given prophylactic antihistamines. H_2-antagonist antihistamines such as cimetidine, and proton pump inhibitors such as omeprazole, are used to manage gastrointestinal symptoms, particularly gastritis and peptic ulcer disease. Bisphosphonates may be helpful for osteopenia and bone pain. Sodium cromoglicate is given to manage abdominal pain, nausea, and diarrhoea. It may also provide some relief of headache, neuropsychiatric symptoms, and skin symptoms in some patients. Photochemotherapy using an oral psoralen with ultraviolet A irradiation (PUVA—see p. 1712.1) has been used to reduce cutaneous manifestations of mastocytosis, but urticaria pigmentosa usually recurs within several weeks. Topical PUVA appears to be ineffective. Mastocytomas that cause symptoms may be treated with local PUVA or potent topical corticosteroids. Although surgical removal may be considered, the majority of mastocytomas will involute spontaneously.

Other treatments have also been tried in the treatment of small numbers of patients with aggressive systemic mastocytosis. Mixed results have been reported with the use of interferon alfa.[1] There is a report of ciclosporin with methylprednisolone being used successfully.[4] Imatinib has been used successfully in systemic mastocytosis with associated eosinophilia and with a mutation of the platelet-derived growth factor receptor-α gene on chromosome 4q12.[8] Beneficial responses to cladribine have also occurred in a small number of patients with systemic disease.[8,9]

1. Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; **144:** 682–95.
2. Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child* 2002; **86:** 315–19.
3. Castells MC. Mastocytosis: classification, diagnosis, and clinical presentation. *Allergy Asthma Proc* 2004; **25:** 33–6.
4. Valent P, *et al*. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; **37:** 435–53.
5. de la Hoz B, *et al*. Guías clínicas para el diagnóstico, tratamiento y seguimiento de las mastocitosis. *An Sist Sanit Navar* 2008; **31:** 11–32.
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7. Almahroos M, Kurban AK. Management of mastocytosis. *Clin Dermatol* 2003; **21:** 274–7.
8. Tefferi A, Pardanani A. Systemic mastocytosis: current concepts and treatment advances. *Curr Hematol Rep* 2004; **3:** 197–202.
9. Kluin-Nelemans HC, *et al*. Cladribine therapy for systemic mastocytosis. *Blood* 2003; **102:** 4270–6.

Rhinitis and conjunctivitis. Many drugs, including sodium cromoglicate, are used in the management of allergic rhinitis (p. 612.1) and conjunctivitis (p. 611.1). There is some evidence that nedocromil[1] or lodoxamide[2] may be more effective than cromoglicate in the management of vernal keratoconjunctivitis.

1. El Hennawi M. A double-blind placebo controlled group comparative study of ophthalmic sodium cromoglycate and nedocromil sodium in the treatment of vernal keratoconjunctivitis. *Br J Ophthalmol* 1994; **78:** 365–9.
2. Leonardi A, *et al*. Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol* 1997; **81:** 23–6.

Sickle-cell disease. Sodium cromoglicate has been investigated[1,2] for its potential benefits in patients with sickle-cell disease (p. 1123.2).

1. Toppet M, *et al*. Antisickling activity of sodium cromoglicate in sickle-cell disease. *Lancet* 2000; **356:** 309.
2. Karimi M, *et al*. Clinical response of patients with sickle cell anemia to cromolyn sodium nasal spray. *Am J Hematol* 2006; **81:** 809–16.

Adverse Effects

Inhalation of sodium cromoglicate may cause transient bronchospasm, wheezing, cough, nasal congestion, and irritation of the throat. Nausea, headache, dizziness, an unpleasant taste, and joint pain and swelling have been reported. Other reactions include aggravation of existing asthma, urticaria, rashes, pulmonary infiltrates with eosinophilia, dysuria, and urinary frequency. Severe hypersensitivity reactions such as marked bronchospasm, laryngeal oedema, angioedema, hypotension, and anaphylaxis have been reported rarely.

Intranasal use of sodium cromoglicate may cause transient irritation of the nasal mucosa, sneezing, and occasionally epistaxis. Nausea, skin rashes, and joint pains have occurred when it is taken orally. Transient burning and stinging have occasionally been reported after use of sodium cromoglicate eye drops.

Formulation. Some of the adverse effects reported with sodium cromoglicate may be due to its formulation: there is a view that some of the irritant effects reported on inhalation may be due to the use of dry powder inhalers. It has also been suggested that in some patients receiving sodium cromoglicate via a nebuliser, hypotonicity of the nebuliser solution may induce bronchospasm,[1] although others consider this debatable.[2] Nausea, bloating, abdominal cramps, and flatulence developed in a 24-year-old lactase-deficient woman 2 hours after the use of sodium cromoglicate (*Intal*) inhalation capsules via a turbo-haler for exercise-induced asthma.[3] These symptoms recurred on rechallenge and were attributed to ingestion of lactose contained within the capsules.

1. Chin TW, Nussbaum E. Detrimental effect of hypotonic cromolyn sodium. *J Pediatr* 1992; **120:** 641–3.
2. Rachelefsky GS, *et al*. Detrimental effects of hypotonic cromolyn sodium. *J Pediatr* 1992; **121:** 992.
3. Brandstetter RD, *et al*. Lactose intolerance associated with Intal capsules. *N Engl J Med* 1986; **315:** 1613–14.

Precautions

Sodium cromoglicate has no role in the treatment of acute asthmatic attacks. Withdrawal of sodium cromoglicate may lead to recurrence of the symptoms of asthma. Should withdrawal be necessary it has been suggested that the dose be reduced gradually over a period of one week; patients in whom sodium cromoglicate therapy has permitted a reduction of corticosteroid dosage may require restoration of full corticosteroid cover.

Systemic corticosteroid therapy that has been reduced or stopped in asthmatic patients may need to be reinstated if symptoms increase, during periods of stress such as infection, illness, trauma, or severe antigen challenge, or where airways obstruction impairs inhalation of sodium cromoglicate.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium cromoglicate as probably not porphyrinogenic when used intranasally; it may be used as a drug of first choice and no precautions are needed. It is classified as not porphyrinogenic when used orally, by inhalation, or ophthalmically.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Pregnancy. Sodium cromoglicate is generally considered a low-risk drug for use during pregnancy.[1] Experience with nedocromil is more limited, but licensed product information for both sodium cromoglicate and nedocromil states that cumulative clinical experience of use during pregnancy suggests that they have no adverse effects on fetal development. However, a prospective case-control study,[2] while finding that gestational exposure to asthma medications was safe overall, was unable to rule out an increased risk of musculoskeletal malformations associated with cromones (sodium cromoglicate and nedocromil) based on a small number of exposures.

1. Gilbert C, *et al*. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. *Drug Safety* 2005; **28:** 707–19.
2. Tata LJ, *et al*. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax* 2008; **63:** 981–7.

Pharmacokinetics

After inhalation as a powder or aerosol, the amount of sodium cromoglicate absorbed from the respiratory tract is about 10%. Less than 7% of an intranasal dose is absorbed via the nasal mucosa, and about 0.03% of an ophthalmic dose is reported to be absorbed.

Most of an inhaled or intranasal dose is exhaled or deposited in the oropharynx, swallowed, and excreted via the gastrointestinal tract, as only about 1% of a dose is absorbed from the gut. The portion that is absorbed is excreted unchanged in the urine and bile in about equal amounts. The terminal elimination half-life has been reported to be about 20 minutes after intravenous dosage, but the elimination half-life after oral doses or inhalation is about 80 minutes.

A study[1] in patients with exercise-induced asthma concluded that the plasma concentration of cromoglicate was almost certainly not related directly to its protective effect, although another study in asthmatic children given sodium cromoglicate by dry-powder inhalation, found both blood concentration and clinical response to be correlated with inhalation technique.[2]

1. Patel KR, *et al*. Plasma concentrations of sodium cromoglycate given by nebulisation and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect. *Br J Clin Pharmacol* 1986; **21:** 231–3.
2. Yahav Y, *et al*. Sodium cromoglycate in asthma: correlation between response and serum concentrations. *Arch Dis Child* 1988; **63:** 592–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Claroftal; Intal; Klonalcrom; ***Austral.***: Cromese†; Cromolux; Intal; Opticrom; Rynacrom; ***Austria***: Acromax†; Allergo-COMOD; Cromoglin; Intal; Lomusol; Vividrin; ***Belg.***: Cromabak; Cromonez-Pos†; Cromophta-Pos†; Lomudal; Lomusol; Opticrom; ***Braz.***: Cromabak; Cromocato; Cromolerg; Intal; Maxicrom; Rilan; ***Canad.***: Apo-Cromolyn; Cromolyn; Nalcrom; Opticrom; Rhinaris-CS; ***Chile***: Oftacon†; ***China***: Runbo (润博); Shuanglang (双朗); ***Cz.***: Allergo-COMOD; Allergocrom Kombi; Allergocrom; Cromobene†; Cromohexal; Cusicrom†; Lecrolyn†; Nalcrom; ***Denm.***: Lecrolyn; Lomudal; ***Fin.***: Glinor; Lecrolyn; Lomudal; ***Fr.***: Allergo-COMOD; Alloptrex†; Cromabak; Cromadoses; Cromoptic; Cromorhinol; Cromosoft†; Humex; Intercron; Lomudal; Lomusol; Multicrom; Ophtacalm; Ophtacalmfree; Opticron; ***Ger.***: Allergo-COMOD; Allergocrom; Allergoval; Colimune; Crom-Ophtal; Cromo; Cromohexal†; Cromopp†; Dispacromil; DNCG; Flui-DNCG†; Intal; IsoCrom†; Lomupren†; Opticrom†; Padiacrom†; Pentatop; Vividrin; ***Gr.***: Allergojovis; Allergostop; Allergotin; Botastin; Crolidin; Cromabak; Cromo-POS; Cromodal; Cromolergin UD; Doxalpha; Duobetic; Erystamine-K; Fluvet; Indoprex; Iopanchol; Kaosyl; Lomudal; Nalcrom; Smarodax; Spaziron; Ufocollyre; Vekfanol; Vividrin; Zineli; Zulboral; ***Hong Kong***: Cromabak; Cromal†; Cromolyn†; Dadcrome; Mitayaku; Stadaglicin†; ***Hung.***: Cromohexal†; Cromosandoz; Intal†; Lecrolyn; Opticrom; Taleum; ***India***: Actal; Allercrom; Chromotop; Cromal; Cromate; Fintal; Ifiral; ***Indon.***: Crom-Ophtal; ***Irl.***: Cromogen†; Hay-Crom; Intal; Nalcrom; Opticrom; Rynacrom†; Vividrin; ***Israel***: Cromo-COMOD; Cromolyn; Cromoptic; Cronase; Lomudal; Opticrom; ***Ital.***: Brunicrom; Cromabak; Gastrofrenal; Lomudal; Nalcrom; Sificrom; ***Jpn***: Intal; ***Malaysia***: Allergocrom; Cromal; Cusicrom; Opticrom; Stadaglicin†; ***Mex.***: Alercrom; Alleoftal; Cryl; Intal; Livari; Maxicrom; Oftavit; Opticrom; Rynacrom; Spralyn; ***Mon.***: Cromedil; Zallyre†; ***Neth.***: Allerg-Abak; Allergo-COMOD; Lomudal; Lomusol; Nalcrom; Opticrom; Prevalin; Vividrin†; ***Norw.***: Lecrolyn; Lomudal; ***NZ***: Cromolux; Intal; Nalcrom; Opticrom†; Optrex Hayfever Allergy†; Rexacrom; Rynacrom†; Vicrom; ***Philipp.***: Cromabak; Ifiral; Lecrolyn†; Vividrin; ***Pol.***: Allergo-COMOD; Allergocrom; Cromogen†; Cromohexal; Cromosol†; Cromoxal; Cropoz G†; Cusicrom; Lecrolyn†; Nalcrom†; Polcrom; Vividrin; ***Port.***: Cromabak; Davicrome†; Fenolip; Intal; Opticrom; ***Rus.***: Crom-Allerg (Кром-Аллерг); Cromoglin (Кромоглин); Cromohexal (Кромогексал); Cropoz (Кропоз)†; Nay-Crom (Хай-кром); Ifiral (Ифирал); Intal (Интал); Lecrolyn (Лекролин); Nalcrom (Налкром); ***S.Afr.***: Cromabak; Cromohexal; Stop-Allerg; Vividrin; ***Singapore***: Allergocrom; Cromabak; Cromax; Intal; Opticrom; Rynacrom; Stadaglicin†; Vividrin; ***Spain***: Alergocrom†; Cusicrom; Frenal†; Nebulasma†; Nebulcrom; Renocil†; Rinilyn†; Rinofrenal†; ***Swed.***: Lecrolyn; Lomudal; Pollyferm; ***Switz.***: Allergo-COMOD; Cromabak; Cromodyn; Cromosol ophta; Cromosol UD; Lomudal; Lomusol; Nalcrom; Opticrom; Vividrin†; ***Thai.***: Intal; Opticrom; Rynacrom; Vividrin; ***Turk.***: Allergo-COMOD; Allergocrom; Allersol; Cromabak; Intal; Opticrom†; Rynacrom; Vividrin; ***UK***: Catacrom; Clariteyes†; Clarityn†; Hay-Crom; Hayfever Eye Drops†; Intal; Murine Hayfever; Nalcrom; Opticrom; Optrex Allergy; Pollenase Allergy; Rynacrom; Vivicrom†; Vividrin; ***Ukr.***: Cromo Sandoz (Кромо Сандоз); Cromoglin (Кромоглин); Cromohexal (КромоГЕКСАЛ)†; Cromopharm (Кромофарм); ***USA***: Crolom; Gastrocrom; Intal†; Nasalcrom†; Opticrom; ***Venez.***: Cromisol; Cromoftal.

Multi-ingredient Preparations. ***Arg.***: Hyalcrom; Rinogel; ***Ger.***: Aarane N; Allergospasmin; ***India***: Asthacrom†; ***Ital.***: Cromozil; Rinofrenal; Visuglican; ***Rus.***: Ditec (Дитек)†; ***Spain***: Frenal Compositum†; Rinofrenal Plus†; ***Turk.***: Rynacrom Compound.

Pharmacopoeial Preparations

BP 2014: Sodium Cromoglicate Eye Drops; Sodium Cromoglicate Inhalation Powder, hard capsule;

USP 36: Cromolyn Sodium Inhalation Powder; Cromolyn Sodium Inhalation Solution; Cromolyn Sodium Nasal Solution; Cromolyn Sodium Ophthalmic Solution.

Suplatast Tosilate *(rINN)*

IPD-1151T; Suplatast, Tosilate de; Suplatast, tosilato de; Suplatast Tosylate; Suplatasti Tosilas; Suplatastum Tosilas; Tosilato de suplatast; Суплатаст Тозилат.

(±)-(2-{[*p*-(3-Ethoxy-2-hydroxypropoxy)phenyl]carbamoyl}ethyl)dimethylsulphonium *p*-toluenesulphonate; (3-{[4-(3-Ethoxy-2-hydroxypropoxy)phenyl]amino}-3-oxopropyl)dimethylsulphonium *p*-toluenesulphonate.

$C_{23}H_{33}NO_7S_2$=499.6

CAS — 94055-76-2.

UNII — C9J89787U1.

Profile

Suplatast tosilate is an anti-allergic given orally in the prophylactic management of asthma and other allergic conditions.

References.

1. Sano Y, *et al*. Anti-inflammatory effect of suplatast tosilate on mild asthma. *Chest* 1997; **112:** 862–3.
2. Nihei Y, *et al*. Suplatast tosilate (IPD), a new immunoregulator, is effective in vitiligo treatment. *J Dermatol* 1998; **25:** 250–5.
3. Tamaoki J, *et al*. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. *Lancet* 2000; **356:** 273–8.
4. Shioya T, *et al*. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on cough variant asthma. *Eur J Clin Pharmacol* 2002; **58:** 171–6.
5. Matsuda Y, *et al*. Improvement of alanine aminotransferase by administration of suplatast tosilate plus ursodeoxycholic acid in patients with resistance to ursodeoxycholic acid monotherapy on hepatitis C virus-related chronic liver disease. *Intern Med* 2002; **41:** 774–9.
6. Sakuma-Oyama Y, *et al*. A case of recurrent cutaneous eosinophilic vasculitis: successful adjuvant therapy with suplatast tosilate. *Br J Dermatol* 2003; **149:** 901–3.
7. Sano T, *et al*. Higashishikoku Asthma Research Group. Add-on effects of suplatast tosilate in bronchial asthma patients treated with inhaled corticosteroids. *Lung* 2003; **181:** 227–35.

8. Teraki Y, Fukuda T. Pemphigoid nodularis associated with psoriatic erythroderma: successful treatment with suplatast tosilate. *Br J Dermatol* 2008; **158:** 424–6.
9. Yoshihara S, *et al.* Early intervention with suplatast tosilate for prophylaxis of pediatric atopic asthma: a pilot study. *Pediatr Allergy Immunol* 2009; **20:** 486–92.
10. Wada M, *et al.* Effect of suplatast tosilate on antileukotriene non-responders with mild-to-moderate persistent asthma. *Allergol Int* 2009; **58:** 389–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: IPD.

Terbutaline Sulfate

(BANM, USAN, rINNM) ⊗

KWD-2019; Sulfato de terbutalina; Terbutaliinisulfaatti; Terbutalin Sülfat; Terbutalina, sulfato de; Terbutaline, Sulfate de; Terbutaline Sulphate; Terbutalini Sulfas; Terbutalino sulfatas; Terbutalinsulfat; Terbutalin-sulfát; Terbutalin-szulfát; Тербуталина Сульфат.

2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol sulphate.

$(C_{12}H_{19}NO_3)_2,H_2SO_4$=548.6

CAS — 23031-25-6 (terbutaline); 23031-32-5 (terbutaline sulfate).

ATC — R03AC03; R03CC03.

ATC Vet — QR03AC03; QR03CC03.

UNII — 576PU70Y8E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Terbutaline Sulfate). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol.

USP 36: (Terbutaline Sulfate). A white to grey-white crystalline powder; odourless or has a faint odour of acetic acid. Soluble in water and in 0.1N hydrochloric acid; insoluble in chloroform; slightly soluble in methyl alcohol. Store at 15 degrees to 30 degrees. Protect from light.

Uses and Administration

Terbutaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has actions and uses similar to those of salbutamol (p. 1220.2).

Terbutaline is given as the sulfate for its bronchodilating properties in reversible airways obstruction, as occurs in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). It also decreases uterine contractility and may be used to arrest premature labour (p. 2131.1).

On inhalation, the bronchodilating effect of terbutaline usually begins within 5 minutes and lasts for up to 6 hours. The onset of action after oral doses is 30 to 45 minutes and its duration is up to 8 hours; the maximum effect occurs 1 to 4 hours after the dose.

Current asthma guidelines (see p. 1195.2) recommend that inhaled short-acting $beta_2$ agonists such as terbutaline be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of terbutaline, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, terbutaline indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

- To relieve **acute bronchospasm** the usual dose is 1 inhalation of terbutaline sulfate 250 or 500 micrograms as required from a breath-actuated metered-dose *powder inhaler*. The maximum recommended daily dose varies; in the UK a maximum of 2 mg is suggested, whereas in some other countries higher doses of up to 4 mg are allowed.
- When inhalation is ineffective, terbutaline sulfate may be given *orally*; the usual initial dose is 2.5 or 3 mg three times daily increased up to 5 mg three times daily as necessary. Modified-release tablets are also available; the usual adult dose is 5 or 7.5 mg twice daily.
- Severe or unresponsive bronchospasm may require the use of terbutaline sulfate intermittently via a *nebuliser*. A usual dose is 2.5 to 10 mg inhaled up to 4 times daily. Single-dose units or a suitable dilution of a concentrated solution containing terbutaline sulfate 1% are used for this purpose.

Guidelines also allow for $beta_2$ agonists to be given more frequently or by continuous dosage at a higher rate in acute severe asthma (see under Asthma, p. 1195.2).

- In the treatment of severe forms of bronchospasm, terbutaline sulfate may be given by subcutaneous, intramuscular, or slow intravenous *injection*; a dose of 250 to 500 micrograms may be given up to 4 times daily. Terbutaline sulfate may also be given by *intravenous infusion*, as a solution containing 3 to 5 micrograms/mL at a rate of 0.5 to 1 mL/minute.

Terbutaline sulfate is also used to arrest uncomplicated **premature labour** between 22 and 37 weeks of gestation. It is given by *intravenous infusion* in glucose 5%, preferably by syringe pump when the concentration is 100 micrograms/mL. If no syringe pump is available then the concentration of the infusion should be 10 micrograms/mL. The recommended initial rate of infusion is 5 micrograms/minute, increased by 2.5 micrograms/minute at intervals of 20 minutes until contractions stop. Usually, a rate of up to 10 micrograms/minute is sufficient; rates in excess of 20 micrograms/minute should not be used and if that maximum rate does not delay labour then the infusion should be stopped. The maternal pulse should be monitored throughout the infusion which should be adjusted to avoid a maternal heart rate of more than 135 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. Once contractions have ceased, the infusion should be continued for 1 hour, then the dose may be decreased by 2.5 micrograms/minute at 20-minute intervals to the lowest maintenance dose that produces continued suppression of contractions. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3).

Oral or *rectal* $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, terbutaline sulfate could be given orally in a dose of 5 mg three times daily, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

For terbutaline sulfate doses used for bronchospasm in children, see Administration in Children, below.

Administration in children. For the treatment of reversible airways obstruction, including nocturnal asthma, and prevention of exercise-induced **bronchospasm** in children, the *BNFC* recommends a dose of 500 micrograms of terbutaline sulfate, inhaled via a metered-dose *powder inhaler*, up to four times daily in children aged 5 years and over. *Oral* doses, although not recommended, may be given as follows:

- 1 month to 7 years of age: 75 micrograms/kg (maximum dose 2.5 mg) three times daily
- 7 to 15 years of age: 2.5 mg two or three times daily
- over 15 years of age: as for adults (see Uses and Administration, above)

Severe or unresponsive bronchospasm may require the use of terbutaline sulfate inhaled via a *nebuliser*. UK licensed product information gives doses based on weight and age:

- under 3 years of age, average body-weight 10 kg: 2 mg given 2 to 4 times daily
- 3 to 5 years of age, average body-weight 15 kg: 3 mg given 2 to 4 times daily
- 6 to 7 years of age, average body-weight 20 kg: 4 mg given 2 to 4 times daily
- 8 years of age and over, average body-weight 25 kg or more: 5 mg given 2 to 4 times daily

In the treatment of severe bronchospasm, terbutaline sulfate may be given by subcutaneous or slow intravenous *injection*; in children 2 to 15 years of age, the *BNFC* recommends a dose of 10 micrograms/kg (maximum dose 300 micrograms) up to four times daily. Children over 15 years of age may be given the adult dose.

Terbutaline sulfate may also be given by continuous *intravenous infusion*; the *BNFC* recommends an initial dose of 2 to 4 micrograms/kg, then 1 to 10 micrograms/kg per hour according to response and heart rate. Although the injection is unlicensed in the UK for children under 2 years of age, the *BNFC* allows this dose for children from 1 month of age.

Cardiac disorders. A case report on the use of oral terbutaline for chronotropic support, in the setting of acute rejection after heart transplantation, found it to be effective and without any significant adverse effects.[1]

1. Coons JC, *et al.* Terbutaline for chronotropic support in heart transplantation. *Ann Pharmacother* 2004; **38:** 586–9.

Hypoglycaemia. Giving terbutaline 5 mg orally at night reduced the risk of nocturnal hypoglycaemia in a study in patients with type 1 diabetes.[1] A later study[2] reproduced these results in 21 patients with type 1 diabetes; however, hyperglycaemia was seen the next morning. There is some evidence[3] to suggest that reducing the dose of terbutaline to 2.5 mg at night might allow for control of nocturnal hypoglycaemia without morning hyperglycaemia, but further study is needed.

1. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; **20:** 1231–6.
2. Raju B, *et al.* Nocturnal hypoglycaemia in type 1 diabetes: an assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 2006; **91:** 2087–92.
3. Cooperberg BA, *et al.* Terbutaline and the prevention of nocturnal hypoglycemia in type 1 diabetes. *Diabetes Care* 2008; **31:** 2271–2.

Myasthenia gravis. Results of a pilot study[1] suggested that oral terbutaline 2.5 mg three times daily was of modest benefit as an adjunct in the management of myasthenia gravis (p. 684.1).

1. Soliven B, *et al.* Terbutaline in myasthenia gravis: a pilot study. *J Neurol Sci* 2009; **277:** 150–4.

Systemic capillary leak syndrome. Systemic capillary leak syndrome is a rare disorder marked by shifts of plasma from the intravascular to the extracellular space, and is often fatal. Acute attacks are treated with intravenous fluid resuscitation, but there is some anecdotal evidence that treatment with terbutaline combined with aminophylline or theophylline, both orally, may be useful in preventing further attacks.[1-3] Infusion of epoprostenol has also been used in acute management.[4]

1. Droder RM, *et al.* Control of systemic capillary leak syndrome with aminophylline and terbutaline. *Am J Med* 1992; **92:** 523–6.
2. Amoura Z, *et al.* Systemic capillary leak syndrome: report on 13 patients with special focus on course and treatment. *Am J Med* 1997; **103:** 514–19.
3. Tahirkheli NK, Greipp PR. Treatment of the systemic capillary leak syndrome with terbutaline and theophylline: a case series. *Ann Intern Med* 1999; **130:** 905–9.
4. Fellows IW, *et al.* Epoprostenol in systemic capillary leak syndrome. *Lancet* 1988; **ii:** 1143.

Urticaria. Patients with various types of urticaria unresponsive to conventional therapy with antihistamines (see p. 1689.2) have obtained benefit from treatment with a combination of terbutaline and ketotifen; the urticarias have included chronic idiopathic urticaria,[1] dermographism,[1] and cold urticaria.[1,2] Terbutaline on its own was relatively ineffective and the mechanism of the combination was believed to be due to a stabilising effect on mast cells.[1]

Treatment of cold urticaria with a combination of terbutaline and aminophylline has also been studied.[3] The efficacy of this combined therapy was reported to vary considerably between patients, but complete remission of the urticarial response was eventually seen in 37 of the 42 patients. Treatment was stopped in 3 patients in the first week due to cardiac adverse effects.

1. Saihan EM. Ketotifen and terbutaline in urticaria. *Br J Dermatol* 1981; **104:** 205–6.
2. Edge JA, Osborne JP. Terbutaline and ketotifen in cold urticaria in a child. *J R Soc Med* 1989; **82:** 439–40.
3. Husz S, *et al.* Treatment of cold urticaria. *Int J Dermatol* 1994; **33:** 210–13.

Adverse Effects, Treatment, and Precautions

As for Salbutamol, p. 1221.3.

An increased tendency for bleeding after caesarean section has been reported in patients being treated with terbutaline for preterm labour. Should bleeding occur, an intravenous injection of propranolol 1 to 2 mg may be given (caution is required in patients with a history of bronchospasm, see p. 1320.3).

Overdosage. An overdose of terbutaline due to transcutaneous absorption has been reported after inappropriate topical application to skin infected with tinea.[1] Transcutaneous absorption should be considered especially when children with facial eczema or dermatitis are given terbutaline via a nebuliser and mask.

For general effects of $beta_2$ agonists after overdose, see Salbutamol p. 1222.2.

1. Ingrams GJ, Morgan FB. Transcutaneous overdose of terbutaline. *BMJ* 1993; **307:** 484.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terbutaline as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including terbutaline, for premature labour.[1] The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, p. 1222.3.

1. Perry KG, *et al.* Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion. *Am J Obstet Gynecol* 1995; **173:** 1273–7.

Tolerance. As with other $beta_2$ agonists (see p. 1222.3) there is some evidence[1] that tolerance may develop to terbutaline when it is used regularly.

1. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; **14:** 283–7.

Tooth erosion. The pH of some inhaled powder formulations of terbutaline, as well as of some corticosteroids, was found to be below 5.5, and it was suggested that this might contribute to the dissolution of enamel surfaces of teeth.[1] A later cohort study[2] found no association between asthma and tooth erosion; however only about 10% of

the medication prescribed for asthma in the cohort had a pH lower than 5.5.

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; **317:** 820.
2. Dugmore CR, Rock WP. Asthma and tooth erosion: is there an association? *Int J Paediatr Dent* 2003; **13:** 417–24.

Interactions

As for Salbutamol, p. 1223.1.

Histamine. For the effect of terbutaline on histamine given exogenously, see p. 2525.3.

Xanthines. The metabolic and cardiovascular responses to terbutaline infusion were significantly enhanced by *theophylline* in a study in 7 healthy subjects; in particular the fall in serum potassium was greater when both drugs were given.[1] Careful monitoring of serum potassium is recommended in severe asthma where theophylline and $beta_2$-agonists may be given together.

Terbutaline conversely has an effect on theophylline. Terbutaline can reduce serum-theophylline concentrations by increasing its systemic clearance. This may, or may not, have clinical implications, as improved clinical scores have still occurred with combined therapy despite the theophylline concentration being lower than when used alone; if respiratory symptoms persist, an increase in dosage may be contemplated while monitoring theophylline adverse effects and concentration.[2]

1. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; **21:** 451–3.
2. Garty M, *et al*. Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; **36:** 25–8.

Pharmacokinetics

On inhalation of terbutaline, less than 10% of the drug is absorbed from the airways. The remainder is swallowed where it is variably absorbed from the gastrointestinal tract. Fasting bioavailability after oral doses is reported to be about 14 to 15% and is reduced by food. Terbutaline undergoes extensive first-pass metabolism by sulfate (and some glucuronide) conjugation in the liver and the gut wall. It is excreted in the urine and faeces partly as the inactive sulfate conjugate and partly as unchanged terbutaline, the ratio depending upon the route by which it is given. The terminal half-life after single and multiple dosing is reported to be between 16 and 20 hours. There is some placental transfer. Trace amounts are distributed into breast milk.

Stereoselectivity. Terbutaline, like many other sympathomimetics, exists in two stereoisometric forms but only the (-)-enantiomer of terbutaline is pharmacologically active. Pharmacokinetic studies have been conducted on the two enantiomers and on the racemate.

The oral bioavailability of (-)-terbutaline was 14.8%, which was similar to that of the racemate; the bioavailability of (+)-terbutaline was much lower at 7.5%. The difference in bioavailability between the two enantiomers was mainly due to a difference in absorption (about 75% and 50% respectively) although a small difference in subsequent first-pass metabolism also occurred, with the (+)-isomer undergoing slightly more metabolism. It appeared that the (+)-isomer governed the elimination behaviour, both first-pass metabolism and renal clearance, of the racemate whereas the (-)-isomer determined the absorption.[1]

Other studies have also shown stereoselective sulfate conjugation of terbutaline with sulfation of the (+)-enantiomer being double that of the (-)-enantiomer.[2] The primary site of terbutaline sulfation for both enantiomers appears to be in the gut and is significantly correlated with the activity of catechol sulfotransferase.[3]

1. Borgström L, *et al*. Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate. *Br J Clin Pharmacol* 1989; **27:** 49–56.
2. Walle T, Walle UK. Stereoselective sulphate conjugation of racemic terbutaline by human liver cytosol. *Br J Clin Pharmacol* 1990; **30:** 127–33.
3. Pacifici GM, *et al*. (+) and (-) terbutaline are sulphated at a higher rate in human intestine than in the liver. *Eur J Clin Pharmacol* 1993; **45:** 483–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bricanyl; ***Austral.***: Bricanyl; ***Austria***: Bricanyl; ***Belg.***: Bricanyl; ***Braz.***: Adrenyl; Bricanyl; Terbutil; ***Canad.***: Bricanyl; ***China***: Bi Ai (比艾); Bricanyl (博利康尼); Bricasol (喘康速); Bu Rui Ping (布瑞平); Chuan Ting (川婷); Fei Ke Tan (菲科坦); Hui Bang (慧邦); Su Shun (苏顺); ***Cz.***: Bricanyl; ***Denm.***: Bricanyl; Dracanyl†; Terbasmin; ***Fin.***: Bricanyl; ***Fr.***: Bricanyl; ***Ger.***: Aerodur; Bricanyl; Terbul†; ***Gr.***: Bricanyl; Dracanyl; ***Hong Kong***: Anvelin†; Ataline; Bricanyl; Dhatalin; Framagon†; Lanterbine†; Terbron†; Terbuline†; Terbuta; Uni-Breth†; Vicktaline†; Vida-Butaline†; ***Hung.***: Bricanyl; ***India***: Asmaril; BGT; Bricanyl; ***Indon.***: Astherin†; Brasmatic†; Bricasma; Forasma; Lasmalin; Nairet; Neosma; Pulmobron; Relivan; Sedakter; Tabas; Terasma†; Tismalin; Yarisma; ***Irl.***: Bricanyl; ***Israel***: Bricalin; Terbulin; ***Ital.***: Bricanyl; ***Malaysia***: Ataline; Bricanyl; Britaline; Bucanil; Butaline; Tolbin; ***Mex.***: Terbuken; ***Neth.***: Bricanyl; Terbasmin†; ***Norw.***: Bricanyl; ***NZ***: Bricanyl; ***Philipp.***: Alloxygen; Astebron; Bricalin; Bricanyl; Bronchodam; Pulmolin; Pulmonyl; Pulmoxcel; Terbulin; ***Port.***: Bricanyl; ***S.Afr.***: Bricanyl; ***Singapore***: Asmalin; Ataline†; Bricanyl; Butylin; Dhatalin; Terbuline; Tolbin; ***Spain***: Tedipulmo†; Terbasmin; ***Swed.***: Bricanyl; ***Switz.***: Bricanyl; ***Thai.***: Asmadon; Asmaline; Asthmasian; Asthmic; B-lene; Bricanyl†; Broncholine; Bronchonyl; Bronco Asmo†; Bucanyl; Bucaril; Butalin; Cencanyl†; Fasma†; Framagon; P-Canyl; Proasma-T; Sulterline†; Terbu; Terbulin; Terbuline; Terbuno†; Terbusin; Tolbin; Vacanyl; ***Turk.***: Bricanyl; ***UK***: Bricanyl; ***USA***: Brethine†.

Multi-ingredient Preparations. ***Braz.***: Bricanyl Composto; ***Hong Kong***: Terbuta-Expect†; Uni-Breth Expectorant†; ***India***: Adcold-BR; Adcold-SBG; Alpha-Zedex; Altec; Ambrol Plus; Ambrol-TG; Ambrolax; Ambrosin-T; Ambroter; Ambrowin; Amriz; Anacuf; Arcuf Plus; Arikof-P; Arolin-XN; Ascodryl; Ascoril Expectorant; Ascoril; Asi-Ril; Asma-ZED; Asmotone Plus; Asthakind; Atoril; Axol-XL; Bluetus; Brachy; Bricarex A; Bricarex; Bricof; Bro-Zedex; Brocin; Brocoter-A; Brocoter; Bromcough; Bronchosolvin; Broncorex; Broncozone; Bronkex; Bronq; Bronsim; Browin Junior; Browin-TG; Broxter; Brozeet; Cadicoff Exp; Calscot-AX; Capex-Bron Exp; Capex-DMR; Cinkof; Clear Chest; Cleartuss-T; Cleded-AT; Cledex-AT; Coburу-AX; Codril-AT; Cof QX; Cofaid-EX; Cofal; Coftex-BT; Cogof-A; Coldman; Combicold; Corico-CS; Corid-B; Corophen-A; Cos-P; Coscoril; Cosome-A; Cosyp-E; Cratex; Cufdex-EX; Cufokin; Decofed-X; Deletus-BX; Dilo-BM; Eascof Exp; Efelin-X; Eledyl; Elsol-T; Esma-PD; Estharil Plus; Etoxin-B Exp; Etoxin-B; Euphomin Plus; Ex-GTM; Exiplon-BR; Exolit; Expect-T; Grilinctus-BM; Historil; Indikof-B; Ingahist-X; Intacof-S; Kafban; Kazibrox-BT; Kickkof; Kofarest Expectorant; Kofban-EX; Koforil; Kuff-Q; Kuff-X; Kufgen-X; Kufkair; Libitus Plus; Litcoff-P; Litcoff; Mags; Marex; Medkof; Megaril; Mucaryl-AX; Mucomelt-XP; Mucopen; Mucoresp Plus; Mucorid; Mucosma-T; Mucosol; Munorm; Muscarin; Mutech; New Zephrol; Nomorcuf; Norvent; NSI-Ril; NT-Kuf-AM; NT-Kuf-M; Nutuss-A; Nutuss-BR; Okaril Plus; Oox; Optex-AT; Suprivent-A; Suprivent; Tergil-T†; Tergil†; Terpect; Terpect; Terphylate; Terphylin; Theobric; Toscof; Tuspel Plus; ***Indon.***: Bricasma Expectorant†; Terasma Expectorant†; ***Irl.***: Bricanyl Expectorant†; ***Malaysia***: Tolbin Expectorant; ***Mex.***: Bricanyl EX; ***Philipp.***: Bricanyl Expectorant; ***S.Afr.***: Benylin Bronchospect†; Bronchoped; ***Spain***: Terbasmin Expectorante; ***Thai.***: Asmaline Expectorant; Asthnyl; Benyl; Bricanyl Expectorant†; Broncet; Broncholac; Bronchonyl; Cofbron; Terbu Expectorant; Terbulin Expectorant; Terbusin Expectorant; Terline; Tolbin; ***Turk.***: Bricanyl Expektoran; ***Ukr.***: Bro-Zedex (Бро-Зедекс)†.

Pharmacopoeial Preparations
BP 2014: Terbutaline Tablets;
USP 36: Terbutaline Oral Suspension; Terbutaline Sulfate Inhalation Aerosol; Terbutaline Sulfate Injection; Terbutaline Sulfate Tablets.

Theobromine (BAN)

Santheose; Teobromiini; Teobromin; Teobromina; Teobrominas; Theobromin; Théobromine; Theobrominum; Теобромин.

3,7-Dihydro-3,7-dimethylpurine-2,6(1*H*)-dione; 3,7-Dimethylxanthine.

$C_7H_8N_4O_2$=180.2

CAS — 83-67-0.

ATC — C03BD01; R03DA07.

ATC Vet — QC03BD01; QR03DA07.

UNII — OBD445WZ5P.

Pharmacopoeias. In *Eur.* (see p. vii)

Ph. Eur. 8: (Theobromine). A white or almost white powder. Very slightly soluble in water and in dehydrated alcohol; slightly soluble in ammonia. It dissolves in dilute solutions of alkali hydroxides and in mineral acids.

Profile

Theobromine has the general properties of the other xanthines (see Theophylline, below). It has a weaker activity than theophylline or caffeine and has practically no stimulant effect on the CNS. Large doses can cause nausea and vomiting. Theobromine has been used for its bronchodilating properties and in the treatment of cardiovascular disorders. Theobromine and calcium salicylate (theosalicin), theobromine and sodium acetate, and theobromine and sodium salicylate (themisalum, theobromsal) have all been used similarly to theobromine.

Theobromine is the chief xanthine in the beverage cocoa (p. 2648.2). It is also present in chocolate and in small amounts in tea. Theobroma oil may contain up to 2% theobromine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Cellenergy.

Theophylline (BAN)

Anhydrous Theophylline; Teocina; Teofilin; Teofilina; Teofilinas; Teofillin; Teofillina; Teofylliini; Teofyllin; Theofylin; Theophyllin; Théophylline; Theophyllinum; Теофиллин.

3,7-Dihydro-1,3-dimethylpurine-2,6(1*H*)-dione; 1,3-Dimethylxanthine.

$C_7H_8N_4O_2$=180.2

CAS — 58-55-9.

ATC — R03DA04.

ATC Vet — QR03DA04.

UNII — C137DTR5RG (theophylline); 0I55128JYK (anhydrous theophylline).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 8: (Theophylline). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 36: (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Theophylline Hydrate (BANM)

Teofilina monohidrato; Teofilinas monohidratas; Teofylliinimonohydraatti; Teofyllinmonohydrat; Theofylin monohydrát; Theophyllin-Monohydrat; Theophylline Monohydrate; Théophylline monohydratée; Theophyllinum Monohydricum; Теофиллина Гидрат.

$C_7H_8N_4O_2.H_2O$=198.2

CAS — 5967-84-0.

ATC — R03DA04.

ATC Vet — QR03DA04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 8: (Theophylline Monohydrate; Theophylline Hydrate BP 2014). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 36: (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Stability. Alcohol-free theophylline liquid repackaged in clear or amber polypropylene oral syringes could be stored at room temperature under continuous fluorescent lighting for at least 180 days without significant change in the concentration of theophylline.[1] However, it was recommended that solutions be protected from light because of the potential for discoloration.

Extemporaneous oral preparations of theophylline 5 mg/mL in commercial suspension vehicles were found[2] to be stable for up to 90 days in amber plastic bottles stored at 23 degrees to 25 degrees.

1. Johnson CE, Drabik BT. Stability of alcohol-free theophylline liquid repackaged in plastic oral syringes. *Am J Hosp Pharm* 1989; **46:** 980–1.
2. Johnson CE, *et al*. Stability of anhydrous theophylline in extemporaneously prepared alcohol-free oral suspensions. *Am J Health-Syst Pharm* 2005; **62:** 2518–20.

Uses and Administration

Theophylline is a xanthine (p. 1195.2) and relaxes bronchial smooth muscle, relieves bronchospasm, and has a stimulant effect on respiration. It stimulates the myocardium and CNS, decreases peripheral resistance and venous pressure, and causes diuresis. It is still not clear how theophylline exerts these effects. Inhibition of phosphodiesterase with a resulting increase in intracellular cyclic adenosine monophosphate (cyclic AMP) occurs, and may play a role. Other proposed mechanisms of action include adenosine receptor antagonism, prostaglandin antagonism, and effects on intracellular calcium. In addition, theophylline may also have an anti-inflammatory effect.

Theophylline is used as a bronchodilator in the management of reversible airways obstruction, such as in asthma. Although selective $beta_2$ adrenoceptor stimulants ($beta_2$ agonists) such as salbutamol are generally the preferred bronchodilators for initial treatment, theophylline is commonly used as an adjunct to $beta_2$ agonist and corticosteroid therapy in patients requiring an additional bronchodilating effect. Some patients with chronic obstructive pulmonary disease also have a beneficial

response to theophylline therapy. Theophylline is also used to relieve apnoea in neonates. It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease.

Theophylline may be given in the anhydrous form or as the hydrate. Doses of theophylline are usually expressed as anhydrous theophylline; theophylline hydrate 1.1 mg is equivalent to about 1 mg of theophylline.

The pharmacokinetics of theophylline may be altered by factors including age, smoking, disease, diet, and drug interactions (see under Precautions p. 1233.1, Interactions p. 1233.3, and Pharmacokinetics p. 1236.3). Theophylline doses should therefore be adjusted for each individual patient according to clinical response, adverse effects, and serum-theophylline concentrations.

- Optimum **therapeutic serum concentrations** of theophylline are traditionally considered to range from 10 to 20 micrograms/mL (55 to 110 micromoles/litre) and toxic effects are more common above 20 micrograms/mL. A range of 5 to 15 micrograms/mL may be effective, and associated with fewer adverse effects.

For long-term use, once a maintenance dose has been established, monitoring of serum-theophylline concentrations at 6- to 12-monthly intervals has been recommended.

In the management of **acute severe bronchospasm**, theophylline may be given by *intravenous infusion* where available, though usually aminophylline is preferred (see p. 1201.3). (Anhydrous theophylline 1 mg is equivalent to about 1.18 mg anhydrous aminophylline or 1.28 mg aminophylline hydrate.)

- In patients who have not received theophylline, aminophylline, or other xanthine-containing medications in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes followed by a suggested maintenance dose of 400 to 600 micrograms/kg per hour. Lower doses should be used in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose. Dosage should be calculated in terms of lean or ideal body-weight.
- Intravenous theophylline therapy is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in an increase of serum-theophylline concentration of 1 microgram/mL.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* in conventional dosage forms; modified-release preparations are not suitable.

- In adults not currently taking theophylline or xanthine-containing products a suggested loading dose is 5 mg/kg, to produce an average peak serum concentration of 10 micrograms/mL. Doses should again be reduced in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose.

In the long-term management of **chronic bronchospasm**, theophylline may be given orally in doses ranging from 300 to 1000 mg daily in divided doses as conventional tablets, capsules, liquid preparations, or modified-release preparations. For conventional dosage forms the divided doses are generally given every 6 to 8 hours. However, modified-release preparations are more commonly used as they reduce adverse effects and the need for frequent dosing, especially in patients with a rapid theophylline clearance.

- A usual dose of modified-release theophylline is 175 to 500 mg every 12 hours, though the bioavailability of different modified-release theophylline preparations may not be comparable and retitration of dosage is required if the patient is changed from one modified-release preparation to another. Larger doses may be given in either the evening or the morning to achieve optimum therapeutic effect when symptoms are most severe. Modified-release preparations which are given once daily are also available; usual doses are 400 or 600 mg daily.
- Initially, low doses of theophylline should be given and they should be gradually adjusted according to clinical response and serum-theophylline measurements. In the USA a preferred approach to initial dosage titration in adults may be to begin with 300 mg daily, in divided doses, for 3 days; if well tolerated, the total daily dose is increased to 400 mg for 3 days, and then, if tolerated and required, to 600 mg. For doses of theophylline used in children, see Administration in Children, below.

Intramuscular injection and dosage by suppository are not recommended due to severe local irritation and slow unreliable absorption.

Theophylline is an ingredient of some preparations promoted for coughs.

There are topical cosmetic preparations containing theophylline derivatives, particularly aminophylline, that have been promoted for the local reduction of body fat (p. 1202.2).

Theophylline monoethanolamine (theophylline olamine), theophylline calcium salicylate, theophylline and sodium acetate (theophylline sodium acetate), theophylline sodium glycinate (theophylline sodium aminoacetate), theophylline calcium glycinate, and theophylline glycinate have all been used similarly to theophylline.

General references.

1. Vasallo R, Lipsky JJ. Theophylline: recent advances in the understanding of its mode of action and uses in clinical practice. *Mayo Clin Proc* 1998; **73:** 346–54.
2. Barnes PJ. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med* 2003; **167:** 813–18.

Administration. Various methods have been proposed for estimating theophylline pharmacokinetic parameters to enable optimisation of initial dosage but none should be substituted for the subsequent determination of serum-theophylline concentrations and clearance at steady state.[1-3]

It was noted in 1997 that dosage requirements for theophylline had declined relative to those of historical controls, apparently due to a downward shift in theophylline clearance in the US population (perhaps due to environmental changes, such as a decrease in exposure to tobacco smoke).[4] It was suggested that earlier dosage guidelines for theophylline needed to be revised in the light of these data, so that the initial oral dose did not exceed 300 mg daily—for an approach to initial dosage titration consonant with this view, see Uses and Administration, p. 1229.3.

1. Erdman SM, *et al.* An updated comparison of drug dosing methods part II: theophylline. *Clin Pharmacokinet* 1991; **20:** 280–92.
2. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; **123:** 651–6.
3. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; **41:** 191–200.
4. Asmus MJ, *et al.* Apparent decrease in population clearance of theophylline: implications for dosage. *Clin Pharmacol Ther* 1997; **62:** 483–9.

Administration in children. In the management of **acute severe bronchospasm** in children, theophylline may be given by *intravenous infusion* where available, although aminophylline is preferred (see p. 1202.1). In children who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. Initial maintenance doses are designed to achieve a serum-theophylline concentration of 10 micrograms/mL. The following doses, based on lean or ideal body-weight, have been suggested:

- 1 to 9 years of age: 800 micrograms to 1 mg/kg per hour
- 9 to 12 years of age: 700 to 770 micrograms/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments. See Administration in Infants, below for doses used in children under 1 year of age. Children 12 years of age and over can receive similar doses to adults, see Uses and Administration, p. 1229.3.

If intravenous theophylline therapy is considered necessary in children who are already being given theophylline, aminophylline or other xanthine-containing medicine, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in a 1-microgram/mL increase in serum-theophylline concentration.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* using immediate-release preparations to children aged 1 year old and above, using doses similar to those used in adults, see Uses and Administration, p. 1229.3. For doses used in children under 1 year of age, see Administration in Infants, below.

Oral modified-release preparations of theophylline are given to children from 6 months of age in the long-term management of **chronic bronchospasm**. Dose and dosage frequency depend on the preparation being used, and licensed product information should be consulted; different formulations are not considered interchangeable.

ADMINISTRATION IN INFANTS. Theophylline clearance is reduced in premature neonates and infants under 1 year of age due to an immature hepatic microsomal enzyme system (see under Metabolism and Excretion in Pharmacokinetics, p. 1237.1). Postconceptional age may have a slight influence on theophylline clearance but postnatal age is thought to be more significant.[1]

Theophylline dosage guidelines for infants under 1 year of age were issued by the FDA[2] in 1985, but some clinicians considered that higher doses might be necessary.[1,3,4] Subsequent guidelines for *oral* theophylline,[5] issued in 1995, suggested a modified regimen: premature infants should be given initial doses of 1 mg/kg every 12 hours if less than 24 days postnatal age, or 1.5 mg/kg every 12 hours if more than 24 days; in full-term infants up to 1 year of age initial daily dosage (to be given in 3 or 4 divided doses) could be calculated on the basis of the equation:

$$\text{Daily dose (mg/kg)} = (0.2 \times \text{age in weeks}) + 5.0$$

Subsequent dosage should be adjusted based on steady-state serum-theophylline concentrations, which might take as long as 5 days to be achieved in premature neonates if a loading dose is not used.[5] The recommended serum concentrations were 5 to 10 micrograms/mL in neonates and 10 to 15 micrograms/mL in older infants. If a loading dose is considered necessary, 5 mg/kg (or 1 mg/kg for each 2 micrograms/mL increase in serum-theophylline concentration in those already being given theophylline) has been suggested.

Other equations and models of population pharmacokinetics have been proposed for the calculation of appropriate theophylline doses in neonates.[6-8]

Theophylline may be given by *intravenous infusion*, where available, in the management of **acute severe bronchospasm** in infants, although aminophylline is preferred (see p. 1202.1). In infants who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. In neonates the following initial maintenance doses have been suggested by the *American Hospital Formulary Service*[9] to achieve a serum-theophylline concentration of 7.5 micrograms/mL:

- neonate, postnatal age 24 days or less: 1 mg/kg every 12 hours
- neonate, postnatal age over 24 days: 1.5 mg/kg every 12 hours

To achieve a serum-theophylline concentration of 10 micrograms/mL the following initial maintenance doses have been suggested by the *Canadian Pharmacists Association*:

- neonate: 170 micrograms/kg per hour
- 6 weeks to 6 months of age: 430 micrograms/kg per hour
- 6 months to 1 year of age: 500 to 600 micrograms/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments.

Theophylline may be given prophylactically to reduce some of the adverse renal consequences of perinatal asphyxia (see p. 1231.2).

Theophylline has been used in **neonatal apnoea**, although caffeine is preferred. See Neonatal Apnoea, under Caffeine p. 1204.3.

1. Gilman JT, Gal P. Inadequacy of FDA dosing guidelines for theophylline use in neonates. *Drug Intell Clin Pharm* 1986; **20:** 481–4.
2. Anonymous. Use of theophylline in infants. *FDA Drug Bull* 1985; **15:** 16–17.
3. Murphy JE, *et al.* New FDA guidelines for theophylline dosing in infants. *Clin Pharm* 1986; **5:** 16.
4. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
5. Hendeles L, *et al.* Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy* 1995; **15:** 409–27.
6. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; **123:** 651–6.
7. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; **41:** 191–200.
8. Gagnon AJ. Aminophylline dosing in the treatment of apnea of prematurity—a commentary. *Pharmacotherapy* 1996; **16:** 317–18.
9. McEvoy GK (ed), AHFS Drug Information. online] Bethesda, MD: American Society of Health-System Pharmacists. Available at: http://www.medicinescomplete.com (accessed 13/10/09)

Administration in hepatic impairment. Theophylline clearance is reduced by 50% or more in patients with hepatic insufficiency such as cirrhosis, acute hepatitis, or cholestasis. Careful attention to dose reduction and frequent monitoring of serum-theophylline concentrations are required.

Asthma. Theophylline and its derivatives may be used in the treatment of chronic asthma (p. 1195.2) as an adjunct to $beta_2$ agonists and corticosteroid therapy when an additional bronchodilator is indicated. Modified-release preparations can be useful in the control of nocturnal asthma. Evidence for use in acute severe attacks is more mixed,[1,2] and guidelines differ in their recommendations.

Evidence suggests[3,4] that adding low-dose oral theophylline to inhaled corticosteroids is as effective as increasing the dose of corticosteroid in patients with moderate asthma and persistent symptoms. A systematic review[5] of studies that compared theophylline with long-acting $beta_2$ agonists found that they were both effective for control of nocturnal asthma, but that long-acting $beta_2$ agonists may be more effective in reducing asthma

symptoms, including night waking and the need for rescue medication, and are associated with fewer adverse effects.

1. Mitra A, *et al*. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 19/03/08).
2. Parameswaran K, *et al*. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).
3. Wang Y, *et al*. Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. *Respirology* 2005; **10:** 189–95.
4. Lim S, *et al*. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000; **55:** 837–41.
5. Tee AKH, *et al*. Long acting beta-agonists versus theophylline for maintenance treatment of asthma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).

Cardiac arrhythmias. Theophylline and aminophylline have been tried in various bradyarrhythmias, usually when other treatment has failed or is contra-indicated.[1-6] Aminophylline appears to be of little value in bradyasystolic cardiac arrest.[7,8]

1. Viskin S, *et al*. Aminophylline for bradyasystolic cardiac arrest refractory to atropine and epinephrine. *Ann Intern Med* 1993; **118:** 279–81.
2. Sra JS, *et al*. Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl J Med* 1993; **328:** 1085–90.
3. Bertolet BD, *et al*. Theophylline for the treatment of atrioventricular block after myocardial infarction. *Ann Intern Med* 1995; **123:** 509–11.
4. Alboni P, *et al*. Effects of permanent pacemaker and oral theophylline in sick sinus syndrome: the THEOPACE study: a randomized controlled trial. *Circulation* 1997; **96:** 260–6.
5. Ling CA, Crouch MA. Theophylline for chronic symptomatic bradycardia in the elderly. *Ann Pharmacother* 1998; **32:** 837–9.
6. Cawley MJ, *et al*. Intravenous theophylline — an alternative to temporary pacing in the management of bradycardia secondary to AV nodal block. *Ann Pharmacother* 2001; **35:** 303–7.
7. Abu-Laban RB, *et al*. Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial. *Lancet* 2006; **367:** 1577–84.
8. Hayward E, *et al*. Aminophylline in bradyasystolic cardiac arrest. *Emerg Med J* 2007; **24:** 582–3.

Cheyne-Stokes respiration. Oral theophylline considerably reduced Cheyne-Stokes respiration (periodic breathing) and episodes of central apnoea in 2 studies in patients with stable heart failure and left ventricular systolic dysfunction.[1,2] This was associated with an improvement in arterial-oxygen saturation during sleep. One study[1] saw no significant change in cardiac function, although pulmonary function did improve. Theophylline was also effective in a patient with Cheyne-Stokes respiration possibly related to diabetic autonomic neuropathy[3] (the use of the term Cheyne-Stokes respiration to describe this patient's respiratory disorder has been questioned[4,5]).

1. Javaheri S, *et al*. Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996; **335:** 562–7.
2. Hu K, *et al*. The effect of theophylline on sleep-disordered breathing in patients with stable chronic congestive heart failure. *Chin Med J* 2003; **116:** 1711–16.
3. Pesek CA, *et al*. Theophylline therapy for near-fatal Cheyne-Stokes respiration: a case report. *Ann Intern Med* 1999; **130:** 427–30.
4. Sin DD, Bradley TD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713.
5. Geigel EJ, Chediak AD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713–14.

Chronic obstructive pulmonary disease. In the treatment of chronic obstructive pulmonary disease (p. 1199.1), the bronchodilators of first choice are usually either an antimuscarinic such as ipratropium bromide, or a beta$_2$ agonist such as salbutamol, given by inhalation. However the addition of an oral xanthine such as theophylline may be of value in some patients to maximise respiratory function and for its positive cardiac inotropic effects.

A systematic review[1] of studies comparing oral theophylline with placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD), found that theophylline treatment improved lung function, ventilatory capacity, and arterial blood gas tensions. A decrease in thoracic gas entrapment and hyperinflation, and an increase in respiratory muscle function and diaphragmatic strength could be responsible for the improvement in symptoms. Improvements in arterial blood gas tensions may result from an increased tidal volume caused by either a direct positive inotropic effect on the respiratory muscles, or a central stimulatory action, or both. The authors concluded that theophylline produced an improvement in lung function similar to that reported for long acting beta$_2$ agonists in COPD patients, and that with close monitoring beneficial effects may be obtained from theophylline therapy in those patients who remain symptomatic from COPD despite first-line bronchodilator therapy. Theophylline has been reported to exert an inhibitory effect on airway inflammation in COPD, particularly at plasma concentrations below 10 micrograms/mL.[2] During acute exacerbations of COPD, low-dose theophylline was noted to have an effect on inflammatory markers, prompting the suggestion that it may increase the anti-inflammatory effect of systemic corticosteroids given for exacerbations and improve corticosteroid responsiveness.[3]

1. Ram FSF, *et al*. Oral theophylline for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 19/03/08).
2. Barnes PJ. Theophylline for COPD. *Thorax* 2006; **61:** 742–4.
3. Cosio BG, *et al*. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. *Thorax* 2009; **64:** 424–9.

Contrast nephropathy. For mention of theophylline as a potential protectant against kidney damage induced by iodinated contrast media, see Effects on the Kidneys, under Amidotrizoic Acid, p. 1582.2.

ECT. For mention of the use of theophylline as an adjunct to electroconvulsive therapy, see under Precautions, p. 1233.2.

Erythrocytosis. When pharmacological treatment is required for secondary erythrocytosis (p. 1283.1), UK guidelines[1,2] recommend an ACE inhibitor or an angiotensin II receptor antagonist as the usual drugs of first choice. Although theophylline appears to be less effective than an ACE inhibitor in post-transplantation erythrocytosis[3] an oral daily dose of 8 mg/kg has produced beneficial effects.[4,5] Theophylline may be of use given either alone or with an ACE inhibitor in those who fail to respond to first-line therapy. Theophylline treatment may also reduce erythrocytosis associated with chronic obstructive pulmonary disease.[6]

1. McMullin MF, *et al*. General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 19/03/08)
2. McMullin MF, *et al*. National Cancer Research Institute, Myeloproliferative Disorder Subgroup. British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. *Br J Haematol* 2007; **138:** 821–2. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_amendment_07.pdf (accessed 19/03/08)
3. Ok E, *et al*. Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
4. Bakris GL, *et al*. Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 1990; **323:** 86–90.
5. Ilan Y, *et al*. Erythrocytosis after renal transplantation: the response to theophylline treatment. *Transplantation* 1994; **57:** 661–4.
6. Oren R, *et al*. Effect of theophylline on erythrocytosis in chronic obstructive pulmonary disease. *Arch Intern Med* 1997; **157:** 1474–8.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p. 827.1.

Perinatal asphyxia. Perinatal asphyxia frequently results in damage to the kidneys;[1] vasomotor nephropathy or acute renal failure may develop as a result of decreased perfusion to the kidneys.[2] Theophylline has been studied for the prevention of renal dysfunction associated with perinatal asphyxia in both term and preterm neonates.[1-3] Beneficial effects have been seen after early use of intravenous theophylline, including significant decreases in serum creatinine[1-3] and urinary β2-microglobulin (an indicator of tubular performance),[1,3] and a significant increase in creatinine clearance.[1-3] A single dose of 8 mg/kg theophylline, by slow intravenous injection in the first hour of life, was given to neonates at term.[1,3] Lower doses were used for preterm neonates; 1 mg/kg daily for 3 consecutive days.[2]

1. Bhat MA, *et al*. Theophylline for renal function in term neonates with perinatal asphyxia: a randomised, placebo-controlled trial. *J Pediatr* 2006; **149:** 180–4.
2. Cattarelli D, *et al*. A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F80–F84.
3. Jenik AG, *et al*. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. *Pediatrics* 2000; **105:** e45. Also available at: http://pediatrics.aappublications.org/cgi/content/full/105/4/e45 (accessed 19/03/08)

Adverse Effects

The commonest adverse effects of theophylline and xanthine derivatives, irrespective of the route, are gastrointestinal irritation and stimulation of the CNS. Serum concentrations of theophylline greater than 20 micrograms/mL (110 micromol/litre) are associated with an increased risk of adverse effects (but see below).

Theophylline may cause nausea, vomiting, abdominal pain, diarrhoea, and other gastrointestinal disturbances, insomnia, headache, anxiety, irritability, restlessness, tremor, and palpitations. Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis, convulsions, and death. Severe toxicity may not be preceded by milder symptoms. Convulsions, cardiac arrhythmias, severe hypotension, or cardiac arrest may follow rapid intravenous injection, and fatalities have been reported. The drug is too irritant for intramuscular use. Proctitis may follow repeated use of suppositories.

Adverse effects are uncommon at **serum-theophylline concentrations** of 5 to 10 micrograms/mL but become more frequent at 15 micrograms/mL or above, and are greatly increased in frequency and severity at concentrations greater than 20 micrograms/mL.[1-3] The severity of **toxicity** is generally correlated with age, underlying disease, and serum-theophylline concentration, but a distinction has been made between acute and chronic theophylline intoxication; symptoms appear to occur at a lower theophylline concentration in chronic toxicity than after acute ingestion of large amounts.[1,2,4,5] Young infants and the elderly (over 60 years) appear to be at particular risk from chronic intoxication with theophylline.[6,7] Older patients with chronic intoxication may be at greater risk of major toxic effects, such as arrhythmias, seizures, and death, than those with acute intoxication.[5]

Common clinical manifestations of theophylline toxicity after overdosage of aminophylline or theophylline include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Metabolic disturbances such as hypokalaemia, hyperglycaemia, hypophosphataemia, hypercalcaemia, metabolic acidosis, and respiratory alkalosis often occur.[1-3] Other toxic effects reported include dementia,[8] toxic psychosis,[9] symptoms of acute pancreatitis,[10] rhabdomyolysis[11-13] with associated renal failure,[11] and acute compartment syndrome.[14]

Serious toxic symptoms may not be preceded by minor symptoms. In acute intoxication with modified-release preparations the onset of major toxic symptoms may be delayed for up to 24 hours[1] and prolonged monitoring of such patients is required. Patients have recovered despite serum-theophylline concentrations in excess of 200 micrograms/mL[12,14] but fatalities have occurred with much lower serum concentrations.[10,15,16] Mortality in severe poisoning may be as high as 10%.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151:** 689–93.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
3. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37:** 96–101.
4. Olson KR, *et al*. Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3:** 386–94.
5. Shannon M. Life-threatening events after theophylline overdose: a 10-year prospective analysis. *Arch Intern Med* 1999; **159:** 989–94.
6. Shannon M, Lovejoy FH. Effect of acute versus chronic intoxication on clinical features of theophylline poisoning in children. *J Pediatr* 1992; **121:** 125–30.
7. Shannon M. Predictors of major toxicity after theophylline overdose. *Ann Intern Med* 1993; **119:** 1161–7.
8. Drummond I. Aminophylline toxicity in the elderly. *BMJ* 1982; **285:** 779–80.
9. Wasser WG, *et al*. Theophylline madness. *Ann Intern Med* 1981; **95:** 191.
10. Burgan THS, *et al*. Fatal overdose of theophylline simulating acute pancreatitis. *BMJ* 1982; **284:** 939–40.
11. Macdonald JB, *et al*. Rhabdomyolysis and acute renal failure after theophylline overdose. *Lancet* 1985; **i:** 932–3.
12. Rumpf KW, *et al*. Rhabdomyolysis after theophylline overdose. *Lancet* 1985; **i:** 1451–2.
13. Modi KB, *et al*. Theophylline poisoning and rhabdomyolysis. *Lancet* 1985; **ii:** 160–1.
14. Lloyd DM, *et al*. Acute compartment syndrome secondary to theophylline overdose. *Lancet* 1990; **ii:** 312.
15. Whyte KF, Addis GJ. Toxicity of salbutamol and theophylline together. *Lancet* 1983; **ii:** 618–19.
16. Davies RJ, Hawkey CJ. Fatal theophylline toxicity precipitated by in situ pulmonary artery thrombosis. *Postgrad Med J* 1989; **65:** 49–50.

Effects on carbohydrate metabolism. Hyperglycaemia is frequent in theophylline intoxication, and is thought to be secondary to theophylline-induced adrenal catecholamine release.[1,2] Whether the effects on blood glucose are significant at more modest serum concentrations of theophylline is unclear, although in 29 preterm infants, mean plasma-glucose concentrations were significantly higher after treatment with intravenous aminophylline and oral theophylline than in those not treated. Two of 15 treated infants developed clinically significant hyperglycaemia and glycosuria. It was recommended that plasma-glucose concentrations be monitored in preterm infants receiving theophylline.[3]

1. Kearney TE, *et al*. Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Shannon M. Hypokalemia, hyperglycemia and plasma catecholamine activity after severe theophylline intoxication. *J Toxicol Clin Toxicol* 1994; **32:** 41–7.
3. Srinivasan G, *et al*. Plasma glucose changes in preterm infants during oral theophylline therapy. *J Pediatr* 1983; **103:** 473–6.

Effects on electrolytes. Hypokalaemia is a common metabolic disturbance in theophylline intoxication, but it has also been reported[1] in patients with plasma-theophylline concentrations within the therapeutic range. It is considered to be secondary to theophylline-induced adrenal catecholamine release, with cellular influx of potassium ions.[2] It is recommended[1] that plasma-potassium is moni-

tored during intravenous theophylline therapy particularly if other drugs predisposing to hypokalaemia are also given (see also Interactions, p. 1233.3). Hypophosphataemia[1,3] and hyponatraemia[1] can also occur at therapeutic plasma-theophylline concentrations. Hypomagnesaemia[4] and hypercalcaemia[5] have occurred in theophylline overdose.

1. Zantvoort FA, *et al*. Theophylline and serum electrolytes. *Ann InternMed* 1986; **104:** 134–5.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
3. Laaban J-P, *et al*. Hypophosphatemia complicating management of acute severe asthma. *Ann Intern Med* 1990; **112:** 68–9.
4. Hall KW, *et al*. Metabolic abnormalities associated with intentional theophylline overdose. *Ann Intern Med* 1984; **101:** 457–62.
5. McPherson ML, *et al*. Theophylline-induced hypercalcemia. *Ann Intern Med* 1986; **105:** 52–4.

Effects on the heart. *ARRHYTHMIAS.* Theophylline or aminophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions at therapeutic serum-theophylline concentrations[1] and in overdose.[2,3] Multifocal atrial tachycardia has also been associated with both theophylline overdose[2] and serum-theophylline concentrations within the generally accepted therapeutic range of 10 to 20 micrograms/mL.[4] Use of theophylline with oral beta-adrenoceptor stimulants is associated with a significant increase in the mean heart rate.[5,6]

1. Josephson GW, *et al*. Cardiac dysrhythmias during the treatment of acute asthma: a comparison of two treatment regimens by a double blind protocol. *Chest* 1980; **78:** 429–35.
2. Greenberg A, *et al*. Severe theophylline toxicity: role of conservative measures, antiarrhythmic agents, and charcoal hemoperfusion. *Am J Med* 1984; **76:** 854–60.
3. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
4. Levine JH, *et al*. Multifocal atrial tachycardia: a toxic effect of theophylline. *Lancet* 1985; **i:** 12–14.
5. Coleman JJ, *et al*. Cardiac arrhythmias during the combined use of β-adrenergic agonist drugs and theophylline. *Chest* 1986; **90:** 45–51.
6. Conradson T-B, *et al*. Arrhythmogenicity from combined bronchodilator therapy in patients with obstructive lung disease and concomitant ischemic heart disease. *Chest* 1987; **91:** 5–9.

Effects on the kidneys. For a report of rhabdomyolysis-induced acute renal failure occurring after aminophylline overdose, see the general discussion on toxicity, p. 1231.3.

Effects on mental function. As mentioned in the general discussion on toxicity on p. 1231.3, theophylline toxicity has been associated with reports of dementia and toxic psychosis, as well as the more common adverse effects of anxiety and restlessness.

LEARNING AND BEHAVIOUR PROBLEMS. Several small studies[1-3] have suggested that theophylline may be associated with learning and behaviour problems in children, especially those with a low IQ. However, the FDA has concluded[4] that such studies provide insufficient evidence to support an adverse effect of theophylline on learning behaviour or school performance. Other studies have found no marked behavioural adverse effects that could be attributed to theophylline,[5,6] and a meta-analysis[7] suggested that methylxanthine treatment might even have a small positive effect on behaviour. Additionally, academic achievement generally appeared to be unaffected by either asthma or by treatment with appropriate doses of theophylline.[8]

1. Furukawa CT, *et al*. Learning and behaviour problems associated with theophylline therapy. *Lancet* 1984; **i:** 621.
2. Springer C, *et al*. Clinical, physiologic, and psychologic comparison of treatment by cromolyn or theophylline in childhood asthma. *J Allergy Clin Immunol* 1985; **76:** 64–9.
3. Schlieper A, *et al*. Effect of therapeutic plasma concentrations of theophylline on behavior, cognitive processing, and affect in children with asthma. *J Pediatr* 1991; **118:** 449–55.
4. Anonymous. Theophylline and school performance. *FDA Drug Bull* 1988; **18:** 32–3.
5. Bender B, Milgrom H. Theophylline-induced behavior change in children: an objective evaluation of parents' perceptions. *JAMA* 1992; **267:** 2621–4.
6. Bender BG, *et al*. Neuropsychological behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. *Pediatrics* 1998; **101:** 355–60.
7. Stein MA, *et al*. Behavioral and cognitive effects of methylxanthines: a meta-analysis of theophylline and caffeine. *Arch Pediatr Adolesc Med* 1996; **150:** 284–8.
8. Lindgren S, *et al*. Does asthma or treatment with theophylline limit children's academic performance? *N Engl J Med* 1992; **327:** 926–30.

Effects on the nervous system. *CONVULSIONS.* The risk of convulsions with acute theophylline toxicity is low at serum theophylline concentrations less than 60 micrograms/mL;[1] seizures are most likely in patients with peak concentrations above 100 micrograms/mL.[2] However, the risk of seizures is much greater after chronic overdosage;[1,2] seizure activity has been reported at serum concentrations just above or even within the therapeutic range.[3] Elderly patients or those with previous brain injury or neurological disease may be at increased risk,[2-4] although some have questioned the association.[1] The outcome of seizures appears to be variable: death and severe neurological deficit have occurred,[2,3] but other series have recorded recovery without serious morbidity.[4]

1. Paloucek FP, Rodvold KA. Evaluation of theophylline overdoses and toxicities. *Ann Emerg Med* 1988; **17:** 135–44.
2. Olson KR, *et al*. Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3:** 386–94.
3. Bahls FH, *et al*. Theophylline-associated seizures with "therapeutic" or low toxic serum concentrations: risk factors for serious outcome in adults. *Neurology* 1991; **41:** 1309–12.
4. Covelli HD, *et al*. Predisposing factors to apparent theophylline-induced seizures. *Ann Allergy* 1985; **54:** 411–15.

Effects on the skin. For reports of cutaneous reactions to theophylline and aminophylline, see under Hypersensitivity, below.

Effects on the urinary tract. Although diuresis is more commonly seen, urinary retention has been reported in male patients during therapy with aminophylline[1] or theophylline.[2]

1. Owens GR, Tannenbaum R. Theophylline-induced urinary retention. *Ann Intern Med* 1981; **94:** 212–13.
2. Prakash M, Washburne JD. Theophylline and urinary retention. *Ann Intern Med* 1981; **94:** 823.

Hypersensitivity. Hypersensitivity reactions have been reported after oral or intravenous doses of aminophylline. Reactions include erythematous rash with pruritus,[1,2] erythroderma,[2] and exfoliative dermatitis.[3] Aminophylline can produce both type I (immediate) and type IV (delayed) hypersensitivity reactions, the latter being due to the ethylenediamine component and can be confirmed by skin patch tests.[1-3] If hypersensitivity to ethylenediamine is confirmed it is recommended that aminophylline is avoided and treatment continued with theophylline or another theophylline salt.[1,3,4] Hypersensitivity reactions to theophylline have been reported rarely but type I reactions have occurred.[4] An erythematous, maculopapular rash has been reported[5] during treatment with a modified-release theophylline preparation, which did not occur when another modified-release theophylline product was given.

1. Hardy C, *et al*. Allergy to aminophylline. *BMJ* 1983; **286:** 2051–2.
2. Mohsenifar Z, *et al*. Two cases of allergy to aminophylline. *Ann Allergy* 1982; **49:** 281–2.
3. Nierenberg DW, Glazener FS. Aminophylline-induced exfoliative dermatitis: cause and implications. *West J Med* 1982; **137:** 328–31.
4. Gibb WRG. Delayed-type hypersensitivity to theophylline/aminophylline. *Lancet* 1985; **i:** 49.
5. Mendel S, *et al*. Dermatologic reaction to a sustained-release theophylline product. *Clin Pharm* 1985; **4:** 334–5.

Hyperuricaemia. In a study of 112 asthmatic patients receiving modified-release theophylline 200 to 400 mg 12-hourly, there was a significant correlation of serum-uric acid concentrations and serum-theophylline concentrations.[1] Gout has been reported in a woman receiving theophylline and aminophylline;[2] her serum-uric acid concentration was increased while receiving the xanthines, but subsequently fell when they were stopped, and rose again when treatment was resumed.

1. Morita Y, *et al*. Theophylline increases serum uric acid levels. *J Allergy Clin Immunol* 1984; **74:** 707–12.
2. Toda K, *et al*. Gout due to xanthine derivatives. *Br J Rheumatol* 1997; **36:** 1131–2.

Necrotising enterocolitis. Although there have been reports of neonatal necrotising enterocolitis associated with oral theophylline or aminophylline,[1,2] a study of 275 infants concluded that theophylline did not significantly contribute to its development.[3] It has been suggested that the high osmolality of liquid feeds and drugs including oral theophylline preparations may be involved in the aetiology of necrotising enterocolitis.[4]

1. Robinson MJ, *et al*. Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; **55:** 494–5.
2. Williams AJ. Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; **55:** 973–4.
3. Davis JM, *et al*. Role of theophylline in pathogenesis of necrotizing enterocolitis. *J Pediatr* 1986; **109:** 344–7.
4. Watkinson M, *et al*. Hyperosmolar preparations for neonates. *Pharm J* 1987; **241:** 488.

Withdrawal syndromes. Episodes of apnoea beginning 28 hours after birth and increasing in frequency and severity over the next 4 days occurred in a neonate whose mother had taken aminophylline and theophylline throughout pregnancy. Measurement of serum-theophylline concentration showed the increasing apnoea coincided with falling theophylline concentration. The infant's apnoea resolved on giving theophylline; treatment was stopped after 4 months.[1]

Worsening asthma control may occur when theophylline is withdrawn; there is some evidence of a rebound deterioration in lung function due to the development of tolerance.[2]

1. Horowitz DA, *et al*. Apnea associated with theophylline withdrawal in a term neonate. *Am J Dis Child* 1982; **136:** 73–4.
2. Bennett JA, *et al*. The airway effects of stopping regular oral theophylline in patients with asthma. *Br J Clin Pharmacol* 1998; **45:** 402–4.

Treatment of Adverse Effects

After theophylline or aminophylline overdosage, elimination may be enhanced by repeated oral doses of activated charcoal regardless of the route of overdose (see below). An osmotic laxative may also be considered. Treatment is symptomatic and supportive; ECG monitoring is recommended. Serum-theophylline concentrations should be monitored and if modified-release preparations have been taken monitoring should be prolonged. Metabolic abnormalities, particularly hypokalaemia, should be corrected; hypokalaemia may be so severe as to require intravenous infusion of potassium. In the non-asthmatic patient severe tachycardia, hypokalaemia, and hyperglycaemia may be reversed by a non-selective beta blocker (see also below). Patients with asthma or chronic obstructive pulmonary disease (COPD) who, after correction of hypokalaemia, have severe tachycardia, may be treated with intravenous verapamil. Alternatively direct current (DC) cardioversion may be considered. Ventricular arrhythmias causing haemodynamic compromise should also be treated with DC cardioversion. Isolated convulsions may be controlled by intravenous diazepam or a barbiturate; phenytoin may be less effective. In the most refractory cases general anaesthesia, and neuromuscular blockade, with ventilation, may be required.

Charcoal haemoperfusion or haemodialysis may be required.

Reviews.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151:** 689–93.
2. Skinner MH. Adverse reactions and interactions with theophylline. *Drug Safety* 1990; **5:** 275–85.
3. Minton NA, Henry JA. Treatment of theophylline overdose. *Am J Emerg Med* 1996; **14:** 606–12.

Activated charcoal. Multiple-dose oral activated charcoal is considered the cornerstone of treatment for theophylline and xanthine poisoning. It reduces the absorption of oral theophylline, and also enhances the elimination of theophylline from the body even after absorption or intravenous doses of xanthine. Aggressive antiemetic therapy may be required to allow use and retention of activated charcoal, since theophylline toxicity causes protracted vomiting. A cathartic such as sorbitol may be given with the activated charcoal to aid elimination of theophylline, but can cause fluid and electrolyte disturbances. For oral theophylline overdose the use of gastric lavage before oral activated charcoal may not be better than activated charcoal alone.

References.

1. Neuvonen PJ, *et al*. Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *Eur J Clin Pharmacol* 1983; **24:** 557–62.
2. Berlinger WG, *et al*. Enhancement of theophylline clearance by oral activated charcoal. *Clin Pharmacol Ther* 1983; **33:** 351–4.
3. Mahutte CK, *et al*. Increased serum theophylline clearance with orally administered activated charcoal. *Am Rev Respir Dis* 1983; **128:** 820–2.
4. Park GD, *et al*. Effects of size and frequency of oral doses of charcoal on theophylline clearance. *Clin Pharmacol Ther* 1983; **34:** 663–6.
5. Goldberg MJ, *et al*. The effect of sorbitol and activated charcoal on serum theophylline concentrations after slow-release theophylline. *Clin Pharmacol Ther* 1987; **41:** 108–11.
6. Al-Shareef AH, *et al*. The effects of charcoal and sorbitol (alone and in combination) on plasma theophylline concentrations after a sustained-release formulation. *Hum Exp Toxicol* 1990; **9:** 179–82.
7. Minton NA, *et al*. Prevention of drug absorption in simulated theophylline overdose. *Hum Exp Toxicol* 1995; **14:** 170–4.

Beta blockers. Infusion of propranolol after theophylline overdose in 2 patients was associated with improvement in hyperglycaemia, hypokalaemia, tachycardia, and hypotension. Beta-adrenergic blockade may therefore be of benefit in the management of the metabolic changes of theophylline poisoning, especially in the non-asthmatic patient.[1,2] However, in asthmatic patients, beta blockers should be reserved for those with severe hypokalaemia or cardiac arrhythmias when mechanical ventilation is available as beta blockers can cause bronchoconstriction.[1,2] Propranolol reduces the clearance of theophylline (see under Interactions, p. 1235.2) and it has been suggested that a non-interacting beta blocker may be more appropriate.[3] Esmolol has been used successfully to manage cardiovascular symptoms of overdosage.[4]

1. Kearney TE, *et al*. Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Amin DN, Henry JA. Propranolol administration in theophylline overdose. *Lancet* 1985; **i:** 520–1.
3. Farrar KT, Dunn AM. Beta-blockers in treatment of theophylline overdose. *Lancet* 1985; **i:** 983.
4. Seneff M, *et al*. Acute theophylline toxicity and the use of esmolol to reverse cardiovascular instability. *Ann Emerg Med* 1990; **19:** 671–3.

Endoscopy. Absorption is delayed after overdosage with modified-release oral preparations of aminophylline or theophylline and may be further prolonged by the formation of tablet aggregates, or bezoars, in the stomach.[1-3] Of 11 patients admitted with overdosage, one vomited a bezoar, 2 had bezoars removed at gastroscopy, and in one a bezoar was found at necropsy.[3] If bezoar formation occurs gastric lavage and activated charcoal will have little

if any effect and the patient may appear to stabilise before experiencing increasing serum-theophylline concentration and clinical deterioration;[1,2] fatalities have been reported.[1] Endoscopy should be considered in cases of modified-release theophylline overdosage in which clinical signs and serial concentration measurements suggest continuing drug absorption.[2]

1. Coupe M. Self-poisoning with sustained-release aminophylline: a mechanism for observed secondary rise in serum theophylline. *Hum Toxicol* 1986; **5**: 341–2.
2. Cereda J-M, *et al.* Endoscopic removal of pharmacobezoar of slow release theophylline. *BMJ* 1986; **293:** 1143.
3. Smith WDF. Endoscopic removal of a pharmacobezoar of slow release theophylline. *BMJ* 1987; **294:** 125.

Haemodialysis and haemoperfusion. Extracorporeal theophylline removal techniques after overdosage of aminophylline or theophylline have been reviewed.[1] Neither peritoneal dialysis nor exchange transfusion produced a significant increase in the total body clearance of theophylline, whereas haemodialysis could be expected to double clearance, and haemoperfusion results in four- to sixfold increases in clearance. Charcoal haemoperfusion should be considered if the plasma-theophylline concentration exceeds 100 micrograms/mL in an acute intoxication, or 60 micrograms/mL in chronic overdose (40 micrograms/mL if there is significant respiratory or heart failure, or liver disease) though plasma concentrations alone should not determine its use (see under Adverse Effects, p. 1231.3). If there is intractable vomiting, arrhythmias, or seizures charcoal haemoperfusion should be started without delay. In most patients a 4-hour haemoperfusion allows significant clinical improvement, but treatment should continue until plasma concentrations are below 15 micrograms/mL. Plasma concentrations should be followed at least every 4 hours for the first 12 hours post-perfusion, as rebound increases have been noted on terminating perfusion. Haemodialysis may rarely be an alternative if haemoperfusion is not available, or in series with haemoperfusion if significant rhabdomyolysis is present. There has been a case report[2] of continuous venovenous haemofiltration used to treat severe theophylline toxicity.

1. Heath A, Knudsen K. Role of extracorporeal drug removal in acute theophylline poisoning: a review. *Med Toxicol* 1987; **2:** 294–308.
2. Henderson JH, *et al.* Continuous venovenous haemofiltration for the treatment of theophylline toxicity. *Thorax* 2001; **56:** 242–3.

Precautions

Theophylline or aminophylline should be given with caution to patients with peptic ulceration, porphyria, hyperthyroidism, hypertension, cardiac arrhythmias or other cardiovascular disease, or epilepsy, as these conditions may be exacerbated. They should also be given with caution to patients with heart failure, hepatic dysfunction, acute febrile illness, and to neonates and the elderly, since in all of these circumstances theophylline clearance may be decreased, resulting in increases in serum-theophylline concentrations and serum half-life. Conversely, smoking and alcohol consumption increase theophylline clearance. Many drugs interact with theophylline; for details see Interactions, below.

Intravenous injections of theophylline or aminophylline must be given very slowly to prevent dangerous CNS and cardiovascular adverse effects resulting from the direct stimulant effect.

Dosage requirements of theophylline vary widely between subjects; in view of the many factors affecting theophylline pharmacokinetics, serum concentration monitoring is necessary to ensure concentrations are within the therapeutic range.

Patients should not be transferred from one modified-release theophylline or aminophylline preparation to another without clinical assessment and the measurement of serum-theophylline concentrations because of bioavailability differences.

Acute febrile illness. A reduction in theophylline clearance has been noted in patients presenting with acute respiratory illness[1] and appears to be associated with the severity of the underlying pulmonary disease and the rate of change in the patient's condition.[2] Caution has been advised in giving theophylline to patients with chronic obstructive pulmonary disease with acute exacerbations, since these patients appear most likely to exhibit altered theophylline metabolism.[2]

Similarly, a decrease in theophylline clearance and an increase in the incidence of adverse effects has been reported during acute viral infections such as influenza in children receiving theophylline therapy for chronic asthma.[3,4] Another study in asthmatic children found that acute febrile illness accompanied by increased C-Reactive Protein (CRP) level may affect theophylline metabolism.[5] The authors postulated that cytokines released in the process of acute illness were responsible. Influenza vaccination has also been reported to reduce theophylline clearance (see under Interactions, p. 1236.3). The mechanism by which theophylline metabolism is reduced in these patients may be related to increased interferon production during the acute febrile response. A dosage reduction of one half has been recommended[6] in children receiving chronic theophylline therapy who are febrile for more than 24 hours. Further dose adjustments should be based on serum-theophylline concentrations until the patients have recovered from their acute illness and are restabilised on their usual dosage. However, conflicting results have been reported and in one controlled study RSV infection was found to have no significant effect on theophylline disposition in children.[7]

1. Vozeh S, *et al.* Changes in theophylline clearance during acute illness. *JAMA* 1978; **240:** 1882–4.
2. Richer M, Lam YWF. Hypoxia, arterial pH and theophylline disposition. *Clin Pharmacokinet* 1993; **25:** 283–99.
3. Chang KC, *et al.* Altered theophylline pharmacokinetics during acute respiratory viral illness. *Lancet* 1978; **i:** 1132–3.
4. Kraemer MJ, *et al.* Altered theophylline clearance during an influenza B outbreak. *Pediatrics* 1982; **69:** 476–80.
5. Yamaguchi A, *et al.* Higher incidence of elevated body temperature or increased C-reactive protein level in asthmatic children showing transient reduction of theophylline metabolism. *J Clin Pharmacol* 2000; **40:** 284–9.
6. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; **89:** 781–3.
7. Muslow HA, *et al.* Lack of effect of respiratory syncytial virus infection on theophylline disposition in children. *J Pediatr* 1992; **121:** 466–71.

Age. For the effects of age on the metabolism and excretion of theophylline see under Pharmacokinetics, p. 1237.1. Dosage regimens for infants are discussed under Administration in Infants, in Uses and Administration, p. 1230.2.

Breast feeding. From one study of 3 women it was estimated that less than 1% of the total theophylline eliminated was found in breast milk.[1] Another study of 5 women estimated that a breast-fed infant would receive less than 10% of the maternal dose of theophylline.[2] These amounts were considered unlikely to cause toxicity, but it has been reported that irritability in one infant seemed to occur on the intermittent days when the mother took aminophylline. The American Academy of Pediatrics[3] states that theophylline is usually compatible with breast feeding, although it noted that irritability has been reported in infants whose mothers were receiving theophylline.

1. Stec GP, *et al.* Kinetics of theophylline transfer to breast milk. *Clin Pharmacol Ther* 1980; **28:** 404–8.
2. Yurchak AM, Jusko WJ. Theophylline secretion into breast milk. *Pediatrics* 1976; **57:** 518–20.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

ECT. Patients receiving theophylline are at risk of prolonged seizures during ECT, and status epilepticus has been reported.[1,2] The ability of theophylline to prolong seizures has led to it being used as an adjunct in ECT.[3] Caffeine has been used similarly, see p. 1204.2.

1. Peters SG, *et al.* Status epilepticus as a complication of concurrent electroconvulsive and theophylline therapy. *Mayo Clin Proc* 1984; **59:** 568–70.
2. Rasmussen KG, Zorumski CF. Electroconvulsive therapy in patients taking theophylline. *J Clin Psychiatry* 1993; **54:** 427–31.
3. Leentjens AFG, *et al.* Facilitation of ECT by intravenous administration of theophylline. *Convuls Ther* 1996; **12:** 232–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies theophylline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. It has been recommended[1] that serum-theophylline concentrations are measured at monthly intervals throughout pregnancy and 1 and 4 weeks after delivery since the pharmacokinetics of theophylline may be altered. An increase in the volume of distribution of theophylline, a decrease in plasma-protein binding, and a continuing decrease in clearance throughout pregnancy have been noted in some patients, especially during the later part of pregnancy,[2-4] but other studies have noted an increase in theophylline clearance during pregnancy.[1,5] Some studies have found that after delivery there is a return of clearance values to those existing before pregnancy,[2] while others have not.[4]

In a study of 12 neonates whose mothers received various theophylline preparations throughout their pregnancies[6] maternal, cord, and neonatal heelstick theophylline concentrations ranged from 2.3 to 19.6 micrograms/mL. Transient jitteriness was seen in 2 neonates and tachycardia in one, at cord theophylline concentrations of 11.7 to 17 micrograms/mL. There were no instances of vomiting, seizure, arrhythmias, diarrhoea, or feeding disturbances, which had been reported previously.

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; **293:** 1415–17.
2. Carter BL, *et al.* Theophylline clearance during pregnancy. *Obstet Gynecol* 1986; **68:** 555–9.
3. Frederiksen MC, *et al.* Theophylline pharmacokinetics in pregnancy. *Clin Pharmacol Ther* 1986; **40:** 321–8.
4. Gardner MJ, *et al.* Longitudinal effects of pregnancy on the pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1987; **31:** 289–95.
5. Romero R, *et al.* Pharmacokinetics of intravenous theophylline in pregnant patients at term. *Am J Perinatol* 1983; **1:** 31–5.
6. Labovitz E, Spector S. Placental theophylline transfer in pregnant asthmatics. *JAMA* 1982; **247:** 786–8.

Renal impairment. Theophylline is eliminated mainly by hepatic metabolism and usual doses of aminophylline or theophylline can be given to patients with renal impairment. In patients undergoing haemodialysis the clearance of theophylline is increased and its elimination half-life reduced; mean values of 84.8 and 83 mL/minute and 2.5 and 2.3 hours respectively have been reported.[1,2] Haemodialysis removes up to 40% of a dose of theophylline.[1] Peritoneal dialysis has little effect on the pharmacokinetics of theophylline removing about 3.2% of a dose.[1]

1. Lee C-SC, *et al.* Comparative pharmacokinetics of theophylline in peritoneal dialysis and hemodialysis. *J Clin Pharmacol* 1983; **23:** 274–80.
2. Anderson JR, *et al.* Effects of hemodialysis on theophylline kinetics. *J Clin Pharmacol* 1983; **23:** 428–32.

Smoking. Certain components of tobacco smoke, notably aromatic hydrocarbons, induce hepatic drug-metabolising enzymes and cigarette smoking has been reported[1-3] to increase theophylline clearance and shorten its elimination half-life. The effect of smoking may override factors that tend to decrease theophylline clearance, such as old age.[4] The duration of enzyme induction after stopping smoking is uncertain; theophylline clearance decreased by 38% after one week of abstinence from smoking in one study,[5] while others have found changes in clearance persisting for at least 3 months.[1] Tobacco chewing has also been reported to increase theophylline clearance,[6] but nicotine chewing gum appears to have no effect.[5]

1. Hunt SN, *et al.* Effect of smoking on theophylline disposition. *Clin Pharmacol Ther* 1976; **19:** 546–51.
2. Jusko WJ, *et al.* Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clin Pharmacol Ther* 1978; **24:** 406–10.
3. Grygiel JJ, Birkett DJ. Cigarette smoking and theophylline clearance and metabolism. *Clin Pharmacol Ther* 1981; **30:** 491–6.
4. Cusack B, *et al.* Theophylline kinetics in relation to age: the importance of smoking. *Br J Clin Pharmacol* 1980; **10:** 109–14.
5. Lee BL, *et al.* Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann Intern Med* 1987; **106:** 553–5.
6. Rockwood R, Henann N. Smokeless tobacco and theophylline clearance. *Drug Intell Clin Pharm* 1986; **20:** 624–5.

Interactions

The toxic effects of theophylline, aminophylline, and other xanthines are additive. Use with other xanthine medications should therefore be avoided; if intravenous aminophylline is to be given for acute bronchospasm in patients who have been taking maintenance theophylline therapy, serum-theophylline concentrations should be measured first and the initial dose reduced as appropriate (see Uses and Administration, p. 1229.3).

Theophylline clearance may be reduced by interaction with other drugs including allopurinol, some antiarrhythmics, cimetidine, disulfiram, fluvoxamine, interferon alfa, macrolide antibacterials and quinolones, oral contraceptives, tiabendazole, and viloxazine, and the dose of theophylline may need to be reduced. Phenytoin and some other antiepileptics, ritonavir, rifampicin, and sulfinpyrazone may increase theophylline clearance, and require an increase in dose or dosing frequency of theophylline.

Xanthines can potentiate hypokalaemia caused by hypoxia or associated with the use of $beta_2$-adrenoceptor stimulants ($beta_2$ agonists), corticosteroids, and diuretics. There is a risk of synergistic toxicity if theophylline is given with halothane or ketamine, and it may antagonise the effects of adenosine and of competitive neuromuscular blockers; lithium elimination may be enhanced with a consequent loss of effect. The interaction between theophylline and beta blockers is complex (see p. 1235.2) but use together tends to be avoided on pharmacological grounds since beta blockers produce bronchospasm.

Theophylline is metabolised by several hepatic cytochrome P450 isoenzymes, of which the most important seems to be CYP1A2.[1] Many drugs affect the metabolic clearance of theophylline and aminophylline,[2] but the variability in theophylline pharmacokinetics makes the clinical significance of these interactions difficult to predict. Giving theophylline with drugs that inhibit its metabolism should be avoided but, if unavoidable, the dose of theophylline should be halved.[3] There is some evidence to suggest that less of a dose reduction is required in the presence of severe liver dysfunction,[4] aside from that already required by impaired hepatic metabolism, see

Administration in Hepatic Impairment, p. 1230.3. Subsequent doses should be adjusted based on serum-theophylline monitoring.[3] Even when introducing medication for which no interaction is suspected, a check on the serum-theophylline concentration within 24 hours of beginning the new drug has been advised.[3]

Theophylline reduces liver plasma flow[5] and may therefore prolong the half-life and increase steady-state concentrations of hepatically eliminated drugs but it is claimed to have no effect on antipyrine clearance.[6]

1. Ha HR, *et al.* Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; **39:** 321–6.
2. Upton RA. Pharmacokinetic interactions between theophylline and other medication. *Clin Pharmacokinet* 1991; **20:** 66–80 (part I) and 135–50 (part II).
3. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; **89:** 781–3.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; **79:** 489–99.
5. Onrot J, *et al.* Reduction of liver plasma flow by caffeine and theophylline. *Clin Pharmacol Ther* 1986; **40:** 506–10.
6. Døssing M, *et al.* Effect of theophylline and salbutamol on hepatic drug metabolism. *Hum Toxicol* 1989; **8:** 225–8.

Antiarrhythmics. An increase in serum-theophylline concentration from 93.2 to 194.2 micromol/litre with symptoms of tachycardia, nervousness, and tremors occurred in a patient 9 days after starting *amiodarone* therapy.[1] Elevated theophylline concentrations and/or decreased clearance have also been reported following addition of *mexiletine* to theophylline therapy.[2-6] Amiodarone and mexiletine probably interact with theophylline through inhibition of its hepatic metabolism. *Tocainide* has also been found to impair theophylline metabolism resulting in a reduction in theophylline clearance but the effect was substantially smaller than that of mexiletine.[7] In one patient stabilised on theophylline therapy, an increase in the plasma-theophylline concentration with subsequent toxicity was noted after starting treatment with *propafenone*.[8]

See also under Calcium-channel Blockers, p. 1235.3.

1. Soto J, *et al.* Possible theophylline-amiodarone interaction. *DICP Ann Pharmacother* 1990; **24:** 1115.
2. Stanley R, *et al.* Mexiletine-theophylline interaction. *Am J Med* 1989; **86:** 733–4.
3. Ueno K, *et al.* Interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1990; **24:** 471–2.
4. Hurwitz A, *et al.* Mexiletine effects on theophylline disposition. *Clin Pharmacol Ther* 1991; **50:** 299–307.
5. Loi C-M, *et al.* Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. *Clin Pharmacol Ther* 1991; **49:** 571–80.
6. Ueno K, *et al.* Mechanism of interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1991; **25:** 727–30.
7. Loi C-M, *et al.* The effect of tocainide on theophylline metabolism. *Br J Clin Pharmacol* 1993; **35:** 437–40.
8. Lee BL, Dohrmann ML. Theophylline toxicity after propafenone treatment: evidence for drug interaction. *Clin Pharmacol Ther* 1992; **51:** 353–5.

Antibacterials. *IMIPENEM.* Seizures have been reported in 3 patients receiving theophylline who were given imipenem,[1] although serum concentrations of theophylline were not affected.

1. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. *South Med J* 1991; **84:** 465–8.

ISONIAZID. Isoniazid inhibits oxidative enzymes in the liver and has been found to impair the elimination of theophylline. Both clearance and volume of distribution of theophylline were reduced with an increase in serum-theophylline concentrations in healthy subjects after 14 days of pretreatment with isoniazid[1] and theophylline toxicity has been reported[2] in a patient one month after adding theophylline to isoniazid therapy.

1. Samigun, *et al.* Lowering of theophylline clearance by isoniazid in slow and rapid acetylators. *Br J Clin Pharmacol* 1990; **29:** 570–3.
2. Torrent J, *et al.* Theophylline-isoniazid interaction. *DICP Ann Pharmacother* 1989; **23:** 143–5.

MACROLIDES. There are conflicting reports of the effect of *erythromycin* on the pharmacokinetics of theophylline. Significant decreases in the clearance of theophylline and prolonged elimination half-life have been reported[1-3] but other studies have found no interaction.[4,5] It has also been noted that the serum concentrations and bioavailability of erythromycin may be reduced by theophylline[6,7] (see also p. 294.3). The clearance of theophylline is also markedly decreased by *troleandomycin*,[8-10] but there have been reports that for clinical purposes the pharmacokinetics of theophylline do not seem to be significantly altered by *dirithromycin*,[11-13] *josamycin*,[9,14] *midecamycin*,[10,15,16] *rokitamycin*,[17] *roxithromycin*,[18] or *spiramycin*.[19] *Clarithromycin* also seems unlikely to have a significant effect in most patients, but in a few theophylline dosage may need to be adjusted.[20,21] In one case report, serum-theophylline concentrations fell over a few days after the withdrawal of *azithromycin*.[22] The reduction in theophylline clearance by some macrolides was thought to be due to inhibition of the cytochrome P450 isoenzyme CYP1A2; however, it has been suggested that CYP1A2 inhibition does not play a significant role and the mechanism for the interaction may be due to a combination of CYP3A inactivation and the inhibition of theophylline uptake into hepatocytes.[23]

1. Zarowitz BJM, *et al.* Effect of erythromycin base on theophylline kinetics. *Clin Pharmacol Ther* 1981; **29:** 601–5.
2. Renton KW, *et al.* Depression of theophylline elimination by erythromycin. *Clin Pharmacol Ther* 1981; **30:** 422–6.
3. May DC, *et al.* The effects of erythromycin on theophylline elimination in normal males. *J Clin Pharmacol* 1982; **22:** 125–30.
4. Maddux MS, *et al.* The effect of erythromycin on theophylline pharmacokinetics at steady state. *Chest* 1982; **81:** 563–5.
5. Hildebrandt R, *et al.* Lack of clinically important interaction between erythromycin and theophylline. *Eur J Clin Pharmacol* 1984; **26:** 485–9.
6. Iliopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; **14:** 495–9.
7. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; **32:** 493–8.
8. Weinberger M, *et al.* Inhibition of theophylline clearance by troleandomycin. *J Allergy Clin Immunol* 1977; **59:** 228–31.
9. Brazier JL, *et al.* Retard d'élimination de la théophylline dû à la troléandomycine: absence d'effet de la josamycine. *Therapie* 1980; **35:** 545–9.
10. Lavarenne J, *et al.* Influence d'un nouveau macrolide, la midécamycine, sur les taux sanguins de théophylline. *Therapie* 1981; **36:** 451–6.
11. Bachmann K, *et al.* Changes in the steady-state pharmacokinetics of theophylline during treatment with dirithromycin. *J Clin Pharmacol* 1990; **30:** 1001–5.
12. Bachmann K, *et al.* Steady-state pharmacokinetics of theophylline in COPD patients treated with dirithromycin. *J Clin Pharmacol* 1993; **33:** 861–5.
13. McConnell SA, *et al.* Lack of effect of dirithromycin on theophylline pharmacokinetics in healthy volunteers. *J Antimicrob Chemother* 1999; **43:** 733–6.
14. Ruff F, *et al.* Macrolide et théophylline: absence d'interaction josamycine-théophylline. *Nouv Presse Med* 1981; **10:** 175.
15. Principi N, *et al.* Effect of miocamycin on theophylline kinetics in children. *Eur J Clin Pharmacol* 1987; **31:** 701–4.
16. Couet W, *et al.* Lack of effect of ponsinomycin on the plasma pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1989; **37:** 101–4.
17. Ishioka T. Effect of a new macrolide antibiotic, 3''-O-propionylleucomycin A_5 (rokitamycin) on serum concentrations of theophylline and digoxin in the elderly. *Acta Ther* 1987; **13:** 17–24.
18. Saint-Salvi B, *et al.* A study of the interaction of roxithromycin with theophylline and carbamazine. *J Antimicrob Chemother* 1987; **20** (suppl B): 121–9.
19. Debruyne D, *et al.* Spiramycin has no effect on serum theophylline in asthmatic patients. *Eur J Clin Pharmacol* 1986; **30:** 505–7.
20. Bachand RT. Comparative study of clarithromycin and ampicillin in the treatment of patients with acute bacterial exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1991; **27** (suppl A): 91–100.
21. Gillum JG, *et al.* Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1996; **40:** 1715–16.
22. Pollak PT, Slayter KL. Reduced serum theophylline concentrations after discontinuation of azithromycin: evidence for an unusual interaction. *Pharmacotherapy* 1997; **17:** 827–9.
23. Polasek TM, Miners JO. Macrolide-theophylline interactions: no role for the inhibition of cytochrome P4501A2. *Br J Clin Pharmacol* 2008; **66:** 898–900.

QUINOLONES. The fluoroquinolone antibacterials vary in their propensity to interact with theophylline. *Enoxacin* shows the most marked interaction and has been reported[1] to cause serious nausea and vomiting, tachycardia, and headaches, associated with unexpectedly high plasma-theophylline concentrations in patients with respiratory-tract infections. Studies,[2-5] mainly in healthy subjects, have found that enoxacin decreases theophylline clearance by up to 74%[3] with an increase in the elimination half-life and serum-theophylline concentration.

Ciprofloxacin[2,6-8] and *pefloxacin*[2] interact with theophylline to a lesser extent than enoxacin, decreasing theophylline clearance by about 30%. Eight clinically important interactions between ciprofloxacin and theophylline had been reported to the UK CSM[9] including 1 death. A ciprofloxacin-induced seizure has been reported[10] which may have been due to the combined inhibitory effects of the 2 drugs on GABA binding. It has been recommended that ciprofloxacin should not be used in patients treated with theophylline.[9]

Norfloxacin[4,11-13] and *ofloxacin*[4,11,14] have been reported to have minor effects on the pharmacokinetics of theophylline. Although their effects were usually considered not to be clinically significant, the US FDA had received 9 reports of theophylline toxicity associated with use with norfloxacin, including 1 death.[15] *Fleroxacin*,[16] *flumequine*,[17] *lomefloxacin*,[8,18,19] *moxifloxacin*,[20] and *rufloxacin*[21] have been reported to have no significant effect on the pharmacokinetics of theophylline in small studies in healthy subjects.

The mechanism of interaction involves a reduction in the metabolic clearance of theophylline due to inhibition of hepatic microsomal enzymes. However, the exact mechanism is unknown and it is difficult to predict which patients will be at risk. Extreme caution should be used when giving quinolones with theophylline, particularly in the elderly[15] and it may be advisable to use a non-interacting fluoroquinolone, although theophylline concentrations should still be monitored.

Of the non-fluorinated quinolones, *nalidixic acid*[2] has been reported not to affect theophylline clearance whereas *pipemidic acid* has markedly inhibited theophylline clearance.[19]

1. Wijnands WJA, *et al.* Enoxacin raises plasma theophylline concentrations. *Lancet* 1984; **ii:** 108–9.
2. Wijnands WJA, *et al.* The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986; **22:** 677–83.
3. Beckmann J, *et al.* Enoxacin—a potent inhibitor of theophylline metabolism. *Eur J Clin Pharmacol* 1987; **33:** 227–30.
4. Sano M, *et al.* Inhibitory effect of enoxacin, ofloxacin and norfloxacin on renal excretion of theophylline in humans. *Eur J Clin Pharmacol* 1989; **36:** 323–4.
5. Koup JR, *et al.* Theophylline dosage adjustment during enoxacin coadministration. *Antimicrob Agents Chemother* 1990; **34:** 803–7.
6. Nix DE, *et al.* Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. *J Antimicrob Chemother* 1987; **19:** 263–9.
7. Schwartz J, *et al.* Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. *Antimicrob Agents Chemother* 1988; **32:** 75–7.
8. Robson RA, *et al.* Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29:** 491–3.
9. Bem JL, Mann RD. Danger of interaction between ciprofloxacin and theophylline. *BMJ* 1988; **296:** 1131.
10. Karki SD, *et al.* Seizure with ciprofloxacin and theophylline combined therapy. *DICP Ann Pharmacother* 1990; **24:** 595–6.
11. Sano M, *et al.* Comparative pharmacokinetics of theophylline following two fluoroquinolones co-administration. *Eur J Clin Pharmacol* 1987; **32:** 431–2.
12. Ho G, *et al.* Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1988; **44:** 35–8.
13. Davis RL, *et al.* Effect of norfloxacin on theophylline metabolism. *Antimicrob Agents Chemother* 1989; **33:** 212–14.
14. Gregoire SL, *et al.* Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. *Antimicrob Agents Chemother* 1987; **31:** 375–8.
15. Grasela TH, Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. *Arch Intern Med* 1992; **152:** 617–21.
16. Parent M, *et al.* Safety of fleroxacin coadministered with theophylline to young and elderly volunteers. *Antimicrob Agents Chemother* 1990; **34:** 1249–53.
17. Lacarelle B, *et al.* The quinolone, flumequine, has no effect on theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1994; **46:** 477–8.
18. LeBel M, *et al.* Influence of lomefloxacin on the pharmacokinetics of theophylline. *Antimicrob Agents Chemother* 1990; **34:** 1254–6.
19. Staib AH, *et al.* Interaction of quinolones with the theophylline metabolism in man: investigations with lomefloxacin and pipemidic acid. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 289–93.
20. Stass H, Kubitza D. Lack of pharmacokinetic interaction between moxifloxacin, a novel 8-methoxyfluoroquinolone, and theophylline. *Clin Pharmacokinet* 2001; **40** (suppl 1): 63–70.
21. Kinzig-Schippers M, *et al.* Absence of effect of rufloxacin on theophylline pharmacokinetics in steady state. *Antimicrob Agents Chemother* 1998; **42:** 2359–64.

RIFAMPICIN. Rifampicin induces hepatic oxidative enzymes and an oral dose of 600 mg daily for 6 to 14 days has been shown to increase mean plasma-theophylline clearance by 25 to 82% due to enhancement of hepatic theophylline metabolism. This increase in clearance is sufficient to require dosage adjustment in some patients,[1-4] including children.[5]

1. Straughn AB, *et al.* Effect of rifampin on theophylline disposition. *Ther Drug Monit* 1984; **6:** 153–6.
2. Robson RA, *et al.* Theophylline-rifampicin interaction: non-selective induction of theophylline metabolic pathways. *Br J Clin Pharmacol* 1984; **18:** 445–8.
3. Boyce EG, *et al.* The effect of rifampin on theophylline kinetics. *J Clin Pharmacol* 1986; **26:** 696–9.
4. Adebayo GE, *et al.* Attenuation of rifampicin-induced theophylline metabolism by diltiazem/rifampicin coadministration in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 127–31.
5. Brocks DR, *et al.* Theophylline-rifampin interaction in a pediatric patient. *Clin Pharm* 1986; **5:** 602–4.

TETRACYCLINES. Tetracycline weakly inhibited theophylline clearance after 5 days of therapy in 5 non-smoking adults with chronic obstructive airways disease[1] and theophylline toxicity has been reported[2] in a patient given a 10-day course of tetracycline during theophylline therapy. *Doxycycline* has been reported not to have any significant effect on theophylline pharmacokinetics in healthy subjects.[3]

1. Gotz VP, Ryerson GG. Evaluation of tetracycline on theophylline disposition in patients with chronic obstructive airways disease. *Drug Intell Clin Pharm* 1986; **20:** 694–7.
2. McCormack JP, *et al.* Theophylline toxicity induced by tetracycline. *Clin Pharm* 1990; **9:** 546–9.
3. Jonkman JHG, *et al.* No influence of doxycycline on theophylline pharmacokinetics. *Ther Drug Monit* 1985; **7:** 92–4.

Antidepressants. Significantly reduced clearance and increased plasma concentrations of theophylline have been reported when given with *viloxazine*.[1,2] The dosage of theophylline should be decreased and its plasma concentrations monitored when viloxazine is also prescribed.[2] The interaction probably involves competition between the two drugs for hepatic microsomal enzymes.

Fluvoxamine has also been associated with a significant reduction in theophylline clearance[3,4] and theophylline toxicity has occurred in patients when fluvoxamine was added to their therapy.[5,6] This is due to potent liver enzyme inhibition[7] by fluvoxamine, and has been the subject of a warning by the UK CSM[8] in which they issued the standard advice of avoiding the two drugs if at all possible and, where they could not be avoided, of giving half the dose of theophylline and monitoring plasma concentrations. A small study evaluating the effect of liver cirrhosis on the interaction between fluvoxamine and theophylline saw a decrease in fluvoxamine-induced inhibition of theophylline clearance as the severity of liver cirrhosis increased.[4] The authors suggest that theophylline may require less of a dose reduction in the presence of severe liver dysfunction, aside from that already required by impaired hepatic metabolism (see Administration in Hepatic Impairment, p. 1230.3).

St John's wort may have decreased theophylline concentrations and increased the theophylline dosage requirement in one case report.[9] However, a study[10] in 12 healthy subjects found that 15 days of treatment with St John's wort did not significantly change theophylline pharmacokinetics.

For a mention of the effect of theophylline on the renal clearance of *lithium*, see Xanthines, under Interactions of Lithium, p. 432.3.

1. Thomson AH, *et al*. Theophylline toxicity following coadministration of viloxazine. *Ther Drug Monit* 1988; **10:** 359–60.
2. Perault MC, *et al*. A study of the interaction of viloxazine with theophylline. *Ther Drug Monit* 1989; **11:** 520–2.
3. Donaldson KM, *et al*. The effect [of] fluvoxamine at steady state on the pharmacokinetics of theophylline after a single dose in healthy male volunteers. *Br J Clin Pharmacol* 1994; **37:** 492P.
4. Orlando R, *et al*. Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; **79:** 489–99.
5. Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. *Drug Safety* 1991; **6:** 460–2.
6. Thomson AH, *et al*. Interaction between fluvoxamine and theophylline. *Pharm J* 1992; **249:** 137.
7. Rasmussen BB, *et al*. Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995; **39:** 151–9.
8. CSM/MCA. Fluvoxamine increases plasma theophylline levels. *Current Problems* 1994; **20:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
9. Nebel A, *et al*. Potential metabolic interaction between St John's wort and theophylline. *Ann Pharmacother* 1999; **33:** 502.
10. Morimoto T, *et al*. Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 95–101.

Antiepileptics. *Phenytoin* markedly decreases the elimination half-life and increases the clearance of theophylline, probably due to hepatic enzyme induction, at therapeutic or subtherapeutic serum-phenytoin concentrations[1-4] and even in heavy smokers.[2] An early report suggested that the serum concentration of phenytoin may be decreased simultaneously,[5] perhaps due to enzyme induction by theophylline[5] or reduced phenytoin absorption.[6] The interaction has been reported to occur within 5 to 14 days of taking phenytoin and theophylline, and theophylline clearance has increased by up to 350%, and reductions in serum half-life have ranged from 25 to 70% of initial values.[3,4]

Carbamazepine has also been seen to increase theophylline elimination. In one patient, theophylline serum half-life was decreased by about 24 to 60%, and clearance was increased by about 35 to 100% when carbamazepine was given.[2] In an 11-year-old girl theophylline-serum half-life was almost halved with loss of asthma control after 3 weeks of concurrent carbamazepine therapy.[7] In turn, there has been a report that theophylline may reduce serum concentrations of carbamazepine—see p. 517.3.

Although *phenobarbital* was not found to have a significant effect on the pharmacokinetics of a single dose of theophylline given intravenously,[8] enhanced theophylline clearance has been seen in patients after longer periods of treatment with phenobarbital.[9,10] The magnitude of the changes in theophylline elimination appears to be smaller with phenobarbital than phenytoin. *Pentobarbital* in high doses has also been reported to increase theophylline metabolism.[11] A more recent study[12] has also shown that therapeutic doses of pentobarbital (100 mg daily) increase plasma clearance of theophylline by a mean of 40%, although this was subject to marked interindividual variations. Renal clearance was not affected, suggesting hepatic enzyme induction as the probable mechanism.

1. Marquis J-F, *et al*. Phenytoin-theophylline interaction. *N Engl J Med* 1982; **307:** 1189–90.
2. Reed RC, Schwartz HJ. Phenytoin-theophylline-quinidine interaction. *N Engl J Med* 1983; **308:** 724–5.
3. Sklar SJ, Wagner JC. Enhanced theophylline clearance secondary to phenytoin therapy. *Drug Intell Clin Pharm* 1985; **19:** 34–6.
4. Miller M, *et al*. Influence of phenytoin on theophylline clearance. *Clin Pharmacol Ther* 1984; **35:** 666–9.
5. Taylor JW, *et al*. The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; **14:** 638.
6. Hendeles L, *et al*. Decreased oral phenytoin absorption following concurrent theophylline administration. *J Allergy Clin Immunol* 1979; **63:** 156.
7. Rosenberry KR, *et al*. Reduced theophylline half-life induced by carbamazepine therapy. *J Pediatr* 1983; **102:** 472–4.
8. Piafsky KM, *et al*. Effect of phenobarbital on the disposition of intravenous theophylline. *Clin Pharmacol Ther* 1977; **22:** 336–9.
9. Jusko WJ, *et al*. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. *J Pharm Sci* 1979; **68:** 1358–66.
10. Saccar CL, *et al*. The effect of phenobarbital on theophylline disposition in children with asthma. *J Allergy Clin Immunol* 1985; **75:** 716–19.
11. Gibson GA, *et al*. Influence of high-dose phenobarbital on theophylline pharmacokinetics: a case report. *Ther Drug Monit* 1985; **7:** 181–4.
12. Dahlqvist R, *et al*. Induction of theophylline metabolism by pentobarbital. *Ther Drug Monit* 1989; **11:** 408–10.

Antifungals. There have been reports that *ketoconazole* does not appear significantly to alter the pharmacokinetics of theophylline.[1,2] Licensed product information for *fluconazole* has, however, stated that plasma clearance of theophylline may be decreased by fluconazole. A 16% reduction in theophylline clearance has been reported[3] after oral fluconazole but fluconazole was considered to have only a minor inhibitory effect on theophylline metabolism and theophylline disposition was not significantly affected. Theophylline metabolism has been inhibited to a similar degree by *terbinafine*.[4]

1. Brown MW, *et al*. Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; **37:** 290–7.
2. Heusner JJ, *et al*. Effect of chronically administered ketoconazole on the elimination of theophylline in man. *Drug Intell Clin Pharm* 1987; **21:** 514–17.
3. Konishi H, *et al*. Effect of fluconazole on theophylline disposition in humans. *Eur J Clin Pharmacol* 1994; **46:** 309–12.
4. Trépanier EF, *et al*. Effect of terbinafine on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1998; **42:** 695–7.

Antigout drugs. Oral *allopurinol* 300 mg daily for 7 days was found to have no effect on the pharmacokinetics of theophylline after a single intravenous dose of aminophylline[1,2] or after oral theophylline given to steady state.[1] However, oral allopurinol 600 mg daily for 28 days has been found to inhibit the metabolism of theophylline,[3] increasing the mean half-life by 25% after 14 days and 29% after 28 days and there has been a report of allopurinol increasing peak plasma-theophylline concentrations by 38% in one patient within 2 days of use together.[4]

Probenecid has been reported[5] to have no effect on the hepatic metabolism or total body clearance of theophylline in a single-dose study in healthy subjects.

Sulfinpyrazone 800 mg daily for 7 days increased the total plasma clearance of theophylline by 22% in healthy subjects due to selective induction of certain cytochrome P450 isoenzymes.[6]

1. Grygiel JJ, *et al*. Effects of allopurinol on theophylline metabolism and clearance. *Clin Pharmacol Ther* 1979; **26:** 660–7.
2. Vozeh S, *et al*. Influence of allopurinol on theophylline disposition in adults. *Clin Pharmacol Ther* 1980; **27:** 194–7.
3. Manfredi RL, Vesell ES. Inhibition of theophylline metabolism by long-term allopurinol administration. *Clin Pharmacol Ther* 1981; **29:** 224–9.
4. Barry M, Feely J. Allopurinol influences aminophenazone elimination. *Clin Pharmacokinet* 1990; **19:** 167–9.
5. Chen TWD, Patton TF. Effect of probenecid on the pharmacokinetics of aminophylline. *Drug Intell Clin Pharm* 1983; **17:** 465–6.
6. Birkett DJ, *et al*. Evidence for a dual action of sulphinpyrazone on drug metabolism in man: theophylline-sulphinpyrazone interaction. *Br J Clin Pharmacol* 1983; **15:** 567–9.

Antineoplastics. There has been a report of increased clearance of theophylline in 3 patients given *aminoglutethimide*.[1]

The clearance of theophylline (given as theophylline, aminophylline, or choline theophyllinate) was reported to decrease by an average of 19% in 8 patients with severe corticosteroid-dependent asthma given low-dose weekly intramuscular injections of *methotrexate*.[2] A high degree of interpatient variability was seen. Three patients reported nausea; one of whom required a decrease in theophylline dose. The authors reported that the most likely explanation for the change in theophylline clearance was inhibition of microsomal enzyme activity.

For reference to a possible interaction between theophylline and *lomustine*, see Lomustine, p. 818.2.

1. Lønning PE, *et al*. Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; **36:** 796–802.
2. Glynn-Barnhart AM, *et al*. Effect of low-dose methotrexate on the disposition of glucocorticoids and theophylline. *J Allergy Clin Immunol* 1991; **88:** 180–6.

Antivirals. A single injection of recombinant human *interferon alfa* reduced theophylline clearance by 33 to 81% in 8 of 9 subjects, resulting in a 1.5- to sixfold increase in the theophylline elimination half-life.[1] Injection of interferon alfa once daily for 3 days in 11 healthy subjects also reduced theophylline clearance and increased elimination half-life,[2] but the magnitude of the changes were of a similar order to normal intra-individual variation and the interaction was considered of minor clinical significance.

Licensed product information for *ritonavir* states that it substantially increases the clearance of theophylline; theophylline dosage may need to be increased to maintain efficacy.

There is evidence[3] that *aciclovir* inhibits theophylline metabolism, resulting in accumulation.

1. Williams SJ, *et al*. Inhibition of theophylline metabolism by interferon. *Lancet* 1987; **ii:** 939–41.
2. Jonkman JHG, *et al*. Effects of α-interferon on theophylline pharmacokinetics and metabolism. *Br J Clin Pharmacol* 1989; **27:** 795–802.
3. Maeda Y, *et al*. Inhibition of theophylline metabolism by aciclovir. *Biol Pharm Bull* 1996; **19:** 1591–5.

Benzodiazepines. For reference to the antagonism of benzodiazepine sedation by aminophylline, see Xanthines, under Interactions of Diazepam, p. 1070.3.

Beta blockers. *Propranolol* reduced theophylline clearance by 36% in healthy subjects given aminophylline intravenously. *Metoprolol* did not reduce clearance in the group as a whole, but a reduction was noted in some smokers whose theophylline clearance was initially high.[1] Propranolol is thought to exert a dose-dependent selective inhibitory effect on the separate cytochrome P450 isoenzymes involved in theophylline demethylation and 8-hydroxylation.[2] The less lipophilic beta blockers *atenolol*[3,4] and *nadolol*[4] had no significant effect on the pharmacokinetics of theophylline.

In general, however, beta blockers should be avoided in patients taking theophylline as they can dangerously exacerbate bronchospasm in patients with a history of asthma or chronic obstructive pulmonary disease.

1. Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline elimination. *Clin Pharmacol Ther* 1980; **28:** 463–7.
2. Miners JO, *et al*. Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. *Br J Clin Pharmacol* 1985; **20:** 219–23.
3. Cerasa LA, *et al*. Lack of effect of atenolol on the pharmacokinetics of theophylline. *Br J Clin Pharmacol* 1988; **26:** 800–2.
4. Corsi CM, *et al*. Lack of effect of atenolol and nadolol on the metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29:** 265–8.

Caffeine. Abstention from dietary methylxanthines by healthy subjects has resulted in faster elimination of theophylline.[1] While the addition of extra caffeine to the diet has been reported not to alter theophylline disposition,[2] some studies in healthy subjects have indicated that the ingestion of moderate amounts of caffeine (120 to 900 mg daily), which could be consumed by drinking several cups of coffee daily, can have a pronounced influence on the pharmacokinetics of theophylline.[3,4] In these latter studies the mean theophylline clearance was reduced by 23 and 29% with a corresponding increase in the elimination half-lives.

1. Monks TJ, *et al*. Influence of methylxanthine-containing foods on theophylline metabolism and kinetics. *Clin Pharmacol Ther* 1979; **26:** 513–24.
2. Monks TJ, *et al*. The effect of increased caffeine intake on the metabolism and pharmacokinetics of theophylline in man. *Biopharm Drug Dispos* 1981; **2:** 31–7.
3. Jonkman JHG, *et al*. The influence of caffeine on the steady-state pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1991; **49:** 248–55.
4. Sato J, *et al*. Influence of usual intake of dietary caffeine on single-dose kinetics of theophylline in healthy human subjects. *Eur J Clin Pharmacol* 1993; **44:** 295–8.

Calcium-channel blockers. *Verapamil* has been reported[1] to decrease the clearance of theophylline by a mean of 14% in healthy subjects and although this was not considered to be clinically significant, symptoms of theophylline toxicity, associated with near doubling of the serum-theophylline concentration have occurred in a 76-year-old woman taking theophylline after 6 days of therapy with verapamil.[2] Studies in healthy subjects and asthmatic patients have produced conflicting results of the effect of *nifedipine* on the pharmacokinetics of theophylline. Reduced clearance[1] and an increase in the volume of distribution[3,4] of theophylline have been reported and both decreased[4] and increased[5] serum-theophylline concentrations; theophylline toxicity has been reported.[6,7] However, most studies have concluded that the effects of nifedipine are unlikely to be of clinical importance.[1,4,5,8]

Serum concentrations of theophylline have been reported to be increased by *diltiazem*[5] and reduced by *felodipine*;[9] neither of these effects were considered to be clinically significant.

1. Robson RA, *et al*. Selective inhibitory effects of nifedipine and verapamil on oxidative metabolism: effects on theophylline. *Br J Clin Pharmacol* 1988; **25:** 397–400.
2. Burnakis TG, *et al*. Increased serum theophylline concentrations secondary to oral verapamil. *Clin Pharm* 1983; **2:** 458–61.
3. Jackson SHD, *et al*. The interaction between iv theophylline and chronic oral dosing with slow release nifedipine in volunteers. *Br J Clin Pharmacol* 1986; **21:** 389–92.
4. Adebayo GI, Mabadeje AFB. Effect of nifedipine on antipyrine and theophylline disposition. *Biopharm Drug Dispos* 1990; **11:** 157–64.
5. Smith SR, *et al*. The influence of nifedipine and diltiazem on serum theophylline concentration-time profiles. *J Clin Pharm Ther* 1989; **14:** 403–8.
6. Parrillo SJ, Venditto M. Elevated theophylline blood levels from institution of nifedipine therapy. *Ann Emerg Med* 1984; **13:** 216–17.
7. Harrod CS. Theophylline toxicity and nifedipine. *Ann Intern Med* 1987; **106:** 480.
8. Spedini C, Lombardi C. Long-term treatment with oral nifedipine plus theophylline in the management of chronic bronchial asthma. *Eur J Clin Pharmacol* 1986; **31:** 105–6.
9. Bratel T, *et al*. Felodipine reduces the absorption of theophylline in man. *Eur J Clin Pharmacol* 1989; **36:** 481–5.

Cannabis. A search of the literature[1] revealed 2 studies, both published in the 1970s, that showed that marijuana smoking increased the clearance of theophylline.

1. Brown D. Influence on theophylline clearance. *Pharm J* 1994; **253:** 595.

Corticosteroids. In 3 patients with acute severe asthma given aminophylline intravenously, serum-theophylline concentrations rose rapidly from the therapeutic range to between 40 and 50 micrograms/mL when *hydrocortisone* was given intravenously.[1] In studies in healthy subjects, no significant changes in serum-theophylline concentrations were noted when hydrocortisone, *methylprednisolone*,[2] or *prednisone*[3] were given, although there was a trend towards increased theophylline clearance during corticosteroid therapy.[2,3] In preterm neonates, exposure to

betamethasone in utero stimulated the hepatic metabolism of theophylline,[4,5] but did not affect dosage requirements.

The possibility that adverse effects such as hypokalaemia may be potentiated by use of theophylline with corticosteroids should be borne in mind.

1. Buchanan N, *et al*. Asthma—a possible interaction between hydrocortisone and theophylline. *S Afr Med J* 1979; 56: 1147–8.
2. Leavengood DC, *et al*. The effect of corticosteroids on theophylline metabolism. *Ann Allergy* 1983; **50:** 249–51.
3. Anderson JL, *et al*. Potential pharmacokinetic interaction between theophylline and prednisone. *Clin Pharm* 1984; **3:** 187–9.
4. Jager-Roman E, *et al*. Increased theophylline metabolism in premature infants after prenatal betamethasone administration. *Dev Pharmacol Ther* 1982; **5:** 127–35.
5. Baird-Lambert J, *et al*. Theophylline metabolism in preterm neonates during the first weeks of life. *Dev Pharmacol Ther* 1984; **7:** 239–44.

Disulfiram. In a study involving 20 recovering alcoholic patients, disulfiram decreased the plasma clearance and prolonged the elimination half-life of theophylline in a dose-dependent manner.[1] It was concluded that disulfiram exerts a dose-dependent inhibitory effect on the hepatic metabolism of theophylline and that, in order to minimise the risk of toxicity if given together, the dosage of theophylline may need to be reduced by up to 50%.

1. Loi C-M, *et al*. Dose-dependent inhibition of theophylline metabolism by disulfiram in recovering alcoholics. *Clin Pharmacol Ther* 1989; **45:** 476–86.

Diuretics. Although increased mean serum-theophylline concentrations were noted in 10 patients given continuous intravenous aminophylline infusions after intravenous injection of *furosemide*,[1] in 8 patients with chronic stable asthma, mean peak serum-theophylline concentrations were reduced from 12.14 micrograms/mL with placebo to 7.16 micrograms/mL when furosemide was given. Reduced concentrations were noted for up to 6 hours after furosemide.[2] Decreased theophylline concentrations were also noted in 4 neonates receiving oral or intravenous theophylline when given furosemide.[3] Serum-theophylline concentrations returned to normal when furosemide and theophylline were given more than 2 hours apart.

The possibility that adverse effects such as hypokalaemia may be potentiated if theophylline is given with diuretics should be borne in mind.

1. Conlon PF, *et al*. Effect of intravenous furosemide on serum theophylline concentration. *Am J Hosp Pharm* 1981; **38:** 1345–7.
2. Carpentiere G, *et al*. Furosemide and theophylline. *Ann Intern Med* 1985; **103:** 957.
3. Toback JW, Gilman ME. Theophylline-furosemide inactivation. *Pediatrics* 1983; **71:** 140–1.

Gastrointestinal drugs. Oral *antacids* do not appear to affect the total absorption of theophylline from the gut.[1-5] However, some studies have shown a reduction in the rate of absorption from both immediate-[1] and modified-release theophylline preparations[2] after antacids. Also an increase in peak serum-theophylline concentrations has been noted with certain modified-release formulations.[3]

Cimetidine inhibits the oxidative metabolism of theophylline reducing its clearance by 20 to 35% and prolonging its serum half-life;[6-8] toxic effects have been reported.[6] It has been recommended that the dose of aminophylline should be reduced by about one-third if given with cimetidine.[6] This inhibition of theophylline metabolism may be enhanced by liver disease,[9] but there is wide interindividual variation. The reduction in clearance may be greater in smokers.[10] Studies have suggested that *ranitidine* does not significantly inhibit theophylline metabolism,[11-14] even at very high doses.[15] However, there have been occasional reports of theophylline toxicity after use with ranitidine.[16-18] *Famotidine*[19] has also been reported to not alter theophylline disposition but one small study found a significant decrease in theophylline clearance in some patients with chronic obstructive pulmonary disease.[20]

Omeprazole, lansoprazole, and *pantoprazole* generally have insignificant or no effect on theophylline clearance.[21,22] In CYP2C19 poor metabolisers there may be an increase in omeprazole concentrations and subsequent induction of CYP1A, a major enzyme of theophylline metabolism. A pharmacokinetic study[23] of this induction in 5 poor metabolisers given omeprazole did find a trend towards an increase in theophylline clearance.

1. Arnold LA, *et al*. Effect of an antacid on gastrointestinal absorption of theophylline. *Am J Hosp Pharm* 1979; **36:** 1059–62.
2. Shargel L, *et al*. Effect of antacid on bioavailability of theophylline from rapid and timed-release drug products. *J Pharm Sci* 1981; **70:** 599–602.
3. Darzentas LJ, *et al*. Effect of antacid on bioavailability of a sustained-release theophylline preparation. *Drug Intell Clin Pharm* 1983; **17:** 555–7.
4. Myhre KI, Walstad RA. The influence of antacid on the absorption of two different sustained-release formulations of theophylline. *Br J Clin Pharmacol* 1983; **15:** 683–7.
5. Muir JF, *et al*. Lack of effect of magnesium-aluminium hydroxide on the absorption of theophylline given as a pH-dependent sustained-release preparation. *Eur J Clin Pharmacol* 1993; **44:** 85–8.
6. Bauman JH, *et al*. Cimetidine-theophylline interaction: report of four patients. *Ann Allergy* 1982; **48:** 100–102.
7. Vestal RE, *et al*. Cimetidine inhibits theophylline clearance in patients with chronic obstructive pulmonary disease: a study using stable isotope methodology during multiple oral dose administration. *Br J Clin Pharmacol* 1983; **15:** 411–18.
8. Roberts RK, *et al*. Cimetidine-theophylline interaction in patients with chronic obstructive airways disease. *Med J Aust* 1984; **140:** 279–80.
9. Gugler R, *et al*. The inhibition of drug metabolism by cimetidine in patients with liver cirrhosis. *Klin Wochenschr* 1984; **62:** 1126–31.
10. Grygiel JJ, *et al*. Differential effects of cimetidine on theophylline metabolic pathways. *Eur J Clin Pharmacol* 1984; **26:** 335–40.
11. Breen KJ, *et al*. Effects of cimetidine and ranitidine on hepatic drug metabolism. *Clin Pharmacol Ther* 1982; **31:** 297–300.
12. Seggev JS, *et al*. No evidence for interaction between ranitidine and theophylline. *Arch Intern Med* 1987; **147:** 179–80.
13. Adebayo GI. Effects of equimolar doses of cimetidine and ranitidine on theophylline elimination. *Biopharm Drug Dispos* 1989; **10:** 77–85.
14. Boehning W. Effect of cimetidine and ranitidine on plasma theophylline in patients with chronic obstructive airways disease treated with theophylline and corticosteroids. *Eur J Clin Pharmacol* 1990; **38:** 43–5.
15. Kelly HW, *et al*. Ranitidine at very large doses does not inhibit theophylline elimination. *Clin Pharmacol Ther* 1986; **39:** 577–81.
16. Fernandes E, Melewicz FM. Ranitidine and theophylline. *Ann Intern Med* 1984; **100:** 459.
17. Gardner ME, Sikorski GW. Ranitidine and theophylline. *Ann Intern Med* 1985; **102:** 559.
18. Hegman GW, Gilbert RP. Ranitidine-theophylline interaction—fact or fiction? *DICP Ann Pharmacother* 1991; **25:** 21–5.
19. Chremos AN, *et al*. Famotidine does not interfere with the disposition of theophylline in man: comparison to cimetidine. *Clin Pharmacol Ther* 1986; **39:** 187.
20. Dal Negro R, *et al*. Famotidine and theophylline pharmacokinetics: an unexpected cimetidine-like interaction in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1993; **24:** 255–8.
21. Kokufu T, *et al*. Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. *Eur J Clin Pharmacol* 1995; **48:** 391–5.
22. Dilger K, *et al*. Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. *Br J Clin Pharmacol* 1999; **48:** 438–44.
23. Cavuto NJ, *et al*. Effect of omeprazole on theophylline clearance in poor metabolizers of omeprazole. *Clin Pharmacol Ther* 1995; **57:** 215.

General anaesthetics. There have been several reports[1,2] of increased cardiotoxicity when patients taking theophylline were anaesthetised with *halothane*. There was also an early report of seizures and tachycardia attributed to an interaction between theophylline and *ketamine*.[3]

1. Barton MD. Anesthetic problems with aspirin-intolerant patients. *Anesth Analg* 1975; **54:** 376–80.
2. Richards W, *et al*. Cardiac arrest associated with halothane anesthesia in a patient receiving theophylline. *Ann Allergy* 1988; **61:** 83–4.
3. Hirschman CA, *et al*. Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology* 1982; **56:** 464–7.

Leukotriene inhibitors and antagonists. *Zileuton* prolongs the half-life and reduces the clearance of theophylline;[1] dosage of theophylline should be reduced to avoid toxicity when both drugs are given together, and plasma-theophylline concentrations should be monitored. Use of *zafirlukast* with theophylline decreased zafirlukast plasma concentrations but had no effect on theophylline plasma concentrations in clinical studies. However, toxic serum-theophylline concentrations occurred in one patient when zafirlukast was added to therapy, and recurred on rechallenge.[2] A dose of *montelukast* 10 mg daily did not affect the pharmacokinetics of theophylline, but doses of 200 mg and 600 mg daily reduced the maximum plasma concentration, area under the concentration-time curve, and elimination half-life of theophylline.[3]

1. Granneman GR, *et al*. Effect of zileuton on theophylline pharmacokinetics. *Clin Pharmacokinet* 1995; **29** (suppl 2): 77–83.
2. Katial RK, *et al*. A drug interaction between zafirlukast and theophylline. *Arch Intern Med* 1998; **158:** 1713–15.
3. Malmstrom K, *et al*. Effect of montelukast on single-dose theophylline pharmacokinetics. *Am J Ther* 1998; **5:** 189–95.

Methoxsalen. In a single-dose pharmacokinetic study in 3 healthy subjects, the rate of elimination of theophylline was decreased after a single oral dose of methoxsalen, while urinary excretion of unchanged theophylline increased.[1] Methoxsalen probably inhibits the metabolism of cytochrome P450 isoenzyme CYP1A2,[2] and it has been suggested that theophylline dose reductions are likely to be required when used with systemic methoxsalen but seem unlikely to be necessary with topical PUVA therapy.

1. Apseloff G, *et al*. Inhibition and induction of theophylline metabolism by 8-methoxypsoralen: in vivo study in rats and humans. *Drug Metab Dispos* 1990; **18:** 298–303.
2. Tantcheva-Poór I, *et al*. Liver cytochrome P450 CYP1A2 is markedly inhibited by systemic but not by bath PUVA in dermatological patients. *Br J Dermatol* 2001; **144:** 1127–32.

Neuromuscular blockers. For reference to resistance to neuromuscular block with pancuronium in patients receiving aminophylline, see Xanthines, p. 2033.3.

Oral contraceptives. Oral contraceptives have been reported to decrease the clearance of theophylline by about 30%, and serum concentrations may be increased,[1-3] due to the inhibitory effects of oral contraceptives on hepatic P450 isoenzymes.

1. Tornatore KM, *et al*. Effect of chronic oral contraceptive steroids on theophylline disposition. *Eur J Clin Pharmacol* 1982; **23:** 129–34.
2. Gardner MJ, *et al*. Effects of tobacco smoking and oral contraceptive use on theophylline disposition. *Br J Clin Pharmacol* 1983; **16:** 271–80.
3. Roberts RK, *et al*. Oral contraceptive steroids impair the elimination of theophylline. *J Lab Clin Med* 1983; **101:** 821–5.

Roflumilast. Use of theophylline with roflumilast may result in an increased inhibition of phosphodiesterase type-4, see Interactions, under Roflumilast, p. 1219.3.

Sympathomimetics. The effect of beta-adrenoceptor agonists on the pharmacokinetics of theophylline is unclear. Whereas some studies have found that *orciprenaline*[1] or *terbutaline*[2] had no effect on theophylline disposition, others have shown an increase in theophylline clearance after *isoprenaline*[3,4] or *terbutaline*.[5,6]

Use of theophylline with beta-adrenoceptor agonists can potentiate adverse effects including hypokalaemia,[7,8] hyperglycaemia,[7] tachycardia,[7,8] hypertension,[7] and tremor.[9] Of 9 patients reported to the UK CSM with hypokalaemia during such combined therapy, 4 had clinical sequelae of cardiorespiratory arrest, intestinal pseudo-obstruction, or confusion. Monitoring of serum-potassium concentrations was recommended in patients with severe asthma given both beta-adrenoceptor agonists and xanthine derivatives.[10]

The possibility of an interaction with *phenylpropanolamine* should also be borne in mind, as it has been shown to reduce the clearance of theophylline significantly.[11]

1. Conrad KA, Woodworth JR. Orciprenaline does not alter theophylline elimination. *Br J Clin Pharmacol* 1981; **12:** 756–7.
2. Snidow J, *et al*. Acute effects of short-term subcutaneous terbutaline on theophylline disposition. *Eur J Clin Pharmacol* 1987; **32:** 191–3.
3. Hemstreet MP, *et al*. Effect of intravenous isoproterenol on theophylline kinetics. *J Allergy Clin Immunol* 1982; **69:** 360–4.
4. Griffith JA, Kozloski GD. Isoproterenol-theophylline interaction: possible potentiation by other drugs. *Clin Pharm* 1990; **9:** 54–7.
5. Danziger Y, *et al*. Reduction of serum theophylline levels by terbutaline in children with asthma. *Clin Pharmacol Ther* 1985; **37:** 469–71.
6. Garty M, *et al*. Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; **36:** 25–8.
7. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; **21:** 451–3.
8. Whyte KF, *et al*. Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; **25:** 571–8.
9. van der Vet APH, *et al*. Pharmacodynamics (lungfunction tests, tremor measurements and cAMP determinations) of a single dose of 0.5 mg terbutaline subcutaneously during sustained-release theophylline medication in patients with asthmatic bronchitis. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 569–73.
10. CSM. β_2 agonists, xanthines and hypokalaemia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
11. Wilson HA, *et al*. Phenylpropanolamine significantly reduces the clearance of theophylline. *Am Rev Respir Dis* 1991; **143:** A629.

Tiabendazole. Tiabendazole has been reported[1,2] to increase serum-theophylline concentrations and to decrease theophylline clearance. It has been recommended[2] that theophylline dosage should be reduced by 50% when tiabendazole therapy is started.

1. Sugar AM, *et al*. Possible thiabendazole-induced theophylline toxicity. *Am Rev Respir Dis* 1980; **122:** 501–3.
2. Lew G, *et al*. Theophylline-thiabendazole drug interaction. *Clin Pharm* 1989; **8:** 225–7.

Ticlopidine. Theophylline elimination half-life was increased and plasma clearance was decreased in 10 healthy subjects after the use of oral ticlopidine 500 mg daily for 10 days.[1]

1. Colli A, *et al*. Ticlopidine-theophylline interaction. *Clin Pharmacol Ther* 1987; **41:** 358–62.

Vaccines. Transient inhibition of the hepatic metabolism of theophylline, possibly secondary to interferon production, resulting in increased theophylline serum half-life and concentration has been reported after BCG vaccination[1] and influenza vaccination.[2,3] Other studies have not been able to confirm the interaction with influenza vaccine.[4-7] The differing findings are probably due to differences in vaccine; modern purified subvirion vaccines which do not induce interferon production do not appear to alter theophylline metabolism.[8,9]

1. Gray JD, *et al*. Depression of theophylline elimination following BCG vaccination. *Br J Clin Pharmacol* 1983; **16:** 735–7.
2. Renton KW, *et al*. Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1980; **123:** 288–90.
3. Walker S, *et al*. Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1981; **125:** 243–4.
4. Goldstein RS, *et al*. Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1982; **126:** 470.
5. Fischer RG, *et al*. Influence of trivalent influenza vaccine on serum theophylline levels. *Can Med Assoc J* 1982; **126:** 1312–13.
6. Britton L, Ruben FL. Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1982; **126:** 1375.
7. Patriarca PA, *et al*. Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med* 1983; **308:** 1601–2.
8. Stults BM, Hashisaki PA. Influenza vaccination and theophylline pharmacokinetics in patients with chronic obstructive lung disease. *West J Med* 1983; **139:** 651–4.
9. Winstanley PA, *et al*. Lack of effect of highly purified subunit influenza vaccination on theophylline metabolism. *Br J Clin Pharmacol* 1985; **20:** 47–53.

Pharmacokinetics

Theophylline is rapidly and completely absorbed from liquid preparations, capsules, and uncoated tablets; the rate, but not the extent, of absorption is decreased by food, and food may also affect theophylline clearance. Peak serum-theophylline concentrations occur 1 to 2 hours after ingestion of liquid preparations, capsules, and uncoated tablets. Modified-release preparations exhibit considerable

variability in their absorption characteristics and in the effect of food and are generally not considered to be interchangeable. If a patient needs to be transferred from one such preparation to another then the dose should be retitrated. Rectal absorption is rapid from enemas, but may be slow and erratic from suppositories. Absorption after intramuscular injection is slow and incomplete.

Theophylline is about 40 to 60% bound to plasma proteins, but in neonates, or adults with liver disease, binding is reduced. Optimum therapeutic serum concentrations for bronchodilatation are generally considered to range from 10 to 20 micrograms/mL (55 to 110 micromol/litre) although some consider a lower range appropriate (see Therapeutic Drug Monitoring, below).

Theophylline is metabolised in the liver to 1,3-dimethyluric acid, 1-methyluric acid (via the intermediate 1-methylxanthine), and 3-methylxanthine. Demethylation to 3-methylxanthine (and possibly to 1-methylxanthine) is catalysed by the cytochrome P450 isoenzyme CYP1A2; hydroxylation to 1, 3-dimethyluric acid is catalysed by CYP2E1 and CYP3A3. Both the demethylation and hydroxylation pathways of theophylline metabolism are capacity-limited, resulting in non-linear elimination. The metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine, but in neonates around 50% is excreted unchanged, and a large proportion is excreted as caffeine. Considerable interindividual differences in the rate of hepatic metabolism of theophylline result in large variations in clearance, serum concentrations, and half-lives. Hepatic metabolism is further affected by factors such as age, smoking, disease, diet, and drug interactions. The serum half-life of theophylline in an otherwise healthy, non-smoking asthmatic adult is 7 to 9 hours, in children 3 to 5 hours, in cigarette smokers 4 to 5 hours, in neonates and premature infants 20 to 30 hours, and in elderly non-smokers 10 hours. The serum half-life of theophylline may be increased in patients with heart failure or liver disease. Steady state is usually achieved within 48 hours with a consistent dosing schedule.

Theophylline crosses the placenta; it is also distributed into breast milk.

Absorption. *FOOD.* Food has substantial but variable effects on the absorption of theophylline from modified-release formulations but it is difficult to predict whether a particular formulation will be affected.[1] Some formulations are not affected by the presence of food but for others increases or decreases in the rate and/or extent of absorption have been reported. The composition and fluid content of the food appears to be important and a rapid release of theophylline ('dose-dumping') has occurred with some formulations after a meal, especially one with a high fat content.

A diet high in protein and low in carbohydrate has been reported to increase theophylline clearance, and a low-protein, high-carbohydrate diet to decrease theophylline clearance.[2-6] The consumption of methylxanthines, particularly caffeine, in the diet may decrease theophylline clearance (see Caffeine, under Interactions, p. 1235.3).

1. Jonkman JHG. Food interactions with sustained-release theophylline preparations: a review. *Clin Pharmacokinet* 1989; **16:** 162–79.
2. Kappas A, *et al*. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clin Pharmacol Ther* 1976; **20:** 643–53.
3. Feldman CH, *et al*. Effect of dietary protein and carbohydrate on theophylline metabolism in children. *Pediatrics* 1980; **66:** 956–62.
4. Feldman CH, *et al*. Interaction between nutrition and theophylline metabolism in children. *Ther Drug Monit* 1982; **4:** 69–76.
5. Juan D, *et al*. Effects of dietary protein on theophylline pharmacokinetics and caffeine and aminopyrine breath tests. *Clin Pharmacol Ther* 1986; **40:** 187–94.
6. Juan D, *et al*. Impairment of theophylline clearance by a hypocaloric low-protein diet in chronic obstructive pulmonary disease. *Ther Drug Monit* 1990; **12:** 111–14.

Metabolism and excretion. *AGE.* From about 1 year of age until adolescence, children have a rapid theophylline clearance.[1] Premature infants and those under 1 year of age have a slower clearance[2,3] due to immature metabolic pathways.[3-5] In neonates the capacity of hepatic cytochrome P450 enzymes is much reduced compared with older children and adults, and *N*-demethylation and oxidation reactions play a minor role in the metabolism of theophylline.[4-6] Neonates are, however, capable of methylating theophylline at the N7 position to form caffeine, which is present at about one-third the concentration of theophylline at steady state.[5,6] The proportion of theophylline excreted unchanged is also increased in premature neonates and decreases with age as hepatic enzyme systems develop.[6] More rapid clearance on the first day of life in premature neonates has been reported.[7]

Some studies have found a progressive decline in clearance throughout adult years[8] whereas others have not.[9] Similarly, some studies have noted a decreased clearance in the elderly[10,11] but others have found no significant change.[12,13]

1. Zaske DE, *et al*. Oral aminophylline therapy: increased dosage requirements in children. *JAMA* 1977; **237:** 1453–5.
2. Aranda JV, *et al*. Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 1976; **295:** 413–16.
3. Kraus DM, *et al*. Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 1993; **54:** 351–9.
4. Grygiel JJ, Birkett DJ. Effect of age on patterns of theophylline metabolism. *Clin Pharmacol Ther* 1980; **28:** 456–62.
5. Tserng K-Y, *et al*. Theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1981; **29:** 594–600.
6. Tserng K-Y, *et al*. Developmental aspects of theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1983; **33:** 522–8.
7. Stile IL, *et al*. Pharmacokinetics of theophylline in premature infants on the first day of life. *Clin Ther* 1986; **8:** 336–41.
8. Randolph WC, *et al*. The effect of age on theophylline clearance in normal subjects. *Br J Clin Pharmacol* 1986; **22:** 603–5.
9. Wiffen JK, *et al*. Does theophylline clearance alter within the adult age range? *Br J Clin Pharmacol* 1984; **17:** 219P.
10. Antal EJ, *et al*. Theophylline pharmacokinetics in advanced age. *Br J Clin Pharmacol* 1981; **12:** 637–45.
11. Jackson SHD, *et al*. The relationship between theophylline clearance and age in adult life. *Eur J Clin Pharmacol* 1989; **36:** 29–34.
12. Bauer LA, Blouin RA. Influence of age on theophylline clearance in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1981; **6:** 469–74.
13. Fox RW, *et al*. Theophylline kinetics in a geriatric group. *Clin Pharmacol Ther* 1983; **34:** 60–7.

ELIMINATION KINETICS. There is evidence that the elimination of theophylline is dose-dependent and that at high serum concentrations, a small change in dose of a theophylline preparation could cause a disproportionate increase in serum-theophylline concentration, due to a reduction in clearance.[1-3] However, it is not clear that this effect is clinically significant when serum-theophylline concentrations are within the therapeutic range.[4-8] It has also been suggested that repeated oral dosing of theophylline might result in a decrease of clearance compared with pre-treatment values.[9]

1. Weinberger M, Ginchansky E. Dose-dependent kinetics of theophylline disposition in asthmatic children. *J Pediatr* 1977; **91:** 820–4.
2. Tang-Liu DD-S, *et al*. Nonlinear theophylline elimination. *Clin Pharmacol Ther* 1982; **31:** 358–69.
3. Butcher MA, *et al*. Dose-dependent pharmacokinetics with single daily dose slow release theophylline in patients with chronic lung disease. *Br J Clin Pharmacol* 1982; **13:** 241–3.
4. Koëter GH, *et al*. Pharmacokinetics of sustained release theophylline in low and high multidose regimens. *Br J Clin Pharmacol* 1981; **12:** 647–51.
5. Rovei V, *et al*. Pharmacokinetics of theophylline: a dose-range study. *Br J Clin Pharmacol* 1982; **14:** 769–78.
6. Gundert-Remy U, *et al*. Non-linear elimination processes of theophylline. *Eur J Clin Pharmacol* 1983; **24:** 71–8.
7. Brown PJ, *et al*. Lack of dose dependent kinetics of theophylline. *Eur J Clin Pharmacol* 1983; **24:** 525–7.
8. Milavetz G, *et al*. Dose dependency for absorption and elimination rates of theophylline: implications for studies of bioavailability. *Pharmacotherapy* 1984; **4:** 216–20.
9. Efthimiou H, *et al*. Influence of chronic dosing on theophylline clearance. *Br J Clin Pharmacol* 1984; **17:** 525–30.

GENDER. A higher theophylline clearance and shorter elimination half-life has been reported in healthy premenopausal women than in healthy men, probably due to sex-related differences in hepatic metabolism.[1] Changes in the pharmacokinetics of theophylline in women have also been reported according to the stage of the menstrual cycle;[2,3] another study[4] found no changes.

1. Nafziger AN, Bertino JS. Sex-related differences in theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1989; **37:** 97–100.
2. Brugueroll B, *et al*. Influence of the menstrual cycle on theophylline pharmacokinetics in asthmatics. *Eur J Clin Pharmacol* 1990; **39:** 59–61.
3. Nagata K, *et al*. Increased theophylline metabolism in the menstrual phase of healthy women. *J Allergy Clin Immunol* 1997; **100:** 39–43.
4. Matsuki S, *et al*. Pharmacokinetic changes of theophylline and amikacin through the menstrual cycle in healthy women. *J Clin Pharmacol* 1999; **39:** 1256–62.

Pregnancy and breast feeding. For mention of the pharmacokinetics of theophylline during pregnancy and breast feeding, see under Precautions, p. 1233.2.

Protein binding. Albumin is the major plasma binding protein for theophylline, binding is pH-dependent, and the percentage of theophylline bound at physiological pH is reported to range from about 35 to 45%.[1,2] Some studies have found the plasma protein binding of theophylline to be concentration dependent,[3] but others have not confirmed this.[1,4] Protein binding has been reported to be slightly but significantly higher in patients with bronchial asthma than in healthy controls.[5] Reduced protein binding occurs in patients with hypoalbuminaemia;[6,7] it has also been found in obese subjects[8] (possibly due to elevated concentrations of free fatty acids, which can displace theophylline from binding sites).

1. Buss D, *et al*. Determinants of the plasma protein binding of theophylline in health. *Br J Clin Pharmacol* 1983; **15:** 399–405.
2. Brørs O, *et al*. Binding of theophylline in human serum determined by ultrafiltration and equilibrium dialysis. *Br J Clin Pharmacol* 1983; **15:** 393–7.
3. Gundert-Remy U, Hildebrandt R. Binding of theophylline and its metabolites to human plasma proteins. *Br J Clin Pharmacol* 1983; **16:** 573–4.
4. Buss DC, *et al*. Protein binding of theophylline. *Br J Clin Pharmacol* 1985; **19:** 529–31.
5. Trnavská Z. Theophylline protein binding. *Arzneimittelforschung* 1990; **40:** 166–9.
6. Leopold D, *et al*. The ex vivo plasma protein binding of theophylline in renal disease. *Br J Clin Pharmacol* 1985; **19:** 823–5.
7. Connelly TJ, *et al*. Characterization of theophylline binding to serum proteins in pregnant and nonpregnant women. *Clin Pharmacol Ther* 1990; **47:** 68–72.
8. Shum L, Jusko WJ. Effects of obesity and ancillary variables (dialysis time, drug, albumin, and fatty acid concentrations) on theophylline serum protein binding. *Biopharm Drug Dispos* 1989; **10:** 549–62.

Therapeutic drug monitoring. Dosage requirements of theophylline preparations vary widely between subjects and even vary with time in individuals, since serum-theophylline concentrations are influenced by factors including disease states, other drugs, diet, smoking, and age. Serious toxicity is related to serum concentration and may not be preceded by minor symptoms. For these reasons it is recommended that serum-theophylline concentrations should be monitored.

The generally accepted optimal serum concentration is between 10 and 20 micrograms/mL,[1-4] but this should be regarded as a guide and not a rigid barrier and clinical decisions should never be based solely on the serum concentration.[1] The therapeutic range in the treatment of neonatal apnoea is usually considered to be 5 to 15 micrograms/mL although some babies may respond at lower concentrations.[5] Some now consider that this is a more appropriate range in asthma (except perhaps acute severe asthma).[6] It has been suggested that pulmonary function tests provide a better guide in long-term therapy with theophylline.[7]

Serum-theophylline concentrations were originally measured by spectrophotometry but this is subject to considerable interference from other drugs. High performance liquid chromatography is now the method of choice when extreme accuracy is important and the enzyme multiplied immunoassay technique (EMIT) has become popular because of its rapidity and adaptability to processing large batches.[2] Devices are also available that provide serum-theophylline measurements within several minutes using monoclonal antibody technology.[2,8]

The use of salivary concentrations for monitoring theophylline dosage requirements has been tried, because it is noninvasive, but poor correlations between salivary- and serum-theophylline concentrations mean it has not gained general usage.

1. Hampson JP. The theophylline "therapeutic window"—fact or fallacy? *Pharm J* 1988; **241:** 722–4.
2. Bierman CW, Williams PV. Therapeutic monitoring of theophylline: rationale and current status. *Clin Pharmacokinet* 1989; **17:** 377–84.
3. Holford N, *et al*. Theophylline target concentration in severe airways obstruction—10 or 20 mg/L. A randomised concentration-controlled trial. *Clin Pharmacokinet* 1993; **25:** 495–505.
4. Pesce AJ, *et al*. Standards of laboratory practice: theophylline and caffeine monitoring. *Clin Chem* 1998; **44:** 1124–8.
5. Edwards C. Theophylline and caffeine. *Pharm J* 1986; **237:** 128–9.
6. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37:** 96–101.
7. Ashutosh K, *et al*. Use of serum theophylline level as a guide to optimum therapy in patients with chronic obstructive lung disease. *J Clin Pharmacol* 1990; **30:** 324–9.
8. Clifton GD, *et al*. Accuracy and time requirements for use of three rapid theophylline assay methods. *Clin Pharm* 1988; **7:** 462–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisasma; Drilyna; Nefoben; Teodosis†; Teosona Sol; Teosona; ***Austral.***: Nuelin; ***Austria***: Euphyllin; Respicur; Theospirex; Unifyl; ***Belg.***: Euphyllin; Theolair; Xanthium; ***Braz.***: Codrinan; Talofilina; Teofilab; Teolong; Teophyl†; Teoston; ***Canad.***: Apo-Theo; Novo-Theophyl†; Pulmophylline; Theolair; Uniphyl; ***Chile***: Elixine; ***China***: An Fei Lin (安菲林); Asmalon (埃斯玛隆); Bi Chuan (比川); Etipramid (迪帕米); Protheo (葆乐辉); Quelesu (确乐苏); Shi Er Ping (时尔平); Xi Fu Lin (西弗林); Yan Er (延尔); ***Cz.***: Afonilum; Euphyllin; Spophyllin†; Theoplus; ***Denm.***: Nuelin; Theo-Dur; UniXan; ***Fin.***: Nuelin; Retafyllin; Theofol; ***Fr.***: Euphylline; Theostat; Xanthium; ***Ger.***: Aerobin†; Afonilum†; afpred-THEO†; Bronchoparat; Bronchoretard; Euphylong; Solosin†; Theo; Tromphyllin; Uniphyllin; ***Gr.***: Aberten; Bronchogeril; Cefaphyllin; Euphyllin†; Mediphyllin Chrono; Neo-Antiasthman; Novaphylline; Quibron-R; Theo-Bros; Theo-Dur; Theoplus; Uni-Dur; Uniphyllin; ***Hong Kong***: CP-Theo; Euphylong; Nuelin; Slo-Theo; Slow-Theo; Theotrim†; ***Hung.***: Egifilin; Euphylong; Retafyllin; Theophtard; Theospirex; ***India***: Biryth; Broncordil; Delin; Duralyn; Lontif; Lungfyl; Od-Phyllin; Phylobid; Phyloday; Theo PA; Theobid; Theoday; Theoped; Unicontin; ***Indon.***: Bronchophylin; Brondilex†; Bronsolvan; Bufabron; Euphyllin; Quibron-T†; Retaphyl; Theobron; ***Irl.***: Nuelin; Slo-Phyllin†; Uniphyllin Continus; Zepholin; ***Israel***: Glyphyllin†; Theotard; Theotrim; ***Ital.***: Aminomal; Diffumal; Euphyllina; Frivent; Respicur; Theo-Dur; Theolair; ***Jpn***: Theodur; Theolong; ***Malaysia***: Apo-Theo; Nuelin; Retafyllin; ***Mex.***: Elixofilina; Fluidasa; Pharmafil†; ***Mon.***: Dilatrane; Pneumogeine†; Tedralan; ***Neth.***: Euphylong†; Theolair; ***Norw.***: Nuelin; Theo-Dur; ***NZ***: Nuelin; ***Philipp.***: Asmasolon; Brondil (Reformulated); Nuelin; Phenedrine; Theo-Dur†; ***Pol.***: Afonilum; Euphyllin; Theoplus†; Theospirex; Theovent; ***Port.***: Eufilina; Unicontin; ***Rus.***: Teotard (Теотард); Theopec (Теопэк); ***S.Afr.***: Adco-Alcophyllin; Euphyllin; Microphyllin; Nuelin; Pulmophyllin†; Theophen; Theoplus; Uniphyl; ***Singapore***: Apo-Theo; Nuelin; Spophyllin; Theolin; Xanthium; ***Spain***: Elixifilin; Eufilina; Histafilin†; Pulmeno; Ter-

omol; Theo-Dur; Theolair; Theoplus†; ***Swed.***: Theo-Dur; ***Switz.***: Euphyllin; Theolair†; Unifyl; ***Thai.***: Almarion; Asmasolon; Bronoday†; Duralyn; Franol; Nuelin; Polyasma; Retafyllin†; S-Phylline; Sinmaline; Sinoline; Temaco; Theocap; Theolin; Theori; Theotrim; Xanthium; ***Turk.***: Bronkolin; Pirasmin; Pirazmen; Talotren; Teobag; Teokap; Teosel; Theo-Dur†; Xanthium; ***UAE***: Theophar; ***UK***: Nuelin; Slo-Phyllin; Uniphyllin Continus; ***Ukr.***: Neofilin (Неофиллин); Theotard (Теотард); ***USA***: Accurbron; Aerolate; Asmalix; Elixophyllin; Theo-24; Theochron; Uniphyl†; ***Venez.***: Nuelin; Teobid.

Multi-ingredient Preparations. ***Arg.***: Dexa Teosona; Dexa-Aminofilin; Sedacris; ***Braz.***: Bronquitos; Endotussin†; Franol; Marax; ***Canad.***: ratio-Theo-Bronc; ***Chile***: Cellenergy; ***China***: Antong (安通); Xu Hong (旭宏); Yi Xi Qing (易息晴); ***Cz.***: Oxantil; ***Fin.***: Theofol Comp; ***Ger.***: Broncho-Euphyllin; ***Gr.***: Aminabel; Baladex; Gulamyl; Normavix; Repusan; Silantuss; Tycod; ***Hong Kong***: Noscaphylline†; Sedral†; Uni-Theodal†; ***India***: Agrophyllin; Alergin; Ambro TS; Ambrolax-PD; Ambrolite-ST; Asmapax; Asmatide-BR; Azofen-T; Broncophyl Plus; Broncordil P; Bronko Plus; Carbasma; Delin; Dericip Plus; Dericip; Deriphyllin; Deripil; Durasalyn; Glophyllin; Marax; Mucoresp; Mulitmix; Multimix; Multimix; Tergil-T†; Theo-Asthalin; Theobric; ***Indon.***: Asmadex; Asmano; Asmasolon; Asthma Soho; Neo Napacin†; Prinasma†; Teosal; Theochodil; Tusapres; ***Ital.***: Altadrine Firming†; Binfolipase; ***Malaysia***: Asthma; Theophylline Expectorant; ***Mex.***: Aminoefedrison; ***Philipp.***: Mucophylline; ***Pol.***: Baladex; ***Rus.***: Insanovin (Инсановин); Theophedrinum-N (Теофедринум-Н); ***S.Afr.***: Actophlem; Adco-Metaxol; Alcophyllex; Diatussin; Solphyllex; Solphyllin; Theophen Comp; ***Spain***: Teolixir Compositum†; ***Thai.***: Almasal; Asiabron; Asma-Dec; Bronchil; Brondil†; Brondry; Chintasma; Forasma; Mila-Asma; Polyphed; Qualiton; ***Turk.***: Fenastma; ***UK***: Do-Do ChestEze; ***USA***: Broncomar; Elixophyllin-GG; Elixophyllin-KI; Glyceryl-T; Hydrophed; Marax; Neoasma; Quadrinal; Tedrigen; Theodrine; Theomax DF; ***Venez.***: Metoxifilin.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Theophylline Tablets;

USP 36: Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution; Theophylline Capsules; Theophylline Extended-release Capsules; Theophylline in Dextrose Injection; Theophylline Oral Solution; Theophylline Oral Suspension; Theophylline Sodium Glycinate Elixir; Theophylline Sodium Glycinate Tablets; Theophylline Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Tiotropium Bromide *(BAN, rINN)*

Ba-679; Ba-679BR; Bromuro de tiotropio; Tiotropii Bromidum; Tiotropio, bromuro de; Tiotropium, Bromure de; Tiotropyum Bromür; Тиотропия Бромид.

6β,7β-Epoxy-3β-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide di-2-thienylglycolate.

$C_{19}H_{22}BrNO_4S_2$=472.4

CAS — 186691-13-4 (tiotropium); 139404-48-1 (anhydrous tiotropium bromide or tiotropium bromide hydrate); 136310-93-5 (anhydrous tiotropium bromide); 411207-31-3 (tiotropium bromide monohydrate).

ATC — R03BB04.

ATC Vet — QR03BB04.

UNII — XX112XZP0J (tiotropium bromide); L64SXO195N (tiotropium bromide monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tiotropium Bromide Monohydrate). A white or yellowish-white powder or crystals. Sparingly soluble in water; soluble in methyl alcohol; practically insoluble in dichloromethane.

Uses and Administration

Tiotropium bromide is a quaternary ammonium antimuscarinic that is structurally related to ipratropium but has a prolonged bronchodilator action. It is used similarly to ipratropium (p. 1211.3) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (below); tiotropium is not suitable for the initial treatment of acute bronchospasm. Tiotropium bromide can be given as inhalation powder in capsules containing 22.5 micrograms of tiotropium bromide monohydrate, equivalent to 18 micrograms of tiotropium, and supplying 10 micrograms of tiotropium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled daily, at the same time each day.

Tiotropium bromide can also be given as inhalation solution via a metered-dose inhaler. Each metered dose contains 3.124 micrograms of tiotropium bromide monohydrate equivalent to 2.5 micrograms of tiotropium. Two metered doses are inhaled daily, at the same time each day.

References.

1. Hvizdos KM, Goa KL. Tiotropium bromide. *Drugs* 2002; **62:** 1195–1203.

Chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease (COPD; p. 1199.1) tiotropium bromide has been shown to be effective at improving dyspnoea,[1-3] health-related quality of life,[1,3,4] symptom-limited exercise tolerance,[2] lung function measurements,[3,4] and reducing exacerbations[1,3-6] compared with placebo.

Tiotropium has also been found to be more effective than ipratropium at improving dyspnoea, health-related quality of life,[7] and lung function,[7,8] and reducing exacerbations;[7] consideration of tiotropium as first-line maintenance treatment in COPD has been suggested.[9,10]

Similarly, tiotropium has produced better bronchodilatation, reduced dyspnoea, and improved health-related quality of life scores compared with salmeterol,[11] although its benefits in comparison with a combination of salmeterol and fluticasone are unclear.[12]

Combining tiotropium therapy with an inhaled corticosteroid and a long-acting beta$_2$ agonist did not statistically influence rates of COPD exacerbations but did improve lung function, quality of life, and hospitalisation rates in patients with moderate to severe COPD.[13]

A systematic review[14] and a meta-analysis[15] confirmed that tiotropium reduces exacerbations and related hospitalisations, improves quality of life and symptoms in stable COPD. Tiotropium may also have slowed the decline in forced expiratory volume (FEV) seen in COPD, an observation that was supported by a subgroup analysis of a study in patients with moderate COPD,[16] suggesting that treatment with tiotropium should begin at an early stage of the disease. Further studies are required to evaluate the effect of tiotropium on FEV and to clarify its role in relation to long-acting beta$_2$ agonists.

The role of tiotropium in the management of COPD has been extensively reviewed.[9,17-20]

1. Casaburi R, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; **19:** 217–24.
2. Maltais F, *et al.* Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; **128:** 1168–78.
3. Brusasco V, *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; **58:** 399–404.
4. Tashkin DP, *et al.* UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359:** 1543–54.
5. Niewoehner DE, *et al.* Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; **143:** 317–26.
6. Tashkin DP. Preventing and managing exacerbations in COPD—critical appraisal of the role of tiotropium. *Int J Chron Obstruct Pulmon Dis* 2010; **5:** 41–53.
7. Vincken W, *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; **19:** 209–16.
8. van Noord JA, *et al.* A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000; **55:** 289–94.
9. Chen AM, *et al.* Long-acting bronchodilator therapy for the treatment of chronic obstructive pulmonary disease. *Ann Pharmacother* 2008; **42:** 1832–42.
10. Troosters T, *et al.* UPLIFT Investigators. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. *Eur Respir J* 2010; **36:** 65–73.
11. Donohue JF, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; **122:** 47–55.
12. Welsh EJ, *et al.* Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 14/07/10).
13. Aaron SD, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; **146:** 545–55.
14. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 18/02/08).
15. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; **61:** 854–62. Correction. *ibid.*; **62:** 191.
16. Decramer M, *et al.* UPLIFT investigators. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009; **374:** 1171–8.
17. Gross NJ. Tiotropium bromide. *Chest* 2004; **126:** 1946–53.
18. Olin JL. Tiotropium: an inhaled anticholinergic for chronic obstructive pulmonary disease. *Am J Health-Syst Pharm* 2005; **62:** 1263–9.
19. Somand H, Remington TL. Tiotropium: a bronchodilator for chronic obstructive pulmonary disease. *Ann Pharmacother* 2005; **39:** 1467–75.
20. Burns G, Bianchi S. Chronic obstructive pulmonary disease: the evidence for use of tiotropium. *Br J Hosp Med* 2006; **67:** 85–91.

Adverse Effects and Precautions

As for Ipratropium Bromide (p. 1212.2).

Pharyngitis, sinusitis, rhinitis, and epistaxis have also been reported after inhalation.

Patients with moderate to severe renal impairment (creatinine clearance 50 mL/minute or less) should be closely monitored as tiotropium bromide is mainly excreted by the kidneys.

Effects on the cardiovascular system. For discussion of the possible increased risk of cardiovascular events with inhaled antimuscarinic use, see Ipratropium, p. 1212.2.

Effects on the cerebrovascular system. In March 2008 the FDA reported[1] that the manufacturer of tiotropium bromide (*Boehringer Ingelheim*) had informed them that they had identified a possible increased risk of stroke in patients taking tiotropium bromide. From pooled analysis of 29 clinical studies in patients with chronic obstructive pulmonary disease preliminary estimates of the risk of stroke were 8 per 1000 patients treated for one year with tiotropium compared with 6 per 1000 patients given placebo for one year. However, a self-controlled case series (where cases act as their own controls to reduce confounding), found no evidence that tiotropium bromide was associated with an increased risk of stroke in almost 1000 stroke patients.[2] Similarly, results from UPLIFT,[3] a large, 4-year, placebo-controlled study of tiotropium in about 6000 patients with chronic obstructive pulmonary disease, also showed no increased risk of stroke with tiotropium. Further analysis of the final results of UPLIFT by the FDA[4] confirmed that the data do not support an increased risk of stroke, heart attack, or cardiovascular death.

For further information on the risk to the cardiovascular system associated with tiotropium, see Effects on the Cardiovascular System, under Ipratropium Bromide, p. 1212.2.

1. FDA. Early communication about ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 18th March 2008; updated 7th October 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm070651 (accessed 03/08/10)
2. Grosso A, *et al.* Inhaled tiotropium bromide and risk of stroke. *Br J Clin Pharmacol* 2009; **68:** 731–6.
3. Tashkin DP, *et al.* UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359:** 1543–54.
4. FDA. Follow-up to the October 2008 updated early communication about an ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 14th January 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm197429.htm (accessed 03/08/10)

Effects on the skin. Subacute cutaneous lupus erythematosus has been reported in a patient inhaling tiotropium.[1] Skin lesions developed one week after introduction of the drug, resolved when the drug was stopped, and recurred on rechallenge.

Inhaled tiotropium has also been associated with a photosensitive lichenoid eruption in another patient,[2] 22 months after starting treatment. The lesions resolved when the drug was stopped; patch testing however, gave a negative result. Rechallenge was not attempted.

1. Pham H-C, Saurat J-H. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium. *Arch Dermatol* 2005; **141:** 911–12.
2. Pérez-Pérez L, *et al.* Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatology* 2007; **214:** 97–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tiotropium bromide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p. 1312.3. However, these interactions are not usually seen with antimuscarinics, such as tiotropium, given by inhalation.

Pharmacokinetics

After inhalation, some tiotropium bromide is absorbed from the lung, with the majority deposited in the gastrointestinal tract. In healthy subjects a systemic bioavailability of about 20% is reported after dry powder inhalation, and about 33% after inhalation of the solution. Tiotropium is about 72% bound to plasma proteins. It is excreted largely unchanged in the urine, although it may undergo some metabolism by non-enzymatic cleavage and by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The terminal elimination half-life is between 5 and 6 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Spiriva; ***Austral.***: Spiriva; ***Austria***: Spiriva; ***Belg.***: Spiriva; ***Braz.***: Spiriva; ***Canad.***: Spiriva; ***Chile***: Spiriva; ***China***: Spiriva (思力华); ***Cz.***: Spiriva; ***Denm.***: Spiriva; ***Fin.***: Spiriva; ***Fr.***: Spiriva; ***Ger.***: Spiriva; ***Gr.***: Spiriva; ***Hong Kong***: Spiriva; ***Hung.***: Spiriva; ***India***: Tiova; ***Indon.***: Spiriva; ***Irl.***: Spiriva; ***Israel***: Spiriva; ***Ital.***: Spiriva; ***Jpn***: Spiriva; ***Malaysia***: Spiriva; ***Mex.***: Spiriva; ***Neth.***: Spiriva; ***Norw.***: Spiriva; ***NZ***: Spiriva; ***Philipp.***: Spiriva; ***Pol.***: Spiriva; ***Port.***: Spiriva; ***Rus.***: Spiriva (Спирива); ***S.Afr.***: Forvent; Spiriva; ***Singapore***: Spiriva; ***Spain***: Spiriva; ***Swed.***: Spiriva; ***Switz.***: Spiriva; ***Thai.***: Spiriva; ***Turk.***: Spiriva; ***UK***: Spiriva; ***Ukr.***: Spiriva (Спирива); ***USA***: Spiriva; ***Venez.***: Spiriva.

Multi-ingredient Preparations. ***India***: Duova.

Tipelukast *(USAN, rINN)*

KCA-757; MN-001; Tipélukast; Tipelukastum; Типелукаст.
4-(6-Acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]propoxy}-2-propylphenoxy)butanoic acid.
$C_{29}H_{38}O_7S$=530.7
CAS — 125961-82-2.
UNII — 08379P260O.

Profile

Tipelukast is a leukotriene receptor antagonist (p. 1195.2), a phosphodiesterase inhibitor, and 5-lipoxygenase inhibitor that is under investigation for the treatment of asthma.

Tranilast *(USAN, rINN)*

MK-341; N-5′; Tranilastum; Траниласт.
N-(3,4-Dimethoxycinnamoyl)anthranilic acid.
$C_{18}H_{17}NO_5$=327.3
CAS — 53902-12-8.
UNII — HVF50SMY6E.

Uses and Administration

Tranilast has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1226.1). It is also stated to inhibit collagen synthesis in fibroblasts. It is used in the prophylactic management of asthma (p. 1195.2) and in allergic rhinitis (p. 612.1), conjunctivitis (p. 611.1), and eczema (p. 1684.1). It is also used in the management of keloids and hypertrophic scarring. The usual oral adult dose is 100 mg three times daily. For details of doses in children, see below. Eye drops containing tranilast 0.5% are used four times daily for allergic conjunctivitis.

Tranilast has been investigated for the prevention of restenosis after coronary artery revascularisation procedures but was found to be ineffective. A topical gel containing tranilast is also under investigation to prevent adhesion formation after surgery.

Administration in children. Tranilast is given to children for the prophylactic management of asthma, in allergic rhinitis and eczema, and in the management of keloids and hypertrophic scars. An oral daily dose of 5 mg/kg, given in 3 divided doses, may be used.

Sarcoidosis. For a mention of possible benefit from tranilast in cutaneous sarcoidosis, see p. 1612.2.

Adverse Effects and Precautions

Adverse effects reported with tranilast have included gastrointestinal disturbances, headache, drowsiness or insomnia, dizziness, malaise, and skin rashes and generalised pruritus. Rarely, liver function disturbance or jaundice, renal dysfunction, cystitis-like symptoms, anaemia, leucopenia, thrombocytopenia, palpitations, oedema, facial flushing, and stomatitis may occur. Tranilast should be used with caution in patients with impaired hepatic or renal function. Haematological monitoring is recommended.

Irritation and blepharitis have been reported after topical application to the eye.

Licensed product information advises against the use of tranilast in pregnancy because of teratogenicity in *animal* studies.

Tranilast should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (p. 1227.2) also apply.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Te Min (奥特敏); ***Jpn***: Rizaben.

Multi-ingredient Preparations. ***China***: Shun Qi (顺奇).

Tretoquinol Hydrochloride *(pINN/M)* ⊗

AQ-110 (tretoquinol); Hidrocloruro de tretoquinol; Ro-07-5965; Trétoquinol, Chlorhydrate de; Tretoquinol, hidrocloruro de; Tretoquinoli Hydrochloridum; Trimethoquinol Hydrochloride; Trimetoquinol Hydrochloride; Третохинола Гидрохлорид.
(-)-1,2,3,4-Tetrahydro-1-(3,4,5-trimethoxybenzyl)isoquinoline-6,7-diol hydrochloride monohydrate.
$C_{19}H_{23}NO_5$,HCl,H_2O=399.9
CAS — 30418-38-3 (tretoquinol); 18559-59-6 (anhydrous tretoquinol hydrochloride).
ATC — R03AC09; R03CC09.
ATC Vet — QR03AC09; QR03CC09.
UNII — SS28YGI1ZQ.

Pharmacopoeias. In *Jpn*.

Profile

Tretoquinol is a direct-acting sympathomimetic reported to have a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2). It is given as the hydrochloride for its bronchodilating properties in the management of reversible airways obstruction, as in asthma (p. 1195.2) or in some patients with chronic obstructive pulmonary disease (p. 1199.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Inolin†; ***Indon.***: Inolin; ***Jpn***: Inolin.

Tulobuterol Hydrochloride *(BANM, rINNM)* ⊗

C-78; Hidrocloruro de tulobuterol; HN-078 (tulobuterol); Tulobutérol, Chlorhydrate de; Tulobuterol, hidrocloruro de; Tulobuterolhydroklorid; Tulobuteroli Hydrochloridum; Tulobuterolihydrokloridi; Тулобутерола Гидрохлорид.
2-*tert*-Butylamino-1-*o*-chlorophenylethanol hydrochloride.
$C_{12}H_{18}ClNO$,HCl=264.2
CAS — 41570-61-0 (tulobuterol); 56776-01-3 (tulobuterol hydrochloride).
ATC — R03AC11; R03CC11.
ATC Vet — QR03AC11; QR03CC11.
UNII — VNC1218IT0.

NOTE. The names Berachin, Senikarin-DS, Tulobunist, and Tulobuten have been used as trade marks for tulobuterol or tulobuterol hydrochloride.

Pharmacopoeias. In *Jpn*.

Profile

Tulobuterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2).

Tulobuterol is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). It is given orally in a usual dose of tulobuterol hydrochloride 2 mg twice daily. An increased need for, or decreased duration of effect of, tulobuterol indicates deterioration of asthma control and the need for review of therapy. Tulobuterol has also been given as the base by inhalation from a metered-dose inhaler. A transdermal formulation of tulobuterol base is also available; a dose of 2 mg daily is used with anti-inflammatory therapy.

For doses of tulobuterol used in children aged 14 years and under, see Administration in Children, below.

References to the transdermal formulation of tulobuterol.

1. Uematsu T, *et al.* The pharmacokinetics of the β$_2$-adrenoceptor agonist, tulobuterol, given transdermally and by inhalation. *Eur J Clin Pharmacol.* 1993; **44:** 361–4.
2. Iikura Y, *et al.* Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma. *Ann Allergy* 1995; **74:** 147–51.
3. Fukuchi Y, *et al.* Clinical efficacy and safety of transdermal tulobuterol in the treatment of stable COPD: an open-label comparison with inhaled salmeterol. *Treat Respir Med* 2005; **4:** 447–55.
4. Yoshihara S, *et al.* The use of patch formulation of tulobuterol, a long-acting beta2-adrenoceptor agonist, in the treatment of severe pediatric asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 879–80.
5. Fujimoto K, *et al.* Comparison of the clinical efficacy of salmeterol and sustained-release tulobuterol (patch) on inadequately controlled asthma patients on inhaled corticosteroids. *J Asthma* 2006; **43:** 501–7.
6. Nishiyama O, *et al.* Comparison of the effects of tulobuterol patch and salmeterol in moderate to severe asthma. *Clin Exp Pharmacol Physiol* 2006; **33:** 1016–21.
7. Kobayashi Y, *et al.* Addition of transdermal or inhaled long-acting β$_2$-agonists in adult asthmatic patients treated with inhaled corticosteroids: switchover study from tulobuterol patch to salmeterol dry powder inhaler. *J Asthma* 2007; **44:** 77–81.
8. Yamagata T, *et al.* Comparison of bronchodilatory properties of transdermal and inhaled long-acting β$_2$-agonists. *Pulm Pharmacol Ther* 2008; **21:** 160–5.

Administration in children. Tulobuterol hydrochloride has been used to treat bronchospasm in children in the following *oral* doses:

- 1 to 6 years of age: 250 to 500 micrograms twice daily
- 6 to 10 years of age: 0.5 to 1 mg twice daily
- 10 to 14 years of age: 1 to 1.5 mg twice daily

Children 14 years of age and over may be given the adult dose of tulobuterol, see above.

Transdermal delivery of tulobuterol is also used in children, in the following doses:

- 6 months to 3 years of age: 500 micrograms once daily
- 3 to 9 years of age: 1 mg once daily
- 9 years of age and older: as for adults (see above)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Amiaid (阿米迪); ***Ger.***: Brelomax†; ***Jpn***: Hokunalin; ***Mex.***: Bremax†; ***Philipp.***: Bremax†; ***Venez.***: Bretol.

Vilanterol Trifenatate *(USAN, rINNM)* ⊗

GW-642444M; GW-642444X (vilanterol); Trifenatato de vilanterol; Vilantérol, Trifenatate de; Vilanteroli Trifenatas; Вилантерола Трифенатат.
4-{(1*R*)-2-[(6-{2-[(2,6-Dichlorophenyl)methoxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol triphenylacetate.
$C_{24}H_{33}Cl_2NO_5$,$C_{20}H_{16}O_2$=774.8
CAS — 503068-34-6 (vilanterol); 503070-58-4 (vilanterol trifenatate).
UNII — 028LZY775B (vilanterol); 40AHO2C6DG (vilanterol trifenatate).

Uses and Administration

Vilanterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity specific to beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2), but like salmeterol (p. 1224.1) it has a prolonged duration of action and is therefore not considered suitable for the symptomatic relief of acute attacks of bronchospasm. It is used with regular inhaled corticosteroid when a regular long-acting beta$_2$ agonist is needed for management of asthma (p. 1195.2) and chronic obstructive pulmonary disease (p. 1199.1).

Vilanterol is given as the trifenatate but doses are expressed in terms of the base; 40 micrograms of vilanterol trifenatate is equivalent to about 25 micrograms of vilanterol. It is available in dry powder inhalers, with fluticasone furoate. The dose of vilanterol may be expressed as the amount in each available dose (25 micrograms) or as the delivered dose leaving the mouthpiece (22 micrograms). In both asthma and chronic obstructive pulmonary disease, one dose is inhaled daily.

References.

1. Martinez FJ, *et al.* Fluticasone furoate/vilanterol (100/25; 200/25 micrograms) improves lung function in COPD: a randomised trial. *Respir Med* 2013; **107:** 550–9.
2. Woodcock A, *et al.* Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013; **144:** 1222–9.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3, and Salmeterol Xinafoate, p. 1224.3. Inhalation of vilanterol may be associated with paradoxical bronchospasm. Patients should also be receiving an inhaled corticosteroid.

Long-acting beta$_2$ agonists such as vilanterol are not appropriate for the treatment of acute bronchospasm.

Interactions

As for Salbutamol, p. 1223.1.

Vilanterol is metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with ketoconazole, a CYP3A4 inhibitor, can increase systemic exposure to inhaled vilanterol. Patients should be monitored if treated with both vilanterol and a strong CYP3A4 inhibitor.

Pharmacokinetics

Vilanterol is rapidly absorbed after inhalation and an absolute bioavailability of about 27% has been reported. It is mainly metabolised via the cytochrome P450 isoenzyme CYP3A4, and metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Relvar Ellipta; ***USA***: Breo Ellipta.

Zafirlukast *(BAN, USAN, rINN)*

ICI-204219; Tsafirlukasti; Zafirlukastum; ZD-204219; Зафирлукаст.
Cyclopentyl 3-[2-methoxy-4-[(*o*-tolylsulfonyl)carbamoyl]benzyl]-1-methylindole-5-carbamate.
$C_{31}H_{33}N_3O_6S$=575.7
CAS — 107753-78-6.
ATC — R03DC01.
ATC Vet — QR03DC01.
UNII — XZ629S5L50.

Uses and Administration

Zafirlukast is a selective and competitive antagonist of the leukotriene C_4, D_4, and E_4 receptors (p. 1195.2), stimulation of which by circulating leukotrienes is thought to play a role in the pathogenesis of asthma. The drug suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants, but is not suitable for the management of acute attacks of asthma.

Zafirlukast is used in the management of chronic asthma (see below). It is given orally in doses of 20 mg twice daily, taken at least 1 hour before or 2 hours after meals. For details of doses in children, see below.

General references.

1. García-Marcos L, *et al.* Benefit-risk assessment of antileukotrienes in the management of asthma. *Drug Safety* 2003; **26:** 483–518.
2. Anonymous. Leukotriene receptor antagonists—an update. *Drug Ther Bull* 2005; **43:** 85–8.
3. Currie GP, McLaughlin K. The expanding role of leukotriene receptor antagonists in chronic asthma. *Ann Allergy Asthma Immunol* 2006; **97:** 731–41.
4. Riccioni G, *et al.* Antileukotriene drugs: clinical application, effectiveness and safety. *Curr Med Chem* 2007; **14:** 1966–77.

Administration in children. In the management of chronic asthma, US licensed product information recommends a zafirlukast dose of 10 mg twice daily orally in children aged from 5 to 11 years. Children 12 years of age and over may be given the adult dose, see above. In the UK, zafirlukast is unlicensed in children under 12 years of age.

Asthma. Zafirlukast produces modest improvement in mild-to-moderate asthma (p. 1195.2),[1,2] which was of a similar order to that seen with inhaled sodium cromoglicate in one study,[3] but less than that of inhaled salmeterol in another.[4] It has also been found to be less effective than inhaled fluticasone in persistent asthma.[5-7] In a study in patients presenting to the emergency room with acute severe asthma, adding zafirlukast to standard therapy in hospital and for 28 days after discharge was associated with a reduced rate of relapse, and a reduction in the need for extended care.[8]

1. Suissa S, *et al.* Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 177–83.
2. Fish JE, *et al.* Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. *Clin Ther* 1997; **19:** 675–90.
3. Nathan RA, *et al.* Two first-line therapies in the treatment of mild asthma: use of peak flow variability as a predictor of effectiveness. *Ann Allergy Asthma Immunol* 1999; **82:** 497–503.
4. Busse W, *et al.* Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999; **103:** 1075–80.
5. Busse W, *et al.* Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract* 2001; **50:** 595–602.
6. Nathan RA, *et al.* A comparison of short-term treatment with inhaled fluticasone propionate and zafirlukast for patients with persistent asthma. *Am J Med* 2001; **111:** 195–202.
7. Brabson JH, *et al.* Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. *Am J Med* 2002; **113:** 15–21.
8. Silverman RA, *et al.* Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. *Chest* 2004; **126:** 1480–9.

Rhinitis. Although it was reported to improve symptoms of seasonal allergic rhinitis (p. 612.1) in one study,[1] zafirlukast 20 mg twice daily was not effective when compared with placebo and intranasal beclometasone in another.[2] Some benefits have been reported in perennial allergic rhinitis, in particular an improvement in nasal obstruction.[3,4] A review of the role of leukotrienes in allergic rhinitis concluded that leukotriene receptor antagonists have modest efficacy given alone but can be usefully added to other treatments.[5]

1. Donnelly AL, *et al.* The leukotriene D_4-receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995; **151:** 1734–9.
2. Pullerits T, *et al.* Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1999; **159:** 1814–18.
3. Jiang R-S. Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis. *J Otolaryngol* 2006; **35:** 117–21.
4. Ho C-Y, Tan C-T. Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis. *Am J Rhinol* 2007; **21:** 439–43.
5. Peters-Golden M, Henderson WR. The role of leukotrienes in allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **94:** 609–18.

Urticaria. Leukotriene antagonists, such as zafirlukast, are reported to have some benefit in the management of chronic urticaria (p. 1689.2).

Adverse Effects and Precautions

Headache, an increased incidence of respiratory-tract infection (in the elderly), and gastrointestinal disturbances have been reported with zafirlukast and other leukotriene antagonists. Other adverse effects have included generalised and abdominal pain, arthralgia, myalgia, fever, malaise, insomnia, and dizziness. Elevations in liver enzyme values and severe hepatotoxicity have been reported (see also below); fatalities have occurred. Hypersensitivity reactions, including rashes, pruritus, urticaria, and angioedema, have been reported. There have also been rare reports of agranulocytosis, bleeding, bruising and oedema. There have been a few reports of systemic eosinophilia consistent with Churg-Strauss syndrome in patients receiving leukotriene antagonists (see below); treatment should be withdrawn in these patients.

Zafirlukast and other leukotriene antagonists should not be used for the treatment of acute asthma attacks. Zafirlukast is contra-indicated in patients with hepatic impairment or cirrhosis.

Incidence of adverse effects. An observational study[1] of 7976 patients prescribed zafirlukast found it to be generally well tolerated. Similarly to UK licensed product information, the most frequently reported adverse effects (1 to 2% of patients) were headache, rash, abdominal pain, malaise, and gastrointestinal disturbances such as nausea, diarrhoea, and dyspepsia. Dizziness and palpitations were more common in the first month of treatment. An increased incidence of depression was also noted.

1. Twaites BR, *et al.* Safety of zafirlukast: results of a postmarketing surveillance study on 7976 patients in England. *Drug Safety* 2007; **30:** 419–29.

Churg-Strauss syndrome. Several case series and reports suggest a link between treatment with a leukotriene receptor antagonist and the development of Churg-Strauss syndrome (p. 1603.1). A systematic review[1] of 62 cases found montelukast implicated in 29, pranlukast in 16, and zafirlukast in 17. The lung was the most common site affected followed by nerves and skin; 16 patients had cardiac involvement. It was suggested that patients who developed Churg-Strauss syndrome but had evidence of pre-existing disease were either in the final phase of developing the syndrome when a leukotriene antagonist was started, or the syndrome was unmasked when corticosteroids were reduced or withdrawn; this pattern was identified in 11 patients. However, a significant number of cases did not have any evidence of dormant or existing disease and there was a clear temporal relationship between starting treatment with a leukotriene antagonist and the onset of symptoms within 6 to 12 months. Also, development of Churg-Strauss syndrome was reported in patients with no change in inhaled or oral corticosteroids before or after starting a leukotriene antagonist, and 7 cases were not taking any inhaled or oral corticosteroids when treatment was started.

A retrospective case-control study[2] found montelukast treatment to be associated with an increased risk of developing Churg-Strauss syndrome within 3 months. As oral corticosteroid use also increased the risk, the authors of the study suggested that the onset of Churg-Strauss syndrome may be linked to an escalation in asthma therapy for gradually worsening asthma. It has been suggested that patients should be carefully monitored for signs of Churg-Strauss syndrome when taking leukotriene antagonists and when corticosteroid dosage is reduced.[3]

1. Nathani N, *et al.* Churg-Strauss syndrome and leukotriene antagonist use: a respiratory perspective. *Thorax* 2008; **63:** 883–8.
2. Hauser T, *et al.* The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study. *Thorax* 2008; **63:** 677–82.
3. Keogh KA. Leukotriene receptor antagonists and Churg-Strauss syndrome: cause, trigger or merely an association? *Drug Safety* 2007; **30:** 837–43.

Effects on the CNS. Neuropsychiatric events have been reported postmarketing in some patients taking the anti-leukotrienes montelukast, zafirlukast, and zileuton. Events reported include agitation, aggression, anxiety, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, tremor, suicidal ideation, and suicide.[1,2] A review[3] of 3 studies in which 536 patients received montelukast found no change in emotional well-being compared with placebo or any other treatment drugs and no reports of suicide, depression, or psychiatric disturbances. The authors concluded that although they did not find evidence for general concern about psychiatric adverse effects, they could not exclude the possibility of idiosyncratic reactions to montelukast.

1. FDA. Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast (marketed as Accolate), and zileuton (marketed as Zyflo and Zyflo CR) (issued 12th June 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm (accessed 14/08/09)
2. Health Canada. Montelukast (Singulair): suicidality and other psychiatric adverse reactions. *Can Adverse React News* 2009; **19** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php#a1 (accessed 14/08/09)
3. Holbrook JT, Harik-Khan R. Montelukast and emotional well-being as a marker for depression: results from 3 randomized, double-masked clinical trials. *J Allergy Clin Immunol* 2008; **122:** 828–9.

Effects on the liver. Severe hepatotoxicity has been associated with zafirlukast.[1-4] The Canadian manufacturer reported[4] in April 2004 that from worldwide postmarketing surveillance of zafirlukast there had been 46 reports of hepatitis, 14 of hepatic failure, 3 of which progressed to fulminant hepatitis, and 59 reports of other clinically significant hepatic dysfunction; 7 fatalities had occurred. In most, but not all, cases symptoms had abated and liver enzymes had returned to normal after stopping zafirlukast. It was important that prescribers, patients and/or their carers were alert to the signs and symptoms of hepatotoxicity. UK licensed product information for zafirlukast describes rare cases of hepatic dysfunction without raised liver enzyme values; zafirlukast treatment should be stopped if hepatotoxicity is suspected.

1. Griecoa AJ, Burstein-Stein J. Oral montelukast versus inhaled salmeterol to prevent exercise-induced bronchoconstriction. *Ann Intern Med* 2000; **133:** 392.
2. Reinus JF, *et al.* Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. *Ann Intern Med* 2000; **133:** 964–8.
3. Danese S, *et al.* Severe liver injury associated with zafirlukast. *Ann Intern Med* 2001; **135:** 930.
4. AstraZeneca Canada. Important safety information regarding reports of serious hepatic events in patients receiving Accolate (zafirlukast) (issued 14th April 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/accolate_2_hpc-cps-eng.pdf (accessed 09/07/08)

Lupus. Zafirlukast was thought to be responsible for the development of lupus in a 9-year-old girl.[1]

1. Finkel TH, *et al.* Drug-induced lupus in a child after treatment with zafirlukast (Accolate). *J Allergy Clin Immunol* 1999; **103:** 533–4.

Renal impairment. The UK licensed product information states that zafirlukast should be used with caution in patients with moderate or severe renal impairment because of limited experience in this group. However, the US product information mentions no such caution, and states that the pharmacokinetics of zafirlukast in patients with renal impairment do not appear to differ from those in patients with normal renal function. Only about 10% of a dose is reported to be excreted in the urine.

Tolerance. Tolerance to the beneficial effects of zafirlukast, and rebound exacerbation of asthma symptoms on withdrawal, has been described[1] in patients with persistent asthma.

1. Reid DW, *et al.* Tolerance and rebound with zafirlukast in patients with persistent asthma. *J Negat Results Biomed* 2008; **7:** 3.

Interactions

Zafirlukast is metabolised by hepatic cytochrome P450, specifically the CYP2C9 isoenzyme, and has been shown to inhibit the activity of isoenzymes CYP2C9 and CYP3A4. Therefore, use with other drugs that are metabolised by these hepatic enzymes may result in increases in plasma concentrations, and possibly, adverse effects. Patients receiving warfarin may develop prolongation of the prothrombin time and anticoagulant dosage should be adjusted accordingly. Erythromycin, terfenadine, and theophylline may reduce plasma concentrations of zafirlukast; zafirlukast has rarely been reported to increase plasma-theophylline concentrations. Increased plasma concentrations of zafirlukast have been seen when given with high doses of aspirin.

Pharmacokinetics

Peak plasma concentrations of zafirlukast occur about 3 hours after oral doses. The absolute bioavailability is uncertain, but taking it with food reduces both the rate and extent of absorption, decreasing bioavailability by about 40%. Zafirlukast is about 99% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2C9, and excreted principally in faeces, as unchanged drug and metabolites. About 10% of a dose is excreted in urine as metabolites. The terminal elimination half-life of zafirlukast is about 10 hours. Studies in *animals* suggest that small amounts cross the placenta; it is also distributed into breast milk.

Reviews.

1. Dekhuijzen PNR, Koopmans PP. Pharmacokinetic profile of zafirlukast. *Clin Pharmacokinet* 2002; **41:** 105–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Accolate; ***Austral.***: Accolate†; ***Belg.***: Accolate; Resma; ***Braz.***: Accolate; ***Canad.***: Accolate; ***Chile***: Accolate†; ***China***: Accolate (安可来); ***Cz.***: Accolate; ***Fin.***: Accolate; ***Hong Kong***: Accolate; ***Hung.***: Accolate; ***India***: Zuvair; ***Indon.***: Accolate; ***Irl.***: Accolate; ***Ital.***: Accoleit; Zafirst; ***Mex.***: Accolate; ***Philipp.***: Accolate; ***Pol.***: Accolate; ***Port.***: Accolate; ***Rus.***: Accolate (Аколат); ***S.Afr.***: Accolate; ***Singapore***: Accolate†; ***Spain***: Accolate; Aeronix; Olmoran; ***Switz.***: Accolate; ***Thai.***: Accolate; ***Turk.***: Accolate; Carrox; ***UK***: Accolate; ***USA***: Accolate; ***Venez.***: Accolate.

Zileuton *(BAN, USAN, rINN)*

A-64077; Abbott-64077; Zileutón; Zileutonum; Зилейтон.

(±)-1-(1-Benzo[*b*]thien-2-ylethyl)-*N*-hydroxyurea.

$C_{11}H_{12}N_2O_2S$=236.3
CAS — 111406-87-2.
UNII — V1L22WVE2S.

Pharmacopoeias. In *US.*

USP 36: (Zileuton). A white to off-white powder. Store in airtight containers. Protect from light.

Uses and Administration

Zileuton is an orally active 5-lipoxygenase inhibitor and therefore inhibits leukotriene formation (p. 1195.2). It is used in the management of chronic asthma (see below) but has no bronchodilator properties and is not suitable for the management of acute attacks. Zileuton is given in oral doses of 600 mg 4 times daily as an immediate-release preparation. A controlled-release formulation of zileuton is also available; the usual oral dose is 1.2 g twice daily.

It has also been tried in other disorders including acne, arthritis, allergic rhinitis, and inflammatory bowel disease.

Acne. Zileuton has been investigated for its potential benefits in the treatment of acne (p. 1682.2);[1] oral doses of 600 mg 4 times daily for 3 months have produced reductions in inflammation and sebum lipid secretion in small preliminary studies.

1. Zouboulis CC. Zileuton, a new efficient and safe systemic anti-acne drug. *Dermatoendocrinol* 2009; **1:** 188–92.

Asthma. Zileuton has been found to be of some benefit in asthma (p. 1195.2), including that provoked by cold air, exercise, and NSAIDs. Due to a lack of data on efficacy and the need for liver function monitoring, zileuton is considered a less desirable treatment option for addition to inhaled corticosteroids than the leukotriene receptor antagonists.

An intravenous form of zileuton has been investigated for use in asthma.

References.

1. Israel E, *et al.* The effects of a 5-lipoxygenase inhibitor on asthma induced by cold, dry air. *N Engl J Med* 1990; **323:** 1740–4.
2. Israel E, *et al.* The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann Intern Med* 1993; **119:** 1059–66.
3. McGill KA, Busse WW. Zileuton. *Lancet* 1996; **348:** 519–24.
4. Israel E, *et al.* Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma: a randomized controlled trial. *JAMA* 1996; **275:** 931–6.
5. O'Connor BJ, *et al.* Zileuton added to low-dose inhaled beclomethasone for the treatment of moderate to severe persistent asthma. *Respir Med* 2007; **101:** 1088–96.
6. Berger W, *et al.* Zileuton: clinical implications of 5-lipoxygenase inhibition in severe airway disease. *Int J Clin Pract* 2007; **61:** 663–76.

Inflammatory bowel disease. Despite initial hopes that inhibition of lipoxygenase might prove of benefit in patients with ulcerative colitis,[1] a study in those with mild or moderately active relapsing disease found that the symptomatic benefits of zileuton were confined to those not already receiving sulfasalazine.[2] A subsequent study showed zileuton was not significantly better than placebo in maintaining remission.[3] For a discussion of inflammatory bowel disease and its management, see p. 1811.3.

1. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition in ulcerative colitis. *Lancet* 1990; **335:** 683–5.
2. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition by zileuton in the treatment of relapsing ulcerative colitis: a randomized double-blind placebo-controlled multicentre trial. *Eur J Gastroenterol Hepatol* 1994; **6:** 209–15.
3. Hawkey CJ, *et al.* A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. *Gastroenterology* 1997; **112:** 718–24.

Rhinitis. A study in 8 patients with allergic rhinitis (p. 612.1) found that a single dose of zileuton 800 mg reduced the response to a nasal antigen challenge 3 hours later,[1] including reduced sneezing and nasal congestion.

1. Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; **323:** 1745–8.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with zileuton treatment are headache, pain including pharyngolaryngeal pain, gastrointestinal disturbances, myalgia, and sinusitis. Hypersensitivity, urticaria, rash, and leucopenia have been reported in a few patients. Zileuton has also been associated with raised liver enzyme values and severe hepatic injury.

Zileuton is not suitable for the treatment of acute asthma attacks.

Effects on the CNS. For information on the CNS adverse effects associated with use of anti-leukotrienes, see under Zafirlukast, p. 1240.2.

Effects on the liver. Cases of severe hepatotoxicity including fatalities, jaundice, hyperbilirubinaemia, and raised liver enzymes have been reported in patients taking zileuton. US licensed product information therefore contra-indicates the use of zileuton in patients with active liver disease or liver transaminase elevations greater than or equal to three times the upper limit of normal. Caution is required in patients with a history of liver disease or who consume substantial quantities of alcohol. Alanine aminotransferase (ALT) is considered the most sensitive indicator of liver injury due to zileuton. Most rises in ALT concentrations occurred in the first 3 months of zileuton therapy,[1] and monitoring is therefore recommended before starting zileuton therapy, once a month for the first 3 months of therapy, every 2 to 3 months for the remainder of the first year of therapy, and periodically thereafter.

1. Watkins PB, *et al.* Clinical pattern of zileuton-associated liver injury: results of a 12-month study in patients with chronic asthma. *Drug Safety* 2007; **30:** 805–15.

Interactions

Zileuton has been reported to impair the metabolism of some drugs metabolised via hepatic cytochrome P450 enzymes, including propranolol, terfenadine, theophylline, and warfarin.

Pharmacokinetics

Zileuton is reported to be well absorbed from the gastrointestinal tract after oral dosage, with peak plasma concentrations of immediate-release preparations occurring within about 2 hours of a dose. It is about 93% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2, CYP2C9, and CYP3A4, and excreted in the urine, largely as glucuronide metabolites. The elimination half-life is reported to be about 2.5 hours for the immediate-release preparation and about 3 hours for the controlled-release preparation.

References.

1. Wong SL, *et al.* The pharmacokinetics of single oral doses of zileuton 200 to 800 mg, its enantiomers, and its metabolites, in normal healthy volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 9–21.
2. Awni WM, *et al.* Pharmacokinetics and pharmacodynamics of zileuton after oral administration of single and multiple dose regimens of zileuton 600 mg in healthy volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 22–33.
3. Braeckman RA, *et al.* The pharmacokinetics of zileuton in healthy young and elderly volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 42–8.
4. Awni WM, *et al.* Population pharmacokinetics of zileuton, a selective 5-lipoxygenase inhibitor, in patients with rheumatoid arthritis. *Eur J Clin Pharmacol* 1995; **48:** 155–60.
5. Awni WM, *et al.* The effect of mild or moderate hepatic impairment (cirrhosis) on the pharmacokinetics of zileuton. *Clin Pharmacokinet* 1995; **29** (suppl 2): 49–61.
6. Awni WM, *et al.* Pharmacokinetics of zileuton and its metabolites in patients with renal impairment. *J Clin Pharmacol* 1997; **37:** 395–404.
7. Dubé LM, *et al.* Zileuton, a leukotriene synthesis inhibitor in the management of chronic asthma: clinical pharmacokinetics and safety. *Clin Rev Allergy Immunol* 1999; **17:** 213–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Zyflo.

Cardiovascular Drugs

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- Patent ductus arteriosus, p. 1278
- Phaeochromocytoma, p. 1278
- Pulmonary hypertension, p. 1278
- Shock, p. 1279

This chapter describes drugs used principally in the management of cardiovascular disorders, as well as the choice of treatment for a particular disorder. Blood products, plasma expanders, and haemostatics, which also have a role in cardiovascular disease, are described elsewhere (p. 1121.1).

The Circulatory System

The cardiovascular system consists of the heart and two vascular systems, the pulmonary and systemic circulations. The **heart** (below) pumps blood from the right ventricle through the **pulmonary circulation**, in which gas exchange occurs, and the oxygenated blood then returns to the left side of the heart, where the left ventricle pumps it to the **systemic circulation** which delivers blood to individual organs. Arteries supply blood at high pressure whereas arterioles are smaller vessels with muscular walls which allow direct control of flow through the capillary beds. Capillaries have thin walls, comprising a single layer of endothelial cells, which allow exchange of substances such as nutrients, hormones, and waste products between blood and tissues. Veins return blood from the capillary beds to the heart, and contain about 70% of the circulating blood volume.

Cardiac output is the product of heart rate and stroke volume; typically, in a 70-kg adult, these might be around 70 beats per minute, and 70 mL respectively, giving an output of around 5 litres/minute. Stroke volume in turn is dependent on **preload** (the ventricular volume at the end of diastole, when the ventricle relaxes and fills), **afterload** (the resistance to ventricular ejection, or systemic vascular resistance, determined mainly by the diameter of the arterioles), and **contractility**, or the strength of contraction of the heart muscle, which is influenced by the sympathetic nervous system but also by many other factors, including drugs, acid-base balance, and myocardial oxygen supply. In a healthy individual, cardiac output should adjust to match metabolic demand.

Blood pressure and flow is controlled by complex neurohormonal systems, involving the autonomic nervous system and peptides and regulators released by the kidneys and the circulatory system itself, such as the renin-angiotensin system and the natriuretic peptides. Substances such as nitric oxide and prostacyclin, produced by the endothelium of the vascular system, play an important role in controlling local blood flow.

All these systems can be manipulated by pharmacological therapy with the various drug groups (see below) used in the treatment of cardiovascular disorders (p. 1246.1).

The Heart

The heart acts as a pump, maintaining circulation of blood around the body. It does this by coordinated contraction and relaxation of the cardiac muscle (myocardium). In a normal cardiac cycle the atria contract first (atrial systole), forcing blood into the ventricles, which then contract (ventricular systole), pumping blood out into the blood vessels; atria and ventricles then both relax (diastole), allowing the atria to refill before the cycle begins again. Each cycle corresponds to a heart beat and in a healthy 70-kg person at rest cycles occur regularly at a rate of 70 to 75 beats/minute, although the exact rate varies more widely than this depending on circumstances.

The contraction of myocardial cells is controlled by electrical changes across the cell membrane, which can be represented by the *action potential*. The action potential in cardiac cells has 5 phases, although the exact pattern depends on the type of cell. A typical ventricular action potential is shown in Figure 1 (below).

Figure 1. The action potential.

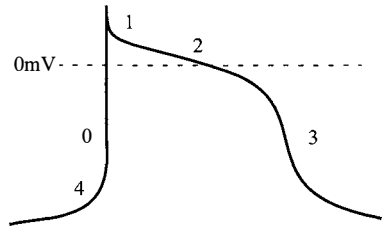

- phase 0 is the depolarisation phase when there is rapid influx of sodium ions (lasting a few milliseconds) and the cell contracts
- in phase 1, there is a transient rapid efflux of potassium ions and the cell begins to repolarise
- a slow influx of calcium ions then occurs which balances the potassium efflux leading to a plateau stage (phase 2) and maintenance of contraction
- this is followed by an increase in potassium efflux, while calcium influx stops, and repolarisation (phase 3) occurs
- the cell then relaxes and finally returns to the resting membrane potential (phase 4), and ion pumps return the balance of sodium and potassium to the baseline state

The depolarisation of one cell triggers action potentials in adjacent cells, allowing the electrical impulse to spread rapidly across the myocardium so that in a healthy heart all of the cells contract at the same time in a coordinated fashion.

Certain cells within the heart undergo spontaneous depolarisation during phase 4 and the initial depolarisation depends mainly on calcium ion influx rather than sodium ions. These *pacemaker cells* are able to initiate impulses. Although a number of cells have this property, impulses are normally generated in the *sino-atrial* (SA) or *sinus node*. They then spread across the atria, causing them to contract, but normally only pass to the ventricles through the specialised conducting cells of the atrioventricular (AV) node. From the AV node, the impulse passes through the bundle of His and down the Purkinje fibres to the ventricles, which then contract. The delay caused by this selective conduction through the AV node means that the atria contract before the ventricles and ensures the forward movement of the blood.

The heart rhythm that results from a normal cardiac cycle originating in the sinus node is known as *sinus rhythm*, and has been defined as a sinus node rate of 60 to 100 beats/minute. The rate is affected by input from the nervous system, and drugs can affect the conduction of impulses at various points in the cycle. For drugs used specifically in the management of heart rhythm disorders, see Antiarrhythmics, p. 1243.1.

The movement of electrical impulses can be recorded as an electrocardiogram (ECG). The ECG corresponds to the phases of the action potential in different parts of the heart and depends on the position of the recording leads; a typical ECG trace is shown in Figure 2, below. The P wave corresponds to atrial depolarisation, while the QRS complex corresponds to ventricular depolarisation; the PR interval corresponds to the delay between atrial and ventricular depolarisation. Phases 0 and 1 of the ventricular action potential produce the R and S waves, and phase 2 corresponds to the ST interval. The T wave represents ventricular repolarisation (phase 3).

Figure 2. A normal ECG trace.

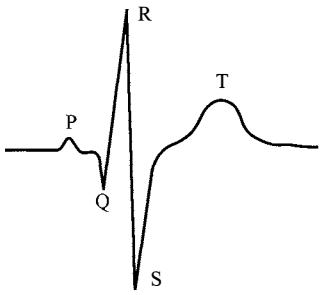

Cardiovascular Drug Groups

Although very diverse, cardiovascular drugs can be broadly classified according to their pharmacological action. Basic details of the major groups follow, together with lists of the drugs described in this chapter.

ACE inhibitors

The main uses of ACE (angiotensin-converting enzyme) inhibitors are in the management of heart failure, hypertension, and myocardial infarction. Their actions and uses are discussed in more detail on p. 1282.2.

Described in this chapter are

- Alacepril, p. 1295.3
- Benazepril, p. 1314.3
- Captopril, p. 1331.2
- Cilazapril, p. 1336.2
- Delapril, p. 1350.2
- Enalapril, p. 1371.1
- Enalaprilat, p. 1371.1
- Fosinopril, p. 1386.2
- Imidapril, p. 1409.1
- Lisinopril, p. 1420.3
- Moexipril, p. 1440.3
- Perindopril, p. 1466.3
- Quinapril, p. 1480.2
- Ramipril, p. 1483.3
- Spirapril, p. 1499.3
- Temocapril, p. 1510.2
- Trandolapril, p. 1517.2
- Zofenopril, p. 1536.3

Adrenergic neurone blockers

Adrenergic neurone blockers are used in hypertension although they have largely been superseded by other drugs less likely to cause orthostatic hypotension. They have also been used in open-angle glaucoma.

Adrenergic neurone blockers act by selectively inhibiting transmission in postganglionic adrenergic nerves. They are believed to act mainly by preventing the release of noradrenaline at nerve endings; they cause the depletion of noradrenaline stores in peripheral sympathetic nerve terminals. They do not prevent the secretion of catecholamines by the adrenal medulla.

Described in this chapter are

Debrisoquine, p. 1349.3
Guanadrel, p. 1395.2
Guanethidine, p. 1395.2

Alpha blockers

Alpha blockers are used mainly in the management of hypertension and to relieve urinary obstruction in benign prostatic hyperplasia.

Alpha blockers are also known as alpha-adrenergic antagonists or alpha-adrenergic receptor antagonists. Some have particular affinities for one of the subtypes of the alpha adrenoceptor. Drugs such as indoramin or prazosin are much more potent in blocking $alpha_1$ than $alpha_2$ adrenoceptors and are often termed selective $alpha_1$ blockers. Blockade of $alpha_1$ adrenoceptors inhibits the vasoconstriction induced by endogenous catecholamines. Both arteriolar and venous vasodilatation may occur resulting in a fall in blood pressure because of decreased peripheral resistance. Blockade of $alpha_2$ adrenoceptors with a selective drug such as yohimbine (p. 2372.3) can conversely lead to a rise in blood pressure. With phenoxybenzamine and phentolamine, which broadly have similar affinities for both the $alpha_1$ and $alpha_2$ subtypes of receptor, any increase in blood pressure due to $alpha_2$ blockade is prevented by the inhibition of vasoconstriction caused by $alpha_1$ blockade. Alpha blockers also act at alpha adrenoceptors in nonvascular smooth muscle, for example in the bladder where alpha blockade produces decreased resistance to urinary outflow; alpha blockers used mainly for urinary disorders are discussed under Urological Drugs, p. 2347.1. Most alpha blockers are reversible or 'competitive' inhibitors of alpha adrenoceptors; phenoxybenzamine is an irreversible or 'non-competitive' alpha blocker and is particularly useful in phaeochromocytoma.

Described in this chapter are

Bunazosin, p. 1329.3
Doxazosin, p. 1369.1
Indoramin, p. 1410.2
Phenoxybenzamine, p. 1468.1
Phentolamine, p. 1468.3
Prazosin, p. 1473.3
Terazosin, p. 1511.1
Moxisylyte, p. 1441.3
Tolazoline, p. 1516.2
Urapidil, p. 1520.2

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Angiotensin II receptor antagonists

Angiotensin II receptor antagonists (angiotensin II receptor blockers) are used in the management of hypertension; they may have a particular role in patients who develop cough with ACE inhibitors. Some are also used in diabetic nephropathy and in the management of heart failure. They act mainly by selective blockade of AT_1 receptors thus reducing the pressor effects of angiotensin II.

Described in this chapter are

Candesartan, p. 1330.2
Eprosartan, p. 1376.2
Irbesartan, p. 1411.1
Losartan, p. 1422.2
Olmesartan, p. 1459.2
Telmisartan, p. 1509.3
Valsartan, p. 1521.2

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Antiarrhythmics

Antiarrhythmics (formerly described as cardiac depressants) are a diverse group of drugs that affect the conduction of electrical impulses within the heart (see p. 1242.1). Many of them, such as beta blockers (p. 1316.3), digoxin (p. 1353.3), lidocaine (p. 1992.1), magnesium (p. 1789.1), and phenytoin (p. 538.2) have important actions in addition to their antiarrhythmic properties and thus, have a wide range of other clinical applications.

The most widely used **classification** of antiarrhythmics is that proposed by Vaughan Williams (later modified by Harrison) and is based largely on their *in-vitro* electrophysiological effects. There are 4 main classes:

Class I includes drugs that block the fast inward sodium channels and therefore interfere with depolarisation (phase 0 of the action potential); these drugs have been called membrane-stabilising drugs and have both antiarrhythmic and local anaesthetic properties. They have different properties depending on their affinity for different states of the sodium channel (open, closed, or inactivated) and can be further subdivided depending on additional characteristics.

Class Ia drugs slow the rate of change of the depolarisation phase of the action potential, although less so than class Ic drugs. They also prolong the repolarisation phase (phase 3), possibly by an effect on potassium channels. They prolong the PR, QRS, and QT intervals on the ECG.

Described in this chapter are

Ajmaline, p. 1295.2
Disopyramide, p. 1363.2
Hydroquinidine, p. 1407.1
Pirmenol, p. 1471.1
Procainamide, p. 1475.3
Quinidine, p. 1481.1

Class Ib drugs have little effect on the rate of change of the depolarisation phase of the action potential in normal cells, but have a more selective effect in ischaemic or diseased tissue; they are also more effective if external potassium concentrations are high. They shorten the repolarisation phase, shorten the QT interval, and elevate the fibrillation threshold. The local anaesthetic lidocaine has class Ib properties.

Described in this chapter are

Aprindine, p. 1306.3
Mexiletine, p. 1436.2
Tocainide, p. 1515.3

Class Ic drugs markedly slow the rate of change of the depolarisation phase of the action potential, but have little effect on the repolarisation phase. They prolong the PR and QRS intervals.

Described in this chapter are

Ethacizine, p. 1379.1
Flecainide, p. 1382.3
Pilsicainide, p. 1470.1
Propafenone, p. 1477.3

Class II drugs are characterised by beta-blocking activity; they reduce both heart rate and myocardial contractility, and also slow conduction of impulses through the myocardial conducting system. They reduce the rate of spontaneous depolarisation in cells with pacemaker activity but have little effect on the action potential in most myocardial cells.

Described in this chapter are

Beta blockers (but sotalol has mainly class III activity), p. 1316.3
Bretylium, p. 1328.2

Class III drugs slow the repolarisation phase (phase 3) and prolong the action potential duration and the QT interval. Various mechanisms may be involved, but most class III drugs act by potassium channel blockade.

Described in this chapter are

Amiodarone, p. 1300.1
Azimilide, p. 1313.3
Bretylium, p. 1328.2
Cibenzoline, p. 1336.1
Dofetilide, p. 1367.1
Ibutilide, p. 1407.2
Nifekalant, p. 1455.1
Sotalol, p. 1498.2

Class IV drugs are calcium-channel blockers (p. 1244.2) that act by blocking the slow inward calcium current and particularly affect the pacemaker cells where calcium influx is relatively more important. However, differences in tissue specificity mean that not all calcium-channel blockers have antiarrhythmic properties.

Described in this chapter are

Cibenzoline, p. 1336.1
Diltiazem, p. 1359.2
Verapamil, p. 1522.1

A major limitation of the Vaughan Williams classification is that many antiarrhythmics have multiple actions, and may not fit neatly into a single class. Some are assigned to several classes, while others are included in one class although they also have characteristics of another. Bretylium is included in both class II and class III, whereas propafenone is usually considered a class Ic drug despite possessing beta-blocking properties. Beta blockers are traditionally described as class II, although some also have class I actions, while sotalol, despite sharing the properties of beta blockers, has mainly class III activity and is usually described as a class III drug. Drugs such as adenosine and digoxin do not fit into the Vaughan Williams classification at all.

Another problem with the Vaughan Williams classification is that the electrophysiological effects of antiarrhythmics are not clearly related to their effectiveness in treating a particular arrhythmia in an individual patient. Alternative classification systems have therefore been suggested, for example based on the cardiac tissue that the drug affects. Thus drugs that act on the sino-atrial node include beta blockers, class IV antiarrhythmics, and cardiac glycosides such as digoxin; class I and class III antiarrhythmics act on the ventricles; and drugs acting on atrial arrhythmias include class Ia, Ic, and III antiarrhythmics and beta blockers. Class Ia and III antiarrhythmics act on accessory pathways and drugs acting on the AV node include class Ic and IV antiarrhythmics, beta blockers, and cardiac glycosides. A simplification of this scheme is to classify drugs into those that act on both ventricular and supraventricular arrhythmias such as amiodarone, beta blockers, disopyramide, procainamide, and quinidine, those that act mainly on ventricular arrhythmias such as lidocaine, mexiletine, and phenytoin, and those that act mainly on supraventricular arrhythmias such as verapamil.

The Sicilian Gambit is another approach based on the mechanisms by which arrhythmias are generated and the ways that drugs could influence them.

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Anticoagulants

Anticoagulants are used in the treatment and prophylaxis of thromboembolic disorders. They may be divided into direct anticoagulants such as the heparins, low-molecular-weight heparins, heparinoids, and direct thrombin inhibitors, and indirect anticoagulants such as the coumarin and indanedione derivatives.

Direct anticoagulants

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa (see Haemostasis, p. 1124.3). The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on antithrombin III's inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect.

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Like heparin, these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factorIIa (antithrombin activity) than heparin. Although the possibility that such selective factor-Xa inhibition would result in antithrombotic activity without anticoagulant, and hence haemorrhagic, effects has not been confirmed by clinical experience, they have more predictable effects and require less monitoring than heparin. Low-molecular-weight heparins also have less effect on platelet aggregation than heparin.

Fondaparinux and idraparinux are synthetic polysaccharides that act as direct inhibitors of factor Xa. Rivaroxaban, apixaban, and edoxaban are orally active factor Xa inhibitors.

Argatroban, bivalirudin, dabigatran, desirudin, and lepirudin are examples of direct thrombin inhibitors.

Described in this chapter are

Apixaban, p. 1306.2
Ardeparin, p. 1307.1
Argatroban, p. 1307.2
Bemiparin, p. 1314.2
Bivalirudin, p. 1326.2
Certoparin, p. 1334.2
Dabigatran, p. 1347.2
Dalteparin, p. 1348.3
Desirudin, p. 1351.1
Enoxaparin, p. 1372.3
Fondaparinux, p. 1385.3
Heparin, p. 1396.3
Idraparinux, p. 1408.1
Lepirudin, p. 1418.2
Low-molecular-weight Heparins, p. 1426.1
Nadroparin, p. 1443.2
Parnaparin, p. 1464.2
Reviparin, p. 1486.3
Rivaroxaban, p. 1487.2
Semuloparin, p. 1489.2
Tinzaparin, p. 1514.2

The *direct thrombin inhibitors* bind to the active thrombin site and inhibit both free and clot-bound thrombin. Most are recombinant forms or synthetic analogues of hirudin and need to be given parenterally, but oral thrombin inhibitors have been developed. Dabigatran, given orally as the prodrug dabigatran etexilate, is used in the prophylaxis of venous thromboembolism.

Described in this chapter are

Argatroban, p. 1307.2
Bivalirudin, p. 1326.2
Dabigatran, p. 1347.2
Desirudin, p. 1351.1
Hirudin, p. 1401.2
Lepirudin, p. 1418.2

References.

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The term *heparinoid* includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly sulfated polysaccharides of similar structure, such as danaparoid and dermatan sulfate. Some compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans, glycosaminoglycan polysulfate compounds, or sulfated mucopolysaccharides.

Described in this chapter are

Danaparoid, p. 1349.2
Dermatan Sulfate, p. 1350.3
Pentosan Polysulfate Sodium, p. 1465.1

Sodium Apolate, p. 1497.1
Suleparoid, p. 1507.2
Sulodexide, p. 1507.3

Indirect anticoagulants

Indirect anticoagulants act by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. Warfarin, a coumarin, is the main drug used; other coumarins (although not all coumarins have anticoagulant activity) and indanediones such as phenindione are also available. Since they act indirectly, they have no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is observed. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Described in this chapter are

Dicoumarol, p. 1352.2
Fluindione, p. 1385.1
Acenocoumarol, p. 1290.1
Phenindione, p. 1467.3
Phenprocoumon, p. 1468.3
Warfarin, p. 1526.3

Antiplatelet drugs

Platelet aggregation is important in haemostasis (p. 1124.3) and is also involved in thrombus formation, particularly in the arterial circulation. Antiplatelet drugs reduce platelet aggregation and are used to prevent further thromboembolic events in patients who have suffered myocardial infarction, ischaemic stroke or transient ischaemic attacks, or unstable angina, and for primary prevention of a thromboembolic event in patients at risk. Some are also used for the prevention of reocclusion or restenosis following angioplasty and bypass procedures.

Antiplatelet drugs act through a wide range of mechanisms. Aspirin (p. 22.2) is the most widely used and studied; it acts by irreversibly inhibiting platelet cyclo-oxygenase and thus preventing synthesis of thromboxane A_2. Reversible cyclo-oxygenase inhibitors such as indobufen are also available, and thromboxane synthase inhibitors and thromboxane receptor antagonists have also been used.

Drugs that interfere with adenosine metabolism have an antiplatelet effect and those used include some prostaglandins, which act by increasing platelet cyclic adenosine monophosphate levels; ticagrelor and the thienopyridines clopidogrel, prasugrel, and ticlopidine, which interfere with adenosine diphosphate mediated platelet activation; and the adenosine reuptake inhibitor dipyridamole.

Thrombin inhibitors such as heparin and the hirudins have antiplatelet and anticoagulant effects. Glycoprotein IIb/IIIa-receptor antagonists, such as abciximab, eptifibatide, and tirofiban, interfere with the final step in platelet aggregation and are used in unstable angina and as adjuncts in reperfusion and revascularisation procedures. Oral glycoprotein IIb/IIIa-receptor antagonists such as orbofiban, sibrafiban, and xemilofiban have also been investigated but results have been disappointing.

Described in this chapter are

Abciximab, p. 1281.1
Cangrelor, p. 1331.1
Cilostazol, p. 1337.1
Clopidogrel, p. 1342.3
Cloricromen, p. 1345.1
Dipyridamole, p. 1362.2
Ditazole, p. 1365.3
Eptifibatide, p. 1376.3
Heparin, p. 1396.3
Indobufen, p. 1410.1
Orbofiban, p. 1463.1
Picotamide, p. 1469.3
Prasugrel, p. 1472.3
Sarpogrelate, p. 1489.1
Ticagrelor, p. 1511.3
Ticlopidine, p. 1512.1
Tirofiban, p. 1515.1
Trapidil, p. 1517.3
Triflusal, p. 1519.3
Xemilofiban, p. 1536.1

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Beta blockers

Beta blockers are competitive antagonists at beta-adrenergic receptor sites and are used in the management of cardiovascular disorders such as hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. They are also given to control symptoms of sympathetic overactivity in alcohol withdrawal, anxiety states, hyperthyroidism, and tremor and in the prophylaxis of migraine and of bleeding associated with portal hypertension. Their actions and uses are discussed in more detail on p. 1316.3.

Beta blockers used mainly as eye drops to reduce raised intra-ocular pressure in glaucoma and ocular hypertension are discussed under Miotics, Mydriatics, and Antiglaucoma Drugs, p. 1999.1.

Described in this chapter are

Acebutolol, p. 1289.1
Alprenolol, p. 1296.3
Amosulalol, p. 1305.1
Arotinolol, p. 1308.1
Atenolol, p. 1308.2
Betaxolol, p. 1322.3
Bevantolol, p. 1323.2
Bisoprolol, p. 1325.3
Bopindolol, p. 1326.3
Bucindolol, p. 1328.2
Bupranolol, p. 1329.3
Carazolol, p. 1332.3
Carteolol, p. 1332.3
Carvedilol, p. 1333.1
Celiprolol, p. 1334.2
Esatenolol, p. 1377.2
Esmolol, p. 1377.3
Indenolol, p. 1410.1
Labetalol, p. 1416.2
Landiolol, p. 1418.1
Metoprolol, p. 1434.3
Nadolol, p. 1442.3
Nebivolol, p. 1444.2
Oxprenolol, p. 1463.2
Penbutolol, p. 1464.3
Pindolol, p. 1470.1
Propranolol, p. 1479.1
Sotalol, p. 1498.2
Talinolol, p. 1509.2
Tertatolol, p. 1511.2
Tilisolol, p. 1513.2
Timolol, p. 1513.2

Calcium-channel blockers

Calcium-channel blockers are used mainly in the management of angina pectoris, hypertension, and cardiac arrhythmias.

Calcium-channel blockers, (calcium antagonists, calcium-entry blockers, or slow-channel blockers) inhibit the cellular influx of calcium that is responsible for maintenance of the plateau phase of the action potential. Thus calcium-channel blockers mainly affect tissues in which depolarisation is dependent upon calcium rather than sodium influx, such as vascular smooth muscle, myocardial cells, and cells within the sino-atrial (SA) and atrioventricular (AV) nodes. The main actions of the calcium-channel blockers include dilatation of coronary and peripheral arteries and arterioles with little or no effect on venous tone, a negative inotropic action, reduction of heart rate, and slowing of AV conduction. However, the effects of individual drugs, and therefore their uses, are modified by their selectivity of action at different tissue sites and by baroreceptor reflexes.

Traditionally, calcium-channel blockers have been classified according to their chemical structure; other methods of classification relate to the subtypes of calcium channels which they block, and their effects on heart rate. There are three major groups that are highly specific blockers of calcium channels.

Dihydropyridine calcium-channel blockers (such as nifedipine) act on slow, L-type (long) channels. They have a greater selectivity for vascular smooth muscle than for myocardium and therefore their main effect is vasodilatation. They are non-rate-limiting, with little or no action at the SA or AV nodes, and negative inotropic activity is rarely seen at therapeutic doses. They are used for their antihypertensive and anti-anginal properties. Some dihydropyridine derivatives, for example nimodipine, cross the blood-brain barrier and are used in cerebral ischaemia.

Benzothiazepine calcium-channel blockers (such as diltiazem) and **phenylalkylamine** calcium-channel blockers (such as verapamil) also act on L-type channels, but they have less selective vasodilator activity than dihydropyridine derivatives. They are classed as rate-limiting and have a direct effect on myocardium, causing depression of SA and AV nodal conduction. They are used for supraventricular arrhythmias as well as angina and hypertension.

Drugs selective for fast T-type (transient) calcium channels have also been investigated. Mibefradil, a benzimidazolyl-substituted tetraline derivative, is an example of this class. It is rate-limiting and causes coronary and peripheral vasodilatation, but is no longer used clinically due to serious drug interactions.

Some drugs with calcium-channel blocking properties, including certain antihistamines such as cinnarizine, and the N-type (neuronal) calcium-channel blocker ziconotide, have non-cardiovascular indications and are described elsewhere.

For further discussion of the actions and uses of the three main groups of calcium-channel blockers, see Nifedipine, p. 1447.2, Diltiazem, p. 1359.2, and Verapamil, p. 1522.1, respectively.

Described in this chapter are

Amlodipine, p. 1304.1
Aranidipine, p. 1307.1
Azelnidipine, p. 1313.2
Barnidipine, p. 1314.1
Benidipine, p. 1316.1
Bepridil, p. 1316.2
Cilnidipine, p. 1337.1
Clevidipine, p. 1338.2
Diltiazem, p. 1359.2
Efonidipine, p. 1370.3
Felodipine, p. 1380.3
Gallopamil, p. 1390.3
Isradipine, p. 1414.2
Lacidipine, p. 1417.3
Lercanidipine, p. 1419.3
Lidoflazine, p. 1420.2
Manidipine, p. 1427.2
Nicardipine, p. 1445.2
Nifedipine, p. 1447.2
Nilvadipine, p. 1455.2
Nimodipine, p. 1455.2
Nisoldipine, p. 1456.2
Nitrendipine, p. 1456.3
Verapamil, p. 1522.1

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Cardiac inotropes

Positive cardiac inotropes increase the force of contraction of the myocardium and are therefore used in the management of acute and chronic heart failure. Some inotropes also increase or decrease the heart rate (positive or negative chronotropes), provide vasodilatation (inodilators), or improve myocardial relaxation (positive lusitropes), and these additional properties influence the choice of drug in specific situations. Drugs that are used mainly for their inotropic effects include the cardiac glycosides and phosphodiesterase inhibitors; sympathomimetics have a role as inotropes but also have other important uses.

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Cardiac glycosides, such as digoxin, possess positive inotropic activity, which is mediated by inhibition of sodium-potassium adenosine triphosphatase (Na/K-ATPase). They also reduce conductivity in the heart, particularly through the atrioventricular node, and therefore have a negative chronotropic effect. The cardiac glycosides have very similar pharmacological effects but differ considerably in their speed of onset and duration of action. They are used to slow the heart rate in supraventricular arrhythmias, especially atrial fibrillation, and are also given in chronic heart failure.

Described in this chapter are

Acetyldigoxin, p. 1290.2
Deslanoside, p. 1351.2
Digitalis Leaf, p. 1352.3
Digitalis Lanata Leaf, p. 1352.3
Digitoxin, p. 1353.1
Digoxin, p. 1353.3
Lanatoside C, p. 1417.3
Metildigoxin, p. 1433.1
Ouabain, p. 1463.1
Proscillaridin, p. 1480.2
Strophanthin-K, p. 1507.2

Type 3 **phosphodiesterase inhibitors** are potent inotropes; they also have vasodilator effects. They are used in the short-term treatment of severe heart failure; long-term oral therapy with some phosphodiesterase inhibitors has been associated with increased mortality.

Described in this chapter are

Amrinone, p. 1305.1
Enoximone, p. 1373.3
Milrinone, p. 1438.1
Olprinone, p. 1460.1
Pimobendan, p. 1470.1

Centrally acting antihypertensives

Centrally acting antihypertensives include alpha$_2$-adrenoceptor agonists such as clonidine and methyldopa. Stimulation of alpha$_2$ adrenoceptors in the CNS results in a reduction in sympathetic tone and a fall in blood pressure. Heart rate is also reduced. They are used in the management of hypertension, although other drugs with fewer adverse effects are generally preferred. Apraclonidine (p. 2003.3) and brimonidine (p. 2004.3) are alpha$_2$-adrenoceptor agonists that are used in the management of glaucoma.

Described in this chapter are

Clonidine, p. 1339.1
Guanabenz, p. 1395.1
Guanfacine, p. 1396.1
Methyldopa, p. 1431.1
Moxonidine, p. 1442.1
Rilmenidine, p. 1487.1

Diuretics

Diuretics promote the excretion of water and electrolytes by the kidneys. They are used in the treatment of heart failure or in hepatic, renal, or pulmonary disease when salt and water retention has resulted in oedema or ascites. Diuretics are also used, either alone or with other drugs, in the treatment of hypertension, although the mechanism for their antihypertensive effect is poorly understood.

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Carbonic anhydrase inhibitors such as acetazolamide (p. 2001.1) are weak diuretics and are used mainly to reduce intra-ocular pressure in glaucoma. They are described under Miotics, Mydriatics, and Antiglaucoma Drugs, p. 1999.1.

'Loop' or **'high-ceiling' diuretics** produce an intense, dose-dependent diuresis of relatively short duration.

Described in this chapter are

Azosemide, p. 1314.1
Bumetanide, p. 1329.1
Etacrynic Acid, p. 1378.2
Furosemide, p. 1387.1
Piretanide, p. 1470.3
Torasemide, p. 1516.3

Osmotic diuretics raise the osmolality of plasma and renal tubular fluid. They are used to reduce or prevent cerebral oedema, to reduce raised intra-ocular pressure, and in acute renal failure.

Described in this chapter are
- Isosorbide, p. 1412.2
- Mannitol, p. 1427.3

Potassium-sparing diuretics have a relatively weak diuretic effect and are normally used with thiazide or loop diuretics. Canrenone, eplerenone, potassium canrenoate, and spironolactone are aldosterone antagonists and are particularly used in conditions where aldosterone contributes to the pathophysiology.

Described in this chapter are
- Amiloride, p. 1299.1
- Canrenone, p. 1331.1
- Eplerenone, p. 1374.2
- Potassium Canrenoate, p. 1472.2
- Spironolactone, p. 1499.3
- Triamterene, p. 1518.3

Thiazides (benzothiadiazines), such as bendroflumethiazide and hydrochlorothiazide, and certain other compounds, such as metolazone, with structural similarities to the thiazides, inhibit sodium and chloride reabsorption in the kidney tubules and produce a corresponding increase in potassium excretion.

Described in this chapter are
- Altizide, p. 1298.2
- Bemetizide, p. 1314.2
- Bendroflumethiazide, p. 1315.2
- Benzthiazide, p. 1316.1
- Benzylhydrochlorothiazide, p. 1316.2
- Butizide, p. 1329.3
- Chlorothiazide, p. 1334.3
- Chlortalidone, p. 1335.2
- Clopamide, p. 1342.3
- Cyclopenthiazide, p. 1347.2
- Epitizide, p. 1374.2
- Hydrochlorothiazide, p. 1403.2
- Hydroflumethiazide, p. 1406.3
- Indapamide, p. 1409.2
- Mefruside, p. 1429.3
- Methyclothiazide, p. 1430.3
- Meticrane, p. 1433.1
- Metipamide, p. 1433.3
- Metolazone, p. 1434.1
- Polythiazide, p. 1472.1
- Teclothiazide, p. 1509.2
- Trichlormethiazide, p. 1519.3
- Tripamide, p. 1520.2
- Xipamide, p. 1536.1

Endothelin receptor antagonists

Endothelin receptor antagonists act by blocking the effects of endothelin, a potent vasoconstrictor. Bosentan blocks both the endothelin ET_A and ET_B receptors, whereas ambrisentan is selective for ET_A. They are used in the management of pulmonary hypertension. Sitaxentan is another selective ET_A antagonist that was used for pulmonary hypertension, but it has been withdrawn. Tezosentan, which blocks both ET_A and ET_B, has been investigated in heart failure.

Described in this chapter are
- Ambrisentan, p. 1298.2
- Bosentan, p. 1327.1
- Sitaxentan, p. 1496.2
- Tezosentan, p. 1511.2

References.

1. Attinà T, *et al*. Endothelin antagonism in pulmonary hypertension, heart failure, and beyond. *Heart* 2005; **91:** 825–31.

Ganglion blockers

Ganglion blockers are nicotinic antagonists that inhibit the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. Their antihypertensive action is due to sympathetic blockade, which produces peripheral vasodilatation; there is also a direct vasodilator effect on peripheral blood vessels.

Described in this chapter are
- Azamethonium, p. 1313.1
- Mecamylamine, p. 1429.1

Lipid regulating drugs

Lipid regulating drugs are used to modify blood lipid concentrations in the management of hyperlipidaemias and for the reduction of cardiovascular risk. The principal groups of lipid regulating drugs are the statins, fibrates, bile-acid binding resins, nicotinates, and omega-3 triglycerides; ezetimibe, an inhibitor of intestinal cholesterol absorption, is also used.

The **statins** are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme for cholesterol synthesis. They reduce cholesterol by stimulating an increase in low-density-lipoprotein (LDL)-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase high-density-lipoprotein (HDL)-cholesterol. They are generally considered to be the most effective lipid lowering drugs.

Described in this chapter are
- Atorvastatin, p. 1309.2
- Fluvastatin, p. 1385.1
- Lovastatin, p. 1425.2
- Pitavastatin, p. 1471.1
- Pravastatin, p. 1473.1
- Rosuvastatin, p. 1488.2
- Simvastatin, p. 1489.2

The **fibrates** include derivatives of fibric acid and related compounds. They are activators of peroxisome proliferator-activated receptor (PPAR)-α and inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of very-low-density lipoproteins (VLDL); they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia.

Described in this chapter are
- Bezafibrate, p. 1323.2
- Ciprofibrate, p. 1338.1
- Clinofibrate, p. 1338.3
- Clofibrate, p. 1338.3
- Etofylline Clofibrate, p. 1379.2
- Fenofibrate, p. 1381.1
- Gemfibrozil, p. 1390.3

Bile-acid binding resins (bile-acid sequestrants) lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting primarily in a reduction of LDL-cholesterol.

Described in this chapter are
- Colesevelam, p. 1345.1
- Colestilan, p. 1345.2
- Colestipol, p. 1345.3
- Colestyramine, p. 1346.1
- Colextran, p. 1347.1

Nicotinates include nicotinic acid (p. 2083.1) and its derivatives. Nicotinic acid is a member of the vitamin B group and, in high doses, has beneficial effects on blood lipids; it reduces triglycerides and increases HDL-cholesterol, and may also modestly reduce LDL-cholesterol. Nicotinates are mainly used in hypertriglyceridaemia. Compounds derived from both nicotinic acid and clofibrate (nicotinate-fibrate derivatives) are also used.

Described in this chapter are
- Acipimox, p. 1290.2
- Etofibrate, p. 1379.2
- Inositol Nicotinate, p. 1410.3
- Niceritrol, p. 1446.1
- Nicotinyl Alcohol, p. 1447.1
- Tocoferil Nicotinate, p. 1516.1
- Xantinol Nicotinate, p. 1535.3

Omega-3 fatty acids are long-chain polyunsaturated fatty acids that primarily reduce triglycerides.

Described in this chapter are
- Omega-3 Fatty Acids, p. 1460.1

Nitrates

Nitrates are peripheral and coronary vasodilators used in the management of angina pectoris, heart failure, and myocardial infarction. Some of them may also be used to control blood pressure during surgery. Nitrates are believed to exert their vasodilator effect through release of nitric oxide (p. 1457.1), which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. Nitrates are thus termed nitrovasodilators. In their action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Nitrates also have a coronary vasodilator effect which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Described in this chapter are
- Glyceryl Trinitrate, p. 1391.2
- Isosorbide Dinitrate, p. 1412.2
- Isosorbide Mononitrate, p. 1413.3
- Linsidomine, p. 1420.3
- Molsidomine, p. 1441.1
- Pentaerithrityl Tetranitrate, p. 1465.1
- Propatylnitrate, p. 1478.3
- Sodium Nitroprusside, p. 1497.1

Potassium-channel openers

Potassium-channel openers (potassium-channel activators) have been used in the management of hypertension; nicorandil is used in angina pectoris. They have a direct relaxant effect on smooth muscle. They act at potassium channels to allow cellular efflux of potassium which hyperpolarises the cell membrane and leads to a reduction in intracellular calcium. The reduction in intracellular calcium produces relaxation of smooth muscle. Activation of potassium channels in blood vessels produces vasodilatation. Potassium-channel openers may also have potential use in other conditions caused by smooth muscle contraction, for example asthma and urinary incontinence.

Described in this chapter are
- Nicorandil, p. 1446.2

Prostaglandins

Prostaglandins (p. 2598.1) are endogenous substances with a wide range of actions. Epoprostenol (the synthetic form of prostacyclin or prostaglandin I_2) and its analogues have vasodilator and antiplatelet properties and are used in pulmonary hypertension and peripheral vascular disease, and to prevent clotting of blood in extracorporeal circuits. Limaprost, an analogue of alprostadil (prostaglandin E_1), has similar properties and is used in peripheral vascular disease.

Described in this chapter are
- Beraprost, p. 1316.2
- Epoprostenol, p. 1374.3
- Iloprost, p. 1408.1
- Limaprost, p. 1420.3
- Treprostinil, p. 1518.1

Sympathomimetics

Sympathomimetics produce either direct or indirect stimulation of adrenergic receptors and have various effects depending on the specific receptors involved. Their actions and uses are described in more detail on p. 1507.3. In cardiovascular disorders, they are mainly used for their $alpha_1$ and $beta_1$ properties to provide haemodynamic support in the management of acute heart failure and shock.

Sympathomimetics with primarily non-cardiovascular uses include alpha agonists, such as phenylephrine (p. 1672.2), pseudoephedrine (p. 1676.1), and naphazoline (p. 1669.3), which are used to produce vasoconstriction of the nasal mucosa for the symptomatic relief of nasal congestion. Apraclonidine (p. 2003.3) and brimonidine (p. 2004.3) are examples of sympathomimetics with $alpha_2$-agonist properties that are used to lower intra-ocular pressure and treat glaucoma. $Beta_2$ agonists are used as bronchodilators and in premature labour and are described under Bronchodilators and Anti-asthma Drugs, p. 1195.1.

Described in this chapter are
- Adrenaline, p. 1292.1
- Amezinium, p. 1298.3
- Denopamine, p. 1350.3
- Dimetofrine, p. 1362.2
- Dobutamine, p. 1365.3
- Docarpamine, p. 1367.1
- Dopamine, p. 1367.2
- Dopexamine, p. 1368.3
- Etilefrine, p. 1379.1
- Ibopamine, p. 1407.1
- Isoprenaline, p. 1411.3
- Mephentermine, p. 1429.3
- Metaraminol, p. 1430.1
- Methoxamine, p. 1430.2
- Midodrine, p. 1437.3
- Noradrenaline, p. 1458.2
- Norfenefrine, p. 1459.1
- Oxedrine, p. 1463.1
- Oxilofrine, p. 1463.2
- Pholedrine, p. 1469.3

Thrombolytics

Thrombolytics are used in the treatment of thromboembolic disorders such as myocardial infarction, peripheral arterial thromboembolism, and venous thromboembolism (deep-vein thrombosis and pulmonary embolism), and some may be used in ischaemic stroke. They are also used to clear blocked cannulas and shunts.

Thrombolytics activate plasminogen to form plasmin, a proteolytic enzyme that degrades fibrin and thus produces dissolution of clots. Some thrombolytics, such as alteplase, act only on fibrin-bound plasminogen and have little effect on circulating, unbound plasminogen; these thrombolytics are termed fibrin-specific agents. Thrombolytics, such as streptokinase, that affect circulating, unbound as well as fibrin-bound plasminogen are termed fibrin-nonspecific agents. Although it has been suggested that the degree of fibrin specificity should influence the risk of haemorrhage, the clinical significance of this has not been established (see Haemorrhage under Adverse Effects of Streptokinase, p. 1505.3).

Described in this chapter are
- Alteplase, p. 1296.3
- Anistreplase, p. 1306.1
- Defibrotide, p. 1350.1
- Desmoteplase, p. 1351.2
- Fibrinolysin, p. 1382.3
- Monteplase, p. 1441.1
- Pamiteplase, p. 1464.2
- Plasminogen, p. 1471.3
- Reteplase, p. 1486.2
- Saruplase, p. 1489.2
- Staphylokinase, p. 1502.3
- Streptokinase, p. 1503.1
- Tenecteplase, p. 1510.2
- Urokinase, p. 1520.3

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2. Verstraete M. Third-generation thrombolytic drugs. *Am J Med* 2000; **109:** 52–8.

Vasodilators

Vasodilator is a broad term applied to drugs that produce dilatation of blood vessels. The main groups of drugs producing vasodilatation are ACE inhibitors (p. 1282.2), nitrates (above), and direct-acting vasodilators.

Direct-acting vasodilators act predominantly on the arterioles reducing peripheral resistance and producing a fall in blood pressure. Their main use is in hypertension, although other drugs are generally preferred. Some of them are used in hypertensive crises.

Described in this chapter are
- Cadralazine, p. 1330.1
- Diazoxide, p. 1351.3
- Dihydralazine, p. 1358.3
- Hydralazine, p. 1401.2
- Minoxidil, p. 1438.3
- Todralazine, p. 1516.1
- Tolazoline, p. 1516.2

Other vasodilators may be used for ischaemic heart disease.

Described in this chapter are
- Dilazep, p. 1359.1
- Fendiline, p. 1381.1
- Hexobendine, p. 1401.1
- Oxyfedrine, p. 1464.1
- Ranolazine, p. 1484.3
- Trapidil, p. 1517.3
- Trimetazidine, p. 1520.1

Vasodilators are also used for cerebral and peripheral vascular disorders. Some of these are now thought to improve microcirculatory flow disturbances by altering the rheological properties of blood or tissue metabolism, and this may be more important than their vasodilator effects. Described in this chapter are

Azapetine, p. 1313.1
Bamethan, p. 1314.1
Bencyclane, p. 1315.1
Buflomedil, p. 1328.3
Calcitonin Gene-related Peptide, p. 1330.1
Cetiedil, p. 1334.3
Cyclandelate, p. 1347.1
Di-isopropylammonium Dichloroacetate, p. 1359.1
Fasudil, p. 1380.2
Ifenprodil, p. 1408.1
Inositol Nicotinate, p. 1410.3
Naftidrofuryl, p. 1443.3
Nicotinyl Alcohol, p. 1447.1
Pentoxifylline, p. 1465.3
Propentofylline, p. 1479.1
Raubasine, p. 1485.1
Xantinol Nicotinate, p. 1535.3

Management of Cardiovascular Disorders

Management of the main cardiovascular disorders is discussed in the following sections. These overviews focus on pharmacological therapy, but other options are also mentioned where they form an important part of treatment.

In the **heart**, disorders of the vessels, valves, myocardium, or rhythm may inhibit its efficiency as a pump, and such disorders are described under Ischaemic Heart Disease (p. 1254.2), Structural Heart Diseases (p. 1261.3), and Disorders of Heart Rhythm (p. 1266.1). In the **circulation**, disorders of arteries, veins, and capillaries may inhibit the delivery of blood to the periphery or its return to the lungs and heart and are discussed in the section named Peripheral Vascular Diseases (p. 1272.3), while disorders that primarily affect delivery of blood to the brain are discussed in the section named Cerebrovascular Diseases (p. 1269.2). The risk of developing cardiovascular disease, and current approaches to reducing this risk, are discussed in the first section, Raised Cardiovascular Risk (below). The final section (p. 1276.2) addresses the management of miscellaneous cardiovascular disorders.

Raised Cardiovascular Risk

The risk of developing cardiovascular disease depends on many factors, and these are described and discussed below along with general approaches to reducing risk. Hyperlipidaemias, atherosclerosis, and hypertension, while not in themselves usually life-threatening or even symptomatic, greatly increase the risk of developing symptomatic cardiovascular disease, and specific approaches to their management are also described in this section.

Cardiovascular risk reduction

Atherosclerotic cardiovascular disease includes ischaemic or coronary heart disease (myocardial infarction and angina pectoris), ischaemic stroke, and peripheral vascular disease. Ischaemic heart disease, in particular, is a major cause of mortality in developed countries, and cardiovascular disease overall is associated with considerable morbidity. The benefits of intervention are well established in patients at high risk of cardiovascular disease, and identification and treatment of such people is therefore an important healthcare strategy.[1-9]

The risk of having a cardiovascular event varies between individuals and epidemiological studies have established several factors, both fixed and modifiable, that are associated with increased risk. Risk factors tend to have cumulative effects, but not all are of equal weight and various algorithms have been developed that allow risk to be calculated at an individual level.[3,4,10,11]

The presence of overt atherosclerosis confers the highest risk. This is particularly so where a cardiovascular event such as myocardial infarction or ischaemic stroke has already occurred but also applies to patients with symptoms of angina or peripheral vascular disease. Patients with diabetes (type 1 or type 2) have a similar level of risk to those with atherosclerosis, even when treated. The presence of left ventricular hypertrophy also indicates high risk. Other fixed factors that add to the risk include age, sex, and family history, and these are also important in the population as a whole.

The established **modifiable risk factors** are tobacco smoking, raised blood pressure, and raised blood-lipid concentrations.[12,13] Other risk factors that have been associated with cardiovascular disease but whose relevance is less clear[14] include lack of exercise, abnormal blood clotting profile, hyperhomocysteinaemia, hyperuricaemia, and raised high-sensitivity C-reactive protein concentrations. Obesity is an established risk factor,[15] but paradoxically appears to be protective in patients with overt cardiovascular disease.[16,17] Psychosocial factors such as stress may also be involved.[18,19] Patients with abdominal obesity, hypertension, dyslipidaemia, and glucose intolerance are considered to have the **metabolic syndrome**, and are at increased risk of both cardiovascular disease and diabetes mellitus.[20-24]

The aim of cardiovascular risk reduction is to prevent clinical events occurring in people without manifestations of atherosclerosis (**primary prevention**) and to prevent further events in those with established atherosclerotic disease (**secondary prevention**). In both cases, the general approach is to abolish or reduce any modifiable risk factors that are present; for secondary prevention specific interventions may be appropriate depending on the existing disease (see individual disease reviews for details). Guidelines[1,3-8] have been published for identification and management at the individual level, including specific guidelines for women,[25] the elderly,[26] diabetics,[27,28] and those with metabolic syndrome.[24] There are also specific guidelines for reduction of cardiovascular risk perioperatively.[29] Since atheroma development may begin in childhood, and the prevalence of risk factors is increasing in young people,[30] approaches to risk reduction should also be considered from an early age,[31] especially in those at high risk.[32]

Lifestyle and dietary modifications are the mainstay of risk reduction, and should be the first step for both primary and secondary prevention. They include advice not to smoke, avoidance of obesity, increased exercise, moderation of alcohol intake, and a diet that is low in saturated fat and high in fruit, vegetables, and fish.[1,3-6,8,33-36] Similar advice is also important at a population level, as part of general health promotion and education, although this may produce only modest changes in the overall levels of risk factors.[37] While the incidence of ischaemic heart disease is falling in many parts of the world, the association between changes in classic risk factors and changes in clinical-event rates is weak, suggesting that further approaches are also needed.[38]

For secondary prevention and for patients with established risk factors, lifestyle modifications are rarely adequate alone and drug therapy is often also needed. Patients at high risk, such as those with manifestations of atherosclerosis, should begin lifestyle measures and drug treatment at the same time, but most other patients should have formal risk assessment before starting drug therapy. Specific strategies to aid smoking cessation may be required, and these are discussed on p. 2570.2. Similarly, while both blood pressure and lipid concentrations may be improved by lifestyle changes, drug therapy is often required for established hypertension (see p. 1251.1) or hyperlipidaemias (p. 1248.1). Drug therapy may also be required for the management of obesity (see p. 2315.1); rimonabant, which showed that endocannabinoid receptor antagonists could improve metabolic risk factors as well as body-weight, was withdrawn from the market due to adverse psychiatric effects, but similar approaches are under investigation.[39] Tight control of blood glucose is important in diabetic patients, although the benefit in terms of cardiovascular outcomes is not established (see Prevention of Diabetic Complications, p. 462.3). Influenza vaccination is also recommended;[40] observational studies suggest the risk of cardiovascular events is reduced in vaccinated patients, although there is a lack of evidence from controlled studies.[41] Antithrombotic therapy has an important role, and is discussed further below, along with the use of lipid regulating drugs, antihypertensives, and other drugs in patients with and without overt disease.

Antithrombotic therapy has been widely used in patients with atherosclerotic cardiovascular disease since most acute events result from thrombosis at the site of an atherosclerotic plaque. *Antiplatelet drugs* have been investigated for primary and secondary prevention of various cardiovascular disorders. Numerous studies[42,43] have established that antiplatelet therapy reduces the risk of subsequent cardiovascular events but that the risk of bleeding is increased, and absolute benefit therefore depends on the individual level of risk. In patients with a previous vascular event, the use of antiplatelet drugs for secondary prevention is well established.[3-6,44] Aspirin, started in the acute phase and continued long-term, reduces the risk of re-infarction and death after myocardial infarction and should be given indefinitely.[42] Long-term prophylaxis with aspirin also reduces the risk of future serious vascular events, including stroke, in patients who have suffered an ischaemic stroke or transient ischaemic attack,[42,45,46] regardless of age.[47] Studies also support the benefits of antiplatelet drugs for primary prevention in individuals with established cardiovascular risk factors. For example, aspirin appears to reduce the risk of myocardial infarction in patients with chronic stable angina,[48] males with risk factors for occlusive vascular disease,[49] and hypertensive patients,[50] but has little effect on the overall incidence of stroke.[43,49,50] In patients with peripheral vascular disease, benefit has been reported with various antiplatelet drugs.[51,52] The Primary Prevention Project,[53] a study in patients with at least one major risk factor, showed a reduction in cardiovascular mortality and in a composite of cardiovascular events including death, myocardial infarction, and stroke. Aspirin is also widely used for primary prevention in diabetics, although specific evidence of benefit is limited.[54-57]

Primary prevention using aspirin in healthy individuals is more controversial; studies have produced conflicting results, and there may be differences between males and females. A study in healthy male physicians in the UK[58] found no reduction in the incidence of fatal and non-fatal myocardial infarction in those who had taken aspirin, while a similar study in the US[59] showed a reduction in subjects 50 years of age or older; both showed a slight non-significant increase in the number of disabling strokes which, in the US study, were attributed to cerebral haemorrhage. In women, a large observational study in healthy US nurses[60] indicated that aspirin might reduce the risk of first myocardial infarction, but a randomised study[61] found no effect on either myocardial infarction or death, although the incidence of stroke was reduced. Meta-analyses[43,62,63] have generally concluded that, while there may be benefit for some outcomes (myocardial infarction in men and stroke in women), the effect on overall cardiovascular events may not outweigh the increased risk of bleeding and routine use of aspirin is not recommended.

Aspirin has been the most widely studied antiplatelet drug and appears to be effective over a range of doses (see p. 22.3). However, some patients have events while taking aspirin and it has been suggested that they may have aspirin resistance, although the clinical significance and implications for management are not clear.[64,65] Alternative antiplatelet drugs may be used in patients who are intolerant of aspirin (although aspirin with a proton pump inhibitor is preferred if intolerance is due to gastrointestinal effects[66]), and combination therapy may also be considered. In the CAPRIE study,[67] clopidogrel was shown to be at least as effective as aspirin in reducing cardiovascular events, including myocardial infarction and stroke, in individuals at high risk. In patients with ischaemic stroke, dipyridamole, given alone or with aspirin, is effective for secondary prevention,[68] but use of clopidogrel with aspirin increases the risk of bleeding without reducing the risk of ischaemic events.[69] Clopidogrel with aspirin is of benefit in patients with acute coronary syndromes, but in patients with high cardiovascular risk who do not present acutely the increased bleeding risk appears to outweigh any benefit.[70]

Oral anticoagulants have been used as an alternative to antiplatelet drugs or as additional therapy. Oral anticoagulants alone may be more effective than antiplatelet therapy but the risk of bleeding is increased,[49,71] and they are generally only recommended in patients unable to take antiplatelet drugs or in whom they are ineffective. The relative risks and benefits of combination therapy are more controversial,[72,73] and there is limited evidence on which to base decisions, particularly in patients with accepted indications for both anticoagulants and antiplatelet drugs. In general, for patients taking anticoagulants for other indications, antiplatelet drugs appear to add little further benefit in terms of cardiovascular risk reduction except in some patients with mechanical heart valves.[72] However, in patients with acute coronary syndromes or coronary stenting, the indication for antiplatelet drugs may be stronger, and decisions are more complex.[73]

Lipid lowering therapy has an established role in cardiovascular risk reduction, and the benefits of statins, in particular, have been shown in a wide range of patients. Meta-analyses[74-79] of randomised studies have found that statins improve outcomes when used for primary or secondary prevention, and a large epidemiological study[80] confirmed these findings. Benefit occurs across a wide range of patients, including those with raised or average cholesterol concentrations, women, and older individuals. The absolute benefit depends on the patient's initial cardiovascular risk and the degree of cholesterol reduction achieved,[77] and increased benefit has been reported[81,82] with the use of intensive lipid lowering regimens. Other lipid lowering drugs that have shown benefit include fibrates[83] and derivatives such as gemfibrozil, which was effective for secondary prevention in a study in men with low HDL-cholesterol.[84] A reduction in cardiovascular mortality has also been found with omega-3 fatty acids in some populations,[85] but their overall effect remains unclear.[86] Ezetimibe, which adds to the LDL-lowering effects of statins, has not yet been shown to have a clinical benefit.[87]

LDL-cholesterol appears to be the most important target, but other mechanisms may be involved. Low HDL-cholesterol is an established risk factor for cardiovascular disease, but the benefits of drugs specifically targeting this are controversial,[88,89] and none of the approaches to increasing HDL-cholesterol yet has an established role.[90]

There has been concern that there might be an association between low cholesterol concentrations and increased morbidity and mortality from non-cardiac causes including haemorrhagic stroke, cancer, accidents and suicide, and chronic respiratory, liver, and bowel disease.[91-96] Although controlled studies suggest that the

risk of haemorrhagic stroke may be increased,[97] meta-analyses have shown that statin therapy reduces both cardiovascular and all-cause mortality,[76,77] and that there is no significant increase in non-illness mortality.[98]

Antihypertensive drugs have an established role for cardiovascular risk reduction in patients with hypertension, and benefit may extend to patients with normal blood pressures, although this is less clear. There is also debate about which types of antihypertensive drugs are most effective; some studies have suggested that certain drug classes have additional benefits, but others dispute these claims. A meta-analysis[99] concluded that, given a similar reduction in blood pressure, the five main classes of antihypertensives had equivalent effects overall, irrespective of the presence or absence of vascular disease and the pretreatment blood pressure, and the authors suggested that combinations of low-dose antihypertensives might have a particular role.

ACE inhibitors are one of the drug groups for which a particular role has been suggested, as they have been shown to reduce cardiovascular events in a wide range of patients. Studies in patients with heart failure,[100,101] and the HOPE study[102] in patients with high cardiovascular risk, suggested benefits beyond lowering of blood pressure, possibly associated with blockade of the renin-angiotensin system.[103] *Angiotensin II receptor antagonists* appear to have similar effects.[104,105]

Several other ***general approaches*** to reducing cardiovascular risk have been tried, mostly targeted against potential risk factors or the atherosclerotic process itself, but none has an established role. Approaches tried include: use of *folic acid and vitamin B supplements* to reduce homocysteine concentrations; dietary *antoxidants* to reduce the progression of atherosclerosis; and *HRT* in women, based on the lower incidence of cardiovascular disease in premenopausal women than in men of a comparable age. These interventions are discussed further under Atherosclerosis (p. 1250.2).

The multifactorial nature of cardiovascular risk, the presence of risk factors in a wide section of the population, and the difficulty in applying lifestyle and dietary changes has led to the suggestion that routine use of a combination of drugs with established effects on cardiovascular risk might be beneficial.[106] It was estimated that a combination preparation (the polypill) containing a statin, aspirin, folic acid, and drugs from three classes of antihypertensive given to all individuals aged over 55 years could prevent about 80% of cardiovascular disease in a western society. Observational studies suggest that combinations of cardiovascular drugs are effective,[107] and formulation of such a combination (without folic acid) appears to be feasible,[108] but clinical evidence of benefit is not yet available and the role of such combinations remains to be confirmed.

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Hyperlipidaemias

Hyperlipidaemia results from a disorder in the synthesis and degradation of plasma lipoproteins. Although the main concern has generally been the overall elevation of plasma lipids (hyperlipidaemia), it is now increasingly recognised that the balance of lipids in the plasma is also important, and the term dyslipidaemia is often used. Dyslipidaemias have genetic and other causes, and are often associated with a high-fat diet. Although patients with hyperlipidaemia may have symptoms that require treatment, the major concern is their increased risk of ischaemic heart disease.

Table 1. Principal lipoproteins and associated lipids.

Lipoprotein	Lipid
Chylomicron	Triglyceride
VLDL	Triglyceride
IDL	Cholesterol and triglyceride
LDL	Cholesterol
HDL	Cholesterol

The **lipids** that are of relevance in hyperlipidaemias are cholesterol, an essential component of cell membranes and a precursor of steroid hormone synthesis, and triglyceride, an important energy source. They are transported in the blood as lipoproteins.

Lipoproteins are complex particles[1,2] comprising a hydrophilic coat of phospholipids, free cholesterol, and specific polypeptides termed apolipoproteins (apoproteins) around a core of varying proportions of triglyceride and cholesterol (present as cholesteryl ester). The lipoproteins are characterised by their density, which in general increases as they are metabolised and the proportion of cholesteryl ester to triglyceride increases. Table 1, below, lists the principal lipoproteins and their associated lipids. The lowest density lipoproteins are the **chylomicrons** which transport triglyceride derived from dietary fat, and the **VLDL** (very low-density lipoproteins; pre-β lipoproteins) which transport endogenous triglyceride mainly synthesised in the liver, to peripheral tissues. The triglyceride is hydrolysed in the peripheral tissues by lipoprotein lipase, which is activated by apolipoprotein CII present in the lipoproteins. Both chylomicrons and VLDL are progressively depleted of triglyceride, yielding increasingly dense lipoprotein particles termed 'remnant' particles. Chylomicron remnants are cleared rapidly from plasma by the liver where they are metabolised, releasing free cholesterol. VLDL remnants, which include **IDL** (intermediate-density lipoproteins; broad β-lipoproteins), may also be cleared by the liver or converted to **LDL** (low-density lipoprotein; β-lipoprotein). **HDL** (high-density lipoproteins; α-lipoproteins) are synthesised in the liver and small intestine and have a role in the transport of cholesterol from the peripheral tissues back to the liver, where it is either utilised or excreted in the bile as bile acids and unesterified cholesterol. The majority is reabsorbed from the intestines and a small proportion is excreted in the faeces.

Defining hyperlipidaemia is difficult due to the marked variation in lipid concentrations between different populations. Apparently 'normal' lipid concentrations may still be associated with a significant risk of cardiovascular disease, and this may depend on which lipids are affected. Epidemiological data show a progressive and continuous relationship between plasma-cholesterol concentrations and mortality from ischaemic heart disease. The Framingham Study[3] found a 9% increase in death from cardiovascular disease for each 10 mg/dL (0.26 mmol/litre) rise in total plasma-cholesterol concentration. Plasma-cholesterol concentrations of 5.2 mmol/litre (200 mg/dL) or less are associated with a low risk of ischaemic heart disease. The increased risk is due mainly to raised LDL-cholesterol. In contrast, HDL-cholesterol is inversely associated with ischaemic heart disease. Low plasma concentrations of HDL-cholesterol (below 1 mmol/litre or 40 mg/dL) are generally associated with increased risk of ischaemic heart disease, whereas high concentrations are protective.[4] There also appears to be an association between plasma-triglyceride concentrations and risk of ischaemic heart disease.[5] Some triglyceride-rich lipoproteins such as chylomicron remnant particles and IDL are atherogenic and the risk of heart disease increases as triglyceride concentrations increase in patients who also have high total cholesterol and low HDL-cholesterol concentrations. Hypertriglyceridaemia alone (greater than 2.3 mmol/litre or 200 mg/dL) may be an independent risk factor for ischaemic heart disease, but any clinical benefit from intervention to lower triglyceride levels is yet to be established.[6] However, the absolute risk for any individual also depends on other cardiovascular risk factors, including smoking and hypertension, and treatment decisions should in general be based on assessment of overall risk (see Cardiovascular Risk Reduction, p. 1246.1).

Hyperlipidaemias may result from several underlying defects and various methods have been used for classification.[7] A simple system is to divide them on the basis of whether raised serum cholesterol (hypercholesterolaemia), triglyceride (hypertriglyceridaemia), or both (mixed or combined hyperlipidaemia) is the predominant abnormality. Alternatively, the Frederickson/WHO method (see Table 2, below) describes them in terms of the lipoprotein abnormality (hyperlipoproteinaemia), although this is less useful clinically. Within these systems, primary hyperlipidaemias are those with an underlying genetic defect, whereas secondary hyperlipidaemias are caused by another disease state or by drug therapy. Primary and secondary causes of hyperlipidaemia may co-exist.

Primary hyperlipidaemias (see Table 3, p. 1249) may be monogenic, relating to a single genetic defect, but much more commonly they are due to the interaction of several genes with dietary and other factors (polygenic). Individuals with common, polygenic (multifactorial) hypercholesterolaemia tend to have only mild or moderate elevations of plasma-cholesterol, whereas those with monogenic hyperlipidaemias tend to have much higher plasma-lipid concentrations.

Secondary hyperlipidaemias may have various causes. Diseases producing hypertriglyceridaemia include diabetes mellitus, chronic renal failure, and bulimia. Hypercholesterolaemia can occur in hypothyroidism, nephrotic syndrome, biliary obstruction, and anorexia nervosa. Drugs that may produce hypertriglyceridaemia and/or hypercholesterolaemia include thiazide diuretics (in high doses), beta blockers, corticosteroids, and antivirals in patients with HIV infection. Excessive alcohol intake may produce elevated plasma-triglyceride concentrations.

The degree of hyperlipidaemia seen in patients with either primary or secondary hyperlipidaemia is influenced by various factors, including, importantly, diet. A diet rich in saturated fat and cholesterol and poor in fibre can produce hypercholesterolaemia. Obesity further predisposes to hyperlipidaemia. Other factors that may influence lipid concentrations include pregnancy, lack of exercise, and smoking. After myocardial infarction cholesterol levels may be temporarily reduced for several weeks; therefore, to measure the patient's usual level of cholesterol, blood samples should be taken within a few hours of the infarction.

The majority of people with hyperlipidaemia have plasma-lipid concentrations that are only mildly or moderately elevated, and they show no **clinical symptoms**. At the other end of the spectrum, severe hypercholesterolaemia can cause tendon, tuberous, or planar xanthomas, xanthelasma, and arcus corneae; it is also associated with an increased risk of ischaemic stroke. Severe hypertriglyceridaemia can cause acute severe abdominal pain due to pancreatitis; hepatic and splenic enlargement, eruptive xanthomas, and lipaemia retinalis may also occur. However, the main concern in patients with hyperlipidaemias is the increased risk of ischaemic heart disease. In patients with very severe hypercholesterolaemia, such as familial hypercholesterolaemia, this may occur at a very young age; in those with the heterozygous form onset of heart disease during their 20s or 30s is not unusual, and in the rarer homozygous form ischaemic heart disease may develop by the age of 10.

Treatment of hyperlipidaemias. In patients with clinical symptoms, treatment is indicated to promote the regression or non-progression of disfiguring xanthomas, or to prevent attacks of acute pancreatitis in those with severe hypertriglyceridaemia. The main aim of treatment, however, particularly in patients with only mildly elevated lipids, is to reduce the risk of ischaemic heart disease.[1,8-15] Although most clinically apparent atherosclerotic disease occurs in adults, it is increasingly recognised that children and adolescents should also be considered for treatment.[16-19]

Table 2. Classification of hyperlipoproteinaemias.

WHO classification	Lipoproteins elevated	Plasma lipids affected	
		Cholesterol	Triglyceride
I	Chylomicrons	Normal or elevated	Elevated
IIa	LDL	Elevated	Normal
IIb	LDL and VLDL	Elevated	Elevated
III	VLDL with abnormally high cholesterol content	Elevated	Elevated
IV	VLDL	Normal or elevated	Elevated
V	Chylomicrons and VLDL	Elevated	Elevated

Table 3. Primary hyperlipidaemias.

	Lipoprotein Abnormality (WHO type)	Prevalence	Typical lipid concentrations (mmol/L) Cholesterol	Triglyceride	Risk of IHD	Pancreatitis
Common (polygenic) hypercholesterolaemia	IIa or IIb	Very common	6.5 to 9.0	< 2.3	+	–
Familial hypercholesterolaemia	IIa or IIb	Moderately common	7.5 to 16.0	< 2.3	+++	–
Familial hypertriglyceridaemia	IV or V	Common	6.5 to 12.0	10 to 30	?	++
Familial combined hyperlipidaemia	IIa, IIb, IV, or V	Common	6.5 to 10.0	2.3 to 12.0	++	–
Familial dysbetalipoproteinaemia or remnant hyperlipoproteinaemia	III	Uncommon	9.0 to 14.0	9.0 to 14.0	++	+
Abnormal lipoprotein lipase function	I	Rare	< 6.5	10.0 to 30.0	–	+++

+ = elevated risk; – = no risk; ? = uncertain risk; IHD = ischaemic heart disease

Since the relationship between plasma-cholesterol concentrations and ischaemic heart disease is continuous, the value of the former at which treatment with lipid regulating drugs should be started has been widely debated. Guidelines recommend that the decision to treat should be based on the overall risk profile of the patient and that other risk factors should also be treated (see Cardiovascular Risk Reduction, p. 1246.1).

- Specifically, British guidelines[20] advise that all high-risk patients should have drug therapy, including patients with established cardiovascular disease, most diabetics, patients with a ratio of total plasma cholesterol to HDL-cholesterol 6.0 or higher, and those with familial dyslipidaemias. In all cases, the target for therapy is total cholesterol below 4.0 mmol/litre and LDL-cholesterol below 2.0 mmol/litre; alternatively, a 25% reduction in total cholesterol and a 30% reduction in LDL-cholesterol should be the target if this results in a lower concentration.
- European guidelines[21] suggest that diabetics and patients with established cardiovascular disease should have a target of total cholesterol below 4.5 mmol/litre (and below 4.0 mmol/litre if feasible) and LDL-cholesterol below 2.5 mmol/litre (and below 2.0 mmol/litre if feasible); patients with total cholesterol above 8 mmol/-litre or LDL-cholesterol above 6 mmol/litre should be treated irrespective of their other risk factors.
- US guidelines[2,22] suggest that drug treatment should be considered if the LDL-cholesterol level is 190 mg/dL or higher. For patients with 2 or more risk factors, drug therapy should be considered if the LDL-cholesterol is 160 mg/dL or higher, and for those with existing cardiovascular disease, diabetes mellitus, or particularly high risk, drug therapy should be considered if LDL-cholesterol is 130 mg/dL or higher. The US guidelines also give target LDL-cholesterol levels of less than 160 mg/dL, less than 130 mg/dL, and less than 100 mg/dL, respectively, for the three risk groups. However, it has been suggested[23] that treatment may be appropriate in some very high risk patients at LDL-cholesterol concentrations below 100 mg/dL and that a goal of below 70 mg/dL may be reasonable; others consider that there is little good clinical evidence to support such targets.[24] Although low HDL-cholesterol is an additional risk factor, the benefits of raising HDL-cholesterol are not established and no target is therefore specified in the current guidelines.

The main methods of treating hyperlipidaemias are dietary and lifestyle changes and the use of lipid regulating drugs.[2,20-22] Some surgical and other procedures may also be used in familial hypercholesterolaemia (see below).

Dietary therapy should be started in all patients with hyperlipidaemia with the aim of weight reduction in the obese and a reduction in total fat intake. Dietary recommendations[20,22] include a reduction in saturated fatty acids, restriction of *trans* fatty acids, increased consumption of fish or other sources of long-chain n-3 polyunsaturated fatty acids, and increased intake of fruit and vegetables; the intake of cholesterol and n-6 polyunsaturated fatty acids should be restricted. Increased physical exercise is also recommended. Moderation of alcohol intake is advised, particularly in patients with hypertriglyceridaemia, in whom alcohol may precipitate pancreatitis. However, more rigorous diet than that often recommended may be necessary for diet alone to be of much value,[25] and most patients will require drug therapy to achieve target lipid concentrations. Patients at low cardiovascular risk should have a trial of dietary therapy before drugs are started, but in those with established cardiovascular disease or major risk factors drug therapy and dietary changes may be started at the same time.

The principal groups of **lipid regulating drugs** (hypolipidaemic drugs) are the statins, fibric acid derivatives and related compounds, bile-acid binding resins, nicotinic acid and its derivatives, the omega-3 marine triglycerides, and ezetimibe.[1,10-12,26,27]

- *Statins* (HMG-CoA reductase inhibitors) reduce cholesterol by stimulating an increase in LDL-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase HDL-cholesterol. They are generally considered to be the most effective lipid lowering drugs.
- *Fibrates* inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of VLDL; they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia.
- *Bile-acid binding resins* lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting mainly in a reduction of LDL-cholesterol.
- *Nicotinic acid* inhibits production of VLDL in the liver; it lowers LDL-cholesterol and triglycerides and increases HDL-cholesterol, but adverse effects may limit its use.
- *Omega-3 fatty acids* mainly reduce triglycerides.
- *Ezetimibe* is a cholesterol absorption inhibitor and reduces intestinal absorption of both dietary and biliary cholesterol.[28]
- *Dietary supplements* containing soluble fibre, such as guar gum or ispaghula, or plant stanols or sterols, may also be used to reduce cholesterol absorption; garlic preparations and other supplements have also been used, although their role is not established.[29]
- *Other drugs* that have been tried include cholesteryl ester transfer protein inhibitors, which increase HDL; however, they have not yet been shown to have clinical benefits,[30] and development of torcetrapib was stopped as it was found to increase mortality. In postmenopausal women, oestrogen therapy reduces lipid concentrations, but the adverse effects may outweigh any benefit (see Effects on the Cardiovascular System, p. 2248.2); soya protein may have a similar effect.

Choice of therapy ideally depends upon the lipid profile of the individual patient since the drug groups differ in their effects on the different lipid components.

In practice, most patients have common, polygenic *hypercholesterolaemia*, and can be treated effectively with statins as first-line therapy. Bile-acid binding resins or nicotinic acid may be alternatives, but are generally less well tolerated. Ezetimibe or fibrates may also be used, but are generally only recommended when patients are unable to take statins.[31,32] Combination therapy may be required in some patients to reach target lipid concentrations, although there is limited evidence that combination therapy has any benefit over high-dose statins.[33] The increased risk of adverse effects in patients taking statins and fibrates together should also be considered (see Effects on Skeletal Muscle under Adverse Effects of Simvastatin, p. 1493.2). Ezetimibe adds to the LDL-lowering effect of statins and appears to be safe, but there is no evidence that this improves clinical outcomes.[34]

In patients with *hypertriglyceridaemia*, statins or fibrates may be used, although fibrates should only be given first-line in severe, isolated hypertriglyceridaemia;[32] resins should not be used alone since they may increase triglyceride concentrations.

Patients with the less common *familial dyslipidaemias*[35] generally have higher lipid concentrations and require more intensive therapy. Specific treatment strategies are as follows:

- ***FAMILIAL HYPERCHOLESTEROLAEMIA.*** Patients with familial hypercholesterolaemia usually have very high plasma-cholesterol concentrations, which rarely respond adequately to diet alone and drug therapy is therefore often necessary in this high-risk group. For children with familial hypercholesterolaemia, drug treatment should be started by the age of 10 years; earlier or more intensive treatment may be considered in those at high risk of early coronary heart disease.[36] Aggressive therapy may lead to regression of atherosclerotic lesions.[37] The first-line drugs are the statins; high-intensity treatment is recommended, with the aim of reducing LDL-cholesterol by more than 50%,[36] but even moderate doses have been shown to reduce the risk of ischaemic heart disease.[38] Ezetimibe has been recommended as an alternative, and may also be given in addition to a statin if a further reduction in LDL-cholesterol is required.[36] Alternatives such as bile-acid binding resins, nicotinic acid, or fibrates, may be required, alone or with statins, in some patients. In some forms of familial hypercholesterolaemia, and where plasma-cholesterol concentrations are very high, plasma-triglyceride concentrations may also be raised. In these cases a fibric acid derivative or nicotinic acid may be effective, and in more severe cases the combination of a bile-acid binding resin together with a fibric acid derivative or a statin may be used.
  In the homozygous form of familial hypercholesterolaemia there may be a complete lack of functional LDL-receptors and drugs that act by increasing LDL-receptors, such as statins and bile-acid binding resins, may be less effective. However, statins may be useful as adjunctive therapy in those patients who have some LDL-receptor function. Mipomersen, an antisense oligonucleotide that inhibits apolipoprotein B synthesis, may also be used as an adjunct to other lipid regulating drugs in homozygous patients.[39] However, concerns about cardiovascular safety and hepatotoxicity may limit its use.
  In patients with the homozygous form liver transplantation is the most definitive treatment. Plasma exchange (weekly or fortnightly) or more selective procedures such as LDL apheresis, including the use of heparin to precipitate LDL (the HELP system—Heparin Extracorporeal LDL Precipitation) may also be used in combination with lipid regulating drugs. Gene therapy is under investigation as a treatment for familial hypercholesterolaemia.
- ***FAMILIAL HYPERTRIGLYCERIDAEMIA.*** In patients with familial hypertriglyceridaemia dietary therapy is generally adequate, but drugs may be required if there is a high risk of acute pancreatitis, such as in patients with chylomicronaemia,[40] or if there is a family history of atherosclerosis. The risk of acute pancreatitis is high when plasma-triglyceride concentrations are above 20 mmol/litre. Nicotinic acid or the fibric acid derivatives, particularly gemfibrozil, are generally recommended and may be used in combination in severe cases. Omega-3 marine triglycerides may also be of value. In severe intractable hypertriglyceridaemia, particularly type V hyperlipoproteinaemia, norethisterone has been suggested for women or oxandrolone for men.
- ***FAMILIAL COMBINED HYPERLIPIDAEMIA.*** Drug therapy may be used in patients who do not respond to dietary therapy alone. The choice will depend on the predominant lipid abnormality. A statin is the first choice, particularly in cases where hypercholesterolaemia is predominant. A fibric acid derivative may be used when hypertriglyceridaemia predominates, and nicotinic acid is useful where plasma concentrations of triglyceride and cholesterol are raised to a similar degree. Bile-acid binding resins should not be used alone since they can aggravate hypertriglyceridaemia, but they may be useful with a triglyceride-lowering drug in some patients.

Treatment with a combination of drugs that lowers both cholesterol and triglyceride concentrations may be required in some patients especially in those with markedly raised plasma concentrations of triglyceride or cholesterol, as treatment of these patients with drugs effective against only the predominant lipid may produce a rise in the plasma-concentrations of the other lipid. The choice of treatment in these cases is largely empirical as responses are not always predictable in individual patients.

- ***FAMILIAL DYSBETALIPOPROTEINAEMIA*** (remnant hyperlipoproteinaemia; remnant particle disease). In this lipid disorder the degree of hyperlipidaemia is usually severe and, although it may respond remarkably to dietary therapy, drug treatment is usually necessary. Fibric acid derivatives, statins, or nicotinic acid may be used.
- ***ABNORMAL LIPOPROTEIN LIPASE FUNCTION*** (chylomicronaemia). Drug therapy is largely ineffective, although fibrates and nicotinic acid may have modest effects. The condition is treated with severe restriction of dietary fat; the diet may be supplemented by medium-chain triglycerides to improve tolerability, but their value is controversial.[8]

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Atherosclerosis

Atherosclerosis is a pathological condition affecting medium and large arteries in which lipid-rich lesions (atheromas) develop in the intimal lining, leading to arterial dysfunction, obstruction of blood flow, and ischaemia. **Ischaemic heart disease** (coronary heart or coronary artery disease; p. 1254.2), which includes angina pectoris (p. 1254.3) and myocardial infarction (p. 1257.1), is the most common manifestation of atherosclerosis and in most industrialised countries ischaemic heart disease is a leading cause of death. Atherosclerosis of peripheral or cerebral arteries leads to peripheral arterial occlusive disease (under Chronic Occlusive Peripheral Arterial Disease, p. 1272.3) or ischaemic stroke (p. 1269.2). Atherosclerotic diseases are thus a major cause of mortality and morbidity and the prevention and treatment of atherosclerosis has an important role in the management of these diseases.

Atherosclerosis is a progressive condition and various stages of atheroma development are recognised.[1-3] Early lesions include fatty streaks, which develop from infancy and are composed of lipid-filled macrophages (foam cells). These progress to fibrous plaques, which consist of a core of lipid and lipid-rich macrophages surrounded by a connective-tissue matrix. Plaques may undergo calcification and may become sufficiently large to obstruct the lumen of the artery. However, acute occlusion more commonly occurs as a result of thrombosis at the site of a plaque, due to endothelial denudation or disruption of the plaque (plaque rupture or fissuring) with exposure of the thrombogenic core. Endothelial dysfunction is an important underlying factor, promoting both the development of atheromas (atherogenesis) and subsequent thrombosis.[4,5] Although symptoms depend on the site of obstruction, atherosclerosis is essentially a systemic condition, and symptoms in one vascular system suggest the presence of more extensive disease. For example, patients with peripheral or cerebrovascular disease are also likely to develop, or to have evidence of, ischaemic heart disease.

The management of atherosclerotic diseases involves treatment of the clinical manifestations (as discussed under the specific diseases) and measures to reduce the risk of cardiovascular events occurring (see Cardiovascular Risk Reduction, p. 1246.1). Approaches targeted more directly at the atherosclerotic process have also been tried, and some of these are discussed below.

Dyslipidaemia is one of the major factors underlying the development of atherosclerosis and lipid lowering has an established role in patients with atherosclerotic disease, reducing the incidence of cardiovascular events and also slowing or even reversing the progression of atherosclerosis. Although low-density lipoprotein (LDL)-cholesterol has been the main target for therapy, it is not entirely clear which lipid fractions are most important or whether some lipid lowering drugs have additional effects. For statins, there appears to be a clear correlation between their effects on LDL and their effects on atherosclerosis, with more intensive therapy leading to lower rates of progression or even to regression of atherosclerotic plaques.[5-7] However, use of adjunctive lipid regulating drugs with statins to further modify the lipid profile is less established. Studies combining statins with ezetimibe[8,9] have failed to show any additional reduction in atherosclerosis, despite further lowering LDL, whereas studies using statins with nicotinic acid,[9,10] which raises high-density lipoprotein (HDL)-cholesterol, have suggested benefit.

Oxidation of LDL is thought to be a crucial step in atherogenesis[11-13] and a number of studies have investigated the use of dietary antoxidants such as vitamins E and C and betacarotene (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1). Although some studies have found a reduction in the progression of atherosclerosis, others have not confirmed this finding, and several large studies have failed to find any effect on the risk of clinical events. Polyphenol compounds found in various foods, including red wine, have also received much attention for their possible role in the prevention of atherosclerosis.

Hyperhomocysteinaemia has been suggested as a risk factor for atherosclerosis, although its importance is not clear.[14] Interventions to reduce homocysteine, such as the use of folic acid or vitamin B supplements (see Cardiovascular Disease, p. 2063.3), have been tried. Some effects on endothelial function have been noted, but there is as yet no evidence that clinical events are reduced. *Hyperuricaemia* may also be a risk factor, although again the benefits of treatment are not yet clear.[15]

Inflammation appears to have an important role in the development and progression of atherosclerosis, and in acute events due to plaque instability.[16,17] Various studies have shown an association between C-reactive protein, a marker of inflammation, and cardiovascular events, although its precise role is unclear.[14] As well as lowering lipids, statins are known to reduce concentrations of C-reactive protein, and this has been shown to correlate with their efficacy.[18] Other non-lipid effects such as improvement of endothelial dysfunction, or an effect on thrombosis, have also been suggested.

Infection is another possible cause of inflammation that has been investigated,[19] and serological and pathological studies have found an association with several organisms. The evidence appears to be strongest for *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), although its precise role in the development or progression of atherosclerosis is unclear.[20] Treatment with antibacterials has been tried in patients with atherosclerotic disorders but any benefit has not yet been confirmed;[19,20] meta-analyses[21,22] of studies using antichlamydial drugs in patients with ischaemic heart disease have found no evidence that they reduced either mortality or further cardiovascular events. There may also be an association between periodontal infection and atherosclerosis, but further study is needed to assess the benefits of treatment.[23]

Coronary artery calcification is associated with the presence of atherosclerosis and measures to reduce calcium deposition have therefore been tried. Raised lipid concentrations appear to be involved in calcification and there is some evidence that statins may reduce progression,[24] although this has not been confirmed in all studies.[25-27] Results with calcium-channel blockers have been mixed (see under Nifedipine, p. 1448.1). Chelation therapy with disodium edetate has also been tried but again, any benefit remains to be established (see Atherosclerosis under Sodium Edetate, p. 1551.1).

Hormonal factors may also play a role in the development of atherosclerosis; women have a lower risk of atherosclerotic disease than men of a comparable age, although the difference narrows with increasing age postmenopausally. HRT lowers lipid concentrations and some angiographic or ultrasound studies have shown beneficial effects on the progress of atherosclerosis, although others have failed to confirm these findings. However, controlled studies do not support a role for HRT in the prevention of cardiovascular disease in postmenopausal women (see Effects on the Cardiovascular System, p. 2248.2).

Therapeutic angiogenesis (the development and growth of blood vessels) is also under investigation to improve perfusion in atherosclerotic diseases. Preliminary studies of growth factor proteins, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), and gene therapy to stimulate VEGF production, have shown promise.[28,29] The use of stem cells is also being investigated.[30] However, since neovascularisation of the vessel wall and plaque angiogenesis may play a role in atherosclerosis, anti-angiogenic therapy may also have potential.[31]

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Hypertension

Hypertension, particularly essential or primary hypertension, is widespread. Although it is usually asymptomatic, hypertension is a major risk factor for cardiovascular morbidity and mortality, especially that associated with stroke, and control of hypertension is therefore a major aspect of cardiovascular risk reduction. National[1-3] and international[4,5] guidelines on management have been published, but several areas of controversy remain,[6,7] and in many patients hypertension continues to be difficult to treat.[8,9]

Definitions. The term ***blood pressure*** generally means arterial blood pressure, that is, the pressure of the blood on artery walls. It is usually measured indirectly in the brachial artery just above the elbow using an appropriately calibrated sphygmomanometer[10] and is expressed in mmHg. Two measurements are made:

- *systolic* or maximum blood pressure (achieved during ventricular contraction of the heart)
- *diastolic* or minimum blood pressure (achieved during ventricular dilatation)

Hypertension means a higher than 'normal' blood pressure; it has been defined as the level of blood pressure above which intervention has been shown to reduce the associated cardiovascular risk. Many factors influence blood pressure, resulting in a bell-shaped distribution curve in the general population, and in consequence it is difficult to define an absolute norm.

Classification and subsequent treatment decisions should be based on blood pressure measurements taken on several occasions over a period that varies according to the severity of hypertension. Ambulatory blood pressure monitoring may have advantages in some situations[1,2,5,10,11] and automated devices for home monitoring may also have a role.[1,5,10] However, home and ambulatory blood pressures tend to be lower than those measured in healthcare settings, and different thresholds for normal and abnormal values apply.[1,5,10,11] Guidelines generally use conventional blood pressure measurements to determine treatment decisions since this is the basis of most outcome studies.

Normal adult blood pressure has been arbitrarily defined as a systolic pressure below 130 mmHg together with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg), but more recent studies have suggested that optimal blood pressure, in terms of cardiovascular risk, may be lower than this. US guidelines[2] now define normal blood pressure as below 120/80 mmHg, while European[5] and British[1] guidelines classify this as optimal. Blood pressures of 130–139/85–89 mmHg are regarded as high normal[1,5] or are included in the classification of *prehypertension*.[2] Although hypertension was formerly defined in terms of diastolic blood pressure alone, it is now recognised that systolic pressure is also important in determining risk, and current guidelines give equal emphasis to both.

Blood pressure above 140 mmHg systolic, and/or 90 mmHg diastolic is generally considered to represent hypertension. Although classifications of *mild*, *moderate*, and *severe hypertension* have been widely used, these terms may be misleading since absolute cardiovascular risk is more important in determining the need for treatment and depends on other factors in addition to blood pressure. Most guidelines[1,4,5] therefore use a grading system to classify hypertension, as follows:

grade 1: 140–159/90–99 mmHg;
grade 2: 160–179/100–109 mmHg;
grade 3: ⩾ 180/⩾ 110 mmHg.

In the US guidelines,[2] stage 1 hypertension corresponds to grade 1, whereas stage 2 includes both grades 2 and 3.

When systolic and diastolic pressure fall into different categories the higher value is used for classification purposes.

The term *malignant* or *accelerated hypertension* has been used for rapidly progressing severe hypertension associated with retinopathy and often renal impairment, but this is now generally considered part of the spectrum of hypertensive crises (see below).

Isolated systolic hypertension occurs mainly in the elderly and has been defined[1,5] as systolic pressure of 140 mmHg or more and diastolic pressure under 90 mmHg.

Origins. In the majority of cases of hypertension the cause is unknown, and such *primary* or *essential* hypertension is probably multifactorial in origin, with genotype, as well as external factors such as diet and body-weight, playing a role.[12,13] Hypertension may also be associated with surgery or pregnancy and is prevalent in diabetics. In a limited number of cases hypertension is *secondary* to some other condition, such as renal disease, Cushing's syndrome, phaeochromocytoma, or the adverse effects of drugs such as oestrogens, and such causes may be suspected particularly in resistant or malignant hypertension.[14] Although treatment of the underlying condition will generally be desirable, the resultant hypertension will not necessarily be abolished by this.

Management of hypertension. Most of what follows relates to primary or essential hypertension in adults. Hypertensive crises, hypertension in children, and hypertension associated with surgery, diabetes, renal disease, or pregnancy are also discussed below under separate headings.

Hypertension may be discovered because of adverse vascular events, especially in the eyes, brain, kidneys, or heart, but is more often asymptomatic and only discovered on routine measurement of blood pressure. Once diagnosed, decisions have to be made about the need for treatment. It is well-established that hypertension is a risk factor for the development of stroke, heart failure, and renal damage, and to a lesser extent ischaemic heart disease, and a reduction in blood pressure is generally beneficial, although mortality remains higher than in non-hypertensives.[15] However, it is important to assess hypertension in the context of overall cardiovascular risk, including the presence of target-organ disease, such as left ventricular hypertrophy or renal disease, associated conditions such as atherosclerosis or diabetes, and other risk factors such as hyperlipidaemia or smoking. Treatment of hypertension may involve both non-pharmacological and pharmacological interventions to reduce blood pressure, as well as assessment and treatment of any other cardiovascular risk factors (see Cardiovascular Risk Reduction, p. 1246.1); any co-existing diseases should also be treated. Differences in the detail of guidelines on the management of hypertension reflect varying judgements on the justification for intervention and the relative risks and benefits of different treatments.

Non-pharmacological treatment. Adopting a healthy lifestyle is beneficial for all individuals, and any patient with raised blood pressure should be encouraged to make lifestyle changes that will reduce their cardiovascular risk. Some of these changes may also reduce blood pressure,[12,16,17] and in those who are at low overall risk no other treatment may be needed; a trial of non-pharmacological treatment is recommended in most patients before starting drug therapy,[1,2,4,5] but should not unnecessarily delay treatment, especially if the patient is at high risk.[1,5] Interventions that have been shown to reduce blood pressure include:

- reduction in excess weight
- reduction in excess alcohol consumption
- reduction in sodium intake
- adequate exercise
- reduced fat intake
- increased fruit and vegetable consumption

Other interventions that have been tried, but with less evidence of benefit, include:

- increased intake of potassium, magnesium, and calcium
- increased polyunsaturated fat intake with reduced saturated fat intake
- relaxation therapies for stress reduction.

These lifestyle changes may also be promoted in the population as a whole, or in individuals most likely to develop hypertension, in strategies for the *primary prevention* of high blood pressure.[18]

Pharmacological treatment. The main decisions in drug treatment relate to the blood pressure at which therapy should be begun, the target blood pressure, and the most appropriate drug regimen to use. Controversies exist in all these areas.

When to intervene with antihypertensive drugs depends on factors including both the measured blood pressure and the overall cardiovascular risk.

- Patients with grade 3 hypertension (180/110 mmHg or higher) should receive prompt drug treatment.[1,2,5]
- In grade 2 hypertension, drug therapy is indicated if blood pressure remains at 160/100 mmHg or higher after a period of lifestyle modification, which varies depending on the overall level of risk;[1,2,5] prompt drug therapy is advised for those at high or very high risk.[5]
- For patients with grade 1 hypertension, the need for treatment is less well established; those with associated risk factors should be given drug therapy if lifestyle modification is inadequate, but some guidelines suggest that antihypertensives are not indicated in those at lower risk,[1] or state that priority should be given to those at highest risk.[4]
- Lower thresholds may apply in patients with renal disease or diabetes (see below), but whether there is any benefit in treating uncomplicated patients with prehypertension is controversial.[19]

For *elderly patients* (over 60 years) there is evidence[20,21] to support the benefit of treating hypertension, including isolated systolic hypertension,[22] and this applies up to at least 80 years of age, suggesting a strict age limit to drug therapy is inappropriate. Guidelines therefore generally recommend that treatment decisions should not be based on age, although slower titration of drugs has been suggested[5] in older patients since they may be more susceptible to adverse effects. In the very old (those over 80 years) the benefit of starting therapy is less clear,[21-23] although a study[24] in patients aged 80 years and over found a reduction in mortality; those already being treated should continue.[1,5]

Target blood pressures are also controversial. There has been concern that over-aggressive reduction of diastolic pressure might increase the risk of ischaemic heart disease,[25,26] although a meta-analysis[27] suggested that any increased mortality at low blood pressures was not linked to antihypertensive therapy but may have been due to poor health as a cause of low blood pressure. The HOT study[28] found that effective control to maintain the diastolic pressure below 90 mmHg (at about 85 mmHg) reduced the rate of cardiovascular events, but lower pressures (of around 70 mmHg) did not provide any further benefit, while a meta-analysis[29] found no evidence of a threshold for treatment benefit down to a blood pressure of at least 115/75 mmHg. Targets for systolic blood pressure are also unclear, although a study[30] in non-diabetics found that tight control (target systolic pressure below 130 mmHg) was better than usual control (target below 140 mmHg). Target blood pressures of below 140/90 mmHg[2,5] or below 140/85 mmHg[1] are now recommended; lower targets may be considered if tolerated by the patient, particularly in patients at high risk.[5] A lower target of below 130/80 mmHg has also been suggested for patients with established ischaemic heart disease,[31] and lower targets may also be appropriate in diabetics and patients with renal disease (see below).

The drug regimen may include drugs with differing pharmacological actions; the antihypertensive mechanism is not fully understood in all cases. Historically, thiazide diuretics and beta blockers have been the mainstay of drug therapy for hypertension, but calcium-channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and alpha blockers are now also widely used.

Choice of initial therapy depends on antihypertensive efficacy, safety, and long term effects on morbidity and mortality.[32,33] Studies such as the TOMHS[34] (comparing chlortalidone, acebutolol, amlodipine, enalapril, and doxazosin), and a similar study[35] (comparing hydrochlorothiazide, atenolol, diltiazem, captopril, prazosin, and clonidine), have shown that the main types of antihypertensive drug reduce blood pressure to a similar extent and in a similar proportion of patients, although the response may also depend on individual factors such as age[36] and race.[37,38] Angiotensin II receptor antagonists also effectively reduce blood pressure. However, it is now generally acknowledged that a single drug is unlikely to control blood pressure adequately and most patients will require more than one

drug to reach their treatment target. Tolerance of the drug groups is also similar, although there has been concern about the metabolic effects of thiazides and beta blockers. Alpha blockers (specifically doxazosin[39]) have been associated with an increased risk of heart failure, which may limit their use. The safety of short-acting dihydropyridine calcium-channel blockers has also been questioned, and they are no longer generally recommended for hypertension (see Effects on Mortality under Adverse Effects of Nifedipine, p. 1450.2); long-acting dihydropyridines, however, are of established benefit.[40]

All of the main drug groups are therefore established as effective antihypertensives, but their effects on long-term mortality and morbidity have been less clear. The different drug groups have differing effects on several surrogate outcomes, such as left ventricular hypertrophy[41] and endothelial dysfunction,[42] but the clinical significance of this has not been established, although there is some evidence[43] that regression of left ventricular hypertrophy is associated with a reduction in clinical events. Diuretics (particularly thiazides) and beta blockers were the first drugs to show an effect on mortality in long-term outcome studies and have therefore been preferred for initial therapy. However, long-term studies with other drug groups have now been performed, and have generally shown comparable effects on mortality and morbidity. A meta-analysis[44] concluded that there was little difference in overall cardiovascular outcomes for regimens based on ACE inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, beta blockers, or diuretics, suggesting the major benefit of treatment related to reduction of blood pressure rather than to specific properties of the individual drugs. However, cause-specific outcomes did differ between the drug groups, and some large studies have also questioned the benefit of certain regimens. A study[45] (ALLHAT) comparing treatment based on a diuretic (chlortalidone), an ACE inhibitor (lisinopril), or a calcium-channel blocker (amlodipine), found no differences in all-cause mortality, but another arm of the study based on an alpha blocker (doxazosin) was stopped early due to an excess of heart failure in this group.[39] Another study[46] (ASCOT-BPLA) was also stopped early when results suggested that a regimen of amlodipine with addition of perindopril if required, prevented major cardiovascular events more effectively than a regimen of atenolol with addition of a thiazide if required. However, blood pressure reductions were greater in patients receiving the amlodipine-based regimen, making the significance of the results unclear. Subsequent meta-analyses[38,47,48] have, however, found that beta blockers may be less effective than the other major groups of antihypertensives, particularly in older patients,[38] and their role in initial therapy has therefore been questioned.

In general, guidelines acknowledge that lowering blood pressure appears to be more important than which drug is chosen for initial therapy, and that most patients will require a combination of drugs, making the initial choice less important. Thiazide diuretics, ACE inhibitors, angiotensin II receptor antagonists, or calcium-channel blockers may all be used, and choice should take into account individual patient characteristics, including age, ethnicity, contra-indications or compelling indications for specific drugs, adverse effects, and relative cost-effectiveness.[1,2,4,5] Strict guidance is therefore not generally given, although for uncomplicated patients US[2] and international[4] guidelines recommend *thiazide diuretics* as first-line, whereas in the UK[3] diuretics or *calcium-channel blockers* are recommended for older patients (55 years or over) and black patients, while in younger, non-black patients *ACE inhibitors* or *angiotensin II receptor antagonists* are preferred. Compelling indications in all the guidelines include the use of ACE inhibitors or angiotensin II receptor blockers in patients with nephropathy, diuretics or calcium-channel blockers in elderly patients, and beta blockers in patients who have had a myocardial infarction. The use of *beta blockers* as initial therapy in patients who have not had a myocardial infarction remains controversial; UK guidelines[3] issued since the publication of ASCOT-BPLA suggest that they should be avoided except in younger patients who are unable to take ACE inhibitors or angiotensin II receptor antagonists and in women of child-bearing potential, whereas more recent European guidelines[5] allow their use in all patients other than those at risk of metabolic effects.

Having decided what drug to use, treatment is started at the lowest recommended dose. If this is ineffective or only partially effective the dose may be increased (except in the case of thiazide diuretics where there is generally no additional benefit, but more adverse effects); alternatively another first-line drug may either be substituted (*sequential therapy*) or added (*combination therapy*). Two-drug combinations will control blood pressure in a higher proportion of patients and may be necessary in most patients to achieve optimal levels. Combination therapy also allows lower doses of the individual drugs to be used with a consequent reduction in adverse effects. For the four main drug groups, the effect of combining two drugs from different groups is roughly additive, and is greater than the effect of increasing the dose of a single drug.[49] Initial treatment with a low-dose combination may be considered in some patients,[2,5,50] and use of a stepped-care treatment algorithm based on this approach has been reported[51] to improve hypertension control.

The most effective combinations involve drugs that act on different physiological systems. Appropriate combinations therefore include:

- diuretic plus beta blocker
- diuretic plus ACE inhibitor
- diuretic plus angiotensin II receptor antagonist
- calcium-channel blocker plus ACE inhibitor
- calcium-channel blocker plus angiotensin II receptor antagonist
- calcium-channel blocker (except verapamil) plus beta blocker

Alpha blockers may be used with any of the other classes but are usually reserved for third-line therapy unless specifically indicated for another reason. A three-drug combination is often required, especially in severe hypertension. In patients who maintain an elevated diastolic blood pressure despite triple therapy the possibility of secondary hypertension should be considered, although factors such as non-compliance, NSAID use, or alcohol abuse may contribute to resistance.[7,8,52]

Other classes of antihypertensive drugs that are sometimes used include: centrally acting drugs such as clonidine, methyldopa, and the less sedating moxonidine; direct-acting vasodilators such as hydralazine and minoxidil; the aldosterone antagonist, eplerenone; and the renin inhibitor, aliskiren. Older drugs like the adrenergic neurone blocker guanethidine and the rauwolfia alkaloid reserpine are rarely recommended now. Endopeptidase inhibitors and endothelin antagonists are among various drug groups that are under investigation. Hypertension vaccines against angiotensin II are also being developed.

Withdrawal of drug treatment. It has been standard teaching that drug treatment for hypertension is continued indefinitely, but there have been some reports of successful withdrawal in selected patients.[53-55] If this is attempted, blood pressure must be closely monitored and lifestyle measures should be continued indefinitely.[3,5]

Hypertension in children. Hypertension is less common in children than in adults but the incidence may be increasing in parallel with an increase in childhood obesity,[56] and guidelines for diagnosis and management have been published.[57] Lifestyle measures are the mainstay of treatment, particularly in children with less severe hypertension and no evidence of target organ damage, since the benefits of treatment and the risks of long-term drug therapy are not established. However, drug treatment may be required in some cases and should generally be based on individual patient characteristics.

Hypertensive crises. Patients with severe hypertension may be divided into those in whom there is evidence of rapid or progressive CNS, cardiovascular, or renal deterioration (hypertensive *emergencies*) and those with no evidence of target-organ damage (urgent hypertensive crises or hypertensive *urgencies*).[2,58-62] In the former case the goal is a reduction in mean arterial blood pressure by 25%, or a fall in diastolic blood pressure to 100 to 110 mmHg, over a period of several minutes to several hours depending on the clinical situation; intravenous therapy is often required although oral therapy may be adequate. In the latter case a drastic reduction in blood pressure is inappropriate and oral therapy is preferred, with the aim of a reduction in blood pressure over several hours to days. In both situations too rapid a reduction of blood pressure may be detrimental and may lead to cerebral infarction and blindness, to deterioration in renal function, and to myocardial ischaemia.

If *oral treatment* can be given and there is no evidence of ongoing target-organ damage, beginning standard antihypertensive therapy is appropriate, although the patient should be closely monitored. Short-acting drugs with a rapid effect are often used, although caution is required since they may lower blood pressure abruptly. Drugs that have been recommended[2,60,61] include the beta blocker labetalol, the centrally acting drug clonidine, the ACE inhibitor captopril, and the alpha blocker prazosin (especially when there are increased circulating catecholamines); calcium-channel blockers such as amlodipine, felodipine, and isradipine may also be suitable.[61] Diuretics may have a role in volume overload but many patients with hypertensive crises are volume depleted and diuretics may therefore be less appropriate in the initial stages. Nifedipine and captopril have been given sublingually for a faster onset, but there appears to be no clearly defined clinical advantage for this route and it is generally considered that nifedipine should not be used.[2,59,61,63]

In the emergency situation, when *parenteral therapy* is required, choice of therapy depends on concomitant clinical conditions.[58,59,61,64,65] Sodium nitroprusside given by intravenous infusion has most often been the drug of choice, but close monitoring is required as toxicity may be a problem.[2,58,60,61] Intravenous labetalol, nicardipine, or fenoldopam are suitable alternatives in most situations, and intravenous clevidipine may also be used. Other drugs that are used in specific indications include glyceryl trinitrate (in patients with coronary ischaemia), phentolamine (in phaeochromocytoma and other states associated with catecholamine excess such as the MAOI-tyramine interaction), enalaprilat (in acute heart failure), esmolol (particularly in aortic dissection or perioperatively), and hydralazine (in eclampsia, but see Hypertension in Pregnancy, below). Trimetaphan[59] and urapidil[61] have also been used.

Hypertensive emergencies in children are managed similarly to those in adults.[57,66,67]

Hypertension during surgery. Containing antihypertensive drugs in patients about to undergo surgery is not only safe but probably best up to and including the morning of surgery.[2,68]

Perioperative hypertension may occur as a result of surgery and often needs to be controlled with parenteral antihypertensives since the oral route may not be available. The parenteral drug of choice is often sodium nitroprusside; others include glyceryl trinitrate (especially after coronary artery bypass), labetalol, enalaprilat, esmolol, fenoldopam, nicardipine, and clevidipine; diazoxide, hydralazine, and methyldopa have also been used.[68-70]

Hypertension in diabetic patients. Hypertension is twice as common in diabetic as in nondiabetic subjects, and up to 50% of patients with type 2 diabetes mellitus become hypertensive.[71,72] The reasons proposed for this increased prevalence are controversial, but insulin resistance has been implicated.[73] In addition to being a major risk factor for atherosclerosis in large blood vessels, hypertension in diabetes appears to contribute to small vessel disease and is a risk factor for diabetic nephropathy and possibly for diabetic retinopathy. The UK Prospective Diabetes Study (UKPDS) Group has reported[74] that tight control of blood pressure (with a target of below 150/85 mmHg) reduces the risk of diabetes-related death and diabetic complications, including diabetic retinopathy, in type 2 diabetics.

The threshold for intervention with drug treatment may be lower in diabetic than in non-diabetic hypertensive patients and treatment targets are also lower. An initial target of 140/80 mmHg has been suggested,[1] while a target below 130/80 mmHg may be optimal and is recommended in many guidelines;[1,2,4,5,14,75] the lower target is particularly advised in type 1 diabetics with nephropathy.

All the main groups of antihypertensive drugs can be used in diabetics,[76] and most patients will require at least two drugs to achieve target blood pressure. ACE inhibitors (with angiotensin II receptor antagonists as an alternative) have been particularly recommended, as there is evidence of benefit in preserving renal function in patients with nephropathy. However, a systematic review[77] found limited evidence to support a specific renoprotective action in diabetics, independent of their effect on blood pressure. Diuretics and beta blockers have often been avoided because of their potential adverse effects on glucose and lipid metabolism, but may be used where indicated. In the UKPDS treatment with an ACE inhibitor (captopril) or a beta blocker (atenolol) was equally effective in reducing the risk of diabetic complications, although the ACE inhibitor appeared to be better tolerated.[78] Although there has been concern regarding the safety of calcium-channel blockers, long-acting calcium-channel blockers have been shown to be a suitable choice.[79]

Hypertension and renal disease. Hypertension is closely linked with the kidney—the kidney may have a role in the pathogenesis of hypertension and it may also be a prime target of damage caused by hypertension. Both renal parenchymal disorders and renovascular disorders may be associated with hypertension. In the former, hypertension is often resistant to treatment and a combination of drugs, including vasodilators, may be required. Antihypertensive therapy is also important in these patients since it may slow the decline in renal function in patients with nephropathy.[80] There is some evidence that ACE inhibitors may have a greater protective effect than other antihypertensives,[81,82] although this is not certain,[77] and they have been recommended as the basis of therapy (with angiotensin II receptor antagonists as an alternative), usually with a diuretic.[1,2,5] The effect of blood pressure reduction appears to be related to the degree of proteinuria, and studies have shown that patients with proteinuria higher than 1 g/day benefit from lower blood pressures.[82] Current guidelines[1,2,5] recommend a target blood pressure of below 130/80 mmHg in patients with nephropathy, with a lower target[1] of 125/75 mmHg in those with proteinuria of 1 g/day or over.

Renovascular hypertension has been defined as arterial hypertension resulting from obliteration or compression of one or both renal arteries, the commonest cause being stenosis due to atherosclerosis.[83] Underperfusion of the kidney leads to increased release of renin and a consequent

rise in blood pressure. However, the relationship between renovascular hypertension and renal artery stenosis is not clear cut; the two conditions may simply co-exist or hypertension may cause the stenosis rather than the other way round.[84,85]

Renovascular hypertension may be difficult to distinguish clinically, but carries a worse prognosis than essential hypertension, may be less amenable to treatment, carries a higher risk of progression to accelerated or malignant hypertension, and may result in irreversible ischaemic failure of the affected kidney.

Diagnostic methods used to detect renovascular hypertension include imaging studies such as ultrasonography and angiography, and functional tests such as the captopril test (see under ACE inhibitors on p. 1283.3 for further details); renal scintigraphy with and without ACE inhibition is also used.

The optimum treatment for renovascular hypertension is unclear. Blood pressure in renovascular hypertension can often be controlled by antihypertensive drugs, but for patients with renal artery stenosis, angioplasty has been widely used, with the aim of preserving renal function. However, there is little evidence that angioplasty is superior to medical therapy; control of blood pressure has been improved in some studies,[85,86] especially in patients with bilateral stenosis, but this finding was not supported by a more recent study,[87] and renal outcomes are similar with either approach. Renal function may deteriorate in patients given antihypertensives since blood flow to the kidney is reduced; however, sudden restoration of blood flow by angioplasty may also have deleterious effects. Reduced blood flow is a particular concern with the use of ACE inhibitors or angiotensin II receptor antagonists, since renal perfusion may be dependent on angiotensin II in patients with renal artery stenosis, and renovascular hypertension is often considered a contra-indication to the use of these drugs, particularly in patients with bilateral stenosis or stenosis affecting the only functioning kidney. However, they may be required in patients with resistant hypertension,[88] although they must be used cautiously and in low doses, with careful monitoring of renal function (see Precautions for ACE inhibitors, p. 1287.2).

Hypertension in pregnancy. Hypertension in pregnancy may be life-threatening to both mother and fetus. It may be pre-existing or may develop for the first time during pregnancy. Definitions vary, but hypertension presenting before 20 weeks of gestation generally continues long-term and is considered chronic hypertension. After the twentieth week (gestational hypertension) it may be transient (pregnancy-induced hypertension), chronic, or represent pre-eclampsia. Gestational hypertension is usually defined as a blood pressure of 140/90 mmHg or more on at least two occasions in a previously normotensive woman; it is considered transient hypertension if the blood pressure has returned to normal limits by the twelfth week postpartum. In pre-eclampsia, increased blood pressure occurs with proteinuria; abnormal coagulation, liver dysfunction, and oedema may also be present. Pre-eclampsia may progress to eclampsia, a convulsive phase.

Recommendations about the treatment of ***gestational*** or ***pre-existing hypertension*** during pregnancy have been controversial. Most women with chronic or transient hypertension will have grade 1 or grade 2 hypertension and a low risk of cardiovascular complications during the short period of pregnancy, and the benefits of treatment in such patients are not established. It is usually agreed that blood pressures of 170/110 mmHg or above should be treated as an emergency,[5,89] but recommendations for management of lower blood pressures are less clear. Although treatment of patients with blood pressures of 140/90 mmHg or above has been suggested,[5,89,90] there is little evidence that this improves maternal or neonatal outcomes, although the incidence of severe hypertension is reduced.[91] Some guidelines allow withdrawal of antihypertensives in pregnant women with pre-existing hypertension, with treatment restarted if the blood pressure exceeds specific threshold values.[2,90,92] However, women with mild hypertension are at an increased risk of developing pre-eclampsia, regardless of whether they receive antihypertensives, and should be closely monitored.

For women with *mild to moderate hypertension* in whom the decision is made to give antihypertensives, optimum choice of drug therapy is unclear. Women with pre-existing hypertension usually continue their existing treatment, although ACE inhibitors and angiotensin II receptor antagonists are contra-indicated in pregnancy and should be changed to an alternative. For gestational hypertension, methyldopa or beta blockers have generally been preferred, although there is little evidence that outcomes differ for any of the main drug groups.[91] A systematic review[93] found no evidence of substantive benefits with beta blockers, but another review[91] found that they reduced the risk of severe hypertension more effectively than methyldopa. Methyldopa has the advantage of reassuring long-term safety results in the infant, whereas there have been concerns about fetal growth retardation with beta blockers, particularly with atenolol.[94-96] Nifedipine[90,97] or hydralazine[90] may also be used. Diuretics are not generally recommended for controlling hypertension in pregnancy because of the theoretical risk of exacerbating the volume depletion of pre-eclampsia; however, they appear to be safe in practice and may be used if necessary.[1,92]

For patients with ***pre-eclampsia***[90,98-102] the definitive *treatment* is delivery (although pre-eclampsia may also develop post partum[101]), but where the maternal condition allows this is usually delayed to allow fetal maturation. Antihypertensive therapy is therefore given to reduce the risk of maternal complications, and prophylactic anticonvulsants, particularly magnesium sulfate, may also be given in those at high risk for eclampsia (see p. 511.1). Evidence to guide choice of antihypertensive in severe hypertension is limited.[103] Oral therapy may be appropriate, in which case methyldopa or beta blockers (preferably labetalol[5,101,104]) are usually first-line; calcium-channel blockers such as nifedipine are an alternative. However, in acute pre-eclampsia or if delivery is imminent, parenteral antihypertensives are required. Intravenous hydralazine is widely used,[2,101,104] although there is some evidence that it may be less effective and have more adverse effects than other drugs,[105] and some guidelines recommend that it should be avoided.[5] Oral or intravenous labetalol, intravenous nicardipine, and oral nifedipine are also used, and sodium nitroprusside may be required in some patients.[2,5,102,104] Glyceryl trinitrate may be used if there is pulmonary oedema.[5] Other drugs that have been given include diazoxide and clonidine.

Prevention of pre-eclampsia. Several interventions have been studied for the prevention of pre-eclampsia,[106] of which low-dose aspirin has the most evidence of benefit. Although the results of individual studies with aspirin have been mixed, meta-analyses[107,108] have concluded that it produces modest reductions in the risk of developing pre-eclampsia and its complications (such as fetal death and premature delivery), with the greatest benefits seen in those deemed at highest risk. In the UK, NICE[104] recommends that pregnant women with 2 or more moderate risk factors (first pregnancy, age of 40 years or over, pregnancy interval greater than 10 years, BMI 35 kg/m^2 or over, family history of pre-eclampsia, or multiple pregnancy) or 1 or more high risk factor (hypertension in previous pregnancy, chronic kidney disease, auto-immune disease including antiphospholipid syndrome, diabetes, or chronic hypertension) should take oral aspirin 75 mg daily from week 12 of pregnancy until birth.

Other drugs that have been tried in the prevention of pre-eclampsia include nitric oxide donors, progesterone, diuretics, and low-molecular-weight heparins, but evidence for each is lacking and NICE[104] does not recommend them for this purpose. Calcium supplementation has also been shown[109] to reduce the risks of pregnancy-induced hypertension and pre-eclampsia, although its role is not yet established. Preliminary evidence suggesting that supplementation with antoxidants such as vitamins C and E might be beneficial has not been confirmed.[110,111]

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Ischaemic Heart Disease

Ischaemic heart disease (coronary heart disease; coronary artery disease) covers a spectrum of disorders caused by an inadequate myocardial blood supply, ranging from stable angina pectoris to acute myocardial infarction. It is usually associated with atherosclerosis (p. 1250.2) of the coronary arteries.

In *stable angina pectoris* (below), atherosclerotic plaques cause a chronic restriction to blood flow. Myocardial blood supply is adequate at rest, but ischaemia and pain occur during exercise or in other situations where myocardial oxygen demand increases; however, there is no permanent damage to the heart muscle.

In *acute coronary syndromes* (below), rupture of a plaque leads to thrombosis and acute obstruction of the artery, and ischaemia and pain occur at rest. If the blockage is transient there is no permanent damage to the heart (unstable angina); prolonged blockage may lead to myocardial necrosis, ranging from non-ST elevation to acute ST-elevation myocardial infarction. Acute coronary syndromes in which there is no ST elevation (unstable angina and non-ST elevation myocardial infarction) are treated similarly and are described under angina pectoris (below); acute ST-elevation myocardial infarction is described separately (see p. 1257.1).

Acute coronary syndromes

Acute coronary syndromes are part of the spectrum of ischaemic heart disease above and include unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and acute ST-elevation myocardial infarction (STEMI). They are usually caused by rupture of an atherosclerotic plaque in one of the coronary arteries. Exposure of the plaque core leads to release of tissue factor and subsequent thrombosis, which obstructs the artery, restricting or preventing blood flow and leading to ischaemia. In unstable angina, blockage of the artery is transient and there is no permanent damage to the heart, whereas more prolonged obstruction causes myocardial necrosis (myocardial infarction). In each case, rapid resolution of thrombosis is necessary to minimise myocardial damage and all forms of acute coronary syndrome are emergency situations. Treatment strategies are the same for unstable angina and NSTEMI, and these are discussed under Angina Pectoris (below); acute STEMI is managed similarly, but additional therapies are also indicated and these are discussed under Myocardial Infarction (p. 1257.1).

Angina pectoris

Angina pectoris is a syndrome that arises from an inadequate myocardial oxygen supply (myocardial ischaemia) and is part of the spectrum of coronary or ischaemic heart disease. Myocardial oxygen supply depends upon coronary blood flow, which normally increases to meet increased oxygen demands. Ischaemia occurs when blood flow either cannot be increased, or is reduced; this may be due to a fixed obstruction in the coronary arteries, vasoconstriction, thrombus formation, or platelet aggregation. The main symptom is transient precordial discomfort ranging from a mild ache to severe pain. Some patients may also have dyspnoea, nausea, sweating, and left arm discomfort.

Three main types of angina have been described: stable angina; unstable angina; and Prinzmetal's angina. Although these are discrete groups, stable angina may become unstable, and Prinzmetal's angina may co-exist with stable or unstable angina.

Stable angina (effort angina) is usually brought on by exertion and relieved by rest. It is often called chronic stable angina and as the name implies the frequency, intensity, and duration of the attacks are stable. The main underlying disorder is coronary atherosclerosis causing a fixed obstruction in one or more coronary arteries. While the restricted coronary blood flow is still adequate for oxygenation of the unstressed heart, it is not capable of being increased to meet the increase in myocardial oxygen demand that may occur during exercise, cold exposure, emotional stress, or after eating.

Unstable angina and the related condition **non-ST elevation myocardial infarction** are acute coronary syndromes intermediate between stable angina pectoris and acute myocardial infarction. There are 3 main presentations:

- angina that presents from the beginning as severe and frequent attacks
- an increase in the frequency, intensity, and/or duration of previously stable angina, often with diminishing responsiveness to sublingual nitrates (crescendo angina)
- recurring or prolonged angina at rest

As in stable angina, the underlying disorder is usually coronary atherosclerosis, but the decreased coronary artery blood flow is usually caused by disruption of an atherosclerotic plaque, which leads to platelet adhesion and aggregation, thrombus formation, and vasoconstriction. This may result in partial occlusion of one or more coronary arteries, and the coronary blood flow can be so restricted that it does not meet the oxygenation demands of the unstressed heart. However, in unstable angina the ischaemia is not severe enough to cause myocardial damage, whereas in non-ST elevation myocardial infarction some degree of myocardial necrosis occurs, although to a lesser extent than in acute myocardial infarction. Patients with the different acute coronary syndromes may present similarly and definitive diagnosis is only possible retrospectively once the results of biochemical measurements such as cardiac troponins or cardiac enzymes are available or the ECG shows evidence of new Q waves. However, patients without ST-elevation on the presenting ECG rarely develop Q waves and are managed as for unstable angina; those with ST-elevation should be treated as for acute myocardial infarction (p. 1257.1). Patients with unstable angina are at an increased risk of sudden death or progression to myocardial infarction, and those with rest pain are at the greatest risk.

Prinzmetal's angina (variant angina) is a rare form of angina caused by coronary vasospasm, although it is often associated with atherosclerosis. It occurs spontaneously at rest and with greater frequency during the night or early hours of the morning. It is associated with transient ST-segment elevation and carries a risk of progression to myocardial infarction. Prolonged vasospasm may also lead to ventricular arrhythmias, heart block, or death.

Patients who have **angina with normal coronary arteries** as shown by angiography may have microvascular dysfunction or altered cardiac pain perception. Prognosis is generally better than in other forms of angina although quality of life may be significantly impaired.[1,2]

In addition to the types of angina described above periods of **silent myocardial ischaemia** (asymptomatic transient myocardial ischaemia) in which there is no anginal pain have been identified during ECG monitoring. In some patients all ischaemic episodes are asymptomatic. However, asymptomatic ischaemic episodes also occur in patients with angina and seem to be more common than symptomatic episodes. It is not clear why some episodes of ischaemia are symptomatic while others are not.

Treatment depends on the type of angina and involves symptomatic management of acute anginal pain, antithrombotic therapy to prevent progression to myocardial infarction, and long-term management both to prevent angina attacks and to reduce the risk of other cardiovascular events. Anti-anginal treatment is used in both stable and

unstable angina and is described in more detail below; it includes drug therapy (nitrates, beta blockers, calcium-channel blockers, and potassium-channel openers), and non-pharmacological interventions. Antithrombotics are used in unstable angina and include anticoagulants and antiplatelet drugs (see Treatment of Unstable Angina, below). Long-term measures to reduce cardiovascular risk are important in all patients, even when symptoms are controlled, and include antiplatelet therapy (which should be given to all patients unless contra-indicated), lipid lowering therapy, and lifestyle changes; these interventions are discussed in more detail under Cardiovascular Risk Reduction, p. 1246.1. Patients with ischaemic heart disease who undergo non-cardiac surgery are at risk of complications resulting from perioperative myocardial ischaemia. Perioperative use of beta blockers is controversial but may be considered in high-risk patients (see Cardiovascular Risk Reduction under Uses of Beta Blockers, p. 1317.2); and use of alpha$_2$ agonists such as mivazerol or clonidine may be considered.[3,4] There is also some evidence that statins are of benefit,[3] and perioperative use has been recommended in high-risk patients.[4]

Anti-anginal drugs act in a variety of ways. Glyceryl trinitrate and other organic *nitrates* have a vasodilator effect with venodilatation predominating over dilatation of the arterioles. Dilatation of veins decreases venous return as a result of venous pooling and lowers left ventricular diastolic volume and pressure (together termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequence of these effects is a reduction in myocardial oxygen demand. Also the vasodilator effect improves regional coronary blood flow to ischaemic areas, and alleviates coronary spasm. *Beta blockers* cause a slowing of the heart rate and reduction in contractility and therefore reduce myocardial oxygen demand. *Calcium-channel blockers* reduce the work of the heart by dilating peripheral arteries, and diltiazem and verapamil also slow the heart rate. Calcium-channel blockers also act on the coronary circulation preventing spasm. *Potassium-channel openers* act as coronary vasodilators, while nicorandil also has a nitrate component that may contribute to its effect. Newer drugs include ivabradine, a selective *sinus node I_f inhibitor*, which acts similarly to beta blockers by lowering heart rate, and ranolazine, the action of which is unclear but may depend on its effects as a *late sodium channel inhibitor*. The *xanthine oxidase inhibitor* allopurinol has been investigated for its apparent anti-ischaemic effects.[5]

The main ***non-pharmacological treatments*** used are *percutaneous coronary interventions* (PCI), such as balloon angioplasty and stenting, and bypass surgery. Balloon angioplasty is a catheter-based technique that mechanically dilates the occluded artery; coronary stents are used to prevent recoil and to reduce the incidence of restenosis. Nitrates and calcium-channel blockers may be given to alleviate coronary spasm due to the procedure. Coronary artery *bypass surgery* uses a vein or artery graft to bypass the occlusion. Both PCI and bypass surgery abolish or reduce episodes of angina in most patients but symptoms commonly recur over a period of time due to restenosis. Adjunctive therapy is therefore needed both to prevent short-term thromboembolic complications and long-term reocclusion (see Reperfusion and Revascularisation Procedures, p. 1259.2). Other non-pharmacological methods that have been tried in refractory angina include enhanced external counterpulsation, transmyocardial revascularisation, and spinal cord stimulation;[6-8] gene- and stem cell-based therapies are also under investigation.[7]

Treatment of stable angina. Management of the patient with stable angina[7,9-15] mainly involves the use of anti-anginal drugs, antiplatelet therapy, and measures to reduce cardiovascular risk. Non-pharmacological measures may also be considered. Any contributory conditions, such as anaemia, should be identified and treated.

Treatment of *infrequent* angina episodes (less than about 2 attacks per week) usually consists of glyceryl trinitrate given when required, generally sublingually; alternatively, a buccal tablet or spray formulation may be used. Isosorbide dinitrate, in the form of sublingual tablets or spray, may be used, although it has a slower onset of action than glyceryl trinitrate. Glyceryl trinitrate in sublingual or buccal forms may also be used before an activity or circumstance that might precipitate an attack.

When episodes occur *more frequently*, sublingual glyceryl trinitrate, at least on its own, may no longer be appropriate, and regular symptomatic treatment has to be considered. Choice depends upon patient characteristics and any concurrent medical conditions.

- Beta blockers are the mainstay of therapy. They are generally considered to be first-line treatment if sublingual glyceryl trinitrate is not adequate since they provide effective symptom control and have also been shown to reduce mortality in certain patients with high cardiovascular risk.[9,10,13] The different beta blockers have similar efficacy in terms of symptom control, but those with beta$_1$-selectivity may be preferred;[13] beta blockers with intrinsic sympathomimetic activity may be less effective for secondary prevention after myocardial infarction and are not recommended.[16]
- Calcium-channel blockers appear to have similar efficacy to beta blockers in terms of symptom control and cardiovascular outcomes[17] and long-acting calcium-channel blockers may be used as alternative first-line therapy,[9,13] particularly in patients unable to tolerate beta blockers. Both dihydropyridines (such as nifedipine) and rate-limiting calcium-channel blockers (diltiazem and verapamil) may be used, with choice depending on individual patient characteristics and adverse effects. Short-acting preparations of nifedipine have been associated with increased mortality and are not recommended (see Effects on Mortality under Adverse Effects of Nifedipine, p. 1450.2).
- Regular nitrate therapy is a further alternative, and includes modified-release forms of glyceryl trinitrate, for example transdermal patches, and the long-acting nitrates such as isosorbide dinitrate or isosorbide mononitrate; it may be particularly suitable in patients with left ventricular dysfunction. Reduced efficacy or tolerance occurs, particularly with nitrate preparations that produce sustained plasma concentrations, and dosage regimens including a nitrate-free period should be used (see Nitrate Tolerance, p. 1394.1).
- Nicorandil, a potassium-channel opener and nitrate, is another alternative that can be used for monotherapy.[10,13] Ivabradine may be used in patients with normal sinus rhythm and a contra-indication or intolerance for beta blockers. Ranolazine is generally used as an adjunct to other anti-anginals but may also be used first-line. Other drugs that are sometimes used include trimetazidine, which has anti-ischaemic effects through a metabolic action and may be of benefit in refractory angina, and the nitrovasodilator molsidomine. Several other vasodilators have also been used (see p. 1245.3) but no longer have an established role.

Where optimal therapy with a single drug fails to control symptoms, *combination therapy* may be used. There is additional benefit from nitrates with beta blockers, since nitrates can moderate the excessive effects that beta blockers may have in increasing left ventricular diastolic volume and pressure and in inducing bradycardia. Calcium-channel blockers may also be used with nitrates; the use of verapamil or diltiazem with a nitrate may be preferrable to nifedipine (or other dihydropyridine derivative) with nitrates as both nifedipine and nitrates cause reflex tachycardia, hypotension, and headaches. Use of beta blockers with calcium-channel blockers may also be of benefit,[18] although adverse effects can be a problem. Combined therapy with beta blockers and dihydropyridines or diltiazem improves exercise tolerance, but caution is needed with dihydropyridines in patients with heart failure (although amlodipine and felodipine appear to be safe) and with diltiazem in patients with conduction disorders. Verapamil should generally be avoided with beta blockers as the risk of conduction disorders is particularly high (see p. 1525.2). Nicorandil and ranolazine are both suitable for use with other anti-anginals, and ivabradine may be used with beta blockers if additional therapy is required.

Triple therapy using a nitrate, a beta blocker, and a calcium-channel blocker may sometimes be used although it is likely to be associated with more adverse effects.

Revascularisation procedures are the main non-pharmacological treatment used in stable angina, and have generally been reserved for patients who are not controlled by medical therapy.[13,19] Both PCI and coronary artery bypass surgery are suitable, and the choice between them is not entirely clear; a systematic review[20] and a meta-analysis[21] found that both procedures had similar effects on mortality, but the need for further revascularisation procedures was lower with bypass surgery. In general, PCI is preferred in patients with single-vessel disease, whereas bypass surgery is usual in patients with triple-vessel disease, disease of the left main coronary artery, or impaired left ventricular function.[22,23] Routine revascularisation of all patients has been investigated, but has no clear advantage over optimal medical therapy. Symptom control and quality of life may be higher with revascularisation,[24,25] but the benefit diminishes with time,[26] and recurrent angina after revascularisation may be challenging to treat.[8] Similarly, there appears to be little difference in terms of mortality or major cardiovascular events, although meta-analyses[27,28] have come to conflicting conclusions.

Treatment of unstable angina. Unstable angina and non-ST segment elevation myocardial infarction are managed similarly,[29-37] and are generally regarded as an emergency. Patients with a change in the pattern of previously stable angina or with recurring or prolonged angina at rest should therefore be hospitalised and rapidly assessed. Presenting symptoms are similar for all the acute coronary syndromes and a resting ECG should be obtained as a priority. This allows identification of patients with ST elevation, who require treatment for acute myocardial infarction (p. 1257.1), and also allows initial risk stratification. In patients without ST elevation, the immediate priority is to control symptoms and reduce ischaemia; at the same time, the risk of progression to acute myocardial infarction should be assessed, and subsequent treatment planned as appropriate. *Initial treatment* involves antiplatelet drugs, anticoagulants, nitrates, beta blockers, and possibly calcium-channel blockers; additional antiplatelet therapy and urgent revascularisation may then be considered. Once the patient has been stabilised, underlying risk factors should be identified and treated, and long-term anti-anginal therapy may be given.

- Aspirin is routinely included in the initial treatment. It inhibits platelet aggregation and substantially reduces the incidence of myocardial infarction and death, although it has not been shown to reduce the number of ischaemic episodes or to relieve pain during the acute phase.
- The thienopyridines may be alternatives if aspirin is not tolerated; clopidogrel has fewer adverse effects than ticlopidine and is generally preferred. Dual antiplatelet therapy with clopidogrel and aspirin, both started immediately, may provide additional benefit[38] and has been recommended.[29,31,36,37] Further oral antiplatelet drugs that may be given include prasugrel (which may be used in patients undergoing planned PCI) and ticagrelor.[39]
- Anticoagulants are generally given in addition to aspirin to reduce thrombin generation and fibrin formation, although the optimum choice is unclear.[29]

  Both unfractionated heparin[40,41] and low-molecular-weight heparin[41] reduce the number of ischaemic episodes and major cardiovascular events during the acute phase, and also longer term. There is some evidence that low-molecular-weight heparins may be more effective than unfractionated heparin.[42-44] They may also be easier to use since low-molecular-weight heparins are given subcutaneously, whereas unfractionated heparin is generally given by continuous infusion for at least 48 hours,[30] although it may also be effective subcutaneously.[45] Reactivation of unstable angina may occur when treatment with either unfractionated[46] or low-molecular-weight heparin[47] is stopped; it is less likely in patients who are also taking aspirin,[46] and the risk may be reduced if treatment is stopped gradually. Guidelines[29,31,36] therefore allow the use of either unfractionated or low-molecular-weight heparin; unfractionated heparin may be preferred in patients undergoing bypass surgery[29] but either is suitable for PCI.[48]

  The pentasaccharide fondaparinux may be an alternative; it is at least as effective as enoxaparin[49] and may be the preferred option in patients for whom urgent PCI is not planned;[31,37] however, the incidence of catheter thrombosis was increased with fondaparinux in patients undergoing PCI[50] and unfractionated heparin should be given at the time of the procedure if PCI is performed.[29,31,37] For patients in whom early PCI is planned, the direct thrombin inhibitor bivalirudin is another alternative;[37] a study[51,52] in patients scheduled for PCI found that bivalirudin was as effective as heparin (unfractionated or low-molecular-weight) and the risk of bleeding was reduced.
- Nitrates are widely used although evidence from controlled studies is limited.[29,31] The initial treatment may be given intravenously to produce a fast response and to provide better dose control than can be achieved with other routes. Glyceryl trinitrate or isosorbide dinitrate are used. Generally, the intravenous route is only used during the acute phase, and once the patient is stabilised the infusion is withdrawn, usually within about 48 hours. Sublingual glyceryl trinitrate may be tried initially in patients with less severe symptoms.
- Treatment with a beta blocker is started during the acute phase to reduce myocardial oxygen demand. Oral treatment is usually preferred,[29,31] although the intravenous route may be used initially if required. Beta blockers with intrinsic sympathomimetic activity do not reduce resting heart rate and are not recommended.[16,29,30]
- Calcium-channel blockers may be added to therapy although they are generally reserved for patients with angina refractory to treatment with the above drugs, or in whom beta blockers are contra-indicated. However, calcium-channel blockers are the drugs of choice if the angina has a vasospastic aetiology, for example in Prinzmetal's angina. The choice of calcium-channel blocker is described under the treatment of stable angina above.
- Thrombolytics have been tried in unstable angina but do not improve outcome and are associated with an excess of bleeding complications; thrombolytic therapy is

therefore not recommended in patients with unstable angina.[29,30]

Once the initial therapy has been started patients at high or intermediate risk of progression to acute myocardial infarction, including those with recurrent ischaemia and those with raised cardiac troponins, should be assessed for *additional treatment*. Patients may be assigned to either an invasive or a conservative strategy. For those in whom an invasive strategy is chosen, early angiography is performed, with urgent revascularisation if appropriate. For those assigned to a conservative strategy and in patients at lower risk, angiography and revascularisation are only performed if medical therapy fails to control symptoms or if indicated by stress testing. Choice between the two remains controversial. Meta-analyses[53-55] have suggested that an invasive strategy is associated with a reduction in recurrent angina; there may also be a reduction in myocardial infarction and mortality in the longer term, although a later review[56] was unable to confirm this. Benefit appears greater in men and high-risk women,[57] and a conservative strategy may be appropriate in those at lower risk. Bleeding risk should also be considered.[58]

- Additional antiplatelet therapy with glycoprotein IIb/IIIa inhibitors may have a role in patients treated invasively or conservatively.[59] Benefit has been established in patients undergoing PCI (see Reperfusion and Revascularisation Procedures, p. 1259.2), but results in patients treated medically have been less consistent. A meta-analysis[60] of studies of glycoprotein IIb/IIIa inhibitors in unstable angina or non-ST elevation myocardial infarction found that they reduced the risk of death or myocardial infarction in patients who were not scheduled for early revascularisation, particularly in those at high risk of progression, such as those with raised troponins. However, many of the patients included in the analysis did receive revascularisation and the use of glycoprotein IIb/IIIa inhibitors in patients not undergoing intervention remains questionable.[29] Whether all the glycoprotein IIb/IIIa inhibitors are effective is also unclear. For patients not undergoing PCI, individual studies have reported beneficial results with: tirofiban and aspirin, alone[61] or with heparin;[62] with eptifibatide[63] in addition to standard therapy; but not with abciximab[64] in addition to aspirin and heparin. The benefit of treatment with glycoprotein IIb/IIIa inhibitors in patients already taking aspirin and clopidogrel is also unproven.[65,66]
- The use of statins early after admission for acute coronary syndromes has been recommended,[31] although meta-analyses have come to differing conclusions regarding their benefit. One analysis[67] found early use of statins had no effect on outcomes at 1 or 4 months after the initial event, but another[68] reported a reduction in cardiovascular events with statin therapy for 6 months or longer; benefit may be increased with high-dose regimens.[69]

After discharge, patients should take aspirin and a beta blocker indefinitely; clopidogrel should also be continued with aspirin for up to 12 months.[29,31,37] Statins should be continued, and other measures to reduce cardiovascular risk should be adopted. Anti-ischaemic drugs should be given as required; some patients are given a long-acting nitrate for long-term prophylaxis, although nitrates have not been shown to protect against subsequent cardiovascular events. Long-term oral anticoagulation has been used but is not routine therapy, and studies of warfarin with aspirin have given mixed results.[70,71] Prolonged use of low-molecular-weight heparins has been investigated,[72,73] but benefit has not been confirmed.

Treatment of Prinzmetal's angina. This should be treated like unstable angina with the addition of a calcium-channel blocker;[74] the selection of an appropriate calcium-channel blocker is described above under the treatment of stable angina. Beta blockers may increase the number of attacks of chest pain in patients with Prinzmetal's angina; this occurs especially with non-cardioselective beta blockers, which should be avoided. Once stabilised, maintenance should include a nitrate, or calcium-channel blocker, or both to protect against further spasm. Surgery may be considered in some patients.

Treatment of angina with normal coronary arteries. Symptomatic treatment with standard anti-anginal drugs is the mainstay in patients with angina but no evidence of coronary artery disease, although response varies. Beta blockers appear to be the most effective treatment and are usually considered first-line.[1,2]

Treatment of silent myocardial ischaemia. Silent myocardial ischaemia has been recognised as a potential risk factor for future cardiovascular morbidity and mortality and research has been undertaken to assess whether suppressing such episodes can improve long-term outcome. Although many of the therapies used in angina reduce the incidence of silent ischaemia it is not yet clear whether complete suppression of ischaemia affects prognosis.[75,76] Other studies have suggested that periods of ischaemia may protect the heart during subsequent myocardial infarction, although the clinical significance of this is unclear.[77,78]

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Myocardial infarction

Myocardial infarction is an acute coronary syndrome (p. 1254.2) in which necrosis of the heart muscle occurs as a result of acute ischaemia. In the initial stages, clinical symptoms are similar to those of unstable angina, but necrosis results in irreversible damage to the myocardium and long-term complications. The definition of myocardial infarction has changed considerably as the accuracy of detecting myocardial necrosis has improved. It is now considered that any degree of necrosis associated with clinical ischaemia should be defined as myocardial infarction,[1] since it is associated with a worse prognosis, although this definition includes many cases that would formerly have been classified as unstable angina. However, most evidence for treatment is based on earlier classifications, and in practice the diagnosis of acute myocardial infarction is generally made on clinical grounds, determined by characteristic symptoms, ECG changes (ST-segment elevation or bundle branch block), and changes in biochemical markers. The following discussion relates to the management of acute ST-elevation myocardial infarction (STEMI); the management of non ST-elevation myocardial infarction (NSTEMI) is discussed under Angina Pectoris (p. 1254.3).

Although the incidence may be declining, myocardial infarction remains a leading cause of mortality in western societies. The introduction of aspirin and reperfusion techniques has transformed the management of acute STEMI, but a significant number of sudden deaths occur within the first hour and therefore before treatment can be begun. While new therapies for the management of acute STEMI may further reduce in-hospital mortality, earlier recognition and presentation for treatment is important if survival is to be improved further, and primary prophylaxis in patients at risk or at a population level may also have a role (see Cardiovascular Risk Reduction, p. 1246.1). Patients who survive a myocardial infarction are at high risk for further cardiovascular events and often develop complications such as arrhythmias, left ventricular failure, persistent angina, and venous thromboembolism. Management of acute STEMI therefore involves both early treatment of the acute condition, and long-term therapy in survivors to reduce risk and to treat and prevent complications.

Myocardial ischaemia generally occurs as a result of coronary artery occlusion, usually due to thrombosis at the site of a recently ruptured atheromatous plaque; in a few patients coronary embolism or spasm, arteritis, spontaneous thrombosis, or a sudden severe rise in blood pressure, as in phaeochromocytoma, is responsible. The immediate consequence of coronary occlusion is myocardial ischaemia, which leads to impaired contractility, arrhythmias, and eventually myocardial cell death. The lay term 'heart attack' describes both sudden cardiac death and myocardial infarction. Sudden death is usually due to ventricular fibrillation and most patients who are resuscitated from ventricular fibrillation develop features of myocardial infarction or have coronary artery disease. In many cases myocardial infarction is asymptomatic or 'silent' and is only diagnosed due to characteristic changes on the ECG.[2]

Early management. Guidelines,[3-7] recommendations,[8] and reviews[9-14] emphasise the importance of rapid recognition and treatment of patients with acute STEMI. The initial symptoms are usually chest pain, breathlessness, and sweating. The chest pain is typically severe and resembles that of angina pectoris, being precordial with radiation to the neck, lower jaw, and left arm; chest pain lasting more than 20 minutes is generally considered to indicate myocardial infarction, although this is absent in many patients. Other signs and symptoms include nausea and vomiting, bradycardia, hypotension, and apprehension. The characteristic ECG changes confirm the clinical diagnosis and guide initial treatment; elevation of biochemical markers such as troponins and cardiac enzymes develops later and is useful for confirming the diagnosis and determining prognosis.

Those patients with myocardial infarction who develop ventricular fibrillation very quickly have a high mortality and require rapid provision of life support measures. Ventricular fibrillation is treated by defibrillation followed by adrenaline and possibly antiarrhythmics if defibrillation alone is unsuccessful (see Cardiac Arrest, p. 1268.3, for further details). Paramedic ambulance teams experienced in defibrillation and programmes aimed at educating the public in the basic techniques of cardiopulmonary resuscitation have an important role. Patients with suspected myocardial infarction should be admitted to hospital and where possible managed in a coronary care unit.

The immediate priority in patients with suspected acute STEMI is to give aspirin (as discussed below), to relieve symptoms such as pain and anxiety, and to confirm the diagnosis so that reperfusion can be achieved as rapidly as possible.

Symptom control. *Pain* should be relieved with an opioid analgesic, usually diamorphine or morphine given intravenously (see Myocardial Infarction Pain, p. 10.1); an antiemetic such as metoclopramide intravenously may also be necessary. Supplemental oxygen is also recommended, although this has been questioned (see under Precautions for Oxygen, p. 1805.2). An inhaled mixture of nitrous oxide and oxygen (Entonox) has sometimes been used to provide pain relief before arrival in hospital; sublingual glyceryl trinitrate or an alternative fast-acting nitrate may also be given. A benzodiazepine may be useful for *anxiety*.

Reperfusion. In patients with confirmed STEMI, the value of rapid reperfusion is well established. The extent of myocardial necrosis or recovery depends on the speed and completeness with which coronary blood flow can be restored,[15] and reperfusion should therefore be achieved as rapidly as possible. Two methods are commonly used: pharmacological reperfusion with intravenous thrombolytics, or mechanical reperfusion with percutaneous coronary intervention (PCI).

Thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium.[16] Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and long-term mortality in patients with ECG evidence of ST elevation or new left bundle branch block (for more details see Ischaemic Heart Disease under Uses of Streptokinase, p. 1503.3). The greatest benefit is seen in those given thrombolytics early;[17] mortality is significantly reduced in those receiving treatment within 6 hours of symptom onset, and there is also benefit up to 12 hours. In those presenting later than 12 hours, the benefits are less well established; there has been some evidence of early excess mortality due to cardiac rupture in some patients given late thrombolytics. Although thrombolytics are often withheld in older patients, there is evidence of a benefit in those aged up to 85 years;[18] the possible increase in short-term mortality may be outweighed by improved longer-term outcomes.[19]

Streptokinase has been the most widely used thrombolytic, although fibrin-specific thrombolytics such as alteplase are increasingly preferred.[6,7,20] Overall efficacy appears to be similar for all the drugs available and factors such as cost, method of use, and contra-indications help to determine the choice. If streptokinase or anistreplase, so-called antigenic thrombolytics, have been used recently, non-antigenic drugs such as alteplase or urokinase should be given. However, choice of thrombolytic is probably less important than ensuring that one is given as soon as possible; recommendations are for a delay of no more than 30 minutes between first contact with the medical system (ambulance arrival or admission to hospital) and thrombolytic therapy,[3-5,7,20] and this should be given before admission where possible. Studies have found that prehospital thrombolysis is feasible and safe in various settings,[21] and it has also been shown to improve short-term[22] and long-term mortality.[23] However, there is some evidence that re-infarction rates are higher after prehospital thrombolysis,[24] and the optimum protocol remains unclear.

Percutaneous coronary interventions include balloon angioplasty, coronary stenting, and similar procedures. They are effective methods for reopening occluded coronary arteries,[25] including in elderly patients,[19] and can be used in acute coronary syndromes (primary PCI) and in stable coronary heart disease. PCI is also safe and effective in patients in whom thrombolytics have failed to achieve adequate reperfusion (rescue PCI)[26] and appears to have benefits over repeated thrombolytics or conservative therapy.[27] Early PCI after successful thrombolysis appears to be of benefit,[28,29] but routine use of thrombolytics or combined thrombolytics and glycoprotein IIb/IIIa receptor antagonists before PCI appears to provide no additional benefit and may be detrimental, particularly if a full dose of thrombolytic has been given.[30,31]

Choice of reperfusion strategy is controversial and depends on patient factors and availability.[15,16,25] PCI is more effective at opening occluded arteries than thrombolysis. Studies have shown that it is associated with lower mortality and re-infarction rates both early and late after STEMI,[32] with benefit maintained up to 5 years,[33] including in patients with cardiogenic shock.[34] However, the advantage of PCI over thrombolysis appears to diminish as the delay to reperfusion increases; although some analyses[35] have found that PCI is superior to thrombolysis irrespective of the time delay, others have suggested[36] that thrombolysis may be preferred if the delay to PCI is 90 minutes or more, although this depends on patient characteristics.[37] Guidelines[3,6,7] therefore recommend that all patients with STEMI presenting within 12 hours should be reperfused, and that primary PCI should be the treatment of choice where it can be performed within 90 minutes, even if this means transferring the patient to another hospital. Where the delay will be longer than 90 minutes, the patient has had symptoms for less than 2 hours, and thrombolysis is available, this should be the preferred strategy, but angiography and rescue PCI should be performed as soon as possible. Patients with cardiogenic shock, heart failure, or contra-indications to thrombolysis should receive primary PCI. PCI is also preferred in patients presenting later than 3 hours after symptom onset, but for those with a delay of more than 12 hours reperfusion (PCI or thrombolysis) should only be performed if there is evidence of ongoing ischaemia.

The overall efficacy of reperfusion is limited by persistent coronary occlusion, re-occlusion, and infrequent but serious bleeding complications (including intracranial haemorrhage with thrombolytics), and long-term restenosis after PCI. Antiplatelet and antithrombin drugs are given as **adjuncts to thrombolytics** to improve reperfusion and limit re-occlusion,[38] and have been given in the ambulance as an adjunct to prehospital thrombolysis.[39] Adjunctive therapy is also necessary with PCI to prevent re-occlusion and restenosis; for a discussion see under Reperfusion and Revascularisation Procedures (p. 1259.2).

Antiplatelet drugs. The value of giving oral aspirin as an antiplatelet drug was shown by the ISIS-2 study,[40] in which aspirin started during the first 24 hours after myocardial infarction reduced mortality and also reduced the incidence of re-infarction and stroke. Use with streptokinase proved to be more effective than either streptokinase or aspirin alone. Aspirin should therefore be taken as soon as possible when myocardial infarction is suspected and the tablet chewed so that some buccal absorption occurs;[3,20]

Additional antiplatelet therapy has been investigated in an attempt to further improve outcomes. There is some evidence that early use of clopidogrel in addition to aspirin and other standard therapies (including thrombolytics) improves outcomes,[41,42] and immediate dual antiplatelet therapy with aspirin and clopidogrel is now recommended.[5-7,20] Glycoprotein IIb/IIIa inhibitors may also add to the effects of aspirin in some patients, although most benefit is in patients undergoing primary PCI. In those given thrombolytics, no mortality benefit has been shown with abciximab,[43,44] although early patency rates may be improved.[45] Similarly disappointing results have been reported with eptifibatide[46] and tirofiban.[47]

Anticoagulants. Heparin was widely used in acute myocardial infarction before thrombolytics were available and anticoagulants have an established role in patients undergoing PCI,[3,7,20] but the necessity for adjuvant anticoagulants in addition to aspirin in patients treated with thrombolytics is not certain. Heparin may provide benefit by preventing re-occlusion of the artery after thrombolysis, a particular problem with fibrin-specific thrombolytics such as alteplase, and many of the studies supporting the use of thrombolytics included unfractionated heparin. An overview of randomised studies[48] found that in patients receiving aspirin, addition of heparin (intravenously or subcutaneously) produced a small reduction in mortality but was associated with an excess of major bleeds,

while a later meta-analysis[49] found no conclusive benefit with intravenous unfractionated heparin, although most of the studies included were underpowered to show an effect on mortality. Low-molecular-weight heparins have also been tried. They appear to be more effective than unfractionated heparin,[49-51] but studies have generally compared short-term unfractionated heparin (up to 48 hours) with longer-term low-molecular-weight heparin (4 to 8 days), and any benefit may reflect the longer duration of treatment. Guidelines[5,7,20] recommend that all patients receiving thrombolytics should be given an anticoagulant, and either unfractionated or low-molecular-weight heparin may be used. Fondaparinux, a direct factor Xa inhibitor, is also effective,[52] and may be used as an alternative,[5-7,20] although it is not suitable in patients undergoing PCI.[20] Direct thrombin inhibitors have generally proved disappointing as adjuncts to thrombolytics (see Ischaemic Heart Disease under Lepirudin, p. 1418.3), although they may have a role in patients with heparin-induced thrombocytopenia.[3] Longer-term use of heparin to prevent systemic embolisation may be considered in patients at risk of developing left ventricular mural thrombosis or in those with complications likely to result in immobility.

Standard early therapy for STEMI therefore consists of antiplatelet drugs, anticoagulants, and immediate pharmacological or mechanical reperfusion. **Other early treatments** that have been tried include beta blockers, nitrates, ACE inhibitors, magnesium, and metabolic support.

Beta blockers. In studies performed before the routine use of thrombolytics, intravenous beta blockers, such as atenolol and metoprolol, given in the early period after myocardial infarction were associated with a reduction in mortality. Contributory mechanisms were considered to be a reduction in size of infarction or number of re-infarctions and an antiarrhythmic effect, although the ISIS-1 study[53] suggested that beta blockers improved early survival by reducing the incidence of cardiac rupture. The role of intravenous beta blockers in the reperfusion era is less clear. A systematic review[54] of randomised studies found that early use of beta blockers provided, at most, a small mortality benefit; most of the studies preceded routine use of reperfusion, although some thrombolytic studies were included. A later randomised study,[55] in which about half of the patients received thrombolytics, found that early intravenous metoprolol followed by oral dosage did not reduce mortality at 28 days; there was a reduction in re-infarction and ventricular fibrillation but this was offset by an increase in deaths due to cardiogenic shock, particularly during the first few days. Current recommendations[5-7] are that intravenous beta blockers should not be used in patients with cardiogenic shock or other contra-indications, and it has been suggested[5] that early use should be reserved for patients with hypertension.

Nitrates. Intravenous nitrates are widely used in acute myocardial infarction, although evidence to support their use in patients undergoing reperfusion is limited. An overview[56] of studies carried out before reperfusion (thrombolysis or PCI) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality, but whether they are of benefit in addition to reperfusion is not clear. However, they appear to be safe[57] and may therefore be given where clinically indicated for ongoing ischaemic pain.[3,6] Nicorandil, which is both a potassium-channel opener and a nitrate, has also been tried in the early stages of myocardial infarction, but results have been mixed.[58,59]

ACE inhibitors. ACE inhibitors have an established role in the long-term management of patients after myocardial infarction, but their use in the early stages is more controversial (see p. 1284.3). A systematic review[60] of studies of ACE inhibitors started within the first 1 to 2 days after acute myocardial infarction found that 30-day mortality and the incidence of heart failure were reduced in those given ACE inhibitors, although the greatest absolute benefit was seen in high-risk patients such as those who had already developed heart failure. Guidelines[3,7] therefore agree that patients with evidence of heart failure should be given early treatment with ACE inhibitors; routine use in all patients may be considered[3,6] but is less well-established. Angiotensin II receptor antagonists may be used if ACE inhibitors are not tolerated.[7]

Magnesium. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium and it has been suggested that use of magnesium in acute myocardial infarction might protect against both arrhythmias and reperfusion injury. Although early studies reported some benefit, larger studies found no effect on mortality, and a systematic review[61] concluded that it was unlikely that magnesium reduced mortality; ventricular arrhythmias were less frequent, but profound hypotension and bradycardia were increased. Routine use of magnesium is therefore not currently recommended.

Metabolic support. Infusions containing glucose, insulin, and potassium have been used in small numbers of patients with the aim of providing metabolic support in the acute phase of myocardial infarction. A meta-analysis of randomised controlled studies that were performed before the widespread use of thrombolytics found that mortality was reduced in recipients of glucose-insulin-potassium,[62] but large randomised studies[63] in patients undergoing reperfusion have found no overall effect on mortality, and routine use is not recommended.[7] Intensive glucose control, including insulin-glucose infusions, is however of benefit in diabetics with acute myocardial infarction (see Myocardial Infarction under Insulin, p. 482.3) and short-term outcomes may also be improved in non-diabetics with hyperglycaemia treated with insulin.[64]

Other early treatments that have been investigated[65] include hypothermia, hyperbaric oxygen, calcium modulation, and complement inhibitors such as pexelizumab. Early use of stem cell infusions[66,67] or colony-stimulating factors[68,69] to promote myocardial repair has also been tried, but the optimum approach remains unclear.[70]

Long-term management. Patients who survive the immediate post-infarction period remain at high risk for cardiovascular mortality. The main predictors of poor outcome are the extent of left ventricular dysfunction, residual myocardial ischaemia, and ventricular arrhythmias. Follow-up should include cardiac rehabilitation and the identification and modification of risk factors for ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1). Angiography should be considered in all patients not treated with primary PCI,[5,7] and echocardiography may be useful for assessing left ventricular function. Exercise testing, myocardial imaging techniques, and pharmacological stress testing (see Myocardial Imaging under Dipyridamole, p. 1362.3) may have a role,[3] particularly in patients where concern about ischaemia continues after angiography.[7]

Drug therapy is important in the long-term management of patients after myocardial infarction, both for symptom control and for secondary prevention,[3,7,71,72] and there is some evidence that increased use of established therapies has reduced overall mortality.[73]

- *Aspirin*, given during the acute phase and then continued for one to two years, has been shown to reduce mortality and re-infarction rates. A meta-analysis[74] confirmed the benefit of prolonged antiplatelet treatment in the secondary prevention of myocardial infarction and patients should receive antiplatelet therapy indefinitely. Clopidogrel appears to be as effective as aspirin[75] and may be used in patients intolerant of, or with contra-indications to, aspirin. Dual antiplatelet therapy with both aspirin and clopidogrel for 2 to 4 weeks may also be considered after acute STEMI,[5,71] and it may be reasonable to continue long-term.[5,7]
- *Oral anticoagulation* is only recommended after acute myocardial infarction if patients have some other indication, although warfarin may be used in patients unable to take antiplatelet drugs.[7,71] There is some evidence that medium-intensity warfarin anticoagulation (INR 2.0 to 2.5) given with aspirin may be more effective than aspirin alone,[76] but bleeding is increased and the combination is only generally recommended as an alternative in patients requiring dual antiplatelet therapy who are unable to take clopidogrel.[71]
- Long-term prophylactic treatment with oral *beta blockers* (most studies have used propranolol, metoprolol, or timolol) has reduced mortality and the rate of re-infarction.[54] In patients with no contra-indications to beta-blocker therapy (see Precautions, p. 1320.3) they are usually started before hospital discharge and continued for a minimum of one year; indefinite use has been recommended.[3,5,7,71] A survey of 201 752 patients who had a myocardial infarction found that low-risk patients and those with conditions often considered to be contra-indications also benefited from a beta blocker.[77] There is also clear evidence of benefit in the elderly,[78,79] although beta blockers have often been underused in such patients.
- *Calcium-channel blockers* are not routinely used in the long-term management of myocardial infarction, although in selected patients without heart failure verapamil or diltiazem may be of some benefit if beta blockers are contra-indicated.
- *ACE inhibitors* reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Myocardial infarction patients with left ventricular dysfunction benefit from long-term oral ACE inhibitors started early after infarction and continued for at least 4 to 6 weeks.[80,81] Long-term use of ACE inhibitors in patients without left ventricular dysfunction is less established, since less benefit has been found in this group. However, the HOPE study[82] found that treatment with ramipril significantly improved outcome in patients at high risk for cardiovascular disease, including patients with previous myocardial infarction but preserved left ventricular function, and some guidelines[5,71] therefore consider that long-term use of ACE inhibitors is reasonable in all patients after myocardial infarction, although it is not mandatory.[7]
- *Angiotensin II receptor antagonists* may be an alternative; a study[83] comparing valsartan with captopril found that both were equally effective, although another study[84] comparing losartan with captopril suggested that ACE inhibitors should remain first-line.
- *Aldosterone receptor blockade* with a drug such as eplerenone improves mortality in patients with left ventricular dysfunction[85] and is recommended in patients with evidence of heart failure.[5-7,71]
- *Statins* are effective in the primary and secondary prevention of myocardial infarction in patients with both high and average cholesterol concentrations and their use has been advocated in all patients who have suffered a myocardial infarction (see Cardiovascular Risk Reduction, p. 1246.1).
- *Omega-3 acid ethyl esters* improve outcomes when added to standard therapy[86] and may be considered if dietary intake is inadequate.[71]
- Some patients, for example those with myocardial ischaemia or poor left ventricular function, may require long-term *nitrates*, but there is no evidence to support their routine use in all patients.[7]

Post-infarction problems such as heart failure (left ventricular dysfunction), angina pectoris, and arrhythmias are discussed on p. 1262.3, p. 1254.3, and p. 1266.1, respectively.

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Reperfusion and revascularisation procedures

Ischaemia due to impaired blood flow is a major factor in cardiovascular disorders such as angina pectoris (p. 1254.3), myocardial infarction (p. 1257.1), peripheral vascular disease (p. 1272.3) and ischaemic stroke (p. 1269.2). The underlying cause is usually atherosclerosis (p. 1250.2); this leads to narrowing of arteries with a consequent reduction in blood flow, while rupture of the atherosclerotic plaque may lead to thrombosis and acute occlusion of the artery. Restoration of blood flow is therefore one of the main aims of treatment for atherosclerotic disorders, and may be achieved by pharmacological and non-pharmacological methods. The choice of method depends on the condition being treated and is discussed under the individual diseases. Pharmacological methods such as thrombolysis are usually only used in acute occlusion to break down the blood clot and restore flow. Non-pharmacological methods may be used in acute occlusion or electively in situations where stenosis of the blood vessel restricts but does not totally obstruct flow. The methods used in the coronary circulation include percutaneous coronary interventions (PCI) such as balloon angioplasty and stenting,[1-3] and surgical procedures such as coronary artery bypass grafting (CABG); similar techniques are used for peripheral vascular and cerebrovascular disease. Where non-pharmacological methods are used, adjunctive drug therapy is required to prevent and treat acute and long-term complications, and this is the focus of the following discussion.

Patients undergoing surgery or PCI are at risk of **thrombosis** during and immediately after the procedure due to damage to the arteries at the site of intervention and the use of angioplasty catheters or extracorporeal circulation. Antithrombotic therapy with anticoagulants and antiplatelet drugs therefore has an important role[2-5] at the time of the procedure and may also be needed long-term (see below). However, use of antithrombotics inevitably increases the risk of bleeding, and it is important to consider the relative risks of thrombosis and bleeding in the individual patient when selecting an antithrombotic strategy.[6]

Anticoagulants are used in both surgery and PCI.

Surgery

- For surgery involving cardiopulmonary bypass, high doses of unfractionated heparin are given by intravenous infusion. The dose is usually adjusted according to the activated clotting time (ACT), although monitoring blood-heparin concentrations may be an alternative. A target ACT of 400 to 480 seconds has been suggested,[7] with reversal of anticoagulation at the end of surgery. Lower doses may be adequate in patients undergoing 'off-pump' or 'beating-heart' surgery (target ACT 250 seconds[7]) and in peripheral bypass surgery, although the optimum degree of anticoagulation is not established.
- Alternatives to heparin have been tried and positive results have been reported with hirudins (bivalirudin[8] and lepirudin[9]) and with the direct thrombin inhibitor argatroban,[10] although they are usually reserved for patients with heparin-induced thrombocytopenia.[7]
- Antifibrinolytics have been given to reduce bleeding complications after surgery, although there is some evidence that use of aprotinin may be detrimental (see Haemorrhagic Disorders under Uses and Administration of Aprotinin, p. 1133.3).

PCI

- In PCI, unfractionated heparin is generally used since it can be rapidly reversed if emergency surgery is required, but the high doses needed to achieve a target ACT of 250 to 350 seconds[2,3] make bleeding a problem. Lower doses of heparin may be effective and safer, particularly if glycoprotein IIb/IIIa-receptor antagonists are also used, and a target ACT of 200 to 250 seconds has been suggested;[2,3] however, an analysis[11] found no clear relation between heparin dose and outcome.
- Low-molecular-weight heparins have been used, although evidence for their efficacy is limited;[2,3,12,13] a meta-analysis[14] that included mostly non-blinded studies found that low-molecular-weight heparin was as safe and effective as unfractionated heparin, and further studies[15,16] have come to similar conclusions. A subsequent meta-analysis concluded that bleeding events were less common with low-molecular-weight heparins in PCI, without reduction in efficacy.[17]
- Direct thrombin inhibitors may be another alternative;[2,3,13] bivalirudin appears to be as effective as heparin,[18-20] and may be safer than heparin in PCI for acute myocardial infarction,[21] while a study with desirudin[22] found fewer early ischaemic events but no long term benefit compared with heparin.
- Fondaparinux has also been tried,[23] but the risk of catheter thrombosis may be increased and additional unfractionated heparin is recommended at the time of the procedure.[3,13]

Antiplatelet drugs have an important role in reducing acute thrombotic complications and in long-term treatment.

Surgery

- In patients undergoing surgical bypass, they are not usually started until after the procedure since they increase the risk of bleeding, and patients who are already taking such drugs usually have them withheld for several days before elective surgery.[24] However, the need for this has been questioned. Blood loss and use of blood products are higher in patients who continue antiplatelets pre-operatively,[25-28] but this is only in those taking higher doses (325 mg or more of aspirin daily),[28] and there is some evidence that use of aspirin pre-operatively may improve outcomes.[29]

PCI

- The use of antiplatelet drugs with anticoagulants during PCI is of established benefit. Aspirin is considered standard therapy,[2,3,13] and patients who are not already taking aspirin are usually given a loading dose at least 2 hours before the procedure; a thienopyridine (such as clopidogrel or ticlopidine) may be used in patients unable to tolerate aspirin. However, aspirin does not completely inhibit platelet function and combination therapy and more potent drugs have also been studied.
- Use of a thienopyridine with aspirin improves outcomes and is now generally recommended,[2,3,13] although the

dose and timing have been debated. Pretreatment appears to be most effective,[30] but the increased bleeding risk may be of concern if emergency surgery is required. For clopidogrel, use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention[2,3] and there is some evidence that it needs to be given at least 15 hours before.[31] A higher dose of 600 mg may be effective if given at least 2 hours before PCI[32,33] and has been recommended,[3] particularly in patients with non-ST elevation acute coronary syndromes.[13] However, in patients with stable angina, routine use of a 600-mg loading dose at least 6 hours before angiography was no more effective than a selective strategy in which the same dose was given immediately after angiography only to those patients proceeding to PCI.[34] Prasugrel, which has a faster onset and more consistent effect than clopidogrel, has been used as an alternative in patients with acute coronary syndromes and may be superior in terms of ischaemic outcomes, but is associated with a higher rate of bleeding.[35]

- Glycoprotein IIb/IIIa-receptor antagonists such as abciximab, eptifibatide, and tirofiban given intravenously improve outcomes in a variety of patients undergoing PCI,[36] including those with acute coronary syndromes, those undergoing elective PCI, and patients receiving intracoronary stents. However, recommendations for their use vary,[2,3,13,37] and some guidelines consider them unnecessary in low-risk patients unless complications occur. Although usually given at the time of the procedure, there is some evidence[38-40] that early use may be beneficial in patients undergoing PCI for acute myocardial infarction.

  In most studies glycoprotein IIb/IIIa-receptor antagonists have been given as adjuncts to heparin and aspirin, and their role in patients also taking clopidogrel is less clear, particularly in patients at lower risk. While some observational studies have suggested improved outcomes,[41] others have found no benefit,[42] and randomised studies have also shown mixed results. For abciximab, improved outcomes have been reported in patients pretreated with clopidogrel undergoing PCI electively[43] or for acute coronary syndromes (although only in those with raised troponins),[44] but a study[45] in patients with acute ST-elevation myocardial infarction found no benefit. For tirofiban, pre-hospital use in addition to clopidogrel improved outcomes in patients undergoing PCI for acute myocardial infarction,[39] and benefit was also seen in patients shown to be poor responders to aspirin and/or clopidogrel.[46] There is also some evidence[47] that use of glycoprotein IIb/IIIa-receptor antagonists (in this case eptifibatide) with both clopidogrel and aspirin may make the routine use of heparin unnecessary.

Other acute complications during PCI include vasospasm, reperfusion injury, and arrhythmias; lack of reflow in the target artery ('no-reflow') may result from vasospasm or distal embolisation. Vasodilators such as nitrates or calcium-channel blockers may be given at the start of the procedure to reduce vasospasm.[2] Where vasospasm causes no-reflow, verapamil, adenosine, or sodium nitroprusside may be used,[2] although they are not recommended for routine prophylaxis.[48] Some benefit has been reported[49] from intracoronary thrombolysis immediately after PCI, but this requires confirmation. Various drugs have been tried for cardioprotection,[50] and to protect against myocardial reperfusion injury,[51] but none yet has an established role.

Long-term treatment. Patients undergoing surgical or percutaneous revascularisation remain at risk of thrombosis after the procedure as the endothelium heals, and are also at risk of further cardiovascular events due to generalised atherosclerosis. Antithrombotic therapy should therefore be continued long-term, and patients should also be assessed for their overall cardiovascular risk and treated as appropriate (see Cardiovascular Risk Reduction, p. 1246.1).

Anticoagulants are usually only given intravenously at the time of the procedure and oral anticoagulants such as warfarin are not routinely used. They may have a role in addition to aspirin in patients at high risk of graft occlusion after peripheral artery bypass,[52] although a study[53] comparing oral anticoagulants with aspirin found no difference in reocclusion or mortality, whereas bleeding was higher in patients receiving anticoagulants. Patients undergoing PCI who are taking oral anticoagulants for other indications require careful assessment, and choice of long-term therapy again depends on the balance between bleeding and thrombotic risks.[54,55]

Antiplatelet drugs have an established role in reducing major coronary events after surgical and percutaneous revascularisation procedures,[55-57] and may also reduce reocclusion after peripheral percutaneous interventions[58] and peripheral-artery bypass grafting.[59] Aspirin is recommended indefinitely in all patients,[13,24,52] although the optimum dose after PCI is unclear.[60] Clopidogrel may be used as an alternative in patients unable to take aspirin, but may also be given as additional therapy. There is evidence that it reduces major coronary events when given with aspirin after PCI,[61] and long-term use of the combination has been recommended,[3,13,24] especially in patients with coronary stents. Prasugrel may be used instead of clopidogrel in patients with acute coronary syndromes, although any increase in efficacy may be offset by the higher incidence of bleeding.[35]

Coronary artery stents[1,62] were initially developed to treat or prevent acute occlusion of the vessel due to elastic recoil after balloon angioplasty, but are now used routinely in most PCI to reduce the risk of restenosis (see below), although their effect on mortality is unclear.[63] Thrombotic occlusion 2 to 14 days after the procedure (subacute stent thrombosis) is a major complication with stent use, and initially led to the use of intensive anticoagulant/antiplatelet regimens.[62] However, with optimal stent deployment and use of heparin during the procedure, oral antiplatelet drugs alone appear to be adequate, and a combination of aspirin with a thienopyridine is now recommended. Aspirin should be continued indefinitely, but the optimum duration for thienopyridine therapy is less clear. Most experience has been with clopidogrel, and recommendations depend on the type of stent used. For patients with bare metal stents, clopidogrel should be given for at least 2 to 4 weeks,[2] and treatment for 12 months has been recommended.[3,24] For patients with drug-eluting stents, the risk of occlusion persists for longer, and the benefit of continuing clopidogrel is better established.[64,65] Combination therapy is therefore recommended for at least 12 months,[3,24,66] and may be continued indefinitely if tolerated.[24] Cilostazol has also been used, both as an alternative to thienopyridines[67,68] (although some have suggested[69] that aspirin plus cilostazol may carry a higher risk of stent thrombosis after PCI than other double regimens), and as part of a triple platelet regimen.[69-71] Heparin-coated stents may also have a role.[72]

Restenosis is a specific long-term complication of percutaneous procedures.[1,73,74] Several pathological processes are believed to be responsible, including platelet aggregation and thrombus formation, elastic recoil, vascular remodelling, and neointimal hyperplasia. Symptomatic restenosis often requires a repeat revascularisation procedure and increases the risk for clinical events. Stents reduce restenosis by preventing elastic recoil and vascular remodelling, but are associated with a higher risk of neointimal hyperplasia, and in-stent restenosis is a particular problem.[75,76] This has led to the investigation of drugs to prevent restenosis, but results with systemic therapy have generally been disappointing. Greater success has been reported with drug-eluting stents, and these are now widely used, as discussed below; however, they are not without complications, and oral therapies continue to be investigated.

Although **systemic therapy** with antiplatelet drugs and anticoagulants reduces the risk of thrombus formation, there is little evidence that they reduce the degree of restenosis; studies with cilostazol have suggested that it may have some effect,[77,78] but this is not yet established. Lipid-regulating drugs are indicated in most PCI patients for cardiovascular risk reduction, but again their effects on restenosis are unclear;[73] there is weak evidence that omega-3 fatty acids[79] reduce restenosis, while mixed results have been reported with statins[80,81] and with probucol.[82,83] Folate therapy (folic acid, vitamin B_6, and vitamin B_{12}) has been tried since it reduces plasma-homocysteine concentrations, a risk factor for atherosclerosis and possibly restenosis, but again results have been mixed.[84]

Antiproliferative drugs have been tried, but early positive results have generally not been confirmed in larger studies.[73,85] Sirolimus, which is widely used in drug-eluting stents, has shown benefit[86-88] when given orally. Other drugs for which positive or mixed results have been reported include angiotensin II receptor antagonists,[89,90] calcium-channel blockers,[91,92] corticosteroids,[93] and thiazolidinediones,[94] but none has an established place in therapy.

The disappointing results with systemic drug treatment may relate to the difficulty in achieving adequate concentrations at the target site and **localised methods** of treatment, including radiotherapy and drugs, have therefore been tried. Intracoronary radiotherapy (brachytherapy) is effective but is complex to perform and not widely available, and drug-based methods are therefore preferred.

Drug-eluting stents are the most common approach. These usually consist of metal stents coated with a polymer containing the drug, which is then released over a period of time, and they allow the localised delivery of high doses of drugs to the site of vessel injury. Stents eluting antiproliferative drugs (mainly sirolimus or paclitaxel) are most widely used and have been shown to reduce neointimal proliferation and clinical events, including the need for repeat revascularisation,[95-97] although whether they have a long-term benefit over bare-metal stents in all patients is not clear.[98-101] They are also effective for the treatment of in-stent restenosis in bare-metal stents. There is some evidence that sirolimus is superior to paclitaxel,[102] but the clinical importance of this seems doubtful.[103,104] Sirolimus analogues such as everolimus, zotarolimus, and umirolimus are also used, while other drugs such as dexamethasone and lanreotide have been tried or are available. Heparin-coated stents, which have been used to reduce periprocedural thrombosis (above), may also have a longer-term effect on restenosis.[72] Other approaches include antibody-coated stents, bioresorbable stents, and local gene therapy. Use of paclitaxel-coated angioplasty balloons has also been tried[105,106] and may overcome some of the problems associated with the long-term presence of stents in the coronary arteries.

One of the main complications reported with the use of drug-eluting stents is late stent thrombosis.[107,108] It appears to be more common than with bare-metal stents,[109] and has been attributed to mechanisms such as delayed endothelialisation caused by the drug or hypersensitivity reactions related to the polymer coating.[110,111] However, analyses using different definitions of late thrombosis have suggested[112] that there is no significant difference between the types of stent, and the clinical relevance of any increase in the incidence of late thrombosis remains unclear. The effect of drug-eluting stents on mortality has also been debated; some analyses[113,114] have reported an increased mortality with drug-eluting stents, whereas others[109,115] have found no significant effect. There is some evidence[116,117] that outcomes with drug-eluting stents are worse in high-risk clinical situations, yet observational studies[118,119] suggest they are as safe as bare metal stents in such patients. The FDA has stated[66] that the concerns about thrombosis do not outweigh the benefits of drug-eluting stents when used for their approved indications, but that outcomes may not be the same in other patients.

Duration of antiplatelet therapy is an important factor in the development of stent thrombosis,[108] but the prolonged requirement for dual antiplatelet therapy may cause problems in patients with drug-eluting stents who require surgery for other indications.[120] There is some evidence that thienopyridines can be safely withheld for a short period if aspirin is continued,[121] but surgery should ideally be delayed for at least the 12 months recommended as a minimum for dual therapy; bare-metal stents may be preferred in patients scheduled for surgery who require PCI.

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Structural Heart Diseases

Cardiomyopathies

Cardiomyopathy is a broad term used to describe diseases of the heart muscle associated with cardiac dysfunction. It was formerly used specifically for disorders without a known cause (idiopathic cardiomyopathy), but advances in diagnostic techniques and an increased understanding of disease mechanisms and genetic factors mean that many of these disorders now have an identified cause, and the definition has broadened. Cardiomyopathies are a major cause of heart failure and the term has sometimes been used for heart failure in general.

Primary cardiomyopathies are those which affect only or mainly the heart muscle, rather than being part of a wider systemic disorder. They have traditionally been classified on the basis of anatomic and functional features into 3 main types: dilated, hypertrophic, and restrictive, of which dilated and hypertrophic are the most common. These classifications are not ideal, and some newly identified forms (such as arrhythmogenic right ventricular cardiomyopathy and ion channelopathies) do not fit into this scheme. Classification based on the origin of the disorder (such as genetic versus

acquired) may therefore be preferred.[1] However, the former definitions remain widely used, particularly in reviews of management,[2-15] and these are the classifications used in the following discussion.

Dilated cardiomyopathy (previously known as congestive cardiomyopathy) is characterised by systolic dysfunction with dilated and poorly contracting ventricles and a low cardiac output. The right, left, or both ventricles may be affected. Although there may be some ventricular hypertrophy, because of the dilatation there is no overall increase in the thickness of the ventricle walls. Genetic forms of dilated cardiomyopathy do occur, but it is usually acquired, developing as a consequence of another cardiovascular or systemic disorder. Ischaemic heart disease is one of the main cardiovascular causes; others include systemic or pulmonary hypertension, valvular disorders, and congenital heart disease. Myocarditis (infectious, or as a result of toxins or drugs),[16,17] metabolic disorders, nutritional deficiencies, pregnancy, and immunological conditions, can also lead to dilated cardiomyopathy. Patients may be asymptomatic for some time but the initial manifestations are commonly those of heart failure; chest pain, systemic and pulmonary embolism, and arrhythmias may also occur. Management of dilated cardiomyopathy is mainly symptomatic and supportive and should generally follow the conventional strategies for heart failure (see below), including ACE inhibitors, diuretics, and beta blockers. Early studies[18-20] of beta blockers in patients with dilated cardiomyopathy found significant improvements in cardiac function and symptoms, and prevention of clinical deterioration, but failed to show a significant effect on overall mortality. However, a further study evaluating carvedilol therapy in patients with heart failure, including patients with dilated cardiomyopathy, was stopped early because mortality was significantly less in the carvedilol groups[21] and the CIBIS-II study[22] using bisoprolol was also stopped early because of favourable results. A long-term study[23] using metoprolol reported better survival in those taking metoprolol for up to 7 years. Although calcium-channel blockers are not usually used in heart failure, symptomatic improvement has also been reported with the calcium-channel blocker diltiazem.[24]

Patients with dilated cardiomyopathy may be at particular risk for systemic or pulmonary thromboembolism, due to blood stasis in the poorly contracting ventricle. Chronic oral anticoagulation has therefore been suggested, although current recommendations generally limit its use to those with atrial fibrillation, previous systemic embolism, or severe left ventricular dysfunction.[2,25] Arrhythmias should be treated as appropriate (see Cardiac Arrhythmias, p. 1266.1); amiodarone may be particularly suitable as it has no negative inotropic effect. Low-dose amiodarone has been tried in patients at high risk of sudden death, but its role has not yet been confirmed.[2,8] Implantable cardioverter-defibrillators may have a role in some patients.[26]

Treatments directed at the underlying cause of the cardiomyopathy have also been tried, but results have generally been disappointing. Metabolic and nutritional supplements such as growth hormone, levothyroxine, and levocarnitine have been investigated, and some positive results have been seen with immunosuppressants or drugs with immunological effects, such as pentoxifylline, in patients with presumed myocarditis. However, none of these has an established role.

Surgical treatments that restore ventricular shape and function have been tried but cardiac transplantation remains the main method of improving survival; mechanical support of the heart may be used as a bridge to recovery or transplantation.

Hypertrophic cardiomyopathy (previously known as obstructive cardiomyopathy) is characterised by ventricular hypertrophy but the ventricles are not dilated. This leads to diastolic dysfunction since diastolic filling is impaired by the stiff hypertrophied ventricular walls. It is an inherited condition occurring as an autosomal dominant trait and can occur at any age although presentation during the second decade of life is common. Patients may be asymptomatic or may have chest pain, syncope, dyspnoea, or arrhythmias. Sudden death associated with emotional stress or exercise is not an uncommon finding and patients should avoid intense exercise. However, overall life expectancy is similar to that of the general population and many patients have little or no disability and do not require treatment.[5,11]

Patients should be investigated for the presence of any arrhythmias and treated appropriately (see Cardiac Arrhythmias, p. 1266.1) although this may not necessarily prevent sudden death. Atrial fibrillation is particularly important and is probably most effectively treated with amiodarone.[4,5,11-13] Anticoagulation should be considered in all patients with sustained atrial fibrillation.[4,5,11-13]

Beta blockers may be used for control of symptoms. They curtail emotion- or exercise-induced tachycardia. Anginal pain is also reduced and syncopal attacks may be prevented. Calcium-channel blockers (usually verapamil) also improve symptoms and exercise tolerance and may be considered in those who continue to have disabling symptoms or who are unable to tolerate beta blockers; however, verapamil may have adverse effects in patients with outflow obstruction and it should be used with caution in such patients.[9-13] In a crossover study,[27] exercise capacity was not improved by either verapamil or nadolol, although most patients preferred one or other of the drugs rather than placebo and quality of life did appear to be improved by verapamil. Other drugs that may provide symptomatic relief include disopyramide, which is used for its negative inotropic effect and is often given with beta blockers. Diuretics may be needed for congestive symptoms but may also reduce cardiac output. Surgery or septal ablation to reduce outflow obstruction may be of benefit in some patients whose symptoms are resistant to drug therapy.[4,5,9-13,28,29]

The risk of sudden death is difficult to assess, particularly in asymptomatic patients. Neither beta blockers nor verapamil, as used for possible symptomatic relief, prevent ventricular arrhythmias. However, there is some evidence[30] that high-dose therapy with beta blockers may improve survival in children with hypertrophic cardiomyopathy. Low-dose amiodarone may have a role in high risk patients, but adverse effects may limit its use;[9,11] implantable cardioverter-defibrillators are also used in some patients.[11-13,31]

In **restrictive cardiomyopathy** the filling of the ventricles is impaired, often due to endomyocardial fibrosis,[32] resulting in mostly diastolic dysfunction. Diuretics may improve congestive symptoms but should be used cautiously as they may decrease cardiac output. Arrhythmias should be treated if they are symptomatic and anticoagulation is advised, particularly in patients with atrial fibrillation, valvular disorders, or a low cardiac output.[6] Surgery may be of benefit in some patients.[32]

Management of **arrhythmogenic right ventricular cardiomyopathy** may involve implantation of a defibrillator, the use of antiarrhythmic drugs (notably sotalol), or catheter ablation.[33-37]

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Heart failure

Heart failure is a clinical diagnosis made in a patient with a known or suspected cardiac disorder who presents with dyspnoea, fatigue, and oedema (peripheral and/or pulmonary). It may be graded as mild, moderate, or severe depending upon whether symptoms such as dyspnoea and fatigue appear on ordinary physical exertion, on little exertion, or at rest, respectively. Another grading system (that of the New York Heart Association) has four grades (NYHA grades I, II, III, IV), again partly classified on appearance of symptoms in relation to exertion (with grade IV representing the most severe form). The discussion that follows focuses on the chronic form of heart failure; acute heart failure, which may result in cardiogenic shock, is covered under Shock, p. 1279.3.

Heart failure is a common condition[1] and is a consequence of abnormalities in cardiac structure or function. It may result from disorders or diseases of the heart muscle, injury, or cardiovascular stress such as hypertension or valve disorders. Myocardial infarction is one of the leading causes of heart failure, and chronic myocardial ischaemia may also be a contributing factor. Cardiomyopathies, cor pulmonale, infections causing myocardial damage, and cardiotoxicity arising from alcoholism or induced by drugs may also lead to heart failure. The increased demands put on the heart by chronic severe anaemia or hyperthyroidism can also be precipitating factors.

Traditionally, heart failure has been thought of in purely haemodynamic terms, as a condition in which the heart is unable to provide an adequate blood flow to meet the metabolic demands of the body. However, it is now appreciated that compensatory neurohormonal mechanisms play just as important a role in its development.[2,3] Echocardiography, the most useful investigative procedure in patients with heart failure, assesses haemodynamic factors; it allows assessment of ventricular function and ejection fraction, enables structural changes to be seen and rapidly identifies patients with potentially correctable abnormalities such as valvular disease. Measurement of blood concentrations of natriuretic peptides has been suggested as another useful investigation;[4-7] this relates to the neurohormonal mechanisms involved.

Echocardiography may identify dysfunction of either the right or left ventricle (right- or left-sided heart failure), although dysfunction of both ventricles is likely to be present to some extent. In most patients, the predominant finding is that of a dilated and poorly contracting left ventricle, with a reduction in both ventricular ejection fraction and cardiac output. This represents left ventricular systolic dysfunction, and is particularly common in patients with heart failure after myocardial infarction. Patients with symptoms of heart failure but a preserved left ventricular ejection fraction are often described as having diastolic dysfunction or isolated left ventricular diastolic dysfunction;[8-10] cardiac output is usually normal in such patients, but fails to increase in response to exercise. Diastolic dysfunction is more common in the elderly and also occurs in some cardiomyopathies (see p. 1261.3); many patients have both diastolic and systolic dysfunction. Asymptomatic left ventricular dysfunction has been found in some patients, especially those in the early postmyocardial infarction period, and although these patients are not strictly defined as having heart failure, treatment is recommended to prevent the development of full symptomatic disease.

Neurohormonal disturbances both result from, and contribute to, the deterioration in ventricular function.[3]

Myocardial injury or impairment leads to an inability of the ventricles to empty adequately during systole. The resulting ventricular dilatation increases wall tension and initially leads to an increase in contraction while the decrease in cardiac output and blood pressure results in activation of the sympathetic nervous system, leading to an increase in the force and frequency of contraction. Reduced renal blood flow also leads to activation of the renin-angiotensin-aldosterone system, resulting in vasoconstriction and fluid retention. At the same time, an increase in wall stress also occurs in the atria, leading to secretion of atrial natriuretic peptide; this inhibits the release of noradrenaline but also has direct vasodilator and natriuretic actions that lower the haemodynamic load on the heart. Thus, in the short term, compensation for myocardial injury can occur and cardiac output may be maintained. In the long term, these compensatory haemodynamic and neurohormonal mechanisms become ineffective. Ventricular dilatation progresses, the sympathetic nervous system and renin-angiotensin system are persistently activated, ventricular hypertrophy occurs, and ventricular function deteriorates progressively.

Management. Heart failure is a progressively disabling condition associated with considerable morbidity and mortality. Management is aimed therefore not only at providing symptomatic relief, but also at improving prognosis, in terms of both progression and mortality. Reviews[11-14] and guidelines[4-7] have been published about the management of heart failure due to left ventricular systolic dysfunction. The management of patients with preserved left ventricular ejection fraction, or diastolic dysfunction, is less clear.[5-10,15] In theory, this should differ from systolic dysfunction, but there have been few studies specifically in such patients. Many of the early studies were based on a clinical diagnosis of heart failure and may have included patients with diastolic dysfunction, and there is evidence that they might benefit from some standard treatments,[16] but therapy for such patients is not established and the following discussion is specific for patients with systolic dysfunction unless stated otherwise.

Treatment involves non-pharmacological and pharmacological interventions. Any underlying cause or exacerbating factors should be corrected, and several general measures may be beneficial. Weight reduction should be considered in the overweight and moderate salt restriction may be undertaken. In acute heart failure bed rest may become necessary, but in controlled chronic heart failure exercise should be encouraged and specific exercise programmes may be of benefit.[4-7,17,18] Immunisation with influenza and pneumococcal vaccines is advised.[4-7] Anaemia may be both a cause and a consequence of heart failure and should be treated appropriately (see p. 1121.2). Drug therapy of heart failure is based on the use of diuretics, ACE inhibitors or angiotensin II receptor antagonists, and beta blockers; aldosterone antagonists, cardiac glycosides, and vasodilators may also be used. Surgical interventions and implantable devices may have a role in selected patients.

Diuretics have been the mainstay in the treatment of heart failure, and continue to have an important role.[19] They provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a *thiazide diuretic*, such as *bendroflumethiazide* or *hydrochlorothiazide*, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a *loop diuretic* such as *furosemide* will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade) may be needed in some patients, especially when there is diuretic resistance.[20] A loop diuretic with either a thiazide or *metolazone* is often used,[4,6,7] but severe fluid and electrolyte disturbances may occur, particularly with metolazone. *Spironolactone* is an aldosterone antagonist and has diuretic and possibly additional effects, as discussed below.

However, diuretics are not a sufficient treatment on their own as clinical stability tends to deteriorate over time. In addition, although a meta-analysis[21] has suggested that diuretics have beneficial effects on symptoms and mortality, there have been no long-term studies assessing the effect of diuretics on prognosis, and drugs that have been shown to have a mortality benefit are also required.

At all stages of chronic heart failure, ***ACE inhibitors*** given orally produce additional clinical benefit to that seen with diuretics. They relieve symptoms such as dyspnoea and improve exercise tolerance. Since angiotensin II appears to be involved in the generation of cardiac arrhythmias, an antiarrhythmic effect has also been suggested, although this has not been established.[22] Studies have shown that ACE inhibitors improve survival and reduce the progression of mild or moderate heart failure to more severe stages.[23] ACE inhibitors may also be beneficial in asymptomatic left ventricular dysfunction.[24] The Studies of Left Ventricular Dysfunction (SOLVD)[25] studies indicated that ACE inhibitors, in this case enalapril, might protect against myocardial infarction, unstable angina, and cardiac death in patients with either symptomatic or asymptomatic disease. ACE inhibitors are recommended[4-7] in all patients with left ventricular systolic dysfunction, whether or not they have symptoms. Where tolerated, doses should be titrated to those found to be effective in randomised studies, rather than according to symptomatic response.

ACE inhibitors have also been given to patients shortly after suffering myocardial infarction (p. 1257.1) but before the development of symptomatic heart failure and appear to be beneficial. However, it is not yet clear which patients should be given such therapy or when it should be started.

Angiotensin II receptor antagonists have been investigated both as alternatives to ACE inhibitors, and also with ACE inhibitors to provide more complete blockade of the renin-angiotensin system. As alternatives to ACE inhibitors, they appear to have a similar efficacy.[26] An early study[27] suggested that *losartan* improved mortality compared with enalapril, but this was not confirmed in the larger ELITE II study,[28] although losartan was found to be better tolerated. Studies with losartan[29] and *valsartan*[30] in patients with heart failure after myocardial infarction also failed to show superiority over ACE inhibitors. However, there were generally fewer adverse effects with angiotensin II receptor antagonists, and a further study[31] found that *candesartan* was of benefit in patients who could not take ACE inhibitors. Guidelines continue to recommend ACE inhibitors as first-line therapy, but angiotensin II receptor antagonists are an acceptable alternative, particularly in those unable to tolerate ACE inhibitors.

Dual inhibition of the renin-angiotensin system using ACE inhibitors and angiotensin II receptor antagonists together may be of benefit; both candesartan[32] and valsartan[33] have been shown to reduce hospitalisation for heart failure when added to ACE inhibitors, although the effects on mortality are unclear. Although one study[33] suggested detrimental effects in patients who were also taking beta blockers, this has not been confirmed. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.[4-6] However, this approach has been criticised.[34]

Beta blockers can inhibit the persistent activation of the sympathetic nervous system that is associated with disease progression. This benefit far outweighs their negative inotropic effects, and the role of selected beta blockers in the long-term management of heart failure is established. Beta blockers are recommended[4-7] in all patients with clinically stable heart failure due to left ventricular systolic dysfunction and should be given with ACE inhibitors and diuretics. They must be introduced cautiously since symptoms may initially worsen, but if tolerated the doses should then be titrated to those found to be effective in randomised studies. Temporary withdrawal or dosage reduction may be necessary in patients with acute decompensation[6] (see below). It is not a class effect: only *bisoprolol*, *carvedilol*, *nebivolol*, and long-acting preparations of *metoprolol* have shown positive effects on mortality and morbidity in patients with varying degrees of heart failure and are recommended for such use.[6] It is unclear which of these provides the greatest effect, but a meta-analysis[35] in patients with mild to moderate heart failure suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation. The degree of heart-rate reduction achieved appears to be more important than specific doses.[36]

Beta blockers also appear to be of value in heart failure due to idiopathic dilated cardiomyopathy (see Cardiomyopathies, p. 1261.3) and possibly in isolated diastolic dysfunction.

Aldosterone antagonists may have a role in some patients with heart failure.[37-39] Raised levels of aldosterone appear to contribute to the pathophysiology of heart failure and, while ACE inhibitors suppress aldosterone production, the effect is not complete. Aldosterone antagonists have therefore been tried as adjuncts to ACE inhibitors. In patients with severe heart failure, addition of low-dose *spironolactone* to ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation.[40] Another aldosterone antagonist, *eplerenone*, has shown benefit,[41] when added to standard therapy in patients with heart failure after myocardial infarction. Guidelines[4-7] therefore recommend that aldosterone antagonists may be added to standard therapy in patients with moderate to severe heart failure, and in patients with heart failure after myocardial infarction. In patients with less severe heart failure, their adjunctive role is less clear, although a small study[42] has suggested that spironolactone may be of benefit and, in a more recent study, eplerenone[43] has been shown to reduce hospitalisation and mortality among mildly symptomatic patients. However, adverse effects may limit use, and all patients taking aldosterone antagonists with ACE inhibitors must have their plasma-potassium concentrations closely monitored. Aldosterone antagonists should not be used in patients who are taking both ACE inhibitors and angiotensin II receptor antagonists.[6]

Cardiac glycosides such as *digoxin* or *digitoxin* have an extremely long history in the management of heart failure. They are positive inotropes and increase the contractility of the heart thereby increasing cardiac output. Additional effects in heart failure appear to be due to neuroendocrine suppression such as inhibition of the sympathetic nervous system and indirect arterial vasodilatation.

The benefit of cardiac glycosides in heart failure accompanied by atrial fibrillation is not disputed although beta blockers are generally preferred. However, their role in patients with sinus rhythm has been debated. There is evidence that withdrawal of digoxin from patients taking diuretics (the PROVED study)[44] or ACE inhibitors (the RADIANCE study)[45] carries a considerable risk of clinical deterioration, and patients stable on such combinations should therefore be continued on them. However, the large DIG study[46] found that, while addition of digoxin to diuretics and ACE inhibitors improved symptoms, there was no effect on mortality, and a systematic review[47] came to a similar conclusion. The role of digoxin therefore appears to be limited, although it may be used in patients who remain symptomatic despite ACE inhibitor, diuretic, and beta-blocker therapy.[4-7] No clear benefit has been found in patients with diastolic heart failure.[48]

Various ***vasodilators*** have been studied in heart failure. There appears to be no specific role for direct-acting vasodilators, but some benefit has been reported with a combination of *isosorbide dinitrate* and *hydralazine*. The rationale for using them together has been that nitrates produce mainly venous dilatation whereas hydralazine produces arterial vasodilatation, although other mechanisms may also be involved. Used together, they alleviate peripheral vasoconstriction and produce symptomatic control, including a benefit on exercise tolerance, but are of somewhat limited efficacy in long-term control. A modest improvement in long-term survival has been noted but this effect is less than that seen with ACE inhibitors. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[49] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality. Use of isosorbide dinitrate with hydralazine may be considered in patients with left ventricular dysfunction who are unable to tolerate ACE inhibitors or angiotensin II receptor antagonists,[4-7] or as an adjunct to ACE inhibitors in those unable to tolerate angiotensin II receptor antagonists or aldosterone antagonists.[6] Additional therapy with hydralazine and isosorbide dinitrate may also be considered in patients who remain symptomatic despite treatment with ACE inhibitors, beta blockers, and angiotensin II receptor blockers or aldosterone antagonists,[4-7] particularly if patients are of African-American descent.

Calcium-channel blockers, especially verapamil, diltiazem, and the short-acting dihydropyridines, are generally contra-indicated in heart failure because of their negative inotropic activity. Amlodipine has been shown not to adversely affect survival, and it may be considered if the use of a calcium-channel blocker is essential for controlling hypertension or angina.[4,6,7]

Phosphodiesterase inhibitors act as both positive inotropes and vasodilators, a combination of mechanisms that appears particularly attractive in heart failure. Short-term use improves haemodynamic variables, and intravenous *amrinone* or *milrinone* may have a role in patients with severe heart failure unresponsive to other treatment. However, studies with long-term oral phosphodiesterase inhibitors have generally been disappointing. A systematic review[50] found that treatment with oral phosphodiesterase inhibitors was associated with a significant increase in mortality in patients with heart failure, and their use is not currently recommended.

Antiarrhythmics are not routinely used in heart failure since many have a negative inotropic effect. However, sudden deaths in patients with severe heart failure have been attributed to ventricular arrhythmias,[51] and antiarrhythmics such as *amiodarone*, which is not a negative inotrope, have therefore been tried. A meta-analysis[52] of 5 studies involving 1452 patients with symptomatic compensated heart failure indicated that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality, but a later study[53] in mild to moderate heart failure found no survival benefit. Adverse effects may also limit the use of amiodarone, and it is currently only recommended in patients who also have symptomatic arrhythmias.[7] Implantable devices may be an alternative. A reduction in mortality has been shown[53] with use of implantable cardioverter-defibrillators, while resynchronisation therapy using biventricular pacemakers improves symptoms and reduces mortality.[54] Both implantable cardioverter-defibrillators and resynchronisation therapy may therefore be

considered in selected patients,[4-7] and there is evidence that they may be used safely together.[55]

The risk of thromboembolism is increased in heart failure, but the role of routine ***antithrombotic*** therapy is unclear.[56-58] Anticoagulants should be given to patients who have additional indications, such as atrial fibrillation, but the role of *aspirin* in heart failure has been controversial, since there has been some suggestion that it might reduce the benefit of ACE inhibitors. However, there is limited evidence for either benefit or harm with use of the combination[6,7] (see NSAIDs, under Interactions of ACE Inhibitors, p. 1288.3), and some guidelines[4] recommend that aspirin should be given to heart failure patients with appropriate indications, such as atherosclerosis.

Miscellaneous drugs targeting various mechanisms have been tried in heart failure. *Ivabradine*, a selective sinus node I_f inhibitor that slows the heart rate, may reduce hospital admissions and deaths associated with heart failure.[59] However, for many other drugs results have been disappointing, and toxicity and increased mortality have also been seen. *Epoprostenol*, a prostaglandin that causes vasodilatation, has been associated with increased mortality. The oral sympathomimetic inotrope *ibopamine*, an oral dopamine agonist, has similarly produced negative effects. Increased mortality has also been reported with long-term intermittent *dobutamine* infusions, although a small study[60] suggested that survival might be increased if patients were also given amiodarone. *Moxonidine*, a centrally-acting antihypertensive, has also been associated with increased mortality. *Endothelin antagonists* such as *bosentan* appear to be ineffective.[61] Disappointing results have also been reported[62] with *tumour necrosis factor antagonists* such as *etanercept* and *infliximab*, and there have been reports[63] of exacerbation of heart failure in some patients.

Other approaches that have been tried include inhibition of neutral endopeptidase, the enzyme that inactivates atrial natriuretic peptide, with drugs such as *candoxatril*. *Omapatrilat*, a dual inhibitor of endopeptidase and angiotensin-converting enzyme, has shown some benefit,[64] but adverse effects may limit its use. *Vasopressin antagonists*, such as *tolvaptan*, are also used; they increase free-water clearance and improve symptoms of fluid overload, but mortality benefits have not yet been shown.[65] The direct renin inhibitor *aliskiren* is under investigation. Positive haemodynamic effects have been reported with *growth hormone*, although further studies are needed.[66] Studies with *statins* have reported mixed results,[67-69] but there may be some benefit with *omega-3 fatty acid* supplementation.[70]

Many patients with chronic heart failure have exacerbations of their condition (**decompensated heart failure**) requiring hospitalisation.[71,72] Guidelines for treatment are limited[6,7,73] although several approaches are under investigation.[74] Treatment of acute decompensation is similar to that for patients with cardiogenic shock (see Shock, p. 1279.3). Standard therapies should be continued where possible; temporary withdrawal or dosage reduction of beta blockers may be considered but is not necessary in most patients.[7,75] Patients with peripheral or pulmonary oedema due to fluid overload may need intravenous diuretics. Intravenous vasodilators reduce cardiac filling pressure and increase cardiac output and may be needed if symptoms are severe or there is an inadequate response to diuretics. Intravenous nitrates are often used; *nesiritide*, a natriuretic peptide with vasodilator properties, is an alternative, although its effects on mortality are controversial.[76] If cardiac output is low, intravenous inotropes, such as dobutamine or milrinone, may be required. *Levosimendan*, a calcium-sensitiser with both vasodilator and inotropic actions, may also be used. Patients who cannot be weaned from intravenous inotropes may require long-term continuous infusions, either as palliative therapy or as a bridge to transplantation, but regular intermittent infusions may increase mortality and are not generally recommended.[7]

Some patients with **refractory heart failure** may be suitable for ***surgical*** management. Heart transplantation is the optimum surgical therapy but availability is limited and various alternatives have been tried.[77] Left ventricular assist devices may be useful as a bridge to recovery or transplantation, but are not yet established for long-term use. Revascularisation or mitral valve repair may have a role in selected patients, but procedures to augment the heart muscle or reduce ventricular dilatation are not generally recommended[6] since there is limited evidence to support their use.

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Valvular heart disease

Valvular heart disease affects the normal function of the heart and leads to disorders of blood circulation. The principal cause of valvular disease in the developing world is rheumatic heart disease. Other causes are more common in western countries; they include congenital abnormalities, cardiovascular disorders such as ischaemic heart disease and hypertension, and degenerative disorders. Any of the heart valves may be affected but disorders of the aortic and mitral valves are most significant; more than one valve may be involved in some patients.

The symptoms of valvular heart disease depend upon the valve that is affected, and whether the problem is stenosis or regurgitation. All valve disorders place a haemodynamic burden on the heart and ultimately lead to heart failure. Other consequences include the development of pulmonary hypertension and arrhythmias. Infective endocarditis and

thromboembolic disorders, in particular stroke or systemic embolism, are important complications.

The main aims of treatment in patients with valvular heart disease are to reduce symptoms, prevent complications, and reduce mortality.[1-3] Surgical management is usually necessary once symptoms develop and may also be warranted in some patients who are asymptomatic. Medical therapy is generally reserved for pre-operative symptom control and for patients who are unsuitable for surgery.

Medical treatment for **symptomatic patients** is similar to that used in other forms of heart failure (see p. 1262.3). In acute situations sodium nitroprusside and inotropes such as dopamine or dobutamine may be indicated, but for chronic therapy diuretics, digoxin, ACE inhibitors, and beta blockers are used. The choice of drug depends on the valve affected. ACE inhibitors and other vasodilators have generally been avoided in *aortic stenosis* since any reduction in blood pressure cannot be balanced by an increase in cardiac output and there is a theoretical risk of severe hypotension. However, symptomatic improvement has been reported[4] with enalapril in patients with severe aortic stenosis and preserved left ventricular function, although it was not tolerated in those with left ventricular dysfunction, and sodium nitroprusside has been used successfully for acute symptoms.[5] Some guidelines also recommend that beta blockers should be avoided in aortic stenosis.[2] For patients with *aortic regurgitation* who require medical therapy, vasodilators may be of particular value, especially in severe forms.[6] Symptomatic benefit has also been reported[7] with ACE inhibitors in *mitral stenosis*. Arrhythmias should be treated with standard antiarrhythmics (see p. 1266.1).

Drug therapy to prevent the progression of valvular disorders has generally been disappointing. Although similarities have been suggested between aortic stenosis and atherosclerosis, an observational study[8] in asymptomatic patients taking ACE inhibitors for hypertension found no effect on the progression of stenosis, and initial indications of benefit[8] with statins in patients with calcific aortic stenosis were not confirmed in later studies.[9,10] The results of an early study[11] indicating that long-term vasodilator therapy with nifedipine improved outcome in asymptomatic patients with severe aortic regurgitation were not confirmed by a later study of long-term therapy with nifedipine or enalapril.[12] Another study[13] found no benefit with ACE inhibitors in asymptomatic patients with mitral regurgitation.

Surgery is the mainstay of treatment in valvular heart disease and generally involves valve replacement with either bioprosthetic (tissue) or mechanical valves; the latter are longer lasting, but pose a greater risk for thromboembolism. Valve repair may be suitable in some cases, particularly for mitral regurgitation, while balloon valvulotomy may have a role in some patients with stenosis.[3] Valve replacement alleviates symptoms, but patients remain at risk for complications.

In **asymptomatic patients** and in those with **prosthetic valves**, the main aim of therapy is to prevent the complications of bacterial endocarditis and of systemic embolism from thrombus formation within the heart. Antibacterial prophylaxis should be given to patients with valvular heart disease where indicated (see Endocarditis, p. 179.2). Antithrombotic therapy has an important role in patients with prosthetic valves[14] but in asymptomatic patients long-term thromboembolism prophylaxis is generally only recommended in those with another risk factor for embolisation, such as atrial fibrillation, a dilated left atrium, left ventricular dysfunction, a hypercoagulable state, or previous systemic embolism.[3,15,16]

Long-term treatment with an oral anticoagulant such as warfarin is generally regarded as essential for patients with a *mechanical prosthetic heart valve*,[2,3,16] but the optimum level of anticoagulation is unclear. The risk of thromboembolism depends upon the type and position of the valve and the presence of other risk factors, but must be balanced against bleeding risk. In the UK, specific target INRs are recommended where the valve type and position are known and vary between 2.5 and 3.5 for valves in the aortic position and between 3.0 and 3.5 for valves in the mitral position. If specific information is not available a generic target of 3.0 is recommended for valves in the aortic position and 3.5 for valves in the mitral position.[17] In the USA, the recommended INR range is 2.5 to 3.5, with a lower range of 2.0 to 3.0 suggested as being adequate for most types of valves in the aortic position when there are no other risk factors.[3,16] However, a large study[18] in patients stratified to different target INR ranges found that the risk of moderate to severe thromboembolism and of bleeding complications was comparable for INRs ranging from 2.0 to 4.5; patients had aortic or mitral valve replacement, or both, and all had one particular type of valve. There is evidence that adding an antiplatelet drug (dipyridamole or low-dose aspirin) further reduces the risk of death and thromboembolism although the risk of bleeding is increased.[19] Adjunctive antiplatelet drugs may be considered, particularly for patients with additional risk factors such as embolism while on warfarin therapy, or ischaemic heart disease.[2,3,16] Alternatively, or in addition, patients with systemic embolism despite an adequate INR may have their target INR range increased.[16]

For patients with *bioprosthetic heart valves* anticoagulants are recommended for the first 3 months after replacement,[16] although aspirin may be equally effective,[20] and it is often used instead of anticoagulants when only the aortic valve is involved. Longer term oral anticoagulant therapy is generally considered necessary only for patients with additional risk factors (as for asymptomatic patients, above).[3,16] An INR of 2.0 to 3.0 appears adequate for patients with bioprosthetic heart valves. Low-dose aspirin has been recommended[3,16] in patients with bioprosthetic valves who do not require oral anticoagulants, although other guidelines[2] state that there is no evidence to support this.

For patients on long-term anticoagulation, interruption of therapy for surgical procedures or due to bleeding complications exposes patients to the risk of thromboembolism. A study[21] in patients with haemorrhage suggested that it is safe to withhold oral anticoagulants. For patients undergoing surgery, the evidence for either withholding anticoagulants or converting to an alternative form of antithrombotic therapy perioperatively is not conclusive, although recommendations have been made.[2,3,22] The decision depends on the relative risks for bleeding and thromboembolism in the individual patient. In procedures with a low bleeding risk, anticoagulation can usually be continued. In procedures with a higher bleeding risk, anticoagulants may be withheld if the risk of thromboembolism is low, but otherwise conversion to heparin is recommended. The optimum type and dose of heparin to use is not clearly established. While some guidelines recommend low-molecular-weight heparin as first-line,[22] there have been concerns about its safety[23] and others suggest that unfractionated heparin should be preferred.[2,3]

The use of anticoagulants is also controversial in patients with infective endocarditis, partly because of the substantial increase in risk of haemorrhage in these patients, but also because of the likelihood that surgery will be required. Routine anticoagulation is not advised, and patients who are already taking oral anticoagulants should generally have their therapy changed to heparin until it is clear that surgery is not required and the patient is stable.[3,16]

If obstruction of prosthetic valves by thrombus formation occurs, surgical intervention is usually recommended.[2,3,24] Thrombolytics such as streptokinase or urokinase may be used[16] but are often ineffective and are associated with high risk. They are therefore usually reserved for patients at greatest risk from surgical intervention,[2,3] although a study[25] of patients with left-sided prosthetic valve thrombosis found thrombolytics to be more successful than surgery, especially in the critically ill. Repeated treatments[26] may increase the success rate. Heparin may have a role in non-obstructive thrombosis. Patients who have had a valve thrombosis should have their anticoagulant control optimised;[2] higher target INRs or adjunctive antiplatelet therapy may be considered.[3,16]

The haemodynamic changes that occur during **pregnancy** may complicate the management of women with valvular heart disease.[27-29] In addition, pregnancy is a known risk-factor for thromboembolism and patients with valvular heart disease who become pregnant are therefore at increased risk.[30] However, long-term prophylaxis with an oral anticoagulant such as warfarin presents a problem since warfarin is generally contra-indicated in pregnancy (see Adverse Effects under Warfarin, p. 1528.2). Women with mechanical prosthetic valves must continue anticoagulation but choice of therapy is unclear.[3,31,32] A systematic review[33] found that continued use of oral anticoagulants increased the risk to the fetus, but that thromboembolic complications were higher with heparin. Most guidelines therefore advise that the choice should be discussed with the patient, balancing the risks for each individual, but specific recommendations vary.[2,3,32] The main risk of embryopathy with warfarin is between weeks 6 and 12 of gestation and heparin therapy is often substituted during this period and also at term (to avoid an anticoagulated neonate). However, satisfactory outcomes have been reported[34] with use of warfarin throughout pregnancy, including the first trimester. The risk of embryopathy appears to be lower with daily warfarin doses of 5 mg or lower,[3] and patients with an adequate INR at this dose may continue warfarin until the 36th week, before switching to heparin.[2] If heparin is substituted for warfarin, either during the first trimester or throughout pregnancy, use of an adequate dosage is critical, and strict monitoring is required. Adjusted-dose subcutaneous heparin, with an initial dose of 17 500 to 20 000 units subcutaneously every 12 hours has been suggested;[32] intravenous heparin may be an alternative, but low-dose subcutaneous heparin should not be used as it provides inadequate protection. Low-molecular-weight heparin has also been used, although this is controversial;[2,3,23] if it is used, anti-factor Xa concentrations should be monitored carefully. Low-dose aspirin may be used as an adjunct to subcutaneous heparin or warfarin in women at high risk of thromboembolism.[3,32]

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Disorders of Heart Rhythm

Cardiac arrhythmias are disorders of the rhythm of the heart (p. 1242.1) that may affect its ability to maintain blood circulation. They can be asymptomatic and in some cases benign, but often cause symptoms and may lead to syncope and sudden death; thromboembolic disorders associated with atrial arrhythmias are a common cause of stroke. Cardiac arrest secondary to arrhythmias requires advanced cardiac life support.

Cardiac arrhythmias

A *cardiac arrhythmia* can be defined as any abnormality of rate, regularity, or site of origin of the cardiac impulse or as a disturbance in conduction that causes an abnormal sequence of activation. Arrhythmias may therefore occur due to disorders of the SA node, affecting initiation of impulses; disorders of the AV node and conducting system, affecting spread of the impulse to the ventricles; or abnormal conduction through other myocardial cells such as accessory pathways. Impulses may be generated outside the SA node (*ectopic pacemakers*), particularly in the AV node or the His-Purkinje system. The normal rate of impulse generation by these ectopic pacemakers is less than that of the SA node and therefore they do not usually trigger the heart beat, although they may become dominant in some situations. Since the action potential depends on the movement of ions across cell membranes, electrolyte disorders may be an important cause of arrhythmias; congenital disorders affecting the ion channels (channelopathies) are also increasingly being recognised as a cause.

Arrhythmias may be classified as bradyarrhythmias (slow) or tachyarrhythmias (fast), depending on the heart rate, and as supraventricular (atrial or AV junctional) or ventricular, depending on their presumed site of origin. They may also be divided on the basis of the underlying mechanism into those associated with abnormal automaticity, re-entry, or triggered activity (see Tachyarrhythmias, below). Symptoms depend on the arrhythmia but may include fatigue, dyspnoea, dizziness, and syncope; sudden death may occur. *Palpitations*, an unacceptable awareness of the beating heart, may occur normally in circumstances such as emotion, exercise, or stress but can also occur with arrhythmias.

Bradyarrhythmias are commonly caused by sinus node dysfunction (sick sinus syndrome), which either depresses impulse generation or disturbs the conduction of impulses from the sinus node to the atria.[1] In some patients periods of bradycardia and tachycardia alternate (bradycardia-tachycardia syndrome), making management difficult. *Heart block* (AV block) is another cause of bradycardia, and involves disturbance of conduction of the atrial impulse to the ventricles. First-degree block, in which the impulse is delayed, is usually asymptomatic but may progress to second- or third-degree block, with intermittent (second-degree) or complete (third-degree) failure of atrial impulses to reach the ventricles. This usually causes bradycardia since the intrinsic rate of ventricular contraction is slower than that of the atria, but in AV dissociation ventricular activity is faster than, and independent of, the atrial activity.

Tachyarrhythmias may arise in either the atria or the ventricles. The precise mechanism is often unclear, but for many of the clinically important tachyarrhythmias it involves *re-entry*. Impulses normally spread in a single direction and die out once ventricular contraction occurs, but in re-entry the impulse continues to propagate in a cyclical manner, reactivating the heart. Abnormal automaticity and triggered activity are alternative mechanisms that may be involved.

Ectopic beats, *extrasystoles*, or *premature contractions* can arise in either the atria or the ventricles and, although their precise meaning and definition differs, for practical purposes they can be considered equivalent. They are usually asymptomatic and of no prognostic importance, but some patients suffer palpitations or other distressing symptoms; in patients with heart disease, ventricular ectopics may be associated with more serious arrhythmias and the risk of sudden cardiac death may be increased.[2]

Diagnosis. The precise identification of an arrhythmia is not always easy, but is important for correct management since inappropriate use of antiarrhythmics may be not only ineffective but actively harmful. Clinical symptoms may be useful, but the mainstay of diagnosis is the electrocardiogram (ECG), which records the electrical rhythm of the heart. A typical normal ECG trace is shown in Figure 2, p. 1242. Many arrhythmias have distinctive ECG patterns, but this is not always the case; an arrhythmia with a narrow QRS complex is always supraventricular in origin whereas a broad QRS complex can indicate either a supraventricular or ventricular origin. Other specialised tests and features relevant to the individual arrhythmias may aid diagnosis.

Management. Treatment of arrhythmias may be indicated to relieve symptoms and/or to improve survival. Choice of therapy depends on the arrhythmia involved, the presence of structural heart disease, and other patient factors such as pregnancy.[3] For tachyarrhythmias, antiarrhythmic drugs (see p. 1243.1 for an explanation of the classification of antiarrhythmics) and external electrical cardioversion have been widely used, although ablation of arrhythmic pathways and implantable cardioverter-defibrillators have an increasing role;[4] management of various tachyarrhythmias is discussed below. For **bradyarrhythmias**, atropine or sympathomimetics are usually used for acute control,[5,6] while cardiac pacing is the treatment of choice for long-term management.[1,5-8]

Atrial fibrillation is a supraventricular tachyarrhythmia with an underlying mechanism of re-entry and is the commonest arrhythmia encountered clinically.[9] It is usually associated with disorders that predispose the atria to re-entry, although it is now recognised that the arrhythmia may start from an ectopic focus, often in the pulmonary vein. The main underlying cardiovascular disorders are ischaemic or hypertensive heart disease and heart failure, and the incidence increases markedly with age. Rheumatic heart disease is also an important cause, although this is now less common in developed countries. Other causes include hyperthyroidism and acute alcohol intoxication. Atrial fibrillation is also relatively common after cardiothoracic surgery, although this is usually self-limiting. In some patients there is no obvious cause ('lone' atrial fibrillation).

Atrial fibrillation is characterised by a an irregular and very rapid atrial rate (usually more than 300 beats/minute) and, although the AV node is incapable of conducting all the impulses adequately, the increased ventricular response results in a rapid and totally irregular ventricular rate. Atrial fibrillation has been classified in several ways, but patients with 2 or more episodes are generally considered to have recurrent atrial fibrillation; this may be classed as paroxysmal (intermittent) if the arrhythmia terminates spontaneously, or persistent (chronic) if it is sustained. Persistent atrial fibrillation that does not respond to cardioversion or where cardioversion is not attempted is classed as permanent.

Atrial fibrillation can cause distressing symptoms such as severe palpitations and exercise intolerance, and occasional patients present with acute haemodynamic instability that is potentially fatal. However, for most patients atrial fibrillation is not immediately life-threatening. The increased heart rate may lead to tachycardia-induced cardiomyopathy, while left atrial dilatation and reduced cardiac output lead to stasis of blood in the left atrium, which can result in thrombus formation and subsequent systemic embolisation, notably ischaemic stroke. Thromboembolic events are relatively rare in lone atrial fibrillation but the risk is very much increased if other cardiovascular disease is present, especially rheumatic heart disease.

Management of atrial fibrillation[9-16] is focused mainly on symptom control and prevention of long-term morbidity and mortality, including thromboembolic complications. The available approaches are to restore and maintain sinus rhythm (*rhythm control*), or to control the ventricular rate while allowing atrial fibrillation to continue (*rate control*). Use of anticoagulation depends on the risk of thromboembolic events but may be required with either strategy. For patients with life-threatening haemodynamic instability, immediate therapy to restore sinus rhythm is required.[16]

- Rate control may be used for both acute management of symptoms and maintenance therapy and generally involves drugs that act on the AV node to slow conduction.[17] Digoxin has traditionally been used, but has a slow onset of action and is not effective during exercise and is no longer considered first-line in most patients. Beta blockers or rate-limiting calcium-channel blockers such as diltiazem or verapamil are usually the preferred treatment; they provide effective rate control, including during exercise, and may be given intravenously when acute control is needed. Digoxin may be used in sedentary patients, and is also useful in patients with heart failure; it is often given with beta blockers or calcium-channel blockers since many patients require more than one drug to maintain an adequate rate. Amiodarone or its analogue dronedarone, which have rate-limiting properties as well as an antifibrillatory effect, may be used if symptoms are not controlled by such combinations; catheter ablation of AV conduction pathways followed by permanent pacing may be necessary in patients intolerant or unresponsive to drug therapy.[9,15,18]
- In a rhythm control approach, restoration of sinus rhythm (cardioversion) may be achieved either by synchronised direct current or with drugs; both methods require thromboprophylaxis (which is discussed below).[9] Choice of method depends on the duration of atrial fibrillation, availability, and preference; direct current cardioversion restores sinus rhythm more rapidly and is more effective than pharmacological cardioversion if atrial fibrillation is not of recent onset but has the disadvantage that it needs to be performed under sedation or general anaesthesia. Pharmacological cardioversion is effective in atrial fibrillation of recent onset[9,14,15,19,20] but by 7 days, cardiac remodelling largely abolishes its value. Flecainide and propafenone are the drugs most widely recommended as first-line;[9,14,15] ibutilide and dofetilide are alternatives.[9,15] Amiodarone may also be used;[9,14,15] it has a slower onset but is equally effective[21] and is particularly useful in patients with structural heart disease.[9,14] Vernakalant is a newer alternative whose place in therapy is yet to be decided. Intravenous magnesium has been tried but results have been mixed.[22,23] Drugs with limited or no evidence of efficacy include digoxin, sotalol, quinidine, disopyramide, and procainamide.[9,15] *Adjunctive* pharmacological therapy may be started before electrical cardioversion to increase the success of the procedure and to reduce the risk of early recurrence;[9,14,15] drugs used include amiodarone, flecainide, ibutilide, propafenone, and sotalol.

  Once sinus rhythm has been achieved, long-term *maintenance* drug therapy needs to be considered since relapse is common. Patients with a first episode of atrial fibrillation are rarely started on maintenance therapy, particularly if a reversible cause has been identified and can be treated.[14,15] However, patients who have troublesome symptoms due to paroxysmal or recurrent atrial fibrillation are usually given long-term antiarrhythmics. The ability of these drugs to maintain sinus rhythm is modest,[24] and choice should be guided by safety considerations rather than efficacy.[9,14] Beta blockers may be tried initially,[9,14] particularly in patients with lone atrial fibrillation,[15] and they have the advantage of providing rate control if relapse occurs, but dronedarone, flecainide, propafenone, or sotalol are often required.[9,18] Amiodarone and dofetilide may also be used; amiodarone may be more effective than other antiarrhythmics[25] but its use is limited by long-term adverse effects and it is generally only recommended in resistant cases or in patients with heart failure who are unsuitable for alternative therapy. Catheter ablation procedures such as isolation of the pulmonary veins are an alternative to drugs in certain patients when drug treatment has failed.[9,18] Since ablation may in fact be more effective than drug treatment its use as first-line therapy might also sometimes be reasonable, but the balance of risks and benefits is still unclear.[9,18] Surgery or implantable defibrillators may be used in selected cases. Patients with infrequent episodes of paroxysmal atrial fibrillation and good response to drugs may be prescribed single doses of flecainide or propafenone for outpatient use ('pill-in-the-pocket') if symptoms recur.[9,14,15,26]

The choice between rate and rhythm control has been debated. Rhythm control has theoretical advantages since restoration of sinus rhythm should both alleviate symptoms and reduce thromboembolic risk. However, the adverse effects and limited efficacy of antiarrhythmic drugs in preventing relapse may limit any benefit. A review[27] and meta-analyses[28,29] of studies comparing rate control with rhythm control found little difference between the two strategies in terms of symptom control or clinical events, and choice therefore depends on patient characteristics and preference.[9,14,15] For elderly patients with minimal symptoms rate control is generally the preferred option, whereas younger patients or those who remain symptomatic despite rate control should be considered for rhythm control.

Prophylaxis of atrial fibrillation may have a role in some situations. Although atrial fibrillation after cardiothoracic surgery is usually self-limiting, it may be associated with increased morbidity and mortality, and prophylaxis should be considered. Beta blockers, amiodarone, and sotalol are effective,[6,9,14,15,30-33] and rate-limiting calcium-channel blockers such as diltiazem or verapamil have also been suggested.[6] Other classes of drug may also be effective.[33] Some benefit has been reported with magnesium,[34,35] although this was not confirmed in a more recent study.[36] Corticosteroids may also be of benefit.[37] Statins appear to reduce the incidence of atrial fibrillation after surgery,[38] and omega-3 fatty acids have also shown some benefit.[39] For non-surgical patients, several 'upstream' therapies have been investigated in an attempt to prevent or delay the cardiac remodelling associated with hypertension, heart failure, or inflammation, and so deter either new occurrences of atrial fibrillation or progression of established disease.[9,40] Results of studies with ACE inhibitors, angiotensin II receptor antagonists, and statins have been promising,[40] but there is not enough evidence to recommend them for prevention in patients without pre-existing licensed indications.[9] Other drugs under investigation include aldosterone antagonists and omega-3 fatty acids.

Prevention of thromboembolic events, particularly ischaemic stroke, is a major aspect of atrial fibrillation management.[41] Patients are at risk both during cardioversion procedures and long-term, and should be given appropriate antithrombotic therapy. If atrial fibrillation has

been present for less than 48 hours, it is safe to perform cardioversion covered only by unfractionated or low-molecular-weight heparin.[9,42] This approach is also acceptable in unstable patients who require urgent cardioversion, regardless of the duration of arrhythmia.[9,42] Atrial fibrillation of 48 hours or longer carries a much greater risk of embolisation, and oral anticoagulants are given for 3 weeks before cardioversion.[9,42] In those who cannot take oral anticoagulants or who require rapid (but not urgent) cardioversion, the presence or absence of thrombi may be revealed with transoesophageal echocardiography. If no thrombi are revealed, cardioversion may be performed under cover of unfractionated or low-molecular-weight heparin. If thrombi are revealed and elimination with a 3-week course of oral anticoagulants is impossible or unsuccessful, adopting a rate-control strategy may be safer than cardioversion.[9] The ventricular rate should be controlled in all patients who are waiting for cardioversion. After cardioversion, every patient should be given oral anticoagulants for at least 4 weeks, except where atrial fibrillation has lasted less than 48 hours in a patient with no risk factors for stroke.[9,42]

Atrial fibrillation increases risk of stroke fivefold, and whether a rate- or rhythm-control strategy has been adopted, indefinite prophylaxis with antithrombotic drugs should be offered to all patients considered at risk, including those whom cardioversion has restored to sinus rhythm. The vitamin K antagonist warfarin is most commonly used, but newer oral anticoagulants such as the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban have also been shown to be effective, and appear to cause less risk of major bleed when compared with warfarin.[43,44] In choosing a drug for prophylaxis, efficacy must always be balanced against an increased bleeding risk. For patients with 1 or more major risk factors (previous stroke, transient ischaemic attack, or thromboembolism; age over 75 years; or valvular heart disease) or 2 or more non-major risk factors (hypertension; heart failure; or diabetes) for stroke, the benefits of anticoagulation are established.[9] For everyone else, the relative risks and benefits are less clear and the decision to treat depends more on individual patient factors.

In those at lower risk of thromboembolism, alternative strategies with a reduced risk of bleeding may be more appropriate. Antiplatelet therapy is an acceptable alternative. There is good evidence that aspirin reduces the risk of stroke,[45,46] but it is less effective than warfarin for both primary[47] and secondary prevention,[48] and is usually only recommended in patients with a particularly high risk of haemorrhage or low risk of stroke, or in those who are unwilling or unable to take anticoagulants.[9] Dual antiplatelet therapy with aspirin and clopidogrel may also be considered.[18]

Further strategies to increase the efficacy of antithrombotic therapy while minimising the bleeding risks have been tried. Use of low-dose warfarin with aspirin has been shown[49,50] to be less effective than adjusted-dose warfarin and is not recommended, although a study[51] using triflusal and moderate-dose phenprocoumon reported beneficial effects. Non-pharmacological approaches such as closure of the left atrial appendage have also shown some success.[52]

Atrial flutter is an arrhythmia somewhat similar in nature to atrial fibrillation[53-55] and is likewise characterised by a rapid (about 300 beats/minute) atrial rate, although the atrial rhythm is more regular and organised, and by a corresponding increase in the ventricular rate. It is far less common than atrial fibrillation, to which it often degenerates if left untreated; it may revert to normal sinus rhythm in some cases. It carries a similar risk of thrombosis, and recommendations for anticoagulation should be followed as for atrial fibrillation.[9,14,15,42] Management strategies for atrial flutter are broadly similar to those outlined above for atrial fibrillation, namely controlling the increased ventricular response rate and cardioversion. However, in general terms drug therapy for either of these interventions is less successful in flutter than in fibrillation. Cardioversion with drug therapy has a relatively low success rate and cardiac pacing is usually used, which often results in a self-terminating atrial fibrillation. Synchronised direct current cardioversion may be used to restore sinus rhythm if pacing fails. Radiofrequency ablation is an alternative for those resistant to, or intolerant of, standard therapy;[53,55] its high success rate and low risk of complications have led some to suggest it as a first-line option for many patients.[54,55]

Other atrial arrhythmias include **atrial premature beats** and various types of **atrial tachycardia**. Premature beats are usually asymptomatic but if symptoms are severe (the awareness of a pause between normal beats) beta blockers may be used.[56] Atrial tachycardia may also be treated with beta blockers or rate-limiting calcium-channel blockers,[57,58] but if it is due to digoxin toxicity, withdrawal of digoxin may be all that is required.[57] For focal atrial tachycardia, flecainide, sotalol, and amiodarone may also be effective, but catheter ablation is generally preferred.[59]

Paroxysmal supraventricular tachycardia is a re-entry arrhythmia. The term paroxysmal atrial tachycardia was formerly used, but became obsolete when it was realised that many such arrhythmias arise in the atrioventricular junction rather than in atrial muscle. The re-entry circuit can be either due to an accessory pathway between the atria and ventricles (atrioventricular reciprocating tachycardia; AVRT) or re-entry can occur at the site of the node itself (atrioventricular nodal reciprocating tachycardia; AVNRT). It is a relatively common arrhythmia occurring in otherwise healthy individuals. It may resolve spontaneously, or reflex vagal stimulation by respiratory manoeuvres, prompt squatting, or pressure over one carotid sinus may restore normal sinus rhythm. If symptoms associated with the rapid heart rate are severe, treatment will be needed. For termination of paroxysmal supraventricular tachycardia adenosine given intravenously is often the drug of choice;[56,57,60-63] intravenous verapamil or diltiazem, or intravenous beta blockers, are alternatives. If there is no response, or in patients with a wide QRS complex and unclear diagnosis, propafenone, flecainide, procainamide, sotalol, amiodarone, or ibutilide may be used.[56,57,61] Direct current cardioversion may be necessary in some cases, particularly in those who are unstable. Long-term maintenance therapy to prevent recurrence is required in some patients, but there is limited evidence to guide choice of therapy.[57] For many patients radiofrequency catheter ablation is the preferred treatment, particularly in those with AVRT and an accessory pathway. Alternatively, pharmacological therapy may be used. Drugs that block AV conduction are first-line and include beta blockers, rate-limiting calcium-channel blockers, and digoxin. Flecainide and propafenone, class Ic drugs that act on atrial refractoriness, may be used if first-line drugs are ineffective; amiodarone is generally preferred if patients have structural heart disease. Other drugs that may be used include sotalol, quinidine, procainamide, and dofetilide.

Wolff-Parkinson-White syndrome[64,65] is a congenital abnormality characterised by an accessory atrioventricular conduction pathway known as a Kent bundle that leads to ventricular pre-excitation. Although many patients remain asymptomatic, there is an increased risk of atrial fibrillation or paroxysmal supraventricular tachycardia with a danger of degeneration into ventricular fibrillation, particularly if AV-blocking drugs are used. Antiarrhythmics should be used with great caution in such patients, and catheter ablation of the accessory pathway is the treatment of choice.[57,61]

Supraventricular tachycardia can occur rarely *in utero* and is associated with hydrops fetalis and perinatal mortality and morbidity. Treatment is with antiarrhythmic drugs such as digoxin, flecainide, sotalol, or amiodarone given to the mother (transplacental therapy).[58,66-68] In resistant cases direct intraperitoneal or intravascular dosage to the fetus may be necessary.

Ventricular tachycardia[69-73] is usually a re-entry arrhythmia and is often associated with underlying cardiovascular disease such as myocardial infarction or cardiomyopathies. It may also be caused by drugs that prolong the QT interval, or by digoxin toxicity. Congenital channelopathies such as Brugada syndrome[74] and long QT syndrome[75] may cause ventricular arrhythmias in patients with structurally normal hearts. The heart rate is about 120 to 250 beats/minute and the tachycardia, which arises in the ventricles below the AV node, can be paroxysmal, consisting of short self-terminating episodes, or can be sustained (lasting 30 seconds or longer). Ventricular tachycardia can be asymptomatic (if the episodes are non-sustained) or cause minimal symptoms such as palpitations, but is potentially a serious condition which may lead to reduced cardiac output, shock, and progression to **ventricular fibrillation** and cardiac arrest. It is one of the most common causes of sudden unexplained cardiac death.[76] The ECG trace of ventricular tachycardia may be confused with that of supraventricular tachycardia but since the treatments differ markedly, every effort should be made to obtain the correct diagnosis; if the diagnosis is unclear the patient should be treated for ventricular tachycardia.[5,57]

The *initial treatment* of ventricular tachycardia depends largely on the haemodynamic status of the patient. Unstable patients with ventricular fibrillation or pulseless ventricular tachycardia, and patients with irregular sustained ventricular tachycardia, should be given defibrillation, as outlined under Advanced Cardiac Life Support (p. 1268.3). More stable patients with regular monomorphic ventricular tachycardia may be treated with intravenous antiarrhythmics or by sedation and direct current cardioversion; pacing may be effective in some patients. Amiodarone is widely recommended;[5,6,77,78] procainamide is an alternative[5,6,77] and may be preferred if a rapid effect is required.[78] Sotalol may also be used,[5,6] and lidocaine (which was previously the drug of choice) may have a role in some patients, although it is generally less effective. Other alternatives that are available in some countries include ajmaline, flecainide, and propafenone. In some patients with non-sustained ventricular tachycardia, beta blockers may be effective; catheter ablation may have a role if termination of the arrhythmia is not urgent.[78]

After restoration of normal sinus rhythm *maintenance therapy* needs to be considered. Long-term treatment is generally not warranted in low risk patients such as those who have had asymptomatic non-sustained ventricular tachycardia, but patients with severe symptoms or those at high risk of sudden cardiac death, such as survivors of ventricular fibrillation and pulseless ventricular tachycardia, require treatment. Although antiarrhythmic drugs have been used, studies have shown that implantable cardioverter defibrillators reduce mortality more effectively, and these are now recommended for most patients,[6,8,78,79] although the adverse effects need to be considered.[80] Beta blockers are also effective and may be used,[6,78] but there is little evidence to support the use of other drugs, even when electrophysiological testing is used, and they are no longer generally recommended. Amiodarone reduces the risk of sudden cardiac death but has no effect on overall mortality.[81] Sotalol, or amiodarone with a beta blocker, may have a role if implantable cardioverter defibrillators are considered inappropriate;[6] they may also be used to prevent frequent device activation in patients with implantable cardioverter defibrillators and recurrent arrhythmias,[78,82] although the effect of drugs on energy requirements for defibrillation needs to be considered.[83] Catheter ablation may be used if drug therapy is ineffective.[73] There is also some evidence that drugs that are beneficial for cardiovascular risk reduction may reduce the risk of ventricular arrhythmias, including ACE inhibitors and omega-3 fatty acids, but their role is not yet established.[78]

Myocardial infarction is a particular risk factor for ventricular arrhythmias and prophylactic treatment has therefore been tried. Arrhythmias are particularly common early after acute myocardial infarction and lidocaine has been used prophylactically; however, there is little evidence of benefit and routine use is no longer recommended.[84,85] Implantable cardioverter defibrillators may be used for primary prevention of sudden cardiac death in patients with evidence of sustained ventricular tachycardia more than 48 hours after acute myocardial infarction, particularly in patients who also have heart failure; beta blockers,[86,87] amiodarone,[88] or sotalol, may also be considered. Patients with asymptomatic ventricular arrhythmias may also be at increased risk of sudden death but use of antiarrhythmic drugs increases mortality[86,87,89] and is not advised.

Primary prophylaxis may also have a role in other cardiac disorders that are known to cause ventricular arrhythmias and sudden cardiac death, including heart failure, cardiomyopathies, and Brugada syndrome or similar congenital disorders. Implantable cardioverter defibrillators are recommended in high risk patients; beta blockers and amiodarone may have a role in specific cases.[78,90]

QT prolongation and drug-induced arrhythmias. Antiarrhythmic drugs also have proarrhythmic properties and may exacerbate or induce arrhythmias of all kinds, and non-cardiac drugs may also have proarrhythmic effects. *Torsade de pointes* is a particularly serious ventricular arrhythmia that is often drug-induced.[91] It is associated with prolongation of the QT interval (prolongation of ventricular repolarisation), which allows afterdepolarisations to trigger a re-entry tachycardia; this is often non-sustained, but may persist for long enough to cause syncope or it may even progress to ventricular fibrillation. Drugs that cause QT prolongation include antiarrhythmics and several non-cardiac drugs[92-97] including phenothiazines, tricyclic antidepressants, antihistamines such as astemizole and terfenadine, antibacterials such as erythromycin, the antimalarial halofantrine, and the lipid lowering drug probucol. Patients with congenital channelopathies may also have QT prolongation and develop torsade de pointes, often in response to stress- or exercise-induced tachycardia;[75] other causes include electrolyte disorders and bradycardia. If torsade de pointes is drug-induced, withdrawal and subsequent avoidance of the offending drug is mandatory. Initial therapy is usually with intravenous magnesium, to correct any contributory magnesium deficiency, with temporary pacing of the atria or ventricles and correction of any other electrolyte disorders as appropriate.[91] Isoprenaline has been given cautiously to increase the heart rate and shorten the QT interval, until pacing is instituted. Congenital long QT syndromes are usually treated with beta blockers and avoidance of trigger factors, with implantable cardioverter defibrillators in selected patients;[75,78,98] pacing may increase the risk of sudden cardiac death and is no longer generally advised.[75]

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Cardiac arrest

Cardiac arrest is the cessation of effective cardiac mechanical activity and may be associated with four arrhythmias, namely **ventricular fibrillation, pulseless ventricular tachycardia, asystole,** and **pulseless electrical activity (electromechanical dissociation)**. In ventricular fibrillation and pulseless ventricular tachycardia there is chaotic electrical and mechanical activity; in asystole a total absence of both activities; and in pulseless electrical activity an absence of mechanical activity, or undetectable activity, in the presence of some electrical activity. The latter two arrhythmias carry a particularly poor prognosis. In adults, ventricular fibrillation is the commonest presentation and usually results from ischaemic heart disease. In children, asystole is more common and usually results from respiratory or circulatory failure.

Cardiac arrest is an emergency and should be treated with full life support measures.

International recommendations[1] for advanced life support and the period surrounding cardiac arrest have been published by the International Liaison Committee on Resuscitation. American,[2] European,[3] and UK[4] guidelines have also been published; these are based on the international recommendations and, apart from some differences in detail, are broadly similar. **Basic life support** (cardiopulmonary resuscitation; CPR) should be started immediately in all unresponsive victims with absent or abnormal breathing, and continued throughout the resuscitation attempt.[1] The purpose of CPR is to maintain cardiorespiratory function until spontaneous circulation can be restored by defibrillation and/or advanced cardiac life support measures, and good quality CPR with a minimum of interruptions greatly increases both the likelihood of conversion to sinus rhythm and overall survival.[1,5] It usually consists of chest compressions and ventilation (mouth-to-mouth/mask or mouth-to-nose), although in witnessed primary cardiac arrest in adults, continuous chest compressions without ventilation are probably as effective as standard CPR and may be given by untrained laypersons

or those unwilling or unable to give ventilation.[1,5,6] For respiratory arrest, CPR with ventilations is preferable.[1]

Subsequent procedures will depend to some extent on the type of arrhythmia present. Rapid electrical **defibrillation** is of paramount importance in converting ventricular fibrillation or pulseless ventricular tachycardia to sinus rhythm by causing momentary asystole that allows the natural pacemakers to resume normal activity. Defibrillation is of no use in asystole or pulseless electrical activity (so-called non-shockable rhythms) and these patients should be treated directly with intravenous drugs as described below.

The first defibrillating shock must be given as quickly as possible;[1] however, prior CPR may increase the likelihood of successful defibrillation, and it is unknown whether or not a specified period of CPR before defibrillation should routinely be given in unwitnessed cardiac arrest.[1,7] After this, CPR should immediately be resumed for 2 minutes before the rhythm is assessed. A further shock should then be given if indicated,[1] followed by immediate resumption of CPR; and this cycle of CPR, assessment, and shock should be continued throughout resuscitation. In adult cases of witnessed cardiac arrest, a precordial thump may be given if a defibrillator is not immediately available; this sometimes aborts the arrhythmia if given within seconds of the loss of cardiac output.[1,8]

CPR and defibrillation alone may be insufficient to convert to or sustain normal rhythm, and **advanced cardiac life support** (ACLS) is often necessary. This includes securing the airway, providing high-flow oxygen, and giving intravenous or intraosseous drugs as indicated.

- *Adrenaline* is given to increase the efficacy of basic life support by improving coronary and cerebral blood flow via its alpha agonist effects.[9] A dose of 1 mg is given intravenously to adults, and should be started after the second[2] or third[3,4] defibrillating shock and repeated every 3 to 5 minutes (every other cycle) while resuscitation continues. For non-shockable rhythms, the same dose and frequency may be started as soon as intravenous or intraosseous access is established.[2-4]
- *Vasopressin* (as argipressin) is an alternative to adrenaline,[1,2] and US guidelines[2] permit a single intravenous dose of 40 units to replace either the first or second dose of adrenaline in patients with any type of cardiac arrest. This is not a universal recommendation, and European guidelines[3] emphasise that since the evidence for adrenaline is stronger it remains first-line.
- *Amiodarone* is the first-line antiarrhythmic for refractory ventricular tachycardia or fibrillation;[1] it is given after the third unsuccessful defibrillating shock.[2-4]
- *Lidocaine* is an alternative to amiodarone, but its performance in studies has been much less convincing and it should be used only when amiodarone is not available.[1-4]
- *Atropine* may be given for symptomatic bradycardia;[1] its routine use during asystole or pulseless electrical activity is no longer recommended.[2-4]
- *Dopamine*, *isoprenaline*, *adrenaline*, *aminophylline*, or *pacing* may be tried in bradycardia refractory to atropine.[2-4]
- The routine use of *sodium bicarbonate* is no longer recommended; however, it may be used if there is hyperkalaemia or after tricyclic antidepressant overdose.[2-4]
- *Other drugs* may be given to treat any reversible causes of cardiac arrest such as hypovolaemia, hypoxia, pneumothorax, pulmonary embolism, drug overdose, electrolyte or glucose imbalances, and hypothermia. Therapy should given promptly once resuscitation has been started.

The principles of cardiac arrest management in **children** are similar to those in adults. However, the cause in children is usually asphyxia and so ventilation during CPR is important; asystole is more common than ventricular fibrillation; and the defibrillating energies and doses of drugs may be different.[1-4,10]

The length of time that a resuscitation attempt should continue is a matter of judgement. In most cases, recovery is unlikely to occur after 20 or 30 minutes of unsuccessful resuscitation, although for persistent ventricular fibrillation or pulseless ventricular tachycardia, or where the cause is hypothermia or drug intoxication, a longer resuscitation attempt is reasonable.[3,11]

Post-resuscitation care should include appropriate management of those sequelae of whole-body ischaemia known as post-cardiac arrest syndrome, notably brain injury, myocardial dysfunction, reperfusion response, and any persistent pathology responsible for the original cardiac arrest.[12-14] Therapeutic hypothermia is recommended in those who remain unconscious after resuscitation, and such patients should be cooled to 32 degrees to 34 degrees for 12 to 24 hours.[1,12-15] Hyperglycaemia should be corrected (and hypoglycaemia avoided), and reperfusion strategies such as thrombolysis and PCI should be performed where indicated.[1,12-14] In survivors of ventricular fibrillation and pulseless ventricular tachycardia in whom it is considered there is a high risk of recurrence, implantable cardioverter defibrillators may be used. Drug therapy may also be used prophylactically (see Ventricular Tachycardia under Cardiac Arrhythmias, p. 1266.1).

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Cerebrovascular Disease

Cerebrovascular disease is a broad term covering any disorder of the cerebral circulation. Ischaemic and haemorrhagic stroke, including subarachnoid haemorrhage, are acute forms, and management of their vascular aspects is discussed in this section. They may also have long-term neurological consequences and are an important cause of vascular dementia (see p. 388.1). Cerebrovascular disease has also been used as a synonym for cerebrovascular insufficiency, also discussed in this section.

Cerebrovascular insufficiency

Drugs with cardiovascular effects have been promoted for the treatment of cognitive impairment attributed to the rather vague concept of 'cerebrovascular insufficiency' (chronic impairment of cerebral blood flow).

Both Alzheimer's disease and vascular dementia share risk factors with atherosclerotic vascular diseases, including coronary and peripheral vascular disease, and there is some evidence that measures for cardiovascular risk reduction (p. 1246.1), particularly antihypertensive drugs, may reduce the incidence of dementia.[1] However, the benefits of cardiovascular drugs in patients with established cognitive impairment are less clear.

Vasodilators have been the main drugs used, but there is little convincing evidence of benefit[2] and those that have been shown to improve symptoms are now thought to do so by altering the rheological properties of blood or by effects on tissue metabolism rather than by cerebral vasodilatation. Similarly, ergot derivatives with vasodilator properties, such as codergocrine mesilate and nicergoline, have been widely used, but there is little evidence to support this. Some benefit has been reported with calcium-channel blockers such as nimodipine and nicardipine, but again they do not have an established role.

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Stroke

Stroke, sometimes called a cerebrovascular accident, is the major consequence of cerebrovascular disease and has been defined as an acute neurological dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas of the brain. The cause may be ischaemic or haemorrhagic,[1-4] and duration of symptoms varies. Signs and symptoms that disappear within a few minutes or hours (24 hours at most) have usually been termed transient ischaemic attacks (below). However, even transient symptoms may be associated with permanent brain damage, and it has been suggested[5] that the term transient ischaemic attack should be reserved for cases where imaging studies show that no infarction has occurred.

- **Ischaemic stroke** is by far the commonest type and generally results from occlusion of cerebral arteries. This may be caused by local thrombosis at sites of atheroma, but more commonly results from thromboemboli arising from outside the brain and lodging in the cerebral vessels; an example of the latter is cardioembolic infarction associated with atrial fibrillation or acute myocardial infarction. Arterial occlusion results in inadequate cerebral perfusion, which leads to ischaemia and subsequently to stroke. If signs and symptoms persist for more than 24 hours or lead to death, it is generally considered that infarction has taken place and the event is termed a *completed stroke*. About 20% of patients with acute ischaemic stroke have worsening of symptoms within a few days of onset. This is termed *progressing stroke*, *stroke-in-evolution*, or *unstable stroke*, and may be due to progression of the thrombosis; haemorrhagic conversion, with bleeding into the infarcted area, may also occur.
- **Transient ischaemic attacks** are acute episodes of focal neurological deficit or monocular visual loss (amaurosis fugax), mainly due to ischaemia associated with atherothrombosis. There is usually complete clinical recovery but a tendency for recurrence, and patients are also at an increased risk of stroke.
- **Haemorrhagic stroke** is secondary to subarachnoid or to intracerebral haemorrhage. *Subarachnoid haemorrhage* is bleeding into the fluid-filled subarachnoid space between the brain and the skull, and usually occurs after rupture of an aneurysm; other causes include arteriovenous malformations and hypertensive microaneurysms. *Intracerebral haemorrhage* is bleeding into the parenchyma of the brain, and may result from rupture of arteries damaged by chronic hypertension. Haemorrhage produces a focal haematoma causing a local increase in pressure which may lead to further bleeding and enlargement of the haematoma. The increase in pressure in the area of the haematoma may also produce local ischaemia.

Clinical **presentation** of stroke can vary enormously in severity and combination of signs and symptoms, and depends on the site and extent of infarction or haemorrhage. Haemorrhagic stroke is typically of sudden onset with severe headache, vomiting, and rapid deterioration of consciousness (all signs of raised intracranial pressure) but mild to moderate haemorrhage may be difficult to distinguish from infarction on the basis of clinical signs alone. Neurological deficits in all forms of stroke may include impairments to speech, balance, vision, touch sensation, and movement. Recovery is variable and patients have been classed as major or minor stroke (reversible ischaemic neurological deficit) victims according to their degree of recovery at a given time after the stroke.

Accurate **diagnosis** of the type of stroke is important since management is very different and interventions that are beneficial in infarction may be dangerous in patients with haemorrhage. Clinical presentation may suggest the type of stroke but this is not always reliable. Imaging is therefore usually required to distinguish between haemorrhagic and ischaemic stroke and should be performed as a matter of urgency.[6-9] Computed tomography (CT) is the most widely used technique, although magnetic resonance imaging (MRI) may be preferred where it is available; MRI is more sensitive but availability is limited and it is not suitable for all patients. Diagnosis of transient ischaemic attacks usually rests on the patient's history as these short attacks are seldom witnessed by a physician and there are no objective confirmatory tests; however, imaging has an important role in determining aetiology and guiding subsequent management.[5,8,10,11]

Management of stroke involves immediate treatment of the acute stroke, treatment and prevention of complications such as swallowing disorders or spasticity, rehabilitation, and long-term treatment for secondary prevention. Where possible, patients should be managed within a stroke unit since this has been shown to improve outcome. Patients with a transient ischaemic attack are at high risk of subsequent stroke and should be started on long-term preventative therapy as soon as possible.[12-14] Primary prevention may be considered in other individuals at risk of ischaemic stroke; this includes those with atrial fibrillation, a major risk factor for stroke (see Cardiac Arrhythmias, p. 1266.1), and those with risk factors for atherosclerosis (see Cardiovascular Risk Reduction p. 1246.1). The role of endarterectomy in individuals with carotid artery stenosis is discussed under Long-term Management, below.

Ischaemic stroke. Reviews[15-21] and guidelines[6-9,22] emphasise that, as in myocardial infarction, early recognition of symptoms and prompt evaluation and treatment of stroke are of vital importance. The aim of treatment is to limit or reverse damage to the brain. Ischaemia deprives the cells of oxygen and glucose, leading

to infarction, but this appears to be time-dependent. While some tissue may be irreversibly damaged when the patient presents, there is evidence that surrounding tissue (the 'ischaemic penumbra') may be salvageable. Restoration or improvement of blood flow is therefore a logical means to preserve this tissue; strategies to protect the cells from the consequences of ischaemia are an alternative approach.

Acute management involves general supportive measures, and specific treatments to reverse ischaemia and protect the brain tissue. General supportive measures include ensuring adequate oxygenation and fluid and electrolyte balances, avoiding hypercapnia and hyperglycaemia or hypoglycaemia, abolishing seizures, and treating fever; nutritional status should also be assessed. Control of hypertension is controversial since lowering the blood pressure may reduce cerebral perfusion and worsen ischaemia, and hypertension usually resolves spontaneously without treatment.[23] Antihypertensive therapy may be indicated in specific patients, such as those with severe hypertension or those being considered for thrombolytic therapy.

Specific therapy for ischaemic stroke is limited. As in myocardial infarction, the main cause of ischaemic stroke is thromboembolic occlusion, and use of antithrombotic drugs such as antiplatelets, heparin, and thrombolytics, therefore appears logical. However, evidence of benefit is not as clear as it is in myocardial infarction, and the risks may be greater; the presence of haemorrhage must be excluded and the risk of potentiating spontaneous secondary brain haemorrhage (haemorrhagic transformation) must be borne in mind. Other strategies to improve blood flow or to limit the effects of ischaemia using neuroprotectants have also been tried, but results to date have been disappointing.

Antiplatelet drugs. Aspirin has been evaluated in two large studies—the International Stroke Trial (IST)[24] and the Chinese Acute Stroke Trial (CAST).[25] The combined results of these studies[25] showed that aspirin 160 mg[25] or 300 mg[24] daily started within 48 hours of symptom onset produced about 9 fewer deaths or non-fatal strokes per 1000 patients in the first few weeks following ischaemic stroke. Aspirin has therefore been recommended for patients with ischaemic stroke who are not receiving thrombolytic or anticoagulant therapy, and should be started within 24 or 48 hours of stroke onset.[6-9,26] For patients treated with thrombolysis, aspirin should be started after 24 hours.[8,9,26] Other antiplatelet drugs are under investigation, but do not yet have an established role;[6,7] a study with the glycoprotein IIb/IIIa antagonist abciximab was stopped early due to an increased incidence of bleeding,[27] although studies using lower doses continue.[28]

Anticoagulants are not routinely recommended in the early management of acute ischaemic stroke,[6,8,9] although they may have a role in selected patients.[7] Anticoagulation should prevent further thrombus formation and limit the size of the cerebral infarct; however, any benefit may be offset by an increase in intracranial haemorrhage, and a systematic review[29] has suggested there is no evidence to support routine use. The IST,[24] which evaluated two dosages of heparin (5000 units or 12 500 units subcutaneously twice daily), found no benefit from either regimen and the higher dose particularly was associated with haemorrhagic stroke and bleeding. Another study,[30] comparing the low-molecular-weight heparin tinzaparin with aspirin, similarly found no benefit. It had been suggested that patients with cardioembolic stroke were likely to benefit from heparin therapy,[31] even though there is a special risk of haemorrhagic transformation in these patients, which means that early anticoagulation is often hazardous. However, the IST[24] failed to show any benefit in this group, and a study[32] of low-molecular-weight heparin in patients with acute ischaemic stroke and atrial fibrillation also showed no benefit. No improvement in outcome was reported after 3 months in a study of danaparoid given in acute ischaemic stroke.[33] A study[34] with ancrod found an improvement in outcome when given within 3 hours of stroke onset, but a further study was terminated due to lack of benefit.

The risk of venous thromboembolism (deep-vein thrombosis and pulmonary embolism) is increased after stroke, particularly in immobile patients, and prophylaxis may be considered in those at high risk.[7,8,26] Low-dose subcutaneous heparin or low-molecular-weight heparin are suitable; use of low-molecular-weight heparin has been recommended[9] based on a study[35] suggesting that enoxaparin was superior to unfractionated heparin, but this remains to be confirmed.

Thrombolytics. Intravenous thrombolytics increase the risk of cerebral haemorrhage and have therefore generally been contra-indicated in both ischaemic and haemorrhagic stroke. However, there is evidence that use of thrombolytics in ischaemic stroke may be of benefit, despite the increased risk of bleeding, and they may have a role in selected patients,[36-38] particularly if they can be given in the early stages.[39] A study[40] with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial) found that clinical outcome was improved, despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[40] and this benefit was maintained at 12 months.[41] However, there was no difference in mortality or rate of recurrence of stroke. On the basis of this study, most guidelines[6-8,26] now recommend alteplase for selected patients if it can be given within 3 hours of stroke onset, and this appears to be safe in practice.[42,43] Use of alteplase up to 4.5 hours after stroke onset has also been recommended.[9,44] An observational study[45] suggested that alteplase was safe within this timeframe, while a randomised study[46] found that alteplase given between 3 and 4.5 hours after stroke onset improved outcomes, although the authors stressed that treatment within 3 hours was still preferred. Other thrombolytics, such as streptokinase, have generally produced less favourable results, and none of these are currently recommended. The intra-arterial route has also been tried and may be used in selected patients.[6,7,9,26] Combined use of intravenous and intra-arterial alteplase,[47] as well as use of adjunctive therapies such as therapeutic ultrasound[48] or antithrombotics, are under investigation but do not yet have an established role.[6]

Other approaches that have been tried include various methods to improve cerebral blood flow. Haemodilution with *dextran* or *pentastarch* has generally been disappointing and is not usually recommended.[6,7,9] Drug-induced hypertension may also increase cerebral blood flow and appears to be safe,[49] but clinical benefit is unproven.[6] Hypoxia and hypocapnia may cause cerebral vasoconstriction as well as directly contributing to ischaemic injury, and there have been anecdotal reports and small studies reporting benefit with *hyperbaric oxygen therapy*, although a systematic review[50] suggested that clinical benefit was unlikely. Treatment with *corticosteroids* or hyperosmolar diuretics such as *glycerol* or *mannitol* in an attempt to reduce the cerebral oedema has also been disappointing. There may be some benefit with glycerol, but further evidence is needed.[51]

Neuroprotection. Ischaemia leads to a complex series of biochemical changes, the 'ischaemic cascade', resulting eventually in cell necrosis. The process is incompletely understood, but steps include calcium influx and release of neurotransmitters. Drugs acting at different steps in this ischaemic cascade, sometimes termed neuroprotectants, have been tried in acute ischaemic stroke in the hope of limiting the damage caused by ischaemia. Results of studies so far have been largely disappointing, and no drug has yet been found to be effective. However, research continues,[52] with early treatment and combination therapies being a particular focus.

Long-term management. Patients who have had an ischaemic stroke or transient ischaemic attack are at risk of further stroke but are also at increased risk of other cardiovascular events, including myocardial infarction and sudden death. Long-term treatment for secondary prevention therefore has an important role.[7-9,12,53-58] All patients should be assessed for standard cardiovascular risk factors, particularly hypertension, and these should be treated as appropriate (see under Raised Cardiovascular Risk, p. 1246.1). There is some evidence that reduction of blood pressure and lipids reduces the risk of stroke irrespective of the presence of hypertension or hyperlipidaemia.[55] Statins reduce the risk of stroke in patients at high risk for cardiovascular events[59,60] and atorvastatin has been shown to reduce the risk of recurrent stroke in patients with isolated cerebrovascular disease;[61] long-term treatment with statins is therefore recommended.[7-9,12] Reduction of blood pressure, whether raised or normal, has also been recommended;[7,9,56] ACE inhibitors or angiotensin II receptor antagonists have been suggested as being particularly beneficial,[62] although the evidence is not conclusive and a subsequent study[63] with the angiotensin II receptor antagonist telmisartan found no effect on the risk of recurrent stroke. Atrial fibrillation is a specific risk factor for stroke and should also be treated (see Cardiac Arrhythmias, p. 1266.1). Hypercoagulability may increase the risk of stroke and blood screening for polycythaemia, thrombocytosis, and abnormal coagulation function has been recommended. Carotid endarterectomy is of established benefit for secondary prevention in patients with clinically significant carotid stenosis,[7-9,64] but its role in primary prevention is less clear and benefits may not outweigh risks.[65,66] Antithrombotic therapy may also have a specific role.

Antiplatelet drugs. Long-term prophylaxis with antiplatelet drugs reduces the risk of future serious vascular events including stroke in patients who have already suffered an ischaemic stroke or transient ischaemic attack,[12,26,56,67] regardless of age.[68] Most evidence relates to aspirin, although the optimum dose is unclear; medium doses of 75 to 325 mg of aspirin daily have been most widely studied[67] and an analysis of studies using aspirin over a dose range of 50 to 1500 mg daily found no relationship between dose and the reduction in risk of stroke.[69] In patients undergoing carotid endarterectomy the risk of stroke, myocardial infarction, and death over 3 months may be lower for those taking medium dose aspirin compared with higher doses.[70] Additional benefit has been reported for aspirin given with dipyridamole, and this combination is now preferred over aspirin monotherapy.[8,9,12,26] Dipyridamole has been given alone but is less effective than the combination[71,72] and is not generally recommended. Clopidogrel alone has a similar efficacy to aspirin with dipyridamole[73] and may be used as an alternative;[7,9,12,26] it is the preferred option in patients unable to tolerate aspirin[8,26] but should not be given with aspirin for stroke prevention since any benefit is offset by an increased risk of bleeding.[74] Ticlopidine has also been used, but adverse effects are a problem and a study[75] in black patients found that it was less effective than aspirin.

Anticoagulants. Oral anticoagulants have an established role in patients with cardioembolic stroke, but in patients with non-cardioembolic stroke or with transient ischaemic attacks they have no clear advantage over antiplatelet drugs,[76,77] and some studies[78,79] comparing warfarin with aspirin have been stopped early due to increased bleeding risks with the anticoagulant. Anticoagulants are therefore not generally recommended for secondary prevention in non-cardioembolic stroke[7-9,12,56] although they have been used in patients with recurrent symptoms despite antiplatelet therapy and may be considered in other selected patients.[7,8,26,56]

Subarachnoid haemorrhage. Aneurysmal subarachnoid haemorrhage[80-84] is associated with high morbidity and mortality, early deaths being due to damage from initial bleeding, recurrence of bleeding, and infarction. Infarction is often a result of vasospasm which is one of the pathophysiological mechanisms that contributes to stopping the bleeding; clot formation and increasing intracranial pressure are other processes involved. Up to a quarter of patients with subarachnoid haemorrhage develop delayed cerebral ischaemia mainly between days 5 and 14 after the initial bleed, and again vasospasm may be a contributory factor.

Early medical treatment aims to prevent delayed cerebral ischaemia, to prevent rebleeding, and to stabilise the patient. Surgical or endovascular interventions to clip or embolise the aneurysm or correct the arteriovenous malformation are then performed to prevent further haemorrhage. Vasospasm and delayed cerebral ischaemia may be prevented by maintaining or slightly increasing plasma volume and blood pressure, and a fluid intake of 2 to 3 litres daily has been recommended.[80] However, there is no good evidence to support routine volume expansion[85] and the main aim should be to maintain normal plasma volume and avoid hypotension. Volume expansion may, however, be a reasonable approach for treating vasospasm if it becomes established.[84]

Oral nimodipine is of benefit[86] and should be started as soon as possible after diagnosis of aneurysmal subarachnoid haemorrhage.[8,84] Antiplatelet drugs have also been tried and may improve outcomes, but this remains to be confirmed.[87] Statin therapy has also been reported to reduce cerebral vasospasm,[88] although a meta-analysis[89] found no significant effect. Established vasospasm may be treated by angioplasty, or intra-arterial vasodilators may be given.[84] There is some evidence of benefit with intra-arterial papaverine,[90] although adverse effects have also been reported;[91] verapamil has also been used.[92] Use of antifibrinolytics such as aminocaproic acid or tranexamic acid to prevent rebleeding is of uncertain benefit. A systematic review[93] found that any benefits were offset by an increase in poor outcomes due to cerebral ischaemia, and antifibrinolytics are therefore generally no longer recommended.[80] However, there is some evidence that short-term use followed by early surgery may reduce rebleeding without increasing ischaemic complications,[94,95] and this has been suggested[84] as a reasonable approach. Paradoxically, high doses of aminocaproic acid have been associated with increased bleeding after subarachnoid haemorrhage (see Effects on the Blood, under Adverse Effects of Aminocaproic Acid, p. 1132.1); the significance of this is unclear. Headache can be managed with analgesics such as paracetamol, codeine, dihydrocodeine, or tramadol.[82,83] Localised haematomas may be amenable to surgical evacuation, and intraventricular thrombolytics have also been used.[96]

Intracerebral haemorrhage. Outcome of intracerebral haemorrhage depends on the location and size of the haematoma (determined by CT), on the level of consciousness, and on the progression of neurological signs, and development of increased intracranial pressure.[97-100] Any known cause of bleeding, such as warfarin anticoagulation, should be reversed.[8,101] Optimum management of blood pressure is uncertain; in those with 150 to 220 mmHg systolic, a rapid reduction to 140 mmHg systolic is probably safe,[101] but hypoperfusion should be avoided. Short-acting antihypertensives such as nicardipine, labeta-

lol, esmolol, or sodium nitroprusside are generally used, although theoretically nitroprusside may increase intracranial pressure and should be avoided if this is already raised.[98] Surgical drainage of the haematoma may sometimes be possible, but its role is uncertain;[9,98,101] routine early surgery for all patients has not been shown to improve outcome,[102] but has been recommended in previously fit patients with hydrocephalus.[8] Instillation of a thrombolytic to improve aspiration of the haematoma has been reported,[103] but benefit has not been established. Raised intracranial pressure should be controlled[101] (see below). Seizures should be treated with antiepileptics, but prophylaxis is not recommended.[101] Use of activated factor VII to reduce the risk of further bleeding provided some benefit,[104] but has not been shown to improve survival or functional outcome.[105] Long-term management of risk factors, particularly hypertension, should be considered for secondary prevention.

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Raised intracranial pressure

The intracranial compartment consists of brain parenchyma, vascular tissue, and cerebrospinal fluid (CSF). Since the skull is a rigid structure an increase in the volume of any one of these components without a compensatory decrease in one of the others will lead to raised intracranial pressure (intracranial hypertension). Conditions that may be associated with an increase in intracranial volume, and thus pressure, include: formation of cerebral oedema after head injury or ischaemic stroke, or around tumours; mass-lesions such as tumours or haemorrhage; CNS infections; and metabolic disorders. Increased dural sinus venous

pressure, increased resistance to CSF outflow, or an increased rate of formation of CSF may also raise intracranial pressure. In idiopathic intracranial hypertension there is no obvious cause. Raised intracranial pressure can produce irreversible damage to the CNS and is potentially fatal; herniation of brain tissue can occur and reduced cerebral blood flow can lead to cerebral ischaemia. Symptoms of raised intracranial pressure include headache, which is often worse in the morning and may wake the patient from sleep, vomiting, drowsiness, and visual disturbances; papilloedema reliably indicates raised intracranial pressure but may not be present in all patients.

Both pharmacological and physical methods may be used to reduce raised intracranial pressure, although evidence for a beneficial effect on outcomes is limited for most therapies.[1] Choice depends to some extent on the underlying cause,[1-11] but in acutely raised intracranial pressure the initial aim is to reduce the volume of the intracranial contents as quickly as possible to prevent brain damage. In most cases, this involves general measures and drug therapy, but for patients with haematoma, ischaemic stroke, or tumours, surgery is often the treatment of choice, although drugs and other methods may be used to control intracranial pressure before surgery.

Cerebral blood flow depends on both intracranial pressure and cerebral perfusion pressure and it is important that ***measures to reduce intracranial pressure*** do not adversely affect cerebral perfusion. Blood pressure should be monitored and intracranial pressure monitoring is also often advised since lowering the intracranial pressure too far is also deleterious. Pain and agitation increase intracranial pressure and patients should receive adequate analgesia; benzodiazepines may be given to control unnecessary movement but if this is ineffective the use of neuromuscular blockers such as pancuronium or atracurium with artificial ventilation should be considered. Raising the patient's head to promote venous drainage may be helpful, although this is controversial since cerebral perfusion pressure may be reduced; however, head elevation by 15 degrees to 30 degrees appears to be safe and is widely used, and the head should be kept in a neutral position.[1,5] Hyperventilation reduces the intracranial pressure by constricting the cerebral blood vessels and controlled hyperventilation has been used. However, cerebral blood flow may also be reduced, so routine use is not generally advised,[1-3,8] although hypoxia should be avoided.[5] Restriction of fluid intake has been advised but, again, cerebral perfusion pressure may be reduced if hypotension occurs and intravenous fluids should therefore be given as appropriate. Fever should be treated,[5] but the use of controlled hypothermia to provide neuroprotection is not established; a review[12] of its use in head injury found no evidence that it improves outcome.

Where these general measures fail to reduce intracranial pressure adequately, **removal of CSF** through a ventricular catheter may be effective, and is particularly suitable if an intraventricular pressure monitor is being used.[1,5] Alternatively, pharmacological treatment may be given.

The mainstay of ***pharmacological treatment*** for acutely raised intracranial pressure is hyperosmolar therapy.[1,5,13] Mannitol is usually the treatment of choice, although hypertonic sodium chloride is increasingly being used. Glycerol or sorbitol are further options, and urea and hypertonic glucose have also been used. Loop diuretics have been given as an alternative to osmotic diuretics or as adjuncts to them.

Osmotic diuretics act by increasing the osmolality of plasma and drawing water out of the tissues, as well as by promoting an osmotic diuresis, but care should be taken to avoid hypovolaemia and they should not be used in patients who are dehydrated. Caution is also required in patients with intracranial haemorrhage since the reduction in intracranial pressure could exacerbate bleeding.[4] Osmotic diuretics may also be used for acute intracranial hypertension associated with brain tumours. They are not routinely recommended for reducing intracranial pressure in cerebral malaria, and use in other CNS infections is controversial; however, they may have a role in patients with bacterial meningitis if intracranial pressure is raised.[9]

- *Mannitol* decreases intracranial pressure and increases cerebral blood flow both by an osmotic effect and by decreasing blood viscosity.[2,13] It is widely used to reduce intracranial pressure after severe head injury,[2,3,6] although evidence from randomised studies is limited.[14] It is also used to control intracranial pressure before surgery, as well as in patients with ischaemic stroke or hepatic failure, and in children with diabetic ketoacidosis.
- In addition to its ability to lower intracranial pressure *glycerol* is reported to be able to increase blood flow to areas of brain ischaemia; it may be given orally or intravenously. There is some evidence[15,16] that routine use of oral glycerol improves neurological outcomes in children with bacterial meningitis. However, there have been reports of severe adverse effects including haemolysis, haemoglobinuria, and renal failure in patients given glycerol.
- *Hypertonic sodium chloride* has been shown to reduce intracranial pressure in several studies and it may have a role in raised intracranial pressure associated with traumatic or non-traumatic causes.[1,2,5,17,18] It has a potential advantage over osmotic diuretics in that it also treats hypovolaemia. However, evidence that its use improves outcomes is not yet available.
- Strongly *hyperosmotic glucose* solutions (25 to 50%) have been used to reduce raised intracranial pressure and cerebral oedema caused by delirium or acute alcohol intoxication.

If control is required for more than a few hours, repeated or continuous dosage of osmotic diuretics may be necessary. Mannitol may accumulate with continuous infusion and repeated bolus doses are generally preferred. Fluid and electrolyte balance and plasma osmolality should be closely monitored.

Corticosteroids have an accepted and important role in the management of raised intracranial pressure associated with tumour-induced cerebral oedema.[1,7] They may be used intravenously in high doses to control acutely raised intracranial pressure due to a rapidly expanding tumour. Lower doses are given orally for maintenance or where the onset of cerebral oedema is more insidious. Corticosteroids have also been tried in patients with stroke, but results have been disappointing. Although corticosteroids have been widely used in traumatic head injury, a large randomised study[19] found that they increased the risk of mortality and they are no longer routinely recommended.[1,3,5,20]

The use of barbiturate-induced coma with intravenous *thiopental* or *pentobarbital* for raised intracranial pressure has been controversial but it may be of benefit in patients refractory to conventional therapies.[2,3] In addition to their effect on intracranial pressure barbiturates may be able to protect the brain from ischaemia. *Propofol* may be an alternative, but caution is required with higher doses.[1,3,11] *Trometamol* reduces raised intracranial pressure, possibly by causing metabolic acidosis leading to vasoconstriction of cerebral vessels, and it may have a role in some patients.[1,13] Use of vasoconstrictors such as *dihydroergotamine* has also been reported.[1]

Idiopathic intracranial hypertension (pseudotumor cerebri) is a rare disorder of unknown cause in which there is a raised intracranial pressure in the absence of an intracranial mass or obstruction to CSF outflow. Although it was previously known as benign intracranial hypertension, since it is not life-threatening and is usually self-limiting, symptoms may be severe or become chronic, and there is a risk of irreversible visual loss.[21,22] Patients are often obese and tend to be young and female. Drug-induced intracranial hypertension may also occur.

Management of mild symptoms usually involves diuretic treatment with furosemide, a thiazide, or acetazolamide. Analgesics, tricyclic antidepressants, or the antiepileptic topiramate may be used to control headache.[21] Corticosteroids can control acute symptoms but long-term adverse effects limit their use. Repeated lumbar puncture to remove CSF may relieve symptoms and has been used every 2 to 5 days to induce remission. In patients who cannot be controlled medically, surgical methods such as lumboperitoneal shunting may be required. There have been reports of beneficial effects with *octreotide* in a few patients.[23,24]

Chronically raised intracranial pressure after CNS infections has also been treated with acetazolamide although there is limited evidence of benefit (see p. 2002.1).

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Other Vascular Disorders

Peripheral vascular disease, in its broadest sense, covers diseases of arteries, veins, and the lymphatic system, and includes atherosclerotic, vasospastic, thromboembolic, and inflammatory disorders. Peripheral vascular disease is commonly used as a synonym for chronic occlusive peripheral arterial disease, the management of which is discussed below. Also discussed in this section are thromboembolic disorders including venous thromboembolism and peripheral arterial thromboembolism, and also vasospastic arterial disorders. For chronic venous disease see also Varicose Veins (p. 2564.1) and Wounds and Ulcers (p. 1690.1).

Various forms of *central* vascular disorder are discussed under Cerebrovascular Disease, p. 1269.2. *Coronary* vascular disease is discussed under Ischaemic Heart Disease, p. 1254.2.

Chronic occlusive peripheral arterial disease

Peripheral arterial occlusive disease is usually caused by atherosclerosis (p. 1250.2) and is therefore very often associated with other cardiovascular diseases.[1] Although often symptomless, it may progress to **intermittent claudication**,[2,3] a condition characterised by pain that develops during exercise and disappears at rest. In severe disease pain may also occur at night or when resting (**critical limb ischaemia**).[4,5] The pain is due to ischaemia (insufficient oxygen supply) resulting from obstruction or vasoconstriction of peripheral arteries. Ischaemia may also result in trophic changes in the skin, and in severe or advanced disease, ulceration of skin and tissues can occur and may progress to gangrene. Some patients develop ulceration without previous symptoms of intermittent claudication, particularly where ischaemia is precipitated by thrombosis. Vasospasm due to smoking may also be a contributory factor. **Thromboangiitis obliterans** (Buerger's disease)[6] is another occlusive arterial disease, but it is a result of inflammatory and proliferative lesions in medium and small arteries and veins of the limbs and is almost invariably caused by tobacco exposure. The lesions are mainly thrombotic in nature. It progresses more rapidly than atherosclerotic disease; severe ulceration and gangrene, necessitating amputation, may often occur.

Management. Patients with occlusive arterial disease are at high risk of other cardiovascular events such as myocardial infarction and stroke, and treatment is important both to reduce this risk and to improve symptoms.[1,7-9] Aggressive measures to reduce cardiovascular risk (see p. 1246.1) should be implemented in all patients whether or not they have symptoms, with particular attention paid to treating obesity, hypertension, dyslipidaemias, and diabetes. Antiplatelet therapy should be given to all patients. Cessation of smoking is essential both to reduce risk and to halt disease progression, and in the case of thromboangiitis obliterans represents the definitive treatment. These measures do not generally improve symptoms in those with intermittent claudication, although supervised exercise programmes have been shown[10] to improve walking distance and are recommended,[7,9] and there is also some evidence[11] that *lipid lowering therapy* may do the same.

Many **drugs** have been used for symptom control in occlusive arterial disease, but studies have often been unsatisfactory and their efficacy and/or overall place in management remains to be firmly established. Analgesia is important in patients with critical limb ischaemia, particularly in those unsuitable for revascularisation.[9] Drugs intended to improve ischaemia have also been widely used, although few have an established role.

Vasoactive drugs have been the most commonly used drugs in intermittent claudication, although any purported benefit is probably due to mechanisms other than vasodilatation, such as actions on blood cells or changes in

blood rheology. *Vasodilators* do not preferentially dilate the affected arteries, which may in any case be fully dilated already. Dilatation of arteries supplying non-ischaemic tissues elsewhere in the body may actually divert blood away from the affected ischaemic area—the so-called 'steal' phenomenon; this is a known risk with all vasodilators, but especially with powerful arterial vasodilators such as hydralazine and this type of drug is not suitable for use in peripheral arterial disease.

- *Naftidrofuryl* is widely used in Europe. It has been shown to increase walking distance[12] and has been recommended as a first-line treatment in the UK.[13]
- *Cilostazol*, which has antiplatelet and vasodilator effects, may also increase walking distance[14] and has also been widely used, particularly in the USA.[1,3,7,9]
- *Pentoxifylline* has shown limited efficacy in small studies, but the evidence is considered insufficient to recommend its use.[3,8,9,13]
- Similarly, *inositol nicotinate*, although licensed in some countries for symptomatic management of intermittent claudication, does not appear to have good evidence of efficacy.[8,13]
- *Prostaglandins* such as *alprostadil* (prostaglandin E_1) and *epoprostenol* (prostacyclin) act as vasodilators and may be of benefit in occlusive arterial disease,[2,4] but their role remains unclear and their use may not be practical in most patients.[7] Oral prostaglandins such as *beraprost* have also been tried but do not appear to be effective and are not recommended.[7-9,15]
- *Other drugs* that have been tried in small studies include arginine, carnitine derivatives, and ginkgo biloba,[2] but in each case the evidence of benefit is scant. Growth factors (given locally) and gene therapy are under investigation.[2,4,5]

For patients with severe intermittent claudication that fails to respond to standard medical treatment, and for those with critical limb ischaemia (pain at rest or ischaemic ulceration), **non-pharmacological therapy** is usually required; intravascular thrombolysis may be used in acute ischaemia (see Peripheral Arterial Thromboembolism, below), but its role in chronic disease is not established.[7,9] Bypass surgery, endarterectomy, and percutaneous techniques such as angioplasty, atherectomy, and stenting are used for revascularisation; amputation may be necessary where ischaemia is irreversible. For treatment to prevent thrombosis and restenosis after revascularisation, see Reperfusion and Revascularisation Procedures, p. 1259.2.

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Thromboembolic disorders

The term thromboembolic disorder has been applied loosely to cardiovascular disorders associated with thrombus and embolus formation in blood vessels. A **thrombus** is a stationary blood clot composed of fibrin and platelets and other cellular elements. **Thrombosis** is occlusion of a vein or artery by a thrombus. An **embolus** is a fragment of blood clot, atheromatous material, or other foreign matter carried along in the bloodstream. Occlusion of a blood vessel by an embolus is termed **embolism** or **thromboembolism**.

Formation of blood clots in the body is the result of a coagulation cascade (see Haemostasis and Fibrinolysis, p. 1124.3). Under normal circumstances systemic coagulation is prevented by natural antithrombotic systems that limit blood clots to sites of vascular injury. Thromboembolic disorders occur when there is an imbalance between these systems. Three factors are involved, namely damage to the endothelial lining of blood vessels, reduced blood flow, or changes in the coagulation mechanisms of the blood. A further factor that increases the risk of clotting is the presence of an artificial surface in contact with the blood, for example mechanical heart valves, intravascular catheters, or during extracorporeal circulation procedures. Thromboembolism can occur in any part of the circulation, including the heart and the capillaries, but the characteristics of the thrombi, the consequences, and the management of thromboembolism depend to a large extent upon whether the arterial or venous system is involved.

The mainstay of management for thromboembolic disorders is antithrombotic drugs. These act at different points in the coagulation cascade and include anticoagulants and antiplatelet drugs, which are used to limit the extent of thrombosis or thromboembolism and to prevent further thromboembolic events occurring, and thrombolytics, which are used to lyse the clot.

Arterial thromboembolism is usually a consequence of damage to the endothelium due to atherosclerosis (p. 1250.2); the atheroma may block the blood vessel or, more commonly, occlusion is a result of thrombus formation at a site of a recently ruptured atheromatous plaque. Arterial thrombi contain more platelets than venous thrombi and tend to remain fixed, but emboli may break off and occlude distal vessels. Arterial emboli may also result from thrombosis within the heart, for example due to arrhythmias or valvular heart disorders.

Thrombosis or thromboembolism in the arterial circulation produces ischaemia in the tissues perfused by the artery, which may lead to infarction. It may therefore result in myocardial infarction (p. 1257.1) or unstable angina (p. 1254.3) if it occurs in coronary arteries, stroke (p. 1269.2) if it occurs in cerebral arteries, or critical limb ischaemia if it occurs in peripheral arteries (below).

Venous thromboembolism (p. 1274.1) is usually a consequence of stasis of the blood, but other factors such as local trauma or coagulation activation are also required. Reduced venous blood flow occurs in many conditions, including obesity, heart failure, and during prolonged immobilisation. Abnormal clotting may occur in conditions such as malignancy, pregnancy, liver disease, and the nephrotic syndrome, or during oestrogen therapy; it may also be due to inherited or acquired clotting disorders or thrombophilias (see below). Surgical operations are particularly associated with venous thromboembolism; trauma activates clotting factors and reduced blood flow may occur during the procedure and recovery period.

Venous thrombi have a 'red tail' of fibrin and red cells that may occlude the vein but which often separates to form an embolus; this is most likely during the early stages when the thrombus is only loosely attached. Thrombosis or thromboembolism in the venous circulation produces oedema or inflammation in the tissue drained by the affected vein. The commonest type of venous thrombosis is deep-vein thrombosis, which is associated especially with immobility and the postoperative period. Pulmonary embolism is the most serious complication of deep-vein thrombosis and occurs when part of the thrombus migrates in the circulation and becomes lodged in the pulmonary artery. Hypercoagulable states may result in deep-vein thrombosis or more generalised clotting in microvessels (microvessel thrombosis), such as thrombotic thrombocytopenic purpura or purpura fulminans (see Thrombotic Microangiopathies, p. 1159.1).

Thrombophilias are acquired or inherited disorders of the clotting system in which the antithrombotic mechanisms are impaired. Inherited deficiencies of antithrombin III, protein C and protein S all predispose to thromboembolism. Resistance to activated protein C has been identified as a major cause of inherited thrombophilia and appears to be due to a mutation in the factor V gene (factor V Leiden). A mutation in the prothrombin (factor II) gene is associated with increased concentrations of prothrombin and risk of thrombosis. Acquired thrombophilias may occur secondary to disorders such as malignancy, infection, or collagen-vascular disorders; in many cases antiphospholipid antibodies (such as lupus anticoagulant) are present. Hyperhomocysteinaemia is another risk factor and may have both inherited and acquired causes.

Inherited thrombophilias generally result in venous thromboembolism; this is often recurrent and may occur in unusual sites or at a young age. They often present when some further risk factor is present, such as pregnancy, use of combined oral contraceptives, or surgery, but the value of screening asymptomatic patients remains unclear. Acquired thrombophilias may lead to arterial or venous thromboembolism.

Patients with thrombophilias who develop thromboembolism should be treated conventionally, with anticoagulants or thrombolytics as appropriate. There continues to be debate regarding the duration of therapy, with some authorities recommending life-long anticoagulant therapy after a single episode and others recommending life-long therapy only in those with recurrent thrombosis. The optimum intensity of long-term anticoagulation in patients with thrombophilia is also debated. If anticoagulation is not continued, thromboprophylaxis should be given during high risk situations. Thromboprophylaxis is probably also necessary during pregnancy, particularly in women with antiphospholipid antibodies who are at risk for recurrent fetal loss (see Systemic Lupus Erythematosus, p. 1613.3), but the risks to the fetus from anticoagulant therapy must also be considered (see Venous Thromboembolism, p. 1274.1). Replacement of antithrombotic factors may have a role in some situations.

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Peripheral arterial thromboembolism. Thromboembolism may occur in various peripheral arteries, but most commonly affects those of the lower limbs, causing reduction in blood flow to the distal portions of the limb, which may lead to critical limb ischaemia. Sudden or acute occlusion (acute limb ischaemia) requires emergency treatment to restore blood flow and preserve the limb; similar approaches may also be necessary in chronic obstruction if the viability of the limb is threatened.

Peripheral arterial thromboembolism produces pain, pallor, and coldness in the affected limb. Numbness and paraesthesia may occur and if the clot is not removed, gangrene develops. Occlusion may be due to embolism or thrombosis, or to a combination of the two. It may occur in structurally normal arteries, particularly in patients with thrombophilia (see Thromboembolic Disorders, above). However, most patients have underlying chronic occlusive peripheral arterial disease (p. 1272.3), although this is often asymptomatic, and occlusion develops at the site of an underlying atherosclerotic plaque. Sudden onset is usually due to an embolus, which often arises from the heart; atrial fibrillation, cardiomyopathy, myocardial infarction, and valvular heart disease are all associated with peripheral arterial embolism. Thrombotic occlusion usually has a more gradual onset, particularly where atherosclerosis has already reduced blood flow and collateral vessels have developed, allowing some perfusion of the limb to be maintained.

Sudden arterial occlusion requires emergency evaluation and treatment so that circulation can be restored as quickly as possible, before loss of viability makes amputation necessary.[1-6] Both pharmacological and non-pharmacological methods may be used, depending on availability and factors such as the location and severity of the occlusion. Where there is imminent danger to the limb, surgical revascularisation (bypass surgery) has often been preferred, but improvements in drug therapy and percutaneous techniques have allowed their role as initial therapy to expand. Anticoagulation with heparin should be

started in all patients to prevent propagation of the clot and embolisation.[1-3,5,7,8] In all but the most urgent cases, angiography should be performed to assess the most suitable revascularisation method. The options available are intra-arterial thrombolytics, percutaneous clot removal, surgical clot removal, or surgical bypass. Studies comparing thrombolysis with surgical revascularisation have generally found outcomes to be similar,[9] although there is some evidence that thrombolysis should be preferred if the duration of occlusion is less than 14 days and surgical bypass should be preferred if the duration is more than 14 days.[8-10] Thrombolysis may also be used to reduce the clot burden before diagnostic angiography or as an adjunct to percutaneous removal or other surgical procedures.[5,6,8,11]

Although thrombolytics have been given systemically there is a high risk of bleeding and intra-arterial (catheter-directed) thrombolysis directly into the clot is now preferred.[2,6-8,10-13] Urokinase and alteplase are the most widely used thrombolytics and appear to be more effective than streptokinase;[10,12,14] reteplase and tenecteplase have also been tried.[2,7,8,10,12] Anticoagulants should be continued during and after thrombolysis to prevent rethrombosis, although the risk of bleeding is increased. Adjunctive antiplatelet therapy with glycoprotein IIb/IIIa-receptor antagonists such as abciximab has also been tried and appears to improve outcomes,[6,15,16] although this requires confirmation in large controlled studies.

Patients in whom an acute occlusion has been successfully treated should be assessed for long-term treatment. Those with underlying atherosclerotic disease should be treated as appropriate (see Chronic Occlusive Peripheral Arterial Disease, p. 1272.3), while those with occlusion due to embolism should be investigated for a possible source and long-term oral anticoagulation should be considered to prevent recurrence.[5]

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Venous thromboembolism. The term venous thromboembolism embraces both deep-vein thrombosis (DVT) and pulmonary embolism (PE). In DVT formation of a thrombus (blood clot), often in the pockets of valves, blocks the veins of the lower limbs or main pelvic veins or, less commonly, the veins of the upper extremities. PE occurs when the thrombus or part of it migrates in the circulation and blocks the pulmonary artery. DVT and PE are manifestations of the same disease process and are considered a single clinical entity; many patients presenting with DVT may also have asymptomatic PE, and vice versa. Various factors underlie the development of thrombosis and there are several conditions that predispose patients to venous thromboembolism (see Thromboembolic Disorders, p. 1273.2). Venous thromboembolism is a common but underdiagnosed condition and causes considerable morbidity and mortality, especially among hospitalised patients.

Prophylaxis of venous thromboembolism. Morbidity, immobilisation, and accidental or surgical trauma put hospitalised patients at great risk of developing venous thromboembolism. Without prophylaxis, the incidence ranges from 10% in the lowest-risk groups to 60% or more in groups undergoing high-risk surgery.[1] Since thromboprophylaxis significantly reduces rates of venous thromboembolism, all patients admitted to hospital should be regularly assessed for their risk of developing the latter, as well as their risk of bleeding, in order to determine the most appropriate prophylactic measures.[2,3]

Patients can be categorised as being at low, moderate, or high risk of thromboembolism.[1-3] For surgical patients, the type and duration of surgery are important factors: minor or day-case operations in mobile patients generally carry a low-risk; general, abdominal, and gynaecological operations carry a moderate risk; while all orthopaedic operations, and operations in cancer patients, are considered high risk. Non-surgical (medical) patients at high risk include those with major trauma or spinal cord injury. Age, immobility, a history of thrombophilia or previous thromboembolism, and conditions such as heart failure and lung disease, increase the risk in both surgical and medical patients, as does the presence of multiple risk factors. Cancer patients are at particularly high risk of venous thromboembolism due to immobility, malignancy, chemotherapy, and indwelling catheters.[4,5] Pregnancy is also a risk factor and is discussed in more detail separately below.

General prophylactic measures to reduce blood stasis, which include early and frequent ambulation and ensuring adequate hydration, as well as minimisation of risk factors (for example, by witholding hormonal contraceptives or removing redundant indwelling catheters) should be adopted in all patients where possible.[1-3,6] They may also be used as the sole method of prophylaxis in patients undergoing minor procedures who have no other risk factors.[1]

Mechanical interventions may help to maintain or improve blood flow in the lower limbs but are not as effective as pharmacological prophylaxis, and good quality evidence of their benefits is lacking; however, they have an important advantage in that they do not cause bleeding.[1,2,6,7] The most widely used method is the graduated compression stocking. These are of value,[8] but only if fitted correctly,[2] and compliance can be poor.[1] More complex mechanical approaches include intermittent pneumatic compression devices and foot pumps.[1-3] Mechanical prophylaxis may be combined with pharmacological prophylaxis; it may also be used as the sole method in patients at low risk, as well as in higher-risk patients unsuitable for anticoagulation (although pharmacological prophylaxis should be started if the bleeding risk drops to an acceptable level).[1-3,6,7] Compression techniques should not be used in patients with significant peripheral vascular disease.

Pharmacological prophylaxis is given to patients at moderate or high risk of venous thromboembolism.[1-3] It is usually based on the use of parenteral or oral anticoagulants, and choice of drug depends on patient factors such as renal impairment or hypersensitivity as well as the level of risk.

The use of ***heparins*** for thromboprophylaxis is well established, and they are the drug of choice for most patients requiring anticoagulants.[1-3,5] They are given in low (non-therapeutic) doses and therefore clotting time (APTT) monitoring is not usually required, although some patients (such as those at extremes of weight or with renal impairment) may benefit.[1,2] Low-molecular-weight heparins offer certain advantages over unfractionated heparin, including once-daily dosing and a lower risk of heparin-induced thrombocytopenia (HIT), and are preferred in most patients.[2,7] However, unfractionated heparin may be more suitable for those with renal impairment and in situations where quick reversal could become necessary.[2,3] ***Fondaparinux*** is an alternative to the heparins.[2] Unfractionated heparin, low-molecular-weight heparins, and fondaparinux have shown similar efficacy in most types of patients including medical, cancer, and general surgery patients.[2] The exception is in orthopaedic surgery, where low-molecular-weight heparins have shown superior efficacy to unfractionated heparin and thus are preferred.[1,2]

Alternatives to heparins in patients who develop, or are at risk of, heparin-induced thrombocytopenia (HIT) include the ***hirudins*** such as lepirudin, and the ***heparinoids*** such as danaparoid.[2]

Dextrans may be given, but are cumbersome to use and must be avoided peri-partum and in renal impairment.[2] (The management of HIT is described more fully in Effects on the Blood under Heparin, p. 1399.1.)

Vitamin K antagonists may be effective, but because they have a delayed onset of action, require careful monitoring, and increase the risk of bleeding after surgery, they are not usually used;[2] however, it has been suggested that those already on long-term warfarin for another indication may continue if appropriate.[2]

Novel oral anticoagulants have been developed with the aim of simplifying administration.[9] These include the direct thrombin inhibitor ***dabigatran*** and the direct factor Xa inhibitor ***rivaroxaban***. They do not require monitoring, but the lack of reversibility is a disadvantage.[2,3,9]

There has been controversy over the use of ***antiplatelet agents***, particularly aspirin, for thromboprophylaxis.[10] Evidence suggests they may provide some protection against venous thrombosis,[10] but most guidelines[1-3] recommend against aspirin as a sole prophylactic agent since anticoagulants are more effective. Those already taking low-dose aspirin for other indications may safely continue to do so, and it may confer a small additional reduction in thrombosis risk, although with an increased risk of bleeding.[2]

Statins have been reported to be protective against venous thromboembolism,[11] but there is not yet sufficient evidence to recommend their use for this purpose.[2,11]

The *duration* of prophylaxis again depends on the balance of risk factors. In medical patients, prophylaxis should continue throughout hospitalisation, or longer where the risk is ongoing.[2] In surgical patients, appropriate prophylaxis may be started either pre- or postoperatively depending on the choice of drug,[1,2] and the duration is usually at least 5 days or until the patient is ambulant.[1-3] However, at least 10 days of prophylaxis is recommended after total hip or knee replacement, and up to 35 days may be beneficial.[1] Extended prophylaxis may also be considered in patients with continued illness or immobility.[1,2] Graduated compression stockings are ideally worn until pre-morbid levels of mobility are reached.[1,2]

Prophylaxis during travel. Any mode of travel requiring immobilisation for 4 or more hours carries a small (2 to 4 fold) increased risk of venous thromboembolism, and this risk may continue for up to 8 weeks post-travel.[1,2,12] Certain prophylactic measures have been suggested for those on long journeys, although most of these lack good evidence of benefit. In healthy individuals, the only preventative measures required are frequent ambulation, wearing loose-fitting clothing, and remaining adequately hydrated; seated leg exercises may also be of benefit.[1,2,12,13] Graduated compression stockings reduce clotting as well as leg discomfort and oedema,[14] although they are probably unnecessary in low-risk patients.[13] They may be of more benefit in medium- or higher-risk patients,[12,13] but if used, it is important that they are fitted correctly.[1,2] Travellers deemed to be at especially high risk of thrombosis, such as those with active malignancy or after recent surgery, may be considered for pharmacological prophylaxis.[1,2,12] Low-molecular-weight heparin has been used for this purpose, and may be given in a single injection before travel.[1,2,12] Fondaparinux is an alternative.[12] Anti-platelet drugs such as aspirin are of little value and are not recommended.[1,12,13]

Treatment of venous thromboembolism. Prompt treatment of venous thromboembolism reduces mortality and morbidity considerably.[15] Patients presenting with signs and symptoms suggestive of venous thromboembolism (such as a painful, swollen calf, chest pain, or severe shortness of breath) should have the diagnosis confirmed or ruled out using D-dimer testing and/or imaging.[2] Symptomless DVT or PE that is discovered inadvertently should be treated as for symptomatic disease;[15] upper-extremity DVT is treated as for lower.[2,15,16] Each patient should also be assessed for their risk of bleeding before a treatment regimen is chosen.[2]

Initial treatment of DVT. The aims of initial treatment are prevention of thrombosis extension, PE development, and acute recurrence.[2,15] Therapeutic doses of parenteral anticoagulants should be started in all patients with suspected DVT if there are no contra-indications,[2,5,6,15,17] and continued until either the diagnosis is refuted, or for at least 5 days until long-term treatment can take its effect.[2,15,17] A ***heparin*** is the initial anticoagulant of choice. Low-molecular-weight heparins are generally preferred to unfractionated heparin as they have shown superior outcomes, and have the advantages of once-daily dosing, predictable pharmacokinetics, and a reduced incidence of HIT.[2,15] Among the low-molecular-weight heparins, there is little difference in efficacy.[2] Unfractionated heparin may be used in patients who have renal impairment or a high bleeding risk, or who are under consideration for thrombolysis.[2,15] In patients with suspected or proven HIT, ***danaparoid*** or a ***direct thrombin inhibitor*** such as lepirudin are given.[2,17] (The management of HIT is discussed more fully under Effects on the Blood under Adverse Effects of Heparin, p. 1399.1.) Alternatives to drug treatment exist, but their roles are less well defined. Inferior vena cava filters may be fitted in patients with absolute contra-indications to anticoagulation,[2,15,17,18] but they carry their own risks of complications, and should be removed and replaced with standard anticoagulation therapy as soon as the contra-indication ceases to apply. Catheter-directed or systemic thrombolytics are not routinely indicated, but

either may be considered in carefully selected patients.[2,15,17] Venous thrombectomy is also an option in certain patients.[15,17]

Initial treatment of PE. The principles of treatment for PE are similar to those for DVT, although additional haemodynamic and respiratory support is often also necessary.[2,17,19,20] The severity of PE has been classified in several ways to guide treatment. Terms such as 'massive', 'sub-massive', and 'non-massive' have been used with respect to the anatomical burden of clotting; however, the current recommendation is to treat patients according to their risk of early mortality, depending on the presence or absence of factors such as cardiogenic shock and severe hypotension.[2,17,19,20] ***Thrombolytics*** may be used in high risk PE;[2,15,17,19,21] they are not given routinely to those with intermediate-risk PE, but may be considered in carefully selected patients such as those with severe haemodynamic compromise and a low risk of bleeding, although the evidence of risks and benefits is incomplete. Thrombolysis is not recommended in low-risk patients.[2,15,17,19] Pulmonary embolectomy may be considered in high-risk patients unable to receive thrombolytics, or in whom they have failed.[15,17,19,20] The optimum treatment of right-heart emboli is uncertain, but anticoagulation alone is probably insufficient, and thrombolytics or embolectomy should probably be used.[19] Patients with suspected PE should be given therapeutic doses of parenteral anticoagulants until the diagnosis is confirmed or refuted.[2,15,19] Unlike for DVT, low-molecular-weight heparin has not been proven superior to unfractionated heparin,[2,19] and therefore either unfractionated heparin, low-molecular-weight heparin, or fondaparinux may be used for the initial treatment of PE.[2,15,19,20] However, low-molecular-weight heparin may be preferred in low-risk PE due to its ease of administration,[15] while intravenous unfractionated heparin is preferred in high-risk PE for its rapid effect, and also in patients with renal failure or at high risk of bleeding, if prompt reversal may be necessary, or if thrombolytics are to be given.[2,15,19,20] A weight-adjusted regimen of unfractionated heparin is preferred to fixed doses.[19,20]

Continued treatment of venous thromboembolism. The aim of long-term treatment is to complete initial treatment and prevent new occurrences of venous thromboembolism as well as reduce long-term consequences.[2,15] The main long-term recommendations do not differ between PE and DVT. ***vitamin K antagonists*** (usually warfarin) are the long-term drug treatment of choice, and may be started as soon as diagnosis is confirmed, often on the same day as the parenteral anticoagulant. (In patients with HIT, warfarin should not be started until the platelet count has fully recovered.) Vitamin K antagonists are at least as effective as the low-molecular-weight heparins for long term treatment,[2] and are therefore used in most patients, with a target INR of 2.5 (2.0 to 3.0).[2,15,17] Exceptions include cancer patients[2,5,17,19] and pregnant women (see below) in whom low-molecular-weight heparins are the basis of therapy. ***Rivaroxaban***, ***apixaban***, and ***dabigatran*** are under investigation for the initial and long term treatment of venous thromboembolism.[19] Early ambulation is recommended after DVT,[15] and graduated compression stockings should be worn.[17] The optimum *duration* of anticoagulation must be carefully considered for each patient. Recurrence is reduced for as long as anticoagulation is continued; therefore, to prevent recurrence, treatment should ideally be continued for as long as the patient is at risk.[2,15] However, risk of recurrence must also be balanced against the risk of haemorrhage. It is generally recommended that treatment should continue for at least 3 months after a first episode of venous thromboembolism.[2,15,17] It may then be stopped if a reversible risk factor no longer applies.[17,19] One month after stopping anticoagulation, a D-dimer test may be used to identify patients who would benefit from resumption.[2,20] The benefits of longer periods of treatment (6 months or longer), or sometimes even indefinite treatment, can outweigh the risks in certain patients such as those with continuing risk factors (including cancer) and those with unprovoked or recurrent thromboembolism.[2,5,15,17,19,20,22] Guidance varies in this area, but the most important recommendation is continual reassessment of risk factors throughout an individual's treatment.[2,15] The use of a ***statin*** or ***aspirin*** has been tried after stopping vitamin K antagonists, but the evidence has been unconvincing and neither is recommended.[2]

Treatment of superficial-vein thrombosis (SVT). Although not traditionally encompassed by the term venous thromboembolism, SVT is a comparable disorder with similar causes.[23] Though long regarded as benign, patients may have concurrent DVT or are at risk of progression to it;[2,23] concurrent DVT should be excluded with imaging, and measures taken to treat symptoms and reduce risk of progression.[2,23] Oral NSAIDs may be effective at reducing extension and recurrence.[2] Graduated compression stockings may also be used,[2] and consideration of low- or intermediate-dose therapy with either unfractionated or low-molecular-weight heparin, or fondaparinux.[2,15] Patients in whom anticoagulants are contra-indicated may receive an 8 to 12-day course of an NSAID.[2]

Venous thromboembolism in children. The epidemiology of venous thromboembolism in children is different to that in adults, and it occurs more rarely. Treatment may be complicated by age-dependent factors that alter response to anticoagulants, as well as practical difficulties in administration.[24] However, few studies have been performed in children, and recommendations are largely based on those for adults.[6,24,25]

Venous thromboembolism in pregnancy. Pregnancy presents a particular risk for venous thromboembolism due to hormonal changes, haemostatic activation, immobility, and vascular trauma during delivery.[26] Some women who become pregnant may also be receiving regular thromboprophylaxis, for example for a mechanical heart valve. Therefore, all pregnant women should be assessed for risk of venous thromboembolism at each maternity contact,[2,27] and those found to be at excess risk should be considered for *prophylaxis*. Graduated compression stockings should be worn by such patients whenever hospitalised or otherwise immobilised.[2,27,28] Determining which patients may benefit from antenatal pharmacological prophylaxis is not always straightforward, but it is usually given to those deemed at high risk, and may also be considered in moderate-risk patients, depending on risk factors such as obesity, thrombophilias or previous unprovoked, recurrent, or oestrogen-related venous thromboembolism.[2,3,27,28] If given, it should be started in the first trimester.[2] In terms of choice, unfractionated heparin and low-molecular-weight heparin are equally effective, but low-molecular-weight heparin has a better safety profile and is usually preferred.[2,27,28] Those who cannot receive heparin may be offered danaparoid.[2,27] Vitamin K antagonists are contra-indicated because of their teratogenicity and, except in very unusual circumstances, those who are already taking vitamin K antagonists should switch to heparin before planned conception or else as soon as pregnancy is confirmed.[2,27,28] Caution is needed in anticoagulated patients peri-partum, especially if an epidural catheter is to be used, and the temporary cessation of anticoagulation is usually necessary. After delivery, regular assessments for risk of thromboembolism should continue. High-risk patients, including those who were receiving pharmacological prophylaxis antenatally, should receive it for a further 6 weeks after delivery.[2,27] Moderate-risk patients should be given pharmacological prophylaxis for at least 7 days after delivery.[2,27] Graduated compression stockings may also be of benefit.[2] If the mother was taking a vitamin K antagonist before pregnancy, it should be restarted no sooner than the third day post partum.[2]

If acute venous thromboembolism occurs during pregnancy, *treatment* is with unfractionated or low-molecular-weight heparin, again with a preference for the latter.[19,26,28] There is a lack of safety data with alternative anticoagulants such as fondaparinux,[19] and the vitamin K antagonists are contra-indicated.[19] Thrombolytics may be given to patients with high-risk PE.[20,26] Recommendations for duration of anticoagulant therapy differ; at least 6 weeks, and up to 6 months or more, of post-partum treatment seems reasonable, depending on additional risk factors.[19,26,28] Breast feeding may safely take place during anticoagulation with heparin or warfarin.[26,28] Although long-term use of unfractionated heparin, and to a lesser extent low-molecular-weight heparin, can cause osteoporosis, the risk in pregnant women appears to be rare and routine monitoring is not deemed necessary.[2]

Post-thrombotic syndrome. Post-thrombotic syndrome, the development of lower-limb symptoms secondary to DVT, occurs in about a third to a half of patients.[29] To prevent it, graduated compression stockings should be worn for as long as the patient tolerates them, but ideally for at least 2 years after the event.[2,15,17,29] Stockings are also the basis of treatment, as is frequent leg elevation[29] Severe oedema may be relieved with intermittent pneumatic compression.[15,17,29] Although various drug therapies, including diuretics, NSAIDs, and horse-chestnut seed have been tried, their efficacy is uncertain.[29]

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Vasospastic arterial disorders

Vasospastic arterial disorders form part of the spectrum of peripheral vascular disease (see p. 1272.3), and represent an inappropriate response to temperature, resulting in vasoconstriction and/or vasospasm; Raynaud's syndrome, acrocyanosis, and chilblains are usually induced by cold, whereas erythromelalgia is caused by heat.

In **Raynaud's syndrome**, paroxysmal attacks of pallor and cyanosis, usually of the digits, occur in response to cold, or sometimes emotional stress.[1-4] Erythema replaces the cyanosis as the attacks resolve. The cause of primary Raynaud's syndrome (Raynaud's disease) is unknown. Features identified include intense vasoconstriction or vasospasm, disturbance of sympathetic nerve supply, changes in circulating catecholamines, enhanced platelet aggregation, red cell deformability, and fibrinolysis. It is probable that not all cases are due to the same mechanism. It has been suggested that the underlying problem may not be an overreaction to the initial cold insult but a defect in the normal ensuing adaptive response. Secondary Raynaud's syndrome (Raynaud's phenomenon) frequently coexists with arterial occlusive disease such as thromboangiitis obliterans and connective tissue disorders, in particular scleroderma (systemic sclerosis). Trauma and certain drugs, notably beta blockers and ergotamine, may also be responsible for inducing secondary Raynaud's syndrome.

Management. In mild cases of Raynaud's syndrome, where attacks are infrequent and of limited severity, protective measures to keep warm are the mainstay of

treatment; this involves wearing appropriate clothing and the use of appliances such as heated gloves. Smoking should be avoided because of the vasoconstriction caused. Any underlying or co-existing disease or cause in secondary Raynaud's syndrome should be treated. Drug therapy is indicated in more severe cases.[1-4] It is directed towards producing vascular smooth muscle relaxation and vasodilatation in order to improve resting blood flow, thereby reducing the extent of tissue ischaemia. Some drugs may also act by modifying endothelial function, platelet aggregation, or blood rheology. Many drugs have been tried in Raynaud's syndrome, although only a few have an established role.

- *Calcium-channel blockers* are of benefit[5] and are generally used as first-line treatment for both primary and secondary disease where drug therapy is required,[1,3] although their usefulness in secondary disease may be limited.[4] Dihydropyridines are usually preferred; the most widely used and studied is *nifedipine*.
- Topical vasodilators such as *glyceryl trinitrate* are an alternative in those with primary disease, although their use is limited by adverse effects. They may be less effective in secondary disease.[3]
- In severe Raynaud's syndrome complicated by ulceration, *prostaglandins* may be given,[1] of which intravenous *iloprost* has accrued the most evidence;[2,4] *alprostadil*, *epoprostenol*, and oral iloprost have also been used.
- Endothelin receptor antagonists have shown benefit in severe disease,[1-3] and *bosentan* is licensed for the prevention of digital ulceration in patients with scleroderma, although it has not been shown to heal existing ulcers nor reduce the frequency or severity of attacks.[4]
- Phosphodiesterase type-5 inhibitors such as *sildenafil* have shown promise in studies of patients with secondary disease, and are suggested[3] as an alternative to prostaglandins or endothelin receptor antagonists. Evidence of a benefit in primary disease is lacking.[4]
- *Other drugs* have shown positive results in small studies, although none has sufficient evidence for firm recommendations. They include: angiotensin receptor antagonists; alpha blockers (although adverse effects may limit their use); statins (which may have pleiotropic effects on the endothelium); calcitonin gene-related peptide; antoxidants such as acetylcysteine; SSRIs; sarpogrelate; and botulinum toxin A.[1-3] The addition to therapy of an antithrombotic such as aspirin or heparin has been suggested by some.[1,3] The *BNF* notes that other drugs that may produce symptomatic benefit include naftidrofuryl or the nicotinic acid derivative inositol nicotinate; pentoxifylline is not of established value.

Acrocyanosis is characterised by a persistent blue discoloration of the skin. There is an abnormal constriction of arterioles, even at normal environmental conditions and this is potentiated by cold. **Chilblains** are an inflammatory condition (perniosis) affecting the extremities and symptoms include erythema, pruritus, and ulceration; they may be acute or chronic. Chilblains are more common in cold damp conditions. Acrocyanosis and chilblains do not generally require specific treatment; smoking cessation, protection from the cold, or symptomatic antipruritic treatment are often sufficient.[4,6] If drug therapy is required, a calcium-channel blocker may be of benefit in chilblains;[6] the role of drug therapy in acrocyanosis is uncertain.[4]

Erythromelalgia (sometimes also called erythermalgia) is a vasospastic condition usually provoked by heat although it may also be drug-induced or secondary to other conditions. It is characterised by painful, red extremities plus a burning sensation and increased skin temperature of the affected area. Aetiologies are numerous; thrombocythaemia (p. 695.2) is the most common underlying cause and, indeed, erythromelalgia may be the presenting feature of this disorder. In thrombocythaemia, arteriolar occlusion may occur as a result of platelet aggregation, and small doses of aspirin have produced considerable relief in some patients, presumably by preventing platelet aggregation. Beta blockers may also be of some help, and there are anecdotal reports of benefit with many other classes of drugs, but none is consistently effective.[4,7] Attacks should be prevented wherever possible by avoiding exposure to heat.

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Other Cardiovascular Disorders

Ascites

Ascites is the accumulation of fluid within the peritoneal cavity. Although it is not strictly a cardiovascular disorder, treatment depends mainly on cardiovascular drugs. Alcoholic hepatic cirrhosis is probably the commonest underlying cause in the western world; others include malignant neoplasms, heart failure, and tuberculosis. The following discussion is restricted mainly to **cirrhotic ascites**.

The mechanism of ascites formation in hepatic cirrhosis has been explained by various hypotheses. Whatever the mechanism, ascites formation is linked to renal sodium and water retention partly as a result of increased circulating renin and aldosterone concentrations. Portal hypertension and hypoalbuminaemia may be contributory factors.

Small amounts of ascitic fluid may go undetected but as it accumulates abdominal distension becomes apparent, and there is a feeling of discomfort. There may be respiratory distress and cardiac dysfunction in severe cases. Peripheral oedema may, or may not, be present, and dilutional hyponatraemia may develop. Renal dysfunction may progress to severe impairment (the hepatorenal syndrome). Patients are at risk of primary (spontaneous) bacterial peritonitis (p. 197.2).

Management[1-12] depends on the severity of ascites but the mainstays are dietary sodium restriction and diuretic treatment. In mild to moderate ascites, sodium restriction alone may sometimes be effective but most patients also require diuretics. Bed rest has been advocated but is no longer generally recommended.[10] Response is monitored by measuring the daily reduction in body-weight. The diuretic of choice is the aldosterone antagonist spironolactone, with the addition of a loop diuretic such as furosemide if necessary. Amiloride or another potassium-sparing diuretic may be used as an alternative to spironolactone if adverse effects are a problem. Spironolactone with furosemide from the outset has also been used. In diuretic-resistant ascites, some benefit has been reported with combined furosemide and albumin;[13] other drugs tried include vasopressin receptor antagonists (satavaptan), vasoconstrictors (terlipressin, octreotide, and midodrine), and clonidine.[11,12] In tense or refractory ascites, large-volume or total paracentesis (removal of ascitic fluid by drainage) is often used initially; patients may then be maintained on diuretics or repeated paracentesis may be used. Plasma volume replacement with albumin or dextrans after paracentesis is usual to reduce haemodynamic complications, particularly if large volumes are removed; alternative approaches that have been tried include use of vasoconstrictors such as terlipressin, midodrine, or noradrenaline, but none of these has an established role.[11] Where ascites remains refractory or repeated paracentesis is not tolerated various shunting procedures have been tried.[11,12] In severe cases liver transplantation may be necessary.

In **malignant ascites** (ascites due to malignant neoplasms; see Malignant Effusions, p. 700.1), paracentesis is often necessary but spironolactone may be of benefit in some patients.

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High-altitude disorders

Rapid ascent (ascent without time to acclimatise) to high altitudes may produce a spectrum of illness (altitude illness) ranging from the usually benign acute mountain sickness to life-threatening pulmonary oedema and cerebral oedema. Factors influencing the development of altitude illness include rate of ascent, altitude attained, sleeping altitude, and length of stay at altitude. Individual susceptibility is also an important factor. Symptoms of altitude sickness are common at altitudes above 2500 metres (8125 feet), although susceptible individuals may be affected at altitudes as low as 2000 metres (6500 feet).[1-6] Reported incidences at higher altitudes vary, but in general symptoms occur in about 50% of people ascending rapidly to altitudes of over 4000 metres (13 000 feet) and in about 75% of people at 4500 metres (14 625 feet); they are severe (pulmonary oedema or cerebral oedema) in about 4%.

Symptoms of **acute mountain sickness** include headache, which is worse in the supine position, nausea, vomiting, anorexia, lethargy, insomnia, and dizziness. These may develop during ascent, but characteristically occur 6 to 48 hours after arrival at altitude. They are usually short-lived and resolve after a few days at altitude. In a very few people symptoms persist for longer. Chronic mountain sickness, characterised by persistent severe hypoxia and polycythaemia, may develop during prolonged residence at high altitude. The discussion that follows is limited to management of the acute forms. A small proportion of people with acute mountain sickness suddenly deteriorate and develop pulmonary oedema or cerebral oedema, both of which may be life-threatening. Occasionally, pulmonary or cerebral oedema develops without symptoms of acute mountain sickness. Symptoms of **pulmonary oedema** include rapid onset of breathlessness and tachypnoea at rest, and a dry cough which may develop into haemoptysis. Symptoms of **cerebral oedema** include increasing headache, ataxia, mental disturbances, drowsiness and eventually coma. Pulmonary and cerebral oedema frequently occur together.

The **pathogenesis** of altitude illness is not fully understood, and it is not known whether the mechanisms of acute mountain sickness and pulmonary or cerebral oedema differ in nature or merely degree. Hypoxia, a result of the reduced partial pressure of oxygen at high altitudes, is considered the primary stimulus in the development of altitude illness.[1-4,6,7] When ascent to high altitudes occurs gradually, the bicarbonate concentration and the pH of extracellular fluid fall progressively. The falling pH increases the sensitivity of chemoreceptors to hypoxia and so permits greater ventilation, thus allowing acclimatisation. Rapid ascent to high altitudes does not allow time for these changes to occur and although the hypoxia stimulates hyperventilation, it produces a respiratory alkalosis which limits the ventilatory response to hypoxia. The hypoxaemia produced leads to neurohumoral and haemodynamic changes that ultimately result in the symptoms of altitude illness.[1] Symptoms are often worse at night when ventilation is reduced leading to a worsening of the hypoxaemia.

Prophylaxis. Altitude illness may be avoided by ascending to high altitudes slowly and thereby allowing time for acclimatisation. This may be achieved by spending several days at 1500 to 3000 metres and avoiding strenuous physical activity, thus allowing the body to adapt to the reduced oxygen pressure and to ascend above 3000 metres without sickness. Acclimatisation may also be achieved when going above 3000 metres by increasing the sleeping altitude by no more than 300 to 600 metres daily and by adding a rest day for every 1000 metres climbed;[1,2,6,7] slower rates of ascent than this have also been advised.

However, when time for acclimatisation is limited or when abrupt arrival at high altitude (for instance by air) cannot be avoided, drug prophylaxis may be considered. Prophylaxis should also be considered for those individuals who have developed symptoms on ascending to high altitudes on previous occasions.

Acetazolamide is the most frequently used drug[1-5,7] and has been shown[8,9] to effectively reduce the frequency of symptoms, although the optimum dose is not clear. It produces a mild metabolic acidosis which has the effect of stimulating chemoreceptors to produce an increase in the rate of respiration and tidal volume, and it therefore accelerates the process of acclimatisation. Although acetazolamide has diuretic actions it does not prevent fluid retention or prevent or protect against pulmonary or cerebral oedema. It improves sleep hypoxaemia and quality of sleep, reduces proteinuria, improves exercise performance, and reduces loss of muscle mass, probably by improving oxygen supply to the tissues.[10] Acetazolamide should be taken on the day of ascent or 1 or 2 days before ascent to altitudes above 3000 metres, and continued for several days at the higher altitudes.[1,7] However, there has been concern that the use of acetazolamide to prevent symptoms of acute mountain sickness may encourage too rapid an ascent and perhaps increase the risk of developing pulmonary or cerebral oedema.[10]

Dexamethasone has also been shown[8] to be effective in the prevention of acute mountain sickness. The rationale for its use is to control the mild cerebral oedema thought to contribute to the symptoms of acute mountain sickness, although it has also been shown to prevent the development of pulmonary oedema.[11] However, as the adverse effects associated with dexamethasone are more severe than those associated with acetazolamide, it is not

considered suitable for routine prophylaxis; it may have a role if acetazolamide is unavailable or contra-indicated.[1,2,6,7] If it is used, dexamethasone should be started a few hours before ascent;[7] adverse effects may be fewer if the dose is tapered before stopping.[8]

Nifedipine has been shown to lower pulmonary artery pressure and to protect against pulmonary oedema in people susceptible to the development of pulmonary symptoms at altitude.[12] It may be considered for prophylaxis in those with a history of high-altitude pulmonary oedema.

Other drugs that have shown some benefit in small studies include *spironolactone*,[8] *sildenafil*,[13,14] and *sumatriptan*.[15] *Ginkgo biloba* has also been used, but a randomised study[9] found no benefit. A study[16] with inhaled *salmeterol* suggested that it reduced the risk of pulmonary oedema in people considered to be at high risk, while *tadalafil* reduced the risk of pulmonary oedema but did not prevent acute mountain sickness.[11] *Aspirin* was reported[17] to reduce the incidence of headache in a small study in people with a history of headache at high altitude, and some benefit in preventing headache has also been reported with *gabapentin*.[18]

Treatment. Once symptoms of altitude illness develop the course of action should be determined by the severity and nature of the symptoms.

When symptoms are ***mild*** and are not suggestive of pulmonary or cerebral oedema, rest and mild analgesics for headache are usually all that is required; symptoms resolve within a few days and further ascent is possible.[1,2,4,5,7] *Acetazolamide* may have some benefit in relieving symptoms[1-3,19] although studies have been small. If mild symptoms of pulmonary oedema are present, such as dyspnoea and cough, rest with supplementary oxygen and further oxygen at night may resolve the symptoms and allow further ascent; however signs and symptoms at altitude may be confusing and it is always safest to descend. The use of hypnotics at altitude is not generally advised since there is a risk that respiratory depression may further reduce oxygen saturation, although some appear to be safe. A small study[20] using the short-acting benzodiazepine *temazepam* reported that sleep quality was improved without an alteration in mean oxygen saturation. Zolpidem or zaleplon may also be used.[21]

When symptoms are ***moderate to severe***, and are progressing or suggestive of cerebral oedema, immediate descent is necessary.[1-5,7] Descending by as little as 400 to 500 metres is beneficial. Various drugs and therapies have been given to alleviate symptoms and to facilitate descent and should also be used when immediate descent is not possible. For example, *dexamethasone* can reduce the symptoms of acute mountain sickness and might be used in emergencies.[22,23] Portable hyperbaric chambers are available[24] and provide rapid but short-term improvement. They may be useful used with dexamethasone, which has a more sustained effect.[25]

If pulmonary oedema is present, oxygen, which relieves hypoxia and reduces pulmonary hypertension, should be given;[1-3,7] *nifedipine*, which suppresses the exaggerated hypoxic pulmonary vasoconstrictor response seen in people with pulmonary oedema, has provided benefit.[26] Positive-pressure expiration may also be useful;[2] it has the effect of increasing oxygen saturation and partial pressure of carbon dioxide at altitude. Inhalation of nitric oxide has also been reported to improve oxygenation but use may not be feasible at altitude.[27]

People with cerebral oedema should be given *dexamethasone* and oxygen therapy.[3]

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Hypotension

As discussed under Hypertension (p. 1251.1) many factors influence blood pressure making it difficult to define an absolute norm. The link between chronically raised blood pressure and cardiovascular risk is well established, and definitions of 'normal' blood pressure are based on estimates of this risk. For adults, a systolic pressure below 130 mmHg, with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg) has generally been considered as normal, although recent guidelines[1,2] have suggested that a blood pressure below 120/80 mmHg may be more desirable. Exactly how far below these values blood pressure can safely be remains uncertain. Although acute hypotension leads to symptoms such as syncope (fainting) or shock, the consequences of chronically low blood pressure are much less clear. Thus, while there are national and international guidelines relating to the diagnosis and treatment of hypertension, there is no accepted definition for low blood pressure or hypotension.

Despite such shortcomings over definition, the existence of several acute and chronic hypotensive disorders is recognised.

Hypotension can occur after haemorrhage or in other forms of shock and the management of this acute and potentially dangerous form of low blood pressure is usually with volume replacement and vasopressors (see Shock, p. 1279.3); sympathomimetics with vasoconstrictor properties, such as noradrenaline and dopamine, are particularly useful when blood pressure is very low. Another situation in which acute hypotension can develop is during anaesthesia and surgery; spinal or epidural block is associated with a greater risk than many other forms of anaesthesia. Hypotension results from venodilatation and decreased cardiac output due to sympathetic block, and the usual treatment is again with sympathomimetics, particularly ephedrine or phenylephrine (see p. 1663.3).

Recurrent forms of acute hypotension may also occur. These include orthostatic (postural) hypotension and neurally mediated hypotension; both are important causes of syncope.[3-5] Orthostatic hypotension may be due to autonomic failure and loss of the reflex vasoconstriction that usually occurs on rising, or may be related to volume depletion. Drug treatment is usually with fludrocortisone (see p. 1634.3). For neurally mediated hypotension, however, choice of therapy is less clear.[4-12]

Neurally mediated hypotension (neurocardiogenic syncope, neurally mediated reflex syncope, vasodepressor syncope, or vasovagal syncope) is a common cause of recurrent lightheadedness (presyncope) and syncope in persons with structurally normal hearts. It is characterised by a paradoxical neurocardiogenic reflex; although the mechanism is not entirely clear, reduced cardiac filling appears to stimulate cardiac receptors that normally respond to hypertension, and there is an inappropriate autonomic response leading to vasodilatation, bradycardia, and hypotension. Diagnostic tests may be required to exclude structural or arrhythmic cardiac disorders as a cause of the syncope, and tilt-testing may be necessary to confirm the diagnosis.[5] Treatment mainly involves reassurance and non-pharmacological measures such as avoidance of triggering factors, an increase in dietary salt and fluid intake, and physical manoeuvres such as crossing the legs or tensing the muscles if presyncope occurs.[4,5,10-12] Tilt-training may be effective but motivating patients is difficult.[4,5] Cardiac pacing may be required in some patients, although there is limited evidence of benefit.[4,5,13]

Drug treatment for neurally mediated hypotension is more controversial and there is little evidence that any drugs are effective.[3-7,9,10,14] Fludrocortisone and beta blockers have been widely used, but controlled studies[15,16] with beta blockers have found no evidence that they are superior to placebo; beta blockers may also lead to an increase in adverse effects and should generally be avoided.[5,9] There is some evidence of benefit with vasoconstrictors such as midodrine,[17,18] an alpha agonist, and this may have a role in some patients.[4-6,10] Disopyramide has also been used, but is not considered first-line.[9] SSRIs have been effective in some cases.[6-8] Antimuscarinics, such as propantheline bromide, have also been tried.[7,9]

One contentious issue has been whether general and non-specific symptoms of ill health such as mental and physical fatigue, depression, and anxiety could be attributed to a chronically low blood pressure (for example, a systolic pressure below 110 mmHg or diastolic pressure below 60 mmHg).[19] In the UK and the USA such an association has not generally been accepted whereas in some European countries (e.g. Germany) a wide range of preparations, usually containing a sympathomimetic, has been available for treatment. There is some evidence that depression[20-22] and reduced general well-being[23] are associated with low blood pressure, and there may also be a link with cognitive impairment.[24] Studies have also suggested an association between chronic fatigue syndrome and either neurally-mediated[25,26] or orthostatic[27] hypotension. However, any implications for treatment are far from clear.

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Kawasaki disease

Cardiac effects including coronary artery abnormalities are the major complications of Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood. Normal immunoglobulin and aspirin are used in its initial management, and antiplatelet therapy, usually with aspirin, may be continued long term to prevent coronary thrombosis, particularly if there are coronary abnormalities. Further details concerning the overall management of Kawasaki disease are provided under Normal Immunoglobulins, p. 2405.2.

Patent ductus arteriosus

The ductus arteriosus is a vascular channel present in the fetal circulation that connects the pulmonary artery and the descending aorta. In some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. Details of its management, including the use of diuretics in infants with signs of heart failure, are given on p. 72.2.

Phaeochromocytoma

Phaeochromocytoma[1-9] is a rare catecholamine-secreting tumour of the adrenal medulla. Patients with phaeochromocytoma are usually hypertensive and suffer headache, palpitations, and excessive sweating; the hypertension may be either episodic or sustained. However, if the tumour is mainly adrenaline-secreting, tachyarrhythmias may be associated with a normal or even decreased arterial pressure and if the tumour secretes mainly noradrenaline, vasoconstriction may lead to contraction of the venous pool and hypovolaemia. If the effects of the release of catecholamines are not controlled a life-threatening crisis ultimately ensues and may range from a shock-like syndrome with multiple organ failure to hypertensive crisis, depending on the predominance of the catecholamine secreted.

For a diagnosis of phaeochromocytoma, history and clinical symptoms are important, but a firm diagnosis requires further investigative techniques.[1-3,6,8,9] Although measurement of urinary or plasma concentrations of adrenaline and noradrenaline has been used, concentrations of their metabolites, metanephrine and normetanephrine, provide a more accurate diagnosis and measurement of these is now preferred. Additional tests such as the clonidine suppression test (p. 1340.2) or the glucagon stimulation test (p. 1554.2) are used infrequently.[8] Imaging procedures such as computed tomography, magnetic resonance imaging, scintigraphy with ^{123}I- or ^{131}I-iobenguane (*m*-iodobenzylguanidine; MIBG), or positron emission tomography, are used to locate the tumour before surgery.

Surgical removal of the tumour is the mainstay of treatment but must be preceded by pharmacological therapy to block the pressor and other effects of the excess catecholamines.[1-4,6-9] This is important for symptom control, but is also necessary in asymptomatic patients undergoing surgery since massive release of catecholamines may occur during induction of anaesthesia or when the tumour is handled. Choice of therapy is not entirely clear since there is a lack of evidence from controlled studies. Alpha blockers, given orally, are widely used, and have the advantage of both reducing blood pressure and allowing plasma volume to return to normal. Phenoxybenzamine is usually the drug of choice; it produces a long-acting, non-competitive alpha blockade that cannot be overridden by surges of catecholamine release, as may happen with competitive blockers. Selective alpha$_1$-adrenoceptor blockers such as prazosin, which causes less tachycardia, may be an alternative in some patients, particularly if the tumour secretes mainly adrenaline. Prazosin may also be preferable to phenoxybenzamine pre-operatively since its effects are more rapidly reversed, reducing the risk of postoperative hypotension. However, hypotension may be a problem, particularly at the start of treatment, and alpha blockers should therefore be started in a low dose, increased gradually until all signs of pressor activity are suppressed. Calcium-channel blockers may be used if alpha blockers are not tolerated, and may also be given with alpha blockers to enable lower doses to be used. They may be more suitable than alpha blockers in patients who are normotensive. Angiotensin receptor blockers have also been used. Beta blockers may be given for tachycardia, but must be used cautiously and must not be started until adequate alpha blockade has been established. A beta$_1$-selective blocker is preferred so that peripheral beta$_2$-mediated vasodilatation is unaffected. α-Methyltyrosine, which suppresses catecholamine synthesis, may have a role in some patients, such as those resistant to alpha blockade or those in whom the effects of alpha or beta blockade may be undesirable. In some centres it is given routinely pre-operatively to suppress catecholamine synthesis and reduce the amount released during surgery.[7]

Control of blood pressure during and after surgery is critical. Patients should be given intravenous fluids to optimise blood volume pre-operatively, and drugs used for premedication and anaesthesia should be chosen so as to avoid those which may cause pressor responses or tachycardia[4] and ideally should suppress the adrenergic response to surgical stimuli. Acute increases in blood pressure may still occur when the tumour is handled and potent vasodilators such as sodium nitroprusside[1,3,4,8,9] or glyceryl trinitrate[4,8] have been given intravenously to prevent dangerously high arterial pressures; the alpha blocker phentolamine has also been advocated[3,4,8] although tachycardia is invariably a problem. The short-acting cardioselective beta blocker esmolol may be used to control tachycardia during surgery.[3,4,8]

In patients who are unsuitable for surgery, or in those who have malignant phaeochromocytoma[5] or in whom not all of the tumour can be removed, therapy with alpha and beta blockers or other antihypertensives may be continued long-term. α-Methyltyrosine may be used as an alternative. In malignant phaeochromocytoma, ^{131}I-iobenguane, given in high doses sufficient to cause radionecrosis, has produced remission for limited periods. Alternatively, some benefit has been reported with antineoplastic therapy, although its role is not established; a regimen of cyclophosphamide, vincristine, and dacarbazine has been most widely used.

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Pulmonary hypertension

In pulmonary hypertension an increase in pulmonary vascular resistance leads to an increase in pulmonary arterial pressure. Mean pulmonary artery pressure in a resting individual at sea level is normally about 15 mmHg and pulmonary hypertension is usually defined as a pressure above 25 mmHg at rest; a pressure above 30 mmHg during exercise has also been considered diagnostic, although the relevance of this is less clear.[1] Pressures will be correspondingly higher at higher altitudes.

Pulmonary hypertension has been classified in several ways and the terminology used has changed as the underlying pathophysiology has become clearer. Previously, pulmonary hypertension was classified as primary or secondary, depending on the presence or absence of an underlying cause, but guidelines[1-4] no longer recommend these terms since they have little meaning in relation to pathophysiology or treatment. Pulmonary arterial hypertension is now the preferred term where the increased pressure is due to a disorder of the pulmonary arteries (precapillary); this may occur in isolation (idiopathic and familial forms; previously classified as primary pulmonary hypertension), or secondary to disorders such as connective tissue disease, congenital heart defects, portal hypertension, HIV infection, drugs and toxins, and pulmonary venous or capillary disease. Management is similar for all forms of pulmonary arterial hypertension and is the main focus of the following discussion. Pulmonary hypertension that is not due to pulmonary arterial dysfunction generally occurs in association with established cardiopulmonary disorders and is also discussed briefly below.

Pulmonary arterial hypertension[5-10] is a progressive disease with a high mortality rate, and patients appear to be prone to sudden death. Idiopathic pulmonary arterial hypertension occurs in patients of all ages and in both sexes but women in the fourth decade of life are those typically seen; it is also relatively common in children.[11,12] A functional classification system similar to the New York Heart Association grades used for heart failure (see p. 1262.3) may be used to indicate severity.[1-3] Initial complaints include dyspnoea on exertion, fatigue, and chest discomfort or pain. In advanced disease, cor pulmonale (an enlargement of the right ventricle due to either dilatation, hypertrophy, or both) occurs and may progress to right-sided heart failure; thromboembolic disease affecting the pulmonary arteries is also common.

Management of pulmonary arterial hypertension has generally been symptomatic, including use of drugs that decrease pulmonary arterial pressure, preferably with an increase in cardiac output. However, the observation that some therapies also improve survival[13,14] and reduce the need for transplantation, along with the development of therapies specifically targeted against the pathophysiological mechanisms underlying the disease, has widened the aims of treatment. Although most studies have been in patients with idiopathic disease, there is some evidence that patients with other forms of pulmonary arterial hypertension respond similarly, and guidelines for treatment are broadly the same.[1,3,4,15] Similar approaches are also used in children.[1,3,4,11,12]

General ***treatment*** for pulmonary arterial hypertension[1,3,4,15] includes measures to prevent hypoxia, since this causes pulmonary vasoconstriction, and treatment of associated right-sided heart failure. Oxygen therapy may be needed in some patients, and anaemia should be avoided. Pneumococcal and influenza vaccines are recommended to reduce the risk of pulmonary infections. *Diuretics* produce symptomatic benefit in patients with fluid retention, and should be given as appropriate. *Digoxin* has been used, although its role is less clearly established unless patients also have atrial fibrillation. *Oral anticoagulation* has been advised for most patients to reduce the risk of both thromboembolism in the pulmonary arteries and venous thromboembolism, but caution is required in those with an increased bleeding risk. Supraventricular arrhythmias have been associated with clinical deterioration and prophylactic *antiarrhythmics* may be considered.[1] Avoidance of pregnancy is also generally recommended,[3,4,16] although successful management is possible.[17]

Specific therapy has generally been based on the use of vasodilators. Vasoconstriction is believed to play an important role in the pathophysiology of pulmonary arterial hypertension, and many of the vasodilators used in systemic hypertension have therefore been tried.[13,18] While most reduce pulmonary artery pressure, they also reduce systemic blood pressure,[19] producing undesirable and sometimes intolerable adverse effects, and this limits their use. Non-specific vasodilators with an established role in pulmonary arterial hypertension include calcium-channel blockers and prostacyclin analogues. Endothelin receptor antagonists and phosphodiesterase inhibitors, which are more selective pulmonary vasodilators and may also have additional effects, are now increasingly used as alternatives or for combination therapy.

Calcium-channel blockers improve pulmonary haemodynamics, and there is some evidence of a survival benefit; an observational study[20] over a 5-year period found that survival was improved in patients given high doses. However, only a small proportion of patients respond,[21] and adverse effects may be a concern. Guidelines[1,3,4,15] therefore recommend that an acute response test should be performed in all patients before starting long-term treatment. Although oral calcium-channel blockers have been used for testing, this has been associated with severe adverse effects and it is now recommended that only short-acting vasodilators such as intravenous epoprostenol, intravenous adenosine, or inhaled nitric oxide, should be used. Those who respond may then be started on oral calcium-channel blockers, with the choice usually being a dihydropyridine (nifedipine or amlodipine) in patients with relative bradycardia, and diltiazem in those with relative tachycardia. The marked negative inotropic effects of verapamil should be avoided. The dose should be increased gradually, as tolerated, and long-term therapy should only be continued in patients with a sustained response.

Prostacyclin is a potent endogenous vasodilator and there is evidence that it may be deficient in patients with pulmonary arterial hypertension. Epoprostenol, a synthetic form of prostacyclin, was originally used in patients with end-stage pulmonary hypertension to sustain them long enough to have a heart-lung transplant. However, some studies have suggested that long-term therapy with epoprostenol may also have a role as an alternative to transplantation. Sustained clinical improvement and improved survival have been reported[22,23] in some patients given long-term intravenous therapy using portable infusion pumps, and guidelines[1,3,4,15] now recommend that epoprostenol may be used in patients with pulmonary arterial hypertension who do not respond to calcium-channel blockers and who are in functional class III or class IV. Use is limited by stability problems; more stable analogues such as continuous intravenous iloprost[24] or intravenous treprostinil[25] are also effective and may be used as an alternative.[1,4,15] Treprostinil can also be given by continuous subcutaneous infusion[26,27] although severe pain at the infusion site may be a problem. It may be useful in patients for whom intravenous treatment is not suitable;[15] small studies[28,29] have reported the safe transfer of patients from epoprostenol to treprostinil therapy. Prostaglandin analogues have also been given by inhalation. Epoprostenol has been used, but iloprost, which has a longer action, is generally preferred;[15,30] treprostinil may also be used.[31,32] Another analogue, beraprost sodium, has been given orally,[33-35] but is not widely available. Although thought to act mainly as vasodilators, epoprostenol and its analogues also affect vascular remodelling and platelet aggregation and this may contribute to their beneficial effects.

Endothelin receptor antagonists act as vasodilators by blocking the effects of endothelin-1, a potent endogenous vasoconstrictor that appears to be overproduced in pulmonary arterial hypertension and which also stimulates vascular remodelling and has pro-inflammatory effects. Oral endothelin receptor antagonists such as bosentan, and the selective endothelin ET_A receptor antagonist ambrisentan are now widely used as first-line therapy in patients with functional class II or III pulmonary arterial hypertension.[1,3,4,15] They have positive effects on haemodynamics and symptoms,[36] and there is some evidence that bosentan improves survival,[37] although this is not established.[36] In

class III patients, outcomes appear to be comparable with first-line use of either bosentan or prostacyclin analogues,[38] and observational studies[16,39] have suggested that some patients started on prostacyclin analogues can be safely transferred to bosentan. However, in unstable functional class IV patients, epoprostenol is usually preferred.[1,3,4,15]

Phosphodiesterase type-5 inhibitors are pulmonary vasodilators and may also have antiproliferative effects.[40] Randomised studies with sildenafil[41,42] and tadalafil[43] have shown them to be of benefit in pulmonary arterial hypertension, and positive effects were also reported with vardenafil in an open-label study.[44] Both sildenafil[1,3,4] and tadalafil[1] have therefore been recommended as first- or second-line therapy in functional class II or III. Like the endothelin receptor antagonists, they have the benefit of oral dosing.

The *guanylate cyclase stimulator*, riociguat, acts on nitric oxide receptors to produce vasodilatation. It represents a new class of drugs used for the treatment of pulmonary arterial hypertension and persistent or recurrent chronic thromboembolic pulmonary hypertension, either after surgical treatment or in inoperable cases.

Combination therapy is increasingly used in patients who fail to respond to monotherapy, or who deteriorate. There is limited evidence to support the safety or efficacy of most combinations,[1,3,6,15] and further studies are needed to confirm their role. However, in functional class IV patients, initial therapy with a combination of drugs may be considered.[1] Alternative treatments that have shown some benefit include imatinib, a platelet-derived growth factor antagonist, but evidence is limited to case reports[45-47] and controlled studies are again needed. Surgical intervention, and ultimately lung or heart-lung transplantation may be needed in patients who do not respond to vasodilator therapy.[1,3,4]

Pulmonary hypertension associated with an established cardiopulmonary disorder is much more common than idiopathic pulmonary arterial hypertension and the clinical manifestations are dominated by those of the underlying condition. Chronic obstructive pulmonary disease is the commonest respiratory cause, but it may also occur in patients with respiratory distress syndromes, sarcoidosis, idiopathic pulmonary fibrosis, or chronic exposure to high altitude. Pulmonary arterial pressure may also be raised in chronic thromboembolic disease, and in patients with impaired left ventricular function, for example associated with myocardial infarction or mitral valve disease. Management generally involves appropriate treatment of the underlying disorder. Inhaled nitric oxide has been used in patients with acute pulmonary hypertension after cardiac surgery or associated with respiratory distress syndrome.[48] There have also been reports[49] of long-term use in patients with chronic lung disease. Standard therapies for pulmonary arterial hypertension may have a role in patients with inoperable chronic thromboembolic disease,[1,4,50] but are not generally recommended in other disorders.[51]

Persistent pulmonary hypertension of the newborn, sometimes also termed persistent fetal circulation, is a form of pulmonary arterial hypertension specifically affecting neonates. It can be primary in nature (that is, idiopathic, affecting infants with an anatomically normal heart and no pulmonary disease) or secondary, being associated with a number of cardiopulmonary conditions including congenital heart disease, diaphragmatic hernia, meconium aspiration, respiratory distress syndrome, or sepsis. The pulmonary hypertension and altered vasoreactivity lead to a right-to-left shunting of blood across the patent ductus arteriosus or foramen ovale and this often results in critical hypoxaemia.

Management generally involves high-frequency oscillatory ventilation (to achieve optimal lung inflation) and, if necessary, extracorporeal membrane oxygenation. Treatment to reduce pulmonary vascular resistance may also be tried. Mechanical hyperventilation has been used to induce alkalosis, since this reduces pulmonary vasoconstriction; intravenous sodium bicarbonate may be an alternative.[52] Inhaled *nitric oxide* which is a potent, selective pulmonary vasodilator, is also widely used.[53] Studies[54-58] have shown that it can cause marked improvement in oxygenation and a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been found. Early concerns that the use of nitric oxide might adversely affect neurodevelopmental outcomes have not been confirmed on long-term follow-up,[59-61] but there is also no evidence of a long-term benefit,[61] although an observational study[62] found a reduced incidence of cerebral palsy in premature infants given nitric oxide. Use of inhaled nitric oxide in combination with high-frequency oscillatory ventilation may have additional benefits.[63]

Nitric oxide is not effective in all patients and alternatives may be required.[64,65] Intravenous *epoprostenol* is used and it has also been given by inhalation,[66,67] which may reduce systemic effects. Intravenous vasodilators have also been used, although, as discussed above, this is generally limited by their systemic effects. *Tolazoline* may be given intravenously or by the endotracheal route. *Phosphodiesterase inhibitors* may have a role; dipyridamole has been used, and there have been reports[68,69] of benefit with sildenafil, including when used long-term.[70] Intravenous sildenafil has also been used.[71] Other vasodilators that have been tried include intravenous *adenosine*,[72,73] intravenous *magnesium sulfate*,[74-76] and inhaled *sodium nitroprusside*,[77] but none of these has an established role.

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Shock

Shock is a complex clinical syndrome in which there is a failure of the circulatory system to maintain cellular

perfusion and function. There are many aetiologies, but the underlying defect is either inadequate venous return to the heart due to an absolute or relative reduction in plasma volume, or failure of the pumping action of the heart. A traditional approach has been to place the cause of shock into one of several basic groups:

- *Hypovolaemic shock* results from fluid loss; cardiac output is reduced due to inadequate filling pressure. Haemorrhagic causes include severe gastrointestinal bleeding and traumatic injury, while non-haemorrhagic causes include severe vomiting and diarrhoea, polyuria, and burns. Hypovolaemia can also be present in other forms of shock; in septic or anaphylactic shock fluid loss from the vasculature may occur due to capillary leakage, while peripheral vasodilatation may lead to relative hypovolaemia
- *Cardiogenic shock* usually results from acute cardiac dysfunction or failure, leading to an inadequate stroke volume and reduced cardiac output. It has several causes, but is most often associated with acute myocardial infarction. Other cardiac causes include valvular heart disease, cardiomyopathies, and severe cardiac arrhythmias; episodes of acute heart failure may also occur due to decompensation in patients with chronic heart failure. Shock due to circulatory disorders such as massive pulmonary embolism is also sometimes classified as cardiogenic. Other forms of shock may also have a cardiac component
- *Septic shock* occurs as a complication of infectious disease and is described and defined in more detail under Septicaemia, p. 203.2. Hypotension occurs mainly due to peripheral vasodilatation, but fluid loss and direct effects on the heart may also be involved. Cardiac output may be reduced due to hypovolaemia; however, if circulatory volume is adequate, cardiac output is often high
- *Anaphylactic shock* (p. 1293.2) is the result of a hypersensitivity reaction and is similar haemodynamically to septic shock

In the early stages of shock, compensatory mechanisms are usually sufficient to maintain the blood pressure, but these generally become inadequate and patients in decompensated shock classically present with hypotension, tachycardia, and tachypnoea. The skin is often cold, clammy, and cyanotic, due to compensatory peripheral vasoconstriction, while impaired organ perfusion results in dulled mental alertness, which may progress to stupor or coma; oliguria or anuria, due to impaired renal perfusion, are also frequent. Pulmonary oedema may occur as a result of impaired cardiac output in cardiogenic shock. Complications of shock include disseminated intravascular coagulation due to platelet sludging and microvascular insufficiency, acute respiratory distress syndrome (previously termed 'shock lung') (p. 1599.3), and acute renal failure. The terms multiple organ failure syndrome (MOFS) and multiple organ dysfunction syndrome (MODS) are applied to the consequences of shock where several organs or body systems have become hypoperfused and are unable to maintain their normal function.

Management. The initial aim of treatment in all forms of shock is to restore tissue perfusion by correcting hypovolaemia and hypotension and restoring cardiac output.[1-6] Hypoxaemia should be avoided and supplemental oxygen or mechanical ventilation may be required. Intravenous opioid analgesics may be needed for pain, and an adequate diuresis should be maintained in order to prevent renal failure. Diuretics may also be required if there is pulmonary oedema; mechanical fluid removal by ultrafiltration may be an alternative, particularly in patients with renal impairment.[6,7] Impaired tissue perfusion often leads to lactic acidosis, but the need for specific treatment (see Metabolic Acidosis, p. 1777.2) is unclear; sodium bicarbonate may be given for severe acidosis,[1] although some[4] consider that it should not be used. Other electrolyte abnormalities should be corrected as appropriate.

Hypovolaemia. Restoration of the circulating volume is essential, both to replace lost fluids in hypovolaemia and to maintain cardiac filling pressure in other forms of shock; small volumes may be beneficial in cardiogenic shock, but should be given cautiously to prevent pulmonary oedema. Replacement fluids available include blood products and crystalloid or colloid plasma expanders,[8-10] and the choice depends on the clinical situation. Blood products are expensive and not always available, while the relative merits of crystalloids and colloids continue to be debated.

In haemorrhage, volume expansion to maintain organ perfusion is initially the most important consideration,[11] although in trauma patients the optimum timing and quantity of fluid to give is not clear.[9,10,12] Anaemia is generally better tolerated than hypovolaemia, but where blood loss is extensive (usually considered as 40% or more of the total blood volume), red cell replacement is also required.[11,13] This usually takes the form of packed red cells with plasma expanders, and other plasma components as required. Blood substitutes are also under investigation as an alternative to red cell products, but none yet has an established role.[9,10]

In non-haemorrhagic hypovolaemia, plasma expanders alone are used. Crystalloids (solutions containing solutes such as glucose or sodium chloride that can pass a semipermeable membrane) rapidly expand both the intravascular and extravascular compartments, which could be beneficial since both become depleted in hypovolaemia. However, large volumes may be required and the duration of effect is short as fluid is rapidly redistributed. Hypertonic crystalloid solutions may allow smaller volumes to be used. Colloids (solutions containing large molecules such as albumin, dextrans, gelatins, and etherified starches, which do not pass semipermeable membranes) expand the intravascular space more effectively; they have a longer duration of effect and smaller volumes are required. This may be beneficial since it causes less haemodilution, but the exact significance of this has been questioned; the risk of hypersensitivity reactions, including anaphylaxis, may also be a concern.

Studies comparing the use of crystalloids and colloids in hypovolaemia have generally been of poor quality and the results are difficult to interpret. A systematic review[14] of studies in critically ill patients concluded that there was a small increase in mortality associated with the use of colloids, and that since they were more expensive and of no proven benefit they should not be routinely used. A further review,[15] looking specifically at the use of albumin, also suggested an increased mortality with use of the colloid. Both reviews were severely criticised,[16-18] and the relative benefits of the different types of fluid continue to be debated. A large study[19] comparing the use of albumin and sodium chloride 0.9% in intensive care patients who required fluid resuscitation found no difference in mortality at 28 days. Updates to both reviews[20,21] to include this study found that there was no evidence of any benefit for colloids compared with crystalloids, and the authors continued to state that colloids should not be routinely used. However, there was no clear difference in mortality between patients given colloids or crystalloids, other than a suggestion[21] that albumin might increase mortality in patients with burns or hypoproteinaemia. In practice, a mixture of colloids and crystalloids tends to be given. Choice of the best crystalloid or colloid to give remains unclear; systematic reviews have found no evidence that one colloid is better than another,[22] or that hypertonic solutions are better than isotonic solutions if crystalloids are used.[23]

Hypotension and low cardiac output. Although correction of hypovolaemia may be sufficient to restore blood pressure, hypotension in shock may be profound (sometimes a systolic pressure of less than 70 mmHg) despite fluid replacement, and additional therapy with inotropes and vasopressors is often needed to improve cardiac output and reverse signs of impaired organ function.[1,4] Sympathomimetics are often used since they may have effects on the heart and the vasculature, but alternative vasoconstrictors and inotropes may also have a role.[24] Choice depends on individual patient characteristics and the type of shock, although this is generally based on theoretical considerations. A systematic review[25] of the use of vasopressors in shock found insufficient evidence to make any recommendations, while a study[26] comparing dopamine with noradrenaline as the first-line vasopressor found no significant difference in outcome, although dopamine was associated with more adverse effects.

In cardiogenic or hypovolaemic shock cardiac output is usually low but peripheral resistance is high and drugs that have mainly inotropic effects, such as dobutamine or dopamine, are often chosen. Dobutamine causes some peripheral vasodilatation and is useful where hypotension is not significant; dopamine similarly causes peripheral vasodilatation at low doses but at higher doses vasoconstriction occurs. Low-dose dopamine has been widely used as an adjunct to other inotropes since it was thought that the vasodilatation would lead to renal protection, but clinical benefit has not been established and such use is no longer recommended (see Surgery and Intensive Care, p. 1367.3). Phosphodiesterase inhibitors such as amrinone and milrinone can also be considered in low cardiac output states; they have positive inotropic activity and produce peripheral vasodilatation, and may be particularly useful in patients with decompensated chronic heart failure who have been taking beta blockers.[2,4,6] Levosimendan, a calcium sensitiser with inotropic and vasodilator properties, is another alternative and is also suitable for patients taking beta blockers.[6] Vasodilators such as intravenous glyceryl trinitrate or sodium nitroprusside may also be beneficial for patients in shock with a low cardiac output but adequate blood pressure, as well as in patients with pulmonary oedema.[1,2,6,7] They act by reducing cardiac afterload but must be used with care as there is a risk of precipitating hypotension. Mechanical circulatory support with an intra-aortic balloon pump or ventricular assist device may be required in some patients.[6,7]

Where cardiac output is high but peripheral resistance is low, for example in septic shock, vasoconstrictors such as noradrenaline or dopamine are usually preferred;[1,5] they may be given with more potent inotropes such as dobutamine or adrenaline. Adrenaline has also been given alone although renal artery vasoconstriction may limit its use; it has also been reported to cause lactic acidosis,[27] but a study[28] comparing noradrenaline plus dobutamine with adrenaline alone found no difference in outcomes in patients with septic shock. Vasopressin may be an alternative,[5,29,30] particularly in patients with vasodilatation that is resistant to sympathomimetics, but is not recommended for routine use. It may also be used as an adjunct to sympathomimetics, although no clear benefit has been shown compared with sympathomimetics alone.[31]

The opioid antagonist naloxone may also improve blood pressure in shock,[32] but its role is not established.

Specific therapies are indicated in some types of shock. In cardiogenic shock associated with ***myocardial infarction***,[2,7,33] specific therapy to restore myocardial perfusion is also required (see p. 1257.1).

In ***septic shock*** appropriate antibacterial therapy should be given as outlined under Septicaemia on p. 203.2. Methods of inhibiting endogenous mediators released in response to sepsis that are thought to be responsible for the haemodynamic effects are also under investigation but clinical benefits have not yet been shown.[3,34] Improved outcomes have been reported[35,36] with the use of low-dose corticosteroids. In severe sepsis recombinant activated protein C has been used,[5] but a systematic review[37] found no evidence to support a beneficial effect.

Adrenaline is the cornerstone of management in ***anaphylactic shock*** (see p. 1293.2).

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Abciximab *(BAN, USAN, rINN)*

7E3; Abciximabum; Absiksimab; Absiksimabi; Absiximab; c7E3; c7E3 Fab; Абциксимаб.

Immunoglobulin G (human-mouse monoclonal c7E3 clone p7E3V_HhC_γ4 Fab fragment anti-human platelet glycoprotein IIb/IIIa complex), disulphide with human-mouse monoclonal c7E3 clone p7E3V_κhC_κ light chain.

$C_{2101}H_{3229}N_{551}O_{673}S_{15}$=47456.0

CAS — 143653-53-6.

ATC — B01AC13.

ATC Vet — QB01AC13.

UNII — X85G7936GV.

Uses and Administration

Abciximab is the Fab fragment of the chimeric monoclonal antibody 7E3. It binds to the glycoprotein IIb/IIIa receptor on the surface of platelets. This prevents binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the receptor sites and inhibits platelet aggregation. It is used as an adjunct to heparin and aspirin therapy for the prevention of acute ischaemic complications in patients undergoing percutaneous coronary interventions such as angioplasty, atherectomy, and stenting. It is also used in patients with unstable angina who are candidates for such procedures. It has been investigated in acute ischaemic stroke, although results have been disappointing; it has also been tried in peripheral arterial occlusion.

Abciximab is given intravenously as a bolus injection over 1 minute in a dose of 250 micrograms/kg followed immediately by an infusion of 0.125 micrograms/kg per minute (to a maximum dose of 10 micrograms/minute). For stabilisation in patients with unstable angina the bolus dose followed by the infusion should be started up to 24 hours before the possible intervention and continued for 12 hours after; for other patients the bolus should be given 10 to 60 minutes before the intervention followed by the infusion for 12 hours.

General references.

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Administration. For reference to use of the **intracoronary** route for abciximab see Ischaemic Heart Disease, below.

Ischaemic heart disease. Antiplatelet drugs have an established role as adjuncts to medical or interventional treatment in patients with ischaemic heart disease (stable angina, unstable angina, or myocardial infarction) and abciximab has been used to provide additional antiplatelet effects during interventional procedures and in patients with acute coronary syndromes.

In patients undergoing acute or elective *percutaneous coronary intervention* (PCI; see Reperfusion and Revascularisation Procedures, p. 1259.2), use of abciximab as an adjunct to heparin and aspirin improves short-term[1-3] and long-term[4,5] outcomes in various groups of patients, including those receiving coronary stents.[6-8] Most benefit has been seen in patients given abciximab as a bolus injection immediately before intervention followed by intravenous infusion for 12 hours,[1,2] and in a study[9] in which abciximab was given for 18 to 24 hours before angioplasty and for 1 hour after, the initial benefit was not maintained at 6 months.

For patients undergoing PCI who are pretreated with both aspirin and clopidogrel, the role of abciximab is less clear. In stable patients undergoing elective PCI, no benefit was found at 30 days,[10] or at 1 year.[11] A study[12] in diabetic patients also found no effect on mortality or risk of myocardial infarction at 1 year, despite their higher risk, although restenosis was reduced. However, in patients undergoing PCI for *non-ST elevation acute coronary syndromes* (see Angina Pectoris, p. 1254.3), use of abciximab in addition to aspirin and clopidogrel pretreatment improved clinical outcomes at 30 days and at 1 year,[13] although the effect at 30 days was restricted to patients with raised troponins.[14] Positive results have also been reported[15,16] with abciximab given as a single bolus injection without subsequent infusion in patients undergoing coronary stenting.

In *acute ST-elevation myocardial infarction* (p. 1257.1), abciximab has been used as an adjunct to primary PCI, and has been shown to reduce re-infarction rates and mortality,[17] including specifically in patients receiving coronary stents,[18] with benefit persisting long-term.[19] The optimum timing and dosage regimen have not yet been established. Abciximab started as soon as possible after diagnosis rather than immediately before the procedure has shown benefit in some studies,[20,21] but not others,[22] and no advantage has been seen with use of both abciximab and a thrombolytic before the procedure.[22] In patients treated with thrombolytics instead of primary PCI, use of adjunctive abciximab has shown some benefit,[23] but this appears to be offset by an increased bleeding rate, even when reduced doses of thrombolytics are used.[24,25] In patients with *unstable angina* (p. 1254.3) receiving noninterventional treatment, a large study[26] with abciximab failed to show any benefit over placebo, although other glycoprotein IIb/IIIa inhibitors have a role in such patients.

Some promising results have been reported with *intracoronary* abciximab in patients with acute coronary syndromes,[27] and with abciximab-coated stents in patients with acute myocardial infarction.[28] A meta-analysis[27] of studies involving 2301 patients with acute coronary syndromes concluded that intracoronary abciximab was associated with reduced mortality and a trend towards fewer major adverse cardiac events; this was most marked in patients with acute ST-segment elevation myocardial infarction and on short-term (1 month) rather than longer term follow-up. However, some studies[29] have not reported additional benefit from use of the intracoronary route, and further studies are ongoing.[30-32]

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Adverse Effects

Bleeding during the first 36 hours after a dose is the most common adverse effect of abciximab. Other adverse effects include hypotension, nausea and vomiting, back pain, chest pain, headache, haematoma, bradycardia, fever, cardiac tamponade, and thrombocytopenia. Hypersensitivity reactions (see Precautions, p. 1282.1) have occurred on repeated use.

Effects on the blood. In clinical studies increased bleeding has been the most common adverse effect of abciximab, and this has also been reported[1] during clinical use. Thrombocytopenia is also a well documented adverse effect of abciximab therapy. In a review[2] of the major clinical studies of abciximab, mild thrombocytopenia was reported in 4.2% of patients and severe thrombocytopenia in 1.0%; patients also received heparin. There have also been case reports of patients developing severe thrombocytopenia.[3,4] It is recommended that platelet counts should be monitored before and 2 hours after starting abciximab, and that the drug should be withdrawn if thrombocytopenia occurs.[3] However, pseudothrombocytopenia also occurs in some patients and should be excluded before withdrawing therapy.[5,6] Although there have been case reports, the incidence of thrombocytopenia does not appear to be increased with other glycoprotein IIb/IIIa receptor inhibitors,[2] and there have been reports of the successful use of eptifibatide[7] and tirofiban[8] in patients who developed thrombocytopenia with abciximab.

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Precautions

Abciximab should not be given to patients who are actively bleeding or to patients at increased risk of haemorrhage. Such patients include: those with haemorrhagic disorders, including thrombocytopenia; those with cerebrovascular disorders, including intracerebral neoplasms, aneurysms, or arteriovenous malformation, and those with a history of stroke; those with uncontrolled hypertension; or those who have recently undergone major surgery or severe trauma. Other patients in whom caution is required include those with severe renal impairment, vasculitis, haemorrhagic retinopathy, acute pericarditis, or aortic dissection. Abciximab should be stopped if serious uncontrolled bleeding occurs or emergency surgery is required. Abciximab should not be given to patients with severe renal impairment requiring haemodialysis, or to those with severe hepatic impairment, in whom coagulation may be affected. Platelet counts should be monitored before and after giving abciximab.

Antibodies may develop 2 to 4 weeks after a dose of abciximab and hypersensitivity reactions could occur when other monoclonal antibodies are used or after readministration of abciximab (see below). Hypersensitivity reactions have not been noted after a single dose but the possibility should be considered.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies abciximab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Readministration. Antibodies to abciximab develop in about 5.8% of patients after use and could lead to hypersensitivity reactions or to reduced efficacy if use of abciximab is repeated. In a retrospective study[1] in 164 patients given a second course of therapy with abciximab, efficacy was not affected and no allergic or anaphylactic reactions occurred. However, severe thrombocytopenia was noted in 4% of patients, and the incidence was highest in those receiving abciximab within 2 weeks of the first course. Similar results were reported from a larger registry study;[2] the patients included had received abciximab at least 7 days previously without developing thrombocytopenia, suggesting that platelet counts need to be monitored in patients receiving a first or repeated course of abciximab.

1. Madan M, *et al.* Efficacy of abciximab readministration in coronary intervention. *Am J Cardiol* 2000; **85:** 435–40.
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Interactions

There may be an increased risk of bleeding if abciximab is given with other drugs that affect bleeding, including anticoagulants, other antiplatelet drugs, or thrombolytics.

Pharmacokinetics

After intravenous doses of abciximab free plasma concentrations fall rapidly due to binding to platelet receptors. Platelet function recovers over about 48 hours although abciximab may remain in the circulation for 15 days or more in a platelet-bound state.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: ReoPro; ***Austral.***: ReoPro; ***Austria***: ReoPro; ***Belg.***: ReoPro; ***Braz.***: ReoPro; ***Canad.***: ReoPro; ***Chile***: ReoPro; ***Cz.***: ReoPro; ***Denm.***: ReoPro; ***Fin.***: ReoPro; ***Fr.***: ReoPro; ***Ger.***: ReoPro; ***Gr.***: ReoPro; ***Hong Kong***: ReoPro; ***India***: ReoPro; ***Irl.***: ReoPro; ***Israel***: ReoPro; ***Ital.***: ReoPro; ***Malaysia***: ReoPro; ***Mex.***: ReoPro; ***Neth.***: ReoPro; ***Norw.***: ReoPro; ***NZ***: ReoPro; ***Pol.***: ReoPro; ***Port.***: ReoPro; ***Rus.***: ReoPro (Реопро); ***S.Afr.***: ReoPro; ***Singapore***: ReoPro; ***Spain***: ReoPro; ***Swed.***: ReoPro; ***Switz.***: ReoPro; ***Thai.***: Clotinab; ReoPro; ***UK***: ReoPro; ***USA***: ReoPro.

Acadesine *(BAN, USAN, rINN)*

Acadesina; Acadésine; Acadesinum; AICA Riboside; GP-1-110-0; GP-1-110; Акадезин.

5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide.

$C_9H_{14}N_4O_5$=258.2

CAS — 2627-69-2.

ATC — C01EB13.

ATC Vet — QC01EB13.

UNII — 531EF47846.

Profile

Acadesine is a purine nucleoside analogue reported to have cardioprotective effects. It is being investigated in the management of myocardial ischaemia, particularly in patients undergoing coronary artery bypass graft surgery. Acadesine may protect against further ischaemia by influencing metabolism in ischaemic cells, enhancing the release of adenosine in preference to inosine after the breakdown of adenosine monophosphate.

Acadesine is also under investigation for chronic lymphocytic leukaemia.

References.

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ACE Inhibitors

ACE-Hemmer; Angiotensin-converting Enzyme Inhibitors; Inhibidores de la ECA; ИАПФ; Ингибитор АПФ; Ингибитор Ангиотензин-Превращающего Фермента.

There appear to be few significant differences between individual ACE inhibitors. They may be distinguished from each other by the presence or absence of a sulfhydryl group, whether they are prodrugs or not, their route of elimination, and their affinity for angiotensin-converting enzyme in vascular and other tissue, although whether these characteristics modify pharmacodynamics and therefore clinical efficacy is uncertain. Differences in these characteristics do however influence onset and duration of action of ACE inhibitors.

Uses and Administration

ACE inhibitors are antihypertensive drugs that act as vasodilators and reduce peripheral resistance. They inhibit angiotensin-converting enzyme (ACE), which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect. ACE is identical to bradykininase (kininase II) and ACE inhibitors also reduce the degradation of bradykinin, which is a direct vasodilator and is also involved in the generation of prostaglandins. The pharmacological actions of ACE inhibitors are thought to be mainly due to the inhibition of the renin-angiotensin-aldosterone system, but since they also effectively reduce blood pressure in patients with low renin concentrations other mechanisms are probably also involved. ACE inhibitors produce a reduction in both preload and afterload in patients with heart failure. They also reduce left ventricular remodelling, a process that sometimes follows myocardial infarction. Normally, renal blood flow is increased without a change in glomerular filtration rate. ACE inhibitors also reduce proteinuria associated with glomerular kidney disease.

ACE inhibitors are used in the treatment of hypertension and heart failure and are given to improve survival after myocardial infarction and for the prophylaxis of cardiovascular events in patients with certain risk factors. They are also used in the treatment of diabetic nephropathy. They are generally given orally.

In some hypertensive patients there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor and the first dose should preferably be given at bedtime; if possible, any diuretic therapy should be stopped a few days beforehand and resumed later if necessary.

In patients with heart failure taking loop diuretics, severe first-dose hypotension is common on introduction of an ACE inhibitor, but temporary withdrawal of the diuretic may cause rebound pulmonary oedema. Thus treatment should start with a low dose under close medical supervision.

Reviews.

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Action. The renin-angiotensin system plays a major role in regulation of cardiovascular and renal function and blockade of this system has complex physiological effects.[1] Although the main target for ACE inhibitors was initially thought to be the endocrine renin-angiotensin system in the circulation this mechanism alone cannot readily explain all the actions of ACE inhibitors.[2] Endogenous renin-angiotensin systems exist in many tissues and ACE inhibitors also have localised effects.[3] This may underlie some of the long-term effects of ACE inhibition, including improved endothelial function, increased arterial wall compliance, improved left ventricular function in heart failure, regression of vascular and left ventricular hypertrophy, and delayed progression of diabetic nephropathy. ACE inhibitors differ in their degree of binding to tissue ACE and in their tissue distribution, but the clinical significance of this is not clear. In one study[4] endothelial function improved with quinapril, which has high tissue specificity, but a similar effect was not seen with the less-specific enalapril, despite an earlier study[5] showing it to be effective.

ACE inhibitors also have effects on the kinin system and there is some evidence that the cardiovascular actions of ACE inhibitors also involve localised accumulation of kinins.[6-8] It has been suggested[9] that the free radical scavenging property of captopril may contribute to some of its actions, although not all studies have confirmed this effect.[10]

1. Schmieder RE, *et al.* Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; **369:** 1208–19.
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9. Chopra M, *et al.* Captopril: a free radical scavenger. *Br J Clin Pharmacol* 1989; **27:** 396–9.
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Bartter's syndrome. Captopril has been reported to produce beneficial responses in patients with Bartter's syndrome[1-5] (p. 1779.3), which is characterised by hyperaldosteronism, hypokalaemia, and hyperreninaemia, but with normal or reduced blood pressure. Captopril may also be used diagnostically with scintigraphy.[6]

1. Aurell M, Rudin A. Effects of captopril in Bartter's syndrome. *N Engl J Med* 1981; **304:** 1609.
2. Hené RJ, *et al.* Long-term treatment of Bartter's syndrome with captopril. *BMJ* 1982; **285:** 695.
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6. Dondi M, *et al.* Bartter's syndrome: renal scintigraphic appearance after captopril administration. *J Nucl Med* 1996; **37:** 1688–90.

Diabetic complications. Control of blood pressure plays a major role in the prevention of the sequelae of diabetes mellitus (p. 463.3). ACE inhibitors have been reported[1] to reduce the risk of major cardiovascular events in patients, including a broad range of diabetics, with either a history of cardiovascular disease or at least one additional cardiovascular risk factor. A study[2] of diabetics with no cardiovascular disease (but unknown risk factors) also found a reduction in mortality with use of ACE inhibitors. Some of the studies of ACE inhibitors for cardiovascular risk reduction have also suggested that ACE inhibitors may prevent the development of diabetes in non-diabetic patients,[3-7] but a randomised study[8] in subjects with moderately impaired glucose metabolism but low cardiovascular risk was unable to confirm this effect.

ACE inhibitors may also have benefits in other diabetic complications. They have an established role in the management of nephropathy in patients with type 1 and type 2 diabetes (see Kidney Disorders, p. 1284.1).

It has been reported[9,10] that ACE inhibitors may reduce the progression of retinopathy in normotensive patients with type 1 diabetes mellitus.

A preliminary report[11] has also suggested that ACE inhibitors may improve peripheral neuropathy in diabetic patients, but further studies are needed.

1. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355:** 253–9. Correction. *ibid.*; **356:** 860.
2. Eurich DT, *et al*. Reduced mortality associated with the use of ACE inhibitors in patients with type 2 diabetes. *Diabetes Care* 2004; **27:** 1330–4.
3. Yusuf S, *et al*. Ramipril and the development of diabetes. *JAMA* 2001; **286:** 1882–5.
4. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27:** 247–55.
5. Gillespie EL, *et al*. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–6.
6. Abuissa H, *et al*. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46:** 821–6.
7. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66:** 1169–77.
8. Bosch J, *et al*. DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006; **355:** 1551–62.
9. Chaturvedi N, *et al*. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. *Lancet* 1998; **351:** 28–31.
10. Mauer M, *et al*. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; **361:** 40–51.
11. Malik RA, *et al*. Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. *Lancet* 1998; **352:** 1978–81.

Erythrocytosis. Secondary erythrocytosis (secondary polycythaemia) is an absolute increase in red cell mass that may occur as a result of tissue hypoxia (as in chronic obstructive airways disease), or excessive erythropoietin production (as in some renal tumours or after renal transplantation). Treatment may be necessary for hyperviscosity symptoms and to reduce the risk of thromboembolic complications, and mainly involves removal of red blood cells by venesection and the use of drugs such as ACE inhibitors that inhibit erythropoiesis.

Post-transplantation erythrocytosis may resolve spontaneously in some patients but for the remainder the aim of therapy is to minimise the risk of thromboembolic and other complications by reducing the haematocrit to less than 45%. Originally treatment was by venesection but this led to severe iron deficiency. There is now evidence of beneficial effects using ACE inhibitors[1-4] or angiotensin II receptor antagonists such as losartan[5-9] and guidelines recommend these drugs for first-line therapy.[10,11] Theophylline may also be used but appears to be less effective than ACE inhibitors[1] and is usually reserved for patients who do not respond to first-line therapy; it may also be used with an ACE inhibitor but venesection may need to be used until the haematocrit falls to 45%.

Guidelines[11] recommend that patients who develop **erythrocytosis secondary to hypoxic pulmonary disease** should first be considered for methods to improve oxygenation, including long-term oxygen therapy. Those who have hyperviscosity or a haematocrit greater than 56% should undergo venesection. ACE inhibitors or angiotensin II receptor antagonists might be of use for patients who do not tolerate venesection;[11] beneficial responses have been reported with enalapril in altitude polycythaemia,[12] and with losartan in erythrocytosis secondary to chronic obstructive pulmonary disease.[13] Theophylline has also been reported to be of benefit.

1. Ok E, *et al*. Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
2. Beckingham IJ, *et al*. A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. *Nephrol Dial Transplant* 1995; **10:** 2316–20.
3. Hernández E, *et al*. Usefulness and safety of treatment with captopril in posttransplant erythrocytosis. *Transplant Proc* 1995; **27:** 2239–41.
4. MacGregor MS, *et al*. Treatment of postrenal transplant erythrocytosis. *Nephron* 1996; **74:** 517–21.
5. Klaassen RJL, *et al*. Losartan, an angiotensin-II receptor antagonist, reduces hematocrits in kidney transplant recipients with posttransplant erythrocytosis. *Transplantation* 1997; **64:** 780–2.
6. Navarro JF, *et al*. Effects of losartan on the treatment of posttransplant erythrocytosis. *Clin Nephrol* 1998; **49:** 370–2.
7. Julian BA, *et al*. Losartan, an angiotensin II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. *J Am Soc Nephrol* 1998; **9:** 1104–8.
8. Iñigo P, *et al*. Treatment with losartan in kidney transplant recipients with posttransplant erythrocytosis. *Transplant Proc* 1999; **31:** 2321.
9. Yildiz A, *et al*. Comparison of the effects of enalapril and losartan on posttransplantation erythrocytosis in renal transplant recipients: prospective randomized study. *Transplantation* 2001; **72:** 542–5.
10. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.9.3. Haematological complications: erythrocytosis. *Nephrol Dial Transplant* 2002; **17** (suppl 4): 49–50. Also available at: http://ndt.oxfordjournals.org/cgi/reprint/17/suppl_4/49-a.pdf (accessed 20/11/06)
11. McMullin MF, *et al*. British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 20/11/06)
12. Plata R, *et al*. Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: a prospective randomised trial. *Lancet* 2002; **359:** 663–6.
13. Vlahakos DV, *et al*. Losartan reduces hematocrit in patients with chronic obstructive pulmonary disease and secondary erythrocytosis. *Ann Intern Med* 2001; **134:** 426–7.

Genetic disorders. Small studies have suggested that ACE inhibitors may be of benefit in patients with cardiac disorders associated with Marfan syndrome,[1,2] as well as in Duchenne muscular dystrophy.[3,4]

1. Yetman AT, *et al*. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *Am J Cardiol* 2005; **95:** 1125–7.
2. Ahimastos AA, *et al*. Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA* 2007; **298:** 1539–47.
3. Duboc D, *et al*. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005; **45:** 855–7.
4. Duboc D, *et al*. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J* 2007; **154:** 596–602.

Heart failure. ACE inhibitors given orally produce clinical benefit in all stages of chronic heart failure (p. 1262.3) additional to that seen with diuretics. They relieve symptoms and improve survival and reduce the progression of mild or moderate heart failure to more severe stages. Thus, it is now recommended that all patients with heart failure due to left ventricular systolic dysfunction should receive ACE inhibitors, even if they are asymptomatic with diuretics alone.

The studies that have shown a benefit with ACE inhibitors have tended to use higher doses than those used in practice. A study[1] with lisinopril found that higher doses reduced the combined end-point of death or hospitalisation more than low doses and were equally well tolerated, suggesting that higher doses should be used. Studies with enalapril have failed to show a benefit of standard doses over lower doses,[2] or high doses over standard doses.[3] It is recommended[4,5] that doses should be titrated to those found to be effective in randomised studies, rather than according to symptomatic response, although lower doses may still be of benefit if higher doses are not tolerated.[4] Combination of ACE inhibitors with angiotensin II receptor antagonists to produce a more complete blockade of the renin-angiotensin system may also be of benefit,[6-8] and may therefore be considered[4,5] in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.

ACE inhibitors may also have a role in patients with asymptomatic left ventricular dysfunction, although this is less well established; no effect on short-term mortality was found in asymptomatic patients in the SOLVD study, but a significant survival benefit was found on long-term follow-up.[9] In patients with heart failure and preserved left ventricular function (diastolic dysfunction) the role of ACE inhibitors is unclear, although they may provide symptomatic benefit.[10] ACE inhibitors may be beneficial in patients with heart failure associated with valve disorders (but see under Precautions, p. 1287.3 for discussion of their use in aortic stenosis). There is also some evidence that ACE inhibitors may prevent the development of antineoplastic-induced cardiotoxicity,[11] although this remains to be confirmed.

The mechanism of action in heart failure is not established. ACE inhibitors have beneficial haemodynamic effects; they produce arterial and venous dilatation,[12] reducing both preload and afterload and thus improving cardiac output without increasing heart rate. Their neurohormonal effects also play a part,[13] as do their effects on cytokines. Further actions that may contribute include reduction of left ventricular hypertrophy, and an indirect action to prevent cardiac arrhythmias.[14-16]

Captopril and enalapril have both been used in infants with severe heart failure (see Administration in Children, p. 1331.3, and p. 1371.2, respectively).

1. Packer M, *et al*. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; **100:** 2312–18.
2. The NETWORK investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J* 1998; **19:** 481–9.
3. Nanas JN, *et al*. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. *J Am Coll Cardiol* 2000; **36:** 2090–5.
4. Jessup M, *et al*. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119:** 1977–2016. Correction. *ibid.*; **121:**e258. Also published in *J Am Coll Cardiol* 2009; **53:** e1–e90. Correction. *ibid.*; **54:** 2464. Also available at: http://circ.ahajournals.org/cgi/reprint/119/14/1977.pdf (accessed 11/10/10) and at: http://content.onlinejacc.org/cgi/reprint/53/15/e1.pdf (accessed 11/10/10)
5. Dickstein K, *et al*. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; **29:** 2388–2442. Correction. *ibid*. 3069. [dose] Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf (accessed 14/10/08)
6. Struckman DR, Rivey MP. Combined therapy with an angiotensin II receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure. *Ann Pharmacother* 2001; **35:** 242–8.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.
8. McMurray JJV, *et al*. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.
9. Jong P, *et al*. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003; **361:** 1843–8.
10. Cleland JGF, *et al*. PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur HeartJ* 2006; **27:** 2338–45.
11. Cardinale D, *et al*. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006; **114:** 2474–81.
12. Capewell S, *et al*. Acute and chronic arterial and venous effects of captopril in congestive cardiac failure. *BMJ* 1989; **299:** 942–5.
13. Deedwania PC. Angiotensin-converting enzyme inhibitors in congestive heart failure. *Arch Intern Med* 1990; **150:** 1798–1805.
14. Wesseling H, *et al*. Cardiac arrhythmias—a new indication for angiotensin-converting enzyme inhibitors? *J Hum Hypertens* 1989; **3** (suppl 1): 89–95.
15. Campbell RWF. ACE inhibitors and arrhythmias. *Heart* 1996; **76** (suppl 3): 79–82.
16. Healey JS, *et al*. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45:** 1832–9.

Hypertension. ACE inhibitors have an established role in the management of hypertension (p. 1251.1) and appear to have comparable effects to the other main groups of antihypertensives.[1] The Captopril Prevention Project (CAPPP) study,[2] which compared captopril-based therapy with beta blocker- or diuretic-based therapy, suggested that cardiovascular mortality was lower with captopril, although the risk of stroke was increased in those given captopril and overall mortality did not differ between the groups. In the large ALLHAT study,[3] which compared an ACE inhibitor with a calcium-channel blocker or a diuretic, overall mortality did not differ significantly between any of the groups, although there were slightly higher rates of stroke and heart failure in those given the ACE inhibitor compared with the diuretic group. ACE inhibitors are particularly recommended in diabetic patients with nephropathy as they may have beneficial effects on the kidney, and also in patients with heart failure. Other advantages that have been suggested include their lack of adverse effects on serum lipids, a reduction in left ventricular hypertrophy,[4] and a reduction in plasma fibrinogen concentrations,[5] but the clinical significance of these effects is not established.

The antihypertensive actions of ACE inhibitors may be potentiated by drugs that activate the renin-angiotensin system. Hence, combination therapy with diuretics or with calcium-channel blockers may be particularly useful.

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362:** 1527–35.
2. Hansson L, *et al*. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; **353:** 611–16.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.
4. Schmieder RE, *et al*. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. *JAMA* 1996; **275:** 1507–13.
5. Fogari R, *et al*. Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive patients. *Br J Clin Pharmacol* 1995; **39:** 471–6.

DIAGNOSIS OF RENOVASCULAR HYPERTENSION. Captopril has been used to diagnose renovascular hypertension, since the increase in plasma renin activity after blockade of the conversion of angiotensin I to angiotensin II is greater in renovascular hypertension than in primary hypertension.[1] However, a meta-analysis[2] of various tests used for the diagnosis of renovascular hypertension found that the accuracy of the captopril test is low when compared with imaging methods such as computed tomography or magnetic resonance angiography. Captopril is also used to enhance the sensitivity and specificity of renal scintigraphy.[3] For reference to the use of captopril scintigraphy to diagnose Bartter's syndrome see p. 1282.3.

1. Muller FB, *et al*. The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med* 1986; **80:** 633–44.
2. Vasbinder GBC, *et al*. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med* 2001; **135:** 401–411.
3. Dowling RJ, *et al*. Imaging and stenting for renal artery stenosis. *Hosp Med* 1999; **60:** 329–34.

Ischaemic heart disease. ACE inhibitors have clinical benefits in patients with ischaemic heart disease and other atherosclerotic conditions. They have an established role

in the treatment of patients after acute myocardial infarction (see below) and may also have a preventative effect; in the SAVE[1] and SOLVD[2] studies, use of ACE inhibitors in patients with heart failure was noted to lead to a reduction in the incidence of myocardial infarction. In the HOPE study,[3] treatment with ramipril significantly reduced the rate of death, myocardial infarction, and stroke in patients at high risk for cardiovascular disease, while in the EUROPA study[4] perindopril was found to reduce cardiovascular events in patients with stable ischaemic heart disease. In the QUO VADIS study,[5] giving quinapril for 1 year after coronary artery bypass grafting reduced the incidence of clinical ischaemic events although there was no effect on ischaemia during exercise testing or Holter monitoring.

The mechanisms by which ACE inhibitors produce benefit in these patients is less clear. Although a direct action to reduce atherosclerosis (p. 1250.2) has been suggested, studies have failed to confirm this effect. In the TREND study,[6] giving quinapril for 6 months was reported to improve endothelial dysfunction in patients with ischaemic heart disease, but apparently no effects on the progression of atherosclerosis or the incidence of cardiac events were found in the QUIET study[7] which used a lower dose of quinapril given for 3 years. In the PART-2 study,[8] ramipril had no effect on the progression of carotid atherosclerosis, while the PARIS study[9] found an increase in angiographic restenosis after use of quinapril. A review[10] based mainly on results from the EUROPA study considered that perindopril upregulated endothelial nitric oxide synthase activity, normalised the balance between angiotensin II and bradykinin, and reduced endothelial apoptosis; however, it noted that the ability to produce these effects varied between different ACE inhibitors, as did affinity for tissue ACE and penetration of atherosclerotic plaque.

A lack of acute anti-ischaemic effect has been found with short-term use of captopril and enalapril in patients with stable angina,[11] and with enalapril in Prinzmetal's angina;[12] however, a further study[13] in patients with stable angina reported an improvement in the results of maximal exercise testing after sublingual captopril dosage. Symptomatic benefit has also been reported[14] in patients with atherosclerotic peripheral arterial disease, and a case-control study[15] has suggested that patients with aortic disease may have a lower risk of ruptured aortic aneurysm if they are taking ACE inhibitors.

1. Pfeffer MA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; **327:** 669–77.
2. Yusuf S, *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992; **340:** 1173–8.
3. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.
4. EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362:** 782–8.
5. Oosterga M, *et al.* Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study): QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol* 2001; **87:** 542–6.
6. Mancini GBJ, *et al.* Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on Reversing Endothelial Dysfunction) study. *Circulation* 1996; **94:** 258–65.
7. Cashin-Hemphill L, *et al.* Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. *Am J Cardiol* 1999; **83:** 43–7.
8. MacMahon S, *et al.* Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *J Am Coll Cardiol* 2000; **36:** 438–43.
9. Meurice T, *et al.* Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2001; **357:** 1321–4.
10. Ferrari R, Fox K. Insight into the mode of action of ACE inhibition in coronary artery disease: the ultimate 'EUROPA' story. *Drugs* 2009; **69:** 265–77.
11. Longobardi G, *et al.* Failure of protective effect of captopril and enalapril on exercise and dipyridamole-induced myocardial ischemia. *Am J Cardiol* 1995; **76:** 255–8.
12. Guazzi M, *et al.* Ineffectiveness of angiotensin converting enzyme inhibition (enalapril) on overt and silent myocardial ischemia in vasospastic angina and comparison with verapamil. *Clin Pharmacol Ther* 1996; **59:** 476–81.
13. Gemici K, *et al.* The effects of sublingual administration of captopril on parameters of exercise test and neurohormonal activation in patients with stable angina pectoris. *Int J Angiol* 1998; **7:** 238–43.
14. Ahimastos AA, *et al.* Ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med* 2006; **144:** 660–4.
15. Hackam DG, *et al.* Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 2006; **368:** 659–65.

Kidney disorders. The effects of ACE inhibitors on the kidney are complex. Although they may reduce renal function and should be used with caution in patients with renal impairment (see Adverse Effects and Treatment, p. 1285.2), ACE inhibitors may also have beneficial effects in diabetic and nondiabetic renal disease. Reducing blood pressure protects renal function regardless of the class of antihypertensive used,[1] since hypertension and the resultant proteinuria both cause kidney damage. Several studies have shown that ACE inhibitors and other drugs that block the renin-angiotensin-aldosterone system (RAS), such as angiotensin II receptor antagonists, are particularly effective[1] and they may therefore be preferred for blood pressure control in kidney disorders. However, whether they have a specific renoprotective effect beyond their antihypertensive effect is unclear.[2]

Most experience has been gained in patients with diabetic nephropathy (see p. 465.1), which is often associated with hypertension and may progress from microalbuminuria to the nephrotic syndrome and end-stage renal failure. In diabetic patients with marked proteinuria, treatment with ACE inhibitors has been reported to slow progression to end-stage renal disease, and to have a mortality benefit.[3] However, although it has been assumed that this could be extended to patients with earlier disease, this now seems to be less clear. Studies have reported that ACE inhibitors can slow progression of microalbuminuria,[4,5] and their use has been recommended, with tight glycaemic control, in all microalbuminuric diabetic patients.[6] However, the 5-year RASS study in type 1 diabetic patients without any proteinuria, which directly measured renal structural changes, found neither enalapril nor losartan to be of benefit for primary prevention of renal damage (although progression of retinopathy was slowed).[7] Further uncertainty about the benefits of blockade of the renin-angiotensin system has been produced by the results of the ONTARGET study. Angiotensin II receptor antagonists have also been reported to be effective in slowing the progression of proteinuria[3,4,8] (though mortality benefit has not been shown[3]), and dual therapy with these drugs and an ACE inhibitor had been thought to offer benefits over either alone,[9,10] but ONTARGET, which compared treatment with ramipril, telmisartan, or both in patients over 55 with atherosclerotic vascular disease or diabetes with end-organ damage,[11] found that combination therapy, despite reducing proteinuria more than either drug alone, was actually associated with a higher risk of renal events. Again, most of the patients in this study did not have proteinuria. Although the study was not powered to detect differences of major renal outcomes, this has thrown doubt on the value of combination therapy in such patients.

ACE inhibitors may also be of benefit in renal disease unrelated to diabetes, although their role is less established. Proteinuria is an important indicator of glomerular kidney disease (p. 1604.3) of various causes and may range from asymptomatic to severe. Several studies[12-19] have reported that ACE inhibitors reduce both proteinuria and the rate of decline of renal function in patients with various non-diabetic renal disorders. Meta-analyses[20,21] have concluded that ACE inhibitors are more effective than other antihypertensives, although others suggest this is uncertain.[2] There is less evidence for angiotensin II receptor antagonists alone in non-diabetic renal disease.[8] Again, dual therapy with one of these drugs and an ACE inhibitor has been suggested to offer additional renal benefit,[9] but the ONTARGET results[11] throw some doubt on this.

Patients with systemic sclerosis (see Scleroderma, p. 1942.3) are considered to be at high risk of adverse effects from ACE inhibitors; however there is evidence that these drugs are of benefit in the management of scleroderma-associated hypertension and renal crisis.[22]

1. Ravera M, *et al.* Importance of blood pressure control in chronic kidney disease. *J Am Soc Nephrol* 2006; **17** (4 suppl 2): S98–S103.
2. Casas JP, *et al.* Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; **366:** 2026–33.
3. Strippoli GFM, *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 25/04/08).
4. Thomas MC, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. *Drugs* 2006; **66:** 2213–34.
5. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001; **134:** 370–9.
6. Mogensen CE, *et al.* Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; **346:** 1080–4.
7. Mauer M, *et al.* Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; **361:** 40–51.
8. Thurman JM, Schrier RW. Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on blood pressure and the kidney. *Am J Med* 2003; **114:** 588–98.
9. MacKinnon M, *et al.* Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; **48:** 8–20.
10. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148:** 30–48.
11. Mann JF, *et al.* ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; **372:** 547–53.
12. Gansevoort RT, *et al.* Long-term benefits of the antiproteinuric effect of angiotensin-converting enzyme inhibition in nondiabetic renal disease. *Am J Kidney Dis* 1993; **22:** 202–6.
13. Hannedouche T, *et al.* Randomised controlled trial of enalapril and β blockers in non-diabetic chronic renal failure. *BMJ* 1994; **309:** 833–7.
14. Maschio G, *et al.* Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; **334:** 939–45.
15. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349:** 1857–63.
16. Ruggenenti P, *et al.* Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998; **352:** 1252–6.
17. Ruggenenti P, *et al.* Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; **354:** 359–64.
18. Agodoa LY, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; **285:** 2719–28.
19. Hou FF, *et al.* Efficacy and safety ofbenazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; **354:** 131–40.
20. Giatras I, *et al.* Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. *Ann Intern Med* 1997; **127:** 337–45.
21. Jafar TH, *et al.* Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level data. *Ann Intern Med* 2001; **135:** 73–87.
22. Steen VD, *et al.* Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990; **113:** 352–7.

Malignant neoplasms. *Animal* and *in vitro* studies have suggested that ACE inhibitors may protect against the development of cancer. Regression of Kaposi's sarcoma was reported[1] in a patient treated with captopril (but see Effects on the Skin, p. 1286.3), and a retrospective cohort study[2] suggested that the incidence of cancer in hypertensive patients receiving ACE inhibitors was lower than expected. In a prospective cohort study[3] of 7983 patients, blocking the renin-angiotensin system appeared to protect against cancer in individuals with a polymorphism for high plasma-ACE concentrations; however, a case control study[4] in postmenopausal women found no evidence of a reduced risk of breast cancer associated with ACE inhibitor therapy.

1. Vogt B, Frey FJ. Inhibition of angiogenesis in Kaposi's sarcoma by captopril. *Lancet* 1997; **349:** 1148.
2. Lever AF, *et al.* Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998; **352:** 179–84.
3. van der Knaap R, *et al.* Renin-angiotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer: the Rotterdam Study. *Cancer* 2008; **112:** 748–57.
4. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.

Marfan syndrome. For mention of the use of ACE inhibitors in patients with Marfan syndrome see Genetic Disorders, p. 1283.2.

Migraine. Observations that attacks of migraine occurred less frequently in hypertensive patients treated with lisinopril, were confirmed by a small placebo-controlled study[1] in 47 non-hypertensive patients with migraine (p. 670.3); low oral doses (5 mg daily) may be adequate.[2]

1. Schrader H, *et al.* Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001; **322:** 19–22.
2. Schuh-Hofer S, *et al.* Efficacy of lisinopril in migraine prophylaxis – an open label study. *Eur J Neurol* 2007; **14:** 701–3.

Muscular dystrophy. For reference to the use of ACE inhibitors in patients with Duchenne muscular dystrophy see Genetic Disorders, p. 1283.2.

Myocardial infarction. ACE inhibitors may be of benefit in both the prevention and treatment of myocardial infarction (p. 1257.1). They reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Studies in patients with evidence of left ventricular dysfunction have shown benefit from long-term oral use of ACE inhibitors such as captopril (the SAVE study),[1] ramipril (the AIRE and AIRE extension (AIREX) studies),[2-4] or trandolapril (the TRACE study)[5,6] started about 3 days, or more, after infarction, and long-term ACE inhibitors are now established therapy in such patients.[7,8]

Early treatment with ACE inhibitors as an adjunct to standard thrombolytic therapy is less well established. Favourable results have been reported in the GISSI-3[9] and the ISIS-4[10] studies where lisinopril and captopril, respectively, were given orally starting within 24 hours of the onset of chest pain and in the Chinese Cardiac Study[11] (CCS-1) where captopril was given orally within 36 hours of the onset of symptoms. In the GISSI-3 study the beneficial effects were maintained at 6 months.[12] However, the CONSENSUS II study was stopped early when it was found that enalapril, given intravenously as enalaprilat and begun within 24 hours of the onset of chest pain, did not improve survival during the 180 days after infarction.[13] A substudy on some of the patients did however suggest that they may have benefited from early treatment since left ventricular dilatation was attenuated.[14] An interaction between aspirin and enalapril was postulated as one of the reasons for the overall lack of benefit seen, and further analysis of the CONSENSUS II results found that the beneficial effect of

enalapril was reduced in those patients already taking aspirin,[15] although a systematic overview[16] failed to support this finding. A systematic review of the CONSENSUS II, GISSI-3, ISIS-4, and CCS-1 studies found lower 30-day cumulative mortality and incidence of non-fatal heart failure among ACE inhibitor recipients.[17] However, the size of benefit in these studies of largely unselected patients is much smaller than in the studies of patients with left ventricular dysfunction, and there remains no clear consensus as to whether all patients should be given ACE inhibitors or only those who develop evidence of left ventricular dysfunction.

1. Pfeffer MA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; **327:** 669–77.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; **342:** 821–8.
3. Hall AS, *et al.* Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE extension (AIREX) study. *Lancet* 1997; **349:** 1493–7.
4. Cleland JGF, *et al.* Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: a report from the AIRE study investigators. *Eur Heart J* 1997; **18:** 41–51.
5. Køber L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; **333:** 1670–6.
6. Torp-Pedersen C, Køber L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. *Lancet* 1999; **354:** 9–12.
7. Borghi C, Ambrosioni E. A risk-benefit assessment of ACE inhibitor therapy post-myocardial infarction. *Drug Safety* 1996; **14:** 277–87.
8. Murdoch DR, McMurray JJV. ACE inhibitors in acute myocardial infarction. *Hosp Med* 1998; **59:** 111–15.
9. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
10. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.
11. Chinese Cardiac Study collaborative group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995; **345:** 686–7.
12. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; **27:** 337–44.
13. Swedberg K, *et al.* Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; **327:** 678–84.
14. Bonarjee VVS, *et al.* Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. *Am J Cardiol* 1993; **72:** 1004–9.
15. Nguyen KN, *et al.* Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol* 1997; **79:** 115–19.
16. Latini R, *et al.* Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. *J Am Coll Cardiol* 2000; **35:** 1801–7.
17. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation* 1998; **97:** 2202–12.

Pneumonia. Use of ACE inhibitors has been suggested to be of potential value in reducing the risk of community-acquired pneumonia in the elderly, particularly in those with neurological and cerebrovascular abnormalities (see also Stroke, below). A systematic review[1] considered that there was some evidence for this approach, but noted that it mostly came from studies in Asian patients. Given potential polymorphisms in ACE metabolism, future studies should include genetic data.

1. Rafailidis PI, *et al.* Use of ACE inhibitors and risk of community-acquired pneumonia: a review. *Eur J Clin Pharmacol* 2008; **64:** 565–73.

Raynaud's syndrome. ACE inhibitors are among many drugs that have been tried in Raynaud's syndrome, a vasospastic arterial disorder (p. 1275.3). Variable effects have been reported. In a patient with Raynaud's syndrome captopril improved blood circulation in the fingers both acutely and during long-term therapy with a dose of 37.5 mg daily; the effect was apparently related to its effects on kinins rather than inhibition of angiotensin II formation.[1] However, a double-blind crossover study in 15 patients with Raynaud's phenomenon given captopril 25 mg or placebo three times daily for 6 weeks found that the drug improved blood flow but not the frequency or severity of attacks;[2] a similar study in patients given enalapril failed to find any subjective or objective benefits;[3] and use of quinapril for 3 years did not reduce vascular manifestations of systemic sclerosis or Raynaud's syndrome.[4] A review[5] concluded that ACE inhibitors provide only minor benefits in the treatment of Raynaud's syndrome.

In one patient, captopril[6] rapidly reversed ergotamine-induced peripheral ischaemia.

1. Miyazaki S, *et al.* Relief from digital vasospasm by treatment with captopril and its complete inhibition by serine proteinase inhibitors in Raynaud's phenomenon. *BMJ* 1982; **284:** 310–11.
2. Rustin MHA, *et al.* The effect of captopril on cutaneous blood flow in patients with primary Raynaud's phenomenon. *Br J Dermatol* 1987; **117:** 751–8.
3. Challenor VF, *et al.* Subjective and objective assessment of enalapril in primary Raynaud's phenomenon. *Br J Clin Pharmacol* 1991; **31:** 477–80.
4. Gliddon AE, *et al.* Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis Rheum* 2007; **56:** 3837–46.
5. Wood HM, Ernst ME. Renin-angiotensin system mediators and Raynaud's phenomenon. *Ann Pharmacother* 2006; **40:** 1998–2002.
6. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288:** 364.

Stroke. Antihypertensive therapy reduces the risk of stroke (p. 1269.2) in patients with hypertension. However, in patients who have had a stroke, antihypertensive therapy has often been avoided due to the perceived risk of reducing cerebral perfusion. A study[1] of blood-pressure lowering with the ACE inhibitor perindopril, alone or with a diuretic, found that the risk of recurrent stroke was reduced in patients with a history of stroke or transient ischaemic attack, irrespective of whether they had a normal or raised blood pressure at study entry. Retrospective studies[2,3] have also suggested that stroke severity may be reduced in patients who are already taking ACE inhibitors. The beneficial effects of ACE inhibitors in stroke may not be entirely due to their antihypertensive effects; in the HOPE study,[4] ramipril reduced the incidence of stroke in patients with high cardiovascular risk despite only a small reduction in blood pressure.

There have also been reports[5,6] that ACE inhibitors may reduce the risk of pneumonia in patients with a history of stroke, possibly by an effect on symptomless dysphagia.[7] See also Pneumonia, above.

1. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358:** 1033–41. Corrections. *ibid.*; 1556 and 2002; **359:** 2120.
2. Kumar S, *et al.* Antiplatelets, ACE inhibitors, and statins combination reduces stroke severity and tissue at risk. *Neurology* 2006; **66:** 1153–8.
3. Chitravas N, *et al.* Is prestroke use of angiotensin-converting enzyme inhibitors associated with better outcome? *Neurology* 2007; **68:** 1687–93.
4. Bosch J, *et al.* Use of ramipril in preventing stroke: double blind randomised trial. *BMJ* 2002; **324:** 699–702.
5. Sekizawa K, *et al.* ACE inhibitors and pneumonia. *Lancet* 1998; **352:** 1069.
6. Arai T, *et al.* ACE inhibitors and pneumonia in elderly people. *Lancet* 1998; **352:** 1937–8.
7. Arai T, *et al.* ACE inhibitors and symptomless dysphagia. *Lancet* 1998; **352:** 115–6.

Adverse Effects and Treatment

Many of the adverse effects of ACE inhibitors relate to their pharmacological action and all therefore have a similar spectrum of adverse effects. Some effects, such as taste disturbances and skin reactions, were at one time attributed to the presence of a sulfhydryl group (as in captopril) but have now also been reported with other ACE inhibitors; however, they may be more common with captopril.

The most common adverse effects are due to the vascular effects of ACE inhibitors and include hypotension, dizziness, fatigue, headache, and nausea and other gastrointestinal disturbances.

Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and in sodium- or volume-depleted patients (for example, those given previous diuretic therapy). Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations, and chest pain.

Deterioration in renal function, including increasing blood concentrations of urea and creatinine, may occur, and reversible acute renal failure has been reported. Renal effects are most common in patients with existing renal or renovascular dysfunction or heart failure, in whom vasodilatation reduces renal perfusion pressure; this may be aggravated by hypovolaemia. Proteinuria has also occurred and in some patients has progressed to nephrotic syndrome. Hyperkalaemia and hyponatraemia may develop due to decreased aldosterone secretion.

Other adverse effects include persistent dry cough and other upper respiratory tract symptoms, and angioedema; these may be related to effects on bradykinin or prostaglandin metabolism. Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur; photosensitivity, alopecia, and other hypersensitivity reactions have also been reported.

Blood disorders have been reported with ACE inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and in those with collagen vascular disorders such as SLE and scleroderma), thrombocytopenia, and anaemias.

Other less common adverse effects reported with ACE inhibitors include stomatitis, abdominal pain, pancreatitis, hepatocellular injury or cholestatic jaundice, muscle cramps, paraesthesias, mood and sleep disturbances, and impotence.

ACE inhibitors have been associated with fetal toxicity (see Pregnancy under Precautions, p. 1288.1).

Most of the adverse effects of ACE inhibitors are reversible on withdrawing therapy. Symptomatic hypotension, including that after overdosage, generally responds to volume expansion with an intravenous infusion of sodium chloride 0.9%.

General reviews.

1. Parish RC, Miller LJ. Adverse effects of angiotensin converting enzyme (ACE) inhibitors: an update. *Drug Safety* 1992; **7:** 14–31.
2. Alderman CP. Adverse effects of the angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996; **30:** 55–61.
3. Agusti A, *et al.* Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction: meta-analysis of randomised clinical trials. *Drug Safety* 2003; **26:** 895–908.
4. Adam A, *et al.* Physiopathologie des effets secondaires aigus des inhibiteurs de l'enzyme de conversion de l'angiotensine. *Bull Acad Natl Med* 2007; **191:** 1433–43.

Angioedema. See under Hypersensitivity, p. 1287.1.

Cough. Treatment with ACE inhibitors has been associated with the development of cough in up to 20% of hypertensive patients; cough may be less troublesome in those with heart failure,[1] although the incidence may be higher.[2] The cough is reported to be persistent, paroxysmal, and non-productive; it causes irritation of the throat, may be accompanied by voice changes (hoarseness or huskiness), and is often worse when lying down.[1,3,4] It is more common in women and non-smokers, and may be delayed in onset by weeks or even months.

The majority of reports of this adverse effect concern captopril and enalapril,[3,4] but it has also occurred in patients receiving many of the other ACE inhibitors,[5] suggesting that the effect is common to all drugs of this class.

The mechanism that produces the reaction is uncertain but appears to be related to the non-specific blockade of ACE since angiotensin II receptor antagonists are associated with a much lower incidence of cough.[6] The sensitivity of the cough reflex is increased.[7] Prostaglandins released in the respiratory tract have been proposed as mediators,[3] but other mediators such as bradykinin[8] or substance P,[9] both of which are substrates for ACE, have been suggested. However, attempts to show a link between the effects of ACE inhibitors on cough, and bronchial hyperreactivity of the type found in obstructive airways disease and asthma have produced conflicting evidence, with bronchial hyperreactivity being shown in some studies[10] but not in others.[11]

Where the patient can tolerate the cough, it may be reasonable to continue treatment; in some cases reducing the dose may help. Spontaneous recovery or improvement in the cough has been reported.[12] Changing to an alternative ACE inhibitor is not advised since it is rarely effective.[7] Drugs that inhibit prostaglandin synthesis, including the NSAIDs sulindac[13] and indometacin,[14] have been reported to suppress the cough, but NSAIDs and ACE inhibitors may interact adversely (see under Interactions, p. 1288.3). The calcium-channel blocker nifedipine also reduced cough, although to a lesser extent than indometacin, possibly by a similar mechanism.[14] Inhaled bupivacaine,[15] inhaled sodium cromoglicate,[16,17] oral baclofen,[18] oral picotamide,[19] and oral ferrous sulfate,[20] have also been reported to be of help. However, in many patients there will be no alternative but to withdraw the ACE inhibitor, and this is recommended by some in all patients presenting with ACE inhibitor-induced cough.[21] Angiotensin II receptor antagonists may be a suitable alternative in patients with hypertension.[21]

1. Anonymous. Cough caused by ACE inhibitors. *Drug Ther Bull.* 1994; **32:** 28 and 55–6.
2. Ravid D, *et al.* Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and congestive heart failure. *J Clin Pharmacol* 1994; **34:** 1116–20.
3. Coulter DM, Edwards IR. Cough associated with captopril and enalapril. *BMJ* 1987; **294:** 1521–3.
4. Berkin KE, Ball SG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1279–80.
5. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. *Ann Intern Med* 1992; **117:** 234–42.
6. Pylypchuk GB. ACE inhibitor- versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother* 1998; **32:** 1060–6.
7. Overlack A. ACE inhibitor-induced cough and bronchospasm. *Drug Safety* 1996; **15:** 72–8.
8. Ferner RE, *et al.* Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme. *BMJ* 1987; **294:** 1119–20.
9. Morice AH, *et al.* Angiotensin-converting enzyme and the cough reflex. *Lancet* 1987; **ii:** 1116–18.
10. Bucknall CE, *et al.* Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors. *BMJ* 1988; **296:** 86–8.
11. Boulet L-P, *et al.* Pulmonary function and airway responsiveness during long-term therapy with captopril. *JAMA* 1989; **261:** 413–16.
12. Reisin L, Schneeweiss A. Spontaneous disappearance of cough induced by angiotensin-converting enzyme inhibitors (captopril or enalapril). *Am J Cardiol* 1992; **70:** 398–9.

13. Nicholls MG, Gilchrist NL. Sulindac and cough induced by converting enzyme inhibitors. *Lancet* 1987; **i:** 872.
14. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; **19:** 670–3.
15. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1741.
16. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; **341:** 560.
17. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; **345:** 13–16.
18. Dicpinigaitis PV. Use of baclofen to suppress cough induced by angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996; **30:** 1242–5.
19. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; **350:** 15–18.
20. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
21. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129** (suppl): 169S–173S.

Effects on the blood. Blood disorders have occurred in patients receiving ACE inhibitors, although there have been few reports in the literature. A reduction in haemoglobin concentration and haematocrit may occur but is not usually clinically significant, although an unfavourable effect on recovery from anaemia has been reported;[1] ACE inhibitors have also been used therapeutically to reduce the haematocrit (see Erythrocytosis under Uses, p. 1283.1). Cases of neutropenia and agranulocytosis (particularly in patients with renal or collagen vascular disorders), and thrombocytopenia have been noted. Aplastic anaemia has also occurred[2,3] and may be fatal.[3]

1. Ripamonti V, *et al.* Angiotensin-converting enzyme inhibitors slow recovery from anemia following cardiac surgery. *Chest* 2006; **130:** 79–84.
2. Kim CR, *et al.* Captopril and aplastic anemia. *Ann Intern Med* 1989; **111:** 187–8.
3. Harrison BD, *et al.* Fatal aplastic anaemia associated with lisinopril. *Lancet* 1995; **346:** 247–8.

Effects on the kidneys. ACE inhibitors have complex effects on the kidney;[1,2] they have established renoprotective effects but also cause acute deterioration in renal function in some patients. These apparently contradictory effects are related to the action of ACE inhibitors on the renin-angiotensin-aldosterone system.

The renin-angiotensin-aldosterone system has an important role in maintaining normal renal blood flow and renal function. A reduction in renal perfusion, for example due to hypovolaemia, heart failure, or renal artery stenosis, leads to activation of this system and an increase in angiotensin II release. This results mainly in postglomerular renal vasoconstriction, which maintains renal glomerular pressure and thus glomerular filtration, despite the fall in renal blood flow.

In normal individuals with unrestricted sodium intake, the renin-angiotensin-aldosterone system is suppressed and ACE inhibitors have little effect on renal function. In patients with essential hypertension ACE inhibitors generally increase renal blood flow despite the reduction in arterial blood pressure, since this is exceeded by the effects of renal vasodilatation. However, filtration fraction falls since the pressure within the glomerulus is reduced, and there are only minor changes in glomerular filtration rate. The increase in renal blood flow is more pronounced during sodium restriction and in younger patients.

These effects are generally beneficial. However, in patients with reduced renal perfusion, glomerular filtration rate may be critically dependent on the renin-angiotensin-aldosterone system and the use of ACE inhibitors may provoke problems. Severe renal function loss or even anuria have been reported in patients with a single transplanted kidney with renal artery stenosis, or patients with bilateral renal artery disease. The stenotic kidney maintains its filtering capacity by preferential vasoconstriction of the efferent arterioles, a mechanism mainly mediated by the renin-angiotensin system; under ACE inhibition, vasodilatation of the efferent arterioles combined with the drop in arterial pressure can result in a critical decrease in filtration pressure. Hypovolaemia or sodium depletion, for example due to diuretics, also leads to activation of the renin-angiotensin-aldosterone system and predisposes patients to renal impairment. Most patients developing renal insufficiency have been using diuretics and sodium repletion can restore renal function despite continuing ACE inhibition.

Patients with heart failure may also be at risk of a decline in renal function on long-term ACE inhibitor therapy. This is because in chronic heart failure, angiotensin-II mediated systemic and renal vasoconstriction is again important in the maintenance of renal perfusion pressure. The decline may be alleviated by reduction of the dosage of diuretics or liberalisation of dietary salt intake, despite continuing the ACE inhibitor. An additional risk factor in elderly patients with heart failure is the high incidence of occult renovascular disease in these patients.[3]

Moderate impairment of renal function either before or during use of ACE inhibitors is not necessarily an indication to stop therapy. The effects of ACE inhibitors on renal function are generally reversible, and the reduction in filtration pressure may result in renoprotection. A review[4] of studies of the use of ACE inhibitors in patients with renal impairment found that those who initially lost renal function had the greatest long-term benefit.

In addition to pathophysiological effects ACE inhibitors may induce membranous glomerulopathy or interstitial nephritis. The former has been associated with captopril use, particularly at high doses, but is rare, and seems less likely to occur at the lower doses favoured today. The proteinuria usually clears without appreciable renal function loss irrespective of whether or not the drug is continued, although persistent proteinuria and renal function loss have been described. Proven interstitial nephritis has also been reported rarely, and may possibly be due to an allergic mechanism.

1. Navis G, *et al.* ACE inhibitors and the kidney: a risk-benefit assessment. *Drug Safety* 1996; **15:** 200–11.
2. Schoolwerth AC, *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001; **104:** 1985–91.
3. MacDowall P, *et al.* Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998; **352:** 13–16.
4. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000; **160:** 685–93.

Effects on the liver. Hepatotoxicity has been reported with ACE inhibitors, including captopril,[1,2] enalapril,[2] fosinopril,[3] lisinopril,[2] and ramipril.[4] Most reports have been associated with captopril. In a report[1] of 3 cases of liver disease apparently caused or aggravated by captopril, it was noted that jaundice due to captopril is usually mainly cholestatic in nature but acute hepatocellular injury has also been seen. Of 29 cases of liver dysfunction due to captopril and reported to the UK CSM, 9 had hepatocellular jaundice, with 2 deaths; 8 were cholestatic jaundice, with 1 fatality; and 3 patients had hepatorenal syndrome, all of whom died. Worldwide, excluding the UK, 164 cases of hepatic adverse reactions had been notified to the WHO by January 1989. The incidence of such reactions is estimated at 0.09 per 1000 patients but this is likely to be an underestimate. Resolution may take a long time and the drug should be withdrawn immediately at the earliest hint of liver sensitivity.

1. Bellary SV, *et al.* Captopril and the liver. *Lancet* 1989; **ii:** 514.
2. Hagley MT, *et al.* Hepatotoxicity associated with angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1993; **27:** 228–31.
3. Chou J-W, *et al.* Successful treatment of fosinopril-induced severe cholestatic jaundice with plasma exchange. *Ann Pharmacother* 2008; **42:** 1887–92.
4. Yeung E, *et al.* Ramipril-associated hepatotoxicity. *Arch Pathol Lab Med* 2003; **127:** 1493–7.

Effects on the mouth. Aphthous and tongue ulcers may occur during treatment with ACE inhibitors. There have been a few reports of a 'scalded mouth syndrome', described as similar to being scalded by hot liquids, associated with captopril,[1] enalapril,[1] and lisinopril[2] therapy.

1. Vlasses PH, *et al.* "Scalded mouth" caused by angiotensin-converting enzyme inhibitors. *BMJ* 1982; **284:** 1672–3.
2. Savino LB, Haushalter NM. Lisinopril-induced "scalded mouth syndrome." *Ann Pharmacother* 1992; **26:** 1381–2.

Effects on the nervous system. Encephalopathy and focal neurological signs,[1] and peripheral neuropathy,[2,3] including Guillain-Barré neuropathy,[3] have been reported in patients receiving captopril. Some CNS effects of captopril may be attributable to alterations in cerebral blood flow. In a study in patients with severe heart failure, cerebral blood flow in patients aged under 65 was improved by a single dose of captopril 12.5 mg, but in patients aged over 70 there was a 13% reduction.[4] Two patients in whom captopril 6.25 mg produced impaired consciousness and paraesthesias, and dizziness, blurred vision, and aphasia, were found to have stenosis of the carotid arteries.[5] Agitation, panic, extreme depression, and insomnia was reported in a patient 4 weeks after starting treatment with enalapril; depressive episodes recurred on rechallenge.[6] There have been reports of mania possibly precipitated by captopril,[7] and visual hallucinations have been reported in association with captopril and enalapril therapy.[8]

1. Rapoport S, Zyman P. Captopril and central nervous system effects. *Ann Intern Med* 1983; **98:** 1023.
2. Samanta A, Burden AC. Peripheral neuropathy due to captopril. *BMJ* 1985; **291:** 1172.
3. Chakraborty TK, Ruddell WSJ. Guillain-Barré neuropathy during treatment with captopril. *Postgrad Med J* 1987; **63:** 221–2.
4. Britton KE, *et al.* Angiotensin-converting-enzyme inhibitors and treatment of heart failure. *Lancet* 1985; **ii:** 1236.
5. Jensen H, *et al.* Carotid artery stenosis exposed by an adverse effect of captopril. *BMJ* 1986; **293:** 1073–4.
6. Ahmad S. Enalapril-induced acute psychosis. *DICP Ann Pharmacother* 1991; **25:** 558–9.
7. Peet M, Peters S. Drug-induced mania. *Drug Safety* 1995; **12:** 146–53.
8. Haffner CA, *et al.* Hallucinations as an adverse effect of angiotensin converting enzyme inhibition. *Postgrad Med J* 1993; **69:** 240.

Effects on the pancreas. By 1994 the UK CSM[1] noted that there had been 23 reports of pancreatitis associated with ACE inhibitors (captopril 11, enalapril 10, fosinopril 1, and quinapril 1), and since then, pancreatitis (in some cases fatal) has been reported with most of the commonly used ACE inhibitors. Causality has proved difficult to establish,[2] however, and a retrospective cohort study[3] was unable to confirm an association between ACE inhibitors and pancreatitis in elderly patients, despite the large sample size.

1. CSM/MCA. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)
2. Singh S. Angiotensin-converting enzyme (ACE) inhibitor-induced acute pancreatitis: in search of the evidence. *South Med J* 2006; **99:** 1327–8.
3. Cheng RMS, *et al.* Association between ACE inhibitors and acute pancreatitis in the elderly. *Ann Pharmacother* 2003; **37:** 994–8.

Effects on the respiratory system. Cough is a recognised adverse effect of ACE inhibitors but evidence for a link with bronchial hyperreactivity or airways obstruction is conflicting (see Cough, p. 1285.3). In reports of adverse respiratory reactions to ACE inhibitors submitted to the Swedish Adverse Drug Reactions Advisory Committee and to WHO, symptoms of airway obstruction such as dyspnoea, asthma, and bronchospasm occurred rarely, usually within the first few weeks of treatment.[1] However, the evidence for a causal link between ACE inhibitors and these symptoms was questioned.[2]

Severe nasal obstruction was associated with enalapril treatment in a 45-year-old woman with a history of mild rhinorrhoea and sneezing. Symptoms cleared within 2 days of stopping enalapril and recurred on rechallenge.[3] Another woman taking enalapril developed obstructive sleep apnoea,[4] which improved when the enalapril was stopped.

There have been case reports of pneumonitis associated with treatment with captopril[5] and perindopril.[6]

1. Lunde H, *et al.* Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1994; **308:** 18–21.
2. Inman WHW, *et al.* Angiotensin converting enzyme inhibitors and asthma. *BMJ* 1994; **308:** 593–4.
3. Fennerty A, *et al.* Enalapril-induced nasal blockage. *Lancet* 1986; **ii:** 1395–6.
4. Cicolin A, *et al.* Angiotensin-converting enzyme inhibitors and obstructive sleep apnea. *Mayo Clin Proc* 2006; **81:** 53–5.
5. Kidney JC, *et al.* Captopril and lymphocytic alveolitis. *BMJ* 1989; **299:** 981.
6. Benard A, *et al.* Perindopril-associated pneumonitis. *Eur Respir J* 1996; **9:** 1314–16.

Effects on skeletal muscle. Severe muscle pain and weakness, accompanied by morning stiffness, was reported[1] in a patient taking enalapril. Symptoms resolved within a few days of stopping the drug.

1. Leloët X, *et al.* Pseudopolymyalgia rheumatica during treatment with enalapril. *BMJ* 1989; **298:** 325.

Effects on the skin. Skin rashes may occur during treatment with ACE inhibitors; they have been reported in 1 to 6% of patients receiving captopril. Angioedema is also an adverse effect of ACE inhibitors (see Hypersensitivity, p. 1287.1). There have been reports of bullous pemphigoid,[1] hyperhidrosis,[2] Kaposi's sarcoma,[3] lichen planus,[4] onycholysis,[5,6] pemphigus,[7,8] exacerbation of psoriasis,[9] and cutaneous hypersensitivity vasculitis[10] associated with use of captopril. Kaposi's sarcoma has also been reported[11] with lisinopril. Onycholysis has also occurred with enalapril,[12] pemphigus with enalapril[13,14] and ramipril,[15] and bullous pemphigoid with lisinopril.[16] Lichen planus pemphigoides has been reported with ramipril.[17] A severe cutaneous reaction, resembling early mycosis fungoides, and possibly allergic in nature, has been reported after use of captopril or enalapril.[18] An interstitial granulomatous drug reaction presenting as erythroderma was reported with enalapril.[19] Vulvovaginal pruritus with dysuria[20] has also been noted in a patient receiving enalapril.

1. Mallet L, *et al.* Bullous pemphigoid associated with captopril. *DICP Ann Pharmacother* 1989; **23:** 63.
2. Morse MH. Hyperhidrosis: a possible side effect of captopril treatment. *BMJ* 1984; **289:** 1272.
3. Puppin D, *et al.* Kaposi's sarcoma associated with captopril. *Lancet* 1990; **336:** 1251–2.
4. Cox NH, *et al.* Lichen planus associated with captopril: a further disorder demonstrating the 'tin-tack' sign. *Br J Dermatol* 1989; **120:** 319–21.
5. Brueggemeyer CD, Ramirez G. Onycholysis associated with captopril. *Lancet* 1984; **i:** 1352–3.
6. Borders JV. Captopril and onycholysis. *Ann Intern Med* 1986; **105:** 305–6.
7. Parfrey PS, *et al.* Captopril-induced pemphigus. *BMJ* 1980; **281:** 194.
8. Butt A, Burge SM. Pemphigus vulgaris induced by captopril. *Br J Dermatol* 1995; **132:** 315–16.
9. Hamlet NW, *et al.* Does captopril exacerbate psoriasis? *BMJ* 1987; **295:** 1352.
10. Miralles R, *et al.* Captopril and vasculitis. *Ann Intern Med* 1988; **109:** 514.
11. Bilen N, *et al.* Possible causal role of lisinopril in a case of Kaposi's sarcoma. *Br J Dermatol* 2002; **147:** 1042–4.
12. Gupta S, *et al.* Nail changes with enalapril. *BMJ* 1986; **293:** 140.
13. Kuechle MK, *et al.* Angiotensin-converting enzyme inhibitor-induced pemphigus: three case reports and literature review. *Mayo Clin Proc* 1994; **69:** 1166–71.
14. Frangogiannis NG, *et al.* Pemphigus of the larynx and esophagus. *Ann Intern Med* 1995; **122:** 803–4.
15. Vignes S, *et al.* Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; **135:** 657–8.
16. Kalińska-Bienias A, *et al.* Can pemphigoid be provoked by lisinopril? *Br J Dermatol* 2006; **155:** 854–5.

All cross-references refer to entries in Volume A

17. Ogg GS, *et al.* Ramipril-associated lichen planus pemphigoides. *Br J Dermatol* 1997; **136:** 412–14.
18. Furness PN, *et al.* Severe cutaneous reactions to captopril and enalapril; histological study and comparison with early mycosis fungoides. *J Clin Pathol* 1986; **39:** 902–7.
19. Chen Y-C, *et al.* Interstitial granulomatous drug reaction presenting as erythroderma: remission after discontinuation of enalapril maleate. *Br J Dermatol* 2008; **158:** 1143–5.
20. Heckerling PS. Enalapril and vulvovaginal pruritus. *Ann Intern Med* 1990; **112:** 879–80.

Gynaecomastia. Painful unilateral gynaecomastia was reported in a patient with SLE and renal impairment who was given captopril for hypertension.[1] In view of reports of breast enlargement in women given penicillamine it was suggested that the sulfhydryl structure might be responsible; however, gynaecomastia has also been reported in 2 patients receiving enalapril,[2,3] which does not contain the sulfhydryl grouping.

1. Markusse HM, Meyboom RHB. Gynaecomastia associated with captopril. *BMJ* 1988; **296:** 1262–3.
2. Nakamura Y, *et al.* Gynaecomastia induced by angiotensin converting enzyme inhibitor. *BMJ* 1990; **300:** 541.
3. Llop R, *et al.* Gynecomastia associated with enalapril and diazepam. *Ann Pharmacother* 1994; **28:** 671–2.

Hypersensitivity. Some of the adverse effects of ACE inhibitors might be mediated by the immune system, but evidence of specific **hypersensitivity reactions** seems to be limited. An IgG antibody to captopril was present in the serum of 2 of 45 patients taking the drug but the clinical significance was unclear.[1] A reaction resembling serum sickness was reported in a patient given captopril, with deposition of immune complexes in the glomerular basement membrane, and symptoms of rash, arthralgia, epidermolysis, fever, and lymphadenopathy.[2] Eosinophilia has also been reported.[3] The formation of antinuclear antibodies and lupus-like reactions have been described.[4,5]

Treatment with ACE inhibitors (enalapril, captopril, or lisinopril) has been associated with **anaphylactoid reactions** in patients undergoing high-flux haemodialysis using polyacrylonitrile membrane (AN69).[6,7] The UK CSM has advised that the combined use of ACE inhibitors and such membranes should be avoided.[8] Similar anaphylactoid reactions have occurred in patients taking ACE inhibitors while being treated for severe hypercholesterolaemia by extracorporeal removal of low-density lipoproteins (LDL-apheresis) with dextran sulfate columns.[9] These reactions are thought to be bradykinin-mediated. Prolonging the interval between the last dose of ACE inhibitor and dextran sulfate apheresis has averted the reaction;[10] successful prevention has also been reported with the bradykinin receptor antagonist icatibant acetate (p. 2531.1).[11] Hypotensive reactions associated with blood transfusion through bedside leucoreduction filters in patients taking ACE inhibitors have also been attributed to bradykinin.[12] There have also been rare reports of severe allergic reactions, including anaphylaxis, occurring in patients taking ACE inhibitors who were stung by insects or during desensitisation with Hymenoptera venom (e.g. bee or wasp venom).[13]

Angioedema, a known adverse effect of ACE inhibitors,[14-18] is reported to occur in 0.1 to 0.2% of patients.[16,17] The incidence may be higher in black American[19] or Afro-Caribbean[20] patients. There is no evidence that it results from an immunological mechanism in these patients and it has been suggested that the effect is due to impaired kinin degradation. However, angioedema has been reported with lisinopril in a patient who had previously tolerated captopril.[21] The onset of angioedema has usually been within hours or at most a week of starting treatment with the ACE inhibitor,[16] but can occur after prolonged therapy for several months or years.[22-25] It may also occur episodically with long symptom-free intervals.[25] Visceral angioedema, presenting as abdominal pain with diarrhoea, nausea, and vomiting,[26,27] cerebral angioedema,[28] and penile angioedema,[29] have also been reported. If angioedema occurs the ACE inhibitor should be withdrawn and if there is swelling affecting the tongue, glottis, or larynx likely to cause airway obstruction, adrenaline should be given (see p. 1292.3). Fatalities have occurred.[30] Angiotensin II receptor antagonists have been suggested as an alternative in patients unable to tolerate ACE inhibitors, but there have also been reports of angioedema associated with their use (see under Losartan Potassium, p. 1424.1). For a report of angioedema occurring after use of alteplase for stroke in patients taking ACE inhibitors, see under Interactions of Alteplase, p. 1298.1.

1. Coleman JW, *et al.* Drug-specific antibodies in patients receiving captopril. *Br J Clin Pharmacol* 1986; **22:** 161–5.
2. Hoorntje SJ, *et al.* Serum-sickness-like syndrome with membranous glomerulopathy in patient on captopril. *Lancet* 1979; **ii:** 1297.
3. Kayanakis JG, *et al.* Eosinophilia during captopril treatment. *Lancet* 1980; **ii:** 923.
4. Schwartz D, *et al.* Enalapril-induced antinuclear antibodies. *Lancet* 1990; **336:** 187.
5. Pelayo M, *et al.* Drug-induced lupus-like reaction and captopril. *Ann Pharmacother* 1993; **27:** 1541–2.
6. Verresen L, *et al.* Angiotensin-converting-enzyme inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1990; **336:** 1360–2.
7. Tielmans C, *et al.* ACE inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1991; **337:** 370–1.
8. CSM. Anaphylactoid reactions to high-flux polyacrylonitrile membranes in combination with ACE inhibitors. *Current Problems* 33 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)
9. Olbricht CJ, *et al.* Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. *Lancet* 1992; **340:** 908–9.
10. Keller C, *et al.* LDL-apheresis with dextran sulphate and anaphylactoid reactions to ACE inhibitors. *Lancet* 1993; **341:** 60–1.
11. Davidson DC, *et al.* Prevention with icatibant of anaphylactoid reactions to ACE inhibitor during LDL apheresis. *Lancet* 1994; **343:** 1575.
12. Quillen K. Hypotensive transfusion reactions in patients taking angiotensin-converting-enzyme inhibitors. *N Engl J Med* 2000; **343:** 1422–3.
13. Stumpf JL, *et al.* Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother* 2006; **40:** 699–703.
14. Wood SM, *et al.* Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *BMJ* 1987; **294:** 91–2.
15. Hedner T, *et al.* Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1992; **304:** 941–6.
16. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. *Ann Intern Med* 1992; **117:** 234–42.
17. Vleeming W, *et al.* ACE inhibitor-induced angioedema. *Drug Safety* 1998; **18:** 171–88.
18. Bas M, *et al.* Das ACE-Hemmer-induzierte Angioödem. *Laryngorhinootologie* 2007; **86:** 804–8.
19. Brown NJ, *et al.* Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther* 1996; **60:** 8–13.
20. Gibbs CR, *et al.* Angioedema due to ACE inhibitors: increased risk in patients of African origin. *Br J Clin Pharmacol* 1999; **48:** 861–5.
21. McElligott S, *et al.* Angioedema after substituting lisinopril for captopril. *Ann Intern Med* 1992; **116:** 426–7.
22. Chin HL, Buchan DA. Severe angioedema after long-term use of an angiotensin-converting enzyme inhibitor. *Ann Intern Med* 1990; **112:** 312–13.
23. Edwards TB. Adverse effects of ACE inhibitors. *Ann Intern Med* 1993; **118:** 314.
24. Chu TJ, Chow N. Adverse effects of ACE inhibitors. *Ann Intern Med* 1993; **118:** 314.
25. Adverse Drug Reactions Advisory Committee (ADRAC). Angioedema – still a problem with ACE inhibitors. *Aust Adverse Drug React Bull* 2005; **24:** 7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.htm (accessed 06/11/06)
26. Mullins RJ, *et al.* Visceral angioedema related to treatment with an ACE inhibitor. *Med J Aust* 1996; **165:** 319–21.
27. Byrne TJ, *et al.* Isolated visceral angioedema: an underdiagnosed complication of ACE inhibitors? *Mayo Clin Proc* 2000; **75:** 1201–4.
28. Decloedt E, *et al.* Cerebral angioedema associated with enalapril. *Br J Clin Pharmacol* 2009; **68:** 271–3.
29. McCabe J, *et al.* Penile angioedema associated with the use of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers. *Am J Health-Syst Pharm* 2008; **65:** 420–1.
30. Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J* 2007; **97:** 244–5.

Overdosage. There have been reports of overdosage with captopril,[1,2] enalapril,[3-6] and lisinopril.[7,8] The main adverse effect is hypotension which usually responds to supportive treatment and volume expansion. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. If hypotension persists, sympathomimetics may be given, although they are not usually required. Specific therapy with angiotensinamide (p. 1306.1) may be considered if conventional therapy is ineffective,[5,6,8] but it is not widely available. There has also been a report[9] of the successful use of naloxone after captopril overdosage.

1. Augenstein WL, *et al.* Captopril overdose resulting in hypotension. *JAMA* 1988; **259:** 3302–5.
2. Graham SR, *et al.* Captopril overdose. *Med J Aust* 1989; **151:** 111.
3. Waeber B, *et al.* Self poisoning with enalapril. *BMJ* 1984; **288:** 287–8.
4. Lau CP. Attempted suicide with enalapril. *N Engl J Med* 1986; **315:** 197.
5. Jackson T, *et al.* Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; **341:** 703.
6. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; **40:** 103–4.
7. Dawson AH, *et al.* Lisinopril overdose. *Lancet* 1990; **335:** 487–8.
8. Trilli LE, Johnson KA. Lisinopril overdose and management with intravenous angiotensin II. *Ann Pharmacother* 1994; **28:** 1165–8.
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; **20:** 1125–7.

Precautions

ACE inhibitors are usually contra-indicated in patients with aortic stenosis or outflow tract obstruction (but see below). They should not generally be used in patients with renovascular disease or suspected renovascular disease, but are occasionally necessary for severe resistant hypertension in such patients, when they should only be given with great caution and under close specialist supervision. The elderly, or patients with peripheral vascular diseases or generalised atherosclerosis, may be at high risk because they may have clinically silent renovascular disease. Renal function should be assessed in all patients before use of ACE inhibitors and should be monitored during therapy. Patients with existing renal disease or taking high doses should be monitored regularly for proteinuria. Regular white blood cell counts may be necessary in patients with collagen vascular disorders, such as SLE and scleroderma, or in patients also given immunosuppressive therapy, especially when they also have impaired renal function. ACE inhibitors should be used with caution in patients with a history of idiopathic or hereditary angioedema.

Patients with heart failure and patients who are likely to be sodium or water depleted (for example, those receiving treatment with diuretics or dialysis) may develop symptomatic hypotension during the initial stages of ACE inhibitor therapy. Treatment should therefore be started under close medical supervision, using a low dose and with the patient in a recumbent position to minimise this effect.

Anaphylactoid reactions have occurred in patients taking ACE inhibitors during haemodialysis using high-flux polyacrylonitrile membranes, during LDL-apheresis with dextran sulfate columns, and during desensitisation with wasp or bee venom (see Hypersensitivity under Adverse Effects, above).

ACE inhibitors have been associated with fetal toxicity and should not be used during pregnancy (see p. 1288.1).

Aortic stenosis. Vasodilators, including ACE inhibitors, are usually contra-indicated in obstructive cardiac disorders such as aortic stenosis since cardiac output cannot increase to compensate for systemic vasodilatation and there is a risk of severe hypotension. However, a study[1] in patients with symptomatic aortic stenosis found that enalapril was well-tolerated and improved symptoms, and a drug withdrawal study[2] in hypertensive patients with asymptomatic aortic stenosis suggested that ACE inhibitors had beneficial haemodynamic effects. Another study[3] in patients with heart failure and perceived contra-indications to ACE inhibitors (including 17.3% with aortic stenosis) found that survival was improved in those given ACE inhibitors. There is also some evidence that ACE inhibitors may slow the progression of calcific aortic stenosis, but this remains to be confirmed.[4]

1. Chockalingam A, *et al.* Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot study of Enalapril in Aortic Stenosis (SCOPE-AS). *Am Heart J* 2004; **147:** E19.
2. Jiménez-Candil J, *et al.* Effects of angiotensin converting enzyme inhibitors in hypertensive patients with aortic valve stenosis: a drug withdrawal study. *Heart* 2005; **91:** 1311–18.
3. Ahmed A, *et al.* A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. *Am Heart J* 2005; **149:** 737–43.
4. Newby DE, *et al.* Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both? *Heart* 2006; **92:** 729–34.

Breast feeding. In the UK the MHRA and Committee on Human Medicines advise that there is some evidence of transfer of ACE inhibitors into breast milk, and since, although the concentrations are unlikely to be clinically significant, there are insufficient data to exclude the possibility of profound neonatal hypertension (particularly in premature infants), these drugs should not be used during breast feeding.[1] Captopril, enalapril, or quinapril, for which there are the most data, should be avoided during the first few weeks after delivery, but may be considered once the infant is older; other ACE inhibitors should be avoided altogether in favour of drugs with better established safety profiles during breast feeding. Angiotensin II receptor antagonists should also be avoided in view of the lack of established safety profiles.

For the contrary view of the American Academy of Pediatrics that use of captopril is usually compatible with breast feeding see p. 1332.1.

1. MHRA/CHM. ACE inhibitors and angiotensin II receptor antagonists: recommendations on use during breastfeeding. *Drug Safety Update* 2009; **2** (10): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON046452&RevisionSelectionMethod=LatestReleased (accessed 19/07/10)

Diarrhoea. Several reports[1-5] have indicated that patients taking ACE inhibitors may develop life-threatening hypotension and signs of renal failure after volume depletion due to diarrhoea.

1. McMurray J, Matthews DM. Effect of diarrhoea on a patient taking captopril. *Lancet* 1985; **i:** 581.
2. Benett PR, Cairns SA. Captopril, diarrhoea, and hypotension. *Lancet* 1985; **i:** 1105.
3. McMurray J, Matthews DM. Consequences of fluid loss in patients treated with ACE inhibitors. *Postgrad Med J* 1987; **63:** 385–7.
4. Stirling C, *et al.* Diarrhoea, vomiting and ACE inhibitors: an important cause of acute renal failure. *J Hum Hypertens* 2003; **17:** 419–23.
5. McGuigan J, *et al.* Life threatening hyperkalaemia with diarrhoea during ACE inhibition. *Emerg Med J* 2005; **22:** 154–5.

Ethnicity. ACE inhibitors are less effective as antihypertensives in Afro-Caribbean black patients than in white patients. A similar difference has been reported in heart failure; in a pooled analysis[1] of the Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials, treatment with enalapril significantly reduced the risk of hospitalisation for heart failure in white patients with left ventricular dysfunction, but not in similar black patients. However, analysis[2] of the prevention arm alone showed that enalapril reduced the relative risk of disease progression to a similar extent in black and white patients.

1. Exner DV, *et al.* Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001; **344:** 1351–7.

2. Dries DL, *et al.* Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *J Am Coll Cardiol* 2002; **40:** 311–17. Correction. *ibid.*; 1019.

Hepatic cirrhosis. It has been suggested that in patients with cirrhosis, captopril could cause a marked reduction in arterial pressure and severely compromise renal function, since maintenance of glomerular filtration rate might be mediated by angiotensin II in these patients.[1] This theory was supported by a report of a reduction in glomerular filtration rate in response to a fall in mean arterial pressure in 4 patients with resistant ascites secondary to hepatic cirrhosis.[2] The fall in mean arterial pressure was associated with orthostatic hypotension and increasing encephalopathy. Severe confusion has also been reported in 2 patients with cirrhosis during treatment with captopril 6.25 to 12.5 mg three times daily.[3] Licensed product information for another ACE inhibitor, cilazapril, advises against use in patients with ascites.

1. Ring T. Captopril and resistant ascites: a word of caution. *Lancet* 1983; **ii:** 165.
2. Wood LJ, *et al.* Adverse effects of captopril in treatment of resistant ascites, a state of functional bilateral renal artery stenosis. *Lancet* 1985; **ii:** 1008–9.
3. Jørgensen F, *et al.* Captopril and resistant ascites. *Lancet* 1983; **ii:** 405.

Huntington's disease. The condition of a woman with Huntington's disease deteriorated dramatically during treatment with captopril and improved on withdrawal of the drug.[1]

1. Goldblatt J, Bryer A. Huntington's disease: deterioration in clinical state during treatment with angiotensin converting enzyme inhibitor. *BMJ* 1987; **294:** 1659–60.

Peripheral vascular disease. Patients with peripheral vascular disease may have a high incidence of renal artery stenosis and are therefore at high risk of renal failure with ACE inhibitor therapy (see Effects on the Kidneys, p. 1286.1). Mild renal artery stenosis was found in 64 of 374 patients (17%) with peripheral vascular disease, and severe renal artery stenosis in 52 (14%); the stenosis was bilateral in 43 (12%).[1] Renal function should be carefully monitored in any patient with peripheral vascular disease who receives ACE inhibitors.

1. Salmon P, Brown MA. Renal artery stenosis and peripheral vascular disease: implications for ACE inhibitor therapy. *Lancet* 1990; **336:** 321.

Pregnancy. ACE inhibitors are contra-indicated in pregnancy as they have been associated with fetal toxicity in both *animals* and humans. The effects on the fetus appear to result from uterine blood-flow reduction and fetal hypotension due to blockade of the renin-angiotensin system, leading to impaired fetal renal function, and limited amniotic fluid output.[1] The dangers of exposure to ACE inhibitors during the second and third trimesters are clear; reports include oligohydramnios and anuria, intrauterine growth retardation, premature labour, renal failure, bony malformations, limb contractures, patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, neonatal hypotension, skull ossification defects, and fetal or neonatal death.[1-3] The association between adverse fetal outcomes and first-trimester exposures has been harder to establish, however. Although use of ACE inhibitors in the first trimester had been thought to carry a lesser risk,[4-6] a review of the available experimental and clinical data concluded that the use of ACE inhibitors should be avoided throughout pregnancy.[7] A later cohort study[8] of 29 507 infants found a significantly increased risk of major congenital malformations in 209 who had been exposed to ACE inhibitors alone in the first trimester; the FDA[9] and the MHRA[10] subsequently advised that ACE inhibitors should be avoided in those planning pregnancy, and stopped immediately upon diagnosis of pregnancy. They should only be used in pregnant women where the expected benefit clearly outweighs the risk.

1. Branch RL, Martin U. Adverse effects of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in pregnancy. *Adverse Drug React Bull* 2007; (Oct.): 943–6.
2. Hanssens M, *et al.* Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol* 1991; **78:** 128–35.
3. Piper JM, *et al.* Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol* 1992; **80:** 429–32.
4. CDC. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy—United States, Canada, and Israel, 1987-1995. *JAMA* 1997; **277:** 1193–4.
5. Lip GYH, *et al.* Angiotensin-converting-enzyme inhibitors in early pregnancy. *Lancet* 1997; **350:** 1446–7.
6. Steffensen FH, *et al.* Pregnancy outcome with ACE-inhibitor use in early pregnancy. *Lancet* 1998; **351:** 596.
7. Shotan A, *et al.* Risk of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. *Am J Med* 1994; **96:** 451–6.
8. Cooper WO, *et al.* Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; **354:** 2443–51.
9. FDA. FDA Public Health Advisory: angiotensin-converting enzyme inhibitor (ACE inhibitor) drugs and pregnancy (issued 7th June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm053113.htm (accessed 30/07/09)
10. MHRA/CHM. ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy. *Drug Safety Update* 2007; **1** (5): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033217&RevisionSelectionMethod=LatestReleased (accessed 30/07/09)

Interactions

Excessive hypotension may occur when ACE inhibitors are used with diuretics, other antihypertensives, or other agents, including alcohol, that lower blood pressure. An additive hyperkalaemic effect is possible in patients receiving ACE inhibitors with potassium-sparing diuretics, potassium supplements (including potassium-containing salt substitutes), or other drugs that can cause hyperkalaemia (such as ciclosporin or indometacin), and serum-potassium concentrations should be monitored. Potassium-sparing diuretics and potassium supplements should generally be stopped before starting ACE inhibitors in patients with heart failure. However, ACE inhibitor therapy does not obviate the possible need for potassium supplementation in patients given potassium-wasting diuretics and potassium concentrations should also be monitored in these patients. The adverse effects of ACE inhibitors on the kidneys may be potentiated by other drugs, such as NSAIDs, that can affect renal function. For advice on the use of ACE inhibitors with the angiotensin II receptor antagonist losartan, see p. 1424.3. The use of ACE inhibitors with the renin inhibitor aliskiren is generally not recommended, and should be avoided in some patients (see p. 1296.2).

General references.

1. Shionoiri H. Pharmacokinetic drug interactions with ACE inhibitors. *Clin Pharmacokinet* 1993; **25:** 20–58.
2. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–7.

Allopurinol. For reports of reactions in patients taking captopril and allopurinol, see p. 603.1.

Antacids. Use of captopril with antacids reduced the bioavailability of captopril although this did not significantly alter the effects on blood pressure and heart rate.[1] The bioavailability of fosinopril, and possibly other ACE inhibitors, may also be reduced by use with antacids.

1. Mäntylä R, *et al.* Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 626–9.

Antidiabetics. Hypoglycaemia was noted in 3 type 1 diabetics when captopril was added to their therapeutic regimen; it was also seen in a type 2 diabetic, in whom withdrawal of hypoglycaemic drugs became necessary.[1] Subsequent study suggested that the effect was due to enhanced insulin sensitivity.[1] Similar instances of a reduction in blood sugar in both non-diabetic[2] and diabetic[3] patients given enalapril have occurred. Two case-control studies in diabetic patients receiving insulin or oral hypoglycaemics suggested that patients treated with ACE inhibitors were at increased risk of developing severe hypoglycaemia.[4,5] However, other studies in diabetic patients given captopril or enalapril have failed to find any significant alterations in blood-glucose control,[6,7] and ACE inhibitors are widely used in the treatment of hypertension in diabetic patients (see p. 1251.1) and also have a role in the management of diabetic complications such as nephropathy (see Kidney Disorders under Uses, p. 1284.1).

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
2. Helgeland A, *et al.* Enalapril, atenolol, and hydrochlorothiazide in mild to moderate hypertension: a comparative multicentre study in general practice in Norway. *Lancet* 1986; **i:** 872–5.
3. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345:** 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
6. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; **i:** 1447.
7. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; **ii:** 461.

Azathioprine. Leucopenia has been reported in a patient given captopril with azathioprine; the effect did not occur when either drug was given alone.[1] In a similar report, neutropenia in a patient taking a regimen including azathioprine and captopril did not recur when captopril was reintroduced after stopping azathioprine.[2]

1. Kirchertz EJ, *et al.* Successful low dose captopril rechallenge following drug-induced leucopenia. *Lancet* 1981; **i:** 1363.
2. Edwards CRW, *et al.* Successful reintroduction of captopril following neutropenia. *Lancet* 1981; **i:** 723.

Ciclosporin. An additive hyperkalaemic effect with ACE inhibitors and ciclosporin is possible. Also, acute renal failure has been reported in 2 patients on ciclosporin after renal transplantation who were given enalapril.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; **16:** 66–9.

Digoxin. For reports of an increase in serum-digoxin concentrations during therapy with ACE inhibitors, see p. 1356.1.

Diuretics. Excessive hypotension may occur when ACE inhibitors are used with diuretics. Deterioration in renal function has also been reported with *metolazone* (see p. 1434.2) when added to captopril therapy. Severe hyperkalaemia may occur if ACE inhibitors are used with *spironolactone* (see p. 1502.2).

Epoetins. An additive hyperkalaemic effect may occur when ACE inhibitors are given with epoetins. ACE inhibitors have also been reported to antagonise the haematopoietic effects of epoetins.

General anaesthetics. Marked hypotension may occur during general anaesthesia in patients taking ACE inhibitors. In addition corrected cerebral blood flow was significantly lower in 11 patients who took captopril before general anaesthesia induced with thiopental and maintained with nitrous oxide and enflurane, than in 9 patients pretreated with metoprolol and 9 untreated controls.[1] Although there were no complications of anaesthesia associated with captopril pretreatment, stopping ACE inhibitor therapy before anaesthesia should be considered. However, others have suggested[2] that since there is no clear evidence for stopping them, ACE inhibitors may be continued with care.

1. Jensen K, *et al.* Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril. *Br J Anaesth* 1989; **62:** 321–3.
2. Anonymous. Drugs in the peri-operative period: 4 – cardiovascular drugs. *Drug Ther Bull* 1999; **37:** 89–92.

Gold salts. The nitritoid reaction (flushing, nausea, dizziness, and hypotension associated with the first weeks of injectable gold treatment) has been seen[1,2] after starting treatment with an ACE inhibitor. The patients had been given sodium aurothiomalate for at least 2 years, and the reaction occurred up to 15 months after starting the ACE inhibitor.

1. Healey LA, Backes MB. Nitritoid reactions and angiotensin-converting-enzyme inhibitors. *N Engl J Med* 1989; **321:** 763.
2. Nixon J, Pande I. Gold, nitritoid reactions and angiotensin-converting enzyme inhibitors. *Rheumatology (Oxford)* 2006; **45:** 118–19.

Interferons. Severe granulocytopenia has been reported[1] in 3 patients with mixed cryoglobulinaemia treated with interferon alfa-2a who also received ACE inhibitors. The effect was considered to be due to synergistic haematological toxicity. However, in a further report,[2] 2 patients developed only mild granulocytopenia that was reversible despite continued therapy, while a third patient retained a normal granulocyte count.

1. Casato M, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1995; **99:** 386–91.
2. Jacquot C, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1996; **101:** 235–6.

Interleukin-3. Marked hypotension occurred in 3 patients[1] taking ACE inhibitors who were given interleukin-3 after chemotherapy; blood pressure returned to normal when the ACE inhibitors were stopped.

1. Dercksen MW, *et al.* Hypotension induced by interleukin-3 in patients on angiotensin-converting enzyme inhibitors. *Lancet* 1995; **345:** 448.

Lithium. For reports of lithium toxicity in patients taking ACE inhibitors, see p. 431.2.

Muscle relaxants. For a report of severe hypotension in a patient taking lisinopril and tizanidine, see p. 2027.2.

NSAIDs. *Indometacin* and possibly other NSAIDs, including aspirin, have been reported to reduce or abolish the hypotensive action of ACE inhibitors. A similar effect has been reported[1] with *rofecoxib*. NSAIDs cause sodium and water retention and thus may attenuate the effects of various antihypertensives. It has also been suggested that part of the hypotensive effect of ACE inhibitors is prostaglandin-dependent, which might explain this interaction with drugs such as NSAIDs that block prostaglandin synthesis. However, in a double-blind study designed to assess the role of prostaglandins,[2] indometacin did not influence the hypotensive effect of captopril or enalapril, suggesting that the effects on prostaglandins are not significant.

The possibility of an interaction between low-dose *aspirin* and ACE inhibitors has caused concern.[3-5] Both ACE inhibitors and aspirin have well-established benefits in patients with both heart failure and ischaemic heart disease, but there is limited specific evidence to support their use together. Retrospective analysis of some studies of ACE inhibitors in patients with heart failure after myocardial infarction suggested that outcome was poorer in those who were also receiving aspirin, and some small studies have suggested that aspirin antagonises the haemodynamic effects of ACE inhibitors, although results have been

conflicting and the clinical relevance of these findings is not clear. Observational studies[6,7] in patients with both ischaemic and non-ischaemic heart failure have found no evidence for a detrimental effect in patients taking both aspirin and ACE inhibitors, and a systematic review[8] of long-term studies concluded that ACE inhibitors had clinically important benefits, irrespective of the use of aspirin.

The combination of NSAIDs and ACE inhibitors may also have variable effects on renal function since they act at different parts of the glomerulus.[9] When given to patients whose kidneys are underperfused, for example because of heart failure, liver cirrhosis, or haemorrhage, renal function may deteriorate. Use of NSAIDs in patients taking ACE inhibitors with diuretics may be particularly hazardous.[10] However, specific patient groups without reduced renal perfusion may benefit from combining an NSAID with an ACE inhibitor.

Indometacin, and possibly other NSAIDs, may have an additive hyperkalaemic effect.

1. Brown CH. Effect of rofecoxib on the antihypertensive activity of lisinopril. *Ann Pharmacother* 2000; **34:** 1486.
2. Gerber JG, *et al*. The hypotensive action of captopril and enalapril is not prostacyclin dependent. *Clin Pharmacol Ther* 1993; **54:** 523–32.
3. Stys T, *et al*. Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? *Arch Intern Med* 2000; **160:** 1409–13.
4. Mahé I, *et al*. Interaction between aspirin and ACE inhibitors in patients with heart failure. *Drug Safety* 2001; **24:** 167–82.
5. Olson KL. Combined aspirin/ACE inhibitor treatment for CHF. *Ann Pharmacother* 2001; **35:** 1653–8.
6. McAlister FA, *et al*. Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. *Circulation* 2006; **113:** 2572–8.
7. Masoudi FA, *et al*. Aspirin use in older patients with heart failure and coronary artery disease: national prescription patterns and relationship with outcomes. *J Am Coll Cardiol* 2005; **46:** 955–62.
8. Teo KK, *et al*. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002; **360:** 1037–43. Correction. *ibid*. 2003; **361:** 90.
9. Sturrock NDC, Struthers AD. Non-steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors: a commonly prescribed combination with variable effects on renal function. *Br J Clin Pharmacol* 1993; **35:** 343–8.
10. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Beware the triple whammy! *Aust Adverse Drug React Bull* 2006; **25:** 18. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 04/04/08)

Probenecid. Giving probenecid to 4 healthy subjects during intravenous infusion of captopril caused increases in the steady-state plasma-captopril concentration. This was thought to be because probenecid reduced the tubular secretion of captopril.[1]

1. Singhvi SM, *et al*. Renal handling of captopril: effect of probenecid. *Clin Pharmacol Ther* 1982; **32:** 182–9.

Pharmacokinetics

Most ACE inhibitors are given orally. Apart from captopril and lisinopril, they are generally prodrugs and after absorption undergo rapid metabolism by ester hydrolysis to the active diacid form; for example, enalapril is converted to enalaprilat. Metabolism occurs mainly in the liver. Excretion as active drug or active metabolite is mainly in the urine; some, such as benazeprilat and fosinoprilat, are also excreted via the biliary tract. Elimination of the diacid is polyphasic and there is a prolonged terminal elimination phase, which is considered to represent binding to the angiotensin-converting enzyme at a saturable binding site. This bound fraction does not contribute to accumulation of drug after multiple doses. The terminal elimination half-life does not therefore predict the kinetics seen with multiple dosing and the effective half-life for accumulation is the value usually quoted.

Reviews.

1. Burnier M, Biollaz J. Pharmacokinetic optimisation of angiotensin converting enzyme (ACE) inhibitor therapy. *Clin Pharmacokinet* 1992; **22:** 375–84.
2. Hoyer J, *et al*. Clinical pharmacokinetics of angiotensin converting enzyme (ACE) inhibitors in renal failure. *Clin Pharmacokinet* 1993; **24:** 230–54.
3. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; **41:** 207–24.

Acebutolol *(BAN, USAN, rINN)* ⊗

Acébutolol; Acebutololum; Asebutolol; Asebutololi; Ацебутолол.

(±)-3′-Acetyl-4′-(2-hydroxy-3-isopropylaminopropoxy)butyranilide.

$C_{18}H_{28}N_2O_4$=336.4

CAS — 37517-30-9.

ATC — C07AB04.

ATC Vet — QC07AB04.

UNII — 67P356D8GH.

Acebutolol Hydrochloride *(BANM, rINNM)* ⊗

Acébutolol, Chlorhydrate d'; Acebutolol, hidrocloruro de; Acebutolol-hidroklorid; Acebutololhydrochlorid; Acebutolol-hydrochlorid; Acebutololhydroklorid; Acebutololi Hydrochloridum; Acebutololio hidrochloridas; Acebutololu chlorowodorek; Asebutololihydrokloridi; Hidrocloruro de acebutolol; IL-17803A; M&B-17803A; Ацебутолола Гидрохлорид.

$C_{18}H_{28}N_2O_4$,HCl=372.9

CAS — 34381-68-5.

ATC — C07AB04.

ATC Vet — QC07AB04.

UNII — B025Y34C54.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Acebutolol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

USP 36: (Acebutolol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane; practically insoluble in ether. pH of a 1% solution in water is between 4.5 and 7.0. Store in airtight containers.

Uses and Administration

Acebutolol is a cardioselective beta blocker (p. 1316.3). It is reported to have some intrinsic sympathomimetic activity and membrane stabilising properties.

Acebutolol is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and cardiac arrhythmias (p. 1266.1).

Acebutolol is used as the hydrochloride, but doses are usually expressed in terms of the base; 110.8 mg of acebutolol hydrochloride is equivalent to 100 mg of base. It is generally given orally although slow intravenous injection has been used for the emergency treatment of arrhythmias.

In **hypertension** the usual initial oral dose is 400 mg once daily or 200 mg twice daily, increased if necessary after 2 weeks to 400 mg twice daily. Doses up to 1.2 g daily in divided doses may be given.

The usual oral dose for **angina pectoris** is 400 mg once daily or 200 mg twice daily, but up to 300 mg three times daily may be required for severe cases and total daily doses of 1.2 g have been given.

The usual initial oral dose for **cardiac arrhythmias** is 200 mg twice daily, increased according to response; up to 1.2 g daily in divided doses has been required.

Reduced doses may be required in patients with impaired renal function (see below). Elderly patients may also require lower maintenance doses; doses greater than 800 mg daily should be avoided.

Action. Acebutolol is generally considered to be a cardioselective beta blocker but there has been considerable controversy as to the degree of its selectivity and the selectivity of its primary metabolite, diacetolol.[1-3] In a review of beta blockers,[4] acebutolol was stated to be less cardioselective than other drugs such as atenolol or metoprolol. It was proposed[5] that this may be because the metabolite accumulates during chronic dosage to reach concentrations that affect both $beta_1$ and $beta_2$ receptors since cardioselectivity is only a relative and dose-related phenomenon. This remains uncertain and there is some evidence[6] that at least after single doses, diacetolol is actually more cardioselective than acebutolol itself.

1. Whitsett TL, *et al*. Comparison of the $beta_1$ and $beta_2$ adrenoceptor blocking properties of acebutolol and propranolol. *Chest* 1982; **82:** 668–73.
2. Nair S, *et al*. The effect of acebutolol, a beta adrenergic blocking agent, and placebo on pulmonary functions in asthmatics. *Int J Clin Pharmacol Ther Toxicol* 1981; **19:** 519–26.
3. Leary WP, *et al*. Respiratory effects of acebutolol hydrochloride: a new selective beta-adrenergic blocking agent. *S Afr Med J* 1973; **47:** 1245–8.
4. Feely J, *et al*. Beta-blockers and sympathomimetics. *BMJ* 1983; **286:** 1043–7.
5. Feely J, Maclean D. New drugs: beta blockers and sympathomimetics. *BMJ* 1983; **286:** 1972.
6. Thomas MS, Tattersfield AE. Comparison of beta-adrenoceptor selectivity of acebutolol and its metabolite diacetolol with metoprolol and propranolol in normal man. *Eur J Clin Pharmacol* 1986; **29:** 679–83.

Administration in renal impairment. The dose of acebutolol should be reduced in patients with renal impairment. It is recommended that the dose should be reduced by 50% in patients with a creatinine clearance between 25 and 50 mL/minute and by 75% in those with a creatinine clearance of less than 25 mL/minute. The dose frequency should not exceed once daily.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Concentrations of acebutolol and its active metabolite diacetolol in breast milk are higher than those in maternal plasma.[1] Pharmacological effects in the neonate, including hypotension, bradycardia, and tachypnoea, have been reported,[1] and the American Academy of Pediatrics therefore considers[2] that acebutolol should be given with caution to breast-feeding mothers.

1. Boutroy MJ, *et al*. To nurse when receiving acebutolol: is it dangerous for the neonate? *Eur J Clin Pharmacol* 1986; **30:** 737–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the liver. Six cases of hepatotoxicity associated with acebutolol were reported[1] in the USA to the FDA between 1985 and 1989. The syndrome consisted of markedly elevated transaminase concentrations, moderately elevated alkaline phosphatase concentrations, and other constitutional symptoms such as fever, nausea, abdominal pain, and headache. The duration of therapy before onset of symptoms ranged from 10 to 31 days; 5 patients received a daily dose of 400 mg; the dose was unspecified in the sixth patient. The syndrome resolved when acebutolol was stopped but reappeared in 2 patients who were rechallenged.

1. Tanner LA, *et al*. Hepatic toxicity after acebutolol therapy. *Ann Intern Med* 1989; **111:** 533–4.

Effects on respiratory function. Bronchospasm is a recognised adverse effect of beta blockers, but other respiratory disorders have also been reported. Pleurisy and pulmonary granulomas developed in a patient given acebutolol and a diuretic; acebutolol was considered to be responsible.[1] Hypersensitivity pneumonitis has also been reported in a patient taking acebutolol.[2]

1. Wood GM, *et al*. Pleurisy and pulmonary granulomas after treatment with acebutolol. *BMJ* 1982; **285:** 936.
2. Akoun GM, *et al*. Acebutolol-induced hypersensitivity pneumonitis. *BMJ* 1983; **286:** 266–7.

Hypersensitivity. See Effects on Respiratory Function, above and Lupus, below.

Lupus. An increase in antinuclear antibodies has been seen with acebutolol.[1] A report of a lupus syndrome in an elderly patient given acebutolol and clonidine described remission of symptoms when acebutolol was withdrawn, but the high antinuclear antibody titre persisted for more than 9 months.[2] Acebutolol was also reported to have caused subacute cutaneous lupus erythematosus in a 57-year-old woman. The condition had resolved completely 4 months after acebutolol was stopped.[3] The authors noted that there had been 9 previous reports of lupus in patients taking acebutolol, but only one had skin manifestations.

1. Wilson JD. Antinuclear antibodies and cardiovascular drugs. *Drugs* 1980; **19:** 292–305.
2. Hourdebaigt-Larrusse P, *et al*. Une nouvelle observation de lupus induit par acébutolol. *Ann Cardiol Angeiol (Paris)* 1985; **34:** 421–3.
3. Fenniche S,*et al*. Acebutolol-induced subacute cutaneous lupus erythematosus. *Skin Pharmacol Physiol* 2005; **18:** 230–3.

Pregnancy. Both acebutolol and its active metabolite diacetolol cross the placenta. In a study[1] in 29 pregnant women who had received acebutolol for at least one month before delivery, there was evidence of bradycardia in 12 of the 31 offspring and tachypnoea in 6.

1. Boutroy MJ, *et al*. Infants born to hypertensive mothers treated by acebutolol. *Dev Pharmacol Ther* 1982; **4** (suppl 1): 109–15.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Acebutolol is well absorbed from the gastrointestinal tract, but undergoes extensive first-pass metabolism in the liver. Although the bioavailability of acebutolol is reported to be only about 40%, the major metabolite diacetolol is active. After oral doses, peak plasma concentrations of acebutolol and diacetolol occur in about 2 and 4 hours, respectively.

Acebutolol and diacetolol are widely distributed in the body, but they have low to moderate lipid solubility and penetration into the CSF is poor. They cross the placenta and higher concentrations occur in breast milk than in maternal plasma. Acebutolol is only about 26% bound to plasma proteins, but is about 50% bound to erythrocytes. The plasma elimination half-lives for acebutolol and diacetolol are 3 to 4 hours and 8 to 13 hours respectively. Half-life values for acebutolol and diacetolol may be increased in the elderly and the half-life for diacetolol may be prolonged up to 32 hours in patients with severe renal impairment. Acebutolol and diacetolol are excreted in the urine and in the bile and may undergo enterohepatic recycling; acebutolol is also reported to be excreted directly from the intestinal wall, and more than 50% of an oral dose

can be recovered from the faeces. Acebutolol and diacetolol are removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Sectral; ***Canad.***: Rhotral†; Sectral; ***Chile***: Beloc; Grifobutol; ***Cz.***: Acecor; Apo-Acebutol; Sectral; ***Denm.***: Diasectral†; ***Fin.***: Diasectral; Espesil; ***Fr.***: Sectral; ***Ger.***: Prent†; ***Hong Kong***: Sectral; ***Israel***: Sectral; ***Ital.***: Prent; Sectral; ***Neth.***: Sectral; ***NZ***: ACB†; ***Pol.***: Abutol†; Sectral; ***Port.***: Prent; ***S.Afr.***: Butobloc; Sectral; ***Singapore***: ACB; Sectral; ***Turk.***: Prent; ***UK***: Sectral; ***USA***: Sectral.

Multi-ingredient Preparations. ***Belg.***: Sectrazide; ***Ger.***: Sali-Prent; Tredalat; ***Indon.***: Sectrazide†.

Pharmacopoeial Preparations
BP 2014: Acebutolol Capsules; Acebutolol Tablets;
USP 36: Acebutolol Hydrochloride Capsules.

Acenocoumarol *(BAN, rINN)*

Acénocoumarol; Acenocoumarolum; Acenocumarin; Acenocumarol; Acenokumarol; Asenokumarol; G-23350; Nicoumalone; Nikumalon; Аценокумарол.

(*RS*)-4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]coumarin.

$C_{19}H_{15}NO_6$=353.3

CAS — 152-72-7.

ATC — B01AA07.

ATC Vet — QB01AA07.

UNII — I6WP63U32H.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Acenocoumarol). An almost white to buff-coloured odourless or almost odourless powder. It exhibits polymorphism. Practically insoluble in water and in ether; slightly soluble in alcohol and in chloroform; dissolves in aqueous solutions of alkali hydroxides.

Uses and Administration

Acenocoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p. 1527.2). It is used in the management of thromboembolic disorders (p. 1273.2). The usual dose is 4 mg on the first day and 4 to 8 mg on the second day; subsequent maintenance doses range from 1 to 8 mg depending on the response. Acenocoumarol is given in a single dose at the same time every day.

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p. 1528.2.

Effects on the fetus. In a group of women given acenocoumarol for anticoagulant prophylaxis of mechanical heart valves during pregnancy,[1] fetal loss occurred in 13 of 61 pregnancies where oral anticoagulation was continued during the first trimester. Apart from 1 case of hydrocephalus no malformations were reported in the other neonates.

1. Meschengieser SS, *et al.* Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart* 1999; **82:** 23–6.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p. 1529.3). Specific references to interactions involving acenocoumarol can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antibacterials; antidepressants; antiepileptics; antifungals; antigout drugs; antihistamines; antineoplastics; antiplatelets; antivirals; diuretics; gastrointestinal drugs; immunosuppressants; lipid regulating drugs; sex hormones; and vaccines.

Pharmacokinetics

Acenocoumarol is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 to 3 hours of a single dose. About 60% of a dose is excreted as inactive metabolites in the urine, and about 30% via the faeces. It is extensively bound to plasma proteins, and has an elimination half-life of 8 to 11 hours. Acenocoumarol crosses the placenta; only small quantities have been detected in breast milk. It is given as a racemic mixture: the S-isomer is the more potent of the two, but it has a much shorter half-life and therefore anticoagulation activity is more dependent on the R-isomer. Both isomers are metabolised via the cytochrome P450 isoenzyme CYP2C9; the R-isomer is also metabolised by CYP1A2 and CYP2C19.

References.

1. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44:** 1227–46.
2. Beinema M, *et al.* Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. *Thromb Haemost* 2008; **100:** 1052–7.
3. Teichert M, *et al.* Genotypes associated with reduced activity of VKORC1 and CYP2C9 and their modification of acenocoumarol anticoagulation during the initial treatment period. *Clin Pharmacol Ther* 2009; **85:** 379–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acenotromb; Antitrom; Azecar; Cumarol; Dercualon; Fortonol; Hemotran; Saxion; Sintrom; ***Austria***: Sintrom; ***Belg.***: Sintrom; ***Canad.***: Sintrom; ***Chile***: Acebron; Acenox; Coarol; Isquelium; Neo-Sintrom; ***Fr.***: Mini-Sintrom; Sintrom; ***Gr.***: Sintrom; ***Hung.***: Syncumar; ***India***: Acitrom; Nistrom; ***Israel***: Sintrom; ***Ital.***: Sintrom; ***Mex.***: Sintrom; ***Pol.***: Sintrom; Syncumar; ***Port.***: Sintrom; ***Rus.***: Syncumar (Синкумар); ***Spain***: Sintrom; ***Switz.***: Sintrom; ***UK***: Sinthrome; ***Ukr.***: Sincumar (Синкумар).

Pharmacopoeial Preparations
BP 2014: Acenocoumarol Tablets.

Acetyldigoxin

Acetildigoxina; Acetyldigoxin-beta; β-Acetyldigoxinum; Acetyldigoxinum; Acetyldigoxinum Beta; β-Acetylodigoksyna; Asetyylidigoksiini; Desglucolanatoside C; Ацетилдигоксин.

3β-[(*O*-3-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide (α-acetyldigoxin); 3β-[(*O*-4-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide (β-acetyldigoxin).

$C_{43}H_{66}O_{15}$=823.0

CAS — 5511-98-8 (α-acetyldigoxin); 5355-48-6 (β-acetyldigoxin).

ATC — C01AA02.

ATC Vet — QC01AA02.

UNII — P7K44M64CW.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (β-Acetyldigoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Acetyldigoxin is a cardiac glycoside with positive inotropic activity. It has the general properties of digoxin (p. 1353.3) and has been used similarly in the management of some cardiac arrhythmias (p. 1266.1) and in heart failure (p. 1262.3). Usual oral maintenance doses for the β-isomer are 200 to 400 micrograms daily; the α-isomer has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Corotal†; Lanatilin; Novodigal†; ***Ger.***: Digostada†; Digotab†; Digox†; Novodigal; ***Gr.***: Cedigocine.

Acipimox *(BAN, rINN)*

Acipimoxum; Asipimoks; Asipimoksi; K-9321; Аципимокс.

5-Methylpyrazine-2-carboxylic acid 4-oxide.

$C_6H_6N_2O_3$=154.1

CAS — 51037-30-0.

ATC — C10AD06.

ATC Vet — QC10AD06.

UNII — K9AY9IR2SD.

Uses and Administration

Acipimox is a lipid regulating drug related to nicotinic acid (p. 2083.1). It is used to reduce cholesterol and triglycerides in the management of hyperlipidaemias (see Action, below), including type IIa, IIb, or IV hyperlipoproteinaemias.

Acipimox is given orally in a usual dose of 250 mg two or three times daily, taken with meals. Doses of up to 1200 mg daily have been used. The dose should be adjusted in renal impairment (see below).

Action. Acipimox is used in the management of hyperlipidaemias (p. 1248.1); it is a derivative of nicotinic acid and has similar effects on plasma lipoproteins but is better tolerated.[1] Its primary action is inhibition of lipolysis, leading to a reduction in circulating free fatty acids and consequently a reduction in very-low-density lipoprotein (VLDL) production in the liver. This results in a reduction of triglycerides, particularly in patients with hypertriglyceridaemia;[2] there may also be a decrease in low-density lipoprotein (LDL)-cholesterol and total cholesterol, and an increase in high-density lipoprotein (HDL)-cholesterol. Similar effects have been reported in patients with mixed hyperlipoproteinaemias, although the reduction of triglycerides and LDL-cholesterol was not significant.[3]

Reduction of free fatty acids by acipimox has several other physiological effects that have been utilised. Insulin secretion and sensitivity may be modified, and acipimox has been tried in type 2 diabetes mellitus; it improves plasma lipids and may also reduce blood-glucose concentrations,[4] and has been of benefit in patients with type A insulin resistance.[5] Beneficial effects have also been reported[6] in patients with HIV-associated lipodystrophy and insulin resistance. Growth hormone secretion is stimulated in obese subjects, and acipimox has been used in the investigation of growth hormone disorders.[7] There is also an increase in glucose uptake by the heart, and acipimox has been used to enhance myocardial imaging in ^{18}F-fluorodeoxyglucose positron-emission tomography.[8]

1. Tornvall P, Walldius G. A comparison between nicotinic acid and acipimox in hypertriglyceridaemia—effects on serum lipids, lipoproteins, glucose tolerance and tolerability. *J Intern Med* 1991; **230:** 415–21.
2. Ball MJ, *et al.* Acipimox in the treatment of patients with hyperlipidaemia: a double blind trial. *Eur J Clin Pharmacol* 1986; **31:** 201–4.
3. Otto C, *et al.* Effects of acipimox on haemorheology and plasma lipoproteins in patients with mixed hyperlipoproteinaemia. *Br J Clin Pharmacol* 1998; **46:** 473–8.
4. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; **17:** 373–80.
5. Kumar S, *et al.* Suppression of non-esterified fatty acids to treat type A insulin resistance syndrome. *Lancet* 1994; **343:** 1073–4.
6. Hadigan C, *et al.* Inhibition of lipolysis improves insulin sensitivity in protease inhibitor-treated HIV-infected men with fat redistribution. *Am J Clin Nutr* 2003; **77:** 490–4.
7. Cordido F, *et al.* Effect of acute pharmacological reduction of plasma free fatty acids on growth hormone (GH) releasing hormone-induced GH secretion in obese adults with and without hypopituitarism. *J Clin Endocrinol Metab* 1998; **83:** 4350–4.
8. Knuuti MJ, *et al.* Enhancement of myocardial [fluorine-18] fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med* 1994; **35:** 989–98.

Administration in renal impairment. Acipimox is contra-indicated in patients with a creatinine clearance below 30 mL/minute. In patients with creatinine clearance between 30 and 60 mL/minute, the interval between doses should be increased.

Adverse Effects and Precautions

Acipimox may cause peripheral vasodilatation resulting in flushing, itching, and a sensation of heat. Rash and erythema may occur. Gastrointestinal disturbances including heartburn, epigastric pain, nausea, and diarrhoea have been reported, as well as headache, malaise, myalgia, myositis, arthralgia, and dry eye. Urticaria, angioedema, and bronchospasm may occur rarely.

Acipimox is contra-indicated in patients with peptic ulcer disease. It should be used with caution in renal impairment.

Incidence of adverse effects. In a study involving 3009 hyperlipidaemic patients with type 2 diabetes,[1] adverse effects associated with acipimox occurred in 8.8%, resulting in withdrawal in 5.5% of patients. The most frequent adverse effects involved the skin (57.6%), gastrointestinal tract (25.8%), and CNS (9.7%). Labial oedema occurred in 3 cases and an urticarial eruption, collapse, and dyspnoea in another. The incidence of adverse effects was almost twice as high in females as in males, the difference being mainly due to a greater incidence of flushing, pruritus, and skin rashes. The incidence was not affected by age. There was a mean 15.3% reduction in fasting blood-glucose concentrations and an 8.5% reduction in glycosylated haemoglobin during treatment with acipimox.

1. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; **17:** 373–80.

Pharmacokinetics

Acipimox is rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur within 2 hours. It does not bind to plasma proteins and the plasma half-life is about 2 hours. It is not significantly metabolised and is excreted in the urine, largely unchanged.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Olbetam; ***Belg.***: Olbetam; ***Chile***: Olbetam; ***China***: Olbetam (乐知苹); Si Li Meng (司里蒙); YiPing (益平); ***Denm.***: Olbetam; ***Gr.***: Olbetam; ***Hong Kong***: Olbetam; ***Hung.***: Olbetam; ***Israel***: Olbetam; ***Ital.***: Olbetam; ***Neth.***: Nedios; Olbetam; ***NZ***: Olbetam; ***S.Afr.***: Olbetam; ***Singapore***: Olbetam; ***Switz.***: Olbetam; ***Thai.***: Olbetam; ***UK***: Olbetam.

Adenosine *(BAN, USAN)*

Adenocin; Adenosiini; Adenosin; Adenosina; Adénosine; Adenosinum; Adenozin; Adenozinas; Adenozyna; SR-96225; SUNY-4001; Аденозин.

6-Amino-9-β-D-ribofuranosyl-9*H*-purine.

$C_{10}H_{13}N_5O_4$=267.2

CAS — 58-61-7.

ATC — C01EB10.

ATC Vet — QC01EB10.

UNII — K72T3FS567.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Adenosine). A white, or almost white, crystalline powder. Slightly soluble in water; soluble in hot water; practically insoluble in alcohol and in dichloromethane; dissolves in dilute mineral acids.

USP 36: (Adenosine). A white, odourless crystalline powder. Slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

Stability. Adenosine was found to be stable[1] when mixed with glucose 5%, lactated Ringer's, sodium chloride 0.9%, or a mixture of glucose 5% and lactated Ringer's and stored in polypropylene syringes or PVC bags.

1. Ketkar VA, *et al.* Stability of undiluted and diluted adenosine at three temperatures in syringes and bags. *Am J Health-Syst Pharm* 1998; **55:** 466–70.

Uses and Administration

Adenosine is an endogenous adenine nucleoside that is one of the components of nucleic acids (p. 2573.1) and many coenzymes; as such, it is involved in many biological processes. It acts as an antiarrhythmic by stimulating adenosine A_1-receptors and slowing conduction through the AV node. It does not fit into the usual classification of antiarrhythmics (p. 1243.1). It also produces peripheral and coronary vasodilatation by stimulating adenosine A_2-receptors.

Adenosine is used to restore sinus rhythm in the treatment of paroxysmal supraventricular tachycardia, including that associated with the Wolff-Parkinson-White syndrome (but see Effects on the Heart, below). It is also used for the differential diagnosis of broad or narrow complex supraventricular tachycardias and in myocardial imaging.

In the treatment of **paroxysmal supraventricular tachycardia**, adenosine may be given in an initial dose of 3 mg by rapid intravenous injection. If this dose is not effective within 1 to 2 minutes, 6 mg may be given and if necessary, 12 mg after a further 1 to 2 minutes. Alternatively, an initial dose of 6 mg followed if necessary by two further doses of 12 mg at 1 to 2 minute intervals may be used, but this higher initial dose should not be given to heart transplant patients as they have an increased sensitivity to adenosine. For differential **diagnosis of supraventricular tachycardias** a similar dosage regimen is used, beginning with a dose of 3 mg followed by 6 mg and then 12 mg at 1 to 2 minute intervals if required. Doses for children with paroxysmal supraventricular tachycardia are discussed below.

In **myocardial imaging** adenosine is given by intravenous infusion in a dose of 140 micrograms/kg per minute for 6 minutes. The radionuclide is injected after 3 minutes of the infusion.

Adenosine and its derivatives, such as adenosine phosphate (p. 2430.2) and adenosine triphosphate (p. 2430.3), have been used in various metabolic disorders because of their role in biological processes. Adenosine triphosphate, as the disodium salt, has been used as an antiarrhythmic.

General references.

1. Innes JA. Adenosine use in the emergency department. *Emerg Med Australas* 2008; **20:** 209–15.
2. Eltzschig HK. Adenosine: an old drug newly discovered. *Anesthesiology* 2009; **111:** 904–15.

Administration in children. Adenosine may be given by rapid intravenous injection for the management of paroxysmal supraventricular tachycardia in children. Dosage recommendations vary. Licensed product information in the USA states that children weighing less than 50 kg, including neonates and infants, may be given an initial dose of 50 to 100 micrograms/kg; if this is not effective the dose may be increased by 50 to 100 micrograms/kg increments at 1 to 2 minute intervals until the arrhythmia is controlled or a single dose of 300 micrograms/kg is reached. Paediatric advanced cardiac life support guidelines[1] in the USA recommend an initial dose of 100 micrograms/kg (maximum 6 mg) followed by a second dose of 200 micrograms/kg (maximum 12 mg) if required, and are applicable to infants and children. In the UK, the *BNFC* recommends an initial intravenous injection of 100 micrograms/kg for children aged 1 to 12 years, or 150 micrograms/kg for neonates and infants up to 1 year; the dose may be increased by increments of 50 to 100 micrograms/kg at 1 to 2 minute intervals, to a maximum single dose of 300 micrograms/kg for neonates and 500 micrograms/kg for infants and children.

1. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support. *Circulation* 2005; **112:** (suppl 1): IV167–IV187. Also available at: http://circ.ahajournals.org/cgi/reprint/112/24_suppl/IV-167 (accessed 10/07/07)

Cardiac arrhythmias. Adenosine is used for the termination of paroxysmal supraventricular tachycardia[1-4] (p. 1266.1) and may often be the drug of choice. Bolus intravenous injection of adenosine produces a rapid response and the extremely short plasma half-life (less than 10 seconds) allows dosage titration every 1 to 2 minutes so that most episodes can be controlled within 5 minutes without the danger of drug accumulation.

Adenosine has been used successfully in pregnant women with paroxysmal supraventricular tachycardia[5-8] and cardioversion of fetal supraventricular tachycardia by direct fetal therapy with adenosine has been reported.[9,10]

Adenosine can be used for the differential **diagnosis** of broad complex tachycardia where the mechanism is unknown.[1] If the cause is supraventricular, adenosine will terminate the arrhythmia or produce AV block to reveal the underlying atrial rhythm. If the cause is ventricular, adenosine will have no effect on the tachycardia, whereas if an alternative treatment such as verapamil is given to these patients severe hypotension and cardiac arrest can occur.

1. Faulds D, *et al.* Adenosine: an evaluation of its use in cardiac diagnostic procedures, and in the treatment of paroxysmal supraventricular tachycardia. *Drugs* 1991; **41:** 596–624.
2. Rankin AC, *et al.* Adenosine and the treatment of supraventricular tachycardia. *Am J Med* 1992; **92:** 655–64.
3. Anonymous. Adenosine for acute cardiac arrhythmias. *Drug Ther Bull* 1993; **31:** 49–50.
4. Holdgate A, Foo A. Adenosine versus intravenous calcium channel antagonists for the treatment of supraventricular tachycardia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 16/02/10).
5. Mason BA, *et al.* Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol* 1992; **80:** 478–80.
6. Afridi I, *et al.* Termination of supraventricular tachycardia with intravenous adenosine in a pregnant woman with Wolff-Parkinson-White syndrome. *Obstet Gynecol* 1992; **80:** 481–3.
7. Hagley MT, Cole PL. Adenosine use in pregnant women with supraventricular tachycardia. *Ann Pharmacother* 1994; **28:** 1241–2.
8. Hagley MT, *et al.* Adenosine use in a pregnant patient with supraventricular tachycardia. *Ann Pharmacother* 1995; **29:** 938.
9. Blanch G, *et al.* Cardioversion of fetal tachyarrhythmia with adenosine. *Lancet* 1994; **344:** 1646.
10. Kohl T, *et al.* Direct fetal administration of adenosine for the termination of incessant supraventricular tachycardia. *Obstet Gynecol* 1995; **85:** 873–4.

Ischaemic heart disease. Adenosine produces coronary vasodilatation and may be used to provide a pharmacological stress in patients undergoing assessment of their ischaemic heart disease when exercise stress is inappropriate.[1] It has been used with radionuclide imaging, echocardiography, and magnetic resonance imaging.

Adenosine has also been tried as an adjunct to prevent reperfusion injury in the management of acute myocardial infarction. Improved coronary blood flow has been reported[2] with intracoronary adenosine, and both intracoronary[3] and intravenous[4] adenosine have reduced infarct size, but no improvement in clinical outcomes has been shown.[5-7] A reduction in myonecrosis has also been reported[8] with intracoronary adenosine given at the start of non-urgent percutaneous coronary interventions.

1. Ali Raza J, *et al.* Pharmacological stress agents for evaluation of ischemic heart disease. *Int J Cardiol* 2001; **81:** 157–67.
2. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; **92:** 1278–84.
3. Claeys MJ, *et al.* Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94:** 9–13.
4. Mahaffey KW, *et al.* Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999; **34:** 1711–20.
5. Ross AM, *et al.* A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005; **45:** 1775–80.
6. Quintana M, *et al.* Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis: results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003; **59:** 1–9.
7. Petronio AS, *et al.* Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J* 2005; **150:** 1015. Full version: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870305007313.pdf (accessed 26/06/07)
8. Lee C-H, *et al.* Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after non-urgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J* 2007; **28:** 19–25.

Pain. Adenosine receptors are present in the CNS and there is some evidence[1,2] that adenosine, given intravenously or intrathecally, may have an analgesic effect.

1. Hayashida M, *et al.* Clinical application of adenosine and ATP for pain control. *J Anesth* 2005; **19:** 225–35.
2. Gan TJ, Habib AS. Adenosine as a non-opioid analgesic in the perioperative setting. *Anesth Analg* 2007; **105:** 487–94.

Pulmonary hypertension. Vasodilators have been tried in persistent pulmonary hypertension of the newborn (p. 1278.2), but their use is generally restricted by lack of selectivity for the pulmonary circulation. A randomised placebo-controlled study[1] in 18 term infants with persistent pulmonary hypertension indicated that intravenous infusion of adenosine improved oxygenation without causing hypotension or tachycardia; however, the study was too small to assess any effect on mortality and/or the need for extracorporeal membrane oxygenation. Another observational study[2] in neonates with an inadequate response to inhaled nitric oxide suggested that addition of adenosine infusion also improved oxygenation.

1. Konduri GG, *et al.* Adenosine infusion improves oxygenation in term infants with respiratory failure. *Pediatrics* 1996; **97:** 295–300.
2. Ng C, *et al.* Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. *Pediatr Crit Care Med* 2004; **5:** 10–13.

Adverse Effects, Treatment, and Precautions

Adverse effects of adenosine are usually transient, lasting less than a minute, due to its very short plasma half-life. They include nausea, lightheadedness, flushing, headache, angina-like chest pain, apprehension, and dyspnoea. Bronchospasm has been reported. Like other antiarrhythmics, adenosine may worsen arrhythmias. Bradycardia and heart block have been reported. Adenosine is a vasodilator and reduces blood pressure; the larger doses given by intravenous infusion may rarely produce significant hypotension and reflex tachycardia. Infusion may also be associated with abdominal, throat, neck, and jaw discomfort. Treatment is rarely needed for adverse effects but in persistent cases aminophylline or theophylline may be given.

Adenosine is contra-indicated in patients with second- or third-degree AV block or in those with sick sinus syndrome (unless they have a pacemaker) and should be avoided or used with caution in patients with QT prolongation since torsade de pointes has occurred very rarely. It is also contra-indicated in severe hypotension, in decompensated heart failure, and asthmatic subjects and those with chronic obstructive pulmonary disease. Intravenous infusion of adenosine should be used with caution in patients who may develop hypotensive complications such as those with autonomic dysfunction, pericarditis, or stenotic valvular heart disease. Patients with recent heart transplantation may have increased sensitivity to the cardiac effects of adenosine.

Use of the *University of Wisconsin solution* [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)] for the hypothermic storage of kidneys before transplantation has been associated with bradycardia, prolonged PR intervals, and heart block.[1,2] The solution contains hetastarch, allopurinol, glutathione, and adenosine. The adenosine was considered to be the arrhythmogenic factor. Some centres had used the solution to flush kidneys before implantation,[2] a use for which it was never intended.[3] When used properly the adenosine in solution is catabolised to hypoxanthine and inosine, which do not cause cardiac problems, but this takes some time in hypothermic conditions.[3]

1. Prien T, *et al.* Bradyarrhythmia with University of Wisconsin preservation solution. *Lancet* 1989; **i:** 1319–20.
2. Vanrenterghem Y, *et al.* University of Wisconsin preservation solute and bradyarrhythmia. *Lancet* 1989; **ii:** 745.
3. Belzer FO. Correct use of University of Wisconsin preservation solution. *Lancet* 1990; **335:** 362.

Effects on the heart. Like most antiarrhythmics, adenosine can worsen arrhythmias, and both bradyarrhythmias and tachyarrhythmias have been reported.[1] Atrial fibrillation may develop in patients given adenosine for paroxysmal supraventricular tachycardia, and in a prospective study[2] occurred in 12% of 200 patients. Although most arrhythmias are of minor importance, ventricular arrhythmias and haemodynamic compromise have been reported[3,4] in patients given adenosine for presumed supraventricular tachycardia who were later discovered to have Wolff-Parkinson-White syndrome. Fatal cardiac arrest has also occurred[5] after the use of adenosine for arrhythmias in 2 patients with underlying cardiopulmonary disorders.

There have also been reports[6,7] of myocardial infarction in patients with ischaemic heart disease given adenosine during stress imaging.

For arrhythmias associated with the use of adenosine in organ preservation solutions see above.

1. Mallet ML. Proarrhythmic effects of adenosine: a review of the literature. *Emerg Med J* 2004; **21:** 408–10.

2. Strickberger SA, *et al.* Adenosine-induced atrial arrhythmia: a prospective analysis. *Ann Intern Med* 1997; **127:** 417–22.
3. Exner DV, *et al.* Proarrhythmia in patients with the Wolff-Parkinson-White syndrome after standard doses of intravenous adenosine. *Ann Intern Med* 1995; **122:** 351–2.
4. Nagappan R, *et al.* Potential dangers of the Valsalva maneuver and adenosine in paroxysmal supraventricular tachycardia—beware pre-excitation. *Crit Care Resusc* 2002; **4:** 107–11.
5. Haynes BE. Two deaths after prehospital use o f adenosine. *J Emerg Med* 2001; **21:** 151–4.
6. Polad JE, Wilson LM. Myocardial infarction during adenosine stress test. Abstract: *Heart* 2002; **87:** 106. Full version: http://heart.bmj.com/cgi/reprint/87/2/e2.pdf (accessed 10/07/07)
7. Reyes E, *et al.* Acute myocardial infarction during adenosine myocardial perfusion imaging. *J Nucl Cardiol* 2004; **11:** 97–9.

Effects on the respiratory system. Acute exacerbation of asthma can be provoked by inhalation of adenosine. Bronchospasm has also been reported in patients with asthma[1,2] or a history of asthma[3] given adenosine intravenously and bronchospasm followed by respiratory failure in a patient with obstructive pulmonary disease.[4] Respiratory arrest has also been reported in an asthmatic patient.[5]

1. DeGroff CG, Silka MJ. Bronchospasm after intravenous administration of adenosine in a patient with asthma. *J Pediatr* 1994; **125:** 822–3.
2. Drake I, *et al.* Bronchospasm induced by intravenous adenosine. *Hum Exp Toxicol* 1994; **13:** 263–5.
3. Hintringer F, *et al.* Supraventricular tachycardia. *N Engl J Med* 1995; **333:** 323.
4. Burkhart KK. Respiratory failure following adenosine administration. *Am J Emerg Med* 1993; **11:** 249–50.
5. Patton JW, Sharma GK. Adenosine-induced respiratory arrest in an asthmatic patient. *South Med J* 2008; **101:** 328–9.

Migraine. A 35-year-old man with a history of migraine developed symptoms identical to those of his usual episodes of migraine immediately after 2 intravenous bolus doses of adenosine.[1]

1. Brown SGA, Waterer GW. Migraine precipitated b y adenosine. *Med J Aust* 1995; **162:** 389–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adenosine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Dipyridamole inhibits adenosine uptake and therefore may potentiate the action of adenosine; if use of the two drugs is essential the dosage of adenosine should be reduced. Theophylline and other xanthines are competitive antagonists of adenosine. The risk of AV block may be increased if adenosine is used with other drugs that slow AV conduction.

Pharmacokinetics

Intravenous adenosine is rapidly taken up by an active transport system into erythrocytes and vascular endothelial cells where it is metabolised to inosine and adenosine monophosphate. The plasma half-life is less than 10 seconds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Adenocor; Adenoscan; ***Belg.***: Adenocor; ***Braz.***: Adenocard; ***Canad.***: Adenocard; Adenoscan†; ***Chile***: Tricor; ***China***: Adenocor (艾吉伴); Ai Duo (艾朵); Ai Wen (艾文); Xin Yi (欣颐); ***Cz.***: Adenocor; ***Denm.***: Adenocor; ***Fin.***: Adenocor; Adenoscan†; ***Fr.***: Adenoscan; Krenosin; ***Ger.***: Adenoscan; Adrekar; ***Gr.***: Adenocor; Adenoscan; ***Hong Kong***: Adenoscan; ***Hung.***: Adenocor; ***India***: Adenocor; Adenoject; Cadsine; Carnosin; ***Irl.***: Adenocor; Adenoscan†; ***Israel***: Adenocor; ***Ital.***: Adenoscan; Krenosin; ***Jpn***: Adenoscan; ***Malaysia***: Adenocor; ***Mex.***: Krenosin; Pisdeno; ***Neth.***: Adenocor; Adenoscan; ***Norw.***: Adenocor†; ***NZ***: Adenocor; ***Philipp.***: Cardiovert; ***Pol.***: Adenocor; ***Port.***: Adenocor; Adenoscan; ***Rus.***: Vita-Iodurol (Вита-иодурол); ***S.Afr.***: Adenocor; ***Singapore***: Adenocor; Adenoscan; ***Spain***: Adenocor; Adenoscan; ***Switz.***: Krenosine; ***Thai.***: Adenocor; ***UK***: Adenocor; Adenoscan; ***USA***: Adenocard; Adenoscan.

Multi-ingredient Preparations. ***Austria***: Vita-Gerin; ***Braz.***: Anekron; Biohepax†; Enterofigon; Epativan; Epocler; Hepatox; Necro B6; ***Gr.***: Collyre Vitaphakol; Suprin; ***Hong Kong***: Vitacic†; ***Mon.***: Vitacic; ***Philipp.***: Godex†; Mitodex; ***Rus.***: Oftan Catachrom (Офтан Катахром); ***Ukr.***: Hepadif (Гепадиф); Vita-Iodurol (Вита-Йодурол)†.

Pharmacopoeial Preparations
USP 36: Adenosine Injection.

Adrenaline *(BANM)* ⊗

Adrenaliini; Adrenalin; Adrenalina; Adrénaline; Adrenalinum; Epinefriini; Epinefrin; Epinefrina; Epinefryna; Epinephrin/Adrenalin; Epinephrine (rINN); Epinephrine (BAN); Épinéphrine; Epinephrinum; Epirenamine; Levorenin; Suprarenin; Эпинефрин.

(*R*)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol.

$C_9H_{13}NO_3$=183.2

CAS — 51-43-4.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

UNII — YKH834O4BH.

NOTE. Endogenous adrenaline and the monograph substance are the laevo-isomer.

ADN and EPN are codes approved by the BP 2014 for use on single unit doses of eye drops containing adrenaline where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes the racemic substances Racepinephrine (Racepinefrine (*rINN*)) and Racepinephrine Hydrochloride (Racepinefrine Hydrochloride (*rINNM*)).

Ph. Eur. 8: (Adrenaline). A white or almost white crystalline powder, becoming coloured on exposure to air and light. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in hydrochloric acid. Store under nitrogen. Protect from light.

USP 36: (Epinephrine). A white to practically white, odourless, microcrystalline powder or granules, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonia water or alkali carbonates. Very slightly soluble in water and in alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Adrenaline Acid Tartrate *(BANM)* ⊗

Adrenaliinitartraatti; Adrenaline Bitartrate; Adrenaline Tartrate; Adrénaline, Tartrate d'; Adrenalini Bitartras; Adrenalini Tartras; Adrenalinii Tartras; Adrenalinium Hydrogentartaricum; Adrenalino tartratas; Adrenalin-tartarát; Adrenalintartrat; Bitartrato de adrenalina; Bitartrato de epinefrina; Epinefrina, bitartrato de; Epinefrin-tartarát; Epinefryny wodorowinian; Epinephrine Acid Tartrate (BANM); Epinephrine Bitartrate (rINNM); Épinéphrine, Bitartrate d'; Epinephrine Hydrogen Tartrate; Epinephrinhydrogentartrat/Adrenalinhydrogentartrat; Epinephrini Bitartras; Epinephrini Tartras; Epirenamine Bitartrate; Эпинефрина Битартрат.

$C_9H_{13}NO_3,C_4H_6O_6$=333.3

CAS — 51-42-3.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

UNII — 30Q7KI53AK.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Adrenaline Tartrate; Adrenaline Acid Tartrate BP 2014; Epinephrine Acid Tartrate BP 2014). A white to greyish-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably in a sealed tube under vacuum or under an inert gas. Protect from light.

USP 36: (Epinephrine Bitartrate). A white, or greyish-white or light brownish-grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 3 of water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its solutions in water are acid to litmus, having a pH of about 3.5. Store in airtight containers. Protect from light.

Stability. Studies on the stability of adrenaline injections.

1. Taylor JB, *et al.* Effect of sodium metabisulphite and anaerobic processing conditions on the oxidative degradation of adrenaline injection BP [1980]. *Pharm J* 1984; **232:** 646–8.
2. Stepensky D *et al.* Long-term stability study of L-adrenaline injections: kinetics of sulfonation and racemization pathways of drug degradation. *J Pharm Sci* 2004; **93:** 969–80.

Adrenaline Hydrochloride *(BANM)* ⊗

Adrenalin Hidroklorür; Epinefrina, hidrocloruro de; Épinéphrine, Chlorhydrate d'; Epinephrine Hydrochloride (BANM); Epinephrine Hydrochloride (rINNM); Epinephrini Hydrochloridum; Hidrocloruro de epinefrina; Эпинефрина Гидрохлорид.

$C_9H_{13}NO_3$,HCl=219.7

CAS — 55-31-2.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

UNII — WBB047OO38.

Uses and Administration

Adrenaline is an endogenous substance that is produced in the adrenal medulla and has important physiological effects. It is also used pharmacologically as a direct-acting sympathomimetic (see p. 1507.3). It is a potent agonist at both alpha and beta adrenoceptors, although the effect on beta adrenoceptors is more marked, particularly at lower doses. These properties explain many aspects of its pharmacology, although the reflex compensating responses of the body also modulate its effects.

The major effects of adrenaline are dose-related and include:

- increased speed and force of cardiac contraction (with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with higher doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha receptors increases peripheral resistance)
- increased blood flow to skeletal muscle (reduced with higher doses); reduced blood flow in the kidneys, mucosa, and skin; little direct effect on cerebral blood flow
- relaxation of bronchial smooth muscle
- hyperglycaemia and markedly increased oxygen consumption due to metabolic effects

Adrenaline has an important role in advanced cardiac life support and in anaphylaxis and anaphylactic shock (for details of dosing, see p. 1293.1 and p. 1293.2). Adrenaline has been used in the treatment of acute asthma but more selective drugs are available, and it has no role in the chronic management of asthma (p. 1195.2). It has been given by nebulisation in severe croup (p. 1603.3). Other uses include the control of minor bleeding from the skin and mucous membranes, the management of open-angle (simple) glaucoma (p. 1999.1), and use as an adjunct to local anaesthesia (p. 1980.1).

Adrenaline is usually given b y intramuscular injection, although it may also be given subcutaneously. In extreme emergencies, where a more rapid effect is required, adrenaline may be given as a dilute solution (typically 1 in 10 000) by slow intravenous injection or by slow intravenous infusion. Alternatively, if intravenous access cannot be obtained, it may also be given by the intraosseous (usually into the marrow of the tibia) or endotracheal routes. Adrenaline has sometimes been injected directly in the heart but current guidelines for the management of cardiac emergencies recommend intravenous injection; this may be into a central vein or peripherally, but in the latter case should be followed by 20 mL of intravenous fluid. Adrenaline may also be applied topically or given by inhalation. Aqueous solutions of adrenaline are usually prepared using the acid tartrate or the hydrochloride but the dosage is generally stated in terms of the equivalent content of adrenaline. Adrenaline acid tartrate 1.8 mg or adrenaline hydrochloride 1.2 mg is equivalent to about 1 mg of adrenaline.

Adrenaline relaxes the bronchial musculature and has sometimes been injected subcutaneously or intramuscularly in the management of **acute asthmatic attacks**. However, in general, the use of adrenaline in asthma has been superseded by beta$_2$ agonists, such as salbutamol, which can alleviate bronchospasm with fewer effects on the heart. If adrenaline is to be used, the adult dose is 0.3 to 0.5 mL of a 1 in 1000 aqueous solution (300 to 500 micrograms); children have received 0.01 mL/kg (10 micrograms/kg) to a maximum of 0.5 mL (500 micrograms). Adrenaline and racepinefrine (racemic adrenaline) have also been inhaled for bronchodilatation.

Adrenaline is often added to **local anaesthetics** to retard diffusion and limit absorption, to prolong the duration of effect, and to lessen the danger of toxicity. A concentration of 1 in 200 000 (5 micrograms/mL) is usually used; adrenaline should not be added when procedures involve digits, ears, nose, penis, or scrotum because of the risk of ischaemic tissue necrosis. A concentration of up to 1 in 80 000 (12.5 micrograms/mL) may be used in dental preparations where the total dose given is small.

Adrenaline constricts arterioles and capillaries and causes blanching when applied locally to mucous membranes and exposed tissues. It is used as an aqueous solution in strengths up to a 1 in 1000 dilution to check capillary **bleeding**, epistaxis, and bleeding from superficial wounds and abrasions, but it does not stop internal haemorrhage. It is usually applied as a spray or on pledgets of cotton wool or gauze.

In ophthalmology, adrenaline solutions of 0.5%, 1%, or 2% have been used as eye drops to reduce intra-ocular pressure in open-angle **glaucoma** and ocular hypertension

but other drugs are now preferred. An adrenaline borate complex (epinephryl borate) has also been used.

Advanced cardiac life support. Adrenaline has an important role in advanced cardiac life support (see Cardiac Arrest, p. 1268.3) since, through its alpha agonist effects, it causes peripheral vasoconstriction, thus increasing myocardial and cerebral blood flow. This should improve the efficacy of cardiopulmonary resuscitation or basic life support procedures, although there is no clinical study evidence for benefit.[1] Depending on the arrhythmia that has led to cardiac arrest, treatment starts with cardiopulmonary resuscitation and defibrillation. If these measures fail to restore a conventional rhythm, the next step involves the use of adrenaline.

For **adults**, adrenaline is given in a 1-mg dose, ideally intravenously into a central vein. If such venous access is not practicable adrenaline may be given through a peripheral vein followed by a flush of 20 mL or more of sodium chloride injection; however, the response is slower than with central venous injection. This intravenous 1-mg dose may be given about every 3 to 5 minutes[2-5] in further cycles of cardiopulmonary resuscitation and, if necessary, shocks. A higher dose of 5 mg or 100 micrograms/kg has been given but there is insufficient evidence of benefit and this is no longer recommended. The length of time that a resuscitation attempt should continue is a matter of judgement, but in most cases recovery is unlikely to occur after 20 to 30 minutes, although for persistent ventricular fibrillation or tachycardia, or where the cause is hypothermia or drug intoxication, a longer attempt is reasonable.

The initial dose of 1 mg is reported to be based on the dose that was given by intracardiac injection, so it would be expected that a higher dose would be required for intravenous use. Although myocardial and cerebral perfusion are increased more with higher doses, a meta-analysis[6] of studies in adults found no evidence that this gave any survival benefit.

The intravenous dose for **children** is 10 micrograms/kg.[3-5] Higher doses of 100 or 200 micrograms/kg have been used for the second and subsequent doses; however, as with adults, the use of the higher dose is not routinely recommended and both retrospective[7] and prospective[8] studies have found no improvement in outcome.

The intraosseous route is a practicable alternative to intravenous injection for adults as well as for children; doses are identical to those given intravenously.[3-5] Alternatively, adrenaline can be given to children through the endotracheal tube that will have been inserted, but only if the intravenous or intraosseous route is unavailable. Doses of 100 micrograms/kg have been suggested.[3,4] The adrenaline solution should be diluted and administered deeply using a catheter; several rapid ventilations or inflations should follow. It is recognised that the endotracheal route is imperfect[2-4] and some workers consider it to be ineffective.[9]

Although covering a somewhat different clinical situation some guidelines also include resuscitation of newborn infants (during the first few hours after birth).[2-5] Adrenaline may be used when the heart rate remains below 60 beats/minute despite adequate ventilation and chest compression. The dose of adrenaline is 10 to 30 micrograms/kg given intravenously (generally into the umbilical vein) or by intraosseous injection. If neither of these routes are available, it may be given via the endotracheal tube; standard doses are probably ineffective[10] and doses of up to 100 micrograms/kg may be required, although there is little evidence to support this.[2-4]

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2. The International Liaison Committee on Resuscitation (ILCOR). 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2010; **122** (suppl 2): S249–S638. Also available at: http://circ.ahajournals.org/content/vol122/16_suppl_2/ (accessed 21/01/11) Also published in: *Resuscitation* 2010; **81** (suppl 1): e1–e332. Also available at: http://www.resuscitationjournal.com/issues?issue_key=S0300-9572%2810%29X0010-7 (accessed 21/01/11)
3. The American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; **122** (suppl 3): S639–S946. Also available at: http://circ.ahajournals.org/content/vol122/18_suppl_3/ (accessed 21/01/11)
4. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2010. *Resuscitation* 2010; **81:** 1219–1451. Also available at: http://www.cprguidelines.eu/2010 (accessed 07/02/11)
5. Resuscitation Council (UK). 2010 Resuscitation Guidelines. Available at: http://www.resus.org.uk/pages/GL2010.pdf (accessed 21/01/11)
6. Vandycke C, Martens P. High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis. *Resuscitation* 2000; **45:** 161–6.
7. Carpenter TC, Stenmark KR. High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest. *Pediatrics* 1997; **99:** 403–8.
8. Perondi MBM, *et al*. A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. *N Engl J Med* 2004; **350:** 1722–30.
9. McCrirrick A, Monk CR. Comparison of i.v. and intra-tracheal administration of adrenaline. *Br J Anaesth* 1994; **72:** 529–32.
10. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics* 2006; **118:** 1028–34.

Anaphylaxis and anaphylactic shock. Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction, characterised by the rapid onset of respiratory and/or circulatory problems, and usually associated with skin and mucosal changes.[1-8] It occurs when exposure to a trigger causes either an allergic reaction, most commonly involving IgE-mediated activation of basophils and mast cells, or a non-allergic (previously termed 'anaphylactoid') reaction, where the trigger has a direct action on the basophils and mast cells. In both cases this leads to the systemic release of inflammatory mediators.[2,4-10] The two forms of resulting reaction may be equally severe, and treatment is the same regardless of pathophysiology.

Many trigger substances may cause anaphylaxis, but those most commonly implicated are foods, drugs, and insect venom.[1-4,6-8,11] In a minority of cases, the cause is idiopathic, unidentifiable, or requires a co-trigger such as exercise. The signs and symptoms of anaphylaxis may closely resemble other syndromes such as hereditary angioedema, and the history is important in aiding diagnosis: usually an attack closely follows exposure to a trigger,[1,6-8,11] although in rare cases reactions may be delayed.[2,4] Common early signs and symptoms of anaphylaxis are skin and mucosal changes such as erythema, urticaria, and angioedema (seen in about 80% of reactions), rhinitis, conjunctivitis, anxiety, confusion, and gastrointestinal disturbances such as abdominal pain, vomiting, and diarrhoea.[1-3,6,8,9,11] Stridor and hoarseness of voice indicate airway obstruction, which is caused by pharyngeal and laryngeal oedema. Bronchoconstriction may occur, and can be particularly severe and difficult to treat in asthmatics. Hypotension and shock may develop from myocardial depression, vasodilatation, and capillary leak. Ultimately, cardiovascular and respiratory collapse may lead to death, with a case fatality of about 0.65 to 2%.[8] Risk of death is increased in asthma, particularly if poorly controlled.[1,5,7,8] Other (especially cardiovascular) diseases, and certain medications such as ACE inhibitors, may also increase severity.[4,5,7]

Anaphylaxis is a medical emergency and prompt treatment is vital. *Adrenaline* is the most important drug used in anaphylaxis. It acts on alpha-receptors to reverse peripheral vasodilatation and reduce oedema, and on beta-receptors to dilate the airways, increase force of myocardial contraction, suppress leukotriene and histamine release, and inhibit mast cells.[1,2,8,12] Early use is essential.[1,2,5,9,11,12] Delay has been associated with biphasic reactions and fatality,[4-6,8,9,12] and some have suggested that if the diagnosis or severity of a reaction is in doubt, it may be preferable to err on the side of caution and inject adrenaline rather than waiting too long.[8-12] There are no absolute contra-indications to its use. Adverse effects are rare and usually associated with the intravenous route;[1,2,6,10,11] although adrenaline may rarely cause cardiac ischaemia and arrhythmias, these may also be caused by anaphylaxis itself.[1,6,13]

In early anaphylaxis, adrenaline is given by *intramuscular* injection into the mid-point of the anterolateral thigh.[1-6,8,10-12] The subcutaneous and inhaled routes have also been used, but are not generally recommended due to their unfavourable pharmacokinetics.[1,2] Novel routes of administration, such as the sublingual route, are also under investigation.[4,6,8] Absorption of adrenaline from the intramuscular route is rapid, occurring within about 8 minutes. Pre-filled auto-injectors for intramuscular use may be given to those at high risk of developing anaphylactic shock, allowing patients to self-administer initial emergency treatment; however, they should still seek medical assistance as additional treatment may be required.

The dose of adrenaline for intramuscular injection is usually 300 to 500 micrograms as 0.3 to 0.5 mL of a 1 in 1000 (1 mg/mL) solution; this may be repeated at 5 to 15 minute intervals until improvement occurs.

Various intramuscular adrenaline dosage regimens have been suggested for children. A dose of 10 micrograms/kg, or the following age-specific intramuscular doses, given as a 1 in 1000 (1 mg/mL) solution, have been used:

- under 6 months: 50 micrograms (0.05 mL)
- 6 months to 6 years: 120 micrograms (0.12 mL)
- 6 to 12 years: 250 micrograms (0.25 mL)

However, to simplify dosing, particularly where auto-injectors are used, the UK Resuscitation Council[1] now recommends an intramuscular dose of 150 micrograms (0.15 mL) for children aged 6 years and younger (including those under 6 months) and 300 micrograms (0.3 mL) for those aged over 6 years; children aged over 12 years may be given 300 or 500 micrograms depending on body size and pubertal status. This may represent a relative overdose in children aged under 6 months but this may be considered acceptable if it allows an auto-injector to be used.

As anaphylaxis progresses the intravascular volume becomes depleted, leading to shock. At this stage it is probably necessary to give adrenaline *intravenously*, since absorption from other routes will be compromised; however, this route is hazardous and should only be used in life-threatening situations, and by those experienced in its use. The general principles used in the management of hypovolaemia and hypotension in shock are outlined on p. 1279.3.

A dilute solution of 1 in 10 000 (100 microgram/mL) is used intravenously with cardiac monitoring, although this may be further diluted to 1 in 100 000 (10 micrograms/mL) to allow for greater accuracy in titrating very small doses. The UK Resuscitation Council[1] recommends a slow intravenous injection of 50 micrograms (0.5 mL of the 1 in 10 000 solution), repeated according to response. Higher doses of 100 to 200 micrograms have been used in patients under anaesthesia, for whom intensive monitoring and life support are immediately available.[3,9,14] If repeated injections are required, an infusion may be started at a rate of 1 to 4 micrograms/minute.[1,3,9,10] If intravenous access is delayed or impossible, adrenaline and fluids may be given via the intra-osseous route.[1,8,11]

In children, intravenous therapy should only be used in specialist paediatric settings. The *BNFC* recommends slow intravenous injections of the 1 in 10 000 (100 micrograms/mL) solution in single doses not exceeding 50 micrograms, although some children may require as little as 1 microgram/kg (0.01 mL/kg). Again, if multiple doses are required, an intravenous infusion should be considered.

Ancillary interventions aid management,[1-6,8,9,11] although they should not delay use of adrenaline. Where possible, the likely allergen should be removed, for example, by scraping away an embedded insect sting or stopping a drug or blood transfusion. High flow oxygen should be given as soon as available, and the airways secured if necessary. Intravenous fluids should be given rapidly to restore volume. Cardiac arrest should be managed using a standard protocol (see Cardiac Arrest, p. 1268.3), including appropriate doses of adrenaline as required.[2,3,8,9,11]

The use of *antihistamines* in the management of anaphylaxis has been a matter of some debate.[15] During acute treatment they are unlikely to be life-saving, and should never be used alone.[1,5,6,8,11,15] However, some advocate an intramuscular or slow intravenous injection of an H_1-antagonist such as chlorphenamine, given after adrenaline and repeated over the next 24 to 48 hours, to counter histamine-mediated vasodilatation and bronchoconstriction[1,11] and relieve angioedema, pruritus, and urticaria.[15] Addition of intravenous H_2-antagonists such as ranitidine has also been suggested.[2,3,15]

Intravenous *corticosteroids* have little place in the immediate management of anaphylaxis since their beneficial effects are delayed for several hours. However, in severely ill patients early use of intramuscular or slow intravenous hydrocortisone may avert late sequelae[2,5,9,11] and help prevent or shorten protracted reactions,[1,11] although it is doubtful whether it prevents biphasic attacks.[9,11] Corticosteroids may be particularly useful in patients with an asthmatic component.[1,2,5,11]

Bronchodilators such as salbutamol, ipratropium, aminophylline, and magnesium sulfate, given by nebulisation or, if necessary, intravenously, are useful in those with bronchospasm.[1,5,6,8,9]

Some patients are refractory to adrenaline, especially those taking beta blockers, and *alternative vasopressors and inotropes* such as glucagon, noradrenaline, metaraminol, salbutamol, terlipressin, and vasopressin have been used successfully, while *atropine* may be useful in those who develop bradycardia.[1-3,5,9,10,14,16,17]

Biphasic reactions occur in up to 20% of cases and it is difficult to identify those at risk, so patients should be observed for at least 4 to 6 hours after an attack.[1,2,8,11] On discharge, a 3-day course of oral antihistamine and corticosteroid therapy may be considered for suppression of urticaria and prevention of further attacks.[1,11] Measuring mast cell tryptase or histamine concentrations in plasma may help confirm the diagnosis,[1,4-9,11] although such tests have suboptimal specificity and sensitivity. The risk of recurrence is substantial,[1] and the identification and avoidance of triggers is paramount in the prevention of further attacks; other measures include allergen immunotherapy (see p. 2435.1), particularly in those who have reacted to bee or wasp venom.[4-6,8] Stopping beta blockers in those at risk of anaphylaxis should be considered.[1,6]

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3. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10.6: anaphylaxis. *Circulation* 2005; **112:** (suppl 1):

IV143–IV145. Available at: http://circ.ahajournals.org/cgi/content/full/112/24_suppl/IV-143 (accessed 22/03/10)
4. Simons FER. Anaphylaxis: recent advances in assessment and treatment. *J Allergy Clin Immunol* 2009; **124:** 625–36.
5. El-Shanawany T, *et al*. Clinical immunology review series: an approach to the patient with anaphylaxis. *Clin Exp Immunol* 2008; **153:** 1–9.
6. Simons FER. Anaphylaxis. *J Allergy Clin Immunol* 2010; **125** (suppl 2): S161–S181.
7. Simons FER, *et al*. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007; **120** (suppl): S2–S24.
8. Muraro A, *et al*. EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007; **62:** 857–71.
9. Dewachter P, *et al*. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009; **111:** 1141–50.
10. Kemp SF, *et al*. World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008; **63:** 1061–70.
11. Tse Y, Rylance G. Emergency management of anaphylaxis in children and young people: new guidance from the Resuscitation Council (UK). *Arch Dis Child Educ Pract Ed* 2009; **94:** 97–101.
12. Sicherer SH, Simons FE. Section on Allergy and Immunology, American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics* 2007; **119:** 638–46.
13. Simons FER. Emergency treatment of anaphylaxis. *BMJ* 2008; **336:** 1141–2.
14. Hussain AM, *et al*. Vasopressin for the management of catecholamine-resistant anaphylactic shock. *Singapore Med J* 2008; **49:** e225–e228.
15. Andreae DA, Andreae MH. Should antihistamines be used to treat anaphylaxis? *BMJ* 2009; **339:** 290–1.
16. Schummer C, *et al*. The pivotal role of vasopressin in refractory anaphylactic shock. *Anesth Analg* 2008; **107:** 620–4.
17. Rocq N, *et al*. Successful use of terlipressin in post-cardiac arrest resuscitation after an epinephrine-resistant anaphylactic shock to suxamethonium. *Anesthesiology* 2007; **107:** 166–7.

Diagnosis and testing. Long-QT syndrome is a congenital channelopathy that can cause potentially lethal arrhythmias in individuals with otherwise structurally normal hearts. At rest, the ECGs of such individuals may be normal or equivocal, and catecholamine provocation testing has been used to unmask concealed abnormalities. A bolus infusion (Shimizu protocol) or escalating infusion (Mayo protocol) of adrenaline will paradoxically lengthen the absolute QT interval in a high proportion of individuals with long-QT syndrome, and may also permit identification of specific genetic subtypes.[1-3]

1. Shimizu W, *et al*. Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* 2004; **1:** 276–83.
2. Vyas H, *et al*. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation* 2006; **113:** 1385–92.
3. Vyas H, Ackerman MJ. Epinephrine QT stress testing in congenital long QT syndrome. *J Electrocardiol* 2006; **39** (4 suppl): S107–S113.

Haemorrhage. Adrenaline has a long history of topical use to check minor bleeding. It constricts arterioles and capillaries and causes blanching. Local injection of adrenaline under endoscopic control is highly effective in controlling bleeding peptic ulcers (p. 1816.2), and is more effective if combined with other endoscopic therapies.[1] Nebulised adrenaline has been reported[2] to successfully control oropharyngeal haemorrhage.

1. Vergara M, *et al*. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 28/05/10).
2. Rowlands RG, *et al*. Novel use of nebulised adrenaline in the treatment of secondary oropharyngeal haemorrhage. *J Laryngol Otol* 2002; **116:** 123–4.

Priapism. Alpha agonists such as adrenaline may be effective in the treatment of priapism (see under Metaraminol, p. 1430.2). Low doses of dilute adrenaline solution have been given by intracavernosal injection in priapism caused by alprostadil (see p. 2353.2). Aspiration of blood followed by intracavernosal irrigation with a dilute adrenaline solution was also reported to be effective treatment for priapism in a group of young patients (age range, 3.9 to 18.3 years) with sickle-cell disease.[1]

1. Mantadakis E, *et al*. Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. *Blood* 2000; **95:** 78–82.

Respiratory-tract disorders. Nebulised adrenaline may be used to reverse airway obstruction in inflammatory disorders such as croup since it relieves inflammation and also causes bronchodilatation. Although some studies in acute viral bronchiolitis (see Respiratory Syncytial Virus Infection, p. 961.3) have shown improvement in clinical scores,[1,2] randomised studies have failed to find any difference in outcome between infants treated with adrenaline and either salbutamol[3] or placebo.[4] A systematic review[5] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients.

However, the *BNFC* states that for severe croup not effectively controlled with corticosteroids, nebulised adrenaline solution 1 in 1000 may be given with close clinical monitoring in a dose of 400 micrograms/kg (up to a maximum of 5 mg) repeated after 30 minutes if necessary. The effects of nebulised adrenaline are expected to last 2 to 3 hours.

There has also been a report[6] of the successful use of nebulised adrenaline in a 15-month-old child with airway inflammation secondary to the ingestion of sodium hypochlorite.

1. Reijonen T, *et al*. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–92.
2. Menon K, *et al*. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–7.
3. Patel H, *et al*. A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141:** 818–24.
4. Wainwright C, *et al*. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 2003; **349:** 27–35.
5. Hartling L, *et al*. Epinephrine for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 07/10/05).
6. Ziegler D, Bent G. Caustic-induced upper airway obstruction responsiveness to nebulized adrenaline. *Pediatrics* 2001; **107:** 807–8.

Adverse Effects

Adrenaline is a potent sympathomimetic and may show the adverse effects typical of both alpha- and beta-adrenoceptor stimulation (see p. 1508.2). Adverse effects such as anxiety, dyspnoea, hyperglycaemia, restlessness, palpitations, tachycardia (sometimes with anginal pain), tremors, sweating, hypersalivation, weakness, dizziness, headache, and coldness of extremities may occur even with low doses. Since adrenaline does not readily cross the blood-brain barrier, its central effects may be largely a somatic response to its peripheral effects. Overdosage may cause cardiac arrhythmias and a sharp rise in blood pressure (sometimes leading to cerebral haemorrhage and pulmonary oedema); these effects may occur at normal dosage in susceptible subjects.

Adrenaline is a potent vasoconstrictor and gangrene may occur if adrenaline-containing local anaesthetic solutions are infiltrated into digits. Extravasation of parenteral adrenaline also results in intense vasoconstriction, leading to tissue necrosis and sloughing. Topical application of adrenaline to mucosal surfaces similarly causes vasoconstriction, which may induce hypoxia leading to compensatory rebound congestion of the mucosa. Inhalation of adrenaline has been associated with epigastric pain, which has been attributed to ingestion of some of the inhalation; it can be minimised by rinsing the mouth and throat with water after inhaling.

Adrenaline eye drops may produce severe smarting, blurred vision, and photophobia on instillation; they may also leave melanin-like deposits in the cornea and conjunctiva, and this has led to obstruction of the nasolachrymal ducts. Repeated use may cause oedema, hyperaemia, and inflammation of the eyes.

Effects on the eyes. In addition to the possibility of pigment deposition and local pain (see above) adrenaline eye drops have been associated with maculopathy, particularly in aphakic eyes (those devoid of a lens).[1] In one report,[2] maculopathy was noted in 15 patients over a period of 4 years; the patients were using adrenaline eye drops containing the hydrochloride, acid tartrate, or adrenaline borate complex (epinephryl borate). Blurring and distortion of vision were followed by decreased visual acuity, and by the appearance of oedema and sometimes haemorrhage in the macular region. A few patients developed cysts near the fovea. These effects appeared within a few weeks of, or several months after, starting therapy and were usually reversible. All except 1 of the patients were aphakic, and retrospective studies have suggested that the incidence of this complication may be up to 30% in aphakic patients.[1,2]

1. Classé JG. Epinephrine maculopathy. *J Am Optom Assoc* 1980; **51:** 1091–3.
2. Kolker AE, Becker B. Epinephrine maculopathy. *Arch Ophthalmol* 1968; **79:** 552–62.

Overdosage. Solutions of racepinefrine for nebulisation have inadvertently been given intravenously, resulting in severe overdosage of adrenaline. A 13-month-old infant[1] was given the equivalent of about 327 micrograms/kg of laevo-adrenaline. Marked pallor, pulselessness, and profound bradycardia developed, but the child responded to cardiopulmonary resuscitation and was subsequently discharged with no evidence of long-term sequelae. However, a 2-year-old child[2] given the equivalent of about 1.8 mg/kg developed hypertension, tachycardia, and pulmonary oedema, followed by hypotension and subsequent renal failure, requiring transplantation. Subcutaneous overdosage with laevo-adrenaline in another child[3] led to arrhythmias and myocardial ischaemia, and there has also been a report[4] of myocardial infarction and acute renal failure in an adult after injection of the solution from an adrenaline inhaler.

1. Kurachek SC, Rockoff MA. Inadvertent intravenous administration of racemic epinephrine. *JAMA* 1985; **253:** 1441–2.
2. Dybvik T, *et al*. Accidental intravenous administration of 50 mg of racemic adrenaline in a 2-year-old boy. *Eur J Anaesthesiol* 1995; **12:** 181–3.
3. Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. *Pediatr Emerg Care* 1999; **15:** 116–18.
4. Woodard ML, Brent LD. Acute renal failure, anterior myocardial infarction, and atrial fibrillation complicating epinephrine abuse. *Pharmacotherapy* 1998; **18:** 656–8.

Treatment of Adverse Effects

As for Sympathomimetics, p. 1508.3. Adrenaline has a short duration of activity due to inactivation in the body and treatment of severe toxic reactions in hypersensitive patients or after overdose is mainly supportive.

Digital injection. Inadvertent digital injection of adrenaline from autoinjector devices may cause acute ischaemia. Phentolamine injection has been successfully used to reverse the vasoconstriction,[1] and there has also been a report[2] of the use of iloprost infusion followed by a stellate ganglion block.

1. Velissariou I, *et al*. Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen. *Emerg Med J* 2004; **21:** 387–8.
2. Barkhordarian AR, *et al*. Accidental digital injection of adrenaline from an autoinjector device. *Br J Dermatol* 2000; **143:** 1359.

Precautions

As for Sympathomimetics, p. 1508.3. Adrenaline is frequently used in emergency situations and any contra-indications are therefore relative.

Adrenaline may delay the second stage of labour and some licensed product information recommends that it should not be used during this time.

Adrenaline eye drops are contra-indicated in angle-closure glaucoma unless an iridectomy has been carried out.

Contact lenses. Adrenochrome staining of soft-contact lenses of patients using adrenaline eye drops has been reported.[1] Melanin deposits may also become locked into the lens; such deposits may be broken down by hydrogen peroxide. The prodrug, dipivefrine hydrochloride (p. 2495.1) has been used without staining soft lenses.

1. Ingram DV. Spoiled soft contact lenses. *BMJ* 1986; **292:** 1619.

Infection. An open study[1] comparing adrenaline with dopamine for cardiovascular support in 23 patients critically ill with severe sepsis or malaria suggested that use of adrenaline was limited by the development of lactic acidosis. However, it has been pointed out[2] that 20 of the patients had responded to fluids, a situation in which the use of inotropic or vasopressor support was considered questionable, and that adrenaline has been widely used in the treatment of septic shock. A further controlled study[3] found that although adrenaline led to higher lactate concentrations than noradrenaline with dobutamine, the effect was transient. Nevertheless, it has been recommended[4] that adrenaline should only be used in septic shock if other treatments are ineffective.

1. Day NPJ, *et al*. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; **348:** 219–23. Correction. *ibid.*; 902.
2. Barry B, Bodenham A. Effects of dopamine and adrenaline infusions in severe infection. *Lancet* 1996; **348:** 1099–1100.
3. Levy B, *et al*. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997; **23:** 282–7.
4. Hollenberg SM, *et al*. American College of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; **32:** 1928–48.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adrenaline as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3; adrenaline has direct alpha- and beta-agonist actions and its interactions are complex and may be hazardous. Particular caution is needed if adrenaline is given to patients taking beta blockers since severe hypertension may result; patients taking beta blockers may also have an impaired response to adrenaline if it is needed for anaphylaxis.

Local anaesthetics. It is common practice to give adrenaline with a local anaesthetic to produce vasoconstriction; the lowest effective concentration of adrenaline should be used. However, use with *cocaine* may increase the risk of

cardiac arrhythmias and particular caution is required. See p. 1990.3 for a report of severe complications with use of such a combination in otolaryngology.

Pharmacokinetics

As a result of enzymatic degradation in the gut and first-pass metabolism in the liver, adrenaline is almost totally inactive when given orally. Systemic absorption can occur after topical application for example of eye drops. Adrenaline acts rapidly after intramuscular and subcutaneous injection; the latter route is, however, sometimes considered to be slower and therefore less reliable for emergency use. Although absorption is slowed by local vasoconstriction it can be hastened by massaging the injection site.

Most adrenaline that is either injected into the body or released into the circulation from the adrenal medulla, is very rapidly inactivated by processes that include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues. The half-life of circulating adrenaline is only about 1 minute. One of the enzymes responsible for the chemical inactivation of adrenaline is catechol-*O*-methyltransferase (COMT), the other is monoamine oxidase (MAO). In general, adrenaline is methylated to metanephrine by COMT followed by oxidative deamination by MAO and eventual conversion to 4-hydroxy-3-methoxymandelic acid (formerly termed vanillylmandelic acid; VMA), or oxidatively deaminated by MAO and converted to 3,4-dihydroxymandelic acid which, in turn, is methylated by COMT, once again to 4-hydroxy-3-methoxymandelic acid; the metabolites are excreted in the urine mainly as their glucuronide and ethereal sulfate conjugates.

The ability of COMT to effect introduction of a methyl group is an important step in the chemical inactivation of adrenaline and similar catecholamines (in particular, noradrenaline). It means that the termination of the pharmacological response of catecholamines is not simply dependent upon MAO. In its role of neurotransmitter intraneuronal catecholamine (mainly noradrenaline) is, however, enzymatically regulated by MAO.

Adrenaline crosses the placenta to enter fetal circulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: EpiPen; ***Austral.***: Anapen; EpiPen; ***Austria***: Anapen; EpiPen; Suprarenin; ***Belg.***: EpiPen; ***Braz.***: Drenalin; Efrinalin; Epifrin; ***Canad.***: Anapen; Epi EZ†; Epifrin†; EpiPen; Twinject; ***Chile***: Adreject; ***Cz.***: Anapen; EpiPen; Twinject; ***Denm.***: EpiPen; Jext; ***Fin.***: EpiPen; Jext; ***Fr.***: Anahelp†; Anapen; ***Ger.***: Anapen; Fastjekt; InfectoKrupp; Suprarenin; ***Gr.***: Anapen; Epifrin; EpiPen; ***Hung.***: Anapen; EpiPen; Tonogen; ***India***: Adrena; Naline; ***Irl.***: Anapen; EpiPen†; Jext; ***Israel***: EpiPen; ***Ital.***: Fastjekt; ***Malaysia***: EpiPen†; ***Mex.***: Pinadrina†; ***Neth.***: Anapen; EpiPen; Jext; ***Norw.***: EpiPen; Jext; ***NZ***: Anapen; EpiPen; ***Philipp.***: Adrenin; ***Pol.***: Anapen; EpiPen; Fastjekt; ***Port.***: Anapen; EpiPen†; Twinject; ***S.Afr.***: Adrenotone; Ana-Guard†; EpiPen; Eppy†; Simplene†; ***Singapore***: Anapen; EpiPen; ***Spain***: Adreject†; Altellus; Epiject†; Jext; ***Swed.***: Anapen; EpiPen; Jext; ***Switz.***: Anapen; EpiPen; Jext; ***Thai.***: EpiPen; ***UK***: Anapen; EpiPen; ***USA***: Adrenaclick; AsthmaHaler Mist; AsthmaNefrin; Auvi-Q; Epinal†; EpiPen; microNefrin†; Nephron†; Primatene Mist Suspension†; Primatene Mist†; S-2.

Multi-ingredient Preparations. ***Arg.***: Asmopul; Yanal; ***Austral.***: Rectinol; ***Canad.***: Sil Trax Plus†; ***Cz.***: Avenoc†; ***Fr.***: Avenoc; ***Gr.***: Hemorroidal; ***Hung.***: Hemorid; ***India***: Brovon; ***Irl.***: Ganda†; ***Spain***: Coliriocilina Adren Astr†; Epistaxol; ***UK***: Brovon; ***USA***: Ana-Kit; Emergent-Ez.

Used as an adjunct in:. ***Arg.***: Caina G; Duracaine; Gobbicaina; Larjancaina; Lidanest; Xylocaina; ***Austral.***: Bucanest; Deltazine; Marcain; Nurocain†; Septanest; Xylocaine; ***Austria***: Neo-Xylestesin; Scandonest; Septanest; Sopira Citocartin; Ubistesin; Ultracain Dental; Xylanaest; Xylocain; ***Belg.***: Citanest; Marcaine; Xylocaine; ***Braz.***: Bupiabbott Plus; Bupstesic; Lidocabbott; Marcaina; Neocaina; Novabupi; Xylestesin; Xylocaina; ***Canad.***: Astracaine†; Citanest; Marcaine; Octocaine; Scandonest; Sensorcaine; Septanest; Ultracaine D-S; Vivacaine; Xylocaine; Zorcaine; ***China***: Primacaine Adrenaline (必兰); Scandonest (斯康杜尼); ***Cz.***: Scandonest†; Septanest S; Supracain; Ubistesin; ***Denm.***: Carbocain; Dentocaine; Marcain; Scandonest; Septanest; Septocaine; Sopira Citocartin; Ubistesin; Xylocain; Xyloplyin; ***Fin.***: Dentocaine; Marcain; Septocaine; Ubistesin; Ultracain D-Suprarenin; Xylocain; ***Fr.***: Alphacaine; Articadent; Artinibsa; Biodicaine†; Bucanest†; Deltazine; Primacaine; Scandicaine; Septanest; Ubistesin Adrenalinee; Xylocaine; Xylonor; Xylorolland; Ziacaine; ***Ger.***: Sopira Citocartin; Ubistesin; Ultracain D-S; Ultracain Suprarenin; Xylocain; Xylocitin; Xylonest; ***Gr.***: Artikamine; Ecocain; Lidonet; Lignospan; Marcaine; Optocain; Septanest; Ubistesin; Xylestesin-A; Xylestesin-S Special; Xylocaine; ***Hong Kong***: Lidocaton†; Marcain; Ubistesin; Xylestesin-A; Xylocaine; ***Hung.***: Ubistesin; Ultracain D-S; ***India***: Gesicain; Lignocad; Lignodent; Lignoloc; Lignosafe; Lignox; Lox; Xylocaine; ***Indon.***: Extracaine†; Pehacain; ***Irl.***: Espestesin; Lignospan; Marcain; Scandonest; Xylocaine; ***Israel***: Kamacaine; Lidocadren; Lignospan; Marcaine; Octocaine; Septanest; Ubistesin; ***Ital.***: Alfacaina; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Carboplyina; Carbosen; Cartidont; Citocartin; Ecocain; Lident Adrenalina; Lident Adrenor; Mepi-Mynol; Mepicain; Mepident; Mepiforan; Mepisolver; Mepivamol; Optocain; Sarticain; Scandonest; Septanest; Ubistesin; Xilo-Mynol; Xylonor; Xyloplyina; ***Malaysia***: Denkan; Marcain; ***Mex.***: Buvacaina†; Pisacaina†; Unicaine; Xylocaina; ***Neth.***: Citocartin; Lignospan; Loncarti; Marcaine; Scandicaine†; Septanest; Ubistesin; Ultracain D-S; Xylocaine; ***Norw.***: Marcain; Septocaine; Xylocain; ***NZ***: Marcain; Septanest; Topicaine; Ubistesin; Xylestesin-A; Xylocaine; ***Philipp.***: Dentocaine; Epicaine; ***Pol.***: Marcaine; ***Port.***: Alphacaine†; Artinibsa; Artinostrum; Lidonostrum; Lincaina; Meganest; Octocaine; Scandinibsa; Septanest; Ubistesin; Xilonibsa; ***Rus.***: Alphacaine (Альфакаин); Artifrin (Артифрин); Brilocaine (Брилокаин); Citocartin (Цитокартин); Primacaine Adrenaline (Примакаин С Адреналином); Septanest (Септанест); Ubistesin (Убистезин); Ultracain (Ультракаин); ***S.Afr.***: Macaine; Scandonest; Xylotox; ***Singapore***: Ubistesin; Xylestesin-A; Xylocaine; ***Spain***: Anestesia Topi Braun C/A†; Artinibsa; Inibsacain; Meganest; Octocaine; Scandinibsa; Septanest; Ubistesin; Ultracain; Xilonibsa; Xylonor Especial; ***Swed.***: Carbocain; Marcain; Septocaine; Ubistesin; Xylocain; ***Switz.***: Alphacaine; Carbostesin; Rapidocaine; Rudocain; Scandonest; Septanest; Ubistesin; Ultracaine D-S; Xylocain; Xylonest; ***Thai.***: Drocanil-A; Lidocation; Medicaine; Xylocaine; ***Turk.***: Jetokain; Jetosel; Locanest-A; Ultracain; ***UAE***: Ecocain; ***UK***: Septanest; Xylocaine; ***Ukr.***: Artifrin (Артифрин); Ultracain D-S (Ультракаин Д-С); ***USA***: Citanest; Marcaine; Octocaine; Orabloc; Sensorcaine; Septocaine; Xylocaine.

Homoeopathic Preparations. ***Canad.***: Avenoc†; Breathe More; ***Fr.***: Diabene; L 25; L 28; Santaherba; Tarentula Complexe No 71; Vespa Complexe No 46†; ***Port.***: Avenoc†; ***USA***: Estrex.

Pharmacopoeial Preparations

BP 2014: Adrenaline and Cocaine Intranasal Solution; Adrenaline Eye Drops; Adrenaline Injection; Adrenaline Solution; Bupivacaine and Adrenaline Injection; Dilute Adrenaline Injection 1 in 10,000; Lidocaine and Adrenaline Injection;

USP 36: Articaine Hydrochloride and Epinephrine Injection; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Epinephrine Bitartrate for Ophthalmic Solution; Epinephrine Bitartrate Inhalation Aerosol; Epinephrine Bitartrate Ophthalmic Solution; Epinephrine Inhalation Aerosol; Epinephrine Inhalation Solution; Epinephrine Injection; Epinephrine Nasal Solution; Epinephrine Ophthalmic Solution; Epinephryl Borate Ophthalmic Solution; Lidocaine Hydrochloride and Epinephrine Injection; Prilocaine and Epinephrine Injection; Procaine Hydrochloride and Epinephrine Injection; Racepinephrine Inhalation Solution.

Ajmaline

Aimaliini; Ajmalin; Ajmalina; Ajmalinum; Rauwolfina; Rauwolfine; Аймалин.

(17*R*,21*R*)-Ajmalan-17,21-diol.

$C_{20}H_{26}N_2O_2$=326.4

CAS — 4360-12-7.

ATC — C01BA05.

ATC Vet — QC01BA05.

UNII — 1PON08459R.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Ajmaline is an alkaloid obtained from the root of *Rauwolfia serpentina* (Apocynaceae). It is a class Ia antiarrhythmic (p. 1243.1) used in the treatment of supraventricular and ventricular arrhythmias (p. 1266.1) and for differential diagnosis of Wolff-Parkinson-White syndrome. Ajmaline is given by intravenous injection in a usual dose of 50 mg over at least 5 minutes. It may also be given by intravenous infusion, and has been given orally and by intramuscular injection.

Ajmaline has also been used as the hydrochloride, monoethanolate, and phenobarbital salts.

Brugada syndrome. Brugada syndrome is a congenital disorder affecting myocardial sodium channels and may be associated with sudden cardiac death. Class 1a antiarrhythmics such as ajmaline block the sodium channel and may have a role in the diagnosis of Brugada syndrome, although they are not suitable for treatment.

References.

1. Rolf S, *et al.* The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24:** 1104–12.
2. Veltmann C, *et al.* Response to intravenous ajmaline: a retrospective analysis of 677 ajmaline challenges. *Europace* 2009; **11:** 1345–52.

Adverse Effects

Ajmaline depresses the conductivity of the heart, and at high doses can cause heart block. At very high doses it may produce a negative inotropic effect. High doses may cause cardiac arrhythmias, coma, and death. Arrhythmias have also been reported after usual intravenous doses (see below). Adverse neurological effects have been reported including eye twitching, convulsions, and respiratory depression. Hepatotoxicity and agranulocytosis may occasionally occur.

Effects on the heart. Electrophysiologic study[1] in 1955 patients revealed that ajmaline 1 mg/kg given intravenously could induce arrhythmias; 63 developed a supraventricular arrhythmia and 7 an atrioventricular reentrant tachycardia. Ventricular tachycardia[2,3] and torsade de pointes[4] have been reported during diagnostic use.

1. Brembilla-Perrot B, Terrier de la Chaise A. Provocation of supraventricular tachycardias by an intravenous class I antiarrhythmic drug. *Int J Cardiol* 1992; **34:** 189–98.
2. Rolf S, *et al.* The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24:** 1104–12.
3. Pinar Bermúdez E, *et al.* Spontaneous sustained monomorphic ventricular tachycardia after administration of ajmaline in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2000; **23:** 407–9.
4. Haverkamp W, *et al.* Torsade de pointes induced by ajmaline. *Z Kardiol* 2001; **90:** 586–90.

Precautions

As for Quinidine, p. 1482.3.

Interactions

Antiarrhythmics. Oral use of *quinidine* with ajmaline increased plasma concentrations of ajmaline considerably in 4 healthy subjects; the elimination half-life of ajmaline was increased about twofold.[1] The pharmacokinetics of quinidine did not seem to be affected by ajmaline.

1. Hori R, *et al.* Quinidine-induced rise in ajmaline plasma concentration. *J Pharm Pharmacol* 1984; **36:** 202–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Gilurytmal; ***Ger.***: Gilurytmal; ***Gr.***: Gilurytmal.

Alacepril *(rINN)*

Alacépril; Alaceprilum; DU-1219; Ацеприл.

N-{1-[(*S*)-3-Mercapto-2-methylpropionyl]-L-prolyl}-3-phenyl-L-alanine acetate.

$C_{20}H_{26}N_2O_5S$=406.5

CAS — 74258-86-9.

UNII — X39TL7JDPF.

Pharmacopoeias. In *Jpn*.

Profile

Alacepril is an ACE inhibitor (p. 1282.2) used in the treatment of hypertension (p. 1251.1). It is converted to captopril and desacetylalacepril (DU-1227) in the body after oral doses. It is given orally in a usual dose of 25 to 75 mg daily, as a single dose or in two divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cetapril.

Aliskiren Fumarate *(BANM, USAN, rINNM)*

Aliskiren Hemifumarate; Aliskirène, Fumarate de; Aliskireni Fumaras; CGP-60536B; Fumarato de aliskireno; SPP-100 (aliskiren or aliskiren fumarate); Алискирена Фумарат.

Bis(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy) benzyl]-8-methylnonanamide fumarate (2:1).

$(C_{30}H_{53}N_3O_6)_2.C_4H_4O_4$=1219.6

CAS — 173334-57-1 (aliskiren); 173334-58-2 (aliskiren fumarate).

ATC — C09XA02.

ATC Vet — QC09XA02.

UNII — C8A0P8G029.

Uses and Administration

Aliskiren is an orally active renin inhibitor used in the management of hypertension (p. 1251.1); it prevents the conversion of angiotensinogen into angiotensin I and therefore inhibits the production of angiotensin II and aldosterone. It is given as the fumarate but doses are expressed in terms of the base; 165.8 mg of aliskiren fumarate is equivalent to about 150 mg of aliskiren. The usual initial oral dose of aliskiren is 150 mg once daily, increased to 300 mg once daily if necessary. In elderly patients, no clinically meaningful additional blood pressure reduction is seen by increasing the dose to 300 mg daily. Doses may be taken with or without food, but patients should establish a routine pattern with regard to meals.

Reviews.

1. Van Tassell BW, Munger MA. Aliskiren for renin inhibition: a new class of antihypertensives. *Ann Pharmacother* 2007; **41:** 456–64.

2. Chrysant SG. Aliskiren-hydrochlorothiazide combination for the treatment of hypertension. *Expert Rev Cardiovasc Ther* 2008; **6:** 305–14.
3. Jensen C, *et al.* Aliskiren: the first renin inhibitor for clinical treatment. *Nat Rev Drug Discov* 2008; **7:** 399–410.
4. Sureshkumar KK, *et al.* Aliskiren: clinical experience and future perspectives of renin inhibition. *Expert Opin Pharmacother* 2008; **9:** 825–37.
5. Kappert K, *et al.* Aliskiren. *Dtsch Med Wochenschr* 2008; **133:** 1308–12.
6. Musini VM, *et al.* Blood pressure lowering efficacy of renin inhibitors for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 10/12/13).
7. Sanoski CA. Aliskiren: an oral direct renin inhibitor for the treatment of hypertension. *Pharmacotherapy* 2009; **29:** 193–212.
8. Pimenta E, Oparil S. Role of aliskiren in cardio-renal protection and use in hypertensives with multiple risk factors. *Vasc Health Risk Manag* 2009; **5:** 453–63.
9. Moutzouri E, *et al.* Aliskiren, a direct renin inhibitor, in clinical practice: a new approach in the treatment of hypertension. *Curr Vasc Pharmacol* 2010; **8:** 344–62.
10. Duggan ST, *et al.* Aliskiren: a review of its use as monotherapy and as combination therapy in the management of hypertension. *Drugs* 2010; **70:** 2011–49. Correction. *ibid.* 2011; **71:** 1280.

Heart failure. Studies[1-3] of aliskiren in patients with heart failure (p. 1262.3).

1. McMurray JJ, *et al.* Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008; **1:** 17–24.
2. Gheorghiade M, *et al.* Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA* 2013; **309:** 1125–35. Correction. *ibid.*; 1461.
3. Maggioni AP, *et al.* Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial. *Eur Heart J* 2013; **34:** 3117–27.

Adverse Effects

Aliskiren is generally well-tolerated but may produce dose-related gastrointestinal adverse effects including diarrhoea, abdominal pain, dyspepsia, and gastro-oesophageal reflux. Other adverse effects include hypotension, headache, dizziness, fatigue, back pain, and cough; rashes, hyperuricaemia, gout, hyperkalaemia, and renal calculi may also occur. Severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis are reported uncommonly; oral mucosal reactions, pruritus, and urticaria have also been noted. Angioedema has been reported rarely, and there have also been reports of seizures. As with other inhibitors of the renin-angiotensin system, dose-related decreases in haemoglobin have been reported.

Precautions

Aliskiren is contra-indicated in patients with a history of angioedema with the drug, and in those who have hereditary or idiopathic angioedema; it should be used with caution in patients who have a history of angioedema associated with other drugs. Aliskiren should be avoided in pregnancy since drugs acting on the renin-angiotensin system have been associated with fetal and neonatal morbidity and mortality.

As with other drugs that affect the renin-angiotensin system, aliskiren may cause changes in renal function; consequently, it should be used with caution in those with conditions predisposing to kidney dysfunction (such as volume depletion, heart, liver, or kidney disease, or diabetes), and renal function should be monitored periodically. Use of aliskiren is not recommended in patients with severe renal impairment (GFR < 30 mL/minute). Due to the risk of hyperkalaemia, periodic serum-potassium monitoring is recommended; patients at particular risk include those with renal insufficiency or diabetes, or those taking other medications that inhibit the renin-angiotensin system or increase serum potassium. Patients with sodium or volume depletion (for example those receiving high-dose diuretics) may have symptomatic hypotension on starting aliskiren and treatment should begin under close medical supervision.

See also Diabetes Mellitus, below, for precautions regarding the use of aliskiren with ACE inhibitors or angiotensin II receptor antagonists in patients with renal impairment or diabetes.

Diabetes mellitus. The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) study investigated the role of aliskiren in reducing cardiovascular and renal events in patients with type 2 diabetes and pre-existing renal disease;[1-3] aliskiren was added to conventional care which included an ACE inhibitor or an angiotensin-receptor blocker (ARB). However, analysis of interim data showed that patients were unlikely to benefit from the addition of aliskiren and that, furthermore, the risk of adverse events related to non-fatal stroke, renal complications, hyperkalaemia, and hypotension was increased with aliskiren when compared with placebo. The study was stopped early and, as a consequence of the interim findings, licensed product information contra-indicated the use of aliskiren with an ACE inhibitor or ARB in patients with diabetes, and recommended avoidance of such combinations in those with moderate to severe renal impairment (GFR < 60 mL/minute).[2]

1. Novartis, UK. Direct healthcare professional communication on potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease treated with aliskiren (Rasilez) (issued 30th December, 2011). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con140611.pdf (accessed 17/01/11)
2. FDA. FDA drug safety communication: new warning and contra-indication for blood pressure medicines containing aliskiren (Tekturna) (issued 20th April, 2012). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm (accessed 19/06/12)
3. Parving HH, *et al.* ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; **367:** 2204–13.

Interactions

An additive effect may be noted when aliskiren is given with other antihypertensives or drugs that cause hypotension. Use of aliskiren with other drugs that increase serum potassium may increase the risk of hyperkalaemia. NSAIDs can reduce the anti-hypertensive effects of aliskiren, and combined use in patients who are elderly, volume-depleted, or have renal impairment could cause further deterioration of renal function.

The use of aliskiren with ACE inhibitors or angiotensin II receptor antagonists is generally not recommended; if such therapy is considered necessary then patients must be closely monitored. Such combinations should be avoided in renally-impaired patients with a GFR of less than 60 mL/minute, and are contra-indicated in diabetic patients due to increased adverse events (see Diabetes Mellitus, under Precautions, above).

Aliskiren is a substrate for P-glycoprotein and should not be given with strong P-glycoprotein inhibitors such as ciclosporin, itraconazole, and quinidine; caution is advised if aliskiren is to be used with moderate inhibitors such as amiodarone, clarithromycin, erythromycin, ketoconazole, telithromycin, and verapamil. Aliskiren is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4 but few significant interactions have been reported. Plasma-aliskiren concentrations may be reduced by irbesartan and increased by atorvastatin and ketoconazole but the clinical relevance is not clear.

Aliskiren may reduce the plasma concentrations of furosemide and torasemide.

Pharmacokinetics

Aliskiren is poorly absorbed from the gastrointestinal tract with a bioavailability of about 2.5%. Peak plasma concentrations occur about 1 to 3 hours after an oral dose. Absorption is reduced when aliskiren is taken with a high-fat meal. Aliskiren is about 50% bound to plasma proteins. It is excreted mainly in the faeces, possibly via the bile; about 25% of the absorbed dose is excreted in the urine as unchanged drug. Aliskiren is a substrate for the cytochrome P450 isoenzyme CYP3A4 but metabolism appears to be minimal. The elimination half-life is about 24 to 40 hours, and steady-state concentrations are reached in about 7 to 8 days.

Reviews.

1. Vaidyanathan S, *et al.* Clinical pharmacokinetics and pharmacodynamics of aliskiren. *Clin Pharmacokinet* 2008; **47:** 515–31.
2. Buczko W, Hermanowicz JM. Pharmacokinetics and pharmacodynamics of aliskiren, an oral direct renin inhibitor. *Pharmacol Rep* 2008; **60:** 623–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rasilez; ***Austria***: Rasilez; ***Belg.***: Rasilez; ***Braz.***: Rasilez; ***Canad.***: Rasilez; ***Chile***: Rasilez; ***China***: Rasilez (锐思力); ***Cz.***: Enviage†; Rasilez; Riprazo; Sprimeo†; Tekturna†; ***Denm.***: Rasilez; ***Fr.***: Rasilez; ***Ger.***: Rasilez; ***Gr.***: Enviage†; Rasilez; Riprazo; Sprimeo†; ***Hong Kong***: Rasilez; ***Hung.***: Rasilez; ***Indon.***: Rasilez; ***Irl.***: Enviage†; Rasilez; Riprazo; Sprimeo†; ***Israel***: Rasilez; ***Ital.***: Rasilez; ***Malaysia***: Rasilez; ***Mex.***: Rasilles; ***Neth.***: Enviage†; Rasilez; Riprazo; Sprimeo†; ***Norw.***: Rasilez; ***Philipp.***: Rasilez; ***Pol.***: Rasilez HCT; Rasilez; Riprazo; Sprimeo†; ***Port.***: Enviage†; Rasilez; Riprazo; Sprimeo†; Tekturna†; ***Rus.***: Rasilez (Расилез); ***Singapore***: Rasilez; ***Spain***: Rasilez; ***Swed.***: Rasilez; ***Switz.***: Rasilez; ***Thai.***: Rasilez; ***Turk.***: Rasilez; ***UK***: Rasilez; ***Ukr.***: Rasilez (Расилез); ***USA***: Tekturna.

Multi-ingredient Preparations. ***Arg.***: Rasilez D; ***Austria***: Rasilez HCT; ***Belg.***: Rasilez HCT; ***Braz.***: Rasilez HCT; ***Canad.***: Rasilez HCT; ***Chile***: Rasilez D; ***Cz.***: Rasilamlo; Rasilez HCT; Riprazo HCT†; ***Denm.***: Rasilez HCT†; ***Fr.***: Rasilez HCT; ***Ger.***: Rasilez HCT; ***Gr.***: Rasilez HCT; ***Irl.***: Rasilamlo; Rasilez HCT; Rasitrio; Riprazo HCT†; Sprimeo HCT†; ***Neth.***: Rasilamlo; Rasilez HCT; Rasitrio; ***Philipp.***: Rasilez HCT; ***Port.***: Rasilez HCT; ***Rus.***: Co-Rasilez (Ко-Расилез); ***Singapore***: Rasilez HCT; ***Spain***: Rasilez HCT; ***Swed.***: Rasitrio†; ***Switz.***: Rasilez HCT; ***USA***: Tekamlo; Tekturna HCT.

Alprenolol *(BAN, rINN)* ⊗

Alprénolol; Alprenololi; Alprenololum; Алпренолол.

1-(2-Allylphenoxy)-3-isopropylaminopropan-2-ol.

$C_{15}H_{23}NO_2$=249.4

CAS — 13655-52-2.

ATC — C07AA01.

ATC Vet — QC07AA01.

UNII — 877K5MQ27W.

Alprenolol Benzoate *(BANM, rINNM)* ⊗

Alprénolol, benzoate d'; Alprenolol, benzoato de; Alprenololi Benzoas; Benzoato de alprenolol; Альпренолола Бензоат.

$C_{22}H_{29}NO_4$=371.5

ATC — C07AA01.

ATC Vet — QC07AA01.

UNII — T3H696761C.

Alprenolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Alprénolol, Chlorhydrate d'; Alprenolol, hidrocloruro de; Alprenolol-hidroklorid; Alprenololhydrochlorid; Alprenolol-hydrochlorid; Alprenololhydroklorid; Alprenololi hydrochloridum; Alprenololihydrokloridi; Alprenololio hidrochloridas; H56/28; Hidrocloruro de alprenolol; Альпренолола Гидрохлорид.

$C_{15}H_{23}NO_2$,HCl=285.8

CAS — 13707-88-5.

ATC — C07AA01.

ATC Vet — QC07AA01.

UNII — 2502C2OIRK.

NOTE. The names Atenenol and Skajilol have been used as trade marks for alprenolol hydrochloride.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Alprenolol Hydrochloride). A white, or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Alprenolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to have intrinsic sympathomimetic activity and some membrane-stabilising properties.

Alprenolol has been given orally, as the benzoate or hydrochloride, in the management of hypertension, angina pectoris, and cardiac arrhythmias.

Alteplase *(BAN, USAN, rINN)*

Alteplaasi; Alteplas; Alteplasa; Altéplase; Alteplasum; Alteplaz; G-11021 (2-chain form); G-11035; G-11044; Recombinant Tissue-type Plasminogen Activator; rt-PA; Альтеплаза.

CAS — 105857-23-6.

ATC — B01AD02; S01XA13.

ATC Vet — QB01AD02; QS01XA13.

UNII — 1RXS4UE564.

Description. Alteplase is a glycosylated protein of 527 residues having the amino acid sequence of human tissue plasminogen activator (t-PA) and produced by recombinant DNA technology.

Pharmacopoeias. In *US. Eur.* (see p. vii) includes Alteplase for Injection.

Ph. Eur. 8: (Alteplase for Injection; Alteplasum ad Iniectabile). A sterile, freeze-dried preparation of alteplase, a tissue plasminogen activator produced by recombinant DNA technology. It has a potency of not less than 500 000 units/mg of protein. It is a white or slightly yellow powder or friable mass. The reconstituted preparation has a pH of 7.1 to 7.5. Store in colourless glass containers, under vacuum or an inert gas, at a temperature between 2 degrees and 30 degrees. Protect from light. Alteplase consists of 527 amino acids with carbohydrate moieties attached.

USP 36: (Alteplase). A highly purified glycosylated serine protease with fibrin-binding properties and plasminogen-specific proteolytic activities. It is produced by recombinant DNA synthesis in mammalian cell culture. It has a potency of 522 000 to 667 000 USP units/mg of protein. Store in airtight containers in the frozen state at a temperature of -20 degrees or below.

Incompatibility and stability. Alteplase has been reported[1] to be incompatible with dobutamine, dopamine, glyceryl trinitrate, and heparin, although a subsequent study found no incompatibility between alteplase and glyceryl trinitrate.[2] Another study[3] found that dilution of a proprietary preparation of alteplase (Activase) to 90 and 160 micrograms/mL with glucose 5% resulted in precipitation of the drug. Alteplase is formulated with arginine as a

solubilising agent, and dilution with glucose 5% to concentrations below 500 micrograms/mL of alteplase makes precipitation possible. Dilution with sodium chloride 0.9% is possible to concentrations down to 200 micrograms/mL before precipitation becomes a risk.

Studies have suggested that a 1 mg/mL solution of alteplase retains its activity when frozen at -20 degrees or below for up to 6 months,[4,5] or -80 degrees for up to 7 years.[6]

1. Lee CY, *et al*. Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
2. Lam XM, *et al*. Stability and activity of alteplase with injectable drugs commonly used in cardiac therapy. *Am J Health-Syst Pharm* 1995; **52:** 1904–9.
3. Frazin BS. Maximal dilution of Activase. *Am J Hosp Pharm* 1990; **47:** 1016.
4. Calis KA, *et al*. Bioactivity of cryopreserved alteplase solutions. *Am J Health-Syst Pharm* 1999; **56:** 2056–7.
5. Wiernikowski JT, *et al*. Stability and sterility of recombinant tissue plasminogen activator at -30 degreesC. *Lancet* 2000; **355:** 2221–2.
6. Shaw GJ, *et al*. Long-term stability of recombinant tissue plasminogen activator at -80 C. *BMC Res Notes* 2009; **2:** 117. Available at: http://www.biomedcentral.com/content/pdf/1756-0500-2-117.pdf (accessed 04/08/10)

Units

The activity of alteplase can be measured in terms of international units using the third International Standard for tissue plasminogen activator recombinant, human, established in 1999, although doses are generally expressed by weight.

Uses and Administration

Alteplase is a thrombolytic drug. It is a mainly single-chain form of the endogenous enzyme tissue plasminogen activator and is produced by recombinant DNA technology. Like endogenous tissue plasminogen activator, alteplase converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Alteplase has relatively little effect on circulating, unbound plasminogen and thus may be termed a fibrin-specific thrombolytic (see p. 1245.3).

Alteplase is used similarly to streptokinase (p. 1503.1) in the treatment of thromboembolic disorders, particularly myocardial infarction (p. 1257.1) and venous thromboembolism (p. 1274.1), and to clear occluded catheters (see below). Alteplase may also be used in patients with acute ischaemic stroke (p. 1269.2).

In the treatment of acute **myocardial infarction**, alteplase is given intravenously as soon as possible after the onset of symptoms in a total dose of 100 mg; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The total dose may be given either over 1½ hours (accelerated or 'front-loaded' alteplase) or over 3 hours. The accelerated schedule has been recommended if given within 6 hours of myocardial infarction and is as follows: 15 mg as an intravenous bolus, then 750 micrograms/kg, up to a maximum of 50 mg, by intravenous infusion over 30 minutes, followed by the remainder infused over the subsequent 60 minutes. The longer schedule recommended when used more than 6 hours after myocardial infarction is as follows: 10 mg as an intravenous bolus, then 50 mg by intravenous infusion over 1 hour, followed by the remainder infused over the subsequent 2 hours.

In the treatment of acute, massive **pulmonary embolism** a total dose of 100 mg is given; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The first 10 mg is given as an intravenous bolus and the remainder by intravenous infusion over 2 hours.

In acute **ischaemic stroke**, alteplase is given in a dose of 900 micrograms/kg up to a maximum total dose of 90 mg. The dose is given intravenously over 60 minutes with 10% of it as a bolus during the first minute. Alteplase should be given as soon as possible, and up to 3 to 4.5 hours after the onset of stroke symptoms (for further information, see p. 1269.2).

To **restore function in central venous lines,** alteplase is instilled into the catheter at a concentration of 1 mg/mL. The usual dose is 2 mg, repeated after 2 hours if necessary. A total dose of 4 mg should not be exceeded. For patients weighing less than 30 kg, the dose is 110% of the internal lumen volume of the catheter, but should not exceed 2 mg, and may be repeated after 2 hours if necessary.

General references.

1. Gillis JC, *et al*. Alteplase: a reappraisal of its pharmacological properties and therapeutic use in acute myocardial infarction. *Drugs* 1995; **50:** 102–36.
2. Wagstaff AJ, *et al*. Alteplase: a reappraisal of its pharmacology and therapeutic use in vascular disorders other than acute myocardial infarction. *Drugs* 1995; **50:** 289–316.
3. Semba CP, *et al*. Society of Cardiovascular and Interventional Radiology (SCVIR). Alteplase and tenecteplase: applications in the peripheral circulation. *Tech Vasc Interv Radiol* 2001; **4:** 99–106.
4. Lindley RI, *et al*. Alteplase and ischaemic stroke: have new reviews of old data helped? *Lancet Neurol* 2005; **4:** 249–53.
5. De Keyser J, *et al*. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke* 2007; **38:** 2612–8.
6. Quinn TJ, *et al*. Past, present and future of alteplase for acute ischemic stroke. *Expert Rev Neurother* 2008; **8:** 181–92.
7. Hacke W, *et al*. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359:** 1317–29.
8. Micieli G, *et al*. Safety and efficacy of alteplase in the treatment of acute ischemic stroke. *Vasc Health Risk Manag* 2009; **5:** 397–409.

Administration in children. Information on usage and doses of alteplase in children is given under the individual headings below, and also under Administration in Children under Streptokinase, p. 1503.2.

Catheters and cannulas. Alteplase has been used successfully to clear thrombi in central venous catheters.[1,2] Typical doses have been 2 mg injected as a bolus into the blocked catheter. Children have been treated similarly; in one study[3] in patients weighing from 3 kg, doses ranged from 0.1 to 2 mg (as a 1 mg/mL solution), depending on the size of the catheter. Similarly, a later study using a 1 mg/mL solution gave doses of 2 mg to children weighing 30 kg or more, and a volume equal to 110% of the calculated internal volume of the catheter (rounded to the nearest 0.1 mL and not to exceed 2 mL in total) in children weighing less than 30 kg.[4] The dwell time was up to 2 hours, and doses were repeated once in patients in whom catheter function was not restored after this period. A cohort study[5] used doses of 500 micrograms for children weighing 10 kg or under, and 1 to 2 mg above this weight, with a dwell time of 2 to 4 hours. In another report, 2 children[6] were successfully treated with intravenous alteplase in doses of 10 to 50 micrograms/kg per hour for venous thrombosis associated with indwelling intravascular catheters.

Alteplase has also been instilled into central haemodialysis lines to preserve patency between dialysis sessions.[7] In a randomised, controlled study of 225 haemodialysis patients, substituting alteplase (1 mg per lumen) for one of three post-dialysis heparin instillations (5000 units/mL) each week significantly reduced the incidence of catheter malfunction and bacteraemia compared with thrice-weekly heparin.[8] Urokinase has also been used to maintain catheter patency in children with long-term venous access devices for antineoplastic therapy.[9]

For reports covering the use of alteplase to treat intracardiac thrombosis resulting from the placement of central venous lines, see Intracardiac Thrombosis, below.

1. Paulsen D, *et al*. Use of tissue plasminogen activator for reopening of clotted dialysis catheters. *Nephron* 1993; **64:** 468–9.
2. Haire WD, *et al*. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. *Thromb Haemost* 1994; **72:** 543–7.
3. Jacobs BR, *et al*. Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. *J Pediatr* 2001; **139:** 593–6.
4. Blaney M, *et al*. CAPS Investigators. Alteplase for the treatment of central venous catheter occlusion in children: results of a prospective, open-label, single-arm study (The Cathflo Activase Pediatric Study). *J Vasc Interv Radiol* 2006; **17:** 1745–51.
5. Choi M, *et al*. The use of alteplase to restore patency of central venous lines in pediatric patients: a cohort study. *J Pediatr* 2001; **139:** 152–6.
6. Doyle E, *et al*. Thrombolysis with low dose tissue plasminogen activator. *Arch Dis Child* 1992; **67:** 1483–4.
7. Gittins NS, *et al*. Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. *Arch Dis Child* 2007; **92:** 499–501.
8. Hemmelgarn BR, *et al*. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med* 2011; **364:** 303–12.
9. Dillon PW, *et al*. Prophylactic urokinase in the management of long-term venous access devices in children: a Children's Oncology Group study. *J Clin Oncol* 2004; **22:** 2718–23.

Intracardiac thrombosis. Alteplase has been used, in a dose of 100 mg given intravenously over 2 hours, for thrombosis of prosthetic heart valves.[1]

Alteplase has been used successfully in a neonate to treat intracardiac thrombosis associated with the use of a central venous line.[2] A dose of 500 micrograms/kg given over 10 minutes was followed by infusion of 200 micrograms/kg per hour for 3 days. In another report,[3] 4 preterm infants were treated successfully. All received 400 to 500 micrograms/kg of alteplase in a 20 to 30 minute bolus. This was followed in one case by a 3-hour infusion at 100 micrograms/kg per hour.

Although thrombolytics are usually contra-indicated in patients with infective endocarditis (see Precautions for Streptokinase, p. 1506.3), alteplase has been used successfully in children with indwelling catheters who developed infective endocarditis; coagulation was monitored and fresh frozen plasma was given to maintain fibrinogen concentrations.[4]

1. Astengo D, *et al*. Recombinant tissue plasminogen activator for prosthetic mitral-valve thrombosis. *N Engl J Med* 1995; **333:** 259.
2. Van Overmeire B, *et al*. Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. *Arch Dis Child* 1992; **67:** 443–5.
3. Ferrari F, *et al*. Early intracardiac thrombosis in preterm infants and thrombolysis with recombinant tissue type plasminogen activator. *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F66–F69.
4. Levitas A, *et al*. Successful treatment of infective endocarditis with recombinant tissue plasminogen activator. *J Pediatr* 2003; **143:** 649–52.

Microvessel thrombosis. Alteplase has been used in conditions where the underlying pathology is occlusion of small blood vessels by microthrombi.

Purpura and loss of circulation in the hands of a patient recovering from **fulminant meningococcaemia**[1] responded to intra-arterial infusion of alteplase 20 to 40 micrograms/kg per hour for 22 hours in the right hand, and 20 micrograms/kg per hour for 11 hours in the left. Perfusion was successfully restored to both hands, and full function subsequently attained in them. Improvement was also achieved when alteplase was given to 2 infants with septic shock and purpura fulminans caused by meningococcal infection.[2]

Intra-arterial infusion of alteplase has also been used in the treatment of severe **frost bite**. In a small retrospective study,[3] improved tissue perfusion and a reduced incidence of amputation were seen among patients treated with alteplase (along with heparin) within 24 hours of injury. Initial intra-arterial doses of 0.5 to 1 mg/hour were infused and adjusted as required over a mean duration of 26 hours (range 8 to 42 hours). Intra-arterial heparin was given at a rate of 500 units/hour.

Six patients[4] with ulcers caused by **livedoid vasculitis** and refractory to conventional treatment were treated with alteplase 10 mg infused intravenously over 4 hours daily for 14 days. Most ulcers healed rapidly; one patient required retreatment with concomitant anticoagulation. Healing of ulcers associated with **calciphylaxis** has also been reported[5] with a similar alteplase regimen.

A 4-year-old girl[6] with **haemolytic-uraemic syndrome** (see under Thrombotic Microangiopathies, p. 1159.1) responded to treatment with an intravenous infusion of alteplase 200 micrograms/kg per hour for 5 hours, subsequently reduced to 50 micrograms/kg per hour for 14 days.

Alteplase use has been reviewed[7] and mixed results found, in patients with **veno-occlusive disease of the liver**, a serious complication of bone marrow transplantation that may be caused by diffuse thrombi in the hepatic venules. Although results in patients with established veno-occlusive disease have been disappointing,[8] one study[9] suggested that alteplase given early in the course of the disease improves response rate.

1. Keeley SR, *et al*. Tissue plasminogen activator for gangrene in fulminant meningococcaemia. *Lancet* 1991; **337:** 1359.
2. Zenz W, *et al*. Recombinant tissue plasminogen activator treatment in two infants with fulminant meningococcemia. *Pediatrics* 1995; **96:** 44–8.
3. Bruen KJ, *et al*. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* 2007; **142:** 546–51.
4. Klein KL, Pittelkow MR. Tissue plasminogen activator for treatment of livedoid vasculitis. *Mayo Clin Proc* 1992; **67:** 923–33.
5. Sewell LD, *et al*. Low-dose tissue plasminogen activator for calciphylaxis. *Arch Dermatol* 2004; **140:** 1045–8.
6. Kruez W, *et al*. Successful treatment of haemolytic uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; **341:** 1665–6.
7. Terra SG, *et al*. A review of tissue plasminogen activator in the treatment of veno-occlusive liver disease after bone marrow transplantation. *Pharmacotherapy* 1997; **17:** 929–37.
8. Bearman SI, *et al*. Treatment of hepatic venocclusive disease with recombinant human tissue plasminogen activator and heparin in 42 marrow transplant patients. *Blood* 1997; **89:** 1501–6.
9. Schriber J, *et al*. Tissue plasminogen activator (tPA) as therapy for hepatotoxicity following bone marrow transplantation. *Bone Marrow Transplant* 1999; **24:** 1311–14.

Ocular disorders. Intra-ocular alteplase has been used to treat postoperative fibrinous deposits that can form after procedures such as surgery for cataracts[1] or glaucoma,[2] including cataracts in children.[3] Doses ranging from 6 to 25 micrograms have been used. Intra-ocular bleeding has occurred as a complication of such use.[2,4] Alteplase has also been used prophylactically in children undergoing surgery for congenital cataracts.[5]

Intra-ocular alteplase has also been used for treatment of subhyaloid haemorrhage,[6,7] including that seen in shaken baby syndrome.[8] Successful treatment of subretinal macular haemorrhage with alteplase injected directly into the subretinal area around the clot has also been reported.[9]

1. Heiligenhaus A, *et al*. Recombinant tissue plasminogen activator in cases with fibrin formation after cataract surgery: a prospective randomised multicentre study. *Br J Ophthalmol* 1998; **82:** 810–15.
2. Lundy DC, *et al*. Intracameral tissue plasminogen activator after glaucoma surgery: indications, effectiveness, and complications. *Ophthalmology* 1996; **103:** 274–82.
3. Mehta JS, Adams GGW. Recombinant tissue plasminogen activator following paediatric cataract surgery. *Br J Ophthalmol* 2000; **84:** 983–6.
4. Azuara-Blanco A, Wilson RP. Intraocular and extraocular bleeding after intracameral injection of tissue plasminogen activator. *Br J Ophthalmol* 1998; **82:** 1345–6.
5. Siatiri H, *et al*. Intracameral tissue plasminogen activator to prevent severe fibrinous effusion after congenital cataract surgery. *Br J Ophthalmol* 2005; **89:** 1458–61.
6. Schmitz K, *et al*. Therapy of subhyaloidal haemorrhage by intravitreal application of rtPA and SF_6 gas. *Br J Ophthalmol* 2000; **84:** 1324–5.
7. Koh HJ, *et al*. Treatment of subhyaloid haemorrhage with intravitreal tissue plasminogen activator and C_3F_8 gas injection. *Br J Ophthalmol* 2000; **84:** 1329–30.
8. Conway MD, *et al*. Intravitreal tPA and SF_6 promote clearing of premacular subhyaloid hemorrhages in shaken and battered baby syndrome. *Ophthalmic Surg Lasers* 1999; **30:** 435–41.
9. Singh RP, *et al*. Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator. *Br J Ophthalmol* 2006; **90:** 429–31.

Peripheral arterial thromboembolism. Although surgery has been the first-line therapy for peripheral arterial thromboembolism (p. 1273.3), thrombolytics have an increasingly important role, either alone or as an adjunct to surgery or percutaneous interventions.[1] Alteplase has been given intravenously but intra-arterial infusion directly into the clot is now preferred. Such treatment, which is usually reserved for patients who have had limb ischaemia for less than 14 days, may be limb-sparing; a small case series[2] found that successful thrombolysis was associated with a greatly reduced rate of subsequent amputation. Alteplase may also be given intra-arterially to remove distal clots during surgical and percutaneous procedures. The optimum dose is unclear.[3,4] For direct intra-arterial infusion into the clot, doses in the range of 0.2 to 1 mg/hour have been commonly used,[5] while for distal clots alteplase has been given intra-arterially as three doses of 5 mg at 10-minute intervals.[4,6]

An *intravenous* dose of 500 micrograms/kg per hour for the first hour followed by 250 micrograms/kg per hour until clot lysis occurred has been used in infants.[7] Treatment of arterial thrombosis in neonates has been reported, using doses of alteplase ranging from 100 to 500 micrograms/kg per hour *intravenously*.[8,9] The *BNFC* recommends a dose for any intravascular thrombosis in neonates and children of 100 to 500 micrograms/kg per hour by intravenous infusion over 3 to 6 hours; a second dose may be given if needed. The maximum daily dose should not exceed 100 mg. However, a retrospective study[10] of 80 infants and children with arterial or venous thrombi found that although treatment with alteplase may be effective, it is associated with a low safety margin and an unknown risk-benefit ratio.

1. Norgren L, *et al*. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; **45** (suppl S): S5–S67.
2. Disini L, *et al*. Successful intra-arterial alteplase infusion is a predictor of 12-month limb survival in patients with lower limb arterial occlusion. *Clin Radiol* 2008; **63:** 636–41.
3. Ward AS, *et al*. Peripheral thrombolysis with tissue plasminogen activator: results of two treatment regimens. *Arch Surg* 1994; **129:** 861–5.
4. Giannini D, Balbarini A. Thrombolytic therapy in peripheral arterial disease. *Curr Drug Targets Cardiovasc Haematol Disord* 2004; **4:** 249–58.
5. Henke PK, Stanley JC. The treatment of acute embolic lower limb ischemia. *Adv Surg* 2004; **38:** 281–91.
6. Chester JF, *et al*. Peroperative t-PA thrombolysis. *Lancet* 1991; **337:** 861–2.
7. Zenz W, *et al*. Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. *Br Heart J* 1993; **70:** 382–5.
8. Weiner GM, *et al*. Successful treatment of neonatal arterial thromboses with recombinant tissue plasminogen activator. *J Pediatr* 1998; **133:** 133–6.
9. Farnoux C, *et al*. Recombinant tissue-type plasminogen activator therapy of thrombosis in 16 neonates. *J Pediatr* 1998; **133:** 137–40.
10. Gupta AA, *et al*. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr* 2001; **139:** 682–8.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Allergic reactions are less likely with alteplase than with streptokinase and repeated use may be possible.

Hypersensitivity. Alteplase is considered non-antigenic, and hypersensitivity reactions are rare; however, the risk may be increased in those taking ACE inhibitors—see ACE Inhibitors under Interactions, below. For further discussion of hypersensitivity reactions with thrombolytics, including anaphylactoid reactions in atopic patients given alteplase, see under Streptokinase, p. 1506.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alteplase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Thrombin generation. Alteplase produces considerable thrombin generation which may result from direct activation of the coagulation system by plasmin or by positive feedback of the coagulation system by clot-bound thrombin. This excessive thrombin generation was considered a possible cause of myocardial infarction in a patient undergoing thrombolytic therapy with alteplase for venous thrombosis.[1] Streptokinase produced no evidence of excessive thrombin generation.

1. Baglin TP, *et al*. Thrombin generation and myocardial infarction during infusion of tissue-plasminogen activator. *Lancet* 1993; **341:** 504–5.

Interactions

As for Streptokinase, p. 1507.1.

ACE inhibitors. Angioedema has been reported rarely in patients treated with alteplase, but the risk may be increased in those taking ACE inhibitors.[1-3] A prospective study[1] found that out of 176 patients treated with alteplase for acute stroke, 9 developed angioedema; the risk was strongly associated with use of an ACE inhibitor (7 of the 9). Similarly, of 312 patients treated[3] with alteplase for acute stroke, 8 developed angioedema of whom 6 were taking an ACE inhibitor.

1. Hill MD, *et al*. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology* 2003; **60:** 1525–7.
2. Hill MD, *et al*. Anaphylactoid reactions and angioedema during alteplase treatment of acute ischemic stroke. *CMAJ* 2000; **162:** 1281–4.
3. Ottomeyer C, *et al*. Raising awareness of orolingual angioedema as a complication of thrombolysis in acute stroke patients. *Cerebrovasc Dis* 2009; **27:** 307–8.

Glyceryl trinitrate. Although thrombolytics and nitrates are both frequently used in acute myocardial infarction a report suggested that this combination may result in impaired thrombolysis. Giving alteplase and glyceryl trinitrate intravenously to 36 patients with acute myocardial infarction produced lower plasma-antigen concentrations of tissue-plasminogen activator than alteplase given alone to 11 patients.[1] Reperfusion was sustained in only 44% of patients receiving both drugs compared with 91% of patients given alteplase alone. The authors of a subsequent study[2] suggested that these lower plasma concentrations may be due to increased hepatic metabolism of alteplase as a result of glyceryl trinitrate's effect of increasing hepatic blood flow.

1. Nicolini FA, *et al*. Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. *Am J Cardiol* 1994; **74:** 662–6.
2. Romeo F, *et al*. Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. *Am Heart J* 1995; **130:** 692–7.

Pharmacokinetics

Alteplase is cleared rapidly from the plasma, mainly by metabolism in the liver. It has an initial half-life of 4 to 5 minutes and a terminal half-life of about 40 minutes.

References.

1. Krause J. Catabolism of tissue-type plasminogen activator (t-PA), its variants, mutants and hybrids. *Fibrinolysis* 1988; **2:** 133–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actilyse; ***Austral.***: Actilyse; ***Austria***: Actilyse; ***Belg.***: Actilyse; ***Braz.***: Actilyse; ***Canad.***: Activase; Cathflo; ***Chile***: Actilyse; ***China***: Actilyse (爱通立); ***Cz.***: Actilyse; ***Denm.***: Actilyse; ***Fin.***: Actilyse; ***Fr.***: Actilyse; ***Ger.***: Actilyse; ***Gr.***: Actilyse; Cathflo Activase; ***Hong Kong***: Actilyse; ***Hung.***: Actilyse; ***India***: Actilyse; ***Indon.***: Actilyse; ***Irl.***: Actilyse; ***Israel***: Actilyse; ***Ital.***: Actilyse; ***Jpn***: Activacin; ***Malaysia***: Actilyse; ***Mex.***: Actilyse; ***Neth.***: Actilyse; ***Norw.***: Actilyse; ***NZ***: Actilyse; ***Philipp.***: Actilyse; ***Pol.***: Actilyse; ***Port.***: Actilyse; ***Rus.***: Actilyse (Актилизе); ***S.Afr.***: Actilyse; ***Singapore***: Actilyse; ***Spain***: Actilyse; ***Swed.***: Actilyse; ***Switz.***: Actilyse; ***Thai.***: Actilyse; ***Turk.***: Actilyse; ***UK***: Actilyse; ***Ukr.***: Actilyse (Актилизе); ***USA***: Activase; ***Venez.***: Actilyse.

Pharmacopoeial Preparations

USP 36: Alteplase for Injection.

Altizide *(BAN, rINN)* ⊗

Althiazide (USAN); Altizid; Altizida; Altizidum; P-1779; Альтизид.

3-Allylthiomethyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{11}H_{14}ClN_3O_4S_3$=383.9

CAS — 5588-16-9.

UNII — GI8CB72B0D.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Altizide). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; practically insoluble in dichloromethane. It exhibits polymorphism.

Profile

Altizide is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) that is used in the treatment of oedema and hypertension. It is frequently used with spironolactone.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Aldactazine; ***Fr.***: Aldactazine; Practazin†; Spiroctazine; ***Gr.***: Aldactazine; ***Port.***: Aldactazine; ***Spain***: Aldactacine.

Ambrisentan *(BAN, rINN)*

Ambrisentán; Ambrisentanum; BSF-208075; LU-208075; Амбризентан.

(+)-(2*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

$C_{22}H_{22}N_2O_4$=378.4

CAS — 177036-94-1.

ATC — C02KX02.

ATC Vet — QC02KX02.

UNII — HW6NV07QEC.

Uses and Administration

Ambrisentan is an endothelin receptor antagonist (p. 1245.1) with similar actions to bosentan (p. 1327.1), although it has a higher selectivity for the endothelin ET_A-receptor. It is used in the management of pulmonary hypertension functional class II or III (p. 1278.2). It is given orally in an initial dose of 5 mg once daily; the dose may be increased to 10 mg once daily if tolerated. When used with ciclosporin the dose should not exceed 5 mg daily (see also Interactions, below).

References.

1. Galiè N, *et al*. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46:** 529–35.
2. Vatter H, Seifert V. Ambrisentan, a non-peptide endothelin receptor antagonist. *Cardiovasc Drug Rev* 2006; **24:** 63–76.
3. Barst RJ. A review of pulmonary arterial hypertension: role of ambrisentan. *Vasc Health Risk Manag* 2007; **3:** 11–22.
4. Galiè N, *et al*. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008; **117:** 3010–19.
5. Hrometz SL, Shields KM. Role of ambrisentan in the management of pulmonary hypertension. *Ann Pharmacother* 2008; **42:** 1653–9. Correction. *ibid.* 2009; **43:** 794. [dose]
6. Croxtall JD, Keam SJ. Ambrisentan. *Drugs* 2008; **68:** 2195–2204.
7. Kingman M, *et al*. Ambrisentan, an endothelin receptor type A-selective endothelin receptor antagonist, for the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother* 2009; **10:** 1847–58.
8. Oudiz RJ, *et al*. ARIES Study Group. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54:** 1971–81.

Adverse Effects and Precautions

As for Bosentan, p. 1327.3.

Interactions

Ambrisentan is a substrate for several enzymes and transporters and interactions could potentially occur with inducers or inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19, P-glycoprotein, uridine diphosphate glucuronosyltransferases, and organic anion transporting polypeptide (OATP). Ciclosporin increases plasma concentrations of ambrisentan by about 50% and more than doubles the AUC; therefore doses of ambrisentan should be kept low when they are given together—see under Uses, above.

Ciclosporin. An open-label, pharmacokinetic study[1] in 28 healthy subjects indicated that exposure to ambrisentan was doubled when used with ciclosporin. Also, there was a corresponding increase in adverse effects such as headache when the 2 drugs were given together.

1. Spence R, *et al*. Potential for pharmacokinetic interactions between ambrisentan and cyclosporine. *Clin Pharmacol Ther* 2010; **88:** 513–20.

Pharmacokinetics

Ambrisentan is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after oral doses. It is about 99% bound to plasma proteins. Ambrisentan is excreted mainly by the liver, although the relative contribution of hepatic metabolism and biliary excretion is unknown. The terminal elimination half-life is about 15 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Volibris; ***Austria***: Volibris; ***Belg.***: Volibris; ***Braz.***: Volibris; ***Canad.***: Volibris; ***China***: Volibris (凡瑞克); ***Cz.***: Volibris; ***Denm.***: Volibris; ***Fr.***: Volibris; ***Ger.***: Volibris; ***Gr.***: Volibris; ***Hung.***: Volibris; ***Irl.***: Volibris; ***Israel***: Volibris; ***Ital.***: Volibris; ***Malaysia***: Volibris; ***Neth.***: Volibris; ***Norw.***: Volibris; ***NZ***: Volibris; ***Pol.***: Volibris; ***Port.***: Volibris; ***Spain***: Volibris; ***Swed.***: Volibris; ***Switz.***: Volibris; ***UK***: Volibris; ***USA***: Letairis.

Amezinium Metilsulfate *(rINN)* ⊗

Ametsiniummetilsulfaatti; Amezinii Metilsulfas; Amezinio, metilsulfato de; Amezinium Methylsulphate; Amézinium, Métilsulfate d'; Ameziniummetilsulfat; Metilsulfato de amezinio; Амезиния Метилсульфат.

4-Amino-6-methoxy-1-phenylpyridazinium methylsulfate.

$C_{12}H_{15}N_3O_5S$=313.3

CAS — 30578-37-1.

ATC — C01CA25.

ATC Vet — QC01CA25.

UNII — 03NR868ICX.

Profile

Amezinium metilsulfate is a sympathomimetic (p. 1507.3) used for its vasopressor effects in the treatment of hypotensive states (p. 1277.2). It is given orally in a usual dose of 10 mg up to three times daily. It has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Regulton; ***Ger.***: Regulton; Supratonin†; ***Jpn***: Risumic.

Amiloride Hydrochloride

(BANM, USAN, rINNM) ⊗

Amilorid Hidroklorür; Amilorid hydrochlorid dihydrát; Amilorida, hidrocloruro de; Amiloride, Chlorhydrate d'; Amilorid-hidroklorid; Amiloridhydrochlorid; Amiloridhydroklorid; Amiloridi Hydrochloridum; Amiloridi Hydrochloridum Dihydricum; Amiloridihydrokloridi; Amilorido hidrochloridas; Amilorydu chlorowodorek; Amipramizide; Cloridrato de Amilorida; Hidrocloruro de amilorida; MK-870; Амилорида Гидрохлорид.

N-Amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride dihydrate.

$C_6H_8ClN_7O,HCl,2H_2O$=302.1

CAS — 2609-46-3 (amiloride); 2016-88-8 (anhydrous amiloride hydrochloride); 17440-83-4 (amiloride hydrochloride dihydrate).

ATC — C03DB01.

ATC Vet — QC03DB01.

UNII — FZJ37245UC.

NOTE. Compounded preparations of amiloride hydrochloride may be represented by the following names:

- Co-amilofruse (*BAN*)—amiloride hydrochloride 1 part and furosemide 8 parts (w/w)
- Co-amilozide (*BAN*)—amiloride hydrochloride 1 part and hydrochlorothiazide 10 parts (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. & (Amiloride Hydrochloride). A pale yellow to greenish-yellow powder. Slightly soluble in water and in dehydrated alcohol. Protect from light.

USP 36: (Amiloride Hydrochloride). A yellow to greenish-yellow, odourless or practically odourless, powder. Slightly soluble in water; insoluble in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethyl sulfoxide; sparingly soluble in methyl alcohol.

Uses and Administration

Amiloride is a weak diuretic that appears to act mainly on the distal renal tubules. It is described as potassium-sparing since, like spironolactone, it increases the excretion of sodium and reduces the excretion of potassium. Unlike spironolactone, however, it does not act by specifically antagonising aldosterone. Amiloride does not inhibit carbonic anhydrase. It takes effect about 2 hours after oral dosage and its diuretic action reaches a peak in 6 to 10 hours and has been reported to persist for about 24 hours.

Amiloride diminishes the kaliuretic effects of other diuretics, and may produce an additional natriuretic effect. It is mainly used as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the long-term treatment of oedema associated with hepatic cirrhosis (including ascites, p. 1276.2) and heart failure (p. 1262.3). It is also used with other diuretics in the treatment of hypertension (p. 1251.1). Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics such as amiloride, is discussed under Effects on Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p. 1404.2. Amiloride is sometimes used to manage hypokalaemia in primary hyperaldosteronism (p. 1501.1).

Amiloride by inhalation has also been investigated in the management of cystic fibrosis patients with lung disease (see below).

In the treatment of **oedema** amiloride is given orally as the hydrochloride and doses are expressed in terms of the anhydrous substance. 1 mg of anhydrous hydrochloride is equivalent to about 1.14 mg of the hydrated substance. Treatment may be started with a dose of 5 to 10 mg daily, increased, if necessary, to a maximum of 20 mg daily. An initial dose of 2.5 mg once daily may be used in patients already taking other diuretics or antihypertensives. Similar doses to those given for oedema are used to reduce potassium loss in patients receiving thiazide or loop diuretics.

Potassium supplements should not be given.

For doses in children, see below.

Administration in children. Although amiloride is unlicensed in the UK for use in children, the *BNFC* suggests that it may be given with thiazides or loop diuretics in the treatment of oedema or congestive heart failure in neonates, infants, and children at an oral dose of 100 to 200 micrograms/kg twice daily (maximum total daily dose of 20 mg).

Cystic fibrosis. Pulmonary disease is the major cause of mortality in cystic fibrosis (p. 177.2). Experimental treatment aimed at modifying the pulmonary disease process has included giving amiloride by inhalation.[1,2] No evidence of pulmonary or systemic toxicity was seen in 14 patients treated for 25 weeks.[1] The mechanism of action is unclear but could be the sodium-channel blocking effect[1] or anti-inflammatory effects[3] of amiloride. Concern has been expressed[4] over possible consequences of the inhibition of endogenous urokinase by amiloride although others[5] considered this to be unlikely at the concentrations studied. However, a systematic review[6] found no evidence that amiloride was of clinical benefit.

1. Knowles MR, *et al.* A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **322:** 1189–94.
2. App EM, *et al.* Acute and long-term amiloride inhalation in cystic fibrosis lung disease: a rational approach to cystic fibrosis therapy. *Am Rev Respir Dis* 1990; **141:** 605–12.
3. Gallo RL. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 996–7.
4. Henkin J. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 997.
5. Knowles MR, *et al.* Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 997–8.
6. Burrows E, *et al.* Sodium channel blockers for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/04/08).

Diabetes insipidus. Thiazide diuretics are commonly used in nephrogenic diabetes insipidus (p. 2348.2) and NSAIDs may also be employed; both result in an overall decrease in urine production. Hydrochlorothiazide with amiloride has been reported to be at least as effective as hydrochlorothiazide plus indometacin in 5 patients.[1] In addition, amiloride obviated the need for potassium supplements. Hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; **117:** 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; **80:** 548–52.

Renal calculi. Patients with idiopathic hypercalciuria and a history of renal calculi (p. 2350.3) are usually given a thiazide diuretic such as hydrochlorothiazide to reduce calcium excretion. In patients with calcium oxalate calculi an inherited cellular defect in oxalate transport may also be involved and this might be corrected by amiloride.[1]

1. Baggio B, *et al.* An inheritable anomaly of red-cell oxalate transport in "primary" calcium nephrolithiasis correctable with diuretics. *N Engl J Med* 1986; **314:** 599–604.

Adverse Effects

Amiloride can cause hyperkalaemia, particularly in elderly patients, diabetics, and patients with renal impairment. Hyponatraemia has been reported in patients taking amiloride with other diuretics. Amiloride may cause nausea, vomiting, abdominal pain, diarrhoea or constipation, paraesthesia, thirst, dizziness, rashes, pruritus, weakness, muscle cramps, headache, and minor psychiatric or visual changes. Orthostatic hypotension and rises in blood-urea-nitrogen concentrations have been reported. Other adverse effects of amiloride may include alopecia, cough, dyspnoea, jaundice, encephalopathy, impotence, angina pectoris, arrhythmias, and palpitations.

Effects on electrolyte balance. There have been reports of metabolic acidosis associated with amiloride or triamterene[1] and with co-amilozide.[2]

1. Kushner RF, Sitrin MD. Metabolic acidosis: development in two patients receiving a potassium-sparing diuretic and total parenteral nutrition. *Arch Intern Med* 1986; **146:** 343–5.
2. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; **56:** 348–50.

POTASSIUM. Hyperkalaemia is the main adverse effect when amiloride is given alone but may also occur when amiloride is given with a potassium-wasting diuretic. Severe hyperkalaemia has been reported during co-amilozide therapy, particularly in patients with renal impairment[1,2] and has been accompanied by metabolic acidosis in one such patient.[3]

1. Whiting GFM, *et al.* Severe hyperkalaemia with Moduretic. *Med J Aust* 1979; **1:** 409.
2. Jaffey L, Martin A. Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. *Lancet* 1981; **i:** 1272.
3. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; **56:** 348–50.

SODIUM. For reports of severe hyponatraemia in patients taking diuretics such as amiloride with potassium-wasting diuretics, see Hydrochlorothiazide, p. 1404.3.

Effects on the skin. For a report of photosensitivity reactions in patients taking co-amilozide, see Hydrochlorothiazide, p. 1405.3.

Precautions

Amiloride has the same precautions as spironolactone with regard to hyperkalaemia (see p. 1502.1). It should be stopped at least 3 days before glucose-tolerance tests are performed in patients who may have diabetes mellitus because of the risks of provoking severe hyperkalaemia.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amiloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

There is an increased risk of hyperkalaemia if amiloride is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may also occur in patients given amiloride with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients taking amiloride with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may increase the risk of lithium toxicity by reducing its excretion, but such toxicity does not appear to occur with amiloride. Severe hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients taking chlorpropamide. Amiloride may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, amiloride may enhance the effects of other antihypertensive drugs.

Digoxin. For the effects of amiloride on digoxin clearance and inotropic activity, see p. 1357.2.

Quinidine. For a report of amiloride producing arrhythmias in patients receiving quinidine, see p. 1483.2.

Pharmacokinetics

Amiloride is incompletely absorbed from the gastrointestinal tract; bioavailability is about 50% and is reduced by food. It is not significantly bound to plasma proteins and has a plasma half-life of 6 to 9 hours; the terminal half-life may be 20 hours or more. It is excreted unchanged by the kidneys.

General references.

1. Weiss P, *et al.* The metabolism of amiloride hydrochloride in man. *Clin Pharmacol Ther* 1969; **10:** 401–6.

Hepatic impairment. In patients with acute hepatitis the terminal half-life of amiloride was 33 hours compared with 21 hours in healthy subjects.[1] The proportion of the dose excreted in the urine was increased from 49 to 80%.

1. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; **33:** 493–8.

Renal impairment. Studies of the pharmacokinetics of amiloride[1,2] have reported an increase in terminal elimination half-life from 20 hours in healthy subjects to 100 hours in patients with end-stage renal disease. The natriuretic effect of amiloride was reduced[1] in patients with creatinine clearance below 50 mL/minute. In patients with renal impairment amiloride could aggravate potassium retention due to renal disease. Studies in elderly patients have found increased half-life[3] and steady-state concentrations[4] associated with reduced renal function.

1. Knauf H, *et al.* Limitation on the use of amiloride in early renal failure. *Eur J Clin Pharmacol* 1985; **28:** 61–6.
2. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; **33:** 493–8.
3. Sabanathan K, *et al.* A comparative study of the pharmacokinetics and pharmacodynamics of atenolol, hydrochlorothiazide and amiloride in normal young and elderly subjects and elderly hypertensive patients. *Eur J Clin Pharmacol* 1987; **32:** 53–60.
4. Ismail Z, *et al.* The pharmacokinetics of amiloride-hydrochlorothiazide combination in the young and elderly. *Eur J Clin Pharmacol* 1989; **37:** 167–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bisdiur; ***Austral.***: Kaluril; Midamor†; ***Canad.***: Midamor; ***China***: Bi Da Shu (必达疏); ***Cz.***: Amiclaran†; ***Fr.***: Modamide; ***NZ***: Midamor†; ***UK***: Amilamont; ***USA***: Midamor.

Multi-ingredient Preparations. ***Arg.***: Diflux; Diur Pot; Diurex A; Errolon A; Hidrenox A; Lasiride; Moduretic; Nuriban A; Plenacor D; Ren-Ur; Vericordin Compuesto; ***Austral.***: Amizide;

Moduretic; ***Austria***: Amiloretik; Amilorid comp; Amilostad HCT; Loradur; Moducrin†; Moduretic; ***Belg.***: Co-Amiloride; Frusamil; Moduretic; ***Braz.***: Amilorid; Amiretic; Ancloric; Diupress; Diurezin-A; Diurisa; Moduretic; ***Canad.***: Apo-Amilzide; Gen-Amilazide†; Moduret†; Novamilor; Nu-Amilzide; ***Chile***: Furdiuren; Hidrium; Hidropid†; ***China***: Fuluobi (福洛必); Mengdaqing (蒙达清); Wu Du Li (武都力); ***Cz.***: Amicloton; Amilorid/HCT; Apo-Amilzide; Loradur; Moduretic; Rhefluin; ***Denm.***: Amilco; Frusamil; Sparkal; ***Fin.***: Amitrid; Diuramin; Diurex; Miloride; Sparkal; ***Fr.***: Logirene; Moducren; Moduretic; ***Ger.***: Amilocomp beta†; Amiloretik†; Amilorid comp; Amilorid/HCT†; Diaphal; Diursan†; Moducrin; Moduretik†; Tensoflux; ***Gr.***: Frumil; Ividol; Moduretic; Scandrex; Tiaden; ***Hong Kong***: Amithiazide; Apo-Amilzide; Moducren†; Moduretic; Navispare; Sefaretic; ***Hung.***: Amilorid Comp; Amilozid-B; ***India***: Amifru; Amilochlor; Amimide; Beta-Biduret; Biduret; Bp-Loride; Exna-K; Frumil; Hipres-D; Lasiride; ***Indon.***: Lorinid; ***Irl.***: Buram†; Fru-Co; Frumil; Moducren†; Moduret; ***Israel***: Kaluril; ***Ital.***: Moduretic; ***Malaysia***: Ami-Hydrotride; Amizide†; Apo-Amilzide; Moduretic; Moduride; ***Mex.***: Moduretic; ***Neth.***: Moduretic; ***Norw.***: Moduretic; Normorix; ***NZ***: Amizide†; Frumil; Moduretic; ***Pol.***: Tialorid; ***Port.***: Diurene†; Moduretic; ***S.Afr.***: Adco-Retic; Amiloretic; Betaretic; GSA-Retic; Hexaretic†; Moducren†; Moduretic; Servatrin; ***Singapore***: Apo-Amilzide; ***Spain***: Ameride; Diuzine; Kalten; ***Swed.***: Amiloferm; Moduretic†; Normorix; Sparkal; ***Switz.***: Amiloride/HCT†; Comilorid; Ecodurex; Escoretic†; Grodurex; Kalten†; Moduretic; Rhefluin; ***Thai.***: Amilozide; Bilduretic; Buretic; Hydrozide Plus; Hyperretic; Meditic; Miduret; Minitic; Miretic; Modupac; Moduretic; Moure-M†; Mourinate; Poli-Uretic; Renaset†; Sefaretic†; ***Turk.***: Moduretic; ***UK***: Amil-Co; Aridil; Fru-Co; Frumil; Kalten; Komil; Moduret; Moduretic; Navispare; ***USA***: Moduretic; ***Venez.***: Furdiuren; Moduretic.

Pharmacopoeial Preparations

BP 2014: Amiloride Tablets; Co-amilofruse Tablets; Co-amilozide Oral Solution; Co-amilozide Tablets;

USP 36: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Amiloride Hydrochloride Tablets.

Amiodarone *(BAN, USAN, rINN)*

Amiodaron; Amiodarona; Amiodaroni; Amiodaronum; L-3428; 51087-N; SKF-33134-A; Амиодарон.

2-Butylbenzofuran-3-yl 4-(2-diethylaminoethoxy)-3,5-diiodophenyl ketone.

$C_{25}H_{29}I_2NO_3$=645.3

CAS — 1951-25-3.

ATC — C01BD01.

ATC Vet — QC01BD01.

UNII — N3RQ532IUT.

Amiodarone Hydrochloride *(BANM, rINNM)*

Amiodaron Hidroklorür; Amiodarona, hidrocloruro de; Amiodarone, chlorhydrate d'; Amiodaron-hidroklorid; Amiodaronhydrochlorid; Amiodaron-hydrochlorid; Amiodaronhydroklorid; Amiodaroni Hydrochloridum; Amiodaronihydrokloridi; Amjodarono hidrochloridas; Hidrocloruro de amiodarona; Амиодарона Гидрохлорид.

$C_{25}H_{29}I_2NO_3$,HCl=681.8

CAS — 19774-82-4.

ATC — C01BD01.

ATC Vet — QC01BD01.

UNII — 976728SY6Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Amiodarone Hydrochloride). A white or almost white, fine crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Store at a temperature not exceeding 30 degrees. Protect from light.

USP 36: (Amiodarone Hydrochloride). White or almost white, fine, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in dichloromethane. A 5% solution in water has a pH of 3.2 to 3.8. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Adsorption. Amiodarone is known to be adsorbed by PVC, although the amount of adsorption has varied in different studies. A study[1] using amiodarone hydrochloride 600 micrograms/mL in glucose 5% found that the concentration fell by 10% in 3 hours followed by a steady decrease to 60% of the initial concentration after 5 days when stored in flexible PVC bags at ambient temperature.[1] However, another study[2] using amiodarone hydrochloride 1.8 to 2 mg/mL in glucose 5% found only that the concentration remained 97.3% of the initial value after 24 hours in PVC infusion bags. In the first study, perfusion of the solution through PVC giving sets resulted in the concentration falling to 82% after 15 minutes, whereas the second study found the concentration fell to 95.1% after 1 hour but then returned to the initial value. No loss was noted in either study when glass or rigid PVC containers were used, suggesting that the losses were caused by the plasticiser, di-2-ethylhexylphthalate (DEHP). Amiodarone may also leach out DEHP and other plasticisers, and it has been suggested that bags and tubing containing DEHP should not be used for giving amiodarone in order to minimise patient exposure.

1. Weir SJ, *et al*. Sorption of amiodarone to polyvinyl chloride infusion bags and administration sets. *Am J Hosp Pharm* 1985; **42:** 2679–83.
2. Peters PG, Hayball PJ. A comparative analysis of the loss of amiodarone from small and large volume PVC and non-PVC infusion systems. *Anaesth Intensive Care* 1990; **18:** 241–5.

Incompatibility. Amiodarone injection has been reported to be incompatible with aminophylline,[1] flucloxacillin,[2] heparin,[3] and sodium bicarbonate.[4] A further study[5] reported incompatibility with ampicillin/sulbactam sodium, ceftazidime sodium, digoxin, furosemide, imipenem/cilastatin sodium, magnesium sulfate, piperacillin sodium, piperacillin/tazobactam sodium, potassium phosphate, and sodium phosphate. UK licensed product information states that it is incompatible with sodium chloride solutions.

1. Hasegawa GR, Eder JF. Visual compatibility of amiodarone hydrochloride injection with other injectable drugs. *Am J Hosp Pharm* 1984; **41:** 1379–80.
2. Taylor A, Lewis R. Amiodarone and injectable drug incompatibility. *Pharm J* 1992; **248:** 533.
3. Cairns CJ. Incompatibility of amiodarone. *Pharm J* 1986; **236:** 68.
4. Korth-Bradley JM. Incompatibility of amiodarone hydrochloride and sodium bicarbonate injections. *Am J Health-Syst Pharm* 1995; **52:** 2340.
5. Chalmers JR, *et al*. Visual compatibility of amiodarone hydrochloride injection with various intravenous drugs. *Am J Health-Syst Pharm* 2001; **58:** 504–6.

Stability. An oral suspension prepared from tablets[1] and containing amiodarone hydrochloride 5 mg/mL was stable for 3 months at 4 degrees and 6 weeks at 25 degrees.

1. Nahata MC. Stability of amiodarone in an oral suspension stored under refrigeration and at room temperature. *Ann Pharmacother* 1997; **31:** 851–2.

Uses and Administration

Amiodarone is an antiarrhythmic with mainly class III properties (see p. 1243.1). It is used in the control of ventricular and supraventricular arrhythmias, including arrhythmias associated with Wolff-Parkinson-White syndrome. It has been tried for the prevention of arrhythmias in patients with myocardial infarction or heart failure.

Amiodarone hydrochloride is given orally in initial doses of 200 mg three times daily for a week, then 200 mg twice daily for a week, and then a usual maintenance dosage of 200 mg or less daily, according to response. In the USA, amiodarone is only licensed for ventricular arrhythmias and higher doses are used: loading doses of amiodarone hydrochloride are up to 1.6 g daily for 1 to 3 weeks, followed by 600 to 800 mg daily for a month, then a usual maintenance dose of 400 mg daily. Consideration should be given to potential adverse effects, and patients should be given the minimum effective dose.

Amiodarone hydrochloride may be given intravenously where facilities for close monitoring of cardiac function and resuscitation are available. It is usually given as a dilute solution in glucose 5%. Solutions containing less than 600 micrograms/mL are unstable but high concentrations are irritating to the veins, and solutions containing more than 2 mg/mL should be given via a central catheter; a central catheter is also preferred if repeated or continuous infusion is required. The usual dose is 1 to 1.2 g over 24 hours, given by intermittent or continuous infusion as follows:

- in the UK, an initial infusion of 5 mg/kg in 250 mL of glucose 5% is given over 20 to 120 minutes; the infusion may be repeated if required, up to a total dose of 1.2 g in 24 hours, diluted in up to 500 mL of glucose 5%
- in the USA, an initial dose of 150 mg in 100 mL of glucose 5% is given over 10 minutes, followed by 900 mg in 500 mL of glucose 5% over 24 hours, given at a rate of 1 mg/minute for 6 hours and then 500 micrograms/minute for 18 hours; if necessary the maintenance infusion may be continued at a rate of 500 micrograms/minute using a 1 to 6 mg/mL solution
- In emergencies, amiodarone hydrochloride may be given in doses of 150 to 300 mg in 10 to 20 mL of glucose 5% by slow intravenous injection over a period of not less than 3 minutes; a second injection should not be given until at least 15 minutes after the first

For the use of amiodarone in children, see below.

General references.

1. Goldschlager N, *et al*. Practical guidelines for clinicians who treat patients with amiodarone. *Arch Intern Med* 2000; **160:** 1741–8.
2. Anonymous. Using oral amiodarone safely. *Drug Ther Bull* 2003; **41:** 9–12. Correction. *ibid.*; 40.
3. Siddoway LA. Amiodarone: guidelines for use and monitoring. *Am Fam Physician* 2003; **68:** 2189–96.
4. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007; **298:** 1312–22.

Administration. Addition of amiodarone hydrochloride to an intravenous infusion solution reduces the drop size delivered[1,2] and the reduction in size is greater as the concentration of amiodarone is increased. This resulted[1] in a reduction of about 30% in the expected delivery rate when amiodarone hydrochloride 1.2 g was given in 500 mL of glucose 5%. The reduction in drop size has been attributed to a reduction in surface tension caused by inclusion of Tween 80 (polysorbate 80) in the standard intravenous formulation.[1] Allowances should be made for the changes in drop size causing a reduction of the delivery rate of infusions of amiodarone hydrochloride. US licensed product information for the standard formulation (*Cordarone; Wyeth-Ayerst*) contra-indicates the use of drop-counter infusion sets and requires the use of a volumetric infusion pump when intravenous amiodarone is given. Aqueous formulations of amiodarone that do not contain polysorbate 80 have been developed and may be available in some countries, including the USA (*Nexterone; Prism*).

1. Capps PA, Robertson AL. Influence of amiodarone injection on the delivery rate of intravenous fluids. *Pharm J* 1985; **234:** 14–15.
2. Chouhan UM, Lynch E. Amiodarone intravenous infusion. *Pharm J* 1985; **235:** 466.

Administration in children. Amiodarone has been used orally and intravenously in infants and children[1-3] (but see Precautions, p. 1303.1 for a warning about benzyl alcohol in some intravenous preparations). In the management of cardiac arrhythmias, amiodarone hydrochloride may be given orally in a loading dose of 10 to 20 mg/kg daily (or 500 mg/m^2 daily) for 7 to 10 days, followed by the lowest possible maintenance dose, ranging from 5 to 10 mg/kg daily (or 250 mg/m^2 daily) according to response. It has also been given intravenously in a loading dose of 5 mg/kg given over 20 minutes to 2 hours, followed by a maintenance dose of 10 to 15 mg/kg daily. The *BNFC* suggests intravenous infusions of 5 mg/kg given over 30 minutes and repeated every 12 to 24 hours for neonates, and 5 to 10 mg/kg given over 20 minutes to 2 hours and followed by continuous infusion of 300 micrograms/kg per hour (maximum 1.5 mg/kg per hour) for infants and children up to 18 years. An intravenous injection of 5 mg/kg (maximum 300 mg) given over at least 3 minutes may be used in neonates and children up to 18 years for the termination of ventricular fibrillation or pulseless ventricular tachycardia that is unresponsive to defibrillation.

1. Shuler CO, *et al*. Efficacy and safety of amiodarone in infants. *Am Heart J* 1993; **125:** 1430–2.
2. Figa FH, *et al*. Clinical efficacy and safety of intravenous amiodarone in infants and children. *Am J Cardiol* 1994; **74:** 573–7.
3. Saul JP, *et al*. Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. *Circulation* 2005; **112:** 3470–7.

Advanced cardiac life support. Cardiac arrest should be treated by starting full life support measures (see p. 1268.3). Amiodarone may be considered in cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia that is refractory to rapid defibrillation. Although higher doses have been used, guidelines[1-3] now recommend an intravenous dose of 300 mg, with a further dose of 150 mg if necessary; it may be given by intraosseous injection if the intravenous route is not available. In the UK[3] and European guidelines,[2] this may be followed by an infusion of 900 mg over 24 hours. A study[4] in patients with cardiac arrest outside hospital found that amiodarone improved survival to admission, while another study[5] found that it was more effective than lidocaine in this setting. Retrospective studies[6,7] of its use in cardiac arrest occurring in hospital, however, have not found it to be of benefit.

1. The American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; **122** (suppl 3): S639–S946. Also available at: http://circ.ahajournals.org/content/vol122/18_suppl_3/ (accessed 21/01/11)
2. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2010. *Resuscitation* 2010; **81:** 1219–1451. Also available at: http://www.cprguidelines.eu/2010 (accessed 07/02/11)
3. Resuscitation Council (UK). 2010 Resuscitation Guidelines. Available at: http://www.resus.org.uk/pages/GL2010.pdf (accessed 21/01/11)
4. Kudenchuk PJ, *et al*. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; **341:** 871–8.
5. Dorian P, *et al*. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002; **346:** 884–90. Correction. *ibid.*; **347:** 955.
6. Pollak PT, *et al*. The use of amiodarone for in-hospital cardiac arrest at two tertiary care centres. *Can J Cardiol* 2006; **22:** 199–202.
7. Rea RS, *et al*. Comparing intravenous amiodarone or lidocaine, or both, outcomes for inpatients with pulseless ventricular arrhythmias. *Crit Care Med* 2006; **34:** 1617–23.

Cardiac arrhythmias. Amiodarone is an effective drug for the treatment of symptomatic supraventricular and ventricular arrhythmias[1,2] (p. 1266.1); it has a relatively low risk of cardiovascular adverse effects and may be particularly useful in patients with structural heart disease. It is also used to prevent recurrence of both supraventricular and ventricular arrhythmias, although non-cardiac toxicity

may limit its long-term use;[2] a small study[3] suggested that short-term use (4 weeks) delayed the recurrence of atrial fibrillation after electrical cardioversion, but the benefits of this approach require confirmation in larger studies. Amiodarone has been used in children (see p. 1300.3), and has been given by various routes to terminate fetal arrhythmias.[4,5]

Perioperative use[6-8] reduces the incidence of atrial fibrillation and other arrhythmias after cardiac surgery. Amiodarone may also have a role in the management of **cardiac arrest** (see Advanced Cardiac Life Support, p. 1300.3); it has been tried for its antiarrhythmic effect in the management of **heart failure** (see below).

Amiodarone has been used for the prevention of sudden cardiac death in patients with asymptomatic ventricular arrhythmias following myocardial infarction, in patients with a history of aborted sudden cardiac death, and in patients with hypertrophic cardiomyopathy or other cardiac disorders that place them at high risk. Although amiodarone may reduce mortality the effect appears to be small,[2,9,10] and early use of high doses after myocardial infarction may be detrimental.[11] For long-term prophylaxis, implantable cardioverter defibrillators are more effective than antiarrhythmic drugs and are usually preferred; amiodarone may have a role as an adjunct to implantable cardioverter defibrillators to prevent frequent shocks,[12] and may also be used in patients who cannot be given an implantable cardioverter defibrillator.

While amiodarone can cause torsade de pointes it appears to do so rarely[13] and patients who have had this form of ventricular tachycardia as a result of other antiarrhythmic therapy have been given amiodarone subsequently without a recurrence.[14]

1. Desai AD, *et al*. The role of intravenous amiodarone in the management of cardiac arrhythmias. *Ann Intern Med* 1997; **127:** 294–303. Correction. *ibid*. 1998; **128:** 505.
2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999; **100:** 2025–34.
3. Boos C, *et al*. A short course of oral amiodarone improves sinus rhythm maintenance post-cardioversion for atrial fibrillation. *Heart* 2004; **90:** 1063–4.
4. Flack NJ, *et al*. Amiodarone given by three routes to terminate fetal atrial flutter associated with severe hydrops. *Obstet Gynecol* 1993; **82:** 714–16.
5. Strasburger JF, *et al*. Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004; **109:** 375–9.
6. Aasbo JD, *et al*. Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis. *Ann Intern Med* 2005; **143:** 327–36.
7. Mitchell LB, *et al*. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. *JAMA* 2005; **294:** 3093–3100.
8. Khanderia U, *et al*. Amiodarone for atrial fibrillation following cardiac surgery: development of clinical practice guidelines at a university hospital. *Clin Cardiol* 2008; **31:** 6–10.
9. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–24.
10. Hilleman DE, Bauman JL. Role of antiarrhythmic therapy in patients at risk for sudden cardiac death: an evidence-based review. *Pharmacotherapy* 2001; **21:** 556–75.
11. Elizari MV, *et al*. Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. *Eur Heart J* 2000; **21:** 198–205.
12. Connolly SJ, *et al*. Comparison of β-blockers, amiodarone plus β-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006; **295:** 165–71.
13. Hohnloser SH, *et al*. Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; **121:** 529–35.
14. Mattioni TA, *et al*. Amiodarone in patients with previous drug-mediated torsade de pointes: long-term safety and efficacy. *Ann Intern Med* 1989; **111:** 574–80.

Heart failure. Sudden deaths in patients with severe heart failure (p. 1262.3) have been attributed to ventricular arrhythmias but routine use of antiarrhythmics is not recommended since many have a negative inotropic effect. Amiodarone, which is not a negative inotrope, is usually the drug of choice in patients with heart failure and symptomatic arrhythmias, but its role for prophylaxis is less clear. In the GESICA study (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina)[1] amiodarone appeared to reduce mortality in patients with severe chronic heart failure who were without symptomatic ventricular arrhythmias. The decrease in mortality appeared to be greater than could be expected from antiarrhythmic activity alone. However, in the CHF-STAT study (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure)[2] involving patients with heart failure and premature ventricular contractions, overall survival did not appear to be improved by amiodarone. A meta-analysis[3] including these and 3 further studies concluded that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality. However, further studies[4,5] found that amiodarone had no effect on long-term survival, whereas implantable cardioverter defibrillators reduced mortality by about 25%, and a retrospective analysis[6] of a study in patients with heart failure after acute myocardial infarction found that mortality was higher in those taking amiodarone. Although some studies[1,7,8] have suggested that amiodarone may also improve cardiac function, adverse effects limit its use, and it is not currently recommended in heart failure except in patients with symptomatic ventricular arrhythmias.

1. Doval HC, *et al*. Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; **344:** 493–8.
2. Singh SN, *et al*. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; **333:** 77–82.
3. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–24.
4. Bardy GH, *et al*. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–37.
5. Packer DL, *et al*. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the Sudden Cardiac Death in Heart Failure Trial. *Circulation* 2009; **120:** 2170–6.
6. Thomas KL, *et al*. Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality. *Am Heart J* 2008; **155:** 87–93.
7. Takemura K, *et al*. Low-dose amiodarone for patients with advanced heart failure who are intolerant of beta-blockers. *Circ J* 2002; **66:** 441–4.
8. Choo DC, *et al*. Amiodarone rescue therapy for severe decompensated heart failure initially unsuitable for beta-blockers. *J Cardiovasc Pharmacol Ther* 2003; **8:** 187–92.

Adverse Effects and Treatment

Adverse effects are common with amiodarone. Many are dose-related and reversible with reduction in dose; however, because of its long half-life this can take some time and adverse effects may develop after treatment is stopped.

Adverse cardiovascular effects associated with amiodarone include severe bradycardia, sinus arrest, and conduction disturbances. Severe hypotension may follow intravenous use, particularly (though not exclusively) at rapid infusion rates. Amiodarone may also produce ventricular tachyarrhythmias; torsade de pointes has been reported but appears to be less of a problem with amiodarone than other antiarrhythmics. Rarely, heart failure may be precipitated or aggravated.

Amiodarone reduces the peripheral transformation of thyroxine (T_4) to tri-iodothyronine (T_3) and increases the formation of reverse-T_3. It can affect thyroid function and may induce hypo- or hyperthyroidism.

There have been reports of severe pulmonary toxicity including pulmonary fibrosis and interstitial pneumonitis; these effects are usually reversible on withdrawal of amiodarone but are potentially fatal. Pulmonary haemorrhage has also been noted rarely.

Amiodarone can adversely affect the liver. There may be abnormal liver function tests and cirrhosis or hepatitis; fatalities have been reported.

Prolonged use of amiodarone causes the development of benign yellowish-brown corneal microdeposits in the majority of patients, sometimes associated with coloured haloes of light; these are reversible on stopping therapy. Photosensitivity reactions are also common and more rarely blue-grey discoloration of the skin may occur.

Other adverse effects reported include benign intracranial hypertension, haemolytic or aplastic anaemia, peripheral neuropathy, paraesthesias, myopathy, ataxia, tremor, nausea, vomiting, a metallic taste, nightmares, headaches, sleeplessness, fatigue, and epididymitis.

Thrombophlebitis can occur if amiodarone is injected regularly or infused for prolonged periods into a peripheral vein. Rapid intravenous injection has been associated with anaphylactic shock, hot flushes, sweating, and nausea.

It has been suggested that amiodarone-induced phospholipidosis may explain some of its adverse effects. Amiodarone's iodine content contributes to its thyrotoxicity.

Reviews of the adverse effects of amiodarone.

1. Naccarelli GV, *et al*. Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 246–53.
2. Kerin NZ, *et al*. Long-term efficacy and toxicity of high- and low-dose amiodarone regimens. *J Clin Pharmacol* 1989; **29:** 418–23.
3. Perkins MW, *et al*. Intraoperative complications in patients receiving amiodarone: characteristics and risk factors. *DICP Ann Pharmacother* 1989; **23:** 757–63.
4. Vrobel TR, *et al*. A general overview of amiodarone toxicity: its prevention, detection, and management. *Prog Cardiovasc Dis* 1989; **31:** 393–426.
5. Morgan DJR. Adverse reactions profile: amiodarone. *Prescribers' J* 1991; **31:** 104–11.
6. CSM/MCA. Amiodarone (Cordarone X). *Current Problems* 1996; **22:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 21/06/07)
7. Vorperian VR, *et al*. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997; **30:** 791–8.
8. Bongard V, *et al*. Incidence rate of adverse drug reactions during long-term follow-up of patients newly treated with amiodarone. *Am J Ther* 2006; **13:** 315–19.

Effects on electrolyte balance. Hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone has been reported[1-4] in patients taking amiodarone. In each case, the hyponatraemia improved when the dose was reduced or amiodarone was stopped.

1. Odeh M, *et al*. Hyponatremia during therapy with amiodarone. *Arch Intern Med* 1999; **159:** 2599–2600.
2. Ikegami H, *et al*. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by amiodarone: a report on two cases. *J Cardiovasc Pharmacol Ther* 2002; **7:** 25–8.
3. Patel GP, Kasiar JB. Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. *Pharmacotherapy* 2002; **22:** 649–51.
4. Aslam MK, *et al*. Syndrome of inappropriate antidiuretic hormone secretion induced by amiodarone therapy. *Pacing Clin Electrophysiol* 2004; **27:** 831–2.

Effects on the eyes. Slit-lamp examination showed corneal abnormalities in 103 of 105 patients treated with amiodarone for 3 months to 7 years.[1] The most advanced abnormality comprised whorled patterns with uniform granular opacities. The corneal deposits became denser if amiodarone dosage was increased and regressed if dosage was reduced. Ocular symptoms were reported in only 12 patients. Photophobia was reported in 3 patients, while 2 had visual haloes, 1 had blurring of vision, and a further 6 had lid irritation. However, lid irritation was considered a photosensitive skin reaction and blurred vision was probably not due to amiodarone. No patient had any deterioration in visual acuity attributable to amiodarone. In 16 patients amiodarone was withdrawn with complete clearing of corneal abnormalities within 7 months and routine ophthalmological monitoring was considered unnecessary in patients without ocular symptoms. Optic neuropathy[2-4] and neuritis with visual impairment have also been reported with amiodarone although it has been suggested[5] that the association is dubious and that the incidence of optic neuropathy in patients given amiodarone is low enough to support a hypothesis that the drug actually reduces the risk of idiopathic anterior ischaemic optic neuropathy. Nonetheless, licensed product information recommends that annual ophthalmological examinations should be performed.

A sicca syndrome with diminished tear and saliva production has been reported[6] during amiodarone treatment.

1. Ingram DV, *et al*. Ocular changes resulting from therapy with amiodarone. *Br J Ophthalmol* 1982; **66:** 676–9.
2. Feiner LA, *et al*. Optic neuropathy and amiodarone therapy. *Mayo Clin Proc* 1987; **62:** 702–17.
3. Macaluso DC, *et al*. Features of amiodarone-induced optic neuropathy. *Am J Ophthalmol* 1999; **127:** 610–12.
4. Johnson LN, *et al*. The clinical spectrum of amiodarone-associated optic neuropathy. *J Natl Med Assoc* 2004; **96:** 1477–91.
5. Mindel JS. Amiodarone and optic neuropathy. *Am Heart J* 2008; **156:** 411–13.
6. Dickinson EJ, Wolman RL. Sicca syndrome associated with amiodarone therapy. *BMJ* 1986; **293:** 510.

Effects on the genitalia. Epididymal swelling and scrotal pain have been reported with amiodarone.[1-3] Time to onset varied from 7 to 71 months after starting treatment, and resolution occurred within 10 weeks despite continuation of amiodarone in some patients. The mechanism of the reaction is unknown, but in 1 patient[2] the concentration of desethylamiodarone in semen was fivefold that in serum.

Brown discoloration of semen and sweat has also been associated with amiodarone therapy.[4]

1. Gasparich JP, *et al*. Non-infectious epididymitis associated with amiodarone therapy. *Lancet* 1984; **ii:** 1211–12.
2. Ward MJ, *et al*. Association of seminal desethylamiodarone concentration and epididymitis with amiodarone treatment. *BMJ* 1988; **296:** 19–20.
3. Sadek I, *et al*. Amiodarone-induced epididymitis: report of a new case and literature review of 12 cases. *Can J Cardiol* 1993; **9:** 833–6.
4. Adams PC, *et al*. Amiodarone in testis and semen. *Lancet* 1985; **i:** 341.

Effects on the heart. Amiodarone has the potential to provoke arrhythmias; it prolongs the QT interval and there have been reports of torsade de pointes. However, a review of the literature[1] indicated that the frequency of proarrhythmic events was low. The risk of torsade de pointes also appears to be lower with amiodarone than with other class III antiarrhythmics, possibly due to additional actions of amiodarone such as blockade of calcium channels.[2]

1. Hohnloser SH, *et al*. Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; **121:** 529–35.
2. Brendorp B, *et al*. A benefit-risk assessment of class III antiarrhythmic agents. *Drug Safety* 2002; **25:** 847–65.

Effects on lipid metabolism. Amiodarone increases phospholipid concentrations in tissues and this may be responsible for some of its adverse effects.[1] Although hyperlipidaemia may result from hypothyroidism, amiodarone can also increase serum-cholesterol concentrations independently of any effect on the thyroid.[2,3] The effect on triglyceride concentrations is not clear.[3]

1. Kodavanti UP, Mehendale HM. Cationic amphiphilic drugs and phospholipid storage disorder. *Pharmacol Rev* 1990; **42:** 327–54.
2. Wiersinga WM, *et al*. An increase in plasma cholesterol independent of thyroid function during long-term amiodarone therapy: a dose-dependent relationship. *Ann Intern Med* 1991; **114:** 128–32.

3. Lakhdar AA, *et al.* Long-term amiodarone therapy raises serum cholesterol. *Eur J Clin Pharmacol* 1991; **40:** 477–80.

Effects on the liver. Plasma concentrations of liver enzymes are often increased in patients taking amiodarone but this is usually asymptomatic. However, there have been reports of hepatic injury,[1-3] including hepatitis and cirrhosis, with histological changes resembling alcoholic liver disease.[1] Fatal cirrhosis has been reported, usually in patients receiving high doses or long-term therapy,[4-9] and may develop after stopping amiodarone. However, rapidly progressive fatal hepatic failure has occurred[10] only one month after starting treatment. There have also been reports of severe cholestasis, including a case that was reversible,[11] and another that was fatal, despite amiodarone being stopped.[12] Acute hepatitis occurring within 24 hours of intravenous amiodarone has been reported,[13-15] but in 1 case[14] did not recur with subsequent oral therapy, suggesting that the reaction may have been related to the vehicle used in the intravenous formulation.

1. Simon JB, *et al.* Amiodarone hepatotoxicity simulating alcoholic liver disease. *N Engl J Med* 1984; **311:** 167–72.
2. Babatin M, *et al.* Amiodarone hepatotoxicity. *Curr Vasc Pharmacol* 2008; **6:** 228–36.
3. Raja K, *et al.* Drug-induced steatohepatitis leading to cirrhosis: long-term toxicity of amiodarone use. *Semin Liver Dis* 2009; **29:** 423–8.
4. Lim PK, *et al.* Neuropathy and fatal hepatitis in a patient receiving amiodarone. *BMJ* 1984; **288:** 1638–9.
5. Tordjman K, *et al.* Amiodarone and the liver. *Ann Intern Med* 1985; **102:** 411–12.
6. Rinder HM, *et al.* Amiodarone hepatotoxicity. *N Engl J Med* 1986; **314:** 318–19.
7. Richer M, Robert S. Fatal hepatotoxicity following oral administration of amiodarone. *Ann Pharmacother* 1995; **29:** 582–6.
8. Singhal A, *et al.* Low dose amiodarone causing pseudo-alcoholic cirrhosis. *Age Ageing* 2003; **32:** 224–5.
9. Oikawa H, *et al.* Liver cirrhosis induced by long-term administration of a daily low dose of amiodarone: a case report. *World J Gastroenterol* 2005; **11:** 5394–7.
10. Lwakatare JM, *et al.* Fatal fulminating liver failure possibly related to amiodarone treatment. *Br J Hosp Med* 1990; **44:** 60–1.
11. Morse RM, *et al.* Amiodarone-induced liver toxicity. *Ann Intern Med* 1988; **109:** 838–40.
12. Chang C-C, *et al.* Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug: a case report and review of the literature. *Arch Pathol Lab Med* 1999; **123:** 251–6.
13. Pye M, *et al.* Acute hepatitis after parenteral amiodarone administration. *Br Heart J* 1988; **59:** 690–1.
14. James PR, Hardman SMC. Acute hepatitis complicating parenteral amiodarone does not preclude subsequent oral therapy. *Heart* 1997; **77:** 583–4.
15. Chan AL, *et al.* Fatal amiodarone-induced hepatotoxicity: a case report and literature review. *Int J Clin Pharmacol Ther* 2008; **46:** 96–101.

Effects on the lungs. Pulmonary toxicity is one of the most severe adverse effects associated with amiodarone therapy. Reviews have suggested that it may occur in 5%[1] to up to 10%[2] of patients (although the incidence in controlled studies appears to be lower[3]) and fatalities have been reported.[1,4,5] The onset is usually chronic, and patients often present several months after starting amiodarone with increasing dyspnoea, cough, and pleuritic chest pain; however, the onset may also be more acute, and in one patient[6] occurred within days of starting amiodarone. Acute reactions have also developed in patients undergoing surgery or other procedures;[3,7] two patients with amiodarone pulmonary toxicity died less than 1 hour and 24 hours, respectively after pulmonary angiography.[8] Different forms of toxicity have been reported, including interstitial and alveolar infiltration,[9] fibrosis,[4] pneumonitis,[10] and pleural effusion;[11,12] amiodarone-induced asthma has also been reported.[13] The mortality rate is estimated to be about 10% in those with pneumonitis; mortality is highest (about 50%) in patients who develop symptoms suggestive of acute respiratory distress syndrome.[1] Toxicity has been associated with increasing age, duration of treatment, and dose,[1,9,14] but it has also occurred at low doses,[15] and different mechanisms may be involved;[2,7] some patients have evidence of direct toxicity, while in others[10] an immunological reaction appears to be involved. Most patients recover gradually if amiodarone is stopped, but treatment with corticosteroids may be given if necessary,[1,2,9] and has been particularly recommended[7] in acute lung injury.

1. Papiris SA, *et al.* Amiodarone: review of pulmonary effects and toxicity. *Drug Safety* 2010; **33:** 539–58.
2. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: recognition and pathogenesis. *Chest* 1988; **93:** 1067–75 (part 1) and 1242–8 (part 2).
3. Sunderji R, *et al.* Pulmonary effects of low dose amiodarone: a review of the risks and recommendations for surveillance. *Can J Cardiol* 2000; **16:** 1435–40.
4. Morera J, *et al.* Amiodarone and pulmonary fibrosis. *Eur J Clin Pharmacol* 1983; **24:** 591–3.
5. CSM. Recurrent ventricular tachycardia: adverse drug reactions. *BMJ* 1986; **292:** 50.
6. Goldstein I, *et al.* Very early onset of acute amiodarone pulmonary toxicity presenting with hemoptysis. *Chest* 1997; **111:** 1446–7.
7. Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? *Chest* 2001; **120:** 275–82.
8. Wood DL, *et al.* Amiodarone pulmonary toxicity: report of two cases associated with rapidly progressive fatal adult respiratory distress syndrome after pulmonary angiography. *Mayo Clin Proc* 1985; **60:** 601–3.
9. Marchlinski FE, *et al.* Amiodarone pulmonary toxicity. *Ann Intern Med* 1982; **97:** 839–45.
10. Venet A, *et al.* Five cases of immune-mediated amiodarone pneumonitis. *Lancet* 1984; **i:** 962–3.
11. Mittal SR, Maheshwari M. Amiodarone-induced exudative pleural effusion—a case report and review of literature. *Indian Heart J* 2006; **58:** 352–5.
12. Uong V, *et al.* Amiodarone-induced loculated pleural effusion: case report and review of the literature. Abridged version: *Pharmacotherapy* 2010; **30:** 218. Full version: http://www.pharmacotherapy.org/Case_Reports/Pharm3002e_Uong-CR.pdf (accessed 16/02/10)
13. Yavuzgil O, *et al.* New-onset bronchial asthma induced by low-dose amiodarone. *Ann Pharmacother* 2005; **39:** 385–6.
14. Ernawati DK, *et al.* Amiodarone-induced pulmonary toxicity. *Br J Clin Pharmacol* 2008; **66:** 82–7.
15. Ott MC, *et al.* Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest* 2003; **123:** 646–51.

Effects on mental state. There have been isolated reports of patients (age range 54 to 80 years) developing delirium within about 4 to 17 days of starting amiodarone therapy.[1-3] Mental status improved on withdrawal of amiodarone. Amiodarone-associated depression has also been reported.[4,5]

1. Trohman RG, *et al.* Amiodarone-induced delirium. *Ann Intern Med* 1988; **108:** 68–9.
2. Barry JJ, Franklin K. Amiodarone-induced delirium. *Am J Psychiatry* 1999; **156:** 1119.
3. Athwal H, *et al.* Amiodarone-induced delirium. *Am J Geriatr Psychiatry* 2003; **11:** 696–7.
4. Ambrose A, Salib E. Amiodarone-induced depression. *Br J Psychiatry* 1999; **174:** 366–7.
5. Cheesman N, Taylor D. Psychosis and depression associated with alteration to amiodarone therapy. *J Psychopharmacol* 2010; **24:** 131–3.

Effects on the nervous system. Neurological toxicity is a recognised adverse effect of amiodarone. A study[1] in 10 patients treated with amiodarone for more than 2 years found that 3 had evidence of peripheral neuropathy, possibly correlated with high doses and high serum concentrations of amiodarone. A later analysis[2] based on retrospective review of records for 707 patients treated with amiodarone found the cumulative incidence of neurotoxic events possibly related to the drug to be just under 3%; these included tremor, ataxia, peripheral neuropathy, and cognitive impairment. The main risk factor was considered to be duration of treatment.

1. Fraser AG, McQueen INF. Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287:** 612.
2. Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. *Arch Neurol* 2009; **66:** 865–9.

Effects on the pancreas. Pancreatitis has been reported[1] in a patient 4 days after starting amiodarone. Symptoms resolved after withdrawal of the drug but returned on re-exposure.

1. Bosch X, Bernadich O. Acute pancreatitis during treatment with amiodarone. *Lancet* 1997; **350:** 1300.

Effects on the skin and hair. The most common adverse skin reaction associated with amiodarone is photosensitivity. This is a phototoxic rather than a photoallergic reaction[1-3] and the wavelengths responsible extend from the long-wave ultraviolet (UVA) into the visible light range.[1] Affected patients should be advised to wear protective clothing and avoid exposure to sunlight. Topical sunblock preparations, such as those containing zinc or titanium oxides, may reduce the risk of reaction and a reduction in amiodarone dosage may also be useful.[1] Although pyridoxine has been reported[4] to protect against amiodarone-induced photosensitivity, results from a double-blind placebo-controlled study[5] indicated that it may enhance the photosensitivity. Photosensitivity may continue for several weeks after withdrawal of amiodarone due to its extensive distribution, and persistence for longer periods has been reported.[6] There have also been reports[7] of basal cell carcinoma, possibly related to amiodarone-induced photosensitivity.

Blue-grey[2,3,8] and golden-brown[3] pigmentation of light-exposed skin have been reported during long-term amiodarone use. The pigmentation is usually slowly reversible on withdrawing amiodarone but may not completely disappear. The mean concentrations of amiodarone and its desethyl metabolite in light-exposed pigmented skin have been found to be 10 times the concentrations in non-exposed skin.[2] Discoloration of semen and sweat has also been noted (see Effects on the Genitalia, p. 1301.3).

Cutaneous vasculitis,[9,10] exfoliative dermatitis,[11] and fatal toxic epidermal necrolysis[12,13] have been reported. Alopecia[14,15] has been associated with amiodarone but increased hair growth,[3] possibly due to the vasodilator activity of amiodarone, has also been reported. Extravasation of amiodarone injection has caused severe skin necrosis.[16]

1. Ferguson J, *et al.* Prevention of amiodarone-induced photosensitivity. *Lancet* 1984; **ii:** 414.
2. Zachary CB, *et al.* The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; **110:** 451–6.
3. Ferguson J, *et al.* A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; **113:** 537–49.
4. Kaufmann G. Pyridoxine against amiodarone-induced photosensitivity. *Lancet* 1984; **i:** 51–2.
5. Mulrow JP, *et al.* Pyridoxine and amiodarone-induced photosensitivity. *Ann Intern Med* 1985; **103:** 68–9.
6. Yones SS, *et al.* Persistent severe amiodarone-induced photosensitivity. *Clin Exp Dermatol* 2005; **30:** 500–502.
7. Hall MA, *et al.* Basalioma after amiodarone therapy—not only in Britain. *Br J Dermatol* 2004; **151:** 932–3.
8. Ammoury A, *et al.* Photodistribution of blue-gray hyperpigmentation after amiodarone treatment: molecular characterization of amiodarone in the skin. *Arch Dermatol* 2008; **144:** 92–6.
9. Starke ID, Barbatis C. Cutaneous vasculitis associated with amiodarone therapy. *BMJ* 1985; **291:** 940.
10. Gutierrez R, *et al.* Vasculitis associated with amiodarone treatment. *Ann Pharmacother* 1994; **28:** 537.
11. Moots RJ, Banerjee A. Exfoliative dermatitis after amiodarone treatment. *BMJ* 1988; **296:** 1332–3.
12. Bencini PL, *et al.* Toxic epidermal necrolysis and amiodarone treatment. *Arch Dermatol* 1985; **121:** 838.
13. Yung A, *et al.* Two unusual cases of toxic epidermal necrolysis. *Australas J Dermatol* 2002; **43:** 35–8.
14. Samanta A, *et al.* Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287:** 503.
15. Samuel LM, *et al.* Amiodarone and hair loss. *Postgrad Med J* 1992; **68:** 771.
16. Russell SJ, Saltissi S. Amiodarone induced skin necrosis. *Heart* 2006; **92:** 1395.

Effects on thyroid function. Amiodarone has complex effects on thyroid function[1-5] and, while the majority of euthyroid patients receiving amiodarone remain clinically euthyroid, both hypo- and hyperthyroidism may occur. Amiodarone has direct effects on the thyroid gland, but also alters serum concentrations of thyroid hormones, complicating the interpretation of thyroid function tests. Use of amiodarone results in a reduction of the peripheral conversion of thyroxine (T_4) to tri-iodothyronine (T_3) with a resulting increase in T_4, a modest fall in T_3, and an increase in reverse-T_3 concentrations; the basal serum-TSH (thyroid-stimulating hormone; thyrotrophin) concentration rises initially but tends to return to normal after about 3 months of treatment.

The prevalence of clinical hypo- and hyperthyroidism appears to correlate with dietary iodine intake, with hypothyroidism being more common in areas of adequate iodine intake and hyperthyroidism in areas of lower intake; the overall incidence of thyroid disorders has been suggested[2] to be anywhere between 1 to 32%. Although the exact mechanism for the toxicity is unknown, amiodarone has a high iodine content (about 75 mg of iodine in each 200-mg tablet) and the large iodine load may affect the thyroid, particularly in patients with an underlying subclinical thyroid defect. Auto-immune mechanisms may also contribute and antithyroid antibodies have been detected during amiodarone therapy. The high iodine load appears to be the main mechanism for hypothyroidism, but for hyperthyroidism two mechanisms may be involved. Type I amiodarone-induced thyrotoxicosis appears to be precipitated by the iodine load, whereas type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis that is probably caused by a direct toxic effect on the thyroid gland.

Assessment of thyroid function is recommended in patients before starting amiodarone treatment and periodically during treatment; TSH concentrations should be measured, along with free T_3 and T_4.

Amiodarone-induced hypothyroidism usually presents similarly to other forms of hypothyroidism[1-3] and treatment is with levothyroxine, starting with a low dose and gradually increasing until control is achieved; amiodarone may be continued.

Amiodarone-induced hyperthyroidism is a more complex problem and may be difficult to diagnose and manage.[1-3,6] Patients may present with classical symptoms such as tachycardia, tremor, weight loss, nervousness, and irritability, but in other cases reappearance of angina, or a worsening of arrhythmia may be the only indication. Amiodarone is usually stopped if clinical hyperthyroidism develops, but may be continued if necessary while the hyperthyroidism is treated.[1-3,6-8] Management depends on whether the patient has type I or type II hyperthyroidism. Treatment of type I is usually with the thiourea drugs carbimazole, thiamazole, or propylthiouracil; in resistant cases potassium perchlorate may be used with a thiourea to reduce the thyroid iodine load. Lithium carbonate has been used as an alternative, but its role is not yet established.[1,2] In type II thyrotoxicosis, treatment is usually with corticosteroids, and they may also be used with thioureas where the type is mixed or unclear.[8] Oral cholecystographic contrast media such as iopanoic acid have also been used, but appear to be less effective.[9] Radio-iodine can be used but may not be effective if the uptake of radio-iodine by the thyroid is low due to the iodine load from amiodarone; radio-iodine has also been used[10] to allow amiodarone to be restarted in patients with a history of amiodarone-induced hyperthyroidism. Thyroidectomy may have a role[1-3,6,8,11] in the treatment of resistant amiodarone-induced hyperthyroidism.

1. Loh K-C. Amiodarone-induced thyroid disorders: a clinical review. *Postgrad Med J* 2000; **76:** 133–40.
2. Martino E, *et al.* The effects of amiodarone on the thyroid. *Endocr Rev* 2001; **22:** 240–54.
3. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med* 2005; **118:** 706–14.

4. Eskes SA, Wiersinga WM. Amiodarone and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; **23:** 735–51.
5. Cohen-Lehman J, *et al.* Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol* 2010; **6:** 34–41.
6. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61:** 494–502.
7. Uzan L, *et al.* Continuation of amiodarone therapy despite type II amiodarone-induced thyrotoxicosis. *Drug Safety* 2006; **29:** 231–6.
8. Bahn RS, *et al.* Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011; **21:** 593–646. Also printed in *Endocr Pract* 2011; **17:** 456–520. Also available at: https://www.aace.com/sites/default/files/HyperGuidelines2011.pdf (accessed 28/06/11)
9. Bogazzi F, *et al.* Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab* 2003; **88:** 1999–2002.
10. Hermida J-S, *et al.* Radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis. *Am J Med* 2004; **116:** 345–8.
11. Gough IR, Gough J. Surgical management of amiodarone-associated thyrotoxicosis. *Med J Aust* 2002; **176:** 128–9.

Lupus. There have been reports[1-3] of lupus developing in patients treated with amiodarone; the condition improved when amiodarone was stopped.

1. Susano R, *et al.* Amiodarone induced lupus. *Ann Rheum Dis* 1999; **58:** 655–6.
2. Sheikhzadeh A, *et al.* Drug-induced lupus erythematosus by amiodarone. *Arch Intern Med* 2002; **162:** 834–6.
3. Kundu AK. Amiodarone-induced systemic lupus erythematosus. *J Assoc Physicians India* 2003; **51:** 216–17.

Precautions

Amiodarone should not be given to patients with bradycardia, sino-atrial block, AV block or other severe conduction disorders (unless the patient has a pacemaker), severe hypotension, or severe respiratory failure. It may be used, but with caution, in patients with heart failure. Electrolyte disorders should be corrected before starting treatment. The use of amiodarone should be avoided in patients with iodine sensitivity, or evidence or history of thyroid disorders. Patients taking amiodarone should avoid exposure to sunlight.

Thyroid function should be monitored regularly in order to detect amiodarone-induced hyper- or hypothyroidism. Thyroxine, tri-iodothyronine, and thyrotrophin (thyroid-stimulating hormone; TSH) concentrations should be measured; clinical assessment is important but is unreliable alone. See also Effects on Thyroid Function under Adverse Effects and Treatment, p. 1302.3.

Tests of liver and pulmonary function should also be carried out regularly in patients on long-term therapy. Ophthalmological examinations should be performed annually. Although urinary excretion is not a major route for the elimination of amiodarone or its metabolites, there is a possibility of iodine accumulation in renal impairment.

Intravenous injections of amiodarone should be given slowly: if prolonged or repeated infusions are envisaged, the use of a central venous catheter should be considered. Some intravenous preparations of amiodarone contain benzyl alcohol, a preservative that has caused fatal 'gasping syndrome' in neonates (see Neonates, under Benzyl Alcohol, p. 1741.1), and should be avoided in infants and children up to 3 years old.

Some of the contra-indications for amiodarone may not apply when it is given intravenously in emergency situations.

Administration. For the problems of controlling the delivery rate of amiodarone by intravenous infusion, see under Uses and Administration, p. 1300.3.

Breast feeding. Amiodarone is distributed into breast milk[1,2] and significant amounts may be ingested if infants are breast fed. Licensed product information therefore contra-indicates the use of amiodarone during breast feeding, and the American Academy of Pediatrics considers[3] that the use of amiodarone may be of concern due to the risk of hypothyroidism in the infant. In one study,[2] amiodarone was still detectable in breast milk several weeks after amiodarone was stopped, suggesting that caution is still required. However, there has been a report[4] of an infant who was successfully breast fed with close monitoring of thyroid function; the mother stopped amiodarone at delivery.

1. Pitcher D, *et al.* Amiodarone in pregnancy. *Lancet* 1983; **i:** 597–8.
2. Plomp TA, *et al.* Use of amiodarone during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992; **43:** 201–7.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)
4. Hall CM, McCormick KPB. Amiodarone and breast feeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F255–F258.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amiodarone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Each 200-mg tablet of amiodarone contains about 75 mg of iodine. The potential effect of this iodine load on the fetus has limited the use of amiodarone in pregnancy since iodine freely crosses the placenta and may cause thyroid disorders in the fetus. In addition, amiodarone and desethylamiodarone both cross the placenta, with respective concentrations in cord blood at delivery of about 10% and 25% of the maternal plasma concentrations, and direct effects on the fetus are therefore possible. However, a review[1] of 64 reported cases of amiodarone use during pregnancy found no evidence of an increased incidence of fetal malformations; hypothyroidism occurred in 14 neonates (22%), but only 2 had detectable goitre, and 2 neonates had transient hyperthyroidism. Neurodevelopmental follow-up was limited, but mild abnormalities were reported in some cases; this appeared to be independent of thyroid status, suggesting it may have been due to a direct effect of amiodarone.

1. Bartalena L, *et al.* Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001; **24:** 116–30.

Interactions

Amiodarone should be used with caution with other drugs liable to induce bradycardia, such as beta blockers or calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, particularly drugs that prolong the QT interval such as fluoroquinolones, phenothiazine antipsychotics, tricyclic antidepressants, halofantrine, and terfenadine, should be avoided. Drugs that cause hypokalaemia or hypomagnesaemia may also increase the risk of arrhythmias with amiodarone. Amiodarone is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8 and interactions may occur with inhibitors of these enzymes, particularly with inhibitors of CYP3A4 such as HIV-protease inhibitors, cimetidine, and grapefruit juice. Enzyme inducers such as rifampicin and phenytoin may reduce amiodarone concentrations. In addition, amiodarone is an inhibitor of some cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6, resulting in higher plasma concentrations of other drugs metabolised by these enzymes. Examples of these include ciclosporin, clonazepam, digoxin, flecainide, phenytoin, procainamide, quinidine, simvastatin, and warfarin. Amiodarone also inhibits P-glycoprotein and could affect drugs that are P-glycoprotein substrates.

Reviews.

1. Marcus FI. Drug interactions with amiodarone. *Am Heart J* 1983; **106:** 924–30.
2. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.

Agalsidase. For the effect of the use of amiodarone with *agalsidase alfa* or *beta*, see p. 2438.1.

Antibacterials. Palpitations and activation of an implantable cardioverter defibrillator occurred[1] in a woman receiving amiodarone when *rifampicin* was added. Serum concentrations of amiodarone were reduced, probably due to induction of metabolising enzymes by rifampicin.

1. Zarembski DG, *et al.* Impact of rifampin on serum amiodarone concentrations in a patient with congenital heart disease. *Pharmacotherapy* 1999; **19:** 249–51.

Antiepileptics. The interaction between *phenytoin* and amiodarone resulting in increased plasma-phenytoin concentrations is widely recognised (see p. 542.3). However, phenytoin is a hepatic enzyme inducer and has been reported[1] to decrease serum-amiodarone concentrations by 32 and 49% after 1 and 2 weeks of use respectively.

1. Nolan PE, *et al.* Effect of phenytoin on the clinical pharmacokinetics of amiodarone. *J Clin Pharmacol* 1990; **30:** 1112–19.

Antivirals. A potential interaction has been suggested between amiodarone and HIV-protease inhibitors due to inhibition of amiodarone metabolism. Raised serum concentrations of amiodarone have been reported[1] in a patient given *indinavir* for postexposure prophylaxis; no clinical signs of toxicity occurred.

1. Lohman JJHM, *et al.* Antiretroviral therapy increases serum concentrations of amiodarone. *Ann Pharmacother* 1999; **33:** 645–6.

Contrast media. For mention of prolonged QT intervals in patients taking amiodarone who were given *iohexol*, see p. 1590.2.

Grapefruit juice. A study[1] in healthy subjects reported that grapefruit juice decreased the metabolism of amiodarone; the area under the plasma concentration-time curve (AUC) and the peak plasma concentration of amiodarone were both increased.

1. Libersa CC, *et al.* Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol* 2000; **49:** 373–8.

Histamine H_2-antagonists. *Cimetidine* inhibits hepatic metabolism and an increase in the serum-amiodarone concentration has been reported[1] in 8 out of 12 patients given amiodarone and cimetidine.

1. Hogan C, *et al.* Cimetidine-amiodarone interaction. *J Clin Pharmacol* 1988; **28:** 909.

Theophylline. For a report of increased serum-theophylline concentrations and resultant adverse effects in a patient when amiodarone was added to therapy, see Antiarrhythmics, p. 1234.1.

Pharmacokinetics

Amiodarone is absorbed variably and erratically from the gastrointestinal tract; the average bioavailability is about 50%, but varies widely, and both the rate and extent of absorption are increased by food. It is extensively distributed to body tissues and accumulates notably in fat as well as in skeletal muscles and highly perfused tissues such as liver, lungs, and spleen; it has been reported to be about 96% bound to plasma proteins. The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy a pharmacological effect is evident for a month or more. A major metabolite, desethylamiodarone, has antiarrhythmic properties. There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being in faeces via the bile; some enterohepatic recycling may occur. Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

After intravenous injection the maximum effect occurs within 1 to 30 minutes and persists for 1 to 3 hours.

Reviews.

1. Latini R, *et al.* Clinical pharmacokinetics of amiodarone. *Clin Pharmacokinet* 1984; **9:** 136–56.
2. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. *Am J Cardiol* 1993; **72:** 45F–50F.
3. Pollak PT, *et al.* Population pharmacokinetics of long-term oral amiodarone therapy. *Clin Pharmacol Ther* 2000; **67:** 642–52.
4. Kotake T, *et al.* Serum amiodarone and desethylamiodarone concentrations following nasogastric versus oral administration. *J Clin Pharm Ther* 2006; **31:** 237–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Amiocar; Angoten; Asulblan; Atlansil; Cistimela†; Coronax; Coronovo; Miodarona; Miotenk; Ritmocardyl; ***Austral.***: Aratac; Cardinorm†; Cordarone X; Rithmik; ***Austria***: Sedacoron; ***Belg.***: Cordarone; ***Braz.***: Amiobal; Amioron; Ancoron; Angiodarona; Angyton; Atlansil; Cardicoron; Cor Mio; Diodarone†; Hiperterona; Miocor; Miocoron; Miodaren; Miodarid; Miodaron; Miodon; ***Canad.***: Cordarone; ***Chile***: Atlansil; Cordarone; Ritmocardyl; ***China***: Cordarone (可达龙); ***Cz.***: Amiohexal; Amiokordin; Cordarone; Ritmopuls†; Rivodaron; Sedacoron; ***Denm.***: Amiodar†; Angoron; Cordan; Cordarone; ***Fin.***: Cordarone; ***Fr.***: Corbionax; Cordarone; ***Ger.***: Amiodarex†; Amiogamma; Amiohexal†; Cordarex†; Cornaron†; ***Gr.***: Angoron; ***Hong Kong***: Aratac†; Cordarone; Sedacoron; ***Hung.***: Cordarone; Sedacoron†; ***India***: Aldarone; Amiodar; Amiodon; Biodaron; Cardasol; Cardichek; Cordarone; Duron; Eurythmic; Panaron; ***Indon.***: Cordarone; Kendaron; Tiaryt; ***Irl.***: Cordarone X; ***Israel***: Amiocor; Amiodacore; Procor; ***Ital.***: Amiodar; Angoron; Cordarone; ***Jpn***: Ancaron; ***Malaysia***: Aratac†; Cardilor; Cordarone; ***Mex.***: Braxan; Cordarone; Forken; Keritmon; Sinarona; ***Neth.***: Cordarone; ***Norw.***: Cordarone; ***NZ***: Aratac; Cordarone X; ***Philipp.***: Amio; Anoion; Arrythgo; Cordarone; Myodial; ***Pol.***: Amiokordin; Cordarone; Opacorden; ***Port.***: Corbionax; Cordarone; Miodrone; ***Rus.***: Amiokordin (Амиокордин); Cardiodarone (Кардиодарон); Cordarone (Кордарон); Rhythmiodarone (Ритмиодарон); Rythmorest (Ритморест); Sedacoron (Седакорон); ***S.Afr.***: Adcorone; Amiotach; Arycor; Cordarone X; Hexarone; ***Singapore***: Aratac; Cordarone; ***Spain***: Trangorex; ***Swed.***: Cordarone; ***Switz.***: Amiodar; Cordarone; Escodaron; Rivodarone; ***Thai.***: Aldarone; Amdarone†; Amidarone 200; Aratac†; Cardilor; Cordarone; ***Turk.***: Cordarone; ***UAE***: Amirone; ***UK***: Amyben; Cordarone X; ***Ukr.***: Amidaron (Амидарон); Amiokordin (Амиокордин); Aritmil (Аритмил); Cardiodaron (Кардиодарон); Cordarone (Кордарон); Miorytmil (Миоритмил); ***USA***: Cordarone; Nexterone; Pacerone; ***Venez.***: Coradona; Diarona; Eudarona; Novarona; Trangorex.

Multi-ingredient Preparations. ***Ukr.***: Tiodaron (Тиодарон).

Pharmacopoeial Preparations

BP 2014: Amiodarone Infusion; Amiodarone Oral Suspension; Amiodarone Tablets;

USP 36: Amiodarone Hydrochloride Oral Suspension.

Amlodipine *(BAN, rINN)*

Amlodipiini; Amlodipin; Amlodipina; Amlodipino; Amlodipinum; Амлодипин.

3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate.

$C_{20}H_{25}ClN_2O_5$=408.9

CAS — 88150-42-9.

ATC — C08CA01.

ATC Vet — QC08CA01.

UNII — 1J444QC288.

Amlodipine Besilate *(BANM, rINNM)*

Amlodipiinibesilaatti; Amlodipin Besilat; Amlodipinbesilat; Amlodipin-besylát; Amlodipin-bezilát; Amlodipine, Bésilate d'; Amlodipine Besylate (USAN); Amlodipini Besilas; Amlodipino besilatas; Amlodipino, besilato de; Besilato de amlodipino; UK-48340-26; Амлодипина Безилат.

$C_{20}H_{25}ClN_2O_5C_6H_6O_3S$=567.0

CAS — 111470-99-6.

ATC — C08CA01.

ATC Vet — QC08CA01.

UNII — 864V2Q084H.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Amlodipine Besilate). A white or almost white powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in dehydrated alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Amlodipine Besylate). A white or almost white powder. Slightly soluble in water and isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Amlodipine Maleate *(BANM, USAN, rINNM)*

Amlodipine, Maléate d'; Amlodipini Maleas; Maleato de amlodipino; UK-48340-11; Амлодипина Малеат.

$C_{20}H_{25}ClN_2O_5C_4H_4O_4$=525.0

CAS — 88150-47-4.

ATC — C08CA01.

ATC Vet — QC08CA01.

UNII — CQ27G2BZJM.

Uses and Administration

Amlodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3).

Amlodipine is given orally as the besilate, but doses are usually expressed in terms of the base; amlodipine besilate 6.9 mg is equivalent to about 5 mg of amlodipine. The camsilate, maleate, and mesilate are also used.

In hypertension the usual initial dose is 5 mg once daily, increased, if necessary, to 10 mg once daily. Similar doses are given in the treatment of stable angina and Prinzmetal's angina. Lower initial doses may be used in elderly patients and those with hepatic impairment (see below).

Levamlodipine besilate, the (*S*)-isomer of amlodipine besilate, has also been used.

Amlodipine has been investigated for its apparent antibacterial activity.

Reviews.

1. Murdoch D, Heel RC. Amlodipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1991; **41:** 478–505.
2. Haria M, Wagstaff AJ. Amlodipine: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs* 1995; **50:** 560–86.
3. Siragy HM. Improving vascular function in hypertension: potential benefits of combination therapy with amlodipine and renin-angiotensin-aldosterone system blockers. *J Hypertens* 2010; **28:** 2–8.

Administration in children. Several studies have examined dosing regimens of amlodipine in children and adolescents with hypertension.[1-4] Amlodipine clearance is faster in younger children[5] and they need proportionally higher doses than older children.[3,4] Some younger children may also benefit from twice-daily dosing.[4] Amlodipine was well-tolerated in each of the studies; it also appears to be safe and effective when given long-term.[6]

US licensed product information suggests that for the treatment of hypertension in children aged 6 to 17 years, an oral dose of 2.5 to 5 mg once daily may be given. Amlodipine is not licensed for use in children in the UK; however, the *BNFC* suggests the following doses for the treatment of hypertension:

- an initial oral dose of 100 to 200 micrograms/kg once daily may be given to those aged 1 month to 12 years; this may be increased if necessary, at intervals of 1 to 2 weeks, to a maximum dose of 400 micrograms/kg or 10 mg once daily
- older children may be given the usual adult dose (see above)

1. Pfammatter JP, *et al.* Amlodipine once-daily in systemic hypertension. *Eur J Pediatr* 1998; **157:** 618–21.
2. Flynn JT, *et al.* A randomized, placebo-controlled trial of amlodipine in children with hypertension. *J Pediatr* 2004; **145:** 353–9.
3. Tallian KB, *et al.* Efficacy of amlodipine in pediatric patients with hypertension. *Pediatr Nephrol* 1999; **13:** 304–10.
4. Flynn JT, *et al.* Treatment of hypertensive children with amlodipine. *Am J Hypertens* 2000; **13:** 1061–6.
5. Flynn JT, *et al.* Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; **46:** 905–16.
6. Flynn JT. Efficacy and safety of prolonged amlodipine treatment in hypertensive children. *Pediatr Nephrol* 2005; **20:** 631–5.

Administration in hepatic impairment. The clearance of amlodipine is reduced in patients with hepatic impairment and lower doses should be considered; US licensed product information recommends an initial oral dose of 2.5 mg once daily.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Incidence of adverse effects. Of 1091 patients prescribed amlodipine for hypertension, 128 (11.7%) stopped the drug because of adverse effects.[1] The commonest adverse effects were ankle oedema, flushing, headache, rash, and fatigue.

1. Benson E, Webster J. The tolerability of amlodipine in hypertensive patients. *Br J Clin Pharmacol* 1995; **39:** 578P–579P.

Heart failure. Calcium-channel blockers are normally avoided in patients with heart failure but amlodipine has not been found to have any adverse effects on morbidity or mortality in patients with severe heart failure receiving the drug.[1] Therefore, its use to treat angina pectoris or hypertension may be possible in such patients.

1. Packer M, *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996; **335:** 1107–14.

Porphyria. Although there have been reports[1,2] of the successful use of amlodipine in patients with porphyria, acute exacerbation has also occurred.[3] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, nevertheless classifies amlodipine as probably not porphyrinogenic and considers that it may be used as a drug of first choice and no precautions are needed.[4]

1. Gorchein A. Drug treatment of hypertension in acute intermittent porphyria: doxazosin and amlodipine. *Br J Clin Pharmacol* 1997; **43:** 339–40.
2. Cinemre H, *et al.* Safety of amlodipine use in patients with acute intermittent porphyria. *Br J Clin Pharmacol* 2007; **64:** 246–7.
3. Kepple A, Cernek PK. Amlodipine-induced acute intermittent porphyria exacerbation. *Ann Pharmacother* 1997; **31:** 253.
4. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Amlodipine is well absorbed after oral doses and peak blood concentrations occur after 6 to 12 hours. The bioavailability varies but is usually about 60 to 65%. Amlodipine is reported to be about 98% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. Amlodipine is extensively metabolised in the liver; metabolites are mostly excreted in urine, with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

References.

1. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992; **22:** 22–31.
2. Kang D, *et al.* Population analyses of amlodipine in patients living in the community and patients living in nursing homes. *Clin Pharmacol Ther* 2006; **79:** 114–24.
3. Flynn JT, *et al.* PATH-2 Investigators. Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; **46:** 905–16.

Absorption. Results of studies involving 24 healthy subjects indicated that absorption of amlodipine from a capsule was equivalent to that from a solution, suggesting that the slow transfer of amlodipine into the blood is a property of the drug not of the dosage form; absorption was not affected by food.[1]

1. Faulkner JK, *et al.* Absorption of amlodipine unaffected by food: solid dose equivalent to solution dose. *Arzneimittelforschung* 1989; **39:** 799–801.

Metabolism. The metabolites of amlodipine have been characterised in *animals* and in human subjects.[1] Metabolism of amlodipine is complex and extensive, and in common with other dihydropyridines oxidation to the pyridine analogue represents a major step. About 5% of a dose was recovered from urine as unchanged amlodipine.

1. Beresford AP, *et al.* Biotransformation of amlodipine. *Arzneimittelforschung* 1989; **39:** 201–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abloom; Amloc; Amlodicord; Amlodine; Amlotens; Amze; Anexa; Angiofilina; Angipec; Arteriosan; Calpres; Carboplex†; Cardiorex; Cardivas; Coroval; Dronalden; Fabocef; Hipertensal; Ilduc; Mitokor; Nexotensil; Nikor; Pelmec; Pultex; Tensimed; Terloc; Tervalon; Zundic; ***Austral.***: Amlo; Nordip; Norvapine; Norvasc; Ozlodip; Perivasc; ***Austria***: Amlodibene; Amlodilan; Amlodinova; Amlohyp†; Amlotyrol†; Coradipin†; Edidipin†; Norvasc; ***Belg.***: Amlor; ***Braz.***: Amilopil; Amlocor; Amlodil; Amlovasc; Anlo; Anlodibal; Anlodil†; Besilapin; Cordarex; Cordipina; Lodipen; Lodipil†; Nicord; Norvasc; Pressat; Roxflan; Tendipina; Tensaliv; Tensidipin†; Tensodin; ***Canad.***: Norvasc; ***Chile***: Amdipin; Amloc; Molsicor; Norvasc; Presilam; Presovasc; Terloc; ***China***: An Nei Zhen (安内真); Ao Wan Lu (奥万路); Fuleqing (伏络清); Ke Ping (可苹); Lan Di (兰迪); Ning Li Ping (宁立平); Norvasc (络活喜); Nuo Er Ma (诺尔玛); Ping Neng (平能); Shi Hui Da (施慧达); Xi Luo Ning (西络宁); XinLuoPing (欣络平); Xinshu (欣纾); Xinta (欣他); Ya Shi Da (压氏达); Ya Si Ke Ping (亚斯克平); ***Cz.***: Afiten; Agen; Alozur; Amilostad; Amlodigamma†; Amlopp; Amloratio; Amlotenz†; Amlozek; Apo-Amlo; Cardilopin; Genam; Hipres; Normodipine; Norvasc†; Orcal; Recotens; Tensigal; Torella; Zeppeliton; Zorem; Zufalm; ***Denm.***: Amdepin†; Amdin†; Amlobesyl; Amlohexal; Amlokamman†; Amlomas†; Amlopharm; Dipinohex; Dipinosticht; Norvasc; ***Fin.***: Amloratio; Beslodipin†; Coveram; Norvasc; ***Fr.***: Amlor; ***Ger.***: Amlo Tad†; Amlo-Isis†; Amlo-Q†; Amlobesilat†; Amlobeta; Amlocard†; Amloclair; Amlodigamma; Amlodoc†; AmloLich†; Amparo; Norvasc; ***Gr.***: Abesyl; Aggovask; Aldosion; Alister; Amilopid; Amlibon; Amlodil; Amlodin; Amlopen; Amlopress; Amloretin; Amlosilat; Amlotens; Amodipan; Angioretic; Awadik; Axyplot; Baruden; Beglaryl; Dafor; Evangio; Flodil; Hypertel; Karpin; Lavi-Press; Lodipin; Naxuril; Nolvac; Nordex; Norfan; Normodin; Norvagen; Norvalet; Norvasc; Pidolen; Precardin; Ramlet; Rovoxid; Vascodin; ***Hong Kong***: A-phine; Actapin; Amdol; Amedin; Amlod; Amlodigamma; Amlong; Amlopin†; Amlopres; Amlovas; Amlozen; CP-Lovac; Derox; Hypress; Lofral; Norvasc; Stadovas; Zynor; ***Hung.***: Agen; Alozur; Amlipin; Amlobesyl; Amlodep; Amlodigamma; Amlodipress; Amlodowin; Amlozek; Cardilopin; Normodipine; Norvasc; Tenox; ***India***: Aamin; Acord; Adipin; ADP; Aglodepin; Alodip; Am; Amcard; Amchek; Amdepin; Amdip; Amlan; Amlibon; Amlin; Amlip; Amlo CB; Amloact; Amlocan; Amlocom; Amlocor; Amlodac; Amlogard; Amlogen; Amlokath; Amlokind; Amlokos; Amlol; Amlong; Amlopin; Amlopres; Amlosafe; Amlostat; Amlosun; Amlosyl; Amlot; Amlotab; Amlotal; Amlotrac; Amlotrust; Amlovas; Amlovin; Amloz; Amodep; Amone; Amopin; Ampine; Amrap; Amsach; Amset; Amsyn; Amtas; Amzel; Angicam,; Angiguard; Atemos; Bp-Mide; C-Amlo; Calchek; Camlo; Candez; Card; Cardpin; Carvasc; Corvadil; Defidin; Diavasc; Dilsave; Dip; Dipal; Diplom; Dipress; Emadine; Esamlovin; Gamlo; Klodip; Lama; Lodi; Malodip; Milopin; Myamlo; Myodura; Myozar; Nicol; Norvate; Numlo; Nusar-AM; ***Indon.***: A-B Vask; Actapin; Amcor; Amdixal; Calsivas; Cardicap; Cardisan; Cardivask; Compidin; Divask; Ethivask; Gensia; Gravask; Intervask; Lopiten; Lovask; Normoten; Norvask; Pehavask; Sandovask; Simvask; Tensivask; Theravask; Vasgard; ***Irl.***: Amlid; Amlist; Amlode; Amlotan; Istin; Istolde; Myostin; Rustin; ***Israel***: Amlow; Caduet; Norvasc; ***Ital.***: Abis; Almidis; Amlopol; Antacal; Balarm; Krudipin; Makadip; Monopina; Norvasc; Pressac; Zauris; ***Jpn***: Amlodin; Norvasc; ***Malaysia***: Amlibon; Amlodac; Amlong; Amvaz; Anlodin; Avevasc; Camlodin; Covasc; Hovasc; Lofral; Nordipine; Norvasc; Sunvasc; Vamlo; Zynor; ***Mex.***: Aken; Amlibon Bes; Amlibon; Amtev; Avistar; Cropinex; Inivical; Lodicord; Nexus; Norpled; Norvas; Oralcam; Pequisy; Poltroon; Preslopin; Presone-1; Sistopres; Spinodin; Zadivonal; Zagapsol; Zaxinat; ***Neth.***: Amlober; Amlodno; Amlostad; Amlosyl†; Norvasc; ***Norw.***: Norvasc; ***NZ***: Calvasc; Norvasc; ***Philipp.***: Aforbes; Amaday; Ambes; Ambesyl; Ambloc; Amcal; Amlix; Amlobes; Amlocor; Amlodac; Amlodine; Amlonex; Amlong; Amlopine; Amlosyl; Amnique; Amvasc; Asomex; Besylon; Bezam; Calbloc; Calcheck; Calcivas; Corvex; Dailyvasc; Derox; Hartvasc; Lodicap; Lodip; Lopicard; Medipin; Norbloc; Norvasc; Odasyl; Provasc; Sedipin; Stalip; Stamlo; Swamlo; Teneze; Vasalat; Vaselec; Vasprim; ***Pol.***: Adipine; Agen; Aldan; Amlonor; Amlopin; Amloratio; Amlozek; Apo-Amlo; Cardilopin; Lofral; Normodipine; Norvasc; Suplar; Tenox; Vilpin; ***Port.***: Adivaz†; Amlocor; Cardionox; Dilocea; Drime; Freccia; Ibotec†; Mibral; Monodin†; Norvasc; Orexene; Tencemed; Teufin†; Tiflodipina†; Vasoplus†; Zabart†; ***Rus.***: Agen (Аген); Akridipin (Акридипин); Amlodac (Амлодак); Amlodil (Амлодил)†; Amlong (Амлонг); Amlonorm (Амлонорм); Amlorus (Амлорус); Amlotop (Амлотоп); Amlovas (Амловас); Calchek (Калчек); Cardilopin (Кардилопин); Cordi Cor (Корди Кор); Corvadil (Корвадил); EsCordi Cor (ЭсКорди Кор); Normodipine (Нормодипин); Norvadin (Норвадин); Norvasc (Норваск); Omelar Cardio (Омелар Кардио); Stamlo M (Стамло М); Tenox (Тенокс); ***S.Afr.***: Almadin; Amlate; Amloc; Amlodac; Amlosyn; Amtas; Calbloc; Ciplavasc; Corvadil; Keysal; Klodip; Lomanor; Norcard; Norvasc; Stamlo; ***Singapore***: Actapin; Amloc; Amlong; Amlotens; Amtas; Avevasc; Norvasc; Stamlo; ***Spain***: Amlor†; Arainno; Astudal; Norvas; Presdeten†; Zabart; ***Swed.***: Amlarrow; Amlobesyl†; Amloratio; Norvasc; ***Switz.***: Amlo eco†; Amlopin†; Amlovasc; Norvasc; ***Thai.***: Ambes; Amcardia; Amlod; Amlodac; Amlopine;

Amvas; Deten; Lovas; Narvin; Norvasc; ***Turk.***: Amlodis; Amlohex; Amlokard; Amlovas; Biocard†; Dilopin; Lipinox; Monovas; Nipidol; Norlopin; Normopres; Norvadin; Norvasc; Penvasc; Vasocard; Vasonorm; Vazkor; ***UAE***: Amlophar; ***UK***: Amlostin; Istin; ***Ukr.***: Agen (Аген); Aladin (Аладин); Amlodil (Амлодил); Amlong (Амлонг); Amlopril (Амлоприл); Amlosandoz (Амлосандоз); Asomex (Азомекс); Duactin (Дуактин); Emlodin (Эмлодин); Norvadin (Норвадин)†; Norvasc (Норваск); Stamlo (Стамло); Tenox (Тенокс); ***USA***: Norvasc; ***Venez.***: Amlibon; Amlip; Amlopin; Amlovas; Angiovan; Dilotex; Lodipin; Norvasc; Pinam.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
USP 36: Amlodipine and Benazepril Hydrochloride Capsules; Amlodipine Besylate Tablets; Amlodipine Oral Suspension.

Amosulalol Hydrochloride *(rINNM)* ⊗

Amosulalol, Chlorhydrate d'; Amosulalol, hidrocloruro de; Amosulaloli Hydrochloridum; Hidrocloruro de amosulalol; YM-09538; Амосулалола Гидрохлорид.
(±)-5-(1-Hydroxy-2-{[2-(*o*-methoxyphenoxy)ethyl]amino}ethyl)-*o*-toluenesulphonamide hydrochloride.
$C_{18}H_{24}N_2O_5S,HCl$=416.9
CAS — 85320-68-9 (amosulalol); 70958-86-0 (amosulalol hydrochloride); 93633-92-2 (amosulalol hydrochloride).
UNII — 4O4S698PEE.

NOTE. The name Lowgan has been used as a trade mark for amosulalol hydrochloride.

Pharmacopoeias. In *Jpn*.

Profile

Amosulalol is a beta blocker (p. 1316.3); it also has alpha-blocking activity. It has been given orally as the hydrochloride in the management of hypertension.

Amrinone *(BAN, rINN)*

Amrinon; Amrinona; Amrinoni; Amrinonum; Inamrinone (USAN); Win-40680; Амринон.
5-Amino-3,4′-bipyridyl-6(1*H*)-one.
$C_{10}H_9N_3O$=187.2
CAS — 60719-84-8.
ATC — C01CE01.
ATC Vet — QC01CE01.
UNII — JUT23379TN.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Inamrinone). A pale yellow to tan powder; odourless or with a faint odour. Practically insoluble in water and in chloroform; slightly soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Amrinone Lactate *(BANM, rINNM)*

Amrinona, lactato de; Amrinone, Lactate d'; Amrinoni Lactas; Lactato de amrinona; Амринона Лактат.
$C_{10}H_9N_3O.C_3H_6O_3$=277.3
CAS — 75898-90-7.
ATC — C01CE01.
ATC Vet — QC01CE01.
UNII — I229274Y5B.

Incompatibility. The manufacturer has reported that amrinone lactate injection is physically incompatible with glucose-containing solutions and with furosemide.

Precipitation occurred[1] when amrinone was mixed with sodium bicarbonate injection, probably because of the reduced solubility of amrinone in alkaline solutions.

1. Riley CM, Junkin P. Stability of amrinone and digoxin, procainamide hydrochloride, propranolol hydrochloride, sodium bicarbonate, potassium chloride, or verapamil hydrochloride in intravenous admixtures. *Am J Hosp Pharm* 1991; **48:** 1245–52.

Uses and Administration

Amrinone is a phosphodiesterase type 3 inhibitor that has vasodilator and positive inotropic properties. It is used in the management of heart failure (p. 1262.3). Although amrinone is effective when given orally this route has been associated with an unacceptable level of adverse effects, and the drug is now only given intravenously for the short-term management of heart failure unresponsive to other forms of therapy.

The mode of action is not fully known, but appears to involve an increase in cyclic adenosine monophosphate concentration secondary to inhibition of phosphodiesterase, leading to an increased contractile force in cardiac muscle.

Amrinone is given intravenously as the lactate and doses are expressed in terms of the base. Amrinone lactate 1.48 mg is equivalent to about 1 mg of amrinone. The initial loading dose is 750 micrograms/kg by slow intravenous injection over 2 to 3 minutes. This is followed by a maintenance infusion, although the loading dose may be repeated after 30 minutes if necessary. Maintenance doses are 5 to 10 micrograms/kg per minute by infusion to a usual maximum total dose (including loading doses) of 10 mg/kg in 24 hours. Doses of up to 18 mg/kg daily have been used for short periods in a limited number of patients.

Administration in children. Pharmacokinetic and pharmacodynamic studies[1,2] in infants undergoing cardiac surgery indicated that the dose needed for infants to achieve a plasma-amrinone concentration of 2 to 7 micrograms/mL was an initial intravenous bolus of 3 to 4.5 mg/kg in divided doses followed by a continuous infusion of 10 micrograms/kg per minute. Neonates appear to eliminate amrinone more slowly than infants, possibly due to their immature renal function;[1,3] it was therefore suggested[1] that neonates should receive a similar bolus dose to infants, followed by a continuous infusion of 3 to 5 micrograms/kg per minute. In a further study[4] that included mainly infants and older children, amrinone clearance and volume of distribution varied widely between patients but did not appear to be related to age.

1. Lawless S, *et al.* Amrinone in neonates and infants after cardiac surgery. *Crit Care Med* 1989; **17:** 751–4.
2. Lawless ST, *et al.* The acute pharmacokinetics and pharmacodynamics of amrinone in pediatric patients. *J Clin Pharmacol* 1991; **31:** 800–3.
3. Laitinen P, *et al.* Pharmacokinetics of amrinone in neonates and infants. *J Cardiothorac Vasc Anesth* 2000; **14:** 378–82.
4. Allen-Webb EM, *et al.* Age-related amrinone pharmacokinetics in a pediatric population. *Crit Care Med* 1994; **22:** 1016–24.

Adverse Effects

Amrinone produces gastrointestinal disturbances that may necessitate withdrawal of treatment. It produces dose-dependent thrombocytopenia. Hepatotoxicity may occur, particularly during long-term oral treatment. Hypotension and cardiac arrhythmias have been reported. Other adverse effects include headache, fever, chest pain, nail discoloration, and decreased tear production. Hypersensitivity reactions including myositis and vasculitis have been reported. Local pain and burning may occur at the site of intravenous injection.

The adverse effects associated with oral use have made this route unacceptable and amrinone is now only given intravenously for short-term use. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can increase the mortality rate.

References.
1. Wynne J, *et al.* Oral amrinone in refractory congestive heart failure. *Am J Cardiol* 1980; **45:** 1245–9.
2. Wilmshurst PT, Webb-Peploe MM. Side effects of amrinone therapy. *Br Heart J* 1983; **49:** 447–51.
3. Wilmshurst PT, *et al.* The effects of amrinone on platelet count, survival and function in patients with congestive cardiac failure. *Br J Clin Pharmacol* 1984; **17:** 317–24.
4. Silverman BD, *et al.* Clinical effects and side effects of amrinone: a study of 24 patients with chronic congestive heart failure. *Arch Intern Med* 1985; **145:** 825–9.
5. Webster MWI, Sharpe DN. Adverse effects associated with the newer inotropic agents. *Med Toxicol* 1986; **1:** 335–42.
6. Mattingly PM, *et al.* Pancytopenia secondary to short-term, high-dose intravenous infusion of amrinone. *DICP Ann Pharmacother* 1990; **24:** 1172–4.
7. Ross MP, *et al.* Amrinone-associated thrombocytopenia: pharmacokinetic analysis. *Clin Pharmacol Ther* 1993; **53:** 661–7.

Precautions

Amrinone should be used with caution in severe obstructive aortic or pulmonary valvular disease or in hypertrophic cardiomyopathy. Blood pressure and heart rate should be monitored during parenteral use. The fluid and electrolyte balance should be maintained. Platelet counts and liver function should also be monitored.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amrinone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Although amrinone is rapidly absorbed from the gastrointestinal tract it is no longer given orally. The half-life is variable and after intravenous injection has been reported to be about 4 hours in healthy subjects and about 6 hours in patients with heart failure. Binding to plasma proteins is generally low. Amrinone is partially metabolised in the liver and excreted in the urine as unchanged drug and metabolites; up to about 40% is excreted as unchanged drug after intravenous use. About 18% of an oral dose has been detected in the faeces over 72 hours.

General references.
1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:**(contents page).

Infants. For reference to the pharmacokinetics of amrinone in neonates and infants, see Administration in children under Uses and Administration, above.

Renal impairment. Studies in a child with multi-organ failure and anuria[1] and in 3 adults with anuria after cardiac surgery[2] have shown that amrinone is effectively removed by haemofiltration but clearance varies widely between patients. Non-renal clearance may also be altered in critically ill patients and monitoring of plasma-amrinone concentrations has been suggested.[2]

1. Lawless S, *et al.* Effect of continuous arteriovenous haemofiltration on pharmacokinetics of amrinone. *Clin Pharmacokinet* 1993; **25:** 80–2.
2. Hellinger A, *et al.* Elimination of amrinone during continuous veno-venous haemofiltration after cardiac surgery. *Eur J Clin Pharmacol* 1995; **48:** 57–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Amicor; Amrisol; Cardiotone; ***Israel***: Inocor†; ***Mex.***: Inocor†; ***USA***: Inocor.

Pharmacopoeial Preparations
USP 36: Inamrinone Injection.

Anacetrapib *(USAN, rINN)*

Anacétrapib; Anacetrapibum; MK-0859; Анацетрапиб.
(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)(1,1′-biphenyl)-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one.
$C_{30}H_{25}F_{10}NO_3$=637.5
CAS — 875446-37-0.
UNII — P7T269PR6S.

Profile

Anacetrapib is an inhibitor of cholesteryl ester transfer protein (CETP) that is under investigation for the treatment of dyslipidaemias and atherosclerosis.

References.
1. Bloomfield D, *et al.* Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. *Am Heart J* 2009; **157:** 352–360.e2.
2. Masson D. Anacetrapib, a cholesterol ester transfer protein (CETP) inhibitor for the treatment of atherosclerosis. *Curr Opin Investig Drugs* 2009; **10:** 980–7.
3. Cannon CP, *et al.* Determining the Efficacy and Tolerability Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010; **363:** 2406–15.
4. Kumar S, *et al.* Metabolism and excretion of anacetrapib, a novel inhibitor of the cholesteryl ester transfer protein, in humans. *Drug Metab Dispos* 2010; **38:** 474–83.
5. Miyares MA. Anacetrapib and dalcetrapib: two novel cholesteryl ester transfer protein inhibitors. *Ann Pharmacother* 2011; **45:** 84–94.

Ancrod *(BAN, USAN, rINN)*

Ancrodo; Ancrodum; Анкрод.
CAS — 9046-56-4.
ATC — B01AD09.
ATC Vet — QB01AD09.
UNII — EL55307L15.

Description. Ancrod is an enzyme obtained from the venom of the Malayan pit-viper (*Calloselasma rhodostoma* = *Agkistrodon rhodostoma*).

Uses and Administration

Ancrod is an anticoagulant. It reduces the blood concentration of fibrinogen by the cleavage of microparticles of fibrin which are rapidly removed from the circulation by fibrinolysis or phagocytosis. It reduces blood viscosity but has no effect on established thrombi. Haemostatic concentrations of fibrinogen are normally restored in about 12 hours and normal concentrations in 10 to 20 days.

Ancrod has been used in the management of thromboembolic disorders, particularly in the prevention and treatment of deep-vein thrombosis (p. 1274.1) in hospitalised patients, including as an alternative to heparin in those with heparin-induced thrombocytopenia. It has also been given for priapism. Ancrod has been investigated in ischaemic stroke, with disappointing results.

References.
1. Sherman DG, *et al.* Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. *JAMA* 2000; **283:** 2395–2403.
2. Hennerici MG, *et al.* ESTAT investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial. *Lancet* 2006; **368:** 1871–8.
3. Levy DE, *et al.* Ancrod Stroke Program (ASP) Study Team. Ancrod for acute ischemic stroke: a new dosing regimen derived from analysis of prior ancrod stroke studies. *J Stroke Cerebrovasc Dis* 2009; **18:** 23–7.

4. Levy DE, *et al.* Ancrod in acute ischemic stroke: results of 500 subjects beginning treatment within 6 hours of stroke onset in the Ancrod Stroke Program. *Stroke* 2009; **40:** 3796–3803.

Adverse Effects and Treatment

Haemorrhage may occur during treatment with ancrod and usually responds to its withdrawal. If haemorrhage is severe, cryoprecipitate can be used to raise plasma fibrinogen concentrations; plasma may be used if cryoprecipitate is not available. An antivenom has been used to neutralise ancrod.

Rashes, transient chills, and fever have been reported with the use of ancrod.

Precautions

As for Heparin, p. 1399.3.

Ancrod should not be given to patients with severe infections or disseminated intravascular coagulation. It should be used cautiously in patients with cardiovascular disorders that may be complicated by defibrination. It is very important that when ancrod is given by intravenous infusion it should be given slowly to prevent the formation of large amounts of unstable fibrin.

Ancrod is not recommended during pregnancy; high doses in *animals* have caused placental haemorrhage and fetal death.

Interactions

Ancrod should not be used with antifibrinolytics such as aminocaproic acid or with plasma volume expanders such as dextrans.

Angiotensinamide *(BAN, rINN)*

Angiotensiiniamidi; Angiotensin Amide (USAN); Angiotensin Amide; Angiotensinamid; Angiotensinamida; Angiotensinamidum; NSC-107678; Ангиотензинамид.

Asn-Arg-Val-Tyr-Val-His-Pro-Phe; [1-Asparagine,5-valine] angiotensin II.

$C_{45}H_{70}N_{14}O_{11}$=1031.2

CAS — 11128-99-7 (angiotensin II); 53-73-6 (angiotensinamide).

ATC — C01CX06.

ATC Vet — QC01CX06.

UNII — 7WAL1X78KV.

Profile

Angiotensinamide is a vasopressor related to the naturally occurring peptide angiotensin II. It increases the peripheral resistance mainly in cutaneous, splanchnic, and renal blood vessels. The increased blood pressure is accompanied by a reflex reduction in heart rate, and cardiac output may also be reduced.

Angiotensinamide has been used in the treatment of hypotension associated with shock. It has also been given in the management of overdosage of ACE inhibitors, when conventional therapy has been ineffective.

Angiotensinamide should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment as a hypertensive crisis may be precipitated.

References.

1. Jackson T, *et al.* Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; **341:** 703.
2. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; **40:** 103–4.
3. Yunge M, Petros A. Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child* 2000; **82:** 388–9.

Anistreplase *(BAN, USAN, rINN)*

Anisoylated Plasminogen Streptokinase Activator Complex; Anistreplaasi; Anistreplas; Anistreplasa; Anistreplasum; APSAC; BRL-26921; Анистреплаза.

p-Anisoylated (human) lys-plasminogen streptokinase activator complex (1:1).

CAS — 81669-57-0.

ATC — B01AD03.

ATC Vet — QB01AD03.

UNII — 5O8V541HJ6.

Storage. The manufacturer has recommended that anistreplase should be stored at 2 degrees to 8 degrees.

Uses and Administration

Anistreplase is a thrombolytic drug. It consists of a complex of the lys-form of plasminogen and streptokinase with the addition of a *p*-anisoyl group. After intravenous injection the anisoyl group undergoes deacylation at a steady rate to release the active complex which converts plasminogen to plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3.

Anistreplase has been used similarly to streptokinase (p. 1503.1) in the treatment of acute myocardial infarction (p. 1257.1). It has been given as a single intravenous injection in a dose of 30 units over 5 minutes, as soon as possible after the onset of symptoms.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Like streptokinase, anistreplase appears to be antigenic and may be neutralised by streptokinase antibodies.

Back pain. For references to back pain associated with anistreplase infusion, see under Streptokinase, p. 1505.1.

Interactions

As for Streptokinase, p. 1507.1.

Pharmacokinetics

Anistreplase is reported to be cleared from plasma at about half the rate of streptokinase and has a fibrinolytic half-life of about 90 minutes. It is metabolised to the plasminogen-streptokinase complex at a steady rate.

References.

1. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; **31:** 143–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Eminase†; ***Gr.***: Eminase.

Apixaban *(USAN, rINN)*

Apixabán; Apixabanum; BMS-562247-01; Апиксабан.

1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide.

$C_{25}H_{25}N_5O_4$=459.5

CAS — 503612-47-3.

ATC — B01AF02.

ATC Vet — QB01AF02.

UNII — 3Z9Y7UWC1J.

Uses and Administration

Apixaban is an oral direct inhibitor of factor Xa (activated factor X) with actions and uses similar to those of rivaroxaban (p. 1487.2).

For the prevention of venous thromboembolism (p. 1274.1) in patients undergoing hip or knee replacement surgery, apixaban is given at a dose of 2.5 mg twice daily. The initial dose should be given 12 to 24 hours after surgery, and the recommended duration of treatment is 10 to 14 days after knee surgery and 32 to 38 days after hip surgery.

For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (see Thromboembolic Diseases, below), a dose of 5 mg twice daily is given long term. A lower dose of 2.5 mg twice daily is recommended for patients who also have at least 2 of the following characteristics: aged ≥80 years, body-weight ≤60 kg, or serum-creatinine ≥1.5 mg per 100 mL (133 micromoles/litre). See also Administration in Renal Impairment (below) for further details on dose adjustment. A dose of 2.5 mg twice daily has also been recommended when apixaban is given with strong dual inhibitors of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein; such combinations should be avoided in patients already taking apixaban 2.5 mg twice daily.

References.

1. Watson J, *et al.* Apixaban: first global approval. *Drugs* 2011; **71:** 2079–89.

Administration in renal impairment. An apixaban dose of 2.5 mg orally twice daily should be used for the prevention of stroke in patients with non-valvular atrial fibrillation who have severe renal impairment (creatinine clearance 15 to 29 mL/minute). Apixaban should also be used with caution in patients with severe impairment who are given it for the prevention of venous thromboembolism after hip or knee replacement surgery. It is not recommended in patients with creatinine clearance of less than 15 mL/minute and those undergoing haemodialysis because of a lack of information.

No dose adjustment is considered necessary in mild or moderate renal impairment (but see also Uses and Administration, above, for dose adjustment in patients with renal impairment who are elderly or have low body-weight).

Thromboembolic diseases. Apixaban has been compared with enoxaparin in the prophylaxis of venous thromboembolism in patients undergoing hip[1] or knee[2,3] replacement surgery, and its use in this indication has been reviewed.[4] Apixaban may also be used in the prevention of stroke and embolic events in patients with atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1). In the ARISTOTLE study[5] apixaban was found to reduce the risk of stroke or systemic embolism by 21%, major bleed by 31%, and death by 11% compared with warfarin in patients with atrial fibrillation and at least one other risk factor for stroke. Among patients for whom warfarin therapy was inappropriate, the AVERROES study[6] found apixaban to substantially reduce the risk of stroke and other embolic events compared with aspirin without significantly increasing the risk of major bleeding or intracranial hemorrhage. In both trials, a dose of 5 mg orally twice daily was used for most patients, although the dose was halved for patients with at least two of the following criteria: advanced age (≥80 years), low body-weight (≤60 kg), and renal dysfunction (serum creatinine ≥133 micromoles/litre).[5,6]

Apixaban has been investigated as an anticoagulant in the management of several other thromboembolic diseases.[7,8] It has also been investigated in the management of acute coronary syndromes (p. 1254.2), with disappointing results.[9]

1. Lassen MR, *et al.* ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010; **363:** 2487–98.
2. Lassen MR, *et al.* Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009; **361:** 594–604.
3. Lassen MR, *et al.* Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010; **375:** 807–15.
4. Deeks ED. Apixaban: a review of its use in the prevention of venous thromboembolism after knee or hip replacement surgery. *Drugs* 2012; **72:** 1271–91.
5. Granger CB, *et al.* ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365:** 981–92.
6. Connolly SJ, *et al.* AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364:** 806–17.
7. Goldhaber SZ, *et al.* ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011; **365:** 2167–77.
8. Prom R, Spinler SA. The role of apixaban for venous and arterial thromboembolic disease. *Ann Pharmacother* 2011; **45:** 1262–83.
9. Alexander JH, *et al.* APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; **365:** 699–708.

Adverse Effects, Treatment, and Precautions

As for Rivaroxaban, p. 1488.1. Apixaban should be used with caution in mild or moderate hepatic impairment (Child-Pugh score A or B). It is not recommended in severe hepatic impairment. The dose of apixaban may need adjustment in renal impairment. Apixaban should be stopped at least 48 hours before surgery or invasive procedures with a moderate or high risk of bleeding, and at least 24 hours before those with a low bleeding risk; it should be restarted as soon as possible after the surgery or procedure provided there is adequate haemostasis.

Interactions

As for Rivaroxaban, p. 1488.1. The dose of apixaban should be adjusted when it is given with strong inhibitors of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein (see Uses and Administration, above).

Pharmacokinetics

Apixaban is rapidly absorbed with an absolute bioavailability of about 50% and peak plasma concentrations occurring 3 to 4 hours after an oral dose. Plasma protein binding is about 87%. Apixaban is metabolised in the liver mainly via the P450 cytochromes CYP3A4 and CYP3A5, and is excreted renally and in the faeces as unchanged drug and inactive metabolites. The half-life is about 12 hours. Apixaban is a substrate of the transport protein P-glycoprotein.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Eliquis; ***Canad.***: Eliquis; ***Denm.***: Eliquis; ***Fr.***: Eliquis; ***Ger.***: Eliquis; ***Irl.***: Eliquis; ***Israel***: Eliquis; ***Jpn***: Eliquis; ***Neth.***: Eliquis; ***Norw.***: Eliquis; ***Spain***: Eliquis; ***Swed.***: Eliquis; ***Switz.***: Eliquis; ***UK***: Eliquis; ***USA***: Eliquis.

Aprindine Hydrochloride *(BANM, USAN, rINNM)*

AC-1802; Aprindina, hidrocloruro de; Aprindine, Chlorhydrate d'; Aprindini Hydrochloridum; Compound 83846; Compound 99170 (aprindine); Hidrocloruro de aprindina; Априндина Гидрохлорид.

N-(3-Diethylaminopropyl)-*N*-indan-2-ylaniline hydrochloride; *NN*-Diethyl-*N'*-indan-2-yl-*N'*-phenyltrimethylenediamine hydrochloride.
$C_{22}H_{30}N_2$,HCl=359.0
CAS — 37640-71-4 (aprindine); 33237-74-0 (aprindine hydrochloride).
ATC — C01BB04.
ATC Vet — QC01BB04.
UNII — PB5EKT7Q2V.

NOTE. The names Aspenon and Apritone have been used as trade marks for aprindine.

Uses and Administration

Aprindine is a class Ib antiarrhythmic (p. 1243.1) used in the management of ventricular and supraventricular arrhythmias (p. 1266.1).

Aprindine is given orally as the hydrochloride. Therapy should be monitored by ECG during initial stabilisation of the dose and intermittently thereafter. Aprindine has also been given intravenously.

Adverse Effects and Precautions

Adverse effects of aprindine are usually dose-related and most commonly affect the CNS. They include tremor, vertigo, ataxia, diplopia, memory impairment, hallucinations, and convulsions. Gastrointestinal effects include nausea, vomiting, and bloating. There have been reports of agranulocytosis, including fatalities. Hepatitis and cholestatic jaundice have occasionally been reported; blood and liver function tests should be performed during treatment.

Aprindine is contra-indicated in patients with advanced heart failure or severe conduction disturbances. Some licensed product information has recommended that aprindine should not be used in patients with parkinsonism or convulsive disorders. It should be used with caution in patients with bradycardia, hypotension, and hepatic or renal impairment.

Effects on the nervous system. A study[1] in Japanese patients suggested that neurological adverse effects (such as dizziness and tremor) were present in about half of patients in whom serum concentrations of aprindine were above 1 microgram/mL, but almost absent in those whose concentrations were maintained below this value.

1. Tsuchishita Y, *et al*. Relationship between serum aprindine concentration and neurologic side effects in Japanese. *Biol Pharm Bull* 2009; **32:** 637–9.

Interactions

Antiarrhythmics. Steady-state plasma-aprindine concentrations increased in 2 patients after starting *amiodarone* and this coincided with the appearance of adverse effects.[1]

1. Southworth W, *et al.* Possible amiodarone-aprindine interaction. *Am Heart J* 1982; **104:** 323.

Pharmacokinetics

Aprindine is readily absorbed from the gastrointestinal tract. It has a long plasma half-life, usually between 20 and 27 hours, and is about 85 to 95% bound to plasma proteins. It is excreted in the urine and the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Fiboran; ***Neth.***: Fiboran†.

Aranidipine *(rINN)*

Aranidipino; Aranidipinum; MPC-1304; Аранидипин.
(±)-Acetonyl methyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.
$C_{19}H_{20}N_2O_7$=388.4
CAS — 86780-90-7.
UNII — 4Y7UR6X2PO.

Profile

Aranidipine is a dihydropyridine calcium-channel blocker used orally in the management of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Bec; Sapresta.

Ardeparin Sodium *(USAN, rINN)*

Ardeparina sódica; Ardéparine Sodique; Ardeparinum Natricum; Wy-90493-RD; Ардепарин Натрий.

CAS — 9041-08-1.
UNII — N3927D01PB.

Description. Ardeparin sodium is prepared by peroxide degradation of heparin obtained from the intestinal mucosa of pigs. The end chain structure appears to be the same as the starting material with no unusual sugar residues present. The molecular weight of 98% of the components is between 2000 and 15 000 and the average molecular weight is about 5500 to 6500. The degree of sulfation is about 2.7 per disaccharide unit.

Profile

Ardeparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity that has been used for the prevention of postoperative venous thromboembolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Indeparin.

Argatroban *(BAN, USAN, rINN)*

Argatrobana; Argatrobanum; Argipidine; DK-7419; GN-1600; MCI-9038; MD-805; Аргатробан.
(2*R*,4*R*)-4-Methyl-1-[(*S*)-N^2-{[(*RS*)-1,2,3,4-tetrahydro-3-methyl-8-quinolyl]sulfonyl}arginyl]pipecolic acid.
$C_{23}H_{36}N_6O_5S$=508.6
CAS — 74863-84-6 (anhydrous argatroban); 141396-28-3 (argatroban monohydrate).
ATC — B01AE03.
ATC Vet — QB01AE03.
UNII — OCY3U280Y3 (anhydrous argatroban); IY90U61Z3S (argatroban monohydrate).

Incompatibility. Trace evidence of precipitation was seen immediately after mixing solutions of argatroban and amiodarone.[1] No visual incompatibility was noted for solutions of argatroban with furosemide, nesiritide, sodium nitroprusside, or a total parenteral nutrition solution, but changes in pH occurred over 24 hours, suggesting such mixtures should be used with caution.[1]

1. Honisko ME, *et al.* Compatibility of argatroban with selected cardiovascular agents. *Am J Health-Syst Pharm* 2004; **61:** 2415–18.

Uses and Administration

Argatroban is a synthetic direct thrombin inhibitor (see Lepirudin, p. 1418.2) with anticoagulant and antiplatelet activity. It is used for the treatment and prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Heparin, p. 1399.1), and as an adjunct in patients undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p. 1259.2) who have or are at risk of heparin-induced thrombocytopenia. It has also been used in other thromboembolic disorders.

In the management of heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 2 micrograms/kg per minute, adjusted according to the activated partial thromboplastin time (APTT), to a maximum dose of 10 micrograms/kg per minute.

In percutaneous coronary interventions in patients at risk of or with heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 25 micrograms/kg per minute, and an intravenous injection of 350 micrograms/kg is given simultaneously over 3 to 5 minutes. Close monitoring of the activated clotting time (ACT) is required. If necessary, additional intravenous bolus doses of 150 micrograms/kg may be given, and the infusion rate adjusted to between 15 and 40 micrograms/kg per minute.

Doses should be reduced in patients with hepatic impairment (see below).

For doses in children, see below.

References.

1. McKeage K, Plosker GL. Argatroban. *Drugs* 2001; **61:** 515–22.
2. Verme-Gibboney CN, Hursting MJ. Argatroban dosing in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; **37:** 970–5.
3. Lewis BE, *et al*. Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 2006; **129:** 1407–16.
4. Bartholomew JR, *et al*. Argatroban anticoagulation for heparin-induced thrombocytopenia in elderly patients. *Drugs Aging* 2007; **24:** 489–99.
5. Beiderlinden M, *et al.* Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 2007; **31:** 461–5.
6. Ansara AJ, *et al*. Weight-based argatroban dosing nomogram for treatment of heparin-induced thrombocytopenia. *Ann Pharmacother* 2009; **43:** 9–18.
7. Babuin L, Pengo V. Argatroban in the management of heparin-induced thrombocytopenia. *Vasc Health Risk Manag* 2010; **6:** 813–19.

Administration in children. Case reports of the use of argatroban in children were reviewed.[1] Argatroban appeared to provide therapeutic levels of anticoagulation in a variety of settings including thromboprophylaxis and treatment, cardiac catheterisation, haemodialysis, and extracorporeal membrane oxygenation. However, argatroban was associated with an unacceptably high bleeding risk in patients undergoing cardiopulmonary bypass.

Based on a study[2] in 18 children aged from birth to 16 years, US licensed product information suggests the following doses of argatroban in children with heparin-induced thrombocytopenia:

- in those with normal liver function, a continuous infusion of 750 nanograms/kg per minute, adjusted in increments of 100 to 250 nanograms/kg per minute according to the activated partial thromboplastin time.
- in those with impaired liver function, a continuous infusion of 200 nanograms/kg per minute, adjusted in increments of no more than 50 nanograms/kg per minute according to the activated partial thromboplastin time.

1. Hursting MJ, *et al.* Argatroban anticoagulation in pediatric patients: a literature analysis. *J Pediatr Hematol Oncol* 2006; **28:** 4–10.
2. Madabushi R, *et al*. Pharmacokinetic and pharmacodynamic basis for effective argatroban dosing in pediatrics. *J Clin Pharmacol* 2011; **51:** 19–28.

Administration in hepatic impairment. In patients with heparin-induced thrombocytopenia with hepatic impairment the initial dose of argatroban should be reduced.[1] US licensed product information recommends an initial dose of 500 nanograms/kg per minute in moderate hepatic impairment. Reversal of anticoagulant effects after stopping argatroban may take more than 4 hours, due to decreased clearance and increased elimination half-life. High doses of argatroban should not be used in patients with significant hepatic impairment undergoing percutaneous coronary interventions.

Reduced initial doses have also been suggested for those with conditions that might *indirectly* decrease hepatic function—see Critical Illness under Adverse Effects and Precautions, below.

1. Levine RL, *et al*. Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest* 2006; **129:** 1167–75.

Administration in renal impairment. Argatroban is not significantly excreted by the kidneys and dosage adjustment is not usually required in renal impairment, although excessive anticoagulation has been reported in critically ill patients, including some with compromised renal function (see Critical Illness under Adverse Effects, below). The use of argatroban in patients with renal impairment has been reviewed.[1]

For a discussion of the use of direct thrombin inhibitors, including argatroban, as alternatives to heparin in patients undergoing haemodialysis or haemofiltration, see Extracorporeal Circuits under Lepirudin, p. 1418.2.

1. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. *Nephron Clin Pract* 2008; **109:** c80–c94.

Adverse Effects, Treatment, and Precautions

As for Lepirudin, p. 1419.2.

If argatroban and warfarin are given together there is an effect on the measurement of the INR values. The manufacturer provides guidelines for interpreting the INR during the change from combined therapy to warfarin alone.

Critical illness. Critically ill patients appear to be particularly sensitive to argatroban and may require doses lower than those licensed. Four critically ill patients became excessively anticoagulated[1] when treatment with argatroban was started after cardiac surgery, despite use of only the recommended doses or lower. All 4 had relatively normal hepatic function. Clearance of the drug appeared to be prolonged after it was stopped. In a patient[2] who had no significant direct hepatic dysfunction but severe hepatic congestion secondary to acute renal failure, the effect of argatroban was prolonged and reduction in dose was necessary. Haemodialysis had little or no effect on clearance. Further cases of excessive anticoagulation have been reported in patients with multiple organ failure,[3] and in an elderly patient with multiple comorbidities.[4] In a subsequent study, of 53 patients given argatroban for heparin-induced thrombocytopenia (HIT), 47 (of whom 33 were classed as critically ill) required doses lower than the licensed doses, and 16 (of whom 15 were classed as critically ill) required doses lower than 500 nanograms/kg per minute.[5] A review[6] of argatroban in HIT considered that reduced initial doses should be given to those with conditions that might indirectly decrease hepatic function, and that for many patients doses within the range of 0.5 to 1.2 micrograms/kg per minute appeared to be adequate.

1. Reichert MG, *et al*. Excessive argatroban anticoagulation for heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; **37:** 652–4.

2. de Denus S, Spinler SA. Decreased argatroban clearance unaffected by hemodialysis in anasarca. *Ann Pharmacother* 2003; **37:** 1237–40.
3. Beiderlinden M, *et al.* Argatroban anticoagulation in critically ill patients. *Ann Pharmacother* 2007; **41:** 749–54.
4. Kubiak DW, *et al.* Extensive prolongation of aPTT with argatroban in an elderly patient with improving renal function, normal hepatic enzymes, and metastatic lung cancer. *Ann Pharmacother* 2005; **39:** 1119–23.
5. Keegan SP, *et al.* Effects of critical illness and organ failure on therapeutic argatroban dosage requirements in patients with suspected or confirmed heparin-induced thrombocytopenia. *Ann Pharmacother* 2009; **43:** 19–27.
6. Hursting MJ, Soffer J. Reducing harm associated with anticoagulation: practical considerations of argatroban therapy in heparin-induced thrombocytopenia. *Drug Safety* 2009; **32:** 203–18.

Overdosage. A critically ill patient receiving low-dose continuous intravenous argatroban for thromboembolism prophylaxis was mistakenly given an additional infusion of 125 mg of argatroban over 1 hour (26.1 micrograms/kg per minute).[1] He was given repeated doses of fresh frozen plasma and no bleeding complications occurred, but the prothrombin time remained prolonged for over 48 hours. Although the total dose given was comparable to doses used in other indications, critically ill patients may be particularly sensitive to the effects of argatroban (see p. 1307.3).

1. Yee AJ, Kuter DJ. Successful recovery after an overdose of argatroban. *Ann Pharmacother* 2006; **40:** 336–9.

Interactions

As for Lepirudin, p. 1419.3.

Warfarin. Although caution is necessary in interpreting the INR when argatroban and warfarin are given together (see Adverse Effects and Precautions, p. 1307.3), a study in healthy subjects[1] showed no pharmacokinetic interaction.

1. Brown PM, Hursting MJ. Lack of pharmacokinetic interactions between argatroban and warfarin. *Am J Health-Syst Pharm* 2002; **59:** 2078–83.

Pharmacokinetics

Argatroban is about 54% bound to plasma proteins. Metabolism, mainly hydroxylation and aromatisation, takes place in the liver, with the main metabolite having weak anticoagulant activity. Anticoagulant effects are seen immediately upon starting infusion; steady-state concentrations occur within 1 to 3 hours and are maintained until the infusion is stopped or the dose adjusted. The terminal elimination half-life of argatroban is between 39 and 51 minutes. It is excreted primarily in the faeces, via the bile as metabolites and as unchanged drug. About 16% of a dose is excreted unchanged in the urine, and at least 14% unchanged in faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Argatra; ***China***: Da Bei (达贝); Novastan (诺保思泰); ***Denm.***: Novastan; ***Fin.***: Novastan; ***Fr.***: Arganova; ***Ger.***: Argatra; ***Ital.***: Novastan; ***Jpn***: Argaron; Gartban; Novastan; Slonnon; Slovastan†; ***Neth.***: Arganova; ***Norw.***: Novastan; ***Swed.***: Novastan; ***UK***: Exembol.

Arotinolol Hydrochloride *(rINNM)* ⊗

Arotinolol, Chlorhydrate d'; Arotinolol, hidrocloruro de; Arotinolol Hydrochloridum; Hidrocloruro de arotinolol; S-596; Аротинолола Гидрохлорид.

(±)-5-[2-{[3-(*tert*-Butylamino)-2-hydroxypropyl]thio}-4-thiazolyl]-2-thiophenecarboxamide hydrochloride.

$C_{15}H_{21}N_3O_2S_3$,HCl=408.0

CAS — 68377-92-4 (arotinolol); 68377-91-3 (arotinolol hydrochloride).

UNII — 9DOI1HT306.

NOTE. The names Acemail, Alochinon, Arotinoil, Astonil, and Ceonomal have been used as trade marks for arotinolol hydrochloride.

Pharmacopoeias. In *Jpn.*

Profile

Arotinolol is a non-cardioselective beta blocker (p. 1316.3); it also has alpha$_1$-blocking activity. It is used as the hydrochloride in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and essential tremor (p. 1318.3). The usual oral dose is 20 mg daily in 2 divided doses although up to 30 mg daily may be given. The initial dose for essential tremor is 10 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Almarl (阿尔马尔); ***Jpn***: Almarl.

Atenolol *(BAN, USAN, rINN)* ⊗

Aténolol; Atenololi; Atenololis; Atenololum; ICI-66082; Атенолол.

2-{*p*-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl}acetamide.

$C_{14}H_{22}N_2O_3$=266.3

CAS — 29122-68-7; 60966-51-0.

ATC — C07AB03.

ATC Vet — QC07AB03.

UNII — 50W3VW0TI.

NOTE. Compounded preparations of atenolol may be represented by the following names:
- Co-tenidone (*BAN*)—atenolol 4 parts and chlortalidone 1 part (w/w)
- Co-tenidone (*PEN*)—atenolol and chlortalidone.

Distinguish atenolol from Atenenol, which has been used as a trade mark for alprenolol hydrochloride (p. 1296.3).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8 (Atenolol). A white or almost white powder. Sparingly soluble in water; soluble in dehydrated alcohol; slightly soluble in dichloromethane.

USP 36: (Atenolol). White or practically white, odourless powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol.

Uses and Administration

Atenolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Atenolol is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and myocardial infarction (p. 1257.1). It may also be used for the prophylaxis of migraine (p. 670.3).

In **hypertension** atenolol is given orally in a dose of 25 to 100 mg daily, as a single dose, although doses over 50 mg daily are rarely needed. The full effect is usually evident within 1 to 2 weeks.

The usual dose for **angina pectoris** is 50 to 100 mg daily orally, given as a single dose or in divided doses. Additional benefit is not usually obtained from higher doses of atenolol although up to 200 mg daily has been given.

For the emergency treatment of **cardiac arrhythmias** atenolol may be given by intravenous injection in a dose of 2.5 mg injected at a rate of 1 mg/minute, repeated if necessary every 5 minutes to a maximum total dosage of 10 mg. Alternatively atenolol may be given by intravenous infusion over 20 minutes in a dose of 150 micrograms/kg. The injection or infusion procedure may be repeated every 12 hours if necessary. When control is achieved maintenance oral doses of 50 to 100 mg daily may be given.

Atenolol is also used in the early management of acute **myocardial infarction**. Treatment should be given within 12 hours of the onset of chest pain; atenolol 5 to 10 mg should be given by slow intravenous injection at a rate of 1 mg/minute, followed after 15 minutes with 50 mg orally, provided no adverse effects result from the injection; alternatively an intravenous dose of 5 mg may be repeated after 10 minutes followed by an oral dose of 50 mg after a further 10 minutes. A further 50 mg may be given orally after 12 hours, and subsequent dosage maintained, after a further 12 hours, with 100 mg daily.

In the prophylaxis of **migraine** an oral dose of 50 to 200 mg daily has been used.

Reduced doses may be required in patients with impaired renal function (see below).

For doses in children, see Administration in Children, below.

The *S* (-)-isomer of atenolol, esatenolol (p. 1377.2), is used similarly to atenolol.

Administration in children. Atenolol may be given orally to children in the treatment of hypertension or arrhythmias. The *BNFC* recommends the following doses, given as a single dose once daily or in 2 divided doses:
- neonates and children up to 12 years: 0.5 to 2 mg/kg daily up to the maximum adult dose of 100 mg daily, although doses higher than 50 mg daily rarely necessary for hypertension
- children from 12 to 18 years may be given the usual oral adult dose for these indications, see Uses and Administration, above

Administration in renal impairment. The dose of atenolol should be reduced in patients with renal impairment, depending on the creatinine clearance (CC) as follows:
- CC 15 to 35 mL/minute per 1.73 m^2: 50 mg daily orally or 10 mg once every two days intravenously
- CC less than 15 mL/minute per 1.73 m^2: 25 mg daily or 50 mg on alternate days orally or 10 mg once every four days intravenously
- dialysis patients: 25 to 50 mg orally after each dialysis.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Atenolol is distributed into breast milk and there has been a report of cyanosis and bradycardia in a breast-fed neonate whose mother had been taking atenolol (see under Pharmacokinetics, below). The American Academy of Pediatrics therefore considers[1] that it should be given with caution to breast-feeding mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the eyes. Visual symptoms without headache were associated with atenolol for migraine prophylaxis in a patient who had had a similar reaction with nadolol.[1]

1. Kumar KL, Cooney TG. Visual symptoms after atenolol therapy for migraine. *Ann Intern Med* 1990; **112:** 712–13. Correction. *ibid.*; **113:** 257.

Effects on the heart. Beta blockers are used in the management of cardiac arrhythmias. However, atenolol 2.5 mg by intravenous injection induced atrial fibrillation in 6 of 12 predisposed patients.[1]

1. Rassmussen K, *et al.* Atrial fibrillation induced by atenolol. *Eur Heart J* 1982; **3:** 276–81.

Effects on lipid metabolism. For a report of acute pancreatitis due to hypertriglyceridaemia in a patient taking metoprolol followed by atenolol, see p. 1320.1.

Effects on the liver. Adverse hepatic reactions in patients receiving atenolol have included reversible cholestatic hepatitis in one[1] and hepatic dysfunction in another.[2]

1. Schwartz MS, *et al.* Atenolol-associated cholestasis. *Am J Gastroenterol* 1989; **84:** 1084–6.
2. Yusuf SW, Mishra RM. Hepatic dysfunction associated with atenolol. *Lancet* 1995; **346:** 192.

Overdosage. Atenolol appears to lack membrane-stabilising activity and may have fewer adverse cardiac effects than some other beta blockers. However, cardiovascular toxicity has been noted after massive overdosage: ventricular asystole[1] and hypotension with ECG abnormalities[2] have been reported. Severe cardiovascular effects also occurred[3] in a patient with mixed overdosage including atenolol and diltiazem, and were attributed to additive toxicity.

1. Stinson J, *et al.* Ventricular asystole and overdose with atenolol. *BMJ* 1992; **305:** 693.
2. Love JN, Elshami J. Cardiovascular depression resulting from atenolol intoxication. *Eur J Emerg Med* 2002; **9:** 111–14.
3. Snook CP, *et al.* Severe atenolol and diltiazem overdose. *J Toxicol Clin Toxicol* 2000; **38:** 661–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atenolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

About 50% of an oral dose of atenolol is absorbed. Peak plasma concentrations occur in 2 to 4 hours. Atenolol has low lipid solubility. It crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved. Only small amounts are reported to cross the blood-brain barrier, and plasma-protein binding is minimal. The plasma half-life is about 6 to 7 hours. Atenolol undergoes little or no hepatic metabolism and is excreted mainly in the urine. It is removed by haemodialysis.

Breast feeding. Atenolol diffuses into breast milk in concentrations similar[1] to or higher[2] than those in maternal blood. Cyanosis and bradycardia associated with ingestion of atenolol in breast milk has been reported in a 5-day-old term infant. The baby improved when breast feeding was stopped.[3]

1. Thorley KJ, McAinsh J. Levels of the beta-blockers atenolol and propranolol in the breast milk of women treated for hypertension in pregnancy. *Biopharm Drug Dispos* 1983; **4:** 299–301.
2. White WB, *et al.* Atenolol in human plasma and breast milk. *Obstet Gynecol* 1984; **63:** 42S–44S.
3. Schimmel MS, *et al.* Toxic effects of atenolol consumed during breast feeding. *J Pediatr* 1989; **114:** 476–8.

Pregnancy. Creatinine clearance increases during pregnancy, and a study in 17 pregnant patients found that the elimination half-life was shorter and renal clearance of

atenolol faster during the second and third trimesters compared with three months post partum.[1] In another study,[2] postpartum samples were taken from the maternal and umbilical serum of 6 women who had been taking atenolol for at least 6 days before delivery; atenolol was detected in both maternal and cord blood in about equal concentrations. Atenolol was not detected in the maternal or cord blood of another patient who had stopped taking atenolol one day before delivery; the authors concluded that atenolol levels in the mother and fetus are equal at steady state, and that fetal accumulation does not occur. Atenolol concentrations in 35 term neonates whose mothers had received atenolol were examined.[3] It was found that the elimination rate for the neonates was 4 times slower than in adults, possibly because of immaturity of renal function. Transient bradycardia developed in 14 neonates.

1. Hebert MF, *et al.* Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. *J Clin Pharmacol* 2005; **45:** 25–33.
2. Melander A, *et al.* Transplacental passage of atenolol in man. *Eur J Clin Pharmacol* 1978; **14:** 93–4.
3. Rubin PC, *et al.* Atenolol elimination in the neonate. *Br J Clin Pharmacol* 1983; **16:** 659–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atel†; Atelan†; Atenoblock; Atenopharma; Atenovit; Cardioblock; Corpaz; Fabotenol; Felobits; Ilaten; Myocord; Plenacor; Prenormine; Telvodin; Tensilol†; Tozolden; Vericordin; ***Austral.***: Anselol; Atehexal†; Noten; Tenormin; Tensig; ***Austria***: Atehexal; Atenolan; Tenormin; ***Belg.***: Atenotop†; Docateno†; Tenormin; ***Braz.***: Ablok; Angiless; Angipress; Atecard; Atenegran; Ateneo; Ateneum; Atenobal; Atenokin†; Atenol; Atenolab; Atenopress; Atenorm; Atenoton; Atensiol; Atenuol; Atepress; Plenacor; Telol; ***Canad.***: Apo-Atenol; Novo-Atenol†; Nu-Atenol; Tenormin; ***Chile***: Atomex; Betacar; Grifotenol; Labotensil; Sotacor; ***Cz.***: Apo-Atenol; Atehexal; Atenobene; Tenormin; ***Denm.***: Atenet†; Atenodan; Atenor†; Tenormin; Uniloc; ***Fin.***: Atenblock; Tenoblock; Tenoprin; ***Fr.***: Betatop; Tenormine; ***Ger.***: Ate Lich†; Atebeta; Atehexal†; Ateno†; Atenogamma†; Juvental†; Tenormin; ***Gr.***: Adenamin; Azectol; Blikonol; Blocotenol; Eptonal; Estanolin; Fealin; Galol; Hemon; Londofis; Mesonex; Mezarid; Neocardon; Osel; Presentil; Silder; Synarome; Tenormin; Tradiver; Umoder; ***Hong Kong***: Apo-Atenol; Artenol†; Atenemeal†; CP-Atenol; Hajime†; Hypernol; Lo-Ten; Martenol†; Normaten; Nortelol; Noten†; Oraday†; Telol; Tenormin; Tensig†; Ternolol; Totamol†; Tredol; Vascoten; Velorin; ***Hung.***: Atenobene; Atenomel; Blokium†; Prinorm; ***India***: Agloten; Alinor; Anol; Atbeta; Atcardil; Atcom; Atecard; Atekind; Atelol; Aten; Atenex; Atenij; Atenova; Atensia; Atepres; Atezys; Atol; Atop; Atormin; Atpark; Atzee; B-Bloc; Beta; Betacard; Beten; Biduten; Bp Norm; Bp-Act; Bp-Nol; Bpgard; C-Tol; Cadpres; Cardaten; Carden; Catenol; Coronol; Dilcare; Esamlo AT; Etopres; G-Ten; Harten; Hibesor; Hipres; Hyten; Lakten; Lonol; Manoten; Natenol; Novaten; O-Beta; Odinol; Teno; Tenolol; Tenormin; Tensimin; ***Indon.***: Betablok; Farnormin; Hiblok; Internolol; Tenblok; Tenormin; Tensinorm†; Zumablok; ***Irl.***: Amolin; Atecor; Ateni; Atenogen; Atenomel; Nortenolol; Tenormin; Trantalol; ***Israel***: Normalol; Normiten; ***Ital.***: Atenol; Atermin†; Seles Beta; Tenomax; Tenormin; Tensiblock; ***Malaysia***: Apo-Atenol; Aveten; Beten; Loten†; Normaten; Noten†; Ranlol; Tenormin; Urosin; Vascoten; Velorin; ***Mex.***: Atenol†; Atoken; Betadure; Biofilen; Blotex; Lesaten; Min-T; Nosbal; Tenormin; Trebanol; ***Norw.***: Tenormin; Uniloc; ***NZ***: Lo-Ten†; ***Philipp.***: Aloten; Aten; Atestad; Cardioten; Durabeta; Tenor-Bloc; Tenormin; Tenorvas; Tenostat†; Tensimin; Therabloc; Trubloc; Velorin; Zenolen†; ***Pol.***: Normocard†; ***Port.***: Bril; Corzil; Tenormin; Tessifol†; ***Rus.***: Atenolan (Атенолан)†; Betacard (Бетакард); Catenol (Катенол)†; Estekor (Эстекор); Hypoten (Хайпотен)†; Prinorm (Принорм); Tenolol (Тенолол); Tenormin (Тенормин); ***S.Afr.***: Atenoblok†; B-Block; Hexa-Blok; Ten-Bloka; Tenopress; Tenormin; Venapulse†; ***Singapore***: Aiti; Alonet; Apo-Atenol; Catenol; Hypernol; Normaten; Noten; Prenolol; Pretenol; Tenol; Tenolol; Tenormin; Tensig; Ternolol; Urosin; Vascoten; Velorin; ***Spain***: Blokium; Neatenol†; Tanser†; Tenormin; ***Swed.***: Tenormin; ***Switz.***: Atenil; Cardaxen†; Selobloc; Tenormin; ***Thai.***: Atcard; Atenol; Betaday; Coratol†; Daynol†; Enolol; Eutensin; Nolol†; Nortelol†; Oraday; Preloc; Prenolol; Tenocard; Tenocor†; Tenol†; Tenolol; Tenormin; Tenrol; Tetalin; Tolol; Vascoten†; Velorin; ***Turk.***: Atolteva; Nortan; Tensidif†; Tensinor; ***UAE***: Tensotin; ***UK***: Antipressan; Atenix†; Tenormin; ***Ukr.***: Atenobene (Атенобене); ***USA***: Tenormin; ***Venez.***: Beloc; Blokium; Ritmilan; Tenormin.

Multi-ingredient Preparations. ***Arg.***: Plenacor D; Prenoretic; Vericordin Compuesto; ***Austria***: Atenolan comp; Atenolol comp; Beta-Adalat; Nif-Ten; Polinorm†; Tenoretic; ***Belg.***: Tenif; Tenoretic; ***Braz.***: Ablok Plus; Anaten; Angipress CD; Atelidona; Atenorese; Atenoric; Atenuol CRT; Betacard Plus; Betalor; Diublok; Nifelat; Tenoretic; ***Canad.***: Apo-Atenidone; Novo-Atenolthalidone†; Tenoretic; ***Cz.***: Tenoretic; ***Denm.***: Tenidon; Tenoretic; ***Fin.***: Nif-Ten†; ***Fr.***: Beta-Adalate; Tenordate; Tenoretic; ***Ger.***: Ate Lich comp†; Atehexal comp†; Atel†; AteNif beta†; Ateno comp†; Atenogamma comp†; Atenolol comp; Bresben†; Diu-Atenolol†; Nif-Ten; Nifatenol†; Teneretic; TRI-Normin; ***Gr.***: Apress; Chlotenor; Merendal; Obosan; Ogerol; Tenoretic; Typofen; Vagosinol; ***Hong Kong***: Nif-Ten; Target†; Tenoret; Tenoretic; ***Hung.***: Blokium Diu; ***India***: Aamin-A; Acord-A; Adpine-AT; Aglodepin-AT; Alodip-AT; Amcard-AT; Amchek AT; Amdepin-AT; Amdip-AT; Amdonex-AT; Amfast-AT; Amlat; Amlip Beta; Amlo-AT; Amloact-AT; Amlobet; Amlocal-AT; Amlocan-TN; Amlocard Forte; Amlocom-AT; Amlodac-AT; Amlogen-AT; Amlokath-A; Amlokind-AT; Amlokos-AT; Amlong-A; Amlonol; Amlonova; Amlopin-AT; Amlopres AT; Amlosafe-AT; Amlostat-AT; Amlot-AT; Amlotal-AT; Amlotec-AT; Amloten; Amlovas-AT; Amloz AT; Amodep-AT; Amone-AT; Amozen-AT; Ampine-AT; Amrap-AT; Amset-XT; Amsten; Amtas-AT; Amtenol; Angicam-Beta; Angitol Plus; Angizaar-AT; Anol-AD; Anol-Plus; Asomex-AT; Atamo; Atecard-AM; Atecard-D; Atelol-D; Atemos-AT; Aten-AM; Aten-D; Aten-H; Atenex-AM; Atenodip; Atenova H; Atenova-SA; Atensia-AM; Atloma; Atol-AM; Atzee-AM; Beta Amlol; Beta-Biduret; Beta-Nicardia; Beta-Nifedipine; Betacard H; Betacard-AM; Betanif; Betatrop; Beten-AM; Bibidip; Bp-Cure-AT; Bp-Loride; Bp-Mide Plus; C-Amlo Plus; Cardif Beta†; Cardipin-AT; Cardules Plus; Carvasc-A; Cinamat; Coronol-AM; Corvadil-A; Coslo; Defidin-A; Depten; Diavasc-AT; Dipal-AT; Dipress-Plus; Emadine AT; Esam AT; Esdil AT; Eslo-AT; Espin-AT; Etopres-AT; Etotan-AT; Gamlo AT; Hipres-D; Hypernorm; Inat; Indap-AT; Joglit; Losar-Beta-H; Losar-Beta; Lotensyl-AT; Maat; Malodip-AT; Melol; Moldep-AT; Myamlo-AT; Myo-24; Natenol-AM; NBal-AT; Neocard-Atn; Nicol-AT; Nifetolol; Nilol; Novadep-AT; Numlo-AT; Nusar-ATN; Odinol-AM; Olpine-AT; Presolar; Tenochek; Tenoclor; Tenofed; Tenolol-AM; Tenolol-D; Tenoric; ***Indon.***: Nif-Ten; Tenoret†; Tenoretic†; ***Irl.***: Atecor CT; Atenetic; Beta-Adalat; Nif-Ten; Tenoret; Tenoretic; ***Ital.***: Atenigron; Carmian; Clortanol; Diube; Eupres; Igroseles; Nif-Ten; Normopress; Target; Tenoretic; ***Malaysia***: Apo-Atenidone; Pretenol C; Target; Tenoret; Tenoretic; ***Mex.***: Higroton Blok; Plenacor; Tenoretic; ***Philipp.***: Nif-Ten†; Tenoretic; ***Port.***: Tenoretic; ***Rus.***: Atehexal Compositum (Атегексал Композитум); Atenolol Compositum (Атенолол Композитум); Tenochek (Теночек); Tenonorm (Тенонорм); Tenoretic (Теноретик); Tenoric (Тенорик); Tenorox (Тенороκс); ***S.Afr.***: Adco-Loten; Tenchlor; Tenoret; Tenoretic; ***Singapore***: Beta Nicardia; Nif-Ten; Nifetex; Pretenol C; Target; Tenoret†; Tenoretic†; ***Spain***: Blokium Diu; Kalten; Neatenol Diu; Neatenol Diuvas†; Normopresil; Tenoretic; ***Switz.***: Atedurex; Beta-Adalat; Cardaxen plus; Co-Atenolol; Cotenolol-Neo; Kalten†; Nif-Ten; Tenoretic; ***Thai.***: Catenol; ***Turk.***: Atexal; Tenoretic; ***UK***: AtenixCo; Beta-Adalat; Kalten; Tenchlor; Tenif; Tenoret; Tenoretic; Totaretic; ***Ukr.***: Dinorik (Диноpик); Neocard-Atn (Неокард-Атн)†; Tenochek (Теночек); Tenoric (Тенорик); Tonorma (Тонорма); ***USA***: Tenoretic; ***Venez.***: Blokiuret; Tenoretic.

Pharmacopoeial Preparations

BP 2014: Atenolol Injection; Atenolol Oral Solution; Atenolol Tablets; Co-tenidone Tablets;

USP 36: Atenolol and Chlorthalidone Tablets; Atenolol Injection; Atenolol Oral Solution; Atenolol Tablets.

Atorvastatin Calcium

(BANM, USAN, rINNM)

Atorvastatina cálcica; Atorvastatine calcique; Atorvastatinum calcicum; Calcii Atorvastatinum; CI-981; Кальций Аторвастатин.

Calcium (βR,δR)-2-(*p*-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid (1:2) trihydrate.

$C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$=1209.4

CAS — 134523-00-5 (atorvastatin); 134523-03-8 (atorvastatin calcium); 344423-98-9 (atorvastatin calcium trihydrate).

ATC — C10AA05.

ATC Vet — QC10AA05.

UNII — 48A5M73Z4Q (atorvastatin calcium hydrate); C0GEJ5QCSO (anhydrous atorvastatin calcium).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Atorvastatin Calcium Trihydrate). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

USP 36: (Atorvastatin Calcium). A white to off-white, crystalline powder. Very slightly soluble in water, in pH 7.4 phosphate buffer, and in acetonitrile; insoluble in aqueous solutions of pH 4 and below; slightly soluble in alcohol; freely soluble in methyl alcohol.

Uses and Administration

Atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p. 1248.1), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and dysbetalipoproteinaemia (type III). Atorvastatin can be effective as adjunctive therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. It is also used for primary and secondary prophylaxis of cardiovascular events (see Cardiovascular Risk Reduction, p. 1246.1) in patients with multiple risk factors, including diabetes mellitus.

Atorvastatin is given orally as the calcium salt although doses are expressed in terms of the base (atorvastatin magnesium has also been used); 10.82 mg of atorvastatin calcium trihydrate is equivalent to 10 mg of base. The usual initial dose is 10 to 20 mg of atorvastatin once daily; an initial dose of 40 mg daily may be used in patients who require a large reduction in LDL-cholesterol. The dose may be adjusted at intervals of at least 4 weeks up to a maximum of 80 mg daily.

For patients taking drugs that interact with atorvastatin, dose reduction is advised as follows:

- patients taking *ciclosporin*, maximum dose 10 mg once daily
- patients taking *clarithromycin*, initial dose 10 mg once daily and maximum dose 20 mg once daily
- patients taking *itraconazole*, initial dose 10 mg once daily and maximum dose 40 mg once daily
- patients taking *ritonavir-boosted lopinavir* or *ritonavir-boosted saquinavir*, doses above 20 mg once daily should be used with caution

For the use of atorvastatin in children and adolescents, see below.

General reviews.

1. Lea AP, McTavish D. Atorvastatin: a review of its pharmacology and therapeutic potential in the management of hyperlipidaemias. *Drugs* 1997; **53:** 828–47.
2. Malinowski JM. Atorvastatin: a hydroxymethylglutaryl-coenzyme A reductase inhibitor. *Am J Health-Syst Pharm* 1998; **55:** 2253–67.
3. Malhotra HS, Goa KL. Atorvastatin: an updated review of its pharmacological properties and use in dyslipidaemia. *Drugs* 2001; **61:** 1835–81.
4. Croom KF, Plosker GL. Atorvastatin: a review of its use in the primary prevention of cardiovascular events in patients with type 2 diabetes mellitus. *Drugs* 2005; **65:** 137–52.
5. Doggrell SA. Is atorvastatin superior to other statins? Analysis of the clinical trials with atorvastatin having cardiovascular endpoints. *Rev Recent Clin Trials* 2006; **1:** 143–53.
6. Poli A. Atorvastatin: pharmacological characteristics and lipid-lowering effects. *Drugs* 2007; **67** (suppl 1): 3–15.
7. Bybee KA, *et al.* Cumulative clinical trial data on atorvastatin for reducing cardiovascular events: the clinical impact of atorvastatin. *Curr Med Res Opin* 2008; **24:** 1217–29.
8. Acharjee S, Welty FK. Atorvastatin and cardiovascular risk in the elderly—patient considerations. *Clin Interv Aging* 2008; **3:** 299–314.

Administration in children. In patients aged 10 to 17 years with hypercholesterolaemia or combined (mixed) hyperlipidaemia, atorvastatin is licensed for use orally in an initial dose of 10 mg once daily, adjusted if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg once daily. A 6-month study[1] with this dose regimen in children with familial or severe hypercholesterolaemia found that atorvastatin was both safe and effective. Atorvastatin has also been used in children with hyperlipidaemia associated with renal[2] or heart[3] transplantation.

1. McCrindle BW, *et al.* Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003; **143:** 74–80.
2. Argent E, *et al.* Atorvastatin treatment for hyperlipidemia in pediatric renal transplant recipients. *Pediatr Transplant* 2003; **7:** 38–42.
3. Chin C, *et al.* Efficacy and safety of atorvastatin after pediatric heart transplantation. *J Heart Lung Transplant* 2002; **21:** 1213–17.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

General references.

1. Black DM, *et al.* An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med* 1998; **158:** 577–84.
2. Bernini F, *et al.* Safety of HMG-CoA reductase inhibitors: focus on atorvastatin. *Cardiovasc Drugs Ther* 2001; **15:** 211–18.
3. Waters DD. Safety of high-dose atorvastatin therapy. *Am J Cardiol* 2005; **96** (suppl 5A): 69F–75F.
4. Arca M. Atorvastatin: a safety and tolerability profile. *Drugs* 2007; **67** (suppl 1): 63–9.

Effects on the skin. Toxic epidermal necrolysis apparently caused by atorvastatin has been reported.[1] The authors were not aware of this adverse effect previously having been associated with any of the statin lipid regulating drugs.

1. Pfeiffer CM, *et al.* Toxic epidermal necrolysis from atorvastatin. *JAMA* 1998; **279:** 1613–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atorvastatin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Simvastatin, p. 1494.2.

Pharmacokinetics

Atorvastatin is rapidly absorbed from the gastrointestinal tract. It has low absolute bioavailability of about 12% due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action. Atorvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 to several active metabolites. It is 98% bound to plasma proteins. The mean plasma elimination half-life of atorvastatin is about 14 hours although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours due to the contribution of the active metabolites. Atorvastatin is excreted as metabolites, primarily in the bile.

Reviews.

1. Lennernäs H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; **42:** 1141–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ampliar; Atarva; Ateroclar; Atormax; Atorvastan; Faboxim; Finlipol; Liparex; Lipibec; Lipifen; Lipitor; Lipocambi; Lipofin; Lipokemia; Liponorm; Lipostop; Lipovastatin; Normalip; Normolipol; Plan; Sincol; Tecoplax; Tialipol†; Torivas; Trimstat; Vanator; Vastina; Zarator; ***Austral.***: Lipitor; ***Austria***: Sortis; ***Belg.***: Lipitor; ***Braz.***: Atorless; Citalor; Kolevas; Lipigran; Lipistat; Lipitor; Volunta; Zarator; ***Canad.***: Lipitor; ***Chile***: Atenfar; Atorlip; Dislipor; Hipolixan; Lipitor; Lipotropic; Lipox; Lowden; Zarator; Zurinel†; ***China***: Ale (阿乐); Lipitor (立普妥); You Jia (尤佳); ***Cz.***: Atogal†; Atorgamma; Atoris; Atorpharm; Atraven; Bisatum†; Corat; Larus; Pharmtina; Sortis; Spatizalex; Torvacard; Torvazin; Triglyx; Tulip; Vaston†; Voredanin; Xippatin†; ***Denm.***: Atorin; Erostatin; Lipitor; Prevencor; Sortis; Tahor†; Torvast; Zarator; ***Fin.***: Atorvaratio; Lipitor; Orbeos; ***Fr.***: Tahor; ***Ger.***: Sortis; ***Gr.***: Altoram; Antorcin; Arvastatil; Ator-Chol; Atorgon; Atorlip; Atorlonga; Atorstat; Atorval; Atorvalet; Atorvanox; Atorvin; Atrost; Atrosterol; Atrovita; Biger; Card-OK; Danelip; Delipost; Doss; Fluxol; Holisten; Latrovin; Lipigan; Lipitor; Lipium-Raldex; Lipizem; Lipodial; Lipostatin; Lipovast; Lorvaten; Rotova; Torvaplus; Torvastin; Vastazor; Xanator; Zarator; ***Hong Kong***: Atacor; Lipitor; ***Hung.***: Atorgamma; Atoris; Atorva; Atorvep; Atorvox; Copator; Decholest; Dislipat; Hypolip; Liprimar†; Obradon; Sortis; Torvacard; Torvalipin; ***India***: A-Vin; Alip; Alnavas; Altovas; Aova; Aqualip; Arpitor; Astin; Asvasin; Atba; Atchol; Atevan; Atheart; Atherochek; Atix; Ato; Atocor; Atofast; Atone; Atorbest; Atordin; Atorec; Atorem; Atorfit; Atoril; Atorin; Atoriv; Atorlip; Atormac; Atornet; Atoroll; Atorsi; Atortin; Atortus; Atorva; Atorvasia; Atorvik; Atosar; Atover; Atozide; Atria; Atrolar; Atrostat; Atstat; Attor; Atv; Atvas; Avas; Avascare; Avastin; Avistatin; Aztor; Barostatin; Biostat; Caat; Carato; Cardinova; Cardistat; Cholecheck; Cholestat; Dipolip; Dyslip; Dysliptin; Elvas; Esia; Eto; Etovas; Gatovas; Genlip; Genxvast; Hartor; Hivas; Jvastor; Kobit; LDTor; Lesstrol; Lipichek; Lipicon; Lipicor; Lipicure; Lipid; Lipidrop; Lipikind; Lipiles; Lipira; Lipiric; Lipirol; Lipitab; Lipivas; Lipofix; Liponorm; Liporest; Lipvas; Ministat; Modlip; Monotorva; Noclog; Nustat; Omnitor; Orvas; Ostin; Xtor; ***Indon.***: Atofar; Atorsan; Lipitor; Stator; Truvaz; ***Irl.***: Atorvas; Lipitor; Lipvastin; Torvacol; ***Israel***: Caduet; Lipitor; Litorva; Torid; ***Ital.***: Atosener; Erouclast; Haepcard; Lipitor; Rovas; Sopavi; Torastin; Torvast; Totalip; Tovanira; Xarator; ***Jpn***: Lipitor; ***Malaysia***: Lipitor; Rotaqor; Storvas; ***Mex.***: Lipitor; ***Neth.***: Atofloc; Atolux; AtoraB; Lipitor; Prevencor†; Sortis†; ***Norw.***: Lipitor; ***NZ***: Lipitor; ***Philipp.***: Atopitar; Ator; Atroact; Avamax; Carvastin; Lipitor; Redulip; Stalip; ***Pol.***: Apo-Atorva; Atorgamma; Atoris; Atorvasterol; Atorvox; Atractin; Atrox; Corator; Larus; Sortis; Storvas; Torvacard; Torvalipin; Tulip; Xavitor; ***Port.***: Atorvan; Avarte; Colip†; Kalcor; Kasitrin†; Minilip†; Sortis†; Telvarte; Texzor; Vartrual; Vastor; Zarator; ***Rus.***: Anvistat (Анвистат); Atomax (Атомакс); Atoris (Аторис); Atorvox (Аторвокс); Lipoford (Липофорд); Lipona (Липона); Liprimar (Липримар); Liptonorm (Липтонорм); Torvacard (Торвакард); Tulip (Тулип); ***S.Afr.***: Aspavor; Atolip; Lipitor; Lipogen; ***Singapore***: Lipitor; ***Spain***: Atoris; Cardyl; Prevencor; Thervan; Zarator; ***Swed.***: Atorbir; Atorstad; Lipitor; Tavara; ***Switz.***: Atorva; Sortis; ***Thai.***: Atorsan; Lipitor; ***Turk.***: Alvastin; Ateroz; Ator; Avitorel; Cardyn; Cholvast; Colastin-L; Divator; Kolestor; Lipidra; Lipitaksin; Lipitor; Saphire; Tarden; Torvaxal; ***UAE***: Lipigard; ***UK***: Lipitor; ***Ukr.***: Amvastan (Амвастан); Astin (Астин); Atocor (Атокор); Atoris (Аторис); Atorvacor (Аторвакор); Atorvasterol (Аторвастерол); Liprimar (Липримар); Livostor (Ливостор); Storvas (Сторвас); Tolevas (Толевас); Torvacard (Торвакард); Tulip (Тулип); ***USA***: CTR; Lipitor; ***Venez.***: Atovarol; Glustar; Lipitor; Tarimyl.

Multi-ingredient Preparations. ***Arg.***: Ampliar Duo; Ampliar Plus; Ateroclar Combi; Ateroclar Duo; Colmibe; Hipertensal Combi; Liparex Duo; Liparex Plus; Lipibec Duo; Lipibec Plus; Lipoarteriosan; Lipocambi Plus; Liponorm Duo; Pelmec Plus; Plan Duo; Temax; Torimibe; Torivas AT; ***Austral.***: Caduet; ***Austria***: Caduet; ***Braz.***: Caduet; ***Canad.***: Caduet; ***Chile***: Caduet; ***China***: Caduet (多达一); ***Cz.***: Caduet; ***Fr.***: Caduet; ***Hong Kong***: Caduet; ***Hung.***: Caduet; ***India***: A-Vin-AS; A1A; AFF; Alip-AM; Alnavas-A; Alnavas-EZ; Altovas-EZ; Amat; Amdepin Duo; Amlopin Plus; Amtor; Aova-EZ; Aova-F; Atchol Asp; Atchol-F; Atheart-EZ; Atherochek-10; Atherochek-5; Atherotwo; Atix-EZ; Atofast-EZ; Atofast-F; Atofast-M; Atoplus; Atorem-F; Atorfen; Atorin-EZ; Atorin-F; Atorlip-EZ; Atorlip-F; Atormac-TG; Atornet-F; Atoroll-EZ; Atortus-EZ; Atorva-TG; Atorvik-EZ; Atosa; Atozide-F; Avas AM; Avas EZ; Avas Plus; Avascare-EZ; Aztor Asp; Aztor EZ; Bitorva; Caduet; Cardipill; Cardisoz-AT; Deplatt-CV; Diakit-4; Dilutex Plus; Diplitor; Duocad; Dyslip-EZ; Dyslip-TG; Dysliptin-EZ; Dysliptin-TG; Ecosprin Gold; Ecosprin-AV; Ecostat; Eslova; Etovas-EZ; Ezemax-A; Ezevas; Fenostat; Fibator EZ; Fibator; Fibrovas; Genlip-EZ; Genxvast-F; Gissistat; Inovas-F; Jstat; Jvastor-EZ; Kobit-AS; Kobit-M; LDTor-Z; Lesstrol-AM; Lesstrol-EZ; Lesstrol-N; Lipi-EZ; Lipicard AV; Lipicure-AS; Lipidrop-V; Lipifol Plus; Lipikind-AM; Lipikind-EZ; Lipivas EZ; Liplofin; Lipofix-EX; Liponorm-EZ; Lorisk; Lorlip-EZ; Lorlip; Modlip Asp; Modlip-AM; Modlip-EZ; Niyat; Noclog-EZ; Noklot-CV; Nurokind Hart; Omnitor-EZ; Orvaz-EZ; Orvaz-FT; Zetitor; ***Indon.***: Caduet; ***Malaysia***: Caduet; ***Mex.***: Caduet; ***Philipp.***: Envacar; ***Port.***: Caduet; ***Rus.***: Caduet (Кадуэт); ***S.Afr.***: Caduet; ***Singapore***: Caduet; ***Spain***: Astucor; Caduet; ***Switz.***: Caduet; ***Thai.***: Caduet; ***Turk.***: Caduet; ***Ukr.***: Azi-Ator (Ази-Атор); Caduet (Кадует); ***USA***: Caduet; Liptruzet; ***Venez.***: Caduet.

Atropine *(BAN)*

Atropiini; Atropin; Atropină; Atropina; Atropinas; Atropinum; DL-Hiosciamina; Атропин; (±)-Hiosciamina; (±)-Hyoscyamine.

(1*R*,3*r*,5*S*,8*r*)-Tropan-3-yl (*RS*)-tropate.

$C_{17}H_{23}NO_3$=289.4

CAS — 51-55-8.

ATC — A03BA01; S01FA01.

ATC Vet — QA03BA01; QS01FA01.

UNII — 7C0697DR9I.

Description. Atropine is an alkaloid that may be obtained from solanaceous plants, or prepared by synthesis.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Atropine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Atropine). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 460 of water, 1 in 90 of water at 80 degrees, 1 in 2 of alcohol, 1 in 1 of chloroform, and 1 in 25 of ether; soluble in glycerol. Its saturated solution in water is alkaline to phenolphthalein. Store in airtight containers. Protect from light.

Atropine Methobromide *(BANM)*

Atropina, metilbromuro de; Atropine Methylbromide; Methylatropine Bromide; Méthylatropine, bromure de; Methylatropini Bromidum; Methylatropinii Bromidum; Methylatropinium Bromatum; Methylatropinium-bromid; Methylatropiniumbromid; Metilatropin-bromid; Metilatropino bromidas; Metylatropinbromid; Metyyliatropiinibromidi; Mydriasine; Атропина Метобромид.

(1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium bromide.

$C_{18}H_{26}BrNO_3$=384.3

CAS — 2870-71-5.

ATC — A03BA01.

ATC Vet — QA03BA01.

UNII — 63IFT0IX9N.

Atropine Methonitrate *(BANM, rINN)*

Atrop. Methonit.; Atropiinimetonitraatti; Atropina, metilnitrato de; Atropine, Méthonitrate d'; Atropini Methonitras; Atropinmetonitrat; Methylatropine Nitrate (USAN); Methylatropine Nitrate; Méthylatropine, nitrate de; Methylatropini nitras; Methylatropinii Nitras; Methylatropinium nitrát; Methylatropiniumnitrat; Metilatropin-nitrát; Metilatropino nitratas; Metilnitrato de atropina; Metonitrato de atropina; Metylatropinnitrat; Metyyliatropiininitraatti; Атропина Метонитрат.

(1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium nitrate.

$C_{18}H_{26}N_2O_6$=366.4

CAS — 52-88-0.

ATC — A03BB02.

ATC Vet — QA03BB02.

UNII — Q4BD9J47K2.

Stability. Aqueous solutions of atropine methonitrate are unstable; stability is enhanced in acid solutions of pH below 6.

Atropine Sulfate *(BANM)*

Atrop. Sulph.; Atropiinisulfaatti; Atropin Sülfat; Atropina, sulfato de; Atropine, sulfate d'; Atropine Sulphate; Atropini sulfas; Atropini Sulfas Monohydricus; Atropino sulfatas; Atropinsulfat; Atropin-sulfát monohydrát; Atropin-szulfát; Atropiny siarczan; Атропина Сульфат.

$(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$=694.8

CAS — 55-48-1 (anhydrous atropine sulfate); 5908-99-6 (atropine sulfate monohydrate).

ATC — A03BA01; S01FA01.

ATC Vet — QA03BA01; QS01FA01.

UNII — KAE4PSB0Z3 (anhydrous atropine sulfate); 03J5ZE7KA5 (atropine sulfate monohydrate).

NOTE. Compounded preparations of atropine sulfate may be represented by the following names:

- Co-phenotrope (*BAN*)—atropine sulfate 1 part and diphenoxylate hydrochloride 100 parts (w/w).

ATR is a code approved by the BP 2014 for use on single unit dose eye drops containing atropine sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Atropine Sulfate). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Protect from light.

USP 36: (Atropine Sulfate). Odourless, colourless crystals or white crystalline powder. It effloresces in dry air. Soluble 1 in 0.5 of water, 1 in 2.5 of boiling water, 1 in 5 of alcohol, and 1 in 2.5 of glycerol. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility between atropine sulfate and hydroxybenzoate preservatives has been seen,[1] resulting in a total loss of the atropine in 2 to 3 weeks.

1. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; **230:** 481.

Uses and Administration

Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions (see below). It is usually given as the sulfate. It first stimulates and then depresses the CNS and has antispasmodic actions on smooth muscle and reduces secretions, especially salivary and bronchial secretions; it also reduces perspiration, but has little effect on biliary or pancreatic secretion. Atropine depresses the vagus and thereby increases the heart rate. When given orally atropine reduces smooth-muscle tone and diminishes gastric and intestinal motility but has little effect on gastric secretion in usual therapeutic doses. Quaternary ammonium derivatives, such as the methonitrate, have less effect on the CNS but strong ganglion-blocking activity.

Because of its effects on heart rate, atropine is used in the treatment of bradycardia and asystole of various causes (p. 1311.2), including in acute cardiopulmonary resuscitation procedures. It has also had many other uses, including: in anaesthetic practice as a premedicant and to counteract the muscarinic effects of anticholinesterases such as neostigmine and other parasympathomimetics (p. 1311.1); as an antispasmodic in gastrointestinal disorders (p. 1311.2); as an adjunct to opioid analgesics for the symptomatic relief of biliary or renal colic (p. 1311.2); to treat or prevent bronchospasm (p. 1312.1); and in the treatment of poisoning with mushrooms that contain muscarine and in organophosphorus pesticide poisoning (p. 1311.3). Atropine is used topically as a mydriatic and cycloplegic in ophthalmology (p. 1311.2).

Actions of antimuscarinics. Antimuscarinic drugs such as atropine are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves; they are also inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation. They have been described as parasympatholytic, atropinic, atropine-like, and as anticholinergic, although the latter term should encompass compounds that also have antinicotinic actions.

At least 5 different pharmacologically identifiable types of **muscarinic receptor** (M_1, M_2, M_3, M_4, and M_5) have been described as have 5 different molecular forms (m_1, m_2, m_3, m_4, and m_5) of these receptors. While the traditional antimuscarinics appear to be relatively non-specific, newer compounds like pirenzepine and telenzepine have a selective action on the M_1 receptors within ganglia supplying cholinergic postganglionic nerves to the gastrointestinal tract.

Antimuscarinics can be classified as **tertiary amine** or **quaternary ammonium** compounds. Atropine and other naturally occurring alkaloids such as hyoscine and hyoscyamine are tertiary amines, that is they have a tertiary nitrogen atom; semisynthetic derivatives or synthetic antimuscarinics may be either tertiary (e.g. homatropine or trihexyphenidyl) or quaternary ammonium (e.g. homatropine methylbromide or ipratropium) compounds.

At therapeutic doses tertiary amine antimuscarinics have little effect on the actions of acetylcholine at nicotinic receptors. However, the quaternary ammonium antimuscarinics have a greater degree of antinicotinic potency, and some of their effects at high doses are due to ganglionic blockade; excessively high doses may even produce neuromuscular block. There are also pharmacokinetic

differences between tertiary amine and quaternary ammonium antimuscarinics. Quaternary ammonium compounds are less lipid soluble than tertiary amines; their gastrointestinal absorption is poor and they do not readily pass the blood-brain barrier or conjunctiva.

Antimuscarinics can produce a wide range of effects at therapeutic doses. The **peripheral** antimuscarinic effects that are produced as the dose increases are:

- decreased production of secretions from the salivary, bronchial, and sweat glands
- dilatation of the pupils (mydriasis) and paralysis of accommodation (cycloplegia)
- increased heart rate
- inhibition of micturition and reduction in gastrointestinal tone
- inhibition of gastric acid secretion

As for **central** effects, with the exception of hyoscine, which causes CNS depression at therapeutic doses, tertiary amines stimulate the medulla and higher cerebral centres producing mild central vagal excitation and respiratory stimulation. At toxic doses all tertiary amines, including hyoscine, cause stimulation of the CNS with restlessness, disorientation, hallucinations, and delirium. As the dose increases stimulation is followed by central depression and death from respiratory paralysis. Synthetic tertiary amines are less potent in their central effects than natural tertiary amines; quaternary ammonium compounds have negligible central effects.

Anaesthesia. Antimuscarinics, including *atropine*, *hyoscine*, and *glycopyrronium*, have been used pre-operatively to inhibit salivation and excessive secretions of the respiratory tract during anaesthesia (p. 1899.1), although this use is less important now that less irritating anaesthetics are used. Atropine and glycopyrronium are also given to reduce intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol, or after vagal stimulation. Glycopyrronium causes less tachycardia than atropine when given intravenously. When hyoscine is used as a premedicant it also provides some amnesia, sedation, and antiemesis but, unlike atropine, may cause bradycardia rather than tachycardia. Atropine or, preferably, glycopyrronium is also used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects (see Uses and Administration of Neostigmine, p. 687.2).

For **premedication** 300 to 600 micrograms of atropine sulfate may be given by subcutaneous or intramuscular injection, usually 30 to 60 minutes before anaesthesia. Alternatively 300 to 600 micrograms of atropine sulfate may be given intravenously immediately before induction of anaesthesia.

The *BNFC* suggests that suitable paediatric subcutaneous or intramuscular premedication doses of atropine sulfate are:

- neonates: 10 micrograms/kg
- children aged 1 month to 12 years: 10 to 30 micrograms/kg (minimum 100 micrograms, maximum 600 micrograms)
- children aged 12 to 18 years: the adult dose

It also suggests the following intravenous doses:

- neonates: 10 micrograms/kg
- children aged 1 month to 12 years: 20 micrograms/kg (minimum 100 micrograms, maximum 600 micrograms)
- children aged 12 to 18 years: the adult dose

The *BNFC* also lists oral doses to be given 1 to 2 hours before induction:

- neonates: 20 to 40 micrograms/kg
- children aged 1 month to 18 years: 20 to 40 micrograms/kg (maximum 900 micrograms).

For intra-operative **bradycardia** the *BNF* states that 300 to 600 micrograms may be given intravenously; larger doses may be used in emergencies.

The *BNFC* suggests that a suitable intravenous dose is:

- neonates and children aged 1 month to 12 years: 10 to 20 micrograms/kg
- children aged 12 to 18 years: the adult dose.

To counteract the muscarinic effects of **anticholinesterases** when they are used to reverse the effects of competitive muscle relaxants, adults are given atropine sulfate 0.6 to 1.2 mg by intravenous injection before or with neostigmine; the *BNF* considers the 0.6 mg dose to be sufficient with edrophonium.

The *BNFC* suggests that a suitable intravenous dose for use with neostigmine is:

- neonates and children aged 1 month to 12 years: 20 micrograms/kg (maximum 1.2 mg)
- children aged 12 to 18 years: the adult dose

and that a suitable intravenous dose for use with edrophonium is:

- children aged 1 month to 18 years: 7 micrograms/kg (maximum 600 micrograms)

Biliary and renal colic. Atropine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p. 6.3).

Cardiac disorders. Atropine depresses the vagus and thereby increases the heart rate. It is therefore used in a variety of disorders or circumstances in which bradyarrhythmias occur. It is frequently used in sudden onset bradyarrhythmias and although it may also be given for the initial treatment of chronic arrhythmias (p. 1266.1), cardiac pacing is generally preferred for long-term control. Examples of acute use include the prevention and treatment of arrhythmias associated with anaesthesia (see above), the treatment of other drug-induced arrhythmias, and in bradycardia after cardiac arrest (p. 1268.3). Atropine sulfate has been used in the management of bradycardia of acute myocardial infarction; however, caution is required, as atropine may exacerbate ischaemia or infarction in these patients.

In **bradycardia** after cardiac arrest, atropine is given[1-3] in doses of 500 micrograms intravenously repeated every 3 to 5 minutes to a total dose of 3 mg. Doses lower than 500 micrograms may paradoxically slow the heart.[1-3]

If an intravenous line cannot be established, atropine can be given via an endotracheal tube, although this route is considered less reliable and higher doses are generally required. For children, a suggested dose is 30 micrograms/kg, flushed with 5 mL of sodium chloride 0.9% followed by 5 manual ventilations.[2]

1. The American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; **122** (18 suppl 3): S639–S946. Also available at: http://circ.ahajournals.org/content/vol122/18_suppl_3/ (accessed 21/01/11)
2. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2010. *Resuscitation* 2010; **81:** 1219–1451. Also available at: www.cprguidelines.eu/2010 (accessed 07/02/11)
3. Resuscitation Council (UK). 2010 Resuscitation Guidelines. Available at: http://www.resus.org.uk/pages/GL2010.pdf (accessed 21/01/11)

Eye disorders. Ophthalmic application of atropine produces mydriasis and cycloplegia (p. 2000.2). One local application takes up to 40 minutes or more to produce mydriasis, which lasts for 7 or more days; marked cycloplegia is obtained in 1 to 3 hours with recovery in 6 to 12 days. Atropine is used to prevent the formation of adhesions and relieve painful ciliary muscle spasm in inflammatory eye disorders such as uveitis (p. 1615.1). It is used to prevent or reverse amblyopia (lazy eye) by producing cycloplegia in the stronger eye, for example in those with strabismus (p. 2000.3), and may be considered as effective as conventional occlusion.[1] It has also been used to aid ophthalmic examination, for example in the determination of refraction; however, other antimuscarinics such as cyclopentolate, homatropine, or tropicamide are usually preferred, especially in adults, because of their faster onset and shorter duration of action.

Atropine sulfate eye drops are usually available in a strength of 1%, although a 0.5% solution or a 1% ointment are obtainable in some countries and may be more suitable where the avoidance of systemic absorption is important, for example in infants and young children. Systemic absorption may also be reduced by compressing the lachrymal sac after instillation.

In the treatment of **inflammatory eye disorders** such as uveitis, atropine sulfate is applied to the eye(s) 1 to 4 times daily. To prevent or reverse **amblyopia**, atropine sulfate may be applied to the stronger eye once daily, although its long duration of action may permit less frequent application.[2-4] To aid **determination of refraction** and other ophthalmic examinations, atropine sulfate is applied to the eye(s) twice daily for up to 3 days before the procedure.

Daily application of atropine sulfate 1% in 400 children aged from 6 to 12 years was shown[5] to slow the progression of myopia, although the same treatment in a similar study did not show an effect on astigmatism.[6]

Atropine borate has also been used in ophthalmic preparations.

1. Li T, Shotton K. Conventional occlusion versus pharmacologic penalization for amblyopia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 22/04/10).
2. Stolovitch C, *et al.* Atropine cycloplegia: how many instillations does one need? *J Pediatr Ophthalmol Strabismus* 1992; **29:** 175–6.
3. Repka MX, *et al.* Pediatric Eye Disease Investigator Group. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. *Ophthalmology* 2004; **111:** 2076–85.
4. Repka MX, *et al.* Pediatric Eye Disease Investigator Group. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *J AAPOS* 2009; **13:** 258–63.
5. Chua WH, *et al.* Atropine for the treatment of childhood myopia. *Ophthalmology* 2006; **113:** 2285–91.
6. Chia A, *et al.* Effect of topical atropine on astigmatism. *Br J Ophthalmol* 2009; **93:** 799–802.

Gastrointestinal disorders. Antimuscarinics may be used in gastrointestinal disorders as antispasmodics (see p. 1806.3), because of their marked inhibitory effect on gastrointestinal motility, and for their antisecretory effects. Atropine (as the sulfate or quaternary derivatives such as the methobromide or methonitrate) has been used to reduce smooth-muscle tone and diminish motility, but has little effect on gastric secretion at usual therapeutic doses. It has been tried as an adjunct to the treatment of benign gastric and duodenal ulcers and the antispasmodic action of atropine has been used to facilitate radiological examination of the gut. Atropine sulfate has also been used in the treatment of irritable bowel syndrome. Atropine oxide hydrochloride is also used for gastrointestinal disorders.

Poisoning. Atropine is used in the management of overdosage or poisoning due to anticholinesterase compounds including organophosphorus pesticides,[1,2] chemical warfare nerve gases,[3] and parasympathomimetics such as neostigmine. It is also used to antagonise the effects of cholinomimetic substances in the treatment of overdosage with parasympathomimetics such as bethanechol, and in the treatment of poisoning with mushrooms that contain muscarine. Atropine blocks the action of these compounds at muscarinic receptors, reversing bradycardia and decreasing tracheobronchial secretions, bronchoconstriction, intestinal secretions, and intestinal motility.

- In the treatment of poisoning with organophosphorus **pesticides** or chemical warfare **nerve gases** atropine sulfate may be given to adults in an initial intravenous dose of 2 mg every 5 minutes until muscarinic effects disappear or signs of atropine toxicity are seen. In severe poisoning, some sources have suggested doubling the dose of atropine every 5 to 10 minutes until improvement is seen. Continuous infusion has also been used.[4,5] Some have suggested a dose of at least 50 micrograms/kg intravenously or intramuscularly for children affected by nerve agents;[6] the *BNFC* includes an intravenous dose of 20 micrograms/kg (maximum 2 mg) given every 5 to 10 minutes for pesticide poisoning.
- In moderate to severe poisoning a state of atropinisation is usually maintained for at least 2 days and continued for as long as symptoms are evident. In severely poisoned patients this may entail prolonged treatment.[7,8] As large amounts of atropine may be required it is important to use a preservative-free preparation to avoid the potential toxicity associated with use of excess quantities of preservatives such as benzyl alcohol or chlorobutanol.
- Since atropine is ineffective against any nicotinic effects of these compounds a cholinesterase reactivator such as pralidoxime (p. 1571.2) may be used as an adjunct.

The use of atropine in poisoning or overdosage with **other compounds** having muscarinic actions is similar to that for organophosphorus pesticides but the duration of treatment necessary is usually shorter. An initial dose of 1 to 2 mg given subcutaneously, intramuscularly, or intravenously and repeated every 2 to 4 hours may be adequate for overdosage with cholinomimetics such as bethanechol.

1. Singh S, *et al.* Is atropine alone sufficient in acute severe organophosphorus poisoning: experience of a North West Indian hospital. *Int J Clin Pharmacol Ther* 1995; **33:** 628–30.
2. Eddleston M, *et al.* Management of severe organophosphorus pesticide poisoning. *Crit Care* 2002; **6:** 259.
3. Anonymous. Treatment of nerve gas poisoning. *Med Lett Drugs Ther* 1995; **37:** 43–4.
4. Ram JS, *et al.* Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. *J Assoc Physicians India* 1991; **39:** 190–3.
5. Sungur M, Güven M. Intensive care management of organophosphate insecticide poisoning. *Crit Care* 2001; **5:** 211–15.
6. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; **112:** 648–58.
7. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; **4:** 339–40.
8. Afzaal S, *et al.* High dose atropine in organophosphorus poisoning. *Postgrad Med J* 1990; **66:** 70–1.

Reflex anoxic seizures. A reflex anoxic seizure[1,2] is a paroxysmal event triggered by a noxious stimulus which, by vagal stimulation, causes pronounced bradycardia or cardiac arrest and consequent relative cerebral ischaemia. Depending on the degree of vagal hypersensitivity or noxious stimulus, attacks may occur infrequently or several times daily. Certain features of the attack may lead to a misdiagnosis of epilepsy. To avoid confusion with epileptic seizures (p. 506.1), reflex anoxic seizures have also been called white, pallid, or type 2 breath holding attacks. In susceptible individuals, a reflex anoxic seizure may provoke a true epileptic seizure, but this is rare.[3]

Infants and young children are mainly affected and the condition usually resolves by early childhood. It is generally benign and children do not suffer cardiac or cerebral damage. Treatment is seldom necessary, but atropine has been advocated to prevent vagal hypersensitivity in those children with frequent, persistent attacks. As atropine may require frequent doses with an attendant risk of overdosage, transdermal hyoscine has been tried as an alternative;[4] cardiac pacing has also been used successfully.[5,6]

1. Appleton RE. Reflex anoxic seizures. *BMJ* 1993; **307:** 214–5.
2. Stephenson JB. Anoxic seizures: self-terminating syncopes. *Epileptic Disord* 2001; **3:** 3–6.

3. Horrocks IA, *et al.* Anoxic-epileptic seizures: observational study of epileptic seizures induced by syncopes. *Arch Dis Child* 2005; **90:** 1283–7.
4. Palm L, Blennow G. Transdermal anticholinergic treatment of reflex anoxic seizures. *Acta Paediatr Scand* 1985; **74:** 803–4.
5. McLeod KA, *et al.* Cardiac pacing for severe childhood neurally mediated syncope with reflex anoxic seizures. *Heart* 1999; **82:** 721–5.
6. Wilson D, *et al.* Cardiac pacing in the management of severe pallid breath-holding attacks. *J Paediatr Child Health* 2005; **41:** 228–30.

Respiratory-tract disorders. Although atropine is a potent bronchodilator its use in the management of reversible airways obstruction has largely been replaced by other antimuscarinics such as ipratropium (p. 1211.3). Atropine is sometimes used in combination preparations with antihistamines and decongestants for the symptomatic relief of symptoms of the common cold.

References.

1. Sur S, *et al.* A random double-blind trial of the combination of nebulized atropine methylnitrate and albuterol in nocturnal asthma. *Ann Allergy* 1990; **65:** 384–8.
2. Vichyanond P, *et al.* Efficacy of atropine methylnitrate alone and in combination with albuterol in children with asthma. *Chest* 1990; **98:** 637–42.

Adverse Effects

The pattern of adverse effects seen with atropine and other antimuscarinics can mostly be related to their pharmacological actions at muscarinic and, at high doses, nicotinic receptors (see Actions of Antimuscarinics, p. 1310.3). These effects are dose-related and are usually reversible when therapy is stopped. The **peripheral** effects of atropine and other antimuscarinics are a consequence of their inhibitory effect on muscarinic receptors within the autonomic nervous system. At therapeutic doses, adverse effects include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition, as well as reduction in the tone and motility of the gastrointestinal tract leading to constipation. Some of the **central** effects of atropine and other tertiary antimuscarinics seen at toxic doses (see below) may also occur at therapeutic doses.

In **overdosage**, the peripheral effects become more pronounced and other symptoms such as hyperthermia, hypertension, increased respiratory rate, and nausea and vomiting may occur. A rash may appear on the face or upper trunk. Toxic doses also cause CNS stimulation marked by restlessness, confusion, excitement, ataxia, incoordination, paranoid and psychotic reactions, hallucinations and delirium, and occasionally seizures. However, in severe intoxication, central stimulation may give way to CNS depression, coma, circulatory and respiratory failure, and death.

There is considerable variation in susceptibility to atropine; recovery has occurred even after 1 g, whereas deaths have been reported from doses of 100 mg or less for adults and 10 mg for children.

Quaternary ammonium antimuscarinics, such as atropine methobromide or methonitrate and propantheline bromide, have some ganglion-blocking activity and high doses may cause orthostatic hypotension and impotence; in toxic doses non-depolarising neuromuscular block may be produced.

Systemic toxicity may be produced by the **local** instillation of antimuscarinic eye drops, particularly in children and in the elderly. Prolonged application of atropine to the eye may lead to local irritation, hyperaemia, oedema, and conjunctivitis. An increase in intra-ocular pressure may occur, especially in patients with angle-closure glaucoma.

Hypersensitivity to atropine is not uncommon and may occur as conjunctivitis or a rash.

Effects on body temperature. Atropine can cause hyperthermia as a result of inhibition of sweating. This may be attenuated by atropine's ability to dilate cutaneous blood vessels. However, there has been a report of hypothermia in a 14-year-old feverish patient after intravenous use of atropine.[1]

For reports of fatal heat stroke in patients taking an antimuscarinic with an antipsychotic see under Interactions in Benzatropine, p. 895.1.

1. Lacouture PG, *et al.* Acute hypothermia associated with atropine. *Am J Dis Child* 1983; **137:** 291–2.

Effects on the eyes. In addition to the expected ocular effects of atropine (see above) there have been instances of acute angle-closure glaucoma in patients receiving nebulised atropine.[1]

1. Berdy GJ, *et al.* Angle closure glaucoma precipitated by aerosolized atropine. *Arch Intern Med* 1991; **151:** 1658–60.

Effects on the gastrointestinal tract. Antimuscarinics reduce gastrointestinal tone and paralytic ileus has been reported[1] in a 77-year-old man with Parkinson's disease who had been receiving atropine sulfate orally to control excess salivation. An increased risk of oesophageal cancer has also been reported[2] with antimuscarinics, possibly due to reductions in lower oesophageal sphincter tone increasing the risk of gastro-oesophageal reflux.

1. Beatson N. Atropine and paralytic ileus. *Postgrad Med J* 1982; **58:** 451–3.
2. Lagergren J, *et al.* Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 2000; **133:** 165–75.

Effects on the heart. Atropine sulfate, to a total of 1 mg per 70 kg body-weight, given intravenously to 79 patients before surgery produced arrhythmias in over 20% of patients, especially in the young.[1] Atrioventricular dissociation was the most common disturbance in adults and in children atrial rhythm disturbances were common. In another study[2] premedication including atropine or glycopyrronium given intramuscularly resulted in a significantly greater incidence of tachycardia during anaesthetic induction and intubation compared with controls who received no antimuscarinic drug. Patients who received glycopyrronium also had a higher incidence of tachycardia during surgery than the controls. No significant difference in bradycardia or extrasystoles was found in the atropine- or the glycopyrronium-treated patients. Atrial fibrillation has been reported in 2 elderly glaucoma patients after post-surgical application of atropine ointment or eye drops to the eye.[3]

1. Dauchot P, Gravenstein JS. Effects of atropine on the electrocardiogram in different age groups. *Clin Pharmacol Ther* 1971; **12:** 274–80.
2. Shipton EA, Roelofse JA. Effects on cardiac rhythm of premedication with atropine or glycopyrrolate. *S Afr Med J* 1984; **66:** 287–8.
3. Merli GJ, *et al.* Cardiac dysrhythmias associated with ophthalmic atropine. *Arch Intern Med* 1986; **146:** 45–7.

Effects on mental function. A study[1] in patients with Parkinson's disease and healthy control subjects suggested that although short-term memory was impaired in patients receiving long-term antimuscarinic therapy the effect was reversible on stopping. An epidemiological study[2] similarly reported lower cognitive performance in elderly patients receiving antimuscarinics.

See also under Trihexyphenidyl (p. 918.1) and under Oxybutynin (p. 2362.1).

1. Van Herwaarden G, *et al.* Short-term memory in Parkinson's disease after withdrawal of long-term anticholinergic therapy. *Clin Neuropharmacol* 1993; **16:** 438–43.
2. Lechevallier-Michel N, *et al.* Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol* 2005; **59:** 143–51.

Hypersensitivity. A report[1] of anaphylactic shock developing in a 38-year-old woman after an intravenous injection of atropine.

1. Aguilera L, *et al.* Anaphylactic reaction after atropine. *Anaesthesia* 1988; **43:** 955–7.

Overdosage. Reports of atropine poisoning or overdosage have included a respiratory therapist[1] who had given 10 atropine sulfate aerosol treatments in the preceding 24 hours and children who had taken overdoses of a preparation containing diphenoxylate and atropine.[2]

1. Larkin GL. Occupational atropine poisoning via aerosol. *Lancet* 1991; **337:** 917.
2. McCarron MM, *et al.* Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature). *Pediatrics* 1991; **87:** 694–700.

Treatment of Adverse Effects

If a patient presents within an hour of an oral overdose of atropine the stomach may be emptied or activated charcoal given to reduce absorption. Supportive therapy (p. 1537.1) should be given as required; in particular, hypoxia and hypotension should be corrected. Metabolic acidosis that persists despite correction of hypoxia and adequate fluid replacement may require treatment with intravenous sodium bicarbonate. Arrhythmias are best managed by correction of hypoxia and acidosis; antiarrhythmics should not be given. Diazepam has been used to manage repeated or prolonged convulsions (lorazepam has also been given), and for sedation in agitated adults.

Physostigmine has been tried for antimuscarinic poisoning (see p. 2010.1) but such use can be hazardous and is not generally recommended.

Precautions

Atropine should be used with caution in children and the elderly, who may be more susceptible to its adverse effects. It is contra-indicated in patients with prostatic enlargement, in whom it may lead to urinary retention, and in those with paralytic ileus or pyloric stenosis. In patients with ulcerative colitis its use may lead to ileus or megacolon, and its effects on the lower oesophageal sphincter may exacerbate reflux. Caution is generally advisable in any patient with diarrhoea. It should not be given to patients with myasthenia gravis except to reduce adverse muscarinic effects of an anticholinesterase.

Atropine should not be given to patients with angle-closure glaucoma or with a narrow angle between the iris and the cornea, since it may raise intra-ocular pressure and precipitate an acute attack. Acute angle-closure glaucoma has been reported in patients receiving nebulised atropine. Some licensed product information recommends that atropine eye drops should not be used in infants aged less than 3 months due to the possible association between the induced cycloplegia and the development of amblyopia. Systemic reactions have followed the absorption of atropine from eye drops; overdosage is less likely if the eye ointment is used. In the event of blurred vision after topical application of atropine to the eye patients should not drive or operate machinery. Systemic use of antimuscarinics may also cause blurred vision, dizziness, and other effects that may impair a patient's ability to perform skilled tasks such as driving.

Because of the risk of provoking hyperthermia, atropine should not be given to patients, especially children, when the ambient temperature is high. It should also be used cautiously in patients with fever.

Atropine and other antimuscarinics need to be used with caution in conditions characterised by tachycardia such as thyrotoxicosis, heart failure, and in cardiac surgery, where they may further accelerate the heart rate. Care is required in patients with acute myocardial infarction, as ischaemia and infarction may be made worse, and in patients with hypertension.

Atropine may cause confusion, especially in the elderly. Reduced bronchial secretion caused by systemic atropine may be associated with the formation of mucous plugs.

In the treatment of parkinsonism, increases in dosage and transfer to other forms of treatment should be gradual and the antimuscarinic should not be withdrawn abruptly. Minor reactions may be controlled by reducing the dose until tolerance has developed.

Persons with Down's syndrome appear to have an increased susceptibility to some of the actions of atropine, whereas those with albinism may have a reduced susceptibility.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving atropine, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atropine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

The effects of atropine and other antimuscarinics may be enhanced by use with other drugs having antimuscarinic properties, such as amantadine, some antihistamines, phenothiazine antipsychotics, and tricyclic antidepressants. Inhibition of drug-metabolising enzymes by MAOIs may possibly enhance the effects of antimuscarinics. The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs. Antimuscarinics may also antagonise the gastrointestinal effects of cisapride, domperidone, and metoclopramide. Antimuscarinics and parasympathomimetics may counteract each others effects.

Pharmacokinetics

Atropine is readily absorbed from the gastrointestinal tract; it is also absorbed from mucous membranes, the eye, and to some extent through intact skin. It is rapidly cleared from the blood and is distributed throughout the body. It crosses the blood-brain barrier. It is incompletely metabolised in the liver and is excreted in the urine as unchanged drug and metabolites. A half-life of about 4 hours has been reported. Atropine crosses the placenta and traces appear in breast milk.

Quaternary ammonium salts of atropine, such as the methonitrate, are less readily absorbed after oral doses. They are highly ionised in body fluids and being poorly soluble in lipids they do not readily cross the blood-brain barrier.

Pregnancy. Studies of the pharmacokinetics of atropine in mother and fetus in late pregnancy[1-3] indicated that atropine rapidly crosses the placenta. However, whereas peak concentrations of atropine in fetal cord blood were reached about 5 minutes after intravenous doses, the max-

imum effect on fetal heart rate occurred after about 25 minutes.

1. Barrier G, *et al.* La pharmacocinétique de l'atropine chez la femme enceinte et le foetus en fin de grossesse. *Anesth Analg Reanim* 1976; **33:** 795–800.
2. Onnen I, *et al.* Placental transfer of atropine at the end of pregnancy. *Eur J Clin Pharmacol* 1979; **15:** 443–6.
3. Kanto J, *et al.* Placental transfer and pharmacokinetics of atropine after a single maternal intravenous and intramuscular administration. *Acta Anaesthesiol Scand* 1981; **25:** 85–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Endotropina; Klonatropina; ***Austral.***: Atropt; ***Belg.***: Stellatropine; ***Braz.***: Atropion; Santropina; ***China***: Di Shan (迪善); ***Ger.***: Dysurgal; ***India***: Atp; Atro; Atroren-P; Atrosun; Bell Pino-Atrin†; ***Indon.***: Isotic Cycloma; ***Israel***: Atrospan; ***Mex.***: Atro Grin; Atro Ofteno; Atropisa†; Tropyn; ***NZ***: Atropt; ***Philipp.***: Anespin; Atropol; ***Port.***: Atropocil; ***Singapore***: Atrosol; ***Switz.***: Bellafit N; ***Thai.***: Atroren-P; ***Turk.***: Atrosol; ***USA***: AtroPen; Ocu-Tropine†; Sal-Tropine†.

Multi-ingredient Preparations. ***Arg.***: Asmopul; Neoastrin; Yanal; ***Austral.***: Donnagel; Donnalix; Donnatab; ***Braz.***: Espasmocron†; Neogrein; Ormigrein; Tonaton; Vagostesyl; ***Chile***: Buton; Colicor; Dipatropin; Dolospam; ***Fr.***: Ineurope; ***Hong Kong***: Alubar†; Alutal†; Virulex Forte; ***India***: Atrisolon; Atrocin; Brovon; Deco-AT; Pino-Cort†; ***Indon.***: Aludonna; ***Israel***: Spasmalgin; ***Ital.***: Cardiostenol; Deltamidrina; ***Mex.***: Paliatil; Redotex NF; Redotex; ***Pol.***: Tolargin†; ***S.Afr.***: Colstat; Donnatal†; Famucaps†; Millerspas†; ***Spain***: Abdominol†; Midriatico†; Sulmetin Papaver†; Tabletas Quimpe†; ***Swed.***: Palladon Comp†; ***Switz.***: Spasmosol†; ***Thai.***: Alkamine†; Alumag; Alupep; ANH Mat; Droximag-P; Sinlumag; Stomac†; ***UK***: Actonorm; Brovon; Nerve Agent Antidote L4A1; Valonorm; ***USA***: Alkabel; Antispasmodic Elixir; Atrosept; Bellahist-D; Bellatal; Donnatal; DuoDote; Emergent-Ez; Hyosophen; MHP-A; PB-Hyos; Quadrapax; Se-Donna PB HYOS; Servira; Stahist; Susano; UAA; Uriseptic; Uritact; ***Venez.***: Butropina; Carbargal con Atropina; Eumidral.

Used as an adjunct in:. ***Austral.***: Lofenoxal; Lomotil; ***Braz.***: Colestase; Lomotil; ***Canad.***: Lomotil; ***Cz.***: Reasec; ***Gr.***: Reasec; ***Hong Kong***: Dhamotil; Diamotil†; Diarest†; Diatrol†; Dimotil; Lomotil; Syncomil†; ***Hung.***: Reasec; ***India***: Lomofen; Lomotil; ***Irl.***: Lomotil; ***Malaysia***: Beamotil; Dhamotil; Diphenoxylate A; ***NZ***: Diastop; ***Pol.***: Reasec; ***S.Afr.***: Lomotil; ***Singapore***: Beamotil; Dhamotil; Sun-Dianox; ***Thai.***: Ditropine; Lomotil; Spasil; ***Turk.***: Lomotil; ***UAE***: Intard; ***UK***: Dymotil; Lomotil; ***USA***: Enlon-Plus; Logen; Lomotil; Lonox; Motofen; Neostigmine Min-I-Mix.

Homoeopathic Preparations. ***Austria***: Meditonsin; Tonsiotren; ***Canad.***: Ervopax†; ***Cz.***: Spascupreel S†; ***Fr.***: Apomorphinum Complexe No 97†; Argentum Complexe no 98; Bilinum Complexe No 113; Billerol; Nervopax; Oenanthe Crocata Complexe No 78; ***Ger.***: Cefaspasmon N†; Cefatropin N†; Hevertotox; Meditonsin; Migrane Hevert; Rufebran allergo†; Rufebran gastro†; Sensiotin; Spascupreel; Tonsiotren H; ***Hung.***: Spascupreel; ***Rus.***: Tonsilotren (Тонзилотрен); ***Ukr.***: Tonsilotren (Тонзилотрен).

Pharmacopoeial Preparations

BP 2014: Atropine Eye Drops; Atropine Eye Ointment; Atropine Injection; Atropine Tablets; Morphine and Atropine Injection;
USP 36: Atropine Sulfate Injection; Atropine Sulfate Ophthalmic Ointment; Atropine Sulfate Ophthalmic Solution; Atropine Sulfate Tablets; Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Azamethonium Bromide *(BAN, rINN)*

Azamethonii Bromidum; Azaméthonium, Bromure d'; Bromuro de azametonio; Pentamethazene Bromide; Pentaminum; Азаметония Бромид.

2,2′-Methyliminobis(diethyldimethylammonium) dibromide.

$C_{13}H_{33}Br_2N_3$=391.2

CAS — 60-30-0 (azamethonium); 306-53-6 (azamethonium bromide).

UNII — 4K6NE1OMSR.

Profile

Azamethonium bromide is a ganglion blocker that has been used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Pentamin (Пентамин).

Azapetine Phosphate *(BANM)*

Atsapetiinifosfaatti; Azapethine Phosphate; Azapetina, fosfato de; Azapetinfosfat; Azepine Phosphate; Ro-2-3248; Азапетина Фосфат.

6-Allyl-6,7-dihydro-5*H*-dibenz[*c,e*]azepine dihydrogen phosphate.

$C_{17}H_{17}N,H_3PO_4$=333.3

CAS — 146-36-1 (azapetine); 130-83-6 (azapetine phosphate).

ATC — C04AX30.

ATC Vet — QC04AX30.

UNII — 0N2U15U85W.

Profile

Azapetine is a vasodilator that has been used, as the phosphate, in peripheral vascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Peridil.

Azelnidipine *(rINN)*

Azelnidipino; Azelnidipinum; CS-905; Азелнидипин.

3-[1-(Diphenylmethyl)-3-azetidinyl] 5-isopropyl (±)-2-amino-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

$C_{33}H_{34}N_4O_6$=582.7

CAS — 123524-52-7.

UNII — PV23P19YUG.

Profile

Azelnidipine is a long-acting dihydropyridine calcium-channel blocker used in the management of hypertension.

References.

1. Wellington K, Scott LJ. Azelnidipine. *Drugs* 2003; **63:** 2613–21.
2. Yamamoto T, *et al.* Azelnidipine-induced chyloperitoneum in a patient with microscopic polyangiitis. *Clin Exp Nephrol* 2010; **14:** 496–500.
3. Zhao X, *et al.* Azelnidipine and amlodipine: a comparison of their effects and safety in a randomized double-blinded clinical trial in Chinese essential hypertensive patients. *Clin Exp Hypertens* 2010; **32:** 372–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Beiqi (贝琪); ***Jpn***: Calblock.

Azilsartan *(USAN, rINN)*

Azilsartán; Azilsartanum; TAK-536; Азилсартан.

2-Ethoxy-1-[[2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylic acid.

$C_{25}H_{20}N_4O_5$=456.5

CAS — 147403-03-0.

UNII — F9NUX55P23.

Azilsartan Kamedoxomil *(USAN, rINNM)*

Azilsartan Medoxomil Potassium; TAK-491.

Potassium 3-[4′-[(2-ethoxy-7-[[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy]carbonyl}-1*H*-benzimidazol-1-yl)methyl]biphenyl-4-yl}-5-oxo-1,2,4-oxadiazol-4(5*H*)-ide.

$C_{30}H_{23}KN_4O_8$=606.6

CAS — 863031-24-7.

UNII — WEC6I2K1FC.

Azilsartan Medoxomil *(USAN, rINN)*

Azilsartan Médoxomil; Azilsartán Medoxomilo; Azilsartanum Medoxomilum; TAK-491; Азильсартан Медоксомил.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-yl]methyl}-1*H*-benzimidazol-7-carboxylate.

$C_{30}H_{24}N_4O_8$=568.5

CAS — 863031-21-4.

UNII — LL0G25K7I2.

Uses and Administration

Azilsartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1).

Azilsartan is given as the potassium salt of the medoxomil ester but doses are expressed in terms of the ester; azilsartan kamedoxomil 10.7 mg is equivalent to about 10 mg of azilsartan medoxomil. A starting dose corresponding to azilsartan medoxomil 40 mg is given orally once daily, particularly in patients also taking high doses of diuretics. A starting dose of 20 mg once daily may be considered necessary in patients over 75 years of age, who can be at risk of hypotension, and in patients with volume or salt depletion. The dose may be increased to 80 mg once daily. Reduced doses may also be considered in patients with hepatic impairment (see below).

References.

1. Zaiken K, Cheng JW. Azilsartan medoxomil: a new angiotensin receptor blocker. *Clin Ther* 2011; **33:** 1577–89.
2. Baker WL, White WB. Azilsartan medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. *Ann Pharmacother* 2011; **45:** 1506–15.
3. Takagi H, *et al.* A meta-analysis of randomized controlled trials of azilsartan therapy for blood pressure reduction. *Hypertens Res* 2013. Available at: doi:10.1038/hr.2013.142

Administration in hepatic impairment. There is limited experience of the use of azilsartan in patients with hepatic impairment, but exposure to the drug may be slightly increased. A starting dose equivalent to azilsartan medoxomil 20 mg orally once daily may be considered in patients with mild to moderate hepatic impairment, and use of the drug possibly avoided in those with severe impairment.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1 and p. 1424.3.

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Azilsartan medoxomil is hydrolysed in the gastrointestinal tract to its active metabolite azilsartan, which is then absorbed with a bioavailability of about 60%. Peak plasma concentrations occur within 1.5 to 3 hours. Azilsartan is highly bound to plasma proteins (> 99%). It is metabolised in the liver by *O*-dealkylation and decarboxylation, mainly via the cytochrome P450 isoenzyme CYP2C9, to its inactive metabolites. The elimination half-life of azilsartan is about 11 hours. About 55% of a dose is excreted in the faeces and about 42% in the urine, 15% as azilsartan. It is not removed by haemodialysis.

Studies in *rats* indicate that azilsartan crosses the placenta and is distributed to the fetus. It is also distributed into the milk of lactating *rats*.

References.

1. Angeli F, *et al.* Pharmacokinetic evaluation and clinical utility of azilsartan medoxomil for the treatment of hypertension. *Expert Opin Drug Metab Toxicol* 2013; **9:** 379–85.
2. Preston RA, *et al.* Single-center evaluation of the single-dose pharmacokinetics of the angiotensin II receptor antagonist azilsartan medoxomil in renal impairment. *Clin Pharmacokinet* 2013; **52:** 347–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Edarbi; ***Jpn***: Azilva; ***Neth.***: Edarbi; Ipreziv; ***Switz.***: Edarbi; ***UK***: Edarbi; ***USA***: Edarbi.

Multi-ingredient Preparations. ***USA***: Edarbyclor.

Azimilide Hydrochloride *(BANM, rINNM)*

Azimilida, hidrocloruro de; Azimilide, Chlorhydrate d'; Azimilide Dihydrochloride (USAN); Azimilidi Hydrochloridum; Hidrocloruro de azimilida; NE-10064; Азимилида Гидрохлорид.

1-{[5-(*p*-Chlorophenyl)furfurylidene]amino}-3-[4-(4-methyl-1-piperazinyl)butyl]hydantoin dihydrochloride.

$C_{23}H_{28}ClN_5O_3$,2HCl=530.9

CAS — 149908-53-2 (azimilide); 149888-94-8 (azimilide hydrochloride).

UNII — 6E6VJP68KR.

Profile

Azimilide hydrochloride is a class III antiarrhythmic (p. 1243.1) being studied in the management of supraventricular arrhythmias. It has also been tried in ventricular arrhythmias.

References.

1. Clemett D, Markham A. Azimilide. *Drugs* 2000; **59:** 271–7.
2. Pritchett ELC, *et al.* Effects of azimilide on heart rate and ECG conduction intervals during sinus rhythm in patients with a history of atrial fibrillation. *J Clin Pharmacol* 2002; **42:** 388–94.
3. Connolly SJ, *et al.* Symptoms at the time of arrhythmia recurrence in patients receiving azimilide for control of atrial fibrillation or flutter: results from randomized trials. *Am Heart J* 2003; **146:** 489–93.
4. Singer I, *et al.* Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2004; **43:** 39–43.
5. Camm AJ, *et al.* Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004; **109:** 990–6.
6. Dorian P, *et al.* Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004; **110:** 3646–54.
7. Pritchett ELC, *et al.* Antiarrhythmic efficacy of azimilide in patients with atrial fibrillation: maintenance of sinus rhythm after conversion to sinus rhythm. *Am Heart J* 2006; **151:** 1043–9.
8. Kerr CR, *et al.* Efficacy of azimilide for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation in the presence and absence of structural heart disease. *Am J Cardiol* 2006; **98:** 215–18.
9. Pratt CM, *et al.* Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. *J Am Coll Cardiol* 2006; **48:** 471–7.
10. Lombardi F, *et al.* Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial. *Eur Heart J* 2006; **27:** 2224–31.

11. Page RL, *et al.* Azimilide for the treatment of atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia: results of a randomized trial and insights on the concordance of symptoms and recurrent arrhythmias. *J Cardiovasc Electrophysiol* 2008; **19:** 172–7.

Azosemide *(USAN, rINN)* ⊗

Azosemida; Azosémide; Azosemidum; BM-02001; Ple-1053; Азосемид.
2-Chloro-5-(1*H*-tetrazol-5-yl)-4-(2-thenylamino)benzenesulphonamide.
$C_{12}H_{11}ClN_6O_2S_2$=370.8
CAS — 27589-33-9.
UNII — MR4OVT1L8Z.

NOTE. The names Azoselic, Daitalic, and Diart have been used as trade names for azosemide.

Profile

Azosemide is a diuretic with actions similar to those of furosemide (p. 1387.1) that has been used in the management of oedema.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ya Li (雅利).

Bamethan Sulfate *(BANM, USAN, rINNM)*

Bametán, sulfato de; Bametanu siarczan; Baméthan, Sulfate de; Bamethan Sulphate; Bamethani Sulfas; Sulfato de bametán; Баметана Сульфат.
2-Butylamino-1-(4-hydroxyphenyl)ethanol sulfate.
$(C_{12}H_{19}NO_2)_2,H_2SO_4$=516.6
CAS — 3703-79-5 (bamethan); 5716-20-1 (bamethan sulfate).
ATC — C04AA31.
ATC Vet — QC04AA31.
UNII — W2L3E1W827.

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Bamethan sulfate is a vasodilator used in the management of peripheral vascular disorders.

Bamethan nicotinate and bamethan succinate have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dilartan; ***Braz.***: Vasculat.

Multi-ingredient Preparations. ***Arg.***: Flaval; Grafic Forte; ***Fr.***: Escinogel†.

Barnidipine Hydrochloride *(rINNM)*

Barnidipine, Chlorhydrate de; Barnidipini Hydrochloridum; Barnidipino, hidrocloruro de; Hidrocloruro de barnidipino; LY-198561; Mepirodipine Hydrochloride; YM-730; YM-09730-5; Барнидипина Гидрохлорид.
(+)-(3′*S*,4*S*)-1-Benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.
$C_{27}H_{29}N_3O_6$,HCl=528.0
CAS — 104713-75-9 (barnidipine); 104757-53-1 (barnidipine hydrochloride).
ATC — C08CA12.
ATC Vet — QC08CA12.
UNII — 7LZ6R3AEM1.

Profile

Barnidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is given orally as the hydrochloride in the management of hypertension (p. 1251.1). The initial dose is 5 to 10 mg once daily, increased, according to response, to a usual maintenance dose of 10 to 20 mg once daily.

Reviews.

1. Malhotra HS, Plosker GL. Barnidipine. *Drugs* 2001; **61:** 989–96.
2. Liau CS. Barnidipine: a new calcium channel blocker for hypertension treatment. *Expert Rev Cardiovasc Ther* 2005; **3:** 207–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Vasexten; ***China***: Hypoca (合普卡); ***Cz.***: Vasexten; ***Gr.***: Vasexten; ***Ital.***: Libradin; Osipine; Vasexten; ***Jpn***: Hypoca; ***Neth.***: Cyress; Libradin; Vasexten; ***Philipp.***: Hypoca†; ***Port.***: Cyress; Libradin†; Vasexten†; ***Spain***: Barnix; Libradin†; ***Thai.***: Hypoca†; ***Turk.***: Libradin.

Bemetizide *(BAN, rINN)* ⊗

Bemetizida; Bémétizide; Bemetizidum; Diu-60; Беметизид.
6-Chloro-3,4-dihydro-3-(α-methylbenzyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.
$C_{15}H_{16}ClN_3O_4S_2$=401.9
CAS — 1824-52-8.
UNII — EZN4D2O31B.

Profile

Bemetizide is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) that is used, often with triamterene, in the treatment of oedema and hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: dehydro sanol tri; Diucomb.

Bemiparin Sodium *(BAN, rINN)*

Bemiparina sódica; Bémiparine Sodique; Bemiparinum Natricum; Бемипарин Натрий.
CAS — 9041-08-1.
ATC — B01AB12.
ATC Vet — QB01AB12.

Description. Bemiparin sodium is prepared by alkaline degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The average relative molecular mass is about 3600 (3000 to 4200). The degree of sulfation is about 2 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Bemiparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity. It is used for the prevention and treatment of venous thromboembolism (p. 1274.1), and to prevent clotting during extracorporeal circulation.

In the *prophylaxis* of **venous thromboembolism** during general surgery with moderate risk, bemiparin sodium is given subcutaneously in a dose of 2500 units once daily, with the first dose given 2 hours before or 6 hours after surgery; in patients undergoing orthopaedic surgery with high risk of thromboembolism the dose should be 3500 units initially and then once daily. Prophylaxis should be continued for at least 7 to 10 days and until the patient is fully ambulant. For *treatment* of thromboembolism, a dose of 115 units/kg is given subcutaneously once daily.

In some countries bemiparin sodium is used for prophylaxis in non-surgical patients at moderate or high risk of venous thromboembolism, a dose of 2500 or 3500 units being given daily according to risk. Bemiparin sodium is also used in some countries for secondary prevention of venous thromboembolism in patients with transitory risk factors, a dose of 3500 units being given daily for up to 3 months as an alternative to oral anticoagulant therapy.

For the prevention of clotting in the extracorporeal circulation during **haemodialysis**, bemiparin sodium is given into the arterial side of the dialyser in a single dose of 2500 units for patients weighing less than 60 kg and 3500 units for patients weighing more than 60 kg.

An oral formulation of bemiparin is under investigation.

References.

1. Chapman TM, Goa KL. Bemiparin: a review of its use in the prevention of venous thromboembolism and treatment of deep vein thrombosis. *Drugs* 2003; **63:** 2357–77.
2. Martínez-González J, *et al.* Bemiparin: second-generation, low-molecular-weight heparin for treatment and prophylaxis of venous thromboembolism. *Expert Rev Cardiovasc Ther* 2008; **6:** 793–802.
3. Rullan M, *et al.* Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial. *Diabet Med* 2008; **25:** 1090–5.
4. Martínez-González J, Rodríguez C. New challenges for a second-generation low-molecular-weight heparin: focus on bemiparin. *Expert Rev Cardiovasc Ther* 2010; **8:** 625–34.
5. Sánchez-Ferrer CF. Bemiparin: pharmacological profile. *Drugs* 2010; **70** (suppl 2): 19–23.
6. Abad Rico JI, *et al.* Clinical experience with bemiparin. *Drugs* 2010; **70** (suppl 2): 25–33.
7. Monreal Bosch M, *et al.* Bemiparin in oncology. *Drugs* 2010; **70** (suppl 2): 35–42.
8. Boj JF. New frontiers with bemiparin: use in special populations. *Drugs* 2010; **70** (suppl 2): 43–7.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with bemiparin sodium may be reduced by intravenous protamine sulfate; 1.4 mg of protamine sulfate is stated to inhibit the effects of about 100 units of bemiparin sodium.

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Bemiparin sodium is rapidly absorbed after subcutaneous injection with a bioavailability of about 96%. Peak plasma activity occurs in about 2 to 4 hours, depending on the dose. The elimination half-life is about 5 to 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Badyket; ***Austria***: Ivor; Ivorat; ***Cz.***: Zibor; ***Gr.***: Ivor; Ivormax; ***Hung.***: Zibor; ***India***: Hibor; ***Irl.***: Zibor; ***Ital.***: Ivor; ***Port.***: Ivor; ***Rus.***: Cibor (Цибор); ***Spain***: Hepadren; Hibor; ***Turk.***: Hibor; ***UK***: Zibor†; ***Ukr.***: Zibor (Цибор).

Benazepril Hydrochloride

(BANM, USAN, rINNM)

Benatsepriilihydrokloridi; Bénazépril, chlorhydrate de; Benazepril, hidrocloruro de; Benazepril Hidroklorür; Benazeprilhydrochlorid; Benazeprilhydroklorid; Benazeprili Hydrochloridum; CGS-14824A (benazepril or benazepril hydrochloride); Hidrocloruro de benazepril; Беназеприла Гидрохлорид.
{(3*S*)-3-[(1*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}acetic acid hydrochloride; 1-Carboxymethyl-3-[1-ethoxycarbonyl-3-phenyl-(1*S*)-propylamino]-2,3,4,5-tetrahydro-1*H*-1(3*S*)-benzazepin-2-one hydrochloride.
$C_{24}H_{28}N_2O_5$,HCl=461.0
CAS — 86541-75-5 (benazepril); 86541-74-4 (benazepril hydrochloride).
ATC — C09AA07.
ATC Vet — QC09AA07.
UNII — N1SN99T69T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Benazepril Hydrochloride). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in dehydrated alcohol; practically insoluble in cyclohexane; very slightly soluble in ethyl acetate. Store in airtight containers. Protect from light.

USP 36: (Benazepril Hydrochloride). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol. Store at a temperature below 30 degrees, preferably between 15 degrees and 30 degrees.

Uses and Administration

Benazepril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Benazepril owes its activity to benazeprilat to which it is converted after oral dosage. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Benazepril is given orally as the hydrochloride.

In the treatment of **hypertension**, the usual initial dose of benazepril hydrochloride is 10 mg once daily. An initial dose of 5 mg once daily is suggested for patients with renal impairment (see p. 1315.1) or who are receiving a *diuretic*; if possible the diuretic should be withdrawn 2 or 3 days before benazepril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, which may be given in 2 divided doses if control is inadequate with a single dose; doses of up to 80 mg daily have been used.

In the treatment of **heart failure** the usual initial dose of benazepril hydrochloride is 2.5 mg once daily, adjusted according to response to a maximum dose of 20 mg daily.

Administration in children. Experience with benazepril in children is limited. US licensed product information recommends an initial oral dose of 200 micrograms/kg once daily for hypertension in children 6 years of age and over. Maintenance doses up to 600 micrograms/kg daily (maximum 40 mg daily) have been studied. Insufficient evidence is available to recommend doses for younger children or for any children with creatinine clearance below 30 mL/minute.

Administration in renal impairment. In patients with a creatinine clearance of less than 30 mL/minute, the initial dose of benazepril hydrochloride for hypertension is 5 mg once daily and the maintenance dose should not exceed 40 mg daily.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Benazepril acts as a prodrug of the diacid benazeprilat, its active metabolite. At least 37% of an oral dose of benazepril is absorbed. Benazepril is almost completely metabolised in the liver to benazeprilat. Peak plasma concentrations of benazeprilat after an oral dose of benazepril have occurred in 1 to 2 hours in the fasting state or 2 to 4 hours in the nonfasting state. Both benazepril and benazeprilat are about 95% bound to plasma proteins. Benazeprilat is excreted mainly in the urine; about 11 to 12% is excreted in the bile. The effective half-life for accumulation of benazeprilat is 10 to 11 hours after multiple doses of benazepril. The elimination of benazeprilat is slowed in renal impairment, although biliary excretion may compensate to some extent. Small amounts of benazepril and benazeprilat are distributed into breast milk.

References.

1. Kaiser G, *et al.* Pharmacokinetics of the angiotensin converting enzyme inhibitor benazepril HCl (CGS 14 824A) in healthy volunteers after single and repeated administration. *Biopharm Drug Dispos* 1989; **10:** 365–76.
2. Kaiser G, *et al.* Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations. *Am Heart J* 1989; **117:** 746–51.
3. Kaiser G, *et al.* Pharmacokinetics and pharmacodynamics of the ace inhibitor benazepril hydrochloride in the elderly. *Eur J Clin Pharmacol* 1990; **38:** 379–85.
4. Macdonald N-J, *et al.* A comparison in young and elderly subjects of the pharmacokinetics and pharmacodynamics of single and multiple doses of benazepril. *Br J Clin Pharmacol* 1993; **36:** 201–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Boncordin; ***Belg.***: Cibacen; ***Braz.***: Lotensin; ***Canad.***: Lotensin; ***China***: Di Ya Ping (敌亚平); Lotensin (洛汀新); Pu Li Duo (普力多); Zaprace (倍尼); ***Denm.***: Cibacen; Jenaril; Lazeril; ***Fr.***: Briem; Cibacene; ***Ger.***: Cibacen; ***Gr.***: Cibacen; ***Hung.***: Lotensin; ***India***: Benace; ***Indon.***: Cibacen†; ***Irl.***: Cibacen; ***Ital.***: Cibacen; Tenkuoren; Tensanil†; Zinadril; ***Mex.***: Lotensin; ***Neth.***: Cibacen; ***Philipp.***: Cibacen; ***Pol.***: Lisonid; Lotensin; ***Rus.***: Lotensin (Лотензин); ***S.Afr.***: Ciback; ***Spain***: Cibacen; Labopal†; ***Switz.***: Cibacen; ***Turk.***: Cibacen; ***USA***: Lotensin.

Multi-ingredient Preparations. ***Arg.***: Amlopril; Arteriosan Plus; Coroval B; Ilduc Duo; Pelmec Duo; Terloc Duo; ***Braz.***: Lotensin H; Press Plus; ***China***: Cibadrex (依思汀); Zaprace-D (双赛普利); ***Fr.***: Briazide; Cibadrex; ***Ger.***: Benazeplus†; Benazepril comp; Cibadrex; ***Gr.***: Cibadrex; ***Hung.***: Lotensin HCT; ***India***: Amace-BP; Amlo-B; ***Ital.***: Cibadrex; Tensadiur; Zinadiur; ***Mex.***: Amlipril†; ***Neth.***: Cibadrex; ***Pol.***: Lisonid HCT; Lotensin HCT; ***S.Afr.***: Cibadrex; ***Spain***: Cibadrex; Labodrex†; ***Switz.***: Cibadrex; ***Turk.***: Cibadrex; ***USA***: Lotensin HCT; Lotrel; ***Venez.***: Amlibon B.

Pharmacopoeial Preparations

USP 36: Amlodipine and Benazepril Hydrochloride Capsules; Benazepril Hydrochloride Tablets.

Bencyclane Fumarate *(rINNM)*

Benciclano, fumarato de; Bencyclane, Fumarate de; Bencyclane Hydrogen Fumarate; Bencyclani Fumaras; Bensiklan Hidrojen Fumarat; Fumarato de benciclano; Бенциклана Фумарат.

3-(1-Benzylcycloheptyloxy)-*NN*-dimethylpropylamine hydrogen fumarate.

$C_{19}H_{31}NO,C_4H_4O_4$=405.5

CAS — 2179-37-5 (bencyclane); 14286-84-1 (bencyclane fumarate).

ATC — C04AX11.

ATC Vet — QC04AX11.

UNII — OZN2MG334O.

Profile

Bencyclane fumarate is a vasodilator used in the management of peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2) in usual oral doses of 100 to 200 mg three times daily. It has also been given intravenously.

Bencyclane acefyllinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Fludilat; ***Gr.***: Diacyclan; Fludilat; ***Hung.***: Halidor; ***Indon.***: Fludilat; ***Pol.***: Halidor; ***Rus.***: Halidor (Галидор); ***Thai.***: Fludilat†; ***Turk.***: Angiodel; ***Ukr.***: Halidor (Галидор); ***Venez.***: Fludilat.

Bendroflumethiazide *(BAN, rINN)* ⊗

Bencidroflumetiazida; Bencilhidroflumetiazida; Bendrofluaz; Bendrofluazida; Bendrofluazide; Bendroflumethiazid; Bendroflumétháizide; Bendroflumethiazidum; Bendroflumetiatsidi; Bendroflumetiazid; Bendroflumetiazida; Bendroflumetiazidas; Benzydroflumethiazide; FT-81; Бендрофлуметиазид.

3-Benzyl-3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{15}H_{14}F_3N_3O_4S_2$=421.4

CAS — 73-48-3.

ATC — C03AA01.

ATC Vet — QC03AA01.

UNII — 5Q52X6ICJI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Bendroflumethiazide). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone.

USP 36: (Bendroflumethiazide). A white to cream-coloured, finely divided, crystalline powder. Is odourless or has a slight odour. Practically insoluble in water; soluble 1 in 23 of alcohol and 1 in 200 of ether; freely soluble in acetone. Store in airtight containers.

Uses and Administration

Bendroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It is used for hypertension (p. 1251.1), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. It is also used for oedema, including that associated with heart failure (p. 1262.3), and with renal or hepatic disorders. Other indications have included the suppression of lactation.

Bendroflumethiazide is given orally; diuresis starts in about 2 hours after a dose, peaks after about 3 to 6 hours, and lasts for 12 to 18 hours or longer.

In the treatment of **hypertension** bendroflumethiazide 2.5 mg daily, either alone or with other antihypertensives, is usually adequate although initial doses of up to 20 mg daily have sometimes been suggested.

In the treatment of **oedema** the usual initial dose is 5 to 10 mg daily or on alternate days; in some cases initial doses of up to 20 mg may be necessary. Maintenance dosage schedules have varied from 5 to 30 mg weekly in divided doses in the UK, to 2.5 to 5 mg daily or intermittently in the USA.

For doses in children, see below.

Doses of 5 mg twice daily for about 5 days have been used to **suppress lactation**.

In the management of **idiopathic hypercalciuria** (see Renal Calculi, p. 2350.3) the *BNF* considers that, with increased fluid intake, a sufficient dose is 2.5 mg daily.

Administration in children. In the UK, bendroflumethiazide may be given to children in the treatment of oedema or hypertension in the following initial oral doses according to age, and adjusted according to response:

- 1 month to 2 years: 50 to 100 micrograms/kg daily
- 2 to 12 years: 50 to 400 micrograms/kg daily (maximum of 10 mg), followed by 50 to 100 micrograms/kg daily, adjusted according to response
- 12 to 18 years: hypertension, 2.5 mg daily; oedema, 5 to 10 mg daily or on alternate days

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Breast feeding. Bendroflumethiazide has been used to suppress lactation (see Uses above). However, the American Academy of Pediatrics considers[1] that it is usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bendroflumethiazide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Overdosage. Tonic-clonic convulsions occurred in a previously healthy 14-year-old girl after ingestion of bendroflumethiazide 150 to 200 mg.[1] The convulsions were not associated with any measurable disturbance of serum electrolytes.

1. Hine KR, *et al.* Bendrofluazide convulsions. *Lancet* 1982; **i:** 564.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and to have a plasma half-life of about 3 or 4 hours. It is highly bound to plasma proteins. There are indications that bendroflumethiazide is fairly extensively metabolised; about 30% is excreted unchanged in the urine.

References.

1. Beermann B, *et al.* Pharmacokinetics of bendroflumethiazide. *Clin Pharmacol Ther* 1977; **22:** 385–8.
2. Beermann B, *et al.* Pharmacokinetics of bendroflumethiazide in hypertensive patients. *Eur J Clin Pharmacol* 1978; **13:** 119–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aprinox†; ***Denm.***: Centyl†; ***Gr.***: Aprinox; Pluryl; ***Irl.***: Centyl; ***Norw.***: Centyl†; ***NZ***: Neo-NaClex; ***Swed.***: Salures; ***UK***: Aprinox; Neo-NaClex†.

Multi-ingredient Preparations. ***Arg.***: Pertenso; Sumal; ***Austria***: Sali-Aldopur; ***Braz.***: Diserim; ***Denm.***: Centyl med Kaliumklorid; ***Fr.***: Precyclan†; Tensionorme; ***Ger.***: Dociretic; Pertenso N; Tensoflux; ***Gr.***: Centyl K; Corzide; ***Irl.***: Centyl K; Low Centyl K; Prestim; ***Mex.***: Corgaretic; ***Norw.***: Centyl med Kaliumklorid; ***S. Afr.***: Corgaretic†; ***Spain***: Neatenol Diu; Neatenol Diuvas†; ***Swed.***: Centyl K; ***UK***: Centyl K†; Neo-NaClex-K; Prestim; ***USA***: Corzide.

Pharmacopoeial Preparations

BP 2014: Bendroflumethiazide Tablets;

USP 36: Bendroflumethiazide Tablets; Nadolol and Bendroflumethiazide Tablets.

Benfluorex Hydrochloride *(BANM, pINNM)* ⊗

Benfluoreksihydroklorīdi; Benfluorekso hidrochloridas; Benfluorex, Chlorhydrate de; Benfluorex, hidrocloruro de; Benfluorex-hidroklorid; Benfluorex-hydrochlorid; Benfluorex-hydroklorid; Benfluorexi Hydrochloridum; Hidrocloruro de benfluorex; JP-992; SE-780; Бенфлуорекса Гидрохлорид.

2-[α-Methyl-3-(trifluoromethyl)phenethylamino]ethyl benzoate hydrochloride.

$C_{19}H_{20}F_3NO_2$,HCl=387.8

CAS — 23602-78-0 (benfluorex); 35976-51-3 (± benfluorex); 23642-66-2 (benfluorex hydrochloride).

ATC — A10BX06.

ATC Vet — QA10BX06.

UNII — X7O165XZ00.

Profile

Benfluorex hydrochloride is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). It has also been used as an adjunct in the management of type 2 diabetes mellitus (p. 459.1). Benfluorex is structurally related to fenfluramine (p. 2322.3) and has been used similarly as an anorectic; like fenfluramine, it has been associated with cardiovascular adverse effects (see below).

Benfluorex hydrochloride has been given orally in usual doses of 150 mg three times daily with meals.

Adverse effects. Fenfluramine and dexfenfluramine were withdrawn from the world market after cardiovascular adverse effects including pulmonary hypertension and valvular heart disease were associated with their use (for a discussion, see p. 2322.3). There have been reports[1-4] of similar adverse effects with benfluorex, a related compound, and in 2009 the EMEA recommended the withdrawal of benfluorex from the European market.[5]

1. Noize P, *et al.* Valvular heart disease in a patient taking benfluorex. *Fundam Clin Pharmacol* 2006; **20:** 577–8.
2. Boutet K, *et al.* Fenfluramine-like cardiovascular side-effects of benfluorex. *Eur Respir J* 2009; **33:** 684–8.
3. Frachon I, *et al.* Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS One* 2010; **5:** e10128. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010128 (accessed 10/06/10)
4. Anonymous. Benfluorex: increasing reports of valve disorders. *Prescrire Int* 2010; **19:** 17.
5. EMEA. European Medicines Agency recommends withdrawal of benfluorex from the market in European Union (issued 18th December 2009). Available at: http://www.ema.europa.eu/pdfs/human/referral/benfluorex/Benfluorex_81503309en.pdf (accessed 10/06/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Mediator†; ***Gr.***: Lipophoral; ***Hong Kong***: Mediaxal; ***Malaysia***: Axal; Mediaxal†; ***Port.***: Mediator†; ***Singapore***: Mediaxal†; ***Venez.***: Lipascor.

Benidipine Hydrochloride *(rINNM)*

Bénidipine, Chlorhydrate de; Benidipini Hydrochloridum; Benidipino, hidrocloruro de; Hidrocloruro de benidipino; KW-3049; Nakadipine Hydrochloride; Бенидипина Гидрохлорид.

(±)-(*R**)-3-[(*R**)-1-Benzyl-3-piperidyl]methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

$C_{28}H_{31}N_3O_6$,HCl=542.0

CAS — 105979-17-7 (benidipine); 91599-74-5 (benidipine hydrochloride).

ATC — C08CA15.

ATC Vet — QC08CA15.

UNII — 0A6746FWDL.

Pharmacopoeias. In *Jpn*.

Profile

Benidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is given orally as the hydrochloride in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). In hypertension, the usual dose is 2 to 4 mg once daily, increased to 8 mg once daily if necessary. In angina pectoris, the usual dose is 4 mg twice daily.

References.

1. Yao K, *et al*. Pharmacological, pharmacokinetic, and clinical properties of benidipine hydrochloride, a novel, long-acting calcium channel blocker. *J Pharmacol Sci* 2006; **100:** 243–61.
2. Suzuki H, *et al*. Clinical efficacy of benidipine for vasospastic angina pectoris. *Arzneimittelforschung* 2007; **57:** 20–5.
3. Wang HY, *et al*. Efficacy and safety of benidipine therapy of essential hypertension in elderly Chinese patients. *Arzneimittelforschung* 2008; **58:** 505–9.
4. Ohta M, *et al*. Effects of benidipine, a long-acting T-type calcium channel blocker, on home blood pressure and renal function in patients with essential hypertension: a retrospective, 'real-world' comparison with amlodipine. *Clin Drug Invest* 2009; **29:** 739–46.
5. Peng T, *et al*. A comparative study of the renoprotective effects of benidipine and valsartan in primary hypertensive patients with proteinuria. *Arzneimittelforschung* 2009; **59:** 647–50.
6. Miyagawa K, *et al*. Renoprotective effect of calcium channel blockers in combination with an angiotensin receptor blocker in elderly patients with hypertension. A randomized crossover trial between benidipine and amlodipine. *Clin Exp Hypertens* 2010; **32:** 1–7.
7. Oikawa Y, *et al*. Effects of treatment with once-daily nifedipine CR and twice-daily benidipine on prevention of symptomatic attacks in patients with coronary spastic angina pectoris—Adalat Trial vs Coniel in Tokyo against Coronary Spastic Angina (ATTACK CSA). *J Cardiol* 2010; **55:** 238–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Coniel (可力洛); Yuan Zhi (元治); ***India***: Caritec; ***Jpn***: Coniel; ***Philipp.***: Coniel; ***Turk.***: Coniel.

Benzthiazide *(BAN, rINN)* ⊗

Benzthiazidum; Benztiazida; P-1393; Бензтиазид.

3-Benzylthiomethyl-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{15}H_{14}ClN_3O_4S_3$=431.9

CAS — 91-33-8.

UNII — 1TD8J48L61.

Profile

Benzthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and has also been used for hypertension (p. 1251.1). It has been given alone but is often given with triamterene. The usual initial oral dose for oedema is 75 mg daily, although higher doses have been given. The dose is reduced for maintenance; intermittent dosing may be adequate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Ditide; ***Switz.***: Dyrenium compositum†; ***UK***: Dytide†.

Benzylhydrochlorothiazide ⊗

Su-6227.

3-Benzyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{14}H_{14}ClN_3O_4S_2$=387.9

CAS — 1824-50-6.

UNII — 176437APQH.

Profile

Benzylhydrochlorothiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1). The usual initial oral dose is 4 to 8 mg twice daily reduced to two or three times weekly for maintenance therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Behyd.

Multi-ingredient Preparations. ***Jpn***: Behyd-RA.

Bepridil Hydrochloride *(BANM, USAN, rINNM)*

Bepridiilihydrokloridi; Bépridil, Chlorhydrate de; Bepridil, hidrocloruro de; Bepridilhydroklorid; Bepridili Hydrochloridum; CERM-1978; Hidrocloruro de bepridil; Org-5730; Бепридила Гидрохлорид.

N-Benzyl-*N*-(3-isobutoxy-2-pyrrolidin-1-ylpropyl)aniline hydrochloride monohydrate.

$C_{24}H_{34}N_2O$,HCl,H_2O=421.0

CAS — 64706-54-3 (bepridil); 49571-04-2 (bepridil); 64616-81-5 (anhydrous bepridil hydrochloride); 74764-40-2 (bepridil hydrochloride monohydrate).

ATC — C08EA02.

ATC Vet — QC08EA02.

UNII — 4W2P15D93M.

Profile

Bepridil is a calcium-channel blocker (p. 1244.2). It has similar properties to nifedipine (p. 1447.2) but reduces the heart rate and does not usually cause reflex tachycardia. It also has antiarrhythmic activity. It is not related chemically to other calcium-channel blockers such as diltiazem, nifedipine, or verapamil.

Bepridil is used as the hydrochloride in the management of angina pectoris (p. 1254.3) and cardiac arrhythmias (p. 1266.1). Ventricular arrhythmias, including torsade de pointes, and agranulocytosis have been associated with bepridil and, as a result, it has usually been reserved for patients who have not responded adequately to other anti-anginal drugs. Frequent ECG monitoring has been advised, and reducing or stopping doses should be considered if QT-interval prolongation occurs.

Bepridil hydrochloride has been given in oral doses of 100 to 300 mg daily.

References.

1. Hollingshead LM, *et al*. Bepridil: a review of its pharmacological properties and therapeutic use in stable angina pectoris. *Drugs* 1992; **44:** 835–57.
2. Awni WM, *et al*. Pharmacokinetics of bepridil and two of its metabolites in patients with end-stage renal disease. *J Clin Pharmacol* 1995; **35:** 379–83.
3. Yasuda M, *et al*. Clinical evaluation of adverse effects during bepridil administration for atrial fibrillation and flutter. *Circ J* 2006; **70:** 662–6.
4. Taguchi M, *et al*. Nonlinear mixed effects model analysis of the pharmacokinetics of routinely administered bepridil in Japanese patients with arrhythmias. *Biol Pharm Bull* 2006; **29:** 517–21.
5. Izumi D, *et al*. Bepridil for drug-refractory ventricular tachyarrhythmias. *Intern Med* 2007; **46:** 119–24.
6. Miyaji K, *et al*. Efficacy and safety of the additional bepridil treatment in patients with atrial fibrillation refractory to class I antiarrhythmic drugs. *Circ J* 2007; **71:** 1250–7.
7. Imai S, *et al*. Use of bepridil in combination with Ic antiarrhythmic agent in converting persistent atrial fibrillation to sinus rhythm. *Circ J* 2008; **72:** 709–15.
8. Yamashita T, *et al*. Dose-response effects of bepridil in patients with persistent atrial fibrillation monitored with transtelephonic electrocardiograms: a multicenter, randomized, placebo-controlled,double-blind study (J-BAF Study). *Circ J* 2009; **73:** 1020–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kaike (开克); ***Fr.***: Unicordium†; ***Jpn***: Bepricor.

Beraprost Sodium *(USAN, rINNM)*

Beraprost sódico; Béraprost Sodique; ML-1129; ML-1229 (beraprost); Natrii Beraprostum; TRK-100; Натрий Берапрост.

Sodium (±)-(1*R*,2*R*,3a*S*,8b*S*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1*H*-cyclopenta[*b*]benzofuran-5-butyrate.

$C_{24}H_{29}NaO_5$=420.5

CAS — 88430-50-6 (beraprost); 88475-69-8 (beraprost sodium).

ATC — B01AC19.

ATC Vet — QB01AC19.

UNII — 15K99VDU5F.

Profile

Beraprost is a synthetic analogue of epoprostenol (prostacyclin) that causes vasodilatation and prevents platelet aggregation. It is given orally as the sodium salt in the management of pulmonary hypertension (p. 1278.2). It has also been promoted for peripheral vascular disorders (p. 1272.3) although good evidence of value is lacking.

In pulmonary arterial hypertension, beraprost sodium is given in an initial dose of 60 micrograms daily in three divided doses; this may be increased gradually if necessary to 180 micrograms daily in three or four divided doses. For peripheral vascular disease a dose of 120 micrograms daily in three divided doses has been used.

Adverse effects of beraprost include headache, flushing, nausea, diarrhoea, and increased liver enzyme, bilirubin, and triglyceride concentrations.

Cardiovascular disorders. References to the use of beraprost for pulmonary hypertension or intermittent claudication;[1-8] results of studies for the latter indication have been conflicting. It has been tried with sildenafil in patients with pulmonary hypertension.[9,10]

1. Nagaya N, *et al*. Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999; **34:** 1188–92.
2. Lievre M, *et al*. Oral beraprost sodium, a prostaglandin I_2 analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. *Circulation* 2000; **102:** 426–31.
3. Melian EB, Goa KL. Beraprost: a review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. *Drugs* 2002; **62:** 107–33.
4. Galiè N, *et al*. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002; **39:** 1496–1502.
5. Mohler ER, *et al*. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I_2 analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003; **41:** 1679–86.
6. Barst RJ, *et al*. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; **41:** 2119–25.
7. Hashiguchi M, *et al*. Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E1 for the treatment of intermittent claudication. *Yakugaku Zasshi* 2004; **124:** 321–32.
8. Oyamada J, *et al*. Long-term administration of beraprost sodium for pulmonary arterial hypertension associated with congenital heart disease. *Intern Med* 2009; **48:** 1531–4.
9. Ikeda D, *et al*. Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45:** 286–9.
10. Kim SY, *et al*. Sildenafil and beraprost combination therapy in patients with pulmonary hypertension undergoing valvular heart surgery. *J Heart Valve Dis* 2010; **19:** 333–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Dorner (德纳); ***Indon.***: Dorner; ***Jpn***: Belnarl; Beplarid†; Beradorlin; Berastolin; Berasus; Beruler; Bestorner†; Careload; Dornalin; Dorner; Procylin; Prodoner; Prorner; Prosner; Prostalin; Senaprost; ***Philipp.***: Dorner; ***Thai.***: Dorner.

Beta Blockers ⊗

β-Bloqueantes; Бета-блокаторы.

Beta blockers (beta-adrenoceptor blocking drugs or antagonists) are competitive antagonists of catecholamines at beta-adrenergic receptors in a wide range of tissues. Although they have broadly similar properties they differ in their affinity for $beta_1$ or $beta_2$ receptor subtypes, intrinsic sympathomimetic activity, membrane-stabilising activity, blockade of alpha-adrenergic receptors, and pharmacokinetic properties including differences in lipid solubility (see Table 4, p. 1317, for some of these characteristics). These differences may affect the choice of drug in specific situations.

Uses and Administration

Beta blockers are competitive antagonists of the effects of catecholamines at beta-adrenergic receptor sites. The different types of adrenergic receptor are described under the Actions and Uses of Sympathomimetics (see p. 1507.3). Blockade of beta receptors has the following effects:

- $beta_1$ blockade mainly affects the heart, reducing heart rate, myocardial contractility, and rate of conduction of impulses through the conducting system (class II antiarrhythmic effect, see p. 1243.1). It also leads to suppression of adrenergic-induced renin release and lipolysis

Table 4. Characteristics of beta blockers.

Beta blocker	$Beta_1$ selectivity	ISA*	MSA**	Vasodilator activity
Acebutolol	+	+	+	0
Alprenolol	0	+	0	0
Atenolol	+	0	0	0
Betaxolol	+	0	0	0
Bisoprolol	+	0	0	0
Carteolol	0	+	0	0
Carvedilol	0	0	0	+
Celiprolol	+	+	–	+
Esmolol	+	0	0	0
Labetalol	0	0	0	+
Levobunolol	0	0	0	0
Metipranolol	0	0	0	0
Metoprolol	+	0	0	0
Nadolol	0	0	0	0
Nebivolol	+	0	0	+
Oxprenolol	0	+	+	0
Penbutolol	0	0	0	0
Pindolol	0	++	0	0
Propranolol	0	0	++	0
Sotalol	0	0	0	0
Timolol	0	0	0	0

0 = absent or low; + = moderate; ++ = high; – = no information

* ISA = Intrinsic sympathomimetic activity

** MSA = Membrane-stabilising activity

- $beta_2$ blockade leads to increased bronchial resistance and inhibition of catecholamine-induced glucose metabolism; there may also be an effect on heart rate. $Beta_2$ blockade also appears to be the main mechanism for the reduction in intra-ocular pressure associated with beta blockers
- the role of $beta_3$ blockade is not clear

Beta blockers differ in their affinity for the subtypes of beta receptor, as well as in their actions at other receptors and ancillary properties (see Table 4, above). The cardiovascular effects of beta blockers relate to their action at $beta_1$ receptors, and all clinically used beta blockers are $beta_1$ antagonists. Propranolol and other nonselective beta blockers also have antagonist effects at $beta_2$ receptors, and this may be responsible for many of their adverse effects. Beta blockers with a higher affinity for $beta_1$ than $beta_2$ receptors, such as atenolol and metoprolol, cause fewer noncardiovascular effects and are described as cardioselective or second generation. However, selectivity is relative and, as doses are increased, activity at $beta_2$ receptors becomes clinically important. Beta blockers with additional properties such as vasodilatation have been described as third generation, and include carvedilol, celiprolol, and nebivolol.

Beta blockers such as acebutolol, celiprolol, oxprenolol, and pindolol also possess intrinsic (partial) sympathomimetic activity in that they activate beta receptors in the absence of catecholamines and are therefore partial agonists. Beta blockers with intrinsic sympathomimetic activity produce less resting bradycardia than beta blockers without.

At high blood concentrations, propranolol and some other beta blockers also possess a membrane-stabilising effect. This effect may not be evident at therapeutic doses but may be important in overdose. The non-cardioselective beta blocker sotalol also has class III antiarrhythmic activity.

Beta blockers that cause vasodilatation may do so by several mechanisms: carvedilol and labetalol block $alpha_1$ receptors; celiprolol has $beta_2$ agonist effects; and nebivolol has a direct action on the endothelium, possibly involving nitric oxide release.

Beta blockers are used in the treatment of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and myocardial infarction (p. 1257.1) and also have a role in heart failure (p. 1318.1). They are also used to control symptoms of sympathetic overactivity in the management of alcohol withdrawal (p. 1735.1), in anxiety disorders (below), in hyperthyroidism (p. 2332.2), and in tremor (p. 1318.3). Beta blockers are used in the prophylaxis of migraine (p. 1318.2) and of variceal bleeding associated with portal hypertension (p. 2563.1). They are also used, with an alpha blocker, in the initial management of phaeochromocytoma (p. 1318.3). Some beta blockers are used as eye drops in the management of glaucoma and ocular hypertension (p. 1318.1).

Choice of beta blocker. The selection of a specific beta blocker for an individual patient depends on the condition being treated and patient characteristics such as liver and kidney function or existing disease such as diabetes. Patient tolerance also varies for different beta blockers. The characteristics of the beta blocker, for example, $beta_1$ selectivity and intrinsic sympathomimetic activity may also influence selection, as may additional pharmacological properties such as vasodilator activity. Although the clinical significance of these differences has been debated, only certain beta blockers have a proven benefit in some conditions (for example, heart failure) and this will also influence choice.

References.

1. Anonymous. Which beta-blocker? *Med Lett Drugs Ther* 2001; **43:** 9–11.
2. Brown MJ. A rational basis for selection among drugs of the same class. *Heart* 2003; **89:** 687–94.

Anxiety disorders. Beta blockers have been used in patients with various anxiety disorders,[1] including generalised anxiety disorder (p. 1028.1), panic disorder (p. 1029.1), and performance anxiety[1] (see under Phobic Disorders, p. 1029.1). However, their benefits do not appear to be particularly great and they are probably most useful in reducing symptoms such as tremor or palpitations that are mediated through beta stimulation. Improvement usually occurs within 1 to 2 hours with relatively low doses of beta blockers (propranolol 40 mg, oxprenolol 40 to 80 mg, nadolol 40 mg). Some patients require higher doses and longer periods of treatment for a beneficial effect.

1. Tyrer P. Current status of β-blocking drugs in the treatment of anxiety disorders. *Drugs* 1988; **36:** 773–83.

Burns. Beta blockers have been tried in major burn injury (p. 1683.1) to attenuate the hypermetabolism and marked catabolism that may result. A study[1] in children with severe burns found that oral propranolol reduced energy expenditure and muscle-protein catabolism, suggesting beta blockers could have an anabolic effect.

1. Herndon DN, *et al.* Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001; **345:** 1223–9.

Cardiomyopathy. See Heart Failure, p. 1318.1.

Cardiovascular risk reduction. Beta blockers have established benefits in patients with *ischaemic heart disease*,[1] and long-term therapy with beta blockers has an important role in reducing cardiovascular risk in patients with angina pectoris (p. 1254.3), and particularly in patients who have had a myocardial infarction (p. 1257.1). They have also been used to reduce ischaemia and cardiac events in patients undergoing surgery, but their benefits in this situation are less clear.

Perioperative use of beta blockers is controversial (see Precautions, p. 1320.3); they reduce the risk of ischaemia and arrhythmias, but increase the risk of hypotension, and they have often been stopped pre-operatively to enable better control of blood pressure during surgery. However, there is some evidence that continuing or starting beta blockers perioperatively may be of benefit in patients at risk of cardiovascular events, although not all studies have come to the same conclusions. A systematic review[2] of studies with beta blockers suggested a reduction in myocardial ischaemia, non-fatal myocardial infarction, and mortality from cardiovascular causes in patients at high cardiovascular risk undergoing major noncardiac surgery, and a retrospective study[3] also suggested that perioperative beta blockers reduced in-hospital mortality in high-risk patients, although there was no benefit (and possible harm) in low-risk patients. However, another systematic review and meta-analysis[4] concluded that, while the evidence for the use of beta blockers was encouraging, it was too unreliable for definitive conclusions to be drawn. More recent studies[5,6] using perioperative metoprolol have found no benefit, and a further large study (the POISE study)[7] and subsequent meta-analyses[8,9] found fewer cardiac events but a higher risk of stroke and death in patients given beta blockers, although meta-analysis may be heavily weighted by the results from POISE. A regimen of high-dose, long-acting metoprolol started on the day of surgery in the POISE study has been criticised,[10-14] and the resulting hypotension and bradycardia may have contributed to the higher mortality in the active arm. Another meta-analysis[9] that included the results of POISE suggested that the increased risk of stroke with perioperative beta blockers was greatest in those with the lowest baseline risk of the condition.

The conflicting conclusions may relate to the wide range of protocols used in the beta blocker studies, whether patients were already taking beta blockers, and the different selection criteria used for the reviews and analyses. Recognising these limitations, consensus guidelines for non-cardiac surgery in the USA recommend[15] that beta blockers should be continued perioperatively in patients receiving them for accepted indications, and that patients undergoing vascular surgery who are at high risk of cardiovascular events (confirmed by pre-operative testing) should probably have beta blockers started; in patients at lower risk, use of beta blockers may be considered, but there is less evidence of benefit. All patients in whom beta blockers are started require careful dose titration well before the procedure with the aim of avoiding hypotension and bradycardia. It is not clear which beta blockers should be preferred, but a retrospective study[16] found that patients who took atenolol pre- and postoperatively had a lower risk of events than patients who took metoprolol. Some suggest that short-acting,[17] cardioselective[18] beta blockers should be chosen.

Beta blockers may also have benefits in patients undergoing cardiac surgery. Observational studies have found that prior[19] or pre-operative[20] use of beta blockers reduces ischaemic complications, while perioperative[21] and postoperative[22] beta blockers have been shown to reduce the risk of atrial fibrillation, although one study found[23] that the effects on atrial fibrillation only applied to patients already taking beta blockers pre-operatively.

Although beta blockers effectively lower blood pressure, they do not reduce cardiovascular events to the same extent as some other antihypertensives and may not be first choice for *hypertension* (p. 1251.1).[24,25]

1. Ellison KE, Gandhi G. Optimising the use of β-adrenoceptor antagonists in coronary artery disease. *Drugs* 2005; **65:** 787–97.
2. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA* 2002; **287:** 1435–44.
3. Lindenauer PK, *et al.* Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005; **353:** 349–61.
4. Devereaux PJ, *et al.* How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; **331:** 313–16.
5. The DIPOM Trial Group. Effect of perioperative β blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. Abridged version: *BMJ* 2006; **332:** 1482–5. Full version: http://www.bmj.com/cgi/reprint/332/7556/1482 (accessed 10/01/08)
6. Yang H, *et al.* The effects of perioperative β-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006; **152:** 983–90.
7. Devereaux PJ, *et al.* Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371:** 1839–47.
8. Bangalore S, *et al.* Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* 2008; **372:** 1962–76.
9. Talati R, *et al.* Outcomes of perioperative beta-blockade in patients undergoing noncardiac surgery: a meta-analysis. *Ann Pharmacother* 2009; **43:** 1181–8.
10. Keane M. Beta-blocker therapy in non-cardiac surgery. *Lancet* 2008; **372:** 1145.
11. Caramelli B, *et al.* Beta-blocker therapy in non-cardiac surgery. *Lancet* 2008; **372:** 1145.
12. Trevelyan J. Beta-blocker therapy in non-cardiac surgery. *Lancet* 2008; **372:** 1145–6.
13. Riedel B, *et al.* Beta-blocker therapy in non-cardiac surgery. *Lancet* 2008; **372:** 1146–7.
14. Poldermans D, Devereaux PJ. The experts debate: perioperative beta-blockade for noncardiac surgery—proven safe or not? *Cleve Clin J Med* 2009; **76** (suppl 4): S84–S92.
15. Fleisher LA, *et al.* 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery:

a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009; **120:** e169–e276. Also available at: http://circ.ahajournals.org/cgi/reprint/120/21/e169.pdf (accessed 25/01/10)
16. Redelmeier DA, *et al*. β blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ* 2005; **331:** 932–4.
17. Domanski D, Schwarz ER. Is the perioperative use of beta-blockers still recommended? A critical review of recent controversies. *J Cardiovasc Pharmacol Ther* 2009; **14:** 258–68.
18. Poldermans D, *et al*. Perioperative strokes and beta-blockade. *Anesthesiology* 2009; **111:** 940–5.
19. Sharma SK, *et al*. Cardioprotective effect of prior β -blocker therapy in reducing creatine kinase-MB elevation after coronary intervention: benefit is extended to improvement in intermediate-term survival. *Circulation* 2000; **102:** 166–72.
20. Ferguson TB, *et al*. Preoperative β -blocker use and mortality and morbidity following CABG surgery in North America. *JAMA* 2002; **287:** 2221–7. Correction. *ibid*.; 3212.
21. Crystal E, *et al*. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 10/01/08).
22. Coleman CI, *et al*. Impact of prophylactic postoperative β -blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. *Ann Pharmacother* 2004; **38:** 2012–16.
23. Crystal E, *et al*. Metoprolol prophylaxis against postoperative atrial fibrillation increases length of hospital stay in patients not on pre-operative beta blockers: the beta blocker length of stay (BLOS) trial. *Heart* 2004; **90:** 941–2.
24. Lindholm LH, *et al*. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; **366:** 1545–53.
25. Wiysonge CS, *et al*. Beta-blockers for hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 12/06/08).

Extrapyramidal disorders. Beta blockers (in low doses) have been suggested for the management of antipsychotic-induced akathisia although evidence of benefit is limited (see under Chlorpromazine, p. 1049.2).

Glaucoma and ocular hypertension. Topical beta blockers are often the drugs of first choice for the initial treatment and maintenance of open-angle glaucoma and other chronic glaucomas (p. 1999.1). They are believed to inhibit beta receptors in the ciliary epithelium and reduce the secretion of aqueous humour. Clinical studies have established that betaxolol, carteolol, levobunolol, metipranolol, and timolol are effective, generally reducing intra-ocular pressure to a similar extent,[1-5] although a meta-analysis suggested that timolol might be slightly more effective than betaxolol in lowering intra-ocular pressure.[6] The possibility of systemic effects after topical use needs to be borne in mind (see Effects after Ophthalmic Use, p. 1320.1), especially in the elderly.[7]

Beta blockers have also been used for prophylaxis of postoperative ocular hypertension.[8,9]

1. LeBlanc RP, *et al*. Timolol: long-term Canadian Multicentre Study. *Can J Ophthalmol* 1985; **20:** 128–30.
2. Stewart RH, *et al*. Betaxolol vs timolol: a six-month double-blind comparison. *Arch Ophthalmol* 1986; **104:** 46–8.
3. Geyer O, *et al*. Levobunolol compared with timolol: a four-year study. *Br J Ophthalmol* 1988; **72:** 892–6.
4. Krieglstein GK, *et al*. Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort. *Br J Ophthalmol* 1987; **71:** 250–3.
5. Scoville B, *et al*. A double-masked comparison of carteolol and timolol in ocular hypertension. *Am J Ophthalmol* 1988; **105:** 150–4.
6. van der Valk R, *et al*. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology* 2005; **112:** 1177–85.
7. O'Donoghue E. β Blockers and the elderly with glaucoma: are we adding insult to injury? *Br J Ophthalmol* 1995; **79:** 794–6.
8. West DR, *et al*. Comparative efficacy of the β -blockers for the prevention of increased intraocular pressure after cataract extraction. *Am J Ophthalmol* 1988; **106:** 168–73.
9. Odberg T. Primary argon laser trabeculoplasty after pretreatment with timolol. *Acta Ophthalmol (Copenh)* 1990; **68:** 317–19.

Heart failure. Beta blockers have negative inotropic properties and have in the past been contra-indicated in patients with heart failure (p. 1262.3). However, evidence shows that their inhibition of the persistent activation of the sympathetic nervous system associated with disease progression can outweigh this. Reviews,[1-4] meta-analyses,[5,6] and long-term studies[7,8] have confirmed that the beta blockers bisoprolol, carvedilol, and long-acting preparations of metoprolol all improve mortality in patients with chronic heart failure, and another study[9] has shown benefit with nebivolol in elderly patients. A further meta-analysis[10] found that fewer patients were withdrawn from treatment with beta blockers than placebo, suggesting that the benefits outweigh their adverse effects. Sub-group analysis[11] of one of the large studies also confirmed that metoprolol was well tolerated and of benefit in diabetics, despite potential effects on diabetic control (see Effects on Carbohydrate Metabolism under Adverse Effects, p. 1319.2). Beta blockers have also improved functional status in patients with chronic heart failure.[12] Selected beta blockers are therefore now recommended, as part of standard therapy, given with ACE inhibitors and diuretics, in all patients with clinically stable heart failure due to left ventricular systolic dysfunction where there are no contra-indications; the benefit in patients with preserved left ventricular function is less clear, although the empirical use of beta blockers to reduce heart rate and improve myocardial ischaemia has been suggested.[13]

The benefit of beta blockers in heart failure may not be a class effect, and in general only those with an established benefit should be used. Not all beta blockers have been studied in heart failure, but there is also evidence that some are ineffective; a study[14] with bucindolol was stopped early because no mortality benefit was found. For those that have been shown to improve mortality, it is not clear if they are all equally effective.[15] A meta-analysis[16] has suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation, and a large study[17] comparing carvedilol with metoprolol also found a greater mortality reduction with carvedilol, although the equivalence of the doses used in the study was questioned.[18] The optimum dose is also unclear; many patients are unable to tolerate the target doses used in clinical studies, but an analysis[19] of a study with metoprolol suggested that the mortality benefit was equal in those receiving low or high doses and a meta-analysis[20] found that the magnitude of survival benefit seen with beta blockers was associated with the magnitude of heart rate reduction rather than the dose.

Beta blockers may also be of value in some patients with heart failure due to cardiomyopathy (p. 1261.3). Some beta blockers have provided symptomatic benefit in idiopathic dilated cardiomyopathy, and the heart failure studies that showed a mortality benefit included patients with dilated cardiomyopathy. In hypertrophic cardiomyopathy, beta blockers may be of value for symptomatic management to curtail tachycardia, reduce anginal pain, and prevent syncope.

1. Foody JM, *et al*. β -Blocker therapy in heart failure: scientific review. *JAMA* 2002; **287:** 883–9.
2. Pritchett AM, Redfield MM. β -Blockers: new standard therapy for heart failure. *Mayo Clin Proc* 2002; **77:** 839–46.
3. Goldstein S. Benefits of β -blocker therapy for heart failure: weighing the evidence. *Arch Intern Med* 2002; **162:** 641–8.
4. Klapholz M. Beta-blocker use for the stages of heart failure. *Mayo Clin Proc* 2009; **84:** 718–29.
5. Lechat P, *et al*. Clinical effects of β -adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998; **98:** 1184–91.
6. Brophy JM, *et al*. β -Blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med* 2001; **134:** 550–60.
7. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.
8. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353:** 2001–7.
9. Flather MD, *et al*. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26:** 215–25.
10. Ko DT, *et al*. Adverse effects of β -blocker therapy for patients with heart failure: a quantitative overview of randomized trials. *Arch Intern Med* 2004; **164:** 1389–94.
11. Deedwania PC, *et al*. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005; **149:** 159–67.
12. Abdulla J, *et al*. Effect of beta-blocker therapy on functional status in patients with heart failure: a meta-analysis. *Eur J Heart Fail* 2006; **8:** 522–31.
13. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β -adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
14. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; **344:** 1659–67.
15. McBride BF, White CM. Critical differences among beta-adrenoreceptor antagonists in myocardial failure: debating the MERIT of COMET. *J Clin Pharmacol* 2005; **45:** 6–24.
16. Bonet S, *et al*. β -Adrenergic blocking agents in heart failure: benefits of vasodilating and nonvasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. *Arch Intern Med* 2000; **160:** 621–7.
17. Poole-Wilson PA, *et al*. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; **362:** 7–13.
18. Dargie HJ. β -Blockers in heart failure. *Lancet* 2003; **362:** 2–3.
19. Wikstrand J, *et al*. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002; **40:** 491–8.
20. McAlister FA, *et al*. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009; **150:** 784–94.

Hypotension. Beta blockers have a hypotensive effect and are usually used to reduce blood pressure in patients with hypertension, or occasionally to produce controlled hypotension during surgery. Paradoxically, however, they may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p. 1277.2), although there is limited evidence to support their use, and adverse effects may be a concern. Beta blockers with partial agonist activity have been used in orthostatic hypotension due to autonomic failure (p. 1634.3) but are potentially dangerous.

Migraine and tension type headache. Beta blockers (usually propranolol or metoprolol) are considered[1] by many to be the drugs of choice in patients requiring prophylactic treatment for migraine (p. 670.3). Their mechanism of action in this disorder is not fully understood. Other beta blockers reported to be effective include atenolol, nadolol, and timolol; those with intrinsic sympathomimetic activity may not be effective.

Beta blockers may sometimes also be of benefit in patients with chronic tension-type headache (p. 671.3).

Propranolol has been tried in the treatment of children with abdominal migraine (see under Pizotifen, p. 678.2).

1. Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on β -adrenoceptor blockers. *Br J Clin Pharmacol* 2001; **52:** 237–43.

Peripheral vascular disease. Beta blockers may cause coldness of the extremities and have been reported to induce secondary Raynaud's syndrome. However, they may be of some help in the management of erythromelalgia (see under Vasospastic Arterial Disorders on p. 1275.3).

Phaeochromocytoma. Beta blockers are used, with an alpha blocker, in the initial management of phaeochromocytoma (p. 1278.1). Beta blockers reduce the responses to the beta-adrenoceptor stimulating effects of adrenaline. Treatment must be started with the alpha blocker and only when alpha blockade is successfully established can tachycardia be controlled by the cautious use of a beta blocker. A $beta_1$-selective blocker is preferred so that peripheral $beta_2$-mediated vasodilatation is unaffected. In most cases modest doses are sufficient although higher doses may be required for a tumour that is mainly adrenaline-secreting.

Tetanus. Autonomic overactivity, usually due to excessive catecholamine release, may occur as a complication of tetanus and is usually controlled with sedation (see p. 2029.2). Beta blockers have also been used but may produce severe hypertension and are therefore not usually recommended. Labetalol has both alpha- and beta-blocking properties and intravenous labetalol has been used successfully to control the cardiovascular effects of tetanus,[1] although it has not been shown to offer any advantage over propranolol in this situation. Esmolol, a short-acting beta blocker, has also been used.[2]

1. Domenighetti GM, *et al*. Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol. *BMJ* 1984; **288:** 1483–4.
2. King WW, Cave DR. Use of esmolol to control autonomic instability of tetanus. *Am J Med* 1991; **91:** 425–8.

Tetralogy of Fallot. For the use of beta blockers in the management of tetralogy of Fallot, see under Uses of Propranolol, p. 1479.3.

Tremor. Tremor is a rhythmical oscillation of part of the body caused by involuntary contraction of opposing muscles. It may occur during action, maintenance of posture, or at rest, and varies in frequency and amplitude. Resting tremor is associated mainly with parkinsonism (p. 889.1), whereas action tremor, which includes postural tremor and kinetic tremor, occurs in a wide variety of disorders. Treatment of the underlying disorder may remove the tremor. Drugs such as bronchodilators, tricyclic antidepressants, lithium, and caffeine may induce tremor; withdrawal of the causative drug usually alleviates the tremor. However, tremor often has no known underlying cause. Such tremor is referred to as **essential tremor** or benign essential tremor; it is usually postural and tends to affect the hands, head, voice, and sometimes the legs and trunk. It is exacerbated by emotional stress and anxiety. Essential tremor may appear at any age and is a lifelong condition that may progress with increasing age. In many cases there is a family history of the disorder (familial essential tremor).

Mild cases of essential tremor may not require regular drug treatment. Single doses of a beta blocker or a benzodiazepine may be useful in acute circumstances to control exacerbations provoked by stress. A single dose of propranolol usually produces a maximum effect after 1 to 2 hours and the effect may persist for several hours. Small amounts of alcohol may also provide effective temporary relief of essential tremor, although its regular use is obviously discouraged.

For more severe cases of essential tremor long-term drug treatment may be required (and may also be tried in other forms of tremor).[1-5] A beta blocker (usually a non-cardioselective beta blocker such as propranolol) is often the first drug used. Up to 70% of people have been reported to respond, although the average tremor reduction is only about 50 to 60%. The beneficial effect appears to be mainly due to blockade of peripheral $beta_2$ receptors on extrafusal muscle fibres and muscle spindles, although there may also be a CNS effect. Adverse effects may be troublesome on long-term use. Primidone may also be tried[6] although there may be a high incidence of acute adverse reactions after initial doses. Concern has been expressed that patients may become tolerant to these drugs given long-term. However, 3 small studies found a reduced response on long-term therapy in only a few patients.[7-9]

Local injection of botulinum A toxin has been tried in refractory essential tremor. Benzodiazepines, and antimuscarinic or dopaminergic antiparkinsonian drugs may be effective in some forms of tremor.[1] Other drugs that have shown some benefit include gabapentin and topiramate.[1-4,10] Many other drugs have been tried, but there is little evidence to support their use.[10] In very severe disabling cases, surgery (thalamotomy or deep brain stimulation) may have to be considered.

1. Habib-ur-Rehman. Diagnosis and management of tremor. *Arch Intern Med* 2000; **160:** 2438–44.
2. Louis ED. Essential tremor. *N Engl J Med* 2001; **345:** 887–91.
3. Lyons K, *et al.* Benefits and risks of pharmacological treatments for essential tremor. *Drug Safety* 2003; **26:** 461–81.
4. Pahwa R, Lyons KE. Essential tremor: differential diagnosis and current therapy. *Am J Med* 2003; **115:** 134–42.
5. Benito-León J, Louis ED. Clinical update: diagnosis and treatment of essential tremor. *Lancet* 2007; **369:** 1152–4.
6. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
7. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. *Neurology* 1989; **39:** 1587–8.
8. Calzetti S, *et al.* Clinical and computer-based assessment of long-term therapeutic efficacy of propranolol in essential tremor. *Acta Neurol Scand* 1990; **81:** 392–6.
9. Sasso E, *et al.* Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990; **13:** 67–76.
10. Zesiewicz TA, *et al.* Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2011; **77:** 1752–5. Also available at: http://www.neurology.org/content/77/19/1752.full.pdf+html (accessed 01/05/12)

Adverse Effects

Beta blockers are generally well tolerated and most adverse effects are mild and transient. Reactions may be more severe after intravenous than oral doses; ocular use has also been associated with systemic adverse effects. The most frequent and serious adverse effects are related to their beta-adrenergic blocking activity. Among the most serious adverse effects are heart failure, heart block, and bronchospasm. Troublesome subjective effects include fatigue and coldness of the extremities; when beta blockers are used for long-term treatment of asymptomatic diseases such as hypertension, such effects may be an important determinant of patient compliance.

Cardiovascular effects include bradycardia and hypotension; heart failure or heart block may be precipitated or worsened in patients with underlying cardiac disorders. Abrupt withdrawal of beta blockers may exacerbate angina and may lead to sudden death. (For further details on withdrawal of beta blockers, see Precautions, p. 1320.3.)

Bronchospasm, shortness of breath, and dyspnoea may be precipitated, particularly in patients with a history of obstructive airways disease, due to blockade of $beta_2$ receptors in bronchial smooth muscle. Drugs with selectivity for $beta_1$ receptors or with intrinsic sympathomimetic activity at $beta_2$ receptors may be less likely to induce bronchospasm (but see Precautions, p. 1320.3). Pneumonitis, pulmonary fibrosis, and pleurisy have also been reported.

CNS effects include headache, depression, dizziness, hallucinations, confusion, amnesia, and sleep disturbances including nightmares. Coma and convulsions have been reported after beta-blocker overdosage. Beta blockers that are lipid soluble are more likely to enter the brain and would be expected to be associated with a higher incidence of CNS adverse effects, although this is not proven.

Fatigue is a common adverse-effect of beta blockers. Paraesthesia, arthralgia, and myopathies, including muscle cramps, have been reported. Reduced peripheral circulation can produce coldness of the extremities and may exacerbate peripheral vascular disease such as Raynaud's syndrome.

Adverse gastrointestinal effects include nausea and vomiting, diarrhoea, constipation, and abdominal cramping.

Beta blockers interfere with carbohydrate and lipid metabolism and can produce hypoglycaemia, hyperglycaemia, and changes in blood concentrations of triglycerides and cholesterol (see under Effects on Carbohydrate Metabolism, below and Effects on Lipid Metabolism, p. 1320.1 for further details).

Rashes, pruritus, exacerbation of psoriasis, excess sweating, and reversible alopecia have occurred with use of beta blockers.

Decreased tear production, blurred vision, conjunctivitis, and soreness are among the ocular symptoms that have been reported. Adverse effects specific to ocular use are also discussed on p. 1320.1.

Haematological reactions include nonthrombocytopenic purpura, thrombocytopenia, and rarely agranulocytosis. Transient eosinophilia can occur.

An asymptomatic increase in antinuclear antibodies has occurred with many beta blockers; SLE has also been reported. Other adverse effects reported with some beta blockers include dry mouth, raised liver enzymes, male impotence, sclerosing peritonitis, and retroperitoneal fibrosis.

Effects on bones and joints. Adverse effects on the bones and joints have occurred in patients receiving beta blockers. Five cases of arthralgia associated with the use of metoprolol had been reported to the FDA;[1] there had also been 6 reports of similar symptoms with propranolol, and 1 with atenolol. A case of polymyalgia rheumatica-like syndrome has also been reported.[2]

However, epidemiological studies have also suggested that beta blockers may increase bone mineral density[3] and reduce the risk of fractures,[3,4] although another study[5] could not confirm this effect.

1. Sills JM, Bosco L. Arthralgia associated with β-adrenergic blockade. *JAMA* 1986; **255:** 198–9.
2. Snyder S. Metoprolol-induced polymyalgia-like syndrome. *Ann Intern Med* 1991; **114:** 96–7.
3. Pasco JA, *et al.* β-Adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res* 2004; **19:** 19–24.
4. Schlienger RG, *et al.* Use of β-blockers and risk of fractures. *JAMA* 2004; **292:** 1326–32.
5. Reid IR, *et al.* β-Blocker use, BMD, and fractures in the study of osteoporotic fractures. *J Bone Miner Res* 2005; **20:** 613–18.

Effects on the breast. A 54-year-old woman developed breast pain and swelling a few weeks after starting atenolol for hypertension;[1] it resolved when the atenolol was stopped.

1. Kelleher JA. Atenolol-induced breast pain in a woman with hypertension. *Ann Pharmacother* 2006; **40:** 990–2.

Effects on carbohydrate metabolism. The sympathetic nervous system is involved in the control of carbohydrate metabolism and beta blockers can interfere with carbohydrate and insulin regulation; both hypoglycaemia and hyperglycaemia have been reported in patients with no history of diabetes, as well as in patients with types 1 or 2 diabetes mellitus.

Beta blockers cause hypoglycaemia in non-diabetics, possibly by increasing peripheral glucose uptake through increased insulin sensitivity.[1] Those most at risk include fasting or nutritionally-compromised patients, haemodialysis patients, neonates after maternal treatment with beta blockers, and patients with liver disease;[1] those undertaking vigorous exercise[2] and children may also be at risk. Glucose metabolism is controlled by the action of catecholamines at the $beta_2$ receptor, and therefore cardioselective beta blockers are less likely to cause hypoglycaemia than their non-cardioselective counterparts;[1] however, hypoglycaemia was reported[3] in a non-diabetic patient given the cardioselective beta blocker metoprolol pre-operatively for cardiovascular protection.

Traditionally beta blockers have been considered unsafe in diabetics because of reports that they may precipitate and prolong hypoglycaemia, an effect that was first seen in the 1960s in adult type 1 diabetics taking propranolol; however, in a long-term study[4] in type 2 diabetics, there was no difference in the incidence of hypoglycaemia in patients receiving captopril or the cardioselective beta blocker atenolol, and both significantly improved outcome. A case-control study[5] and a review[6] of the use of beta blockers in diabetic patients both concluded that the incidence of hypoglycaemia was not increased and that beta blockers were appropriate therapy for diabetics. Nonetheless, beta blockers may mask the adrenaline-mediated symptoms of hypoglycaemia such as tachycardia and tremor, and non-cardioselective beta blockers may delay recovery in patients given glucose for hypoglycaemia;[6] cardioselective beta blockers are less likely to mask the signs of hypoglycaemia and are therefore preferred in diabetics.[7]

Both cardioselective and non-cardioselective beta blockers may increase fasting blood glucose concentrations in non-diabetic hypertensive patients,[8,9] and epidemiological studies have shown that the risk of developing diabetes mellitus is increased by beta blockers.[10-12] The mechanism is possibly through inhibition of pancreatic insulin release,[1,13] although it has been suggested that hypertensive patients are predisposed to diabetes mellitus and beta blockers act as a precipitating factor;[10,14] changes in body-weight in some of the studies may also have confounded the results.[6] Hyperglycaemia can also occur in diabetic patients treated with beta blockers;[14] however, the established benefits generally outweigh the risk.

Although the adverse effects of beta blockers on carbohydrate metabolism are well-established, there is some evidence that the newer, vasodilating beta blockers, such as carvedilol[15,16] and nebivolol,[17,18] may have beneficial effects on insulin resistance or glucose control, and weight gain may be less with carvedilol.[19] New onset diabetes was also more likely to occur with metoprolol than carvedilol in a study on patients with heart failure.[20]

1. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
2. Holm G, *et al.* Severe hypoglycaemia during physical exercise and treatment with beta-blockers. *BMJ* 1981; **282:** 1360.
3. Brown DR, Brown MJ. Hypoglycemia associated with preoperative metoprolol administration. *Anesth Analg* 2004; **99:** 1427–8.
4. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; **317:** 713–20.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21:** 1387–1400.
6. Sawicki PT, Siebenhofer A. Betablocker treatment in diabetes mellitus. *J Intern Med* 2001; **250:** 11–17.
7. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
8. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol or hydrochlorothiazide alone for the initial treatment of hypertension IV: effect on plasma glucose and glucose tolerance. *Hypertension* 1985; **7:** 1008–16.
9. Pollare T, *et al.* Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ* 1989; **298:** 1152–7.
10. Samuelsson O, *et al.* Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial in Göteborg, Sweden. *J Hum Hypertens* 1994; **8:** 257–63.
11. Gress TW, *et al.* Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 905–12.
12. Taylor EN, *et al.* Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29:** 1065–70.
13. Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA* 2001; **286:** 1945–8.
14. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part 1). *Drugs* 1990; **40:** 6–18.
15. Bakris GL, *et al.* Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; **292:** 2227–36. Correction. *ibid.*; 2583.
16. Giugliano D, *et al.* Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 955–9.
17. Celik T, *et al.* Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *J Hypertens* 2006; **24:** 591–6.
18. Poirier L, *et al.* Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients. *J Hypertens* 2001; **19:** 1429–35.
19. Messerli FH, *et al.* Body weight changes with beta-blocker use: results from GEMINI. *Am J Med* 2007; **120:** 610–15.
20. Torp-Pedersen C, *et al.* Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; **93:** 968–73.

Effects on the circulation. Hypotension is a recognised adverse effect of beta blockers, and severe reactions have been reported. Near-fatal shock occurred[1] in an elderly patient with chronic bronchitis and angina pectoris within 40 minutes of taking acebutolol 400 mg. (For discussion of hypotension possibly associated with increased mortality in patients given beta blockers perioperatively see Cardiovascular Risk Reduction, under Uses, p. 1317.2.) Hypotension, leading to a rise in serum creatinine indicative of kidney ischaemia, occurred[2] in 2 women after a single oral dose of atenolol 100 mg or 2 oral doses of atenolol 50 mg; both had presented with severe hypertension, hyponatraemia, hypokalaemia, and high renin activity. Renal artery thrombosis believed to be due to the hypotensive effect of atenolol was reported[3] in a 70-year-old man with a history of circulatory and cardiac disorders. He had received atenolol 100 mg for treatment of moderate hypertension.

Beta blockers have been tried in neurally mediated hypotension (see Hypotension under Uses, p. 1318.2), but this may be hazardous: a 27-year-old man had[4] ten episodes of syncope with severe bradycardia after taking atenolol for recurrent vasovagal syncope; episodes ceased on stopping the atenolol. The authors suggested that the atenolol aggravated the vasovagal syncope, and recommended careful monitoring of patients given beta blockers for this condition.

1. Tirlapur VG, *et al.* Shock syndrome after acebutolol. *Br J Clin Pract* 1986; **40:** 33–4.
2. Kholeif M, Isles C. Profound hypotension after atenolol in severe hypertension. *BMJ* 1989; **298:** 161–2.
3. Shaw AB, Gopalka SK. Renal artery thrombosis caused by antihypertensive treatment. *BMJ* 1982; **285:** 1617.
4. Wang C-C, *et al.* Worsening of vasovagal syncope after beta-blocker therapy. *Chest* 1994; **106:** 963–5.

Effects on the gastrointestinal tract. Sclerosing peritonitis was noted as part of the 'oculomucocutaneous syndrome' that occurred with practolol. However, while both sclerosing peritonitis and retroperitoneal fibrosis have also been reported with some other beta blockers, including atenolol,[1,2] metoprolol,[3,4] oxprenolol,[5] propranolol,[6,7] sotalol,[8] and timolol,[9,10] a review[11] of 100 cases of retroperitoneal fibrosis concluded that beta blockers could not be considered as the cause.

Abdominal pain and bloody diarrhoea were reported[12] in a patient the day after treatment was started with propranolol; symptoms were attributed to splanchnic vasoconstriction caused by the drug, which may have exacerbated pre-existing mesenteric ischaemia.

1. Nielsen BV, Pedersen KG. Sclerosing peritonitis associated with atenolol. *BMJ* 1985; **290:** 518.
2. Johnson JN, McFarland J. Retroperitoneal fibrosis associated with atenolol. *BMJ* 1980; **280:** 864.

3. Thompson J, Julian DG. Retroperitoneal fibrosis associated with metoprolol. *BMJ* 1982; **284:** 83–4.
4. Clark CV, Terris R. Sclerosing peritonitis associated with metoprolol. *Lancet* 1983; **i:** 937.
5. McCluskey DR, *et al.* Oxprenolol and retroperitoneal fibrosis. *BMJ* 1980; **281:** 1459–60.
6. Pierce JR, *et al.* Propranolol and retroperitoneal fibrosis. *Ann Intern Med* 1981; **95:** 244.
7. Kalra S, *et al.* Sclerosing encapsulating peritonitis associated with propranolol usage: a case report and review of the literature. *J Dig Dis* 2009; **10:** 332–5.
8. Laakso M, *et al.* Retroperitoneal fibrosis associated with sotalol. *BMJ* 1982; **285:** 1085–6.
9. Baxter-Smith DC, *et al.* Sclerosing peritonitis in patient on timolol. *Lancet* 1978; **ii:** 149.
10. Rimmer E, *et al.* Retroperitoneal fibrosis associated with timolol. *Lancet* 1983; **i:** 300.
11. Pryor JP, *et al.* Do beta-adrenoceptor blocking drugs cause retroperitoneal fibrosis? *BMJ* 1983; **287:** 639–41.
12. Köksal AŞ, *et al.* Propranolol-exacerbated mesenteric ischemia in a patient with hyperthyroidism. *Ann Pharmacother* 2005; **39:** 559–62.

Effects on lipid metabolism. The adrenergic system is involved in the control of lipid metabolism and beta blockers may therefore have effects on plasma-lipid concentrations. In general, beta blocker therapy results in increased concentrations of very-low-density lipoprotein and triglycerides, a reduction in high-density lipoprotein, and no change in low-density lipoprotein.[1] These effects may be less pronounced with $beta_1$ cardioselective drugs, beta blockers with intrinsic sympathomimetic activity, and beta blockers that also block alpha-adrenergic receptors. For example, pindolol,[2,3] a beta blocker with intrinsic sympathomimetic activity, and arotinolol[4] and carvedilol,[5] which possess alpha-adrenergic blocking properties, are reported to have no adverse effects on plasma-lipid concentrations, although acute pancreatitis due to severe hypertriglyceridaemia has been reported[6] in a patient treated with metoprolol followed by atenolol. However, the effects on lipid concentrations are generally fairly small, and a review of the subject[7] concluded that there was little or no evidence that such effects negated the beneficial effects of beta blockers on cardiovascular outcomes.

1. Krone W, Nägele H. Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J* 1988; **116:** 1729–34.
2. Hunter Hypertension Research Group. Effects of pindolol, or a pindolol/clopamide combination preparation, on plasma lipid levels in essential hypertension. *Med J Aust* 1989; **150:** 646–52.
3. Terént A, *et al.* Long-term effect of pindolol on lipids and lipoproteins in men with newly diagnosed hypertension. *Eur J Clin Pharmacol* 1989; **36:** 347–50.
4. Sasaki J, *et al.* Effects of arotinolol on serum lipid and apolipoprotein levels in patients with mild essential hypertension. *Clin Ther* 1989; **11:** 580–3.
5. Sharp RP, *et al.* Impact of carvedilol on the serum lipid profile. *Ann Pharmacother* 2008; **42:** 564–71.
6. Durrington PN, Cairns SA. Acute pancreatitis: a complication of beta-blockade. *BMJ* 1982; **284:** 1016.
7. Weir MR, Moser M. Diuretics and β-blockers: is there a risk for dyslipidemia? *Am Heart J* 2000; **139:** 174–84.

Effects on mental state. Beta blockers can cross the blood-brain barrier and there are many reports of adverse psychiatric effects. Theoretically this is more likely with lipophilic drugs (such as propranolol, timolol, and metoprolol) but there have also been reports of psychosis[1] and delirium[2] with atenolol.

Although beta blockers have been associated with depression,[3] the risk may not be as high as has sometimes been suggested; a review[4] of randomised studies in myocardial infarction, heart failure, or hypertension, which included over 35 000 patients, found no significant increase in the risk of depression in those taking beta blockers.

1. Viadero JJ, *et al.* Acute psychotic behavior associated with atenolol. *Am J Psychiatry* 1983; **140:** 1382.
2. Arber N, *et al.* Delirium induced by atenolol. *BMJ* 1988; **297:** 1048.
3. Parker WA. Propranolol-induced depression and psychosis. *Clin Pharm* 1985; **4:** 214–18.
4. Ko DT, *et al.* β-Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002; **288:** 351–7.

Effects after ophthalmic use. Ophthalmic use of beta blockers may produce ocular irritation (including hypersensitivity), blepharitis, keratitis, decreased corneal sensitivity, visual disturbances, diplopia, photophobia, and ptosis. Hypersensitivity to ophthalmic beta blockers has caused allergic conjunctivitis and contact dermatitis; cross-sensitivity between beta blockers has been reported.[1] Uveitis has been reported with metipranolol eye drops.[2] Iris depigmentation has occurred[3] after the use of topical levobunolol. Older patients using topical beta blockers may be at greater risk of decreased corneal sensitivity or corneal anaesthesia with the consequent risk of keratitis.[4]

Systemic absorption may occur after the use of beta blockers in eye drops. Excess drug can drain into the lachrymal ducts to be absorbed through the nasal mucosa. Absorption also occurs via the ophthalmic and facial veins. After such absorption the beta blocker reaches the systemic circulation without undergoing first-pass hepatic metabolism.

The main systemic effects associated with topical ocular use of beta blockers are on the pulmonary, cardiovascular, and central nervous systems.[5,6]

Both cardioselective and non-cardioselective topical beta blockers have been shown to cause pulmonary effects, and these can occur in patients without a history of obstructive airways disease.[7] Reported events include acute pulmonary oedema associated with use of metipranolol eye drops,[8] and wheezing after a single dose of topical levobunolol, which developed into severe respiratory distress requiring hospitalisation after a second dose.[9] Myocardial infarction has been reported[10] shortly after a single dose of betaxolol eye drops; the patient was also taking atenolol and indapamide for hypertension. Systemic effects have also been reported in patients using timolol eye drops, including depression and bradycardia, with a rise in blood pressure and neurological signs of stroke after rapid withdrawal of the drops,[11] syncope and falls,[12] and severe nausea and vomiting, which resolved within a few days of withdrawal but recurred on rechallenge.[13] Cases of alopecia associated with ocular use of beta blockers have also been reported.[14]

1. Jappe U, *et al.* Allergic contact dermatitis due to β-blockers in eye drops: a retrospective analysis of multicentre surveillance data 1993–2004. *Acta Derm Venereol* 2006; **86:** 509–14.
2. Akingbehin T, Villada JR. Metipranolol-associated granulomatous anterior uveitis. *Br J Ophthalmol* 1991; **75:** 519–23.
3. Doyle E, Liu C. A case of acquired iris depigmentation as a possible complication of levobunolol eye drops. *Br J Ophthalmol* 1999; **83:** 1405–6.
4. Weissman SS, Asbell PA. Effects of topical timolol (0.5%) and betaxolol (0.5%) on corneal sensitivity. *Br J Ophthalmol* 1990; **74:** 409–12.
5. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
6. Vander Zanden JA, *et al.* Systemic adverse effects of ophthalmic β-blockers. *Ann Pharmacother* 2001; **35:** 1633–7.
7. Kirwan JF, *et al.* Do selective topical β antagonists for glaucoma have respiratory side effects? *Br J Ophthalmol* 2004; **88:** 196–8.
8. Johns MD, Ponte CD. Acute pulmonary edema associated with ocular metipranolol use. *Ann Pharmacother* 1995; **29:** 370–3.
9. Stubbs GM. Betagan drops. *Med J Aust* 1994; **161:** 576.
10. Chamberlain TJ. Myocardial infarction after ophthalmic betaxolol. *N Engl J Med* 1989; **321:** 1342.
11. Rao MR, *et al.* Systemic hazards of ocular timolol. *Br J Hosp Med* 1993; **50:** 553.
12. Müller ME, *et al.* Syncope and falls due to timolol eye drops. *BMJ* 2006; **332:** 960–1.
13. Wolfhagen FHJ, *et al.* Severe nausea and vomiting with timolol eye drops. *Lancet* 1998; **352:** 373.
14. Fraunfelder FT, *et al.* Alopecia possibly secondary to topical ophthalmic β-blockers. *JAMA* 1990; **263:** 1493–4.

Hypersensitivity. For the suggestion that beta blockers may exacerbate anaphylactic reactions, see under Precautions, p. 1321.1.

See also under Effects after Ophthalmic Use, above.

Overdosage. Many cases of beta-blocker overdosage[1] are uneventful, but some patients develop severe and occasionally fatal cardiovascular depression. Effects can include bradycardia, cardiac conduction block, hypotension, heart failure, and cardiogenic shock. Convulsions, coma, respiratory depression, and bronchoconstriction can also occur, although infrequently. Most reports of serious toxic reactions after overdosage concern beta blockers with significant membrane-stabilising activity, such as propranolol or oxprenolol, which may have quinidine-like effects (see p. 1482.1). Overdosage of beta blockers with intrinsic sympathomimetic activity may present with tachycardia and hypertension. Overdosage of sotalol, a beta blocker with class II and III antiarrhythmic properties, usually presents as ventricular tachyarrhythmia.

1. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and β-blocker toxicity. *Toxicol Rev* 2004; **23:** 223–38.

Treatment of Adverse Effects

Beta blockers are generally well tolerated and adverse effects usually respond to a reduction in dose. In overdosage, use of activated charcoal or gastric lavage should be considered if the patient presents within 1 hour of ingestion. Mild hypotension may respond to intravenous fluids. If hypotension continues, intravenous glucagon should be given; sympathomimetics may be used as an alternative or given with glucagon. Isoprenaline has been the sympathomimetic of choice since it acts mainly at beta receptors, but other sympathomimetics are often used; very high doses may be required (see Overdosage, below). Atropine may be given intravenously for bradycardia; sympathomimetics or a cardiac pacemaker may also be required. $Beta_2$ agonists or xanthines may be given for bronchospasm; hypoglycaemia may respond to glucose or glucagon. Haemodialysis may be of benefit for severe overdosage with renally excreted beta blockers, but is usually unnecessary.

Overdosage. Atropine, glucagon, and sympathomimetics are the mainstay of treatment for severe beta blocker overdosage (see above). Very high doses of sympathomimetics have been used in some patients; a woman[1] who had taken acebutolol, labetalol, and trimipramine required isoprenaline at a rate of 1660 micrograms/minute and dopamine at a rate of 200 micrograms/kg per minute to maintain her blood pressure. However, standard therapy is not effective in all patients and alternatives have been tried.

The phosphodiesterase inhibitor enoximone has been used successfully in patients resistant to standard treatment,[2,3] and a dramatic response to calcium chloride has been reported in a patient with electromechanical dissociation after propranolol overdosage.[4] It has been suggested[5,6] that high doses of insulin given with glucose (hyperinsulinaemia/euglycaemia therapy) may be of benefit, although there is no clinical evidence to support this. There has also been a report[7] of the successful use of sodium bicarbonate in a patient with cardiac arrest after overdosage with multiple drugs, including propranolol; it was suggested that the increased sodium load counteracted the sodium-channel blocking effect of propranolol.

1. Lewis M, *et al.* Survival following massive overdose of adrenergic blocking agents (acebutolol and labetalol). *Eur Heart J* 1983; **4:** 328–32.
2. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335:** 1538.
3. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; **50:** 759–61.
4. Brimacombe JR, *et al.* Propranolol overdose—a dramatic response to calcium chloride. *Med J Aust* 1991; **155:** 267–8.
5. Shepherd G. Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; **63:** 1828–35.
6. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and β-blocker poisoning. *Toxicol Rev* 2004; **23:** 215–22.
7. Shanker UR, *et al.* Sodium bicarbonate to treat massive β blocker overdose. *Emerg Med J* 2003; **20:** 393.

Precautions

Beta blockers should not be given to patients with bronchospasm or asthma or to those with a history of obstructive airways disease. This contra-indication generally applies even to those beta blockers considered to be cardioselective. However, cardioselective beta blockers may be used with extreme caution when there is no alternative treatment (see Obstructive Airways Disease, p. 1321.1). Other contra-indications include metabolic acidosis, cardiogenic shock, hypotension, severe peripheral arterial disease, sinus bradycardia, and second- or third-degree AV block; caution should be observed in first-degree block. Although beta blockers are used in the management of heart failure, they should not be given to patients with uncontrolled heart failure and treatment should be begun with great care, starting with a low dose and cautiously titrating upwards. Patients with phaeochromocytoma should not be given beta blockers without alpha-adrenoceptor blocking therapy as well.

Beta blockers may mask the symptoms of hyperthyroidism and of hypoglycaemia. They may unmask myasthenia gravis. Psoriasis may be aggravated. Beta blockers may increase the number of attacks of chest pain in patients with Prinzmetal's angina; this occurs especially with non-cardioselective beta blockers, which should be avoided. Beta blockers increase sensitivity to allergens and also the severity of anaphylactoid reactions; patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking beta blockers (see Hypersensitivity, p. 1321.1).

Abrupt withdrawal of beta blockers has sometimes resulted in angina, myocardial infarction, ventricular arrhythmias, and death. Patients on long-term treatment with a beta blocker should have their medication stopped gradually over a period of 1 to 2 weeks. In patients undergoing surgery, beta blockers may reduce the risk of arrhythmias but increase the risk of hypotension; the decision to withdraw or continue therapy depends on individual patient risk—see Cardiovascular Risk Reduction, p. 1317.2. If beta blockers are withdrawn, this should take place at least 24 to 48 hours before surgery; if they are continued, atropine may be given to counter increases in vagal tone and anaesthetics causing myocardial depression, such as ether, cyclopropane, and trichloroethylene, are best avoided. It is of the greatest importance that the anaesthetist is aware that beta blockers are being taken.

Use of beta blockers in pregnancy shortly before delivery has occasionally resulted in bradycardia and other adverse effects such as hypoglycaemia and hypotension in the neonate. Many beta blockers are distributed into breast milk.

Similar precautions apply when beta blockers are used as eye drops since systemic absorption can occur.

Cocaine toxicity. Although beta blockers are useful in the acute and chronic management of myocardial ischaemia, the problem of unopposed α-adrenergic stimulation and potential for exacerbating coronary vasoconstriction make them a hazardous choice where ischaemia is induced by cocaine, and fatalities have been reported.[1,2] Some guidelines[3,4] recommend against their use, while others[5] suggest that the cautious use of a combined alpha- and beta-blocking agent such as labetalol may be reasonable if

hypertension and tachycardia are present and the patient has also received a vasodilator;[5] carvedilol has been suggested as an alternative.[2] There is little guidance on the long-term safety of beta blockers after cocaine-induced myocardial ischaemia, but the likelihood of continued cocaine ingestion should be borne in mind.[2]

1. Fareed FN, *et al.* Death temporally related to the use of a beta adrenergic receptor antagonist in cocaine associated myocardial infarction. *J Med Toxicol* 2007; **3:** 169–72.
2. Page RL, *et al.* Should β-blockers be used in the treatment of cocaine-associated acute coronary syndrome? *Ann Pharmacother* 2007; **41:** 2008–13.
3. Antman EM, *et al.* ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Executive summary: *Circulation* 2004; **110:** 588–636. Correction. *ibid.* 2005; **111:** 2013. Full guidelines available at: http://circ.ahajournals.org/cgi/reprint/110/9/e82 (accessed 26/01/10)
4. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112:** (suppl 1): IV1–IV203. Available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 26/01/10)
5. Anderson JL, *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). Full text: *Circulation* 2007; **116:** e148–e304. Also available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.181940 (accessed 26/01/10) Executive summary: *Circulation* 2007; **116:** 803–77. Also available at: http://circ.ahajournals.org/cgi/reprint/116/7/803 (accessed 26/01/10)

Contact lenses. Beta blockers may reduce tear flow, leading to irritation of the eye in wearers of contact lenses and potentially to the dehydration of soft lenses.[1]

1. McGuire T. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; **17:** 55–6.

Hypersensitivity. Anaphylactic reactions to stings and other antigens may be potentiated by beta blockers[1-3] and the risk of serious reactions may be increased. In addition, beta blockers may antagonise the effects of adrenaline in the management of anaphylaxis (see Interactions under Sympathomimetics, p. 1509.1). Particular caution is necessary when beta blockers are used in patients with a history of anaphylaxis.[3]

1. Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983; **308:** 1536.
2. Pedersen DL. Hymenoptera stings and beta-blockers. *Lancet* 1989; **ii:** 619.
3. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of β-blockers. *Drug Safety* 1995; **12:** 299–304.

Obstructive airways disease. Beta blockers may precipitate bronchospasm and are generally contra-indicated in patients with obstructive airways disease.[1,2] However, systematic reviews have suggested that short-term use of cardioselective beta blockers does not produce adverse respiratory effects in patients with mild to moderate asthma[3] or chronic obstructive pulmonary disease.[4] The reviewers concluded that, given the established benefits of beta blockers in cardiovascular disorders, they should not be withheld in such patients, although patients should be carefully monitored since long-term effects were less clear. A retrospective study[5] found that use of beta blockers increased the rate of hospitalisations and emergency department visits in patients with asthma, but not in those with non-asthmatic chronic obstructive pulmonary disease, suggesting that the benefits and risks need to be assessed for each patient individually. Another study[6] found that patients with acute exacerbations of chronic obstructive pulmonary disease who were given beta blockers had lower mortality than those who were not.

1. CSM/MCA. Reminder: beta-blockers contraindicated in asthma. *Current Problems* 1996; **22:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 10/01/08)
2. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
3. Salpeter S, *et al.* Cardioselective beta-blockers for reversible airway disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 10/01/08).
4. Salpeter S, *et al.* Cardioselective beta-blockers for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 10/01/08).
5. Brooks TWA, *et al.* Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking β-blockers. *Pharmacotherapy* 2007; **27:** 684–90.
6. Dransfield MT, *et al.* Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; **63:** 301–5.

Pregnancy. Many beta blockers cross the placenta, and use shortly before delivery may result in neonatal adrenergic blockade, with symptoms of bradycardia, hypoglycaemia or hypotension. Furthermore, the treatment of maternal hypertension with beta blockers, particularly atenolol, in early pregnancy or for a long duration has been associated with growth retardation of the fetus.[1-3] However, beta blockers are recommended therapy for maternal conditions such as hypertension, pre-eclampsia, cardiac arrhythmias, and ischaemic heart disease;[4,5] cardioselective agents with no effect on uterine contraction are preferred.[5]

1. Butters L, *et al.* Atenolol in essential hypertension during pregnancy. *BMJ* 1990; **301:** 587–9.
2. Lydakis C, *et al.* Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999; **12:** 541–7.
3. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 10/01/08).
4. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; **24:** 761–81.
5. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.

Withdrawal. The abrupt withdrawal of beta blockers may lead to rebound hypertension or overshoot hypertension where the patient's blood pressure is higher than before treatment. Angina can be exacerbated, myocardial infarction induced, and fatalities have occurred.[1,2]

1. Houston MC, Hodge R. Beta-adrenergic blocker withdrawal syndromes in hypertension and other cardiovascular diseases. *Am Heart J* 1988; **116:** 515–23.
2. Psaty BM, *et al.* The relative risk of incident coronary heart disease associated with recently stopping the use of β-blockers. *JAMA* 1990; **263:** 1653–7.

Interactions

Both pharmacodynamic and pharmacokinetic interactions have been reported with beta blockers. **Pharmacodynamic** interactions may occur with drugs whose actions enhance or antagonise the various effects of beta blockers at $beta_1$ and $beta_2$ receptors, including their antihypertensive effect, cardiodepressant effect, effect on carbohydrate metabolism, or effect on bronchial $beta_2$ receptors. The characteristics of the individual beta blocker must therefore be borne in mind when considering likely interactions; for more details on the characteristics of different beta blockers, see Uses and Administration, p. 1316.3.

Drugs that enhance the antihypertensive effects of beta blockers, such as ACE inhibitors, calcium-channel blockers, and clonidine may be useful in controlling hypertension (but see Antihypertensives, p. 1322.1). Drugs that cause hypotension such as aldesleukin and general anaesthetics also enhance the antihypertensive effects of beta blockers while other drugs, for example NSAIDs, antagonise the antihypertensive effects.

Use of beta blockers with other cardiac depressants such as antiarrhythmics and rate-limiting calcium-channel blockers can precipitate bradycardia and heart block; the combination of intravenous verapamil and beta blockers should especially be avoided. Sotalol is particularly prone to interactions with other drugs affecting cardiac conduction (see p. 1499.2). Beta blockers may potentiate bradycardia due to digoxin.

The interaction between beta blockers and sympathomimetics is complex and depends on the selectivity of both drugs (see under Sympathomimetics, p. 1509.1). Patients taking beta blockers may have an exaggerated hypertensive response to adrenaline, caused by unopposed alpha-mediated vasoconstriction, while the bronchodilator effects are inhibited; the response to adrenaline given for anaphylaxis may also be reduced in patients on long-term treatment with beta blockers.

In diabetic patients beta blockers can reduce the response to insulin and oral hypoglycaemics through their effects on pancreatic beta receptors (see Effects on Carbohydrate Metabolism, p. 1319.2).

Pharmacokinetic interactions occur with drugs that alter the absorption or metabolism of beta blockers. Although these interactions may alter the beta blocker plasma concentration, they are not usually clinically significant since there is little association between plasma concentrations and therapeutic effect or toxicity and there are wide interindividual differences in steady-state plasma concentrations of beta blockers.

Drugs that reduce absorption include aluminium salts (but see also Antacids, below) and bile-acid binding resins such as colestyramine.

Metabolism of some beta blockers can be increased by drugs such as barbiturates and rifampicin and decreased with drugs such as cimetidine, erythromycin, fluvoxamine, and hydralazine. Drugs that alter hepatic blood flow also affect metabolism of some beta blockers. For example, cimetidine and hydralazine decrease hepatic blood flow and this contributes to the decreased hepatic clearance seen with these drugs. Drugs that influence hepatic metabolism affect beta blockers that are extensively metabolised, such as labetalol, propranolol, and timolol, while beta blockers that are excreted largely unchanged, for example atenolol and nadolol, are unaffected.

Since systemic absorption can occur after ocular use of beta blockers the possibility of similar interactions should be considered.

General references.
1. McDevitt DG. Interactions that matter: 12. β-adrenoceptor antagonists. *Prescribers' J* 1988; **28:** 25–30.
2. Blaufarb I, *et al.* β-Blockers: drug interactions of clinical significance. *Drug Safety* 1995; **13:** 359–70.
3. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittelforschung* 2003; **53:** 814–22.

Antacids. Bioavailability of metoprolol was increased when given with an antacid containing aluminium and magnesium salts, but the bioavailability of atenolol was reduced. Variable results on bioavailability of propranolol have been reported when aluminium hydroxide was given with propranolol.[1]

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.

Antiarrhythmics. Use of beta blockers with antiarrhythmic drugs and other drugs affecting cardiac conduction can precipitate bradycardia and heart block.

Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after starting beta-blocker therapy in patients receiving *amiodarone*.[1] Amiodarone was found to increase plasma-metoprolol concentrations in patients with cardiac arrhythmias, probably through inhibition of the cytochrome P450 isoenzyme CYP2D6 by the metabolite desethylamiodarone.[2] However, an analysis[3] of the CAMIAT and EMIAT studies in patients after myocardial infarction found that patients taking amiodarone and beta blockers had better outcomes than patients on one, or neither, drug, suggesting that any interaction may not always be detrimental. Use of *flecainide* with propranolol produced additive negative inotropic effects on the heart and increased serum concentrations of both drugs.[4] In a pharmacokinetic study in 12 healthy males, giving *propafenone* with propranolol resulted in increases in serum-propranolol concentrations but only modest enhancement of beta-blocking activity.[5] An increase in serum-metoprolol concentration has been reported after use of propafenone with metoprolol.[6] The metabolism of metoprolol may be decreased by *quinidine*.[7] Both quinidine and beta blockers have a negative inotropic action on the heart; bradycardia[8] and hypotension[9] have occurred in patients given quinidine with beta blockers.

For a report of reduced clearance of *disopyramide* by atenolol, see p. 1365.2.

The interactions of sotalol are discussed on p. 1499.2.

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.
2. Fukumoto K, *et al.* Effect of amiodarone on the serum concentration/dose ratio of metoprolol in patients with cardiac arrhythmia. *Drug Metab Pharmacokinet* 2006; **21:** 501–5.
3. Boutitie F, *et al.* Amiodarone interaction with β-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 1999; **99:** 2268–75.
4. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; **33:** 97–9.
5. Kowey PR, *et al.* Interaction between propranolol and propafenone in healthy volunteers. *J Clin Pharmacol* 1989; **29:** 512–17.
6. Wagner F, *et al.* Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* 1987; **24:** 213–20.
7. Leemann T, *et al.* Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. *Eur J Clin Pharmacol* 1986; **29:** 739–41.
8. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; **103:** 890–1.
9. Loon NR, *et al.* Orthostatic hypotension due to quinidine and propranolol. *Am J Med* 1986; **81:** 1101–4.

Antibacterials. Serum-atenolol concentrations in 6 healthy subjects were reduced by a 1-g oral dose of *ampicillin*.[1] Plasma concentrations of propranolol,[2] metoprolol,[3] celiprolol,[4] and bisoprolol[5] may be reduced by *rifampicin*. Licensed product information for *telithromycin* states that it causes increased plasma concentrations of metoprolol.

1. Schäfer-Korting M, *et al.* Atenolol interaction with aspirin, allopurinol, and ampicillin. *Clin Pharmacol Ther* 1983; **33:** 283–8.
2. Shaheen O, *et al.* Influence of debrisoquin phenotype on the inducibility of propranolol metabolism. *Clin Pharmacol Ther* 1989; **45:** 439–43.
3. Bennett PN, *et al.* Effect of rifampicin on metoprolol and antipyrine kinetics. *Br J Clin Pharmacol* 1982; **13:** 387–91.
4. Lilja JJ, *et al.* Rifampicin reduces plasma concentrations of celiprolol. *Eur J Clin Pharmacol* 2004; **59:** 819–24.
5. Kirch W, *et al.* Interaction of bisoprolol with cimetidine and rifampicin. *Eur J Clin Pharmacol* 1986; **31:** 59–62.

Anticoagulants. For the effect of beta blockers on the pharmacokinetics of some oral anticoagulants, see p. 1533.1.

Antidepressants. Bradycardia and heart block, occurring shortly after starting *fluoxetine* therapy, have been reported in patients receiving metoprolol[1] and propranolol.[2] Possible mechanisms include impaired conduction through the AV node and inhibition by fluoxetine of the oxidative metabolism of beta blockers. Use of fluoxetine also increased the plasma concentration of carvedilol in

patients with heart failure but no clinical effects were noted.[3]

Fluvoxamine and *paroxetine* inhibit oxidative metabolism; increased plasma concentrations of propranolol have been noted in patients also taking fluvoxamine, and of metoprolol[4,5] in those also taking paroxetine. The latter combination has resulted in complete AV block.[5]

For the use of pindolol in augmenting antidepressant therapy, see Psychiatric Disorders under Pindolol, p. 1470.2..

1. Walley T, *et al.* Interaction of metoprolol and fluoxetine. *Lancet* 1993; **341:** 967–8.
2. Drake WM, Gordon GD. Heart block in a patient on propranolol and fluoxetine. *Lancet* 1994; **343:** 425–6.
3. Graff DW, *et al.* Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and autonomic balance in heart failure patients. *J Clin Pharmacol* 2001; **41:** 97–106.
4. Goryachkina K, *et al.* Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI). *Eur J Clin Pharmacol* 2008; **64:** 275–82.
5. Onalan O, *et al.* Complete atrioventricular block associated with concomitant use of metoprolol and paroxetine. *Mayo Clin Proc* 2008; **83:** 595–9.

Antihypertensives. An enhanced antihypertensive effect is seen when other antihypertensives are given with beta blockers. However, some combinations should be avoided (see Calcium-channel Blockers, below). Beta blockers can potentiate the severe orthostatic hypotension that may follow the initial dose of alpha blockers such as prazosin and can exacerbate rebound hypertension after withdrawal of clonidine treatment (see Precautions, p. 1341.3).

Antimalarials. Antimalarials such as *halofantrine*, *mefloquine*, and *quinine* can cause cardiac conduction defects and caution is necessary if they are used with beta blockers. Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient taking propranolol.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Antimigraine drugs. For the effect of propranolol on *rizatriptan*, see p. 679.2.

See also under Ergotamine Tartrate, p. 675.3, for further interactions with drugs used in the treatment of migraine.

Antineoplastics. Licensed product information for *gefitinib* states that it has been reported to increase exposure to metoprolol by about 30%.

Anxiolytics and antipsychotics. Plasma concentrations of some beta blockers may be reduced by *barbiturates*.[1-3] Increased plasma-propranolol concentrations and bioavailability, and reduced metabolism, have been reported in healthy subjects also given *chlorpromazine*.[4]

See p. 1069.2 for the effect of beta blockers on the pharmacokinetics of some *benzodiazepines*.

1. Sotaniemi EA, *et al.* Plasma clearance of propranolol and sotalol and hepatic drug-metabolizing enzyme activity. *Clin Pharmacol Ther* 1979; **26:** 153–61.
2. Haglund K, *et al.* Influence of pentobarbital on metoprolol plasma levels. *Clin Pharmacol Ther* 1979; **26:** 326–9.
3. Seideman P, *et al.* Decreased plasma concentrations and clinical effects of alprenolol during combined treatment with pentobarbitone in hypertension. *Br J Clin Pharmacol* 1987; **23:** 267–71.
4. Vestal RE, *et al.* Inhibition of propranolol metabolism by chlorpromazine. *Clin Pharmacol Ther* 1979; **25:** 19–24.

Calcium-channel blockers. Use of calcium-channel blockers with beta blockers has resulted in hypotension, bradycardia, conduction defects, and heart failure.[1]

Beta blockers should be avoided if possible with rate-limiting calcium-channel blockers such as *verapamil* (see p. 1525.2) and *diltiazem*. Although they are reportedly safe with dihydropyridines such as *nifedipine*,[2] heart failure and severe hypotension have been reported (see under Nifedipine, p. 1453.3). Reported pharmacokinetic interactions include increased plasma concentrations of propranolol and of metoprolol with concurrent use of diltiazem[3] or verapamil,[1] and increased plasma concentrations of propranolol with *nicardipine*.[4]

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; **18:** 295–317.
2. Reid JL. First-line and combination treatment for hypertension. *Am J Med* 1989; **86** (suppl 4A): 2–5.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; **36:** 67–70.
4. Schoors DF, *et al.* Influence of nicardipine on the pharmacokinetics and pharmacodynamics of propranolol in healthy volunteers. *Br J Clin Pharmacol* 1990; **29:** 497–501.

Cardiac glycosides. For reference to interactions between beta blockers and *digoxin*, see p. 1357.2.

Ciclosporin. For the effect of carvedilol on plasma-ciclosporin concentrations, see p. 1957.3.

Ergot derivatives. *Nicergoline* enhanced the cardiac depressant action of propranolol in healthy subjects.[1]

For reports of enhanced vasoconstrictor action in patients taking *ergot alkaloids* and beta blockers, see p. 675.3.

1. Boismare F, *et al.* Potentiation by an alpha-adrenolytic agent, nicergoline, of the cardiac effects of propranolol. *Methods Find Exp Clin Pharmacol* 1983; **5:** 83–8.

Food. Studies in healthy subjects found that *grapefruit juice* greatly reduced the plasma concentration of celiprolol[1] and talinolol,[2] but had much less effect on acebutolol.[3] An effect on gastrointestinal absorption was suggested as the mechanism.[1,2] Studies with *orange juice* have found a similar effect on celiprolol[4] and, to a lesser extent, atenolol.[5]

1. Lilja JJ, *et al.* Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther* 2003; **73:** 192–8.
2. Schwarz UI, *et al.* Grapefruit juice ingestion significantly reduces talinolol bioavailability. *Clin Pharmacol Ther* 2005; **77:** 291–301.
3. Lilja JJ, *et al.* Effects of grapefruit juice on the pharmacokinetics of acebutolol. *Br J Clin Pharmacol* 2005; **60:** 659–63.
4. Lilja JJ, *et al.* Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. *Clin Pharmacol Ther* 2004; **75:** 184–90.
5. Lilja JJ, *et al.* Effects of orange juice on the pharmacokinetics of atenolol. *Eur J Clin Pharmacol* 2005; **61** 337–40.

General anaesthetics. Beta blockers are usually continued perioperatively although the anaesthetist must be informed of their use (see Precautions, p. 1320.3). However, the hypotensive effects of beta blockers may be potentiated by general anaesthetics, and anaesthetics that cause myocardial depression, such as *ether*, *cyclopropane*, and *trichloroethylene* should preferably be avoided.

Histamine. For the effect of beta blockers, including propranolol, on histamine given exogenously, see p. 2525.3.

Histamine H_2-antagonists. Plasma concentrations of propranolol and metoprolol may be increased by *cimetidine*;[1] pharmacokinetic studies indicate that cimetidine exerts its effect by reducing hepatic blood flow and impairing beta blocker metabolism. Cimetidine has been reported to increase the bioavailability of labetalol,[1] and to increase the systemic effects of timolol eye drops.[2]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.
2. Ishii Y, *et al.* Drug interaction between cimetidine and timolol ophthalmic solution: effect on heart rate and intraocular pressure in healthy Japanese volunteers. *J Clin Pharmacol* 2000; **40:** 193–9.

Local anaesthetics. For details of the effect of beta blockers in reducing the clearance of *bupivacaine*, see p. 1986.1, and of *lidocaine*, see p. 1995.1. For the effects of propranolol with *cocaine*, see p. 1990.3.

Neuromuscular blockers. For the effects of beta blockers on the activity of neuromuscular blockers, see under Atracurium, p. 2032.2.

NSAIDs. The antihypertensive effect of beta blockers may be impaired by some NSAIDs, possibly due to their inhibition of renal synthesis of vasodilating prostaglandins. This interaction probably occurs with all beta blockers but may not occur with all NSAIDs. For example, *sulindac* appears to affect blood pressure control less than *indometacin*.[1]

A randomised study[2] in 12 healthy subjects found that *celecoxib* significantly inhibited the metabolism of metoprolol by the cytochrome P450 isoenzyme CYP2D6.

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; **18:** 295–317.
2. Werner U, *et al.* Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clin Pharmacol Ther* 2003; **74:** 130–7.

Opioid analgesics. Bioavailability of propranolol and metoprolol was increased in subjects given *dextropropoxyphene*;[1] dextropropoxyphene is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and was reported[2] to increase serum concentrations of metoprolol, a CYP2D6 substrate, in a patient given both drugs, resulting in bradycardia. Intravenous *morphine* may increase serum concentrations of esmolol.[3]

1. Lundborg P, *et al.* The effect of propoxyphene pretreatment on the disposition of metoprolol and propranolol. *Clin Pharmacol Ther* 1981; **29:** 263–4.
2. Marraffa JM, *et al.* Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. *Clin Pharmacol Ther* 2006; **79:** 282–6.
3. Lowenthal DT, *et al.* Clinical pharmacology, pharmacodynamics and interactions with esmolol. *Am J Cardiol* 1985; **56:** 14F–17F.

Oral contraceptives. Plasma-metoprolol concentrations were increased in some women taking oral contraceptives.[1]

1. Kendall MJ, *et al.* Metoprolol pharmacokinetics and the oral contraceptive pill. *Br J Clin Pharmacol* 1982; **14:** 120–2.

Parasympathomimetics. For the effect of beta blockers on the response to *anticholinesterases*, see p. 689.1.

Thyroid drugs. For a discussion of thyroid status and its effect on plasma-propranolol concentrations and the effects of propranolol on *thyroid hormone* metabolism, see p. 2341.3.

Xanthines. For details of reduced *theophylline* clearance in patients receiving some beta blockers, see p. 1235.2.

Pharmacokinetics

Beta blockers differ widely in their pharmacokinetic properties. Differences in lipid solubility contribute to these varying pharmacokinetic properties.

Beta blockers with high lipid solubility (lipophilic beta blockers) include alprenolol and propranolol.

Hydrophilic beta blockers, such as atenolol and nadolol, have low lipid solubility and when compared with lipophilic beta blockers generally:

- tend to be less readily absorbed from the gastrointestinal tract
- are less extensively metabolised
- have low plasma-protein binding
- have relatively long plasma half-lives
- cross the blood-brain barrier less readily

Beta blockers cross the placenta and most are known to distribute into breast milk.

There is no clear correlation between plasma concentrations of beta blockers and therapeutic activity, especially when the beta blocker undergoes metabolism to active metabolites.

Betaxolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ALO-1401-02; Betaksolol Hidroklorür; Betaksololihydrokloridi; Betaksololio hidrochloridas; Bétaxolol, Chlorhydrate de; Betaxolol, hidrocloruro de; Betaxolol-hidroklorid; Betaxolol-hydrochlorid; Betaxolol-hydrochlorid; Betaxololhydroklorid; Betaxololi hydrochloridum; Hidrocloruro de betaxolol; SL-75212-10; Бетаксолола Гидрохлорид.

1-{4-[2-(Cyclopropylmethoxy)ethyl]phenoxy}-3-isopropylaminopropan-2-ol hydrochloride.

$C_{18}H_{29}NO_3$,HCl=343.9

CAS — 63659-18-7 (betaxolol); 63659-19-8 (betaxolol hydrochloride).

ATC — C07AB05; S01ED02.

ATC Vet — QC07AB05; QS01ED02.

UNII — 6X97D2XT0O.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Betaxolol Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in dichloromethane. Protect from light.

USP 36: (Betaxolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. pH of a 2% solution in water is between 4.5 and 6.5. Store in airtight containers.

Uses and Administration

Betaxolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and to have little membrane-stabilising activity.

Betaxolol is used as the hydrochloride in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and glaucoma (p. 1999.1).

In **hypertension** betaxolol hydrochloride is given in an initial oral dose of 10 mg once daily, which may be doubled if necessary after 1 to 2 weeks. Doses above 20 mg daily do not usually give additional benefit, but up to 40 mg daily has been tolerated. Similar doses are used in **angina pectoris**.

An initial dose of 5 mg daily is suggested for elderly patients. Reduced dosages should also be used in patients with severe renal impairment (see below).

Eye drops containing the equivalent of 0.25 or 0.5% betaxolol as the hydrochloride are instilled twice daily to reduce raised intra-ocular pressure in ocular hypertension and open-angle **glaucoma**.

General references.

1. Buckley MM-T, *et al.* Ocular betaxolol: a review of its pharmacological properties, and therapeutic efficacy in glaucoma and ocular hypertension. *Drugs* 1990; **40:** 75–90.

Administration in children. Betaxolol hydrochloride eye drops can be used in children for the treatment of glaucoma; the *BNFC* suggests that drops can be applied in children as in adults (see Uses and Administration, above).

Administration in renal impairment. The clearance of betaxolol is reduced in patients with renal impairment and the dose may therefore need to be reduced. Licensed US product information recommends an initial dose of betaxolol hydrochloride 5 mg daily in patients with severe

renal impairment or on dialysis; the dose may be increased by 5 mg every 2 weeks, to a maximum of 20 mg daily.

Speech disorders. A 50-year-old man who had stuttered since childhood obtained striking improvement in his stuttering when he was given betaxolol 20 mg daily for essential hypertension.[1]

1. Burris JF, *et al.* Betaxolol and stuttering. *Lancet* 1990; **335:** 223.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies betaxolol as possibly porphyrinogenic when used systematically; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. Eye drops of betaxolol are classified as not porphyrinogenic.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Betaxolol is completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism, resulting in a high oral bioavailability of about 90%. It has high lipid solubility. Betaxolol is about 50% bound to plasma proteins. It crosses the placenta and is distributed into breast milk where higher concentrations have been achieved than in maternal blood. The plasma elimination half-life of betaxolol ranges from 14 to 22 hours. The primary route of elimination is via hepatic metabolism and urinary excretion; only about 15% is excreted in the urine as unchanged drug.

Pregnancy and breast feeding. The pharmacokinetics of betaxolol were investigated in the perinatal period in 28 pregnant hypertensive patients receiving doses of 10 to 40 mg daily.[1] Pharmacokinetic values were similar to those seen in non-pregnant patients. Umbilical-cord concentrations were similar to maternal blood concentrations and showed a negative correlation between concentration in cord blood and timing of the last dose of betaxolol. Thus the betaxolol concentration in neonates can be considerably reduced by stopping maternal drug use 16 to 18 hours before birth. The blood-betaxolol half-life in the neonates ranged from 14.8 to 38.5 hours. The mean apparent half-life in infants with gestational age less than 36 weeks was about 32% higher than in full-term neonates. Betaxolol concentrations in milk and/or colostrum were determined in 3 mothers. In all samples the milk-to-blood ratio was greater than 2.

1. Morselli PL, *et al.* Placental transfer and perinatal pharmacokinetics of betaxolol. *Eur J Clin Pharmacol* 1990; **38:** 477–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Betasel; Tonobexol; ***Austral.***: Betoptic; Betoquin; ***Austria***: Betoptic; ***Belg.***: Betoptic; Kerlone; ***Braz.***: Betoptic; Presmin; Visoptic; ***Canad.***: Betoptic; ***Chile***: Bemaz†; Beof; Betoptic; BTX Ofteno; ***China***: Betoptic (贝特舒); Kerlone (卡尔仑); ***Cz.***: Betalmic; Betamed; Betaxa; Betoptic; Lokren; ***Denm.***: Betoptic; ***Fin.***: Betoptic; Kerlon; ***Fr.***: Betoptic; Kerlone; ***Ger.***: Betoptima; Kerlone; ***Gr.***: Armament; Betoptic; Eifel; Kerlone; Pertaxol; ***Hong Kong***: Betoptic; ***Hung.***: Betoptic; Lokren; ***India***: Bulol; Glucoptic; Iobet; Ocubeta; Optipres; ***Indon.***: Betoptima; Optibet; ***Irl.***: Betoptic; ***Israel***: Betoptic; ***Ital.***: Betoptic; Kerlon; ***Jpn***: Kerlong; ***Malaysia***: Axoptic; Betac; Betoptic; Kerlone; ***Mex.***: Betoptic; BTX-HA Ofteno; ***Neth.***: Betoptic; Kerlon; ***Norw.***: Betoptic; ***NZ***: Betoptic; ***Philipp.***: Betoptic; Kerlone; Oxol; ***Pol.***: Betabion†; Betoptic; Lokren; Optibetol; ***Port.***: Bertocil; Betoptic; Davixolol†; ***Rus.***: Betac (Betak); Betalmic (Беталмик); Betoftan (Бетофтан); Betoptic (Бетоптик); Lokren (Локрен); Xonef (Ксонеф); ***S.Afr.***: Betoptic; ***Singapore***: Acculol; Betac; Betoptic; Kerlone; ***Spain***: Betoptic; ***Swed.***: Betoptic; ***Switz.***: Betoptic; ***Thai.***: Betoptic; ***Turk.***: Betoptic; Eifel; ***UK***: Betoptic; ***Ukr.***: Betacor (Бетакор); Betoptic (Бетоптик S); Lokren (Локрен); ***USA***: Betoptic; Kerlone†; ***Venez.***: Betaxol; Betoptic.

Pharmacopoeial Preparations

BP 2014: Betaxolol Eye Drops, Solution; Betaxolol Eye Drops, Suspension;

USP 36: Betaxolol Ophthalmic Solution; Betaxolol Tablets.

Bevantolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Bévantolol, Chlorhydrate de; Bevantolol, hidrocloruro de; Bevantololhydroklorid; Bevantololi Hydrochloridum; Bevantololihydrokloridi; CI-775; Hidrocloruro de bevantolol; NC-1400; Бевантолола Гидрохлорид.

1-(3,4-Dimethoxyphenethylamino)-3-*m*-tolyloxypropan-2-ol hydrochloride.

$C_{20}H_{27}NO_4$,HCl=381.9

CAS — 59170-23-9 (bevantolol); 42864-78-8 (bevantolol hydrochloride).

ATC — C07AB06.

ATC Vet — QC07AB06.

UNII — 4VB9HU07BC.

Profile

Bevantolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack significant intrinsic sympathomimetic activity but has weak membrane-stabilising properties and also has vasodilator activity. It has been given orally as the hydrochloride in the management of hypertension and angina pectoris.

References.

1. Frishman WH, *et al.* Bevantolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1988; **35:** 1–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Calvan (卡理稳); ***Jpn***: Calvan.

Bezafibrate *(BAN, USAN, rINN)*

Betsafibraatti; Bezafibrat; Bezafibrát; Bezafibratas; Bézafibrate; Bezafibrato; Bezafibratum; BM-15075; LO-44; Безафибрат.

2-[4-(2-*p*-Chlorobenzamidoethyl)phenoxy]-2-methylpropionic acid.

$C_{19}H_{20}ClNO_4$=361.8

CAS — 41859-67-0.

ATC — C10AB02.

ATC Vet — QC10AB02.

UNII — Y9449Q51XH.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Bezafibrate). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dimethylformamide; it dissolves in dilute solutions of alkali hydroxides.

Uses and Administration

Bezafibrate, a fibric acid derivative, is a lipid regulating drug. It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. Bezafibrate and other fibrates reduce triglycerides by reducing the concentration of very-low-density lipoprotein (VLDL). They reduce low-density lipoprotein (LDL)-cholesterol to a lesser extent, although the effect is variable, and may also increase high-density lipoprotein (HDL)-cholesterol. Although evidence that this leads to a reduction in cardiovascular events is less good than for statins, some fibrates may have a role in cardiovascular risk reduction (see below).

Bezafibrate is given in a usual oral dose of 200 mg three times daily taken with or after food; gastrointestinal disturbances may be reduced in susceptible patients by increasing the dose gradually over 5 to 7 days; 200 mg twice daily may occasionally be adequate for maintenance particularly in the treatment of hypertriglyceridaemia. A modified-release tablet is also available and is given as a single daily dose of 400 mg.

The dose of bezafibrate should be reduced in patients with renal impairment (see below). See also below for doses in children.

General reviews.

1. Goa KL, *et al.* Bezafibrate: an update of its pharmacology and use in the management of dyslipidaemia. *Drugs* 1996; **52:** 725–53.
2. Goldenberg I, *et al.* Update on the use of fibrates: focus on bezafibrate. *VascHealth Risk Manag* 2008; **4:** 131–41.

Action. Bezafibrate is a typical member of the fibric acid derivative group of drugs (the fibrates) used in the treatment of hyperlipidaemias (p. 1248.1). One of the primary actions of the fibrates is to promote the catabolism of triglyceride-rich lipoproteins, in particular very-low-density lipoproteins (VLDL), apparently mediated by an enhanced activity of lipoprotein lipase.[1] They may also interfere with the synthesis of VLDL, possibly by inhibiting hepatic acetyl coenzyme A carboxylase. The effect of fibrates on low-density lipoprotein (LDL)-cholesterol depends on the overall lipoprotein status of the patient but concentrations tend to decrease if high at baseline and increase if low at baseline. High-density lipoprotein (HDL)-cholesterol concentrations are increased, although there have been a few reports of unexpected falls in HDL-cholesterol with bezafibrate[2,3] and ciprofibrate.[4,5]

Fibrates have three actions on sterol metabolism:[1] they inhibit the synthesis of cholesterol, they inhibit the synthesis of bile acids, and they enhance the secretion of cholesterol in bile. It is these latter two effects which are responsible for the raised cholesterol saturation of bile, which may lead to the formation of gallstones in some patients (see Gallstones, under Adverse Effects, p. 1325.1).

The effects of fibrates are mediated by their agonist action at peroxisome proliferator-activated receptors (PPARs).[6,7] Fibrates are agonists of PPAR-α, which plays an important role in fatty acid metabolism; some, such as bezafibrate, may also activate other receptors including PPAR-γ (which plays a role in glucose homoeostasis).[7]

1. Grundy SM, Vega GL. Fibric acids: effects on lipids and lipoprotein metabolism. *Am J Med* 1987; **83** (suppl 5B): 9–20.
2. Capps NE. Lipid profiles on fibric-acid derivatives. *Lancet* 1994; **344:** 684–5.
3. McLeod AJ, *et al.* Abnormal lipid profiles on fibrate derivatives. *Lancet* 1996; **347:** 261.
4. Chandler HA, Batchelor AJ. Ciprofibrate and lipid profile. *Lancet* 1994; **344:** 128–9.
5. McLeod AJ, *et al.* Ciprofibrate and lipid profile. *Lancet* 1994; **344:** 955.
6. Fruchart J-C, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today* 2006; **42:** 39–64.
7. Robinson JG. Should we use PPAR agonists to reduce cardiovascular risk? *PPAR Res* 2008; **2008:** 891425.

Administration in children. Bezafibrate is not licensed in the UK for use in children, and the *BNFC* considers that, given the limited evidence supporting its use in children, bezafibrate should be used only when a statin or bile-acid binding drug is unsuitable. For the treatment of hyperlipidaemias including familial hypercholesterolaemia, it suggests that children aged 10 years or over may be given bezafibrate in an oral dose of 200 mg once daily, adjusted according to response to a maximum of 200 mg three times daily.

Administration in renal impairment. Bezafibrate is mainly excreted in the urine and dosage alterations may be necessary in patients with renal impairment; fibrates may also impair renal function (see Effects on the Kidneys under Adverse Effects, p. 1324.3). Modified-release preparations are contra-indicated in patients with creatinine clearance (CC) below 60 mL/minute and the dosage of conventional-release formulations should be reduced depending on CC, as follows:

- CC 40 to 60 mL/minute: 400 mg daily
- CC 15 to 40 mL/minute: 200 mg daily or on alternate days
- CC less than 15 mL/minute unless on dialysis: contra-indicated
- dialysis patients: 200 mg every 3 days, with careful monitoring

In a study in patients with renal impairment[1] the half-life of bezafibrate was reported to be prolonged to 4.6 hours in 3 patients with CC greater than 40 mL/minute, 7.8 hours in 8 patients with CC of 20 to 40 mL/minute, and 20.1 hours in a patient with CC of 13 mL/minute.

1. Anderson P, Norbeck H-E. Clinical pharmacokinetics of bezafibrate in patients with impaired renal function. *Eur J Clin Pharmacol* 1981; **21:** 209–14.

Biliary-tract disorders. Bezafibrate may be able to prevent damage to the biliary tract[1] (perhaps by modulating phospholipid secretion via an action at the peroxisome proliferator-activated receptor-α (PPAR-α)). It has been used[2,3] with ursodeoxycholic acid in the treatment of primary biliary cirrhosis (p. 2638.3); fenofibrate has been tried similarly.[4] Bezafibrate has also been tried in primary sclerosing cholangitis.[5]

1. Nakamuta M, *et al.* Therapeutic effect of bezafibrate against biliary damage: a study of phospholipid secretion via the PPARα-MDR3 pathway. *Int J Clin Pharmacol Ther* 2010; **48:** 22–8.
2. Iwasaki S, *et al.* Study Group of Intractable Liver Diseases for Research on a Specific Disease, Health Science Research Grant, Ministry of Health, Labour and Welfare of Japan. The efficacy of ursodeoxycholic acid and bezafibrate combination therapy for primary biliary cirrhosis: a prospective, multicenter study. *Hepatol Res* 2008; **38:** 557–64.
3. Hazzan R, Tur-Kaspa R. Bezafibrate treatment of primary biliary cirrhosis following incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2010; **44:** 371–3.
4. Liberopoulos EN, *et al.* Fenofibrate in primary biliary cirrhosis: a pilot study. *Open Cardiovasc Med J* 2010; **4:** 120–6.
5. Mizuno S, *et al.* Bezafibrate for the treatment of primary sclerosing cholangitis. *J Gastroenterol* 2010; **45:** 758–62.

Cardiovascular risk reduction. Lipid lowering therapy has an important role in patients at risk of cardiovascular disease (p. 1246.1). Although the evidence is less good than for statins, several studies have shown that fibrates may

reduce both the progression of atherosclerosis and the incidence of cardiovascular events.[1]

In the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)[2,3] treatment with bezafibrate for 5 years in young men (less than 45 years of age) after myocardial infarction resulted in fewer coronary events and slowed the progression of focal coronary atherosclerosis when compared with placebo. However, in older men with peripheral vascular disease,[4] bezafibrate had no effect on the incidence of coronary events and stroke together, although the severity of intermittent claudication was reduced and, in men under 65 years, there were fewer non-fatal coronary events. In the Diabetes Atherosclerosis Intervention Study (DAIS),[5] fenofibrate reduced the angiographic progression of coronary atherosclerosis in type 2 diabetics, and there were also fewer clinical events in those receiving fenofibrate. However, another study in type 2 diabetics, the FIELD study,[6] found no reduction in the risk of major coronary events with fenofibrate, although there were fewer non-fatal myocardial infarctions and revascularisations. A meta-analysis[7] of studies including type 2 diabetics concluded that fibrates reduce the incidence of cardiovascular events, but the effect on mortality was not significant.

The best evidence for a reduction in cardiovascular events is for gemfibrozil. The Helsinki Heart Study[8] assessed gemfibrozil for the primary prevention of ischaemic heart disease in 4081 middle-aged men with hyperlipidaemia. There was an overall reduction of 34% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the greatest reduction seen during years 3 to 5. Follow-up for a further 3.5 years[9] suggested that long-term treatment with gemfibrozil seemed to postpone coronary events for about 5 years. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[10] assessed gemfibrozil for the secondary prevention of ischaemic heart disease in 2531 older men (mean age 64 years) whose primary lipid abnormality was a low HDL-cholesterol level. There was an overall reduction of 22% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the beneficial effects of gemfibrozil becoming apparent about 2 years after randomisation. There was also a reduction in the incidence of stroke.[11]

1. Després J-P, *et al.* Role of fibric acid derivatives in the management of risk factors for coronary heart disease. *Drugs* 2004; **64:** 2177–98.
2. Ericsson C-G, *et al.* Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet* 1996; **347:** 849–53.
3. Ericsson C-G, *et al.* Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)). *Am J Cardiol* 1997; **80:** 1125–9.
4. Meade T, *et al.* Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002; **325:** 1139–43.
5. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001; **357:** 905–910. Correction. *ibid.;* 1890.
6. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.
7. Allemann S, *et al.* Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *Curr Med Res Opin* 2006; **22:** 617–23.
8. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
9. Heinonen OP, *et al.* The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. *J Intern Med* 1994; **235:** 41–9.
10. Bloomfield Rubins H, *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999; **341:** 410–18.
11. Bloomfield Rubins H, *et al.* Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation* 2001; **103:** 2828–33.

Dementia. For reference to a possible reduction in the incidence of dementia associated with lipid regulating drugs, including fibrates, see under Uses of Simvastatin, p. 1491.2.

Diabetic complications. In diabetic patients, fibrates may have a role in cardiovascular risk reduction (see p. 1323.3) and there has been interest in their possible effects on microvascular diabetic complications (p. 462.2). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, designed to assess the effects of fenofibrate on cardiovascular outcomes in type 2 diabetics, included microvascular complications as tertiary outcomes; patients were given fenofibrate or placebo for about 5 years. There was evidence for a reduction in the onset of markers of nephropathy (p. 465.1) such as microalbuminuria or progression to macroalbuminuria, and more regression of albuminuria, in patients given fenofibrate.[1,2] The Diabetes Atherosclerosis Intervention Study (DAIS) also showed reduced progression to microalbuminuria in patients given fenofibrate.[3] Additionally from the FIELD study, the need for first laser treatment of retinopathy (p. 464.2) was reduced in the fenofibrate group.[4] Fenofibrate was also associated with a reduction in the risk of first minor amputation in patients without documented large vessel (atherosclerotic) disease, but for those with large vessel disease the risk of either minor or major amputation was not affected.[5] These effects on microvascular complications in the FIELD study did not seem to be related to plasma-lipid concentrations. Results of a retrospective cohort study in patients treated with bezafibrate compared with patients given other fibrates have also suggested that bezafibrate might have some benefit in preventing or delaying progression of diabetes mellitus itself.[6]

1. The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.
2. Davis TM, *et al.* Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 2011; **54:** 280–90.
3. Ansquer J-C, *et al.* Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis* 2005; **45:** 485–93.
4. Keech AC, *et al.* The FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007; **370:** 1687–97.
5. Rajamani K, *et al.* The FIELD Study Investigators. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* 2009; **373:** 1780–8.
6. Flory JH, *et al.* Antidiabetic action of bezafibrate in a large observational database. *Diabetes Care* 2009; **32:** 547–51.

Adverse Effects and Precautions

The commonest adverse effects of bezafibrate therapy are gastrointestinal disturbances including anorexia, nausea, and gastric discomfort. Other adverse effects reported to occur less frequently include headache, dizziness, vertigo, fatigue, skin rashes, pruritus, photosensitivity, alopecia, impotence, anaemia, leucopenia, and thrombocytopenia. Raised serum-aminotransferase concentrations have occasionally been reported. Elevated creatine phosphokinase concentrations during bezafibrate therapy may be associated with a syndrome of myositis, myopathy, and rarely rhabdomyolysis; patients with hypoalbuminaemia resulting from nephrotic syndrome or with renal impairment may be at increased risk. Bezafibrate should not be given with statins in patients with risk factors for myopathy. Bezafibrate may increase the lithogenic index, and there have been isolated reports of gallstones, although the risk from fibrates as a class is unclear (see Gallstones, p. 1325.1).

Bezafibrate should not be given to patients with severe hepatic impairment or significant liver disease, gallstones or gallbladder disorders, or hypoalbuminaemic states such as nephrotic syndrome. It should be used with caution in renal impairment and is contra-indicated if creatinine clearance is below 15 mL/minute unless the patient is on dialysis (see under Uses and Administration, p. 1323.3).

Reviews.
1. Davidson MH, *et al.* Safety considerations with fibrate therapy. *Am J Cardiol* 2007; **99**(Issue 6 suppl 1): 3C–18C.
2. Florentin M, *et al.* Fibrate-associated adverse effects beyond muscle and liver toxicity. *Curr Pharm Des* 2008; **14:** 574–87.

Effects on glucose metabolism. Use of fibrates in diabetic patients has generally been reported to either improve[1-3] or have no effect[4-6] on insulin sensitivity and glucose metabolism, and they are considered a suitable treatment for type 2 diabetics with hypertriglyceridaemia.[7] There is also some evidence that fibrates may reduce the incidence or delay the onset of diabetes in patients with obesity[8] or impaired glucose tolerance.[9] However, there has been a report[10] of recurrent hypoglycaemia in a type 2 diabetic when gemfibrozil was added to high-dose insulin therapy although eventually a reduced insulin dosage, with fibrate therapy, produced good glucose control. Gemfibrozil is contra-indicated in patients receiving repaglinide due to the risk of severe hypoglycaemia (see p. 496.1). Conversely, a study in 20 diabetic patients[11] given gemfibrozil reported a slight increase in requirements for antidiabetic therapy (oral hypoglycaemics or insulin) in 9 and a decrease in 1.

1. Ogawa S, *et al.* Bezafibrate reduces blood glucose in type 2 diabetes mellitus. *Metabolism* 2000; **49:** 331–4.
2. Jones IR, *et al.* Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. *Diabetes Care* 1990; **13:** 855–63.
3. Notarbartolo A, *et al.* Effects of gemfibrozil in hyperlipidemic patients with or without diabetes. *Curr Ther Res* 1993; **53:** 381–93.
4. Leaf DA, *et al.* The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. *JAMA* 1989; **262:** 3154–60.
5. Pagani A, *et al.* Effect of short-term gemfibrozil administration on glucose metabolism and insulin secretion in non-insulin-dependent diabetics. *Curr Ther Res* 1989; **45:** 14–20.
6. Hernández-Mijares A, *et al.* Ciprofibrate effects on carbohydrate and lipid metabolism in type 2 diabetes mellitus subjects. *Nutr Metab Cardiovasc Dis* 2000; **10:** 1–6.
7. Buse JB, *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007; **115:** 114–26. Also available at: http://circ.ahajournals.org/cgi/reprint/115/1/114.pdf (accessed 28/08/09) Also published in *Diabetes Care* 2007; **30:** 162–72. Also available at: http://care.diabetesjournals.org/content/30/1/162.full.pdf (accessed 28/08/09)
8. Tenenbaum A, *et al.* Effect of bezafibrate on incidence of type 2 diabetes mellitus in obese patients. *Eur Heart J* 2005; **26:** 2032–8.
9. Tenenbaum A, *et al.* Peroxisome proliferator-activated receptor ligand bezafibrate for prevention of type 2 diabetes mellitus in patients with coronary artery disease. *Circulation* 2004; **109:** 2197–2202.
10. Klein J, *et al.* Recurrent hypoglycaemic episodes in a patient with type 2 diabetes under fibrate therapy. *J Diabetes Complications* 2002; **16:** 246–8.
11. Konttinen A, *et al.* The effect of gemfibrozil on serum lipids in diabetic patients. *Ann Clin Res* 1979; **11:** 240–5.

Effects on the kidneys. Small increases in creatinine concentration are common during treatment with bezafibrate and have also been reported with other fibrates,[1,2] although possibly not with gemfibrozil. Such increases, which are not necessarily associated with changes in renal function, are reversible on stopping the drug, although serum-creatinine values may take several weeks to return to baseline.[2] There have also been reports of acute renal failure associated with treatment with bezafibrate,[3] and with clofibrate,[4,5] and an accelerated decline in renal function has been reported with bezafibrate in patients with chronic renal failure.[6] Renal failure may also occur due to rhabdomyolysis in patients receiving fibrates, including gemfibrozil (see Effects on Skeletal Muscle, p. 1325.1).

1. Broeders N, *et al.* Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? *Nephrol Dial Transplant* 2000; **15:** 1993–9.
2. Sica DA. Fibrate therapy and renal function. *Curr Atheroscler Rep* 2009; **11:** 338–42.
3. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; **341:** 371.
4. Dosa S, *et al.* Acute-on-chronic renal failure precipitated by clofibrate. *Lancet* 1976; **i:** 250.
5. Cumming A. Acute renal failure and interstitial nephritis after clofibrate treatment. *BMJ* 1980; **281:** 1529–30.
6. Williams AJ, *et al.* The short term effects of bezafibrate on the hypertriglyceridaemia of moderate to severe uraemia. *Br J Clin Pharmacol* 1984; **18:** 361–7.

Effects on the nervous system. Adverse effects on the peripheral nervous system have been reported with fibrates. Peripheral neuropathy has been reported[1] with bezafibrate, and was substantiated by nerve conduction studies. There have also been reports of peripheral neuropathy with clofibrate,[2] and with fenofibrate,[3] which resolved when therapy was withdrawn. In addition, by 1993, the Adverse Drug Reactions Advisory Committee in Australia had received reports of paraesthesia occurring in 6 patients in association with gemfibrozil treatment.[4]

1. Ellis CJ, *et al.* Peripheral neuropathy with bezafibrate. *BMJ* 1994; **309:** 929.
2. Gabriel R, Pearce JMS. Clofibrate-induced myopathy and neuropathy. *Lancet* 1976; **ii:** 906.
3. Corcia P, *et al.* Severe toxic neuropathy due to fibrates. *J Neurol Neurosurg Psychiatry* 1999; **66:** 410.
4. Anonymous. Paraesthesia and neuropathy with hypolipidaemic agents. *Aust Adverse Drug React Bull* 1993; **12:** 6.

Effects on the pancreas. Acute pancreatitis has been reported[1] in a patient receiving bezafibrate, and recurred on 2 occasions when bezafibrate was restarted. There has also been a report[2] of acute pancreatitis in a patient receiving both fenofibrate and simvastatin, although simvastatin was considered more likely to be responsible. An increased incidence of pancreatitis was also reported with fenofibrate in the FIELD study,[3] although the number of cases was small.

1. Gang N, *et al.* Relapsing acute pancreatitis induced by re-exposure to the cholesterol lowering agent bezafibrate. *Am J Gastroenterol* 1999; **94:** 3626–8.
2. McDonald KB, *et al.* Pancreatitis associated with simvastatin plus fenofibrate. *Ann Pharmacother* 2002; **36:** 275–9.
3. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.

Effects on sexual function. Sexual dysfunction has occurred with some fibrates. *Erectile dysfunction* and *loss of libido* has been reported in 3 patients[1-3] during gemfibrozil treatment. In 2 of the men[1,2] bezafibrate did not produce this adverse effect. The UK CSM was reported to be aware of a further 6 cases.[2] Of a further 3 cases of erectile dysfunction associated with gemfibrozil reported from Spain, 1 patient had previously reacted similarly to clofibrate.[4] A systematic review,[5] including these and other reports, supported the conclusion that fibrates could cause erectile dysfunction.

Gynaecomastia was reported[6] in a 56-year-old man receiving fenofibrate and recurred on rechallenge; there were no other effects on sexual function.

1. Pizarro S, *et al.* Geinfibrozil-induced impotence. *Lancet* 1990; **336:** 1135.
2. Bain SC, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; **336:** 1389.
3. Bharani A. Sexual dysfunction after gemfibrozil. *BMJ* 1992; **305:** 693.
4. Figueras A, *et al.* Gemfibrozil-induced impotence. *Ann Pharmacother* 1993; **27:** 982.
5. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; **19:** 95–8.
6. Gardette V, *et al.* Gynecomastia associated with fenofibrate. *Ann Pharmacother* 2007; **41:** 508–11.

Effects on skeletal muscle. Muscle disorders including myositis and myopathy are well known to occur with lipid regulating drugs such as fibrates.[1] Rhabdomyolysis, presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, has also been reported but appears to be rare. Patients with renal impairment, and possibly with hypothyroidism, may be at increased risk of muscle toxicity. The UK CSM has advised[1] that patients treated with fibrates should consult their doctor if they develop muscle pain, tenderness, or weakness, and treatment should be stopped if muscle toxicity is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising.

Other lipid regulating drugs, particularly the statins, have also been associated with myopathy and the risk of muscle toxicity is increased if fibrates and statins are taken together (see Lipid Regulating Drugs under Interactions of Simvastatin, p. 1495.3); combination therapy may be appropriate in some patients but careful monitoring is required.[2]

1. CSM/MCA. Rhabdomyolysis associated with lipid-lowering drugs. *Current Problems* 1995; **21:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; **35:** 908–917.

Gallstones. Fibrates, including fenofibrate[1-3] and gemfibrozil[4] have been reported to increase indices of bile lithogenicity, and some studies[5,6] have suggested an increased risk of gallstones in patients receiving fibrates. However, in the Helsinki Heart Study[7] no significant increase in gallstone operations was reported among 2051 patients taking gemfibrozil compared with 2030 taking placebo, although a follow-up study[8] reported that cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period.

1. Brown WV. Treatment of hypercholesterolaemia with fenofibrate: a review. *Curr Med Res Opin* 1989; **11:** 321–30.
2. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med* 1987; **83** (suppl 5B): 26–36.
3. Palmer RH. Effects of fibric acid derivatives on biliary lipid composition. *Am J Med* 1987; **83** (suppl 5B): 37–43.
4. Leiss O, *et al.* Effect of gemfibrozil on biliary lipid metabolism in normolipemic subjects. *Metabolism* 1985; **34:** 74–82.
5. Mamdani MM, *et al.* Is there an association between lipid-lowering drugs and cholecystectomy? *Am J Med* 2000; **108:** 418–21.
6. Caroli-Bosc F-X, *et al.* Role of fibrates and HMG-CoA reductase inhibitors in gallstone formation: epidemiological study in an unselected population. *Dig Dis Sci* 2001; **46:** 540–4.
7. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
8. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J InternMed* 1994; **235:** 31–9.

Headache. Severe recurrent headaches have been reported[1] in a patient receiving bezafibrate. The headaches started about 24 hours after therapy with bezafibrate began, and recurred about 1 hour after each dose. Headaches occurred 30 to 90 minutes after each dose of gemfibrozil in 2 patients.[2,3] In both patients, the headaches were accompanied by dry mouth, and in 1 also by blurred vision. The headaches stopped when gemfibrozil was withdrawn and recurred one week after re-exposure.

1. Hodgetts TJ, Tunnicliffe C. Bezafibrate-induced headache. *Lancet* 1989; **i:** 163.
2. Arellano F, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; **i:** 705.
3. Alvarez-Sabin J, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; **ii:** 1246.

Hyperhomocysteinaemia. Hyperhomocysteinaemia has been associated with an increased risk for cardiovascular disease. Small studies have found that both bezafibrate[1,2] and fenofibrate[1,3] increase plasma-homocysteine concentrations, although the clinical significance of this is not clear.[4] Folic acid and vitamin B_{12} have been given[4,5] with fenofibrate to reduce homocysteine concentrations, but the role of such treatment is not established.

1. Dierkes J, *et al.* Serum homocysteine increases after therapy with fenofibrate or bezafibrate. *Lancet* 1999; **354:** 219–20.
2. Jonkers IJAM, *et al.* Implication of fibrate therapy for homocysteine. *Lancet* 1999; **354:** 1208.
3. de Lorgeril M, *et al.* Lipid-lowering drugs and homocysteine. *Lancet* 1999; **353:** 209–10.
4. Dierkes J, *et al.* Fenofibrate-induced hyperhomocysteinaemia: clinical implications and management. *Drug Safety* 2003; **26:** 81–91.
5. Melenovsky V, *et al.* Effect of folic acid on fenofibrate-induced elevation of homocysteine and cysteine. *Am Heart J* 2003; **146:** 110. Full version available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870303001224.pdf (accessed 30/05/08)

Photosensitivity. Fibrates have been associated with photosensitivity reactions[1] and there may be cross-sensitivity with ketoprofen (see under Adverse Effects of Ketoprofen, p. 79.3).

1. Serrano G, *et al.* Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen. *J Am Acad Dermatol* 1992; **27:** 204–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bezafibrate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Bezafibrate and other fibrates are highly protein-bound and may displace other drugs from protein binding sites. Interactions may also occur through changes in the activity of cytochrome P450 isoenzymes, particularly CYP3A4.

Fibrates may enhance the effects of oral anticoagulants; the dose of anticoagulant should be reduced when treatment with a fibrate is started, and then adjusted gradually if necessary. Recommendations vary; licensed product information for bezafibrate suggests a reduction of up to 50% in the dosage of anticoagulant. The mechanism of the interaction is unclear; fibrates have been reported to displace warfarin from protein binding sites but other mechanisms are probably also involved.

Other drugs that may be displaced from plasma proteins by fibrates include tolbutamide and other sulfonylurea antidiabetics, phenytoin, and, in patients with hypoalbuminaemia, furosemide. The interaction with antidiabetics is complex since fibrates may alter glucose tolerance in diabetic patients (see Effects on Glucose Metabolism, p. 1324.2). The dosage of antidiabetics may need adjusting during bezafibrate therapy.

There is an increased risk of myopathy if fibrates are used with statins (see Lipid Regulating Drugs under Interactions of Simvastatin, p. 1495.3).

Fibrates may interact with ciclosporin, although reports have been conflicting (see p. 1958.1). However, nephrotoxicity associated with increased ciclosporin concentrations has been reported with bezafibrate and renal function should be monitored.

Cholestasis has been reported in a patient given fenofibrate with raloxifene (see p. 2304.1).

References.

1. Lozada A, Dujovne CA. Drug interactions with fibric acids. *Pharmacol Ther* 1994; **63:** 163–76.

Antidiabetics. A paradoxical, reversible decrease in plasma high-density-lipoprotein cholesterol has been reported[1-6] in patients taking fibrates with thiazolidinediones. The mechanism is unclear, although it is unlikely to be a pharmacokinetic interaction.

1. Normén L, *et al.* Combination therapy with fenofibrate and rosiglitazone paradoxically lowers serum HDL cholesterol. *Diabetes Care* 2004; **27:** 2241–2.
2. Health Canada. Rosiglitazone (Avandia): decreased high-density lipoprotein cholesterol levels. *Can Adverse React News* 2005; **15** (3): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3-eng.pdf (accessed 04/08/10)
3. Senba H, *et al.* Severe decrease in serum HDL-cholesterol during combination therapy of bezafibrate and pioglitazone. *J Atheroscler Thromb* 2006; **13:** 263–4.
4. Shetty C, *et al.* Paradoxical HDL-C reduction during rosiglitazone and fibrate treatment. *Diabet Med* 2007; **24:** 94–7.
5. Keidar S, *et al.* High incidence of reduced plasma HDL cholesterol in diabetic patients treated with rosiglitazone and fibrate. *Pharmacoepidemiol Drug Safety* 2007; **16:** 1192–4.
6. Venero CV, *et al.* Reduced high-density lipoprotein cholesterol in patients receiving rosiglitazone and fenofibrate. *Am J Med* 2008; **121:** e3–e4. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-9343/PIIS0002934308006645.pdf (accessed 23/07/09)

Lipid regulating drugs. The bioavailability of gemfibrozil was reduced by *colestipol*, but was unaffected when gemfibrozil was taken either 2 hours before or 2 hours after colestipol.[1]

For discussion of the interaction between fibrates and *statins*, see p. 1495.3.

1. Forland SC, *et al.* Apparent reduced absorption of gemfibrozil when given with colestipol. *J Clin Pharmacol* 1990; **30:** 29–32.

NSAIDs. Acute renal failure due to rhabdomyolysis in a patient has been attributed to an interaction between ciprofibrate and *ibuprofen*.[1] Ibuprofen was believed to have displaced ciprofibrate from protein binding sites. The use of radiological contrast media may also have been a contributory factor.

1. Ramachandran S, *et al.* Acute renal failure due to rhabdomyolysis in presence of concurrent ciprofibrate and ibuprofen treatment. *BMJ* 1997; **314:** 1593.

Pharmacokinetics

Bezafibrate is readily absorbed from the gastrointestinal tract. Plasma protein binding is about 95%. The plasma elimination half-life is about 1 to 2 hours. Most of a dose is excreted in the urine, about half as unchanged drug, the remainder as metabolites including 20% as glucuronides. A small proportion (about 3%) of the dose appears in the faeces. Elimination may be increased by forced diuresis. The drug is not dialysable.

References.

1. Abshagen U, *et al.* Disposition pharmacokinetics of bezafibrate in man. *Eur J Clin Pharmacol* 1979; **16:** 31–8.
2. Abshagen U, *et al.* Steady-state kinetics of bezafibrate and clofibrate in healthy female volunteers. *Eur J Clin Pharmacol* 1980; **17:** 305–8.

The elderly. In a study comparing the pharmacokinetics of bezafibrate in 19 elderly patients with younger healthy subjects,[1] peak plasma concentrations were 1.6 times higher in the elderly group (median 12.1 mg/litre against 7.7 mg/litre) and half-life was increased by 3.8 times (median 6.6 hours against 1.7 hours). The differences could not be attributed solely to diminished renal function in elderly patients. Dosage adjustments in elderly patients should not therefore be based on renal function alone.

1. Neugebauer G, *et al.* Steady-state kinetics of bezafibrate retard in hyperlipidemic geriatric patients. *Klin Wochenschr* 1988; **66:** 250–6.

Renal impairment. The half-life of bezafibrate may be prolonged in patients with renal impairment (see under Uses and Administration, p. 1323.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bezacur; Bezalip; Elpi Lip; Nebufurd; ***Austria***: Bezacur†; Bezalip; Bezastad; ***Belg.***: Cedur; Eulitop; ***Braz.***: Cedur; ***Canad.***: Bezalip; ***Chile***: Nimus; Oralipin; ***China***: Abeita (阿贝他); Yi Zhi Te (益之特); ***Cz.***: Regadrin B†; ***Fin.***: Bezalip; ***Fr.***: Befizal; ***Ger.***: Befibrat; Bezabeta†; Bezadoc†; Bezagamma†; Cedur†; Lipox†; ***Gr.***: Bezachol; Bezalip; Fibrate; Getup; Verbital; ***Hong Kong***: Bezalip; ***Hung.***: Bezalip; ***India***: Beza; Bezalip; Bizalip; ***Indon.***: Decrilip; ***Israel***: Norlip; ***Ital.***: Bezalip; ***Jpn***: Bezalip; ***Malaysia***: Bezalip; ***Mex.***: Befitec; Bexalcor; Bezafisal; Bezalex†; Bezalip†; Bifaren; Bionolip; Colser; Fazebit; Fibroxol; Lesbest; Lipocin; Neptalip; Nivetril; Redalip; Safital; Saprame; Zaf; ***Neth.***: Bezalip; ***NZ***: Bezalip; Fibalip; ***Philipp.***: Bezastad; ***Pol.***: Bezamidin†; ***Port.***: Bezalip; ***Rus.***: Cholestenorm (Холестенорм); ***S.Afr.***: Bezachole; Bezalip; ***Singapore***: Bezalip; Zafibral; ***Spain***: Difaterol; Eulitop; ***Swed.***: Bezalip; ***Switz.***: Cedur; ***Thai.***: Bezalip; Bezamil; Evicta; Lipolip†; Polyzalip; Raset; ***UAE***: Lipitrol; ***UK***: Bezagen; Bezalip Mono; Bezalip; Fibrazate; Zimbacol; ***Venez.***: Bezalip.

Pharmacopoeial Preparations

BP 2014: Bezafibrate Tablets; Prolonged-release Bezafibrate Tablets.

Bisoprolol Fumarate

(BANM, USAN, rINNM) ⊗

Bisoprolol Fumarat; Bisoprolol, Fumarate de; Bisoprolol, fumarato de; Bisoprolol Hemifumarate; Bisoprolol, hémifumarate de; Bisoprololfumarat; Bisoprololi Fumaras; Bisoprololi hemifumaras; Bisoprololifumaraatti; CL-297939; EMD-33512 (bisoprolol or bisoprolol fumarate); Fumarato de bisoprolol; Бизопролола Фумарат.

1-[4-(2-Isopropoxyethoxymethyl)phenoxy]-3-isopropylaminopropan-2-ol fumarate.

$(C_{18}H_{31}NO_4)_2C_4H_4O_4$=767.0

CAS — 66722-44-9 (bisoprolol); 66722-45-0 (bisoprolol fumarate); 104344-23-2 (bisoprolol fumarate).

ATC — C07AB07.

ATC Vet — QC07AB07.

UNII — UR59KN573L.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Bisoprolol Fumarate). A white or almost white, slightly hygroscopic powder. It exhibits polymorphism. Very soluble in water; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Bisoprolol Fumarate). A white crystalline powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol, in chloroform, and in glacial acetic acid; slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Uses and Administration

Bisoprolol is a cardioselective beta blocker (p. 1316.3). It is reported to be devoid of intrinsic sympathomimetic and membrane-stabilising properties.

Bisoprolol is given as the fumarate in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). It is also used as an adjunct to standard therapy in patients with stable chronic heart failure (p. 1262.3).

In **hypertension** or **angina pectoris** the usual dose of bisoprolol fumarate is 5 to 10 mg orally as a single daily dose; the maximum recommended dose is 20 mg daily. A reduction in dose may be necessary in patients with hepatic or renal impairment (see p. 1326.1).

In **heart failure** the initial oral dose of bisoprolol fumarate is 1.25 mg once daily. If tolerated, the dose should be doubled after 1 week, and then increased gradually at 1 to 4 week intervals to the maximum dose tolerated; this should not exceed 10 mg once daily.

References.

1. Johns TE, Lopez LM. Bisoprolol: is this just another beta-blocker for hypertension or angina? *Ann Pharmacother* 1995; **29:** 403–14.

2. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.
3. McGavin JK, Keating GM. Bisoprolol: a review of its use in chronic heart failure. *Drugs* 2002; **62:** 2677–96.
4. Rosenberg J, Gustafsson F. Bisoprolol for congestive heart failure. *Expert Opin Pharmacother* 2008; **9:** 293–300.

Administration in hepatic or renal impairment. US licensed product information recommends that the initial dose of bisoprolol fumarate for hypertension should be 2.5 mg daily and that the dose should be increased cautiously in patients with severe hepatic impairment or renal impairment (creatinine clearance less than 40 mL/minute). UK licensed product information recommends a maximum dose of 10 mg daily for both angina pectoris and hypertension in patients with severe hepatic impairment or with a creatinine clearance of less than 20 mL/minute.

Bisoprolol is not dialysable.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bisoprolol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Bisoprolol is almost completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism resulting in an oral bioavailability of about 90%. Peak plasma concentrations occur 2 to 4 hours after oral doses. Bisoprolol is about 30% bound to plasma proteins. It has a plasma elimination half-life of 10 to 12 hours. Bisoprolol is moderately lipid-soluble. It is metabolised in the liver and excreted in urine, about 50% as unchanged drug and 50% as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Concor; Corbis; Lostaprolol; ***Austral.***: Bicard; Bicor; Bispro; ***Austria***: Bisocor; Bisostad; Concor; Rivacor; ***Belg.***: Bisoprotop†; Bisosandoz†; Docbisopro†; Emconcor; Isoten; ***Braz.***: Concardio; Concor; ***Canad.***: Monocor†; ***Chile***: Concor; ***China***: An Shi (安适); Bo Su (博苏); Concor (康可); Luo Ya (洛雅); Rong Ning (荣宁); ***Cz.***: Bisoblock†; Bisocard; Bisogamma; Bisogen; Bisprotin; Bivaxol†; Byol†; Concor Cor; Concor; Kordobis†; Rivocor; ***Denm.***: Bisoact; Bisocor†; Bisprotin; Cardicor; Emconcor; ***Fin.***: Bisomerck†; Bisomyl; Bisoproact; Caraprol; Emconcor; Orloc; ***Fr.***: Bisoce; Cardensiel; Cardiocor; Detensiel; ***Ger.***: Biso Lich†; Biso-Hennig; Biso-Puren†; Bisobeta; Bisogamma; Bisohexal†; Concor; Jutabis†; ***Gr.***: Abitrol; Blocatens; Concor; Pactens; Speridol; ***Hong Kong***: Concor; ***Hung.***: Bisoblock; Bisocard; Bisogamma; Bisogen†; Concor Cor; Concor; Coviogal; ***India***: Bebedol; Bisbeta; Biselect; Bisocar HT; Bisod; Cadrol; Concor; Corbis; ***Indon.***: B-Beta; Beta-One; Bipro; Biscor; Concor; Hapsen; Lodoz; Maintate; ***Irl.***: Bellimcor; Bisocor; Bisop; Bisopine; Cardicor; Emcolol; Emcor; Emvasc†; Soprol; ***Israel***: Bisolol†; Cardiloc; Concor; ***Ital.***: Cardicor; Concor; Congescor; Pluscor; Sequacor; ***Jpn***: Bisono; Maintate; ***Malaysia***: Concor; ***Mex.***: Concor; ***Neth.***: Bisoblock†; Emcor; ***Norw.***: Emconcor; ***Philipp.***: Concore; ***Pol.***: Antipres; Bicardef; Bisocard; Bisohexal; Bisopromerck; Bisoratio; Concor; Corectin; Coronal; ***Port.***: Concor; Libracor†; ***Rus.***: Aritel (Арител); Bidop (Бидоп); Biol (Биол); Biprol (Бипрол); Bisocard (Бисокард); Bisogamma (Бисогамма); Concor (Конкор); Corbis (Корбис); Cordinorm (Кординорм); Coronal (Коронал); Lodoz (Лодоз); Niperten (Нипертен); ***S.Afr.***: Adco-Bisocor; Bilocor; Bisohexal; Cardicor; Concor; Ziapro; ***Singapore***: Bisohexal; Concor; ***Spain***: Emconcor; Euradal; ***Swed.***: Bisocard; Bisomerck†; Bisostad; Emconcor; ***Switz.***: Bilol; Concor; Rivocor; ***Thai.***: Concor; Hypercor; Novacor; ***Turk.***: Concor; Soprano; ***UK***: Cardicor; Emcor; Vivacor; ***Ukr.***: Biprolol (Випролол); Bisocard (Бисокард); Bisoprol (Бисопрол); Bisostad (Бисостад); Concor (Конкор); Coronal (Коронал); ***USA***: Zebeta; ***Venez.***: Concor.

Multi-ingredient Preparations. ***Arg.***: Concor Plus; Corbis D; Ziac; ***Austria***: Bisocombin†; Bisoprolol Comp; Bisoprolol-HCT; Bisostad plus; Concor Plus; Rivacor Plus; ***Belg.***: Co-Bisoprolol; Emcoretic; Lodoz; Maxsoten; ***Braz.***: Biconcor; ***Chile***: Ziac; ***Cz.***: Betapres; Lodoz; Tebis Plus H†; ***Fin.***: Bisoprolol Comp; Bisostad†; Emconcor Comp; Orloc Comp; ***Fr.***: Lodoz; Wytens; ***Ger.***: Biso comp†; Biso-Puren comp†; Bisobeta comp; Bisohexal plus†; BisoLich comp†; Bisoplus†; Bisoprolol Comp; Bisoprolol HCT†; Bisoprolol HCTad†; Bisoprolol Plus†; Concor Plus; ***Hong Kong***: Lodoz; ***Hung.***: Concor Plus; Coviogal Plusz; ***India***: Concor-AM; Corbis-H; Lodoz; ***Ital.***: Lodoz; ***Malaysia***: Lodoz; ***Mex.***: Biconcor; ***Neth.***: Emcoretic†; ***Norw.***: Lodoz; ***Philipp.***: Ziac; ***Port.***: Concor Plus; ***Rus.***: Aritel Plus (Арител Плюс); ***S.Afr.***: Ziak; ***Singapore***: Lodoz; ***Spain***: Emcoretic; ***Switz.***: Bilol comp.; Concor Plus; Lodoz; ***Thai.***: Lodoz; ***Turk.***: Lodoz; ***Ukr.***: Alotendin (Алотендин); ***USA***: Ziac; ***Venez.***: Biconcor; Ziac.

Pharmacopoeial Preparations

BP 2014: Bisoprolol Tablets;

USP 36: Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Bisoprolol Fumarate Tablets.

Bivalirudin *(BAN, USAN, rINN)*

BG-8967; Bivalirudina; Bivalirudine; Bivalirudinum; Biwalirudyna; Hirulog; Бивалирудин.

$C_{98}H_{138}N_{24}O_{33}$=2180.3

CAS — 128270-60-0.

ATC — B01AE06.

ATC Vet — QB01AE06.

UNII — TN9BEX005G.

Incompatibility. Licensed product information for bivalirudin states that it is incompatible with: alteplase, amiodarone hydrochloride, amphotericin B, chlorpromazine hydrochloride, diazepam, prochlorperazine edisilate, reteplase, streptokinase, and vancomycin hydrochloride. It also states that dobutamine hydrochloride, famotidine, haloperidol lactate, labetalol hydrochloride, lorazepam, and promethazine hydrochloride show concentration-dependent incompatibility with bivalirudin.

Uses and Administration

Bivalirudin, an analogue of the peptide hirudin (p. 1401.2), is a direct thrombin inhibitor with actions similar to Lepirudin, p. 1418.2. It is used as an anticoagulant in patients undergoing percutaneous coronary interventions, including those with, or at risk of, heparin-induced thrombocytopenia. It is also used in patients with acute coronary syndromes in whom early intervention is planned, and has been investigated in patients with acute coronary syndromes treated medically (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p. 1418.3).

Some preparations state that bivalirudin is present as the hydrate of the trifluoroacetate salt but doses are given in terms of bivalirudin.

In the management of patients undergoing **planned or primary percutaneous coronary intervention** (PCI), the initial dose of bivalirudin is 750 micrograms/kg by intravenous injection followed immediately by an intravenous infusion of 1.75 mg/kg per hour. In the USA, it is recommended that the activated clotting time is measured 5 minutes after the initial injection and a second injection of 300 micrograms/kg is given if anticoagulation is inadequate. The infusion should be given for the duration of the procedure and may be continued for up to 4 hours afterwards; licensed prescribing information in the UK then allows a reduced dose of 250 micrograms/kg per hour to be infused for a further 4 to 12 hours if necessary, or in the USA 200 micrograms/kg per hour for a further 20 hours.

As part of the management of patients with **acute coronary syndromes**, the initial dose of bivalirudin is 100 micrograms/kg by intravenous injection, followed by an intravenous infusion of 250 micrograms/kg per hour. Again, if measurement of activated clotting time 5 minutes after the initial bolus indicates inadequate anticoagulation, a second bolus of 300 micrograms/kg may be given. In patients managed *medically*, the infusion may be continued for up to 72 hours. For those who proceed to *PCI or coronary artery bypass surgery without cardiopulmonary bypass*, a further intravenous injection of 500 micrograms/kg should be given, and the infusion should be increased to 1.75 mg/kg per hour for the duration of the procedure; after PCI, the infusion may be continued at a dose of 250 micrograms/kg per hour for a further 4 to 12 hours if required. For those who proceed to *coronary artery bypass surgery with cardiopulmonary bypass*, the infusion should be stopped 1 hour before the procedure and the patient should be treated with unfractionated heparin.

The dose of bivalirudin should be reduced in patients with renal impairment (see below).

References.
1. Stone GW, *et al.* ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.
2. Ahrens I, *et al.* Direct thrombin inhibition with bivalirudin as an antithrombotic strategy in general and interventional cardiology. *Expert Opin Drug Metab Toxicol* 2007; **3:** 609–20.
3. Hartmann F. Safety and efficacy of bivalirudin in acute coronary syndromes. *Curr Pharm Des* 2008; **14:** 1191–6.
4. Deeks ED, Curran MP. Bivalirudin: in patients with acute coronary syndromes planned for urgent or early intervention. *Drugs* 2008; **68:** 2345–56.
5. Czosnowski QA, *et al.* Bivalirudin for patients with heparin-induced thrombocytopenia undergoing cardiovascular surgery. *Ann Pharmacother* 2008; **42:** 1304–9.
6. White HD. Pharmacological and clinical profile of bivalirudin in the treatment of patients with acute coronary syndrome. *Expert Opin Drug Metab Toxicol* 2009; **5:** 529–38.
7. Curran MP. Bivalirudin: in patients with ST-segment elevation myocardial infarction. *Drugs* 2010; **70:** 909–18.

Administration in renal impairment. The dose of bivalirudin may need to be adjusted in patients with renal impairment and the activated clotting time should be monitored. UK licensed product information recommends the following doses, depending on the glomerular filtration rate (GFR):

- GFR 30 to 59 mL/minute: usual bolus doses (see Uses and Administration, above) but in those undergoing percutaneous coronary intervention (PCI) for any indication the infusion rate should be reduced to 1.4 mg/kg per hour during the procedure
- GFR below 30 mL/minute or dialysis-dependent: contra-indicated

US licensed product information recommends the following doses for those undergoing PCI, based on creatinine clearance (CC):

- CC 30 to 59 mL/minute: usual bolus and infusion doses
- CC below 30 mL/minute: usual bolus doses but infusion rate reduced to 1 mg/kg per hour
- Haemodialysis patients: usual bolus doses but infusion rate reduced to 250 micrograms/kg per hour

For a discussion of the use of direct thrombin inhibitors, including bivalirudin, as alternatives to heparin in patients undergoing haemodialysis or haemofiltration, see Extracorporeal Circuits under Lepirudin, p. 1418.2.

Adverse Effects, Treatment, and Precautions

As for Lepirudin, p. 1419.2.

Interactions

As for Lepirudin, p. 1419.3.

Pharmacokinetics

Bivalirudin is partly metabolised and partly excreted by the kidney. When given intravenously the plasma half-life is about 25 minutes in patients with normal renal function but is prolonged in renal impairment. Bivalirudin does not bind to plasma proteins and is removed by haemodialysis.

References.
1. Robson R, *et al.* Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002; **71:** 433–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Angiomax; ***Austral.***: Angiomax; ***Austria***: Angiox; ***Belg.***: Angiox; ***Canad.***: Angiomax; ***Chile***: Angiomax; ***Cz.***: Angiox; ***Denm.***: Angiox; ***Fin.***: Angiox; ***Fr.***: Angiox; ***Ger.***: Angiox; ***Gr.***: Angiox; ***Hung.***: Angiox; ***India***: Bivaflo; ***Irl.***: Angiox; ***Israel***: Angiomax; ***Ital.***: Angiox; ***Neth.***: Angiox; ***Norw.***: Angiox; ***NZ***: Angiomax; ***Pol.***: Angiox; ***Port.***: Angiox; ***Spain***: Angiox; ***Swed.***: Angiox; ***Switz.***: Angiox; ***UK***: Angiox; ***Ukr.***: Angiox (Ангиокс)†; ***USA***: Angiomax.

Bopindolol Malonate *(rINNM)* ⊗

Bopindolol Hydrogen Malonate; Bopindolol, Malonate de; Bopindolol, malonato de; Bopindololi Malonas; LT-31-200; Malonato de bopindolol; Бопиндолола Малонат.

(±)-1-(*tert*-Butylamino)-3-[(2-methylindol-4-yl)oxy]propan-2-ol benzoate malonate.

$C_{23}H_{28}N_2O_3$,$C_3H_4O_4$=484.5

CAS — 62658-63-3 (bopindolol); 82857-38-3 (bopindolol malonate).

ATC — C07AA17.

ATC Vet — QC07AA17.

UNII — S3UWR70991.

Profile

Bopindolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess some intrinsic sympathomimetic activity.

Bopindolol is given orally as the malonate but doses are expressed in terms of the base; 1.27 mg of bopindolol malonate is equivalent to about 1 mg of base. It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3) in daily doses equivalent to 0.5 to 2 mg of bopindolol.

References.
1. Harron DWG, *et al.* Bopindolol: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1991; **41:** 130–49.
2. Nagatomo T, *et al.* Bopindolol: pharmacological basis and clinical implications. *Cardiovasc Drug Rev* 2001; **19:** 9–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Sandonorm†; ***Gr.***: Sandonorm; ***Hung.***: Sandonorm; ***Switz.***: Sandonorm†.

Multi-ingredient Preparations. ***Switz.***: Sandoretic†.

Bosentan (BAN, USAN, rINN)

Bosentaani; Bosentán; Bosentano; Bosentanum; Ro-47-0203/029; Боентан.

p-tert-Butyl-*N*-[6-(2-hydroxyethoxy)-5-(*o*-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide.

$C_{27}H_{29}N_5O_6S$=551.6

CAS — 147536-97-8 (anhydrous bosentan); 157212-55-0 (bosentan monohydrate).

ATC — C02KX01.

ATC Vet — QC02KX01.

UNII — Q326023R30 (bosentan); XUL93R30K2 (anhydrous bosentan).

Uses and Administration

Bosentan is an endothelin receptor antagonist (p. 1245.1) used in the management of pulmonary hypertension (below) and systemic sclerosis (see Scleroderma, below). It has also been investigated in heart failure and in hypertension.

In **pulmonary hypertension**, patients over 12 years of age may be given bosentan orally in an initial dose of 62.5 mg twice daily, increased after 4 weeks to a maintenance dose of 125 mg twice daily. In those with low body-weight (below 40 kg) both the initial and maintenance doses are 62.5 mg twice daily. For the use of bosentan in children, see below.

In **systemic sclerosis** with ongoing digital ulcer disease, bosentan is given in the same doses as for pulmonary hypertension; there are no data on safety or efficacy in patients under 18 years of age.

Use with ritonavir (including ritonavir-boosted HIV-protease inhibitors) increases bosentan plasma concentrations, and US licensed product information for bosentan recommends the following dosage reductions of bosentan in patients taking both drugs together:

- in those who are already taking ritonavir and have been doing so for at least 10 days, start bosentan at an oral dose of 62.5 mg once daily or on alternate days, depending on patient tolerability
- in those who are already taking bosentan, stop bosentan for at least 36 hours before starting ritonavir. After at least 10 days of ritonavir, restart bosentan at a dose of 62.5 mg once daily or on alternate days, depending on patient tolerability

For use in hepatic impairment, see Administration in Hepatic Impairment, below.

References.

1. Dingemanse J, van Giersbergen PLM. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin Pharmacokinet* 2004; **43:** 1089–1115.
2. Oldfield V, Lyseng-Williamson KA. Bosentan: a review of its use in pulmonary arterial hypertension and systemic sclerosis. *Am J Cardiovasc Drugs* 2006; **6:** 189–208.

Administration in children. A short-term study[1] in 19 children with pulmonary hypertension aged 3 to 15 years found that treatment with bosentan resulted in haemodynamic improvement and was well tolerated, and another small study[2] suggested that addition of bosentan allowed epoprostenol dosage to be reduced or stopped. Longer-term studies[3,4] have reported that benefit is maintained and that bosentan may have a role in children with both idiopathic pulmonary hypertension and pulmonary hypertension secondary to heart or lung disease.

Licensed product information in the UK states that in children aged 2 years and above, oral doses greater than 2 mg/kg twice daily are unlikely to increase efficacy. There is limited clinical experience in those aged under 2 years. It notes that the studies cited above used the following doses; these doses are also recommended in the *BNFC*, for children aged 2 to 18 years:

- body-weight 10 to 20 kg: initial dose 31.25 mg once daily, increased to 31.25 mg twice daily after 4 weeks
- body-weight 20 to 40 kg: initial dose 31.25 mg twice daily, increased to 62.5 mg twice daily after 4 weeks
- body-weight over 40 kg and age 12 to 18 years: as for adults (see above)

1. Barst RJ, *et al.* Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther* 2003; **73:** 372–82.
2. Ivy DD, *et al.* Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. *Am J Cardiol* 2004; **93:** 943–6.
3. Maiya S, *et al.* Response to bosentan in children with pulmonary hypertension. *Heart* 2006; **92:** 664–70.
4. Rosenzweig EB, *et al.* Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46:** 697–704.

Administration in hepatic impairment. Oral bosentan therapy should not be *started* in patients with liver transaminase concentrations more than 3 times the upper limit of normal (ULN). If transaminase concentrations increase *during* treatment, the following modifications are recommended:

- for increases to between 3 and 5 times the ULN, bosentan should be stopped or the dose reduced to the usual initial dose (see Uses and Administration, above). Enzyme concentrations should be monitored every 2 weeks until they return to pretreatment values; therapy may then be continued or reintroduced at the usual initial dose, but aminotransferase concentrations should be checked within 3 days, after a further 2 weeks, and then monthly
- for increases to more than 5 times the ULN up to 8 times the ULN, bosentan should be stopped; reintroduction at the usual initial dose may be considered when concentrations return to pretreatment values
- for increases above 8 times the ULN or if there are symptoms of hepatotoxicity or increases in total bilirubin levels greater than twice the ULN, treatment should be stopped and not reintroduced

Pulmonary hypertension. Pulmonary hypertension (p. 1278.2) is a progressive and incurable disease associated with an increase in pulmonary arterial pressure. Treatment usually involves the use of vasodilators such as calcium-channel blockers, intravenous epoprostenol, or sildenafil, though systemic effects may limit their use. Patients with pulmonary hypertension have raised plasma concentrations of the potent vasoconstrictor endothelin I, and endothelin antagonists such as bosentan are widely used.[1] Studies[2,3] with oral bosentan in patients with mainly functional class III pulmonary arterial hypertension have shown improvement in exercise tolerance and in time to clinical progression; an open study[4] showed sustained benefit with treatment for 1 year or more. However, no effect on mortality has yet been found in randomised studies, although there is some evidence[5,6] that survival may be improved. Some benefit has also been reported with bosentan alone in class II patients.[7] Bosentan has also been tried with other drugs but the role of combination therapy is not clear. When given with epoprostenol[8] there was a non-significant trend towards greater improvement in the group receiving both drugs compared with epoprostenol alone. Bosentan has also been given successfully with sildenafil.[9-11]

There is some evidence that bosentan may be of benefit in pulmonary hypertension associated with congenital heart disease,[12,13] including Eisenmenger syndrome,[13-15] and in pulmonary hypertension associated with HIV infection[16,17] and COPD.[18] Positive results have also been reported[19-21] in chronic thromboembolic pulmonary hypertension.

1. Raja SG, Dreyfus GD. Current status of bosentan for treatment of pulmonary hypertension. *Ann Card Anaesth* 2008; **11:** 6–14.
2. Channick RN, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; **358:** 1119–23.
3. Rubin LJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346:** 896–903. Correction. *ibid.*; 1258.
4. Sitbon O, *et al.* Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003; **124:** 247–54.
5. McLaughlin VV, *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; **25:** 244–9.
6. Sitbon O, *et al.* Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax* 2005; **60:** 1025–30.
7. Galiè N, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; **371:** 2093–2100.
8. Humbert M, *et al.* Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; **24:** 353–9.
9. Porhownik NR, *et al.* Addition of sildenafil in patients with pulmonary arterial hypertension with inadequate response to bosentan monotherapy. *Can Respir J* 2008; **15:** 427–30.
10. Gruenig E, *et al.* Acute hemodynamic effects of single-dose sildenafil when added to established bosentan therapy in patients with pulmonary arterial hypertension: results of the COMPASS-1 study. *J Clin Pharmacol* 2009; **49:** 1343–52.
11. Launay D, *et al.* Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology (Oxford)* 2010; **49:** 490–500.
12. Apostolopoulou SC, *et al.* Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. *Heart* 2007; **93:** 350–4.
13. Diller G-P, *et al.* Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. *Heart* 2007; **93:** 974–6.
14. Galiè N, *et al.* for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; **114:** 48–54.
15. D'Alto M, *et al.* Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. *Heart* 2007; **93:** 621–5.
16. Barbaro G, *et al.* Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006; **92:** 1164–6.
17. Degano B, *et al.* Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. *Eur Respir J* 2009; **33:** 92–8.
18. Valerio G, *et al.* Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2009; **3:** 15–21.
19. Hughes R, *et al.* Bosentan in inoperable chronic thromboembolic pulmonary hypertension. *Thorax* 2005; **60:** 707.
20. Hoeper MM, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2363–7.
21. Bonderman D, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2599–2603.

Scleroderma. Bosentan has an established role in pulmonary hypertension secondary to scleroderma (p. 1942.3) or other connective tissue disorders, but may also have additional benefits. Several case reports[1-3] have suggested that treatment with bosentan may be associated with healing of refractory digital ulcers in patients with scleroderma, and a controlled study[4] found that bosentan reduced the incidence of new digital ulcers, although there was no improvement in the healing of existing ulcers. Relatively long-term treatment may need to be given.[5,6]

1. Humbert M, Cabane J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan. *Rheumatology (Oxford)* 2003; **42:** 191–3.
2. Snyder MJ, *et al.* Resolution of severe digital ulceration during a course of bosentan therapy. *Ann Intern Med* 2005; **142:** 802–3.
3. Tillon J, *et al.* Successful treatment of systemic sclerosis-related digital ulcers and sarcoidosis with endothelin receptor antagonist (bosentan) therapy. *Br J Dermatol* 2006; **154:** 1000–1002.
4. Korn JH, *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; **50:** 3985–93.
5. García de la Peña-Lefebvre P, *et al.* Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. *Rheumatology (Oxford)* 2008; **47:** 464–6.
6. Tsifetaki N, *et al.* Bosentan for digital ulcers in patients with systemic sclerosis: a prospective 3-year followup study. *J Rheumatol* 2009; **36:** 1550–1.

Adverse Effects

Adverse effects reported with bosentan include headache, nasopharyngitis, flushing, oedema, hypotension, dizziness, palpitations, gastrointestinal disturbances, pruritus, rashes, fatigue, muscle cramps, and anaemia. Anaphylaxis and angioedema have been reported rarely. Dose-related increases in liver aminotransferases may also occur, and hepatic cirrhosis and liver failure have been reported.

Bosentan is teratogenic in *animals*; there is also some suggestion that endothelin antagonists may impair testicular function and spermatogenesis.

Effects on the liver. In a postmarketing study,[1] increases in liver aminotransferases to more than 3 times the upper limit of normal occurred in 352 (7.6%) of 4623 patients started on *bosentan* for pulmonary hypertension; treatment was continued or successfully reintroduced after temporary withdrawal in 165 (47%) of these patients. Adverse liver effects may occur less frequently in younger children: postmarketing data[2] showed elevated aminotransferases in 2.7% of children aged under 12 years compared with 7.8% of those aged 12 years and over.

1. Humbert M, *et al.* Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007; **30:** 338–44.
2. Beghetti M, *et al.* Safety experience with bosentan in 146 children 2–11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance program. *Pediatr Res* 2008; **64:** 200–204.

Effects on the skin. Vasculitis was reported[1] in a patient receiving bosentan shortly after the dose was increased to 125 mg twice daily. She was also taking metolazone and acenocoumarol long term, and spironolactone had recently been added. The skin lesions improved slowly over a period of weeks after bosentan was stopped. All other treatment was continued and it was concluded that the lesions were attributable to bosentan alone or to a previously unknown interaction. A pruritic, erythematous drug eruption occurred[2] in a patient 10 days after being given bosentan for systemic sclerosis. The eruption improved after stopping the drug and treatment with corticosteroids, and recurred on rechallenge.

1. Gasser S, *et al.* Severe necrotising leucocytoclastic vasculitis in a patient taking bosentan. *BMJ* 2004; **329:** 430.
2. Nagai Y, *et al.* Drug eruption due to bosentan in a patient with systemic sclerosis. *Mod Rheumatol* 2006; **16:** 188–90.

Precautions

Bosentan is contra-indicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). Liver-aminotransferase concentrations should be measured before starting therapy, at monthly intervals during therapy, and 2 weeks after any increase in dose; treatment may need to be modified if enzyme concentrations are increased (see Administration in Hepatic Impairment, above).

Haemoglobin concentrations should be monitored every 3 months during therapy, more frequently at the start.

Bosentan should not be given to patients with hypotension. Pulmonary oedema has been reported rarely when vasodilating agents, including endothelin receptor antagonists, have been used in patients with veno-occlusive disease. Therefore, if a patient develops acute pulmonary oedema when starting therapy, the possibility of veno-

occlusive disease should be considered, and the drug discontinued if confirmed.

Although there is no evidence of rebound effects after stopping bosentan, it is recommended that therapy should be withdrawn gradually.

Bosentan and related endothelin receptor antagonists are teratogenic in *rats* and should not be used in pregnancy or in women of child-bearing potential who are not using a reliable method of contraception; hormonal contraceptives alone may not be adequate and additional measures may be required (see Interactions, below).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bosentan as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Bosentan is metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is also an inducer of the same isoenzymes. It may also possibly induce CYP2C19. Interactions may therefore occur with other drugs that are either metabolised by, or inhibit, these isoenzymes. Concomitant use of bosentan with both a CYP2C9 inhibitor and a CYP3A4 inhibitor should be avoided. Use with ciclosporin is contra-indicated since plasma concentrations of bosentan are significantly increased (see below). Use with ritonavir also increases bosentan plasma concentrations, and reduced doses of bosentan have been recommended—see Uses and Administration, p. 1327.1. There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide and such use should be avoided; the hypoglycaemic effect of glibenclamide may also be reduced. Bosentan reduces exposure to sildenafil. Bosentan has also reduced the plasma concentrations of some hormonal contraceptives and additional contraceptive measures are advised (see Endothelin Receptor Antagonists, p. 2243.3).

Anticoagulants. For reports of bosentan decreasing the anticoagulant effect of *warfarin*, see Endothelin Receptor Antagonists, p. 1534.1.

Ciclosporin. There appears to be a complex interaction between bosentan and ciclosporin. In a pharmacokinetic study[1] in healthy subjects given both drugs, doses of ciclosporin needed increasing to achieve target trough ciclosporin concentrations; it was calculated that plasma concentrations of ciclosporin would otherwise have been reduced by about half in the presence of bosentan. In addition, plasma concentrations of bosentan were almost doubled by ciclosporin. Licensed product information for bosentan states that plasma concentrations at steady state are 3 to 4 times higher in the presence of ciclosporin and contra-indicates the combination.

1. Binet I, *et al.* Renal hemodynamics and pharmacokinetics of bosentan with and without cyclosporine A. *Kidney Int* 2000; **57:** 224–31.

Urological drugs. For a two-way interaction between bosentan and *sildenafil*, see Cardiovascular Drugs under Sildenafil, p. 2366.3.

Pharmacokinetics

Bosentan is absorbed from the gastrointestinal tract with an absolute bioavailability of about 50%. Peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is more than 98% bound to plasma proteins, mainly to albumin. Bosentan is metabolised in the liver by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is an inducer of these enzymes and possibly also of CYP2C19; after multiple dosing, plasma concentrations of bosentan decrease gradually to 50 to 65% of those seen after a single dose. Bosentan has three metabolites, one of which is active. Bosentan is excreted almost entirely as metabolites in the bile; less than 3% of an oral dose is excreted in the urine. The terminal elimination half-life is about 5 hours.

References.

1. Weber C, *et al.* Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. *J Clin Pharmacol* 1999; **39:** 703–14.
2. van Giersbergen PLM, *et al.* Influence of mild liver impairment on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *J Clin Pharmacol* 2003; **43:** 15–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tracleer; Usenta†; ***Austral.***: Tracleer; ***Austria***: Tracleer; ***Belg.***: Tracleer; ***Braz.***: Tracleer; ***Canad.***: Tracleer; ***Chile***: Usenta; ***China***: Tracleer (全可利); ***Cz.***: Tracleer; ***Denm.***: Tracleer; ***Fin.***: Tracleer; ***Fr.***: Tracleer; ***Ger.***: Tracleer; ***Gr.***: Tracleer; ***Hong Kong***: Tracleer; ***Hung.***: Tracleer; ***Irl.***: Tracleer; ***Israel***: Tracleer; ***Ital.***: Tracleer; ***Malaysia***: Tracleer; ***Neth.***: Tracleer; ***Norw.***: Tracleer; ***NZ***: Tracleer; ***Pol.***: Tracleer; ***Port.***: Tracleer; ***Rus.***: Tracleer (Траклир); ***Singapore***: Tracleer; ***Spain***: Tracleer; ***Swed.***: Tracleer; ***Switz.***: Tracleer; ***Thai.***: Tracleer; ***Turk.***: Tracleer; ***UK***: Tracleer; ***USA***: Tracleer.

Bretylium Tosilate *(BAN, rINN)*

ASL-603; Bretilio, tosilato de; Bretyli Tosilas; Bretylii Tosilas; Brétylium, Tosilate de; Bretylium Tosylate (USAN); Bretylitosilat; Bretyylitosilaatti; Tosilato de bretilio; Бретилия Тозилат.

(2-Bromobenzyl)ethyldimethylammonium toluene-4-sulphonate.

$C_{11}H_{17}BrN,C_7H_7O_3S$=414.4

CAS — 59-41-6 (bretylium); 61-75-6 (bretylium tosilate).

ATC — C01BD02.

ATC Vet — QC01BD02.

UNII — 78ZP3YR353.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Bretylium Tosilate). A white crystalline powder. M.p. about 98 degrees. It exhibits polymorphism. Freely soluble in water, in alcohol, and in methyl alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Bretylium Tosylate). A white, hygroscopic, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ether, in ethyl acetate, and in hexane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Bretylium is a quaternary ammonium compound with class II and class III antiarrhythmic activity (p. 1243.1); it causes an initial release of noradrenaline and then blocks adrenergic transmission by preventing noradrenaline release from adrenergic nerve endings. It suppresses ventricular fibrillation and other ventricular arrhythmias, but its exact mode of action is unknown. It has been given parenterally as the tosilate in the management of ventricular arrhythmias.

Bretylium has also been investigated in complex regional pain syndrome.

References.

1. Bacaner M, Dembo DH. Arrhythmia and acute coronary syndrome suppression and cardiac resuscitation management with bretylium. *Am J Ther* 2009; **16:** 534–42.

Adverse Effects and Precautions

The most common adverse effect of bretylium is hypotension, which may be severe. Bretylium may also cause a transient initial increase in blood pressure and heart rate, and a worsening of cardiac arrhythmias due to a release of noradrenaline. Nausea and vomiting may occur particularly during rapid intravenous infusion. Intramuscular injection of bretylium can lead to local tissue necrosis and muscle atrophy. Caution is required in patients with renal impairment, and in patients with severe aortic stenosis or pulmonary hypertension in whom cardiac output may not increase in response to the fall in peripheral resistance produced by bretylium.

Interactions

Bretylium may exacerbate arrhythmias caused by digitalis toxicity and may enhance the effects of sympathomimetics.

Pharmacokinetics

Bretylium is incompletely absorbed from the gastrointestinal tract. It is well absorbed after intramuscular injection. It is not metabolised and is largely excreted unchanged in the urine. The half-life is reported to be between 4 and 17 hours in patients with normal renal function and is prolonged in patients with renal impairment. Bretylium is dialysable.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Singapore***: Bretylate.

Pharmacopoeial Preparations

BP 2014: Bretylium Injection;

USP 36: Bretylium Tosylate in Dextrose Injection; Bretylium Tosylate Injection.

Bucindolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Bucindolol, Chlorhydrate de; Bucindolol, hidrocloruro de; Bucindololi Hydrochloridum; Hidrocloruro de bucindolol; MJ-13105-1; Буциндолола Гидрохлорид.

2-[2-Hydroxy-3-(2-indol-3-yl-1,1-dimethylethylamino)propoxy]benzonitrile hydrochloride.

$C_{22}H_{25}N_3O_2$,HCl=399.9

CAS — 71119-11-4 (bucindolol); 70369-47-0 (bucindolol hydrochloride).

UNII — SH683G4QII.

NOTE. The name Gencaro has been used as a trade mark for bucindolol hydrochloride.

Profile

Bucindolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess weak alpha$_1$-blocking activity and direct vasodilating activity; the degree of intrinsic sympathomimetic activity is unclear. Bucindolol hydrochloride has been investigated in the management of hypertension, heart failure, and other cardiac disorders, but development was halted. However, it has been suggested that it may be of benefit in a genetically identifiable subgroup of patients.

References.

1. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; **344:** 1659–67.
2. Anderson JL, *et al.* Beta-Blocker Evaluation of Survival Trial (BEST) Investigators. Failure of benefit and early hazard of bucindolol for class IV heart failure. *J Card Fail* 2003; **9:** 266–77.
3. Ali I, *et al.* Importance of a history of hypertension for the prognosis after acute myocardial infarction—for the Bucindolol Evaluation in Acute myocardial infarction Trial (BEAT) study group. *Clin Cardiol* 2004; **27:** 265–9.
4. Bristow MR, *et al.* An α_{2C}-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the beta-blocker bucindolol in chronic heart failure. *Circ Heart Fail* 2010; **3:** 21–8.

Buflomedil Hydrochloride *(BANM, rINNM)*

Buflomedililihydrokloridi; Buflomédil, Chlorhydrate de; Buflomedil, hidrocloruro de; Buflomedil-hidroklorid; Buflomedil-hydrochlorid; Buflomedilhydrochlorid; Buflomedilhydroklorid; Buflomedili Hydrochloridum; Buflomedilio hidrochloridas; Hidrocloruro de buflomedil; LL-1656; Буфломедила Гидрохлорид.

2′,4′,6′-Trimethoxy-4-(pyrrolidin-1-yl)butyrophenone hydrochloride.

$C_{17}H_{25}NO_4$,HCl=343.8

CAS — 55837-25-7 (buflomedil); 35543-24-9 (buflomedil hydrochloride).

ATC — C04AX20.

ATC Vet — QC04AX20.

UNII — 3J944AFS8S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Buflomedil Hydrochloride). A white or almost white microcrystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 6.5.

Uses and Administration

Buflomedil hydrochloride is a vasodilator that has been used in the treatment of cerebrovascular and peripheral vascular disorders. It has been given orally or by intramuscular or intravenous injection. Serious neurological adverse effects including convulsions and status epilepticus, and cardiovascular effects including severe hypotension and arrhythmias, particularly tachycardia and cardiac arrest, have occurred. These were seen particularly in elderly patients and in patients with renal impairment who did not receive an appropriately reduced dose. Consequently, the EMA recommended the withdrawal of buflomedil in Europe.

References.

1. EMA. European Medicines Agency recommends suspension of all buflomedil-containing medicines (issued 17th November, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117792.pdf (accessed 02/01/14)
2. Bucolo C, *et al.* Safety profile assessment of buflomedil: an overview of adverse reactions between 1975 and 2011. *Pharmacoepidemiol Drug Safety* 2012; **21:** 1190–6.
3. de Backer TLM, Vander Stichele R. Buflomedil for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2013 (accessed 02/01/14).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arteriol; Buflomed; Lofton; ***Austria***: Buflohexal†; Buflomed†; Loftyl†; ***Belg.***: Loftyl†; ***Braz.***: Bufedil; ***China***: An Si Tuo Li (安思孚利); Ao Nuo Ya (奥诺娅); Ba Yang Pu Rui (巴阳普瑞); Bu Fu Mai (步复迈); Fonzylane (弗斯兰); Hai Si Xin Da (海斯欣达); Huo Nuo Lin (活诺林); Ikelan (麦道可兰); Jia Er (加尔); Lai Si Duo Wei (莱斯多维); Li Xin Kang (力欣康); Ning Xue Xin (宁雪欣); Qian Tong (前通); Qing Jian (清健); Rui Li Da (瑞立达); Sai Mei Ao (赛美澳); Sai Mu Si (赛姆斯); Sailaile (赛莱乐); Shi Duo Tai (世多泰); Si Jian (斯健); Si Mi Kang (司米康); Xin Zhi Ming (欣智明); Xing Bi De (兴必得); Xu Luo Ling (绪络菱); Yisu (意速); ***Fr.***: Fonzylane†; ***Ger.***: Bufedil†; Buflo-POS†; Buflo-Puren†; Complamin†; Defluina†;

Gr.: Bladiron†; Botamiral†; Buflodil†; Chlorofarm-S†; Cordimedil†; Dialon-T†; Dicasin†; Farmidil†; Flubir†; Gaveril†; Gondofil†; Irrodan†; Loftyl†; Melirgan†; Odeoxil†; Ostramont†; Palimodon†; Penpurin†; Spediol†; Sulodil†; Thiocodin†; Vanogel†; Vardolin†; Zelian†; ***Hong Kong***: Fonzylane†; Irrodan; ***Indon.***: Loftyl; ***Ital.***: Buflan†; Buflocit†; Flomed†; Irrodan†; Loftyl†; ***Neth.***: Loftyl†; ***Pol.***: Buflox†; Buvasodil†; ***Port.***: Loftyl†; ***S. Afr.***: Loftyl; ***Spain***: Lofton†; ***Switz.***: Loftyl†; ***Thai.***: Irrodan†; ***Venez.***: Loftyl.

Multi-ingredient Preparations. ***Arg.***: Mimixin.

Bumetanide *(BAN, USAN, rINN)* ⊗

Bumetanid; Bumetanida; Bumetanidas; Bumétanide; Bumetanidi; Bumetanidum; Ro-10-6338; Буметанид.

3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid.

$C_{17}H_{20}N_2O_5S$=364.4

CAS — 28395-03-1.

ATC — C03CA02.

ATC Vet — QC03CA02.

UNII — 0Y2S3XUQ5H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Bumetanide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol and in acetone; slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Bumetanide). A practically white powder. Slightly soluble in water; soluble in alkaline solutions. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Although chemically unrelated, bumetanide is a loop diuretic with actions and uses similar to those of furosemide (p. 1387.1). Bumetanide is used in the treatment of oedema associated with heart failure (p. 1262.3) and with renal and hepatic disorders. It is given in high doses in the management of oliguria due to renal failure or insufficiency. Bumetanide has also been used in hypertension (p. 1251.1).

Diuresis starts within about 30 minutes to an hour after an oral dose, reaches a peak at 1 to 2 hours, and lasts for about 4 hours but may be prolonged to 6 hours after high doses; after intravenous injection its effects are evident within a few minutes and last for about 2 hours. As a general guide bumetanide 1 mg produces a diuretic effect similar to furosemide 40 mg although this should not be used for direct substitution at higher doses.

In the treatment of **oedema** the usual oral dose is 1 mg in the morning or early evening; a second dose may be given 6 to 8 hours later if necessary. A dose of 500 micrograms daily may be adequate in some elderly patients.

In refractory oedema higher doses may be necessary. An initial dose of 5 mg daily has been advocated, increased by 5 mg every 12 to 24 hours as required; however other sources have suggested a maximum total dose of 10 mg daily. Twice daily dosing may be preferred at higher doses. For maintenance therapy doses may be given daily or intermittently. In an emergency or when oral therapy cannot be given 0.5 to 1 mg may be given by intramuscular or slow intravenous injection, subsequently adjusted according to response. A dose for pulmonary oedema is 1 to 2 mg by intravenous injection, repeated 20 minutes later if necessary. Alternatively, 2 to 5 mg may be given over 30 to 60 minutes in 500 mL of a suitable infusion fluid.

For doses in children, see below.

In the treatment of **hypertension** bumetanide has been given in oral doses of 0.5 to 1 mg daily, although higher doses have been used.

When very high doses of bumetanide are used careful laboratory control is essential for furosemide (see p. 1387.1; high-dose therapy).

Administration in children. Although unlicensed in the UK for children aged under 12 years, the *BNFC* suggests that bumetanide may be given to children aged from 1 month in the treatment of oedema. An *oral* dose of 15 to 50 micrograms/kg (maximum 2 mg) may be given up to 4 times daily; the maximum daily dose is 5 mg. Alternatively, 25 to 50 micrograms/kg may be given by *intravenous infusion* over 30 to 60 minutes.

Adverse Effects

As for Furosemide, p. 1388.3. Bumetanide may cause muscle pain, particularly at high doses.

Effects on the ears. Early reports suggested that bumetanide might be less ototoxic than furosemide.[1] However, both drugs can cause deafness, especially when given in large doses to patients with renal impairment.

1. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; **28:** 426–64.

Effects on the lungs. Alveolitis, presenting as haemoptysis and steadily increasing dyspnoea in a 79-year-old man, was found to coincide with the use of bumetanide for congestive heart failure.[1] When the diuretic was replaced with furosemide the condition gradually resolved.

1. van Tellingen C. Suspension of disbelief - or the bumetanide paradox. *Neth Heart J* 2007; **15:** 31–2.

Effects on the muscles. Bumetanide, particularly in high doses in patients with chronic renal impairment, may cause severe musculoskeletal pain. A curious muscle stiffness distinct from cramp, with tenderness to compression and pain on movement, was noted in 4 patients with end-stage renal failure.[1] The calf muscles were the first to be affected; shoulder girdle and thigh muscle tenderness also occurred in 2 patients, and 1 patient also had neck stiffness. The adverse effect appeared to be dose-related for the individual patients.

1. Barclay JE, Lee HA. Clinical and pharmacokinetic studies on bumetanide in chronic renal failure. *Postgrad Med J* 1975; **51** (suppl 6): 43–6.

Effects on the skin. Bullous pemphigoid developed in a patient about 6 weeks after starting bumetanide.[1] Healing occurred after withdrawal without the need for corticosteroids.

1. Boulinguez S, *et al*. Bullous pemphigoid induced by bumetanide. *Br J Dermatol* 1998; **138:** 548–9.

Precautions

Bumetanide's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bumetanide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Furosemide, p. 1389.3.

Pharmacokinetics

Bumetanide is almost completely and fairly rapidly absorbed from the gastrointestinal tract; the bioavailability is reported to be about 80 to 95%. It has a plasma elimination half-life of about 1 to 2 hours. It is about 95% bound to plasma proteins. About 80% of the dose is excreted in the urine, about 50% as unchanged drug, and 10 to 20% in the faeces.

References to the pharmacokinetics of bumetanide in healthy subjects.

1. Halladay SC, *et al*. Diuretic effect and metabolism of bumetanide in man. *Clin Pharmacol Ther* 1977; **22:** 179–87.
2. Pentikäinen PJ, *et al*. Fate of [^{14}C]-bumetanide in man. *Br J Clin Pharmacol* 1977; **4:** 39–44.
3. Holazo AA, *et al*. Pharmacokinetics of bumetanide following intravenous, intramuscular, and oral administrations to normal subjects. *J Pharm Sci* 1984; **73:** 1108–13.
4. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; **28:** 426–64.
5. McCrindle JL, *et al*. Effect of food on the absorption of frusemide and bumetanide in man. *Br J Clin Pharmacol* 1996; **42:** 743–6.

Hepatic impairment. In a study of 8 patients with chronic hepatic disease,[1] the diuretic response to bumetanide 1 mg was impaired but bumetanide excretion rates were normal.

1. Marcantonio LA, *et al*. The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; **15:** 245–52.

Renal impairment. Renal excretion of bumetanide has been shown to be reduced in patients with chronic renal impairment with a subsequent attenuation of diuretic effect.[1-3] The cumulative pharmacodynamic effects of oral and intravenous doses were essentially similar in patients with renal impairment and transition from intravenous to oral maintenance regimens should pose no special problems.[2]

1. Marcantonio LA, *et al*. The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; **15:** 245–52.
2. Lau HSH, *et al*. Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with chronic renal failure. *Clin Pharmacol Ther* 1986; **39:** 635–45.
3. Howlett MR, *et al*. Metabolism of the diuretic bumetanide in healthy subjects and patients with renal impairment. *Eur J Clin Pharmacol* 1990; **38:** 583–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Burinex; ***Austria***: Burinex; ***Belg.***: Burinex; ***Braz.***: Burinax; ***Canad.***: Burinex; ***China***: Bai Chang (百畅); Chang Ze (畅泽); Huiyuan (慧源); Lang Qing (朗清); Ni Chang (尼畅); Shu Tong (抒彤); Wei Xin Hong (卫信宏); Xin Di (辛帝); You Bu Ding (优布丁); ***Denm.***: Burinex; ***Fr.***: Burinex; ***Ger.***: Burinex†; ***Gr.***: Burinex; ***Hong Kong***: Burinex; ***Irl.***: Burinex; ***Malaysia***: Burinex; ***Mex.***: Drenural; Miccil; ***Neth.***: Burinex; ***Norw.***: Burinex; ***NZ***: Burinex; ***Philipp.***: Burinex; ***S.Afr.***: Burinex; ***Singapore***: Burinex; ***Spain***: Fordiuran; ***Swed.***: Burinex; ***Switz.***: Burinex†; ***Turk.***: Bumid; ***UK***: Burinex†; ***USA***: Bumex†; ***Venez.***: Bumelex.

Multi-ingredient Preparations. ***Denm.***: Burinex med kaliumklorid†; ***Gr.***: Burinex K; ***Irl.***: Buram†; ***S.Afr.***: Burinex K; ***Singapore***: Burinex K.

Pharmacopoeial Preparations

BP 2014: Bumetanide and Prolonged-release Potassium Tablets; Bumetanide Injection; Bumetanide Oral Solution; Bumetanide Tablets;

USP 36: Bumetanide Injection; Bumetanide Tablets.

Bunazosin Hydrochloride *(rINNM)*

Bunazosina, hidrocloruro de; Bunazosine, Chlorhydrate de; Bunazosini Hydrochloridum; E-643; Hidrocloruro de bunazosina; Буназозина Гидрохлорид.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-butyrylhexahydro-1*H*-1,4-diazepine monohydrochloride.

$C_{19}H_{27}N_5O_3$,HCl=409.9

CAS — 80755-51-7 (bunazosin); 52712-76-2 (bunazosin hydrochloride).

UNII — 18V54TZ7U6.

Pharmacopoeias. In *Jpn*.

Profile

Bunazosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with general properties similar to those of prazosin (p. 1473.3). It is given orally as the hydrochloride in the management of hypertension; the usual maintenance dose of bunazosin hydrochloride is 3 to 6 mg daily after food but up to 12 mg daily has been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Detantol R (迪坦妥); ***Ger.***: Andante†; ***Indon.***: Detantol†; ***Jpn***: Detantol; ***Thai.***: Detantol†.

Bupranolol Hydrochloride *(rINNM)* ⊗

B-1312; Bupranolol, Chlorhydrate de; Bupranolol, hidrocloruro de; Bupranololi Hydrochloridum; Hidrocloruro de bupranolol; KL-255; Бупранолола Гидрохлорид.

1-*tert*-Butylamino-3-(6-chloro-*m*-tolyloxy)propan-2-ol hydrochloride.

$C_{14}H_{22}ClNO_2$,HCl=308.2

CAS — 14556-46-8 (bupranolol); 15148-80-8 (bupranolol hydrochloride).

ATC — C07AA19.

ATC Vet — QC07AA19.

UNII — DTC2G3GDPL.

Pharmacopoeias. In *Jpn*.

Profile

Bupranolol is a beta blocker (p. 1316.3). It is given as the hydrochloride in usual oral doses of 100 to 400 mg daily in the management of cardiovascular disorders.

Bupranolol eye drops have been used in the management of glaucoma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Betadrenol†.

Multi-ingredient Preparations. ***Austria***: Betamed.

Butizide *(rINN)* ⊗

Buthiazide (USAN); Buthiazide; Butitsidi; Butizid; Butizida; Butizidum; Isobutylhydrochlorothiazide; Thiabutazide; Бутизид.

6-Chloro-3,4-dihydro-3-isobutyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{11}H_{16}ClN_3O_4S_2$=353.8

CAS — 2043-38-1.
UNII — W00SSD35VW.

Profile

Butizide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Butizide is given orally, usually with spironolactone; the usual maintenance dose for oedema or hypertension is 5 to 10 mg daily. It has also been given with other antihypertensive drugs.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Aldactone Saltucin; ***Indon.***: Aldazide; ***Ital.***: Kadiur; ***Mex.***: Aldazida; ***Philipp.***: Aldazide; ***S.Afr.***: Aldazide; ***Switz.***: Aldozone†.

Cadralazine *(BAN, rINN)*

Cadralazina; Cadralazinum; CGP-18684/E; ISF-2469; Kadralatsiini; Kadralazin; Кадралазин.

Ethyl 3-{6-[ethyl(2-hydroxypropyl)amino]pyridazin-3-yl}carbazate.

$C_{12}H_{21}N_5O_3$=283.3

CAS — 64241-34-5.
ATC — C02DB04.
ATC Vet — QC02DB04.
UNII — 8T96I3U713.

NOTE. The name Cadral has been used as a trade mark for cadralazine.

Profile

Cadralazine is a vasodilator with actions and uses similar to those of hydralazine (p. 1401.2). It has been used in the management of hypertension.

Reviews.

1. McTavish D, *et al.* Cadralazine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension. *Drugs* 1990; **40:** 543–60.

Cafedrine Hydrochloride *(BANM, pINNM)*

Cafedrina, hidrocloruro de; Cafédrine, Chlorhydrate de; Cafedrini Hydrochloridum; H-8351; Hidrocloruro de cafedrina; Kafedrin Hydrochloride; Кафедрина Гидрохлорид.

7-[2-(β-Hydroxy-α-methylphenethylamino)ethyl]theophylline hydrochloride.

$C_{18}H_{23}N_5O_3$,HCl=393.9

CAS — 58166-83-9 (cafedrine); 3039-97-2 (cafedrine hydrochloride).
ATC — C01CA21.
ATC Vet — QC01CA21.
UNII — L0N3M64B9R.

Profile

Cafedrine hydrochloride is a derivative of theophylline (p. 1229.3), used mainly in preparations with theodrenaline hydrochloride in the treatment of hypotensive states.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Akrinor†; ***Fr.***: Praxinor; ***Ger.***: Akrinor; ***Indon.***: Akrinor; ***S.Afr.***: Akrinor.

Calcitonin Gene-related Peptide

CGRP; Péptido relacionado con el gen de la calcitonina; Пептид, Кодируемый Геном Кальцитонина; Генетически Родственный Кальцитонину Пептид.

Profile

Calcitonin gene-related peptide is an endogenous peptide derived from the calcitonin gene. It has vasodilating activity and has been investigated in the management of peripheral vascular disease (Raynaud's syndrome), heart failure, and for ischaemia following neurosurgery for subarachnoid haemorrhage. The endogenous substance may be involved in the pathophysiology of headache and migraine, and antagonists are under investigation in the management of these conditions.

References.

1. Johnston FG, *et al.* Effect of calcitonin-gene-related peptide on postoperative neurological deficits after subarachnoid haemorrhage. *Lancet* 1990; **335:** 869–72.
2. Shawkett S, *et al.* Prolonged effect of CGRP in Raynaud's patients: a double-blind randomised comparison with prostacyclin. *Br J Clin Pharmacol* 1991; **32:** 209–13.
3. Shekhar YC, *et al.* Effects of prolonged infusion of human alpha calcitonin gene-related peptide on haemodynamics, renal blood flow and hormone levels in congestive heart failure. *Am J Cardiol* 1991; **67:** 732–6.
4. European CGRP in Subarachnoid Haemorrhage Study Group. Effect of calcitonin-gene-related peptide in patients with delayed postoperative cerebral ischaemia after aneurysmal subarachnoid haemorrhage. *Lancet* 1992; **339:** 831–4.
5. Bunker CB, *et al.* Calcitonin gene-related peptide in treatment of severe peripheral vascular insufficiency in Raynaud's phenomenon. *Lancet* 1993; **342:** 80–2.
6. Feuerstein G, *et al.* Clinical perspectives of calcitonin gene related peptide pharmacology. *Can J Physiol Pharmacol* 1995; **73:** 1070–4.
7. Gherardini G, *et al.* Venous ulcers: improved healing by iontophoretic administration of calcitonin gene-related peptide and vasoactive intestinal peptide. *Plast Reconstr Surg* 1998; **101:** 90–3.
8. Márquez-Rodas I, *et al.* Pathophysiology and therapeutic possibilities of calcitonin gene-related peptide in hypertension. *J Physiol Biochem* 2006; **62:** 45–56.
9. Recober A, Russo AF. Calcitonin gene-related peptide: an update on the biology. *Curr Opin Neurol* 2009; **22:** 241–6.

Candesartan Cilexetil

(BANM, USAN, rINNM)

Candésartan, Cilexétil de; Candesartán cilexetilo; Candesartani Cilexetilum; CV-11974 (candesartan); H-212/91; Kandesartan Sileksetil; TCV-116; Кандесартана Силексетил.

Cyclohexyl carbonate ester of (±)-1-hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate.

$C_{33}H_{34}N_6O_6$=610.7

CAS — 139481-59-7 (candesartan); 145040-37-5 (candesartan cilexetil).
ATC — C09CA06.
ATC Vet — QC09CA06.
UNII — R85M2X0D68.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Candesartan Cilexetil). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; freely soluble in dichloromethane.

USP 36: (Candesartan Cilexetil). A white to off-white powder. Practically insoluble in water; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature between 20 degrees and 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Candesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1) and may also be used in heart failure in patients with impaired left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors, (see under Losartan Potassium, p. 1423.2).

Candesartan is given orally as the ester prodrug candesartan cilexetil. Onset of antihypertensive action occurs about 2 hours after a dose and the maximum effect is achieved within about 4 weeks of starting therapy.

In the management of **hypertension** the usual initial dose of candesartan cilexetil is 8 mg once daily in the UK, or 16 mg once daily in the USA. The dose should be adjusted according to response; the usual maintenance dose is 8 mg once daily, but doses up to 32 mg daily, as a single dose or in 2 divided doses, may be used. Lower initial doses should be considered in patients with intravascular volume depletion; in the UK an initial dose of 4 mg once daily is suggested. Patients with renal or hepatic impairment may also require low initial doses (see below). For doses in children, see Administration in Children, below.

In **heart failure,** candesartan cilexetil is given in an initial dose of 4 mg once daily. The dose should be doubled at intervals of not less than two weeks up to 32 mg once daily if tolerated; blood pressure should be monitored during dose increases.

Reviews.

1. See S, Stirling AL. Candesartan cilexetil: an angiotensin II-receptor blocker. *Am J Health-Syst Pharm* 2000; **57:** 739–46.
2. Easthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. *Drugs* 2002; **62:** 1253–87.
3. Fenton C, Scott LJ. Candesartan cilexetil: a review of its use in the management of chronic heart failure. *Drugs* 2005; **65:** 537–58.
4. McKelvie RS. Candesartan for the management of heart failure: more than an alternative. *Expert Opin Pharmacother* 2006; **7:** 1945–56.
5. Meredith PA. Candesartan cilexetil—a review of effects on cardiovascular complications in hypertension and chronic heart failure. *Curr Med Res Opin* 2007; **23:** 1693–1705.
6. Mendis B, Page SR. Candesartan: widening indications for this angiotensin II receptor blocker? *Expert Opin Pharmacother* 2009; **10:** 1995–2007.

Administration in children. Candesartan cilexetil is used for the treatment of hypertension in children from 1 year of age. It is given in the following oral doses, either as a single daily dose or in 2 divided doses:

- 1 up to 6 years: initially 200 micrograms/kg daily, adjusted according to response to 50 to 400 micrograms/kg daily
- 6 up to 17 years and weighing less than 50 kg: initially 4 to 8 mg daily, adjusted according to response to 2 to 16 mg daily
- 6 up to 17 years and weighing more than 50 kg: initially 8 to 16 mg daily, adjusted according to response to 4 to 32 mg daily

Administration in hepatic impairment. The elimination of candesartan cilexetil is reduced in patients with hepatic impairment. For patients with *hypertension*, an initial oral dose of 4 mg once daily is recommended in the UK in those with mild or moderate impairment. In the USA, no adjustment is considered necessary for patients with mild impairment; an initial oral dose of 8 mg once daily is recommended for those with moderate impairment.

For patients with *heart failure*, no dose adjustments are considered necessary in those with mild to moderate impairment as initial doses are lower for this condition (see Uses and Administration, above).

There is no experience of use in patients with severe hepatic impairment.

Administration in renal impairment. The elimination of candesartan cilexetil is reduced in patients with renal impairment (including patients on haemodialysis[1]) and lower doses may therefore be required.

For patients with *hypertension*, an initial oral dose of 4 mg once daily is recommended in the UK, including for patients on haemodialysis. In the USA, no initial dose adjustment is recommended for renal impairment, although dose reduction may be considered if patients are volume depleted.

For patients with *heart failure*, dose adjustments are not necessary as initial doses are lower for this condition (see Uses and Administration, above).

Candesartan may also have adverse effects on renal function and regular monitoring is advised; treatment may need to be withheld or stopped if renal function deteriorates.

1. Ottosson P, *et al.* Candesartan cilexetil in haemodialysis patients. *Clin Drug Invest* 2003; **23:** 545–50.

Diabetic complications. For mention of the potential use of angiotensin II receptor antagonists, including candesartan, in the management of diabetic complications such as retinopathy see under Losartan, p. 1423.1.

Migraine. For reference to the use of angiotensin II receptor antagonists, including candesartan, in the prophylaxis of migraine, see under Losartan, p. 1423.3.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies candesartan as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Candesartan cilexetil is an ester prodrug that is hydrolysed to the active form candesartan during absorption from the gastrointestinal tract. The absolute bioavailability for candesartan is about 40% when candesartan cilexetil is given as a solution and about 14% when given as tablets. Peak plasma concentrations of candesartan occur about 3 to 4 hours after oral doses as tablets. Candesartan is more than 99% bound to plasma proteins. It is excreted in urine and bile mainly as unchanged drug with a small amount as inactive metabolites. The terminal elimination half-life is about 9 hours. Candesartan is not removed by haemodialysis.

Reviews.

1. Gleiter CH, Mörike KE. Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* 2002; **41:** 7–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atacand; Dacten; Tiadyl; ***Austral.***: Atacand; ***Austria***: Atacand; Blopress; ***Belg.***: Atacand; ***Braz.***: Atacand; Blopress; ***Canad.***: Atacand; ***Chile***: Atacand; Bilaten; Blopress; Blox; Candex; ***China***: Ao Bi Xin (奥必欣); Blopress (必洛斯); Bo Li Gao (搏力高); Da Mai (达迈); Di Zhi Ya (迪之雅); Ni Li An (倪利安); Su Na (苏纳); Wei Er Ya (维尔

亚); Xi Jun Ning (悉君宁); ***Cz.***: Atacand†; Texacand; Xaleec; ***Denm.***: Amias; Atacand; Candemox; Candexetil†; ***Fin.***: Atacand; Candemox; Candestad; Candexetil; Kandrozid; ***Fr.***: Atacand; Kenzen; ***Ger.***: Atacand; Blopress; ***Gr.***: Atacand; ***Hong Kong***: Blopress; ***Hung.***: Atacand; ***India***: Candelong; Candesar; Candestan; Cantar; Ipsita; ***Indon.***: Blopress; ***Irl.***: Atacand; Blopress; Candist; Catasart; ***Israel***: Atacand; ***Ital.***: Blopress; Ratacand; ***Jpn***: Blopress; ***Malaysia***: Atacand; Blopress; ***Mex.***: Atacand; Blopress; ***Neth.***: Aldireca; Amias†; Atacand; Blopress; Casarlic; Kairasec; Karbis; Omegacand; Ratacand†; Silardaf; Texacand; ***Norw.***: Amias; Atacand; ***NZ***: Atacand; Cardosart; ***Philipp.***: Blopress; Candelong; Candez; ***Pol.***: Atacand; Karbis; ***Port.***: Atacand; Blopress; ***Rus.***: Atacand (Атаканд); ***S.Afr.***: Atacand; ***Singapore***: Atacand; ***Spain***: Atacand; Blopress; Karbis; Parapres; ***Swed.***: Atacand; Candesarstad; Candexetil; ***Switz.***: Atacand; Blopress; Cansartan; Pemzek; ***Thai.***: Blopress; ***Turk.***: Atacand; Ayra; Candexil; Cantab; Tensart; ***UK***: Amias; ***Ukr.***: Atacand (Атаканд); Candesar (Кандесар); Kasark (Касарк); ***USA***: Atacand; Candepressin; ***Venez.***: Atacand; Blopress.

Multi-ingredient Preparations. ***Arg.***: Atacand D; Atacand Duo; Dacten D; Tiadyl Plus; ***Austral.***: Atacand Plus; ***Austria***: Atacand Plus; Blopress Plus; ***Belg.***: Atacand Plus; ***Braz.***: Atacand Comb; Atacand HCT; ***Canad.***: Atacand Plus; ***Chile***: Atacand Plus; Bilaten-D; Blopress D; Blox-D; Candex-D; ***China***: Bokaiqing (波开清); ***Cz.***: Atacand Plus†; Texacandozid; Xaleec Combi; ***Denm.***: Atacand Zid; Atazid†; Candemox Comp; Candexetil comp; Hytacand; Ratacand Plus; Ratacand Zid†; ***Fin.***: Atacand Plus; Candemox Comp; Candestad Comp; Candexetil Comp; ***Fr.***: Cokenzen; Hytacand; ***Ger.***: Atacand Plus; Blopress Plus; ***Gr.***: Atacand Plus; ***Hong Kong***: Blopress Plus; ***Hung.***: Atacand Plus; ***India***: Candelong-H; Candesar-H; ***Indon.***: Blopress Plus; ***Irl.***: Atacand Plus; Blopress Plus; Candist Plus; Catasart Plus; ***Israel***: Atacand Plus; Candesartan Plus; ***Ital.***: Blopresid; Ratacand Plus; ***Jpn***: Unisia; ***Malaysia***: Atacand Plus; ***Mex.***: Atacand Plus; Blopress Plus; ***Neth.***: Atacand Plus; Blopresid; Cocardax; Omegacand HCT; Texacand HCT; ***Norw.***: Atacand Plus; ***Philipp.***: Blopress Plus; ***Pol.***: Candepres HCT; ***Port.***: Blopress Comp; Hytacand; ***Rus.***: Atacand Plus (Атаканд Плюс); ***S.Afr.***: Atacand Plus; ***Singapore***: Atacand Plus; ***Spain***: Atacand Plus; Blopress Forte; Blopress Plus; Karbicombi; Parapres Plus; ***Swed.***: Atacand Plus; Candemox Comp; ***Switz.***: Atacand Plus; Blopress Plus; Cansartan Plus; Co-Candesartan; Pemzek Plus; ***Thai.***: Blopress Plus; ***Turk.***: Atacand Plus; Ayra Plus; Candexil Plus; Co-Cantab; Tensart Plus; ***Ukr.***: Atacand Plus (Атаканда Плюс); Candesar H (Кандесар Н); Kasark H (Касарк Н); Kasark HD (Касарк HD); ***USA***: Atacand HCT; Candepressin Plus; ***Venez.***: Atacand Plus; Blopress Plus.

Cangrelor Tetrasodium *(BANM, USAN, rINNM)*

AR-C69031MX (cangrelor tetrasodium); AR-C69931XX (cangrelor); Cangrelor tetrasódico; Cangrélor tetrasodique; Cangrelorum tetranatricum; Кангрелор Тетранатрий.

N-[2-(Methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-5′-adenylic acid monoanhydride with tetrasodium (dichloromethylene)diphosphonate.

$C_{17}H_{21}Cl_2F_3N_5Na_4O_{12}P_5S_2$=864.3

CAS — 163706-06-7 (cangrelor); 163706-36-3 (cangrelor tetrasodium).

UNII — 2144G00Y7W.

Profile

Cangrelor is an adenosine triphosphate analogue, similar to ticagrelor (p. 1511.3). It has a short half-life and is given intravenously. It is under investigation as an antiplatelet drug in the management of acute coronary syndromes but large studies have not shown any benefit over currently available drugs.

References.

1. Harrington RA, *et al.* Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009; **361:** 2318–29.
2. Bhatt DL, *et al.* CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009; **361:** 2330–41.

Canrenone *(USAN, pINN)* ⊗

Aldadiene; Canrenona; Canrénone; Canrenonum; RP-11614; SC-9376; Канренон.

17-Hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylic acid γ-lactone.

$C_{22}H_{28}O_3$=340.5

CAS — 976-71-6.

ATC — C03DA03.

ATC Vet — QC03DA03.

UNII — 78O20X9J0U.

Profile

Canrenone is a potassium-sparing diuretic with properties similar to those of spironolactone (p. 1501.2) and is given orally in the treatment of refractory oedema associated with heart failure (p. 1262.3), renal, or hepatic disease, and in hypertension (p. 1251.1). It is a metabolite of both spironolactone and potassium canrenoate (p. 1472.2). It is given in usual doses of 50 to 200 mg daily. Doses of up to 300 mg daily may be required in some patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Luvion.

Captopril *(BAN, USAN, rINN)*

Captoprilum; Kaptopriili; Kaptopril; Kaptoprilis; SQ-14225; Каптоприл.

1-[(2*S*)-3-Mercapto-2-methylpropionyl]-L-proline.

$C_9H_{15}NO_3S$=217.3

CAS — 62571-86-2.

ATC — C09AA01.

ATC Vet — QC09AA01.

UNII — 9G64RSX1XD.

NOTE. Compounded preparations of captopril may be represented by the following names:

- Co-zidocapt (*BAN*)—captopril 2 parts and hydrochlorothiazide 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Captopril). A white or almost white crystalline powder. Soluble in water; freely soluble in dichloromethane and in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 2.0 to 2.6.

USP 36: (Captopril). A white or off-white crystalline powder which may have a characteristic sulfide-like odour. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers.

Stability. Although captopril itself is relatively stable[1] at temperatures up to 50 degrees, and extemporaneously prepared powders (made by triturating the tablets with lactose) have been reported to be stable for at least 12 weeks at room temperature,[2] aqueous solutions are subject to oxidative degradation, mainly to captopril disulfide,[1] which increases[3] with increase in pH above 4. The manufacturers report that a liquid form of captopril prepared from pulverised tablets in distilled water containing 1 mg/mL retained 96.6% of the original concentration of drug after storage at room temperature for 5 days, but they advise that since it contains no preservative it should be used within 2 days of preparation.[4] Others have reported wide variations in stability depending upon the formulation. In one study[5] the shelf-life of a solution of captopril 1 mg/mL prepared from crushed tablets and tap water was estimated to be 27 days when stored at 5 degrees. However, in another study[6] captopril was much less stable; in sterile water for irrigation captopril was stable for at least 3 days when stored at 5 degrees, but in tap water it disappeared at a much faster rate. Increased stability has been reported after the addition of sodium ascorbate to the solution,[7] and with captopril powder rather than crushed tablets.[8] A 1 mg/mL preparation made with crushed tablets and undiluted syrup has also been reported to be stable for 30 days at 5 degrees and may be more palatable than aqueous formulations.[9]

1. Lund W, Cowe HJ. Stability of dry powder formulations. *Pharm J* 1986; **237:** 179–80.
2. Taketomo CK, *et al.* Stability of captopril in powder papers under three storage conditions. *Am J Hosp Pharm* 1990; **47:** 1799–1801.
3. Timmins P, *et al.* Factors affecting captopril stability in aqueous solution. *Int J Pharmaceutics* 1982; **11:** 329–36.
4. Andrews CD, Essex A. Captopril suspension. *Pharm J* 1986; **237:** 734–5.
5. Pereira CM, Tam YK. Stability of captopril in tap water. *Am J Hosp Pharm* 1992; **49:** 612–15.
6. Anaizi NH, Swenson C. Instability of aqueous captopril solutions. *Am J Hosp Pharm* 1993; **50:** 486–8.
7. Nahata MC, *et al.* Stability of captopril in three liquid dosage forms. *Am J Hosp Pharm* 1994; **51:** 95–6.
8. Chan DS, *et al.* Degradation of captopril in solutions compounded from tablets and standard powder. *Am J Hosp Pharm* 1994; **51:** 1205–7.
9. Lye MYF, *et al.* Effects of ingredients on stability of captopril in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54:** 2483–7.

Uses and Administration

Captopril is a sulfhydryl-containing ACE inhibitor (p. 1282.2). It is used in the management of hypertension (p. 1251.1), in heart failure (p. 1262.3), after myocardial infarction (p. 1257.1), and in diabetic nephropathy (see Kidney Disorders, p. 1284.1).

After oral doses captopril produces a maximum effect within 1 to 2 hours, although the full effect may not develop for several weeks during chronic dosing. The duration of action is dose-dependent and may persist for 6 to 12 hours.

In the treatment of **hypertension** the initial oral dose is 12.5 mg twice daily, increased gradually at intervals of 2 to 4 weeks according to the response. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 6.25 mg twice daily is recommended if captopril is given in addition to a *diuretic* or to elderly patients; if possible the diuretic should be stopped 2 or 3 days before introducing captopril. The usual maintenance dose is 25 to 50 mg twice daily and should not normally exceed 50 mg three times daily. If hypertension is not satisfactorily controlled at this dosage, addition of a second drug or substitution of an alternative drug should be considered. In the USA higher doses of up to 150 mg three times daily have been suggested for patients with hypertension uncontrolled by lower doses of captopril used with diuretic therapy.

In the treatment of **heart failure** severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus an initial oral dose of 6.25 to 12.5 mg of captopril is given under close medical supervision; the usual maintenance dose is 25 mg two or three times daily, and doses should not normally exceed 50 mg three times daily. Again, in the USA higher doses of up to 150 mg three times daily have been suggested.

After **myocardial infarction**, captopril is used prophylactically in clinically stable patients with symptomatic or asymptomatic left ventricular dysfunction to improve survival, delay the onset of symptomatic heart failure, and reduce recurrent infarction. Captopril is licensed for *acute* treatment starting within 24 hours of the onset of symptoms in patients with stable haemodynamics. A 6.25-mg test dose is given, followed by 12.5 mg after 2 hours, and 25 mg after another 12 hours. If tolerated, a dose of 50 mg twice daily may be started the following day and continued for 4 weeks, before considering adjustment to the maintenance dose for chronic treatment described below.

If not given within 24 hours of the onset of symptoms, *chronic* treatment with captopril may be started within 3 to 16 days post-infarction at an initial dose of 6.25 mg, followed by 12.5 mg three times daily for 2 days, then 25 mg three times daily. The maintenance dose is between 75 and 150 mg daily in 2 or 3 divided doses.

In **diabetic nephropathy** (microalbuminuria greater than 30 mg/day) in type 1 diabetics, 75 to 100 mg of captopril may be given daily, in divided oral doses. Other antihypertensives may be used with captopril if a further reduction in blood pressure is required.

For doses in children, see below.

Doses may need to be reduced in patients with renal impairment (see p. 1332.1).

Administration. Captopril is generally given orally. Sublingual[1] and intravenous[2,3] dosage has also been tried, but these routes are not established.

1. Angeli P, *et al.* Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies: a randomized, single-blind clinical trial. *Arch Intern Med* 1991; **151:** 678–82.
2. Savi L, *et al.* A new therapy for hypertensive emergencies: intravenous captopril. *Curr Ther Res* 1990; **47:** 1073–81.
3. Langes K, *et al.* Efficacy and safety of intravenous captopril in congestive heart failure. *Curr Ther Res* 1993; **53:** 167–76.

Administration in children. Experience with captopril in children is limited, but it may be given orally for indications similar to those in adults (see Uses and Administration, above). UK licensed product information suggests an initial dose of 300 micrograms/kg in children and adolescents; half this dose should be given initially to neonates and infants (including premature infants), and children with renal impairment. The dose is adjusted according to response to a maximum of 6 mg/kg daily in 2 or 3 divided doses.

Captopril, given in an initial dose of 250 micrograms/kg daily, increased to up to 2.5 or 3.5 mg/kg daily in 3 divided doses, has also been reported to produce benefit in infants with severe heart failure secondary to congenital defects (mainly manifesting as left-to-right shunt).[1,2]

The following doses of captopril are suggested by the *BNFC* for hypertension, heart failure, or proteinuria in nephritis:

- neonate: test dose, 10 to 50 micrograms/kg (if the neonate is less than 37 weeks postmenstrual age give 10 micrograms/kg) with careful monitoring of blood pressure for 1 to 2 hours; if tolerated, give 10 to 50 micrograms/kg 2 or 3 times daily, increased as necessary to a maximum of 2 mg/kg daily in divided doses (maximum of 300 micrograms/kg daily in divided doses if the neonate is less than 37 weeks postmenstrual age)
- child 1 month to 12 years: test dose, 100 micrograms/kg (maximum 6.25 mg) with careful monitoring of blood pressure for 1 to 2 hours; if tolerated, give 100 to 300 micrograms/kg 2 or 3 times daily, increased as necessary to a maximum of 6 mg/kg daily in divided doses (maximum of 4 mg/kg daily in divided doses in child 1 month to 1 year)
- child 12 years to 18 years: test dose, 100 micrograms/kg or 6.25 mg with careful monitoring of blood pressure for 1 to 2 hours; if tolerated, give 12.5 to 25 mg 2 or 3 times

daily, increased as necessary to a maximum of 150 mg daily in divided doses

The *BNFC* also suggests the same dose in children aged 12 years and over for diabetic nephropathy.

1. Scammell AM, *et al*. Captopril in treatment of infant heart failure: a preliminary report. *Int J Cardiol* 1987; **16:** 295–301.
2. Shaw NJ, *et al*. Captopril in heart failure secondary to a left to right shunt. *Arch Dis Child* 1988; **63:** 360–3.

Administration in renal impairment. The dose of captopril should be reduced or the dosage interval increased in adults with renal impairment, depending on their creatinine clearance (CC) per 1.73m². The following doses have been suggested:

- CC 21 to 40 mL/minute: initial daily dose 25 mg and maximum daily dose 100 mg
- CC 10 to 20 mL/minute: initial daily dose 12.5 mg and maximum daily dose 75 mg
- CC below 10 mL/minute: initial daily dose 6.25 mg and maximum daily dose 37.5 mg

If a diuretic also needs to be given, a loop diuretic should be chosen rather than a thiazide.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Captopril has been reported to cause false positive results in tests for acetone in urine.

Incidence of adverse effects. Results of postmarketing surveillance[1] in 30 515 hypertensive patients taking captopril showed that 4.9% had their therapy stopped because of adverse effects thought to be due to the drug. The mean initial daily dose was 46 mg; at final evaluation the mean daily dose was 58 mg. The adverse effect most commonly reported was headache (in 1.8%); others included dizziness (1.6%), rashes (1.1%), nausea (1.0%), taste disturbances (0.9%), and cough (0.8%). This study excluded patients with renal impairment but an earlier survey[2] in 6737 patients taking captopril alone or in combination found that rash and dysgeusia were more frequent in patients with renal impairment (occurring in 6.2% and 3.2% respectively of those receiving 150 mg daily or less of captopril) than in those with normal serum creatinine (4.3% and 2.2%). The frequency of both symptoms was somewhat higher in those given higher doses. Symptoms of hypotension occurred in about 5% of patients and were not influenced by dose or renal function. The cumulative frequency of withdrawal due to adverse effects was estimated at 5.8% in this study, which is similar to that in the larger survey. In another postmarketing surveillance study[3] involving more than 60 000 patients, captopril was withdrawn in 8.9% because of adverse effects.

For further reference to some of these adverse effects, see under ACE Inhibitors, p. 1285.2.

1. Schoenberger JA, *et al*. Efficacy, safety, and quality-of-life assessment of captopril antihypertensive therapy in clinical practice. *Arch Intern Med* 1990; **150:** 301–6.
2. Jenkins AC, *et al*. Captopril in hypertension: seven years later. *J Cardiovasc Pharmacol* 1985; **7** (suppl 1): S96–S101.
3. Chalmers D, *et al*. Postmarketing surveillance of captopril for hypertension. *Br J Clin Pharmacol* 1992; **34:** 215–23.

Breast feeding. Captopril is distributed into breast milk and licensed product information advises that breast feeding should be avoided. However, a study[1] in 12 women found that the concentration of captopril in breast milk was about 1% of maternal blood concentrations, suggesting that the amount ingested by the infant would be very low. No adverse effects were noted in the infants in this study, and the American Academy of Pediatrics considers[2] that captopril is therefore usually compatible with breast feeding.

For advice from UK regulatory authorities against the use of any ACE inhibitor during at least the early weeks of breast feeding see under Precautions of ACE Inhibitors, p. 1287.3.

1. Devlin RG, Fleiss PM. Captopril in human blood and breast milk. *J Clin Pharmacol* 1981; **21:** 110–113.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies captopril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

About 60 to 75% of a dose of captopril is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about an hour. Absorption has been reported to be reduced in the presence of food, but this may not be clinically relevant (see below). Captopril is about 30% bound to plasma proteins. It crosses the placenta and is found in breast milk at about 1% of maternal blood concentrations. It is largely excreted in the urine, 40 to 50% as unchanged drug, the rest as disulfide and other metabolites. The elimination half-life has been reported to be 2 to 3 hours but this is increased in renal impairment. Captopril is removed by haemodialysis.

Reviews.

1. Duchin KL, *et al*. Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases. *Clin Pharmacokinet* 1988; **14:** 241–59.

Absorption. The bioavailability and peak plasma concentrations of captopril have been shown to be reduced by 25 to 55% when given with food in single dose studies[1-4] and with chronic dosing.[5] However, this may not be clinically significant since several studies[3,4,6] indicated that food intake had no effect on the antihypertensive activity of captopril.

1. Williams GM, Sugerman AA. The effect of a meal, at various times relative to drug administration, on the bioavailability of captopril. *J Clin Pharmacol* 1982; **22:** 18A.
2. Singhvi SM, *et al*. Effect of food on the bioavailability of captopril in healthy subjects. *J Clin Pharmacol* 1982; **22:** 135–40.
3. Mäntylä R, *et al*. Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 626–9.
4. Müller HM, *et al*. The influence of food intake on pharmacodynamics and plasma concentration of captopril. *J Hypertens* 1985; **3** (suppl 2): S135–S136.
5. Öhman KP, *et al*. Pharmacokinetics of captopril and its effects on blood pressure during acute and chronic administration and in relation to food intake. *J Cardiovasc Pharmacol* 1985; **7** (suppl 1): S20–S24.
6. Izumi Y, *et al*. Influence of food on the clinical effect of angiotensin I converting enzyme inhibitor (SQ 14225). *Tohoku J Exp Med* 1983; **139:** 279–86.

Renal impairment. A study of 9 patients with chronic renal failure undergoing dialysis found that after a single dose of captopril, peak plasma concentrations were 2.5 times higher than in patients with normal renal function, and peak concentrations of its disulfide metabolites were 4 times higher.[1] Peak concentrations occurred later in uraemic patients and the apparent half-life of total captopril was 46 hours in uraemic patients compared with 2.95 hours in patients with normal renal function.

1. Drummer OH, *et al*. The pharmacokinetics of captopril and captopril disulfide conjugates in uraemic patients on maintenance dialysis: comparison with patients with normal renal function. *Eur J Clin Pharmacol* 1987; **32:** 267–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antasten†; ***Austral.***: Acenorm; Capoten; Captohexal†; Topace†; Zedace; ***Austria***: Capace†; Debax; ***Belg.***: Capoten; Capriltop†; Doccaptopri†; ***Braz.***: Aorten; Capobal; Capoten; Capotrat; Capotrineo; Capox; Capril; Captolab; Captomed; Captomido; Capton; Captopiril; Captopron; Captotec; Captrizin†; Catoprol†; Ductopril; Hipoten; Normapril; Pressomax†; Prilpressin; Repril; ***Canad.***: Apo-Capto; Capoten; Novo-Captoril†; Nu-Capto; ***Chile***: Capoten; Properil; ***China***: An Ting (安汀); Bang De Mei (邦德美); Capoten (开博通); Kai Fu Lin (开富林); Ya Ning (压宁); ***Cz.***: Capoten†; Tensiomin; ***Denm.***: Capoten†; Captol; Captovis; ***Fin.***: Captomin†; Captostad†; Lopril; ***Fr.***: Captolane†; Lopril; ***Ger.***: ACE-Hemmer; Adocor†; Capto†; Captobeta; Captodoc†; Captoflux†; Captogamma; Captohexal†; cor tensobon†; Jucapt†; Lopirin†; Tensiomin-Cor†; Tensiomin†; Tensobon†; Tensostad†; ***Gr.***: Capoten; Cregar; Ftonavil; Hypotensor; Neo-Ipertas; Normolose; Odupril; Pertacilon; Sancap; ***Hong Kong***: Capoten†; Kimafan†; Novo-Captoril†; Ropril†; Tensiomin; ***Hung.***: Aceomel; Captogamma†; Tensiomin; ***India***: Aceten; Capace; Capotril; ***Indon.***: Acepress; Capoten†; Captensin; Casipril†; Dexacap; Farmoten; Forten†; Locap†; Lotensin; Metopril; Otoryl; Praten†; Scantensin; Tenofax†; Tensicap; Tensobon; Vapril; ***Irl.***: Aceomel; Capoten; Caprill†; Captor; Geroten†; ***Israel***: Aceril; ***Ital.***: Acepress†; Capoten; ***Malaysia***: Apuzin; Kimafan; ***Mex.***: Altiver; Atrisol; Biodezil; Bioxil; Brucap; Bugazon†; Capotena; Captoser; Captral; Cardipril; Catona; Cryopril; Eca Presan; Ecapril; Ecaten; Enlace; Hipertex; Kenolan; Lenpryl; Midrat; Miocap†; Novapress; Ospil; Precaptil†; Prinarten; Proldin; Ranpres; Reductel; Reduprec; Rilten; Romir; Tenca-1; Tensil; Toprifar; Toprilem†; Tropix-HC†; Varaxil; ***Norw.***: Capoten†; ***NZ***: Capoten; Captohexal†; ***Philipp.***: Ace-Bloc; Bloc-Med; Capomed; Capotec; Capoten†; Captogen; Captor; Captril; Cardiovaz; Conamid; Hartylox; Normil; Prelat; Primace; Retensin; Spec-Ace; Tensoril; Unihype; Vasostad; ***Port.***: Capoten; Capritin; Carencil; Hipertil†; Hipotensil; Pressil; Prilovase†; Vidapril; ***Rus.***: Aceten (Ацетен)†; Angiopril (Ангиоприл); Apo-Capto (Апо-капто)†; Blocordil (Блокордил); Capopharm (Капофарм); Capoten (Капотен); Rilcapton (Рилкаптон); ***S.Afr.***: Aceten†; Adco-Captomax; Capace; Capoten; Captohexal; Cardiace†; Zapto; ***Singapore***: Apo-Capto; Catoplin; Dexacap; Epsitron; Kapril; Rilcapton; ***Spain***: Capoten; Captosina; Cesplon†; Dilabar†; Tensoprel; ***Switz.***: Captosol; Lopirin†; ***Thai.***: Capoten†; Capril; Epsitron; Gemzil; Tensiomin; ***Turk.***: Kapril; Kaptoril; ***UAE***: Captophar; ***UK***: Acepril; Capoten; Ecopace; Kaplon; Tensopril†; ***USA***: Capoten; ***Venez.***: Capoten; Tabulan.

Multi-ingredient Preparations. ***Austria***: Capozide; Captohexal Comp†; Captopril-HCT; Co-Captopril; Veracapt; ***Braz.***: Capox H; Captotec + HCT; Hidropril; Lopril-D; ***China***: Kai Fu Te (开富特); ***Denm.***: Capozid†; Capthydro; ***Fr.***: Captea; Ecazide; ***Ger.***: ACE-Hemmer comp; Adocomp†; Capozide†; Capto Comp†; Capto Plus†; Captobeta Comp; Captodoc Comp†; Captogamma HCT; Captohexal Comp†; Captopril Comp†; Captopril HCT†; Captopril Plus†; Cardiagen HCT†; Jutacor comp†; Tensobon comp; ***Gr.***: Anastol; Captopress; Captospes+H; Dosturel; Ekzevit; Empirol; Fetylan; Ketazide; Kifarol; Loren-Press; Normolose-H; Pentatec; Piesital; Return; Sancazid; Sedapressin; Superace; Uresan; Zidepril; ***India***: Acezide; Angiopril-DU; Capotril-H; ***Indon.***: Capozide†; ***Irl.***: Capozide; Captor-HCT; Half Capozide; ***Ital.***: Acediur; Aceplus; ***Mex.***: Capozide; Captral ASA; Co-Captral; ***NZ***: Capozide; ***Port.***: Lopiretic; ***Rus.***: Capozide (Капозид); ***S.Afr.***: Capozide†; Captoretic†; Zapto Co; ***Spain***: Cesplon Plus†; Dilabar Diu; Ecadiu†; Ecazide; ***Switz.***: Capozide†; Captosol comp; Tensobon comp†; ***UK***: Acezide; Capozide; Capto-Co; ***Ukr.***: Capotiasid (Капотиазид); Captopres (Каптопрес); Normopres (Нормопрес); ***USA***: Capozide; ***Venez.***: Capozide.

Pharmacopoeial Preparations

BP 2014: Captopril Oral Solution; Captopril Tablets;
USP 36: Captopril and Hydrochlorothiazide Tablets; Captopril Oral Solution; Captopril Oral Suspension; Captopril Tablets.

Carazolol *(BAN, rINN)* ⊗

BM-51052; Carazololum; Каразолол.
1-(Carbazol-4-yloxy)-3-isopropylaminopropan-2-ol.
$C_{18}H_{22}N_2O_2$=298.4
CAS — 57775-29-8.
ATC Vet — QC07AA90.
UNII — 29PW755S2A.

Profile

Carazolol is a beta blocker (p. 1316.3) that is used in veterinary medicine.

Carperitide *(USAN, rINN)* ⊗

Carperitida; Carpéritide; Carperitidum; SUN-4936; Карперитид.
CAS — 89213-87-6.
UNII — GZ8FA500J0.

Profile

Carperitide is a recombinant atrial natriuretic peptide (see p. 1444.1) used in the management of acute heart failure.

References.

1. Suwa M, *et al*. Multicenter prospective investigation on efficacy and safety of carperitide for acute heart failure in the 'real world' of therapy. *Circ J* 2005; **69:** 283–90.
2. Hata N, *et al*. Effects of carperitide on the long-term prognosis of patients with acute decompensated chronic heart failure: the PROTECT multicenter randomized controlled study. *Circ J* 2008; **72:** 1787–93.
3. Nomura F, *et al*. Multicenter prospective investigation on efficacy and safety of carperitide as a first-line drug for acute heart failure syndrome with preserved blood pressure. COMPASS: Carperitide Effects Observed Through Monitoring Dyspnea in Acute Decompensated Heart Failure Study. *Circ J* 2008; **72:** 1777–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Hanp.

Carteolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Abbott-43326; Cartéolol, Chlorhydrate de; Carteolol, hidrocloruro de; Carteololhydrochlorid; Carteololi Hydrochloridum; Hidrocloruro de carteolol; Karteolol Hidroklorür; Karteolol-hidroklorid; Karteolol-hydrochlorid; Karteololhydroklorid; Karteololihydrokloridi; Karteololio hidrochloridas; OPC-1085; Картеолола Гидрохлорид.
5-(3-*tert*-Butylamino-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one hydrochloride.
$C_{16}H_{24}N_2O_3$,HCl=328.8
CAS — 51781-06-7 (carteolol); 51781-21-6 (carteolol hydrochloride).
ATC — C07AA15; S01ED05.
ATC Vet — QC07AA15; QS01ED05.
UNII — 4797W6I0T4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Carteolol Hydrochloride). White or almost white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A

1% solution in water has a pH of 5.0 to 6.0. Store in airtight containers.

USP 36: (Carteolol Hydrochloride). pH of a 1% solution in water is between 5.0 and 6.0.

Uses and Administration

Carteolol is a non-cardioselective beta blocker (see p. 1316.3). It is reported to possess intrinsic sympathomimetic activity but lacks significant membrane-stabilising activity.

Carteolol is used as the hydrochloride in the management of glaucoma (p. 1999.1), hypertension (p. 1251.1), and some cardiac disorders such as angina pectoris (p. 1254.3) and cardiac arrhythmias (p. 1266.1).

Eye drops containing carteolol hydrochloride 1% or 2% are instilled twice daily to reduce raised intra-ocular pressure in open-angle **glaucoma** and ocular hypertension.

In **hypertension**, **angina pectoris**, and **arrhythmias**, carteolol hydrochloride is given orally in a usual dose range of 2.5 to 30 mg daily, adjusted according to response.

The oral dose of carteolol hydrochloride should be reduced in patients with renal impairment (see below).

Reviews.

1. Chrisp P, Sorkin EM. Ocular carteolol: a review of its pharmacological properties, and therapeutic use in glaucoma and ocular hypertension. *Drugs Aging* 1992; **2:** 58–77. Correction. *ibid.* 1994; **4:** 62.
2. Henness S, *et al*. Ocular carteolol: a review of its use in the management of glaucoma and ocular hypertension. *Drugs Aging* 2007; **24:** 509–28.

Administration in renal impairment. The oral dose of carteolol hydrochloride should be reduced in patients with renal impairment. A suggested regimen based on creatine clearance (CC) for patients with hypertension is as follows:

- CC 30 to 80 mL/minute: 10 mg daily
- CC less than 30 mL/minute: use not recommended

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carteolol as not porphyrinogenic when used as eye drops; it may be used as a drug of first choice and no precautions are needed. A classification is not given for systemic carteolol.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Carteolol is well absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours of oral doses. The bioavailability is about 84%. It has low lipid solubility. About 20 to 30% is protein bound. The plasma half-life is reported to be 3 to 6 hours. The major route of elimination is renal with 50 to 70% of a dose being excreted unchanged in the urine; carteolol therefore accumulates in patients with renal disease. Major metabolites are 8-hydroxycarteolol and glucuronic acid conjugates of carteolol and 8-hydroxycarteolol. The 8-hydroxycarteolol metabolite is active; its half-life is reported to be 8 to 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cartens; Elebloc; Glacout†; Glauteolol; Poenglaucol; Singlauc; Tenoftal; ***Belg.***: Arteoptic; Carteabak; Carteol; ***China***: Mikelan (美开朗); ***Cz.***: Arteoptic; Carteol; ***Fr.***: Carteabak†; Carteol; Mikelan; ***Ger.***: Arteoptic; Endak; ***Gr.***: Cardelol; Carteodose; Fortinol; Glautelol; Napolit; Stobol; Vinitus; Zymoptic; ***Hong Kong***: Arteoptic; ***Hung.***: Fortinol†; ***Irl.***: Teoptic†; ***Israel***: Carteol; ***Ital.***: Carteabak; Carteol; Fortinol; ***Jpn***: Mikelan; ***Neth.***: Arteoptic†; Carteabak; Teoptic; ***Philipp.***: Mikelan; ***Pol.***: Arteoptic; Carteol; ***Port.***: Arteoptic; Carteabak; Physioglau; ***S.Afr.***: Teoptic†; ***Spain***: Arteolol†; Arteoptic; Elebloc; Mikelan; ***Switz.***: Arteoptic; ***Thai.***: Arteoptic; ***Turk.***: Carteol; ***UK***: Teoptic; ***USA***: Cartrol†.

Multi-ingredient Preparations. ***Belg.***: Carteopil†; ***Fr.***: Carpilo†; ***Switz.***: Arteopilo†.

Pharmacopoeial Preparations

BP 2014: Carteolol Eye Drops;
USP 36: Carteolol Hydrochloride Ophthalmic Solution; Carteolol Hydrochloride Tablets.

Carvedilol *(BAN, USAN, rINN)* ⊗

BM-14190; Carvédilol; Carvedilolum; Karvedilol; Karvediloli; Karvedilolis; Карведилол.

1-Carbazol-4-yloxy-3-[2-(2-methoxyphenoxy)ethylamino] propan-2-ol.

$C_{24}H_{26}N_2O_4$=406.5

CAS — 72956-09-3.

ATC — C07AG02.

ATC Vet — QC07AG02.

UNII — 0K47UL67F2.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Carvedilol). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane; practically insoluble in dilute acids.

USP 36: (Carvedilol). A white or nearly white, crystalline powder. Practically insoluble in water and in dilute acids; slightly soluble in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Carvedilol is a non-cardioselective beta blocker (p. 1316.3). It has vasodilating properties, which are attributed mainly to its blocking activity at $alpha_1$ receptors; at higher doses calcium-channel blocking activity may contribute. It also has antioxidant properties. Carvedilol is reported to have no intrinsic sympathomimetic activity and only weak membrane-stabilising activity.

Carvedilol is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3), and as an adjunct to standard therapy in symptomatic heart failure (p. 1262.3). It is also used to reduce mortality in patients with left ventricular dysfunction after myocardial infarction.

In **hypertension** carvedilol is given in an initial oral dose of 12.5 mg once daily, increased after two days to 25 mg once daily. Alternatively, an initial dose of 6.25 mg is given twice daily, increased after one to two weeks to 12.5 mg twice daily. The dose may be increased further, if necessary, at intervals of at least two weeks, to 50 mg once daily or in divided doses. A dose of 12.5 mg once daily may be adequate for elderly patients.

In **angina pectoris** an initial oral dose of 12.5 mg is given twice daily, increased after two days to 25 mg twice daily.

In **heart failure**, the initial oral dose is 3.125 mg twice daily. It should be taken with food to reduce the risk of hypotension. If tolerated, the dose should be doubled after two weeks to 6.25 mg twice daily and then increased gradually, at intervals of not less than two weeks, to the maximum dose tolerated; this should not exceed 25 mg twice daily in patients with severe heart failure or in those weighing less than 85 kg, or 50 mg twice daily in patients with mild to moderate heart failure weighing more than 85 kg. For doses in children, see below.

In patients with **left ventricular dysfunction after myocardial infarction**, the initial dose is 6.25 mg twice daily, increased after 3 to 10 days, if tolerated, to 12.5 mg twice daily and then to a target dose of 25 mg twice daily. A lower initial dose may be used in symptomatic patients.

A controlled-release preparation containing carvedilol phosphate hemihydrate is available in some countries.

References.

1. Dunn CJ, *et al*. Carvedilol: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1997; **54:** 161–85.
2. Frishman WH. Carvedilol. *N Engl J Med* 1998; **339:** 1759–65.
3. Naccarelli GV, Lukas MA. Carvedilol's antiarrhythmic properties: therapeutic implications in patients with left ventricular dysfunction. *Clin Cardiol* 2005; **28:** 165–73.
4. Carreira RS, *et al*. Carvedilol: just another beta-blocker or a powerful cardioprotector? *Cardiovasc Hematol Disord Drug Targets* 2006; **6:** 257–66.
5. Doughty RN, White HD. Carvedilol: use in chronic heart failure. *Expert Rev Cardiovasc Ther* 2007; **5:** 21–31.
6. Kveiborg B, *et al*. Carvedilol in the treatment of chronic heart failure: lessons from the Carvedilol Or Metoprolol European Trial. *Vasc Health RiskManag* 2007; **3:** 31–7.
7. Frishman WH, *et al*. Controlled-release carvedilol in the management of systemic hypertension and myocardial dysfunction. *Vasc Health Risk Manag* 2008; **4:** 1387–1400.
8. Stafylas PC, Sarafidis PA. Carvedilol in hypertension treatment. *Vasc Health Risk Manag* 2008; **4:** 23–30.
9. Bakris GL, Weber MA. Appropriate dose transition to a controlled-release formulation of carvedilol in patients with hypertension. *Rev Cardiovasc Med* 2008; **9:** 96–105.
10. Carter NJ, Keating GM. Controlled-release carvedilol. *Am J Cardiovasc Drugs* 2008; **8:** 271–82.
11. Machado V, *et al*. Carvedilol as a protector against the cardiotoxicity induced by anthracyclines (doxorubicin). *Rev Port Cardiol* 2008; **27:** 1277–96.
12. Fonarow GC. Role of carvedilol controlled-release in cardiovascular disease. *Expert Rev Cardiovasc Ther* 2009; **7:** 483–98.
13. Chakraborty S, *et al*. Clinical updates on carvedilol: a first choice beta-blocker in the treatment of cardiovascular diseases. *Expert Opin Drug Metab Toxicol* 2010; **6:** 237–50.

Administration in children. Carvedilol has been used in children with **heart failure**, although experience is limited.[1] Beneficial effects have been reported, including improvement in symptoms and ejection fraction, and delaying the need for heart transplantation, and carvedilol appears to be well tolerated. However, a randomised study[2] in 161 children and adolescents with heart failure found that carvedilol was not significantly better than placebo: clinical improvement occurred in 56% of those taking carvedilol and 56% of those taking placebo, although the study may have been underpowered. A subsequent study[3] in 27 patients with heart failure due to congenital heart disease, about three-quarters of whom were children, found that lower doses and more cautious dose-escalation (increments of 50 to 100 micrograms/kg per month) reduced adverse effects and retained efficacy when compared with the doses used in previous studies.

Carvedilol at an oral dose of about 400 micrograms/kg daily has improved symptoms and left ventricular ejection fraction when added to standard therapy in the management of **dilated cardiomyopathy** in children,[4,5] although up to 6 months of treatment may be required before a significant benefit is seen.[5]

Doses used in paediatric studies have varied, with initial oral doses ranging from 10 to 180 micrograms/kg daily and average oral maintenance doses ranging from 200 to 700 micrograms/kg (maximum 50 mg) daily, usually given in two divided doses. A pharmacokinetic study[6] in 41 children and adolescents aged under 20 years found that, with carvedilol clearance decreasing with increased age, a total oral daily dose of 3 mg/kg in those aged under 2 years, 2 mg/kg in those aged 2 to 11 years, and 1 mg/kg in those aged 12 years and above, were necessary to maintain adequate carvedilol exposure for treatment of heart failure. The authors considered that doses in previous studies may have been too low.

In the UK, the *BNFC* recommends that children aged 2 to 18 years with heart failure may be given an initial oral dose of 50 micrograms/kg (maximum 3.125 mg) twice daily, increased as tolerated, by doubling the dose at intervals of at least 2 weeks, to a maintenance dose of 350 micrograms/kg (maximum 25 mg) twice daily.

1. Greenway SC, Benson LN. The use of carvedilol in pediatric heart failure. *Cardiovasc Hematol Disord Drug Targets* 2006; **6:** 35–42.
2. Shaddy RE, *et al*. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007; **298:** 1171–9.
3. Nishiyama M, *et al*. Efficacy and safety of carvedilol for heart failure in children and patients with congenital heart disease. *Heart Vessels* 2009; **24:** 187–92.
4. Askari H, *et al*. Carvedilol therapy in pediatric patients with dilated cardiomyopathy. *Turk J Pediatr* 2009; **51:** 22–7.
5. Bajcetic M, *et al*. Effects of carvedilol on left ventricular function and oxidative stress in infants and children with idiopathic dilated cardiomyopathy: a 12-month, two-center, open-label study. *Clin Ther* 2008; **30:** 702–14.
6. Albers S, *et al*. Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol* 2008; **65:** 511–22.

Administration in the elderly. Licensed product information for carvedilol recommends an initial dose of 12.5 mg daily for all adults with **hypertension**. A study in 16 elderly hypertensive patients (mean age 70 years) given single doses of 12.5 mg and 25 mg found a high incidence of orthostatic hypotension[1] and the authors suggested that a starting dose lower than 12.5 mg might be necessary in elderly patients.

In contrast, a retrospective study[2] found that standard initial doses for **heart failure** (see Uses and Administration, above) were well tolerated in elderly patients and that the mean achieved dose was similar in those aged under 70 years and those aged 70 years and older, after adjustment for weight. Adverse effects were more common in the older group, but could generally be managed without stopping carvedilol.

1. Krum H, *et al*. Postural hypotension in elderly patients given carvedilol. *BMJ* 1994; **309:** 775–6.
2. Lawless CE, *et al*. Titration of carvedilol in elderly heart failure patients. *Am J Geriatr Cardiol* 2005; **14:** 230–5.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Liver function abnormalities, reversible on stopping treatment with carvedilol, have been reported rarely. Carvedilol is extensively metabolised in the liver and is not recommended in patients with hepatic impairment. Acute renal failure and renal abnormalities have been reported in patients with heart failure who also suffered from diffuse vascular disease and/or renal impairment.

The risk of hypotension may be reduced by taking carvedilol with food to decrease the rate of absorption.

Effects on the liver. Pruritus and elevated serum transaminase concentrations occurred[1] in a man who had been taking carvedilol for 6 months. Liver function tests returned to normal within 3 weeks of stopping carvedilol. However, pruritus recurred when the patient was started on metoprolol about 1 year later.

1. Hagmeyer KO, Stein J. Hepatotoxicity associated with carvedilol. *Ann Pharmacother* 2001; **35:** 1364–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies carvedilol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; the absolute bioavailability is about 25%. Peak plasma concentrations occur 1 to 2 hours after an oral dose. It has high lipid solubility. Carvedilol is more than 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP2C9, and the metabolites are excreted mainly in the bile. The elimination half-life is about 6 to 10 hours. Carvedilol has been shown to accumulate in breast milk in *animals*.

References.

1. McTavish D, *et al*. Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993; **45**: 232–58.
2. Morgan T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 1994; **26:** 335–46.
3. Tenero D, *et al*. Steady-state pharmacokinetics of carvedilol and its enantiomers in patients with congestive heart failure. *J Clin Pharmacol* 2000; **40:** 844–53.
4. Tenero DM, *et al*. Pharmacokinetic properties of a new controlled-release formulation of carvedilol. *Am J Cardiol* 2006; **98:** 5L–16L.
5. Packer M, *et al*. 369 Study Group. Pharmacokinetic profile of controlled-release carvedilol in patients with left ventricular dysfunction associated with chronic heart failure or after myocardial infarction. *Am J Cardiol* 2006; **98:** 39L–45L.
6. Takekuma Y, *et al*. Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. *Biol Pharm Bull* 2007; **30:** 537–42.
7. Tanwar YS, *et al*. Development and evaluation of carvedilol transdermal patches. *Acta Pharm* 2007; **57:** 151–9.
8. Albers S, *et al*. Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol* 2008; **65:** 511–22.
9. Horiuchi I, *et al*. Pharmacokinetics of R- and S-carvedilol in routinely treated Japanese patients with heart failure. *Biol Pharm Bull* 2008; **31:** 976–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antibloc; Bidecar; Cardionorm; Carvedil; Corafen; Coritensil; Corubin; Dicarpen; Dilatrend; Duobloc; Filten; Hipoten; Isobloc; Kollosteril; Nexocardil; Pluscor; Rodipal; Rudoxil; Veraten; Vicardol; ***Austral.***: Dicarz; Dilasig; Dilatrend; Kredex†; Vedilol; ***Austria***: Dilatrend; ***Belg.***: Dimitone; Kredex; ***Braz.***: Becarve; Cardilol; Carvedilat; Coreg; Cronocor; Divelol; Ictus; Karvil; ***Chile***: Betaplex; Blocar; Dicartel; Dilatrend; Dualten; Lodipres; Off-Ten; ***China***: Carvidol (辛维络); Dilatrend (达利全); Jin Luo (金络); Kailuo (凯络); Kang Da Xin (康达欣); Ke Wei De (克为德); Luode (络德); Rui Xin Le (瑞欣乐); Shuheng (枢衡); Tuo Er (妥尔); Zhuo Yi (卓异); ***Cz.***: Apo-Carve; Atram; Carvedigamma†; Carvesan; Carvetrend†; Coryol; Dilatrend; Talliton; ***Denm.***: Dimitone†; ***Fin.***: Cardiol; Carveratio; ***Fr.***: Kredex; ***Ger.***: CarLich†; Carve-Q†; Carve†; Carvecard†; Carvedigamma; Dilatrend; Dimetil†; Querto; ***Gr.***: Carvedilen; Carvepen; Dilatrend; ***Hong Kong***: Dilatrend; Talliton; ***Hung.***: Carvedigamma; Carvetrend; Carvol; Coryol; Dilatrend; Talliton; ***India***: Caditone; Cadmos; Carca; Cardivas; Carelol; Carloc; Cartab; Carvas; Carvedil; Carvel; Carvetrend; Carvil; Carvimed; Carvipress; Carvizest; Carzec; Caslot; Cevas; Conpres; CVL; Oricar; ***Indon.***: Blorec; Carbloxal; Dilbloc; V-Bloc; ***Irl.***: Biocard; Eucardic; ***Israel***: Carvedexxon; Dimitone†; ***Ital.***: Acarden; Caravel; Carvipress; Colver; Curcix; Dilatrend; Dilocar†; Omeria; Trakor; ***Malaysia***: Cardiol; Carvepen; Caslot; Cavel; Dilatrend; ***Mex.***: Bloqadre; Dilatrend†; ***Neth.***: Carived; Eucardic; ***NZ***: Dilatrend; ***Philipp.***: Betacard; Cardipres; Carvid; Dilatrend; Karvil; Psicardiol; Vasolexin; Xicard; ***Pol.***: Atram; Avedol; Carvedigamma; Carvetrend; Carvilex; Coryol; Dilatrend; Hypoten; Symtrend; Vivacor; ***Port.***: Carbetesil†; Coronat; Dilbloc; Dinertone; Vedivril; ***Rus.***: Acridilole (Акридилол); Atram (Атрам); Bagodilol (Багодилол); Cardivas (Кардивас); Carvedigamma (Карведигамма); Carvenal (Карвенал); Carvetrend (Карветренд); Carvidil (Карвидил); Coryol (Кориол); Dilatrend (Дилатренд); Talliton (Таллитон); Vedicardol (Ведикардол); ***S.Afr.***: Carloc; Carvetrend; Dilatrend; Vediblok; ***Singapore***: Carvepen; Dilatrend; ***Spain***: Coropres; Normotride; Palacimol†; ***Swed.***: Carveratio; Kredex; ***Switz.***: Dilatrend; ***Thai.***: Caraten; Dilatrend; Tocarlol; ***Turk.***: Arlec; Calcibor; Carvesan; Carvexal; Coronis; Dilatrend; Kinetra; ***UK***: Eucardic†; ***Ukr.***: Cardiostad (Кардиостад); Carvedigamma (Карведигамма)†; Carvetrend (Карветренд); Carvidex (Карвидекс); Corvasan (Корвазан); Coryol (Кориол); Talliton (Таллитон); ***USA***: Coreg; ***Venez.***: Carbatil; Carvedil; Coventrol; Dilatrend.

Multi-ingredient Preparations. ***Arg.***: Carvedil D; Dilatrend D; Filten D; Gliocarvedil; Isobloc D; ***Austria***: Co-Dilatrend.

Pharmacopoeial Preparations
USP 36: Carvedilol Tablets.

Celiprolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Céliprolol, Chlorhydrate de; Celiprolol, hidrocloruro de; Celiprololhydrochlorid; Celiprolol-hydrochlorid; Celiprolol-hydroklorid; Celiprololi hydrochloridum; Celiprololio hidrochloridas; Celiproiolu chlorowodorek; Hidrocloruro de celiprolol; Seliprololihydrokloridi; Целипролола Гидрохлорид.

3-{3-Acetyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl}-1,1-diethylurea hydrochloride.

$C_{20}H_{33}N_3O_4$,HCl=416.0

CAS — 56980-93-9 (celiprolol); 57470-78-7 (celiprolol hydrochloride).

ATC — C07AB08.

ATC Vet — QC07AB08.

UNII — G1M3398594.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Celiprolol Hydrochloride). A white or very slightly yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

Uses and Administration

Celiprolol is a cardioselective beta blocker (p. 1316.3). It is reported to possess intrinsic sympathomimetic activity and direct vasodilator activity. Celiprolol is used as the hydrochloride in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). The usual oral dose of celiprolol hydrochloride is 200 to 400 mg once daily before food. Reduced doses may be required in patients with renal impairment (see below).

References.

1. Milne RJ, Buckley MM-T. Celiprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cardiovascular disease. *Drugs* 1991; **41:** 941–69.
2. Anonymous. Celiprolol: theory and practice. *Lancet* 1991; **338:** 1426–7.
3. Anonymous. Celiprolol—a better beta blocker? *Drug Ther Bull* 1992; **30:** 35–6.
4. Kendall MJ, Rajman I. A risk-benefit assessment of celiprolol in the treatment of cardiovascular disease. *Drug Safety* 1994; **10:** 220–32.
5. Riddell J. Drugs in focus 18: celiprolol. *Prescribers' J* 1996; **36:** 165–8.

Administration in renal impairment. Celiprolol should not be given to patients with a creatinine clearance (CC) of less than 15 mL/minute. Patients with a CC between 15 and 40 mL/minute may be given 100 to 200 mg daily.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Tremor and palpitations associated with intrinsic sympathomimetic activity at $beta_2$ receptors have been reported.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Celiprolol is absorbed from the gastrointestinal tract in a non-linear fashion; the percentage of the dose absorbed increases with increasing dose. The plasma elimination half-life is about 5 to 6 hours. Celiprolol crosses the placenta. It has low lipid solubility and is about 25% bound to plasma proteins. Metabolism is minimal and celiprolol is mainly excreted unchanged in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Selectol; ***Belg.***: Selectol; ***Chile***: Selectol; ***China***: Delaien (得来恩); Su Ya (苏亚); ***Cz.***: Tenoloc; ***Fin.***: Selectol; ***Fr.***: Celectol; ***Ger.***: Celipro†; Celipro-gamma†; Selectol; ***Gr.***: Aplonit; Selectol; Versatil; Zilovis; ***Hong Kong***: Selectol; ***Irl.***: Selectol; ***Ital.***: Cordiax; ***Jpn***: Selectol; ***Neth.***: Dilanorm; ***NZ***: Celol; ***Pol.***: Celipres; ***Rus.***: Celiprol (Целипрол); ***Spain***: Cardem; ***Switz.***: Selectol; ***UK***: Celectol.

Multi-ingredient Preparations. ***Austria***: Selecturon.

Pharmacopoeial Preparations
BP 2014: Celiprolol Tablets.

Certoparin Sodium *(BAN, rINN)*

Certoparin; Certoparina sódica; Certoparine Sodique; Certoparinum Natricum; Цертопарин Натрий.

Description. Certoparin sodium is prepared by amyl nitrite degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannose structure at the reducing end of their chain. The molecular weight of 70% of the components is less than 10 000 and the average molecular weight is about 6000. The degree of sulfation is about 2 to 2.5 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Certoparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity used for the prevention of postoperative venous thromboembolism (p. 1274.1). It is given by subcutaneous injection in a dose of 3000 units 1 to 2 hours before the procedure, followed by 3000 units daily for 7 to 10 days or until the patient is fully ambulant.

References.

1. Kolb G, *et al*. Reduction of venous thromboembolism following prolonged prophylaxis with the low molecular weight heparin certoparin after endoprothetic joint replacement or osteosynthesis of the lower limb in elderly patients. *Thromb Haemost* 2003; **90:** 1100–5.
2. Riess H, *et al*. Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003; **90:** 252–9.
3. Diener HC, *et al*. Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial. *Stroke* 2006; **37:** 139–44.
4. Tebbe U, *et al*. AFFECT: a prospective, open-label, multicenter trial to evaluate the feasibility and safety of a short-term treatment with subcutaneous certoparin in patients with persistent non-valvular atrial fibrillation. *Clin Res Cardiol* 2008; **97:** 389–96.
5. Riess H, *et al*. A randomized, double-blind study of certoparin versus UFH to prevent venous thromboembolic events in acutely ill, non-surgical patients: CERTIFY study. *J Thromb Haemost* 2010; **8:** 1209–15.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with certoparin may be reduced by the slow intravenous injection of protamine salts; 1 mg of protamine hydrochloride is stated to inhibit the effects of about 80 to 120 units of certoparin sodium.

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Certoparin sodium is rapidly and completely absorbed after subcutaneous injection. Peak plasma activity occurs within 2 to 4 hours. The half-life of anti-factor Xa activity is about 4 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Sandoparin; ***Ger.***: Mono-Embolex; ***Switz.***: Sandoparine.

Cetiedil Citrate *(USAN, rINNM)*

Cétiédil, Citrate de; Cetiedil, citrato de; Cetiedili Citras; Citrato de cetiedil; Цетиедила Цитрат.

2-(Perhydroazepin-1-yl)ethyl α-cyclohexyl-α-(3-thienyl) acetate dihydrogen citrate monohydrate.

$C_{20}H_{31}NO_2S,C_6H_8O_7,H_2O$=559.7

CAS — 14176-10-4 (cetiedil); 16286-69-4 (anhydrous cetiedil citrate).

ATC — C04AX26.

ATC Vet — QC04AX26.

UNII — IE65P4OE02.

Profile

Cetiedil citrate is a vasodilator with antimuscarinic activity that has been used in the management of peripheral vascular disease.

Chlorothiazide *(BAN, rINN)* ⊗

Chlorothiazid; Chlorothiazidum; Clorotiazidas; Clorotiazyd; Clorotiazida; Klooritiatsidi; Klorotiazid; Klortiazid; Хлоротиазид.

6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_7H_6ClN_3O_4S_2$=295.7

CAS — 58-94-6.

ATC — C03AA04.

ATC Vet — QC03AA04.

UNII — 77W477J15H.

Pharmacopoeias. In *US.*

USP 36: (Chlorothiazide). A white or practically white, odourless, crystalline powder. Very slightly soluble in water; practically insoluble in chloroform, in ether, and in benzene; freely soluble in dimethylformamide and dimethyl sulfoxide; slightly soluble in methyl alcohol and in pyridine. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Alkaline solutions undergo decomposition due to hydrolysis upon standing or heating.

Chlorothiazide Sodium *(BANM, USAN, rINNM)* ⊗

Chlorothiazide Sodique; Clorotiazida sódica; Natrii Chlorothiazidum; Sodium Chlorothiazide; Натрий Хлоротиазид.

$C_7H_5ClN_3NaO_4S_2$=317.7

CAS — 7085-44-1.

ATC — C03AA04.

ATC Vet — QC03AA04.

UNII — SN86FG7N2K.

Pharmacopoeias. *US* includes Chlorothiazide Sodium for Injection.

Incompatibility. The alkaline nature of chlorothiazide in injectable form suggests that incompatibilities with acidic drugs could be expected; US licensed product information states that the injection may be diluted with glucose or sodium chloride solutions.

Uses and Administration

Chlorothiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

After oral doses of chlorothiazide diuresis usually occurs in about 2 hours, reaches a peak at about 4 hours, and is maintained for 6 to 12 hours.

In the treatment of **oedema** the usual dose of chlorothiazide is 0.5 to 1 g orally once or twice daily; therapy on alternate days or on 3 to 5 days weekly may be adequate.

In the treatment of **hypertension** the recommended initial dose is 0.5 to 1 g daily orally, given as a single or divided dose, although the *American Hospital Formulary Service* have suggested lower initial doses of 125 to 250 mg daily, increased to a maximum of 500 mg daily. US licensed product information states that patients may rarely require up to 2 g daily, given in divided doses.

For the use of chlorothiazide in children, see below.

Chlorothiazide has also been given intravenously as the sodium salt, in doses similar to those given orally. Chlorothiazide sodium 537 mg is equivalent to about 500 mg of chlorothiazide. It is not suitable for subcutaneous or intramuscular injection and extravasation should be avoided. The diuretic effect lasts for up to 2 hours after intravenous injection.

Administration in children. Chlorothiazide may be used in children for the management of *heart failure* or *hypertension.* Usual oral doses are as follows:

- neonates and infants aged 1 to 6 months: 10 to 20 mg/kg twice daily
- age 6 months to 12 years: 10 mg/kg twice daily, to a maximum of 1 g daily
- age 12 to 18 years: 0.25 to 1 g once daily or 125 to 500 mg twice daily

For *diabetes insipidus* in children, the *BNFC* suggests an oral dose of 10 to 20 mg/kg twice daily, to a maximum of 1 g daily.

Chlorothiazide also has a hyperglycaemic effect and has been used in children with *chronic hypoglycaemia* (see under Uses of Glucagon, p. 1554.3). It is usually given with diazoxide and has the added benefit of reducing diazoxide-associated sodium and water retention. The *BNFC* suggests an oral dose of 3 to 5 mg/kg twice daily.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2. Chlorothiazide sodium injection is alkaline: when giving chlorothiazide by intravenous infusion, care should be taken to ensure that extravasation does not occur.

Breast feeding. Chlorothiazide is distributed into breast milk in small amounts. A single 500-mg oral dose of chlorothiazide was given[1] to 11 women and blood and milk samples taken after 1, 2, and 3 hours; all the samples had concentrations below 1 microgram/mL and it was calculated that an infant would receive no more than 1 mg of drug each day. The American Academy of Pediatrics states that no adverse effects have been seen in infants and therefore considers[2] that chlorothiazide is usually compatible with breast feeding.

1. Werthmann MW, Krees SV. Excretion of chlorothiazide in human breast milk. *J Pediatr* 1972; **81:** 781–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Chlorothiazide is incompletely and variably absorbed from the gastrointestinal tract. It has been estimated to have a plasma half-life of 45 to 120 minutes although the clinical effects may last for up to about 12 hours. It is excreted unchanged in the urine. Chlorothiazide crosses the placental barrier and small amounts are reported to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Diurigen; Diuril.

Multi-ingredient Preparations. ***Gr.***: Neourizine; ***USA***: Aldoclor; Diupres.

Pharmacopoeial Preparations

USP 36: Chlorothiazide Oral Suspension; Chlorothiazide Sodium for Injection; Chlorothiazide Tablets; Methyldopa and Chlorothiazide Tablets; Reserpine and Chlorothiazide Tablets.

Chlortalidone *(BAN, rINN)* ⊗

Chlorotalidon; Chlortalidon; Chlortalidonas; Chlortalidonum; Chlorthalidone (USAN); Chlorthalidone; Clorotalidona; Clortalidona; G-33182; Klooritalidoni; Klortalidon; Klórtalidon; NSC-69200; Хлорталидон.

2-Chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl)benzenesulphonamide.

$C_{14}H_{11}ClN_2O_4S$=338.8

CAS — 77-36-1.

ATC — C03BA04.

ATC Vet — QC03BA04.

UNII — Q0MQD1073Q.

NOTE. Compounded preparations of chlortalidone may be represented by the following names:

- Co-tenidone (*BAN*)—chlortalidone 1 part and atenolol 4 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Chlortalidone). A white or yellowish-white powder. Very slightly soluble in water; soluble in acetone and in methyl alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. It exhibits polymorphism.

USP 36: (Chlorthalidone). A white or yellowish-white crystalline powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol; soluble in methyl alcohol.

Uses and Administration

Chlortalidone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is given orally for hypertension (p. 1251.1), and for oedema, including that associated with heart failure (p. 1262.3). Other indications include diabetes insipidus (p. 2348.2).

Diuresis begins about 2 hours after an oral dose and lasts for 48 to 72 hours.

The usual dose in the treatment of **hypertension** is 25 mg daily, given either alone or with other antihypertensives, increasing to 50 mg daily if necessary.

In the treatment of **oedema** the usual initial dose is 25 to 50 mg daily. In severe cases a daily dose of 100 to 200 mg may be given. If possible lower doses should be used for maintenance; 25 to 50 mg daily or on alternate days may be adequate.

For doses in children, see below.

In **diabetes insipidus** an initial dose of 100 mg twice daily has been used, reduced to a maintenance dose of 50 mg daily.

In the USA, a preparation is available with improved bioavailability; suggested doses range from 15 to 50 mg daily for hypertension and 30 to 120 mg daily for oedema.

References.

1. Taler SJ. Should chlorthalidone be the diuretic of choice for antihypertensive therapy? *Curr Hypertens Rep* 2008; **10:** 293–7.
2. Ernst ME, *et al.* All thiazide-like diuretics are not chlorthalidone: putting the ACCOMPLISH study into perspective. *J Clin Hypertens (Greenwich)* 2009; **11:** 5–10.
3. Sica DA. Chlorthalidone—a renaissance in use? *Expert Opin Pharmacother* 2009; **10:** 2037–9.
4. Massie BM. Prevention of heart failure with chlorthalidone in ALLHAT: placing the results into perspective. *J Clin Hypertens (Greenwich)* 2009; **11:** 462–5.
5. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. *Cardiol Rev* 2010; **18:** 51–6.
6. Ernst ME, *et al.* Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens* 2010; **23:** 440–6.

Administration in children. Chlortalidone may be given to children aged from 5 years in the treatment of hypertension, oedema associated with the nephrotic syndrome, stable heart failure, and ascites. The *BNFC* suggests the following oral doses:

- aged 5 to 12 years: usual dose 0.5 to 1 mg/kg on alternate days; maximum dose 1.7 mg/kg on alternate days
- aged over 12 years: usual dose 25 to 50 mg daily. In hypertension, the lower dose is preferred. In heart failure, the dose may be increased to 100 to 200 mg daily if necessary, reduced to the lowest effective dose for maintenance

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Breast feeding. Chlortalidone is distributed into breast milk, but a study[1] in 9 women given a dose of 50 mg daily found that the concentration in milk was only about 5% of that in the blood. However, caution was advised since chlortalidone elimination may be slower in neonates. The American Academy of Pediatrics considers[2] that chlortalidone is usually compatible with breast feeding.

1. Mulley BA, *et al.* Placental transfer of chlorthalidone and its elimination in maternal milk. *Eur J Clin Pharmacol* 1978; **13:** 129–31.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Anticoagulants. For references to the interaction between *warfarin* and chlortalidone, see p. 1533.3.

Pharmacokinetics

Chlortalidone is erratically absorbed from the gastrointestinal tract and bioavailability varies according to the preparation used. It has a prolonged elimination half-life from plasma and blood of 40 to 60 hours and is highly bound to red blood cells; the receptor to which it is bound has been identified as carbonic anhydrase. Chlortalidone is much less strongly bound to plasma proteins. Chlortalidone is mainly excreted unchanged in the urine. It crosses the placental barrier and is distributed into breast milk.

References.

1. Riess W, *et al.* Pharmacokinetic studies with chlorthalidone (Hygroton) in man. *Eur J Clin Pharmacol* 1977; **12:** 375–82.
2. Fleuren HLJ, *et al.* Absolute bioavailability of chlorthalidone in man: a cross-over study after intravenous and oral administration. *Eur J Clin Pharmacol* 1979; **15:** 35–50.
3. Fleuren HLJ, *et al.* Dose-dependent urinary excretion of chlorthalidone. *Clin Pharmacol Ther* 1979; **25:** 806–12.
4. Mulley BA, *et al.* Pharmacokinetics of chlorthalidone: dependence of biological half life on blood carbonic anhydrase levels. *Eur J Clin Pharmacol* 1980; **17:** 203–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Euretico; Hygroton; ***Austral.***: Hygroton; ***Austria***: Hydrosan; ***Belg.***: Hygroton; ***Braz.***: Clortalil; Clortil; Drenidra; Higromil; Higroton; Neolidona; ***Ger.***: Hygroton; ***Gr.***: Hygroton; ***Hung.***: Hygroton; ***India***: Hythalton; Thalizide; ***Indon.***: Hygroton; ***Israel***: Aquadon†; ***Ital.***: Igroton; ***Mex.***: Anilid; Bioralin; Hidrona†; Hidropharm; Higroton; Lortal; Sinhidron; Tensoral; ***NZ***: Hygroton; ***Pol.***: Hygroton; Urandil†; ***Port.***: Hygroton; ***Rus.***: Oxodoline (Оксодолин); ***S.Afr.***: Hygroton; ***Spain***: Higrotona; ***Switz.***: Hygroton; ***Turk.***: Hygroton†; ***UK***: Hygroton; ***USA***: Hygroton†; Thalitone.

Multi-ingredient Preparations. ***Arg.***: Bemplas; Prenoretic; ***Austria***: Atenolan comp; Atenolol comp; Polinorm†; Selecturon; Tenoretic; ***Belg.***: Logroton; Tenoretic; ***Braz.***: Ablok Plus; Angipress CD; Atelidona; Atenorese; Atenoric; Atenuol CRT; Betacard Plus; Diublok; Diupress; Higroton Reserpina; Tenoretic; ***Canad.***: Apo-Atenidone; Novo-Atenolthalidone†; Tenoretic; ***Cz.***: Amicloton; Neocrystepin†; Tenoretic; ***Denm.***: Tenidon; Tenoretic; ***Fr.***: Logroton; Tenoretic; Trasitensine†; ***Ger.***: Ate Lich comp†; Atehexal comp†; Atel†; Ateno comp†; Atenogamma comp†; Atenolol comp; Diu-Atenolol†; Prelis comp; Teneretic; TRI-Normin; ***Gr.***: Apress; Bestocalm; Chlotenor; Hygroton-Reserpine; Merendal; Obosan; Ogerol; Santapertas; Tenoretic; Trasitensin; Typofen; Vagosinol; ***Hong Kong***: Target†; Tenoret; Tenoretic; ***Hung.***: Blokium Diu; ***India***: Atecard-D; Catapres Diu; Clothalton; Tenoclor; Tenoric; ***Indon.***: Tenoret†; Tenoretic†; ***Irl.***: Atecor CT; Atenetic; Tenoret; Tenoretic; ***Ital.***:

Atenigron; Carmian; Clortanol; Diube; Eupres; Igroseles; Igroton-Lopresor; Igroton-Reserpina; Target; Tenoretic; Trandiur; Trasitensin; ***Malaysia***: Apo-Atenidone; Logroton; Pretenol C; Target; Tenoret; Tenoretic; ***Mex.***: Higroton Blok; Higroton-Res; Tenoretic; ***Philipp.***: Tenoretic; ***Port.***: Tenoretic; ***Rus.***: Atehexal Compositum (Атегексал Композитум); Atenolol Compositum (Атенолол Композитум); Tenonorm (Тенонорм); Tenoretic (Теноретик); Tenoric (Тенорик); Tenorox (Тенорокс); ***S.Afr.***: Adco-Loten; Tenchlor; Tenoret; Tenoretic; ***Singapore***: Logroton; Pretenol C; Target; Tenoret†; Tenoretic†; ***Spain***: Aldoleo; Blokium Diu; Higrotensin†; Normopresil; Tenoretic; Trasitensin; ***Switz.***: Atedurex; Cardaxen plus; Co-Atenolol; Cotenolol-Neo; Hygroton-Reserpine†; Logroton; Sandoretic†; Slow-Trasitensine; Tenoretic; ***Turk.***: Atexal; Regroton; Tenoretic; ***UK***: AtenixCo; Kalspare; Tenchlor; Tenoret; Tenoretic; Totaretic; ***Ukr.***: Dinorik (Диноpик); Tenoric (Тенорик); Tonorma (Тонорма); ***USA***: Clorpres; Demi-Regroton; Edarbyclor; Regroton; Tenoretic; ***Venez.***: Blokiuret; Tenoretic.

Pharmacopoeial Preparations
BP 2014: Chlortalidone Tablets; Co-tenidone Tablets;
USP 36: Atenolol and Chlorthalidone Tablets; Chlorthalidone Tablets; Clonidine Hydrochloride and Chlorthalidone Tablets.

Cibenzoline *(BAN, rINN)*

Cibenzolina; Cibenzolinum; Cifenline (USAN); Ro-22-7796; Ro-22-7796/001 (cibenzoline succinate); UP-339-01; Цибензолин.
(±)-2-(2,2-Diphenylcyclopropyl)-2-imidazoline.
$C_{18}H_{18}N_2$=262.4
CAS — 53267-01-9 (cibenzoline); 100678-32-8 (cibenzoline succinate).
ATC — C01BG07.
ATC Vet — QC01BG07.
UNII — Z7489237QT.

Uses and Administration

Cibenzoline is a class I antiarrhythmic (p. 1243.1) that has been classified as either Ia or Ic; it also has some class III and class IV properties. It is used in the management of ventricular and supraventricular arrhythmias (p. 1266.1). Cibenzoline is given orally as the succinate or intravenously as a mixture of the base and succinate, but doses for both routes are expressed in terms of the base; 145 mg of cibenzoline succinate is equivalent to about 100 mg of base. The usual oral dose of cibenzoline succinate is the equivalent of 260 to 390 mg cibenzoline daily in divided doses. The usual intravenous dose is the equivalent of about 1 mg/kg cibenzoline base given over 2 to 5 minutes. Dosage should be reduced in the elderly (below), and in renal impairment (below).

Reviews.
1. Harron DW, *et al.* Cibenzoline: a review of its pharmacological properties and therapeutic potential in arrhythmias. *Drugs* 1992; **43:** 734–59.

Administration in the elderly. The renal and non-renal clearance of cibenzoline was found to decrease with increasing age in healthy subjects.[1] The mean elimination half-life was 7 hours in the 20- to 30-year age group and 10.5 hours in the 70- to 80-year age group. The reduction in renal clearance was considered to be related to the decrease in creatinine clearance with increasing age. The results suggested that older patients may need lower doses than younger patients to maintain therapeutic plasma-cibenzoline concentrations. Licensed product information recommends a dosage of 130 mg daily in two divided doses in elderly patients.
1. Brazzell RK, *et al.* Age and cibenzoline disposition. *Clin Pharmacol Ther* 1984; **36:** 613–19.

Administration in renal impairment. A study[1] in patients with normal or impaired renal function has suggested that in renal impairment initial loading doses of cibenzoline may be equivalent to those used in normal renal function although maintenance doses should be reduced to about two-thirds of normal. Oral doses recommended in licensed product information, based on creatinine clearance (CC), are as follows:
- CC 20 to 40 mL/min: the equivalent of 3 mg/kg daily
- CC 10 to 20 mL/min: the equivalent of 2.5 mg/kg daily

1. Aronoff G, *et al.* Bioavailability and kinetics of cibenzoline in patients with normal and impaired renal function. *J Clin Pharmacol* 1991; **31:** 38–44.

Adverse Effects and Precautions

Cibenzoline may cause neurological and gastrointestinal adverse effects including vertigo, tremor, nausea, vomiting, and diarrhoea. Other adverse effects include fatigue, visual disturbances, and hypoglycaemia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias. It also has a negative inotropic effect and may reduce blood pressure.

Cibenzoline is contra-indicated in patients with heart block and severe heart failure. It should be used with caution in the elderly and in renal impairment, and doses should be reduced.

Effects on the neuromuscular system. Myasthenia-like symptoms have been reported[1-3] in patients with renal impairment taking cibenzoline, including severe respiratory depression in some cases.[2,3]
1. Kasuga A, *et al.* Myasthenia-like syndrome induced by overdosage of cibenzoline. *Intern Med* 1996; **35:** 512–14.
2. Similowski T, *et al.* Neuromuscular blockade with acute respiratory failure in a patient receiving cibenzoline. *Thorax* 1997; **52:** 582–4.
3. Inada K, *et al.* A case of severe respiratory depression due to cibenzoline overdosage induced by a transient renal dysfunction. *Int J Cardiol* 2002; **82:** 177–8.

Hypoglycaemia. Cibenzoline therapy was associated with severe hypoglycaemia in a 67-year-old patient.[1] The plasma-cibenzoline concentration was 1800 nanograms/mL which would probably be considered toxic since the accepted therapeutic trough range is 200 to 600 nanograms/mL. A case-control study[2] also suggested that the risk of hypoglycaemia is increased by cibenzoline.
1. Hilleman DE, *et al.* Cibenzoline-induced hypoglycemia. *Drug Intell Clin Pharm* 1987; **21:** 38–40.
2. Takada M, *et al.* The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; **56:** 335–42.

Interactions

Cibenzoline should not be used with other drugs that prolong the QT interval since the risk of arrhythmias may be increased.

Histamine H_2-antagonists. Increased blood concentrations and prolonged half-lives of cibenzoline occurred in healthy subjects given *cimetidine* but the clinical importance of this was unknown.[1] The interaction did not occur with *ranitidine*.
1. Massarella JW. The effects of cimetidine and ranitidine on the pharmacokinetics of cifenline. *Br J Clin Pharmacol* 1991; **31:** 481–3.

Pharmacokinetics

Cibenzoline is well absorbed from the gastrointestinal tract after oral use, with a bioavailability of about 90%. It is about 50 to 60% bound to plasma proteins. About 60% of a dose is excreted unchanged in the urine and the elimination half-life is reported to be about 7 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Cipralan; ***Fr.***: Cipralan; Exacor; ***Jpn***: Cibenol.

Cicletanine *(BAN, USAN, rINN)* ⊗

Ciclétanine; Cicletaninum; Win-90000; Циклетанин; (±)-BN-1270; (±)-Cycletanide.
(±)-3-(*p*-Chlorophenyl)-1,3-dihydro-6-methylfuro[3,4-*c*]pyridin-7-ol.
$C_{14}H_{12}ClNO_2$=261.7
CAS — 89943-82-8.
ATC — C03BX03.
ATC Vet — QC03BX03.
UNII — CHG7QC509W.

Cicletanine Hydrochloride *(BANM, rINNM)* ⊗

Cicletanina, hidrocloruro de; Ciclétanine, Chlorhydrate de; Cicletanini Hydrochloridum; Hidrocloruro de cicletanina; Циклетанина Гидрохлорид.
$C_{14}H_{12}ClNO_2$,HCl=298.2
CAS — 89943-82-8.
ATC — C03BX03.
ATC Vet — QC03BX03.
UNII — T0SY6373OQ.

Profile

Cicletanine hydrochloride is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2). It is used in the treatment of hypertension (p. 1251.1) in a usual oral dose of 50 to 100 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Tenstaten.

Cilazapril *(BAN, USAN, rINN)*

Cilazapril monohydrát; Cilazaprilis; Cilazaprilum; Cilazaprilum Monohydricum; Ro-31-2848 (anhydrous cilazapril); Ro-31-2848/006 (cilazapril monohydrate); Silatsapriili; Silazapril; Цилазаприл.
(1*S*,9*S*)-9-[(*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-10-oxoperhydropyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid monohydrate.
$C_{22}H_{31}N_3O_5$,H_2O=435.5
CAS — 88768-40-5 (anhydrous cilazapril); 92077-78-6 (cilazapril monohydrate).
ATC — C09AA08.
ATC Vet — QC09AA08.
UNII — 8Q9454114Q (anhydrous cilazapril); 19KW7PI29F (cilazapril monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Cilazapril). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

Uses and Administration

Cilazapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Cilazapril owes its activity to cilazaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 3 to 7 hours. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Cilazapril is given orally as the monohydrate, but doses are expressed in terms of the anhydrous substance. Cilazapril 1.04 mg as the monohydrate is equivalent to about 1 mg of anhydrous cilazapril.

In the treatment of **hypertension** the initial dose is 1 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 2.5 to 5 mg daily. In the elderly, in patients with mild to moderate renal impairment or with liver cirrhosis, or those taking *diuretics*, a usual initial dose is 500 micrograms daily. If possible the diuretic should be withdrawn 2 to 3 days before cilazapril is started and resumed later if necessary.

In the treatment of **heart failure** severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus therapy should begin with a low dose under close medical supervision. Cilazapril is given in an initial dose of 500 micrograms once daily, increased if tolerated to a usual maintenance dose of 1 to 2.5 mg once daily. The usual maximum dose is 5 mg daily.

Reduced doses may be necessary in patients with renal impairment (see below).

References.
1. Deget F, Brogden RN. Cilazapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cardiovascular disease. *Drugs* 1991; **41:** 799–820.

Administration in renal impairment. In patients with a creatinine clearance of 10 to 40 mL/minute, the initial dose of cilazapril is 500 micrograms once daily and the maintenance dose should not exceed 2.5 mg once daily. Cilazapril should be avoided in patients with a creatinine clearance below 10 mL/minute. In patients receiving haemodialysis, cilazapril should be given on the non-dialysis days and the dose should be adjusted according to response.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Licensed product information contra-indicates cilazapril in patients with ascites.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cilazapril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]
1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Cilazapril acts as a prodrug of the diacid cilazaprilat, its active metabolite. After oral dosage and absorption of cilazapril it is rapidly metabolised in the liver to cilazaprilat, the bioavailability of which is about 60%. Peak plasma concentrations of cilazaprilat occur within 2 hours of an oral dose of cilazapril. Cilazaprilat is eliminated unchanged in the urine. The effective half-life of cilazaprilat is reported to be 9 hours after once-daily dosing. The elimination of

cilazaprilat is reduced in renal impairment. Both cilazapril and cilazaprilat are removed to a limited extent by haemodialysis.

Reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of the newer ACE inhibitors: a review. *Clin Pharmacokinet* 1990; **19:** 177–96.
2. Kloke HJ, *et al*. Pharmacokinetics and haemodynamic effects of the angiotensin converting enzyme inhibitor cilazapril in hypertensive patients with normal and impaired renal function. *Br J Clin Pharmacol* 1996; **42:** 615–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Inhibace; ***Belg.***: Inhibace; ***Braz.***: Vascase; ***Canad.***: Inhibace; ***Chile***: Inhibace; ***China***: Inhibace (…平苏); ***Cz.***: Cazaprol; Inhibace; ***Fr.***: Justor; ***Ger.***: Dynorm; ***Gr.***: Vascase; ***Hong Kong***: Inhibace†; ***Hung.***: Inhibace; ***Irl.***: Vascace; ***Israel***: Cilaril; Vascace†; ***Ital.***: Inibace; Initiss; ***Jpn***: Inhibace; ***Neth.***: Vascase; ***NZ***: Inhibace; Zapril; ***Philipp.***: Vascace; ***Pol.***: Cazaprol; Cilan; Inhibace; Inhibestril; ***Port.***: Inibace; Vascase; ***Rus.***: Inhibace (Инхибейс); ***S.Afr.***: Inhibace; ***Singapore***: Inhibace; ***Spain***: Inhibace; Inocar; ***Swed.***: Inhibace†; ***Switz.***: Inhibace; ***Thai.***: Inhibace; ***Turk.***: Aceprix; Inhibace; ***UK***: Vascace†; ***Venez.***: Inhibace.

Multi-ingredient Preparations. ***Austria***: Inhibace Plus; ***Belg.***: Co-Inhibace; ***Braz.***: Vascase Plus; ***Canad.***: Inhibace Plus; ***Chile***: Inhibace Plus; ***Cz.***: Cazacombi; Inhibace Plus; ***Ger.***: Dynorm Plus; ***Gr.***: Vascase Plus; ***Hung.***: Inhibace Plus; ***Israel***: Cilaril Plus; Cilazapril Plus; Vascace Plus†; ***Ital.***: Inibace Plus; Initiss Plus; ***NZ***: Inhibace Plus; ***Philipp.***: Vascace Plus; ***Pol.***: Cazacombi; Inhibace Plus; ***Port.***: Inibace Plus; Vascase Plus; ***Rus.***: Ampliton (Амплитон); Sonoprel (Сонопрел); ***S.Afr.***: Inhibace Plus; ***Spain***: Inhibace Plus; Inocar Plus; ***Swed.***: Inhibace comp†; ***Switz.***: Inhibace Plus; ***Turk.***: Aceprix Plus; Inhibace Plus.

Cilnidipine *(rINN)*

Cilnidipino; Cilnidipinum; FRC-8653; Цилнидипин.

(±)-(*E*)-Cinnamyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

$C_{27}H_{28}N_2O_7$=492.5

CAS — 132203-70-4.

ATC — C08CA14.

ATC Vet — QC08CA14.

UNII — 97T5AZ1JIP.

Profile

Cilnidipine is a dihydropyridine calcium-channel blocker (p. 1244.2) given orally in the management of hypertension (p. 1251.1). The usual dose is 5 to 10 mg once daily, increased to 20 mg once daily if necessary.

References.

1. Takei K, *et al*. Comparison of the anti-hypertensive effects of the L/N-type calcium channel antagonist cilnidipine, and the L-type calcium channel antagonist amlodipine in hypertensive patients with cerebrovascular disease. *Intern Med* 2009; **48:** 1357–61.
2. Takahara A. Cilnidipine: a new generation Ca channel blocker with inhibitory action on sympathetic neurotransmitter release. *Cardiovasc Ther* 2009; **27:** 124–39.
3. Abe M, *et al*. Comparison between the antiproteinuric effects of the calcium channel blockers benidipine and cilnidipine in combination with angiotensin receptor blockers in hypertensive patients with chronic kidney disease. *Expert Opin Invest Drugs* 2010; **19:** 1027–37.
4. Konoshita T, *et al*. A new-generation N/L-type calcium channel blocker leads to less activation of the renin-angiotensin system compared with conventional L type calcium channel blocker. *J Hypertens* 2010; **28:** 2156–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jiuyue (久悦); Xi Le (西乐); Zhi Xin (致欣); ***India***: Cilacar; ***Jpn***: Atelec; Cinalong†; ***Port.***: Tenvasc.

Cilostazol *(BAN, USAN, pINN)*

Cilostazolum; OPC-21; OPC-13013; Цилостазол.

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril.

$C_{20}H_{27}N_5O_2$=369.5

CAS — 73963-72-1.

ATC — B01AC23; C04AX33.

ATC Vet — QB01AC23.

UNII — N7Z035406B.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cilostazol). White to off-white crystals. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in chloroform. Store in airtight containers.

Uses and Administration

Cilostazol is a phosphodiesterase type-3 inhibitor with antiplatelet and vasodilating activity. It is used in the management of peripheral vascular disorders (p. 1272.3) and has been tried as an adjunct to coronary stenting in ischaemic heart disease (below) and in other atherothrombotic disorders.

Cilostazol is used to improve walking distance in intermittent claudication; in the EU, it is restricted to second-line use in patients for whom lifestyle changes and other drug treatments are insufficient. The usual dose is 100 mg orally twice daily, at least 30 minutes before or 2 hours after food; doses should be reduced to 50 mg twice daily if given to patients also taking inhibitors of the cytochrome P450 isoenzymes CYP3A4 or CYP2C19. Response to treatment may occur in 2 to 4 weeks, but up to 12 weeks may be required. Patients should be assessed 3 months after starting cilostazol; treatment may need to be withdrawn if there is no clinical improvement.

Reviews.

1. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl* 2005; **6:** 3–11.
2. Weintraub WS. The vascular effects of cilostazol. *Can J Cardiol* 2006; **22** (suppl B): 56B–60B.
3. Dalainas I. Cilostazol in the management of vascular disease. *Int Angiol* 2007; **26:** 1–7.

Ischaemic heart disease. Percutaneous coronary intervention and stenting are widely used in the management of ischaemic heart disease but thrombotic complications and restenosis complicate their use. Antiplatelet drugs (usually aspirin plus a thienopyridine) are given to reduce thrombosis (see Reperfusion and Revascularisation Procedures, p. 1259.2) but generally have little effect on restenosis. Cilostazol has both antiplatelet and antiproliferative actions[1] and there is some evidence that it may reduce the incidence of restenosis,[1-3] particularly with use of bare metal stents. The addition of cilostazol to standard antiplatelet therapy ('triple therapy') appears to be safe[4-6] and may improve outcomes[7] especially in patients at high risk of restenosis including the elderly and those with diabetes mellitus or clopidogrel resistance.[6,8] Further studies are needed to confirm its role, including a possible role in preventing restenosis of peripheral vascular stents (see below).

1. El-Beyrouty C, Spinler SA. Cilostazol for prevention of thrombosis and restenosis after intracoronary stenting. *Ann Pharmacother* 2001; **35:** 1108–13.
2. Biondi-Zoccai GGL, *et al*. Systematic review and meta-analysis of randomized clinical trials appraising the impact of cilostazol after percutaneous coronary intervention. *Am Heart J* 2008; **155:** 1081–9.
3. Tamhane U, *et al*. Efficacy of cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials. *EuroIntervention* 2009; **5:** 384–93.
4. Singh I, *et al*. Triple antiplatelet therapy vs. dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: an evidence-based approach to answering a clinical query. *Br J Clin Pharmacol* 2009; **68:** 4–13.
5. Jennings DL, Kalus JS. Addition of cilostazol to aspirin and a thienopyridine for prevention of restenosis after coronary artery stenting: a meta-analysis. *J Clin Pharmacol* 2010; **50:** 415–21.
6. Rogers KC, *et al*. Use of cilostazol in percutaneous coronary interventions. *Ann Pharmacother* 2012; **46:** 839–50.
7. Chen KY, *et al*. Korea Acute Myocardial Infarction Registry Investigators. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 2009; **119:** 3207–14.
8. Park KW, *et al*. Cilostazol attenuates on-treatment platelet reactivity in patients with CYP2C19 loss of function alleles receiving dual antiplatelet therapy: a genetic substudy of the CILON-T randomised controlled trial. *Heart* 2011; **97:** 641–7.

Peripheral vascular disease. Intermittent claudication is a major feature of occlusive arterial disease of the lower limbs (p. 1272.3) and is characterised by pain in the legs that develops during exercise and disappears at rest. Many drugs have been used for symptom control, but their efficacy and/or overall place in management remains to be firmly established.

Several randomised, double-blind studies[1] have shown that cilostazol improves walking distances in patients with intermittent claudication, and US guidelines have recommended a trial of cilostazol in all patients with lifestyle-limiting intermittent claudication in the absence of heart failure.[2] However, in the UK, NICE does not favour its use[3] and the EMA has restricted it to second-line treatment after lifestyle changes and other appropriate interventions have failed to provide sufficient improvement.[4] Long-term benefit has not been assessed[1] and, since patients with intermittent claudication are at high risk of other cardiovascular events, appropriate therapy to reduce cardiovascular risk (p. 1246.1) is still required. It has also been investigated[5] for a potential role in preventing restenosis in peripheral vascular stents after endovascular therapy for peripheral vascular disease.

1. Roblessp, *et al*. Cilostazol for peripheral arterial disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).
2. Hirsch AT, *et al*. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation* 2006; **113:** e463–e654. Available at: http://www.americanheart.org/downloadable/heart/1135028673759PAD_Full%20Text.pdf (accessed 27/06/06)
3. NICE. Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (TA 223: issued May 2011). Available at: http://www.nice.org.uk/nicemedia/live/13477/54546/54546.pdf (accessed 14/10/13)
4. EMA. Press release: European Medicines Agency recommends restricting use of cilostazol-containing medicines (issued 22nd March, 2013). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/03/WC500140672.pdf (accessed 28/05/13)
5. Dindyal S, Kyriakides C. A review of cilostazol, a phosphodiesterase inhibitor, and its role in preventing both coronary and peripheral arterial restenosis following endovascular therapy. *Recent Pat Cardiovasc Drug Discov* 2009; **4:** 6–14.

Stroke. A review of 3 controlled trials of cilostazol in the secondary prevention of ischaemic stroke in Asian patients suggested cilostazol may be safer and more effective than aspirin in such patients.[1]

1. Ansara AJ, *et al*. Use of cilostazol for secondary stroke prevention: a n old dog with new tricks? *Ann Pharmacother* 2012; **46:** 394–402.

Adverse Effects and Precautions

Adverse effects of cilostazol include headache, dizziness, palpitations, and diarrhoea; oedema, nausea and vomiting, cardiac arrhythmias, chest pain, rhinitis, ecchymosis, and rashes have also been reported. There is a risk of haemorrhage with cilostazol and patients should report any episode of bleeding or easy bruising; if retinal bleeding occurs, cilostazol should be stopped. Haematological abnormalities including leucopenia, thrombocytopenia, agranulocytosis, and aplastic anaemia have been reported rarely. Cardiovascular toxicity has been reported in *animal* studies of cilostazol, and prolonged oral use of other phosphodiesterase inhibitors (such as amrinone, p. 1305.1) for the treatment of heart failure has been associated with increased mortality. The use of cilostazol in patients with any degree of heart failure is therefore contra-indicated. It is also contra-indicated in patients with a known predisposition to bleeding, including those treated with two or more antiplatelet or anticoagulant drugs. It should not be used in those with a history of severe tachyarrhythmia or ventricular arrhythmias, QT interval prolongation, unstable angina, recent myocardial infarction, or coronary intervention within the previous 6 months. It should also be avoided in patients with severe renal impairment or moderate to severe hepatic impairment and in pregnant or breast-feeding women.

Cilostazol should be avoided or used in reduced doses in patients taking inhibitors of the cytochrome P450 isoenzymes CYP3A4 or CYP2C19 (see Interactions, below).

References.

1. Hiatt WR, *et al*. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: a study in long-term effects). *J Vasc Surg* 2008; **47:** 330–6.

Interactions

Cilostazol is extensively metabolised to active and inactive metabolites by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Cilostazol should therefore be used with caution in patients taking drugs metabolised by these enzymes; in patients taking enzyme inhibitors it should be avoided or a reduced dose should be considered (see Uses and Administration, above).

The risk of bleeding is increased if cilostazol is given with clopidogrel and aspirin; its use, therefore, is contra-indicated in patients receiving two or more other antiplatelet or anticoagulant drugs.

Pharmacokinetics

Cilostazol is absorbed after oral doses and absorption is increased if taken with a high fat meal. Cilostazol is extensively metabolised in the liver by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19, to both active and inactive metabolites; these are mainly excreted in the urine (74%) with the remainder in the faeces (20%). The active metabolites have apparent elimination half-lives of 11 to 13 hours. Cilostazol is 95 to 98% protein bound.

References.

1. Woo SK, *et al*. Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; **71:** 246–52.
2. Yoo H-D, *et al*. Population pharmacokinetic analysis of cilostazol in healthy subjects with genetic polymorphisms of CYP3A5, CYP2C19 and ABCB1. *Br J Clin Pharmacol* 2010; **69:** 27–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aclusin; Cibrogan; Cilaal; Cilostal; Cilovas; Licuagen; Pletaal; Policor; Trastocir; Trombonot; Zolplat; ***Austral.***: Pletal; ***Braz.***: Cebralat; Claudic; Vasativ; Vasogard; ***Chile***: Artesol; Ilostal; Kostal†; ***China***: Bang Ping (邦平); Pletaal (培达); Si Te Li Pu (斯特里普); Xi Luo (希络); ***Fr.***: Pletal†; ***Ger.***: Pletal; ***Hong Kong***: Pletaal; ***India***: Cilodac; Cletus; Pletoz; Stiloz; Zilast; ***Indon.***: Aggravan; Agrezol†; Alista; Antiplat; Citaz; Ilos; Naletal; Pletaal; Qital; Stazol; ***Irl.***: Pletal†; ***Ital.***: Pletal; ***Jpn***: Pletaal; ***Malaysia***: Pletaal; ***Mex.***: Caudaline; ***Philipp.***: Aggravan; Ciletin; Clazol; Pletaal; Trombocil; ***Spain***: Ekistol; Pletal; ***Swed.***: Pletal; ***Thai.***: Cilosol; Pletaal; ***Turk.***: Pletal; ***UK***: Pletal; ***USA***: Pletal.

Multi-ingredient Preparations. ***Arg.***: Trastocir Duo.

Pharmacopoeial Preparations
USP 36: Cilostazol Tablets.

Cinepazide Maleate *(BANM, rINNM)*

Cinepazida, maleato de; Cinépazide, Maléate de; Cinepazidi Maleas; Maleato de cinepazida; MD-67350; Цинепазида Малеат.
1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.
$C_{22}H_{31}N_3O_5.C_4H_4O_4$=533.6
CAS — 23887-46-9 (cinepazide); 26328-04-1 (cinepazide maleate).
ATC — C04AX27.
ATC Vet — QC04AX27.
UNII — Y35B3VA60V.

Profile

Cinepazide maleate is a vasodilator that has been used in peripheral vascular disorders, but has been withdrawn from the market in some countries after reports of agranulocytosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ke Lin Ao (克林澳).

Ciprofibrate *(BAN, USAN, rINN)*

Ciprofibrat; Ciprofibrát; Ciprofibratas; Ciprofibrato; Ciprofibratum; Siprofibraatti; Win-35833; Ципрофибрат.
2-[4-(2,2-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid.
$C_{13}H_{14}Cl_2O_3$=289.2
CAS — 52214-84-3.
ATC — C10AB08.
ATC Vet — QC10AB08.
UNII — FB252JGO9S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ciprofibrate). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in toluene. Store in airtight containers. Protect from light.

Uses and Administration

Ciprofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p. 1323.2).

It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, and type IV hyperlipoproteinaemias. The usual oral dose is 100 mg daily. The dose should be reduced in renal impairment (see below).

Administration in renal impairment. Ciprofibrate is contra-indicated in patients with severe renal impairment. Licensed product information suggests reducing the dose to 100 mg every other day for patients with moderate renal impairment.

Renal clearance of ciprofibrate was reduced and elimination half-life about doubled in patients with severe renal impairment.[1] Mild renal impairment slowed the urinary excretion of ciprofibrate but not its extent. The clearance of ciprofibrate was unaffected by haemodialysis.

1. Ferry N, *et al.* The influence of renal insufficiency and haemodialysis on the kinetics of ciprofibrate. *Br J Clin Pharmacol* 1989; **28:** 675–81.

Adverse Effects and Precautions

As for Bezafibrate, p. 1324.2.

Interactions

As for Bezafibrate, p. 1325.2.

Pharmacokinetics

Ciprofibrate is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours. Ciprofibrate is highly protein bound. It is excreted in the urine as unchanged drug and as glucuronide conjugates. The elimination half-life varies from about 38 to 86 hours in patients on long-term therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Estaprol; Fixeril; ***Belg.***: Hyperlipen; ***Braz.***: Cibrato; Ciprolip; Lipless; Lipneo; Oroxadin; ***Chile***: Estaprol; ***China***: Modalim (卡比瑞克); ***Cz.***: Lipanor; ***Fr.***: Lipanor; ***Gr.***: Savilen; ***Hung.***: Lipanor; ***Indon.***: Modalim; ***Israel***: Lipanor; ***Malaysia***: Modalim; ***Mex.***: Oroxadin; ***Neth.***: Modalim; ***Philipp.***: Modalim; ***Pol.***: Lipanor; ***Port.***: Fibranin; Lipanor; ***Rus.***: Lipanor (Липанор); ***Singapore***: Modalim; ***Switz.***: Hyperlipen; ***UK***: Modalim†; ***Venez.***: Hiperlipen.

Clevidipine *(USAN, rINN)*

Clévidipine; Clevidipino; Clevidipinum; H-324/38; Клевидипин.
(Butanoyloxy)methyl methyl (4*RS*)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate; (±)-Hydroxymethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate butyrate.
$C_{21}H_{23}Cl_2NO_6$=456.3
CAS — 166432-28-6; 167221-71-8.
ATC — C08CA16.
ATC Vet — QC08CA16.
UNII — 19O2GP3B7Q.

Uses and Administration

Clevidipine is a dihydropyridine calcium-channel blocker (p. 1244.2); in the USA it is known as clevidipine butyrate. It is used in the management of hypertension (p. 1251.1) as an alternative to oral therapy, and is given by intravenous infusion. The initial dose is 1 to 2 mg/hour, increased if necessary according to the patient's response by doubling the dose, initially every 90 seconds but at longer intervals of 5 to 10 minutes as the desired blood pressure is reached. A dose of 4 to 6 mg/hour is adequate in most patients, with a usual maximum dose of 16 mg/hour; however, up to 32 mg/hour has been required in severe hypertension.

Clevidipine injection has a high lipid content (about 200 mg/mL) and no more than 1 litre should be given in 24 hours.

References.

1. Noviawaty I, *et al.* Drug evaluation of clevidipine for acute hypertension. *Expert Opin Pharmacother* 2008; **9:** 2519–29.
2. Aronson S, *et al.* The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* 2008; **107:** 1110–21.
3. Nguyen HM, *et al.* Clevidipine for the treatment of severe hypertension in adults. *Clin Ther* 2010; **32:** 11–23.
4. Ndefo UA, *et al.* Clevidipine: a new intravenous option for the management of acute hypertension. *Am J Health-Syst Pharm* 2010; **67:** 351–60.
5. Peacock FW, *et al.* Clevidipine for severe hypertension in acute heart failure: a VELOCITY trial analysis. *Congest Heart Fail* 2010; **16:** 55–9.
6. Awad AS, Goldberg ME. Role of clevidipine butyrate in the treatment of acute hypertension in the critical care setting: a review. *Vasc Health Risk Manag* 2010; **6:** 457–64.

Administration in children. In a retrospective review,[1] ten children aged from 9 to 18 years and weighing from 26 to 96 kg were given clevidipine either to control hypertension, induce hypotension, or improve distal perfusion. The initial dose was 500 nanograms/kg per minute in 8 patients, and 1 microgram/kg per minute in 2 patients, adjusted by increments of 500 nanograms/kg per minute every 3 to 5 minutes; the highest dose given was 3.5 micrograms/kg per minute. The durations of infusion ranged from 1.5 to 34 hours, and target blood pressures were reached within 10 minutes. Tachycardia required treatment with beta blockers in 2 patients.

1. Towe E, Tobias JD. Preliminary experience with clevidipine in the pediatric population. *J Intensive Care Med* 2010; **25:** 349–52.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2). Clevidipine injection is formulated as an emulsion containing soybean oil and egg-yolk phospholipids and should not be used in patients with soy or egg allergies or with defective lipid metabolism.

Interactions

Clevidipine would be expected to have similar pharmacological interactions to other dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2), although published studies are lacking. Clevidipine is reported not to affect cytochrome P450 isoenzymes.

Pharmacokinetics

Clevidipine is rapidly distributed when given intravenously and is metabolised by esterases in the blood and extravascular tissues to the inactive carboxylic acid metabolite. The half-life of the initial phase is about 1 minute and accounts for 85 to 90% of clevidipine elimination; the terminal half-life is about 15 minutes. The metabolite is further metabolised by glucuronidation or oxidation to the pyridine derivative and is eliminated mainly in the urine and faeces, with a terminal half-life of about 9 hours. Clevidipine is more than 99.5% bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Cleviprex; ***Switz.***: Cleviprex; ***UK***: Cleviprex; ***USA***: Cleviprex.

Clinofibrate *(rINN)*

Clinofibrato; Clinofibratum; S-8527; Клинофибрат.
2,2′-[Cyclohexylidenebis(4-phenyleneoxy)]bis[2-methylbutyric acid].
$C_{28}H_{36}O_6$=468.6
CAS — 30299-08-2.
UNII — 0374EZJ8CU.

Pharmacopoeias. In *Jpn.*

Profile

Clinofibrate, a fibric acid derivative (see Bezafibrate, p. 1323.2), is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Lipoclin.

Clofibrate *(BAN, USAN, rINN)*

AY-61123; Clofibrat; Clofibrato; Clofibratum; Ethyl *p*-Chlorophenoxyisobutyrate; Ethyl Clofibrate; ICI-28257; Klofibraatti; Klofibrat; Klofibrát; Klofibratas; NSC-79389; Клофибрат.
Ethyl 2-(4-chlorophenoxy)-2-methylpropionate.
$C_{12}H_{15}ClO_3$=242.7
CAS — 637-07-0 (clofibrate); 882-09-7 (clofibric acid).
ATC — C10AB01.
ATC Vet — QC10AB01.
UNII — HPN91K7FU3.

NOTE. The name Binograc has been used as a trademark for clofibrate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Clofibrate). A clear, almost colourless liquid. Very slightly soluble in water; miscible with alcohol.

USP 36: (Clofibrate). A colourless to pale yellow liquid with a characteristic odour. Insoluble in water; soluble in alcohol, in acetone, in chloroform, and in benzene. Store in airtight containers. Protect from light.

Aluminium Clofibrate *(BAN, rINN)*

Alufibrate; Aluminii Clofibras; Aluminium, Clofibrate d'; Aluminiumklofibraatti; Aluminiumklofibrat; Aluminum Clofibrate; Clofibrato de aluminio; Алюминия Клофибрат.
Bis[2-(4-chlorophenoxy)-2-methylpropionato]hydroxyaluminium.
$C_{20}H_{21}AlCl_2O_7$=471.3
CAS — 24818-79-9; 14613-01-5.
ATC — C10AB03.
ATC Vet — QC10AB03.
UNII — 56203T2K2X.

Calcium Clofibrate *(rINN)*

Calcii Clofibras; Clofibrate de Calcium; Clofibrato de calcio; Кальция Клофибрат.
$C_{20}H_{20}CaCl_2O_6$=467.4
CAS — 39087-48-4.
UNII — TT85QFR500.

Magnesium Clofibrate *(rINN)*

Clofibrato de magnesio; Clomag; Magnesii Clofibras; Magnésium, Clofibrate de; UR-112; Магния Клофибрат.

$C_{20}H_{20}Cl_2MgO_6$=451.6

CAS — 14613-30-0.

UNII — Y11SP157PJ.

Profile

Clofibrate, a fibric acid derivative, is a lipid regulating drug with similar properties to bezafibrate (p. 1323.2). It is used to reduce triglycerides and possibly total cholesterol in the management of hyperlipidaemias (p. 1248.1), particularly in patients with hypertriglyceridaemia. Because of the incidence of adverse effects during long-term treatment it should not be used for the prophylaxis of ischaemic heart disease (see Adverse Effects, below). A typical oral daily dose is 0.75 to 1.5 g given in 2 or 3 divided doses, although daily doses of up to 2 g have been used.

The aluminium, calcium, and magnesium salts of clofibrate have also been used.

Adverse effects. Large-scale, long-term studies[1,2] with clofibrate indicated that it was generally well-tolerated but that there was an increased incidence of serious effects, including cholelithiasis, cholecystitis, thromboembolic disorders, and certain cardiac arrhythmias. In one of the studies,[2] an increased mortality rate was unexpectedly found in patients taking clofibrate, producing serious concern over its long-term safety and its use is now generally restricted; the causes of death were spread over a range of malignant and non-malignant disorders.

1. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; **231:** 360–80.
2. Oliver MF, *et al.* A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978; **40:** 1069–1118.

Neonatal jaundice. Clofibrate has been used in the treatment of jaundice in term infants[1,2] and for prophylaxis in premature infants.[1] In a study[1] involving 93 term infants with jaundice, clofibrate 50 mg/kg as a single oral dose reduced the intensity and duration of jaundice compared with placebo. As a prophylactic measure, clofibrate was shown[1] to reduce the degree of jaundice in premature infants when the plasma concentration of clofibric acid reached 140 micrograms/mL within 24 hours of an oral dose. The dose required to achieve this was estimated to be 100 to 150 mg/kg.

1. Gabilan JC, *et al.* Clofibrate treatment of neonatal jaundice. *Pediatrics* 1990; **86:** 647–8.
2. Mohammadzadeh A, *et al.* Effect of clofibrate in jaundiced term newborns. *Indian J Pediatr* 2005; **72:** 123–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Elpi†; ***Gr.***: Atromid-S; ***Hong Kong***: Lipilim†.

Multi-ingredient Preparations. ***Braz.***: Lipofacton†.

Pharmacopoeial Preparations
BP 2014: Clofibrate Capsules;
USP 36: Clofibrate Capsules.

Clonidine *(BAN, USAN, rINN)*

Clonidina; Clonidinum; Klonidiini; Klonidin; ST-155-BS; Клонидин.

2-(2,6-Dichloroanilino)-2-imidazoline; 2,6-Dichloro-*N*-(imidazolidin-2-ylidene)aniline.

$C_9H_9Cl_2N_3$=230.1

CAS — 4205-90-7.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

UNII — MN3L5RMN02.

Pharmacopoeias. In *US*.

USP 36: (Clonidine). A white to almost white, crystalline powder. Freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Clonidine Hydrochloride *(BANM, USAN, rINNM)*

Clonidina, hidrocloruro de; Clonidine, chlorhydrate de; Clonidinhydrochlorid; Clonidini Hydrochloridum; Hidrocloruro de clonidina; Klonidiinihydrokloridi; Klonidin-hidroklorid; Klonidin-hydrochlorid; Klonidinhydroklorid; Klonidino hidrochloridas; Klonidyny chlorowodorek; ST-155; Клонидина Гидрохлорид.

$C_9H_9Cl_2N_3$,HCl=266.6

CAS — 4205-91-8.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

UNII — W76I6XXF06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clonidine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 4.0 to 5.0.

USP 36: (Clonidine Hydrochloride). pH of a 5% solution in water is between 3.5 and 5.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Clonidine is an imidazoline antihypertensive that appears to act centrally to reduce sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate. The exact mechanism is unclear; clonidine stimulates alpha$_2$ adrenoceptors and central imidazoline receptors, but it is unknown which receptors mediate which effects. It also acts peripherally, and this peripheral activity may be responsible for the transient increase in blood pressure seen during rapid intravenous injection as well as contributing to the hypotensive effect during chronic use. Peripheral resistance is reduced during continuous treatment. Cardiovascular reflexes remain intact so orthostatic hypotension is uncommon.

Clonidine is used in the management of hypertension (p. 1251.1), including hypertensive crises, although other drugs with fewer adverse effects are now generally preferred. It may be given with a thiazide diuretic, but use with a beta blocker should be avoided where possible. Clonidine has also been used in the prophylactic treatment of migraine or recurrent vascular headaches (but see p. 1340.1) and in the treatment of menopausal flushing. It is used with opioids in the management of cancer pain and has been tried for various other forms of pain (p. 1340.2). It is also used in the management of ADHD (see Hyperactivity p. 1340.1). Other uses of clonidine have included the symptomatic treatment of opioid withdrawal (see under Substance Dependence, p. 1340.3), the diagnosis of phaeochromocytoma (p. 1340.2), and as eye drops in the management of glaucoma (p. 1999.1). It has also been tried in Tourette's syndrome (p. 1341.1) and many other disorders.

Clonidine is used as the hydrochloride. When given orally, its haemodynamic effects appear in about 30 to 60 minutes, reaching a maximum after 2 to 4 hours and lasting up to 8 hours. Tolerance to clonidine has been reported. Withdrawal of clonidine should be gradual because of the risk of rebound hypertension.

In **hypertension**, the usual initial oral dose of clonidine hydrochloride is 50 to 100 micrograms three times daily (or in the USA, 100 micrograms twice daily), increased every second or third day according to response; the usual maintenance dose is 300 to 1200 micrograms daily but doses of 1800 micrograms or more daily may sometimes be required. Modified-release preparations have been used. Clonidine may also be given by transdermal delivery systems that are applied once a week and deliver 100 to 300 micrograms of clonidine base daily at a constant rate.

Clonidine hydrochloride may be given by slow intravenous injection over 10 to 15 minutes in hypertensive crises, usually in doses of 150 to 300 micrograms. The effect usually appears within 10 minutes, but transient hypertension may precede hypotension if the injection is given too rapidly. The hypotensive effect reaches a maximum about 30 to 60 minutes after injection and the duration is about 3 to 7 hours; up to 750 micrograms may be given intravenously over 24 hours. Oral dosage does not produce a sufficiently rapid hypotensive effect for use in emergencies; however, for less urgent reduction of severe hypertension, clonidine has been given orally in an initial dose of 100 to 200 micrograms, followed by 50 to 200 micrograms every hour until blood pressure was controlled or a maximum total dose of 500 to 700 micrograms given.

For doses in children, see below.

In the prophylaxis of **migraine** or recurrent vascular headaches and in the treatment of **menopausal flushing**, an oral dose of 50 micrograms twice daily has been used, increased, if there is no remission after 2 weeks, to 75 micrograms twice daily.

In the management of severe **cancer pain**, clonidine hydrochloride may be given by continuous epidural infusion with an opioid, in an initial dose of 30 micrograms/hour, adjusted according to response.

Administration in children. Although unlicensed for use in children, the *BNFC* suggests that clonidine may be given to treat severe hypertension in children aged 2 years and above in doses according to weight. A suggested initial oral daily dose is 1.5 to 3 micrograms/kg in 3 divided doses, increased gradually if necessary to a maximum daily dose of 25 micrograms/kg (not exceeding 1.2 mg daily) given in divided doses. A slow intravenous injection of 2 to 6 micrograms/kg (maximum of 300 micrograms) may be given as a single dose over 10 to 15 minutes.

See p. 1340.1, p. 1340.3 and p. 1341.1 for details of doses used in ADHD, neonatal abstinence syndrome (Substance Dependence, under Opioid Analgesics), and Tourette's syndrome, respectively.

Anxiety disorders. Clonidine has been tried in various anxiety disorders but evidence of efficacy is limited. A review[1] of its use in panic disorder (p. 1029.1) considered that it might be useful as a last-line anxiolytic in patients unresponsive to standard treatment as occasional success had been obtained in a few patients. There have also been isolated reports of small numbers of patients with post-traumatic stress disorder (p. 1029.2) who have benefited from clonidine.[2]

For mention of clonidine as an adjuvant to sedative drugs in the intensive care unit see p. 1033.1.

1. Puzantian T, Hart LL. Clonidine in panic disorder. *Ann Pharmacother* 1993; **27:** 1351–3.
2. Harmon RJ, Riggs PD. Clonidine for posttraumatic stress disorder in preschool children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 1247–9.

Cardiac arrhythmias. Atrial fibrillation (p. 1266.1) is managed by treatment to slow the increased ventricular responses or by cardioversion. Control of ventricular rate is usually achieved with digoxin, beta blockers, or calcium-channel blockers but clonidine, which reduces sympathetic tone and thus reduces heart rate, has also been tried.[1-3]

1. Roth A, *et al.* Clonidine for patients with rapid atrial fibrillation. *Ann Intern Med* 1992; **116:** 388–90.
2. Scardi S, *et al.* Oral clonidine for heart rate control in chronic atrial fibrillation. *Lancet* 1993; **341:** 1211–12.
3. Simpson CS, *et al.* Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation; a prospective, randomized clinical trial. *Am Heart J* 2001; **142:** e3.

Diarrhoea. Some studies have shown that clonidine possesses antidiarrhoeal properties. Clonidine may stimulate alpha$_2$ adrenoceptors on enterocytes thus promoting fluid and electrolyte absorption and inhibiting anion secretion. It may also modify intestinal motility or rectal sphincter tone.

Most experience with clonidine is in diabetic diarrhoea (see p. 464.1). Oral clonidine 100 to 600 micrograms every 12 hours reduced diabetic diarrhoea in 3 patients with type 1 diabetes[1] and good results have also been reported in such patients when transdermal clonidine was used.[2,3] Benefit has also been reported in patients with symptoms of diabetic gastroparesis in addition to diarrhoea.[3,4] However, oral (but perhaps not transdermal) clonidine may worsen orthostatic hypotension in patients with diabetic diarrhoea and this may limit its usefulness.[5] Clonidine has also been tried in patients with high intestinal output after small bowel transplantation[6] or jejunostomy,[7] and in diarrhoea-predominant irritable bowel syndrome[8] or for the gastrointestinal effects of opioid withdrawal.[9]

1. Fedorak RN, *et al.* Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985; **102:** 197–9.
2. Sacerdote A. Topical clonidine for diabetic diarrhea. *Ann Intern Med* 1986; **105:** 139.
3. Sacerdote AS. Topical clonidine and diabetic gastroparesis. *Ann Intern Med* 1990; **112:** 796.
4. Migliore A, *et al.* Diabetic diarrhea and clonidine. *Ann Intern Med* 1988; **109:** 170–1.
5. Ogbonnaya KI, Arem R. Diabetic diarrhea: pathophysiology, diagnosis, and management. *Arch Intern Med* 1990; **150:** 262–7.
6. Rovera G, *et al.* The use of clonidine for the treatment of high intestinal output following small bowel transplantation. *Transplant Proc* 1997; **29:** 1853–4.
7. Buchman AL, *et al.* Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study. *J Parenter Enteral Nutr* 2006; **30:** 487–91.
8. Camilleri M, *et al.* A randomized, controlled exploratory study of clonidine in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2003; **1:** 111–21.
9. Ma H, *et al.* The effect of clonidine on gastrointestinal side effects associated with ultra-rapid opioid detoxification. *Anesth Analg* 2003; **96:** 1409–12.

Extrapyramidal disorders. There is limited evidence[1] from small studies that clonidine might reduce symptoms of antipsychotic-induced akathisia and tardive dyskinesia (p. 1049.2). However, adverse effects such as sedation and hypotension may limit use.

1. Ahmed I, Takeshita J. Clonidine: a critical review of its role in the treatment of psychiatric disorders. *CNS Drugs* 1996; **6:** 53–70.

Growth retardation. Clonidine has been reported to be a stimulant of growth hormone release, presumably as a result of central alpha-adrenergic stimulation, and has been tried in the diagnosis and management of growth retardation (p. 1921.3). It may be given orally as a provocative test for growth hormone deficiency,[1,2] particularly in children,[3] although some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) to be more useful than provocative tests. A combination of both may be required to confirm diagnosis;[4] guidelines have been suggested.[5] Caution is required when perform-

ing the test in children since severe hypoglycaemia has been reported.[6] Clonidine has also been tried in the treatment of growth retardation, both in children with growth hormone deficiency and in short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[7-9]

1. Gil-Ad I, *et al.* Oral clonidine as a growth hormone stimulation test. *Lancet* 1979; **ii:** 278–80.
2. Hoffman WH, *et al.* Relationship of plasma clonidine to growth hormone concentrations in children and adolescents. *J Clin Pharmacol* 1989; **29:** 538–42.
3. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
4. Cianfarani S, *et al.* Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? *Clin Endocrinol (Oxf)* 2002; **57:** 161–7.
5. Evans C, Gregory JW. The investigation of short stature: a survey of practice in Wales and suggested practical guidelines. *J Clin Pathol* 2004; **57:** 126–30.
6. Huang C, *et al.* Hypoglycemia associated with clonidine testing for growth hormone deficiency. *J Pediatr* 2001; **139:** 323–4.
7. Pintor C, *et al.* Clonidine treatment for short stature. *Lancet*; 1987; **i:** 1226–30.
8. Pescovitz OH, Tan E. Lack of benefit of clonidine treatment for short stature in a double-blind, placebo-controlled trial. *Lancet* 1988; **ii:** 874–7.
9. Allen DB. Effects of nightly clonidine administration on growth velocity in short children without growth hormone deficiency: a double-blind, placebo-controlled study. *J Pediatr* 1993; **122:** 32–6.

Hyperactivity. Drug treatment of attention deficit hyperactivity disorder (ADHD, p. 2314.1) is usually begun with a central stimulant; clonidine may be an alternative, either as monotherapy or as an adjunct to stimulant therapy. In the USA, an oral modified-release preparation is available for children and adolescents aged from 6 to 17 years. It is given in an initial dose of 100 micrograms once daily at bedtime, adjusted according to response in weekly increments of 100 micrograms, to a maximum daily dose of 400 micrograms. Daily doses of 200 micrograms and above should be given in two divided doses, split either equally or with the larger dose given at bedtime. When stopping therapy, the dose should be tapered in decrements of 100 micrograms every 3 to 7 days.

A meta-analysis[1] of clonidine used to treat ADHD occurring alone or with other conditions, including tic disorders (see Tourette's Syndrome, p. 1341.1), concluded that clonidine might be a useful second-line treatment but was less effective than stimulants and was associated with many adverse effects. There have been reports[2] of sudden death when clonidine has been used with stimulants, but the role of the drugs in these events is unclear. A study[3] in children with both ADHD and Tourette's syndrome found that clonidine used with methylphenidate was more effective than either drug alone, and only 1 child had evidence of adverse cardiac effects. Others have since reported on the efficacy[4] and safety[5] of clonidine in ADHD, alone or with methylphenidate.

Clonidine has also been tried in the management of children with disturbed behaviour (p. 1030.2).

1. Connor DF, *et al.* A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 1551–9.
2. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5:** 155–6.
3. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* 2002; **58:** 527–36.
4. Palumbo DR, *et al.* Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 180–8.
5. Daviss WB, *et al.* Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 189–98.

Menopausal disorders. Although HRT is the mainstay of treatment for menopausal disorders (p. 2245.1) clonidine has been of some use in countering vasomotor symptoms in patients who cannot use HRT;[1,2] however, some studies have failed to show a reduction in hot flushes. The adverse effects reported in normotensive women, including orthostatic hypotension, may mean that it is best reserved for women who are also hypertensive.

Clonidine has also been tried[3] for hot flushes in women receiving tamoxifen.

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40:** 220–30.
2. Lucero MA, McCloskey WW. Alternatives to estrogen for the treatment of hot flashes. *Ann Pharmacother* 1997; **31:** 915–17.
3. Pandya KJ, *et al.* Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000; **132:** 788–93.

Migraine. Propranolol is probably the most well established drug for prophylaxis of migraine (p. 670.3). Many other drugs have been used, including clonidine, but a review of clinical studies[1] indicated that it was a poor first choice and seemed unlikely to work even as a last resort. It has been used in patients whose attacks may be precipitated by tyramine-containing foods.

1. Anonymous. Clonidine in migraine prophylaxis—now obsolete. *Drug Ther Bull* 1990; **28:** 79–80.

Orthostatic hypotension. Paradoxically, clonidine has produced beneficial effects in a few patients with orthostatic hypotension (p. 1634.3), including that due to autonomic neuropathy[1] and that possibly due to brimonidine and betaxolol eye drops in a hypertensive woman with glaucoma;[2] clonidine improved both the orthostatic hypotension and the supine hypertension.

1. Acott PD, *et al.* Effectiveness of clonidine in congenital orthostatic hypotension. *J Pediatr* 1990; **116:** 666–7.
2. Brahmbhatt R, *et al.* Normalization of blood pressure in a patient with severe orthostatic hypotension and supine hypertension using clonidine. *Hypertension* 2001; **37:** e24.

Pain. Giving opioids and local anaesthetics by the epidural or intrathecal routes can produce effective analgesia but adverse effects are common. Many other drugs, including clonidine, have been tried by these routes, alone or as adjuncts. Clonidine is thought to produce analgesia by a direct action on alpha$_2$ adrenoceptors in the spinal cord. It has been used in various types of pain, such as postoperative pain (p. 6.1), labour pain (p. 8.3), and the pain associated with cancer (p. 7.1), particularly neuropathic pain (p. 10.1). It has been used alone but is more usually given with local anaesthetics and/or opioids; it has been given by various routes including epidural, intrathecal, intravenous, intramuscular, oral, and transdermal use. An early meta-analysis[1] of postoperative epidural use of clonidine was unable to reach a conclusion owing to the large number of variables. Subsequent systematic reviews considered that addition of clonidine to intermediate-acting local anaesthetics improved their activity in certain peripheral nerve and plexus blocks,[2,3] and that adding clonidine to intrathecal local anaesthetics reduced intra-operative pain, although it increased the risk of hypotension.[4] Adding clonidine to peripheral or plexus blocks seemed to prolong the duration of postoperative analgesia by about 2 hours; it was unclear to what extent the effects of clonidine were dose-responsive.[3] The role and appropriate dosage of clonidine in local anaesthesia remains unclear.[2-4] For further discussion of pain and its management, see p. 4.1. See also Premedication, below.

1. Armand S, *et al.* Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task. *Br J Anaesth* 1998; **81:** 126–34.
2. McCartney CJL, *et al.* Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* 2007; **32:** 330–8.
3. Pöpping DM, *et al.* Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *Anesthesiology* 2009; **111:** 406–15.
4. Elia N, *et al.* Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* 2008; **33:** 159–67.

Phaeochromocytoma. Clonidine acts centrally to suppress catecholamine release and may be used[1] in the diagnosis of phaeochromocytoma (p. 1278.1). Experience gained with the clonidine suppression test and a review of published studies indicated that it is of value in selected patients with moderately elevated plasma and/or urinary catecholamine concentrations.[2]

1. Bravo EL, *et al.* Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981; **305:** 623–6.
2. Lenz T, *et al.* Clonidine suppression test revisited. *Blood Pressure* 1998; **7:** 153–9.

Premedication. Clonidine has been given pre-operatively for its sedative, anxiolytic, and analgesic effects (see also Pain, above), and to provide haemodynamic stability and reduce anaesthetic requirements; it is often given orally, although other routes such as intranasal and intravenous have also been tried. It has often been tried in children,[1] in whom pre-operative use has also been reported to reduce postoperative vomiting[2] (similar results have been reported in adult women[3]); a meta-analysis concluded that it was superior to benzodiazepines in producing sedation at induction, decreasing emergence agitation, and producing early postoperative analgesia, although comparative benefits in reducing postoperative nausea and vomiting were less clear.[4] Clonidine may attenuate the perioperative stress response and has been shown to reduce perioperative oxygen consumption, which is a marker of sympathetic activation.[5] It may also reduce the risk of perioperative myocardial ischaemia.[6]

1. Bergendahl H, *et al.* Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. *Acta Anaesthesiol Scand* 2006; **50:** 135–43.
2. Mikawa K, *et al.* Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; **42:** 977–81.
3. Oddby-Muhrbeck E, *et al.* Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. *Anesthesiology* 2002; **96:** 1109–14.
4. Dahmani S, *et al.* Premedication with clonidine is superior to benzodiazepines: a meta analysis of published studies. *Acta Anaesthesiol Scand* 2010; **54:** 397–402.
5. Taittonen MT, *et al.* Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; **78:** 400–406.
6. Nishina K, *et al.* Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. *Anesthesiology* 2002; **96:** 323–9.

Restless legs syndrome. Many drugs have been tried for the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2). Symptomatic improvement has been reported with clonidine in several case studies[1,2] and small controlled studies,[3] but adverse effects may limit its use.

1. Handwerker JV, Palmer RF. Clonidine in the treatment of "restless leg" syndrome. *N Engl J Med* 1985; **313:** 1228–9.
2. Zoe A, *et al.* High-dose clonidine in a case of restless legs syndrome. *Ann Pharmacother* 1994; **28:** 878–81.
3. Wagner ML, *et al.* Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996; **19:** 52–8.

Shivering. Many drugs, including clonidine, have been tried for the treatment of postoperative shivering (p. 1900.2). Clonidine's central and peripheral effects could both account for its antishivering activity, but some have suggested that it acts by resetting the central threshold temperature for shivering. Several studies[1-3] have suggested that clonidine is effective for the treatment of postoperative shivering. Typical doses of 75 to 150 micrograms intravenously have been used. Clonidine given intraoperatively,[4-7] including to neurosurgical patients after mild hypothermia,[8] has also been reported to reduce the incidence of postoperative shivering. However, studies[9,10] have found nefopam to be superior to clonidine for prevention of postoperative shivering.

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79:** 532–9.
2. Capogna G, Celleno D. IV clonidine for post-extradural shivering in parturients: a preliminary study. *Br J Anaesth* 1993; **71:** 294–5.
3. Schwarzkopf KRG, *et al.* A comparison between meperidine, clonidine and urapidil in the treatment of postanesthetic shivering. *Anesth Analg* 2001; **92:** 257–60.
4. Steinfath M, *et al.* Clonidine administered intraoperatively prevents postoperative shivering. *Br J Clin Pharmacol* 1995; **39:** 580P–581P.
5. Vanderstappen I, *et al.* The effect of prophylactic clonidine on postoperative shivering: a large prospective double-blind study. *Anaesthesia* 1996; **51:** 351–5.
6. Sia S. I.v. clonidine prevents post-extradural shivering. *Br J Anaesth* 1998; **81:** 145–6.
7. Piper SN, *et al.* A comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. *Anesth Analg* 2000; **90:** 954–7.
8. Stapelfeldt C, *et al.* Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg* 2005; **100:** 226–32.
9. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; **59:** 559–64.
10. Bilotta F, *et al.* Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. *Anaesthesia* 2005; **60:** 124–8.

Spasticity. Clonidine, given alone or as an adjunct to baclofen, has been tried in patients with various forms of spasticity (p. 2014.2) including those refractory to baclofen.[1-5]

1. Nance PW, *et al.* Clonidine in spinal cord injury. *Can Med Assoc J* 1985; **133:** 41–2.
2. Donovan WH, *et al.* Clonidine effect on spasticity: a clinical trial. *Arch Phys Med Rehabil* 1988; **69:** 193–4.
3. Sandford PR, *et al.* Clonidine in the treatment of brainstem spasticity: case report. *Am J Phys Med Rehabil* 1992; **71:** 301–3.
4. Middleton JW, *et al.* Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study. *Arch Phys Med Rehabil* 1996; **77:** 824–6.
5. Lubsch L, *et al.* Oral baclofen and clonidine for treatment of spasticity in children. *J Child Neurol* 2006; **21:** 1090–2.

Substance dependence. *ALCOHOL* Although drug treatment of alcohol withdrawal (p. 1735.1) is usually with a benzodiazepine, clonidine has shown benefit[1] in mild to moderate withdrawal, although it has no effect on convulsions or delirium tremens and should not be used as sole therapy. It may be considered with a benzodiazepine when opioid withdrawal is also taking place.

1. Mayo-Smith MF, *et al.* Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; **278:** 144–51.

OPIOID ANALGESICS. Clonidine has been reported to be useful in controlling withdrawal symptoms after abrupt withdrawal of opioids (p. 109.2). However, a systematic review[1] of the use of alpha$_2$-adrenoceptor agonists, including clonidine, concluded that, for gradual withdrawal, they were no more effective than reducing doses of methadone over a period of around 10 days, and patients had more adverse effects and therefore stopped treatment sooner with clonidine. Clonidine is usually given orally in three or four divided doses to a maximum of 1 mg daily.

Clonidine has also been used with naltrexone to shorten the withdrawal syndrome, allowing withdrawal to be achieved within 6 days.[2] Subsequent modification to the regimen allowed 38 of 40 patients addicted to methadone to withdraw completely in 4 to 5 days.[3] Patients required a mean of 2.3 mg of clonidine on the first day which reduced, but did not abolish, symptoms. A further modification was reported allowing opioid withdrawal with minimal drop-out over 2 to 3 days.[4]

Clonidine has also been used in the management of neonatal abstinence syndrome (p. 110.1) in infants born to opioid-addicted mothers maintained on methadone.[5,6] Benefit occurred in 6 of 7 such infants given an initial

clonidine dose of 0.5 to 1 microgram/kg orally, increased over 1 to 2 days to 3 to 5 micrograms/kg daily in divided doses. Total length of treatment ranged from 6 to 17 days. The infant who failed to respond was born to a mother also given haloperidol, desipramine, and theophylline.[6] In another study in 80 infants with neonatal abstinence syndrome,[7] clonidine 1 microgram/kg six times daily shortened treatment duration compared with placebo when given with diluted tincture of opium. However, a systematic review[8] found insufficient evidence to support the use of clonidine in the management of neonatal abstinence syndrome.

1. Gowing L, *et al*. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 24/09/09).
2. Charney DS, *et al*. Clonidine and naltrexone: a safe, effective, and rapid treatment of abrupt withdrawal from methadone therapy. *Arch Gen Psychiatry* 1982; **39:** 1327–32.
3. Charney DS, *et al*. The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. *Am J Psychiatry* 1986; **143:** 831–7.
4. Brewer C, *et al*. Opioid withdrawal and naltrexone induction in 48-72 hours with minimal drop-out, using a modification of the naltrexone-clonidine technique. *Br J Psychiatry* 1988; **153:** 340–3.
5. Hoder EL, *et al*. Clonidine in neonatal narcotic-abstinence syndrome. *N Engl J Med* 1981; **305:** 1284.
6. Hoder EL, *et al*. Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res* 1984; **13:** 243–51.
7. Agthe AG, *et al*. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics* 2009; **123:** e849–e856.
8. Osborn DA, *et al*. Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 03/03/06).

SMOKING. Nicotine dependence may be managed using behavioural or psychological counselling. In addition, nicotine replacement therapy (see Smoking Cessation, p. 2570.2) can help alleviate withdrawal symptoms. Other drugs, including clonidine, have also been tried. A systematic review[1] found clonidine given in doses of 200 to 400 micrograms daily orally or the equivalent transdermally to be effective; however adverse effects limit its usefulness and clonidine should be reserved for second-line treatment under close medical supervision in those who have severe agitation and anxiety when stopping smoking.

Some individual studies have found clonidine to be more effective in women although the authors of the systematic review[1] recommended that these results be interpreted cautiously since some studies also found that women were less successful in giving up smoking unaided than men; treatment with clonidine, however, resulted in similar success rates in both men and women.

1. Gourlay SG, *et al*. Clonidine for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 26/09/05).

Tourette's syndrome. Clonidine is one of many drugs that have been tried in the management of Tourette's syndrome (see Tics, p. 1030.1).

Disturbance of monoamine metabolism (including dopamine, noradrenaline, and serotonin) has been implicated in Tourette's syndrome. Clonidine is thought to reduce central noradrenergic activity and may also affect other neurochemical systems, and these properties may account for its beneficial effects in this disorder. Studies of clonidine in Tourette's syndrome have produced mixed results,[1-5] although this may reflect the difficulty in study design for a disease that can vary considerably in severity and presence of comorbid conditions and whose symptoms wax and wane. A retrospective study[6] in juvenile patients given clonidine suggested that those showing improvement in the attention deficit hyperactivity disorder associated with Tourette's syndrome had previously had a longer duration of vocal tics; older children had a better overall response than younger children, who tended to suffer more from clonidine-induced drowsiness. However, no predictors of response could be identified. Nevertheless, clonidine is increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics pimozide and haloperidol, although exacerbation of tics and a marked sensation of heat have been reported[7] in one patient. Clonidine has also been reported to successfully control symptoms in some children with Tourette's syndrome unresponsive to haloperidol.[1] The range of oral doses used in these studies was wide, but a typical example[6] was 1.5 to 9.5 micrograms/kg daily (average about 5 micrograms/kg daily) in 53 children aged from 5 to 18 years. Transdermal clonidine has also shown some benefit when given to children at 1 mg weekly (weight under 40 kg), 1.5 mg weekly (weight 40 to 60 kg), or 2 mg weekly (weight over 60 kg).[8]

Clonidine has also been used with stimulants in children with Tourette's syndrome and attention deficit hyperactivity disorder, although there have been concerns about the toxicity of such combinations (see Hyperactivity, p. 1340.1).

1. Cohen DJ, *et al*. Clonidine in Tourette's syndrome. *Lancet* 1979; **ii:** 551–3.
2. Shapiro AK, *et al*. Treatment of Gilles de la Tourette's syndrome with clonidine and neuroleptics. *Arch Gen Psychiatry* 1983; **40:** 1235–40.
3. Leckman JF, *et al*. Short- and long-term treatment of Tourette's syndrome with clonidine: a clinical perspective. *Neurology* 1985; **35:** 343–51.
4. Goetz CG, *et al*. Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. *Ann Neurol* 1987; **21:** 307–10.
5. Leckman JF, *et al*. Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1991; **48:** 324–8.
6. Lichter DG, Jackson LA. Predictors of clonidine response in Tourette syndrome: implications and inferences. *J Child Neurol* 1996; **11:** 93–7.
7. Kessler AR. Clonidine treatment increases tics in patients with Tourette syndrome: case report. *J Child Neurol* 2001; **16:** 380–1.
8. Du Y-S, *et al*. Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. *Aust N Z J Psychiatry* 2008; **42:** 807–13.

Adverse Effects and Treatment

Drowsiness, dry mouth, dizziness, and headache are common when starting therapy with clonidine. Constipation is also common, and other adverse effects reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, orthostatic hypotension, and dry, itching, or burning sensations in the eye. Fluid retention may occur and is usually transient, but may be responsible for a reduction in the hypotensive effect during continued treatment. Clonidine can cause rashes and pruritus, and these are more common with transdermal delivery systems. Bradycardia, including sinus bradycardia with AV block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome, gynaecomastia, and transient abnormalities in liver function tests have been reported less often. Large doses have been associated with initial increases in blood pressure and transient hyperglycaemia, although these do not persist during continued therapy.

Symptoms of overdosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma. Treatment consists of general supportive measures. An alpha blocker may be given if necessary for hypertension, and atropine may be required for bradycardia and associated hypotension. Cardiac pacing may be needed rarely.

Sudden withdrawal of clonidine may produce rebound hypertension—see Precautions, below.

Effects on the gastrointestinal tract. Constipation is a relatively common adverse effect of clonidine, US licensed product information reporting an incidence of about 10%. Ileus or pseudo-obstruction of the bowel have been reported;[1-3] withdrawal of clonidine was associated with a return of bowel function to normal. Abdominal pain mimicking acute appendicitis occurred in another patient; symptoms recurred on restarting the drug and subsided on withdrawal.[4]

1. Davidov M, *et al*. The antihypertensive effects of an imidazoline compound. *Clin Pharmacol Ther* 1967; **8:** 810–16.
2. Bear R, Steer K. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1:** 197.
3. Bauer GE, Hellestrand KJ. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1:** 769.
4. Mjörndal T, Mellbring G. Abdominal pain associated with clonidine. *BMJ* 1986; **292:** 174.

Effects on the heart. Clonidine has been associated with impaired atrioventricular conduction in a few patients,[1,2] although some of these may have had underlying conduction defects and had previously received digitalis, which may have contributed to their condition. Other ECG abnormalities may also occur. Sudden death has been reported in 3 children receiving clonidine and methylphenidate,[3,4] although the significance of these reports has been questioned.[5]

1. Kibler LE, Gazes PC. Effect of clonidine on atrioventricular conduction. *JAMA* 1977; **238:** 1930–2.
2. Abiuso P, Abelow G. Atrioventricular dissociation in a patient receiving clonidine. *JAMA* 1978; **240:** 108–9.
3. Maloney MJ, Schwam, JS. Clonidine and sudden death. *Pediatrics* 1995; **96:** 1176–7.
4. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5:** 155–6.
5. Blackman JA, *et al*. Clonidine and electrocardiograms. *Pediatrics* 1996; **98:** 1223–4.

Effects on mental function. There have been occasional reports of disturbed mental state in patients given clonidine.[1-4]

1. Lavin P, Alexander CP. Dementia associated with clonidine therapy. *BMJ* 1975; **1:** 628.
2. Enoch MD, Hammad GEM. Acute hallucinosis due to clonidine. *Curr Med Res Opin* 1977; **4:** 670–1.
3. Brown MJ, *et al*. Clonidine hallucinations. *Ann Intern Med* 1980; **93:** 456–7.
4. Delaney J, *et al*. Clonidine-induced delirium. *Int J Cardiol* 2006; **113:** 276–8.

Effects on the skin. Skin reactions have been reported in up to 50% of patients using clonidine transdermal patches.[1] Localised erythema and irritation during early treatment are usually mild, but allergic contact dermatitis may develop.[2-4] Skin reactions may become commoner during prolonged treatment; although only mild skin reactions were seen in a study of transdermal clonidine during 8 to 14 weeks of treatment in 15 patients, severe skin reactions occurred after an average of 20 weeks in 4 of 5 patients who continued treatment.[5] Despite a claim that skin reactions were due to a component in the patch and not to clonidine itself,[6] positive patch tests to clonidine have been obtained.[2,4] Subsequent reaction to oral clonidine in patients who develop skin reactions to the transdermal patch is reported to be rare.[7,8]

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10:** 151–9.
2. Groth H, *et al*. Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii:** 850–1.
3. McMahon FG, Weber MA. Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii:** 851.
4. Boekhorst JC. Allergic contact dermatitis with transdermal clonidine. *Lancet* 1983; **ii:** 1031–2.
5. Dick JBC, *et al*. Skin reactions to long-term transdermal clonidine. *Lancet* 1987; **i:** 516.
6. Anonymous. Transdermal clonidine sensitiser identified? *Pharm J* 1984; **233:** 16.
7. Bigby M. Transdermal clonidine dermatitis. *JAMA* 1987; **258:** 1819.
8. Burris JF. Transdermal clonidine dermatitis. *JAMA* 1987; **258:** 1819–20.

PEMPHIGOID. Anogenital cicatricial pemphigoid has been reported[1] in a patient receiving long-term clonidine therapy.

1. van Joost T, *et al*. Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102:** 715–18.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Analysis by the UK National Poisons Information Service[1] of poisoning by clonidine in 133 children and 37 adults between 1976 and 1977 revealed that there were no deaths but clinical features were often severe. Supportive measures were usually adequate but atropine was often needed for severe and persistent bradycardia. Forced diuresis was not advised because hypotension could be enhanced and there was no evidence that excretion of clonidine was increased. More recently, death has been reported[2] in a 23-month old child.

Direct medical evaluation has been recommended[3] for children who have ingested the following amounts: 100 micrograms or more in those aged 4 years and under; more than 200 micrograms in those aged 5 to 8 years; and 400 micrograms or more in older children; 4 hours may be long enough to detect full onset of symptoms. However, others[4] believe that medical evaluation is indicated in any child who has unintentionally ingested more than a weight-appropriate therapeutic dose.

Although naloxone has been suggested as an antidote for clonidine overdose, no reversal of the hypotensive effects of clonidine 300 micrograms was noted in 6 hypertensive subjects given naloxone by intravenous infusion.[5] In a retrospective analysis of 47 children with clonidine poisoning, only 3 of 19 given naloxone showed definite improvement;[6] it was concluded that naloxone is at best an inconsistent antidote for clonidine poisoning.

Severe symptoms of overdosage have also been reported after the ingestion of clonidine transdermal patches,[7] and after probable subcutaneous injection during filling of an epidural pump reservoir.[8]

1. Stein B, Volans GN. Dixarit overdose: the problem of attractive tablets. *BMJ* 1978; **2:** 667–8.
2. Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. *Arch Pediatr Adolesc Med* 2002; **156:** 392–6.
3. Spiller HA, *et al*. Toxic clonidine ingestion in children. *J Pediatr* 2005; **146:** 263–6.
4. Langhan M, Chan GM. Clonidine exposures, not toxicity. *J Pediatr* 2006; **148:** 565.
5. Rogers JF, Cubeddu LX. Naloxone does not antagonise the antihypertensive effect of clonidine in essential hypertension. *Clin Pharmacol Ther* 1983; **34:** 68–73.
6. Wiley JF, *et al*. Clonidine poisoning in young children. *J Pediatr* 1990; **116:** 654–8.
7. Raber JH, *et al*. Clonidine patch ingestion in an adult. *Ann Pharmacother* 1993; **27:** 719–22. Correction. *ibid*.; 1143.
8. Frye CB, Vance MA. Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 2000; **34:** 611–15.

Precautions

Clonidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including myocardial infarction, renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.

Clonidine causes drowsiness and patients should not drive or operate machinery where loss of attention could be dangerous.

Systemic effects also occur after epidural use and patients should be closely monitored, particularly during the first few days of therapy.

Intravenous injections of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already taking other antihypertensives such as guanethidine or reserpine.

Withdrawal of clonidine antihypertensive therapy should be gradual as stopping suddenly may cause rebound hypertension, sometimes severe. Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may also occur. Beta blockers can exacerbate the rebound hypertension and if both are being used, clonidine should not be stopped until several days after the withdrawal of the beta blocker. Patients should be warned of the risk of missing a dose or stopping the drug without consulting their doctor and should carry a reserve supply.

Although hypotension may occur during anaesthesia in clonidine-treated patients clonidine should not be withdrawn; indeed, if necessary it should be given intravenously during the operation to avoid the risk of rebound hypertension.

Abuse. Despite its central effects and ability to cause a form of physical dependence, WHO rated the likelihood of abuse as very low.[1] However, clonidine may potentiate the psychoactive effects of morphine and abuse has been reported.[2]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 19/08/08)
2. Sullivan JT, *et al*. Does clonidine alter the abuse potential of morphine? *Clin Pharmacol Ther* 1995; **57:** 163.

Diabetes mellitus. The effects of clonidine on carbohydrate metabolism appear to be variable. Some studies suggest that it does not affect carbohydrate metabolism in diabetic[1] or non-diabetic hypertensive patients,[2] although there has been a report of a diabetic patient in whom clonidine was associated with elevated fasting blood-glucose values,[3] and increased insulin requirements were noted in a diabetic child treated with clonidine for tics.[4] Conversely, clonidine was associated with severe hypoglycaemia in children when used as a provocative test for growth hormone deficiency (see Growth Retardation, p. 1339.3). However, a study in 10 diabetic hypertensive patients found that although clonidine impaired response to an acute glucose load, it did not significantly affect diabetic control over a 10-week period.[5] Problems may arise when clonidine is given to diabetics with autonomic neuropathy: both severe orthostatic hypotension[6] and paradoxical hypertension[7] have been reported.

For discussion of the use of clonidine in diabetic diarrhoea see p. 1339.3.

1. Nilsson-Ehle P, *et al*. Lipoproteins and metabolic control in hypertensive type II diabetics treated with clonidine. *ActaMed Scand* 1988; **224:** 131–4.
2. Molitch ME, *et al*. Effects of antihypertensive medications on carbohydrate metabolism. *Curr Ther Res* 1986; **39:** 398–407.
3. Okada S, *et al*. Effect of clonidine on insulin secretion: a case report. *J Int Med Res* 1986; **14:** 299–302.
4. Mimouni-Bloch A, Mimouni M. Clonidine-induced hyperglycemia in a young diabetic girl. *Ann Pharmacother* 1993; **27:** 980.
5. Guthrie GP, *et al*. Clonidine in patients with diabetes and mild hypertension. *Clin Pharmacol Ther* 1983; **34:** 713–17.
6. Moffat B. Postural hypotension induced by clonidine in insulin dependent diabetes. *BMJ* 1985; **290:** 822.
7. Young E, *et al*. Paradoxical hypertension from clonidine. *Ann Intern Med* 1984; **101:** 282–3.

ECT. Maximal ECT stimuli were unsuccessful in producing seizures in 4 of 7 treatment attempts in a 66-year-old patient receiving clonidine.[1] It was suggested that clonidine may elevate the seizure threshold.

1. Elliott RL. Case report of a potential interaction between clonidine and electroconvulsive therapy. *Am J Psychiatry* 1983; **140:** 1237–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clonidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The hypotensive effect of clonidine may be enhanced by diuretics, other antihypertensives, and drugs that cause hypotension. However, beta blockers may exacerbate rebound hypertension after clonidine withdrawal (see Precautions, p. 1341.3), and tricyclic antidepressants may antagonise the hypotensive effect. The sedative effect of clonidine may be enhanced by CNS depressants.

Antidepressants. Although tricyclic antidepressants commonly cause orthostatic hypotension, they may antagonise the hypotensive effects of clonidine. Blood pressure control was lost in 4 of 5 hypertensive patients taking clonidine and a diuretic when they were given *desipramine* 75 mg daily.[1] Increase in blood pressure generally occurred in the second week of treatment, but 1 patient had a dramatic rise in blood pressure within 24 hours of starting treatment. The mechanism is thought to be due to a central interaction between clonidine and the tricyclic antidepressant, although a peripheral effect cannot be completely excluded.[2] Loss of blood pressure control also occurred in a patient receiving guanfacine, another alpha$_2$-adrenoceptor agonist, when *amitriptyline* was given.[3] The reaction recurred with *imipramine*. However, in another study clonidine was given to 11 patients taking amitriptyline or imipramine, and 10 achieved good blood pressure control, although 4 developed an acute rise in blood pressure when methyldopa or guanethidine was added.[4] *Maprotiline*[5] or *mianserin*[6] do not appear to interact with clonidine.

There have been reports[7,8] of hypertensive crisis when the tetracyclic antidepressant *mirtazapine* was given with clonidine. Clonidine exerts an effect at central alpha$_2$ receptors; mirtazapine is an antagonist at these receptors and may displace clonidine at high doses.

1. Briant RH, *et al*. Interaction between clonidine and desipramine in man. *BMJ* 1973; **1:** 522–3.
2. van Spanning HW, van Zwieten PA. The interference of tricyclic antidepressants with the central hypotensive effect of clonidine. *Eur J Pharmacol* 1973; **24:** 402–4.
3. Buckley M, Feely J. Antagonism of antihypertensive effect of guanfacine by tricyclic antidepressants. *Lancet* 1991; **337:** 1173–4.
4. Raftos J, *et al*. Clonidine in the treatment of severe hypertension. *Med J Aust* 1973; **1:** 786–93.
5. Gundert-Remy U, *et al*. Lack of interaction between the tetracyclic antidepressant maprotiline and the centrally acting antihypertensive drug clonidine. *Eur J Clin Pharmacol* 1983; **25:** 595–9.
6. Elliott HL, *et al*. Absence of an effect of mianserin on the actions of clonidine or methyldopa in hypertensive patients. *Eur J Clin Pharmacol* 1983; **24:** 15–19.
7. Abo-Zena RA, *et al*. Hypertensive urgency induced by an interaction of mirtazapine and clonidine. *Pharmacotherapy* 2000; **20:** 476–8.
8. Troncoso AL, Gill T. Hypertensive urgency with clonidine and mirtazepine. *Psychosomatics* 2004; **45:** 449–50.

Antipsychotics. Acute, severe hypotension occurred in 2 agitated hypertensive patients after use of clonidine with either *chlorpromazine* or *haloperidol*. Both patients had mitral insufficiency.[1]

1. Fruncillo RJ, *et al*. Severe hypotension associated with concurrent clonidine and antipsychotic medication. *Am J Psychiatry* 1985; **142:** 274.

Dopaminergic antiparkinsonian drugs. For a report of the inhibition of the therapeutic effect of *levodopa* by clonidine, see Antihypertensives, p. 907.2.

Histamine. For the effect of clonidine on histamine given exogenously, see p. 2525.3.

Immunosuppressants. For a report of clonidine increasing whole blood-*ciclosporin* concentrations, see p. 1958.1.

Pharmacokinetics

Clonidine is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is about 20 to 40% protein bound. About 50% of a dose is metabolised in the liver. It is excreted in the urine as unchanged drug and metabolites, 40 to 60% of an oral dose being excreted in 24 hours as unchanged drug; about 20% of a dose is excreted in the faeces, probably via enterohepatic circulation. The elimination half-life has been variously reported to range between 6 and 24 hours, extended to up to 41 hours in patients with renal impairment. Clonidine crosses the placenta and is distributed into breast milk.

It is absorbed through the skin; absorption is reported to be better from the chest or arm than from the thigh. Therapeutic plasma concentrations are achieved 2 or 3 days after application of a transdermal patch and are roughly equivalent to trough concentrations achieved after oral dosage. Therapeutic plasma concentrations are maintained for about 8 hours after removal of the delivery system and then decline slowly over several days.

Reviews.

1. Lowenthal DT, *et al*. Clinical pharmacokinetics of clonidine. *Clin Pharmacokinet* 1988; **14:** 287–310.
2. Potts AL, *et al*. Clonidine disposition in children; a population analysis. *Paediatr Anaesth* 2007; **17:** 924–33.

Pregnancy. A study in 5 pregnant women treated with clonidine for pre-eclampsia[1] reported an average ratio of cord- to plasma-concentrations of 0.87, indicating placental transfer of clonidine. Similar ratios were seen in another study[2] in 17 women given clonidine in mid or late pregnancy. The oral clearance of clonidine was found to increase during pregnancy (although renal clearance appeared to remain unchanged), and higher or more frequent dosing might thus be needed.

1. Boutroy MJ, *et al*. Clonidine placental transfer and neonatal adaption. *Early Hum Dev* 1988; **17:** 275–86.
2. Buchanan ML, *et al*. Clonidine pharmacokinetics in pregnancy. *Drug Metab Dispos* 2009; **37:** 702–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clonidural; ***Austral.***: Catapres; ***Austria***: Catapresan; Isoglaucon; ***Belg.***: Catapressan; Dixarit; ***Braz.***: Atensina; ***Canad.***: Catapres; Dixarit; ***Chile***: Catapresan; ***China***: Run Rui (润瑞); ***Cz.***: Aruclonin; Catapresan†; ***Denm.***: Catapresan; Dixarit; ***Fin.***: Catapresan; ***Fr.***: Catapressan; ***Ger.***: Catapresan; Clonid-Ophtal; Clonistada†; Dispaclonidin†; Haemiton†; Isoglaucon; Paracefan; ***Gr.***: Catapres; Catapresan; ***Hong Kong***: Dixarit†; ***Hung.***: Aruclonin†; ***India***: Arkamin; Catapres; Cloneon; ***Indon.***: Catapres; ***Irl.***: Catapres; Dixarit; ***Israel***: Clonnirit; Normopresan; ***Ital.***: Catapresan; Isoglaucon; ***Jpn***: Catapres; ***Mex.***: Catapresan; Epiclodina; ***Neth.***: Catapresan; Dixarit; ***Norw.***: Catapresan; ***NZ***: Catapres; Dixarit; ***Philipp.***: Catapin; Catapres; Melzin; ***Pol.***: Iporel; ***Port.***: Catapresan; Edolglau; ***Rus.***: Clophelin (Клофелин); Haemiton (Гемитон) †; ***S.Afr.***: Dixarit; Menograine; ***Singapore***: Dixarit; ***Spain***: Catapresan; Isoglaucon†; ***Swed.***: Catapresan; ***Switz.***: Catapresan; ***Thai.***: Catapres†; Hypodine; ***UK***: Catapres; Dixarit; ***Ukr.***: Clophelin (Клофелин); ***USA***: Catapres; Duraclon; Jenloga; Kapvay; Nexiclon†; ***Venez.***: Catapresan; Lowpres; Naclodin; Velaril.

Multi-ingredient Preparations. ***Arg.***: Bemplas; Pertenso; ***India***: Arkamin-H; Catapres Diu; Clothalton; ***Rus.***: Proxofeline (Проксофелин); ***USA***: Clorpres.

Pharmacopoeial Preparations

BP 2014: Clonidine Injection; Clonidine Tablets;
USP 36: Clonidine Hydrochloride and Chlorthalidone Tablets; Clonidine Hydrochloride Tablets; Clonidine Transdermal System.

Clopamide *(BAN, USAN, rINN)* ⊗

Clopamid; Clopamida; Clopamidum; DT-327; Klopamid; Klopamidi; Клопамид.

4-Chloro-*N*-(2,6-dimethylpiperidino)-3-sulphamoylbenzamide; *cis*-3-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethyl-1-piperidinyl)benzamide.

$C_{14}H_{20}ClN_3O_3S$=345.8

CAS — 636-54-4.
ATC — C03BA03.
ATC Vet — QC03BA03.
UNII — 17S83WON0I.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clopamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in anhydrous alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Clopamide is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis starts in 1 to 2 hours after an oral dose, reaches a maximum in about 3 to 6 hours, and lasts for up to 24 hours.

In the treatment of oedema a usual oral maintenance dose has been 10 to 20 mg daily or on alternate days. For hypertension doses of 5 to 10 mg daily, either alone, or with other antihypertensives have been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Brinaldix; ***India***: Brinaldix.

Multi-ingredient Preparations. ***Austria***: Brinerdin; ***Belg.***: Viskaldix; ***Braz.***: Viskaldix; ***Chile***: Viskaldix; ***Cz.***: Crystepin†; ***Fr.***: Viskaldix; ***Ger.***: Briserin N; Viskaldix†; ***Gr.***: Viskaldix; ***Hung.***: Viskaldix; ***Irl.***: Viskaldix†; ***Ital.***: Brinerdina; ***Malaysia***: Viskaldix; ***Neth.***: Viskaldix†; ***Philipp.***: Viskaldix; ***Pol.***: Normatens; ***Rus.***: Brinerdin (Бринердин); Crystepin (Кристепин); Normatens (Нормотенс); Viskaldix (Вискалдикс); ***S.Afr.***: Brinerdin; ***Switz.***: Brinerdine; Viskaldix; ***Thai.***: Bedin; Brinerdin; Briscotin†; ***UK***: Viskaldix; ***Ukr.***: Normatens (Нормотенс).

Clopidogrel Bisulfate

(BANM, USAN, rINNM)

Bisulfato de clopidogrel; Clopidogrel, Bisulfate de; Clopidogrel, bisulfato de; Clopidogrel Bisulphate; Clopidogrel Hydrogen Sulphate; Clopidogreli Bisulfas; PCR-4099 (clopidogrel); SR-25990C; Клопидогрела Бисульфат.

Methyl (*S*)-2-chlorophenyl(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)acetate bisulphate; Methyl (+)-(*S*)-α-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate sulphate.

$C_{16}H_{16}ClNO_2S,H_2SO_4$=419.9

CAS — 113665-84-2 (clopidogrel); 94188-84-8 (clopidogrel); 120202-66-6 (clopidogrel bisulfate).
ATC — B01AC04.
ATC Vet — QB01AC04.
UNII — 08I79HTP27.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Clopidogrel Hydrogen Sulfate). A white or almost white powder. It exhibits polymorphism. Freely

soluble in water and in methyl alcohol; practically insoluble in cyclohexane. Protect from light.

USP 36: (Clopidogrel Bisulfate). A white to off-white powder.

Uses and Administration

Clopidogrel is a thienopyridine antiplatelet drug used in thromboembolic disorders. An analogue of ticlopidine (p. 1512.1), it is a platelet $P2Y_{12}$-receptor antagonist that acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It is given prophylactically as an alternative to aspirin in patients with chronic occlusive peripheral arterial disease (p. 1272.3) or other atherosclerotic complications increasing the risk of thromboembolic disorders such as myocardial infarction (p. 1257.1), peripheral arterial thromboembolism (p. 1273.3), and stroke (p. 1269.2). Clopidogrel is also used with aspirin in acute coronary syndromes, including acute myocardial infarction and unstable angina (p. 1254.3), and in coronary stenting (see Reperfusion and Revascularisation Procedures, below).

Clopidogrel is given orally as the besilate, bisulfate, or the hydrochloride but doses are expressed in terms of the base; 75 mg of the base is equivalent to:

- 111.86 mg of clopidogrel besilate
- 97.86 mg of clopidogrel bisulfate
- 83.50 mg of clopidogrel hydrochloride

For the **prophylaxis of thromboembolic events**, the usual dose of clopidogrel is 75 mg once daily.

In the management of **acute ST-elevation myocardial infarction**, clopidogrel is used with aspirin as an adjunct in medically-treated patients. It is given in a dose of 75 mg once daily; patients under 75 years of age may be given a loading dose of 300 mg. Treatment should be continued for at least 4 weeks.

In the management of **unstable angina** and **non-Q-wave myocardial infarction**, clopidogrel is used with aspirin as an adjunct to either medical or interventional treatment, including coronary stenting. A single loading dose of 300 mg is given, followed by 75 mg once daily.

Reviews.

1. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129:** 394–405.
2. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. *Drugs* 2000; **60:** 347–77.
3. Solet DJ, *et al.* The role of adenosine 5′-diphosphate receptor blockade in patients with cardiovascular disease. *Am J Med* 2001; **111:** 45–53.
4. Zambahari R, *et al.* Clinical use of clopidogrel in acute coronary syndrome. *Int J Clin Pract* 2007; **61:** 473–81.
5. Eshaghian S, *et al.* Role of clopidogrel in managing atherothrombotic cardiovascular disease. *Ann Intern Med* 2007; **146:** 434–41.
6. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. *Drugs* 2007; **67:** 613–46.

Administration in children. Clopidogrel is not licensed for paediatric use in either the UK or the USA, although it has been given to small numbers of patients.

A retrospective study[1] of the use of clopidogrel in 15 children aged from 6 weeks to 16 years, 14 of whom had congenital heart disease, found that it was safe and effective; nearly all of the children were also taking aspirin and/or anticoagulants, and severe bleeding was reported in only 1 of them. The usual dose ranged from 1 to 3 mg/kg once daily, although a dose of 6 mg/kg daily was tolerated when given in error to 1 patient. However, another retrospective study[2] in similar children found that daily doses of 0.5 to 1 mg/kg were associated with an increased risk of bleeding complications, and the dose was subsequently reduced to 200 to 300 micrograms/kg. Younger children in particular may require lower doses; a randomised study[3] in children aged 0 to 24 months found that a dose of 200 micrograms/kg daily produced a similar antiplatelet effect to a 75-mg dose in adults.

A cohort study[4] of the use of clopidogrel alone or with aspirin in 17 children aged 1.5 to 17 years with arterial ischaemic stroke found that a daily dose of 0.5 to 2.4 mg/kg (target dose 1 mg/kg) was well tolerated, although subdural haematomas developed in 2 patients who were also taking aspirin.

1. Finkelstein Y, *et al.* Clopidogrel use in children. *J Pediatr* 2005; **147:** 657–61.
2. Mertens L, *et al.* Safety and efficacy of clopidogrel in children with heart disease. *J Pediatr* 2008; **153:** 61–4.
3. Li JS, *et al.* Dosing of clopidogrel for platelet inhibition in infants and young children: primary results of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial. *Circulation* 2008; **117:** 553–9.
4. Soman T, *et al.* The risks and safety of clopidogrel in pediatric arterial ischemic stroke. *Stroke* 2006; **37:** 1120–2.

Atherosclerotic disorders. The use of aspirin to reduce the risk of cardiovascular events in patients with atherosclerotic vascular disorders is well established. Clopidogrel may have a role as an alternative. The CAPRIE study[1] compared clopidogrel with aspirin in 19 185 patients at risk of ischaemic events, and found that clopidogrel reduced the risk of ischaemic stroke, myocardial infarction, or death from vascular causes to a greater extent than aspirin, although the absolute difference was small.

In acute coronary syndromes, clopidogrel may provide benefit when used in addition to aspirin. In patients with *unstable angina or non-ST elevation myocardial infarction*, the CURE study[2] found that the risk of cardiovascular death, myocardial infarction, or stroke was lower in patients treated with clopidogrel and aspirin, compared with those receiving aspirin alone. Clopidogrel was given in a loading dose of 300 mg, started within 24 hours of the onset of symptoms, followed by 75 mg daily for 3 to 12 months.

Similar results have been reported in patients with acute *ST-elevation myocardial infarction.* Clopidogrel given with aspirin and thrombolytic therapy improved the patency of the affected artery and reduced the incidence of ischaemic complications at 30 days,[3] while a further study[4] found that addition of clopidogrel to aspirin and standard therapy (including thrombolytics in over half of the patients) also reduced early mortality.

Use of clopidogrel with aspirin has also been studied in *ischaemic stroke* but any benefit appears to be outweighed by an increased risk of bleeding. In the MATCH study,[5] adding aspirin to clopidogrel did not reduce the incidence of vascular events compared with clopidogrel alone, but the risk of major or life-threatening bleeding was increased. However, clopidogrel alone appears to have similar efficacy and safety to aspirin with dipyridamole.[6]

In the CHARISMA study in patients with *stable atherosclerotic disease or multiple risk factors*, addition of clopidogrel to aspirin had no significant effect on the incidence of cardiovascular events, but the risk of moderate to severe bleeding was increased.[7,8]

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; **348:** 1329–39.
2. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502. Correction. *ibid.;* 1716.
3. Sabatine MS, *et al.* for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352:** 1179–89.
4. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1607–21.
5. Diener H-C, *et al.* Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364:** 331–7.
6. Sacco RL, *et al.* PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; **359:** 1238–51.
7. Bhatt DL, *et al.* CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354:** 1706–17.
8. Berger PB, *et al.* CHARISMA Investigators. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Circulation* 2010; **121:** 2575–83.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention (PCI) has an established role in the management of both acute and stable coronary disease (see p. 1259.2). Adjunctive antiplatelet therapy is given to reduce the risk of thrombosis, both during and after the procedure; a regimen of clopidogrel with aspirin improves outcomes[1] and is now generally recommended,[2,3] particularly if coronary stents are used. Although ticlopidine with aspirin was used initially in patients receiving stents, clopidogrel appears to be as effective as ticlopidine[4,5] but has a lower risk of haematological toxicity and is now generally preferred. A randomised study (CLASSICS)[6] found that, in patients given long-term aspirin, clopidogrel in a dose of 75 mg daily for 28 days, with or without a 300-mg loading dose, was as effective as ticlopidine; it was also better tolerated.

Pretreatment with clopidogrel appears to be most effective, but the increased bleeding risk may be of concern if emergency surgery is required. Use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention, and there is some evidence that it needs to be given at least 15 hours before.[7] A higher dose of 600 mg may be effective if given at least 2 hours before PCI,[8,9] and has been recommended in patients undergoing PCI for non-ST elevation acute coronary syndromes.[2]

The duration of combination therapy depends on the clinical situation. For patients given bare-metal stents, clopidogrel in a dose of 75 mg daily is usually given with aspirin for 2 to 4 weeks, and aspirin is then continued indefinitely. In patients with drug-eluting stents, the risk of occlusion persists for longer and combination therapy is usually recommended for at least 3 to 6 months; there is some evidence[10-12] that extending the duration further may provide additional benefit, and treatment for 12 months or longer has been suggested.[3] See also under Withdrawal, p. 1344.1. Prolonged combination therapy may also be of benefit in patients undergoing PCI for unstable angina, whether or not they receive stents.[1]

1. Mehta SR, *et al.* Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358:** 527–33.
2. Harrington RA, *et al.* Antithrombotic therapy for non-ST-elevation acute coronary syndromes: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 670S–707S.
3. Becker RC, *et al.* The primary and secondary prevention of coronary artery disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 776S–814S.
4. Mishkel GJ, *et al.* Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *J Am Coll Cardiol* 1999; **34:** 1884–90.
5. Berger PB. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999; **34:** 1891–4.
6. Bertrand ME, *et al.* Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; **102:** 624–9.
7. Steinhubl SR, *et al.* The CREDO Investigators. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. *J Am Coll Cardiol* 2006; **47:** 939–43.
8. Longstreth KL, Wertz JR. High-dose clopidogrel loading in percutaneous coronary intervention. *Ann Pharmacother* 2005; **39:** 918–22.
9. Hochholzer W, *et al.* Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005; **111:** 2560–4.
10. Zimarino M, *et al.* Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. *Drugs* 2005; **65:** 725–32.
11. Steinhubl SR, *et al.* Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288:** 2411–20. Correction. *ibid.* 2003; **289:** 987.
12. Eisenstein EL, *et al.* Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007; **297:** 159–68.

Adverse Effects and Precautions

As for Ticlopidine, p. 1512.2.

The incidence of adverse effects, particularly blood dyscrasias, is lower with clopidogrel, although fatalities have been reported (see Effects on the Blood, p. 1512.3). Routine blood counts are not necessary, although they should be performed promptly when clinical signs suggest blood dyscrasias. Other adverse effects, reported rarely, include serum sickness, interstitial pneumonitis, erythema multiforme, Stevens-Johnson syndrome, lichen planus, and myalgia.

Consideration should be given to stopping clopidogrel 5 to 7 days before elective surgery (but see Withdrawal, p. 1344.1).

Effects on the blood. For reports of blood dyscrasias associated with clopidogrel therapy see under Adverse Effects of Ticlopidine, p. 1512.3.

Effects on taste. Loss of taste occurred in 2 patients 6 to 8 weeks after starting treatment with clopidogrel, but recovered fully when clopidogrel was withdrawn.[1] Rechallenge in 1 of the patients led to recurrence of the taste loss, which persisted when treatment was stopped.

1. Golka K, *et al.* Reversible ageusia as an effect of clopidogrel treatment. *Lancet* 2000; **355:** 465–6.

Hypersensitivity. Clopidogrel has been associated with hypersensitivity reactions including angioedema.[1] There have also been reports[2-5] of a hypersensitivity syndrome comprising fever, rash, and varying additional symptoms. Successful desensitisation protocols have been described.[6,7]

1. Fischer TC, *et al.* Clopidogrel-associated angioedema. *Am J Med* 2003; **114:** 77–8.
2. Sarrot-Reynauld F, *et al.* Severe hypersensitivity associated with clopidogrel. *Ann Intern Med* 2001; **135:** 305–6.
3. Phillips EJ, *et al.* Serum sickness-like reaction associated with clopidogrel. *Br J Clin Pharmacol* 2003; **56:** 583.
4. Wolf I, *et al.* Clopidogrel-induced systemic inflammatory response syndrome. *Mayo Clin Proc* 2003; **78:** 618–20.
5. Doogue MP, *et al.* Clopidogrel hypersensitivity syndrome with rash, fever, and neutropenia. *Mayo Clin Proc* 2005; **80:** 1368–70.
6. von Tiehl KF, *et al.* Clopidogrel desensitization after drug-eluting stent placement. *J Am Coll Cardiol* 2007; **50:** 2039–43.
7. Oppedijk B, *et al.* Rapid oral desensitisation procedure in clopidogrel hypersensitivity. *Neth Heart J* 2008; **16:** 21–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clopidogrel as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Resistance. Results from platelet aggregation studies suggest that there is considerable variation in response to clopidogrel, although the clinical relevance of a low response (clopidogrel resistance) is unclear.[1,2] There is some evidence that the risk of cardiovascular events is higher in patients with clopidogrel resistance,[3] but this is not established. A study[4] using loading doses of clopidogrel based on platelet monitoring reported improved outcomes after percutaneous coronary intervention. Factors that may contribute to clopidogrel resistance include drug interac-

tions; conditions such as diabetes mellitus[5] or acute coronary syndromes, which appear to attenuate response;[6] and genetic variation in platelet sensitivity or clopidogrel metabolism.[1,2] A genetic polymorphism in the cytochrome P450 isoenzyme CYP2C19, which is involved in formation of the active metabolite, has been shown to affect the pharmacokinetics and pharmacodynamics of clopidogrel,[7,8] and studies[9-12] have suggested that patients with the reduced function polymorphism are at higher risk for clinical events. However, causality has not been established, and alternative theories have been discussed.[13,14] Screening for genetic polymorphisms and monitoring residual platelet aggregation have been suggested to identify resistant individuals and guide dosing,[15-17] although the clinical benefits require confirmation.

1. Nguyen TA, *et al*. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005; **45:** 1157–64.
2. Angiolillo DJ, *et al*. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007; **49:** 1505–16.
3. Geisler T, *et al*. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27:** 2420–5.
4. Bonello L, *et al*. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol* 2008; **51:** 1404–11.
5. Geisler T, *et al*. Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007; **30:** 372–4.
6. Geisler T, *et al*. Residual platelet activity is increased in clopidogrel- and ASA-treated patients with coronary stenting for acute coronary syndromes compared with stable coronary artery disease. *Heart* 2008; **94:** 743–7.
7. Brandt JT, *et al*. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007; **5:** 2429–36.
8. Kim KA, *et al*. The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. *Clin Pharmacol Ther* 2008; **84:** 236–42.
9. Mega JL, *et al*. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009; **360:** 354–62.
10. Simon T, *et al*. French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; **360:** 363–75.
11. Collet J-P, *et al*. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet* 2009; **373:** 309–17.
12. Shuldiner AR, *et al*. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009; **302:** 849–57.
13. Ford NF. Clopidogrel resistance: pharmacokinetic or pharmacogenetic? *J Clin Pharmacol* 2009; **49:** 506–12.
14. Momary KM, *et al*. Genetic causes of clopidogrel nonresponsiveness: which ones really count? *Pharmacotherapy* 2010; **30:** 265–74.
15. Bonello L, *et al*. Emergence of the concept of platelet reactivity monitoring of response to thienopyridines. *Heart* 2009; **95:** 1214–19.
16. Kuliczkowski W, *et al*. Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2009; **30:** 426–35.
17. Gladding P, *et al*. Pharmacogenetic testing for clopidogrel using the rapid INFINITI analyzer: a dose-escalation study. *JACC Cardiovasc Interv* 2009; **2:** 1095–1101.

Withdrawal. In patients given dual antiplatelet therapy after implantation of drug-eluting stents, there is some evidence that the incidence of late in-stent thrombosis increases after withdrawal of clopidogrel,[1] even after prolonged courses.[2] The optimum duration of dual antiplatelet therapy remains to be established, but it has been suggested[2] that it should be continued indefinitely in patients at low risk of bleeding. Although withdrawal of clopidogrel before planned surgery is usually recommended, it may be preferable to assess each patient individually and only stop clopidogrel in those for whom the risk of bleeding outweighs the risk of an acute coronary event.[3] Similar considerations apply in patients undergoing endoscopy.[4]

1. Ho PM, *et al*. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; **299:** 532–9.
2. Bhatt SH, Hauser TH. Very late stent thrombosis after dual antiplatelet therapy discontinuation in a patient with a history of acute stent thrombosis. *Ann Pharmacother* 2008; **42:** 708–12.
3. Chassot P-G, *et al*. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; **99:** 316–28.
4. Veitch AM, *et al*. Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures. *Gut* 2008; **57:** 1322–9.

Interactions

Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs. Drugs that inhibit the activity of cytochrome P450 isoenzymes involved in the metabolism of clopidogrel may reduce its antiplatelet effect. Clopidogrel may inhibit the isoenzyme CYP2C9 and interactions with drugs metabolised by this isoenzyme are theoretically possible; it may also inhibit CYP2B6 (see Bupropion, below).

Anticoagulants. Use of clopidogrel with oral anticoagulants increases the risk of haemorrhagic events,[1] particularly if patients are also taking aspirin,[2] and the risks and benefits of treatment should be assessed for each individual.

1. Johnson SG, *et al*. Outcomes associated with combined antiplatelet and anticoagulant therapy. *Chest* 2008; **133:** 948–54.
2. Hermosillo AJ, Spinler SA. Aspirin, clopidogrel, and warfarin: is the combination appropriate and effective or inappropriate and too dangerous? *Ann Pharmacother* 2008; **42:** 790–805.

Antifungals. A study[1] in healthy subjects found that *ketoconazole* decreased the plasma concentration of the active metabolite of clopidogrel; platelet inhibitory action was also reduced.

1. Farid NA, *et al*. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007; **81:** 735–41.

Bupropion. A study[1] in healthy subjects found that clopidogrel reduced the conversion of bupropion to its active metabolite, suggesting that clopidogrel inhibits the cytochrome P450 isoenzyme CYP2B6.

1. Turpeinen M, *et al*. Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2005; **77:** 553–9.

Ciclosporin. For reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin, see Statins, below.

Proton pump inhibitors. Proton pump inhibitors (PPIs) are recommended to reduce the risk of gastrointestinal bleeding in patients taking aspirin for cardiovascular indications.[1] However, clopidogrel is metabolised to an active metabolite by the cytochrome P450 isoenzyme CYP2C19, and PPIs, which exhibit competitive inhibition of CYP2C19 to varying degrees, may reduce its antiplatelet effect if patients are taking clopidogrel as well as aspirin, or are given a PPI with clopidogrel alone. A randomised study[2] in patients given aspirin and clopidogrel after coronary stenting suggested that addition of *omeprazole* reduced the antiplatelet effect of clopidogrel, and a small pharmacokinetic study[3] in healthy subjects taking clopidogrel with *lansoprazole* found a similar effect. Epidemiological studies[4-6] in patients taking clopidogrel for cardiovascular indications have also shown an increase in cardiovascular events in those taking PPIs as well; in one of the studies[5] it was suggested that this did not apply to patients taking *pantoprazole*, but it is unclear whether the difference between pantoprazole and other PPIs was significant, and others have reported a higher incidence of cardiovascular events in clopidogrel-treated patients taking pantoprazole than with other PPIs.[7] Since pantoprazole is thought to have a lower affinity for the cytochrome[5] it has been suggested that other mechanisms may also be involved.[7,8] A meta-analysis[9] of 23 studies concluded that the data on cardiovascular outcomes and overall mortality was conflicting and inconsistent, and study quality often poor, and that clinicians should consider the potential gastrointestinal harm from clopidogrel before witholding PPIs.

The MHRA in the UK,[10] the EMEA,[11] and the FDA[12] discourage the use of clopidogrel with either *omeprazole* or *esomeprazole*, but no longer consider there to be sufficient grounds to extend the warning across all PPIs.

1. Bhatt DL, *et al*. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; **118:** 1894–1909.
2. Gilard M, *et al*. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008; **51:** 256–60.
3. Small DS, *et al*. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol* 2008; **48:** 475–84.
4. Pezalla E, *et al*. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. *J Am Coll Cardiol* 2008; **52:** 1038–9.
5. Juurlink DN, *et al*. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009; **180:** 713–18.
6. Ho PM, *et al*. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; **301:** 937–44.
7. MHRA/CHM. Clopidogrel and proton pump inhibitors: interaction. *Drug Safety Update* 2009; **2** (12): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON051771&RevisionSelectionMethod=LatestReleased (accessed 16/08/10)
8. EMEA. Public statement on possible interaction between clopidogrel and proton pump inhibitors (issued 29th May 2009). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf (accessed 16/08/10)
9. Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010; **31:** 810–23.
10. MHRA/CHM. Clopidogrel and proton pump inhibitors: interaction—updated advice. *Drug Safety Update* 2010; **3** (9): 4–5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON076503&RevisionSelectionMethod=LatestReleased (accessed 09/06/10)
11. EMEA. Interaction between clopidogrel and proton-pump inhibitors: CHMP updates warning for clopidogrel-containing medicines (issued 17th March 2010). Available at: http://www.ema.europa.eu/humandocs/PDFs/EPAR/Plavix/17494810en.pdf (accessed 09/06/10)
12. FDA. Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC) (issued 17th November 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190784.htm (accessed 09/06/10)

Statins. There have been reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin (atorvastatin,[1,2] lovastatin,[3] or simvastatin[3]). Rhabdomyolysis is a recognised adverse effect when ciclosporin and statins are used together (see Immunosuppressants under Interactions of Simvastatin, p. 1495.3), but the patients in these reports had previously received the combination without incident and developed rhabdomyolysis 1 to 3 weeks after clopidogrel was started. It has been suggested[2] that the mechanism is a three way interaction involving competition for binding sites on the cytochrome P450 isoenzyme CYP3A4 between statins and clopidogrel, exacerbated by ciclosporin-mediated enzyme inhibition.

Although it has been suggested that statins may decrease the antiplatelet effect of clopidogrel, evidence for such an interaction has been conflicting;[4] short-term clinical follow-up[5] of around 1000 patients has suggested no adverse outcome from using this drug combination.

1. Anon. Clopidogrel (Plavix): suspected drug interaction with atorvastatin (Lipitor) and cyclosporine resulting in rhabdomyolysis. *Can Adverse React News* 2005; **15** (Apr): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2_e.pdf (accessed 01/09/05)
2. Burton JR, *et al*. Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. *Ann Pharmacother* 2007; **41:** 133–7.
3. Uber PA, *et al*. Clopidogrel and rhabdomyolysis after heart transplantation. *J Heart Lung Transplant* 2003; **22:** 107–8.
4. Tafreshi MJ, *et al*. Combination of clopidogrel and statins: a hypothetical interaction or therapeutic dilemma? *Pharmacotherapy* 2006; **26:** 388–94.
5. Geisler T, *et al*. Statins do not adversely affect post-interventional residual platelet aggregation and outcomes in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Eur Heart J* 2008; **29:** 1635–43.

Pharmacokinetics

Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%. It is a prodrug and is extensively metabolised in the liver, mainly to the inactive carboxylic acid derivative; metabolism is mediated by cytochrome P450 isoenzymes including CYP3A4 and CYP2B6, CYP1A2, CYP1A1, and CYP2C19. The active metabolite appears to be a thiol derivative; it has been identified *in vitro* but appears to be too unstable to be isolated from plasma. Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antiplaq; Ariclopin; Clodian; Iscover; Klopik; Nabratin; Nadenel; Nefazan; Plavix; Pleyar; Troken; ***Austral.***: Clovix; Iscover; Piax; Plavix; ***Austria***: Clogombix; Clogrelhexal; Cloroden; Grepid; Plavix; ***Belg.***: Plavix; ***Braz.***: Clopido-Gran; Clopidror; Iscover; Lopigrel; Plagrel; Plaquevix; Plavix; ***Canad.***: Plavix; ***Chile***: Agreplat; Artevil; Clentel; Eurogrel; Iskimil; Plavix; Ravalgen; Sildecross; ***China***: Plavix (波立维); Talcom (泰嘉); ***Cz.***: Agrelex; Carder; Clopidostad; Clopigamma; Clopithan; Cloroden; Defrozyp; Egitromb; Grepid; Hemafluid; Iscover; Kloptimar; Lofradyk; Lopigalel; Nofardom; Perclod†; Picturlop; Platarex; Plavix; Plavocorin; Sarovex; Sudroc; Teclop; Tessyron; Trogran; Trombex; Tuxedon; Vatoud; Zopya; Zylagren; Zyllt; ***Denm.***: Biriklopi†; Clohys; Clonoren†; Clopidonorm; Clopitom; Cloriocard; Derichem; Glopenel; Grepid; Iscover†; Janogrel; Klandryn†; Klepisal; Klodigan; Kloptimar; Pelidren†; Platarex†; Plavix; Plegrin†; Redras; Relidop; Roclas; Sidoklop; Sudroc; ***Fin.***: Cloriocard; Plavix; ***Fr.***: Plavix; ***Ger.***: Clopidocard†; Clopidocor†; Clopidolut; Clopigamma; Iscover; Plavix; ***Gr.***: Bidogrel; Carder; Clodel; Clodelib; Clopidosyn; Cloriocard; Cloroden; Clotromboz; Clovelen; Clovix; Dapixol; Darxa; Dasogrel-S; Diclop; Espelio; Globel; Glopenel; Greligen; Grepid; Heart-Free; Iscover; Larvin; Niaclop; Novigrel; Optigrel; Plasiver; Platel; Plavelate; Plavidosa; Plavix; Plavogrel; Sanvix; Tansix; Throimper; Unplaque; Zystol; ***Hong Kong***: Clopistad; Clopivas; Clopivid; Lopirel; Plavix; ***Hung.***: Atrombin; Clopidep; Clopigamma; Clopithan; Egitromb; Kardogrel; Kerberan; Lopigalel; Nofardom; Plagrel; Plavix; Trombex; Tuxedon; ***India***: Aclotil; Adplatt; Antiban; Antiplar; Aplatin; Aptogrel; Blothin; C-Grel; Caplor; Carpigrel; Cenoza; Ceruvin; Cidogrel; Class; Clavix; Clodrel; Cloflow; Clofre; Clolyse; Clopact; Clopi; Clopicard; Clopid; Clopigrel; Clopikare; Clopilet; Clopirad; Clopitab; Clopivas; Clopizide; Cloplat; Clopod; Cloprez; Clotsafe; Deplatt; Glory; Grelet; Klov; Noklot; Noplaq; Nugrel; Orawis; Plavix; ***Indon.***: Artepid; Clogin; Clopisan; Clotix; Copidrel; CPG; Pidovix; Placta; Pladel; Pladogrel; Plavix; Vaclo; ***Irl.***: Clodel; Grepid; Iscover; Plavix; Zopya; Zylagren; Zyllt; ***Israel***: Clood; Clopid; Clopidexcel; Plavix; ***Ital.***: Plavix; Vatoud; ***Jpn***: Plavix;

Malaysia: Ceruvin; Clopivid; Kogrel; Plavix; ***Mex.***: Iscover; Plavix; ***Neth.***: Clopidocor†; Grepid; Iscover; Plavix; Plegrin†; Vatoud; Zopya†; Zylagren; Zyllt; ***Norw.***: Plavix; ***NZ***: Plavix; ***Philipp.***: Antiplar; Atheros; Cardogrel; Clomex; Clopida; Clopido; Clopimet; Clopivaz; Clopix; Cloplat; Clotiz; Clovax; Clovix; Deplatt; Dogrel; Hemaflow; Klopide; Noklot; Norplat; Plagerine; Platexan; Plavihex; Plavix; Plogrel; Syclopid; Trombix; Vivelon; ***Pol.***: Agregex; Areplex; Carder; Clogrel; Clopidim; Clopidix; Clopinovo; Egitromb; Grepid; Iscover; Klepisal; Miflexin; Plavix; Plavocorin; Sudroc; Tessyron; Trogran; Trombex; Zopya; Zylagren; Zyllt; ***Port.***: Atlabiclo; DuoCover; DuoPlavin; Grepid; Hemopass; Ketapi; Plavix; Rasec†; Sades†; Satoxi; Ticofarma†; Vasagrin; Vastec; Zopya; Zylagren; Zyllt; ***Rus.***: Agregal (Агрегаль); Clopilet (Клопилет); Detromb (Детромб); Egitromb (Эгитромб); Listab (Листаб); Lopirel (Лопирел); Plagril (Плагрил); Plavix (Плавикс); Plogrel (Плогрель); Troken (Трокен); Zillt (Зилт); Zyllt (Зилт); ***S.Afr.***: Clopivas; Mistro; Plagrol; Plavix; ***Singapore***: Deplatt; Placta; Plagril; Plavix; ***Spain***: Agrelan; Arapamin; Iscover; Maboclop; Plavix; Vatoud; Zyllt; ***Swed.***: Clopiocard; Grepid; Plavix; ***Switz.***: Clogrel†; Clopidrax; Plavix; ***Thai.***: Apolets; Ceruvin; Pidogen†; Plavix; ***Turk.***: Atervix; Clopra; Diloxol; Diporel; Karum; Klopis; Opirel; Pingel; Planor; Plavix; ***UK***: Grepid; Plavix; ***Ukr.***: Areplex (Ареплекс)†; Aterocard (Атерокард); Atrogrel (Атрогрел); Cardogrel (Кардогрель); Clopix (Клопикс); Lopigrol (Лопигрол); Lopirel (Лопирел); Pingel (Пингель); Plagril (Плагрил); Plavix (Плавикс); Reodar (Реодар); Reomax (Реомакс); Tessiron (Тессирон); Trombonet (Тромбонет); Zilt (Зилт); ***USA***: Plavix; ***Venez.***: Plavix.

Multi-ingredient Preparations. ***Arg.***: Nefazan Compuesto; ***Austral.***: CoPlavix; DuoCover; ***Fr.***: DuoPlavin; ***Ger.***: DuoCover; DuoPlavin; ***Gr.***: DuoCover; DuoPlavin; ***India***: Antiban-ASP; Asicom Plus; C-Grel Plus; Caplor-AS; Cenoza A; Ceruvin-A; Cidogrel-A; Clasprin; Class-A; Clavix-AS; Clodrel Forte; Clodrel Plus; Clofre AS; Clopact A; Clopid-AS; Clopigrel-A; Clopirad-A; Clopisa; Clopitab-A; Clopivas AP; Clopizide-A; Clopod-A; Cloprez-A; Clouds; Complatt; Deplatt-A; Deplatt-CV; Dospin; Ecosprin Gold; Grelet-A; Kabitrol; Myogrel-AP; Noklot Plus; Noklot-CV; Nugrel Plus; ***Irl.***: DuoCover; DuoPlavin; ***Israel***: CoPlavix; ***Ital.***: DuoPlavin; ***Neth.***: DuoCover; DuoPlavin; ***Pol.***: DuoCover; DuoPlavin; ***Singapore***: CoPlavix; ***Spain***: DuoPlavin; ***Switz.***: DuoPlavin; ***Thai.***: CoPlavix; ***Ukr.***: Clopix Forte (Клопикс Форте).

Pharmacopoeial Preparations
USP 36: Clopidogrel Tablets.

Cloricromen *(rINN)*

Cloricromène; Cloricromeno; Cloricromenum; Клорикромен.
Ethyl ({8-chloro-3-[2-(diethylamino)ethyl]-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl}oxy)acetate.
$C_{20}H_{26}ClNO_5$=395.9
CAS — 68206-94-0.
ATC — B01AC02.
ATC Vet — QB01AC02.
UNII — B9454PE93C.

Profile

Cloricromen is an antiplatelet drug with vasodilating activity and is used in thromboembolic disorders (p. 1273.2). It is given as the hydrochloride in arterial vascular disorders where there is a risk of thrombosis. It may be given orally in a dose of 100 mg two or three times daily or intravenously in a dose of 30 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Proendotel.

Colesevelam Hydrochloride

(BANM, USAN, rINNM)

Colésévélam, Chlorhydrate de; Colesevelam, hidrocloruro de; Colesevelami Hydrochloridum; GT31-104HB; Hidrocloruro de colesevelam; Колезевелама Гидрохлорид.
Allylamine polymer with epichlorohydrin (1-chloro-2,3-epoxypropane), [6-(allylamino)hexyl]trimethylammonium chloride and *N*-allyldecylamine, hydrochloride.
$(C_3H_7N)_m(C_3H_5ClO)_n(C_{12}H_{27}ClN_2)_o(C_{13}H_{27}N)_p.xHCl$
CAS — 182815-44-7.
ATC — C10AC04.
ATC Vet — QC10AC04.
UNII — P4SG24WI5Q.

Uses and Administration

Colesevelam hydrochloride is a nonabsorbable hydrogel. It binds bile acids in the intestine and has actions similar to those of colestyramine (p. 1346.1). It is used for the treatment of hypercholesterolaemia (see Hyperlipidaemias, p. 1248.1), particularly type IIa hyperlipoproteinaemia, either alone or with a statin and/or ezetimibe. It may also be used as an adjunct to improve glycaemic control in type 2 diabetes mellitus (p. 459.1). The usual oral dose is 3.75 g daily, as a single dose or in two divided doses, with meals. When used as monotherapy for hypercholesterolaemia, the dose may be increased to 4.375 g daily if required. When used with a statin and/or ezetimibe, the dose is 2.5 to 3.75 g daily.

For use in children, see below.

References.
1. Davidson MH, *et al.* Colesevelam hydrochloride (Cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999; **159:** 1893–1900.
2. Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother* 2001; **35:** 898–907.
3. Steinmetz KL. Colesevelam hydrochloride. *Am J Health-Syst Pharm* 2002; **59:** 932–9.
4. Bays H, Jones PH. Colesevelam hydrochloride: reducing atherosclerotic coronary heart disease risk factors. *Vasc Health Risk Manag* 2007; **3:** 733–42.
5. Florentin M, *et al.* Colesevelam hydrochloride in clinical practice: a new approach in the treatment of hypercholesterolaemia. *Curr Med Res Opin* 2008; **24:** 995–1009.
6. Corsini A, *et al.* Colesevelam hydrochloride: usefulness of a specifically engineered bile acid sequestrant for lowering LDL-cholesterol. *Eur J Cardiovasc Prev Rehabil* 2009; **16:** 1–9.
7. Sonnett TE, *et al.* Colesevelam hydrochloride for the treatment of type 2 diabetes mellitus. *Clin Ther* 2009; **31:** 245–59.
8. Goldfine AB, Fonseca VA. The use of colesevelam HCl in patients with type 2 diabetes mellitus: combining glucose- and lipid-lowering effects. *Postgrad Med* 2009; **121** (suppl 1): 13–18.
9. Handelsman Y. The role of colesevelam HCl in type 2 diabetes mellitus therapy. *Postgrad Med* 2009; **121** (suppl 1): 19–24.

Administration in children. US licensed product information allows the use of colesevelam hydrochloride to treat heterozygous familial hypercholesterolaemia in boys and postmenarchal girls from 10 years of age. It is given either alone or with a statin in an oral dose of 3.75 g daily, as a single dose or in 2 divided doses.

Adverse Effects and Precautions

As for Colestyramine, p. 1346.3.

Interactions

Colesevelam, like colestyramine (see p. 1347.1), has the potential to interfere with the absorption of other drugs; those with a narrow therapeutic range should be given at least 1 hour before or 4 hours after colesevelam unless there is known to be no interaction.

References.
1. Donovan JM, *et al.* Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 2000; **14:** 681–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Cholestagel; ***Canad.***: Lodalis; ***Cz.***: Cholestagel; ***Denm.***: Cholestagel; ***Ger.***: Cholestagel; ***Gr.***: Cholestagel; ***Irl.***: Cholestagel; ***Israel***: Cholestagel; ***Neth.***: Cholestagel; ***Norw.***: Cholestagel; ***Pol.***: Cholestagel; ***Port.***: Cholestagel; ***Spain***: Cholestagel; ***Swed.***: Cholestagel; ***UK***: Cholestagel; ***USA***: Welchol.

Colestilan *(rINN)*

Colestilan Chloride (USAN); Colestilanum; Colestimide; MCI-196; Колестилан.
2-Methylimidazole polymer with 1-chloro-2,3-epoxypropane.
$(C_4H_6N_2.C_3H_5ClO)_n$
CAS — 95522-45-5.

Uses and Administration

Colestilan is a bile-acid binding and phosphate adsorbing anion exchange resin. It is a lipid regulating drug with similar properties to colestyramine (p. 1346.1) and is used to reduce cholesterol in the management of hyperlipidaemias (p. 1248.1). Colestilan is also used as a phosphate binder in the treatment of hyperphosphataemia (p. 1778.3).

In hyperlipidaemias, colestilan is given orally in a usual dose of 1.5 g twice daily with food.

For the treatment of hyperphosphataemia in patients with severe renal impairment receiving haemodialysis or peritoneal dialysis, colestilan is given orally, with food, at a starting dose of 6 to 9 g daily in 3 divided doses. The dose should then be adjusted, according to serum-phosphorus concentration, and may be increased in steps of 3 g every 2 to 3 weeks. A maximum of 15 g daily has been given.

It is also under investigation in diabetes mellitus.

References.
1. Kurihara S, *et al.* Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in haemodialysis patients: a double-blind, placebo-controlled, short-term trial. *Nephrol Dial Transplant* 2005; **20:** 424–30.
2. Yamakawa T, *et al.* Effect of colestimide therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. *Endocr J* 2007; **54:** 53–8.
3. Taniai M, *et al.* Treatment of nonalcoholic steatohepatitis with colestimide. *Hepatol Res* 2009; **39:** 685–93.
4. Locatelli F, *et al.* Effect of MCI-196 on serum phosphate and cholesterol levels in haemodialysis patients with hyperphosphataemia: a double-blind, randomized, placebo-controlled study. *Nephrol Dial Transplant* 2010; **25:** 574–81.
5. Kondo K, Kadowaki T. Colestilan monotherapy significantly improves glycaemic control and LDL cholesterol levels in patients with type 2 diabetes: a randomized double-blind placebo-controlled study. *Diabetes Obes Metab* 2010; **12:** 246–51.

Adverse Effects and Precautions

As for Colestyramine, p. 1346.3 and p. 1347.1. Hypocalcaemia and decreased appetite are common with colestilan. Serious gastrointestinal haemorrhage has occurred uncommonly. Other uncommon effects include dizziness, hypotension, musculoskeletal pain, and raised hepatic enzymes. There have been rare cases of intestinal obstruction and colestilan is contra-indicated in patients with bowel obstruction.

Interactions

As for Colestyramine (p. 1347.1); other drugs should be given at least 1 hour before or 3 hours after colestilan.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cholebine; ***UK***: BindRen.

Colestipol Hydrochloride

(BANM, USAN, rINNM)

Colestipol, chlorhydrate de; Colestipol, hidrocloruro de; Colestipoli Hydrochloridum; Hidrocloruro de colestipol; Kolestipol Hidroklorür; U-26597A; Колестипола Гидрохлорид.
CAS — 26658-42-4 (colestipol); 50925-79-6 (colestipol); 37296-80-3 (colestipol hydrochloride).
ATC — C10AC02.
ATC Vet — QC10AC02.
UNII — X7D10K905G.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Colestipol Hydrochloride). A copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.7 mEq of sodium cholate, calculated as the cholate binding capacity and with reference to the dried substance. Yellow to orange hygroscopic beads. Swells but does not dissolve in water and in dilute solutions of acids or alkalis. Practically insoluble in alcohol and in dichloromethane. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

USP 36: (Colestipol Hydrochloride). A basic anion-exchange resin. It is the hydrochloride of a copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.6 mEq of sodium cholate, calculated as cholate binding capacity. Yellow to orange beads. Swells but does not dissolve in water or dilute aqueous solutions of acids or alkalis. Insoluble in common organic solvents. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

Uses and Administration

Colestipol hydrochloride is a bile-acid binding resin and lipid regulating drug with actions similar to those of colestyramine (p. 1346.1). It is used to reduce cholesterol in the treatment of hyperlipidaemias (p. 1248.1), particularly type IIa hyperlipoproteinaemia.

Colestipol hydrochloride is available as granules and is given orally as a suspension in water or a flavoured vehicle. The initial dose is 5 g daily or twice daily, increasing gradually at intervals of 1 to 2 months to up to 30 g daily in a single dose or two divided doses as necessary.

Colestipol hydrochloride is also available as tablets; doses range from 2 to 16 g daily.

Adverse Effects and Precautions

As for Colestyramine, p. 1346.3.

Effects on thyroid function. Reductions in total serum-thyroxine and thyroxine-binding globulin concentrations were found during routine monitoring of thyroid function in patients receiving colestipol and nicotinic acid, but were considered to be benign.[1] This effect has been used thera-

peutically in patients with hyperthyroidism (see under Uses of Colestyramine, below).

1. Cashin-Hemphill L, *et al.* Alterations in serum thyroid hormonal indices with colestipol-niacin therapy. *Ann Intern Med* 1987; **107:** 324–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies colestipol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Colestyramine, p. 1347.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Colestid; ***Belg.***: Colestid; ***Canad.***: Colestid; ***Denm.***: Lestid; ***Fin.***: Lestid†; ***Gr.***: Lestid; ***Israel***: Colestid; ***Norw.***: Lestid; ***NZ***: Colestid; ***Port.***: Colestid; ***Spain***: Colestid; ***Swed.***: Lestid; ***Switz.***: Colestid; ***UK***: Colestid; ***USA***: Colestid.

Pharmacopoeial Preparations
BP 2014: Colestipol Granules;
USP 36: Colestipol Hydrochloride for Oral Suspension; Colestipol Hydrochloride Tablets.

Colestyramine *(BAN, rINN)*

Cholestyramine; Cholestyramine Resin; Colestiramina; Colestyramin; Colestyraminum; Divistyramine; Kolestiramin; Kolestiraminas; Kolestyramiini; Kolestyramin; Kolestyramina; MK-135; Колестирамин.

CAS — 11041-12-6.
ATC — C10AC01.
ATC Vet — QC10AC01.
UNII — 4B33BGI082.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Colestyramine). A strongly basic anion-exchange resin in the chloride form, consisting of styrene-divinylbenzene copolymer with quaternary ammonium groups. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated with reference to the dried material. A white or almost white, fine, hygroscopic powder. Insoluble in water, in alcohol, and in dichloromethane. A 1% suspension in water has a pH of 4.0 to 6.0 after standing for 10 minutes. Store in airtight containers.

USP 36: (Cholestyramine Resin). A strongly basic anion-exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated on the dried basis. It is used in the chloride form. A white to buff-coloured, hygroscopic, fine powder, odourless or has not more than a slight amine-like odour. It loses not more than 12% of its weight on drying. Insoluble in water, in alcohol, in chloroform, and in ether. A 1% slurry in water has a pH of 4.0 to 6.0. Store in airtight containers.

Uses and Administration

Colestyramine is a bile-acid binding resin and lipid regulating drug. It is used to reduce cholesterol in the treatment of hyperlipidaemias (p. 1248.1), particularly type IIa hyperlipoproteinaemia, and for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1) in middle-aged men with primary hypercholesterolaemia. Colestyramine is also used for the relief of diarrhoea associated with ileal resection, Crohn's disease, vagotomy, diabetic vagal neuropathy, and radiation, and to relieve the pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction or primary biliary cirrhosis.

Colestyramine is not absorbed from the gastrointestinal tract and binds with bile acids in the intestine to form an insoluble complex that is excreted in the faeces. The normal reabsorption of bile acids is thus prevented and this leads to an increased oxidation of cholesterol to bile acids to replace those partially removed from the enterohepatic circulation, and an increased synthesis of low-density lipoprotein (LDL)-cholesterol receptors on hepatocytes. The overall effect is a reduction of total plasma-cholesterol concentration, mainly by lowering LDL-cholesterol; this may be accompanied by moderate increases in plasma triglyceride and high-density lipoprotein (HDL)-cholesterol concentrations. Since the uses of colestyramine are based upon the removal of intestinal bile acids it is unlikely that a response will be achieved in patients with complete biliary obstruction.

Colestyramine may be introduced gradually over 3 to 4 weeks to minimise gastrointestinal effects: the *BNF* suggests an initial dose of 4 g, increased by 4 g at weekly intervals.

In hyperlipidaemias and diarrhoea the usual oral dose is 12 to 24 g daily, given either as a single dose or in up to 4 divided doses. Dosage should be adjusted according to the patient's response and may be increased to 36 g daily if necessary. Lower doses may be adequate in some forms of hyperlipidaemia.

In pruritus doses of 4 to 8 g daily are usually sufficient.

For the use of colestyramine in children, see below.

Colestyramine should be given as a suspension in water or a flavoured vehicle.

General references.
1. Insull W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J* 2006; **99:** 257–73.

Administration in children. Colestyramine has been used in children and small studies[1,2] have found that it is effective in familial hypercholesterolaemia with no adverse effects on physical growth when taken long-term;[2] however, compliance may be a problem.[1]

For *hypercholesterolaemia*, the *BNFC* gives the usual oral dose for children aged 6 to 12 years as 4 g once daily, increased to 4 g up to 3 times daily according to response. Children aged 12 to 18 years may be given the usual adult dose (see above). Alternatively, licensed doses are calculated from body-weight, either as a percentage of the adult (70 kg) dose, or as a dose of 240 mg/kg daily in divided doses.

For *pruritus* or *diarrhoea*, the *BNFC* recommends the following oral doses based on age:

- 1 month to 1 year: initially 1 g once daily, adjusted according to response to a maximum dose of 9 g daily in 2 to 4 divided doses
- 1 to 6 years: initially 2 g once daily, adjusted according to response to a maximum dose of 18 g daily in 2 to 4 divided doses
- 6 to 12 years: initially 4g once daily, adjusted according to response to a maximum dose of 24 g daily in 2 to 4 divided doses
- 12 to 18 years: initially 4 to 8 g once daily, adjusted according to response to a maximum dose of 36 g daily in 2 to 4 divided doses

1. West RJ, Lloyd JK. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet* 1980; **ii:** 873–5.
2. Tonstad S, *et al.* Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996; **129:** 42–9.

Antibiotic-associated colitis. Colestyramine binds *Clostridium difficile* toxins and there are a few reports of use as an alternative, or as an adjunct, to vancomycin or metronidazole in patients with diarrhoea associated with *C. difficile* toxins after antibacterial therapy (p. 183.1). However, evidence of benefit is limited and in general its use is not recommended.

Biliary disorders. Colestyramine is used to relieve diarrhoea (p. 1808.2) associated with bile acid malabsorption and to manage pruritus and hypercholesterolaemia in patients with primary biliary cirrhosis (p. 2638.3). It has been used for pruritus in cholestasis of pregnancy,[1] although such use has been associated with severe fetal intracranial haemorrhage.[2] Beneficial responses have been reported with colestyramine in the management of congenital nonobstructive nonhaemolytic hyperbilirubinaemia (Crigler-Najjar disease)[3,4] and in sclerosing cholangitis.[5]

1. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002; **36:** 1462–5.
2. Sadler LC, *et al.* Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1995; **102:** 169–70.
3. Arrowsmith WA, *et al.* Comparison of treatments for congenital nonobstructive nonhaemolytic hyperbilirubinaemia. *Arch Dis Child* 1975; **50:** 197–201.
4. Odièvre M, *et al.* Case of congenital nonobstructive, nonhaemolytic jaundice: successful long-term phototherapy at home. *Arch Dis Child* 1978; **53:** 81–2.
5. Polter DE, *et al.* Beneficial effect of cholestyramine in sclerosing cholangitis. *Gastroenterology* 1980; **79:** 326–33.

Diabetes mellitus. Bile acids may have a role in modulating carbohydrate metabolism and small studies have shown that bile-acid binding resins such as colestyramine reduce blood glucose.[1] Their role in type 2 diabetes mellitus (p. 459.1) is under investigation; colesevelam (p. 1345.1) may be used as an adjunct to standard therapy to improve glycaemic control.

1. Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007; **67:** 1383–92.

Diarrhoea. In addition to its use in diarrhoea (p. 1808.2) associated with biliary disorders (above), colestyramine has been investigated in the management of diarrhoea and faecal incontinence from other causes.[1-4] See also Antibiotic-associated Colitis, above.

1. Baert D, *et al.* Chronic diarrhoea in non collagenous microscopic colitis: therapeutic effect of cholestyramine. *Acta Clin Belg* 2004; **59:** 258–62.
2. Balagani R, *et al.* Cholestyramine improves tropical-related diarrhea. *Am J Ther* 2006; **13:** 281–2.
3. Flieger D, *et al.* Phase II clinical trial for prevention of delayed diarrhea with cholestyramine/levofloxacin in the second-line treatment with irinotecan biweekly in patients with metastatic colorectal carcinoma. *Oncology* 2007; **72:** 10–16.
4. Remes-Troche JM, *et al.* Cholestyramine—a useful adjunct for the treatment of patients with fecal incontinence. *Int J Colorectal Dis* 2008; **23:** 189–94.

Hyperthyroidism. Bile-acid binding resins also bind thyroid hormones and may interfere with their enterohepatic circulation. Reduced serum-thyroxine concentrations have occurred in patients given bile-acid binding resins for hyperlipidaemias (see Effects on Thyroid Function under Colestipol, p. 1345.3) and both colestyramine[1-3] and colestipol[4] have been tried as adjunctive treatment for hyperthyroidism (p. 2332.2). Colestyramine has also been used in thyroxine overdose.[5,6]

1. Mercado M, *et al.* Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. *J Clin Endocrinol Metab* 1996; **81:** 3191–3.
2. Tsai W-C, *et al.* The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. *Clin Endocrinol (Oxf)* 2005; **62:** 521–4.
3. Kaykhaei MA, *et al.* Low doses of cholestyramine in the treatment of hyperthyroidism. *Endocrine* 2008; **34:** 52–5.
4. Hagag P, *et al.* Role of colestipol in the treatment of hyperthyroidism. *J Endocrinol Invest* 1998; **21:** 725–31.
5. Shakir KMM, *et al.* The use of bile acid sequestrants to lower serum thyroid hormones in iatrogenic hyperthyroidism. *Ann Intern Med* 1993; **118:** 112–13.
6. de Luis DA, *et al.* Light symptoms following a high-dose intentional L-thyroxine ingestion treated with cholestyramine. *Horm Res* 2002; **57:** 61–3.

Adverse Effects

The most common adverse effect of colestyramine is constipation; faecal impaction may develop and haemorrhoids may be aggravated. Other gastrointestinal adverse effects include abdominal discomfort or pain, heartburn, flatulence, nausea, vomiting, and diarrhoea.

Colestyramine in high doses may cause steatorrhoea by interfering with the absorption of fats from the gastrointestinal tract and therefore decreased absorption of fat-soluble vitamins, such as vitamins A, D, E, and K, may occur. Chronic use of colestyramine may thus result in an increased bleeding tendency due to hypoprothrombinaemia associated with vitamin K deficiency; it also has a potential to cause osteoporosis due to impaired calcium and vitamin D absorption. Colestyramine may increase plasma-triglyceride concentrations, see Uses and Administration, above.

Colestyramine is the chloride form of an anion-exchange resin and prolonged use may produce hyperchloraemic acidosis, particularly in children.

Skin rashes and pruritus of the tongue, skin, and perianal region have occasionally occurred.

Reviews.
1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 47C–55C.

Incidence of adverse effects. Results of the Lipid Research Clinics Coronary Primary Prevention Trial[1] involving 3806 men given colestyramine or placebo for an average of 7.4 years showed that gastrointestinal adverse effects occurred frequently in both groups but especially in the colestyramine group. In the first year 68% of the colestyramine group had at least 1 gastrointestinal adverse effect compared with 43% of the placebo group; by the seventh year the incidence had fallen to 29% and 26% respectively. Constipation and heartburn, especially, were more frequent in the colestyramine group, which also reported more abdominal pain, belching or bloating, gas, and nausea. These adverse effects were usually not severe and could be dealt with by standard clinical means.

The incidence of malignant neoplasms was similar in the 2 groups although there were differences in incidence at some sites. In particular, there were 21 cases of malignancy in the gastrointestinal tract (8 fatal) in the colestyramine group compared with 11 cases (1 fatal) in the placebo group. Rare cancers of the buccal cavity or pharynx were more common with colestyramine; during the study[1] there were 6 cases in the colestyramine group and none in the placebo group, and after follow-up[2] for a further 6 years and reassessment of the original diagnoses the incidences were 8 and 2, respectively. However, there was no clear dose relationship, and cigarette smoking may have been a confounder.[2] Colorectal malignancies were similar in the 2 groups, although at follow-up more non-malignant colorectal neoplasms had occurred in the colestyramine group.[2]

1. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA* 1984; **251:** 351–64.
2. The Lipid Research Clinics Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial: results of 6 years of post-trial follow-up. *Arch Intern Med* 1992; **152:** 1399–1410.

Precautions

Colestyramine powder should be given as a suspension in water or a flavoured vehicle to minimise the risk of oesophageal obstruction.

Colestyramine should not be used in patients with complete biliary obstruction as it is unlikely to be effective.

Because of the risk of vitamin deficiencies, supplements of vitamins A, D, E, and K should be considered during prolonged therapy with colestyramine; if given orally they need to be in a water-miscible form. Parenteral supplementation, particularly of vitamin K for hypoprothrombinaemia, may be necessary if a deficiency becomes established. Reduced serum-folate concentrations have also been reported in children with familial hypercholesterolaemia and supplementation with folic acid should be considered in such circumstances.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies colestyramine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Colestyramine may delay or reduce the absorption of other drugs, particularly acidic drugs. Enterohepatic circulation may be reduced. Delayed or reduced absorption of thiazide diuretics, propranolol, digoxin and related glycosides, loperamide, phenylbutazone, barbiturates, oestrogens, progestogens, thyroid hormones, warfarin, deferasirox, and some antibacterials, has either been reported or may be expected. It is therefore recommended that other drugs should be taken at least 1 hour before, or 4 to 6 hours after, the use of colestyramine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Questran; ***Austral.***: Questran; ***Austria***: Quantalan; ***Belg.***: Questran; ***Braz.***: Questran; ***Canad.***: Novo-Cholamine; Olestyr; ***Cz.***: Questran†; Vasosan; ***Denm.***: Questran; ***Fin.***: Questran; ***Fr.***: Questran; ***Ger.***: Colestyr†; Lipocol; Quantalan; Vasosan; ***Gr.***: Questran; ***Hong Kong***: Questran†; ***Indon.***: Questran†; ***Irl.***: Questran; ***Mex.***: Questran; ***Neth.***: Questran; ***Norw.***: Questran; ***NZ***: Questran; ***Pol.***: Vasosan; ***Port.***: Quantalan; ***S.Afr.***: Questran; ***Singapore***: Resincolestiramina; ***Spain***: Efensol; Resincolestiramina; ***Swed.***: Questran; ***Switz.***: Ipocol; Quantalan; ***Thai.***: Questran; Resincolestiramina; ***Turk.***: Kolestran; ***UK***: Questran; ***USA***: Locholest; Prevalite; Questran.

Pharmacopoeial Preparations
BP 2014: Colestyramine Oral Powder;
USP 36: Cholestyramine for Oral Suspension.

Colextran Hydrochloride *(rINNM)*

Colextran, Chlorhydrate de; Colextrán, hidrocloruro de; Colextrani Hydrochloridum; DEAE-dextran Hydrochloride; Detaxtran Hydrochloride; Diethylaminoethyl-dextran Hydrochloride; Hidrocloruro de colextrán; Колекстрана Гидрохлорид.

Dextran 2-(diethylamino)ethyl ether hydrochloride.

CAS — 9015-73-0 (colextran); 9064-91-9 (colextran hydrochloride).
ATC — C10AC03.
ATC Vet — QC10AC03.
UNII — 85AMG1WQ9L.

Profile

Colextran hydrochloride, an anion-exchange resin that binds bile acids in the intestine, is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). It is given in a usual dose of 2 to 3 g daily orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Pulsar; Rationale; ***Spain***: Dexide.

Cyclandelate *(BAN, rINN)*

BS-572; Ciclandelato; Cyclandélate; Cyclandelatum; Cyklandelat; Syklandelaatti; Циклanделат.

3,3,5-Trimethylcyclohexyl mandelate.

$C_{17}H_{24}O_3$=276.4

CAS — 456-59-7.
ATC — C04AX01.
ATC Vet — QC04AX01.
UNII — 4139O1OAY2.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Cyclandelate). A white crystalline powder. M.p. about 58 degrees. Practically insoluble in water; very soluble in alcohol, in acetonitrile, and in ether. Store in airtight containers below 40 degrees, preferably between 15 degrees and 30 degrees. Protect from light.

Profile

Cyclandelate is a vasodilator used in the management of cerebrovascular (p. 1269.2) and peripheral vascular disorders (p. 1272.3). It is given orally in an initial dosage of up to 2 g daily in divided doses; a usual maintenance dose is 0.8 to 1.2 g daily.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclandelate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Cyclophilin; Cyclospasmol; ***India***: Cyclasyn; Cyclospasmol; Martispasmol.

Cyclopenthiazide *(BAN, USAN, rINN)* ⊗

Ciclopentiazida; Cyclopenthiaz.; Cyclopenthiazidum; Ciklopentiazid; NSC-107679; Su-8341; Syklopentiatsidi; Циклопентиазид.

6-Chloro-3-cyclopentylmethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{13}H_{18}ClN_3O_4S_2$=379.9

CAS — 742-20-1.
ATC — C03AA07.
ATC Vet — QC03AA07.
UNII — VX4S2N85F5.

NOTE. Compounded preparations of cyclopenthiazide may be represented by the following names:

- Co-prenozide (*BAN*)—cyclopenthiazide 1 part and oxprenolol hydrochloride 640 parts (w/w).

Pharmacopoeias. In *Br.*

BP 2014: (Cyclopenthiazide). A white, odourless or almost odourless powder. Practically insoluble in water; soluble in alcohol and in acetone; practically insoluble in chloroform; very slightly soluble in ether.

Profile

Cyclopenthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is given orally for hypertension (p. 1251.1), and for oedema, including that associated with heart failure (p. 1262.3).

Diuresis is induced in 1 to 3 hours after an oral dose, reaches a peak in 4 to 8 hours, and lasts up to about 12 hours.

In the treatment of hypertension the usual dose is 250 to 500 micrograms daily either alone, or with other antihypertensives. In the treatment of oedema the usual initial dose is 250 to 500 micrograms daily; up to 1 mg daily may be given in heart failure but higher doses rarely achieve any further benefit. The dose should be reduced to the lowest effective dose for maintenance.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Navidrex.

Multi-ingredient Preparations. ***Hong Kong***: Navispare; ***S.Afr.***: Lenurex-K†; ***UK***: Navispare; Trasidrex†.

Pharmacopoeial Preparations
BP 2014: Cyclopenthiazide Tablets.

Dabigatran *(BAN, USAN, rINN)*

BIBR-953; BIBR-953ZW; Dabigatrán; Dabigatranum; Дабигатран.

N-{[2-[(*p*-Amidinoanilino)methyl]-1-methyl-5-benzimidazolyl]carbonyl}-*N*-2-pyridyl-β-alanine.

$C_{25}H_{25}N_7O_3$=471.5

CAS — 211914-51-1.
ATC — B01AE07.
ATC Vet — QB01AE07.
UNII — I0VM4M70GC.

Dabigatran Etexilate *(BAN, USAN, rINN)*

BIBR-1048; BIBR-1048/BS/RS1; Dabigatran Étexilate; Dabigatrán etexilato; Dabigatranetexilat; Dabigatranum Etexilatum; Etexilato de dabigatrana; Дабигатран Этексилат.

Ethyl 3-({[2-({[4-({[(hexyloxy)carbonyl]amino}iminomethyl)phenyl]amino}methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}(pyridin-2-yl)amino)propanoate.

$C_{34}H_{41}N_7O_5$=627.7

CAS — 211915-06-9.
ATC — B01AE07.
ATC Vet — QB01AE07.
UNII — 2E18WX195X.

Dabigatran Etexilate Mesilate *(rINNM)*

BIBR-1048MS; Dabigatran Étexilate, Mésilate de; Dabigatran Etexilate Mesylate (USAN); Dabigatrani Etexilati Mesilas; Mesilato de dabigatrán etexilato; Дабигатрана Этексилата Мезилат.

$C_{35}H_{45}N_7O_8S$=723.8

CAS — 593282-20-3.
ATC — B01AE07.
ATC Vet — QB01AE07.
UNII — SC7NUW5IIT.

Uses and Administration

Dabigatran is a direct thrombin inhibitor given orally as the mesilate of the prodrug dabigatran etexilate; doses are expressed in terms of the equivalent amount of dabigatran etexilate.

It is used for the prophylaxis of venous thromboembolism (p. 1274.1) in patients undergoing elective orthopaedic surgery, and for the prevention of stroke and systemic embolisation in patients with non-valvular atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1).

In **orthopaedic** patients, the usual initial dose is 110 mg given within 1 to 4 hours of the completion of surgery, followed by 220 mg once daily. A reduced dose of 150 mg once daily should be given if taken with *amiodarone*, *quinidine*, or *verapamil*; (where this is necessary, the 2 drugs should be taken at the same time). Treatment should be continued for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

In patients with **atrial fibrillation** the usual dose is 150 mg twice daily. A reduced dose of 110 mg twice daily should be given if taken at the same time as verapamil. This dose may also be considered for patients at increased risk of bleeding.

Appropriate dosage for use in the elderly and in patients with renal impairment is discussed on p. 1348.1. For advice on switching to an alternative anticoagulant, see Administration, below.

References.
1. Wolowacz SE, *et al.* Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty: a meta-analysis. *Thromb Haemost* 2009; **101:** 77–85.
2. Schulman S, *et al.* RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; **361:** 2342–52.
3. Siddiqui FM, Qureshi AI. Dabigatran etexilate, a new oral direct thrombin inhibitor, for stroke prevention in patients with atrial fibrillation. *Expert Opin Pharmacother* 2010; **11:** 1403–11.
4. Friedman RJ, *et al.* RE-MOBILIZE, RE-MODEL, RE-NOVATE Steering Committees. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res* 2010; **126:** 175–82.
5. Garnock-Jones KP. Dabigatran etexilate: a review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Am J Cardiovasc Drugs* 2011; **11:** 57–72.
6. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation* 2011; **123:** 1436–50.
7. Schulman S, Majeed A. A benefit-risk assessment of dabigatran in the prevention of venous thromboembolism in orthopaedic surgery. *Drug Safety* 2011; **34:** 449–63.
8. Blommel ML, Blommel AL. Dabigatran etexilate: a novel oral direct thrombin inhibitor. *Am J Health-Syst Pharm* 2011; **68:** 1506–19.
9. Bovio JA, *et al.* Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease. *Ann Pharmacother* 2011; **45:** 603–14.
10. Burness CB, McKeage K. Dabigatran etexilate: a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. *Drugs* 2012; **72:** 963–86.

Administration. If patients receiving dabigatran therapy must be switched to another anticoagulant, the following regimens have been suggested based on creatinine clearance (CC).

In patients with atrial fibrillation, parenteral anticoagulants may be started 12 hours after the last dose of dabigatran; or after 24 hours in patients with CC < 30 mL/minute.

Warfarin should be *started*:

- CC more than 50 mL/minute: 3 days *before stopping* dabigatran
- CC 30 to 50 mL/minute: 2 days *before stopping* dabigatran
- CC 15 to 30 mL/minute: 1 day *before stopping* dabigatran
- CC less than 15 mL/minute: no recommendation can be made

In patients receiving short-term dabigatran after orthopaedic surgery, it is suggested that a period of 24 hours should elapse after the last dose of dabigatran before starting a parenteral anticoagulant.

Administration in the elderly. There is limited clinical experience with dabigatran in patients over the age of 75 years but plasma concentrations appear to be higher in older subjects[1] and dose reduction should be considered.

For **orthopaedic** patients, UK licensed product information recommends an initial oral dose of 75 mg of dabigatran etexilate (as the mesilate) given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement. For patients with **atrial fibrillation**, those aged 80 years and over should be given a dose of 110 mg twice daily. This dose may also be considered in those who are aged from 75 to 80 years and at a high risk of bleeding.

1. Stangier J, *et al*. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008; **47:** 47–59.

Administration in renal impairment. Dabigatran is excreted mainly by the kidneys but only limited clinical experience with its use in renal impairment has been published.[1]

UK licensed product information has recommended reduced doses in patients with creatinine clearance (CC) between 30 and 50 mL/minute (moderate impairment). In **orthopaedic** patients, the initial oral dose should be the equivalent of 75 mg of dabigatran etexilate given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement. A maximum daily dose of 75 mg should be considered in those with moderate renal impairment who are also taking *verapamil*. In patients with **atrial fibrillation**, a reduced dose of 110 mg twice daily should be considered in patients with moderate renal impairment and an increased risk of bleeding; otherwise the normal dose may be given. UK information contra-indicates dabigatran in all patients with a CC below 30 mL/minute.

US licensed product information (where the sole indication is for atrial fibrillation) recommends a reduced dose of 75 mg twice daily in patients with a CC of 15 to 30 mL/minute (severe impairment); this reduced dose should also be considered for patients with a CC of 30 to 50 mL/minute (moderate impairment) who are taking either systemic *ketoconazole* or *dronedarone* with dabigatran. No dosing recommendations are made for CC below 15 mL/minute or for patients on dialysis.

1. Stangier J, *et al*. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010; **49:** 259–68.

Adverse Effects and Treatment

The most common adverse effect with dabigatran is bleeding. Gastrointestinal disturbances such as dyspepsia, nausea, and diarrhoea are also common. Raised liver enzyme values have been reported. There is no antidote to dabigatran. If haemorrhagic complications occur treatment should be stopped; surgical haemostasis or blood volume replacement may be considered.

Effects on the liver. Jaundice, fatigue, and anorexia, with raised liver enzyme values indicating mild hepatic dysfunction, developed in a 71-year-old man about 1 month after starting dabigatran. He recovered within 2 weeks after stopping the drug.[1] Isolated cases of severe hepatitis have also occurred.

1. Rochwerg B, *et al*. Dabigatran-induced acute hepatitis. *Clin Appl Thromb Hemost* 2012; **18:** 549–50.

Overdosage. There is no antidote to dabigatran etexilate. Management of bleeding may include delaying or stopping the drug, local compression, and surgical haemostasis. Oral activated charcoal may be considered if the patient presents within 1 to 2 hours. Infusion of fresh frozen plasma could be appropriate, depending on associated coagulopathies, but it will not reverse the anticoagulant effects of dabigatran specifically. Although it has been suggested that other blood components might be tried in life-threatening bleeding, this is generally based on *animal* studies; these treatments include recombinant factor VIIa [eptacog alfa (activated)] and prothrombin complex concentrates (activated or non-activated).[1] In a study of 12 healthy subjects, however, a single dose of a non-activated prothrombin complex concentrate did not reverse the effects of dabigatran on blood coagulation tests.[2] Nevertheless, the use of a prothrombin complex concentrate with fresh frozen plasma was reported to decrease the activated partial thromboplastin time (aPTT) and stabilise haemoglobin concentrations in a case of dabigatran-induced gastrointestinal bleeding.[3]

Dabigatran is removed by haemodialysis.[1]

In an emergency, the most useful indicators of bleeding risk are thrombin time (TT) and activated partial thromboplastin time (APTT), although APTT is less sensitive at supratherapeutic dabigatran levels. Prothrombin time is relatively insensitive to dabigatran, and the international normalised ratio (INR) should not be used. The ecarin clotting time is highly sensitive to the anticoagulant effects of dabigatran but a test is not readily available for clinical use.[1]

1. van Ryn J, *et al*. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; **103:** 1116–27.
2. Eerenberg ES, *et al*. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; **124:** 1573–9.
3. Dumkow LE, *et al*. Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. *Am J Health-Syst Pharm* 2012; **69:** 1646–50.

Precautions

Dabigatran should not be used in patients with clinically significant bleeding or who are at high risk for bleeding. It is contra-indicated in patients with mechanical prosthetic heart valves because of an increased risk of both thromboembolism and major bleeding. US licensed product information also warns that dabigatran is not recommended for thromboembolic prophylaxis in atrial fibrillation in patients with other forms of valvular heart disease or with a bioprosthetic heart valve, because information is lacking. In patients already taking dabigatran, treatment should generally be stopped 1 to 2 days before surgery or invasive procedures; longer withdrawal intervals may be needed before major surgery, spinal puncture or catheter placement, and in patients with renal impairment.

It may be best used with caution in patients with hepatic impairment and should be used in reduced doses or avoided in patients with renal impairment (see Administration in Renal Impairment under Uses and Administration, above).

The elderly. Elderly patients may be at increased risk of bleeding from dabigatran, particularly those with impaired renal function or low body-weight.[1-5] See Administration in the Elderly (above) for recommended dose reductions.

1. Legrand M, *et al*. The use of dabigatran in elderly patients. *Arch Intern Med* 2011; **171:** 1285–6.
2. Harper P, *et al*. Bleeding risk with dabigatran in the frail elderly. *N Engl J Med* 2012; **366:** 864–6.
3. Wychowski MK, Kouides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. *Ann Pharmacother* 2012; **46:** e10.
4. Béné J, *et al*. Rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. *Ann Pharmacother* 2012; **46:** e14.
5. Freshour JE, *et al*. Epistaxis associated with dabigatran in an elderly patient with reduced creatinine clearance. *Am J Health-Syst Pharm* 2012; **69:** 1184–6.

Interactions

Dabigatran should not be given with other drugs that affect coagulation, such as anticoagulants and thrombolytics. It should be used with caution, if at all, with antiplatelet drugs, NSAIDs, SSRIs, or serotonin and noradrenaline reuptake inhibitors (SNRIs), since the risk of bleeding may be increased. Dabigatran is a substrate for the efflux transporter P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function, although advice given in UK and US licensed product information varies. In the UK, recommendations vary slightly between the two indications:

- use with P-glycoprotein inducers (such as rifampicin, St John's wort, carbamazepine, and phenytoin) should be avoided in all patients
- the strong P-glycoprotein inhibitors ciclosporin, dronedarone, itraconazole, systemic ketoconazole, and tacrolimus are contra-indicated in all patients
- when taken with verapamil the dose of dabigatran should be reduced in all patients
- when taken with amiodarone or quinidine the dose of dabigatran should be reduced in orthopaedic patients, but not in atrial fibrillation patients (although caution is required)
- use with clarithromycin requires caution in all patients
- use with ticagrelor requires caution in all patients because of both its antiplatelet effect and P-glycoprotein inhibition

(For details of dosage reductions, see Uses and Administration, p. 1347.3).

In the USA (where the sole indication is atrial fibrillation), licensed product information also advises that the concomitant use of dabigatran and P-glycoprotein inducers such as rifampicin should generally be avoided. Dosage adjustments of dabigatran are not considered necessary when given with amiodarone, quinidine, clarithromycin, ketoconazole, or verapamil in patients with normal renal function, although a reduced dose may be necessary for use with ketoconazole or dronedarone in patients with moderate renal impairment (see Administration in Renal Impairment, above). However, in those with severe renal impairment (creatinine clearance < 30 mL/minute) US licensed product information advises that concomitant use with P-glycoprotein inhibitors should be avoided.

Pharmacokinetics

When given orally, dabigatran etexilate is rapidly and completely hydrolysed to its active metabolite, dabigatran, by an esterase-catalysed reaction. The absolute oral bioavailability of dabigatran when given as dabigatran etexilate is about 3 to 7%. Oral bioavailability of dabigatran etexilate from both the UK and US proprietary products may be increased by up to 75% if the pellets are taken without the capsule shell. Peak plasma concentrations of dabigatran occur within 0.5 to 2 hours after an oral dose. Food delays the time to peak concentrations but the bioavailability is not affected. Dabigatran has low plasma-protein binding (about 35%). It is metabolised to a limited extent to active acylglucuronide conjugates; about 80 to 85% of a dose is excreted in the urine, mainly as unchanged dabigatran. The terminal plasma half-life is about 12 to 17 hours. Dabigatran is removed by dialysis.

Reviews.

1. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008; **47:** 285–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pradaxa; ***Austral.***: Pradaxa; ***Austria***: Pradaxa; ***Belg.***: Pradaxa; ***Braz.***: Pradaxa; ***Canad.***: Pradax; ***Chile***: Pradaxa; ***Cz.***: Pradaxa; ***Denm.***: Pradaxa; ***Fr.***: Pradaxa; ***Ger.***: Pradaxa; ***Gr.***: Pradaxa; ***Hong Kong***: Pradaxa; ***Hung.***: Pradaxa; ***Indon.***: Pradaxa; ***Irl.***: Pradaxa; ***Israel***: Pradaxa; ***Ital.***: Pradaxa; ***Jpn***: Prazaxa; ***Malaysia***: Pradaxa; ***Neth.***: Pradaxa; ***Norw.***: Pradaxa; ***NZ***: Pradaxa; ***Philipp.***: Pradaxa; ***Pol.***: Pradaxa; ***Port.***: Pradaxa; ***Rus.***: Pradaxa (Прадакса); ***Singapore***: Pradaxa; ***Spain***: Pradaxa; ***Swed.***: Pradaxa; ***Switz.***: Pradaxa; ***Thai.***: Pradaxa; ***UK***: Pradaxa; ***Ukr.***: Pradaxa (Прадакса); ***USA***: Pradaxa.

Dalteparin Sodium *(BAN, USAN, rINN)*

Daltepariininatrium; Dalteparin-Natrium; Dalteparin sodná sůl; Dalteparin Sodyum; Dalteparina sódica; Daltéparine sodique; Dalteparinnatrium; Dalteparin-nátrium; Dalteparino natrio druska; Dalteparinum Natricum; Dalteparyna sodowa; Kabi-2165; Tedelparin Sodium; Дальтепарин Натрий.

CAS — 9041-08-1.
ATC — B01AB04.
ATC Vet — QB01AB04.
UNII — 12M44VTJ7B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dalteparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by nitrous acid depolymerisation of heparin from porcine intestinal mucosa. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5600 and 6400, with a characteristic value of about 6000. The mass percentage of chains lower than 3000 is not more than 13.0% and the mass percentage of chains higher than 8000 ranges between 15.0% and 25.0%. The degree of sulfation is 2.0 to 2.5 per disaccharide unit.

The potency is not less than 110 units and not more than 210 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

Stability. The anti-Xa activity of dalteparin remained stable for 4 weeks[1] when diluted by a factor of 10 in preservative-free normal saline and stored in syringes at 4 degrees.

1. Goldenberg NA, *et al*. Anti-Xa stability of diluted dalteparin for pediatric use. *Ann Pharmacother* 2008; **42:** 511–15.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Dalteparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p. 1254.3).

Dalteparin is given by subcutaneous or intravenous injection. Doses are expressed in terms of units of anti-factor Xa activity.

For *prophylaxis* of **venous thromboembolism** during surgical procedures, dalteparin is usually started pre-operatively.

- For patients at moderate risk of thrombosis 2500 units of dalteparin sodium are given by subcutaneous injection 1 to 2 hours before the procedure, followed by 2500 units once daily for 5 to 7 days or until the patient is fully ambulant.
- For patients at high risk, such as those undergoing orthopaedic surgery, 2500 units are given 1 to 2 hours before and 8 to 12 hours after the procedure followed by 5000 units daily. Alternatively, 5000 units may be given the evening before surgery followed by 5000 units each subsequent evening for 5 to 10 days, or up to 5 weeks after hip replacement surgery.
- A further option in patients undergoing hip replacement surgery is to omit the pre-operative dose; treatment is begun with a dose of 2500 units given 4 to 8 hours postoperatively followed by 5000 units daily.
- For prophylaxis in medical patients, a dose of 5000 units once daily may be given for 14 days or longer.

In the *treatment* of established deep-vein thrombosis, pulmonary embolism, or both, dalteparin sodium is given subcutaneously in a dose of 200 units/kg daily. This may be given as a single dose, or in pregnant patients and those at higher risk of bleeding complications, in two divided doses. The maximum recommended dose is 18 000 units daily. (In pregnant patients, early-pregnancy body-weight should be used.)

Patients with symptomatic venous thromboembolism and cancer may be given 200 units/kg subcutaneously once daily for 30 days, followed by 150 units/kg once daily for up to 5 months. Again, the maximum recommended dose is 18 000 units daily. In those who develop chemotherapy-induced thrombocytopenia, the total daily dose of dalteparin should be reduced by 2500 units while platelet counts are below 100 000 cells/mm^3; treatment should be temporarily stopped if platelet counts are below 50 000 cells/mm^3.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** or **haemofiltration** in adults with chronic renal impairment an intravenous injection of dalteparin sodium 30 to 40 units/kg is followed by an intravenous infusion of 10 to 15 units/kg per hour. A single injection of 5000 units may be given for a haemodialysis or haemofiltration session lasting less than 4 hours. The dose of dalteparin sodium should be reduced in patients at high risk of bleeding complications or who are in acute renal failure; in such patients an intravenous injection of 5 to 10 units/kg is followed by an infusion of 4 to 5 units/kg per hour.

In the management of **unstable angina**, dalteparin sodium is given subcutaneously in a dose of 120 units/kg every 12 hours; the maximum dose is 10 000 units every 12 hours. Treatment is continued for 5 to 8 days and low-dose aspirin should also be given. For patients who require treatment for longer than 8 days while awaiting a revascularisation procedure, a dose of 5000 units (7500 units in men weighing 70 kg or over and women weighing 80 kg or over) may be given every 12 hours for up to 45 days until the procedure is performed.

For administration in children, see below.

References.
1. Dunn CJ, Sorkin EM. Dalteparin sodium: a review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs* 1996; **52:** 276–305.
2. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacother* 1997; **31:** 192–203.
3. Dunn CJ, Jarvis B. Dalteparin: an update of its pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2000; **60:** 203–37.
4. Pineo GF, Hull RD. Dalteparin: pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic diseases. *Eur J Med Res* 2004; **9:** 215–24.
5. Bick RL. Cancer-associated thrombosis: focus on extended therapy with dalteparin. *J Support Oncol* 2006; **4:** 115–20.
6. Linkins LA. Management of venous thromboembolism in patients with cancer: role of dalteparin. *Vasc Health Risk Manag* 2008; **4:** 279–87.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* suggests that dalteparin may be given to neonates and children aged up to 12 years in the following subcutaneous doses:

- for the *prophylaxis* of venous thromboembolism, 100 units/kg once daily
- for the *treatment* of venous thromboembolism, 100 units/kg twice daily

Those aged 12 years and over may be given the usual adult doses (see p. 1348.3).

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with dalteparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of about 100 units of dalteparin sodium.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dalteparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Dalteparin is almost completely absorbed after subcutaneous doses, with a bioavailability of about 87%. Peak plasma activity occurs in about 4 hours. The terminal half-life is about 2 hours after intravenous injection and 3 to 5 hours after subcutaneous injection. Dalteparin is excreted via the kidneys and the half-life is prolonged in patients with renal impairment.

Renal impairment. Dalteparin may accumulate in patients with renal impairment, although possibly to a lesser extent than with other low-molecular-weight heparins. In small studies, dalteparin appeared to accumulate when given to patients with severe renal impairment at therapeutic,[1] but not prophylactic,[2] doses; however, there was considerable variation, and any dose adjustment would need to be individualised, based on anti-factor Xa activity.[1]

1. Schmid P, *et al.* Study of bioaccumulation of dalteparin at a therapeutic dose in patients with renal insufficiency. *J Thromb Haemost* 2009; **7:** 1629–32.
2. Schmid P, *et al.* Study of bioaccumulation of dalteparin at a prophylactic dose in patients with various degrees of impaired renal function. *J Thromb Haemost* 2009; **7:** 552–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ligofragmin; ***Austral.***: Fragmin; ***Austria***: Fragmin; ***Belg.***: Fragmin; ***Braz.***: Fragmin; ***Canad.***: Fragmin; ***Chile***: Fragmin; ***China***: Fragmin (法安明); ***Cz.***: Fragmin; ***Denm.***: Fragmin; ***Fin.***: Fragmin; ***Fr.***: Fragmine; ***Ger.***: Fragmin; ***Gr.***: Fragmin; ***Hong Kong***: Fragmin; ***Hung.***: Fragmin; ***India***: Dalpin; Daltehep; Fragmin; ***Israel***: Fragmin; ***Ital.***: Fragmin; ***Mex.***: Fragmin; ***Neth.***: Fragmin; ***Norw.***: Fragmin; ***NZ***: Fragmin; ***Phil.ipp.***: Eurodal; Fragmin†; ***Pol.***: Fragmin; ***Port.***: Fragmin; ***Rus.***: Fragmin (Фрагмин); ***S.Afr.***: Fragmin; ***Singapore***: Fragmin; ***Spain***: Fragmin; ***Swed.***: Fragmin; ***Switz.***: Fragmin; ***Turk.***: Fragmin; ***UK***: Fragmin; ***Ukr.***: Fragmin (Фрагмин); ***USA***: Fragmin; ***Venez.***: Fragmin.

Pharmacopoeial Preparations
BP 2014: Dalteparin Sodium Injection.

Danaparoid Sodium *(BAN, USAN, rINN)*

Danaparoid-Natrium; Danaparoid sodná sůl; Danaparoid sodowy; Danaparoide sódico; Danaparoïde sodique; Danaparoidum Natricum; Lomoparan; Org-10172; Данапароид Натрий.

CAS — 83513-48-8.
ATC — B01AB09.
ATC Vet — QB01AB09.
UNII — 5004UU3156.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Danaparoid Sodium). A preparation containing the sodium salts of a mixture of sulfated glycosaminoglycans present in porcine tissues. It is prepared from the intestinal mucosa of pigs and the major constituents are suleparoid (heparan sulfate) (p. 1507.2) and dermatan sulfate (p. 1350.3). It has a potency of 11.0 to 17.0 anti-factor Xa units per milligram, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Uses and Administration

Danaparoid sodium is a low-molecular-weight heparinoid. It is an anticoagulant and, like heparin (p. 1397.1), enhances the action of antithrombin III. Like low-molecular-weight heparins (p. 1426.1) it has a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin, but is reported to be a much more selective inhibitor of factor Xa than the low-molecular-weight heparins. It was therefore hoped that danaparoid might be associated with a low incidence of bleeding complications, although this has not been established.

Danaparoid sodium is used in the prophylaxis of venous thromboembolism (p. 1274.1) in patients undergoing surgery. It may be used as an anticoagulant for prophylaxis or treatment in patients with heparin-induced thrombocytopenia providing there is no cross-reactivity. Danaparoid has been investigated in acute ischaemic stroke.

Doses of danaparoid sodium are expressed in terms of units of anti-factor Xa activity. In the prophylaxis of **venous thromboembolism** it is given by subcutaneous injection in a dose of 750 units twice daily for 7 to 10 days. The first dose should be given 1 to 4 hours before surgery.

For patients with **heparin-induced thrombocytopenia** requiring anticoagulation, danaparoid sodium is given intravenously. The initial bolus dose is 2500 units (or 1250 units for patients weighing less than 55 kg, or 3750 units for patients weighing more than 90 kg) followed by an infusion of 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days. Monitoring of plasma anti-factor Xa activity is recommended for patients with renal impairment, or those weighing more than 90 kg. For administration in children, see below.

References.
1. Skoutakis VA. Danaparoid in the prevention of thromboembolic complications. *Ann Pharmacother* 1997; **31:** 876–87.
2. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997; **54:** 903–24.
3. Ibbotson T, Perry CM. Danaparoid: a review of its use in thromboembolic and coagulation disorders. *Drugs* 2002; **62:** 2283–2314.
4. Magnani HN, Gallus A. Heparin-induced thrombocytopenia (HIT): a report of 1,478 clinical outcomes of patients treated with danaparoid (Orgaran) from 1982 to mid-2004. *Thromb Haemost* 2006; **95:** 967–81.
5. Schindewolf M, *et al.* Danaparoid in der Schwangerschaft bei Heparinunverträglichkeit–Einsatz in 59 Fällen. *Hamostaseologie* 2007; **27:** 89–97.
6. Magnani HN. An analysis of clinical outcomes of 91 pregnancies in 83 women treated with danaparoid (Orgaran). *Thromb Res* 2010; **125:** 297–302.
7. Magnani HN. A review of 122 published outcomes of danaparoid anticoagulation for intermittent haemodialysis. *Thromb Res* 2010; **125:** e171–e176.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* suggests that danaparoid may be given to treat venous thromboembolism in neonates and children aged up to 16 years with heparin-induced thrombocytopenia as an initial intravenous injection of 30 units/kg (to a maximum of 1250 units for those weighing under 55 kg, or 2500 units for those over 55 kg), followed by an intravenous infusion of 1.2 to 2 units/kg per hour, adjusted according to coagulation activity.

Adverse Effects and Treatment

Haemorrhage may occur after use of danaparoid sodium (although there is a possible decreased risk of bleeding complications compared with heparin this has not been definitely established). Liver enzymes may be transiently elevated. Other adverse effects include hypersensitivity reactions, thrombocytopenia, and pain at the site of injection.

Protamine sulfate only partially neutralises the anticoagulant effect of danaparoid sodium and cannot be relied on to reverse bleeding associated with overdosage.

Precautions

As for Heparin, p. 1399.3.

Danaparoid sodium should not be given to patients who have developed thrombocytopenia with heparin if they show cross-reactivity in an *in-vitro* test.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies danaparoid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Pharmacokinetics

After subcutaneous dosage danaparoid sodium is well absorbed and peak anti-factor Xa activity occurs in about 4 to 5 hours. The elimination half-lives of anti-factor Xa and anti-factor IIa (antithrombin) activities are about 25 and 7 hours, respectively. Danaparoid sodium is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Orgaran; ***Austria***: Orgaran; ***Belg.***: Orgaran; ***Canad.***: Orgaran; ***Fr.***: Orgaran; ***Ger.***: Orgaran; ***Gr.***: Orgaran; ***Irl.***: Orgaran; ***Neth.***: Orgaran; ***NZ***: Orgaran†; ***Port.***: Orgaran; ***Swed.***: Orgaran; ***Switz.***: Orgaran; ***UK***: Orgaran.

Debrisoquine Sulfate *(BANM, rINNM)*

Debrisoquin Sulfate (USAN); Debrisoquina, sulfato de; Débrisoquine, Sulfate de; Debrisoquine Sulphate; Debriso-

quini Sulfas; Isocaramidine Sulfate; Ro-5-3307/1; Sulfato de debrisoquina; Дебризохина Сульфат.
1,2,3,4-Tetrahydroisoquinoline-2-carboxamidine sulfate.
$(C_{10}H_{13}N_3)_2.H_2SO_4$=448.5
CAS — 1131-64-2 (debrisoquine); 581-88-4 (debrisoquine sulfate).
ATC — C02CC04.
ATC Vet — QC02CC04.
UNII — Q94064N9NW.

Pharmacopoeias. In *Br.*

BP 2014: (Debrisoquine Sulfate). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 3% solution in water has a pH of 5.3 to 6.8. Protect from light.

Uses and Administration

Debrisoquine is an antihypertensive with actions and uses similar to those of guanethidine (p. 1395.2), but it causes less depletion of noradrenaline stores. When given orally, debrisoquine acts within about 4 to 10 hours and has effects lasting for 9 to 24 hours. It has been used in the management of hypertension (p. 1251.1), but has largely been superseded by other drugs.

For reference to the use of debrisoquine in identifying metabolic phenotypes, see Genetic Polymorphism, below.

Adverse Effects, Treatment, and Precautions

As for Guanethidine Monosulfate, p. 1395.3.

Diarrhoea is rare with debrisoquine sulfate. Treatment should not be stopped abruptly as this may lead to rebound hypertension.

The metabolism of debrisoquine is subject to genetic polymorphism and non-metabolisers may show a marked response to doses that have little or no effect in metabolisers.

Interactions

As for Guanethidine Monosulfate, p. 1396.1.

Pharmacokinetics

Debrisoquine is rapidly absorbed from the gastrointestinal tract. The major metabolite is 4-hydroxydebrisoquine; metabolism is subject to genetic polymorphism.

A study[1] in 15 hypertensive patients and 4 healthy subjects indicated that debrisoquine undergoes pre-systemic metabolism to 4-hydroxydebrisoquine, but the mechanism appears to be saturable and increases in the dose of debrisoquine could therefore produce disproportionate decreases in blood pressure. The estimated half-life of elimination for debrisoquine and 4-hydroxydebrisoquine ranged from 11.5 to 26 hours and from 5.8 to 14.5 hours respectively.

1. Silas JH, *et al.* The disposition of debrisoquine in hypertensive patients. *Br J Clin Pharmacol* 1978; **5:** 27–34.

Genetic polymorphism. Debrisoquine, along with sparteine and several other drugs, is a substrate for the cytochrome P450 isoenzyme CYP2D6, a polymorphic enzyme coded by a gene mapped to chromosome 22. Patients homozygous for the mutant allele are termed *poor metabolisers* and express little or no active enzyme. The prevalence of the poor-metaboliser phenotype is about 5% in most Caucasian populations, while studies in other genetic groups have indicated a range of about 2 to 10% although in some groups, such as the Japanese, poor metabolisers have yet to be identified. Poor metabolisers of debrisoquine are unable to 4-hydroxylate the drug adequately to its inactive metabolite and are thus prone to excessive hypotension. Many other drugs are metabolised by the same enzyme, but the clinical consequences of polymorphism in patients taking them depends on the relative activity and toxicity of parent drug and metabolite, and the availability and relative importance of other routes of metabolism. Phenotype has been determined by giving a drug that is metabolised by this enzyme and assaying parent drug and metabolite in urine collected over a defined period of time, but DNA-based tests may represent a more convenient and safer alternative.

References.
1. Relling MV. Polymorphic drug metabolism. *Clin Pharm* 1989; **8:** 852–63.
2. Zanger UM, *et al.* Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004; **369:** 23–37.
3. Llerena A, *et al.* Pharmacogenetics of debrisoquine and its use as a marker for CYP2D6 hydroxylation capacity. *Pharmacogenomics* 2009; **10:** 17–28.

Defibrotide *(BAN, rINN)*

Defibrotida; Défibrotide; Defibrotidum; Дефибротид.
CAS — 83712-60-1.
ATC — B01AX01.
ATC Vet — QB01AX01.
UNII — 438HCF2X0M.

Profile

Defibrotide consists of polydeoxyribonucleotides from bovine lung; the molecular weights range between 45 000 and 55 000. Preparations derived from porcine tissues and with a lower molecular weight range are also used. Defibrotide has antithrombotic and fibrinolytic properties, although its mechanism of action is uncertain; it appears to increase levels of prostaglandin E_2 and prostacyclin, to alter platelet activity, and to increase tissue plasminogen activator function at the same time as decreasing activity of tissue plasminogen activator inhibitor. It is used in the management of thromboembolic disorders. Oral and parenteral formulations have been used in typical doses of 800 mg daily.

Defibrotide is being investigated for use in the treatment of hepatic veno-occlusive disease and thrombotic thrombocytopenic purpura.

References.
1. Palmer KJ, Goa KL. Defibrotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. *Drugs* 1993; **45:** 259–94.
2. Richardson PG, *et al.* Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood* 1998; **92:** 737–44.
3. Pogliani EM, *et al.* Defibrotide in recurrent thrombotic thrombocytopenic purpura. *Clin Appl Thromb Hemost* 2000; **6:** 69–70.
4. Chopra R, *et al.* Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br J Haematol* 2000; **111:** 1122–9.
5. Corti P, *et al.* Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. *Bone Marrow Transplant* 2002; **29:** 542–3.
6. Richardson PG, *et al.* Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood* 2002; **100:** 4337–43.
7. Kornblum N, *et al.* Defibrotide, a polydisperse mixture of single-stranded phosphodiester oligonucleotides with lifesaving activity in severe hepatic veno-occlusive disease: clinical outcomes and potential mechanisms of action. *Oligonucleotides* 2006; **16:** 105–14.
8. Ho VT, *et al.* Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant* 2008; **41:** 229–37.
9. Qureshi A, *et al.* Defibrotide in the prevention and treatment of veno-occlusive disease in autologous and allogeneic stem cell transplantation in children. *Pediatr Blood Cancer* 2008; **50:** 831–2.
10. Morabito F, *et al.* Insights into defibrotide: an updated review. *Expert Opin Biol Ther* 2009; **9:** 763–72.

Adverse effects. Anaphylaxis was reported[1] in a patient given defibrotide for chronic venous insufficiency. A positive skin-prick test confirmed a type 1 hypersensitivity reaction.

1. Artesani MC. Anaphylactic shock to defibrotide. *Allergy* 2006; **61:** 1022.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Noravid; ***Ital.***: Noravid†; Prociclide†.

Delapril Hydrochloride *(USAN, rINNM)*

Alindapril Hydrochloride; CV-3317; Délapril, Chlorhydrate de; Delapril, hidrocloruro de; Delaprili Hydrochloridum; Hidrocloruro de delapril; Indalapril Hydrochloride; REV-6000A; Делаприла Гидрохлорид.
Ethyl (*S*)-2-{[(*S*)-1-(carboxymethyl-2-indanylcarbamoyl)ethyl]amino}-4-phenylbutyrate hydrochloride.
$C_{26}H_{32}N_2O_5.HCl$=489.0
CAS — 83435-66-9 (delapril); 83435-67-0 (delapril hydrochloride).
ATC — C09AA12.
ATC Vet — QC09AA12.
UNII — 2SMM3M5ZMH.

Profile

Delapril is an ACE inhibitor (p. 1282.2). It is converted in the body to two metabolites to which it owes its activity. It is given orally as the hydrochloride in the treatment of hypertension (p. 1251.1), in usual maintenance doses of 30 to 60 mg daily in two divided doses.

Reviews.
1. McCormack PL, Keating GM. Delapril/manidipine. *Drugs* 2006; **66:** 961–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Delacard; ***Ital.***: Delaket; ***Jpn***: Adecut; ***Philipp.***: Cupressin; ***Singapore***: Cupressin†; ***Spain***: Beniod; Trinordiol; ***Thai.***: Cupressin; ***Turk.***: Delaket.

Multi-ingredient Preparations. ***Austria***: Delapride†; Vivace†; ***Braz.***: Hipertil; ***Ger.***: Vivace; ***Gr.***: Dinapres; Vivace; ***Ital.***: Delapride; Dinapres; ***Spain***: Bimade; Vivace; ***Turk.***: Delapride.

Denopamine *(rINN)*

Denopamina; Dénopamine; Denopaminum; TA-064; Денопамин.
(-)-(*R*)-α-{[(3,4-Dimethoxyphenethyl)amino]methyl}-*p*-hydroxybenzyl alcohol.
$C_{18}H_{23}NO_4$=317.4
CAS — 71771-90-9.
UNII — V5F60UPD8P.

NOTE. The name Herpamine has been used as a trademark for denopamine.

Profile

Denopamine is a sympathomimetic (p. 1507.3) with mainly beta-adrenergic activity selective to $beta_1$ receptors. It acts as a partial agonist and is used orally in the treatment of heart failure at a daily dose of 15 to 30 mg in 3 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Kalgut.

Dermatan Sulfate

Chondroitin Sulfate B; Dermataanisulfaatti; Dermatan solfato; Dermatán, sulfato de; Dermatan Sulphate; LMW-DS (depolymerised dermatan sulfate); MF-701; OP-370 (depolymerised dermatan sulfate); Sulfat dermatà; Дерматан Сульфат; Дерматансульфат.
CAS — 24967-94-0.
ATC — B01AX04.
ATC Vet — QB01AX04.

Dermatan Sulfate Sodium

Chondroitin Sulfate B Sodium; Dermatan Sulphate Sodium; Дерматана Сульфат Натрия.
CAS — 54328-33-5.
ATC — B01AX04.
ATC Vet — QB01AX04.

Profile

Dermatan sulfate is a naturally occurring glycosaminoglycan used as an anticoagulant for prophylaxis of venous thromboembolism (p. 1274.1). It is given as the sodium salt in a dose of 100 to 300 mg daily by intramuscular injection. The dose may be increased to 300 mg twice daily in patients at high risk of thromboembolism, such as those undergoing major orthopaedic surgery.

Dermatan sulfate is a component of sulodexide (p. 1507.3) and its sodium salt is a component of danaparoid sodium (p. 1349.2).

Dermatan sulfate has been investigated for the treatment of venous thromboembolism, heparin-induced thrombocytopenia, and to prevent clotting during haemodialysis. Low-molecular-weight (depolymerised) dermatan sulfate has also been studied.

References.
1. Dawes J, *et al.* The pharmacokinetics of dermatan sulphate MF701 in healthy human volunteers. *Br J Clin Pharmacol* 1991; **32:** 361–6.
2. Gianese F, *et al.* The pharmacokinetics and pharmacodynamics of dermatan sulphate MF701 during haemodialysis for chronic renal failure. *Br J Clin Pharmacol* 1993; **35:** 335–9.
3. Miglioli M, *et al.* Bioavailability of Desmin, a low molecular weight dermatan sulfate, after subcutaneous administration to healthy volunteers. *Int J Clin Lab Res* 1997; **27:** 195–8.
4. Nenci GG. Dermatan sulphate as an antithrombotic drug. *Pathophysiol Haemost Thromb* 2002; **32:** 303–7.
5. Yamada S, Sugahara K. Potential therapeutic application of chondroitin sulfate/dermatan sulfate. *Curr Drug Discov Technol* 2008; **5:** 289–301.
6. Vitale C, *et al.* Effects of dermatan sulfate for anticoagulation in continuous renal replacement therapy. *J Nephrol* 2008; **21:** 205–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Mistral; ***Port.***: Venorix.

Deserpidine *(BAN, rINN)*

Canescine; Deserpidiini; Deserpidin; Deserpidina; Déserpidine; Deserpidinum; 11-Desmethoxyreserpine; Raunormine; Recanescine; Дезерпидин.
Methyl 11-demethoxy-*O*-(3,4,5-trimethoxybenzoyl)reserpate.
$C_{32}H_{38}N_2O_8$=578.7
CAS — 131-01-1.

ATC — C02AA05.
ATC Vet — QC02AA05.
UNII — 9016E3VB47.

Profile

Deserpidine is an ester alkaloid isolated from the root of *Rauwolfia canescens*. It has properties similar to those described under reserpine (p. 1485.3) and has been used in the treatment of hypertension and psychoses.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***China***: Enduronyl (降压乐).

Desirudin *(BAN, USAN, rINN)*

CGP-39393; Desirudiini; Desirudina; Désirudine; Desirudinum; Desirudyna; Desulphatohirudin; Дезирудин.
63-Desulfohirudin (*Hirudo medicinalis* isoform HV1).
$C_{287}H_{440}N_{80}O_{110}S_6$=6963.5
CAS — 120993-53-5.
ATC — B01AE01.
ATC Vet — QB01AE01.
UNII — U0JZ726775.

Uses and Administration

Desirudin is a recombinant hirudin (p. 1401.2) that is a direct inhibitor of thrombin with actions similar to Lepirudin, p. 1418.2. It is used as an anticoagulant for the prevention of postoperative venous thromboembolism (p. 1274.1) in patients undergoing orthopaedic surgery. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina, and as an adjunct in angioplasty procedures (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p. 1418.3).

In the prevention of venous thromboembolism, desirudin is given subcutaneously in a dose of 15 mg twice daily, the first dose 5 to 15 minutes before surgery, but after induction of regional block anaesthesia, if used. Treatment is continued until the patient is fully ambulant, usually for 9 to a maximum of 12 days.

Response to desirudin should be monitored using activated partial thromboplastin time (APTT) in patients with hepatic or renal impairment, or increased risk of bleeding. Doses may need to be reduced in patients with renal impairment (see below).

References.
1. Matheson AJ, Goa KL. Desirudin: a review of its use in the management of thrombotic disorders. *Drugs* 2000; **60:** 679–700.

Administration in renal impairment. The dose of desirudin should be reduced in patients with renal impairment, depending on creatinine clearance (CC) and activated partial thromboplastin time (APTT), which should be measured daily. US licensed product information recommends the following subcutaneous doses:

- CC 31 to 60 mL/minute per 1.73 m^2, initial dose 5 mg every 12 hours, subsequently adjusted according to APTT
- CC below 31 mL/minute per 1.73 m^2, initial dose 1.7 mg every 12 hours, subsequently adjusted according to APTT

However, a study[1] of pharmacokinetic data from patients with moderate renal impairment (CC 31 to 60 mL/minute) suggested that in fact standard doses of 15 mg twice daily subcutaneously without additional monitoring of APTT would be appropriate in this group.

1. Nafziger AN, Bertino JS. Desirudin dosing and monitoring in moderate renal impairment. *J Clin Pharmacol* 2010; **50:** 614–22.

Adverse Effects and Precautions

As for Lepirudin, p. 1419.2.

Teratogenicity has been seen in *animals*.

Interactions

As for Lepirudin, p. 1419.3.

Pharmacokinetics

Peak plasma concentrations of desirudin occur 1 to 3 hours after subcutaneous injection. Desirudin is metabolised and excreted by the kidney, and 40 to 50% of a dose is excreted unchanged in the urine. After subcutaneous or intravenous injection the terminal elimination half-life of desirudin is 2 to 3 hours.

References.
1. Lefèvre G, *et al.* Effect of renal impairment on the pharmacokinetics and pharmacodynamics of desirudin. *Clin Pharmacol Ther* 1997; **62:** 50–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Revasc†; ***Austria***: Revasc; ***Cz.***: Revasc; ***Fr.***: Revasc†; ***Ger.***: Revasc; ***Gr.***: Revasc; ***Irl.***: Revasc; ***Neth.***: Revasc; ***NZ***: Revasc†; ***Pol.***: Revasc; ***Port.***: Revasc; ***Spain***: Revasc; ***USA***: Iprivask.

Deslanoside *(BAN, rINN)*

Deacetyl-lanatoside C; Desacetyl-lanatoside C; Deslanosid; Deslanosídeo; Deslanosidi; Deslanósido; Deslanosidum; Deslanozidas; Dezlanozid; Дезланозид.
3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.
$C_{47}H_{74}O_{19}$=943.1
CAS — 17598-65-1.
ATC — C01AA07.
ATC Vet — QC01AA07.
UNII — YGY317RK75.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Deslanoside). A white or almost white, crystalline or finely crystalline hygroscopic powder. Practically insoluble in water; very slightly soluble in alcohol. In an atmosphere of low relative humidity, it loses water. Store in airtight, glass containers at a temperature below 10 degrees. Protect from light.

USP 36: (Deslanoside). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Deslanoside, a cardiac glycoside with positive inotropic activity, is a derivative of lanatoside C. It has the general properties of digoxin (p. 1353.3) and has been used similarly in the management of some cardiac arrhythmias and in heart failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Cedilanide; Deslanol.

Pharmacopoeial Preparations
USP 36: Deslanoside Injection.

Desmoteplase *(USAN, rINN)*

bat-PA; Bat Plasminogen Activator; Desmoteplasa; Desmotéplase; Desmoteplasum; ds-PA; rDSPA alpha 1; SH-576; Дезмотеплаз.
Plasminogen activator (*Desmodus rotundus* isoform α1 protein moiety reduced).
CAS — 145137-38-8.
UNII — T36L245S3T.

Profile

Desmoteplase is a recombinant form of a plasminogen activator originally isolated from the saliva of the vampire bat *Desmodus rotundus* (Desmodontinae). It converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Desmoteplase is a highly fibrin-specific thrombolytic (see p. 1245.3) with a relatively long terminal half-life. It is under investigation in the management of stroke (p. 1269.2), particularly in patients treated more than 3 hours after onset.

References.
1. Hacke W, *et al.* The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005; **36:** 66–73.
2. Furlan AJ, *et al.* Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke* 2006; **37:** 1227–31.
3. Hacke W, *et al.* Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2009; **8:** 141–50.
4. Tebbe U, *et al.* Desmoteplase in acute massive pulmonary thromboembolism. *Thromb Haemost* 2009; **101:** 557–62.
5. Paciaroni M, *et al.* Desmoteplase. *Expert Opin Biol Ther* 2009; **9:** 773–8.

Detajmium Bitartrate *(rINN)*

Bitartrato de detajmio; Detajmii Bitartras; Détajmium, Bitartrate de; Детаймия Битартрат.
4-[3-(Diethylamino)-2-hydroxypropyl]ajmalinium hydrogen tartrate monohydrate.
$C_{31}H_{47}N_3O_9,H_2O$=623.7

CAS — 53862-81-0.
UNII — 916D901058.

Profile

Detajmium is a class I antiarrhythmic (p. 1243.1). It has been given orally as the bitartrate, in the treatment of supraventricular and ventricular arrhythmias (p. 1266.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Tachmalcor†; ***Ger.***: Tachmalcor†.

Diazoxide *(BAN, USAN, rINN)*

Diatsoksidi; Diazoksidas; Diazoksit; Diazoxid; Diazóxido; Diazoxidum; NSC-64198; Sch-6783; SRG-95213; Диазоксид.
7-Chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide.
$C_8H_7ClN_2O_2S$=230.7
CAS — 364-98-7.
ATC — C02DA01; V03AH01.
ATC Vet — QC02DA01; QV03AH01.
UNII — O5CB12L4FN.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Diazoxide). A white or almost white, fine or crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide; very soluble in dilute solutions of alkali hydroxides.

USP 36: (Diazoxide). White or cream-white crystals or crystalline powder. Practically insoluble to sparingly soluble in water and in most organic solvents; freely soluble in dimethylformamide; very soluble in strong alkaline solutions. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Diazoxide increases the concentration of glucose in the plasma; it inhibits the secretion of insulin by the beta cells of the pancreas, and may increase the hepatic output of glucose. When given intravenously, it produces a fall in blood pressure by a vasodilator effect on the arterioles and a reduction in peripheral resistance. Diazoxide is closely related structurally to the thiazide diuretics, but has an antidiuretic action and thus produces fluid and electrolyte retention; it may be given with a diuretic to reduce fluid retention.

Diazoxide is used orally in the management of intractable hypoglycaemia (see under Glucagon, p. 1554.3) and intravenously in the management of hypertensive crises (p. 1251.1), particularly when first-line drugs such as sodium nitroprusside are ineffective or unsuitable. Diazoxide is not suitable for the chronic treatment of hypertension because of its severe adverse effects.

In **hypoglycaemia**, the initial dose is 3 to 5 mg/kg daily in 2 or 3 divided oral doses, then adjusted according to response. Usual maintenance doses are from 3 to 8 mg/kg daily but total doses of up to 10 to 15 mg/kg daily have been given to adults with refractory hypoglycaemia, as with insulinoma (see Neuroendocrine Tumours, p. 716.3). The hyperglycaemic effect normally begins within 1 hour of a dose and lasts for up to 8 hours.

In **hypertensive crises**, a bolus intravenous injection of 1 to 3 mg/kg is given within 30 seconds, up to a maximum dose of 150 mg, and repeated after 5 to 15 minutes if required.

For doses in children, see below.

Reduced doses may be necessary in patients with renal impairment.

Administration in children. Diazoxide may be given to neonates, infants, and children in the treatment of intractable hypoglycaemia, and for hypertensive emergencies and resistant hypertension.

In **hypoglycaemia**, diazoxide may be given orally or by intravenous injection in the following doses according to age:

- neonates: initially 5 mg/kg twice daily, adjusted according to response to a usual maintenance dose of 1.5 to 3 mg/kg two or three times daily, although up to 7 mg/kg three times daily may be required in some cases
- children aged 1 month and above: initially 1.7 mg/kg three times daily, adjusted according to response to a usual maintenance dose of 1.5 to 3 mg/kg two or three times daily, although up to 5 mg/kg three times daily may be required in some cases

Diazoxide may be given to neonates and children in the treatment of resistant **hypertension** in an initial oral dose of 1.7 mg/kg three times daily, adjusted according to response to a usual daily maximum of 15 mg/kg. It may be

given to those aged 1 month and over in the treatment of **hypertensive emergencies** in an initial intravenous injection of 1 to 3 mg/kg (maximum 150 mg) as a single dose, repeated after 5 to 15 minutes until blood pressure is controlled. A maximum of 4 doses may be given every 24 hours.

Adverse Effects

In addition to inappropriate hypotension and hyperglycaemia (which includes ketoacidosis and hyperosmolar nonketotic coma), adverse effects often include oedema due to salt and water retention, which may precipitate heart failure. Other adverse effects include: dysgeusia, nausea, anorexia, and other gastrointestinal disturbances; mild hyperuricaemia; extrapyramidal symptoms; eosinophilia and thrombocytopenia; dyspnoea; hypertrichosis; and headache, dizziness, tinnitus, and blurred vision. Hypersensitivity has occurred, manifesting as rashes, leucopenia, and fever.

During intravenous therapy, particularly after large bolus injections, adverse effects may be associated with too rapid a reduction in blood pressure and include: coronary ischaemia leading to angina, cardiac arrhythmias, marked ECG changes, tachycardia, palpitations, and bradycardia; cerebral ischaemia leading to confusion, convulsions, loss of consciousness, and neurological deficit; renal impairment; and symptoms of vasodilatation.

Diazoxide may cause a burning sensation in the injected vein; extravasation of the alkaline solution is painful.

Effects on the blood. A 26-year-old man with hypertension developed reversible haemolytic anaemia when treated with diazoxide orally on 3 separate occasions.[1]

1. Best RA, Clink HM. Haemolysis associated with diazoxide, used for the control of hypertension. *Postgrad Med J* 1975; **51:** 402–4.

Effects on the hair. *Hirsutism* and *hypertrichosis* are different types of excessive hair growth, but the terms have often been used interchangeably. Hirsutism is androgen-related whereas hypertrichosis is thought to be independent of hormone stimulation. Hypertrichosis is acknowledged to be a frequent adverse effect of diazoxide in children receiving long-term treatment for idiopathic hypoglycaemia.[1] Two such children had unusually deep (low-pitched) voices as well as marked hypertrichosis.[2] A woman on continuous diazoxide therapy who developed so-called hirsutism without signs of virilisation had raised serum concentrations of androgens.[3]

Alopecia has been reported[4] in 4 infants born to mothers who had been on long-term treatment with diazoxide during pregnancy; the condition was still present to some extent when the infants were last seen at the ages of 5 months to 1 year.

1. Burton JL, *et al*. Hypertrichosis due to diazoxide. *Br J Dermatol* 1975; **93:** 707–11.
2. West RJ. Side effects of diazoxide. *BMJ* 1978; **2:** 506.
3. Hallengren B, Hökfelt B. Increase of serum androgens during diazoxide treatment. *Lancet* 1984; **ii:** 1044–5.
4. Milner RDG, Chouksey SK. Effects of fetal exposure to diazoxide in man. *Arch Dis Child* 1972; **47:** 537–43.

Extrapyramidal effects. In a study[1] of 100 hypertensive patients receiving diazoxide, the incidence of extrapyramidal symptoms was 15%.

1. Pohl JEF. Development and management of extrapyramidal symptoms in hypertensive patients treated with diazoxide. *Am Heart J* 1975; **89:** 401–2.

Pancreatitis. Ten patients with severe hypertension and renal failure were treated with diazoxide in a last attempt to avert nephrectomy; 1 patient developed acute pancreatitis and another diabetic ketoacidosis.[1] Both patients recovered from these effects when diazoxide was withdrawn.

1. De Broe M, *et al*. Oral diazoxide for malignant hypertension. *Lancet* 1972; **i:** 1397.

Voice changes. See Effects on the Hair, above.

Treatment of Adverse Effects

Treatment is largely symptomatic. Severe hyperglycaemia may be corrected by giving insulin: less severe hyperglycaemia may respond to oral hypoglycaemics. Hypotension may be managed with intravenous fluids. Severe hypotension may require sympathomimetics. Antiparkinsonian drugs, such as procyclidine, have been given to control extrapyramidal effects while a diuretic may be required for salt and water retention. Diazoxide can be removed from the body by dialysis but recovery is relatively low owing to extensive protein binding.

Precautions

Diazoxide should be used with care in patients with impaired cardiac or cerebral circulation and in patients with aortic coarctation, arteriovenous shunt, heart failure, or other cardiac disorders in which an increase in cardiac output could be detrimental. During prolonged therapy blood-glucose concentrations and blood pressure should be monitored and the blood should be examined regularly for signs of leucopenia and thrombocytopenia; in children, bone and psychological maturation, and growth, should be regularly assessed. Caution is necessary in patients with renal impairment.

If given during labour, diazoxide may cause cessation of uterine contractions and delay delivery unless oxytocin is also given.

Pregnancy. Transplacental transfer of diazoxide was considered[1] to be responsible for an inappropriately low plasma-insulin concentration in an infant whose mother had received a dose of 150 mg daily for 47 days before delivery. For reference to alopecia in neonates whose mothers had received diazoxide during pregnancy, see Effects on the Hair under Adverse Effects, above.

For reports of sedation, hypotonia, and apnoea among infants born to mothers given both diazoxide and clomethiazole for the treatment of toxaemia of pregnancy, see Precautions, Pregnancy, in Clomethiazole Edisilate, p. 1055.1. Diazoxide is nonetheless one of the drugs that has been used for hypertensive emergencies in pregnancy (see Hypertension, p. 1251.1) and a study found that mini-boluses of diazoxide 15 mg intravenously successfully reduced blood pressure and were well tolerated.[2]

1. Smith MJ, *et al*. Neonatal hyperglycaemia after prolonged maternal treatment with diazoxide. *BMJ* 1982; **284:** 1234.
2. Hennessy A, *et al*. A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol* 2007; **47:** 279–85.

Interactions

The hyperglycaemic, hyperuricaemic, and hypotensive actions of diazoxide may be enhanced by diuretics. Use of diazoxide with other antihypertensives or vasodilators may lead to increased risk of hypotension.

Chlorpromazine. Chlorpromazine was reported[1] to enhance the hyperglycaemic effect of diazoxide in a 2-year-old child.

1. Aynsley-Green A, Illig R. Enhancement by chlorpromazine of hyperglycaemic action of diazoxide. *Lancet* 1975; **ii:** 658–9.

Phenytoin. For the effect of diazoxide on serum-phenytoin concentrations, see Antihypertensives, p. 543.3.

Pharmacokinetics

Diazoxide is readily absorbed from the gastrointestinal tract and more than 90% bound to plasma proteins, although protein binding is decreased in uraemic patients. Its plasma half-life has been estimated to range from about 20 to 45 hours but values of up to 60 hours have been reported. The half-life is reported to be prolonged in renal impairment and shorter for children. The plasma half-life greatly exceeds the duration of vascular activity. Diazoxide is partly metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites; only small amounts are recovered from the faeces. It crosses the placenta and the blood-brain barrier.

Children. In 4 children with hypoglycaemia the plasma half-life of diazoxide was 9.5 to 24 hours, which is considerably shorter than that in adults.[1]

1. Pruitt AW, *et al*. Disposition of diazoxide in children. *Clin Pharmacol Ther* 1973; **14:** 73–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Proglicem; ***Braz.***: Tensuril; ***Canad.***: Proglycem; ***Fr.***: Proglicem; ***Ger.***: Proglicem; ***Gr.***: Eudemine; Proglicem; ***Ital.***: Proglicem; ***Jpn***: Aroglycem; ***Mex.***: Sefulken; ***Neth.***: Proglicem; ***Singapore***: Proglicem; ***Switz.***: Proglicem; ***UK***: Eudemine; Eudemine; ***USA***: Hyperstat†; Proglycem.

Pharmacopoeial Preparations
BP 2014: Diazoxide Injection; Diazoxide Tablets;
USP 36: Diazoxide Capsules; Diazoxide Injection; Diazoxide Oral Suspension.

Dicoumarol *(rINN)*

Bishydroxycoumarin; Dicoumarin; Dicoumarolum; Dicumarol (USAN); Dicumarolo; Dikumarol; Dikumaroli; Melitoxin; Дикумарол.

3,3′-Methylenebis(4-hydroxycoumarin).

$C_{19}H_{12}O_6$=336.3

CAS — 66-76-2.

ATC — B01AA01.

ATC Vet — QB01AA01.

UNII — 7QID3E7BG7.

Pharmacopoeias. In *Int.*

Profile

Dicoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p. 1527.1). It has been used in the management of thromboembolic disorders, but because of its unpredictable response and high incidence of gastrointestinal effects it has been largely replaced by warfarin.

Digitalis Leaf

Digit. Fol.; Digit. Leaf; Digital, hoja de; Digitale Pourprée; Digitale Pourprée, Feuille de; Digitaliksenlehti; Digitalis; Digitalis Folium; Digitalis Purpureae Folium; Digitalisblad; Digitalis-purpurea-Blätter; Feuille de Digitale; Fingerhutblatt; Folha de Dedaleira; Foxglove Leaf; Hoja de Digital; List náprstníku červeného; Piros gyűszűviráglevél; Rusmenių lapai.

ATC — C01AA03.

ATC Vet — QC01AA03.

ATC Herb — HC01AA5002 (Digitalis purpurea: *leaf*).

UNII — F1T8QT9U8B.

NOTE. The term 'digitalis' is often used to describe the entire class of cardiac glycosides.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Digitalis Leaf). The dried leaf of *Digitalis purpurea*. It contains not less than 0.3% of cardenolic glycosides, expressed as digitoxin, and calculated with reference to the drug dried at 100 degrees to 105 degrees. Protect from light and moisture.

USP 36: (Digitalis). The dried leaf of *Digitalis purpurea* (Scrophulariaceae). The potency is such that, when assayed as directed, 100 mg is equivalent to not less than 1 USP unit. Store in containers that protect it from absorbing moisture.

Profile

Digitalis leaf contains several cardiac glycosides with positive inotropic activity, including digitoxin, gitoxin, and gitaloxin. It has the general properties described under digoxin (p. 1353.3) and has been used similarly in the management of heart failure. However, when treatment with a cardiac glycoside is required a single glycoside is preferred to digitalis, and digoxin or digitoxin are most commonly used.

Digitalis is used in herbal medicine.

Homoeopathy

Digitalis leaf has been used in homoeopathic medicines under the following names: Digitalis; Digitalis purpurea; Dig. pur.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Augentropfen Stulln†; ***Ger.***: Augentropfen Stulln Mono; Unguentum lymphaticum†; ***Switz.***: Augentonicum; Collypan; ***Venez.***: Linfoderm.

Homoeopathic Preparations. ***Austria***: Cora; Corasan; Pumpan; ***Canad.***: Headache & Migraine L77; Headache & Migraine; ***Fr.***: Abbe Chaupitre no 20†; Abbe Chaupitre no 82†; Boripharm No 23; Boripharm No 31; Phapax; Vinicard†; ***Ger.***: Conva-cyl Ho-Len-Complex; Derivatio H; Derivatio; Habstal-Cor N; Lowe-Komplex Nr 13; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; ***Neth.***: Phonix Solidago comp; ***Rus.***: Pumpan (Пумпан); ***Ukr.***: Pumpan (Пумпан).

Pharmacopoeial Preparations
USP 36: Digitalis Capsules; Digitalis Tablets.

Digitalis Lanata Leaf

Austrian Digitalis; Austrian Foxglove; Digitalis lanata, hoja de; Digitalis Lanatae Folium; Woolly Foxglove Leaf.

CAS — 17575-20-1 (lanatoside A).

ATC Herb — HC01AA5001 (Digitalis lanata: *leaf*).

UNII — R80JPF49ZY.

Profile

Digitalis lanata leaf consists of the dried leaves of the woolly foxglove, *Digitalis lanata* (Scrophulariaceae), containing about 1 to 1.4% of a mixture of cardioactive glycosides, including digoxin, digitoxin, acetyldigoxin, acetyldigitoxin, lanatoside A, and deslanoside.

Digitalis lanata leaf is used as a source for the manufacture of digoxin and other glycosides.

There have been reports[1] of toxicity after ingestion of dietary supplements contaminated with *Digitalis lanata*.

1. Slifman NR, *et al.* Contamination of botanical dietary supplements by *Digitalis lanata*. *N Engl J Med* 1998; **339:** 806–11.

Digitoxin *(BAN, rINN)*

Digitaline Cristallisée; Digitoksiini; Digitoksinas; Digitoksyna; Digitoxina; Digitoxine; Digitoxinum; Digitoxoside; Dijitoksin; Дигитоксин.

3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14β-hydroxy-5β-card-20(22)-enolide.

$C_{41}H_{64}O_{13}$=765.0

CAS — 71-63-6.

ATC — C01AA04.

ATC Vet — QC01AA04.

UNII — E90NZP2L9U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Digitoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in a mixture of equal volumes of chloroform and methyl alcohol. Protect from light.

USP 36: (Digitoxin). A cardiotonic glycoside obtained from *Digitalis purpurea*, *Digitalis lanata* (Scrophulariaceae), or other suitable species of *Digitalis*. A white or pale buff-coloured, odourless, microcrystalline powder. Practically insoluble in water; soluble 1 in 150 of alcohol and 1 in 40 of chloroform; very slightly soluble in ether. Store in airtight containers.

Adsorption. Binding to an in-line intravenous filter containing a cellulose ester membrane accounted for a reduction[1] in digitoxin concentration of up to 25% from solutions of digitoxin 200 micrograms in 50 mL of glucose 5% or sodium chloride 0.9%. Pretreatment of the filter with a polymer coating reduced adsorption by about half.[2]

Digitoxin was found to be adsorbed onto glass and plastic in substantial amounts from simple aqueous solutions but not from solutions in 30% alcohol, or in plasma, or urine.[3]

1. Butler LD, *et al.* Effect of inline filtration on the potency of low-dose drugs. *Am J Hosp Pharm* 1980; **37:** 935–41.
2. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
3. Molin L, *et al.* Solubility, partition, and adsorption of digitalis glycosides. *Acta Pharm Suec* 1983; **20:** 129–44.

Uses and Administration

Digitoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (below) and is used in the management of some cardiac arrhythmias (p. 1266.1) and in heart failure (p. 1262.3).

Digitoxin is the most potent of the digitalis glycosides and is the most cumulative in action. The onset of its action is slower than that of the other cardiac glycosides and it may therefore be less suitable than digoxin for rapid digitalisation; after oral doses its effects may be evident in about 2 hours and its full effects in about 12 hours. Its effects persist for about 3 weeks.

As described under digoxin, dosage should be carefully adjusted to the needs of the individual patient. Steady-state therapeutic plasma concentrations of digitoxin may range from 10 to 35 nanograms/mL; higher values may be associated with toxicity. In adults 1 to 1.5 mg has been given orally in divided doses over 24 hours for rapid digitalisation, while for slow digitalisation an oral dose of 200 micrograms twice daily for 4 days has been given. The usual maintenance dose is 100 to 200 micrograms daily, but 100 micrograms on alternate days may be adequate. Digitoxin may also be given by slow intravenous injection when vomiting or other conditions prevent oral use; maintenance doses of 70 to 100 micrograms daily have been used. It has also been given intramuscularly but injections may be irritant.

Administration in children. Children were found to have a greater volume of distribution of digitoxin than adults and a shorter mean half-life, although individual variation was considerable. The increase in total clearance in children compared with adults was attributed to greater metabolic clearance. Single digitalisation doses of 20 micrograms/kg were well tolerated.[1]

1. Larsen A, Storstein L. Digitoxin kinetics and renal excretion in children. *Clin Pharmacol Ther* 1983; **33:** 717–26.

Administration in the elderly. Digitoxin half-life, apparent volume of distribution, and clearance were not found to differ in elderly subjects compared with young adults after intravenous injection in a single-dose study. The long half-life may make once weekly dosing possible in poorly compliant patients.[1]

1. Donovan MA, *et al.* The effect of age on digitoxin pharmacokinetics. *Br J Clin Pharmacol* 1981; **11:** 401–2.

Administration in renal disease. The pharmacokinetics of digitoxin were changed significantly in 5 patients with nephrotic syndrome. The apparent volume of distribution of digitoxin was increased and protein binding decreased. Such patients should be maintained at lower serum-digitoxin concentrations than other patients but will need larger doses because of the shortened serum half-life and the increased renal excretion of digitoxin and its cardioactive metabolites.[1]

1. Storstein L. Studies on digitalis VII: influence of nephrotic syndrome on protein binding, pharmacokinetics, and renal excretion of digitoxin and cardioactive metabolites. *Clin Pharmacol Ther* 1976; **20:** 158–66.

Malignant neoplasms. There has been some interest in the potential anticancer activity of digitoxin and related compounds.

References.

1. Haux J. Digitoxin is a potential anticancer agent for several types of cancer. *Med Hypotheses* 1999; **53:** 543–8.
2. Haux J, *et al.* Digitoxin medication and cancer: case control and internal dose-response studies. *BMC Cancer* 2001; **1:** 11.
3. Johansson S, *et al.* Cytotoxicity of digitoxin and related cardiac glycosides in human tumor cells. *Anticancer Drugs* 2001; **12:** 475–83.
4. López-Lázaro M, *et al.* Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients. *J Nat Prod* 2005; **68:** 1642–5.
5. López-Lázaro M. Digitoxin as an anticancer agent with selectivity for cancer cells: possible mechanisms involved. *Expert Opin Ther Targets* 2007; **11:** 1043–53.

Adverse Effects, Treatment, and Precautions

As for Digoxin, p. 1354.3. Toxicity may be more prolonged after withdrawal of digitoxin because of the longer half-life.

References.

1. Lely AH, van Enter CHJ. Large-scale digitoxin intoxication. *BMJ* 1970; **3:** 737–40.
2. Gilfrich H-J, *et al.* Treatment of massive digitoxin overdose by charcoal haemoperfusion and cholestyramine. *Lancet* 1978; **i:** 505.
3. Pond S, *et al.* Treatment of digitoxin overdose with oral activated charcoal. *Lancet* 1981; **ii:** 1177–8.
4. Kurowski V, *et al.* Treatment of a patient with severe digitoxin intoxication by Fab fragments of anti-digitalis antibodies. *Intensive Care Med* 1992; **18:** 439–42.
5. Schmitt K, *et al.* Massive digitoxin intoxication treated with digoxin-specific antibodies in a child. *Pediatr Cardiol* 1994; **15:** 48–9.
6. Lehmann G, *et al.* Digitoxin intoxication in a 79-year-old patient: a description of a case and review of the literature. *Int J Cardiol* 2000; **75:** 109–13.
7. Hippius M, *et al.* Adverse drug reaction monitoring—digitoxin overdosage in the elderly. *Int J Clin Pharmacol Ther* 2001; **39:** 336–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies digitoxin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Digoxin, p. 1356.1. Since digitoxin is significantly metabolised in the liver it may be affected by drugs that induce microsomal enzymes, including rifampicin (see below) and antiepileptics such as phenobarbital.

Antibacterials. Acute heart failure has been reported in a patient taking digitoxin when treatment with *rifampicin* and isoniazid was started; plasma-digitoxin concentrations fell from a pretreatment steady-state value of 27 nanograms/mL to 10 nanograms/mL. The reduction in the digitoxin concentration was attributed to induction of digitoxin metabolism by rifampicin.[1]

Digitoxin toxicity has been described in 2 patients after addition of *azithromycin* to their therapy.[2]

1. Boman G, *et al.* Acute cardiac failure during treatment with digitoxin—an interaction with rifampicin. *Br J Clin Pharmacol* 1980; **10:** 89–90.
2. Thalhammer F, *et al.* Azithromycin-related toxic effects of digitoxin. *Br J Clin Pharmacol* 1998; **45:** 91–2.

Antineoplastics. A mean overall increase of 109% was seen in digitoxin clearance in 5 patients also given *aminoglutethimide*. The interaction was attributed to the induction of hepatic enzymes by aminoglutethimide.[1]

1. Lønning PE, *et al.* Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; **36:** 796–802.

Calcium-channel blockers. Steady-state plasma concentrations of digitoxin increased by an average of 35% over 2 to 3 weeks in 8 of 10 patients when *verapamil* 240 mg daily was added to their therapy. Total body clearance and extra-renal clearance of digitoxin were reduced by 27% and 29% respectively although renal excretion was unchanged. Plasma-digitoxin concentrations increased by a mean of 21% in 5 of 10 patients treated with *diltiazem* but were not increased by *nifedipine*.[1]

1. Kuhlman J. Effects of verapamil, diltiazem, and nifedipine on plasma levels and renal excretion of digitoxin. *Clin Pharmacol Ther* 1985; **38:** 667–73.

Diuretics. *Spironolactone* has been reported to decrease the half-life and the urinary elimination of unchanged digitoxin when given for at least 10 days to 8 patients on oral maintenance digitoxin therapy.[1] However, increased digitoxin half-life has been reported[2] in 3 healthy subjects when spironolactone was added to digitoxin therapy. The interaction was judged to be of minor clinical importance.

1. Wirth KE, *et al.* Metabolism of digitoxin in man and its modification by spironolactone. *Eur J Clin Pharmacol* 1976; **9:** 345–54.
2. Carruthers SG, Dujovne CA. Cholestyramine and spironolactone and their combination in digitoxin elimination. *Clin Pharmacol Ther* 1980; **27:** 184–7.

Pharmacokinetics

Digitoxin is readily and completely absorbed from the gastrointestinal tract. Therapeutic plasma concentrations may range from 10 to 35 nanograms/mL but there is considerable interindividual variation. Digitoxin is more than 90% bound to plasma proteins. It is very slowly eliminated from the body and is metabolised in the liver. Most metabolites are inactive; the major active metabolite is digoxin. Enterohepatic recycling occurs and digitoxin is excreted in the urine, mainly as metabolites. It is also excreted in the faeces and this route becomes significant in renal impairment. Digitoxin has an elimination half-life of up to 7 days or more. The half-life is generally unchanged in renal impairment.

The pharmacokinetics of digitoxin may be affected by age and by concurrent diseases (see under Uses and Administration, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Digimerck; ***Braz.***: Digitaline; ***Ger.***: Digimed†; Digimerck; ***Gr.***: Digitaline; ***Hung.***: Digimerck; ***USA***: Crystodigin.

Multi-ingredient Preparations. ***China***: Stulln (施图伦); Stulln (施图伦).

Pharmacopoeial Preparations

BP 2014: Digitoxin Tablets;
USP 36: Digitoxin Injection; Digitoxin Tablets.

Digoxin *(BAN, rINN)*

Digoksiini; Digoksin; Digoksinas; Digoksyna; Digoxina; Digoxine; Digoxinum; Digoxosidum; Дигоксин.

3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14β-dihydroxy-5β-card-20(22)-enolide.

$C_{41}H_{64}O_{14}$=780.9

CAS — 20830-75-5.

ATC — C01AA05.

ATC Vet — QC01AA05.

UNII — 73K4184T59.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Digoxin). A white or almost white powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol; soluble in a mixture of equal volumes of dichloromethane and methyl alcohol. Protect from light.

USP 36: (Digoxin). A cardiotonic glycoside obtained from the leaves of *Digitalis lanata* (Scrophulariaceae). Clear to white, odourless, crystals, or a white, odourless, crystalline powder. Practically insoluble in water and in ether; slightly soluble in diluted alcohol and in chloroform; freely soluble in pyridine. Store in airtight containers.

Uses and Administration

Digoxin is a cardiac glycoside used in the management of supraventricular arrhythmias, particularly atrial fibrillation (p. 1266.1), and in heart failure (p. 1262.3).

The principal actions of digoxin are an increase in the force of myocardial contraction (positive inotropic activity) and a reduction in the conductivity of the heart, particularly in conduction through the atrioventricular (AV) node. Digoxin also has a direct action on vascular smooth muscle and indirect effects mediated mainly by the autonomic nervous system, and particularly by an increase in vagal activity. There are also reflex alterations in autonomic activity due to the effects on the circulation. Overall, these actions result in positive inotropic effects, negative chronotropic effects, and decreased AV nodal activity.

Cardiac arrhythmias. In atrial arrhythmias digoxin's actions cause a decrease in the conduction velocity through the AV node and an increase in the effective refractory

period, thus reducing ventricular rate. In addition there is a decrease in the refractory period of the cardiac muscle and depression of the sinus node partly in response to the increase in vagal activity.

Digoxin is thus given to slow the increased ventricular rate that occurs in response to *atrial fibrillation*, although other drugs may be preferred; treatment is usually long term. In patients with the Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can cause rapid ventricular rates, and possibly ventricular fibrillation, and should be avoided. In *atrial flutter*, the ventricular rate is normally more difficult to control with digoxin. Drug therapy is not the preferred method of treatment, but treatment with digoxin may restore sinus rhythm, or it may convert the flutter to fibrillation and sinus rhythm may then be induced by subsequent withdrawal of digoxin. Digoxin may be given to relieve an attack of *paroxysmal supraventricular tachycardia* and has also been given to prevent further attacks.

Heart failure. Digoxin and other cardiac glycosides directly inhibit the activity of the enzyme sodium-potassium adenosine triphosphatase (Na/K-ATPase), which is required for the active transport of sodium from myocardial cells. The result is a gradual increase in the intracellular sodium concentration and a decrease in the intracellular potassium concentration. The increased concentration of sodium inside the cells leads, by stimulation of sodium-calcium exchange, to an increase in the intracellular calcium concentration with enhancement of mechanical contractile activity and an increased inotropic effect.

When used in heart failure the increased force of myocardial contraction results in increased cardiac output, decreased end-systolic volume, decreased heart size, and decreased end-diastolic pressure and volume. Increased blood flow through the kidneys results in diuresis with a reduction in oedema and blood volume. The decrease in pulmonary venous pressure relieves dyspnoea and orthopnoea. Digoxin may thus provide symptomatic improvement in patients with heart failure and is mainly used for adjunctive therapy.

Dosage. When given orally, digoxin may take effect within about 2 hours and the maximum effect may be reached in about 6 hours. Initially a loading dose may be given to digitalise the patient, although this may not be necessary in, for example, mild heart failure.

Dosage should be carefully adjusted to the needs of the individual patient. Factors that may be considered include the patient's age, lean body-mass, renal status, thyroid status, electrolyte balance, degree of tissue oxygenation, and the nature of the underlying cardiac or pulmonary disease. Bearing in mind the above factors, steady-state plasma-digoxin concentrations (in a sample taken at least 6 hours after a dose) of 0.5 to 2 nanograms/mL are generally considered acceptable, although concentrations at the lower end of the range may be more appropriate in patients with heart failure. For reference to therapeutic drug monitoring, see below.

If rapid digitalisation is required then a loading dose is given to allow for the large volume of distribution. A total *oral* loading dose of 750 to 1500 micrograms of digoxin may be given during the initial 24-hour period, either as a single dose, or where there is less urgency or greater risk of toxicity, in divided doses at 6-hourly intervals. Alternatively, a total oral loading dose of 10 to 15 micrograms/kg may be given in divided doses (50% initially, then 25% portions given 6 to 8 hourly). A less rapid digitalisation may be achieved with an oral loading dose of 250 to 750 micrograms daily for 1 week. If the loading dose is not necessary, it may be omitted and treatment started with the maintenance dose. The usual oral maintenance dose of digoxin is 125 to 250 micrograms daily, but may range from 62.5 to 500 micrograms daily. Steady-state plasma concentrations occur within 1 to 3 weeks, depending on renal function.

In urgent cases, provided that the patient has not received cardiac glycosides during the previous 2 weeks, digoxin may initially be given *intravenously*. It generally produces a definite effect on the heart rate within 30 minutes, reaching a maximum within about 5 hours. A total loading dose of 500 to 1000 micrograms, or 8 to 12 micrograms/kg is used; the loading dose is given in divided doses (50% initially, then smaller portions given 4 to 8 hourly), with each infused over 5 to 20 minutes. Maintenance treatment is then usually given orally. Oral doses are typically around one-third higher than intravenous doses, due to the lower bioavailability of oral formulations. Digoxin has also been given intramuscularly but this route is not generally recommended since such injections may be painful and tissue damage has been reported. Digoxin should not be given subcutaneously as intense local irritation may occur.

For doses in children, see below.

For administration in elderly patients or in those with renal impairment, see below.

General reviews on the actions and uses of digoxin and the other cardiac glycosides.

1. Opie LH. Digitalis and sympathomimetic stimulants. *Lancet* 1980; **i:** 912–18.
2. Taggart AJ, McDevitt DG. Digitalis: its place in modern therapy. *Drugs* 1980; **20:** 398–404.
3. Chamberlain DA. Digitalis: where are we now? *Br Heart J* 1985; **54:** 227–33.
4. Doherty JE. Clinical use of digitalis glycosides: an update. *Cardiology* 1985; **72:** 225–54.
5. Smith TW. Digitalis: mechanisms of action and clinical use. *N Engl J Med* 1988; **318:** 358–65.
6. Hampton JR. Digoxin. *Br J Hosp Med* 1997; **58:** 321–3.
7. Riaz K, Forker AD. Digoxin use in congestive heart failure: current status. *Drugs* 1998; **55:** 747–58.
8. Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. *Med J Aust* 2003; **179:** 98–102.
9. Gheorghiade M, *et al*. Digoxin for the treatment of chronic and acute heart failure syndromes. *Acute Card Care* 2009; **11:** 83–7.
10. Master J, Schweitzer P. Is there a role for digoxin in atrial fibrillation without heart failure? *Cardiol J* 2009; **16:** 483–6.

Administration in children. Digoxin is given to neonates, infants, and children in the treatment of supraventricular tachycardias such as atrial fibrillation. It may also be used to treat heart failure, particularly when the response to diuretics and ACE inhibitors has been inadequate.

In comparison with adults, neonates have immature renal function and require lower doses proportional to body-weight, while infants and young children require proportionally higher doses. Daily maintenance doses in those aged under 10 years may be given as a single dose or 2 divided doses. Children aged over 10 years may be given adult doses (see p. 1353.3).

It is usually given orally, but may be given by intravenous infusion if necessary. The *BNFC* recommends the following doses according to age and body-weight:

- neonate under 1.5 kg: initially 25 micrograms/kg orally, or 20 micrograms/kg intravenously, in 3 divided doses for 24 hours, then 4 to 6 micrograms/kg daily
- neonate of 1.5 to 2.5 kg: initially 30 micrograms/kg orally or intravenously in 3 divided doses for 24 hours, then 4 to 6 micrograms/kg daily
- neonate over 2.5 kg: initially 45 micrograms/kg orally, or 35 micrograms/kg intravenously, in 3 divided doses for 24 hours, then 10 micrograms/kg daily
- child aged 1 month to 2 years: initially 45 micrograms/kg orally, or 35 micrograms/kg intravenously, in 3 divided doses for 24 hours, then 10 micrograms/kg daily
- child aged 2 to 5 years: initially 35 micrograms/kg orally or intravenously in 3 divided doses for 24 hours, then 10 micrograms/kg daily
- child aged 5 to 10 years: initially 25 micrograms/kg (maximum 750 micrograms orally or 500 micrograms intravenously) in 3 divided doses for 24 hours, then 6 micrograms/kg (maximum 250 micrograms) daily

Administration in the elderly. The volume of distribution of digoxin and the elimination half-life increase with age.[1] Therefore there are problems in giving digoxin to elderly patients since steady-state plasma concentrations may not be reached for up to 2 weeks. Fears of toxicity have led some practitioners to use a fixed 'geriatric' dose of 62.5 micrograms daily. However, such a dose can produce subtherapeutic concentrations.[2] The routine use of very low doses of digoxin in the elderly is inappropriate and dosage should be individualised.

1. McMurray J, McDevitt DG. Treatment of heart failure in the elderly. *Br Med Bull* 1990; **46:** 202–29.
2. Nolan L, *et al*. The need for reassessment of digoxin prescribing for the elderly. *Br J Clin Pharmacol* 1989; **27:** 367–70.

Administration in renal impairment. The pharmacokinetics of cardiac glycosides in patients with renal impairment have been reviewed.[1] The rate but not the extent of digoxin absorption is reduced in renal impairment but this is unlikely to be clinically important. Plasma-protein binding may also be reduced but since digoxin is poorly bound to these proteins and has a large apparent volume of distribution this also is unlikely to be important. The apparent volume of distribution is reduced by one-third to one-half and the loading dose of digoxin should therefore be reduced; an oral loading dose of 10 micrograms/kg is suggested (but see also under Therapeutic Drug Monitoring, below). Non-renal clearance of digoxin is unaffected or only slightly reduced but renal clearance is reduced, the extent being closely related to creatinine clearance. The elimination half-life of digoxin is prolonged and it therefore takes longer to reach steady state and longer for toxicity to resolve. Because of the reduction in renal clearance of digoxin, maintenance doses must be reduced in line with renal function. Serum-digoxin concentration should be monitored although the presence of digoxin-like immunoreactive substances may make interpretation difficult. In addition, the presence of hyperkalaemia in patients with renal impairment may reduce sensitivity to the effects of digoxin.[2]

Since digoxin has such a large distribution volume, procedures such as peritoneal dialysis and haemodialysis remove only very small amounts of drug from the body and no dosage supplement is needed.

1. Aronson JK. Clinical pharmacokinetics of cardiac glycosides in patients with renal dysfunction. *Clin Pharmacokinet* 1983; **8:** 155–78.
2. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency: minimising renal and extrarenal toxicity. *Drug Safety* 1997; **16:** 205–31.

Therapeutic drug monitoring. Digoxin has a narrow therapeutic index. It is generally considered that plasma-digoxin concentrations required for a therapeutic effect are usually between 0.5 and 2.0 nanograms/mL,[1-3] although some studies[4-6] have suggested that concentrations of 0.5 to 0.9 nanograms/mL are adequate for heart failure; concentrations at the upper end of the range may be associated with worse outcomes.[5,6] The factor for converting nanograms/mL to nanomoles/litre is 1.28.

Digoxin dosage can be calculated in uncomplicated cases by considering the patient's weight, renal function, and clinical status. Therapeutic drug monitoring is *not* considered to be necessary in patients with a satisfactory clinical response to conventional doses in the absence of signs or symptoms of toxicity.[1,2] Measurement of plasma-digoxin concentrations is useful if poor compliance is suspected, if response is poor or there is a deterioration in response without apparent reason, if renal function is fluctuating, when it is unknown if a cardiac glycoside has been previously taken, during drug interactions, and to confirm clinical toxicity.[1,3,7] A plasma concentration should never be considered in isolation and should be used with other patient data as an important component in clinical decision making. This is particularly important in the diagnosis of digoxin toxicity since signs and symptoms of toxicity may be difficult to distinguish from the underlying disease and can occur within the usual therapeutic range.

Several factors may influence the response to digoxin and thus the interpretation of digoxin assays. These include renal impairment, extremes of age, thyroid disease, patient compliance, drug interactions, and electrolyte disturbances.[1-3,7] Variations in the bioavailability of different digoxin preparations have also caused problems. Renal impairment and hypokalaemia are two of the most important factors affecting dosage of digoxin and whenever plasma-digoxin concentrations are assayed renal function and plasma potassium should also be measured. A dosing nomogram has been proposed[8] relating dose in patients with heart failure to renal function and either height or ideal body weight: for most patients with moderate or severe renal impairment (creatinine clearance below 60 mL/minute) an oral dose of 125 micrograms every other day was considered sufficient. The interpretation of digoxin assays is further confounded by the presence of digoxin-like immunoreactive substances in patients with renal or hepatic impairment, in pregnant women, and in neonates. Blood samples for digoxin assay should be taken at least 6 hours after a dose to allow for distribution.[1,3,7] In addition, reported assay values for the same sample may vary widely enough between laboratories to mandate different clinical management.[9]

The usefulness of plasma-digoxin concentrations in the diagnosis of toxicity in children is unclear. For children older than 12 months the adult guidelines can probably be followed, and for younger children the trend for increased risk of toxicity at increased plasma-digoxin concentrations appears to hold but the threshold for toxicity may be higher, especially in children less than 3 months old.[1]

1. Aronson JK. Indications for the measurement of plasma digoxin concentrations. *Drugs* 1983; **26:** 230–42.
2. Lee TH, Smith TW. Serum digoxin concentration and diagnosis of digitalis toxicity: current concepts. *Clin Pharmacokinet* 1983; **8:** 279–85.
3. Aronson JK, Hardman M. Digoxin. *BMJ* 1992; **305:** 1149–52.
4. Adams KF, *et al*. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; **39:** 946–53.
5. Rathore SS, *et al*. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; **289**: 871–8.
6. Adams KF, *et al*. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial: a retrospective analysis. *J Am Coll Cardiol* 2005; **46:** 497–504.
7. Brodie MJ, Feely J. Practical clinical pharmacology: therapeutic drug monitoring and clinical trials. *BMJ* 1988; **296:** 1110–14.
8. Bauman JL, *et al*. A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006; **166:** 2539–45.
9. Rogers NM, *et al*. Frequently discordant results from therapeutic drug monitoring for digoxin: clinical confusion for the prescriber. *Intern Med J* 2010; **40:** 52–6.

Adverse Effects

Digoxin and the other cardiac glycosides commonly produce adverse effects because the margin between the therapeutic and toxic doses is small; plasma concentrations of digoxin in excess of 2 nanograms/mL are considered to be an indication that the patient is at special risk although there is considerable interindividual variation. There have been many fatalities, particularly due to cardiotoxicity.

Nausea, vomiting, and anorexia may be among the earliest symptoms of digoxin toxicity or overdosage; diarrhoea and abdominal pain may occur. Certain neurological effects are also common symptoms of digoxin

overdosage and include headache, facial pain, fatigue, weakness, dizziness, drowsiness, disorientation, mental confusion, bad dreams and more rarely delirium, acute psychoses, and hallucinations. Convulsions have been reported. Visual disturbances including blurred vision may occur; colour vision may be affected with objects appearing yellow or, less frequently, green, red, brown, blue, or white. Hypersensitivity reactions are rare; thrombocytopenia has been reported. The cardiac glycosides may have some oestrogenic activity and occasionally cause gynaecomastia at therapeutic doses.

Rapid intravenous injection of digoxin may cause vasoconstriction and transient hypertension. Intramuscular or subcutaneous injection can cause local irritation.

The most serious adverse effects are those on the heart. Toxic doses may cause or aggravate heart failure. Supraventricular or ventricular arrhythmias and defects of conduction are common and may be an early indication of excessive dosage, particularly in children. In general the incidence and severity of arrhythmias is related to the severity of the underlying heart disease. Almost any arrhythmia may ensue, but particular note should be made of supraventricular tachycardia, especially AV junctional tachycardia and atrial tachycardia with block. Ventricular arrhythmias including extrasystoles, sinoatrial block, sinus bradycardia, and AV block may also occur.

Hypokalaemia predisposes to digoxin toxicity; adverse reactions to digoxin may be precipitated if hypokalaemia occurs, for example after prolonged use of diuretics. Hyperkalaemia occurs in acute digoxin overdosage.

As digoxin has a shorter half-life than digitalis or digitoxin any toxic effects will tend to resolve more rapidly.

General references to digitalis toxicity.

1. Pentel PR, Salerno DM. Cardiac drug toxicity: digitalis glycosides and calcium-channel and β -blocking agents. *Med J Aust* 1990; **152:** 88–94.
2. Wells TG, *et al*. Age-related differences in digoxin toxicity and its treatment. *Drug Safety* 1992; **7:** 135–51.
3. Johnston GD. Adverse reaction profile: digoxin. *Prescribers' J* 1993; **33:** 29–35.
4. Kernan WN, *et al*. Incidence of hospitalization for digitalis toxicity among elderly Americans. *Am J Med* 1994; **96:** 426–31.
5. Li-Saw-Hee FL, Lip GYH. How safe is digoxin? *Adverse Drug React Bull* 1998; (Feb): 715–18.
6. Gittelman MA, *et al*. Acute pediatric digoxin ingestion. *Pediatr Emerg Care* 1999; **15:** 359–62.
7. López-Gómez D, *et al*. Intoxicación grave por digoxina: utilización exitosa del tratamiento clásico. *Rev Esp Cardiol* 2000; **53:** 471–2.
8. Ma G, *et al*. Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med* 2001; **20:** 145–52.
9. Demiryürek AT, Demiryürek S. Cardiotoxicity of digitalis glycosides: roles of autonomic pathways, autacoids and ion channels. *Auton Autacoid Pharmacol* 2005; **25:** 35–52.
10. Bauman JL, *et al*. Mechanisms, manifestations, and management of digoxin toxicity in the modern era. *Am J Cardiovasc Drugs* 2006; **6:** 77–86.
11. Haynes K, *et al*. Declining public health burden of digoxin toxicity from 1991 to 2004. *Clin Pharmacol Ther* 2008; **84:** 90–4.

Effects on the blood. Thrombocytopenia has been reported[1] in a small number of patients taking digoxin. An association between several cardiovascular drugs, including digitalis glycosides (digoxin and acetyldigoxin), and agranulocytosis was also found in an international study[2] although again the incidence was low.

1. George JN, *et al*. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998; **129:** 886–90.
2. Kelly JP, *et al*. Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: the international agranulocytosis and aplastic anemia study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects in the elderly. Elderly patients may be particularly susceptible to digoxin toxicity, even at therapeutic plasma concentrations.[1] Adverse effects reported in elderly patients with toxic plasma-digoxin concentrations have included chorea,[2] profuse watery diarrhoea,[3] and dysphagia with dysphonia.[4]

1. Miura T, *et al*. Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother* 2000; **34:** 427–32.
2. Mulder LJMM, *et al*. Generalised chorea due to digoxin toxicity. *BMJ* 1988; **296:** 1262.
3. Andrews PA, Wilkinson PR. Diarrhoea as a side effect of digoxin. *BMJ* 1990; **301:** 1398.
4. Cordeiro MF, Arnold KG. Digoxin toxicity presenting as dysphagia and dysphonia. *BMJ* 1991; **302:** 1025.

Hypersensitivity. Hypersensitivity reactions to cardiac glycosides are rare but skin reactions have been reported. An 86-year-old man developed a generalised, pruritic, erythematous rash after digoxin was given intravenously.[1] The rash recurred on rechallenge with digoxin tablets.

1. Martin SJ, Shah D. Cutaneous hypersensitivity reaction to digoxin. *JAMA* 1994; **271:** 1905.

Treatment of Adverse Effects

In *acute poisoning* with cardiac glycosides such as digoxin, repeated doses of activated charcoal may be given to reduce absorption and enterohepatic recycling if the patient presents within 1 to 2 hours of ingestion. Binding resins such as colestyramine and colestipol have also been used. Gastric lavage has also been tried. Attempts to remove cardiac glycosides by haemodialysis or peritoneal dialysis have generally been ineffective and the value of haemoperfusion is controversial.

For the treatment of *chronic poisoning* temporary withdrawal of digoxin or other cardiac glycosides may be all that is necessary, with subsequent doses adjusted according to the needs of the patient.

Cardiotoxicity in acute or chronic poisoning should be treated under ECG control and serum electrolytes should be regularly monitored and imbalances corrected. Progressive hyperkalaemia can occur with massive overdose and is fatal unless reversed; soluble insulin with glucose, or if the hyperkalaemia is refractory, dialysis may be tried. Any antiarrhythmic treatment for cardiac glycoside toxicity should be determined by the specific arrhythmia present (see p. 1266.1). Atropine is given intravenously to correct bradycardia and in patients with heart block. Pacing may be necessary if atropine is not effective.

Digoxin-specific antibody fragments (p. 1549.1) may be used to treat acute and chronic digoxin, or digitoxin overdoses, but are generally restricted to the treatment of severe intoxication in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

References.

1. Allen NM, Dunham GD. Treatment of digitalis intoxication with emphasis on the clinical use of digoxin immune Fab. *DICP Ann Pharmacother* 1990; **24:** 991–8.
2. Dick M, *et al*. Digitalis intoxication recognition and management. *J Clin Pharmacol* 1991; **31:** 444–7.
3. Critchley JAJH, Critchley LAH. Digoxin toxicity in chronic renal failure: treatment by multiple dose activated charcoal intestinal dialysis. *Hum Exp Toxicol* 1997; **16:** 733–5.
4. Kirrane BM, *et al*. Inconsistent approach to the treatment of chronic digoxin toxicity in the United States. *Hum Exp Toxicol* 2009; **28:** 285–92.
5. Bilbault P, *et al*. Emergency step-by-step specific immunotherapy in severe digoxin poisoning: an observational cohort study. *Eur J Emerg Med* 2009; **16:** 145–9.
6. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev* 2004; **23:** 135–43.

Precautions

Digoxin is generally contra-indicated in patients with hypertrophic obstructive cardiomyopathy unless there is severe cardiac failure, since the outflow obstruction may be worsened. It is also contra-indicated in patients with the Wolff-Parkinson-White syndrome or other evidence of an accessory pathway, especially if it is accompanied by atrial fibrillation, since ventricular tachycardia or fibrillation may be precipitated. Although digoxin is used to treat supraventricular arrhythmias it is not an appropriate form of therapy for any *ventricular* arrhythmia.

Digoxin toxicity is common and may result from raised plasma concentrations or an increase in sensitivity to digoxin. Almost any deterioration in the condition of the heart or circulation may increase the sensitivity to digoxin and it should be used with caution in all patients with cardiovascular disease. Early signs of digoxin toxicity should be watched for and the heart rate should generally be maintained above 60 beats per minute. Toxicity may result from giving loading doses too rapidly and from accumulation of maintenance doses as well as from acute poisoning. Even with intravenous doses a response may take several hours, and persistence of tachycardia is therefore not a reason to exceed the recommended intravenous dose.

Digoxin should be used with caution in partial heart block since complete heart block may be induced; it should also be used with care in sinus node disorders. Caution is also required in acute myocarditis (such as rheumatic carditis), in acute myocardial infarction, in advanced heart failure, and in severe pulmonary disease, due to the increased myocardial sensitivity. Digoxin may also enhance the occurrence of arrhythmias in patients undergoing cardioversion and should be withdrawn 1 to 2 days before such procedures if possible. If cardioversion is essential and digoxin has already been given, low energy shocks must be used.

Electrolyte imbalances may affect the sensitivity to digoxin, as may thyroid dysfunction. The effects of digoxin are enhanced by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, and hypothyroidism and doses may need to be reduced until these conditions are corrected. Resistance to the effects of digoxin may occur in hyperthyroidism. Digoxin should be given with care, and possibly in reduced dosage, to patients who have received it or other cardiac glycosides within the previous 2 to 3 weeks.

Digoxin doses should generally be reduced and plasma-digoxin concentrations monitored in patients with renal impairment, in the elderly, and in premature infants (see Uses and Administration, p. 1353.3).

Breast feeding. Studies[1,2] have shown that digoxin is distributed into breast milk, although the amount was considered too small to have an effect on the child. No adverse effects have been seen in breast-feeding infants whose mothers were receiving digoxin, and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Levy M, *et al*. Excretion of drugs in human milk. *N Engl J Med* 1997; **297:** 789.
2. Chan V, *et al*. Transfer of digoxin across the placenta and into breast milk. *Br J Obstet Gynaecol* 1978; **85:** 605–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Gastrointestinal disorders. Absorption from tablets of digoxin may be decreased due to inadequate dissolution in patients with malabsorption syndromes or small bowel resections and it has been recommended that liquid dosage forms of digoxin should be used in the latter case.[1] However, only 40 to 60% of a digoxin dose given as elixir was absorbed in a patient with a small bowel resection[2] compared with about 80% in patients with normal gastrointestinal function, suggesting a need for slightly increased oral maintenance doses of digoxin in patients with resections. In a further patient with a similar resection[3] a therapeutic plasma-digoxin concentration was not achieved with any oral formulation.

1. Kumer KP, *et al*. Perspectives on digoxin absorption from small bowel resections. *Drug Intell Clin Pharm* 1983; **17:** 121–3.
2. Vetticaden SJ, *et al*. Digoxin absorption in a patient with short-bowel syndrome. *Clin Pharm* 1986; **5:** 62–4.
3. Ehrenpreis ED, *et al*. Malabsorption of digoxin tablets, gel caps, and elixir in a patient with an end jejunostomy. *Ann Pharmacother* 1994; **28:** 1239–40.

Heart surgery. Patients undergoing cardiac surgery appear to have increased sensitivity to digoxin toxicity and thus an increased risk of arrhythmias.[1] Digoxin has been found[2] to be no better than placebo in preventing postoperative arrhythmias after coronary artery bypass surgery, and actually induced supraventricular arrhythmias in 2 patients. Arrhythmias compatible with digoxin intoxication have occurred postoperatively[1] although serum-digoxin concentrations ranged from 0 to 2.8 nanograms/mL; therefore, the arrhythmias may have been due to either the surgical procedures or to increased sensitivity to digoxin.

1. Rose MR, *et al*. Arrhythmias following cardiac surgery: relation to serum digoxin levels. *Am Heart J* 1975; **89:** 288–94.
2. Weiner B, *et al*. Digoxin prophylaxis following coronary artery bypass surgery. *Clin Pharm* 1986; **5:** 55–8.

Interference with digoxin assays. The presence of endogenous digoxin-like substances in neonates, and in patients with liver or kidney dysfunction, may be responsible for elevated values or false-positive results in some plasma-digoxin assays.[1] Some patients may have antibodies that react with the assay system and produce falsely elevated values.[2]

Some drugs may also interfere with plasma-digoxin assays; these include prednisolone[1] and ginseng.[3] Raised serum-digoxin concentrations (but without signs of digoxin toxicity) were noted in an elderly man after the use of Siberian ginseng (*Eleutherococcus senticosus*). However, concentrations remained high even when digoxin was discontinued and returned to the therapeutic range only after the ginseng was stopped. Siberian ginseng contains eleutherosides, which are chemically related to cardiac glycosides such as digoxin, and the assay may have measured these compounds, or their derivatives, as well as digoxin. Although it has been suggested that this reaction may have been due to the substitution of the unrelated cardiotoxic herb *Periploca sepium*,[4] both ginseng and Siberian ginseng have been shown to interfere with some digoxin assays *in vitro* and *in vivo*.[5] Spironolactone may interfere with digoxin assays but may also produce changes in digoxin concentrations (see Diuretics under Interactions, p. 1357.2).

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–89.
2. Liendo C, *et al*. A new interference in some digoxin assays: anti-murine heterophilic antibodies. *Clin Pharmacol Ther* 1996; **60:** 593–8.
3. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *Can Med Assoc J* 1996; **155:** 293–5.
4. Awang DVC. Siberian ginseng toxicity may be case of mistaken identity. *Can Med Assoc J* 1996; **155:** 1237.
5. Dasgupta A, *et al*. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* 2003; **119:** 298–303.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies digoxin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. There is considerable evidence that digoxin crosses the placenta freely with serum-digoxin concentrations at term similar in the newborn and mother. No significant adverse effects attributed to digoxin have been

noted in the fetus or neonate although adverse fetal effects, including fetal death, have been reported in mothers with digitalis toxicity. Some concern has been expressed that maternal digitalis therapy may occasionally cause low birth-weights in infants of mothers with heart disease, but the underlying disease might also be important.[1] The presence of endogenous digoxin-like immunoreactive substances in the serum of pregnant women and neonates could make the interpretation of digoxin assays difficult. In one study,[2] high concentrations of endogenous digoxin-like immunoreactivity in cord blood suggested that it might be synthesised during delivery, in which case the placental transfer of digoxin might be overestimated.

1. Rotmensch HH, *et al.* Management of cardiac arrhythmias during pregnancy: current concepts. *Drugs* 1987; **33:** 623–33.
2. Lupoglazoff JM, *et al.* Endogenous digoxin-like immunoreactivity during pregnancy and at birth. *Br J Clin Pharmacol* 1993; **35:** 251–4.

Interactions

There may be interactions between digoxin and drugs that alter its absorption, interfere with its excretion, or have additive effects on the myocardium. Drugs that cause electrolyte disturbances increase the risk of toxicity from cardiac glycosides. Thiazides and loop *diuretics* cause hypokalaemia and also hypomagnesaemia which may lead to cardiac arrhythmias. Other causes of hypokalaemia include treatment with *corticosteroids*, *beta$_2$ agonists* (such as salbutamol), *amphotericin B*, *sodium polystyrene sulfonate*, *carbenoxolone*, and dialysis. Hypercalcaemia may also increase toxicity and intravenous use of *calcium salts* is best avoided in patients taking cardiac glycosides. Serum-digoxin concentrations may be significantly increased by *quinidine*, *amiodarone*, *dronedarone* and *propafenone* and reduction of digoxin dosage may be required. Other antiarrhythmics may have additive effects on the myocardium increasing the likelihood of adverse effects; *beta blockers* may potentiate bradycardia due to digoxin. *Calcium-channel blockers* may increase digoxin concentrations.

Digoxin is a substrate for P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function (see Metabolism and Excretion under Pharmacokinetics, p. 1358.3).

Reviews of drug interactions occurring with digoxin.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; **15:** 227–44.
2. Magnani B, Malini PL. Cardiac glycosides: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 97–109.

ACE inhibitors. Although increased serum-digoxin concentrations have been reported in patients with severe chronic heart failure given *captopril*,[1] other studies have failed to confirm this effect.[2,3] Studies with various other ACE inhibitors have also failed to show any significant effect on serum-digoxin concentrations. However, ACE inhibitors may cause a deterioration in renal function and this could lead to an increase in serum-digoxin concentration due to impaired digoxin excretion.[4]

1. Cleland JGF, *et al.* Interaction of digoxin and captopril. *Br J Clin Pharmacol* 1984; **17:** 214P.
2. Magelli C, *et al.* Lack of effect of captopril on serum digoxin in congestive heart failure. *Eur J Clin Pharmacol* 1989; **36:** 99–100.
3. Rossi GP, *et al.* Effect of acute captopril administration on digoxin pharmacokinetics in normal subjects. *Curr Ther Res* 1989; **46:** 439–44.
4. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–47.

Alpha blockers. *Prazosin*[1] has been reported to increase the mean plasma-digoxin concentration in patients receiving a maintenance dose of digoxin.

1. Çopur S, *et al.* Effects of oral prazosin on total plasma digoxin levels. *Fundam Clin Pharmacol* 1988; **2:** 13–17.

Angiotensin II receptor antagonists. In a study[1] in healthy subjects, *telmisartan* increased peak serum-digoxin concentrations but trough concentrations were unaffected and it was suggested that the effect was unlikely to be clinically significant. No interaction was found when digoxin was given with *losartan*[2] or with *eprosartan*[3] in healthy subjects.

1. Stangier J, *et al.* The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. *J Clin Pharmacol* 2000; **40:** 1373–9.
2. de Smet M, *et al.* Effect of multiple doses of losartan on the pharmacokinetics of single doses of digoxin in healthy volunteers. *Br J Clin Pharmacol* 1995; **40:** 571–5.
3. Martin DE, *et al.* Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43:** 661–4.

Antiarrhythmics. *AMIODARONE.* An interaction between digoxin and amiodarone resulting in increased plasma-digoxin concentrations has been reported[1-5] on several occasions; the concentration may be doubled.[5] An increase in serum-digoxin concentrations of 68 to 800% has been reported[2] during amiodarone therapy in children. The interaction does not appear to be due to a reduction in urinary excretion alone[3,4] and seems to be dose-related. It has been recommended[1,6] that the initial dose of digoxin should be halved when amiodarone is given.

1. Moysey JO, *et al.* Amiodarone increases plasma digoxin concentrations. *BMJ* 1981; **282:** 272.
2. Koren G, *et al.* Digoxin toxicity associated with amiodarone therapy in children. *J Pediatr* 1984; **104:** 467–70.
3. Douste-Blazy P, *et al.* Influence of amiodarone on plasma and urine digoxin concentrations. *Lancet* 1984; **i:** 905.
4. Mingardi G. Amiodarone and plasma digoxin levels. *Lancet* 1984; **i:** 1238.
5. Johnston A, *et al.* The digoxin-amiodarone interaction. *Br J Clin Pharmacol* 1987; **24:** 253P.
6. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 246–53.

DISOPYRAMIDE. Disopyramide appears to have no clinically significant effect on the pharmacokinetics of digoxin in healthy subjects[1,2] but has been reported to modify the cardiovascular effects of digoxin.[1]

1. Elliott HL, *et al.* Pharmacodynamic and pharmacokinetic evaluation of the interaction between digoxin and disopyramide. *Br J Clin Pharmacol* 1982; **14:** 141P.
2. Risler T, *et al.* On the interaction between digoxin and disopyramide. *Clin Pharmacol Ther* 1983; **34:** 176–80.

DRONEDARONE. Increased serum digoxin concentrations and an increased incidence of gastrointestinal disorders have been reported when dronedarone was given with digoxin. Dronedarone inhibits the P-glycoprotein transport system resulting in a 2.5-fold increase in digoxin exposure, therefore the dose of digoxin should be reduced by about 50% when dronedarone therapy is started in patients already taking digoxin; if appropriate, digoxin treatment should be stopped.

Digoxin may potentiate the electrophysiologic effects of dronedarone such as decreased AV node conduction.

FLECAINIDE. Giving flecainide 200 mg twice daily to 15 healthy subjects taking digoxin caused a mean increase of 24% in predose digoxin concentrations and of 13% in digoxin concentrations 6 hours after the digoxin dose.[1] It was considered that in most cases these increases in plasma-digoxin concentrations would not present a clinical problem, but that patients with higher plasma-digoxin concentrations or atrioventricular nodal dysfunction should be monitored.

1. Weeks CE, *et al.* The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin levels. *J Clin Pharmacol* 1986; **26:** 27–31.

PROPAFENONE. Increased serum-digoxin concentrations have been reported when propafenone is also given.[1-4] There is considerable interindividual variation in the extent of the interaction; increases in serum-digoxin concentrations of up to 254% have been reported. If digoxin and propafenone are given together, the dose of digoxin should be reduced and serum-digoxin concentration should be monitored.

1. Nolan PE, *et al.* Effects of coadministration of propafenone on the pharmacokinetics of digoxin in healthy volunteer subjects. *J Clin Pharmacol* 1989; **29:** 46–52.
2. Calvo MV, *et al.* Interaction between digoxin and propafenone. *Ther Drug Monit* 1989; **11:** 10–15.
3. Zalzstein E, *et al.* Interaction between digoxin and propafenone in children. *J Pediatr* 1990; **116:** 310–12.
4. Bigot M-C, *et al.* Serum digoxin levels related to plasma propafenone levels during concomitant treatment. *J Clin Pharmacol* 1991; **31:** 521–6.

QUINIDINE. Quinidine causes an increase in serum-digoxin concentration in almost all patients given the two drugs together.[1-3] The serum-digoxin concentration may be increased by up to 500% but is usually approximately doubled.[1] Signs and symptoms of digoxin toxicity may occur although some workers[4] have suggested that these may be accounted for by an additive effect of the 2 drugs rather than by the effect on serum-digoxin concentration. The exact mechanism of interaction is not clear but a substantial decrease in the renal and nonrenal clearance of digoxin has been found.[5] The distribution volume of digoxin may also be reduced[2] reflecting impaired tissue binding, and there is increased systemic availability.[1] It is generally recommended that the dose of digoxin is halved in digitalised patients who are to be given quinidine.[2] Subsequently, serum-digoxin concentrations should be monitored, especially during the first 1 to 2 weeks after which the new steady-state digoxin concentration should be achieved.[2]

1. Bigger JT, Leahey EB. Quinidine and digoxin: an important interaction. *Drugs* 1982; **24:** 229–39.
2. Pedersen KE. Digoxin interactions: the influence of quinidine and verapamil on the pharmacokinetics and receptor binding of digitalis glycosides. *Acta Med Scand* 1985; **697** (suppl): 1–40.
3. Mordel A, *et al.* Quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. *Clin Pharmacol Ther* 1993; **53:** 457–62.
4. Walker AM, *et al.* Drug toxicity in patients receiving digoxin and quinidine. *Am Heart J* 1983; **105:** 1025–8.
5. Hedman A, *et al.* Interactions in the renal and biliary elimination of digoxin: stereoselective difference between quinine and quinidine. *Clin Pharmacol Ther* 1990; **47:** 20–6.

VERAPAMIL. For a discussion on the interaction between digoxin and verapamil, see under Calcium-channel Blockers, p. 1357.2.

Antibacterials. About 10% of patients receiving digoxin may metabolise 40% or more of the drug to cardio-inactive metabolites.[1] Gut flora contribute greatly to this process, and the use of antibacterials such as *erythromycin* or *tetracycline* in these patients appears to reduce this metabolic process resulting in higher serum concentrations.[2] Digoxin toxicity has been reported in digitalised patients given erythromycin,[3,4] *azithromycin*,[5] *clarithromycin*,[6-8] and *roxithromycin*.[9] A Canadian population-based case-control study investigating the risk of digoxin toxicity associated with concomitant macrolide treatment found that the increase in risk was highest with clarithromycin (almost 15-fold) and was less marked with erythromycin or *azithromycin* (about a fourfold increase in risk).[10] It has been postulated[5,11] that the macrolide antibacterials may also inhibit P-glycoprotein-mediated renal tubular secretion of digoxin. Oral *neomycin* may reduce serum-digoxin concentrations by reducing digoxin absorption.

Rifampicin may reduce serum-digitoxin concentrations by inducing its metabolism (see p. 1353.2) although a study[12] in healthy subjects suggested that this reduction might rather be due to induction of intestinal P-glycoprotein. Digoxin is mainly excreted unchanged in the urine but rifampicin increased digoxin dose requirements substantially in 2 patients dependent on dialysis.[13] When rifampicin was stopped digoxin requirements fell by about 50%.

1. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; **305:** 827–8.
2. Lindenbaum J, *et al.* Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med* 1981; **305:** 789–94.
3. Maxwell DL, *et al.* Digoxin toxicity due to interaction of digoxin with erythromycin. *BMJ* 1989; **298:** 572.
4. Morton MR, Cooper JW. Erythromycin-induced digoxin toxicity. *DICP Ann Pharmacother* 1989; **23:** 668–70.
5. Ten Eick AP, *et al.* Possible drug interaction between digoxin and azithromycin in a young child. *Clin Drug Invest* 2000; **20:** 61–64.
6. Midoneck SR, Etingin OR. Clarithromycin-related toxic effects of digoxin. *N Engl J Med* 1995; **333:** 1505.
7. Nawarskas JJ, *et al.* Digoxin toxicity secondary to clarithromycin therapy. *Ann Pharmacother* 1997; **31:** 864–6.
8. Laberge P, Martineau P. Clarithromycin-induced digoxin intoxication. *Ann Pharmacother* 1997; **31:** 999–1002.
9. Corallo CE, Rogers IR. Roxithromycin-induced digoxin toxicity. *Med J Aust* 1996; **165:** 433–4.
10. Gomes T, *et al.* Macrolide-induced digoxin toxicity: a population-based study. *Clin Pharmacol Ther* 2009; **86:** 383–6.
11. Wakasugi H, *et al.* Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. *Clin Pharmacol Ther* 1998; **64:** 123–8.
12. Greiner B, *et al.* The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J Clin Invest* 1999; **104:** 147–53.
13. Gault H, *et al.* Digoxin-rifampin interaction. *Clin Pharmacol Ther* 1984; **35:** 750–4.

Antidepressants. In a study[1] in healthy subjects, use of digoxin with an extract of *St John's wort* for 10 days resulted in a significant decrease in the plasma-digoxin concentration. It was suggested that the interaction might be due to induction of the P-glycoprotein transporter. In a study[2] in healthy male subjects, *nefazodone* increased steady-state plasma-digoxin concentrations by about 30% but no adverse or clinical effects were associated with the increase. However, due to the narrow therapeutic range of digoxin, it was suggested that plasma-digoxin concentrations should be monitored in patients also given nefazodone. Similar recommendations have been made for *trazodone*.

Digoxin toxicity developed in a patient shortly after starting *paroxetine* and was associated with increased serum-digoxin concentrations.[3] However, the role of paroxetine in the reaction has been queried.[4,5]

1. Johne A, *et al.* Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). *Clin Pharmacol Ther* 1999; **66:** 338–45.
2. Dockens RC, *et al.* Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. *J Clin Pharmacol* 1996; **36:** 160–7.
3. Yasui-Furukori N, Kaneko S. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **367:** 788.
4. Bateman DN, *et al.* Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **368:** 1962–3.
5. Hallberg P, Melhus H. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **368:** 1963.

Antidiabetics. Subtherapeutic plasma-digoxin concentrations were noted in a diabetic woman receiving *acarbose* and digoxin.[1] The plasma concentration of digoxin increased to a therapeutic level when acarbose was stopped. A study[2] in healthy subjects suggested that the interaction was due to inhibition of the absorption of digoxin by acarbose.

Canagliflozin may cause a minor increase in digoxin exposure.

1. Serrano JS, *et al.* A possible interaction of potential clinical interest between digoxin and acarbose. *Clin Pharmacol Ther* 1996; **60:** 589–92.
2. Miura T, *et al.* Impairment of absorption of digoxin by acarbose. *J Clin Pharmacol* 1998; **38:** 654–7.

Antiepileptics. *Phenytoin* caused a marked decrease in steady-state serum-digoxin concentrations when given with digoxin and acetyldigoxin to 6 healthy subjects for 7 days.[1] Total digoxin clearance was increased by an average of 27% and elimination half-life was reduced by an average of 30%. This interaction may be more likely with digitoxin, since digitoxin is more dependent on the liver for elimination.

A brief report of an open study[2] in 12 subjects indicated a slight but significant decrease in digoxin bioavailability when *topiramate* was also given, although half-life and renal clearance of digoxin did not appear to be affected.

1. Rameis H. On the interaction between phenytoin and digoxin. *Eur J Clin Pharmacol* 1985; **29:** 49–53.
2. Liao S, Palmer M. Digoxin and topiramate drug interaction study in male volunteers. *Pharm Res* 1993; **10** (suppl): S405.

Antifungals. Two men given *itraconazole* while receiving digoxin developed signs and symptoms of digoxin toxicity and elevated serum-digoxin concentrations.[1,2] A further case report[3] suggested that the interaction was due to a reduction in the renal clearance of digoxin when itraconazole was given.

Additive adverse effects due to hypokalaemia may occur when digoxin is given with *amphotericin B*.

1. Rex J. Itraconazole–digoxin interaction. *Ann Intern Med* 1992; **116:** 525.
2. Alderman CP, Jersmann HPA. Digoxin–itraconazole interaction. *Med J Aust* 1993; **159:** 838–9.
3. Alderman CP, Allcroft PD. Digoxin-itraconazole interaction: possible mechanisms. *Ann Pharmacother* 1997; **31:** 438–40.

Antimalarials. In 6 subjects given *quinine sulfate,* total body clearance of digoxin after an intravenous dose was decreased by 26%, mainly through a reduction in nonrenal clearance.[1] Increased urinary excretion of digoxin was consistent with alterations in the nonrenal clearance of digoxin and might be due to changes in the metabolism or biliary secretion of digoxin. Quinine increased the mean elimination half-life of digoxin from 34.2 to 51.8 hours but did not consistently change the volume of distribution.

An increase in the plasma-digoxin concentration, but without symptoms of toxicity, was noted in 2 women given *hydroxychloroquine* (for rheumatoid arthritis) in addition to long-term digoxin therapy.[2]

1. Wandell M, *et al.* Effect of quinine on digoxin kinetics. *Clin Pharmacol Ther* 1980; **28:** 425–30.
2. Leden I. Digoxin–hydroxychloroquine interaction? *Acta Med Scand* 1982; **211:** 411–12.

Antineoplastics. A study[1] in patients undergoing antineoplastic therapy found that the absorption of digoxin from tablets was reduced by an average of 46.5%, whereas that of digoxin from liquid-filled capsules was not significantly changed. Another study[2] in similar patients found that the steady-state concentration of digoxin after giving acetyldigoxin was reduced, but that digitoxin concentrations were maintained. It was suggested that the interaction was due to reduced absorption of digitalis glycosides through the damaged gastrointestinal mucosa and that liquid-filled capsules or digitoxin might be preferred in these patients.

Licensed product information for *lenalidomide* states that it may increase plasma exposure of digoxin and recommends that digoxin concentrations should be monitored.

1. Bjornsson TD, *et al.* Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. *Clin Pharmacol Ther* 1986; **39:** 25–8.
2. Kuhlmann J. Inhibition of digoxin absorption but not of digitoxin during cytostatic drug therapy. *Arzneimittelforschung* 1982; **32:** 698–704.

Antithyroid drugs. Reduced peak serum-digoxin concentrations were noted in 9 of 10 healthy subjects after a single oral dose of *carbimazole* although conversely in the tenth subject digoxin concentrations rose.[1] Caution is also needed since changes in thyroid function may independently affect sensitivity to digoxin (see Precautions, p. 1355.2).

1. Rao BR, *et al.* Influence of carbimazole on serum levels and haemodynamic effects of digoxin. *Clin Drug Invest* 1997; **13:** 350–4.

Antivirals. A woman stabilised on digoxin and tolerating lamivudine, indinavir and stavudine for HIV infection, developed symptoms of digoxin toxicity 3 days after *ritonavir* was added to her treatment.[1] It was suggested that the interaction might be due to inhibition of the P-glycoprotein transporter system by ritonavir. A pharmacokinetic study[2] showing significant inhibition of renal digoxin clearance by ritonavir seemed to support this hypothesis.

1. Phillips EJ, *et al.* Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein? *AIDS* 2003; **17:** 1577–8.
2. Ding R, *et al.* Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. *Clin Pharmacol Ther* 2004; **76:** 73–84.

Benzodiazepines. Raised serum-digoxin concentrations have been reported in patients also taking *diazepam*[1] or *alprazolam*.[2,3] The clearance of digoxin was reduced by these benzodiazepines.

1. Castillo-Ferrando JR, *et al.* Digoxin levels and diazepam. *Lancet* 1980; **ii:** 368.
2. Tollefson G, *et al.* Alprazolam-related digoxin toxicity. *Am J Psychiatry* 1984; **141:** 1612–14.
3. Guven H, *et al.* Age-related digoxin-alprazolam interaction. *Clin Pharmacol Ther* 1993; **54:** 42–4.

Beta$_2$ agonists. A single intravenous[1,2] or oral[3] dose of *salbutamol* has been reported to decrease steady-state serum-digoxin concentrations by up to 16% and 22% respectively in healthy subjects. Although salbutamol had no significant effect on the concentration of digoxin in skeletal muscle, it was considered that increased binding to skeletal muscle could explain the interaction. Beta$_2$ agonists such as salbutamol can also cause hypokalaemia which may increase susceptibility to digoxin-induced arrhythmias.

1. Edner M, Jogestrand T. Effect of salbutamol on digoxin concentration in serum and skeletal muscle. *Eur J Clin Pharmacol* 1989; **36:** 235–8.
2. Edner M, *et al.* Effect of salbutamol on digoxin pharmacokinetics. *Eur J Clin Pharmacol* 1992; **42:** 197–201.
3. Edner M, Jogestrand T. Oral salbutamol decreases serum digoxin concentration. *Eur J Clin Pharmacol* 1990; **38:** 195–7.

Beta blockers. Beta blockers may increase the risk of heart block and bradycardia with digoxin. In addition, *carvedilol* has been reported[1-3] to increase plasma concentrations of digoxin, although the effect is generally small and probably not clinically significant. However, a study[4] in 8 children (aged 2 weeks to 7.8 years) found that the clearance of digoxin was about halved by carvedilol and 2 of the children developed digoxin toxicity. An increase in digoxin bioavailability has also been reported with *talinolol*.[5]

1. Grunden JW, *et al.* Augmented digoxin concentrations with carvedilol dosing in mild-moderate heart failure. *Am J Ther* 1994; **1:** 157–161.
2. Wermeling DP, *et al.* Effects of long-term oral carvedilol on the steady-state pharmacokinetics of oral digoxin in patients with mild to moderate hypertension. *Pharmacotherapy* 1994; **14:** 600–6.
3. De Mey C, *et al.* Carvedilol increases the systemic bioavailability of oral digoxin. *Br J Clin Pharmacol* 1990; **29:** 486–90.
4. Ratnapalan S, *et al.* Digoxin-carvedilol interactions in children. *J Pediatr* 2003; **142:** 572–4.
5. Westphal K, *et al.* Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. *Clin Pharmacol Ther* 2000; **68:** 6–12.

Calcium-channel blockers. Studies on interactions between digoxin and calcium-channel blockers appear to show that *verapamil* increases plasma-digoxin concentrations[1-3] by up to 70%. The effect of *nifedipine* is not as clear. Although it has been reported[1] to produce a 45% increase in plasma-digoxin concentrations, other studies[4,5] have reported little or no increase and the interaction is unlikely to be of clinical significance for most patients. Studies on the interaction between digoxin or metildigoxin and *diltiazem* have also produced conflicting results. Increases in plasma-digoxin concentrations of 20% and up to 59% have been reported[6,7] and an increase in metildigoxin concentrations[7] of up to 51%. However, other studies[8,9] have shown no diltiazem-induced change in digoxin pharmacokinetics or plasma concentration. *Bepridil*,[10] *gallopamil*,[1] *nisoldipine*,[11] and *nitrendipine*[12] have all been reported to increase plasma-digoxin concentrations. Bepridil increased the concentration by 34% and it was recommended that patients given this combination be monitored carefully. *Felodipine*[13,14] and *isradipine*[3] have both been reported to increase peak serum-digoxin concentrations, but steady-state digoxin concentrations were not affected and the interactions were unlikely to be of clinical relevance.

The mechanism of interaction between calcium-channel blockers and digoxin is not completely understood but appears to be related to decreased renal and nonrenal clearance of digoxin. The pharmacodynamic effects of digoxin and calcium-channel blockers may also be additive.

1. Belz GG, *et al.* Interaction between digoxin and calcium antagonists and antiarrhythmic drugs. *Clin Pharmacol Ther* 1983; **33:** 410–17.
2. Pedersen KE, *et al.* Influence of verapamil on the inotropism and pharmacokinetics of digoxin. *Eur J Clin Pharmacol* 1983; **25:** 199–206.
3. Rodin SM, *et al.* Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. *Clin Pharmacol Ther* 1988; **43:** 668–72.
4. Schwartz JB, Migliore PJ. Effect of nifedipine on serum digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1984; **36:** 19–24.
5. Kleinbloesem CH, *et al.* Interactions between digoxin and nifedipine at steady state in patients with atrial fibrillation. *Ther Drug Monit* 1985; **7:** 372–6.
6. Rameis H, *et al.* The diltiazem-digoxin interaction. *Clin Pharmacol Ther* 1984; **36:** 183–9.
7. Oyama Y, *et al.* Digoxin-diltiazem interaction. *Am J Cardiol* 1984; **53:** 1480–1.
8. Beltrami TR, *et al.* Lack of effects of diltiazem on digoxin pharmacokinetics. *J Clin Pharmacol* 1985; **25:** 390–2.
9. Elkayam U, *et al.* Effect of diltiazem on renal clearance and serum concentration of digoxin in patients with cardiac disease. *Am J Cardiol* 1985; **55:** 1393–5.
10. Belz GG, *et al.* Digoxin and bepridil: pharmacokinetic and pharmacodynamic interactions. *Clin Pharmacol Ther* 1986; **39:** 65–71.
11. Kirch W, *et al.* Influence of nisoldipine on haemodynamic effects and plasma levels of digoxin. *Br J Clin Pharmacol* 1986; **22:** 155–9.
12. Kirch W, *et al.* Nitrendipine increases digoxin plasma levels dose dependently. *J Clin Pharmacol* 1986; **26:** 553.
13. Rehnqvist N, *et al.* Pharmacokinetics of felodipine and effect on digoxin plasma levels in patients with heart failure. *Drugs* 1987; **34** (suppl 3): 33–42.
14. Dunselman PHJM, *et al.* Digoxin-felodipine interaction in patients with congestive heart failure. *Eur J Clin Pharmacol* 1988; **35:** 461–5.

Diuretics. *Amiloride* increased renal clearance of digoxin and reduced the extrarenal digoxin clearance in 6 healthy subjects after a single intravenous dose of digoxin.[1] Amiloride also inhibited the digoxin-induced positive inotropic effect, but the clinical implications in cardiac patients are unknown. A further study[2] failed to confirm this effect.

Spironolactone and its metabolites have been reported to interfere with serum-digoxin determinations by radioimmunoassay or fluorescence-polarisation immunoassay resulting in falsely elevated measurements.[3,4] The interference with digoxin assays is neither consistent nor predictable and falsely low readings have also been reported.[5] Serum-digoxin concentrations should be interpreted with caution when digoxin is given with spironolactone or *canrenoate*, especially since spironolactone has also been reported to decrease digoxin clearance by a median of 26% resulting in a true increase in the serum-digoxin concentration.[6]

Diuretic therapy with *triamterene* in association with a thiazide or loop diuretic increased the mean serum-digoxin concentration; this interaction was considered unlikely to be of clinical importance, except perhaps in patients with renal impairment.[7]

1. Waldorff S, *et al.* Amiloride-induced changes in digoxin dynamics and kinetics: abolition of digoxin-induced inotropism with amiloride. *Clin Pharmacol Ther* 1981; **30:** 172–6.
2. Richter JP, *et al.* The acute effects of amiloride and potassium canrenoate on digoxin-induced positive inotropism in healthy volunteers. *Eur J Clin Pharmacol* 1993; **45:** 195–6.
3. Paladino JA, *et al.* Influence of spironolactone on serum digoxin concentration. *JAMA* 1984; **251:** 470–1.
4. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12:** 82–4.
5. Steimer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354:** 1176–7.
6. Waldorff S, *et al.* Spironolactone-induced changes in digoxin kinetics. *Clin Pharmacol Ther* 1978; **24:** 162–7.
7. Impivaara O, Iisalo E. Serum digoxin concentrations in a representative digoxin-consuming adult population. *Eur J Clin Pharmacol* 1985; **27:** 627–32.

Gastrointestinal drugs. Some gastrointestinal drugs can affect the absorption of digoxin by binding to it or by changing gastrointestinal motility. The problem has often been related to the bioavailability of the digoxin formulation and appears to be less important with currently used preparations. Some *antacids*,[1,2] particularly liquid formulations, and *adsorbents*[1] such as kaolin-pectin, can reduce the absorption of digoxin from the gastrointestinal tract and doses should probably be separated by at least 2 hours. *Activated charcoal*, and *ion-exchange resins* such as colestyramine and colestipol, also reduce digoxin absorption. *Sucralfate*[3] may also reduce the absorption of digoxin.

Omeprazole, and possibly other gastric acid inhibitors, may reduce the gastrointestinal metabolism and enhance the absorption of unchanged digoxin,[4] resulting in small increases in digoxin plasma concentrations that are unlikely to be clinically significant in most patients,[5] although toxicity was reported in a woman whose digoxin concentration increased from 1.1 nanograms/mL to 3.9 nanograms/mL one month after starting omeprazole.[6]

Drugs that increase gastrointestinal motility can reduce the absorption of digoxin, especially if digoxin is given as a slowly dissolving formulation. Reduced absorption of digoxin has occurred when digoxin and *metoclopramide* have been given together,[7] and a similar effect has been reported with *cisapride*[8] and *tegaserod*.[9] Conversely, *anticholinergics* reduce motility, and propantheline has increased digoxin absorption.

Sulfasalazine has been found to impair the absorption of digoxin and to reduce the serum-digoxin concentration,[10] but the mechanism is unclear.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; **15:** 227–44.
2. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.
3. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; **25:** 745–6.
4. Cohen AF, *et al.* Influence of gastric acidity on the bioavailability of digoxin. *Ann Intern Med* 1991; **115:** 540–5.
5. Oosterhuis B, *et al.* Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 1991; **32:** 569–72.
6. Kiley CA, *et al.* Omeprazole-associated digoxin toxicity. *South Med J* 2007; **100:** 400–2.
7. Johnson BF, *et al.* Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984; **36:** 724–30.
8. Kubler PA, *et al.* Possible interaction between cisapride and digoxin. *Ann Pharmacother* 2001; **35:** 127–8.
9. Zhou H, *et al.* The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. *J Clin Pharmacol* 2001; **41:** 1131–9.
10. Juhl RP, *et al.* Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* 1976; **20:** 387–94.

Ginseng. Varieties of ginseng may interfere with plasma-digoxin assays (see under Precautions, p. 1355.3).

Immunosuppressants. Increased serum-digoxin concentrations with symptoms of toxicity have been reported in patients when *ciclosporin* was added to their digoxin therapy.[1,2]

1. Dorian P, *et al.* Digoxin-cyclosporine interaction: severe digitalis toxicity after cyclosporine treatment. *Clin Invest Med* 1988; **ii:** 108–12.

2. Robieux I, *et al.* The effects of cardiac transplantation and cyclosporine therapy on digoxin pharmacokinetics. *J Clin Pharmacol* 1992; **32:** 338–43.

Lipid regulating drugs. Small increases in plasma-digoxin concentrations have been reported with some *statins*, although the clinical significance is not clear. *Atorvastatin* at doses of 80 mg, but not of 10 mg, has been shown[1] to increase plasma-digoxin concentrations by about 20%. This may be due to the inhibition of P-glycoprotein-mediated secretion of digoxin in the intestine by atorvastatin.

1. Boyd RA, *et al.* Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol* 2000; **40:** 91–98.

Neuromuscular blockers. *Pancuronium* or *suxamethonium* may interact with digitalis glycosides resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.[1]

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; **58:** 567–9.

NSAIDs. An increase in serum-digoxin concentration has been reported with *aspirin*, *ibuprofen*, *indometacin*, *fenbufen*, and *diclofenac*.[1] Potentially toxic serum-digoxin concentrations occurred in preterm infants[2] with patent ductus arteriosus receiving digoxin when given indometacin orally in a mean total dose of 320 micrograms/kg; it was recommended that the dose of digoxin should be halved initially if indometacin is also given. (For the possible effect of digoxin on indometacin see Half-life, under Pharmacokinetics of Indometacin, p. 74.1.) Lack of increase in serum-digoxin concentrations has also been reported with aspirin or indometacin, as well as with *ketoprofen*, and *tiaprofenic acid*,[1] and also with *etoricoxib*[3] and *rofecoxib*,[4] but some of these studies were in healthy subjects and it is advised that digoxin therapy be monitored carefully whenever any NSAID is started or stopped in digitalised patients.

1. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1990; **19:** 44–66.
2. Koren G, *et al.* Effects of indomethacin on digoxin pharmacokinetics in preterm infants. *Pediatr Pharmacol* 1984; **4:** 25–30.
3. Schwartz JI, *et al.* Evaluation of the pharmacokinetics of digoxin in healthy subjects receiving etoricoxib. *Br J Clin Pharmacol* 2008; **66:** 811–17.
4. Schwartz JI, *et al.* Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* 2001; **41:** 107–112.

Penicillamine. Digoxin concentrations can be reduced by penicillamine. One manufacturer of penicillamine (*Alliance, UK*) recommends that digoxin should not be given within 2 hours of penicillamine, as oral absorption of digoxin may be reduced. However, serum-digoxin concentrations were reduced when an oral dose of penicillamine was given either 2 or 16 hours after an oral dose of digoxin, or 2 hours after an intravenous dose,[1] indicating that the interaction is not entirely related to reduced oral absorption of digoxin. Reductions in the serum-digoxin concentration were also noted in children on oral digoxin given oral penicillamine.[2]

1. Moezzi B, *et al.* The effect of penicillamine on serum digoxin levels. *Jpn Heart J* 1978; **19:** 366–75.
2. Moezzi B, *et al.* Reversal of digoxin-induced changes in erythrocyte electrolyte concentrations by penicillamine in children. *Jpn Heart J* 1980; **21:** 335–9.

Urological drugs. *Mirabegron*, a beta$_3$-adrenoceptor agonist, was reported to increase the peak plasma concentration and AUC of digoxin by 29 and 27%, respectively; therefore the lowest initial dose of digoxin should be given to patients who are starting concomitant therapy and serum-digoxin concentrations monitored.

Vasopressin receptor antagonists. The vasopressin receptor antagonists *conivaptan* and *tolvaptan* can reduce the clearance, and subsequently increase concentrations, of digoxin.

Pharmacokinetics

The absorption of digoxin from the gastrointestinal tract is variable depending upon the formulation used. About 70% of a dose is absorbed from tablets which comply with BP or USP specifications, 80% is absorbed from an elixir, and over 90% is absorbed from liquid-filled soft gelatin capsules. The generally accepted therapeutic plasma concentration range is 0.5 to 2.0 nanograms/mL but there is considerable interindividual variation. Digoxin has a large volume of distribution and is widely distributed in tissues, including the heart, brain, erythrocytes, and skeletal muscle. The concentration of digoxin in the myocardium is considerably higher than in plasma. From 20 to 30% is bound to plasma proteins. Digoxin has been detected in CSF and breast milk; it also crosses the placenta. It has an elimination half-life of 1.5 to 2 days.

Digoxin is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion; reabsorption also occurs. Extensive metabolism has been reported in a minority of patients (see under Metabolism and Excretion, below). Excretion of digoxin is proportional to the glomerular filtration rate. After intravenous injection 50 to 70% of the dose is excreted unchanged. Digoxin is not removed from the body by dialysis, and only small amounts are removed by exchange transfusion and during cardiopulmonary bypass.

Reviews of the clinical pharmacokinetics of digoxin.

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; **2:** 1–16.
2. Aronson JK. Clinical pharmacokinetics of digoxin 1980. *Clin Pharmacokinet* 1980; **5:** 137–49.
3. Mooradian AD. Digitalis: an update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. *Clin Pharmacokinet* 1988; **15:** 165–79.

Absorption. Studies in 6 healthy subjects found that food decreased the rate but not the extent of absorption of digoxin.[1]

1. Johnson BF, *et al.* Effect of a standard breakfast on digoxin absorption in normal subjects. *Clin Pharmacol Ther* 1978; **23:** 315–19.

Bioavailability. Large variations in the content, disintegration, and dissolution of solid dosage forms of digoxin preparations have led to large variations in plasma concentrations from different proprietary preparations. Other factors involved in varying bioavailability include the pharmaceutical formulation and presentation (capsules, solution, or tablets), particle size, and biological factors. Serious problems occurred in the UK[1] in 1972 and in Israel[2] in 1975 after changes in the manufacturing procedure for *Lanoxin* led to a twofold increase in bioavailability.

1. Anonymous. Therapeutic non-equivalence. *BMJ* 1972; **3:** 599–600.
2. Danon A, *et al.* An outbreak of digoxin intoxication. *Clin Pharmacol Ther* 1977; **21:** 643–6.

Distribution and protein binding. Digoxin has been reported to be 5 to 60% bound to plasma proteins,[1] depending partly on the method of measurement, but the figure is usually around 20%. Protein binding is reduced in patients undergoing haemodialysis; mean reductions of about 8 and 10% have been reported.[1,2] Injection of heparin has produced a similar reduction.[2]

Digoxin is widely distributed to tissues and serum-digoxin concentrations have been reported to be increased during immobilisation[3] and decreased during exercise[4,5] due to changes in binding to tissues such as skeletal muscle.

1. Storstein L. Studies on digitalis V: the influence of impaired renal function, hemodialysis, and drug interaction on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; **20:** 6–14.
2. Storstein L, Janssen H. Studies on digitalis VI: the effect of heparin on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; **20:** 15–23.
3. Pedersen KE, *et al.* Effects of physical activity and immobilization on plasma digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1983; **34:** 303–8.
4. Joreteg T, Jogestrand T. Physical exercise and digoxin binding to skeletal muscle: relation to exercise intensity. *Eur J Clin Pharmacol* 1983; **25:** 585–8.
5. Joreteg T, Jogestrand T. Physical exercise and binding of digoxin to skeletal muscle—effect of muscle activation frequency. *Eur J Clin Pharmacol* 1984; **27:** 567–70.

The elderly. For references to alterations in the pharmacokinetics of digoxin in the elderly, see under Uses and Administration, p. 1354.2.

Infants and neonates. Digoxin has been widely used in the treatment of cardiac disorders in neonates and infants and its pharmacokinetics in this age group have been reviewed.[1,2] In full-term neonates or infants, 80 to 90% of a dose of digoxin given orally in liquid form is absorbed, with peak plasma concentrations occurring within 30 to 120 minutes. The rate of absorption may be slower in preterm and low birth-weight infants, with peak concentrations at 90 to 180 minutes, and may be significantly reduced in severe heart failure and in malabsorption syndromes. After digoxin is given intravenously there is a rapid distribution phase with an apparent half-life of 20 to 40 minutes followed by a slower exponential decay of plasma concentrations. In full-term neonates, digoxin has an apparent volume of distribution of 6 to 10 litres/kg. Low birth-weight infants have a volume of distribution of 4.3 to 5.7 litres/kg while in older infants the volume may range from 10 to 22 litres/kg which is 1.5 to 2 times reported adult values. This large volume of distribution in full-term neonates and infants is thought to be due to increased tissue binding, a larger extracellular fluid volume, and slightly lower plasma protein binding.

The apparent plasma half-life in healthy and sick neonates is generally very long and may range from 20 to 70 hours in full-term neonates or from 40 to 180 hours in preterm neonates. Digoxin is eliminated at a considerably faster rate in infants than in neonates and, in parallel with maturation of kidney function, a marked increase in clearance rate is usually seen between the second and third month of life. The large apparent volume of distribution, higher clearance values, and greater concentrations of digoxin in the myocardial tissue and red cells of infants might justify the traditional assumption that infants tolerate digoxin better than adults and that higher doses are consequently needed in infants. However, studies have shown that in infants, as in adults, toxic signs become evident at plasma-digoxin concentrations above 3 nanograms/mL and that the therapeutic range may be 1.5 to 2 nanograms/mL.

1. Morselli PL, *et al.* Clinical pharmacokinetics in newborns and infants: age-related differences and therapeutic implications. *Clin Pharmacokinet* 1980; **5:** 485–527.
2. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface. *Clin Pharmacokinet* 1988; **14:** 189–216 (part I) and 261–86 (part II).

Metabolism and excretion. Although digoxin is reported to be excreted mainly unchanged in the urine there is evidence to suggest that metabolism may sometimes be extensive. Metabolites that have been detected in the urine include digoxigenin, dihydrodigoxigenin, the mono- and bisdigitoxosides of digoxigenin, and dihydrodigoxin. Digoxigenin mono- and bisdigitoxosides are known to be cardioactive whereas dihydrodigoxin is probably much less active than digoxin.[1]

In about 10% of patients there is considerable reduction to cardio-inactive metabolites, chiefly dihydrodigoxin, and 40% or more of a dose may be excreted in the urine as dihydrodigoxin.[2-4] Bacterial flora in the gastrointestinal tract appear to be responsible for this metabolism and antibacterials can reduce the process. Oral digoxin formulations with a high bioavailability are mostly absorbed in the stomach and upper small intestine and little digoxin is available in the lower intestine for bacterial degradation to dihydrodigoxin.[4]

The excretion of digoxin is thought to be mediated by the efflux pump, P-glycoprotein,[5] which transports its substrates out of the cell. This may be the basis for some interactions hitherto poorly understood,[6] although the hypothesis has been questioned.[7]

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; **2:** 1–16.
2. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; **305:** 827–8.
3. Rund DG, *et al.* Decreased digoxin cardioinactive-reduced metabolites after administration of an encapsulated liquid concentrate. *Clin Pharmacol Ther* 1983; **34:** 738–43.
4. Lofts F, *et al.* Digoxin metabolism to reduced products: clinical significance. *Br J Clin Pharmacol* 1986; **21:** 600P.
5. Tanigawara Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit* 2000; **22:** 137–40.
6. Fromm MF. P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. *Int J Clin Pharmacol Ther* 2000; **38:** 69–74.
7. Chiou WL, *et al.* A comprehensive account on the role of efflux transporters in the gastrointestinal absorption of 13 commonly used substrate drugs in humans. *Int J Clin Pharmacol Ther* 2001; **39:** 93–101.

Renal impairment. For references to alterations in the pharmacokinetics of digoxin in patients with renal impairment, see under Uses and Administration, p. 1354.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cardiogoxin; Digocard-G; Lanicor; Lanoxin; ***Austral.***: Lanoxin; Sigmaxin; ***Belg.***: Lanoxin; ***Braz.***: Cardcor; Cardionil; Cimecard; Digitax†; Digobal; Digoxen; Digoxil; Valoxin; ***Canad.***: Lanoxin; Toloxin; ***China***: Ke Li (可力); ***Fr.***: Hemigoxine Nativelle; ***Ger.***: Digacin; Lanicor; Lenoxin; ***Gr.***: Lanoxin; ***Hong Kong***: Lanoxin†; ***India***: Digitran; Digosyp; Digox; Dixin; Geoxin; Lanoxin; ***Indon.***: Fargoxin; Lanoxin; ***Irl.***: Lanoxin; ***Israel***: Lanoxin; ***Ital.***: Eudigox; Lanoxin; ***Jpn***: Digosin; ***Malaysia***: Lanoxin; ***Mex.***: Bioxalyt; Lanoxin; Mapluxin; Valvulan; ***Neth.***: Lanoxin; ***Norw.***: Lanoxin; ***NZ***: Lanoxin; ***Philipp.***: Cardioxin; Lanox; Lanoxin; ***Port.***: Lanoxin; ***S.Afr.***: Lanoxin; Purgoxin; ***Singapore***: Lanoxin; ***Spain***: Lanacordin; ***Swed.***: Lanoxin; ***Thai.***: Cardial; Grexin; Lanoxin; Toloxin; ***UK***: Lanoxin; ***USA***: Lanoxin; ***Venez.***: Lanicor.

Pharmacopoeial Preparations

BP 2014: Digoxin Injection; Digoxin Tablets; Paediatric Digoxin Injection; Paediatric Digoxin Oral Solution;
USP 36: Digoxin Elixir; Digoxin Injection; Digoxin Tablets.

Dihydralazine Sulfate *(BANM, rINNM)*

Dihidralazina, sulfato de; Dihidralazino sulfatas, hidratuotas; Dihidralazin-szulfát-hidrát; Dihydralatsiinisulfaatti, hydratoitu; Dihydralazine, Sulfate de; Dihydralazine (sulfate de) hydraté; Dihydralazine Sulphate; Dihydralazini Sulfas; Dihydralazini sulfas hydricus; Dihydralazin-sulfát; Dihydralazinsulfat, hydratiserat; Dihydralazinum Sulfuricum; Dihydralazyny siarczan; Dihydrallazine Sulphate; Sulfato de dihidralazina; Дигидралазина Сульфат.

Phthalazine-1,4-diyldihydrazine sulfate hemipentahydrate.

$C_8H_{10}N_6.H_2SO_4.2½H_2O$=333.3

CAS — 484-23-1 (dihydralazine); 7327-87-9 (dihydralazine sulfate).

ATC — C02DB01.
ATC Vet — QC02DB01.
UNII — 1C2B1W91NK.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Dihydralazine Sulfate, Hydrated). A white or slightly yellow crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol. It dissolves in dilute mineral acids.

Profile

Dihydralazine is a vasodilator with actions and uses similar to those of hydralazine (p. 1401.2). It is given orally as the sulfate. Dihydralazine sulfate hemipentahydrate 14.45 mg is equivalent to about 12.5 mg of anhydrous dihydralazine sulfate. In hypertension (p. 1251.1) the usual initial dose is the equivalent of 12.5 mg of anhydrous dihydralazine sulfate twice daily and the maximum recommended dose is 50 mg twice daily. Higher doses have been used in the management of heart failure.

Other salts of dihydralazine that have been used in oral preparations include the hydrochloride and the tartrate. The mesilate is given by injection.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dihydralazine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nepresol†; ***Fr.***: Nepressol; ***Ger.***: Depressan†; Nepresol; ***Gr.***: Nepresol; ***Hung.***: Depressan; ***India***: Apresol; Nepresol; ***Thai.***: Nepresol†.

Multi-ingredient Preparations. ***China***: Fufang Lixueping (复方利血平); No 0 (0号); ***Ger.***: Triniton†; ***India***: Adelphane-Esidrex; Adelphane; Beptazine-H†; Beptazine†; Genophane; ***Indon.***: Dellasidrex†; ***Rus.***: Adelphane-Esidrex (Адельфан-эзидрекс); Triresid K (Трирезид К)†; ***Turk.***: Adelphan-Esidrex†; Adelphan†; ***Ukr.***: Adelphane-Esidrex (Адельфан-Эзидрекс).

Di-isopropylammonium Dichloroacetate

Diisopropilamina, dicloroacetato de; Di-isopropylamine Dichloroacetate; Di-isopropylamine Dichloroethanoate; DIPA-DCA.

$C_8H_{17}Cl_2NO_2$=230.1
CAS — 660-27-5.
UNII — BA6QDP0R4E.

Profile

Di-isopropylammonium dichloroacetate is a vasodilator that has been given in peripheral and cerebral vascular disorders. Preparations containing it have sometimes been described as 'pangamic acid' (p. 2582.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bo Lang (博朗); Ke Rui Te (克瑞特); Ya Pu Yi (雅普宜); ***Israel***: Kit For Tc-99 Labeled DIPA; ***Mex.***: Ditrei.

Multi-ingredient Preparations. ***China***: Compound Diisopropylamine Dichloroacetate (复方二氯醋酸二异丙胺); Er Qi (尔祺); ***Spain***: Vitaber A E.

Dilazep Hydrochloride *(rINNM)*

Asta C-4898; Dilazep, Chlorhydrate de; Dilazep, hidrocloruro de; Dilazepi Hydrochloridum; Hidrocloruro de dilazep; Дилазепа Гидрохлорид.

Perhydro-1,4-diazepin-1,4-diylbis(trimethylene 3,4,5-trimethoxybenzoate) dihydrochloride.

$C_{31}H_{44}N_2O_{10}$,2HCl=677.6
CAS — 35898-87-4 (dilazep); 20153-98-4 (dilazep hydrochloride).
ATC — C01DX10.
ATC Vet — QC01DX10.

Pharmacopoeias. *Jpn* includes the monohydrate.

Profile

Dilazep hydrochloride is an oral vasodilator that is used in ischaemic heart disease at a dose of 50 mg three times daily, and in the treatment of proteinuria at a dose of 100 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Cormelian; ***Jpn***: Comelian.

Diltiazem Hydrochloride

(BANM, USAN, rINNM)

CRD-401; Diltiatseemihydrokloridi; Diltiazem, chlorhydrate de; Diltiazem, hidrocloruro de; Diltiazem Hidroklorür; Diltiazem hydrochlorid; Diltiazem-hidroklorid; Diltiazemhydrochlorid; Diltiazemhydroklorid; Diltiazemi Hydrochloridum; Diltiazemo hidrochloridas; Diltiazemu chlorowodorek; Hidrocloruro de diltiazem; Latiazem Hydrochloride; MK-793 (diltiazem malate); Дилтиазема Гидрохлорид.

(+)-*cis*-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride; (2*S*,3*S*)-5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate hydrochloride.

$C_{22}H_{26}N_2O_4S$,HCl=451.0
CAS — 42399-41-7 (diltiazem); 33286-22-5 (diltiazem hydrochloride); 144604-00-2 (diltiazem malate).
ATC — C08DB01.
ATC Vet — QC08DB01.
UNII — OLH94387TE.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Diltiazem Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in dichloromethane, and in methyl alcohol; slightly soluble in dehydrated alcohol. The pH of a 1% solution in water is 4.3 to 5.3. Store in airtight containers. Protect from light.

USP 36: (Diltiazem Hydrochloride). A white, odourless, crystalline powder, or small crystals. Freely soluble in water, in chloroform, in formic acid, and in methyl alcohol; sparingly soluble in dehydrated alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Uses and Administration

Diltiazem is a benzothiazepine calcium-channel blocker (p. 1244.2) and class IV antiarrhythmic (p. 1243.1). It is a peripheral and coronary vasodilator with limited negative inotropic activity but its vasodilator properties are less marked than those of the dihydropyridine calcium-channel blocker nifedipine (p. 1447.2). Unlike nifedipine, diltiazem inhibits cardiac conduction, particularly at the sino-atrial and atrioventricular nodes.

Diltiazem hydrochloride is given orally in the management of angina pectoris (p. 1254.3) and hypertension (p. 1251.1). In some countries it is available for intravenous use in the treatment of various cardiac arrhythmias (atrial fibrillation or flutter and paroxysmal supraventricular tachycardia) (p. 1266.1). It has also been used topically in the management of anal fissure (see below).

The variety of formulations means that dosage is dependent on the preparation used. Reduced doses may be required in the elderly or those with renal or hepatic impairment (see below).

In **angina pectoris** an initial dose is 60 mg orally three times daily (or 30 mg four times daily in the USA), increased if necessary to 360 mg daily; up to 480 mg daily has sometimes been given. Formulations suitable for once- or twice-daily use may be given in doses of 120 to 480 mg daily; up to 540 mg daily has been used.

In **hypertension** diltiazem hydrochloride may be given as modified-release capsules or tablets. Depending on the formulation, an initial dose is 90 to 120 mg twice daily, increased as required to a maximum of 360 mg daily. Formulations suitable for once-daily dosage may be given in similar daily doses, although up to 540 mg daily has been given.

In **cardiac arrhythmias** an initial dose of 250 micrograms/kg by bolus intravenous injection over 2 minutes has been suggested; a further dose of 350 micrograms/kg may be given after 15 minutes if the response is inadequate. Subsequent doses should be individualised for each patient. For those with atrial fibrillation or flutter, a continued reduction in heart rate may be achieved with an intravenous infusion of diltiazem hydrochloride after the bolus injection. An initial infusion rate of 5 to 10 mg/hour, may be increased as necessary in increments of 5 mg/hour up to a rate of 15 mg/hour. The infusion may be continued for up to 24 hours.

General reviews.

1. Buckley MM-T, *et al.* Diltiazem: a reappraisal of its pharmacological properties and therapeutic use. *Drugs* 1990; **39:** 757–806.
2. Weir MR. Diltiazem: ten years of clinical experience in the treatment of hypertension. *J Clin Pharmacol* 1995; **35:** 220–32.
3. Ezeugo U, Glasser SP. Clinical benefits versus shortcomings of diltiazem once-daily in the chronotherapy of cardiovascular diseases. *Expert Opin Pharmacother* 2009; **10:** 485–91.

Action. The haemodynamic and electrophysiological effects of diltiazem appear to resemble those of verapamil more than those of nifedipine.[1] It inhibits sino-atrial and atrioventricular nodal function in doses used clinically. The effects on sino-atrial function are more pronounced than those seen after verapamil. Diltiazem causes a decrease in the rate-pressure product indicating that decreased oxygen demand is a likely mechanism of action in relieving angina pectoris. Like verapamil, but unlike nifedipine, diltiazem does not appear to cause significant increases in coronary blood flow. The negative inotropic effect of diltiazem is presumably counteracted by afterload reduction.

1. Soward AL, *et al.* The haemodynamic effects of nifedipine, verapamil and diltiazem in patients with coronary artery disease: a review. *Drugs* 1986; **32:** 66–101.

Administration in hepatic or renal impairment. The dose of diltiazem hydrochloride may need to be reduced in patients with hepatic or renal impairment, and in the elderly. In the UK an initial oral dose of 120 mg daily is usually suggested, as a single dose or in 2 divided doses depending on the formulation. The dose may be increased cautiously, but only if the heart rate remains above 50 beats/minute.

Anorectal disorders. Topical nitrates have been commonly used in the management of chronic *anal fissure* (p. 2017.3) because of their ability to relax the anal sphincter. Calcium-channel blockers, including diltiazem, have also been used successfully. Oral diltiazem has been compared[1] with topical therapy; fewer adverse effects were reported in those given topical therapy, which also appeared to be more effective, although this did not reach statistical significance. A systematic review[2] that compared topical diltiazem 2% with topical glyceryl trinitrate found therapeutic effect and recurrence rate were similar with the two treatments, but those using diltiazem had fewer adverse effects; the use of diltiazem as a first-line drug was suggested. Diltiazem has also been tried[3] in patients with resistance to, or intolerance of, nitrates: about half of the patients were healed with diltiazem. A sustained benefit after a 6-week course of topical diltiazem 2% has been seen[4] in some (including a small number of nitrate-resistant cases) although many required further treatment during an average follow-up of 2 years.

Beneficial responses to diltiazem reported[5,6] in 2 patients with *proctalgia fugax* may have been due to smooth muscle relaxation. The resting pressure of the internal anal sphincter was decreased by a mean of 20.6% in all but 1 of 13 subjects given a single 60-mg oral dose of diltiazem.[6]

1. Jonas M, *et al.* A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.
2. Sajid MS, *et al.* The efficacy of diltiazem and glyceryltrinitrate for the medical management of chronic anal fissure: a meta-analysis. *Int J Colorectal Dis* 2008; **23:** 1–6.
3. Jonas M, *et al.* Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; **45:** 1091–5.
4. Nash GF, *et al.* The long-term results of diltiazem treatment for anal fissure. *Int J Clin Pract* 2006; **60:** 1411–13.
5. Boquet J, *et al.* Diltiazem for proctalgia fugax. *Lancet* 1986; **i:** 1493.
6. Jonard P, Essamri B. Diltiazem and internal anal sphincter. *Lancet* 1987; **i:** 754.

Cardiomyopathies. Although calcium-channel blockers should be used with caution in patients with heart failure, symptomatic improvement has been reported in patients with dilated cardiomyopathy (p. 1261.3) given diltiazem.[1]

1. Figulla HR, *et al.* Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; **94:** 346–52.

Connective tissue and muscular disorders. Subcutaneous deposition of calcium (calcinosis) can occur in several inflammatory conditions, particularly in juvenile dermatomyositis (see Polymyositis and Dermatomyositis, p. 1611.1). Treatment of calcinosis is difficult, but there have been reports of the successful use of diltiazem in children[1-3] and adults[4,5] with dermatomyositis, as well as in adults with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome,[6] scleroderma,[7] Sjögren's syndrome,[8] and lupus panniculitis.[9] Another study,[10] however, found only a limited response in patients with systemic sclerosis.

1. Oliveri MB, *et al.* Regression of calcinosis during diltiazem treatment in juvenile dermatomyositis. *J Rheumatol* 1996; **23:** 2152–5.
2. Ichiki Y, *et al.* An extremely severe case of cutaneous calcinosis with juvenile dermatomyositis, and successful treatment with diltiazem. *Br J Dermatol* 2001; **144:** 894–7.
3. Jiang X, *et al.* A case of juvenile dermatomyositis with severe calcinosis and successful treatment with prednisone and diltiazem. *Int J Dermatol* 2011; **50:** 74–7.
4. Vinen CS, *et al.* Regression of calcinosis associated with adult dermatomyositis following diltiazem therapy. *Rheumatology (Oxford)* 2000; **39:** 333–4.
5. Abdallah-Lotf M, *et al.* Regression of cutis calcinosis with diltiazem in adult dermatomyositis. *Eur J Dermatol* 2005; **15:** 102–4.
6. Palmieri GMA, *et al.* Treatment of calcinosis with diltiazem. *Arthritis Rheum* 1995; **38:** 1646–54.

7. Dolan AL, *et al.* Diltiazem induces remission of calcinosis in scleroderma. *Br J Rheumatol* 1995; **34:** 576–8.
8. Llamas-Velasco M, *et al.* Calcinosis cutis and Sjögren's syndrome. *Lupus* 2010; **19:** 762–4.
9. Morgan KW, *et al.* Calcifying lupus panniculitis in a patient with subacute cutaneous lupus erythematosus: response to diltiazem and chloroquine. *J Rheumatol* 2001; **28:** 2129–32.
10. Vayssairat M, *et al.* Clinical significance of subcutaneous calcinosis in patients with systemic sclerosis: does diltiazem induce its regression? *Ann Rheum Dis* 1998; **57:** 252–4.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p. 1449.1). Diltiazem has been reported to reduce urinary protein excretion without exacerbating pre-existing renal dysfunction in diabetic patients.[1,2] A small study[3] in 15 hypertensive patients with type 2 diabetes mellitus, albuminuria, and renal impairment found that diltiazem only reduced urinary albumin excretion when patients received a restricted dietary sodium intake of 50 mmol daily.

Diltiazem may also reduce the nephrotoxicity associated with certain drugs. Reduced nephrotoxicity has been reported when diltiazem is given to healthy subjects receiving netilmicin,[4] but diltiazem does not appear to modify the acute renal failure associated with tubular damage which may be caused by methotrexate.[5] Diltiazem may reduce ciclosporin-induced nephrotoxicity (see Transplantation, below).

1. Bakris GL. Effects of diltiazem or lisinopril on massive proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **112:** 707–8.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996; **125:** 201–4.
4. Lortholary O, *et al.* Calcium antagonists and aminoglycoside nephrotoxicity. *Am J Med* 1990; **88:** 445.
5. Deray G, *et al.* The effects of diltiazem on methotrexate-induced nephrotoxicity. *Eur J Clin Pharmacol* 1989; **37:** 337–40.

Migraine. For reference to the use of calcium-channel blockers, including diltiazem, in the management of migraine, see under Nifedipine, p. 1449.1.

Myocardial infarction. For reference to the use of diltiazem in the acute and long-term management of myocardial infarction, see under Uses of Verapamil, p. 1523.2.

Peripheral vascular disease. Diltiazem has occasionally, like other calcium-channel blockers, been used in the treatment of Raynaud's syndrome, including in adolescents; the *BNFC* suggests that an oral dose of 30 to 60 mg two or three times daily may be appropriate from 12 years of age. For mention of the use of diltiazem in CREST syndrome, symptoms of which include secondary Raynaud's syndrome, see Connective Tissue and Muscular Disorders, p. 1359.3.

Pulmonary hypertension. For the use of calcium-channel blockers, including diltiazem, in pulmonary hypertension, see under Nifedipine, p. 1450.1.

Transplantation. Diltiazem increases blood-*ciclosporin* concentrations when given orally in doses of 60 to 180 mg daily to transplant patients receiving ciclosporin therapy.[1-3] In consequence, ciclosporin doses can be reduced by about one-third, at a considerable saving in cost.[2-4] However, the effect may not occur in all patients,[5] and may vary with differing formulations[6] (most studies have been with older formulations, although benefit has been reported with newer micro-emulsifying preparations of ciclosporin[4]), and it has been suggested that blood-ciclosporin concentrations should be closely monitored if diltiazem is used for this purpose. In addition to this effect, which is apparently due to non-competitive inhibition of ciclosporin metabolism by diltiazem,[7] there is evidence of improved renal graft-function in patients given the combined therapy, suggesting that diltiazem may reduce ciclosporin-induced nephrotoxicity.[1,2] However, a 4-year follow-up study in patients treated with ciclosporin and diltiazem found that diltiazem had no effect on the progression to chronic allograft nephropathy.[8] Improved survival has been reported[9,10] in retrospective studies of patients given diltiazem for its ciclosporin-sparing effect, perhaps because of a reduction in hepatotoxicity and ciclosporin-associated nephrotoxicity.[10]

A sparing effect has also been seen when diltiazem is used with *tacrolimus*.[11]

1. Wagner K, Neumayer H-H. Prevention of delayed graft function in cadaver kidney transplants by diltiazem. *Lancet* 1985; **ii:** 1355–6.
2. Neumayer H-H, Wagner K. Diltiazem and economic use of cyclosporin. *Lancet* 1986; **ii:** 523.
3. Bourge RC, *et al.* Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; **90:** 402–4.
4. Kumana CR, *et al.* Diltiazem co-treatment in renal transplant patients receiving microemulsion cyclosporin. *Br J Clin Pharmacol* 2003; **56:** 670–8.
5. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; **42:** 642–4.
6. Jones TE, *et al.* Formulation of diltiazem affects cyclosporin-sparing activity. *Eur J Clin Pharmacol* 1997; **52:** 55–8.
7. Brockmöller J, *et al.* Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; **38:** 237–42.
8. Ingsathit A, *et al.* Co-administration of diltiazem and cyclosporine for kidney transplant recipients: a four year follow-up study. *J Med Assoc Thai* 2006; **89** (suppl 2): S235–S241.
9. McDonald SP, Russ GR. Associations between use of cyclosporine-sparing agents and outcome in kidney transplant recipients. *Kidney Int* 2002; **61:** 2259–65.
10. Xue W, *et al.* Long-term follow-up of co-administration of diltiazem and cyclosporine in Chinese kidney transplant recipients. *Ren Fail* 2010; **32:** 314–19.
11. Kothari J, *et al.* Diltiazem use in tacrolimus-treated renal transplant recipients. *J Clin Pharm Ther* 2004; **29:** 425–30.

Adverse Effects

Treatment with diltiazem is generally well tolerated. Headache, ankle oedema, hypotension, dizziness, flushing, fatigue, mood disturbances, and nausea and other gastrointestinal disturbances (including anorexia, vomiting, constipation or diarrhoea, taste disturbances, and weight gain) may occur. Gingival hyperplasia has been reported. Rashes, possibly due to hypersensitivity, are normally mild and transient, but in a few cases erythema multiforme or exfoliative dermatitis has developed; photosensitivity reactions may also occur. Transient elevations in liver enzyme values, and occasionally hepatitis, have been reported.

Diltiazem may depress cardiac conduction and has led to AV block, bradycardia, and rarely asystole or sinus arrest.

Overdosage with diltiazem may be associated with bradycardia, with or without AV conduction defects, and hypotension.

Diltiazem has been shown to be teratogenic in *animal* studies.

Effects on mortality. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see under Nifedipine, p. 1450.2.

Angioedema. Periorbital angioedema, accompanied by pruritus or burning and erythema developed in 2 patients given diltiazem.[1]

1. Sadick NS, *et al.* Angioedema from calcium channel blockers. *J Am Acad Dermatol* 1989; **21:** 132–3.

Effects on the blood. Thrombocytopenia has been reported with diltiazem.[1,2]

1. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
2. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on the bones and joints. For a report of arthralgia in a patient receiving diltiazem, see Effects on the Neuromuscular System under Nifedipine, p. 1451.3.

Effects on carbohydrate metabolism. Although raised blood-glucose concentrations and insulin requirements have been reported[1] in a patient with type 1 diabetes mellitus during diltiazem therapy, particularly at high doses, a study[2] in 11 obese black women, who were nondiabetic but had a family history of type 2 diabetes, failed to find any effect of diltiazem 240 mg daily on plasma-glucose and C-peptide concentrations, nor any clinical signs of glucose intolerance.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; **257:** 930–1.
2. Jones BJ, *et al.* Effects of diltiazem hydrochloride on glucose tolerance in persons at risk for diabetes mellitus. *Clin Pharm* 1988; **7:** 235–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the gastrointestinal tract. Gastrointestinal disturbances including nausea, vomiting, and constipation, may occur with calcium-channel blockers. A case[1] of intestinal pseudo-obstruction was reported in a 74-year-old neutropenic man receiving chemotherapy for leukaemia after diltiazem was added to treat new-onset atrial fibrillation. A diagnosis of neutropenic enterocolitis was ruled out and symptoms resolved when diltiazem was stopped; it was concluded that diltiazem was the probable cause.

A similar case attributed to verapamil[2] has been reported.

1. Young RP, Wu H. Intestinal pseudo-obstruction caused by diltiazem in a neutropenic patient. *Ann Pharmacother* 2005; **39:** 1749–51.
2. Schultz HS, Vernon B. Intestinal pseudo-obstruction related to using verapamil. *West J Med* 1989; **151:** 556–8.

Effects on the heart. *AV BLOCK.* AV block appears to be uncommon in patients taking diltiazem, but is potentially serious when it occurs. Prescription-event monitoring[1] of a cohort of 10 119 patients for 1 year found 22 reports of AV block during diltiazem use. At least 8 patients had third-degree heart block, and 12 required a pacemaker; 3 died within 72 hours of the onset of heart block. Many of these patients were also taking beta blockers, which is in line with other reports.[2,3] (See also Beta Blockers under Interactions, p. 1361.3.)

There is some evidence that the incidence of this effect may depend on the serum concentration of diltiazem. In a study[4] in patients taking diltiazem after myocardial infarction, patients with serum-diltiazem concentrations greater than 150 nanograms/mL were more likely to have AV block than patients with lower concentrations of diltiazem.

1. Waller PC, Inman WHW. Diltiazem and heart block. *Lancet* 1989; **i:** 617.
2. Hossack KF. Conduction abnormalities due to diltiazem. *N Engl J Med* 1982; **307:** 953–4.
3. Ishikawa T, *et al.* Atrioventricular dissociation and sinus arrest induced by oral diltiazem. *N Engl J Med* 1983; **309:** 1124–5.
4. Nattel S, *et al.* Determinants and significance of diltiazem plasma concentrations after acute myocardial infarction. *Am J Cardiol* 1990; **66:** 1422–8.

MYOCARDIAL INFARCTION. Results from at least one large multicentre study (the Multicenter Diltiazem Postinfarction Trial) suggest that diltiazem, although apparently of benefit after myocardial infarction in patients with normal left ventricular function (as indicated by absence of pulmonary congestion), was associated with an increased risk of cardiac death or non-fatal re-infarction in patients with impaired left ventricular function.[1] Long-term follow-up[2] indicated that diltiazem also increased the risk of late-onset heart failure in postinfarction patients with left ventricular dysfunction.

1. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319:** 385–92.
2. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991; **83:** 52–60.

WITHDRAWAL. Life-threatening coronary vasospasm, which was fatal in one patient, occurred in 4 patients after coronary revascularisation for unstable angina.[1] Treatment with a calcium-channel blocker (diltiazem or nifedipine) had been stopped between 8 and 18 hours before the procedure and this abrupt withdrawal was thought to be responsible for the rebound vasospasm. The coronary vasospasm was managed with glyceryl trinitrate and nifedipine.

Withdrawal of diltiazem over a 4-day period from a patient with stable angina pectoris was followed by recurrence of anginal attacks.[2] Ambulatory ECG monitoring confirmed worsening myocardial ischaemia that responded to re-introduction of diltiazem. Two further patients had a similar withdrawal effect.

1. Engelman RM, *et al.* Rebound vasospasm after coronary revascularization in association with calcium antagonist withdrawal. *Ann Thorac Surg* 1984; **37:** 469–72.
2. Subramanian VB, *et al.* Calcium antagonist withdrawal syndrome: objective demonstration with frequency-modulated ambulatory ST-segment monitoring. *BMJ* 1983; **286:** 520–1.

Effects on the kidneys. Diltiazem may be of benefit in various kidney disorders (see under Uses, above). However, there are a few reports of acute renal failure associated with diltiazem use.[1,2] Acute interstitial nephritis has been proposed as a mechanism.[2,3]

1. ter Wee PM, *et al.* Acute renal failure due to diltiazem. *Lancet* 1984; **ii:** 1337–8.
2. Abadín JA, *et al.* Probable diltiazem-induced acute interstitial nephritis. *Ann Pharmacother* 1998; **32:** 656–8.
3. Achenbach V, *et al.* Acute renal failure due to diltiazem. *Lancet* 1985; **i:** 176.

Effects on the lungs. Eosinophilic pleural effusion developed[1] in a 68-year-old woman given diltiazem for hypertension. Symptoms resolved on stopping the drug.

1. Raptis L, *et al.* Diltiazem-induced eosinophilic pleural effusion. *Pharmacotherapy* 2007; **27:** 600–2.

Effects on mental function. By September 1989, the WHO collaborative programme for international drug monitoring had gathered 8 cases of mental depression (severe in 2) associated with diltiazem therapy.[1] Time of onset of symptoms varied from a few hours to a few months after starting treatment with diltiazem. There was some evidence that the problem might be dose-related as 5 of the 8 cases were receiving doses of 180 mg daily or more.

Psychoses have been reported rarely with diltiazem. A patient[2] who developed hallucinations (both auditory and visual) and paranoid delusions after 2 days of diltiazem therapy was subsequently treated with nifedipine without abnormal effects. For a report of a psychotic reaction attributed to an interaction between diltiazem and lithium, see p. 1361.3.

1. Biriell C, *et al.* Depression associated with diltiazem. *BMJ* 1989; **299:** 796.
2. Bushe CJ. Organic psychosis caused by diltiazem. *J R Soc Med* 1988; **81:** 296–7.

Effects on the mouth. A study involving 115 patients given nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers.[1]

1. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.

Effects on the skin. Contact dermatitis has been seen in patients using *topical* diltiazem for anal fissure.[1] Skin disorders have also been associated with oral therapy, including acute pustular dermatitis,[2-4] cutaneous vasculitis,[5,6] erythema multiforme,[7,8] pruritic macular rashes,[4,9] severe toxic erythema,[10] subacute lupus erythematosus-like eruptions,[11] and photosensitivity reactions.[12,13] Analysis of cutaneous adverse reactions to diltiazem indicated that acne, rash, and urticaria were among the commonest.[14] There have also been a few reports of exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis.[4,14]

For a report of periorbital skin rash associated with diltiazem, see Angioedema, p. 1360.2.

Cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between diltiazem and amlodipine.[15]

1. Rose RF, Wilkinson SM. Contact sensitization to topical diltiazem. *Contact Dermatitis* 2009; **60:** 347–8.
2. Lambert DG, *et al.* Acute generalized exanthematous pustular dermatitis induced by diltiazem. *Br J Dermatol* 1988; **118:** 308–9.
3. Vicente-Calleja JM, *et al.* Acute generalized exanthematous pustulosis due to diltiazem: confirmation by patch testing. *Br J Dermatol* 1997; **137:** 837–9.
4. Knowles S, *et al.* The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; **38:** 201–6.
5. Carmichael AJ, Paul CJ. Vasculitic leg ulcers associated with diltiazem. *BMJ* 1988; **297:** 562.
6. Sheehan-Dare RA, Goodfield MJ. Severe cutaneous vasculitis induced by diltiazem. *Br J Dermatol* 1988; **119:** 134.
7. Berbis P, *et al.* Diltiazem associated erythema multiforme. *Dermatologica* 1989; **179:** 90.
8. Sanders CJG, Neumann HAM. Erythema multiforme, Stevens-Johnson syndrome, and diltiazem. *Lancet* 1993; **341:** 967.
9. Wirebaugh SR, Geraets DR. Reports of erythematous macular skin eruptions associated with diltiazem therapy. *DICP Ann Pharmacother* 1990; **24:** 1046–9.
10. Wakeel RA, *et al.* Severe toxic erythema caused by diltiazem. *BMJ* 1988; **296:** 1071.
11. Crowson AN, Magro CM. Diltiazem and subacute cutaneous lupus erythematosus-like lesions. *N Engl J Med* 1995; **333:** 1429.
12. Saladi RN, *et al.* Diltiazem induces severe photodistributed hyperpigmentation: case series, histoimmunopathology, management, and review of the literature. *Arch Dermatol* 2006; **142:** 206–10.
13. Kubo Y, *et al.* Diltiazem-associated photodistributed hyperpigmentation: report of two Japanese cases and published work review. *J Dermatol* 2010; **37:** 807–11.
14. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
15. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28:** 118–19.

Extrapyramidal disorders. For reports of extrapyramidal disorders occurring with calcium-channel blockers including diltiazem, see under Nifedipine, p. 1452.2.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p. 1452.3, but see also below.

Diltiazem and its metabolites are poorly dialysable.

Overdosage. The consequences and treatment of diltiazem overdosage are similar to nifedipine (p. 1452.3), although death and life-threatening complications might be more common with diltiazem.[1] Up to 1994, 6 cases of fatal overdose with diltiazem had been reported in the literature.[2] Measurement of diltiazem concentrations to assist in diagnosis and management of overdosage has been suggested,[2] but others[3] have disputed its value.

The following are individual reports of overdosage with diltiazem:

- A patient who took about 10.8 g of diltiazem developed hypotension and complete heart block. Dopamine, isoprenaline, and calcium chloride were required to maintain the blood pressure. The ECG reverted to sinus rhythm after 31 hours. The plasma-diltiazem concentration was 1.67 micrograms/mL 43 hours after ingestion and fell to 12.1 nanograms/mL over a further 55.5 hours with an elimination half-life of 7.9 hours.[4]
- In a further case a patient took 5.88 g of diltiazem with alcohol, and developed severe junctional bradycardia, hypotension, and reduced cardiac function that did not respond to intravenous calcium gluconate. The peak plasma-diltiazem concentration of 6.09 micrograms/mL occurred 7 hours after presentation. About half of the dose was vomited after treatment with activated charcoal. The patient was treated with cardiac pacing and a dopamine infusion; he reverted to sinus rhythm within 24 hours, and a subsequent episode of atrial fibrillation was treated successfully with digoxin.[5]
- Charcoal haemoperfusion had a limited effect in improving the clearance of diltiazem in a patient who had taken 14.94 g of diltiazem.[6] The patient developed severe hypotension, complete heart block, and acute renal failure. Supportive care included cardiac pacing and several vasopressors including intravenous glucagon and infusions of dopamine, adrenaline, and noradrenaline.

As with other calcium-channel blockers the use of insulin in the management of overdose has been described.[7]

1. Buckley NA, *et al.* Overdose with calcium channel blockers. *BMJ* 1994; **308:** 1639.
2. Roper TA. Overdose of diltiazem. *BMJ* 1994; **308:** 1571.
3. Lip GYH, Ferner RE. Overdose of diltiazem. *BMJ* 1994; **309:** 193.
4. Malcolm N, *et al.* Massive diltiazem overdosage: clinical and pharmacokinetic observations. *Drug Intell Clin Pharm* 1986; **20:** 888.
5. Ferner RE, *et al.* Pharmacokinetics and toxic effects of diltiazem in massive overdose. *Hum Toxicol* 1989; **8:** 497–9.
6. Williamson KM, Dunham GD. Plasma concentrations of diltiazem and desacetyldiltiazem in an overdose situation. *Ann Pharmacother* 1996; **30:** 608–11.
7. Abeysinghe N, *et al.* Diltiazem overdose: a role for high-dose insulin. *Emerg Med J* 2010; **27:** 802–3.

Precautions

Diltiazem is contra-indicated in patients with the sick sinus syndrome, pre-existing second- or third-degree AV block, or marked bradycardia, and should be used with care in patients with lesser degrees of AV block or bradycardia. Diltiazem has been associated with the development of heart failure and great care is required in patients with impaired left ventricular function. Sudden withdrawal of diltiazem might be associated with an exacerbation of angina.

Treatment with diltiazem should begin with reduced doses in elderly patients and in patients with hepatic or renal impairment.

Abuse. Abuse of diltiazem by body builders and rugby players has been alleged. Such abuse is possibly because of evidence that diltiazem increases maximum oxygen consumption after training. A body builder who admitted to taking diltiazem in high doses suffered severe abdominal cramps.[1]

1. Richards H, *et al.* Use of diltiazem in sport. *BMJ* 1993; **307:** 940.

Breast feeding. Diltiazem is distributed into breast milk; in a woman taking oral diltiazem 60 mg four times daily, concentrations in breast milk were similar to those in serum.[1] Licensed product information therefore recommends that diltiazem should generally be avoided during breast feeding. However, in another report,[2] a mother breast fed twins for at least 6 months while taking diltiazem and no adverse effects were reported in the infants. Since there had been no reports of adverse effects, the last available guidance from the American Academy of Pediatrics considered[3] that diltiazem was usually compatible with breast feeding.

1. Okada M, *et al.* Excretion of diltiazem in human milk. *N Engl J Med* 1985; **312:** 992–3.
2. Lubbe WF. Use of diltiazem during pregnancy. *N Z Med J* 1987; **100:** 121.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diltiazem as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Renal impairment. A patient with end-stage renal failure requiring haemodialysis developed hypotension, bradycardia, metabolic acidosis, hyperkalaemia, and acute congestive heart failure about 60 hours after his last haemodialysis.[1] The patient had been taking diltiazem 60 mg three times daily. The symptoms were attributed to diltiazem toxicity due to accumulation of diltiazem and its metabolites which are poorly dialysed and normally excreted partially in the urine.

1. Patel R, *et al.* Toxic effects of diltiazem in a patient with chronic renal failure. *J Clin Pharmacol* 1994; **34:** 273–4.

Interactions

Increased depression of cardiac conduction with risk of bradycardia and AV block may occur when diltiazem is given with drugs such as amiodarone, beta blockers, digoxin, and mefloquine. Enhanced antihypertensive effect may occur if used with other antihypertensive drugs or drugs that cause hypotension such as aldesleukin and antipsychotics. Diltiazem is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and may also inhibit the metabolism of drugs sharing the same pathway. Interactions may also be expected with enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and rifampicin, and with enzyme inhibitors, such as cimetidine and HIV-protease inhibitors.

Antidepressants. For a report of diltiazem increasing the bioavailability of *imipramine* and *nortriptyline*, see Calcium-channel Blockers under the Interactions of Amitriptyline, p. 407.1.

Antiepileptics. For reports of diltiazem use precipitating *carbamazepine* and *phenytoin* toxicity, see Calcium-channel Blockers, p. 517.2 and p. 544.2, respectively.

Benzodiazepines. For the effects of diltiazem on plasma concentrations of *midazolam* or *triazolam*, see Calcium-channel Blockers under Interactions of Diazepam, p. 1069.3.

Beta blockers. Profound bradycardia has been reported in several patients when diltiazem was used with a beta blocker.[1,2] Diltiazem decreases the clearance of a single dose of *propranolol* or *metoprolol*, though not *atenolol*, and elevated concentrations of beta blocker may be responsible for the bradycardic effects.[3] This is unlikely to be the full story, however, since atenolol, which was unaffected in this study, has been implicated in producing bradycardia when diltiazem was added in a patient with myocardial ischaemia.[2]

1. Hassell AB, Creamer JE. Profound bradycardia after the addition of diltiazem to a β blocker. *BMJ* 1989; **298:** 675.
2. Nagle RE, *et al.* Diltiazem and heart block. *Lancet* 1989; **i:** 907.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; **36:** 67–70.

Calcium-channel blockers. For the effect of diltiazem and *nifedipine* on each other's plasma concentrations, see p. 1454.1.

Ciclosporin. For reports of a potentially beneficial interaction between diltiazem and ciclosporin, see Transplantation under Uses and Administration, p. 1360.1.

Corticosteroids. Diltiazem has been reported to reduce the clearance of *methylprednisolone* (see Calcium-channel Blockers, p. 1620.2).

Digoxin. For a discussion of interactions between digoxin and calcium-channel blockers including diltiazem, see p. 1357.2.

General anaesthetics. Two patients on diltiazem therapy developed impaired myocardial conduction during anaesthesia with *enflurane*;[1] one of the patients had severe sinus bradycardia that progressed to asystole. Additive cardiodepressant effects of diltiazem and enflurane were considered responsible. The authors of a review[2] concluded that intravenous diltiazem or verapamil should not be used in patients anaesthetised with either halothane or enflurane, particularly in those with heart failure or conduction disturbances.

1. Hantler CB, *et al.* Impaired myocardial conduction in patients receiving diltiazem therapy during enflurane anesthesia. *Anesthesiology* 1987; **67:** 94–6.
2. Durand P-G, *et al.* Calcium-channel blockers and anaesthesia. *Can J Anaesth* 1991; **38:** 75–89.

Histamine H_2-antagonists. *Cimetidine* caused increases in plasma-diltiazem concentrations and in plasma-deacetyldiltiazem concentrations in 6 subjects given a single oral dose of diltiazem 60 mg. *Ranitidine* produced a similar, though less marked effect.[1]

1. Winship LC, *et al.* The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. *Pharmacotherapy* 1985; **5:** 16–19.

Lithium. Extrapyramidal symptoms[1,2] including cogwheeling, rigidity, and ataxia, and in one case a psychotic reaction,[1] have been attributed to a synergistic interaction between diltiazem and lithium.

1. Binder EF, *et al.* Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151:** 373–4.
2. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46:** 540–1.

Muscle relaxants. For a report of hyperkalaemia occurring when *dantrolene* was given to a patient taking diltiazem, see Calcium-channel Blockers under Interactions of Dantrolene, p. 2024.3.

Theophylline. For the effect of diltiazem on plasma-theophylline concentrations, see Calcium-channel Blockers, p. 1235.3.

Tolvaptan. For the effect of diltiazem on tolvaptan concentrations, see p. 2633.1.

Pharmacokinetics

Diltiazem is almost completely absorbed from the gastrointestinal tract after oral doses, but undergoes extensive first-pass hepatic metabolism resulting in a bioavailability of about 40%. Peak plasma concentrations occur about 3 to 8 hours after an oral dose, depending on the dosage form. Diltiazem is about 80% bound to plasma proteins. It is distributed into breast milk. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4; one of the metabolites, desacetyldiltiazem, has been reported to have 25 to 50% of the activity of the parent compound. The half-life of diltiazem is reported to be about 3 to 8 hours, again depending on the dosage form. About 2 to 4% of a dose is excreted in urine as unchanged diltiazem with the remainder excreted as metabolites in bile and urine. Diltiazem and its metabolites are poorly dialysable.

General reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.

Bioavailability. Studies of the pharmacokinetics of diltiazem in healthy subjects after single and multiple doses,[1-3] indicated that bioavailability was increased after multiple doses, probably because of decreased presystemic elimination.[3]

1. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated multiple-dose treatments in healthy volunteers. *Ther Drug Monit* 1989; **11:** 543–50.
2. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated single dosing in healthy volunteers. *Ther Drug Monit* 1989; **11:** 551–7.
3. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after single and multiple dosing in healthy volunteers. *Ther Drug Monit* 1989; **11:** 558–66.

Renal impairment. The pharmacokinetics of diltiazem and its major metabolite desacetyldiltiazem in patients with severe renal impairment were similar to those in patients with normal renal function.[1] Nevertheless, reduced doses may be necessary in patients with renal impairment (see under Uses and Administration p. 1359.3). See also under Precautions, p. 1361.2.

1. Pozet N, *et al.* Pharmacokinetics of diltiazem in severe renal failure. *Eur J Clin Pharmacol* 1983; **24:** 635–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acalix; Angular†; Corodrox; Dilahim†; Diltenk; Dilzen-G; Hart; Incoril; Kaltiazem; Tilazem; ***Austral.***: Cardizem; Coras; Diltahexal; Dilzem; Vasocardol; ***Austria***: Diltiastad; Dilzem†; ***Belg.***: Progor; Tildiem; ***Braz.***: Angiolong; Balcor; Calzem; Cardizem; Cordil; Dilcor; Diltiacor; Diltipress; Diltizem; Diltor†; Incoril; ***Canad.***: Apo-Diltiaz; Cardizem; Novo-Diltazem†; Nu-Diltiaz; Tiazac; ***Chile***: Acasmul; Grifodilzem; Incoril; Tilazem; Tildiem; ***China***: Ao De Zhen (奥的镇); Bei Luo Xin (贝洛信); Di Er Song (迪尔松); Ergolan (艾克朗); Herbesser (合贝爽); Hu Er Xing (乎尔兴); Jian Er Xin (健尔信); Ling Shuang (灵爽); Mono-Tildiem (蒂尔丁); Qian Ke (芊克); Qin Er Kang (沁尔康); Tai Wei Te (太韦特); Tian Er Xin (恬尔薪); Xintai (心泰); ***Cz.***: Blocalcin†; Diacordin; ***Denm.***: Cardil; Cardizem; Dilcor†; Myonil; Tildiem; Tilker†; ***Fin.***: Cardizem; Dilmin; Dilpral†; Dilzem; ***Fr.***: Bi-Tildiem; Deltazen; Diacor†; Dilrene; Mono-Tildiem; Tildiem; ***Ger.***: Dil-Sanorania†; Dilsal†; Diltabeta†; Diltahexal†; Diltaretard†; Diltil†; Diltiagamma†; Dilzanton†; Dilzem; ***Gr.***: Alfener; Cardil; Corotrend; Corsenile; Diltelan; Diltem; Dilzanol; Dipen; Elvesil; Ergoclavin; Mavitalon; Mycarzem; Natasadol; Rubiten; Saubasin; Ternel; Tildiem; Usno; Zem; Zilden; ***Hong Kong***: Altiazem; Apo-Diltiaz; Coras†; Dazil†; Herbesser; Wontizem†; ***Hung.***: Blocalcin; Dilrene; Dilzem; ***India***: Angizem; Cardem; Cardisec; Channel; Coriem; Dicard; Dilam; Dilcal; Dilcardia; Dilcontin; Dilgard; Dilgina; Dilocor; Dilter CD; Diltiaz; Dilticard; Diltigesic; Diltime; Diltisyn; Diltp; Dilzem; Dilzor; DTM; DZ; Heartil; Herbesser; Icidil; Ionozem; Isdil; Iski; Kaizem; Masdil; Onzem; ***Indon.***: Cordizem; Dilmen; Dilso†; Farmabes; Herbesser; Lanodil; ***Irl.***: Adizem; Diacardyne; Diltam; Dilzem; DTZ†; Entrydil; Tildiem; ***Israel***: Adizem; Dilatam; ***Ital.***: Altiazem; Angizem; Diladel; Dilem; Dilter†; Dilzene; Etyzem; Longazem; Tildiem; ***Jpn***: Herbesser; ***Malaysia***: Cardil; Cascor; Herbesser; Mono-Tildiem; ***Mex.***: Angiotrofin; Anremed; Sertidel; Tilazem; ***Neth.***: Tildiem; ***Norw.***: Cardizem; ***NZ***: Cardizem; Diltahexal†; Dilzem; ***Philipp.***: Angiozem; Cordazem†; Corvizem; Dilatam; Dilcardia; Diltelan†; Diltime†; Dilzem; Dyalac; Filazem†; Mono-Tildiem†; Tildiem; Vasmulax; Zandil†; Zemtrial†; ***Pol.***: Blocalcin†; Diacordin†; Dilocard; Dilzem; Oxycardil; ***Port.***: Dilfar; Diltiangina; Diltiem; Etizem; Herbesser; Tilker†; ***Rus.***: Altiazem (Алтиазем); Blocalcin (Блокальцин)†; Cardil (Кардил); Diacordin (Диакордин); Diazem (Диазем); Dilcardia (Дилкардия)†; ***S.Afr.***: Adco-Zildem; Dilatam†; Tilazem; ***Singapore***: Beatizem; Cardil; Cardium; Herbesser; Mono-Tildiem; ***Spain***: Angiodrox; Cardiser; Carreldon; Clobendian†; Corolater†; Cronodine; Dilaclan; Diltiwas; Dinisor; Doclis; Lacerol; Masdil; Tilker; Trumsal; Uni Masdil; ***Swed.***: Cardizem; Coramil; ***Switz.***: Coridil; Dilzem; Tildiem†; ***Thai.***: Angizem; Cardil; Carzem†; Cascor; Denazox; Dilcardia; Dilem; Dilizem; Diltec; Dilzem; Ditizem; Herbesser; Herbie; Progor; ***Turk.***: Altizem; Dilticard; Diltizem; Kardil; Progor; Tildiem†; ***UK***: Adizem; Angitil; Calcicard; Dilcardia; Dilzem; Disogram; Optil; Slozem; Tildiem; Viazem; Zemtard; ***Ukr.***: Cardil (Кардил); ***USA***: Cardizem; Cartia; Dilacor; Dilt-CD; Dilt-XR; Diltia†; Diltzac; Matzim; Taztia; Tiazac; ***Venez.***: Acalix; Corazem; Cordisil; Daltazen; Presoquin; Tilazem.

Multi-ingredient Preparations. ***USA***: Teczem.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Diltiazem Tablets;
USP 36: Diltiazem Hydrochloride Extended-release Capsules; Diltiazem Hydrochloride Oral Solution; Diltiazem Hydrochloride Oral Suspension; Diltiazem Hydrochloride Tablets.

Dimetofrine Hydrochloride *(rINNM)* ⊗

Dimetofrina, hidrocloruro de; Dimétofrine, Chlorhydrate de; Dimetofrini Hydrochloridum; Dimetophrine Hydrochloride; Hidrocloruro de dimetofrina; Диметофрина Гидрохлорид.

4-Hydroxy-3,5-dimethoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride.

$C_{11}H_{17}NO_4$,HCl=263.7

CAS — 22950-29-4 (dimetofrine); 22775-12-8 (dimetofrine hydrochloride).

ATC — C01CA12.

ATC Vet — QC01CA12.

Profile

Dimetofrine hydrochloride is a sympathomimetic (p. 1507.3) that has been used for its vasopressor effects in the treatment of hypotensive states. It has also been used in preparations for cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Raffreddoremed.

Dipyridamole *(BAN, USAN, rINN)*

Dipiridamol; Dipiridamolis; Dipirydamol; Dipyridamol; Dipyridamoli; Dipyridamolum; NSC-515776; RA-8; Дипиридамол.

2,2′,2″,2‴-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol.

$C_{24}H_{40}N_8O_4$=504.6

CAS — 58-32-2.

ATC — B01AC07.

ATC Vet — QB01AC07.

UNII — 64ALC7F90C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dipyridamole). A bright yellow crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in acetone. It dissolves in dilute solutions of mineral acids. Protect from light.

USP 36: (Dipyridamole). An intensely yellow, crystalline powder or needles. Slightly soluble in water; very soluble in chloroform, in alcohol, and in methyl alcohol; very slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Uses and Administration

Dipyridamole is an adenosine reuptake inhibitor and phosphodiesterase inhibitor with antiplatelet and vasodilating activity and is used in thromboembolic disorders (p. 1273.2). Oral dipyridamole is used for the prophylaxis of thromboembolism after cardiac valve replacement (p. 1264.3) and in the management of stroke (below); it has also been used in the management of myocardial infarction (p. 1257.1). Dipyridamole given intravenously results in marked coronary vasodilatation and is used in stress testing in patients with ischaemic heart disease (see Myocardial Imaging, below).

For the prophylaxis of **thromboembolism** after cardiac valve replacement, dipyridamole is given with an oral anticoagulant. The usual oral dose is 300 to 600 mg daily in divided doses before meals. For doses in children see below.

For the secondary prevention of **stroke** or transient ischaemic attack dipyridamole is given as a modified-release preparation, alone or with aspirin, in a dose of 200 mg twice daily.

General references.

1. FitzGerald GA. Dipyridamole. *N Engl J Med* 1987; **316:** 1247–57.
2. Gibbs CR, Lip GYH. Do we still need dipyridamole? *Br J Clin Pharmacol* 1998; **45:** 323–8.
3. Kim H-H, Liao JK. Translational therapeutics of dipyridamole. *Arterioscler Thromb Vasc Biol* 2008; **28:** s39–s42.

Administration in children. Dipyridamole is not licensed in the UK for the prophylaxis of **thromboembolism** in children, but the *BNFC* suggests the following oral doses for prevention of thrombus formation after cardiac surgery:

- children 1 month to 12 years of age: 2.5 mg/kg twice daily
- 12 to 18 years: as for adults (above)

The *BNFC* also includes a suggested dose for dipyridamole in the management of childhood **Kawasaki disease** (p. 2405.2); children aged 1 month to 12 years may be given oral dipyridamole 1 mg/kg three times daily.

Intravenous dipyridamole may be used in stress testing in children similarly to in adults (see Myocardial Imaging, below).

Myocardial imaging. Perfusion abnormalities due to coronary artery disease are usually absent at rest but are present during stress, and stress imaging may therefore be used in the assessment of myocardial function. The stress is usually supplied by exercise, but when exercise is inappropriate pharmacological methods such as dipyridamole may be used.

Dipyridamole has been used with thallium-201 scintigraphy in adults and children and is usually given intravenously in a dose of 567 micrograms/kg over 4 minutes. Thallium-201 is given within 3 to 5 minutes after completion of the infusion of dipyridamole. Initial images are obtained after 5 minutes and delayed images are obtained 2.5 to 4 hours later. Dipyridamole (300 to 400 mg) has also been given as an oral suspension; thallium-201 is given about 45 minutes later to coincide with peak dipyridamole-serum concentrations.

Dipyridamole has also been used in echocardiography.[1,2] The intravenous dipyridamole dose used to obtain maximum sensitivity is often higher (750 to 840 micrograms/kg) than the dose used in scintigraphy.[1]

1. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.
2. Buchalter MB, *et al.* Dipyridamole echocardiography: the bedside stress test for coronary artery disease. *Postgrad Med J* 1990; **66:** 531–5.

Stroke. The value of long-term antiplatelet therapy with aspirin in patients who have suffered an ischaemic stroke (p. 1269.2) or transient ischaemic attack is well-established, with a reduction in the risk of both stroke and other vascular events.[1] The use of dipyridamole has been more controversial. Early studies with dipyridamole, used alone or with aspirin, failed to show any benefit over aspirin alone. The European Stroke Prevention Study-2 (ESPS-2),[2] which compared aspirin and dipyridamole, alone or together, with placebo, found that both drugs reduced the risk of stroke and that the effects appeared to be additive. The study used a low dose of aspirin and a modified-release formulation of dipyridamole, which may explain the discrepancy with earlier studies.[3] Subsequent meta-analyses[3-6] have confirmed that dipyridamole, alone or with aspirin, reduces the risk of recurrent stroke, but have been based mainly on the ESPS-2, which may be a limitation.[3] However, a further large study[7] comparing aspirin alone with aspirin and dipyridamole also found that the incidence of vascular events (including stroke) was lower in those receiving both drugs. Most guidelines[8,9] therefore now recommend aspirin with dipyridamole as one of the preferred options for long-term management of ischaemic stroke.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106. Correction. *ibid.*; 1540.
2. Diener HC, *et al.* European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; **143:** 1–13.
3. Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 1999; **56:** 1087–92.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86. Correction. *ibid.*; 141.
5. Leonardi-Bee J, *et al.* Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke* 2005; **36:** 162–8.
6. De Schryver ELLM, *et al.* Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
7. Halkes PH, *et al.* ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367:** 1665–73. Correction. *ibid.* 2007; **369:** 274.
8. European Stroke Organisation (ESO) Executive Committee. ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25:** 457–507. Also available at: http://www.eso-stroke.org/pdf/ESO08_Guidelines_English.pdf (accessed 11/07/08)
9. Albers GW, *et al.* Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 630S–669S.

Adverse Effects, Treatment, and Precautions

Gastrointestinal disturbances, including nausea, vomiting, and diarrhoea, headache, dizziness, faintness, hypotension, facial flushing, and skin rash and other hypersensitivity reactions may occur after use of dipyridamole. Dipyridamole can also induce chest pain or lead to a worsening of the symptoms of angina. Cardiac arrhythmias have been reported in patients given dipyridamole during thallium-

201 imaging. Aminophylline may reverse some of the adverse effects.

Dipyridamole should be used with caution in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, or coagulation disorders. Intravenous dipyridamole should not be given to patients with these conditions or to those with arrhythmias, conduction disorders, asthma, or a history of bronchospasm (but see Myocardial Imaging, below). Oral dipyridamole should be stopped 24 hours before intravenous use for stress testing.

Effects on the biliary tract. Gallstones containing unconjugated dipyridamole were removed from 2 patients who had been taking dipyridamole for 15 and 10 years, respectively.[1] A gallstone containing unconjugated dipyridamole recurred in a patient who continued to take the drug after endoscopic removal of a similar stone 18 months earlier.[2]

1. Moesch C, *et al.* Biliary drug lithiasis: dipyridamole gallstones. *Lancet* 1992; **340:** 1352–3.
2. Sautereau D, *et al.* Recurrence of biliary drug lithiasis due to dipyridamole. *Endoscopy* 1997; **29:** 421–3.

Effects on the heart. Transient myocardial ischaemia occurred in 4 patients with unstable angina and multivessel coronary artery disease during oral treatment with dipyridamole.[1] See Myocardial Imaging, below, for additional reports.

1. Keltz TN, *et al.* Dipyridamole-induced myocardial ischemia. *JAMA* 1987; **257:** 1515–16.

Effects on the muscles. Symptoms resembling acute pseudopolymyalgia rheumatica developed in a patient taking dipyridamole.[1]

1. Chassagne P, *et al.* Pseudopolymyalgia rheumatica with dipyridamole. *BMJ* 1990; **301:** 875.

Effects on taste. A disagreeable taste associated with other gastrointestinal symptoms occurred in a patient taking dipyridamole.[1] Two similar cases had been reported to the UK CSM.

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983; **100:** 368–71.

Myocardial imaging. Dipyridamole may be used in association with thallium-201 in myocardial stress imaging. Safety data from over 3900 patients has been summarised.[1] Adverse effects which occurred within 24 hours of dipyridamole intravenously (mean dose 560 micrograms/kg) were recorded. Ten patients had major adverse effects and 1820 patients experienced minor adverse effects. Myocardial infarction occurred in 4 patients, 3 of whom had unstable angina before scanning. Six patients developed acute bronchospasm, 4 of whom had a history of asthma or had wheezing before using dipyridamole. Adverse effects considered to be minor included chest pain in 19.7% of patients, ST-T-segment depression in 7.5%, ventricular extrasystoles in 5.2%, headache in 12.2%, dizziness in 11.8%, nausea in 4.6%, and hypotension in 4.6%. Aminophylline was effective in relieving symptoms of adverse effects in 97% of 454 patients.

Hypersensitivity reactions including anaphylaxis and angioedema have been reported.[2,3]

UK licensed product information contra-indicates intravenous dipyridamole in patients with hypotension, unstable angina, left ventricular outflow obstruction, recent myocardial infarction, decompensated heart failure, arrhythmias, conduction disorders, asthma, or a history of bronchospasm. However, a review[4] of pharmacological stress testing suggested that with appropriate patient selection and adequate monitoring, the incidence of life-threatening adverse reactions is negligible. It was also considered that dipyridamole-thallium-201 imaging could be safely performed in the early post-myocardial infarction period.

1. Ranhosky A, *et al.* The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990; **81:** 1205–9.
2. Weinmann P, *et al.* Anaphylaxis-like reaction induced by dipyridamole during myocardial scintigraphy. *Am J Med* 1994; **97:** 488.
3. Angelides S, *et al.* Acute reaction to dipyridamole during myocardial scintigraphy. *N Engl J Med* 1999; **340:** 394.
4. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dipyridamole as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Dipyridamole may enhance the actions of oral anticoagulants due to its antiplatelet effect and additive effects may also occur with other antiplatelet drugs. It inhibits the reuptake of adenosine and may enhance its effects; the dose of adenosine must be reduced if both drugs are given. Dipyridamole may also inhibit the uptake of fludarabine and may reduce its efficacy.

The absorption of dipyridamole may be reduced by drugs such as antacids that increase gastric pH.

Anticoagulants. Dipyridamole may induce bleeding in patients receiving oral anticoagulants without altering prothrombin times (see Antiplatelets, under Warfarin, Interactions, p. 1532.3).

Xanthines. Xanthines may antagonise some of the effects of dipyridamole due to their action as adenosine antagonists. *Aminophylline* may be used to reverse some of the adverse effects of dipyridamole. Intravenous *caffeine* has been reported[1] to attenuate the haemodynamic response to dipyridamole and it has been suggested that caffeine should be avoided for at least 24 hours before the test in patients receiving dipyridamole for myocardial imaging.

1. Smits P, *et al.* Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* 1991; **50:** 529–37.

Pharmacokinetics

Dipyridamole is incompletely absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 75 minutes after an oral dose. Dipyridamole is more than 90% bound to plasma proteins. A terminal half-life of 10 to 12 hours has been reported. Dipyridamole is metabolised in the liver and is mainly excreted as glucuronides in the bile. Excretion may be delayed by enterohepatic recirculation. A small amount is excreted in the urine. Dipyridamole is distributed into breast milk.

References.

1. Mahony C, *et al.* Dipyridamole kinetics. *Clin Pharmacol Ther* 1982; **31:** 330–8.
2. Mahony C, *et al.* Plasma dipyridamole concentrations after two different dosage regimens in patients. *J Clin Pharmacol* 1983; **23:** 123–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Maxicardil; Persantin; Sedangor†; ***Austral.***: Persantin; ***Austria***: Persantin; ***Belg.***: Coronair†; Docdipyri†; Persantine; ***Braz.***: Persantin; ***Canad.***: Persantine; ***Chile***: Persantin; ***China***: Ai Ke Xin (爱克辛); Kai Le Di (凯乐迪); Pu Qi Ao (普奇澳); Shengda (升达); ***Denm.***: Persantin; Persantine; ***Fin.***: Dipyrin†; Persantin; ***Fr.***: Cleridium; Persantine; ***Gr.***: Adezan; Ethrine; Persantin; ***Hong Kong***: Persantin; Procardin†; ***India***: Cardiwell; Deplatol; Dynacard; Persantin; ***Indon.***: Cardial; Persantin; Vasokor; Vasotin; ***Irl.***: Persantin; ***Israel***: Cardoxin; ***Ital.***: Corosan; Novodil†; Persantin; ***Jpn***: Persantin; ***Mex.***: Digal; Dipres; Dirinol; Lodimol; Persantin; Pracem; Trepol†; Vadinar; ***Neth.***: Persantin; ***Norw.***: Persantin; ***NZ***: Persantin; Pytazen; ***Philipp.***: Persantin; ***Port.***: Persantin; ***Rus.***: Curantyl (Курантил); Persantin (Персантин); ***S.Afr.***: Persantin; Plato; ***Singapore***: Perazodin; Persantin; Procardin; ***Spain***: Persantin; ***Swed.***: Persantin; ***Thai.***: Agremol; Persantin; Posanin†; ***Turk.***: Drisentin; Kardisentin; Tromboliz; Trombosentin; ***UK***: Persantin; ***Ukr.***: Curantil (Курантил); ***USA***: Persantine; ***Venez.***: Persantin.

Multi-ingredient Preparations. ***Arg.***: Agrenox; Licuamon; ***Austral.***: Asasantin; ***Austria***: Asasantin; ***Belg.***: Aggrenox; ***Canad.***: Aggrenox; ***China***: A Si Pan (阿司潘); De Li Shu (德力舒); Heng Yi (恒宜); SaiTong (赛同); SiNaGe (斯纳格); ***Cz.***: Aggrenox; ***Denm.***: Aggrenox; Asasantin; Asasantine; ***Fin.***: Asasantin; Orisantin; ***Fr.***: Asasantine; ***Ger.***: Aggrenox; ***Gr.***: Aggrenox; Fluxin; ***Hong Kong***: Aggrenox; ***Hung.***: Asasantin; ***India***: Arreno; Cardiwell Plus; Dynasprin; ***Indon.***: Aggrenox; ***Irl.***: Asasantin; ***Israel***: Aggrenox; ***Ital.***: Aggrenox; ***Neth.***: Asasantin; ***Norw.***: Asasantin; ***Philipp.***: Aggrenox; ***Port.***: Aggrenox; ***Rus.***: Aggrenox (Агренокс); ***S.Afr.***: Asasantin; ***Swed.***: Asasantin; ***Switz.***: Asasantine; ***Thai.***: Aggrenox; ***UK***: Asasantin; ***Ukr.***: Agrenox (Агренокс); ***USA***: Aggrenox.

Pharmacopoeial Preparations

BP 2014: Dipyridamole Infusion; Dipyridamole Oral Suspension; Dipyridamole Tablets; Prolonged-release Dipyridamole Capsules; **USP 36:** Dipyridamole Injection; Dipyridamole Oral Suspension; Dipyridamole Tablets.

Disopyramide *(BAN, USAN, rINN)*

Disopiramida; Disopyramid; Disopyramidi; Disopyramidum; Dizopiramid; Dizopiramidas; SC-7031; Дизопирамид.

4-Di-isopropylamino-2-phenyl-2-(2-pyridyl)butyramide.

$C_{21}H_{29}N_3O$=339.5

CAS — 3737-09-5.

ATC — C01BA03.

ATC Vet — QC01BA03.

UNII — GFO928U8MQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Disopyramide). A white or almost white powder. Slightly soluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

Disopyramide Phosphate *(BANM, USAN, rINNM)*

Disopiramida, fosfato de; Disopyramide, Phosphate de; Disopyramidfosfat; Disopyramid-fosfát; Disopyramidi Phosphas; Disopyramidifosfaatti; Disopyramidphosphat; Dizopiramid Fosfata; Dizopiramid-foszfát; Dizopiramido fosfatas; Dyzopiramidu fosforan; Fosfato de disopiramida; SC-13957; Дизопирамида Фосфат.

$C_{21}H_{29}N_3O,H_3PO_4$=437.5

CAS — 22059-60-5.

UNII — N6BOM1935W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Disopyramide Phosphate). A white or almost white powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Disopyramide Phosphate). A white or practically white, odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Uses and Administration

Disopyramide is a class Ia antiarrhythmic (p. 1243.1) with an action on the heart similar to that of quinidine (p. 1481.3). It also has antimuscarinic and negative inotropic properties.

Disopyramide is used in the management of supraventricular and ventricular arrhythmias (p. 1266.1).

It may be given orally as either the base or the phosphate or intravenously as the phosphate; doses are expressed in terms of the base. Disopyramide phosphate 1.3 g is equivalent to about 1 g of disopyramide. The usual *oral* dose is 300 to 800 mg daily in divided doses adjusted according to response. A modified-release preparation can be used, enabling 12-hourly dosage intervals.

Disopyramide may be given by slow *intravenous* injection in a dose of 2 mg/kg to a maximum of 150 mg, at a rate not exceeding 30 mg/minute; this is followed by 200 mg orally immediately on completion of the injection and every 8 hours for 24 hours. If the arrhythmia recurs the intravenous injection may be repeated, but a total intravenous dose of 4 mg/kg (maximum 300 mg) should not be exceeded in the first hour, nor should the total by both intravenous and oral routes exceed 800 mg in 24 hours.

Alternatively, the initial intravenous injection may be followed by intravenous infusion of 400 micrograms/kg per hour (or 20 to 30 mg/hour) to a maximum of 800 mg daily. Patients receiving disopyramide intravenously or in high oral doses should be monitored by ECG.

Dosage reduction and/or increased dosage interval may be necessary in patients with hepatic or renal impairment (see below and p. 1364.1, respectively) and in some elderly patients (see, below). Doses should also be adjusted in patients with heart failure to compensate for the prolonged half-life.

For the dosage of disopyramide in children, see below.

Action. A study in 6 patients with atrial flutter suggested that the antiarrhythmic activity of racemic disopyramide resides in the S(+)-enantiomer.[1]

1. Lima JJ, *et al.* Antiarrhythmic activity and unbound concentrations of disopyramide enantiomers in patients. *Ther Drug Monit* 1990; **12:** 23–8.

Administration in children. An optimum dosage regimen for children has not been fully established, but US product information suggests the following oral doses:

- under 1 year: 10 to 30 mg/kg daily
- age 1 to 4 years: 10 to 20 mg/kg daily
- age 4 to 12 years: 10 to 15 mg/kg daily
- age 12 to 18 years: 6 to 15 mg/kg daily

Administration in the elderly. The clearance of disopyramide was reduced in elderly non-smoking patients compared with young subjects, but the reduction was less marked in elderly patients who smoked more than 20 cigarettes daily.[1] It was recommended that the dose of disopyramide should be reduced by about 30% in elderly non-smokers.

1. Bonde J, *et al.* The influence of age and smoking on the elimination of disopyramide. *Br J Clin Pharmacol* 1985; **20:** 453–8.

Administration in hepatic impairment. The plasma half-life of disopyramide may be increased in hepatic impairment and dosage reduction should be considered; US licensed product information recommends an oral dose of 400 mg daily in divided doses. In patients with liver cirrhosis there is also a significant reduction in the plasma concentration of α_1-acid glycoprotein;[1,2] in addition, its binding capacity for disopyramide is reduced.[1] This is associated with an increase in the free fraction of disopyramide such that measurement of total disopyramide in plasma may not be a safe indicator for dosing, and a thera-

peutic range 50% lower than in patients with normal hepatic function should be considered.[2]

1. Bonde J, *et al*. Kinetics of disopyramide in decreased hepatic function. *Eur J Clin Pharmacol* 1986; **31:** 73–7.
2. Echizen H, *et al*. Protein binding of disopyramide in liver cirrhosis and in nephrotic syndrome. *Clin Pharmacol Ther* 1986; **40:** 274–80.

Administration in renal impairment. Disopyramide is excreted mainly in the urine and a reduction in clearance with an increase in elimination half-life has been reported[1] in patients with renal impairment. Dosage reduction should therefore be considered. US licensed product information recommends the following oral doses based on creatinine clearance (CC):

- CC greater than 40 mL/minute: 400 mg daily in divided doses
- CC 30 to 40 mL/minute: 100 mg every 8 hours
- CC 15 to 30 mL/minute: 100 mg every 12 hours
- CC less than 15 mL/minute: 100 mg every 24 hours

Modified-release preparations should be avoided in patients with CC less than 40 mL/minute.

At therapeutic concentrations disopyramide is not significantly removed by haemodialysis;[2] the half-life is similar both on and off dialysis (16.8 versus 16.1 hours). An increased free fraction of disopyramide has been seen[3] during haemodialysis associated with an elevation in free fatty acids in plasma and in such cases free plasma-disopyramide concentrations should be monitored.

1. Francois B, *et al*. Pharmacokinetics of disopyramide in patients with chronic renal failure. *Eur J Drug Metab Pharmacokinet* 1983; **8:** 85–92.
2. Sevka MJ, *et al*. Disopyramide hemodialysis and kinetics in patients requiring long-term hemodialysis. *Clin Pharmacol Ther* 1981; **29:** 322–6.
3. Horiuchi T, *et al*. Inhibitory effect of free fatty acids on plasma protein binding of disopyramide in haemodialysis patients. *Eur J Clin Pharmacol* 1989; **36:** 175–80.

Hypertrophic cardiomyopathy. Patients with hypertrophic cardiomyopathy (p. 1261.3) may have exercise intolerance due to left ventricular outflow obstruction. Beta blockers are usually used when symptoms are associated with exercise or emotional factors, but may not be effective in patients with symptoms at rest. Disopyramide has been used for its negative inotropic effect in such patients and a retrospective study[1] found that it improved symptoms without having a proarrhythmic effect. It has been reported to have a synergistic effect when combined with electrical pacing.[2]

For precautions in patients with cardiomyopathy see below.

1. Sherrid MV, *et al*. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; **45:** 1251–8.
2. Haruki S, *et al*. Possible acute and chronic synergistic effect of dual chamber pacing and disopyramide in obstructive hypertrophic cardiomyopathy: a case report. *Eur J Heart Fail* 2010; **12:** 94–7.

Hypotension. Disopyramide has been widely used in the management of neurally mediated hypotension (p. 1277.2) but there is limited evidence to support its use. Although some reports[1,2] have suggested benefit, a controlled study[3] found that it was no more effective than placebo in preventing tilt-induced syncope. Adverse effects also limit the use of disopyramide, and it is generally no longer considered first line.

1. Milstein S, *et al*. Usefulness of disopyramide for prevention of upright tilt-induced hypotension-bradycardia. *Am J Cardiol* 1990; **65:** 1339–44.
2. Bhaumick SK, *et al*. Oral disopyramide in the treatment of recurrent neurocardiogenic syncope. *Int J Clin Pract* 1997; **51:** 342.
3. Morillo CA, *et al*. A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993; **22:** 1843–8.

Adverse Effects and Treatment

The adverse effects most commonly associated with disopyramide relate to its antimuscarinic properties and are dose-related. They include dry mouth, blurred vision, urinary hesitancy, impotence, and constipation; the most serious effect is urinary retention. Gastrointestinal effects, which are less common, include nausea, bloating, and abdominal pain. Other adverse effects reported include skin rashes, hypoglycaemia, dizziness, fatigue, muscle weakness, headache, and urinary frequency. Insomnia and depression have also been associated with disopyramide. There have been rare reports of psychosis, cholestatic jaundice, elevated liver enzymes, thrombocytopenia, and agranulocytosis. Disopyramide prolongs the QT interval and may induce or worsen arrhythmias, particularly ventricular tachycardia and fibrillation; heart block and conduction disturbances may occur. It is also a negative inotrope and may cause heart failure, and hypotension.

Over-rapid intravenous injection of disopyramide may cause profuse sweating and severe cardiovascular depression.

In overdose cardiovascular and antimuscarinic effects are pronounced, and there may be apnoea, loss of consciousness, loss of spontaneous respiration, and asystole. Treatment of overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

A review of the adverse effects associated with the class Ia antiarrhythmic drugs disopyramide, procainamide, and quinidine, and their clinical management.[1]

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; **5:** 393–420.

Incidence of adverse effects. During long-term therapy with disopyramide 400 to 1600 mg daily in 40 patients, 28 (70%) had one or more adverse effects.[1] Dry mouth occurred in 15 (38%), constipation in 12 (30%), blurred vision in 11 (28%), urinary hesitancy in 9 (23%), nausea in 9 (23%), impotence in 2 (5%), and dyspareunia in one patient (3%). In addition 3 of the 9 patients with pre-existing heart failure had worsening of their condition due to disopyramide. Adverse effects were sufficiently severe for disopyramide to be stopped in 7 patients, and for dosage reductions in another 7.

1. Bauman JL, *et al*. Long-term therapy with disopyramide phosphate: side effects and effectiveness. *Am Heart J* 1986; **111:** 654–60.

Effects on the blood. Granulocytopenia was associated on 2 occasions with the use of disopyramide phosphate in a 61-year-old man.[1]

1. Conrad ME, *et al*. Agranulocytosis associated with disopyramide therapy. *JAMA* 1978; **240:** 1857–8.

Effects on the eyes. The antimuscarinic activity of disopyramide may cause adverse effects such as dilated pupils,[1] severe blurring of vision,[1] and acute glaucoma.[2,3] Disopyramide should be avoided in patients with glaucoma and used with caution if there is a family history of glaucoma.

1. Frucht J, *et al*. Ocular side effects of disopyramide. *Br J Ophthalmol* 1984; **68:** 890–1.
2. Trope GE, Hind VMD. Closed-angle glaucoma in patient on disopyramide. *Lancet* 1978, **i:** 329.
3. Ahmad S. Disopyramide: pulmonary complications and glaucoma. *Mayo Clin Proc* 1990; **65:** 1030–1.

Effects on the heart. Disopyramide has a strong negative inotropic effect and reversible heart failure has been reported[1] after its use. As many as 50% of patients with a history of heart failure may have a recurrence of the disease with an incidence of less than 5% in other patients.

As disopyramide can prolong the QT interval it can induce ventricular tachyarrhythmias. A case of fatal torsade de pointes has been reported.[2]

1. Podrid PJ, *et al*. Congestive heart failure caused by oral disopyramide. *N Engl J Med* 1980; **302:** 614–17.
2. Schattner A, *et al*. Fatal torsade de pointes following jaundice in a patient treated with disopyramide. *Postgrad Med J* 1989; **65:** 333–4.

Effects on the liver. Cholestatic jaundice with raised liver enzyme values has been associated with disopyramide.[1-3] Laboratory and clinical abnormalities disappear on withdrawal although liver enzyme values may remain elevated for several months.

Severe hepatocellular damage with disseminated intravascular coagulation[4] has also been reported.

1. Craxi A, *et al*. Disopyramide and cholestasis. *Ann Intern Med* 1980; **93:** 150–1.
2. Edmonds ME, Hayler AM. *Eur J Clin Pharmacol* 1980; **18:** 285–6.
3. Bakris GL, *et al*. Disopyramide-associated liver dysfunction. *Mayo Clin Proc* 1983; **58:** 265–7.
4. Doody PT. Disopyramide hepatotoxicity and disseminated intravascular coagulation. *South Med J* 1982; **75:** 496–8.

Effects on mental state. Agitation and distress leading to paranoia and auditory and visual hallucinations have been reported[1,2] in patients shortly after starting disopyramide therapy. Complete recovery occurred on withdrawal.

1. Falk RH, *et al*. Mental distress in patient on disopyramide. *Lancet* 1977; **i:** 858–9.
2. Padfield PL, *et al*. Disopyramide and acute psychosis. *Lancet* 1977; **i:** 1152.

Effects on the nervous system. Peripheral neuropathy affecting the feet and severe enough to prevent walking was associated with disopyramide in a 72-year-old patient.[1] There was gradual improvement on withdrawal of disopyramide with the patient being symptom-free after 4 months. Another patient[2] developed a peripheral polyneuropathy 4 years after starting disopyramide; symptoms improved over several months after disopyramide was stopped.

A 75-year-old woman with atrial fibrillation suffered a tonic-clonic seizure followed by respiratory arrest after receiving disopyramide 150 mg intravenously over a period of 10 minutes.[3] On recovery she complained of a dry mouth and blurred vision and it was considered that the seizure was caused by the antimuscarinic action of disopyramide, although it may have been due to a direct stimulant action.

1. Dawkins KD, Gibson J. Peripheral neuropathy with disopyramide. *Lancet* 1978; **i:** 329.
2. Briani C, *et al*. Disopyramide-induced neuropathy. *Neurology* 2002; **58:** 663.
3. Johnson NM, *et al*. Epileptiform convulsion with intravenous disopyramide. *Lancet* 1978; **ii:** 848.

Effects on sexual function. Impotence has been reported[1-3] in patients receiving disopyramide, and is usually attributed to its antimuscarinic effects, although other antimuscarinic symptoms may not be apparent. In one patient[1] full recovery of sexual function occurred when the dose was reduced (plasma concentration reduced from 14 to 3 micrograms/mL); another patient[3] developed impotence shortly after starting disopyramide, despite a low plasma concentration (1.5 micrograms/mL), but the condition resolved without changing therapy.

1. McHaffie DJ, *et al*. Impotence in patient on disopyramide. *Lancet* 1977; **i:** 859.
2. Ahmad S. Disopyramide and impotence. *South Med J* 1980; **73:** 958.
3. Hasegawa J, Mashiba H. Transient sexual dysfunction observed during antiarrhythmic therapy by long-acting disopyramide in a male Wolff-Parkinson-White patient. *Cardiovasc Drugs Ther* 1994; **8:** 277.

Effects on the urinary tract. In a report of 9 cases of urinary retention associated with disopyramide and a review of the literature,[1] it was noted that urinary retention secondary to disopyramide use was most likely to develop in male patients over the age of 65 in whom there was some pre-existing renal dysfunction; there was an increased risk in patients with evidence of prostatic hyperplasia.

1. Danziger LH, Horn JR. Disopyramide-induced urinary retention. *Arch Intern Med* 1983; **143:** 1683–6.

Hypersensitivity. Worsening of ventricular arrhythmia and an anaphylactoid reaction occurred in a 58-year-old man after a single oral dose of disopyramide 300 mg.[1] Two hours later he complained of a swollen tongue and difficulty in breathing. He became cyanotic but his respiratory status improved when given diphenhydramine 25 mg intravenously.

1. Porterfield JG, *et al*. Respiratory difficulty after use of disopyramide. *N Engl J Med* 1980; **303:** 584.

Hypoglycaemia. After the manufacturer received reports of hypoglycaemia associated with disopyramide, 2 controlled studies were conducted in healthy subjects.[1] Disopyramide produced a small decrease in blood-glucose concentration but there were no symptoms of hypoglycaemia, although it was considered that the glucose-lowering effect might be clinically significant in patients with hepatic or renal impairment. A review[2] found that renal impairment, advanced age, and malnutrition were the main risk factors for hypoglycaemia, and hypoglycaemia with reduced insulin requirements has also been reported[3] in a patient with type 2 diabetes mellitus. An interaction with clarithromycin has also been reported as a possible cause (see Antibacterials under Interactions, p. 1365.2). However, the overall incidence appears to be low[2] and a case-control study[4] in 91 patients with hypoglycaemia failed to confirm an association with disopyramide.

For a report of severe hypoglycaemia associated with the use of disopyramide with glimepiride see Antidiabetics, under Interactions p. 1365.2.

1. Strathman I, *et al*. Hypoglycemia in patients receiving disopyramide phosphate. *Drug Intell Clin Pharm* 1983; **17:** 635–8.
2. Cacoub P, *et al*. Disopyramide-induced hypoglycemia: case report and review of the literature. *Fundam Clin Pharmacol* 1989; **3:** 527–35.
3. Reynolds RM, Walker JD. Hypoglycaemia induced by disopyramide in a patient with type 2 diabetes mellitus. *Diabet Med* 2001; **18:** 1009–10.
4. Takada M, *et al*. The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; **56:** 335–42.

Overdosage. A 2-year-old boy suffered hypotension, cardiac arrhythmias, and convulsions and died 28 hours after ingestion of 600 mg of disopyramide.[1] In a report[2] of 5 cases of fatal overdosage with disopyramide the most common clinical finding appeared to be an early loss of consciousness after an episode of respiratory arrest. Four of the patients responded to resuscitation at first but then deteriorated rapidly, with cardiac arrhythmias and loss of spontaneous respiration; in 4 of the cases post-mortem examination found pulmonary congestion secondary to left ventricular failure.

1. Hutchison A, Kilham H. Fatal overdosage of disopyramide in a child. *Med J Aust* 1978; **2:** 335–6.
2. Hayler AM, *et al*. Fatal overdosage with disopyramide. *Lancet* 1978; **i:** 968–9.

Precautions

Disopyramide is contra-indicated in complete heart block (unless the patient has a pacemaker) and in cardiogenic shock. It should be used with extreme caution in patients with other conduction disorders or uncompensated heart failure. As for quinidine (see Precautions for Quinidine, p. 1482.3), if disopyramide is used to treat atrial tachycardia it may be necessary to pre-treat with digoxin. Hypokalaemia should be corrected before disopyramide is started. Patients with cardiomyopathy should be given doses at the lower end of the range initially, and should be carefully monitored for the development of hypotension and heart failure.

Care should be taken in patients susceptible to hypoglycaemia, including those with heart failure, hepatic

or renal impairment, and patients taking drugs that affect glucose metabolism.

Intravenous injections of disopyramide should be given slowly to avoid hypotension and it is recommended that facilities for cardiac monitoring and defibrillation should be available when the injection is used.

Dosage reduction may be necessary in patients with hepatic or renal impairment and in patients with heart failure.

Owing to its antimuscarinic properties, disopyramide should be avoided in patients with glaucoma or a tendency to urinary retention, as in benign prostatic hyperplasia, and also in patients with myasthenia gravis because of the risk of precipitating a myasthenic crisis. It should be used with caution in patients with a family history of glaucoma.

For dosage adjustments in the elderly and in patients with hepatic or renal impairment, see under Uses and Administration, p. 1363.3 and p. 1364.1.

Breast feeding. Disopyramide is distributed into breast milk and milk to plasma ratios of 0.4, about 0.5, and 0.9 have been reported.[1-3] Disopyramide has been detected in the plasma of breast-fed infants, but was not associated with adverse effects. The American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding. However, the infant should be monitored for adverse effects, especially antimuscarinic effects.

1. MacKintosh D, Buchanan N. Excretion of disopyramide in human breast milk. *Br J Clin Pharmacol* 1985; **19:** 856–7.
2. Hoppu K, *et al.* Disopyramide and breast feeding. *Br J Clin Pharmacol* 1986; **21:** 553.
3. Barnett DB, *et al.* Disopyramide and its N-monodesalkyl metabolite in breast milk. *Br J Clin Pharmacol* 1982; **14:** 310–12.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies disopyramide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Disopyramide is not usually recommended in pregnancy since it may induce uterine contractions. Although no adverse effects were noted in a patient given disopyramide 200 mg every 8 hours from 26 weeks of gestation until delivery,[1] another patient who was given 4 oral doses of disopyramide 100 to 300 mg at six-hourly intervals in week 32 of pregnancy had uterine contractions 1 to 2 hours after each dose.[2] A further patient[3] given disopyramide at 36 weeks of gestation developed painful uterine contractions 40 minutes after a single 150-mg dose orally; active labour and haemorrhage developed after a second dose was given, and an emergency caesarean section was required. A double-blind, placebo-controlled study[4] involving 20 women hospitalised for induction of labour confirmed that disopyramide induces uterine contractions. All 10 women given disopyramide 150 mg every 6 hours for 48 hours began contractions and in 8 delivery was induced.

1. Shaxted EJ, Milton PJ. Disopyramide in pregnancy: a case report. *Curr Med Res Opin* 1979; **6:** 70–2.
2. Leonard RF, *et al.* Initiation of uterine contractions by disopyramide during pregnancy. *N Engl J Med* 1978; **299:** 84–5.
3. Abbi M, *et al.* Preterm labor and accidental hemorrhage after disopyramide therapy in pregnancy: a case report. *J Reprod Med* 1999; **44:** 653–5.
4. Tadmor OP, *et al.* The effect of disopyramide on uterine contractions during pregnancy. *Am J Obstet Gynecol* 1990; **162:** 482–6.

Interactions

Disopyramide should be used cautiously with drugs that have negative inotropic effects or that affect conduction, including beta blockers and other class I antiarrhythmics; it prolongs the QT interval and should not be given with other arrhythmogenic drugs. Disopyramide is metabolised by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with inhibitors or inducers of this enzyme and with other drugs metabolised by CYP3A4. Use of disopyramide with other antimuscarinic drugs produces enhanced antimuscarinic effects.

Anti-anginals. For reference to disopyramide reducing the efficacy of sublingual *isosorbide dinitrate*, see p. 1413.1.

Antiarrhythmics. The effects of disopyramide on cardiac conduction are additive to those of other class I antiarrhythmic drugs.[1] Disopyramide may prolong the QT interval, a factor associated with torsade de pointes, particularly when given with drugs that have a similar effect; this effect was noted in a few patients given *amiodarone* with disopyramide.[2] Also the serum concentration of disopyramide has been increased by *quinidine*;[3] there was a reciprocal decrease in the serum-quinidine concentration but this was less important clinically.

1. Ellrodt G, Singh BN. Adverse effects of disopyramide (Norpace): toxic interactions with other antiarrhythmic agents. *Heart Lung* 1980; **9:** 469–74.
2. Tartini R, *et al.* Dangerous interaction between amiodarone and quinidine. *Lancet* 1982; **i:** 1327–9.
3. Baker BJ, *et al.* Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. *Am Heart J* 1983; **105:** 12–15.

Antibacterials. The metabolism of disopyramide may be increased by enzyme inducers such as *rifampicin*;[1,2] the increased clearance of disopyramide may lead to subtherapeutic plasma concentrations.

Conversely, enzyme inhibitors may increase serum-disopyramide concentrations[3] and ventricular arrhythmias have been noted in patients given azithromycin,[4] clarithromycin,[5-7] and erythromycin.[3] Hypoglycaemia attributed to increased disopyramide concentrations has also been reported[8,9] with clarithromycin.

1. Aitio M-L, *et al.* The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; **11:** 279–85.
2. Staum JM. Enzyme induction: rifampin-disopyramide interaction. *DICP Ann Pharmacother* 1990; **24:** 701–3.
3. Ragosta M, *et al.* Potentially fatal interaction between erythromycin and disopyramide. *Am J Med* 1989; **86:** 465–6.
4. Granowitz EV, *et al.* Potentially fatal interaction between azithromycin and disopyramide. *Pacing Clin Electrophysiol* 2000; **23:** 1433–5.
5. Paar D, *et al.* Life-threatening interaction between clarithromycin and disopyramide. *Lancet* 1997; **349:** 326–7.
6. Hayashi Y, *et al.* Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. *Pacing Clin Electrophysiol* 1999; **22:** 672–4.
7. Choudhury L, *et al.* Torsades de pointes due to drug interaction between disopyramide and clarithromycin. *Heart Dis* 1999; **1:** 206–7.
8. Iida H, *et al.* Hypoglycemia induced by interaction between clarithromycin and disopyramide. *Jpn Heart J* 1999; **40:** 91–96.
9. Morlet-Barla N, *et al.* Hypoglycémie grave et récidivante secondaire à l'interaction disopyramide-clarithromicine. *Presse Med* 2000; **29:** 1351.

Antidiabetics. Disopyramide can induce hypoglycaemia and care is needed if it is used with drugs that can lower blood glucose. Severe hypoglycaemia developed in a woman with type 2 diabetes when disopyramide was added to existing therapy with low-dose *glimepiride*; she had no previous history of such episodes and hypoglycaemia resolved once disopyramide was stopped.[1] Subsequent study *in vitro* suggested that each drug blocked K_{ATP} potassium channels by about 50 to 60% but when given together they produced almost total inhibition, which would result in membrane depolarisation of islet cells and stimulate release of insulin.

1. Negishi M, *et al.* Mechanism of disopyramide-induced hypoglycaemia in a patient with type 2 diabetes. *Diabet Med* 2009; **26:** 76–8.

Antiepileptics. The clearance of disopyramide may be increased by enzyme inducers such as *phenytoin* and *phenobarbital*, and a small study[1] found that phenytoin reduced serum-disopyramide concentrations.

1. Aitio M-L, *et al.* The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; **11:** 279–85.

Beta blockers. Beta blockers have negative inotropic effects that may be potentiated if they are given with disopyramide. A pharmacokinetic interaction may also occur with beta blockers since the clearance of disopyramide has been reported[1] to be reduced by about 16% during *atenolol* therapy.

1. Bonde J, *et al.* Atenolol inhibits the elimination of disopyramide. *Eur J Clin Pharmacol* 1985; **28:** 41–3.

Pharmacokinetics

Disopyramide is readily and almost completely absorbed from the gastrointestinal tract; peak plasma concentrations occur about 0.5 to 3 hours after oral doses.

Disopyramide is partially metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4. The major metabolite is mono-*N*-dealkylated disopyramide which retains some antiarrhythmic and antimuscarinic activity. The major route of excretion is through the kidney, about 50% as the unchanged drug, 20% as the *N*-dealkylated metabolite, and 10% as other metabolites. About 10% is excreted in the faeces. The clearance of disopyramide does not appear to be influenced by urinary pH.

Disopyramide protein binding varies with the plasma concentration, limiting the usefulness of plasma concentration monitoring as a guide to therapy; protein binding is reported to be 50 to 65% at therapeutic plasma concentrations (about 2 to 4 micrograms/mL). Estimations of the plasma half-life of disopyramide range from about 4 to 10 hours. The half-life is increased in hepatic and renal impairment, and in heart failure.

Disopyramide crosses the placental barrier and is distributed into breast milk.

Reviews.

1. Siddoway LA, Woosley RL. Clinical pharmacokinetics of disopyramide. *Clin Pharmacokinet* 1986; **11:** 214–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Rythmodan; ***Belg.***: Rythmodan; ***Braz.***: Dicorantil; ***Canad.***: Rythmodan; ***Fin.***: Disomet†; ***Fr.***: Rythmodan; ***Gr.***: Dicorynan; Ritmodan; Rythmodan; ***Hung.***: Palpitin-PP; ***India***: Norpace; ***Irl.***: Rythmodan; ***Israel***: Rythmical; ***Ital.***: Ritmodan; ***Jpn***: Rythmodan; ***Mex.***: Biolytan; Dimodan; ***Mon.***: Isorythm; ***Neth.***: Ritmoforine; ***Norw.***: Durbis; ***NZ***: Rythmodan; ***S.Afr.***: Norpace; Rythmodan; ***Spain***: Dicorynan; ***Swed.***: Durbis; ***Turk.***: Norpace; ***UK***: Rythmodan; ***USA***: Norpace.

Pharmacopoeial Preparations

BP 2014: Disopyramide Capsules; Disopyramide Phosphate Capsules;

USP 36: Disopyramide Phosphate Capsules; Disopyramide Phosphate Extended-release Capsules.

Ditazole *(rINN)*

Diethamphenazole; Ditazol; Ditazolum; S-222; Дитазол.

2,2′-[(4,5-Diphenyloxazol-2-yl)imino]diethanol.

$C_{19}H_{20}N_2O_3$=324.4

CAS — 18471-20-0.

ATC — B01AC01.

ATC Vet — QB01AC01.

UNII — H2BQI5Z8FT.

Profile

Ditazole is an inhibitor of platelet aggregation used in the management of thromboembolic disorders (p. 1273.2) in oral doses of 400 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Ageroplas†.

Dobutamine Hydrochloride

(BANM, USAN, rINNM)

46236; Compound 81929 (dobutamine); Dobutamiinihydrokloridi; Dobutamina, hidrocloruro de; Dobutamine, chlorhydrate de; Dobutamin-hidroklorid; Dobutaminhydroklorid; Dobutamin-hydrochlorid; Dobutaminhydroklorid; Dobutamini Hydrochloridum; Dobutamino hidrochloridas; Hidrocloruro de dobutamina; LY-174008 (dobutamine tartrate); Добутамина Гидрохлорид.

(±)-4-(2-{[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino}ethyl) pyrocatechol hydrochloride.

$C_{18}H_{23}NO_3$,HCl=337.8

CAS — 34368-04-2 (dobutamine); 49745-95-1 (dobutamine hydrochloride); 101626-66-8 (dobutamine tartrate).

ATC — C01CA07.

ATC Vet — QC01CA07.

UNII — 0WR771DJXV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dobutamine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; soluble in methyl alcohol. Protect from light.

USP 36: (Dobutamine Hydrochloride). A white to practically white crystalline powder. Sparingly soluble in water and in methyl alcohol; soluble in alcohol and in pyridine. Store in airtight containers at a temperature of 15 degrees to 30 degrees.

Incompatibility. Dobutamine is incompatible with alkaline solutions such as sodium bicarbonate 5% and alkaline drugs such as aminophylline, furosemide,[1] and thiopental sodium;[1] physical incompatibility with bumetanide, calcium gluconate, insulin, diazepam, and phenytoin has also been suggested. There have also been reports of incompatibility with alteplase,[2] heparin,[3] and warfarin sodium.[4]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
4. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Uses and Administration

Dobutamine is a sympathomimetic (p. 1507.3) with direct effects on $beta_1$-adrenergic receptors, giving it a prominent inotropic action on the heart. It also has some alpha- and $beta_2$-agonist properties. Although it is structurally related to dopamine (p. 1367.2), it has no specific dopaminergic properties; however, like dopamine, the inotropic action of

dobutamine on the heart is associated with less cardiac-accelerating effect than that of isoprenaline.

Dobutamine is used to increase the contractility of the heart in acute heart failure, as occurs in cardiogenic shock (p. 1279.3) and myocardial infarction (p. 1257.1); it is also used in septic shock. Other circumstances in which its inotropic activity may be useful are during cardiac surgery and positive end-expiratory pressure ventilation.

Dobutamine is used as the hydrochloride but doses are expressed in terms of the base; 1.12 micrograms of the hydrochloride is equivalent to about 1 microgram of base. It is given by intravenous infusion as a dilute solution (0.25 to 5 mg/mL), in glucose 5% or sodium chloride 0.9%: other fluids may also be suitable and the manufacturers' guidelines should be consulted.

In the management of **acute heart failure**, dobutamine is given at a usual rate of 2.5 to 10 micrograms/kg per minute, according to the patient's heart rate, blood pressure, cardiac output, and urine output. A range of 0.5 up to 40 micrograms/kg per minute has occasionally been required. It has been recommended that treatment with dobutamine should be stopped gradually.

Dobutamine is also used as an alternative to exercise in **cardiac stress testing**. A solution containing 1 mg/mL is given via an infusion pump in a dose of 5 micrograms/kg per minute for 8 minutes. The dose is then increased by increments of 5 micrograms/kg per minute up to a usual maximum of 20 micrograms/kg per minute, with each dose being infused for 8 minutes before the next increase; doses of up to 40 micrograms/kg per minute have sometimes been used. The ECG should be monitored continuously and the infusion stopped if arrhythmias, marked ST segment depression, or other adverse effects occur.

For doses in children, see below.

Action. Although dobutamine is usually considered to be a $beta_1$ agonist, *animal* studies suggest that its ability to stimulate $alpha_1$- and $beta_2$-adrenergic receptors may be as great as its $beta_1$-stimulant properties. It has been proposed that the inotropic action results from a combination of alpha-stimulant activity on myocardial $alpha_1$ receptors, a property residing mainly in the (-)-enantiomer, with $beta_1$ stimulation by the (+)-enantiomer; peripherally, alpha-mediated vasoconstriction would be opposed by the $beta_2$-agonist properties of the (+)-enantiomer, resulting in the net inotropic action with relatively little effect on blood pressure seen with the racemic mixture used clinically.[1]

Dobutamine has a thermogenic effect,[2] increasing oxygen delivery and utilisation in healthy individuals. However, using it for this purpose in critically ill patients did not improve patient outcome and in some cases might have been harmful.[3]

1. Ruffolo RR. The mechanism of action of dobutamine. *Ann Intern Med* 1984; **100:** 313–14.
2. Bhatt SB, *et al.* Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *Br J Anaesth* 1992; **69:** 298–303.
3. Hayes MA, *et al.* Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; **330:** 1717–22.

Administration in children. Dobutamine and dopamine are both used for inotropic support in children. A study[1] in children undergoing cardiac surgery suggested that dobutamine may be preferred to dopamine since the latter could cause pulmonary vasoconstriction (see under Precautions for Dopamine, p. 1368.2). In preterm infants, low systemic blood flow is associated with cerebral haemorrhage and neurodevelopmental disability, and both dobutamine and dopamine have been studied for their effects on outcomes. Of the two drugs, dopamine produces the greater reduction in hypotension,[2,3] but dobutamine increases superior vena cava flow to a greater extent.[3] Although it has been argued[3] that superior vena cava flow, rather than blood pressure, provides a more meaningful indication of systemic blood flow in neonates, in reality the difference may not be clinically important: while low superior vena cava flow was associated with neurodevelopmental delays at 3 years of age, there was no significant difference in combined death and disability rates between infants given dobutamine or dopamine to correct it.[4]

Neonates, infants, and children may be given dobutamine by continuous intravenous infusion for inotropic support in an initial dose of 5 micrograms/kg per minute, adjusted according to response to between 2 and 20 micrograms/kg per minute.

1. Booker PD, *et al.* Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; **74:** 419–23.
2. Osborn D, *et al.* Randomized trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr* 2002; **140:** 183–91.
3. Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 07/10/05).
4. Osborn DA, *et al.* Low superior vena cava flow and effect of inotropes on neurodevelopment to 3 years in preterm infants. *Pediatrics* 2007; **120:** 372–80.

Diagnosis and testing. Dynamic exercise is the established mode of stress for the assessment of cardiac function. In patients who are unable to exercise, a dobutamine infusion is one of the best alternative ways of producing a pharmacological stress.[1,2] It is widely used as an adjunct in echocardiography, often combined with atropine, and may give better sensitivity than adenosine or dipyridamole;[1,3] it may also have a role with other imaging techniques such as magnetic resonance imaging.[4] However there have been instances of severe cardiovascular complications attributable to dobutamine,[5] a topic which has been reviewed.[6,7]

1. Cheitlin MD, *et al.* ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Summary article: *Circulation* 2003; **108:** 1146–62. Full text: http://www.americanheart.org/downloadable/heart/1060182581039Echocleanfulltext.pdf (accessed 07/10/05)
2. Marwick TH. Stress echocardiography. *Heart* 2003; **89:** 113–18.
3. Martin TW, *et al.* Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. *Ann Intern Med* 1992; **116:** 190–6.
4. Paetsch I, *et al.* Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation* 2004; **110:** 835–42.
5. Lattanzi F, *et al.* Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. *Drug Safety* 2000; **22:** 251–62.
6. Karabinos I, *et al.* Prevalence and potential mechanisms of sustained ventricular arrhythmias during dobutamine stress echocardiography: a literature review. *J Am Soc Echocardiogr* 2008; **21:** 1376–81.
7. Geleijnse ML, *et al.* Incidence, pathophysiology, and treatment of complications during dobutamine-atropine stress echocardiography. *Circulation* 2010; **121:** 1756–67.

Heart failure. Dobutamine may be used in the management of acute heart failure, including decompensated chronic heart failure (see Cardiogenic Shock, under Shock, p. 1279.3). It may also have a role in patients with severe chronic heart failure (p. 1262.3), either as a bridge to transplantation or for palliative therapy. In less severe cases, intermittent infusions of dobutamine have been tried. A study[1] using pulsed therapy with dobutamine (30 minutes daily for 4 days each week for 3 weeks) reported symptomatic improvements similar to those achieved with exercise, but another study[2] using intermittent therapy (24 hours every 2 to 3 weeks for 6 months) failed to show any benefit. There have also been reports of sudden death in patients receiving dobutamine as infusions for 48 hours per week, and another study[3] was halted for this reason. Long-term use of intermittent dobutamine is therefore not generally recommended.[4]

1. Adamopoulos S, *et al.* Effects of pulsed β-stimulant therapy on β-adrenoceptors and chronotropic responsiveness in chronic heart failure. *Lancet* 1995; **345:** 344–9.
2. Elis A, *et al.* Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther* 1998; **63:** 682–5.
3. Dies F, *et al.* Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. *Circulation* 1986; **74:** (suppl II): 38.
4. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 19/08/08)

Adverse Effects and Treatment

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Dobutamine has mainly $beta_1$-agonist properties and its principal adverse effects include dose-related increases in heart rate and blood pressure, ectopic beats, angina or chest pain, and palpitations; dosage should be reduced or temporarily stopped if they occur. Ventricular tachycardia may occur rarely; cardiac rupture has been reported rarely during dobutamine stress testing.

Effects on body temperature. A 71-year-old woman with heart failure developed a fever on 2 separate occasions 8 to 12 hours after starting an infusion of dobutamine.[1]

1. Robison-Strane SR, Bubik JS. Dobutamine-induced fever. *Ann Pharmacother* 1992; **26:** 1523–4.

Effects on the cardiovascular system. For reference to severe cardiovascular complications of dobutamine stress echocardiography, see Diagnosis and Testing under Uses and Administration, above.

For reference to fatalities occurring in patients given dobutamine, see Heart Failure under Uses and Administration, above.

Effects on the neuromuscular system. Myoclonus has been reported[1,2] in patients with renal impairment given dobutamine infusion for heart failure.

1. Wierre L, *et al.* Dobutamine-induced myoclonia in severe renal failure. *Nephrol Dial Transplant* 2004; **19:** 1336–7.
2. Boord A, Benson B. Myoclonus associated with continuous dobutamine infusion in a patient with end-stage renal disease. *Am J Health-Syst Pharm* 2007; **64:** 2241–3.

Effects on the skin. Troublesome pruritus of the scalp has been reported[1] in a patient receiving dobutamine infusions. It was suggested that this might be a direct effect of dobutamine since the reaction was so localised.

1. McCauley CS, Blumenthal MS. Dobutamine and pruritus of the scalp. *Ann Intern Med* 1986; **105:** 966.

Hypersensitivity. Hypersensitivity reactions have been reported in patients receiving dobutamine infusions, possibly due to sodium sulfite in the formulation. Redness, swelling, itching, and a sensation of warmth developed[1] around the infusion site in a patient receiving dobutamine; the reaction recurred when the infusion was repeated a week later. Eosinophilic reactions have also been reported, including hypersensitivity myocarditis[2-4] and asthma.[5]

1. Cernek PK. Dermal cellulitis—a hypersensitivity reaction from dobutamine hydrochloride. *Ann Pharmacother* 1994; **28:** 964.
2. Spear GS. Eosinophilic explant carditis with eosinophilia: ?hypersensitivity to dobutamine infusion. *J Heart Lung Transplant* 1995; **14:** 755–60.
3. Takkenberg JJM, *et al.* Eosinophilic myocarditis in patients awaiting heart transplantation. *Crit Care Med* 2004; **32:** 714–21.
4. Butany J, *et al.* Hypersensitivity myocarditis complicating hypertrophic cardiomyopathy heart. *Can J Cardiol* 2004; **20:** 911–14.
5. Aranda JM, *et al.* Dobutamine-related asthma in a patient awaiting cardiac transplantation: the eosinophilic dilemma. *J Heart Lung Transplant* 2004; **23:** 260–1.

Overdosage. A patient received an accidental overdose[1] of dobutamine when given an intravenous infusion at a rate of more than 130 micrograms/kg per minute for 30 minutes, this being three times the recommended maximum. Characteristic adverse effects such as emesis, palpitations, chest pain, dyspnoea, and paraesthesia developed, together with urinary incontinence, an effect not previously associated with dobutamine.

1. Paulman PM, *et al.* Dobutamine overdose. *JAMA* 1990; **264:** 2386–7.

Precautions

As for Sympathomimetics, p. 1508.3. Dobutamine has inotropic effects and should be avoided or used only with great caution in patients with marked obstruction of cardiac ejection, such as idiopathic hypertrophic subaortic stenosis. It should also be used with caution in patients with acute myocardial infarction, and in cardiogenic shock complicated by severe hypotension. Hypovolaemia should be corrected before treatment.

Interference with diagnostic tests. Contamination of blood samples with dobutamine has been reported to produce falsely decreased creatinine values in an enzymatic test.[1] Colorimetric measurements of creatinine were not affected.

1. Daly TM, *et al.* "Bouncing" creatinine levels. *N Engl J Med* 1996; **334:** 1749–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dobutamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Most interactions with dobutamine are due to its direct $beta_1$ agonist effects on the heart, but use with beta blockers may allow its alpha- and $beta_2$-agonist effects to become apparent.

Pharmacokinetics

Like adrenaline (p. 1295.1), dobutamine is inactive when given orally, and it is rapidly inactivated in the body by similar processes. It has a half-life of about 2 minutes. Conjugates of dobutamine and its major metabolite 3-*O*-methyldobutamine are excreted mainly in urine, with small amounts eliminated in the faeces.

The main mechanism of clearance of dobutamine appears to be distribution to other tissues, and not metabolism or elimination. It has a half-life of about 2 minutes and plasma concentrations of dobutamine reach steady state about 10 to 12 minutes after the start of an infusion. Dobutamine is used mainly for the short-term treatment of heart failure and any pharmacokinetic changes in this condition have no clinical implications in dosage titration.[1]

The pharmacokinetics of dobutamine and other cardiovascular drugs in children have been reviewed.[2]

1. Shammas FV, Dickstein K. Clinical pharmacokinetics in heart failure: an updated review. *Clin Pharmacokinet* 1988; **15:** 94–113.
2. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; **27:** 345–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dobucard; Duvig; ***Austral.***: Dobutrex; ***Austria***: Inotop; ***Belg.***: Dobutrexmylan; ***Braz.***: Dobtan; Dobutabbott; Dobuton; Neobutamina; ***China***: Anchang (安畅); Ao Wan Yuan (奥万源); Bin Fen (滨纷); Chen Sheng Fen (辰生芬); Dobutrex (独步催); Feng Hai Fen (丰海芬); Kang Li Tuo (康利托); ***Cz.***: Dobuject; Dobutrex†; ***Denm.***: Dobutrex; ***Fin.***: Dobuject; ***Gr.***: Dobutan; Inotrex; ***India***: Cardiforce; Cardiject; Dobicard; Dobier; Dobion; Dobonis; Dobucard; Dobucef; Dobucin; Dobugen; Dobunex; Doburan; Dobusol; Dobustat; Dobutam; Dobutasys; Dobutrex; Dobutrop; Dotamin; Icidob; Inoject; Kardia; ***Indon.***: Cardiject; Dobucef; Dobuject; Doburan; Dobutel; Dominic; Inotrop; ***Irl.***: Posiject; ***Israel***: Butamine; Dobuject; ***Ital.***: Miozac; ***Jpn***: Dobupum; ***Mex.***: Cryobutol; Dobuject; Dobutrex; Oxiken†; ***Philipp.***: Cardomin; Dobuject; Dobulex; Dobunex; Dobutrex; Dobutrim; Inocard†; ***Pol.***: Dobuject; ***Port.***: Dasomin; Dobucor; Dobutina; Inotrex; ***S.Afr.***: Cardiject; Dobutrex; ***Singapore***: Dobuject; ***Spain***: Dobucor†; ***Swed.***: Dobutrex†; ***Switz.***: Dobutrex; ***Thai.***: Cardiject; Dobuject; ***Turk.***: Dobuject; Dobutabag; Dobutrex; ***Venez.***: Doburan; Dobuxin.

Pharmacopoeial Preparations

BP 2014: Dobutamine Infusion;

USP 36: Dobutamine for Injection; Dobutamine in Dextrose Injection; Dobutamine Injection.

Docarpamine *(rINN)*

Docarpamina; Docarpaminum; TA-870; TA-8704; Докарпамин.

(-)-(*S*)-2-Acetamido-*N*-(3,4-dihydroxyphenethyl)-4-(methylthio)butyramide bis(ethyl carbonate) ester.

$C_{21}H_{30}N_2O_8S$=470.5

CAS — 74639-40-0.

UNII — RPQ57D8S72.

Profile

Docarpamine is an orally active prodrug of dopamine (below) that has been used in the treatment of acute heart failure in a usual oral dose of 750 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Tanadopa.

Dofetilide *(BAN, USAN, rINN)*

Dofetilid; Dofetilida; Dofétilide; Dofetilidi; Dofetilidum; UK-68798; Дофетилид.

β-[(*p*-Methanesulfonamidophenethyl)methylamino]methanesulfono-*p*-phenetidide.

$C_{19}H_{27}N_3O_5S_2$=441.6

CAS — 115256-11-6.

ATC — C01BD04.

ATC Vet — QC01BD04.

UNII — R4Z9X1N2ND.

Pharmacopoeias. In *US*.

USP 36: (Dofetilide). A white to off-white powder. Very slightly soluble in water and in isopropyl alcohol; soluble in acetone, in 0.1N hydrochloric acid, and in 0.1N sodium hydroxide. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Dofetilide is a class III antiarrhythmic (p. 1243.1); it selectively blocks one of the potassium channels involved in repolarisation and therefore prolongs the action potential. It is used in the treatment of atrial fibrillation and flutter (p. 1266.1) in patients who are highly symptomatic. The initial oral dose in patients with a corrected QT interval of 440 milliseconds or less is 500 micrograms twice daily; the maintenance dose must be reduced if the QT interval becomes prolonged after the first dose, and treatment should be stopped if the QT interval exceeds 500 milliseconds. Doses should be reduced in renal impairment (see below).

References.

1. McClellan KJ, Markham A. Dofetilide: a review of its use in atrial fibrillation and atrial flutter. *Drugs* 1999; **58:** 1043–59.
2. Kalus JS, Mauro VF. Dofetilide: a class III-specific antiarrhythmic agent. *Ann Pharmacother* 2000; **34:** 44–56.
3. Mounsey JP, DiMarco JP. Dofetilide. *Circulation* 2000; **102:** 2665–70.
4. Roukoz H, Saliba W. Dofetilide: a new class III antiarrhythmic agent. *Expert Rev Cardiovasc Ther* 2007; **5:** 9–19.

Administration in renal impairment. Doses of dofetilide should be reduced in patients with renal impairment based on creatinine clearance (CC). Initial doses are:

- CC 40 to 60 mL/minute: 250 micrograms twice daily
- CC 20 to 39 mL/minute: 125 micrograms twice daily
- CC below 20 mL/minute: contra-indicated

Adverse Effects and Precautions

The most frequent adverse effects with dofetilide are headache, chest pain, and dizziness. Dofetilide prolongs the QT interval and may cause severe ventricular arrhythmias, including torsade de pointes; it should not be given to patients with congenital or acquired long QT syndromes. Hypokalaemia increases the risk of arrhythmias and potassium concentrations should be corrected before starting dofetilide. The dosage of dofetilide must be individualised according to QT interval and creatinine clearance, which must be measured before starting therapy; dofetilide is contra-indicated if the corrected QT interval is above 440 milliseconds (or above 500 milliseconds in patients with ventricular conduction abnormalities) or if the creatinine clearance is less than 20 mL/minute. Treatment should begin under ECG monitoring, which must be continued for at least 3 days, and both ECG and renal function should be monitored at least every 3 months during treatment.

Interactions

Dofetilide should not be given with other drugs that prolong the QT interval. Class I or class III antiarrhythmics should be stopped at least 3 half-lives before dofetilide is given. Potassium-depleting diuretics may cause hypokalaemia or hypomagnesaemia, increasing the potential for torsade de pointes; US licensed product information for dofetilide states that hydrochlorothiazide is contra-indicated since it also causes significant increases in plasma-dofetilide concentrations. Dofetilide is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4, and drugs or foods that inhibit this isoenzyme, such as macrolide antibacterials, HIV-protease inhibitors, diltiazem, and grapefruit juice, should be used with caution. Cimetidine, dolutegravir, trimethoprim, ketoconazole, prochlorperazine, and megestrol, should not be given as they inhibit the renal excretion of dofetilide; verapamil is also contra-indicated as it too may substantially increase dofetilide concentrations.

References.

1. Yamreudeewong W, *et al*. Potentially significant drug interactions of class III antiarrhythmic drugs. *Drug Safety* 2003; **26:** 421–38.

Pharmacokinetics

The oral bioavailability of dofetilide is more than 90%. Peak plasma concentrations occur after 2 to 3 hours and steady state concentrations after 2 to 3 days. The terminal half-life is about 10 hours. Protein binding is 60 to 70%. Dofetilide undergoes limited metabolism. About 80% of a dose is excreted in the urine, with about 80% of this as unchanged drug and 20% as 5 minimally active or inactive metabolites; metabolism may be mediated to some extent by the cytochrome P450 isoenzyme CYP3A4. Renal elimination involves both glomerular filtration and active tubular secretion via the cation transport system. The clearance of dofetilide decreases with decreasing creatinine clearance.

References.

1. Allen MJ, *et al*. The pharmacokinetics and pharmacodynamics of oral dofetilide after twice daily and three times daily dosing. *Br J Clin Pharmacol* 2000; **50:** 247–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Tikosyn.

Dopamine Hydrochloride

(BANM, USAN, pINNM)

ASL-279; Dopamiinihydrokloridi; Dopamin Hidroklorür; Dopamina, hidrocloruro de; Dopamine, chlorhydrate de; Dopamin-hidroklorid; Dopaminhydrochlorid; Dopaminhydrochlorid; Dopaminhydroklorid; Dopamini Hydrochloridum; Dopamino hidrochloridas; Dopaminy chlorowodorek; Hidrocloruro de dopamina; 3-Hydroxytyramine Hydrochloride; Допамина Гидрохлорид.

4-(2-Aminoethyl)pyrocatechol hydrochloride.

$C_8H_{11}NO_2$,HCl=189.6

CAS — 51-61-6 (dopamine); 62-31-7 (dopamine hydrochloride).

ATC — C01CA04.

ATC Vet — QC01CA04.

UNII — 7L3E358N9L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Dopamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; sparingly soluble in acetone and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Dopamine Hydrochloride). A white to off-white crystalline powder that may have a slight odour of hydrochloric acid. Freely soluble in water and in aqueous solutions of alkali hydroxides; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 4% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Dopamine is inactivated in alkaline solutions such as sodium bicarbonate 5% and is incompatible with alkaline drugs such as furosemide[1] and thiopental sodium;[1] incompatibility with insulin[2] and with alteplase[3] has also been reported, and licensed product information states that it is incompatible with ampicillin and with amphotericin B, and that mixtures with gentamicin sulfate, cefalotin sodium, or oxacillin sodium should be avoided.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Yamashita SK, *et al*. Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
3. Lee CY, *et al*. Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.

Uses and Administration

Dopamine is a catecholamine sympathomimetic (p. 1507.3) with both direct and indirect effects. It is formed in the body by the decarboxylation of levodopa, and is both a neurotransmitter in its own right (notably in the brain) and a precursor of noradrenaline. Dopamine differs from adrenaline and noradrenaline in dilating renal and mesenteric blood vessels and increasing urine output, apparently by a specific dopaminergic mechanism. This effect is predominant at low infusion rates (about 2 micrograms/kg per minute); at slightly higher infusion rates (around 2 to 10 micrograms/kg per minute) it also stimulates beta$_1$-adrenergic receptors in the myocardium, and at 10 to 20 micrograms/kg per minute the effects of alpha-adrenergic stimulation, such as vasoconstriction, predominate. The inotropic action of dopamine on the heart is associated with less cardiac-accelerating effect, and a lower incidence of arrhythmias, than that of isoprenaline.

Dopamine also inhibits release of prolactin from the anterior pituitary.

Dopamine is used in acute heart failure, as occurs in cardiogenic shock (p. 1279.3) and myocardial infarction (p. 1257.1); it is also used in renal failure (but see below, under Surgery and Intensive Care), in cardiac surgery, and in septic shock.

Dopamine is given as the hydrochloride by intravenous infusion as a dilute solution (usually 1.6 or 3.2 mg/mL, although more dilute solutions may be used where fluid expansion is not a problem), in glucose 5%, sodium chloride 0.9%, or other suitable diluents; many fluids are suitable and licensed product information should be consulted. The initial rate is 2 to 5 micrograms/kg per minute, gradually increased by up to 5 to 10 micrograms/kg per minute according to the patient's blood pressure, cardiac output, and urine output. Up to 20 to 50 micrograms/kg per minute may be required in seriously ill patients; higher doses have been given. A reduction in urine flow, without hypotension, may indicate a need to reduce the dose. To avoid tissue necrosis dopamine is best given via a large vein. When gradually stopping dopamine it is advised that care be taken to avoid undue hypotension associated with very low dosage levels, where vasodilatation could predominate.

For doses in children, see below.

Administration in children. The *BNFC* suggests that dopamine hydrochloride may be given for inotropic support by intravenous infusion to neonates in an initial dose of 3 micrograms/kg per minute, and to those aged over 1 month up to 18 years in an initial dose of 5 micrograms/kg per minute. Doses may be adjusted according to response to a maximum dose of 20 micrograms/kg per minute.

For a discussion of the use of dopamine in the treatment of low systemic blood flow in preterm infants, see under Dobutamine, p. 1366.1.

Surgery and intensive care. Dopamine has a n established role as an inotrope in cardiogenic shock and in cardiac surgery; it has also been used as a **renal protectant,** due to the apparently beneficial effects of lower doses on renal function. Studies in healthy *animals* and human subjects have shown that low-dose dopamine increases renal blood flow, natriuresis, diuresis, and possibly glomerular filtration rate. Low doses of dopamine (sometimes termed 'renal-dose' dopamine) have therefore been widely used in patients at risk of renal failure, such as those undergoing major surgery or in intensive care, as well as for the treatment of acute renal failure. However, clinical studies have failed to convincingly show that low-dose dopamine is effective in either preventing acute renal failure in patients at high risk, or in improving renal function or outcome in patients with established acute renal failure. A

placebo-controlled, randomised study[1] in critically-ill patients with early renal dysfunction and meta-analyses[2,3] including studies of varying design, failed to show any clinical benefit in those receiving dopamine. It is now generally considered[2,4,5] that low-dose dopamine has no place as a renal protectant in the routine management of critically ill patients.

Dopexamine, which like dopamine acts as a peripheral dopamine agonist, has been used similarly but evidence of benefit is limited and it is generally not recommended (see Critical Care under Dopexamine, below).

1. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; **356:** 2139–43.
2. Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; **29:** 1526–31.
3. Friedrich JO, *et al*. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; **142:** 510–24.
4. Galley HF. Renal-dose dopamine: will the message now get through? *Lancet* 2000; **356:** 2112–13. Correction. *ibid*. 2001; **357:** 890.
5. Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest* 2003; **123:** 1266–75.

Adverse Effects and Treatment

As for Sympathomimetics, p. 1508.2 and p. 1508.3; dopamine may have adverse effects relating to both its alpha- and beta-agonist properties.

Dopamine has a short duration of action and most adverse effects respond to stopping the infusion or reducing its rate; infiltration with phentolamine may relieve pain and prevent necrosis following extravasation.

Effects on the CNS. Movement disorders are well known adverse effects of the dopamine precursor, levodopa (p. 902.2) but do not usually occur with dopamine since it does not enter the CNS. However, there has been a report[1] of choreoathetosis in a patient receiving dopamine infusion; it was suggested that there must have been disruption to her blood-brain barrier to allow this to occur.

1. Walker VA, Massoumi M. Choreoathetosis with dopamine. *Ann Intern Med* 2005; **142:** 478–9.

Effects on the endocrine system. Dopamine has complex actions on the anterior pituitary[1] and dopamine infusion is associated with endocrine effects including suppression of prolactin, growth hormone, and thyroid hormone release. In postoperative or critically ill patients, dopamine infusion may affect the endocrine response to stress, even when given in low doses. Depression of serum-prolactin concentrations has been reported[2] in critically ill patients given dopamine in a dose of 2.5 micrograms/kg per minute to maintain renal blood flow, while a study[3] in postoperative patients given dopamine 5 micrograms/kg per minute to maintain splanchnic blood flow found that serum concentrations of both prolactin and thyroid stimulating hormone were decreased. It was suggested that these changes could adversely affect immunological function and add to morbidity in such patients.

1. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996; **24:** 1580–90.
2. Bailey AR, Burchett KR. Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients. *Br J Anaesth* 1997; **78:** 97–9.
3. Schilling T, *et al*. Endocrine effects of dopexamine vs. dopamine in high-risk surgical patients. *Intensive Care Med* 2001; **27:** 1908–15.

Effects on the heart. For mention of the arrhythmogenic effects of dopamine on the heart, see p. 1508.2.

Ischaemia and gangrene. Dopamine is converted to noradrenaline, a powerful vasoconstrictor, and there have been reports[1-3] of ischaemia and gangrene of the extremities in patients receiving dopamine infusion, as well as local necrosis after extravasation.[4] Extravasation of catecholamines is usually treated with an alpha blocker such as phentolamine, but there have also been reports of the use of topical glyceryl trinitrate ointment to improve capillary blood flow in patients with dopamine-induced ischaemia of the digits. The ointment was applied either to the affected area,[5] or to the warmest area of skin,[6] such as the chest or abdominal wall.

1. Alexander CS, *et al*. Pedal gangrene associated with the use of dopamine. *N Engl J Med* 1975; **293:** 591.
2. Julka NK, Nora JR. Gangrene aggravation after use of dopamine. *JAMA* 1976; **235:** 2812–13.
3. Maggi JC, *et al*. Gangrene in a neonate following dopamine therapy. *J Pediatr* 1982; **100:** 323–5.
4. Boltax RS, *et al*. Gangrene resulting from infiltrated dopamine solution. *N Engl J Med* 1977; **296:** 823.
5. Gibbs NM, Oh TE. Nitroglycerine ointment for dopamine induced peripheral digital ischaemia. *Lancet* 1983; **ii:** 290.
6. Coakley J. Nitroglycerin ointment for dopamine-induced peripheral ischaemia. *Lancet* 1983; **ii:** 633.

Precautions

As for Sympathomimetics, p. 1508.3.

Children. There have been reports of increased pulmonary artery pressure with the use of dopamine in children after cardiac surgery,[1] and in premature infants with hypotension.[2] It has therefore been suggested that dopamine should be used with caution in children at risk of developing pulmonary hypertension.

1. Booker PD, *et al*. Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; **74:** 419–23.
2. Liet J-M, *et al*. Dopamine effects on pulmonary artery pressure in hypotensive preterm infants with patent ductus arteriosus. *J Pediatr* 2002; **140:** 373–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dopamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Dopamine has both direct and indirect actions and may therefore interact with MAOIs; the dose of dopamine should be substantially reduced in patients taking MAOIs, and an initial dose of one-tenth the usual dose has been suggested.

Antiepileptics. Following a report in 1976 to the FDA of hypotension in patients given *phenytoin* in addition to dopamine infusion, a study[1] of this potential interaction found that dopamine given by intravenous infusion with phenytoin infusion to *dogs*, did not alter the CNS effects of phenytoin nor result in hypotension and cardiovascular collapse. Large doses of phenytoin alone had a reproducible hypotensive effect that was reduced by dopamine, suggesting a possible supportive role in phenytoin-induced hypotension.

1. Smith RD, Lomas TE. Modification of cardiovascular responses to intravenous phenytoin by dopamine in dogs: evidence against an adverse interaction. *Toxicol Appl Pharmacol* 1978; **45:** 665–73.

Dopaminergics. Severe hypertension occurred[1] in a patient who had been receiving *selegiline* for Parkinson's disease when a dopamine infusion was started. Although selegiline is considered to be a selective monoamine oxidase type B inhibitor, at higher doses it also affects monoamine oxidase type A and could have reduced the metabolism of dopamine in this patient. Caution may be necessary if dopamine is given to patients who have been receiving selegiline within the previous 2 weeks.

1. Rose LM, *et al*. A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; **34:** 1020–4.

Histamine. For the effect of dopamine on histamine given exogenously, see p. 2525.3.

Pharmacokinetics

The vasoconstrictor properties of dopamine preclude its use by the subcutaneous or intramuscular route. Like adrenaline (p. 1295.1) it is inactive when given orally, and it is rapidly inactivated in the body by similar processes, with a half-life of about 2 minutes. Dopamine is a metabolic precursor of noradrenaline and a proportion is excreted as the metabolites of noradrenaline. Nevertheless, the majority appears to be directly metabolised into dopamine-related metabolites.

References.

1. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; **27:** 345–67.
2. Juste RN, *et al*. Dopamine clearance in critically ill patients. *Intensive Care Med* 1998; **24:** 1217–20.
3. MacGregor DA, *et al*. Pharmacokinetics of dopamine in healthy male subjects. *Anesthesiology* 2000; **92:** 338–46.
4. Johnston AJ, *et al*. Pharmacokinetics and pharmacodynamics of dopamine and norepinephrine in critically ill head-injured patients. *Intensive Care Med* 2004; **30:** 45–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dopatropin; Inotropin; Megadose; ***Austria***: Giludop; ***Belg.***: Dynatra; ***Braz.***: Constriction; Dopabane; Dopacris; Dopaflex†; Revimine†; Revivan†; ***China***: A Si Ke Ding (阿斯克丁); ***Cz.***: Tensamin; ***Denm.***: Abbodop†; Dopmin; ***Fin.***: Abbodop†; Dopmin; ***Gr.***: Giludop; ***India***: Domin; Dopacard; Dopacef; Dopanis; Dopaplus; Dopar; Dopasol; Dopinga; Dopress; ***Indon.***: Cetadop; Dopac; Indop; Proinfark; Udopa; ***Israel***: Docard†; ***Ital.***: Revivan; ***Jpn***: Catabon; Inovan; PReDopa; ***Malaysia***: Dopmin; ***Mex.***: Drinalken; Inotropisa†; Miocina; Zetarina; ***Neth.***: Dynatra; ***Norw.***: Abbodop†; ***Philipp.***: Cardiofast; Docard†; Dokard; Dopamax; Dopnax; Myocard; ***Port.***: Cordodopa; Medopa; ***Rus.***: Dopmin (Допмин); ***S.Afr.***: Dynos†; Intropin†; ***Swed.***: Abbodop†; Giludop; ***Thai.***: Dopamex; Dopaminex†; Dopin; Dopmin†; Inopin; ***Turk.***: Dopmin; Giludop; Predopam; ***Venez.***: Dopina.

Pharmacopoeial Preparations
BP 2014: Dopamine Infusion;
USP 36: Dopamine Hydrochloride and Dextrose Injection; Dopamine Hydrochloride Injection.

Dopexamine Hydrochloride

(BANM, USAN, rINNM) ⊗

Dopeksamiinihydrokloridi; Dopeksamin Hidroklorür; Dopexamina, hidrocloruro de; Dopexamindihydrochlorid; Dopéxamine, Chlorhydrate de; Dopexamine, dichlorhydrate de; Dopexamine dihydrochloride; Dopexaminhydroklorid; Dopexamini dihydrochloridum; Dopexamini Hydrochloridum; FPL-60278 (dopexamine); FPL-60278AR; Hidrocloruro de dopexamina; Допексамина Гидрохлорид.

4-{2-[6-(Phenethylamino)hexylamino]ethyl}pyrocatechol dihydrochloride.

$C_{22}H_{32}N_2O_2.2HCl$=429.4

CAS — 86197-47-9 (dopexamine); 86484-91-5 (dopexamine dihydrochloride).

ATC — C01CA14.

ATC Vet — QC01CA14.

UNII — 0VN909S60Y.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dopexamine Dihydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 3.7 to 5.7. Protect from light.

Incompatibility. Dopexamine is inactivated in alkaline solutions such as sodium bicarbonate 5%.

Uses and Administration

Dopexamine is a sympathomimetic (p. 1507.3) with direct and indirect effects. It stimulates $beta_2$ adrenoceptors and peripheral dopamine receptors and also inhibits the neuronal reuptake of noradrenaline. These actions result in an increased cardiac output, peripheral vasodilatation, and an increase in renal and mesenteric blood flow.

Dopexamine hydrochloride is used to provide short-term haemodynamic support, for example after cardiac surgery or in exacerbations of chronic heart failure. It is given as an intravenous infusion of either 400 or 800 micrograms/mL in glucose 5%, sodium chloride 0.9%, or other suitable diluents, through a central or large peripheral vein; more concentrated solutions may be given via a central vein but concentrations should not exceed 4 mg/mL. The initial dose is generally 500 nanograms/kg per minute and is then increased to 1 microgram/kg per minute; further increases, in increments of 0.5 to 1 microgram/kg per minute at intervals of not less than 15 minutes, may be made up to a total of 6 micrograms/kg per minute if necessary. Heart rate, blood pressure, urine output, and cardiac output should be monitored. On withdrawal, the dose should be reduced gradually.

References.

1. Fitton A, Benfield P. Dopexamine hydrochloride. *Drugs* 1990; **39:** 308–30.
2. Anonymous. Dopexamine after cardiac surgery. *Drug Ther Bull* 1995; **33:** 30–2.

Critical care. Dopexamine has been reported to increase splanchnic blood flow and it has been used with the aim of preventing renal and gastrointestinal dysfunction in critically-ill patients.[1] Although there may be a reduction in ischaemic damage to the gut,[2] a study[3] in critically-ill patients failed to show any improvement in outcome with the use of dopexamine. Studies[4,5] using dopexamine to increase oxygen delivery in high-risk surgical patients have also failed to show any benefit in terms of postoperative mortality or organ function, and a systematic review[6] found insufficient evidence to recommend the use of dopexamine in either patient group. A later meta-analysis[7] found that overall, perioperative dopexamine infusion reduced the length of hospital stay in patients having major surgery, but showed no survival benefit; however, at low doses (up to 1 microgram/kg per minute) dopexamine infusion seemed also to be associated with improved survival.

Use of low-dose dopamine for renal protection is not recommended (see Surgery and Intensive Care, p. 1367.3).

1. Lisbon A. Dopexamine, dobutamine, and dopamine increase splanchnic blood flow: what is the evidence? *Chest* 2003; **123** (suppl): 460S–463S.
2. Baguneid MS, *et al*. A randomized study to evaluate the effect of a perioperative infusion of dopexamine on colonic mucosal ischemia after aortic surgery. *J Vasc Surg* 2001; **33:** 758–63.
3. Ralph CJ, *et al*. A randomised controlled trial investigating the effects of dopexamine on gastrointestinal function and organ dysfunction in the critically ill. *Intensive Care Med* 2002; **28:** 884–90. Correction. *ibid*; 1001. [dose]
4. Takala J, *et al*. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. *Crit Care Med* 2000; **28:** 3417–23.

5. Stone MD, *et al.* Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth* 2003; **91:** 619–24.
6. Renton MC, Snowden CP. Dopexamine and its role in the protection of hepatosplanchnic and renal perfusion in high-risk surgical and critically ill patients. *Br J Anaesth* 2005; **94:** 459–67.
7. Pearse RM, *et al.* Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care Med* 2008; **36:** 1323–9.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Dopexamine has mainly beta-agonist and dopaminergic actions; its most common adverse effect is tachycardia, and transient hypotension may also occur. Dopexamine may cause a small reduction in platelet counts and should not be given to thrombocytopenic patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dopexamine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. The interactions of dopexamine are mainly due to its beta-agonist and dopaminergic actions; it may also potentiate the effects of noradrenaline and some other sympathomimetics by inhibiting neuronal uptake of noradrenaline.

Pharmacokinetics

Dopexamine has a short half-life in blood of about 6 to 7 minutes. It is excreted as metabolites in bile and in urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Dopacard†; ***Ger.***: Dopacard†; ***Irl.***: Dopacard†; ***UK***: Dopacard.

Doxazosin Mesilate *(BANM, rINNM)*

Doksazosyny mezyłan; Doxazosin Mesylate (USAN); Doxazosin Methanesulphonate; Doxazosina, mesilato de; Doxazosine, Mésilate de; Doxazosini Mesilas; Doxazosinmesilat; Doxazosin-mesylát; Mesilato de doxazosina; UK-33274-27; Доксазозина Мезилат.

1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulphonate.

$C_{23}H_{25}N_5O_5,CH_3SO_3H$=547.6

CAS — 74191-85-8 (doxazosin); 77883-43-3 (doxazosin mesilate).

ATC — C02CA04.

ATC Vet — QC02CA04.

UNII — 86P6PQK0MU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Doxazosin Mesilate). A white or almost white crystalline powder. It exhibits polymorphism and some forms may be hygroscopic. Slightly soluble in water and in methyl alcohol; soluble in a mixture of 15 volumes of water and 35 volumes of tetrahydrofuran; practically insoluble in acetone. Store in airtight containers.

USP 36: (Doxazosin Mesylate). A white to tan-coloured powder. Very slightly soluble in water and in methyl alcohol; freely soluble in formic acid. Store at a temperature below 30 degrees.

Uses and Administration

Doxazosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions and uses similar to those of prazosin (p. 1474.1), but a longer duration of action. It is used in the management of hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction (below).

Doxazosin is given orally as the mesilate, but doses are usually expressed in terms of the base. Doxazosin mesilate 1.2 mg is equivalent to about 1 mg of doxazosin. After an oral dose maximum reduction in blood pressure is reported to occur in 2 to 6 hours and the effects are maintained for 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose, the initial dose is 1 mg, preferably at bedtime. The dose may be doubled at 1 to 2 week intervals according to response. Usual maintenance doses for **hypertension** are up to 4 mg once daily; doses of 16 mg daily should not be exceeded. For **benign prostatic hyperplasia** the usual maintenance dose is 2 to 4 mg daily; doses of 8 mg daily should not be exceeded.

Doxazosin may also be given as a modified-release preparation.

Reviews.

1. Fulton B, *et al.* Doxazosin: an update of its clinical pharmacology and therapeutic applications in hypertension and benign prostatic hyperplasia. *Drugs* 1995; **49:** 295–320.

Benign prostatic hyperplasia. References to the use of doxazosin in patients with benign prostatic hyperplasia (p. 2347.1).

1. Doggrell SA. After ALLHAT: doxazosin for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2004; **5:** 1957–64.
2. MacDonald R, *et al.* Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU Int* 2004; **94:** 1263–70.
3. Goldsmith DR, Plosker GL. Doxazosin gastrointestinal therapeutic system: a review of its use in benign prostatic hyperplasia. *Drugs* 2005; **65:** 2037–47.
4. Wilt TJ, MacDonald R. Doxazosin in the treatment of benign prostatic hypertrophy: an update. *Clin Interv Aging* 2006; **1:** 389–401.
5. Bhardwa J, *et al.* Finasteride and doxazosin alone orin combination for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2007; **8:** 1337–44.

Hypertension. Alpha blockers are among the drug groups that have been used as first-line therapy for hypertension (p. 1251.1). However, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] the doxazosin arm of the study was terminated early due to an increased incidence of heart failure in patients receiving doxazosin compared with those receiving chlortalidone, and alpha blockers are now only recommended for third-line therapy unless indicated for another reason. The role of doxazosin in hypertension has subsequently been reviewed.[2,3] It has been reported to have additional beneficial effects on blood lipoproteins and atherosclerotic plaque formation, perhaps related to a drug-specific effect on HDL-cholesterol biosynthesis,[4] and it has been suggested that it might be of value in hypertensive patients with the metabolic syndrome.[2,4] However, evidence to support the latter is currently lacking.

1. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; **283:** 1967–75. Correction. *ibid.* 2002; **288**: 2976.
2. Dell'Omo G, *et al.* Doxazosin in metabolically complicated hypertension. *Expert Rev Cardiovasc Ther* 2007; **5:** 1027–35.
3. Wykretowicz A, *et al.* Doxazosin in the current treatment of hypertension. *Expert Opin Pharmacother* 2008; **9:** 625–33.
4. Remaley AT. Old drug, new tricks: the unexpected effect of doxazosin on high-density lipoprotein. *Circ Res* 2007; **101:** 116–18.

Pain. For reference to the use of doxazosin in pain, see under Uses of Phentolamine Mesilate, p. 1469.2.

Renal calculi. References[1-3] to the use of doxazosin to assist expulsion of stones from the distal ureter. For further reference to the potential use of alpha blockers to aid the passage of renal calculi see under Uses of Tamsulosin Hydrochloride, p. 2369.2.

1. Liatsikos EN, *et al.* Doxazosin for the management of distal-ureteral stones. *J Endourol* 2007; **21:** 538–41.
2. Aydogdu O, *et al.* Effectiveness of doxazosin in treatment of distal ureteral stones in children. *J Urol (Baltimore)* 2009; **182:** 2880–4.
3. Zehri AA, *et al.* Preliminary study of efficacy of doxazosin as a medical expulsive therapy of distal ureteric stones in a randomized clinical trial. *Urology* 2010; **75:** 1285–8.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3.

Effects on mental function. For a report of acute psychosis associated with doxazosin use, see under Adverse Effects of Prazosin Hydrochloride, p. 1474.3.

Hypotension. Six of 18 hypertensive patients had first-dose orthostatic hypotension after receiving doxazosin 1 mg; three others had substantial but asymptomatic reductions in supine systolic blood pressure after the first dose.[1] The effect might have been exacerbated since all these patients were also receiving beta blockers or diuretics, or both. A further patient, who was also taking methyldopa, withdrew from the study with persistent orthostatic hypotension.

1. Oliver RM, *et al.* The pharmacokinetics of doxazosin in patients with hypertension and renal impairment. *Br J Clin Pharmacol* 1990; **29:** 417–22.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies doxazosin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Urinary incontinence. For reference to urinary incontinence associated with doxazosin, see under Adverse Effects of Prazosin Hydrochloride, p. 1475.1.

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Pharmacokinetics

Doxazosin is well absorbed after oral doses, peak plasma concentrations occurring 2 to 3 hours after a dose. Oral bioavailability is about 65%. It is extensively metabolised in the liver, and excreted in faeces as metabolites and a small amount of unchanged drug. Elimination from plasma is biphasic, with a mean terminal half-life of about 22 hours. The pharmacokinetics are not altered in patients with renal impairment. Doxazosin is about 98% bound to plasma proteins and is not removed by dialysis. Studies in *animals* indicate that doxazosin accumulates in breast milk.

Reviews.

1. Elliott HL, *et al.* Pharmacokinetic overview of doxazosin. *Am J Cardiol* 1987; **59:** 78G–81G.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cardura; Doxasin; Doxolbran; Lafedoxin; Prostazosina; Vazosin; ***Austria***: Ascalan; Doxapress; Hibadren; Prostadilat; Supressin; ***Braz.***: Carduran; Doxaprost; Doxsol; Doxuran; Euprostatin; Mesidox; Prostaflux; Unoprost; Zoflux; ***Canad.***: Cardura; ***Chile***: Alfadoxin; Angicon; Cardura; Dorbantil; ***China***: Beyacin (必亚欣); Cardura (可多华); Dong Gang Tian Le (东港天乐); Duo Xi Lin (多喜林); Jin Chang (今倡); Luo Xin Ping (络欣平); Shuang Jiang Ping (双将平); Yi Li Ping (伊粒平); Yi Shu Tong (伊舒通); Zhong Wei (仲维); ***Cz.***: Cardura; Dosano†; Dozone†; Kamiren; Windoxa; Zoxon; ***Denm.***: Cardoreg; Cardosin; Cardotard; Carduran; Hypereze; Myocard; ***Fr.***: Zoxan; ***Ger.***: Alfamedin†; Cardular; Diblocin†; Doxa-Puren†; Doxacor†; Doxagamma; Doxanar†; Doxazoflo†; Jutalar†; Uriduct†; ***Gr.***: Cardura; Maguran; Protectura; ***Hong Kong***: Cardura; Doxasyn†; Pencor; Prostazocin†; ***Hung.***: Cardura; Doxagal; Doxicard; Dozone; ***India***: Alfazosin; Doxacard; Doxapress; Duracard; Duraten; ***Indon.***: Cardura; ***Irl.***: Cardura; Carsem; Doxacar; Doxane; Doxatan; Doxel; Farmadura; Kamiren; Raporsin; ***Israel***: Cadex; Cardoral; Doxaloc†; ***Ital.***: Atensil; Benur; Cardura; Dedralen; Noradox; Normothen; Quorum; ***Jpn***: Cardenalin; ***Malaysia***: Cardura; Dophilin; Magurol; Pencor; ***Mex.***: Cardura; ***Neth.***: Cardura; Doxacharvi; ***Norw.***: Carduran; ***NZ***: Cardoxan; Dosan†; ***Philipp.***: Alfadil; ***Pol.***: Apo-Doxan; Cardura; Doxagen; Doxanorm; Doxar; Doxaratio†; Doxonex; Kamiren; Prostatic; Vaxosin†; Zoxon; ***Port.***: Cardura; ***Rus.***: Artezine (Артезин); Cardura (Кардура); Doxaprostan (Доксапростан); Kamiren (Камирен); Magurol (Магурол); Tonocardin (Тонокардин); Zoxon (Зоксон); ***S.Afr.***: Cardugen; Cardura; Carzin; ***Singapore***: Cardura; Pencor; ***Spain***: Carduran; Doxatensa; Doximax Neo†; Progandol; ***Swed.***: Alfadil; ***Switz.***: Cardura; ***Thai.***: Cardoxa; Cardura; Carxasin; Cazosin; Dezcard; Dovizin; Dozozin; Duracard; Genzosin; Pencor; Xadosin; ***Turk.***: Cardura; Doksura; Dostineva; Doxacor; Doxamerck; Kardozin; Tendura; ***UK***: Cardozin; Cardura; Doxadura; Raporsin; Slocinx; ***Ukr.***: Cardura (Кардура); Doxonex (Доксонекс)†; Kamiren (Камирен); Zoxon (Зоксон); ***USA***: Cardura; ***Venez.***: Cardura.

Multi-ingredient Preparations. ***Arg.***: Prosdox Duo.

Pharmacopoeial Preparations

USP 36: Doxazosin Tablets.

Dronedarone *(BAN, rINN)*

Dronedarona; Dronédarone; Dronedaronum; SR-33589; Дронедарон.

N-(2-Butyl-3-{*p*-[3-(dibutylamino)propoxy]benzoyl}-5-benzofuranyl)methanesulfonamide.

$C_{31}H_{44}N_2O_5S$=556.8

CAS — 141626-36-0.

ATC — C01BD07.

ATC Vet — QC01BD07.

UNII — JQZ1L091Y2.

Dronedarone Hydrochloride

(BANM, USAN, rINNM)

Dronédarone, Chlorhydrate de; Dronedaroni Hydrochloridum; Hidrocloruro de dronedarona; SR-33598B; Дронедарона Гидрохлорид.

$C_{31}H_{44}N_2O_5S,HCl$=593.2

CAS — 141625-93-6.

ATC — C01BD07.

ATC Vet — QC01BD07.

UNII — FA36DV299Q.

Uses and Administration

Dronedarone is an antiarrhythmic drug that is structurally related to amiodarone, but has a shorter half-life since it is less lipophilic; it also lacks the iodine moiety. It is reported to have properties of all four Vaughn Williams classes,

although it is unclear which of these contribute to its clinical effects.

Dronedarone is used to reduce the risk of hospitalisation due to atrial fibrillation in clinically stable patients with paroxysmal or persistent atrial fibrillation. It is used in such patients who are in sinus rhythm or who currently have atrial fibrillation and will undergo cardioversion. It should only be used after alternative treatment options have been considered. Dronedarone is given as the hydrochloride, but doses are expressed in terms of the base; dronedarone hydrochloride 426.2 mg is equivalent to about 400 mg of dronedarone. It is given with food in an oral dose equivalent to 400 mg twice daily.

References.

1. Dale KM, White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother* 2007; **41:** 599–605.
2. Singh BN, *et al*. EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007; **357:** 987–99.
3. Davy J-M, *et al*. ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008; **156:** 527.e1–527.e9. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870308004778.pdf (accessed 19/08/09)
4. Hohnloser SH, *et al*. ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; **360:** 668–78. Corrections. *ibid.*; 2487, *ibid.* 2011; **364:** 1481.
5. Patel C, *et al*. Dronedarone. *Circulation* 2009; **120:** 636–44.
6. Hoy SM, Keam SJ. Dronedarone. *Drugs* 2009; **69:** 1647–63.
7. Schafer JA, *et al*. Dronedarone: current evidence and future questions. *Cardiovasc Ther* 2010; **28:** 38–47.
8. Christiansen CB, *et al*. Efficacy and safety of dronedarone: a review of randomized trials. *Expert Opin Drug Safety* 2010; **9:** 189–99.

Adverse Effects

The most common adverse effects of dronedarone are gastrointestinal, and include diarrhoea, nausea, vomiting, abdominal pain, and dyspepsia. Rashes and asthenia are also common. Bradycardia has also occurred and prolongation of the QT interval has been noted. An increase in plasma creatinine has been seen after starting treatment with dronedarone; usually, it reaches a plateau after 7 days and is reversible after stopping treatment. Interstitial lung disease including pneumonitis and pulmonary fibrosis has also been reported. Rare but severe cases of hepatocellular liver injury and hepatic failure may occur.

Effects on the liver. The FDA was aware of several reports of liver injury in patients treated with dronedarone,[1] including two cases of acute liver failure necessitating liver transplants in elderly females.

1. FDA. FDA Drug Safety Communication: severe liver injury associated with the use of dronedarone (marketed as Multaq) (issued 14th January, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm (accessed 20/01/11)

Precautions

Dronedarone is contra-indicated in patients with permanent atrial fibrillation in whom normal sinus rhythm cannot be restored and in those with symptomatic heart failure with recent decompensation requiring hospitalisation or with NYHA class IV heart failure. For more information, see Cardiovascular Disorders, below. ECGs should be performed at least every 6 months and treatment stopped in patients who develop symptoms of heart failure or permanent atrial fibrillation while taking the drug. It is also contra-indicated in those with bradycardia (heart rate less than 50 beats/minute), second- or third-degree AV block or sick sinus syndrome (unless a pacemaker is present), or prolonged QT or PR interval. Hypokalaemia and hypomagnesaemia may increase the risk of arrhythmias; electrolyte imbalances should be corrected before starting treatment. Use with drugs that prolong the QT interval or can induce torsade de pointes, or with inhibitors of the cytochrome P450 isoenzyme CYP3A4, should be avoided. For more information on these precautions, see Interactions, below.

Dronedarone is contra-indicated in patients with severe hepatic or renal impairment (creatinine clearance below 30 mL/min). It should also not be given to those with liver or lung toxicity related to the previous use of amiodarone. Due to reports of severe liver injury, regulatory authorities have suggested that liver function is tested before starting treatment, and closely monitored during it; dronedarone should be stopped if there are signs of potential liver damage.

Dronedarone is contra-indicated in **pregnancy**, since teratogenicity has been seen in *animals*.

Cardiovascular disorders. A randomised, placebo-controlled study (referred to as the ANDROMEDA study),[1] in which hospitalised patients with symptomatic heart failure and severe left ventricular dysfunction were given dronedarone, was terminated early when excess mortality (due to worsening heart failure) and hospitalisation (for cardiovascular reasons) were seen in the dronedarone group. Most patients enrolled in this study had NYHA class II (42.3%) or III (55.8%) heart failure, and only 23.2% had atrial fibrillation at randomisation.

Similarly, a later randomised, placebo-controlled study (referred to as the PALLAS study),[2] in patients with permanent atrial fibrillation and additional cardiovascular risk factors was also terminated early because of significant increase in mortality, stroke (within the first 2 weeks of treatment), and hospitalisations for heart failure in the dronedarone group. Most deaths in the dronedarone group were from cardiovascular causes, including those associated with arrhythmia.

1. Køber L, *et al*. Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; **358:** 2678–87.
2. Connolly SJ, *et al*. PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011; **365:** 2268–76.

Interactions

Dronedarone should be used with caution with other drugs liable to induce bradycardia, such as beta blockers or calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, particularly those that prolong the QT interval or can induce torsade de pointes, such as phenothiazine antipsychotics, tricyclic antidepressants, bepridil, some macrolides, class I and III antiarrhythmics, and terfenadine, should be avoided. Drugs that cause hypokalaemia or hypomagnesaemia may also increase the risk of arrhythmias with dronedarone.

Dronedarone is metabolised by the cytochrome P450 isoenzyme CYP3A4; inhibitors (such as ketoconazole, ciclosporin, HIV-protease inhibitors, cimetidine, clarithromycin, erythromycin, nefazodone, and grapefruit juice) or inducers (such as rifampicin, phenobarbital, carbamazepine, phenytoin, and St John's wort) of this enzyme may affect its plasma concentrations, and concomitant use should be avoided. In addition, dronedarone is a moderate inhibitor of CYP3A4 and CYP2D6, and can increase plasma concentrations of other drugs metabolised by these enzymes, including statins, sirolimus and tacrolimus, beta blockers, and calcium-channel blockers. Dronedarone is also a potent inhibitor of P-glycoprotein and raises plasma concentrations of P-glycoprotein substrates, such as warfarin and other vitamin K antagonists, and digoxin (see also p. 1356.2 for advice on dose reductions for digoxin).

Pharmacokinetics

After an oral dose, dronedarone undergoes extensive first-pass metabolism and has an absolute bioavailability of 4%, which increases to 15% when taken with food. Peak plasma concentrations occur within 3 to 6 hours, and steady state occurs within 4 to 8 days of regular use. Dronedarone is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4 to a less active *N*-debutyl metabolite, and several inactive metabolites. Both dronedarone and its active metabolite are extensively bound (more than 98%) to plasma proteins, mainly albumin. The elimination half-life of dronedarone is about 25 to 30 hours, and that of its *N*-debutyl metabolite around 20 to 25 hours. About 6% of an oral dose is excreted in the urine (entirely metabolites) and 84% in the faeces (metabolites and unchanged drug).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Multaq; ***Canad.***: Multaq; ***Cz.***: Multaq; ***Denm.***: Multaq; ***Fr.***: Multaq; ***Ger.***: Multaq; ***Gr.***: Multaq; ***Hong Kong***: Multaq; ***Hung.***: Multaq; ***Irl.***: Multaq; ***Israel***: Multaq; ***Malaysia***: Multaq; ***Neth.***: Multaq; ***Norw.***: Multaq; ***Philipp.***: Multaq; ***Pol.***: Multaq; ***Port.***: Multaq; ***Singapore***: Multaq; ***Spain***: Multaq; ***Swed.***: Multaq; ***Switz.***: Multaq; ***Thai.***: Multaq; ***UK***: Multaq; ***Ukr.***: Multaq (Мультак); ***USA***: Multaq.

Edaravone *(rINN)*

Edaravona; Édaravone; Edaravonum; MCI-186; Norphenazone; Эдаравон.

3-Methyl-1-phenyl-2-pyrazolin-5-one.

$C_{10}H_{10}N_2O$=174.2

CAS — 89-25-8.

UNII — S798V6YJRP.

Profile

Edaravone is a free-radical scavenger used in the management of acute ischaemic stroke (p. 1269.2). It is given by intravenous infusion in a dose of 30 mg twice daily, infused over 30 minutes, beginning within 24 hours of stroke onset and continued for up to 14 days.

Edaravone is also under investigation in other pathologies thought to involve oxidative insult, including cerebral haemorrhage and amyotrophic lateral sclerosis.

References.

1. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction: randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis* 2003; **15:** 222–9.
2. Tsujita K, *et al*. Effects of edaravone on reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94:** 481–4.
3. Tsujita K, *et al*. Long-term efficacy of edaravone in patients with acute myocardial infarction. *Circ J* 2006; **70:** 832–7.
4. Hishida A. Clinical analysis of 207 patients who developed renal disorders during or after treatment with edaravone reported during post-marketing surveillance. *Clin Exp Nephrol* 2007; **11:** 292–6.
5. Watanabe T, *et al*. The novel antioxidant edaravone: from bench to bedside. *Cardiovasc Ther* 2008; **26:** 101–14.
6. Shinohara Y, *et al*. Edaravone (radical scavenger) versus sodium ozagrel (antiplatelet agent) in acute noncardioembolic ischemic stroke (EDO trial). *Cerebrovasc Dis* 2009; **27:** 485–92.
7. Unno Y, *et al*. Does functional outcome in acute ischaemic stroke patients correlate with the amount of free-radical scavenger treatment? A retrospective study of edaravone therapy. *Clin Drug Investig* 2010; **30:** 143–55.

Adverse effects and precautions. Edaravone has been associated with acute deterioration of renal and liver function, and fatal cases of disseminated intravascular coagulation. Renal and liver function should be monitored, and blood counts taken before, during, and after administration, and the infusion stopped immediately if abnormal values are seen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi Cun (必存); Yi Da Sheng (易达生); Youmin (积华尤敏); ***India***: Edvo; Nuravon; ***Jpn***: Radicut.

Edoxaban *(USAN, rINN)*

DU-176; Édoxaban; Edoxabán; Edoxabanum; Эдоксабан.

N-(5-Chloropyridin-2-yl)-*N'*-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]pyridine-2-carboxamido)cyclohexyl]oxamide.

$C_{24}H_{30}ClN_7O_4S$=548.1

CAS — 480449-70-5.

UNII — NDU3J18APO.

Edoxaban Tosilate

DU-176b; Edoxaban Tosylate (USAN).

$C_{24}H_{30}ClN_7O_4S,C_7H_8O_3S$=720.3

CAS — 480449-71-6.

Profile

Edoxaban is an oral direct inhibitor of factor Xa (activated factor X). It is used for the prevention of venous thromboembolism.

References.

1. Ogata K, *et al*. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; **50:** 743–53.
2. Chung N, *et al*. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost* 2011; **105:** 535–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Lixiana.

Efonidipine Hydrochloride *(rINNM)*

Éfonidipine, Chlorhydrate d'; Efonidipinhydrochlorid; Efonidipini Hydrochloridum; Efonidipino, hidrocloruro de; Hidrocloruro de efonidipino; NZ-105; Serefodipine Hydrochloride; Эфонидипина Гидрохлорид.

Cyclic 2,2-dimethyltrimethylene ester of 2-(*N*-benzylanilino) ethyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-5-phosphononicontinate hydrochloride .

$C_{34}H_{38}N_3O_7P,HCl$=668.1

CAS — 111011-63-3 (efonidipine); 111011-53-1 (efonidipine hydrochloride); 111011-76-8 (efonidipine hydrochloride ethanolate).

UNII — 3BR983K69O.

Profile

Efonidipine hydrochloride is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is used as the ethanolate in the treatment of hypertension in usual oral doses equivalent to efonidipine hydrochloride 10 to 20 mg twice daily; in angina pectoris, a dose of 40 mg once daily has typically been given.

References.

1. Tanaka H, Shigenobu K. Efonidipine hydrochloride: a dual blocker of L- and T-type Ca^{2+} channels. *Cardiovasc Drug Rev* 2002; **20:** 81–92.

2. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008; **31:** 2115–27.
3. Sasaki H, *et al.* Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. *J Atheroscler Thromb* 2009; **16:** 568–75.
4. Rakugi H, *et al.* JATOS Study Group. Comparison of strict- and mild-blood pressure control in elderly hypertensive patients: a per-protocol analysis of JATOS. *Hypertens Res* 2010; **33:** 1124–8.
5. Nakano N, *et al.* Effects of efonidipine, an L- and T-type calcium channel blocker, on the renin-angiotensin-aldosterone system in chronic hemodialysis patients. *Int Heart J* 2010; **51:** 188–92.
6. Oh IY, *et al.* Beneficial effect of efonidipine, an L- and T-type dual calcium channel blocker, on heart rate and blood pressure in patients with mild-to-moderate essential hypertension. *Korean Circ J* 2010; **40:** 514–19.

Emoxypine Succinate

Emoxipin Succinate; Emoxipine Succinate.
3-Oxy-6-methyl-2-ethylpyridine succinate; 2-Ethyl-6-methyl-3-hydroxypyridine succinate.
$C_8H_{11}NO,C_4H_6O_4$=255.3
CAS — 2364-75-2 (emoxypine); 127464-43-1 (emoxypine succinate).

Profile

Emoxypine has antoxidant properties and has been used as the succinate in cardiovascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Cerecard (Церекард); Medomexi (Медомекси); Mexicor (Мексикор); Mexidant (Мексидант); Mexidol (Мексидол); Mexifin (Мексифин); Mexiprim (Мексиприм); Neurox (Нейрокс); ***Ukr.***: Armadin (Армадин); Mexicor (Мексикор); Mexidol (Мексидол); Mexiprim (Мексиприм).

Enalapril *(BAN, rINN)*

Enalapriili; Énalapril; Enalaprilum; Эналаприл.
N-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-L-proline.
$C_{20}H_{28}N_2O_5$=376.5
CAS — 75847-73-3.
ATC — C09AA02.
ATC Vet — QC09AA02.
UNII — 69PN84IO1A.

Enalapril Maleate *(BANM, USAN, rINNM)*

Enalapriilimaleaatti; Enalapril Maleat; Énalapril, Maléate d'; Enalapril, maleato de; Enalapril maleinát; Enalaprili Maleas; Enalaprilio maleatas; Enalaprilmaleat; Enalapril-maleát; Maleato de enalapril; MK-421; Эналаприла Малеат.
N-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-L-proline hydrogen maleate.
$C_{20}H_{28}N_2O_5,C_4H_4O_4$=492.5
CAS — 76095-16-4.
ATC — C09AA02.
ATC Vet — QC09AA02.
UNII — 9O25354EPJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Enalapril Maleate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 1% solution in water has a pH of 2.4 to 2.9. Protect from light.

USP 36: (Enalapril Maleate). An off-white crystalline powder. Sparingly soluble in water; soluble in alcohol; freely soluble in dimethylformamide and in methyl alcohol; slightly soluble in semipolar organic solvents; practically insoluble in nonpolar organic solvents.

Stability. Enalapril has been reported[1,2] to be stable for at least 56 days in extemporaneously compounded oral liquids containing enalapril maleate 1 mg/mL in several vehicles.

1. Nahata MC, *et al.* Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1155–7.
2. Allen LV, Erickson MA. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1915–20.

Enalaprilat *(BAN, USAN, rINN)*

Énalaprilate; Énalaprilate dihydraté; Enalaprilatum; Enalaprilatum dihydricum; Enalaprilic acid; MK-422; Эналаприлат.
N-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline dihydrate.
$C_{18}H_{24}N_2O_5,2H_2O$=384.4
CAS — 76420-72-9 (anhydrous enalaprilat); 84680-54-6 (enalaprilat dihydrate).
UNII — GV0O7ES0R3 (enalaprilat dihydrate); Q508Q118JM (anhydrous enalaprilat).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Enalaprilat Dihydrate). A white or almost white, hygroscopic, crystalline powder. It exhibits pseudo-polymorphism. Very slightly soluble or slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in acetonitrile. Store in airtight containers.

USP 36: (Enalaprilat). A white to nearly white, hygroscopic, crystalline powder. Soluble 1 in 200 of water, 1 in 40 of dimethylformamide, and 1 in 68 of methyl alcohol; very slightly soluble in alcohol, in acetone, and in hexane; practically insoluble in acetonitrile and in chloroform; slightly soluble in isopropyl alcohol.

Incompatibility. Enalaprilat was visually incompatible[1] with phenytoin sodium in sodium chloride 0.9%, producing a crystalline precipitate; there was also some visual evidence of incompatibility when mixed with amphotericin B in glucose 5%.

1. Thompson DF, *et al.* Visual compatibility of enalaprilat with selected intravenous medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 2530–1.

Uses and Administration

Enalapril is an ACE inhibitor (p. 1282.2) used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3). It may also be given prophylactically to patients with asymptomatic left ventricular dysfunction to delay the onset of symptomatic heart failure, and has been used in patients with left ventricular dysfunction to reduce the incidence of coronary ischaemic events, including myocardial infarction (p. 1257.1).

Enalapril owes its activity to enalaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 4 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Enalapril is given orally as the maleate.

Enalaprilat is not absorbed orally but is given by intravenous injection; its haemodynamic effects develop within 15 minutes of injection and reach a peak in 1 to 4 hours. The action lasts for about 6 hours at recommended doses. Enalaprilat is given as the dihydrate, but doses are expressed in terms of the anhydrous substance. Enalaprilat 1.38 mg as the dihydrate is equivalent to about 1.25 mg of anhydrous enalaprilat.

In the treatment of **hypertension**, an initial oral dose of 5 mg of enalapril maleate daily may be given. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be given to patients who are receiving a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before enalapril is started and resumed later if necessary. The usual maintenance dose is 10 to 20 mg given once daily, although doses of up to 40 mg daily may be required in severe hypertension. It may be given in 2 divided doses if control is inadequate with a single dose.

When oral therapy of hypertension is impractical enalaprilat may be given in a dose of 1.25 mg by slow intravenous injection or infusion over at least 5 minutes, repeated every 6 hours if necessary; the initial dose should be halved in patients who are receiving a diuretic.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. In patients with heart failure or asymptomatic left ventricular dysfunction enalapril maleate is given orally in an initial dose of 2.5 mg daily. The usual maintenance dose is 20 mg daily as a single dose or in 2 divided doses although up to 40 mg daily in 2 divided doses has been given.

For dosage reduction in renal impairment, see below.
For doses in children, see below.

Administration in children. Enalapril has been subject to both dose-finding and efficacy studies in children with hypertension or heart failure[1-4] and is licensed for use in hypertension in both the UK and the US.

In the UK, recommended oral doses of enalapril maleate for **hypertension** are given according to weight as follows:
- 20 kg to < 50 kg: initial dose of 2.5 mg once daily, increased if necessary to a maximum of 20 mg once daily
- ≥ 50 kg: initial dose of 5 mg once daily, increased if necessary to a maximum of 40 mg once daily

In the USA, an initial dose of 80 micrograms/kg (maximum of 5 mg) once daily is recommended.

The *BNFC* suggests the following doses, which may be given to neonates and children in the treatment of **hypertension**, **heart failure**, or **proteinuria** in nephritis:
- neonate: initial dose of 10 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 500 micrograms/kg daily in 1 to 3 divided doses
- 1 month to 12 years: initial dose of 100 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 1 mg/kg daily in 1 or 2 divided doses
- 12 to 18 years: initial dose of 2.5 mg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased to a usual maintenance dose of 10 to 20 mg daily in 1 or 2 divided doses. Those weighing over 50 kg may be given up to 40 mg daily in 1 or 2 divided doses.

The *BNFC* also suggests the same dose in children aged 12 years and over with **diabetic neuropathy**.

1. Wells T, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol* 2002; **42:** 870–80.
2. Frenneaux M, *et al.* Enalapril for severe heart failure in infancy. *Arch Dis Child* 1989; **64:** 219–23.
3. Lloyd TR, *et al.* Orally administered enalapril for infants with congestive heart failure: a dose-finding study. *J Pediatr* 1989; **114:** 650–4.
4. Leversha AM, *et al.* Efficacy and dosage of enalapril in congenital and acquired heart disease. *Arch Dis Child* 1994; **70:** 35–9.

Administration in renal impairment. An initial oral daily dose of enalapril maleate 2.5 mg, adjusted subsequently according to response, has been recommended for those with a creatinine clearance of 30 mL/min or less; this dose may also be considered in elderly patients. Enalapril is dialysable and an oral dose of 2.5 mg should be given on dialysis days. Where oral therapy is impractical, the initial intravenous dose of enalaprilat for those with a creatinine clearance of less than 30 mL/min and those on haemodialysis is 625 micrograms, given over at least 5 minutes (but preferably longer; up to 1 hour is suggested). This dose may be repeated after 1 hour if there is an inadequate response; additional doses of 1.25 mg may be given at 6-hour intervals if needed and tolerated.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Incidence of adverse effects. Postmarketing surveillance for enalapril was carried out by prescription-event monitoring of 12 543 patients.[1] There were 374 skin events including facial oedema or angioedema in 29 (leading to withdrawal of treatment in 10), 15 cases of photosensitivity, and urticaria in 32 (leading to withdrawal in 5). Syncope and dizziness occurred in 155 and 483 patients respectively, sometimes in association with hypotension. Hypotension occurred in 218 patients, 71 in the first month. Treatment was stopped in 121 patients with hypotension, and dosage reduced in 36. Other adverse effects reported included headache in 310 patients, paraesthesias in 126, taste disturbances in 25, conjunctivitis in 67, tachycardia in 194, cough in 360, renal failure in 82, muscle cramp in 96, diarrhoea in 236, and nausea and vomiting in 326. Of 1098 deaths only 10, due to renal failure, were thought possibly related to enalapril therapy. Dysgeusia and skin reactions appeared to be less common than has been reported for captopril, but precise comparisons were difficult; the range of adverse effects was similar.[2]

Deafness was a possible adverse effect of enalapril noted earlier;[2] it was reported in 19 of the 12 543 patients monitored, but only while they were taking enalapril, there being no record of deafness after treatment stopped.

For further reference to some of these adverse effects, see under ACE Inhibitors, p. 1285.2.

1. Inman WHW, *et al.* Postmarketing surveillance of enalapril I: results of prescription-event monitoring. *BMJ* 1988; **297:** 826–9.
2. Inman WHW, Rawson NSB. Deafness with enalapril and prescription event monitoring. *Lancet* 1987; **i:** 872.

Breast feeding. After a single dose of enalapril 20 mg in 5 women enalaprilat was detected[1] in breast milk in concentrations of 1 to 2.3 nanograms/mL (mean peak 1.72 nanograms/mL); enalapril was also present (mean peak 1.74 nanograms/mL). This compared with peak serum values of 39 to 112 nanograms/mL for enalaprilat and 92 to 151 nanograms/mL for enalapril. Another study[2] found no detectable enalaprilat in the milk of 3 women, while in a further woman[3] both enalapril and enalaprilat were detected, but the concentrations were low. Although enalapril and its metabolite are thus present in small amounts in breast milk it was calculated that the average total daily dose to the neonate would only be about 2 micrograms of enalaprilat.[1] The American Academy of Pediatrics[4] lists no reports of any clinical effect on the

infant associated with the use of enalapril by breast-feeding mothers, and states that therefore it may be considered to be usually compatible with breast feeding.

For advice from UK regulatory authorities against the use of any ACE inhibitor during at least the early weeks of breast feeding see under Precautions of ACE Inhibitors, p. 1287.3.

1. Redman CWG, *et al*. The excretion of enalapril and enalaprilat in human breast milk. *Eur J Clin Pharmacol* 1990; **38:** 99.
2. Huttunen K, *et al*. Enalapril treatment of a nursing mother with slightly impaired renal function. *Clin Nephrol* 1989; **31:** 278.
3. Rush JE, *et al*. Comment. *Clin Nephrol* 1991; **35:** 234.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies enalapril as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Enalapril acts as a prodrug of the diacid enalaprilat, its active form, which is poorly absorbed orally. About 60% of an oral dose of enalapril is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1 hour. Enalapril is extensively hydrolysed in the liver to enalaprilat; peak plasma concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril. Enalaprilat is 50 to 60% bound to plasma proteins. After an oral dose, enalapril is excreted in the urine and in faeces, as enalaprilat and unchanged drug, with the urinary route predominating; more than 90% of an intravenous dose of enalaprilat is excreted in the urine. The elimination of enalaprilat is multiphasic but the effective half-life for accumulation after multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function. Enalaprilat is removed by haemodialysis and by peritoneal dialysis.

References.

1. MacFadyen RJ, *et al*. Enalapril clinical pharmacokinetics and pharmacokinetic-pharmacodynamic relationships: an overview. *Clin Pharmacokinet* 1993; **25:** 274–82.
2. Wells T, *et al*. The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; **41:** 1064–74.
3. Rouini M, *et al*. Relationship of serum ACE inhibition to oral dose of enalapril in normotensive volunteers. *J Clin Pharm Ther* 2002; **27:** 121–6.
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Renal impairment. Comparison of the pharmacokinetics of enalapril in 6 diabetics with persistent proteinuria and glomerular filtration rates (GFR) of 44.1 to 58.4 mL/minute with those in 8 age-matched controls showed that in the diabetic group the peak serum concentration of enalaprilat was higher, the time to peak concentration longer, renal clearance lower, and the areas under the concentration/time curve greater than in controls.[1] Renal clearance of enalaprilat in the diabetics ranged from 56 to 66 mL/minute compared with 105 to 133 mL/minute in controls; clearance correlated with GFR. In another study[2] involving 59 patients with chronic renal failure the pharmacokinetics of enalapril and enalaprilat were investigated in 9, who were given a once-daily oral dose of enalapril between 2.5 and 20 mg. In these patients GFR was between 6 and 60 mL/minute/1.73 m^2, and the clearance of enalaprilat was between 16 and 68 mL/minute. Markedly raised 24-hour trough values of serum enalaprilat were seen in all patients.

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2. Elung-Jensen T, *et al*. High serum enalaprilat in chronic renal failure. *J Renin Angiotensin Aldosterone Syst* 2001; **2:** 240–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Baypril; Defluin; Dentromin; Drepatil; Ecaprilat; Eitan†; Enalafel; Enalapoten; Enaldun; Enatral; Enatrial†; Eritril; Fabotensil; Gadopril; Glioten; Hipertan; Kinfil; Lotrial; Maxen; Nalapril; Presi Regul; Priltenk; Renitec; Sulocten; Tencas; Vapresan; Vasopril; ***Austral.***: Acetec; Alphapril; Amprace; Auspril; Enahexal†; Enalabell†; Renitec; ***Austria***: Alapril; Enac; Enapril; Mepril; Renistad; Renitec; ***Belg.***: Renitec; ***Braz.***: Atens; Enalabal; Enalamed; Enalatec; Enalil†; Enalprin; Enaprotec; Enatil†; Eupressin; Glioten; Malena; Multipressim; Pressel; Pressotec; Prodopressin†; Pryltec; Renalapril; Renipress; Renitec; Renopril; Sanvapress†; Vasopril; ***Canad.***: Vasotec; ***Chile***: Bajaten; Enalten; Enatrial; Esalfon; Glioten†; Grifopril; Hiperson; Hipoartel; Lotrial†; ***China***: Ai Li Ya (埃利雅); Benalapril (柏纳力); Fu Tan Le (福天乐); Invoril (因弗尔); Qin Ke Xi (勤可息); Renitec (悦宁定); Yi Na Lin (怡那林); Yi Su (依苏); ***Cz.***: Berlipril; Ednyt; Enalatin; Enap; Enapril; Invoril†; Renitec; ***Denm.***: Corodil; Enacodan; Enamaxin; ***Fin.***: Enalatin†; Linatil; Renitec; ***Fr.***: Renitec; ***Ger.***: Benalapril; Corvo†; Ena-Puren†; Ena; Enabeta; Enadigal†; Enahexal†; Enalagamma; EnaLich†; Jutaxan†; Xanef; ***Gr.***: Agioten; Analept; Antiprex; Arnaril; Erxetilan; Gnostocardin; Kaparlon-S; Kontic; Leovinezal; Megapress; Octorax; Ofnifenil; Protal; Rablas; Renitec; Stadelant; Supotron; Ulticadex; Virfen; Vitobel; ***Hong Kong***: CP-Enala†; Danssan†; Enaldun†; Enap; Lapril; Renitec; ***Hung.***: Acepril; Berlipril; Ednyt; Enalatidin; Enap; Enapril; Renapril†; Renitec; ***India***: Anze; BQL; Canvas; Converten; Dilpril; Dilvas; E-Pril; El; Ena; EnAce; Enal; Enalap; Enam; Enamate; Enapil; Enapril; Encardil; Enlacard; Enlow; Enpril; ENTP; Envas; EPM; Hytrol; Invoril; Lupinace; Minipril; Myoace; Newace; Normace; Nuril; Oren; ***Indon.***: Meipril; Renacardon; Tenace; Tenaten; ***Irl.***: Enap; Enapril; Innovace; ***Israel***: Convertin; Enaladex; Enalapri; ***Ital.***: Converten; Enapren; Lanex; Naprilene; Prilenor; Silverit; ***Malaysia***: Acetec; Danssan; Enapril; Invoril; Renitec; ***Mex.***: Adytenn; Albec†; Apo-Pyl; Bimetdad; Bionafil; Blocatril; EK-3; Enaladil; Enoval; Euronal; Feliberal; Glioten; Imotoran; Lipraken; Nalabest; Norpril; Olavac; Palane; Pulsol; Ralser; Renitec; Vexotil; ***Neth.***: Renitec; ***Norw.***: Renitec; ***NZ***: Enahexal†; Renitec; ***Philipp.***: Acebitor; Enace; Hipertal; Hypace; Hypril; Naprilate; Renitec; Stadenace; Vasopress; ***Pol.***: Benalapril; Ednyt; Enap†; Enarenal; Enazil†; Epril†; Maprył; ***Port.***: Balpril; Cetampril; Chipil†; Denapril; Diasistol; Enapress; Hipobar†; Prilan; Renitec; Tensazol; ***Rus.***: Bagopril (Багоприл); Berlipril (Берлиприл); Ednyt (Эднит); Enafarm (Энафарм); Enam (Энам); Enan (Энан); Enap (Энап); Enarenal (Энаренал); Envas (Энвас); Invoril (Инворил); Kalpiren (Кальпирен)†; Myopril (Миоприл)†; Renipril (Рениприл); Renitec (Ренитек); Vasopren (Вазопрен)†; ***S.Afr.***: Alapren; Ciplatec; Enap; Envas; Pharmapress; Renitec; ***Singapore***: Anapril; Corprilor; Enap; Enaril; Glioten; Invoril; Korandil; Renitec; ***Spain***: Acetensil; Baripril; Bitensil; Clipto; Controlvas†; Crinoren; Dabonal; Ditensor†; Herten; Hipoartel; Iecatec; Insup; Naprilene; Neotensin†; Pressitan†; Reca†; Renitec; ***Swed.***: Linatil†; Renitec; ***Switz.***: Acepril†; Elpradil; Enapril; Enatec; Epril; Reniten; ***Thai.***: Anapril; Enace; Enam; Enapril†; Enaril; Envas; Iecatec; Invoril; Istopril†; Korandil; Lapril; Myopril; Nalopril; Naritec†; Renitec; Unaril†; ***Turk.***: Enalap; Enapril; Konveril; Renitec; Vasolapril; ***UAE***: Naraprił; ***UK***: Innovace; ***Ukr.***: Berlipril (Берлиприл); Enahexal (Энагексал)†; Enalozid Mono (Эналозид Моно); Enam (Энам); Enap (Энап); ***USA***: Epaned; Vasotec; ***Venez.***: Cosil; Dinid; Enecal; Fibrosan; Hiperpril; Prilace; Redopril; Reminal; Renitec.

Multi-ingredient Preparations. ***Arg.***: Co-Renitec; Defluin Plus; Eritril Plus; Fabotensil D; Gadopril D; Gliocarvedil; Gliotenzide; Kinfil D; Lotrial D; Maxen D; Presi Regul D; Sulocten D; Tencas D; Vapresan Diur; ***Austral.***: Renitec Plus; Zan-Extra; ***Austria***: Cenipres; Co-Enac; Co-Enalapril; Co-Mepril; Co-Renistad; Co-Renitec; Enac Plus; Enalacomp; Enalapril Comp; Enalapril-HCT; Lercaprel; Renitec Plus; Zanipril; ***Belg.***: Co-Enalapril; Co-Renitec; Zanicombo; ***Braz.***: Atens H†; Atmos; Co-Enalil†; Co-Pressoless; Co-Pressotec; Co-Renitec; Coenaplex; Duopril; Eupressin-H; Gliotenzide; Malena HCT; Pryltec-H; Sinergen; Vasopril Plus; ***Canad.***: Vaseretic; ***Chile***: Bajaten D; Enalten D; Enalten DN; Esalfon-D; Grifopril-D; Hiperson-D; Lotrial D†; Normaten Plus; Normaten; ***China***: Jiu Bao Ke (久保克); Yi Shuang (依双); ***Cz.***: Enap-H; Enap-HL; Lercaprel; Zanicombo; ***Denm.***: Corodil Comp; Enabeta comp; Enacecor; Enahexal comp; Enahyton; Enarese comp; Synerpril†; Zanipress; ***Fin.***: Enalapril Comp; Linatil Comp; Renitec Comp; Renitec Plus; Zanipress; ***Fr.***: Co-Renitec; Lercapress; Zanextra; ***Ger.***: Benalapril Plus; Carmen ACE; Corvo HCT†; Enabeta comp; Enadigal HCT†; Enahexal comp†; Enala-Q comp†; Enalagamma HCT; Enalapril Comp; Enalapril HCT†; Enalapril plus†; Enalapril-saar Plus†; EnaLich comp†; Enaplus†; Eneas; Renacor; Zaneril; Zanipress; ***Gr.***: Bumeftyl; Co-Renitec; Coredopril; Eneas; Enit; Hemodilax; Iperton; Lercaprel; Modinexil; Nolarmin; Penopril; Protal complex; Savosan; Siberian; Zaneril; ***Hong Kong***: Co-Renitec; CP-Enala Co†; ***Hung.***: Acepril PlusZ; Co-Enalapril; Co-Renitec; Ednyt HCT; Ednyt Plus†; Enalapril Hexal Plus; Enalapril-HCT†; Enap-HL; Renapril Plus†; Renitec Plus; ***India***: Amace; Amlogen-EL; Amtas-E; Amzel-EL; Dilvas AM; EnAce-D; Enam-D; Enapril-HT; Enapril-LD; Enaretic; ENTP-A; Envas-H; Envas-RB; Enzide; Hytrol-AM; Invozide; Klodip Ace; Lo-E; Normace-D; ***Indon.***: Tenazide; ***Irl.***: Innozide; Lercaril; ***Israel***: Naprizide†; Vasodip Combo; ***Ital.***: Acesistem; Condiuren; Elektra; Gentipress; Keprilan; Lanetik; Neoprex; Sinertec; Vasoretic; ***Mex.***: Co-Feliberal; Co-Renitec; Gliotenzide; ***Neth.***: Co-Renitec; Lercaprel†; Lertec; Renitec Plus; ***Norw.***: Enalapril Comp; Renitec Comp; Zanipress; ***NZ***: Co-Renitec; ***Philipp.***: Co-Renitec; ***Pol.***: Enap H; Enap HL; ***Port.***: Diasistol Plus; Enatia; Eneas; Enit; Laprilen†; Lesten; Neodur†; Norpramin; Renidur; Renipril Plus; Zanipress; Zanitek; ***Rus.***: Co-Renitec (Ко-Ренитек); Enam-H (Энам-Н); Enap-H (Энап Н); Enap-HL (Энап-НЛ); Enzix (Энзикс); Prilenap (Приленап); Renipril HT (Ренприл ГТ); ***S.Afr.***: Co-Renitec; Enap-Co; Pharmapress Co; Zaneril; ***Singapore***: Co-Renitec; Enap-HL; Gliotenzide; ***Spain***: Acediur; Acetensil Plus; Baripril Diu; Bitensil Diu; Co-Renitec; Coripren; Crinoretic; Dabonal Plus; Ditenside†; Eneas; Enit; Herten Plus; Hipoartel Plus; Lercapress; Neotensin Diu†; Pressitan Plus†; Renitecmax; Vipres; Zanipress; ***Swed.***: Enalapril Comp; Linatil Comp; Renitec Comp; Synerpril; ***Switz.***: Co-Acepril; Co-Enalapril; Co-Enatec; Co-Epril; Co-Reniten; Elpradil HCT; Epril Plus; Reniten Plus; Zanipress; ***Turk.***: Eneas; Enit; Konveril Plus; ***UK***: Innozide; ***Ukr.***: Berlipril Plus (Берлиприл Плюс); Coripren (Корипрен); Enafril (Энафрил); Enahexal Compositum (Энагексал Композитум)†; Enalapril-H (Эналаприл-Н); Enalozid (Эналозид); Enap H (Энап Н); Enap HL (Энап HL); Eneas (Энеас); Enzix (Энзикс); ***USA***: Teczem; Vaseretic; ***Venez.***: Co-Renitec; Duopres; Reminalet.

Pharmacopoeial Preparations

BP 2014: Enalapril Tablets;

USP 36: Enalapril Maleate and Hydrochlorothiazide Tablets; Enalapril Maleate Oral Suspension; Enalapril Maleate Tablets; Enalaprilat Injection.

Enoxaparin Sodium *(BAN, USAN, rINN)*

Enoksapariininatrium; Enoksaparin Sodyum; Enoksaparino natrio druska; Enoksaparyna sodowa; Enoxaparin-Natrium; Enoxaparin sodná sůl; Enoxaparina sódica; Énoxaparine sodique; Enoxaparinnatrium; Enoxaparin-nátrium; Enoxaparinum Natricum; PK-10169; RP-54563; Эноксапарин Натрий.

CAS — 9041-08-1; 679809-58-6.

ATC — B01AB05.

ATC Vet — QB01AB05.

UNII — 8NZ41MIK1O.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Enoxaparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain; 15 to 25% of the components have a 1,6-anhydro structure at the reducing end of their chain. The mass-average molecular mass ranges between 3800 and 5000 with a characteristic value of about 4500. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 90 units and not more than 125 units of anti-factor Xa activity per mg, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 20 units and not more than 35 units per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7.

USP 36: (Enoxaparin Sodium). The sodium salt of a depolymerised heparin obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin sodium consists of a complex set of oligosaccharides that have not yet been completely characterised. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. About 20% of the components contain a 1,6-anhydro derivative on the reducing end of the chain. The mass-average molecular weight of enoxaparin sodium is 4,500, the range being between 3,800 and 5,000.

It has a potency of not less than 90 units and not more than 125 units of anti-factor Xa per mg, and not less than 20 units and not more than 35 units of anti-factor IIa per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7. Store in airtight containers at a temperature below 40 degrees.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Enoxaparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p. 1254.3) and in myocardial infarction (p. 1257.1).

In the *prophylaxis* of **venous thromboembolism** during surgical procedures, enoxaparin sodium is given by subcutaneous injection; treatment is usually continued for 7 to 10 days or until the patient is ambulant.

- Patients at low to moderate risk are given 20 mg (2000 units) once daily with the first dose about 2 hours pre-operatively.
- In patients at high risk, such as those undergoing orthopaedic surgery, the dose should be increased to 40 mg (4000 units) once daily with the initial dose given about 12 hours before the procedure. Alternatively, a dose of 30 mg (3000 units) may be given subcutaneously twice daily, starting within 12 to 24 hours after the operation. After hip replacement surgery, enoxaparin sodium may be continued in a dose of 40 mg (4000 units) once daily for a further 3 weeks.
- For the prophylaxis of thromboembolism in immobilised medical patients, the dose is 40 mg (4000 units) once

daily for at least 6 days; treatment should be continued until the patient is fully ambulant, up to a maximum of 14 days.

For the *treatment* of deep-vein thrombosis enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours, or 1.5 mg/kg (150 units/kg) once daily, for at least 5 days and until oral anticoagulation is established. (In pregnant patients, early-pregnancy body-weight should be used to calculate the dose.)

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, enoxaparin sodium 1 mg/kg (100 units/kg) is introduced into the arterial line of the circuit at the beginning of the dialysis session. A further dose of 0.5 to 1 mg/kg (50 to 100 units/kg) may be given if required. The dose should be reduced in patients at high risk of haemorrhage.

In the management of **unstable angina** or **non ST-elevation myocardial infarction**, enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours. Treatment is usually continued for 2 to 8 days.

In **acute ST-elevation myocardial infarction** the initial dose of enoxaparin is 30 mg (3000 units) intravenously, with a subcutaneous dose of 1 mg/kg (100 units/kg) given at the same time. Further doses of 1 mg/kg (100 units/kg) should be given subcutaneously every 12 hours for 8 days or until hospital discharge. The first 2 subcutaneous doses should not exceed 100 mg (10 000 units) each. For patients who undergo a percutaneous coronary intervention, an additional intravenous dose of 300 micrograms/kg (30 units/kg) should be given at the time of the procedure if the last subcutaneous dose was given more than 8 hours previously. Patients aged 75 years and older should be given subcutaneous doses only; the recommended dose is 750 micrograms/kg (75 units/kg) every 12 hours, with a maximum of 75 mg (7500 units) for each of the first 2 doses.

The dose of enoxaparin sodium should be reduced in patients with severe renal impairment (see below).

References.

1. Noble S, *et al*. Enoxaparin: a reappraisal of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disease. *Drugs* 1995; **49:** 388–410.
2. Noble S, Spencer CM. Enoxaparin: a review of its clinical potential in the management of coronary artery disease. *Drugs* 1998; **56:** 259–72.
3. Harvey DM, Offord RH. Management of venous and cardiovascular thrombosis: enoxaparin. *Hosp Med* 2000; **61:** 628–36.
4. Ibbotson T, Goa KL. Enoxaparin: an update of its clinical use in the management of acute coronary syndromes. *Drugs* 2002; **62:** 1407–31.
5. Fareed J, *et al*. Pharmacodynamic and pharmacokinetic properties of enoxaparin: implications for clinical practice. *Clin Pharmacokinet* 2003; **42:** 1043–57.
6. Siddiqui MAA, Wagstaff AJ. Enoxaparin: a review of its use as thromboprophylaxis in acutely ill, nonsurgical patients. *Drugs* 2005; **65:** 1025–36.
7. Carter NJ, *et al*. Enoxaparin: a review of its use in ST-segment elevation myocardial infarction. *Drugs* 2008; **68:** 691–710.
8. Schwarz AK, Zeymer U. Enoxaparin in patients with primary percutaneous coronary intervention for acute ST segment elevation myocardial infarction. *Future Cardiol* 2009; **5:** 43–9.

Administration in children. Increasing numbers of infants and children are given anticoagulants for the management of thromboembolism. Few controlled studies have been carried out in this age group and recommendations for therapy have generally been adapted from adult guidelines. Low-molecular-weight heparins may have several advantages in children. Enoxaparin has been used for the prophylaxis[1] of thromboembolism in children including neonates, and for treatment in children including neonates[1-3] and preterm infants.[1,3-5] Younger children (and in particular neonates[6]) may require a higher dose than older children. US guidelines recommend the following doses for *treatment*[7] of thromboembolism:

- under 2 months of age: 1.5 mg/kg (150 units/kg) every 12 hours
- over 2 months of age: 1 mg/kg (100 units/kg) every 12 hours

Doses for *prophylaxis*[7] are:

- under 2 months of age: 750 micrograms/kg (75 units/kg) every 12 hours
- over 2 months of age: 500 micrograms/kg (50 units/kg) every 12 hours

Similar doses are recommended in the UK by the *BNFC*, although it specifies slightly modified *treatment* doses for neonates, in whom it recommends enoxaparin sodium 1.5 to 2 mg/kg (150 to 200 units/kg) twice daily. A maximum daily dose of 40 mg (4000 units) for *prophylaxis* in children over 2 months of age is also suggested.

1. Dix D, *et al*. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000; **136:** 439–45.
2. Massicotte P, *et al*. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr* 1996; **128:** 313–18.
3. Streif W, *et al*. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F365–F370.
4. Dunaway KK, *et al*. Use of enoxaparin in a preterm infant. *Ann Pharmacother* 2000; **34:** 1410–13.
5. Michaels LA, *et al*. Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics* 2004; **114:** 703–7.
6. Malowany JI, *et al*. Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thromb Res* 2008; **122:** 826–30.
7. Monagle P, *et al*. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.

Administration in renal impairment. Careful monitoring is required when enoxaparin sodium is given to patients with mild to moderate renal impairment.[1] In severe renal impairment (creatinine clearance less than 30 mL/minute) the dose should be reduced. For *prophylaxis* of venous thromboembolism, UK licensed product information recommends a dose of 20 mg (2000 units) subcutaneously once daily whereas US licensed product information recommends a subcutaneous dose of 30 mg (3000 units) once daily. For *treatment* of venous thromboembolism, unstable angina, or non ST-elevation myocardial infarction, a dose of 1 mg/kg (100 units/kg) is given subcutaneously once daily. This dose may also be used to treat patients with acute ST-elevation myocardial infarction, in which case those aged under 75 years are given an additional single intravenous injection of 30 mg (3000 units) with the first subcutaneous dose. However, the adequacy of a once-daily dose in patients with acute coronary syndromes has been questioned and alternative dosage regimens have been suggested.[2,3]

1. Brophy DF, Sica DA. Use of enoxaparin in patients with chronic kidney disease: safety considerations. *Drug Safety* 2007; **30:** 991–4.
2. Hulot J-S, *et al*. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. *Clin Pharmacol Ther* 2005; **77:** 542–52.
3. Green B, *et al*. Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 2005; **59:** 281–90.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3. Patients with low body-weight (women below 45 kg, men below 57 kg) may be at higher risk of bleeding with prophylactic doses of enoxaparin and require careful monitoring.

Caution is required in renal impairment, and doses may need to be reduced.

Severe bleeding with enoxaparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of about 1 mg (100 units) of enoxaparin sodium.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies enoxaparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Interactions

As for Heparin, p. 1400.2.

Pharmacokinetics

Enoxaparin is rapidly and almost completely absorbed after subcutaneous injection with a bioavailability of about 100%. Peak plasma activity occurs within 1 to 5 hours. The elimination half-life is about 4 to 5 hours but anti-factor Xa activity may persist for up to 24 hours after a 40-mg dose. Elimination is prolonged in patients with renal impairment. Enoxaparin is metabolised in the liver and excreted in the urine, as unchanged drug and metabolites.

References.

1. Hulot JS, *et al*. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit* 2004; **26:** 305–10.
2. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J* 2004; **148:** 582–9.
3. Lebaudy C, *et al*. Changes in enoxaparin pharmacokinetics during pregnancy and implications for antithrombotic therapeutic strategy. *Clin Pharmacol Ther* 2008; **84:** 370–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clexane; Dilutol; Enoxdowm; Fibrinox†; Loparine; Omatex; ***Austral.***: Clexane; ***Austria***: Lovenox; ***Belg.***: Clexane; ***Braz.***: Clexane; Dripanina†; Endocris; Enoxalow; ***Canad.***: Lovenox; ***Chile***: Clexane; Henoxil; Nu-Rox; ***China***: Clexane (克赛); ***Cz.***: Clexane; ***Denm.***: Klexane; ***Fin.***: Klexane; ***Fr.***: Lovenox; ***Ger.***: Clexane; ***Gr.***: Clexane; ***Hong Kong***: Clexane; ***Hung.***: Clexane; ***India***: Clexane; Cutenox; Dynalix; Enoxarin; Exowin; Flothin; Grefac; Hepanox; LMWX; Lomonox; Lomorin-NX; Loparin; Lupenox; Macparin; Maxiparine; Megaparin; ***Indon.***: Lovenox; ***Irl.***: Clexane; ***Israel***: Clexane; ***Ital.***: Clexane; ***Malaysia***: Clexane; ***Mex.***: Clexane; ***Neth.***: Clexane; ***Norw.***: Klexane; ***NZ***: Clexane; ***Philipp.***: Clexa†; Clexane; Hepaclex; Lomoh; ***Pol.***: Clexane; ***Port.***: Klexane†; Lovenox; ***Rus.***: Clexane (Клексан); Hemapaxan (Гемапаксан); ***S. Afr.***: Clexane; ***Singapore***: Clexane; ***Spain***: Clexane; ***Swed.***: Klexane; ***Switz.***: Clexane; ***Thai.***: Clexane; ***Turk.***: Clexane; ***UK***: Clexane; ***Ukr.***: Clexane (Клексан); Flenox (Фленокс); ***USA***: Lovenox; ***Venez.***: Clexane; Enoparin.

Multi-ingredient Preparations. ***Cz.***: Clexane anti Xa-IU†.

Pharmacopoeial Preparations

BP 2014: Enoxaparin Sodium Injection;
USP 36: Enoxaparin Sodium Injection.

Enoximone *(BAN, USAN, rINN)*

Enoksimoni; Enoximon; Enoximona; Énoximone; Enoximonum; Fenoximone; MDL-17043; MDL-19438; RMI-17043; YMDL-17043; Эноксимон.

4-Methyl-5-[4-(methylthio)benzoyl]-4-imidazolin-2-one.

$C_{12}H_{12}N_2O_2S$=248.3

CAS — 77671-31-9.
ATC — C01CE03.
ATC Vet — QC01CE03.
UNII — C7Z4ITI7L7.

Incompatibility. Crystal formation has occurred when enoximone injection was mixed in glass containers or syringes; licensed product information recommends that only plastic containers or syringes are used for dilutions. It also recommends that only sodium chloride 0.9% or water be used as diluents. Glucose solutions should not be used for dilution as crystal formation may occur.

Uses and Administration

Enoximone is a phosphodiesterase type 3 inhibitor similar to amrinone (p. 1305.1) with positive inotropic and vasodilator activity. It is given intravenously in the short-term management of heart failure. In some long-term studies it was given orally, but an increased mortality rate was reported.

The usual initial dose of enoximone by intravenous injection is 0.5 to 1.0 mg/kg given at a rate not greater than 12.5 mg/minute. This may be followed by doses of 500 micrograms/kg every 30 minutes until a satisfactory response is obtained or a total dose of 3 mg/kg has been given. Alternatively, the initial dose may be given as a continuous intravenous infusion in a dose of 90 micrograms/kg per minute over 10 to 30 minutes until the desired response is achieved.

For maintenance therapy the initial dose (up to a total of 3 mg/kg) may be repeated as required every 3 to 6 hours or a continuous or intermittent infusion may be given in a dose of 5 to 20 micrograms/kg per minute.

The total dose over 24 hours should not exceed 24 mg/kg.

Dosage may need to be reduced in patients with hepatic or renal impairment (see below).

General references.

1. Vernon MW, *et al*. Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991; **42:** 997–1017.

Administration in hepatic and renal impairment. The elimination half-life of enoximone after intravenous administration was 2.16 hours in a patient with hepatic impairment and 1.33 hours in a patient with renal impairment. The mean elimination half-life in patients with normal hepatic and renal function was 1.26 hours. It was suggested that patients with renal impairment should be monitored and have plasma concentrations measured during continuous infusions and that in hepatic disease the dosage may need to be modified.[1] Similarly, in a study[2] in paediatric patients receiving intravenous enoximone clearance was reduced in those with renal or hepatic impairment and it was suggested that the infusion rate should be decreased in such patients.

1. Desager JP, *et al*. Plasma enoximone concentrations in cardiac patients. *Curr Ther Res* 1990; **47:** 743–52.
2. Booker PD, *et al*. Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Beta blocker overdosage. Enoximone, given intravenously as a bolus dose of 500 micrograms/kg followed by an infusion of 15 micrograms/kg per minute, successfully increased the cardiac output and stroke volume in a woman who had ingested 10 g of metoprolol.[1] It was suggested that enoximone may be useful in such patients since its action does not involve the beta-adrenergic system. Use to treat propranolol overdose has also been described.[2]

1. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335:** 1538.
2. Sandroni C, *et al*. Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; **50:** 759–61.

Heart failure. Enoximone is one of several drugs that may be used in heart failure (p. 1262.3), but because of an increased mortality rate reported following long-term oral use of phosphodiesterase type 3 inhibitors[1] it is only given intravenously for short-term management of heart failure

unresponsive to other treatments. In a comparison of oral enoximone and placebo in patients with moderate to moderately severe heart failure,[2] enoximone was no better than placebo in improving exercise duration over the 16-week study period. Although the overall incidence of adverse effects was similar in the two groups, 5 patients receiving enoximone died compared with none in the placebo group. In a later study,[3] low doses of oral enoximone (generally 25 or 50 mg three times daily) appeared to be safe when given to patients with advanced heart failure also taking beta blockers, but again outcomes were not improved. Similar oral doses have also been tried in an attempt to wean patients with severe (NYHA class IV) heart failure from intravenous inotropic support, but with little or only limited success.[4]

1. Amsallem E, *et al*. Phosphodiesterase III inhibitors for heart failure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 29/04/10).
2. Uretsky BF, *et al*. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. *Circulation* 1990; **82:** 774–80.
3. Metra M, *et al*. ESSENTIAL Investigators. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J* 2009; **30:** 3015–26.
4. Feldman AM, *et al*. EMOTE Study Group. Low-dose oral enoximone enhances the ability to wean patients with ultra-advanced heart failure from intravenous inotropic support: results of the oral enoximone in intravenous inotrope-dependent subjects trial. *Am Heart J* 2007; **154:** 861–9.

Adverse Effects

Long-term oral treatment with enoximone has been reported to increase the mortality rate and enoximone is now only given intravenously for short-term use.

Enoximone may cause ventricular and supraventricular tachyarrhythmias, ectopic beats, and hypotension.

Adverse effects of enoximone affecting the gastrointestinal tract include diarrhoea, nausea, and vomiting. Other adverse effects include headache, insomnia, chills, oliguria, fever, urinary retention, and limb pain. There have been reports of thrombocytopenia and abnormal liver enzyme values.

Effects on the nervous system. Tonic-clonic convulsions have been reported[1] in a patient given enoximone 6 micrograms/kg per minute by intravenous infusion. The convulsions subsided when enoximone was stopped.

1. Appadurai I, *et al*. Convulsions induced by enoximone administered as a continuous intravenous infusion. *BMJ* 1990; **300:** 613–14.

Hyperosmolality. Hyperosmolality occurred in an infant during intravenous infusion of enoximone 20 micrograms/kg per minute. The probable cause was propylene glycol in the enoximone injection providing a dose of 2.4 mg/kg per minute.[1]

1. Huggon I, *et al*. Hyperosmolality related to propylene glycol in a n infant treated with enoximone infusion. *BMJ* 1990; **301:** 19–20.

Precautions

Enoximone should be used with caution in patients with hypertrophic cardiomyopathy or severe obstructive aortic or pulmonary valvular disease.

Blood pressure, heart rate, ECG, fluid and electrolyte status, and renal function should be monitored during therapy. Platelet count and liver enzyme values should also be monitored.

The injection has a high pH (about 12) and must be diluted before use (but see. Incompatibility, p. 1373.3). Extravasation should be avoided.

Doses may need to be reduced in hepatic or renal impairment (see under Uses and Administration, p. 1373.3).

Pharmacokinetics

Although enoximone is absorbed from the gastrointestinal tract it is no longer given orally. The plasma elimination half-life varies widely; it may be about 1 to 4 hours in healthy subjects and about 3 to 8 hours in patients with heart failure, but longer times have been reported. Enoximone is about 85% bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites. After intravenous doses about 70% of a dose is excreted in the urine as metabolites and less than 1% as unchanged drug.

General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid*. 1988; **14:**(contents page).
2. Booker PD, *et al*. Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Perfan†; ***Fr.***: Perfane; ***Ger.***: Perfan; ***Irl.***: Perfan; ***Ital.***: Perfan; ***Neth.***: Perfan; ***UK***: Perfan.

Epitizide *(BAN, rINN)* ⊗

Epithiazide (USAN); Epitizida; Épitizide; Epitizidum; Eptizida; NSC-108164; P-2105; Эпитизид.

6-Chloro-3,4-dihydro-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{10}H_{11}ClF_3N_3O_4S_3$=425.8

CAS — 1764-85-8.

UNII — 5B266B85J1.

Profile

Epitizide is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) used in the treatment of hypertension and oedema, often with triamterene.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Dyta-Urese; ***Neth.***: Dyta-Urese.

Eplerenone *(BAN, USAN, rINN)* ⊗

CGP-30083; Eplerenona; Éplérénone; Eplerenonum; Epoxymexrenone; SC-66110; Эплеренон.

9,11α-Epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone methyl ester.

$C_{24}H_{30}O_6$=414.5

CAS — 107724-20-9.

ATC — C03DA04.

ATC Vet — QC03DA04.

UNII — 6995V82D0B.

Uses and Administration

Eplerenone is an aldosterone antagonist with properties similar to those of spironolactone (p. 1500.1) but with a higher selectivity for the aldosterone receptor. It is given orally in the management of hypertension (p. 1251.1) and heart failure (p. 1262.3).

In the management of **hypertension**, eplerenone may be given alone or with other antihypertensives. It is given in an initial dose of 50 mg daily, increasing if necessary to a maximum of 50 mg twice daily. While eplerenone should not be given with potent CYP3A4 inhibitors (see Interactions, below), patients taking mild to moderate inhibitors may be given eplerenone; the initial dose should be reduced to 25 mg daily.

Eplerenone is given as an adjunct to standard therapy for the management of **heart failure** in patients with NYHA class II symptoms and left ventricular ejection fraction (LVEF) ≤30%, or in those with clinical evidence of heart failure and LVEF ≤ 40% after a recent myocardial infarction. It is given in an initial dose of 25 mg daily, increasing to 50 mg daily within 4 weeks if tolerated. Eplerenone should be withdrawn or the dose should be reduced to 25 mg daily, or on alternate days, if hyperkalaemia develops. Eplerenone may be used in patients given mild to moderate CYP3A4 inhibitors, at a dose not exceeding 25 mg daily.

Doses of eplerenone may need to be adjusted in patients with renal impairment. For details, see Administration in Renal Impairment, below.

References and reviews.

1. Zillich AJ, Carter BL. Eplerenone—a novel selective aldosterone blocker. *Ann Pharmacother* 2002; **36:** 1567–76.
2. Pitt B, *et al*. , for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348:** 1309–21. Correction. *ibid*.; 2271.
3. Keating GM, Plosker GL. Eplerenone: a review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 2004; **64:** 2689–707.
4. Pitt B, *et al*. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; **46:** 425–31.
5. Anonymous. Eplerenone after myocardial infarction? *Drug Ther Bull* 2008; **46:** 1–3.
6. McManus F, *et al*. Eplerenone, a mineralocorticoid-receptor antagonist. *Nat Clin Pract Endocrinol Metab* 2008; **4:** 44–52.
7. Muldowney JA, *et al*. The clinical pharmacology of eplerenone. *Expert Opin Drug Metab Toxicol* 2009; **5:** 425–32.
8. Zannad F, *et al*. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364:** 11–21.
9. Swedberg K, *et al*. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol* 2012; **59:** 1598–603.

Administration in renal impairment. There is an increased risk of hyperkalaemia with eplerenone in patients with renal impairment and, as such, its use in all patients with a creatinine clearance (CC) of 30 mL/minute or less should be avoided. In addition, patients with a CC of 50 mL/minute or less should not receive eplerenone for the treatment of hypertension.

In those with less severe impairment, the judicious use of eplerenone is permitted. Serum-potassium levels should be monitored and dosages adjusted accordingly. UK licensed product information suggests that, for heart failure patients, no initial dose adjustment is needed in those with mild impairment (CC above 60 mL/minute); a starting dose of 25 mg orally on alternate days may be considered in those with moderate impairment (CC 30 to 60 mL/minute).

Adverse Effects

As for Spironolactone, p. 1501.2. Hypercholesterolaemia, hypertriglyceridaemia, and increases in liver enzymes have also occurred.

Precautions

As for Spironolactone, p. 1502.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eplerenone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Spironolactone, p. 1502.2.

Eplerenone is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and significantly increased plasma concentrations of eplerenone have occurred when potent inhibitors of this enzyme have been given. These include clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, and ritonavir, and use with eplerenone is contra-indicated. Mild to moderate inhibitors of this enzyme, such as erythromycin, fluconazole, saquinavir, and verapamil, have a less marked effect, although a reduced dose of eplerenone may be necessary (see under Uses, above). Grapefruit juice causes only a small increase in exposure to eplerenone. Conversely, inducers of this enzyme system, such as carbamazepine, St John's wort, phenobarbital, phenytoin, and rifampicin, may reduce plasma concentrations of eplerenone.

Pharmacokinetics

Peak plasma concentrations of eplerenone occur about 1.5 hours after a n oral dose; they are dose proportional for doses of 25 to 100 mg, and less than proportional above 100 mg. Protein binding, primarily to α_1-acid glycoprotein, is about 50%. Eplerenone metabolism is mainly mediated by the cytochrome P450 isoenzyme CYP3A4; less than 5% of a dose is excreted unchanged. About 32% of a dose is excreted in the faeces, and the remainder in the urine. The elimination half-life is about 4 to 6 hours. Eplerenone is not removed by dialysis.

References.

1. Ravis WR, *et al*. Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. *J Clin Pharmacol* 2005; **45:** 810–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aldactone EP; Oldren; Suficard; ***Austral.***: Inspra; ***Austria***: Inspra; ***Belg.***: Inspra; ***Canad.***: Inspra; ***Chile***: Inspra†; ***Cz.***: Inspra; ***Denm.***: Inspra; ***Fin.***: Inspra; ***Fr.***: Inspra; ***Ger.***: Inspra; ***Gr.***: Inspra; ***Hong Kong***: Inspra; ***Hung.***: Inspra; ***India***: Epleran; Eptus; ***Irl.***: Eplefa; Inspra; ***Israel***: Inspra; ***Mex.***: Inspra; ***Neth.***: Inspra; ***Norw.***: Inspra; ***Pol.***: Inspra; ***Port.***: Inovic; Inspra; ***SAfr.***: Inspra; ***Singapore***: Inspra; ***Spain***: Elecor; Inspra; ***Swed.***: Inspra; ***Switz.***: Inspra; ***UK***: Inspra; ***Ukr.***: Inspra (Инспра); ***USA***: Inspra.

Epoprostenol *(USAN, rINN)*

Époprosténol; Epoprostenoli; Epoprostenolum; PGI_2; PGX; Prostacyclin; Prostacyclinum; Prostacyklin; Prostaglandin I_2; Prostaglandin X; Prostasykliini; U-53217; Эпопростенол.

(5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-5,13-dienoic acid; (*Z*)-5-{(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]perhydrocyclopenta[*b*]furan-2-ylidene}valeric acid.

$C_{20}H_{32}O_5$=352.5

CAS — 35121-78-9.

ATC — B01AC09.

ATC Vet — QB01AC09.
UNII — DCR9Z582X0.

NOTE. In *Martindale* the term epoprostenol is used for the exogenous substance and prostacyclin for the endogenous substance.

Epoprostenol Sodium *(BAN, USAN, rINNM)*

Epoprostenol sódico; Époprosténol Sodique; Natrii Epoprostenolum; U-53217A; Натрий Эпопростенол.

$C_{20}H_{31}NaO_5$=374.5
CAS — 61849-14-7.
ATC — B01AC09.
ATC Vet — QB01AC09.
UNII — 4K04IQ1OF4.

Stability in solution. Epoprostenol is unstable at physiological pH and solutions for infusion are prepared in an alkaline glycine buffer at pH 10.5. The half-life in aqueous solution of pH 7.4 has been reported[1] to be less than 3 minutes at 37 degrees, but increased stability has been reported in plasma, albumin, or whole blood.[1,2]

1. El Tahir KEH, *et al.* Stability of prostacyclin in human plasma. *Clin Sci* 1980; **59:** 28P–29P.
2. Mikhailidis DP, *et al.* Infusion of prostacyclin (epoprostenol). *Lancet* 1982; **ii:** 767.

Uses and Administration

Epoprostenol is a prostaglandin (p. 2598.1) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostacyclin. Epoprostenol is used mainly in extracorporeal procedures and in pulmonary hypertension.

Epoprostenol is given as the sodium salt and doses are expressed in terms of the base; 1.06 nanograms of epoprostenol sodium is equivalent to about 1 nanogram of epoprostenol. The drug is unstable in solution at physiological pH and also has a very short duration of action because of its rapid hydrolysis *in vivo*. It must therefore be given by continuous infusion. Great care must be taken in preparing a suitably diluted solution for infusion and only diluent as supplied by the manufacturer should be used to reconstitute epoprostenol.

Epoprostenol is used to **prevent platelet aggregation** when blood is brought into contact with nonbiological surfaces in procedures such as extracorporeal circulation, especially in renal dialysis patients. It is indicated for use when heparin carries a high risk of causing or exacerbating bleeding, or is otherwise contra-indicated. Epoprostenol is given by continuous intravenous infusion or into the blood supplying the extracorporeal circulation. The usual dose for renal dialysis is 4 nanograms/kg per minute intravenously before dialysis, then 4 nanograms/kg per minute into the arterial inlet of the dialyser during dialysis.

In the long-term treatment of **pulmonary hypertension**, including that associated with scleroderma, epoprostenol is given by continuous intravenous infusion through a central catheter, although a peripheral intravenous catheter may be used until central access is established. A dose-ranging procedure is performed first. Epoprostenol infusion is started at a rate of 2 nanograms/kg per minute, then increased by increments of 2 nanograms/kg per minute at intervals of at least 15 minutes until the maximum haemodynamic benefit or dose-limiting effects occur. Epoprostenol is then given at a rate 4 nanograms/kg per minute *less than* the maximum-tolerated infusion rate; if the maximum-tolerated infusion rate is less than 5 nanograms/kg per minute, then the initial rate should be one-half of this maximum rate. The maintenance dose is subsequently adjusted according to the patient's response. If symptoms recur or if adverse effects occur the dosage may be increased or decreased by steps of 1 to 2 nanograms/kg per minute at intervals of at least 15 minutes until a new maintenance dose is established.

For the use of epoprostenol in neonates and children, see below.

Action. The discovery, properties, and clinical applications of prostacyclin have been reviewed.[1] Prostacyclin is the main product of arachidonic acid in vascular tissues, endothelial cells from vessel walls being the most active producers. It is a strong hypotensive agent through vasodilatation of vascular beds, including the pulmonary and cerebral circulations, and is also a potent endogenous inhibitor of platelet aggregation. Inhibition of aggregation is achieved by stimulation of adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP) levels in the platelets. By inhibiting several steps in the activation of the arachidonic acid metabolic cascade, prostacyclin exerts an overall control of platelet aggregability.

Endogenous prostacyclin and thromboxane A_2 may be of more physiological and pathological importance[2] than the more classical prostanoids prostaglandin E_2 and prostaglandin $F_{2\alpha}$. They have directly opposing pharmacological actions in many systems, such as on platelet function, vascular smooth muscle, bronchopulmonary function, and gastrointestinal integrity. Thus prostanoid-mediated control of cellular and tissue function may reflect an interactive modulation between prostacyclin and thromboxane A_2 with imbalance resulting in dysfunction, for example in platelet and vascular disorders. Thromboxane A_2 has both bronchoconstrictor and pulmonary irritant actions and has brought about marked changes in respiratory function in experimental models; prostacyclin may oppose these effects on both the pulmonary vasculature and bronchial smooth muscle. Thromboxane A_2 has induced marked renal vasoconstriction *in vitro* whereas renal vasodilatation and stimulation of the release of renin has followed the administration of epoprostenol [exogenous prostacyclin] in *animals*. In contrast to the pro-ulcerogenic actions of thromboxane A_2, epoprostenol and its analogues, like other prostaglandins, have potent gastrointestinal anti-ulcer properties which can be disassociated from their gastric antisecretory properties. The term 'cytoprotection' has been used to describe this ability of exogenous prostaglandins to prevent gastrointestinal damage; endogenous prostaglandins might have a similar protective role. Epoprostenol also has a cytoprotective effect against experimental damage in the gastric mucosa, myocardium, and liver whereas thromboxane A_2 has a cytolytic effect.

1. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. *Am J Cardiol* 1995; **75:** 3A–10A.
2. Whittle BJR, Moncada S. Pharmacological interactions between prostacyclin and thromboxanes. *Br Med Bull* 1983; **39:** 232–8.

Acute respiratory distress syndrome. Encouraging results[1-3] have been seen with inhaled epoprostenol in the treatment of acute respiratory distress syndrome (p. 1599.3).

1. Walmrath D, *et al.* Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342:** 961–2.
2. Walmrath D, *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153:** 991–6.
3. van Heerden PV, *et al.* Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* 2000; **117:** 819–27.

Administration in children. Although epoprostenol is not licensed for the treatment of children, it has been used successfully in children with pulmonary hypertension[1,2] and in neonates with persistent pulmonary hypertension of the newborn.[3] It is usually given by continuous intravenous infusion, but in neonates the inhaled[4] and endotracheal[5] routes have also been used.

For children aged 1 month to 18 years with *idiopathic pulmonary arterial hypertension*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, increasing as necessary to 40 nanograms/kg per minute. Children on prolonged treatment can become tolerant to epoprostenol and higher doses have been used.[1,2]

For neonates with *persistent pulmonary hypertension of the newborn*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, adjusted according to response up to a usual maximum of 20 nanograms/kg per minute (rarely up to 40 nanograms/kg per minute).

1. Barst RJ, *et al.* Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999; **99:** 1197–1208.
2. Lammers AE, *et al.* Epoprostenol treatment in children with severe pulmonary hypertension. *Heart* 2007; **93:** 739–43.
3. Eronen M, *et al.* Prostacyclin treatment for persistent pulmonary hypertension of the newborn. *Pediatr Cardiol* 1997; **18:** 3–7.
4. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141:** 830–2.
5. De Jaegere APMC, van den Anker JN. Endotracheal instillation of prostacyclin in preterm infants with persistent pulmonary hypertension. *Eur Respir J* 1998; **12:** 932–4.

Heart failure. Epoprostenol has been investigated for the treatment of heart failure but development was abandoned due to an increase in mortality associated with long-term use.[1,2]

1. Phillips BB, Gandhi AJ. Epoprostenol in the treatment of congestive heart failure. *Am J Health-Syst Pharm* 1997; **54:** 2613–15.
2. Califf RM, *et al.* A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997; **134:** 44–54.

Peripheral vascular disease. Various prostaglandins including epoprostenol have been used for their vasodilating effect in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3) that is complicated by ulceration and gangrene.

References.

1. Szczeklik A, *et al.* Successful therapy of advanced arteriosclerosis obliterans with prostacyclin. *Lancet* 1979; **i:** 1111–14.
2. Belch JJF, *et al.* Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome: a double-blind controlled trial. *Lancet* 1983; **i:** 313–15.
3. Belch JJF, *et al.* Epoprostenol (prostacyclin) and severe arterial disease: a double-blind trial. *Lancet* 1983; **i:** 315–17.
4. De San Lazaro C, *et al.* Prostacyclin in severe peripheral vascular disease. *Arch Dis Child* 1985; **60:** 370–84.
5. Leaker B, *et al.* Treatment of acute renal failure, symmetrical peripheral gangrene, and septicaemia with plasma exchange and epoprostenol. *Lancet* 1987; **i:** 156.
6. Negus D, *et al.* Intra-arterial prostacyclin compared to Praxilene in the management of severe lower limb ischaemia: a double-blind trial. *J Cardiovasc Surg* 1987; **28:** 196–9.
7. Kingma K, *et al.* Double-blind, placebo-controlled study of intravenous prostacyclin on hemodynamics in severe Raynaud's phenomenon: the acute vasodilatory effect is not sustained. *J Cardiovasc Pharmacol* 1995; **26:** 388–93.
8. Denton CP, Black CM. Raynaud's phenomenon and scleroderma. In: Snaith ML, ed. *ABC of rheumatology.* 3rd ed. London: BMJ Publishing Group, 2004: 87–91.

Pulmonary hypertension. Epoprostenol was originally introduced into the management of end-stage pulmonary hypertension (p. 1278.2) to sustain patients long enough for them to have heart-lung transplantation. There is good evidence of short-term benefit from intravenous use.[1] However, long-term therapy may also have a role as an alternative to transplantation; sustained clinical improvement and improved survival have been reported[2-5] in some patients with idiopathic pulmonary arterial hypertension given long-term intravenous therapy using portable infusion pumps, as well as in patients with pulmonary arterial hypertension associated with other diseases.[5-8] It has been combined with sildenafil.[9]

Inhaled epoprostenol, a route that may overcome some of the adverse effects associated with parenteral use, has had some success in adults[1,10-12] with pulmonary hypertension and in neonates[13,14] with persistent pulmonary hypertension.

1. Paramothayan NS, *et al.* Prostacyclin for pulmonary hypertension in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 08/03/10).
2. Higenbottam T, *et al.* Long term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; **80:** 151–5.
3. Herner SJ, Mauro LS. Epoprostenol in primary pulmonary hypertension. *Ann Pharmacother* 1999; **33:** 340–7.
4. McLaughlin VV, *et al.* Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; **106:** 1477–82.
5. Kuhn KP, *et al.* Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; **167:** 580–6.
6. McLaughlin VV, *et al.* Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999; **130:** 740–3.
7. Badesch DB, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 425–34.
8. Fisher KA, *et al.* Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest* 2006; **130:** 1481–8.
9. Simonneau G, *et al.* PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; **149:** 521–30. Corrections. *ibid.* 2009; **150:** 63 and **151:** 435.
10. Olschewski H, *et al.* Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996; **124:** 820–4.
11. Mikhail G, *et al.* An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. *Eur Heart J* 1997; **18:** 1499–1504.
12. Buckley MS, Feldman JP. Inhaled epoprostenol for the treatment of pulmonary arterial hypertension in critically ill adults. *Pharmacotherapy* 2010; **30:** 728–40.
13. Bindl L, *et al.* Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child Fetal Neonatal Ed* 1994; **71:** F214–F216.
14. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141:** 830–2.

Stroke. Results with epoprostenol in patients with acute stroke have been inconclusive and a systematic review of randomised studies concluded that too few patients had been studied for the effect of epoprostenol on survival to be determined.[1]

1. Bath PMW. Prostacyclin and analogues for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 04/07/05).

Thrombotic microangiopathies. Platelet aggregation has a major role in the pathogenesis of thrombotic thrombocytopenic purpura and the related disorder, haemolytic-uraemic syndrome (p. 1159.1). Prostacyclin deficiency has been found in both conditions, but case reports of epoprostenol[1,2] or iloprost[3,4] treatment have indicated variable results.

1. Bobbio-Pallavicini E, *et al.* Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79:** 429–37.
2. Series C, *et al.* Interet de la prostacycline dans le traitement du syndrome hémolytique et urémique: à propos d'un cas. *Rev Med Interne* 1996; **17:** 76–8.
3. Sagripanti A, *et al.* Iloprost in the treatment of thrombotic microangiopathy: report of thirteen cases. *Biomed Pharmacother* 1996; **50:** 350–6.
4. Salvi F, *et al.* Unsuccessful treatment of resistant thrombotic thrombocytopenic purpura with prostacyclin. *Haematologica* 2000; **85:** 1329–30.

Adverse Effects and Precautions

The incidence of adverse reactions to epoprostenol is dose-related. Adverse effects during intravenous infusion

commonly include hypotension, increased heart rate, flushing, and headache. Dosage should be reduced or the epoprostenol infusion stopped if excessive hypotension occurs. Bradycardia with pallor, sweating, nausea, and abdominal discomfort may occur. Erythema over the intravenous infusion site has been noted. Other adverse effects reported have included nausea and vomiting, diarrhoea, jaw pain or non-specific musculoskeletal pain, anxiety, nervousness, tremor, flu-like symptoms, hyperglycaemia, drowsiness, and chest pain.

Epoprostenol is a potent inhibitor of platelet aggregation and should be used with caution in patients at risk of bleeding. Coagulation of blood in the dialysis circuit has been reported rarely in patients given epoprostenol but no conventional anticoagulant. The use of epoprostenol for pulmonary hypertension is contra-indicated in patients with congestive heart failure due to severe left ventricular systolic dysfunction, and in patients who develop pulmonary oedema during dose-ranging. Sudden withdrawal of epoprostenol should be avoided because of the risk of rebound pulmonary hypertension. Haematological and cardiovascular monitoring is required in patients receiving epoprostenol infusions. Care should be taken to avoid extravasation.

Incidence of adverse effects. A study in 24 healthy subjects investigated the incidence of adverse effects with intravenous infusions of epoprostenol of up to 10 nanograms/kg per minute for up to 100 minutes.[1] Subjects varied in their susceptibility to epoprostenol but the same sequence of events was usually present. A change in pre-ejection period and facial flushing was often apparent at an infusion rate of 2 to 2.5 nanograms/kg per minute. A rise in heart rate and change in other cardiovascular variables was present when the infusion rate had increased to 4 to 5 nanograms/kg per minute; headache, generally the dose-limiting factor, was usually present at this dose and increased as the dose was raised, as did the other effects. Erythema over the vein and 'vagal reflex' only appeared after at least 1 hour of infusion; 'vagal reflex' took only a few seconds to develop.

Early studies showing that high doses were well tolerated had been conducted using a form of epoprostenol probably only half as potent as the commercially available product. It was proposed that 4 nanograms/kg per minute should in general be the maximum infusion rate for prolonged infusions, although higher rates could be tolerated in anaesthetised patients. Careful attention to infusion technique is necessary and monitoring of the heart rate is advisable in view of the suddenness with which the 'vagal reflex' can occur. Most of the adverse effects reported here have responded to a reduction in dosage.

1. Pickles H, O'Grady J. Side effects occurring during administration of epoprostenol (prostacyclin, PGI_2), in man. *Br J Clin Pharmacol* 1982; **14:** 177–85.

Effects on the blood. Reports of rebound platelet activation during continuous epoprostenol infusion.[1,2]

1. Yardumian DA, Machin SJ. Altered platelet function in patients on continuous infusion of epoprostenol. *Lancet* 1984; **i:** 1357.
2. Sinzinger H, *et al.* Rebound platelet activation during continuous epoprostenol infusion. *Lancet* 1984; **ii:** 759.

Effects on the cardiovascular system. Evidence that epoprostenol and its analogue iloprost can induce myocardial ischaemia in patients with coronary artery disease.[1]

1. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; **38:** 101–8.

Effects on mental state. Symptoms of depression were associated with intravenous epoprostenol therapy in 4 patients.[1]

1. Ansell D, *et al.* Depression and prostacyclin infusion. *Lancet* 1986; **ii:** 509.

Hypersensitivity. Severe erythroderma occurred in a woman with undifferentiated connective tissue disease who was treated with epoprostenol for pulmonary hypertension.[1] Diffuse erythema, pruritus, and scaling, with chills, nausea, vomiting, and diarrhoea, developed about 2 months after starting therapy, and resolved with epoprostenol withdrawal and corticosteroid treatment.

1. Ahearn GS, *et al.* Severe erythroderma as a complication of continuous epoprostenol therapy. *Chest* 2002; **122:** 378–80.

Interactions

Since epoprostenol is a potent vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants. Epoprostenol may slightly increase serum concentrations of digoxin, and may reduce the thrombolytic effect of alteplase by increasing its hepatic clearance. The hypotensive effects of epoprostenol may be exacerbated by using acetate in dialysis fluids.

Anticoagulants. The incidence of bleeding complications was examined in a retrospective review[1] of 31 patients with pulmonary arterial hypertension who had been treated with continuous intravenous epoprostenol and oral *warfarin*. Nine patients developed 11 bleeding episodes, including 9 episodes of alveolar haemorrhage. The international normalised ratio (INR) was maintained in the therapeutic range for 8 of these patients, suggesting that the effect was not caused by overdose of warfarin. The risk of bleeding appeared to be increased in patients who received high-dose epoprostenol (mean dose 89 nanograms/kg per minute).

1. Ogawa A, *et al.* Risk of alveolar hemorrhage in patients with primary pulmonary hypertension—anticoagulation and epoprostenol therapy. *Circ J* 2005; **69:** 216–20.

Pharmacokinetics

Endogenous prostacyclin is a product of arachidonic acid metabolism with a very short half-life. On intravenous infusion epoprostenol is hydrolysed rapidly to the more stable but much less active 6-keto-prostaglandin $F_{1\alpha}$ (6-oxo-prostaglandin $F_{1\alpha}$). A second metabolite, 6,15-diketo-13,14-dihydro-prostaglandin $F_{1\alpha}$, is formed by enzymatic degradation. Unlike many other prostaglandins, epoprostenol is not inactivated in the pulmonary circulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Flolan; ***Belg.***: Flolan; ***Canad.***: Flolan; ***Cz.***: Flolan; ***Denm.***: Flolan; ***Fr.***: Flolan; ***Gr.***: Flolan; ***Irl.***: Flolan; ***Israel***: Flolan; ***Ital.***: Flolan; ***Neth.***: Flolan; ***Norw.***: Flolan; ***Singapore***: Flolan; ***Spain***: Dynovase; Flolan; ***Switz.***: Flolan; Veletri; ***UK***: Flolan; Veletri; ***USA***: Flolan; Veletri.

Eprosartan Mesilate *(BANM, rINNM)*

Éprosartan, Mésilate d'; Eprosartán, mesilato de; Eprosartan Mesylate (USAN); Eprosartani Mesilas; Mesilato de eprosartán; SKF-108566-J; Эпрозартана Мезилат.

(*E*)-2-Butyl-1-(*p*-carboxybenzyl)-α-2-thenylimidazole-5-acrylic acid methanesulfonate.

$C_{23}H_{24}N_2O_4S,CH_4O_3S$=520.6

CAS — 133040-01-4 (eprosartan); 144143-96-4 (eprosartan mesilate).

ATC — C09CA02.

ATC Vet — QC09CA02.

UNII — 8N2L1NX8S3.

Uses and Administration

Eprosartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1).

Eprosartan is given orally as the mesilate but doses are expressed in terms of the base; eprosartan mesilate 1.2 mg is equivalent to about 1 mg of eprosartan. The onset of antihypertensive effect occurs about 1 to 2 hours after a dose and the maximum effect is achieved within 2 to 3 weeks of starting therapy.

In the management of hypertension, eprosartan is given in an initial dose of 600 mg once daily. The dose should be adjusted according to response; the usual maintenance dose is 400 to 800 mg daily in a single dose or in two divided doses. For advice on dose adjustments in patients with renal impairment, see below.

Reviews.

1. McClellan KJ, Balfour JA. Eprosartan. *Drugs* 1998; **55:** 713–18.
2. Robins GW, Scott LJ. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2005; **65:** 2355–77.
3. Ram CV, Rudmann MA. Unique dual mechanism of action of eprosartan: effects on systolic blood pressure, pulse pressure, risk of stroke and cognitive decline. *Expert Rev Cardiovasc Ther* 2007; **5:** 1003–11.
4. Blankestijn PJ, Rupp H. Clinical profile of eprosartan: a different angiotensin II receptor blocker. *Cardiovasc Hematol Agents Med Chem* 2008; **6:** 253–7.
5. Plosker GL. Eprosartan: a review of its use in hypertension. *Drugs* 2009; **69:** 2477–99.
6. Xu FY, *et al.* Antihypertensive effects and safety of eprosartan: a meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol* 2012; **68:** 195–205.

Administration in renal impairment. In patients with moderate or severe renal impairment (creatinine clearance < 60 mL/minute), the maximum daily oral dose of eprosartan should not exceed 600 mg.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eprosartan as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Eprosartan is absorbed from the gastrointestinal tract with an absolute oral bioavailability of about 13%. Peak plasma concentrations occur about 1 to 2 hours after an oral dose in the fasted state; giving doses with food delays absorption but this is not clinically significant. Eprosartan is about 98% bound to plasma proteins. It is excreted in the bile and in the urine, mainly as the unchanged drug; after oral doses about 7% of the drug is excreted in the urine, with about 2% as the acyl glucuronide. The terminal elimination half-life is about 5 to 9 hours.

References.

1. Martin DE, *et al.* Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. *J Clin Pharmacol* 1998; **38:** 129–37.
2. Tenero DM, *et al.* Effect of age and gender on the pharmacokinetics of eprosartan. *Br J Clin Pharmacol* 1998; **46:** 267–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Teveten; ***Austria***: Teveten; ***Belg.***: Teveten; ***Canad.***: Teveten; ***China***: Teveten (泰盛欣); ***Cz.***: Teveten; ***Denm.***: Teveten†; Tevetenz†; ***Fin.***: Teveten; ***Fr.***: Teveten; ***Ger.***: Emestar Mono†; Teveten; ***Gr.***: Epratenz; Teveten; ***Hong Kong***: Teveten; ***Hung.***: Teveten; ***Indon.***: Teveten; ***Irl.***: Teveten; ***Ital.***: Tevetenz; ***Mex.***: Tevetenz; ***Neth.***: Teveten; ***Norw.***: Teveten; ***NZ***: Teveten; ***Philipp.***: Teveten; ***Pol.***: Teveten; ***Port.***: Larutan†; Teveten; ***Rus.***: Naviten (Навитен); Teveten (Тевeтен); ***S.Afr.***: Teveten; ***Spain***: Futuran; Navixen; Regulaten; Tevetens; ***Swed.***: Teveten; ***Switz.***: Eprotan; Teveten; ***Thai.***: Teveten†; ***Turk.***: Teveten; ***UK***: Teveten; ***Ukr.***: Teveten (Тевeтен); ***USA***: Teveten.

Multi-ingredient Preparations. ***Austral.***: Teveten Plus; ***Austria***: Coepratenz Plus; Teveten Plus; ***Belg.***: Teveten Plus; ***Canad.***: Teveten Plus; ***Cz.***: Teveten Plus H; ***Denm.***: Teveten Comp; ***Fin.***: Coepratenz Comp†; Teveten Comp; ***Fr.***: Coteveten†; ***Ger.***: Emestar plus; Eprosartan comp; Teveten Plus; ***Gr.***: Epratenz Plus; Teveten Plus; ***Hong Kong***: Teveten Plus; ***Irl.***: Coepratenz Plus; Teveten Plus; ***Ital.***: Tiartan; ***Mex.***: Tevetenz Dox; ***Neth.***: Teveten Plus; ***Norw.***: Teveten Comp; ***Philipp.***: Teveten Plus; ***Port.***: Medinor†; Tensival†; Teveten Plus; ***Rus.***: Teveten Plus (Тевeтен Плюс); ***S.Afr.***: Teveten Plus; ***Spain***: Futuran Plus; Navixen Plus; Regulaten Plus; Tevetens Plus; ***Swed.***: Teveten Comp; ***Switz.***: Eprotan Plus; Teveten Plus; ***Turk.***: Teveten Plus; ***USA***: Teveten HCT.

Eptifibatide *(BAN, rINN)*

C68-22; Eptifibatid; Eptifibatida; Eptifibatidi; Eptifibatidum; Integrelin; Intrifiban; SB-1; Sch-60936; Эптифибатид.

N^6-Amidino-N^2-(3-mercaptopropionyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide; S^1,S^6-Cyclo[N^6-carbamimidoyl-N^2-(3-sulfanylpropanoyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide].

$C_{35}H_{49}N_{11}O_9S_2$=832.0

CAS — 148031-34-9; 157630-07-4.

ATC — B01AC16.

ATC Vet — QB01AC16.

UNII — NA8320J834.

Uses and Administration

Eptifibatide is an antiplatelet drug that reversibly inhibits binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the glycoprotein IIb/IIIa receptor of platelets. It is used, usually with aspirin and heparin, in the management of unstable angina and in patients undergoing coronary angioplasty and stenting procedures.

In the management of **unstable angina**, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection, followed by 2 micrograms/kg per minute by intravenous infusion, for up to 72 hours. If percutaneous coronary intervention is performed during eptifibatide therapy, the infusion should be continued for 18 to 24 hours after the procedure, to a maximum total duration of 96 hours of therapy.

In patients undergoing **angioplasty**, though not presenting with unstable angina, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection immediately before the procedure, followed by 2 micrograms/kg per minute by intravenous infusion, with a second 180 micrograms/kg intravenous injection given 10 minutes after the first. The infusion should be continued until hospital discharge or for up to 18 to 24 hours; a minimum of 12 hours is recommended.

The dose of eptifibatide may need to be reduced in patients with renal impairment (see p. 1377.1).

General references.
1. Gilchrist IC. Platelet glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention: focus on the pharmacokinetic-pharmacodynamic relationships of eptifibatide. *Clin Pharmacokinet* 2003; **42:** 703–20.
2. Curran MP, Keating GM. Eptifibatide: a review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. *Drugs* 2005; **65:** 2009–35.
3. Tricoci P, *et al*. Present and evolving role of eptifibatide in the treatment of acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2007; **5:** 401–12.
4. Zeymer U. The role of eptifibatide in patients undergoing percutaneous coronary intervention. *Expert Opin Pharmacother* 2007; **8:** 1147–54.
5. Zeymer U, Wienbergen H. A review of clinical trials with eptifibatide in cardiology. *Cardiovasc Drug Rev* 2007; **25:** 301–15.

Administration in renal impairment. The clearance of eptifibatide is reduced in renal impairment and plasma-eptifibatide concentrations are about doubled in patients with a creatinine clearance (CC) below 50 mL/minute.[1] Eptifibatide should not be used in severe renal impairment; it is contra-indicated in patients with CC below 30 mL/minute in the UK, and in dialysis-dependent patients in the USA. In patients with moderate renal impairment (CC below 50 mL/minute), the same bolus doses may be given as in those with normal renal function but the infusion dose should be reduced to 1 microgram/kg per minute.

1. Gretler DD, *et al*. Pharmacokinetic and pharmacodynamic properties of eptifibatide in subjects with normal or impaired renal function. *Clin Ther* 2004; **26:** 390–398.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. In patients with *unstable angina* (p. 1254.3), eptifibatide has been used as an adjunct to both medical and interventional therapy. In the PURSUIT study,[1] which compared eptifibatide with placebo in over 10 000 patients with ischaemic chest pain, the incidence of death and non-fatal myocardial infarction up to 30 days after treatment was reduced in those receiving eptifibatide; most patients also received aspirin and heparin and the number of percutaneous interventions was similar in each group. The optimal timing of such use has, however, yet to be determined. The EARLY ACS study[2] found no advantage from early use of eptifibatide before angiography in patients with acute coronary syndromes without ST-segment elevation, compared with provisional use after angiography.

Eptifibatide has also been of benefit as an adjunct to standard therapy in patients undergoing *elective percutaneous interventions* (see Reperfusion and Revascularisation Procedures, p. 1259.2). In the IMPACT-II study[3] of over 4000 patients undergoing elective or emergency percutaneous coronary revascularisation, the incidence of death, myocardial infarction, and further unplanned coronary intervention was reduced in those receiving eptifibatide compared with placebo. Similar results were also obtained in a further study (ESPRIT)[4] in patients who were undergoing percutaneous coronary revascularisation with stent implantation, and benefit was maintained at 6-month follow-up.[5] Although most studies have given eptifibatide with unfractionated heparin, use with low-molecular-weight heparin also appears to be safe.[6]

In patients with *acute myocardial infarction* (p. 1257.1), eptifibatide has been tried as an adjunct to thrombolysis or percutaneous intervention. In a study (INTRO AMI)[7] comparing eptifibatide and thrombolysis with thrombolysis alone, early patency rates were improved in those receiving eptifibatide but there was no significant difference in outcomes at 30 days. In patients undergoing interventional therapy, an observational study[8] found that eptifibatide was less effective than abciximab, but other studies[9,10] have reported similar outcomes in patients treated with abciximab or eptifibatide. Positive results have also been seen[11] with eptifibatide given in addition to thrombolytics before percutaneous intervention.

There have been reports of successful intracoronary use[12,13] of eptifibatide, and also prolonged intravenous use[14] in a patient unable to take oral antiplatelet drugs. It has also been used as bridging therapy to prevent stent thrombosis in patients with coronary stents who subsequently require coronary artery bypass grafts (in whom clopidogrel must therefore be stopped several days before surgery to prevent excess bleeding).[15]

1. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339:** 436–43.
2. Giugliano RP, *et al*. Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009; **360:** 2176–90.
3. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997; **349:** 1422–8.
4. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000; **356:** 2037–44. Correction. *ibid*. 2001; **357:** 1370.
5. O'Shea JC, *et al*. Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT Trial: a randomized controlled trial. *JAMA* 2001; **285:** 2468–73.
6. Bhatt DL, *et al*. Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. *J Am Coll Cardiol* 2003; **41:** 20–5.
7. Brener SJ, *et al*. Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. *J Am Coll Cardiol* 2002; **39:** 377–86.
8. Deliargyris EN, *et al*. Superior in-hospital and 30-day outcomes with abciximab versus eptifibatide: a contemporary analysis of 495 consecutive percutaneous coronary interventions. *J Invasive Cardiol* 2004; **16:** 611–16.
9. Suleiman M, *et al*. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, eptifibatide and abciximab: outcomes, complications and thrombocytopenia during percutaneous coronary intervention. *J Invasive Cardiol* 2003; **15:** 319–23.
10. Raveendran G, *et al*. Eptifibatide vs abciximab as adjunctive therapy during primary percutaneous coronary intervention for acute myocardial infarction. *Mayo Clin Proc* 2007; **82:** 196–202.
11. ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. *Am Heart J* 2005; **150:** 116–22. Correction. *ibid*.; 391.
12. Deibele AJ, *et al*. Intracoronary bolus administration of eptifibatide during percutaneous coronary stenting for non ST elevation myocardial infarction and unstable angina. *J Thromb Thrombolysis* 2006; **22:** 47–50.
13. Deibele AJ, *et al*. Intracoronary eptifibatide bolus administration during percutaneous coronary revascularization for acute coronary syndromes with evaluation of platelet glycoprotein IIb/IIIa receptor occupancy and platelet function: the Intracoronary Eptifibatide (ICE) Trial. *Circulation* 2010; **121:** 784–91.
14. Jaffe R, *et al*. Prolonged intravenous eptifibatide infusion for prevention of coronary stent thrombosis. *Int J Cardiol* 2007; **114:** 409–11.
15. Pickett AM, *et al*. Prolonged infusion of eptifibatide as bridge therapy between bare-metal stent insertion and cardiovascular surgery: case report and review of the literature. *Pharmacotherapy* 2010; **30:** 127e–133e.

Adverse Effects

Bleeding is the most common adverse effect of eptifibatide. Hypotension has been reported. Antibodies to eptifibatide have not been detected.

Effects on the blood. Thrombocytopenia is an established adverse effect of the glycoprotein IIb/IIIa-receptor antagonist abciximab (see p. 1281.3) but appears to be less common with eptifibatide. However, there have been several reports[1-6] of severe thrombocytopenia associated with eptifibatide.

1. Paradiso-Hardy FL, *et al*. Severe thrombocytopenia possibly related to readministration of eptifibatide. *Catheter Cardiovasc Interv* 2001; **54:** 63–7.
2. Hongo RH, Brent BN. Association of eptifibatide and acute profound thrombocytopenia. *Am J Cardiol* 2001; **88:** 428–31.
3. Yoder M, Edwards RF. Reversible thrombocytopenia associated with eptifibatide. *Ann Pharmacother* 2002; **36:** 628–30.
4. Coons JC, *et al*. Eptifibatide-associated acute, profound thrombocytopenia. *Ann Pharmacother* 2005; **39:** 368–72.
5. Refaat M, *et al*. Eptifibatide-induced thrombocytopenia. *J Thromb Thrombolysis* 2008; **25:** 204–6.
6. Russell KN, *et al*. Acute profound thrombocytopenia associated with readministration of eptifibatide: case report and review of the literature. *Pharmacotherapy* 2009; **29:** 867–74.

Precautions

As for Abciximab, p. 1282.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eptifibatide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pharmacokinetics

Antiplatelet effects of eptifibatide persist for about 4 hours after stopping a continuous infusion. Plasma elimination half-life is about 2.5 hours. Eptifibatide is about 25% bound to plasma proteins. Renal clearance, as eptifibatide and metabolites excreted in the urine, accounts for about 50% of total body clearance.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Integrilin; ***Austria***: Integrilin; ***Belg.***: Integrilin; ***Canad.***: Integrilin; ***Cz.***: Integrilin; ***Denm.***: Integrilin; ***Fin.***: Integrilin; ***Fr.***: Integrilin; ***Ger.***: Integrilin; ***Gr.***: Integrilin; ***Hong Kong***: Integrilin; ***Hung.***: Integrilin; ***India***: Antigrilin; Clotide; Coromax; Eptifab; Fleta Bolus; ***Indon.***: Integrilin; ***Irl.***: Integrilin; ***Israel***: Integrilin; ***Ital.***: Integrilin; ***Malaysia***: Integrilin; ***Neth.***: Integrilin; ***Norw.***: Integrilin; ***NZ***: Integrilin; ***Philipp.***: Integrilin†; ***Pol.***: Integrilin; ***Port.***: Integrilin; ***Rus.***: Integrilin (Интегрилин); ***S.Afr.***: Integrilin; ***Singapore***: Integrilin; ***Spain***: Integrilin; ***Swed.***: Integrilin; ***Switz.***: Integrilin; ***Thai.***: Integrilin; ***UK***: Integrilin; ***Ukr.***: Integrilin (Интегрилин); ***USA***: Integrilin.

Esatenolol *(rINN)* ⊗

(-)-Atenolol; *S*-Atenolol; Ésaténolol; Esatenololum; Эзатенолол.

2-{*p*-[(2*S*)-2-Hydroxy-3-(isopropylamino)propoxy]phenyl} acetamide.

$C_{14}H_{22}N_2O_3$=266.3

CAS — 93379-54-5.

ATC — C07AB11.

ATC Vet — QC07AB11.

UNII — DPF757BOSR.

Profile

Esatenolol, the *S* (-)-isomer of atenolol, has been used similarly to atenolol (p. 1308.2) in the treatment of cardiovascular disorders in usual oral doses of 25 to 100 mg daily.

References.
1. McCoy RA, *et al*. Pharmacodynamics of racemic and S(-)-atenolol in humans. *J Clin Pharmacol* 1994; **34:** 816–22.
2. Clementi WA, *et al*. Single dose pharmacokinetics of (S)-atenolol administered orally as a single enantiomer formulation and as a racemic mixture (Tenormin). *Chirality* 1994; **6:** 169–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Adbeta; Atpure; ***Thai.***: Esnolol; ***Ukr.***: Asoten (Азотен)†.

Multi-ingredient Preparations. ***India***: Adbeta-H.

Esmolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ASL-8052; Esmolol, Chlorhydrate d'; Esmolol, hidrocloruro de; Esmolol Hidroklorür; Esmololi Hydrochloridum; Hidrocloruro de esmolol; Эсмолола Гидрохлорид.

Methyl 3-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl] propionate hydrochloride.

$C_{16}H_{25}NO_4$,HCl=331.8

CAS — 81147-92-4 (esmolol); 84057-94-3 (esmolol); 103598-03-4 (esmolol); 81161-17-3 (esmolol hydrochloride).

ATC — C07AB09.

ATC Vet — QC07AB09.

UNII — V05260LC8D.

Pharmacopoeias. In *US*.

USP 36: (Esmolol Hydrochloride). A white to off-white crystalline powder. Very soluble in water; freely soluble in alcohol. pH 3.0 to 5.0. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Do not allow to freeze.

Incompatibility. Licensed product information advises against mixing esmolol hydrochloride with sodium bicarbonate because of incompatibility. There has also been a report[1] of immediate haze formation after admixture of esmolol hydrochloride with warfarin sodium.

1. Bahal SM, *et al*. Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Uses and Administration

Esmolol is a cardioselective short-acting beta blocker (p. 1316.3). It is reported to be lacking in intrinsic sympathomimetic and membrane-stabilising properties.

Esmolol is used as the hydrochloride in the management of supraventricular arrhythmias (p. 1266.1). It is also used for the control of hypertension (p. 1251.1) and tachycardia during the perioperative period.

Esmolol hydrochloride is given intravenously at a concentration usually not exceeding 10 mg/mL.

For the rapid temporary control of ventricular rate in patients with **supraventricular arrhythmias**, a loading dose of 500 micrograms/kg given over 1 minute is followed by an initial maintenance infusion of 50 micrograms/kg per minute for 4 minutes. If the response is satisfactory this maintenance infusion should be continued at 50 micrograms/kg per minute. If a suitable response is not obtained within the first 5 minutes a further loading dose of 500 micrograms/kg over 1 minute may be given and the maintenance infusion may be increased to 100 micrograms/kg per minute for 4 minutes. If necessary, this procedure may be repeated once or twice more, until a satisfactory response is obtained, increasing the maintenance infusion each time by 50 micrograms/kg per minute to a maximum of 200 micrograms/kg per minute. Little additional benefit is obtained from further increases in maintenance dosage. Once a satisfactory response is obtained infusion may be continued, if necessary, for up to 48 hours.

When transferring a patient to another antiarrhythmic drug, the infusion rate of esmolol hydrochloride is reduced by 50% thirty minutes after starting the alternative drug, and may be stopped one hour after the second dose of that drug.

In the control of perioperative **hypertension** and/or **tachycardia**, esmolol hydrochloride may be given intravenously as follows:

- *during* anaesthesia, a loading dose of 80 mg over 15 to 30 seconds followed by an infusion of 150 micrograms/kg per minute, increased as necessary up to 300 micrograms/kg per minute
- on *waking* from anaesthesia, an infusion of 500 micrograms/kg per minute for 4 minutes, followed by an infusion of 300 micrograms/kg per minute as required
- *postoperatively*, a stepped dosage schedule, as described under control of supraventricular arrhythmias above, although maintenance infusions may be increased up to 300 micrograms/kg per minute as necessary.

For the use of esmolol in children, see below.

References.

1. Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. *Clin Pharmacokinet* 1995; **28:** 190–202.

Administration in children. Although esmolol is unlicensed for use in children, the *BNFC* suggests that it may be given for the treatment of **cardiac arrhythmias** or **hypertensive emergencies** in those aged 1 month and over. An intravenous loading dose of 500 micrograms/kg given over 1 minute may be followed by an intravenous infusion of 50 micrograms/kg per minute for 4 minutes. (The dose may be given at a slower rate if the blood pressure or heart rate is too low.) If the response is inadequate, the loading dose may be repeated, and the maintenance infusion increased by 50 microgram/kg per minute increments, until a satisfactory response is obtained or a maximum infusion rate of 200 micrograms/kg per minute is reached.

For doses given in the treatment of **tetralogy of Fallot**, see below.

References.

1. Trippel DL, *et al*. Cardiovascular and antiarrhythmic effects of esmolol in children. *J Pediatr* 1991; **119:** 142–7.
2. Wiest DB, *et al*. Esmolol for the management of pediatric hypertension after cardiac operations. *J Thorac Cardiovasc Surg* 1998; **115:** 890–7.
3. Tabbutt S, *et al*. The safety, efficacy, and pharmacokinetics of esmolol for blood pressure control immediately after repair of coarctation of the aorta in infants and children: a multicenter, double-blind, randomized trial. *J Thorac Cardiovasc Surg* 2008; **136:** 321–8.

Tetralogy of Fallot. Beta blockers have been used in the management of tetralogy of Fallot (see under Uses of Propranolol, p. 1479.3). The *BNFC* recommends that neonates may be given esmolol hydrochloride in an initial dose of 600 micrograms/kg by intravenous injection over 1 to 2 minutes; if necessary, this may be followed by an intravenous infusion at a dose of 300 to 900 micrograms/kg per minute.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Hypotension is the most frequently reported adverse effect associated with the infusion of esmolol hydrochloride; it generally resolves within 30 minutes once the dosage is reduced or the infusion is stopped. Local irritation at the site of infusion, inflammation, induration, and thrombophlebitis have occurred and necrosis is a hazard of extravasation. These local effects have occurred with concentrations of 20 mg/mL and it is recommended that concentrations of standard formulations should not normally exceed 10 mg/mL, particularly if given peripherally, and that the infusion should not be made into a small vein.

Effects on the CNS. Generalised tonic-clonic seizures occurred in an elderly patient given esmolol hydrochloride.[1]

1. Das G, Ferris JC. Generalized convulsions in a patient receiving ultra short-acting beta-blocker infusion. *Drug Intell Clin Pharm* 1988; **22:** 484–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies esmolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

After intravenous doses esmolol is rapidly hydrolysed by esterases in the red blood cells. Steady-state blood concentrations occur within 30 minutes with doses of 50 to 300 micrograms/kg per minute. The time to steady state may be reduced to 5 minutes by giving an appropriate loading dose. Blood concentrations decline in a biphasic manner with a distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Esmolol has low lipid solubility and is about 55% bound to plasma proteins. It is excreted in urine, mainly as the de-esterified metabolite.

References.

1. Adamson PC, *et al*. The pharmacokinetics of esmolol in pediatric subjects with supraventricular arrhythmias. *Pediatr Cardiol* 2006; **27:** 420–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dublon; ***Austral.***: Brevibloc; ***Austria***: Brevibloc; ***Belg.***: Brevibloc; ***Braz.***: Brevibloc; Esmolan; ***Canad.***: Brevibloc; ***China***: Ai Luo (爱络); Ao Yi Xin (奥一心); Xin Luo Ping (欣洛平); ***Cz.***: Brevibloc; Esmocard; ***Denm.***: Brevibloc; ***Fin.***: Brevibloc; Esmocard; ***Fr.***: Brevibloc; ***Ger.***: Brevibloc; Esmocard; ***Gr.***: Brevibloc; Esmocard; ***Hong Kong***: Brevibloc; ***Hung.***: Brevibloc; ***India***: Cardesmo; Esmocard; Esocard; Miniblock; Neotach; ***Irl.***: Brevibloc; Esmocard; ***Ital.***: Brevibloc; ***Neth.***: Brevibloc; ***Norw.***: Brevibloc; ***NZ***: Brevibloc; ***Port.***: Brevibloc; Esmocard; ***Rus.***: Breviblok (Бревиблок); ***S.Afr.***: Brevibloc†; ***Singapore***: Brevibloc; ***Spain***: Brevibloc; ***Swed.***: Brevibloc; ***Switz.***: Brevibloc; ***Thai.***: Brevibloc; ***Turk.***: Brevibloc; ***UK***: Brevibloc; ***USA***: Brevibloc.

Etacrynic Acid *(BAN, rINN)* ⊗

Acide étacrynique; Acide Étacrynique; Ácido etacrínico; Acidum Etacrynicum; Etacrínico, ácido; Etacrynsäure; Etakrino rūgštis; Etakrinsav; Etakrynsyra; Etakryynihappo; Ethacrynic Acid (USAN); Kwas etakrynowy; Kyselina etakrynová; MK-595; NSC-85791; Этакриновая Кислота.

[2,3-Dichloro-4-(2-ethylacryloyl)phenoxy]acetic acid; [2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid.

$C_{13}H_{12}Cl_2O_4$=303.1

CAS — 58-54-8.

ATC — C03CC01.

ATC Vet — QC03CC01.

UNII — M5DP350VZV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Etacrynic Acid). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol. It dissolves in ammonia and in dilute solutions of alkali hydroxides and carbonates.

USP 36: (Ethacrynic Acid). A white or practically white, odourless or practically odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 1.6 of alcohol, 1 in 6 of chloroform, and 1 in 3.5 of ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Sodium Etacrynate *(BANM, rINNM)* ⊗

Etacrinato sódico; Étacrynate de Sodium; Etacrynate Sodium; Ethacrynate Sodium (USAN); Natrii Etacrynas; Sodium Ethacrynate; Натрий Этакринат.

$C_{13}H_{11}Cl_2NaO_4$=325.1

CAS — 6500-81-8.

ATC — C03CC01.

ATC Vet — QC03CC01.

UNII — K41MYV7MPM.

Pharmacopoeias. In *Chin.*

Pol. and *US* include sodium etacrynate for injection.

Stability. Solutions in water of sodium etacrynate containing the equivalent of etacrynic acid 0.1% have a pH of 6.3 to 7.7. Solutions are relatively stable at about pH 7 at room temperatures for short periods and less stable at higher pH values and temperatures. They are incompatible with solutions with a pH below 5. The injection should be protected from light.

Uses and Administration

Although chemically unrelated, etacrynic acid is a loop diuretic with actions and uses similar to those of furosemide (p. 1387.1). Etacrynic acid is used in the treatment of oedema associated with heart failure (p. 1262.3) and with renal and hepatic disorders.

Diuresis begins within about 30 minutes after an oral dose, peaks after 2 hours, and lasts for about 6 to 8 hours; after intravenous injection of its sodium salt, the effects are evident within a few minutes.

In the treatment of **oedema**, the usual initial oral dose is 50 mg in the morning. The dose may be increased, if necessary, by 25- to 50-mg increments daily to the minimum effective dose. Severe cases have required gradual titration of the dose up to a maximum of 400 mg daily, but the effective range is usually between 50 and 200 mg daily. Dosage of more than 50 mg daily should be given in divided doses. All doses should be taken with food. Maintenance doses may be taken daily or intermittently.

In emergencies, such as acute pulmonary oedema, or when oral therapy cannot be given, etacrynic acid may be given intravenously. It is given as its salt, sodium etacrynate, but doses are expressed in terms of the acid. 10.7 mg of sodium etacrynate is equivalent to about 10 mg of etacrynic acid. The usual dose is 50 mg, or 0.5 to 1 mg/kg, as a 1 mg/mL solution in glucose 5% (provided the pH is above 5) or sodium chloride 0.9%, given by slow intravenous injection either directly or into the tubing of a running infusion. Should a subsequent injection be required the site should be changed to avoid thrombophlebitis. Single doses of 100 mg have been given intravenously in critical situations. It is not suitable for subcutaneous or intramuscular injection.

For doses in children, see below.

If very high doses of etacrynic acid are used careful laboratory control is essential as described for furosemide (p. 1387.1; high-dose therapy).

Administration in children. Etacrynic acid may be given to children aged over 2 years in the treatment of oedema at an initial oral dose of 25 mg daily, increased cautiously as necessary by 25 mg daily.

Adverse Effects

As for Furosemide, p. 1388.3. Gastrointestinal disturbances may be more common and severe with etacrynic acid; profuse watery diarrhoea is an indication for stopping therapy. Gastrointestinal bleeding has been associated with etacrynic acid. Tinnitus and deafness, particularly after high parenteral doses, may also be more common. Other adverse effects include confusion, fatigue, nervousness, and apprehension. Haematuria has been reported rarely.

Local irritation and pain may follow intravenous injection.

Effects on carbohydrate metabolism. Although etacrynic acid is generally considered to have less pronounced effects on carbohydrate metabolism than furosemide or the thiazide diuretics, adverse effects have been reported. Reductions in glucose tolerance[1] after etacrynic acid 200 mg daily for 6 weeks were similar to those produced by hydrochlorothiazide 200 mg daily. The effect was most pronounced in diabetic patients. Hyperosmolar hyperglycaemic coma[2] and symptomatic hypoglycaemia with convulsions[3] have been reported in patients receiving high doses of etacrynic acid.

1. Russell RP, *et al*. Metabolic and hypotensive effects of ethacrynic acid: comparative study with hydrochlorothiazide. *JAMA* 1968; **205:** 11–16.
2. Cowley AJ, Elkeles RS. Diabetes and therapy with potent diuretics. *Lancet* 1978; **i:** 154.
3. Maher JF, Schreiner GE. Studies on ethacrynic acid in patients with refractory edema. *Ann Intern Med* 1965; **62:** 15–29.

Effects on the ears. Drug-induced deafness occurred in 2 of 184 patients given etacrynic acid intravenously.[1,2] Deafness accompanied by nystagmus was reported in a patient[3] after an intravenous infusion of etacrynic acid. Symptoms resolved within 1 hour. He had previously been taking furosemide and etacrynic acid orally.

1. Boston Collaborative Drug Surveillance Program. Drug-induced deafness: a cooperative study. *JAMA* 1973; **224:** 515–16.
2. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; **i:** 587–8.
3. Gomolin IH, Garshick E. Ethacrynic acid-induced deafness accompanied by nystagmus. *N Engl J Med* 1980; **303:** 702.

Precautions

Etacrynic acid's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Etacrynic acid, especially in the form of dust, is irritating to the skin, eyes, and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etacrynic acid as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Furosemide, p. 1389.3. The risks of gastrointestinal bleeding may be enhanced by use of etacrynic acid with other gastric irritants or with anticoagulants.

Anticoagulants. For reference to the interaction between *warfarin* and etacrynic acid, see p. 1533.3.

Pharmacokinetics

Etacrynic acid is fairly rapidly absorbed from the gastrointestinal tract. The plasma half-life is 30 to 60 minutes. It is excreted both in the bile and the urine, partly

unchanged and partly in the form of metabolites. It is extensively bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Edecrin; ***Canad.***: Edecrin; ***Hung.***: Uregyt; ***Ital.***: Reomax; ***Rus.***: Uregyt (Урегит); ***Ukr.***: Uregyt (Урегит); ***USA***: Edecrin.

Pharmacopoeial Preparations
BP 2014: Sodium Etacrynate Injection;
USP 36: Ethacrynate Sodium for Injection; Ethacrynic Acid Tablets.

Ethacizine

Aethacizin; Etacizin; Ethacizin; Ethacyzin; EZ-55; NIK-244; Этацизин.
Ethyl 10-[3-(diethylamino)propionyl]phenothiazine-2-carbamate.
$C_{22}H_{27}N_3O_3S$=413.5
CAS — 33414-33-4 (ethacizine); 57530-40-2 (ethacizine hydrochloride).

Profile

Ethacizine, an analogue of moracizine (p. 1441.2), is reported to be a class Ic antiarrhythmic. It is used in the treatment of ventricular and supraventricular arrhythmias and has been given orally in doses starting at 50 mg three times daily, increased if necessary to a maximum of 100 mg three times daily. It has also been given intravenously.

Etilefrine Hydrochloride *(BANM, rINNM)* ⊗

Ethyladrianol Hydrochloride; Ethylnorphenylephrine Hydrochloride; Etilefriinihydrokloridi; Etilefrina, hidrocloruro de; Étiléfrine, chlorhydrate d'; Etilefrin-hidroklorid; Etilefrinhydrochlorid; Etilefrin-hydrochlorid; Etilefrinhydroklorid; Etilefrini Hydrochloridum; Etilefrino hidrochloridas; Hidrocloruro de etilefrina; M-I-36; Этилэфрина Гидрохлорид.
2-Ethylamino-1-(3-hydroxyphenyl)ethanol hydrochloride.
$C_{10}H_{15}NO_2$,HCl=217.7
CAS — 709-55-7 (etilefrine); 943-17-9 (etilefrine hydrochloride).
ATC — C01CA01.
ATC Vet — QC01CA01.
UNII — ZBI6Q5FH3S.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Etilefrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Etilefrine is a direct-acting sympathomimetic (p. 1507.3) with $beta_1$-agonist properties, and some alpha- and $beta_2$-agonist actions. It is used for the treatment of hypotensive states (p. 1277.2). It is given orally as the hydrochloride in usual doses of 5 or 10 mg three times daily; modified-release dosage forms may be given in doses of 25 mg once or twice daily. Etilefrine hydrochloride can also be given parenterally.

Etilefrine polistirex has been used in the management of rhinitis.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etilefrine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Priapism. Priapism is a common complication of sickle-cell disease (p. 1123.2) and is often treated with intracavernosal alpha agonists (see under Uses of Metaraminol, p. 1430.2). There have also been reports of the successful use of etilefrine, both by intracavernosal injection for acute treatment,[1,2] and orally for prophylaxis.[1-3]

1. Virag R, *et al.* Preventive treatment of priapism in sickle cell disease with oral and self-administered intracavernous injection of etilefrine. *Urology* 1996; **47:** 777–81.
2. Gbadoé AD, *et al.* Management of sickle cell priapism with etilefrine. *Arch Dis Child* 2001; **85:** 52–3.
3. Okpala I, *et al.* Etilefrine for the prevention of priapism in adult sickle cell disease. *Br J Haematol* 2002; **118:** 918–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Corcanfol; Effortil; Etil Adrianol; Menegradil; ***Austria***: Effortil; ***Belg.***: Effortil; ***Braz.***: Efortil; Etilefril; ***Chile***: Effortil†; ***Fin.***: Effortil; ***Fr.***: Effortil; ***Ger.***: Bioflutin; Effortil; Etil; Pholdyston; Thomasin; ***Gr.***: Effortil; Efortil; ***Ital.***: Effortil; ***Jpn***: Effortil; ***Mex.***: Effortil; Quimtatil; ***Pol.***: Effortil; ***Port.***: Effortil; ***S.Afr.***: Effortil†; ***Spain***: Efortil; ***Swed.***: Effortil; ***Switz.***: Effortil; ***Thai.***: Buracard; Circula; Circuman; Effortil†; Effrine; Efxine; Hyposia; Hyprosia†; ***Venez.***: Effontil.

Multi-ingredient Preparations. ***Austria***: Agilan; Amphodyn†; Effortil comp; Hypodyn†; Influbene†; ***Ger.***: Dihydergot plus; Effortil plus†; ***Switz.***: Dihydergot plus†; Effortil plus†.

Etofibrate *(rINN)*

Étofibrate; Etofibrato; Etofibratum; Этофибрат.
2-Nicotinoyloxyethyl 2-(4-chlorophenoxy)-2-methylpropionate.
$C_{18}H_{18}ClNO_5$=363.8
CAS — 31637-97-5.
ATC — C10AB09.
ATC Vet — QC10AB09.
UNII — 23TF67G79M.

Profile

Etofibrate, a derivative of clofibrate (p. 1338.3) and nicotinic acid (p. 2083.1), is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 500 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Tricerol; ***Ger.***: Lipo-Merz†; ***Hong Kong***: Lipo-Merz; ***Port.***: Lipo-Merz.

Etofylline Clofibrate *(rINN)*

Clofibrato de etofilina; Etofilina, clofibrato de; Étofylline, Clofibrate d'; Etofyllini Clofibras; ML-1024; Theofibrate (USAN); Theofibrate; Этофиллина Клофибрат.
2-(Theophyllin-7-yl)ethyl 2-(4-chlorophenoxy)-2-methylpropionate.
$C_{19}H_{21}ClN_4O_5$=420.8
CAS — 54504-70-0.
UNII — 14UH1JQP6L.

Profile

Etofylline clofibrate, a fibric acid derivative (see Bezafibrate, p. 1323.2), is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p. 1248.1). An oral dose of 250 mg two or three times daily has been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Duolip†; ***Ger.***: Duolip†; ***Hong Kong***: Duolip†.

Ezetimibe *(BAN, USAN, rINN)*

Ezetimiba; Ézétimibe; Ezetimibum; Sch-58235; Эзетимиб.
(3*R*,4*S*)-1-(*p*-Fluorophenyl)-3-[(3*S*)-3-(*p*-fluorophenyl)-3-hydroxypropyl]-4-(*p*-hydroxyphenyl)-2-azetidinone.
$C_{24}H_{21}F_2NO_3$=409.4
CAS — 163222-33-1.
ATC — C10AX09.
ATC Vet — QC10AX09.
UNII — EOR26LQQ24.

Uses and Administration

Ezetimibe is an inhibitor of intestinal sterol absorption and inhibits the absorption of cholesterol and plant sterols. It is used to reduce total cholesterol, low-density lipoprotein (LDL)-cholesterol, and apolipoprotein B in the management of hyperlipidaemias (below), and to reduce sitosterol and campesterol in patients with homozygous familial sitosterolaemia. It is given orally in a usual dose of 10 mg once daily.

For use in children, see below.

Reviews.
1. Sudhop T, von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* 2002; **62:** 2333–47.
2. Mauro VF, Tuckerman CE. Ezetimibe for management of hypercholesterolemia. *Ann Pharmacother* 2003; **37:** 839–48.
3. Bays HE, *et al.* Ezetimibe: cholesterol lowering and beyond. *Expert Rev Cardiovasc Ther* 2008; **6:** 447–70.
4. Anonymouse. Ezetimibe—an update. *Drug Ther Bull* 2009; **47:** 91–5.

Administration in children. Experience with ezetimibe in children is limited, but UK licensed product information states that adolescent boys of Tanner stage II and above, and girls at least 1 year post-menarche, and who are aged over 10 years, may be given ezetimibe for the same indications and at the same doses as in adults (see above).

Hyperlipidaemias. Ezetimibe inhibits the absorption of dietary cholesterol[1] and, although there is a compensatory increase in cholesterol synthesis in the liver,[1] overall plasma LDL-cholesterol concentrations are reduced.[2] Ezetimibe may be used alone[3] in the management of hyperlipidaemias (p. 1248.1) but use with lipid regulating drugs that act by reducing cholesterol synthesis may produce additive effects. In patients already taking statins, addition of ezetimibe results in a further reduction in LDL-cholesterol,[4] which may increase the number of patients achieving lipid targets, or allow lower doses of statins to be used. However, the clinical relevance of this is unclear; a study[5] in patients with familial hypercholesterolaemia found no difference in the progression of carotid atherosclerosis (measured by intima-media thickness) in those given ezetimibe with simvastatin compared with those given simvastatin alone, despite a larger reduction in LDL-cholesterol. Similar effects on LDL-cholesterol have been reported[6] for ezetimibe with fibrates.

As well as inhibiting cholesterol absorption, ezetimibe also blocks the absorption of plant sterols such as campesterol and sitosterol, and may be effective in patients with sitosterolaemia,[7] an inherited disorder in which increased absorption of plant sterols leads to premature atherosclerosis.

1. Sudhop T, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002; **106:** 1943–8.
2. Knopp RH, *et al.* Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003; **24:** 729–41.
3. Pandor A, *et al.* Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009; **265:** 568–80.
4. Pearson TA, *et al.* A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc* 2005; **80:** 587–95.
5. Kastelein JJP, *et al.* The ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; **358:** 1431–43.
6. McKenney JM, *et al.* Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol* 2006; **47:** 1584–7.
7. Salen G, *et al.* Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation* 2004; **109:** 966–71.

Adverse Effects and Precautions

Ezetimibe is generally well tolerated. The most common adverse effects include headache, abdominal pain, and diarrhoea; other gastrointestinal disorders, hypersensitivity reactions including rash and angioedema, fatigue, chest pain, and arthralgia have also been reported. Rare adverse effects include raised liver enzymes or hepatitis, pancreatitis, thrombocytopenia, cholelithiasis, and cholecystitis. Myalgia has occurred in patients taking ezetimibe either alone or when added to a statin (see Effects on Skeletal Muscle, p. 1380.1). Ezetimibe should be stopped if myopathy is suspected or creatine phosphokinase increases significantly.

Ezetimibe should be avoided in patients with moderate or severe hepatic impairment.

Reviews.
1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 47C–55C.
2. Kashani A, *et al.* Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. *Am J Cardiol* 2008; **101:** 1606–13.

Carcinogenicity. *Statins* are not thought to cause cancer (for a discussion, see Malignant Neoplasms under Uses and Administration of Simvastatin, p. 1491.3). However, an excess of incident cancer and fatal cancer was seen[1] in patients given combination therapy with simvastatin and ezetimibe when compared with placebo. To better examine the association, the data were pooled with those of two large, uncompleted studies;[2] the authors concluded that there was no evidence that the combination caused cancer, a conclusion that has been criticised.[3-5] Neither the FDA[6] nor MHRA[7] considered that a conclusion could be drawn as to the effect of ezetimibe on cancer.

1. Rossebø AB, *et al.* SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; **359:** 1343–56.
2. Peto R, *et al.* Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008; **359:** 1357–66.
3. Drazen JM, *et al.* Ezetimibe and cancer—an uncertain association. *N Engl J Med* 2008; **359:** 1398–9.
4. Nissen SE. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2009; **360:** 86–7.
5. Fleming TR. Identifying and addressing safety signals in clinical trials. *N Engl J Med* 2008; **359:** 1400–2.
6. FDA. Early communication about an ongoing safety review of ezetimibe/simvastatin (marketed as Vytorin), simvastatin (marketed as Zocor) and ezetimibe (marketed as Zetia) (issued 21st August 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm162899.htm (accessed 12/06/09)
7. MHRA/CHM. Ezetimibe and results of SEAS study: possible increased risk of cancer. *Drug Safety Update* 2008; **2** (4): 7. Available at: http://

www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON030924&RevisionSelectionMethod=LatestReleased (accessed 12/06/09)

Effects on the liver. Ezetimibe may cause an increase in liver enzymes and there have also been reports of acute hepatitis,[1,2] sometimes developing after addition of ezetimibe to long-term statin therapy.[3,4] Both auto-immune[3,4] and cholestatic hepatitis[4] have been described. In some patients,[1-3] symptoms resolved and liver enzymes normalised when ezetimibe was stopped, and in 1 patient a statin was successfully restarted.[3] However, of 2 patients who had been receiving ezetimibe and atorvastatin, 1 required treatment with corticosteroids,[4] while the other[4] had persistent liver changes 4 months later, despite both drugs being stopped in each case.

1. Liu Q, *et al*. Drug-induced liver injury associated with ezetimibe therapy. *Dig Dis Sci* 2007; **52:** 602–5.
2. Castellote J, *et al*. Serious drug-induced liver disease secondary to ezetimibe. *World J Gastroenterol* 2008; **14:** 5098–9.
3. van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. *Ann Clin Biochem* 2005; **42:** 402–4.
4. Stolk MF, *et al*. Severe hepatic side effects of ezetimibe. *Clin Gastroenterol Hepatol* 2006; **4:** 908–11.

Effects on the pancreas. Pancreatitis has been reported[1] in patients taking ezetimibe. In one case,[2] acute pancreatitis developed 2 weeks after starting ezetimibe and resolved when the drug was stopped, suggesting an immunological cause.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 30/05/08)
2. Ahmad I, *et al*. Ezetimibe-induced acute pancreatitis. *South Med J* 2007; **100:** 409–10.

Effects on skeletal muscle. Muscle disorders such as myalgia and myopathy are well known to occur with lipid regulating drugs such as statins and fibrates and have also been reported with ezetimibe, both alone,[1,2] and when added to treatment with statins;[1,3] rhabdomyolysis has also occurred, but is rare in patients taking ezetimibe alone. Up to August 2005, the Australian Adverse Drug Reactions Advisory Committee[4] had received 44 reports of muscle disorders with ezetimibe, including myalgia, muscle cramp, weakness and pain; in 5 of these cases a statin was also being taken.

1. Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Can J Cardiol* 2006; **22:** 141–4.
2. Havranek JM, *et al*. Monotherapy with ezetimibe causing myopathy. *Am J Med* 2006; **119:** 285–6.
3. Fux R, *et al*. Ezetimibe and statin-associated myopathy. *Ann Intern Med* 2004; **140:** 671–2.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Ezetimibe and muscle disorders. *Aust Adverse Drug React Bull* 2005; **24:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 30/05/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ezetimibe as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Colestyramine reduces the absorption of ezetimibe and should not be given at the same time of day. Ciclosporin has been reported to increase the plasma concentration of ezetimibe (see below) and patients receiving both drugs should be carefully monitored; the effect may be greater in patients with severe renal impairment. An increased INR has been reported in patients given ezetimibe and oral anticoagulants.

Ciclosporin. Pharmacokinetic studies[1] have shown that plasma-ezetimibe concentrations are higher in renal transplant patients taking ciclosporin than in historical controls, and there has been a report[2] of a supratherapeutic response to ezetimibe in a heart transplant patient taking ciclosporin. Ezetimibe causes a small increase in plasma-ciclosporin concentrations,[3] but the clinical relevance of this is not clear.

1. Bergman AJ, *et al*. Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. *J Clin Pharmacol* 2006; **46:** 328–36.
2. Koshman SL, *et al*. Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005; **39:** 1561–5.
3. Bergman AJ, *et al*. Effects of ezetimibe on cyclosporine pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2006; **46:** 321–7.

Pharmacokinetics

Ezetimibe is rapidly absorbed when given orally and undergoes extensive conjugation in the small intestine and liver to an active glucuronide metabolite, which is the main circulating form. Both ezetimibe and the glucuronide are more than 90% bound to plasma proteins. Ezetimibe is excreted primarily in the faeces via bile and undergoes enterohepatic recycling; after an oral dose, about 78% is excreted in the faeces, mainly as ezetimibe, and about 11% is excreted in the urine, mainly as the glucuronide. The elimination half-life for both ezetimibe and the glucuronide is about 22 hours. Ezetimibe is distributed into breast milk in *rats*.

Reviews

1. Kosoglou T, *et al*. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005; **44:** 467–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acotral; Alin; Alipas; Cerclerol; Cetrakam†; Coracil; Enediex; Ezetrol; Ixacor; Lipimibe†; Nalecol; Sinterol; Trilip; Vadel; Zetia; ***Austral.***: Ezetrol; ***Austria***: Ezetrol; ***Belg.***: Ezetrol; ***Braz.***: Ezetrol; Zetia; ***Canad.***: Ezetrol; ***Chile***: Ezetrol; Zient; ***China***: Ezetrol (益适纯); ***Cz.***: Ezetrol; Zient†; ***Denm.***: Ezetrol; ***Fin.***: Ezetrol; ***Fr.***: Ezetrol; ***Ger.***: Ezetrol; ***Gr.***: Ezetrol; ***Hong Kong***: Ezetrol; ***Hung.***: Ezetrol; ***India***: Esia; Ezedoc; Ezentia; Ezerem; Ezetib†; Ezibloc; Ezta; Ezzicad; Imbibe†; Lipezet; Mibe; ***Indon.***: Ezetrol; ***Irl.***: Ezetrol; ***Israel***: Ezetrol; ***Ital.***: Ezetrol; Zetia; ***Malaysia***: Ezetrol; ***Mex.***: Ezetrol; Zient; ***Neth.***: Ezetrol; ***Norw.***: Ezetrol; ***NZ***: Ezetrol; ***Philipp.***: Ezetrol; ***Pol.***: Ezetrol; ***Port.***: Adacai; Ezetrol; ***Rus.***: Ezetrol (Эзетрол); ***S.Afr.***: Ezetrol; ***Singapore***: Ezetrol; ***Spain***: Absorcol; Ezetrol; ***Swed.***: Ezetrol; ***Switz.***: Ezetrol; ***Thai.***: Ezetrol; ***Turk.***: Colebyn; Ezetrol; Kolez; ***UK***: Ezetrol; ***USA***: Zetia; ***Venez.***: Ezetrol; Zetia; Zient.

Multi-ingredient Preparations. ***Arg.***: Alipas Duo; Ampliar Duo; Ampliar Plus; Ateroclar Combi; Ateroclar Duo; Coleflux Duo; Colmibe; Craveril Duo; Labistatin Duo; Liparex Duo; Liparex Plus; Lipibec Duo; Lipibec Plus; Lipocambi Plus; Liponorm Duo; Minuslip Duo; Plan Duo; Redusterol Duo; Salvaxil Plus; Sinterol Compuesto; Torimibe; Vasotenal EZ; Vytorin; Zimetek; ***Austral.***: Vytorin; ***Austria***: Inegy; ***Belg.***: Inegy; ***Braz.***: Vytorin; Zetsim; ***Chile***: Adacai; Vytorin; Zintrepid; ***China***: Vytorin (葆至能); ***Cz.***: Inegy; ***Denm.***: Inegy; ***Fin.***: Inegy; ***Fr.***: Inegy; Vytorin; ***Ger.***: Inegy; ***Gr.***: Inegy; Vytorin; ***Hong Kong***: Vytorin; ***Hung.***: Inegy; ***India***: Alnavas-EZ; Altovas-EZ; Aova-EZ; Atheart-EZ; Atherotwo; Atix-EZ; Atofast-EZ; Atorin-EZ; Atorlip-EZ; Atoroll-EZ; Atortus-EZ; Atorvik-EZ; Avas EZ; Avascare-EZ; Aztor EZ; Bitorva; Cardisoz-AT; Dilutex Plus; Dyslip-EZ; Dysliptin-EZ; Ecostat; Etovas-EZ; Ezemax-A; Ezevas; Fibator EZ; Genlip-EZ; Jvastor-EZ; LDTor-Z; Lesstrol-EZ; Lipi-EZ; Lipikind-EZ; Lipivas EZ; Lipofix-EX; Liponorm-EZ; Lorlip-EZ; Modlip-EZ; Noclog-EZ; Omnitor-EZ; Orvaz-EZ; Zetitor; ***Indon.***: Vytorin; ***Irl.***: Inegy; ***Israel***: Inegy; ***Ital.***: Goltor; Inegy; Vytorin; Zeklen; ***Malaysia***: Vytorin; ***Mex.***: Vytorin; Zintrepid; ***Neth.***: Inegy; ***Norw.***: Inegy; ***NZ***: Vytorin; ***Philipp.***: Vytorin; ***Port.***: Inegy; Vytorin; ***Rus.***: Inegy (Инеджи); ***Singapore***: Vytorin; ***Spain***: Inegy; Vytorin; ***Swed.***: Inegy; ***Switz.***: Inegy; ***Thai.***: Vytorin; ***Turk.***: Inegy; ***UK***: Inegy; ***Ukr.***: Azi-Ator (Ази-Атор); ***USA***: Liptruzet; Vytorin; ***Venez.***: Adacai; Vytorin; Zintrepid.

Fasudil Hydrochloride *(rINNM)*

AT-877; Fasudil, Chlorhydrate de; Fasudil, hidrocloruro de; Fasudili Hydrochloridum; HA-1077; Hidrocloruro de fasudil; Фазудила Гидрохлорид.

Hexahydro-1-(5-isoquinolylsulfonyl)-1*H*-1,4-diazepine hydrochloride.

$C_{14}H_{17}N_3O_2S,HCl$=327.8

CAS — 103745-39-7 (fasudil); 105628-07-7 (fasudil hydrochloride).

ATC — C04AX32.

ATC Vet — QC04AX32.

UNII — SQ04N8S7BR.

Profile

Fasudil is a selective inhibitor of Rho-kinase, a protein kinase involved in contraction of vascular smooth muscle. Fasudil is used as the hydrochloride hemihydrate for its vasodilating properties in the management of cerebrovascular disorders including vasospasm after surgery for subarachnoid haemorrhage. It is under investigation for the treatment of angina pectoris, acute cerebral thrombosis, and pulmonary hypertension.

References.

1. Shibuya M, *et al*. Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: results of a prospective placebo-controlled double-blind trial. *J Neurosurg* 1992; **76:** 571–7.
2. Masumoto A, *et al*. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation* 2002; **105:** 1545–7.
3. Shimokawa H, *et al*. Anti-anginal effect of fasudil, a Rho-kinase inhibitor, in patients with stable effort angina: a multicenter study. *J Cardiovasc Pharmacol* 2002; **40:** 751–61.
4. Vicari RM, *et al*. Efficacy and safety of fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol* 2005; **46:** 1803–11.
5. Suzuki Y, *et al*. A postmarketing surveillance study of fasudil treatment after aneurysmal subarachnoid hemorrhage. *Surg Neurol* 2007; **68:** 126–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Chuanwei (川威); Eril (依立卢); ***Jpn***: Eril.

Felodipine *(BAN, USAN, rINN)*

Felodipiini; Felodipin; Felodipina; Felodipinas; Félodipine; Felodipino; Felodipinum; H-154/82; Фелодипин.

Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{18}H_{19}Cl_2NO_4$=384.3

CAS — 72509-76-3; 86189-69-7.

ATC — C08CA02.

ATC Vet — QC08CA02.

UNII — OL961R6O2C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Felodipine). A white or light yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Protect from light.

USP 36: (Felodipine). A light yellow to yellow, crystalline powder. Insoluble in water; freely soluble in acetone and in methyl alcohol; very slightly soluble in heptane. Store in airtight containers. Protect from light.

Uses and Administration

Felodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3).

Felodipine is given orally, generally in a modified-release formulation for use once daily in the morning. In **hypertension** the usual initial dose is 5 mg daily, adjusted as required; the usual maintenance dose is 2.5 to 10 mg daily and doses above 20 mg daily are not usually needed. In **angina** the usual initial dose is 5 mg daily increased if necessary to 10 mg daily.

Lower doses may be required in patients with hepatic impairment (see below) and in the elderly.

Reviews.

1. Todd PA, Faulds D. Felodipine: a review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. *Drugs* 1992; **44:** 251–77.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel-blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12:** 261–75.

Administration in hepatic impairment. In 9 patients with liver cirrhosis given felodipine 750 micrograms by intravenous infusion over 20 minutes and 10 mg orally as single doses on separate occasions the mean oral bioavailability was 17.1% which was not significantly different from published values in healthy subjects, but the peak plasma concentrations were almost twice as high as normal, apparently due to reduced systemic clearance and volume of distribution.[1] The fact that bioavailability was not increased suggests that much pre-systemic metabolism takes place in the gut rather than the liver. Although increased adverse effects were not associated with the raised felodipine concentrations in this study it is recommended that therapy in cirrhotic patients begin at lower doses than in patients with normal liver function. US licensed product information recommends that an initial dose of 2.5 mg once daily should be used in patients with hepatic impairment.

1. Regårdh CG, *et al*. Pharmacokinetics of felodipine in patients with liver disease. *Eur J Clin Pharmacol* 1989; **36:** 473–9.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies felodipine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Felodipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism, with a bioavailability of about 15% (range 10 to 25%). It is extensively metabolised

in the gut and the liver and is excreted almost entirely as metabolites, about 70% of a dose being excreted in urine and the remainder in faeces. The terminal elimination half-life is reported to be about 11 to 16 hours after oral dosage with an immediate-release preparation, but longer with a modified-release formulation. Felodipine is about 99% bound to plasma proteins (mainly albumin).

Reviews.
1. Dunselman PHJM, Edgar B. Felodipine clinical pharmacokinetics. *Clin Pharmacokinet* 1991; **21:** 418–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Munobal; Plendil; ***Austral.***: Felodil; Felodur; Plendil; ***Austria***: Felodistad; Munobal; Plendil; ***Belg.***: Plendil; Renedil; ***Braz.***: Splendil; ***Canad.***: Plendil; Renedil; ***Chile***: Splendil; ***China***: DeWei (得维); Keliping (可立平); Lianhuan Erding (联环尔定); Plendil (波依定); XiaoDing (笑定); ***Cz.***: Auronal; Felocor; Plendil; Presid; ***Denm.***: Felodin; Plendil; Plendur†; ***Fin.***: Hydac; Plendil; ***Fr.***: Flodil; ***Ger.***: Felo-Puren†; Felobeta; Felocor†; Felogamma; Modip; Munobal; ***Gr.***: Plendil; ***Hong Kong***: Felogard; Plendil; ***Hung.***: Plendil; Presid; ***India***: Felogard; ***Indon.***: Nirmadil; Plendil; ***Irl.***: Plendil; ***Israel***: Penedil; ***Ital.***: Feloday; Plendil; Prevex; ***Jpn***: Splendil; ***Malaysia***: Plendil; ***Mex.***: Dylofen; Eutens; Fedin; Hofodilan; Munobal; Nafapin; Nafpin; Plendil; Xysvol; ***Neth.***: Plendil; ***Norw.***: Plendil; ***NZ***: Felo; Plendil; ***Philipp.***: Dilahex; Dilofen; Felim†; Felop; Felpin; Lodistad; Plendil; Versant; ***Pol.***: Felohexal†; Plendil; ***Port.***: Mencor†; Plendil; Preslow; ***Rus.***: Felodip (Фелодип); Plendil (Плендил); ***S.Afr.***: Plendil; ***Singapore***: Plendil; ***Spain***: Perfudal†; Plendil; ***Swed.***: Plendil; ***Switz.***: Felodil†; Plendil; ***Thai.***: Fedil; Felim; Felohexal†; Felopine; Feloten; Plendil; Topidil; ***Turk.***: Plendil; ***UK***: Cardioplen; Felotens; Keloc; Neofel; Parmid; Plendil; Vascalpha; ***Ukr.***: Felodip (Фелодип); Felohexal (Фелогексал)†; ***Venez.***: Plendil.

Multi-ingredient Preparations. ***Arg.***: Atacand Duo; Triacor; ***Austral.***: Triasyn; ***Belg.***: Logimat; Tazko; ***Braz.***: Atacand Comb; ***Canad.***: Altace Plus Felodipine; ***Cz.***: Triasyn; ***Denm.***: Logimax; ***Fin.***: Logimax; Unimax; ***Fr.***: Logimax; ***Ger.***: Delmuno; Mobloc; Unimax; ***Gr.***: Logimax; Triacor; Unitens; ***Hong Kong***: Logimax; ***Hung.***: Logimax; Triasyn; ***Irl.***: Triapin; ***Israel***: Logimax†; ***Ital.***: Triapin; ***Mex.***: Logimax; Triacor; ***Neth.***: Triapin; ***Philipp.***: Logimax; Triapin; ***Pol.***: Delmuno; ***Port.***: Triapin; Unimax†; ***Rus.***: Logimax (Логимакс); ***S.Afr.***: Tri-Plen; ***Spain***: Logimax; Triapin; ***Swed.***: Logimax; ***Switz.***: Logimax; Unimax†; ***UK***: Triapin.

Pharmacopoeial Preparations
BP 2014: Prolonged-release Felodipine Tablets;
USP 36: Felodipine Extended-Release Tablets.

Fendiline Hydrochloride *(pINNM)*

Fendilina, hidrocloruro de; Fendiline, Chlorhydrate de; Fendilini Hydrochloridum; Hidrocloruro de fendilina; Фендилина Гидрохлорид.

N-(2-Benzhydrylethyl)-α-methylbenzylamine hydrochloride.

$C_{23}H_{25}N,HCl$=351.9

CAS — 13042-18-7 (fendiline); 13636-18-5 (fendiline hydrochloride).

ATC — C08EA01.

ATC Vet — QC08EA01.

UNII — HEM3Z10IIK.

Profile

Fendiline hydrochloride is a calcium-channel blocker used as a vasodilator in ischaemic heart disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Sensit.

Fenofibrate *(BAN, rINN)*

Fenofibraatti; Fenofibrat; Fenofibrát; Fenofibratas; Fénofibrate; Fenofibrato; Fenofibratum; LF-178; Procetofen; Procetofene; Фенофибрат.

Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate.

$C_{20}H_{21}ClO_4$=360.8

CAS — 49562-28-9 (fenofibrate); 42017-89-0 (fenofibric acid).

ATC — C10AB05.

ATC Vet — QC10AB05.

UNII — U202363UOS.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Fenofibrate). A white or almost white, crystalline powder. M.p. 79 degrees to 82 degrees. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Fenofibrate). A white or almost white, crystalline powder. M.p. 79 degrees to 82 degrees. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

Choline Fenofibrate *(USAN, rINN)*

ABT-335; Cholini Fenofibratum; Fénofibrate de Choline; Fenofibrato de colina; Холин Фенофибрат.

2-Hydroxy-*N*,*N*,*N*-trimethylethanaminium 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate.

$C_5H_{14}NO,C_{17}H_{14}ClO_4$=421.9

CAS — 856676-23-8.

ATC — C10AB05.

ATC Vet — QC10AB11.

UNII — 4BMH7IZT98.

Uses and Administration

Fenofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p. 1323.2).

It is used to reduce low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and apolipoprotein B, and to increase high-density lipoprotein (HDL)-cholesterol, in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias.

Fenofibrate is given orally as the base or choline salt. It is usually given with food to improve bioavailability although this may not be necessary with all preparations (see Bioavailability, below). It is available in a range of formulations with differing bioavailabilities and the dose is therefore specific to the preparation.

Standard micronised formulations of fenofibrate are available as 67-mg capsules to be taken several times daily, or as 200- or 267-mg capsules for once daily dosage. The usual initial dose is 67 mg three times daily or 200 mg once daily; the dose may be reduced to 67 mg twice daily or increased to 67 mg four times daily or 267 mg once daily according to response.

Preparations with improved bioavailability may be given in doses of around 40 to 160 mg once daily.

Non-micronised formulations may also be available and are given in an initial dose of 200 to 300 mg daily in divided doses, adjusted according to response to between 200 and 400 mg daily; 100 mg of non-micronised fenofibrate is therapeutically equivalent to 67 mg of the standard micronised form.

Choline fenofibrate is also given orally; doses are expressed in terms of fenofibric acid. It is given in a dose of 45 to 135 mg once daily.

Doses of fenofibrate and choline fenofibrate should be reduced in renal impairment (see below). For the dose of fenofibrate in children, see also below.

Fenofibric acid is also used similarly to fenofibrate.

Reviews.
1. Keating GM, Croom KF. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs* 2007; **67:** 121–53.

Administration in children. Experience with fenofibrate in children is limited and it should only be given under specialist advice. The *BNFC* considers that, given the limited evidence supporting its use in children, fenofibrate should be used only when a statin or bile-acid binding drug is unsuitable. The dose depends on the formulation:

- For *standard micronised* fenofibrate the *BNFC* recommends that children are given the 67-mg capsule formulation. The oral dose is one 67-mg capsule per 20 kg bodyweight daily for children aged 4 to 15 years; those aged 15 to 18 years may be given the adult dose (see above).
- *Non-micronised* fenofibrate is licensed for use in some countries in children from the age of 10 years, in a maximum oral dose of 5 mg/kg daily.

Administration in renal impairment. A single-dose study[1] in patients with mild (creatinine clearance (CC) 30 to 50 mL/minute) or severe renal impairment (CC below 10 mL/minute or undergoing haemodialysis) found that the plasma elimination half-life of fenofibric acid was prolonged, with a range of 54 to 362 hours; no correlation was found between half-life and serum creatinine or CC. Fenofibrate metabolites were not removed by haemodialysis, and repeated dosing in patients undergoing regular haemodialysis led to significant accumulation of fenofibric acid.[1]

Fenofibrate is therefore not generally recommended in patients with severe renal impairment although UK licensed product information allows a dose of 134 mg of *standard micronised* fenofibrate daily for patients with CC between 20 and 60 mL/minute and 67 mg daily for patients with CC below 20 mL/minute.

US licensed product information for *improved bioavailability formulations* suggests initial daily doses of about 40 to 50 mg (equivalent to about 67 mg of standard micronised fenofibrate) in patients with renal impairment, but contra-indicates use in those with severe impairment. *Choline fenofibrate* may be given to those with mild to moderate renal impairment in an initial dose of 45 mg once daily; the dose may be increased if necessary after evaluation of the effect on renal function. It should be avoided in severe renal impairment.

1. Desager JP, *et al.* Effect of hemodialysis on plasma kinetics of fenofibrate in chronic renal failure. *Nephron* 1982; **31:** 51–4.

Biliary disorders. For mention of the use of fenofibrate with ursodeoxycholic acid in the treatment of primary biliary cirrhosis see under Bezafibrate, p. 1323.3.

Adverse Effects and Precautions

As for Bezafibrate, p. 1324.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fenofibrate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Bezafibrate, p. 1325.2.

UK licensed product information for fenofibrate suggests that in patients taking oral anticoagulants, the dose of anticoagulant should be reduced by about one-third when treatment with fenofibrate is started, and then adjusted gradually if necessary.

Pharmacokinetics

Fenofibrate is readily absorbed from the gastrointestinal tract when taken with food; absorption may be reduced if fenofibrate is given on an empty stomach, although this depends on the formulation (see Bioavailability, below). When given as the choline salt, which is also readily absorbed from the gastrointestinal tract, its bioavailability is not affected by food.

Fenofibrate is rapidly hydrolysed to its active metabolite fenofibric acid which is about 99% bound to plasma albumin. The plasma elimination half-life is about 20 hours. Fenofibric acid is excreted mainly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronide. It is not removed by haemodialysis.

References.
1. Chapman MJ. Pharmacology of fenofibrate. *Am J Med* 1987; **83** (suppl 5B): 21–5.

Bioavailability. Fenofibrate is poorly soluble in water and has a low bioavailability when given orally.[1] Bioavailability is increased by food, particularly if there is a high fat content, and fenofibrate is therefore usually given with meals. Changes to the formulation, particularly with regard to the particle size, have been made to improve solubility,[1] with the aim of increasing bioavailability and reducing the influence of food. Micronisation improves bioavailability to a certain extent, and allows a lower dose to be given; 300 mg of non-micronised fenofibrate is usually considered equivalent to about 200 mg of the standard micronised form. Microcoating may further improve bioavailability,[2] but absorption is still affected by the presence of food.[3] Nanoparticle,[4] stabilised microparticle,[3] or semi-solid formulations,[5] however, appear to have a more consistent bioavailability and may be given with or without food, as may choline fenofibrate.

1. Vogt M, *et al.* Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. *Eur J Pharm Biopharm* 2008; **68:** 283–8.
2. Guichard JP, *et al.* A new formulation of fenofibrate: suprabioavailable tablets. *Curr Med Res Opin* 2000; **16:** 134–8.
3. Guivarc'h PH, *et al.* A new fenofibrate formulation: results of six single-dose, clinical studies of bioavailability under fed and fasting conditions. *Clin Ther* 2004; **26:** 1456–69.
4. Sauron R, *et al.* Absence of a food effect with a 145 mg nanoparticle fenofibrate tablet formulation. *Int J Clin Pharmacol Ther* 2006; **44:** 64–70.
5. Sonet B, *et al.* Randomised crossover studies of the bioequivalence of two fenofibrate formulations after administration of a single oral dose in healthy volunteers. *Arzneimittelforschung* 2002; **52:** 200–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Controlip; Craveril; Daunlip; Fenobrate; Minuslip; Procetoken; Sclerofin; ***Austral.***: Lipidil; ***Austria***: Apteor; Fenolip; Lipanthyl; Lipcor; Lipsin; ***Belg.***: Docfenofi†; Fenofitop†; Fenogal; Fenosup; Lipanthyl; Lipanthylnano; ***Braz.***: Lipanon; Lipidil; Reducofen; ***Canad.***: Apo-Feno; Feno-Micro; Fenomax; Lipidil; Pro-Feno; ***Chile***: Fibronil; Lipidil†; ***China***: Eticer (爱得生)†; Guan Zhi Ning (冠之柠); Ke Li Qing (可立清); Lipanthyl (力平之); Lipilfen (利必非); Lipilo (非诺贝特); Qi Shu (祺抒); Tai Wei Luo (太韦络); ***Cz.***: Apo-Feno; Febira; Fenofix; Lipanthyl; Lipirex; Lipohexal; Suprelip; ***Fin.***: CIL; Fenosup; Lipanthyl; ***Fr.***: Fegenor; Lipanthyl; Secalip; ***Ger.***: CIL†; Fenobeta; Fenofanton†; Lipidil;

Normalip pro†; ***Gr.***: Chlorosteran; Climage; Fagratyl; Fenobrat; Gestefol; Letomode; Lichol; Lipanthyl; Liperial; Lipidil; Lisomyex; Neo-Disterin; Planitrix; Sitronella; Xafenor; Zerlubron; ***Hong Kong***: Apo-Feno; Fegenor†; Lexemin; Lipanthyl; Qualipantyl; ***Hung.***: Feno-Micro†; Fenobrat; Fenoswiss; Lipanthyl; Lipidil; ***India***: Fenacor; Fenobate; Fenocor; Fenolip; Fibral; Fibrate; Finate; Lipicard; Lotgl; ***Indon.***: Evothyl; Felosma; Fibramed; Hyperchol; Lifen; Lipanthyl; Profibrat; Trichol; Trolip; Yosenob; Zumafib; ***Irl.***: Lipantil; ***Ital.***: Fulcro; Fulcrosupra; Liperial; Lipofene; Lipsin; Nolipax†; Tilene; ***Jpn***: Tricor; ***Malaysia***: Apo-Feno-Micro; Fenosup; Lexemin; Lipanthyl; ***Mex.***: Controlip; Lipidil; ***Philipp.***: Fenof; Fenoflex; Fenogal; Fibrafen; Fibril; Lipanthyl; Lipiduce; Lipilfen; Lipway; Lofibra; Lofibra; Nubrex; Trichek; Trolip; ***Pol.***: Apo-Feno; Fenardin; Fenoratio; Grofibrat; Lipanthyl; ***Port.***: Apteor†; Catalip; Lipanthyl†; Lipofen; Supralip; ***Rus.***: Lipanthyl (Липантил); Tricor (Трайкор); ***S. Afr.***: Lipanthyl; ***Singapore***: Apo-Feno-Micro; Fenogal Lidose; Fenosup; Lexemin; Lipanthyl; Trolip; ***Spain***: Liparison†; Secalip; ***Swed.***: Lipanthyl; ***Switz.***: Lipanthyl; ***Thai.***: Adfen; Colestrim; Febrate; Fenomed; Fenosup†; Fenox; Fibril; Fibrolan; Lexemin; Lipanthyl; Lipothin; Stanlip; Supralip; ***Turk.***: Fenogal; Lipanthyl; Lipofen; Secalip; ***UK***: Fenogal; Lipantil; Supralip; ***Ukr.***: Lipanthyl (Липантил)†; Lipicard (Ліпікард); Lipofen (Липофен); Tricor (Трайкор)†; ***USA***: Antara; Fenoglide; Fibricor; Lipofen; Lofibra; Tricor; Triglide; Trilipix.

Multi-ingredient Preparations. ***Arg.***: Craveril Duo; Minuslip Duo; ***Cz.***: Pravafenix; ***India***: AFF; Aova-F; Atchol-F; Atofast-F; Atorem-F; Atorfen; Atorin-F; Atorlip-F; Atormac-TG; Atornet-F; Atorva-TG; Atozide-F; Diplitor; Dyslip-TG; Dysliptin-TG; Fenostat; Fibator EZ; Fibator; Fibmet; Fibrovas; Genxvast-F; Inovas-F; Lipicard AV; Liplofin; Lorisk; Lorlip-EZ; Lorlip; Orvaz-FT; ***Irl.***: Pravafenix; ***Mex.***: Felocor.

Pharmacopoeial Preparations
USP 36: Fenofibrate Capsules; Fenofibrate Tablets.

Fenoldopam Mesilate *(BANM, rINNM)*

Fénoldopam, Mésilate de; Fenoldopam, mesilato de; Fenoldopam Mesylate (USAN); Fenoldopami Mesilas; Mesilato de fenoldopam; SKF-82526-j; Фенолдопама Мезилат.

6-Chloro-2,3,4,5-tetrahydro-1-(*p*-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol methanesulfonate.

$C_{16}H_{16}ClNO_3,CH_4O_3S$=401.9

CAS — 67227-56-9 (fenoldopam); 67227-57-0 (fenoldopam mesilate).
ATC — C01CA19.
ATC Vet — QC01CA19.
UNII — HA3R0MY016.

Pharmacopoeias. In *US.*

USP 36: (Fenoldopam Mesylate). A white to off-white powder. Soluble in water. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from moisture.

Incompatibility. Physical incompatibility has been reported[1] with fenoldopam 80 micrograms/mL (as the mesilate) in 0.9% sodium chloride injection and the following drugs during simulated Y-site administration: aminophylline; ampicillin sodium; amphotericin B; bumetanide; cefoxitin sodium; dexamethasone sodium phosphate; diazepam; fosphenytoin sodium; furosemide; ketorolac tromethamine; methohexital sodium; methylprednisolone sodium succinate; pentobarbital sodium; phenytoin sodium; prochlorperazine edisilate; sodium bicarbonate; and thiopental sodium.

1. Trissel LA, *et al.* Compatibility of fenoldopam mesylate with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2003; **60:** 80–5.

Stability. Fenoldopam mesilate, at concentrations ranging from 4 to 300 micrograms/mL in glucose 5% or sodium chloride 0.9%, has been reported[1] to be stable for 72 hours when stored at temperatures of 4 degrees or 23 degrees.

1. Trissel LA, *et al.* Stability of fenoldopam mesylate in two infusion solutions. *Am J Health-Syst Pharm* 2002; **59:** 846–8.

Uses and Administration

Fenoldopam is a dopamine agonist that is reported to have a selective action at dopamine D_1-receptors, leading to vasodilatation. It is used in the short-term management of severe hypertension (below) and has also been tried in heart failure.

Fenoldopam is given intravenously as the mesilate, although doses are expressed in terms of the base; 1.31 micrograms of fenoldopam mesilate is equivalent to about 1 microgram of fenoldopam.

In the management of hypertensive crises, fenoldopam mesilate is given by continuous intravenous infusion for up to 48 hours, as a solution containing 40 micrograms/mL of fenoldopam. The dose should be adjusted according to response, in usual increments of 50 to 100 nanograms/kg per minute at not less than 15-minute intervals. The usual dose range is from 100 to 1600 nanograms/kg per minute.

For the use of fenoldopam in children, see below.

Administration in children. Fenoldopam has been used to induce hypotension in children undergoing surgery. A placebo-controlled study[1] in 76 children aged between 3 weeks and 12 years found that infusion at rates below 200 nanograms/kg per minute was ineffective, and that a dose of 800 nanograms/kg per minute was the most effective and well tolerated. Dose increases beyond this were associated with tachycardia but no further blood pressure reduction.

Fenoldopam has also been investigated to protect renal function and improve urine output in neonates undergoing cardiopulmonary bypass[2,3] (for example by infusion of 100 nanograms/kg per minute over 72 hours[3]) and in critically ill children,[4] but as in adults (see Nephrotoxicity, below) the extent of any benefit is unclear.

1. Hammer GB, *et al.* Pharmacokinetics and pharmacodynamics of fenoldopam mesylate for blood pressure control in pediatric patients. *BMC Anesthesiol* 2008; **8:** 6.
2. Costello JM, *et al.* Initial experience with fenoldopam after cardiac surgery in neonates with an insufficient response to conventional diuretics. *Pediatr Crit Care Med* 2006; **7:** 28–33.
3. Ricci Z, *et al.* Fenoldopam in newborn patients undergoing cardiopulmonary bypass: controlled clinical trial. *Interact Cardiovasc Thorac Surg* 2008; **7:** 1049–53.
4. Moffett BS, *et al.* Renal effects of fenoldopam in critically ill pediatric patients: a retrospective review. *Pediatr Crit Care Med* 2008; **9:** 403–6.

Hypertension. Fenoldopam has a rapid onset of action and short elimination half-life and may be used as an alternative to sodium nitroprusside in the management of hypertensive crises (see under Hypertension, p. 1251.1). Its use has been reviewed.[1-3] Comparative studies with sodium nitroprusside in patients with acute severe hypertension have shown fenoldopam to be equally effective in rapidly lowering blood pressure. Additionally, in contrast to nitroprusside, urine output, creatinine clearance, and sodium excretion may be increased by fenoldopam. Fenoldopam may therefore be particularly useful in patients with renal impairment, although this remains to be established.

1. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. *Drugs* 1997; **54:** 634–50.
2. Post JB, Frishman WH. Fenoldopam: a new dopamine agonist for the treatment of hypertensive urgencies and emergencies. *J Clin Pharmacol* 1998; **38:** 2–13.
3. Murphy MB, *et al.* Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med* 2001; **345:** 1548–57.

Nephrotoxicity. Fenoldopam increases renal blood flow and has been tried to reduce the renal toxicity that may be associated with use of contrast media (see Effects on the Kidneys under Adverse Effects of Amidotrizoic Acid, p. 1582.2). Small studies in patients at risk of renal toxicity have shown benefit with fenoldopam,[1,2] but larger randomised studies[3,4] have found no advantage with fenoldopam plus hydration compared with hydration using sodium chloride 0.45% alone. However, a later meta-analysis[5] in patients undergoing cardiovascular surgery, who are at risk of acute renal failure, found that fenoldopam consistently reduced the need for renal replacement therapy, and reduced mortality. For mention of use in children and neonates see above.

A study[6] in patients undergoing liver transplantation (p. 1940.3) suggested that fenoldopam may have a role in preserving renal function, possibly by counteracting the renal toxicity associated with ciclosporin.

1. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; **35:** 1278–82. Correction. *ibid.*; 1677.
2. Lepor NE. A review of contemporary prevention strategies for radiocontrast nephropathy: a focus on fenoldopam and N-acetylcysteine. *Rev Cardiovasc Med* 2003; **4** (suppl 1): S15–S20.
3. Allaqaband S, *et al.* Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Catheter Cardiovasc Interv* 2002; **57:** 279–83.
4. Stone GW, *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; **290:** 2284–91.
5. Landoni G, *et al.* Fenoldopam reduces the need for renal replacement therapy and in-hospital death in cardiovascular surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2008; **22:** 27–33.
6. Biancofiore G, *et al.* Use of fenoldopam to control renal dysfunction early after liver transplantation. *Liver Transpl* 2004; **10:** 986–92.

Adverse Effects and Precautions

The adverse effects of fenoldopam are mainly due to vasodilatation and include hypotension, flushing, dizziness, headache, and reflex tachycardia. Nausea and vomiting, and ECG abnormalities have also been reported. Hypokalaemia has occurred and serum-electrolyte concentrations should be monitored during therapy; blood pressure and heart rate should also be monitored. Fenoldopam may increase intra-ocular pressure and it should be used with caution in patients with glaucoma. Caution is also required in patients in whom hypotension could be deleterious, such as those with acute cerebral infarction or haemorrhage.

Effects on the heart. Although fenoldopam is usually associated with reflex tachycardia, precipitous bradycardia in 2 patients given fenoldopam infusion in a clinical study[1] forced the drug to be stopped.

1. Taylor AA, *et al.* Sustained hemodynamic effects of the selective dopamine-1 agonist, fenoldopam, during 48-hour infusions in hypertensive patients: a dose-tolerability study. *J Clin Pharmacol* 1999; **39:** 471–9.

Interactions

The hypotensive effects of fenoldopam may be enhanced by other drugs with hypotensive actions. Beta blockers may block fenoldopam-induced reflex tachycardia and use of the drugs together is not recommended.

Pharmacokinetics

Steady-state plasma concentrations of fenoldopam occur about 20 minutes after starting continuous intravenous infusion. Fenoldopam is extensively metabolised with only about 4% of a dose being excreted unchanged. It is metabolised by conjugation (mainly glucuronidation, methylation, and sulfation). Fenoldopam and its metabolites are excreted mainly in the urine, and the remainder in the faeces. The elimination half-life of fenoldopam is about 5 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Corlopam; ***USA***: Corlopam.

Pharmacopoeial Preparations
USP 36: Fenoldopam Mesylate Injection.

Fibrinolysin ⊗

Fibrinase; Fibrinolisina (humana); Fibrinolysin (Human) (BAN); Fibrinolysin (Human) (rINN); Fibrinolysine (humaine); Fibrinolysinum (humanum); Plasmiini; Plasmin; Plasminum; Фибринолизин (Человека).

CAS — 9001-90-5 (fibrinolysin); 9004-09-5 (human fibrinolysin).
ATC — B01AD05.
ATC Vet — QB01AD05.
UNII — A4028U842W.

NOTE. In *Martindale* the term fibrinolysin is used for the exogenous substance and plasmin for the endogenous substance.

Profile

Fibrinolysin is a proteolytic enzyme derived from the activation of human plasminogen. Fibrinolysin derived from cattle (bovine fibrinolysin) and other animals is also available. Fibrinolysin converts fibrin into soluble products and also hydrolyses some other proteins. The role of plasmin (endogenous fibrinolysin) in the control of haemostasis is described further on p. 1124.3.

Fibrinolysin is used (generally as bovine fibrinolysin) with deoxyribonuclease for the debridement of wounds. It was formerly given parenterally for the treatment of thrombotic disorders. Ocriplasmin (p. 2574.1), a truncated form of fibrinolysin, is used in the treatment of vitreomacular adhesion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Saibai (赛百).

Multi-ingredient Preparations. ***Arg.***: Clorfibrase; ***Austria***: Fibrolan; ***Braz.***: Cauterex; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino Cauterex; Gino Fibrase; ***Chile***: Elase; ***Cz.***: Fibrolan†; ***Fr.***: Elase; ***Hung.***: Fibrolan; ***Indon.***: Plasmin; ***Malaysia***: Elase; ***Mex.***: Fibrase SA; Fibrase; ***Philipp.***: Plasmin; ***Pol.***: Fibrolan; ***Switz.***: Fibrolan.

Flecainide Acetate *(BANM, USAN, rINNM)*

Acetato de flecainida; Flecainida, acetato de; Flecainidacetat; Flécaïnide, acétate de; Flecainidi Acetas; Flekainidacetat; Flekainid-acetát; Flekainidiasetaatti; Flekainido acetatas; R-818; Флекаинида Ацетат.

N-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate.

$C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$=474.4

CAS — 54143-55-4 (flecainide); 54143-56-5 (flecainide acetate).
ATC — C01BC04.
ATC Vet — QC01BC04.
UNII — MBU465Q1WQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Flecainide Acetate). A white or almost white, very hygroscopic crystalline powder. Soluble in water and in dehydrated alcohol; freely soluble in dilute acetic acid; practically insoluble in dilute hydrochloric acid. A 2.5% solution in water has a pH of 6.7 to 7.1. Store in airtight containers. Protect from light.

USP 36: (Flecainide Acetate). A white to slightly off-white crystalline powder; pK_a is 9.3. Soluble in water; freely soluble in alcohol.

Stability. Storage of an extemporaneously prepared flecainide syrup in a refrigerator led to crystallisation of the drug and a toxic dose being given.[1] It was suggested that oral liquid formulations of flecainide should be freshly reconstituted from a powder before each dose. However, other extemporaneous formulations have been reported[2,3] to be stable at room temperature and under refrigeration.

1. Stuart AG, *et al.* Is there a genetic factor in flecainide toxicity? *BMJ* 1989; **298:** 117–18.
2. Wiest DB, *et al.* Stability of flecainide acetate in an extemporaneously compounded oral suspension. *Am J Hosp Pharm* 1992; **49:** 1467–70.
3. Allen LV, Erickson MA. Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996; **53:** 2179–84.

Uses and Administration

Flecainide is a class Ic antiarrhythmic (p. 1243.1) used for the treatment of severe symptomatic ventricular arrhythmias such as sustained ventricular tachycardia; for premature ventricular contractions or non-sustained ventricular tachycardia resistant to other therapy; and for severe symptomatic supraventricular arrhythmias (AV nodal reciprocating tachycardia, arrhythmias associated with the Wolff-Parkinson-White syndrome, and paroxysmal atrial fibrillation in the absence of left ventricular dysfunction).

Flecainide is given orally or intravenously as the acetate. Treatment should be started in hospital. Doses should be adjusted after 3 to 5 days and reduced once control has been achieved. A suggested therapeutic plasma concentration range is 0.2 to 1 micrograms/mL.

In ventricular arrhythmias the usual initial oral dose of flecainide acetate is 100 mg twice daily; the maximum total dose is 400 mg daily although most patients will not need more than 300 mg daily. In supraventricular arrhythmias the usual initial oral dose is 50 mg twice daily and the maximum total dose is 300 mg daily.

For rapid control of arrhythmias flecainide acetate 2 mg/kg may be given intravenously over 10 to 30 minutes, to a maximum dose of 150 mg; the ECG should be monitored. If longer term parenteral therapy is necessary it is started with intravenous injection of 2 mg/kg over 30 minutes, as above, then continued by intravenous infusion of 1.5 mg/kg over the first hour, and 100 to 250 micrograms/kg per hour thereafter. The maximum cumulative dose in the first 24 hours should not exceed 600 mg. Infusion should not generally continue for more than 24 hours and oral therapy should be substituted as soon as possible.

The dose of flecainide should be reduced in renal impairment (see below).

For the use of flecainide in children, see below.

Flecainide has also been tried in the treatment of refractory neuropathic pain.

Administration. Flecainide is usually given orally or intravenously, but rapid and reliable absorption has been reported from a rectal solution in healthy subjects.[1] The mean time to achieve peak serum concentration was 0.67 hours and the mean bioavailability was 98%, compared with 1 hour and 78% for an oral solution and 4 hours and 81% for a tablet. The absorption of flecainide given rectally to 2 critically ill patients was good in one but poor in the other[2] and it was recommended that rectal dosage be reserved for patients unresponsive to maximal parenteral therapy and in whom the oral or nasogastric routes cannot be used.

1. Lie-A-Huen L, *et al.* Absorption kinetics of oral and rectal flecainide in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 595–8.
2. Quattrocchi FP, Karim A. Flecainide acetate administration by enema. *DICP Ann Pharmacother* 1990; **24:** 1233–4.

Administration in children. Flecainide has been used successfully to treat arrhythmias in children,[1,2] including neonates,[2,3] and beneficial results have also been reported[4] with flecainide and sotalol together. US licensed product information recommends an initial oral dose of flecainide acetate 50 mg/m² daily in divided doses for those aged under 6 months and 100 mg/m² daily for those aged over 6 months; a dose of 200 mg/m² daily should not be exceeded.

The *BNFC* recommends the following doses of flecainide acetate:

- neonates: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response, or 1 to 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled
- children aged 1 month to 12 years: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response to a maximum of 8 mg/kg or 300 mg daily, or 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled (maximum cumulative dose 600 mg in 24 hours)
- children aged 12 to 18 years: as for adults (see Uses and Administration, above); the maximum oral dose should not exceed 300 mg daily in most children

1. Perry JC, Garson A. Flecainide acetate for treatment of tachyarrhythmias in children: review of world literature on efficacy, safety, and dosing. *Am Heart J* 1992; **124:** 1614–21.
2. O'Sullivan JJ, *et al.* Digoxin or flecainide for prophylaxis of supraventricular tachycardia in infants? *J Am Coll Cardiol* 1995; **26:** 991–4.
3. Ferlini M, *et al.* Flecainide as first-line treatment for supraventricular tachycardia in newborns. *J Cardiovasc Med (Hagerstown)* 2009; **10:** 372–5.
4. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39:** 517–20.

Administration in renal impairment. The plasma elimination half-life for flecainide may be prolonged in patients with renal impairment[1-3] and doses should be reduced. For patients with a creatinine clearance equal to or less than 35 mL/minute per 1.73 m² licensed product information states that the initial oral dose of flecainide acetate should not exceed 100 mg daily and plasma concentrations should be monitored; intravenous doses should be halved.

Special care with dosage adjustments should be taken in patients with renal impairment who are also poor metabolisers (see Metabolism, p. 1384.3).

1. Braun J, *et al.* Pharmacokinetics of flecainide in patients with mild and moderate renal failure compared with patients with normal renal function. *Eur J Clin Pharmacol* 1987; **31:** 711–14.
2. Forland SC, *et al.* Oral flecainide pharmacokinetics in patients with impaired renal function. *J Clin Pharmacol* 1988; **28:** 259–67.
3. Williams AJ, *et al.* Pharmacokinetics of flecainide acetate in patients with severe renal impairment. *Clin Pharmacol Ther* 1988; **43:** 449–55.

Cardiac arrhythmias. Flecainide has an established role in the management of ventricular and supraventricular arrhythmias (p. 1266.1). It has been used in children (see above) and has also been successfully given to pregnant women (transplacental therapy) to treat fetal arrhythmias,[1,2] although there have been reports[3,4] of neonatal toxicity.

Use in patients with asymptomatic arrhythmias after myocardial infarction is not recommended since an increase in mortality was found in the Cardiac Arrhythmia Suppression Trial (CAST), in which flecainide[5-7] and the related class Ic antiarrhythmics encainide[5-7] and moracizine[8] were used in an attempt to reduce the risk of sudden death in post-infarction patients with premature ventricular contractions.

Flecainide has also been used in the diagnosis of Brugada syndrome.[9] This syndrome is characterised by syncope or aborted cardiac arrest due to ventricular tachycardia in the absence of organic heart disease, and is thought to be due to a deficiency in the inward sodium current in cardiac cells. Flecainide, because of its sodium-channel blocking action, exaggerates this deficiency and the resulting ST-segment elevation, and aids in diagnosis; however, it may precipitate serious ventricular arrhythmias[10] and must not be used for treatment.

1. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.
2. Krapp M, *et al.* Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. *Ultrasound Obstet Gynecol* 2002; **19:** 158–64.
3. Rasheed A, *et al.* Neonatal ECG changes caused by supratherapeutic flecainide following treatment for fetal supraventricular tachycardia. *Heart* 2003; **89:** 470.
4. Hall CM, Ward Platt MP. Neonatal flecainide toxicity following supraventricular tachycardia treatment. *Ann Pharmacother* 2003; **37:** 1343–4.
5. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. CAST and beyond: implications of the cardiac arrhythmias suppression trial. *Circulation* 1990; **81:** 1123–7. [Simultaneous publication occurred in *Eur Heart J* 1990; **11:** 194–9].
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; **321:** 406–12.
7. Echt DS, *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; **324:** 781–8.
8. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327:** 227–33.
9. Singleton CB, McGuire MA. The Brugada syndrome: a recently recognised genetic disease causing sudden cardiac death. *Med J Aust* 2000; **173:** 415–8.
10. Gasparini M, *et al.* Flecainide test in Brugada syndrome: a reproducible but risky tool. *Pacing Clin Electrophysiol* 2003; **26:** 338–41.

Pain. Class Ic antiarrhythmics such as flecainide are among the drugs that have been used as analgesic adjuvants in neuropathic pain (p. 10.1), although the evidence for benefit with flecainide is limited. A positive response has been reported[1,2] in patients with severe pain due to nerve infiltration, but a controlled study had to be stopped[3] when supplies of the drug were withdrawn after the finding of increased mortality in a study in post-infarction patients (CAST; see Cardiac Arrhythmias, above), and later studies[4,5] found that flecainide was effective in only a minority of patients with cancer pain, although its effects could be substantial in responders.[5] A small study[6] has suggested that flecainide may be effective in postherpetic neuralgia.

1. Dunlop R, *et al.* Analgesic effects of oral flecainide. *Lancet* 1988; **i:** 420–1.
2. Sinnott C, *et al.* Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
3. DunlopRJ, *et al.* Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
4. Chong SF, *et al.* Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997; **13:** 112–17.
5. von Gunten CF, *et al.* Flecainide for the treatment of chronic neuropathic pain: a Phase II trial. *Palliat Med* 2007; **21:** 667–72.
6. Ichimata M, *et al.* Analgesic effects of flecainide on postherpetic neuralgia. *Int J Clin Pharmacol Res* 2001; **21:** 15–19.

Adverse Effects

The most common adverse effects caused by flecainide affect the CNS and include dizziness, visual disturbances, and lightheadedness. Nausea, vomiting, headache, tremor, peripheral neuropathy, ataxia, and paraesthesia may also occur. These effects are generally transient and respond to dosage reduction. Other adverse CNS effects that have been reported rarely include hallucinations, amnesia, confusion, depression, dyskinesias, and convulsions. Skin reactions, including rare cases of urticaria, have also occurred and there have been isolated cases of photosensitivity. Disturbances of liver function have been reported rarely. Corneal deposits, pulmonary fibrosis, and pneumonitis have occurred during long-term therapy. Cardiovascular effects are less common than those on the CNS, but can be serious and sometimes fatal. Ventricular tachyarrhythmias have been reported, particularly in patients with a history of ventricular tachyarrhythmias and taking high doses of flecainide. Chest pain and myocardial infarction have also occurred. Flecainide produced an increased mortality rate when it was assessed for the control of asymptomatic ventricular arrhythmias in patients who had previously suffered a myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, above).

Incidence of adverse effects. In a report of the non-cardiac adverse effects of flecainide from 1 short-term and 3 longer-term studies,[1] the most common adverse effects during both short- and long-term studies were dizziness and visual disturbances, which occurred in about 30% of patients. Headache and nausea both occurred in about 10% of patients. Other adverse effects reported include dyspnoea, chest pain, asthenia, fatigue, and tremor. Therapy was stopped because of non-cardiac adverse effects in 10% of patients in the short-term study, and in 6% of those in the chronic studies. A review of 60 studies using flecainide[2] reported that non-cardiac adverse effects (mainly gastrointestinal and CNS adverse effects) occurred in 12% of patients. The UK CSM stated in June 1991 that it had received reports of neurological (4 patients with sensory neuropathy, 2 with ataxia), corneal (2 with corneal deposits), and pulmonary (3 with pulmonary fibrosis and pneumonitis) reactions associated with the long-term use of flecainide.[3]

1. Gentzkow GD, Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984; **53:** 101B–105B.
2. Hohnloser SH, Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. *Am J Cardiol* 1992; **70:** 3A–10A.
3. CSM. Multi-system adverse reactions following long-term flecainide therapy. *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 08/05/07)

Effects on the blood. Severe granulocytopenia believed to be related to flecainide occurred in a 66-year-old man 3 months after starting therapy.[1] Haematological findings suggested an immune-mediated reaction in which flecainide binds to normal neutrophils with subsequent recognition by specific antibodies resulting in enhanced destruction of mature granulocytes in peripheral blood and bone marrow.

1. Samlowski WE, *et al.* Flecainide-induced immune neutropenia: documentation of a hapten-mediated mechanism of cell destruction. *Arch Intern Med* 1987; **147:** 383–4.

Effects on the eyes. In addition to visual disturbance, symptomatic corneal deposits have been reported[1] in patients taking flecainide. A study[2] in 38 patients found small corneal deposits in 14.5%, but visual function tests were normal.

1. Ulrik H, *et al.* Corneal deposits associated with flecainide. *BMJ* 1991; **302:** 506–7.
2. Ikäheimo K, *et al.* Adverse ocular effects of flecainide. *Acta Ophthalmol Scand* 2001; **79:** 175–6.

Effects on the heart. Like most antiarrhythmics, flecainide can have proarrhythmic effects,[1] and severe ventricular arrhythmias have been reported,[2] including fatal ventricular fibrillation[3] in a neonate given flecainide for supraventricular tachycardia. There has also been a report[4] of torsade de pointes, although this is generally less common with class Ic than with class Ia antiarrhythmics. For reports of increased cardiac mortality in patients given flecainide for asymptomatic arrhythmias, see Cardiac Arrhythmias under Uses and Administration, p. 1383.2.

1. Herre JM, *et al*. Inefficacy and proarrhythmic effects of flecainide and encainide for sustained ventricular tachycardia and ventricular fibrillation. *Ann Intern Med* 1990; **113:** 671–6.
2. Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med* 1989; **111:** 107–11.
3. Ackland F, *et al*. Flecainide induced ventricular fibrillation in a neonate. *Heart* 2003; **89:** 1261.
4. Nogales Asensio JM, *et al*. Torsade-de-pointes in a patient under flecainide treatment: an unusual case of proarrhythmicity. *Int J Cardiol* 2007; **114:** e65–e67.

Effects on the liver. Elevated liver enzymes and jaundice, reversible on stopping treatment, have been reported rarely with flecainide.

Conjugated hyperbilirubinaemia with jaundice developed in a newborn infant after maternal treatment with flecainide for fetal supraventricular tachycardia.[1]

1. Vanderhal AL, *et al*. Conjugated hyperbilirubinemia in a newborn infant after maternal (transplacental) treatment with flecainide acetate for fetal tachycardia and fetal hydrops. *J Pediatr* 1995; **126:** 988–90.

Effects on the lungs. There have been reports[1-4] of interstitial pneumonitis associated with flecainide. See also under Incidence of Adverse Effects, p. 1383.3.

1. Akoun GM, *et al*. Flecainide-associated pneumonitis. *Lancet* 1991; **337:** 49.
2. Hanston P, *et al*. Flecainide-associated interstitial pneumonitis. *Lancet* 1991; **337:** 371–2.
3. Robain A, *et al*. Flecainide-associated pneumonitis with acute respiratory failure in a patient with the LEOPARD syndrome. *Acta Cardiol* 2000; **55:** 45–7.
4. Pesenti S, *et al*. Diffuse infiltrative lung disease associated with flecainide: report of two cases. *Respiration* 2002; **69:** 182–5.

Effects on mental state. Dysarthria and visual hallucinations were associated with elevated plasma concentration of flecainide (2500 nanograms/mL) in a patient.[1] A serial rise and fall in plasma-bilirubin concentration during flecainide therapy also suggested possible direct hepatotoxicity. There has also been a report[2] of paranoid psychosis in a patient receiving flecainide for neuropathic pain.

1. Ramhamadany E, *et al*. Dysarthria and visual hallucinations due to flecainide toxicity. *Postgrad Med J* 1986; **62:** 61–2.
2. Bennett MI. Paranoid psychosis due to flecainide toxicity in malignant neuropathic pain. *Pain* 1997; **70:** 93–4.

Effects on the nervous system. Peripheral neuropathy, reversible on stopping treatment, has been reported[1,2] in patients receiving flecainide long-term. The authors of one report[1] stated that, at the time (1992), the UK CSM had received 4 other reports possibly associated with flecainide and 3 reports of aggravation of pre-existing neuropathy;[1] not all cases were reversible.

1. Palace J, *et al*. Flecainide induced peripheral neuropathy. *BMJ* 1992; **305:** 810.
2. Malesker MA, *et al*. Flecainide-induced neuropathy. *Ann Pharmacother* 2005; **39:** 1580.

Lupus erythematosus. There has been a report[1] of a patient who developed painful eye movement during flecainide therapy. The pain resolved on withdrawal but recurred when flecainide was restarted, and was accompanied by lateral rectus spasm, a facial rash, and positive antinuclear factor, suggestive of lupus erythematosus.

1. Skander M, Isaacs PET. Flecainide, ocular myopathy, and antinuclear factor. *BMJ* 1985; **291:** 450.

Treatment of Adverse Effects

In oral overdosage with flecainide activated charcoal may be considered if the patient presents within 1 hour of ingestion. Treatment is largely symptomatic and supportive and may need to be continued for extended periods of time because of the long half-life and the possibility of non-linear elimination at very high doses. Haemodialysis or haemoperfusion are unlikely to enhance elimination.

Overdosage. Severe cardiovascular toxicity in flecainide overdosage may be resistant to pacing and inotropes, and hypoperfusion of the kidneys and liver may reduce the elimination of flecainide, prolonging the toxic effects. Gastric decontamination is of uncertain benefit; forced diuresis has been used,[1] but probably had a negligible effect, and haemodialysis and haemoperfusion are not effective.[2] Patients may therefore require intensive and prolonged supportive treatment,[1,3] and there have been reports of the use of extracorporeal membrane oxygenation,[4] cardiopulmonary bypass,[5,6] or intra-aortic balloon pumping,[7] to maintain organ perfusion and allow flecainide elimination to occur, with complete recovery in some cases.[3,4,6,7] There have been reports[8-10] of the successful use of intravenous hypertonic sodium bicarbonate, including in children,[10] and it has been suggested that it may antagonise the sodium channel blockade produced by flecainide, as well as reversing the metabolic acidosis that commonly occurs. Magnesium sulfate has also been used in the management of electrocardiographic abnormalities secondary to overdosage.[11]

1. Winkelmann BR, Leinberger H. Life-threatening flecainide toxicity: a pharmacodynamic approach. *Ann Intern Med* 1987; **106:** 807–14.
2. Braun J, *et al*. Failure of haemoperfusion to reduce flecainide intoxication: a case study. *Med Toxicol* 1987; **2:** 463–7.
3. Hanley NA, *et al*. Survival in a case of life-threatening flecainide overdose. *Intensive Care Med* 1998; **24:** 740–2.
4. Auzinger GM, Scheinkestel CD. Successful extracorporeallife support in a case of severe flecainide intoxication. *Crit Care Med* 2001; **29:** 887–90.
5. Yasui RK, *et al*. Flecainide overdose: is cardiopulmonary support the treatment? *Ann Emerg Med* 1997; **29:** 680–2.
6. Corkeron MA, *et al*. Extracorporeal circulatory support in near-fatal flecainide overdose. *Anaesth Intensive Care* 1999; **27:** 405–8.
7. Timperley J, *et al*. Flecainide overdose—support using an intra-aortic balloon pump. *BMC Emerg Med* 2005; **5:** 10.
8. Goldman MJ, *et al*. Sodium bicarbonate to correct widened QRS in a case of flecainide overdose. *J Emerg Med* 1997; **15:** 183–6.
9. Lovecchio F, *et al*. Hypertonic sodium bicarbonate in an acute flecainide overdose. *Am J Emerg Med* 1998; **16:** 534–7.
10. D'Alessandro LC, *et al*. Life-threatening flecainide intoxication in a young child secondary to medication error. *Ann Pharmacother* 2009; **43:** 1522–7.
11. Williamson DG, *et al*. Management of persistent wide QRS in flecainide overdose with magnesium sulphate. *Emerg Med J* 2010; **27:** 487–8.

Precautions

Flecainide treatment should be started in hospital or under specialist supervision and pacing rescue should be available when it is used in patients with conduction defects. Its use is limited to serious or life-threatening arrhythmias and it should not be given to control asymptomatic arrhythmias especially in patients with a history of myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, p. 1383.2). Flecainide has some negative inotropic activity and may precipitate or aggravate heart failure in patients with compromised left ventricular function; it should therefore be used with extreme caution, if at all, in patients with heart failure. Flecainide has been shown to increase the endocardial pacing threshold and should be used with caution in patients with pacemakers. Electrolyte imbalances should be corrected before starting flecainide therapy. Reduction of dosage may be necessary in patients with renal impairment; extreme caution is needed in patients with pronounced hepatic impairment.

Breast feeding. Flecainide is distributed into breast milk but there have been no reports of infant exposure. Flecainide 100 mg was given orally every 12 hours to 11 healthy women, beginning 1 day after delivery and continuing for 5½ days.[1] The mean elimination half-life of flecainide from milk was 14.7 hours, very similar to the plasma elimination half-life. The mean milk to plasma ratios on study days 2 to 5 were 3.7, 3.2, 3.5, and 2.6 respectively but it was considered that the risk to breastfed infants of ingesting toxic amounts of flecainide in breast milk would be very low. In another woman[2] who had been taking flecainide 100 mg twice daily since before pregnancy for ventricular arrhythmias, the ratio was 1.57 on day 5 postpartum and 2.18 on day 7. The American Academy of Pediatrics considers[3] flecainide to be usually compatible with breast feeding.

1. McQuinn RL, *et al*. Flecainide excretion in human breast milk. *Clin Pharmacol Ther* 1990; **48:** 262–7.
2. Wagner X, *et al*. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119:** 700–2.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flecainide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Flecainide crosses the placenta (see under Pharmacokinetics, p. 1385.1) and has been used for transplacental therapy of fetal cardiac arrhythmias (see under Uses and Administration, p. 1383.2). However, hyperbilirubinaemia was reported in an infant after maternal treatment with flecainide for fetal supraventricular tachycardia (see Effects on the Liver, above).

Interactions

Use of flecainide with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Use with a beta blocker produces additive negative inotropic effects. Flecainide undergoes hepatic metabolism and its activity may be influenced by drugs that affect the enzymes responsible for its metabolism, including the cytochrome P450 isoenzyme CYP2D6.

Antiarrhythmics. *Amiodarone* increases the plasma-flecainide concentration when the two drugs are given together.[1] It has been recommended that the dose of flecainide should be reduced by about one-half, but because the effect of amiodarone differs widely between patients, plasma-flecainide concentrations should be monitored. The clearance of flecainide may be decreased by *quinidine* in patients who are extensive metabolisers, since quinidine inhibits the enzyme responsible for the metabolism of flecainide.[2] Cardiogenic shock and asystole occurred in 2 patients receiving flecainide when *verapamil* was added to their therapy.[3]

1. Shea P, *et al*. Flecainide and amiodarone interaction. *J Am Coll Cardiol* 1986; **7:** 1127–30.
2. Birgersdotter UM, *et al*. Stereoselective genetically-determined interaction between chronic flecainide and quinidine in patients with arrhythmias. *Br J Clin Pharmacol* 1992; **33:** 275–80.
3. Buss J, *et al*. Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; **340:** 546.

Antimalarials. *Quinine* has been reported[1] to inhibit metabolism of flecainide in healthy subjects without altering its renal elimination, resulting in a reduction of total clearance and prolongation of the elimination half-life.

1. Munafo A, *et al*. Altered flecainide disposition in healthy volunteers taking quinine. *Eur J Clin Pharmacol* 1990; **38:** 269–73.

Beta blockers. Use of flecainide and *propranolol* in healthy subjects increases the plasma concentration of both drugs. The negative inotropic effects of the two drugs on cardiac function are at most only additive, but combined treatment should be started with caution in patients with impaired left ventricular function.[1] Addition of *sotalol* to flecainide has produced profound bradycardia and AV block followed by cardiac arrest and death in a man with ventricular tachycardia.[2]

1. Holtzman JL, *et al*. The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; **33:** 97–9.
2. Warren R, *et al*. Serious interactions of sotalol with amiodarone and flecainide. *Med J Aust* 1990; **152:** 277.

Digoxin. For reference to an interaction between flecainide and digoxin leading to increased concentrations of digoxin, see Antiarrhythmics, under Interactions of Digoxin, p. 1356.2.

Food. *Milk* feeds reduced the absorption of flecainide in an infant who required a dose of 40 mg/kg daily to control supraventricular tachycardias. When milk feeds were replaced by glucose, the serum-flecainide concentration increased from 990 to 1824 nanograms/mL. Milk-fed infants on high doses of flecainide should have the dose reduced if milk is stopped or reduced.[1]

1. Russell GAB, Martin RP. Flecainide toxicity. *Arch Dis Child* 1989; **64:** 860–2.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase the bioavailability of flecainide in healthy subjects, probably due to a decrease in the metabolism of flecainide. Elimination half-life and renal clearance were unchanged.[1]

1. Tjandra-Maga TB, *et al*. Altered pharmacokinetics of oral flecainide by cimetidine. *Br J Clin Pharmacol* 1986; **22:** 108–10.

Pharmacokinetics

Flecainide is almost completely absorbed after oral doses and does not undergo extensive first-pass hepatic metabolism. Although absorption is not affected by food or antacids, milk may inhibit absorption in infants (see above). Flecainide is metabolised to 2 major metabolites, *m-O*-dealkylated flecainide and *m-O*-dealkylated lactam of flecainide; both may have some activity, but this is unlikely to be clinically significant. Metabolism of flecainide appears to involve the cytochrome P450 isoenzyme CYP2D6 and is subject to genetic polymorphism (see Metabolism, below). It is excreted mainly in the urine, about 30% as unchanged drug and the remainder as metabolites. About 5% is excreted in the faeces. Excretion of flecainide is decreased in renal impairment, heart failure, and in alkaline urine. Haemodialysis removes only about 1% of an oral dose as unchanged flecainide.

The therapeutic plasma concentration range is generally accepted as 0.2 to 1 micrograms/mL. The elimination half-life of flecainide is about 20 hours and it is about 40% bound to plasma proteins.

Flecainide crosses the placenta and is distributed into breast milk.

Metabolism. Oxidative metabolism is an important route of flecainide elimination.[1] It is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. The mean elimination half-life of flecainide in poor metabolisers (5 to 10% of the population) was

found to be 11.8 hours compared with 6.8 hours in extensive metabolisers and the amounts of a dose excreted as unchanged drug in the urine were 51% and 31% respectively. These differences in pharmacokinetics will not usually be of clinical importance. However, in patients with renal impairment who are poor metabolisers, special care should be taken with dosage adjustments.

1. Mikus G, *et al.* The influence of the sparteine-debrisoquin phenotype on the disposition of flecainide. *Clin Pharmacol Ther* 1989; **45:** 562–7.

Pregnancy. A study of the pharmacokinetics of flecainide, given to a mother during the third trimester of pregnancy for the treatment of fetal supraventricular tachycardia,[1] indicated that close to term flecainide crosses the placenta easily without accumulating in fetal blood, but with a high concentration in the amniotic fluid.

See also Effects on the Liver, p. 1384.1.

1. Bourget P, *et al.* Flecainide distribution, transplacental passage and accumulation in the amniotic fluid during the third trimester of pregnancy. *Ann Pharmacother* 1994; **28:** 1031–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diondel; ***Austral.***: Flecatab; Tambocor; ***Austria***: Aristocor; ***Belg.***: Apocard; Docflecai†; Tambocor; ***Canad.***: Tambocor; ***Chile***: Tambocor†; ***Cz.***: Tambocor; ***Denm.***: Flecin; Tambocor; ***Fin.***: Tambocor; ***Fr.***: Flecaine; ***Ger.***: Flecagamma; Tambocor; ***Gr.***: Tambocor; ***Hong Kong***: Tambocor; ***Irl.***: Tambocor; ***Israel***: Tambocor; ***Ital.***: Almarytm; ***Malaysia***: Tambocor; ***Mex.***: Tambocor; ***Neth.***: Flecajuna; Tambocor; ***Norw.***: Tambocor; ***NZ***: Tambocor; ***Philipp.***: Tambocor; ***Port.***: Apocard; ***S.Afr.***: Tambocor; ***Singapore***: Tambocor; ***Spain***: Apocard; ***Swed.***: Tambocor; ***Switz.***: Tambocor; ***Thai.***: Tambocor; ***UK***: Tambocor; ***USA***: Tambocor.

Pharmacopoeial Preparations
BP 2014: Flecainide Injection; Flecainide Tablets;
USP 36: Flecainide Acetate Oral Suspension; Flecainide Acetate Tablets.

Fluindione *(rINN)*

Fluindiona; Fluindionum; Fluorindione; LM-123; Флуиндион.
2-(4-Fluorophenyl)indan-1,3-dione.
$C_{15}H_9FO_2$=240.2
CAS — 957-56-2.
UNII — EQ35YMS20Q.

Profile

Fluindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p. 1526.3). It is used in the management of thromboembolic disorders (p. 1273.2) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p. 1467.3), its use is limited.

The usual initial dose is 20 mg daily; the dose is then adjusted according to coagulation tests.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Previscan.

Fluvastatin Sodium *(BANM, USAN, rINNM)*

Fluvastatin-Natrium; Fluvastatina sódica; Fluvastatine Sodique; Fluvastatinum natricum; Natrii Fluvastatinum; XU-62-320; Натрий Флувастатин.
Sodium (±)-(3*R**,5*S**,6*E*)-7-[3-(*p*-Fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate.
$C_{24}H_{25}FNNaO_4$=433.5
CAS — 93957-54-1 (fluvastatin); 93957-55-2 (fluvastatin sodium).
ATC — C10AA04.
ATC Vet — QC10AA04.
UNII — PYF7O1FV7F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. & (Fluvastatin Sodium). A white or almost white, or pale yellow to pale reddish-yellow, very hygroscopic, amorphous or crystalline powder. It exhibits polymorphism. It may be anhydrous or contain a variable quantity of water. Soluble in water; freely soluble in methyl alcohol; practically insoluble in acetonitrile. A 5% solution in water has a pH of 8 to 10. Store in airtight containers. Protect from light.

USP 36: (Fluvastatin Sodium). A white to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder. Soluble in water, in alcohol, and in methyl alcohol. A 1% solution in water has a pH of 8.0 to 10.0. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light and moisture.

Uses and Administration

Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3). It is used to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol, in the treatment of hyperlipidaemias (p. 1248.1), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias). It is also given as secondary prophylaxis for cardiovascular risk reduction (p. 1246.1) in patients with ischaemic heart disease, including patients who have had a percutaneous coronary intervention.

Fluvastatin is given orally as the sodium salt, but doses are expressed in terms of the base; 21.06 mg of fluvastatin sodium is equivalent to about 20 mg of base. The usual initial dose is 20 to 40 mg of fluvastatin once daily in the evening. This may be increased, if necessary, at intervals of 4 weeks or more, up to 80 mg daily, in two divided doses or as a once-daily modified-release preparation; patients requiring a large reduction in LDL-cholesterol may be started on the 80 mg daily dose. A dose of 80 mg daily may also be used in patients who have had a percutaneous coronary intervention.

For the use of fluvastatin in children, see below.

References.

1. Langtry HD, Markham A. Fluvastatin: a review of its use in lipid disorders. *Drugs* 1999; **57:** 583–606.
2. Corsini A, *et al.* Fluvastatin: clinical and safety profile. *Drugs* 2004; **64:** 1305–23.
3. Winkler K, *et al.* Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. *Clin Ther* 2007; **29:** 1987–2000.
4. McDonald KJ, Jardine AG. The use of fluvastatin in cardiovascular risk management. *Expert Opin Pharmacother* 2008; **9:** 1407–14.

Administration in children. Fluvastatin may be used in the management of children aged 9 years and over (or from 10 years in the USA) with heterozygous familial hypercholesterolaemia.[1] Suitable oral doses range from 20 mg once daily to 80 mg daily in 2 divided doses or as a once-daily modified release preparation, adjusted according to severity and response. US licensed product information recommends that dosage adjustments should be made at 6-week intervals.

1. van der Graaf A, *et al.* Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr* 2006; **95:** 1461–6.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluvastatin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of statins with other drugs are described under simvastatin (p. 1494.2). Fluvastatin is metabolised mainly by the cytochrome P450 isoenzyme CYP2C9 and does not have the same interactions with CYP3A4 inhibitors as simvastatin, although caution has been advised when such combinations are used. However, interactions may occur with inhibitors of CYP2C9, such as fluconazole; use with rifampicin, a CYP2C9 inducer, may reduce the bioavailability of fluvastatin by about 50%.

Pharmacokinetics

Fluvastatin is rapidly and completely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. Metabolism is mainly by the cytochrome P450 isoenzyme CYP2C9, with only a small amount metabolised by CYP3A4. An absolute bioavailability of about 24% has been reported. It is more than 98% bound to plasma proteins. About 90% is excreted in the faeces, mainly as metabolites, with only about 6% being excreted in the urine.

General reviews.

1. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet* 2001; **40:** 263–81.
2. Neuvonen PJ, *et al.* Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; **47:** 463–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lescol; ***Austral.***: Lescol; Vastin; ***Austria***: Lescol; ***Belg.***: Lescol; ***Braz.***: Fluvastat; Lescol; ***Canad.***: Lescol; ***China***: Lescol (来适可); ***Cz.***: Fluvakarav; Fuvatalip; Lescol; Vuyator; ***Denm.***: Dortelwestin; Edemestized†; Fedivan†; Flustatin†; Flutisan†; Fluvactalin; Fluvacur†; Fluvamyl; Fluvanidda; Fluvaratio; Fluvastadig; Fluvastaham; Fluvastamil; Fluvastasof; Fluvatamed†; Fluvatifi†; Fluviatin; Fluxstatin; Imasemamed; Lavesten; Lescol; Luvastix; Luvinsta; Lyavinmed†; Stadifluven; Stavatin; ***Fin.***: Lescol; ***Fr.***: Fractal; Lescol; ***Ger.***: Cranoc†; LOCOL; ***Gr.***: Hovalin; Lescol; ***Hong Kong***: Lescol; ***Hung.***: Lescol; Lochol†; Stipatin; ***India***: Lescol; ***Indon.***: Lescol; ***Irl.***: Fluvat; Lescol; Lochol; Luvinsta†; Statease; ***Israel***: Lescol; ***Ital.***: Lescol; Lipaxan; Primesin; ***Jpn***: Lochol; ***Malaysia***: Lescol; ***Mex.***: Lescol; Vastaflux†; ***Neth.***: Lescol; Vaditon†; ***Norw.***: Lescol; ***Philipp.***: Lescol; ***Pol.***: Lescol; ***Port.***: Canef; Cardiol; Fluvaphar†; Lescol; ***Rus.***: Lescol (Лескол); ***S.Afr.***: Lescol; ***Singapore***: Lescol; ***Spain***: Digaril; Lescol; Liposit; Lymetel†; Vaditon; ***Swed.***: Lescol; ***Switz.***: Lescol; ***Thai.***: Lescol; ***Turk.***: Lescol; ***UK***: Dorisin; Lescol; Luvinsta; Sinfatix; ***Ukr.***: Lescol (Лескол); ***USA***: Lescol.

Pharmacopoeial Preparations
USP 36: Fluvastatin Capsules.

Fondaparinux Sodium *(BAN, USAN, rINN)*

Fondaparin Sodium; Fondaparinuks Sodyum; Fondaparinuuksinatrium; Fondaparinux sódico; Fondaparinux Sodique; Fondaparinuxnatrium; Fondaparinuxum Natricum; Fondaparinuxum Natrium; Org-31540; SR-90107A; Фондапаринукс Натрия.
CAS — 114870-03-0.
ATC — B01AX05.
ATC Vet — QB01AX05.
UNII — X0Q6N9USOZ.

Uses and Administration

Fondaparinux is a synthetic pentasaccharide anticoagulant that acts as a selective inhibitor of factor Xa (activated factor X). It is used as the sodium salt in the management of venous thromboembolism (p. 1274.1), unstable angina (p. 1254.3), and acute myocardial infarction (p. 1257.1). It has also been used in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Adverse Effects of Heparin, p. 1399.1).

For *prophylaxis* of **venous thromboembolism** in abdominal and orthopaedic surgery, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily, starting at least 6 to 8 hours after surgery and continued for at least 5 to 9 days, or up to 32 days in hip fracture. For prophylaxis in high-risk medical patients, the same dose is given once daily for 6 to 14 days.

In the initial *treatment* of venous thromboembolism, fondaparinux sodium is given by subcutaneous injection once daily at a dose of 5 mg for patients weighing less than 50 kg, 7.5 mg for weight 50 to 100 kg, and 10 mg for weight over 100 kg. Treatment is usually continued for 5 to 9 days, and at least until oral anticoagulation is established. In the treatment of superficial-vein thrombosis, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily and continued for 30 to 45 days.

Fondaparinux is also used in **unstable angina** and acute ST-elevation **myocardial infarction**, but is only indicated in patients for whom urgent percutaneous coronary intervention is not planned. It is given in a dose of 2.5 mg subcutaneously once daily for up to 8 days, with the first dose given intravenously in acute ST-elevation myocardial infarction. Heparin should be given at the time of the procedure if percutaneous coronary intervention is performed and fondaparinux should be restarted when clinically appropriate.

Doses of fondaparinux may need to be reduced in patients with renal impairment (see p. 1386.1).

References.

1. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; **349:** 1695–1702.
2. Reynolds NA, *et al.* Fondaparinux sodium: a review of its use in the prevention of venous thromboembolism following major orthopaedic surgery. *Drugs* 2004; **64:** 1575–96.
3. Büller HR, *et al.* Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; **140:** 867–73.
4. The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; **295:** 1519–30.
5. Cohen AT, *et al.* ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Abridged version: *BMJ* 2006; **332:** 325–9. Full version: http://www.bmj.com/cgi/reprint/332/7537/325 (accessed 14/05/08)
6. Yusuf S, *et al.* Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 1464–76.
7. Mehta SR, *et al.* OASIS 5 and 6 Investigators. Antithrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: an individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 and 6) randomized trials. *Circulation* 2008; **118:** 2038–46.

8. Karthikeyan G, *et al*. Fondaparinux in the treatment of acute coronary syndromes: evidence from OASIS 5 and 6. *Expert Rev Cardiovasc Ther* 2009; **7:** 241–9.
9. Blackmer AB, *et al*. Fondaparinux and the management of heparin-induced thrombocytopenia: the journey continues. *Ann Pharmacother* 2009; **43:** 1636–46.
10. Decousus H, *et al*. CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med* 2010; **363:** 1222–32.
11. Sharma T, *et al*. Update on fondaparinux: role in management of thromboembolic and acute coronary events. *Cardiovasc Hematol Agents Med Chem* 2010; **8:** 96–103.

Administration in renal impairment. Fondaparinux is eliminated renally and should be used with caution in patients with renal impairment. US licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 30 mL/minute, and advises caution in those with CC between 30 and 50 mL/minute. In the UK, recommendations are based on indication, as follows:

- in the *treatment of acute coronary syndromes*: contra-indicated if CC is below 20 mL/min
- in the *treatment of venous thromboembolism*: contra-indicated if CC is below 30 mL/min
- in the *prophylaxis of venous thromboembolism and in the treatment of superficial-vein thrombosis*: contra-indicated if CC is below 20 mL/min; reduce dose to 1.5 mg daily if CC is between 20 and 50 mL/min

Adverse Effects

As for Heparin, p. 1398.3.

Treatment of Adverse Effects

If bleeding occurs fondaparinux should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for fondaparinux (but see below).

Overdosage. Activated eptacog alfa (recombinant factor VIIa) given 2 hours after an injection of fondaparinux was found[1] in healthy subjects to normalise coagulation times and thrombin generation for up to 6 hours, suggesting that it may be useful to treat bleeding complications, or if acute surgery is needed. A subsequent review[2] concluded that activated eptacog alfa was of benefit in the management of bleeding associated with certain anticoagulants including fondaparinux. Although the lowest effective dose was uncertain, 90 micrograms/kg had been reported to be effective for fondaparinux reversal. Use of repeat doses of eptacog alfa was not recommended.

1. Bijsterveld NR, *et al*. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; **106:** 2550–54.
2. Vavra KA, *et al*. Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; **44:** 718–26.

Precautions

As for Heparin, p. 1399.3.

Fondaparinux should be used cautiously in those with a history of heparin-induced thrombocytopenia, and it should not be given to patients who have developed thrombocytopenia with heparin and who also have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) in the presence of fondaparinux itself.

Fondaparinux is contra-indicated in severe renal impairment, and special care is required in patients with body-weight below 50 kg.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fondaparinux as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Interactions

As for Heparin, p. 1400.2.

Pharmacokinetics

After subcutaneous injection fondaparinux sodium is rapidly and completely absorbed, with bioavailability of 100%. It is extensively bound in plasma, mainly to antithrombin III. It is excreted in the urine, with 64 to 77% of a dose excreted unchanged. The elimination half-life is between 17 and 21 hours, but is prolonged in patients with renal impairment, in the elderly, and in those weighing less than 50 kg.

References.

1. Donat F, *et al*. The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet* 2002; **41** (suppl 2): 1–9.
2. Paolucci F, *et al*. Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. *Clin Pharmacokinet* 2002; **41** (suppl 2): 11–18.
3. Turpie AG, *et al*. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. *Blood Coag Fibrinol* 2009; **20:** 114–21.
4. Delavenne X, *et al*. Population pharmacokinetics of fondaparinux administered at prophylactic doses after major orthopaedic surgery in everyday practice. *Thromb Haemost* 2010; **104:** 252–60.

Pregnancy. Although an *in vitro* study[1] reported that fondaparinux does not cross the placenta, a small study[2] in pregnant women who had received fondaparinux found that anti-factor Xa activity was elevated in umbilical cord blood, suggesting that a small amount of placental transfer had taken place.

1. Lagrange F, *et al*. Fondaparinux sodium does not cross the placental barrier: study using the in-vitro human dually perfused cotyledon model. *Clin Pharmacokinet* 2002; **41** (suppl 2): 47–9.
2. Dempfle C-EH. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004; **350:** 1914–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arixtra; ***Austral.***: Arixtra; ***Austria***: Arixtra; ***Belg.***: Arixtra; ***Braz.***: Arixtra; ***Canad.***: Arixtra; ***Chile***: Arixtra; ***China***: Arixtra (安卓); ***Cz.***: Arixtra; ***Denm.***: Arixtra; ***Fin.***: Arixtra; ***Fr.***: Arixtra; ***Ger.***: Arixtra; ***Gr.***: Arixtra; ***Hung.***: Arixtra; ***India***: Arixtra; ***Indon.***: Arixtra; ***Irl.***: Arixtra; ***Israel***: Arixtra; ***Ital.***: Arixtra; ***Jpn***: Arixtra; ***Malaysia***: Arixtra; ***Mex.***: Arixtra; ***Neth.***: Arixtra; Quixidar†; ***Norw.***: Arixtra; ***Philipp.***: Arixtra; ***Pol.***: Arixtra; ***Port.***: Arixtra; ***Rus.***: Arixtra (Арикстра); ***S.Afr.***: Arixtra; ***Singapore***: Arixtra; ***Spain***: Arixtra; ***Swed.***: Arixtra; ***Switz.***: Arixtra; ***Thai.***: Arixtra; ***Turk.***: Arixtra; ***UK***: Arixtra; ***Ukr.***: Arixtra (Арикстра); ***USA***: Arixtra.

Fosinopril Sodium *(BANM, USAN, rINNM)*

Fosinoprilinatrium; Fosinopril-Natrium; Fosinopril sódico; Fosinopril Sodique; Fosinopril Sodyum; Fosinoprilnatrium; Fosinoprilum natricum; Natrii Fosinoprilum; SQ-28555; Натрий Фозиноприл.

(4*S*)-4-Cyclohexyl-1-{[(*RS*)-2-methyl-1-(propionyloxy)propoxy]-(4-phenylbutyl)phosphinylacetyl}-L-proline sodium.

$C_{30}H_{45}NNaO_7P$=585.7

CAS — 97825-24-6 (fosinopril); 98048-97-6 (fosinopril); 88889-14-9 (fosinopril sodium).

ATC — C09AA09.

ATC Vet — QC09AA09.

UNII — NW2RTH6T2N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Fosinopril Sodium). A white or almost white, crystalline powder. It shows polymorphism. Freely soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in hexane.

USP 36: (Fosinopril Sodium). Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Fosinopril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Fosinopril owes its activity to fosinoprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after 2 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Fosinopril is given orally as the sodium salt.

In the treatment of **hypertension**, the initial dose of fosinopril sodium is 10 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 10 to 40 mg once daily. In patients already taking diuretic therapy the diuretic should be withdrawn if possible several days before starting fosinopril, and resumed later if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Fosinopril sodium is given in an initial dose of 10 mg once daily and, if well tolerated, increased to a maximum of 40 mg once daily. An initial dose of 5 mg may be given in patients at high risk of hypotension.

For doses in children, see below.

Reviews.

1. Murdoch D, McTavish D. Fosinopril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in essential hypertension. *Drugs* 1992; **43:** 123–40.
2. Wagstaff AJ, *et al*. Fosinopril: a reappraisal of its pharmacology and therapeutic efficacy in essential hypertension. *Drugs* 1996; **51:** 777–91.
3. Davis R, *et al*. Fosinopril: a review of its pharmacology and clinical efficacy in the management of heart failure. *Drugs* 1997; **54:** 103–16.

Administration in children. US licensed product information recommends that fosinopril sodium may be given to children weighing over 50 kg in the treatment of hypertension in an oral dose of 5 to 10 mg once daily.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fosinopril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Fosinopril acts as a prodrug of the diacid fosinoprilat, its active metabolite. About 36% of an oral dose of fosinopril is absorbed. Fosinopril is rapidly and completely hydrolysed to fosinoprilat in both gastrointestinal mucosa and liver. Peak plasma concentrations of fosinoprilat occur about 3 hours after an oral dose of fosinopril. Fosinoprilat is more than 95% bound to plasma proteins. It is excreted both in urine and in the faeces via the bile; it has been detected in breast milk. The effective half-life for accumulation of fosinoprilat after multiple doses of fosinopril is about 11.5 hours in patients with hypertension and about 14 hours in patients with heart failure.

References.

1. Singhvi SM, *et al*. Disposition of fosinopril sodium in healthy subjects. *Br J Clin Pharmacol* 1988; **25:** 9–15.
2. Kostis JB, *et al*. Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. *Clin Pharmacol Ther* 1995; **58:** 660–5.

Renal impairment. Total body clearance of fosinoprilat, the active metabolite of fosinopril, is slower in patients with renal impairment. However, pharmacokinetic studies in patients with varying degrees of impairment,[1-5] including those requiring dialysis, indicate that decreases in renal clearance may be compensated for, at least in part, by increases in hepatic clearance.

1. Hui KK, *et al*. Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 1991; **49:** 457–67.
2. Gehr TWB, *et al*. Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. *Eur J Clin Pharmacol* 1991; **41:** 165–9.
3. Sica DA, *et al*. Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991; **20:** 420–7.
4. Gehr TWB, *et al*. The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. *Eur J Clin Pharmacol* 1993; **45:** 431–6.
5. Greenbaum R, *et al*. Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 2000; **49:** 23–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fospril; Monace; Monopril; ***Austria***: Fositens; ***Belg.***: Fosinil; ***Braz.***: Fospraz; Monopril; ***Canad.***: Monopril; ***Chile***: Monopril†; ***China***: Monopril (蒙诺); ***Cz.***: Apo-Fosinop; Fenosimed; Fosinogen; Monace; Monopril; ***Fr.***: Fozitec; ***Ger.***: Dynacil†; Fosinorm†; ***Gr.***: Monopril; Sinopril; ***Hong Kong***: Monopril†; ***Hung.***: Monopril; Noviform; ***India***: Fosinace; Fovas; ***Indon.***: Acenor-M†; ***Ital.***: Eliten; Fosipres; Tensogard; ***Mex.***: Monopril; ***Neth.***: NewAce†; ***Philipp.***: BPNorm; ***Pol.***: Monopril†; ***Port.***: Fositen; ***Rus.***: Fosicard (Фозикард); Monopril (Моноприл); ***S.Afr.***: Monopril; ***Spain***: Fositens; Hiperlex†; Tenso Stop; Tensocardil†; ***Swed.***: Monopril†; ***Switz.***: Fositen†; ***Thai.***: Monopril†; ***Turk.***: Forsace; Monopril; ***UAE***: Fosipril; ***UK***: Staril†; ***Ukr.***: Fosicard (Фозикард); ***USA***: Monopril; ***Venez.***: Monopril.

Multi-ingredient Preparations. ***Austral.***: Fosetic; Hyforil; Monoplus; ***Austria***: Fosicomb; ***Braz.***: Monoplus; ***Chile***: Monopril Plus†; ***Cz.***: Foprin Plus H†; Monace Combi; ***Fr.***: Foziretic; ***Ger.***: Dynacil comp; Fosinorm comp†; ***Gr.***: Fozide; Monoplus; ***Hung.***: Duopril; Fosicard Plus; Noviform Plusz; ***Ital.***: Fosicombi; Tensozide; ***Neth.***: Diurace†; ***Port.***: Fositen Plus; ***Rus.***: Fosicard H (Фозикард Н); Fozide (Фозид); ***S.Afr.***: Monozide†; ***Spain***: Fositens Plus; Hiperlex Plus†; Tenso Stop Plus; ***Switz.***: Fosicomp; ***Thai.***: Monoplus; ***Turk.***: Forsace Plus; Monopril Plus; ***Ukr.***: Fosicard H (Фозикард Н); ***USA***: Monopril-HCT; ***Venez.***: Monopril Plus.

Pharmacopoeial Preparations

USP 36: Fosinopril Sodium and Hydrochlorothiazide Tablets; Fosinopril Sodium Tablets.

Furosemide (BAN, USAN, rINN) ⊗

Frusemide; Furosemid; Furosemida; Furosémide; Furosemidi; Furosemidum; Furoszemid; Furozemidas; LB-502; Фуросемид.

4-Chloro-*N*-furfuryl-5-sulphamoylanthranilic acid.

$C_{12}H_{11}ClN_2O_5S$=330.7

CAS — 54-31-9.

ATC — C03CA01.

ATC Vet — QC03CA01.

UNII — 7LXU5N7ZO5.

NOTE. Compounded preparations of furosemide may be represented by the following names:

- Co-amilofruse (*BAN*)—furosemide 8 parts and amiloride hydrochloride 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Furosemide). A white or almost white, crystalline powder. Practically insoluble in water and in dichloromethane; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light. It shows polymorphism.

USP 36: (Furosemide). A white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; very slightly soluble in chloroform; slightly soluble in ether; soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Solutions for injection are prepared with the aid of sodium hydroxide, giving solutions with a pH of 8.0 to 9.3.

Incompatibility. Solutions of furosemide for injection are alkaline and should not be mixed or diluted with glucose injection or other acidic solutions.

Furosemide injection has been reported[1] to be visually incompatible with injections of diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, labetalol hydrochloride, midazolam hydrochloride, milrinone lactate, nicardipine hydrochloride, and vecuronium bromide. Incompatibility has also been noted with parenteral nutrient solutions,[2] with cisatracurium besilate,[3] with levofloxacin,[4] with phenylephrine,[5] and with vasopressin.[5]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1295–1300.
3. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
4. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
5. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; **63:** 906–8.

Stability. A study[1] showed that furosemide injection (10 mg/mL) in 25% human albumin solution was stable for 48 hours at room temperature when protected from light, and for 14 days under refrigeration. No bacterial or fungal growth was found.

1. Elwell RJ, *et al.* Stability of furosemide in human albumin solution. *Ann Pharmacother* 2002; **36:** 423–6.

Uses and Administration

Furosemide is a potent diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of oedema associated with heart failure (p. 1388.1), including pulmonary oedema, and with renal and hepatic disorders (but see Precautions, p. 1389.2) and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Furosemide is also used in the treatment of hypertension (p. 1251.1), either alone or with other antihypertensives.

Furosemide inhibits the reabsorption of electrolytes mainly in the thick ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase. See Action, below, for further reference to its mechanism of action.

Administration and dosage. Furosemide's effects are evident within 30 minutes to 1 hour after an oral dose, peak at 1 to 2 hours, and last for about 6 hours; after intravenous injection its effects are evident in about 5 minutes and last for about 2 hours. It is given orally, usually in the morning. Alternatively it may be given intramuscularly or intravenously as the sodium salt; doses are expressed in terms of furosemide base. 10.7 mg of furosemide sodium is equivalent to about 10 mg of furosemide base. Licensed product information recommends that whether by direct intravenous injection or by infusion the rate of intravenous dosage should not exceed 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly. In patients with renal impairment, a lower maximum infusion rate of 2.5 mg/minute has been suggested.

Unlike the thiazide diuretics where, owing to their flat dose-response curve, very little is gained by increasing the dose, furosemide has a steep dose-response curve, which gives it a wide therapeutic range.

In the treatment of **oedema**, the usual initial oral dose is 40 mg once daily, adjusted as necessary according to response. Mild cases may respond to 20 mg daily or 40 mg on alternate days. Some patients may need doses of 80 mg or more daily given as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600 mg daily. In an emergency or when oral therapy cannot be given, 20 to 50 mg of furosemide may be given by slow intravenous injection; intramuscular injection may be given in exceptional cases but is not suitable for acute conditions. If necessary further doses may be given, increasing by 20-mg increments and not given more often than every 2 hours, up to a maximum daily dose of 1.5 g. If doses above 50 mg are required they should be given by slow intravenous infusion. For pulmonary oedema, if an initial slow intravenous injection of 40 mg does not produce a satisfactory response within one hour, a further 80 mg may be given slowly intravenously.

In the treatment of **hypertension**, furosemide is given in oral doses of 40 to 80 mg daily, either alone, or with other antihypertensives.

High-dose therapy. In the management of **oliguria** in acute or chronic renal failure where the glomerular filtration rate is less than 20 mL/minute but greater than 5 mL/minute, furosemide 250 mg diluted to 250 mL in a suitable diluent is infused over one hour. If urine output is insufficient within the next hour, this dose may be followed by 500 mg added to an appropriate infusion fluid, the total volume of which must be governed by the patient's state of hydration, and infused over about 2 hours. If a satisfactory urine output has still not been achieved within one hour of the end of the second infusion then a third dose of 1 g may be infused over about 4 hours. The rate of infusion should never exceed 4 mg/minute. In oliguric patients with significant fluid overload, the injection may be given without dilution directly into the vein, using a constant rate infusion pump with a micrometer screw-gauge adjustment; the rate should still never exceed 4 mg/minute. Patients who do not respond to a dose of 1 g probably require dialysis. If the response to either dosage method is satisfactory, the effective dose (of up to 1 g) may then be repeated every 24 hours. Dosage adjustments should subsequently be made according to the patient's response. Alternatively, oral treatment may be maintained; 500 mg should be given orally for each 250 mg required by injection.

When used in chronic renal impairment, an initial oral dose of 250 mg may be given, increased, if necessary in steps of 250 mg every 4 to 6 hours to a maximum of 1.5 g in 24 hours; in exceptional cases up to 2 g in 24 hours may be given. Dosage adjustments should subsequently be made according to the patient's response.

For doses in children, see below.

Action. The mechanism of action of furosemide is not fully understood.[1] It appears to act mainly by inhibiting active reabsorption of chloride ions in the ascending limb of the loop of Henle. Urinary excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium, ammonium, bicarbonate, and possibly phosphate is increased; the chloride excretion exceeds that of sodium and there is an enhanced exchange of sodium for potassium leading to greater excretion of potassium. The resulting low osmolality of the medulla inhibits the reabsorption of water by the kidney. There is a possibility that furosemide may also act at a more proximal site.

In addition to its diuretic actions, furosemide has been shown to increase peripheral venous capacitance and reduce forearm blood flow. It also reduces renal vascular resistance with a resultant increase in renal blood flow the degree of which is proportional to the initial resistance.

Furosemide has been shown to increase plasma-renin activity, plasma-noradrenaline concentrations, and plasma-arginine-vasopressin concentrations. Alterations in the renin-angiotensin-aldosterone system may play a part in the development of acute tolerance. Furosemide increases renal-prostaglandin concentrations but it is unknown whether this is due to increased synthesis or inhibition of degradation or both. Prostaglandins appear to mediate the diuretic/natriuretic action. The primary effects appear to be alterations in renal haemodynamics with subsequent increases in electrolyte and fluid excretion.

The diuretic response to furosemide is related to the concentration in the urine, not to that in the plasma. Furosemide is delivered to the renal tubules by a non-specific organic acid pump in the proximal tubules.[1]

In some cases sodium intake may be sufficient to overcome the diuretic effect, and limiting sodium intake could restore responsiveness.[2]

1. Ponto LLB, Schaenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; **18:** 381–408.
2. Brater DC. Resistance to loop diuretics: why it happens and what to do about it. *Drugs* 1985; **30:** 427–43.

Administration. Continuous intravenous infusion of loop diuretics may be more effective than intermittent intravenous bolus injection and may provide a more consistent urine flow with fewer alterations in urine balance.[1,2] Bumetanide was more effective by continuous infusion than as bolus doses in 8 patients with severe chronic renal impairment.[3] In 20 patients with chronic heart failure requiring high-dose furosemide therapy, furosemide given by continuous infusion was more effective than the same dose by bolus injection.[4] The lower plasma concentrations associated with continuous infusion may also reduce the risk of toxicity.

1. Yelton SL, *et al.* The role of continuous infusion loop diuretics. *Ann Pharmacother* 1995; **29:** 1010–14.
2. Gulbis BE, Spencer AP. Efficacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother* 2006; **40:** 1797–1803.
3. Rudy DW, *et al.* Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991; **115:** 360–6.
4. Dormans TPJ, *et al.* Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; **28:** 376–82.

Administration in children. Furosemide has been given to neonates, infants, and children in the treatment of oedema and oliguria. For **oedema**, UK licensed product information allows an *oral* dose of 1 to 3 mg/kg daily in the morning, to a maximum of 40 mg daily, or an *intravenous* injection or infusion of 0.5 to 1.5 mg/kg daily, to a maximum of 20 mg daily. Alternatively, the *BNFC* suggests the following regimens, given according to age:

Oral

- neonate: 0.5 to 2 mg/kg every 12 to 24 hours (every 24 hours if postmenstrual age is under 31 weeks)
- 1 month to 12 years: 0.5 to 2 mg/kg given 2 or 3 times daily (every 24 hours if postmenstrual age is under 31 weeks); higher doses may be required in resistant oedema. Maximum daily dose is the smaller of 12 mg/kg or 80 mg
- 12 to 18 years: usually 20 to 40 mg daily; 80 to 120 mg daily is permitted in resistant oedema

Slow intravenous injection

- neonate: 0.5 to 1 mg/kg every 12 to 24 hours (every 24 hours if postmenstrual age under 31 weeks)
- 1 month to 12 years: 0.5 to 1 mg/kg (maximum 2 mg/kg or 40 mg, whichever is smaller) every 8 hours as necessary
- 12 to 18 years: 20 to 40 mg every 8 hours as necessary. Resistant oedema may require higher doses

Continuous intravenous infusion

- 1 month to 18 years: 0.1 to 2 mg/kg per hour. After cardiac surgery, the lower dose of 100 micrograms/kg per hour should be given initially, and doubled every 2 hours until urine output exceeds 1 mL/kg per hour

In the treatment of **oliguria**, the *BNFC* suggests the following doses:

Oral

- 12 to 18 years: an initial dose of 250 mg daily, adjusted if necessary by 250 mg increments given every 4 to 6 hours. A maximum single dose of 2 g is permitted.

Intravenous infusion

- 1 month to 12 years: 2 to 5 mg/kg up to 4 times daily (maximum 1 g daily)
- 12 to 18 years: an initial dose of 250 mg given over 1 hour. If a satisfactory urine output is not obtained, a further 500 mg may be given over 2 hours, then a further 1 g over 4 hours if necessary. If no response is obtained, dialysis is probably required. The effective dose (up to 1 g) may be repeated every 24 hours.

Ascites. Dietary sodium restriction and diuretics are mainstays of the management of cirrhotic ascites (p. 1276.2). Spironolactone is usually the diuretic of first choice, but furosemide may be added to therapy as necessary.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids (see p. 1602.1). Additional supportive therapy may include the use of diuretics such as furosemide.

Alternate-day therapy with oral furosemide 4 mg/kg has produced modest benefits in pulmonary status in the absence of a diuretic effect, and few adverse effects.[1] Improved pulmonary function has occurred in infants

given furosemide 1 mg/kg parenterally after packed red blood cell transfusions, given to improve oxygen-carrying capacity.[2] The successful use of nebulised furosemide in a dose of 1 mg/kg has been reported;[3,4] again pulmonary status was improved without production of diuresis or renal adverse effects. However, a single inhaled dose of 1 mg/kg failed to improve pulmonary mechanics in another study involving older infants with more severe disease.[5] Systematic reviews of the use of intravenous or oral,[6] or nebulised[7] diuretics in preterm infants with chronic lung disease concluded that, although there were improvements in pulmonary function, there was insufficient evidence to recommend routine use.

1. Rush MG, *et al.* Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1990; **117:** 112–18.
2. Stefano JL, Bhutani VK. Role of furosemide therapy after booster-packed erythrocyte transfusions in infants with bronchopulmonary dysplasia. *J Pediatr* 1990; **117:** 965–8.
3. Rastogi A, *et al.* Nebulized furosemide in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; **125:** 976–9.
4. Prabhu VG, *et al.* Pulmonary function changes after nebulised and intravenous frusemide in ventilated premature infants. *Arch Dis Child* 1997; **77:** F32–F35.
5. Kugelman A, *et al.* Pulmonary effect of inhaled furosemide in ventilated infants with severe bronchopulmonary dysplasia. *Pediatrics* 1997; **99:** 71–5.
6. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 24/06/05).
7. Brion LP, *et al.* Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 07/05/08).

Haemolytic-uraemic syndrome. Renal failure is a possible consequence of the haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p. 1159.1). Correction of any hypovolaemic state with adequate fluids and of oliguria by inducing diuresis with furosemide may be used to prevent this.

Of 54 children with haemolytic-uraemic syndrome given intravenous furosemide 2.5 to 4 mg/kg every 3 to 4 hours immediately after diagnosis 24% eventually required dialysis.[1] In contrast, a retrospective analysis of 39 patients treated conservatively showed that 82% had required dialysis. The results therefore suggested that high-dose furosemide could prevent the progression of oliguria to anuria in these patients by increasing urate clearance.

1. Rousseau E, *et al.* Decreased necessity for dialysis with loop diuretic therapy in hemolytic uremic syndrome. *Clin Nephrol* 1990; **34:** 22–5.

Heart failure. Diuretics have been the mainstay in the treatment of heart failure (p. 1262.3) but drugs such as ACE inhibitors that have been shown to improve mortality are now generally recommended for first-line therapy along with diuretics. Diuretics provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a loop diuretic such as furosemide will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade), namely a loop diuretic with a thiazide or potassium-sparing diuretic, may be needed in some patients, especially when there is diuretic resistance.

Patients have been successfully treated using continuous intravenous infusions[1] or high doses (up to 8 g daily) of furosemide given by intravenous infusion[2,3] or orally.[3] A patient who was successfully maintained on intravenous furosemide at home has been described.[4] Combination of furosemide with thiazide diuretics[5] or metolazone[6,7] has been reported. There is a danger of overdiuresis with both of these strategies, and careful monitoring of electrolytes and renal function is essential.[8] Delivery of furosemide to the renal tubules may be enhanced by combined therapy with hydralazine[9] or captopril.[10] The use of captopril and furosemide may also correct hyponatraemia without fluid restriction.[11] In elderly patients not responding adequately to low-dose furosemide with optimum doses of ACE inhibitors, increasing the dose of furosemide (to an average of 297 mg daily orally) has been reported[12] to be of benefit. However, caution is necessary when using furosemide with antihypertensives and especially ACE inhibitors since these combinations can result in sudden and profound hypotension and renal toxicity. Low-dose dopamine infusion has been suggested as an alternative to high-dose furosemide infusion and may cause less toxicity. In a study[13] in patients with severe refractory heart failure given optimal therapy with ACE inhibitors, oral diuretics, nitrates, and digoxin, additional therapy with low-dose intravenous dopamine (4 micrograms/kg per minute) and low-dose oral furosemide (80 mg daily) was as effective as intravenous high-dose furosemide (10 mg/kg daily) but caused less hypokalaemia and renal impairment. Use of intravenous hypertonic saline has also been reported[14] to augment the effect of furosemide.

For the suggestion that torasemide may be a better choice of loop diuretic in patients with heart failure see p. 1516.3.

1. Lawson DH, *et al.* Continuous infusion of frusemide in refractory oedema. *BMJ* 1978; **2:** 476.
2. O'Rourke MF, *et al.* High-dose furosemide in cardiac failure. *Arch Intern Med* 1984; **144:** 2429.
3. Gerlag PGG, van Meijel JJM. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988; **148:** 286–91.
4. Hattersley AT, *et al.* Home intravenous diuretic therapy for patient with refractory heart failure. *Lancet* 1989; **i:** 446.
5. Channer KS, *et al.* Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 1990; **335:** 922–3.
6. Aravot DJ, *et al.* Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727.
7. Friedland JS, Ledingham JGG. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727–8.
8. Oster JR, *et al.* Combined therapy with thiazide-type and loop diuretic agents for resistant-sodium retention. *Ann Intern Med* 1983; **99:** 405–6.
9. Nomura A, *et al.* Effect of furosemide in congestive heart failure. *Clin Pharmacol Ther* 1981; **30:** 177–82.
10. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100:** 777–82.
11. Hamilton RW, Buckalew VM. Sodium, water, and congestive heart failure. *Ann Intern Med* 1984; **100:** 902–4.
12. Waterer G, Donaldson M. High-dose frusemide for cardiac failure. *Lancet* 1995; **346:** 254.
13. Cotter G, *et al.* Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; **62:** 187–93.
14. Paterna S, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; **2:** 305–13.

Hypercalcaemia. Hypercalcaemia (p. 1778.1) usually results from an underlying disease and long-term management involves treating the cause. However, if significant symptoms are present, treatment is necessary to reduce plasma-calcium concentrations. This mainly involves rehydration, but loop diuretics such as furosemide have traditionally been used after rehydration to promote urinary calcium excretion, a practice that has been questioned.[1-3] Drugs such as bisphosphonates that inhibit bone resorption are now generally considered first-line where specific therapy is warranted, although loop diuretics may still have a role in the prevention of fluid overload or heart failure. Licensed doses used for hypercalcaemia have ranged from 20 to 240 mg of furosemide daily, given intravenously.

1. LeGrand SB, *et al.* Narrative review. Furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med* 2008; **149:** 259–63.
2. Robey RB, *et al.* Does furosemide have a role in the management of hypercalcemia? *Ann Intern Med* 2009; **150:** 146–7.
3. LeGrand SB. Does furosemide have a role in the management of hypercalcemia? *Ann Intern Med* 2009; **150:** 147.

Obstructive airways disease. In patients with *asthma*, furosemide given by oral inhalation has been found to protect against bronchoconstriction induced by exercise[1] and external stimuli,[2,3] although it did not improve bronchial hyperresponsiveness in a 4-week study[4] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[5] Mechanisms have been suggested for the protective effect of furosemide, including inhibition of electrolyte transport across epithelium, inhibition of inflammatory mediators, or an effect on mast cell function.[6] The potential for clinical applications remains unclear[6] and furosemide is not a part of the accepted schedules for the treatment of asthma (p. 1195.2).

Small studies in patients with *chronic obstructive pulmonary disease* have reported improvements in dyspnoea[7,8] and exercise capacity[8] with inhaled furosemide.

Inhaled furosemide has also been used to relieve *dyspnoea in patients with terminal cancer*.[9]

1. Munyard P, *et al.* Inhaled frusemide and exercise-induced bronchoconstriction in children with asthma. *Thorax* 1995; **50:** 677–9.
2. Bianco S, *et al.* Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N Engl J Med* 1989; **321:** 1069–73.
3. Seidenberg J, *et al.* Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992; **67:** 214–17.
4. Yates DH, *et al.* Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. *Am J Respir Crit Care Med* 1995; **152:** 2173–5.
5. González-Sánchez R, *et al.* Furosemide plus albuterol compared with albuterol alone in children with acute asthma. *Allergy Asthma Proc* 2002; **23:** 181–4.
6. Floreani AA, Rennard SI. Experimental treatments for asthma. *Curr Opin Pulm Med* 1997; **3:** 30–41.
7. Ong K-C, *et al.* Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169:** 1028–33.
8. Jensen D, *et al.* Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. *Thorax* 2008; **63:** 606–13.
9. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Patent ductus arteriosus. The usual initial treatment for a haemodynamically significant ductus is reduction of fluid intake, correction of anaemia, support of respiration, and giving a diuretic. If that fails to control symptoms then indometacin is generally given to promote closure of the ductus (see p. 72.2).

Furosemide is often the diuretic chosen. It is effective and widely used but there has been concern that it might delay closure (and even increase the incidence of patent ductus arteriosus in infants treated for respiratory distress syndrome — see Effects in Infants and Neonates under Adverse Effects, p. 1389.1). A systematic review[1] of those treated for patent ductus concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

1. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2001 (accessed 12/07/05).

Raised intracranial pressure. Osmotic diuretics such as mannitol are first-line drugs for the management of raised intracranial pressure (p. 1271.3) but loop diuretics such as furosemide may be used as adjuncts.

Tinnitus. Furosemide is one of many drugs that have been tried in tinnitus (p. 1994.1), but although reported to be effective in some patients, it is rarely used because of problems with adverse effects.

Adverse Effects

Most adverse effects of furosemide occur with high doses, and serious effects are uncommon. The most common adverse effect is fluid and electrolyte imbalance including hyponatraemia, hypokalaemia, and hypochloraemic alkalosis, particularly after large doses or prolonged use. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, oliguria, cardiac arrhythmias, and gastrointestinal disturbances. Hypovolaemia and dehydration may occur, especially in the elderly. The risk of hypokalaemia may be less with loop diuretics such as furosemide, which have a short duration of action, than with thiazide diuretics. Unlike the thiazides, furosemide increases the urinary excretion of calcium and nephrocalcinosis has been reported in preterm infants.

Furosemide may cause hyperuricaemia and precipitate gout in some patients. It may provoke hyperglycaemia and glycosuria, but probably to a lesser extent than the thiazide diuretics.

Pancreatitis and cholestatic jaundice seem to occur more often than with the thiazides. Other adverse effects include blurred vision, yellow vision, dizziness, headache, and orthostatic hypotension. Other adverse effects occur rarely. Rashes and photosensitivity reactions may be severe; hypersensitivity reactions include interstitial nephritis and vasculitis; fever has also been reported. Bone marrow depression may occur: there have been reports of agranulocytosis, thrombocytopenia, and leucopenia. Tinnitus and deafness may occur, in particular during rapid high-dose parenteral furosemide. Deafness may be permanent, especially in patients taking other ototoxic drugs.

Incidence of adverse effects. In a survey of 553 hospital inpatients[1] receiving furosemide 220 patients (40%) had 480 adverse reactions. Electrolyte disturbances occurred in 130 (23.5%) patients and extracellular volume depletion in 50 (9%). Adverse reactions were more common in those with liver disease, and hepatic coma occurred in 20 patients with hepatic cirrhosis. A similar survey in 585 hospital inpatients[2] revealed 177 adverse effects in 123 (21%). These included volume depletion in 85 patients (14.5%), hypokalaemia in 21 (3.6%), and hyponatraemia in 6 (1%). Hypokalaemia was considered to be life-threatening in 2 patients. Hyperuricaemia occurred in 54 patients (9.2%), of whom 40 also had volume depletion, and clinical gout developed in 2.

1. Naranjo CA, *et al.* Frusemide-induced adverse reactions during hospitalization. *Am J Hosp Pharm* 1978; **35:** 794–8.
2. Lowe J, *et al.* Adverse reactions to frusemide in hospital inpatients. *BMJ* 1979; **2:** 360–2.

Carcinogenicity. See under Hydrochlorothiazide, p. 1404.2.

Dementia. Licensed product information states that more deaths were seen in elderly patients with dementia who were taking risperidone and furosemide than in those taking either drug alone; use of risperidone with other diuretics (mainly low-dose thiazides) was not associated with such findings. See also under Risperidone, p. 1105.1.

Effects on bone. The hypercalciuria caused by loop diuretics may alter bone metabolism, but the clinical significance of this is unknown. Results of studies have been conflicting: some have failed to show an adverse effect on bone mineral density[1] or risk of fracture[2] with loop diur-

etics, while others have reported a greater degree of bone loss[2,3] and an increased risk of fractures[4,5] in both men and women taking loop diuretics. However, the magnitude of effect has, at best, been modest, and interpretation of results has been complicated by confounding factors.

For mention of effects on bone in children (possibly associated with secondary hyperparathyroidism) see Effects in Infants and Neonates, below.

1. Lim LS, *et al.* Diuretic use and bone mineral density in older USA men: the osteoporotic fractures in men (MrOS) study. *Age Ageing* 2005; **34:** 504–7.
2. Lim LS, *et al.* Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. *J Am Geriatr Soc* 2009; **57:** 855–62.
3. Lim LS, *et al.* Osteoporotic Fractures in Men (MrOS) Study Group. Loop diuretic use and increased rates of hip bone loss in older men: the Osteoporotic Fractures in Men Study. *Arch Intern Med* 2008; **168:** 735–40.
4. Rejnmark L, *et al.* Fracture risk in patients treated with loop diuretics. *J Intern Med* 2006; **259:** 117–24.
5. Carbone LD, *et al.* Loop diuretic use and fracture in postmenopausal women: findings from the Women's Health Initiative. *Arch Intern Med* 2009; **169:** 132–40.

Effects on the ears. Ototoxicity and deafness during furosemide therapy is most frequently associated with elevated blood concentrations resulting from rapid intravenous infusion[1] or delayed excretion in patients with renal impairment.[2] Of 29 cases of furosemide-induced deafness reported to the FDA[3] in the USA, most patients had renal disease or had received the drug intravenously. Eight patients had also received another ototoxic drug. However, deafness occurred in 11 patients after oral use, and in 4 of these hearing loss occurred in the absence of renal disease or other ototoxic drugs. Hearing loss was generally transient, lasting from one-half to 24 hours, but permanent hearing loss occurred in 3 patients, one of whom had taken furosemide orally. Deafness was not always associated with high doses; six patients had received a total of 200 mg or less of furosemide.

See also Precautions, below.

1. Heidland A, Wigand ME. Einfluss hoher Furosemiddosen auf die Gehörfunktion bei Urämie. *Klin Wochenschr* 1970; **48:** 1052–6.
2. Schwartz GH, *et al.* Ototoxicity induced by furosemide. *N Engl J Med* 1970; **282:** 1413–14.
3. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. *Ann Intern Med* 1979; **91:** 744–5.

Effects on electrolyte balance. *CALCIUM.* Furosemide increases renal calcium excretion. There is a danger of hypocalcaemic tetany during furosemide use in hypoparathyroid patients[1] and it has also been reported[2] in a patient with latent hypoparathyroidism following thyroidectomy.

The decrease in serum-calcium concentrations could also induce hyperparathyroidism. In a study involving 36 patients with heart failure, furosemide was associated with elevations in both parathyroid hormone and alkaline phosphatase concentrations, possibly indicating accelerated bone remodelling such as that found in primary hyperparathyroidism.[3]

For the suggestion that hypercalciuria in those taking loop diuretics may affect bone metabolism, see Effects on Bone, p. 1388.3. For reports of hypercalciuria, rickets, renal calculi, and hyperparathyroidism in neonates given furosemide, see Effects in Infants and Neonates, below.

1. Gabow PA, *et al.* Furosemide-induced reduction in ionized calcium in hypoparathyroid patients. *Ann Intern Med* 1977; **86:** 579–81.
2. Bashey A, MacNee W. Tetany induced by frusemide in latent hypoparathyroidism. *BMJ* 1987; **295:** 960–1.
3. Elmgreen J, *et al.* Elevated serum parathyroid hormone concentration during treatment with high ceiling diuretics. *Eur J Clin Pharmacol* 1980; **18:** 363–4.

MAGNESIUM, POTASSIUM, AND SODIUM. For discussions of the effects of diuretics on these electrolytes see under the Adverse Effects of Hydrochlorothiazide, p. 1404.2 and p. 1404.3.

Effects in infants and neonates. Furosemide is commonly used in the treatment of cardiac and pulmonary disorders in premature infants and neonates. This age group appears to be particularly susceptible to adverse effects arising from the increase in urinary calcium excretion which occurs during long-term use. Increases in parathyroid hormone concentration[1,2] and evidence of bone resorption[1,3] support the suggestion that the increased calcium loss causes secondary hyperparathyroidism. There have been reports of decreased mineral content of bone,[1,3] rickets,[4] fractures,[3] and renal calcification.[1,5-7] An observation[5] that renal calcification could be reversed by the addition of a thiazide diuretic was supported by other workers.[6] There is evidence[8] that furosemide-related renal calcifications in very low birth-weight infants might be associated with long-term renal impairment. Renal calcification has also been reported after furosemide use in older infants.[9]

It has been suggested[10] that a sodium deficit in infants given furosemide for heart failure may contribute to a failure to thrive.

Concern has been expressed over the finding[11] that furosemide use in premature infants with respiratory distress syndrome increases the incidence of patent ductus arteriosus. The mechanism is thought to be connected with stimulation of renal prostaglandin E_2. However, the increased incidence of patent ductus arteriosus did not adversely affect the mortality in infants given furosemide, and a subsequent study[12] failed to find any increase in the incidence of patent ductus arteriosus in infants treated with furosemide compared with a control group. Paradoxically, furosemide has been used in the management of delayed closure of ductus (see Patent Ductus Arteriosus under Uses and Administration, p. 1388.2). There is a possibility that furosemide may not be effective in infants given indometacin[13] but it can prevent the decline in urine output that occurs during indometacin use.[14,15]

1. Venkataraman PS, *et al.* Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. *Am J Dis Child* 1983; **187:** 1157–61.
2. Vileisis RA. Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease. *Pediatrics* 1990; **85:** 316–22.
3. Morgan MEI, Evans SE. Osteopenia in very low birthweight infants. *Lancet* 1986; **ii:** 1399–1400.
4. Chudley AE, *et al.* Nutritional rickets in 2 very low birthweight infants with chronic lung disease. *Arch Dis Child* 1980; **55:** 687–90.
5. Hufnagle KG, *et al.* Renal calcifications: a complication of long-term furosemide therapy in preterm infants. *Pediatrics* 1982; **70:** 360–3.
6. Noe HN, *et al.* Urolithiasis in pre-term neonates associated with furosemide therapy. *J Urol (Baltimore)* 1984; **132:** 93–4.
7. Pearse DM, *et al.* Sonographic diagnosis of furosemide-induced nephrocalcinosis in newborn infants. *J Ultrasound Med* 1984; **3:** 553–6.
8. Downing GJ, *et al.* Kidney function in very low birth weight infants with furosemide-related renal calcifications at ages 1 to 2 years. *J Pediatr* 1992; **120:** 599–604.
9. Alon US, *et al.* Nephrocalcinosis and nephrolithiasis in infants with congestive heart failure treated with furosemide. *J Pediatr* 1994; **125:** 149–51.
10. Salmon AP, *et al.* Sodium balance in infants with severe congestive heart failure. *Lancet* 1989; **ii:** 875.
11. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with respiratory-distress syndrome. *N Engl J Med* 1983; **308:** 743–8.
12. Yeh TF, *et al.* Early furosemide therapy in premature infants (⩽ 2000 gm) with respiratory distress syndrome: a randomized controlled trial. *J Pediatr* 1984; **105:** 603–9.
13. Friedman Z, *et al.* Urinary excretion of prostaglandin E following the administration of furosemide and indomethacin to sick low-birthweight infants. *J Pediatr* 1978; **93:** 512–15.
14. Yeh TF, *et al.* Furosemide prevents the renal side effects of indomethacin therapy in premature infants with patent ductus arteriosus. *J Pediatr* 1982; **101:** 433–7.
15. Nahata MC, *et al.* Furosemide can prevent decline in urine output in infants receiving indomethacin for patent ductus closure: a multidose study. *Infusion* 1988; **12:** 11–12 and 15.

Effects on lipid metabolism. Most studies into the effects of diuretics on blood-lipid concentrations have used thiazides (see Hydrochlorothiazide, p. 1405.2). The few studies into the effects of furosemide suggest that, like thiazides, it may adversely influence blood-lipid concentrations during short-term use.[1]

1. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins I: diuretics. *Drugs* 1986; **32:** 260–78.

Precautions

Precautions and contra-indications for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Although furosemide is used in high doses for oliguria due to chronic or acute renal impairment it should not be given in anuria or in renal failure caused by nephrotoxic or hepatotoxic drugs nor in renal failure associated with hepatic coma. Furosemide should not be given in pre-comatose states associated with hepatic cirrhosis. It should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

To reduce the risk of ototoxicity, licensed product information recommends that furosemide should not be injected intravenously at a rate exceeding 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly.

Furosemide should be used with caution during pregnancy and breast feeding since it crosses the placenta and also appears in breast milk. Furosemide may compromise placental perfusion by reducing maternal blood volume; it may also inhibit lactation.

Hepatic impairment. In patients with chronic heart failure and moderate liver congestion, high-dose furosemide therapy could produce increases in liver enzymes suggestive of hepatitis.[1] Special care should be taken in such patients to avoid severe ischaemic liver damage caused by a drop in systemic blood pressure.

As with the thiazides, furosemide should be avoided in patients with severe hepatic impairment.

1. Lang I, *et al.* Furosemide and increases in liver enzymes. *Ann Intern Med* 1988; **109:** 845.

Hypersensitivity. Furosemide is a sulfa-containing diuretic and hypersensitivity reactions may occur, although they are rare; cross-reactivity with other sulfa-containing drugs is also possible. However, 2 patients who had in the distant past shown serious adverse reactions to sulfa-containing diuretics were successfully treated[1] with furosemide using a rechallenge protocol. They were given an initial dose of 50 micrograms which was increased gradually each day to 20 mg by day 10, and were discharged from hospital on a maintenance dose of 40 mg twice daily. Another patient[2] with a history of sulfonamide-induced pancreatitis developed pancreatitis with furosemide, which recurred with bumetanide and torasemide and on rechallenge with furosemide. She underwent a rapid desensitisation regimen and was subsequently successfully stabilised on oral furosemide. Others have also described rapid desensitisation protocols.[3] For further information on cross-reactivity between sulfa-containing drugs see under Sulfamethoxazole, p. 365.3.

1. Earl G, *et al.* Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann Intern Med* 2003; **138:** 358–9.
2. Juang P, *et al.* Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. *Ann Pharmacother* 2006; **40:** 128–34.
3. Alim N, Patel JY. Rapid oral desensitization to furosemide. *Ann Allergy Asthma Immunol* 2009; **103:** 538.

Hypoparathyroidism. For comments on the possibility of hypocalcaemic tetany in hypoparathyroid patients taking furosemide, see Effects on Electrolyte Balance, above.

Infants and neonates. Caution must be exercised in using furosemide in infants, particularly for long periods. The immaturity of the renal system can result in unexpectedly high blood concentrations and extended half-lives. **Fluid and electrolyte balances** should therefore be monitored carefully. Neonates appear to be particularly susceptible to increases in urinary calcium concentrations after long-term use. There have also been reports[1] of an increased incidence of patent ductus arteriosus in infants given furosemide, although this did not adversely affect mortality.

Secondly, several studies[2-4] have shown furosemide to be a potent displacer of **bilirubin** from albumin binding sites and it should be used with caution in jaundiced infants. On a molar basis chlorothiazide, furosemide, and etacrynic acid were at least as potent as sulfafurazole in displacing bilirubin from albumin.[3] Doses of furosemide 1 mg/kg probably do not produce a significant increase in free bilirubin in most jaundiced infants,[3,4] although doses greater than 1.5 mg/kg or repeated dosing could potentially do so.[4] Chlorothiazide 15 to 20 mg/kg would not be an appropriate alternative to furosemide[3] since it could produce higher plasma bilirubin concentrations in jaundiced infants.

In addition, there is some evidence from an *in vitro* study[5] that bilirubin may displace furosemide from binding sites to a greater extent in neonates than in adults. The clearance of furosemide is much slower in neonates than in adults, with an eightfold prolongation in plasma half-life, and this should be taken into account during repeat dosing.[4]

1. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. *N Engl J Med* 1983; **308:** 743–8.
2. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr* 1977; **90:** 642–6.
3. Wennberg RP, *et al.* Displacement of bilirubin from human albumin by three diuretics. *J Pediatr* 1977; **90:** 647–50.
4. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; **93:** 507–11.
5. Viani A, Pacifici GM. Bilirubin displaces furosemide from serum protein: the effect is greater in newborn infants than adult subjects. *Dev Pharmacol Ther* 1990; **14:** 90–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies furosemide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of furosemide that are due to its effects on fluid, electrolyte, and carbohydrate balance are similar to those of hydrochlorothiazide (see p. 1406.1).

Furosemide may enhance the nephrotoxicity of cephalosporin antibacterials such as cefalotin and can enhance the ototoxicity of aminoglycoside antibacterials and other ototoxic drugs.

Aliskiren. Licensed product information for aliskiren states that it may decrease furosemide and torasemide concentrations.

Antiepileptics. The diuretic effect of furosemide has been shown to be substantially reduced by mixed antiepileptic therapy that included *phenytoin*.[1,2] The mean diuretic effect of furosemide 20 mg or 40 mg orally in patients on such therapy was 68% and 51% that of healthy controls respectively.[1]

For the effect of furosemide on *phenobarbital*, see p. 538.1.

Symptomatic hyponatraemia has been associated with the use of furosemide or hydrochlorothiazide with *carbamazepine*.[3]

1. Ahmad S. Renal insensitivity to frusemide caused by chronic anticonvulsant therapy. *BMJ* 1974; **3:** 657–9.
2. Fine A, *et al*. Malabsorption of frusemide caused by phenytoin. *BMJ* 1977; **2:** 1061–2.
3. Yassa R, *et al*. Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; **48:** 281–3.

Diuretics. Severe electrolyte disturbances may occur in patients given *metolazone* with furosemide.

Hypnotics. A syndrome of flushing, tachycardia, elevated blood pressure, and severe diaphoresis was reported after intravenous dosage of furosemide in 6 patients who had taken *cloral hydrate* orally during the preceding 24 hours.[1] The reaction recurred in 1 patient on a subsequent occasion when given both drugs but not when furosemide was used without cloral hydrate. A subsequent retrospective study[2] among 43 patients who had received both cloral hydrate and furosemide showed that 1 patient had suffered a similar reaction; of 2 further patients who had possibly been affected, 1 had subsequently taken both drugs without adverse effects. A similar interaction has been reported in an 8-year-old child.[3]

1. Malach M, Berman N. Furosemide and chloral hydrate: adverse drug interaction. *JAMA* 1975; **232:** 638–9.
2. Pevonka MP, *et al*. Interaction of chloral hydrate and furosemide: a controlled retrospective study. *Drug Intell Clin Pharm* 1977; **11:** 332–5.
3. Dean RP, *et al*. Interaction of chloral hydrate and intravenous furosemide in a child. *Clin Pharm* 1991; **10:** 385–7.

Lithium. For reports of a possible increase in plasma-lithium concentrations in patients receiving loop diuretics, see p. 432.2.

NSAIDs. NSAIDs may antagonise the diuretic effect of furosemide and other diuretics.[1] Use of NSAIDs with diuretics may increase the risk of nephrotoxicity, although it has also been suggested that furosemide may protect against the renal effects of *indometacin* in infants (see Effects in Infants and Neonates, p. 1389.1).

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Probenecid. Probenecid has been shown[1-4] to reduce the renal clearance of furosemide, and to reduce the diuretic effect.[2,3]

1. Honari J, *et al*. Effects of probenecid on furosemide kinetics and natriuresis in man. *Clin Pharmacol Ther* 1977; **22:** 395–401.
2. Odlind B, Beermann B. Renal tubular secretion and effects of furosemide. *Clin Pharmacol Ther* 1980; **27:** 784–90.
3. Smith DE, *et al*. Preliminary evaluation of furosemide-probenecid interaction in humans. *J Pharm Sci* 1980; **69:** 571–5.
4. Vree TB, *et al*. Probenecid inhibits the renal clearance of frusemide and its acyl glucuronide. *Br J Clin Pharmacol* 1995; **39:** 692–5.

Tobacco. The effects of tobacco smoking on the pharmacokinetics of furosemide have been reviewed.[1,2] Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide. However, this effect is attenuated in habitual smokers.

1. Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; **17:** 90–108.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.

Xanthines. For the effect of furosemide on *theophylline*, see Diuretics, p. 1236.1.

Pharmacokinetics

Furosemide is fairly rapidly absorbed from the gastrointestinal tract; bioavailability has been reported to be about 60 to 70% but absorption is variable and erratic. The half-life of furosemide is up to about 2 hours although it is prolonged in neonates and in patients with renal and hepatic impairment. Furosemide is up to 99% bound to plasma albumin, and is mainly excreted in the urine, largely unchanged. There is also some excretion via the bile and non-renal elimination is considerably increased in renal impairment. Furosemide crosses the placental barrier and is distributed into breast milk. The clearance of furosemide is not increased by haemodialysis.

The pharmacokinetics of furosemide have been extensively reviewed.[1-6] The development of an analytical method using HPLC with fluorescence has produced greater sensitivity and more consistent results. Absorption after oral use is erratic and is subject to large inter- and intra-individual variation. It is influenced by the dosage form, underlying disease processes, and by the presence of food. Furosemide absorption in patients with heart failure has been reported to be even more erratic than in healthy subjects. The bioavailability of furosemide from oral dosage forms is also highly variable with reported values ranging from 20 to 100%. It is influenced by factors affecting absorption but the poor solubility of furosemide does not appear to have a major influence on bioavailability and *in vitro* dissolution data may not reflect *in vivo* bioavailability. Bioavailability tends to be decreased by about 10% in patients with renal disease, and slightly increased in liver disease. Values are erratic in patients with heart disease.

Furosemide is highly bound to plasma proteins, almost exclusively to albumin. The proportion of free (unbound) furosemide is higher in patients with heart disease, renal impairment, and cirrhosis of the liver. Patients with liver disease also have an increased apparent volume of distribution which is proportionally greater than the decrease seen in protein binding. Patients with nephrotic syndrome have significant proteinuria and secondary hypoalbuminaemia. This results in reduced protein binding in the blood, particularly at higher blood concentrations, and binding to proteins present in the urine, which may account for the resistance to furosemide therapy reported in these patients.

A glucuronide metabolite of furosemide is produced in varying amounts. The site of metabolism is unknown at present. There is debate over another potential metabolite, 4-chloro-5-sulfamoyl anthranilic acid (CSA). It has been argued[3] that it is an artefact produced during the extraction procedures although there is some evidence to refute this.[4]

A half-life for furosemide in healthy subjects has generally been reported in the range of 30 to 120 minutes. In patients with end-stage renal disease the average half-life is 9.7 hours. The half-life may be slightly longer in patients with hepatic dysfunction and a range of 50 to 327 minutes has been reported in patients with heart failure. In severe multi-organ failure the half-life may range from 20 to 24 hours.

Furosemide clearance is influenced by age, underlying disease state, and drug interactions. Clearance reduces with increasing age, probably due to declining renal function. Renal impairment in renal or cardiac disease reduces renal clearance, although this may be compensated for by increases in non-renal clearance. Hepatic impairment has little impact on clearance. Renal and non-renal clearance may be reduced by probenecid and indometacin.

The efficacy of furosemide as a diuretic depends upon it reaching its site of action, the renal tubules, unchanged. About one-half to two-thirds of an intravenous dose or one-quarter to one-third of an oral dose are excreted unchanged, the difference being largely due to the poor bioavailability from the oral route. The effect of furosemide is more closely related to its urinary excretion than to the plasma concentration. Urinary excretion may be reduced in renal impairment due to reduced renal blood flow and reduced tubular secretion.

1. Cutler RE, Blair AD. Clinical pharmacokinetics of frusemide. *Clin Pharmacokinet* 1979; **4:** 279–96.
2. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. *J Pharmacokinet Biopharm* 1979; **7:** 1–27.
3. Hammarlund-Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update. *J Pharmacokinet Biopharm* 1989; **17:** 1–46.
4. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; **18:** 381–408.
5. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part II). *Clin Pharmacokinet* 1990; **18:** 460–71.
6. Vrhovac B, *et al*. Pharmacokinetic changes in patients with oedema. *Clin Pharmacokinet* 1995; **28:** 405–18.

Infants and neonates. The half-life of furosemide in term and preterm neonates is markedly prolonged compared with that in adults.[1,2] Half-lives of 4.5 to 46 hours have been reported and it has been suggested that the prolongation may be greater in preterm than in term neonates. This effect is due mainly to immature renal function and if repeated doses are necessary over a short period accumulation may occur.[1]

1. Besunder JB, *et al*. Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part II). *Clin Pharmacokinet* 1988; **14:** 261–86.
2. Aranda JV, *et al*. Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; **93:** 507–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Errolon; Fabofurox; Furagrand; Furital; Furix; Furotral; Fursemida; Furtenk; Kolkin; Lasix; Nuriban; Retep; ***Austral.***: Frusehexal†; Frusid; Lasix; Uremide; Urex; ***Austria***: Furohexal; Furon; Furostad; Lasix; ***Belg.***: Docfurose†; Furotop†; Lasix; ***Braz.***: Closenid; Diuremida; Fluxil; Furesin†; Furomida; Furosan; Furosantisa; Furosem†; Furosemin; Furosetron; Furosix; Furozix; Fursemida; Lasix; Neosemid; Rovelan; Urasix; ***Canad.***: Lasix; Novo-Semide†; ***Chile***: Asax; ***China***: A Xi Ya (阿西亚); Ai Ge (艾格); ***Cz.***: Furon; Furorese; ***Denm.***: Diural; Furix; Lasix; ***Fin.***: Furesis; Furomin†; Lasix; Vesix; ***Fr.***: Lasilix; ***Ger.***: Diurapid†; Furanthril; Furo-Puren†; Furo†; Furobeta; Furogamma; Furorese†; Furosal†; Fusid†; Jufurix†; Lasix†; ***Gr.***: Fudesix; Furanthril; Hydroflux; Inzury; Lasix; Riomid; Semid; ***Hong Kong***: CP-Furo; Diurex†; Lasix; Naqua†; Urex; ***Hung.***: Furon; ***India***: Fru; Frusemix; Frusenex; Frusim; Frusix; Lasix; ***Indon.***: Cetasix†; Classic; Diurefo†; Diuvar; Edemin; Farsix; Furosix; Impugan; Lasix; Naclex; Silax; Uresix; ***Irl.***: Fruside; Lasix; ***Israel***: Furovenir; Fusid; Miphar; ***Ital.***: Lasix; ***Malaysia***: Akoset; Dirine; Fruside; Lasix; Rasitol; Suopinchon; ***Mex.***: Biomisen; Butosali; Diurmessel; Edenol; Furosan; Henexal†; Klimyn; Lasix; Luzamida; Osemin; Selectofur†; Zafimida; ***Neth.***: Lasiletten; Lasix; ***Norw.***: Diural; Furix; Lasix; ***NZ***: Diurin; Frusid; Lasix; Urex; ***Philipp.***: Diuril†; Diuspec; Edemann; Flexamide; Fremid; Fretic; Frusema; Furide; Furolink; Furoscan; Fusimex; Lasix; Pharmix†; Pisamor; Rasitol; Rofunil; ***Port.***: Lasix; Naqua†; ***Rus.***: Lasix (Лазикс); ***S.Afr.***: Aquarid; Beuresis; Beurises; Dino-Retic; Diuresix; Lasix; Puresis; Uretic†; ***Singapore***: Dirine; Furmide; Lasix; Rasitol; Sunmide; ***Spain***: Seguril; ***Swed.***: Furix; Impugan; Lasix; ***Switz.***: Furodrix; Fursol; Lasix; Oedemex; ***Thai.***: Dema; Dirine; Femide; Frusil; Fudirine; Furetic; Furide; Furine; Furomed; Furomide; Furozide; Fuseride; Fusesian; H-Mide; Hawkmide; Lasiven; Lasix; Prosix; Rosemide†; ***Turk.***: Desal; Furomid; Lasix; Lizik; Urever; Urex; ***UAE***: Salurin; ***UK***: Froop; Frusid; Frusol; Lasix; Rusyde; ***Ukr.***: Lasix (Лазикс); ***USA***: Lasix; ***Venez.***: Biosemida; Edemid; Inclens; Lasix; Lifurox; Salca; Terysol.

Multi-ingredient Preparations. ***Arg.***: Aldactone-D; Diflux; Errolon A; Lasilacton; Lasiride; Nuriban A; ***Austria***: Furo-Spirobene; Lasilacton; Lasitace; Spirono comp; ***Belg.***: Frusamil; ***Braz.***: Diurana; Diurisa; Furosemide Composto; Hidrion; Lasilactona; ***Chile***: Furdiuren; Hidrium; Hidropid†; ***China***: Fuluobi (福洛必); ***Denm.***: Frusamil; ***Fin.***: Furesis comp; ***Fr.***: Aldalix; Logirene; ***Ger.***: Betasemid; Diaphal; Furo-Aldopur†; Furorese Comp†; Osyrol Lasix†; Spiro comp; Spiro-D†; ***Gr.***: Frumil; ***India***: Aldostix; Amifru-S; Amifru; Amimide; Aquamide; Diucontin-K; Exna-K; Frumil; Fruselac; Frusemene; Lasilactone; Lasiride; Minilactone; Spiromide; ***Irl.***: Diumide-K Continus†; Fru-Co; Frumil; ***Ital.***: Fluss; Lasitone; Spirofur; ***Mex.***: Lasilacton; ***NZ***: Frumil; ***Philipp.***: Diumide-K; ***Switz.***: Furospir; Lasilactone; ***UK***: Aridil; Fru-Co; Frumil; Frusene; Komil; Lasikal; Lasilactone; ***Venez.***: Furdiuren.

Pharmacopoeial Preparations

BP 2014: Co-amilofruse Tablets; Furosemide Injection; Furosemide Tablets;

USP 36: Furosemide Injection; Furosemide Oral Solution; Furosemide Tablets.

Gallopamil Hydrochloride *(BANM, rINNM)*

D-600 (gallopamil); Gallopamil, Chlorhydrate de; Gallopamilhydroklorid; Gallopamilli Hydrochloridum; Gallopamillihydrokloridi; Galopamilo, hidrocloruro de; Hidrocloruro de galopamilo; Methoxyverapamil Hydrochloride; Галлопамила Гидрохлорид.

5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4,5-trimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

$C_{28}H_{40}N_2O_5$,HCl=521.1

CAS — 16662-47-8 (gallopamil); 16662-46-7 (gallopamil hydrochloride).

ATC — C08DA02.

ATC Vet — QC08DA02.

UNII — VT4VR32A0T.

Profile

Gallopamil is a calcium-channel blocker (see p. 1244.2) with antiarrhythmic activity and is chemically related to verapamil. It is used in the management of angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and hypertension (p. 1251.1). Gallopamil hydrochloride is given orally in doses of 25 to 50 mg every 6 to 12 hours up to a maximum total dose of 200 mg daily. Modified-release preparations are also available and are given once or twice daily in similar total daily doses.

Reviews.

1. Brogden RN, Benfield P. Gallopamil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in ischaemic heart disease. *Drugs* 1994; **47:** 93–115.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Procorum; ***China***: Procorum (普可佳); ***Ger.***: Gallobeta†; Procorum; ***Hung.***: Procorum†; ***Ital.***: Algocor; Procorum; ***Mex.***: Procorum†; ***Philipp.***: Procorum†; ***Thai.***: Procorum†.

Gemfibrozil *(BAN, USAN, rINN)*

CI-719; Gemfibrotsiili; Gemfibrozilo; Gemfibrozilum; Gemfibrozyl; Гемфиброзил.

2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid.

$C_{15}H_{22}O_3$=250.3

CAS — 25812-30-0.

ATC — C10AB04.

ATC Vet — QC10AB04.

UNII — Q8X02027X3.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Gemfibrozil). A white or almost white, waxy, crystalline powder. M.p. 58 degrees to 61 degrees. Practically insoluble in water; freely soluble in dehydrated

alcohol and in methyl alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Gemfibrozil). A white waxy crystalline solid. M.p. 58 degrees to 61 degrees. Practically insoluble in water; soluble in alcohol, in methyl alcohol, and in chloroform. Store in airtight containers.

Uses and Administration

Gemfibrozil, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p. 1323.2).

Gemfibrozil is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. It is also indicated for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1) in hyperlipidaemic men: in the USA this use is restricted to type IIb patients who also have low HDL-cholesterol concentrations and who have not responded to dietary and other measures. The usual oral dose is 1.2 g daily in 2 divided doses given 30 minutes before the morning and evening meals. Alternatively, a single daily dose of 900 mg has been given 30 minutes before the evening meal.

Reviews.

1. Spencer CM, Barradell LB. Gemfibrozil: a reappraisal of its pharmacological properties and place in the management of dyslipidaemia. *Drugs* 1996; **51:** 982–1018.

Administration in renal impairment. Gemfibrozil is contra-indicated in patients with severe renal impairment. However, UK licensed prescribing information allows its use in patients with mild to moderate impairment (glomerular filtration rate 30 to 80 mL/minute per 1.73 m^2); the initial dose should be reduced to 900 mg daily and renal function should be assessed before increasing the dose.

In a study[1] of the pharmacokinetics of gemfibrozil in 17 patients with stable chronic renal failure the mean plasma half-life was 1.8 and 1.9 hours after multiple and single doses respectively, which was comparable with that reported in patients with normal renal function. Gemfibrozil clearance was independent of renal function, but the kinetics of gemfibrozil metabolites were not evaluated.

Beneficial responses[2] were seen in lipid and lipoprotein concentrations in 5 of 6 uraemic patients treated with gemfibrozil 1.2 g daily for six months and in 6 nephrotic patients given gemfibrozil 800 mg daily for 4 months. No significant adverse effects or signs of organ toxicity were seen. Results of a secondary prevention study[3] also suggested that gemfibrozil at a dose of 1.2 g daily was safe and effective in patients with mild to moderate renal impairment.

1. Evans JR, *et al*. The effect of renal function on the pharmacokinetics of gemfibrozil. *J Clin Pharmacol* 1987; **27:** 994–1000.
2. Manninen V, *et al*. Gemfibrozil treatment of dyslipidaemias in renal failure with uraemia or in the nephrotic syndrome. *Res Clin Forums* 1982; **4:** 113–18.
3. Tonelli M, *et al*. for the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) Investigators. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; **66:** 1123–30.

Adverse Effects and Precautions

As for Bezafibrate, p. 1324.2.

Incidence of adverse effects. In the Helsinki Heart Study,[1] 11.3% of 2051 patients taking gemfibrozil reported various moderate to severe upper gastrointestinal tract symptoms during the first year of treatment compared with 7% of 2030 patients taking placebo. No differences were seen between gemfibrozil and placebo groups in haemoglobin concentrations, urinary-protein, or urinary-sugar concentrations.

There was no significant difference in the total number of cancers between the gemfibrozil and placebo groups nor in the number of operations for gallstones or for cataract surgery. A higher number of deaths in the gemfibrozil group was mainly due to accident or violence and intracranial haemorrhage.

A follow-up study[2] reported that gastrointestinal symptoms remained more common in patients taking gemfibrozil. Although there was no significant difference between the gemfibrozil and placebo groups cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period. Cancer occurred equally in both groups, but there was increased mortality attributable to cancer in the gemfibrozil group, mainly during the last 1.5 years of follow-up; this difference was no longer apparent after 18 years.[3]

1. Frick MH, *et al*. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
2. Huttunen JK, *et al*. The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235:** 31–9.
3. Tenkanen L, *et al*. Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med* 2006; **166:** 743–8.

Effects on the skin. Psoriasis was exacerbated in a patient within 2 weeks of starting gemfibrozil therapy and recurred when gemfibrozil was subsequently reintroduced.[1]

1. Fisher DA, *et al*. Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; **124:** 854–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gemfibrozil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Bezafibrate, p. 1325.2.

Gemfibrozil is an inhibitor of several cytochrome P450 isoenzymes, including CYP2C8, CYP2C9, CYP2C19, and CYP1A2 and may increase the plasma concentration of drugs metabolised by these isoenzymes; it also inhibits some UDP-glucuronosyltransferases. Increased plasma concentration of bexarotene (see p. 749.1), pioglitazone (see p. 494.2), and rosiglitazone (see p. 499.1) have been reported with gemfibrozil, and use of gemfibrozil in patients receiving repaglinide is contra-indicated due to the risk of serious hypoglycaemia (see p. 496.1).

Pharmacokinetics

Gemfibrozil is readily absorbed from the gastrointestinal tract; bioavailability is close to 100% and is highest when gemfibrozil is taken 30 minutes before food. Peak concentrations in plasma occur within 1 to 2 hours; the half-life is about 1.5 hours. Plasma protein binding of gemfibrozil is about 98%. About 70% of a dose is excreted in the urine mainly as glucuronide conjugates of gemfibrozil and its metabolites; little is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gedun; Hipolixan; Lopid; ***Austral.***: Ausgem; Gemhexal; Jezil; Lipazil; Lipigem; Lopid; ***Austria***: Gevilon; ***Braz.***: Lopid; Lozil; ***Canad.***: Lopid; ***Chile***: Grifogemzilo; Lipotril; Lopid; ***China***: Chang Heng Lin (常衡林); Luo Ping (洛平); Uragem (尤瑞旨); Weijiangzhi (维绛知); Xin Si Da (新斯达); ***Denm.***: Lopid; ***Fin.***: Lopid; ***Fr.***: Lipur; ***Ger.***: Gemfi†; Gevilon; ***Gr.***: Adrotan; Amedran; Antilipid; Cholhepan; Clipostat; Dosamont; Drisofal; Eklipid; Entianthe; Fibrolip; Fibrospes; Gebrozil; Gedizil; Gemfolid; Gemlipid; Gineton; Hobatolex; Leptokin; Lisolip; Lopid; Noxobran; Parnoxil; Prelisin; Renolip; Solulip; Terostrant; Tiazam; ***Hong Kong***: Fibrozo; Gemzil†; Gen-Fibro†; Ipolipid; Lipison; Lipistorol; Lipofor; Lopid; Lowin†; Marbrozil†; Qualipid; Ronox†; Saffid†; Synbrozil†; ***Hung.***: Innogem; Minilip; ***India***: Gempar; Lipizyl; Lopid; Losterol; Normolip; ***Indon.***: Detrichol; Fetinor; Fibralip†; Hypofil; Inobes†; Lapibroz; Lifibron; Lipira; Lipitrop; Lokoles; Lopid; Lowlip†; Mersikol; Nufalemzil; Progemzal†; Renabrazin; Scantipid; Zenibroz; Zilop; ***Irl.***: Lopid; ***Ital.***: Gemlipid†; Genlip; Lopid; ***Malaysia***: Brozil; Ipolipid; Lipofor†; ***Mex.***: Apo-Fide; Lopid; Raypid; ***Neth.***: Lopid; ***NZ***: Lipazil; ***Philipp.***: Eogem; Lipigem; Lipison†; Lipizile; Lipozid†; Lopid; Reducel; ***Port.***: Lipoite; Lopid; ***Rus.***: Ipolipid (Иполипид); ***S.Afr.***: Lopid; ***Singapore***: Brozil; Gemd†; Hidil; Ipolipid; Lipison; Lipistorol; Lipofor; Recozil; ***Spain***: Lopid; Pilder†; Trialmin; ***Swed.***: Lopid; ***Switz.***: Gevilon; ***Thai.***: Bisil; Delipid; Dropid; Fibropid; Gembropac; Gemfibril; Gemox; GFB; Gozid; Hidil; Lespid; Lipidys†; Lipison; Lipolo; Lipozil†; Locholes†; Lodil; Lopicare; Lopid; Lopol; Manobrozil; Mariston†; Milpid; Norpid; Pharzil†; Poli-Fibrozil; Polyxit; Ronox; Tiba†; Tolip; U-Pid; ***Turk.***: Lopid; ***UK***: Lopid; ***USA***: Lopid; ***Venez.***: Lipontal; Lopid.

Pharmacopoeial Preparations

BP 2014: Gemfibrozil Capsules; Gemfibrozil Tablets;
USP 36: Gemfibrozil Capsules; Gemfibrozil Tablets.

Glyceryl Trinitrate

Glicerin-trinitrát; Glicerolio trinitratas; Gliseril Trinitrat; Glonoin; Glyceroli Trinitras; Glyceroli Trinitratis; Glyceroltrinitrát; Glycéryle, trinitrate de; Glyceryltrinitrat; Glyseryylitrinitraatti; GTN; Nitrato de glicerilo; Nitroglicerina; Nitrogliserin; Nitroglycerin; Nitroglycerol; NTG; Trinitrato de glicerilo; Trinitrin; Trinitroglicerina; Trinitroglycerin; Глицерилтринитрат.

Propane-1,2,3-triol trinitrate.

$C_3H_5(NO_3)_3$=227.1

CAS — 55-63-0.

ATC — C01DA02; C05AE01.

ATC Vet — QC01DA02; QC05AE01.

UNII — G59M7S0WS3.

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.* include glyceryl trinitrate as diluted solutions.

Ph. Eur. 8: (Glyceryl Trinitrate Solution). An ethanolic solution containing 1 to 10% w/w of glyceryl trinitrate. It is a clear, colourless or slightly yellow solution. Miscible with dehydrated alcohol and with acetone.

Pure glyceryl trinitrate is practically insoluble in water; freely soluble in dehydrated alcohol; miscible with acetone.

Protect from light. Diluted solutions (1%) should be stored at 2 degrees to 15 degrees; more concentrated solutions may be stored at 15 degrees to 20 degrees.

USP 36: (Diluted Nitroglycerin). A mixture of glyceryl trinitrate with lactose, glucose, alcohol, propylene glycol, or other suitable inert excipient, usually containing not more than 10% glyceryl trinitrate. When diluted in either alcohol or propylene glycol it is a clear, colourless, or pale yellow liquid. When diluted with lactose, it is a white odourless powder. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Prevent exposure to temperatures above 40 degrees. Protect from light.

Undiluted glyceryl trinitrate is a white to pale yellow, thick, flammable, explosive liquid. Slightly soluble in water; soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in dichloromethane, in ether, in ethyl acetate, in glacial acetic acid, in methyl alcohol, in benzene, in toluene, in nitrobenzene, and in phenol.

Handling. Undiluted glyceryl trinitrate can be exploded by percussion or excessive heat and only exceedingly small amounts should be isolated.

Incompatibility. Studies have found glyceryl trinitrate to be incompatible with phenytoin,[1] alteplase,[2] and levofloxacin.[3]

1. Klamerus KJ, *et al*. Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
2. Lee CY, *et al*. Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Saltsman CL, *et al*. Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability. *INTRAVENOUS SOLUTIONS.* The loss of glyceryl trinitrate from solution by adsorption or absorption into some plastics of intravenous giving sets has been recognised for some years,[1,2] although adsorption does not appear to occur to any great extent with polyolefin[3,4] or polyethylene.[5-7] It is not only infusion containers and plastic tubing that may be involved; some in-line filters can adsorb glyceryl trinitrate.[8,9]

1. Grouthamel WG, *et al*. Loss of nitroglycerin from plastic intravenous bags. *N Engl J Med* 1978; **299:** 262.
2. Roberts MS, *et al*. The availability of nitroglycerin from parenteral solutions. *J Pharm Pharmacol* 1980; **32:** 237–44.
3. Wagenknecht DM, *et al*. Stability of nitroglycerin solutions in polyolefin and glass containers. *Am J Hosp Pharm* 1984; **41:** 1807–11.
4. Trissel LA, *et al*. Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
5. Schaber DE, *et al*. Nitroglycerin adsorption to a combination polyvinyl chloride, polyethylene intravenous administration set. *Drug Intell Clin Pharm* 1985; **19:** 572–5.
6. Tracy TS, *et al*. Nitroglycerin delivery through a polyethylene-lined intravenous administration set. *Am J Hosp Pharm* 1989; **46:** 2031–5.
7. Martens HJ, *et al*. Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
8. Baaske DM, *et al*. Nitroglycerin compatibility with intravenous fluid filters, containers, and administration sets. *Am J Hosp Pharm* 1980; **37:** 201–5.
9. Kanke M, *et al*. Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.

TABLETS. Many studies have shown that glyceryl trinitrate tablets are unstable and subject to considerable loss of potency in contact with packaging components such as adhesive labels, cotton and rayon fillers, and plastic bottles and caps. Both the Council of the Royal Pharmaceutical Society of Great Britain and the FDA in the USA have issued packaging and dispensing guidelines. Glyceryl trinitrate tablets should be dispensed only in glass containers sealed with a foil lined cap and containing no cotton wool wadding. In addition, the Council of the Royal Pharmaceutical Society of Great Britain recommends that no more than 100 tablets should be supplied and that the container should be labelled with an indication that any tablets should be discarded after 8 weeks in use.

Uses and Administration

Glyceryl trinitrate is a nitrovasodilator used in the management of angina pectoris (p. 1254.3), heart failure (p. 1262.3), and myocardial infarction (p. 1392.3). Other indications include inducing hypotension and controlling hypertension during surgery.

Glyceryl trinitrate is believed to exert its vasodilator effect through release of nitric oxide, which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. In its action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Glyceryl trinitrate also has a coronary vasodilator effect, which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Glyceryl trinitrate may be given by the sublingual, buccal, oral, transdermal, or intravenous route. The dose and choice of formulation depend upon the clinical situation.

In the management of **acute angina** glyceryl trinitrate is given as sublingual tablets, a sublingual aerosol spray, or buccal tablets, which all produce a rapid onset of therapeutic effect and provide rapid relief of anginal pain. These dosage forms may also be used before an activity or stress which might provoke an attack. One sublingual tablet (usual strength 300 to 600 micrograms) is placed under the tongue. The dose may be repeated as required but patients should be advised to seek medical care if pain persists after a total of 3 doses within 15 minutes. If an aerosol spray is used one or two sprays of 400 micrograms each are directed onto or under the tongue, then the mouth is closed; three sprays may be used if necessary. Buccal tablets of glyceryl trinitrate are placed between the upper lip and gum (see below for precautions to be observed during use). The usual dose is 2 mg when required, increased to 3 mg if necessary; a dose of 5 mg may be given in severe angina.

In the long-term management of **stable angina** glyceryl trinitrate is given as modified-release tablets or capsules, transdermal formulations, or buccal tablets, which all provide a long duration of action. Dosage varies according to the specific formulation. In the USA, for example, modified-release oral capsules may be taken in a usual starting dose of 2.5 to 6.5 mg three or four times daily, increased up to 26 mg four times daily if needed. The transdermal formulations available are ointments and patches. With the ointment a measured amount (½ to 2 inches of glyceryl trinitrate ointment 2%) is applied 2 to 4 times daily, or every 3 to 4 hours if necessary, to a hairless area of the chest, arm, thigh, or back. Transdermal patches applied to the chest, upper arm, or shoulder are more convenient. Patches are generally designed to release glyceryl trinitrate at a constant rate; they are available in a range of sizes, releasing about 100 to 800 micrograms/hr (equivalent to about 2.5 to 20 mg in 24 hours, although the patches are generally removed for part of this period to prevent tolerance developing). A maximum daily dose of 20 mg has been suggested. Glyceryl trinitrate ointment and patches should be applied to a fresh area of skin and several days should elapse before re-application to formerly used sites. Buccal tablets are used in doses of 2 to 5 mg three times daily. The tablets are retained in the buccal cavity; the rate of dissolution of the tablet can be increased by touching the tablet with the tongue or drinking hot liquids. It is common practice to remove the tablets at bedtime because of the risk of aspiration. Also patients using buccal tablets should be advised to alternate placement sites and pay close attention to oral hygiene to reduce the risk of dental caries. The tablets are not intended to be chewed; if the buccal tablet is inadvertently swallowed, another may be placed in the buccal cavity.

Tolerance tends to develop in the majority of patients on continuous nitrate therapy and nitrate-free intervals are often employed to avoid this problem (see p. 1394.1 under Precautions, Nitrate Tolerance for further details).

In the management of **unstable angina** glyceryl trinitrate may be given by intravenous infusion. Manufacturers' guidelines for dilution of glyceryl trinitrate injection specify glucose 5% or sodium chloride 0.9% as the diluent. During intravenous use of glyceryl trinitrate there should be haemodynamic monitoring of the patient with the dose being adjusted gradually to produce the desired response. The plastic used in the infusion equipment may adsorb glyceryl trinitrate (see Stability, p. 1391.3) and allowance may have to be made for this. The usual initial dose for unstable angina is 5 to 10 micrograms/minute. Most patients respond to doses between 10 and 200 micrograms/minute. The sublingual and buccal routes may also be used; doses of up to 5 mg as buccal tablets may be required to relieve pain in patients with unstable angina.

In the management of acute **heart failure** glyceryl trinitrate is given intravenously in an initial dose of 5 to 25 micrograms/minute. Buccal tablets have been used in doses of 5 mg repeated as needed until symptoms are controlled. In chronic heart failure buccal tablets may be given in doses of 5 to 10 mg three times daily.

Glyceryl trinitrate is also used intravenously in acute **myocardial infarction**, and to induce hypotension or control hypertension during **surgery**. The initial dose is 5 to 25 micrograms/minute, adjusted according to response. The usual range is 10 to 200 micrograms/minute but some surgical patients may require up to 400 micrograms/minute.

Glyceryl trinitrate has also been used as transdermal patches in the prophylactic treatment of **phlebitis and extravasation** secondary to venous cannulation. One 5-mg patch is applied distal to the intravenous site; the patch should be replaced at a different skin site either daily or after 3 to 4 days, depending on the patch. This treatment should continue only as long as the intravenous infusion is maintained.

Glyceryl trinitrate may also be used as a 0.4% ointment for the relief of pain due to chronic **anal fissure** (below). A measured amount equivalent to about 1.5 mg is applied intra-anally every 12 hours for up to 8 weeks.

Administration in children. Although such use is unlicensed in children in the UK, the *BNFC* suggests that an intravenous infusion of glyceryl trinitrate may be used to produce vasodilatation in neonates, infants, and children in an initial dose of 200 to 500 nanograms/kg per minute, adjusted according to response to a usual dose of 1 to 3 micrograms/kg per minute. The dose should not exceed 10 micrograms/kg per minute, or 200 micrograms/minute.

In the management of anal fissures in children, the *BNFC* suggests the application of a glyceryl trinitrate 0.05 or 0.1% ointment.

Anal fissure. Nitrates such as glyceryl trinitrate are used for the treatment of chronic anal fissure (p. 2017.3) because of their ability to relax the anal sphincter. Topical application of glyceryl trinitrate ointment in concentrations of 0.2 to 0.8% has relieved pain and aided healing of anal fissures both in uncontrolled[1-3] and controlled studies,[4,5] although only the effect on pain appears to be significant.[6] One study[5] found that a concentration of 0.6% had no additional benefit over 0.2%. Follow-up[5,7] of some of the patients indicated that after 6 to 38 months most had not had further problems or had had occasional recurrences (relapses of about one-quarter to one-third) which in the majority of cases had responded to further topical treatment. A small placebo-controlled study specifically in children, however, did not find topical glyceryl trinitrate to be of benefit in this patient population.[8]

There is evidence that application of a glyceryl trinitrate patch may be as effective as topical application of a 0.2% ointment.[9]

Encouraging results have also been obtained in an uncontrolled study using a 1% ointment of isosorbide dinitrate.[10]

1. Gorfine SR. Topical nitroglycerin therapy for anal fissures and ulcers. *N Engl J Med* 1995; **333:** 1156–7.
2. Lund JN *et al.* Use of glyceryl trinitrate ointment in the treatment of anal fissure. *Br J Surg* 1996; **83:** 776–7.
3. Watson SJ, *et al.* Topical glyceryl trinitrate in the treatment of chronic anal fissure. *Br J Surg* 1996; **83:** 771–5.
4. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; **349:** 11–14. Correction. *ibid.*; 656.
5. Carapeti EA, *et al.* Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut* 1999; **44:** 727–30.
6. Fenton C, *et al.* 0.4% Nitroglycerin ointment: in the treatment of chronic anal fissure pain. *Drugs* 2006; **66:** 343–9.
7. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; **352:** 1681.
8. Kenny SE, *et al.* Double blind randomised controlled trial of topical glyceryl trinitrate in anal fissure. *Arch Dis Child* 2001; **85:** 404–7.
9. Zuberi BF, *et al.* A randomized trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures. *Int J Coloractal Dis* 2000; **15:** 243–5.
10. Schouten WR, *et al.* Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. *Gut* 1996; **39:** 465–9.

Erectile dysfunction. Erectile dysfunction (p. 2348.2) is usually managed with oral or intracavernosal vasodilators. Several studies have investigated topical alternatives, mostly glyceryl trinitrate applied either as ointment or as a transdermal patch to the penis.[1-5] Nitrates are believed to act by providing the smooth muscle relaxation and vasodilatation necessary for penile erection, and such treatment can produce erections in some subjects, although response rates vary.

Topical application of a cream containing isosorbide dinitrate, codergocrine mesilate, and aminophylline produced satisfactory erections in 21 of 36 men with erectile dysfunction due to various causes.[6] Eight out of 9 men with erectile dysfunction of psychogenic origin reported a satisfactory response. However, another study[7] was abandoned after the cream produced no effect in 10 consecutive patients. A further study in 14 patients who used a total of 77 applications of the cream reported no benefit over placebo.[8] Topical treatment with a cream containing isosorbide dinitrate, codergocrine mesilate, and testosterone has also been tried for erectile dysfunction; in a study in 42 men with low sexual interest and low or slightly depressed testosterone levels, 28 reported beneficial results.[9]

It has been recommended that a condom be worn to prevent drug transfer to the partner,[4] although the effects of the ointment on condom integrity do not seem to have been studied.

Topical nitrates should be avoided in those already taking phosphodiesterase type-5 inhibitors—see under Interactions, p. 1394.2.

1. Heaton JPW, *et al.* Topical glyceryl trinitrate causes measurable penile arterial dilation in impotent men. *J Urol (Baltimore)* 1990; **143:** 729–31.
2. Meyhoff HH, *et al.* Non-invasive management of impotence with transcutaneous nitroglycerin. *Br J Urol* 1992; **69:** 88–90.
3. Nunez BD, Anderson DC. Nitroglycerin ointment in the treatment of impotence. *J Urol (Baltimore)* 1993; **150:** 1241–3.
4. Anderson DC, Seifert CF. Topical nitrate treatment of impotence. *Ann Pharmacother* 1993; **27:** 1203–5.
5. Gramkow J, *et al.* Transcutaneous nitroglycerine in the treatment of erectile dysfunction: a placebo controlled clinical trial. *Int J Impot Res* 1999; **11:** 35–9.
6. Gomaa A, *et al.* Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate. *BMJ* 1996; **312:** 1512–15.
7. Naude JH, Le Roux PJ. Topical treatment of erectile dysfunction did not show results. *BMJ* 1998; **316:** 1318.
8. Le Roux PJ, Naude JH. Topical vasoactive cream in the treatment of erectile failure: a prospective, randomized placebo-controlled trial. *BJU Int* 1999; **83:** 810–11.
9. Gomaa A, *et al.* The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. *Int J Impot Res* 2001; **13:** 93–9.

Gallstones. Endoscopic removal of gallstones (p. 2639.1) in a small series of 15 patients was facilitated by glyceryl trinitrate 1.2 to 3.6 mg applied as a spray to the tongue. Glyceryl trinitrate 1.2 mg was shown to relax the sphincter of Oddi to about 30% of its normal pressure.[1] The ability of glyceryl trinitrate to relax smooth muscle has also been used to relieve biliary colic (p. 6.3) in 3 patients with gallstones;[2] in one of these patients standard managements for the pain such as oral opioids had been only moderately effective.

1. Staritz M, *et al.* Nitroglycerine dilatation of sphincter of Oddi for endoscopic removal of bileduct stones. *Lancet* 1984; **i:** 956.
2. Hassel B. Treatment of biliary colic with nitroglycerin. *Lancet* 1993; **342:** 1305.

Migraine. Although use of glyceryl trinitrate may precipitate or exacerbate migraine (p. 670.3) inhalation of glyceryl trinitrate at the onset of a migraine aura aborted attacks in a patient at risk of permanent neurological damage from migraine. Standard prophylactic therapy had previously been unsuccessful.[1]

1. Mitchell GK. Nitroglycerine by inhaler as treatment for migraine causing cerebral ischaemia. *Med J Aust* 1999; **171:** 336.

Myocardial infarction. Intravenous nitrates are widely used in acute myocardial infarction (p. 1257.1), although evidence to support their use in patients undergoing reperfusion is limited. An overview of studies carried out before reperfusion (thrombolysis or percutaneous coronary intervention) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality,[1] but whether they are of benefit in addition to reperfusion is less clear. However, empirical use of intravenous glyceryl trinitrate appears to be safe, and it should therefore be given where clinically indicated for ongoing ischaemic pain. In the GISSI-3 study,[2] glyceryl trinitrate was given by intravenous infusion during the first 24 hours, starting at 5 micrograms/minute and increasing by 5 to 20 micrograms/minute every 5 minutes for the first half hour until systolic blood pressure fell by at least 10% provided it remained above 90 mmHg; after 24 hours it was replaced by a transdermal patch providing 10 mg daily.

Long-term use of nitrates after myocardial infarction may be indicated in patients with myocardial ischaemia or poor left ventricular function, but there is no evidence to support their routine use. In the GISSI-3 study there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks[2] and 6 months[3] post-infarction and in the ISIS-4 study[4] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Yusuf S, *et al.* Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988; **i:** 1088–92.
2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
3. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks

after myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; **27:** 337–44.
4. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.

Obstetrics and gynaecology. The smooth muscle relaxant properties of glyceryl trinitrate have been used in various obstetric or gynaecological situations although most reports are anecdotal or include small numbers of patients. The intravenous injection of glyceryl trinitrate 50 to 100 micrograms repeated to a total dose of 200 micrograms if necessary has produced sufficient uterine relaxation in postpartum women for the manual extraction of retained placentas.[1,2] Use as a sublingual spray has also successfully aided breech extraction in a set of twins.[3]

Glyceryl trinitrate has been given as a sublingual spray to relax the cervix before IUD insertion. In a series of over 100 patients one or two doses of 400 micrograms sublingually were usually adequate.[4]

Beneficial results have been reported in women with possible premature labour (p. 2131.1) after application of glyceryl trinitrate patches to the abdomen.[5,6] In one study[7] this was as effective as ritodrine infusion, but another[8] found transdermal glyceryl trinitrate to be less effective than beta agonists. A study[9] comparing glyceryl trinitrate and magnesium sulfate, both given intravenously, found that glyceryl trinitrate was associated with a higher failure rate and a greater reduction in maternal blood pressure. A systematic review[10] concluded that there was insufficient evidence to support the routine use of glyceryl trinitrate.

Transdermal glyceryl trinitrate has been tried for controlling pain in severe and moderate-to-severe dysmenorrhoea[11,12] (p. 8.2).

Glyceryl trinitrate has been given in the management of pre-eclampsia (see under Hypertension, p. 1251.1). Intravenous use was reported to reduce blood pressure without compromising uterine blood flow,[13] but a systematic review of nitric oxide donors (given by any route) considered the evidence insufficient to draw conclusions about efficacy.[14]

Isosorbide mononitrate given vaginally has been found to produce cervical ripening[15] and although there is some evidence[16] that it is less effective, it may be an alternative to standard treatments such as prostaglandins (see Termination of Pregnancy p. 2131.3). Isosorbide dinitrate has been used similarly after missed abortion.[17]

1. DeSimone CA, *et al*. Intravenous nitro-glycerin aids manual extraction of a retained placenta. *Anesthesiology* 1990; **73:** 787.
2. Lowenwirt IP, *et al*. Safety of intravenous glyceryl trinitrate in management of retained placenta. *Aust N Z J Obstet Gynaecol* 1997; **37:** 20–4.
3. Greenspoon JS, Kovacic A. Breech extraction facilitated by glyceryl trinitrate sublingual spray. *Lancet* 1991; **338:** 124–5.
4. Yadava RP. Sublingual glyceryl trinitrate spray facilitates IUD insertion. *Br J Sex Med* 1990; **17:** 217.
5. Lees C, *et al*. Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994; **343:** 1325–6.
6. Smith GN, *et al*. Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. *Br J Obstet Gynaecol* 1999; **106:** 736–9.
7. Lees CC, *et al*. Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. *Obstet Gynecol* 1999; **94:** 403–8.
8. Bisits A, *et al*. The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004; **191:** 683–90.
9. El-Sayed YY, *et al*. Randomized comparison of intravenous nitroglycerin and magnesium sulfate for treatment of preterm labor. *Obstet Gynecol* 1999; **93:** 79–83.
10. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 28/11/07).
11. Pittrof R, *et al*. Crossover study of glyceryl trinitrate patches for controlling pain in women with severe dysmenorrhoea. *BMJ* 1996; **312:** 884.
12. The Transdermal Nitroglycerine/Dysmenorrhoea Study Group. Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhoea: a multinational pilot study. *J Int Med Res* 1997; **25:** 41–4.
13. Grunewald C, *et al*. Effects of nitroglycerin on the uterine and umbilical circulation in severe preeclampsia. *Obstet Gynecol* 1995; **86:** 600–4.
14. Meher S, Duley L. Nitric oxide for preventing pre-eclampsia and its complications. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 30/03/10).
15. Thomson AJ, *et al*. Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first-trimester termination of pregnancy. *Lancet* 1998; **352:** 1093–6.
16. Chen FC-K, *et al*. Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. *Eur J Obstet Gynecol Reprod Biol* 2008; **138:** 176–9.
17. Arteaga-Troncoso G, *et al*. Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. *BJOG* 2005; **112:** 1615–19.

Oesophageal motility disorders. Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. Nitrates such as isosorbide dinitrate have been reported to produce effective relaxation and to reduce symptoms when given sublingually. They have a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p. 1816.2).

Nitrates may also be employed in oesophageal disorders such as variceal haemorrhage (see below).

Pain. Nitrates have been tried topically in the management of pain. Beneficial results have been reported with glyceryl trinitrate, applied as patches[1] or as a spray,[2] and isosorbide dinitrate spray,[3] in patients with painful diabetic neuropathy. Glyceryl trinitrate has also been used topically in musculoskeletal disorders[4] (see also Soft-tissue Rheumatism, below), and in surgical pain,[5,6] and intravenously as an adjunct to regional anaesthesia.[7]

Glyceryl trinitrate is also used topically to relieve pain in patients with anal fissure (p. 1392.2). For reference to its use in biliary colic, see Gallstones, p. 1392.3.

1. Rayman G, *et al*. Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care* 2003; **26:** 2697–8.
2. Agrawal RP, *et al*. Glyceryl trinitrate spray in the management of painful diabetic neuropathy: a randomized double blind placebo controlled cross-over study. *Diabetes Res Clin Pract* 2007; **77:** 161–7.
3. Yuen KCJ, *et al*. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes Care* 2002; **25:** 1699–1703.
4. Paoloni JA, *et al*. Topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow: a randomized, double-blinded, placebo-controlled clinical trial. *Am J Sports Med* 2003; **31:** 915–20.
5. McCabe JE, *et al*. A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate. *BJU Int* 2007; **100:** 536–8.
6. Karanlik H, *et al*. The effect of glyceryl trinitrate ointment on posthemorrhoidectomy pain and wound healing: results of a randomized, double-blind, placebo-controlled study. *Dis Colon Rectum* 2009; **52:** 280–5.
7. Sen S, *et al*. The analgesic effect of nitroglycerin added to lidocaine on intravenous regional anesthesia. *Anesth Analg* 2006; **102:** 916–20.

Peripheral vascular disease. Nitrates have been used as vasodilators and smooth muscle relaxants to improve resting blood flow in vasospastic arterial disorders (p. 1275.3) and atherosclerotic peripheral vascular disorders (p. 1272.3). Some benefit has been reported with topical glyceryl trinitrate in atherosclerotic distal limb ischaemia,[1] and in Raynaud's syndrome,[2-4] but its use is not established.

1. Fletcher S, *et al*. Locally applied transdermal nitrate patches for the treatment of ischaemic rest pain. *Int J Clin Pract* 1997; **51:** 324–5.
2. Franks AG. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. *Lancet* 1982; **i:** 76–7.
3. Coppock JS, *et al*. Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. *Postgrad Med J* 1986; **62:** 15–18.
4. Teh LS, *et al*. Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; **34:** 636–41.

Pulmonary hypertension. Glyceryl trinitrate reduces total pulmonary resistance in most patients with pulmonary arterial hypertension (p. 1278.2),[1,2] including when given by inhalation.[3] However, other vasodilators such as calcium-channel blockers, epoprostenol, or bosentan are generally preferred for long-term treatment.

1. Pearl RG, *et al*. Acute hemodynamic effects of nitroglycerin in pulmonary hypertension. *Ann Intern Med* 1983; **99:** 9–13.
2. Weir EK, *et al*. The acute administration of vasodilators in primary pulmonary hypertension. *Am Rev Respir Dis* 1989; **140:** 1623–30.
3. Goyal P, *et al*. Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease. *Br J Anaesth* 2006; **97:** 208–14.

Quinine oculotoxicity. Intravenous nitrate has been suggested for the management of quinine oculotoxicity (p. 667.3) and its benefit may be due to an increase in retinal vascular bed flow.[1]

1. Moore D, *et al*. Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Soft-tissue rheumatism. There is evidence from *animal* studies that nitric oxide plays an important role in tendon healing, and randomised studies in patients with tennis elbow (epicondylitis), Achilles tendinosis (tendinitis), and supraspinatus tendinosis showed enhanced subjective and objective recovery when a glyceryl trinitrate patch (releasing 1.25 mg over 24 hours) was applied over the area of tenderness once daily.[1] The benefits of such treatment appeared to be sustained on 3-year follow-up,[2] suggesting that it was not just an analgesic effect; however, the same group found that a different glyceryl trinitrate patch was ineffective in another group of patients.[3] Glyceryl trinitrate patches have also been tried in rotator cuff disease, and a systematic review[4] considered that there may be some evidence for a reduction in acute symptoms, although insufficient evidence of a longer-term efficacy. Glyceryl trinitrate has also been tried in musculoskeletal pain (see Pain, above). For the general management of soft-tissue rheumatism see p. 14.2.

1. Murrell GAC. Using nitric oxide to treat tendinopathy. *Br J Sports Med* 2007; **41:** 227–31.
2. Paoloni JA, Murrell GAC. Three-year followup study of topical glyceryl trinitrate treatment of chronic noninsertional Achilles tendinopathy. *Foot Ankle Int* 2007; **28:** 1064–8.
3. Paoloni JA, *et al*. Randomised, double-blind, placebo-controlled clinical trial of a new topical glyceryl trinitrate patch for chronic lateral epicondylosis. *Br J Sports Med* 2009; **43:** 299–302.
4. Cumpston M, *et al*. Topical glyceryl trinitrate for rotator cuff disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 30/03/10).

Variceal haemorrhage. The usual treatment in variceal haemorrhage (p. 2563.1) is injection sclerotherapy or banding ligation which may be performed during the emergency endoscopy procedure. Where endoscopy is unavailable drug therapy may be used; it may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy. Vasoconstrictors that are used include vasopressin and its analogue terlipressin, given with glyceryl trinitrate which counteracts the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure; somatostatin is also used.

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed. It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought and isosorbide mononitrate (as adjunctive therapy with a beta blocker) has been investigated, both for prophylaxis of a first bleed[1,2] and in the prevention of rebleeding.[3] Early emergency treatment (before endoscopy) with terlipressin given intravenously and glyceryl trinitrate transdermally controlled bleeding and lowered mortality rates in patients with gastrointestinal bleeding and a history or clinical signs of cirrhosis.[4] However, use of oral isosorbide mononitrate with somatostatin infusion for acute variceal bleeding was less effective than somatostatin alone and induced more adverse effects.[5]

1. Angelico M, *et al*. Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993; **104:** 1460–5.
2. Merkel C, *et al*. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Lancet* 1996; **348:** 1677–81.
3. Villanueva C, *et al*. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996; **334:** 1624–9.
4. Levacher S, *et al*. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; **346:** 865–8.
5. Junquera F, *et al*. Somatostatin plus isosorbide 5-mononitrate versus somatostatin in the control of acute gastro-oesophageal variceal bleeding: a double blind, randomised, placebo controlled clinical trial. *Gut* 2000; **46:** 127–32.

Venepuncture. Glyceryl trinitrate patches applied to skin adjacent to intravenous infusion sites are used in the prophylactic treatment of phlebitis and extravasation.[1]

Local application of glyceryl trinitrate 1 to 2 mg as ointment was found to be a useful aid to venepuncture in a study of 50 patients undergoing surgery,[2] but conflicting results have been reported in children and neonates.[3,4]

1. Tjon JA, Ansani NT. Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. *Ann Pharmacother* 2000; **34:** 1189–92.
2. Hecker JF, *et al*. Nitroglycerine ointment as an aid to venepuncture. *Lancet* 1983; **i:** 332–3.
3. Vaksmann G, *et al*. Nitroglycerine ointment as aid to venous cannulation in children. *J Pediatr* 1987; **111:** 89–91.
4. Maynard EC, Oh W. Topical nitroglycerin ointment as an aid to insertion of peripheral venous catheters in neonates. *J Pediatr* 1989; **114:** 474–6.

Adverse Effects

Glyceryl trinitrate may cause flushing of the face, dizziness, tachycardia, and throbbing headache. Large doses cause vomiting, restlessness, blurred vision, hypotension (which can be severe), syncope, and rarely cyanosis, and methaemoglobinaemia; impairment of respiration and bradycardia may ensue. Contact dermatitis has been reported in patients using topical glyceryl trinitrate preparations; local irritation and erythema may also occur. Preparations applied to the oral mucosa frequently produce a localised burning sensation.

Chronic poisoning may occur in industry but tolerance develops when glyceryl trinitrate is regularly handled and nitrate dependence can lead to severe withdrawal symptoms in subjects abruptly removed from chronic exposure. Loss of such tolerance is rapid and may cause poisoning on re-exposure. Tolerance may occur during clinical use and is usually associated with preparations that produce sustained plasma concentrations.

Effects on the heart. Tachycardia, hypotension, and bradycardia are recognised adverse cardiac effects of glyceryl trinitrate. Rarely reported adverse effects include asystole[1] and complete heart block.[2]

1. Ong EA, *et al*. Nitroglycerin-induced asystole. *Arch Intern Med* 1985; **145:** 954.
2. Lancaster L, Fenster PE. Complete heart block after sublingual nitroglycerin. *Chest* 1983; **84:** 111–12.

Effects on taste. A 61-year-old man experienced loss of bitter and salty taste sensations 2 weeks after addition of glyceryl trinitrate patches to his post-myocardial infarction

drug regimen.[1] The patient had complete loss of taste after 6 weeks; his taste sensation returned to normal within 1 week of stopping glyceryl trinitrate patches. Taste sensation was again altered on rechallenge.

1. Ewing RC, *et al*. Agesusia associated with transdermal nitroglycerin. *Clin Pharm* 1989; **8:** 146–7.

Hypersensitivity. Contact dermatitis has been reported in patients using glyceryl trinitrate ointment and patches.[1] Both glyceryl trinitrate and formulation components may be involved in these reactions.

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10:** 151–9.

Intravenous administration. Some formulations of glyceryl trinitrate for intravenous use may contain substantial quantities of alcohol in the solvent. There have been several reports of alcohol intoxication occurring in patients during high-dose intravenous glyceryl trinitrate infusion.[1-3] In a patient[3] who required glyceryl trinitrate 2 mg/minute, a blood-alcohol concentration of 2.67 mg/mL was reported. PVC tubing had been used for the infusion and it was suggested that adsorption of glyceryl trinitrate onto the tubing may have increased the dose requirement and thus the amount of alcohol given.

Propylene glycol is also used as a solvent in some formulations of glyceryl trinitrate. Infusion of solutions with propylene glycol can lead to hyperosmolarity: see under Propylene Glycol, p. 2205.3, for details.

1. Shook TL, *et al*. Ethanol intoxication complicating intravenous nitroglycerin therapy. *Ann Intern Med* 1984; **101:** 498–9.
2. Daly TJ, *et al*. "Cocktail"-coronary care. *N Engl J Med* 1984; **310:** 1123.
3. Korn SH, Comer JB. Intravenous nitroglycerin and ethanol intoxication. *Ann Intern Med* 1985; **102:** 274.

Treatment of Adverse Effects

Syncope and hypotension should be treated by keeping the patient in a recumbent position with the head lowered; pressor agents may be necessary in extreme hypotension. Oxygen, with assisted respiration, may be needed in severe poisoning and infusion of plasma expanders or suitable electrolyte solutions may be required to maintain the circulation. If methaemoglobinaemia occurs methylthioninium chloride may be given intravenously. In the case of severe poisoning with tablets the stomach may be emptied by lavage. If large amounts have been ingested within 1 hour, activated charcoal may be considered.

Precautions

Glyceryl trinitrate should not be used in patients with severe hypotension, hypovolaemia, marked anaemia, heart failure due to obstruction (including constrictive pericarditis), or raised intracranial pressure due to head trauma or cerebral haemorrhage. Although it has been suggested that glyceryl trinitrate may increase intra-ocular pressure in patients with angle-closure glaucoma and should be avoided in such patients there appears to be no evidence for such a contra-indication.

Glyceryl trinitrate should be used with caution in patients with severe renal or severe hepatic impairment, hypothyroidism, malnutrition, or hypothermia. Metal-containing transdermal patches should be removed before cardioversion or diathermy. Buccal administration has rarely been associated with dental caries; patients should be advised to alternate the site of application and maintain good dental hygiene. Those with xerostomia should moisten the mouth before using buccal tablets; however, the sublingual spray may be a more suitable formulation in such patients.

Nitrate tolerance. Although organic nitrates are effective anti-anginal drugs, their use is limited by the development of tolerance and the loss or attenuation of their anti-anginal and anti-ischaemic effects.[1,2] This can occur with all of the organic nitrates, particularly if frequent or continuous dosing is used.[1-3]

The mechanisms of nitrate tolerance are incompletely understood. The vasodilator effect of organic nitrates may depend on their conversion to nitric oxide, a process which requires the presence of a sulfhydryl donor such as cysteine or another thiol. Repeated doses of a nitrate exhaust tissue stores of sulfhydryl groups and this is one mechanism that may account for the development of tolerance.[1,2] The activation of neurohormonal systems, which releases vasoconstrictor hormones that counteract the effects of organic nitrates, has also been proposed as a mechanism.[1,2] An increase in free-radical production during nitrate therapy has also been suggested,[1] and may inhibit bioactivation of the nitrate.[3] Nitrate-induced expansion of plasma volume may also contribute, leading to reversal of the effects of nitrates on ventricular preload.[1,2]

The method most commonly used to avoid the development of tolerance is to provide a nitrate-free interval.[1,2] The optimum duration is not clear, but a nitrate-free period of 10 to 12 hours has been suggested.[1,2] With transdermal glyceryl trinitrate systems, the patch can be removed at night. For oral, buccal, and ointment preparations, the dose given at the end of the day can be omitted. However, rebound myocardial ischaemia may occur during this time,[1] and may require the use of short-acting nitrate preparations.[2] Whether a nitrate-free interval is necessary for all patients is unknown as many patients using continuous nitrates do not show clinical tolerance. A transdermal patch with a higher release rate during the first part of a 24-hour period has been found not to prevent the development of tolerance.[4]

Various drugs have been reported to reduce the development of nitrate tolerance, including sulfhydryl donors and drugs with antioxidant properties, but none has an established role.[1,3]

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med* 1998; **338:** 520–31.
2. Rutherford JD. Nitrate tolerance in angina therapy: how to avoid it. *Drugs* 1995; **49:** 196–9.
3. Münzel T, *et al*. Explaining the phenomenon of nitrate tolerance. *Circ Res* 2005; **97:** 618–28.
4. Wiegand A, *et al*. Pharmacodynamic and pharmacokinetic evaluation of a new transdermal delivery system with a time-dependent release of glyceryl trinitrate. *J Clin Pharmacol* 1992; **32:** 77–84.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glyceryl trinitrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Transdermal patches. An explosion occurred during defibrillation in a patient with a glyceryl trinitrate transdermal patch on the left side of the chest.[1] There was no visible injury to the patient. Subsequent studies suggested that this was caused by an electrical arc between the defibrillator paddle and the aluminium backing of the patch rather than explosion of the glyceryl trinitrate.

Although removal of transdermal patches before diathermy is usually recommended, a maximum rise in patch temperature of only 2.2 degrees was reported when patches were exposed to power densities up to 800 watts/m^2. It was considered that exposure of transdermal patches to microwave diathermy, for example as part of physiotherapy treatment, was unlikely to cause direct thermal injury to the wearer.[2]

1. Babka JC. Does nitroglycerin explode? *N Engl J Med* 1983; **309:** 379.
2. Moseley H, *et al*. The influence of microwave radiation on transdermal delivery systems. *Br J Dermatol* 1990; **122:** 361–3.

Interactions

The hypotensive effects of glyceryl trinitrate may be enhanced by alcohol, and by vasodilators and other drugs with hypotensive actions. The efficacy of sublingual and buccal tablet preparations may be reduced by drugs that cause dry mouth (such as tricyclic antidepressants and other antimuscarinics) since dissolution may be delayed (see also Precautions, above).

Anticoagulants. For the effects of glyceryl trinitrate on the activity of *heparin*, see p. 1400.2.

Ergot alkaloids. For the effects of glyceryl trinitrate on *dihydroergotamine*, see under Interactions of Ergotamine, p. 675.3.

Phosphodiesterase type-5 inhibitors. The concurrent use of nitrates and phosphodiesterase type-5 inhibitors such as sildenafil is contra-indicated. Significant hypotension may occur due to potentiation of the vasodilator actions of nitrates.[1] Deaths due to a possible interaction have been reported.[2]

1. Webb DJ, *et al*. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; **36:** 25–31.
2. Cheitlin MD, *et al*. Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* 1999; **33:** 273–82. Correction. *ibid.*; **34:** 1850.

Thrombolytics. For the effects of glyceryl trinitrate and *alteplase* when given together, see p. 1298.2.

Pharmacokinetics

Glyceryl trinitrate is rapidly absorbed from the oral mucosa. It is also well absorbed from the gastrointestinal tract and through the skin. Bioavailability is less than 100% when given by any of these routes due to pre-systemic clearance; bioavailability is further reduced after oral use owing to extensive first-pass metabolism in the liver.

Therapeutic effect is apparent within 1 to 3 minutes of use of sublingual tablets, sublingual spray, or buccal tablets; within 30 to 60 minutes of applying an ointment or transdermal patch; and within 1 to 2 minutes after intravenous doses.

Duration of action is about 30 to 60 minutes with sublingual tablets or spray and 3 to 5 hours with modified-release buccal tablets. Transdermal patches are designed to release a stated amount of drug over 24 hours, while therapeutic effects after application of glyceryl trinitrate ointment 2% persist for up to 8 hours. Duration of action after intravenous dosage is about 3 to 5 minutes.

Glyceryl trinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. This reaction requires the presence of cysteine or another thiol. Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly metabolised in the liver by glutathione-organic nitrate reductase to dinitrates and mononitrates. The dinitrates are less potent vasodilators than glyceryl trinitrate; the mononitrates may have some vasodilator activity.

References.
1. Bogaert MG. Clinical pharmacokinetics of glyceryl trinitrate following the use of systemic and topical preparations. *Clin Pharmacokinet* 1987; **12:** 1–11.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
3. Ridout G, *et al*. Pharmacokinetic considerations in the use of newer transdermal formulations. *Clin Pharmacokinet* 1988; **15:** 114–31.
4. Hashimoto S, Kobayashi A. Clinical pharmacokinetics and pharmacodynamics of glyceryl trinitrate and its metabolites. *Clin Pharmacokinet* 2003; **42:** 205–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dauxona; Enetege; Minitran; Niglinar; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitrodom; Nitrogray; ***Austral.***: Anginine; Lycinate; Minitran; Nitro-Dur; Nitrolingual; Rectogesic; Transiderm-Nitro; ***Austria***: Deponit; Nitro Mack†; Nitro Pohl; Nitro-Dur†; Nitroderm; Nitrolingual; Perlinganit; ***Belg.***: Deponit; Diafusor; Minitran; Nitroderm; Nitrolingual; Nitropohl†; Nysconitrine†; Rectogesic; Trinipatch; Willlong†; ***Braz.***: Nitradisc; Nitroderm TTS; Tridil; ***Canad.***: Gen-Nitro†; Minitran; Mylan-Nitro; Nitro-Dur; Nitroject; Nitrol; Nitrolingual; Nitrostat; Rho-Nitro; Transderm-Nitro; Trinipatch; ***Chile***: Angiolingual; Nitrocor†; Nitroderm; ***China***: Deponit (帖保哼); Nitrocine (异述欣); Nitrolingual; Nitrostat (耐较哼); Pailuo (派洛); Ruo Bi Xun (若必循); Ruo Xin Lai (若欣莱); XinShu (信舒); ***Cz.***: Nit-Ret†; Nitro Pohl; Nitromint; Perlinganit; Rectogesic; ***Denm.***: Discotrine; Glytrin; Nitrolingual; Nitromex†; Rectogesic; ***Fin.***: Deponit; Minitran; Nitro; Nitromex†; Perlinganit; Rectogesic; Transiderm-Nitro; ***Fr.***: Cordipatch; Diafusor; Discotrine; Epinitril; Natispray; Nitriderm TTS; Nitronal; Rectogesic; Trinipatch; ***Ger.***: Aquo-Trinitrosan†; Corangin Nitrospray†; Deponit†; MinitranS; Nitrangin†; Nitro Carino; Nitroderm TTS; Nitrolingual; Perlinganit†; Rectogesic; Trinitrosan†; ***Gr.***: Apirol; Cardiplast; Carina; Epinitril; Glyconitron; Nilmadin; Nitro Mack; Nitrocerin; Nitrodyl; Nitrolingual; Nitronal; Nitrong; Nitroretard; Nitrosylon; Pancoran; Rectogesic; Sodemethin; Solinitrina; Supranitrin; Trinipatch; Trinitrine Simple Laleuf; ***Hong Kong***: Angised; Deponit; Nitro Mack†; Nitro-Dur†; Nitrocine; Nitroderm TTS; Nitrolingual; ***Hung.***: Nitro Pohl; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitromint; Rectogesic; Sustac; ***India***: Angised; Angispan-TR; Glynit; GTN Sorbitrate; Leonite; Millisrol†; Myonit; Myovin; NG-Care; NGLong; NGTel; Nig; Nitrocerin; Nitrocin; Nitrocontin; Nitrocure; Nitroday; Nitroderm TTS; Nitrofast; Nitrogesic; Nitroglyn; Nitroject; Nitrolife; Nitrolingual†; Nitroplus; Nitrosol; Nitrovir; Nizo; ***Indon.***: Nitrocine†; Nitrokaf; ***Irl.***: Deponit†; Dermatrans; Epinitril; Glytrin; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin†; Nitronal†; Rectogesic; Suscard; Sustac†; Transiderm-Nitro; ***Israel***: Deponit; Nitrocine; Nitroderm TTS; Nitrolingual; Rectogesic; ***Ital.***: Adesitrin; Deponit; Dermatrans; Epinitril; Keritrina; Minitran; Natispray; Nitraket; Nitro-Dur; Nitrocor; Nitroderm TTS; Nitrosylon; Perganit; Rectogesic; Top-Nitro; Triniplas; Trinitrina; Venitrin; ***Jpn***: Meditrans; Millisrol; Vasolator; ***Malaysia***: Deponit; Nitrocine; Nitroderm; ***Mex.***: Angiopohl; Anglix; Cardinit; Minitran; Nitradisc; Nitro-Dur; Nitroder; Nitroderm TTS; ***Neth.***: Deponit; Glytrin; Minitran; Nitro Pohl; Nitro-Dur; Nitrolingual; Rectogesic†; Transiderm TTS; Transiderm-Nitro; Trinipatch; ***Norw.***: Minitran; Nitro-Dur; Nitrolingual; Nitromex†; Nitroven; Rectogesic; Transiderm-Nitro; ***NZ***: Glytrin; Lycinate; Minitran; Nitroderm; Nitrolingual; Nitronal; Rectogesic; ***Philipp.***: Deponit; Minitran; Nitrolingual; Nitronal; Nitrostat; Nyserin; Perlinganit; Transderm-Nitro; ***Pol.***: Nitracor; Nitrocard; Nitroderm; Nitromint; Perlinganit; Rectogesic†; Sustonit; Trimonit; ***Port.***: Dermatrans; Difusor†; Discotrine†; Epinitril; Glytrin; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitromint; Plastranit; Rectogesic; ***Rus.***: Deponit (Депонит); Nirmin (Нирмин)†; Nitro (Нитро); Nitrocor (Нитрокор); Nitrogranulong (Нитрогранулонг); Nitroject (Нитроджект); Nitromint (Нитроминт); Nitrong (Нитронг); Nitrospray (Нитроспрей); Perlinganit (Перлинганит); Sustac (Сустак); Sustonit (Сустонит); Trinitrolong (Тринитролонг); ***S.Afr.***: Angised; Nitrocine; Nitrolingual; Tridil†; ***Singapore***: Angised; Deponit†; Glytrin; Nitrocine; Nitrolingual; Rectogesic; ***Spain***: Cordiplast; Dermatrans; Diafusor; Epinitril; Minitran; Nitradisc; Nitro-Dur; Nitroderm; Nitrofix; Nitroplast; Rectogesic; Solinitrina; Trinipatch; Trinispray; Vernies; ***Swed.***: Glytrin; Minitran; Nitrolingual; Nitromex†; Rectogesic; Suscard†; Transiderm-Nitro; ***Switz.***: Deponit; Minitran; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitronal†; Perlinganit; Trinitrine; ***Thai.***: Glytrin†; Nitrocine†; Nitroderm; Nitroject; Nitromint; ***Turk.***: Deponit; Nitroderm

TTS; Nitrolingual†; Nitronal; Perlinganit; ***UK***: Coro-Nitro; Deponit; Glytrin; Minitran; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Percutol; Rectogesic; Suscard†; Transiderm-Nitro; Trintek†; ***Ukr.***: Nitro (Нитро); Nitromint (Нитромint)†; Nitrong (Нитронг); Sustac (Сустак)†; ***USA***: Minitran; Nitrek; Nitro-Bid; Nitro-Derm†; Nitro-Dur; Nitro-Time; Nitrodisc†; Nitrogard†; Nitrolingual; NitroMist; NitroQuick†; Nitrostat; Rectiv; Transderm-Nitro†; Transdermal-NTG†; ***Venez.***: Nitro Mack; Nitrocor; Nitroderm.

Multi-ingredient Preparations. ***Arg.***: Trinitron; ***Gr.***: Trinitrine Cafein Dubois; ***Pol.***: Pentaerythritol Compositum; ***Rus.***: Carniland (Карниланд); ***Spain***: Cafinitrina; ***USA***: Emergent-Ez.

Homoeopathic Preparations. ***Austria***: Cactus compositum; Rytmopasc; ***Canad.***: Headache & Migraine; Homeo-Form MI†; HPB Complex†; Menopause L122; Travel Sickness; ***Cz.***: Glonoinum; Ypsiloheel; ***Fr.***: Actheane; Agnus Castus Complexe No 2†; Cocculus Complexe No 73; Crataegus Complexe No 15; Lachesis Complexe No 122; Sclero-Drainol†; ***Ger.***: Arte-cyl Ho-Len-Complex; Cefangipect†; Cefavora Cor; Homviocorin spezial; Lowe-Komplex Nr 3; Migrane Hevert†; Migrane Hevert; Naranocor HM; Neuro-Do; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pectapas SL; Rytmopasc; Schworocard; Strophanthus comp; Vertigo-Hevert; Viscum-Entoxin N; Ypsiloheel N; ***Neth.***: Gletar; ***Rus.***: Tonginal (Тонгинал); ***Ukr.***: Tonginal (Тонгинал).

Pharmacopoeial Preparations
BP 2014: Glyceryl Trinitrate Ointment; Glyceryl Trinitrate Sublingual Spray; Glyceryl Trinitrate Tablets; Glyceryl Trinitrate Transdermal Patches;
USP 36: Nitroglycerin Injection; Nitroglycerin Ointment; Nitroglycerin Tablets.

Guanabenz Acetate *(USAN, rINNM)*

Acetato de guanabenzo; Guanabenz, Acétate de; Guanabenzi Acetas; Guanabenzo, acetato de; NSC-68982 (guanabenz); Wy-8678 (guanabenz); Гуанабенза Ацетат.
(2,6-Dichlorobenzylideneamino)guanidine acetate.
$C_8H_8Cl_2N_4,C_2H_4O_2$=291.1
CAS — 5051-62-7 (guanabenz); 23256-50-0 (guanabenz acetate).
UNII — 443O19GK1A.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Guanabenz Acetate). A white or almost white powder with not more than a slight odour. Sparingly soluble in water and in 0.1N hydrochloric acid; soluble in alcohol and in propylene glycol. A 0.7% solution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Uses and Administration

Guanabenz is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p. 1339.2). It is used in the management of hypertension (p. 1251.1), either alone or with other antihypertensives, particularly thiazide diuretics.

Guanabenz is given orally as the acetate, but doses are usually expressed in terms of the base. Guanabenz acetate 5 mg is equivalent to about 4 mg of guanabenz.

In hypertension, the usual dose is 4 mg twice daily initially; the daily dose may be increased by amounts of 4 to 8 mg every 1 to 2 weeks according to response. Doses of up to 32 mg twice daily have been used.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p. 1341.2.

Overdosage. Overdosage with guanabenz has been reported.[1] The main symptoms were lethargy, drowsiness, bradycardia, and hypotension. A 45-year-old woman who had taken 200 to 240 mg of guanabenz with alcohol recovered after gastric lavage and intravenous fluids; a 3-year-old child who had taken 12 mg of guanabenz responded to atropine and dopamine. Naloxone had little effect in either patient.

1. Hall AH, *et al*. Guanabenz overdose. *Ann Intern Med* 1985; **102:** 787–8.

Interactions

As for Clonidine Hydrochloride, p. 1342.1.

Pharmacokinetics

About 75% of an oral dose of guanabenz is absorbed and undergoes extensive first-pass metabolism. Peak plasma concentrations occur about 2 to 5 hours after a dose. It is about 90% bound to plasma proteins. Guanabenz is mainly excreted in urine, almost entirely as metabolites, with less than 1% as unchanged drug; about 10 to 30% is excreted in faeces. The average elimination half-life is reported to range from 4 to 14 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Lisapres; ***USA***: Wytensin†.

Pharmacopoeial Preparations
USP 36: Guanabenz Acetate Tablets.

Guanadrel Sulfate *(USAN, rINNM)*

CL-1388R; Guanadrel, Sulfate de; Guanadrel, sulfato de; Guanadrel Sulphate; Guanadreli Sulfas; Sulfato de guanadrel; U-28288D; Гуанадрела Сульфат.
1-(Cyclohexanespiro-2′-[1′,3′]dioxolan-4′-ylmethyl)guanidine sulfate; 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine sulfate.
$(C_{10}H_{19}N_3O_2)_2,H_2SO_4$=524.6
CAS — 40580-59-4 (guanadrel); 22195-34-2 (guanadrel sulfate).
UNII — MT147RMO91.

Pharmacopoeias. In *US*.

USP 36: (Guanadrel Sulfate). A white to off-white crystalline powder. Soluble in water; slightly soluble in alcohol and in acetone; sparingly soluble in methyl alcohol.

Profile

Guanadrel is an antihypertensive with properties similar to those of guanethidine (below). After oral administration, guanadrel acts within 2 hours with the maximum effect after 4 to 6 hours. The hypotensive effect is reported to last for 4 to 14 hours after a single dose. It has been given orally as the sulfate in the management of hypertension, although it has largely been superseded by other drugs less likely to cause orthostatic hypotension.

Preparations

Pharmacopoeial Preparations
USP 36: Guanadrel Sulfate Tablets.

Guanethidine Monosulfate

(BANM, USAN, rINNM)

Guanéthidine, Monosulfate de; Guanethidine Monosulphate; Guanethidini Monosufas; Guanethidini Monosulfas; Guanethidin-monosulfát; Guanetidiinimonosulfaatti; Guanetidina, monosulfato de; Guanetidinmonosulfat; Guanetidinmonoszulfát; Guanetidino monosulfatas; Monosulfato de guanetidina; NSC-29863 (guanethidine hemisulfate); Su-5864 (guanethidine hemisulfate); Гуанетидина Моносульфат.
1-[2-(Perhydroazocin-1-yl)ethyl]guanidine monosulfate.
$C_{10}H_{21}N_4,H_2SO_4$=296.4
CAS — 55-65-2 (guanethidine); 60-02-6 (guanethidine hemisulfate); 645-43-2 (guanethidine monosulfate).
ATC — C02CC02; S01EX01.
ATC Vet — QC02CC02; QS01EX01.
UNII — 5UBY8Y002G.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Chin. includes the hemisulfate.

Ph. Eur. 8: (Guanethidine Monosulfate). A colourless crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 4.7 to 5.5. Protect from light.

USP 36: (Guanethidine Monosulfate). A white to off-white crystalline powder. Very soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform. A 2% solution in water has a pH of 4.7 to 5.7.

Uses and Administration

Guanethidine is an antihypertensive that acts by selectively inhibiting transmission in postganglionic adrenergic nerves. It is believed to act mainly by preventing the release of noradrenaline at nerve endings. Guanethidine causes the depletion of noradrenaline stores in peripheral sympathetic nerve terminals but does not prevent the secretion of catecholamines by the adrenal medulla.

When given orally its maximal effects may take 1 to 3 weeks to appear on continued dosing and persist for 1 to 3 weeks after treatment has been stopped. It causes an initial reduction in cardiac output but its main hypotensive effect is to cause peripheral vasodilatation; it reduces the vasoconstriction which normally results from standing up and which is the result of reflex sympathetic nervous activity. In the majority of patients it reduces standing blood pressure but has a lesser effect on supine blood pressure. When applied topically to the eye guanethidine reduces the production of aqueous humour.

Guanethidine is used in the management of hypertension (p. 1251.1). Eye drops of guanethidine have been used for open-angle glaucoma (p. 1999.1) and for lid retraction associated with hyperthyroidism. Guanethidine has also been used in the management of neuropathic pain syndromes (see below).

Guanethidine is used in the treatment of hypertension when other drugs have proved inadequate, but it has largely been superseded by other drugs less likely to cause orthostatic hypotension. Tolerance to guanethidine has occurred in some patients; this may be countered by concomitant diuretic therapy.

In **hypertension**, the usual initial oral dose of guanethidine monosulfate has been 10 mg daily. This is increased by increments of 10 to 12.5 mg, not more often than every 5 to 7 days, according to response. The usual maintenance dose has been 25 to 50 mg once daily.

Guanethidine monosulfate has been given intramuscularly in the treatment of hypertensive crises, including severe pre-eclampsia, but more suitable drugs are available. An intramuscular dose of 10 to 20 mg is reported to produce a fall in blood pressure within 30 minutes.

Eye drops containing guanethidine monosulfate have been used in the treatment of open-angle **glaucoma** (usually combined with adrenaline), and for the lid retraction that may accompany hyperthyroidism.

Pain syndromes. Sympathetic nerve blocks may be used in the management of acute or chronic pain associated with a well-defined anatomical site. Guanethidine is one of several drugs that have been used for intravenous regional sympathetic block in the management of neuropathic pain (see Complex Regional Pain Syndrome, p. 8.1), to reduce pain and to maintain blood flow. However, reviews and some studies[1,2] in patients with reflex sympathetic dystrophy failed to find any benefit from guanethidine.

1. Jadad AR, *et al*. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; **10:** 13–20.
2. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. *J Bone Joint Surg Br* 2002; **84:** 380–6.

Adverse Effects

The commonest adverse effects of guanethidine are severe postural and exertional hypotension and diarrhoea which may be particularly troublesome during the initial stages of therapy and during dose adjustment. Dizziness, syncope, muscle weakness, and lassitude are liable to occur, especially on rising from sitting or lying. Orthostatic hypotension may be severe enough to provoke angina, renal impairment, and transient cerebral ischaemia. Other frequent adverse effects are bradycardia, failure of ejaculation, fatigue, headache, and salt and water retention and oedema, which may be accompanied by breathlessness and may occasionally precipitate overt heart failure.

Nausea, vomiting, dry mouth, nasal congestion, parotid tenderness, blurring of vision, depression, myalgia, muscle tremor, paraesthesias, hair loss, dermatitis, disturbed micturition, priapism, aggravation or precipitation of asthma, and exacerbation of peptic ulcer disease have also been reported. Guanethidine may possibly cause anaemia, leucopenia, and thrombocytopenia.

When guanethidine is used as eye drops, common adverse effects are conjunctival hyperaemia and miosis. Burning sensations and ptosis have also occurred. Superficial punctate keratitis has been reported particularly after prolonged use of high doses.

Treatment of Adverse Effects

Withdrawal of guanethidine or dose reduction reverses many adverse effects. Diarrhoea may also be controlled by giving codeine phosphate or antimuscarinics. If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour. Hypotension may respond to placing the patient in the supine position with the feet raised. If hypotension is severe it may be necessary to give intravenous fluid replacement and small doses of vasopressors may be given cautiously. The patient must be monitored for several days.

Precautions

Guanethidine should not be given to patients with phaeochromocytoma, as it may cause a hypertensive crisis, or to patients with heart failure not caused by hypertension.

It should be used with caution in patients with renal impairment, cerebrovascular disorders, or ischaemic heart disease, or with a history of peptic ulcer disease or asthma. Exercise and heat may increase the hypotensive effect of guanethidine, and dosage requirements may be reduced in patients who develop fever.

There may be an increased risk of cardiovascular collapse or cardiac arrest in patients undergoing surgery while taking guanethidine, but authorities have differed as to whether the drug should be stopped before elective surgery. Former US licensed product information recommended stopping up to 2 or 3 weeks beforehand. In patients undergoing emergency procedures or where treatment has not been interrupted large doses of atropine should be given before induction of anaesthesia.

Patients undergoing treatment with eye drops containing guanethidine should be examined regularly for signs of conjunctival damage.

Interactions

Patients taking guanethidine may show increased sensitivity to the action of adrenaline, amfetamine, and other sympathomimetics, resulting in exaggerated pressor effects. The hypotensive effects may also be antagonised by tricyclic antidepressants, MAOIs, and phenothiazine derivatives and related antipsychotics (although phenothiazines may also exacerbate orthostatic hypotension, which may be more relevant clinically). In the UK licensed product information suggests that MAOIs should be stopped at least 14 days before beginning guanethidine, although in the USA a minimum of a week has been recommended as adequate. It has been reported that oral contraceptives may reduce the hypotensive action of guanethidine. Use of digoxin or other digitalis derivatives with guanethidine may cause excessive bradycardia.

The hypotensive effects of guanethidine may be enhanced by thiazide diuretics, other antihypertensives, and levodopa. Alcohol may cause orthostatic hypotension in patients taking guanethidine.

Pharmacokinetics

Guanethidine is variably and incompletely absorbed from the gastrointestinal tract with less than 50% of the dose reaching the systemic circulation. It is actively taken up into adrenergic neurones by the mechanism responsible for noradrenaline reuptake. A plasma concentration of 8 nanograms/mL is reported to be necessary for adrenergic blockade, but the dose required to achieve this varies between individuals due to differences in absorption and metabolism. Guanethidine is partially metabolised in the liver, and is excreted in the urine as metabolites and unchanged guanethidine. It has a terminal half-life of about 5 days. Guanethidine does not penetrate the blood-brain barrier significantly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ismelin†; ***Gr.***: Ismelin; ***UK***: Ismelin†.

Multi-ingredient Preparations. ***Ger.***: Thilodigon†; ***Gr.***: Thilodigon; ***India***: Optex; ***Irl.***: Ganda†; ***USA***: Esimil.

Pharmacopoeial Preparations
BP 2014: Guanethidine Tablets;
USP 36: Guanethidine Monosulfate Tablets.

Guanfacine Hydrochloride

(BANM, USAN, rINNM)

BS-100-141; Guanfacina, hidrocloruro de; Guanfacine, Chlorhydrate de; Guanfacini Hydrochloridum; Hidrocloruro de guanfacina; LON-798; Гуанфацина Гидрохлорид.

N-Amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride.

$C_9H_9Cl_2N_3O,HCl$=282.5

CAS — 29110-47-2 (guanfacine); 29110-48-3 (guanfacine hydrochloride).
ATC — C02AC02.
ATC Vet — QC02AC02.
UNII — PML56A160O.

Pharmacopoeias. In *US*.

USP 36: (Guanfacine Hydrochloride). Store in airtight containers. Protect from light.

Uses and Administration

Guanfacine is a centrally acting alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p. 1339.2). It is used in the management of hypertension (p. 1251.1), although other drugs are usually preferred. It may be used alone or with other antihypertensives, particularly thiazide diuretics. It is also used in the management of attention deficit hyperactivity disorder in children and adolescents (see Administration in Children, below) and has been tried in the management of opioid withdrawal.

Guanfacine is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Guanfacine hydrochloride 1.15 mg is equivalent to about 1 mg of guanfacine. In hypertension the usual initial dose is 1 mg daily increasing after 3 to 4 weeks to 2 mg daily if necessary.

Reviews.
1. Cornish LA. Guanfacine hydrochloride: a centrally acting antihypertensive agent. *Clin Pharm* 1988; **7:** 187–97.

Administration in children. For the treatment of attention deficit hyperactivity disorder (below) guanfacine may be given to children aged 6 years and above. It is given orally as a modified-release tablet in an initial dose of 1 mg once daily, increased if necessary by increments of 1 mg at intervals of no less than 1 week to a maximum of 4 mg once daily.

Hyperactivity. Drug treatment of attention deficit hyperactivity disorder (ADHD, p. 2314.1) is usually begun with a central stimulant. Alpha$_{2A}$-agonists such as clonidine and guanfacine have also been used, and guanfacine has been shown to be a safe and effective treatment in children (for recommended doses see above).

References.
1. Posey DJ, McDougle CJ. Guanfacine and guanfacine extended release: treatment for ADHD and related disorders. *CNS Drug Rev* 2007; **13:** 465–74.
2. Biederman J, *et al*. SPD503 Study Group. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics* 2008; **121:** e73–e84.
3. Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. *Neuropsychiatr Dis Treat* 2008; **4:** 499–506.
4. Biederman J, *et al*. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. *CNS Spectr* 2008; **13:** 1047–55.
5. Sallee FR, *et al*. Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2009; **19:** 215–26.
6. Sallee FR, *et al*. SPD503 STUDY GROUP. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2009; **48:** 155–65.
7. Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. *J Atten Disord* 2010; **13:** 532–8.
8. Connor DF, Rubin J. Guanfacine extended release in the treatment of attention deficit hyperactivity disorder in children and adolescents. *Drugs Today* 2010; **46:** 299–314.

Tourette's syndrome. Guanfacine may be used as an alternative to clonidine in the management of patients with mild to moderate symptoms of Tourette's syndrome (see Tics, p. 1030.1). First-line use of these drugs is increasingly favoured in such patients because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p. 1341.2. Rebound hypertension may occur but is delayed due to the longer half-life.

References.
1. Jerie P. Clinical experience with guanfacine in long-term treatment of hypertension, part II: adverse reactions to guanfacine. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 157S–164S.
2. Board AW, *et al*. A postmarketing evaluation of guanfacine hydrochloride in mild to moderate hypertension. *Clin Ther* 1988; **10:** 761–75.
3. Horrigan JP, Barnhill LJ. Guanfacine and secondary mania in children. *J Affect Disord* 1999; **54:** 309–14.
4. McGrath JC, Klein-Schwartz W. Epidemiology and toxicity of pediatric guanfacine exposures. *Ann Pharmacother* 2002; **36:** 1698–1703.
5. Boreman CD, Arnold LE. Hallucinations associated with initiation of guanfacine. *J Am Acad Child Adolesc Psychiatry* 2003; **42:** 1387.
6. Minns AB, *et al*. Guanfacine overdose resulting in initial hypertension and subsequent delayed, persistent orthostatic hypotension. *Clin Toxicol* 2010; **48:** 146–8.

Withdrawal. Rapid reduction of the guanfacine dosage resulted in rebound hypertension leading to generalised seizures and coma in a 47-year-old patient with renal failure who was receiving haemodialysis.[1] Use with phenobarbital may have enhanced the metabolism of guanfacine and contributed to the development of the withdrawal effect.

1. Kiechel JR, *et al*. Pharmacokinetic aspects of guanfacine withdrawal syndrome in a hypertensive patient with chronic renal failure. *Eur J Clin Pharmacol* 1983; **25:** 463–6.

Interactions

As for Clonidine Hydrochloride, p. 1342.1. The metabolism of guanfacine may be altered by strong inhibitors and inducers of the cytochrome P450 isoenzyme CYP3A4.

Pharmacokinetics

Guanfacine is rapidly absorbed after oral doses and peak plasma concentrations occur 1 to 4 hours after ingestion of an immediate-release dosage form. The oral bioavailability is reported to be about 80%. It is about 70% bound to plasma proteins. It is excreted in urine as unchanged drug and metabolites; about 50% of a dose is reported to be eliminated unchanged. The normal elimination half-life ranges from 10 to 30 hours, tending towards the upper range in older patients.

Renal impairment. A study[1] in patients with normal or impaired renal function found that guanfacine clearance and serum concentrations were not significantly different in the 2 groups, suggesting that non-renal elimination plays an important role in patients with renal impairment.

1. Kirch W, *et al*. Elimination of guanfacine in patients with normal and impaired renal function. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 33S–35S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Estulic; ***Fr.***: Estulic†; ***Hung.***: Estulic; ***Rus.***: Estulic (Эстулик); ***Ukr.***: Estulic (Эстулик); ***USA***: Intuniv; Tenex.

Pharmacopoeial Preparations
USP 36: Guanfacine Tablets.

Heparin *(BAN)*

Eparina; Heparíini; Heparina; Heparine; Héparine; Heparinum; Heparyna; Гепарин.

CAS — 9005-49-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.
UNII — T2410KM04A.

Description. Heparin is an anionic polysaccharide of mammalian origin with irregular sequence. It consists principally of alternating iduronate and glucosamine residues, most of which are sulfated. It may be described as a sulfated glucosaminoglycan. Heparin has the characteristic property of delaying the clotting of freshly shed blood. It may be prepared from the lungs of oxen or the intestinal mucosa of oxen, pigs, or sheep.

Heparin is often described in the literature as **standard heparin** or **unfractionated heparin** to distinguish it from low-molecular-weight heparins.

Heparin Calcium *(BANM)*

Calcium Heparin; Heparíinikalsium; Heparin-Calcium; Heparin Kalsiyum; Heparin Sodyum; Heparin vápenatá sůl; Heparina cálcica; Héparine calcique; Heparinkalcium; Heparino kalcio druska; Heparinum calcicum; Heparyna wapniowa; Гепарин Кальция.

CAS — 37270-89-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.
UNII — M4F288ZCTR.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Ph. Eur. 8: (Heparin Calcium). The calcium salt of a sulfated glycosaminoglycan present in mammalian tissues. It is prepared either from lungs of cattle or from the intestinal mucosa of pigs, cattle, or sheep. It has a potency of not less than 180 international units per mg calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Incompatibility. See Heparin Sodium, p. 1397.1.

Heparin Sodium *(BANM, rINN)*

Heparíininatrium; Heparin-Natrium; Heparin sodná sůl; Heparina sódica; Héparine Sodique; Heparinnatrium; Heparino natrio druska; Heparinum Natricum; Heparyna sodowa; Sodium Heparin; Soluble Heparin; Гепарин Натрий.

CAS — 9041-08-1.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.
UNII — ZZ45AB24CA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Heparin Sodium). The sodium salt of a sulfated glycosaminoglycan present in mammalian tissues. It is prepared either from lungs of cattle or from the intestinal mucosa of pigs, cattle, or sheep. It has a potency of not less than 180 international units per mg calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

USP 36: (Heparin Sodium). The sodium salt of heparin with a potency, calculated on the dried basis, of not less than 180 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A white or pale-coloured amorphous, odourless or almost odourless, hygroscopic powder. Soluble 1 in 20 of water. A 1% solution in water has a pH of 5.0 to 7.5. Store in

airtight containers at temperatures below 40 degrees, preferably between 15 and 30 degrees.

Incompatibility. Licensed product information states that incompatibility has been reported between heparin calcium or sodium and alteplase, amikacin sulfate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, ciprofloxacin lactate, cisatracurium besilate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulfate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, labetalol hydrochloride meticillin sodium, nicardipine hydrochloride, netilmicin sulfate, some opioid analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulfate, reteplase, streptomycin sulfate, tetracycline hydrochloride, tobramycin sulfate, vancomycin hydrochloride, and vinblastine sulfate. Heparin sodium has also been reported to be incompatible with levofloxacin[1] and vinorelbine tartrate.[2] Although visually compatible,[3] cefmetazole sodium is reported to inactivate heparin sodium.

Glucose can have variable effects,[4,5] but glucose-containing solutions are generally considered suitable diluents for heparin. Incompatibility has also been reported between heparin and fat emulsion.

1. Saltsman CL, *et al*. Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
2. Balthasar JP. Concentration-dependent incompatibility of vinorelbine tartrate and heparin sodium. *Am J Health-Syst Pharm* 1999; **56:** 1891.
3. Hutching SR, *et al*. Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
4. Anderson W, Harthill JE. The anticoagulant activity of heparins in dextrose solutions. *J Pharm Pharmacol* 1982; **34:** 90–6.
5. Wright A, Hecker J. Long term stability of heparin in dextrose-saline intravenous fluids. *Int J Pharm Pract* 1995; **3:** 253–5.

Units

The fifth International Standard for unfractionated heparin was established in 1998. The USP 36 states that USP and international units are not equivalent, although doses expressed in either appear to be essentially the same.

Uses and Administration

Heparin is an anticoagulant used mainly in the treatment and prophylaxis of thromboembolic disorders (p. 1273.2). It is often described as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins (p. 1426.1).

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). Heparin increases the rate of this inhibition, but in a manner that is dependent on its dose. With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa. The inhibition of thrombin blocks the conversion of fibrinogen to fibrin, and the inhibition of factor Xa blocks the conversion of prothrombin to thrombin. The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p. 1124.3.

Heparin is used in the treatment and prophylaxis of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p. 1274.1), especially prophylaxis in surgical patients and in those pregnant women at particular risk. It is also used in the management of arterial thromboembolism including that associated with unstable angina pectoris (p. 1254.3), myocardial infarction (p. 1257.1), and acute peripheral arterial thromboembolism (p. 1273.3). It is often used as a precursor to oral anticoagulation and is withdrawn once the oral anticoagulant is exerting its full effect.

Heparin has been tried in the treatment of disseminated intravascular coagulation. It is also used to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures such as cardiopulmonary bypass. Other uses include the anticoagulation of blood for transfusion or blood samples and the flushing of catheters and cannulas to maintain patency.

Heparin and its salts are constituents of many topical preparations for the treatment of various inflammatory disorders.

Administration and dosage. Heparin is given intravenously, preferably by continuous infusion, or by subcutaneous injection. It may be given as the calcium or sodium salt and it is generally accepted that there is little difference in their effects. Oral formulations of heparin are under investigation.

Doses of heparin for treatment (sometimes termed 'full-dose' heparin), and in some cases prophylaxis, of thromboembolism should be monitored and determined as discussed below under Control of Heparin Therapy. The subcutaneous doses of heparin commonly used for prophylaxis (often termed 'low-dose') do not require routine monitoring. A test dose has been recommended for patients with a history of allergy. Although international and USP units are not strictly equivalent, doses expressed in either appear to be essentially the same.

For **treatment of venous thromboembolism**, an intravenous loading dose of 75 to 80 units/kg or 5000 units is given (10 000 units may be required in severe pulmonary embolism). This is followed by a continuous intravenous infusion of 18 units/kg per hour (usually in the range of 1000 to 2000 units/hour), adjusted according to response. Alternatively, a similar maintenance dose may be given by intermittent subcutaneous injection: ranges of 15 000 to 20 000 units every 12 hours or 8000 to 10 000 units every 8 hours have been suggested. Another alternative is an intermittent intravenous injection of 5000 to 10 000 units given every 4 to 6 hours.

For **prophylaxis** of **postoperative venous thromboembolism**, subcutaneous doses used are 5000 units 2 hours before surgery then every 8 to 12 hours for 7 days or until the patient is ambulant. Similar doses are used to prevent thromboembolism during pregnancy in women with a history of deep-vein thrombosis or pulmonary embolism; the dosage may need to be increased to 10 000 units every 12 hours during the third trimester.

In the management of **unstable angina** or acute **peripheral arterial embolism,** heparin may be given by continuous intravenous infusion in the same doses as those recommended for the treatment of venous thromboembolism. For the prevention of re-occlusion of the coronary arteries after thrombolytic therapy in **myocardial infarction**, intravenous doses of 60 units/kg (maximum 4000 units) are recommended, or a bolus of 5000 units if streptokinase was used. This is followed by 12 units/kg per hour (maximum 1000 units/hour) with a duration of treatment of 48 hours.

For administration in children, see below. Treatment doses for children may also be considered in small adults.

Control of heparin therapy. Treatment with full-dose heparin must be monitored to ensure that the dose is providing the required effect on antithrombin III. The most commonly used test to monitor the action of heparin is the activated partial thromboplastin time (APTT). The APTT of patients on full-dose heparin should generally be maintained at 1.5 to 2.5 times the control value although the optimum therapeutic range varies between individual laboratories depending on the APTT reagent in use. Regular monitoring is essential, preferably on a daily basis. Prophylaxis with low-dose subcutaneous heparin is not routinely monitored; the APTT is not significantly prolonged in these patients. Other tests used include the activated clotting time (ACT). The value of measuring heparin concentration in the blood is uncertain.

General references to anticoagulation with heparin.

1. Hirsh J. Heparin. *N Engl J Med* 1991; **324:** 1565–74.
2. Freedman MD. Pharmacodynamics, clinical indications, and adverse effects of heparin. *J Clin Pharmacol* 1992; **32:** 584–96.
3. Hyers TM. Heparin therapy: regimens and treatment considerations. *Drugs* 1992; **44:** 738–49.
4. Hirsh J, Fuster V. Guide to anticoagulant therapy part I: heparin. *Circulation* 1994; **89:** 1449–68.
5. Baglin T, *et al*. for the British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; **133:** 19–34. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05953.x/pdf (accessed 21/10/11)
6. Hirsh J, *et al*. Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S. Also available at: http://www.chestjournal.org/content/133/6_suppl/141S.full.pdf (accessed 27/08/09)
7. Vardi M, *et al*. Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 03/06/10).
8. Gray E, *et al*. Heparin and low-molecular-weight heparin. *Thromb Haemost* 2008; **99:** 807–18.

Action. Heparin is well established as an anticoagulant and antithrombotic and acts mainly by binding to, and enhancing the activity of, antithrombin III. However, it has other actions and the physiological role of endogenous heparin has not been clearly defined, despite its presence in mast cells, its ability to interact with many proteins, and its close structural similarity to heparan sulfate (suleparoid), the ubiquitous cell-surface glycosaminoglycan.[1-3] Endogenous heparin activity may have a role in protecting against atherosclerosis.[4] Non-anticoagulant properties of heparin or low-molecular-weight heparins have been reported to include anti-inflammatory activity,[5] with a possible application in, for example, asthma[6-8] or inflammatory bowel disease; however, studies in patients with active ulcerative colitis have not found any benefit.[9] For mention of the use of aerosolised heparin alternating with acetylcysteine to treat inhalation injury, see Burns, under Acetylcysteine, p. 1653.1. The risk of bleeding is a major obstacle to the use of heparin for non-anticoagulant purposes.

1. Lane DA, Adams L. Non-anticoagulant uses of heparin. *N Engl J Med* 1993; **329:** 129–30.
2. Page CP. Proteoglycans: the "Teflon" of the airways? *Thorax* 1997; **52:** 924–5.
3. Ludwig RJ. Therapeutic use of heparin beyond anticoagulation. *Curr Drug Discov Technol* 2009; **6:** 281–9.
4. Engelberg H. Actions of heparin in the atherosclerotic process. *Pharmacol Rev* 1996; **48:** 327–52.
5. Young E. The anti-inflammatory effects of heparin and related compounds. *Thromb Res* 2008; **122:** 743–52.
6. Martineau P, Vaughan LM. Heparin inhalation for asthma. *Ann Pharmacother* 1995; **29:** 71–2.
7. Ahmed T, *et al*. Prevention of exercise-induced bronchoconstriction by inhaled low-molecular-weight heparin. *Am J Respir Crit Care Med* 1999; **160:** 576–81.
8. Stelmach I, *et al*. The effect of inhaled heparin on airway responsiveness to histamine and leukotriene D4. *Allergy Asthma Proc* 2003; **24:** 59–65.
9. Chande N, *et al*. Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 21/10/11).

Administration. The activated partial thromboplastin time (APTT) is the test most commonly used to monitor intravenous full-dose heparin therapy.[1] Heparin dosing algorithms have been developed[2,3] so that the time taken to achieve a therapeutic APTT and maintain it in the therapeutic range (usually 1.5 to 2.5 times the control value) is shortened and thus the risk of recurrent thrombosis and major bleeding complications is reduced. An automated method of monitoring and regulation has been tried.[4] Although use of ideal body-weight for dosage calculation in obese patients has been suggested, actual body-weight may be more appropriate,[5,6] but maximum bolus doses and infusion rates should be set, to avoid overdosage in morbidly obese patients. A weight-based algorithm for treatment doses of subcutaneous heparin in deep-vein thrombosis has also been proposed.[7]

However, the therapeutic ranges used in such algorithms are not applicable to all APTT reagents because the latter vary in their sensitivity to heparin.[8] The optimum therapeutic range therefore varies between individual laboratories depending on the APTT reagent used. Dosing algorithms may be adapted by calibrating the therapeutic APTT with plasma-heparin concentrations.[8,9]

Anti-factor Xa monitoring,[10] and the activated clotting time (ACT) have been used as alternatives to APTT monitoring.

1. Eikelboom JW, Hirsh J. Monitoring unfractionated heparin with the aPTT: time for a fresh look. *Thromb Haemost* 2006; **96:** 547–52.
2. Cruickshank MK, *et al*. A standard heparin nomogram for the management of heparin therapy. *Arch Intern Med* 1991; **151:** 333–7.
3. Raschke RA, *et al*. The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. *Ann Intern Med* 1993; **119:** 874–81.
4. Newby LK, *et al*. An automated strategy for bedside aPTT determination and unfractionated heparin infusion adjustment in acute coronary syndromes: insights from PARAGON A. *J Thromb Thrombolysis* 2002; **14:** 33–42.
5. Yee WP, Norton LL. Optimal weight base for a weight-based heparin dosing protocol. *Am J Health-Syst Pharm* 1998; **55:** 159–62.
6. Yee WP, Norton LL. Clarification of weight-based heparin protocol. *Am J Health-Syst Pharm* 2002; **59:** 1788.
7. Prandoni P, *et al*. Use of an algorithm for administering subcutaneous heparin in the treatment of deep venous thrombosis. *Ann Intern Med* 1998; **129:** 299–302.
8. Brill-Edwards P, *et al*. Establishing a therapeutic range for heparin therapy. *Ann Intern Med* 1993; **119:** 104–9.
9. Volles DF, *et al*. Establishing an institution-specific therapeutic range for heparin. *Am J Health-Syst Pharm* 1998; **55:** 2002–6.
10. Smith ML, Wheeler KE. Weight-based heparin protocol using antifactor Xa monitoring. *Am J Health-Syst Pharm* 2010; **67:** 371–4.

Administration in children. Heparin may be given to children for the *treatment* of venous thromboembolism. An intravenous loading dose of 50 units/kg may be followed by an intravenous infusion of 15 to 25 units/kg per hour, or a subcutaneous injection of 250 units/kg twice daily. Alternatively, the *BNFC* suggests the following doses, adjusted according to activated partial thromboplastin time (APTT):

- neonates and infants aged up to 1 year: an initial intravenous injection of 75 units/kg (or 50 units/kg if under 35 weeks post-menstrual age), followed by an intravenous infusion of 25 units/kg per hour
- children aged 1 to 18 years: an initial intravenous injection of 75 units/kg, followed by an intravenous infusion of 20 units/kg per hour

Although unlicensed in the UK for the *prophylaxis* of venous thromboembolism in children, the *BNFC* suggests that those aged 1 month to 18 years may be given a dose of 100 units/kg (to a maximum of 5000 units) twice daily by subcutaneous injection, adjusted according to APTT.

The pharmacokinetics and activity of heparin appear to be age dependent; infants may require relatively larger doses and higher infusion rates to achieve therapeutic anticoagulation and similar prolongation of thromboplastin time than do older children and adults. A review[1] of the

topic considered that current management strategies for heparin therapy in infants and children were suboptimal.

1. Newall F, *et al*. Unfractionated heparin therapy in infants and children. Abstract: *Pediatrics* 2009; **123:** 896. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/3/e510.pdf (accessed 13/10/09)

Catheters and cannulas. Solutions of heparin sodium 10 or 100 units/mL in sodium chloride 0.9% are used for flushing intravenous catheters, cannulas, and other indwelling intravenous infusion devices used for intermittent dosing (heparin locks). A meta-analysis[1] of controlled studies was, however, unable to show any major advantage of either strength of heparin sodium solution over sodium chloride 0.9% alone in maintaining peripheral cannula patency or reducing the incidence of thrombophlebitis, and sodium chloride 0.9% is therefore recommended for cannulas intended to be in place for 48 hours or less. Less use of heparin flush solutions could minimise the risk of adverse effects such as thrombocytopenia and reduce the risk of incompatibilities with intravenous drugs.

Use of heparin-bonded catheters or the addition of heparin to intravenous fluids such as total parenteral nutrition solutions has also been tried in an attempt to maintain indwelling intravenous infusion devices (but see Catheters and Cannulas under Precautions, p. 1400.1). Continuous infusion of heparin-containing fluids may prolong the patency of peripheral arterial catheters.[1] To maintain the patency of umbilical artery catheters in neonates, US guidelines[2] suggest continuous infusion of heparin at a concentration of 0.25 to 1 unit/mL.

Central venous catheters are also subject to thrombus formation and their use may be complicated by vascular thrombosis and systemic infection. A meta-analysis[3] found that the use of unfractionated heparin, low-molecular-weight heparin, or low-dose warfarin reduced the risk of venous thromboembolism in patients with central venous catheters, but the effect on outcomes was unclear. The benefits seen in early studies might have diminished in part due to improvements in catheter technology, placement, and aftercare,[4] although this has been disputed.[3] More specific systematic reviews have found that continuous infusion of heparin reduces the incidence of catheter occlusion in neonates with peripherally-placed central venous catheters,[5] and that heparin-bonded catheters may reduce the risk of catheter occlusion in children with central venous catheters.[6] Very low doses of warfarin (typically 1 mg daily) have been used to prevent thrombosis in cancer patients with central venous catheters; however, results from studies have been conflicting.[4,7-11] Guidelines[12] do not currently recommend the use of low-dose warfarin or low-molecular-weight heparin for the prevention of central venous catheter-related thrombosis in cancer patients. Malignancy itself carries a risk of thrombosis—see below.

1. Randolph AG, *et al*. Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. *BMJ* 1998; **316:** 969–75.
2. Monagle P, *et al*. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S. Also available at: http://www.chestjournal.org/content/133/6_suppl/887S.full.pdf (accessed 27/08/09)
3. Kirkpatrick A, *et al*. Prevention of central venous catheter-associated thrombosis: a meta-analysis. *Am J Med* 2007; **120:** 901–10.
4. Young AM, *et al*. WARP Collaborative Group, UK. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. *Lancet* 2009; **373:** 567–74.
5. Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/05/08).
6. Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous catheters in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 15/05/08).
7. Bern MM, *et al*. Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 1990; **112:** 423–8.
8. Couban S, *et al*. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol* 2005; **23:** 4063–9.
9. Boraks P, *et al*. Prevention of central venous catheter associated thrombosis using minidose warfarin in patients with haematological malignancies. *Br J Haematol* 1998; **101:** 483–6.
10. Magagnoli M, *et al*. Prophylaxis of central venous catheter-related thrombosis with minidose warfarin in patients treated with high-dose chemotherapy and peripheral-blood stem-cell transplantation: retrospective analysis of 228 cancer patients. *Am J Hematol* 2006; **81:** 1–4.
11. Chan A, *et al*. Systemic anticoagulant prophylaxis for central catheter-associated venous thrombosis in cancer patients. *Ann Pharmacother* 2007; **41:** 635–41.
12. Geerts WH, *et al*. American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; **133** (suppl): 381S–453S. Also available at: http://www.chestjournal.org/content/133/6_suppl/381S.full.pdf (accessed 27/08/09)

Disseminated intravascular coagulation. Heparin has been used with some success in disseminated intravascular coagulation (p. 1126.1) associated with a variety of conditions. This use has been considered by some to be controversial and is usually reserved for specific situations where the risk of bleeding is relatively minor in comparison with the possible beneficial effect on formation of microthromboses. Guidelines[1] suggest that in cases where thrombosis predominates, *therapeutic* doses of heparin should be considered. If there is a co-existing high risk of bleeding, a continuous infusion of heparin in a weight-adjusted dose (10 units/kg per hour is suggested) may be used with careful monitoring. *Prophylactic* doses of heparin or low-molecular-weight heparin are recommended in critically ill, non-bleeding patients.

1. Levi M, *et al*. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009; **145:** 24–33.

Extracorporeal circulation. Anticoagulation with heparin is necessary during procedures such as cardiopulmonary bypass and haemodialysis and haemofiltration. In the case of bypass, heparin is added to the crystalloid solution and any stored blood used for priming the bypass machine and is given intravenously before cannulation of the heart and major blood vessels. Activated clotting time (ACT) is monitored throughout. After bypass is stopped, anticoagulation can be reversed with protamine but caution is advised because of potential toxicity on the cardiopulmonary circulation.

At the start of haemodialysis sessions patients generally get a loading dose of heparin followed by continuous infusion into the exit line of the extracorporeal circuit until about one hour before the end of dialysis. The dose of heparin varies widely depending on body-weight, volume of the extracorporeal circulation, dialysis membrane biocompatibility, and pump speed.

Malignant neoplasms. Cancer is a risk factor for thromboembolism and anticoagulants are often used in patients with malignant neoplasms. There is some evidence that outcomes are improved in patients treated with heparin, and both unfractionated and low-molecular-weight heparins have therefore been studied in patients with malignant neoplasms but no other indication for anticoagulation. Systematic reviews[1,2] have found that there may be a clinically significant improvement in survival, although the risk of bleeding is also increased. However, further study is needed and current guidelines do not recommend the use of anticoagulants in cancer patients without other risk factors.[3,4]

1. Akl EA, *et al*. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2011 (accessed 21/10/11).
2. Lazo-Langner A, *et al*. The effect of low-molecular-weight heparin on cancer survival. A systematic review and meta-analysis of randomized trials. *J Thromb Haemost* 2007; **5:** 729–37.
3. Geerts WH, *et al*. American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; **133** (suppl): 381S–453S. Also available at: http://chestjournal.chestpubs.org/content/133/6_suppl/381S.full.pdf (accessed 03/08/10)
4. Mandalà M, *et al*. ESMO Guidelines Working Group. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guidelines for the management. *Ann Oncol* 2010; **21** (suppl 5): v274–v276.

Pregnancy. Heparin or low-molecular-weight heparins are the anticoagulants of choice for use in pregnancy although they are not without risk for the fetus (see Pregnancy, under Precautions, p. 1400.1), and for the mother.

Guidelines on thrombosis associated with pregnancy have been published.[1-3] Pregnant women may require anticoagulation for the treatment or prophylaxis of venous thromboembolism (p. 1274.1), or for the prevention of systemic thromboembolism associated with prosthetic heart valves (p. 1264.3). Patients with a history of thromboembolism or a thrombophilic abnormality such as inherited deficiencies of antithrombin III, protein C, or protein S or acquired antiphospholipid antibodies may be at particular risk. Women with antiphospholipid antibodies may also be at increased risk of fetal loss (see Systemic Lupus Erythematosus, p. 1613.3) and prophylaxis with low-dose aspirin is usually recommended.[3] Addition of heparin has been reported to further reduce the risk,[4-6] and treatment with heparin or low-molecular-weight heparin, in addition to aspirin, has therefore also been recommended.[2] However, a systematic review[7] concluded that there was inadequate evidence to support extrapolation of such use to prevent miscarriages without apparent cause other than inherited thrombophilia. Another systematic review[6] noted that in contrast to unfractionated heparin the efficacy of low-molecular-weight heparins plus aspirin in increasing live births in women with antiphospholipid syndromes remained unproven, and that large controlled studies were urgently needed.

1. Royal College of Obstetricians and Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management (February 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT28ThromboembolicDisease2007.pdf (accessed 03/08/10)
2. Bates SM, *et al*. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S. Also available at: http://www.chestjournal.org/content/133/6_suppl/844S.full.pdf (accessed 27/08/09)
3. Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium (November 2009). Available at: http://www.rcog.org.uk/files/rcog-corp/GT37ReducingRiskThrombo.pdf (accessed 03/08/10)
4. Rai R, *et al*. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997; **314:** 253–7.
5. Empson M, *et al*. Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. *Obstet Gynecol* 2002; **99:** 135–44.
6. Ziakas PD, *et al*. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. *Obstet Gynecol* 2010; **115:** 1256–62.
7. Kaandorp S, *et al*. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 15/04/09).

Reperfusion and revascularisation procedures. Heparin has an established role as an adjunct to percutaneous vascular interventions and bypass surgery, to prevent perioperative thrombosis of the target artery, and is usually given with aspirin or other antiplatelet drugs (see Reperfusion and Revascularisation Procedures, p. 1259.2). High doses are used, particularly in patients undergoing bypass surgery with extracorporeal circulation, and bleeding is a common problem. Although heparin may have an antiproliferative effect, treatment with systemic heparin (unfractionated or low-molecular-weight) appears to have no effect on restenosis;[1] however, a study using local application of enoxaparin suggested that restenosis was reduced.[2] Heparin-coated intracoronary stents have also been used; they improve outcomes compared with balloon angioplasty,[3] but have not been shown to be superior to bare-metal stents[4] or to have any additional effect on restenosis.[5,6] Heparin-coated stents have also been used successfully in cerebrovascular interventions.[7]

1. Grassman ED, *et al*. A randomized trial of the low-molecular-weight heparin certoparin to prevent restenosis following coronary angioplasty. *J Invasive Cardiol* 2001; **13:** 723–8.
2. Kiesz RS, *et al*. Local delivery of enoxaparin to decrease restenosis after stenting: results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). *Circulation* 2001; **103:** 26–31.
3. Serruys PW, *et al*. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; **352:** 673–81. Correction. *ibid*.; 1478.
4. Mehran R, *et al*. An Internet-based registry examining the efficacy of heparin coating in patients undergoing coronary stent implantation. *Am Heart J* 2005; **150:** 1171–6.
5. Wöhrle J, *et al*. Comparison of the heparin coated vs the uncoated Jostent—no influence on restenosis or clinical outcome. *Eur Heart J* 2001; **22:** 1808–16.
6. Semiz E, *et al*. Comparison of initial efficacy and long-term follow-up of heparin-coated Jostent with conventional NIR stent. *Jpn Heart J* 2003; **44:** 889–98.
7. Parkinson RJ, *et al*. Use of heparin-coated stents in neurovascular interventional procedures: preliminary experience with 10 patients. *Neurosurgery* 2006; **59:** 812–21.

Adverse Effects

Heparin can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated. The incidence of thrombocytopenia is reported to be greater with bovine than porcine heparin.

Hypersensitivity reactions may occur, as may local irritant effects, and skin necrosis. Alopecia and osteoporosis resulting in spontaneous fractures have occurred after prolonged use of heparin.

When used to flush intravenous devices, the low levels of heparin that reach the systemic circulation are unlikely to cause adverse effects; however, immune-mediated thrombocytopenia and thrombosis have been reported rarely.

Effects on the adrenal glands. Heparin inhibits the secretion of aldosterone and so may cause **hyperkalaemia**.[1] Although all patients treated with heparin may develop reduced aldosterone concentrations, most are able to compensate through the renin-angiotensin system. Patients on prolonged heparin therapy or those unable to compensate, such as patients with diabetes mellitus or renal impairment or those also receiving potassium-sparing drugs such as ACE inhibitors, may present with symptoms of hyperkalaemia. The UK CSM suggests[2] that plasma-potassium concentration should be monitored in all patients with risk factors, particularly those receiving heparin for more than 7 days. The hyperkalaemia is usually transient or resolves when heparin is stopped and treatment is not generally required; fludrocortisone was successfully used to treat resistant hyperkalaemia in a patient in whom continued heparin therapy was necessary.[3]

Adrenal insufficiency secondary to adrenal haemorrhage has also been associated with heparin; heparin-induced thrombocytopenia may be implicated.[4]

1. Oster JR, *et al*. Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; **98:** 575–86.
2. CSM/MCA. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/

idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
3. Sherman DS, *et al*. Fludrocortisone for the treatment of heparin-induced hyperkalemia. *Ann Pharmacother* 2000; **34:** 606–10.
4. Dahlberg PJ, *et al*. Adrenal insufficiency secondary to adrenal hemorrhage: two case reports and a review of cases confirmed by computed tomography. *Arch Intern Med* 1990; **150:** 905–9.

Effects on the blood. *Haemorrhage* is a recognised risk with heparin. The risk of major bleeding may be lower with continuous intravenous infusion than with intermittent intravenous injection; risk may increase with heparin dose and patient age.[1] It is unclear whether the risk is lower with *low-molecular-weight heparins*, see p. 1426.3.

Heparin has been associated with the development of *thrombocytopenia*, which may be of two types. The first is a common, acute, but usually mild, fall in platelet count occurring within 1 to 4 days of starting therapy and which often resolves without stopping treatment.[2] A direct effect of heparin on platelet aggregation appears to be responsible. The second type of thrombocytopenia (heparin-induced thrombocytopenia; HIT) is a more serious, immune-mediated reaction. In about a fifth of heparin-treated patients, antibodies are seen against a complex formed between heparin and platelet factor-4 (found on platelets and endothelial cells). In a small subset of these patients, a cycle of platelet activation, thrombocytopenia, and life- and limb-threatening venous or arterial thrombosis develops; bleeding has also occurred.[2-4] HIT usually occurs after 5 to 14 days although its onset may be more rapid in patients previously exposed to heparin;[3,4] delayed presentation up to 40 days after stopping heparin has also been reported.[5,6] The reaction is independent of dose or route; there have been reports of thrombocytopenia after use of heparin flushes[7] or heparin-coated catheters.[8]

The incidence of HIT varies considerably between different patient populations.[9] It is more common in surgical patients than medical, and less common in obstetric patients. It occurs more often with bovine heparin than porcine, and less often with low-molecular-weight heparins. Duration of exposure is a factor, as is recent exposure. Patients with lupus anticoagulant may also be more susceptible.[10] Based on these factors, patients can be classified according to their risk of developing HIT: high (> 1%), medium (0.1 to 1%), and low (< 0.1%); and this may be used to decide if platelet-count **monitoring** is necessary.[9] A baseline platelet count has been recommended in all patients who are to receive any type of heparin.[11] A second count should then be taken after 24 hours in patients who have received unfractionated heparin within the last 100 days; otherwise, counts should be repeated every 2 days in those at high risk or every 2 or 3 days in those at medium risk, from day 4 to 14 of therapy or until heparin is stopped.[9] Regular monitoring is not considered necessary in those at low risk.[9,11]

HIT should be suspected in any patient who develops new thrombosis or a drop in platelets during or shortly after heparin therapy. This includes thrombosis in those whose platelet count appears to be normal, since thrombosis may occasionally precede thrombocytopenia.[2,9] Testing for HIT antibodies may be used to exclude a diagnosis, but false positive results are common.[4,9]

Management of HIT involves stopping heparin and replacing it immediately with a suitable *non-heparin* anticoagulant.[2,4,9]

- The direct thrombininhibitors lepirudin, argatroban, and bivalirudin are recommended licensed choices,[9] although bivalirudin is currently licensed to treat HIT only in those undergoing PCI.
- Danaparoid, a heparinoid, is another recommended choice. Because it may very rarely produce cross-reactivity, licensed product information suggests the use of *in-vitro* testing before use; however, current guidelines[9] do not consider this to be of value.
- The pentasaccharide fondaparinux has been used; however, it is not licensed for the treatment of HIT, and evidence of benefit is not yet considered adequate to make firm recommendations.[2,9]
- Other drugs that have been tried in the acute treatment of HIT include: the anticoagulant dermatan;[12] aspirin and dipyridamole or normal immunoglobulin to correct severe thrombocytopenia;[13] and thrombolytics for occlusive thrombosis.[14,15]
- A coumarin may be given for longer-term treatment of thrombosis caused by HIT. Use should be postponed until the platelet count has recovered since coumarins have caused microvascular thrombosis and venous limb gangrene if given earlier.[2,4,9] A non-heparin parenteral anticoagulant should be started first and overlapped with the coumarin for at least 5 days and until the INR is stable.[9] The coumarin may then be continued for 3 to 6 months.[2]

HIT antibodies usually clear within about 100 days in most individuals. Since the risks associated with re-exposure are uncertain, future avoidance is generally considered prudent.[2]

The principles of monitoring and treatment in **children** are similar to those in adults.[16]

There may be a relationship between heparin-induced thrombocytopenia and skin necrosis (see below).

1. Schulman S, *et al*. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
2. Shantsila E, *et al*. Heparin-induced thrombocytopenia: a contemporary clinical approach to diagnosis and management. *Chest* 2009; **135:** 1651–64.
3. Hassell K. Heparin-induced thrombocytopenia: diagnosis and management. *Thromb Res* 2008; **123** (suppl 1): S16–S21.
4. Greinacher A, *et al*. Heparin-induced thrombocytopenia. *Hamostaseologie* 2010; **30:** 17–28.
5. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med* 2001; **135:** 502–6.
6. Rice L, *et al*. Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002; **136:** 210–15.
7. Heeger PS, Backstrom JT. Heparin flushes and thrombocytopenia. *Ann Intern Med* 1986; **105:** 143.
8. Laster JL, *et al*. Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. *Arch Intern Med* 1989; **149:** 2285–7.
9. Warkentin T, *et al*. American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 340S–380S. Also available at: http://chestjournal.chestpubs.org/content/139/5/1261.full.pdf (accessed 25/10/11) Correction. *ibid*. 2011; **139:** 1261. [dose]
10. Auger WR, *et al*. Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: a preliminary report. *Am J Med* 1995; **99:** 392–6.
11. Keeling D, *et al*. on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin induced thrombocytopenia. *Br J Haematol* 2006; **133:** 259–69. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2006.06018.x/pdf (accessed 21/10/11)
12. Taliani MR, *et al*. Dermatan sulphate in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1999; **104:** 87–9.
13. Frame JN, *et al*. Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; **111:** 946–7.
14. Krueger SK, *et al*. Thrombolysis in heparin-induced thrombocytopenia with thrombosis. *Ann Intern Med* 1985; **103:** 159.
15. Clifton GD, Smith MD. Thrombolytic therapy in heparin-associated thrombocytopenia with thrombosis. *Clin Pharm* 1986; **5:** 597–601.
16. Risch L, *et al*. Heparin-induced thrombocytopenia in paediatrics: clinical characteristics, therapy and outcomes. *Intensive Care Med* 2004; **30:** 1615–24.

Effects on the bones. Osteoporosis is a rare complication of long-term heparin therapy. Treatment and prophylaxis of thromboembolism in pregnancy is one of the few indications for long term use of heparin, so most reports and studies of heparin-induced osteoporosis have been in pregnant women.[1] The incidence of symptomatic osteoporosis in patients given heparin long term has been estimated to be about 2%.[1,2] Subclinical reduction in bone density occurs in up to one-third of patients,[2,3] but it is not possible to predict which of these patients will develop osteoporotic fractures. Pregnancy normally causes reversible bone demineralisation, so the combination of pregnancy and heparin therapy may therefore result in symptomatic osteoporosis in susceptible individuals.[1,4] Bone changes may be reversible.[1] Although some evidence suggests that bone demineralisation is dose- and duration-dependent, this has not been conclusively established.[1,4] Use of low-molecular-weight heparins seems to be associated with a lower risk of heparin-induced osteoporosis,[2,3,5] and there is some evidence that while heparin both reduces bone formation and increases resorption, the low-molecular-weight heparins act only in the former manner.[3]

1. Nelson-Piercy C. Heparin-induced osteoporosis. *Scand J Rheumatol* 1998; **27** (suppl 107): 68–71.
2. Bates SM, *et al*. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S. Also available at: http://www.chestjournal.org/content/133/6_suppl/844S.full.pdf (accessed 27/08/09)
3. Rajgopal R, *et al*. The effects of heparin and low molecular weight heparins on bone. *Thromb Res* 2008; **122:** 293–8.
4. Farquharson RG. Heparin, osteoporosis and pregnancy. *Br J Hosp Med* 1997; **58:** 205–7.
5. Lefkou E, *et al*. Review: low-molecular-weight heparin-induced osteoporosis and osteoporotic fractures: a myth or an existing entity? *Lupus* 2010; **19:** 3–12.

Effects on electrolyte balance. See Effects on the Adrenal Glands, p. 1398.3.

Effects on lipid metabolism. Use of heparin leads to the release of lipoprotein lipase into the plasma. Postprandial lipidaemia is reduced due to increased hydrolysis of triglycerides into free fatty acids and glycerol. Raised concentrations of free fatty acids have been reported after heparin use but the magnitude of this effect may have been overestimated.[1] Rebound hyperlipidaemia may occur when heparin is withdrawn. With long-term use reserves of lipoprotein lipase may be depleted; severe hypertriglyceridaemia reported in a pregnant woman was attributed to long-term heparin prophylaxis that was thought to have resulted in lipoprotein lipase deficiency.[2]

1. Riemersma RA, *et al*. Heparin-induced lipolysis, an exaggerated risk. *Lancet* 1981; **ii:** 471.
2. Watts GF, *et al*. Lipoprotein lipase deficiency due to long-term heparinization presenting as severe hypertriglyceridaemia in pregnancy. *Postgrad Med J* 1991; **67:** 1062–4.

Effects on the liver. Increases in transaminase values, usually reversible on stopping therapy, have been reported in patients given therapeutic[1-3] or prophylactic[3] doses of heparin. A prospective study[4] found increased transaminases that were assessed as probably due to heparin in 8 of 54 patients; the reaction seemed to occur more frequently with therapeutic doses. Increased transaminases have also been reported[5,6] in patients receiving low-molecular-weight heparins (enoxaparin).

1. Sonnenblick M, *et al*. Hyper-transaminasemia with heparin therapy. *BMJ* 1975; **3:** 77.
2. Dukes GE, *et al*. Transaminase elevations in patients receiving bovine or porcine heparin. *Ann Intern Med* 1984; **100:** 646–50.
3. Monreal M, *et al*. Adverse effects of three different forms of heparin therapy: thrombocytopenia, increased transaminases, and hyperkalaemia. *Eur J Clin Pharmacol* 1989; **37:** 415–18.
4. Guevara A, *et al*. Heparin-induced transaminase elevations: a prospective study. *Int J Clin Pharmacol Ther Toxicol* 1993; **31:** 137–41.
5. Hui C-K, *et al*. Low molecular weight heparin-induced liver toxicity. *J Clin Pharmacol* 2001; **41:** 691–4.
6. Baker EL, *et al*. Probable enoxaparin-induced hepatotoxicity. *Am J Health-Syst Pharm* 2009; **66:** 638–41.

Effects on sexual function. Priapism has been associated with the use of heparin.[1,2] The prognosis is poor, impotence following more often than in priapism of other aetiologies. The mechanism of heparin-induced priapism is unclear. Priapism has also been reported[3] with low-molecular-weight heparins (dalteparin).

1. Baños JE, *et al*. Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
2. Bschleipfer TH, *et al*. Heparin-induced priapism. *Int J Impot Res* 2001; **13:** 357–9.
3. Lin PH, *et al*. Low molecular weight heparin induced priapism. *J Urol (Baltimore)* 2004; **172:** 263.

Effects on the skin. Skin necrosis is a rare complication of heparin use.[1,2] It may be a localised reaction at the site of subcutaneous injection or possibly be related to heparin-induced thrombocytopenia (see Effects on the Blood, above). An immune mechanism may be responsible.

More common is a delayed (type IV) hypersensitivity reaction to subcutaneous heparin, characterised by erythema or eczema around the injection site.[3] This type of hypersensitivity shows a high cross-reactivity with low-molecular-weight heparins, heparinoids such as danaparoid and pentosan, and fondaparinux. Hirudins such as lepirudin, bivalirudin and argatroban are reported to be safe alternatives. The risk of a generalised reaction to intravenous heparin appears to be minimal, although its safety in patients with type IV hypersensitivity to subcutaneous heparin is uncertain.

Recurrent fixed eczematous lesions have been attributed to heparin used intravenously during haemodialysis.[4]

1. Ulrick PJ, Manoharan A. Heparin-induced skin reaction. *Med J Aust* 1984; **140:** 287–9.
2. Fowlie J, *et al*. Heparin-associated skin necrosis. *Postgrad Med J* 1990; **66:** 573–5.
3. Trautmann A, Seitz CS. Heparin allergy: delayed-type non-IgE-mediated allergic hypersensitivity to subcutaneous heparin injection. *Immunol Allergy Clin North Am* 2009; **29:** 469–80.
4. Mohammed KN. Symmetric fixed eruption to heparin. *Dermatology* 1995; **190:** 91.

Hypersensitivity. An increased incidence of severe hypersensitivity reactions, including fatalities, was reported with some heparin preparations in early 2008;[1] it has been confirmed that the presence of an over-sulfated chondroitin sulfate contaminant was responsible.[1-3]

See Effects on the Blood and Effects on the Skin, above, for further hypersensitivity reactions associated with heparin.

1. FDA. Update to healthcare facilities and healthcare professionals about heparin and heparin-containing medical products. Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135355.htm (accessed 03/08/10)
2. Blossom DB, *et al*. Outbreak of adverse reactions associated with contaminated heparin. *N Engl J Med* 2008; **359:** 2674–84.
3. McKee J, *et al*. Structure elucidation and biological activity of the oversulfated chondroitin sulfate contaminant in Baxter heparin. *J Clin Pharmacol* 2010; **50:** 1159–70.

Treatment of Adverse Effects

Asymptomatic overdosage can usually be managed by stopping heparin. Protamine can be used as described on p. 1572.1 to reverse the effects of heparin if large doses have been given or if there is evidence of haemorrhage. Further management is symptomatic; hypovolaemia is treated with intravenous fluids and blood transfusion as needed.

Thrombocytopenia. For reference to the treatment of heparin-induced thrombocytopenia and associated thromboembolic complications, see Effects on the Blood, above.

Precautions

Heparin should not be given to patients who are haemorrhaging. In general it should not be given to

patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, thrombocytopenia, peptic ulcer disease, cerebrovascular disorders, bacterial endocarditis, severe hypertension, oesophageal varices, or patients who have recently undergone surgery at sites where haemorrhage would be an especial risk. Caution is required in hepatic and renal impairment; severe hepatic impairment may be a contra-indication. Heparin should not be given by intramuscular injection. Since heparin has caused thrombocytopenia with severe thromboembolic complications, platelet counts should be monitored in certain patients (see Effects on the Blood, p. 1399.1). Heparin should be stopped if thrombocytopenia develops. A test dose has been recommended for patients with a history of allergy.

Dosage of heparin may need to be reduced in the elderly; elderly women appear to be especially susceptible to haemorrhage after use of heparin.

Catheters and cannulas. Serum concentrations of sodium and potassium could be falsely elevated in samples obtained through heparin-bonded umbilical catheters due to release of benzalkonium chloride used in the manufacturing process of some catheters.[1] It was unknown if the amount released would be toxic to small premature neonates.

1. Gaylord MS, *et al.* Release of benzalkonium chloride from a heparin-bonded umbilical catheter with resultant factitious hypernatremia and hyperkalemia. *Pediatrics* 1991; **87:** 631–5.

Hyperkalaemia. For recommendations concerning the monitoring of patients susceptible to developing hyperkalaemia, such as those with diabetes mellitus or renal impairment, see Effects on the Adrenal Glands under Adverse Effects, p. 1398.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies heparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Pregnancy. Heparin does not cross the placenta, and therefore adverse effects on the fetus would not be expected.[1,2] A review[1] of the literature, however, indicated 2 spontaneous abortions and 17 still-births in 135 pregnancies exposed to heparin; 29 infants were premature, 10 of whom died. Another literature review[2] found adverse outcomes in 21.7% of heparin-treated patients, but this dropped to 10.4% when pregnancies with comorbid conditions were excluded. A further drop to 3.6% was seen when cases of prematurity with normal outcome were also excluded. The death rate of 2.5% and prematurity rate of 6.8% in heparin-treated patients was similar to that found in the normal population. It was concluded that heparin appears safer for the fetus than warfarin when used during pregnancy. Similar results have also been reported with low-molecular-weight heparins; a systematic review[3] found an adverse outcome in 9.3% of 486 pregnancies in which low-molecular-weight heparin was used, but this dropped to 3.1% in women without comorbid conditions.

Some heparin preparations contain the preservative benzyl alcohol and should be used with caution, if at all, in pregnant women—see below.

For further details on the use of heparin and low-molecular-weight heparins in pregnancy, see under Uses and Administration, p. 1398.2.

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68:** 122–40.
2. Ginsberg JS, Hirsh J. Optimum use of anticoagulants in pregnancy. *Drugs* 1988; **36:** 505–12.
3. Sanson B-J, *et al.* Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999; **81:** 668–72.

Preservative. The preservatives used in heparin preparations have been implicated in unwanted effects. Benzyl alcohol in heparinised flushing solutions has been suspected of causing toxicity in neonates (see p. 1740.3), and therefore any heparin preparation containing it should be used with caution, if at all, in susceptible patients such as premature babies, neonates, and pregnant women.

Chlorobutanol present in another heparin preparation caused a sharp fall in blood pressure (see Effects on the Cardiovascular System under Chlorobutanol, p. 1748.3).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred after spinal or epidural anaesthesia or analgesia (Central Nerve Block, p. 1981.2) in patients given heparin or low-molecular-weight heparins. The risk of haematoma appears to be higher in patients with indwelling epidural catheters, and in those with coagulopathies or who have also been given other drugs that affect haemostasis. Age may also be a risk factor.[1]

Recommendations[1] to avoid this vary depending on the type of heparin used and the dosing regimen.

- Central nerve blocks are not considered to be contra-indicated in those receiving *unfractionated heparin* in prophylactic doses (5000 units twice daily subcutaneously).
- Safety with higher or more frequent dosing of unfractionated heparin is unknown. In patients receiving high doses for vascular surgery, it is recommended that
  - pre-operative doses of heparin are given no sooner than 1 hour after placement of the catheter for anaesthesia
  - that the catheter is removed no sooner than 2 to 4 hours after the last heparin dose
  - and that postoperative heparin is given no sooner than 1 hour after catheter removal
- For those taking prophylactic doses of a *low-molecular-weight heparin*, placement of the catheter for anaesthesia should occur no sooner than 10 to 12 hours after the last dose.
- Patients given once-daily prophylactic doses of a low-molecular-weight heparin should be re-heparinised 6 to 8 hours after the operation, with the second postoperative dose given no sooner than 24 hours after the first. Indwelling catheters may be maintained; removal should occur no sooner than 10 to 12 hours after the last dose of heparin, and at least 2 hours before the next dose.
- Twice-daily prophylactic dosing of low-molecular-weight heparin carries a greater risk of haematoma, and catheter removal should occur before re-heparinisation. The first postoperative heparin dose should be delayed for 24 hours and at least 2 hours after removal of the catheter.
- The safety of indwelling catheters in patients taking treatment doses of a low-molecular-weight heparin is less clear, and alternative methods of anaesthesia might be preferable.

1. Horlocker TT, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35:** 64–101.

Interactions

Heparin should be used with care with oral anticoagulants or drugs, such as aspirin and dipyridamole, that affect platelet function. NSAIDs may also increase the risk of haemorrhage. Other drugs that affect the coagulation process and which may therefore increase the risk of haemorrhage include dextrans, thrombolytic enzymes such as streptokinase, high doses of penicillins and some cephalosporins, some contrast media, asparaginase, and epoprostenol; for use of heparin with drotrecogin alfa (activated) see p. 1161.3. Estimations of oral anticoagulant control may be modified by heparin's action on prothrombin.

ACE inhibitors. For reference to hyperkalaemia in patients on heparin and ACE inhibitors, see Effects on the Adrenal Glands, p. 1398.3.

Alcohol. Heavy drinkers were found to be at greater risk of major heparin-associated bleeding than moderate drinkers or non-drinkers.[1]

1. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA* 1980; **244:** 1209–12.

Aprotinin. For comment on the use of heparin with aprotinin, see Effects on Coagulation Tests under Aprotinin, p. 1134.2.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to reduce the activity of heparin when both drugs are given simultaneously by the intravenous route.[1] This effect has been seen even with low doses of glyceryl trinitrate.[2] Propylene glycol present in the glyceryl trinitrate formulation may[3] or may not[1] contribute to the effect. No interaction was reported when glyceryl trinitrate was given immediately after heparin.[4]

1. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. *Arch Intern Med* 1987; **147:** 857–60.
2. Brack MJ, *et al.* The effect of low dose nitroglycerine on plasma heparin concentrations and activated partial thromboplastin times. *Blood Coag Fibrinol* 1993; **4:** 183–6.
3. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; **110:** 171–3.
4. Bode V, *et al.* Absence of drug interaction between heparin and nitroglycerin. *Arch Intern Med* 1990; **150:** 2117–19.

Palifermin. For precautions when giving heparin to patients also receiving palifermin, see p. 2579.2.

Tobacco. Reduced half-life and increased elimination of heparin have been reported in smokers compared with non-smokers.[1]

1. Cipolle RJ, *et al.* Heparin kinetics: variables related to disposition and dosage. *Clin Pharmacol Ther* 1981; **29:** 387–93.

Pharmacokinetics

Heparin is not absorbed from the gastrointestinal tract. After intravenous or subcutaneous injection heparin is extensively bound to plasma proteins. It does not cross the placenta and it is not distributed into breast milk. The half-life of heparin depends on its dose and route as well as the method of calculation and is subject to wide inter- and intra-individual variation; a range of 1 to 6 hours with an average of 1.5 hours has been cited. It may be slightly prolonged in renal impairment, decreased in patients with pulmonary embolism, and either increased or decreased in patients with liver disorders. Heparin is taken up by the reticuloendothelial system. It is excreted in the urine, mainly as metabolites, although after large doses up to 50% may be excreted unchanged.

References.

1. Estes JW. Clinical pharmacokinetics of heparin. *Clin Pharmacokinet* 1980; **5:** 204–20.
2. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Calciparine; Cervep; Croneparina; Cycloparin; Hepatriet; Parinix; Riveparin; Serianon; Sobrius; Sodiparin; ***Austria***: Lioton; Thrombophob-S; Thrombophob; Venoruton Heparin; Viatromb; ***Braz.***: Actparin; Alimax; Disotron; Hemofol; Hepamax; Heptar; Liquemine; Trombofob; ***Canad.***: Hepalean-Lok†; Hepalean†; ***China***: Hepudiod (海普林); Jipailin (吉派林); Kai Rui (凯瑞); Mei De Xi (美得喜); Sai Luo Xi Ping (赛络喜平); ***Cz.***: Lioton; Viatromb; ***Fin.***: Hepaflex; ***Fr.***: Calciparine; ***Ger.***: Calciparin†; Essaven 60 000†; Exhirud Heparin; Hepa-Gel; Hepa-Salbe; Hepathromb; Hepathrombin; Parin-POS; Sportino†; Thrombareduct†; Thrombophob; Venalitan†; Venoruton Emulgel†; Vetren; ***Gr.***: Calciparine; Croneparina; Hepsal; Monoparin; Multiparin; ***Hong Kong***: Lioton; Multiparin†; ***Hung.***: Heparibene; Lioton; ***India***: Beparine; Beprin; Bioclot; Blockasol; Caprin; Cathflush; Declot; Hep; Heparen; Hepgel; Heplock; Ignava; Inhep; Keparin; Line Flush; No-Clot; Nuparin; Thrombophob; ***Indon.***: Hico; Inviclot; Thrombophob; ***Irl.***: Hepsal†; Monoparin†; Multiparin†; ***Ital.***: Ateroclar†; Calciparina; Clarisco; Disebrin; Ecafast; Ecasolv; Emoklar; Eparinlider; Eparinovis; Eparven; Epsoclar; Epsodilave; Flusolv; Isoclar†; Normoparin†; Pharepa; Reoflus; Sosefluss; Trombolisin; Veracer; Zepac; ***Malaysia***: Unihepa; ***Mex.***: Hep-Tec; Proparin; ***Norw.***: Hepaflex; ***NZ***: Multiparin; ***Philipp.***: Hemastat; Heprin; Heptin; Lioton; Lipactin; Meparin; Nuparin; ***Pol.***: Coaparin; Heparizen; Lioton; Lipohep; ***Rus.***: Lavenum (Лавенум); Lioton (Лиотон); Trombless (Тромблесс); ***S.Afr.***: Calciparine†; Thrombophob†; ***Spain***: Menaven; ***Switz.***: Calciparine; Demovarin; Gelparin; HepaGel; Hepasol Lipogel†; Lioton; Liquemine; Lyman Mono; Sportium uno; ***Turk.***: Calciparine; Liparin-S; Liquemine; Nevparin; ***UK***: Canusal†; Hepsal†; Monoparin†; Multiparin†; ***Ukr.***: Heparil (Гепарил); Lioton (Лиотон); Lyogel (Лиогель); ***USA***: Hep-Lock; Hepflush; ***Venez.***: Hirox; Riveparin.

Multi-ingredient Preparations. ***Arg.***: Contractubex; Integrum; Venostasin; ***Austria***: Ambenat†; Contractubex; Derivon; Dolo-Menthoneurin; Dolobene; Etrat; Heparin Comp; Ichthalgan forte; Lipactin; Pasta Cool; Sensicutan; Thrombophob; Venobene; Vetren; ***Belg.***: Lipactin; ***Braz.***: Contractubex; Dolobene†; Trombofob; Venalot H; ***Canad.***: Lipactin; ***China***: Contractubex (康瑞保); Dolobene (瑞乐平); ***Cz.***: Contractubex; Dolobene; Sensicutan; ***Fin.***: Lipactin; Trombosol; ***Fr.***: Cirkan a la Prednacinolone; Esberiven; Flector Tissugel Heparine; ***Ger.***: Contractubex; Dolobene†; Lipactin; Sensicutan; ***Gr.***: Contractubex; ***Hong Kong***: Contractubex; Dolobene†; ***Hung.***: Contractubex; Dolobene; Pasta Cool; ***India***: Beparine; Contractubex; Hexilak; Proctosedyl; Thrombophob; ***Indon.***: Thrombophob; ***Ital.***: Flebs; Idracemi Eparina; Luxazone Eparina; Proctosoll; Venoplant; Viamal Trauma; Viteparin; Xantervit Eparina; ***Mex.***: Contractubex; ***Philipp.***: Contractubex; ***Pol.***: Alcepalan†; Biherpan†; Cepan; Contractubex; Dolobene†; Savarix; Tointex†; ***Port.***: DM Gel; ***Rus.***: Contractubex (Контрактубекс); Dolobene (Долобене); Heparin Ointment (Гепариновая Мазь); Hepatrombin (Гепатромбин); Hepatrombin H (Гепатромбин Г); Hepazolon (Гепазолон); Nigepan (Нигепан); Proctosedyl (Проктоседил); Venitan Forte (Венитан Форте); Venolife (Венолайф); ***Spain***: Essavenon†; Venacol†; ***Switz.***: Assan thermo; Assan; Butaparin†; Contractubex; Dolo-Arthrosenex; Dolobene; Flectoparin; Gorgonium; Heparinol†; Keli-med; Keppur; Keppur; Lipactin; Lyman; Sportium; Sportusal assan thermo; Sportusal; Venucreme; Venugel; ***Turk.***: Contractubex; ***Ukr.***: Contractubex (Контрактубекс); Dolobene (Долобене); Hepathrombin (Гепатромбин); Hepathrombin H (Гепатромбин Г); Phytobene (Фитобене); Proctosedyl (Проктоседил); Venitan Forte (Венитан); Venoheparol (Веногепанол); Venosan (Веносан).

Homoeopathic Preparations. ***Ger.***: NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations
BP 2014: Heparin Injection;
USP 36: Anticoagulant Heparin Solution; Heparin Lock Flush Solution; Heparin Sodium Injection.

Heparinoids

Heparinoide; Heparinoides; Гепариноиды.

Profile

The term heparinoid includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly-sulfated polysaccharides of similar structure. Such compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans; glycosaminoglycan polysulfate compounds; or sulfated mucopolysaccharides.

The following anticoagulants may be described as heparinoids:

- Danaparoid Sodium, p. 1349.2
- Dermatan Sulfate, p. 1350.3
- Pentosan Polysulfate Sodium, p. 1465.1
- Sodium Apolate, p. 1497.1
- Suleparoid, p. 1507.2
- Sulodexide, p. 1507.3

Heparinoid preparations are available with uses ranging from anticoagulation to the alleviation of inflammation (applied topically); some are claimed to have hypolipidaemic properties.

The proprietary names listed in this monograph refer to preparations containing undefined or less readily defined heparinoids that are used in a range of conditions including musculoskeletal and joint disorders, haemorrhoids, lipid disorders, and thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fleboderma; Hirudoid; ***Austral.***: Hirudoid; Lasonil†; ***Austria***: Hemeran; Hirudoid; ***Belg.***: Hemeran; Hirudoid; ***Braz.***: Hirudoid; Topcoid; ***Chile***: Hirudoid†; ***China***: Hirudoid (喜辽妥); ***Cz.***: Heparoid; Hirudoid; ***Denm.***: Hirudoid; ***Fin.***: Hirudoid; ***Ger.***: Hirudoid; ***Gr.***: Arteparon†; Hemeran; Hirudoid; Lasonil N; ***Hong Kong***: Hepacare; Hirudoid; ***Hung.***: Hirudoid; ***India***: Hirudoid; ***Indon.***: Hirudoid†; ***Ital.***: Ateroid; Condral; Hirudoid; Matrix†; ***Neth.***: Hirudoid; ***Norw.***: Hirudoid; ***NZ***: Hirudoid; Lasonil; ***Philipp.***: Hirudoid; ***Pol.***: Hirudoid; ***Port.***: Hemeran; Hirudoid; Lasonil†; ***Rus.***: Balarpan (Баларпан); Heparoid (Гепароид); ***Singapore***: Hirudoid; ***Spain***: Dinoven†; Hirudoid; ***Swed.***: Hirudoid; ***Switz.***: Hemeran; Hirudoid; ***Thai.***: Hirudoid; Varidoid; ***Turk.***: Hirudoid; Lasonil; ***UK***: Bruiseze; Hirudoid; ***Ukr.***: Heparoid (Гепароид)†; ***Venez.***: Hirudoid.

Multi-ingredient Preparations. ***Arg.***: Mantus; ***Austria***: Mobilat; Mobilisin plus; Mobilisin; Moviflex; ***Belg.***: Mobilat; Mobilisin; ***Braz.***: Mobilat; Mobilisin Composto; ***Chile***: Mobilat†; Repariven; ***Cz.***: Ibu-Hepa; Mobilat; ***Fin.***: Mobilat; ***Gr.***: Bayolin; Lasonil; Movilisin; ***Hung.***: Mobilat N; ***India***: Movelisin; ***Ital.***: Flebs; Mobilisin; Momendol; ***Mex.***: Mobilat; ***Neth.***: Mobilat; ***Philipp.***: Hiruscar; Mobilat; ***Pol.***: Helason; Ibalgin Sport; Lumbolin†; Mobilat; ***Port.***: Anacal; Mobilat; Mobilisin; Mobilisin; Rimanal; ***Singapore***: Hiruscar; ***Spain***: Movilat; Movilisin†; ***Switz.***: Mobilat Intense; Mobilat; Mobilisin†; ***Thai.***: Mobilat; ***UK***: Anacal; Movelat; ***Venez.***: Bargonil; Permucal.

Hexobendine *(BAN, USAN, rINN)*

Hexobendina; Hexobendinum; Гексобендин.
$C_{30}H_{44}N_2O_{10}$=592.7
CAS — 54-03-5.
ATC — C01DX06.
ATC Vet — QC01DX06.
UNII — B6X45YR93B.

Hexobendine Hydrochloride *(BANM, rINNM)*

Hexobendina, hidrocloruro de; Hexobendine, Chlorhydrate d'; Hexobendini Hydrochloridum; Hidrocloruro de hexobendina; ST-7090; Гексобендина Гидрохлорид.
NN'-Ethylenebis(3-methylaminopropyl 3,4,5-trimethoxybenzoate) dihydrochloride.
$C_{30}H_{44}N_2O_{10}$,2HCl=665.6
CAS — 50-62-4.
ATC — C01DX06.
ATC Vet — QC01DX06.

Profile

Hexobendine hydrochloride is a vasodilator that has been used in ischaemic heart disease. It is also included in multi-ingredient preparations used in cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Instenon; ***Rus.***: Instenon (Инстенон); ***Ukr.***: Instenon (Инстенон).

Hirudin

Hirudiini; Hirudina; Hirudine; Hirudyna; Гирудин.

Profile

Hirudin is a 65-amino-acid protein that is a direct inhibitor of thrombin (see Lepirudin, p. 1418.2). It has been extracted from leeches (p. 1418.1) and this form is used in various topical preparations for peripheral vascular disorders. Recombinant hirudins, such as desirudin (p. 1351.1) and lepirudin (p. 1418.2) and analogues of hirudin, such as bivalirudin (p. 1326.2), are used as anticoagulants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Exhirud†; ***Fr.***: Hirucreme.

Hydralazine Hydrochloride

(BANM, rINNM)

Apressinum; Hidralazina, hidrocloruro de; Hidralazinhidroklorid; Hidralazino hidrochloridas; Hidrocloruro de hidralazina; Hydralatsiinihydrokloridi; Hydralazin hydrochlorid; Hydralazin Hydrochloridum; Hydralazine, chlorhydrate d'; Hydralazinhydrochlorid; Hydralazinhydroklorid; Hydralazini hydrochloridum; Hydrallazine Hydrochloride; Idralazina; Гидралазина Гидрохлорид.
1-Hydrazinophthalazine hydrochloride.
$C_8H_8N_4$,HCl=196.6
CAS — 86-54-4 (hydralazine); 304-20-1 (hydralazine hydrochloride).
ATC — C02DB02.
ATC Vet — QC02DB02.
UNII — FD171B778Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Hydralazine Hydrochloride). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 3.5 to 4.2. Protect from light.

USP 36: (Hydralazine Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 500 of alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 3.5 to 4.2. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Discoloration of hydralazine injection was seen on several occasions after storage in a syringe for up to 12 hours.[1] Hydralazine reacts with metals and therefore the injection should be prepared using a nonmetallic filter and should be used as quickly as possible after being drawn through a needle into a syringe.

A study of the rate of degradation of hydralazine hydrochloride, 1 mg/mL in sweetened, aqueous oral liquids showed that glucose, fructose, lactose, and maltose reduced the stability of the drug.[2] In solutions containing mannitol or sorbitol, there was less than 10% degradation of hydralazine after 3 weeks. UK licensed product information states that contact with glucose causes hydralazine to be rapidly broken down and that hydralazine injection is therefore not compatible with glucose solutions.

1. Enderlin G. Discoloration of hydralazine injection. *Am J Hosp Pharm* 1984; **41:** 634.
2. Das Gupta V, *et al.* Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986; **11:** 215–23.

Uses and Administration

Hydralazine is a direct-acting vasodilator that acts mainly on the arterioles. It reduces blood pressure and peripheral resistance but produces fluid retention. Tachycardia and an increase in cardiac output occur mainly as a reflex response to the reduction in peripheral resistance. Hydralazine tends to improve renal and cerebral blood flow and its effect on diastolic pressure is more marked than on systolic pressure.

Hydralazine hydrochloride is given orally for the treatment of hypertension (p. 1251.1), usually with a beta blocker and a thiazide diuretic. In addition to an additive antihypertensive effect, this combination reduces the reflex tachycardia and fluid retention caused by hydralazine. Hydralazine may be given intravenously in hypertensive crises. It is also used with isosorbide dinitrate in the management of heart failure (but see Precautions, p. 1402.3). For further discussion of this use of hydralazine, see below.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment.

In **hypertension**, the usual initial oral dose of hydralazine hydrochloride is 40 to 50 mg daily in divided doses, increased according to response. In the UK it is recommended that the dose should not be increased above 100 mg daily without checking acetylator status, although the recommended maximum dose for hypertension is 200 mg daily; doses above 100 mg daily are associated with an increased incidence of lupus erythematosus, particularly in women and in slow acetylators.

In hypertensive crises, hydralazine hydrochloride is given by intravenous or intramuscular injection. In the UK, a dose of 5 to 10 mg is given by slow intravenous injection, repeated if necessary after 20 to 30 minutes. Alternatively, a continuous intravenous infusion is given in an initial dose of 200 to 300 micrograms/minute; the usual maintenance dose range is 50 to 150 micrograms/minute. In the USA, higher doses are used; a dose of 20 to 40 mg is given by rapid intravenous or intramuscular injection, repeated as necessary.

For chronic **heart failure**, hydralazine hydrochloride is given (with a nitrate) in a usual initial oral dose of 25 mg 3 or 4 times daily, increased to a usual maintenance dose of 50 to 75 mg 4 times daily. Lower doses and slower titration may be necessary if adverse effects occur. In self-identified black patients, hydralazine may also be given as an oral combination preparation with isosorbide dinitrate; the dose is 37.5 mg of hydralazine hydrochloride with 20 mg of isosorbide dinitrate three times daily, and may be doubled if necessary.

Administration in children. Hydralazine hydrochloride has been used for hypertension in children. The usual oral dose is 750 micrograms/kg daily initially in four divided doses, increased gradually over 3 to 4 weeks to a maximum of 7.5 mg/kg or 200 mg daily. An intravenous or intramuscular dose of 1.7 to 3.5 mg/kg daily is given in 4 to 6 divided doses.

In the UK, the *BNFC* suggests that hydralazine hydrochloride may be given to neonates and children in the treatment of hypertension in the following doses:

- orally: 250 to 500 micrograms/kg every 8 to 12 hours, increased if necessary to a maximum of 2 to 3 mg/kg every 8 hours (neonates) or 7.5 mg/kg (maximum 200 mg) daily (those aged 1 month and over). Those aged 12 years and over may be given the usual adult dose (see above)
- slow intravenous injection: 100 to 500 micrograms/kg, repeated every 4 to 6 hours as necessary (maximum 3 mg/kg or 60 mg daily). Those aged 12 years and over may be given 5 to 10 mg, repeated every 4 to 6 hours as necessary
- continuous intravenous infusion (the preferred route in cardiac patients): 12.5 to 50 micrograms/kg per hour, to a maximum of 2 mg/kg daily (neonates) or 3 mg/kg daily (1 month to 12 years). Those aged 12 years and over may be given 3 to 9 mg/hour (maximum 3 mg/kg daily)

Heart failure. Hydralazine with isosorbide dinitrate may have a role[1] in the management of patients with heart failure (p. 1262.3) who remain symptomatic despite standard therapy or in whom standard therapy is contra-indicated or not tolerated. Although a meta-analysis of studies[2] of vasodilator therapy for heart failure failed to show a benefit in terms of improved functional status or reduced mortality in patients given hydralazine alone, there is evidence from the Veterans Administration Cooperative Study[3] of reduced mortality from the use of hydralazine with nitrates. This has been confirmed in a second study (V-HeFTII),[4] although hydralazine with isosorbide dinitrate was less effective than enalapril. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[5] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality.

Hydralazine has also been tried in children with heart failure,[6,7] but experience is limited.

1. Thadani U, Jacob RG. Isosorbide dinitrate/hydralazine: its role in the treatment of heart failure. *Drugs Today* 2008; **44:** 925–37.
2. Mulrow CD, *et al.* Relative efficacy of vasodilator therapy in chronic congestive heart failure: implications of randomized trials. *JAMA* 1988; **259:** 3422–6.
3. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study. *N Engl J Med* 1986; **314:** 1547–52.
4. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325:** 303–10.
5. Taylor AL, *et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57. Correction. *ibid.* 2005; **352:** 1276.

6. Artman M, *et al.* Hemodynamic effects of hydralazine in infants with idiopathic dilated cardiomyopathy and congestive heart failure. *Am Heart J* 1987; **113:** 144–50.
7. Rao PS, Andaya WG. Chronic afterload reduction in infants and children with primary myocardial disease. *J Pediatr* 1986; **108:** 530–4.

Adverse Effects

Adverse effects are common with hydralazine, particularly tachycardia, palpitations, angina pectoris, severe headache, and gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhoea. These adverse effects, and flushing, dizziness, and nasal congestion, which occur less often, may be seen at the start of treatment, especially if the dose is increased quickly. They generally subside with continued treatment. Other less common adverse effects include orthostatic hypotension, fluid retention with oedema and weight gain, conjunctivitis, lachrymation, tremor, and muscle cramps.

Hydralazine may deplete pyridoxine in the body, and can produce peripheral neuropathy with numbness and tingling of the extremities. Occasionally, hepatotoxicity, blood dyscrasias, haemolytic anaemia, difficulty in urinating, glomerulonephritis, constipation, paralytic ileus, depression, and anxiety occur.

Hypersensitivity reactions including fever, chills, pruritus, and rashes have been reported, and eosinophilia may occur.

Antinuclear antibodies may develop after prolonged use of large doses, and a condition resembling SLE may occur. The incidence is greater in slow acetylators, patients with renal impairment, women, and patients taking more than 100 mg of hydralazine daily. The symptoms usually disappear when the drug is withdrawn; some patients may require treatment with corticosteroids.

Acute overdosage may produce hypotension, tachycardia, myocardial ischaemia, arrhythmias, shock, and coma.

Carcinogenicity. Although earlier reports suggested that hydralazine might be carcinogenic, there was no evidence from a survey of 1978 patients with lung or colorectal cancer and 6807 controls that there was an increased risk of these neoplasms.[1]

1. Kaufman DW, *et al.* Hydralazine use in relation to cancers of the lung, colon, and rectum. *Eur J Clin Pharmacol* 1989; **36:** 259–64.

Effects on the blood. Three cases of thrombocytopenia were reported[1] in neonates whose mothers had been treated with hydralazine for some months before delivery. The thrombocytopenia and bleeding was transient with full recovery occurring within a few weeks. No adverse effects were noticed in the mothers.

1. Widerlöv E, *et al.* Hydralazine-induced neonatal thrombocytopenia. *N Engl J Med* 1980; **303:** 1235.

Effects on the cardiovascular system. Paradoxical severe hypertension developed after oral or intramuscular hydralazine on 3 occasions in a patient with renal artery stenosis.[1]

1. Webb DB, White JP. Hypertension after taking hydrallazine. *BMJ* 1980; **280:** 1582.

Effects on the kidneys. Rapidly progressive glomerulonephritis with focal and segmental lesions, usually accompanied by necrosis and crescent formation, has been reported in patients given hydralazine.[1-4] The condition is reported to be associated with the presence of antinuclear antibodies[3] and slow acetylator status,[2] factors associated with the development of hydralazine-induced lupus erythematosus.[5] However, renal involvement is much less common in drug-induced lupus,[5] and in a report of 15 such cases men and women and fast and slow acetylators were equally affected;[3] in addition the criteria for SLE were not usually fulfilled in these patients and it was suggested that the condition should be distinguished from lupus nephritis. A report[6] commented that glomerulonephritis represents an ANCA-positive hydralazine-induced vasculitis, and that patients with such symptoms typically have a more severe course than those with hydralazine-induced lupus, and require more aggressive treatment. Immediate withdrawal of hydralazine generally results in some improvement in renal function but complete recovery is uncommon; severe cases may require immunosuppressive therapy.[3]

1. Björck S, *et al.* Rapidly progressive glomerulonephritis after hydralazine. *Lancet* 1983; **ii:** 42.
2. Kincaid-Smith P, Whitworth JA. Hydralazine-associated glomerulonephritis. *Lancet* 1983; **ii:** 348.
3. Björck S, *et al.* Hydralazine-induced glomerulonephritis. *Lancet* 1985; **i:** 392.
4. Dobre M, *et al.* Hydralazine-induced ANCA-positive pauci-immune glomerulonephritis: a case report and literature review. *Ren Fail* 2009; **31:** 745–8.
5. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.
6. Yokogawa N, Vivino FB. Hydralazine-induced autoimmune disease: comparison to idiopathic lupus and ANCA-positive vasculitis. *Mod Rheumatol* 2009; **19:** 338–47.

Effects on the skin. Pruritus and rashes have been reported with hydralazine use.

A 59-year-old woman who had been taking hydralazine 25 mg three times daily for 6 months developed symptoms of Sweet's syndrome (erythematous plaques and nodules and haemorrhagic blisters).[1] Symptoms began to subside on withdrawal of the drug but recurred on rechallenge. The condition resolved when hydralazine was stopped and prednisolone given.

1. Gilmour E, *et al.* Drug-induced Sweet's syndrome (acute febrile neutrophilic dermatosis) associated with hydralazine. *Br J Dermatol* 1995; **133:** 490–1.

Lupus erythematosus. Lupus erythematosus is a well-documented adverse effect of hydralazine. Onset is typically delayed from 1 month to 5 years from the start of treatment, and the most common symptoms are arthralgia or arthritis, usually non-deforming, in up to 95% of patients, fever and myalgia in about 50%, and pleuropulmonary involvement, manifesting as pleurisy, pleural effusions, or pulmonary infiltrates in up to 30%.[1-4] Renal involvement is reported to be less common than in idiopathic SLE and there is some uncertainty as to whether the glomerulonephritis sometimes seen in patients receiving hydralazine should be considered lupus nephritis (see Effects on the Kidneys, above). Nonetheless, a 20% incidence of renal involvement has been reported.[1] Other complications and symptoms associated with lupus erythematosus in patients taking hydralazine include cutaneous vasculitis,[5-7] orogenital and cutaneous ulceration,[8] bilateral retinal vasculitis,[9] reactive hypoglycaemia (although the attribution is uncertain),[10] life-threatening cardiac tamponade,[11] and hoarseness and stridor secondary to vocal cord palsy, which progressed to respiratory arrest.[12] Rashes are reported to be less prominent than with the idiopathic form of the disease.[1] Fatalities have occurred,[13,14] but appear to be rare. A lupus-like syndrome was also reported[15] in a neonate whose mother was given hydralazine during pregnancy.

Estimates of the overall incidence of hydralazine-associated lupus erythematosus vary from about 1.2 to 5% or more.[16-19] The syndrome appears to occur only in patients who develop antinuclear antibodies while receiving hydralazine, but the incidence of positive antinuclear antibody tests is much higher than that of lupus, at up to 60%, so the presence of antinuclear antibodies alone is not diagnostic.[18] There is a strong relationship with drug dose,[17,19] acetylator status,[16,18,19] and patient gender,[19] the syndrome being more common in slow acetylators and women, and in patients receiving 100 mg daily or more.

Although it has been reported that hydralazine-associated lupus was more frequent in patients with the HLA-DR4 antigen[20] this was not confirmed by others[21] and subsequent work has suggested that the association is rather with the non-expressing or null forms of the adjacent complement C4 gene.[22] Hydralazine can inactivate complement C4 *in vitro*[23] and might exacerbate complement deficiency (which is known to be associated with idiopathic SLE) in patients with an already low level of C4 due to a null allele.[22]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.
2. Cohen MG, Prowse MV. Drug-induced rheumatic syndromes: diagnosis, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 199–218.
3. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; **12:** 283–90.
4. Finks SW, *et al.* Hydralazine-induced lupus: maintaining vigilance with increased use in patients with heart failure. *South Med J* 2006; **99:** 18–22.
5. Bernstein RM, *et al.* Hydrallazine-induced cutaneous vasculitis. *BMJ* 1980; **280:** 156–7.
6. Peacock A, Weatherall D. Hydralazine-induced necrotising vasculitis. *BMJ* 1981; **282:** 1121–2.
7. Finlay AY, *et al.* Hydrallazine-induced necrotising vasculitis. *BMJ* 1981; **282:** 1703–4.
8. Neville E, *et al.* Orogenital ulcers, SLE and hydrallazine. *Postgrad Med J* 1981; **57:** 378–9.
9. Doherty M, *et al.* Hydralazine induced lupus syndrome with eye disease. *BMJ* 1985; **290:** 675.
10. Blackshear PJ, *et al.* Reactive hypoglycaemia and insulin autoantibodies in drug-induced lupus erythematosus. *Ann Intern Med* 1983; **99:** 182–4.
11. Anandadas JA, Simpson P. Cardiac tamponade, associated with hydralazine therapy, in a patient with rapid acetylator status. *Br J Clin Pract* 1986; **40:** 305–6.
12. Chong WK, *et al.* Acute laryngeal stridor with respiratory arrest in drug induced systemic lupus erythematosus. *BMJ* 1988; **297:** 660–1.
13. Sturman SG, *et al.* Fatal hydralazine-induced systemic lupus erythematosus. *Lancet* 1988; **ii:** 1304.
14. Birnbaum B, *et al.* Fulminating hydralazine-induced lupus pneumonitis. *Arthritis Rheum* 2006; **55:** 501–6.
15. Yemini M, *et al.* Lupus-like syndrome in a mother and newborn following administration of hydralazine; a case report. *Eur J Obstet Gynecol Reprod Biol* 1989; **30:** 193–7.
16. Bing RF, *et al.* Hydrallazine in hypertension: is there a safe dose? *BMJ* 1980; **281:** 353–4.
17. Freestone S, *et al.* Incidence of hydrallazine-associated autoimmune disease. *Br J Clin Pharmacol* 1982; **13:** 291P–292P.
18. Mansilla-Tinoco R, *et al.* Hydralazine, antinuclear antibodies, and the lupus syndrome. *BMJ* 1982; **284:** 936–9.
19. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *BMJ* 1984; **289:** 410–12.
20. Batchelor JR, *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; **i:** 1107–9.
21. Brand C, *et al.* Hydralazine-induced lupus: no association with HLA-DR4. *Lancet* 1984; **i:** 462.
22. Speirs C, *et al.* Complement system protein C4 and susceptibility to hydralazine-induced systemic lupus erythematosus. *Lancet* 1989; **i:** 922–4.
23. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; **ii:** 422–4.

Treatment of Adverse Effects

Withdrawal of hydralazine or dosage reduction reverses many of the adverse effects. Peripheral neuropathy has been reported to be alleviated by pyridoxine.

If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour of ingestion. Symptomatic and supportive treatment, including plasma expanders for shock and a beta blocker for tachycardia, should be given as necessary. Hypotension may respond to placing the patient in the supine position with the feet raised. If possible, pressor drugs should be avoided. If a pressor is necessary, one should be chosen that will not cause tachycardia or exacerbate arrhythmias; adrenaline should not be used.

Precautions

Hydralazine is contra-indicated in patients with severe tachycardia, dissecting aortic aneurysm, heart failure with high cardiac output, cor pulmonale, or myocardial insufficiency due to mechanical obstruction, for example aortic or mitral stenosis or constrictive pericarditis. Hydralazine is also contra-indicated in patients with idiopathic SLE and related disorders.

Hydralazine-induced vasodilatation produces myocardial stimulation. It should therefore be used with caution in patients with ischaemic heart disease since it can increase angina and it should not be given after myocardial infarction until the patient's condition has stabilised. Patients with suspected or confirmed ischaemic heart disease should be given hydralazine under cover of a beta blocker, which should be started a few days before hydralazine, in order to prevent myocardial stimulation. If given to patients with heart failure they should be monitored for orthostatic hypotension and tachycardia during the initial stages of therapy, preferably in hospital. If treatment with hydralazine is to be stopped in patients with heart failure it should generally be withdrawn gradually. Hydralazine should be used with caution in patients with cerebrovascular disorders.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment. Complete blood counts and antinuclear antibody determinations should be carried out about every 6 months during long-term therapy. Urine analysis (for microhaematuria and proteinuria) is also recommended.

Hydralazine is teratogenic in some species of *animals* and UK licensed product information recommends that hydralazine be avoided during the first two trimesters of pregnancy.

Patients may have impaired reactions, especially at the start of therapy, and should not drive or operate machinery if affected.

Breast feeding. Hydralazine is distributed into breast milk in small amounts (see under Pharmacokinetics, p. 1403.2) but no adverse effects have been seen in infants and the American Academy of Pediatrics therefore considers[1] hydralazine to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydralazine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. For reports of thrombocytopenia and a lupus-like syndrome occurring in neonates after maternal treatment with hydralazine during pregnancy, see Effects on the Blood and Lupus Erythematosus respectively, under Adverse Effects, above.

Interactions

The hypotensive effect of hydralazine may be enhanced by other drugs with a hypotensive action. Severe hypotension may occur if hydralazine and diazoxide are given together. However, some interactions with antihypertensives may be beneficial: thiazide diuretics also counteract the fluid

retention caused by hydralazine, and beta blockers diminish the cardiac-accelerating effects.

Indometacin. A study[1] in 9 healthy subjects found that indometacin 100 mg daily did not lessen the hypotensive effect of hydralazine. However, another study[2] showed that indometacin 200 mg daily, while having no effect on heart rate, renal or limb blood flow, or plasma-catecholamine concentration, did reduce the hypotensive effect of hydralazine.

1. Jackson SHD, Pickles H. Indomethacin does not attenuate the effects of hydralazine in normal subjects. *Eur J Clin Pharmacol* 1983; **25:** 303–5.
2. Cinquegrani MP, Liang C. Indomethacin attenuates the hypotensive action of hydralazine. *Clin Pharmacol Ther* 1986; **39:** 564–70.

Pharmacokinetics

Hydralazine given orally is rapidly absorbed from the gastrointestinal tract but undergoes considerable first-pass metabolism by acetylation in the gastrointestinal mucosa and liver. The rate of metabolism is genetically determined and depends upon the acetylator status of the individual. The bioavailability of hydralazine has been reported to be about 35% in slow acetylators and less in fast acetylators; thus plasma concentrations after a given dose are higher in slow acetylators. Peak plasma concentrations have been reported to occur after about one hour.

Hydralazine is chiefly present in plasma as a hydrazone conjugate with pyruvic acid. Plasma protein binding is about 90%. The drug is widely distributed, notably into arterial walls.

Systemic metabolism in the liver is by hydroxylation of the ring system and conjugation with glucuronic acid; most sources suggest that *N*-acetylation is not of major importance in systemic clearance and that therefore acetylator status does not affect elimination. Hydralazine is excreted mainly in urine as metabolites.

The apparent average half-life for hydralazine has been reported to vary from about 45 minutes to about 8 hours, with several sources giving the average as about 2 to 4 hours. Some of the variation may be due to problems with the analytical procedures—see below. The half-life is prolonged in renal impairment and may be up to 16 hours in patients with a creatinine clearance of less than 20 mL/minute.

Hydralazine crosses the placenta and is distributed into breast milk.

Attempts to describe the pharmacokinetics of hydralazine have been complicated by the instability of the drug itself in plasma and in alkaline solutions, and the instability of its circulating metabolites during analysis. This has meant that many techniques for the measurement of hydralazine have proved non-selective and yield overestimates of unchanged drug.[1] Studies using less selective methods have yielded an apparent bioavailability for oral hydralazine of 38 to 69% in slow acetylators and 22 to 32% in fast acetylators; in contrast, more selective assays have yielded values of 31 to 35% and 10 to 16% for slow and rapid acetylators respectively. Similarly, hydralazine plasma clearance is lower and the half-life longer when based upon the results of non-selective assay procedures; mean elimination half-life has ranged from 2.2 to 3.6 hours based upon these methods compared with 0.67 to 0.96 hours using a more selective assay. Improved pharmacokinetic data have indicated that while the first-pass effect is dependent upon acetylator phenotype, systemic clearance is only minimally dependent upon acetylation. The formation of the pyruvic acid hydrazone, which is without significant vasodilator activity, contributes to extrahepatic phenotype-independent clearance.

Although some workers have correlated the hypotensive effect of hydralazine with concentrations,[2] others have been unable to do so.[3] Moreover, the duration of hypotensive effect has been shown to exceed considerably that predicted from the rate of elimination.[4,5] Possible explanations are the accumulation of hydralazine at its sites of action in the arterial walls[6] or the existence of active metabolites.[7-9]

Concurrent intake of food has been found to enhance considerably the bioavailability of hydralazine[10] but food-related reductions in plasma-hydralazine concentrations with reduced vasodilator effect have also been reported.[11] The discrepancy was thought to be due to the greater specificity of the assay used in the latter study and to differences in the timing of food and hydralazine administration in the two studies.[12,13]

1. Ludden TM, *et al.* Clinical pharmacokinetics of hydralazine. *Clin Pharmacokinet* 1982; **7:** 185–205.
2. Zacest R, Koch-Weser J. Relation of hydralazine plasma concentration to dosage and hypotensive action. *Clin Pharmacol Ther* 1972; **13:** 420–5.
3. Talseth T, *et al.* Hydralazine slow-release: observations on serum profile and clinical efficacy in man. *Curr Ther Res* 1977; **21:** 157–68.
4. O'Malley K, *et al.* Duration of hydralazine action in hypertension. *Clin Pharmacol Ther* 1975; **18:** 581–6.
5. Shepherd AMM, *et al.* Hydralazine kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1980; **28:** 804–11.
6. Moore-Jones D, Perry HM. Radioautographic localization of hydralazine-1-C_{14} in arterial walls. *Proc Soc Exp Biol Med* 1966; **122:** 576–9.
7. Barron K, *et al.* Comparative evaluation of the in vitro effects of hydralazine and hydralazine acetonide on arterial smooth muscle. *Br J Pharmacol* 1977; **61:** 345–9.
8. Haegele KD, *et al.* Identification of hydrallazine and hydrallazine hydrazone metabolites in human body fluids and quantitative in vitro comparisons of their smooth muscle relaxant activity. *Br J Clin Pharmacol* 1978; **5:** 489–94.
9. Reece PA, *et al.* Interference in assays for hydralazine in humans by a major plasma metabolite, hydralazine pyruvic acid hydrazone. *J Pharm Sci* 1978; **67:** 1150–3.
10. Melander A, *et al.* Enhancement of hydralazine bioavailability by food. *Clin Pharmacol Ther* 1977; **22:** 104–7.
11. Shepherd AMM, *et al.* Effect of food on blood hydralazine levels and response in hypertension. *Clin Pharmacol Ther* 1984; **36:** 14–18.
12. Melander A, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; **38:** 475.
13. Shepherd AMM, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; **38:** 475–6.

Pregnancy and breast feeding. Hydralazine concentrations were found to be similar in maternal and umbilical-cord blood in a study of 6 women being treated with hydralazine for pronounced hypertension during pregnancy.[1] Hydralazine was determined in the breast milk of 1 mother, but amounts detected were unlikely to produce clinically relevant concentrations in the infant.

1. Liedholm H, *et al.* Transplacental passage and breast milk concentrations of hydralazine. *Eur J Clin Pharmacol* 1982; **21:** 417–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hidral; Hydrapres; ***Austral.***: Alphapress; Apresoline; ***Braz.***: Apresolina; Nepresol; ***Canad.***: Apresoline; Novo-Hylazin†; Nu-Hydral; ***Hong Kong***: Alphapress†; ***Irl.***: Apresoline; ***Mex.***: Apresolina; Bionobal; ***Norw.***: Apresolin; ***NZ***: Apresoline; ***Philipp.***: Apresoline; Aprezin; ***S. Afr.***: Apresoline†; Hyperphen; ***Singapore***: Apresoline; ***Spain***: Hydrapres; ***Swed.***: Apresolin; ***Thai.***: Apresoline; Cesoline; ***UK***: Apresoline; ***USA***: Apresoline†.

Multi-ingredient Preparations. ***Austria***: Polinorm†; Triloc†; ***Ger.***: Pertenso N; TRI-Normin; ***India***: Corbetazine; ***Indon.***: Ser-Ap-Es; ***Spain***: Neatenol Diuvas†; ***Thai.***: Hydrares; Mano-Ap-Es; Reser; Ser-Ap-Es†; ***USA***: BiDil; Hydra-zide; Marpres.

Pharmacopoeial Preparations
BP 2014: Hydralazine Injection; Hydralazine Tablets;
USP 36: Hydralazine Hydrochloride Injection; Hydralazine Hydrochloride Oral Solution; Hydralazine Hydrochloride Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Hydrochlorothiazide (BAN, rINN) ⊗

Hidrochlorotiazidas; Hidroclorotiazida; Hidroklorotiazid; Hydrochlorothiazid; Hydrochlorothiazidum; Hydrochlorotiazyd; Hydroklooritiatsidi; Hydroklortiazid; Гидрохлоротиазид.

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_7H_8ClN_3O_4S_2$=297.7

CAS — 58-93-5.

ATC — C03AA03.

ATC Vet — QC03AA03.

UNII — 0J48LPH2TH.

NOTE. Compounded preparations of hydrochlorothiazide may be represented by the following names:

- Co-amilozide (*BAN*)—hydrochlorothiazide 10 parts and amiloride hydrochloride 1 part (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide
- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide
- Co-zidocapt (*BAN*)—hydrochlorothiazide 1 part and captopril 2 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Hydrochlorothiazide). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Hydrochlorothiazide). A white or practically white, practically odourless crystalline powder. Very slightly soluble in water; insoluble in chloroform, in ether, and in dilute mineral acids; freely soluble in dimethylformamide, in *n*-butylamine, and in sodium hydroxide solution; sparingly soluble in methyl alcohol.

Uses and Administration

Hydrochlorothiazide and the other thiazide diuretics are used in the treatment of hypertension (p. 1251.1), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. They are also used to treat oedema associated with heart failure (p. 1262.3) and with renal and hepatic disorders. Other indications have included the treatment of oedema accompanying the premenstrual syndrome (p. 2272.3), the prevention of water retention associated with corticosteroids and oestrogens, the treatment of diabetes insipidus (p. 1404.1), and the prevention of renal calculus formation in patients with hypercalciuria (p. 1404.1).

Thiazides are moderately potent diuretics and exert their diuretic effect by reducing the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. They act mainly at the beginning of the distal tubules. The excretion of other electrolytes, notably potassium and magnesium, is also increased. The excretion of calcium is reduced. They also reduce carbonic-anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. They may also reduce the glomerular filtration rate.

Their hypotensive effect is probably partly due to a reduction in peripheral resistance; they also enhance the effects of other antihypertensives. Paradoxically, thiazides have an antidiuretic effect in patients with diabetes insipidus.

Administration and dosage. Thiazides are usually given in the morning so that sleep is not interrupted by diuresis. Diuresis starts in about 2 hours after oral doses of hydrochlorothiazide, reaches a peak in about 4 hours, and lasts for 6 to 12 hours.

The dosage of thiazides should be adjusted to the minimum effective dose. In general lower doses are required for the treatment of hypertension than for oedema, although the maximum therapeutic effect may not be seen for several weeks.

They may be given to patients with mild renal impairment, but thiazides are generally not effective at a creatinine clearance of less than 30 mL/minute.

Hydrochlorothiazide is given orally.

In the treatment of **hypertension** an initial dose of 12.5 mg may be sufficient, increasing to 25 to 50 mg daily if necessary, either alone or with other antihypertensives. Doses of up to 100 mg have been suggested but are rarely necessary.

In the treatment of **oedema** the usual dose is 25 to 100 mg daily, reduced to a dose of 25 to 50 mg daily or intermittently; in severe cases initial doses of up to 200 mg daily have been suggested, but the more powerful loop diuretics (see Furosemide, p. 1387.1) are preferred in such patients.

In the treatment of nephrogenic **diabetes insipidus** an initial dose of up to 100 mg daily may be used.

For doses in children, see below.

For discussion of potassium supplementation in patients taking thiazide diuretics see Effects on Electrolyte Balance, under Adverse Effects, p. 1404.2.

General references.

1. Ellison DH, Loffing J. Thiazide effects and adverse effects: insights from molecular genetics. *Hypertension* 2009; **54:** 196–202.
2. Moser M, Feig PU. Fifty years of thiazide diuretic therapy for hypertension. *Arch Intern Med* 2009; **169:** 1851–6.
3. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med* 2009; **361:** 2153–64.
4. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. *Cardiol Rev* 2010; **18:** 51–6.

Administration in children. Hydrochlorothiazide has been given to infants and children for the treatment of hypertension or oedema in an oral dose of 1 to 2 mg/kg daily in single or 2 divided doses. Infants aged under 6 months may need up to 3 mg/kg daily in 2 divided doses. The total daily dose should not exceed 37.5 mg in those aged under 2 years, or 100 mg in those aged from 2 to 12 years.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p. 1602.1) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p. 1387.3); results with hydrochlorothiazide or spironolactone have been more ambiguous. No beneficial effects on lung function or oxygenation were found in a study of 12 infants after 1 week of treatment with hydrochlorothiazide and spironolactone.[1] However, hydrochlorothiazide and spironolactone therapy was found to improve total respiratory system compliance with decreased lung damage and increased survival rate in 34 premature infants with bronchopulmonary dysplasia after 8 weeks of therapy.[2] In the latter study furosemide was also given if clinically indicated.

1. Engelhardt B, *et al.* Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1989; **114:** 619–24.
2. Albersheim SG, *et al.* Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989; **115:** 615–20.

Diabetes insipidus. Thiazide diuretics are used in nephrogenic diabetes insipidus (p. 2348.2), sometimes with potassium-sparing diuretics. For instance, hydrochlorothiazide with amiloride was effective in controlling nephrogenic diabetes insipidus in 5 boys and compared favourably with treatment with hydrochlorothiazide and indometacin.[1] Treatment was well tolerated in 4 patients. Abdominal pain and anorexia necessitated withdrawal of amiloride in the fifth patient after 6 months. The use of hydrochlorothiazide with amiloride avoided the need for potassium supplements, which were required with hydrochlorothiazide and indometacin. The use of hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; **117:** 499–502.
2. Kirchlechner V, *et al*. Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; **80:** 548–52.

Hypoparathyroidism. In hypoparathyroidism (p. 1171.2), treatment is usually with oral vitamin D compounds to correct the hypocalcaemia. Thiazides may be useful in some patients. Beneficial effects on serum-calcium concentrations in patients with hypoparathyroidism have been reported after chlortalidone plus dietary salt restriction,[1] and with bendroflumethiazide.[2] However, chlortalidone has not been found to be effective in all patients,[3] and the reduction in urinary calcium excretion by thiazides has been shown to be diminished in patients with hypoparathyroidism,[4] suggesting that this effect may be dependent on the presence of active parathyroid hormone. Care should be taken when giving diuretics to hypoparathyroid patients with co-existing adrenal insufficiency[3] or metabolic alkalosis.[5]

1. Porter RH, *et al*. Treatment of hypoparathyroid patients with chlorthalidone. *N Engl J Med* 1978; **298:** 577–81.
2. Newman GH, *et al*. Effect of bendrofluazide on calcium reabsorption in hypoparathyroidism. *Eur J Clin Pharmacol* 1984; **27:** 41–6.
3. Gertner JM, Genel M. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **298:** 1478.
4. Middler S, *et al*. Thiazide diuretics and calcium metabolism. *Metabolism* 1973; **22:** 139–45.
5. Barzel US. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **289:** 1478.

Ménière's disease. In Ménière's disease (p. 611.2) there is an excess of endolymph fluid in the ear and diuretics such as hydrochlorothiazide have been used in attempts to relieve symptoms by reducing the amount of fluid.

Osteoporosis. Although some epidemiological studies have indicated beneficial effects of thiazides on bone (reduced rates of bone loss[1] and a reduced risk of hip fracture[2-5]) a comprehensive analysis involving 9704 women over the age of 65 years[6] showed only a small effect on bone mass, no effect on the risk for falls, and no overall protective effect against fractures. A further prospective study[7] reported a reduction in forearm fracture, but hip fracture was only reduced in postmenopausal women. Randomised, controlled studies[8,9] have confirmed that hydrochlorothiazide reduces bone loss, but again the effects were small. Thus, thiazides have no established role in the prevention or treatment of osteoporosis (p. 1168.1). They might, however, be useful to reduce hypercalciuria in patients taking glucocorticoids[10] but serum-potassium concentrations should be monitored closely.

1. Wasnich R, *et al*. Effect of thiazide on rates of bone mineral loss: a longitudinal study. *BMJ* 1990; **301:** 1303–5. Correction. *ibid*. 1991; **302:** 218.
2. Ray WA, *et al*. Long-term use of thiazide diuretics and risk of hip fracture. *Lancet* 1989; **i:** 687–90.
3. LaCroix AZ, *et al*. Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med* 1990; **322:** 286–90.
4. Felson DT, *et al*. Thiazide diuretics and the risk of hip fracture: results from the Framingham Study. *JAMA* 1991; **265:** 370–3.
5. Schoofs MWCJ, *et al*. Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003; **139:** 476–82.
6. Cauley JA, *et al*. Effects of thiazide diuretic therapy on bone mass, fractures, and falls. *Ann Intern Med* 1993; **118:** 666–73.
7. Feskanich D, *et al*. A prospective study of thiazide use and fractures in women. *Osteoporosis Int* 1997; **7:** 79–84.
8. Reid IR, *et al*. Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. *Am J Med* 2000; **109:** 362–70.
9. LaCroix AZ, *et al*. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133:** 516–26.
10. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; **112:** 352–64.

Renal calculi. A thiazide diuretic may be given to prevent the recurrence of calcium-containing renal calculi (p. 2350.3) in patients with hypercalciuria.[1,2]

1. Pearle MS, *et al*. Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; **13:** 679–85.
2. Tiselius H-G, *et al*. European Association of Urology. Guidelines on urolithiasis (issued March 2008). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2008/Full/17%20Urolithiasis.pdf (accessed 24/07/08)

Adverse Effects

Hydrochlorothiazide and other thiazide diuretics may cause metabolic disturbances especially at high doses. They may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. They may cause hyperuricaemia and precipitate attacks of gout in some patients. Thiazide diuretics may be associated with electrolyte imbalances including hypochloraemic alkalosis, hyponatraemia, and hypokalaemia. Hypokalaemia intensifies the effect of digitalis on cardiac muscle and treatment with digitalis or its glycosides may have to be temporarily suspended. Patients with cirrhosis of the liver are particularly at risk from hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses used with restricted salt in the diet. The urinary excretion of calcium is reduced. Hypomagnesaemia has also occurred. Adverse changes in plasma lipids have also been noted but their clinical significance is unclear.

Signs of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps, seizures, oliguria, hypotension, and gastrointestinal disturbances.

Other adverse effects include anorexia, gastric irritation, nausea, vomiting, constipation, diarrhoea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paraesthesia, impotence, and yellow vision. Hypersensitivity reactions include rashes, fever, pulmonary oedema, pneumonitis, anaphylaxis, and toxic epidermal necrolysis. Cholestatic jaundice, pancreatitis, and blood dyscrasias including thrombocytopenia and, more rarely, granulocytopenia, leucopenia, and aplastic and haemolytic anaemia have been reported.

Intestinal ulceration has occurred after the use of tablets containing thiazides with an enteric-coated core of potassium chloride (see also under Potassium, p. 1796.3).

Carcinogenicity. Several studies have suggested that long-term diuretic therapy may be associated with the development of cancer. A meta-analysis[1] of 9 case control studies and 3 cohort studies found an increased risk of renal cell carcinoma in patients receiving diuretics, and a further retrospective study[2] found that the risk of colon cancer was also increased. While the risk is probably not significant in most patients, it was suggested[1,2] that it should be taken into consideration when choosing long-term therapy for younger patients.

1. Grossman E, *et al*. Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol* 1999; **83:** 1090–3.
2. Tenenbaum A, *et al*. Is diuretic therapy associated with an increased risk of colon cancer? *Am J Med* 2001; **110:** 143–5.

Effects on the blood. There have been case reports of intravascular immune haemolysis in patients taking hydrochlorothiazide and methyldopa.[1-3] In each of these 3 cases the hydrochlorothiazide was identified as the probable cause of haemolysis on serological data, although methyldopa could have been a contributory factor. One of these patients died[3] during the haemolytic episode although post-mortem examination failed to reveal a cause of death.

1. Vila JM, *et al*. Thiazide-induced immune hemolytic anemia. *JAMA* 1976; **236:** 1723–4.
2. Garratty G, *et al*. Acute immune intravascular hemolysis due to hydrochlorothiazide. *Am J Clin Pathol* 1981; **76:** 73–8.
3. Beck ML, *et al*. Fatal intravascular immune hemolysis induced by hydrochlorothiazide. *Am J Clin Pathol* 1984; **81:** 791–4.

Effects on electrolyte balance. *MAGNESIUM AND POTASSIUM.* The clinical **consequences** of diuretic-induced hypokalaemia have been controversial.[1-3] Of major concern has been the possibility that diuretic-induced hypokalaemia could predispose to cardiac arrhythmias and sudden cardiac death in some patients, and it has been suggested that this could explain the lower than expected reduction in deaths due to ischaemic heart disease found in some hypertension studies. Indeed, some case-control studies[4,5] have suggested an association between an increased risk of sudden cardiac death and the use of thiazides or other non-potassium-sparing diuretics; the addition of a potassium supplement had little effect on this risk, whereas addition of a potassium-sparing diuretic to the thiazide lowered the risk.[4] However, no reduction in cardiac arrhythmias after the correction of hypokalaemia has been seen[6] nor any evidence of increased arrhythmias associated with diuretic-induced hypokalaemia.[7] Several reviews[8,9] have argued that there is no proof of a causal relationship between hypokalaemia and serious dysrhythmias and this was endorsed by a randomised study.[10]

It is generally agreed that routine potassium **supplementation** in patients taking diuretics is unnecessary; however, supplementation will be required if the serum-potassium concentration falls below 3.0 mmol/litre. Potassium replacement or conservation is also likely to be necessary in patients at risk from the cardiac effects of hypokalaemia[11] such as those with severe heart disease, those taking digitalis preparations or high doses of diuretics, and in patients with severe liver disease.

The amount of potassium in fixed combination diuretic and potassium preparations has long been considered insufficient to correct hypokalaemia and the efficacy of oral potassium supplements in increasing body stores of potassium has been questioned.[12-14] Hypokalaemia may be overcome by adding a potassium-sparing diuretic such as amiloride or triamterene[15] to the regimen, but there is a danger of hyperkalaemia if they are used indiscriminately. The *routine* use of fixed-dose combination preparations of a thiazide or loop diuretic with a potassium-sparing diuretic is considered unnecessary.[16] Potassium-sparing diuretics will not correct the potassium deficit unrelated to diuretic therapy in patients with severe heart failure.[17] When thiazides are given with drugs that may induce hyperkalaemia, such as beta blockers, ACE inhibitors, or angiotensin II receptor antagonists, the diuretic-induced hypokalaemia may be ameliorated, but not necessarily corrected completely. Hypokalaemia has been reported[18-20] in patients taking fixed-dose combinations of thiazides and beta blockers.

Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium,[21] although it is unlikely to be of clinical significance.[22]

Magnesium depletion has also been implicated as a risk factor for arrhythmias.[9,23]

1. Materson BJ. Diuretic-associated hypokalemia. *Arch Intern Med* 1985; **145:** 1966–7.
2. Kaplan NM, *et al*. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1985; **312:** 746–9.
3. Kassirer JP, Harrington JT. Fending off the potassium pushers. *N Engl J Med* 1985; **312:** 785–7.
4. Siscovick DS, *et al*. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994; **330:** 1852–7.
5. Hoes AW, *et al*. Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995; **123:** 481–7.
6. Papademetriou V, *et al*. Diuretic-induced hypokalemia in uncomplicated systemic hypertension: effect of plasma potassium correction on cardiac arrhythmias. *Am J Cardiol* 1983; **52:** 1017–22.
7. Papademetriou V, *et al*. Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med* 1988; **148:** 1272–6.
8. Harrington JT, *et al*. Our national obsession with potassium. *Am J Med* 1982; **73:** 155–9.
9. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; **149:** 2640–8.
10. Siegel D, *et al*. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992; **267:** 1083–9.
11. Anonymous. Potassium-sparing diuretics—when are they really needed? *Drug Ther Bull* 1985; **23:** 17–20.
12. Jackson PR, *et al*. Relative potency of spironolactone, triamterene and potassium chloride in thiazide-induced hypokalaemia. *Br J Clin Pharmacol* 1982; **14:** 257–63.
13. Shenfield GM. Fixed combination drug therapy. *Drugs* 1982; **23:** 462–80.
14. Papademetriou V, *et al*. Effectiveness of potassium chloride or triamterene in thiazide hypokalemia. *Arch Intern Med* 1985; **145:** 1986–90.
15. Kohvakka A. Maintenance of potassium balance during long-term diuretic therapy in chronic heart failure patients with thiazide-induced hypokalemia: comparison of potassium supplementation with potassium chloride and potassium-sparing agents, amiloride and triamterene. *Int J Clin Pharmacol Ther Toxicol* 1988; **26:** 273–7.
16. Anonymous. Routine use of potassium-sparing diuretics. *Drug Ther Bull* 1991; **29:** 85–7.
17. Davidson C, *et al*. The effects of potassium supplements, spironolactone or amiloride on the potassium status of patients with heart failure. *Postgrad Med J* 1978; **54:** 405–9.
18. Skehan JD, *et al*. Hypokalaemia induced by a combination of a beta-blocker and a thiazide. *BMJ* 1982; **284:** 83.
19. Odugbesan O, *et al*. Hazards of combined beta-blocker/diuretic tablets. *Lancet* 1985; **i:** 1221–2.
20. Jacobs L. Hypokalaemia with beta-blocker/thiazide combinations. *J R Coll Gen Pract* 1986; **36:** 39.
21. Dyckner T. Relation of cardiovascular disease to potassium and magnesium deficiencies. *Am J Cardiol* 1990; **65:** 44–6.
22. Papademetriou V. Magnesium depletion and thiazide hypokalemia. *Arch Intern Med* 1986; **146:** 1026.
23. Ryan MP. Diuretics and potassium/magnesium depletion: directions for treatment. *Am J Med* 1987; **82** (suppl 3A): 38–47.

SODIUM. Diuretics are a common cause of hyponatraemia;[1-6] of 307 reports of hyponatraemia received by the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[6] between May 2005 and October 2008, 126 involved a diuretic as the single suspected cause. Dilutional hyponatraemia may occur in patients with heart failure, but hyponatraemia may also result from sodium depletion[1] or inappropriate antidiuretic hormone secretion.[7] Other suggested mechanisms include decreased renal clearance of free water, hypomagnesaemia, and intracellular potassium depletion.[3,8] There have been reports suggesting that hyponatraemia may be a particular problem with combinations of hydrochlorothiazide and potassium-sparing diuretics,[9-11] especially in elderly patients. The effect may be exacerbated by the relatively high doses of thiazide present in some fixed-dose preparations.[12] The symptoms of hyponatraemia may be non-specific and include nausea, lethargy, weakness, mental confusion, and anorexia,[1,2] but it may be an important cause of morbidity.[2,8] Severe sequelae of hyponatraemia include tonic-clonic seizures[13] and clinical features resembling subarachnoid haemorrhage.[14,15] Some patients, especially the elderly, may be particularly susceptible to the hyponatraemic effects of thiazides, possibly as

a result of inappropriate secretion of antidiuretic hormone.[7] Plasma electrolyte concentrations should be monitored in patients taking long-term diuretic therapy.[3,13] Measurement of serum-sodium concentration and bodyweight after a single dose of thiazide could be useful in identifying patients at increased risk of developing hyponatraemia.[8]

1. Roberts CJC, *et al*. Hyponatraemia: adverse effect of diuretic treatment. *BMJ* 1977; **1:** 210.
2. Kennedy PGE, *et al*. Severe hyponatraemia in hospital inpatients. *BMJ* 1978; **2:** 1251–3.
3. Walters EG, *et al*. Hyponatraemia associated with diuretics. *Br J Clin Pract* 1987; **41:** 841–4.
4. Spital A. Diuretic-induced hyponatremia. *Am J Nephrol* 1999; **19:** 447–52.
5. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. *J Clin Hypertens (Greenwich)* 2008; **10:** 477–84.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced hyponatraemia. *Aust Adverse Drug React Bull* 2008; **27:** 19–20. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0810.htm (accessed 18/02/10)
7. Sonnenblick M, *et al*. Thiazide-induced hyponatremia and vasopressin release. *Ann Intern Med* 1989; **110:** 751.
8. Friedman E, *et al*. Thiazide-induced hyponatremia: reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med* 1989; **110:** 24–30.
9. Strykers PH, *et al*. Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA* 1984; **252:** 389.
10. Roberts CJC, *et al*. Hyponatraemia induced by a combination of hydrochlorothiazide and triamterene. *BMJ* 1984; **288:** 1962.
11. Millson D, *et al*. Hyponatraemia and Moduretic (amiloride plus hydrochlorothiazide). *BMJ* 1984; **289:** 1308–9.
12. Bayer AJ, *et al*. Plasma electrolytes in elderly patients taking fixed combination diuretics. *Postgrad Med J* 1986; **62:** 159–62.
13. Johnston C, *et al*. Hyponatraemia and Moduretic-grand mal seizures: a review. *J R Soc Med* 1989; **82:** 479–83.
14. Benfield GFA, *et al*. Dilutional hyponatraemia masquerading as subarachnoid haemorrhage in patient on hydrochlorothiazide/amiloride/timolol combined drug. *Lancet* 1986; **ii:** 341.
15. Bain PG, *et al*. Thiazide-induced dilutional hyponatraemia masquerading as subarachnoid haemorrhage. *Lancet* 1986; **ii:** 634.

Effects on the gallbladder. There is an increased risk of cholecystitis in patients taking thiazides,[1] with some indication that risk increases with the duration of use;[2,3] some workers concluded that this increased risk was confined to patients with pre-existing gallstones.[3] In a study in 10 healthy subjects,[4] hydrochlorothiazide was found to induce modest changes in biliary lipid concentrations although it was not associated with supersaturation of the bile. These changes could not wholly explain any increase in gallbladder disease in patients taking thiazides. However, evidence is conflicting; other studies[5,6] have found no association between thiazides and cholecystitis, except possibly in women who are not overweight.[6]

1. González-Pérez A, García Rodríguez LA. Gallbladder disease in the general population: association with cardiovascular morbidity and therapy. *Pharmacoepidemiol Drug Safety* 2007; **16:** 524–31.
2. Rosenberg L, *et al*. Thiazides and acute cholecystitis. *N Engl J Med* 1980; **303:** 546–8.
3. van der Linden W, *et al*. Acute cholecystitis and thiazides. *BMJ* 1984; **289:** 654–5.
4. Angelin B. Effect of thiazide treatment on biliary lipid composition in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 95–6.
5. Porter JB, *et al*. Acute cholecystitis and thiazides. *N Engl J Med* 1981; **304:** 954–5.
6. Kakar F, *et al*. Thiazide use and the risk of cholecystectomy in women. *Am J Epidemiol* 1986; **124:** 428–33.

Effects on glucose metabolism. The adverse effects of thiazides on glucose metabolism, such as insulin resistance, impaired glucose tolerance, precipitation of overt diabetes, and worsening of diabetic control, are well established but appear to be dose-related and may not be significant at lower doses (for example, hydrochlorothiazide 6.25 or 12.5 mg).[1] A study[2] in 16 non-diabetic hypertensive patients found that bendroflumethiazide, in a dose of 1.25 mg daily, had no effect on insulin sensitivity whereas a daily dose of 5 mg produced hepatic insulin resistance. Similarly, the high doses, for example bendroflumethiazide 5 mg twice daily, used in the Medical Research Council Study on Mild to Moderate Hypertension[3] resulted in an incidence of glucose intolerance that led to withdrawal from the study of 9.38 per 1000 patient-years in men and 6.01 per 1000 patient-years in women compared with 2.51 and 0.82 per 1000 patient-years respectively in patients taking placebo. A later prospective study[4] in non-diabetic hypertensive patients found that those taking thiazides [doses not specified] were at no greater risk for developing diabetes than those not receiving antihypertensive therapy. However, a prospective cohort study[5] in men aged between 50 and 60 found that those taking antihypertensive treatment (mainly thiazides, beta blockers, or both) showed an increase in blood-glucose concentrations which was an independent risk factor for myocardial infarction, even when baseline insulin resistance was accounted for. Another prospective study[6] of 3 cohorts of men or women also found that use of thiazides was independently associated with a higher risk of diabetes.

It has been suggested[7] that the effect of thiazides on glucose metabolism is related to their effect on potassium and that control of hypokalaemia may prevent the development of diabetes, but this remains to be confirmed.

1. Neutel JM. Metabolic manifestations of low-dose diuretics. *Am J Med* 1996; **101** (suppl 3A): 71S–82S.
2. Harper R, *et al*. Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ* 1994; **309:** 226–30.
3. Greenburg G. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; **ii:** 539–43.
4. Gress TW, *et al*. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 905–12.
5. Dunder K, *et al*. Increase in blood glucose concentration during antihypertensive treatment as a predictor of myocardial infarction: population based cohort study. *BMJ* 2003; **326:** 681–4.
6. Taylor EN, *et al*. Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29:** 1065–70.
7. Zillich AJ, *et al*. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006; **48:** 219–24.

Effects on the kidneys. Thiazides can produce acute renal failure either from over-enthusiastic use producing sodium depletion and hypovolaemia or, occasionally, as a result of a hypersensitivity reaction.[1] Acute interstitial nephritis has been reported.[2,3] They can occasionally cause the formation of non-opaque urate calculi.[4]

1. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: I. *BMJ* 1977; **2:** 242–4.
2. Linton AL, *et al*. Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. *Ann Intern Med* 1980; **93:** 735–41.
3. Anonymous. Case records of the Massachusetts General Hospital: case 42-1983. *N Engl J Med* 1983; **309:** 970–8.
4. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: II. *BMJ* 1977; **2:** 375–7.

Effects on lipid metabolism. Thiazides have been reported to adversely affect the plasma-lipid profile in the short term by increasing concentrations of low-density and very-low-density lipoprotein cholesterol, as well as of triglycerides, but not of high-density lipoprotein cholesterol.[1] These effects are probably dose-related[2] and it has been argued that changes in plasma lipids are likely to be slight at the relatively low doses now used in hypertension. There is some evidence to suggest that these lipid changes may not persist long-term.[3] In the Treatment of Mild Hypertension Study (TOMHS),[4] plasma total cholesterol concentrations were increased after 12 months in patients receiving chlortalidone but this effect was no longer present after 24 months. Although there has been concern that any hyperlipidaemic effect might offset the benefits of treating hypertension in patients at risk of ischaemic heart disease, studies such as ALLHAT[5] have shown that thiazide-like diuretics (in this case chlortalidone) are as effective as other antihypertensives in reducing the incidence of cardiovascular events in patients with hypertension and at least one other risk factor for ischaemic heart disease.

1. Ames R. Effects of diuretic drugs on the lipid profile. *Drugs* 1988; **36** (suppl 2): 33–40.
2. Carlsen JE, *et al*. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990; **300:** 975–8.
3. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; **149:** 2640–8.
4. Grimm RH, *et al*. Long-term effects on plasma lipids of diet and drugs to treat hypertension. *JAMA* 1996; **275:** 1549–56.
5. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid*. 2003; **289:** 178.

Effects on the nervous system. A 40-year old woman appeared sleepy and confused 1 week after starting hydrochlorothiazide.[1] Although her plasma-potassium concentrations had fallen they were still in the normal range, and it was concluded that her symptoms were due to an adverse reaction to the drug itself.

1. Daugherty KK, Subramanian J. Cognitive and neurologic impairment with hydrochlorothiazide. *Am J Health-Syst Pharm* 2005; **62:** 2630–3.

Effects on respiratory function. Acute interstitial pneumonitis and acute pulmonary oedema are rare but potentially dangerous complications of thiazides and may be due to a hypersensitivity reaction. Several cases have been reported,[1-7] frequently after a single dose of hydrochlorothiazide or chlorothiazide. The presenting symptoms could be mistakenly attributed to myocardial infarction.

1. Steinberg AD. Pulmonary edema following ingestion of hydrochlorothiazide. *JAMA* 1968; **204:** 167–9.
2. Beaudry C, Laplante L. Severe allergic pneumonitis from hydrochlorothiazide. *Ann Intern Med* 1973; **78:** 251–3.
3. Parfrey NA, Herlong HF. Pulmonary oedema after hydrochlorothiazide. *BMJ* 1984; **288:** 1880.
4. Watrigant Y, *et al*. Pneumopathie à l'hydrochlorothiazide d'évolution subaiguë: etude cytologique du lavage broncho-alvéolaire. *Rev Mal Respir* 1986; **4:** 227–9.
5. Klein MD. Noncardiogenic pulmonary edema following hydrochlorothiazide ingestion. *Ann Emerg Med* 1987; **16:** 901–3.
6. Bowden FJ. Non-cardiogenic pulmonary oedema after ingestion of chlorothiazide. *BMJ* 1989; **298:** 605.
7. Bernal C, Patarca R. Hydrochlorothiazide-induced pulmonary edema and associated immunologic changes. *Ann Pharmacother* 1999; **33:** 172–4.

Effects on sexual function. Adverse effects on sexual function have been reported in hypertensive patients given thiazides and other antihypertensives but it is not clear how much this is due to the underlying disease and how much is due to the drugs. In the Treatment of Mild Hypertension Study (TOMHS),[1] a double-blind randomised controlled study that allocated patients to treatment with one of five groups of antihypertensives, the incidence of erectile dysfunction in men was relatively low but was highest in the diuretic group (chlortalidone treatment). The incidence was significantly higher in chlortalidone recipients than in placebo recipients at 24 months (17.1 and 8.1% respectively), but the difference was no longer significant at 48 months (18.3 and 16.7% respectively).

1. Grimm RH, *et al*. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: Treatment of Mild Hypertension Study (TOMHS). *Hypertension* 1997; **29:** 8–14.

Effects on the skin. Rashes and skin reactions have been reported in patients taking thiazides. *Photosensitivity* reactions are among the most frequently reported skin reactions. In Australia[1] co-amilozide was the preparation most commonly implicated in photosensitivity reactions in reports to the Australian Drug Reactions Advisory Committee, although this may reflect the high usage of this preparation. The most likely mechanism is thought to be phototoxicity[1,2] involving mainly UVA radiation although UVB may be involved in some cases.[2] Chronic photosensitivity does not usually occur after stopping the drug[2] although photosensitivity may persist for longer in some patients than in others.[2,3] Eruptions resembling *lichen planus*[4] and *subacute cutaneous lupus erythematosus*[5-7] may be due to photosensitivity reactions.

Other reported skin reactions include *vasculitis*,[8,9] *erythema multiforme*,[9] and *pseudoporphyria*.[10]

1. Stone K. Photosensitivity reactions to drugs. *Aust J Pharm* 1985; **66:** 415–18.
2. Addo HA, *et al*. Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol* 1987; **116:** 749–60.
3. Robinson HN, *et al*. Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; **121:** 522–4.
4. Graham-Brown R. Lichen planus and lichen-planus-like reactions. *Br J Hosp Med* 1986; **36:** 281–4.
5. Jones SK, *et al*. Thiazide diuretic-induced subacute cutaneous lupus-like syndrome. *Br J Dermatol* 1985; **113** (suppl 29): 25.
6. Reed BR, *et al*. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985; **103:** 49–51.
7. Darken M, McBurney EI. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *J Am Acad Dermatol* 1988; **18:** 38–42.
8. Björnberg A, Gisslén H. Thiazides: a cause of necrotising vasculitis? *Lancet* 1965; **ii:** 982–3.
9. Hardwick N, Saxe N. Patterns of dermatology referrals in a general hospital. *Br J Dermatol* 1986; **115:** 167–76.
10. Motley RS. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; **300:** 1468.

Gout. Thiazides have been associated with hyperuricaemia and gout in some patients. In a single-blinded study,[1] men taking bendroflumethiazide had higher incidences of gout than those receiving placebo (12.23 and 1.03 per 1000 patient-years, respectively). The risk appears to be dose-related; in a retrospective study[2] in patients aged 65 or older receiving antihypertensive therapy, there was a significantly increased risk of starting anti-gout therapy in patients taking the equivalent of 25 mg hydrochlorothiazide or more daily, but not in those on lower doses.

1. Greenburg G. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; **ii:** 539–43.
2. Gurwitz JH, *et al*. Thiazide diuretics and the initiation of anti-gout therapy. *J Clin Epidemiol* 1997; **50:** 953–9.

Withdrawal. For a report of oedema after abrupt withdrawal of thiazides, see under Precautions, p. 1406.1.

Treatment of Adverse Effects

Hypokalaemia in patients treated with thiazides may be avoided or treated by use with potassium or a potassium-sparing diuretic (but see the discussion on potassium supplements, under Effects on Electrolyte Balance in Adverse Effects, p. 1404.2). Hypokalaemia can also be reduced by moderate sodium restriction. With the exception of patients with conditions such as hepatic failure or renal disease, chloride deficiency is usually mild and does not require specific treatment. Apart from the rare occasions when it is life-threatening, dilutional hyponatraemia is best treated with water restriction rather than salt therapy; in true hyponatraemia, appropriate replacement is the treatment of choice (see p. 1780.1).

In massive overdosage, treatment should be symptomatic and directed at fluid and electrolyte replacement. Use of activated charcoal should be considered if the patient presents within 1 hour of ingestion.

Precautions

All diuretics produce changes in fluid and electrolyte balance (see Adverse Effects, p. 1404.2). They should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as the elderly. They should be avoided in patients with severe hepatic impairment, in whom encephalopathy may be precipitated. Patients with hepatic cirrhosis are also more likely to develop hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses of thiazides and restricted salt intake. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Thiazides should not be given to patients with Addison's disease.

Diuretics should also be given with caution in renal impairment since they can further reduce renal function. Most thiazides are not effective in patients with a creatinine clearance of less than 30 mL/minute. They should not be used in patients with severe renal impairment or anuria.

Thiazides may precipitate attacks of gout in susceptible patients. They may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change. Thiazides can reduce urinary excretion of calcium, sometimes resulting in mild hypercalcaemia; they should not be given to patients with pre-existing hypercalcaemia. There is a possibility that thiazides may exacerbate or activate SLE in susceptible patients. For a suggestion that thiazides may increase the risk of developing gallstones, see Effects on the Gallbladder, p. 1405.1.

Thiazides cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion. Treatment with large doses can inhibit lactation.

Breast feeding. Hydrochlorothiazide has been shown to pass into breast milk. In a woman taking 50 mg hydrochlorothiazide daily, peak milk concentrations were found[1] 5 to 10 hours after a dose and were about 25% of peak blood concentrations. No drug could be detected in the infant's blood, and his serum electrolytes, blood glucose, and blood urea nitrogen were normal. The American Academy of Pediatrics considers[2] that hydrochlorothiazide is usually compatible with breast feeding.

1. Miller ME, *et al.* Hydrochlorothiazide disposition in a mother and her breast-fed infant. *J Pediatr* 1982; **101:** 789–91.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Hyperparathyroidism. Hypertension is a complication of primary hyperparathyroidism but thiazides have often been withheld for fear of exacerbating hypercalcaemia. However, no differences in plasma-calcium concentrations were found in 13 patients given thiazides intermittently for up to 18 months. It was therefore concluded that thiazides are not contra-indicated in such patients.[1] They should, however, be stopped before parathyroid function is tested.

1. Farquhar CW, *et al.* Failure of thiazide diuretics to increase plasma calcium in mild primary hyperparathyroidism. *Postgrad Med J* 1990; **66:** 714–16.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydrochlorothiazide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Withdrawal. In patients with mild hypertension whose blood pressure is consistently controlled, reduction in dosage or withdrawal of antihypertensive drugs may be possible. Serious oedema occurred in 8 patients with controlled hypertension within 2 weeks of abrupt withdrawal of thiazide diuretics.[1] Thiazides were resumed and gradually tapered without recurrence of oedema.

1. Brandspigel K. Diuretic-withdrawal edema. *N Engl J Med* 1986; **314:** 515.

Interactions

Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance. Diuretic-induced hypokalaemia may enhance the toxicity of digitalis glycosides and increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole, terfenadine, halofantrine, pimozide, and sotalol. Thiazides may also enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effect. The potassium-depleting effect of diuretics may be enhanced by corticosteroids, corticotropin, beta$_2$ agonists such as salbutamol, carbenoxolone, amphotericin B, or reboxetine.

Diuretics can enhance the effect of other antihypertensives, particularly the first-dose hypotension that occurs with alpha blockers or ACE inhibitors. Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates, or opioids. The antihypertensive effects of diuretics may be antagonised by drugs that cause fluid retention, such as corticosteroids, NSAIDs, or carbenoxolone; the nephrotoxicity of NSAIDs may also be enhanced. Thiazides have been reported to diminish the response to pressor amines, such as noradrenaline, but the clinical significance of this effect is uncertain.

Thiazides should not usually be used with lithium since the association may lead to toxic blood concentrations of lithium. Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracyclines. Thiazides may alter the requirements for hypoglycaemics in diabetic patients.

Antibacterials. Severe hyponatraemia has been reported in patients taking *trimethoprim* with co-amilozide[1] and hydrochlorothiazide.[2]

1. Eastell R, Edmonds CJ. Hyponatraemia associated with trimethoprim and a diuretic. *BMJ* 1984; **289:** 1658–9.
2. Hart TL, *et al.* Hyponatremia secondary to thiazide-trimethoprim interaction. *Can J Hosp Pharm* 1989; **42:** 243–6.

Antiepileptics. There has been a report of symptomatic hyponatraemia associated with the use of hydrochlorothiazide or furosemide and *carbamazepine*.[1]

1. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; **48:** 281–3.

Bile-acid binding resins. Gastrointestinal absorption of both chlorothiazide and hydrochlorothiazide has been reported to be reduced by *colestipol* and *colestyramine*.[1-3] In a study in healthy subjects[2] colestyramine had the greatest effect on hydrochlorothiazide, decreasing absorption by 85% compared with a decrease of 43% with colestipol. Even when colestyramine was given 4 hours after hydrochlorothiazide[3] reductions of absorption of at least 30 to 35% could be expected.

1. Kauffman RE, Azarnoff DL. Effect of colestipol on gastrointestinal absorption of chlorothiazide in man. *Clin Pharmacol Ther* 1973; **14:** 886–90.
2. Hunninghake DB, *et al.* The effect of cholestyramine and colestipol on the absorption of hydrochlorothiazide. *Int J Clin Pharmacol Ther Toxicol* 1982; **20:** 151–4.
3. Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. *Clin Pharmacol Ther* 1986; **39:** 329–34.

Calcium salts. The milk-alkali syndrome, characterised by hypercalcaemia, metabolic alkalosis, and renal failure, developed in a patient taking chlorothiazide and moderately large doses of calcium carbonate.[1] Patients taking thiazides may be at increased risk of developing the syndrome because of their reduced ability to excrete excess calcium. Hypercalcaemia may also occur in patients taking thiazides with drugs that increase calcium levels, such as vitamin D.

1. Gora ML, *et al.* Milk-alkali syndrome associated with use of chlorothiazide and calcium carbonate. *Clin Pharm* 1989; **8:** 227–9.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p. 892.2.

NSAIDs. NSAIDs cause fluid retention and may antagonise the diuretic actions of thiazides.[1]

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Sex hormones. For a discussion of the possible interaction between hydrochlorothiazide and *drospirenone*, see Diuretics, p. 2269.3.

Pharmacokinetics

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

References.
1. Beermann B, *et al.* Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol Ther* 1976: **19:** 531–7.
2. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in man. *Eur J Clin Pharmacol* 1977; **12:** 297–303.
3. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in patients with congestive heart failure. *Br J Clin Pharmacol* 1979:**7:** 579–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diural; Diurex; Tandiur; ***Austral.***: Dithiazide; ***Braz.***: Clorana; Clorizin; Diurepina†; Diuretic; Diuretil; Diurezin; Diurix; Drenol; Hidrazim; Hidroclorozil†; Hidrolan; Hidromed; Hidrosan; Neo Hidroclor; ***Canad.***: Apo-Hydro; Novo-Hydrazide†; Nu-Hydro; Urozide; ***Chile***: Hidroronol; ***Cz.***: Losathia†; ***Denm.***: Hydromed; ***Fin.***: Hydrex; ***Fr.***: Esidrex; ***Ger.***: Disalunil; Esidrix; HCT-Beta; HCT-gamma; HCT-ISIS†; HCT; HCTad†; ***Gr.***: Diuren; Esidrex; ***Hong Kong***: Apo-Hydro†; Hydrozide; ***Hung.***: Hypothiazid; ***India***: Aquazide; BPzide; Esidrex; Hydrazide; Hydride; Hyzide; Klorzide; Selopres; ***Indon.***: HCT; Lodoz; ***Israel***: Disothiazide; ***Ital.***: Esidrex; ***Malaysia***: Apo-Hydro; Hydrozide; ***Mex.***: Rofucal; Top-K; ***Norw.***: Esidrex; ***Philipp.***: Cotrazid; Diuzid; Diuzide; Hytaz; Lorzan; Urilzid; ***Pol.***: Rasilez HCT; ***Rus.***: Hypothiazid (Гипотиазид); Lodoz (Лодоз); ***S.Afr.***: Hexazide; Ridaq; ***Singapore***: Apo-Hydro; Di-Ertride; Didralin; Hydrochlorzide; Hydrotride; Hydrozide; ***Spain***: Acuretic†; Esidrex; Hidrosaluretil; ***Swed.***: Esidrex; ***Switz.***: Esidrex; ***Thai.***: Dichlotride; Diric; Diuret-P; Dragotab; HCTZ; Hychlozide; Hydrozide; Urazide; ***Ukr.***: Hypothiazid (Гипотиазид); ***USA***: HydroDiuril; Microzide; Mictrin; ***Venez.***: Di-Eudrin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Co-amilozide Oral Solution; Co-amilozide Tablets; Co-triamterzide Tablets; Hydrochlorothiazide Tablets;

USP 36: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Captopril and Hydrochlorothiazide Tablets; Enalapril Maleate and Hydrochlorothiazide Tablets; Fosinopril Sodium and Hydrochlorothiazide Tablets; Hydrochlorothiazide Capsules; Hydrochlorothiazide Tablets; Irbesartan and Hydrochlorothiazide Tablets; Lisinopril and Hydrochlorothiazide Tablets; Losartan Potassium and Hydrochlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Propranolol Hydrochloride and Hydrochlorothiazide Extended-release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Quinapril and Hydrochlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets; Spironolactone and Hydrochlorothiazide Oral Suspension; Spironolactone and Hydrochlorothiazide Tablets; Telmisartan and Hydrochlorothiazide Tablets; Timolol Maleate and Hydrochlorothiazide Tablets; Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Valsartan and Hydrochlorothiazide Tablets.

Hydroflumethiazide *(BAN, rINN)* ⊗

Hidroflumetiazida; Hydrofluméthiazide; Hydroflumethiazidum; Hydroflumetiatsidi; Hydroflumetiazid; Trifluoromethylhydrothiazide; Гидрофлуметиазид.

3,4-Dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_8H_8F_3N_3O_4S_2$=331.3

CAS — 135-09-1.

ATC — C03AA02.

ATC Vet — QC03AA02.

UNII — 501CFL162R.

NOTE. Compounded preparations of hydroflumethiazide may be represented by the following names:

- Co-flumactone (*BAN*)—hydroflumethiazide and spironolactone in equal parts (w/w).

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Hydroflumethiazide). White or almost white, odourless or almost odourless, glistening crystals or crystalline powder. Practically insoluble in water; soluble in alcohol; practically insoluble in chloroform and in ether.

USP 36: (Hydroflumethiazide). A white to cream-coloured, odourless, finely divided crystalline powder. Very slightly soluble in water and in chloroform; soluble 1 in 39 of alcohol and 1 in 2500 of ether; freely soluble in acetone. A 1% dispersion in water has a pH of 4.5 to 7.5. Store in airtight containers.

Uses and Administration

Hydroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis begins about 2 hours after an oral dose and has been reported to last for up to 24 hours.

In the treatment of **oedema** the usual initial dose is 50 to 200 mg daily, in one or two divided doses, reduced to a dose of 25 to 50 mg on alternate days or intermittently. In the treatment of **hypertension** the usual dose is 25 to 50 mg daily either alone, or with other antihypertensives. An initial dose of 12.5 mg has been used.

For doses in children, see p. 1407.1.

Administration in children. Hydroflumethiazide may be given to children in the treatment of hypertension and oedema at an initial dose of 1 mg/kg daily, reduced for maintenance.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Hydroflumethiazide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a beta-phase biological half-life of about 17 hours and a metabolite with a longer half-life that is extensively bound to red blood cells. Hydroflumethiazide is excreted in the urine; its metabolite has also been detected in the urine.

References.
1. Brørs O, *et al.* Pharmacokinetics of a single dose of hydroflumethiazide in health and in cardiac failure. *Eur J Clin Pharmacol* 1978; **14:** 29–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Saluron.

Multi-ingredient Preparations. ***India***: Aldactide; ***Irl.***: Aldactide†; ***S.Afr.***: Protensin-M†; ***UK***: Aldactide.

Pharmacopoeial Preparations
BP 2014: Hydroflumethiazide Tablets;
USP 36: Hydroflumethiazide Tablets.

Hydroquinidine Hydrochloride

Dihydrochinidin Hydrochloride; Dihydroquinidine Hydrochloride; Hidrocloruro de dihidroquinidina; Hidroquinidina, hidrocloruro de; Hydroconchinine Hydrochloride; Гидрохинидина Гидрохлорид.

(8*R*,9*S*)-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrochloride.

$C_{20}H_{26}N_2O_2$,HCl=362.9

CAS — 1435-55-8 (hydroquinidine); 1476-98-8 (hydroquinidine hydrochloride).

UNII — 6BR4G8VAHM.

Pharmacopoeias. In *Fr.*

Profile

Hydroquinidine is a class Ia antiarrhythmic with actions and uses similar to those of quinidine (p. 1481.1). It is given orally as the hydrochloride in a usual maintenance dose of 600 mg daily in divided doses.

Hydroquinidine alginate and quinalbital (the hydroquinidine salt of amobarbital) have also been used in the treatment of cardiac arrhythmias.

References.
1. Hermida J-S, *et al.* Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004; **43:** 1853–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Serecor; ***Gr.***: Ydroquinidine; ***Spain***: Lentoquine.

Ibopamine *(BAN, USAN, rINN)* ⊗

Ibopamina; Ibopaminum; SB-7505; SKF-100168; Ибопамин.

4-(2-Methylaminoethyl)-*o*-phenylene di-isobutyrate.

$C_{17}H_{25}NO_4$=307.4

CAS — 66195-31-1.

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

UNII — 8ZCA2I2L11.

Ibopamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de ibopamina; Ibopamiinihydrokloridi; Ibopamina, hidrocloruro de; Ibopamine, Chlorhydrate d'; Ibopaminhydroklorid; Ibopamini Hydrochloridum; Ибопамина Гидрохлорид.

$C_{17}H_{25}NO_4$,HCl=343.8

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

UNII — 3VXW2HU8G5.

Uses and Administration

Ibopamine is a prodrug and is rapidly converted to its active metabolite, epinine, which is a peripheral dopamine agonist and sympathomimetic (p. 1507.3). At low doses its dopaminergic effects predominate, leading to vasodilatation and a weak positive inotropic effect; at high concentrations it has a stimulant action on alpha and beta adrenoceptors.

Ibopamine is used in the management of mild heart failure (p. 1262.3). It is given as the hydrochloride but doses are often expressed in terms of the base; 111.9 mg of hydrochloride is equivalent to about 100 mg of base. Doses of 100 to 200 mg orally two or three times daily have been used.

Ibopamine is also used topically as a mydriatic (p. 2000.2) in the form of eye drops containing ibopamine hydrochloride 2%.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Ibopamine should not be used in patients with severe heart failure as it has been reported to increase the risk of death.

Effects on the cardiovascular system. A multicentre study (PRIME II) of the use of ibopamine in patients with severe (NYHA class III or IV) heart failure was stopped early when it was found that the drug was associated with an increased risk of death.[1] Subgroup analysis found that use of an antiarrhythmic drug was independently predictive of an adverse effect in ibopamine-treated patients. Excess mortality in heart failure has also been reported with dobutamine and xamoterol, and with the phosphodiesterase inhibitors amrinone, enoximone, milrinone, and vesnarinone, all of which produce positive inotropic effects through catecholamine-receptor stimulation or post-receptor pathway stimulation.[2] The association with antiarrhythmic therapy in the ibopamine study might reflect an interaction with amiodarone, the most commonly used antiarrhythmic in this study, or might simply be a marker for patients at risk of ibopamine-induced tachyarrhythmias.

1. Hampton JR, *et al.* Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997; **349:** 971–7.
2. Niebauer J, Coats AJS. Treating chronic heart failure: time to take stock. *Lancet* 1997; **349:** 966–7.

Interactions

As for Sympathomimetics, p. 1508.3. It has been recommended that ibopamine should not be given to patients taking amiodarone in the light of the increased mortality seen in the PRIME II study in patients given both drugs (see above), although it is not clear that this represents a genuine interaction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Scandine; ***Ital.***: Scandine; Trazyl†; ***Neth.***: Inopamil†.

Ibutilide Fumarate *(BANM, USAN, rINNM)*

Fumarato de ibutilida; Ibutilida, fumarato de; Ibutilide, Fumarate d'; Ibutilidi Fumaras; U-70226E; Ибутилида Фумарат.

(±)-4′-[4-(Ethylheptylamino)-1-hydroxybutyl]methanesulfonanilide fumarate (2:1).

$(C_{20}H_{36}N_2O_3S)_2C_4H_4O_4$=885.2

CAS — 122647-31-8 (ibutilide); 122647-32-9 (ibutilide fumarate).

ATC — C01BD05.

ATC Vet — QC01BD05.

UNII — 9L5X4M5L6I.

Uses and Administration

Ibutilide is a class III antiarrhythmic (p. 1243.1) used for the acute treatment of atrial fibrillation or flutter (p. 1266.1).

Ibutilide is given intravenously as the fumarate. For the termination of atrial fibrillation or flutter, ibutilide fumarate is given as a single dose of 1 mg in patients weighing 60 kg and over, or 10 micrograms/kg in patients weighing less than 60 kg, infused over 10 minutes; the infusion should be stopped as soon as the arrhythmia is terminated. If the arrhythmia persists 10 minutes after completion of the infusion, a second infusion of the same dose may be given.

References.
1. Foster RH, *et al.* Ibutilide: a review of its pharmacological properties and clinical potential in the acute management of atrial flutter and fibrillation. *Drugs* 1997; **54:** 312–30.
2. Granberry MC. Ibutilide: a new class III antiarrhythmic agent. *Am J Health-Syst Pharm* 1998; **55:** 255–60.
3. Howard PA. Ibutilide: an antiarrhythmic agent for the treatment of atrial fibrillation or flutter. *Ann Pharmacother* 1999; **33:** 38–47.
4. Doggrell SA, Hancox JC. Ibutilide—recent molecular insights and accumulating evidence for use in atrial flutter and fibrillation. *Expert Opin Invest Drugs* 2005; **14:** 655–69.
5. Kafkas NV, *et al.* Conversion efficacy of intravenous ibutilide compared with intravenous amiodarone in patients with recent-onset atrial fibrillation and atrial flutter. *Int J Cardiol* 2007; **118:** 321–5.
6. Hoyer AW, Balaji S. The safety and efficacy of ibutilide in children and in patients with congenital heart disease. *Pacing Clin Electrophysiol* 2007; **30:** 1003–8.
7. Giudici MC, *et al.* Ibutilide therapy for atrial fibrillation: 5-year experience in a community hospital. *J Cardiovasc Nurs* 2008; **23:** 484–8.
8. Fragakis N, *et al.* Acute beta-adrenoceptor blockade improves efficacy of ibutilide in conversion of atrial fibrillation with a rapid ventricular rate. *Europace* 2009; **11:** 70–4.

Adverse Effects

Adverse cardiovascular effects associated with ibutilide include heart block, hypotension, hypertension, and bradycardia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias, including torsade de pointes. Other adverse effects include nausea and vomiting.

Effects on the heart. Ibutilide prolongs the QT interval and has been associated with torsade de pointes, particularly in women.[1] A small study[2] suggested that this effect could be prevented by magnesium sulfate (p. 1790.1), which might therefore be suitable for use as prophylaxis. Although magnesium could theoretically reduce the antiarrhythmic effect of ibutilide as well as the proarrhythmic effect, a retrospective study[3] found that the rate of cardioversion was higher in patients given both ibutilide and magnesium than in those given ibutilide alone, an effect confirmed in a later study.[4] An episode of asystole lasting for 7 seconds in an elderly woman given ibutilide for cardioversion[5] was thought to be caused by the drug unmasking and exacerbating latent sick sinus syndrome.

1. Gowda RM, *et al.* Female preponderance in ibutilide-induced torsade de pointes. *Int J Cardiol* 2004; **95:** 219–22.
2. Caron MF, *et al.* Effects of intravenous magnesium sulfate on the QT interval in patients receiving ibutilide. *Pharmacotherapy* 2003; **23:** 296–300.
3. Kalus JS, *et al.* Impact of prophylactic i.v. magnesium on the efficacy of ibutilide for conversion of atrial fibrillation or flutter. *Am J Health-Syst Pharm* 2003; **60:** 2308–12.
4. Tercius AJ, *et al.* Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. *Pacing Clin Electrophysiol* 2007; **30:** 1331–5.
5. Neumayr G, *et al.* Ibutilide and sinus arrest. *Herz* 2007; **32:** 342.

Effects on the kidneys. Acute renal failure with biopsy evidence of acute tubular necrosis developed in a 52-year-old man shortly after he received 2 doses of ibutilide for an episode of atrial flutter.[1] Renal function returned to normal after 4 sessions of haemodialysis.

1. Franz M, *et al.* Acute renal failure after ibutilide. *Lancet* 1999; **353:** 467.

Precautions

ECG monitoring should be carried out during, and for at least 4 hours after, ibutilide infusion, and the infusion should be stopped if the QT interval becomes markedly prolonged. Electrolyte abnormalities should be corrected before treatment is started.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibutilide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Use of ibutilide with other antiarrhythmics or drugs that prolong the QT interval should be avoided.

Magnesium. For the synergistic effect of magnesium and ibutilide in producing cardioversion, see Effects on the Heart, above.

Pharmacokinetics

Ibutilide is widely distributed in the body after intravenous infusion. It has low plasma protein binding (about 40%) and undergoes extensive metabolism in the liver to form several metabolites. Ibutilide is excreted mainly in the urine, as metabolites and a small amount of unchanged drug (about 7%), with about 19% being excreted in the faeces. The elimination half-life is reported to range from 2 to 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Corvert; ***Canad.***: Corvert; ***Fin.***: Corvert; ***Fr.***: Corvert†; ***Gr.***: Corvert; ***Ital.***: Corvert; ***Neth.***: Corvert; ***Norw.***: Corvert; ***Rus.***: Corvert (Корверт); ***Swed.***: Corvert; ***Switz.***: Corvert; ***USA***: Corvert.

Idraparinux Sodium *(USAN, rINN)*

Idraparinux sódico; Idraparinux Sodique; Idraparinuxum Natricum; Org-34006; SANORG-34006; SR-34006; Идрапаринукс Натрия.

Methyl *O*-2,3,4-tri-*O*-methyl-6-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-β-D-glucopyranuronosyl-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-*O*-sulfo-D-glucopyranoside nonasodium.

$C_{38}H_{55}Na_9O_{49}S_7$=1727.1

CAS — 162610-17-5 (idraparinux); 149920-56-9 (idraparinux sodium).

UNII — H84IXP29FN.

Profile

Idraparinux is a pentasaccharide inhibitor of factor Xa that acts in a similar manner to fondaparinux (p. 1385.3). It has a long half-life and has been investigated in once-weekly doses for the management of venous thromboembolism; however, results have been disappointing, with bleeding being a particular problem. A biotinylated version, idrabiotaparinux, whose action may be reversed by the glycoprotein avidin, is under development in an attempt to improve the safety profile of the drug.

References.

1. Buller HR, *et al.* Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007; **357:** 1094–1104.
2. Buller HR, *et al.* Extended prophylaxis of venous thromboembolism with idraparinux. *N Engl J Med* 2007; **357:** 1105–12.
3. Bousser MG, *et al.* Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008; **371:** 315–21.
4. Prandoni P, *et al.* Idraparinux: review of its clinical efficacy and safety for prevention and treatment of thromboembolic disorders. *Expert Opin Invest Drugs* 2008; **17:** 773–7.
5. Harenberg J. Development of idraparinux and idrabiotaparinux for anticoagulant therapy. *Thromb Haemost* 2009; **102:** 811–15.
6. van Doormaal FF, *et al.* Idraparinux versus standard therapy in the treatment of deep venous thrombosis in cancer patients: a subgroup analysis of the Van Gogh DVT trial. *Thromb Haemost* 2010; **104:** 86–91.
7. Paty I, *et al.* Reversibility of the anti-FXa activity of idrabiotaparinux (biotinylated idraparinux) by intravenous avidin infusion. *J Thromb Haemost* 2010; **8:** 722–9.
8. Equinox Investigators. Efficacy and safety of once weekly subcutaneous idrabiotaparinux in the treatment of patients with symptomatic deep venous thrombosis. *J Thromb Haemost* 2011; **9:** 92–9.

Ifenprodil Tartrate *(rINNM)*

Ifenprodil, Tartrate d'; Ifenprodil, tartrato de; Ifenprodili Tartras; RC-61-91; Tartrato de ifenprodil; Ифенпродила Тартрат.

(±)-2-(4-Benzylpiperidino)-1-(4-hydroxyphenyl)propan-1-ol tartrate.

$(C_{21}H_{27}NO_2)_2,C_4H_6O_6$=801.0

CAS — 23210-56-2 (ifenprodil); 23210-58-4 (ifenprodil tartrate).

ATC — C04AX28.

ATC Vet — QC04AX28.

UNII — 89CTB4XUF7.

Pharmacopoeias. In *Jpn*.

Profile

Ifenprodil tartrate is a vasodilator, with alpha-adrenoceptor blocking properties, used in peripheral vascular disorders (p. 1272.3). It is given in usual oral doses of 40 to 60 mg daily, and has also been given by deep intramuscular injection, slow intravenous injection, or intravenous infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vadilex; ***Gr.***: Vadilex.

Iloprost *(BAN, USAN, rINN)*

Ciloprost; E-1030; Iloprosti; Iloprostum; SH-401; ZK-00036374; ZK-36374; Илопрост.

(*E*)-(3a*S*,4*R*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),\delta}$-pentalenevaleric acid.

$C_{22}H_{32}O_4$=360.5

CAS — 73873-87-7; 78919-13-8.

ATC — B01AC11.

ATC Vet — QB01AC11.

UNII — JED5K35YGL.

Iloprost Trometamol *(BANM, rINNM)*

Ciloprost Tromethamine; Iloprost Trométamol; Iloprost Tromethamine; Iloprostum Trometamolum; Илопрост Трометамол.

$C_{22}H_{32}O_4.C_4H_{11}NO_3$=481.6

ATC — B01AC11.

ATC Vet — QB01AC11.

Uses and Administration

Iloprost, a vasodilator and platelet aggregation inhibitor, is a stable analogue of the prostaglandin epoprostenol (prostacyclin). It is given as the trometamol salt in the treatment of peripheral vascular disease and pulmonary hypertension but doses are described in terms of iloprost; 1.3 nanograms of iloprost trometamol is equivalent to about 1 nanogram of iloprost.

The usual dose for **peripheral vascular disease** is the equivalent of iloprost 0.5 to 2 nanograms/kg per minute for 6 hours daily by intravenous infusion. The course of treatment may be up to 4 weeks. For **pulmonary hypertension**, the dose is 1 to 8 nanograms/kg per minute for 6 hours daily; alternatively, iloprost may be given by nebulised solution at a dose of 2.5 or 5 micrograms inhaled 6 to 9 times daily. Doses should be reduced in patients with hepatic or renal impairment (see below).

Oral iloprost is under investigation.

Reviews.

1. Grant SM, Goa KL. Iloprost: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. *Drugs* 1992; **43:** 889–924.

Administration in children. Although iloprost is unlicensed in the UK for use in children, the *BNFC* suggests that it may be given intravenously to children aged 12 years and over in the treatment of **Raynaud's syndrome**, and by nebulisation to those aged 8 years and over in the treatment of **pulmonary hypertension**, in the usual adult doses (see above), although treatment duration should be limited to 3 to 5 days in Raynaud's syndrome.

References.

1. Zulian F, *et al.* Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases. *Rheumatology (Oxford)* 2004; **43:** 229–33.
2. Ivy DD, *et al.* Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2008; **51:** 161–9.
3. Tissot C, Beghetti M. Review of inhaled iloprost for the control of pulmonary artery hypertension in children. *Vasc Health Risk Manag* 2009; **5:** 325–31.

Administration in hepatic or renal impairment. The dose of intravenous iloprost should be reduced, and may need to be halved, in patients with liver cirrhosis or renal impairment requiring dialysis. In hepatic impairment, the initial dose of inhaled iloprost should be 2.5 micrograms given at intervals of at least 3 hours to a maximum of 6 times daily; the dose may be cautiously increased or given more frequently according to patient response.

Peripheral vascular disease. Prostaglandins, including iloprost,[1-10] have been used in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3), that is complicated by ulceration. Systematic review[10] suggests that intravenous iloprost produces prolonged benefit in Raynaud's phenomenon secondary to scleroderma. The benefits of oral iloprost are less clear. It is also unclear whether iloprost infusion is of benefit in occlusive peripheral arterial disease due to atherosclerosis: although a meta-analysis of (conflicting) controlled studies did suggest an effect,[6] firm conclusions are difficult.

1. Waller PC, *et al.* Placebo controlled trial of iloprost in patients with stable intermittent claudication. *Br J Clin Pharmacol* 1986; **21:** 562P–563P.
2. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; **298:** 561–4.
3. Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. *Lancet* 1990; **335:** 555–7.
4. Zahavi J, *et al.* Ischaemic necrotic toes associated with antiphospholipid syndrome and treated with iloprost. *Lancet* 1993; **342:** 862.
5. Tait IS, *et al.* Management of intra-arterial injection injury with iloprost. *Lancet* 1994; **343:** 419.
6. Loosemore TM, *et al.* A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994; **13:** 133–42.
7. Wigley FM, *et al.* Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis Rheum* 1998; **41:** 670–7.
8. Black CM, *et al.* Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br J Rheumatol* 1998; **37:** 952–60.
9. Scorza R, *et al.* Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized, controlled study. *Clin Exp Rheumatol* 2001; **19:** 503–8.
10. Pope J, *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 16/06/05).

Pulmonary hypertension. Epoprostenol is an accepted part of the management of pulmonary hypertension (p. 1278.2) and the use of iloprost, a stable analogue, has been studied. Inhaled iloprost may have a role;[1,2] it was found[3] to improve walking-test distances, reduce severity of heart failure, and stabilise haemodynamic measures in a 12-week study of patients with severe pulmonary hypertension, while long-term treatment of at least 1 year has been reported to have sustained beneficial effects.[4,5] It has been used for management in children.[6] Iloprost has also been used successfully in a few cases to manage pulmonary hypertension in pregnant women.[7] There are also reports of effective combination therapy using inhaled iloprost with intravenous epoprostenol,[8] oral sildenafil,[9] or oral bosentan.[10] Continuous intravenous infusion[11] has also been tried with beneficial results over several weeks, and short-term intravenous infusion for 7 days[12] has been successfully used for pulmonary hypertension after pulmonary thromboendarterectomy.

1. Baker SE, Hockman RH. Inhaled iloprost in pulmonary arterial hypertension. *Ann Pharmacother* 2005; **39:** 1265–73.
2. Krug S, *et al.* Inhaled iloprost for the control of pulmonary hypertension. *Vasc Health Risk Manag* 2009; **5:** 465–74.
3. Olschewski H, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; **347:** 322–9.
4. Hoeper MM, *et al.* Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000; **342:** 1866–70.
5. Olschewski H, *et al.* Long-term therapy with inhaled iloprost in patients with pulmonary hypertension. *Respir Med* 2010; **104:** 731–40.
6. Tissot C, Beghetti M. Review of inhaled iloprost for the control of pulmonary artery hypertension in children. *Vasc Health Risk Manag* 2009; **5:** 325–31.
7. Elliot CA, *et al.* The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. *Eur Respir J* 2005; **26:** 168–73.
8. Petkov V, *et al.* Aerosolised iloprost improves pulmonary haemodynamics in patients with primary pulmonary hypertension receiving continuous epoprostenol treatment. *Thorax* 2001; **56:** 734–6.
9. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; **136:** 515–22.
10. McLaughlin VV, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; **174:** 1257–63.
11. Higenbottam TW, *et al.* Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart* 1998; **79:** 175–9.
12. Hsu H-H, *et al.* Short-term intravenous iloprost for treatment of reperfusion lung oedema after pulmonary thromboendarterectomy. *Thorax* 2007; **62:** 459–61.

Thrombotic microangiopathies. For reports of the use of iloprost in patients with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, see under Epoprostenol, p. 1375.3.

Adverse Effects and Precautions

As for Epoprostenol, p. 1375.3. Inhaled iloprost may cause cough.

Effects on the cardiovascular system. Hypotension was seen[1] in 2 of 6 patients given iloprost. Both patients recovered rapidly when iloprost was stopped, although one required intravenous atropine to correct sinus bradycardia.

Evidence of myocardial ischaemia was reported in 4 of 33 patients with coronary artery disease during iloprost infusion.[2] The same authors[3] noted a similar effect in 4 of 28 patients with stable angina in a subsequent study. According to one study,[4] there might be an increased risk of thromboembolism in some patients given iloprost, due to platelet activation and enhanced coagulation.

1. Upward JW, *et al.* Hypotension in response to iloprost, a prostacyclin analogue. *Br J Clin Pharmacol* 1986; **21:** 241–3.
2. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; **38:** 101–8.
3. Bugiardini R, *et al.* Effects of iloprost, a stable prostacyclin analog, on exercise capacity and platelet aggregation in stable angina pectoris. *Am J Cardiol* 1986; **58:** 453–9.
4. Kovacs IB, *et al.* Infusion of a stable prostacyclin analogue, iloprost, to patients with peripheral vascular disease: lack of antiplatelet effect but risk of thromboembolism. *Am J Med* 1991; **90:** 41–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iloprost as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. For reference to the successful use of iloprost in pregnancy see Pulmonary Hypertension, under Uses and Administration, above.

Interactions

Iloprost may increase the effect of other vasodilators and antihypertensives. The use of iloprost with other inhibitors of platelet aggregation may increase the risk of bleeding.

Pharmacokinetics

On intravenous infusion iloprost is rapidly cleared from the plasma by oxidation. About 80% of the metabolites are excreted in urine and 20% in the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ventavis; ***Austral.***: Ventavis; ***Austria***: Ilomedin; Ventavis; ***Belg.***: Ventavis; ***Chile***: Ventavis; ***China***: Ventavis (万他维); ***Cz.***: Ilomedin†; Ventavis; ***Denm.***: Ilomedin; Ventavis; ***Fin.***: Ilomedin; Ventavis; ***Fr.***: Ilomedine; Ventavis; ***Ger.***: Ilomedin; Ventavis; ***Gr.***: Ilomedin; Ventavis; ***Hong Kong***: Ilomedin; Ventavis; ***Hung.***: Ilomedin; Ventavis; ***Indon.***: Ventavis; ***Irl.***: Ventavis; ***Israel***: Ilomedin; Ventavis; ***Ital.***: Endoprost; Ventavis; ***Malaysia***: Ilomedin; Ventavis; ***Mex.***: Ventavis; ***Neth.***: Ilomedine; Ventavis; ***Norw.***: Ilomedin; Ventavis; ***NZ***: Ilomedin; Ventavis; ***Pol.***: Ilomedin; Ventavis; ***Port.***: Ilomedin; Ventavis; ***Rus.***: Ilomedin (Иломедин); Ventavis (Вентавис); ***Singapore***: Ventavis; ***Spain***: Ilomedin; Ventavis; ***Swed.***: Ilomedin; Ventavis; ***Switz.***: Ilomedin; Ventavis; ***Thai.***: Ilomedin; Ventavis; ***Turk.***: Ilomedin; Ventavis; ***UK***: Ventavis; ***USA***: Ventavis.

Imidapril Hydrochloride *(BANM, rINNM)*

EG-006; Hidrocloruro de imidapril; Imidapriilihydrokloridi; Imidapril, Chlorhydrate d'; Imidapril, hidrocloruro de; Imidaprilhydroklorid; Imidaprili Hydrochloridum; TA-6366; Имидаприла Гидрохлорид.

(*S*)-3-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1-methyl-2-oxoimidazoline-4-carboxylic acid hydrochloride.

$C_{20}H_{27}N_3O_6$,HCl=441.9

CAS — 89371-37-9 (imidapril); 89396-94-1 (imidapril hydrochloride).

ATC — C09AA16.

ATC Vet — QC09AA16.

UNII — 7NSF9GG1NU.

NOTE. The name Vitor has been used as a trade mark for imidapril.

Uses and Administration

Imidapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1). Imidapril owes its activity to imidaprilat, to which it is converted after oral doses. The maximum haemodynamic effect occurs 6 to 8 hours after a dose, although the full effect may not develop for several weeks during chronic dosing. Imidapril is given orally as the hydrochloride.

In the treatment of hypertension, the usual initial dose of imidapril hydrochloride is 5 mg once daily, before food. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be used in the elderly, in patients with renal or hepatic impairment, or in those receiving a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before imidapril is started and resumed later if necessary. The usual maintenance dose is 10 mg daily, although up to 20 mg daily may be given if required. The maximum dose for elderly patients is 10 mg daily.

Imidapril is being investigated for the treatment of cachexia in cancer patients.

Reviews.

1. Robinson DM, *et al.* Imidapril: a review of its use in essential hypertension, type 1 diabetic nephropathy and chronic heart failure. *Drugs* 2007; **67:** 1359–78.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Imidapril acts as a prodrug of the diacid imidaprilat, its active metabolite. After oral doses, imidapril is rapidly but incompletely absorbed; absorption is about 70% and is reduced in the presence of food. Imidapril is metabolised in the liver to imidaprilat. The bioavailability of imidaprilat is about 42% after oral doses of imidapril, and peak plasma concentrations of imidaprilat occur in about 7 hours. Both imidapril and imidaprilat are moderately bound to plasma proteins. About 40% of an oral dose is excreted in the urine, the rest in the faeces. The terminal half-life of imidaprilat is more than 24 hours. Imidapril and imidaprilat are removed by haemodialysis.

References.

1. Hoogkamer JFW, *et al.* Pharmacokinetics of imidapril and its active metabolite imidaprilat following single dose and during steady state in patients with impaired liver function. *Eur J Clin Pharmacol* 1997; **51:** 489–91.
2. Hoogkamer JFW, *et al.* Pharmacokinetics of imidapril and its active metabolite imidaprilat following single dose and during steady state in patients with chronic renal failure. *Eur J Clin Pharmacol* 1998; **54:** 59–61.
3. Harder S, *et al.* Single dose and steady state pharmacokinetics and pharmacodynamics of the ACE-inhibitor imidapril in hypertensive patients. *Br J Clin Pharmacol* 1998; **45:** 377–80.
4. Tsuruoka S, *et al.* Clearance of imidapril, an angiotensin-converting enzyme inhibitor, during hemodialysis in hypertensive renal failure patients: comparison with quinapril and enalapril. *J Clin Pharmacol* 2007; **47:** 259–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tanatril; ***Austria***: Tanatril; ***China***: Tanatril (达爽); ***Cz.***: Tanatril; ***Fr.***: Tanatril; ***Ger.***: Tanatril†; ***Gr.***: Tanatril; ***Hong Kong***: Tanatril; ***India***: Tanatril; ***Indon.***: Tanapress; ***Jpn***: Tanatril; ***Malaysia***: Tanatril; ***Philipp.***: Norten; Vascor; ***Pol.***: Tanatril; ***Port.***: Cardipril; ***Singapore***: Tanatril; ***Spain***: Hipertene; ***Thai.***: Tanatril; ***UK***: Tanatril.

Multi-ingredient Preparations. ***Philipp.***: Norplus; Vascoride.

Indapamide *(BAN, USAN, rINN)* ⊗

Indapamid; Indapamida; Indapamidi; Indapamidum; SE-1520; Индапамид.

4-Chloro-*N*-(2-methylindolin-1-yl)-3-sulphamoylbenzamide.

$C_{16}H_{16}ClN_3O_3S$=365.8

CAS — 26807-65-8 (anhydrous indapamide).

ATC — C03BA11.

ATC Vet — QC03BA11.

UNII — F089I0511L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Indapamide). A white or almost white powder. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 36: (Indapamide). A white to off-white crystalline powder. Practically insoluble in water; soluble in alcohol, in glacial acetic acid, in acetonitrile, in ethyl acetate, and in methyl alcohol; very slightly soluble in chloroform and in ether.

Uses and Administration

Indapamide is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is used for hypertension (p. 1251.1), and also for oedema, including that associated with heart failure (p. 1262.3).

In some countries indapamide is described as the hemihydrate. In the treatment of **hypertension** the usual oral dose is 1.25 to 2.5 mg once daily, either alone, or with other antihypertensives; a modified-release preparation may be given in a dose of 1.5 mg daily. At higher doses the diuretic effect may become apparent without appreciable additional antihypertensive effect although US licensed product information suggests that the dose may be increased to 5 mg after 4 weeks. In the treatment of **oedema** the usual dose is 2.5 mg once daily increasing to 5 mg daily after 1 week if necessary.

Reviews.

1. Chaffman M, *et al.* Indapamide: a review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs* 1984; **28:** 189–235.
2. Robinson DM, Wellington K. Indapamide sustained release: a review of its use in the treatment of hypertension. *Drugs* 2006; **66:** 257–71.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Effects on the blood. A 58-year-old woman[1] had bleeding from the mucous membrane of the tongue 18 months after starting treatment with a modified-release form of indapamide; she was found to have mild thrombocytopenia, and petechiae were seen. After withdrawal of the drug, bleeding stopped immediately; the platelet count returned to normal within 10 days and the skin lesions faded quickly.

1. Hasanova EA, Agasiyeva NE. Bleeding associated with indapamide SR therapy. *Ann Pharmacother* 2005; **39:** 199–200.

Effects on carbohydrate and lipid metabolism. Several studies have reported no changes in blood-glucose concentrations during indapamide treatment,[1-3] although elevated concentrations have been reported in individual patients.[4,5] There have been reports of increases in total cholesterol[2] and of no change.[3] No adverse biochemical changes were found in studies[6] of a modified-release preparation.

1. Velussi M, *et al.* Treatment of mild-to-moderate hypertension with indapamide in type II diabetics: midterm (six months) evaluation. *Curr Ther Res* 1988; **44:** 1076–86.
2. Prisant LM, *et al.* Biochemical, endocrine, and mineral effects of indapamide in black women. *J Clin Pharmacol* 1990; **30:** 121–6.
3. Leonetti G, *et al.* Long-term effects of indapamide: final results of a two-year Italian multicenter study in systemic hypertension. *Am J Cardiol* 1990; **65:** 674–714.
4. Slotkoff L. Clinical efficacy and safety of indapamide in the treatment of edema. *Am Heart J* 1983; **106:** 233–7.
5. Beling S, *et al.* Long term experience with indapamide. *Am Heart J* 1983; **106:** 258–62.
6. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. *Drug Safety* 2001; **24:** 1155–65.

Effects on electrolyte balance. By 2002, 164 cases of hyponatraemia with indapamide had been reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC),[1] of which 68 also described hypokalaemia. Most patients were elderly women. A review[2] of some of these cases suggested that hyponatraemia was more commonly reported with indapamide than with chlorothiazide, although it was pointed out[3] that the true incidence cannot be determined from spontaneous reports. ADRAC recommends that indapamide should be used cautiously. It may be that indapamide has no clinical advantage over low-dose thiazide diuretics.

1. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Indapamide and hyponatraemia. *Aust Adverse Drug React Bull* 2002; **21:** 11. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0208.htm (accessed 06/07/04)
2. Chapman MD, *et al.* Hyponatraemia and hypokalaemia due to indapamide. *Med J Aust* 2002; **176:** 219–21.
3. Howes LG. Hyponatraemia and hypokalaemia caused by indapamide. *Med J Aust* 2002; **177:** 53–4.

Effects on the kidneys. Acute interstitial nephritis was associated with indapamide treatment in a 74-year-old patient.[1]

1. Newstead CG, *et al.* Interstitial nephritis associated with indapamide. *BMJ* 1990; **300:** 1344.

Effects on the skin. Sixteen cases of rash attributed to indapamide had been reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs.[1] All patients had taken indapamide 2.5 mg daily for hypertension. The rash was accompanied by fever in 5 cases. In all cases the rash subsided within 14 days of withdrawal, and 11 patients subsequently took thiazides, furosemide, or clopamide without recurrence. Among 188 cases of rash attributed to indapamide reported to the WHO Collaborating Centre for International Drug Monitoring were 4 cases of erythema multiforme and 2 of epidermal necrolysis. A further case of toxic epidermal necrolysis was reported by independent authors.[2]

1. Stricker BHC, Biriell C. Skin reactions and fever with indapamide. *BMJ* 1987; **295:** 1313–14.
2. Black RJ, *et al.* Toxic epidermal necrolysis associated with indapamide. *BMJ* 1990; **301:** 1280–1.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Indapamide is rapidly and completely absorbed from the gastrointestinal tract. Elimination is biphasic with a half-life in whole blood of about 14 hours. Indapamide is strongly bound to red blood cells. It is extensively metabolised. About 60 to 70% of the dose has been reported to be excreted in the urine; only about 5 to 7% is excreted unchanged. About 16 to 23% of dose is excreted in the faeces. Indapamide is not removed by haemodialysis but does not accumulate in patients with renal impairment.

References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.
2. Schiavi P, *et al.* Pharmacokinetics of sustained and immediate release formulations of indapamide after single and repeated oral administration in healthy volunteers. *Fundam Clin Pharmacol* 2000; **14:** 139–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bajaten; Duremid; Natrilix; Noranat; ***Austral.***: Dapa-Tabs; Indahexal; Insig; Napamide; Natrilix; ***Austria***: Fludex; ***Belg.***: Docindapa†; Fludex; ***Braz.***: Indapen; Natrilix; ***Canad.***: Lozide; ***Chile***: Indapress; Natrilix; ***China***: An Tai Da (安泰达); Millibar (美利巴); Na Si Li Tuo (纳斯力妥); Natrilix (纳催离); Ping Zhi (平至); Sheng Chang (圣畅); Shoubishan (寿比山); Xi Er Da (希尔达); Ya Rong (雅荣); Yi Te An (伊特安); Yue Nan Shan (悦南珊); ***Cz.***: Indap; Izepox; Rawel; Tertensif; ***Denm.***: Indacar; Natrilix; Tertensif†; ***Fin.***: Natrilix; Tertensif; ***Fr.***: Fludex; ***Ger.***: Inda-Puren†; Natrilix; ***Gr.***: Dixamid; Fludex; Magniton-R; Transipen; ***Hong Kong***: CP-Indap†; Dapa-Tabs; Diflerix†; Frumeron†; Indalix; Millibar†; Natrilix; Rinalix†; ***Hung.***: Apadex; Indastad; Lapiden; Narva; Pretanix; Rawel; ***India***: CGMide; Diurix; Divret; Fanton; In; Ind; Indacard; Indap; Indicontin†; Inditor; Inzu; Lorvas; Natrilix; ***Indon.***: Natrilix; ***Irl.***: Agelan†; Napamide; Natrilix; ***Israel***: Pamid; ***Ital.***: Damide†; Indaflex; Indamol; Ipamix; Millibar; Natrilix; Pressural; Veroxil; ***Malaysia***: Dapa†; Diflerix†; Indalix; Napamide; Natrilix; Rinalix†; ***Mex.***: Natrilix; ***Neth.***: Flu-

dex; ***NZ***: Dapa-Tabs; Napamide; Natrilix; ***Philipp.***: Natrilix; Vazamide; ***Pol.***: Apo-Indap; Diuresin; Indapen; Indapres; Indapsan†; Indix; Ipres; Opamid; Rawel; Symapamid; Tertensif; ***Port.***: Arifon†; Eulex; Fludex; Fluidema; Indir; Norpress; Pamir†; Rawel; Tandix; Vasodipin; ***Rus.***: Akripamide (Акрипамид); Arifon (Арифон); Arindap (Ариндап); Indap (Индап); Indipam (Индипам); Indiur (Индиур); Ionik (Ионик); Ipres (Ипрес); Lorvas (Лорвас); Rawel (Равел); Retapres (Ретапрес); ***S.Afr.***: Adco-Dapamax; Catexan; Daptril; Hydro-Less; Indalix†; Lixamide; Natrilix; ***Singapore***: Dapa-Tabs; Frumeron; Napamide; Natrilix; Rinalix; ***Spain***: Extur; Tertensif; ***Switz.***: Fludapamide; Fludex; ***Thai.***: Frumeron; Inpamide; Intril; Napamide; Natrilix; ***Turk.***: Flubest; Fludex; Fludin; Flupamid; Flutans; Indamid; Indapen; Indurin; ***UAE***: Indanorm; ***UK***: Ethibide; Indipam; Natrilix; Tensaid; ***Ukr.***: Arifon (Арифон); Hemopamid (Хемопамид); Indap (Индап); Indapen (Индапен); Indiure (Индиур)†; Indopres (Индопрес); Ipamid (Ипамид); Ravel (Равел); ***Venez.***: Natrilix.

Multi-ingredient Preparations. ***Arg.***: Bipreterax†; Preterax; ***Austral.***: Coversyl Plus; Doprilamide; Perindo Combi; ***Austria***: Delapride†; Preterax; ***Belg.***: Bi Preterax†; Coperindo; Coversyl Plus; Preterax; ***Braz.***: Coversyl Plus; ***Canad.***: Coversyl Plus; Preterax†; ***China***: Biprel (百普乐); ***Cz.***: Coverex Combi; Noliprel; Noliterax; Pamocombi; Parateraх; Perinpa; Prenewel; Prestarium Combi; Prestarium Neo Combi; ***Denm.***: Coprenessa; Coprindomid†; Coversyl Arginine Plus; Coversyl Comp Novum; Domanion Comp†; Parateraх; Tertensif kombi; ***Fin.***: Acertil Comp; Coprenessa; Coversyl Comp; Noliterax; Teraxans; ***Fr.***: Bipreteraх; Parateraх; Preterax; ***Ger.***: Bipreteraх; Coversum Combi†; Preterax; ***Gr.***: Dinapres; Pediur; Preterax; ***Hong Kong***: Acertil Plus; Predonium; ***Hung.***: Armix Komb; Armix Prekomb; Co-Perineva; Co-Prenessa; Coverex Komb; Coverex Prekomb†; Pretanix Komb; ***India***: Atelol-D; Aten-D; Coversyl Plus; Eviper-D; Inat; Indap-AT; Perigard-D; Perigard-DF; Tenolol-D; ***Indon.***: Bioprexum Plus; ***Irl.***: Bipreteraх; Coversyl Plus; Pendrex Plus; Preterax; Prindavan; Teraxans; ***Ital.***: Delapride; Dinapres; Normopress; Prelectal; Preterax; ***Malaysia***: Coversyl Plus; ***Mex.***: Preterax; ***Neth.***: Comaranil; Coversyl Plus; Noliterax; Predonium†; Preterax; Preterian; ***NZ***: Coversyl Plus; Predonium; ***Philipp.***: Bi-Preterax; Coversyl Plus; Preterax; ***Pol.***: Co-Prenessa; Noliprel; Prestarium Plus†; Tertensif Bi-Kombi; Tertensif Kombi; ***Port.***: Bi Predonium; Bi Preterax; Imprex; Predonium; Preterax; Prilpa; Tecazo; ***Rus.***: Enzix (Энзикс); Noliprel (Нолипрел); Noliprel A (Нолипрел А); Sonoprel (Сонопрел); ***S. Afr.***: Acesyl Co; Bipreteraх†; Coversyl Plus; Pearinda Plus; Preterax; Prexum Plus; Vectoryl Plus; ***Singapore***: Coversyl Plus; Preteraх†; ***Spain***: Bipreteraх; Preterax; ***Switz.***: Coversum Combi; Preteraх†; ***Thai.***: Coversyl Plus; ***Turk.***: Bipreteraх; Coversyl Plus; Delapride; Perivel Plus; Preterax; Serperil Plus; ***UK***: Coversyl Plus; ***Ukr.***: Co-Prenesa (Ко-Пренеса); Enzix (Энзикс); Noliprel (Нолипрел); Prestarium Combi (Престариум Комби); ***Venez.***: Bipreteraх; Preterax.

Pharmacopoeial Preparations
BP 2014: Indapamide Tablets; Prolonged-release Indapamide Tablets;
USP 36: Indapamide Tablets.

Indenolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de indenolol; Indénolol, Chlorhydrate d'; Indenolol, hidrocloruro de; Indenololi Hydrochloridum; Sch-28316Z (indenolol); YB-2; Инденолола Гидрохлорид.

1-*H*-Inden-4(*or* 7)-yloxy-3-isopropylaminopropan-2-ol hydrochloride.

$C_{15}H_{21}NO_2$,HCl=283.8

CAS — 60607-68-3 (indenolol); 68906-88-7 (indenolol hydrochloride).

UNII — 2VLW0IV0ZQ.

Pharmacopoeias. In *Jpn.*

Profile

Indenolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess potent membrane-stabilising properties and intrinsic sympathomimetic activity.

Indenolol has been used orally as the hydrochloride in the management of various cardiovascular disorders.

Indobufen *(rINN)*

Indobufén; Indobufène; Indobufenum; K-3920; Индобуфен.

(±)-2-[4-(1-Oxo-isoindolin-2-yl)phenyl]butyric acid.

$C_{18}H_{17}NO_3$=295.3

CAS — 63610-08-2.

ATC — B01AC10.

ATC Vet — QB01AC10.

UNII — 6T9949G4LZ.

Profile

Indobufen is an inhibitor of platelet aggregation used in various thromboembolic disorders (p. 1273.2) in oral doses of 200 to 400 mg daily given in 2 divided doses. For patients over the age of 65, the dose should be reduced to 100 to 200 mg daily. Doses should also be reduced in renal impairment (see below). Indobufen has also been given parenterally as the sodium salt.

References.

1. Wiseman LR, *et al.* Indobufen: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cerebral, peripheral and coronary vascular disease. *Drugs* 1992; **44:** 445–64.
2. Bhana N, McClellan KJ. Indobufen: an updated review of its use in the management of atherothrombosis. *Drugs Aging* 2001; **18:** 369–88.

Administration in renal impairment. In patients with renal impairment the dose of indobufen should be reduced to 100 mg twice daily; it should not be used if the creatinine clearance is under 30 mL/minute.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: XinBei (辛贝); Yin Si Da (引思达); ***Cz.***: Ibustrin; ***Ital.***: Ibustrin; ***Mex.***: Ibustrin; ***Pol.***: Ibustrin; ***Port.***: Ibustrin; ***Rus.***: Ibustrin (Ибустрин); ***Venez.***: Ibustrin.

Indoramin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de indoramina; Indoramina, hidrocloruro de; Indoramine, Chlorhydrate d'; Indoramini Hydrochloridum; Wy-21901 (indoramin); Индорамина Гидрохлорид.

N-[1-(2-Indol-3-ylethyl)-4-piperidyl]benzamide hydrochloride.

$C_{22}H_{25}N_3O$,HCl=383.9

CAS — 26844-12-2 (indoramin); 33124-53-7 (indoramin hydrochloride); 38821-52-2 (indoramin hydrochloride).

ATC — C02CA02.

ATC Vet — QC02CA02.

UNII — DQ0Z3K8W92.

Pharmacopoeias. In *Br.*

BP 2014: (Indoramin Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in alcohol; very slightly soluble in ether; soluble in methyl alcohol. A 2% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Indoramin is a selective and competitive alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1); it is also reported to have membrane-stabilising properties and to be a competitive antagonist at histamine H_1 and 5-hydroxytryptamine receptors. Indoramin is used in the management of hypertension (p. 1251.1), and in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction. It has also been used in the prophylactic treatment of migraine.

Indoramin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Indoramin hydrochloride 11.0 mg is equivalent to about 10 mg of indoramin.

In **hypertension**, the initial dose is 25 mg twice daily, increased in steps of 25 or 50 mg at intervals of 2 weeks to a maximum of 200 mg daily in 2 or 3 divided doses.

In **benign prostatic hyperplasia**, the initial dose is 20 mg twice daily, increased if necessary by 20 mg at 2-week intervals, to a maximum of 100 mg daily in divided doses.

Lower doses may be required in the elderly.

Reviews.

1. Holmes B, Sorkin EM. Indoramin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and related vascular, cardiovascular and airway diseases. *Drugs* 1986; **31:** 467–99.

Migraine. Although propranolol is probably the most well-established drug for prophylaxis of migraine (p. 670.3) other drugs, including indoramin, have been used. In a double-blind study,[1] indoramin in a dose of 25 mg twice daily was reported to be as effective as dihydroergotamine mesilate in reducing the frequency of migraine attacks.

1. Pradalier A, *et al.* Etude comparative indoramine versus dihydroergotamine dans le traitement préventif de la migraine. *Therapie* 1988; **43:** 293–7.

Adverse Effects, Treatment, and Precautions

The most common adverse effects in patients receiving indoramin are sedation and dizziness; dry mouth, nasal congestion, headache, fatigue, depression, weight gain (almost certainly due to fluid retention), and failure of ejaculation may also occur. Tachycardia does not seem to be a problem with therapeutic doses but orthostatic hypotension may occur and may produce syncope. Extrapyramidal disturbances have been reported.

After overdosage, coma, convulsions, and hypotension may occur; hypothermia has been reported in *animals*. In acute poisoning appropriate symptomatic and supportive care should be given; if the patient presents within 1 hour, activated charcoal may be considered.

Indoramin should be avoided in patients with heart failure; it has been recommended that incipient heart failure should be controlled before giving indoramin. Caution should be observed in patients with hepatic or renal impairment, a history of depression, epilepsy, or Parkinson's disease. Elderly patients may respond to lower doses.

Because indoramin can cause drowsiness care should be taken in patients who drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Cataract Surgery, under Precautions for Tamsulosin Hydrochloride, p. 2369.3.

Effects on mental function. Sleep disturbances and vivid dreams were reported during a study in hypertensive patients when indoramin was added to therapy with a thiazide diuretic and a beta blocker.[1]

1. Marshall AJ, *et al.* Evaluation of indoramin added to oxprenolol and bendrofluazide as a third agent in severe hypertension. *Br J Clin Pharmacol* 1980; **10:** 217–21.

Overdosage. A 43-year-old woman with a long history of heavy alcohol intake died after taking 100 tablets of indoramin 25 mg.[1] The main clinical features were deep sedation, respiratory depression, hypotension, and convulsions. Although the hypotension was satisfactorily controlled the CNS effects were resistant to treatment and proved fatal. Other clinical features included areflexia, metabolic acidosis, tachycardia, and later bradyarrhythmias. In another report,[2] self-poisoning with indoramin was associated with development of torsade de pointes.

1. Hunter R. Death due to overdose of indoramin. *BMJ* 1982; **285:** 1011.
2. Nisse P, *et al.* Torsade de pointes: a severe and unknown adverse effect in indoramin self-poisoning. *Int J Cardiol* 2009; **133:** e73–e75.

Interactions

The hypotensive effects of indoramin may be enhanced by diuretics and other antihypertensives. It has been reported that the ingestion of alcohol can increase the rate and extent of absorption and the sedative effects of indoramin (see below) and that indoramin should not be given to patients already receiving MAOIs.

Alcohol. In a study[1] in 9 healthy subjects alcohol 500 mg/kg significantly enhanced plasma-indoramin concentrations after an oral dose of 50 mg. The effect was most marked in the early period, corresponding to the absorptive phase. The mean peak plasma-indoramin concentration was increased from 15.0 to 23.7 nanograms/mL by alcohol; the area under the concentration/time curve was increased by 25%. Alcohol did not affect the pharmacokinetics of intravenous indoramin. The results suggest that alcohol increases indoramin bioavailability either by enhancing absorption or reducing first-pass metabolism. The combination was more sedative than either drug alone.

1. Abrams SML, *et al.* Pharmacokinetic interaction between indoramin and ethanol. *Hum Toxicol* 1989; **8:** 237–41.

Pharmacokinetics

Indoramin is readily absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism. It is reported to be about 90% bound to plasma proteins. It has a half-life of about 5 hours which is reported to be prolonged in elderly patients. It is extensively metabolised and is excreted mainly as metabolites in the urine and faeces. There is evidence to suggest that some metabolites may have some alpha-adrenoceptor blocking activity.

The elderly. The plasma half-life of indoramin in 5 healthy elderly subjects after a single oral dose ranged from 6.6 to 32.8 hours with a mean of 14.7 hours.[1] The increased half-life may have been caused by reduced clearance in elderly patients.

1. Norbury HM, *et al.* Pharmacokinetics of oral indoramin in elderly and middle-aged female volunteers. *Eur J Clin Pharmacol* 1984; **27:** 247–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vidora; ***Ger.***: Wydora†; ***Gr.***: Wydora; ***Irl.***: Doralese†; ***S.Afr.***: Baratol†; ***UK***: Baratol†; Doralese.

Pharmacopoeial Preparations
BP 2014: Indoramin Tablets.

Inositol Nicotinate *(BAN, rINN)*

Inositol Niacinate (USAN); Inositol, Nicotinate d'; Inositoli Nicotinas; Inositolinikotinaatti; Inositolnikotinat; Nicotinato de inositol; NSC-49506; Win-9154; Инозитола Никотинат.

meso-Inositol hexanicotinate; *myo*-Inositol hexanicotinate.
$C_{42}H_{30}N_6O_{12}$=810.7
CAS — 6556-11-2.
ATC — C04AC03.
ATC Vet — QC04AC03.
UNII — A99MK953KZ.

Pharmacopoeias. In *Br.*

BP 2014: (Inositol Nicotinate). A white or almost white, odourless or almost odourless powder. Practically insoluble in water, in alcohol, in acetone, and in ether; sparingly soluble in chloroform. It dissolves in dilute mineral acids.

Profile

Inositol nicotinate is a vasodilator and is believed to be slowly hydrolysed to nicotinic acid (p. 2083.1). It is given orally in the management of peripheral vascular disorders (p. 1272.3) although good evidence of efficacy is lacking. The usual dose is 3 g daily given in divided doses. The dose may be increased to 4 g daily if necessary.

Inositol nicotinate has been used in hyperlipidaemias.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Nianate; ***Gr.***: Hexaniton; ***India***: Nicovas; ***Irl.***: Hexopal; ***UK***: Hexopal.

Multi-ingredient Preparations. ***S.Afr.***: Geratar†.

Pharmacopoeial Preparations
BP 2014: Inositol Nicotinate Tablets.

Irbesartan *(BAN, USAN, rINN)*

BMS-186295; Irbesartaani; Irbesartán; Irbésartan; Irbesartanum; SR-47436; Ирбесартан.
2-Butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one.
$C_{25}H_{28}N_6O$=428.5
CAS — 138402-11-6.
ATC — C09CA04.
ATC Vet — QC09CA04.
UNII — J0E2756Z7N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Irbesartan). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in dichloromethane.

USP 36: (Irbesartan). A white to off-white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Store in airtight containers at a temperature below 30 degrees.

Uses and Administration

Irbesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1) including the treatment of renal disease in hypertensive diabetic patients (see Kidney Disorders, under Uses of Losartan, p. 1423.3). Irbesartan is also under investigation in heart failure.

Irbesartan is given orally. After a dose the hypotensive effect peaks within 3 to 6 hours and persists for at least 24 hours. The maximum hypotensive effect is achieved within 4 to 6 weeks after starting therapy.

In **hypertension**, irbesartan is given in a dose of 150 mg once daily increased, if necessary, to 300 mg once daily. A lower initial dose of 75 mg once daily may be considered in elderly patients over 75 years, for patients with intravascular volume depletion, and for those receiving haemodialysis.

For the treatment of **renal disease** in hypertensive type 2 diabetics, irbesartan should be given in an initial dose of 150 mg once daily, increased to 300 mg once daily for maintenance.

Irbesartan has been used similarly as the hydrochloride.

Reviews.

1. Ravera M, *et al.* Prevention and treatment of diabetic nephropathy: the program for irbesartan mortality and morbidity evaluation. *J Am Soc Nephrol* 2005; **16** (suppl 1): S48–S52.
2. Palmer AJ, *et al.* Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis. *Int J Clin Pract* 2007; **61:** 1626–33.
3. Flack JM. Maximising antihypertensive effects of angiotensin II receptor blockers with thiazide diuretic combination therapy: focus on irbesartan/hydrochlorothiazide. *Int J Clin Pract* 2007; **61:** 2093–1102.
4. Croom KF, Plosker GL. Irbesartan: a review of its use in hypertension and diabetic nephropathy. *Drugs* 2008; **68:** 1543–69.
5. Negro R. Endothelial effects of antihypertensive treatment: focus on irbesartan. *Vasc Health Risk Manag* 2008; **4:** 89–101.
6. Bramlage P, *et al.* The value of irbesartan in the management of hypertension. *Expert Opin Pharmacother* 2009; **10:** 1817–31.
7. Bramlage P, Schindler C. Differences in pharmacology and their translation into differences in clinical efficacy—a comparison of the renin angiotensin blocking agents irbesartan and losartan. *Expert Opin Pharmacother* 2010; **11:** 521–35.

Administration in children. Although irbesartan appears to be well-tolerated in children with hypertension and has been shown to reduce blood pressure in small studies,[1] US licensed product information notes that doses of up to 4.5 mg/kg once daily were ineffective in children aged 6 to 16 years and no longer recommends use in such patients.

In children with chronic kidney diseases, irbesartan has been reported to reduce blood pressure and proteinuria.[2,3] The initial dose was 37.5 mg once daily for children weighing 10 to 20 kg, 75 mg once daily for those weighing 21 to 40 kg, and 150 mg once daily for those weighing more than 40 kg; doses could be doubled if the blood pressure response was inadequate.

1. Sakarcan A, *et al.* The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J Clin Pharmacol* 2001; **41:** 742–9.
2. Franscini LMD, *et al.* Effectiveness and safety of the angiotensin II antagonist irbesartan in children with chronic kidney diseases. *Am J Hypertens* 2002; **15:** 1057–63.
3. Gartenmann AC, *et al.* Better renoprotective effect of angiotensin II antagonist compared to dihydropyridine calcium channel blocker in childhood. *Kidney Int* 2003; **64:** 1450–4.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies irbesartan as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Irbesartan is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of 60 to 80%. Peak plasma concentrations of irbesartan occur 1.5 to 2 hours after an oral dose. Irbesartan is about 96% bound to plasma proteins. It undergoes some metabolism in the liver, primarily by the cytochrome P450 isoenzyme CYP2C9, to inactive metabolites. It is excreted as unchanged drug and metabolites in the bile and in urine; about 20% of an oral or intravenous dose is excreted in the urine, with less than 2% as unchanged drug. The terminal elimination half-life is about 11 to 15 hours.

References.

1. Sica DA, *et al.* The pharmacokinetics of irbesartan in renal failure and maintenance hemodialysis. *Clin Pharmacol Ther* 1997; **62:** 610–18.
2. Marino MR, *et al.* Pharmacokinetics and pharmacodynamics of irbesartan in healthy subjects. *J Clin Pharmacol* 1998; **38:** 246–55.
3. Marino MR, *et al.* Pharmacokinetics and pharmacodynamics of irbesartan in patients with hepatic cirrhosis. *J Clin Pharmacol* 1998; **38:** 347–56.
4. Vachharajani NN, *et al.* Oral bioavailability and disposition characteristics of irbesartan, an angiotensin antagonist, in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 702–7.
5. Vachharajani NN, *et al.* The effects of age and gender on the pharmacokinetics of irbesartan. *Br J Clin Pharmacol* 1998; **46:** 611–13.
6. Sakarcan A, *et al.* The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J Clin Pharmacol* 2001; **41:** 742–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adana; Aprovel; Avapro; ***Austral.***: Avapro; Karvea; ***Belg.***: Aprovel; ***Braz.***: Aprovel; Avapro; ***Canad.***: Avapro; ***Chile***: Aprovel; ***China***: An Lai (安来); Aprovel (安博维); Gan Yue Xi (甘悦喜); Geping (格平); Ji Jia (吉加); KeSu (科苏); Pu Li Ning (普利宁); Ruo Peng (若朋); Su Shi (苏适); Xin Ping (欣平); Yi Da Li (伊达力); Yi Kang Ning (伊康宁); Yi Tai Qing; ***Cz.***: Aprovel; Ifirmasta; Irbec; Isame; Karvea; ***Denm.***: Aprovel; Ifirmasta; Irbenidda†; ***Fin.***: Aprovel†; ***Fr.***: Aprovel; ***Ger.***: Aprovel; Karvea; ***Gr.***: Alvein; Aprovel; Besartan; Irven; Karvea; ***Hong Kong***: Aprovel; ***Hung.***: Aprovel; Ebrit; Irabel; Irprestan; Pribercor; ***India***: Aprovel; Irbest; Irovel; Xarb; ***Indon.***: Aprovel; Elzar; Fritens; Iretensa; Irtan; Irvask; Irvell; ***Irl.***: Aprovel; Irbesan; Karvea; Licolin; ***Ital.***: Abesart; Aprovel; Karvea; Quarlintan; Rabesat; Sykratan; ***Malaysia***: Aprovel; ***Mex.***: Aprovel; Avapro; ***Neth.***: Abesart; Agepin; Aprovel; Ardinel; Artibesan; Bersin; Gemot; Ifirmasta; Irbec; Irbenahyp; Irbenidda†; Irberan; Irsalico; Junelic; Karvea; Licolin; Saberve; Vilconir†; Ybersigax; ***Norw.***: Aprovel; ***NZ***: Karvea†; ***Philipp.***: Aprovel; Bezart; Izart; ***Pol.***: Aprovel; Ifirmasta; Karvea; ***Port.***: Abavil; Aprovel; Ifirmasta; Karvea; Trabiran†; ***Rus.***: Aprovel (Апровель); Firmasta (Фирмаста); ***S.Afr.***: Aprovel; Irbewin; ***Singapore***: Aprovel; ***Spain***: Aprovel; Ifirmasta; Karvea; ***Swed.***: Aprovel; ***Switz.***: Aprovel; ***Thai.***: Aprovel; Irbenox; Presolin; ***Turk.***: Irda; Karvea; ***UK***: Aprovel; Sabervel; ***Ukr.***: Aprovel (Апровель); Irebetan (Ирбетан); ***USA***: Avapro; ***Venez.***: Aprovel.

Multi-ingredient Preparations. ***Arg.***: Adana Plus; Avapro HCT; CoAprovel; ***Austral.***: Avapro HCT; Karvezide; ***Belg.***: CoAprovel; ***Braz.***: Aprozide; ***Canad.***: Avalide; ***Chile***: CoAprovel; ***China***: An Li Bo (安利博); CoAprovel (安博诺); ***Cz.***: CoAprovel; Irbesartan HCT; Irbezyd Combi; Karvezide; Lartokaz; ***Denm.***: CoAprovel; ***Fr.***: CoAprovel; ***Ger.***: CoAprovel; Karvezide; ***Gr.***: CoAprovel; Karvezide; ***Hong Kong***: CoAprovel; ***Hung.***: CoAprovel; Ebrit HCT; Irprestan HCT; ***India***: CoAprovel; Irovel-H; Xarb-H; ***Indon.***: CoAprovel; Irtan Plus; ***Irl.***: CoAprovel; Ifirmacombi; Karvezide; ***Ital.***: CoAprovel; Karvezide; ***Jpn***: Aimix; Irtra; ***Malaysia***: CoAprovel; ***Mex.***: Avalide; CoAprovel; ***Neth.***: Arablocktans; Bloketangil; CoAprovel; Dazirok; Ebirintazide; Ifirmacombi; Karvezide; Lartokaz; Licarbetida; ***Norw.***: CoAprovel; ***NZ***: Karvezide†; ***Philipp.***: CoAprovel; ***Pol.***: CoAprovel; Karvezide; ***Port.***: CoAprovel; Karvezide; ***Rus.***: CoAprovel (Коапровель); ***S.Afr.***: Co-Irbewin; CoAprovel; ***Singapore***: CoAprovel; ***Spain***: CoAprovel; Ifirmacombi; Karvezide; ***Swed.***: CoAprovel; ***Switz.***: CoAprovel; ***Thai.***: CoAprovel; ***Turk.***: Co-Irda; Karvezide; ***UK***: CoAprovel; ***Ukr.***: Co-Irbesan (Ко-Ирбесан); ***USA***: Avalide; ***Venez.***: CoAprovel.

Pharmacopoeial Preparations
BP 2014: Irbesartan Tablets;
USP 36: Irbesartan and Hydrochlorothiazide Tablets; Irbesartan Tablets.

Isoprenaline *(BAN, rINN)* ⊗

Isoprenaliini; Isoprenalin; Isoprenalina; Isoprénaline; Isoprenalinum; Isopropilarterenol; Isopropilnoradrenalina; Isopropilnorepinefrina; Isopropylarterenol; Isopropylnoradrenaline; Isoproterenol; Изопреналин.
1-(3,4-Dihydroxyphenyl)-2-isopropylaminoethanol.
$C_{11}H_{17}NO_3$=211.3
CAS — 7683-59-2.
ATC — C01CA02; R03AB02; R03CB01.
ATC Vet — QC01CA02; QR03AB02; QR03CB01.
UNII — L628TT009W.

Isoprenaline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de isoprenalina; Isoprenaliinihydrokloridi; Isoprenalina, hidrocloruro de; Isoprénaline, Chlorhydrate d'; Isoprenalinhydrochlorid; Isoprenalin-hydrochlorid; Isoprenalinhydroklorid; Isoprenalini Hydrochloridum; Isopropylarterenol Hydrochloride; Isopropylnoradrenaline Hydrochloride; Isoproterenol Hydrochloride; Izoprenalin Hidroklorür; Izoprenalin-hidroklorid; Izoprenalino hidrochloridas; Изопреналина Гидрохлорид.
$C_{11}H_{17}NO_3$,HCl=247.7
CAS — 51-30-9.
ATC — C01CA02; R03AB02; R03CB01.
ATC Vet — QC01CA02; QR03AB02; QR03CB01.
UNII — DIA2A74855.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Isoprenaline Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Isoproterenol Hydrochloride). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to air and light. Soluble 1 in 3 of water and 1 in 50 of alcohol; less soluble in dehydrated alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing exposed to air and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Isoprenaline Sulfate *(BANM, rINNM)* ⊗

Isoprenaliinisulfaatti; Isoprenalin sulfát dihydrát; Isoprenalina, sulfato de; Isoprénaline, Sulfate d'; Isoprenaline Sulphate; Isoprenalini Sulfas; Isoprenalini Sulfas Dihydricus; Isoprenalinsulfat; Isopropylarterenol Sulphate; Isopropylnoradrenaline Sulphate; Isoproterenol Sulfate; Izoprenalino sulfatas; Izoprenalin-szulfát; Izoprenaliny siarczan; Sulfato de isoprenalina; Изопреналина Сульфат.
$(C_{11}H_{17}NO_3)_2,H_2SO_4,2H_2O$=556.6
CAS — 299-95-6 (anhydrous isoprenaline sulfate); 6700-39-6 (isoprenaline sulfate dihydrate).
ATC — C01CA02; R03AB02; R03CB01.
ATC Vet — QC01CA02; QR03AB02; QR03CB01.
UNII — 052RYF6JDD (anhydrous isoprenaline sulfate); 925FX3X776 (isoprenaline sulfate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Isoprenaline Sulfate). A white or almost white crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Isoproterenol Sulfate). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to light and air. Soluble 1 in 4 of water; very slightly soluble in alcohol, in chloroform, in ether, and in benzene. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing

exposed to air, and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Uses and Administration

Isoprenaline is a sympathomimetic (p. 1507.3) that acts almost exclusively on beta-adrenergic receptors. It has a powerful stimulating action on the heart and increases cardiac output, excitability, and rate; it also causes peripheral vasodilatation and produces a fall in diastolic blood pressure and usually maintains or slightly increases systolic blood pressure. In addition, isoprenaline has bronchodilating properties. It also stimulates the CNS.

Isoprenaline has been used in the temporary control of bradycardia that is unresponsive to atropine or dobutamine, in heart block, and in Stokes-Adams attacks, until a pacemaker is fitted; however, other drugs are often preferred. It has also been used as an adjunct in shock (p. 1279.3), congestive heart failure (p. 1262.3), and torsade de pointes (see Cardiac Arrhythmias, p. 1266.1). High doses may be of particular use in beta-blocker overdose. Isoprenaline has been used in the diagnosis of congenital heart defects and of coronary artery disease.

For **cardiac disorders** isoprenaline is given intravenously as the hydrochloride under ECG control; the dose is adjusted according to response and the patient's condition. In emergencies, a slow intravenous infusion is given in doses typically ranging from 0.5 to 5 micrograms/min, although higher doses may be necessary. Alternatively, a slow intravenous injection is given in initial doses ranging from 20 to 60 micrograms; repeat injections of 10 to 200 micrograms may be given if necessary. In extreme emergencies, an intracardiac injection of 20 micrograms may be given by those experienced in the technique. In less urgent situations, intramuscular or subcutaneous injections may be given in a typical initial dose of 200 micrograms, with subsequent doses adjusted according to response. Tablets of isoprenaline hydrochloride have been given orally or sublingually.

Isoprenaline has been used as a bronchodilator in the management of **reversible airways obstruction** but sympathomimetics with a selective action on $beta_2$ receptors, such as salbutamol, are now preferred (see Asthma, p. 1195.2). It has been given as the sulfate or hydrochloride, usually by inhalation; sublingual tablets have also been used. Low-dose injections of isoprenaline have been given to control bronchospasm during anaesthesia.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Isoprenaline has almost exclusively beta-agonist properties but also stimulates the CNS; its main adverse effects include tachycardia and cardiac arrhythmias, palpitations, hypotension, tremor, headache, sweating, and facial flushing. Prolonged use of isoprenaline has been associated with swelling of the parotid glands.

Prolonged use of sublingual tablets may also cause severe damage to the teeth due to the acidic nature of the drug. Sublingual use or inhalation may colour the saliva or sputum red.

Increased mortality. For a discussion of the increased mortality and morbidity that has sometimes been seen in asthmatic patients using beta agonists and reference to an early epidemic associated with isoprenaline inhalers, see Fenoterol, p. 1208.3.

Interactions

As for Sympathomimetics, p. 1508.3. Due to the risk of arrhythmias, isoprenaline should not be used with other potent $beta_1$ agonists such as adrenaline.

Theophylline. For reports of increased theophylline clearance following use of isoprenaline, see Sympathomimetics, p. 1236.3.

Pharmacokinetics

As a result of sulfate conjugation in the gut, isoprenaline is considerably less active orally than after parenteral doses. It is absorbed through the oral mucosa and has accordingly been given sublingually, but absorption by this route remains very erratic. Isoprenaline in the body is resistant to metabolism by monoamine oxidase, but is metabolised by catechol-*O*-methyltransferase in the liver, lungs, and other tissues, the metabolite then being conjugated before excretion in the urine. Whereas the sulfate conjugate of isoprenaline is inactive the methylated metabolite has weak activity.

After intravenous injection isoprenaline has a plasma half-life of about one to several minutes according to whether the rate of injection is rapid or slow; it is almost entirely excreted in the urine as unchanged drug and metabolites within 24 hours. A much slower onset of action and a more extended initial half-life has been found after oral dosage. Isoprenaline is reported to have a duration of action of up to about 2 hours after inhalation; it has been shown that a large proportion of an inhaled dose is swallowed.

References.

1. Blackwell EW, *et al.* The fate of isoprenaline administered by pressurized aerosols. *Br J Pharmacol* 1970; **39:** 194P–195P.
2. Conolly ME, *et al.* Metabolism of isoprenaline in dog and man. *Br J Pharmacol* 1972; **46:** 458–72.
3. Blackwell EW, *et al.* Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dog. *Br J Pharmacol* 1974; **50:** 587–91.
4. Reyes G, *et al.* The pharmacokinetics of isoproterenol in critically ill pediatric patients. *J Clin Pharmacol* 1993; **33:** 29–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Isuprel; ***Belg.***: Isuprel; ***Cz.***: Isuprel†; ***Fr.***: Isuprel; ***Gr.***: Isuprel; Neo-Elixir†; ***India***: Autohaler; Isolin; Isosol; Neo-Epinine; ***Indon.***: Isuprel†; ***Israel***: Isuprel†; ***NZ***: Isuprel; ***S.Afr.***: Imuprel†; ***Spain***: Aleudrina; ***Thai.***: Isuprel; ***USA***: Isuprel; Medihaler-Iso†.

Multi-ingredient Preparations. ***Spain***: Aldo Asma†; Frenal Compositum†; ***USA***: Norisodrine with Calcium Iodide.

Pharmacopoeial Preparations

BP 2014: Isoprenaline Injection;

USP 36: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Isoproterenol Hydrochloride Inhalation Aerosol; Isoproterenol Hydrochloride Injection; Isoproterenol Hydrochloride Tablets; Isoproterenol Inhalation Solution; Isoproterenol Sulfate Inhalation Aerosol; Isoproterenol Sulfate Inhalation Solution.

Isosorbide *(BAN, USAN, rINN)* ⊗

AT-101; Isosorbida; Isosorbidum; NSC-40725; Изосорбид.

1,4:3,6-Dianhydro-D-glucitol.

$C_6H_{10}O_4$=146.1

CAS — 652-67-5.

UNII — WXR179L51S.

Pharmacopoeias.

In *Jpn.*

US includes Isosorbide Concentrate.

USP 36: (Isosorbide Concentrate). An aqueous solution containing 70.0 to 80.0% w/w of isosorbide. A colourless to slightly yellow liquid. Soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Isosorbide is an osmotic diuretic with properties similar to those of mannitol (p. 1427.3). It is reported to cause less nausea and vomiting than other oral osmotic diuretics.

Isosorbide is used for short-term reduction of intraocular pressure in acute glaucoma or before surgery (p. 1999.1). The usual oral dose is 1 to 3 g/kg 2 to 4 times daily. Its action usually begins within 30 minutes and lasts for up to 5 or 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Ismotic†.

Pharmacopoeial Preparations

USP 36: Isosorbide Concentrate; Isosorbide Oral Solution.

Isosorbide Dinitrate *(BAN, USAN, rINN)*

Dinitrato de isosorbida; ISDN; Isosorbid dinitrát; Isosorbida, dinitrato de; Isosorbiddinitrat; Isosorbide, Dinitrate d'; Isosorbidi dinitras; Isosorbididinitraatti; Izosorbid Dinitrat; Izosorbido dinitratas; Izosorbidu diazotan; Izoszorbid-dinitrát; Sorbide Nitrate; Изосорбида Динитрат.

1,4:3,6-Dianhydro-D-glucitol 2,5-dinitrate.

$C_6H_8N_2O_8$=236.1

CAS — 87-33-2.

ATC — C01DA08; C05AE02.

ATC Vet — QC01DA08; QC05AE02.

UNII — IA7306519N.

Pharmacopoeias.

In *Chin.* and *Jpn.*

Eur. (see p. vii), *Int.*, and *US* include diluted isosorbide dinitrate.

Ph. Eur. 8: (Isosorbide Dinitrate, Diluted). A dry mixture of isosorbide dinitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone.

USP 36: (Diluted Isosorbide Dinitrate). A dry mixture of isosorbide dinitrate (usually about 25%) with lactose, mannitol, or other suitable inert excipients, the latter being added to minimise the risk of explosion. It may contain up to 1% of a suitable stabiliser such as ammonium phosphate. It is an ivory-white, odourless powder. Store in airtight containers.

Undiluted isosorbide dinitrate occurs as white crystalline rosettes. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone; freely soluble in chloroform.

Handling. Undiluted isosorbide dinitrate may explode if subjected to percussion or excessive heat.

Stability. The loss of isosorbide dinitrate from solution during infusion was found to be 30% with PVC plastic intravenous infusion sets but negligible when polyolefin or glass delivery systems were used.[1] Another study reported a 23% decrease in isosorbide dinitrate concentration after 24 hours of storage at 21 degrees in PVC containers; most of the loss occurred in the first 6 hours. Loss of potency was not noted when isosorbide dinitrate was stored under similar conditions in glass bottles or polyethylene, nylon, and polypropylene laminated bags.[2]

1. Kowaluk EA, *et al.* Drug loss in polyolefin infusion systems. *Am J Hosp Pharm* 1983; **40:** 118–19.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Uses and Administration

Isosorbide dinitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p. 1391.3). It is used in the management of angina pectoris (p. 1254.3) and of heart failure (below). It has also been investigated in myocardial infarction (p. 1257.1).

Isosorbide dinitrate may be given by the sublingual, oral, transdermal, or intravenous route.

In **angina** isosorbide dinitrate may be given as sublingual tablets or spray for the relief of an acute attack, although glyceryl trinitrate may be preferred because it has a faster onset of action. Isosorbide dinitrate may also be used before an activity or stress which might provoke an attack. The usual dose in acute angina is 2.5 to 10 mg sublingually. As an alternative, one to three sprays (1.25 mg/spray) may be directed under the tongue.

Isosorbide dinitrate is also used in the long-term management of angina in oral doses of 20 to 120 mg daily in divided doses according to the patient's needs. Increases in dosage should be gradual to avoid adverse effects. Up to 240 mg daily in divided doses may be necessary. Modified-release formulations may be used in equivalent doses. Transdermal preparations such as topical sprays or ointments may also be used.

Isosorbide dinitrate is given by intravenous infusion for unstable angina. The dose is titrated according to patient response; doses in the range of 2 to 12 mg/hour are usually suitable but up to 20 mg/hour may be necessary in some patients. Some plastics used in the infusion equipment may adsorb isosorbide dinitrate (see Stability, above) and allowance may have to be made for this.

During percutaneous transluminal coronary angioplasty isosorbide dinitrate may be given by the intracoronary route to allow prolonged balloon inflation and to prevent or relieve coronary spasm. Only injections of isosorbide dinitrate which are approved for intracoronary use should be given by this route as preparations intended for normal intravenous use may contain additives that are harmful if injected into diseased coronary vessels. The usual dose is 1 mg as a bolus before balloon inflation. The maximum recommended dose is 5 mg within a 30-minute time period.

Isosorbide dinitrate is also used in the management of **heart failure**. It is given in doses of 5 to 10 mg sublingually every 2 hours as required, or in oral doses of 60 to 160 mg daily in divided doses. Oral doses of up to 240 mg daily may be required. It may also be given intravenously using the intravenous doses given above for angina. An oral combination preparation with hydralazine is also available for use in self-identified black patients. It is given in a dose of 20 mg of isosorbide dinitrate with 37.5 mg of hydralazine hydrochloride three times daily; the dose may be doubled if necessary.

Heart failure. Although direct-acting vasodilators do not have a major role in the management of chronic heart failure (p. 1262.3) there is some evidence that use of hydralazine with isosorbide dinitrate may be of benefit,[1] although the effect on mortality is less than that seen with ACE inhibitors.[2] Subgroup analysis suggested that the effect might be greater in black patients, and a later study[3] in black patients found that addition of isosorbide dinitrate

and hydralazine to standard therapy improved both morbidity and mortality.

1. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314:** 1547–52.
2. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325:** 303–10.
3. Taylor AL, *et al.* African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57. Correction. *ibid.* 2005; **352:** 1276.

Non-cardiovascular disorders. Nitrates such as isosorbide dinitrate have been tried in conditions including anal fissure, erectile dysfunction, obstetric and gynaecological disorders, oesophageal motility disorders such as achalasia and spasm, and pain. Further details of these uses are given under Glyceryl Trinitrate (p. 1392.2).

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p. 1393.3.

Effects on the blood. Haemolysis occurred in 2 patients with G6PD deficiency during treatment with isosorbide dinitrate.[1]

1. Aderka D, *et al.* Isosorbide dinitrate-induced hemolysis in G6PD-deficient subjects. *Acta Haematol (Basel)* 1983; **69:** 63–4.

Headache. The most common adverse effect of nitrate therapy is headache which usually decreases after a few days. There has been a report[1] of a severe continuous unilateral headache with an oculosympathetic paresis on the same side associated with isosorbide dinitrate therapy.

1. Mueller RA, Meienberg O. Hemicrania with oculosympathetic paresis from isosorbide dinitrate. *N Engl J Med* 1983; **308:** 458–9.

Hypersensitivity. Laryngeal oedema developed on two occasions in a woman after the use of isosorbide dinitrate spray;[1] nifedipine was also given sublingually which on the second occasion caused a noticeable increase in the laryngeal swelling induced by the nitrate.

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.

Nitrate tolerance. Continuous use of organic nitrates is associated with tolerance to their haemodynamic effects; for an overview of nitrate tolerance, see under Precautions for Glyceryl Trinitrate, p. 1394.1.

A study in 12 patients with chronic stable angina[1] showed that after treatment for one week with isosorbide dinitrate 30 mg two or three times daily, treadmill-walking time was longer throughout a 5-hour testing period compared with placebo. In contrast, after treatment for one week with isosorbide dinitrate 30 mg four times daily, treadmill-walking time was prolonged at 1 hour but not at 3 or 5 hours. These results support the concept that clinical efficacy of isosorbide dinitrate is maintained if given in a dose schedule which provides a nitrate-free or a low-nitrate period.

The effect of sublingual isosorbide dinitrate in patients receiving chronic therapy with isosorbide dinitrate was evaluated in 24 patients with angina.[2] Sublingual use produced less reduction of aortic systolic pressure and left ventricular end-diastolic pressure and less dilatation of coronary artery diameter in patients who received chronic isosorbide dinitrate therapy compared with patients not receiving chronic therapy.

1. Parker JO, *et al.* Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med* 1987; **316:** 1440–4.
2. Naito H, *et al.* Effects of sublingual nitrate in patients receiving sustained therapy of isosorbide dinitrate for coronary artery disease. *Am J Cardiol* 1989; **64:** 565–68.

Oedema. Reports of ankle oedema associated with isosorbide dinitrate therapy in 3 patients with heart failure.[1]

1. Rodger JC. Peripheral oedema in patients treated with isosorbide dinitrate. *BMJ* 1981; **283:** 1365–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isosorbide dinitrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Glyceryl Trinitrate, p. 1394.2.

Disopyramide. The efficacy of sublingual isosorbide dinitrate was reduced in a patient taking disopyramide.[1] The interaction was considered to be due to diminished salivary secretions caused by the antimuscarinic action of disopyramide, which inhibited the dissolution of the sublingual isosorbide dinitrate tablet.

1. Barletta MA, Eisen H. Isosorbide dinitrate-disopyramide phosphate interaction. *Drug Intell Clin Pharm* 1985; **19:** 764.

Pharmacokinetics

Like glyceryl trinitrate, isosorbide dinitrate is readily absorbed from the oral mucosa. Isosorbide dinitrate is also readily absorbed when given orally but owing to extensive first-pass metabolism in the liver and pre-systemic clearance its bioavailability is reduced. Isosorbide dinitrate is also absorbed through the skin from an ointment basis.

After sublingual doses, anti-anginal effect is apparent within 2 to 5 minutes and persists for about 1 to 2 hours. After oral dosage with conventional tablets, anti-anginal activity is present in less than 1 hour and lasts for 4 to 6 hours.

Isosorbide dinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. It is also rapidly metabolised in the liver to the major active metabolites isosorbide 2-mononitrate and isosorbide 5-mononitrate (see Isosorbide Mononitrate, below).

After sublingual doses, isosorbide dinitrate has a plasma half-life of 45 to 60 minutes. Plasma half-lives of 20 minutes and 4 hours have been reported after intravenous and oral dosage, respectively. During prolonged use, the half-life is increased due to accumulation of the isosorbide 5-mononitrate metabolite which reduces hepatic isosorbide dinitrate extraction. Both primary metabolites have longer half-lives than the parent compound.

References.

1. Abshagen U, *et al.* Pharmacokinetics and metabolism of isosorbide-dinitrate after intravenous and oral administration. *Eur J Clin Pharmacol* 1985; **27:** 637–44.
2. Straehl P, Galeazzi RL. Isosorbide dinitrate bioavailability, kinetics, and metabolism. *Clin Pharmacol Ther* 1985; **38:** 140–9.
3. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
4. Schneider W, *et al.* Concentrations of isosorbide dinitrate, isosorbide-2-mononitrate and isosorbide-5-mononitrate in human vascular and muscle tissue under steady-state conditions. *Eur J Clin Pharmacol* 1990; **38:** 145–7.
5. Vogt D, *et al.* Pharmacokinetics and haemodynamic effects of ISDN following different dosage forms and routes of administration. *Eur J Clin Pharmacol* 1994; **46:** 319–24.
6. Bergami A, *et al.* Pharmacokinetics of isosorbide dinitrate in healthy volunteers after 24-hour intravenous infusion. *J Clin Pharmacol* 1997; **37:** 828–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cortespasmo†; Isoket; Isordil; Medocor; ***Austral.***: Isordil; Sorbidin; ***Austria***: Cedocard†; Iso Mack†; Isoket; ***Belg.***: Cedocard; ***Braz.***: Angil; Isordil; ***Canad.***: Apo-ISDN; Cedocard†; Novo-Sorbide†; ***China***: Ai Bei (爱倍); An Nuo Xin Mei (安诺欣美); Angiolong (安其伦); Di Xin Ni (狄欣尼); Er Fu Xin (尔复新); Hao Xin (好欣); Iso Mack (易顺脉); Isoket (异舒吉); Kai Wei Xin (凯慰欣); Ling Xin (灵欣); Pei Xin (培欣); Pu Xin Qing (普辛清); Rui Li Xi (瑞立喜); Wei Xin Ping (卫昕平); Xin He Ping (欣荷平); Xin Shu (欣舒); Yan De (燕德); Yi Shu Da (易舒达); Zhong Sheng Rui Xing (众生瑞欣); ***Cz.***: Cardiket; Dinisan†; Iso Mack†; Isoket; Isopelet; ***Denm.***: Cardopax; ***Fin.***: Dinit; Nitrosid; ***Fr.***: Isocard; Langoran; Risordan; ***Ger.***: Diconpin†; Iso-Puren†; Isoket; Jenacard; Nitrosorbon†; ***Gr.***: Isotrate; Orbipront; Pensordil; Risordan; ***Hong Kong***: Apo-ISDN; Isoket; Isorem; Sorbidin†; ***India***: Anzidin; Cardicap; Isordil; Sorbitrate; ***Indon.***: Cedocard; Farsorbid; Hapisor†; Isoket†; Isorbid; Isordil†; Sorbidin†; Vascardin; ***Irl.***: Isoket; ***Israel***: Cordil†; Isoket; Isolong†; ***Ital.***: Carvasin; Diniket; Nitrosorbide; ***Jpn***: Antup; Isobide; Nitorol; ***Malaysia***: Angsobide; Isoket; ***Mex.***: Biderit†; Biordyn; Debisor; Insucar; Isoket; Isorbid; Zanisor; ***Neth.***: Cedocard; Isordil; ***Norw.***: Sorbangil; ***Philipp.***: Bideren; Flasorbid; Isobar; Isobenil; Isoket; Isordil; Nitrosorbon; Novisor†; ***Pol.***: Aerosonit; Cardonit†; Isoket†; Sorbonit; ***Port.***: Flindix; Isoket; ***Rus.***: Dinisorb (Динисорб); Isoket (Изокет); Isolong (Изолонг); Kardiket (Кардикет); ***S.Afr.***: Angi-Spray†; Dinospray; Isoket; Isordil; ***Singapore***: Angsobide; Apo-ISDN; Isoket†; ***Spain***: Iso; ***Swed.***: Sorbangil; ***Switz.***: Iso Mack†; Isoket; Sorbidilat; ***Thai.***: Angitrit†; Corodil; Hartsorb; Isobide; Isobinate; Isoket; Isordil†; Isorem; Isotrate; Sorbidin†; Sornil; ***Turk.***: Cardioket; Isordil; Nitrofix; ***UK***: Angitak; Cedocard†; Isoket; ***Ukr.***: Cardiket (Кардикет); Dicor (Дикор); Isodinitrat (Изодинитрат)†; Isoket (Изокет); ***USA***: Dilatrate; Isochron†; Isordil; ***Venez.***: Isoket; Isomack.

Multi-ingredient Preparations. ***USA***: BiDil.

Pharmacopoeial Preparations

BP 2014: Isosorbide Dinitrate Injection; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets;

USP 36: Isosorbide Dinitrate Chewable Tablets; Isosorbide Dinitrate Extended-release Capsules; Isosorbide Dinitrate Extended-release Tablets; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets.

Isosorbide Mononitrate

(BAN, USAN, rINN)

AHR-4698; BM-22145; IS-5-MN; Isosorbid mononitrát; Isosorbida, mononitrato de; Isosorbide, Mononitrate d'; Isosorbide-5-mononitrate; Isosorbidi Mononitras; Izosorbid Mononitrat; Izosorbido mononitratas; Izoszorbid-mononitrát; Mononitrato de isosorbida; Изозорбида Мононитрат.

1,4:3,6-Dianhydro-D-glucitol 5-nitrate.

$C_6H_9NO_6$=191.1

CAS — 16051-77-7.

ATC — C01DA14.

ATC Vet — QC01DA14.

UNII — LX1OH63030.

Pharmacopoeias. *Eur.* (see p. vii) and *US* include diluted isosorbide mononitrate.

Ph. Eur. 8: (Isosorbide Mononitrate, Diluted). A dry mixture of isosorbide mononitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide mononitrate is a white or almost white, crystalline powder. Freely soluble in water, in alcohol, in acetone, and in dichloromethane.

USP 36: (Diluted Isosorbide Mononitrate). A dry mixture of isosorbide mononitrate with lactose or other suitable excipients to permit safe handling. Store in airtight containers between 20 degrees and 30 degrees.

Uses and Administration

Isosorbide mononitrate is an active metabolite of the vasodilator isosorbide dinitrate and is used in the long-term management of angina pectoris (p. 1254.3) and heart failure (p. 1262.3). It has also been investigated in myocardial infarction (below).

The usual oral dose is 20 mg two or three times daily, although doses ranging from 20 to 120 mg daily have been given. Modified-release oral preparations have been developed for use in angina.

Myocardial infarction. Long-term management of myocardial infarction (p. 1257.1) can involve many drug therapies and some patients, for example those with myocardial ischaemia or poor left ventricular function, may require the long-term use of nitrates, although recent studies have thrown doubt on their routine use. In the GISSI-3 study[1] there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks post-infarction and in the ISIS-4 study[2] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
2. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.

Osteoporosis. Isosorbide mononitrate has been tried[1] in the management of osteoporosis (for more conventional management see p. 1168.1). Oral treatment with isosorbide mononitrate 20 mg daily was reported to produce comparable improvement in bone mineral density to alendronate 70 mg weekly in a study involving 60 postmenopausal women with osteoporosis but no history of fractures.

1. Nabhan AF, Rabie NH. Isosorbide mononitrate versus alendronate for postmenopausal osteoporosis. *Int J Gynaecol Obstet* 2008; **103:** 213–16.

Termination of pregnancy. For mention of the use of isosorbide mononitrate to ripen the cervix before termination of pregnancy, see Obstetrics and Gynaecology, under Glyceryl Trinitrate, p. 1393.1.

Variceal haemorrhage. For reference to the use of isosorbide mononitrate in the management of variceal haemorrhage, see under Glyceryl Trinitrate, p. 1393.3.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p. 1393.3.

Myalgia has been reported very rarely.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isosorbide mononitrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Glyceryl Trinitrate, p. 1394.2.

Pharmacokinetics

Isosorbide mononitrate is readily absorbed from the gastrointestinal tract. After oral doses of conventional tablets, peak plasma concentrations occur in 30 minutes to 1 hour; onset of action occurs within 20 minutes and lasts for about 8 to 10 hours. Unlike isosorbide dinitrate, isosorbide mononitrate does not undergo first-pass hepatic metabolism and bioavailability is nearly 100%. Isosorbide mononitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. Isosorbide mononitrate is metabolised to inactive metabolites, including isosorbide and isosorbide glucuronide. Only about 2% of isosorbide mononitrate is excreted unchanged in the urine. An elimination half-life of about 4 to 5 hours has been reported.

References.

1. Taylor T, *et al.* Isosorbide 5-mononitrate pharmacokinetics in humans. *Biopharm Drug Dispos* 1981; **2:** 255–63.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
3. McClennen W, *et al.* The plasma concentrations of isosorbide 5-mononitrate (5-ISMN) administered in an extended-release form to patients with acute myocardial infarction. *Br J Clin Pharmacol* 1995; **39:** 704–8.
4. Hutt V, *et al.* Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide-5-mononitrate preparations in healthy volunteers. *Arzneimittelforschung* 1995; **45:** 142–5.
5. Baxter T, Eadie CJ. Twenty-four hour plasma profile of sustained-release isosorbide mononitrate in healthy volunteers and in patients with chronic stable angina: two open label trials. *Br J Clin Pharmacol* 1997; **43:** 333–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cilatron; Medocor; Monoket; Monotrin; ***Austral.***: Arsorb†; Duride; Imdur; Imtrate; Isomonit; Monodur; ***Austria***: Elantan†; Isomonat; Mono Mack; Monoket; Myocardon mono†; Olicardin; ***Braz.***: Cincordil; Coronar; Monocordil; Vexell; ***Canad.***: Apo-ISMN; Imdur; PMS-ISMN; ***Chile***: Ismo; Monopack; ***China***: Ai Mai Shu (艾麦舒); Ai Si Mo (艾司莫); Ai Tong (艾同); Ai Xin (艾欣); Ai Xin Mo Er (爱欣莫尔); An Lan Shu (安兰舒); Ao Di Ya (奥帝亚); Da Fen Shu Ji (达芬舒吉); Danlixin (丹力欣); Danzuo (丹佐); De Rui Ning (德瑞宁); Di Su Ni (狄苏尼); Efforeen (艾复哼); Elantan (异乐定); Etimonis (艾狄莫尼); Fei Ke Xin Kang (菲克芯康); Feng Nuo (丰诺); Fu Shun (孚顺); Fu Xin Tian (富欣恬); Gefenda (格芬达); Huaren XinShu (华仁欣舒); Imdur (依姆多); Isomonit (索尼特); Jin Xin Tai (晋新泰); Kaiweifu (开韦夫); Ke Er Le (科尔乐); Li Wei (力唯); Li Xin Tong (理新彤); Mono Mack (安辛迈); Monotrate (莫诺确特); Nuo Ke Da (诺可达); Pentacard (盘得高); Ping Fu (平福); Qi Hao (奇豪); Qian Xin (千新); Ruideming (瑞德明); Sai Da Lin (赛达林); Shan Su (山苏); Shu Bi Lai Te (舒必莱特); Shu Tan (舒坦); Shu Ya (舒亚); Xin Ao Le (欣奥乐); Xin Kang (欣康); Xin Tai (欣泰); Xinle (欣乐); Ya Xu (亚旭); Yan Nuo Xin (延诺信); Yi Mai Qing (伊迈清); Yi Xin Jian (易欣建); Yisuoman (伊索曼); Zai Sheng (再晟); Zaijia (再佳); ***Cz.***: Conpin†; Ismin†; Mono Mack; Monosan; Monosor; Monotab; Olicard; Sorbimon; ***Denm.***: Fem-Mono; Imdur; Isodur; ***Fin.***: Imdur; Isangina; Ismexin; Ismox; Isosor†; Ormox; ***Fr.***: Monicor; ***Ger.***: Coleb†; Conpin†; Corangin†; Elantan†; IS 5 Mono; Ismanton†; Ismo; Isomonit†; Moni-Sanorania†; Monit-Puren†; mono corax†; Mono Mack; Monobeta†; Monoclair; Monolong†; Mononitrat†; Monopur†; Nitrolingual protect†; Olicard†; Turimonit†; ***Gr.***: Angioval; Dilavenil; G-Dil; Imdur; Isomon; Monoginal; Monoket; Monorythm; Monosordil; Nitramin; Nitrilan; Procardol; ***Hong Kong***: Apo-ISMN; Duride†; Elantan; Imdex; Imdur; Monocinque; ***Hung.***: Cardisorb†; Isospan; Mono Mack; Olicard; Rangin; ***India***: 5-Mono; Angicor; Anginex; Angitab; Diltrate; IHD; Imdur; Imnit; Ismo; Isocor; Isomin; Isonorm; Isotop; Monet; Monicor; Monit; Monn; Monocontin; Monomen; Monopark; Monosorbitrate; Monotrace; Monotrate; Nican; Nitrofix; Nitrovas; ***Indon.***: Cardismo; Imdur; Isomonit; Monecto; Pentacard†; ***Irl.***: Cardox; Elantan; Imdur; Isomel; Isomonit; Sormon; ***Israel***: Monocord; Monolong; Mononit; ***Ital.***: Duronitrin; Elan; Ismo; Leicester; Monocinque; Monoket; Vasdilat; ***Malaysia***: Duride†; Elantan; Imdex; Imdur; Ismo; ***Mex.***: Elantan; Imdur; Kenbrid; Monocorat; ***Neth.***: Mono-Cedocard; Promocard; ***Norw.***: Imdur; Ismo; Monoket; ***NZ***: Corangin; Duride; Imtrate; Ismo; ***Philipp.***: Angistad; Elantan; Imdur; Isomonit; Isonate; Monosorb; Vasotrate; ***Pol.***: Effox; Isomonit†; Isosor; Izonit†; Mono Mack; Mono Tad; Monocard†; Mononit; Monosan; Olicard; ***Port.***: Imdur; Ismo; Monoket; Monopront; Orasorbil; ***Rus.***: Effox (Эфокс); Monisol (Монизол); Mono Mack (Моно Мак); Mono Rom (Моно Ром); Monocinque (Моночинкве); Monolong (Монолонг); Monosan (Моносан); Olicard (Оликард); Pektrol (Пектрол); ***S.Afr.***: Angitrate†; Elantan; Imdur; Ismo; Monicor; ***Singapore***: Elantan†; Imdex; Imdur; Ismo; Vasotrate; ***Spain***: Cardionil; Coronur; Dolak; Pertil†; Uniket; ***Swed.***: Imdur; Ismo; Isodur†; Monoket; ***Switz.***: Corangine; ***Thai.***: Elantan†; Imdex; Imdur; Ismo; Isopen; Monolin; Monosorb; Monotrate; Solotrate; Sorbinate; ***Turk.***: Isorat; Monodur; Monoket; Monolong; ***UK***: Angeze; Chemydur; Cibral; Dynamin; Elantan; Imdur; Isib; Ismo; Isodur; Isotard; Modisal; Monigen; Monomax; Monomil; Monosorb; Trangina; Xismox; Zemon; ***Ukr.***: Efox Long (Эфокс Лонг); Mononitrosid (Мононітросид); Monosan (Моносан); Olicard (Оликард); ***USA***: Imdur; Ismo; Monoket; ***Venez.***: Elantan; Ismo; Mono Mack.

Multi-ingredient Preparations. ***Braz.***: Vasclin; ***China***: Jia Yi Ke (佳伊可); Li Li Kai (利力凯); Mei Lan Te (美兰特); Si Yue (司悦); Zi Lin (滋霖); ***India***: Aspitrate; Ecosmin; Ismorin; Isoact; Monit-AS; Mono-A; Monosprin; Nitren; Nitrofix-AS; Nitroprin; Solosprin.

Pharmacopoeial Preparations

BP 2014: Isosorbide Mononitrate Tablets; Prolonged-release Isosorbide Mononitrate Capsules; Prolonged-release Isosorbide Mononitrate Tablets;

USP 36: Isosorbide Mononitrate Extended-Release Tablets; Isosorbide Mononitrate Tablets.

Isradipine *(BAN, USAN, rINN)*

Isradipiini; Isradipin; Isradipinas; Isradipino; Isradipinum; Izradypina; PN-200-110; İsradipin; Израдипин.

Isopropyl methyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{19}H_{21}N_3O_5$=371.4

CAS — 75695-93-1.

ATC — C08CA03.

ATC Vet — QC08CA03.

UNII — YO1UK1S598.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Isradipine). A yellow crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol. Protect from light.

USP 36: (Isradipine). A yellow fine crystalline powder. Protect from light.

Stability. An oral preparation of isradipine 1 mg/mL, prepared using the powder from capsules of isradipine suspended in syrup,[1] was stable when stored at 4 degrees for up to 35 days after preparation.

1. MacDonald JL, *et al.* Stability of isradipine in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1994; **51:** 2409–11.

Uses and Administration

Isradipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the treatment of hypertension (p. 1251.1).

The usual initial oral dose of isradipine is 2.5 mg twice daily increased if necessary after 3 to 4 weeks to 5 mg twice daily. Some patients may require 10 mg twice daily. In elderly patients an initial dose of 1.25 mg twice daily may be preferable; a maintenance dose of 2.5 or 5 mg once daily may sometimes be sufficient. A reduced dose should also be used in patients with hepatic or renal impairment (see below).

The dose of isradipine should be reduced in patients who are also taking cimetidine (see Interactions, below).

For doses in children, see below.

A modified-release preparation allowing once-daily dosing is available in some countries.

Reviews.

1. Fitton A, Benfield P. Isradipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1990; **40:** 31–74.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12:** 261–75.
3. Brogden RN, Sorkin EM. Isradipine: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of mild to moderate hypertension. *Drugs* 1995; **49:** 618–49.

Administration in children. Retrospective studies in limited numbers of patients have reported on the use of isradipine alone or as an adjunct in the treatment of hypertension in children. In 12 patients aged from 10 days to 11 years an initial oral dose of 100 micrograms/kg was increased as necessary by 50 to 100 micrograms/kg every 3 to 6 doses, doses being given at an interval of 6 or 8 hours.[1] The dose range needed to control blood pressure was from 300 to 1200 micrograms/kg per day. Similarly, a study[2] in 72 children aged from 1 week to 16 years reported initial oral doses of 50 to 100 micrograms/kg given every 8 hours, or every 6 hours if necessary. The dose range needed to control blood pressure was from 70 to 900 micrograms/kg per day, which appeared significantly higher than doses usually given to adults.

To prevent steep drops in blood pressure, some[3] have suggested that children aged under 2 years should be given initial doses of no more than 50 micrograms/kg.

1. Strauser LM, *et al.* Initial experience with isradipine for the treatment of hypertension in children. *South Med J* 2000; **93:** 287–93.
2. Flynn JT, Warnick SJ. Isradipine treatment of hypertension in children: a single-center experience. *Pediatr Nephrol* 2002; **17:** 748–53.
3. Miyashita Y, *et al.* Isradipine for treatment of acute hypertension in hospitalized children and adolescents. *J Clin Hypertens (Greenwich)* 2010; **12:** 850–5.

Administration in hepatic or renal impairment. In patients with hepatic or renal impairment UK licensed product information recommends an initial dose of isradipine of 1.25 mg twice daily. The dose may be increased as required, but a maintenance dose of 2.5 or 5 mg once daily may be sufficient in some patients.

Neurological disorders. Although preclinical data had suggested that isradipine might be of benefit in **cocaine dependence** by antagonising the abuse potential of the drug, a small double-blind crossover study in 12 cocaine-dependent subjects indicated that it enhanced, rather than antagonised, the subjective effects of cocaine.[1]

As with related dihydropyridines (see under Nifedipine, p. 1449.2) there has been some interest in the potential neuroprotective effect of isradipine in patients with **parkinsonism**, and the tolerability of the drug has been investigated in patients with early Parkinson's disease.[2] Studies in *animals* have also suggested potential benefit in the management of **Alzheimer's disease**.[3]

1. Roache JD, *et al.* Effects of repeated-dose isradipine on the abuse liability of cocaine. *Exp Clin Psychopharmacol* 2005; **13:** 319–26.
2. Simuni T, *et al.* Tolerability of isradipine in early Parkinson's disease: a pilot dose escalation study. *Mov Disord* 2010; **25:** 2863–6.
3. Anekonda TS, *et al.* L-type voltage-gated calcium channel blockade with isradipine as a therapeutic strategy for Alzheimer's disease. *Neurobiol Dis* 2011; **41:** 62–70.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Incidence of adverse effects. Multicentre studies[1,2] have reported adverse effects in about half of all patients taking isradipine, the commonest being flushing, palpitations, dizziness, oedema, fatigue, headache, and pruritus. The incidence of adverse effects has been reported to be higher than with a thiazide[1] and similar to that with an ACE inhibitor.[2] However, in another study,[3] spontaneously reported adverse effects occurred less frequently in patients taking isradipine (18.4% of 103 patients) than in those taking amlodipine (33.3% of 102 patients). In particular, ankle oedema was less frequent, severe, and prolonged with isradipine than with amlodipine.

1. Carlsen JE, Køber L. Blood pressure lowering effect and adverse events during treatment of arterial hypertension with isradipine and hydrochlorothiazide. *Drug Invest* 1990; **2:** 10–16.
2. Johnson BF, *et al.* A multicenter comparison of adverse reaction profiles of isradipine and enalapril at equipotent doses in patients with essential hypertension. *J Clin Pharmacol* 1995; **35:** 484–92.
3. Hermans L, *et al.* At equipotent doses, isradipine is better tolerated than amlodipine in patients with mild-to-moderate hypertension: a double-blind, randomized, parallel-group study. *Br J Clin Pharmacol* 1994; **38:** 335–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isradipine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Cimetidine increases the bioavailability of isradipine and the dose of isradipine should be reduced by 50% in patients receiving both drugs.

Pharmacokinetics

Isradipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism; the bioavailability is reported to be 15 to 24%. Peak plasma concentrations occur about 2 hours after oral dosage. It is about 95% bound to plasma proteins. Isradipine is extensively metabolised in the liver, at least partly by the cytochrome P450 isoenzyme CYP3A4. About 70% of an oral dose is reported to be excreted as metabolites in urine, the remainder in faeces. The terminal elimination half-life is often stated to be about 8 hours although a value of less than 4 hours has also been reported.

In single-dose and steady-state pharmacokinetic studies of isradipine in 9 hypertensive subjects using a specific HPLC assay, isradipine was rapidly absorbed with peak concentrations occurring 1.2 (steady state) to 1.5 (single dose) hours after dosing.[1] The mean terminal elimination half-life at steady state was 3.8 hours, suggesting that duration of action is likely to be short and that isradipine would need to be given at least twice daily. There was considerable interindividual variation in the pharmacokinetics. In an earlier study[2] in healthy subjects the effective half-life of isradipine was calculated to be 8.8 hours, but

radiolabelled isradipine was used and the assay method might have been less specific for unchanged drug.

1. Shenfield GM, *et al.* The pharmacokinetics of isradipine in hypertensive subjects. *Eur J Clin Pharmacol* 1990; **38:** 209–11.
2. Tse FLS, Jaffe JM. Pharmacokinetics of P N 200-110 (isradipine), a new calcium antagonist, after oral administration in man. *Eur J Clin Pharmacol* 1987; **32:** 361–5.

Hepatic impairment. Systemic availability after a radiolabelled oral dose of isradipine 5 mg was no different at 15.6% in 7 patients with non-cirrhotic chronic liver disease from the value of 16.5% in 8 healthy subjects.[1] However, in 8 patients with cirrhosis of the liver availability was markedly increased to a mean of 36.9%; this was associated with decreased clearance (1.6 litres/minute, compared with 9.9 in controls). Terminal half-life, as measured after intravenous dosage, was greater at 11.9 hours in cirrhotic patients than the 5.1 hours seen in controls.

Reduced doses in patients with hepatic impairment have been recommended—see Administration in Hepatic or Renal Impairment under Uses and Administration, p. 1414.3.

1. Cotting J, *et al.* Pharmacokinetics of isradipine in patients with chronic liver disease. *Eur J Clin Pharmacol* 1990; **38:** 599–603.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lomir; ***Belg.***: Lomir; ***Braz.***: Lomir; ***Cz.***: Lomir; ***Denm.***: Lomir; ***Fin.***: Lomir; ***Fr.***: Icaz; ***Ger.***: Lomir†; Vascal; ***Gr.***: Lomir; ***Hong Kong***: Dynacirc; ***Hung.***: Lomir; ***Ital.***: Clivoten; Esradin; Lomir; ***Malaysia***: Dynacirc; ***Mex.***: Dynacirc; ***Neth.***: Lomir; ***Norw.***: Lomir; ***NZ***: Dynacirc; ***Philipp.***: Icaz; ***Pol.***: Lomir; ***Port.***: Dilatol; Lomir; ***Rus.***: Lomir (Ломир); ***S.Afr.***: Dynacirc; ***Singapore***: Dynacirc; ***Spain***: Lomir†; ***Swed.***: Lomir; ***Switz.***: Lomir; ***Thai.***: Dynacirc†; ***Turk.***: Dynacirc; ***UK***: Prescal†; ***USA***: Dynacirc.

Pharmacopoeial Preparations
BP 2014: Isradipine Tablets;
USP 36: Isradipine Capsules; Isradipine Oral Suspension.

Ivabradine *(BAN, rINN)*

Ivabradina; Ivabradinum; S-16257; Ивабрадин.
3-[3-({[(7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}methylamino)propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one.
$C_{27}H_{36}N_2O_5$=468.6
CAS — 155974-00-8.
ATC — C01EB17.
ATC Vet — QC01E817.
UNII — 3H48L0LPZQ.

Ivabradine Hydrochloride *(BANM, rINNM)*

Ivabradina, hidrocloruro de; Ivabradine, Chlorhydrate de; Ivabradinum Hydrochloridum; S-16257-2; Ивабрадина Гидрохлорид.
$C_{27}H_{36}N_2O_5$,HCl=505.1
CAS — 148849-67-6.
ATC — C01EB17.
ATC Vet — QC01EB17.
UNII — TP19837BZK.

Uses and Administration

Ivabradine is a selective sinus node I_f inhibitor that lowers the heart rate. It is used in the treatment of stable angina pectoris (p. 1254.3) in patients unable to take beta blockers, or it is added to beta blockers when angina is not adequately controlled and the patient has a heart rate of more than 60 beats/minute. Ivabradine is also used in chronic heart failure (p. 1262.3) in patients whose heart rate is 75 beats/minute or more; it may be added to standard therapy including beta blockers, or given when beta blockers cannot be used. It is given as the hydrochloride, but doses are expressed in terms of the base; 5.4 mg of ivabradine hydrochloride is equivalent to about 5 mg of ivabradine. It is given orally with food in a usual initial dose of 5 mg twice daily. In stable angina pectoris the dose may be increased after 3 to 4 weeks if necessary to 7.5 mg twice daily. In patients with heart failure the dose may be adjusted after 2 weeks, and increased to 7.5 mg twice daily if the heart rate is persistently above 60 beats/minute. If the heart rate falls persistently below 50 beats/minute in patients with either indication, or there are symptoms of bradycardia, the dose should be titrated downwards to as low as 2.5 mg twice daily if necessary. Treatment should be stopped if this low heart rate or symptoms of bradycardia persist.

In the elderly (75 years or above), a lower initial dose of 2.5 mg twice daily should be considered, before increasing if necessary.

References.
1. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I_f current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004; **64:** 1757–65.
2. Sulfi S, Timmis AD. Ivabradine—the first selective sinus node I_f channel inhibitor in the treatment of stable angina. *Int J Clin Pract* 2006; **60:** 222–8.
3. Menown IBA. Ivabradine: a new strategy for management of stable angina. *Br J Hosp Med* 2007; **68:** 321–5.
4. Böhm M, Reil J-C. Perspectives of I_f inhibition by ivabradine in cardiology. *Drugs* 2007; **67** (suppl 2): 43–9.
5. Fox K, *et al.* BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372:** 807–16.
6. Tardif JC, *et al.* ASSOCIATE Study Investigators. Efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009; **30:** 540–8.
7. Rakovec P. Treatment of inappropriate sinus tachycardia with ivabradine. *Wien Klin Wochenschr* 2009; **121:** 715–8.
8. Köster R, *et al.* REDUCTION Study Group. Treatment of stable angina pectoris by ivabradine in every day practice: the REDUCTION study. *Am Heart J* 2009; **158:** e51–e57.
9. Borer JS, Tardif JC. Efficacy of ivabradine, a selective I(f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. *Am J Cardiol* 2010; **105:** 29–35.
10. Swedberg K, *et al.* SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; **376:** 875–85. Correction. *ibid.*; 1988.

Adverse Effects

The most common adverse effects seen with ivabradine are luminous phenomena in the visual field (phosphenes). They generally begin within the first 2 months of treatment and may occur repeatedly, although they will resolve during therapy in most patients. Bradycardia is another common effect of ivabradine, and signs and symptoms such as dizziness, syncope, hypotension, asthenia, and fatigue may be related. Other adverse effects include blurred vision, other cardiac arrhythmias, nausea, constipation, diarrhoea, headache, dyspnoea, muscle cramps, skin reactions, and cases of angioedema. Hyperuricaemia, eosinophilia, and elevated blood-creatinine concentrations have been reported.

Reviews.
1. Savelieva I, Camm AJ. I_f inhibition with ivabradine: electrophysiological effects and safety. *Drug Safety* 2008; **31:** 95–107.

Precautions

Ivabradine should not be started in patients with resting heart rate below 60 beats/minute, or in patients with cardiogenic shock, severe conduction defects, acute myocardial infarction, or unstable angina. Heart failure should be stable before ivabradine is started; it should be used with caution in severe heart failure. Ivabradine should not be used in patients with congenital QT prolongation. Ivabradine is not recommended in atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function, and regular monitoring for such arrhythmias should be performed. If resting heart rate falls below 50 beats/minute the dose should be reduced; treatment should be stopped if this rate persists.

Ivabradine is contra-indicated in severe hypotension and severe hepatic impairment, and should be used with caution in severe renal impairment (creatinine clearance of less than 15 mL/minute).

If unexpected deterioration in visual function occurs, stopping treatment may be considered. Caution is advisable in patients with retinitis pigmentosa.

Studies in *animals* have shown that ivabradine is embryotoxic and teratogenic, and is distributed into breast milk.

Interactions

Ivabradine should not generally be used with drugs that prolong the QT interval.

Ivabradine is metabolised by the cytochrome P450 isoenzyme CYP3A4, and should not be used with potent inhibitors of this enzyme, including azole antifungals such as ketoconazole and itraconazole, macrolide antibacterials such as clarithromycin, HIV-protease inhibitors such as nelfinavir and ritonavir, and nefazodone. Use with the moderate CYP3A4 inhibitors diltiazem and verapamil is also not recommended as the increase in exposure to ivabradine may cause an additional reduction in heart rate. Ivabradine may be used cautiously with other moderate inhibitors, such as fluconazole, at a lower starting dose of 2.5 mg orally twice daily, with monitoring of the heart rate. Consumption of grapefruit juice should be restricted.

Use with CYP3A4 inducers, such as rifampicin and phenytoin, may require an increase in the dose of ivabradine. St John's wort reduces the exposure to ivabradine by half and its use should be restricted.

Pharmacokinetics

Ivabradine is almost completely absorbed after oral doses but bioavailability is about 40% because of first-pass metabolism. Peak plasma concentrations occur after about 1 hour in the fasting state but this is delayed by 1 hour by food and the extent of absorption increased by 20 to 30%. Ivabradine is about 70% bound to plasma proteins.

Ivabradine undergoes extensive metabolism in the liver and gut via the cytochrome P450 isoenzyme CYP3A4 to its main active metabolite *N*-desmethyl-ivabradine (S-18982). This is further metabolised to some degree by CYP3A4. Ivabradine has a plasma elimination half-life of 2 hours and an effective half-life of 11 hours. Its metabolites are excreted to a similar extent in the urine and faeces. About 4% of a dose appears in the urine as the parent drug. *Animal* studies indicate that ivabradine is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Procoralan; ***Austral.***: Coralan; ***Austria***: Procoralan; ***Belg.***: Procoralan; ***Braz.***: Procoralan; ***Cz.***: Corlentor; Procoralan; ***Denm.***: Procoralan; ***Fr.***: Procoralan; ***Ger.***: Procoralan; ***Gr.***: Procoralan; ***Hong Kong***: Coralan; ***Hung.***: Procoralan; ***India***: Bradia; Ivabid; Ivabrad; Ivazine; ***Indon.***: Coralan; ***Irl.***: Corlentor; Procoralan; ***Israel***: Coralan; ***Ital.***: Corlentor; Procoralan; ***Malaysia***: Coralan; ***Neth.***: Corlentor; Procoralan; ***Philipp.***: Coralan; ***Pol.***: Corlentor; Procoralan; ***Port.***: Corlentor; Procoralan; ***Rus.***: Coraxan (Кораксан); ***S.Afr.***: Coralan; ***Singapore***: Coralan; ***Spain***: Corlentor; Procoralan; ***Swed.***: Procoralan; ***Switz.***: Procoralan; ***Thai.***: Coralan; ***Turk.***: Coralan; ***UK***: Procoralan; ***Ukr.***: Coraxan (Кораксан).

Ketanserin *(BAN, USAN, rINN)*

Ketanseriini; Ketanserina; Kétansérine; Ketanserinum; R-41468; Кетансерин.
3-{2-[4-(4-Fluorobenzoyl)piperidino]ethyl}quinazoline-2,4(1*H*,3*H*)-dione.
$C_{22}H_{22}FN_3O_3$=395.4
CAS — 74050-98-9.
ATC — C02KD01.
ATC Vet — QC02KD01; QD03AX90.
UNII — 97F9DE4CT4.

Ketanserin Tartrate *(BANM, rINNM)*

Ketanserina, tartrato de; Kétansérine, Tartrate de; Ketanserini Tartras; R-49945; Tartrato de ketanserina; Кетансерина Тартрат.
$C_{22}H_{22}FN_3O_3$,$C_4H_6O_6$=545.5
CAS — 83846-83-7.
ATC — C02KD01.
ATC Vet — QC02KD01.
UNII — 645498QK7H.

Uses and Administration

Ketanserin is a serotonin antagonist with a high affinity for peripheral 5-HT^{2A} receptors and thus inhibits serotonin-induced vasoconstriction, bronchoconstriction, and platelet aggregation. It is also a less potent antagonist at 5-HT_{2C}, $alpha_1$, and histamine H_1 receptors, but the clinical significance of this is unclear. Ketanserin has no significant effect on 5-HT_1, 5-HT_3, or 5-HT_4 receptors.

Ketanserin is mainly used in the management of hypertension (p. 1251.1).

Ketanserin is given as the tartrate, but doses are usually expressed in terms of the base. Ketanserin tartrate 27.6 mg is equivalent to about 20 mg of ketanserin.

Ketanserin produces a gradual hypotensive effect when given orally, and 2 or 3 months of therapy may be required to produce the maximum reduction in blood pressure. After intravenous injection a fall in blood pressure is generally produced in 1 or 2 minutes and lasts for 30 to 60 minutes.

In **hypertension** the usual initial oral dose is 20 mg twice daily, increasing, if necessary, after 4 weeks, to 40 mg twice daily. It has also been given by intravenous or intramuscular injection. The dose of ketanserin may need to be reduced, or the dosage intervals increased, in patients with hepatic impairment (see below).

Reviews.
1. Brogden RN, Sorkin EM. Ketanserin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in hypertension and peripheral vascular disease. *Drugs* 1990; **40:** 903–49.

Administration in hepatic impairment. A study[1] in patients with cirrhosis found that the half-life and volume of distribution of ketanserin were decreased but the area under the concentration-time curve was markedly increased; the rate of metabolism was reduced. The results suggested that the dosage should be reduced or the dosage interval increased when ketanserin is given to patients with cirrhosis.

Licensed product information recommends a maximum oral dose of 20 mg twice daily for patients with severe hepatic impairment.

1. Lebrec D, *et al.* Pharmacokinetics of ketanserin in patients with cirrhosis. *Clin Pharmacokinet* 1990; **19:** 160–6.

Administration in renal impairment. Results from a study in 12 patients with chronic renal impairment, of whom 6 required haemodialysis, suggested that no adjustment of a dose of ketanserin 20 mg twice daily was required in patients with renal impairment.[1]

1. Barendregt JNM, *et al.* Ketanserin pharmacokinetics in patients with renal failure. *Br J Clin Pharmacol* 1990; **29:** 715–23.

Peripheral vascular disease. Ketanserin is one of many drugs that have been tried in the management of peripheral vascular disorders (p. 1272.3) but results have been contradictory. Subgroup analysis of the multicentre Prevention of Atherosclerotic Complications with Ketanserin Trial (PACK),[1] involving 3899 patients with intermittent claudication, suggested that ketanserin might be of benefit in preventing limb amputation in some patients. Conflicting results have also been reported in patients with Raynaud's syndrome. A systematic review[2] found that ketanserin led to a small improvement in Raynaud's syndrome in patients with systemic sclerosis but that adverse effects increased; the authors concluded that ketanserin was not clinically beneficial in such patients. For the general management of Raynaud's syndrome see Vasospastic Arterial Disorders, p. 1275.3.

Ketanserin has also been tried in other conditions associated with impaired peripheral blood flow: see Wounds and Ulcers, below.

1. Prevention of Atherosclerotic Complications with Ketanserin Trial Group. Prevention of atherosclerotic complications: controlled trial of ketanserin. *BMJ* 1989; **298:** 424–30. Correction. *ibid.*: 644.
2. Pope JE, *et al.* Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 26/09/05).

Shivering. Many drugs, including ketanserin, have been tried for the treatment of postoperative shivering (p. 1900.2). Ketanserin 10 mg given intravenously has stopped shivering after general anaesthesia.[1,2]

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79:** 532–9.
2. Crisinel D, *et al.* Efficacité de la kétansérine sur le frisson postanesthésique. *Ann Fr Anesth Reanim* 1997; **16:** 120–5.

Wounds and ulcers. Several coutrolled studies[1-6] have noted improved healing of decubitus, venous, and ischaemic ulcers (see Wounds and Ulcers, p. 1690.1) after topical use of ketanserin 2%. However, when applied topically to surgical wounds no improvement was found and it was suggested that ketanserin is only of benefit where blood supply is compromised.[7]

1. Tytgat H, van Asch H. Topical ketanserin in the treatment of decubitus ulcers: a double-blind study with 2% ketanserin ointment against placebo. *Adv Therapy* 1988; **5:** 143–52.
2. Roelens P. Double-blind placebo-controlled study with topical 2% ketanserin ointment in the treatment of venous ulcers. *Dermatologica* 1989; **178:** 98–102.
3. Janssen PAJ, *et al.* Use of topical ketanserin in the treatment of skin ulcers: a double-blind study. *J Am Acad Dermatol* 1989; **21:** 85–90.
4. Martinez-de Jesus FR, *et al.* Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers. *Arch Med Res* 1997; **28:** 95–9.
5. Salazar JJ, *et al.* Use of topical ketanserin for the treatment of ulcers in leprosy patients. *Indian J Lepr* 2001; **73:** 103–10.
6. Quatresooz P, *et al.* Healing effect of ketanserin on chronic leg ulcers in patients with diabetes. *J Eur Acad Dermatol Venereol* 2006; **20:** 277–81.
7. Lawrence CM, *et al.* The effect of ketanserin on healing of fresh surgical wounds. *Br J Dermatol* 1995; **132:** 580–6.

Adverse Effects and Precautions

Ketanserin has been reported to cause sedation, fatigue, light-headedness, dizziness, headache, dry mouth, and gastrointestinal disturbances. Oedema has been reported rarely. In patients with predisposing factors such as QT prolongation, chronic use of ketanserin has been associated with ventricular arrhythmias including torsade de pointes; ketanserin should be used with caution in patients taking antiarrhythmics and should not be used in second- or third-degree AV block. Care should be taken to avoid the development of hypokalaemia in patients taking ketanserin, for example if diuretics are also given.

Because ketanserin may cause drowsiness care should be taken in patients who drive or operate machinery.

Ketanserin is reported to be better tolerated in elderly than in younger patients.

Interactions

The hypotensive effects of ketanserin may be enhanced by diuretics and other antihypertensives. Ketanserin should be used with caution in patients taking antiarrhythmics or drugs that cause hypokalaemia since the risk of arrhythmias is increased.

Beta blockers. Profound hypotension occurred in 2 patients one hour after taking ketanserin 40 mg orally.[1] Both patients were also taking a beta blocker which may have exacerbated the reaction.

1. Waller PC, *et al.* Profound hypotension after the first dose of ketanserin. *Postgrad Med J* 1987; **63:** 305–7.

Pharmacokinetics

Ketanserin is rapidly absorbed from the gastrointestinal tract but has a bioavailability of about 50% due to first-pass hepatic metabolism. Peak plasma concentrations occur between 30 and 120 minutes after an oral dose. Ketanserin is about 95% bound to plasma proteins. The terminal half-life is stated to be between 13 and 18 hours but some studies report that after multiple doses the half-life is 19 to 29 hours. The metabolite ketanserinol has a terminal half-life of 31 to 35 hours after multiple doses, and it has been suggested that reconversion of ketanserinol to ketanserin may be responsible for the prolonged half-life of the parent compound during chronic use.

About 68% of an oral dose is excreted in urine, and 24% in faeces, mainly as metabolites. Ketanserin readily crosses the placenta (see also below). Studies in *animals* suggest that it is also present, with metabolites, in breast milk.

References.

1. Persson B, *et al.* Clinical pharmacokinetics of ketanserin. *Clin Pharmacokinet* 1991; **20:** 263–79.

Pregnancy. A study[1] in 22 mothers (23 neonates) showed that ketanserin readily crossed the placenta, resulting in high levels of the drug and its metabolite, ketanserinol, in both umbilical cord and neonate. Despite pharmacologically significant plasma concentrations in the neonates, and slower clearance than in adults, no neonatal adverse effects were noted.

1. Hanff LM, *et al.* Ketanserin in pre-eclamptic patients: transplacental transmission and disposition in neonates. *BJOG* 2004; **111:** 863–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Aseranox; ***Mex.***: Sufrexal; ***Neth.***: Ketensin.

Multi-ingredient Preparations. ***Mex.***: Sufrexal P.

Labetalol Hydrochloride

(BANM, USAN, rINNM) ⊗

AH-5158A; Hidrocloruro de labetalol; Ibidomide Hydrochloride; Labétalol, chlorhydrate de; Labetalol, hidrocloruro de; Labetalol hydrochlorid; Labetalol-hidroklorid; Labetalol-hydrochlorid; Labetalolhydroklorid; Labetaloli Hydrochloridum; Labetalolihydrokloridi; Labetalolio hidrochloridas; Sch-15719W; Лабеталола Гидрохлорид.

5-[1-Hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylamide hydrochloride.

$C_{19}H_{24}N_2O_3HCl$=364.9

CAS — 36894-69-6 (labetalol); 32780-64-6 (labetalol hydrochloride).

ATC — C07AG01.

ATC Vet — QC07AG01.

UNII — 1GEV3BAW9J.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Labetalol Hydrochloride). A white or almost white powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.0.

USP 36: (Labetalol Hydrochloride). A white to off-white powder. Soluble in water and in alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Labetalol hydrochloride is compatible with standard intravenous solutions such as glucose 5% and sodium chloride 0.9%. However, precipitation has been reported when labetalol hydrochloride is added to sodium bicarbonate injection 5%.[1] The precipitate is probably labetalol base.[2]

Immediate formation of a precipitate has also been reported when labetalol (generally 5 mg/mL in glucose 5%) was mixed with other drugs including ceftriaxone,[3] furosemide,[4] heparin,[5] insulin,[5] proton pump inhibitors such as pantoprazole,[6] and thiopental.[4] There has also been a report of immediate haze after admixture of labetalol hydrochloride (800 micrograms/mL) with warfarin sodium.[7]

1. Yuen P-HC, *et al.* Compatibility and stability of labetalol hydrochloride in commonly used intravenous solutions. *Am J Hosp Pharm* 1983; **40:** 1007–9.
2. Alam AS. Identification of labetalol precipitate. *Am J Hosp Pharm* 1984; **41:** 74.
3. Leader WG, Jones JM. Incompatibility between ceftriaxone sodium and labetalol hydrochloride. *Am J Health-Syst Pharm* 1996; **53:** 2639.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
5. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
6. Péré H, *et al.* Compatibilité du pantoprazole injectable lors d'administration en Y. *Pharmactuel* 2004; **37:** 193–6.
7. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Uses and Administration

Labetalol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess some intrinsic sympathomimetic and membrane-stabilising activity. In addition, it has selective alpha$_1$-blocking properties which decrease peripheral vascular resistance. The ratio of alpha- to beta-blocking activity has been estimated to be about 1:3 after oral doses and 1:7 after intravenous doses.

Labetalol is used as the hydrochloride in the management of hypertension (p. 1251.1). It is also used to induce hypotension during surgery. Labetalol decreases blood pressure more rapidly than other beta blockers; the full antihypertensive effect may be seen within 1 to 3 hours of an oral dose.

In **hypertension** labetalol hydrochloride is usually given in an initial oral dose of 100 mg twice daily with food, gradually increased if necessary according to response and standing blood pressure, to 200 to 400 mg twice daily; total daily doses of 2.4 g, in two to four divided doses, have occasionally been required. Lower doses may be adequate in elderly patients; an initial dose of 50 to 100 mg twice daily has been recommended, and the usual maintenance dose is 100 to 200 mg twice daily.

For the emergency treatment of hypertension labetalol hydrochloride may be given by slow intravenous injection. In the UK a dose of 50 mg is recommended, given over a period of at least 1 minute; if necessary this dose may be repeated at intervals of 5 minutes until a total of 200 mg has been given. In the USA an initial dose of 20 mg is recommended, given over 2 minutes; subsequent doses of 40 to 80 mg may be given every 10 minutes, if necessary, up to a maximum of 300 mg. Blood pressure should be monitored, and the patient should remain supine during the injection and for 3 hours afterwards, to avoid excessive orthostatic hypotension. After bolus intravenous injection a maximum effect is usually obtained within 5 minutes and usually lasts up to 6 hours, although it may extend as long as 18 hours.

Labetalol hydrochloride has also been given by intravenous infusion in usual doses of 2 mg/minute. Suggested concentrations for intravenous infusions are 1 mg/mL or 2 mg/3 mL of suitable diluent. In hypertension in pregnancy, labetalol infusion may be started at the rate of 20 mg/hour, then doubled every 30 minutes until a satisfactory response is obtained or a dose of 160 mg/hour is reached. In hypertension after myocardial infarction, labetalol infusion may be started at the rate of 15 mg/hour and gradually increased until a satisfactory response is obtained or a dose of 120 mg/hour is reached.

The initial dose in **hypotensive anaesthesia** is 10 to 20 mg intravenously, with increments of 5 to 10 mg if satisfactory hypotension is not achieved after 5 minutes. A higher initial dose may be required in patients who do not receive halothane anaesthesia.

For the use of labetalol in children, see below.

Action. Labetalol has 2 optical centres; it is used as the racemic mixture of the 4 stereoisomers. The *R,R*-isomer is responsible for the beta-blocking activity and has limited alpha-blocking activity; it also has beta-adrenergic mediated peripheral vasodilating activity. The *S,R*-isomer has the most potent alpha-blocking activity. The *S,S*-isomer has some alpha-blocking activity and the *R,S*-isomer does not appear to have either alpha- or beta-adrenergic blocking effect.[1] The pure *R,R*-isomer, dilevalol, was withdrawn from the market because of hepatotoxicity.

1. Gold EH, *et al.* Synthesis and comparison of some cardiovascular properties of the stereoisomers of labetalol. *J Med Chem* 1982; **25:** 1363–70.

Administration in children. Labetalol has been used in the management of hypertension in children,[1] although experience is limited. The *BNFC* suggests the following doses:

for **hypertensive emergencies**, labetalol hydrochloride may be given by intravenous infusion as follows:

- neonates: 500 micrograms/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 4 mg/kg per hour

- 1 month to 12 years: 0.5 to 1 mg/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 3 mg/kg per hour
- 12 to 18 years: 30 to 120 mg/hour adjusted at intervals of at least 15 minutes according to response

for **hypertension**, labetalol hydrochloride may be given as follows:

- 1 month to 12 years: 1 to 2 mg/kg three or four times daily by mouth or a single intravenous injection in a dose of 250 to 500 micrograms/kg to a maximum of 20 mg
- 12 to 18 years: similar doses to adults (see p. 1416.3) although a lower initial oral dose of 50 to 100 mg twice daily is recommended

1. Bunchman TE, *et al.* Intravenously administered labetalol for treatment of hypertension in children. *J Pediatr* 1992; **120:** 140–4.

Adverse Effects

The adverse effects associated with beta blockers are described on p. 1319.1. Labetalol also has alpha-blocking activity, which contributes to its adverse effects and these effects may predominate. Orthostatic hypotension may be a problem with high doses or at the start of treatment. Other effects associated with alpha blockade include dizziness, scalp tingling, and nasal congestion. Male sexual function may be impaired to a greater extent than with beta blockade alone. Muscle weakness, tremor, urinary retention, hepatitis, and jaundice have also been reported.

Effects on the liver. By 1990, the FDA had received 11 reports of hepatocellular damage associated with labetalol therapy.[1] Three patients died. Liver function should be monitored and labetalol stopped in patients who develop liver function abnormalities. The *R,R*-isomer of labetalol, dilevalol, was withdrawn from the market because of hepatotoxicity.[2]

1. Clark JA, *et al.* Labetalol hepatotoxicity. *Ann Intern Med* 1990; **113:** 210–13.
2. Harvengt C. Labetalol hepatotoxicity. *Ann Intern Med* 1991; **114:** 341.

Hypersensitivity. Hypersensitivity reactions associated with labetalol may manifest as fever.[1-3] Anaphylactoid reaction to labetalol has also been reported.[4]

1. D'Arcy PF. Drug reactions and interactions: drug fever with labetalol. *Int Pharm J* 1987; **1:** 43–4.
2. Stricker BH, *et al.* Fever induced by labetalol. *JAMA* 1986; **256:** 619–20.
3. Kamel J, *et al.* Drug fever due to labetalol. *Intern Med J* 2008; **38:** 871–2.
4. Ferree CE. Apparent anaphylaxis from labetalol. *Ann Intern Med* 1986; **104:** 729–30.

Overdosage. Acute oliguric renal failure developed after a short period of moderate hypotension in a patient who ingested labetalol 16 g. Renal function subsequently recovered.[1] Renal failure has also been reported[2] after ingestion of labetalol 6 g. The patient recovered after treatment with glucagon, isoprenaline, and dialysis. Another patient[3] developed circulatory collapse and impaired consciousness after being given labetalol 800 mg orally for hypertensive crisis; glucagon and sympathomimetics were given to restore blood pressure, but amrinone infusion was also needed to improve cardiac output and mental state. In contrast to this, a large intravenous overdose of labetalol 17.2 mg/kg was reported[4] to produce only mild and transient symptoms of drowsiness and hypotension in an 8-month-old infant after cardiac surgery.

1. Smit AJ, *et al.* Acute renal failure after overdose of labetalol. *BMJ* 1986; **293:** 1142–3.
2. Korzets A, *et al.* Acute renal failure associated with a labetalol overdose. *Postgrad Med J* 1990; **66:** 66–7.
3. Kollef MH. Labetalol overdose successfully treated with amrinone and alpha-adrenergic receptor agonists. *Chest* 1994; **105:** 626–7.
4. Thorsteinsson A, *et al.* Severe labetalol overdose in an 8-month-old infant. *Paediatr Anaesth* 2008; **18:** 435–8.

Precautions

As for Beta Blockers, p. 1320.3.

Because labetalol causes orthostatic hypotension it is recommended that injections are given to patients when they are lying down and that patients should remain lying down for the next 3 hours.

Labetalol should be withdrawn from patients who develop signs of hepatic impairment.

Breast feeding. Labetalol is distributed into breast milk, although it has been suggested[1] that the proportion of a maternal dose likely to be ingested by the infant is very low. In a study[2] in 25 patients, the mean concentration of labetalol in breast milk was less than in maternal plasma in patients given doses between 330 and 800 mg daily, although in 1 patient given 1200 mg daily a higher concentration was found in breast milk. In another study,[3] the concentration of drug in milk exceeded maternal plasma concentration in 2 of 3 mothers, and in 1 infant the plasma-labetalol concentration was similar to that of the mother. However, no adverse effects have been seen in breast-feeding infants whose mothers were given labetalol, and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Atkinson H, Begg EJ. Concentrations of beta-blocking drugs in human milk. *J Pediatr* 1990; **116:** 156.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28:** 597–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies labetalol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Labetalol is readily absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism. Bioavailability varies widely between patients and may be increased in the presence of food. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Labetalol has low lipid solubility and only very small amounts appear to cross the blood-brain barrier in *animals*. It is about 50% protein bound. Labetalol crosses the placenta and is distributed into breast milk (see above). Labetalol is metabolised mainly in the liver, the metabolites being excreted in the urine with only small amounts of unchanged labetalol; its major metabolite has not been found to have significant alpha- or beta-blocking effects. Excretion also occurs in the faeces via the bile. The elimination half-life at steady state is reported to be about 6 to 8 hours. On intravenous infusion, the elimination half-life is about 5.5 hours. Labetalol is not removed by dialysis.

The elderly. Analysis[1] of data from 4 single-dose studies and 3 multidose studies indicated that age did not appear to be a significant factor in oral clearance in elderly patients receiving labetalol for long-term management of hypertension.

1. Rocci ML, *et al.* Effects of age on the elimination of labetalol. *Clin Pharmacokinet* 1989; **17:** 452–7.

Pregnancy. The concentration of labetalol has been found to be lower in amniotic fluid[1] and fetal plasma[2] than in maternal plasma. A ratio of infant to maternal drug concentration of 0.2 to 0.8 has been reported[2] based on concentration in infant cord blood at delivery [time since last maternal dose not stated]. In another study,[3] however, higher concentrations were found in cord plasma than in maternal plasma at delivery when infants were delivered 12 to 24 hours after the last maternal dose.

The half-life of labetalol was reported as 24 hours in a neonate of 37 weeks' gestation whose mother had received labetalol 600 mg daily for 11 weeks before delivery.[4]

1. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28:** 597–9.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Boulton DW, *et al.* Transplacental distribution of labetalol stereoisomers at delivery. *Br J Clin Pharmacol* 1999; **47:** 573–4.
4. Haraldsson A, Geven W. Half-life of maternal labetalol in a premature infant. *Pharm Weekbl (Sci)* 1989; **11:** 229–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biascor; Blocamine; ***Austral.***: Presolol; Trandate; ***Austria***: Trandate; ***Belg.***: Trandate; ***Canad.***: Trandate; ***Chile***: Trandate; ***China***: Xin Yu Sen (欣宇森); ***Cz.***: Trandate; ***Denm.***: Trandate; ***Fin.***: Albetol; ***Fr.***: Trandate; ***Gr.***: Ftalined; Lircapil; Salmagne; Trandate; ***Hong Kong***: Presolol†; Trandate†; ***India***: Labesol; Labeta; Labil; Lobet; ***Irl.***: Trandate; ***Israel***: Trandate; ***Ital.***: Ipolab; Trandate; ***Malaysia***: Trandate; Trantalol; ***Neth.***: Trandate; ***Norw.***: Trandate; ***NZ***: Hybloc; Trandate; ***S.Afr.***: Trandate; ***Singapore***: Trandate; Trantalol; ***Spain***: Trandate; ***Swed.***: Trandate; ***Switz.***: Trandate; ***Thai.***: Avexa; Trandate; ***UK***: Trandate; ***USA***: Trandate.

Multi-ingredient Preparations. ***Ital.***: Trandiur.

Pharmacopoeial Preparations
BP 2014: Labetalol Injection; Labetalol Tablets;
USP 36: Labetalol Hydrochloride Injection; Labetalol Hydrochloride Oral Suspension; Labetalol Hydrochloride Tablets.

Lacidipine *(BAN, USAN, rINN)*

GR-43659X; GX-1048; Lacidipin; Lacidipino; Lacidipinum; Lasidipiini; Lasidipin; Лацидипин.

Diethyl 4-[2-[(*tert*-butoxycarbonyl)vinyl]phenyl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{26}H_{33}NO_6$=455.6

CAS — 103890-78-4.

ATC — C08CA09.

ATC Vet — QC08CA09.

UNII — 260080034N.

Pharmacopoeias. In *Br.*

BP 2014: (Lacidipine). A white to pale yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone and in dichloromethane.

Uses and Administration

Lacidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the treatment of hypertension (p. 1251.1).

The usual initial oral dose of lacidipine is 2 mg once daily, increased if necessary after 3 to 4 weeks or more to 4 mg daily; a further increase in dose to 6 mg daily may be necessary in some patients. Reduced doses may be required in patients with severe hepatic impairment.

Lacidipine has been investigated for its apparent antimicrobial properties.

Reviews.

1. Lee CR, Bryson HM. Lacidipine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of hypertension. *Drugs* 1994; **48:** 274–96.
2. Zanchetti A, ed. Cardiovascular advantages of a third generation calcium antagonist: symposium on lacidipine. *Drugs* 1999; **57** (suppl 1): 1–29.
3. McCormack PL, Wagstaff AJ. Lacidipine: a review of its use in the management of hypertension. *Drugs* 2003; **63:** 2327–56.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Lacidipine is rapidly but poorly absorbed from the gastrointestinal tract after oral doses and undergoes extensive first-pass metabolism; the bioavailability has been reported to be 2 to 9%, or 18.5% (range 4 to 52%) using a more sensitive assay method. Peak plasma concentrations occur within 30 to 150 minutes. It is more than 95% bound to plasma proteins. Lacidipine is eliminated by metabolism in the liver and metabolites are excreted mainly by the biliary route. About 70% of an oral dose is eliminated in the faeces, the remainder in the urine. The average steady-state terminal elimination half-life of lacidipine is 13 to 19 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Motens; ***Braz.***: Lacipil; Midotens; ***China***: Lacipil (乐息平); Sileping (司乐平); ***Cz.***: Lacipil; ***Denm.***: Lacipil; Midotens; Motens; ***Fr.***: Caldine; ***Gr.***: Balnox; Lacipil; Lacitens; Motens; ***Hong Kong***: Lacipil†; ***Hung.***: Lacipil; ***India***: Lacivas; Sinopil; ***Indon.***: Lacipil†; ***Ital.***: Aponil; Lacipil; Lacirex; Ladip; Viapres; ***Malaysia***: Lacipil; ***Mex.***: Lacipil; Midotens; ***Neth.***: Motens; ***Philipp.***: Lacipil; ***Pol.***: Lacipil; ***Port.***: Lacipil; Tens; ***Rus.***: Lacipil (Лаципил); Sakure (Сакур); ***Singapore***: Lacipil; ***Spain***: Lacimen; Lacipil; Motens; ***Switz.***: Motens; ***Thai.***: Motens†; ***Turk.***: Lacipil; ***UK***: Motens; ***Venez.***: Lacipil.

Pharmacopoeial Preparations
BP 2014: Lacidipine Tablets.

Lanatoside C *(BAN, rINN)*

Celanide; Celanidum; Lanatosid C; Lanatosidi C; Lanatósido C; Lanatosidum C; Lanatozyd c; Ланатозид С.

3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-3-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.

$C_{49}H_{76}O_{20}$=985.1

CAS — 17575-22-3.

ATC — C01AA06.

ATC Vet — QC01AA06.

UNII — 5RR3JFZ771.

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Lanatoside C is a cardiac glycoside with positive inotropic activity. It is obtained from digitalis lanata leaf (p. 1352.3). It has general properties similar to those of digoxin (p. 1353.3) and has been used in the treatment of some cardiac arrhythmias and in heart failure.

Mixtures of lanatosides A, B, and C have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Cedilanid; ***Rus.***: Celanid (Целанид); ***Ukr.***: Celanid-KMP (Целанид-КМП)†.

Landiolol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de landiolol; Landiolol, Chlorhydrate de; Landiolol, hidrocloruro de; Landiololi Hydrochloridum; ONO-1101; Ландиолола Гидрохлорид.

(-)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl *p*-((*S*)-2-hydroxy-3-{[2-(4-morpholinecarboxamido)ethyl]amino}propoxy) hydrocinnamate hydrochloride.

$C_{25}H_{39}N_3O_8$,HCl=546.1

CAS — 133242-30-5 (landiolol); 144481-98-1 (landiolol hydrochloride).

UNII — G8HQ634Y17.

Profile

Landiolol is a short-acting, cardioselective beta blocker given intravenously as the hydrochloride in the management of intra- and postoperative cardiac arrhythmias.

References.

1. Kitamura A, *et al*. Efficacy of an ultrashort-acting beta-adrenoceptor blocker (ONO-1101) in attenuating cardiovascular responses to endotracheal intubation. *Eur J Clin Pharmacol* 1997; **51:** 467–71.
2. Atarashi H, *et al*. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000; **68:** 143–50.
3. Mizuno J, *et al*. Age and sex-related differences in dose-dependent hemodynamic response to landiolol hydrochloride during general anesthesia. *Eur J Clin Pharmacol* 2007; **63:** 243–52.
4. Inoue S, *et al*. The efficacy of landiolol for suppressing the hyperdynamic response following laryngoscopy and tracheal intubation: a systematic review. *Anaesth Intensive Care* 2009; **37:** 893–902.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn.*** Corebeta; Onoact.

Lappaconitine Hydrobromide

Лаппаконитина Гидробромид.

(1α,14α,16β)-20-Ethyl-1,14,16-trimethoxyaconitane-4,8,9-triol 4-[2-(acetylamino)benzoate] hydrobromide.

$C_{32}H_{44}N_2O_8$,HBr=665.6

CAS — 32854-75-4 (lappaconitine); 97792-45-5 (lappaconitine hydrobromide).

Profile

Lappaconitine hydrobromide is an antiarrhythmic drug given orally in a usual dose of 25 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bo Si Te (博斯特); Hai Feng Quan (海丰泉); Jie Qing (捷清); Jin Da Xin (金达欣); Li Kang Ping (隶慷平); Lin Yuan Li Shu (林源立舒); Ning Sheng Xin (宁圣欣); Pu Le (朴乐); Qing Tong (清通); Wu Hen (无衡); Xi Song (西松); You Yi Xin (优一欣); Zhi Teng (知腾); Zhuo Ning (卓宁); ***Rus.***: Allapinin (Аллапинин).

Leech

Blodigel; Bloedzuiger; Blutegel; Dēle; Dėlė; Egel; Hirudo; Iilimato; Juotikas; Kaan; Pijavka; Pijawka; Pióca; Sangonera; Sangsue; Sanguessugas; Sanguijuela; Sanguisuga; Sülük; Пиявка; Пиявици.

Description. *Hirudo medicinalis* is the leech commonly used in medicine and is a fresh-water annelid.

NOTE. The substance described in the *Chin. P.* as Hirudo (Leech) is the dried body of *Whitmania pigra, Hirudo nipponica,* or *Whitmania acranulata.*

Profile

Leeches are used for withdrawing blood from congested areas and have been found to be of value in plastic surgery. The buccal secretion of the leech contains the anticoagulant hirudin (p. 1401.2). Once used a leech should not be applied to another patient.

There have been reports of wound infection from *Aeromonas hydrophila* transmitted by leeches. Prolonged bleeding for up to 10 hours may occur from the site of attachment after removal of the leech.

Leeches are commonly used in plastic surgery and this has been reviewed.[1,2]

Wound infection by *Aeromonas hydrophila,* an organism normally found in the gut of the leech, is a recognised complication of the use of leeches for decongestion after plastic surgery. Other infecting organisms include *Aeromonas sobria* and *Serratia marcescens.* Infections have caused minor wound drainage, cellulitis, abscess, tissue loss, and sepsis, and a case of meningitis secondary to *Aeromonas* infection has been reported.[3] The following protocol has been suggested:[1] the site of application should first be cleaned with heparinised saline, and antibacterial prophylaxis with a quinolone and an aminoglycoside given for the duration of application. Patients discharged with open wounds should continue with oral antibacterials until wound closure.

In addition to its anticoagulant properties the buccal secretion of the leech contains anti-inflammatory substances, and leeches have been reported to provide subjective relief of osteoarthritis[4,5] and cancer pain.[6]

1. Whitaker IS, *et al*. Hirudo medicinalis and the plastic surgeon. *Br J Plast Surg* 2004; **57:** 348–53.
2. Porshinsky BS, *et al*. Clinical uses of the medicinal leech: a practical review. *J Postgrad Med* 2011; **57:** 65–71.
3. Ouderkirk JP, *et al*. *Aeromonas* meningitis complicating medicinal leech therapy. Abstract: *Clin Infect Dis* 2004; **38**: 603. Full version: http://www.journals.uchicago.edu/doi/full/10.1086/381438 (accessed 19/08/08)
4. Michalsen A, *et al*. Effect of leeches therapy (Hirudo medicinalis) in painful osteoarthritis of the knee: a pilot study. *Ann Rheum Dis* 2001; **60:** 986.
5. Michalsen A, *et al*. Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2003; **139:** 724–30.
6. Kalender ME, *et al*. Leech therapy for symptomatic relief of cancer pain. *Pain Med* 2010; **11:** 443–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Piyavit (Пиявит).

Multi-ingredient Preparations. ***Hung.***: Antikeloid; Forte Hirudo; Medhirud; Plerudin; ***Malaysia***: NeuroAid; ***Singapore***: NeuroAid.

Lepirudin *(BAN, rINN)*

HBW-023; Lepirudiini; Lepirudina; Lépirudine; Lepirudinum; Лепирудин.

1-L-Leucine-2-L-threonine-63-desulfohirudin (*Hirudo medicinalis* isoform HV1).

$C_{287}H_{440}N_{80}O_{111}S_6$=6979.5

CAS — 138068-37-8.

ATC — B01AE02.

ATC Vet — QB01AE02.

UNII — Y43GF64R34.

Uses and Administration

Lepirudin is a recombinant hirudin (p. 1401.2) that is a direct inhibitor of thrombin. It is used as an anticoagulant in the management of thromboembolic disorders (p. 1273.2) in patients with heparin-induced thrombocytopenia. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina.

In the management of thromboembolism in patients with heparin-induced thrombocytopenia, lepirudin is given in an initial dose of 400 micrograms/kg by slow intravenous injection. This may be followed by a maintenance dose of 150 micrograms/kg per hour by continuous intravenous infusion, adjusted according to response, usually for 2 to 10 days. Response should be monitored according to the activated partial thromboplastin time (APTT) ratio to achieve a target of 1.5 to 2.5. Doses must not exceed those based on a patient weight of 110 kg and in general an infusion rate of 210 micrograms/kg per hour should not be exceeded.

Doses of lepirudin should be reduced in patients with renal impairment, and it should generally be avoided in those on haemodialysis. Some have found licensed doses to be excessive, and lower doses have been suggested for both patients with normal renal function and those with renal impairment. For a discussion of these doses, see Heparin-induced Thrombocytopenia, below.

Administration in renal impairment. For both licensed and alternative doses of lepirudin in patients with renal impairment, see Heparin-induced Thrombocytopenia, below.

Extracorporeal circulation. Heparin is the anticoagulant most frequently used to prevent occlusion of extracorporeal circuits during haemodialysis and haemofiltration. The direct thrombin inhibitors have been tried as alternatives, and may be especially useful when heparin is contra-indicated because of heparin-induced thrombocytopenia (HIT). *Lepirudin* has been used with moderate efficacy,[1,2] although it is renally cleared and bleeding may be a problem. *Bivalirudin* was tried successfully in a patient who developed HIT during continual venovenous haemofiltration (CVVH).[3] A subsequent randomised study[4] in 10 adults undergoing CVVH found that bivalirudin was effective, with a similar tolerability and improved haemofilter survival compared with heparin. *Argatroban* was also effective in 5 patients with HIT requiring haemodialysis or CVVH.[5] The drug was not significantly removed by dialysis or CVVH, and no dosage adjustment was required.

1. Vargas Hein O, *et al*. Hirudin versus heparin for anticoagulation in continuous renal replacement therapy. *Intensive Care Med* 2001; **27:** 673–9.
2. Hein OV, *et al*. Intermittent hirudin versus continuous heparin for anticoagulation in continuous renal replacement therapy. *Ren Fail* 2004; **26:** 297–303.
3. Mueller SW, *et al*. Prefilter bivalirudin for preventing hemofilter occlusion in continuous renal replacement therapy. *Ann Pharmacother* 2009; **43:** 1360–5.
4. Kiser TH, *et al*. Bivalirudin versus unfractionated heparin for prevention of hemofilter occlusion during continuous renal replacement therapy. *Pharmacotherapy* 2010; **30:** 1117–26.
5. Tang IY, *et al*. Argatroban and renal replacement therapy in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2005; **39:** 231–6.

Heparin-induced thrombocytopenia. Lepirudin is effective for the management of thromboembolism in patients with heparin-induced thrombocytopenia[1] (see Effects on the Blood under Adverse Effects of Heparin, p. 1399.1). Bleeding is the main complication during treatment and use of lower doses[1-4] than those licensed has been suggested for both patients with normal renal function and those with renal impairment.

Licensed doses of lepirudin in patients with renal impairment are as follows: the initial dose should be reduced to 200 micrograms/kg, and the maintenance infusion rate reduced according to creatinine clearance (CC):

- CC 45 to 60 mL/minute: 75 micrograms/kg per hour
- CC 30 to 44 mL/minute: 45 micrograms/kg per hour
- CC 15 to 29 mL/minute: 22.5 micrograms/kg per hour
- CC below 15 mL/minute: infusion of lepirudin should be avoided, although in haemodialysis patients or cases of acute renal failure further intravenous bolus doses of 100 micrograms/kg may be used on alternate days, according to response

However, in one centre experience[3] in 68 patients led to the suggestion that lower doses may be more appropriate, with the initial intravenous injection omitted altogether and the infusion rates as follows:

- normal renal function: 80 micrograms/kg per hour
- CC 30 to 60 mL/minute: 40 micrograms/kg per hour
- CC less than 30 mL/minute: 10 to 20 micrograms/kg per hour

American College of Chest Physicians (ACCP) guidelines[4] also suggest that the initial injection may be omitted, or an initial dose of 200 micrograms/kg may be given to those with life- or limb-threatening thrombosis. Suggested infusion rates, based on serum-creatinine concentrations, are:

- creatinine less than 90 micromoles/litre: 100 micrograms/kg per hour
- creatinine 90 to 140 micromoles/litre: 50 micrograms/kg per hour
- creatinine 140 to 400 micromoles/litre: 10 micrograms/kg per hour
- creatinine more than 400 micromoles/litre: 5 micrograms/kg per hour

The ACCP also recommends that APTT is monitored at 4-hourly intervals with a target ratio of 1.5 to 2.0.

1. Lubenow N, *et al*. HIT Investigators Group. Lepirudin in patients with heparin-induced thrombocytopenia—results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005; **3:** 2428–36.
2. Tardy B, *et al*. GEHT-HIT Study Group. Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood* 2006; **108:** 1492–6.
3. Tschudi M, *et al*. Dosing lepirudin in patients with heparin-induced thrombocytopenia and normal or impaired renal function: a single-center experience with 68 patients. *Blood* 2009; **113:** 2402–9.
4. Warkentin TE, *et al*. American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; **133** (suppl): 340S–380S. Also available at: http://chestjournal.chestpubs.org/content/139/5/1261.full.pdf (accessed 25/10/11) Correction. *ibid.* 2011; **139:** 1261. [dose]

Ischaemic heart disease. Recombinant hirudins have been investigated as alternatives to heparin in the management of acute ST-elevation myocardial infarction (p. 1257.1) and in non-ST elevation myocardial infarction and unstable angina (see Angina Pectoris, p. 1254.3), and have been used as adjuncts to medical or interventional treatment. Overall they appear to have some benefit over heparin,[1] but their precise role in each situation remains to be confirmed.

Initial studies comparing heparin with the recombinant hirudins desirudin[2,3] (p. 1351.1) or lepirudin[4] in patients with acute ST-elevation **myocardial infarction** treated with thrombolytics had to be stopped because of higher than expected haemorrhagic stroke rates,[5,6] and subsequent studies using lower doses of desirudin[7,8] or lepirudin[9] failed to show a clear benefit over heparin. A study[10] with bivalirudin, a synthetic analogue of hirudin, in similar patients also found no mortality benefit; there were fewer re-infarctions in the bivalirudin group, but the risk of bleeding was increased. The role of hirudins is therefore not established in patients treated with thrombolytics, although they may be useful in patients with heparin-induced thrombocytopenia. They may also have a role in PCI (see below).

Studies in patients with **acute coronary syndromes** (non-ST elevation myocardial infarction and unstable angina) suggest that lepirudin is superior to heparin in preventing cardiovascular death, myocardial infarction, and refractory angina.[11,12] A study[13] comparing desirudin with heparin in unstable angina found that angiographic outcomes were better with desirudin, but another study[7] found little benefit in terms of mortality or recurrent ischaemia. Bivalirudin appears to be as effective as heparin in patients with acute coronary syndromes, but unlike the other hirudins the risk of major bleeding may be reduced.[14,15]

Hirudins have also been studied in patients undergoing **percutaneous coronary interventions** (see Reperfusion and Revascularisation Procedures, p. 1259.2). Desirudin has been used in patients undergoing angioplasty[16,17] and appears to be safe, although no benefit has been shown over heparin. Lepirudin has been used as an alternative to heparin in patients with heparin-induced thrombocytopenia.[18-20] Bivalirudin is an effective alternative to heparins during percutaneous coronary interventions in patients with stable coronary artery disease,[21,22] or acute coronary syndromes,[21-24] or acute myocardial infarction,[25] and may reduce the need for adjunctive glycoprotein IIb/IIIa inhibitors.[21-23] Again there is evidence[26,27] that it is associated with less bleeding than heparin.

In patients undergoing **coronary artery bypass grafting**, hirudins may be an alternative to unfractionated heparin, and positive results have been reported with bivalirudin[28] and with lepirudin;[29] however, postoperative bleeding is increased and it was suggested[29] that hirudins should be reserved for patients with contra-indications to heparin, such as those with heparin-induced thrombocytopenia.

1. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002; **359:** 294–302.
2. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994; **90:** 1631–7.
3. Antman EM, *et al.* Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. *Circulation* 1994; **90:** 1624–30.
4. Neuhaus K-L, *et al.* Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study: a study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte (ALKK). *Circulation* 1994; **90:** 1638–42.
5. Zeymer U, Neuhaus K-L. Hirudin and excess bleeding: implications for future use. *Drug Safety* 1995; **12:** 234–9.
6. Conrad KA. Clinical pharmacology and drug safety: lessons from hirudin. *Clin Pharmacol Ther* 1995; **58:** 123–6.
7. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; **335:** 775–82.
8. Antman EM. Hirudin in acute myocardial infarction: thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. *Circulation* 1996; **94:** 911–21.
9. Neuhaus K-L, *et al.* Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. *J Am Coll Cardiol* 1999; **34:** 966–73.
10. The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001; **358:** 1855–63.
11. Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. *Circulation* 1997; **96:** 769–77.
12. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999; **353:** 429–38.
13. Topol EJ, *et al.* Recombinant hirudin for unstable angina pectoris: a multicenter, randomized angiographic trial. *Circulation* 1994; **89:** 1557–66.
14. Kong DF, *et al.* Clinical outcomes of bivalirudin for ischemic heart disease. *Circulation* 1999; **100:** 2049–53.
15. Stone GW, *et al.* The ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.
16. van den Bos AA, *et al.* Safety and efficacy of recombinant hirudin (CGP 39 393) versus heparin in patients with stable angina undergoing coronary angioplasty. *Circulation* 1993; **88:** 2058–66.
17. Serruys PW, *et al.* A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1995; **333:** 757–63.
18. Manfredi JA, *et al.* Lepirudin as a safe alternative for effective anticoagulation in patients with known heparin-induced thrombocytopenia undergoing percutaneous coronary intervention: case reports. *Catheter Cardiovasc Interv* 2001; **52:** 468–72.
19. Pinto DS, *et al.* Combination platelet glycoprotein IIb/IIIa receptor and lepirudin administration during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. *Catheter Cardiovasc Interv* 2003; **58:** 65–8.
20. Cochran K, *et al.* Use of lepirudin during percutaneous vascular interventions in patients with heparin-induced thrombocytopenia. *J Invasive Cardiol* 2003; **15:** 617–21.
21. Lincoff AM, *et al.* Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003; **289:** 853–63. Correction. *ibid.*; 1638.
22. Lincoff AM, *et al.* Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004; **292:** 696–703. Correction. *ibid.* 2006; **296:** 46.
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24. White HD, *et al.* Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol* 2008; **52:** 807–14.
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26. Stone GW, *et al.* HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358:** 2218–30.
27. Kastrati A, *et al.* ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008; **359:** 688–96.
28. Dyke CM, *et al.* A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. *J Thorac Cardiovasc Surg* 2006; **131:** 533–9.
29. Riess F-C, *et al.* Recombinant hirudin for cardiopulmonary bypass anticoagulation: a randomized, prospective, and heparin-controlled pilot study. *Thorac Cardiovasc Surg* 2007; **55:** 233–8.

Adverse Effects and Precautions

The most frequent adverse effect of the direct thrombin inhibitors is bleeding. Hypersensitivity reactions have been reported. There have been reports of severe anaphylactic reactions, including death, with many occurring on re-exposure. There may be cross-reactivity with other hirudins or hirudin analogues.

Intramuscular injection should be avoided as it may cause local haematoma.

Direct thrombin inhibitors should be used with caution or avoided in patients with hepatic or renal impairment, and in those who are bleeding or at serious risk of bleeding, including those with haemorrhagic blood disorders, recent major bleeding, cerebrovascular disorders, bacterial endocarditis, severe hypertension, or patients who have recently undergone major surgery or puncture of large vessels or organ biopsy.

Effects on the blood. Lepirudin is reported[1] to have twice induced thrombocytopenia in a patient with recurrent venous thrombosis and a recent history of heparin-induced thrombocytopenia. Both drops in platelet count occurred when administration was changed from the intravenous to the subcutaneous route.

1. Schroeder WS, *et al.* Lepirudin-induced thrombocytopenia following subcutaneous administration. *Am J Health-Syst Pharm* 2009; **66:** 834–7.

Hypersensitivity. The EMEA reported[1] in October 2002 that it was aware of 7 cases of severe anaphylactic reactions in patients given lepirudin; in 6 cases this followed re-exposure to the drug, and in 5 cases the patient died. A review[2] of the manufacturer's safety database identified 9 patients with severe anaphylactic reactions associated with lepirudin; 4 patients died, all of whom had received lepirudin within the previous 1 to 12 weeks. Although the risk of severe anaphylaxis was estimated to be low (0.015% on first exposure and 0.16% on re-exposure),[2] alternative treatment should be considered before re-exposure to lepirudin and it should only be used where treatment for an anaphylactic reaction is available.[1,2]

1. EMEA. EMEA public statement on Refludan (lepirudin)—fatal anaphylactic reactions (issued October 2002). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/08/WC500095474.pdf (accessed 10/08/10)
2. Greinacher A, *et al.* Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; **108:** 2062–5.

Treatment of Adverse Effects

If bleeding occurs lepirudin should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for lepirudin (but see below).

Overdosage. A review[1] concluded that the use of activated eptacog alfa (recombinant factor VIIa) was of benefit in the management of bleeding associated with certain anticoagulants, including direct thrombin inhibitors. Although the lowest effective dose was uncertain, 30 to 90 micrograms/kg had been reported to be effective for direct thrombin inhibitor reversal. Use of repeat doses of eptacog alfa was not recommended.

1. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; **44:** 718–26.

Interactions

Use of direct thrombin inhibitors with thrombolytics, oral anticoagulants, or drugs that affect platelet function may increase the risk of bleeding.

Pharmacokinetics

Lepirudin is metabolised and excreted by the kidney. About 45% of an intravenous dose is detected in the urine and about 35% is excreted unchanged. The terminal elimination half-life of lepirudin is about 1.3 hours. In patients with severe renal impairment the half-life may be prolonged to about 2 days.

Breast feeding. Three hours after injection, plasma concentrations of hirudin in a woman receiving lepirudin 50 mg subcutaneously twice daily were 0.5 to 1 microgram/mL, but no hirudin was detected in the breast milk.

1. Lindhoff-Last E, *et al.* Hirudin treatment in a breastfeeding woman. *Lancet* 2000; **355:** 467–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Refludan; ***Austria***: Refludan†; ***Belg.***: Refludan†; ***Canad.***: Refludan; ***Cz.***: Refludan†; ***Fr.***: Refludan†; ***Ger.***: Refludan†; ***Gr.***: Refludan†; ***Hung.***: Refludan†; ***Irl.***: Refludan†; ***Ital.***: Refludan†; ***Neth.***: Refludan†; ***Norw.***: Refludan†; ***NZ***: Refludan†; ***Pol.***: Refludan†; ***Port.***: Refludan†; ***S.Afr.***: Refludin; ***Spain***: Refludin†; ***Swed.***: Refludan†; ***Switz.***: Refludan†; ***UK***: Refludan†; ***USA***: Refludan†.

Lercanidipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lercanidipino; Lercandipinhydrochlorid; Lercanidipine, Chlorhydrate de; Lercanidipini Hydrochloridum; Lercanidipino, hidrocloruro de; Lerkanidipin Hidroklorür; Masnidipine Hydrochloride; R-75; Rec-15-2375; Лерканидипина Гидрохлорид.

(±)-2-[(3,3-Diphenylpropyl)methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

$C_{35}H_{41}N_3O_6$,HCl=648.2

CAS — 100427-26-7 (lercanidipine); 132866-11-6 (lercanidipine hydrochloride).

ATC — C08CA13.

ATC Vet — QC08CA13.

UNII — OA8TFX68PE.

Uses and Administration

Lercanidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the treatment of hypertension (p. 1251.1).

Lercanidipine is given orally as the hydrochloride in a usual initial dose of 10 mg once daily before food, increased if necessary, after at least 2 weeks, to 20 mg daily.

Reviews.

1. McClellan KJ, Jarvis B. Lercanidipine: a review of its use in hypertension. *Drugs* 2000; **60:** 1123–40.
2. Bang LM, *et al.* Lercanidipine: a review of its efficacy in the management of hypertension. *Drugs* 2003; **63:** 2449–72.
3. Beckey C, *et al.* Lercanidipine in the treatment of hypertension. *Ann Pharmacother* 2007; **41:** 465–74.
4. Burnier M, *et al.* Treatment of essential hypertension with calcium channel blockers: what is the place of lercanidipine? *Expert Opin Drug Metab Toxicol* 2009; **5:** 981–7.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2). Lercanidipine should not be used in those with severe hepatic impairment or renal impairment (creatinine clearance less than 30 mL/minute).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lercanidipine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Tolerability. A meta-analysis[1] of 8 comparative studies suggested that oedema was less likely with lercanidipine than

with first-generation dihydropyridine calcium-channel blockers such as amlodipine, felodipine, or nifedipine, and lercanidipine-treated patients were less likely to withdraw from treatment due to adverse effects; however, no difference could be shown versus the lipophilic second-generation drugs lacidipine or manidipine. There were no differences in the incidence of flushing or headache versus either generation of drugs.

1. Makarounas-Kirchmann K, *et al.* Results of a meta-analysis comparing the tolerability of lercanidipine and other dihydropyridine calcium channel blockers. *Clin Ther* 2009; **31:** 1652–63.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Lercanidipine is completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive saturable first-pass metabolism. Bioavailability is low but is increased in the presence of food. Peak plasma concentrations occur about 1.5 to 3 hours after oral dosage. Lercanidipine is rapidly and widely distributed. It is more than 98% bound to plasma proteins. Lercanidipine is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP3A4, mainly to inactive metabolites; about 50% of an oral dose is excreted in the urine. A terminal elimination half-life of about 2 to 5 hours has been reported, but studies using a more sensitive assay have suggested a value of 8 to 10 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lercadip; ***Austral.***: Lercadip; Lercan; Zanidip; Zircol; ***Austria***: Zanidip; ***Belg.***: Zanidip; ***Braz.***: Zanidip; ***Chile***: Zanidip†; ***China***: Zanidip (哌尼平); ***Cz.***: Kapidin; Lerpin; ***Denm.***: Lercastad; Lercatio; Lercinigen; Nircadel†; Zanedip†; Zanidip; ***Fin.***: Nircadel†; Oridip; Zanidip; ***Fr.***: Lercan; Zanidip; ***Ger.***: Carmen; Corifeo; ***Gr.***: Lercadip; Zanidip; ***Hong Kong***: Zanidip; ***Hung.***: Lercaton; Zanidip; ***India***: Landip; Lerez; Lerka; Lervasc; Lotensyl; ***Indon.***: Zanidip; ***Irl.***: Lecalpin; Zanidip; ***Israel***: Lercapress; Vasodip; ***Ital.***: Cardiovasc; Lercadip; Zanedip; ***Malaysia***: Zanidip; ***Mex.***: Evipress; Zanidip; ***Neth.***: Lerdip; ***Norw.***: Zanidip; ***NZ***: Zanidip; ***Philipp.***: Zanidip; ***Port.***: Calcan; Zanicor; Zanidip; ***Rus.***: Lercamen (Леркамен); ***S.Afr.***: Zanidip; ***Spain***: Lercadip; Lerzam; Zanidip; ***Swed.***: Zanidip; ***Switz.***: Zanidip; ***Thai.***: Zanidip; ***Turk.***: Lercadip; ***UK***: Zanidip; ***Ukr.***: Lercamen (Леркамен); Zanidip (Занидип); ***Venez.***: Lercadip; Zanidip.

Multi-ingredient Preparations. ***Austral.***: Zan-Extra; ***Austria***: Lercaprel; Zanipril; ***Belg.***: Zanicombo; ***Cz.***: Lercaprel; Zanicombo; ***Denm.***: Zanipress; ***Fin.***: Zanipress; ***Fr.***: Lercapress; Zanextra; ***Ger.***: Carmen ACE; Zaneril; Zanipress; ***Gr.***: Lercaprel; Zaneril; ***India***: Lotensyl-AT; ***Irl.***: Lercaril; ***Israel***: Vasodip Combo; ***Neth.***: Lercaprel†; Lertec; ***Norw.***: Zanipress; ***Port.***: Zanipress; Zanitek; ***S.Afr.***: Zaneril; ***Spain***: Coripren; Lercapress; Zanipress; ***Switz.***: Zanipress; ***Ukr.***: Coripren (Коприпен).

Levosimendan *(USAN, rINN)*

Levosimendán; Lévosimendan; Levosimendanum; (-)-OR-1259; Левосимендан.

Mesoxalonitrile (-)-{*p*-[(*R*)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl}hydrazone.

$C_{14}H_{12}N_6O$=280.3

CAS — 141505-33-1.

ATC — C01CX08.

ATC Vet — QC01CX08.

UNII — C6T4514L4E.

Uses and Administration

Levosimendan is a cardiac inotrope and vasodilator with calcium-sensitising properties, used in the management of acute heart failure (p. 1262.3), although its place in therapy is unclear. It is given intravenously in a loading dose of 6 to 12 micrograms/kg over 10 minutes followed by a continuous infusion of 50 to 200 nanograms/kg per minute, adjusted according to response. The recommended duration of infusion is 24 hours.

Levosimendan has been tried in several other indications including cardiogenic and septic shock, and calcium-channel blocker toxicity.

References.

1. Figgitt DP, *et al.* Levosimendan. *Drugs* 2001; **61:** 613–27.
2. Follath F, *et al.* Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; **360:** 196–202.
3. McBride BF, White CM. Levosimendan: implications for clinicians. *J Clin Pharmacol* 2003; **43:** 1071–81.
4. Innes CA, Wagstaff AJ. Levosimendan: a review of its use in the management of acute decompensated heart failure. *Drugs* 2003; **63:** 2651–71.
5. Earl GL, Fitzpatrick JT. Levosimendan: a novel inotropic agent for treatment of acute, decompensated heart failure. *Ann Pharmacother* 2005; **39:** 1888–96.
6. De Luca L, *et al.* Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* 2006; **27:** 1908–20.
7. Antila S, *et al.* Clinical pharmacology of levosimendan. *Clin Pharmacokinet* 2007; **46:** 535–52.
8. Mebazaa A, *et al.* Levosimendan vs dobutamine: outcomes for acute heart failure patients on β -blockers in SURVIVE. *Eur J Heart Fail* 2009; **11:** 304–11.
9. Follath F. Newer treatments for decompensated heart failure: focus on levosimendan. *Drug Des Devel Ther* 2009; **3:** 73–8.
10. Antoniades C, *et al.* Relationship between the pharmacokinetics of levosimendan and its effects on cardiovascular system. *Curr Drug Metab* 2009; **10:** 95–103.
11. Delaney A, *et al.* Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials. *Int J Cardiol* 2010; **138:** 281–9.
12. Landoni G, *et al.* Levosimendan reduces mortality in critically ill patients: a meta-analysis of randomized controlled studies. *Minerva Anestesiol* 2010; **76:** 276–86.

Adverse Effects and Precautions

Hypotension, headache, and ventricular tachycardia are reported to be the most frequent adverse effects with levosimendan; extrasystoles, atrial fibrillation, hypokalaemia, insomnia, dizziness, gastrointestinal disturbances, and anaemia are also reported to be common.

It should not be used in patients with severe hypotension and tachycardia, or with mechanical obstruction affecting ventricular filling or outflow. It should be given with care and under close ECG monitoring to patients with ongoing coronary ischaemia or long QTc interval regardless of aetiology; care is also required in those with potentially life-threatening arrhythmias, tachycardia, or atrial fibrillation with rapid ventricular response; it is contra-indicated where there is a history of torsade de pointes. Serum-potassium concentrations should be measured during treatment. Haemodynamic effects should continue to be monitored for several days after the end of infusion, as they may be prolonged. Levosimendan should be used with caution in patients with renal or hepatic impairment and should be avoided if these are severe.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levosimendan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

On infusion of levosimendan it is extensively metabolised, with a half-life of about 1 hour. Its active metabolites OR-1855 and OR-1896 are interconverted by acetylation and de-acetylation and have half-lives of about 75 to 80 hours, producing a prolonged duration of action. Metabolites and a small amount of unchanged drug are excreted in urine and faeces. More than 95% of a dose is excreted within one week. Levosimendan is about 98% bound to plasma proteins, mainly albumin, but the active metabolites have much lower protein binding of about 40%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Simdax; ***Austria***: Simdax; ***Braz.***: Simdax; ***Chile***: Daxim; ***Cz.***: Simdax; ***Fin.***: Simdax; ***Gr.***: Simdax; ***Hong Kong***: Simdax†; ***Hung.***: Simdax; ***Israel***: Simdax; ***Ital.***: Simdax; ***Mex.***: Simdax; ***Norw.***: Simdax; ***NZ***: Simdax; ***Port.***: Simdax; ***Rus.***: Simdax (Симдакс); ***Singapore***: Simdax†; ***Spain***: Simdax; ***Swed.***: Simdax; ***Turk.***: Simdax; ***Ukr.***: Simdax (Симдакс); ***Venez.***: Daxim.

Lidoflazine *(BAN, USAN, rINN)*

Lidoflazin; Lidoflazina; Lidoflazinum; McN-JR-7904; Ordiflazine; R-7904; Лидофлазин.

4-[3-(4,4′-Difluorobenzhydryl)propyl]piperazin-1-ylaceto-2′,6′-xylidide.

$C_{30}H_{35}F_2N_3O$=491.6

CAS — 3416-26-0.

ATC — C08EX01.

ATC Vet — QC08EX01.

UNII — J4ZHN3HBTE.

Profile

Lidoflazine is a calcium-channel blocker (p. 1244.2) that reduces AV conduction. It has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Clinium†; ***S.Afr.***: Clinium†.

Limaprost *(rINN)*

Limaprostum; ONO-1206; OP-1206; Лимапрост.

(*E*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-5-oxocyclopentyl}-2-heptenoic acid.

$C_{22}H_{36}O_5$=380.5

CAS — 74397-12-9 (limaprost); 88852-12-4 (limaprost alfadex).

UNII — L02U804092.

Pharmacopoeias. *Jpn* includes limaprost alfadex.

Profile

Limaprost is a synthetic analogue of alprostadil (prostaglandin E_1) used in the management of peripheral vascular disorders (p. 1272.3). It is given orally as limaprost alfadex, in a dose equivalent to limaprost 15 to 30 micrograms daily in three divided doses.

References.

1. Shono T, Ikeda K. Rapid effect of oral limaprost in Raynaud's disease in childhood. *Lancet* 1989; **i:** 908.
2. Murai C, *et al.* Oral limaprost for Raynaud's phenomenon. *Lancet* 1989; **ii:** 1218.
3. Aoki Y, *et al.* Possible participation of a prostaglandin E1 analogue in the aggravation of diabetic nephropathy. *Diabetes Res Clin Pract* 1992; **16:** 233–8.
4. Sato Y, *et al.* Effect of oral administration of prostaglandin E1 on erectile dysfunction. *Br J Urol* 1997; **80:** 772–5.
5. Swainston Harrison T, Plosker GL. Limaprost. *Drugs* 2007; **67:** 109–18.

Interactions. A woman who had been taking limaprost for peripheral vascular symptoms had 2 episodes of massive epistaxis about a month after starting *paroxetine*,[1] the second after a reduction in paroxetine dose. No further episodes of epistaxis occurred once the dose of limaprost was reduced from 15 to 10 micrograms daily. Limaprost dosage was subsequently returned to 15 micrograms daily without a recurrence in epistaxis, but evidence of subconjunctival bleeding developed.

1. Sugiyama N, *et al.* Massive epistaxis and subconjunctival hemorrhage due to combination of paroxetine and limaprost alfadex: a case report. *Prim Care Companion J Clin Psychiatry* 2007; **9:** 240–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Opalmon.

Linsidomine Hydrochloride *(rINNM)*

Hidrocloruro de linsidomina; Linsidomina, hidrocloruro de; Linsidomine, Chlorhydrate de; Linsidomini Hydrochloridum; Линсидомина Гидрохлорид.

3-Morpholinosydnonimine hydrochloride.

$C_6H_{10}N_4O_2$,HCl=206.6

CAS — 33876-97-0 (linsidomine); 16142-27-1 (linsidomine hydrochloride).

ATC — C01DX18.

ATC Vet — QC01DX18.

UNII — Y0054U597M.

Profile

Linsidomine is a nitrovasodilator and a metabolite of molsidomine (p. 1441.1) and has been given intravenously or via the intracoronary route for coronary vasodilatation.

References.

1. Delonca J, *et al.* Comparative efficacy of the intravenous administration of linsidomine, a direct nitric oxide donor, and isosorbide dinitrate in severe unstable angina: a French multicentre study. *Eur Heart J* 1997; **18:** 1300–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Corvasal†.

Lisinopril *(BAN, USAN, rINN)*

L-154826; Lisinopriili; Lisinoprilum; Lizinopril; Lizinoprilis; MK-521; Лизиноприл.

N-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate.

$C_{21}H_{31}N_3O_5$,$2H_2O$=441.5

CAS — 76547-98-3 (anhydrous lisinopril); 83915-83-7 (lisinopril dihydrate).

ATC — C09AA03.

ATC Vet — QC09AA03.
UNII — E719951YWR (lisinopril); 7Q3P4BS2FD (anhydrous lisinopril).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Lisinopril Dihydrate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dehydrated alcohol and in acetone; sparingly soluble in methyl alcohol.

USP 36: (Lisinopril). A white crystalline powder. Soluble 1 in 10 of water and 1 in 70 of methyl alcohol; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in ether.

Suspension. The US licensed prescribing information provides the following method for making 200 mL of a suspension containing lisinopril 1 mg/mL. Add 10 mL of purified water to a polyethylene terephthalate bottle containing ten 20-mg tablets (*Prinivil, Merck* or *Zestril, AstraZeneca*) and shake for at least 1 minute. Add 30 mL of *Bicitra* (*Alza, USA*) and 160 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and gently shake for several seconds. The suspension should be stored at or below 25 degrees and can be stored for up to 4 weeks. Studies of the characteristics of this and other liquid dosage forms of lisinopril have been published.[1,2]

1. Thompson KC, *et al*. Characterization of an extemporaneous liquid formulation of lisinopril. *Am J Health-Syst Pharm* 2003; **60:** 69–74.
2. Nahata MC, Morosco RS. Stability of lisinopril in two liquid dosage forms. *Ann Pharmacother* 2004; **38:** 396–9.

Uses and Administration

Lisinopril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3), prophylactically after myocardial infarction (p. 1257.1), and in diabetic nephropathy (see Kidney Disorders, p. 1284.1).

The haemodynamic effects of lisinopril are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours after once-daily dosing. Lisinopril is given orally as the dihydrate, but doses are expressed in terms of the anhydrous substance. Lisinopril 2.72 mg as the dihydrate is equivalent to about 2.5 mg of anhydrous lisinopril. The dose of lisinopril should be reduced in patients with renal impairment (see below).

In the treatment of **hypertension**, the usual initial dose is 10 mg daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and such patients should be given a lower initial dose of 2.5 to 5 mg once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before lisinopril is started and resumed later if required; if this is not possible, an initial dose of 5 mg once daily should be given. The usual maintenance dose is 20 mg given once daily, though up to 80 mg daily may be given if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should be started with a low dose under close medical supervision. Lisinopril is given in an initial dose of 2.5 mg (or 5 mg in the USA) daily, increased as necessary in steps of no more than 10 mg at intervals of at least 2 weeks, to a maximum maintenance dose of 35 mg (or 40 mg in the USA) daily.

After **myocardial infarction**, lisinopril is licensed for use starting within 24 hours of the onset of symptoms in an initial dose of 5 mg once daily for two days, then increased to 10 mg once daily. An initial dose of 2.5 mg once daily is recommended for patients with a low systolic blood pressure.

In the management of **diabetic nephropathy**, hypertensive type 2 diabetics with microalbuminuria may be given a dose of 10 mg once daily, increased if necessary to 20 mg once daily to achieve a sitting diastolic blood pressure below 90 mmHg.

For doses in children, see below.

Reviews.
1. Lancaster SG, Todd PA. Lisinopril: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 1988; **35:** 646–69.
2. Goa KL, *et al*. Lisinopril: a review of its pharmacology and clinical efficacy in the early management of acute myocardial infarction. *Drugs* 1996; **52:** 564–88.
3. Goa KL, *et al*. Lisinopril: a review of its pharmacology and use in the management of the complications of diabetes mellitus. *Drugs* 1997; **53:** 1081–1105.
4. Simpson K, Jarvis B. Lisinopril: a review of its use in congestive heart failure. *Drugs* 2000; **59:** 1149–67.

Administration in children. Lisinopril has been reported to be an effective and well-tolerated antihypertensive in children 6 years of age and older;[1] it has also been used successfully in younger children.[2] US licensed product information recommends for hypertension an oral starting dose for lisinopril of 70 micrograms/kg (up to 5 mg) once daily for children 6 years of age and older (but see also Administration in Renal Impairment, below). The *BNFC* recommends similar doses for children aged 6 to 12 years with hypertension or proteinuria in nephritis and states that this dose may be increased at intervals of 1 to 2 weeks to a maximum of 600 micrograms/kg or 40 mg once daily. For children between 12 and 18 years of age with hypertension, proteinuria in nephritis, or diabetic nephropathy, the *BNFC* recommends an initial dose of 5 mg once daily increased as necessary; the usual maintenance dose is 10 to 20 mg once daily (maximum 80 mg once daily).

In the treatment of heart failure in children between 12 and 18 years of age the *BNFC* recommends an initial dose of 2.5 mg once daily increased as necessary in steps of no more than 10 mg at intervals of at least 2 weeks to a maximum of 35 mg once daily.

1. Soffer B, *et al*. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens* 2003; **16:** 795–800.
2. Raes A, *et al*. Lisinopril in paediatric medicine: a retrospective chart review of long-term treatment in children. *J Renin Angiotensin Aldosterone Syst* 2007; **8:** 3–12.

Administration in renal impairment. In *adult* patients with renal impairment, the initial dose of lisinopril should be reduced depending on the creatinine clearance (CC) as follows:
- CC 31 to 80 mL/minute: 5 to 10 mg once daily
- CC 10 to 30 mL/minute: 2.5 to 5 mg once daily
- CC less than 10 mL/minute or on dialysis: 2.5 mg once daily

The dose should be adjusted according to response, to a maximum of 40 mg once daily.

US licensed prescribing information states that lisinopril should not be given to *children* with a glomerular filtration rate of less than 30 mL/minute per 1.73 m^2 but gives no guidance on dosage in other children with renal impairment.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lisinopril as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Lisinopril is slowly and incompletely absorbed after oral doses. About 25% of a dose is absorbed on average, but the amount varies considerably between individuals, ranging from about 6 to 60%. It is already an active diacid and does not need to be metabolised *in vivo*. Peak concentrations in plasma are reported to occur after about 7 hours. Lisinopril is reported not to be significantly bound to plasma proteins. It is excreted unchanged in the urine. The effective half-life for accumulation after multiple doses is 12 hours in patients with normal renal function. Lisinopril is removed by haemodialysis.

References.
1. Till AE, *et al*. The pharmacokinetics of lisinopril in hospitalized patients with congestive heart failure. *Br J Clin Pharmacol* 1989; **27:** 199–204.
2. Neubeck M, *et al*. Pharmacokinetics and pharmacodynamics of lisinopril in advanced renal failure: consequence of dose adjustment. *Eur J Clin Pharmacol* 1994; **46:** 537–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Doxapril; Lisinal; Sedotensil; Tensopril; Tersif; Zestril; ***Austral.***: Fibsol; Liprace; Lisinobell†; Lisodur; Prinivil; Zestril; ***Austria***: Acemin; Acetan; Lisihexal; Lisinostad; ***Belg.***: Zestril; ***Braz.***: Lisinovil; Lisopril; Listril; Lonipril; Prilcor; Prinivil; Prinopril; Vasojet; Zestril; Zinopril; ***Canad.***: Prinivil; Zestril; ***Chile***: Acerdil; Lipreren†; Presokin†; Tonotensil; ***China***: Diyiluo (帝益洛); Yi Mai Ou (益迈欧); Yijikang (易集康); Zestril (捷赐瑞); ***Cz.***: Dapril; Diroton; Lipribela†; Lisigamma†; Lisipril; Prinivil†; ***Denm.***: Cardiostad; Lisinomed†; Lisinomer; Lisinotens; ***Fin.***: Cardiostad; Lisipril; ***Fr.***: Prinivil; Zestril; ***Ger.***: Acerbon†; Coric†; Lisi Lich; Lisi-Puren†; Lisi; Lisibeta; Lisidigal; Lisidoc†; Lisigamma; Lisihexal†; ***Gr.***: Adicanil; Axelvin; Gnostoval; Hyperliz; Icoran; Landolaxin; Leruze; Lisinospes; Lisodinol; Mealis; Nafordyl; Perenal; Press-12; Pressamea; Pressuril; Prinivil; Terolinal; Thriusedon; Tivirlon; Vercol; Veroxil; Z-Bec; Zestril; ***Hong Kong***: Cipril; Prinivil; Zestril; ***Hung.***: Conpres†; Linipril; Lisopress; Press-12; ***India***: Acebitor; Biopril; Cipril; Dilace; Dilis; ES; Hipril; L-Pril; Lesopril; Linopril; Linoril; Linvas; Lipril; Liscard; Lisicard; Lisinace; Lisir; Lisiriv; Lisitec; Lislo; Lisnop; Lisoril; Lisotec; Listril; Nivant; Normopril; Odace; ***Indon.***: Inhitril; Interpril; Linoxal; Noperten; Nopril; Odace; Tensinop; Tensiphar; Zestril; ***Irl.***: Bellisin; ByZestra; Caracet†; Lestace; Lisopress; Lispril; Zesger; Zestan; Zestril; ***Israel***: Tensopril; ***Ital.***: Alapril; Prinivil; Zestril; ***Jpn***: Longes; ***Malaysia***: Acepril; Dapril; Lisdene; Ranopril; Zestril; ***Mex.***: Alfaken; Dosteril; Fersivag; Linospril†; Noril†; Priniser; Prinivil; Zestril; ***Neth.***: Zestril; ***Norw.***: Vivatec†; Zestril; ***NZ***: Prinivil; ***Philipp.***: Listril; Sinolip†; Zestril; ***Pol.***: Diroton; Ikapril; Lisdene†; Lisihexal; Lisinoratio; Lisiprol; Prinivil; Ranopril; ***Port.***: Benzin†; Ecapril; Lipril; Lisinol†; Lisopress†; Prinivil; Zestril; ***Rus.***: Dapril (Даприл); Diropress (Диропресс); Diroton (Диротон); Irumed (Ирумед); Lisacard (Лизакард); Lisigamma (Лизигамма); Lisinoton (Лизинотон); Lisoril (Лизорил); Listril (Листрил); Liten (Литэн); Lysonorm (Лизонорм); Rilace (Рилейс); Sinopril (Синоприл); ***S.Afr.***: Adco-Zetomax; Lizro; Lysin; Prinivil†; Sinopren; Zemax; Zeprosil†; Zestril; ***Singapore***: Dapril; Hipril; Lisdene; Lisoril; Noperten; Prinivil; Zestril; ***Spain***: Belprel†; Doneka; Iricil†; Likenil; Prinivil; Tensikey†; Zestril; ***Swed.***: Zestril; ***Switz.***: Lisitril; Lisopril; Prinil; Zestril; ***Thai.***: Lisdene; Lisir; Lispril; Zestril; ***Turk.***: Acerilin; Inhibril; Rilace; Sinopryl; Zestril; ***UAE***: Lisotec; ***UK***: Carace†; Zestril; ***Ukr.***: Diroton (Диротон); Linotor (Линотор); Lipril (Липрил); Lisigamma (Лизигамма)†; Lisihexal (ЛизиГЕКСАЛ)†; Lopril (Лоприл); Vitopril (Витоприл); ***USA***: Prinivil; Zestril; ***Venez.***: Cotensil; Lisilet; Prinivil; Rantex; Tonoten.

Multi-ingredient Preparations. ***Arg.***: Tensopril D; Zestoretic; ***Austria***: Acecomb; Acelisino comp; Co-Acetan; Co-Lisinostad; Lisihexal comb; Lisinocomp; Lisinopril comp; ***Belg.***: Co-Lisinopril; Zestoretic; ***Braz.***: Lisoclor; Lonipril-H; Prinzide; Zestoretic; ***Canad.***: Prinzide; Zestoretic; ***Chile***: Acerdil-D; Tonotensil D; ***Cz.***: Amesos; Lipribela plus H†; Skopryl Plus H; ***Denm.***: Evapril comp†; Krinolis; Lisinoplus; ***Fin.***: Lisipril Comp; ***Fr.***: Prinzide; Zestoretic; ***Ger.***: Acercomp; Coric Plus†; Lisi HCT; Lisi-Puren comp†; Lisibeta comp; Lisidigal HCT; Lisigamma HCT; Lisihexal comp†; LisiLich comp†; Lisinopril comp; Lisinopril HCT†; Lisiplus†; ***Gr.***: Prinzide; Z-Bec Plus; Zestoretic; ***Hong Kong***: Zestoretic; ***Hung.***: Lisonorm; Lisopress HCT; ***India***: Aamin-L; Acedip; Acinopril; Alis-Plus; Alis; Amchek L; Amdepin-L; Amlace; Amlo-L; Amlodac-L; Amlokath-L; Amlopres L; Amlosafe-LS; Amlot-L; Amlovas-L; Amtas-LP; Biopril AM; Calchek L; Carvasc-L; Cipril-H; Dip-A; Hipril-A; Inace; Lipril-AM; Lipril-H; Lismol; Lisoril-5HT; Listril AM; Listril Plus; Listril-SM; Neocard-Lis; Numlo-L; ***Indon.***: Zestoretic; ***Irl.***: Carace Plus†; Lisprilhydrochlorothiazide; Zesger Plus; Zestoretic; ***Ital.***: Nalapres; Prinzide; Zestoretic; ***Mex.***: Prinzide; Zestoretic; ***Neth.***: Lisidigal HCT; Lizam; Zestoretic; ***Norw.***: Vivatec Comp†; Zestoretic; ***Philipp.***: Zestoretic; ***Pol.***: Dironorm; ***Port.***: Ecamais; Lisoplus†; Prinzide; Tiazinol†; Zestoretic; ***Rus.***: Co-Diroton (Ко-Диротон); Ekvator (Экватор); Irudid (Ирудид); Lisinoton H (Лизинотон Н); Lisoretic (Лизоретик); Listril Plus (Листрил Плюс); Liten H (Литэн Н); Rilace Plus (Рилейс Плюс); Sinorezid (Синорезид); ***S. Afr.***: Adco-Zetomax Co†; Diace Co; Hexal-Lisinopril Co; Lisinozide; Lisoretic; Lisozide; Zestoretic; Zestozide; ***Spain***: Doneka Plus; Iricil Plus†; Prinivil Plus; Secubar Diu†; Tensikey Complex; Zestoretic; ***Swed.***: Zestoretic†; ***Switz.***: Co-Lisinopril; Lisitril comp; Lisopril plus; Prinzide; Zestoretic; ***Turk.***: Rilace Plus; Sinoretik; Zestoretic; ***UK***: Carace Plus; Caralpha; Lisicostad; Zestoretic; ***Ukr.***: Co-Diroton (Ко-Диротон); Combipril (Комбиприл); Ekvator (Экватор); Hypril-A (Гиприл-А); Liprazid (Липразид); Lisopres (Лизопрес); Lisoretic (Лизоретик); Lisotiasid (Лизотиазид); Lopril H (Лоприл Н); Neocard-Lis (Неокард-Ліз)†; ***USA***: Prinzide; Zestoretic; ***Venez.***: Lisiletic.

Pharmacopoeial Preparations
BP 2014: Lisinopril Oral Solution; Lisinopril Tablets;
USP 36: Lisinopril and Hydrochlorothiazide Tablets; Lisinopril Oral Suspension; Lisinopril Tablets.

Lomitapide *(USAN, rINN)*

AEGR-733; BMS-201038-01; Lomitapida; Lomitapidum; Ломитапид.

N-(2,2,2-Trifluoroethyl)-9-(4-{4-[4′-(trifluoromethyl)(1,1′-biphenyl)-2-carboxamido]piperidin-1-yl}butyl)-9*H*-fluorene-9-carboxamide.

$C_{39}H_{37}F_6N_3O_2$=693.7

CAS — 182431-12-5.
ATC — C10AX12.
ATC Vet — QC10AX12.
UNII — 82KUB0583F.

Lomitapide Mesilate *(rINNM)*

AEGR-733; BMS-201038-04; BMS-201038; Lomitapide, Mésilate de; Lomitapide Mesylate (USAN); Lomitapidi Mesilas; Mesilato de Lomitapida; Ломитапида Мезилат.

$C_{39}H_{37}F_6N_3O_2.CH_4O_3S$=789.8

CAS — 202914-84-9.
ATC — C10AX12.
ATC Vet — QC10AX12.
UNII — X4S83CP54E.

Uses and Administration

Lomitapide directly binds to and inhibits microsomal triglyceride transfer protein, thereby inhibiting the synthesis of chylomicrons and very-low-density lipoprotein. It is used in the treatment of homozygous familial hypercholesterolaemia as an adjunct to dietary measures and other lipid-lowering treatments to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol.

Lomitapide is given as the mesilate but doses are expressed as the base; lomitapide mesilate 11.4 mg is equivalent to about 10 mg of lomitapide. It is taken orally on an empty stomach once daily; during treatment, patients should take daily vitamin E and fatty acids supplementation to reduce the risk of a fat-soluble nutrient deficiency. An initial dose of 5 mg daily is given for at least 2 weeks and then is increased incrementally according to response and tolerance:

- 10 mg daily for at least 4 weeks
- 20 mg daily for at least 4 weeks
- 40 mg daily for at least 4 weeks
- 60 mg daily (maximum dose)

When lomitapide is given with weak cytochrome P450 isoenzyme CYP3A4 inhibitors, the maximum dose should be 30 mg daily; moderate and strong CYP3A4 inhibitors should not be used with lomitapide, see Interactions, below. Treatment may need to be modified for hepatic or renal impairment, see below.

References.

1. Anonymous. Lomitapide. *Am J Cardiovasc Drugs* 2011; **11:** 347–52.
2. Cuchel M, *et al.* Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet* 201 3; **381:** 40–6.

Administration in hepatic impairment. Patients with active liver disease, including unexplained persistent increases in serum transaminases, and those with pre-existing moderate or severe hepatic impairment (defined as Child-Pugh class B or C) should not be treated with lomitapide. Exposure to lomitapide was increased by about 50% in patients with mild hepatic impairment (Child-Pugh class A) and the oral dose of lomitapide should not exceed 40 mg daily in these patients.

Treatment should also be modified for increases in serum transaminases occurring during lomitapide therapy.

- for increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations between 3 times the upper limit of normal (ULN) and 5 times the ULN: reduce the dose of lomitapide and repeat liver function tests weekly; withhold dosing if there are other associated signs of abnormal hepatic function such as increased bilirubin or INR, or if transaminases do not recover to below 3 times the ULN within about 4 weeks. If resuming lomitapide treatment once transaminases have recovered to below 3 times the ULN, consider reducing the dose and measure liver function tests more frequently
- for ALT or AST concentrations 5 times the ULN or above: withhold lomitapide. If resuming lomitapide treatment once transaminases have recovered to below 3 times the ULN, reduce the dose and measure liver function tests more frequently
- if increased transaminase concentrations are accompanied by signs of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, and flu-like symptoms), active liver disease, or increases in bilirubin 2 or more times the ULN, lomitapide should be stopped

Administration in renal impairment. Exposure to lomitapide was increased by about 50% in patients with end-stage renal disease on dialysis and the oral dose of lomitapide should not exceed 40 mg daily in these patients; licensed product information states that there is no data to guide dosing in other patients with renal impairment.

Adverse Effects and Precautions

Gastrointestinal adverse effects, particularly diarrhoea, and also nausea, vomiting, dyspepsia, constipation, and abdominal pain are commonly reported with lomitapide. There may be reduced absorption of fat-soluble vitamins and serum fatty acids, and supplements are required.

Increases in liver enzyme values have been seen and lomitapide should not be used in patients with moderate or severe hepatic impairment or those with active liver disease. It may also cause hepatic steatosis, which is thought to be reversible upon stopping treatment. Liver function tests should be measured before starting treatment and then for the first year repeated at least every month and before any increase in dose. Thereafter, tests should be repeated at least every 3 months and before any increase in dose. Treatment may need to be modified if hepatotoxicity occurs, see Administration in Hepatic Impairment, above.

Lomitapide is teratogenic in some *animals* and should not be used in pregnant women.

Interactions

Lomitapide is metabolised by the cytochrome P450 isoenzyme CYP3A4. The potent CYP3A4 inhibitor ketoconazole increased exposure to lomitapide 27-fold, and both moderate and potent CYP3A4 inhibitors should not be given with lomitapide; dose modification may be necessary if weak CYP3A4 inhibitors are used, see Uses and Administration, above.

Lomitapide also inhibits CYP3A4 and can increase exposure to CYP3A4 substrates, such as simvastatin; dose adjustments may be required, see Uses and Administration of Simvastatin, p. 1489.3.

Lomitapide is also an inhibitor of P-glycoprotein and may increase the absorption of P-glycoprotein substrates; dose reduction of the P-glycoprotein substrate should be considered.

Lomitapide increases warfarin concentrations and may affect INR.

Pharmacokinetics

Peak plasma concentrations of lomitapide occur about 6 hours after an oral dose. The absolute bioavailability is about 7% and plasma-protein binding is 99.8%. It is extensively metabolised in the liver, with cytochrome P450 isoenzyme CYP3A4 an important pathway; CYP1A2, CYP2B6, CYP2C8, and CYP2C19 may play a minor role. Just over half of a dose is excreted in the urine and about a third in the faeces. The mean terminal half-life is 39.7 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Lojuxta; ***USA***: Juxtapid.

Losartan Potassium *(BANM, USAN, rINNM)*

DuP-753; E-3340; Kalii Losartanum; Losartaanikalium; Losartan-Kalium; Losartán potásico; Losartan Potassique; Losartan Potasyum; Losartankalium; Losartanum Kalicum; MK-0954; Калия Лозартан.

2-Butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol potassium.

$C_{22}H_{22}ClKN_6O$=461.0

CAS — 114798-26-4 (losartan); 124750-99-8 (losartan potassium).

ATC — C09CA01.

ATC Vet — QC09CA01.

UNII — 3ST302B24A.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Losartan Potassium). A white or almost white, hygroscopic crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; slightly soluble in acetonitrile. Store in airtight containers.

USP 36: (Losartan Potassium). A white to off-white powder. Freely soluble in water; slightly soluble in acetonitrile; soluble in isopropyl alcohol.

Uses and Administration

Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II. It is used in the management of hypertension (p. 1251.1) and heart failure (p. 1262.3), particularly in patients who develop cough with ACE inhibitors. It is also used to reduce the risk of stroke in patients with left ventricular hypertrophy, and in the treatment of diabetic nephropathy (see Kidney Disorders, p. 1423.3), and has been tried in myocardial infarction (p. 1257.1).

Losartan is given orally as the potassium salt. The maximum hypotensive effect is achieved in about 3 to 6 weeks after starting treatment.

In **hypertension** the usual dose of losartan potassium is 50 mg once daily. The dose may be increased, if necessary, to 100 mg daily as a single dose or in two divided doses. An initial dose of 25 mg once daily should be given to patients with intravascular fluid depletion, and to those with hepatic impairment.

Losartan potassium is used for **heart failure** in those aged 60 years and over. An initial dose of 12.5 mg is given once daily, and may be doubled at weekly intervals to a usual maintenance dose of 50 mg once daily.

In **diabetic nephropathy** losartan potassium is given in an initial dose of 50 mg once daily, increased to 100 mg once daily depending on the blood pressure.

For the use of losartan in children, see below.

Reviews.

1. Carr AA, Prisant LM. Losartan: first of a new class of angiotensin antagonists for the management of hypertension. *J Clin Pharmacol* 1996; **36:** 3–12.
2. Goa KL, Wagstaff AJ. Losartan potassium: a review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. *Drugs* 1996; **51:** 820–45.
3. Schaefer KL, Porter JA. Angiotensin II receptor antagonists: the prototype losartan. *Ann Pharmacother* 1996; **30:** 625–36.
4. Burrell LM. A risk-benefit assessment of losartan potassium in the treatment of hypertension. *Drug Safety* 1997; **16:** 56–65.
5. McConnaughey MM, *et al.* Practical considerations of the pharmacology of angiotensin receptor blockers. *J Clin Pharmacol* 1999; **39:** 547–59.
6. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; **355:** 637–45.
7. Dina R, Jafari M. Angiotensin II-receptor antagonists: an overview. *Am J Health-Syst Pharm* 2000; **57:** 1231–41.
8. Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. *Am J Health-Syst Pharm* 2001; **58:** 671–81. Correction. *ibid.*; 1658.
9. Moen MD, Wagstaff AJ. Losartan: a review of its use in stroke risk reduction in patients with hypertension and left ventricular hypertrophy. *Drugs* 2005; **65:** 2657–74.

Administration. Although the conventional dose of losartan in adults with heart failure is 50 mg daily (see above) it has been suggested that higher doses might produce greater benefit. A large multicentre study[1] in patients with moderate to severe heart failure who were intolerant of ACE inhibitors compared treatment with losartan 50 mg daily (in 1913 patients) and 150 mg daily (in 1921). Over a median follow-up of 4.7 years, patients in the higher dose group had a reduced rate of death or hospital admission for heart failure. Renal impairment, hypotension, and hyperkalaemia were more common in patients taking the higher dose than in those on the lower, but these adverse events did not result in a significantly increased rate of stopping the drug. Angioedema occurred in 6 patients in the high-dose group, 4 of whom stopped the drug, and in none of those taking the lower dose. It was suggested that increased doses of an angiotensin II receptor antagonist are needed to produce optimum benefit in this population.

1. Konstam MA, *et al.* HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; **374:** 1840–8. Correction. *ibid.*; 1888.

Administration in children. Losartan has been studied in a limited number of children with **hypertension**. A study[1] in children aged 6 to 16 years, about half of whom also had renal disorders, found that losartan effectively lowered blood pressure and was well tolerated. Another study,[2] in which all of the children had hypertension associated with chronic renal disorders, also found that losartan was effective.

Children aged from 6 years and weighing from 20 to 50 kg may be given losartan potassium in a usual initial oral dose of 700 micrograms/kg (maximum 25 mg) daily, adjusted if necessary to a maximum of 50 mg daily. Those weighing over 50 kg may be given an initial oral dose of 1.4 mg/kg (maximum 50 mg) daily, adjusted if necessary to a maximum of 100 mg daily.

There are no data to recommend doses for children with a glomerular filtration rate below 30 mL/min per 1.73 m^2. In the UK, use of losartan in children with hepatic impairment is also not recommended.

Losartan has also been used in children with **proteinuria associated with renal disorders** and appears to have an antiproteinuric and renoprotective effect.[2-4]

A retrospective cohort study[5] in 18 children with **Marfan's syndrome,** suggested that angiotensin II receptor antagonists (losartan in 17; irbesartan in 1) may reduce the progression of aortic root dilatation, but these results require confirmation.

1. Shahinfar S, *et al.* A double-blind, dose-response study of losartan in hypertensive children. *Am J Hypertens* 2005; **18:** 183–90.
2. Ellis D, *et al.* Antihypertensive and renoprotective efficacy and safety of losartan: a long-term study in children with renal disorders. *Am J Hypertens* 2004; **17:** 928–35.
3. Ellis D, *et al.* Long-term antiproteinuric and renoprotective efficacy and safety of losartan in children with proteinuria. *J Pediatr* 2003; **143:** 89–97.
4. Lubrano R, *et al.* Renal and cardiovascular effects of angiotensin-converting enzyme inhibitor plus angiotensin II receptor antagonist therapy in children with proteinuria. Abstract: *Pediatrics* 2006; **118:** e833. Full text: http://pediatrics.aappublications.org/cgi/reprint/118/3/e833 (accessed 13/03/08)
5. Brooke BS, *et al.* Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med* 2008; **358:** 2787–95.

Administration in hepatic impairment. Lower initial doses are recommended in mild or moderate hepatic impairment—see above. Losartan is contra-indicated in severe hepatic impairment.

Cardiac arrhythmias. Long-term studies of angiotensin II receptor antagonists for heart failure or hypertension have suggested that they may reduce the incidence of new-onset atrial fibrillation.[1,2] There is also some evidence[3,4] that they may increase the efficacy of amiodarone for preventing recurrence of atrial fibrillation after cardioversion. However, addition of valsartan to established therapies in

patients with a history of atrial fibrillation had no effect on the risk of the arrhythmia recurring,[5] and the role of angiotensin II receptor blockers in the management of cardiac arrhythmias (p. 1266.1) remains to be established.

1. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45:** 1832–9.
2. Schmieder RE, *et al.* Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens* 2008; **26:** 403–11.
3. Madrid AH, *et al.* Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation* 2002; **106:** 331–6.
4. Fogari R, *et al.* Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. *J Cardiovasc Pharmacol* 2006; **47:** 46–50.
5. Disertori M, *et al.* GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 2009; **360:** 1606–17. Correction. *ibid.*; 2379.

Cardiovascular risk reduction. Antihypertensive drugs have an established role in patients with high cardiovascular risk (see Cardiovascular Risk Reduction, p. 1246.1) and it has been suggested that those targeting the renin-angiotensin system have particular benefits. Angiotensin II receptor antagonists have been shown to reduce the incidence of cardiovascular events, but whether they are superior to other antihypertensives remains unclear. In the LIFE study,[1] losartan reduced cardiovascular events more than a beta blocker (atenolol), despite a similar effect on blood pressure. In VALUE,[2] there was no difference in the incidence of cardiovascular events between valsartan and a calcium-channel blocker (amlodipine), although the calcium-channel blocker reduced blood pressure to a greater extent. However, in hypertensive stroke patients,[3] eprosartan reduced the risk of cardiovascular and cerebrovascular events more than another calcium-channel blocker (nitrendipine); blood pressure reduction was similar with both drugs. A study[4] comparing telmisartan with the ACE inhibitor ramipril, found that both reduced cardiovascular events to a similar extent; there was no additional benefit in patients given both drugs. Use of telmisartan in patients unable to tolerate ACE inhibitors was associated with a modest benefit in terms of cardiovascular death, myocardial infarction, and stroke, but there was no effect on hospitalisations for heart failure.[5]

Some studies have suggested that angiotensin II receptor antagonists may be particularly effective at reducing the incidence of stroke.[3,6] However, use of candesartan to treat hypertension in patients with acute stroke[7] had no effect on cerebrovascular events, although cardiovascular mortality was reduced, while a study[8] in patients with recent ischaemic stroke found that telmisartan had no significant effect on recurrent stroke or major cardiovascular events.

Based on the results of VALUE, there has been concern that angiotensin II receptor antagonists may increase the risk of myocardial infarction, but a systematic review and meta-analysis[9] of 37 randomised controlled studies (including 147 020 patients) found no evidence of excess risk.

1. Dahlöf B, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995–1003.
2. Julius S, *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363:** 2022–31.
3. Schrader J, *et al.* Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; **36:** 1218–24.
4. Yusuf S, *et al.* ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358:** 1547–59.
5. Yusuf S, *et al.* Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; **372:** 1174–83. Correction. *ibid.*; 1384.
6. Moen MD, Wagstaff AJ. Losartan: a review of its use in stroke risk reduction in patients with hypertension and left ventricular hypertrophy. *Drugs* 2005; **65:** 2657–74.
7. Schrader J, *et al.* The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke* 2003; **34:** 1699–1703.
8. Yusuf S, *et al.* PRoFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; **359:** 1225–37.
9. Bangalore S, *et al.* Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. *BMJ* 2011; **342:** d2234.

Diabetic complications. Although angiotensin II receptor antagonists have been associated with a reduced awareness of hypoglycaemia (see Diabetes Mellitus under Precautions, p. 1424.3) they have an established role as an alternative to ACE inhibitors in the management of diabetic nephropathy (see Kidney Disorders, below). ACE inhibitors may also reduce the progression of retinopathy in type 1 diabetics (see Diabetic Complications under Uses of ACE Inhibitors, p. 1282.3) and angiotensin II antagonists have therefore been investigated for similar effects. Studies with candesartan in type 1 and type 2 diabetics have suggested little effect on the progression of retinopathy,[1,2] but the incidence of retinopathy in type 1 diabetics was reduced.[1]

There is also some evidence[3-7] that angiotensin II receptor antagonists may prevent the development of diabetes in non-diabetic patients.

1. Chaturvedi N, *et al.* Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet* 2008; **372:** 1394–1402.
2. Sjølie AK, *et al.* Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. *Lancet* 2008; **372:** 1384–93.
3. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27:** 247–55.
4. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–6.
5. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46:** 821–6.
6. Yusuf S, *et al.* Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112:** 48–53. Correction. *ibid.*; e292.
7. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66:** 1169–77.

Erythrocytosis. For reference to the use of losartan in the management of secondary erythrocytosis, see under ACE inhibitors, p. 1283.1

Heart failure. Angiotensin II receptor antagonists have been studied as an alternative to ACE inhibitors in the management of heart failure (p. 1262.3). In the ELITE study,[1] which compared losartan with captopril, both drugs had similar effects on renal function but other adverse effects were fewer with losartan and there was also a reduction in mortality in patients taking losartan. However, the larger ELITE II study[2] failed to confirm any survival benefit with losartan, and studies with losartan[3] and valsartan[4] in patients with heart failure after myocardial infarction have also failed to show superiority over ACE inhibitors. ACE inhibitors therefore remain first-line therapy, although angiotensin II receptor antagonists may be used as an alternative, particularly in patients unable to tolerate ACE inhibitors.[5,6] The combination of angiotensin II receptor antagonists with ACE inhibitors has also shown some benefit.[6] In the ValHeFT study,[7] valsartan was added to standard therapy (including ACE inhibitors in most patients) and reduced the combined end-point of death or hospitalisation for heart failure, although the effect on mortality alone was not significant. In the CHARM-Added study,[8] addition of candesartan to therapy including an ACE inhibitor also led to a reduction in cardiovascular events. However, in the VALIANT study,[4] no additional benefit was found from using valsartan with captopril. There has been some concern that use of triple therapy with angiotensin II receptor antagonists, ACE inhibitors, and beta blockers might be detrimental, but this has not been confirmed. In ValHeFT,[7] mortality appeared to be increased in patients taking all three drug classes, but in both CHARM-Added[8] and VALIANT[4] use of beta blockers had no effect on the results. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients taking beta blockers.[9,10]

For a study reporting greater benefit in heart failure with increased doses of an angiotensin II receptor antagonist see Administration, p. 1422.3.

1. Pitt B, *et al.* Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; **349:** 747–52.
2. Pitt B, *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355:** 1582–7.
3. Dickstein K, *et al.* Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; **360:** 752–60.
4. Pfeffer MA, *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349:** 1893–1906. Correction. *ibid.* 2004; **350:** 203.
5. Granger CB, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362:** 772–6.
6. Jong P, *et al.* Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002; **39:** 463–70.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.
9. NICE. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf (accessed 13/10/10)
10. Dickstein K, *et al.* Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; **29:** 2388–2442. Correction. *ibid.* 3069. [dose] Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf (accessed 14/10/08)

Kidney disorders. ACE inhibitors have an established role in the management of type 1 and type 2 diabetics with nephropathy, whether or not they are hypertensive, and may also slow the progression of nephropathy in diabetics with microalbuminuria (but see p. 1284.1). A number of studies have investigated the effects of angiotensin II receptor antagonists in type 2 diabetics with varying degrees of nephropathy (see p. 465.1). Irbesartan,[1,2] losartan,[3,4] olmesartan,[5] and valsartan[6] have all been reported to reduce the progression of nephropathy independently of their effect on blood pressure. The magnitude of the benefit in retarding progression of nephropathy seems to be similar with angiotensin II receptor antagonists and ACE inhibitors,[7-9] and the American Diabetes Association considers them equal first choices in the management of the condition.[10] However, the value of these drugs in very early disease has been questioned by a 5-year study of losartan or enalapril in patients with type 1 diabetes who were normotensive and had no albuminuria at the start;[11] this study, which directly measured structural changes in the kidney, found that neither drug slowed the progression of nephropathy.[11]

Angiotensin II receptor antagonists have also reduced urinary albumin excretion in non-diabetic patients, including those with hypertension,[12] and those with IgA nephropathy.[13]

A study[14] in diabetics using a combination of candesartan with lisinopril found that blood pressure and microalbuminuria were reduced more with combination therapy than with either drug alone. However, in another study[15] in patients at high vascular risk but mostly without evidence of advanced renal disease, telmisartan had similar effects on renal outcomes to the ACE inhibitor ramipril, but combination therapy had detrimental effects.

1. Lewis EJ, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345:** 851–60.
2. Parving H-H, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345:** 870–8.
3. Brenner BM, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345:** 861–9.
4. Zandbergen AAM, *et al.* Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus: a randomized clinical trial. *Ann Intern Med* 2003; **139:** 90–6.
5. Haller H, *et al.* Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011; **364:** 907–17.
6. Viberti G, Wheeldon NM. MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 2002; **106:** 672–8.
7. Barnett AH, *et al.* Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; **351:** 1952–61. Correction. *ibid.* 2005; **352:** 1731.
8. Strippoli GFM, *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 15/06/09).
9. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148:** 30–48.
10. American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S79–S83. Also available at: http://care.diabetesjournals.org/content/27/suppl_1/s79.full.pdf (accessed 15/06/09)
11. Mauer M, *et al.* Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; **361:** 40–51.
12. Vogt L, *et al.* Angiotensin II Receptor Antagonist Telmisartan Micardis in Isolated Systolic Hypertension (ARAMIS) Study Group. The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2005; **23:** 2055–61.
13. Li PK-T, *et al.* Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006; **47:** 751–60.
14. Mogensen CE, *et al.* Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; **321:** 1440–4.
15. Mann JFE, *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; **372:** 547–53.

Marfan's syndrome. See Administration in Children, p. 1422.3.

Migraine. Angiotensin II receptor antagonists may reduce the incidence of headache. A randomised study[1] in 60 patients with migraine suggested that candesartan might be effective for prophylaxis, and beneficial results have also been reported[2] with olmesartan. However, there has been a report of migraine caused by losartan (see under Adverse Effects, p. 1424.2).

1. Tronvik E, *et al.* Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003; **289:** 65–9.
2. Charles JA, *et al.* Prevention of migraine with olmesartan in patients with hypertension/prehypertension. *Headache* 2006; **46:** 503–7.

Stroke. See Cardiovascular Risk Reduction, above.

Uricosuric action. Losartan has been found to increase urinary uric acid excretion and reduce serum uric acid concentrations in healthy subjects[1] and in hypertensive

patients.[2,3] However, the effect is generally small and the clinical significance is not clear. Other angiotensin II receptor antagonists do not appear to have such an effect.[2,3]

1. Nakashima M, *et al.* Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol* 1992; **42:** 333–5.
2. Puig JG, *et al.* Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens* 1999; **17:** 1033–9.
3. Würzner G, *et al.* Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens* 2001; **19:** 1855–60.

Adverse Effects

Adverse effects of losartan have been reported to be usually mild and transient, and include dizziness, headache, and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received high-dose diuretics). Impaired renal function and, rarely, rash, urticaria, pruritus, angioedema, and raised liver enzyme values may occur. Hyperkalaemia, myalgia, and arthralgia have been reported. Losartan appears less likely than ACE inhibitors to cause cough. Other adverse effects that have been reported with angiotensin II receptor antagonists include respiratory-tract disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia. Rhabdomyolysis has been reported rarely.

Reviews.

1. Mazzolai L, Burnier M. Comparative safety and tolerability of angiotensin II receptor antagonists. *Drug Safety* 1999; **21:** 23–33.

Angioedema. Angioedema is a recognised adverse effect of ACE inhibitors and is thought to be due to accumulation of bradykinins. Although angiotensin II receptor antagonists were thought to lack effects on bradykinin, several have been associated with reports[1-7] of angioedema, and increased levels of bradykinin have been shown[8] with losartan. In some cases patients had previously experienced angioedema with ACE inhibitors and caution is advised when using angiotensin II receptor antagonists in such patients.[4,9]

1. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan. *N Engl J Med* 1995; **333:** 1572.
2. van Rijnsoever EW, *et al.* Angioneurotic edema attributed to the use of losartan. *Arch Intern Med* 1998; **158:** 2063–5.
3. Adverse Drug Reactions Advisory Committee. Angiotensin II receptor antagonists. *Aust Adverse Drug React Bull* 1999; **18:** 2. Available at: http://www.tga.gov.au/adr/aadrb/aadr9902.pdf (accessed 13/03/08)
4. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? *Drug Safety* 2002; **25:** 73–6.
5. Irons BK, Kumar A. Valsartan-induced angioedema. *Ann Pharmacother* 2003; **37:** 1024–7.
6. Nykamp D, Winter EE. Olmesartan medoxomil-induced angioedema. *Ann Pharmacother* 2007; **41:** 518–20.
7. McCabe J, *et al.* Penile angioedema associated with the use of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers. *Am J Health-Syst Pharm* 2008; **65:** 420–1.
8. Campbell DJ, *et al.* Losartan increases bradykinin levels in hypertensive humans. *Circulation* 2005; **111:** 315–20.
9. Warner KK, *et al.* Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000; **34:** 526–8.

Carcinogenicity. A meta-analysis[1] that combined cancer-related findings from randomised controlled studies of angiotensin receptor blockers (ARBs) found that they were associated with a modest increase in occurrence of new cancers, with an absolute excess risk of cancer over four years of 1.2%. Later meta-analyses[2,3] did not support an association between use of ARBs and increased cancer risk, although an increased risk associated with the combined use of ARBs and ACE inhibitors could not be discounted.[2] In 2011, both the FDA[4] and EMEA[5] completed safety reviews examining the risk of cancer associated with ARB use; both agencies concluded that available evidence did not support a link between ARB use and increased cancer risk.

The possibility of a class variation in the risk of cancer with individual ARBs has also been suggested. A case-control study[6] in diabetic patients found that although ARBs as a class had no effect on cancer risk, an increased risk was noted for candesartan and telmisartan, individually, while losartan had a decreased risk.

1. Sipahi I, *et al.* Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol* 2010; **11:** 627–36.
2. Bangalore S, *et al.* Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324 168 participants from randomised trials. *Lancet Oncol* 2011; **12:** 65–82.
3. Yoon C, *et al.* Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and cancer risk: a meta-analysis of observational studies. *CMAJ* 2011; **183:** E1073–E1084.
4. FDA. Drug Safety Communication: no increase in risk of cancer with certain blood pressure drugs—angiotensin receptor blockers (ARBs) (issued 2nd June, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm (accessed 07/02/12)
5. EMEA. European Medicines Agency concludes that benefit-risk balance of angiotensin II receptor antagonists remains positive (issued 20th October, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/10/WC500116865.pdf (accessed 07/02/11)
6. Chang CH, *et al.* Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. *J Clin Oncol* 2011; **29:** 3001–7.

Effects on the blood. Symptomatic anaemia occurred[1] in a patient with a renal transplant 6 weeks after starting therapy with losartan. Decreased haemoglobin concentrations have also been reported[2] in patients with severe renal impairment undergoing haemodialysis.

Immune thrombocytopenia has been reported[3] in a patient shortly after starting losartan.

1. Horn S, *et al.* Losartan and renal transplantation. *Lancet* 1998; **351:** 111.
2. Schwarzbeck A, *et al.* Anaemia in dialysis patients as a side-effect of sartanes. *Lancet* 1998; **352:** 286.
3. Ada S, *et al.* Immune thrombocytopenia after losartan therapy. *Ann Intern Med* 2002; **137:** 704.

Effects on the liver. Raised liver enzyme values have occurred rarely in patients receiving losartan. Severe, acute hepatotoxicity developed in a patient 1 month after losartan was substituted for enalapril because of ACE inhibitor-induced cough.[1] The patient recovered when losartan was withdrawn but symptoms and raised liver enzyme concentrations recurred following rechallenge. Acute, reversible hepatotoxicity also occurred in a patient who had been taking losartan 150 mg daily for 6 weeks.[2] A case of cholestatic jaundice associated with irbesartan therapy has also been reported;[3] the jaundice resolved slowly once irbesartan was withdrawn.

1. Bosch X. Losartan-induced hepatotoxicity. *JAMA* 1997; **278:** 1572.
2. Andrade RJ, *et al.* Hepatic injury associated with losartan. *Ann Pharmacother* 1998; **32:** 1371.
3. Hariraj R, *et al.* Prolonged cholestasis associated with irbesartan. *BMJ* 2000; **321:** 547.

Effects on the skin. Atypical cutaneous lymphoid infiltrates developed in 2 patients receiving losartan for hypertension.[1] In both cases the lesions disappeared within a few weeks of stopping the drug.

Henoch-Schönlein purpura has been reported[2,3] in patients taking losartan; in 1 case[2] the reaction recurred on rechallenge. A purpuric rash with evidence of vasculitis has been reported with candesartan;[4] the patient also developed acute nephritis.

A polycyclic rash associated with systemic illness developed in a patient who had been taking irbesartan for 2 years;[5] improvement occurred within 2 days of stopping the drug.

Patients have been reported[6] in whom psoriasis either developed or was exacerbated after treatment with an angiotensin II receptor antagonist; the drugs involved included candesartan, irbesartan, losartan, and valsartan. In most cases the lesions regressed after the drug was withdrawn.

1. Viraben R, *et al.* Losartan-associated atypical cutaneous lymphoid hyperplasia. *Lancet* 1997; **350:** 1366.
2. Bosch X. Henoch-Schönlein purpura induced by losartan therapy. *Arch Intern Med* 1998; **158:** 191–2.
3. Brouard M, *et al.* Schönlein-Henoch purpura associated with losartan treatment and presence of antineutrophil cytoplasmic antibodies of x specificity. *Br J Dermatol* 2001; **145:** 362–3.
4. Morton A, *et al.* Rash and acute nephritic syndrome due to candesartan. *BMJ* 2004; **328:** 25.
5. Constable S, *et al.* Systemic illness with skin eruption, fever and positive lymphocyte transformation test in a patient on irbesartan. *Br J Dermatol* 2006; **155:** 491–3.
6. Marquart-Elbaz C, *et al.* Sartans, angiotensin II receptor antagonists, can induce psoriasis. *Br J Dermatol* 2002; **147:** 617–18.

Effects on taste. Taste disturbances, in some cases progressing to complete taste loss, have occurred[1,2] in patients receiving losartan for hypertension. In each case taste returned to normal after stopping losartan therapy. Taste impairment has also been reported with both candesartan[3,4] and valsartan[4] in healthy subjects.

1. Schlienger RG, *et al.* Reversible ageusia associated with losartan. *Lancet* 1996; **347:** 471–2.
2. Heeringa M, van Puijenbroek EP. Reversible dysgeusia attributed to losartan. *Ann Intern Med* 1998; **129:** 72.
3. Tsuruoka S, *et al.* Subclinical alteration of taste sensitivity induced by candesartan in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 807–12.
4. Tsuruoka S, *et al.* Angiotensin II receptor blocker-induces blunted taste sensitivity: comparison of candesartan and valsartan. *Br J Clin Pharmacol* 2005; **60:** 204–7.

Hypersensitivity. See Angioedema and Effects on the Skin, above.

Migraine. Severe migraine has been reported[1] in a patient after use of losartan. The patient had no history of migraine and symptoms recurred on rechallenge. However, angiotensin II receptor antagonists have also been reported to reduce the incidence of migraine (see under Uses and Administration, p. 1423.3).

1. Ahmad S. Losartan and severe migraine. *JAMA* 1995; **274:** 1266–7.

Pancreatitis. Acute pancreatitis has been reported[1,2] in 2 patients receiving losartan. However, 1 of the patients subsequently developed pancreatitis unrelated to losartan.[3] The other patient[2] had also developed acute pancreatitis during enalapril therapy. Acute pancreatitis has also been reported[4] with irbesartan; the patient was also taking hydrochlorothiazide but in a dose lower than that usually associated with thiazide-induced pancreatitis. Biochemical alterations suggestive of acute pancreatitis have been reported after telmisartan overdosage.[5]

1. Bosch X. Losartan-induced acute pancreatitis. *Ann Intern Med* 1997; **127:** 1043–4.
2. Birck R, *et al.* Pancreatitis after losartan. *Lancet* 1998; **351:** 1178.
3. Bosch X. Correction: losartan, pancreatitis, and microlithiasis. *Ann Intern Med* 1998; **129:** 755.
4. Fisher AA, Bassett ML. Acute pancreatitis associated with angiotensin II receptor antagonists. *Ann Pharmacother* 2002; **36:** 1883–6.
5. Baffoni L, *et al.* Acute pancreatitis induced by telmisartan overdose. *Ann Pharmacother* 2004; **38:** 1088.

Vasculitis. For mention of the development of Henoch-Schönlein purpura and other vasculitic disorders in patients receiving angiotensin II receptor antagonists see Effects on the Skin, above.

Precautions

Losartan is contra-indicated in pregnancy (see below) and in severe hepatic impairment. Lower doses should be considered in mild or moderate hepatic impairment (see Uses and Administration, p. 1422.2). Losartan should be used with caution in renal artery stenosis, and in patients with volume depletion (for example those who have received high-dose diuretic therapy), who are at risk of hypotension; volume depletion should be corrected before starting therapy, or a low initial dose should be used. Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium-sparing diuretics should generally be avoided.

Diabetes mellitus. After reports of reduced awareness of hypoglycaemia in type 1 diabetic patients receiving losartan, a study[1] in healthy subjects found that losartan slightly attenuated the symptomatic and hormonal responses to hypoglycaemia. Although the clinical significance was not established, the authors recommended that losartan should be used with caution in diabetics with reduced awareness of hypoglycaemia. However, losartan and other angiotensin II receptor antagonists may have a role in the management of some diabetic complications (see under Uses, p. 1423.1).

1. Deininger E, *et al.* Losartan attenuates symptomatic and hormonal responses to hypoglycemia in humans. *Clin Pharmacol Ther* 2001; **70:** 362–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies losartan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. Losartan and other angiotensin II receptor antagonists are contra-indicated in all trimesters of pregnancy; they have been associated with fetal toxicity in *animal* studies and fetal toxicity has also occurred in humans.[1] The effects appear to be due to blockade of the renin-angiotensin system and are similar to those of ACE inhibitors (see p. 1288.1). Oligohydramnios with subsequent fetal death occurred in a patient given losartan during weeks 20 to 31 of pregnancy;[2] a number of similar cases have subsequently been reported with losartan,[3,4] candesartan,[5] and valsartan.[4,6,7] Angiotensin II receptor antagonists should be avoided in those planning pregnancy, and stopped immediately upon diagnosis of pregnancy. They should only be used in pregnant women where the benefit clearly outweighs the risk.[8]

1. Branch RL, Martin U. Adverse effects of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in pregnancy. *Adverse Drug React Bull* 2007; (Oct): 943–6.
2. Saji H, *et al.* Losartan and fetal toxic effects. *Lancet* 2001; **357:** 363.
3. Lambot M-A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; **357:** 1619–20.
4. Martinovic J, *et al.* Fetal toxic effects and angiotensin-II-receptor antagonists. *Lancet* 2001; **358:** 241–2.
5. Hinsberger A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; **357:** 1620.
6. Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacother* 2001; **35:** 859–61.
7. Bos-Thompson M-A, *et al.* Fetal toxic effects of angiotensin II receptor antagonists: case report and follow-up after birth. *Ann Pharmacother* 2005; **39:** 157–61. Correction. *ibid.*; 389.
8. MHRA/CHM. ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy. *Drug Safety Update* 2007; **1** (5): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033217&RevisionSelectionMethod=LatestReleased (accessed 30/07/09)

Interactions

The antihypertensive effects of losartan may be potentiated by drugs or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalaemia; losartan and potassium-sparing diuretics should not generally be given together. NSAIDs should be used with caution in patients taking

losartan as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of NSAIDs may also attenuate the hypotensive effect of losartan. The use of losartan with an ACE inhibitor may increase the risk of hyperkalaemia, hypotension, and syncope, particularly in patients with atherosclerotic disease or heart failure, or in diabetics who have end-organ damage. Such combinations should be reserved for selected cases with close monitoring of renal function. Additionally, the use of angiotensin II receptor antagonists with the renin inhibitor aliskiren is generally not recommended, and should be avoided in some patients (see p. 1296.2). Losartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

Lithium. For reference to toxicity resulting from a possible interaction between lithium and angiotensin II receptor antagonists, see p. 431.3.

Pharmacokinetics

Losartan is readily absorbed from the gastrointestinal tract after oral doses, but undergoes substantial first-pass metabolism resulting in a systemic bioavailability of about 33%. It is metabolised to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is mainly by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about 1 hour and 3 to 4 hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine and about 6% is excreted in urine as the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

References.
1. Sica DA, *et al.* Clinical pharmacokinetics of losartan. *Clin Pharmacokinet* 2005; **44:** 797–814.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biablan; Cartan; Corticosan; Cozaarex; Enromic; Fabosic; Fensartan; Klosartan; Loctenk; Loplac; Losacor; Losargal; Losarlan†; Niten; Paxon; Presinor; Prisonil; Tacardia; Tacicul; Temisartan; Troezel; Vasexten; ***Austral.***: Cozaar; ***Austria***: Cosaar; ***Belg.***: Cozaar; Loortan; ***Braz.***: Anzacor; Aradois; Corus; Cozaar; Lanzacor; Lorsacor; Losaprin; Losartec; Losartion; Lotanol; Torlos; Valtrian; Zaarpress; ***Canad.***: Cozaar; ***Chile***: Aratan; Corodin; Cozaar; Lopren; Losapres; Losarbon; Sanipresin; Simperten; Valinor; ***China***: Cozaar (科素亚); ***Cz.***: Arionecs; Arionex; Cozaar; Giovax†; Lakea; Lorista; Losacor; Losagen; Losartic†; Losathia†; Lozap; Nopretens; Sangona; Sidok; ***Denm.***: Ancozan; Cozaar; Licolos; Locardin; Losanin; Losarstad; Losatrix; Losindia†; Lostankal; Lotanec; ***Fin.***: Cozaar; Losarstad; Losatrix; ***Fr.***: Cozaar; ***Ger.***: Lorzaar Protect; Lorzaar; Losargamma; ***Gr.***: Cozaar; Cozapert; Golasan; Hypozar; Loben; Locardan; Lorfast; Lorotens; Losadrac; Losalet; Losametan; Losarb; Lozanel; Lozatan; Lyosan; Mozartan; Ozarium; Press-Down; Proelsartan; Rabolan; Rapifast; ***Hong Kong***: Cozaar; Emlosar; Lopress; Zaart; ***Hung.***: Arbartan; Artager†; Cozaar; Lavestra; Lozarep; Portiron; Prelow; Rasoltan; Stadazar; Tervalon; ***India***: Actilop; Alsartan; Angilo; Angilos; Angizaar; Arblos; Asipress; Biozaar; Blosar; Cardikare; Cosart; Covance; Czar; Czartan; Etotan; Giftan; Gosart; Hypart; Lanxes; Lap; Lara; Lartan; Lo; Loril; Lortan; Losacar; Losaday; Losaden; Losagard; Losain; Losakare; Losakind; Losamax; Losan; Losanorm; Losapot; Losar; Losarep; Losariv; Losartas; Losasun; Losatec; Losatrust; Losavas; Losavik; Loscard; Loscom; Losin; Losit; Losium; Lospi; Lospot; Lossar; Lostat; Lot; Lotace; Lotan; Lozitan; LSP; LTP; Miotin; Nusar; Osart; Zaart; ***Indon.***: Acetensa; Angioten; Cozaar; Insaar; Kaftensar; Lifezar; Sartaxal; Tensaar†; ***Irl.***: Cosartal; Cozaar; Cozatan; Lotanos; Lozitar; Myzaar; Solvatan; ***Israel***: Losardex; Losarta; Lotan; Loxar†; Ocsaar; Tiasar; ***Ital.***: Dalosar; Lortaan; Losaprex; Neo-Lotan; Precten; ***Jpn***: Nu-Lotan; ***Malaysia***: Cozaar; ***Mex.***: Bimidal; Conciluk; Cozaar; Lodestar; Lopred; Lospotar; Punab; Saravanta; Takilpam; Tevalos; Viopexa; ***Neth.***: Cozaar; Entrizen; Loridan†; Losafox; Losahelm; Losamater†; Losanox; Lozitan†; ***Norw.***: Cozaar; ***NZ***: Cozaar; ***Philipp.***: Angisartan; Angizaar†; Anzar; ARA; Arbloc; Bepsar; Besartan; Cotenace; Cozaar; Doxar; Ecozar; Eseflah; Getzar; Hartzar; Hextan; Hylos; Hyperthree; Hyzart; Jensar; Kenzar; Lifezar; Lorzan; Losacar; Losargard; Losart; Lostar; Lozaris; Myotan; Myzar; Neosartan; Nipartan; Normoten; Provizar; Qxar; Wilopres; Xartan; Zarnat; Zarten; ***Pol.***: Apo-Lozart; Cozaar; Lakea; Lorista; Losacor; Losagen; Losartic; Lozap; Presartan; Rasoltan; Sarve; Xartan; ***Port.***: Aratis; Cozaar; Decara; Lortaan; Losab; Losarmed; Loteak; Monocer; Rogbaz; Sartal; Satarmed; Tarnasol†; Tiasar; Varsil; ***Rus.***: Bloctran (Блоктран); Cardomin (Кардомин); Cozaar (Козаар); Lorista (Лориста); Losarel (Лозарел); Lozap (Лозап); Presartan (Презартан); Renicard (Реникард); Vasotenz (Вазотенз); Zysacar (Зисакар); ***S.Afr.***: Ciplazar; Cozaar; Hytenza; Lepitrin; Los-Arb; Renicard; Zartan; ***Singapore***: Angizaar; Cozaar; Losartas; ***Spain***: Cozaar; Lavestra; Soluvass; ***Swed.***: Cozaar; Losarstad; Losatrix; Lostankal; ***Switz.***: Cosaar; Losartax; ***Thai.***: Cozaar; Lanzaar; Loranta; Tanzaril; Tosan; ***Turk.***: Aston; Cozaar; Eklips; Felow; Hilos; Losartil; Loxibin; Sarilen; Sarvas; ***UK***: Cozaar; ***Ukr.***: Angizaar (Ангизар); Lorista (Лориста); Lozap (Лозап); Presartan (Пресартан); Sentor (Сентор); ***USA***: Cozaar; ***Venez.***: Biortan; Cormac; Cozaar; Hyzaar; Nefrotal; Presartan; Sortal.

Multi-ingredient Preparations. ***Arg.***: Biablan D; Cartan D; Cozaarex D; Fensartan D; Klosartan-D; Loctenk D; Loplac-D; Losacor D; Niten D; Paxon D; Pelmec Max D; Pelmec Max; Presinor D; Prisonil D; Tacardia D; Temisartan Diur; Terloc Max; Vasexten-D; ***Austria***: Cosaar Plus; Fortzaar; Losarcomp; ***Belg.***: Co-Losartan; Cozaar Plus; Loortan Plus; ***Braz.***: Aradois H; Branta; Corus H; Hyzaar; Lorsar + HCT; Lotar; Neopress; Torlos H; Valtrian HCT; Zaarpress HCT; ***Canad.***: Hyzaar; ***Chile***: Aratan D; Corodin D; Hyzaar; Lopren-D; Losapres-D; Sanipresin-D; Simperten-D; Tensivel-D; ***China***: Hyzaar (海捷亚); ***Cz.***: Apo-Combilos; Arionex Combi; Artager†; Giovax plus H; Hyzaar; Lorista H; Losagen Combi; Losaratio Plus H; Loscomb; Lozap H; Nopretens Plus H; Prelow; Sangona Combi; Zalarlos comp; ***Denm.***: Anartan Comp; Cosaar Plus†; Cozaar Comp; Cozaar Plus; Esparaloz Comp; Fortzaar†; Forzaar†; Hyzaar†; Kemlosar comp†; Losapensa Comp†; Losarstad Comp; Losatrix Comp†; Losazid†; Marozid†; Tanlozid; Zalarlos comp; ***Fin.***: Cozaar Comp; Losamyl Comp†; Losarstad Comp; Losatrix Comp; ***Fr.***: Fortzaar; Hyzaar; ***Ger.***: Fortzaar; Lorzaar plus; Losargamma HCT; Losarplus; Losartan comp; Losartan Plus; ***Gr.***: CardZaar; Co-Rabolan; Faxiven; Hysadrac; Hyzaar; Loben Plus; Logika; Lopernal; Lorotens Plus; Lortazil Plus; Losachlor; Losalet Plus; Losarb Plus; Losazide; Maxartan; Normatens Plus; Press-Down-Plus; Sartafin Plus; Zotefox; ***Hong Kong***: Hyzaar Plus; Hyzaar; ***Hung.***: Co-Arbartan; Hyzaar; Lavestra H; Lost-HCT; Lostanorm Plus; Portiron HCT; Prelow Plus; Stadazar HCT; Tervalon HCT; ***India***: Acord-L; Actilop-H; Adpace; Alsartan-AM; Alsartan-H; Amcard-LP; Amchek-Z; Amlokind-L; Amlokos L; Amlopres Z; Amlotin; Amlozaar; Angicam-LT; Angilo-AM; Angilo-H; Angilos-H; Angizaar-AT; Angizaar-H; Arblos-H; Asipress-H; Asomex-LT; Biozaar-AM; Cardikare-H; Cosart-H; Covamlo; Covance-D; Czar-AM; Czar-H; Envas-RB; Esam LT; Eslo Tan; Espin-LT; Etotan-AT; Etotan-H; Etotan-HR; Etotan-R; Giftan-HC; Hypart-H; Hysartas; Lanxes-A; Lanxes-H; Lap Plus; Lara-H; Lartan-AM; Lartan-H; Lo-E; Lo-H; Loar-H; Locin-H; Lok-H; Loram-H; Loram; Loril-HT; Losacar-A; Losacar-H; Losaday-H; Losaden-AM; Losaden-H; Losagen-H; Losain-H; Losakare-H; Losakind-H; Losamax-H; Losanorm-HR; Losapot-H; Losar-A; Losar-Beta-H; Losar-Beta; Losar-H; Losarep-H; Losartar H; Losartas-HT; Losasun-HT; Losatec-H; Losatrust-H; Losavas-H; Losavik-H; Loscard-H; Loscom-H; Loscom-R; Losium-H; Lospot-AM; Lospot-H; Lostat H; Lot-H; Lotace-H; Lotan-A; Lotemos-HT; Lozadip; LR; LSP Plus; LSR-H; LTP-H; Nicol-LS; Nusar-AM Low; Nusar-ATN; Nusar-H; Omnitan H; Osart-H; Zaart-H; ***Indon.***: Hyzaar; ***Irl.***: Cozaar Comp; Cozatan Comp; Lotanos Comp; Lozitar Comp; Myzaar Comp; ***Israel***: Cotiasar; Losartan Plus; Lotan Plus†; Ocsaar Plus; ***Ital.***: Forzaar; Hizaar; Kemlosar; Losazid; lozid; Neo-Lotan Plus; ***Malaysia***: Fortzaar; Hyzaar; ***Mex.***: Co-Tarsan; Hyzaar; Lodestar Zid; Proloscan; Saravanta D; ***Neth.***: Cozaar Comp†; Cozaar Plus; Entrizen/HCT; Fortzaar; Hyzaar; Lavesta†; Lodarin†; Lonita†; Losahelm/HCTZ; Losathia†; Losazid†; Lotazin†; Lozatin†; ***Norw.***: Cozaar Comp; ***NZ***: Hyzaar; ***Philipp.***: 2Zaris; Angizaar-H†; AnzaPlus; Co-Normoten; Combizar; Duosar; Ecozar Plus; Hyzaar; Kenzar Plus; Losacar-H; Losargard Plus; Neosartan Plus; Nipartan-H; Tozam; Vazortan-H; Wilopres Plus; ***Pol.***: Hyzaar; Lakea HCT; Lorista H; Lozap HCT; Presartan H; ***Port.***: Arazid; Cotiasar; Cozaar Plus; Fortzaar; Hicloran; Hicortal; Hipara; Hiperozida†; Hizialos†; Hyzaar; Lociaze†; Lorista; Lortaan Plus; Losarbio; Losarerin; Odix; Rominguer; Siaara†; Tecnilor†; Vilbitan†; ***Rus.***: Cardomin Plus (Кардомин Плюс); Hyzaar (Гизаар); Lorista H (Лориста H); Lorista HD (Лориста НД); Lozap Plus (Лозап Плюс); Vasotenz H (Вазотенз H); ***S.Afr.***: Cozaar Comp; Fortzaar; Lohype Plus; Lohype Plus; Losaar Plus; Losaar Plus; Lozaan Co; Netrasol Co; Sartoc; Zartan Co; ***Singapore***: Hyzaar; ***Spain***: Cozaar Plus; Fortzaar; ***Swed.***: Cozaar Comp; Losamyl Comp†; Losarstad Comp; Losatrix Comp; Marozid; Tanlozid; ***Switz.***: Co-Losartan; Cosaar Plus; ***Thai.***: Fortzaar; Hyzaar; ***Turk.***: Aston Plus; Co-Hilos; Eklips Fort; Eklips Plus; Hyzaar; Losapres Plus; Losartil Plus; Loxibin Plus; Sarilen Plus; Sarvastan; ***UK***: Cozaar Comp; ***Ukr.***: Angizaar Plus (Ангизар Плюс); Co-Sentor (Ко-Сентор); Lo-Asomex (Ло-Азомекс); Lorista H (Лориста H); Lorista HD (Лориста HD); Lozap Plus (Лозап Плюс); Sardip (Сардип); ***USA***: Hyzaar; ***Venez.***: Cormatic; Hyzaar Plus; Nefrotal H.

Pharmacopoeial Preparations
BP 2014: Losartan Potassium Tablets;
USP 36: Losartan Potassium and Hydrochlorothiazide Tablets; Losartan Potassium Tablets.

Lovastatin *(BAN, USAN, rINN)*

L-154803; Lovastatilni; Lovastatina; Lovastatinas; Lovastatine; Lovastatinum; Lovasztatin; MB-530B; 6α-Methylcompactin; Mevinolin; MK-803; Monacolin K; MSD-803; Ловастатин.

(3*R*,5*R*)-7-{(1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl}-3-hydroxyheptan-5-olide.

$C_{24}H_{36}O_5$=404.5

CAS — 75330-75-5.

ATC — C10AA02.

ATC Vet — QC10AA02.

UNII — 9LHU78OQFD.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lovastatin). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone. Store under nitrogen at a temperature of 2 degrees to 8 degrees.

USP 36: (Lovastatin). A white to off-white crystalline powder. Insoluble in water; sparingly soluble in alcohol; practically insoluble in petroleum spirit; freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methyl alcohol. Store under nitrogen in airtight containers at a temperature not exceeding 8 degrees.

Uses and Administration

Lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3).

Lovastatin is used to reduce cholesterol in the treatment of hyperlipidaemias (p. 1248.1), particularly in type IIa and IIb hyperlipoproteinaemias. It is also given for cardiovascular risk reduction (p. 1246.1) in both primary and secondary prevention of ischaemic heart disease.

Lovastatin is given in an initial oral dose of 10 to 20 mg daily in the evening with food, increased, if necessary, at intervals of 4 weeks or more to 80 mg daily as a single dose or in 2 divided doses. Lower doses of lovastatin should be used in patients at risk of myopathy, including patients with severe renal impairment (see below) and those taking drugs that interact with lovastatin; an initial dose of 10 mg daily is recommended in patients taking *ciclosporin* or *danazol*, and the daily dose should not exceed 20 mg in patients taking *ciclosporin*, *danazol*, *fibric acid derivatives*, or *nicotinic acid*, or 40 mg in those taking *amiodarone* or *verapamil*.

For the use of lovastatin in children, see below.

General reviews.
1. Curran MP, Goa KL. Lovastatin extended release: a review of its use in the management of hypercholesterolaemia. *Drugs* 2003; **63:** 685–99.

Administration in children. Lovastatin reduces plasma-cholesterol concentrations in children and adolescents with heterozygous familial hypercholesterolaemia[1-3] and has been given safely for up to 48 weeks in boys,[2] and up to 24 weeks in girls.[3] In the USA it is licensed in children aged 10 to 17 years and is given orally in an initial dose of 10 to 20 mg once daily, increased at intervals of 4 weeks or more, if necessary, to a maximum dose of 40 mg once daily.

1. Lambert M, *et al.* Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics* 1996; **97:** 619–28.
2. Stein EA, *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; **281:** 137–44.
3. Clauss SB, *et al.* Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics* 2005; **116:** 682–8.

Administration in renal impairment. Patients with renal impairment may be at increased risk of myopathy and US licensed product information states that doses of lovastatin above 20 mg daily should be used cautiously in patients with a creatinine clearance below 30 mL/minute.

Adrenoleucodystrophy. A preliminary study[1] has shown that lovastatin may be useful in the treatment of adrenoleucodystrophy (see under Lorenzo's Oil, p. 2545.2). Lovastatin reduced the plasma levels of very-long-chain fatty acids which are known to be elevated in patients with this rare metabolic disorder.

1. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; **69:** 312–22.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Incidence of adverse effects. Adverse effects led to withdrawal of lovastatin in 21 of 745 patients receiving the drug for about 5 years.[1] They included asymptomatic elevation of hepatic aminotransferases in 10 patients, gastrointestinal symptoms in 3, rash in 2, myopathy in 2, myalgia in 1, arthralgia in 1, insomnia in 1, and weight gain in 1.

1. Lovastatin Study Groups. Lovastatin 5-year safety and efficacy study: Lovastatin Study Groups I through IV. *Arch Intern Med* 1993; **153:** 1079–87.

Interactions

As for Simvastatin, p. 1494.2.

For specific dosage reductions in patients taking lovastatin with interacting drugs, see Uses and Administration, above.

Pharmacokinetics

Lovastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Three other metabolites have also been isolated. Lovastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action; less than 5% of an oral dose has been reported to reach the circulation. Peak plasma concentrations occur within 2 to 4 hours, and steady-state concentrations are achieved after 2 to 3 days with daily dosage. Both lovastatin and its β-hydroxyacid metabolite are more than 95% bound to plasma proteins. Lovastatin is mainly excreted in the bile as metabolites; about 85% of a dose has been recovered from the faeces and about 10% from the urine. The half-life of the active metabolite is 1 to 2 hours.

General reviews.

1. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; **31:** 348–71.
2. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; **32:** 403–25.
3. Neuvonen PJ, *et al.* Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; **47:** 463–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hipovastin; Mevlor; ***Austria***: Mevacor; ***Braz.***: Lipoclin; Lovaton; Mevacor; Mevalip; Reducol; Redustatin; ***Canad.***: Mevacor; ***Chile***: Hiposterol; Lispor; Lovacol; Sanelor; ***China***: Ai Le Ting (艾乐汀); Deolip (海立); Du Le (都乐); Gengxian (更先); Jun Ning (俊宁); Le Huo (乐活); Lefuxin (乐福欣); Luo Zhi Da (洛之达); Luohuaning (罗华宁); Meixinjie (美辛杰); Ming Wei Xin (明维欣); Su Er Qing (苏尔清); Su Xin (苏欣); Xin Lu (欣露); Xue Qing (雪庆); ***Cz.***: Holetar†; Medostatin; Mevacor†; Rancor†; ***Denm.***: Lovacodan; Lovastad; ***Fin.***: Lovacol†; ***Ger.***: Lovabeta; Lovagamma; Lovahexal†; Mevinacor†; ***Gr.***: Aurostatin; Cecural; Ilopar; Liferzit; Lipidless; Lostin; Lovadrug; Lovapen; Lovasten; Lovatex; Lovatop; Lowlipid; Medovascin; Mevacor; Mevastin; Mevinol; Misodomin; Nabicortin; Terveson; Velkalov; Viking; ***Hong Kong***: Ellanco†; Lomar†; Medostatin; Mevacor†; ***Hung.***: Stoplip†; ***India***: Aztatin; Elstatin; Favolip; Lestric; Lipistat; Lochol; Lostatin; Lotin; Lova; Lovacard; Lovadac; Lovalip; Lovameg; Lovastat; Lovastrol; Lovatin; Lovex; Pro HDL; Rovacor; ***Indon.***: Cholvastin; Justin; Lipovas; Lofacol; Lotivas; Lotyn; Lovatrol; ***Ital.***: Lovinacor; Rextat; Tavacor; ***Malaysia***: Ellanco; Lestric; Lostatin†; Lovarem; Lovastin; Medostatin; ***Mex.***: Casbame; Dilucid†; Liperol†; Mevacor; ***Norw.***: Mevacor†; ***Pol.***: Anlostin†; Apo-Lova†; Liprox; Lovasterol; Lovastin; ***Port.***: Flozul†; Lipdaune; Lipus; Mevinacor; Mevlor; Tecnolip; ***Rus.***: Apextatin (Апекстатин); Cardiostatin (Кардиостатин); Holetar (Холетар); Lovasterol (Ловастерол); Medostatin (Медостатин); Mevacor (Мевакор); Rovacor (Ровакор); ***S.Afr.***: Lovachol; ***Singapore***: Ellanco; Elstatin; Lochol; Lofacol; Lostatin; Lovastin; Medostatin; Mevacor; Rovacor; ***Spain***: Aterkey†; Colesvir; Liposcler; Mevacor; Mevasterol†; Nergadan; Taucor; ***USA***: Altoprev; Mevacor; ***Venez.***: Levistan; Lovanil; Mevacor.

Multi-ingredient Preparations. ***Canad.***: Advicor†; ***USA***: Advicor.

Pharmacopoeial Preparations
USP 36: Lovastatin Tablets.

Low-molecular-weight Heparins

Depolymerised Heparins; Heparina Massae Molecularis Minoris; Heparinas de baja masa molecular; Heparinas de bajo peso molecular; Heparinas fraccionadas; Hepariner, lågmolekylära; Héparines de basse masse moléculaire; Hepariny nízkomolekulární; LMW Heparins; Low-molecular-mass Heparins; Mažos molekulinės masės heparinai; Pienimolekyyliset hepariinit; Низкомолекулярные Гепарины.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Heparins, Low-molecular Mass; Low-molecular-weight Heparins BP 2014). Salts of sulfated glucosaminoglycans having a mass-average molecular mass less than 8000. They are obtained by fractionation or depolymerisation of heparin of natural origin and display different chemical structures at the reducing or the non-reducing end of the polysaccharide chains.

The potency is not less than 70 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is not less than 1.5.

A white or almost white hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Units

The second International Standard for low-molecular-weight heparin was agreed in 2003 and is used to calibrate products for both anti-factor Xa and anti-factor IIa activities. Potency is expressed in terms of units of anti-factor Xa activity per mg and the ratio of anti-factor Xa to anti-factor IIa activity. This ratio differs for individual low-molecular-weight heparins and neither they nor unfractionated heparin can be used interchangeably unit for unit.

Uses and Administration

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Those included in *Martindale* are:

- Ardeparin, p. 1307.1
- Bemiparin, p. 1314.2
- Certoparin, p. 1334.2
- Dalteparin, p. 1348.3
- Enoxaparin, p. 1372.3
- Nadroparin, p. 1443.2
- Parnaparin, p. 1464.2
- Reviparin, p. 1486.3
- Tinzaparin, p. 1514.2

Like heparin (p. 1397.1), these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin. Low-molecular-weight heparins have less effect on platelet aggregation than heparin. They have no significant effect on blood coagulation tests such as activated partial thromboplastin time (APTT). Therapy may be monitored by measurement of plasma-anti-factor-Xa activity but monitoring is less frequently required than with heparin since low-molecular-weight heparins have a more predictable effect.

Low-molecular-weight heparins are used for the prophylaxis and treatment of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p. 1274.1). They are given by subcutaneous injection once or twice daily. They are also used intravenously to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures. They may be given subcutaneously in the management of unstable angina (p. 1254.3) and both intravenously and subcutaneously in acute myocardial infarction (p. 1257.1).

Doses are expressed either in terms of the weight of low-molecular-weight heparin or in terms of units of anti-factor Xa activity. Since low-molecular-weight heparins differ in their relative inhibition of factor Xa and thrombin, doses, even when expressed in terms of anti-factor-Xa activity, cannot be equated. Different preparations of the same low-molecular-weight heparin may appear to have different doses depending on the reference preparation used.

References.

1. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S.
2. Canales JF, Ferguson JJ. Low-molecular-weight heparins: mechanisms, trials, and role in contemporary interventional medicine. *Am J Cardiovasc Drugs* 2008; **8:** 15–25.
3. Jeske WP, *et al.* Differentiating low-molecular-weight heparins based on chemical, biological, and pharmacologic properties: implications for the development of generic versions of low-molecular-weight heparins. *Semin Thromb Hemost* 2008; **34:** 74–85.
4. Gray E, *et al.* Heparin and low-molecular-weight heparin. *Thromb Haemost* 2008; **99:** 807–18.
5. Nowak-Göttl U, *et al.* Pharmacokinetics, efficacy, and safety of LMWHs in venous thrombosis and stroke in neonates, infants and children. *Br J Pharmacol* 2008; **153:** 1120–7.
6. Camporese G, Bernardi E. Low-molecular-weight heparin for thromboprophylaxis. *Curr Opin Pulm Med* 2009; **15:** 443–54.
7. Lim W. Using low molecular weight heparin in special patient populations. *J Thromb Thrombolysis* 2010; **29:** 233–40.
8. Kalyani BS, Roberts CS. Low molecular weight heparin: current evidence for its application in orthopaedic surgery. *Curr Vasc Pharmacol* 2011; **9:** 19–23.

Diabetic foot ulcers. Subcutaneous injection of some low-molecular-weight heparins has been investigated, with some apparent benefit, in the management of diabetic foot ulceration (p. 464.2) in patients with diabetes mellitus.

References.

1. Kalani M, *et al.* Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2003; **26:** 2575–80.
2. Kalani M, *et al.* Beneficial effects of dalteparin on haemostatic function and local tissue oxygenation in patients with diabetes, severe vascular disease and foot ulcers. *Thromb Res* 2007; **120:** 653–61.
3. Rullan M, *et al.* Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial. *Diabet Med* 2008; **25:** 1090–5.

Inflammatory bowel disease. Modified-release oral preparations of low-molecular-weight heparin have been investigated in the treatment of ulcerative colitis, and may be of benefit in mild to moderate disease.[1] Subcutaneous low-molecular-weight heparin did not appear to be of value. The overall management of inflammatory bowel disease is discussed on p. 1811.3.

1. Chande N, *et al.* Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 06/04/11).

Sickle-cell disease. Thrombosis may be a frequent complication of sickle-cell disease. A placebo-controlled study[1] in 253 patients with sickle-cell crisis found that the severity and duration of acute crises were reduced by tinzaparin given in a subcutaneous dose of 175 units/kg once daily for 7 days. However, a review[2] concluded that the evidence of benefit with anticoagulants in such patients was insufficient to recommend their use.

The overall management of sickle-cell disease is described on p. 1123.2.

1. Qari MH, *et al.* Reduction of painful vaso-occlusive crisis of sickle cell anaemia by tinzaparin in a double-blind randomized trial. *Thromb Haemost* 2007; **98:** 392–6.
2. Charneski L, Congdon HB. Effects of antiplatelet and anticoagulant medications on the vasoocclusive and thrombotic complications of sickle cell disease: A review of the literature. *Am J Health-Syst Pharm* 2010; **67:** 895–900.

Adverse Effects

As for Heparin, p. 1398.3, although incidence of some adverse effects may be lower with the low-molecular-weight heparins.

Reviews.

1. Gouin-Thibault I, *et al.* Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Safety* 2005; **28:** 333–49.

Effects on the adrenal glands. Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins.[1-4] The UK CSM suggests[5] that plasma-potassium concentrations should be monitored in all patients with risk factors for hyperkalaemia, particularly those receiving low-molecular-weight heparins for more than 7 days (see Heparin, p. 1398.3).

1. Levesque H, *et al.* Low molecular weight heparins and hypoaldosteronism. *BMJ* 1990; **300:** 1437–8.
2. Canova CR, *et al.* Effect of low-molecular-weight heparin on serum potassium. *Lancet* 1997; **349:** 1447–8.
3. Wiggam MI, Beringer TRO. Effect of low-molecular-weight heparin on serum concentrations of potassium. *Lancet* 1997; **350:** 292–3.
4. Gheno G, *et al.* Variations of serum potassium level and risk of hyperkalemia in inpatients receiving low-molecular-weight heparin. *Eur J Clin Pharmacol* 2003; **59:** 373–7.
5. CSM/MCA. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)

Effects on the blood. It was hoped that, because of their higher ratio of anti-factor Xa to anti-thrombin activity compared with heparin, low-molecular-weight heparins might cause less *bleeding* while maintaining their antithrombotic activity. Some large studies[1,2] have suggested less bleeding with low-molecular-weight heparins than with unfractionated heparin. However, meta-analyses and reviews[3,4] have been unable to confirm a significant reduction in major haemorrhage in patients treated with low-molecular-weight heparins, compared with heparin, for venous thromboembolism, although they confirmed that low-molecular-weight heparins are not associated with an increase in risk. There may be an increased risk of bleeding in patients with renal impairment,[5-7] (see Precautions, p. 1427.1) although the criterion of creatinine clearance 30 mL/minute or less as a guide to selecting patients at increased risk has been questioned;[8] pharmacokinetic response may vary according to the low-molecular-weight heparin used.

Like unfractionated heparin, low-molecular-weight heparins may cause *thrombocytopenia*, including the more severe, immune-mediated form known as heparin-induced thrombocytopenia (HIT). Incidence is much lower with the low-molecular-weight heparins, but platelet-count monitoring is recommended in certain patients depending on other risk factors.[9] The principles of management are the same as for unfractionated heparin, and are described under Heparin, p. 1399.1.

There have been reports[10] of the spontaneous development of spinal haematomas after the use of low-molecular-weight heparins.

1. Levine MN, *et al.* Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; **114:** 545–51.
2. Hull RD, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; **326:** 975–82. Correction. *ibid.* **327:** 140.
3. Gould MK, *et al.* Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; **130:** 800–809.
4. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.

5. Cestac P, *et al.* Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Safety* 2003; **26:** 197–207.
6. Lim W, *et al.* Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006; **144:** 673–84.
7. Crowther M, Lim W. Low molecular weight heparin and bleeding in patients with chronic renal failure. *Curr Opin Pulm Med* 2007; **13:** 409–13.
8. Nagge J, *et al.* Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002; **162:** 2605–9.
9. Warkentin TE, *et al.* American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133** (suppl): 340S–380S. Also available at: http://chestjournal.chestpubs.org/content/139/5/1261.full.pdf (accessed 25/10/11) Correction. *ibid.* 2011; **139:** 1261. [dose]
10. Heppner PA, *et al.* Spontaneous spinal hematomas and low-molecular-weight heparin. Report of four cases and review of the literature. *J Neurosurg Spine* 2004; **1:** 232–6.

Effects on the skin. Adverse effects of low-molecular-weight heparins on the skin have been reviewed.[1] Most low-molecular-weight heparins have been implicated. Urticarial rash or immediate hypersensitivity has been reported (see below). Delayed hypersensitivity skin reactions have occurred mainly in women. These women were generally postmenopausal, pregnant, or in the postpartum period, suggesting a hormonal influence on pathogenesis. About half of these patients also had a history of allergy to unfractionated heparin.[1] Cross-reactivity between heparins appears to be common.[2] Whether molecular weight influences cross-reactivity between the heparins and heparinoids has been a matter of debate.[3-6]

Skin necrosis reactions are usually localised to the subcutaneous injection site, although distant lesions have also been reported. There has been a report[7] of diffuse skin necrosis leading to fatality in a patient given enoxaparin.

1. Wütschert R, *et al.* Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Safety* 1999; **20:** 515–25.
2. Palacios Colom L, *et al.* Delayed-type hypersensitivity to heparins: different patterns of cross-reactivity. *Contact Dermatitis* 2008; **59:** 375–7.
3. Grims RH, *et al.* Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. *Br J Dermatol* 2007; **157:** 514–17.
4. Ludwig RJ, *et al.* Molecular weight determines the frequency of delayed type hypersensitivity reactions to heparin and synthetic oligosaccharides. *Thromb Haemost* 2005; **94:** 1265–9.
5. Gómez-Outes A, *et al.* Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. Commentary. *Br J Dermatol* 2008; **158:** 869–70.
6. Ludwig RJ, *et al.* The influence of heparin's molecular weight and the incidence of delayed type hypersensitivity reactions revisited; in response to Grims et al., *Br J Dermatol* 2008; **158:** 849–51.
7. Nadir Y, *et al.* A fatal case of enoxaparin induced skin necrosis and thrombophilia. *Eur J Haematol* 2006; **77:** 166–8.

Hypersensitivity. Hypersensitivity reactions to heparin and low-molecular-weight heparins are not uncommon,[1] and include urticaria,[2,3] angioedema,[2] and delayed hypersensitivity skin reactions (see above).

1. Jappe U. Allergy to heparins and anticoagulants with a similar pharmacological profile: an update. *Blood Coag Fibrinol* 2006; **17:** 605–13.
2. Odeh M, Oliven A. Urticaria and angioedema induced by low-molecular-weight heparin. *Lancet* 1992; **340:** 972–3.
3. Weber HO, *et al.* Recall urticaria induced by skin tests with heparin. *Br J Dermatol* 2009; **161:** 187–9.

Treatment of Adverse Effects

Severe bleeding with low-molecular-weight heparins, usually caused by accidental overdosage, may be reduced by the slow intravenous injection of protamine sulfate (p. 1572.1). The recommended doses of protamine sulfate are given in the individual monographs and should completely neutralise the anti-thrombin effect of the low-molecular-weight heparin but will only partially neutralise the anti-factor-Xa effect.

Overdosage. A review[1] concluded that the use of eptacog alfa (recombinant factor VIIa) was of benefit in the management of refractory bleeding associated with certain anticoagulants, including low-molecular-weight heparins. Although the lowest effective dose was uncertain, 20 to 120 micrograms/kg had been reported to be effective for low-molecular-weight heparin reversal. Repeat doses of eptacog alfa were not recommended.

1. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; **44:** 718–26.

Precautions

As for Heparin, p. 1399.3.

Low-molecular-weight heparins should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) with the particular low-molecular-weight heparin to be used.

Monitoring of plasma-anti-factor-Xa activity may be considered in patients with an increased risk of bleeding, for example the elderly or those with renal impairment or extremes of body-weight, and in patients with active bleeding.

Licensed product information for some low-molecular-weight heparins contra-indicates their use in patients with prosthetic heart valves as they may not provide adequate prophylaxis against thromboembolism even at high doses (but see under Valvular Heart Disease, p. 1264.3, for references to their use).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred in patients receiving low-molecular-weight heparins with spinal or epidural anaesthesia or analgesia (see p. 1400.1).

Interactions

As for Heparin, p. 1400.2.

Pharmacokinetics

Although the precise pharmacokinetic parameters of different low-molecular-weight heparins vary (see individual monographs), they generally have a greater bioavailability after subcutaneous injection and a longer half-life than heparin.

References.
1. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.
2. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost* 2000; **26** (suppl 1): 31–8.

Lubeluzole *(BAN, USAN, rINN)*

Lubeluzol; Lubéluzole; Lubeluzolum; R-87926; Лубелузол.

(*S*)-1-{4-[1,3-Benzothiazol-2-yl(methyl)amino]piperidino}-3-(3,4-difluorophenoxy)propan-2-ol.

$C_{22}H_{25}F_2N_3O_2S$=433.5

CAS — 144665-07-6.

UNII — V2SIB71583.

Profile

Lubeluzole is a neuroprotectant that has been investigated for ischaemic stroke, but results have been disappointing.

References.
1. Gandolfo C, *et al.* Lubeluzole for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/06/05).

Macitentan *(USAN, rINN)*

ACT-064992; Macitentán; Macitentanum; Мацитентан.

N-[5-(4-Bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]ethoxy}pyrimidin-4-yl]-*N'*-propylsulfuric diamide.

$C_{19}H_{20}Br_2N_6O_4S$=588.3

CAS — 441798-33-0.

UNII — Z9K9Y9WMVL.

Profile

Macitentan is an endothelin receptor antagonist used in the management of pulmonary hypertension (p. 1278.2). It is given orally in a usual dose of 10 mg once daily.

Macitentan may cause fetal harm and should not be taken by pregnant women. Effective contraception should be used by women who could become pregnant, and pregnancy should be excluded before, and monthly during, treatment. Other adverse effects include anaemia and hepatotoxicity.

The metabolism of macitentan is dependent on the cytochrome P450 isoenzyme system, mainly CYP3A4, and strong CYP3A4 inhibitors or inducers can affect exposure to macitentan.

References.
1. Patel T, McKeage K. Macitentan: first global approval. *Drugs* 2013. Available at: doi:10.1007/s40265-013-0156-6
2. Dingemanse J, *et al.* Efficacy, safety and clinical pharmacology of macitentan in comparison to other endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. *Expert Opin Drug Safety* 2013. Available at: 10.1517/14740338.2014.859674

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Opsumit; ***USA***: Opsumit.

Manidipine Hydrochloride *(rINNM)*

CV-4093; Franidipine Hydrochloride; Hidrocloruro de manidipino; Manidipina Cloridrato; Manidipine, Chlorhydrate de; Manidipinhydrochlorid; Manidipini Hydrochloridum; Manidipino, hidrocloruro de; Манидипина Гидрохлорид.

2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride.

$C_{35}H_{38}N_4O_6$,2HCl=683.6

CAS — 120092-68-4 (manidipine); 89226-75-5 (manidipine hydrochloride); 126229-12-7 (manidipine hydrochloride).

ATC — C08CA11.

ATC Vet — QC08CA11.

UNII — ZL507UZ6QL.

Pharmacopoeias. In *Jpn.*

Profile

Manidipine is a dihydropyridine calcium-channel blocker (see Nifedipine, p. 1447.2). It is given orally as the hydrochloride in the management of hypertension (p. 1251.1) in a usual dose of 10 to 20 mg once daily.

Reviews.
1. McKeage K, ScottLJ. Manidipine: a review of its use in the management of hypertension. *Drugs* 2004; **64:** 1923–40.
2. Roca-Cusachs A, Triposkiadis F. Antihypertensive effect of manidipine. *Drugs* 2005; **65** (suppl 2): 11–19.
3. Richy FF, Laurent S. Efficacy and safety profiles of manidipine compared with amlodipine: a meta-analysis of head-to-head trials. *Blood Pressure* 2010; **20:** 54–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Manivasc; ***Fr.***: Iperten; ***Ger.***: Manyper; ***Gr.***: Manyper; ***Hung.***: Iperten; ***Ital.***: Iperten; Vascoman; ***Jpn***: Calslot; ***Philipp.***: Caldine; ***Spain***: Artedil; ***Thai.***: Madiplot.

Multi-ingredient Preparations. ***Austria***: Vivace†; ***Braz.***: Hipertil; ***Ger.***: Vivace; ***Gr.***: Vivace; ***Spain***: Bimade; Vivace.

Mannitol ⊗

Cordycepic Acid; E421; Fraxinina; Manita; Manitol; Manitolis; Manna Sugar; Mannit; Mannite; Mannitoli; Mannitolum; Маннит; Маннитол.

D-Mannitol.

$C_6H_{14}O_6$=182.2

CAS — 69-65-8.

ATC — A06AD16; B05BC01; B05CX04; R05CB16.

ATC Vet — QA06AD16; QB05BC01; QB05CX04; QR05CB16.

UNII — 3OWL53L36A.

Description. Mannitol is a hexahydric alcohol related to mannose ($C_6H_{12}O_6$= 180.2). It is isomeric with sorbitol (p. 2092.1).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Mannitol). White or almost white crystals or powder. It exhibits polymorphism. Freely soluble in water; practically insoluble in alcohol.

USP 36: (Mannitol). A white odourless crystalline powder or free-flowing granules with a sweet taste. Soluble 1 in 5.5 of water; very slightly soluble in alcohol; practically insoluble in ether; slightly soluble in pyridine; soluble in alkaline solutions.

Incompatibility. Mannitol should never be added to whole blood for transfusion or given through the same set by which blood is being infused. For details of the adverse effects of mannitol on red blood cells, see Effects on the Blood under Adverse Effects, p. 1428.3.

Supersaturated solutions. Supersaturated aqueous solutions are prepared with the aid of heat. Any crystals that form during storage of the injection should be dissolved by warming before use; this may be a particular problem with the 20 and 25% injections which are supersaturated. A 5.07% solution in water is iso-osmotic with serum.

Uses and Administration

Mannitol is an osmotic agent. Although an isomer of sorbitol, it has little energy value, since it is largely eliminated from the body before any metabolism can take place.

Mannitol is mainly used, with adequate rehydration, to increase urine flow in patients with acute renal failure and to reduce raised intracranial pressure (p. 1271.3) and treat cerebral oedema (although it may be of no benefit or even harmful in patients with cerebral malaria—see p. 1428.3). It is also used in the short-term management of glaucoma (p. 1999.1), especially to reduce intra-ocular pressure before ophthalmic surgery, and to promote the excretion of toxic substances by forced diuresis.

Other indications include bladder irrigation during transurethral resection of the prostate in order to reduce haemolysis and it has been used as an oral osmotic laxative for bowel preparation. It is given by inhalation for a mucolytic effect in cystic fibrosis and in the diagnosis of bronchial hyperresponsiveness in asthma (see Respiratory Disorders, p. 1428.2). Mannitol is used as a diluent, a

bulking agent for freeze-drying, and an excipient in pharmaceutical preparations and as a bulk sweetener.

When given parenterally, mannitol raises the osmotic pressure of the plasma thus drawing water out of body tissues and producing an osmotic diuresis. Reduction of CSF and intra-ocular fluid pressure occurs within 15 minutes of the start of a mannitol infusion and lasts for 3 to 8 hours after the infusion is stopped; diuresis occurs after 1 to 3 hours.

When used as an osmotic diuretic, mannitol is given by intravenous infusion. Careful monitoring of fluid balance, electrolytes, renal function, and vital signs is necessary during infusion to prevent fluid and electrolyte imbalance, including circulatory overload and tissue dehydration. Solutions containing more than 15% of mannitol may crystallise during storage, particularly at low temperatures; crystals may be redissolved by warming before use; the giving set should include a filter.

Mannitol may be used to treat patients in the oliguric phase of **renal failure** or those suspected of inadequate renal function after correction of plasma volume, provided a test dose of about 200 mg/kg given by rapid intravenous infusion of a 15 to 25% solution over 3 to 5 minutes produces a diuresis of at least 30 to 50 mL/hour during the next 2 to 3 hours; a second test dose is permitted if the response to the first is inadequate. The usual adult dose of mannitol ranges from 50 to 100 g in a 24 hour period, given by intravenous infusion of a 5 to 20% solution. The rate of infusion is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hour.

For doses in children, see below.

The total dosage, the concentration, and the rate of infusion depend on the fluid requirement, the urinary output, and the nature and severity of the condition being treated. Mannitol infusion has also been used to prevent acute renal failure during cardiovascular and other types of surgery, or after trauma.

To reduce **raised intracranial** or **intra-ocular pressure** mannitol may be given by intravenous infusion as a 15 to 25% solution in a dose of 0.25 to 2 g/kg over 30 to 60 minutes. Rebound increases in intracranial or intra-ocular pressure may occur but are less frequent than with urea.

During **transurethral prostatic resection** a 2.5 to 5% solution of mannitol has been used for irrigating the bladder.

In the management of **cystic fibrosis**, in patients aged 18 years and over, the initial dose of mannitol is given in an escalating dosage regimen to assess bronchial hyperresponsiveness. Baseline measures of FEV_1 and oxygen saturation in the blood (SpO_2) are followed by an inhaled bronchodilator. After a further 5 to 15 minutes mannitol powder is given by inhalation as:

- 40 mg, followed by SpO_2 measurement after 60 seconds, then
- 80 mg, followed by SpO_2 measurement after 60 seconds, then
- 120 mg, followed by FEV_1 and SpO_2 measurement after 60 seconds, then
- 160 mg, followed by FEV_1 and SpO_2 measurement after 60 seconds, then
- FEV_1 measured after 15 minutes

Hyperresponsiveness is defined as any of the following:

- $\geqslant$ 10% fall from baseline in SpO_2 at any time during the assessment
- FEV_1 has fallen from baseline $\geqslant$ 20% at a cumulative dose of 240 mg
- FEV_1 has fallen 20 to < 50% from baseline at the end of the assessment and does not return to < 20% below baseline within 15 minutes
- FEV_1 has fallen $\geqslant$ 50% from baseline at the end of the assessment

Patients who are not hyperresponsive may be started on a maintenance dose of mannitol 400 mg inhaled twice daily. Doses should be given 5 to 15 minutes after an inhaled bronchodilator and before physiotherapy or exercise and any other inhaled treatments such as dornase alfa and inhaled antibacterials.

Inhaled mannitol is also used as a **bronchial provocation test** for asthma in patients aged 6 years and older who do not have clinically apparent asthma, and have a baseline FEV_1 of 70% or more of predicted value. Mannitol powder is given by inhalation in incremental doses of 5, 10, 20, 40, 80, 160, 160, and 160 mg. Each dose is followed by measurement of FEV_1, until a positive response occurs (a 15% fall in FEV_1 from baseline or a 10% incremental fall between doses) or a total of 635 mg has been given.

Administration in children. Mannitol may be given to children in the treatment of oliguria in acute renal failure, cerebral and peripheral oedema, ascites, and raised intra-ocular pressure. A test dose is first given, as in adults (see Uses and Administration, p. 1427.3).

In the oliguric phase of **renal failure**, children may be given a 0.25 to 2 g/kg or 60 g/m^2 intravenous infusion of a 15 to 20% solution over 2 to 6 hours.

For **raised intracranial** or **intra-ocular pressure**, a dose of 1 to 2 g/kg or 30 to 60 g/m^2 of a 15 to 25% solution may be infused over 30 to 60 minutes. In small or debilitated patients, a dose of 500 mg/kg may suffice. An alternative dose suggested by the *BNFC* for children aged 1 month to 12 years is 0.25 to 1.5 g/kg infused over 30 to 60 minutes and repeated once or twice after 4 to 8 hours if necessary.

In the treatment of **peripheral oedema** and **ascites**, the *BNFC* suggests that children aged 1 month to 18 years may be given an infusion of 1 to 2 g/kg over 2 to 6 hours.

Mannitol may be used as a **bronchial provocation test** in children (see Uses and Administration, p. 1427.3).

Ciguatera poisoning. Ciguatera poisoning occurs throughout the Caribbean and Indopacific as a result of the consumption of certain fish contaminated with ciguatoxin; it is increasingly seen elsewhere, in travellers returning from these areas or as a result of eating imported fish. Nausea, vomiting, diarrhoea, and abdominal pain usually start within 24 hours and resolve within about 4 days. Neurological symptoms generally develop after the acute gastrointestinal illness, and include paraesthesias of the extremities and oral region, and a bizarre reversal of hot and cold sensation. Some neurological symptoms, pruritus, arthralgia, and fatigue, may persist for years.[1,2] Painful ejaculation and dyspareunia have been reported, as well as the occurrence of symptoms in sexual partners, suggesting that ciguatoxin can been transferred during intercourse.[2]

Treatment is usually symptomatic since there is no specific antidote. Dramatic reversal of neuromuscular symptoms with slower resolution of gastrointestinal upset has been reported after giving mannitol 1 g/kg by intravenous infusion over 30 to 45 minutes in the acute phase of the illness.[3-5] Mannitol may also be beneficial up to a week after poisoning.[6] However, a double-blind study[7] found mannitol to be no better than normal saline at relieving symptoms at 24 hours. Despite the weak and conflicting evidence for its efficacy, mannitol has been recommended for patients who are diagnosed within 48 to 72 hours after fish consumption; repeat treatment may be necessary if symptoms recur. After 72 hours, mannitol may be considered on an individual basis.[1] Amitriptyline has been found on several occasions[8-10] to relieve neurological symptoms (dysaesthesias and paraesthesias) and pruritus. Gabapentin has also been reported to be of benefit.[11]

1. Friedman MA, *et al*. Ciguatera fish poisoning: treatment, prevention and management. *Mar Drugs* 2008; **6:** 456–79.
2. Stewart I, *et al*. Emerging tropical diseases in Australia. Part 2. Ciguatera fish poisoning. *Ann Trop Med Parasitol* 2010; **104:** 557–71.
3. Palafox NA, *et al*. Successful treatment o f ciguatera fish poisoning with intravenous mannitol. *JAMA* 1988; **259:** 2740–2.
4. Pearn JH, *et al*. Ciguatera and mannitol: experience with a new treatment regimen. *Med J Aust* 1989; **151:** 77–80.
5. Williamson J. Ciguatera and mannitol: a successful treatment. *Med J Aust* 1990; **153:** 306–7.
6. Fenner PJ, *et al*. A Queensland family with ciguatera after eating coral trout. *Med J Aust* 1997; **166:** 473–5.
7. Schnorf H, *et al*. Ciguatera fish poisoning: a double-blind randomized trial of mannitol therapy. *Neurology* 2002; **58:** 873–80.
8. Bowman PB. Amitriptyline and ciguatera. *Med J Aust* 1984; **140:** 802.
9. Davis RT, Villar LA. Symptomatic improvement with amitriptyline in ciguatera fish poisoning. *N Engl J Med* 1986; **315:** 65.
10. Calvert GM, *et al*. Treatment of ciguatera fish poisoning with amitriptyline and nifedipine. *J Toxicol Clin Toxicol* 1987; **25:** 423–8.
11. Perez CM, *et al*. Treatment of ciguatera poisoning with gabapentin. *N Engl J Med* 2001; **344:** 692–3.

Gastrointestinal disorders. *BOWEL PREPARATION.* Mannitol, 1000 mL of a 10% solution or 500 mL of 10 or 20% solution, given orally, has been used to prepare the bowel for surgical and diagnostic procedures.[1,2] The potential for formation of explosive gas in the bowel should be borne in mind (see Effects on the Gastrointestinal Tract, below).

1. Palmer KR, Khan AN. Oral mannitol: a simple and effective bowel preparation for barium enema. *BMJ* 1979; **2:** 1038.
2. Newstead GL, Morgan BP. Bowel preparation with mannitol. *Med J Aust* 1979; **2:** 582–3.

DIAGNOSIS AND TESTING. Mannitol has been used with lactulose[1,2] and with cellobiose[3,4] in the detection of abnormal small bowel permeability, particularly that occurring in coeliac disease. For further information on the use of differential sugar absorption tests, see Lactulose, p. 1854.1.

1. Pearson ADJ, *et al*. The gluten challenge—biopsy v permeability. *Arch Dis Child* 1983; **58:** 653.
2. Cooper BT. Intestinal permeability in coeliac disease. *Lancet* 1983; **i:** 658–9.
3. Juby LD, *et al*. Cellobiose/mannitol sugar test—a sensitive tubeless test for coeliac disease: results on 1010 unselected patients. *Gut* 1989; **30:** 476–80.
4. Hodges S, *et al*. Cellobiose: mannitol differential permeability in small bowel disease. *Arch Dis Child* 1989; **64:** 853–5.

Respiratory disorders. Inhalation of dry powder mannitol improves mucus clearance and small studies have suggested it may be of benefit in bronchiectasis.[1,2] In patients with cystic fibrosis (p. 177.2) it can improve FEV_1 and reduce the risk of pulmonary exacerbations requiring intravenous antibacterial therapy.[3-5] Inhaled mannitol may also be used as a bronchial provocation test in the diagnosis of asthma.[6-9]

1. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 24/08/12).
2. Gjoerup J, *et al*. Inhaled mannitol in the treatment of non-cystic fibrosis bronchiectasis in adults. *Respirology* 2012; **17:** 927–32.
3. Bilton D, *et al*. CF301 Study Investigators. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. *Eur Respir J* 2011; **38:** 1071–80.
4. Aitken ML, *et al*. CF302 Investigators. Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study. *Am J Respir Crit Care Med* 2012; **185:** 645–52.
5. Burness CB, Keating GM. Mannitol dry powder for inhalation: in patients with cystic fibrosis. *Drugs* 2012; **72:** 1411–21.
6. Brannan JD, *et al*. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005; **6:** 144. Available at: http://respiratory-research.com/content/pdf/1465-9921-6-144.pdf (accessed 25/02/10)
7. Anderson SD, *et al*. A305 Study Group. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009; **10:** 4.
8. Sverrild A, *et al*. Diagnostic properties of inhaled mannitol in the diagnosis of asthma: a population study. *J Allergy Clin Immunol* 2009; **124:** 928–32.
9. Sverrild A, *et al*. The use of inhaled mannitol in the diagnosis and management of asthma. *Expert Opin Pharmacother* 2012; **13:** 115–23.

Adverse Effects and Precautions

The most common adverse effect associated with intravenous mannitol therapy is fluid and electrolyte imbalance including circulatory overload and acidosis at high doses. The expansion of extracellular volume can precipitate pulmonary oedema and congestive heart failure. The shift of fluid from the intracellular to extracellular compartment can cause tissue dehydration; dehydration of the brain, particularly in patients with renal failure, may give rise to CNS symptoms. Excessive diuresis can cause serious electrolyte imbalance.

Intravenous infusion of mannitol has been associated with nausea, vomiting, thirst, headache, dizziness, chills, fever, tachycardia, chest pain, hyponatraemia, dehydration, blurred vision, urticaria, and hypotension or hypertension. Large doses have been associated rarely with acute renal failure. Hypersensitivity reactions have occurred. Extravasation of the solution may cause oedema and skin necrosis; thrombophlebitis may occur.

Intravenous mannitol is contra-indicated in patients with severe pulmonary congestion or frank pulmonary oedema, intracranial bleeding (except during craniotomy), heart failure, severe dehydration, and in patients with renal failure unless a test dose has produced a diuretic response. All patients given mannitol should be carefully observed for signs of fluid and electrolyte imbalance and renal function should be monitored.

Mannitol should not be given with whole blood.

When given orally, mannitol causes diarrhoea.

Inhaled mannitol produces bronchospasm. Cough, wheezing, local irritation and pain, and headache are common; dizziness, nausea and vomiting, and haemoptysis can also occur.

Cerebral malaria. Mannitol has been used to treat raised intracranial pressure that is caused by oedema associated with cerebral malaria. However, a study in children found no benefit in measures of recovery or mortality,[1] and a study in adults reported that mannitol prolonged coma duration and may be harmful.[2]

1. Namutangula B, *et al*. Mannitol as adjunct therapy for childhood cerebral malaria in Uganda: a randomized clinical trial. *Malar J* 2007; **6:** 138. Available at: http://www.malariajournal.com/content/pdf/1475-2875-6-138.pdf (accessed 28/08/12)
2. Mohanty S, *et al*. Brain swelling and mannitol therapy in adult cerebral malaria: a randomized trial. *Clin Infect Dis* 2011; **53:** 349–55.

Effects on the blood. Agglutination and irreversible crenation of erythrocytes occurred when blood was mixed with varying proportions of a 10% mannitol solution.[1] It was suggested that intravenous infusions should be carefully controlled and given at a slow rate. This observation could have particular relevance to patients with sickle-cell disease.[2,3] Although agglutination and crenation had been seen *in vitro*, dilutional effects would make *in-vivo* interaction with blood cells less likely.[4]

1. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 421–2.
2. Konotey-Ahulu FID. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
3. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
4. Samson JH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 1191.

Effects on the gastrointestinal tract. Potentially explosive intracolonic concentrations of hydrogen gas have been measured in patients given mannitol before colonoscopy,[1,2] and cases of colonic explosion, including fatalities, have been reported in patients undergoing colonoscopic electrocautery, who had received mannitol bowel preparation. However, the risk of explosion was considered to be small when air or carbon dioxide insufflation

and suction were used during the colonoscopy procedure.[2,3]

Colonic perforation and subsequent death has been attributed to the use of mannitol for the treatment of constipation.[4]

1. La Brooy SJ, *et al.* Potentially explosive colonic concentrations of hydrogen after bowel preparation with mannitol. *Lancet* 1981; **i:** 634–6.
2. Avgerinos A, *et al.* Bowel preparation and the risk of explosion during colonoscopic polypectomy. *Gut* 1984; **25:** 361–4.
3. Trotman I, Walt R. Mannitol and explosions. *Lancet* 1981; **i:** 848.
4. Moses FM. Colonic perforation due to oral mannitol. *JAMA* 1988; **260:** 640.

Effects on the kidneys. Focal osmotic nephrosis occurred in a patient given mannitol 20% intravenously.[1]

Acute oliguric renal failure has been associated with the use of large doses of mannitol in patients with previously normal renal function,[2-4] and acute renal failure developed[5] in a patient with diabetes mellitus complicated by nephropathy after he was given 420 g of mannitol intravenously over 4 days.

1. Goodwin WE, Latta H. Focal osmotic nephrosis due to the therapeutic use of mannitol: a case of perirenal hematoma after renal biopsy. *J Urol (Baltimore)* 1970; **103:** 11–14.
2. Whelan TV, *et al.* Acute renal failure associated with mannitol intoxication. *Arch Intern Med* 1984; **144:** 2053–5.
3. Goldwasser P, Fotino S. Acute renal failure following massive mannitol infusion: appropriate response of tubuloglomerular feedback? *Arch Intern Med* 1984; **144:** 2214–16.
4. Rabetoy GM, *et al.* Where the kidney is concerned, how much mannitol is too much? *Ann Pharmacother* 1993; **27:** 25–8.
5. Matsumura M. Mannitol-induced toxicity in a diabetic patient receiving losartan. *Am J Med* 2001; **110:** 331.

Overdosage. Severe mannitol intoxication was reported in 8 patients with renal failure given large, and sometimes enormous, amounts of mannitol intravenously over 1 to 3 days.[1] These patients had CNS involvement out of proportion to uraemia, severe hyponatraemia, a large osmolality gap, and fluid overload. Six patients were treated with haemodialysis and this was considered to be more effective than peritoneal dialysis, which was used in 1 patient.

1. Borges HF, *et al.* Mannitol intoxication in patients with renal failure. *Arch Intern Med* 1982; **142:** 63–6.

Pharmacokinetics

Only small amounts of mannitol are absorbed from the gastrointestinal tract or after inhalation. After intravenous injection mannitol is excreted rapidly by the kidneys before any very significant metabolism can take place in the liver. Mannitol does not cross the blood-brain barrier or penetrate the eye. An elimination half-life of about 100 minutes has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aridol; Mede-Prep†; Osmitrol; ***Canad.***: Osmitrol; Resectisol; ***China***: Feng Hai Lu (丰海露); Pu Ke (普可); Shen Ning (伸宁); ***Cz.***: Ardeaosmosol MA; Mannisol†; ***Denm.***: Bronchitol; Osmohale; ***Fin.***: Aridol; ***Fr.***: Aridol; ***Ger.***: Aridol; Deltamannit; Mannit-Losung; Osmofundin 15% N; Osmosteril; ***Gr.***: Aridol; ***Hong Kong***: Osmitrol†; ***Hung.***: Mannisol; ***India***: Neurotol-M; Osmitrol; ***Indon.***: Infusan M; ***Irl.***: Osmohale; ***Israel***: Osmitrol; ***Ital.***: Isotol; Osmohale; ***Mex.***: Osmorol†; ***Neth.***: Bronchitol; Osmohale; Osmosteril; ***Norw.***: Aridol; ***Port.***: Aridol; Osmofundina; ***Singapore***: Osmitrol; ***Spain***: Osmofundina Concentrada; Osmohale; ***Swed.***: Aridol; ***Switz.***: Aridol; Mannite; ***Turk.***: Resectisol; Rezosel; ***UK***: Bronchitol; Osmohale; ***USA***: Aridol; Osmitrol.

Multi-ingredient Preparations. ***Chile***: Gelsolets; Solucion Irrigacion Vesical†; ***Denm.***: Pharmalgen Albumin; ***Ger.***: Flacar; Freka-Drainjet Purisole†; Hya-ject Plus; Infi-tract V; ***Hong Kong***: Osmofundin†; ***India***: Kratol; Mannigyl; Mengy; Neurotol; ***Ital.***: Levoplus; Naturalass; Plurilac; ***Mex.***: Jarabe de Manzanas; ***Pol.***: Purisole SM†; ***Port.***: Purisole; Xarope de Macas Reinetas; ***Rus.***: Rheogluman (Реоглюман); ***Singapore***: Osmofundin; ***Spain***: Hidrofundin; Osmofundina; Salmagne; ***Thai.***: Dimedon; ***Ukr.***: Turusol (Турусол).

Used as an adjunct in:. ***China***: Chen Ya (辰雅).

Pharmacopoeial Preparations
BP 2014: Mannitol Infusion;
USP 36: Chlorothiazide Sodium for Injection; Cisplatin for Injection; Mannitol in Sodium Chloride Injection; Mannitol Injection.

Mecamylamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mecamilamina; Mecamilamina, hidrocloruro de; Mecamine Hydrochloride; Mécamylamine, Chlorhydrate de; Mecamylamini Hydrochloridum; Мекамиламина Гидрохлорид.

N-Methyl-2,3,3-trimethylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

$C_{11}H_{21}N,HCl$=203.8

CAS — 60-40-2 (mecamylamine); 826-39-1 (mecamylamine hydrochloride).

ATC — C02BB01.
ATC Vet — QC02BB01.
UNII — 4956DJR58O.

Pharmacopoeias. In *US.*

USP 36: (Mecamylamine Hydrochloride). Store in airtight containers.

Uses and Administration

Mecamylamine hydrochloride is a ganglion blocker that acts to reduce transmission of nerve impulses in sympathetic and parasympathetic ganglia, resulting via the former action in peripheral vasodilatation and a fall in blood pressure. It is given orally in the management of hypertension (p. 1251.1). However, it may be limited to patients with severe hypertension or uncomplicated malignant hypertension and other antihypertensives with fewer adverse effects are generally preferred.

The usual initial dose is 2.5 mg twice daily gradually adjusted, usually in steps of 2.5 mg at intervals of not less than 2 days, until a satisfactory dose is obtained. The average maintenance dose is 25 mg daily in three divided doses. Tolerance may develop. Sudden withdrawal of mecamylamine may cause rebound hypertension therefore a gradual withdrawal is recommended.

Reviews.

1. Young JM, *et al.* Mecamylamine: new therapeutic uses and toxicity/risk profile. *Clin Ther* 2001; **23:** 532–65.

Smoking cessation. Mecamylamine acts centrally as a nicotinic antagonist and might be of some benefit in assisting withdrawal from smoking. Two studies[1,2] have shown that addition of low-dose oral mecamylamine (2.5 to 5 mg twice daily) appeared to enhance the efficacy of nicotine skin patches. However, a later controlled study[3] found that a patch containing both mecamylamine and nicotine was not significantly better than transdermal nicotine alone. Smoking cessation is discussed under Nicotine, p. 2570.2.

1. Rose JE, *et al.* Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin Pharmacol Ther* 1994; **56:** 86–99.
2. Rose JE, *et al.* Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol* 1998; **6:** 331–43.
3. Glover ED, *et al.* A randomized, controlled trial to assess the efficacy and safety of a transdermal delivery system of nicotine/mecamylamine in cigarette smokers. *Addiction* 2007; **102:** 795–802.

Tourette's syndrome. Mecamylamine has been tried[1-3] in the management of Tourette's syndrome (see under Tics, p. 1030.1) although results have been mixed.

1. Sanberg PR, *et al.* Treatment of Tourette's syndrome with mecamylamine. *Lancet* 1998; **352:** 705–6.
2. Silver AA, *et al.* Mecamylamine in Tourette's syndrome: a two-year retrospective case study. *J Child Adolesc Psychopharmacol* 2000; **10:** 59–68.
3. Silver AA, *et al.* Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 1103–10.

Adverse Effects and Precautions

The adverse effects of mecamylamine are mainly due to ganglionic blockade. A reduction in gastrointestinal motility may cause constipation or paralytic ileus (sometimes preceded by frequent liquid stools). Dry mouth, glossitis, and other gastrointestinal disturbances such as anorexia, nausea, or vomiting, may occur. Orthostatic hypotension and dizziness may be seen. Other adverse effects include blurred vision, urinary retention, erectile dysfunction, weakness, and fatigue. Pulmonary oedema and fibrosis have been reported. Mecamylamine crosses the blood-brain barrier and may also cause tremor, convulsions, choreiform movements, insomnia, sedation, dysarthria, and mental aberrations. Use is contra-indicated in patients with coronary insufficiency or recent myocardial infarction; it should also be avoided in those with glaucoma, pyloric stenosis, or marked renal impairment.

Pharmacokinetics

Mecamylamine hydrochloride is almost completely absorbed from the gastrointestinal tract. It crosses the placenta and the blood-brain barrier. About 50% of the dose is excreted unchanged in the urine over 24 hours, but the rate is diminished in alkaline urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Inversine†.

Pharmacopoeial Preparations
USP 36: Mecamylamine Hydrochloride Tablets.

Mefruside *(BAN, USAN, rINN)* ⊗

Bay-1500; FBA-1500; Mefrusid; Mefrusida; Méfruside; Mefrusidi; Mefrusidum; Мефрузид.

4-Chloro-N^1-methyl-N^1-(tetrahydro-2-methylfurfuryl)benzene-1,3-disulphonamide.

$C_{13}H_{19}ClN_2O_5S_2$=382.9

CAS — 7195-27-9.
ATC — C03BA05.
ATC Vet — QC03BA05.
UNII — X1NS9SN592.

NOTE. The names Escaron and Mebread have been used as trade names for mefruside.

Pharmacopoeias. In *Jpn.*

Profile

Mefruside is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is used for hypertension (p. 1251.1).

Diuresis begins about 2 to 4 hours after an oral dose and reaches a peak between 6 and 12 hours.

Mefruside is given with other antihypertensives in a usual oral dose of 10 to 50 mg daily, either as a single dose or in two divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Sali-Adalat; Sali-Prent.

Meldonium *(rINN)*

Meldonio; MET-88; 3-(2,2,2-Trimethylhydrazinium)propionate; Мельдоний.

3-(2,2,2-Trimethyldiazaniumyl)propanoate.

$C_6H_{14}N_2O_2$=146.2

CAS — 76144-81-5 (meldonium); 86426-17-7 (meldonium dihydrate).
UNII — 73H7UDN6EC.

Profile

Meldonium is an inhibitor of carnitine synthesis and is reported to have cardioprotective and anti-ischaemic effects. It has been used in a variety of disorders. In the management of ischaemic heart disease and ischaemic cerebrovascular disturbances typical oral doses have ranged from 500 mg to 1 g daily. A course of 500 mg given four times daily for 7 to 10 days has been used in alcohol abstinence syndrome. Meldonium has also been given intravenously in doses similar to those used orally.

References.

1. Dambrova M, *et al.* Mildronate: cardioprotective action through carnitine-lowering effect. *Trends Cardiovasc Med* 2002; **12:** 275–9.
2. Sjakste N, *et al.* Mildronate: an antiischemic drug for neurological indications. *CNS Drug Rev* 2005; **11:** 151–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Cardionate (Кардионат); Idrinol (Идринол); Midolat (Мидолат); Mildronate (Милдронат); Mildroxyn (Милдроксин); ***Ukr.***: Metamax (Метамакс); Methyldronat (Метилдронат)†; Metonat (Метонат); Mildronate (Милдронат); Trizipin (Тризипин); Vazonat (Вазонат); Vazopro (Вазопро).

Mephentermine Sulfate *(BANM, rINNM)* ⊗

Mefentermina, sulfato de; Méphentermine, Sulfate de; Mephentermine Sulphate; Mephentermini Sulfas; Mephetedrine Sulphate; Sulfato de mefentermina; Мефентермина Сульфат.

N,α,α-Trimethylphenethylamine sulphate dihydrate.

$(C_{11}H_{17}N)_2,H_2SO_4,2H_2O$=460.6

CAS — 100-92-5 (mephentermine); 1212-72-2 (anhydrous mephentermine sulfate); 6190-60-9 (mephentermine sulfate dihydrate).
ATC — C01CA11.
ATC Vet — QC01CA11.
UNII — 580655Z8RR.

Uses and Administration

Mephentermine is a sympathomimetic (p. 1507.3) with mainly indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity, and a slight stimulating effect on the CNS. It has an inotropic effect on the heart.

Mephentermine has been used to maintain blood pressure in hypotensive states, for example after spinal anaesthesia. It is given as the sulfate but doses are expressed in terms of the base; 21 mg of sulfate is equivalent to about

15 mg of base. Typical doses have ranged from 15 to 45 mg by slow intravenous or intramuscular injection.

References.
1. Kansal A, *et al.* Randomised trial of intravenous infusion of ephedrine or mephentermine for management of hypotension during spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60:** 28–34.
2. Mohta M, *et al.* Comparison of potency of ephedrine and mephentermine for prevention of post-spinal hypotension in caesarean section. *Anaesth Intensive Care* 2008; **36:** 360–4.
3. Mohta M, *et al.* Potency of mephentermine for prevention of post-spinal hypotension. *Anaesth Intensive Care* 2009; **37:** 568–70.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; adverse effects may be related to alpha- or beta-adrenergic stimulation. Mephentermine may produce CNS stimulation, especially in overdosage; anxiety, drowsiness, incoherence, hallucinations, and convulsions have been reported.

Interactions

As for Sympathomimetics, p. 1508.3.

Pharmacokinetics

Mephentermine acts in about 5 to 15 minutes after intramuscular injection and has a duration of action of up to about 4 hours; it acts almost immediately after intravenous injection with a duration of action of up to about 30 minutes. It is rapidly metabolised in the body by demethylation; hydroxylation may follow. It is excreted as unchanged drug and metabolites in the urine; excretion is more rapid in acidic urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Mephentine.

Multi-ingredient Preparations. ***USA***: Emergent-Ez.

Metaraminol Tartrate *(BANM, rINNM)* ⊗

Bitartrato de metaraminol; Hydroxynorephedrine Bitartrate; Metaradrine Bitartrate; Metaraminol Acid Tartrate; Metaraminol Bitartrate; Métaraminol, Tartrate de; Metaraminol, tartrato de; Metaraminoli Tartras; Tartrato de metaraminol; Метараминола Тартрат.

(-)-2-Amino-1-(3-hydroxyphenyl)propan-1-ol hydrogen tartrate.

$C_9H_{13}NO_2,C_4H_6O_6$=317.3

CAS — 54-49-9 (metaraminol); 33402-03-8 (metaraminol tartrate).

ATC — C01CA09.

ATC Vet — QC01CA09.

UNII — ZC4202M9P3.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Metaraminol Tartrate). An odourless or almost odourless, white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 3.2 to 3.5.

USP 36: (Metaraminol Bitartrate). A 5% solution in water has a pH of between 3.2 and 3.5. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Metaraminol is a sympathomimetic (p. 1507.3) with direct and indirect effects on adrenergic receptors. It has alpha-and beta-adrenergic activity, the former being predominant. Metaraminol has an inotropic effect and acts as a peripheral vasoconstrictor, thus increasing cardiac output, peripheral resistance, and blood pressure. Coronary blood flow is increased and the heart rate slowed.

Metaraminol tartrate is used for its pressor action in **hypotensive states** such as those that may occur after spinal anaesthesia. Doses are expressed in terms of the base; metaraminol tartrate 9.5 mg is equivalent to about 5 mg of metaraminol. An intravenous infusion of 15 to 100 mg of metaraminol in 500 mL of glucose 5% or sodium chloride 0.9% may be used for maintaining the blood pressure, the rate of infusion being adjusted according to blood pressure response. Higher concentrations have been given. As the maximum effects are not immediately apparent, at least 10 minutes should elapse before increasing the dose and the possibility of a cumulative effect should be borne in mind. In an emergency an initial dose of 0.5 to 5 mg may be given by direct intravenous injection followed by an intravenous infusion as above.

Metaraminol tartrate has also been given by intramuscular or subcutaneous injection for the prevention of hypotension in doses equivalent to 2 to 10 mg of metaraminol. Subcutaneous injection increases the risk of local tissue necrosis and sloughing.

Priapism. Priapism[1,2] or prolonged penile erection may occur due to either decreased venous outflow (low-flow priapism) or increased arterial inflow (high-flow priapism). Low-flow priapism is a medical emergency since inflow is also impaired, leading to the development of ischaemia. It may be related to the use of drugs that cause smooth muscle relaxation, such as alpha blockers; intraluminal obstruction, such as in sickle-cell disease, may also be a cause. It is usually treated with corporal aspiration, followed if necessary by irrigation with a low dosage of a dilute solution of an alpha agonist such as metaraminol.

Intracavernosal metaraminol has been used successfully to treat drug-induced priapism,[3] as well as priapism associated with chronic myeloid leukaemia,[4] haemodialysis,[5] spinal block,[6] or fentanyl-induced general anaesthesia.[6] It may also be used to reverse the effects of alprostadil or papaverine given intracavernosally for the management of some types of erectile dysfunction, although this has been associated with fatal hypertensive crisis (see also Alprostadil, p. 2353.2).

Alternative alpha agonists that are used include intracavernosal phenylephrine,[7] and intracavernosal adrenaline, again in a low dosage and dilute solution. Phenylpropanolamine,[7] or pseudoephedrine,[8] given orally, have also been used. In patients with priapism due to sickle-cell disease, intracavernosal irrigation with a dilute adrenaline solution (see p. 1294.1) or intracavernosal injection of etilefrine have been used; oral etilefrine has been given for prophylaxis. Many other drugs have been tried or suggested, including baclofen, gabapentin, terbutaline, and, paradoxically, low doses of phosphodiesterase type-5 inhibitors such as sildenafil or tadalafil.[2] Surgery is usually favoured in low-flow priapism unresponsive to drug therapy.

In high-flow priapism, which is less of an emergency, embolisation of the source of abnormal inflow is the usual treatment.

1. Maan Z, *et al.* Priapism—a review of the medical management. *Expert Opin Pharmacother* 2003; **4:** 2271–7.
2. Yuan J, *et al.* Insights of priapism mechanism and rationale treatment for recurrent priapism. *Asian J Androl* 2008; **10:** 88–101.
3. Brindley GS. New treatment for priapism. *Lancet* 1984; **ii:** 220–1.
4. Stanners A, Colin-Jones D. Metaraminol for priapism. *Lancet* 1984; **ii:** 978.
5. Branger B, *et al.* Metaraminol for haemodialysis-associated priapism. *Lancet* 1985; **i:** 641.
6. Tsai SK, Hong CY. Intracavernosal metaraminol for treatment of intraoperative penile erection. *Postgrad Med J* 1990; **66:** 831–3.
7. Harmon WJ, Nehra A. Priapism: diagnosis and management. *Mayo Clin Proc* 1997; **72:** 350–5.
8. Millard RJ, *et al.* Risks of self-injection therapy for impotence. *Med J Aust* 1996; **165:** 117–18.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. The adverse effects of metaraminol mainly relate to its alpha-agonist action. Metaraminol has a longer duration of action than adrenaline or noradrenaline and therefore an excessive vasopressor response may cause a prolonged rise in blood pressure. Tissue necrosis can occur as a result of accidental extravasation during intravenous injection.

Interactions

As for Sympathomimetics, p. 1508.3. The interactions of metaraminol relate to both its direct and indirect actions.

Pharmacokinetics

Metaraminol acts about 10 minutes after intramuscular injection with a duration of action of up to about 1 hour. Effects are seen 1 to 2 minutes after intravenous injection with a duration of action of about 20 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fadamine; ***Austral.***: Aramine†; ***Braz.***: Aramin; ***NZ***: Aramine†; ***Singapore***: Aramine; ***Thai.***: Aramine; ***USA***: Aramine†.

Pharmacopoeial Preparations
BP 2014: Metaraminol Injection;
USP 36: Metaraminol Bitartrate Injection.

Methoxamine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de metoxamina; Methoxamedrine Hydrochloride; Méthoxamine, Chlorhydrate de; Methoxamini Hydrochloridum; Metoxamina, hidrocloruro de; Метоксамина Гидрохлорид.

2-Amino-1-(2,5-dimethoxyphenyl)propan-1-ol hydrochloride.

$C_{11}H_{17}NO_3$,HCl=247.7

CAS — 390-28-3 (methoxamine); 61-16-5 (methoxamine hydrochloride).

ATC — C01CA10.

ATC Vet — QC01CA10.

UNII — 8MB4MJ9R7L.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Methoxamine Hydrochloride). Colourless crystals or white plate-like crystals or white crystalline powder; odourless or almost odourless. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. A 2% solution in water has a pH of 4.0 to 6.0.

Profile

Methoxamine is a sympathomimetic (p. 1507.3) with mainly direct effects on adrenergic receptors. It has alpha-adrenergic activity entirely; beta-adrenergic activity is not demonstrable and beta-adrenoceptor blockade may occur at high doses. Methoxamine hydrochloride has been used parenterally for its pressor action in the management of hypotensive states, particularly in anaesthesia, and also in the management of paroxysmal supraventricular tachycardia. A typical dose, given by intramuscular injection, is 10 to 15 mg. Alternatively, 3 to 10 mg may be given in emergencies by slow intravenous injection. It has also been used topically as a vasoconstrictor in the management of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Mexan†.

Pharmacopoeial Preparations
BP 2014: Methoxamine Injection.

Methyclothiazide *(BAN, USAN, rINN)* ⊗

Méthyclothiazide; Methyclothiazidum; Meticlotiazida; Metyklotiatsidi; Metyklotiazid; NSC-110431; Метиклотиазид.

6-Chloro-3-chloromethyl-3,4-dihydro-2-methyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_9H_{11}Cl_2N_3O_4S_2$=360.2

CAS — 135-07-9.

ATC — C03AA08.

ATC Vet — QC03AA08.

UNII — L3H46UAC61.

Pharmacopoeias. In *US*.

USP 36: (Methyclothiazide). A white or practically white crystalline powder, odourless or with a slight odour. Very slightly soluble to practically insoluble in water and in chloroform; soluble 1 in 92.5 of alcohol and 1 in 2700 of ether; freely soluble in acetone and in pyridine; sparingly soluble in methyl alcohol; very slightly soluble in benzene.

Profile

Methyclothiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (see p. 1403.2). It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis starts in about 2 hours, reaches a peak at about 6 hours, and lasts for 24 hours or more.

In the treatment of oedema the usual initial dose is 2.5 to 5 mg daily, increasing to a maximum dose of 10 mg daily if necessary. In the treatment of hypertension the usual dose is 2.5 to 5 mg daily, either alone, or with other antihypertensives. Doses of up to 10 mg daily have been suggested, but this may not result in an increased hypotensive effect.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methyclothiazide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Enduron.

Multi-ingredient Preparations. ***China***: Enduronyl (降压乐); ***Fr.***: Isobar.

Pharmacopoeial Preparations
USP 36: Methyclothiazide Tablets.

Methyldopa (BAN, USAN, rINN)

Alpha-methyldopa; Méthyldopa; Methyldopum; Methyldopum Hydratum; Metildopa; Metyldopa; Metyylidopa; MK-351; Метилдопа.

(-)-3-(3,4-Dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate; (-)-2-Amino-2-(3,4-dihydroxybenzyl)propionic acid sesquihydrate.

$C_{10}H_{13}NO_4,1½H_2O$=238.2

CAS — 555-30-6 (anhydrous methyldopa); 41372-08-1 (methyldopa sesquihydrate).

ATC — C02AB01 (laevorotatary); C02AB02 (racemic).

ATC Vet — QC02AB01 (laevorotatary); QC02AB02 (racemic).

UNII — 56LH93261Y.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn*, and *US.*

Ph. Eur. 8: (Methyldopa). Colourless or almost colourless crystals or a white to yellowish-white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; freely soluble in dilute mineral acids. Protect from light.

USP 36: (Methyldopa). A white to yellowish-white odourless fine powder which may contain friable lumps. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in ether; very soluble in 3N hydrochloric acid. Protect from light.

Methyldopate Hydrochloride (BANM, USAN)

Cloridrato de Metildopato; Metildopato, hidrocloruro de.

The hydrochloride of the ethyl ester of anhydrous methyldopa; Ethyl (-)-2-amino-2-(3,4-dihydroxybenzyl) propionate hydrochloride.

$C_{12}H_{17}NO_4HCl$=275.7

CAS — 2544-09-4 (methyldopate); 2508-79-4 (methyldopate hydrochloride).

UNII — 7PX435DN5A.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 36: (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of between 3.0 and 5.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. A haze developed over 3 hours when methyldopate hydrochloride 1 mg/mL was mixed with amphotericin B 200 micrograms/mL in glucose; crystals were produced with methohexital sodium 200 micrograms/mL in sodium chloride, and a haze developed when they were mixed in glucose. A crystalline precipitate occurred with tetracycline hydrochloride 1 mg/mL in glucose, and with sulfadiazine sodium 4 mg/mL in glucose or sodium chloride.[1]

1. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28:** 228–40.

Uses and Administration

Methyldopa is an antihypertensive that is thought to have a mainly central action. It is decarboxylated in the CNS to alpha-methylnoradrenaline, which is thought to stimulate $alpha_2$ adrenoceptors resulting in a reduction in sympathetic tone and a fall in blood pressure. It may also act as a false neurotransmitter, and have some inhibitory actions on plasma renin activity. Methyldopa reduces the tissue concentrations of dopamine, noradrenaline, adrenaline, and serotonin.

Methyldopa is used in the management of hypertension (p. 1251.1), although other drugs with fewer adverse effects are generally preferred. Methyldopa may, however, be the treatment of choice for hypertension in pregnancy. Oedema and tolerance sometimes associated with methyldopa therapy may be reduced when it is given with a thiazide diuretic.

Methyldopa is given orally as the sesquihydrate, but doses are usually expressed in terms of anhydrous methyldopa. Methyldopa sesquihydrate 1.13 g is equivalent to about 1 g of anhydrous methyldopa. For hypertensive crises, methyldopa has been given intravenously as methyldopate hydrochloride.

When methyldopa is given orally its effects reach a maximum in 4 to 6 hours after a single dose, although the maximum hypotensive effect may not occur until the second or third day of continuous treatment; some effect is usually apparent for 48 hours after withdrawal of methyldopa. When given intravenously the hypotensive effect may be obtained within 4 to 6 hours and last for 10 to 16 hours. It lowers the standing, and to a lesser extent the supine, blood pressure.

In hypertension, the usual initial adult oral dose is 250 mg of methyldopa two or three times daily for 2 days; this is then adjusted, not more frequently than every 2 days according to response, up to a usual maximum dose of 3 g daily. The usual maintenance dosage is 0.5 to 2 g of methyldopa daily. In the elderly an initial dose of 125 mg twice daily has been used; this dose may be increased gradually if necessary, but should not exceed 2 g daily.

References.

1. Mah GT, *et al.* Methyldopa for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 09/03/10).

Administration in children. Children aged under 12 years may be given methyldopa in the management of hypertension at an initial oral dose of 10 mg/kg daily in 2 to 4 divided doses. This may be adjusted to a maximum daily dose of 65 mg/kg or 3 g, whichever is the smaller. It has been suggested that dosage adjustments are made at intervals of at least 2 days.

Adverse Effects

The adverse effects of methyldopa are mostly consequences of its pharmacological action. The incidence of adverse effects overall may be as high as 60% but most are transient or reversible. Drowsiness is common, especially initially and after an increase in dosage. Dizziness and lightheadedness may be associated with orthostatic hypotension; nausea, headache, weakness and fatigue, and decreased libido and impotence have also been reported quite often.

The mental and neurological effects of methyldopa have included impaired concentration and memory, mild psychoses, depression, disturbed sleep and nightmares, paraesthesias, Bell's palsy, involuntary choreoathetotic movements, and parkinsonism.

As well as orthostatic hypotension, methyldopa is often associated with fluid retention and oedema, which responds to diuretics but may rarely progress to heart failure. Angina pectoris may be aggravated. Bradycardia, syncope, and prolonged carotid sinus hypersensitivity have been reported. Intravenous methyldopate has been associated with a paradoxical rise in blood pressure.

Methyldopa may produce gastrointestinal disturbances including nausea and vomiting, diarrhoea, constipation, and rarely pancreatitis and colitis. A black or sore tongue, and inflammation of the salivary glands, have occurred, and dry mouth is quite common.

A positive Coombs' test may occur in 10 to 20% of all patients on prolonged therapy but only a small proportion develop haemolytic anaemia. Thrombocytopenia and leucopenia, notably granulocytopenia, have occurred and warrant prompt withdrawal. Other hypersensitivity effects have included myocarditis, fever, eosinophilia, and disturbances of liver function. Hepatitis may develop, particularly in the first 2 or 3 months of therapy, and is generally reversible on stopping, but fatal hepatic necrosis has occurred. Antinuclear antibodies may develop and cases of a lupus-like syndrome have been reported.

Other adverse effects that have been reported in patients taking methyldopa include rashes, lichenoid and granulomatous eruptions, toxic epidermal necrolysis, a flu-like syndrome (of fever, myalgia, and mild arthralgia), nocturia, uraemia, nasal congestion, and retroperitoneal fibrosis. Hyperprolactinaemia may occur, with breast enlargement or gynaecomastia, galactorrhoea, and amenorrhoea.

Methyldopa may occasionally cause urine to darken on exposure to the air because of the breakdown of the drug or its metabolites.

Reviews.

1. Furhoff A-K. Adverse reactions with methyldopa—a decade's reports. *Acta Med Scand* 1978; **203:** 425–8.
2. Lawson DH, *et al.* Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96:** 572–9.

Effects on the blood. An analysis of drug-induced blood dyscrasias reported to the Swedish Adverse Drug Reaction Committee for the 10-year period 1966 to 1975 showed that haemolytic anaemia attributable to methyldopa had been reported on 69 occasions and had caused 3 deaths. This represented the vast majority of all the reports of drug-induced haemolytic anaemia.[1] However, the actual incidence of haemolytic anaemia in patients receiving methyldopa is quite low; data from the Boston Collaborative Drug Surveillance Program indicated that only 2 of 1067 patients receiving methyldopa developed haemolytic anaemia,[2] an incidence of about 0.2%. The proportion of patients with a positive Coombs' test is much higher, being variously reported[3-5] at 10 to 20%. It has been suggested that the high incidence of autoantibody formation may be due to inhibition of suppressor T-cells by methyldopa[4] while the relatively low incidence of resultant haemolysis may be due to drug-associated impairment of the reticuloendothelial system which would normally clear the antibody-sensitised cells from the circulation.[5] Although the use of methyldopa has now declined, reports of methyldopa-induced haemolytic anaemia still occasionally occur.[6]

Autoantibodies were detected in the neonate of a mother who took methyldopa during pregnancy—see Pregnancy under Precautions, p. 1432.2.

1. Böttiger LE, *et al.* Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205:** 457–61.
2. Lawson DH, *et al.* Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96:** 572–9.
3. Carstairs K, *et al.* Methyldopa and haemolytic anaemia. *Lancet* 1966; **i:** 201.
4. Kirtland HH, *et al.* Methyldopa inhibition of suppressor-lymphocyte function: a proposed cause of autoimmune hemolytic anemia. *N Engl J Med* 1980; **302:** 825–32.
5. Kelton JG. Impaired reticuloendothelial function in patients treated with methyldopa. *N Engl J Med* 1985; **313:** 596–600.
6. Thomas A, *et al.* Methyldopa-induced autoimmune haemolytic anaemia revisited. *N Z Med J* 2009; **122:** 53–6.

Effects on the gastrointestinal tract. *COLITIS.* There has been a report of 6 cases of colitis associated with methyldopa.[1] An auto-immune mechanism was proposed.

1. Graham CF, *et al.* Acute colitis with methyldopa. *N Engl J Med* 1981; **304:** 1044–5.

DIARRHOEA. Severe chronic diarrhoea was associated with methyldopa over periods of 2 and 7 years;[1,2] it stopped in both cases on withdrawal of the drug.

1. Quart BD, Guglielmo BJ. Prolonged diarrhea secondary to methyldopa therapy. *Drug Intell Clin Pharm* 1983; **17:** 462.
2. Gloth FM, Busby MJ. Methyldopa-induced diarrhea: a case of iatrogenic diarrhea leading to request for nursing home placement. *Am J Med* 1989; **87:** 480–1.

PANCREATITIS. Increases in serum- and urinary-amylase activity accompanied by fever and suggestive of pancreatitis were associated with methyldopa in 2 patients,[1] one of whom had symptoms of severe pancreatitis. Symptoms reappeared on rechallenge in both patients. A further report of acute pancreatitis in a patient who had recently begun methyldopa therapy (with a diuretic) also confirmed a recurrence of symptoms on rechallenge.[2] In contrast to the acute form, chronic pancreatitis is not generally attributable to drug use.[3] However, a case of florid chronic pancreatitis, with exocrine and endocrine insufficiency and heavy calcification over 30 months, associated with 2 periods of methyldopa treatment, has been reported.[4] Symptoms in this patient, who was also receiving a thiazide, included severe diabetic ketoacidosis.

1. van der Heide H, *et al.* Pancreatitis caused by methyldopa. *BMJ* 1981; **282:** 1930–1.
2. Anderson JR, *et al.* Drug-associated recurrent pancreatitis. *Dig Surg* 1985; **2:** 24–6.
3. Banergee AK, *et al.* Drug-induced acute pancreatitis. *Med Toxicol Adverse Drug Exp* 1989; **4:** 186–98.
4. Ramsay LE, *et al.* Methyldopa-induced chronic pancreatitis. *Practitioner* 1982; **226:** 1166–9.

Effects on the heart. Sudden death in patients receiving methyldopa has been associated with myocarditis (often with hepatitis and pneumonitis).[1,2] The effect is thought to be due to hypersensitivity. Hypersensitivity myocarditis is generally marked by ECG changes, a slight rise in cardiac enzymes, cardiomegaly, and persistent sinus tachycardia, along with peripheral blood eosinophilia, and most patients will recover within days if the drug is withdrawn in time.[3]

1. Mullick FG, McAllister HA. Myocarditis associated with methyldopa therapy. *J AMA* 1977; **237:** 1699–1701. Correction. *ibid.*; **238:** 399.
2. Seeverens H, *et al.* Myocarditis and methyldopa. *Acta Med Scand* 1982; **211:** 233–5.
3. Anonymous. Myocarditis related to drug hypersensitivity. *Lancet* 1985; **ii:** 1165–6.

Effects on the liver. In a report of 6 cases of hepatitis in patients taking methyldopa, including a review of 77 cases from the literature,[1] most patients presented with symptoms including malaise, fatigue, anorexia, weight loss, nausea, and vomiting, and histopathological changes resembling those of viral hepatitis. Fever occurred in 28 of the 83 patients; rashes and eosinophilia occurred rarely. Symptoms usually began 1 to 4 weeks after the first dose of methyldopa. Clinically apparent jaundice occurred as early as 1 week and as late as 3 years after the start of therapy, although only 6 or 7 patients presented with jaundice later than 3 months. Liver damage was not dose-related and had features suggestive of an immunologically-mediated hypersensitivity reaction. The histological changes included chronic active hepatitis, massive fatal necrosis, and cirrhosis.

In a further analysis of 36 patients with liver damage due to methyldopa, hepatic injury tended to occur in 2 phases—acute and chronic.[2] Acute damage developed within a few months of starting treatment, and was considered to be an allergic reaction to methyldopa metabolites. The chronic form usually occurred at least a year after starting methyldopa, and was characterised by an accumulation of fat in the liver. Recovery after withdrawal of methyldopa was directly related to duration of exposure and degree of

liver damage. There was also a suggestion of genetic predisposition, as acute methyldopa-induced liver damage occurred in 4 members of a family. Idiosyncratic metabolism of methyldopa in susceptible patients may be responsible for expression of an antigen on the surface of liver cells with which circulating antibodies react.[3]

See also Fever, below.

1. Rodman JS, *et al.* Methyldopa hepatitis: a report of six cases and review of the literature. *Am J Med* 1976; **60:** 941–8.
2. Sotaniemi EA, *et al.* Hepatic injury and drug metabolism in patients with alpha-methyldopa-induced liver damage. *Eur J Clin Pharmacol* 1977; **12:** 429–35.
3. Neuberger J, *et al.* Antibody mediated hepatocyte injury in methyldopa induced hepatotoxicity. *Gut* 1985; **26:** 1233–9.

Effects on mental function. Anecdotal reports have implicated methyldopa in disturbances of mental acuity including inability to concentrate, impaired calculating ability, and forgetfulness.[1-3] These have been confirmed to some extent by psychometric studies. Impaired verbal but not visual memory has been reported in 10 patients receiving methyldopa with a diuretic.[4] A crossover study in 16 patients also indicated impairment of cognitive function by methyldopa.[5]

1. Adler S. Methyldopa-induced decrease in mental activity. *JAMA* 1974; **230:** 1428–9.
2. Ghosh SK. Methyldopa and forgetfulness. *Lancet* 1976; **i:** 202–3.
3. Fernandez PG. Alpha methyldopa and forgetfulness. *Ann Intern Med* 1976; **85:** 128.
4. Solomon S, *et al.* Impairment of memory function by antihypertensive medication. *Arch Gen Psychiatry* 1983; **40:** 1109–12.
5. Johnson B, *et al.* Effects of methyldopa on psychometric performance. *J Clin Pharmacol* 1990; **30:** 1102–5.

DEPRESSION. Depression has been associated with methyldopa therapy, although the exact relationship is unclear.[1] One review[2] reported the incidence to be 3.6% and suggested that depression was more common in patients with a previous history.

1. Patten SB, Love EJ. Drug-induced depression. *Drug Safety* 1994; **10:** 203–19.
2. Paykel ES, *et al.* Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol* 1982; **2:** 14–39.

Effects on the nervous system. Involuntary choreoathetotic movements resembling those of Huntington's chorea began in a 59-year-old man with cerebrovascular disease after an increase of his methyldopa dose from 1 to 1.5 g daily. He recovered when the drug was withdrawn.[1] In another report methyldopa was associated with the development of bilateral choreiform movements in a patient without cerebrovascular disease but with chronic renal failure.[2]

1. Yamadori A, Albert ML. Involuntary movement disorder caused by methyldopa. *N Engl J Med* 1972; **286:** 610.
2. Neil EM, Waters AK. Generalized choreiform movements as a complication of methyldopa therapy in chronic renal failure. *Postgrad Med J* 1981; **57:** 732–3.

Effects on sexual function. Methyldopa has been associated with many cases of sexual dysfunction. In males failure to maintain erection, decreased libido, impaired ejaculation, and gynaecomastia have occurred, while in females decreased libido, painful breast enlargement, and delayed or absent orgasm have been reported.[1] The reported incidence varies and there is some evidence[2] that sexual dysfunction may be underreported: while only 2 of 30 men receiving methyldopa spontaneously reported erection failure the actual incidence on questioning was 16 of 30.

1. Stevenson JG, Umstead GS. Sexual dysfunction due to antihypertensive agents. *Drug Intell Clin Pharm* 1984; **18:** 113–21.
2. Alexander WD, Evans JI. Side effects of methyldopa. *BMJ* 1975; **2:** 501.

Fever. In a report of 78 cases of methyldopa-induced fever,[1] fever occurred 5 to 35 days after the first exposure to methyldopa in 77 patients and 1 day after restarting methyldopa in the remaining patient. Rigors, headache, and myalgia were common accompanying symptoms, but eosinophilia and skin rashes were not seen. The majority of patients did not appear seriously ill, but 4 patients presented with symptoms of septic shock. Biochemical evidence of liver damage was found in 61% of patients but jaundice was uncommon. In the majority of patients, symptoms were relieved within 48 hours of stopping the drug.

1. Stanley P, Mijch A. Methyldopa: an often overlooked cause of fever and transient hepatocellular dysfunction. *Med J Aust* 1986; **144:** 603–5.

Lupus erythematosus. The incidence of antinuclear antibodies was 13% in 269 hypertensive patients taking methyldopa (irrespective of other medication), compared with 3.8% in 448 hypertensive patients not taking methyldopa.[1] However, methyldopa-induced lupus has been reported[2] only rarely.

1. Wilson JD, *et al.* Antinuclear antibodies in patients receiving non-practolol beta-blockers. *BMJ* 1978; **1:** 14–16.
2. Dupont A, Six R. Lupus-like syndrome induced by methyldopa. *BMJ* 1982; **285:** 693–4.

Overdosage. Ingestion of methyldopa 2.5 g produced coma, hypothermia, hypotension, bradycardia, and dry mouth in a 19-year-old man.[1] His serum-methyldopa concentration 10 hours after ingestion was 19.2 micrograms/mL compared with serum concentrations of about 2 micrograms/mL in patients receiving therapeutic doses of methyldopa. He recovered after treatment with intravenous fluids.

1. Shnaps Y, *et al.* Methyldopa poisoning. *J Toxicol Clin Toxicol* 1982; **19:** 501–3.

Retroperitoneal fibrosis. A 60-year-old patient developed retroperitoneal fibrosis and a positive direct Coombs' test associated with methyldopa given in a daily dose of 750 mg with bendroflumethiazide 2.5 mg for about 5 years.[1]

1. Iversen BM, *et al.* Retroperitoneal fibrosis during treatment with methyldopa. *Lancet* 1975; **ii:** 302–4.

Treatment of Adverse Effects

Withdrawal of methyldopa or reduction in dosage causes the reversal of many adverse effects. If overdosage occurs, the benefit of gastric decontamination is uncertain, but patients who present within 1 hour may be given activated charcoal. Treatment is largely symptomatic, but if necessary, intravenous fluid infusions may be given to promote urinary excretion, and vasopressors given cautiously. Atropine may be given for bradycardia. Severe hypotension may respond to placing the patient in the supine position with the feet raised.

Methyldopa is dialysable.

Precautions

Methyldopa should be used with caution in the elderly, and in patients with hepatic or renal impairment or with a history of haemolytic anaemia, liver disease, or depression. Care is also advisable in patients with parkinsonism. It should not be given to patients with active liver disease or depression and it is not recommended for phaeochromocytoma.

It is advisable to make periodic blood counts and to perform liver function tests at intervals during the first 6 to 12 weeks of treatment or if the patient develops an unexplained fever. Patients taking methyldopa may produce a positive response to a direct Coombs' test; if blood transfusion is required, prior knowledge of a positive direct Coombs' test reaction will aid cross-matching.

Methyldopa may cause sedation; if affected, patients should not drive or operate machinery.

Breast feeding. Methyldopa is distributed into breast milk in small amounts.[1] In a study[2] of 3 breast-feeding women, concentrations of free methyldopa in the breast milk were found to be between 19 and 30% of those in the plasma after a 500-mg dose. Detectable concentrations were found in the plasma of only 1 infant and adverse effects were seen in none. It was estimated that the amount of methyldopa a breast-fed infant would receive would be about 0.02% of the maternal dose. In another study[3] over a 3-month period no adverse effects were found in a breast-feeding infant whose mother was taking methyldopa, although the drug was detectable in the infant's urine. The American Academy of Pediatrics considers[4] that methyldopa is therefore usually compatible with breast feeding.

1. Jones HMR, Cummings AJ. A study of the transfer of α -methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; **6:** 432–4.
2. White WB, *et al.* Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants. *Clin Pharmacol Ther* 1985; **37:** 387–90.
3. Hauser GJ, *et al.* Effect of α -methyldopa excreted in human milk on the breast-fed infant. *Helv Paediatr Acta* 1985; **40:** 83–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the laevo-isomer of methyldopa as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients. Racemic methyldopa is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. Methyldopa is commonly used in the management of hypertension during pregnancy (p. 1251.1). There is little evidence of adverse effects on fetal development. However, it crosses the placenta[1] and reduced blood pressure has been reported in infants born to mothers receiving the drug.[2] There has also been a report of tremor in 7 infants associated with maternal methyldopa use in pregnancy.[3] Depressed noradrenaline concentrations in the CSF were noted in the 3 infants examined leading to successful treatment of the other 4 infants with atropine: tremor was abolished in 2 and substantially reduced in the other 2. Suppurative parotitis occurred[4] in a CMV-infected neonate whose mother took methyldopa throughout pregnancy. Autoantibodies were detected[5] in another neonate whose mother had taken methyldopa throughout pregnancy, although it seemed likely that they had crossed the placenta from the mother, who also tested positive, rather than being produced by the fetus itself.

1. Jones HMR, Cummings AJ. A study of the transfer of α -methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; **6:** 432–4.
2. Whitelaw A. Maternal methyldopa treatment and neonatal blood pressure. *BMJ* 1981; **283:** 471.
3. Bódis J, *et al.* Methyldopa in pregnancy hypertension and the newborn. *Lancet* 1982; **ii:** 498–9.
4. Todoroki Y, *et al.* Neonatal suppurative parotitis possibly associated with congenital cytomegalovirus infection and maternal methyldopa administration. *Pediatr Int* 2006; **48:** 185–6.
5. Özdemir ÖMA, *et al.* A newborn with positive antiglobulin test whose mother took methyldopa in pregnancy. *Turk J Pediatr* 2008; **50:** 592–4.

Interactions

The hypotensive effects of methyldopa are potentiated by diuretics, other antihypertensives, and drugs with hypotensive effects. However, there have been reports of paradoxical antagonism of the hypotensive effects by tricyclic antidepressants, antipsychotics, and beta blockers. Sympathomimetics may also antagonise the hypotensive effects.

There may be an interaction between methyldopa and MAOIs and care is required if they are given together. Caution is also needed with catechol-*O*-methyltransferase inhibitors, such as entacapone, since they might reduce the metabolism of methyldopa.

Patients receiving methyldopa may require lower doses of general anaesthetics.

Alpha blockers. Urinary incontinence occurred when methyldopa was given with *phenoxybenzamine* in a patient who had undergone bilateral lumbar sympathectomy.[1]

1. Fernandez PG, *et al.* Urinary incontinence due to interaction of phenoxybenzamine and α -methyldopa. *Can Med Assoc J* 1981; **124:** 174–5.

Antipsychotics. Antipsychotics may enhance the hypotensive effects of methyldopa but a paradoxical increase in blood pressure has also been reported. A woman with SLE taking *trifluoperazine* up to 15 mg daily and prednisone up to 120 mg daily was given methyldopa up to 2 g and triamterene for high blood pressure.[1] Her blood pressure rose further to 200/140 mmHg. After stopping trifluoperazine blood pressure returned to 160/100 mmHg.

In another report, 2 patients with essential hypertension who had been taking methyldopa for 3 years and 18 months respectively developed symptoms of dementia within days of taking *haloperidol* for anxiety.[2] In both patients the symptoms resolved rapidly on stopping haloperidol.

1. Westervelt FB, Atuk NO. Methyldopa-induced hypertension. *JAMA* 1974; **227:** 557.
2. Thornton WE. Dementia induced by methyldopa with haloperidol. *N Engl J Med* 1976; **294:** 1222.

Cephalosporins. A pustular pruritic eruption occurred after use of *cefazolin* by a patient taking methyldopa.[1] A previous similar case involved use of *cefradine* with methyldopa.

1. Stough D, *et al.* Pustular eruptions following administration of cefazolin: a possible interaction with methyldopa. *J Am Acad Dermatol* 1987; **16:** 1051–2.

Digoxin. Syncope associated with carotid sinus hypersensitivity has been reported to be possibly enhanced by methyldopa in a patient taking digoxin and chlortalidone.[1] In another report,[2] sinus bradycardia developed in 2 patients taking methyldopa and digoxin.

1. Bauernfeind R, *et al.* Carotid sinus hypersensitivity with alpha methyldopa. *Ann Intern Med* 1978; **88:** 214–15.
2. Davis JC, *et al.* Sinus node dysfunction caused by methyldopa and digoxin. *JAMA* 1981; **245:** 1241–3.

Iron. After results in healthy subjects indicated that the absorption of methyldopa was reduced by 73% and 61% respectively when taken with a dose of *ferrous sulfate* or *ferrous gluconate*, 5 hypertensive patients taking methyldopa were also given ferrous sulfate 325 mg three times daily for 2 weeks.[1] All patients had a rise in systolic pressure, and 4 had a rise in diastolic pressure, amounting to more than 15/10 mmHg in some patients after 2 weeks. Blood pressure fell again when the ferrous sulfate was stopped.

1. Campbell N, *et al.* Alteration of methyldopa absorption, metabolism, and blood pressure control caused by ferrous sulfate and ferrous gluconate. *Clin Pharmacol Ther* 1988; **43:** 381–6.

Levodopa. For reference to a mutual interaction between methyldopa and levodopa, see Antihypertensives, under Levodopa, Interactions, p. 907.2.

Lithium. For reference to the development of lithium toxicity when given with methyldopa, see p. 432.2.

Sympathomimetics. A 31-year-old man whose hypertension was well controlled with methyldopa and oxprenolol suffered a severe hypertensive episode when he took a preparation containing *phenylpropanolamine* for a cold.[1]

1. McLaren EH. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxprenolol. *BMJ* 1976; **2:** 283–4.

Pharmacokinetics

After oral use methyldopa is variably and incompletely absorbed, apparently by an amino-acid active transport system. The mean bioavailability has been reported to be about 50%. It is extensively metabolised and is excreted in urine mainly as unchanged drug and the *O*-sulfate conjugate. It crosses the blood-brain barrier and is decarboxylated in the CNS to active alpha-methylnoradrenaline.

The elimination is biphasic with a half-life of about 1.7 hours in the initial phase; the second phase is more prolonged. Clearance is decreased and half-life prolonged in renal impairment. Plasma protein binding is reported to be minimal. Methyldopa crosses the placenta; small amounts are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aldomet; Dopagrand; Dopatral; ***Austral.***: Aldomet; Hydopa; ***Austria***: Aldometil; ***Belg.***: Aldomet; ***Braz.***: Aldomet; Aldotensin; Alfuzina; Angimet†; Cardiodopa; Dimipress; Dopametil; Ductomet; Etildopanan; Kindomet†; Metil-DT†; Metilpress; Metilprod†; Tensioval; Tildomet†; Venopressin; ***Canad.***: Novo-Medopa; Nu-Medopa; ***Cz.***: Dopegyt; ***Denm.***: Aldomet†; ***Fr.***: Aldomet; ***Ger.***: Dopegyt; Presinol; ***Gr.***: Aldomet; Dopatens; ***Hong Kong***: Dopamet; Dopatab†; Dopegyt; Hydopa†; ***Hung.***: Dopegyt; ***India***: Alphadopa; Dopagyt; Emdopa; Gynapres; ***Indon.***: Dopamet; Medopa†; ***Irl.***: Aldomet; ***Israel***: Aldomin; ***Ital.***: Aldomet; ***Malaysia***: Dopegyt; ***Mex.***: Aldomet; Amender; Hipermessel; Medopal†; Selm; Toparal; ***Neth.***: Aldomet†; ***Norw.***: Aldomet†; ***NZ***: Prodopa; ***Philipp.***: Aldomet; Dopamet; ***Pol.***: Dopegyt; ***Port.***: Aldomet; ***Rus.***: Dopegyt (Допегит); ***S.Afr.***: Aldomet†; Hy-Po-Tone; Normopress†; ***Singapore***: Aldomet; ***Spain***: Aldomet; ***Swed.***: Aldomet†; ***Switz.***: Aldomet; ***Thai.***: Adomet; Aldomet; Aldomine; Dopamed; Dopasian; Dopegyt†; Isomet; Medopa; Mefpa; Metpata; Nudopa; Siamdopa; ***Turk.***: Alfamet; ***UK***: Aldomet; ***Ukr.***: Dopegyt (Допегит); ***Venez.***: Aldomet.

Multi-ingredient Preparations. ***Braz.***: Hydromet; ***Canad.***: Apo-Methazide; PMS-Dopazide; ***Gr.***: Hydromet; Rabemylon; ***Ital.***: Medozide†; ***USA***: Aldoclor.

Pharmacopoeial Preparations

BP 2014: Methyldopa Tablets; Methyldopate Injection;
USP 36: Methyldopa and Chlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Methyldopa Oral Suspension; Methyldopa Tablets; Methyldopate Hydrochloride Injection.

Meticrane *(rINN)* ⊗

Méticrane; Meticrano; Meticranum; SD-17102; Метикран.
6-Methylthiochroman-7-sulphonamide 1,1-dioxide.
$C_{10}H_{13}NO_4S_2$=275.3
CAS — 1084-65-7.
ATC — C03BA09.
ATC Vet — QC03BA09.
UNII — I7EKN1924Q.

Pharmacopoeias. In *Jpn*.

Profile

Meticrane is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2). It is used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Arresten.

Metildigoxin *(BAN, rINN)*

Medigoxin; β-Methyl Digoxin; β-Methyldigoxin; Metildigoksiini; Metildigoxina; Métildigoxine; Metildigoxinum; Metyylidigoksiini; Метилдигоксин.
3β-[(*O*-2,6-Dideoxy-4-*O*-methyl-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide.
$C_{42}H_{66}O_{14}$=795.0
CAS — 30685-43-9.
ATC — C01AA08.
ATC Vet — QC01AA08.
UNII — I7GG1YUCSV.

Pharmacopoeias. In *Chin.* In *Jpn.* as $C_{42}H_{66}O_{14}$,½C_3H_6O.

Uses and Administration

Metildigoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (p. 1353.3) and may be used in the treatment of some cardiac arrhythmias (p. 1266.1) and in heart failure (p. 1262.3).

The onset of action of metildigoxin is more rapid than that of digoxin. When metildigoxin is given orally an effect may appear within 5 to 20 minutes and a maximum effect on the myocardium may be seen in 15 to 30 minutes. The duration of action is similar to or a little longer than that of digoxin; therapeutic plasma concentrations are also similar. In stabilised patients on oral therapy a dose of 300 micrograms of metildigoxin is as effective as 500 micrograms of digoxin.

Metildigoxin may be given orally or intravenously. Initial oral doses of 100 to 600 micrograms daily may be given depending upon whether rapid or slow digitalisation is desired; digitalisation is usually performed over about 2 to 5 days and the larger doses are given in divided daily doses. Similar doses may also be given intravenously. Oral maintenance therapy is continued with 50 to 400 micrograms daily in single or divided doses.

Dosage should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Fairly good non-linear correlation was found between creatinine clearance and metildigoxin half-life in a study of 15 patients with chronic renal impairment, including 8 undergoing haemodialysis, and 4 patients with heart failure and unimpaired renal function. The mean elimination half-life was 5.62 days in patients undergoing dialysis (clearance essentially 0 mL/minute) and 3.41 days in the other patients with chronic renal impairment (clearance 15 to 50 mL/minute) compared with 1.49 days in patients with normal renal function (clearance 62 to 96 mL/minute). It was recommended that patients undergoing dialysis should be given 30 to 50% of the usual dose initially.[1] Other studies have suggested[2] that dose reduction may be necessary in renal impairment when creatinine clearance is below 50 mL/minute per 1.48 m^2.

1. Trovato GM, *et al.* Relationship between β -methyl-digoxin pharmacokinetic and degree of renal impairment. *Curr Ther Res* 1983; **33:** 158–64.
2. Tsutsumi K, *et al.* Pharmacokinetics of beta-methyldigoxin in subjects with normal and impaired renal function. *J Clin Pharmacol* 1993; **33:** 154–60.

Adverse Effects, Treatment, and Precautions

As for Digoxin, p. 1354.3.

Interactions

As for Digoxin, p. 1356.1.

Calcium-channel blockers. For a report of an interaction between metildigoxin and *diltiazem*, see Calcium-channel Blockers, under Interactions of Digoxin, p. 1357.2.

Pharmacokinetics

Metildigoxin is rapidly and almost completely absorbed from the gastrointestinal tract and at steady state has a half-life of 36 to 47.5 hours. Demethylation to digoxin occurs. About 60% of an oral or intravenous dose is excreted in the urine as unchanged drug and metabolites over 7 days.

Hepatic impairment. Hepatic demethylation of metildigoxin was reduced in 12 patients with cirrhosis of the liver compared with 12 healthy subjects. This resulted in a reduction in metildigoxin clearance, a smaller volume of distribution, and a significantly higher serum concentration.[1]

1. Rameis H, *et al.* Changes in metildigoxin pharmacokinetics in cirrhosis of the liver: a comparison with β -acetyldigoxin. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 145–51.

Renal impairment. For reference to the pharmacokinetics of metildigoxin in patients with renal impairment, see under Uses and Administration, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lanitop; ***Belg.***: Lanitop; ***China***: Beikeli (贝可力); ***Ger.***: Lanitop; ***Gr.***: Lanitop; ***Hong Kong***: Lanitop†; ***Ital.***: Lanitop; ***Jpn***: Lanirapid; ***Pol.***: Bemecor; Medigox†; ***Port.***: Lanitop; ***Spain***: Lanirapid; ***Venez.***: Lanitop.

Metipamide ⊗

Metipamid; Metipamidum; VÚFB-14429.
3-(Aminosulfonyl)-4-chlorobenzoic acid 2-methyl-2-phenylhydrazide.
$C_{14}H_{14}ClN_3O_3S$=339.8
CAS — 85683-41-6.

Profile

Metipamide is a diuretic structurally related to indapamide (p. 1409.2); it is used as an antihypertensive.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Hypotylin.

Metirosine *(BAN, rINN)*

L-588357-0; Metirosiini; Metirosin; Metirosina; Métirosine; Metirosinum; Metyrosine (USAN); MK-781; Метирозин.
(-)-α-Methyl-L-tyrosine; 4-Hydroxy-α-methylphenylalanine.
$C_{10}H_{13}NO_3$=195.2
CAS — 672-87-7 (metirosine); 620-30-4 (racemetirosine).
ATC — C02KB01.
ATC Vet — QC02KB01.
UNII — DOQ0J0TPF7.

NOTE. The term α-methyltyrosine (α-MPT; α-MT; α-methyl-*p*-tyrosine; AMPT) is used below since although metirosine, the (-)-isomer, is the active form the manufacturers state that some racemate (racemetirosine; (±)-α-methyl-DL-tyrosine) is produced during synthesis but that the material supplied contains mainly (-)-isomer with a small amount of (+)-isomer.

The code name MK-781, applied to earlier investigational material, may have described a racemate or a preparation containing a smaller proportion of (-)-isomer than the product now available commercially.

Potency of the proprietary preparation (*Demser*) is expressed in terms of metirosine.

Pharmacopoeias. In *US*.

Uses and Administration

α-Methyltyrosine is an inhibitor of the enzyme tyrosine hydroxylase, and consequently of the synthesis of catecholamines. It is used to control the symptoms of excessive sympathetic stimulation in patients with phaeochromocytoma (p. 1278.1) and decreases the frequency and severity of hypertensive attacks and related symptoms in most patients. It may be given for pre-operative preparation, or for long-term management in those for whom surgery is contra-indicated or who have malignant phaeochromocytoma.

In the management of phaeochromocytoma, α-methyltyrosine is given orally in a dose of 250 mg four times daily, increased daily by 250 mg or 500 mg to a maximum of 4 g daily in divided doses. The optimum dose, achieved by monitoring clinical symptoms and catecholamine excretion, is usually in the range of 2 to 3 g daily and when used pre-operatively it should be given for at least 5 to 7 days before surgery. The use of alpha blockers may also be necessary.

α-Methyltyrosine is not effective in controlling essential hypertension.

α-Methyltyrosine has also been tried in patients with schizophrenia.

Adverse Effects

Sedation occurs in almost all patients receiving α-methyltyrosine. Other adverse effects include extrapyramidal symptoms, such as trismus and frank parkinsonism; anxiety, depression, and psychic disturbances including hallucinations, disorientation, and confusion; and diarrhoea, which may be severe. Crystalluria, transient dysuria, and haematuria have been seen in a few patients. There have also been occasional reports of slight swelling of the breast, galactorrhoea, nasal congestion, decreased salivation, gastrointestinal disturbances, headache, impotence or failure of ejaculation, and hypersensitivity reactions. Eosinophilia, raised serum aspartate aminotransferase, and peripheral oedema have been reported rarely.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome occurred after the use of the dopamine-deplet-

ing drugs tetrabenazine and α-methyltyrosine in a patient with Huntington's chorea.[1]

1. Burke RE, *et al.* Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. *Neurology* 1981; **31:** 1022–6.

Precautions

To minimise the risk of crystalluria, patients receiving α-methyltyrosine should have a fluid intake sufficient to maintain a urine volume of at least 2 litres daily and their urine should be examined regularly for the presence of crystals.

α-Methyltyrosine has sedative effects and patients should be warned of the hazards of driving a motor vehicle or operating machinery while receiving the drug. Symptoms of psychic stimulation and insomnia may occur when α-methyltyrosine is withdrawn.

When α-methyltyrosine is used pre-operatively in patients with phaeochromocytoma, blood pressure and the ECG should be monitored continuously during surgery as the danger of hypertensive crises and arrhythmias is not eliminated. Concomitant alpha blockade (e.g. with phentolamine) may be required; a beta blocker or lidocaine may be needed for the management of arrhythmias. Blood volume must be maintained during and after surgery, particularly if an alpha blocker is used, to avoid hypotension.

Interactions

The sedative effects of α-methyltyrosine may be potentiated by alcohol and other CNS depressants. Use with phenothiazines or haloperidol may exacerbate extrapyramidal effects.

Pharmacokinetics

α-Methyltyrosine is well absorbed from the gastrointestinal tract and is excreted mainly unchanged by the kidneys. A plasma half-life of 3.4 to 7.2 hours has been reported. Less than 1% of a dose may be excreted as the metabolites α-methyldopa, α-methyldopamine, α-methylnoradrenaline, and α-methyltyramine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Demser.

Pharmacopoeial Preparations
USP 36: Metyrosine Capsules.

Metolazone *(BAN, USAN, rINN)* ⊗

Metolatsoni; Metolazon; Metolazona; Métolazone; Metolazonum; SR-720-22; Метолазон.
7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolylquinazoline-6-sulphonamide.
$C_{16}H_{16}ClN_3O_3S$=365.8
CAS — 17560-51-9.
ATC — C03BA08.
ATC Vet — QC03BA08.
UNII — TZ7V40X7VX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Metolazone). A white or slightly yellowish, crystalline powder. It exhibits polymorphism. Very slightly soluble in water and dichloromethane; sparingly soluble in methyl alcohol; slightly soluble in ethyl acetate. Protect from light.

USP 36: (Metolazone). Store in airtight containers. Protect from light.

Uses and Administration

Metolazone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Unlike thiazides in general, metolazone is reported to be effective in patients with a glomerular filtration rate of less than 20 mL/minute. Diuresis starts in about 1 hour, reaches a peak in about 2 hours, and lasts for 12 to 24 hours depending on the dose.

In the treatment of **oedema** the usual dose is 5 to 10 mg daily; in some cases doses of 20 mg or more may be required. No more than 80 mg should be given in any 24-hour period. In refractory cases, metolazone has been used with furosemide or other loop diuretics, but the electrolyte balance should be monitored closely.

For doses in children, see below.

In the treatment of **hypertension** the usual dose is 2.5 to 5 mg daily either alone, or with other antihypertensives. An initial dose of 1.25 mg has also been used. The dosage may be adjusted after 3 to 4 weeks according to response. A maintenance dose of 5 mg on alternate days may be used.

A formulation with enhanced bioavailability has also been available and was given in doses of 0.5 to 1 mg daily in the treatment of hypertension.

Administration in children. A study in 14 children aged from 1.5 to 14 years with furosemide-resistant oedema found that the addition of metolazone at an oral dose of 400 to 800micrograms/kg daily in 2 divided doses safely induced diuresis. The two drugs appeared to work synergistically.[1]

Although metolazone is unlicensed in the UK for children, the *BNFC* suggests that it may be given in the treatment of oedema at the following oral doses according to age:

- 1 month to 12 years: 100 to 200 micrograms/kg once or twice daily
- 12 to 18 years: 5 to 10 mg once daily in the morning, increased to 5 to 10 mg twice daily in resistant oedema

1. Arnold WC. Efficacy of metolazone and furosemide in children with furosemide-resistant edema. *Pediatrics* 1984; **74:** 872–5.

Adverse Effects and Treatment

As for Hydrochlorothiazide, p. 1404.2. Metolazone has also been reported to cause palpitations, chest pain, and chills.

Effects on the blood. Profound neutropenia was seen in a 58-year-old woman within 10 days of starting treatment with metolazone.[1] Neutropenia persisted for a further 10 days after metolazone was withdrawn. No other haematological abnormalities were seen.

1. Donovan KL. Neutropenia and metolazone. *BMJ* 1989; **299:** 981.

Effects on the nervous system. Two patients had acute muscle cramps with impairment of consciousness and epileptiform movements after taking metolazone 5 mg (single dose) or 2.5 mg daily for 3 days.[1]

1. Fitzgerald MX, Brennan NJ. Muscle cramps, collapse, and seizures in two patients taking metolazone. *BMJ* 1976; **1:** 1381–2.

Precautions

As for Hydrochlorothiazide, p. 1406.1.

Interactions

As for Hydrochlorothiazide, p. 1406.1. Severe electrolyte disturbances may occur when metolazone and furosemide are used together.

ACE inhibitors. Deterioration in renal function occurred in a 65-year-old woman when metolazone 5 mg [daily] was added to *captopril*, furosemide, spironolactone, and digoxin for heart failure.[1] An interaction between captopril and metolazone was suspected and both drugs were stopped with a subsequent return to normal renal function. It was suggested that natriuresis and a fall in blood pressure caused by the diuretic may have compromised an already low renal perfusion pressure when autoregulatory mechanisms were blocked by captopril.

1. Hogg KJ, Hillis WS. Captopril/metolazone induced renal failure. *Lancet* 1986; **i:** 501–2.

Antidiabetics. Hypoglycaemia occurred in a patient with type 2 diabetes mellitus controlled with *glibenclamide* 40 hours after starting therapy with metolazone 5 mg daily.[1] Studies of protein binding *in vitro* did not reveal any evidence of displacement of glibenclamide from binding sites.

1. George S, *et al.* Possible protein binding displacement interaction between glibenclamide and metolazone. *Eur J Clin Pharmacol* 1990; **38:** 93–5.

Ciclosporin. An increase in serum-creatinine concentration in a renal transplant patient was attributed to a toxic drug interaction between metolazone and ciclosporin.[1] Serum-creatinine concentrations returned to pretreatment values when metolazone was stopped.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; **294:** 578.

Pharmacokinetics

Metolazone is slowly and incompletely absorbed from the gastrointestinal tract. An average of about 65% of a dose has been reported to be absorbed after oral doses in healthy subjects, and an average of about 40% in patients with cardiac disease. In some countries a formulation with enhanced bioavailability is available. About 95% of the drug is bound in the circulation: about 50 to 70% to the red blood cells and between 15 and 33% to plasma proteins. The half-life has been reported to be 8 to 10 hours in whole blood, and 4 to 5 hours in plasma, but the diuretic effect persists for up to 24 hours or more. About 70 to 80% of the amount of metolazone absorbed is excreted in the urine, of which 80 to 95% is excreted unchanged. The remainder is excreted in the bile and some enterohepatic circulation has been reported. Metolazone crosses the placenta and is distributed into breast milk.

References.

1. Tilstone WJ, *et al.* Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther* 1974; **16:** 322–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Zaroxolyn; ***Chile***: Pavedal; ***Gr.***: Metenix; ***Hong Kong***: Zaroxolyn; ***India***: Diurem; Mela; Metadure; Metoral; Metoz; ***Israel***: Zaroxolyn; ***Ital.***: Zaroxolyn; ***Port.***: Diulo; ***Singapore***: Metenix; ***UK***: Metenix†; ***USA***: Mykrox; Zaroxolyn.

Pharmacopoeial Preparations
USP 36: Metolazone Oral Suspension; Metolazone Tablets.

Metoprolol *(BAN, USAN, rINN)* ⊗

Métoprolol; Metoprololi; Metoprololum; Метопролол.
(±)-1-Isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.
$C_{15}H_{25}NO_3$=267.4
CAS — 54163-88-1; 37350-58-6.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — GEB06NHM23.

Metoprolol Fumarate *(BANM, USAN, rINNM)* ⊗

CGP-2175C; Fumarato de metoprolol; Métoprolol, Fumarate de; Metoprolol, fumarato de; Metoprololi Fumaras; Метопролола Фумарат.
$(C_{15}H_{25}NO_3)_2,C_4H_4O_4$=650.8
CAS — 119637-66-0.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — IO1C09Z674.

Pharmacopoeias. In *US.*

USP 36: (Metoprolol Fumarate). A 10% solution in water has a pH of between 5.5 and 6.5. Store in airtight containers. Protect from light.

Metoprolol Succinate *(BANM, USAN, rINNM)* ⊗

Métoprolol, succinate de; Metoprolol, succinato de; Metoprolol Süksinat; Metoprololi Succinas; Metoprololio sukcinatas; Metoprololisuksinaatti; Metoprololsuccinat; Metoprolol-sukcinát; Metoprolol-szukcinát; Succinato de metoprolol; Метопролола Суксинат.
$(C_{15}H_{25}NO_3)_2,C_4H_6O_4$=652.8
CAS — 98418-47-4.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — TH25PD4CCB.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Metoprolol Succinate). A white or almost white crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; very slightly soluble in ethyl acetate. A 2% solution in water has a pH of between 7.0 and 7.6. Protect from light.

USP 36: (Metoprolol Succinate). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol. A 6.5% solution in water has a pH of between 7.0 and 7.6. Store in airtight containers at controlled room temperature.

Metoprolol Tartrate *(BANM, USAN, rINNM)* ⊗

CGP-2175E; H-93/26; Metoprolol Tartarat; Metoprolol tartarát; Métoprolol, Tartrate de; Metoprolol, tartrato de; Metoprololi Tartras; Metoprololio tartratas; Metoprololitartraatti; Metoprolol-tartarát; Metoprololtartrat; Tartrato de metoprolol; Метопролола Тартрат.
$(C_{15}H_{25}NO_3)_2,C_4H_6O_6$=684.8
CAS — 56392-17-7.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — W5S57Y3A5L.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Metoprolol Tartrate). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of between 6.0 and 7.0. Protect from light.

USP 36: (Metoprolol Tartrate). A white crystalline powder. Very soluble in water; freely soluble in alcohol, in

chloroform, and in dichloromethane; slightly soluble in acetone; insoluble in ether. A 10% solution in water has a pH of between 6.0 and 7.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Stability. Metoprolol tartrate 400 micrograms/mL in glucose 5% or sodium chloride 0.9% was stable for 36 hours when stored at 24 degrees in PVC bags.[1]

1. Belliveau PP, *et al.* Stability of metoprolol tartrate in 5% dextrose injection or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1993; **50:** 950–2.

Uses and Administration

Metoprolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and to have little or no membrane-stabilising activity.

It is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), myocardial infarction (p. 1257.1), and heart failure (p. 1262.3). It is also used in the management of hyperthyroidism (p. 2332.2) and in the prophylactic treatment of migraine (p. 670.3).

Metoprolol is given orally and intravenously as the tartrate. Modified-release tablets usually contain the tartrate or the succinate, but the fumarate has also been used. Doses are usually expressed in terms of the tartrate; 95 mg of metoprolol fumarate or metoprolol succinate is equivalent to about 100 mg of metoprolol tartrate.

The bioavailability of metoprolol is increased if taken with food and it has been recommended that some preparations are taken with or immediately after a meal.

Reduced doses should be given to patients with hepatic impairment.

In **hypertension** metoprolol tartrate is usually given in an initial oral dose of 100 mg daily, as a single dose or in two divided doses. The dose may be increased weekly, according to response; the usual maintenance dose is 100 to 200 mg daily, but up to 400 mg daily may be given.

The usual oral dose for **angina pectoris** is 50 to 100 mg two or three times daily.

In the treatment of **cardiac arrhythmias** the usual oral dose is 50 mg two or three times daily, increased if necessary up to 300 mg daily in divided doses.

For the emergency treatment of cardiac arrhythmias metoprolol tartrate may be given intravenously in an initial dose of up to 5 mg, at a rate of 1 to 2 mg/minute; this may be repeated, if necessary, at intervals of 5 minutes to a total dose of 10 to 15 mg.

Arrhythmias may be prevented on induction of anaesthesia, or controlled during anaesthesia, by the slow intravenous injection of 2 to 4 mg; further injections of 2 mg may be repeated as necessary to a maximum total dose of 10 mg.

Metoprolol is also used as an adjunct in the early management of acute **myocardial infarction.** Treatment should be given within 12 hours of the onset of chest pain; metoprolol tartrate 5 mg should be given intravenously at 2-minute intervals to a total of 15 mg, where tolerated. After 15 minutes, in patients who have received the full intravenous dose, oral treatment should be started; 50 mg is given every 6 hours for 2 days. In patients who have failed to tolerate the full intravenous dose a reduced oral dose should be given as, and when, their condition permits. Subsequent oral maintenance dosage is 100 mg given twice daily. In patients not given metoprolol by intravenous injection as part of the early management of myocardial infarction, metoprolol may be started once the clinical condition of the patient stabilises, in a dose of 200 mg daily in 2 or 4 divided doses.

In the management of stable, symptomatic **heart failure** metoprolol succinate may be given as an oral modified-release preparation. The initial dose is the equivalent of metoprolol tartrate 12.5 to 25 mg once daily, increased as tolerated, at intervals of 2 weeks, with a target dose of 200 mg once daily.

As an adjunct in the treatment of **hyperthyroidism** metoprolol tartrate may be given in oral doses of 50 mg four times daily. Doses of 100 to 200 mg are given daily in divided doses for **migraine** prophylaxis.

General references.

1. Plosker GL, Clissold SP. Controlled release metoprolol formulations: a review of their pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. *Drugs* 1992; **43:** 382–414.
2. Prakash A, Markham A. Metoprolol: a review of its use in chronic heart failure. *Drugs* 2000; **60:** 647–78.
3. Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. *Ann Pharmacother* 2003; **37:** 701–10.
4. Papadopoulos DP, Papademetriou V. Metoprolol succinate combination in the treatment of hypertension. *Angiology* 2009; **60:** 608–13.

Administration in children. Metoprolol has been used in children, although experience is limited. A study[1] in children aged 6 to 16 years with hypertension found that modified-release metoprolol succinate was well tolerated in doses of up to the equivalent of metoprolol tartrate 2 mg/kg daily, although efficacy was not established. US licensed product information nevertheless allows the use of oral doses of metoprolol succinate once daily in children aged 6 to 16 years; the initial dose is the equivalent of metoprolol tartrate 1 mg/kg daily (maximum 50 mg), adjusted according to response to a maximum of 2 mg/kg (not more than 200 mg) daily.

The *BNFC* recommends that for hypertension children aged 1 month to 12 years may be given standard formulations of metoprolol tartrate in an initial dose of 1 mg/kg twice daily orally, increased if necessary to a maximum dose of 8 mg/kg daily in 2 to 4 divided doses. Children over 12 years may be given the adult dose (see above).

1. Batisky DL, *et al.* Efficacy and safety of extended release metoprolol succinate in hypertensive children 6 to 16 years of age: a clinical trial experience. *J Pediatr* 2007; **150:** 134–9.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Studies[1-3] have shown that the concentration of metoprolol distributed into breast milk is higher than that in plasma. However, the amount ingested by an infant is likely to be small, and the concentration of metoprolol in infant plasma has been found[3] to be undetectable or very low. No adverse effects have been seen in breast-fed infants whose mothers were given metoprolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Sandström B, Regårdh C-G. Metoprolol excretion into breast milk. *Br J Clin Pharmacol* 1980; **9:** 518–19.
2. Liedholm H, *et al.* Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 229–31.
3. Kulas J, *et al.* Atenolol and metoprolol: a comparison of their excretion into human breast milk. *Acta Obstet Gynecol Scand Suppl* 1984; **118:** 65–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on hearing. Loss of hearing in a patient receiving metoprolol appeared to be dose-related;[1] hearing gradually improved over several months once the drug was withdrawn.

1. Fäldt R, *et al.* β Blockers and loss of hearing. *BMJ* 1984; **289:** 1490–2.

Effects on lipid metabolism. Beta blockers may increase serum-triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in a patient taking metoprolol followed by atenolol, see p. 1320.1.

Effects on the liver. Acute hepatitis associated with metoprolol has been reported in a 56-year-old woman.[1] The hepatotoxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.

For a discussion of the relationship between polymorphic oxidation of metoprolol and the incidence of adverse effects, see Metabolism, under Pharmacokinetics, below.

1. Larrey D, *et al.* Metoprolol-induced hepatitis: rechallenge and drug oxidation phenotyping. *Ann Intern Med* 1988; **108:** 67–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metoprolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Surgery. The oral bioavailability, rate of absorption, AUC, and peak plasma concentrations of metoprolol were significantly reduced in 12 patients after coronary artery bypass surgery, and did not return to their pre-operative levels until the third postoperative day.[1] The authors warned of the possibility of inducing beta-blocker withdrawal syndrome (p. 1321.2), and suggested that the intravenous route may be more appropriate in surgical patients requiring beta blockers.

1. Valtola A, *et al.* Does coronary artery bypass surgery affect metoprolol bioavailability. *Eur J Clin Pharmacol* 2007; **63:** 471–8.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of metoprolol and that the dose of metoprolol may need to be reduced if used together.

Pharmacokinetics

Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. It is moderately lipid-soluble.

Metoprolol is widely distributed; it crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is about 12% bound to plasma protein. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, *O*-dealkylation followed by oxidation, and aliphatic hydroxylation. The metabolites are excreted in the urine with only small amounts of unchanged metoprolol. The rate of metabolism by CYP2D6 is determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3 to 4 hours, whereas in poor hydroxylators it is about 7 hours.

The elderly. Several studies[1-3] indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol.

1. Quarterman CP, *et al.* The effect of age on the pharmacokinetics of metoprolol and its metabolites. *Br J Clin Pharmacol* 1981; **11:** 287–94.
2. Regårdh CG, *et al.* Pharmacokinetics of metoprolol and its metabolite α-OH-metoprolol in healthy, non-smoking, elderly individuals. *Eur J Clin Pharmacol* 1983; **24:** 221–6.
3. Larsson M, *et al.* Pharmacokinetics of metoprolol in healthy, elderly, non-smoking individuals after a single dose and two weeks of treatment. *Eur J Clin Pharmacol* 1984; **27:** 217–22.

Metabolism. Metoprolol is metabolised by the cytochrome P450 isoenzyme CYP2D6 and therefore shows a debrisoquine-type genetic polymorphism.[1-3] Poor, intermediate, extensive, and ultrarapid metabolisers of metoprolol have been identified, and studies[4-6] have confirmed that plasma-metoprolol concentrations correlate with metaboliser status. However, the clinical relevance of these differences is less clear. Subtherapeutic levels have been reported[7] in extensive metabolisers, while a fivefold higher risk of adverse effects[8] and significantly greater reductions in heart rate and blood pressure[9] have been reported among poor metabolisers. However, other studies[10,11] have found no correlation between the incidence of adverse effects and metaboliser status, and controlled studies in patients with hypertension[5] and in healthy subjects[4] have found that there is little or no relationship between plasma concentrations or metaboliser status and either the incidence of adverse effects or the response to therapy.

The subject may be further confused by variations in the phenotype between ethnic groups. Although the incidence of the poor metaboliser phenotype in whites of European origin is reported to be about 9%, a study in 138 Nigerians[12] failed to identify evidence of polymorphic metabolism, and the authors caution against extrapolation of data between different racial groups.

1. Lennard MS, *et al.* Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1982; **14:** 301–3.
2. Lennard MS, *et al.* Oxidation phenotype—a major determinant of metoprolol metabolism and response. *N Engl J Med* 1982; **307:** 1558–60.
3. McGourty JC, *et al.* Metoprolol metabolism and debrisoquine oxidation polymorphism—population and family studies. *Br J Clin Pharmacol* 1985; **20:** 555–66.
4. Kirchheiner J, *et al.* Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2004; **76:** 302–12.
5. Zineh I, *et al.* Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther* 2004; **76:** 536–44.
6. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *J Clin Pharm Ther* 2006; **31:** 99–109.
7. Goryachkina K, *et al.* CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. *Eur J Clin Pharmacol* 2008; **64:** 1163–73.
8. Wuttke H, *et al.* Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* 2002; **72:** 429–37.
9. Rau T, *et al.* Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a prospective longitudinal study. *Clin Pharmacol Ther* 2009; **85:** 269–72.
10. Clark DWJ, *et al.* Adverse effects from metoprolol are not generally associated with oxidation status. *Br J Clin Pharmacol* 1984; **18:** 965–6.
11. Fux R, *et al.* Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther* 2005; **78:** 378–87.
12. Iyun AO, *et al.* Metoprolol and debrisoquin metabolism in Nigerians: lack of evidence for polymorphic oxidation. *Clin Pharmacol Ther* 1986; **40:** 387–94.

Pregnancy. The clearance of metoprolol was increased fourfold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant state.[1]

The disposition of metoprolol was investigated in neonates of mothers treated with metoprolol 50 to 100 mg twice daily.[2] In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the postnatal period, then declined over the next 15 hours; 5 of these infants had no detectable metoprolol concentrations

in the umbilical plasma. No infant showed signs of beta blockade.

1. Högstedt S, *et al.* Increased oral clearance of metoprolol in pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 217–20.
2. Lundborg P, *et al.* Disposition of metoprolol in the newborn. *Br J Clin Pharmacol* 1981; **12:** 598–600.

Renal impairment. A single dose of a modified-release tablet of metoprolol produced similar plasma-metoprolol concentrations and values for the area under the concentration/time curve in both normal subjects and those with renal impairment.[1] Mean plasma concentrations of the metabolite α-hydroxymetoprolol were increased two to threefold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blockade.

1. Lloyd P, *et al.* The effect of impaired renal function on the pharmacokinetics of metoprolol after single administration of a 14/190 metoprolol OROS system. *Am Heart J* 1990; **120:** 478–82.

Surgery. Oral bioavailability of metoprolol may be significantly reduced after surgery—see under Adverse Effects, Treatment, and Precautions, p. 1435.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Belozok; Lopresor; ***Austral.***: Betaloc; Lopresor; Metohexal; Metrol; Minax; Toprol; ***Austria***: Beloc; Lanoc; Metohexal; Seloken; ***Belg.***: Lopresor; Selo-Zok; Seloken; Slow-Lopresor; ***Braz.***: Lopressor; Miclox; Selo-Zok; Seloken; ***Canad.***: Betaloc; Lopresor; Novo-Metoprol†; Nu-Metop; ***Chile***: Betaloc Zok; ***China***: Betaloc (倍他乐克); JunQing (均青); Meng De Kang (蒙得康); Shumeng (舒梦); Tuo Xi Er Kang (托西尔康); ***Cz.***: Belenzok†; Betaloc; Egilok; Emzok; Lidazoc; Vasocardin; ***Denm.***: Betaloc Zok†; Isalok; Mepronet; Mertolok; Metocar; Metomylan; Metoratio; Metostad; Rukolok; Selo-Zok; Seloken; ***Fin.***: Metohexal; Metomylan; Metoprolin; Seloken ZOC; Seloken; Selopral; Spesicor; Spesimax; ***Fr.***: Lopressor; Seloken; Selozok; ***Ger.***: Beloc-Zok; Beloc; Jeprolol; Jutabloc†; Lopresor; Meprolol; Meto-Succinat†; Meto-Tablinen†; Meto; Metobeta; Metodoc†; Metohexal†; Metoprogamma; Prelis; ***Gr.***: Inophylin; Lofarbil; Lopresor; Styralonax; Venolone; ***Hong Kong***: Betaloc; CP-Metolol†; Minax; Novo-Metoprol†; Sefloc†; ***Hung.***: Betaloc; Egilok; ***India***: Actiblok-IPR; Betacon; Betaloc; Betaone; Blumet; CGRol; Embeta; Gudpres; Intramet; Kimet; Libmet; Lopresor; Lopressor; Mepol; Met; Metapro; Meto; Metocard; Metocare; Metofin; Metolar; Metomac; Metosafe; Metzok; Mexes; Motoblock; MT-Loc; Revelol; Selopres; ***Indon.***: Cardiosel†; Lopresor; Loprolol; Seloken; ***Irl.***: Betaloc; Lopresor†; Metocor; Metop; ***Israel***: Lopresor; Neobloc; ***Ital.***: Lopresor; Seloken; ***Jpn***: Seloken; ***Malaysia***: Betaloc; Betawin; Denex; ***Mex.***: Bioprol; Eurolol; Futaline; Kenaprol; Lopresor; Metopresol; Proken M; Prolaken†; Promiced; Prontol; Ritmolol; Selectadril; Seloken; Sermetrol; Tiazidol†; ***Neth.***: Selokeen; ***Norw.***: Selo-Zok; Seloken; ***NZ***: Betaloc; Lopresor; Myloc; Slow-Lopresor; ***Philipp.***: Angimet; Angiobloc; Angionorm; Betaloc; Betaryx; Betazok; Cardiosel; Cardiostat; Cardiotab; Carditec; Gerbloc; Hypetor; Hyprofil; Metobloc; Metocare; Metoprim; Metospec; Metostad; Montebloc; Neobloc; Prolohex†; Valvexin; Zionel; ***Pol.***: Betaloc; Beto; Metocard; Metogen; Metohexal†; ***Port.***: Lopresor; ***Rus.***: Betaloc (Беталок ЗОК); Corvitol (Корвадил); Egilok (Эгилок); Emzok (Эмзок); Metocard (Метокард); Serdol (Сердол); Vasocardin (Вазокардин); ***S.Afr.***: Lopresor; ***Singapore***: Betaloc†; Denex; Sefloc; ***Spain***: Beloken; Lopresor; ***Swed.***: Metomylan; Metoratio†; Seloken ZOC; Seloken; ***Switz.***: Beloc-Zok; Beloc; Lopresor; Meto Zerok; Metopress; ***Thai.***: Betaloc; Cardeloc; Cardoxone; Meloc; Melol; Metoblock; Metolol†; Metprolol; Minax†; Sefloc; ***Turk.***: Beloc; Lopresor; Problok; Saneloc; ***UK***: Betaloc; Lopresor; ***Ukr.***: Anepro (Анепро)†; Betaloc (Беталок); Corvitol (Корвитол); Egilok (Эгилок); ***USA***: Lopressor; Toprol; ***Venez.***: Lopresor.

Multi-ingredient Preparations. ***Austria***: Beloc comp†; Metoprolol compositum; Seloken retard Plus; Triloc†; ***Belg.***: Logimat; Logroton; Zok-Zid; ***Braz.***: Selopress; ***Denm.***: Logimax; Zok-Zid; ***Fin.***: Logimax; Selocomp ZOC; ***Fr.***: Logimax; Logroton; ***Ger.***: Belnif; Beloc-Zok comp; Meto-Succinat HCT†; Metobeta comp; Metohexal comp†; Metoprolol comp; Metoprolol HCT†; Metoprololsuccinat plus†; Metostad Comp†; Mobloc; Prelis comp; ***Gr.***: Logimax; ***Hong Kong***: CP-Metolol Co†; Logimax; ***Hung.***: Logimax; ***India***: Amlovas-M; Betaloc H; Meto ER HT; Metolar-H; Motoblock-AM; Olsar-M; ***Irl.***: Co-Betaloc†; ***Israel***: Logimax†; ***Ital.***: Igroton-Lopresor; ***Malaysia***: Logroton; ***Mex.***: Logimax; Selopres; ***Neth.***: Selokomb; ***Philipp.***: Betazide†; Logimax; ***Rus.***: Logimax (Логимакс); ***Singapore***: Logroton; ***Spain***: Higrotensin†; Logimax; ***Swed.***: Logimax; ***Switz.***: Logimax; Logroton; ***Turk.***: Meprolol; ***USA***: Dutoprol; Lopressor HCT.

Pharmacopoeial Preparations

BP 2014: Metoprolol Injection; Metoprolol Tartrate Tablets; Prolonged-release Metoprolol Tartrate Tablets;

USP 36: Metoprolol Succinate Extended-Release Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Metoprolol Tartrate Injection; Metoprolol Tartrate Oral Solution; Metoprolol Tartrate Oral Suspension; Metoprolol Tartrate Tablets.

Metreleptin *(USAN, rINN)*

Metreleptina; Métréleptine; Metreleptinum; r-metHuLeptin; Метрелептин.

N-Methionylleptin (human).

$C_{714}H_{1167}N_{191}O_{221}S_6$

CAS — 186018-45-1.

UNII — TL60C27RLH.

Profile

Metreleptin is a recombinant methionyl analogue of human leptin. It is given by subcutaneous injection in the treatment of lipodystrophy. Starting doses of 20 to 40 micrograms/kg daily are increased to a maintenance dose of 40 to 80 micrograms/kg daily within 1 month.

References.

1. Chan JL, *et al.* Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. *Endocr Pract* 201 l; **17:** 922–32.
2. Chou K, Perry CM. Metreleptin: first global approval. *Drugs* 2013; **73:** 989–97.
3. Frank S, *et al.* Long-term stabilization effects of leptin on brain functions in a leptin-deficient patient. *PLoS One* 2013; **8:** e65893.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Metreleptin.

Mexiletine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mexiletina; Kö-1173; Meksiletiinihydrokloridi; Meksiletin Hidroklorür; Meksiletino hidrochloridas; Mexiletina, hidrocloruro de; Mexilétine, chlorhydrate de; Mexiletin-hidroklorid; Mexiletin-hydrochlorid; Mexiletinhydrochlorid; Mexiletinhydroklorid; Mexiletini Hydrochloridum; Мексилетина Гидрохлорид.

1-Methyl-2-(2,6-xylyloxy)ethylamine hydrochloride.

$C_{11}H_{17}NO,HCl=215.7$

CAS — 31828-71-4 (mexiletine); 5370-01-4 (mexiletine hydrochloride).

ATC — C01BB02.

ATC Vet — QC01BB02.

UNII — 606D60I538.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Mexiletine Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5.

USP 36: (Mexiletine Hydrochloride). A white powder. Freely soluble in water and in dehydrated alcohol; practically insoluble in ether; slightly soluble in acetonitrile. A 10% solution in water has a pH of between 3.5 and 5.5. Store in airtight containers.

Uses and Administration

Mexiletine is a class Ib antiarrhythmic (p. 1243.1) with actions similar to those of lidocaine (p. 1992.2), to which it is structurally related. Unlike lidocaine it undergoes little hepatic first-pass metabolism and can be given orally.

Mexiletine is used for the treatment of ventricular **arrhythmias** (p. 1266.1). It is given orally or intravenously as the hydrochloride.

Mexiletine hydrochloride is given orally in a usual loading dose of 400 mg followed by 200 to 300 mg three times daily, starting 2 to 8 hours after the loading dose. The usual maintenance dosage is 600 to 900 mg daily in divided doses; doses up to 1.2 g daily may be given. Oral doses should be taken with food and swallowed with plenty of liquid to avoid oesophageal ulceration. Modified-release preparations have been used. Higher loading doses have been given to patients after myocardial infarction to overcome delayed absorption, especially if they have received an opioid analgesic.

Mexiletine hydrochloride has also been given by slow intravenous injection and infusion.

Mexiletine has been tried in the treatment of refractory neuropathic **pain** (see below).

Administration in children. Mexiletine may be effective for ventricular arrhythmias in children; a study[1] of 42 children and young adults (age range 5 months to 34 years) found that mexiletine, given orally in a dose of 1.4 to 5 mg/kg every 8 hours, was effective in 30 patients (71%), with long-term control reported in 18. Treatment was more effective in children with congenital heart disease than in those with cardiomyopathy or no heart disease. Another report[2] found that young children required higher mg/kg doses than adults; a 2-week-old girl and a 20-month-old boy required oral doses of 25 and 15 mg/kg daily, respectively, to produce therapeutic plasma concentrations and control of tachycardia.

1. Moak JP, *et al.* Mexiletine: an effective antiarrhythmic drug for treatment of ventricular arrhythmias in congenital heart disease. *J Am Coll Cardiol* 1987; **10:** 824–9.
2. Holt DW, *et al.* Paediatric use of mexiletine and disopyramide. *BMJ* 1979; **2:** 1476–7.

Administration in the elderly. The rate of absorption of mexiletine was slower in a group of 7 elderly subjects compared with 8 young subjects given mexiletine 100 mg orally, but the extent of absorption was probably not affected.[1] Elimination of mexiletine was not significantly different between the 2 groups and there was no pharmacokinetic basis for dosage modification of mexiletine in the elderly. An observational study[2] in patients receiving mexiletine found a small decrease in clearance with age, but again this was not considered to warrant dosage adjustment.

1. Grech-Bélanger O, *et al.* Pharmacokinetics of mexiletine in the elderly. *J Clin Pharmacol* 1989; **29:** 311–15.
2. Ueno K, *et al.* Pharmacokinetics of mexiletine in middle-aged and elderly patients. *Clin Pharm* 1993; **12:** 768–70.

Administration in renal impairment. The pharmacokinetics of mexiletine do not appear to be affected by renal impairment,[1] although one study[2] found that in patients with creatinine clearance below 10 mL/minute the steady-state plasma concentration and half-life were increased, suggesting that dosage should be adjusted according to plasma concentrations in such patients. Haemodialysis[1] and continuous ambulatory peritoneal dialysis[3] do not appear to affect mexiletine clearance.

1. Wang T, *et al.* Pharmacokinetics and nondialyzability of mexiletine in renal failure. *Clin Pharmacol Ther* 1985; **37:** 649–53.
2. El Allaf D, *et al.* Pharmacokinetics of mexiletine in renal insufficiency. *Br J Clin Pharmacol* 1982; **14:** 431–5.
3. Guay DRP, *et al.* Mexiletine clearance during peritoneal dialysis. *Br J Clin Pharmacol* 1985; **19:** 857–8.

Myotonia. Reference[1] to the use of mexiletine in the management of myotonic dystrophy type 1. Oral doses of 150 or 200 mg three times daily appeared to be of benefit in relieving myotonia and were well tolerated in small placebo-controlled crossover groups.

1. Logigian EL, *et al.* Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. *Neurology* 2010; **74:** 1441–8.

Pain. Neuropathic pain (p. 10.1) is often insensitive to opioid analgesics; alternatives that have been tried include mexiletine. Mexiletine may be of benefit in diabetic neuropathy,[1] although studies have given conflicting results; two of the studies that reported no difference between treatment and placebo found that a subset of patients (those with stabbing or burning pain, heat sensations, and formication) appeared to benefit.[2,3] There have also been reports of improvement in patients with central post-stroke pain (thalamic pain syndrome),[4] and in neuropathic pain associated with cancer,[5-7] and a systematic review[8] concluded that mexiletine was safe and effective in various types of neuropathic pain.

Other painful states in which mexiletine has been reported to be of benefit include: Dercum's disease (a condition involving painful fatty deposits),[9] and erythromelalgia.[10-12] It has also been tried in refractory chronic daily headache.[13] However, it proved ineffective in a study in patients with postamputation pain.[14]

1. Jarvis B, Coukell AJ. Mexiletine: a review of its therapeutic use in painful diabetic neuropathy. *Drugs* 1998; **56:** 691–707.
2. Stracke H, *et al.* Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care* 1992; **15:** 1550–5.
3. Wright JM, *et al.* Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. *Ann Pharmacother* 1997; **31:** 29–34.
4. Awerbuch GI, Sandyk R. Mexiletine for thalamic pain syndrome. *Int J Neurosci* 1990; **55:** 129–33.
5. Colclough G, *et al.* Mexiletine for chronic pain. *Lancet* 1993; **342:** 1484–5.
6. Sloan P, *et al.* Mexiletine as an adjuvant analgesic for the management of neuropathic cancer pain. *Anesth Analg* 1999; **89:** 760–1.
7. Fassoulaki A, *et al.* The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* 2002; **95:** 985–91.
8. Challapalli V, *et al.* Systemic administration of local anesthetic agents to relieve neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/07).
9. Petersen P, *et al.* Treating the pain of Dercum's disease. *BMJ* 1984; **288:** 1880.
10. Kuhnert SM, *et al.* Lidocaine and mexiletine therapy for erythromelalgia. *Arch Dermatol* 1999; **135:** 1447–9.
11. Nathan A, *et al.* Primary erythromelalgia in a child responding to intravenous lidocaine and oral mexiletine treatment. Abstract: *Pediatrics* 2005; **115:** 1066. Full version: http://pediatrics.aappublications.org/cgi/content/full/115/4/e504 (accessed 10/07/07)
12. Iqbal J, *et al.* Experience with oral mexiletine in primary erythromelalgia in children. *Ann Saudi Med* 2009; **29:** 316–8.
13. Marmura MJ, *et al.* Mexiletine for refractory chronic daily headache: a report of nine cases. *Headache* 2008; **48:** 1506–10.
14. Wu CL, *et al.* Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology* 2008; **109:** 289–96.

Adverse Effects and Treatment

Mexiletine has a narrow therapeutic ratio; although many of its adverse effects are dose-related and will respond to

dosage reduction they may be severe enough to force treatment to be stopped and symptomatic and supportive therapy to be given. Toxicity is common with oral or parenteral loading doses when plasma concentrations are high.

The most common adverse effects involve the gastrointestinal tract and CNS. Effects on the gastrointestinal tract include nausea, vomiting, constipation, and diarrhoea; oesophageal ulceration has also been reported. Effects on the nervous system include tremor, confusion, lightheadedness, dizziness, blurred vision and other visual disturbances, sleep disturbances, and speech difficulties. The most frequent cardiovascular effects are hypotension, sinus bradycardia, heart block and AV dissociation, and atrial fibrillation. As with other antiarrhythmics mexiletine may exacerbate arrhythmias. Other adverse effects that have been reported include rashes, abnormal liver function tests, thrombocytopenia, positive antinuclear factor titres, and convulsions. The Stevens-Johnson syndrome has been reported rarely.

Incidence of adverse effects. In a study involving 100 patients with ventricular arrhythmias, mexiletine had to be stopped in 49 patients because of intolerable adverse effects.[1] The most common of these affected the gastrointestinal system (27%) and included nausea (10%), vomiting (6%), heartburn (6%), and oesophageal spasm (3%). Intolerable effects on the CNS occurred in 10% of patients and these were most commonly tremor (4%), ataxia (2%), dyskinesia (1%), and tinnitus (1%). When mexiletine was used with another antiarrhythmic, the incidence of intolerable effects was 56%.

Tolerable adverse effects with mexiletine alone were transient and dose-dependent and occurred in 18% of patients. They most often affected the gastrointestinal tract. No irreversible adverse effects were reported and no proarrhythmic effects were seen.

1. Kerin NZ, *et al.* Mexiletine: long-term efficacy and side effects in patients with chronic drug-resistant potentially lethal ventricular arrhythmias. *Arch Intern Med* 1990; **150:** 381–4.

Effects on the lungs. Pulmonary fibrosis has been reported in an elderly patient receiving mexiletine; the manufacturer was aware of 3 other cases.[1] A case of the hypersensitivity syndrome DRESS (drug rash with eosinophilia and systemic symptoms), manifesting as eosinophilic pneumonia, has also been reported[2] in a patient given mexiletine.

1. Bero CJ, Rihn TL. Possible association of pulmonary fibrosis with mexiletine. *DICP Ann Pharmacother* 1991; **25:** 1329–31.
2. Lee S-P, *et al.* A case of mexiletine-induced hypersensitivity syndrome presenting as eosinophilic pneumonia. *J Korean Med Sci* 2010; **25:** 148–51.

Precautions

Mexiletine is contra-indicated in cardiogenic shock and in second- or third-degree AV block (unless the patient has a pacemaker). It should be used with caution in patients with sinus node dysfunction, other conduction disorders, bradycardia, hypotension, heart failure, or hepatic impairment. ECG and blood pressure monitoring should be carried out during treatment.

Absorption of oral mexiletine may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Breast feeding. Mexiletine is distributed into human breast milk in higher concentrations than in maternal serum. A woman[1] given 200 mg of mexiletine three times daily during the last trimester of pregnancy (see below), went on to breast feed the infant. Concentrations of mexiletine in the maternal milk and serum were found to be 600 and 300 nanograms/mL respectively on the second day postpartum, and 800 and 700 nanograms/mL respectively after 6 weeks. This represented a milk to serum ratio of 2.0 and 1.1 respectively. However, mexiletine was undetectable in the infant's serum on both occasions and no adverse effects were seen. In another report[2] a woman taking a similar dose of mexiletine for the last 5 months of her pregnancy also breast fed her infant. In samples of maternal milk and blood collected between the second and fifth day postpartum the milk to plasma ratio varied between 0.78 and 1.89 with a mean of 1.45. It was considered unlikely that the infant would ingest more than 1.25 mg of mexiletine in any 24-hour period, and this amount was not thought to be enough to cause adverse effects. Failure to feed was noted[3] in the first 17 days in an infant whose mother was taking 750 mg daily of mexiletine and 50 mg daily of atenolol. After maternal education and formula supplementation an acceptable growth curve was established. Breast feeding continued until the infant was 3 months old, and no adverse effects were seen at 10 months. The American Academy of Pediatrics[4] therefore considers that mexiletine is usually compatible with breast feeding.

1. Timmis AD, *et al.* Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; **ii:** 647–8.
2. Lewis AM, *et al.* Mexiletine in human blood and breast milk. *Postgrad Med J* 1981; **57:** 546–7.
3. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; **157:** 446–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mexiletine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Mexiletine crosses the placenta but there have been several reports of its use in pregnant women with no apparent long-term effects on the infants. A normal infant was born to a woman given mexiletine with propranolol for the control of ventricular tachycardia during the third trimester of pregnancy.[1] During the first 6 hours after delivery the infant had a heart rate of only 90 beats/minute, probably due to the propranolol; it was normal thereafter. At delivery the serum concentration of mexiletine in mother and infant was the same. A woman[2] who received mexiletine and atenolol throughout pregnancy also delivered a normal infant; failure to feed was noted at 17 days but at 10 months no adverse effects were seen. In another case[3] where the mother took mexiletine throughout pregnancy, the infant had a low Apgar score at 1 minute and hypoglycaemia was also noted, but the relationship to mexiletine was unclear; cord and maternal blood concentrations at the time of delivery were 400 nanograms/mL and 600 nanograms/mL, respectively.

1. Timmis AD, *et al.* Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; **ii:** 647–8.
2. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; **157:** 446–7.
3. Gregg AR, Tomich PG. Mexilitene [sic] use in pregnancy. *J Perinatol* 1988; **8:** 33–5.

Interactions

Mexiletine undergoes extensive metabolism in the liver particularly by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6, and possibly CYP3A4, and interactions may occur with other drugs metabolised by the same enzymes. Plasma concentrations of mexiletine may be reduced by hepatic enzyme inducers such as phenytoin and rifampicin; increased plasma concentrations may occur with enzyme inhibitors.

Absorption of mexiletine may be delayed by drugs that slow gastric emptying such as opioid analgesics and atropine. The rate of absorption may be increased by metoclopramide; the extent of absorption is unaffected.

Drugs that acidify or alkalinise the urine enhance or reduce the rate of elimination of mexiletine, respectively.

There may be an increased risk of arrhythmias if mexiletine is used with other antiarrhythmics or with arrhythmogenic drugs.

Mexiletine has been reported to increase theophylline concentrations (see Antiarrhythmics, p. 1234.1) and to precipitate lidocaine toxicity (p. 1995.1).

Pharmacokinetics

Mexiletine is readily and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 90%, although absorption may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Mexiletine is metabolised in the liver to several metabolites; metabolism may involve cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4, and genetic polymorphism in relation to CYP2D6 has been identified. Mexiletine is excreted in the urine, mainly in the form of its metabolites with about 10% excreted unchanged; clearance is increased in acid urine.

Mexiletine is widely distributed throughout the body and is about 50 to 70% bound to plasma proteins. Mexiletine crosses the placenta and is distributed into breast milk. It has an elimination half-life of about 10 hours in healthy subjects but this may be prolonged in patients with heart disease, hepatic impairment, or severe renal impairment. Its therapeutic effect has been correlated with plasma concentrations of 0.5 to 2 micrograms/mL, but the margin between therapeutic and toxic concentrations is narrow, and severe toxicity may occur within this range.

References.

1. Labbé L, Turgeon J. Clinical pharmacokinetics of mexiletine. *Clin Pharmacokinet* 1999; **37:** 361–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mexitilen; ***Austral.***: Mexitil†; ***Belg.***: Mexitil†; ***Braz.***: Mexitil; ***Cz.***: Katen†; ***Ger.***: Mexitil†; ***Gr.***: Antiaril; Mexitil; Myovek; ***Hung.***: Ritalmex; ***India***: Mexitil; ***Irl.***: Mexitil†; ***Ital.***: Mexitil; ***Jpn***: Mexitil; ***Malaysia***: Meletin; ***NZ***: Mexitil; ***Pol.***: Mexicord†; ***Rus.***: Ritalmex (Риталмекс); ***Turk.***: Mexitil; ***Ukr.***: Mexaritm (Мексаритм); ***USA***: Mexitil; ***Venez.***: Tumetil.

Pharmacopoeial Preparations
BP 2014: Mexiletine Capsules; Mexiletine Injection;
USP 36: Mexiletine Hydrochloride Capsules.

Midodrine Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de midodrina; Midodrina, hidrocloruro de; Midodrine, Chlorhydrate de; Midodrini Hydrochloridum; ST-1085 (midodrine or midodrine hydrochloride); Мидодрина Гидрохлорид.

2-Amino-*N*-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide hydrochloride; (*RS*)-*N*^{1}-(β-Hydroxy-2,5-dimethoxyphenethyl) glycinamide hydrochloride.

$C_{12}H_{18}N_2O_4$,HCl=290.7

CAS — 42794-76-3 (midodrine); 3092-17-9 (midodrine hydrochloride).

ATC — C01CA17.

ATC Vet — QC01CA17.

UNII — 59JV96YTXV.

Pharmacopoeias. In *US.*

USP 36: (Midodrine Hydrochloride). A white crystalline powder. Soluble in water; sparingly soluble in methyl alcohol. A 5% solution in water has a pH of 4.0 to 5.0. Store in airtight containers.

Uses and Administration

Midodrine is a direct-acting sympathomimetic (p. 1507.3) with selective alpha-agonist activity; the main active moiety has been stated to be its major metabolite, deglymidodrine. It acts as a peripheral vasoconstrictor but has no direct cardiac stimulatory effects.

Midodrine hydrochloride is used in the treatment of hypotensive states (p. 1277.2) and in particular of orthostatic hypotension (p. 1634.3). Alpha-agonist drugs such as midodrine have also been used as an adjunct in the management of urinary incontinence (p. 2349.2).

In **hypotensive states**, the usual initial oral dose of midodrine hydrochloride is 2.5 mg two or three times daily, adjusted gradually according to response; up to 10 mg three times daily may be required. The potential for supine hypertension is reduced by taking the last dose of the day at least 4 hours before bedtime.

An oral dose for **urinary incontinence** is 2.5 to 5 mg two or three times daily.

Midodrine hydrochloride has also been given in similar doses by slow intravenous injection. It has also been used orally or by injection in the treatment of **retrograde ejaculation**.

References.

1. McClellan KJ, *et al.* Midodrine: a review of its therapeutic use in the management of orthostatic hypotension. *Drugs Aging* 1998; **12:** 76–86.
2. Prakash S, *et al.* Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; **19:** 2553–8.
3. Karwa R, Woodis CB. Midodrine and octreotide in treatment of cirrhosis-related hemodynamic complications. *Ann Pharmacother* 2009; **43:** 692–9.
4. Safarinejad MR. Midodrine for the treatment of organic anejaculation but not spinal cord injury: a prospective randomized placebo-controlled double-blind clinical study. *Int J Impot Res* 2009; **21:** 213–20.
5. Soler JM, *et al.* Oral midodrine for prostaglandin E1 induced priapism in spinal cord injured patients. *J Urol (Baltimore)* 2009; **182:** 1096–1100.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Midodrine has mainly alpha-agonist properties and the most serious adverse effect of midodrine is supine hypertension. Paraesthesias, dysuria, pilomotor reaction (goose flesh), pruritus and rashes have been reported.

Interactions

As for Sympathomimetics, p. 1508.3.

Pharmacokinetics

Midodrine is well absorbed from the gastrointestinal tract and undergoes enzymatic hydrolysis in the systemic circulation to its active metabolite, deglymidodrine (desglymidodrine; ST-1059). Midodrine itself reaches its peak plasma concentrations about half an hour after an oral dose, and has a plasma half-life of about 25 minutes. The active metabolite reaches its peak plasma concentration

about an hour after oral dosage and has a terminal elimination half-life of about 3 hours. Deglymidodrine undergoes some further metabolism in the liver. Midodrine is mainly excreted in the urine as metabolites and a small amount of unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gutron; ***Austria***: Gutron; ***Canad.***: Amatine†; ***Chile***: Gutron; ***China***: An De Lin (安得林); Gutron (管通); Mi Wei (米维); ***Cz.***: Gutron; ***Fr.***: Gutron; ***Ger.***: Gutron; ***Gr.***: Gutron; ***Hong Kong***: Gutron; ***Hung.***: Gutron; ***Irl.***: Midon; ***Israel***: Gutron†; ***Ital.***: Gutron; Xerotil; ***Jpn***: Metligine; ***Neth.***: Gutron; ***NZ***: Gutron; ***Pol.***: Gutron; ***Port.***: Gutron; ***Rus.***: Gutron (Гутрон); ***Singapore***: Gutron; ***Spain***: Gutron; ***Switz.***: Gutron; ***USA***: ProAmatine.

Pharmacopoeial Preparations
USP 36: Midodrine Hydrochloride Tablets.

Milrinone *(BAN, USAN, rINN)*

Milrinona; Milrinonum; Win-47203-2; YM-018; Мильринон.
1,6-Dihydro-2-methyl-6-oxo[3,4′-bipyridine]-5-carbonitrile.
$C_{12}H_9N_3O$=211.2
CAS — 78415-72-2.
ATC — C01CE02.
ATC Vet — QC01CE02.
UNII — JU9YAX04C7.

Pharmacopoeias. In *US.*

USP 36: (Milrinone). A white to tan, hygroscopic, crystalline solid. Practically insoluble in water and in chloroform; very slightly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers.

Milrinone Lactate *(BANM, rINNM)*

Lactato de milrinona; Milrinona, lactato de; Milrinone, Lactate de; Milrinoni Lactas; Мильринона Лактат.
$C_{12}H_9N_3O,C_3H_6O_3$=301.3
ATC — C01CE02.
ATC Vet — QC01CE02.
UNII — 9K8XR81MO8.

Incompatibility. UK licensed product information states that milrinone lactate injection is incompatible with furosemide and bumetanide, and it should not be diluted with sodium bicarbonate injection. Physical incompatibility with imipenem-cilastatin sodium has also been reported.[1]

1. Veltri MA, Conner KG. Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. *Am J Health-Syst Pharm* 2002; **59:** 452–4.

Uses and Administration

Milrinone is a phosphodiesterase type 3 inhibitor similar to amrinone (p. 1305.1) with positive inotropic and vasodilator activity. It is, however, reported to have greater positive inotropic activity than amrinone. It is given intravenously, as the lactate, in the short-term management of severe heart failure unresponsive to other forms of therapy and in acute heart failure after cardiac surgery. In some longer-term studies milrinone was given orally, but an increased mortality rate was reported.

Doses of milrinone lactate are expressed in terms of the base; milrinone lactate 1.43 mg is equivalent to about 1 mg of milrinone. The initial loading dose is the equivalent of milrinone 50 micrograms/kg given over 10 minutes followed by a continuous maintenance infusion. The maintenance infusion may be titrated between 375 and 750 nanograms/kg per minute but a total daily dose of 1.13 mg/kg should not be exceeded.

Dosage should be reduced in patients with renal impairment (see below).

Use of milrinone by inhalation is being investigated in the management of pulmonary hypertension.

Administration in children. Milrinone has been used in children with septic shock or heart failure after cardiac surgery. Pharmacokinetic studies[1,2] have suggested that steady-state plasma concentrations of milrinone are lower in children than in adults given similar doses, and that milrinone clearance is faster in children. Higher doses in proportion to body-weight may therefore be necessary in children than in adults. For neonates and children aged 1 month to 18 years with heart failure, low cardiac output after cardiac surgery, or shock, the *BNFC* recommends an initial dose of 50 to 75 micrograms/kg by intravenous infusion over 30 to 60 minutes, followed by continuous intravenous infusion at a dose of 30 to 45 micrograms/kg per hour (500 to 750 nanograms/kg per minute). The infusion may be continued for 2 to 3 days, but is usually given for 12 hours after cardiac surgery.

Milrinone also appears to be effective for the prevention of low cardiac output in children undergoing cardiac surgery.[3] It has been tried for the prevention of low systemic blood flow in premature infants, but further studies are needed to confirm its role.[4]

A study[5] of adverse effects in children given milrinone has suggested that arrhythmias are less common than in adults whereas thrombocytopenia is more common.

1. Lindsay CA, *et al.* Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998; **132:** 329–34.
2. Ramamoorthy C, *et al.* Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998; **86:** 283–9.
3. Hoffman TM, *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; **107:** 996–1002.
4. Paradisis M, *et al.* Pilot study of milrinone for low systemic blood flow in very preterm infants. *J Pediatr* 2006; **148:** 306–13.
5. Watson S, *et al.* Use of milrinone in the pediatric critical care unit. *Pediatrics* 1999; **104** (suppl): 681–2.

Administration in renal impairment. Doses of milrinone should be reduced in patients with renal impairment. The following doses for maintenance infusion are recommended based on creatinine clearance (CC):

- CC 50 mL/min per 1.73 m²: 430 nanograms/kg per minute
- CC 40 mL/min per 1.73 m²: 380 nanograms/kg per minute
- CC 30 mL/min per 1.73 m²: 330 nanograms/kg per minute
- CC 20 mL/min per 1.73 m²: 280 nanograms/kg per minute
- CC 10 mL/min per 1.73 m²: 230 nanograms/kg per minute
- CC 5 mL/min per 1.73 m²: 200 nanograms/kg per minute

Heart failure. Milrinone is one of several drugs that may be used in heart failure (p. 1262.3), but because of an increased mortality rate reported after long-term oral use of phosphodiesterase type 3 inhibitors[1] it is usually only given intravenously for short-term management of heart failure unresponsive to other treatments. The PROMISE (Prospective Randomized Milrinone Survival Evaluation) study[2] showed that oral milrinone increased morbidity and mortality in patients with severe chronic heart failure. However, longer-term continuous intravenous use for up to 8 weeks was subsequently studied in patients awaiting heart transplantation and appeared to be well tolerated.[3] Intermittent use on several days a week has also been tried.[4]

In patients with acute exacerbation of heart failure, a prospective study[5] found no benefit from the routine use of short-term intravenous milrinone.

1. Amsallem E, *et al.* Phosphodiesterase III inhibitors for heart failure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 29/04/10).
2. Packer M, *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991; **325:** 1468–75.
3. Mehra MR, *et al.* Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997; **80:** 61–4.
4. Cesario D, *et al.* Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: a preliminary study. *Am Heart J* 1998; **135:** 121–9.
5. Cuffe MS, *et al.* Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; **287:** 1541–7.

Adverse Effects and Precautions

Prolonged oral use of milrinone has increased the mortality rate and milrinone is now only used intravenously for short-term use.

Supraventricular and ventricular arrhythmias (including torsade de pointes), hypotension, angina-like chest pain, and headache have been reported. Hypokalaemia, tremor, thrombocytopenia, bronchospasm, anaphylaxis, and infusion site reactions may occur. The incidence of arrhythmias may be lower in *children* whereas the risk of thrombocytopenia may be higher (see Administration in Children, above).

Milrinone should be used with caution in patients with severe obstructive aortic or pulmonary valvular disease or with hypertrophic cardiomyopathy. Since milrinone may facilitate conduction through the atrioventricular node it can increase the ventricular response rate in patients with atrial flutter or fibrillation. Digitalisation should be considered in these patients before milrinone therapy is started.

Blood pressure, heart rate, ECG, fluid and electrolyte balance, and renal function should be monitored during milrinone therapy.

Milrinone should be given in reduced doses to patients with renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies milrinone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Although milrinone is rapidly and almost completely absorbed from the gastrointestinal tract, it is only given intravenously. It is about 70% bound to plasma proteins. Elimination occurs mainly via the urine; about 83% of a dose is excreted as unchanged drug. The elimination half-life is about 2.3 hours.

General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:**(contents page).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Corotrope; ***Austral.***: Primacor; ***Austria***: Corotrop; ***Belg.***: Corotrope; ***Braz.***: Primacor; ***Chile***: Corotrope; ***China***: Lunan Likang (鲁南力康); Primacor (伊克维); ***Cz.***: Corotrop; ***Fr.***: Corotrope; ***Ger.***: Corotrop†; ***Gr.***: Corotrope; ***Hong Kong***: Primacor; ***Hung.***: Corotrope; ***India***: Milicor; Milron; Myolong; ***Indon.***: Coritrope; Inovad; ***Israel***: Primacor; ***Jpn***: Milrila; ***Malaysia***: Primacor; ***Mex.***: Primacor; ***Neth.***: Corotrope; ***NZ***: Primacor; ***Pol.***: Corotrope; ***Port.***: Corotrope; ***Singapore***: Primacor; ***Spain***: Corotrope; ***Swed.***: Corotrop; ***Switz.***: Corotrop; ***Thai.***: Primacor; ***UK***: Primacor; ***USA***: Primacor†; ***Venez.***: Corotrope.

Minoxidil *(BAN, USAN, rINN)*

Minoksidiili; Minoksidilis; Minoxidilum; U-10858; Миноксидил.
2,6-Diamino-4-piperidinopyrimidine 1-oxide.
$C_9H_{15}N_5O$=209.3
CAS — 38304-91-5.
ATC — C02DC01; D11AX01.
ATC Vet — QC02DC01.
UNII — 5965120SH1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Minoxidil). A white or almost white crystalline powder. Slightly soluble in water; soluble in methyl alcohol and in propylene glycol. Protect from light.

USP 36: (Minoxidil). A white or off-white crystalline powder. Slightly soluble in water; soluble in alcohol and in propylene glycol; practically insoluble in acetone, in chloroform, in ethyl acetate, and in petroleum spirit; sparingly soluble in methyl alcohol.

Uses and Administration

Minoxidil is an antihypertensive that acts mainly by causing direct peripheral vasodilatation of the arterioles. It produces effects on the cardiovascular system similar to those of hydralazine (p. 1401.2). Minoxidil is given orally for the treatment of severe hypertension unresponsive to standard therapy (p. 1251.1). When applied topically to the scalp minoxidil may stimulate hair growth to a limited extent and is used in the treatment of alopecia.

In the treatment of **hypertension** minoxidil is given with a beta blocker, or with methyldopa, to diminish the cardiac-accelerating effects, and with a diuretic, usually a loop diuretic, to control oedema. After a single oral dose, the maximum hypotensive effect usually occurs after 2 to 3 hours, although the full effects may not occur until after 3 to 7 days of continuous treatment. An initial dose of 5 mg of minoxidil daily (or 2.5 mg daily in the elderly) is gradually increased at intervals of not less than 3 days to 40 or 50 mg daily according to response; in exceptional circumstances up to 100 mg daily has been given. If more rapid control of blood pressure is required, dosage increments of 5 mg may be made every 6 hours with careful monitoring. The daily dose may be given as a single dose or in 2 divided doses.

For doses in children, see below.

Reduced doses may be required in patients with renal impairment (see below).

In the treatment of **alopecia androgenetica** (male-pattern baldness) 1 mL of a 2% solution or gel or 5% solution of minoxidil is applied twice daily to the scalp. The 5% solution is not recommended for women.

Administration in children. Minoxidil may be used in children aged 12 years and under to treat severe hypertension unresponsive to standard therapy. The initial oral dose is 200 micrograms/kg daily in 1 or 2 divided doses, increased according to response by 100 to 200 micrograms/kg increments at intervals of not less than 3 days to a maximum daily dose of 1 mg/kg or 50 mg.

Administration in renal impairment. A study of the pharmacokinetics of minoxidil in patients with varying degrees

of renal impairment found that the non-renal clearance was also impaired as renal function worsened.[1] Substantial accumulation of minoxidil might occur in these patients during multiple-dose therapy. It was advised that minoxidil be started with smaller doses or at longer dosage intervals in patients with renal impairment.

1. Halstenson CE, *et al.* Disposition of minoxidil in patients with various degrees of renal function. *J Clin Pharmacol* 1989; **29:** 798–802.

Alopecia. Minoxidil is used topically to stimulate hair growth in alopecia (p. 1682.3), although its mechanism of action is poorly understood.[1] Increases in pigmented non-vellus hair may be due to thickening and pigmentation of existing vellus rather than new growth.[2] Measurement over 96 weeks showed[3] that minoxidil in solutions of 2 or 5% had a greater effect on hair weight than number of hairs in men with androgenetic alopecia (male-pattern baldness) with the 5% solution being more effective; 24 weeks after treatment was stopped both values had returned to baseline. Another study[4] also showed that 5% minoxidil had a greater effect than 2%, and produced an earlier response. However, 5% minoxidil has been found[5] less effective than oral finasteride. Even with continued use there is a waning of effect with minoxidil.[6,7] It may be more effective in retarding the progression of male-pattern baldness than in reversing it,[2] and users are advised to abandon treatment if there is insufficient benefit after a year.[8]

Minoxidil has also been used in women with female pattern hair loss,[9] and as with men the 5% solution has been found[10] more effective than the 2%. In women with no evidence of biochemical hyperandrogenism minoxidil 2% was more effective[11] than oral cyproterone; where there was such evidence, cyproterone was superior.

Topical minoxidil has been shown to be safe in a large prospective study[12] of men and women with androgenetic alopecia.

Minoxidil appeared to have no beneficial effect on alopecia areata,[13] although one study indicated that topical minoxidil with 0.5% dithranol cream was more effective than either treatment alone.[14]

1. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol* 2004; **150:** 186–94.
2. Katz HI. Topical minoxidil: review of efficacy and safety. *Cutis* 1989; **43:** 94–8.
3. Price VH, *et al.* Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. *J Am Acad Dermatol* 1999; **41:** 717–21.
4. Olsen EA, *et al.* A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol* 2002; **47:** 377–85.
5. Arca E, *et al.* An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia. *Dermatology* 2004; **209:** 117–25.
6. de Groot AC, *et al.* Minoxidil: hope for the bald? *Lancet* 1987; **i:** 1019–22.
7. Anonymous. Topical minoxidil does little for baldness. *Drug Ther Bull* 1989; **27:** 74–5.
8. Shrank AB. Treating young men with hair loss. *BMJ* 1989; **298:** 847–8.
9. Camacho-Martínez FM. Hair loss in women. *Semin Cutan Med Surg* 2009; **28:** 19–32.
10. Lucky AW, *et al.* A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol* 2004; **50:** 541–53.
11. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; **146:** 992–9.
12. Shapiro J. Safety of topical minoxidil solution: a one-year, prospective, observational study. *J Cutan Med Surg* 2003; **7:** 322–9.
13. Anonymous. Topical minoxidil for baldness: a reappraisal. *Med Lett Drugs Ther* 1994; **36:** 9–10.
14. Fiedler VC, *et al.* Treatment-resistant alopecia areata. *Arch Dermatol* 1990; **126:** 756–9.

CHEMOTHERAPY-INDUCED ALOPECIA. Minoxidil 2% solution was applied daily to the scalp of a boy with acute lymphoblastic leukaemia whose hair had failed to regrow satisfactorily after intensive chemotherapy.[1] Almost normal hair growth, achieved over a 9-month period, was attributed to the use of minoxidil.

A small study[2] in women undergoing combination chemotherapy including doxorubicin found that topical minoxidil applied throughout therapy and for up to 4 months afterwards reduced the duration of alopecia by an average of 50 days.

Other methods for reducing chemotherapy-induced alopecia are described under the Treatment of Adverse Effects of Antineoplastics, p. 730.3.

1. Vickers MA, Barton CJ. Minoxidil induced hair growth after leukaemia treatment? *Arch Dis Child* 1995; **73:** 184.
2. Duvic M, *et al.* A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol* 1996; **35:** 74–8.

Adverse Effects and Treatment

Adverse effects commonly caused by minoxidil include reflex tachycardia, fluid retention accompanied by weight gain, oedema, and sometimes deterioration of existing heart failure and changes in the ECG. Hypertrichosis develops in up to 80% of patients within 3 to 6 weeks of the start of minoxidil therapy but is slowly reversible on stopping. Pericardial effusion, sometimes with associated tamponade, has been reported in about 3% of patients. Pericarditis may also occur. Minoxidil may aggravate or uncover angina pectoris. Other less frequent adverse effects include headache, nausea, gynaecomastia and breast tenderness, polymenorrhoea, allergic rashes, Stevens-Johnson syndrome, and thrombocytopenia.

Reflex tachycardia can be overcome by the use of a beta blocker, or alternatively methyldopa, and a diuretic (usually a loop diuretic) is used to reduce fluid retention. If excessive hypotension occurs, an intravenous infusion of sodium chloride 0.9% can be given to maintain the blood pressure. If a pressor agent is necessary, drugs such as adrenaline, which can aggravate tachycardia, should be avoided; phenylephrine, angiotensinamide, vasopressin, or dopamine may be given if there is evidence of inadequate perfusion of a vital organ.

Topical application of minoxidil may be associated with contact dermatitis, pruritus, local burning, and flushing; sufficient may be absorbed to produce systemic adverse effects. Changes in hair colour or texture may occur.

Effects on the eyes. Bilateral optic neuritis and retinitis occurred in a patient during treatment with minoxidil for hypertension after a renal transplant.[1] The patient was also taking prednisolone and azathioprine.

1. Gombos GM. Bilateral optic neuritis following minoxidil administration. *Ann Ophthalmol* 1983; **15:** 259–61.

Effects on the hair. The hypertrichosis frequently associated with oral minoxidil makes it generally unsuitable for women. There have also been reports of changes in hair colour.[1] In addition a case has been reported of increased hair loss, followed by subsequent regrowth of differently-coloured hair.[2] Substantial hair loss occurred in a woman after withdrawal of minoxidil and she had to wear a wig.[3]

Severe hypertrichosis has also been reported in 5 of 56 women applying minoxidil 5% solution topically for androgenetic alopecia.[4] Facial, arm, and leg hypertrichosis were reported 2 to 3 months after starting treatment. Hypertrichosis had disappeared 5 months after stopping minoxidil.

1. Traub YM, *et al.* Treatment of severe hypertension with minoxidil. *Isr J Med Sci* 1975; **11:** 991–8.
2. Ingles RM, Kahn T. Unusual hair changes with minoxidil therapy. *Int J Dermatol* 1983; **22:** 120–2.
3. Kidwai BJ, George M. Hair loss with minoxidil withdrawal. *Lancet* 1992; **340:** 609–10.
4. Peluso AM, *et al.* Diffuse hypertrichosis during treatment with 5% topical minoxidil. *Br J Dermatol* 1997; **136:** 118–20.

Effects on skeletal muscle. A polymyalgia syndrome, manifesting as fatigue, anorexia, weight loss, and severe pain in the shoulders and pelvic girdle, was seen in 4 men using topical minoxidil.[1] All symptoms improved within 2 to 4 weeks of stopping the drug. In 2 of the patients rechallenge produced a recurrence of symptoms.

1. Colamarino R, *et al.* Polymyalgia and minoxidil. *Ann Intern Med* 1990; **113:** 256–7.

Effects on the skin. Skin reactions to systemic minoxidil do not appear to be common. However, fatal toxic epidermal necrolysis has been associated with minoxidil,[1] and cases of classic Stevens-Johnson syndrome have also been reported.[2,3] Stevens-Johnson syndrome generally responds to withdrawal and corticosteroid therapy; in one case[2] subsequent rechallenge provoked a recurrence. In another patient an extensive erythematous weeping rash with lesions consistent with actinic keratosis also appeared to be due to minoxidil; bullous lesions recurred on re-exposure.[4] After topical application itching, scaling, flushing, and dermatitis have been the most common adverse effects; allergic contact dermatitis has been reported in rare instances.[5,6]

For other lesions associated with Kaposi's sarcoma and angioma, see Neoplasms, below, and for effects on the hair, see above.

1. Karaoui LR, Chahine-Chakhtoura C. Fatal toxic epidermal necrolysis associated with minoxidil. *Pharmacotherapy* 2009; **29:** 460–7.
2. DiSantis DJ, Flanagan J. Minoxidil-induced Stevens-Johnson syndrome. *Arch Intern Med* 1981; **141:** 1515.
3. Callen EC, *et al.* Stevens-Johnson syndrome associated with oral minoxidil: a case report. *J Nephrol* 2007; **20:** 91–3.
4. Ackerman BH, *et al.* Pruritic rash with actinic keratosis and impending exfoliation in a patient with hypertension managed with minoxidil. *Drug Intell Clin Pharm* 1988; **22:** 702–3.
5. Clissold SP, Heel RC. Topical minoxidil: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in alopecia areata and alopecia androgenetica. *Drugs* 1987; **33:** 107–22.
6. Rodríguez-Martín M, *et al.* Pustular allergic contact dermatitis from topical minoxidil 5%. *J Eur Acad Dermatol Venereol* 2007; **21:** 701–2.

Neoplasms. Two haemorrhagic lesions with Kaposi's features appeared on the forehead, an unusual location for HIV-associated Kaposi's sarcoma, in an HIV-positive patient who had applied topical minoxidil there for 3 months.[1] In a healthy patient an angioma of the scalp developed after 2 months of topical minoxidil therapy. The patient had had a similar lesion as a baby. Minoxidil may induce angiogenesis or may stimulate endothelial cells, fibroblasts, and muscle cells to proliferate. Care should be taken when minoxidil is applied to the skin of people who are predisposed to neo-angiogenesis, or who are HIV-positive.

For other effects of minoxidil on the skin following topical application, see above.

1. Pavlovitch JH, *et al.* Angiogenesis and minoxidil. *Lancet* 1990; **336:** 889.

Precautions

Minoxidil is contra-indicated in phaeochromocytoma. It should be used with caution after a recent myocardial infarction, and in patients with pulmonary hypertension, angina pectoris, chronic heart failure, and significant renal impairment.

Topical application of minoxidil should be restricted to the scalp; it should not be applied to inflamed scalp skin or areas affected by psoriasis, severe sunburn, or severe excoriations, because of the risk of increased absorption. Patients being treated for hypertension should be monitored if topical minoxidil is used concurrently.

AIDS. For recommendations that topical minoxidil should be used with caution in HIV-positive patients, see Neoplasms under Adverse Effects, above.

Breast feeding. Study[1] of a breast-feeding mother showed that minoxidil was rapidly distributed into breast milk, achieving similar concentrations to those in the maternal plasma. No adverse effects were seen in the infant after 2 months and the American Academy of Pediatrics considers[2] that minoxidil is therefore usually compatible with breast feeding.

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; **102:** 135.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the dermatological form of minoxidil as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. The oral form is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. There are reports of uneventful pregnancies that resulted in healthy infants when *oral* minoxidil was taken throughout pregnancy with either propranolol and furosemide[1] or metoprolol and prazosin,[2] although temporary hypertrichosis was seen in one infant.[2] However, multiple congenital abnormalities and hypertrichosis occurred in another infant whose mother took minoxidil, propranolol, and captopril throughout pregnancy,[3] and congenital cardiac abnormalities were fatal in an infant whose mother took minoxidil, methyldopa, hydralazine, furosemide, and phenobarbital.[2] Caudal agenesis requiring second-trimester termination occurred after *topical* maternal application of 2% minoxidil solution daily, 2 weeks of co-trimoxazole, and 1 week of erythromycin during pregnancy.[4] Multiple abnormalities were also detected in another fetus whose mother applied 2% minoxidil daily throughout pregnancy, but had taken no other medications except a single dose of paracetamol.[5]

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; **102:** 135.
2. Rosa FW, *et al.* Fetal minoxidil exposure. *Pediatrics* 1987; **80:** 120.
3. Kaler SG, *et al.* Hypertrichosis and congenital anomalies associated with maternal use of minoxidil. *Pediatrics* 1987; **79:** 434–6.
4. Rojansky N, *et al.* Extreme caudal agenesis. Possible drug-related etiology? *J Reprod Med* 2002; **47:** 241–5.
5. Smorlesi C, *et al.* Topically applied minoxidil may cause fetal malformation: a case report. *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 997–1001.

Interactions

The antihypertensive effect of minoxidil may be enhanced by use of other hypotensive drugs. Severe orthostatic hypotension may occur if minoxidil and sympathetic blocking drugs such as guanethidine are given concurrently.

Topical minoxidil should not be used with other topical agents known to enhance absorption, such as corticosteroids, retinoids, or occlusive ointment bases.

Tretinoin. Percutaneous absorption of minoxidil is enhanced by tretinoin as a result of increased stratum corneum permeability.[1]

1. Ferry JJ, *et al.* Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. *Clin Pharmacol Ther* 1990; **47:** 439–46.

Pharmacokinetics

About 90% of an oral dose of minoxidil is absorbed from the gastrointestinal tract. The plasma half-life is about 4.2 hours although the haemodynamic effect may persist for up to 75 hours, presumably due to accumulation at its site of action. Minoxidil is not bound to plasma proteins. It is distributed into breast milk. Minoxidil is extensively metabolised by the liver. It requires sulfation to become active, but the major metabolite is a glucuronide conjugate. Minoxidil is excreted chiefly in the urine mainly in the form of metabolites. Minoxidil and its metabolites are dialysable, although the pharmacological effect is not reversed.

About 0.3 to 4.5% of a topical dose of minoxidil is absorbed from intact scalp.

References.
1. Pacifici GM, *et al.* Minoxidil sulphation in human liver and platelets: a study of interindividual variability. *Eur J Clin Pharmacol* 1993; **45:** 337–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anagen; Ivix; Locemix; Macbirs Minoxidil; Minoxile; Tricolocion; Tricoplus; Ylox; ***Austral.***: Hair A-Gain; Hair Retreva; Loniten; Regaine; ***Austria***: Loniten; Regaine; Rogaine; ***Belg.***: Alopexy; Neoxidil; Regaine†; ***Braz.***: Loniten; Regaine; ***Canad.***: Apo-Gain; Hair Regrowth; Loniten; Minox; Rogaine; ***Chile***: Alopek; Regaine†; Tricoxane; ***China***: Da Fei Xin (达霏欣); Si Bi Shen (斯必申); Xue Rui (学瑞); ***Cz.***: Neocapil; Regaine; ***Denm.***: Regaine; ***Fin.***: Recrea; Rogaine; ***Fr.***: Alopexy; Alostil; Lonoten; Regaine†; Unipexil; ***Ger.***: Alopexy; Lonolox; Regaine; ***Gr.***: Axelan; Botafex; Dermolantyl; Dilaine; Ebersedin; Hairway; Hamarityl; Loniten; Lonoten; Lotorin; Minodril; Monoxidil; Neo-Pruristam; Nherea; Oxofenil; Regaine; Stemeral; Vius; ***Hong Kong***: Hairgrow; Hargro†; Headway; Loniten†; Minoxi†; Regaine; Regro; Renew†; ***Hung.***: Neocapil; Regaine; ***India***: Coverit; Gromane; Hair 4 U; Hairex; Hygaine; Inoxi; Manexil; Minscalp; Mintop; Morr; Multigain; ***Indon.***: Aloxid; Eminox; Regaine†; Regrou; ***Irl.***: Loniten; Regaine; ***Israel***: Alopexy; Hair-Treat; Hairgain; Minoxi; Noxidil; Regaine; ***Ital.***: Aloxidil; Carexidil; Loniten; Minovital; Minoximen; Regaine; Tricoxidil; ***Malaysia***: Apo-Gain; Headway†; Regaine; Regro; ***Mex.***: Folcres; Regaine; ***Neth.***: Alopexy†; Lonoten; Regaine; ***Norw.***: Recrea; Rogaine†; ***NZ***: Headway†; Loniten; Rogaine; ***Philipp.***: Regroe; Relive; ***Pol.***: Loxon; Piloxidil; Regaine; ***Port.***: Biocrinal; Crinalsofex; Folcare; Hairtene†; Mantai; Minocalve; Minox; Neoxidil; Regaine; Tricovivax; Zeldilon; ***Rus.***: Cosilon (Косилон); Regaine (Регейн); ***S.Afr.***: Loniten; Regaine; ***Singapore***: Growell; Loniten; Minoxi; Minoxitrim†; Regaine; Regro; ***Spain***: Alopexy; Aloxidil; Carexidil†; Dinaxcinco; Dinaxil Capilar; Lacovin; Loniten; Regaine†; Regaxidil; ***Swed.***: Recrea; Rogaine; ***Switz.***: Alopexy; Loniten; Neocapil; Regaine; ***Thai.***: Loniten; Manoxidil; Minodil; Minor; Modil; Noxidil; Nuhair; Regaine; Regrowth; Reten; SM; ***Turk.***: Rogan; ***UK***: Loniten; Regaine; ***Ukr.***: Pilfud (Пилфуд); Regaine (Регейн)†; ***USA***: Rogaine; ***Venez.***: Guayaten; Topixidil; Zitoxil.

Pharmacopoeial Preparations
BP 2014: Minoxidil Scalp Application;
USP 36: Minoxidil Tablets; Minoxidil Topical Solution.

Mipomersen *(rINN)*

Mipomersén; Mipomersenum; Мипомерсен.
$C_{230}H_{305}N_{67}O_{122}P_{19}S_{19}$=7158.0
CAS — 1000120-98-8.
ATC — C10AX11.
ATC Vet — QC10AX11.
UNII — 9GJ8S4GU0M.

Mipomersen Sodium *(USAN, rINNM)*

Isis-301012; Mipomersén sódico; Mipomersen Sodique; Natrii Mipomersenum; Натрий Мипомерсен.
$C_{230}H_{305}N_{67}Na_{19}O_{122}P_{19}S_{19}$=7594.8
CAS — 629167-92-6.
ATC — C10AX11.
ATC Vet — QC10AX11.
UNII — 18EAY4870E.

Uses and Administration

Mipomersen is an antisense oligonucleotide that inhibits apolipoprotein B synthesis. It is used, as an adjunct to other lipid regulating drugs and dietary modification, to reduce low-density lipoprotein (LDL)-cholesterol and other lipoproteins in patients with homozygous familial hypercholesterolaemia (see Hyperlipidaemias, p. 1248.1). Mipomersen sodium 200 mg is given by subcutaneous injection once weekly. If a dose is missed it should be given at least 3 days before the next weekly dose. The patient should be assessed after 6 months of treatment to determine whether the achieved reduction in LDL-cholesterol is sufficient to warrant ongoing therapy, when balanced against the risk of liver toxicity.

References.
1. Gelsinger C, *et al.* Therapeutic potential of mipomersen in the management of familial hypercholesterolaemia. *Drugs* 2012; **72:** 1445–55.
2. Visser ME, *et al.* Antisense oligonucleotides for the treatment of dyslipidaemia. *Eur Heart J* 2012; **33:** 1451–8.
3. Stein EA, *et al.* Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. *Circulation* 2012; **126:** 2283–92.
4. Hair P, *et al.* Mipomersen sodium: first global approval. *Drugs* 2013; **73:** 487–93.

Adverse Effects and Precautions

Elevation of serum transaminases and hepatic fat accumulation occur in a significant proportion of patients given mipomersen. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin should be measured before starting treatment; ALT and AST should be monitored monthly during the first year of therapy and three-monthly thereafter. Mipomersen is contra-indicated in patients with moderate to severe hepatic impairment or active liver disease.

Flu-like symptoms, typically occurring within 2 days after a dose, and injection-site reactions are very common in patients given mipomersen. Other adverse effects include gastrointestinal disturbances, headache, and insomnia. Cardiovascular effects such as hypertension, angina, and palpitations have also been reported.

The EMA refused marketing authorisation for mipomersen in 2012, which was reconfirmed in 2013. There was uncertainty about the long-term cardiovascular safety of mipomersen, and concerns about hepatotoxicity and high rates of withdrawal from studies because of intolerance.

Effects on the liver. Hepatic steatosis occurred in the majority of patients given mipomersen in phase 3 studies for familial hypercholesterolaemia. This effect is inherent to the drug's mode of action, which results in impaired excretion of triglycerides and hence accumulation of fat in the liver. Steatosis is a risk factor for advanced liver disease including steatohepatitis and cirrhosis, although it has been suggested that the fat accumulation associated with mipomersen differs from that associated with these conditions. Follow-up of about 141 patients treated for more than 2 years found that hepatic fat content plateaued between 6 and 12 months, then decreased despite continuing mipomersen therapy. Nevertheless, safety data from large numbers of patients treated long term are lacking.[1]

The elevation of hepatic transaminases (mainly alanine aminotransferase; ALT), without elevation of bilirubin or jaundice, is a common adverse effect of mipomersen. It has been reported to be reversible despite continuing treatment, and might correlate with hepatic fat content.[1]

1. Sjouke B, *et al.* Is mipomersen ready for clinical implementation? A transatlantic dilemma. *Curr Opin Lipidol* 2013; **24:** 301–6.

Pharmacokinetics

A peak plasma concentration of mipomersen is usually reached within 3 to 4 hours after subcutaneous injection, and the estimated bioavailability over a dose range of 50 to 400 mg ranges from 54 to 78%. Mipomersen is highly bound to plasma proteins and has a distribution plasma half-life of 2 to 5 hours. Steady state is usually achieved within 6 months with weekly dosing. Mipomersen is metabolised in tissues by endonucleases to form shorter oligonucleotides that are substrates for exonucleases, and both mipomersen and its metabolites are eliminated mainly in the urine. The elimination half-life of mipomersen after subcutaneous injection is about 1 to 2 months.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Kynamro.

Mivazerol *(rINN)*

Mivazérol; Mivazerolum; UCB-22073; Мивазерол.
α-Imidazol-4-yl-2,3-cresotamide.
$C_{11}H_{13}N_3O_2$=217.2
CAS — 125472-02-8.
UNII — W5P1SSA8KD.

Profile

Mivazerol is an alpha$_2$-adrenoceptor agonist that has been investigated for the prevention of perioperative complications resulting from myocardial ischaemia in patients with ischaemic heart disease undergoing non-cardiac surgery.

References.
1. Oliver MF, *et al.* Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: the European Mivazerol Trial (EMIT). *Anesthesiology* 1999: **91:** 951–61.

Moxipril Hydrochloride

(BANM, USAN, rINNM)

CI-925; Hidrocloruro de moxipril; Moeksipril Hidroklorür; Moxipril, Chlorhydrate de; Moxipril, hidrocloruro de; Moxiprili Hydrochloridum; RS-10085-197; SPM-925; Моэксиприла Гидрохлорид.
(3*S*-{2[*R**(*R**)],3*R**})-2-(2-{[1-(Ethoxycarbonyl)-3-phenylpropyl]amino}-1-oxopropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline-carboxylic acid hydrochloride.
$C_{27}H_{34}N_2O_7$,HCl=535.0
CAS — 103775-10-6 (moxipril); 82586-52-5 (moxipril hydrochloride).
ATC — C09AA13.
ATC Vet — QC09AA13.
UNII — Q1UMG3UH45.

Uses and Administration

Moxipril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1).

Moxipril owes its activity to moxiprilat, to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for 2 to 4 weeks during chronic dosing. Moxipril is given orally as the hydrochloride.

The usual initial dose of moxipril hydrochloride is 7.5 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 3.75 mg once daily, given under close medical supervision, is suggested for patients who are taking a *diuretic*; if possible the diuretic should be withdrawn 2 or 3 days before moxipril is started and resumed later if necessary. An initial dose of 3.75 mg once daily is also recommended for patients with renal or hepatic impairment and for the elderly.

The usual maintenance dose is 7.5 to 30 mg daily, which may be given in 2 divided doses if control is inadequate with a single dose.

Reviews.
1. Brogden RN, Wiseman LR. Moexipril: a review of its use in the management of essential hypertension. *Drugs* 1998; **55:** 845–60.
2. Chrysant SG, Chrysant GS. Pharmacological and clinical profile of moexipril: a concise review. *J Clin Pharmacol* 2004; **44:** 827–36.

Administration in renal impairment. In patients with renal impairment (creatinine clearance 40 mL/minute or less) an initial dose of moexipril hydrochloride 3.75 mg is given; in the USA it is required that the maximum dose in such patients should not exceed 15 mg daily.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moexipril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Moexipril acts as a prodrug of the diacid moexiprilat, its active metabolite. After oral doses moexipril is rapidly but incompletely absorbed and is metabolised to moexiprilat in the gastrointestinal mucosa and liver. Absorption is reduced in the presence of food. The bioavailability of moexiprilat is about 13% after oral doses of moexipril, and peak plasma concentrations of moexiprilat occur in about 1.5 hours. Both moexipril and moexiprilat are moderately bound to plasma proteins. Moexipril is excreted mainly in the urine as moexiprilat, unchanged drug, and other metabolites; some moexiprilat may also be excreted in the faeces. The functional elimination half-life of moexiprilat is about 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Moex; ***Fr.***: Moex; ***Ger.***: Fempress; ***Gr.***: Tensotec; ***Hong Kong***: Moex†; ***Israel***: Perdix; ***Ital.***: Femipres; ***Mex.***: Renoprotec; ***Philipp.***: Univasc; ***Pol.***: Cardiotensin†; ***Port.***: Tensotec†; ***Rus.***: Moex (Моэкс); ***S.Afr.***: Perdix†;

Turk.: Univasc; ***UK***: Perdix; ***Ukr.***: Моех (Моэкс); ***USA***: Univasc.

Multi-ingredient Preparations. ***Ger.***: Fempress Plus; ***Ital.***: Enulid; Femipres Plus; ***Philipp.***: Uniretic; ***Rus.***: Moex Plus (Моэкс Плюс); ***Turk.***: Uniretic; ***USA***: Uniretic.

Molsidomine *(BAN, USAN, rINN)*

CAS-276; Molsidomiini; Molsidomin; Molsidomina; Molsidominum; Morsydomine; SIN-10; Молсидомин.

N-Ethoxycarbonyl-3-morpholinosydnonimine.

$C_9H_{14}N_4O_4$=242.2

CAS — 25717-80-0.

ATC — C01DX12.

ATC Vet — QC01DX12.

UNII — D46583G77X.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Molsidomine). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in anhydrous alcohol and in dichloromethane. A 1% solution in water has a pH of 5.5 to 7.5. Protect from light.

Profile

Molsidomine is a nitrovasodilator used in angina pectoris (p. 1254.3). It may also be used in heart failure (p. 1262.3) and after myocardial infarction (below).

Molsidomine is given in usual oral doses of 1 to 4 mg two to four times daily. Modified-release preparations are also available. It is also given intravenously in single doses of 2 to 4 mg and doses of 2 mg may be repeated at intervals of at least 2 hours if necessary; total doses of up to 40 mg daily have been given. Infusions may be given at a rate of up to 3 mg/hour.

Molsidomine is metabolised to linsidomine (p. 1420.3), an active metabolite.

Carcinogenicity. Molsidomine tends to degrade into morpholine (even when protected from the light), a compound considered potentially carcinogenic. This finding led to the suspension of marketing of one molsidomine formulation;[1] an earlier temporary suspension was related to evidence of carcinogenicity in some *animals*, although this has not been confirmed in humans.

1. Anonymous. Corvaton Tropfen. *Dtsch Apotheker Ztg* 1989; **129** (49): VI.

Myocardial infarction. Although intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) may be used in the management of acute myocardial infarction (p. 1257.1), molsidomine and its active metabolite linsidomine (a nitric oxide donor) had no effect on mortality.[1]

1. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group. The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. *Lancet* 1994; **344:** 91–7.

Pharmacokinetics. The pharmacokinetics of molsidomine have been reviewed.[1] Molsidomine is metabolised in the liver to linsidomine and other morpholine derivatives. Prolonged elimination half-lives of molsidomine and linsidomine due to reduced plasma clearance have been reported in patients with liver cirrhosis.[2]

1. Rosenkranz B, *et al.* Clinical pharmacokinetics of molsidomine. *Clin Pharmacokinet* 1996; **30:** 372–84.
2. Spreux-Varoquaux O, *et al.* Pharmacokinetics of molsidomine and its active metabolite, linsidomine, in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; **32:** 399–401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Molsicor†; Molsidaine; ***Austria***: Molsidolat; Molsihexal†; ***Belg.***: Coruno; Corvaton; ***Cz.***: Corvaton; Molsihexal; Molsiket; ***Fr.***: Corvasal; ***Ger.***: Corvaton†; Molsi-Puren†; Molsibeta; Molsigamma; Molsihexal†; molsiket; ***Hung.***: Corvaton; ***Ital.***: Corvalgan; Sidomol; ***Rus.***: Corvamin (Корвамин); Corvaton (Корватон); Dilasidom (Диласидом); Sydnopharm (Сиднофарм); ***Spain***: Corpea†; Molsidain; ***Switz.***: Corvaton; ***Turk.***: Molsicor; ***Ukr.***: Dilasidom (Диласидом)†; Sydnopharm (Сиднофарм).

Multi-ingredient Preparations. ***Ukr.***: Advocard (Адвокард).

Monteplase *(rINN)*

E-6010; Monteplasa; Montéplase; Monteplasum; Монтеплаза.

$C_{2569}H_{3896}N_{746}O_{783}S_{39}$=59010.2

CAS — 156616-23-8.

Profile

Monteplase is a thrombolytic related to alteplase (p. 1296.3) that is used in acute myocardial infarction (p. 1257.1) and pulmonary embolism (see Venous Thromboembolism, p. 1274.1). For acute myocardial infarction, the usual dose is 27 500 units/kg given by intravenous injection as soon as possible after the onset of symptoms. For pulmonary embolism, the usual dose is 13 750 units/kg to 27 500 units/kg.

References.

1. Kawai C, *et al.* A prospective, randomized, double-blind multicenter trial of a single bolus injection of the novel modified t-PA E6010 in the treatment of acute myocardial infarction: comparison with native t-PA. *J Am Coll Cardiol* 1997; **29:** 1447–53.
2. Inoue T, *et al.* A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COmbining Monteplase with Angioplasty (COMA) trial. *Am Heart J* 2002; **144:** E5.
3. Inoue T, *et al.* Long-term benefits of monteplase before coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 2005; **95:** 506–8.
4. Inoue T, *et al.* Therapeutic potential of monteplase in acute myocardial infarction. *Am J Cardiovasc Drugs* 2005; **5:** 225–31.
5. Yamamoto T, *et al.* Thrombolysis with a novel modified tissue-type plasminogen activator, monteplase, combined with catheter-based treatment for major pulmonary embolism. *Circ J* 2009; **73:** 106–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn.* Cleactor.

Moracizine *(BAN, rINN)*

EN-313; Moracizina; Moracizinum; Moricizine (USAN); Морацизин.

Ethyl [10-(3-morpholinopropionyl)phenothiazin-2-yl]carbamate.

$C_{22}H_{25}N_3O_4S$=427.5

CAS — 31883-05-3.

ATC — C01BG01.

ATC Vet — QC01BG01.

UNII — 2GT1D0TMX1.

Moracizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moracizina; Moracizina, hidrocloruro de; Moracizine, Chlorhydrate de; Moracizinhydroklorid; Moracizini Hydrochloridum; Morasitsiinihydrokloridi; Морацизина Гидрохлорид.

$C_{22}H_{25}N_3O_4S$,HCl=464.0

CAS — 29560-58-5.

ATC — C01BG01.

ATC Vet — QC01BG01.

UNII — 71OK3Z1ESP.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Moricizine Hydrochloride). A white to off-white crystalline powder. Soluble in water and in alcohol. Store in airtight containers.

Uses and Administration

Moracizine is a phenothiazine compound that has class I antiarrhythmic activity (p. 1243.1) but does not readily fall into the subclasses a, b, or c. It has been given orally as the hydrochloride in the treatment of serious symptomatic ventricular arrhythmias.

Reviews.

1. Clyne CA, *et al.* Moricizine. *N Engl J Med* 1992; **327:** 255–60.

Cardiac arrhythmias. Like other class I antiarrhythmics (see Cardiac Arrhythmias under Flecainide, p. 1383.2), moracizine has been associated with increased mortality when used prophylactically after myocardial infarction.[1] However, limited evidence suggested that it might be useful in some patients with supraventricular arrhythmias.[2,3]

1. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327:** 227–33.
2. Mehta AV, *et al.* Experience with moricizine HCl in children with supraventricular tachycardia. *Int J Cardiol* 1996; **57:** 31–5.
3. Geller JC, *et al.* Efficacy and safety of moricizine in the maintenance of sinus rhythm in patients with recurrent atrial fibrillation. *Am J Cardiol* 2001; **87:** 172–7.

Adverse Effects and Precautions

As for Flecainide Acetate, p. 1383.3.

Like other antiarrhythmics moracizine can provoke or worsen arrhythmias. This may range from an increase in the frequency of premature ventricular contractions to induction or worsening of ventricular tachycardia.

An increased mortality rate occurred when moracizine was tested in the control of asymptomatic ventricular arrhythmias in post-infarction patients (see Cardiac Arrhythmias under Uses and Administration, above).

Effects on body temperature. Fever with elevated creatine phosphokinase and hepatic transaminase concentrations was associated with moracizine in 2 patients.[1] The fever abated within 48 hours of stopping moracizine and recurred within 24 hours of rechallenge in both patients. Results suggested a similarity to the neuroleptic malignant syndrome that is associated with other phenothiazine derivatives.

1. Miura DS, *et al.* Ethmozine toxicity: fever of unknown origin. *J Clin Pharmacol* 1986; **26:** 153–5.

Interactions

Use of moracizine with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Moracizine undergoes metabolism in the liver and its activity may be influenced by other drugs affecting the enzymes responsible for its metabolism; it is itself an inducer of those enzymes and may thus affect the activity of other drugs.

Pharmacokinetics

Moracizine is readily and almost completely absorbed from the gastrointestinal tract. It undergoes significant first-pass hepatic metabolism so that the oral bioavailability is about 38%. Moracizine is extensively metabolised and some of its many metabolites may be active. It induces its own metabolism; the plasma elimination half-life is about 2 hours after multiple doses. Although plasma concentrations are reduced with multiple dosing, clinical response is not affected. It is about 95% bound to plasma proteins. Moracizine is distributed into breast milk. About 56% of a dose is excreted in the faeces and about 39% in the urine.

References.

1. Benedek IH, *et al.* Enzyme induction by moricizine: time course and extent in healthy subjects. *J Clin Pharmacol* 1994; **34:** 167–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Etmozine (Этмозин).

Pharmacopoeial Preparations

USP 36: Moricizine Hydrochloride Tablets.

Moxisylyte Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moxisilita; Moksisylyyttihydrokloridi; Moxisilita Clorhidrato; Moxisilita, hidrocloruro de; Moxisylyte, Chlorhydrate de; Moxisylythydroklorid; Moxisylyti Hydrochloridum; Moxisylytum Hydrochloridum; Thymoxamine Hydrochloride; Моксизилита Гидрохлорид.

4-(2-Dimethylaminoethoxy)-5-isopropyl-2-methylphenyl acetate hydrochloride.

$C_{16}H_{25}NO_3$,HCl=315.8

CAS — 54-32-0 (moxisylyte); 964-52-3 (moxisylyte hydrochloride).

ATC — C04AX10; G04BE06.

ATC Vet — QC04AX10; QG04BE06.

UNII — WK2KZM9V6X.

NOTE. MOX, formerly THY, is a code approved by the BP 2014 for use on single unit doses of eye drops containing moxisylyte hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Br.*

BP 2014: (Moxisylyte Hydrochloride). A white, odourless or almost odourless, crystalline powder. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether and in petroleum spirit. A 5% solution in water has a pH of 4.5 to 5.5. Protect from light.

Uses and Administration

Moxisylyte is an alpha-adrenoceptor blocker with vasodilating activity. It is used orally in the treatment of peripheral vascular disorders (p. 1272.3) and has been self-administered by intracavernosal injection in erectile dysfunction (p. 2348.2).

Moxisylyte is given as the hydrochloride but the dose may be expressed in terms of the base. Moxisylyte hydrochloride 45.2 mg is equivalent to about 40 mg of moxisylyte.

In the management of **peripheral vascular disease**, the usual oral dose is the equivalent of 40 mg of moxisylyte four times daily increased if necessary to 80 mg four times daily. It should be withdrawn if there is no response in 2 weeks.

Moxisylyte has been used locally in the eye to reverse the mydriasis caused by phenylephrine and other sympathomimetics. It has also been used orally in benign prostatic hyperplasia, although such use has been associated with hepatotoxicity; the doses used in prostatic hyperplasia were generally higher than those in peripheral vascular disease.

Reviews.

1. Marquer C, Bressolle F. Moxisylyte: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in impotence. *Fundam Clin Pharmacol* 1998; **12:** 377–87.

Adverse Effects

Moxisylyte hydrochloride may cause nausea, diarrhoea, headache, vertigo, flushing of the skin, dry mouth, and nasal congestion. Hepatotoxicity has been reported. Overdosage may cause hypotension.

Transient ptosis has occurred occasionally after ophthalmic application. Prolonged erections or priapism have occurred rarely after intracavernosal injection and systemic effects may also occur.

Effects on the liver. Hepatic adverse reactions with moxisylyte first appeared in France after its use in benign prostatic hyperplasia, a condition in which relatively high doses were used (up to 480 mg daily compared with up to 320 mg daily for peripheral vascular disease). The UK CSM subsequently received reports associated with lower doses.[1] Thirteen hepatic reactions, accounting for 17% of all reports of suspected adverse reactions to moxisylyte, had been received as of November 1993. These comprised 3 cases of hepatic function abnormalities, 3 of jaundice, 4 of cholestatic jaundice, 2 of hepatitis, and 1 of hepatitis with jaundice. In most cases the reaction occurred within 5 weeks of the start of treatment and resolved on drug withdrawal. In 9 cases the dosage of moxisylyte was known and varied from 80 to 320 mg daily with 7 patients receiving 160 mg or less daily.

1. CSM/MCA. Hepatic reactions with thymoxamine (Opilon). *Current Problems* 1993; **19:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 10/04/08)

Precautions

Moxisylyte hydrochloride should not be given to patients with active liver disease; monitoring of liver function is recommended, especially if therapy is prolonged or if high doses are being used. It should be given with care to patients with diabetes mellitus as it may theoretically decrease insulin requirements. Intracavernosal injection of moxisylyte is contra-indicated in patients with conditions that predispose to priapism.

Interactions

Moxisylyte may enhance the effects of antihypertensives and the hypotensive effect of moxisylyte may be enhanced by tricyclic antidepressants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Carlytene; ***Irl.***: Opilon†; ***UK***: Opilon.

Pharmacopoeial Preparations
BP 2014: Moxisylyte Tablets.

Moxonidine *(BAN, USAN, rINN)*

BDF-5895; BDF-5896; BE-5895; LY-326869; Moksonidi; Moksonidiini; Moksonidin; Moksonidinas; Moxonid; Moxonidin; Moxonidina; Moxonidinum; Moxonidum; Моксонидин.

4-Chloro-5-(2-imidazolin-2-ylamino)-6-methoxy-2-methylpyrimidine.

$C_9H_{12}ClN_5O$=241.7

CAS — 75438-57-2.

ATC — C02AC05.

ATC Vet — QC02AC05.

UNII — CC6X0L40GW.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Moxonidine). A white or almost white powder. Very slightly soluble in water and in acetonitrile; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol.

Uses and Administration

Moxonidine is a centrally acting antihypertensive structurally related to clonidine (p. 1339.1). It appears to act through stimulation of central imidazoline receptors to reduce sympathetic tone, and also has alpha$_2$-adrenoceptor agonist activity. It is used in the treatment of hypertension (p. 1251.1) and has also been investigated for heart failure (but see below).

In the treatment of hypertension, moxonidine is given orally in a usual initial dose of 200 micrograms once daily. The dose may be increased if necessary, after 3 weeks, to 400 micrograms daily as a single dose or in 2 divided doses, and after a further 3 weeks, to a maximum dose of 600 micrograms daily in 2 divided doses. The dose should be reduced in patients with renal impairment (see below).

References.
1. Chrisp P, Faulds D. Moxonidine: a review of its pharmacology, and therapeutic use in essential hypertension. *Drugs* 1992; **44:** 993–1012.
2. Schachter M, *et al.* Safety and tolerability of moxonidine in the treatment of hypertension. *Drug Safety* 1998; **19:** 191–203.
3. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; **58:** 799–812.
4. Schachter M. Moxonidine. *Prescribers' J* 1999; **39:** 113–17.
5. Fenton C, *et al.* Moxonidine: a review of its use in essential hypertension. *Drugs* 2006; **66:** 477–96.

Administration in renal impairment. UK licensed product information states that in patients with moderate renal impairment (GFR 30 to 60 mL/minute) single doses of moxonidine should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms; moxonidine should not be given in severe impairment (GFR less than 30 mL/minute).

Heart failure. Heart failure is usually treated with diuretics, ACE inhibitors, and beta blockers (see p. 1262.3). Beta blockers are thought to act by suppressing the sympathetic nervous system, which is activated in heart failure. Centrally-acting antihypertensives such as moxonidine also suppress sympathetic activation and might therefore have a role in heart failure. A study[1] in patients with heart failure found that moxonidine reduced plasma-noradrenaline concentrations and increased left ventricular ejection fraction, but also led to an increase in adverse effects. A further study[2] was stopped early due to increased mortality in the group receiving moxonidine.

1. Swedberg K, *et al.* Effects of sustained-release moxonidine, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation* 2002; **105:** 1797–1803.
2. Cohn JN, *et al.* Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003; **5:** 659–67.

Adverse Effects and Treatment

Moxonidine has similar adverse effects to clonidine (p. 1341.2) but causes less sedation. The incidence of dry mouth may also be lower.

Precautions

Moxonidine should not be used in patients with conduction disorders, bradycardia, severe arrhythmias, severe heart failure, severe ischaemic heart disease, severe hepatic or renal impairment, or a history of angioedema. Licensed product information suggests that it should also be avoided in patients with intermittent claudication or Raynaud's disease, Parkinson's disease, epilepsy, glaucoma, and depression. Moxonidine is distributed into breast milk and should not be used during breast feeding.

Although rebound hypertension has not been reported after moxonidine withdrawal it should not be stopped abruptly but should be withdrawn gradually over 2 weeks. As for clonidine (p. 1341.3), if patients are also receiving a beta blocker, this should be stopped several days before moxonidine is withdrawn.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moxonidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The hypotensive effect of moxonidine may be enhanced by other antihypertensives and drugs that cause hypotension. The effect of sedatives and hypnotics, including benzodiazepines, may be enhanced by moxonidine.

Pharmacokinetics

Moxonidine is well absorbed when given orally and has a bioavailability of about 88%. Peak plasma concentrations occur 0.5 to 3 hours after an oral dose. It is excreted almost entirely in the urine as unchanged drug and metabolites; about 50 to 75% of an oral dose is excreted as unchanged drug. The mean plasma elimination half-life is 2 to 3 hours and is prolonged in renal impairment. Moxonidine is about 7% bound to plasma proteins. It is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Physiotens; ***Austria***: Moxonibene; Normohex; ***Belg.***: Moxon; ***Braz.***: Cynt; ***Chile***: Norcynt; ***Cz.***: Cynt; Moxogamma; Moxostad; Physiotens†; ***Denm.***: Moxonat; Physiotens†; ***Fin.***: Physiotens; ***Fr.***: Physiotens; ***Ger.***: Cynt; Moxobeta; Moxocard†; Moxogamma; Physiotens; ***Gr.***: Cynt; Fisiotens; Gilutensin; ***Hong Kong***: Physiotens†; ***Hung.***: Cynt; Moxogamma; Moxostad; Physiotens; ***Indon.***: Physiotens; ***Ital.***: Fisiotens; ***Malaysia***: Physiotens; ***Mex.***: Norcynt; ***Neth.***: Jacomox†; Moxamar; Moxaviv†; Moxoham†; Moxonur; Moxovasc†; ***Norw.***: Physiotens; ***Philipp.***: Physiotens; ***Pol.***: Moxogamma†; Physiotens; ***Port.***: Moxon; ***Rus.***: Cynt (Цинт); Moxonitex (Моксонитекс); Physiotens (Физиотенз); Tenzotran (Тензотран); ***S.Afr.***: Cynt; Moxotens; Physiotens; ***Singapore***: Physiotens†; ***Spain***: Moxon; ***Swed.***: Physiotens; ***Switz.***: Physiotens; ***Turk.***: Cynt; Physiotens; ***UK***: Physiotens; ***Ukr.***: Moxogamma (Моксогамма); Moxonid (Моксонид)†; Physiotens (Физиотенз).

Nadolol *(BAN, USAN, rINN)* ⊗

Nadololi; Nadololis; Nadololum; SQ-11725; Надолол.

(2*R*,3*S*)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol.

$C_{17}H_{27}NO_4$=309.4

CAS — 42200-33-9.

ATC — C07AA12.

ATC Vet — QC07AA12.

UNII — FEN504330V.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nadolol). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in alcohol; practically insoluble in acetone.

USP 36: (Nadolol). A white or off-white, practically odourless, crystalline powder. Soluble in water at pH 2; slightly soluble in water at pH 7 to 10; freely soluble in alcohol and in methyl alcohol; insoluble in acetone, in ether, in petroleum spirit, in trichloroethane, and in benzene; slightly soluble in chloroform, in dichloromethane, and in isopropyl alcohol.

Uses and Administration

Nadolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity. Nadolol is given orally in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and cardiac arrhythmias (p. 1266.1). It is also used in the management of hyperthyroidism (p. 2332.2) and in the prophylactic treatment of migraine (p. 670.3).

In the treatment of **hypertension**, nadolol is usually given in an initial dose of 40 to 80 mg once daily, increased weekly according to response to 240 mg or more daily.

In **angina pectoris**, the usual initial dose is 40 mg once daily, increased weekly according to response to usual doses of up to 160 mg daily; some patients may require up to 240 mg daily. Doses of 40 to 160 mg once daily have also been given for **cardiac arrhythmias**.

Doses of 40 to 160 mg once daily are used in **migraine** prophylaxis.

As an adjunct in the treatment of **hyperthyroidism**, doses of 80 to 160 mg once daily have been given; most patients are reported to require the higher dose.

Patients with renal impairment may require a reduction in dose (see below).

Administration in renal impairment. Nadolol is excreted mainly in the urine and doses should be reduced in patients with renal impairment, usually by increasing the dosage interval. For patients with hypertension or angina pectoris, US licensed product information recommends the following dosage intervals, based on creatinine clearance (CC):

- CC between 31 and 50 mL/minute per 1.73 m^2: give every 24 to 36 hours
- CC between 10 and 30 mL/minute per 1.73 m^2: give every 24 to 48 hours
- CC less than 10 mL/minute per 1.73 m^2: give every 40 to 60 hours.

Variceal haemorrhage. References[1-7] to the use of nadolol, alone or with isosorbide mononitrate, in the management of variceal haemorrhage (p. 2563.1).

1. Merkel C, *et al.* Gruppo Triveneto per l'Ipertensione Portale. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology* 2004; **127:** 476–84.
2. Mann NS. Nadolol versus band ligation for prevention of variceal bleeding. *Gastrointest Endosc* 2004; **60:** 1036–7.
3. de la Peña J, *et al.* Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. *Hepatology* 2005; **41:** 572–8.
4. Romero G, *et al.* Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. *Aliment Pharmacol Ther* 2006; **24:** 601–11.
5. Wang HM, *et al.* Comparison of endoscopic variceal ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first variceal bleeding in cirrhotic patients. *J Chin Med Assoc* 2006; **69:** 453–60.
6. Villanueva C, *et al.* Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. *Aliment Pharmacol Ther* 2009; **29:** 397–408.
7. García-Pagán JC, *et al.* Spanish Variceal Bleeding Study Group. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of recurrent bleeding: a multicentre randomised controlled trial. *Gut* 2009; **58:** 1144–50.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Concentrations of nadolol distributed into breast milk are higher than those in maternal plasma. In a study[1] in 12 normotensive women given nadolol 80 mg daily by mouth for 5 days, the mean nadolol concentration in milk for the 24 hours after the last dose was 357 nanograms/mL; the equivalent mean serum-nadolol concentration was only 77 nanograms/mL. It was calculated that a 5-kg infant would therefore ingest about 2 to 7% of an equivalent adult dose. No adverse effects have been seen in breast-fed infants whose mothers were given nadolol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Devlin RG, *et al.* Nadolol in human serum and breast milk. *Br J Clin Pharmacol* 1981; **12:** 393–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Hypersensitivity pneumonitis was associated with nadolol in a patient given the drug for migraine.[1] Symptoms improved when nadolol was withdrawn.

1. Levy MB, *et al.* Nadolol and hypersensitivity pneumonitis. *Ann Intern Med* 1986; **105:** 806–7.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Nadolol is incompletely absorbed from the gastrointestinal tract to give peak plasma concentrations about 3 or 4 hours after a dose. It has low lipid solubility. Nadolol is widely distributed and concentrations found in breast milk have been higher than those in serum. It is only about 30% bound to plasma proteins. It does not appear to be metabolised and is excreted mainly in the urine. The plasma half-life has been reported as ranging from about 12 to 24 hours. Nadolol is reported to be dialysable.

In 4 patients with mild hypertension given nadolol 2 mg orally or intravenously, the elimination half-life from plasma was an average of 10 to 12 hours (a range of 5.9 to 12.2 hours after intravenous doses, and a range of 9.6 to 14.2 hours after oral doses). Calculations based on urinary excretion and plasma concentration data suggested that about 33% was absorbed after oral dosage. There was evidence of biliary as well as urinary excretion since after intravenous dosage about 73% was excreted in urine and 23% in faeces. Nadolol did not appear to be metabolised.[1] In a similar study of therapeutic oral doses, terminal half-lives ranging from 14 to 17 hours were reported for nadolol 80 mg given as a single dose and the same dose daily in a multiple dosage regimen.[2]

1. Dreyfuss J, *et al.* Metabolic studies in patients with nadolol: oral and intravenous administration. *J Clin Pharmacol* 1977; **17:** 300–7.
2. Dreyfuss J, *et al.* Pharmacokinetics of nadolol, a beta-receptor antagonist: administration of therapeutic single- and multiple-dosage regimens to hypertensive patients. *J Clin Pharmacol* 1979; **19:** 712–20.

Children. The pharmacokinetics of nadolol given intravenously and orally were studied in six children aged 3 months to 14 years.[1] The elimination half-lives for the two oldest children aged 10 and 14 years were 7.3 and 15.7 hours, respectively. These values are similar to those reported for adults whereas in the children 22 months of age or younger, shorter half-lives of 3.2 to 4.3 hours were found. The shorter half-lives were probably a result of a reduction in the total apparent volume of distribution of nadolol in the youngest children. Elimination rates were similar after either intravenous or oral dosage.

1. Mehta AV, *et al.* Pharmacokinetics of nadolol in children with supraventricular tachycardia. *J Clin Pharmacol* 1992; **32:** 1023–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Corgard; ***Belg.***: Corgard†; ***Braz.***: Corgard; ***Canad.***: Apo-Nadol; ***Chile***: Corgard; ***Fr.***: Corgard; ***Gr.***: Corgard; ***Ital.***: Corgard†; ***Mex.***: Corgard; ***NZ***: Corgard; ***S.Afr.***: Corgard†; ***Spain***: Solgol; ***UK***: Corgard; ***USA***: Corgard; ***Venez.***: Corgard.

Multi-ingredient Preparations. ***Gr.***: Corzide; ***Mex.***: Corgaretic; ***S. Afr.***: Corgaretic†; ***USA***: Corzide.

Pharmacopoeial Preparations

USP 36: Nadolol and Bendroflumethiazide Tablets; Nadolol Tablets.

Nadroparin Calcium *(BAN, rINN)*

CY-216; CY-216D; Nadropariinikalsium; Nadroparin-Calcium; Nadroparin Kalsiyum; Nadroparin vápenatá sůl; Nadroparina cálcica; Nadroparine calcique; Nadroparin-kalcium; Nadroparinkalcium; Nadroparino kalcio druska; Nadroparinum Calcicum; Надропарин Кальций.

ATC — B01AB06.

ATC Vet — QB01AB06.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nadroparin Calcium). It is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3600 and 5000, with a characteristic value of 4300. The mass percentage of chains lower than 2000 is not more than 15%. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 95 units and not more than 130 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 2.5 and 4.0.

Profile

Nadroparin calcium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p. 1254.3).

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used. For *prophylaxis* of **venous thromboembolism** during surgery, patients at moderate risk of thrombosis are given 2850 units of nadroparin calcium by subcutaneous injection daily for at least 7 days or until the patient is ambulant; the first dose is given 2 to 4 hours before the procedure. For patients at high risk of thrombosis the dose is adjusted according to body-weight. Usual doses are 38 units/kg 12 hours before surgery, 12 hours post-operatively and then daily until 3 days after the procedure; the dose is then increased by 50% to 57 units/kg daily. The total duration of treatment should be at least 10 days.

For the *treatment* of thromboembolism, nadroparin calcium is given in a dose of 171 units/kg once daily. For patients at increased risk of bleeding, the total daily dose may be given in 2 divided doses.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** sessions lasting less than 4 hours, a single dose of nadroparin calcium is given into the arterial line of the circuit at the beginning of the dialysis session. The usual dose is 2850 units for patients weighing less than 50 kg, 3800 units for patients weighing 50 to 69 kg, and 5700 units for patients weighing 70 kg or more. Doses should be halved in patients at high risk of haemorrhage.

In the management of unstable **angina**, nadroparin calcium is given in an initial intravenous injection of 86 units/kg, followed by a subcutaneous dose of 86 units/kg every 12 hours for about 6 days. Low-dose aspirin should also be given.

Elimination of nadroparin is prolonged in renal impairment, and doses may need to be reduced in moderate or severe impairment.

References.

1. Barradell LB, Buckley MM. Nadroparin calcium: a review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. *Drugs* 1992; **44:** 858–88.
2. Davis R, Faulds D. Nadroparin calcium: a review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs Aging* 1997; **10:** 299–322.
3. Egger B, *et al.* Efficacy and safety of weight-adapted nadroparin calcium vs. heparin sodium in prevention of clinically evident thromboembolic complications in 1,190 general surgical patients. *Dig Surg* 2000; **17:** 602–9.
4. Makatsaria AD, *et al.* Use of the low-molecular-weight heparin nadroparin during pregnancy: a review. *Curr Med Res Opin* 2003; **19:** 4–12.
5. Simonneau G, *et al.* FX140 Study Investigators. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. *J Thromb Haemost* 2006; **4:** 1693–1700.
6. van Ommen CH, *et al.* Nadroparin therapy in pediatric patients with venous thromboembolic disease. *J Pediatr Hematol Oncol* 2008; **30:** 230–4.
7. Agnelli G, *et al.* PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009; **10:** 943–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nadroparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fraxiparine; ***Austria***: Fraxiparin; ***Belg.***: Fraxiparine; Fraxodi; ***Braz.***: Fraxiparina; ***Canad.***: Fraxiparine; ***Chile***: Fraxiparine; ***China***: Fraxiparine (速碧林); Fraxodi (速碧劲); ***Cz.***: Fraxiparine; ***Fr.***: Fraxiparine; Fraxodi; ***Ger.***: Fraxiparin; Fraxodi; ***Gr.***: Fraxiparine; ***Hong Kong***: Fraxiparine; ***Hung.***: Fraxiparine; Fraxodi; ***India***: Cardioparin; Fraxiparine; Fraxodi; Nadrohep; ***Indon.***: Fraxiparine; ***Israel***: Fraxiparine; ***Ital.***: Fraxiparina; Fraxodi; Seledie; Seleparina; ***Malaysia***: Fraxiparine; ***Mex.***: Fraxiparine; Fraxodi†; ***Neth.***: Fraxiparine; Fraxodi; ***Philipp.***: Fraxiparine; ***Pol.***: Fraxiparine; Fraxodi; ***Port.***: Fraxiparina; Fraxodi; ***Rus.***: Fraxiparine (Фраксипарин); ***S.Afr.***: Fraxiparine; ***Singapore***: Fraxiparine; ***Spain***: Fraxiparina; ***Switz.***: Fraxiforte; Fraxiparine; ***Thai.***: Fraxiparine; ***Turk.***: Fraxiparine; Fraxodi; ***Ukr.***: Fraxiparine (Фраксипарин); ***Venez.***: Fraxiparina.

Naftidrofuryl Oxalate *(BANM, rINNM)*

EU-1806; LS-121; Nafronyl Oxalate (USAN); Nafronyl Oxalate; Naftidrofuril-hidrogén-oxalát; Naftidrofurilio-vandenilio oksalatas; Naftidrofurilo, oxalato de; Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl, hydrogénooxalate de; Naftidrofuryl, Oxalate de; Naftidrofurylhydrogenoxalat; Naftidrofuryli Hydrogenooxalas; Naftidrofuryli Oxalas; Naftidrofuryl-oxalát; Naftidrofurylväteoxalat; Naftidrofuryylivetyoksalaatti; Oxalato de naftidrofurilo; Нафтидрофурила Оксалат.

2-Diethylaminoethyl 3-(1-naphthyl)-2-tetrahydrofurfurylpropionate hydrogen oxalate.

$C_{24}H_{33}NO_3,C_2H_2O_4$=473.6

CAS — 31329-57-4 (naftidrofuryl); 3200-06-4 (naftidrofuryl oxalate).

ATC — C04AX21.

ATC Vet — QC04AX21.

UNII — 5ADB8D9388.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl Oxalate BP 2014). A white or almost white powder. Freely soluble in water; freely soluble or soluble in alcohol; slightly or sparingly soluble in acetone.

Uses and Administration

Naftidrofuryl oxalate is used as a vasodilator in the treatment of peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2). It is also claimed to enhance cellular oxidative capacity thereby protecting cells against the results of ischaemia.

Naftidrofuryl oxalate is given orally in usual doses of 100 to 200 mg three times daily for peripheral vascular disorders and 100 mg three times daily for cerebrovascular disorders.

Naftidrofuryl oxalate has also been given parenterally. However, intravenous use has been associated with serious adverse effects (see below) and intravenous preparations have been withdrawn.

References.

1. De Backer TLM, *et al.* Naftidrofuryl for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).

Adverse Effects

Naftidrofuryl oxalate given orally may cause nausea and epigastric pain. Rash has been reported occasionally. Hepatitis or hepatic failure has occurred rarely. Convulsions and depression of cardiac conduction may occur after overdosage. After intravenous use cardiac arrhythmias, hypotension, and convulsions have been reported and intravenous preparations have been withdrawn from the market (see below).

In early 1995 the UK CSM published details of adverse reactions to naftidrofuryl.[1] After parenteral doses of naftidrofuryl 47 reports of 79 reactions had been received, the most serious consequences being 9 cases of cardiac arrhythmias, 3 of convulsions, and 2 of hypotension. It was also noted that 2 fatal cases of cardiac arrest had occurred in Germany after bolus intravenous doses and it was stressed that the drug must not be given as a bolus but as a slow intravenous infusion. Additionally, 16 reports, including one fatality, of hepatitis or hepatic failure associated with oral naftidrofuryl had been received although this appeared to be a rare reaction.

Later in 1995, after a review conducted in the UK and Europe, it was announced by the CSM that intravenous naftidrofuryl was to be withdrawn.[2] It was considered that the risks of cardiac and neurological toxicity outweighed the benefits of intravenous dosage in peripheral vascular

disease. The oral form of naftidrofuryl would remain available.

1. CSM/MCA. Adverse reactions with naftidrofuryl (Praxilene). *Current Problems* 1995; **21:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)
2. CSM/MCA. Withdrawal of naftidrofuryl infusion (Praxilene Forte). *Current Problems* 1995; **21:** 7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)

Effects on the kidneys. Calcium oxalate crystals in the renal tubules of 2 patients with acute renal failure[1] were associated with the high amounts of oxalate they had received when naftidrofuryl oxalate was given intravenously.

1. Moesch C, *et al.* Renal intratubular crystallisation of calcium oxalate and naftidrofuryl oxalate. *Lancet* 1991; **338:** 1219–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dusodril; ***Belg.***: Praxilene; ***Braz.***: Iridux; ***Cz.***: Enelbin; ***Fr.***: Di-Actane; Gevatran; Naftilux; Praxilene; ***Ger.***: Dusodril; Nafti; Naftilong†; ***Gr.***: Praxilene; ***Hong Kong***: Praxilene; ***Hung.***: Naftilong; ***Indon.***: Frilix; Nafoxal; Praxilene; Vascuprax; ***Irl.***: Praxilene; ***Ital.***: Praxilene; ***Mex.***: Iridus; ***Philipp.***: Praxilene; ***Port.***: Praxilene; ***Rus.***: Dusopharm (Дузофарм); Enelbin (Энелбин); ***Singapore***: Praxilene; ***Spain***: Praxilene; ***Switz.***: Praxilene; Sodipryl retard; ***Thai.***: Praxilene; ***UK***: Praxilene; ***Venez.***: Iridus.

Pharmacopoeial Preparations
BP 2014: Naftidrofuryl Capsules.

Natriuretic Peptides ⊗

Péptidos natriuréticos; Натрийуретические Пептиды.

Profile

Natriuretic peptides are endogenous substances that possess diuretic, natriuretic, and vasodilator properties. Three types are known. *Atrial natriuretic peptide* (ANP), also known as atrial natriuretic factor (ANF), atriopeptin, auriculin, or cardionatrin, is produced mainly in the cardiac atria, although another form, ularitide (urodilatin), is produced in the kidney. *Brain natriuretic peptide* (BNP, B-type natriuretic peptide) was originally isolated from brain tissue but is now known to be mainly produced by the cardiac ventricles. *C-type natriuretic peptide* (CNP) is produced by the endothelium and appears to act locally as a vasodilator but has little natriuretic effect.

Natriuretic peptides have an important physiological role in fluid and electrolyte homoeostasis and in the regulation of blood pressure, and they interact closely with other complex systems such as the renin-angiotensin-aldosterone cascade. Plasma concentrations of atrial natriuretic peptide and brain natriuretic peptide are altered in some pathological states and have been used as indicators of cardiac function. Natriuretic peptides that have been investigated for therapeutic use include anaritide, a synthetic form of atrial natriuretic peptide, and ularitide; both have been studied in acute renal failure, and ularitide has also been studied in heart failure. Recombinant forms of atrial natriuretic peptide (carperitide, p. 1332.3) and brain natriuretic peptide (nesiritide, below) are used in the management of acute heart failure.

The currently available natriuretic peptides have short half-lives and have to be given parenterally. Other approaches to manipulating their effects have been investigated, including the use of atriopeptidase inhibitors (neutral endopeptidase inhibitors; neutral metalloendopeptidase inhibitors), such as candoxatrilat and ecadotril (sinorphan) to prolong the half-life of endogenous atrial natriuretic peptide. Compounds such as omapatrilat (p. 1460.1) that inhibit both neutral endopeptidase and angiotensin-converting enzyme are also being studied.

References.

1. Tan ACITL, *et al.* Atrial natriuretic peptide: an overview of clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 1993; **24:** 28–45.
2. Richards A M. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. *Heart* 1996; **76** (suppl 3): 36–44.
3. Forssmann W, *et al.* The renal urodilatin system: clinical implications. *Cardiovasc Res* 2001; **51:** 450–62.
4. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006; **92:** 843–9.
5. Mitrovic V, *et al.* Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006; **27:** 2823–32.
6. Lüss H, *et al.* Renal effects of ularitide in patients with decompensated heart failure. *Am Heart J* 2008; **155:** 1012.e1–8.
7. Rubattu S, *et al.* Natriuretic peptides: an update on bioactivity, potential therapeutic use, and implication in cardiovascular diseases. *Am J Hypertens* 2008; **21:** 733–41.
8. Jankowski M. B-type natriuretic peptide for diagnosis and therapy. *Recent Pat Cardiovasc Drug Discov* 2008; **3:** 77–83.
9. Das BB, Solinger R. Role of natriuretic peptide family in cardiovascular medicine. *Cardiovasc Hematol Agents Med Chem* 2009; **7:** 29–42.
10. Shimada M, *et al.* Role of natriuretic peptides in cardiovascular surgery. *Expert Rev Cardiovasc Ther* 2009; **7:** 515–19.
11. Nigwekar SU, *et al.* Atrial natriuretic peptide for preventing and treating acute kidney injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 26/10/09).
12. Krupička J, *et al.* Natriuretic peptides — physiology, pathophysiology and clinical use in heart failure. *Physiol Res* 2009; **58:** 171–7.

Nebivolol *(BAN, USAN, rINN)* ⊗

Narbivolol; Nébivolol; Nebivololi; Nebivololum; R-65824; Небиволол.

(1*RS*,1′*RS*)-1,1′-[(2*RS*,2′*SR*)-Bis(6-fluorochroman-2-yl)]-2,2′-iminodiethanol.

$C_{22}H_{25}F_2NO_4$=405.4

CAS — 99200-09-6; 118457-14-0.

ATC — C07AB12.

ATC Vet — QC07AB12.

UNII — 030Y90569U.

Nebivolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de nebivolol; Nébivolol, Chlorhydrate de; Nebivolol, hidrocloruro de; Nebivololi Hydrochloridum; R-067555; R-67555; Небиволола Гидрохлорид.

$C_{22}H_{25}F_2NO_4$,HCl=441.9

CAS — 169293-50-9; 152520-56-4.

ATC — C07AB12.

ATC Vet — QC07AB12.

UNII — JGS34J7L9I.

Uses and Administration

Nebivolol is a cardioselective beta blocker (p. 1316.3). It has vasodilating activity, which appears to be due to a direct action on the endothelium, possibly involving nitric oxide release. It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Nebivolol is used in the management of hypertension (p. 1251.1), and as an adjunct to standard therapy in patients aged 70 years and older with stable chronic heart failure (p. 1262.3). It is given orally as the hydrochloride although doses are expressed in terms of the base; 5.45 mg of nebivolol hydrochloride is equivalent to about 5 mg of base.

In **hypertension** the usual initial dose of nebivolol is 5 mg once daily. US licensed product information allows the dose to be increased, if necessary, at intervals of 2 weeks, to a maximum dose of 40 mg once daily. Dosage reduction may be necessary in the elderly and in patients with hepatic or renal impairment (see below).

In **heart failure** the initial dose of nebivolol is 1.25 mg once daily. If tolerated, the dose should be doubled every 1 to 2 weeks up to a maximum of 10 mg once daily.

Reviews.

1. Moen MD, Wagstaff AJ. Nebivolol: a review of its use in the management of hypertension and chronic heart failure. *Drugs* 2006; **66:** 1389–1409.
2. Veverka A, *et al.* Nebivolol: a third-generation β -adrenergic blocker. *Ann Pharmacother* 2006; **40:** 1353–60.
3. Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a β-adrenoceptor antagonist with unique characteristics. *Drugs* 2007; **67:** 1097–1107.
4. Veverka A, Salinas JL. Nebivolol in the treatment of chronic heart failure. *Vasc Health Risk Manag* 2007; **3:** 647–54.
5. Prisant LM. Nebivolol: pharmacologic profile of an ultraselective, vasodilatory β_1-blocker. *J Clin Pharmacol* 2008; **48:** 225–39.
6. Cheng JW. Nebivolol: a third-generation beta-blocker for hypertension. *Clin Ther* 2009; **31:** 447–62.
7. Münzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. *J Am Coll Cardiol* 2009; **54:** 1491–9.

Administration in the elderly. Some UK licensed product information state that, for hypertension, patients over 65 years of age should be given an initial dose of 2.5 mg of nebivolol once daily, increased to 5 mg once daily if required.

Administration in hepatic impairment. UK licensed product information contra-indicates the use of nebivolol in patients with hepatic impairment. In the USA, licensed product information also contra-indicates nebivolol in severe hepatic impairment (Child-Pugh higher than class B) but patients with moderate hepatic impairment may be given nebivolol for hypertension in an initial oral dose of 2.5 mg once daily, increased with caution if required.

Administration in renal impairment. UK licensed product information states that in hypertension the initial dose of nebivolol should be reduced to 2.5 mg once daily in patients with renal impairment, increased to 5 mg once daily for maintenance if required. US licensed product information similarly recommends an initial dose of 2.5 mg once daily in patients with severe renal impairment (creatinine clearance below 30 mL/minute); the dose may be increased cautiously if required.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Nebivolol is rapidly absorbed after oral doses. It is extensively metabolised in the liver by alicyclic and aromatic hydroxylation, *N*-dealkylation, and glucuronidation; the hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism, and bioavailability and half-life vary widely. In fast metabolisers the elimination half-life of nebivolol is about 10 hours and that of the hydroxy metabolites is about 24 hours. Peak plasma concentrations of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolisers and the half-lives of nebivolol and its hydroxy metabolites are prolonged.

Nebivolol is about 98% bound to plasma proteins. It has high lipid solubility. It is excreted in the urine and faeces, almost entirely as metabolites. Nebivolol is distributed into breast milk in *animals*.

Metabolism. Despite wide variations in nebivolol bioavailability, peak plasma concentrations, and elimination half-life in 37 patients identified as either poor or extensive metabolisers of CYP2D6, metaboliser status did not significantly affect the nature and frequency of adverse effects nor the clinical response during treatment of essential hypertension.[1]

1. Lefebvre J, *et al.* The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension. *Br J Clin Pharmacol* 2007; **63:** 575–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nabila; Nebilet; Syncrocor; ***Austral.***: Nebilet; ***Austria***: Hypoloc; Nebilan; Nomexor; ***Belg.***: Hypoloc; Nobiten; ***Braz.***: Nebilet; ***Chile***: Anfibol; Nebilet; Pertium; ***Cz.***: Ezocem; Nebilan†; Nebilet; Nebinorm; Nebiscal; Nebispes†; Nebitrix; ***Denm.***: Dublock; Hypoloc; Lobivon; Nebicon; Nebidelta; Nebithan; ***Fin.***: Hypoloc; Nebilet; ***Fr.***: Nebilox; Temerit; ***Ger.***: Nebilet; ***Gr.***: Bivol; Dublock; Hypoloc; Lobibeta; Lobivon; Nebicur; Noviblock; Nozac; ***Hung.***: Esteban; Ezocem; Nebacop; Nebaletor; Nebibeta; Nebilet; Nebispes; Nebivep; Nebivogen; Nevotens; ***India***: Endolol; Nebest; Nebicard; Nebilol; Nebilong; Nebimac; Nebinex; Nebipil; Nebistar; Nebiten; Nebivas; Nebula; Nevol; Niavas; Nodon; Nubeta; NYFE; ***Irl.***: Nebilet; Nebimel; Nebol; Nebtev†; Nelet; ***Ital.***: Lobivon; Nebilox; ***Malaysia***: Nebilet; ***Neth.***: Ebivol†; Hypoloc; Lobivon; Nebilet; Nebiloc; Nebilostad; ***Philipp.***: Nebicar; Nebicard; ***Pol.***: Ebivol; Ezocem; Nebicard; Nebilenin; Nebilet; Nebinad; Nebispes; Nebitrix; Nebivor; Nedal; ***Port.***: Blokat; Hypoloc; Nebilet; Nebimarin; ***Rus.***: Binelol (Бинелол); Nebilet (Небилет); Nebivator (Небиватор); ***S.Afr.***: Nebilet; ***Singapore***: Nebilet; ***Spain***: Lobivon; Silostar; ***Swed.***: Hypoloc; ***Switz.***: Nebilet; ***Thai.***: Nebilet; ***Turk.***: Nebinorm; Nexivol; Vasoxen; ***UK***: Nebilet; ***Ukr.***: Nebilet (Небилет); Nebilong (Небилонг); Nebival (Небівал); ***USA***: Bystolic; ***Venez.***: Nebilet.

Multi-ingredient Preparations. ***Austria***: Nomexor plus HCT; ***Belg.***: Hyporetic; Nobiretic; ***Cz.***: Nebilet Plus H; ***Denm.***: Nebilet Comp†; ***Fin.***: Hypoloc Comp; ***Fr.***: Conebilox; Temerituo; ***Gr.***: Hypoloc Plus; Lobivon-Plus; ***India***: Amlopres-NB; Amlovas-SN; Nebest-H; Nebicard-H; Nebicard-SM; Nebicard-V; Nebilol-H; Nebilong-AM; Nebilong-H; Nebimac-H; Nebinex-AM; Nebipril-SA; Nebistar-SA; Nebiten-H; Nebivas-H; Nebivas-SA; Nevol-H; Niavas-D; Nodon-AM; Nodon-H; Nubeta-H; Nubeta-SM; NYFE-SA; ***Irl.***: Nebilet Plus; ***Neth.***: Hyporetic; Lobiretic; Nebiretic; ***Spain***: Lobivon Plus; Silostar Plus; ***Switz.***: Nebilet Plus.

Nesiritide Citrate *(USAN, rINNM)* ⊗

Citrato de nesiritida; Nésiritide, Citrate de; Nesiritidi Citras; Nesiritida, citrato de; Незиритида Цитрат.

$C_{143}H_{244}N_{50}O_{42}S_4$,$xC_6H_8O_7$

CAS — 124584-08-3 (nesiritide); 189032-40-4 (nesiritide citrate).

ATC — C01DX19.

ATC Vet — QC01DX19.

UNII — EL5U85UKD2.

Incompatibility. The manufacturer states that nesiritide injection is physically and/or chemically incompatible with heparin, insulin, sodium etacrynate, bumetanide, enalaprilat, hydralazine, furosemide, and the preservative sodium metabisulfite. Nesiritide binds to heparin and should not be given through heparin-coated central catheters.

Uses and Administration

Nesiritide is a recombinant brain natriuretic peptide (see p. 1444.1) used in the management of acutely decompensated heart failure (below). It is given intravenously as the citrate, but dosage is expressed in terms of the base. The initial dose of nesiritide is 2 micrograms/kg by intravenous injection over 1 minute, followed by a maintenance infusion of 10 nanograms/kg per minute.

Heart failure. The use of nesiritide in acute decompensated heart failure (p. 1262.3) has been reviewed.[1-4] It may be used for short-term treatment as an alternative to standard intravenous therapy with vasodilators, inotropes, or diuretics, and appears to have no proarrhythmic effects; however, its effects on mortality are controversial (see under Adverse Effects and Precautions, below) and its role in therapy remains unclear. There is some evidence that it may be safely used in addition to standard therapy[5-7] and may have a role as a more prolonged treatment in patients awaiting cardiac transplantation.[8] Nesiritide has also been given intermittently for outpatient management of chronic heart failure,[9,10] but some have advised against such use.[11]

1. Vichiendilokkul A, *et al.* Nesiritide: a novel approach for acute heart failure. *Ann Pharmacother* 2003; **37:** 247–58.
2. Keating GM, Goa KL. Nesiritide: a review of its use in acute decompensated heart failure. *Drugs* 2003; **63:** 47–70.
3. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; **30:** 765–81.
4. Tong AT, Rozner MA. The role of nesiritide in heart failure. *Expert Opin Drug Metab Toxicol* 2009; **5:** 823–34.
5. O'Dell KM, *et al.* Nesiritide for secondary pulmonary hypertension in patients with end-stage heart failure. *Am J Health-Syst Pharm* 2005; **62:** 606–9.
6. Smull DL, Jorde UP. Concomitant use of nesiritide and milrinone in decompensated congestive heart failure. *Am J Health-Syst Pharm* 2005; **62:** 291–5.
7. Sakr A, *et al.* Nesiritide in the initial management of acute decompensated congestive heart failure. *Conn Med* 2008; **72:** 517–23.
8. Witteles R, *et al.* B-type natriuretic peptide is effective therapy before care. *Ann Intern Med* 2004; **141:** 895.
9. Sheikh-Taha M. Intermittent nesiritide therapy in outpatients with chronic heart failure. *Am J Health-Syst Pharm* 2005; **62:** 196–8.
10. Schwarz ER, *et al.* Intermittent outpatient nesiritide infusion reduces hospital admissions in patients with advanced heart failure. *J Cardiovasc Pharmacol Ther* 2007; **12:** 232–6.
11. Bauer JB, Randazzo MA. Nesiritide for outpatient treatment of heart failure. *Am J Health-Syst Pharm* 2005; **62:** 2639–42.

Adverse Effects and Precautions

The most common adverse effects of nesiritide relate to vasodilatation and include hypotension, headache, and dizziness. Nausea and vomiting, abdominal pain, back pain, angina pectoris, insomnia, and anxiety, have also been reported. Cardiac arrhythmias have occurred but may be associated with the underlying condition. Adverse effects on renal function have been reported. If hypotension occurs the infusion of nesiritide should be stopped or the dose reduced and general supportive measures should be used; the hypotension may persist for several hours.

Nesiritide should not be used as primary therapy in patients with cardiogenic shock or with hypotension. It is not recommended in patients with low cardiac filling pressures or in those for whom vasodilators are inappropriate, such as those with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, or pericardial tamponade.

Effects on the kidneys. Nesiritide has both haemodynamic and neurohormonal effects on the kidneys and has been reported to worsen renal function. A meta-analysis[1] found that nesiritide significantly increased the risk of worsening renal function in patients with acute heart failure, and there is some evidence[2] that this may be related to the duration of treatment. However, a randomised study[3] in patients with acute heart failure and pre-existing renal impairment found that the effect of nesiritide on renal function was neutral. A review[4] of the data concluded that nesiritide should nevertheless be used with extreme caution in those with renal dysfunction; it has been suggested[5] that omission of the initial bolus dose might lessen renal hypoperfusion.

1. Sackner-Bernstein JD, *et al.* Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; **111:** 1487–91. Correction. *ibid.*; 2274.
2. Chow SL, *et al.* Effect of nesiritide infusion duration on renal function in acutely decompensated heart failure patients. *Ann Pharmacother* 2007; **41:** 556–61.
3. Witteles RM, *et al.* Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007; **50:** 1835–40.
4. Dontas IO, *et al.* Impact of nesiritide on renal function and mortality in patients suffering from heart failure. *Cardiovasc Drugs Ther* 2009; **23:** 221–33.
5. Witteles RM. Nesiritide, heart failure, and renal dysfunction: irrational exuberance or throwing the baby out with the bathwater. *Cardiovasc Drugs Ther* 2009; **23:** 183–6.

Effects on mortality. Although nesiritide improves haemodynamics in patients with acute decompensated heart failure, its effects on mortality are controversial.[1] A retrospective study[2] comparing nesiritide with inotrope therapy or glyceryl trinitrate in patients with acute decompensated heart failure found a similar risk of in-hospital mortality with nesiritide and glyceryl trinitrate, which was significantly lower than the risk with inotrope therapy. However, a meta-analysis[3] of controlled studies comparing nesiritide with non-inotrope control therapy found that there was a trend to higher mortality at 30 days in patients given nesiritide; the results were not statistically significant, but became so after correction of the number of deaths in one of the studies.[4] A later meta-analysis[5] also found a trend towards increased mortality with nesiritide at 30 days, but the results again were not statistically significant, and there was no difference in mortality between nesiritide and control patients at 180 days.

1. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; **30:** 765–81.
2. Abraham WT, *et al.* In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46:** 57–64.
3. Sackner-Bernstein JD, *et al.* Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293:** 1900–5.
4. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA* 2006; **296:** 1465–6.
5. Arora RR, *et al.* Short and long-term mortality with nesiritide. *Am Heart J* 2006; **152:** 1084–90.

Interactions

The risk of hypotension may be increased in patients receiving nesiritide with other drugs that lower blood pressure.

Pharmacokinetics

Nesiritide is cleared from the circulation by 3 mechanisms: uptake into cells; proteolytic cleavage by endopeptidases; and excretion by the kidneys. It has a biphasic elimination, with a terminal elimination half-life of 18 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Natrecor; ***Canad.:*** Natrecor; ***Indon.:*** Natrecor†; ***Israel:*** Noratak; ***Singapore:*** Natrecor†; ***Switz.:*** Noratak†; ***USA:*** Natrecor; ***Venez.:*** Natrecor.

Nicardipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de nicardipino; Nicardipina Cloridrato; Nicardipine, Chlorhydrate de; Nicardipini Hydrochloridum; Nicardipino, hidrocloruro de; Nikardipiinihydrokloridi; Nikardipin Hidroklorür; Nikardipinhydroklorid; RS-69216; RS-69216-XX-07-0; YC-93; Никардипина Гидрохлорид.

2-[Benzyl(methyl)amino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate hydrochloride.

$C_{26}H_{29}N_3O_6,HCl$=516.0

CAS — 55985-32-5 (nicardipine); 54527-84-3 (nicardipine hydrochloride).

ATC — C08CA04.

ATC Vet — QC08CA04.

UNII — K5BC5011K3.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Nicardipine Hydrochloride). Store in airtight containers. Protect from light.

Incompatibility. Licensed product information recommends that a solution containing nicardipine hydrochloride 100 micrograms/mL is used for intravenous infusion. Suitable diluents are solutions of glucose or sodium chloride. Sodium bicarbonate and lactated Ringer's are incompatible with nicardipine infusion. Nicardipine hydrochloride (1 mg/mL in glucose 5%) has also been reported[1] to be visually incompatible with furosemide, heparin, and thiopental.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.

Uses and Administration

Nicardipine is a dihydropyridine calcium-channel blocker with actions and uses similar to nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3).

Nicardipine hydrochloride is generally given orally although the intravenous route has been used for the short-term treatment of hypertension.

Oral doses of nicardipine hydrochloride are similar for both **hypertension** and **angina**. The initial dose is 20 mg three times daily and may be increased at intervals of at least 3 days until the required effect is achieved. The usual maintenance dose is 30 mg three times daily, but daily doses of between 60 and 120 mg in divided doses may be given. Modified-release preparations of nicardipine hydrochloride for dosage twice daily are also available.

Nicardipine hydrochloride may be given by slow intravenous infusion as a 100 micrograms/mL solution in the short-term treatment of hypertension. An initial infusion rate of 5 mg/hour is recommended, increased, as necessary, up to a maximum of 15 mg/hour and subsequently reduced to 3 mg/hour. For more information regarding suitable diluents and incompatibilities, see Incompatibility, above. For intravenous use in children, see below.

Reduced oral doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment (see below).

Reviews.

1. Curran MP, *et al.* Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. *Drugs* 2006; **66:** 1755–82.

Administration in children. Intravenous infusion of nicardipine has been used in both infants and children for the management of hypertension. In studies[1-4] in patients aged between 2 days and 17 years, initial doses ranged from 0.2 to 5 micrograms/kg per minute, with maintenance infusions of 0.15 to 6 micrograms/kg per minute. Adverse effects were rare; one study[4] reported adverse effects in 5 of 31 treatment courses, including tachycardia, flushing, palpitations, and hypotension. There has also been a report[5] of the successful use of intravenous infusion of nicardipine in 8 preterm infants (gestational age 28 to 36 weeks). Infusions were given at a dose of 0.5 to 2 micrograms/kg per minute and continued for periods of 3 to 36 days. Hypotension, oedema, or tachycardia were not seen.

The *BNFC* suggests that neonates and children up to age 18 years may be given nicardipine hydrochloride by continuous intravenous infusion for the management of hypertensive crises. The initial dose is 500 nanograms/kg per minute, adjusted according to response; the usual maintenance dose is 1 to 4 micrograms/kg per minute, with a maximum dose of 250 micrograms/minute.

1. Treluyer JM, *et al.* Intravenous nicardipine in hypertensive children. *Eur J Pediatr* 1993; **152:** 712–4.
2. Sartori SC, *et al.* Intravenous nicardipine for treatment of systemic hypertension in children. *Pediatrics* 1999; **104** (suppl): 676–7.
3. Tobias JD. Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children. *Am J Ther* 2001; **8:** 3–6.
4. Flynn JT, *et al.* Intravenous nicardipine for treatment of severe hypertension in children. *J Pediatr* 2001; **139:** 38–43.
5. Gouyon JB, *et al.* Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child* 1997; **76:** F126–F127.

Administration in hepatic or renal impairment. Reduced doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment. US licensed product information has recommended an initial oral dose of 20 mg twice daily in patients with hepatic impairment.

Cerebrovascular disorders. Nimodipine (p. 1455.3) is the dihydropyridine calcium-channel blocker that is usually used for cerebrovascular disorders. Nicardipine is also a potent cerebral vasodilator[1,2] and has been investigated for the vasospasm after subarachnoid haemorrhage, as well as for controlling acute hypertension after ischaemic stroke or intracerebral haemorrhage (for these conditions see Stroke, p. 1269.2). It has also been tried in cerebrovascular insufficiency and vascular dementia.

Some studies have reported positive or favourable results in *subarachnoid haemorrhage*[1,3] although a systematic review (which assessed oral and intravenous use) concluded that there was no evidence that nicardipine has a significant effect on functional outcome.[2] The use of nicardipine prolonged-release implants (into the basal cistern) may, however, be of benefit.[4,5] Other preliminary observations in patients with refractory vasospasm after subarachnoid haemorrhage have suggested that alternative routes such as intraventricular[6] and intra-arterial[7] use should be investigated in more detail.

Both oral and intravenous nicardipine have also been studied for the reduction of hypertension after acute *ischaemic stroke*. Although some studies have shown positive results,[3] the data are too limited to draw firm conclusions[1,3,8] and a review considered that it should be used only in patients who cannot be given a better established alternative such as labetalol.[8] A similar conclusion was reached about the use of nicardipine for hypertension after *intracerebral haemorrhage*.[8]

Comparison of studies in different clinical situations in patients with *cerebrovascular insufficiency* or *vascular dementia* is difficult but a review considered that there does appear to

be a favourable effect on cognitive function with nicardipine.[1,3]

1. Amenta F, *et al.* Nicardipine: a hypotensive dihydropyridine-type calcium antagonist with a peculiar cerebrovascular profile. *Clin Exp Hypertens* 2008; **30:** 808–26.
2. Dorhout Mees S, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/07/08).
3. Amenta F, *et al.* Nicardipine use in cerebrovascular disease: a review of controlled clinical studies. *J Neurol Sci* 2009; **283:** 219–23.
4. Barth M, *et al.* Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study. *Stroke* 2007; **38:** 330–6.
5. Krischek B, *et al.* Nicardipine prolonged-release implants for preventing cerebral vasospasm after subarachnoid hemorrhage: effect and outcome in the first 100 patients. *Neurol Med Chir (Tokyo)* 2007; **47:** 389–94.
6. Goodson K, *et al.* Intraventricular nicardipine for refractory cerebral vasospasm after subarachnoid hemorrhage. *Neurocrit Care* 2008; **8:** 247–52.
7. Tejada JG, *et al.* Safety and feasibility of intra-arterial nicardipine for the treatment of subarachnoid hemorrhage-associated vasospasm: initial clinical experience with high-dose infusions. *AJNR Am J Neuroradiol* 2007; **28:** 844–8.
8. Reddy P, Yeh YC. Use of injectable nicardipine for neurovascular indications. *Pharmacotherapy* 2009; **29:** 398–409.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nicardipine is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first-pass hepatic metabolism. Bioavailability of about 35% has been reported after a 30-mg dose at steady state. The pharmacokinetics of nicardipine are non-linear due to the saturable first-pass hepatic metabolism and an increase in dose may produce a disproportionate increase in plasma concentration. There is also considerable interindividual variation in plasma-nicardipine concentrations. Nicardipine is more than 95% bound to plasma proteins. Nicardipine is extensively metabolised in the liver and is excreted in the urine and faeces, mainly as inactive metabolites. The terminal plasma half-life is about 8.6 hours, thus steady-state plasma concentrations occur after 2 to 3 days of dosing three times daily.

References.

1. Graham DJM, *et al.* Pharmacokinetics of nicardipine following oral and intravenous administration in man. *Postgrad Med J* 1984; **60** (suppl 4): 7–10.
2. Graham DJM, *et al.* The metabolism and pharmacokinetics of nicardipine hydrochloride in man. *Br J Clin Pharmacol* 1985; **20:** 23S–28S.
3. Razak TA, *et al.* The effect of hepatic cirrhosis on the pharmacokinetics and blood pressure response to nicardipine. *Clin Pharmacol Ther* 1990; **47:** 463–9.
4. Porchet HC, Dayer P. Serum concentrations and effects of (±)-nicardipine compared with nifedipine in a population of healthy subjects. *Clin Pharmacol Ther* 1990; **48:** 155–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Rydene; ***China***: A Fa Duo Xin (阿法多欣); Bei Er Ping (贝尔平); Bei Li Ning (贝立宁); Ka Ni Ya (卡尼亚); Ka Shu Tai (卡舒泰); Perdipine (佩尔); Xian Li (仙立); Xin Shu Li Da (欣舒力达); Yu Luo Tong (毓罗通); ***Fr.***: Loxen; ***Ger.***: Antagonil†; ***Indon.***: Blistra; Perdipine; ***Ital.***: Bionicard; Cardioten†; Cardip†; Lisanirc; Nicapress†; Nicardal; Nicarpin†; Nicaven; Perdipina; Vasodin; ***Jpn***: Perdipine; ***Malaysia***: Cardepine; ***Neth.***: Cardene; ***Philipp.***: Cardepine; Perdipine; ***Port.***: Nerdipina; ***Singapore***: Cardibloc; ***Spain***: Dagan; Flusemide; Lecibral; Lincil; Lucenfal†; Nerdipina; Vasonase; ***Thai.***: Cardepine; ***Turk.***: Loxen; ***UK***: Cardene; ***USA***: Cardene.

Niceritrol *(BAN, rINN)*

Nicéritrol; Niceritrolum; Nikeritroli; PETN; Ницеритрол.

Pentaerythritol tetranicotinate; 2,2-Bis(hydroxymethyl)propane-1,3-diol tetranicotinate.

$C_{29}H_{24}N_4O_8$=556.5

CAS — 5868-05-3.

ATC — C10AD01.

ATC Vet — QC10AD01.

UNII — F54EHJ34MV.

NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.

Pharmacopoeias. In *Jpn*.

Profile

Niceritrol, an ester of pentaerythritol and nicotinic acid, has general properties similar to those of nicotinic acid (p. 2083.1), to which it is slowly hydrolysed. Niceritrol has been used as a lipid regulating drug in hyperlipidaemias and as a vasodilator in the treatment of peripheral vascular disease.

References.

1. Owada A, *et al.* Antiproteinuric effect of niceritrol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. *Am J Med* 2003; **114:** 347–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Perycit.

Nicomol *(rINN)*

K-31; Nicomolum; Никомол.

2-Hydroxy-1,1,3,3-cyclohexanetetramethanol 1,1,3,3-tetranicotinate.

$C_{34}H_{32}N_4O_9$=640.6

CAS — 27959-26-8.

UNII — 215U8X2R44.

Pharmacopoeias. In *Jpn*.

Profile

Nicomol is a derivative of, and has general properties similar to, nicotinic acid (p. 2083.1) to which it is hydrolysed. It is used as a lipid regulating drug in hyperlipidaemias, and as a vasodilator in the treatment of peripheral circulatory disorders such as chilblains, Raynaud's syndrome, and limb arterial occlusive disease. The usual oral dosage is 600 to 1200 mg daily in 3 divided doses after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cholexamin.

Nicorandil *(BAN, USAN, rINN)*

Nicorandilum; SG-75; Никорандил.

N-[2-(Nitroxy)ethyl]-3-pyridinecarboxamide.

$C_8H_9N_3O_4$=211.2

CAS — 65141-46-0.

ATC — C01DX16.

ATC Vet — QC01DX16.

UNII — 260456HAM0.

Pharmacopoeias. In *Br.* and *Jpn*.

BP 2014: (Nicorandil). A white crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in methyl alcohol. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Nicorandil is a nitrate derivative of nicotinamide (p. 2083.1) and acts as a vasodilator. It is a potassium-channel opener (p. 1245.2) providing vasodilatation of arterioles and large coronary arteries and its nitrate component produces venous vasodilatation through stimulation of guanylate cyclase. It thus reduces both preload and afterload, and improves coronary blood flow.

Nicorandil is given orally for prevention and long-term treatment of **angina pectoris**, including reduction of the risk of acute coronary events in high-risk patients (p. 1254.3). The usual initial oral dose is 10 mg twice daily (or 5 mg twice daily in patients susceptible to headache), increased as necessary to a maximum of 30 mg twice daily; the usual therapeutic dose is in the range of 10 to 20 mg twice daily.

Nicorandil is also given intravenously in the management of **unstable angina** and **acute heart failure** (p. 1262.3). For unstable angina, a solution containing 100 to 300 micrograms/mL is given by intravenous infusion in a dose of 2 mg/hour, adjusted according to response, to a maximum dose of 6 mg/hour. For acute heart failure, a solution containing 400 to 2500 micrograms/mL is used; the usual dose is 200 micrograms/kg given by intravenous injection over 5 minutes, followed by continuous intravenous infusion at a dose of 200 micrograms/kg per hour. The dosage should be adjusted according to response, within the range of 50 to 200 micrograms/kg per hour.

General references.

1. Markham A, *et al.* Nicorandil: an updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs* 2000; **60:** 955–74.
2. Gomma AH, *et al.* Potassium channel openers in myocardial ischaemia: therapeutic potential of nicorandil. *Drugs* 2001; **12:** 1705–10.
3. Anonymous. Nicorandil for angina – an update. *Drug Ther Bull* 2003; **41:** 86–8.
4. Simpson D, Wellington K. Nicorandil: a review of its use in the management of stable angina pectoris, including high-risk patients. *Drugs* 2004; **64:** 1941–55.

Ischaemic heart disease. A large multicentre double-blind randomised placebo-controlled study[1] suggested that nicorandil, in addition to its anti-anginal effects, may have cardioprotective properties. The incidence of major coronary events, particularly unplanned admission for chest pain, was significantly reduced in patients with stable angina at high risk of future adverse events. Mortality may also be reduced.[2] Nicorandil may mimic the mechanism of ischaemic pre-conditioning, whereby a brief period of ischaemia makes the myocardium resistant to damage from a further episode,[3] but it is not clear how much this mechanism contributes to its effects. There is some evidence[4-9] that nicorandil improves outcomes when given at the time of percutaneous coronary intervention, although a large study[10] in patients with myocardial infarction failed to confirm a benefit. It has been suggested[6] that an antioxidant effect may be part of the mechanism involved.

1. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002; **359:** 1269–75. Correction. *ibid.*; **360:** 806.
2. Horinaka S, *et al.* JCAD Study Investigators. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese Coronary Artery Disease (JCAD) study. *Circ J* 2010; **74:** 503–9.
3. Lesnefsky EJ. The IONA study: preparing the myocardium for ischaemia? *Lancet* 2002; **359:** 1262–3.
4. Matsuo H, *et al.* Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K+ channel opener nicorandil. *Eur Heart J* 2003; **24:** 1296–1303.
5. Ikeda N, *et al.* Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction. *Heart* 2004; **90:** 181–5.
6. Ono H, *et al.* Nicorandil improves cardiac function and clinical outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: role of inhibitory effect on reactive oxygen species formation. *Am Heart J* 2004; **148:** E15.
7. Ishii H, *et al.* Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation* 2005; **112:** 1284–8.
8. Ishii H, *et al.* Effects of intravenous nicorandil before reperfusion for acute myocardial infarction in patients with stress hyperglycemia. *Diabetes Care* 2006; **29:** 202–6.
9. Iwakura K, *et al.* Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. *Circ J* 2009; **73:** 925–31.
10. Kitakaze M, *et al.* J-WIND investigators. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet* 2007; **370:** 1483–93.

Adverse Effects and Precautions

Adverse effects reported with nicorandil are headache (which is usually transitory and seen at the start of therapy), cutaneous vasodilatation and flushing, nausea, vomiting, dizziness, and weakness. Rarely reported effects include myalgia, rashes, and oral ulceration, and there have been very rare reports of angioedema and hepatic function abnormalities. A reduction in blood pressure and/or an increase in heart rate may occur with high doses.

Nicorandil is contra-indicated in patients with cardiogenic shock, left ventricular failure with low filling pressures, and hypotension. In patients with hypovolaemia, low systolic blood pressure, acute pulmonary oedema, or acute myocardial infarction with acute left ventricular failure and low filling pressures, nicorandil should preferably be avoided but may be used with caution.

Incidence of adverse effects. Postmarketing surveillance for nicorandil was carried out by prescription-event monitoring[1] of 13 620 patients, and showed that adverse reactions occurred in 175. The most frequent was headache, occurring in 58 patients, mainly in the first month of treatment. Unspecified adverse effects occurred in 36 patients. Other effects included dizziness (19 patients), nausea (17 patients), malaise (13 patients), palpitations (8 patients), flushing and vomiting (6 patients each), and lassitude (4 patients). Rare adverse effects included 3 cases each of angioedema and photosensitivity.

1. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; **8:** 197–205.

Ulceration. Nicorandil has been associated with ulceration of mucosal surfaces. Painful, large aphthous ulcers on the *tongue* and *oral mucosa* have been reported[1-3] in patients receiving nicorandil for angina. The ulcers were usually resistant to treatment but all healed when nicorandil was withdrawn. Colchicine or thalidomide treatment has improved ulcers associated with nicorandil in a few patients, but relapse occurred when the colchicine or thalidomide was stopped.[3] However, a large study[4] casts some doubt on the evidence for a causal link between nicorandil and oral ulceration, although it was suggested that this could be further investigated.

Anal ulceration has been reported[5-7] in patients taking nicorandil. Healing of the ulcers occurred in those patients in whom nicorandil was withdrawn.

Multiple ulcers of the upper and lower *gastrointestinal tract*, in addition to oral and anal ulceration, have been reported[8] in a patient taking nicorandil; all of the ulcers healed when nicorandil was stopped. There have also been several cases of *peristomal* ulceration, which resolved after stopping nicorandil.[9]

Perivulval[10-13] and vaginal[12,14] ulceration has also been reported, and may be associated with *cutaneous*[10] or inguinal[13] ulceration. Another patient[15] developed both perianal and leg ulcers, both of which improved rapidly when nicorandil was stopped.

1. Cribier B, *et al*. Chronic buccal ulceration induced by nicorandil. *Br J Dermatol* 1998; **138:** 372–3.
2. Desruelles F, *et al*. Giant oral aphthous ulcers induced by nicorandil. *Br J Dermatol* 1998; **138:** 712–13.
3. Agbo-Godeau S, *et al*. Association of major aphthous ulcers and nicorandil. *Lancet* 1998; **352:** 1598–9.
4. Dunn N, *et al*. Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; **8:** 197–205.
5. Watson A, *et al*. Nicorandil associated anal ulceration. *Lancet* 2002; **360:** 546–7.
6. Vella M, Molloy RG. Nicorandil-associated anal ulceration. *Lancet* 2002; **360:** 1979.
7. Passeron T, *et al*. Chronic anal ulceration due to nicorandil. *Br J Dermatol* 2004; **150:** 394–6.
8. Egred M, *et al*. Nicorandil may be associated with gastrointestinal ulceration. *BMJ* 2006; **332:** 889.
9. Ogden S, *et al*. Nicorandil-induced peristomal ulcers: is nicorandil also associated with gastrointestinal fistula formation? *Br J Dermatol* 2007; **156:** 608–9.
10. Claeys A, *et al*. Cutaneous, perivulvar and perianal ulcerations induced by nicorandil. *Br J Dermatol* 2006; **155:** 494–6.
11. Fraser SJ, *et al*. Vulval ulceration induced by the potassium-channel activator Nicorandil: a case series of five patients. *BJOG* 2009; **116:** 1400–2.
12. Chan SK, *et al*. Vulvovaginal ulceration during prolonged treatment with nicorandil. *BJOG* 2009; **116:** 1403–5.
13. El-Dars LD, *et al*. Nicorandil associated vulval and inguinal ulceration. *J Obstet Gynaecol* 2009; **29:** 674–5.
14. van de Nieuwenhof HP, *et al*. Never forget medication as a cause: vaginal ulceration caused by nicorandil. *Am J Obstet Gynecol* 2009; **201:** e5–e6.
15. McKenna DJ, *et al*. Nicorandil-induced leg ulceration. *Br J Dermatol* 2007; **156:** 394–6.

Interactions

Nicorandil should not be used with phosphodiesterase type-5 inhibitors such as sildenafil as the hypotensive effect of nicorandil may be significantly enhanced.

Pharmacokinetics

Nicorandil is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 30 to 60 minutes after oral doses. Metabolism is mainly by denitration and about 20% of a dose is excreted in the urine mainly as metabolites. The elimination half-life is about 1 hour. Nicorandil is only slightly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ikorel; ***Austria***: Dancor; ***China***: Sigmart (喜格迈); ***Denm.***: Angicor; Dancor; Ikorel; ***Fr.***: Adancor; Ikorel; ***Gr.***: Ikotril; ***India***: Av-Cor; Corflo; Dilnicon; Duorandil; K-Cor; Korandil; Nicoduce; Nikoran; Nucoril; Zynicor; ***Irl.***: Ikorel; Nicozone; ***Jpn***: Sigmart; ***Neth.***: Dancor†; Doranic; Ikorel; ***NZ***: Ikorel; ***Philipp.***: Aprior; Nikoran; ***Port.***: Dancor; Nikoril†; ***Switz.***: Dancor; ***Turk.***: Ikorel; ***UK***: Ikorel.

Pharmacopoeial Preparations
BP 2014: Nicorandil Tablets.

Nicotinyl Alcohol *(BAN, USAN)*

3-Hydroxymethylpyridine; Nicomethanol; Nicotinic Alcohol; Nicotinílico, alcohol; NSC-526046; NU-2121; 3-Pyridinemethanol; β-Pyridylcarbinol; Ro-1-5155; Никотиниловый Спирт.

3-Pyridylmethanol.

C_6H_7NO=109.1

CAS — 100-55-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

UNII — 9TF312056Y.

Nicotinyl Alcohol Tartrate *(BANM)*

Alcohol nicotinílico, tartrato de; Nicotinyl Tartrate.

3-Pyridylmethanol hydrogen (2*R*,3*R*)-tartrate.

$C_6H_7NO,C_4H_6O_6$=259.2

CAS — 6164-87-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

UNII — 5G605ZIE90.

Pharmacopoeias. In *Br.*

BP 2014: (Nicotinyl Alcohol Tartrate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.8 to 3.7.

Profile

Nicotinyl alcohol is a vasodilator and lipid regulating drug with general properties similar to those of nicotinic acid (p. 2083.1), to which it is partly hydrolysed.

Nicotinyl alcohol has been given orally, as the tartrate, in the management of peripheral vascular disease, and has also been used in Ménière's disease and in hyperlipidaemias. The hydrofluoride derivative, nicomethanol hydrofluoride, is used as a fluoride source in oral hygiene products.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Cetacol†.

Multi-ingredient Preparations. ***Braz.***: Lipofacton†.

Pharmacopoeial Preparations
BP 2014: Nicotinyl Alcohol Tablets.

Nifedipine *(BAN, USAN, rINN)*

Bay-a-1040; Nifedipiini; Nifedipin; Nifedipina; Nifedipinas; Nifédipine; Nifedipino; Nifedipinum; Нифедипин.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

$C_{17}H_{18}N_2O_6$=346.3

CAS — 21829-25-4.

ATC — C08CA05.

ATC Vet — QC08CA05.

UNII — I9ZF7L6G2L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Nifedipine). A yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 36: (Nifedipine). A yellow powder. Practically insoluble in water; soluble 1 in 10 of acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Store in airtight containers. Protect from light.

Stability. Yellow food colourings such as curcumin have been used[1] to slow photodegradation of nifedipine solutions. An extemporaneously prepared solution of nifedipine in a peppermint-flavoured vehicle was reported[2] to be stable for at least 35 days when stored in amber glass bottles.

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.
2. Dentinger PJ, *et al*. Stability of nifedipine in an extemporaneously compounded oral solution. *Am J Health-Syst Pharm* 2003; **60:** 1019–22.

Uses and Administration

Nifedipine is a dihydropyridine calcium-channel blocker (p. 1244.2). It is a peripheral and coronary vasodilator, but, unlike the rate-limiting calcium-channel blockers verapamil or diltiazem, has little or no effect on cardiac conduction and negative inotropic activity is rarely seen at therapeutic doses. Use of nifedipine results primarily in vasodilatation, with reduced peripheral resistance, blood pressure, and afterload, increased coronary blood flow, and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output. Nifedipine has no antiarrhythmic activity. Nicardipine and newer dihydropyridines such as amlodipine, felodipine, isradipine, and lacidipine may be even more selective than nifedipine for vascular smooth muscle. Nimodipine acts particularly on cerebral blood vessels. Most of the dihydropyridine calcium-channel blockers (nifedipine and lacidipine are exceptions) are chiral compounds used as racemic mixtures.

Nifedipine may be used in the management of hypertension; in the management of angina pectoris particularly when a vasospastic element is present, as in Prinzmetal's angina, though it is not suitable for relief of an acute attack; and in the treatment of Raynaud's syndrome. Nifedipine has also been tried in many non-vascular disorders. For further information on its uses see below.

Nifedipine is usually given orally. It is available in several formulations. Liquid-filled capsules with a relatively rapid onset but short duration of action are given three times daily. This short-acting preparation is not recommended for the management of hypertension or angina in adults. There are also tablets and capsules with a slower onset and longer duration of action, enabling twice-daily dosage; although these are often referred to by nomenclature implying extended or sustained release they should be distinguished from the true extended-release preparations available in some countries that allow dosage once daily.

Doses of nifedipine are dependent upon the formulation used; they may need to be reduced in the elderly or those with impaired liver function.

For **hypertension** a long-acting preparation of nifedipine may be given in doses of 10 to 40 mg twice daily, or 20 to 90 mg once daily, depending on the preparation used.

For **angina pectoris**, nifedipine may be given as a long-acting preparation in a dose of 10 to 40 mg twice daily or 30 to 90 mg once daily, depending on the preparation. Although the liquid-filled capsules have been given in a dose of 5 to 20 mg three times daily, this is no longer recommended and longer-acting preparations are preferred.

Nifedipine has been given by injection via a coronary catheter for the treatment of coronary spasm during coronary angiography and balloon angioplasty. Blood pressure and heart rate should be monitored carefully.

In the management of **Raynaud's syndrome**, nifedipine may be given as liquid-filled capsules in a dose of 5 to 20 mg three times daily.

For the use of nifedipine in children, see below.

General references.

1. Croom KF, Wellington K. Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 2006; **66:** 497–528.
2. Meredith PA, Elliott HL. Benefits of nifedipine GITS in stable coronary artery disease: further analysis of the "ACTION" database. *Adv Therapy* 2010; **27:** 297–306.

Administration in children. Nifedipine has been used in the management of various disorders in children. The *BNFC* recommends the following oral doses:

Hypertension; angina in Kawasaki disease or progeria:
- age 1 month to 12 years: 200 to 300 micrograms/kg 3 times daily, increased to a maximum daily dose of 3 mg/kg or 90 mg
- age 12 to 18 years: 5 to 20 mg 3 times daily, increased to a maximum daily dose of 90 mg

Dosage frequency may vary depending on the preparation used

Hypertensive crises; acute angina in Kawasaki disease or progeria:
- age 1 month to 18 years: 250 to 500 micrograms/kg (maximum 20 mg) as a single dose

(although such use is deprecated in adults, the *BNFC* considers that for rapid effect an immediate-release liquid-filled capsule may be bitten and the contents swallowed; a liquid preparation may be used if the unit doses available in such capsules are inappropriate)

Raynaud's syndrome:
- age 2 to 18 years: 2.5 to 10 mg 2 to 4 times daily; treatment should start with low doses at night, increased gradually to avoid orthostatic hypotension

Neonatal hyperinsulinaemic hypoglycaemia:
- see p. 1448.2

Use of nifedipine capsules for acute hypertension is no longer recommended in adults because of the risk of severe adverse effects related to precipitous reductions in blood pressure (see Effects on Mortality under Adverse Effects, p. 1450.2). Although there have been reports of adverse effects in children,[1-3] they may be less susceptible than adults, and the use of nifedipine capsules may still be appropriate.[4] A study[5] in 12 children aged 6 to 15 years with acute severe hypertension reported that sublingual nifedipine in a mean dose of 240 micrograms/kg (range 180 to 320 micrograms/kg) was safe and effective. A retrospective study[6] in 182 children also found that short-acting nifedipine in a mean dose of 220 micrograms/kg (range 43 to 670 micrograms/kg) was safe and effective, while another retrospective study[1] in 117 children found that nifedipine safely reduced blood pressure, and that precipitous declines only occurred with doses higher than 250 micrograms/kg; a third retrospective study[2] in 166 children found that nifedipine in a mean dose of 300 micrograms/kg (range 40 to 1300 micrograms/kg) was generally safe, although children with acute CNS injury were at higher risk of neurological adverse effects.

Other routes that have been used include rectal[7] and intranasal,[8] but these are less established.

1. Blaszak RT, *et al*. The use of short-acting nifedipine in pediatric patients with hypertension. *J Pediatr* 2001; **139:** 34–7.
2. Egger DW, *et al*. Evaluation of the safety of short-acting nifedipine in children with hypertension. *Pediatr Nephrol* 2002; **17:** 35–40.
3. Flynn JT. Nifedipine in the treatment of hypertension in children. *J Pediatr* 2002; **140:** 787–8.
4. Sahney S. A review of calcium channel antagonists in the treatment of pediatric hypertension. *Pediatr Drugs* 2006; **8:** 357–73.
5. Evans JHC, *et al*. Sublingual nifedipine in acute severe hypertension. *Arch Dis Child* 1988; **63:** 975–7.
6. Yiu V, *et al*. The safety and use of short-acting nifedipine in hospitalized hypertensive children. *Pediatr Nephrol* 2004; **19:** 644–50.
7. Uchiyama M, Ogawa I. Rectal nifedipine in acute severe hypertension in young children. *Arch Dis Child* 1989; **64:** 632–3.

8. Lopez-Herce J, *et al.* Treatment of hypertensive crisis with intranasal nifedipine. *Crit Care Med* 1988; **9:** 914.

Amaurosis fugax. Amaurosis fugax is a form of monocular visual loss that is usually attributed to a transient ischaemic attack and is treated with antiplatelet drugs or anticoagulants (see Stroke, p. 1269.2). Vasospasm may be an alternative cause and might explain the efficacy of the calcium-channel blockers nifedipine and verapamil reported[1] in a few patients unresponsive to standard therapy.

1. Winterkorn JMS, *et al.* Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med* 1993; **329:** 396–8.

Anal fissure. Topical nitrates have commonly been used in the management of chronic anal fissure (p. 2017.3) because of their ability to relax the anal sphincter. Calcium-channel blockers, including nifedipine, have also been tried with success. Both oral[1] and topical[2] treatment have been tried, although most studies have used the latter. Oral nifedipine[3] was not as effective as surgery and compliance was poor. Topical nifedipine 0.2% was found[4] to be more effective and cause fewer adverse effects than glyceryl trinitrate, and appeared to be safe and effective in the long term,[5] although recurrences were common. Aggressive treatment with nifedipine 0.5% ointment has shown improved responses in terms of recurrence rate[6] and has compared favourably with surgery,[7] leading to the view that it might be considered a first-line treatment.

1. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; **86:** 1269–73.
2. Perrotti P, *et al.* Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. *Dis Colon Rectum* 2002; **45:** 1468–75.
3. Ho KS, Ho YH. Randomized clinical trial comparing oral nifedipine with lateral anal sphincterotomy and tailored sphincterotomy in the treatment of chronic anal fissure. *Br J Surg* 2005; **92:** 403–8.
4. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; **46:** 805–8.
5. Lysy J, *et al.* Long-term results of "chemical sphincterotomy" for chronic anal fissure: a prospective study. *Dis Colon Rectum* 2006; **49:** 858–64.
6. Katsinelos P, *et al.* Aggressive treatment of acute anal fissure with 0.5% nifedipine ointment prevents its evolution to chronicity. *World J Gastroenterol* 2006; **12:** 6203–6.
7. Katsinelos P, *et al.* Topical 0.5% nifedipine vs. lateral internal sphincterotomy for the treatment of chronic anal fissure: long-term follow-up. *Int J Colorectal Dis* 2006; **21:** 179–83.

Angina pectoris. Both dihydropyridines (such as nifedipine) and rate-limiting calcium-channel blockers (diltiazem and verapamil) may be used in the management of angina (p. 1254.3), with choice depending on individual patient characteristics and adverse effects. Short-acting preparations of nifedipine have been associated with increased mortality and are not recommended in adults (see under Adverse Effects, p. 1450.2) though they may be used in children (p. 1447.3).

Atherosclerosis. The use of drugs that interfere with atherogenesis (the development of atheromas) has been suggested as a means of reducing diseases associated with atherosclerosis (p. 1250.2). Calcium is thought to be necessary for several steps in atherogenesis and studies in *animals* have shown that calcium-channel blockers slow the development and progression of atherosclerotic lesions. However, studies in humans have been less convincing.[1] In a placebo-controlled study,[2] amlodipine had no demonstrable effect on angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events although it was associated with fewer admissions to hospital for unstable angina and revascularisation. Similar results have been reported with nisoldipine.[3] Results with nifedipine have been mixed: no significant effect was seen on plaque progression,[4,5] although it may improve coronary endothelial function.[5] In a study[6] comparing lacidipine with a beta blocker, there was less progression of atherosclerosis in those receiving lacidipine and also a trend towards fewer cardiovascular events.

Calcium-channel blockers have also been tried in the prevention of restenosis after percutaneous coronary interventions. A meta-analysis[7] found that addition of calcium-channel blockers to standard therapy reduced the risk of restenosis and the occurrence of clinical events.

1. Borcherding SM, *et al.* Calcium-channel antagonists for prevention of atherosclerosis. *Ann Pharmacother* 1993; **27:** 61–7.
2. Pitt B, *et al.* Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000; **102:** 1503–10.
3. Dens JA, *et al.* Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. *Heart* 2003; **89:** 887–92.
4. Motro M, *et al.* Tracking coronary calcification and atherosclerotic lesions in patients with stable angina pectoris undergoing nifedipine therapy. *Cardiology* 2007; **107:** 165–71.
5. Lüscher TF, *et al.* A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study. *Eur Heart J* 2009; **30:** 1590–7.
6. Zanchetti A, *et al.* Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002; **106:** 2422–7.
7. Dens J, *et al.* An updated meta-analysis of calcium-channel blockers in the prevention of restenosis after coronary angioplasty. *Am Heart J* 2003; **145:** 404–8.

Cardiomyopathies. Calcium-channel blockers may have a role in some forms of cardiomyopathy (p. 1261.3). In *hypertrophic cardiomyopathy* verapamil is probably the calcium-channel blocker of choice (see p. 1522.3). Nifedipine does not appear to reduce left ventricular outflow tract obstruction, and has produced conflicting results with respect to improvement in the diastolic function abnormality.[1] The use of calcium-channel blockers is not standard therapy in *dilated cardiomyopathy* although symptomatic improvement has been reported[2] with diltiazem.

1. Richardson PJ. Calcium antagonists in cardiomyopathy. *Br J Clin Pract* 1988; **42** (suppl 60): 33–7.
2. Figulla HR, *et al.* Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; **94:** 346–52.

Cough. Nifedipine has been reported to reduce the severity of cough induced by captopril,[1] possibly by inhibiting prostaglandin synthesis. For further details on cough associated with ACE inhibitors, see p. 1285.3.

1. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; **19:** 670–3.

Hiccup. Hiccups (p. 1046.3) result from involuntary spasmodic contraction of the diaphragm. Intractable hiccups resolved completely with nifedipine 20 mg every 8 hours in a patient.[1] In a further 7 such patients,[2] nifedipine in doses of 20 to 80 mg daily stopped hiccups in 4 and improved them in another. Resolution of intractable hiccups has also been reported[3] in 2 patients given nimodipine; the drug was given orally in one patient and intravenously in the other.

For the treatment of hiccups in palliative care the *BNF* suggests that nifedipine at a dose of 10 mg three times daily can be tried.

1. Mukhopadhyay P, *et al.* Nifedipine for intractable hiccups. *N Engl J Med* 1986; **314:** 1256.
2. Lipps DC, *et al.* Nifedipine for intractable hiccups. *Neurology* 1990; **40:** 531–2.
3. Hernández JL, *et al.* Nimodipine treatment for intractable hiccups. *Am J Med* 1999; **106:** 600.

High-altitude disorders. Nifedipine lowers pulmonary artery pressure and is one of several drugs that are used in high-altitude disorders (p. 1276.2), success being reported for both the treatment[1,2] and prevention[2,3] of symptoms of pulmonary oedema.

In a study conducted at 4559 m above sea-level[1] nifedipine 10 mg sublingually and 20 mg as a modified-release dosage form was given to 6 subjects to **treat** symptoms of high-altitude pulmonary oedema. The sublingual dose was repeated if tolerated after 15 minutes and the subjects subsequently received modified-release nifedipine 20 mg every 6 hours while they remained at high altitude. Symptoms of high-altitude pulmonary oedema were relieved within 1 hour of beginning nifedipine and radiographic signs of oedema regressed during treatment despite remaining at high altitude for 36 hours and participating in mountaineering activities. Raised pulmonary arterial pressure was also reduced to control values by nifedipine.

Successful treatment of pulmonary oedema in a climber at 6550 m has been described with doses of 20 mg every 8 hours for 36 hours and such doses also **prevented** the development of symptoms in 2 climbers who had taken nifedipine from the start of the climb.[2] Doses of 20 mg every 8 hours have been reported to allow rapid ascent to 4559 m without development of pulmonary oedema in 9 of 10 subjects who received nifedipine compared with 4 of 11 who received only placebo.[3] Some consider that prophylactic treatment with nifedipine 60 mg daily in divided doses, as a modified-release oral preparation, should be started the day before ascent in climbers with a history of high-altitude pulmonary oedema and continued until descent or until 5 days has been spent at the target elevation.[4] Drug prophylaxis is not generally recommended in those without such a history, and although it is reasonable that many climbers carry nifedipine in case of an attack,[5] prophylactic nifedipine is not an alternative to slow ascent and acclimatisation.[4,5]

1. Oelz O, *et al.* Nifedipine for high altitude pulmonary oedema. *Lancet* 1989; **ii:** 1241–4. Correction. *ibid.* 1991; **337:** 556.
2. Jamieson A, Kerr GW. Treatment of high-altitude pulmonary oedema. *Lancet* 1992; **340:** 1468.
3. Bärtsch P, *et al.* Prevention of high-altitude pulmonary oedema by nifedipine. *N Engl J Med* 1991; **325:** 1284–9.
4. Luks AM, *et al.* Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med* 2010; **21:** 146–55. Correction. *ibid.*; 386.
5. A'Court CHD, *et al.* Doctor on a mountaineering expedition. *BMJ* 1995; **310:** 1248–52.

Hyperinsulinaemic hypoglycaemia. Nifedipine may have effects on blood-glucose levels due to inhibition of insulin release[1] (see Effects on Carbohydrate Metabolism, under Adverse Effects, p. 1451.1). There have been reports[1-4] of the successful use of nifedipine to increase blood-glucose levels in infants with hyperinsulinaemic hypoglycaemia (see under Uses of Glucagon, p. 1554.3), and it may have a role[5,6] as adjunctive therapy in such patients. The *BNFC* suggests that neonates with persistent hyperinsulinaemic hypoglycaemia may be given oral nifedipine in a dose of 100 to 200 micrograms/kg 4 times daily, increased to a maximum of 600 micrograms/kg 4 times daily if required.

1. Lindley KJ, *et al.* Ionic control of beta cell function in nesidioblastosis: a possible therapeutic role for calcium channel blockade. *Arch Dis Child* 1996; **74:** 373–8.
2. Eichmann D, *et al.* Treatment of hyperinsulinaemic hypoglycaemia with nifedipine. *Eur J Pediatr* 1999; **158:** 204–6.
3. Bas F, *et al.* Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 1999; **12:** 873–8.
4. Shanbag P, *et al.* Persistent hyperinsulinemic hypoglycemia of infancy—successful therapy with nifedipine. *Indian J Pediatr* 2002; **69:** 271–2.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.
6. Müller D, *et al.* Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia? *Arch Dis Child* 2004; **89:** 83–5.

Hypertension. Long-acting calcium-channel blockers are among the drug groups that may be used as first-line therapy in uncomplicated hypertension (p. 1251.1); meta-analyses[1,2] and large studies[3] have shown them to be broadly comparable in safety and efficacy to other first-line antihypertensives, and they are particularly recommended in older patients. One systematic review[2] suggested that diuretics were associated with fewer cardiovascular events than calcium-channel blockers, but that the latter were superior to beta blockers. Dihydropyridine calcium-channel blockers are also useful in patients who require combination therapy[4,5] and are particularly effective when given with a beta blocker or an ACE inhibitor. However, the use of short-acting calcium-channel blockers is not recommended since they may increase mortality (see under Adverse Effects, p. 1450.2).

Calcium-channel blockers may also be used in **hypertensive crises**, particularly in hypertensive urgencies where oral therapy is suitable. Nifedipine has been given sublingually, or by biting the capsule and swallowing the contents, but such use may cause dangerous hypotension and is no longer recommended in adults, although the *BNFC* considers it appropriate in children. In hypertensive emergencies, where parenteral antihypertensives are required, intravenous nicardipine may be used. One study concluded that intravenous nicardipine was as effective as sodium nitroprusside in the treatment of postoperative hypertension.[6]

For **hypertension in pregnancy**, first-line treatment is usually methyldopa or a beta blocker but calcium-channel blockers may also be used. Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been tried in a limited number of patients with pre-eclampsia. Although a high rate of caesarean deliveries, premature births, and small-for-date infants was reported[7] in patients given nifedipine as a second-line drug, assessment of the role of nifedipine is difficult because outcome is often poor in such severely compromised pregnancies.[8] Fetal nifedipine concentrations have been reported to be 75% of maternal values 2 to 3 hours after sublingual doses.[9] However, nifedipine in a single 20-mg oral dose lowered blood pressure without compromising blood flow in the fetus in 9 women in the third trimester with normal haemodynamics.[8] This is in line with other reports,[10] although there has also been a report[11] of severe hypotension and fetal distress after sublingual nifedipine. In a randomised controlled study,[12] nifedipine 10 to 30 mg sublingually followed by 10 mg orally as capsules every 6 hours, increasing to 20 mg every 4 hours if necessary, was compared with hydralazine 12.5 mg intravenously as required followed by 20 to 30 mg orally every 6 hours, with added methyldopa if necessary. Both groups also received intravenous magnesium sulfate. Effective control of blood pressure was achieved in 23 of 24 patients given nifedipine compared with only 17 of 25 given hydralazine and 9 nifedipine patients achieved term delivery compared with only 2 of those receiving hydralazine. The average gestational age was greater in infants in the nifedipine group; hence these neonates weighed more and had fewer neonatal complications when compared with neonates from the hydralazine treated group.

1. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002; **39:** 315–22. Correction. *ibid.*; 1409–10.
2. Chen N, *et al.* Calcium channel blockers versus other classes of drugs for hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 24/11/10).
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.

4. Epstein BJ, *et al*. Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007; **67:** 1309–27.
5. Haller H. Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. *Int J Clin Pract* 2008; **62:** 781–90.
6. Halpern NA, *et al*. Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Crit Care Med* 1992; **20:** 1637–43.
7. Constantine G, *et al*. Nifedipine as a second line antihypertensive drug in pregnancy. *Br J Obstet Gynaecol* 1987; **94:** 1136–42.
8. Hanretty KP, *et al*. Effect of nifedipine on Doppler flow velocity waveforms in severe pre-eclampsia. *BMJ* 1989; **299:** 1205–6.
9. Pirhonen JP, *et al*. Single dose of nifedipine in normotensive pregnancy: nifedipine concentrations, hemodynamic responses, and uterine and fetal flow velocity waveforms. *Obstet Gynecol* 1990; **76:** 807–11.
10. Pirhonen JP, *et al*. Uterine and fetal flow velocity wave forms in hypertensive pregnancy: the effect of a single dose of nifedipine. *Obstet Gynecol* 1990; **76:** 37–41.
11. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. *Br J Obstet Gynaecol* 1993; **100:** 959–61.
12. Fenakel K, *et al*. Nifedipine in the treatment of severe preeclampsia. *Obstet Gynecol* 1991; **77:** 331–7.

Kidney disorders. Although nifedipine can adversely affect renal function (see under Adverse Effects, p. 1451.2) there is evidence that calcium-channel blockers may be of benefit in some kidney disorders. Proteinuria is an important indicator of glomerular kidney disease (p. 1604.3) of various causes and the effects of calcium-channel blockers on proteinuria and renal dysfunction have been studied in a variety of patients. Results have been mixed and if there is a protective effect of calcium-channel blockers on renal function it is not clear if this is due to their antihypertensive action or whether they also have additional effects. Monotherapy with dihydropyridine calcium-channel blockers has not been shown to adequately protect renal function in patients with non-diabetic proteinuria, despite good blood pressure control,[1] whereas the renal benefits of ACE inhibitors and angiotensin II receptor antagonists are somewhat better established (see p. 1284.1 and p. 1423.3, respectively). However, reviews[2-5] have concluded that a calcium-channel blocker may safely be added when first-line therapy is insufficient in reducing blood pressure in patients with diabetic or non-diabetic proteinuria. Calcium-channel blockers may also delay the progression of chronic renal insufficiency although non-dihydropyridine calcium-channel blockers appear to slow renal decline and reduce proteinuria more consistently than dihydropyridines in patients with diabetic or non-diabetic renal disease, even at similar rates of blood pressure reduction.[2,6-9]

Nifedipine has also been used in the management of renal calculi (see p. 1450.1), and has been reported to protect against ciclosporin-induced nephrotoxicity in renal transplant patients (see Transplantation, p. 1450.2).

1. Ziakka S, *et al*. Calcium channels blockers and progression of kidney disease. *Ren Fail* 2007; **29:** 1003–12.
2. Toto RD. Management of hypertensive chronic kidney disease: role of calcium channel blockers. *J Clin Hypertens (Greenwich)* 2005; **7** (4 suppl 1): 15–20.
3. Segura J, *et al*. Calcium channel blockers and renal protection: insights from the latest clinical trials. *J Am Soc Nephrol* 2005; **16** (suppl 1): S64–S66.
4. Rahn KH. The role of calcium antagonists in patients with chronic renal failure. *Pediatr Nephrol* 2005; **20:** 1208–13.
5. Nosadini R, Tonolo G. Cardiovascular and renal protection in type 2 diabetes mellitus: the role of calcium channel blockers. *J Am Soc Nephrol* 2002; **13** (suppl 3): S216–S223.
6. Nathan S, *et al*. Calcium antagonists: effects on cardio-renal risk in hypertensive patients. *Hypertension* 2005; **46:** 637–42.
7. Bakris GL, *et al*. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004; **65:** 1991–2002.
8. Derwa A, *et al*. Calcium channel blockers in the prevention of end stage renal disease: a review. *Acta Clin Belg* 2004; **59:** 44–56.
9. Toto RD. Reducing cardiovascular events in high-risk patients: the challenge of managing hypertension in patients with diabetic renal disease. *J Clin Hypertens (Greenwich)* 2007; **9** (11 suppl 4): 16–25.

Migraine and cluster headache. Drugs with calcium-channel blocking activity have been given in the management of headaches considered to have a vascular component such as migraine (p. 670.3) and cluster headache (p. 670.1).

In migraine prophylaxis, of those drugs with calcium-channel blocking activity studied, flunarizine (p. 630.1) has the best documented efficacy, and verapamil may be useful. Other calcium-channel blockers such as diltiazem, nifedipine, and nimodipine have been tried, but results have been conflicting. Verapamil has also been used successfully in patients with hemiplegic migraine, both intravenously to abort attacks,[1,2] and orally for prophylaxis.[2]

Beneficial effects have been reported[3-7] with calcium-channel blockers in the prevention of cluster headache during cluster periods. Verapamil appears to have been the most widely used. In one double-blind study it was found to be of similar efficacy to lithium[8] and appeared to produce fewer adverse effects. High doses of oral verapamil (up to 1.2 g daily in some patients) have been used;[7] the mode of action is unclear. There have also been reports[9] of the successful use of nimodipine in patients with thunderclap headache.

1. Ng TMH, *et al*. The effect of intravenous verapamil on cerebral hemodynamics in a migraine patient with hemiplegia. *Ann Pharmacother* 2000; **34:** 39–43.
2. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. *Neurology* 2003; **60:** 120–1.
3. Jónsdóttir M, *et al*. Efficacy, side effects and tolerance compared during headache treatment with three different calcium blockers. *Headache* 1987; **27:** 364–9.
4. Gabai IJ, Spierings ELH. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989; **29:** 167–8.
5. Leone M, *et al*. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000; **54:** 1382–5.
6. Matharu MS, *et al*. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003; **63:** 1637–77.
7. Tfelt-Hansen P, Tfelt-Hansen J. Verapamil for cluster headache: clinical pharmacology and possible mode of action. *Headache* 2009; **49:** 117–25.
8. Bussone G, *et al*. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30:** 411–17.
9. Lu S-R, *et al*. Nimodipine for treatment of primary thunderclap headache. *Neurology* 2004; **62:** 1414–16.

Oesophageal motility disorders. Results from a number of studies have indicated that nifedipine, usually in doses of 10 to 20 mg sublingually, may be of benefit in patients with achalasia, reducing lower oesophageal sphincter pressure and producing some symptomatic improvement.[1-5] Nifedipine has a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p. 1816.2).

See also Effects on the Oesophagus under Adverse Effects, p. 1451.3.

1. Bortolotti M, Labò G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. *Gastroenterology* 1981; **80:** 39–44.
2. Gelfond M, *et al*. Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. *Gastroenterology* 1982; **83:** 963–9.
3. Traube M, *et al*. Effects of nifedipine in achalasia and in patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1984; **252:** 1733–6.
4. Román FJ, *et al*. Effects of nifedipine in achalasia and patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1985; **253:** 2046.
5. Coccia G, *et al*. Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. *Gut* 1991; **32:** 604–6.

Parkinson's disease. Case-control studies[1,2] have found that long-term use of calcium-channel blockers (but not of ACE inhibitors, angiotensin II receptor antagonists, or beta blockers) may be associated with a significantly reduced risk of developing Parkinson's disease, although other studies have reported no benefit.[3] The authors of one study[2] that differentiated between types of calcium-channel blocker suggested that only centrally acting L-type calcium-channel blockers might be expected to have an effect. They reported a 26 to 30% risk reduction with all dihydropyridines except amlodipine, which does not easily cross the blood-brain barrier. No risk reduction was seen with verapamil or diltiazem.

1. Becker C, *et al*. Use of antihypertensives and the risk of Parkinson disease. *Neurology* 2008; **70:** 1438–44.
2. Ritz B, *et al*. L-type calcium channel blockers and Parkinson disease in Denmark. *Ann Neurol* 2010; **67:** 600–6.
3. Simon KC, *et al*. Calcium channel blocker use and risk of Parkinson's disease. *Mov Disord* 2010; **25:** 1818–22.

Peripheral vascular disease. Vasospastic arterial diseases (p. 1275.3) such as Raynaud's syndrome are due to an inappropriate response to temperature, usually cold, when vasoconstriction and/or vasospasm occurs. Calcium-channel blockers have been of benefit in Raynaud's syndrome, and are usually the first choice if drug therapy is needed, but it is not entirely clear which of their pharmacological actions is responsible. The most widely used and studied is nifedipine. Evidence of subjective benefit has been seen both in primary idiopathic disease[1] and in Raynaud's phenomenon secondary to systemic sclerosis,[2-5] SLE,[2,3] rheumatoid arthritis,[3] and cancer chemotherapy,[6] or associated with breast feeding.[7-9] Objective improvement as shown by evidence of improved digital blood flow has been seen in some[10-13] but not all[4] studies. Patients with Raynaud's syndrome usually receive an immediate-release formulation of nifedipine; however, a modified-release preparation has also been tried[14] and may reduce the incidence of adverse effects.

Nifedipine in doses of 20 to 60 mg daily has also been reported to be of benefit in the treatment of another vasospastic condition, chilblains, both for established chilblains and in the prevention of relapse.[15,16] Diltiazem appears to be less effective.[16]

1. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005; **44:** 145–50.
2. Smith CD, McKendry RJR. Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982; **ii:** 1299–1301.
3. Kahan A, *et al*. Nifedipine for Raynaud's phenomenon. *Lancet* 1983; **i:** 131.
4. Rademaker M, *et al*. Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; **298:** 561–4.
5. Thompson AE, *et al*. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum* 2001; **44:** 1841–7.
6. Hantel A, *et al*. Nifedipine and oncologic Raynaud phenomenon. *Ann Intern Med* 1988; **108:** 767.
7. Garrison CP. Nipple vasospasms, Raynaud's syndrome, and nifedipine. *J Hum Lact* 2002; **18:** 382–5.
8. Anderson JE, *et al*. Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding. *Pediatrics* 2004; **113:** e360–4.
9. Page SM, McKenna DS. Vasospasm of the nipple presenting as painful lactation. *Obstet Gynecol* 2006; **108:** 806–8.
10. Gasser P. Reaction of capillary blood cell velocity in nailfold capillaries to nifedipine and ketanserin in patients with vasospastic disease. *J Int Med Res* 1991; **19:** 24–31.
11. Thomas RHM, *et al*. Nifedipine in the treatment of Raynaud's phenomenon in patients with systemic sclerosis. *Br J Dermatol* 1987; **117:** 237–41.
12. Nilsson H, *et al*. Treatment of digital vasospastic disease with the calcium-entry blocker nifedipine. *Acta Med Scand* 1984; **215:** 135–9.
13. Finch MB, *et al*. The peripheral vascular effects of nifedipine in Raynaud's disease. *Br J Clin Pharmacol* 1986; **21:** 100P–101P.
14. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon: results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med* 2000; **160:** 1101–8.
15. Rustin MHA, *et al*. The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. *Br J Dermatol* 1989; **120:** 267–75.
16. Patra AK, *et al*. Diltiazem vs. nifedipine in chilblains: a clinical trial. *Indian J Dermatol Venereol Leprol* 2003; **69:** 209–11.

Phaeochromocytoma. Pharmacological management of phaeochromocytoma (p. 1278.1) is mainly with alpha-adrenergic blockade, and tachycardia may subsequently be controlled by cautious addition of a beta blocker. There have also been some reports[1-4] of the use of nifedipine to treat cardiovascular symptoms in adults and children with phaeochromocytoma.

1. Serfas D, *et al*. Phaeochromocytoma and hypertrophic cardiomyopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. *Lancet* 1983; **ii:** 711–13.
2. Lenders JWM, *et al*. Treatment of a phaeochromocytoma of the urinary bladder with nifedipine. *BMJ* 1985; **290:** 1624–5.
3. Favre L, Vallotton MB. Nifedipine in pheochromocytoma. *Ann Intern Med* 1986; **104:** 125.
4. Deal JE, *et al*. Phaeochromocytoma—investigation and management of 10 cases. *Arch Dis Child* 1990; **65:** 269–74.

Premature labour. Calcium-channel blockers (of which nifedipine is the most studied) have become increasingly favoured[1-3] as first-line tocolytics to postpone premature labour (p. 2131.1) over more traditionally-used drugs such as $beta_2$ agonists or magnesium. Meta-analyses and systematic reviews[4-7] have concluded that calcium-channel blockers were at least as effective as $beta_2$ agonists for tocolysis and caused fewer maternal adverse effects, although atosiban may be safer than either.[8] A meta-analysis[7] also found nifedipine to be as effective as, and associated with fewer adverse effects than, magnesium sulfate for tocolysis. The role of calcium-channel blockers in maintenance therapy is much less clear,[7,9,10] and some have found them to be ineffective.[7] There is also no evidence that nifedipine tocolysis is of value in facilitating external cephalic version (unlike $beta_2$ agonists) in women with breech or transverse presentation of the fetus.[11] A systematic review[12] that examined 31 studies of the efficacy of nifedipine in premature labour concluded that their overall quality was poor. Others[13] have expressed concern about the safety of calcium-channel blockers, reviewing cases of dyspnoea and pulmonary oedema in particular. They suggest that these drugs should not be used with intravenous beta agonists, that high doses should be avoided in women with cardiovascular compromise or multiple gestations, and that blood pressure and fetal heart rate should be monitored during use of short-acting preparations, which should not be chewed.

1. Tsatsaris V, Carbonne B. Tocolyse par les inhibiteurs calciques. *J Gynecol Obstet Biol Reprod (Paris)* 2001; **30:** 246–51.
2. Papatsonis DNM, *et al*. Update on the controversies of tocolytic therapy for the prevention of preterm birth. *Acta Obstet Gynecol Scand* 2004; **83:** 414.
3. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007; **357:** 477–87.
4. Ray JG. Meta-analysis of nifedipine versus beta-sympathomimetic agents for tocolysis during preterm labour. *J Soc Obstet Gynaecol Can* 1998; **20:** 259–69.
5. Tsatsaris V, *et al*. Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. *Obstet Gynecol* 2001; **97:** 840–7.
6. King JF, *et al*. Calcium channel blockers for inhibiting preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 03/03/09).
7. Conde-Agudelo A, *et al*. Nifedipine in the management of preterm labor: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2011; **204:** 134.e1–134.e20.
8. de Heus R, *et al*. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. *BMJ* 2009; **338:** b744.
9. Gaunekar NN, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 03/03/09).
10. Kim A, Shim JY. Emerging tocolytics for maintenance therapy of preterm labour: oxytocin antagonists and calcium channel blockers. *BJOG* 2006; **113** (suppl 3): 113–15.
11. Wilcox C, *et al*. Effectiveness of nifedipine tocolysis to facilitate external cephalic version: a systematic review. *BJOG* 2011; **118:** 423–8.
12. Lamont RF, *et al*. Steering Group of the International Preterm Labour Council. The quality of nifedipine studies used to assess tocolytic efficacy: a systematic review. *J Perinat Med* 2005; **33:** 287–95.
13. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. *Eur J Obstet Gynecol Reprod Biol* 2006; **126:** 137–45.

Pulmonary hypertension. Vasodilators have been tried in pulmonary arterial hypertension (p. 1278.2) on the premise that pulmonary vasoconstriction is an important component of the condition, and calcium-channel blockers have been widely used. However, in practice only a small proportion (< 10%)[1-3] of patients respond to calcium-channel blockers, and their empirical use in pulmonary hypertension is not recommended. Instead, the subset of responders may be identified using an acute response test in which a short-acting vasodilator such as inhaled nitric oxide or intravenous epoprostenol is given.[2] (The use of calcium-channel blockers themselves is no longer recommended for acute testing as severe adverse effects, including fatalities, have occurred.[4]) Cautious treatment with calcium-channel blockers may be started in those who respond.[1-3,5] Improved survival was seen in a study[6] in patients treated with high doses of nifedipine (120 to 240 mg daily) or diltiazem (540 to 900 mg daily) over a 5-year period, and these remain the drugs with which most experience lies. Choice may be influenced by baseline heart rate, nifedipine usually being given to those with relative bradycardia and diltiazem to those with relative tachycardia. Amlodipine has also been tried; verapamil is too strong a negative inotrope and should be avoided.[3,5] Patients should be monitored closely as the dose is titrated and assessed after 1 and 3 months, and additional or alternative therapy tried if the response is inadequate.[1,3,5]

1. National Pulmonary Hypertension Centres of the UK and Ireland. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. *Thorax* 2008; **63** (suppl 2): ii1–ii41. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pulmonary%20hypertension/PulmHyper_ThoraxMarch08.pdf (accessed 04/03/09)
2. Sitbon O, *et al*. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; **111:** 3105–11.
3. McLaughlin VV, *et al*. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *Circulation* 2009; **119:** 2250–94. Available at: http://circ.ahajournals.org/cgi/reprint/119/16/2250.pdf (accessed 29/03/11)
4. Badesch DB, *et al*. American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; **126** (1 suppl): 35S–62S. Also available at: http://chestjournal.chestpubs.org/content/126/1_suppl/35S.full.pdf (accessed 29/03/11)
5. Badesch DB, *et al*. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007; **131:** 1917–28. Also available at: http://www.chestjournal.org/cgi/reprint/131/6/1917 (accessed 04/03/09)
6. Rich S, *et al*. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; **327:** 76–81.

Renal calculi. There is some interest in the possible use of drug treatment to ease the spontaneous passage of renal calculi (p. 2350.3) in patients with uncomplicated lower ureteral stones. It has been suggested that the combination of a calcium-channel blocker (to reduce ureteral spasm) with a corticosteroid (to reduce oedema) may be useful. Small studies[1-3] have used modified-release preparations of nifedipine, given in oral doses of 30 mg daily for up to 28 days, with oral deflazacort 30 mg daily for up to 10 days. If the stone had not been expelled within 28 days, the patient was treated with extracorporeal shock wave lithotripsy or ureteroscopy. Treatment with nifedipine and deflazacort was found to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements.

The use of a 10-day course of nifedipine and deflazacort has also been studied[4] as adjunctive therapy after lithotripsy. It was found to ease the passage of stone fragments, reduce analgesic requirements, and increase the number of patients who were stone-free after 45 days. A 14-day course of nifedipine with ketoprofen after lithotripsy also resulted[5] in improved stone-free rates at 1 and 2 months, and a lower percentage of patients needing retreatment compared with controls.

1. Porpiglia F, *et al*. Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology* 2000; **56:** 579–83.
2. Porpiglia F, *et al*. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; **172:** 568–71.
3. Dellabella M, *et al*. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; **174:** 167–72.
4. Porpiglia F, *et al*. Role of adjunctive medical therapy with nifedipine and deflazacort after extracorporeal shock wave lithotripsy of ureteral stones. *Urology* 2002; **59:** 835–8.
5. Micali S, *et al*. Efficacy of expulsive therapy using nifedipine or tamsulosin, both associated with ketoprofene, after shock wave lithotripsy of ureteral stones. *Urol Res* 2007; **35:** 133–7.

Tardive dyskinesia. Calcium-channel blockers have been tried in the treatment of tardive dyskinesia (p. 1049.3). However, a systematic review[1] concluded that their effects are unclear and they should not be used.

1. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 28/03/06).

Transplantation. The main adverse effect of ciclosporin is reversible, dose-related nephrotoxicity. There is some evidence that nifedipine may be of value in protecting against this effect. Retrospective analysis[1] of 106 ciclosporin-treated renal transplant patients found that patients taking nifedipine for hypertension had better graft function, despite having shorter graft duration and therefore requiring higher dosage of ciclosporin, than hypertensive patients given other drug treatment. Subsequent studies have similarly reported improved graft function[2] in patients receiving nifedipine and suggest that graft survival is also improved.[3,4] A nephroprotective effect has also been reported with amlodipine,[5] felodipine,[6] isradipine,[7] lacidipine,[8] and nitrendipine,[9] and with the non-dihydropyridines diltiazem and verapamil (see p. 1360.1 and p. 1523.3 respectively), although a study[10] with nicardipine failed to show any improvement in graft function. However, a systematic review[11] concluded that although calcium-channel blockers given in the perioperative period appear to reduce the incidence of acute tubular necrosis in renal transplant patients, the results should be viewed cautiously due to the lack of good quality data.

For a report of adverse effects attributed to reduced metabolism of nifedipine in patients taking ciclosporin, see Immunosuppressants, under Interactions, p. 1454.1.

1. Feehally J, *et al*. Does nifedipine ameliorate cyclosporin A nephrotoxicity? *BMJ* 1987; **295:** 310.
2. Shin GT, *et al*. Effect of nifedipine on renal allograft function and survival beyond one year. *Clin Nephrol* 1997; **47:** 33–6.
3. Weinrauch LA, *et al*. Role of calcium channel blockers in diabetic renal transplant patients: preliminary observations on protection from sepsis. *Clin Nephrol* 1995; **44:** 185–92.
4. Mehrens T, *et al*. The beneficial effects of calcium channel blockers on long-term kidney transplant survival are independent of blood-pressure reduction. *Clin Transplant* 2000; **14:** 257–61.
5. Venkat Raman G, *et al*. Renal effects of amlodipine in normotensive renal transplant recipients. *Nephrol Dial Transplant* 1999; **14:** 384–8.
6. Madsen JK, *et al*. The effect of felodipine on renal function and blood pressure in cyclosporin-treated renal transplant recipients during the first three months after transplantation. *Nephrol Dial Transplant* 1998; **13:** 2327–34.
7. van Riemsdijk IC, *et al*. Addition of isradipine (Lomir) results in a better renal function after kidney transplantation: a double-blind, randomized, placebo-controlled, multi-center study. *Transplantation* 2000; **70:** 122–6.
8. Kuypers DR, *et al*. Lacidipine Study Group. Calcium channel blockade and preservation of renal graft function in cyclosporine-treated recipients: a prospective randomized placebo-controlled 2-year study. *Transplantation* 2004; **78:** 1204–11.
9. Rahn K-H, *et al*. Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: a randomised trial. *Lancet* 1999; **354:** 1415–20.
10. Kessler M, *et al*. Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; **36:** 637–8.
11. Shilliday IR, Sherif M. Calcium channel blockers for preventing acute tubular necrosis in kidney transplant recipients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 05/03/09).

Urticaria. Oral antihistamines are the main drugs used in the management of urticaria (p. 1689.2). Addition of a calcium-channel blocker, such as nifedipine, has been suggested for patients unresponsive to treatment with oral antihistamines alone, but results have been mixed.[1,2]

1. Lawlor F, *et al*. Calcium antagonist in the treatment of symptomatic dermographism: low-dose and high-dose studies with nifedipine. *Dermatologica* 1988; **177:** 287–91.
2. Bressler RB, *et al*. Therapy of chronic idiopathic urticaria with nifedipine: demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. *J Allergy Clin Immunol* 1989; **83:** 756–63.

Adverse Effects

The most common adverse effects of nifedipine are associated with its vasodilator action and often diminish on continued therapy. They include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, and palpitations. Nausea, constipation, and other gastrointestinal disturbances, micturition disorders including increased frequency, lethargy, eye pain, visual disturbances, syncope, vertigo, migraine, and mood disturbances have also occurred. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness.

There have been reports of rashes (including erythema multiforme), fever, and abnormalities in liver function, including cholestasis, due to hypersensitivity reactions. Gingival hyperplasia, pruritus, myalgia, tremor, gynaecomastia, and impotence have been reported.

Some tablets formulated for once-daily use are covered in a membrane which is not digested and may cause gastrointestinal obstruction; bezoars may rarely occur.

Overdosage may be associated with bradycardia and hypotension; hyperglycaemia, metabolic acidosis, and coma may also occur.

Nifedipine has been reported to be teratogenic in *animals*.

Effects on mortality. In the mid-1990s a series of reports and reviews raised concerns about calcium-channel blockers (particularly short-acting nifedipine and high doses) in increasing cardiovascular and overall mortality. Possible links with cancer, haemorrhage, and depression and suicide are discussed separately (see Carcinogenicity and Effects on the Blood, below, and Effects on Mental Function, p. 1451.3, respectively).

In response, the US National Heart, Lung, and Blood Institute issued a statement warning that short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and myocardial infarction,[1] and in some countries short-acting nifedipine preparations were withdrawn. Short-acting calcium-channel blockers can cause a dangerous rebound sympathetic stimulation, but the recommendations were occasionally extrapolated to include long-acting preparations and the general use of calcium-channel blockers fell out of favour. However, a review by the WHO/ISH pointed out that much of the evidence for adverse effects came from observational studies or small randomised studies (many of which had used the older short-acting calcium-channel blockers) and concluded that, as there was insufficient evidence to confirm either benefit or harm, recommendations on the management of angina, hypertension, and myocardial infarction should remain unchanged.[2] Since then, several large studies have found compelling evidence for the use of long-acting calcium-channel blockers in hypertension[3-6] and angina,[5] including an improvement of morbidity and mortality outcomes such as stroke[4] (although calcium-channel blockers do not have a role in myocardial infarction). The use of short-acting preparations of calcium-channel blockers such as nifedipine is no longer recommended for these indications; the once commonplace practice of biting a short-acting nifedipine capsule for the rapid reduction of acute hypertension should also be avoided.

More recently, a retrospective observational study has suggested that the use of dihydropyridine calcium-channel blockers was associated with higher 30-day mortality in patients undergoing surgery for aortic aneurysm.[7]

1. McCarthy M. US NIH issues warning on nifedipine. *Lancet* 1995; **346:** 689–90.
2. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
3. Grossman E, Messerli FH. Are calcium antagonists beneficial in diabetic patients with hypertension? *Am J Med* 2004; **116:** 44–9.
4. Basile J. The role of existing and newer calcium channel blockers in the treatment of hypertension. *J Clin Hypertens (Greenwich)* 2004; **6:** 621–9.
5. Croom KF, Wellington K. Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 2006; **66:** 497–528.
6. Epstein BJ, *et al*. Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007; **67:** 1309–27.
7. Kertai MD, *et al*. Dihydropiridine calcium-channel blockers and perioperative mortality in aortic aneurysm surgery. *Br J Anaesth* 2008; **101:** 458–65.

Carcinogenicity. An observational study carried out between 1988 and 1992 suggested that calcium-channel blockers were associated with an increased risk of cancer.[1] Subsequent studies have failed to support this finding.[2-7] A review by the WHO/ISH concluded that there is no good evidence that calcium-channel blockers increase cancer risk,[8] and the biological basis for an effect of calcium-channel blockers on cancer risk has also been questioned.[9] The large, long-term, randomised Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)[10] found no increase in the incidence of cancer in patients receiving a calcium-channel blocker (amlodipine) compared with those receiving a diuretic (chlortalidone).

1. Pahor M, *et al*. Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348:** 493–7.
2. Jick H, *et al*. Calcium-channel blockers and risk of cancer. *Lancet* 1997; **349:** 525–8.
3. Rosenberg L, *et al*. Calcium channel blockers and the risk of cancer. *JAMA* 1998; **279:** 1000–4.
4. Braun S, *et al*. Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. *J Am Coll Cardiol* 1998; **31:** 804–8.
5. Sajadieh A, *et al*. Verapamil and risk of cancer in patients with coronary artery disease. *Am J Cardiol* 1999; **83:** 1419–22.
6. Meier CR, *et al*. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.
7. Cohen HJ, *et al*. Calcium channel blockers and cancer. *Am J Med* 2000; **108:** 210–15.
8. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
9. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? *J Am Coll Cardiol* 1999; **34:** 1857–66.
10. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid*.; **289:** 178.

Effects on the blood. Treatment with nifedipine significantly reduces platelet aggregation *in vitro*[1] and inhibition of platelet function has been reported in healthy subjects given oral (but not intravenous) nifedipine.[2,3] There has therefore been concern[4] that calcium-channel blockers

might produce **haemorrhagic complications** in surgical patients (specifically, those undergoing coronary bypass surgery). Major surgical bleeding was associated with nimodipine in patients undergoing cardiac valve replacement,[5] although it has been used in other situations apparently without an increased risk of bleeding.[6] A later systematic review[7] found that dihydropyridines significantly increased endogenous fibrinolytic activity, although not in healthy subjects; the authors suggested that the effect might be due to interaction with anticoagulant or fibrinolytic drugs.

Conflicting results have been reported with regard to the risk of gastrointestinal bleeding. A prospective cohort study in 1636 elderly hypertensive patients,[8] and a subsequent case-control study,[9] reported that calcium-channel blockers were associated with an increased risk of gastrointestinal haemorrhage compared with beta blockers. However, it was suggested[10] that this may have been due to a protective effect of beta blockers rather than an adverse effect of calcium-channel blockers, and another study[11] also suggested that the risk of gastrointestinal bleeding was not materially increased by calcium-channel blockers.

Calcium-channel blockers have also been associated with **blood dyscrasias**; there have been case reports of aplastic anaemia with nifedipine,[12] and of thrombocytopenia with amlodipine[13] and with diltiazem.[14,15]

1. Ośmiałwska Z, *et al.* Effect of nifedipine monotherapy on platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* 1990; **39:** 403–4.
2. Winther K, *et al.* Dose-dependent effects of verapamil and nifedipine on in vivo platelet function in normal volunteers. *Eur J Clin Pharmacol* 1990; **39:** 291–3.
3. Walley TJ, *et al.* The effects of intravenous and oral nifedipine on ex vivo platelet function. *Eur J Clin Pharmacol* 1989; **37:** 449–52.
4. Becker RC, Alpert JS. The impact of medical therapy on hemorrhagic complications following coronary artery bypass grafting. *Arch Intern Med* 1990; **150:** 2016–21.
5. Wagenknecht LE, *et al.* Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995; **310:** 776–7.
6. Öhman J and others. Surgical bleeding and calcium antagonists. *BMJ* 1995; **311:** 388–9. [Several letters.]
7. Vergouwen MDI, *et al.* Dihydropyridine calcium antagonists increase fibrinolytic activity: a systematic review. *J Cereb Blood Flow Metab* 2007; **27:** 1293–1308.
8. Pahor M, *et al.* Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347:** 1061–5.
9. Kaplan RC, *et al.* Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch Intern Med* 2000; **160:** 1849–55.
10. Suissa S, *et al.* Antihypertensive drugs and the risk of gastrointestinal bleeding. *Am J Med* 1998; **105:** 230–5.
11. Kelly JP, *et al.* Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet* 1999; **353:** 559.
12. Laporte J-R, *et al.* Fatal aplastic anaemia associated with nifedipine. *Lancet* 1998; **352:** 619–20.
13. Usalan C, *et al.* Severe thrombocytopenia associated with amlodipine treatment. *Ann Pharmacother* 1999; **33:** 1126–7.
14. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
15. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on the bone and joints. For reports of arthralgia associated with calcium-channel blockers see under Effects on the Neuromuscular System, below.

Effects on the brain. Cerebral ischaemia[1,2] has been reported in small numbers of patients given nifedipine.

1. Nobile-Orazio E, Sterzi R. Cerebral ischaemia after nifedipine treatment. *BMJ* 1981; **283:** 948.
2. Schwartz M, *et al.* Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. *Arch Intern Med* 1990; **150:** 686–7.

Effects on carbohydrate metabolism. There are reports of deterioration of diabetes,[1] reduction in glucose tolerance,[2] and development of diabetes[1,3] in patients given nifedipine. Nifedipine has also been reported to increase plasma-glucose concentrations.[3,4] However, other reports and studies have found no change in glucose tolerance in either diabetic or non-diabetic patients taking nifedipine.[5-10]

See also Diabetes Mellitus under Precautions, p. 1453.1.

1. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 19.
2. Giugliano D, *et al.* Impairment of insulin secretion in man by nifedipine. *Eur J Clin Pharmacol* 1980; **18:** 395–8.
3. Zezulka AV, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 437–8.
4. Charles S, *et al.* Hyperglycaemic effect of nifedipine. *BMJ* 1981; **283:** 19–20.
5. Harrower ADB, Donnelly T. Hyperglycaemic effect of nifedipine. *BMJ* 1981; **283:** 796.
6. Greenwood RH. Hyperglycaemic effect of nifedipine. *BMJ* 1982; **284:** 50.
7. Abadie E, Passa P. Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 438.
8. Dante A. Nifedipine and fasting glycemia. *Ann Intern Med* 1986; **104:** 125–6.
9. Whitcroft I, *et al.* Calcium antagonists do not impair long-term glucose control in hypertensive non-insulin dependent diabetics (NIDDS). *Br J Clin Pharmacol* 1986; **22:** 208P.
10. Tentorio A, *et al.* Insulin secretion and glucose tolerance in non-insulin dependent diabetic patients after chronic nifedipine treatment. *Eur J Clin Pharmacol* 1989; **36:** 311–13.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the eyes. Individual reports have implicated nifedipine in the development of transient retinal ischaemia and blindness,[1] and of periorbital oedema.[2] In a post-marketing survey painful or stinging eyes were more common in patients receiving nifedipine (178 of 757 evaluable) than in those given captopril (45 of 289), although the cause was uncertain.[3] Nifedipine has also been suggested as a risk factor in the development of cataract,[4,5] but the numbers involved in this analysis are small[6] and it is possible that the risk, if it exists,[7] relates to hypertension rather than nifedipine treatment.[6]

1. Pitlik S, *et al.* Transient retinal ischaemia induced by nifedipine. *BMJ* 1983; **287:** 1845–6.
2. Silverstone PH. Periorbital oedema caused by nifedipine. *BMJ* 1984; **288:** 1654.
3. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; **296:** 1086–8.
4. van Heyningen R, Harding JJ. Do aspirin-like analgesics protect against cataract? *Lancet* 1986; **i:** 1111–13.
5. Harding JJ, van Heyningen R. Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide. *Br J Ophthalmol* 1988; **72:** 809–14.
6. van Heyningen R, Harding JJ. Aspirin-like analgesics and cataract. *Lancet* 1986; **ii:** 283.
7. Kewitz H, *et al.* Aspirin and cataract. *Lancet* 1986; **ii:** 689.

Effects on the heart. The use of nifedipine has been associated with the development of heart disorders in some patients. Complete heart block has been reported in an elderly patient who had previously developed heart block with verapamil,[1] and sudden circulatory collapse has been reported in 4 patients receiving nifedipine who underwent routine coronary bypass surgery.[2] One patient died despite all attempts at resuscitation.[2] However, most reports seem to have concerned the development or aggravation of cardiac ischaemia, up to and including frank myocardial infarction after use of short-acting nifedipine.[3-6] Such cases appear to be chiefly associated with a too-rapid fall in blood pressure after the use of sublingual nifedipine for hypertensive urgencies or emergencies,[5,6] or occur in patients with a history of ischaemic heart disease.[3,4] The use of short-acting preparations of nifedipine, especially sublingually in the treatment of hypertensive crises, is no longer recommended (see Hypertension, p. 1251.1).

For discussion of the effects of calcium-channel blockers on cardiovascular mortality, see p. 1450.2.

1. Chopra DA, Maxwell RT. Complete heart block with low dose nifedipine. *BMJ* 1984; **288:** 760.
2. Goiti JJ. Calcium channel blocking agents and the heart. *BMJ* 1985; **291:** 1505.
3. Sia STB, *et al.* Aggravation of myocardial ischaemia by nifedipine. *Med J Aust* 1985; **142:** 48–50.
4. Boden WE, *et al.* Nifedipine-induced hypotension and myocardial ischemia in refractory angina pectoris. *JAMA* 1985; **253:** 1131–5.
5. O'Mailia JJ, *et al.* Nifedipine-associated myocardial ischemia or infarction in the treatment of hypertensive urgencies. *Ann Intern Med* 1987; **107:** 185–6.
6. Leavitt AD, Zweifler AJ. Nifedipine, hypotension, and myocardial injury. *Ann Intern Med* 1988; **108:** 305–6.

WITHDRAWAL. Exacerbation of coronary ischaemia and thrombosis of arteriovenous graft could have resulted from withdrawal of nifedipine in a patient.[1] Abrupt withdrawal of nisoldipine from 15 patients with stable angina pectoris after 6 weeks of therapy resulted in severe unstable angina in 2 patients and acute myocardial infarction in another.[2] It was postulated that the withdrawal effect could be due to an increase in sensitivity of vascular α_2 adrenoceptors to circulating adrenaline.

1. Mysliwiec M, *et al.* Calcium antagonist withdrawal syndrome. *BMJ* 1983; **286:** 1898.
2. Mehta J, Lopez LM. Calcium-blocker withdrawal phenomenon: increase in affinity of alpha$_2$ adrenoceptors for agonist as a potential mechanism. *Am J Cardiol* 1986; **58:** 242–6.

Effects on the kidneys. Calcium-channel blockers may be of benefit in some kidney disorders (see under Uses and Administration, p. 1449.1). However, reversible deterioration in renal function without any noticeable decline in systemic arterial blood pressure has been reported[1] in 4 patients with underlying renal insufficiency taking nifedipine,[1] and in another report[2] nifedipine increased urinary protein excretion and exacerbated renal impairment in 14 type 2 diabetic patients.

Excessive diuresis occurred in a patient given nifedipine for angina pectoris,[3] and nocturia in 9 patients referred for prostatic surgery was also attributed to nifedipine.[4]

1. Diamond JR, *et al.* Nifedipine-induced renal dysfunction: alterations in renal hemodynamics. *Am J Med* 1984; **77:** 905–9.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Antonelli D, *et al.* Excessive nifedipine diuretic effect. *BMJ* 1984; **288:** 760.
4. Williams G, Donaldson RM. Nifedipine and nocturia. *Lancet* 1986; **i:** 738.

Effects on the liver. Cases of hepatitis, apparently due to a hypersensitivity reaction, and frequently accompanied by fever, sweating, chills, rigor, and arthritic symptoms, have been reported in patients receiving nifedipine.[1-4]

1. Rotmensch HH, *et al.* Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; **281:** 976–7.
2. Davidson AR. Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; **281:** 1354.
3. Abramson M, Littlejohn GO. Hepatic reactions to nifedipine. *Med J Aust* 1985; **142:** 47–8.
4. Shaw DR, *et al.* Nifedipine hepatitis. *Aust N Z J Med* 1987; **17:** 447–8.

Effects on the menstrual cycle. Menorrhagia in 2 women[1] and menstrual irregularity with heavy bleeding in another[2] have been reported with nifedipine treatment.

1. Rodger JC, Torrance TC. Can nifedipine provoke menorrhagia? *Lancet* 1983; **ii:** 460.
2. Singh G, *et al.* Can nifedipine provoke menorrhagia? *Lancet* 1983; **ii:** 1022.

Effects on mental function. Insomnia, hyperexcitability, pacing, agitation, and depression were reported[1] in a patient receiving nifedipine. The symptoms disappeared within 2 days of stopping the drug. Four further cases of major depression, which developed within a week of starting nifedipine and resolved within a week of stopping the drug, have been reported.[2]

Although 2 epidemiological studies suggested that calcium-channel blockers may promote suicide,[3] a subsequent study[4] found no evidence of an association between depression and the use of calcium-channel blockers, and the number of suicides was low. Further studies[5-7] have also failed to find an increased risk of suicide with calcium-channel blockers compared with other antihypertensive drugs.

1. Ahmad S. Nifedipine-induced acute psychosis. *J Am Geriatr Soc* 1984; **32:** 408.
2. Hullett FJ, *et al.* Depression associated with nifedipine-induced calcium channel blockade. *Am J Psychiatry* 1988; **145:** 1277–9.
3. Lindberg G, *et al.* Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. *BMJ* 1998; **316:** 741–5.
4. Dunn NR, *et al.* Cohort study on calcium channel blockers, other cardiovascular agents, and the prevalence of depression. *Br J Clin Pharmacol* 1999; **48:** 230–3.
5. Gasse C, *et al.* Risk of suicide among users of calcium channel blockers: population based, nested case-control study. *BMJ* 2000; **320:** 1251.
6. Sørensen HT, *et al.* Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001; **52:** 313–8.
7. Callréus T, *et al.* Cardiovascular drugs and the risk of suicide: a nested case-control study. *Eur J Clin Pharmacol* 2007; **63:** 591–6.

Effects on the mouth. *GINGIVAL HYPERPLASIA.* Gingival hyperplasia has been reported with many of the calcium-channel blockers, particularly the dihydropyridines.[1,2] Of 114 reports of gingival overgrowth in the Australian Adverse Drug Reactions Advisory Committee database[1] in 1999, nifedipine accounted for 25 cases, amlodipine 22 cases, and felodipine 14 cases. Onset ranged from a few days to more than 4 years after starting treatment, and the effect was usually reversible on stopping the drug.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced gingival overgrowth. *Aust Adverse Drug React Bull* 1999; **18:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9906.pdf (accessed 25/07/08)
2. Ioulios P, *et al.* The spectrum of cutaneous reactions associated with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. *Dermatol Online J* 2003; **9:** 6. Available at: http://dermatology.cdlib.org/95/reviews/calcium/ioulios.html (accessed 23/01/09)

PAROTITIS. Acute swelling of the parotid glands occurred in a patient after sublingual administration of nifedipine.[1]

1. Bosch X, *et al.* Nifedipine-induced parotitis. *Lancet* 1986; **ii:** 467.

Effects on the neuromuscular system. Severe muscle cramps have been reported in a few patients taking nifedipine;[1,2] in one patient[2] the cramps were associated with widespread paraesthesia. Severe rhabdomyolysis developed in a patient with a transplanted kidney who was receiving an intravenous infusion of nifedipine.[3] The patient recovered rapidly once the infusion was stopped. There has also been a report[4] of myopathy, myalgia, and arthralgia associated with amlodipine, and of arthralgia in a patient[5] receiving diltiazem.

1. Keidar S, *et al.* Muscle cramps during treatment with nifedipine. *BMJ* 1982; **285:** 1241–2.
2. Macdonald JB. Muscle cramps during treatment with nifedipine. *BMJ* 1982; **285:** 1744.
3. Horn S, *et al.* Severe rhabdomyolysis in a kidney-transplant recipient receiving intravenous nifedipine. *Lancet* 1995; **346:** 848–9.
4. Phillips BB, Muller BA. Severe neuromuscular complications possibly associated with amlodipine. *Ann Pharmacother* 1998; **32:** 1165–7.
5. Smith KM. Arthralgia associated with calcium-channel blockers. *Am J Health-Syst Pharm* 2000; **57:** 55–7.

Effects on the oesophagus. Calcium-channel blockers decrease lower oesophageal sphincter pressure and have been used in oesophageal motility disorders (see p. 1449.2), but a retrospective cohort study[1] found that

calcium-channel blockers may also precipitate or exacerbate gastro-oesophageal reflux disease.

1. Hughes J, *et al.* Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? *Br J Clin Pharmacol* 2007; **64:** 83–9.

Effects on the peripheral circulation. An erythromelalgia-like eruption occurred in a patient 8 weeks after starting therapy with nifedipine. Symptoms included severe burning pain and swelling in the feet and lower legs, which were fiery red, tender, and warm to the touch. Symptoms resolved in 2 days when nifedipine was stopped.[1] Similar effects have been reported in other patients on nifedipine.[2-4] Erythromelalgia has also been reported with nicardipine.[5] This type of erythromelalgia may be termed secondary erythermalgia.[6]

1. Fisher JR, *et al.* Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **98:** 671–2.
2. Grunwald Z. Painful edema, erythematous rash, and burning sensation due to nifedipine. *Drug Intell Clin Pharm* 1982; **16:** 492.
3. Brodmerkel GJ. Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **99:** 415.
4. Sunahara JF, *et al.* Possible erythromelalgia-like syndrome associated with nifedipine in a patient with Raynaud's phenomenon. *Ann Pharmacother* 1996; **30:** 484–6.
5. Levesque H, *et al.* Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon?) *BMJ* 1989; **298:** 1252–3.
6. Drenth JPH, Michiels JJ. Three types of erythromelalgia. *BMJ* 1990; **301:** 454–5.

Effects on the respiratory system. Reversible acute pulmonary oedema (with pleural effusion[1]) has been reported in patients receiving *nifedipine*[1-4] or *nicardipine*.[5] Nifedipine has also been reported to exacerbate impaired tissue oxygenation in patients with cor pulmonale secondary to obstructive airways disease.[6]

For a report of exacerbation of laryngeal oedema, see under Hypersensitivity, below.

1. Chaouat A, *et al.* Pulmonary oedema and pleural effusion in two patients with primary pulmonary hypertension treated with calcium channel blockers. *Heart* 1996; **75:** 383.
2. Gillmer DJ, Kark P. Pulmonary oedema precipitated by nifedipine. *BMJ* 1980; **280:** 1420–1.
3. Aderka D, Pinkhas J. Pulmonary oedema precipitated by nifedipine. *BMJ* 1984; **289:** 1272.
4. Abbas OM, *et al.* Acute pulmonary edema during tocolytic therapy with nifedipine. *Am J Obstet Gynecol* 2006; **195:** e3–e4.
5. Vaast P, *et al.* Acute pulmonary oedema during nicardipine therapy for premature labour: report of five cases. *Eur J Obstet Gynecol Reprod Biol* 2004; **113:** 98–9.
6. Kalra L, Bone MF. Nifedipine and impaired oxygenation in patients with chronic bronchitis and cor pulmonale. *Lancet* 1989; **i:** 1135–6.

Effects on the skin and nails. The commonest skin reactions to nifedipine have been rash, pruritus, urticaria, alopecia, and exfoliative dermatitis;[1] there have been a few reports of erythema multiforme and the Stevens-Johnson syndrome.[1] Erythema multiforme occurred in a patient after substitution of amlodipine for nifedipine[2] and cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between amlodipine and diltiazem.[3] Generalised pruritus has been reported with amlodipine.[4] Other skin reactions that have been reported with nifedipine include severe photosensitivity reactions,[5] nonthrombocytopenic purpuric rashes,[6] and telangiectasias,[7] including photodistributed telangiectasias,[8] and pemphigoid nodularis.[9] Telangiectasias have also been reported with amlodipine[10,11] and felodipine.[12] Lichen planus[13] and hyperpigmentation[14] have also occurred with amlodipine. Nail and periungual pigmentation developed[15] in a 75-year-old man 18 months after starting amlodipine; it was much improved 2 years after the drug was stopped.

For reference to erythromelalgia, see under Effects on the Peripheral Circulation, above.

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
2. Bewley AP, *et al.* Erythema multiforme following substitution of amlodipine for nifedipine. *BMJ* 1993; **307:** 241.
3. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28:** 118–19.
4. Orme S, *et al.* Generalised pruritus associated with amlodipine. *BMJ* 1997; **315:** 463.
5. Thomas SE, Wood ML. Photosensitivity reactions associated with nifedipine. *BMJ* 1986; **292:** 992.
6. Oren R, *et al.* Nifedipine-induced nonthrombocytopenic purpura. *DICP Ann Pharmacother* 1989; **23:** 88.
7. Tsele E, Chu AC. Nifedipine and telangiectasias. *Lancet* 1992; **339:** 365–6.
8. Collins P, Ferguson J. Photodistributed nifedipine-induced facial telangiectasia. *Br J Dermatol* 1993; **129:** 630–3.
9. Ameen M, *et al.* Pemphigoid nodularis associated with nifedipine. *Br J Dermatol* 2000; **142:** 575–7.
10. Basarab T, *et al.* Calcium antagonist-induced photo-exposed telangiectasia. *Br J Dermatol* 1997; **136:** 974–5.
11. Grabczynska SA, Cowley N. Amlodipine induced-photosensitivity presenting as telangiectasia. *Br J Dermatol* 2000; **142:** 1255–6.
12. Al-Niaimi F, Lyon C. Felodipine-induced eruptive telangiectasia following mastectomy and radiotherapy. *Br J Dermatol* 2010; **162:** 210–11.
13. Swale VJ, McGregor JM. Amlodipine-associated lichen planus. *Br J Dermatol* 2001; **144:** 920–1.
14. Erbagci Z. Amlodipine associated hyperpigmentation. *Saudi Med J* 2004; **25:** 103–5.
15. Sladden MJ, *et al.* Longitudinal melanonychia and pseudo-Hutchinson sign associated with amlodipine. *Br J Dermatol* 2005; **153:** 219–20.

Effects on taste. Distortion of taste and smell has been reported in 2 patients taking nifedipine,[1] but a large survey involving 922 patients receiving nifedipine and 343 taking captopril did not show any association of taste disturbances with nifedipine.[2] Sudden loss of taste has also been reported[3] in a patient who had been taking amlodipine for several years; the sense of taste returned when amlodipine was stopped, but taste loss recurred on rechallenge.

1. Levenson JL, Kennedy K. Dysomia, dysgeusia, and nifedipine. *Ann Intern Med* 1985; **102:** 135–6.
2. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; **296:** 1086–8.
3. Sadasivam B, Jhaj R. Dysgeusia with amlodipine—a case report. *Br J Clin Pharmacol* 2007; **63:** 253.

Extrapyramidal disorders. Extrapyramidal effects have been seen with calcium-channel blockers of all chemical classes, although most reports seem to concern the phenylalkylamine, verapamil, rather than the dihydropyridines or diltiazem. **Parkinsonism** has been reported in patients taking amlodipine,[1,2] diltiazem,[3] and verapamil.[4,5] Parkinsonism is also a recognised effect of flunarizine and cinnarizine, which have calcium-channel blocking properties (see under Flunarizine, p. 630.1). However, for the suggestion that some dihydropyridines may reduce the risk of developing Parkinson's disease, see under Uses and Administration, p. 1449.2.

Other movement disorders seen with calcium-channel blockers include **akathisia** with diltiazem,[6,7] **dystonia** with verapamil,[8] **myoclonic dystonia** with verapamil[9] and nifedipine,[10] and **myoclonus** with verapamil.[11,12]

1. Sempere AP, *et al.* Parkinsonism induced by amlodipine. *Mov Disord* 1995; **10:** 115–16.
2. Teive HA, *et al.* Parkinsonian syndrome induced by amlodipine: case report. *Mov Disord* 2002; **17:** 833–5.
3. Dick RS, Barold SS. Diltiazem-induced parkinsonism. *Am J Med* 1989; **87:** 95–6.
4. García-Albea E, *et al.* Parkinsonism unmasked by verapamil. *Clin Neuropharmacol* 1993; **16:** 263–5.
5. Padrell MD, *et al.* Verapamil-induced parkinsonism. *Am J Med* 1995; **99:** 436.
6. Jacobs MB. Diltiazem and akathisia. *Ann Intern Med* 1983; **99:** 794–5.
7. Brink DD. Diltiazem and hyperactivity. *Ann Intern Med* 1984; **100:** 459–60.
8. Pina MA, *et al.* Verapamil and acute dystonia. *J Clin Pharm Ther* 1998; **23:** 79–80.
9. Hicks CB, Abraham K. Verapamil and myoclonic dystonia. *Ann Intern Med* 1985; **103:** 154.
10. de Medina A, *et al.* Nifedipine and myoclonic dystonia. *Ann Intern Med* 1986; **104:** 125.
11. Maiteh M, Daoud AS. Myoclonic seizure following intravenous verapamil injection: case report and review of the literature. *Ann Trop Paediatr* 2001; **21:** 271–2.
12. Vadlamudi L, Wijdicks EFM. Multifocal myoclonus due to verapamil overdose. *Neurology* 2002; **58:** 984.

Gynaecomastia. Unilateral gynaecomastia developed in 3 men 4, 6, and 26 weeks after starting nifedipine therapy.[1] Gynaecomastia has also been reported[2] in 2 patients receiving amlodipine while on haemodialysis; symptoms resolved on stopping the drug.

1. Clyne CAC. Unilateral gynaecomastia and nifedipine. *BMJ* 1986; **292:** 380.
2. Komine N, *et al.* Amlodipine-induced gynecomastia in two patients on long-term hemodialysis therapy. *Clin Exp Nephrol* 2003; **7:** 85–6.

Haemorrhage. See Effects on the Blood, p. 1450.3.

Hypersensitivity. *Nifedipine* is associated with various hypersensitivity reactions including rashes (above) and effects on the liver (p. 1451.3).

Nifedipine, given sublingually, exacerbated laryngeal swelling that developed in a woman after the use of isosorbide dinitrate spray.[1] *Amlodipine* has also been associated with angioedema.[2]

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.
2. Southward J, *et al.* Probable amlodipine-induced angioedema. *Ann Pharmacother* 2009; **43:** 772–6.

Oedema. Oedema of the feet and ankles is a common adverse effect of nifedipine and other dihydropyridine calcium-channel blockers. It occurs typically 2 or more weeks after starting treatment and is caused by pre-capillary arteriolar dilatation rather than fluid retention.[1] Evidence from a study in 10 diabetic subjects beginning nifedipine therapy, 5 of whom developed ankle oedema, suggested that nifedipine abolished the reflex vasoconstriction produced when the feet are below the level of the heart which is believed to prevent excessive fluid filtration into the tissues.[2]

The oedema may respond to simple measures such as elevation of the feet or to a reduction in dosage but if it persists the calcium-channel blocker should be withdrawn.[1]

Generalised oedema[3] and facial and upper extremity oedema[4] have been reported in patients taking amlodipine, but in both cases symptoms resolved on withdrawal of the drug.

For the view that second-generation lipophilic dihydropyridines may be less prone to cause oedema than earlier drugs such as amlodipine or nifedipine see Tolerability, under Lercanidipine, p. 1419.3.

1. Maclean D, MacConnachie AM. Selective side-effects: peripheral oedema with dihydropyridine calcium antagonists. *Prescribers' J* 1991; **31:** 4–6.
2. Williams SA, *et al.* Dependent oedema and attenuation of postural vasoconstriction associated with nifedipine therapy for hypertension in diabetic patients. *Eur J Clin Pharmacol* 1989; **37:** 333–5.
3. Şener D, *et al.* Anasarca edema with amlodipine treatment. *Ann Pharmacother* 2005; **39:** 761–3.
4. Ganeshalingham A, Wong W. Amlodipine-induced bilateral upper extremity edema. *Ann Pharmacother* 2007; **41:** 1536–8.

Treatment of Adverse Effects

Toxicity in calcium-channel blocker overdose may potentially be very severe. Activated charcoal may be given orally to adults or children who present within 1 hour of ingesting a potentially toxic overdose of a calcium-channel blocker, although later use has been suggested for those who have ingested modified-release preparations. Alternatively, gastric lavage may be considered in adults.

Supportive and symptomatic care should be given. Hypotension may respond to placing the patient in the supine position with the feet raised; plasma expanders may be given, although cardiac overload should be avoided. Atropine should be given for symptomatic bradycardia, although cardiac pacing may be more effective if there is evidence of AV conduction delay. Isoprenaline has also been used but may exacerbate hypotension by reducing systemic vascular resistance.

Intravenous calcium should be given to those with significant features of poisoning. A typical dose is up to 6.8 mmol of calcium given by slow intravenous injection over 5 minutes, repeated as required every 10 to 20 minutes up to a maximum of 4 doses. Alternatively, up to about 6.8 mmol per hour of calcium may be given by intravenous infusion. 6.8 mmol of calcium is provided by about 10 mL of calcium chloride 10%, or about 30 mL of calcium gluconate 10%.

In severe cases an insulin and glucose infusion may improve myocardial contractility and systemic perfusion. A lipid infusion may be helpful for unresponsive cardiotoxicity due to lipophilic calcium-channel blockers. Unresponsive hypotension may require use of an adrenoceptor agonist such as noradrenaline or dopamine. Glucagon has also been used to correct myocardial depression and hypotension.

Dialysis is not useful for nifedipine as it is highly protein bound. Plasmapheresis may be beneficial.

Overdosage. Although severe toxicity is more likely in overdosage with non-dihydropyridines such as verapamil or diltiazem, treatment of overdosage is similar for all calcium-channel blockers.[1-4] Management is mainly supportive (see Treatment of Adverse Effects, above). Alternative suggestions to standard therapy have included fampridine[5] as a specific antagonist, and amrinone[1] as an inotrope. Successful use of vasopressin[6] or terlipressin[7] has been reported in patients with resistant hypotension; plasma exchange has also been tried[8] successfully. There is some evidence[9,10] that high-dose insulin (with glucose if required to prevent hypoglycaemia) may be of benefit, particularly in patients with acidosis, and its safety has been shown.[11]

Most reports of overdosage have been with verapamil (see p. 1524.2). The following are some individual reports for nifedipine:

- Hypotension, tachycardia, and flushing, followed by hypokalaemia, were seen in a patient who took nifedipine 600 mg as modified-release tablets together with an overdose of paracetamol, but there was no evidence of heart block.[12] The patient was given calcium gluconate intravenously and subsequently activated charcoal and lactulose. Absorption of nifedipine was essentially complete 10 hours after ingestion. Potassium chloride was given orally to treat hypokalaemia and acetylcysteine was used to manage the paracetamol poisoning.
- Third-degree AV block, progressing to asystole, developed in a 14-month-old child who ingested about 800 mg of nifedipine.[13] During cardiopulmonary resuscitation a total of 700 mg of calcium chloride was given, together with atropine, adrenaline, and sodium bicarbonate. The stomach was subsequently emptied by gastric lavage and activated charcoal given. The child remained tachycardic and hypotensive, with evidence of pulmonary oedema and hyperglycaemia, and was given intravenous electrolytes and dopamine infusions and assisted ventilation and treatment to control tonic-clonic seizures. She eventually made an apparently complete recovery apart from a moderate speech delay.

1. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Safety* 2003; **26:** 65–79.
2. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004; **23:** 223–38.

3. Olson KR, *et al.* Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2005; **43:** 797–822.
4. Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; **63:** 1828–35.
5. Stevens JJWM, Ghosh S. Overdose of calcium channel blockers. *BMJ* 1994; **309:** 193.
6. Kanagarajan K, *et al.* The use of vasopressin in the setting of recalcitrant hypotension due to calcium channel blocker overdose. *Clin Toxicol* 2007; **45:** 56–9.
7. Leone M, *et al.* Terlipressin: a new therapeutic for calcium-channel blockers overdose. *J Crit Care* 2005; **20:** 114–15.
8. Ezidiegwu C, *et al.* A case report on the role of plasma exchange in the management of a massive amlodipine besylate intoxication. *Ther Apher Dial* 2008; **12:** 180–4.
9. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. *Toxicol Rev* 2004; **23:** 215–22.
10. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923–30.
11. Greene SL, *et al.* Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med* 2007; **33:** 2019–24.
12. Ferner RE, *et al.* Pharmacokinetics and toxic effects of nifedipine in massive overdose. *Hum Exp Toxicol* 1990; **9:** 309–11.
13. Wells TG, *et al.* Nifedipine poisoning in a child. *Pediatrics* 1990; **86:** 91–4.

Precautions

Nifedipine should be used with caution in patients with hypotension, in patients whose cardiac reserve is poor, and in those with heart failure since deterioration of heart failure has been noted. Nifedipine should not be used in cardiogenic shock, in patients who have suffered a myocardial infarction in the previous 2 to 4 weeks, or in acute unstable angina. Nifedipine should not be used to treat an anginal attack in chronic stable angina, nor should it be used for the acute reduction of blood pressure in adults, though it may be used for this purpose in children (see p. 1447.3). In patients with severe aortic stenosis nifedipine may increase the risk of developing heart failure. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina. The dose may need to be reduced in patients with hepatic impairment.

Nifedipine should be stopped in patients who have ischaemic pain after use.

Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been used in hypertension in pregnancy (see Hypertension, under Uses and Administration, p. 1448.3).

Breast feeding. Nifedipine is distributed into breast milk[1,2] but the amount present is probably too small to be harmful. There have been no reports of any clinical effects in breast-fed infants whose mothers were receiving nifedipine and the last available guidance from the American Academy of Pediatrics therefore considered[3] that it was usually compatible with breast feeding.

1. Ehrenkranz RA, *et al.* Nifedipine transfer into human milk. *J Pediatr* 1989; **114:** 478–80.
2. Penny WJ, Lewis MJ. Nifedipine is excreted in human milk. *Eur J Clin Pharmacol* 1989; **36:** 427–8.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Cardiac surgery. For the suggestion that dihydropyridine calcium-channel blockers may increase perioperative mortality in patients undergoing aortic aneurysm surgery see Effects on Mortality, under Adverse Effects, p. 1450.2.

Diabetes mellitus. Nifedipine's effect on insulin and glucose responses (see Effects on Carbohydrate Metabolism under Adverse Effects, p. 1451.1) may require antidiabetic therapy to be adjusted. Also some studies have suggested that nifedipine can worsen proteinuria and renal dysfunction in diabetic patients with some degree of renal insufficiency,[1,2] but other studies, (see Kidney Disorders under Uses and Administration, p. 1449.1), have suggested that nifedipine may have a beneficial effect on proteinuria.

Some studies have suggested that patients with diabetes mellitus[3,4] or impaired glucose metabolism[5] may be more susceptible to adverse cardiovascular effects of calcium-channel blockers. The calcium-channel blockers used in these studies were the dihydropyridines nisoldipine, amlodipine, and isradipine (long-acting or intermediate-acting calcium-channel blockers). However, two of the studies[3,4] compared the calcium-channel blocker with an ACE inhibitor and it has been suggested that ACE inhibitors may be particularly beneficial in these patients rather than calcium-channel blockers being particularly harmful.[6] Improved cardiovascular outcomes were seen from adding a long-acting nifedipine formulation to therapy in another study in patients with type 2 diabetes.[7]

1. Mimran A, *et al.* Contrasting effects of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *J Hypertens* 1988; **6:** 919–23.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Estacio RO, *et al.* The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; **338:** 645–52. Correction. *ibid.*; **339:** 1339.
4. Tatti P, *et al.* Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21:** 597–603.
5. Byington RP, *et al.* Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet* 1997; **350:** 1075–6.
6. Poulter NR. Calcium channel blockers and cardiovascular risk in diabetes. *Lancet* 1998; **351:** 1809–10.
7. Elliott HL, *et al.* Improving blood pressure control in patients with diabetes mellitus and high cardiovascular risk. *Int J Hypertens* 2011; **2010:** 490769.

Interference with diagnostic tests. Calcium-channel blockers reduce the plasma aldosterone:renin ratio by increasing renin production and reducing plasma aldosterone concentrations; consequently, primary hyperaldosteronism has been misdiagnosed as essential hypertension in patients taking calcium-channel blockers.[1] A diagnostic ratio was seen in each patient within two weeks of stopping the calcium-channel blocker.

Nifedipine may give falsely elevated spectrophotometric values of urinary vanillylmandelic acid; HPLC estimations are unaffected.

1. Grasko JM, *et al.* Delayed diagnosis of primary hyperaldosteronism. *BMJ* 2010; **340:** 1358.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nifedipine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Withdrawal. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina.

For a report of life-threatening coronary vasospasm occurring after withdrawal of nifedipine before a revascularisation procedure, see under Effects on the Heart, in Diltiazem, p. 1360.3.

Interactions

Nifedipine may enhance the antihypertensive effects of other antihypertensive drugs such as beta blockers although the combination is generally well tolerated. Enhanced antihypertensive effects may also be seen if used with drugs such as aldesleukin and antipsychotics that cause hypotension. Nifedipine may modify insulin and glucose responses (see Effects on Carbohydrate Metabolism, p. 1451.1) and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving nifedipine. Nifedipine is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4, and interactions may occur with other drugs, such as quinidine, sharing the same metabolic pathway, and with enzyme inducers, such as carbamazepine, phenytoin, and rifampicin, and enzyme inhibitors, such as cimetidine, erythromycin, and HIV-protease inhibitors.

Alcohol. A study involving 10 healthy subjects showed that the area under the concentration-time profile for nifedipine 20 mg was increased by 54% when taken orally with alcohol, and maximum pulse rate was achieved more rapidly, which was in line with *animal* and *in-vitro* studies suggesting that the metabolism of nifedipine is inhibited by alcohol.[1]

1. Qureshi S, *et al.* Nifedipine-alcohol interaction. *JAMA* 1990; **264:** 1660–1.

Antiarrhythmics. Nifedipine and *quinidine* probably have a common metabolic pathway in the liver and might be expected to interact if given concurrently. In one study,[1] quinidine appeared to inhibit nifedipine metabolism resulting in increased serum concentrations of nifedipine; quinidine concentrations were unchanged. However, conflicting effects on serum-quinidine concentrations have been reported, see p. 1483.2.

1. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; **33:** 727–31.

Antibacterials. The macrolide antibacterials are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may inhibit the metabolism of calcium-channel blockers. Two days after *clarithromycin* was started,[1] vasodilatory shock and heart block occurred in a 77-year-old man whose antihypertensive medication included nifedipine. Clarithromycin was continued and when his condition improved nifedipine was reintroduced at half the previous dose; his blood pressure was stable on discharge. A population-based, nested, case crossover study[2] of elderly patients who were receiving calcium-channel blockers found that of 7100 who were admitted to hospital for the treatment of hypotension, 176 had been taking a macrolide antibacterial. Analysis indicated that the greatest risk for developing hypotension was with *erythromycin*, followed by clarithromycin, while use of *azithromycin* was not associated with an increased risk.

1. Gerónimo-Pardo M, *et al.* Clarithromycin–nifedipine interaction as possible cause of vasodilatory shock. *Ann Pharmacother* 2005; **39:** 538–42.
2. Wright AJ, *et al.* The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ* 2011; **183:** 303–7.

Antidiabetics. See Diabetes Mellitus under Precautions (above) and Effects on Carbohydrate Metabolism under Adverse Effects, p. 1451.1.

Antiepileptics. The effects of dihydropyridine calcium-channel blockers may be reduced by enzyme-inducing antiepileptics such as *carbamazepine*, *phenobarbital*, and *phenytoin*.[1-4] In contrast, *sodium valproate* has been reported to increase plasma-nimodipine concentrations.[3]

For reports of an interaction between dihydropyridines and *phenytoin* resulting in raised serum-phenytoin concentration, see p. 544.2.

1. Capewell S, *et al.* Reduced felodipine bioavailability in patients taking anticonvulsants. *Lancet* 1988: **ii:** 480–2.
2. Schellens JHM, *et al.* Influence of enzyme induction and inhibition on the oxidation of nifedipine, sparteine, mephenytoin and antipyrine in humans as assessed by a "cocktail" study design. *J Pharmacol Exp Ther* 1989; **249:** 638–45.
3. Tartara A, *et al.* Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1991; **32:** 335–40.
4. Yasui-Furukori N, Tateishi T. Carbamazepine decreases antihypertensive effect of nilvadipine. *J Clin Pharmacol* 2002; **42:** 100–103.

Antifungals. Azole antifungals inhibit the cytochrome P450 enzyme system and may therefore interfere with metabolism of calcium-channel blockers. Two women who had been taking felodipine for about a year developed peripheral oedema a few days after starting treatment with *itraconazole*.[1] Plasma-felodipine concentrations were measured in one of the women before and during a subsequent course of itraconazole and increased considerably when the two drugs were used together. A similar interaction occurred when itraconazole therapy was started in a patient already taking nifedipine.[2] Potentiation of the effects of nifedipine by *fluconazole* has also been reported.[3]

1. Neuvonen PJ, Suhonen R. Itraconazole interacts with felodipine. *J Am Acad Dermatol* 1995; **33:** 134–5.
2. Tailor SAN, *et al.* Peripheral edema due to nifedipine-itraconazole interaction: a case report. *Arch Dermatol* 1996; **132:** 350–2.
3. Kremens B, *et al.* Loss of blood pressure control on withdrawal of fluconazole during nifedipine therapy. *Br J Clin Pharmacol* 1999; **47:** 707–8.

Antihistamines. Severe angina developed in a patient stabilised on nifedipine who took *terfenadine* 60 mg for seasonal allergy. The pain resolved within an hour or two.[1]

1. Falkenberg HM. Possible interaction report. *Can Pharm J* 1988; **121:** 294.

Antineoplastics. For reports of increased *vincristine* toxicity in children also taking itraconazole and nifedipine see Antifungals, under Interactions of Vincristine, p. 884.1. The development of gallstones in a 76-year-old man receiving nifedipine and *imatinib* was thought[1] to result from imatinib interfering with nifedipine metabolism via the cytochrome P450 isoenzyme CYP3A4.

1. Breccia M, *et al.* Can nifedipine and estrogen interaction with imatinib be responsible for gallbladder stone development? *Eur J Haematol* 2005; **75:** 89–90.

Antivirals. The HIV-protease inhibitors are known to inhibit the cytochrome P450 isoenzyme CYP3A4 and may therefore interfere with the metabolism of calcium-channel blockers. A woman stable on felodipine developed oedema[1] in both legs when she was given *nelfinavir* after a needle-stick injury. The oedema resolved on withdrawal of felodipine, and was attributed to inhibition of felodipine metabolism. A man[2] taking nifedipine for hypertension developed symptomatic orthostatic hypotension and heart block when HAART including nelfinavir was started. Symptoms improved when nelfinavir was stopped; they occurred on rechallenge, and again when the HAART was altered to include *ritonavir-boosted indinavir*. A study[3] in healthy subjects found that ritonavir-boosted indinavir increased exposure to both amlodipine and diltiazem.

1. Izzedine H, *et al.* Nelfinavir and felodipine: a cytochrome P450 3A4-mediated drug interaction. *Clin Pharmacol Ther* 2004; **75:** 362–3.
2. Rossi DR, *et al.* Symptomatic orthostasis with extended-release nifedipine and protease inhibitors. *Pharmacotherapy* 2002; **22:** 1312–16.
3. Glesby MJ, *et al.* Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. *Clin Pharmacol Ther* 2005; **78:** 143–53.

Beta blockers. Although nifedipine is often used with beta blockers without untoward effects, heart failure has been reported in a few patients with angina who were given nifedipine and a beta blocker.[1,2] Severe hypotension has been reported in 1 of 15 angina patients given nifedipine and *atenolol*;[3] withdrawal of the beta blocker precipitated severe unstable angina in this patient. Severe hypotension in a patient was attributed to the use of nifedipine with

propranolol, and was thought to have contributed to fatal myocardial infarction.[4]

1. Anastassiades CJ. Nifedipine and beta-blocker drugs. *BMJ* 1980; **281:** 1251–2.
2. Robson RH, Vishwanath MC. Nifedipine and beta-blockade as a cause of cardiac failure. *BMJ* 1982; **284:** 104.
3. Opie LH, White DA. Adverse interaction between nifedipine and β-blockade. *BMJ* 1980; **281:** 1462.
4. Staffurth JS, Emery P. Adverse interaction between nifedipine and beta-blockade. *BMJ* 1981; **282:** 225.

Calcium-channel blockers. Plasma concentrations of nifedipine were increased in a study in 6 healthy subjects when pretreated with *diltiazem*; the elimination half-life of nifedipine was prolonged from 2.54 hours to 3.40 hours after pretreatment with diltiazem 30 mg daily and to 3.47 hours after 90 mg daily. The effect was probably due to reduced hepatic metabolism of nifedipine.[1] Nifedipine and diltiazem are reported to be metabolised by the same hepatic enzyme and, conversely, pretreatment with nifedipine has resulted in increased concentrations of diltiazem.[2] Paralytic ileus was thought[3] to result from elevated nifedipine concentrations in a 62-year-old man when diltiazem was added to his therapy.

1. Tateishi T, *et al*. Dose dependent effect of diltiazem on the pharmacokinetics of nifedipine. *J Clin Pharmacol* 1989; **29:** 994–7.
2. Tateishi T, *et al*. The effect of nifedipine on the pharmacokinetics and dynamics of diltiazem: the preliminary study in normal volunteers. *J Clin Pharmacol* 1993; **33:** 738–40.
3. Harada T, *et al*. Paralytic ileus induced by the combined use of nifedipine and diltiazem in the treatment of vasospastic angina. *Cardiology* 2002; **97:** 113–14.

Digoxin. For the effect of nifedipine and other dihydropyridine calcium-channel blockers on digoxin, see p. 1357.2.

Grapefruit juice. Grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4, particularly in the intestinal wall, and markedly increases the bioavailability of oral calcium-channel blockers;[1-3] calcium-channel blockers given intravenously appear to be unaffected.[4] The interaction may be less significant with calcium-channel blockers such as amlodipine that have a higher bioavailability,[5] but most calcium-channel blockers should not be taken orally at the same time as grapefruit juice.[6] A stereoselective effect has also been reported.[7]

1. Bailey DG, *et al*. Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991; **337:** 268–9.
2. Bailey DG, *et al*. Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharmacol Ther* 1993; **54:** 589–94.
3. Lundahl J, *et al*. Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur J Clin Pharmacol* 1995; **49:** 61–7.
4. Rashid TJ, *et al*. Factors affecting the absolute bioavailability of nifedipine. *Br J Clin Pharmacol* 1995; **40:** 51–8.
5. Vincent J, *et al*. Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. *Br J Clin Pharmacol* 2000; **50:** 455–63.
6. CSM/MCA. Drug interactions with grapefruit juice. *Current Problems* 1997; **23:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
7. Uno T, *et al*. Effect of grapefruit juice on the disposition of manidipine enantiomers in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 533–7.

Histamine H_2-antagonists. Pharmacokinetic studies have indicated that use of nifedipine with *cimetidine* can increase the bioavailability of nifedipine.[1-4] An increase in the area under the plasma concentration-time curve of between 77 and 92% has been reported.[2,3] Potentiation of the hypotensive effect of nifedipine by cimetidine was also shown in 7 hypertensive patients.[1] The mechanism of the interaction was thought to be due to inhibition of the cytochrome P450 system by cimetidine and thus inhibition of the metabolism of nifedipine.

Ranitidine was found to have little effect on the pharmacokinetics of nifedipine, although there was an increase in the bioavailability of nifedipine during use of ranitidine.[5] *Famotidine* has been reported not to interact with nifedipine.[6]

1. Kirch W, *et al*. Einfluss von Cimetidin und Ranitidin auf Pharmakokinetik und antihypertensiven Effekt von Nifedipin. *Dtsch Med Wochenschr* 1983; **108:** 1757–61.
2. Renwick AG, *et al*. Factors affecting the pharmacokinetics of nifedipine. *Eur J Clin Pharmacol* 1987; **32:** 351–5.
3. Smith SR, *et al*. Ranitidine and cimetidine: drug interactions with single dose and steady-state nifedipine administration. *Br J Clin Pharmacol* 1987; **23:** 311–15.
4. Schwartz JB, *et al*. Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1988; **43:** 673–80.
5. Kirch W, *et al*. Ranitidine increases bioavailability of nifedipine. *Clin Pharmacol Ther* 1985; **37:** 204.
6. Kirch W, *et al*. Negative effects of famotidine on cardiac performance assessed by noninvasive hemodynamic measurements. *Gastroenterology* 1989; **96:** 1388–92.

Immunosuppressants. Flushing, paraesthesias, and rashes were reported in 2 patients given nifedipine 40 mg daily while taking *ciclosporin* for psoriasis.[1] A study in 8 psoriatic patients indicated that giving nifedipine with ciclosporin resulted in reduced recovery of the principal metabolite of nifedipine, presumably because ciclosporin reduced nifedipine metabolism through competition for the cytochrome P450 metabolising enzymes.

For reference to the effects of calcium-channel blockers on ciclosporin concentrations in blood, see p. 1957.3. For the possible protective effect of nifedipine against ciclosporin-induced nephrotoxicity, see Transplantation under Uses and Administration, p. 1450.2.

For the effect of nifedipine on *tacrolimus*, see p. 1978.2.

1. McFadden JP, *et al*. Cyclosporin decreases nifedipine metabolism. *BMJ* 1989; **299:** 1224.

Magnesium salts. Profound hypotension has been reported in 2 women in whom a single oral dose of nifedipine 10 mg was added to treatment with magnesium sulfate infusion for pre-eclampsia; both women were also receiving methyldopa.[1] Neuromuscular blockade has been reported in 2 women after use of nifedipine with intravenous magnesium sulfate. In one woman given nifedipine as a tocolytic, symptoms of neuromuscular blockade occurred immediately on injection of magnesium sulfate and resolved within 25 minutes of stopping the injection.[2] In another woman who was receiving a magnesium sulfate infusion for pre-eclampsia, symptoms developed 30 minutes after the second of 2 doses of nifedipine had been given and improved after receiving calcium gluconate injection.[3] However, a chart review[4] of women given intravenous magnesium sulfate with nifedipine for pre-eclampsia found no increase in serious magnesium-related adverse effects compared with women who received magnesium sulfate with either another antihypertensive or no antihypertensive.

1. Waisman GD, *et al*. Magnesium plus nifedipine: potentiation of hypotensive effect in pre-eclampsia? *Am J Obstet Gynecol* 1988; **159:** 308–9.
2. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* 1989; **161:** 35–6.
3. Ben-Ami M, *et al*. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* 1994; **101:** 262–3.
4. Magee LA, *et al*. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol* 2005; **193:** 153–63.

Melatonin. Melatonin may cause a reduction in blood pressure and might be expected to have additive effects if given with antihypertensives. However, in a study[1] in hypertensive patients taking nifedipine, giving melatonin led to an increase in both blood pressure and heart rate.

1. Lusardi P, *et al*. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *Br J Clin Pharmacol* 2000; **49:** 423–7.

Tobacco. In a study of the effects of cigarette smoking and the treatment of angina with nifedipine, propranolol, or atenolol, smoking was shown to have direct and adverse effects on the heart and to interfere with the efficacy of all 3 anti-anginal drugs, with nifedipine being the most affected.[1]

1. Deanfield J, *et al*. Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. *N Engl J Med* 1984; **310:** 951–4.

Xanthines. For the effect of nifedipine on *theophylline*, see Calcium-channel Blockers, p. 1235.3.

Pharmacokinetics

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract, but undergoes extensive hepatic first-pass metabolism. Bioavailability of oral liquid-filled capsules is between 45 and 56%, but is lower for longer-acting formulations. Peak blood concentrations are reported to occur 30 to 60 minutes after oral doses of liquid-filled capsules.

Nifedipine is about 92 to 98% bound to plasma proteins. It is distributed into breast milk. It is extensively oxidised in the liver via the cytochrome P450 isoenzyme CYP3A4, and 80 to 95% of a dose is excreted in the urine, and the remainder in the faeces, almost entirely as inactive metabolites. The half-life is about 2 hours after intravenous doses or oral liquid-filled capsules. Hepatic impairment considerably reduces the clearance of nifedipine (see below), whereas renal impairment has little effect on its pharmacokinetics.

Reviews.

1. Sorkin EM, *et al*. Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related cardiovascular disorders. *Drugs* 1985; **30:** 182–274.
2. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.

Absorption. Studies have indicated that the absorption of nifedipine may be affected by food; the results appear to vary depending upon the preparation used. Decreased peak plasma concentrations[1] and a delay in achieving them[1,2] have been reported with certain preparations when given after a meal; conversely, food has caused an increase in bioavailability[3] and plasma concentrations[3,4] with some preparations, while the pharmacokinetics of others appear to be minimally affected by food.[2,4,5] It has been suggested that traditional measures of bioequivalence may fail to reflect differences in the absorption and distribution characteristics of different nifedipine modified-release formulations.[6-8]

1. Hirasawa K, *et al*. Effect of food ingestion on nifedipine absorption and haemodynamic response. *Eur J Clin Pharmacol* 1985; **28:** 105–7.
2. Schug BS, *et al*. The effect of food on the pharmacokinetics of nifedipine in two slow release formulations: pronounced lag-time after a high fat breakfast. *Br J Clin Pharmacol* 2002; **53:** 582–8.
3. Ueno K, *et al*. Effect of food on nifedipine sustained-release preparation. *DICP Ann Pharmacother* 1989; **23:** 662–5.
4. Wonnemann M, *et al*. Significant food interactions observed with a nifedipine modified-release formulation marketed in the European Union. *Int J Clin Pharmacol Ther* 2006; **44:** 38–48.
5. Ueno K, *et al*. Effect of a light breakfast on the bioavailability of sustained-release nifedipine. *DICP Ann Pharmacother* 1991; **25:** 317–19.
6. Endrenyi L, Tothfalusi L. Do regulatory bioequivalence requirements adequately reflect the therapeutic equivalence of modified-release drug products? *J Pharm Pharm Sci* 2010; **13:** 107–13.
7. Pollak PT. Therapeutically relevant blood pressure differences with two nifedipine (60 mg) osmotic delivery systems of differing design: three case reports. *Int J Clin Pharmacol Ther* 2010; **48:** 400–4.
8. Woodcock BG. Critical questions concerning nifedipine extended release formulations. *Int J Clin Pharmacol Ther* 2010; **48:** 355.

Hepatic impairment. The pharmacokinetics of nifedipine were found to be considerably altered in 7 patients with liver cirrhosis.[1] Systemic plasma clearance was substantially reduced and the elimination half-life was considerably longer than in healthy subjects. In addition, systemic availability of oral nifedipine was much higher in patients with cirrhosis and was complete in 3 patients with surgical portacaval shunt. Patients with liver cirrhosis seemed to be more sensitive to the effects of nifedipine on diastolic blood pressure and heart rate, and this could be explained by the higher free drug concentrations seen. It was concluded that lower doses of nifedipine may be required in patients with liver cirrhosis, and the patient's response should be closely monitored.

1. Kleinbloesem CH, *et al*. Nifedipine: kinetics and hemodynamic effects in patients with liver cirrhosis after intravenous and oral administration. *Clin Pharmacol Ther* 1986; **40:** 21–8.

Interindividual variation. A Dutch study in 53 healthy subjects found a bimodal distribution of plasma concentrations of nifedipine after a single oral dose; it was proposed that the higher plasma concentrations in 17% of subjects represented a slow metaboliser phenotype, with the majority of the population being fast metabolisers.[1] Although further studies[2,3] in European populations have not confirmed these results, a study in 12 Mexican healthy subjects supported the concept of polymorphic metabolism, with 5 fast and 7 slow metabolisers, a much higher proportion of slow metabolisers than in the European studies.[4] Studies have also reported a markedly increased area under the concentration-time curve in those from South Asia,[5,6] Mexico,[7] and Nigeria[8] compared with Caucasians. The difference did not appear to be due to diet.[5,6] The initial dose of nifedipine might need to be lower in these ethnic groups. Another population study[9] found that clearance was slower in blacks compared with whites, and in men compared with women; alcohol ingestion and smoking both also reduced nifedipine clearance.

1. Kleinbloesem CH, *et al*. Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem Pharmacol* 1984; **33:** 3721–4.
2. Renwick AG, *et al*. The pharmacokinetics of oral nifedipine—a population study. *Br J Clin Pharmacol* 1988; **25:** 701–8.
3. Lobo J, *et al*. The intra- and inter-subject variability of nifedipine pharmacokinetics in young volunteers. *Eur J Clin Pharmacol* 1986; **30:** 57–60.
4. Hoyo-Vadillo C, *et al*. Pharmacokinetics of nifedipine slow release tablet in Mexican subjects: further evidence for an oxidation polymorphism. *J Clin Pharmacol* 1989; **29:** 816–20.
5. Ahsan CH, *et al*. Ethnic differences in the pharmacokinetics of oral nifedipine. *Br J Clin Pharmacol* 1991; **31:** 399–403.
6. Ahsan CH, *et al*. The influences of dose and ethnic origins on the pharmacokinetics of nifedipine. *Clin Pharmacol Ther* 1993; **54:** 329–38.
7. Castañeda-Hernández G, *et al*. Interethnic variability in nifedipine disposition: reduced systemic plasma clearance in Mexican subjects. *Br J Clin Pharmacol* 1996; **41:** 433–4.
8. Sowunmi A, *et al*. Ethnic differences in nifedipine kinetics: comparisons between Nigerians, Caucasians and South Asians. *Br J Clin Pharmacol* 1995; **40:** 489–93.
9. Krecic-Shepard ME, *et al*. Race and sex influence clearance of nifedipine: results of a population study. *Clin Pharmacol Ther* 2000; **68:** 130–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adalat; Nifed Sol; Nifedel; ***Austral.***: Adalat; Addos; Adefin; Nifecard†; Nifehexal; Nyefax; Nypine†; ***Austria***: Adalat; Buconif; Fedip; Nifebene; Nifehexal; Ospocard; ***Belg.***: Adalat; Hypan; ***Braz.***: Adalat; Cardalin; Dilaflux; Dilavax†; Dipinal; Neo Fedipina; Nifadil; Nifedax; Nifedicard†; Nioxil; Normopres; Oxcord; Prodopina†; ***Canad.***: Adalat; Apo-Nifed; Nu-Nifed; ***Chile***: Adalat; Cardicon; Coronovo; Nipress; Sulotil; ***China***: Adalat (拜新同); Ai Di Qing (爱地清); De Gao Ning (得高宁); Jiu Bao Ka Di (久保卡迪); Jiubaopine (久保平); Li Huan (利焕); Na Xin Tong (纳欣同); Nifuda (倪福达); Xin Ran (欣然); Yuan Fu (源孚); ***Cz.***: Adalat†; Cordipin; Corinfar†; Nifecard; ***Denm.***: Adalat; Hexadilat; ***Fin.***: Adalat;

Nifangin; **Fr.**: Adalate; Chronadalate; **Ger.**: Adalat; Aprical; Cisday†; Corinfar; Jutadilat†; Nife†; Nifeclair†; Nifecor†; Nifehexal†; Nifelat†; Nifical†; Pidilat†; **Gr.**: Adalat; Antiblut; Citidipine; Coracten; Flecor-N; Ftelile; Glopir; Macorel; Nefelid; Nifedicor; Nifedipat; Nucul; Nydral; Orix; Reanimat; Viscard; **Hong Kong**: Adalat; Coracten; Cordipin; Nadipinia; Nifecard; Nifelat; Vidalat†; **Hung.**: Adalat; Cordaflex; Corinfar; Nifecard†; **India**: Adalat; Angiblock; Calbloc; Calcigard; Calnif; Cardipin; Cardules; Depicor; Depin; Myogard; N-Dip; Needin; NF; Nicardia; Nifcard; Nifedine; Nifelat; Niferil; Novacard; **Indon.**: Adalat; Calcianta; Carvas; Cordalat; Coronipin; Farmalat; Fedipin†; Ficor; Nifedin; Vasdalat; Xepalat; **Irl.**: Adalat; Cardilate†; Nifed; **Israel**: Nifedilong; Osmo-Adalat; Pressolat; **Ital.**: Adalat; Amarkor; Citilat; Coral; Euxat; Fenidina; Nifedicor; Nifesal; Nipin; **Jpn**: Adalat; **Malaysia**: Adalat; Adifen; Calcigard; Fenamon; Nifecip; Nifelat; **Mex.**: Adalat; Anhiten-A; Atenses; Cordilat; Corogal†; Corotrend†; Fusepina†; Gelprim; Linam; Nifar; Nifedigel; Nifedipres; Nifezzard; Nifser; Noviken; Pidef; **Neth.**: Adalat; Nifret†; **Norw.**: Adalat; **NZ**: Adalat; Adefin; Nyefax; **Philipp.**: Adalat; Calcibloc; Calcigard†; Cardicap†; Darat; Hartigard; Heblopin; Hyperten†; Nelapine; Nifestad; Normadil†; Odipin; Tensibloc†; **Pol.**: Adalat†; Cordafen†; Cordipin†; **Port.**: Adalat; Angipina; Meborilan; **Rus.**: Adalat (Адалат); Calcigard (Кальцигард); Carin-Fer (Карин-Фер); Cordafen (Кордафен); Cordaflex (Кордафлекс); Cordipin (Кордипин); Corinfar (Коринфар); Depin-E (Депин-Е); Fenamon (Фенамон)†; Nicardia (Никардия); Nifecard (Нифекард); Nifelat (Нифелат); Osmo-Adalat (Осмо-Адалат); Phenihidin (Фенигидин); **S.Afr.**: Adalat; Adco-Vascard; Cardifen; Cipalat; Fedaloc; Macorel; Nifedalat; **Singapore**: Adalat; Apo-Nifed; Beadalet; Calcigard; Cordipin; Depin-E; Fenamon†; Nifecard; Nifedi-Denk; Nifelat; Nipin; Servidipine†; Stada Uno; Vasdalat; **Spain**: Adalat; Pertensal†; **Swed.**: Adalat; **Switz.**: Adalat; Cardipin; Corotrend; Ecodipine; Nifedicor†; **Thai.**: Adalat; Adipine; Calcigard; Coracten†; Depin-E; Fenamon†; Nelapine; Nicardia; Nifecard†; Nifedi-Denk; Nifelat; Nyefax†; Stada Uno†; **Turk.**: Adalat; Kardilat; Nidicard; Nidilat; **UAE**: Cardiopine; **UK**: Adalat; Adipine; Calchan; Cardilate MR†; Coracten; Fortipine; Hypolar Retard; Nifedipress; Nifopress†; Slofedipine; Tensipine; Valni; **Ukr.**: Adalat (Адалат); Cordipin (Кордипин); Corinfar (Коринфар); Farmadipin (Фармадипин); Nifecard (Нифекафд); Osmo-Adalat (Осмо-Адалат); **USA**: Adalat; Afeditab; Nifediac; Nifedical; Procardia; **Venez.**: Adalat; Conducil; Nifal; Tensomax; Tensopin.

Multi-ingredient Preparations. ***Austria***: Beta-Adalat; Nif-Ten; ***Belg.***: Tenif; ***Braz.***: Nifelat; Orosprevent; ***Canad.***: Adalat XL Plus; ***Fin.***: Nif-Ten†; ***Fr.***: Beta-Adalate; Tenordate; ***Ger.***: AteNif beta†; Belnif; Bresben†; Nif-Ten; Nifatenol†; Sali-Adalat; Tredalat; ***Hong Kong***: Nif-Ten; ***India***: Beta-Nicardia; Beta-Nifedipine; Betanif; Betatrop; Cardules Plus; Depten; Nifetolol; Nilol; Presolar; Tenofed; ***Indon.***: Nif-Ten; ***Irl.***: Beta-Adalat; Nif-Ten; ***Ital.***: Antrolin; Nif-Ten; ***Mex.***: Plenacor; ***Philipp.***: Nif-Ten†; ***Singapore***: Beta Nicardia; Nif-Ten; Nifetex; ***Switz.***: Beta-Adalat; Nif-Ten; ***UK***: Beta-Adalat; Tenif; ***Ukr.***: Tonorma (Тонорма).

Pharmacopoeial Preparations

BP 2014: Nifedipine Capsules; Prolonged-release Nifedipine Capsules; Prolonged-release Nifedipine Tablets;

USP 36: Nifedipine Capsules; Nifedipine Extended-release Tablets.

Nifekalant Hydrochloride *(rINNM)*

Hidrocloruro de nifekalant; MS-551; Nifékalant, Chlorhydrate de; Nifekalant, hidrocloruro de; Nifekalanti Hydrochloridum; Нифекаланта Гидрохлорид.

6-[(2-{(2-Hydroxyethyl)[3-(*p*-nitrophenyl)propyl]amino}ethyl)amino]-1,3-dimethyluracil hydrochloride.

$C_{19}H_{27}N_5O_5$,HCl=441.9

CAS — 130636-43-0 (nifekalant); 130656-51-8 (nifekalant hydrochloride).

Profile

Nifekalant is a class III antiarrhythmic (p. 1243.1) used intravenously as the hydrochloride in the management of life-threatening ventricular arrhythmias (p. 1266.1).

References.

1. Katoh T, *et al.* Emergency treatment with nifekalant, a novel class III anti-arrhythmic agent, for life-threatening refractory ventricular tachyarrhythmias: post-marketing special investigation. *Circ J* 2005; **69:** 1237–43.
2. Yusu S, *et al.* Effects of intravenous nifekalant as a lifesaving drug for severe ventricular tachyarrhythmias complicating acute coronary syndrome. *Circ J* 2009; **73:** 2021–8.
3. Shiga T, *et al.* Refractory VT/VF, Prospective Evaluation to Differentiate Lidocaine Efficacy from Nifekalant (RELIEF) Study Investigators. Nifekalant versus lidocaine for in-hospital shock-resistant ventricular fibrillation or tachycardia. *Resuscitation* 2010; **81:** 47–52.

Effects on the heart. A woman who had been receiving intravenous nifekalant continuously for 10 months was found[1] to have a round mass in the right atrium. This was resected and shown to be a fibrin thrombus containing a large amount of nifekalant in the form of needle crystals.

1. Okamura H, *et al.* Crystals in the heart. *Heart* 2004; **90:** 1106.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Shinbit.

Nilvadipine *(USAN, rINN)*

CL-287389; FK-235; Nilvadipidiini; Nilvadipidin; Nilvadipidinum; Nilvadipin; Nilvadipino; Nilvadipinum; Nivadipine; SKF-102362; Нильвадипин.

5-Isopropyl 3-methyl 2-cyano-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

$C_{19}H_{19}N_3O_6$=385.4

CAS — 75530-68-6.

ATC — C08CA10.

ATC Vet — QC08CA10.

UNII — 0214FUT37J.

Pharmacopoeias. In *Jpn*.

Profile

Nilvadipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1). Nilvadipine is given orally, usually as a modified-release preparation, in a dose of up to 16 mg daily.

References.

1. Brogden RN, McTavish D. Nilvadipine: a review of its pharmacodynamic and pharmacokinetic properties, therapeutic use in hypertension and potential in cerebrovascular disease and angina. *Drugs Aging* 1995; **6:** 150–71. Correction. *ibid.*; **7:** 116.
2. Koseki N, *et al.* A placebo-controlled 3-year study of a calcium blocker on visual field and ocular circulation in glaucoma with low-normal pressure. *Ophthalmology* 2008; **115:** 2049–57.
3. Nakazawa M, *et al.* Effect of nilvadipine on central visual field in retinitis pigmentosa: a 30-month clinical trial. *Ophthalmologica* 2011; **225:** 120–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Tensan; ***Cz.***: Escor†; ***Fin.***: Escor; ***Ger.***: Escor; Nivadil; ***Gr.***: Peroma; ***Irl.***: Nivadil; ***Jpn***: Nivadil; ***Port.***: Nivadil; ***Turk.***: Nilvadis.

Nimodipine *(BAN, USAN, rINN)*

Bay-e-9736; Nimodipiini; Nimodipin; Nimodipina; Nimodipinas; Nimodipino; Nimodipinum; Nimodypina; Нимодипин.

Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

$C_{21}H_{26}N_2O_7$=418.4

CAS — 66085-59-4.

ATC — C08CA06.

ATC Vet — QC08CA06.

UNII — 57WA9QZ5WH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Nimodipine). A light yellow or yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 36: (Nimodipine). A light yellow or yellow crystalline powder, affected by light. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in ethyl acetate. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Licensed product information states that solutions of nimodipine are incompatible with some plastics, including PVC, and that the only plastics suitable for use are polyethylene and polypropylene. Nimodipine solution must not be added to an infusion bag or bottle, or be mixed with other drugs.

Uses and Administration

Nimodipine is a dihydropyridine calcium-channel blocker that has the general properties of nifedipine (p. 1447.2), but acts particularly on cerebral blood vessels. It is used in cerebrovascular disorders (see below), particularly in the prevention and treatment of ischaemic neurological deficits after aneurysmal subarachnoid haemorrhage.

To reduce the incidence and severity of ischaemic neurological deficit after aneurysmal haemorrhage nimodipine is given orally in a dose of 60 mg every 4 hours. Treatment should begin within 4 days of onset of haemorrhage and should continue for 21 days. In patients with hepatic impairment the dose may be reduced (see below) and blood pressure should be closely monitored.

If cerebral ischaemia occurs or has already occurred, neurological deficit may be treated by intravenous infusion of an appropriate formulation of nimodipine. It should be given via a bypass into a running intravenous infusion into a central vein. The initial dose should be nimodipine 1 mg/hour for 2 hours, increased (provided that no severe decrease in blood pressure occurs) to 2 mg/hour. The starting dose should be reduced to 500 micrograms/hour, or even lower if necessary, in patients weighing less than 70 kg and in those with unstable blood pressure; a similar reduction in dosage has been suggested in hepatic impairment, and blood pressure should be closely monitored. Treatment should be started as soon as possible and continued for at least 5 and no more than 14 days; if the patient has already received oral nimodipine, the total duration of nimodipine use should not exceed 21 days.

For doses in children, see below.

Administration in children. The *BNFC* recommends that children aged from 1 month may be given nimodipine orally for the **prevention** of vasospasm after subarachnoid haemorrhage in a dose of 0.9 to 1.2 mg/kg (up to a maximum of 60 mg) six times daily; treatment should start within 4 days of haemorrhage and be continued for 21 days.

For the **treatment** of haemorrhage once cerebral ischaemia has already occurred, it suggests that nimodipine may be given by intravenous infusion under specialist advice. The dose in those from 1 month to 12 years of age is 15 micrograms/kg per hour initially (to a maximum of 500 micrograms/hour), or half this rate if blood pressure is unstable. After 2 hours, provided there is no severe decrease in blood pressure, the rate may be increased up to 30 micrograms/kg per hour (maximum 2 mg/hour) and treatment continued for at least 5 but no more than 14 days. Doses in older children are similar to those in adults.

Administration in hepatic impairment. The clearance of nimodipine is reduced in patients with cirrhosis, and blood pressure should be closely monitored in such patients. US licensed product information recommends that the oral dose of nimodipine should be halved to 30 mg every 4 hours in patients with hepatic cirrhosis. Some manufacturers have also suggested a reduction in the initial intravenous dose to 500 micrograms or less per hour.

Cerebrovascular disorders. Nimodipine is used orally and intravenously in the prevention and treatment of ischaemic neurological deficits caused by arterial vasospasm after aneurysmal *subarachnoid haemorrhage* (see Stroke, p. 1269.2), although the evidence for benefit after intravenous use is limited.[1] Intrathecal[2] and intra-arterial[3] administration have also been proposed. Nimodipine has also been used for traumatic subarachnoid haemorrhage,[4] but results have been mixed,[5,6] and UK licensed product information recommends against such use. In addition to dilating cerebral blood vessels and improving cerebral blood flow, nimodipine may also prevent or reverse ischaemic damage to the brain by limiting transcellular calcium influx. These effects have led to the investigation of nimodipine in other conditions associated with *cerebral ischaemia*.[7] Studies[8,9] of nimodipine given orally after ischaemic stroke have produced conflicting results. A meta-analysis[10] of controlled studies suggested that nimodipine is beneficial if given within 12 hours of stroke onset but a further study[11] failed to confirm this. In a controlled study[12] of 155 patients suffering a cardiac arrest, nimodipine was given by intravenous infusion for 24 hours. Nimodipine had no effect on overall survival, although it did improve survival of patients in whom advanced life support was delayed for more than 10 minutes after arrest, suggesting a possible beneficial effect on anoxic-ischaemic brain injury.

Nimodipine has also been tried in *dementia* (p. 388.1). Two multicentre studies[13] involving a total of 755 patients with dementia of vascular or degenerative origin given nimodipine for up to 6 months reported improvements in cognitive function and disability, and a systematic review[14] concluded that nimodipine could be of some benefit in patients with various forms of dementia.

1. Dorhout Mees S, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 12/03/08).
2. Hänggi D, *et al.* Feasibility and safety of intrathecal nimodipine on posthaemorrhagic cerebral vasospasm refractory to medical and endovascular therapy. *Clin Neurol Neurosurg* 2008; **110:** 784–90.
3. Wolf S, *et al.* Continuous selective intraarterial infusion of nimodipine for therapy of refractory cerebral vasospasm. *Neurocrit Care* 2010; **12:** 346–51.
4. Harders A, *et al.* Traumatic subarachnoid hemorrhage and its treatment with nimodipine. *J Neurosurg* 1996; **85:** 82–9.
5. Langham J, *et al.* Calcium channel blockers for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 12/03/08).
6. Vergouwen MDI, *et al.* Effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage: a systematic review. *Lancet Neurol* 2006; **5:** 1029–32.

7. Tomassoni D, *et al.* Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies. *Clin Exp Hypertens* 2008; **30:** 744–66.
8. Gelmers HJ, *et al.* A controlled trial of nimodipine in acute ischemic stroke. *N Engl J Med* 1988; **318:** 203–7.
9. Trust Study Group. Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. *Lancet* 1990; **336:** 1205–9.
10. Mohr JP, *et al.* Meta-analysis of oral nimodipine trials in acute ischemic stroke. *Cerebrovasc Dis* 1994; **4:** 197–203.
11. Horn J, *et al.* Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke* 2001; **32:** 461–5.
12. Roine RO, *et al.* Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial. *JAMA* 1990; **264:** 3171–7.
13. Parnetti L, *et al.* Nimodipine Study Group. Mental deterioration in old age: results of two multicenter, clinical trials with nimodipine. *Clin Ther* 1993; **15:** 394–406.
14. Birks J, López-Arrieta J. Nimodipine for primary degenerative, mixed and vascular dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 12/07/05).

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including nimodipine, in the management of migraine and cluster headache, see under Nifedipine, p. 1449.1.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Nimodipine should be used with caution in patients with cerebral oedema or severely raised intracranial pressure.

Effects on the heart. Marked bradycardia developed in a patient with acute ischaemic stroke during treatment with nimodipine and was suspected to be related to the drug therapy.[1] Severe myocardial depression occurred[2] in another patient given intravenous nimodipine after an aneurysmal subarachnoid haemorrhage. The authors advised dose-reduction or withholding of nimodipine until the myocardium recovered from the acute insult caused by subarachnoid haemorrhage.

1. Fagan SC, Nacci N. Nimodipine and bradycardia in acute stroke—drug or disease? *DICP Ann Pharmacother* 1991; **25:** 247–9.
2. Subramani K, Ghrew M. Severe myocardial depression following intravenous nimodipine for aneurysmal subarachnoid haemorrhage. *Intensive Care Med* 2004; **30:** 1498–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nimodipine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nimodipine is rapidly absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism in the liver. The oral bioavailability is reported to be about 13%. Peak plasma concentrations occur within 1 hour of ingestion. Nimodipine is more than 95% bound to plasma proteins. It crosses the blood-brain barrier, but concentrations in CSF are lower than those in plasma. Nimodipine is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4. It is excreted in faeces via the bile, and in urine, almost entirely as metabolites. The terminal elimination half-life is reported to be about 9 hours but the initial decline in plasma concentration is much more rapid, equivalent to a half-life of 1 to 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: AC Vascular; Acival; Ampina†; Aniduv; Cebrofort; Dunaden; Eugerial; Explaner; Finacilen; Macobal; Nimo-Somazina; Nimodilat; Nimotop; Nivas; Tenocard; ***Austral.***: Nimotop; ***Austria***: Nimotop; ***Belg.***: Nimotop; ***Braz.***: Eugerial; Neuron; Nimobal; Nimopax; Nimotop; Noodipina; Oxigen; Vasodipina; ***Canad.***: Nimotop; ***Chile***: Grifonimod; Nimotop; Regental; ***China***: Bao Yi Tian; Bu Rui Xi (布瑞喜); En Tong (恩通); Erping (尔平); Hai Meng Hui (海盟惠); JiLi (济立); Ni Da Er (尼达尔); Nilisu (尼立苏); Nimotop (尼膜同); Ping Da Er (平达尔); Xing You Fu (星尤复); Yi Fu Lin (易夫林); Yi Fu Zheng (一夫正); You Ni Xin (尤尼欣); Yuan Gan (元甘); Yun Di En (云迪恩), ***Cz.***: Dilceren; Nimotop; ***Denm.***: Nimotop; ***Fin.***: Nimotop; ***Fr.***: Nimotop; ***Ger.***: Nimotop; ***Gr.***: Arfine; Aurodipine; Befimat; Curban; Figozant; Genovox; Myodipine; Naborel; Nelbinex; Nimodil; Nimotop; Nimovac-V; Nortolan; Rosital; Stigmicarpin; Thrionipen; Vastripine; Zieremex; ***Hong Kong***: Nimotop; ***Hung.***: Nimotop; ***India***: Modipin; Nimocard; Nimocer; Nimodec; Nimodip; Nimotide; Vasotop; ***Indon.***: Ceremax; Nimotop; ***Irl.***: Nimotop; ***Israel***: Nimotop; ***Ital.***: Iskidrop; Nimobrain; Nimotop; Periplum; ***Malaysia***: Nimotop; ***Mex.***: Eugerial†; Imolans†; Kenzolol; Nimotop; Vacer; ***Neth.***: Nimotop; ***Norw.***: Nimotop; ***NZ***: Nimotop; ***Philipp.***: Nimotop; ***Pol.***: Nimotop; ***Port.***: Brainox; Genogrist†; Modibloq; Modina; Nimotop; Niton; Sobrepina; Trinalion; ***Rus.***: Nemotan (Немотан)†; Nimopine (Нимопин); Nimotop (Нимотоп); ***S.Afr.***: Nimotop; ***Singapore***: Nimotop; ***Spain***: Admon†; Brainal; Calnit†; Kenesil; Modus; Nimotop; Remontal†; ***Swed.***: Nimotop; ***Switz.***: Nimotop; ***Thai.***: Nimotop; ***Turk.***: Nimotop; ***UK***: Nimotop; ***Ukr.***: Nimodiphexal (НимодипГЕКСАЛ)†; Nimotop (Нимотоп); ***USA***: Nimotop†; Nymalize; ***Venez.***: Nemodine; Nimotop; Tropocer.

Multi-ingredient Preparations. ***Arg.***: Idenimo; Idesole Plus; Nemocebral Plus; Nimodilat Plus; Nimoreagin; Nivas Plus.

Pharmacopoeial Preparations
BP 2014: Nimodipine Infusion; Nimodipine Tablets.

Nisoldipine *(BAN, USAN, rINN)*

Bay-k-5552; Nisoldipiini; Nisoldipin; Nisoldipina; Nisoldipino; Nisoldipinum; Низольдипин.

Isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl) pyridine-3,5-dicarboxylate.

$C_{20}H_{24}N_2O_6$=388.4

CAS — 63675-72-9.

ATC — C08CA07.

ATC Vet — QC08CA07.

UNII — 4I8HAB65SZ.

Uses and Administration

Nisoldipine is a dihydropyridine calcium-channel blocker with actions and uses similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). Nisoldipine is given orally. Both immediate- and modified-release preparations are available, and doses vary between preparations. Immediate-release preparations are typically given in an initial dose of 5 or 10 mg twice daily, increased if necessary at intervals of no less than 1 week to a maximum of 20 mg twice daily. Similar daily doses may be given as modified-release tablets, which are taken once daily. Alternatively, in the USA, modified-release tablets are indicated for hypertension in an initial dose of 17 mg once daily, adjusted according to response by increments of 8.5 mg at intervals of at least 1 week. The usual maintenance dose is 17 to 34 mg once daily. This preparation should be taken on an empty stomach, at least 1 hour before, or 2 hours after a meal.

Lower initial doses and cautious titration are required in the elderly and in hepatic impairment—see below.

Reviews.

1. Mitchell J, *et al.* Nisoldipine: a new dihydropyridine calcium-channel blocker. *J Clin Pharmacol* 1993; **33:** 46–52.
2. Plosker GL, Faulds D. Nisoldipine coat-core: a review of its pharmacology and therapeutic efficacy in hypertension. *Drugs* 1996; **52:** 232–53.
3. Langtry HD, Spencer CM. Nisoldipine coat-core; a review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of ischaemic heart disease. *Drugs* 1997; **53:** 867–84.
4. White WB. Pharmacologic agents in the management of hypertension—nisoldipine coat-core. *J Clin Hypertens (Greenwich)* 2007; **9:** 259–66.

Administration in hepatic impairment. Licensed product information for nisoldipine recommends that immediate-release preparations are given to the elderly and those with hepatic impairment in a reduced initial oral dose of 5 or 10 mg once daily. In the USA, a modified-release preparation may be given in a reduced initial oral dose of 8.5 mg once daily. Doses should be titrated with caution.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nisoldipine is well absorbed from the gastrointestinal tract after oral doses but undergoes rapid and extensive first-pass metabolism in the gut wall and liver and bioavailability has been reported to be only about 4 to 8%. About 60 to 80% of an oral dose is excreted in the urine and the remainder in the faeces, mainly as metabolites. The terminal elimination half-life is about 7 to 12 hours. Nisoldipine is more than 99% bound to plasma proteins.

A study[1] in 11 patients given oral nisoldipine 10 mg once or twice daily indicated that the pharmacokinetics of nisoldipine could best be described by an open 2-compartment model. Peak plasma concentrations occurred 1 hour after a single oral dose, and varied greatly between the patients. The mean plasma elimination half-life was 11.4 hours after a single dose and 14.0 hours after repeated dosing, which was longer than had been previously reported, perhaps reflecting the greater sensitivity of the assay.

In another study oral, but not intravenous, nisoldipine increased liver blood flow in 10 healthy subjects and thus affected its own systemic availability.[2] Variations in liver blood flow may account for the interindividual variation in the pharmacokinetics of nisoldipine.

1. Ottosson A-M, *et al.* Analysis and pharmacokinetics of nisoldipine in hypertensive patients. *Curr Ther Res* 1989; **45:** 347–58.
2. van Harten J, *et al.* Variability in the pharmacokinetics of nisoldipine as caused by differences in liver blood flow response. *J Clin Pharmacol* 1989; **29:** 714–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Syscor; ***Belg.***: Sular; Syscor; ***Braz.***: Syscor; ***Chile***: Nivas†; ***China***: Bo Ping (博平); Di Yi Xin (蒂益欣); Ji Ni Le Er (吉尼乐尔); Ke Di (可谛); Mo Tai; Ni Er Xin (尼尔欣); Ruidi (锐地); Xin Nuo Jin (欣诺金); Xin Xue Ping (欣雪平); Yi Li (易立); You De Ning (优得宁); ***Fin.***: Syscor; ***Ger.***: Baymycard; ***Gr.***: Syscor; ***Hung.***: Baymycard; ***Ital.***: Syscor; ***NZ***: Syscor; ***Spain***: Sular; Syscor; ***Turk.***: Syscor; ***UK***: Syscor†; ***USA***: Sular.

Nitrendipine *(BAN, USAN, rINN)*

Bay-e-5009; Nitrendipiini; Nitrendipin; Nitrendipina; Nitrendipinas; Nitrendipino; Nitrendipinum; Нитрендипин.

Ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

$C_{18}H_{20}N_2O_6$=360.4

CAS — 39562-70-4.

ATC — C08CA08.

ATC Vet — QC08CA08.

UNII — 9B627AW319.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Nitrendipine). A yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

Uses and Administration

Nitrendipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is given orally in the treatment of hypertension (p. 1251.1).

The usual dose is 20 mg daily as a single dose or as 2 divided doses. The dose may be increased to 20 mg twice daily if necessary for the control of resistant hypertension. In the elderly, an initial dose of 10 mg daily should be used. The dose should also be reduced in hepatic impairment (see below).

Reviews.

1. Santiago TM, Lopez LM. Nitrendipine: a new dihydropyridine calcium-channel antagonist for the treatment of hypertension. *DICP Ann Pharmacother* 1990; **24:** 167–75.

Administration in hepatic impairment. The initial oral dose of nitrendipine should be reduced to 5 to 10 mg once daily in patients with hepatic impairment.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nitrendipine is reported to be well absorbed after oral doses but undergoes extensive first-pass metabolism; the absolute oral bioavailability is reported to range from about 10 to 30%, depending in part on the dosage form. Peak plasma concentrations occur within 1 to 3 hours. Nitrendipine is about 98% bound to plasma proteins. It is extensively metabolised in the liver and is excreted as inactive metabolites in the urine and faeces, with less than 0.1% as unchanged drug. Although early studies reported a terminal elimination half-life of about 2 to 4 hours, later studies, using more sensitive assay procedures, have recorded values between about 10 and 22 hours. The half-life is prolonged in patients with hepatic impairment.

References.
1. Soons PA, Breimer DD. Stereoselective pharmacokinetics of oral and intravenous nitrendipine in healthy male subjects. *Br J Clin Pharmacol* 1991; **32:** 11–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nirapel; Nitrendil; ***Austria***: Baypress; ***Belg.***: Baypress; ***Braz.***: Caltren; Nitrencord; ***Chile***: Cardiazem; Grifonitren; Tensofar†; ***China***: Shu Mai Te (舒麦特); ***Cz.***: Baypress; Lusopress; Nitrepress; Nitresan; Unipres; ***Denm.***: Baypress; ***Fr.***: Baypress; Nidrel; ***Ger.***: Bayotensin; Jutapress†; Nitre-Puren†; Nitregamma; Nitren Lich; Nitrendidoc†; Nitrensal; Nitrepress†; ***Gr.***: Arianit; Aroselin; Baypress; Crivion; G-Press; Issopres; Lanocardique; Leonitren; Lisba; Lostradyl; Midonat; Nelconil; Nifecard; Nitrendilat; Nivitron; Pallohyman; Potional; Pressodipin; Spidox; Tepanil; Thrififin; Ufocard; Zulexen; ***Hong Kong***: Baypress†; ***Hung.***: Baypress; Unipres; ***India***: Nitrepin; ***Ital.***: Baypress; ***Jpn***: Baylotensin; ***Neth.***: Baypress; ***Port.***: Farnitran†; Hiperdipina; ***Spain***: Baypresol; Gericin; Nipriná†; Sub Tensin; Sub-Tensin; Tensogradal; Vastensium†; ***Switz.***: Baypress; ***Thai.***: Baypress; Ditrenil; Miniten; ***Turk.***: Baypress; ***Venez.***: Baypress; Nitrendil.

Multi-ingredient Preparations. ***Austria***: Cenipres; ***Ger.***: Eneas; ***Gr.***: Eneas; Enit; ***India***: Cardif Beta†; ***Port.***: Eneas; Enit; ***Spain***: Eneas; Enit; Vipres; ***Turk.***: Eneas; Enit; ***Ukr.***: Eneas (Энеас).

Nitric Oxide *(USAN)*

Azote, monoxyde d'; Azoto oksidas; Azotu(II) tlenek; Kväveoxid; Mononitrogen Monoxide; Monóxido de nitrógeno; Nitrogen Monoxide; Nitrogenii Oxidum; Nitrogénmonoxid; OHM-11771; Oxid dusnatý; Óxido nítrico; Stickstoffmonoxid; Typpioksidi; Оксид Азота.

NO=30.01

CAS — 10102-43-9.

ATC — R07AX01.

ATC Vet — QR07AX01.

UNII — 31C4KY9ESH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nitric Oxide). A colourless gas that turns brown when exposed to air. At 20 degrees and at a pressure of 101 kPa, 1 volume dissolves in about 21 volumes of water. Store compressed at a pressure not exceeding 2.5 MPa measured at 15 degrees in suitable containers.

Uses and Administration

Nitric oxide is an endogenous chemical messenger that acts mainly by stimulating guanylate cyclase in smooth muscle to cause vasodilatation. It is also involved in platelet aggregation, neurotransmission, and the immune system, and possesses antimicrobial, antitumour, and antiviral activity.

Endogenous nitric oxide is now recognised to be the same substance as endothelium-derived relaxing factor (EDRF). It is synthesised from L-arginine by the enzyme, nitric oxide synthase, of which three isoforms have been identified. Constitutive isoforms occur in endothelial cells (such as in vascular endothelium, platelets, and the heart) and neuronal cells (in some central and peripheral neurones). Small amounts of nitric oxide are regularly produced by these systems. In contrast, an inducible isoform producing larger amounts of nitric oxide is expressed only after activation by external stimuli such as infection or inflammation. This inducible nitric oxide synthase may be expressed in many cells, including macrophages and cells in vascular smooth muscle, the heart, gastrointestinal tract, and liver.

Inhaled nitric oxide is a highly selective pulmonary vasodilator. It is used in the management of term and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. It is also used as a diagnostic tool to test acute vasoreactivity in patients with pulmonary hypertension of various aetiologies, and is being studied in other bronchopulmonary disorders and in different age groups.

In the management of hypoxic respiratory failure in neonates, nitric oxide is given by inhalation in a usual concentration of 20 ppm. Doses have been titrated above and below this concentration but due to the risk of methaemoglobinaemia, doses above 20 ppm are not generally recommended. The concentration should be reduced gradually before stopping treatment.

General reviews.
1. Hart CM. Nitric oxide in adult lung disease. *Chest* 1999; **115:** 1407–17.
2. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. *Heart* 2001; **85:** 342–50.
3. Ichinose F, *et al*. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation* 2004; **109:** 3106–11.
4. Griffiths MJD, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; **353:** 2683–95.
5. Creagh-Brown BC, *et al*. Bench-to-bedside review: inhaled nitric oxide therapy in adults. *Crit Care* 2009; **13:** 221. Available at: http://ccforum.com/content/pdf/cc7734.pdf (accessed 10/03/10)

Respiratory disorders. Inhaled nitric oxide is a potent and highly selective pulmonary vasodilator used in the management of persistent pulmonary hypertension of the newborn (below) and other conditions leading to hypoxic respiratory failure in neonates.

Nitric oxide has also been tried in acute respiratory distress syndrome (below), severe acute respiratory syndrome,[1] respiratory failure,[2] acute severe asthma,[3] pulmonary arterial hypertension[4,5] including that in pregnancy,[6,7] and in pulmonary hypertension associated with a wide range of conditions including chronic obstructive pulmonary disease,[8] heart failure,[9] post-cardiac surgery,[10-13] heart or lung transplantation,[14-16] and high-altitude disorders.[17]

1. Chen L, *et al*. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004; **39:** 1531–5.
2. Dobyns EL, *et al*. Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 1999; **134:** 406–12.
3. Nakagawa TA, *et al*. Life-threatening status asthmaticus treated with inhaled nitric oxide. *J Pediatr* 2000; **137:** 119–22.
4. Kinsella JP, *et al*. Selective and sustained pulmonary vasodilation with inhalational nitric oxide therapy in a child with idiopathic pulmonary hypertension. *J Pediatr* 1993; **122:** 803–6.
5. Goldman AP, *et al*. Is it time to consider domiciliary nitric oxide? *Lancet* 1995; **345:** 199–200.
6. Lam GK, *et al*. Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. *Obstet Gynecol* 2001; **98:** 895–8.
7. Decoene C, *et al*. Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. *Can J Anaesth* 2001; **48:** 584–7.
8. Vonbank K, *et al*. Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 2003; **58:** 289–93.
9. Matsumoto A, *et al*. Inhaled nitric oxide and exercise capacity in congestive heart failure. *Lancet* 1997; **349:** 999–1000. Correction. *ibid.*; **350:** 818.
10. Haydar A, *et al*. Inhaled nitric oxide for postoperative pulmonary hypertension in patients with congenital heart defects. *Lancet* 1992; **340:** 1545.
11. Miller OI, *et al*. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet* 2000; **356:** 1464–9.
12. Journois D, *et al*. Effects of inhaled nitric oxide administration on early postoperative mortality in patients operated for correction of atrioventricular canal defects. *Chest* 2005; **128:** 3537–44.
13. Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/10/09).
14. Rea RS, *et al*. Role of inhaled nitric oxide in adult heart or lung transplant recipients. *Ann Pharmacother* 2005; **39:** 913–17.
15. Botha P, *et al*. Inhaled nitric oxide for modulation of ischemia-reperfusion injury in lung transplantation. *J Heart Lung Transplant* 2007; **26:** 1199–1205.
16. Yerebakan C, *et al*. Effects of inhaled nitric oxide following lung transplantation. *J Card Surg* 2009; **24:** 269–74.
17. Scherrer U, *et al*. Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996; **334:** 624–9.

ACUTE RESPIRATORY DISTRESS SYNDROME. Although inhalation of nitric oxide has been reported to improve oxygenation in patients with acute respiratory distress syndrome (p. 1599.3), meta-analyses[1,2] have failed to confirm any significant mortality benefit, and there is some evidence[2] that nitric oxide increases the risk of renal dysfunction.

1. Afshari A, *et al*. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2010 (accessed 02/08/10).
2. Adhikari NKJ, *et al*. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. Abridged version: *BMJ* 2007; **334:** 779–82. Full version: http://www.bmj.com/cgi/reprint/334/7597/779 (accessed 31/07/08)

RESPIRATORY DISORDERS IN NEONATES. Inhaled nitric oxide is used in the management of hypoxic respiratory failure in term and near-term neonates.[1-3] It has also been studied in premature neonates.[4,5]

Most studies have been in neonates with persistent pulmonary hypertension of the newborn (p. 1278.2), although varying definitions have been used. A systematic review[6] of controlled studies in term and near-term neonates with hypoxic respiratory failure found that oxygenation was improved with inhaled nitric oxide, with a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been shown. A randomised study[7] also found no mortality benefit when nitric oxide was started early in the disease process, although progression was slowed. Neonates with congenital diaphragmatic hernia (CDH), however, have not been shown to benefit,[8,9] and nitric oxide is not recommended in such patients,[6] although the optimal treatment of this condition is controversial; one study[10] suggested that inhaled nitric oxide may have a role in patients with CDH who develop late pulmonary hypertension. Another study[11] suggested that the improvement in oxygenation may not be sustained, and that neonates with pulmonary hypoplasia and dysplasia are less sensitive to nitric oxide.

The dose of nitric oxide found to be effective in most studies has been from 20 to 80 ppm. However, since nitric oxide is associated with dose-related toxicity, lower doses (1 to 2 ppm) have also been studied. One study[12] found no significant difference between high and low doses, but another study[13] found that low doses did not improve oxygenation and diminished the response to subsequent higher doses.

Inhaled nitric oxide has also been reported to improve oxygenation in premature neonates with hypoxic respiratory failure, but its use is not yet established.[14,15] A study[16] in premature infants with respiratory distress syndrome suggested that the incidence of chronic lung disease and death was reduced by nitric oxide, and an open study[17] in very premature infants who had already developed chronic lung disease also found an improvement in oxygenation with nitric oxide therapy. However, a systematic review[18] found that use of rescue nitric oxide therapy in severely ill infants was ineffective, and that late use to prevent chronic lung disease also had no effect. There was some evidence that early routine use in mildly sick infants might improve outcomes, but further studies were needed to identify those infants who were most likely to benefit.

There have been concerns that use of inhaled nitric oxide might adversely affect neurodevelopmental outcome more than conventional therapy particularly in premature infants, but follow-up studies have reported mixed results. Studies in term and near-term infants,[19-21] and in premature infants,[22] have found that use of nitric oxide has no effect on neurodevelopment, but there have also been reports of poor neurodevelopmental outcome[23] and of improved outcome,[24,25] and a review[26] of studies in preterm infants followed up after 4 to 5 years suggested that inhaled nitric oxide may confer neurodevelopmental protection; however, differences in study design make comparisons between studies difficult, and the effect on neurodevelopment remains to be confirmed.

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3. Soll RF. Inhaled nitric oxide in the neonate. *J Perinatol* 2009; **29** (suppl 2): S63–S67.
4. Miller SS, Rhine WD. Inhaled nitric oxide in the treatment of preterm infants. *Early Hum Dev* 2008; **84:** 703–7.
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8. Clark RH, *et al*. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med* 2000; **342:** 469–74.
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15. Kinsella JP, Abman SH. Inhaled nitric oxide in the premature newborn. *J Pediatr* 2007; **151:** 10–15.
16. Schreiber MD, *et al*. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med* 2003; **349:** 2099–2107.
17. Clark PL, *et al*. Safety and efficacy of nitric oxide in chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2002; **86:** F41–F45.
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19. Rosenberg AA, *et al*. Longitudinal follow-up of a cohort of newborn infants treated with inhaled nitric oxide for persistent pulmonary hypertension. *J Pediatr* 1997; **131:** 70–5.
20. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the Neonatal Inhaled Nitric Oxide Study Group (NINOS). *J Pediatr* 2000; **136:** 611–17.
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22. Hintz SR, *et al*. NICHD Neonatal Research Network. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. *J Pediatr* 2007; **151:** 16–22.
23. Cheung P-Y, *et al*. The outcome of very low birth weight neonates (≤1500g) rescued by inhaled nitric oxide: neurodevelopment in early childhood. *J Pediatr* 1998; **133:** 735–9.
24. Mestan KKL, *et al*. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med* 2005; **353:** 23–32.
25. Tanaka Y, *et al*. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; **119:** 1159–64.
26. Marks JD, Schreiber MD. Inhaled nitric oxide and neuroprotection in preterm infants. *Clin Perinatol* 2008; **35:** 793–807.

Sickle-cell disease. Sickle-cell crisis due to vaso-occlusion is an acute complication of sickle-cell disease (p. 1123.2), requiring hospitalisation, with the use of large volumes of intravenous fluids for dehydration, and analgesia including opioids for pain. Concentrations of nitric oxide metab-

olites and L-arginine have been found to be low in vaso-occlusive crisis and a study[1] in paediatric patients showed that inhaled nitric oxide may be of benefit.

1. Weiner DL, *et al.* Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* 2003; **289:** 1136–42.

Adverse Effects

Inhaled nitric oxide may lead to the development of methaemoglobinaemia, particularly at higher doses. Although it is a selective pulmonary vasodilator, systemic hypotension may occur. Abrupt withdrawal of therapy may lead to a deterioration in oxygenation and the development of rebound pulmonary hypertension.

Nitrogen dioxide produced when nitric oxide combines with oxygen can cause acute lung injury; high concentrations of inhaled nitric oxide are directly irritant to the lungs.

A potential complication of inhaled nitric oxide is methaemoglobinaemia but this is probably related to the dose; the risk does not appear to be increased during low-dose (20 ppm) therapy.[1] Another possible adverse event is an increased risk of bleeding due to inhibition of platelet aggregation.[2-5] Rebound pulmonary hypertension[6] and deterioration in oxygenation[7,8] have been reported in some children after stopping nitric oxide therapy. Severe systemic hypotension has also been reported[9] after starting therapy in a neonate with severe left ventricular dysfunction. Pulmonary oedema has been associated with the use of nitric oxide in 2 patients with CREST syndrome, a form of systemic sclerosis.[10] Motor neurone disease in a patient with alcoholism has been partly attributed[11] to the use of nitric oxide for pulmonary hypertension.

1. Kinsella JP, Abman SH. Methaemoglobin during nitric oxide therapy with high-frequency ventilation. *Lancet* 1993; **342:** 615.
2. Högman M, *et al.* Bleeding time prolongation and NO inhalation. *Lancet* 1993; **341:** 1664–5.
3. Joannidis M, *et al.* Inhaled nitric oxide. *Lancet* 1996; **348:** 1448–9.
4. Cheung P-Y, *et al.* Inhaled nitric oxide and inhibition of platelet aggregation in critically ill neonates. *Lancet* 1998; **351:** 1181–2.
5. George TN, *et al.* The effect of inhaled nitric oxide therapy on bleeding time and platelet aggregation in neonates. *J Pediatr* 1998; **132:** 731–4.
6. Miller OI, *et al.* Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide. *Lancet* 1995; **346:** 51–2.
7. Aly H, *et al.* Weaning strategy with inhaled nitric oxide treatment in persistent pulmonary hypertension of the newborn. *Arch Dis Child Fetal Neonatal Ed* 1997; **76:** F118–F122.
8. Davidson D, *et al.* Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn. *Pediatrics* 1999; **104:** 231–6.
9. Henrichsen T, *et al.* Inhaled nitric oxide can cause severe systemic hypotension. *J Pediatr* 1996; **129:** 183.
10. Preston IR, *et al.* Pulmonary edema caused by inhaled nitric oxide therapy in two patients with pulmonary hypertension associated with the CREST syndrome. *Chest* 2002; **121:** 656–9.
11. Tsai GE, Gastfriend DR. Nitric oxide-induced motor neuron disease in a patient with alcoholism. *N Engl J Med* 1995; **332:** 1036.

Precautions

Patients given inhaled nitric oxide should be monitored for methaemoglobinaemia and oxygenation. Inhaled nitric oxide and nitrogen dioxide levels should also be monitored. Treatment should not be stopped abruptly since rebound pulmonary hypertension and deterioration in oxygenation may occur. Caution is required in patients with pre-existing left ventricular dysfunction, as symptoms of heart failure, including pulmonary oedema, may occur.

The exposure of workers to nitric oxide and nitrogen dioxide should be limited.

References.

1. CSM/MCA. Inhaled nitric oxide. *Current Problems* 1996; **22:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 02/06/08)
2. Cuthbertson BH, *et al.* Use of inhaled nitric oxide in British intensive therapy units. *Br J Anaesth* 1997; **78:** 696–700.
3. Phillips ML, *et al.* Assessment of medical personnel exposure to nitrogen oxides during inhaled nitric oxide treatment of neonatal and pediatric patients. *Pediatrics* 1999; **104:** 1095–1100.

Pharmacokinetics

Nitric oxide is absorbed systemically after inhalation but is rapidly inactivated by reaction with haemoglobin to form methaemoglobin and nitrate; it has a half-life of only a few seconds. It is excreted mainly in the urine as nitrate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Noxap; VasoKINOX; ***Canad.***: INOmax; ***Cz.***: INOmax; Noxap; ***Denm.***: INOmax; ***Fin.***: Pulmonox; ***Fr.***: INOmax; Noxap; ***Ger.***: INOmax; ***Gr.***: INOmax; ***Irl.***: INOmax; ***Ital.***: INOmax; ***Neth.***: INOmax; Neophyr; Noxap; ***Pol.***: INOmax; ***Port.***: INOmax; ***Spain***: INOmax; Noxap; VasoKINOX; ***Swed.***: INOmax; ***Switz.***: INOmax; ***USA***: INOmax.

Noradrenaline (BAN) ⊗

Levarterenol; Noradrenaliini; Noradrenalin; Noradrenalina; Noradrenalinum; Norepinefriini; Norepinefrin; Norepinefrina; Norepinephrine (BAN); Norepinephrine (rINN); Norépinéphrine; Norepinephrinum; Norepirenamine; Норэпинефрин.

(*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol.

$C_8H_{11}NO_3$=169.2

CAS — 51-41-2.

ATC — C01CA03.

ATC Vet — QC01CA03.

UNII — X4W3ENH1CV.

Pharmacopoeias. *Jpn* includes the racemic form.

Noradrenaline Acid Tartrate (BANM) ⊗

Arterenol Acid Tartrate; *l*-Arterenol Bitartrate; Bitartrato de noradrenalina; Bitartrato de norepinefrina; Levarterenol Acid Tartrate; Levarterenol Bitartrate; Levarterenoli Bitartras; Noradrenaliinitartraatti; Noradrenaline Bitartrate; Noradrenaline Tartrate; Noradrénaline, tartrate de; Noradrenalini tartras; Noradrenalino tartratas; Noradrenalintartarát; Noradrenalintartrat; Norepinefrin tartarát monohydrát; Norepinefrina, bitartrato de; Norepinefryny wodorowinian; Norepinephrine Acid Tartrate (BANM); *l*-Norepinephrine Bitartrate; Norepinephrine Bitartrate (rINNM); Norepinephrine Bitartrate (USAN); Norépinéphrine, Bitartrate de; Norepinephrini Bitartras; Norepinephrini Tartras Monohydricus; Norepinephrintartrat/Noradrenalintartrat; Tartrato ácido de norepinefrina; Норэпинефрина Битартрат.

$C_8H_{11}NO_3,C_4H_6O_6,H_2O$=337.3

CAS — 51-40-1 (anhydrous noradrenaline acid tartrate); 69815-49-2 (noradrenaline acid tartrate monohydrate).

ATC — C01CA03.

ATC Vet — QC01CA03.

UNII — ZW81GF408B (anhydrous noradrenaline acid tartrate); IFY5PE3ZRW (noradrenaline acid tartrate monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Noradrenaline Tartrate; Noradrenaline Acid Tartrate BP 2014; Norepinephrine Acid Tartrate BP 2014). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

USP 36: (Norepinephrine Bitartrate). A white or faintly grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 2.5 of water and 1 in 300 of alcohol; practically insoluble in chloroform and in ether. Its solutions in water have a pH of about 3.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Noradrenaline acid tartrate is strongly acidic in solution, and would be expected to be incompatible with drugs having an alkaline pH. Licensed product information in the UK states that solutions are reportedly incompatible with alkalis and oxidising agents, barbiturates, chlorphenamine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, and streptomycin. Incompatibility with insulin has also been reported.[1]

1. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.

Noradrenaline Hydrochloride (BANM) ⊗

Hidrocloruro de noradrenalina; Hidrocloruro de norepinefrina; Noradrenaliinihydrokloridi; Noradrénaline, chlorhydrate de; Noradrenalin-hidroklorid; Noradrenalinhydroklorid; Noradrenalini hydrochloridum; Noradrenalino hidrochloridas; Norepinefrin hydrochlorid; Norepinefrina, hidrocloruro de; Norépinéphrine, Chlorhydrate de; Norepinephrine Hydrochloride (rINNM); Norepinephrine Hydrochloride (BANM); Norepinephrinhydrochlorid/Noradrenalinhydrochlorid; Norepinephrini Hydrochloridum; Норэпинефрина Гидрохлорид.

$C_8H_{11}NO_3$,HCl=205.6

CAS — 329-56-6.

ATC — C01CA03.

ATC Vet — QC01CA03.

UNII — 4W6461XR05.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Noradrenaline Hydrochloride; Norepinephrine Hydrochloride BP 2014). A white or brownish-white, crystalline powder. It becomes coloured on exposure to air and light. Very soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.5 to 4.5. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

Uses and Administration

Noradrenaline is a direct-acting catecholamine sympathomimetic (p. 1507.3) with pronounced effects on alpha-adrenergic receptors; it also stimulates $beta_1$ receptors but has little effect on $beta_2$ receptors. It is the major neurotransmitter in postganglionic adrenergic neurones, and is stored in granules in the nerve axons. Some is also present in the adrenal medulla and is released with adrenaline.

The major effects of noradrenaline relate to its alpha-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. Beta-stimulant effects of noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the CNS.

Noradrenaline is used for the emergency restoration of blood pressure in acute hypotensive states such as shock (p. 1279.3). It has also been used in the management of cardiac arrest. Noradrenaline has been used in local anaesthesia to diminish the absorption and localise the effect of the local anaesthetic (see Uses and Administration, p. 1980.1) but adrenaline is now preferred (see also Dental Use under Adverse Effects, below). Locally applied solutions have been used to control bleeding in upper gastrointestinal haemorrhage and similar disorders.

In **acute hypotensive states**, noradrenaline is used as the acid tartrate, or occasionally as the hydrochloride, but doses are expressed in terms of the base; noradrenaline acid tartrate 2 micrograms or noradrenaline hydrochloride 1.2 micrograms are equivalent to about 1 microgram of noradrenaline. It is given by intravenous infusion of a solution containing the equivalent of 4 micrograms of the base per mL in glucose 5%, or sodium chloride 0.9% and glucose 5%. To avoid tissue necrosis the infusion should be given through a central venous catheter or into a large vein high up in a limb, preferably the arm. Some sources have suggested that addition of phentolamine 5 to 10 mg/litre to the infusion may prevent dermal necrosis without affecting the vasopressor action. The infusion is usually given initially at a rate of 2 to 3 mL/minute (8 to 12 micrograms/minute) and adjusted according to the blood pressure response. Blood pressure is initially recorded every 2 minutes and the rate of infusion continuously monitored. The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure. The average maintenance dose is 0.5 to 1 mL/minute (2 to 4 micrograms/minute), but there is a wide variation and higher doses may be required. The concentration of the infusion may be altered according to clinical needs. Alternatively a solution containing the equivalent of 40 micrograms of the base per mL may be given at an initial rate of 0.16 to 0.33 mL/minute via a central venous catheter, using a syringe pump or drip counter.

For doses in children, see below.

Administration in children. In the treatment of acute hypotension, the *BNFC* suggests that neonates, infants, and children may be given noradrenaline by intravenous infusion at a dose (expressed in terms of the base) of 20 to 100 nanograms/kg per minute, adjusted according to response to a maximum of 1 microgram/kg per minute.

Adverse Effects

As for Sympathomimetics, p. 1508.2. Noradrenaline is an extremely potent peripheral vasoconstrictor and its adverse effects include hypertension (possibly associated with reflex bradycardia), headache, and peripheral ischaemia, which may be severe enough to result in gangrene of the extremities. Extravasation may lead to severe phlebitis and sloughing.

Dental use. Severe headache,[1,2] including fatal cerebral haemorrhage,[1,3] has been reported after the use of lidocaine with noradrenaline 1 in 25 000 for dental anaesthesia. It was suggested[1-3] that preparations containing noradrenaline 1 in 25 000 should not be used, and that a concentration of 1 in 80 000 was to be preferred. However, in the UK the *Dental Practitioners' Formulary*[4] (issued in 2002) stated that noradrenaline should not be used as a vasoconstrictor in local anaesthetic solutions since it presented no advantage over adrenaline and carried additional hazard.

1. Boakes AJ, *et al.* Adverse reactions to local anaesthetic/vasoconstrictor preparations: a study of the cardiovascular responses to Xylestesin and Hostacain-with-Noradrenaline. *Br Dent J* 1972; **133:** 137–40.
2. van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anesthesia. *Anesth Prog* 1992; **39:** 87–9.

3. Okada Y, *et al*. Fatal subarachnoid haemorrhage associated with dental local anaesthesia. *Aust Dent J* 1989; **34:** 323–5.
4. *Dental Practitioners' Formulary*. 2002–2004. London: British Dental Association, British Medical Association, and the Royal Pharmaceutical Society of Great Britain; 2002. D6.

Treatment of Adverse Effects

As for Sympathomimetics, p. 1508.3. If extravasation occurs, infiltration with phentolamine (see p. 1469.1) as soon as possible, and certainly within 12 hours, may relieve pain and prevent tissue necrosis.

Precautions

As for Sympathomimetics, p. 1508.3. Noradrenaline has mainly alpha-agonist properties and must be avoided in the presence of hypertension; blood pressure and infusion rate must be monitored frequently. Noradrenaline-induced cardiac arrhythmias are more likely in patients with hypoxia or hypercapnia.

Noradrenaline is a severe tissue irritant and only very dilute solutions should be used. It should be infused centrally or into a large vein if possible, and care should be taken to avoid extravasation.

Noradrenaline may reduce placental perfusion throughout pregnancy and some consider that it and similar vasoconstrictor sympathomimetics are best avoided; also in late pregnancy noradrenaline provokes uterine contractions which can result in fetal asphyxia.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies noradrenaline as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Severe hypertension may occur if noradrenaline is given to patients taking tricyclic antidepressants since tricyclics block the uptake of noradrenaline into nerve endings.

Pharmacokinetics

Like adrenaline (p. 1295.1), noradrenaline is inactive when given orally, and it is rapidly inactivated in the body by similar processes. When given intravenously it is extensively metabolised and only small amounts are excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fioritina; ***Austral.***: Levophed; ***Belg.***: Levophed; Norepine; ***Braz.***: Levophed; ***Canad.***: Levophed; ***Chile***: Adine; ***Ger.***: Arterenol; ***Gr.***: Levophed†; Noradren; ***Hong Kong***: Levophed; ***India***: Adrenor; Adronis; Epinor; Nodresol; Nor-S; Norad; Noradria; Noralin; Norepirin; ***Indon.***: Levophed; N-Epi; Raivas; Vascon; ***Irl.***: Levophed†; ***Israel***: Levophed; ***Malaysia***: Cardiamed; Levophed; ***Mex.***: Pridam; ***NZ***: Levophed; ***Philipp.***: Inotrop; Levofin; Levophed; Norepin; Norphed; ***Pol.***: Levonor; ***Singapore***: Levophed: ***Spain***: Norages; ***Thai.***: Levophed; N-Epi; Norpin; ***USA***: Levophed.

Used as an adjunct in:. ***Austria***: Scandonest; ***Braz.***: Xylestesin; Xylocaina; ***Fr.***: Biodicaine†; Pressicaine N†; Scandicaine; Xylonor; Ziacaine; ***Gr.***: Lidocosil; Narcodon; Neo-Lidocaton; Scandonest; Xylestesin-S Special; Xylestesin; Xylonor Noradrenaline; ***Israel***: Xylonor Noradrenaline; ***Ital.***: Lident Adrenor; Xylonor; ***Port.***: Scandonest; Xilonibsa; ***S.Afr.***: Xylotox; ***Spain***: Xylonor Especial; ***Switz.***: Scandonest.

Pharmacopoeial Preparations
BP 2014: Noradrenaline Injection;
USP 36: Norepinephrine Bitartrate Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Norfenefrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de norfenefrina; Norfenefrin Hidroklorür; Norfenefrina, hidrocloruro de; Norfénéfrine, Chlorhydrate de; Norfenefrini Hydrochloridum; Norphenylephrine Hydrochloride; *m*-Norsynephrine Hydrochloride; WV-569; Норфенефрина Гидрохлорид.

2-Amino-1-(3-hydroxyphenyl)ethanol hydrochloride.

$C_8H_{11}NO_2$,HCl=189.6

CAS — 536-21-0 (norfenefrine); 15308-34-6 (norfenefrine hydrochloride).

ATC — C01CA05.

ATC Vet — QC01CA05.

UNII — 1FCN9TAU6R.

NOTE. *m*-Octopamine has been used as a synonym for norfenefrine. Care should be taken to avoid confusion with octopamine, which is the *p*-isomer.

Profile

Norfenefrine is a sympathomimetic (p. 1507.3) with mainly alpha-adrenergic activity. It has been used as the hydrochloride for its vasopressor effect in the treatment of hypotensive states (p. 1277.2) in a usual oral dose of 15 mg three times daily of norfenefrine hydrochloride. Norfenefrine hydrochloride has also been given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Novadral†; ***Mex.***: AS Cor; ***Switz.***: Novadral†; ***Turk.***: Novadral.

Multi-ingredient Preparations. ***Switz.***: Ortho-Maren retard†.

Olmesartan Medoxomil

(BAN, USAN, rINN)

CS-866; Olmésartan Médoxomil; Olmesartán medoxomilo; Olmesartanum Medoxomilum; RNH-6270 (olmesartan); Ольмезартан Медоксомил.

(5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl ester of 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-{[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl}-1*H*-imidazole-5-carboxylic acid.

$C_{29}H_{30}N_6O_6$=558.6

CAS — 144689-24-7 (olmesartan); 144689-63-4 (olmesartan medoxomil).

ATC — C09CA08.

ATC Vet — QC09CA08.

UNII — 6M97XTV3HD.

NOTE. The name olmesartan has been applied to both the base and to the medoxomil ester.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Olmesartan Medoxomil). A white or almost white, crystalline powder. Practically insoluble in water and in heptane; slightly soluble in alcohol.

USP 36: (Olmesartan Medoxomil). A white to off-white crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol. Store at a temperature below 25 degrees. Protect from moisture.

Uses and Administration

Olmesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1).

Olmesartan is given orally as the ester prodrug olmesartan medoxomil. After a dose the hypotensive effect lasts for 24 hours. Most of the hypotensive effect is apparent within 2 weeks after starting therapy and is maximal within about 8 weeks.

In hypertension, olmesartan medoxomil is given in a usual dose of 20 mg once daily, although in the UK an initial dose of 10 mg once daily is recommended. The dose may be increased to 40 mg once daily if required.

For doses in children, see below.

For doses in hepatic or renal impairment, see below.

References.
1. Mire DE, *et al*. A review of the structural and functional features of olmesartan medoxomil, an angiotensin receptor blocker. *J Cardiovasc Pharmacol* 2005; **46:** 585–93.
2. Takai S, Miyazaki M. Effect of olmesartan medoxomil on atherosclerosis: clinical implications of the emerging evidence. *Am J Cardiovasc Drugs* 2006; **6:** 363–6.
3. Smith DH. Dose-response characteristics of olmesartan medoxomil and other angiotensin receptor antagonists. *Am J Cardiovasc Drugs* 2007; **7:** 347–56.
4. Zannad F, Fay R. Blood pressure-lowering efficacy of olmesartan relative to other angiotensin II receptor antagonists: an overview of randomized controlled studies. *Fundam Clin Pharmacol* 2007; **21:** 181–90.
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10. Barrios V, Escobar C. Beating the clock: reducing cardiovascular risk by rapid blood pressure reduction with olmesartan. *Expert Opin Pharmacother* 2010; **11:** 1549–58.

Administration in children. In the USA, children aged from 6 to 16 years of age may be given olmesartan medoxomil for **hypertension** in recommended initial oral doses of 10 mg once daily in those weighing under 35 kg, or 20 mg once daily in those weighing 35 kg and over. Doses may be doubled once if necessary after 2 weeks. For those who cannot swallow tablets, US licensed product information (*Benicar, Daiichi Sankyo*) provides instructions for making an extemporaneous liquid preparation.

Administration in hepatic or renal impairment. Olmesartan is excreted in both urine and bile and raised plasma concentrations have been noted in patients with renal or hepatic impairment.

- In patients with *renal impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment (creatinine clearance (CC) below 20 mL/minute) since experience is limited, and the maximum dose in mild to moderate impairment (CC 20 to 60 mL/minute) is 20 mg once daily.
- Similarly, in patients with *hepatic impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment since there is no experience. Those with moderate hepatic impairment should be given an initial dose of 10 mg once daily and the maximum dose is 20 mg once daily.

Migraine. For reference to the use of angiotensin II receptor antagonists, including olmesartan, in the prophylaxis of migraine, see under Losartan, p. 1423.3.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Olmesartan medoxomil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form olmesartan. The absolute bioavailability is about 26%. Peak plasma concentrations of olmesartan occur about 1 to 2 hours after oral doses. Olmesartan is at least 99% bound to plasma proteins. It is excreted in the urine and the bile as olmesartan; about 35 to 50% of the absorbed dose is excreted in the urine and the remainder in the bile. The terminal elimination half-life is between 10 and 15 hours.

References.
1. Yoshihara K, *et al*. Population pharmacokinetics of olmesartan following oral administration of its prodrug, olmesartan medoxomil: in healthy volunteers and hypertensive patients. *Clin Pharmacokinet* 2005; **44:** 1329–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Olmec; Olmetec; Tensonit; ***Austral.***: Olmetec; ***Austria***: Mencord; Olmetec; ***Belg.***: Belsar; Olmetec; ***Braz.***: Benicar; Olmetec; ***Canad.***: Olmetec; ***Chile***: Cardioplus; Olmetec; ***China***: Lan Sha (兰沙); Olmetec (傲坦); ***Cz.***: Olmetec; Sarten; ***Denm.***: Benetor; Olkingo; Olkreso; Olmetec; ***Fin.***: Benetor; Olmetec; ***Fr.***: Alteis; Olmetec; ***Ger.***: Olmetec; Votum; ***Gr.***: Olartan; Olmetec; ***Hong Kong***: Olmetec; ***India***: Olmat; Olmax; Olmecip; Olmefast; Olmesar; Olmetor; Olmezest; Olmighty; Olmy; Olsar; Oukat; ***Indon.***: Olmetec; ***Irl.***: Benetor; Omesar; ***Israel***: Olmetec†; ***Ital.***: Olmetec; Olpress; Plaunac; ***Jpn***: Olmetec; ***Malaysia***: Olmetec; ***Mex.***: Almetec; ***Neth.***: Olmetec; ***Norw.***: Olmetec; ***Philipp.***: Alzor; Olmetec; Olmezar; ***Pol.***: Olimestra; ***Port.***: Olmetec; Olsar; ***Rus.***: Cardosal (Кардосал); ***Singapore***: Olmetec; ***Spain***: Ixia; Olmetec; Openvas; ***Switz.***: Olmetec; Votum; ***Thai.***: Olmetec; ***Turk.***: Hipersar; Olmetec; Olmysar; Terminate; ***UK***: Olmetec; ***Ukr.***: Cardosal (Кардосал); ***USA***: Benicar; ***Venez.***: Benicar; Olmetec.

Multi-ingredient Preparations. ***Arg.***: Olmetec D; ***Austral.***: Olmetec Plus; Sevikar; ***Austria***: Amelior; Mencord Plus; Olmetec Plus; Sevikar; ***Belg.***: Belsar Plus; Forzaten HCT; Forzaten; Olmetec Plus; Sevikar; ***Braz.***: Benicar HCT; Olmetec HCT; ***Canad.***: Olmetec Plus; ***Chile***: Cardioplus AM; Cardioplus D; Olmetec Plus; ***China***: Olmetec Plus (复傲坦); ***Cz.***: Olmetec Plus H; Sarten Plus H; Sintonyn; ***Denm.***: Alea; Benetor Comp; Olmetec Plus; Sevikar; ***Fin.***: Benetor Comp; Olmetec Plus; Sevikar; ***Fr.***: Alteisduo; Axeler; CoOlmetec; Sevikar; ***Ger.***: Olmetec Plus; Sevikar HCT; Sevikar; Vocado HCT; Vocado; Votum Plus; ***Gr.***: Olartan Plus; Olmetec Plus; Orizal; Sevikar; ***Hong Kong***: Azoren; Olmetec Plus; ***India***: Hybreed-H; Olmat-AM; Olmat-AMH; Olmat-H; Olmax-H; Olmefast-H; Olmesar-A; Olmesar-H; Olmetor-H; Olmezest-H; Olmighty-H; Olsar-A; Olsar-H; Olsar-M; Oukat-H; ***Irl.***: Benetor Plus; Konverge Plus; Konverge; Omesar Plus; Sevikar Plus; Sevikar; ***Ital.***: Olmegan; Olprezide; Plaunazide; ***Malaysia***: Olmetec Plus; ***Mex.***: Almetec-Co; ***Neth.***: Belfor HCT; Belfor; Capenon HCT; Capenon; Olmetec HCTZ; Sevikar HCT; Sevikar; ***Norw.***: Olmetec Comp; Sevikar; ***Philipp.***: Alzor CCB; Alzor HCT; Normetec; Olmetec Plus; ***Port.***: Olmetec Plus; Olsar Plus; Sevikar; Zolnor; ***Singapore***: Azoren; Olmetec Plus; ***Spain***: Balzak Plus; Balzak; Capenon HCT; Capenon; Ixia Plus; Olmetec Plus; Openvas Plus; Sevikar HCT; Sevikar; ***Switz.***: Olmetec Plus; Sevikar HCT; Sevikar; Vascord; Votum Plus; ***Thai.***: Normetec; Olmetec Plus; ***Turk.***: Hipersar Plus; Olmetec Plus; Olmysar

Plus; *UK*: Olmetec Plus; Sevikar HCT; *Ukr.*: Cardosal Plus (Кардосал Плюс); *USA*: Azor; Benicar HCT.

Olprinone Hydrochloride *(rINNM)*

E-1020; Hidrocloruro de olprinona; Loprinone Hydrochloride; Olprinona, hidrocloruro de; Olprinone, Chlorhydrate d'; Olprinoni Hydrochloridum; Ольпринона Гидрохлорид.
1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxonicotinonitrile hydrochloride.
$C_{14}H_{10}N_4O,HCl$=286.7
CAS — 106730-54-5 (olprinone); 119615-63-3 (olprinone hydrochloride).
UNII — F18B658J56.

Profile

Olprinone is a phosphodiesterase type 3 inhibitor with positive inotropic and vasodilator activity, used in acute heart failure (p. 1262.3). It is given intravenously as the hydrochloride in an initial dose of 10 micrograms/kg given over 5 minutes, followed by a continuous infusion at a rate of 100 to 400 nanograms/kg per minute, according to response.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Coretec.

Omapatrilat *(BAN, USAN, rINN)*

BMS-186716-01; BMS-186716; Omapatrilate; Omapatrilato; Omapatrilatum; Омапатрилат.
(4*S*,7*S*,10a*S*)-Octahydro-4-[(*S*)-α-mercaptohydrocinnamamido]-5-oxo-7*H*-pyrido[2,1-*b*][1,3]thiazepine-7-carboxylic acid.
$C_{19}H_{24}N_2O_4S_2$=408.5
CAS — 167305-00-2.
UNII — 36NLI90E7T.

NOTE. The name Vanlev has been used as a trade mark for omapatrilat.

Profile

Omapatrilat is a vasopeptidase inhibitor. It inhibits both angiotensin-converting enzyme and neutral endopeptidase and is under investigation in the management of hypertension and heart failure. However, its use may be limited by severe angioedema.

References.
1. Tabrizchi R. Dual ACE and neutral endopeptidase inhibitors: novel therapy for patients with cardiovascular disorders. *Drugs* 2003; **63:** 2185–2202.
2. Kostis JB, *et al.* Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004; **17:** 103–11.
3. Solomon SD, *et al.* OVERTURE Investigators. Effect of angiotensin-converting enzyme or vasopeptidase inhibition on ventricular size and function in patients with heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) echocardiographic study. *Am Heart J* 2005; **150:** 257–62.

Omega-3 Fatty Acids

Ácidos grasos omega 3; Омега-3 Жирные Кислоты.
ATC — C10AX06.
ATC Vet — QC10AX06.
UNII — 71M78END5S.

Docosahexaenoic Acid

Cervonic Acid; DHA; Doconexent (rINN); Doconexent; Doconexento; Doconexentum; Доконексент.
(*all-Z*)-Docosahexa-4,7,10,13,16,19-enoic acid.
$C_{22}H_{32}O_2$=328.5
CAS — 6217-54-5; 25167-62-8.
UNII — ZAD9OKH9JC.

NOTE. DHA is also used as a synonym for dihydroxyacetone (p. 1700.1).

Docosahexaenoic Acid Ethyl Ester

Cervonic Acid Ethyl Ester; Doconexent d'Éthyle; Doconexent Ethyl (rINNM); Doconexento de etilo; Ethyl Docosahexaenoate; Ethylum Doconexentum; Этил Доконексент.
$C_{24}H_{36}O_2$=356.6
CAS — 81926-94-5 (all-Z); 84494-72-4.
UNII — 7PO7G8PA8M.

Eicosapentaenoic Acid

Acidum Eicosapentaenoicum; Eikosapentaeenihappo; Eikosapentaensyra; EPA; Icosapent (rINN); Icosapento; Icosapentum; Timnodonic Acid; Икозапент.
(*all-Z*)-Eicosapenta-5,8,11,14,17-enoic acid.
$C_{20}H_{30}O_2$=302.5
CAS — 10417-94-4 (all-z); 1553-41-9.
UNII — AAN7QOV9EA.

NOTE. EPA is also used as a synonym for pheneturide.

Eicosapentaenoic Acid Ethyl Ester

AMR-101; Ethyl Eicosapentaenoate; Ethyl-EPA; Ethyl Icosapentate; Ethyl-eicosapentaenoic acid; Ethylum Icosapentum; Icosapent d'Ethyle; Icosapent Ethyl (USAN); Icosapent Ethyl (rINNM); Icosapento de etilo; LAX-101; Timnodonic Acid Ethyl Ester; Этил Икозапент.
Ethyl (5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-icosa-5,8,11,14,17-pentaenoate.
$C_{22}H_{34}O_2$=330.5
CAS — 73310-10-8 (all-Z); 86227-47-6 (all-Z); 84494-70-2.
UNII — 6GC8A4PAYH.

NOTE. The name Miraxion has been used as a trade mark for eicosapentaenoic acid ethyl ester.

Pharmacopoeias. In *Jpn*.

Linolenic Acid

ALA; Alpha-linolenic Acid; Kwas linolenowy; α-Linolenic Acid; Линоленовая Кислота.
(*all-Z*)-9,12,15-Octadecatrienoic acid.
$C_{18}H_{30}O_2$=278.4
CAS — 463-40-1.
UNII — 0RBV727H71.

NOTE. Do not confuse with γ-linolenic acid (Gamolenic Acid, p. 2509.2)

Omega-3-acid Ethyl Esters *(USAN)*

Ethylestery omega-3-kyselin; K-85; Omega-3 Acidorum Esteri Ethylici; Omega-3 Acidorum Esteri Ettylici; Omega-3 rūgščių etilo esteriai; Omega-3-sav-etilészterek; Омега-3-кислоты Этиловых Эфиров.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Omega-3-Acid Ethyl Esters 60). A mixture of ethyl esters of omega-3 acids. They are obtained by transesterification of the body oil of fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae or from animals of the class Cephalopoda. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acid ethyl esters, eicosapentaenoic acid ethyl esters, and docosahexaenoic acid ethyl esters should be stated on the label. For a total omega-3 acid ethyl ester content of 55%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50% and the content of eicosapentaenoic acid ethyl esters is not less than 40%; for a total omega-3 acid ethyl ester content of 60%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50% and the content of docosahexaenoic acid ethyl esters is not less than 40%; and for a total omega-3 acid ethyl ester content of 65%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50%, the content of eicosapentaenoic acid ethyl esters is not less than 25%, and the content of docosahexaenoic acid ethyl esters is not less than 20%. Antoxidants may be added.

A light yellow liquid with a slight fish-like odour. Practically insoluble in water; very soluble in acetone, in alcohol, in heptane, and in methyl alcohol. Store in airtight containers under inert gas. Protect from light.

Ph. Eur. 8: (Omega-3-Acid Ethyl Esters 90). A mixture of ethyl esters of omega-3 acids. They are obtained by transesterification of the body oil of fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae or from animals of the class Cephalopoda. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acid ethyl esters is not less than 90%, and that of both eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 80%; the content of eicosapentaenoic acid ethyl esters is not less than 40% and of docosahexaenoic acid ethyl esters is not less than 34%. Antoxidants may be added.

A light yellow liquid. Practically insoluble in water; very soluble in acetone, in alcohol, in heptane, and in methyl alcohol. Store in airtight containers under inert gas. Protect from light.

USP 36: (Omega-3 Acids Ethyl Esters). They are obtained by transesterification of the body oil obtained from fish of families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae and subsequent purification processes including urea fractionation followed by molecular distillation. The content of eicosapentaenoic acid ethyl ester plus the content of docosahexaenoic acid ethyl ester is not less than 800 mg/g and not more than 880 mg/g, with not less than 430 mg/g and not more than 495 mg/g of eicosapentaenoic acid ethyl ester and not less than 347 mg/g and not more than 403 mg/g of docosahexaenoic acid ethyl ester. Tocopherol may be added as an antoxidant. Store in airtight containers under an atmosphere of nitrogen at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Omega-3 Marine Triglycerides

Deniz Kaynaklı Omega-3 Trigliseridler; Poisson (huile de) riche en acides oméga-3 (fish oil, rich in omega-3-acids); Saumon d'élevage, huile de (salmon oil, farmed); Triglicéridos marinos omega 3; Омега-3 Триглицериды Морского Происхождения.
UNII — D87YGH4Z0Q.

NOTE. Omega-3 Marine Triglycerides (BAN) is a mixture of triglycerides of fatty acids from marine fish containing the equivalent of about 18% of eicosapentaenoic acid and 12% of docosahexaenoic acid. The content of triglycerides is not the same as that in Omega-3-Marine Triglycerides BP.

Pharmacopoeias. *Eur.* (see p. vii) includes Omega-3-Acid Triglycerides, Fish Oil, Rich in Omega-3-Acids, and Salmon Oil, Farmed. *US* includes Fish Oil containing Omega-3 Acids and Omega-3 Acid Triglycerides.

Ph. Eur. 8: (Omega-3-Acid Triglycerides; Omega-3 Acidorum Triglycerida; Omega-3-Marine Triglycerides). A mixture of mono-, di-, and triesters of omega-3 acids with glycerol, containing mainly triesters. They are obtained by esterification of concentrated and purified omega-3 acids with glycerol or by transesterification of the omega-3 acid ethyl esters with glycerol. The omega-3 acids are from the body oil of fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae or from animals of the class Cephalopoda. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acids expressed as triglycerides is not less than 60% and that of both eicosapentaenoic acid and docosahexaenoic acid together, expressed as triglycerides, is not less than 45%. Antoxidants may be added.

A pale yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled, airtight containers under inert gas. Protect from light.

Ph. Eur. 8: (Fish Oil, Rich in Omega-3-Acids; Piscis Oleum Omega-3 Acidis Abundans). The purified, winterised, and deodorised fatty oil obtained from fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Scombridae (except the genera *Thunnus* and *Sarda*), and Ammodytidae (type I) or from the genera *Thunnus* and *Sarda* within the family Scombridae (type II). The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The minimum content, expressed as triglycerides, is eicosapentaenoic acid 13% (type I) or 4 to 8% (type II), docosahexaenoic acid 9% (type I) or 20% (type II), and total omega-3 acids 28% (type I and II). Antoxidants may be added.

A pale yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled, airtight containers under inert gas. Protect from light.

Ph. Eur. 8: (Salmon Oil, Farmed; Salmonis Domestici Oleum). The purified fatty oil obtained from fresh farmed *Salmo salar*. The positional distribution (β(2)-acyl) is 60 to 70% for docosahexaenoic acid (cervonic acid), 25 to 35% for eicosapentaenoic acid (timnodonic acid), and 40 to 55% for moroctic acid. The sum of the contents of eicosapentaenoic acid and docosahexaenoic acid, expressed as triglycerides, is 10.0 to 28.0%. Antoxidants may be added. A pale pink liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled airtight containers under an inert gas. Protect from light.

USP 36: (Fish Oil containing Omega-3 Acids). The purified, winterised, and deodorised fatty oil obtained from fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Scombroidae, and Ammodytidae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), heneicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid (DHA). It contains not less than 28% (w/w) of total omega-3 acids (expressed as free acids) consisting of not less than 13% of EPA and not less than 9% of DHA. Antoxidants may be added. A pale yellow liquid. Practically insoluble in water; slightly soluble in anhydrous alcohol; very soluble in acetone and in heptane. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. It may be stored under vacuum or under an inert gas. Protect from light.

USP 36: (Omega-3 Acid Triglycerides). A mixture of mono-, di-, and triesters of omega-3 acids with glycerol containing mainly triesters. They are obtained by esterification of concentrated and purified omega-3 acids with glycerol or by transesterification of the omega-3 acid ethyl esters with glycol. The omega-3 acids are from the body oil of fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid. It contains not less than 58% of total omega-3 acids (expressed as triglycerides). Antoxidants may be added. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light. It may be stored under a vacuum or under an inert gas.

Uses and Administration

Omega-3 fatty acids are long-chain polyunsaturated fatty acids containing 18 to 22 carbon atoms and a varying number of double bonds, the first of which is in the n-3 position. They are essential fatty acids and must be obtained from the diet. They have an important role as eicosanoid precursors and as components of cell membranes; in humans, they compete with arachidonic acid (p. 2446.1), an omega-6 fatty acid precursor. Their actions in humans include a hypolipidaemic action (especially a reduction in plasma triglycerides), an anti-inflammatory action, and an antiplatelet effect. The main dietary omega-3 fatty acids are eicosapentaenoic acid and docosahexaenoic acid and are derived from marine fish; other omega-3 fatty acids found in fish oils (defined in terms of number of carbon atoms and number of double bonds) include linolenic acid, moroctic acid (C18:4), eicosatetraenoic acid (C20:4), heneicosapentaenoic acid (C21:5), and clupanodonic acid (C22:5). Linolenic acid is also found in some plant sources and is converted to a limited extent in the body to eicosapentaenoic acid and docosahexaenoic acid.

Fish oils and purified omega-3 fatty acid preparations are used in patients with severe hypertriglyceridaemia (see Hyperlipidaemias, p. 1248.1) and for secondary prevention after myocardial infarction (see Cardiovascular Disorders below). They are also marketed as dietary supplements, and are used in preparations for parenteral nutrition.

The preparations available vary widely in purity and omega-3 fatty acid content, usually expressed in terms of eicosapentaenoic acid and docosahexaenoic acid; the fatty acids may be present as triglycerides or as ethyl esters. Typical oral doses of fish oil for the treatment of hypertriglyceridaemia are 5 g twice daily of a preparation containing 17% eicosapentaenoic acid and 11.5% docosahexaenoic acid, or 2 to 4 g daily of a preparation containing 46% eicosapentaenoic acid and 38% docosahexaenoic acid. For the secondary prevention of myocardial infarction, 1 g daily of a preparation containing 46% eicosapentaenoic acid and 38% docosahexaenoic acid may be given. Eicosapentaenoic acid ethyl ester may also be used alone in the treatment of hyperlipidaemia, and to improve the symptoms associated with arteriosclerosis obliterans.

Linolenic acid and its esters, such as ethyl linolenate, have been included in mixtures known as 'essential fatty acids' (see Uses of Gamolenic Acid, p. 2509.2).

Action. Interest in omega-3 fatty acids arose from observations that populations with a diet rich in marine fish oils generally have a low incidence of cardiovascular disease, while the incidence of asthma, psoriasis, and autoimmune diseases appears to be lower among Eskimos (Inuit) than in populations consuming a typical western diet (although the incidence of haemorrhagic stroke and epilepsy may be higher). Increased omega-3 fatty acid intake has been suggested to underlie these differences, and fish oil and other omega-3 preparations have therefore been promoted as dietary supplements, with benefit suggested for many conditions.

The beneficial health effects of omega-3 fatty acids have been attributed to their effects on eicosanoid balance, lipid metabolism, and cell membranes. Essential fatty acids of both the omega-3 and omega-6 series have an important role as components of cell membranes and as precursors of eicosanoids (prostaglandins, leukotrienes, and thromboxanes). Eicosanoids derived from omega-3 fatty acids generally have anti-inflammatory, antithrombotic, antiarrhythmic, and vasodilator effects, while those derived from omega-6 fatty acids tend to be pro-inflammatory and prothrombotic. Since omega-3 and omega-6 fatty acids compete for the same enzymatic pathways, increasing the intake of omega-3 fatty acids promotes the formation of anti-inflammatory and antithrombotic eicosanoids, and may have beneficial effects. Production of inflammatory cytokines such as interleukins and tumour necrosis factor alpha may also be affected.

For further information on the actions of omega-3 fatty acids in cardiovascular disorders, inflammatory and autoimmune disorders, malignant neoplasms, and neurological and psychiatric disorders, see below and p. 1462.1.

References.

1. Connor WE. Importance of n-3 fatty acids in health and disease. *Am J Clin Nutr* 2000; **71** (suppl): 171S–175S.
2. Covington MB. Omega-3 fatty acids. *Am Fam Physician* 2004; **70:** 133–40.

Cardiovascular disorders. Omega-3 fatty acids have several actions that are potentially beneficial for patients at risk of cardiovascular disease.[1-6] They have a hypolipidaemic effect due to inhibition of very-low-density lipoprotein (VLDL) synthesis in the liver, and this particularly reduces triglyceride concentrations.[7] Heart rate may be reduced,[8] and they may also have an antiarrhythmic effect,[5] possibly due to a direct action on myocardial cells, although evidence is conflicting.[9] Omega-3 fatty acids may also reduce blood pressure in hypertensive patients,[10] as well as increasing erythrocyte deformability and decreasing blood viscosity. They appear to stabilise atherosclerotic plaques,[11] and may reduce progression of atherosclerosis[12] and of restenosis after percutaneous coronary intervention.[13]

Despite these benefits, the role of dietary or supplementary omega-3 fatty acids for cardiovascular risk reduction (p. 1246.1) remains controversial. Epidemiological studies have suggested that increased dietary fish intake is associated with a reduced risk of fatal coronary events,[14] and possibly also ischaemic stroke,[15,16] and there is also evidence for benefit with omega-3 fatty acid supplements, particularly for secondary prevention.[1-4,17] In the GISSI-Prevenzione study,[18] long-term use of omega-3 fatty acid supplements reduced the risk of fatal cardiovascular events in a large group of Italian post-infarction patients studied for 3.5 years,[18] while the JELIS investigators[19] reported a reduction in primary and secondary cardiovascular events in Japanese patients with hypercholesterolaemia. However, a systematic review[20] found no clear benefit from omega-3 fatty acids, whether dietary or supplemental, in people with or without cardiac risk factors.

1. Carroll DN, Roth MT. Evidence for the cardioprotective effects of omega-3 fatty acids. *Ann Pharmacother* 2002; **36:** 1950–6.
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Inflammatory and auto-immune disorders. Omega-3 fatty acids have effects on several immunological and inflammatory mediators[1,2] and have been tried in several inflammatory and auto-immune disorders. Beneficial effects have been reported in rheumatoid arthritis[3] (p. 13.2), and an evidence-based report[4] by the Arthritis Research Campaign considered it to be safe with good evidence for improvement in symptoms in this condition, although there were insufficient data for its use in osteoarthritis. Benefit has also been reported in glomerular kidney disease[5-7] (p. 1604.3), but results in kidney transplantation (p. 1939.2) have been mixed, and systematic reviews[8,9] suggest no significant effect on rejection episodes or graft survival. Some studies have shown benefit in psoriasis (p. 1688.1), both with oral[10,11] and with intravenous dosage,[12,13] but other studies found neither the oral[14] nor the topical[15] route to be effective. Variable benefit has been seen in inflammatory bowel disease[16] (p. 1811.3) although this may relate to the different formulations used. However, systematic reviews have found omega-3 fatty acids to be ineffective in Crohn's disease[17] and ulcerative colitis.[18] Fish oils have also been tried in lung disorders, although systematic reviews have found little evidence of benefit in asthma;[19,20] however, limited benefit has been reported in cystic fibrosis,[21] with one study[22] reporting that fish oil supplementation reduced the need for antibacterial treatment.

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Malignant neoplasms. There is some evidence that the incidence of cancer may be lower in populations with a high fish intake, and *animal* studies have suggested that omega-3 fatty acids may slow the progression of some cancers.[1] However, studies of omega-4 fatty acid intake and

cancer incidence in humans have given conflicting results, and systematic reviews[2,3] have found no evidence of a beneficial effect. It has also been suggested that omega-3 fatty acids might be beneficial in patients with cancer cachexia, but a randomised study[4] found that eicosapentaenoic acid supplementation was less effective than megestrol acetate, and a systematic review[5] found insufficient evidence to establish whether eicosapentaenoic acid was more effective than placebo.

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Neurological and psychiatric disorders. Omega-3 fatty acids concentrate in neuronal membranes and appear to have an important role in brain development and function. Supplementation during pregnancy and in infants has been investigated. There is little evidence that maternal supplements improve neonatal outcomes,[1] but there may be a benefit on growth and neurodevelopment in preterm infants given milk formulas supplemented with both omega-3 and omega-6 fatty acids.[2-5] In older children with phenylketonuria treated with dietary restriction, omega-3 fatty acid supplements may improve motor skills.[6]

Omega-3 fatty acids have also been tried in the treatment of neurological and psychiatric disorders.[7,8] There appears to be a link between deficient fatty acid intake and mood disorders,[9] and there is reasonable evidence to support the use of omega-3 fatty acids as adjuncts in the treatment of depression, including possible benefit in the depressive symptoms of bipolar disorder, but further studies are needed to confirm this.[10-13] Benefit has been shown in schizophrenia, but results have been mixed and the role of omega-3 fatty acids is not established.[14] Some positive results have been reported in hyperactivity and in autism, but further studies are needed.[15,16] Omega-3 fatty acids have also been tried in dementia, but there is not yet sufficient evidence[17,18] to recommend them for prevention.

Eicosapentaenoic acid ethyl ester has been tried in Huntington's disease. An early study suggested improvements in motor function,[19] but this was not borne out in a later study,[20] which found no difference in measures of function, cognition, or global impression when compared with placebo.

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Adverse Effects and Precautions

The most common adverse effects of omega-3 fatty acid preparations are gastrointestinal disturbances, particularly at high doses, including nausea, eructation, vomiting, abdominal distension, diarrhoea, and constipation. There have been rare reports of acne and eczema. Moderate increases in hepatic transaminases have been reported in patients with hypertriglyceridaemia.

Preparations vary widely in concentration and purity. Some preparations contain significant amounts of vitamins A and D and long-term use could cause toxicity. There is a theoretical possibility of vitamin E deficiency with long-term use, although many preparations contain vitamin E as an antoxidant. Concern has been expressed over the high calorific value and cholesterol content of some preparations.

Omega-3 fatty acids have antithrombotic activity and should be given with caution to patients with haemorrhagic disorders or to those receiving anticoagulants or other drugs affecting coagulation. Hepatic function should be monitored in patients with hepatic impairment, particularly if receiving high doses. Caution may also be required in asthmatic patients sensitive to aspirin since omega-3 fatty acids may affect prostaglandin synthesis (see also Inflammatory and Auto-immune Disorders, p. 1461.3, for studies of fish oils in the management of asthma).

Reviews.

1. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 2007; **99** (suppl): 35C–43C.

Effects on the blood. Omega-3 fatty acids have antithrombotic effects and may increase bleeding. In a study[1] in adolescents with familial hypercholesterolaemia, epistaxis occurred in 8 of 11 patients treated with a fish oil supplement; prolonged bleeding time was noted in 3 patients. There have also been case reports of INR elevation and haematoma in patients taking fish oil preparations with antithrombotics (see Lipid Regulating Drugs under Interactions of Warfarin, p. 1534.3), although controlled studies have failed to show an effect.

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Effects on glucose metabolism. Although a deterioration in glycaemic control has been reported in diabetic patients taking omega-3 fatty acids and fish oil preparations, a meta-analysis[1] of studies in type 1 and type 2 diabetics, and a systematic review[2] of controlled studies in type 2 diabetics, both concluded that fish oils effectively lowered triglycerides without a deleterious effect on glycaemic control.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: OMG 3; Regulip; ***Austral.***: Fishaphos†; Kids Fruity Fishies; Maxepa; Omacor; ***Austria***: Omacor; Omegaven; ***Belg.***: Omacor; ***Braz.***: Corabion HC; Votag; ***Canad.***: Flex†; Focus 425†; ***Chile***: DHA Kids; DHA Mathern; Dr Einst Gold; Dr Einstein Mama; Epasan Omega 3; Eykosacol; Omega-3; Omegaven; Prenamin; ***China***: Omegaven (尤文); ***Cz.***: FolGravid; Omacor; Omegaven; ***Denm.***: Omegaven; ***Fr.***: Maxepa†; Molval; OM3†; Omacor; Omegabiane; Omegaven; Psoriacalm; Triglistab; Ysomega; ***Ger.***: Ameu; Eicosan; Eicosapen; Lipiscor; Omacor; Omegaven; Zodin; ***Gr.***: Farlipid; Maxepa; Omacor; Zodin; ***Hong Kong***: Lipomega; Omegaven; Smartfish†; ***Hung.***: Eskimo-3; Omacor; Omegaven; ***India***: Maxepa; Mega-Omega; Natolac; Omegaven; ***Indon.***: Astacor; Champs DHA; Prolacta with DHA for Baby; Prolacta with DHA for Mother; ***Irl.***: Maxepa†; Omacor; ***Israel***: Alsepa Focus; Alsepa Super; Alsepa; Omacor; Omegaven; Tri-Omega Extra EPA; ***Ital.***: Almic; Esapent; Eskim; Fish Factor; Maxepa; Omegaven; Seacor; Triolip; Triomar; ***Jpn***: Emeradole; Epadel; Lotriga; Solmiran; ***Malaysia***: Caprovid; Champs DHA; Mepa†; Quest Gamma EPA Plus; ***Mex.***: Biomega; Colega-3†; Fresomega; Omegavite; ***Neth.***: Omacor; Omegaven; ***Norw.***: Omacor; ***NZ***: Omegaven; ***Philipp.***: Fisol†; Omacor; Omega Gold; Zymechol; ***Pol.***: BioCardine†; Omacor; Omega-3; Omegaven; Trienyl†; ***Port.***: Omacor; Omegaven; Zodin; ***Rus.***: Omacor (Омакор); Omegaven (Омегавен); ***Singapore***: Champs DHA†; ***Spain***: Omacor; ***Swed.***: Omegaven; Pikasol; ***Switz.***: Biorganic Omega-3; Eicosapen; Epacaps; Omegaven; ***Thai.***: Omacor; ***Turk.***: Efa; Marincap; Omega III; Omegaven; Somon; ***UK***: DocOmega; Maxepa; Omacor; Omegaven; Prestylon; Pure Omega; Teromeg; ***Ukr.***: Omacor (Омакор); Omegaven (Омегавен); ***USA***: Cardi-Omega 3; Cholestin; Lovasa; Lovaza; Maxepa; Promega; Sea-Omega; SuperEPA; Vascepa; ***Venez.***: Epax; Fizoil; Marina; Maxepa; Ometrix.

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; Cellasene†; Epasterol; Ocuvite Omega3; Omeganorm†; Percutalfa; ***Austral.***: Arthri Plus†; Arthriforte†; Arthro-Eze; Bonlutin; CardiWell Omega Q10; Conceive Well Gold; EFA Compound; Hypol Cherry; Lutein-Vision Advanced; Maxepa Evening Primrose Oil; NA Neurocard; Once Daily Mens Multi; PM Bright Kids; PM Eye Tonic; PM IQShield; PM Kids Intelligent; PM Procare; Pregnancy & Breast-Feeding Gold; Pregnancy & Breastfeeding Formula; SMOFlipid; Teen Multi; TotalCare†; Zellulean with Escin†; ***Austria***: Lipidem; SMOFlipid; Sulgan 99; ***Belg.***: Lipoplus; ***Braz.***: Borag; Glavit†; Votag O6; ***Canad.***: Balance†; Bionagre plus E†; Herbalifeline†; ***Chile***: A-Colest TG; Celltech; Infor; Naticare; Tonopron Plus; ***Cz.***: Lipoplus; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***Denm.***: Lipidem; SMOFKabiven; SMOFlipid; ***Fin.***: Lipoplus; SMOFKabiven; SMOFlipid; ***Fr.***: Alphalarm; Androlistica; Base; Bi-Osteo; Cardilane; Corvitec; Derm; Difravision; Diomega; Dioptec; DNV; Donaclim; Donalis; Effadiane relipidantes; Elteans; Feminabiane Conception; Gestarelle S; Gynefam; Kotor Articulations; Lero Pervulane; Lero; Lipidem; Liporegul; Macula; Memozan; Menolistica; Mix-Alpha 3; Natalience; Naturophta Macula; Neurovitol; Nutrilarm; Nutrof Total; OM3flex†; OM3junior†; OM3memory†; Omegacoeur; Optibiol; Photoderm; Phyltalzeal; Phytalgic; Phytophanere†; PreserVision; Reanutriflex Omega; Regederm; Reti-Nat†; Rhu; Selomega; Serenite Grossesse; SMOFKabiven; SMOFlipid; Solaire; Sun Vue; Synaptiv; Trioptec; Visioprev; Vitalux Plus; ***Ger.***: Lipidem; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***Gr.***: Atroil; Dynapen-3; Emfrastop; Epadoc; Lipemia; Lipoplus; Loitrol; Mega-Tria; Pazeril; Prolipid; Salmon Oil†; SMOFKabiven; SMOFlipid; ***Hong Kong***: Biomega-3†; Cardiozen; Doctor's Choice Omega 3; Eye Q; Mumomega; PM Eye Tonic†; SMOFlipid; ***Hung.***: Epasel; Epavir; Memolife; SMOFlipid; ***India***: Alphamix-BT; Alphamix; Aqua-E; Bio-10; Bree-C; Cadvion; Catalyst; Celadrin; Coq Forte; Doravit Forte; Ducat Plus; E-Cod Omega; Efalife; Ega; Eldervit-ZC; Elmega-3; Enduranz; Enew; Eriz; Evion Forte; Evox; Exerge; FDH; Fol-DHA; Fol-G2; Fol-Thrive; Folsafe; Folwise; Gissicor; Gissistat; Glace-X; Hartivit; I-Zen; Jivak; Kefive Plus; Maxigard; Maxoflam; Maxolic; Mega-3; Megagin; Megalip; Megaminvit; Megasoft-E; Meskina; MMO3; Mobix; Moisturex-AF; Momvita; Multivite Vision; Multivite-FM Omega; Natrolip; O-NE; Oiz; Olevon; Omegachek; Omegic; Winofit; ***Indon.***: Afomix; Anabion Plus DHA; Asedas; Baliin Q10; Bio-Curlam; Biolysin Smart; Biostrum; Brainvit; Calcidol; Calcimega; Caloma Plus; Calostrum; Cerebrofort AA+DHA; Cerebrofort Gold; Co-Q-10; Curbexon; Curfos; Curmunos; Curvit CL; Dhavit; Flexasur; Folamil Genio; Grafola DHA; Gravimin DHA; Igastrum Plus; Imustrum; Inlacta DHA; Intrum Plus; Kolivit; Kuminta; Lysmin Plus; Maxitrin†; Mulsanol; Natavit; Nufagrabion-GM; Nulacta Plus; Nulacta; Obipluz; Osmetin 3; Pharmaton Matruelle; Prenatal DHA; Prenatin-DF; Procalma; Prohelic; Prokids; Promavit; Scott's Cod Liver Oil; Seltifort Gold; Seltifort Kids; Solvita Baby; Truvit; Vidoran Smart Plus; Vidoran Smart Plus; Vitaplex; Vitazym; Vitro-Mega; ***Irl.***: Lipidem; MorDHA†; MorEPA†; SMOFKabiven; SMOFlipid; ***Israel***: Alsepa 9 Months; SMOFKabiven; SMOFlipid; Tri-Omega Super; Triomar; ***Ital.***: Astar; Chiton; Derman-Oil; Dermana Crema; Dermana Pasta; DHA; Ditrevit K; Ditrevit; Eicovis; Elageno OS; Esterol; Euretin; Eutears; Fitogenase; Fotrec DHA; Gammaplus; LCP; Lipidem; Lipoacid Combi; Natalben; Osvit; Phototrop; SMOFlipid; Trofinerv Antiox; Trofinerv; Venoton; ***Malaysia***: Adult Citrex Multivitamin + Ginseng + Omega 3; Bio-Enhanced Fish Oil Plus; BiOmega†; Celadrin†; DHA Plus; Eurobio Bio-Vizmax; Flexasur; Junior Citrex; Neuro-Plus; Pharmaton†; Provas; Tocovid Emulsion Plus; Tocovid Suprabio with DHA; ***Mex.***: Pharmaton Matruelle; ***Mon.***: Conceptio; ***Neth.***: Lipoplus; SMOFKabiven; SMOFlipid; ***Norw.***: Lipidem; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***NZ***: Efalex; Efamarine; Efamax†; Efanatal; ***Philipp.***: Completia†; Dreamvite; Megavit; Memory Plus; Neurosmart; Nutri-Aid; OB Smart SG; Omegabloc; Omnimune; Pharmaton; Polynerv-E with lecithin; Premium Memori Plus; Trilipid; ***Pol.***: SMOFKabiven; SMOFlipid; ***Port.***: Ever-Fit Dermo; Fortal Vision; Lipoacid Combi; Lipoplus; Rilastil Anti-Oxidante; SMOFKabiven; SMOFlipid; ***Rus.***: Lipoplus (Липоплюс); SMOFlipid (СМОФлипид); ***Singapore***: Androlistica; Arterodiet†; Belvea Pregnancy & Breastfeeding Formula; Biomega†; Cardio Cocktail; CardioCare; Dhaxtra; Eye Q Equazen†; EyeMax; Gissicor; Manhae; Mum-2-B; Mumomega Equazen†; NataBoost; Natal Care; Obimin Pluz; Ocuvite Adult 50+; Optibiol; Seven Seas JointCare High Strength; Seven Seas JointCare Max; Seven Seas JointCare; Seven Seas Pulse High Strength Triomega; VitaEPA Plus; VitaE-PA; ***Spain***: Lipoplus; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***Swed.***: Efalex; Efanatal†; Lipoplus; SMOFKabiven; SMOFlipid; ***Switz.***: Lipoplus; SmofKabiven; SMOFlipid; Sulgan N; Vitafissan N; ***Thai.***: Gilomax; Lipidem; SMOFlipid; ***Turk.***: SMOFlipid; ***UK***: Chol-Aid; Efalex; Efamarine; Efanatal; Fishogar; GlucOsamax; Lacrima; Lipidem; NuTRIflex Omega; Pregnacare Plus; ProBrain; SMOFlipid; Super Antioxidant Plus; ***Ukr.***: Bodimarin (Бодимарин); Doppelherz Aktiv Omega-3 Clean Vessels (Доппельгерц Актив Омега-3 Чистые Сосуды); Femibion 400 (Фемибион 400); Ocuvite Complete (Окювайт Комплит); Optix Forte (Оптикс Форте); Perfectil Plus (Перфектил Плюс); Reytoil (Рейтоил); Smart Omega (Смарт Омега); SMOFlipid (СМОФлипид); Vitrum Cardio Omega-3 (Витрум Кардио Омега-3); ***USA***: Active OB; Animi-3 with Vitamin D; Animi-3; Brainstrong Prenatal Multivitamin plus DHA; Cardio Omega Benefits with Vitamin D-3; Citracal Prenatal + DHA; CitraNatal Harmony; Complete Prenatal Multivitamin/ Prenatal DHA Combo Pack; Dry Eye Omega Benefits with Vitamin D-3; Duet DHA; Extra-Virt Plus DHA; Flex Omega Benefits with Vitamin D-3; Hemenatal OB + DHA; Infanate Balance; Macnatal CN DHA;

Marine Lipid Concentrate; Natalvirt CA; Natalvirt DHA; Nestabs ABC; Nestabs DHA; Nexa Plus; Nexa Select; OB Complete; Omega Essentials with Vitamin D-3; Optinate Omega-3; PNV OB+DHA; PNV-DHA; PR Natal; Prena 1 Plus with Quatrefolic; Prenal with Quatrefolic; Prenaissance DHA; Prenaissance Harmony DHA; Prenaissance Promise; Prenaissance; Prenatal 1; Prenate Essential; Prenate Mini; PreNexa; PreQue 10; Preservision Eye Vitamin; ProtectNatal; Reaphirm Plant Source DHA; Select-OB + DHA; Stuart One; Stuart prenatal + DHA; Tandem DHA; TheraNatal Complete; TL-Assure ONE†; TL-Assure†; Tri-Care Prenatal Compleat; Triveen-PRx RNF; Triveen-Ten; Ultimate OB DHA; V-Natal DHA; Virt-Bal DHA; Virt-PN DHA; Virt-PNV-DHA; Virt-Select; Vitafol-One; Vitafol-Plus; Vitafol-Ultra; VitaMedMD One Rx; VitaMedMD Plus Rx; VP-CH-PNV; VP-Heme One; ***Venez.***: Eidoca; Maternavit; Optibiol; Piscis 3; Provax.

Pharmacopoeial Preparations

USP 36: Fish Oil containing Omega-3 Acids Capsules; Fish Oil containing Omega-3 Acids Delayed-release Capsules; Omega-3-Acid Ethyl Esters Capsules.

Orbofiban Acetate *(USAN, rINNM)*

Acetato de orbofibrán; CS-511; Orbofiban, Acétate d'; Orbofibani Acetas; Orbofibrán, acetato de; SC-57099-B; Орбофибана Ацетат.

N-{[(3*S*)-1-(*p*-Amidinophenyl)-2-oxo-3-pyrrolidinyl]carbamoyl}-β-alanine ethyl ester monoacetate quadrantihydrate.

$C_{17}H_{23}N_5O_4.C_2H_4O_2.¼H_2O$=426.0

CAS — 163250-90-6 (orbofiban); 165800-05-5 (orbofiban acetate).

UNII — UP77J8QOVX.

Profile

Orbofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug in unstable angina and myocardial infarction but has been associated with an increase in mortality.

References.

1. Cannon CP, *et al.* Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000; **102:** 149–56.

Ouabain

Acocantherin; G-Strophanthin; Ouabaiini; Ouabain oktahydrát; Ouabaína; Ouabainas; Ouabaïne; Ouabainum; Ouabainum Octahydricum; Strophanthin-G; Strophanthinum; Strophanthoside-G; Uabaina; Ubaína.

3β-(α-L-Rhamnopyranosyloxy)-1β,5,11α,14,19-pentahydroxy-5β,14β-card-20(22)-enolide octahydrate.

$C_{29}H_{44}O_{12}.8H_2O$=728.8

CAS — 630-60-4 (anhydrous ouabain); 11018-89-6 (ouabain octahydrate).

ATC — C01AC01.

ATC Vet — QC01AC01.

UNII — 5ACL011P69.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Ouabain). Colourless crystals or white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; practically insoluble in ethyl acetate. Protect from light.

Profile

Ouabain is a cardiac glycoside with positive inotropic activity that is obtained from the seeds of *Strophanthus gratus* or from the wood of *Acokanthera schimperi* or *A. ouabaio* (Apocynaceae). It has general properties similar to those of digoxin (p. 1353.3) and may be used in the treatment of heart failure (p. 1262.3). Ouabain is given orally in a dose of up to 24 mg daily; it has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Strodival†.

Oxedrine *(BAN)*

Oksedriini; Oxedrin; Oxedrina; Oxedrinum; Sinefrina; Sympaethaminum; *p*-Synephrine; Synephrine; Окседрин.

(*RS*)-1-(4-Hydroxyphenyl)-2-(methylamino)ethanol.

$C_9H_{13}NO_2$=167.2

CAS — 94-07-5.

ATC — C01CA08; S01GA06.

ATC Vet — QC01CA08; QS01FB90; QS01GA06.

UNII — PEG5DP7434.

NOTE. Synephrine and *p*-synephrine have been used as synonyms for oxedrine. Care should be taken to avoid confusion with *m*-synephrine, which is phenylephrine (p. 1672.2).

Oxedrine Hydrochloride *(BANM)*

Sinefrina, hidrocloruro de; Synephrine Hydrochloride; Окседрина Гидрохлорид.

$C_9H_{13}NO_2.HCl$=203.7

ATC — C01CA08; S01GA06.

ATC Vet — QC01CA08; QS01GA06.

UNII — EN5D1IH09S.

Oxedrine Tartrate *(BANM)*

Aetaphen. Tartrat.; Aethaphenum Tartaricum; Oksedriinitartraatti; Oxedrini Tartras; Oxedrintartrat; Oxyphenylmethylaminoethanol Tartrate; Sinefrina Tartrato; Sinefrina, tartrato de; Synephrine Tartrate; Окседрина Тартрат.

$(C_9H_{13}NO_2)_2.C_4H_6O_6$=484.5

CAS — 16589-24-5 (oxedrine tartrate); 67-04-9 (±oxedrine tartrate).

ATC — C01CA08; S01GA06.

ATC Vet — QC01CA08; QS01GA06.

UNII — 9I99I5995J.

Profile

Oxedrine is a sympathomimetic (p. 1507.3) that has been given as the tartrate in the treatment of hypotensive states in oral doses of about 100 to 150 mg three times daily; it has also been given by subcutaneous, intramuscular, or intravenous injection.

Oxedrine tartrate has been used in eye drops as an ocular decongestant. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Sympatol†; ***Hong Kong***: Ocuton†; ***Hung.***: Sympathomim; ***Ital.***: Sympatol†; ***Switz.***: Sympalept†.

Multi-ingredient Preparations. ***Fr.***: Dacryoboraline†; Polyfra†; Sedacollyre†; Uvicol†.

Oxilofrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de oxilofrina; *p*-Hydroxyephedrine Hydrochloride; Methylsynephrine Hydrochloride; Oxilofrina, hidrocloruro de; Oxilofrine, Chlorhydrate d'; Oxilofrini Hydrochloridum; Oxyephedrine Hydrochloride; Оксилофрина Гидрохлорид.

erythro-*p*-Hydroxy-α-[1-(methylamino)ethyl]benzyl alcohol hydrochloride.

$C_{10}H_{15}NO_2.HCl$=217.7

CAS — 942-51-8.

UNII — 3O9694M5EO.

Profile

Oxilofrine is a sympathomimetic (p. 1507.3) related to ephedrine (p. 1663.1). It has been used orally as the hydrochloride in the treatment of hypotensive states. It has also been used in antitussive preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Carnigen†; ***Ger.***: Carnigen†.

Multi-ingredient Preparations. ***Canad.***: Cophylac.

Oxprenolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Ba-39089; Hidrocloruro de oxiprenolol; Hidrocloruro de oxprenolol; Oksprenolol Hidroklorür; Oksprenololihydrokloridi; Oksprenololio hidrochloridas; Oksprenololu chlorowodorek; Oxprénolol, Chlorhydrate d'; Oxprenolol, hidrocloruro de; Oxprenolol hydrochlorid; Oxprenolol-hidroklorid; Oxprenololhydrochlorid; Oxprenololhydroklorid; Oxprenolol Hydrochloridum; Oxyprenolol Hydrochloride; Окспренолола Гидрохлорид.

1-(*o*-Allyloxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride.

$C_{15}H_{23}NO_3.HCl$=301.8

CAS — 6452-71-7 (oxprenolol); 6452-73-9 (oxprenolol hydrochloride).

ATC — C07AA02.

ATC Vet — QC07AA02.

UNII — F4XSI7SNIU.

NOTE. Compounded preparations of oxprenolol hydrochloride may be represented by the following names:

- Co-prenozide (*BAN*)—oxprenolol hydrochloride 640 parts and cyclopenthiazide 1 part (w/w).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US. Chin.* includes the base.

Ph. Eur. 8: (Oxprenolol Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Oxprenolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, and in chloroform; sparingly soluble in acetone; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 6.0.

Uses and Administration

Oxprenolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess intrinsic sympathomimetic and membrane-stabilising activity.

Oxprenolol is given orally as the hydrochloride in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and cardiac arrhythmias (p. 1266.1). It is also used in anxiety disorders (p. 1028.1).

In **hypertension** oxprenolol hydrochloride is given in a usual dose of 80 to 160 mg daily in two or three divided doses. The dose may be increased at weekly or fortnightly intervals until a satisfactory response is achieved. The usual maximum dose is 320 mg daily although up to 480 mg daily has been given.

The usual dose for **angina pectoris** is 80 to 160 mg daily in two or three divided doses with a usual maximum of 320 mg daily.

For **cardiac arrhythmias** a dose of 40 mg daily to not more than 240 mg daily in two or three divided doses may be used.

To relieve **anxiety** in stressful situations oxprenolol hydrochloride is given in usual doses of 40 to 80 mg daily, either as a single dose or in two divided doses.

Modified-release preparations allowing once daily dosing are also available.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Oxprenolol is distributed into breast milk but the amount likely to be ingested by an infant is small (see under Pharmacokinetics, below). No adverse effects have been seen in breast-fed infants whose mothers were given oxprenolol and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Oxprenolol-induced drug fever has been reported[1] in a patient and was confirmed by a challenge test.

1. Hasegawa K, *et al.* Drug fever due to oxprenolol. *BMJ* 1980; **281:** 27–8.

Overdosage. Rhabdomyolysis with myoglobinuria has been reported[1] as a complication of severe overdosage with oxprenolol.

1. Schofield PM, *et al.* Recovery after severe oxprenolol overdose complicated by rhabdomyolysis. *Hum Toxicol* 1985; **4:** 57–60.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Oxprenolol is well absorbed from the gastrointestinal tract, but is subject to first-pass metabolism resulting in variable bioavailability (20 to 70%). Peak plasma concentrations occur about 1 or 2 hours after a dose. Oxprenolol is about 80% bound to plasma proteins. It crosses the placenta and is distributed into breast milk. It is moderately lipid-soluble and crosses the blood-brain barrier. Oxprenolol is metabolised in the liver and almost entirely excreted in the urine. An elimination half-life of 1 to 2 hours has been reported.

Pregnancy and breast feeding. The placental transfer of oxprenolol and its passage into breast milk was studied[1] in 32 pregnant women given a preparation containing oxprenolol and dihydralazine (*Trasipressol*). At delivery the mean maternal plasma concentration was 0.386 nanomoles/mL compared with 0.071 and 0.081 nanomoles/mL in plasma from the umbilical artery and vein respectively.

Oxprenolol plasma concentrations in the newborn ranged from 0 to 0.186 nanomoles/mL during the first 24 hours of life. The concentrations of oxprenolol in breast milk 3 to 6 days after delivery ranged from 0 to 1.342 nanomoles/mL, and the milk to plasma concentration ratio was 0.45:1. Based on the highest milk concentration seen it was calculated that a breast-fed infant could receive, at a maximum, a daily dose at least 60 times less than an average adult daily dose (240 mg daily) for hypertension. In another study[2] in 12 women given oxprenolol, mean milk to plasma concentration ratios were 0.21:1 to 0.43:1, depending on dose.

1. Sioufi A, *et al*. Oxprenolol placental transfer, plasma concentrations in newborns and passage into breast milk. *Br J Clin Pharmacol* 1984; **18:** 453–6.
2. Fidler J, *et al*. Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; **90:** 961–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Corbeton; ***Canad.***: Trasicor†; ***Fr.***: Trasicor†; ***Ger.***: Trasicor†; ***Gr.***: Drisoftaline; Trasicor; Vrachor; Zetonium; ***Hong Kong***: Corbeton†; ***Neth.***: Trasicor†; ***Spain***: Trasicor†; ***Switz.***: Slow-Trasicor†; Trasicor†; ***Turk.***: Trasicor†; ***UK***: Slow-Trasicor; Trasicor.

Multi-ingredient Preparations. ***Fr.***: Trasitensine†; ***Gr.***: Trasitensin; ***Ital.***: Trasitensin; ***Spain***: Trasitensin; ***Switz.***: Slow-Trasitensine; ***UK***: Trasidrex†.

Pharmacopoeial Preparations
BP 2014: Oxprenolol Tablets;
USP 36: Oxprenolol Hydrochloride Extended-release Tablets; Oxprenolol Hydrochloride Tablets.

Oxyfedrine Hydrochloride *(BANM, rINNM)*

D-563; Hidrocloruro de oxifedrina; Oxifedrina, hidrocloruro de; Oxifedrini Chloridum; Oxyfédrine, Chlorhydrate d'; Oxyfedrini Hydrochloridum; Оксифедрина Гидрохлорид.
L-3-(β-Hydroxy-α-methylphenethylamino)-3′-methoxypropiophenone hydrochloride.
$C_{19}H_{23}NO_3$,HCl=349.9
CAS — 15687-41-9 (oxyfedrine); 16777-42-7 (oxyfedrine hydrochloride).
ATC — C01DX03.
ATC Vet — QC01DX03.
UNII — 63CF9XK7DA.

Profile

Oxyfedrine hydrochloride has vasodilator properties and has been used in angina pectoris, and myocardial infarction. It is metabolised to phenylpropanolamine (p. 1674.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Ildamen; ***Philipp.***: Ildamen; ***Port.***: Ildamen.

Pamabrom *(USAN)*

Pamabromo.
2-Amino-2-methylpropan-1-ol 8-bromotheophyllinate.
$C_4H_{11}NO,C_7H_7BrN_4O_2$=348.2
CAS — 606-04-2.
UNII — UA8U0KJM72.

Pharmacopoeias. In *US*.

Profile

Pamabrom is a weak diuretic that has been used, with analgesics and antihistamines, for symptomatic relief of the premenstrual syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Diurex; ***USA***: Maximum Strength Aqua-Ban.

Multi-ingredient Preparations. ***Arg.***: Everfem; ***Canad.***: Extra Strength Multi-Symptom PMS Relief; Midol PMS; Multi-Symptom PMS Relief; Painaid PMF; Pamprin; Relievol PMS; Tylenol Menstrual; ***Chile***: Dolo-Esan Periodo Menstrual; Kitadol Periodo Menstrual; Minfaden; Panagesic Periodo Menstrual; Predual; Sentual Periodo; Tapsin Periodo Menstrual; Tapsin Periodo Premenstrual; ***China***: Ai Jia (艾佳); ***Malaysia***: Panadol Menstrual; ***Mex.***: Femsedin Kutz; ***Rus.***: Femizol (Фемизол); ***Singapore***: Panadol Menstrual; ***USA***: Lurline PMS; Midol Pre-Menstrual Syndrome; Midol Teen Formula; Painaid PMF Premenstrual Formula; Pamprin; Premsyn PMS; Womens Tylenol Multi-Symptom Menstrual Relief.

Pamiteplase *(rINN)*

Pamiteplasa; Pamitéplase; Pamiteplasum; YM-866; Памитеплаза.
275-L-Glutamic acid-(1–91)-(174–527)-plasminogen activator (human tissue-type protein moiety).
CAS — 151912-42-4.
UNII — KVX79QFV4W.

Profile

Pamiteplase is a thrombolytic related to alteplase (p. 1296.3) that has been used in acute myocardial infarction. It has been investigated in ischaemic stroke.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Solinase†.

Pantethine

Panteteina; Pantetina; Пантетин.
(*R*)-*NN*′-[Dithiobis(ethyleneiminocarbonylethylene)]bis(2,4-dihydroxy-3,3-dimethylbutyramide).
$C_{22}H_{42}N_4O_8S_2$=554.7
CAS — 16816-67-4.
ATC — A11HA32.
ATC Vet — QA11HA32.
UNII — 7K81IL792L.

NOTE. The names Dermorizin, Palfadin, Panholeata, Panpyotin, Parutox, and Youtetine have been used as trade marks for pantethine.

Pharmacopoeias. In *Jpn*.

Profile

Pantethine, a derivative of pantothenic acid (p. 2085.2), is a component of coenzyme A. It is used as a lipid regulating drug in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 0.6 to 1.2 g daily in divided doses.

Pantethine is also used as a nutritional supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Pantetina; ***Jpn***: Pantosin.

Parnaparin Sodium *(BAN, rINN)*

OP-21-23; Parnapariininatrium; Parnaparin-Natrium; Parnaparin sodná sůl; Parnaparin Sodyum; Parnaparina sódica; Parnaparine Sodique; Parnaparinnatrium; Parnaparinnátrium; Parnaparino natrio druska; Parnaparinum natricum; Парнапарин Натрий.
CAS — 9041-08-1.
ATC — B01AB07.
ATC Vet — QB01AB07.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Parnaparin Sodium). It is prepared by hydrogen peroxide and cupric salt depolymerisation of heparin obtained from the intestinal mucosa of pigs and cattle. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average molecular mass ranges between 4000 and 6000, with a characteristic value of about 5000. The mass percentage of chains lower than 3000 is not more than 30%. The degree of sulfation is 2.0 to 2.6 per disaccharide unit. Potency is not less than 75 units and not more than 110 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 3.0.

Profile

Parnaparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity used in the prevention of postoperative venous thromboembolism (p. 1274.1); it has also been used in other thromboembolic disorders. For general surgical procedures it is given by subcutaneous injection in a dose of 3200 units 2 hours before the procedure, followed by 3200 units once daily for 7 days or until the patient is fully ambulant. For higher risk or orthopaedic patients a dose of 4250 units is given 12 hours before the procedure, followed by 4250 units 12 hours postoperatively and then once daily for 10 days.

For treatment of thromboembolism a dose of 6400 units is given by subcutaneous injection twice daily for 7 to 10 days. This may be followed by a once-daily subcutaneous injection of 4250, 6400, or 8500 units for a further 10 to 20 days.

References.

1. Frampton JE, Faulds D. Parnaparin: a review of its pharmacology, and clinical application in the prevention and treatment of thromboembolic and other vascular disorders. *Drugs* 1994; **47:** 652–76.
2. McKeage K, Keating GM. Parnaparin: a review of its use in the management of venous thromboembolism, chronic venous disease and other vascular disorders. *Drugs* 2008; **68:** 105–22.

Inflammatory bowel disease. Oral parnaparin, formulated for colonic release, has been investigated[1,2] in the management of patients with mild to moderate ulcerative colitis (p. 1811.3). See also under Low-molecular-weight Heparins, p. 1426.2.

1. Pastorelli L, *et al*. Oral, colonic-release low-molecular-weight heparin: an initial open study of Parnaparin-MMX for the treatment of mild-to-moderate left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2008; **28:** 581–8.
2. Celasco G, *et al*. Clinical trial: oral colon-release parnaparin sodium tablets (CB-01-05 MMX) for active left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2010; **31:** 375–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fluxum (希弗全); ***Cz.***: Fluxum; ***Gr.***: Thromboparin; Tromboparin; ***Hung.***: Fluxum; ***India***: Fluxum; ***Indon.***: Fluxum; ***Ital.***: Fluxum; Zoltar; ***Mex.***: Fluxum; ***Pol.***: Fluxum†; ***Port.***: Fluxum; Tromboparin; ***Turk.***: Fluxum; ***Venez.***: Tromboparin.

Penbutolol Sulfate *(BANM, USAN, rINNM)* ⊗

Hoe-39-893d; Hoe-893d; Levopenbutolol Sulfate; Penbutolol Hemisulfate; Penbutolol sulfát; Penbutolol, Sulfate de; Penbutolol, sulfato de; Penbutolol Sulphate; Penbutololi sulfas; Penbutololio sulfatas; Penbutololisulfaatti; Penbutololsulfat; Penbutolol-szulfát; Sulfato de penbutolol; Пенбутолола Сульфат.
(*S*)-1-*tert*-Butylamino-3-(2-cyclopentylphenoxy)propan-2-ol hemisulfate.
$(C_{18}H_{29}NO_2)_2,H_2SO_4$=680.9
CAS — 38363-40-5 (penbutolol); 38363-32-5 (penbutolol sulfate).
ATC — C07AA23.
ATC Vet — QC07AA23.
UNII — U571433228.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Penbutolol Sulfate). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in cyclohexane; soluble in methyl alcohol. Protect from light.

USP 36: (Penbutolol Sulfate). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Penbutolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess some intrinsic sympathomimetic activity but lacks membrane-stabilising properties.

Penbutolol is used as the sulfate in the management of hypertension (p. 1251.1). It may also be used in cardiac disorders such as angina pectoris (p. 1254.3).

In **hypertension** penbutolol sulfate is given in an initial oral dose of 20 mg daily; the dose may be increased if necessary to 40 to 80 mg daily. Maximum antihypertensive efficacy is reported to occur within 2 weeks in patients given a dose of 20 mg daily but about 4 weeks may be required for maximum effect in patients given 10 mg daily.

Penbutolol sulfate has also been used in similar doses in cardiac disorders such as **angina**.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Penbutolol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 3 hours after a dose. Penbutolol is 80 to 98% bound to plasma proteins. It has a high lipid solubility. It is extensively metabolised in the liver by hydroxylation and glucuronidation, the metabolites being excreted in the urine with only small amounts of unchanged penbutolol. A plasma elimination half-life of about 20 hours has been reported.

Renal impairment. Glucuronidation was considered more prominent than hydroxylation in the metabolism of

penbutolol and its activity was not altered in patients with renal impairment.[1]

1. Bernard N, *et al.* Pharmacokinetics of penbutolol and its metabolites in renal insufficiency. *Eur J Clin Pharmacol* 1985; **29:** 215–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Betapressin; ***USA***: Levatol.

Multi-ingredient Preparations. ***Ger.***: Betarelix; Betasemid.

Pharmacopoeial Preparations
USP 36: Penbutolol Sulfate Tablets.

Pentaerithrityl Tetranitrate *(BAN, rINN)*

Erynite; Nitropentaerythrol; Nitropenthrite; Pentaérithrityle, Tétranitrate de; Pentaerithrityli Tetranitras; Pentaeritritilio tetranitratas; Pentaeritritilo, tetranitrato de; Pentaeritritol Tetranitrat; Pentaeritrit-tetranitrát; Pentaeritrityltetranitrat; Pentaeritrityylitetranitraatti; Pentaerythritol Tetranitrate; Pentaerythritolum Tetranitricum; Pentaerythrityl Tetranitrate; Pentaérythrityle, tétranitrate de; Pentaerythrityli Tetranitras; Pentaerythrityl-tetranitrát; Pentaerytrityltetranitrat; Pentaerytrityylitetranitraatti; Pentaerytrytylu tetraazotan; Pentanitrol; PETN; Tetranitrato de pentaeritritilo; Tetranitrato de pentaeritritol; Пентаэритритила Тетранитрат.

2,2-Bis(hydroxymethyl)propane-1,3-diol tetranitrate.

$C_5H_8N_4O_{12}$=316.1

CAS — 78-11-5.

ATC — C01DA05.

ATC Vet — QC01DA05.

UNII — 10L39TRG1Z.

NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.

Pharmacopoeias. *Chin.* and *Eur.* (see p. vii) include as diluted pentaerithrityl tetranitrate.

Ph. Eur. 8: (Pentaerithrityl Tetranitrate, Diluted). A mixture of pentaerithrityl tetranitrate with lactose monohydrate or mannitol. Its solubility depends on the diluent and its concentration. Protect from light and heat.

Undiluted pentaerithrityl tetranitrate is a white or slightly yellowish powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone.

Handling. Undiluted pentaerithrityl tetranitrate can be exploded by percussion or excessive heat.

Profile

Pentaerithrityl tetranitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p. 1393.3) but its duration of action is more prolonged.

It is used in angina pectoris (p. 1254.3) in typical oral doses of 50 mg two or three times daily before food, although higher doses have been given. An oral modified-release preparation, given in a dose of 80 mg twice daily, is available in some countries.

Pentaerithrityl trinitrate, an active metabolite of pentaerithrityl tetranitrate, has also been used clinically under the name pentrinitrol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Pentalong; ***Ger.***: Nirason N†; Pentalong†; ***Hung.***: Nitropenton†; ***India***: Peritrate; ***Ital.***: Peritrate; ***Pol.***: Galpent; ***Rus.***: Erynit (Эринит); ***Thai.***: Peritrate; ***Turk.***: Danitrin†.

Multi-ingredient Preparations. ***Chile***: Cardiosedantol; ***Pol.***: Pentaerythritol Compositum; ***Turk.***: Danitrin Fort.

Pentosan Polysulfate Sodium

(BAN, USAN, rINN)

Natrii pentosani polusulfas; Natrii Pentosani Polysulfas; Natriumpentosaanipolysulfaatti; Natriumpentosanpolysulfat; Pentosan Polysulphate Sodium; Pentosane Polysulfate Sodique; Pentosano polisulfato de sodio; PZ-68; Sodium Pentosan Polysulphate; Sodium Xylanpolysulphate; SP-54; Натрия Пентозана Полисульфат.

CAS — 37319-17-8; 116001-96-8.

ATC — C05BA04.

ATC Vet — QC05BA04.

UNII — 914032762Y.

Description. Pentosan polysulfate sodium is a mixture of linear polymers of β-1→4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally (about 1 in every 4 residues) substituted at the 2-position with 4-*O*-methyl-α-D-glucuronic acid 2,3-*O*-sulfate. The average molecular weight lies between 4000 and 6000 with a total molecular weight range of 1000 to 40 000.

Uses and Administration

Pentosan polysulfate sodium is a heparinoid with anticoagulant and fibrinolytic properties; it may also have hypolipidaemic and anti-inflammatory effects. It has been used in thromboembolic disorders, although its anticoagulant effect is less than that of heparin. It is also used in the management of interstitial cystitis (see below) and has been tried in several other conditions, including variant Creutzfeldt-Jakob disease (see below). Pentosan polysulfate sodium has been used orally, parenterally, and topically. It has also been used in veterinary medicine.

In the management of interstitial cystitis, pentosan polysulfate sodium is given orally in a dose of 100 mg three times daily.

Cystitis. Pentosan polysulfate sodium has been used orally in inflammatory conditions of the bladder, including interstitial cystitis (p. 2348.1) and is thought to act by enhancing the protective effect of mucins at the bladder surface.[1] Studies have differed concerning its efficacy in the treatment of interstitial cystitis and an analysis[2] of controlled studies concluded that pentosan polysulfate sodium was more effective than placebo in treating pain, urgency, and frequency, but that the difference was small. Any benefit is usually apparent within 3 to 6 months and only occurs in a minority of patients.[3] Pentosan polysulfate sodium was reported[4] to have minimal long-term efficacy in a group of patients with severe or refractory interstitial cystitis.

A combination of oral and intravesical treatment with the drug has been tried in some patients.[5]

Pentosan polysulfate sodium has also been reported[6-8] to be useful in the control of radiation-induced haemorrhagic cystitis (p. 2347.3).

1. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* 2006; **66:** 821–35.
2. Hwang P, *et al.* Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology* 1997; **50:** 39–43.
3. Anonymous. Pentosan for interstitial cystitis. *Med Lett Drugs Ther* 1997; **39:** 56.
4. Jepsen JV, *et al.* Long-term experience with pentosanpolysulfate in interstitial cystitis. *Urology* 1998; **51:** 381–7.
5. Davis EL, *et al.* Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. *J Urol (Baltimore)* 2008; **179:** 177–85.
6. Parsons CL. Successful management of radiation cystitis with sodium pentosanpolysulfate. *J Urol (Baltimore)* 1986; **136:** 813–14.
7. Hampson SJ, Woodhouse CRJ. Sodium pentosanpolysulphate in the management of haemorrhagic cystitis: experience with 14 patients. *Eur Urol* 1994; **25:** 40–2.
8. Sandhu SS, *et al.* The management of haemorrhagic cystitis with sodium pentosan polysulphate. *BJU Int* 2004; **94:** 845–7.

Prostatitis. Pentosan polysulfate sodium is one of several drugs that have been tried in the management of prostatitis (p. 2350.2). An improvement in symptoms was reported[1] in an uncontrolled study of oral pentosan polysulfate sodium in men with chronic prostatitis/chronic pelvic pain syndrome. A randomised study[2] using pentosan polysulfate sodium 300 mg three times daily found that symptoms were moderately or markedly improved at the end of the 16-week treatment period in more members of the active treatment group than in the group given placebo.

1. Nickel JC, *et al.* Pentosan polysulfate therapy for chronic nonbacterial prostatitis (chronic pelvic pain syndrome category IIIA): a prospective multicenter clinical trial. *Urology* 2000; **56:** 413–17.
2. Nickel JC, *et al.* Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol (Baltimore)* 2005; **173:** 1252–5.

Variant Creutzfeldt-Jakob disease. Variant Creutzfeldt-Jakob disease (vCJD) is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. Pentosan polysulfate sodium has been tried in small numbers of patients with vCJD, although there is little published research data. In 2003 the UK Department of Health[1] took advice from the CJD Therapy Advisory Group and the CSM; both groups considered that there was insufficient information on which to base prescribing regimens, and further work was needed.

1. UK DoH. Use of pentosan polysulphate in the treatment of, or prevention of, vCJD. Available at: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publichealth/Communicablediseases/CJD/CJDgeneralinformation/DH_4031039 (accessed 03/08/10)

Adverse Effects and Precautions

As for Heparin, p. 1398.3. Gastrointestinal disturbances may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Elmiron; ***Austria***: Polyanion†; ***Canad.***: Elmiron; ***Fr.***: Hemoclar; ***Ger.***: Fibrezym; ***Hong Kong***: Elmiron; ***Hung.***: SP 54; ***Ital.***: Fibrase; ***Malaysia***: SP 54; ***Port.***: Fibrocide; ***S.Afr.***: Tavan-SP 54; ***Spain***: Thrombocid; ***Ukr.***: Thrombocid (Тромбоцид); ***USA***: Elmiron.

Multi-ingredient Preparations. ***Austria***: Thrombocid; ***Cz.***: Thrombocid; ***Ger.***: Thrombocid; Thrombocid; ***Hong Kong***: Anso; Thrombocid; ***Port.***: Thrombocid; Thrombocid; ***Spain***: Anso.

Pentoxifylline *(BAN, USAN, rINN)*

BL-191; Okspentifilin; Oxpentifilina; Oxpentifylline; Pentoksifilin; Pentoksifilinas; Pentoksifylliini; Pentoxifilina; Pentoxifillin; Pentoxifylin; Pentoxyfyllin; Pentoxifyllinum; Пентоксифиллин.

3,7-Dimethyl-1-(5-oxohexyl)xanthine.

$C_{13}H_{18}N_4O_3$=278.3

CAS — 6493-05-6.

ATC — C04AD03.

ATC Vet — QC04AD03.

UNII — SD6QCT3TSU.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Pentoxifylline). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Pentoxifylline). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform and in methyl alcohol; slightly soluble in ether.

Uses and Administration

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disorders (p. 1272.3). Although often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation. It is reported to increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid; it has been used in cerebrovascular disorders. Pentoxifylline also inhibits production of the cytokine TNFα, and this property is under investigation in several diseases (see below).

In the treatment of peripheral vascular disease the usual oral dose is 400 mg three times daily in a modified-release formulation; this may be reduced to 400 mg twice daily for maintenance or if adverse effects are troublesome. Doses should be taken with meals to reduce gastrointestinal disturbances. In severe hepatic or renal impairment, doses may need to be reduced (see below). Beneficial effects may not be evident until after 2 to 8 weeks of treatment. Pentoxifylline may also be given parenterally.

General references.

1. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokineticproperties, and its therapeutic efficacy. *Drugs* 1987; **34:** 50–97.
2. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; **30:** 603–21.

Administration in hepatic and renal impairment. The elimination half-life of pentoxifylline and its metabolites is significantly prolonged in patients with hepatic cirrhosis,[1] and some metabolites have a prolonged half-life in renal impairment.[2] UK licensed product information states that in patients with severely impaired hepatic function the dose of pentoxifylline may need to be reduced, while accumulation may occur in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) who receive more than 400 mg once or twice daily.

References.

1. Rames A, *et al.* Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47:** 354–9.
2. Paap CM, *et al.* Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30:** 724–9.

Inhibition of TNFα. Pentoxifylline inhibits production of TNFα, a cytokine that is implicated in the pathogenesis of many diseases, and investigative work with pentoxifylline is being, or has been, carried out in many such disorders. Studies have been performed in patients with alcoholic hepatitis,[1-3] cardiomyopathy,[4] cerebral malaria[5,6] diabetic nephropathy,[7,8] and retinopathy,[9] endometriosis,[10] leishmaniasis,[11,12] leprosy,[13,14] membranous nephropathy,[15] radiation-induced damage,[16-19] severe sepsis or septic shock,[20] recurrent aphthous stomatitis,[21-23] and various vasculitic syndromes, including Behçet's syndrome.[24] Pen-

toxifylline has also been tried for improving graft survival in kidney transplantation.[25,26] For mention of a possible benefit in sarcoidosis, see p. 1612.2. Although promising results have been reported in some of these studies, the place of pentoxifylline in the overall management of these disorders remains to be established.

1. Akriviadis E, *et al*. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119:** 1637–48.
2. De BK, *et al*. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. *World J Gastroenterol* 2009; **15:** 1613–19.
3. Whitfield K, *et al*. Pentoxifylline for alcoholic hepatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 14/06/10).
4. Skudicky D, *et al*. Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. *Circulation* 2001; **103:** 1083–8.
5. Di Perri, *et al*. Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis* 1995; **171:** 1317–22.
6. Looareesuwan S, *et al*. Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand. *Am J Trop Med Hyg* 1998; **58:** 348–53.
7. Navarro JF, *et al*. Urinary protein excretion and serum tumor necrosis factor in diabetic patients with advanced renal failure: effects of pentoxifylline administration. *Am J Kidney Dis* 1999; **33:** 458–63.
8. McCormick BB, *et al*. The effect of pentoxifylline on proteinuria in diabetic kidney disease: a meta-analysis. *Am J Kidney Dis* 2008; **52:** 454–63.
9. Lopes de Jesus CC, *et al*. Pentoxifylline for diabetic retinopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/10/09).
10. Lv D, *et al*. Pentoxifylline versus medical therapies for subfertile women with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 10/09/09).
11. Lessa HA, *et al*. Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *Am J Trop Med Hyg* 2001; **65:** 87–9.
12. Machado PRL, *et al*. Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clin Infect Dis* 2007; **44:** 788–93.
13. Nery JAC, *et al*. The use of pentoxifylline in the treatment of type 2 reactional episodes in leprosy. *Indian J Lepr* 2000; **72:** 457–67.
14. Dawlah ZM, *et al*. A phase 2 open trial of pentoxifylline for the treatment of leprosy reactions. *Int J Lepr Other Mycobact Dis* 2002; **70:** 38–43.
15. Ducloux D, *et al*. Use of pentoxifylline in membranous nephropathy. *Lancet* 2001; **357:** 1672–3.
16. Okunieff P, *et al*. Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol* 2004; **22:** 2207–13.
17. Chiao TB, Lee AJ. Role of pentoxifylline and vitamin E in attenuation of radiation-induced fibrosis. *Ann Pharmacother* 2005; **39:** 516–22.
18. Delanian S, *et al*. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005; **23:** 8570–9.
19. Misirlioglu CH, *et al*. Pentoxifylline and alpha-tocopherol in prevention of radiation-induced lung toxicity in patients with lung cancer. *Med Oncol* 2007; **24:** 308–11.
20. Staubach K-H, *et al*. Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. *Arch Surg* 1998; **133:** 94–100.
21. Pizarro A, *et al*. Treatment of recurrent aphthous stomatitis with pentoxifylline. *Br J Dermatol* 1995; **133:** 659–60.
22. Chandrasekhar J, *et al*. Oxypentifylline in the management of recurrent aphthous oral ulcers: an open clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87:** 564–7.
23. Thornhill MH, *et al*. A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007; **143:** 463–70.
24. Hisamatsu T, *et al*. Combination therapy including pentoxifylline for entero-Behçet's disease. *Bull Tokyo Dent Coll* 2001; **42:** 169–76.
25. Noel C, *et al*. Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor α and adhesion molecules. *Transplantation* 2000; **69:** 1102–7.
26. Shu K-H, *et al*. Effect of pentoxifylline on graft function of renal transplant recipients complicated with chronic allograft nephropathy. *Clin Nephrol* 2007; **67:** 157–63.

Venous leg ulcers. A systematic review[1] of pentoxifylline used in the treatment of venous leg ulcers (p. 1690.1) concluded that it was an effective adjunct to compression bandaging, and may be effective alone.

1. Jull AB, *et al*. Pentoxifylline for treating venous leg ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 08/05/08).

Adverse Effects

Pentoxifylline can cause nausea, gastrointestinal disturbances, dizziness, and headache. Flushing, angina, palpitations, cardiac arrhythmias, and hypersensitivity reactions, including urticaria, rash, and anaphylactic reactions, may also occur. Bleeding events have been reported rarely, usually in association with bleeding risk factors.

Overdosage with pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, and seizures.

Haemorrhage. Three major bleeding episodes including 2 fatal cerebral haemorrhages were reported in a group of patients taking pentoxifylline 400 mg three times daily with acenocoumarol for intermittent claudication.[1] Gastrointestinal bleeding occurred in a 67-year-old patient with a history of duodenal ulcer after a single dose of pentoxifylline for optic neuropathy.[2]

1. APIC Study Group. Acenocoumarol and pentoxifylline in intermittent claudication: a controlled clinical study. *Angiology* 1989; **40:** 237–48.
2. Oren R, *et al*. Pentoxifylline-induced gastrointestinal bleeding. *DICP Ann Pharmacother* 1991; **25:** 315–16.

Overdosage. A 22-year-old woman who took pentoxifylline 4 to 6 g with suicidal intent developed severe bradycardia and first- and second-degree AV block; other effects included nausea, vomiting, abdominal cramps, hypokalaemia, excitation, and insomnia.[1] She recovered after intensive supportive and symptomatic therapy.

1. Sznajder IJ, *et al*. First and second degree atrioventricular block in oxpentifylline overdose. *BMJ* 1984; **288:** 26.

Precautions

Pentoxifylline should be avoided in cerebral haemorrhage, extensive retinal haemorrhage, severe cardiac arrhythmias, and acute myocardial infarction. It should be used with caution in patients with ischaemic heart disease or hypotension. The dose of pentoxifylline may need to be reduced in patients with hepatic or renal impairment (see under Uses and Administration, p. 1465.3).

Interactions

Pentoxifylline may potentiate the effect of antihypertensives. High parenteral doses of pentoxifylline may enhance the action of insulin and oral hypoglycaemics in diabetic patients. Pentoxifylline should not be given with ketorolac as there is reported to be an increased risk of bleeding and/or prolongation of the prothrombin time. There may also be an increased risk of bleeding during use with meloxicam. Serum levels of theophylline may be raised by pentoxifylline.

Cimetidine. A pharmacokinetic study in healthy subjects reported increased average steady-state plasma concentrations of pentoxifylline when given with cimetidine. The clinical relevance of the interaction was not known, but adverse effects such as headache, nausea, and vomiting were reported more often with the combination than with pentoxifylline alone.[1]

1. Mauro VF, *et al*. Alteration of pentoxifylline pharmacokinetics by cimetidine. *J Clin Pharmacol* 1988; **28:** 649–54.

Pharmacokinetics

Pentoxifylline is readily absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Some metabolites are active. The apparent plasma half-life of pentoxifylline is reported to be 0.4 to 0.8 hours; that of the metabolites varies from 1.0 to 1.6 hours. In 24 hours most of a dose is excreted in the urine, mainly as metabolites, and less than 4% is recovered in the faeces. Elimination of pentoxifylline is decreased in elderly patients and patients with hepatic disease. Pentoxifylline and its metabolites are distributed into breast milk.

References.

1. Beermann B, *et al*. Kinetics of intravenous and oral pentoxifylline in healthy subjects. *Clin Pharmacol Ther* 1985; **37:** 25–8.
2. Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. *Am J Obstet Gynecol* 1985; **151:** 1094–7.
3. Smith RV, *et al*. Pharmacokinetics of orally administered pentoxifylline in humans. *J Pharm Sci* 1986; **75:** 47–52.
4. Rames A, *et al*. Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47:** 354–9.
5. Paap CM, *et al*. Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30:** 724–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dospan Pento; Pentolab; Previscan; Tamixol; Trental; ***Austral.***: Trental; ***Austria***: Haemodyn†; Pentohexal; Pentomer; Pentoxi; Pentoximed†; Trental; Vasonit; ***Belg.***: Torental; ***Braz.***: Arteron; Pentalox; Pentox; Pentoxin; Pentral; Pentrat; Peripan†; Prodoxifilina†; Trentafilina; Trental; Trentofil; Vascer; ***Canad.***: Trental; ***Chile***: Trental; ***China***: An Ruo Ning (安若宁); Ao Le Ni (澳乐尼); Ao Nuo Hong (奥诺红); Aotong (奥酮); Bo Shu Te (博舒特); Chang Long Lei (长龙雷); DanKe (丹可); De Bao Xing (德宝星); De Luo Wei (德洛威); Dian Ke Shu (点可舒); Fei Ke Wei Kang (菲克维康); Fu Shu (福枢); Gan Feng (甘风); Jia Li Bo (嘉立博); Ka Kai (卡开); Ni Fu Ping (尼扶平); Pan Duo Xi Lai (潘多喜莱); Pan Ke Fu Lin (潘可福林); Pentomer (瑞潘通); Qi Ming (奇铭); Qiquan (奇全); Run Xin Shu (润心舒); Shu An Ling (舒安灵); Shu Fu Luo (舒芙罗); Shuang Ke (双可); Tai Tong (太通); Tian Cun (天存); Tian Mai (天脉); Wei You (维友); Xi Shu Tong (喜舒同); Xiang Di (祥迪); Xin Ke Duo Na (欣可多那); Xinfu (辛弗); YiShu (益枢); ***Cz.***: Agapurin; Pentilin†; Pentomer; Trental; Vasonit; ***Denm.***: Elorgan; Trental; ***Fin.***: Artal†; Pentoxin; Trental; ***Fr.***: Pentoflux; Torental†; ***Ger.***: Agapurin†; Claudicat; Pento-Puren†; Pentohexal†; Pentox†; Ralofekt†; Rentylin; Trental; ***Gr.***: Razylfin; Tarontal; ***Hong Kong***: Pentong†; Trenlin; Trental; ***Hung.***: Chinotal; Pentoxyl-EP; Trental; ***India***: Flexital; Kinetal; Trental; ***Indon.***: Erytral†; Lentrin; Pentoxifillene†; Platof; Reotal; Tarontal; Tioxad; Trenat; Trenfyl; Trental; Trentox; Trenxy; ***Irl.***: Trental†; ***Israel***: Oxopurin; Trental; ***Ital.***: Behrifil; Trental; ***Malaysia***: Trenlin; Trental; ***Mex.***: Artelife; Eurotofi; Fixoten; Kentadin; Pensiral; Peridane; Profiben; Sinsufyva; Sufisal; Tecxifil; Trental; Vantoxyl; Vasofyl; Vaxolem†; Xinsol†; Xipen; ***Neth.***: Trental; ***Norw.***: Trental; ***NZ***: Trental; ***Philipp.***: C-Vex; Pentox; Pentoxal; Toxipen; Trental; ***Pol.***: Agapurin; Apo-Pentox; Dartelin†; Pentilin†; Pentohexal; Polfilin; Trental; ***Port.***: Claudicat; Trental; ***Rus.***: Agapurin (Агапурин); Flexital (Флекситал); Mellinorm (Меллинорм)†; Pentilin (Пентилин); Trenpental (Тренпентал); Trental (Трентал 400); Vasonit (Вазонит); ***S.Afr.***: Trental†; ***Singapore***: Trenlin; Trental; ***Spain***: Elorgan; Hemovas; Nelorpin; Retimax†; ***Switz.***: Pentoxi; Trental†; ***Thai.***: Agapurin†; Cerator; Ceretal; Elastab†; Flexital; Penlol†; Pentiline; Sipental; Trental; Trepal; ***Turk.***: Hemopene; Penfixteva; Pentox; Trental; Trentilin; Vasoplan; ***UK***: Neotren†; Pentofin†; Trental; ***Ukr.***: Latren (Латрен); Trental (Трентал); ***USA***: Trental; ***Venez.***: Agapurin; Trental.

Multi-ingredient Preparations. ***Arg.***: Ikatral Periferico.

Pharmacopoeial Preparations

USP 36: Pentoxifylline Extended-Release Tablets; Pentoxifylline Oral Suspension.

Perhexiline Maleate *(BANM, USAN, rINNM)*

Maleato de perhexilina; Perhexilina, maleato de; Perhexiline, Maléate de; Perhexilini Maleas; WSM-3978G; Пергексиллина Малеат.

2-(2,2-Dicyclohexylethyl)piperidine hydrogen maleate.

$C_{19}H_{35}N,C_4H_4O_4$=393.6

CAS — 6621-47-2 (perhexiline); 6724-53-4 (perhexiline maleate).

ATC — C08EX02.

ATC Vet — QC08EX02.

UNII — K7V8Y90G0H.

Profile

Perhexiline maleate may be used in the long-term management of severe angina pectoris (p. 1254.3) in patients who have not responded to other anti-anginal drugs. Its mode of action is complex.

The usual initial oral dose is 100 mg daily, subsequently either increased or decreased, as necessary, at intervals of 2 to 4 weeks; it is generally recommended not to give more than 300 mg daily although doses of 400 mg daily have been necessary in some patients. The maintenance of plasma-perhexiline concentrations between 150 and 600 nanograms/mL has been recommended.

Perhexiline occasionally produces severe adverse effects including peripheral neuropathy affecting all four limbs with associated papilloedema, severe and occasionally fatal hepatotoxicity, and metabolic abnormalities with marked weight loss, hypertriglyceridaemia, and profound hypoglycaemia. It is contra-indicated in patients with hepatic or renal impairment. Perhexiline should be used with caution in diabetic patients. Hepatic metabolism of perhexiline is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore caution is advised if perhexiline is used with other drugs that inhibit or are metabolised by this enzyme, and perhexiline toxicity has been reported with SSRIs such as fluoxetine or paroxetine.

References.

1. Killalea SM, Krum H. Systematic review of the efficacy and safety of perhexiline in the treatment of ischemic heart disease. *Am J Cardiovasc Drugs* 2001; **1:** 193–204.
2. Ashrafian H, *et al*. Perhexiline. *Cardiovasc Drug Rev* 2007; **25:** 76–97.
3. Phan TT, *et al*. Multi-centre experience on the use of perhexiline in chronic heart failure and refractory angina: old drug, new hope. *Eur J Heart Fail* 2009; **11:** 881–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Pexsig; ***NZ***: Pexsig.

Perindopril *(BAN, USAN, rINN)*

McN-A-2833; Perindopriili; Périndopril; Perindoprilum; S-9490; Периндоприл.

(2*S*,3a*S*,7a*S*)-1-[*N*-[(*S*)-1-Ethoxycarbonylbutyl]-L-alanyl]perhydroindole-2-carboxylic acid.

$C_{19}H_{32}N_2O_5$=368.5

CAS — 82834-16-0.

ATC — C09AA04.

ATC Vet — QC09AA04.

UNII — Y5GMK36KGY.

Perindopril Arginine *(BANM, rINNM)*

Perindopril arginina; Périndopril Arginine; Perindoprilum Argininum; Периндоприл Аргинин.

CAS — 612548-45-5.

ATC — C09AA04.

ATC Vet — QC09AA04.

UNII — TFT5IM1KGB.

Perindopril Erbumine *(BANM, USAN, rINNM)*

Butylamini Perindoprilum; Butylamin-perindopril; Erbumina de perindopril; McN-A-2833-109; Perindopriili-*tert*-butyyliamiini; Perindopril, erbumina de; Périndopril, Erbumine de; Perindopril Terbutalamin; Perindopril *tert*-Butylamine; Périndopril tert-butylamine; Perindopril-erbumin; Perindoprili Erbuminum; Perindopril-*tert*-butylamin; Perindoprilum Erbuminum; Peryndopryl z tert-butyloaminą; S-9490-3; tert-Butylamini perindoprilum; *tert*-Butilamino perindoprilis; *Tert*-Butylamini Perindoprilum; Периндоприла Эрбумин.

$C_{19}H_{32}N_2O_5,C_4H_{11}N$=441.6

CAS — 107133-36-8.

ATC — C09AA04.

ATC Vet — QC09AA04.

UNII — 1964X464OJ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Perindopril *tert*-Butylamine; Perindopril Erbumine BP 2014). A white or almost white, slightly hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water and in alcohol; soluble or sparingly soluble in dichloromethane. Store in airtight containers.

Uses and Administration

Perindopril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3). It is also used to reduce the risk of cardiovascular events in patients with stable ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1).

Perindopril is converted in the body into its active metabolite perindoprilat. ACE inhibition is reported to occur within 1 hour of a dose, to be at a maximum at about 4 to 8 hours, and to be maintained for 24 hours. Perindopril is given orally as the erbumine or arginine salts; 5 mg of perindopril arginine is equivalent to about 4 mg of perindopril erbumine.

In the treatment of **hypertension** perindopril is given in an initial dose of 4 mg of the erbumine or 5 mg of the arginine salt once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. However, licensed product information for perindopril recommends that doses should be taken in the morning, before food. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and in such patients the initial dose may be halved to 2 or 2.5 mg respectively once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before perindopril is started and resumed later if required; if this is not possible, the initial dose may be halved similarly. The same lower initial dose may also be used in the elderly. The dose of perindopril may be increased after 1 month according to response to a maximum of 8 mg of the erbumine or 10 mg of the arginine salt daily. In the USA a maximum dose of 16 mg of perindopril erbumine daily is allowed in uncomplicated hypertension.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Perindopril is given in an initial dose of 2 mg of the erbumine or 2.5 mg of the arginine salt once daily in the morning, increased after at least 2 weeks to a usual maintenance dose of 4 mg or 5 mg respectively once daily.

In the management of patients with **ischaemic heart disease** perindopril is given in an initial dose of 4 mg (erbumine) or 5 mg (arginine) once daily for 2 weeks, then titrated up to a maintenance dose of 8 or 10 mg respectively once daily if tolerated. Elderly patients should be started on 2 or 2.5 mg once daily for the first week.

Dosage should be reduced in patients with impaired renal function (see below).

References.

1. Todd PA, Fitton A. Perindopril: a review of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1991; **42:** 90–114.
2. Doyle AE, ed. Angiotensin-converting enzyme (ACE) inhibition: benefits beyond blood pressure control. *Am J Med* 1992; **92** (suppl 4B): 1S–107S.
3. Hurst M, Jarvis B. Perindopril: an updated review of its use in hypertension. *Drugs* 2001; **61** 867–96.
4. Simpson D, *et al*. Perindopril: in congestive heart failure. *Drugs* 2002; **62:** 1367–77.
5. Curran MP, *et al*. Perindopril: a review of its use in patients with or at risk of developing coronary artery disease. *Drugs* 2006; **66:** 235–55.
6. Telejko E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. *Curr Med Res Opin* 2007; **23:** 953–60.
7. Snyman JR, Wessels F. Perindopril: do randomised, controlled trials support an ACE inhibitor class effect? A meta-analysis of clinical trials. *Cardiovasc J Afr* 2009; **20:** 127–34.

Administration in renal impairment. The dose of perindopril should be reduced in patients with renal impairment. UK licensed product information recommends the following doses:

- creatinine clearance (CC) between 30 and 60 mL/minute: 2 mg of the erbumine or 2.5 mg of the arginine salt daily
- CC between 15 and 30 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on alternate days
- CC less than 15 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on dialysis days.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

In a postmarketing surveillance study[1] of 47 351 patients receiving perindopril for hypertension, no unexpected adverse effects were reported and serious reactions were rare; 1587 (6.3%) women and 782 (3.5%) men withdrew from therapy due to adverse effects.

Although a study[2] of perindopril use in patients with stable chronic heart failure reported no significant first-dose hypotension, there has been a case report[3] of ischaemic stroke, possibly associated with hypotension, after a single dose of perindopril in a patient with post-infarction heart failure. Standard precautions as for other ACE inhibitors (p. 1287.2) should be followed when starting perindopril therapy.

1. Speirs C, *et al*. Perindopril postmarketing surveillance: a 12 month study in 47 351 hypertensive patients. *Br J Clin Pharmacol* 1998; **46:** 63–70.
2. MacFadyen RJ, *et al*. Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J* 1991; **66:** 206–11.
3. Bagger JP. Adverse event with first-dose perindopril in congestive heart failure. *Lancet* 1997; **349:** 1671–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies perindopril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Perindopril acts as a prodrug of the diacid perindoprilat, its active form. After oral doses perindopril is rapidly absorbed with a bioavailability of about 65 to 75%. It is extensively metabolised, mainly in the liver, to perindoprilat and inactive metabolites including glucuronides. The presence of food is reported to reduce the conversion of perindopril to perindoprilat. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10 to 20% bound to plasma proteins. Perindopril is excreted mainly in the urine, as unchanged drug, as perindoprilat, and as other metabolites. The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of 25 to 30 hours or longer, the latter half-life probably representing strong binding to angiotensin-converting enzyme. The excretion of perindoprilat is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

References.

1. Lecocq B, *et al*. Influence of food on the pharmacokinetics of perindopril and the time course of angiotensin-converting enzyme inhibition in serum. *Clin Pharmacol Ther* 1990; **47:** 397–402.
2. Verpooten GA, *et al*. Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency. *Br J Clin Pharmacol* 1991; **32:** 187–92.
3. Sennesael J, *et al*. The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure. *Br J Clin Pharmacol* 1992; **33:** 93–9.
4. Thiollet M, *et al*. The pharmacokinetics of perindopril in patients with liver cirrhosis. *Br J Clin Pharmacol* 1992; **33:** 326–8.
5. Guérin A, *et al*. The effect of haemodialysis on the pharmacokinetics of perindoprilat after long-term perindopril. *Eur J Clin Pharmacol* 1993; **44:** 183–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Coverene; ***Austral.***: Coversyl; Indopril; Perindo; ***Austria***: Coversum; ***Belg.***: Coversyl; Perindocyl; ***Braz.***: Coversyl; Pericor; ***Canad.***: Coversyl; ***Chile***: Coversyl; ***China***: Acertil (雅施达); ***Cz.***: Apo-Perindo; Cordesyl†; Covedaspen†; Covemarin†; Covemedal†; Covepet†; Coverdosyn†; Coverdyne†; Coverex; Coversidin†; Coversyspes†; Covethanar†; Domanion; Gleperil; Pamonova; Perinalon; Pinbarix; Prenessa; Prestarium Neo; Prestarium; Prexanil†; Pricoron; Valperal; Vidotin; ***Denm.***: Asyntilsan†; Coversyl Arginine; Coversyl Novum; Mariper; Percarnil; Perineva; Prenessa†; Prestarium; Prillana; Rinder; Tanipril†; ***Fin.***: Acertil; Coveram; Coversyl; ***Fr.***: Coversyl; ***Ger.***: Coversum; ***Gr.***: Coversyl; ***Hong Kong***: Acertil; Provinace; ***Hung.***: Armix; Coverex; Levenor; Perindan†; Perineva; Prenessa; Ranbapril; Vidotin; ***India***: Coversyl; Eviper; Perigard; ***Indon.***: Bioprexum; Prexum†; ***Irl.***: Coversyl; Pendrex; Percarnil; Perisom; Prindace; Prindex; Rinoprex; Tevaryl†; ***Ital.***: Coversyl; Procaptan; Romapal; ***Jpn***: Coversyl; ***Malaysia***: Covapril; Coversyl; Covinace; Perigard; Perinace; Provinace; ***Mex.***: Coversyl; ***Neth.***: Coversyl; Permetor†; Prilanil†; ***NZ***: Coversyl; ***Philipp.***: Coversyl; Hypergo; Novaril; Perigard; ***Pol.***: Apo-Perindox; Coverex†; Irpax; Lextril; Perindoran; Prenessa; Prestarium; Stopress; Vidotin; ***Port.***: Coversyl; Ostion†; Prexum†; Ripax; Tensoliber; ***Rus.***: Arentopres (Арентопрес); Coverex (Коверекс); Gypernik (Гипернik); Parnavel (Парнавел); Perineva (Перинева); Perinpress (Перинпресс); Prenessa (Пренесса); Prestarium (Престариум); ***S.Afr.***: Acesyl; Acti-Prex; Bindace; Ciplasyl; Coversyl; Pearinda; Prexum; Vectoryl; ***Singapore***: Coversyl; Perinace; ***Spain***: Coversyl; ***Swed.***: Coversyl Novum; ***Switz.***: Coversum; ***Thai.***: Coversyl; Covrix; ***Turk.***: Coversyl; Serperil; ***UK***: Coversyl; ***Ukr.***: Prenesa (Пренеса); Prestarium (Престариум); ***USA***: Aceon; ***Venez.***: Coversyl.

Multi-ingredient Preparations. ***Arg.***: Bipreterax†; Preterax; ***Austral.***: Coveram; Coversyl Plus; Dopriladmide; Perindo Combi; Reaptan; ***Austria***: Preterax; ***Belg.***: Bi Preterax†; Coperindo; Coveram; Coversyl Plus; Preterax; ***Braz.***: Coversyl Plus; ***Canad.***: Coversyl Plus; Preterax†; ***China***: Biprel (百普乐); ***Cz.***: Coverex Combi; Noliprel; Noliterax; Pamocombi; Parateraх; Perinpa; Prenewel; Prestance; Prestarium Combi; Prestarium Neo Combi; ***Denm.***: Coprenessa; Coprindomid†; Coversical; Coversyl Arginine Plus; Coversyl Comp Novum; Domanion Comp†; Parateraх; Tertensif kombi; ***Fin.***: Acertil Comp; Coprenessa; Coversyl Comp; Noliteraх; Reaptan; Teraxans; ***Fr.***: Bipreterax; Coveram; Parateraх; Preterax; ***Ger.***: Bipreterax; Coversum Combi†; Preterax; ***Gr.***: Coveram; Pediur; Preterax; ***Hong Kong***: Acertil Plus; Predonium; ***Hung.***: Armix Komb; Armix Prekomb; Co-Perineva; Co-Prenessa; Covercard; Coverex Komb; Coverex Prekomb†; Pretanix Komb; ***India***: Adpace; Coversyl Plus; Coversyl-AM; Eviper-D; Perigard-DF; ***Indon.***: Bioprexum Plus; Coveram; ***Irl.***: Acerycal; Bipreteraх; Coversyl Plus; Pendrex Plus; Preterax; Prindavam; Reaptan; Teraxans; ***Ital.***: Coverlam; Prelectal; Preterax; Reaptan; ***Malaysia***: Coveram; Coversyl Plus; ***Mex.***: Preterax; ***Neth.***: Comaranil; Coveram; Coversyl Plus; Noliterax; Predonium†; Preterax; Preterian; ***NZ***: Coversyl Plus; Predonium; ***Philipp.***: Bi-Preterax; Coveram; Coversyl Plus; Preterax; ***Pol.***: Co-Prenessa; Co-Prestarium; Noliprel; Prestarium Plus†; Tertensif Bi-Kombi; Tertensif Kombi; ***Port.***: Bi Predonium; Bi Preterax; Coveram; Imprex; Mixanval; Predonium; Preterax; Prilpa; Tecazo; ***Rus.***: Noliprel (Нолипрел); Noliprel A (Нолипрел А); Prestance (Престанс); ***S. Afr.***: Acesyl Co; Bipreterax†; Coversyl Plus; Pearinda Plus; Preterax; Prexum Plus; Vectoryl Plus; ***Singapore***: Coveram; Coversyl Plus; Preterax†; ***Spain***: Bipreterax; Preterax; ***Switz.***: Coveram; Coversum Combi; Preterax†; ***Thai.***: Coveram; Coversyl Plus; ***Turk.***: Bipreterax; Calversum; Coversyl Plus; Perivel Plus; Preterax; Serperil Plus; ***UK***: Coversyl Plus; ***Ukr.***: Bi-Prestarium (Би-Престариум); Co-Prenesa (Ко-Пренеса); Noliprel (Нолипрел); Prestarium Combi (Престариум Комби); ***Venez.***: Bipreterax; Preterax.

Pharmacopoeial Preparations

BP 2014: Perindopril Erbumine Tablets.

Phenindione *(BAN, rINN)*

Fenindion; Fenindiona; Fenindione; Fenindioni; Phénindione; Phenindionum; Phenylindanedione; Phenylinium; Фениндион.

2-Phenylindan-1,3-dione.

$C_{15}H_{10}O_2$=222.2

CAS — 83-12-5.

ATC — B01AA02.

ATC Vet — QB01AA02.

UNII — 5M7Y6274ZE.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Phenindione). Soft, odourless or almost odourless, white or creamy-white crystals. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Solutions are yellow to red.

Uses and Administration

Phenindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p. 1527.2). It is given in the management of thromboembolic disorders (p. 1273.2), but because of its higher incidence of severe adverse effects is now rarely used.

The usual initial dose of phenindione is 200 mg on the first day, 100 mg on the second day, and then usual maintenance doses of 50 to 150 mg daily according to coagulation tests.

Adverse Effects and Treatment

As for Warfarin Sodium, p. 1528.2. However, phenindione and the other indanediones are generally more toxic than warfarin with hypersensitivity reactions involving many organs and sometimes resulting in death. Some of the reactions include rashes and exfoliative dermatitis, pyrexia, diarrhoea, vomiting, sore throat, liver and kidney damage, myocarditis, agranulocytosis, leucopenia, eosinophilia, and a leukaemoid syndrome.

Phenindione may discolour the urine pink or orange and this is independent of any haematuria.

Effects on the gastrointestinal tract. There have been cases of paralytic ileus, one fatal, associated with phenindione.[1,2]

1. Menon IS. Phenindione and paralytic ileus. *Lancet* 1966; **i:** 1421–2.
2. Nash AG. Phenindione and paralytic ileus. *Lancet* 1966; **ii:** 51–2.

Precautions

As for Warfarin Sodium, p. 1529.2.

Phenindione is not recommended in pregnancy.

Breast feeding. Phenindione is distributed into breast milk, with reported concentrations[1] of 3 to 5 micrograms/mL after a single dose of 50 or 75 mg. A woman given phenindione 50 mg each morning and 50 and 25 mg on alternate nights breast fed her infant son,[2] who required a herniotomy at 5 weeks. After surgery he had an enormous scrotal haematoma with oozing from the wound and was found to have extended prothrombin and partial thromboplastin times. Last available guidance from the American Academy of Pediatrics therefore considered[3] that phenindione should be given with caution to breast-feeding mothers.

1. Goguel M, *et al.* Thérapeutique anticoagulante et allaitement: etude du passage de la phényl-2-dioxo, 1,3 indane dans le lait maternel. *Rev Fr Gynecol Obstet* 1970; **65:** 409–12.
2. Eckstein HB, Jack B. Breast-feeding and anticoagulant therapy. *Lancet* 1970; **i:** 672–3.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

The interactions associated with oral anticoagulants are described in detail under warfarin (p. 1529.3). Specific references to interactions involving phenindione can be found there under the headings for the following drug groups: antibacterials; antifungals; antiplatelets; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenindione is completely absorbed from the gastrointestinal tract, with peak plasma levels attained after 1 to 3 hours and a half-life of 5 to 6 hours. It crosses the placenta and is distributed into breast milk. Metabolites of phenindione excreted in the urine are responsible for any discoloration that may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dindevan; ***Gr.***: Solu-thrombine; ***India***: Dindevan; ***Rus.***: Phenylin (Фенилин).

Pharmacopoeial Preparations
BP 2014: Phenindione Tablets.

Phenoxybenzamine Hydrochloride *(BANM, rINNM)*

Fenoksybenzaminy chlorowodorek; Fenoxibenzamina, hidrocloruro de; Hidrocloruro de fenoxibenzamina; Phénoxybenzamine, Chlorhydrate de; Phenoxybenzamini Hydrochloridum; SKF-688A; Феноксибензамина Гидрохлорид.

Benzyl(2-chloroethyl)(1-methyl-2-phenoxyethyl)amine hydrochloride.

$C_{18}H_{22}ClNO,HCl$=340.3

CAS — 59-96-1 (phenoxybenzamine); 63-92-3 (phenoxybenzamine hydrochloride).

ATC — C04AX02.

ATC Vet — QC04AX02.

UNII — X11EG24OHL.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Phenoxybenzamine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform.

Uses and Administration

Phenoxybenzamine is a powerful alpha-adrenoceptor blocker (p. 1243.1) with a prolonged duration of action; it binds covalently to alpha receptors in smooth muscle to produce an irreversible ('non-competitive') blockade. A single large dose of phenoxybenzamine can cause alpha-adrenoceptor blockade for 3 days or longer.

Phenoxybenzamine is used in the management of phaeochromocytoma (p. 1278.1). It has also been employed in severe shock (p. 1279.3) and in the treatment of urinary retention (p. 2349.2).

Phenoxybenzamine is used as the hydrochloride. It is given orally or by intravenous infusion as a dilute solution.

In **phaeochromocytoma** it is used to control the hypertension associated with excessive catecholamine release during the pre-operative period and in patients whose tumours are inoperable. A beta blocker may also be given to control tachycardia, but not before alpha blockade has completely suppressed the pressor effects of the phaeochromocytoma. The usual initial oral dose of phenoxybenzamine hydrochloride is 10 mg once or twice daily, increased gradually, according to the patient's response, to a usual dose of 1 to 2 mg/kg daily in 2 divided doses. It may be given intravenously for operative cover in patients with phaeochromocytoma in a daily dose of 1 mg/kg in 200 mL of sodium chloride 0.9% infused over at least 2 hours. A similar intravenous dose in 200 to 500 mL of sodium chloride 0.9% has been given in the management of severe **shock**.

For **urinary retention** due to neurogenic bladder an oral dose of 10 mg twice daily has been given.

Adverse Effects and Treatment

The adverse effects of phenoxybenzamine are mainly due to its alpha-adrenoceptor blocking activity. They include orthostatic hypotension and dizziness, reflex tachycardia, nasal congestion, and miosis. Inhibition of ejaculation may occur. These effects may be minimised by using a low initial dose, and may diminish with continued use, but the hypotensive effect can be exaggerated by exercise, heat, a large meal, or alcohol ingestion. Other adverse effects include dry mouth, decreased sweating, drowsiness, fatigue, and confusion. Gastrointestinal effects are usually slight. When phenoxybenzamine is given intravenously, idiosyncratic profound hypotension can occur within a few minutes of starting the infusion. Convulsions have been reported after rapid intravenous infusion of phenoxybenzamine.

Severe hypotension may occur in overdose and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement. Sympathomimetics are considered to be of little value, and adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia. Sources differ as to the value of noradrenaline in overcoming alpha-receptor blockade.

Phenoxybenzamine has been shown to be mutagenic in *in vitro* tests and carcinogenic in *rodents*. There have been case reports of carcinoma in patients given long-term treatment with phenoxybenzamine for bladder dysfunction; US licensed product information therefore advises against long-term use.

Precautions

Phenoxybenzamine should be given with care to patients with heart failure, ischaemic heart disease, cerebrovascular disease, or renal impairment, and should be avoided if a fall in blood pressure would be dangerous. Phenoxybenzamine may aggravate the symptoms of respiratory infections.

When given intravenously, phenoxybenzamine hydrochloride should always be diluted and given by infusion. Intravenous fluids must always be given beforehand to ensure an adequate circulating blood volume and to prevent a precipitous fall in blood pressure. Care should be taken to avoid extravasation. Contamination of the skin should also be avoided since contact sensitisation may occur.

Interactions

Since phenoxybenzamine only blocks alpha receptors, leaving the beta receptors unopposed, use with drugs such as adrenaline that also stimulate beta receptors may enhance the cardiac-accelerating and hypotensive action of phenoxybenzamine.

Pharmacokinetics

Phenoxybenzamine is incompletely and variably absorbed from the gastrointestinal tract. After oral dosage the onset of action is gradual over several hours; the maximum effect is attained in about 1 hour after an intravenous dose. The duration of action is usually 3 or 4 days and is thought to depend on the rate of synthesis of new alpha receptors after irreversible covalent bonding to existing alpha receptors by a reactive intermediate of phenoxybenzamine. The plasma half-life after intravenous dosage is about 24 hours. Phenoxybenzamine is metabolised in the liver and excreted in the urine and bile, but small amounts remain in the body for several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dibenyline†; ***Austria***: Dibenzyran; ***Ger.***: Dibenzyran; ***Gr.***: Dibenyline; Dibenzyran; ***Hong Kong***: Dibeline†; Dibenyline; ***India***: Biophenox; Fenoben; Fenoxene; ***Israel***: Dibenyline; ***NZ***: Dibenyline; ***S.Afr.***: Dibenyline†; ***UK***: Dibenyline; ***USA***: Dibenzyline.

Pharmacopoeial Preparations
BP 2014: Phenoxybenzamine Capsules;
USP 36: Phenoxybenzamine Hydrochloride Capsules.

Phenprocoumon *(BAN, USAN, rINN)*

Femprocumona; Fenprocomón; Fenprocumon; Fenprokumon; Fenprokumoni; Phenprocoumone; Phenprocoumonum; Phenylpropylhydroxycoumarin; Фенпрокумон.

4-Hydroxy-3-(1-phenylpropyl)coumarin.

$C_{18}H_{16}O_3$=280.3

CAS — 435-97-2.

ATC — B01AA04.

ATC Vet — QB01AA04.

UNII — Q08SIO485D.

Uses and Administration

Phenprocoumon is an oral coumarin anticoagulant with actions similar to those of warfarin (p. 1527.2). It is used in the management of thromboembolic disorders (p. 1273.2). Initial doses are up to 9 mg on the first day followed by 6 mg on the second day. Maintenance doses are usually from 1.5 to 6 mg daily, depending on the response.

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p. 1528.2.

Effects on the liver. A woman who had twice previously developed jaundice while taking phenprocoumon developed jaundice and parenchymal liver damage when, after some years, phenprocoumon was again given.[1] Other cases of phenprocoumon-associated liver damage have been reported.[2-4]

1. den Boer W, Loeliger EA. Phenprocoumon-induced jaundice. *Lancet* 1976; **i:** 912.
2. Slagboom G, Loeliger EA. Coumarin-associated hepatitis: report of two cases. *Arch Intern Med* 1980; **140:** 1028–9.
3. Cordes A, *et al.* Phenprocoumon-induziertes Leberversagen. *Dtsch Med Wochenschr* 2003; **128:** 1884–6.
4. Bulang T, *et al.* Akutes Leberversagen durch Phenprocoumon–drei Fallberichte. *Z Gastroenterol* 2004; **42:** 1055–8.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p. 1529.3). Specific references to interactions involving phenprocoumon can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antidepressants; antidiabetics; antigout drugs; antineoplastics; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenprocoumon is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Metabolism is mediated partly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. The half-life is around 6 days. It is excreted in the urine and faeces as conjugated hydroxy metabolites and parent compound. Phenprocoumon is given as a racemic mixture; the *S*-isomer is more potent. The stereo-isomers have different pharmacokinetics.

References.

1. Husted S, Andreasen F. Individual variation in the response to phenprocoumon. *Eur J Clin Pharmacol* 1977; **11:** 351–8.
2. Toon S, *et al.* Metabolic fate of phenprocoumon in humans. *J Pharm Sci* 1985; **74:** 1037–40.
3. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44:** 1227–46.
4. Werner D, *et al.* Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. *Eur J Clin Pharmacol* 2009; **65:** 783–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Marcoumar; ***Belg.***: Marcoumar; ***Braz.***: Marcoumar; ***Denm.***: Marcoumar; ***Ger.***: Falithrom†; Marcumar; marcuphen; Phenpro; Phenprogamma; ***Neth.***: Marcoumar; ***Switz.***: Marcoumar.

Phentolamine Mesilate *(BANM, rINNM)*

Fentolamiinimesilaatti; Fentolamin mesylát; Fentolamina, mesilato de; Fentolaminmesilat; Fentolamin-mezilát; Fento-

lamino mesilatas; Mesilato de fentolamina; Phentolamine, Mésilate de; Phentolamine Mesylate; Phentolamine Methanesulphonate; Phentolamini Mesilas; Phentolaminmesilat; Фентоламина Мезилат.

3-[*N*-(2-Imidazolin-2-ylmethyl)-*p*-toluidino]phenol methanesulphonate.

$C_{17}H_{19}N_3O.CH_4SO_3$=377.5

CAS — 50-60-2 (phentolamine); 73-05-2 (phentolamine hydrochloride); 65-28-1 (phentolamine mesilate).

ATC — C04AB01; V03AB36.

ATC Vet — QC04AB01; QG04BE05.

UNII — Y7543E5K9T.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Phentolamine Mesilate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Phentolamine Mesylate). A white or off-white, odourless crystalline powder. Soluble 1 in 1 of water, 1 in 4 of alcohol, and 1 in 700 of chloroform. Its solutions in water have a pH of about 5 and slowly deteriorate. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Phentolamine is an alpha-adrenoceptor blocker (p. 1243.1) which also has a direct action on vascular smooth muscle. It produces vasodilatation, an increase in cardiac output, and has a positive inotropic effect, but is reported to have little effect on the blood pressure of patients with essential hypertension. The alpha-receptor blocking action is reversible ('competitive') and non-selective, and the duration of effect is relatively short.

Phentolamine is given in the management of hypertensive crises, particularly those due to excessive catecholamine release associated with surgery for phaeochromocytoma (p. 1278.1). It has been used for the differential diagnosis of phaeochromocytoma, but has largely been superseded by estimations of catecholamines in blood and urine.

Phentolamine is also used to prevent or treat dermal necrosis and sloughing associated with the intravenous infusion or extravasation of noradrenaline, and to reverse soft-tissue anaesthesia associated with intra-oral submucosal injection of local anaesthetic preparations containing vasoconstrictors (below). It has been used in the treatment of erectile dysfunction (p. 2348.2).

Phentolamine is given by injection as the mesilate.

In patients with hypertensive crises during surgery for **phaeochromocytoma**, a dose of 2 to 5 mg of phentolamine mesilate is given intravenously and repeated if necessary; blood pressure should be monitored. The intramuscular route may be used pre-operatively and for diagnostic procedures.

For prevention of **dermal necrosis** during intravenous infusion of noradrenaline, 10 mg of phentolamine mesilate is added to each litre of solution containing noradrenaline. For treatment of extravasation of noradrenaline, 5 to 10 mg of phentolamine mesilate in 10 mL of sodium chloride 0.9% is injected into the affected area.

For **reversal of soft-tissue anaesthesia** in the mouth, phentolamine mesilate is given using the same location and technique as for the local anaesthetic. The dose depends on the amount of local anaesthetic used and ranges from 200 to 800 micrograms.

For **erectile dysfunction**, phentolamine mesilate is given by injection into the corpora cavernosa of the penis. It is usually given with papaverine, but a preparation containing phentolamine with aviptadil (vasoactive intestinal peptide) may also be used. Phentolamine has also been tried orally.

For doses in children, see below.

Administration in children. In the treatment of hypertensive crises during surgery for **phaeochromocytoma**, children may be given phentolamine mesilate intravenously (or intramuscularly when used pre-operatively) in a dose of 1 mg. Alternatively, doses of 50 to 100 micrograms/kg or 3 mg/m^2 have been suggested. The dose may be repeated if necessary.

For **reversal of soft-tissue anaesthesia** in the mouth, phentolamine mesilate is given to children aged 6 years and over and weighing 15 to 30 kg in a dose of up to 200 micrograms. The dose depends on the amount of local anaesthetic used, and should be given using the same location and technique as for the local anaesthetic.

Hyperhidrosis. Hyperhidrosis (p. 1685.1) is usually treated with topical aluminium salts or topical antimuscarinics, but intradermal botulinum A toxin or procedures such as endoscopic transthoracic sympathectomy may be needed in severe cases. Phentolamine has been tried as an alternative. Improvement in symptoms has been reported[1] in 2 patients with generalised hyperhidrosis given 100 mg of phentolamine mesilate by intravenous infusion over 6 hours. Improvement lasted for 2 to 3 months and the infusion was repeated, in 1 patient several times.

1. McCleane G. The use of intravenous phentolamine mesilate in the treatment of hyperhidrosis. *Br J Dermatol* 2002; **146:** 533–4.

Pain. Sympathetic nerve block (p. 1981.3) is used in some pain syndromes and usually involves injection of local anaesthetics. Phentolamine has been used as an alternative and beneficial results have been reported in pain associated with chronic pancreatitis,[1] pancreatic and other visceral cancers,[2,3] and chronic gastroparesis.[4]

Complete resolution of pain has also been reported in 2 patients with cutaneous leiomyomata given oral doxazosin.[5]

1. McCleane GJ. Phentolamine abolishes the pain of chronic pancreatitis. *Br J Hosp Med* 1996; **55:** 521.
2. McCleane GJ. Intravenous phentolamine mesylate alleviates the pain of pancreatic carcinoma. *Pain* 1997; **73:** 263–4.
3. Yasukawa M, *et al.* Intravenous phentolamine infusion alleviates the pain of abdominal visceral cancer, including pancreatic carcinoma. *J Anesth* 2007; **21:** 420–3.
4. Phillips WJ, *et al.* Relief of acute pain in chronic idiopathic gastroparesis with intravenous phentolamine. *Ann Pharmacother* 2006; **40:** 2032–6.
5. Batchelor RJ, *et al.* Successful treatment of pain in two patients with cutaneous leiomyomata with the oral alpha-1 adrenoceptor antagonist, doxazosin. *Br J Dermatol* 2004; **150:** 775–6.

Reversal of local anaesthesia. During dental procedures, local anaesthetics are often given with vasoconstrictor sympathomimetics such as adrenaline or noradrenaline to improve the depth and duration of anaesthesia (see Infiltration Anaesthesia, p. 1981.2), but prolonged oral anaesthesia may be a problem after the procedure. Phentolamine, injected intra-orally, reverses the effects of the vasoconstrictor and accelerates systemic absorption of the local anaesthetic,[1] and has been shown to reduce the time to return of normal sensation.[2] The procedure also appears to be safe and effective in children between 4 and 11 years of age.[3]

1. Moore PA, *et al.* Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. *Anesth Prog* 2008; **55:** 40–8.
2. Laviola M, *et al.* Randomized study of phentolamine mesylate for reversal of local anesthesia. *J Dent Res* 2008; **87:** 635–9.
3. Tavares M, *et al.* SoftTissue Anesthesia Reversal Group. Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients. *J Am Dent Assoc* 2008; **139:** 1095–1104. Correction. *ibid.*; 1312.

Adverse Effects and Treatment

The adverse effects of phentolamine are primarily due to its alpha-adrenoceptor blocking activity and include orthostatic hypotension and tachycardia. Myocardial infarction and cerebrovascular spasm or occlusion have been reported occasionally, usually in association with marked hypotension; flushing, sweating, and feelings of apprehension may accompany hypotensive episodes. Anginal pain and arrhythmias have been reported rarely. Nausea, vomiting, and diarrhoea may also occur. Other adverse effects include weakness, dizziness, flushing, and nasal congestion. Hypoglycaemia has been reported after overdosage.

Severe hypotension may occur in overdosage although phentolamine has a short duration of action. Treatment may include support of the circulation by postural measures and parenteral fluid volume replacement. Noradrenaline may be given cautiously to overcome alpha-adrenoceptor blockade. Adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia.

When injected into the corpus cavernosum of the penis phentolamine has been associated with local pain; induration and fibrosis may occur with repeated use. Priapism has occurred.

Precautions

Phentolamine should not generally be given to patients with angina pectoris or other evidence of ischaemic heart disease. Care should be taken in patients with peptic ulcer disease, which may be exacerbated.

Interactions

Since phentolamine only blocks alpha receptors, use with drugs such as adrenaline may lead to severe hypotension and tachycardia due to unopposed beta-adrenoceptor stimulation.

Pharmacokinetics

After intravenous dosage, the half-life of phentolamine has been reported to be 19 minutes. It is extensively metabolised and about 13% of an intravenous dose is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Regitina; ***Austral.***: Regitine; ***Belg.***: Regitine†; ***Braz.***: Herivyl; Vigamed; ***Canad.***: Rogitine; ***China***: AnTing (安挺); He Li Ke (赫立可); He Xin (和欣); Mei Zhen (美珍); Pu Ding Yang (普丁阳); QiWei (启伟); Regitine (利其丁); Zhi Li (至力); ***Gr.***: Regitine; ***Hong Kong***: Regitine†; ***Hung.***: Regitine†; ***India***: Fentanor; ***Israel***: Regitine; ***Neth.***: Regitine; ***NZ***: Invicorp; Regitine; ***Singapore***: Rogitine; ***Switz.***: Regitine; ***UK***: Rogitine†; ***USA***: OraVerse.

Multi-ingredient Preparations. ***Austria***: Androskat; ***Denm.***: Invicorp; ***Neth.***: Androskat; ***USA***: Tri-Mix.

Pharmacopoeial Preparations

BP 2014: Phentolamine Injection;

USP 36: Phentolamine Mesylate for Injection.

Pholedrine Sulfate *(BANM, rINNM)* ⊗

Foledrina, sulfato de; Isodrine Sulphate; Pholédrine, Sulfate de; Pholedrine Sulphate; Pholedrini Sulfas; Sulfato de foledrina; Sympropaminum (pholedrine); Фоледрина Сульфат.

4-(2-Methylaminopropyl)phenol sulfate.

$(C_{10}H_{15}NO)_2,H_2SO_4$=428.5

CAS — 370-14-9 (pholedrine); 6114-26-7 (pholedrine sulfate).

UNII — WB6LNL73BR.

Profile

Pholedrine is a sympathomimetic (p. 1507.3) used in the treatment of hypotensive states. It has been given orally as the sulfate, often in combination with other drugs, and has also been included in preparations promoted for vascular disorders. Pholedrine eye drops have been used as an alternative to hydroxyamfetamine (p. 2529.3) in the diagnosis of Horner's syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Switz.***: Ortho-Maren retard†.

Picotamide *(BAN)*

G-137; Picotamida; Picotamide, monohydrate de; Picotamid-monohidrát; Picotamidum Monohydricum; Pikotamid monohydrát; Pikotamidimonohydraatti; Pikotamidmonohydrat; Pikotamido monohidratas.

4-Methoxy-*N*,*N*′-bis(3-pyridinylmethyl)-1,3-benzenedicarboxamide monohydrate.

$C_{21}H_{20}N_4O_3,H_2O$=394.4

CAS — 32828-81-2 (anhydrous picotamide); 80530-63-8 (picotamide monohydrate).

ATC — B01AC03.

ATC Vet — QB01AC03.

UNII — 654G2VCI4Q.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Picotamide Monohydrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water; soluble in dehydrated alcohol and in dichloromethane; dissolves in dilute mineral acids.

Profile

Picotamide is a thromboxane synthase inhibitor and thromboxane receptor antagonist with antiplatelet activity. It is given orally in thromboembolic disorders (p. 1273.2) in initial doses of 900 to 1200 mg daily in divided doses, reducing to a maintenance dose of 300 to 600 mg daily.

Reviews.

1. Celestini A, Violi F. A review of picotamide in the reduction of cardiovascular events in diabetic patients. *VascHealth Risk Manag* 2007; **3:** 93–8.

ACE inhibitor-induced cough. Cough is a recognised adverse effect of ACE inhibitors (see p. 1285.3). Picotamide led to the disappearance of cough in 8 of 9 patients taking enalapril for hypertension,[1] suggesting that thromboxanes were involved in the aetiology of ACE inhibitor-induced cough.

1. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; **350:** 15–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Plactidil.

Pilsicainide Hydrochloride *(rINNM)*

DU-6552; Hidrocloruro de pilsicainida; Pilsicainida, hidrocloruro de; Pilsicaïnide, Chlorhydrate de; Pilsicainidi Hydrochloridum; Pilzicainide Hydrochloride; SUN-1165; Пильсикаинида Гидрохлорид.

Tetrahydro-1*H*-pyrrolizine-7a(5*H*)-aceto-2',6'-xylidide hydrochloride.

$C_{17}H_{24}N_2O$,HCl=308.8

CAS — 88069-67-4 (pilsicainide); 88069-49-2 (pilsicainide hydrochloride).

UNII — 03C8I9296V.

Profile

Pilsicainide hydrochloride is an antiarrhythmic with class Ic activity (p. 1243.1). It has been given orally in typical doses of 150 mg daily in three divided doses, or intravenously in a dose of 0.75 to 1 mg/kg, in the treatment of tachyarrhythmias.

References.

1. Takabatake T, *et al.* Pharmacokinetics of SUN 1165, a new antiarrhythmic agent, in renal dysfunction. *Eur J Clin Pharmacol* 1991; **40:** 411–14.
2. Okishige K, *et al.* Pilsicainide for conversion and maintenance of sinus rhythm in chronic atrial fibrillation: a placebo-controlled, multicenter study. *Am Heart J* 2000; **140:** 437–44.
3. Kumagai K, *et al.* Single oral administration of pilsicainide versus infusion of disopyramide for termination of paroxysmal atrial fibrillation: a multicenter trial. *Pacing Clin Electrophysiol* 2000; **23:** 1880–2.
4. Ogawa R, *et al.* Population pharmacokinetic and pharmacodynamic analysis of a class IC antiarrhythmic, pilsicainide, in patients with cardiac arrhythmias. *J Clin Pharmacol* 2006; **46:** 59–68.
5. Kumagai K, *et al.* Pilsicainide for atrial fibrillation. *Drugs* 2006; **66:** 2067–73.
6. Plosker GL. Pilsicainide. *Drugs* 2010; **70:** 455–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn.*** Alisrythm; Pilsinic; Rizmsat; Rizumcote; Sunrythm; Tatsupilljin.

Pimobendan *(BAN, USAN, rINN)*

Pimobendaani; Pimobendán; Pimobendanas; Pimobendane; Pimobendanum; UDCG-115; Пимобендан.

4,5-Dihydro-6-[2-(*p*-methoxyphenyl)-5-benzimidazolyl]-5-methyl-3(2*H*)-pyridazinone.

$C_{19}H_{18}N_4O_2$=334.4

CAS — 74150-27-9; 118428-36-7.

ATC Vet — QC01CE90.

UNII — 34AP3BBP9T.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pimobendan). A white or slightly yellowish, hygroscopic powder. Practically insoluble in water; slightly soluble in acetone and in methyl alcohol; freely soluble in dimethylformamide. Store in airtight containers.

Profile

Pimobendan is a phosphodiesterase type 3 inhibitor with calcium-sensitising properties. It has positive inotropic and vasodilator activity and is used as an adjunct to standard therapy in the management of heart failure (p. 1262.3). It is given in a usual oral dose of 1.25 to 2.5 mg twice daily after food, adjusted according to age and response.

Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate.

Pimobendan is also used in veterinary medicine.

References.

1. Przechera M, *et al.* Pharmacokinetic profile and tolerability of pimobendan in patients with terminal renal insufficiency. *Eur J Clin Pharmacol* 1991; **40:** 107–11.
2. The Pimobendan in Congestive Heart Failure (PICO) Investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 1996; **76:** 223–31.
3. Yoshikawa T, *et al.* Effectiveness of carvedilol alone versus carvedilol + pimobendan for severe congestive heart failure. *Am J Cardiol* 2000; **85:** 1495–7.
4. The EPOCH Study Group. Effects of pimobendan on adverse cardiac events and physical activities in patients with mild to moderate chronic heart failure: the effects of pimobendan on chronic heart failure study (EPOCH study). *Circ J* 2002; **66:** 149–57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn.*** Acardi.

Pindolol *(BAN, USAN, rINN)* ⊗

LB-46; Pindololi; Pindololis; Pindololum; Prindolol; Prinodolol; Пиндолол.

1-(Indol-4-yloxy)-3-isopropylaminopropan-2-ol.

$C_{14}H_{20}N_2O_2$=248.3

CAS — 13523-86-9.

ATC — C07AA03.

ATC Vet — QC07AA03.

UNII — BJ4HF6IU1D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Pindolol). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Protect from light.

USP 36: (Pindolol). A white to off-white, crystalline powder with a faint odour. Practically insoluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. Protect from light.

Uses and Administration

Pindolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to have intrinsic sympathomimetic activity but little membrane-stabilising activity.

Pindolol is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and other cardiovascular disorders. It is also used in glaucoma (p. 1999.1). For investigation of its value in psychiatric disorders, see below.

In **hypertension** pindolol is usually given initially in an oral dosage of 5 mg two or three times daily, or 15 mg once daily, subsequently increased according to response. The usual maintenance dose is 15 to 30 mg once daily, but up to 45 mg daily, as a single dose or in divided doses, may be required. Additional benefit is rarely obtained from doses higher than 45 mg daily, although doses up to 60 mg daily have been given.

The usual oral dose for **angina pectoris** is 2.5 to 5 mg up to three times daily; however, doses of up to 40 mg daily have been used.

Eye drops containing pindolol 1% are used in the management of **glaucoma**.

Pindolol has also been given intravenously in the management of cardiac arrhythmias.

Psychiatric disorders. In addition to its beta-blocking properties, pindolol is also a partial agonist at serotonin 5-HT_1-receptors and has been used to augment the effects of SSRIs in patients with depression (p. 398.1).[1,2] Results have been conflicting,[3] but a meta-analysis[4] found that the time to response was shorter in patients given pindolol with an SSRI, although there was no effect on long-term outcomes. Small studies have also reported positive effects with pindolol augmentation of SSRIs in obsessive-compulsive disorder[5] (p. 1028.2) and in panic disorder[6] (p. 1029.1), although no effect was seen in social phobia.[7] Another study[8] found that pindolol augmentation of antipsychotic therapy reduced aggression in patients with schizophrenia (p. 1031.3).

1. Portella MJ, *et al.* Pindolol augmentation enhances response outcomes in first depressive episodes. *Eur Neuropsychopharmacol* 2009; **19:** 516–19.
2. Whale R, *et al.* Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review. *J Psychopharmacol* 2010; **24:** 513–20.
3. Segrave R, Nathan PJ. Pindolol augmentation of selective serotonin reuptake inhibitors: accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. *Hum Psychopharmacol* 2005; **20:** 163–74.
4. Ballesteros J, Callado LF. Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. *J Affect Disord* 2004; **79:** 137–47.
5. Dannon PN, *et al.* Pindolol augmentation in treatment-resistant obsessive compulsive disorder: a double-blind placebo controlled trial. *Eur Neuropsychopharmacol* 2000; **10:** 165–9.
6. Hirschmann S, *et al.* Pindolol augmentation in patients with treatment-resistant panic disorder: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2000; **20:** 556–9.
7. Stein MB, *et al.* Pindolol potentiation of paroxetine for generalized social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry* 2001; **158:** 1725–7.
8. Caspi N, *et al.* Pindolol augmentation in aggressive schizophrenic patients: a double-blind crossover randomized study. *Int Clin Psychopharmacol* 2001; **16:** 111–5.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Effects on lipid metabolism. Beta blockers can affect plasma-lipid concentrations, although this may be less of a problem with those that have intrinsic sympathomimetic activity. For reference to the lack of effect of pindolol, see p. 1320.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piridolol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Tremor. Fine tremor in the extremities of 5 patients during pindolol therapy was considered to have been due to its partial agonist activity.[1]

1. Hod H, *et al.* Pindolol-induced tremor. *Postgrad Med J* 1980; **56:** 346–7.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Pindolol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after an oral dose. It has a bioavailability of about 87%. About 40 to 60% is reported to be bound to plasma proteins. It is moderately lipid-soluble. Pindolol crosses the placenta and is distributed into breast milk. It is only partially metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites. A plasma elimination half-life of 3 to 4 hours has been reported in healthy adults. The half-life may be prolonged in elderly hypertensive patients and in patients with renal or hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Barbloc; Visken; ***Austria***: Visken; ***Belg.***: Visken; ***Braz.***: Visken; ***Canad.***: Apo-Pindol; Novo-Pindol†; Nu-Pindol; Visken; ***Denm.***: Hexapindol; Visken; ***Fin.***: Pinloc; Visken; ***Fr.***: Visken; ***Ger.***: Glauco-Stulln†; Visken†; ***Gr.***: Dranolis; Treparasen; Visken; ***Hong Kong***: Barbloc†; Visken; ***Hung.***: Visken; ***India***: Visken; ***Irl.***: Visken†; ***Israel***: Pinden†; ***Ital.***: Visken; ***Mex.***: Visken; ***Neth.***: Viskeen; ***NZ***: Pindol†; ***Philipp.***: Pyndale; Visken; ***Pol.***: Visken; ***Rus.***: Visken (Вискен); ***Swed.***: Visken; ***Switz.***: Viskene; ***Turk.***: Visken; ***UK***: Visken; ***USA***: Visken.

Multi-ingredient Preparations. ***Belg.***: Viskaldix; ***Braz.***: Viskaldix; ***Canad.***: Viskazide; ***Chile***: Viskaldix; ***Fr.***: Viskaldix; ***Ger.***: Viskaldix†; ***Gr.***: Viskaldix; ***Hung.***: Viskaldix; ***Irl.***: Viskaldix†; ***Malaysia***: Viskaldix; ***Neth.***: Viskaldix†; ***Philipp.***: Viskaldix; ***Rus.***: Viskaldix (Вискалдикс); ***Switz.***: Viskaldix; ***UK***: Viskaldix.

Pharmacopoeial Preparations

BP 2014: Pindolol Tablets;
USP 36: Pindolol Tablets.

Piretanide *(BAN, USAN, rINN)* ⊗

Hoe-118; Piretanid; Piretanida; Piretanidas; Pirétanide; Piretanidi; Piretanidum; S73-4118; Пиретанид.

4-Phenoxy-3-(pyrrolidin-1-yl)-5-sulphamoylbenzoic acid.

$C_{17}H_{18}N_2O_5S$=362.5

CAS — 55837-27-9.

ATC — C03CA03.

ATC Vet — QC03CA03.

UNII — DQ6KK6GV93.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Piretanide). A yellowish-white to yellowish powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in dehydrated alcohol. Protect from light.

Uses and Administration

Piretanide is a loop diuretic with actions and uses similar to those of furosemide (p. 1387.1). It is used for oedema, including that associated with heart failure (p. 1262.3), in oral doses of 3 to 6 mg daily. In the treatment of hypertension (p. 1251.1) it is given in a usual oral dose of 6 to 12 mg daily. The sodium salt is given by injection.

References.

1. Clissold SP, Brogden RN. Piretanide: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1985; **29:** 489–530.

Adverse Effects

As for Furosemide, p. 1388.3. Muscle cramps have been reported after high doses of piretanide.

Precautions

Piretanide's precautions and contra-indications, which are dependent on its effects on fluid and electrolyte balance, are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Patients with impaired micturition or prostatic hyperplasia may develop retention of urine with piretanide.

Interactions

As for Furosemide, p. 1389.3.

Pharmacokinetics

Piretanide has been reported to be almost completely absorbed after oral doses. It is extensively bound to plasma proteins, and is reported to have a half-life of about 1 hour after an oral dose.

References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Arelix; ***Fr.***: Eurelix; ***Ger.***: Arelix†; ***Gr.***: Timonor; ***Irl.***: Arelix; ***Ital.***: Tauliz; ***Mex.***: Diural; ***S. Afr.***: Arelix; ***Spain***: Perbilen; ***Switz.***: Arelix.

Multi-ingredient Preparations. ***Ger.***: Arelix ACE†; Betarelix; Ramitanid†; ***Irl.***: Trialix; ***Ital.***: Prilace; ***Switz.***: Trialix.

Pirmenol Hydrochloride *(USAN, rINNM)*

CI-845; CL-845; Hidrocloruro de pirmenol; Pirménol, Chlorhydrate de; Pirmenol, hidrocloruro de; Pirmenoli Hydrochloridum; Пирменола Гидрохлорид.

(±)-*cis*-2,6-Dimethyl-α-phenyl-α-2-pyridyl-1-piperidinebutanol hydrochloride.

$C_{22}H_{30}N_2O,HCl$=375.0

CAS — 68252-19-7 (pirmenol); 61477-94-9 (pirmenol hydrochloride).

UNII — JA79OMG4QT.

Profile

Pirmenol hydrochloride is an antiarrhythmic with class Ia activity (p. 1243.1).

References.

1. Hampton EM, *et al.* Initial and long-term outpatient experience with pirmenol for control of ventricular arrhythmias. *Eur J Clin Pharmacol* 1986; **31:** 15–22.
2. Stringer KA, *et al.* Enhanced pirmenol elimination by rifampin. *J Clin Pharmacol* 1988; **28:** 1094–7.
3. Janiczek N, *et al.* Pharmacokinetics of pirmenol enantiomers and pharmacodynamics of pirmenol racemate in patients with premature ventricular contractions. *J Clin Pharmacol* 1997; **37:** 502–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Pimenol.

Pitavastatin *(rINN)*

Itavastatin; Nisvastatin; NK-104; Pitavastatina; Pitavastatine; Pitavastatinum; Питавастатин.

(3*R*,5*S*,6*E*)-7-[2-Cyclopropyl-4-(*p*-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoic acid.

$C_{25}H_{24}FNO_4$=421.5

CAS — 147511-69-1.

ATC — C10AA08.

ATC Vet — QC10AA08.

UNII — M5681Q5F9P.

Pitavastatin Calcium *(rINNM)*

Calcii Pitavastatinum; Itavastatin Calcium; Nisvastatin Calcium; NKS-104; Pitavastatina calcica; Pitavastatine Calcique; Кальций Питавастатин.

$(C_{25}H_{24}FNO_4)_2Ca$=883.0

CAS — 147526-32-7.

UNII — IYD54XEG3W.

Uses and Administration

Pitavastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with similar properties to simvastatin (p. 1489.2). It is used as the calcium salt in the treatment of hyperlipidaemias in an oral dose equivalent to 1 to 4 mg of pitavastatin once daily. If given with erythromycin or rifampicin, both of which increase pitavastatin exposure, a maximum dose of pitavastatin of 1 mg or 2 mg respectively should not be exceeded.

Reduced doses should be given in renal impairment (see below).

References.

1. Hayashi T, *et al.* Pitavastatin: efficacy and safety in intensive lipid lowering. *Expert Opin Pharmacother* 2007; **8:** 2315–27.
2. Koshiyama H, *et al.* Effects of pitavastatin on lipid profiles and high-sensitivity CRP in Japanese subjects with hypercholesterolemia: Kansai Investigation of Statin for Hyperlipidemic Intervention in Metabolism and Endocrinology (KISHIMEN) Investigators. *J Atheroscler Thromb* 2008; **15:** 345–50.
3. Teramoto T, *et al.* Effects of pitavastatin (LIVALO Tablet) on high density lipoprotein cholesterol (HDL-C) in hypercholesterolemia. *J Atheroscler Thromb* 2009; **16:** 654–61.
4. Wensel TM, *et al.* Pitavastatin: a new HMG-CoA reductase inhibitor. *Ann Pharmacother* 2010; **44:** 507–14.
5. Sansanayudh N, *et al.* Comparative efficacy and safety of low-dose pitavastatin versus atorvastatin in patients with hypercholesterolemia. *Ann Pharmacother* 2010; **44:** 415–23.
6. Teramoto T, *et al.* New evidence on pitavastatin: efficacy and safety in clinical studies. *Expert Opin Pharmacother* 2010; **11:** 817–28.

Administration in renal impairment. Patients with moderate renal impairment (creatinine clearance [CC] 30 to 60 mL/min) and those on haemodialysis may be given pitavastatin in an initial oral dose of 1 mg once daily, and a maximum dose of 2 mg once daily. Pitavastatin should not be used in those with severe renal impairment (CC less than 30 mL/min) unless on haemodialysis.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Interactions

The interactions of statins with other drugs are described under simvastatin (p. 1494.2). Pitavastatin is only marginally metabolised by the cytochrome P450 isoenzyme CYP2C9 and may not have the same interactions with CYP3A4 inhibitors as simvastatin. However, ciclosporin significantly increases pitavastatin exposure and the combination should be avoided. On theoretical grounds, use with ritonavir-boosted lopinavir is also contra-indicated. Rifampicin and erythromycin also increase pitavastatin exposure; if such combinations must be used, lower doses of pitavastatin should be used (see Uses and Administration, above).

Pharmacokinetics

Peak plasma concentrations of pitavastatin are reached about 1 hour after an oral dose, with an absolute bioavailability of about 51%. Pitavastatin is more than 99% bound to plasma proteins. It is marginally metabolised by the cytochrome P450 isoenzyme CYP2C9 and to a lesser extent by CYP2C8, but the main route of metabolism is by glucuronidation to a lactone metabolite. The majority of a dose is excreted in faeces with only about 15% in urine. The mean plasma elimination half-life of pitavastatin is 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Livalo (力清之); ***Fr.***: Trolise; ***India***: Flovas; ***Irl.***: Alipza; Livazo; ***Jpn***: Livalo; ***Neth.***: Livazo; Vezepra; ***Spain***: Alipza; Livazo; ***Thai.***: Livalo; ***Ukr.***: Livazo (Ливазо); ***USA***: Livalo.

Plant Stanols and Sterols

Phytosterols; Станолы и Стерины из Растений.

Phytosterol

Fitosterolis; Fitoszterin; Fytosterol; Fytosteroli; Phytosterin; Phytostérol; Phytosterolum; Фитостерол; Фитостерин.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Phytosterol). A natural mixture of sterols obtained from plants of the genera *Hypoxis*, *Pinus*, and *Picea*. It contains not less than 70% β-sitosterol, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in tetrahydrofuran; sparingly soluble in ethyl acetate. Store in airtight containers. Protect from light.

Sitostanol

Dihydro-β-sitosterol; Fucostanol; β-Sitostanol; Stigmastanol; Ситостанол.

(3β,5α)-Stigmastan-3-ol.

$C_{29}H_{52}O$=416.7

CAS — 83-45-4.

UNII — C2NJ9WO6O7.

Sitosterol

β-Sitosterin; β-Sitosterina; β-Sitosterol; Ситостерол; Ситостерин.

(3β)-Stigmast-5-en-3-ol.

$C_{29}H_{50}O$=414.7

CAS — 83-46-5.

UNII — S347WMO6M4.

Profile

Stanols and sterols occur naturally in plants and are chemically related to cholesterol. The term phytosterol is used to describe both unsaturated plant sterols and their saturated (hydrogenated) counterparts, plant stanols (phytostanols). Sitosterol, campesterol, and stigmasterol are the commonest phytosterols; their respective stanols are found in lower amounts naturally, but can be produced by hydrogenation of sterols.

Dietary phytosterols have a cholesterol-lowering action; they reduce cholesterol absorption from the intestine and may also have other mechanisms. Sitosterol has been used as a lipid regulating drug, and both sterol and stanol esters (formed by esterification with unsaturated fatty acids) have been incorporated into margarines and other food products for use in the dietary management of hypercholesterolaemia. Sitosterol, sitostanol, and other phytosterols, are also used in nutritional supplements.

Sitosterol is also used in benign prostatic hyperplasia (p. 2347.1), although its mechanism of action is not clear. It is given orally in usual initial doses of 20 mg three times daily.

There have been reports of bleeding complications associated with supplements containing phytosterols.

References.

1. Wilt T, *et al.* Beta-sitosterols for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 24/06/05).
2. Law M. Plant sterol and stanol margarines and health. *BMJ* 2000; **320:** 861–4.
3. Lichtenstein AH, Deckelbaum RJ. Stanol/sterol ester-containing foods and blood cholesterol levels: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation* 2001; **103:** 1177–9. Also available at: http://circ.ahajournals.org/cgi/reprint/103/8/1177.pdf (accessed 01/06/08)
4. Katan MB, *et al.* Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc* 2003; **78:** 965–78.
5. Health Canada. Sterol and sterolin-containing products: hematologic adverse reactions. *Can Adverse React News* 2004; **14** (2): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n2-eng.pdf (accessed 19/08/08)
6. Miettinen TA, Gylling H. Plant stanol and sterol esters in prevention of cardiovascular diseases: a review. *Int J Clin Pharmacol Ther* 2006; **44:** 247–50.
7. Devaraj S, Jialal I. The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. *Nutr Rev* 2006; **64:** 348–54.
8. Moruisi KG, *et al.* Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. *J Am Coll Nutr* 2006; **25:** 41–8.
9. Naruszewicz M, Kozlowska-Wojciechowska M. Plant sterols beyond low-density lipoprotein-cholesterol. *Br J Nutr* 2007; **98:** 454–5.
10. Weingärtner O, *et al.* Pflanzliche Sterole als Nahrungsmitteladditiva zur Prävention kardiovaskulärer Erkrankungen. *Dtsch Med Wochenschr* 2008; **133:** 1201–4.
11. Weingärtner O, *et al.* Controversial role of plant sterol esters in the management of hypercholesterolaemia. *Eur Heart J* 2009; **30:** 404–9.
12. Talati R, *et al.* The comparative efficacy of plant sterols and stanols on serum lipids: a systematic review and meta-analysis. *J Am Diet Assoc* 2010; **110:** 719–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fitoadapt; Prostacur; ***Austria***: Harzol; ***Chile***: A-Colest; ***Ger.***: Azuprostat†; Harzol; Sitosterin; Triastonal†; ***Indon.***: Cholbalance; ***Pol.***: Prostalizyna; Prosterol; ***Thai.***: Mebo; ***UAE***: Mebo.

Multi-ingredient Preparations. ***Austral.***: Cholesterol Health; ***Chile***: Rebakol; ***Fr.***: Acyprost; Bakol; Prostaform; ***Hong Kong***: Basikol; Physiogel; ***Hung.***: Shilajit; ***Ital.***: Sametrix; ***Malaysia***: O'Yes; ***Philipp.***: Trilipid; ***Rus.***: Herbion Urtica (Гербион Уртика); ***Singapore***: Basikol; Bios Life; Centrum Cardio; ES-TriGUARD; ***UK***: Kolestop; Lestrin; ***Ukr.***: Vitrum Cardio (Вітрум Кардио); ***USA***: Animi-3 with Vitamin D; Better Cholesterol; Cholesterol Support; MacuTrition; Prostate Support; Super Beta Prostate.

Plasminogen *(BAN)*

Plasminógeno; Плазминоген.

CAS — 9001-91-6.

Profile

Plasminogen is the specific substance derived from plasma which, when activated to plasmin, has the property of lysing fibrinogen, fibrin, and some other proteins. Its role in the control of haemostasis is described further on p. 1124.3. Plasminogen has been investigated as a thrombolytic and has been used with other blood products in wound-sealant preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Tissucol Duo Quick†; Tissucol†; ***Belg.***: Tissucol Duo; Tissucol Kit; ***Canad.***: Tisseel; ***Cz.***: Tissucol; ***Denm.***: Tisseel Duo Quick; ***Fin.***: Tisseel Duo Quick; ***Fr.***: Tissucol; ***Ger.***: Tissucol Duo S; Tissucol-Kit; ***Hong Kong***: Tisseel; ***Hung.***: Tissucol-Kit; ***Israel***: Tisseel†; ***Rus.***: Tissucol Kit (Тиссукол Кит); ***Spain***: Tissucol Duo; ***Swed.***: Tisseel Duo Quick; ***Switz.***: Tissucol Duo S†; Tissucol†; ***UK***: Tisseel.

Policosanol

Поликосанол.
CAS — 142583-61-7.
ATC — C10AX08.
ATC Vet — QC10AX08.

Octacosanol

Cluytyl Alcohol; Montanyl Alcohol; Octacosyl Alcohol; Октакосанол.
1-Octacosanol.
$C_{28}H_{58}O$=410.8
CAS — 557-61-9.
UNII — 8I12215OVK.

Profile

Policosanol is a mixture of higher primary aliphatic alcohols (fatty alcohols) derived from plant waxes such as sugar cane wax; it is also found in beeswax and in wheat-germ oil (p. 2647.1). The main component is octacosanol. Policosanol appears to have cholesterol-lowering properties and has been used in the treatment of hypercholesterolaemias, although its benefit has been disputed. Both policosanol and octacosanol are used in nutritional supplements.

References.
1. Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J* 2002; **143:** 356–65.
2. Pepping J. Policosanol. *Am J Health-Syst Pharm* 2003; **60:** 1112–5.
3. Berthold HK, *et al*. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. *JAMA* 2006; **295:** 2262–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lipex; ***Austral.***: Policor; ***Chile***: PPG; ***China***: PPG (甲烷嘿); ***India***: Cosanol; ***Indon.***: Polikos†; ***Mex.***: Mercol†; ***S.Afr.***: Phytocor.

Multi-ingredient Preparations. ***India***: Cardistim; Enduranz; Megalip; Natrolip; ***Ital.***: Ad_3; Artedin; Berart; Colesterase; Esterol Plus; Novostatin; Plusvit; ***Singapore***: Bios Life; ***UK***: Chol-Aid; Octacosanol; ***USA***: Otic Edge†.

Polythiazide *(BAN, USAN, rINN)* ⊗

NSC-108161; P-2525; Politiazida; Polythiazidum; Polytiatsidi; Polytiazid; Политиазид.
6-Chloro-3,4-dihydro-2-methyl-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.
$C_{11}H_{13}ClF_3N_3O_4S_3$=439.9
CAS — 346-18-9.
ATC — C03AA05.
ATC Vet — QC03AA05.
UNII — 36780APV5N.

Pharmacopoeias. In *Br.*

BP 2014: (Polythiazide). A white or almost white, crystalline powder with an alliaceous odour. Practically insoluble in water and in chloroform; sparingly soluble in alcohol.

Profile

Polythiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It has been given orally for hypertension, and for oedema, including that associated with heart failure.

Pharmacokinetics. Polythiazide is fairly readily absorbed from the gastrointestinal tract. Diuresis begins within about 2 hours of an oral dose, and lasts for 24 to 48 hours. The estimated plasma elimination half-life is about 26 hours. More than 80% may be bound to plasma proteins. It is excreted mainly in the urine as unchanged polythiazide and metabolites.

References.
1. Hobbs DC, Twomey TM. Kinetics of polythiazide. *Clin Pharmacol Ther* 1978; **23:** 241–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Gr.***: Renese R.

Pharmacopoeial Preparations
BP 2014: Polythiazide Tablets.

Potassium Canrenoate *(BANM, rINN)* ⊗

Aldadiene Potassium; Canrénoate de Potassium; Canrenoate Potassium (USAN); Canrenoato de potasio; Kalii Canrenoas; Kaliumkanrenoaatti; Kaliumkanrenoat; MF-465a; SC-14266; Калия Канреноат.
Potassium 17-hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylate.
$C_{22}H_{25}KO_4$=396.6
CAS — 4138-96-9 (canrenoic acid); 2181-04-6 (potassium canrenoate).
ATC — C03DA02.
ATC Vet — QC03DA02.
UNII — M671F9NLEA.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Potassium canrenoate is a potassium-sparing diuretic with actions and uses similar to those of spironolactone (p. 1500.1), but only about 0.7 times its potency. Canrenone (p. 1331.1) is a metabolite common to both drugs, but its contribution to the pharmacological action is unclear. Potassium canrenoate is used in the treatment of refractory oedema associated with heart failure (p. 1262.3) or hepatic disease when an injectable aldosterone antagonist is required. It may be given in doses of 200 to 400 mg daily, increasing to 800 mg daily in exceptional cases; it is given by slow intravenous injection over a period of 2 to 3 minutes for each 200 mg or by intravenous infusion in glucose 5% or sodium chloride 0.9%.

For doses in children, see below.

Administration in children. Although potassium canrenoate is unlicensed in the UK for children, the *BNFC* suggests that it may be given to neonates, infants, and children for short-term diuresis in heart failure, oedema, and ascites. The intravenous dose, given by injection (over at least 3 minutes) or infusion, is 1 to 2 mg/kg (maximum 200 mg) twice daily.

Adverse Effects and Precautions

As for Spironolactone, p. 1501.2. Irritation or pain may occur at the site of injection.

Effects on endocrine function. A lower incidence of gynaecomastia has been reported in patients with hepatic cirrhosis and ascites during use of potassium canrenoate than with equivalent doses of spironolactone,[1] and spironolactone-induced gynaecomastia disappeared when spironolactone was replaced by potassium canrenoate in a patient with hyperaldosteronism.[2] This suggests that metabolites other than canrenone (a common metabolite of both canrenoate and spironolactone thought to be responsible for their activity) or possibly spironolactone itself may be responsible for the anti-androgenic effects of spironolactone.[3,4]

1. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i:** 626.
2. Dupont A. Disappearance of spironolactone-induced gynaecomastia during treatment with potassium canrenoate. *Lancet* 1985; **ii:** 731.
3. Gardiner P. Spironolactone and potassium canrenoate metabolism. *Lancet* 1985; **ii:** 1432.
4. Overdiek JWPM, Merkus FWHM. Spironolactone metabolism and gynaecomastia. *Lancet* 1986; **i:** 1103.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium canrenoate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11).

Interactions

As for Spironolactone, p. 1502.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Aldactone; ***Belg.***: Canrenol; Soldactone; ***Cz.***: Aldactone; ***Fr.***: Soludactone; ***Ger.***: Aldactone; ***Ital.***: Diurek; Kanrenol; Luvion; ***Neth.***: Soldactone; ***Pol.***: Aldactone; ***Switz.***: Soldactone.

Multi-ingredient Preparations. ***Ital.***: Kadiur.

Prajmalium Bitartrate *(BAN, rINN)*

Bitartrato de prajmalio; GT-1012; NPAB; Prajmalii Bitartras; Prajmaline Bitartrate; Prajmalio, bitartrato de; Prajmalium, Bitartrate de; Праймалия Битартрат.
N-Propylajmalinium hydrogen tartrate.
$C_{23}H_{33}N_2O_2,C_4H_5O_6$=518.6
CAS — 35080-11-6 (prajmalium); 2589-47-1 (prajmalium bitartrate).
ATC — C01BA08.
ATC Vet — QC01BA08.
UNII — H671L9190Z.

Uses and Administration

Prajmalium is a class I antiarrhythmic (p. 1243.1) and is the *N*-propyl derivative of ajmaline (p. 1295.2). It is given orally as the bitartrate in the management of supraventricular and ventricular arrhythmias (p. 1266.1) in initial doses of 60 to 80 mg daily. Maintenance doses of 20 to 40 mg daily in divided doses are used.

Adverse Effects and Precautions

As for Ajmaline, p. 1295.2.

Effects on the liver. Cholestatic jaundice associated with pruritus, chills, and eosinophilia[1] was attributed to an allergic reaction to prajmalium bitartrate in a patient 20 days after the start of treatment.

1. Rotmensch HH, *et al*. Cholestatic jaundice: an immune response to prajmalium bitartrate. *Postgrad Med J* 1980; **56:** 738–41.

Effects on mental state. Confusion and disorientation occurred[1] on 2 occasions in a 67-year-old man given prajmalium bitartrate 100 mg daily for the control of tachycardia; the confusion rapidly disappeared when prajmalium was withdrawn.

1. Lessing JB, Copperman IJ. Severe cerebral confusion produced by prajmalium bitartrate. *BMJ* 1977; **2:** 675.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Neo-Gilurytmal; ***Cz.***: Neo-Gilurytmal; ***Ger.***: Neo-Gilurytmal; ***Hung.***: Neo-Gilurytmal; ***Indon.***: Neo-Gilurytmal.

Multi-ingredient Preparations. ***Spain***: Cresophene.

Prasugrel Hydrochloride

(BANM, USAN, rINNM)

LY-640315; Prasugrel, Chlorhydrate de; Prasugrel, hidrocloruro de; Prasugreli Hydrochloridum; Празугрела Гидрохлорид.
5-[(1*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride.
$C_{20}H_{20}FNO_3S,HCl$=409.9
CAS — 389574-19-0.
ATC — B01AC22.
ATC Vet — QB01AC22.
UNII — G89JQ59I13.

Uses and Administration

Prasugrel hydrochloride is a thienopyridine antiplatelet drug with similar properties to clopidogrel (p. 1342.3). It is given, with aspirin, for the prevention of atherothrombotic events in patients with acute coronary syndromes, including unstable angina (p. 1254.3) and myocardial infarction (p. 1257.1) who are undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p. 1259.2).

Prasugrel is given orally as the hydrochloride, but doses are expressed in terms of the base; 5.5 mg of prasugrel hydrochloride is equal to about 5 mg of base. Treatment should be started with a loading dose of 60 mg and then continued at a dose of 10 mg once daily for up to 12 months. Patients weighing under 60 kg and those aged 75 years and older should be given a maintenance dose of 5 mg, although use in those aged 75 years and older is not generally recommended due to the increased risk of bleeding.

References.
1. Wiviott SD, *et al*. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine $P2Y_{12}$ antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation* 2005; **111:** 3366–73.
2. Jakubowski JA, *et al*. A multiple dose study of prasugrel (CS-747), a novel thienopyridine $P2Y_{12}$ inhibitor, compared with clopidogrel in healthy humans. *Br J Clin Pharmacol* 2006; **63:** 421–30.
3. Brandt JT, *et al*. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007; **153:** 66.
4. Wiviott SD, *et al*. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–15.
5. Wiviott SD, *et al*. PRINCIPLE-TIMI44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and

Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007; **116:** 2923–32.
6. Antman EM, *et al*. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008; **51:** 2028–33.
7. Montalescot G, *et al*. TRITON-TIMI 38 Investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009; **373:** 723–31.
8. Reinhart KM, *et al*. Prasugrel: a critical comparison with clopidogrel. *Pharmacotherapy* 2009; **29:** 1441–51.
9. Duggan ST, Keating GM. Prasugrel: a review o f its use i n patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Drugs* 2009; **69:** 1707–26.
10. Scott DM, *et al*. P2Y12 inhibitors in cardiovascular disease: focus on prasugrel. *Ann Pharmacother* 2009; **43:** 64–76.
11. Mousa SA, *et al*. Antiplatelet therapy prasugrel: a novel platelet ADP P2Y12 receptor antagonist. *Clin Appl Thromb Hemost* 2010; **16:** 170–6.

Adverse Effects and Precautions

As for Ticlopidine, p. 1512.2. The incidence of blood dyscrasias is lower with prasugrel and routine blood counts are not required.

Consideration should be given to stopping prasugrel at least 7 days before elective surgery.

Interactions

Prasugrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelet drugs, and NSAIDs. Clinically significant interactions associated with cytochrome P450 isoenzymes have not been reported; however, prasugrel is a weak inhibitor of CYP2B6 and might affect drugs with a narrow therapeutic window metabolised by this isoenzyme, such as cyclophosphamide and efavirenz.

Pharmacokinetics

Prasugrel is a prodrug. It is rapidly absorbed after oral doses and undergoes hydrolysis in the intestine before being metabolised by several cytochrome P450 isoenzymes to the active metabolite. Peak plasma concentrations of the active metabolite occur in about 30 minutes. Binding of the active metabolite to human serum albumin is about 98%. The active metabolite is further metabolised to 2 inactive compounds which are excreted in the urine and faeces; about 68% of a dose is excreted in urine and about 27% in faeces. The elimination half-life of the active metabolite is about 7.4 hours.

References.

1. Wrishko RE, *et al*. Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. *J Clin Pharmacol* 2009; **49:** 984–98.
2. Mega JL, *et al*. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* 2009; **119:** 2553–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Effient; Nefagrel; Procardia; Trocal; ***Austral.***: Effient; ***Austria***: Efient; ***Belg.***: Efient; ***Braz.***: Effient; ***Canad.***: Effient; ***Cz.***: Efient; ***Denm.***: Efient; ***Fr.***: Efient; ***Ger.***: Efient; ***Gr.***: Efient; ***Hong Kong***: Effient; ***Irl.***: Efient; ***Israel***: Effient; ***Malaysia***: Effient; ***Neth.***: Efient; ***Norw.***: Efient; ***NZ***: Effient; ***Philipp.***: Effient; ***Pol.***: Efient; ***Port.***: Efient; ***Singapore***: Effient; ***Spain***: Efient; ***Swed.***: Efient; ***Switz.***: Efient; ***UK***: Efient; ***USA***: Effient.

Pravastatin Sodium *(BANM, USAN, rINNM)*

CS-514; Eptastatin Sodium; 3β-Hydroxycompactin Sodium; Natrii Pravastatinum; Pravastatiininatrium; Pravastatin-Natrium; Pravastatin sodná sůl; Pravastatina sódica; Pravastatine sodique; Pravastatinnatrium; Pravastatino natrio druska; Pravastatinum Natricum; Pravasztatin-nátrium; SQ-31000; Натрий Правастатин.

Sodium (3*R*,5*R*)-7-{(1*S*,2*S*,6*S*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-6-hydroxy-2-methyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl}-3,5-dihydroxyheptanoate.

$C_{23}H_{35}O_7Na$=446.5

CAS — 81093-37-0 (pravastatin); 81131-70-6 (pravastatin sodium).

ATC — C10AA03.

ATC Vet — QC10AA03.

UNII — 3M8608UQ61.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Pravastatin Sodium). A white to yellowish-white, hygroscopic, powder or crystalline powder. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol. A 5% solution in water has a pH of 7.2 to 9.0. Store in airtight containers.

USP 36: (Pravastatin Sodium). A white to yellowish white hygroscopic powder. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol; practically insoluble in acetonitrile and in chloroform. Store in airtight containers.

Uses and Administration

Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3).

Pravastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p. 1248.1), including hypercholesterolaemias, combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), dysbetalipoproteinaemia (type III), and post-transplantation hyperlipidaemia. It is also used for cardiovascular risk reduction (p. 1246.1), including primary prophylaxis in hypercholesterolaemic patients, and secondary prophylaxis, including prevention of stroke, in patients with clinically-evident ischaemic heart disease.

Pravastatin is given orally as the sodium salt; the usual dose is 10 to 40 mg of pravastatin sodium once daily at bedtime. The dose may be adjusted, according to response, at intervals of not less than 4 weeks. UK licensed product information states that the maximum dose is 40 mg once daily, but US licensed product information allows a maximum of 80 mg once daily in patients with hypercholesterolaemia. Low initial doses are recommended in patients with hepatic or renal impairment (see below).

In patients also taking *ciclosporin*, UK licensed product information recommends an initial dose of 20 mg once daily, but US licensed product information states an initial dose of 10 mg; dose increases should be made with caution.

For the use of pravastatin in children and adolescents, see below.

General reviews.

1. McTavish D, Sorkin EM. Pravastatin: a review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1991; **42:** 65–89.
2. Haria M, McTavish D. Pravastatin: a reappraisal of its pharmacological properties and clinical effectiveness in the management of coronary heart disease. *Drugs* 1997; **53:** 299–336.
3. Bang LM, Goa KL. Pravastatin: a review of its use in elderly patients. *Drugs Aging* 2003; **20:** 1061–82.
4. del Sol AI, Nanayakkara PW. Pravastatin: an evidence-based statin? *Expert Opin Drug Metab Toxicol* 2008; **4:** 821–5.

Administration in children. In children with heterozygous familial hypercholesterolaemia, pravastatin sodium is licensed in doses of 10 to 20 mg once daily in those aged 8 to 13 years and 10 to 40 mg once daily in those aged 14 to 18 years. Short-term studies have suggested that pravastatin effectively reduces cholesterol and is safe in children with familial hypercholesterolaemia[1] and in children taking immunosuppressants after heart transplant,[2] although plasma concentrations may be higher in the latter group. A randomised controlled study[3] and a prospective study[4] have also found that pravastatin is effective and well tolerated in familial hypercholesterolaemia, and there is some evidence[5] that carotid intima media thickness (a marker of atherosclerosis) may be reduced.

1. Hedman M, *et al*. Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. *Clin Pharmacol Ther* 2003; **74:** 178–85.
2. Hedman M, *et al*. Pharmacokinetics and pharmacodynamics of pravastatin in pediatric and adolescent cardiac transplant recipients on a regimen of triple immunosuppression. *Clin Pharmacol Ther* 2004; **75:** 101–109.
3. Wiegman A, *et al*. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; **292:** 331–7.
4. Hedman M, *et al*. Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia: a prospective clinical follow-up study. *J Clin Endocrinol Metab* 2005; **90:** 1942–52.

Administration in hepatic or renal impairment. Patients with moderate or severe renal or significant hepatic impairment should be given pravastatin sodium in an initial dose of 10 mg daily, and the dose should be increased with caution.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pravastatin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of statins with other drugs are described under simvastatin (p. 1494.2). Pravastatin is not significantly metabolised by the cytochrome P450 enzyme system and does not have the same interactions with enzyme inhibitors as simvastatin, although caution has been advised when such combinations are used. Increased plasma-pravastatin concentrations have been reported in some patients receiving ciclosporin and low doses should be used (see Uses and Administration, above).

Pharmacokinetics

Pravastatin is rapidly but incompletely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. The absolute bioavailability of pravastatin is 17%. About 50% of the circulating drug is bound to plasma proteins. The plasma elimination half-life of pravastatin is 1.5 to 2 hours. About 70% of an oral dose of pravastatin is excreted in the faeces, as unabsorbed drug and via the bile, and about 20% is excreted in the urine.

General reviews.

1. Quion JAV, Jones PH. Clinical pharmacokinetics of pravastatin. *Clin Pharmacokinet* 1994; **27:** 94–103.
2. Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet* 2000; **39:** 397–412.
3. Neuvonen PJ, *et al*. Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; **47:** 463–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pravacol; ***Austral.***: Cholstat; Lipostat; Liprachol†; Pravachol; Pravastat; Vastoran†; ***Austria***: Panchol; ***Belg.***: Prareduct; Pravasine; ***Braz.***: Mevalotin; Pravacol; ***Canad.***: Pravachol; ***Chile***: Pravacol; ***China***: Fu Li Ta Zhi (富利他之); Fu Ta Ning (福他宁); Mevalotin (美百乐镇); Pravachol; Pu Hui Zhi (浦惠旨); ***Cz.***: Vitastat; ***Denm.***: Pravachol†; ***Fin.***: Pravachol†; ***Fr.***: Elisor; Vasten; ***Ger.***: Mevalotin†; Prava-Q†; Pravabeta†; Pravagamma†; PravaLich†; Pravalip†; Pravasin; ***Gr.***: Analipin; Antisterin; Asto-Chol; Cholipravin; Cosivatin; Defantum; Liplow; Lipoprav; Maxudin; Ositron; Panlipol; Pravachol; Pravadium; Pravafact; Pravahelp; Pravalen; Pravalip; Pravalong; Pravanox; Pravaxis; Pravedol; Pravin; Pravostin; Privast; Sosmin; Vastil; Zoter; Zyon; ***Hong Kong***: Pravachol†; ***Hung.***: Nikron; Prastin†; Pravastar†; ***India***: Pravator; ***Indon.***: Cholespar; Gravastin; Koleskol; Mevachol; Novales; Pravachol†; Pravinat; ***Irl.***: Bellprav†; Beneprav; ByStat; Cholstat†; Lipaprav; Lipostat; Lipovas; Pravalo†; Pravamel; Pravat; Pravitin; ***Israel***: Pravalip; ***Ital.***: Aplactin; Langiprav; Prasterol; Pravaselect; Sanaprav; Selectin; Setac; Vasticor; ***Jpn***: Mevalotin; ***Malaysia***: Pratin; Pravachol; Pravid; ***Mex.***: Accogard; Astin; Brakhor; Celuterol; Colpradin; Emival†; Kenstatin; Kenvastin; Lexet; Loretsin; Mavitina; Novina; Paver; Piflaxan; Prascolend†; Prasiver; Pravacol; Striacol; Tissulest; Tratinal; Tridanil-H; Valprastin; Vaprasil; Varlex; Vastoran; Xipral; ***Neth.***: Lipratif; Pratiflip; Pravandrea; Selektine; Statifil; Vastatifix; ***Norw.***: Pravachol; ***NZ***: Cholvastin; Lipostat†; Pravachol; ***Philipp.***: Lipostat†; Pravaz; Stanidine†; ***Pol.***: Apo-Prava†; Pravator; ***Port.***: Lipra; Pravacol; Pritanol; Sanaprav; ***S.Afr.***: Colite; Novales; Pixeta; Pixeta; Pranalip†; Prava; Pravacor; Pravacor; ***Singapore***: Pravachol; ***Spain***: Bristacol; Lipemol; Liplat; Minuscol; Prareduct; Pritadol; ***Swed.***: Pravachol†; ***Switz.***: Mevalotin; Pravalotin; Pravasta eco†; Pravastax; Pravatine; Selipran; ***Thai.***: Mevalotin; ***Turk.***: Pravachol; Praxal; ***UK***: Lipostat; ***USA***: Pravachol; ***Venez.***: Mevalotin; Pravacol.

Multi-ingredient Preparations. ***Canad.***: PravASA†; ***Cz.***: Pravafenix; ***Fr.***: Pravadual; ***Indon.***: Novosta; ***Irl.***: Pravafenix.

Pharmacopoeial Preparations

BP 2014: Pravastatin Tablets;
USP 36: Pravastatin Sodium Tablets.

Prazosin Hydrochloride

(BANM, USAN, rINNM)

CP-12299-1; Furazosin Hydrochloride; Hidrocloruro de prazosina; Pratsosiinihydrokloridi; Prazosin Hidroklorür; Prazosina, hidrocloruro de; Prazosine, Chlorhydrate de; Prazosinhydrochlorid; Prazosin-hydrochlorid; Prazosinhydroklorid; Prazosini Hydrochloridum; Prazozin-hidroklorid; Prazozino hidrochloridas; Празозина Гидрохлорид.

2-[4-(2-Furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine hydrochloride.

$C_{19}H_{21}N_5O_4$,HCl=419.9

CAS — 19216-56-9 (prazosin); 19237-84-4 (prazosin hydrochloride).

ATC — C02CA01.

ATC Vet — QC02CA01.

UNII — X0Z7454B90.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Prazosin Hydrochloride). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 36: (Prazosin Hydrochloride). A white to tan powder. Slightly soluble in water, in dimethylacetamide, in

dimethylformamide, and in methyl alcohol; very slightly soluble in alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Prazosin is an alpha blocker (p. 1243.1) that acts by selective blockade of alpha$_1$-adrenoceptors. It is used in the management of hypertension (p. 1251.1), in Raynaud's syndrome (see Peripheral Vascular Disease, below), and to relieve symptoms of urinary obstruction in benign prostatic hyperplasia (p. 2347.1). It has also been used in heart failure (p. 1262.3).

Prazosin produces peripheral dilatation of both arterioles and veins and reduction of peripheral resistance, usually without reflex tachycardia. It reduces both standing and supine blood pressure with a greater effect on the diastolic pressure. It is reported to have no effect on renal blood flow or glomerular filtration rate, and has little effect on cardiac output in hypertensive patients. In patients with heart failure, prazosin reduces both preload and afterload and produces an improvement in cardiac output, although tolerance may develop. In benign prostatic hyperplasia, prazosin may relieve the symptoms of urinary obstruction by reducing smooth muscle tone in the prostate and bladder neck.

Prazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Prazosin hydrochloride 1.1 mg is equivalent to about 1 mg of prazosin. After oral dosage the hypotensive effect is seen within 2 to 4 hours and persists for several hours. Full effects are seen after 4 to 6 weeks.

A low starting dose is given in the evening to lessen the risk of collapse which may occur in some patients after the first dose (see Adverse Effects, below). Doses may need to be reduced in the elderly and in patients with hepatic or renal impairment.

In **hypertension**, the usual initial dose in the UK is 500 micrograms two or three times daily for 3 to 7 days; if tolerated the dose may then be increased to 1 mg two or three times daily for a further 3 to 7 days, and thereafter gradually increased, according to the patient's response, to a usual maximum of 20 mg daily in divided doses. In the US the recommended starting dose is 1 mg two or three times daily and up to 40 mg daily in divided doses has been given; however, the usual maintenance dose is between 6 and 15 mg daily. Smaller doses may be required in patients also taking other antihypertensives. Modified-release preparations may allow once daily dosing.

In **Raynaud's syndrome** and in **benign prostatic hyperplasia** an initial dose of 500 micrograms twice daily may be given, increasing to a maintenance dose not exceeding 2 mg twice daily.

In **heart failure**, treatment has been started with 500 micrograms two to four times daily and increased gradually according to response; the usual maintenance dose has been 4 to 20 mg daily.

Alcohol dependence. Prazosin has been investigated in the maintenance of abstinence (p. 1735.1) in patients with alcohol dependence.[1]

1. Simpson TL, *et al.* A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. *Alcohol Clin Exp Res* 2009; **33:** 255–63.

Erectile dysfunction. Prazosin has been given transurethrally with alprostadil[1] in the management of erectile dysfunction (p. 2348.2). However, alpha blockers have also been reported to cause erectile dysfunction (see Effects on Sexual Function, below).

1. Peterson CA, *et al.* Erectile response to transurethral alprostadil, prazosin and alprostadil-prazosin combinations. *J Urol (Baltimore)* 1998; **159:** 1523–8.

Familial Mediterranean fever. Attacks of familial Mediterranean fever (p. 605.1) are usually treated with prophylactic colchicine, but its use may be limited by adverse effects. A Japanese man who had suffered from attacks for 16 years was treated[1] with prazosin 3 mg daily. There were no further attacks for more than a year after starting treatment, but stopping prazosin resulted in a recurrence.

1. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129:** 424–5.

Muscle cramp. Skeletal muscle cramp may occur during haemodialysis, possibly due to activation of the sympathetic nervous system. Prazosin was reported[1] to reduce the incidence of cramp in 4 of 5 patients with frequent haemodialysis-associated muscle cramp. However, the increased incidence of hypotension reported might limit its use for this indication.

1. Sidhom OA, *et al.* Low-dose prazosin in patients with muscle cramps during hemodialysis. *Clin Pharmacol Ther* 1994; **56:** 445–51.

Peripheral vascular disease. Alpha blockers, including prazosin, may be used in the management of Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3). Studies of the benefits of prazosin have produced varying results. A short-term reduction in number and duration of attacks was reported in 5 of 7 patients given prazosin 2 mg daily but only 1 patient had complete relief from attacks and few could tolerate doses higher than 6 mg daily.[1] Improvements were not maintained during continued treatment for 2 months. Others[2,3] have reported benefit from prazosin 1 mg two or three times daily in the majority of patients, with one study suggesting greater benefit in Raynaud's disease (the primary, idiopathic form) than in secondary Raynaud's syndrome.[2] In a subsequent study, higher doses of prazosin (2 or 4 mg three times daily) were no more effective than 1 mg three times daily, and were associated with a significantly greater incidence of adverse effects.[4] A systematic review[5] concluded that prazosin was modestly effective in the treatment of Raynaud's syndrome secondary to scleroderma.

1. Nielsen SL, *et al.* Prazosin treatment of primary Raynaud's phenomenon. *Eur J Clin Pharmacol* 1983; **24:** 421–3.
2. Allegra C, *et al.* Pharmacological treatment of Raynaud's phenomenon: a new therapeutic approach. *Curr Ther Res* 1986; **40:** 303–11.
3. Wollersheim H, *et al.* Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther* 1986;**40:** 219–25.
4. Wollersheim H, Thien T. Dose-response study of prazosin in Raynaud's phenomenon: clinical effectiveness versus side effects. *J Clin Pharmacol* 1988; **28:** 1089–93.
5. Harding SE, *et al.* Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 24/06/05).

Post-traumatic stress disorder. Post-traumatic stress disorder (PTSD—p. 1029.2) is usually treated with psychotherapy or drugs such as SSRIs. Increased alpha$_1$-adrenergic receptor activity may be a contributory factor, and several studies have reported that treatment with prazosin improves nightmares and sleep disturbances in patients with this condition.[1-3] A reduction in nightmares occurred in 5 patients taking part in a small 6-week open-label study;[4] doses ranged from 1 mg at night to 2 mg night and morning. A similar improvement was found in a retrospective study[5] of combat veterans with chronic treatment-resistant symptoms, where doses of prazosin were increased gradually from 1 mg at night up to a maximum daily dose of 20 mg if required, and in a placebo-controlled study[6] in similar patients given doses of up to 15 mg at night. Another small study[7] and a case report[8] have also reported benefit; doses varied from 1 mg at night to 10 mg daily in 2 divided doses. A cohort study involving retrospective review of 62 patients with PTSD treated with prazosin and 175 given quetiapine found that short-term benefits with the 2 drugs were comparable;[9] however, prazosin was better tolerated and patients were less likely to stop therapy, so long-term efficacy was therefore greater in this group.

1. Dierks MR, *et al.* Prazosin treatment of nightmares related to posttraumatic stress disorder. *Ann Pharmacother* 2007; **41:** 1013–17.
2. Taylor HR, *et al.* Prazosin for treatment of nightmares related to posttraumatic stress disorder. *Am J Health-Syst Pharm* 2008; **65:** 716–22.
3. Miller LJ. Prazosin for the treatment of posttraumatic stress disorder sleep disturbances. *Pharmacotherapy* 2008; **28:** 656–66.
4. Taylor F, Raskind MA. The α_1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 82–5.
5. Raskind MA, *et al.* Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry* 2002; **63:** 565–8.
6. Raskind MA, *et al.* A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 2007; **61:** 928–34.
7. Raskind MA, *et al.* Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 2003; **160:** 371–3.
8. Griffith LJ. Case report: use of prazosin for treatment of posttraumatic stress disorder. *Am Fam Physician* 2005; **72:** 758, 761.
9. Byers MG, *et al.* Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. *J Clin Psychopharmacol* 2010; **30:** 225–9.

Renal calculi. For the potential use of alpha blockers to aid the passage of renal calculi, see under Uses of Tamsulosin Hydrochloride, p. 2369.2.

Scorpion stings. Stings from the Indian red scorpion (*Mesobuthus tamulus*) are potentially fatal. The scorpion venom is a potent sympathetic stimulator resulting in high circulating catecholamines, hypertension, arrhythmias, pulmonary oedema, and circulatory failure. The efficacy of antivenom is questionable and treatment for cardiotoxicity is supportive (see p. 2418.1). Prazosin, given orally, appears to be beneficial and has been suggested[1,2] as first-line treatment, except in cases of severe pulmonary oedema. Prazosin has also been used in other countries to treat stings by dangerous scorpion species.[3-5]

1. Bawaskar HS, Bawaskar PH. Scorpion envenoming and the cardiovascular system. *Trop Doct* 1997; **27:** 6–9.
2. Bawaskar HS, Bawaskar PH. Utility of scorpion antivenin vs prazosin in the management of severe Mesobuthus tamulus (Indian red scorpion) envenoming at rural setting. *J Assoc Physicians India* 2007; **55:** 14–21.
3. Koseoglu Z, Koseoglu A. Use of prazosin in the treatment of scorpion envenomation. *Am J Ther* 2006; **13:** 285–7.
4. Al-Asmari AK, *et al.* Role of prazosin on cardiovascular manifestations and pulmonary edema following severe scorpion stings in Saudi Arabia. *Saudi Med J* 2008; **29:** 299–302.
5. Peker E, *et al.* Prazosin treatment in the management of scorpion envenomation. *Hum Exp Toxicol* 2010; **29:** 231–3.

Adverse Effects

Prazosin hydrochloride can cause orthostatic hypotension which may be severe and produce syncope after the initial dose; it may be preceded by tachycardia. This reaction can be avoided by starting treatment with a low dose, preferably at night (see Uses and Administration, above). The hypotensive effects may be exaggerated by exercise, heat, or alcohol ingestion.

The more common adverse effects include dizziness, drowsiness, headache, lack of energy, nausea, and palpitations, and may diminish with continued prazosin therapy or with a reduction in dosage. Other adverse effects include oedema, chest pain, dyspnoea, constipation, diarrhoea, vomiting, depression and nervousness, sleep disturbances, vertigo, hallucinations, paraesthesia, nasal congestion, epistaxis, dry mouth, urinary frequency and incontinence, reddened sclera, blurred vision, tinnitus, abnormal liver enzyme values, pancreatitis, arthralgia, alopecia, lichen planus, skin rashes, pruritus, and diaphoresis. Impotence and priapism have also been reported.

General reviews.

1. Carruthers SG. Adverse effects of α_1-adrenergic blocking drugs. *Drug Safety* 1994; **11:** 12–20.

Effects on the cardiovascular system. Orthostatic hypotension, preceded by tachycardia and sometimes producing syncope, is an established adverse effect of the initial dose of prazosin. Sinus bradycardia was associated with prazosin in a patient who had light headedness after each daily dose.[1]

Chest pain is a known adverse effect of prazosin, but in a report[2] of acute intermittent left-sided chest pain in a patient being treated with the drug for post-traumatic stress disorder there was no evidence of hypotension or significant abnormalities of heart function, suggesting the symptom was non-specific.

1. Ball J. Symptomatic sinus bradycardia due to prazosin. *Lancet* 1994; **343:** 121.
2. Nuzhat SS, Osser DN. Chest pain in a young patient treated with prazosin for PTSD. *Am J Psychiatry* 2009; **166:** 618–19.

Effects on the gastrointestinal tract. Faecal incontinence in a 52-year-old man receiving prazosin was exacerbated by haemorrhoidectomy and appeared to be due to diminished resting anal tone, presumably because of smooth muscle relaxation secondary to alpha-adrenoceptor blockade.[1] Symptoms ceased almost immediately on stopping the drug.

1. Holmes SAV, *et al.* Faecal incontinence resulting from α_1-adrenoceptor blockade. *Lancet* 1990; **336:** 685–6.

Effects on mental function. Psychiatric symptoms including confusion, paranoia, and hallucinations developed in 3 patients associated with prazosin treatment.[1] Two of the patients had chronic renal failure and the other had mild renal impairment. Abnormal behaviour and dissociative symptoms were reported in another patient[2] given prazosin for post-traumatic stress disorder. Acute psychosis has also been reported with doxazosin.[3]

1. Chin DKF, *et al.* Neuropsychiatric complications related to use of prazosin in patients with renal failure. *BMJ* 1986; **293:** 1347.
2. Reardon CL, Factor RM. Bizarre behavior in a patient treated with prazosin for PTSD. *Am J Psychiatry* 2008; **165:** 774–5.
3. Evans M, *et al.* Drug induced psychosis with doxazosin. *BMJ* 1997; **314:** 1869.

Effects on sexual function. Alpha blockers have complex effects on male sexual function[1] and both priapism and erectile dysfunction have been reported. They promote erection by blocking alpha$_1$-adrenoceptors in the penis, and have been tried in erectile dysfunction (see under Uses and Administration, above), but the reduction in blood pressure they also cause may impair erectile function, leading to impotence. Alpha blockers may also have adverse effects on ejaculation, although this is less clear.

1. van Dijk MM, *et al.* Effects of α_1-adrenoceptor antagonists on male sexual function. *Drugs* 2006; **66:** 287–301.

Hypersensitivity. Urticaria and angioedema in a 70-year-old woman were attributed to prazosin.[1]

1. Ruzicka T, Ring J. Hypersensitivity to prazosin. *Lancet* 1983; **i:** 473–4.

Lupus erythematosus. One study has reported the formation of antinuclear antibodies in patients receiving prazosin,[1] but this is not in agreement with other reports,[2,3] and commentators consider the association unproven.[4] There is no evidence of the development of lupus erythematosus.[1]

1. Marshall AJ, *et al.* Positive antinuclear factor tests with prazosin. *BMJ* 1979; **1:** 165–6.
2. Wilson JD, *et al.* Antinuclear factor in patients on prazosin. *BMJ* 1979; **1:** 553–4.
3. Melkild A, Gaarder PI. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; **1:** 620–1.
4. Kristensen BØ. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; **1:** 621.

Urinary incontinence. There have been reports of urinary incontinence developing in patients receiving prazosin. Analysis[1] of 56 cases reported to the Australian Adverse Drug Reactions Advisory Committee indicated that typically symptoms appeared within 1 or 2 days of the start of therapy and persisted until the drug was withdrawn or the dose reduced. Both stress and urge incontinence occurred, sometimes in the same patient. Of the 56 patients, 51 were women and most were elderly. In a study[2] in women attending a hypertension clinic urinary incontinence was reported in 40.8% of 49 women receiving alpha blockers (prazosin, terazosin, or doxazosin) and in 16.3% of controls. Incontinence might be due to a reduction in urethral pressure induced by alpha-adrenoceptor blockade.

Interestingly, faecal incontinence has also been reported with prazosin—see Effects on the Gastrointestinal Tract, p. 1474.3.

1. Mathew TH, *et al.* Urinary incontinence secondary to prazosin. *Med J Aust* 1988; **148:** 305–6.
2. Marshall HJ, Beevers DG. α -Adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility. *Br J Clin Pharmacol* 1996; **42:** 507–9.

Treatment of Adverse Effects

If overdosage with prazosin occurs activated charcoal should be given if the patient presents within 1 hour of ingestion. Severe hypotension may occur and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement, and if necessary cautious intravenous infusion of a vasopressor. Prazosin is not removed by dialysis.

Precautions

Treatment with prazosin should be introduced cautiously because of the risk of sudden collapse after the initial dose. Extra caution is necessary in patients with hepatic or renal impairment and in the elderly.

Prazosin is not recommended for the treatment of heart failure caused by mechanical obstruction, for example aortic or mitral valve stenosis, pulmonary embolism, and restrictive pericardial disease. It should be used with caution in patients with angina pectoris. Prazosin may cause drowsiness or dizziness; patients so affected should not drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Cataract Surgery, under Precautions for Tamsulosin Hydrochloride, p. 2369.3.

Cerebral haemorrhage. Hypotension with disturbance of consciousness[1] occurred in 3 patients with recent cerebral haemorrhage after an initial dose of prazosin 500 micrograms.

1. Lin M-S, Hsieh W-J. Prazosin-induced first-dose phenomenon possibly associated with hemorrhagic stroke: a report of three cases. *Drug Intell Clin Pharm* 1987; **21:** 723–6.

Tolerance. Although prazosin may be of initial benefit in patients with chronic heart failure, some studies[1,2] have reported the development of tolerance to its haemodynamic effects on prolonged therapy. This may be partly due to upregulation of alpha$_1$ adrenoceptors.[3]

1. Packer M, *et al.* Role of the renin-angiotensin system in the development of hemodynamic and clinical tolerance to long-term prazosin therapy in patients with severe chronic heart failure. *J Am Coll Cardiol* 1986; **7:** 671–80.
2. Bayliss J, *et al.* Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. *BMJ* 1985; **290:** 1861–5.
3. Kersting F, *et al.* Preliminary evidence for the mechanism underlying the development of tolerance to prazosin in congestive heart failure: the α -agonistic properties of dobutamine unmasked by prazosin treatment. *J Cardiovasc Pharmacol* 1993; **21:** 537–43.

Interactions

The hypotensive effects of prazosin may be enhanced by use with diuretics and other antihypertensives, and by alcohol and other drugs that cause hypotension. The risk of first-dose hypotension may be particularly increased in patients receiving beta blockers or calcium-channel blockers.

Analgesics. *Indometacin* reduced prazosin-induced hypotension in 4 of 9 subjects.[1]

1. Rubin P, *et al.* Studies on the clinical pharmacology of prazosin II: the influence of indomethacin and of propranolol on the action and disposition of prazosin. *Br J Clin Pharmacol* 1980; **10:** 33–9.

Antidepressants and antipsychotics. A patient who was taking *amitriptyline* and *chlorpromazine* developed acute agitation when given prazosin.[1] The symptoms settled rapidly when prazosin was stopped. Antidepressants and antipsychotics may enhance the hypotensive effect of prazosin and other alpha blockers.

1. Bolli P, Simpson FO. New vasodilator drugs for hypertension. *BMJ* 1974; **1:** 637.

Calcium-channel blockers. An enhanced hypotensive effect has been reported in normotensive subjects given prazosin with *verapamil*; the effect may be due in part to enhanced bioavailability of prazosin.[1] Markedly increased hypotensive responses have also been reported with combined use of prazosin and *nifedipine*,[2,3] although the validity of such reports has been questioned.[4]

1. Pasanisi F, *et al.* Combined alpha adrenoceptor antagonism and calcium channel blockade in normal subjects. *Clin Pharmacol Ther* 1984; **36:** 716–23.
2. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin in treatment of hypertension. *BMJ* 1983; **287:** 1514.
3. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; **288:** 238–9.
4. Elliott HL, *et al.* Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; **288:** 238.

Digoxin. For reference to the effect of prazosin on serum-digoxin concentrations, see Alpha Blockers under Digoxin, p. 1356.1.

Pharmacokinetics

Prazosin is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. The bioavailability is variable and a range of 43 to 85% has been reported. Prazosin is highly bound to plasma proteins. It is extensively metabolised in the liver and some of the metabolites are reported to have hypotensive activity. It is excreted as the metabolites and 5 to 11% as unchanged prazosin mainly in the faeces via the bile. Less than 10% is excreted in the urine. Small amounts are distributed into breast milk. Its duration of action is longer than would be predicted from its relatively short plasma half-life of about 2 to 4 hours. Half-life is reported to be increased to about 7 hours in patients with heart failure.

The elderly. The bioavailability of prazosin was significantly reduced in the elderly, about 40% less unchanged drug reaching the systemic circulation compared with the young.[1] This was attributed to a reduction in the absorption from the gastrointestinal tract. The half-life was also prolonged in the elderly and this was associated with an increase in the volume of distribution at steady state. However, it was considered unlikely that these effects would have major clinical significance.

1. Rubin PC, *et al.* Prazosin disposition in young and elderly subjects. *Br J Clin Pharmacol* 1981; **12:** 401–4.

Protein binding. Although a study[1] found that prazosin was about 80 to 85% bound to serum albumin and only about 10 to 30% bound to α_1-acid glycoprotein *in vitro*, potential interactions between the binding proteins *in vivo* were not taken into account; binding to α_1-acid glycoprotein might be more significant in clinical practice. A subsequent study[2] indicated that variations in prazosin protein binding pre- and post-operatively were related to variations in concentration of the glycoprotein.

1. Brunner F, Müller WE. Prazosin binding to human α $_1$-acid glycoprotein (orosomucoid), human serum albumin, and human serum: further characterisation of the 'single drug binding site' of orosomucoid. *J Pharm Pharmacol* 1985; **37:** 305–9.
2. Sager G, *et al.* Binding of prazosin and propranolol at variable α $_1$-acid glycoprotein and albumin concentrations. *Br J Clin Pharmacol* 1989; **27:** 229–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Decliten; Minipres; ***Austral.***: Minipress; Pratsiol†; Pressin†; ***Austria***: Minipress; ***Belg.***: Minipress; ***Braz.***: Minipress; ***Canad.***: Apo-Prazo; Minipress; Novo-Prazin†; Nu-Prazo; ***Cz.***: Deprazolin†; ***Fin.***: Pratsiol; ***Fr.***: Alpress; Minipress; ***Ger.***: Adversuten†; ***Gr.***: Minipress; ***Hong Kong***: Apo-Prazo; CP-Prazo; Hyprosin†; Minipress; Mizosin†; ***Hung.***: Minipress; ***India***: Cyber; Czopress; Minipress; Prazocip; ***Irl.***: Hypovase†; ***Jpn***: Minipress; ***Malaysia***: Atodel; Minipress; Minison; Mizosin; ***Mex.***: Anapres†; Ensibest; Minipres; Sinozzard; ***NZ***: Apo-Prazo; Hyprosin†; Pratsiol†; ***S.Afr.***: Pratsiol; ***Singapore***: Apo-Prazo; Atodel; Minipress; Mizosin; ***Spain***: Minipres; ***Thai.***: Atodel; Hyposin; Lopress; Mima; Minipress; Polypress; Pressin; ***Turk.***: Minipress; ***UK***: Hypovase; ***USA***: Minipress; ***Venez.***: Minpres.

Pharmacopoeial Preparations
BP 2014: Prazosin Tablets;
USP 36: Prazosin Hydrochloride Capsules.

Probucol *(BAN, USAN, rINN)*

DH-581; Probucolum; Пробукол.
4,4′-(Isopropylidenedithio)bis(2,6-di-*tert*-butylphenol).
$C_{31}H_{48}O_2S_2$=516.8
CAS — 23288-49-5.
ATC — C10AX02.
ATC Vet — QC10AX02.
UNII — P3CTH044XJ.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Probucol). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in petroleum spirit; freely soluble in chloroform and in propyl alcohol. Protect from light.

Profile

Probucol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p. 1248.1). It lowers total plasma-cholesterol concentrations, mainly by reducing low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol concentrations but has little effect on triglyceride or very-low-density lipoprotein (VLDL)-cholesterol concentrations. It has also been used to prevent restenosis after reperfusion and revascularisation procedures (below), and in scleroderma.

Probucol prolongs the QT interval and has been associated with cardiac arrhythmias.

Reperfusion and revascularisation procedures. Restenosis is common after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Probucol, started a few weeks before the procedure, has been reported to reduce the rate of restenosis after coronary angioplasty,[1] and to reduce the need for repeat interventions,[1,2] although another study[3] found no effect.

1. Tardif J-C, *et al.* Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997; **337:** 365–72.
2. Daida H, *et al.* Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). *Am J Cardiol* 2000; **86:** 550–2.
3. Nunes GL, *et al.* Role of probucol in inhibiting intimal hyperplasia after coronary stent implantation: a randomized study. Abstract: *Am Heart J* 2006; **152:** 914. Full version: http://www.ahjonline.com/article/S0002-8703(06)00463-7/pdf (accessed 07/08/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Lorelco†; ***China***: Chang Tai (畅泰); Zhile (之乐); ***Philipp.***: Lorelco; ***Thai.***: Lurselle.

Pharmacopoeial Preparations
USP 36: Probucol Tablets.

Procainamide Hydrochloride

(BANM, rINNM)

Hidrocloruro de procainimida; Novocainamidum; Procainamida, hidrocloruro de; Procaïnamide, Chlorhydrate de; Procainamidhydrochlorid; Procainamidi Chloridum; Procainamidi hydrochloridum; Prokainiamidihydrokloridi; Prokainamid-hidroklorid; Prokainamid-hydrochlorid; Prokainamid-hydroklorid; Prokainamido hidrochloridas; Prokainamidu chlorowodorek; Прокаинамида Гидрохлорид.
4-Amino-*N*-(2-diethylaminoethyl)benzamide hydrochloride.
$C_{13}H_{21}N_3O$,HCl=271.8
CAS — 51-06-9 (procainamide); 614-39-1 (procainamide hydrochloride).
ATC — C01BA02.
ATC Vet — QC01BA02.
UNII — SI4064O0LX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Procainamide Hydrochloride). A white or very slightly yellow, hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 5.6 to 6.3. Store in airtight containers. Protect from light.

USP 36: (Procainamide Hydrochloride). A white to tan, odourless, crystalline powder. Very soluble in water; soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether and in benzene. A 10% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Procainamide is more stable in neutral solutions such as sodium chloride, than in acidic solutions such as glucose, but patients requiring intravenous procainamide often have heart failure and cannot tolerate the sodium load associated with sodium chloride injections. The stability of procainamide in glucose 5% is improved by neutralising the glucose using sodium bicarbonate, or storing the admixture at 5 degrees. The concentration of procainamide remained above 90% of the initial concentration for 24 hours if the glucose was first neutralised and this was considered more practical than refrigeration if extended stability was required.[1]

The compound formed by mixing procainamide hydrochloride with glucose 5% was shown to be a mixture of α- and β-glucosylamines[2] and about 10 to 15% of the procainamide was lost in this way after 10 hours at room temperature.

An oral liquid,[3] prepared from procainamide capsules, containing 5, 50, or 100 mg/mL of the hydrochloride was stable for at least 6 months when stored at 4 degrees to 6 degrees.

1. Raymond GG, *et al*. Stability of procainamide hydrochloride in neutralized 5% dextrose injection. *Am J Hosp Pharm* 1988; **45:** 2513–17.
2. Sianipar A, *et al*. Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994; **46:** 951–5.
3. Metras JI, *et al*. Stability of procainamide hydrochloride in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1992; **49:** 1720–4.

Uses and Administration

Procainamide is a class Ia antiarrhythmic (p. 1243.1); it has properties similar to those of quinidine (p. 1481.3).

Procainamide is usually reserved for the short-term management of severe or symptomatic ventricular arrhythmias (p. 1266.1) such as those following myocardial infarction. It may also be used in the management of atrial fibrillation.

Therapeutic effect is generally associated with plasma concentrations of 3 to 10 micrograms/mL. The dose of procainamide hydrochloride required will depend on the age, renal and hepatic function, and underlying cardiac condition of the patient: an adult with normal renal function generally requires up to 50 mg/kg daily in divided oral doses every 3 hours. Higher doses may be necessary for atrial arrhythmias. Modified-release preparations are available, and these are usually given at intervals of 6 or 12 hours.

In an emergency and under continuous ECG and blood pressure monitoring, procainamide hydrochloride may be given intravenously. The injection should be diluted in glucose 5% to permit better control of the speed of injection, and should be given in doses of 100 mg every 5 minutes at a rate not exceeding 50 mg/minute until the arrhythmia has been suppressed or a maximum dose of 1 g has been reached. A response may be obtained after 100 to 200 mg has been given and more than 500 or 600 mg is not generally required. Alternatively, procainamide hydrochloride may be given by continuous infusion of 500 to 600 mg over 25 to 30 minutes. Therapeutic plasma concentrations may then be maintained by infusion at a rate of 2 to 6 mg/minute. When transferring to oral therapy, a period of about 3 to 4 hours should elapse between the last intravenous dose and the first oral dose.

Procainamide hydrochloride has also been given intramuscularly.

Procainamide hydrochloride may need to be given in reduced doses or at longer dosing intervals in the elderly and in patients with hepatic or renal impairment. For use in children, see below.

Acecainide (*N*-acetylprocainamide), the active metabolite of procainamide, has class III antiarrhythmic activity and has been used in ventricular arrhythmias.

References.

1. Schreibman DS, *et al*. Usefulness of procainamide challenge for electrophysiologic arrhythmia risk stratification. *Am J Cardiol* 2004; **94:** 1435–8.
2. Kochiadakis GE, *et al*. A comparative study of the efficacy and safety of procainamide versus propafenone versus amiodarone for the conversion of recent-onset atrial fibrillation. *Am J Cardiol* 2007; **99:** 1721–5.
3. Stiell IG, *et al*. Emergency department use of intravenous procainamide for patients with acute atrial fibrillation or flutter. *Acad Emerg Med* 2007; **14:** 1158–64.
4. Contreras ZE, Ximena ZS. Eficacia de procainamida en el tratamiento de la fibrilación ventricular refractaria: descripción de 4 casos clínicos y revisión de la literatura. *Rev Esp Anestesiol Reanim* 2009; **56:** 511–4.

Administration in children. Procainamide hydrochloride has been used successfully in children.[1] In a study in 5 children treated with procainamide for various cardiac arrhythmias the mean elimination half-life was found to be 1.7 hours, and the plasma clearance was higher than that reported in adults.[2] In contrast the total serum clearance of procainamide in 3 neonates with supraventricular tachycardia was found to be similar to that in adults and the mean elimination half-life was 5.3 hours.[3] A loading dose of 10 to 12 mg/kg intravenously was given followed by a continuous infusion of 20 to 75 micrograms/kg per minute. Another, retrospective, study[4] in neonates given procainamide by continuous intravenous infusion found that the mean dose to achieve stable therapeutic drug concentrations was between 37 and 38 micrograms/kg per minute. It was considered that the required doses were not significantly different from those in older children, but doses might need to be reduced in premature infants and those with renal impairment; of 5 patients who developed supratherapeutic drug concentrations, 4 were premature and all had creatinine clearance below 30 mL/minute.

An oral dose of 15 to 50 mg/kg (maximum 4 g) daily given every 3 to 6 hours has been used in children.

1. Chang PM, *et al*. Amiodarone versus procainamide for the acute treatment of recurrent supraventricular tachycardia in pediatric patients. *Circ Arrhythm Electrophysiol* 2010; **3:** 134–40.
2. Singh S, *et al*. Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther* 1982; **32:** 607–11.
3. Bryson SM, *et al*. Therapeutic monitoring and pharmacokinetic evaluation of procainamide in neonates. *DICP Ann Pharmacother* 1991; **25:** 68–71.
4. Moffett BS, *et al*. Therapeutic levels of intravenous procainamide in neonates: a retrospective assessment. *Pharmacotherapy* 2006; **26:** 1687–93.

Adverse Effects

Cardiac effects occur particularly during intravenous use of procainamide and in overdose. Rapid intravenous dosage may result in severe hypotension, ventricular fibrillation, and asystole. High plasma concentrations are also associated with impaired cardiac conduction.

Hypersensitivity reactions to procainamide are common. Procainamide is a frequent cause of drug-induced SLE and the incidence has been reported to be as high as 30% during long-term use. Antinuclear antibodies may be detected in a high proportion of patients, but they do not necessarily develop the symptoms of SLE, which include arthralgia, arthritis, myalgia, pleural effusion, pericarditis, and fever. Agranulocytosis, eosinophilia, neutropenia, thrombocytopenia, and haemolytic anaemia have been reported. Other symptoms of hypersensitivity not necessarily related to SLE may also occur including hepatomegaly, angioedema, rashes, pruritus, urticaria, flushing, and hypergammaglobulinaemia.

Anorexia, nausea, vomiting, a bitter taste, and diarrhoea are more common with higher oral doses. Effects on the CNS such as mental depression, dizziness, and psychosis with hallucinations, have been reported.

Incidence of adverse effects. Out of 488 hospitalised patients in the Boston Collaborative Drug Surveillance Program who had received procainamide, 45 had acute adverse effects attributed to the drug.[1] Life-threatening reactions included heart block (3), tachyarrhythmias (2), and bradycardia and/or hypotension (2). Other reactions included gastrointestinal upsets (19), pyrexia (8), bradycardia and hypotension (5), tachyarrhythmias (3), heart block (1), eosinophilia (1), and urticaria (1).

1. Lawson DH, Jick H. Adverse reactions to procainamide. *Br J Clin Pharmacol* 1977; **4:** 507–11.

Effects on the blood. Adverse haematological effects reported during procainamide therapy include neutropenia,[1-3] agranulocytosis,[2-6] thrombocytopenia,[5] haemolytic anaemia,[7] and pancytopenia.[8] These disorders are usually reversible on withdrawing procainamide although some fatalities have been reported.[3,4] It has been suggested[2,6] that agranulocytosis or severe neutropenia is more likely in patients taking modified-release preparations, but others have found no difference in the incidence between modified-release and conventional-release preparations.[3] An increased risk of agranulocytosis with procainamide has been documented in one large study.[9] Although the precise estimate of excess risk could not be calculated, the order of magnitude was about 3 per million exposed for up to one week. This excess risk was low and of little relevance in the initial choice of therapy.

1. Riker J, *et al*. Bone marrow granulomas and neutropenia associated with procainamide. *Arch Intern Med* 1978; **138:** 1731–2.
2. Ellrodt AG, *et al*. Severe neutropenia associated with sustained-release procainamide. *Ann Intern Med* 1984; **100:** 197–201.
3. Meyers DG, *et al*. Severe neutropenia associated with procainamide: comparison of sustained release and conventional preparations. *Am Heart J* 1985; **109:** 1393–5.
4. Fleet S. Agranulocytosis, procainamide, and phenytoin. *Ann Intern Med* 1984; **100:** 616–17.
5. Christensen DJ, *et al*. Agranulocytosis, thrombocytopenia, and procainamide. *Ann Intern Med* 1984; **100:** 918.
6. Thompson JF, *et al*. Procainamide agranulocytosis: a case report and review of the literature. *Curr Ther Res* 1988; **44:** 872–81.
7. Kleinman S, *et al*. Positive direct antiglobulin tests and inunune hemolytic anemia in patients receiving procainamide. *N Engl J Med* 1984; **311:** 809–12.
8. Bluming AZ, *et al*. Severe transient pancytopenia associated with procainamide ingestion. *JAMA* 1976; **236:** 2520–1.
9. Kelly JP, *et al*. Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: The International Agranulocytosis and Aplastic Anemia Study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects on the gastrointestinal tract. Pseudo-obstruction of the bowel occurred in a diabetic patient when given procainamide both orally and intravenously. It was believed that the anticholinergic properties of procainamide and the diabetic state contributed to the severe hypomotility of the gastrointestinal tract.[1]

1. Peterson AM, *et al*. Procainamide-induced pseudo-obstruction in a diabetic patient. *DICP Ann Pharmacother* 1991; **25:** 1334–5.

Effects on the heart. Procainamide prolongs the QT interval and has been associated with the development of torsade de pointes,[1,2] and fatal cardiovascular toxicity has been reported[3] in patients with renal impairment. Toxicity appears to be related to accumulation of the major metabolite, *N*-acetylprocainamide, and haemodialysis has been used to reduce plasma concentrations and control symptoms,[1,4] although its benefits have been disputed (see Dialysis, under Treatment of Adverse Effects, below). However, symptoms developed in 1 patient[2] despite plasma concentrations of both procainamide and *N*-acetylprocainamide being within the therapeutic range.

1. Nguyen KPV, *et al*. N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104:** 283–4.
2. Habbab MA, El-Sherif N. Drug-induced torsades de pointes: role of early afterdepolarizations and dispersion of repolarization. *Am J Med* 1990; **89:** 241–6.
3. Vlasses PH, *et al*. Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.
4. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8:** 528–31.

Effects on the liver. There have been reports of granulomatous hepatitis[1] and intrahepatic cholestasis[2,3] due to hypersensitivity reactions in patients taking procainamide. Fever and elevation of liver enzyme values also occurred. The reactions were reversible on withdrawing procainamide.

1. Rotmensch HH, *et al*. Granulomatous hepatitis: a hypersensitivity response to procainamide. *Ann Intern Med* 1978; **89:** 646–7.
2. Ahn C-S, Tow DE. Intrahepatic cholestasis due to hypersensitivity reaction to procainamide. *Arch Intern Med* 1990; **150:** 2589–90.
3. Chuang LC, *et al*. Possible case of procainamide-induced intrahepatic cholestatic jaundice. *Ann Pharmacother* 1993; **27:** 434–7.

Effects on mental function. Acute psychosis has been reported[1] in patients receiving therapy with procainamide.

1. Bizjak ED, *et al*. Procainamide-induced psychosis: a case report and review of the literature. *Ann Pharmacother* 1999; **33:** 948–51.

Effects on the muscles. Procainamide may affect neuromuscular transmission and there have been reports of severe generalised skeletal muscle weakness[1-3] in patients receiving procainamide. In 2 patients this was associated with respiratory failure[1,2] and developed shortly after starting therapy. Concentrations of procainamide and its *N*-acetyl metabolite exceeded the normal therapeutic ranges and rapid cycling peritoneal dialysis was used to remove the drug in 1 patient.[2] Adverse muscle symptoms are a feature of procainamide-induced lupus erythematosus (see below), but in such instances symptoms usually develop on long-term treatment.

1. Lewis CA, *et al*. Myopathy after short term administration of procainamide. *BMJ* 1986; **292:** 593–4.
2. Javaheri S, *et al*. Diaphragmatic paralysis. *Am J Med* 1989; **86:** 623–4.
3. Sayler DJ, DeJong DJ. Possible procainamide-induced myopathy. *DICP Ann Pharmacother* 1991; **25:** 436.

Lupus erythematosus. Procainamide is a well-known cause of drug-induced lupus erythematosus.[1,2] It occurs in about 20% of patients on long-term therapy,[2] although the majority of patients taking procainamide for more than 1 year have detectable antinuclear antibodies. There is some evidence[3] that slow acetylators are more likely to develop antibodies than rapid acetylators, and that the antibodies appear more rapidly in slow acetylators, but this may not correlate with the development of clinical symptoms.[4] The clinical syndrome may include fever, polyarthritis, arthralgia, myalgia, and pleuropulmonary and pericardial features, and is usually spontaneously reversible on withdrawal of procainamide.

1. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; **12:** 283–90.
2. Rubin RL. Drug-induced lupus. *Toxicology* 2005; **209:** 135–47.
3. Woosley RL, *et al*. Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N Engl J Med* 1978; **298:** 1157–9.
4. Mongey A-B, *et al*. Acetylation status is associated with serological changes but not clinically significant disease in patients receiving procainamide. *J Rheumatol* 1999; **26:** 1721–6.

Treatment of Adverse Effects

In overdosage with procainamide treatment is largely symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion. The ECG, blood pressure, and renal function should be monitored. Supportive measures include correction of hypotension, assisted ventilation, and electrical pacing. Haemodialysis or haemoperfusion increase the elimination of procainamide and *N*-acetylprocainamide, see below.

SLE will normally respond to withdrawal of procainamide but corticosteroids may be required.

Dialysis. In the UK, the National Poisons Information Service does not recommend the use of haemodialysis or haemofiltration in the treatment of poisoning with class Ia antiarrhythmics. Nonetheless, both procainamide and *N*-acetylprocainamide are removed by haemodialysis, and there are reports[1-4] of the successful use of haemodialysis in patients with procainamide toxicity. However, toxicity has occurred in patients undergoing regular haemodialysis,[2,5,6] suggesting that some accumulation still takes place, and rebound increases in plasma concentrations have also been reported[4,7] after dialysis. Haemoperfusion[5,7] and haemofiltration[6] have also been used, and may be more effective. Peritoneal dialysis may also remove a small amount of procainamide and *N*-acetylprocainamide,[7] and

there has been a report[8] of the successful use of rapid cycling peritoneal dialysis in a patient on maintenance peritoneal dialysis who developed procainamide-induced diaphragmatic paralysis.

1. Atkinson AJ, *et al.* Hemodialysis for severe procainamide toxicity: clinical and pharmacokinetic observations. *Clin Pharmacol Ther* 1976; **20:** 585–92.
2. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8:** 528–31.
3. Nguyen KPV, *et al.* N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104:** 283–4.
4. Rosansky SJ, Brady ME. Procainamide toxicity in a patient with acute renal failure. *Am J Kidney Dis* 1986; **7:** 502–6.
5. Braden GL, *et al.* Hemoperfusion for treatment of N-acetylprocainamide intoxication. *Ann Intern Med* 1986; **105:** 64–5.
6. Domoto DT, *et al.* Removal of toxic levels of N-acetylprocainamide with continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration. *Ann Intern Med* 1987; **106:** 550–2.
7. Low CL, *et al.* Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity. *Nephrol Dial Transplant* 1996; **11:** 881–4.
8. Javaheri S, *et al.* Diaphragmatic paralysis. *Am J Med* 1989; **86:** 623–4.

Precautions

Procainamide is contra-indicated in heart block (unless the patient has a pacemaker) and in SLE, and should be used with caution in patients with myocardial damage or severe organic heart disease. It has been advised that procainamide should not be used in heart failure or hypotension. Patients with torsade de pointes may deteriorate if given procainamide. If it is used to treat atrial tachycardia patients may need to be pre-treated with digoxin. Procainamide should preferably not be used in patients with myasthenia gravis or digoxin toxicity. There may be cross-sensitivity between procaine and procainamide.

Accumulation of procainamide may occur in patients with heart failure or hepatic or renal impairment and dosage reduction may be necessary.

Blood counts and screening for lupus erythematosus and serum antinuclear factor should be carried out regularly during therapy.

Intravenous use of procainamide may lead to severe hypotension; it should be injected slowly and blood pressure and ECG should be monitored.

Breast feeding. There was evidence of accumulation of procainamide and *N*-acetylprocainamide in the breast milk of a woman taking procainamide 500 mg four times daily.[1] Milk and serum samples were obtained at three-hourly intervals for 15 hours. Mean serum concentrations of the drug and metabolite were found to be 1.1 and 1.6 micrograms/mL respectively; those in the milk were 5.4 and 3.5 micrograms/mL respectively. The mean milk:serum ratios were 4.3 (range 1.0 to 7.3) and 3.8 (range 1.0 to 6.2) respectively. However, it was considered that the amount ingested by the infant would not yield clinically significant serum concentrations. Although licensed product information states that procainamide should be avoided in breast-feeding women, there have been no reports of adverse effects in infants, and the American Academy of Pediatrics considers[2] that its use is therefore usually compatible with breast feeding.

1. Pittard WB, Glazier H. Procainamide excretion in human milk. *J Pediatr* 1983; **102:** 631–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Interactions

Procainamide may enhance the effects of antihypertensives, other antiarrhythmics and arrhythmogenic drugs, antimuscarinics, and neuromuscular blockers, and diminish those of parasympathomimetics, such as neostigmine. Procainamide is actively secreted by kidney tubules and interactions may occur with drugs secreted by the same pathway, such as cimetidine and trimethoprim.

Alcohol. The total body clearance of procainamide is increased by alcohol[1] and the elimination half-life reduced. The acetylation rate of procainamide is also increased resulting in a greater proportion of drug present as the active metabolite *N*-acetylprocainamide.

1. Olsen H, Mørland J. Ethanol-induced increase in procainamide acetylation in man. *Br J Clin Pharmacol* 1982; **13:** 203–8.

Antacids. Procainamide is adsorbed by some antacids and reduced bioavailability has been reported[1] in healthy subjects given procainamide with *kaolin-pectin*; the authors recommended that procainamide and adsorbents should not be used together.

1. Al-Shora HI, *et al.* Interactions of procainamide, verapamil, guanethidine and hydralazine with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* 1988; **47:** 209–13.

Antiarrhythmics. *Amiodarone* given orally alters the pharmacokinetic properties of an intravenous dose of procainamide,[1] decreasing clearance and prolonging the plasma elimination half-life. The dosage of intravenous procainamide should be reduced by 20 to 30% during concurrent use. Increased serum-procainamide concentrations have also been reported[2] in patients stabilised on oral procainamide who had amiodarone added to their therapy; the dosage of procainamide had to be reduced in some patients due to signs of toxicity. *Quinidine* has also been reported[3] to increase plasma-procainamide concentrations.

1. Windle J, *et al.* Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. *Clin Pharmacol Ther* 1987; **41:** 603–10.
2. Saal AK, *et al.* Effect of amiodarone on serum quinidine and procainamide levels. *Am J Cardiol* 1984; **53:** 1264–7.
3. Hughes B, *et al.* Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. *Am Heart J* 1987; **114:** 908–9.

Antibacterials. The renal clearance of procainamide and *N*-acetylprocainamide is reduced by *trimethoprim*[1,2] through competition for renal tubular secretion. Serum concentrations may be increased with a resulting increase in pharmacodynamic response. The fluoroquinolones *ciprofloxacin*,[3] *levofloxacin*,[3] and *ofloxacin*[4] have also been reported to reduce the renal clearance of procainamide.

1. Kosoglou T, *et al.* Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988; **44:** 467–77.
2. Vlasses PH, *et al.* Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* 1989; **149:** 1350–3.
3. Bauer LA, *et al.* Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* 2005; **49:** 1649–51.
4. Martin DE, *et al.* Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* 1996; **36:** 85–91.

Histamine H_2-antagonists. Histamine H_2-antagonists compete with other basic drugs for renal tubular secretion. *Cimetidine* reduces the renal clearance of procainamide and *N*-acetylprocainamide[1,2] and a dosage reduction may be necessary. Increases[3,4] and decreases[4] in renal and metabolic clearances of procainamide have occurred with *ranitidine*.

1. Christian CD, *et al.* Cimetidine inhibits renal procainamide clearance. *Clin Pharmacol Ther* 1984; **36:** 221–7.
2. Somogyi A, *et al.* Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. *Eur J Clin Pharmacol* 1983; **25:** 339–45.
3. Somogyi A, Bochner F. Dose and concentration dependent effect of ranitidine on procainamide disposition and renal clearance in man. *Br J Clin Pharmacol* 1984; **18:** 175–81.
4. Rocci ML, *et al.* Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. *J Pharmacol Exp Ther* 1989; **248:** 923–8.

Pharmacokinetics

Procainamide is readily and almost completely absorbed from the gastrointestinal tract. It is widely distributed throughout the body and is only about 15 to 20% bound to plasma proteins. The therapeutic effect of procainamide has been correlated with plasma concentrations of about 3 to 10 micrograms/mL in most patients; progressively severe toxicity is noted at concentrations above 12 micrograms/mL.

Some procainamide undergoes acetylation in the liver to *N*-acetylprocainamide, which also has antiarrhythmic properties. The rate of acetylation of procainamide is genetically determined, there being slow and fast acetylators. Procainamide also undergoes hydrolysis in plasma to para-aminobenzoic acid.

Procainamide is excreted in the urine by active renal secretion, 30 to 70% as unchanged procainamide, with the remainder as *N*-acetylprocainamide and other metabolites. The elimination half-life of procainamide is 2.5 to 5 hours and that of its acetyl metabolite 6 to 7 hours. *N*-Acetylprocainamide may represent a significant fraction of the total drug in the circulation.

Procainamide crosses the placenta and is distributed into breast milk.

References.

1. Grasela TH, Sheiner LB. Population pharmacokinetics of procainamide from routine clinical data. *Clin Pharmacokinet* 1984; **9:** 545–54.

Bioavailability. Modified-release procainamide preparations have been shown[1] to produce similar steady-state serum concentrations of procainamide and *N*-acetylprocainamide when compared with equivalent total doses of immediate-release capsules. However, tablet matrices of a modified-release preparation have been recovered from the stools of a patient with diarrhoea[2] and 3.5 g of procainamide was recovered in these matrices over an 18-hour collection period; the patient had correspondingly low plasma-procainamide concentrations.

1. Vlasses PH, *et al.* Immediate-release and sustained-release procainamide: bioavailability at steady state in cardiac patients. *Ann Intern Med* 1983; **98:** 613–14.
2. Woosley RL, *et al.* Antiarrhythmic therapy: clinical pharmacology update. *J Clin Pharmacol* 1984; **24:** 295–305.

The elderly. Reduced renal clearance of procainamide has been reported in the elderly.[1,2]

1. Reidenberg MM, *et al.* Aging and renal clearance of procainamide and acetylprocainamide. *Clin Pharmacol Ther* 1980; **28:** 732–5.
2. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.

Hepatic impairment. In 20 healthy subjects and 20 patients with chronic liver disease given a single 500-mg oral dose of procainamide hydrochloride about 64 and 33% respectively of the dose was excreted in the urine within 6 hours.[1] Decreased procainamide acetylation in the patients compared with the control group was not correlated with the severity of liver disease, whereas decreased procainamide hydrolysis and increased procainamide-derived aminobenzoic acid acetylation appeared to be related to the degree of hepatic impairment. It was suggested that the decrease in excretion of procainamide and its metabolites in the urine of the patients with liver disease could be due to an impairment in oral absorption since renal function was within the normal range but the variations in acetylation and hydrolysis were related to hepatic function.

1. du Souich P, Erill S. Metabolism of procainamide and p-aminobenzoic acid in patients with chronic liver disease. *Clin Pharmacol Ther* 1977; **22:** 588–95.

Renal impairment. Procainamide and its active *N*-acetyl metabolite are mainly excreted in the urine and accumulation, particularly of the metabolite, may occur in renal impairment. A study[1] in 20 patients found that procainamide clearance correlated with renal function, and that the ratio of *N*-acetylprocainamide to procainamide in the serum increased as renal function declined. Fatal toxicity in patients with renal impairment and plasma-procainamide concentrations within the therapeutic range has been attributed[2] to accumulation of *N*-acetylprocainamide. Both procainamide and *N*-acetylprocainamide are removed by dialysis, although the benefit of these procedures has been disputed (see Dialysis under Treatment of Adverse Effects, p. 1476.3).

1. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.
2. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Pronestyl†; ***Braz.***: Procamide†; ***Canad.***: Procan; ***Gr.***: Biocoryl; Pronestyl; ***India***: Pronestyl; ***Irl.***: Pronestyl†; ***NZ***: Pronestyl; ***S.Afr.***: Pronestyl†; ***Singapore***: Pronestyl; ***Spain***: Biocoryl; ***USA***: Procanbid†.

Pharmacopoeial Preparations

BP 2014: Procainamide Injection; Procainamide Tablets;
USP 36: Procainamide Hydrochloride Capsules; Procainamide Hydrochloride Extended-release Tablets; Procainamide Hydrochloride Injection; Procainamide Hydrochloride Tablets.

Propafenone Hydrochloride

(BANM, USAN, rINNM)

Fenopraine Hydrochloride; Hidrocloruro de fenopraina; Hidrocloruro de propafenona; Propafenon Hidroklorür; Propafenona, hidrocloruro de; Propafénone, chlorhydrate de; Propafenon-hydrochlorid; Propafenonhydrochlorid; Propafenonhydroklorid; Propafenoni Hydrochloridum; Propafenonihydrokloridi; Propafenono hidrochloridas; SA-79; WZ-884642; WZ-884643; Пропафенона Гидрохлорид.

2′-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride.

$C_{21}H_{27}NO_3$,HCl=377.9

CAS — 54063-53-5 (propafenone); 34183-22-7 (propafenone hydrochloride).

ATC — C01BC03.

ATC Vet — QC01BC03.

UNII — 33XCH0HOCD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Propafenone Hydrochloride). Colourless crystals or a white or almost white powder. Slightly soluble in cold water; soluble in hot water and in methyl alcohol; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.0 to 6.2.

USP 36: (Propafenone Hydrochloride). A white powder. Soluble in hot water and in methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone; insoluble in ether and in toluene. A 0.5% solution in water has a pH of 5.0 to 6.2. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Propafenone is a class Ic antiarrhythmic (p. 1243.1) with some negative inotropic and beta-adrenoceptor blocking

activity. It is used in the management of supraventricular and ventricular arrhythmias.

Treatment should be started under close monitoring of the ECG and blood pressure. The usual initial oral dose of propafenone hydrochloride is 150 mg three times daily and this may be increased, if necessary, at intervals of 3 to 4 days up to a maximum of 300 mg three times daily. Reduced doses may be appropriate in patients weighing less than 70 kg and in the elderly; dose reduction may also be necessary in hepatic impairment (see below).

Propafenone hydrochloride is available in some countries as a modified-release preparation. It has also been given by slow intravenous injection or by infusion.

Administration in hepatic impairment. The clearance of propafenone may be reduced in hepatic impairment; careful monitoring is required and lower doses should be considered. US licensed product information states that the dose should be only 20 to 30% of that given in normal hepatic function.

Administration in renal impairment. A study[1] of the disposition of propafenone found that renal function did not affect the pharmacokinetics of propafenone or 5-hydroxypropafenone, and another study[2] suggested that propafenone could be used safely for atrial fibrillation in patients with chronic renal failure. Nevertheless, UK and US licensed product information states that caution is necessary if propafenone is given to patients with renal impairment.

Propafenone does not appear to be removed by haemofiltration.[3]

1. Fromm MF, *et al.* Influence of renal function on the steady-state pharmacokinetics of the antiarrhythmic propafenone and its phase I and phase II metabolites. *Eur J Clin Pharmacol* 1995; **48:** 279–83.
2. Napoli C, *et al.* Propafenone in the conversion of atrial fibrillation in patients suffering from chronic renal failure. *Am J Ther* 1997; **4:** 130–3.
3. Seto W, *et al.* Propafenone disposition during continuous venovenous hemofiltration. *Ann Pharmacother* 1999; **33:** 957–9.

Cardiac arrhythmias. Propafenone is effective in many cardiac arrhythmias.[1,2] It may have a role in the management of supraventricular arrhythmias (see p. 1266.1), including as a single oral loading dose for recent-onset atrial fibrillation.[3,4] It may also be used in ventricular arrhythmias, although in many cases non-pharmacological therapy is preferred. Successful use in children with various arrhythmias has also been reported.[5,6]

1. Capucci A, Boriani G. Propafenone in the treatment of cardiac arrhythmias: a risk-benefit appraisal. *Drug Safety* 1995; **12:** 55–72.
2. Reimold SC, *et al.* Propafenone for the treatment of supraventricular tachycardia and atrial fibrillation: a meta-analysis. *Am J Cardiol* 1998; **82:** 66N–71N.
3. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001; **37:** 542–7.
4. Boriani G, *et al.* Oral loading with propafenone for conversion of recent-onset atrial fibrillation: a review on in-hospital treatment. *Drugs* 2002; **62:** 415–23.
5. Heusch A, *et al.* Clinical experience with propafenone for cardiac arrhythmias in the young. *Eur Heart J* 1994; **15:** 1050–6.
6. Janoušek J, Paul T. Safety of oral propafenone in the treatment of arrhythmias in infants and children (European Retrospective Multicenter Study). *Am J Cardiol* 1998; **81:** 1121–4.

Adverse Effects

Propafenone can cause disturbances in cardiac conduction which can result in bradycardia, heart block, and sinus arrest. It may aggravate heart failure and may cause hypotension. In common with other antiarrhythmics, propafenone may induce or worsen arrhythmias in some patients.

Among the most common adverse effects are gastrointestinal intolerance, dry mouth, a bitter or metallic taste, dizziness, blurred vision, headache, and fatigue. Convulsions, blood dyscrasias, liver disorders, lupus erythematosus, rashes, impotence, and increased breathlessness and worsening of asthma have also been reported.

Effects on the heart. Propafenone may worsen ventricular arrhythmias and there have been reports[1,2] of fatal exacerbations occurring hours to days after starting treatment. Cardiovascular toxicity may also occur in overdosage.[3] Torsade de pointes has been reported[2,4,5] but appears to be less frequent than with class Ia antiarrhythmics. Toxicity may mimic Brugada syndrome,[6,7] and has been mistaken for acute myocardial infarction.[7] Hypertonic sodium bicarbonate infusion may be effective in treating cardiotoxicity induced by propafenone.[8]

1. Nathan AW, *et al.* Fatal ventricular tachycardia in association with propafenone, a new class IC antiarrhythmic agent. *Postgrad Med J* 1984; **60:** 155–6.
2. Buss J, *et al.* Malignant ventricular tachyarrhythmias in association with propafenone treatment. *Eur Heart J* 1985; **6:** 424–8.
3. Clarot F, *et al.* Fatal propafenone overdoses: case reports and a review of the literature. *J Anal Toxicol* 2003; **27:** 595–9.
4. Rosengarten M, Brooks R. Torsade de pointes ventricular tachycardia in a hypothyroid patient treated with propafenone. *Can J Cardiol* 1987; **3:** 234–9.
5. Hii JT, *et al.* Propafenone-induced torsade de pointes: cross-reactivity with quinidine. *Pacing Clin Electrophysiol* 1991; **14:** 1568–70.
6. Hasdemir C, *et al.* Brugada-type ECG pattern and extreme QRS complex widening with propafenone overdose. *J Cardiovasc Electrophysiol* 2006; **17:** 565–6.
7. Chutani S, *et al.* Propafenone-induced Brugada-like ECG changes mistaken as acute myocardial infarction. *Emerg Med J* 2008; **25:** 117–18.
8. Brubacher J. Bicarbonate therapy for unstable propafenone-induced wide complex tachycardia. *CJEM* 2004; **6:** 349–56.

Effects on the liver. A review of liver injury secondary to propafenone therapy concluded that it is a rare occurrence and appears to be due to hepatocellular injury, cholestasis, or a combination.[1]

1. Spinler SA, *et al.* Propafenone-induced liver injury. *Ann Pharmacother* 1992; **26:** 926–8.

Effects on mental function. Delusions, hallucinations, and paranoia have been reported in an elderly patient after 2 doses of propafenone. The manufacturer had received reports of mania and psychosis.[1] Amnesia developed in a 61-year-old man 6 days after starting treatment with propafenone.[2] Symptoms resolved 6 to 7 hours after stopping the drug.

1. Robinson AJ. Paranoia after propafenone. *Pharm J* 1991; **247:** 556.
2. Jones RJ, *et al.* Probable propafenone-induced transient global amnesia. *Ann Pharmacother* 1995; **29:** 586–90.

Effects on the nervous system. Myoclonus has been reported in a patient receiving propafenone.[1] In another patient peripheral neuropathy developed 10 months after starting treatment but symptoms had resolved 6 months after stopping the drug.[2] There have also been reports of ataxia.[3]

1. Chua TP, *et al.* Myoclonus associated with propafenone. *BMJ* 1994; **308:** 113.
2. Galasso PJ, *et al.* Propafenone-induced peripheral neuropathy. *Mayo Clin Proc* 1995; **70:** 469–72.
3. Odeh M, *et al.* Propafenone-induced ataxia: report of three cases. *Am J Med Sci* 2000; **320:** 151–3.

Lupus erythematosus. Symptoms of lupus erythematosus and raised antinuclear antibody titres were associated with propafenone therapy on 2 occasions in a 63-year-old woman.[1]

1. Guindo J, *et al.* Propafenone and a syndrome of the lupus erythematosus type. *Ann Intern Med* 1986; **104:** 589.

Precautions

Propafenone is contra-indicated in patients with uncontrolled heart failure, conduction disturbances including heart block unless controlled by artificial pacing, cardiogenic shock (unless arrhythmia-induced), severe bradycardia, or pronounced hypotension. It may alter the endocardial pacing threshold and adjustment may be necessary in patients with pacemakers.

Propafenone has beta-blocking activity and may exacerbate obstructive airways disease; it should be used with great caution in such disorders and is contra-indicated in severe disease. Propafenone may aggravate myasthenia gravis and should be avoided in patients with this condition. Electrolyte disturbances should be corrected before beginning treatment. Propafenone should be used with caution in patients with hepatic or renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propafenone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy and breast feeding. Experience in a patient given propafenone throughout the last trimester of pregnancy indicated that despite transplacental diffusion propafenone could safely be used at this time without harm to the fetus. Propafenone and its metabolite were detected in breast milk at concentrations considered to represent a markedly subtherapeutic dose to an infant.[1]

1. Libardoni M, *et al.* Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. *Br J Clin Pharmacol* 1991; **32:** 527–8.

Interactions

Propafenone is extensively metabolised by the cytochrome P450 enzyme system, mainly by the isoenzyme CYP2D6, although CYP1A2 and CYP3A4 are also involved. Interactions may therefore occur with other drugs that are metabolised by these enzymes. Plasma-propafenone concentrations may be reduced by enzyme inducers such as rifampicin; enzyme inhibitors, such as cimetidine, fluoxetine, quinidine, and HIV-protease inhibitors, may increase plasma-propafenone concentrations. Propafenone itself may alter the plasma concentrations of other drugs, including beta blockers p. 1321.3, ciclosporin p. 1957.2, desipramine p. 406.2, digoxin p. 1356.1, theophylline p. 1234.1, venlafaxine p. 456.3, and warfarin p. 1530.3. The absorption of propafenone may be reduced by orlistat. There may be an increased risk of arrhythmias if propafenone is given with other antiarrhythmics or arrhythmogenic drugs.

Antiarrhythmics. *Quinidine* inhibits the hepatic metabolism of propafenone and has been reported[1] to increase plasma-propafenone concentrations in extensive metabolisers;[1] the plasma concentration of the active 5-hydroxy metabolite was reduced and that of the *N*-depropyl metabolite increased but there was no change in the clinical response. Another study,[2] however, found that quinidine increased the beta-blocking effect of propafenone in extensive metabolisers, and a study[3] in patients with refractory atrial fibrillation found that addition of quinidine to propafenone was as effective and possibly better tolerated than increasing the propafenone dose.

1. Funck-Brentano C, *et al.* Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* 1989; **27:** 435–44.
2. Mörike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther* 1994; **55:** 28–34.
3. Lau C-P, *et al.* Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* 2000; **86:** 1327–32.

Antibacterials. *Rifampicin* has lowered steady-state plasma concentrations of propafenone with the reappearance of arrhythmia.[1]

1. Castel JM, *et al.* Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. *Br J Clin Pharmacol* 1990; **30:** 155–6.

Histamine H_2-antagonists. *Cimetidine* has been reported[1] to raise plasma-propafenone concentrations. The mean steady-state concentration increased by 22% but the wide interindividual variability meant this change was not significant.

1. Pritchett ELC, *et al.* Pharmacokinetic and pharmacodynamic interactions of propafenone and cimetidine. *J Clin Pharmacol* 1988; **28:** 619–24.

Pharmacokinetics

Propafenone is readily and almost completely absorbed from the gastrointestinal tract. It is metabolised in the liver, largely by the cytochrome P450 isoenzyme CYP2D6, but also to a small extent by CYP1A2 and CYP3A4; the extent of metabolism is genetically determined. In subjects with the extensive metaboliser phenotype there is extensive first-pass metabolism to two active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone, and to other minor inactive metabolites. In the small proportion of subjects with the slow metaboliser phenotype (lacking CYP2D6) little or no 5-hydroxypropafenone is formed. The bioavailability of propafenone is dependent upon metaboliser phenotype but more importantly on dosage as the first-pass metabolism is saturable. In practice doses are high enough to compensate for differences in phenotype. Propafenone and its metabolites also undergo glucuronidation.

Propafenone is more than 95% protein bound.

Propafenone is excreted in the urine and faeces mainly in the form of conjugated metabolites. The elimination half-life is reported to be 2 to 10 hours in extensive metabolisers and 10 to 32 hours in slow metabolisers.

Propafenone crosses the placenta and is distributed into breast milk.

General references.

1. Hii JTY, *et al.* Clinical pharmacokinetics of propafenone. *Clin Pharmacokinet* 1991; **21:** 1–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Normorytmin; ***Austria***: Rytmonorma; ***Belg.***: Rytmonorm; ***Braz.***: Ritmonorm; ***Canad.***: Rythmol; ***Chile***: Ritmocor; ***China***: Rytmonorm (悦复隆); ***Cz.***: Prolekofen; Propanorm; Rytmonorm; ***Denm.***: Rytmonorm; ***Fin.***: Rytmonorm; ***Fr.***: Rythmol; ***Ger.***: Cuxafenon†; Rytmo-Puren†; Rytmonorm; ***Gr.***: Rytmonorm†; ***Hong Kong***: Rytmonorm; ***Hung.***: Rytmonorm; ***Indon.***: Rytmonorm; ***Irl.***: Arythmol; ***Israel***: Profex; Rythmex; ***Ital.***: Cardiofenone; Fenorit; Normarit; Rytmonorm; ***Malaysia***: Rytmonorm; ***Mex.***: Biopafen; Nistaken; Norfenon; ***Neth.***: Rytmonorm; ***NZ***: Rytmonorm; ***Philipp.***: Rytmocard†; ***Pol.***: Polfenon; Rytmonorm; ***Port.***: Arythmol; Rytmonorm; ***Rus.***: Propanorm (Пропанорм); Ritmonorm (Ритмонорм); Rytmonorm (Ритмонорм)†; ***S.Afr.***: Rythmol; ***Singapore***: Rytmonorm; ***Spain***: Rytmonorm; ***Swed.***: Rytmonorm; ***Switz.***: Rytmonorm; ***Thai.***: Rytmonorm; ***Turk.***: Rytmonorm; ***UK***: Arythmol; ***Ukr.***: Propanorm (Пропанорм); ***USA***: Rythmol; ***Venez.***: Rytmonorm.

Propatylnitrate *(BAN, rINN)*

ETTN; Ettriol Trinitrate; Propatilnitrato; Propatyl Nitrate (USAN); Propatylnitrat; Propatylnitratum; Propatyylinitraatti; Trinettriol; Win-9317; Пропатилнитрат.

2-Ethyl-2-hydroxymethylpropane-1,3-diol trinitrate.

$C_5H_{11}N_3O_9$=269.2
CAS — 2921-92-8.
ATC — C01DA07.
ATC Vet — QC01DA07.
UNII — AJT2YN495R.

Profile

Propatylnitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p. 1393.3) that has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.:* Sustrate.

Propentofylline *(BAN, rINN)*

HWA-285; Propentofilina; Propentofyllıini; Propentofyllin; Propentofyllinum; Пропентофиллин.

3-Methyl-1-(5-oxohexyl)-7-propylxanthine.

$C_{15}H_{22}N_4O_3$=306.4
CAS — 55242-55-2.
ATC — N06BC02.
ATC Vet — QC04AD90; QN06BC02; QR03DA90.
UNII — 5RTA398U4H.

Profile

Propentofylline is a xanthine derivative that has been investigated in cerebrovascular disorders including dementia. It is also used in veterinary medicine.

References.

1. Frampton MA, *et al.* Propentofylline for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 22/10/09).
2. Bath PMW, Bath-Hextall FJ. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 22/10/09).

Propranolol Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-64043; Hidrocloruro de propranolol; ICI-45520; NSC-91523; Propanolol-hidroklorid; Propanololi Hydrochloridum; Propranolol, Chlorhydrate de; Propranolol, hidrocloruro de; Propranolol Hidroklorür; Propranolol-hydrochlorid; Propranololhydrochlorid; Propranololhydroklorid; Propranololi Hydrochloridum; Propranololihydrokloridi; Propranololio hidrochloridas; Propranololu chlorowodorek; Пропранолола Гидрохлорид.

(±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride.

$C_{16}H_{21}NO_2$,HCl=295.8
CAS — 525-66-6 (propranolol); 13013-17-7 (propranolol); 318-98-9 (propranolol hydrochloride); 3506-09-0 (propranolol hydrochloride).
ATC — C07AA05.
ATC Vet — QC07AA05.
UNII — FBA3652H1V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Propranolol Hydrochloride). A white or almost white powder. Soluble in water and in alcohol.

USP 36: (Propranolol Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. In aqueous solutions propranolol decomposes with oxidation of the isopropylamine side-chain, accompanied by a reduction in pH and discoloration of the solution. Solutions are most stable at pH 3 and decompose rapidly when alkaline.

Uses and Administration

Propranolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to have membrane-stabilising properties, but does not possess intrinsic sympathomimetic activity.

Propranolol is used as the hydrochloride in the management of hypertension (p. 1251.1), phaeochromocytoma (p. 1278.1), angina pectoris (p. 1254.3), myocardial infarction (p. 1257.1), and cardiac arrhythmias (p. 1266.1). It is also used in hypertrophic cardiomyopathy (p. 1261.3). It is used to control symptoms of sympathetic overactivity in the management of hyperthyroidism (p. 2332.2), anxiety disorders (p. 1028.1), and tremor (p. 1318.3). Other indications include the prophylaxis of migraine (p. 670.3) and of upper gastrointestinal bleeding in patients with portal hypertension (see Variceal Haemorrhage under Monoethanolamine Oleate, p. 2563.1).

Propranolol hydrochloride is usually given orally. In **hypertension** it is given in initial doses of 40 to 80 mg twice daily increased as required to a usual range of 160 to 320 mg daily; some patients may require up to 640 mg daily. Propranolol is *not* suitable for the emergency treatment of hypertension; it should not be given intravenously in hypertension.

In **phaeochromocytoma**, patients treated surgically may be given 60 mg daily on the 3 days before the operation, always with alpha blockade. If the tumour is inoperable prolonged treatment may be given with a daily dose of 30 mg.

In **angina,** initial doses of propranolol hydrochloride 40 mg given 2 or 3 times daily are increased as required to a usual range of 120 to 240 mg daily. Some patients may require up to 320 mg daily.

Propranolol hydrochloride is given within 5 to 21 days of **myocardial infarction** in doses of 40 mg given four times daily for 2 or 3 days followed by 80 mg twice daily. Another regimen is to give 180 to 240 mg daily in divided doses.

Propranolol may be given in doses of 30 to 160 mg daily in divided doses in the long-term management of **cardiac arrhythmias**. For the emergency treatment of cardiac arrhythmias, propranolol hydrochloride may be given by slow intravenous injection over a period of 1 minute, in a dose of 1 mg, repeated if necessary every 2 minutes until a maximum total of 10 mg has been given in conscious patients and 5 mg in patients under anaesthesia. Patients receiving propranolol intravenously should be carefully monitored.

In **hypertrophic cardiomyopathy** the usual dose of propranolol hydrochloride is 10 to 40 mg given three or four times daily.

In **hyperthyroidism** propranolol hydrochloride is given in doses of 10 to 40 mg three or four times daily. If intravenous administration is necessary 1 mg is given over 1 minute, repeated at 2-minute intervals until a response is seen or to a maximum dose of 10 mg in conscious patients or 5 mg in patients under anaesthesia.

The dose for **anxiety** is 40 mg daily; this may be increased to 40 mg two or three times daily.

Essential tremor may be treated with 40 mg given two or three times daily; the dose can be increased at weekly intervals to 160 mg daily although doses up to 320 mg daily may be necessary.

An initial dose of 40 mg two or three times daily is used in **migraine** prophylaxis; the dose can be increased at weekly intervals up to 160 mg daily. Some patients have been given 240 mg daily.

In **portal hypertension,** propranolol hydrochloride should be given in initial doses of 40 mg twice daily; the dose may be increased as required up to 160 mg twice daily.

For the use of propranolol in children, see below.

Administration in children. Propranolol hydrochloride has been used both orally and intravenously in children, although it is not licensed for all indications. Suggested doses are:

for **hypertension**:

- neonates: 250 micrograms/kg orally three times daily, increased as required to a maximum of 2 mg/kg three times daily
- 1 month to 12 years: 0.25 to 1 mg/kg orally three times daily, increased as required to a maximum of 5 mg/kg daily in divided doses
- over 12 years: an adult dose (see above)

for **arrhythmias**, **phaeochromocytoma**, and **hyperthyroidism**:

- neonates: 250 to 500 micrograms/kg orally three times daily. *Alternatively* 20 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring
- 1 month to 18 years: 250 to 500 micrograms/kg orally three or four times daily, adjusted according to response, to a maximum of 1 mg/kg four times daily or a total daily dose of 160 mg. *Alternatively* 25 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring

for **prophylaxis of migraine**:

- children up to 12 years: 10 to 20 mg orally two or three times daily
- over 12 years: an adult dose (see above)

for **haemangiomas** and **tetralogy of Fallot**, see below.

Administration in hepatic impairment. A study of the disposition of oral propranolol at steady state in 9 normal subjects and 7 with cirrhosis found a mean threefold increase in unbound blood-propranolol concentrations in patients with cirrhosis when compared with the controls. Mean half-lives for the 2 groups were 11.2 and 4 hours respectively.[1] Another study of propranolol given as a single dose of a 20-mg tablet and as a 160-mg modified-release preparation daily for 7 days in 10 patients with cirrhosis and portal hypertension found higher plasma concentrations in patients with severe liver disease compared with those reported in normal controls.[2] Others have reported similar findings.[3]

In patients with severe liver disease, it has been suggested that propranolol therapy be started at a low dose such as 20 mg three times daily,[2] 80 mg of a modified-release preparation given once daily,[2] or 160 mg of a modified-release preparation given every other day.[3] Monitoring of beta blockade is essential; checking the heart rate[2] or exercise testing[3] have been suggested as suitable methods to assess the extent of beta blockade in patients with cirrhosis.

1. Wood AJJ, *et al.* The influence of cirrhosis on steady-state blood concentrations of unbound propranolol after oral administration. *Clin Pharmacokinet* 1978; **3:** 478–87.
2. Arthur MJP, *et al.* Pharmacology of propranolol in patients with cirrhosis and portal hypertension. *Gut* 1985; **26:** 14–19.
3. Calès P, *et al.* Pharmacodynamic and pharmacokinetic study of propranolol in patients with cirrhosis and portal hypertension. *Br J Clin Pharmacol* 1989; **27:** 763–70.

Administration in renal impairment. A study of the pharmacokinetics of propranolol in 11 patients with chronic renal insufficiency showed no impairment in the elimination kinetics of propranolol compared with 8 subjects with normal renal function.[1] Peak concentrations of propranolol reported in patients with chronic renal failure have been 2 to 3 times higher than those in patients receiving dialysis or in normal subjects.[1,2] Additional studies indicate that there is no pharmacokinetic reason to amend the dosage of propranolol in patients with renal impairment.[3]

Findings from a study in 8 patients on haemodialysis include a slight elevation of plasma-propranolol concentrations, no elevation of plasma concentration of 4-hydroxypropranolol, but extremely high plasma concentrations of other propranolol metabolites.[4]

1. Lowenthal DT, *et al.* Pharmacokinetics of oral propranolol in chronic renal disease. *Clin Pharmacol Ther* 1974; **16:** 761–9.
2. Bianchetti G, *et al.* Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokinet* 1976; **1:** 373–84.
3. Wood AJJ, *et al.* Propranolol disposition in renal failure. *Br J Clin Pharmacol* 1980; **10:** 561–6.
4. Stone WJ, Walle T. Massive propranolol metabolite retention during maintenance hemodialysis. *Clin Pharmacol Ther* 1980; **28:** 449–55.

Haemangioma. Where medical management of infantile haemangiomas (p. 1605.3) is required, it is usually with corticosteroids or antiproliferative drugs, but the response is often unsatisfactory. A rapid therapeutic effect has been reported[1,2] with propranolol when given orally at an initial dose of 2 to 3 mg/kg daily in 2 or 3 divided doses, although some have advocated[3] a lower initial dose of 480 micrograms/kg daily in 3 divided doses, doubled if tolerated to a maximum total daily dose of 2 mg/kg. Propranolol treatment may be particularly useful for haemangiomas with the potential to obstruct the airways.[4-6]

1. Léauté-Labrèze C, *et al.* Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; **358:** 2649–51.
2. Sans V, *et al.* Propranolol for severe infantile hemangiomas: follow-up report. Abstract: *Pediatrics* 2009; **124:** 983. Full version: http://pediatrics.aappublications.org/cgi/reprint/124/3/e423.pdf (accessed 18/01/10)
3. Siegfried EC, *et al.* More on propranolol for hemangiomas of infancy. *N Engl J Med* 2008; **359:** 2846.
4. Truong MT, *et al.* Propranolol for the treatment of a life-threatening subglottic and mediastinal infantile hemangioma. *J Pediatr* 2010; **156:** 335–8.
5. Denoyelle F, Garabédian EN. Propranolol may become first-line treatment in obstructive subglottic infantile hemangiomas. *Otolaryngol Head Neck Surg* 2010; **142:** 463–4.
6. Maturo S, Hartnick C. Initial experience using propranolol as the sole treatment for infantile airway hemangiomas. *Int J Pediatr Otorhinolaryngol* 2010; **74:** 323–5.

Tetralogy of Fallot. Beta blockers, particularly propranolol, have been used for the treatment[1] and prophylaxis[1-3] of cyanotic attacks in infants and children with tetralogy of Fallot and reversible right-ventricular outflow tract obstruction, although caution is required since bradycardia may develop.[4] Esmolol may be preferred during surgery.[5-7]

In the UK, licensed prescribing information allows an oral dose of propranolol hydrochloride of up to 1 mg/kg given 3 or 4 times daily. It may also be given intravenously in a dose of up to 100 micrograms/kg 3 or 4 times daily, injected slowly under ECG control.

The *BNFC* recommends the following doses:

- Neonates: 0.25 to 1 mg/kg orally 2 or 3 times daily, to a maximum of 2 mg/kg 3 times daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 12 hours if necessary
- Children aged 1 month to 12 years: 0.25 to 1 mg/kg orally 3 or 4 times daily, to a maximum of 5 mg/kg daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 6 to 8 hours if necessary.

1. Cumming GR. Propranolol in tetralogy of Fallot. *Circulation* 1970; **41:** 13–15.
2. Eriksson BO, *et al.* Long-term treatment with propranolol in selected cases of Fallot's tetralogy. *Br Heart J* 1969; **31:** 37–44.

3. Ponce FE, *et al*. Propranolol palliation of tetralogy of Fallot: experience with long-term drug treatment in pediatric patients. *Pediatrics* 1973; **52:** 100–108.
4. Clark DJ, *et al*. Propranolol induced bradycardia in tetralogy of Fallot. *Br Heart J* 1989; **61:** 378–9.
5. Nussbaum J, *et al*. Esmolol for the treatment of hypercyanotic spells in infants with tetralogy of Fallot. *J Cardiothorac Anesth* 1989; **3:** 200–2.
6. Geary V, *et al*. Esmolol in tetralogy of Fallot. *J Cardiothorac Anesth* 1989; **3:** 524–6.
7. Dhir AK, Dhir S. Esmolol in infundibular spasm. *Anaesthesia* 1991; **46:** 998.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Propranolol is distributed into breast milk. A milk/plasma ratio range of 0.33 to 1.65 was reported in a study of 3 women.[1] It was calculated that the maximum dose likely to be ingested by a breast-fed infant would be less than 0.1% of the maternal dose. Other small studies[2,3] have reported similar results. No adverse effects have been seen in breast-fed infants whose mothers were given propranolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Smith MT, *et al*. Propranolol, propranolol glucuronide, and naphthoxylactic acid in breast milk and plasma. *Ther Drug Monit* 1983; **5:** 87–93.
2. Karlberg B, *et al*. Excretion of propranolol in human breast milk. *Acta Pharmacol Toxicol (Copenh)* 1974; **34:** 222–4.
3. Bauer JH, *et al*. Propranolol in human plasma and breast milk. *Am J Cardiol* 1979; **43:** 860–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propranolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Propranolol is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic-tissue binding and first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma concentrations vary greatly between individuals. Propranolol has high lipid solubility. It crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is about 90% bound to plasma proteins. It is metabolised in the liver and at least one of its metabolites (4-hydroxypropranolol) is considered to be active, but the contribution of metabolites to its overall activity is uncertain. The metabolites and small amounts of unchanged drug are excreted in the urine. The plasma half-life of propranolol is about 3 to 6 hours. Propranolol is reported not to be significantly dialysable.

Pregnancy. A study in 6 pregnant patients (32 to 36 weeks' gestation) showed that the disposition of propranolol 120 mg orally and 10 mg intravenously was not altered in pregnancy compared with the postnatal period.[1] Another study[2] in 13 pregnant patients given propranolol to control hypertension showed that the pharmacokinetics of propranolol and most of its major metabolites were not altered during pregnancy. Samples at term[3] in 10 of the women showed that propranolol and all of its known metabolites were present in maternal plasma, cord plasma, and neonatal plasma. At delivery plasma protein binding of propranolol was reported as 87.5% in maternal plasma and 67.2% in cord plasma. Similar results for maternal and cord plasma protein binding have been reported by others.[4]

1. O'Hare MFO, *et al*. Pharmacokinetics of propranolol during pregnancy. *Eur J Clin Pharmacol* 1984; **27:** 583–7.
2. Smith MT, *et al*. Chronic propranolol administration during pregnancy: maternal pharmacokinetics. *Eur J Clin Pharmacol* 1983; **25:** 481–90.
3. Smith MT, *et al*. Metabolism of propranolol in the human maternal-placental-foetal unit. *Eur J Clin Pharmacol* 1983; **24:** 727–32.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α_1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; **29:** 522–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Inderal; Oposim; Pirimetan; Propaneitor; ***Austral.***: Deralin; Inderal; ***Austria***: Inderal; ***Belg.***: Inderal; ***Braz.***: Antitensin; Cardbloc†; Cardix; Hipernolol; Inderal; Pharnolol; Polol; Pradinolol; Pranolal; Propacor; Propanolon; Propanox; Propramed; Rebaten; Sanpronol; Uni Propralol; ***Canad.***: Inderal; Novo-Pranol†; ***Chile***: Coriodal; ***China***: Bai Er Luo (百尔洛); Hang Da Lai (杭达来); Pu Le Xin (普乐欣); Pu Su Xin (普苏欣); ***Denm.***: Propal; ***Fin.***: Propral; Ranoprin; ***Fr.***: Avlocardyl; Hemipralon†; Karnodyl; ***Ger.***: Beta-Tablinen†; Dociton; Obsidan; Prophylux†; Propra-ratiopharm; ***Gr.***: Betadrenol; Dorizan; Frina; Inderal; Kostalerg; Waucoton; Ziserfin; ***Hong Kong***: Deralin†; Inderal; Inpanol; Propa; Synolol†; Uni-Panolol†; ***Hung.***: Huma-Pronol; ***India***: Betabloc; Betabus; Betacap; Betaspan†; Carnol; Ciplar; Corbeta; Inderal; Lol; Manoprolol; Migrabeta TR; Norten; Propal; ***Indon.***: Farmadral; Inderal†; ***Irl.***: Beta-Prograne; Half Beta-Prograne; Half Inderal; Inderal; ***Israel***: Deralin; Inderal†; Prolol; Slow Deralin; ***Ital.***: Inderal; ***Malaysia***: Hipranol; Inderal; ***Mex.***: Inderalici; Propalem; Sintaser; ***Norw.***: Inderal; Pranolol; ***NZ***: Angilol; Cardinol; Inderal; ***Philipp.***: Duranol; Inderal; Parvilox; Phanerol; ***Port.***: Inderal; ***Rus.***: Anaprilin (Анаприлин); Obsidan (Обзидан); ***S.Afr.***: Cardiblok†; Inderal; Indoblok; Prodorol; Pur-Bloka; Purbloka; ***Singapore***: Corbeta; Inderal†; Inpanol; Nalol; Propa; Propanol; Synolol; ***Spain***: Sumial; ***Swed.***: Inderal; ***Switz.***: Inderal; ***Thai.***: Alperol; Betalol; Betapress; Cardenol; Chinnolol; CVS; Emforal; Idelol; Inderal; Normpress; P-Parol; Palon; Perlol; Pralol; Prolol; Pronalol; Propanol; Proral; Ropranolol†; Syntonol; ***Turk.***: Dideral; ***UAE***: Cardilol; ***UK***: Angilol; Bedranol; Beta-Prograne; Half Beta-Prograne; Half Inderal; Inderal; Slo-Pro; Syprol; ***Ukr.***: Pranolol (Пранолол)†; ***USA***: Inderal; InnoPran; ***Venez.***: Algoren; Docitral; Inderal.

Multi-ingredient Preparations. ***Braz.***: Polol-H; Tenadren; ***China***: Di Er Kang Xin (迪尔康欣); ***Ger.***: Beta-Turfa†; Dociretic; Docitereri; Pertenso N; Propra comp; Triamteren tri-comp†; ***India***: Alltop-P; Alprine Plus; Alprine-H; Ambulax-HD; Ambulax-M; Ambulax; Anzi-P; Balmusa Plus; Beptazine-H†; Beptazine†; Calmtec-P; Cam Plus; Cardilax; Ciplar-H; Corbetazine; Diaze-P; Dizepax; Zopax Plus; ***Singapore***: Emforal; ***Ukr.***: Distonin (Дистонин)†.

Pharmacopoeial Preparations
BP 2014: Prolonged-release Propranolol Capsules; Propranolol Injection; Propranolol Tablets;
USP 36: Propranolol Hydrochloride and Hydrochlorothiazide Extended-release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Propranolol Hydrochloride Extended-release Capsules; Propranolol Hydrochloride Injection; Propranolol Hydrochloride Tablets.

Proscillaridin *(BAN, USAN, rINN)*

2936; A-32686; Proscilaridina; Proscillaridiini; Proscillaridin A; Proscillaridine; Proscillaridinum; PSC-801; Просцилларидин.
14-Hydroxy-3β-(α-L-rhamnopyranosyloxy)-14β-bufa-4,20,22-trienolide.
$C_{30}H_{42}O_8$=530.7
CAS — 466-06-8.
ATC — C01AB01.
ATC Vet — QC01AB01.
UNII — KC6BL281EN.

Profile

Proscillaridin is a cardiac glycoside obtained from *Drimia maritima* (Liliaceae). It is a positive inotrope with general properties similar to those of digoxin (p. 1353.3) and is reported to have a rapid onset and a short duration of action.

Proscillaridin has been given orally in the treatment of heart failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Talusin†.

Quinapril Hydrochloride

(BANM, USAN, rINNM)

CI-906 (quinapril); Hidrocloruro de quinapril; Kinapril Hidroklorür; Quinapril, Chlorhydrate de; Quinapril, hidrocloruro de; Quinaprili Hydrochloridum; Хинаприла Гидрохлорид.
(3*S*)-2-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid hydrochloride.
$C_{25}H_{30}N_2O_5$,HCl=475.0
CAS — 85441-61-8 (quinapril); 82586-55-8 (quinapril hydrochloride).
ATC — C09AA06.
ATC Vet — QC09AA06.
UNII — 33067B3N2M.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Quinapril Hydrochloride). A white or almost white or slightly pink, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in acetone. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Quinapril Hydrochloride). A white to off-white powder, with a pink cast at times. Freely soluble in aqueous solvents.

Suspension. Extemporaneous formulations of quinapril 1 mg/mL made by adding crushed Accupril tablets (*Pfizer, US*) to the following vehicles were found to be stable for 6 weeks when stored at 5 degrees:
- *Kphos* 15% (*Beach, US*), *Bicitra* 15% (*Draxis Pharma, US*), *OraSweet* 70% (*Paddock, US*)
- *Kphos* 15%, *Bicitra* 15%, *OraSweet SF* 70%
- *Kphos* 15%, *Bicitra* 15%, simple syrup 70%

The suspension containing *OraSweet SF* was considered to be the formulation of choice.[1]

1. Freed AL, *et al*. The development and stability assessment of extemporaneous pediatric formulations of Accupril. *Int J Pharm* 2005;**304:** 135–44.

Uses and Administration

Quinapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Quinapril is converted in the body to its active metabolite quinaprilat. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic use. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Quinapril is given orally as the hydrochloride, but doses are expressed in terms of the base. Quinapril hydrochloride 10.8 mg is equivalent to about 10.0 mg of quinapril.

In the treatment of **hypertension** the initial dose is 10 mg of quinapril once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily is recommended in the elderly, in patients with renal impairment, or in those taking a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before quinapril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, as a single dose or divided into 2 doses, although up to 80 mg daily has been given.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Quinapril is given in an initial dose of 2.5 mg daily. Usual maintenance doses range from 10 to 20 mg daily, as a single dose or divided into 2 doses; up to 40 mg daily has been given.

Quinaprilat has been given intravenously.

Reviews.

1. Wadworth AN, Brogden RN. Quinapril: a review of its pharmacological properties, and therapeutic efficacy in cardiovascular disorders. *Drugs* 1991; **41:** 378–99.
2. Plosker GL, Sorkin EM. Quinapril: a reappraisal of its pharmacology and therapeutic efficacy in cardiovascular disorders. *Drugs* 1994; **48:** 227–52.
3. Culy CR, Jarvis B. Quinapril: a further update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 2002; **62:** 339–85.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Breast feeding. After of a single dose of quinapril 20 mg in 6 women, quinapril was detected in the breast milk in a milk to plasma ratio of 0.12; no quinaprilat was detected.[1] It was estimated that the dose received by the infant would only be about 1.6% of the maternal dose.

For advice from UK regulatory authorities against the use of any ACE inhibitor during at least the early weeks of breast feeding see under Precautions of ACE Inhibitors, p. 1287.3.

1. Begg EJ, *et al*. Quinapril and its metabolite quinaprilat in human milk. *Br J Clin Pharmacol* 2001; **51:** 478–81.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinapril as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Antibacterials. Quinapril has been reported to reduce the absorption of *tetracyclines* due to the presence of magnesium carbonate in the tablet formulation.

Pharmacokinetics

Quinapril acts as a prodrug of the diacid quinaprilat, its active metabolite. About 60% of an oral dose of quinapril is absorbed. Quinapril is metabolised mainly in the liver to quinaprilat and inactive metabolites. Peak plasma concentrations of quinaprilat occur within 2 hours of an oral dose of quinapril. Quinaprilat is about 97% bound to plasma proteins. After an oral dose, quinapril is excreted in the urine and faeces, as quinaprilat, other metabolites, and unchanged drug, with the urinary route predominating; up to 96% of an intravenous dose of quinaprilat is excreted in the urine. The effective half-life for accumulation of quinaprilat is about 3 hours after multiple doses of quinapril; a long terminal phase half-life of 25 hours may represent strong binding of quinaprilat to angiotensin-converting enzyme.

The pharmacokinetics of both quinapril and quinaprilat are affected by renal and hepatic impairment. Dialysis has little effect on the excretion of quinapril or quinaprilat.

Small amounts of quinapril are distributed into breast milk.

References.

1. Begg EJ, *et al.* The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment. *Br J Clin Pharmacol* 1990; **30:** 213–20.
2. Halstenson CE, *et al.* The pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with various degrees of renal function. *J Clin Pharmacol* 1992; **32:** 344–50.
3. Wolter K, Fritschka E. Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure. *Eur J Clin Pharmacol* 1993; **44** (suppl 1): S53–6.
4. Begg EJ, *et al.* The pharmacokinetics of quinapril and quinaprilat in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; **37:** 302–4.
5. Squire IB, *et al.* Haemodynamic response and pharmacokinetics after the first dose of quinapril in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; **38:** 117–23.
6. Breslin E, *et al.* A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. *J Clin Pharmacol* 1996; **36:** 414–21.
7. Blumer JL, *et al.* Pharmacokinetics of quinapril in children: assessment during substitution for chronic angiotensin-converting enzyme inhibitor treatment. *J Clin Pharmacol* 2003; **43:** 128–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Accupril; ***Austral.***: Accupril; Acquin; Aquinafil; Asig†; Filpril†; Qpril; ***Austria***: Accupro; ***Belg.***: Accupril; ***Braz.***: Accupril; ***Canad.***: Accupril; ***Chile***: Accupril; ***China***: Yiheng (益恒); ***Cz.***: Accupro; ***Denm.***: Accupro; Quinacid†; ***Fin.***: Accupro; ***Fr.***: Acuitel; Korec†; ***Ger.***: Accupro; ***Gr.***: Accupron; ***Hong Kong***: Accupril; ***Hung.***: Accupro; Acumerck†; Quiagen; ***India***: Acupil; ***Indon.***: Accupril; ***Irl.***: Accupro; Quinapro†; ***Ital.***: Accuprin; Acequin; Quinazil; ***Jpn***: Conan; ***Mex.***: Acupril; ***Neth.***: Acupril; ***NZ***: Accupril; ***Philipp.***: Accupril; ***Pol.***: Accupro; Acurenal; AprilGen; Pulsaren; Q-Pril; ***Port.***: Acupril; ***Rus.***: Accupro (Аккупро); Quinaphar (Квинафар); ***S.Afr.***: Accumax; Accupril; Quinace; Quinagen; Quinaspen; ***Singapore***: Accupril; ***Spain***: Acuprel; Acuretic†; Ectren; Lidaltrin; ***Swed.***: Accupro; ***Switz.***: Accupro; Quiril; ***Thai.***: Accupril; Quinaril†; Quinsil; ***Turk.***: Acuitel; Kinateva; ***UK***: Accupro; Quinil; ***Ukr.***: Accupro (Аккупро); Acurenal (Акуренал)†; Quinard (Квінард)†; ***USA***: Accupril; ***Venez.***: Accupril; Quinalar; Solpres.

Multi-ingredient Preparations. ***Arg.***: Accuretic; ***Austral.***: Accuretic; ***Austria***: Accuzide; ***Belg.***: Accuretic; Co-Quinapril; ***Canad.***: Accuretic; ***Chile***: Accuretic; ***Cz.***: Accuzide; Stadapress; ***Fin.***: Accupro Comp; ***Fr.***: Acuilix; Koretic†; ***Ger.***: Accuzide; QuinaLich comp; Quinaplus†; Quinapril comp†; Quinapril plus†; ***Gr.***: Accuretic; Quimea; ***Hung.***: Accuzide; Quinanorm Kombi; Quinapril-HCT; ***India***: Acupil-H; ***Irl.***: Accuretic; ***Ital.***: Accuretic; Acequide; Quinazide; ***Neth.***: Acuzide; ***NZ***: Accuretic; ***Philipp.***: Accuzide; ***Pol.***: Accuzide; ***Port.***: Acuretic; ***Rus.***: Accuzide (Аккузид); ***S.Afr.***: Accumax Co; Accuretic; Adco-Quinaretic; Quinace Co; ***Spain***: Bicetil; Lidaltrin Diu; ***Swed.***: Accupro Comp; ***Switz.***: Accuretic; Quiril comp.; ***Thai.***: Accuretic; ***Turk.***: Accuzide; ***UK***: Accuretic; ***Ukr.***: Accuzide (Аккузид); ***USA***: Accuretic; Quinaretic; ***Venez.***: Accuretic; Quinaretic.

Pharmacopoeial Preparations

USP 36: Quinapril and Hydrochlorothiazide Tablets; Quinapril Tablets.

Quinidine *(BAN)*

Chinidinum; Chinidyna; Kinidiini; Kinidin; Quinidina; Хинидин.

(8*R*,9*S*)-6′-Methoxycinchonan-9-ol; (+)-(α*S*)-α-(6-Methoxy-4-quinolyl)-α-[(2*R*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2$=324.4

CAS — 56-54-2 (anhydrous quinidine); 63717-04-4 (quinidine dihydrate); 72402-50-7 (± quinidine).

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — ITX08688JL.

Description. Quinidine is an isomer of quinine, obtained from the bark of species of *Cinchona* and their hybrids; it may also be obtained from *Remijia pedunculata*, or prepared from quinine.

Quinidine Bisulfate *(BANM)*

Quinidina, bisulfato de; Quinidine Bisulphate; Хинидина Бисульфат.

$C_{20}H_{24}N_2O_2,H_2SO_4$=422.5

CAS — 747-45-5 (anhydrous quinidine bisulfate); 6151-39-9 (quinidine bisulfate tetrahydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — 6K043Q65TR.

Pharmacopoeias. In *Br.*

BP 2014: (Quinidine Bisulphate). Colourless, odourless or almost odourless, crystals. It contains not more than 15% of hydroquinidine bisulfate. Freely soluble in water and in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 2.6 to 3.6. Protect from light.

Quinidine Gluconate *(BANM)*

Quinidina, głuconato de; Quinidinium Gluconate; Хинидина Глюконат.

$C_{20}H_{24}N_2O_2,C_6H_{12}O_7$=520.6

CAS — 7054-25-3.

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — R6875N380F.

Pharmacopoeias. In *US.*

USP 36: (Quinidine Gluconate). A white, odourless powder. It contains not more than 20% of hydroquinidine gluconate. Freely soluble in water; slightly soluble in alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Adsorption. More than 40% of a dose of quinidine gluconate was lost when the drug was given by intravenous infusion using a PVC infusion bag and tubing.[1]

1. Darbar D, *et al.* Loss of quinidine gluconate injection in a polyvinyl chloride infusion system. *Am J Health-Syst Pharm* 1996; **53:** 655–8.

Quinidine Polygalacturonate

Quinidina, poligalacturonato de; Хинидина Полигалактуронат.

Quinidine poly(D-galacturonate) hydrate.

$C_{20}H_{24}N_2O_2,(C_6H_{10}O_7)_x,xH_2O$

CAS — 27555-34-6 (anhydrous quinidine polygalacturonate); 65484-56-2 (quinidine polygalacturonate hydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Quinidine Sulfate *(BANM)*

Chinidin sulfát dihydrát; Chinidini sulfas; Chinidino sulfatas; Chinidinsulfat; Chinidinsulfate; Chinidinum Sulfuricum; Chinidyny siarczan; Kinidiinisulfaatti; Kinidin Sülfat; Kinidinsulfat; Kinidin-szulfát; Quinidina, sulfato de; Quinidine, sulfate de; Quinidine Sulphate; Quinidini Sulfas; Quinidini Sulfas Dihydricus; Хинидина Сульфат.

$(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$=783.0

CAS — 50-54-4 (anhydrous quinidine sulfate); 6591-63-5 (quinidine sulfate dihydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — 140CU2322K (anhydrous quinidine sulfate); J13S2394HE (quinidine sulfate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Quinidine Sulfate). White or almost white, crystalline powder, or silky, colourless needles. It contains not more than 15% of hydroquinidine sulfate. Slightly soluble in water; soluble in boiling water and in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

USP 36: (Quinidine Sulfate). Fine, needle-like, white crystals, frequently cohering in masses, or a fine, white powder. It is odourless and darkens on exposure to light. It contains not more than 20% of hydroquinidine sulfate. Its solutions are neutral or alkaline to litmus. Soluble 1 in 100 of water, 1 in 10 of alcohol, and 1 in 15 of chloroform; insoluble in ether. Protect from light.

Stability. Quinidine sulfate was reported[1] to be stable for up to 60 days in several extemporaneously prepared oral liquid formulations.

1. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1804–9.

Uses and Administration

Quinidine is a class Ia antiarrhythmic (p. 1243.1). It also has antimuscarinic and alpha-adrenoceptor blocking properties. Quinidine is used in the management of supraventricular and ventricular arrhythmias, including cardioversion and maintenance of sinus rhythm in atrial fibrillation, but other drugs or methods are usually preferred (see below).

Quinidine is an isomer of quinine and may be used as an alternative to quinine in the treatment of malaria when quinine is not immediately available.

Quinidine is usually given orally and various salts have been used, including the bisulfate, the gluconate, the polygalacturonate, and the sulfate. Strengths of preparations and doses used may be expressed in terms of the salt actually contained in the preparation, but are commonly expressed as the equivalent amount of anhydrous quinidine base or quinidine sulfate dihydrate. Quinidine bisulfate (anhydrous) 260 mg, quinidine gluconate (anhydrous) 321 mg, quinidine sulfate (dihydrate) 241 mg, and quinidine sulfate (anhydrous) 230 mg are each equivalent to about 200 mg of quinidine (anhydrous).

For the management of **cardiac arrhythmias**, a typical dose of *quinidine sulfate dihydrate* is 200 to 400 mg three or four times daily, adjusted according to response; an initial test dose of 200 mg has been recommended for detecting hypersensitivity. Modified-release preparations may be preferred for maintenance.

Quinidine has also been given parenterally but absorption after intramuscular injection is erratic and incomplete, and intravenous use is associated with a risk of severe hypotension. If parenteral use is necessary for acute conversion of supraventricular or ventricular arrhythmias, *quinidine gluconate* may be given by intravenous infusion at a rate no faster than 250 micrograms/kg per minute; most patients respond to a total dose of less than 5 mg/kg, but up to 10 mg/kg may be given if required. ECG and blood pressure should be monitored throughout the infusion.

For the use of quinidine in the management of **malaria**, see below.

General references.

1. Grace AA, Camm AJ. Quinidine. *N Engl J Med* 1998; **338:** 35–45.
2. Yang F, *et al.* Quinidine revisited. *Am J Med* 2009; **122:** 317–21.

Cardiac arrhythmias. Quinidine is a class Ia antiarrhythmic and has been used in the management of supraventricular and ventricular arrhythmias, but other drugs or non-pharmacological therapies are usually preferred (see Cardiac Arrhythmias, p. 1266.1). Although use of quinidine may have increased after the CAST studies, which found an increased mortality with the use of encainide, flecainide, and moracizine in asymptomatic ventricular arrhythmias, a meta-analysis[1] of studies using quinidine for benign or potentially lethal ventricular arrhythmias found that it was associated with at least as high an incidence of adverse events, including death and early proarrhythmia, as the class Ic drugs flecainide and propafenone. Another meta-analysis[2] found that quinidine was more effective than placebo in maintaining sinus rhythm after cardioversion of atrial fibrillation, but again total mortality was increased. However, some continue to use it for pharmacological cardioversion.[3]

Quinidine has been used[4,5] in patients with Brugada syndrome, a congenital channelopathy that predisposes to ventricular arrhythmias, and may have a role as an alternative to an implantable cardioverter defibrillator. It may also be of use for short QT syndrome,[6] which is characterised by very short QT interval and susceptibility to atrial and ventricular fibrillation.

1. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. *Circulation* 1991; **84:** 1977–83.
2. Coplen SE, *et al.* Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990; **82:** 1106–16. Correction. *ibid.* 1991; **83:** 714.
3. Schwaab B, *et al.* Quinidine for pharmacological cardioversion of atrial fibrillation: a retrospective analysis in 501 consecutive patients. *Ann Noninvasive Electrocardiol* 2009; **14:** 128–36.
4. Belhassen B, *et al.* Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004; **110:** 1731–7.
5. Viskin S, *et al.* Empiric quinidine therapy for asymptomatic Brugada syndrome: time for a prospective registry. *Heart Rhythm* 2009; **6:** 401–4.
6. Kaufman ES. Quinidine in short QT syndrome: an old drug for a new disease. *J Cardiovasc Electrophysiol* 2007; **18:** 665–6.

Congenital myasthenia. Although quinidine may exacerbate the symptoms of myasthenia gravis and should be used with great caution in such patients, beneficial responses have been reported in patients with the slow-channel congenital myasthenic syndrome (see p. 685.1).

Hiccup. Quinidine is one of several drugs that have been tried in intractable hiccups. For details of a protocol for the control of hiccups see Chlorpromazine, p. 1046.3.

Malaria. Quinidine may be more potent than quinine as an antimalarial but it is more likely to cause cardiotoxicity

and hypersensitivity and WHO[1,2] has recommended that parenteral formulations of quinidine should only be used when parenteral quinine or artemisinin derivatives are not immediately available. In these situations intravenous infusions of quinidine could be used to begin treatment for severe chloroquine-resistant malaria. Patients should be transferred to oral therapy with quinine as soon as possible to complete a 7-day course; alternatively a single oral treatment of pyrimethamine-sulfadoxine may be given.

In the USA, the CDC[3] have recommended parenteral quinidine gluconate as the drug of choice for the treatment of complicated falciparum malaria, but only because of the lack of availability of parenteral quinine.

Quinidine is given intravenously as the gluconate and doses have been expressed in terms of the base or salt; it should be given under close control, preferably with continuous ECG monitoring and frequent measurements of blood pressure. Regimens used include one[1,3,4] where the equivalent of 15 mg of the base per kg is infused over 4 hours as a loading dose followed by the equivalent of 7.5 mg of the base per kg every 8 hours as infusions over 4 hours. The patient should be transferred to an oral form of antimalarial as soon as possible, to complete a total 3-day course (or a 7-day course if the malaria was acquired in South-East Asia).[3] An alternative regimen[5] consists of a loading dose of 10 mg of quinidine gluconate per kg given by intravenous infusion over a period of 1 to 2 hours followed by a constant intravenous infusion of 20 micrograms/kg per minute for a maximum of 72 hours or until oral therapy with quinine can be instituted to complete an appropriate length of treatment. It is generally recommended that loading doses should not be used if the patient has received quinine or quinidine within the previous 24 hours or mefloquine within the preceding 7 days.

The overall management of malaria is discussed in the chapter on Antimalarials, p. 644.1.

1. WHO. *Management of severe malaria: a practical handbook*. Geneva: WHO,2000. Available at: http://rbm.who.int/docs/hbsm.pdf (accessed 28/07/10)
2. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Also available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 28/07/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (updated April 2011). Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 27/07/11)
4. Phillips RE, *et al*. Intravenous quinidine for the treatment of severe falciparum malaria: clinical pharmacokinetic studies. *N Engl J Med* 1985; **312:** 1273–8.
5. Miller KD, *et al*. Treatment of severe malaria in the United States with a continuous infusion of quinidine gluconate and exchange transfusion. *N Engl J Med* 1989; **321:** 65–70.

Neurological disorders. For reference to the use of quinidine with dextromethorphan for the management of pseudobulbar affect associated with amyotrophic lateral sclerosis and multiple sclerosis, see p. 1660.3.

Adverse Effects and Treatment

Quinidine and its salts have both cardiac and non-cardiac adverse effects. Gastrointestinal irritation is common, with nausea, vomiting, and diarrhoea.

Hypersensitivity similar to that occurring with quinine may also occur and a test dose has been recommended (see Uses and Administration, p. 1481.3). Reactions include respiratory difficulties, urticaria, pruritus, rashes, purpura, thrombocytopenia and other blood dyscrasias, and, rarely, fever and anaphylaxis. Granulomatous hepatitis and a lupus-like syndrome have been reported.

Quinidine may give rise to cinchonism (see Quinine, p. 666.2) with tinnitus, impaired hearing, visual disturbances, headache, confusion, vertigo, vomiting, and abdominal pain; it is usually associated with large doses, but may occur in idiosyncratic subjects given small doses.

Quinidine may induce hypotension, particularly in overdosage or if intravenous infusions are given too rapidly. It prolongs the QT interval and may precipitate ventricular arrhythmias, including torsade de pointes.

In quinidine overdosage, the cardiac symptoms of intoxication predominate. Quinidine is cumulative in action and inappropriately high plasma concentrations may induce ECG changes, heart block, asystole, ventricular tachycardia, ventricular fibrillation, syncope, seizures, coma, and sometimes death. Treatment of adverse effects and overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

Reviews.

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; **5:** 393–420.

Effects on the blood. Quinidine-induced thrombocytopenia is not uncommon and it is one of the best documented causes of drug-dependent thrombocytopenia.[1] It appears to be a hypersensitivity reaction, with quinidine inducing the production of autoantibodies that cause platelet destruction. Highly specific quinidine-dependent antibodies have been detected in patients with thrombocytopenia, and may have a role in diagnosis.[2] The exact mechanism of the reaction is unclear but it is generally thought that binding of quinidine to the platelet surface induces antibody production;[1] alternatively, an antibody-quinidine complex may be formed, which is then deposited on the platelets.[1,3] The antigenic constituent of the platelet membrane may be glycoprotein Ib although other surface glycoproteins have also been implicated.[3,4]

1. van den Bemt PMLA, *et al*. Drug-induced immune thrombocytopenia. *Drug Safety* 2004; **27:** 1243–52.
2. Reid DM, Shulman NR. Drug purpura due to surreptitious quinidine intake. *Ann Intern Med* 1988; **108:** 206–8.
3. Stricker RB, Shuman MA. Quinidine purpura: evidence that glycoprotein V is a target platelet antigen. *Blood* 1986; **67:** 1377–81.
4. Visentin GP, *et al*. Characteristics of quinine-and quinidine-induced antibodies specific for platelet glycoproteins IIb and IIIa. *Blood* 1991; **77:** 2668–76.

Effects on the eyes. Corneal deposits resembling those found in keratopathy developed in a patient who had been taking quinidine for 2 years.[1] Symptoms had improved and both corneas had cleared completely within 2 months of stopping the drug.

A small number of patients have also been identified[2] who developed uveitis during quinidine treatment.

1. Zaidman GW. Quinidine keratopathy. *Am J Ophthalmol* 1984; **97:** 247–9.
2. Fraunfelder FW, Rosenbaum JT. Drug-induced uveitis: incidence, prevention and treatment. *Drug Safety* 1997; **17:** 197–207.

Effects on the joints. Quinidine has been associated with rheumatic disorders.[1] It is a recognised, though uncommon, cause of drug-induced lupus (see below), but there have also been reports[2-4] of reversible, symmetrical polyarthritis developing in patients with no evidence of antinuclear antibodies. Symptoms were generally milder than in drug-induced lupus, and onset was more rapid; recovery occurred within a week of stopping quinidine and in some patients symptoms recurred on rechallenge. Polymyalgia rheumatica-like symptoms have also been reported.[1]

1. Alloway JA, Salata MP. Quinidine-induced rheumatic syndromes. *Semin Arthritis Rheum* 1995; **24:** 315–22.
2. Kertes P, Hunt D. Polyarthritis complicating quinidine treatment. *BMJ* 1982; **284:** 1373–4.
3. Cohen MG, *et al*. Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108:** 369–71.
4. Naschitz JE, Yeshurun D. Quinidine and rheumatic syndromes. *Ann Intern Med* 1988; **109:** 248–9.

Effects on the liver. Hypersensitivity reactions involving the liver have been reported in about 2% of patients receiving quinidine.[1,2] The main clinical symptom is fever[1-3] but rashes,[1-3] purpura,[2] and hepatomegaly[1] may also occur. Liver enzyme values are raised[1-4] and the platelet count may be reduced.[3] The reaction is reversible on withdrawing quinidine with fever resolving in about 48 hours and liver enzymes values returning to normal within about 2 weeks. Liver biopsy often shows granulomatous hepatitis,[1-3] but other inflammatory changes[2] and cholestatic jaundice[4] have been found.

1. Geltner D, *et al*. Quinidine hypersensitivity and liver involvement: a survey of 32 patients. *Gastroenterology* 1976; **70:** 650–2.
2. Knobler H, *et al*. Quinidine-induced hepatitis. *Arch Intern Med* 1986; **146:** 526–8.
3. Bramlet DA, *et al*. Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. *Arch Intern Med* 1980; **140:** 395–7.
4. Hogan DB, *et al*. Unusual hepatotoxic reaction to quinidine. *Can Med Assoc J* 1984; **130:** 973.

Effects on mental state. Gradually progressive cerebral dysfunction characterised by intermittent confusion, agitation, restlessness, personality change, and paranoid features occurred in a 62-year-old man who had taken quinidine for about 15 years.[1] Within 24 hours of stopping quinidine there was a marked improvement and after 5 days he had returned to normal with no cognitive deficits. It was considered that quinidine had precipitated or exacerbated the functional psychosis.

1. Johnson AG, *et al*. A functional psychosis precipitated by quinidine. *Med J Aust* 1990; **153:** 47–9.

Effects on the skin. Skin reactions reported with quinidine include exacerbation of psoriasis,[1] blue-grey pigmentation,[2] photosensitivity,[3] and fatal toxic epidermal necrolysis.[4] Purpuric bruising, attributed to inhalation of quinidine dust in the workplace, has also been reported.[5]

1. Harwell WB. Quinidine-induced psoriasis. *J Am Acad Dermatol* 1983; **9:** 278.
2. Mahler R, *et al*. Pigmentation induced by quinidine therapy. *Arch Dermatol* 1986; **122:** 1062–4.
3. Marx JL, *et al*. Quinidine photosensitivity. *Arch Dermatol* 1983; **119:** 39–43.
4. Adornato MC. Toxic epidermal necrolysis associated with quinidine administration. *N Y State Dent J* 2000; **66:** 38–40.
5. Salom IL. Purpura due to inhaled quinidine. *JAMA* 1991; **266:** 1220.

Hypoglycaemia. Mean plasma-insulin concentrations increased and mean plasma-glucose concentrations decreased in 8 healthy subjects and 10 patients with malaria given quinidine intravenously.[1] Profound hypoglycaemia occurred in 1 patient with cerebral malaria and acute renal failure. These effects were considered to be associated with stimulation of β-cell secretion of insulin by quinidine and it was concluded that hypoglycaemia may occur in any severely ill fasting patient given parenteral quinidine.

1. Phillips RE, *et al*. Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; **292:** 1319–21.

Lupus erythematosus. There are several well-documented reports of quinidine-induced lupus erythematosus.[1-4] The syndrome involves polyarthritis with a positive antinuclear antibody test. Symptoms do not usually occur until several months after starting quinidine and resolve slowly on stopping the drug. A recurrence of lupus-like symptoms has occurred in patients with a previous reaction to procainamide.[2]

1. West SG, *et al*. Quinidine-induced lupus erythematosus. *Ann Intern Med* 1984; **100:** 840–2.
2. Amadio P, *et al*. Procainamide, quinidine, and lupus erythematosus. *Ann Intern Med* 1985; **102:** 419.
3. Lavie CJ, *et al*. Systemic lupus erythematosus (SLE) induced by quinidine. *Arch Intern Med* 1985; **145:** 446–8.
4. Cohen MG, *et al*. Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108:** 369–71.

Oesophageal stricture. Oral quinidine is a recognised cause of oesophageal injury[1,2] and has been associated with ulceration and stricture formation.

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.
2. Jaspersen D. Drug-induced oesophageal disorders: pathogenesis, incidence, prevention and management. *Drug Safety* 2000; **22:** 237–49.

Precautions

Quinidine is contra-indicated in complete heart block (unless the patient has a pacemaker). It should be used with extreme caution in patients with a prolonged QT interval or a history of torsade de pointes, incomplete heart block, uncompensated heart failure, myocarditis, or severe myocardial damage. Patients should be monitored closely for hypersensitivity reactions after the first dose and quinidine should not be given to those who develop a reaction or those with a history of hypersensitivity to quinidine, including patients who have previously developed thrombocytopenia with quinidine or quinine. Antiarrhythmic therapy with quinidine should be begun with extreme caution, if at all, during acute infections or fever as hypersensitivity reactions may be masked. Care is also required in patients with myasthenia gravis as quinidine can exacerbate the symptoms and may reduce the efficacy of parasympathomimetic drugs.

When quinidine is used to treat atrial flutter or fibrillation, the reduction in AV block may result in a very rapid ventricular rate. This can be avoided by prior digitalisation or by use of a rate-limiting calcium-channel blocker or beta blocker. However, quinidine should be avoided in digitalis overdosage as markedly increased plasma concentrations of digoxin may occur.

Reduced dosage should be considered for the elderly, for patients with hepatic or renal impairment, and on the occasions when it is used in heart failure.

Breast feeding. A woman[1] receiving 2.1 g quinidine daily throughout pregnancy had milk and serum concentrations 5 days after delivery of 6.4 and 9.0 micrograms/mL respectively, giving a milk to serum ratio of 0.71. It was estimated that the amount of quinidine that would be ingested by an infant would be far below the therapeutic range for its weight. No adverse effects have been reported in infants and the American Academy of Pediatrics considers[2] that quinidine is therefore usually compatible with breast feeding.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; **54:** 366–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinidine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. In a report[1] on the use of quinidine sulfate by a woman throughout pregnancy, concentrations in the infant's serum at delivery were similar to the mother's although amniotic fluid concentrations were raised. The infant's weight, ECG, haemoglobin concentration, and platelet count were all found to be within normal limits.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; **54:** 366–8.

Interactions

Quinidine has the potential for both pharmacodynamic and pharmacokinetic interactions with many other drugs.

Use of quinidine with drugs that increase the QT interval or have arrhythmogenic effects should generally be avoided, since there is an increased risk of toxicity. Although quinidine is sometimes given with other antiarrhythmics, caution is required since there may be both pharmacodynamic and pharmacokinetic interactions (see below). Interactions may also occur with other drugs because of the antimuscarinic and alpha-adrenoceptor blocking properties of quinidine; potentiation of the effects of neuromuscular blockers has also been reported.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and may interact with inhibitors or inducers of this isoenzyme. Rifampicin, phenobarbital, and phenytoin increase the metabolism of quinidine and increased doses may be required; HIV-protease inhibitors, which inhibit CYP3A4, may produce toxic concentrations of quinidine.

Urinary excretion of quinidine is dependent on urinary pH; drugs that increase urinary pH such as sodium bicarbonate, some antacids, and carbonic anhydrase inhibitors tend to increase the plasma concentration of quinidine since the proportion of nonionised drug in the urine is increased allowing greater renal tubular reabsorption.

Quinidine itself may also have effects on other drugs; it inhibits cytochrome P450 isoenzyme CYP2D6 and may affect drugs metabolised by this route. Examples of further drugs that may be affected by quinidine include oral anticoagulants, beta blockers, and digoxin; more details are given under the monographs for these drugs. Quinidine is used with dextromethorphan (see Neurological Disorders, p. 1660.3) for its ability to inhibit the metabolism of the latter.

Antiarrhythmics. *Amiodarone* may increase the plasma concentration of quinidine, increasing the risk of toxicity; prolongation of the QT interval with torsade de pointes has been reported.[1] This is probably because amiodarone inhibits hepatic or renal clearance of quinidine or displaces quinidine from binding sites. If the two drugs are used together the dose of quinidine may need to be reduced and the patient should be closely monitored. *Verapamil* given intravenously has been reported[2] to cause severe hypotension in patients also taking quinidine orally. Studies *in vitro* suggest this is due to the additive blockade of α-adrenergic receptors by both drugs and the simultaneous blockade of calcium channels by verapamil; verapamil may also increase the plasma concentration of quinidine. Quinidine itself may increase the plasma concentration of some other antiarrhythmics (see Ajmaline, p. 1295.3, Digoxin, p. 1356.2, Disopyramide, p. 1365.1, Flecainide Acetate, p. 1384.3, Procainamide, p. 1477.1, and Propafenone Hydrochloride, p. 1478.3).

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil. *N Engl J Med* 1985; **312:** 167–70.

Antibacterials. Torsade de pointes has been reported[1] in a patient taking *erythromycin* with quinidine. Like quinidine, erythromycin prolongs the QT interval, and the effect may be greater if the drugs are given together;[2] there is also some evidence[3-5] that erythromycin reduces quinidine clearance.

1. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy* 1997; **17:** 626–30.
2. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacodynamics in healthy volunteers. *Pharmacotherapy* 1997; **17:** 1111.
3. Spinler SA, *et al.* Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther* 1995; **57:** 89–94.
4. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacokinetics in healthy volunteers. *Pharmacotherapy* 1998; **18:** 426–7.
5. Damkier P, *et al.* Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999; **48:** 829–38.

Antifungals. *Ketoconazole* temporarily increased the plasma-quinidine concentration in a patient through reduced hepatic elimination.[1] Another antifungal that inhibits hepatic metabolism, *itraconazole*, has also been reported[2] to increase plasma-quinidine concentrations.

1. McNulty RM, *et al.* Transient increase in plasma quinidine concentrations during ketoconazole-quinidine therapy. *Clin Pharm* 1989; **8:** 222–5.
2. Kaukonen K-M, *et al.* Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther* 1997; **62:** 510–17.

Beta blockers. Quinidine and beta blockers may have additive adverse effects, and pharmacokinetic interactions may also occur. Sinus bradycardia has been reported in a patient prescribed oral quinidine and *timolol* eye drops,[1] and orthostatic hypotension has occurred when quinidine was used with *atenolol*.[2] Use of quinidine or the beta blocker alone was well tolerated in each case with no adverse effects.

1. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; **103:** 890–1.
2. Manolis AS, Estes NAM. Orthostatic hypotension due to quinidine and atenolol. *Am J Med* 1987; **82:** 1083–4.

Calcium-channel blockers. *Nifedipine* has been reported[1] to reduce plasma-quinidine concentrations and increasing the dose of quinidine to up to 20 mg/kg failed to increase the plasma concentration. Withdrawal of nifedipine resulted in a doubling of the quinidine concentration. A pharmacokinetic and pharmacodynamic study in healthy subjects, however, failed to show that modified-release *felodipine* or nifedipine had any effect on quinidine disposition.[2] Another study in healthy subjects suggested that quinidine may inhibit nifedipine metabolism.[3] *Diltiazem* has also been reported[4] to decrease the clearance and increase the half-life of quinidine in healthy subjects, although it was noted that another study had failed to show any interaction.

For the effects of *verapamil* used with quinidine, see Antiarrhythmics, above.

1. Green JA, *et al.* Nifedipine-quinidine interaction. *Clin Pharm* 1983; **2:** 461–5.
2. Bailey DG, *et al.* Quinidine interaction with nifedipine and felodipine: pharmacokinetic and pharmacodynamic evaluation. *Clin Pharmacol Ther* 1993; **53:** 354–9.
3. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; **33:** 727–31.
4. Laganière S, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin Pharmacol Ther* 1996; **60:** 255–64.

Diuretics. *Carbonic anhydrase inhibitors* increase urinary pH and may increase plasma-quinidine concentrations by increasing renal tubular reabsorption. *Thiazides* and *loop diuretics* may increase the risk of arrhythmias by causing hypokalaemia. Arrhythmias occurred in 4 of 10 patients receiving *amiloride* when given quinidine,[1] possibly due to additive sodium-channel blockade.

1. Wang L, *et al.* Amiloride-quinidine interaction: adverse outcomes. *Clin Pharmacol Ther* 1994; **56:** 659–67.

Histamine H_2-antagonists. *Cimetidine* inhibits the hepatic metabolism of quinidine and increases in plasma concentration and half-life with a reduction in clearance have been reported.[1-3]

1. Hardy BG, *et al.* Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. *Am J Cardiol* 1983; **52:** 172–5.
2. Kolb KW, *et al.* Effect of cimetidine on quinidine clearance. *Ther Drug Monit* 1984; **6:** 306–12.
3. MacKichan JJ, *et al.* Effect of cimetidine on quinidine bioavailability. *Biopharm Drug Dispos* 1989; **10:** 121–5.

Pharmacokinetics

Quinidine is rapidly absorbed from the gastrointestinal tract; the time to peak plasma concentration depends on the salt and formulation but is about 2 hours for quinidine sulfate immediate-release tablets. Bioavailability is variable, owing to first-pass metabolism in the liver.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to several metabolites, at least some of which are pharmacologically active. It is excreted in the urine, mainly in the form of its metabolites. The proportion excreted unchanged is dependent on urinary pH; in acidic urine about 20% is excreted as unchanged quinidine but in alkaline urine this is reduced to about 5% due to increased renal tubular reabsorption.

Quinidine is widely distributed throughout the body and is 80 to 90% bound to plasma proteins including α_1-acid glycoprotein. It has a plasma half-life of about 6 to 8 hours but this may show wide variation. Its therapeutic effect has been correlated with plasma concentrations of about 1 to 6 micrograms/mL, depending on the assay method used; older methods that do not differentiate quinidine from its metabolites may give misleading results.

Quinidine crosses the placenta and is distributed into breast milk. Only small amounts are removed by haemodialysis.

Considerable intersubject and intrasubject variability in the pharmacokinetics of quinidine has been noted;[1] in one study the half-life ranged from about 1 to 16 hours regardless of whether the drug was given as a tablet, capsule, oral solution, or intramuscular injection. There may also be considerable variations in absorption depending upon the formulation and the salt used.[2,3] The effect of food on absorption is not clear.[4,5] The heart condition being treated or associated with the arrhythmia may alter quinidine's pharmacokinetics[6,7] as may the age of the patient.[8-10] Hepatic impairment may affect protein binding and prolong quinidine's half-life.[11] Protein binding increases in patients with renal impairment, although it returns to normal during dialysis procedures.[12] Accumulation of quinidine metabolites may occur in patients with renal dysfunction.[13-15]

1. Mason WD, *et al.* Comparative plasma concentrations of quinidine following administration of one intramuscular and three oral formulations to 13 human subjects. *J Pharm Sci* 1976; **65:** 1325–9.
2. Frigo GM, *et al.* Comparison of quinidine plasma concentration curves following oral administration of some short- and long-acting formulations. *Br J Clin Pharmacol* 1977; **4:** 449–54.
3. Mahon WA, *et al.* Comparative bioavailability study of three sustained release quinidine formulations. *Clin Pharmacokinet* 1987; **13:** 118–24.
4. Woo E, Greenblatt DJ. Effect of food on enteral absorption of quinidine. *Clin Pharmacol Ther* 1980; **27:** 188–93.
5. Martinez MN, *et al.* Effect of dietary fat content on the bioavailability of a sustained release quinidine gluconate tablet. *Biopharm Drug Dispos* 1990; **11:** 17–29.
6. Ueda CT, Dzindzio BS. Quinidine kinetics in congestive heart failure. *Clin Pharmacol Ther* 1978; **23:** 158–64.
7. Ueda CT, Dzindzio BS. Bioavailability of quinidine in congestive heart failure. *Br J Clin Pharmacol* 1981; **11:** 571–7.
8. Drayer DE, *et al.* Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. *Clin Pharmacol Ther* 1980; **27:** 72–5.
9. Szefler SJ, *et al.* Rapid elimination of quinidine in pediatric patients. *Pediatrics* 1982; **70:** 370–5.
10. Pickoff AS, *et al.* Age-related differences in the protein binding of quinidine. *Dev Pharmacol Ther* 1981; **3:** 108–15.
11. Kessler KM, *et al.* Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol. *Am Heart J* 1978; **96:** 627–35.
12. Kessler KM, Perez GO. Decreased quinidine plasma protein binding during haemodialysis. *Clin Pharmacol Ther* 1981; **30:** 121–6.
13. Kessler KM, *et al.* Quinidine elimination in patients with congestive heart failure or poor renal function. *N Engl J Med* 1974; **290:** 706–9.
14. Drayer DE, *et al.* Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. *Clin Pharmacol Ther* 1978; **24:** 31–9.
15. Hall K, *et al.* Clearance of quinidine during peritoneal dialysis. *Am Heart J* 1982; **104:** 646–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Kinidin†; ***Braz.***: Quinicardine; ***Canad.***: Apo-Quin-G†; ***Fin.***: Kiniduron; ***Gr.***: Kinidin; Kinidine; Longaquin; ***India***: Natcardine; ***Irl.***: Kinidin†; ***Ital.***: Chinteina†; Longachin; ***Philipp.***: Kinidin†; ***Rus.***: Kinidin (Кинидин); ***S.Afr.***: Quinaglute†; ***Turk.***: Longacor; Natisedine; Quinicardine.

Multi-ingredient Preparations. ***Fr.***: Quinimax; ***Ger.***: Cordichin; ***USA***: Nuedexta.

Pharmacopoeial Preparations

BP 2014: Quinidine Sulphate Tablets;
USP 36: Quinidine Gluconate Extended-release Tablets; Quinidine Gluconate Injection; Quinidine Sulfate Capsules; Quinidine Sulfate Extended-release Tablets; Quinidine Sulfate Oral Suspension; Quinidine Sulfate Tablets.

Ramipril *(BAN, USAN, rINN)*

Hoe-498; Ramipriili; Ramiprilis; Ramiprilum; Рамиприл.

(2*S*,3a*S*,6a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]L-alanyl}perhydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

$C_{23}H_{32}N_2O_5$=416.5

CAS — *87333-19-5.*

ATC — *C09AA05.*

ATC Vet — *QC09AA05.*

UNII — *L35JN3I7SJ.*

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ramipril). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Protect from light.

USP 36: (Ramipril). A white to almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Ramipril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1), heart failure (p. 1262.3), and after myocardial infarction (p. 1257.1) to improve survival in patients with clinical evidence of heart failure. It is also used to reduce the risk of cardiovascular events in patients with certain risk factors (see Cardiovascular Risk Reduction, p. 1246.1).

Ramipril owes its activity to ramiprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic effect is maintained for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** an initial oral dose of 2.5 mg once daily is given (or 1.25 mg in those on diuretics or otherwise at risk of profound hypotension). Since there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Patients taking diuretics should, if possible, have the diuretic stopped 2 to 3 days before starting ramipril, and resumed later if necessary. The usual maintenance dose is 2.5 to 5 mg daily as a single dose,

although up to 10 mg daily may be required. In the USA an initial dose of 2.5 mg once daily in hypertensive patients not taking a diuretic and a maintenance dose of 2.5 to 20 mg daily, as a single dose or in two divided doses, have been suggested.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision; high doses of diuretics should be reduced before starting ramipril. Ramipril is given in an initial dose of 1.25 mg once daily. The usual maximum dose is 10 mg daily; doses of 2.5 mg or more daily may be taken in 1 or 2 divided doses.

After **myocardial infarction**, treatment with ramipril may be started in hospital 3 to 10 days after the infarction at a usual initial dose of 2.5 mg twice daily, increased after two days to 5 mg twice daily. The usual maintenance dose is 2.5 to 5 mg twice daily.

In the treatment of diabetic and non-diabetic **nephropathy**, an initial oral dose of 1.25 mg once daily may be given, doubled at intervals of 2 weeks to a maintenance dose of 5 mg once daily.

For the **prophylaxis of cardiovascular events** in patients considered to be at high risk, ramipril is given in an initial dose of 2.5 mg once daily. The dose should be increased, if tolerated, to 5 mg once daily after 1 week, then to the usual maintenance dose of 10 mg once daily after a further 3 weeks. In patients with hypertension or recent myocardial infarction it may also be given in divided doses.

A reduction in dosage of ramipril may be necessary in patients with impaired hepatic or renal function (see below).

References.

1. Todd PA, Benfield P. Ramipril: a review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. *Drugs* 1990; **39:** 110–35.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; **342:** 821–8.
3. Frampton JE, Peters DH. Ramipril: an updated review of its therapeutic use in essential hypertension and heart failure. *Drugs* 1995; **49:** 440–66.
4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.
5. Warner GT, Perry CM. Ramipril: a review of its use in the prevention of cardiovascular outcomes. *Drugs* 2002; **62:** 1381–1405.
6. Vuong AD, Annis LG. Ramipril for the prevention and treatment of cardiovascular disease. *Ann Pharmacother* 2003; **37:** 412–19.
7. Rokoss MJ, Teo KK. Ramipril in the treatment of vascular diseases. *Expert Opin Pharmacother* 2005; **6:** 1911–19.
8. Anderson VR, *et al*. Ramipril: a review of its use in preventing cardiovascular outcomes in high-risk patients. *Am J Cardiovasc Drugs* 2006; **6:** 417–32.
9. Lüders S, *et al*. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure - a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens* 2008; **26:** 1487–1496.
10. Yusuf S, *et al*. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358:** 1547–59.

Administration in children. Ramipril was a safe and effective antihypertensive and antiproteinuric drug when given to 31 children and adolescents aged from about 2 to 20 years with chronic renal disease and hypertension or proteinuria.[1] A single daily oral starting dose of 1.5 mg/m^2 was adjusted to a range of 1.2 to 5.7 mg/m^2 (mean dose 2.5 mg/m^2). Similar results were also seen with a fixed oral dose of 6 mg/m^2 in 397 children aged from 3 to 18 years with chronic renal failure.[2]

1. Seeman T, *et al*. Ramipril in the treatment of hypertension and proteinuria in children with chronic kidney diseases. *Am J Hypertens* 2004; **17:** 415–20.
2. Wühl E, *et al*. ESCAPE Trial Group. Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. *Kidney Int* 2004; **66:** 768–76.

Administration in hepatic or renal impairment. UK licensed product information for ramipril states that in patients with hepatic impairment the maximum oral daily dose is 2.5 mg. In renal impairment, the following dosage adjustments are required depending on creatinine clearance (CC):

- CC 30 to 60 mL/min: a maximum maintenance dose of 5 mg daily
- CC 10 to 30 mL/min (and haemodialysis patients): an initial dose of 1.25 mg daily and a maximum maintenance dose of 5 mg daily. Doses should be given a few hours after haemodialysis

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ramipril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Ramipril acts as a prodrug of the diacid ramiprilat, its active metabolite. After oral doses at least 50 to 60% is absorbed. Ramipril is metabolised in the liver to ramiprilat; other metabolites are inactive. Peak plasma concentrations of ramiprilat occur 2 to 4 hours after an oral dose of ramipril. Ramiprilat is about 56% bound to plasma proteins. After oral doses ramipril is excreted mainly in the urine, as ramiprilat, other metabolites, and some unchanged drug. About 40% of an oral dose appears in the faeces; this may represent both biliary excretion and unabsorbed drug. The effective half-life for accumulation of ramiprilat is 13 to 17 hours after multiple doses of ramipril 5 to 10 mg, but is much longer for doses of 1.25 to 2.5 mg daily; the difference relates to the long terminal half-life associated with saturable binding to the angiotensin-converting enzyme. The clearance of ramiprilat is reduced in renal impairment.

Reviews.

1. Meisel S, *et al*. Clinical pharmacokinetics of ramipril. *Clin Pharmacokinet* 1994; **26:** 7–15.
2. van Griensven JMT, *et al*. Pharmacokinetics, pharmacodynamics and bioavailability of the ACE inhibitor ramipril. *Eur J Clin Pharmacol* 1995; **47:** 513–8.
3. Fillastre JP, *et al*. Kinetics, safety, and efficacy of ramipril after long-term administration in hemodialyzed patients. *J Cardiovasc Pharmacol* 1996; **27:** 269–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lostapres; Tritace; ***Austral.***: Prilace; Ramace; Tritace; Tryzan; ***Austria***: Hypren; Lannapril; Tritace; ***Belg.***: Tritace; ***Braz.***: Atensec; Ecator; Naprix; Triatec; ***Canad.***: Altace; ***Chile***: Ramipres; Triatec; ***China***: Ruisutan (瑞素坦); Tritace (瑞泰); ***Cz.***: Acesial; Amprilan; Hartil; Medoram; Miril; Piramil; Ramicard; Ramigamma; Ramil; Ramistada†; Ramitren†; Tritace; Vivokar†; ***Denm.***: Alarimed; Mariram; Rolam; Sylerasamed; Triatec; Yamasiv; ***Fin.***: Cardace; ***Fr.***: Triatec; Triateckit†; ***Ger.***: Delix; Ramicard†; Ramiclair; Ramigamma; RamiLich; Vesdil†; ***Gr.***: Piramil; Stibenyl; Triatec; ***Hong Kong***: Tritace; ***Hung.***: Amprilan; Corpril†; Emren; Hartil; Meramyl; Piramil†; Ramace; Ramicard; Ramigamma; Ramiwin†; Tritace; ***India***: Acepril; Alvace; Cardace; Cardiopril; Conram; Cordimil; Corpril; Dexace; Ecator; Emipril; Etoril; Gopril; Hecril; Hopace; Hopecard; Hoperam; Kapril; Megapril; Odipril; Preface; R-Pril; Ramcor; Ramipres; Sclerace; ***Indon.***: Cardace; Hyperil; Ramixal; Redutens; Tenapril†; Triatec; Vivace; ***Irl.***: Bellramil; ByTrite; Loavel; Ramic; Ramilo; Ramitace; Ramyte†; Tritace; ***Israel***: Ramitens; Tritace; ***Ital.***: Norapril; Quark; Ramieca; Triatec; Unipril; ***Malaysia***: Tripril; Tritace; ***Mex.***: Intemipril; Lastace; Ramace; Tritace; Venesden; ***Neth.***: Tritace; ***Norw.***: Triatec; ***NZ***: Tritace†; ***Philipp.***: Ramipro; Tritace; ***Pol.***: Ampril; Apo-Rami; Axtil; Mitrip; Piramil; Polpril; Ramicor; Ramve; Tritace; Vivace; ***Port.***: Brefit; Prilamil; Ramgen†; Romace; Triatec; Verzatec; ***Rus.***: Amprilan (Амприлан); Hartil (Хартил); Piramil (Пирамил); Ramitren (Рамитрен); Tritace (Тритаце); ***S.Afr.***: Ramace; Ramiwin; Rampil; Retace; Tritace; ***Singapore***: Tritace; ***Spain***: Acovil; Carasel; ***Swed.***: Triatec; ***Switz.***: Triatec; ***Thai.***: Acetate; Corpril; Gempril; Mediram; Piramil†; Ramicard; Ramiril†; Ramtace; Tritace; ***Turk.***: Blokace; Delix; Race; Raliks; Revil; Sandace; ***UK***: Tritace; ***Ukr.***: Ampril (Амприл); Hartil (Хартил); Polapril (Полаприл); Rami (Рами); Ramihexal (Рамигексал)†; Ramizes (Рамизес); ***USA***: Altace; ***Venez.***: Altace; Piramil.

Multi-ingredient Preparations. ***Arg.***: Triacor; Tritace-HCT; ***Austral.***: Triasyn; ***Austria***: Hypren plus; Lannapril plus; Lasitace; Ramicomp; Tritazide; ***Belg.***: Co-Ramipril; Tazko; Tritazide; ***Braz.***: Ecator H; Naprix A; Naprix D; Ramipress HCT; Triatec D; ***Canad.***: Altace HCT; Altace Plus Felodipine; ***Cz.***: Amprilan H; Hartil-H; Medoram plus H; Miril plus H; Ramil H; Ramipril H; Ramixa Plus H†; Triasyn; Tritazide; ***Denm.***: Marilamed; Ramiad†; Ranid; Tiavase; Triatec Comp†; Xeviram†; ***Fin.***: Cardace Comp; Unimax; ***Fr.***: Cotriatec; ***Ger.***: Arelix ACE†; Delix Plus; Delmuno; Rami-Q comp†; Ramicard Plus†; Ramiclair Plus; Ramigamma HCT; RamiLich comp; Ramiplus†; Ramipril comp; Ramipril HCT†; Ramipril HCTad†; Ramipril Plus†; Ramitanid†; Unimax; Vesdil plus†; ***Gr.***: Piramil Plus; Stibenyl HCT; Triacor; Triatec Plus; Unitens; ***Hung.***: Amprilan HD; Amprilan HL; Hartil HCT; Meramyl HCT; Ramace Plusz; Ramiwin HCT†; Triasyn; Tritace-HCT; ***India***: Acepril-A; Alis-AT; Alis-R; Amlo-R; Amlokos-R; Ampine-RL; Asomex-R; Cardace-H; Conram H; Corpril-AM; Dexace-H; Diakit-3; Diakit-4; Ecator-H; Esam R; Eslo-Ril; Etotan-HR; Etotan-R; Hopace-AM; Hopace-H; Hopecard AM; Hopecard H; Kapril-H; Loram-H; Loram; Losanorm-HR; Loscom-R; LR; Odipril-H; Olmy-R; Ramcor H; Ramipres H; ***Irl.***: Trialix; Triapin; ***Israel***: Ramipril Plus; Ramitens Plus†; Tritace Comp; ***Ital.***: Idroquark; Prilace; Triapin; Triatec HCT; Uniprildiur; ***Mex.***: Dynyel; Triacor; Tritazide; ***Neth.***: Delitab-HCT†; Prilitab-HCT†; Prilitaril-HCT; Ramitab-HCT†; Triapin; Tritazide; ***Philipp.***: Triapin; ***Pol.***: Ampril HD; Ampril HL; Delmuno; Ramicor Comb†; Tritace Comb; ***Port.***: Ramicor D†; Triapin; Triatec Composto; Unimax†; ***Rus.***: Amprilan ND (Амприлан НД); Amprilan NL (Амприлан НЛ); Hartil-D (Хартил-Д); Ramazid H (Рамазид н); ***S.Afr.***: Tri-Plen; ***Spain***: Triapin; ***Swed.***: Triatec Comp; ***Switz.***: Co-Ramipril; Ramipril HCT; Trialix; Triatec Comp; Unimax†; ***Thai.***: Tritazide; ***Turk.***: Blokace Plus; Delix Plus; Race Plus; Revil Plus; ***UK***: Triapin; ***Ukr.***: Ampril HD (Амприл HD); Ampril HL (Амприл HL); Hartil-H (Хартил-Н); Mipril H (Миприл Н); Rami Compositum (Рами Композитум); Rami-Asomex (Рами-Азомекс); Ramihexal Compositum (Рамигексал Композитум)†; Ramizes Com (Рамизес Ком); Tritace Plus (Тритаце Плюс); ***Venez.***: Altace Plus.

Pharmacopoeial Preparations

BP 2014: Ramipril Capsules; Ramipril Tablets;
USP 36: Ramipril Capsules.

Ranolazine *(BAN, USAN, rINN)*

CVT-303; Ran-D; Ran4; Ranolazina; Ranolazinum; RS-43285-003; Ранолазин.

(±)-*N*-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide.

$C_{24}H_{33}N_3O_4$=427.5

CAS — 95635-55-5.
ATC — C01EB18.
ATC Vet — QC01EB18.
UNII — A6IEZ5M406.

Ranolazine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de ranolazina; Ranolazina, hidrocloruro de; Ranolazine, Chlorhydrate de; Ranolazini Hydrochloridum; RS-43285; Ранолазина Гидрохлорид.

$C_{24}H_{33}N_3O_4$,2HCl=500.5

CAS — 95635-56-6.
ATC — C01EB18.
ATC Vet — QC01EB18.
UNII — F71253DJUN.

Uses and Administration

Ranolazine is an antianginal drug. Its mechanism of action is unclear but may involve inhibition of the late sodium current in cardiac myocytes; it also inhibits fatty acid oxidation, but this does not appear to occur at therapeutic plasma concentrations. It is given orally, as a modified-release dose-form, for the treatment of stable angina pectoris (p. 1254.3).

In the UK, ranolazine is indicated in patients who are unable to tolerate or who have not responded satisfactorily to other antianginals, and should be given as an adjunct to standard therapy. It is given in an initial dose of 375 mg twice daily, increased after 2 to 4 weeks to 500 mg twice daily. The dose may be further increased to a maximum of 750 mg twice daily depending on response; dose reduction may be necessary if adverse effects occur.

In the USA, ranolazine may be used alone or as an adjunct to other antianginal drugs. The initial dose is 500 mg twice daily, increasing to a maximum of 1 g twice daily if necessary. The dose should be limited to 500 mg twice daily in patients taking some interacting drugs (see Interactions, p. 1485.1).

Reviews.

1. Tafreshi MJ, Fisher E. Ranolazine: a new approach to management of patients with angina. *Ann Pharmacother* 2006; **40:** 689–93.
2. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006; **113:** 2462–72.
3. Zerumsky K, McBride BF. Ranolazine in the management of chronic stable angina. *Am J Health-Syst Pharm* 2006; **63:** 2331–8.
4. Keating GM. Ranolazine: a review of its use in chronic stable angina pectoris. *Drugs* 2008; **68:** 2483–2503.
5. Aslam S, Gray D. Ranolazine (Ranexa) in the treatment of chronic stable angina. *Adv Therapy* 2010; **27:** 193–201.
6. Reffelmann T, Klonner RA. Ranolazine: an anti-anginal drug with further therapeutic potential. *Expert Rev Cardiovasc Ther* 2010; **8:** 319–29.

Diabetes mellitus. Ranolazine treatment for acute coronary syndrome has been found to be associated with a reduction in HbA_{1c} both in patients with diabetes mellitus (p. 459.1) and those with no history of the disease;[1] the mechanism was uncertain.

1. Morrow DA, *et al*. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 2009; **119:** 2032–9.

Adverse Effects and Precautions

Adverse effects most commonly seen with ranolazine are nausea, constipation, dizziness, and headache. Palpitations, tinnitus, vertigo, dry mouth, abdominal pain, vomiting, peripheral oedema, and dyspnoea have also been reported. Rarely reported effects include bradycardia, haematuria, paraesthesia, hypotension, and blurred vision. Acute renal failure has also been reported.

Dose-related prolongation of the QT interval may occur; ranolazine should be used with caution in patients with pre-existing QT prolongation, and in those at increased risk of

QT prolongation; it is contra-indicated in patients with significant hepatic impairment and those taking interacting drugs (see Interactions, below). Plasma concentrations are increased in renal impairment and UK licensed product information contra-indicates ranolazine in patients with creatinine clearance below 30 mL/minute.

Interactions

Ranolazine is mainly metabolised by the P450 isoenzyme CYP3A4 and may interact with other drugs that affect or are affected by this enzyme. Ranolazine is contra-indicated with potent inhibitors of CYP3A4, such as ketoconazole and related antifungals, clarithromycin and telithromycin, HIV-protease inhibitors, and nefazodone. It may be used with caution in patients taking moderate CYP3A4 inhibitors or P-glycoprotein inhibitors, such as diltiazem, verapamil, fluconazole, erythromycin, ciclosporin, and grapefruit juice or grapefruit products; US licensed product information recommends a maximum dose of 500 mg twice daily if such combinations are given. Use of ranolazine with CYP3A4 or P-glycoprotein inducers should be avoided.

Ranolazine may itself act as an inhibitor of some enzymes. Plasma concentrations of simvastatin, which is metabolised by CYP3A4, are reported to be doubled when given with ranolazine. Plasma concentrations of digoxin, a P-glycoprotein substrate, may also be increased and dose adjustment may be required; dose reductions may also be needed for drugs metabolised by CYP2D6, such as tricyclic antidepressants and some antipsychotics.

Ranolazine may theoretically interact with other drugs that increase the QT-interval. UK licensed product information contra-indicates its use with class Ia or class III antiarrhythmics.

Pharmacokinetics

Absorption of ranolazine is highly variable and peak plasma concentrations occur about 2 to 5 hours after an oral dose of the modified-release preparation. Ranolazine is extensively metabolised in the gastrointestinal tract and liver. Four main metabolites have been identified. Protein binding of ranolazine is about 62%. About 75% of a dose is excreted in the urine with the remainder in the faeces, with less than 5% as unchanged drug. The apparent terminal half-life for the modified-release preparation of ranolazine is 7 hours, and steady state occurs within 3 days.

Reviews.

1. Jerling M. Clinical pharmacokinetics of ranolazine. *Clin Pharmacokinet* 2006; **45:** 469–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ranexa; ***Cz.***: Ranexa; ***Ger.***: Ranexa; ***Gr.***: Ranexa; ***India***: Caroza; ***Irl.***: Ranexa; ***Israel***: Ranexa; ***Neth.***: Ranexa; ***Pol.***: Ranexa; ***Port.***: Ranexa; ***Spain***: Ranexa; ***Switz.***: Ranexa; ***UK***: Ranexa; ***USA***: Ranexa.

Raubasine

Ajmalicina; Ajmalicine; Alkaloid F; Raubasiini; Raubasin; Raubasina; Raubasinum; δ-Yohimbine; Аймалицин; Рауба-зин.

Methyl 16,17-didehydro-19α-methyl-18-oxayohimban-16-carboxylate.

$C_{21}H_{24}N_2O_3$=352.4

CAS — 483-04-5.

UNII — 4QJL8OX71Z.

Pharmacopoeias. In *Chin.*

Profile

Raubasine is an alkaloid obtained from *Rauwolfia serpentina* (Apocynaceae). It is a vasodilator related chemically to reserpine (below) and has been given orally and by injection in peripheral and cerebral vascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Lamuran.

Multi-ingredient Preparations. ***China***: Duxil (都可喜); ***Fr.***: Iskedyl; ***Hong Kong***: Duxaril; ***Philipp.***: Duxaril; ***Singapore***: Duxaril; ***Thai.***: Duxaril†.

Rauwolfia Serpentina

Chotachand; Rauvolfia; Rauwolfia; Rauwolfiae Radix; Rauwolfiawurzel; Раувольфия Змеиная.

CAS — 8063-17-0 (rauwolfia).

ATC — C02AA04.

ATC Herb — HC02AA5001 (Rauwolfia serpentina: root).

UNII — 3P7VF1UYMO (Rauwolfia serpentina); H192N84N1G (Rauwolfia serpentina root).

Pharmacopoeias. In *Ger.* and *US.*

USP 36: (Rauwolfia Serpentina). The dried roots of *Rauwolfia serpentina* (Apocynaceae). It contains not less than 0.15% of reserpine-rescinnamine group alkaloids calculated as reserpine. Store at 15 degrees to 30 degrees in a dry place.

Profile

Rauwolfia serpentina contains numerous alkaloids, the most active as hypotensive agents being the ester alkaloids, reserpine and rescinnamine. Other alkaloids present have structures related to reserpic acid, but are not esterified, and include ajmaline (rauwolfine), ajmalinine, ajmalicine, isoajmaline (isorauwolfine), serpentine, rauwolfinine, and sarpagine. The actions of rauwolfia serpentina are those of its alkaloids and it has been used for the same purposes as reserpine, below. It has been given orally as the powdered whole root.

Rauwolfia vomitoria has also been used.

A crude form of rauwolfia serpentina has been used in India for centuries as preparations such as Sarpagandha, in the treatment of insomnia and certain forms of mental illness.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Raunatine (Раунатин).

Multi-ingredient Preparations. ***India***: Arjin; Confido; Lukol; Memtone; Nevromine; ***Rus.***: Speman Forte (Спеман Форте); ***Ukr.***: Confido (Конфидо)†.

Homoeopathic Preparations. ***Austria***: Homviotensin; ***Ger.***: Anti-hypertonicum N†; Homviotensin; Lowe-Komplex Nr 3; RauwolfiaViscomp; Viscum album H†; ***Rus.***: Crataegus-Plus (Кратегус-Плюс); ***Ukr.***: Homviotensin (Хомвиотензин).

Pharmacopoeial Preparations

USP 36: Rauwolfia Serpentina Tablets.

Regadenoson *(BAN, USAN, rINN)*

CVT-3146; Regadenosón; Régadénoson; Regadenosonum; Регаденозон.

1-(6-Amino-9-β-D-ribofuranosyl-9*H*-purin-2-yl)-*N*-methyl-1*H*-pyrazole-4-carboxamide monohydrate.

$C_{15}H_{18}N_8O_5$, H_2O=408.4

CAS — 313348-27-5 (regadenoson); 875148-45-1 (regadenoson monohydrate).

ATC — C01EB21.

ATC Vet — QC01EB21.

UNII — 2XLN4Y044H.

Uses and Administration

Regadenoson has similar properties to adenosine (p. 1291.1) but has a greater selectivity for the adenosine A_{2A}-receptor. It is a coronary vasodilator and increases coronary blood flow and is used to provide a pharmacological stress as an adjunct to radionuclide myocardial perfusion imaging. It is given intravenously in a single dose of 400 micrograms by rapid injection over about 10 seconds, followed by 5 mL of sodium chloride 0.9%; the radionuclide should be given 10 to 20 seconds after the sodium chloride.

References.

1. Hendel RC, *et al.* Initial clinical experience with regadenoson, a novel selective A_{2A} agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. *J Am Coll Cardiol* 2005; **46:** 2069–75.
2. Iskandrian AE, *et al.* Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007; **14:** 645–58.
3. Buhr C, *et al.* Regadenoson in the detection of coronary artery disease. *Vasc Health Risk Manag* 2008; **4:** 337–40.
4. Thomas GS, *et al.* The RegEx trial: a randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective A_{2A} adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol* 2009; **16:** 63–72.
5. Al Jaroudi W, Iskandrian AE. Regadenoson: a new myocardial stress agent. *J Am Coll Cardiol* 2009; **54:** 1123–30.
6. Garnock-Jones KP, Curran MP. Regadenoson. *Am J Cardiovasc Drugs* 2010; **10:** 65–71.

Adverse Effects, Treatment, and Precautions

As for Adenosine, p. 1291.3. Regadenoson may be used with caution in patients with asthma or chronic obstructive pulmonary disease.

Interactions

As for Adenosine, p. 1292.1.

Pharmacokinetics

After intravenous injection of regadenoson, peak plasma concentrations occur within 1 to 4 minutes and decline in a multi-exponential fashion. The initial half-life is about 2 to 4 minutes, followed by an intermediate stage with a half-life of about 30 minutes, during which the pharmacodynamic effect is lost; the half-life during the terminal phase is about 2 hours. Regadenoson does not appear to be metabolised; about 57% of a dose is excreted unchanged in the urine.

References.

1. Gordi T, *et al.* A population pharmacokinetic/pharmacodynamic analysis of regadenoson, an adenosine A_{2A}-receptor agonist, in healthy male volunteers. *Clin Pharmacokinet* 2006; **45:** 1201–12.
2. Gordi T, *et al.* Regadenoson pharmacokinetics and tolerability in subjects with impaired renal function. *J Clin Pharmacol* 2007; **47:** 825–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Rapiscan; ***Irl.***: Rapiscan; ***Neth.***: Rapiscan; ***Pol.***: Rapiscan; ***Port.***: Rapiscan; ***UK***: Rapiscan; ***USA***: Lexiscan.

Rescinnamine *(BAN, rINN)*

Rescinamina; Rescinnamin; Rescinnaminum; Resinnamiini; Ресциннамин.

Methyl-*O*-(3,4,5-trimethoxycinnamoyl)reserpate.

$C_{35}H_{42}N_2O_9$=634.7

CAS — 24815-24-5.

ATC — C02AA01.

ATC Vet — QC02AA01.

UNII — Q6W1F7DJ2D.

Profile

Rescinnamine is an ester alkaloid isolated from the root of *Rauwolfia serpentina* or *R. vomitoria*. It has properties similar to those described under reserpine (below) and has been used in the treatment of hypertension.

Reserpine *(BAN, rINN)*

Reserpiini; Reserpin; Reserpina; Réserpine; Reserpinum; Reszerpin; Rezerpin; Rezerpina; Rezerpinas; Резерпин.

Methyl 11,17α-dimethoxy-18β-(3,4,5-trimethoxybenzoyloxy)-3β,20α-yohimbane-16β-carboxylate; Methyl *O*-(3,4,5-trimethoxybenzoyl)reserpate.

$C_{33}H_{40}N_2O_9$=608.7

CAS — 50-55-5.

ATC — C02AA02.

ATC Vet — QC02AA02.

UNII — 8B1QWR724A.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Reserpine). It occurs as small, white to slightly yellow crystals or a crystalline powder. It darkens slowly on exposure to light. Practically insoluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Reserpine). A white or pale buff to slightly yellowish, odourless, crystalline powder. It darkens slowly on exposure to light, but more rapidly when in solution. Insoluble in water; soluble 1 in 1800 of alcohol and 1 in 6 of chloroform; freely soluble in acetic acid; very slightly soluble in ether; slightly soluble in benzene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Stability. Reserpine is unstable in the presence of alkalis, particularly when the drug is in solution.

Uses and Administration

Reserpine is an alkaloid obtained from the roots of certain species of *Rauwolfia* (Apocynaceae), mainly *Rauwolfia serpentina* and *R. vomitoria*, or by synthesis. The material obtained from natural sources may contain closely related alkaloids.

Reserpine is an antihypertensive drug that causes depletion of noradrenaline stores in peripheral sympathetic nerve terminals and depletion of catecholamine and serotonin stores in the brain, heart, and many other organs resulting in a reduction in blood pressure, bradycardia, and CNS depression. The hypotensive effect is mainly due to a reduction in cardiac output and a reduction in peripheral resistance. Cardiovascular reflexes are partially inhibited, but orthostatic hypotension is rarely a problem at the doses used in hypertension. When given orally the full effect is only reached after several weeks of treatment and persists for up to 6 weeks after treatment is stopped.

Reserpine has been used in the management of hypertension (p. 1251.1) and in chronic psychoses (p. 1030.2) such as schizophrenia. It has also been used in the treatment of Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3).

In **hypertension**, reserpine may be given orally in an initial dose of up to 500 micrograms daily for about 2 weeks, subsequently reduced to the lowest dose necessary to maintain the response; some sources recommend an initial dose of 50 to 100 micrograms. A maintenance dose of about 100 to 250 micrograms daily may be adequate and 500 micrograms should not normally be exceeded. To reduce adverse effects and tolerance smaller doses of reserpine may be used with a thiazide diuretic.

Reserpine has been used in chronic **psychoses** in daily doses of up to 1 mg.

References.

1. Shamon SD, Perez MI. Blood pressure lowering efficacy of reserpine for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 27/10/09).

Adverse Effects

Adverse effects commonly include nasal congestion, headache and CNS symptoms including depression, drowsiness, dizziness, lethargy, nightmares, and symptoms of increased gastrointestinal tract motility including diarrhoea, abdominal cramps, and, at higher doses, increased gastric acid secretion. Respiratory distress, cyanosis, anorexia, and lethargy may occur in infants whose mothers have taken reserpine before delivery.

Higher doses may cause flushing, bradycardia, severe depression which may lead to suicide, and extrapyramidal effects. Hypotension, coma, convulsions, respiratory depression, and hypothermia also occur in overdosage. Hypotension is also more common in patients after a cerebrovascular accident.

Breast engorgement and galactorrhoea, gynaecomastia, increased prolactin concentrations, decreased libido, impotence, sodium retention, oedema, decreased or increased appetite, weight gain, miosis, dry mouth, sialorrhoea, dysuria, rashes, pruritus, and thrombocytopenic purpura have also been reported.

Large doses of reserpine have been shown to be tumorigenic in *rodents*. Several reports have suggested an association between reserpine and the development of neoplasms of the breast (see below) but other surveys have failed to confirm this.

Neoplasms of the breast. Although early studies suggested that the incidence of breast cancer was up to 3 to 4 times greater in hypertensive women treated with rauwolfia preparations than in control groups, analysis[1] of both prospective and case-control studies found only a low-grade association between use of rauwolfia preparations and risk of malignancy.

1. Grossman E, *et al*. Antihypertensive therapy and the risk of malignancies. *Eur Heart J* 2001; **22:** 1343–52.

Treatment of Adverse Effects

Withdrawal of reserpine or reduction of the dosage causes the reversal of many adverse effects although mental disorders may persist for months and hypotensive effects may persist for weeks after the cessation of treatment. If overdosage occurs activated charcoal may be considered within 1 hour of ingestion. Treatment is generally supportive and symptomatic. Severe hypotension may respond to placing the patient in the supine position with the feet raised. Direct-acting sympathomimetics may be effective for treatment of severe hypotension, but should be given with caution. The patient must be observed for at least 72 hours.

Precautions

Reserpine should not be used in patients with depression or a history of depression, with active peptic ulcer disease or ulcerative colitis, or in patients with Parkinson's disease. It should also be avoided in phaeochromocytoma.

It should be used with caution in debilitated or elderly patients, and in the presence of cardiac arrhythmias, myocardial infarction, renal insufficiency, gallstones, epilepsy, or allergic conditions such as bronchial asthma.

Reserpine is contra-indicated in patients having ECT and an interval of at least 7 to 14 days should be allowed between the last dose of reserpine and the start of any ECT.

It is probably not necessary to stop reserpine during anaesthesia, although the effects of CNS depressants may be enhanced by reserpine.

Interactions

Patients taking reserpine may be hypersensitive to adrenaline and other direct-acting sympathomimetics, which should not be given except to antagonise reserpine. The effects of indirect-acting sympathomimetics such as ephedrine may be decreased by reserpine. The hypotensive effects of reserpine are enhanced by thiazide diuretics and other antihypertensives. Reserpine may cause excitation and hypertension in patients receiving MAOIs. Use of digitalis or quinidine with reserpine may cause cardiac arrhythmias. Reserpine may enhance the effects of CNS depressants.

Antiparkinsonian drugs. For the inhibitory effect of reserpine on the antiparkinsonian actions of *levodopa*, see Antihypertensives, p. 907.2.

Pharmacokinetics

Reserpine is absorbed from the gastrointestinal tract with a bioavailability of 50%. It is extensively metabolised and is excreted slowly in the urine and faeces. In the first 4 days, about 8% is excreted in the urine, mainly as metabolites, and about 60% in the faeces, mainly unchanged. Reserpine crosses the placenta and the blood-brain barrier and also appears in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Resapin†; Serpasil.

Multi-ingredient Preparations. ***Austria***: Brinerdin; ***Braz.***: Higroton Reserpina; ***China***: Fufang Lixueping (复方利血平); No 0 (0号); ***Cz.***: Crystepin†; Neocrystepin†; ***Fr.***: Tensionorme; ***Ger.***: Briserin N; Triniton†; ***Gr.***: Aditasin; Bestocalm; Hygroton-Reserpine; Neourizine; Renese R; Santapertas; Tensiplex; ***India***: Adelphane-Esidrex; Adelphane; Genophane; ***Indon.***: Dellasidrex†; Ser-Ap-Es; ***Ital.***: Brinerdina; Igroton-Reserpina; ***Jpn***: Behyd-RA; ***Mex.***: Higroton-Res; ***Pol.***: Normatens; ***Rus.***: Adelphane-Esidrex (Адельфан-эзидрекс); Brinerdin (Бринердин); Crystepin (Кристепин); Normatens (Нормотенс); Triresid K (Трирезид К)†; ***S.Afr.***: Brinerdin; Protensin-M†; ***Switz.***: Brinerdine; Hygroton-Reserpine†; ***Thai.***: Bedin; Brinerdin; Briscotin†; Hydrares; Mano-Ap-Es; Reser; Ser-Ap-Es†; ***Turk.***: Adelphan-Esidrex†; Adelphan†; Regroton; ***Ukr.***: Adelphane-Esidrex (Адельфан-Эзидрекс); Normatens (Нормотенс); ***USA***: Demi-Regroton; Diupres; Hydropres; Marpres; Regroton.

Homoeopathic Preparations. ***Austria***: Homviotensin; ***Ger.***: dysto-loges N; dysto-loges S; ***Ukr.***: Homviotensin (Хомвиотензин).

Pharmacopoeial Preparations

USP 36: Reserpine and Chlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine Elixir; Reserpine Injection; Reserpine Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Reteplase *(BAN, USAN, rINN)*

BM-06.022; Reteplaasi; Reteplas; Reteplasa; Rétéplase; Reteplasum; rPA; Ретеплаза.

173-L-Serine-174-L-tyrosine-175-L-glutamine-173–527-plasminogen activator (human tissue-type).

$C_{1736}H_{2653}N_{499}O_{522}S_{22}$=39571.6

CAS — 133652-38-7.

ATC — B01AD07.

ATC Vet — QB01AD07.

UNII — DQA630RIE9.

Description. Reteplase is a nonglycosylated protein produced by recombinant DNA technology. It consists of selected domains of human tissue plasminogen activator.

Incompatibility. Reteplase may precipitate out of solution if it is given with heparin in the same intravenous line.[1] Reteplase and heparin must therefore be given separately; if a single intravenous line is used it must be flushed thoroughly with sodium chloride 0.9% or with glucose 5% before, and after, reteplase injection.

1. CSM/MCA. Reteplase (Rapilysin): incompatibility with heparin. *Current Problems* 2000; **26:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 20/06/06)

Uses and Administration

Reteplase is a thrombolytic drug. It converts plasminogen to plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Reteplase has some fibrin specificity (see Thrombolytics, p. 1245.3).

Reteplase is used similarly to streptokinase (p. 1503.1) in acute myocardial infarction (p. 1257.1). It is given intravenously as soon as possible after the onset of symptoms. The dose is 10 units given by slow intravenous injection (but over not more than 2 minutes), and this dose of 10 units is repeated once, 30 minutes after the start of the first injection.

General references.

1. Noble S, McTavish D. Reteplase: a review of its pharmacological properties and clinical efficacy in the management of acute myocardial infarction. *Drugs* 1996; **52:** 589–605.
2. Wooster MB, Luzier AB. Reteplase: a new thrombolytic for the treatment of acute myocardial infarction. *Ann Pharmacother* 1999; **33:** 318–24.
3. Llevadot J, *et al*. Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001; **286:** 442–9.
4. Simpson D, *et al*. Reteplase: a review of its use in the management of thrombotic occlusive disorders. *Am J Cardiovasc Drugs* 2006; **6:** 265–85.

Catheters and cannulas. Reteplase has been used[1] successfully to clear thrombi in central venous catheters. A single dose of 0.4 units of reteplase was given as a 1 unit/mL solution, further diluted to the volume required to fill the catheter. The minimum dwell time was 30 minutes and the solution was aspirated after treatment. A second dose of 0.4 units was given if necessary.

1. Owens L. Reteplase for clearance of occluded venous catheters. *Am J Health-Syst Pharm* 2002; **59:** 1638–40.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Allergic reactions may be less likely to occur with reteplase than with streptokinase.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies reteplase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Streptokinase, p. 1507.1.

Pharmacokinetics

Based on fibrinolytic activity, reteplase is reported to have an initial half-life of about 14 minutes and a terminal half-life of 1.6 hours in patients with myocardial infarction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Rapilysin; ***Austria***: Rapilysin; ***Belg.***: Rapilysin; ***Canad.***: Retavase; ***China***: Pai Tong Xin (派通欣); Rui Tong Li (瑞通立); ***Cz.***: Rapilysin; ***Denm.***: Rapilysin; ***Fin.***: Rapilysin; ***Fr.***: Rapilysin; ***Ger.***: Rapilysin; ***Gr.***: Rapilysin; ***Hong Kong***: Rapilysin; ***Irl.***: Rapilysin; ***Ital.***: Rapilysin; ***Neth.***: Rapilysin; ***Norw.***: Rapilysin; ***NZ***: Rapilysin; ***Pol.***: Rapilysin; ***Port.***: Rapilysin; ***Singapore***: Rapilysin; ***Spain***: Rapilysin; ***Swed.***: Rapilysin; ***Switz.***: Rapilysin; ***Turk.***: Rapilysin; ***UK***: Rapilysin; ***USA***: Retavase.

Reviparin Sodium *(BAN, rINN)*

Reviparii natrium; Reviparina sódica; Réviparine Sodique; Reviparinnatrium; Reviparinum Natricum; Ревипарин Натрий.

CAS — 9041-08-1.

ATC — B01AB08.

ATC Vet — QB01AB08.

UNII — 5XQ9UBJ16W.

Description. Reviparin sodium is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3150 and 5150 with a characteristic value of about 4150. The degree of sulfation is about 2.1 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Reviparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity. It is used in the prevention and treatment of venous thromboembolism (p. 1274.1) and has been used to prevent coagulation during haemodialysis.

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used.

In the prophylaxis of venous thromboembolism during surgery, reviparin sodium is given subcutaneously in a usual dose of about 1750 or 4200 units once daily, depending on risk, with the first dose given 2 to 4 hours before surgery with the lower dose, or 12 hours before surgery with the higher dose. In the treatment of venous

thromboembolism, a subcutaneous dose of about 175 units/kg is given daily in 2 divided doses.

References.
1. Wellington K, *et al.* Reviparin: a review of its efficacy in the prevention and treatment of venous thromboembolism. *Drugs* 2001; **61:** 1185–209.
2. Yusuf S, *et al.* CREATE Trial Group Investigators. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. *JAMA* 2005; **293:** 427–35.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with reviparin sodium may be reduced by the slow intravenous injection of protamine sulfate; 1.2 mg of protamine sulfate has been stated to inhibit the effect of about 100 units of reviparin sodium.

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Reviparin sodium is absorbed after subcutaneous doses with a bioavailability of about 95%. Peak plasma concentrations occur after about 3 hours. Reviparin sodium is excreted mainly in the urine; the elimination half-life is about 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Clivarin (诺易平); ***Cz.***: Clivarin†; ***Fr.***: Clivarine†; ***Ger.***: Clivarin; ***Gr.***: Clivarin; ***Hong Kong***: Clivarine†; ***Hung.***: Clivarin†; ***India***: Clivarine; ***Ital.***: Clivarina; ***Pol.***: Clivarin†.

Rilmenidine Phosphate *(rINNM)*

Fosfato de rilmenidina; Oxaminozoline Phosphate; Rilmenidiinidivetyfosfaatti; Rilmenidin Dihdrojen Fosfat; Rilmenidin fosfát; Rilmenidina, fosfato de; Rilmenidin-dihidrogénfoszfát; Rilmenidindihydrogenphosphat; Rilmenidindivätefosfat; Rilmenidine Acid Phosphate; Rilmenidine Dihydrogen Phosphate; Rilménidine, dihydrogénophosphate de; Rilmenidine Hydrogen Phosphate; Rilménidine, Phosphate de; Rilmenidini Dihydrogenophosphas; Rilmenidini Phosphas; Rilmenidino divandenilio fosfatas; S-3341-3; Рильменидина Фосфат.

2-[(Dicyclopropylmethyl)amino]-2-oxazoline phosphate.

$C_{10}H_{16}N_2O,H_3PO_4$=278.2

CAS — 54187-04-1 (rilmenidine); 85409-38-7 (rilmenidine phosphate).

ATC — C02AC06.

ATC Vet — QC02AC06.

UNII — 59QD64Q32M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rilmenidine Dihydrogen Phosphate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

Profile

Rilmenidine is a centrally acting antihypertensive that appears to act through stimulation of central imidazoline receptors and also has alpha$_2$-adrenoceptor agonist activity. It has general properties similar to those of clonidine (p. 1339.1), but is reported to cause less sedation and central adverse effects. In the management of hypertension (p. 1251.1) it has been given as the phosphate, but doses are expressed in terms of the base. Rilmenidine phosphate 1.5 mg is equivalent to about 1 mg of rilmenidine. The dose is 1 mg daily, as a single oral dose; this may be increased if necessary, after 1 month, to 2 mg daily in divided doses.

References.
1. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; **58:** 799–812.
2. Reid JL. Rilmenidine: a clinical overview. *Am J Hypertens* 2000; **13:** 106S–111S.
3. Reid JL. Update on rilmenidine: clinical benefits. *Am J Hypertens* 2001; **14:** 322S–324S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hyperium; ***Austria***: Iterium; ***Braz.***: Hyperium; ***China***: Iperdix (爱博克); ***Cz.***: Albarel†; Tenaxum; ***Fr.***: Hyperium; ***Gr.***: Hyperium; ***Hong Kong***: Iperdix†; ***Hung.***: Hyperlex; Tenaxum; ***Philipp.***: Hyperdix†; ***Pol.***: Tenaxum; ***Port.***: Hyperium; ***Rus.***: Albarel (Альбарел); Tenaxum (Тенаксум); ***Thai.***: Hyperdix†; ***Turk.***: Hyperium; ***Ukr.***: Tenaxum (Тенаксум)†; ***Venez.***: Hyperium.

Riociguat *(USAN, rINN)*

BAY-63-2521; Riociguatum; Риоцигуат.

Methyl *N*-(4,6-diamino-2-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)-*N*-methylcarbamate.

$C_{20}H_{19}FN_8O_2$=422.4

CAS — 625115-55-1.

UNII — RU3FE2Y4XI.

Profile

Riociguat is a guanylate cyclase stimulator which acts on nitric oxide receptors to produce vasodilatation. It is used in the treatment of pulmonary arterial hypertension and persistent or recurrent chronic thromboembolic pulmonary hypertension, either after surgical treatment or in inoperable cases (p. 1278.2). It is given orally in 3 divided doses. The usual initial dose is 3 mg daily; patients who do not tolerate the hypotensive effects of riociguat may be given an initial dose of 1.5 mg daily. Thereafter, the dose may be increased in steps of 1.5 mg, at intervals of at least 2 weeks, to a maximum of 7.5 mg daily, provided systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension. The dose should be decreased in steps of 1.5 mg in those who develop symptoms of hypotension.

Riociguat is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP); it is mainly metabolised by the cytochrome P450 isoenzymes CYP1A1, CYP3A, CYP2C8, and CYP2J2. When used with potent P450 isoenzyme or P-gp/BCRP inhibitors such as azole antifungals and HIV-protease inhibitors, the increase in riociguat exposure may result in hypotension; consequently, initial doses should be reduced to 1.5 mg daily. A decrease in riociguat exposure may occur with potent inducers of CYP3A, although there are no recommendations on dosage adjustments in the licensed product information. Tobacco smoking also induces hepatic metabolic enzymes and may decrease the plasma levels of riociguat; if tolerated, doses higher than 7.5 mg daily may be considered for smokers. Conversely, lower doses may be required in those who stop smoking. Riociguat should not be used with nitrates or nitric oxide donors (such as amyl nitrite), or phosphodiesterase (PDE) inhibitors, including both specific PDE-5 inhibitors (such as sildenafil, tadalafil, and vardenafil) and non-specific PDE inhibitors (such as dipyridamole and theophylline), because of additive hypotensive effects.

Riociguat has been shown to be teratogenic and embryotoxic in *animals* and is therefore contra-indicated in pregnant patients. Pregnancy should be excluded before starting therapy, and avoided during and for 1 month after stopping treatment; monthly pregnancy tests are recommended.

Serious bleeding, including haemoptysis and haemorrhage, has been reported with riociguat therapy.

References.
1. Frey R, *et al.* Riociguat (BAY 63-2521) and warfarin: a pharmacodynamic and pharmacokinetic interaction study. *J Clin Pharmacol* 2011; **51:** 1051–60.
2. Schermuly RT, *et al.* Riociguat for the treatment of pulmonary hypertension. *Expert Opin Invest Drugs* 2011; **20:** 567–76.
3. Bonderman D, *et al.* Left Ventricular Systolic Dysfunction associated with Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation* 2013; **128:** 502–11.
4. Ghofrani HA, *et al.* CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013; **369:** 319–29.
5. Ghofrani HA, *et al.* PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; **369:** 330–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Adempas.

Rivaroxaban *(BAN, USAN, rINN)*

Bay-59-7939; Rivaroxabán; Rivaroxabana; Rivaroxabanum; Ривароксабан.

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide.

$C_{19}H_{18}ClN_3O_5S$=435.9

CAS — 366789-02-8.

ATC — B01AF01.

ATC Vet — QB01AF01.

UNII — 9NDF7JZ4M3.

Uses and Administration

Rivaroxaban is a direct inhibitor of factor Xa (activated factor X) with a dose-dependent effect on prothrombin time. It is used for the treatment of deep-vein thrombosis or pulmonary embolism (p. 1274.1) and to prevent recurrence after initial treatment, or for the prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery. It is also used for the prevention of stroke and systemic embolisation in patients with non-valvular atrial fibrillation, and for the prevention of atherothrombotic events in patients after an acute coronary syndrome. Rivaroxaban is given orally; doses of 10 mg can be taken with or without food, whereas larger doses should be taken with food (see also Pharmacokinetics, p. 1488.1).

The recommended dose for the initial treatment of acute deep-vein thrombosis or pulmonary embolism is 15 mg twice daily for the first three weeks, followed by 20 mg once daily for continued treatment and prevention of recurrence.

For prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery, rivaroxaban is given in a dose of 10 mg once daily. The initial dose should be given 6 to 10 hours after surgery, providing haemostasis has been established, and treatment should be continued for 5 weeks after hip surgery and for 12 to 14 days after knee surgery.

For the prevention of stroke in atrial fibrillation, rivaroxaban is given in a dose of 20 mg once daily with the evening meal.

For the prevention of atherothrombotic events in patients after an acute coronary syndrome, rivaroxaban is given either with aspirin alone or with aspirin plus clopidogrel or ticlopidine. The recommended dose of rivaroxaban is 2.5 mg twice daily, started as soon as possible after stabilisation but at least 24 hours after admission to hospital and at the time when parenteral anticoagulation is stopped.

Recommendations for a missed dose depend on the dosing schedule being followed.

- For patients taking 15 mg twice daily: take rivaroxaban immediately to ensure intake of 30 mg per day; two 15-mg tablets may be taken at once if required. The patient should continue with 15 mg twice daily on the following day.
- For patients taking 10 or 20 mg once daily: take rivaroxaban immediately and continue on the following day with the once daily dose as recommended. The dose should not be doubled within the same day to make up for a missed dose.
- For patients taking 2.5 mg twice daily: continue with the next usual dose of rivaroxaban. The dose should not be doubled to make up for a missed dose.

If anticoagulation must be withdrawn to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped at least 24 hours before the procedure. It may be restarted after the procedure as soon as haemostasis has been established.

For administration and dose adjustments in renal impairment, see below.

General references.
1. Fassiadis N. Rivaroxaban, the first oral, direct factor Xa inhibitor. *Expert Opin Pharmacother* 2009; **10:** 2945–6.
2. NICE. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (TA170, issued April 2009). Available at: http://www.nice.org.uk/nicemedia/live/12133/43811/43811.pdf (accessed 19/09/13)
3. Perzborn E, *et al.* Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol* 2010; **30:** 376–81.
4. NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (TA256, issued May 2012). Available at: http://www.nice.org.uk/nicemedia/live/13746/59295/59295.pdf (accessed 19/09/13)
5. NICE. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (TA261, issued July 2012). Available at: http://www.nice.org.uk/nicemedia/live/13805/60040/60040.pdf (accessed 19/09/13)
6. Cohen AT, Dobromirski M. The use of rivaroxaban for short- and long-term treatment of venous thromboembolism. *Thromb Haemost* 2012; **107:** 1035–43.
7. Duggan ST. Rivaroxaban: a review of its use for the prophylaxis of venous thromboembolism after total hip or knee replacement surgery. *Am J Cardiovasc Drugs* 2012; **12:** 57–72.
8. Ahrens I, Bode C. Rivaroxaban for stroke prevention in atrial fibrillation and secondary prevention in patients with a recent acute coronary syndrome. *Future Cardiol* 2012; **8:** 533–41.
9. Turpie AG, *et al.* Management consensus guidance for the use of rivaroxaban–an oral, direct factor Xa inhibitor. *Thromb Haemost* 2012; **108:** 876–86.
10. NICE. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (TA287, issued June 2013). Available at: http://www.nice.org.uk/nicemedia/live/14192/64274/64274.pdf (accessed 19/09/13)
11. Palareti G, *et al.* Clinical management of rivaroxaban-treated patients. *Expert Opin Pharmacother* 2013; **14:** 655–67.
12. Carter NJ, Plosker GL. Rivaroxaban: a review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Drugs* 2013; **73:** 715–39.

Administration in renal impairment. Exposure to rivaroxaban is increased in patients with renal impairment. The usual oral doses can be used in those with mild renal impairment (creatinine clearance (CC) from 50 to 80 mL/minute), but dose adjustments may be needed for some indications in those with moderate (CC from 30 up to 50 mL/minute) to severe (CC from 15 up to 30 mL/minute) impairment.

- For the treatment of deep-vein thrombosis and pulmonary embolism and the prevention of recurrence in

patients with moderate to severe renal impairment, EU licensed product information recommends a reduced initial dose of 15 mg twice daily for the first 3 weeks. Thereafter, the usual recommended dose of 20 mg once daily may be taken, but a reduction to 15 mg once daily should be considered if the risk of bleeding outweighs the risk for recurrent deep-vein thrombosis or pulmonary embolism. In the USA, rivaroxaban is not recommended in patients with severe impairment and the usual dose may be given to those with moderate impairment.

- For the prevention of stroke and systemic embolism in atrial fibrillation in patients with moderate to severe renal impairment, a reduced dose of rivaroxaban 15 mg once daily is suggested.
- For prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery, rivaroxaban is not recommended in patients with severe impairment.

Rivaroxaban should not be used in patients with a CC less than 15 mL/minute, regardless of indication.

Caution is required in patients with renal impairment who are also taking other medication that may increase exposure to rivaroxaban, see Interactions, below.

Adverse Effects and Treatment

The most common adverse effect with rivaroxaban is bleeding. Nausea and increases in liver enzyme values may also occur; other gastrointestinal effects, pruritus, rashes, and renal impairment have been reported but are uncommon. There is no known antidote to rivaroxaban. Haemorrhagic complications should be treated with standard measures; use of factor VIIa may be considered in severe haemorrhage but clinical experience is lacking.

Precautions

Rivaroxaban should not be used in patients with clinically significant bleeding or with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It should be used with caution in other patients at increased risk of bleeding. Plasma concentrations are increased in hepatic or renal impairment and the risk of bleeding may be increased; a reduced dose may be required in renal impairment, see Administration in Renal Impairment, p. 1487.3. There appears to be a possible rebound increased risk of stroke when stopping rivaroxaban in atrial fibrillation, and adequate cover with alternative anticoagulants may be needed. Although rivaroxaban does not require anticoagulant monitoring, it may falsely increase INR values on conversion with another anticoagulant such as warfarin.

Studies in *animals* have shown reproductive toxicity and distribution of rivaroxaban into breast milk and it is therefore contra-indicated in pregnancy and breast feeding.

Interactions

Rivaroxaban is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is also a substrate for P-glycoprotein. It should not be given with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole, itraconazole, posaconazole, voriconazole, or HIV-protease inhibitors, although it may be used cautiously with fluconazole. Drugs that inhibit only one of these pathways or are less potent inhibitors, such as clarithromycin and erythromycin, do not appear to have clinically relevant effects. Potent inducers of CYP3A4, such as rifampicin, may reduce the effect of rivaroxaban.

Caution is needed if rivaroxaban is given with other anticoagulants or with drugs that affect bleeding, including NSAIDs and antiplatelet drugs. (However, another anticoagulant may need to be given when stopping rivaroxaban, see Precautions, above.)

Pharmacokinetics

When given orally, rivaroxaban is rapidly absorbed and peak plasma concentrations occur after 2 to 4 hours. The bioavailability of rivaroxaban is dose-dependent; it is about 80 to 100% for the 2.5-mg and 10-mg doses and is unaffected by food. With larger doses, bioavailability is lower but is increased with food. Plasma protein binding is about 92 to 95%. Rivaroxaban is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2J2 and by other mechanisms. About two-thirds of an oral dose is metabolised, with the metabolites excreted equally in the urine and faeces; the remaining third is excreted unchanged in the urine, mainly by active renal secretion. After an intravenous dose of rivaroxaban the elimination half-life is about 4.5 hours, but on oral dosage elimination is limited by the rate of absorption and the terminal elimination half-life is about 7 to 11 hours.

General references.

1. Mueck W, *et al*. Population pharmacokinetics and pharmacodynamics of rivaroxaban—an oral, direct factor Xa inhibitor—in patients undergoing major orthopaedic surgery. *Clin Pharmacokinet* 2008; **47:** 203–16.
2. Weinz C, *et al*. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos* 2009; **37:** 1056–64.
3. Kubitza D, *et al*. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol* 2010; **70:** 703–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Xarelto; ***Austral.***: Xarelto; ***Austria***: Xarelto; ***Belg.***: Xarelto; ***Braz.***: Xarelto; ***Canad.***: Xarelto; ***Chile***: Xarelto; ***China***: Xarelto (拜瑞妥); ***Cz.***: Xarelto; ***Denm.***: Xarelto; ***Fr.***: Xarelto; ***Ger.***: Xarelto; ***Gr.***: Xarelto; ***Hong Kong***: Xarelto; ***Hung.***: Xarelto; ***Indon.***: Xarelto; ***Irl.***: Xarelto; ***Israel***: Xarelto; ***Ital.***: Xarelto; ***Jpn***: Xarelto; ***Malaysia***: Xarelto; ***Neth.***: Xarelto; ***Norw.***: Xarelto; ***NZ***: Xarelto; ***Philipp.***: Xarelto; ***Pol.***: Xarelto; ***Port.***: Xarelto; ***Rus.***: Xarelto (Ксарелто); ***Singapore***: Xarelto; ***Spain***: Xarelto; ***Swed.***: Xarelto; ***Switz.***: Xarelto; ***Thai.***: Xarelto; ***UK***: Xarelto; ***Ukr.***: Xarelto (Ксарелто); ***USA***: Xarelto.

Rosuvastatin Calcium

(BANM, USAN, rINNM)

Calcii Rosuvastatinum; Rosuvastatina calcica; Rosuvastatine Calcique; S-4522; ZD-4522 (rosuvastatin); Кальций Розувастатин.

(*E*)-(3*R*,5*S*)-7-{4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid calcium (2:1).

$(C_{22}H_{27}FN_3O_6)_2Ca$=1001.1

CAS — 287714-41-4 (rosuvastatin); 147098-20-2 (rosuvastatin calcium).

ATC — C10AA07.

ATC Vet — QC10AA07.

UNII — 83MVU38M7Q.

Uses and Administration

Rosuvastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.2). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the management of hyperlipidaemias (p. 1248.1), including primary hypercholesterolaemia (type IIa), mixed dyslipidaemia (type IIb), and hypertriglyceridaemia (type IV), as well as in patients with homozygous familial hypercholesterolaemia. It may be used to reduce the progression of atherosclerosis in patients with elevated total- or LDL-cholesterol concentrations, and also for the primary prevention of cardiovascular disease in those at high risk.

Rosuvastatin is given orally as the calcium salt, although doses are expressed in terms of the base; 10.4 mg of rosuvastatin calcium is equivalent to about 10 mg of base.

The usual initial dose of rosuvastatin is 5 or 10 mg once daily, depending on plasma-cholesterol concentrations, cardiovascular risk factors, and risk factors for adverse effects. The maintenance dose ranges from 5 to 40 mg once daily, although the 40-mg dose is reserved for patients with high cardiovascular risk who do not achieve their target cholesterol concentration at lower doses and who do not have risk factors for adverse effects. Specific dosage recommendations vary; for dosage in renal impairment, see below.

UK licensed product information recommends an initial dose of 5 or 10 mg once daily; elderly patients, Asian patients, and those taking fibrates or otherwise at risk of myopathy should be given the 5-mg dose. The dose may be increased at intervals of 4 weeks, if necessary, to a usual maximum of 20 mg once daily. A higher dose of 40 mg once daily may be given under specialist supervision in severe hypercholesterolaemia, but should not be given to patients at high risk of myopathy, including those receiving fibrates, and Asian patients; use with *ciclosporin* or *protease inhibitors* is contra-indicated.

US licensed product information recommends a usual initial dose of 10 mg once daily. However, a lower initial dose of 5 mg once daily may be adequate and is recommended for patients at risk of myopathy, including Asian patients; patients with marked hypercholesterolaemia, such as those with homozygous familial hypercholesterolaemia, may be started on 20 mg once daily. The dose should be adjusted after 2 to 4 weeks, to a usual maximum of 20 mg once daily; a dose of 40 mg once daily may be necessary in some patients. Patients receiving *ciclosporin* may be given a maximum of 5 mg once daily, and in those receiving *gemfibrozil* or *ritonavir-boosted lopinavir* the maximum dose is 10 mg once daily; dosage increases should be made with caution in Asian patients.

For doses in children, see below.

General reviews.

1. Chong PH, Yim BT. Rosuvastatin for the treatment of patients with hypercholesterolemia. *Ann Pharmacother* 2002; **36:** 93–101.
2. Carswell CI, *et al*. Rosuvastatin. *Drugs* 2002; **62:** 2075–85.
3. White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J Clin Pharmacol* 2002; **42:** 963–70.
4. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health-Syst Pharm* 2005; **62:** 1033–47.
5. Olsson AG. Expanding options with a wider range of rosuvastatin doses. *Clin Ther* 2006; **28:** 1747–63.
6. Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007; **5:** 161–75.
7. Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk. *Expert Rev Cardiovasc Ther* 2007; **5:** 177–93.
8. Crouse JR. An evaluation of rosuvastatin: pharmacokinetics, clinical efficacy and tolerability. *Expert Opin Drug Metab Toxicol* 2008; **4:** 287–304.
9. Rizzo M, *et al*. Quantitative and qualitative effects of rosuvastatin on LDL-cholesterol: what is the clinical significance? *Int J Clin Pract* 2009; **63:** 478–85.
10. Rubba P, *et al*. Efficacy and safety of rosuvastatin in the management of dyslipidemia. *Vasc Health Risk Manag* 2009; **5:** 343–52.

Administration in children. Rosuvastatin may be given to adolescent boys of Tanner stage II and above, and girls at least 1 year post-menarche, and who are aged 10 years and over, in the management of heterozygous familial hypercholesterolaemia. The usual initial oral dose is 5 mg once daily, which may be adjusted at intervals of at least 4 weeks to a maximum maintenance dose of 20 mg once daily.

Administration in renal impairment. Patients with renal impairment have an increased risk of developing myopathy and statins should be used with caution, particularly in higher doses. In severe renal impairment plasma-rosuvastatin concentrations may be increased and dosage reduction may be necessary.

UK licensed product information recommends the following oral doses according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: initial oral dose of 5 mg once daily and a maximum dose of 20 mg once daily
- CC below 30 mL/minute: contra-indicated

In the USA usual doses (see above) are allowed in moderate impairment but an initial dose of 5 mg once daily and a maximum dose of 10 mg once daily is recommended in those with CC below 30 mL/minute per 1.73 m^2.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively. Systemic exposure to rosuvastatin may be higher in Asian patients (see Ethnicity under Pharmacokinetics, p. 1489.1) and lower doses are advised in Asian patients and in others at high risk of myopathy (see Uses and Administration, above).

Incidence of adverse effects. An analysis[1] of adverse effects reported to the FDA in the first year of marketing found that rosuvastatin was significantly more likely to be associated with severe adverse effects than some other statins. However, further analyses of data from clinical studies[2] and postmarketing studies[3,4] suggest that the risk of adverse effects is similar for all the statins. Another observational study[5] with a median treatment period of 9.8 months found that rosuvastatin was generally well tolerated, although 17.5% of patients stopped taking the drug, with myalgia being the most common reason. Abnormal liver function tests were more common in patients taking higher doses.

1. Alsheikh-Ali AA, *et al*. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. *Circulation* 2005; **111:** 3051–7.
2. Shepherd J, *et al*. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology* 2007; **107:** 433–43.
3. Goettsch WG, *et al*. Results from a rosuvastatin historical cohort study in more than 45 000 Dutch statin users, a PHARMO study. *Pharmacoepidemiol Drug Safety* 2006; **15:** 435–43.
4. McAfee AT, *et al*. The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48 000 initiators of statin therapy. *Pharmacoepidemiol Drug Safety* 2006; **15:** 444–53.
5. Kasliwal R, *et al*. Safety profile of rosuvastatin: results of a prescription-event monitoring study of 11 680 patients. *Drug Safety* 2007; **30:** 157–70.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rosuvastatin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of statins with other drugs are described under simvastatin, p. 1494.2. Rosuvastatin undergoes limited metabolism, principally by the cytochrome P450 isoenzyme CYP2C9, and may not have the same interactions with enzyme inhibitors as simvastatin. However, increased plasma-rosuvastatin concentrations have been reported with ciclosporin, HIV-protease inhibitors, eltrombopag, and, to a lesser extent, with gemfibrozil, and if such combinations cannot be avoided lower doses of rosuvastatin should be used (see Uses and Administra-

tion, p. 1488.2); in UK licensed product information, rosuvastatin is contra-indicated with ciclosporin.

Pharmacokinetics

Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20%. Peak plasma concentrations occur about 5 hours after an oral dose. It is taken up extensively by the liver, its primary site of action, and undergoes limited metabolism, mainly by the cytochrome P450 isoenzyme CYP2C9. It is about 90% bound to plasma proteins. The plasma elimination half-life of rosuvastatin is about 19 hours. About 90% of an oral dose of rosuvastatin appears in the faeces, including absorbed and non-absorbed drug, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine.

Ethnicity. A pharmacokinetic study[1] found that plasma exposure to rosuvastatin and its metabolites was significantly higher in Asian (Chinese, Malay, or Indian) than in Caucasian subjects and lower doses should be used (see Uses and Administration, p. 1488.2).

1. Lee E, *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* 2005; **78:** 330–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Astende; Bilip; Colerragin; Crestor; Lipoglutaren; Nodis; Reovex; Rosedex; Rosimol; Rosustatin; Rosuvast; Rovartal; Roxolan; Sinlip; ***Austral.***: Crestor; Visacor; ***Austria***: Crestor; ***Belg.***: Crestor; ***Braz.***: Crestor; Rosucor; Rosustatin; Rosuvast; Rusovas; Vivacor; ***Canad.***: Crestor; ***Chile***: Cresadex; Crestor; Rosumed; Rosvel; Rux; ***China***: Crestor (可定); Softan (舒夫坦); ***Cz.***: Crestor; Mertenil; Rosucard; Rosumop; Sorvasta; Zahron; ***Denm.***: Crestor; Provisacor; Simestat†; Visacor; ***Fin.***: Crestor; ***Fr.***: Crestor; ***Ger.***: Crestor; ***Gr.***: Crestor; ***Hong Kong***: Crestor; ***Hung.***: Crestor; Xeter; ***India***: Bestor; Crestor; Fortius; LDNil; Novastat; Razel; Rosuvas; ***Indon.***: Crestor; ***Irl.***: Crestor; Rosuva; ***Israel***: Crestor; Stator; ***Ital.***: Crestor; Provisacor; Simestat; ***Jpn***: Crestor; ***Malaysia***: Crestor; ***Mex.***: Crestor; ***Neth.***: Cirantan; Crestor; Provisacor; ***Norw.***: Crestor; ***NZ***: Crestor; ***Philipp.***: Crestor; Rosucol; Rustor; ***Pol.***: Crestor; Rosucard; Suvardio; Zahron; Zaranta; ***Port.***: Crestor; Visacor; ***Rus.***: Crestor (Крестор); Mertenil (Мертенил); ***S.Afr.***: Crestor; ***Singapore***: Crestor; ***Spain***: Crestor; Provisacor; ***Swed.***: Crestor; Visacor†; ***Switz.***: Crestor; ***Thai.***: Crestor; ***Turk.***: Colnar; Crestor; Rosutech; Stage; Ultrox; ***UK***: Crestor; ***Ukr.***: Crestor (Крестор); Mertenil (Мертенил); Rosart (Розарт); Rosulip (Розулип); Roxera (Роксера); Rozucard (Розукард); ***USA***: Crestor; ***Venez.***: Crestor.

Sarpogrelate Hydrochloride *(rINNM)*

Hidrocloruro de sarpogrelato; MCI-9042; Sarpogrélate, Chlorhydrate de; Sarpogrelati Hydrochloridum; Sarpogrelato, hidrocloruro de; Сарпогрелата Гидрохлорид.

(±)-2-(Dimethylamino)-1-{[o-(*m*-methoxyphenethyl)phenoxy]methyl}ethyl hydrogen succinate hydrochloride.

$C_{24}H_{31}NO_6$,HCl=466.0

CAS — 125926-17-2 (sarpogrelate); 135159-51-2 (sarpogrelate hydrochloride).

Profile

Sarpogrelate is a serotonin 5-HT_2-receptor antagonist used as an inhibitor of platelet aggregation in thromboembolic disorders. It is given for occlusive arterial disease (p. 1272.3) in oral doses of 100 mg of the hydrochloride three times daily.

References.

1. Doggrell SA. Sarpogrelate: cardiovascular and renal clinical potential. *Expert Opin Invest Drugs* 2004; **13:** 865–74.
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3. Tamura A, *et al.* Comparison of sarpogrelate and ticlopidine in bare metal coronary stent implantation. *Int J Cardiol* 2008; **126:** 79–83.
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6. Hanawa K, *et al.* Development of sarpogrelate external preparation for intractable pain control. I. Pre-formulation study on application of modified beta-cyclodextrins. *Chem Pharm Bull (Tokyo)* 2010; **58:** 45–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Anplag (安步乐克); ***Jpn***: Anplag.

Saruplase *(BAN, rINN)*

Prourokinase, Non-glycosylated; Recombinant Human Single-Chain Urokinase-type Plasminogen Activator; Saruplasa; Saruplasum; scuPA; Саруплаза.

Prourokinase (enzyme-activating) (human clone pUK4/pUK18), non-glycosylated.

$C_{2031}H_{3121}N_{585}O_{601}S_{31}$=46343.7

CAS — 99149-95-8.

ATC — B01AD08.

ATC Vet — QB01AD08.

NOTE. The term prourokinase has been used for both saruplase and the related compound nasaruplase.

Profile

Saruplase is a thrombolytic drug. It is a urokinase-type plasminogen activator with a single chain structure prepared via recombinant DNA technology and is converted to urokinase (p. 1520.3) in the body by plasmin. It also has some intrinsic plasminogen-activating properties. Saruplase has been investigated in acute myocardial infarction.

References.

1. Tebbe U, *et al.* Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. *J Am Coll Cardiol* 1998; **31:** 487–93.
2. Vermeer F, *et al.* Saruplase is a safe and effective thrombolytic agent; observations in 1,698 patients: results of the PASS study. *J Thromb Thrombolysis* 1999; **8:** 143–50.
3. Spiecker M, *et al.* Thrombolysis with saruplase versus streptokinase in acute myocardial infarction: five-year results of the PRIMI trial. *Am Heart J* 1999; **138:** 518–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Gemase (Гемаза); Purolase (Пуролаза).

Semuloparin Sodium *(USAN, rINN)*

AVE-5026; Semuloparina Sódica; Sémuloparine Sodique; Semuloparinum Natricum; Семулопарин Натрия.

CAS — 9041-08-1.

UNII — V5T10N50RD.

Description. Semuloparin sodium is prepared by phosphazene-promoted depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 4-deoxy-2-*O*-sulfo-α-L-*threo*-hex-4-enopyranosuronic acid structure at the non-reducing end and a 2-deoxy-6-*O*-sulfo-2-(sulfoamino)-D-glucopyranose structure at the reducing end of their chain. The average molecular weight is about 2000 to 3000; no more than 40% of the components are less than 1600 and no more than 11% are more than 4500. The degree of sulfation is about 2 per disaccharide unit.

Profile

Semuloparin sodium is an ultra-low-molecular-weight heparin with anticoagulant activity. It is under investigation for the prevention of venous thromboembolism in patients with cancer, or who have undergone orthopaedic surgery.

References.

1. Agnelli G, *et al.* Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012; **366:** 601–9.

Simvastatin *(BAN, USAN, rINN)*

L-644128-000U; MK-733; Simvastatiini; Simvastatina; Simvastatinas; Simvastatine; Simvastatinum; Sinvinolina; Synvinolin; Szimvasztatin; Velastatin; Velastatina; Симвастатин.

(1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-{2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl}-1-naphthyl 2,2-dimethylbutyrate.

$C_{25}H_{38}O_5$=418.6

CAS — 79902-63-9.

ATC — C10AA01.

ATC Vet — QC10AA01.

UNII — AGG2FN16EV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Simvastatin). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store under nitrogen in airtight containers. Protect from light.

USP 36: (Simvastatin). A white to off-white powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very slightly soluble in petroleum spirit. Store at a temperature between 15 degrees and 30 degrees, or at 2 degrees to 8 degrees.

Uses and Administration

Simvastatin is a lipid regulating drug; it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme for cholesterol synthesis. Inhibition of HMG-CoA reductase leads to reduced cholesterol synthesis in the liver and lower intracellular cholesterol concentrations; this stimulates an increase in low-density-lipoprotein (LDL)-cholesterol receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. HMG-CoA reductase inhibitors (also called statins) reduce total cholesterol, LDL-cholesterol, and very-low-density lipoprotein (VLDL)-cholesterol concentrations in plasma. They also tend to reduce triglycerides and to increase high-density lipoprotein (HDL)-cholesterol concentrations.

Simvastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p. 1248.1). It is used in hypercholesterolaemias, primary (type IIa) or mixed (type IIb) hyperlipidaemia, hypertriglyceridaemia (type IV), and primary dysbetalipoproteinaemia (type III), and may also be used as adjunct therapy in patients with homozygous familial hypercholesterolaemia. Simvastatin is also used for cardiovascular risk reduction (p. 1246.1).

Simvastatin is given orally and doses range from 5 to 80 mg daily, although high doses of 80 mg should be limited to those patients with severe hypercholesterolaemia and high cardiovascular risk, who have not achieved their target cholesterol concentrations at lower doses, provided benefits outweigh the potential risks. For the treatment of **hyperlipidaemias**, the usual initial dose is 10 to 20 mg once daily in the evening; an initial dose of 40 mg may be used in patients who require a large reduction in cholesterol or who are at high cardiovascular risk. The dose may be adjusted at intervals of not less than 4 weeks up to a maximum of 80 mg once daily in the evening. Patients with homozygous familial hypercholesterolaemia may be treated initially with 40 mg once daily in the evening, up to a maximum of 80 mg once daily in the evening.

For **cardiovascular risk reduction** in high-risk patients, such as those with atherosclerotic cardiovascular disease or diabetes mellitus, the usual dose is 20 to 40 mg once daily in the evening.

A lower dose of simvastatin may be needed in patients at risk of myopathy, including patients with severe renal impairment (see p. 1490.3).

Changes to therapy may be required when patients are taking other drugs that interact with simvastatin see Interactions, p. 1494.2, although recommendations vary between countries. UK licensed product information advises:

- simvastatin should not be used with potent inhibitors of cytochrome P450 isoenzyme CYP3A4 or the fibrate gemfibrozil (see below for other fibrates)
- a maximum dose of simvastatin 10 mg once daily for patients also taking fibrates other than gemfibrozil; fenofibrate is an exception and there are no such restrictions but caution is advised
- a maximum dose of simvastatin 20 mg once daily for patients also taking the CYP3A4 inhibitors *amiodarone*, *amlodipine*, *diltiazem*, and *verapamil*
- close monitoring of patients who require *fusidic acid*, withholding simvastatin therapy if necessary
- a maximum dose of simvastatin 40 mg once daily for patients also taking *ticagrelor*, a weak inhibitor of CYP3A4

In the USA, simvastatin dosing should be reduced by half when starting treatment with lomitapide, a CYP3A4 inhibitor, with a maximum daily dose of 20 mg (or 40 mg in those who previously tolerated simvastatin 80 mg daily for at least 1 year).

For the use of simvastatin in children, see p. 1490.2.

General reviews.

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2. Plosker GL, McTavish D. Simvastatin: a reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. *Drugs* 1995; **50:** 334–63.
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6. Robinson JG. Simvastatin: present and future perspectives. *Expert Opin Pharmacother* 2007; **8:** 2159–27.

Action. The effects of statins on *plasma lipids* are well established.[1-4] Their primary action is to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Cholesterol is an important precursor for synthesis of several substances by the liver, and reduced intracellular concentrations stimulate an increase in the expression of low-density lipoprotein (LDL) receptors in the liver. This leads to increased uptake of LDL-cholesterol from the plasma

into liver cells, with a subsequent reduction in both LDL and total cholesterol. Triglycerides are also decreased, due to decreased synthesis of very-low-density lipoprotein (VLDL), while high-density lipoprotein (HDL)-cholesterol is either modestly increased or unchanged, leading to an improvement in the LDL:HDL ratio. An effect on LDL-cholesterol may also occur independent of the effect on receptors; some statins have been shown to lower LDL-cholesterol in patients with homozygous familial hypercholesterolaemia, despite their lack of functional LDL receptors. Statins generally provide a greater reduction in LDL-cholesterol than other classes of lipid regulating drugs, but where large reductions are required combination therapy may be necessary. Statins have been used with bile-acid binding resins and with ezetimibe; they have also been given with fibrates or nicotinic acid, although the increased risk of adverse effects needs to be considered. Cholesterol synthesis in the liver peaks during the early morning (midnight to 3 a.m.) and there is some evidence that statins with short half-lives, such as simvastatin, should be taken in the evening.[5]

Statins have several additional (pleiotropic) actions,[1-4,6,7] although whether these contribute to their cardiovascular effects is controversial.[8]

In *atherosclerosis* they have beneficial effects on endothelial function, which may be partly independent of their effect on lipids, and also appear to stabilise atherosclerotic plaques. Studies[9,10] have also shown that statins reduce concentrations of C-reactive protein (CRP), a marker of inflammation that is raised in atherosclerosis, and there is some evidence that the reduction in CRP is independently associated with a reduction in cardiovascular events[11,12] and regression of atherosclerotic lesions.[13] There is also some evidence of symptomatic improvement in patients with *chronic occlusive peripheral arterial disease* (p. 1272.3). However, studies with statins in calcific aortic stenosis, a condition with similarities to atherosclerosis, have shown mixed results.[14] Statins have some actions that may be beneficial in *heart failure*,[15] but detrimental effects are also possible and their role specifically for heart failure is unclear.[16] Evidence from cohort studies[17-19] suggests statins may improve mortality in heart failure, and analyses of cardiovascular risk reduction studies[20,21] also suggest benefit. However, a randomised study[22] of rosuvastatin in patients with heart failure of ischaemic origin failed to show an effect on mortality, although there were fewer hospitalisations in patients given the active drug. Statins may also have *antihypertensive*[23] and *antiarrhythmic* effects; they reduce the incidence of atrial fibrillation,[24] and have also been associated with a reduced risk of ventricular arrhythmias,[25,26] although this requires confirmation. Beneficial effects have also been reported on some measures of *haemostasis*,[27] and a reduced incidence of venous thromboembolism has been noted in some studies.[28,29] A study[29] has shown that the use of higher doses of statins (rosuvastatin ≥10 mg daily and lovastatin, simvastatin, or atorvastatin 40 mg daily) is associated with a greater antithrombotic effect and that the use of a statin with antiplatelet therapy further reduces the incidence of venous thromboembolism.

Statins also appear to have anti-inflammatory and immunomodulatory actions and these may contribute to their beneficial effects. There is evidence from epidemiological studies that they reduce the risk of bacterial infections, although this has been attributed to a 'healthy-user' effect,[30,31] and they may also reduce mortality in patients with sepsis.[31] Benefit has also been reported in *rheumatoid arthritis* and other inflammatory arthropathies.[32-35] In patients with *organ transplantation*, both cardiovascular and immunomodulatory actions may be of benefit (see p. 1492.1). However, the use of statins in these diseases remains to be confirmed.

For discussion of the use of statins in other non-cardiovascular disorders, including dementia, kidney disorders, malignant neoplasms, and osteoporosis, see from p. 1491.2.

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4. Igel M, *et al.* Pharmacology of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), including rosuvastatin and pitavastatin. *J Clin Pharmacol* 2002; **42:** 835–45.
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7. Balk EM, *et al.* Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Ann Intern Med* 2003; **139:** 670–82.
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12. Ridker PM, *et al.* Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet* 2009; **373:** 1175–82.
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15. Laufs U, *et al.* HMG-CoA reductase inhibitors in chronic heart failure: potential mechanisms of benefit and risk. *Drugs* 2006; **66:** 145–54.
16. van der Harst P, *et al.* Statins in the treatment of chronic heart failure: a systematic review. *PLoS Med* 2006; **3:** e333.
17. Horwich TB, *et al.* Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol* 2004; **43:** 642–8.
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19. Go AS, *et al.* Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006; **296:** 2105–11.
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21. Khush KK, *et al.* Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. *Circulation* 2007; **115:** 576–83.
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23. Strazzullo P, *et al.* Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. *Hypertension* 2007; **49:** 792–8.
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34. ten Cate R, *et al.* Therapy-refractory systemic juvenile idiopathic arthritis successfully treated with statins. *Rheumatology (Oxford)* 2004; **43:** 934–5.
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Administration in children. The management of hyperlipidaemias in children and adolescents is controversial and is usually reserved for those with familial hyperlipidaemias who have a high risk of premature cardiovascular disease. Dietary measures and bile-acid binding resins have traditionally been first-line therapy in children, but may be poorly tolerated or inadequate. Studies with statins in children aged 8 to 18 years with familial hypercholesterolaemia have shown[1,2] that they effectively lower total cholesterol and low-density lipoprotein (LDL)-cholesterol and they are now increasingly preferred where drug therapy is indicated.[3,4] However, there have been concerns about the potential adverse effects of statins on growth and sexual development, since these patients require life-long treatment. Although this does not appear to be a problem, most studies have been relatively short-term, and longer follow-up is needed to confirm statin safety;[3,4] pravastatin was well tolerated in a cohort of 185 children with familial hypercholesterolaemia who were followed for a mean of about 2 years.[5] Preliminary evidence suggests that statins may also be effective in children with hyperlipidaemia related to nephrotic syndrome[6] or organ transplantation.[3,4]

Licensed product information for simvastatin allows its use in children aged 10 to 17 years with familial heterozygous hypercholesterolaemia in an initial oral dose of 10 mg at night, increased at intervals of at least 4 weeks as required to a maximum dose of 40 mg daily. A placebo-controlled study[7] in 173 such children found that simvastatin given orally in a dose of up to 40 mg daily for 48 weeks effectively reduced LDL-cholesterol and was well tolerated, with no effect on growth or sexual development.

The *BNFC* recommends the following oral doses for children with hyperlipidaemia:

- age 5 to 10 years: initial dose 10 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg at night
- age 10 to 18 years: initial dose 10 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 40 mg at night

Doses should be reduced in children who are taking drugs that may interact with simvastatin (see Interactions, p. 1494.2).

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Administration in renal impairment. Statins appear to be safe and effective in patients with dyslipidaemia and renal impairment, and there is some evidence that they may have beneficial effects on renal function (see Kidney Disorders, p. 1491.3). However, patients with severe renal impairment may be at increased risk of developing myopathy or rhabdomyolysis and lower doses may be appropriate in such patients. Dose reduction may also be needed for statins that are excreted by the kidneys.

Simvastatin does not undergo significant renal excretion and no dose modification is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment (creatinine clearance below 30 mL/minute) the recommended initial oral dose is 5 mg once daily and doses above 10 mg once daily should be used with caution.

Cardiovascular risk reduction. Lipid regulating drugs have an important role in cardiovascular risk reduction (p. 1246.1), and statins are widely used for both primary and secondary prevention. The rationale for their use has been the established link between hypercholesterolaemia and atherosclerosis, but they may have additional actions that contribute to their effect (see Action, p. 1489.3). The efficacy of statins in reducing cardiovascular events has been established in a wide range of patient groups and is generally believed to be a class effect, although outcome studies have not been performed for all the statins in every case.

In patients with established ischaemic heart disease, statins reduce the risk of further cardiovascular events, and also reduce both cardiovascular and overall mortality.[1] Statins shown to be effective for secondary prevention in large, randomised studies include simvastatin,[2] pravastatin,[3,4] and fluvastatin.[5,6] For primary prevention in patients at high risk but without prior cardiovascular events, a similar reduction in cardiovascular events, cardiovascular mortality, and overall mortality has been shown.[7] Benefit has been established in studies using pravastatin,[8,9] lovastatin,[10] simvastatin,[11] atorvastatin,[12] and rosuvastatin;[13] the negative results of the ALLHAT-LLT study[14] with pravastatin were attributed to the substantial use of statins in the control group.

Although the main benefit of statins is to reduce mortality and major coronary events, there may also be a reduction in the incidence[15-19] and severity[20] of stroke. (An increase in the risk of haemorrhagic stroke has been suggested,[17] but has not been confirmed.[19]) The incidence of peripheral vascular disease may also be reduced,[21] and some studies have also shown a reduction in coronary[21,22] and peripheral[21,23] ischaemic symptoms. Observational studies have suggested that statins may also reduce postoperative mortality in patients with high cardiovascular risk undergoing surgery, although this remains to be confirmed,[24,25] and there is some evidence that statins may reduce the risk of myocardial damage in patients undergoing percutaneous interventions,[26] although they have not been shown to affect restenosis.[27,28] Early use of statins may also have a role in patients with acute coronary syndromes; one meta-analysis[29] found no evidence of benefit at 1 or 4 months after the initial event, but another[30] reported a reduction in cardiovascular events with statin therapy for 6 months or longer, and some studies[31] have suggested earlier benefit with high-dose regimens.

The main effect of statins appears to relate to their action on lipid concentrations, and increased benefit has been reported[32,33] with the use of intensive lipid lowering regimens, including a reduction in mortality in patients with acute coronary syndromes.[34] However, studies have shown that statins improve outcomes in patients with both raised[8,29] and average[3,4,10,12] cholesterol concentrations, and

meta-analyses[35,36] have concluded that the absolute benefit of statin treatment depends on both the initial cardiovascular risk and the degree of cholesterol reduction achieved. Most benefit has been reported in patients at the highest risk; subgroups in whom particular benefit has been reported include patients with metabolic syndrome compared with those without,[37] and diabetics compared with non-diabetics.[38] Diabetics with renal disease also benefit,[39] although this may not be the case for those with end-stage disease receiving haemodialysis.[40] Another study[41] in patients receiving haemodialysis for end-stage renal disease from various causes similarly found no benefit with statins despite the high risk of cardiovascular events in this subgroup. Early studies included mainly middle-aged men, but later studies and meta-analyses have confirmed that statins also improve outcomes in women[11,35,42] and in the elderly.[9,11,35,43,44] Observational studies[45,46] have confirmed that these benefits extend to the clinical situation.

Statins differ in potency,[47-49] but evidence that they differ in efficacy for cardiovascular risk reduction when given at comparable lipid-lowering doses is limited.[50] Patients who do not achieve target lipid concentrations or who have adverse effects with one statin may find an alternative statin effective and tolerable, although recurrence of myalgia is not uncommon.[51]

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Dementia. Epidemiological studies have reported[1,2] that the prevalence of dementia (p. 388.1) is lower in patients taking statins (prevalence may also be reduced in patients taking fibrates).[2] Some longitudinal studies have reported[3,4] that statins also reduce the incidence of dementia, but others have found no evidence of a reduction in risk,[5-7] and it has been suggested[5] that inappropriate analysis may explain the positive results. There has also been some evidence that statins[8-10] and other lipid regulating drugs[10] may reduce the progression of cognitive decline in patients with dementia, but the effect has generally been small and negative effects on mental function have been reported with some statins (see under Adverse Effects, p. 1493.1).

Although a plausible mechanism can be inferred for a possible beneficial effect of statins on dementia, a systematic review[11] concluded that there was good evidence that statins given in later life have no effect in preventing Alzheimer's disease and dementia, and that they should not be prescribed to that end.

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Kidney disorders. Although proteinuria has been reported with statins (see Effects on the Kidney under Adverse Effects, p. 1492.3) there is also some evidence that statins modestly reduce the progression of proteinuria and loss of renal function.[1-4] However, further studies are required to confirm these effects.

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Malignant neoplasms. Although studies in *animals* suggest[1] that statins could be carcinogenic, evidence for a detrimental effect in humans is limited, and some studies have suggested that statins may be protective. Low plasma-cholesterol concentrations have been associated with cancer, and an increased incidence of cancer was reported in a randomised study of pravastatin for cardiovascular risk reduction in elderly patients,[2] although this was attributed to chance. Conversely, several observational studies have reported[3-7] that statins reduce the incidence of cancer, although the effect has generally been small. Meta-analyses have generally found no association between the use of statins and the incidence of cancer. Analyses including only randomised studies[8,9] have found no significant effect on overall risk, although follow-up may not have been long enough in most studies to be conclusive; there is also little evidence of a protective effect for specific cancers.[10-12] However, another large cohort study[13] in elderly patients found no evidence that statins either increased or reduced the risk, and longer follow-up in a randomised study[14] using simvastatin also found no significant effect.

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Multiple sclerosis. It has been suggested[1-3] that statins might be of benefit in the treatment of multiple sclerosis (p. 996.3) but any definite role remains to be established. There is a report of *increased* disease activity in patients taking beta interferon for relapsing-remitting disease when atorvastatin was added to therapy,[4] although others have suggested that statins had no effect on beta interferon.[5]

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Organ and tissue transplantation. Cardiovascular disease is an important cause of morbidity and mortality after organ transplantation and statins are useful for cardiovascular risk reduction in these patients. They may also have immunomodulatory effects and have reduced the risk of rejection in some studies.[1] Some evidence also suggests that they may reduce the risk of sepsis and post-transplantation infections.[2] A meta-analysis of patients who had undergone heart transplantation (p. 1938.2) considered that treatment with a statin within 3 months of transplantation reduced allograft rejection with haemodynamic compromise and reduced 1-year mortality;[3] it was calculated that one life was saved for every 8.5 treated heart transplant patients. There is some tentative evidence that statin therapy may also reduce acute rejection and the development of obliterative bronchiolitis in patients who have undergone lung transplantation (p. 1941.3),[4] although prospective controlled studies are lacking.

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Osteoporosis. Statins appear to have effects on bone metabolism and preliminary studies[1,2] have suggested that some statins may increase bone mineral density. However, the clinical relevance of any effect is unclear.[3] Several case-control studies[4-6] have also suggested that use of statins may protect against fractures, but another case-control study[7] and an observational study[8] failed to support such an association. A review[9] of 4 further observational studies found that the risk of fracture was lower in women taking statins, but analysis of data from randomised studies of statins for cardiovascular disease[10,11] failed to confirm any effect, and controlled studies are needed[3,12] to confirm the role of statins in the management of osteoporosis (p. 1168.1).

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Adverse Effects

The commonest adverse effects of therapy with simvastatin and other statins are gastrointestinal disturbances. Other adverse effects are generally rare but include headache, rash, dizziness, insomnia, hyperglycaemia and diabetes mellitus, peripheral neuropathy, reversible cognitive impairment, depression, interstitial lung disease, sexual dysfunction, and alopecia. Hypersensitivity reactions have occurred, including anaphylaxis, angioedema, urticaria, photosensitivity, fever, flushing, dyspnoea, thrombocytopenia, toxic epidermal necrolysis, dermatomyositis, vasculitis, and lupus-like syndrome. Reversible increases in serum-transaminase concentrations may occur. Hepatitis, hepatic failure, and pancreatitis have been reported. Dose-related myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported. Drug interactions may increase the risk of myopathy, see Interactions, p. 1494.2. Rarely, rhabdomyolysis with acute renal failure may develop.

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Incidence of adverse effects. By February 1992 the UK CSM had received 738 reports of adverse effects associated with simvastatin,[1] from an estimated 257 000 prescriptions. Abnormal hepatic function and myalgia were 2 of the most frequently reported reactions, with 36 and 48 reports respectively, including 5 reports of hepatitis and 2 of jaundice. Other muscle effects included 3 reports of myositis, 10 of myopathy, and 7 reports of asymptomatic increases in serum creatine kinase concentrations. Gastrointestinal adverse effects accounted for 20% of the reports; skin, neurological and musculoskeletal effects for 15% each; psychiatric effects for 10%; liver effects for 7%; and visual effects for 4%. A systematic review[2] of data from clinical studies confirmed that the risk of liver transaminase elevation was increased by statins but there was no significant increase in the incidence of myalgia (reported in about 15% of patients), creatine kinase elevation (0.9%), or rhabdomyolysis (0.2%), compared with placebo. The incidence of adverse effects may be greater with high-dose therapy.[3,4]

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Carcinogenicity. For discussion of the effects of statins on the risk of cancer, see Malignant Neoplasms under Uses, p. 1491.3.

Effects on the blood. *Thrombocytopenia* has been reported rarely with statin therapy. Serious thrombocytopenic purpura has occurred with simvastatin, with the onset ranging from 1 or 2 days[1,2] to 11 or 12 months[3,4] after starting treatment. Platelet counts improved after stopping simvastatin in each case, although most patients were given corticosteroids, immunoglobulins, or plasma exchange. There has also been a similar report with atorvastatin,[5] which recurred on rechallenge; the patient had previously taken simvastatin without developing thrombocytopenia, suggesting an idiosyncratic reaction.

A case of *haemolytic anaemia* has been reported[6] in a patient taking lovastatin; no adverse effect was seen when the patient was given simvastatin.

Statins have effects on coagulation and fibrinolysis but these are generally beneficial (see Action under Uses, p. 1489.3); there have been rare reports of *ocular haemorrhage*,[7] but the association with statins is not established.

1. McCarthy LJ, *et al.* Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; **352:** 1284–5.
2. Sundram F, *et al.* Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J* 2004; **80:** 551–2.
3. Possamai G, *et al.* Thrombocytopenic purpura during therapy with simvastatin. *Haematologica* 1992; **77:** 357–8.
4. Groneberg DA, *et al.* Simvastatin-induced thrombocytopenia. *Am J Hematol* 2001; **67:** 277.
5. González-Ponte ML, *et al.* Atorvastatin-induced severe thrombocytopenia. *Lancet* 1998; **352:** 1284.
6. Robbins MJ, *et al.* Lovastatin-induced hemolytic anemia: not a class-specific reaction. *Am J Med* 1995; **99:** 328–9.
7. Fraunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004; **20:** 179–82.

Effects on the eyes. Studies in *animals* have suggested that some statins could cause cataracts, but this has not been confirmed in humans. Although a study[1] with lovastatin found lens opacities in 13 of 101 patients after treatment for 18 weeks, no deterioration in visual function was found in 11 of these who continued lovastatin and were followed up for an average of 26 months from the start of treatment. Similarly, no differences were found in the development of lens opacities or in changes in visual acuity between patients treated with lovastatin for 48 weeks and patients taking placebo in a study of 8245 patients.[2] A large case-control study[3] found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin. Further observational studies have suggested that statins may have beneficial effects; in one study[4] there was no effect on the overall incidence of cataract but the risk of developing nuclear cataract appeared to be decreased, while another study[5] reported a reduction in the overall incidence but this was not significant for any specific cataract type.

For mention of ocular haemorrhage in patients taking statins, see Effects on the Blood, above.

1. Hunninghake DB, *et al.* Lovastatin: follow-up ophthalmologic data. *JAMA* 1988; **259:** 354–5.
2. Laties AM, *et al.* The human lens after 48 weeks of treatment with lovastatin. *N Engl J Med* 1990; **323:** 683–4.
3. Schlienger RG, *et al.* Risk of cataract in patients treated with statins. *Arch Intern Med* 2001; **161:** 2021–6.
4. Klein BEK, *et al.* Statin use and incident nuclear cataract. *JAMA* 2006; **295:** 2752–8.
5. Tan JSL, *et al.* Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; **143:** 687–9.

Effects on the hair. Between its introduction in Australia and 1993, 16 cases of alopecia associated with the use of simvastatin had been reported to the Adverse Drug Reactions Advisory Committee.[1] Most cases involved either excessive hair loss or hair thinning, although 2 cases of hair loss in patches and 1 resembling alopecia areata were reported. Onset occurred between 3 days and 15 months after starting therapy. Progressive hair loss has also been reported[2] in a woman within 6 weeks of starting atorvastatin; the hair regrew when atorvastatin was stopped but alopecia recurred when therapy was restarted 5 months later.

1. Anonymous. Simvastatin and alopecia. *Aust Adverse Drug React Bull* 1993; **12:** 7.
2. Segal AS. Alopecia associated with atorvastatin. *Am J Med* 2002; **113:** 171.

Effects on the kidneys. *Proteinuria* was reported in 10 patients taking simvastatin 40 mg daily.[1] The protein loss was of a pattern typical for increased glomerular permeability. In 2 patients proteinuria disappeared when simvastatin was withdrawn and recurred on its subsequent reintroduction. Proteinuria has also been seen with rosuvastatin, and was found to be dose-dependent.[2] However, there is also some evidence that statins may improve proteinuria (see Kidney Disorders under Uses, p. 1491.3).

Acute tubulointerstitial *nephritis* developed[3] in a patient receiving high-dose therapy with rosuvastatin. It resolved over 3 weeks when rosuvastatin was stopped, but recurred 2 weeks after rechallenge. A similar reaction was noted with atorvastatin, but improved with dose reduction, and the patient was finally stabilised on simvastatin without a further recurrence.

Renal failure due to rhabdomyolysis has been reported rarely (see under Effects on Skeletal Muscle, p. 1493.2).

1. Deslypere JP, *et al.* Proteinuria as complication of simvastatin treatment. *Lancet* 1990; **336:** 1453.
2. Agarwal R. Effects of statins on renal function. *Am J Cardiol* 2006; **97:** 748–55.
3. van Zyl-Smit R, *et al.* Renal tubular toxicity of HMG-CoA reductase inhibitors. *Nephrol Dial Transplant* 2004; **19:** 3176–9.

Effects on the liver. Statins cause dose-related increases in liver enzymes but the incidence appears to be low with low to moderate doses[1] and serious hepatic effects appear to be rare.[2] Although monitoring of liver function tests is advised, the value of routine assessment has been questioned.[3] There is some evidence[4] that the incidence of hepatic reactions may be higher with fluvastatin than with other statins, but this is not yet established.

There have also been case reports[5-8] of cholestasis and acute hepatitis in patients receiving statins.

1. de Denus S, *et al.* Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004; **24:** 584–91.
2. Charles EC, *et al.* Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; **118:** 618–24.
3. Kostner K, Howes LG. Statins and monitoring of liver function tests. *Drug Safety* 2007; **30:** 1–4.
4. Conforti A, *et al.* Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. *Drug Safety* 2006; **29:** 1163–72.
5. Jiménez-Alonso J, *et al.* Atorvastatin-induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. *Arch InternMed* 1999; **159:** 1811–12.
6. Wierzbicki AS, Crook MA. Cholestatic liver dysfunction. *Lancet* 1999; **354:** 954.
7. Batey RG, Harvey M. Cholestasis associated with the use of pravastatin sodium. *Med J Aust* 2002; **176:** 561.
8. Rahier JF, *et al.* Severe acute cholestatic hepatitis with prolonged cholestasis and bile-duct injury following atorvastatin therapy: a case report. *Acta Gastroenterol Belg* 2008; **71:** 318–20.

Effects on the lungs. Interstitial lung disorders, including hypersensitivity pneumonitis, have been reported with several statins.[1-5] In some cases the condition improved when the statin was stopped[2] but treatment with corticosteroids and immunosuppressants was required in some patients[1-4] and progressive disease and fatalities have occurred.[4]

1. de Groot REB, *et al.* Interstitial lung disease with pleural effusion caused by simvastin [sic]. *J Intern Med* 1996; **239:** 361–3.
2. Liebhaber MI, *et al.* Polymyalgia, hypersensitivity pneumonitis and other reactions in patients receiving HMG-CoA reductase inhibitors: a report of ten cases. *Chest* 1999; **115:** 886–9.

3. Lantuejoul S, *et al*. Statin-induced fibrotic nonspecific interstitial pneumonia. *Eur Respir J* 2002; **19:** 577–80.
4. Walker T, *et al*. Potential link between HMG-CoA reductase inhibitor (statin) use and interstitial lung disease. *Med J Aust* 2007; **186:** 91–4.
5. Fernández AB, *et al*. Statins and interstitial lung disease: a systematic review of the literature and of Food and Drug Administration adverse event reports. *Chest* 2008; **134:** 824–30.

Effects on mental function. There have been conflicting reports of the effects of statins on mental function, and adverse psychiatric reactions have been reported with statins and with other lipid regulating drugs, although the exact association is unclear.

There have been a few case reports of *depressive symptoms* developing in patients treated with pravastatin[1] or simvastatin.[2] The symptoms appeared during the first few weeks or months of treatment. However, randomised studies investigating the effects of lowering cholesterol on mental function have found no effect on mood disorders (with simvastatin[3]) or psychological well-being (with lovastatin[4] or pravastatin[5]), and epidemiological studies have suggested that use of statins may be associated with improved psychological status[6] and a reduction in the risk of depression and suicide.[7]

Impairment of cognitive function has been reported with statins. In the study using lovastatin,[4] reductions in some measures of cognitive function were noted, and similar results were found in a study using simvastatin.[8] New onset cognitive impairment in a patient a week after starting simvastatin resolved when the drug was stopped but recurred on rechallenge with a lower dose,[9] while analyses of reports to adverse drug reaction reporting databases[10,11] have found several cases of memory loss in patients receiving statins, some of which were confirmed by rechallenge. However, clinical studies have not found statins to have an adverse effect on cognition, and there is epidemiological evidence that use of statins may reduce the incidence of dementia (see under Uses, p. 1491.2). A study with atorvastatin[12] also found beneficial effects on cognitive function.

Other psychiatric effects that have been noted in reports to another adverse drug reaction reporting database[13] include 5 cases of aggressive reactions, all of which resolved when the statin was stopped.

See also Effects on Sleep Patterns, below.

1. Lechleitner M, *et al*. Depressive symptoms in hypercholesterolaemic patients treated with pravastatin. *Lancet* 1992; **340:** 910.
2. Duits N, Bos FM. Depressive symptoms and cholesterol-lowering drugs. *Lancet* 1993; **341:** 114.
3. Wardle J, *et al*. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996; **313:** 75–8.
4. Muldoon MF, *et al*. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000; **108:** 538–47.
5. Stewart RA, *et al*. Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. *Arch Intern Med* 2000; **160:** 3144–52.
6. Young-Xu Y, *et al*. Long-term statin use and psychological well-being. *J Am Coll Cardiol* 2003; **42:** 690–7.
7. Yang C-C, *et al*. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med* 2003; **163:** 1926–32.
8. Muldoon MF, *et al*. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* 2004; **117:** 823–9.
9. Padala KP, *et al*. Simvastatin-induced decline in cognition. *Ann Pharmacother* 2006; **40:** 1880–3.
10. Wagstaff LR, *et al*. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003; **23:** 871–80.
11. Health Canada. Statins and memory loss. *Can Adverse React News* 2005; **15** (4): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n4-eng.pdf (accessed 19/08/08)
12. Parale GP, *et al*. Effects of atorvastatin on higher functions. *Eur J Clin Pharmacol* 2006; **62:** 259–65.
13. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Safety* 2007; **30:** 195–201.

Effects on the nervous system. Treatment with statins may be associated with the development of peripheral neuropathy,[1] although the reaction appears to be rare. Up to 2005, the Australian Adverse Drug Reactions Advisory Committee had received 281 reports[2] of both sensory and sensorimotor peripheral neuropathies associated with statins. Time to onset of symptoms ranged from after the first dose to 4.5 years. Recovery was seen on withdrawal in about half of the cases, including in some diabetics, and there were some reports of positive rechallenge. In 21 cases symptoms persisted at the time of reporting, up to 8 months after the statin was stopped, and in a further 2 reports the symptoms were unresolved after 3 and 5 years respectively. Similar patterns have been noted elsewhere.[3] A case-control study[4] found that the risk of neuropathy was substantially increased in users of statins although the number of cases was small, and the authors concluded that the benefits of therapy generally outweighed the risks.

Reports[5] of upper motor neurone lesions similar to amyotrophic lateral sclerosis (ALS) in patients taking statins prompted the FDA to analyse data from their spontaneous adverse event reporting system; however, the incidence of ALS with statins and placebo was similar.[6]

1. Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother* 2003; **37:** 274–8.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Statins and peripheral neuropathy. *Aust Adverse Drug React Bull* 2005; **24:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.pdf (accessed 30/05/08)
3. de Langen JJ, van Puijenbroek EP. HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre. *Neth J Med* 2006; **64:** 334–8.
4. Gaist D, *et al*. Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002; **58:** 1333–7.
5. Edwards IR, *et al*. Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from Vigibase. *Drug Safety* 2007; **30:** 515–25.
6. Colman E, *et al*. An evaluation of a data mining signal for amyotrophic lateral sclerosis and statins detected in FDA's spontaneous adverse event reporting system. *Pharmacoepidemiol Drug Safety* 2008; **17:** 1068–76.

Effects on the pancreas. Statins may cause pancreatitis but the incidence appears to be low,[1,2] and a case-control study[3] failed to support a strong association.

1. Singh S, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. *Drug Safety* 2006; **29:** 1123–32.
2. Johnson JL, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. *Pharmacotherapy* 2006; **26:** 414–22.
3. Thisted H, *et al*. Statins and the risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2006; **23:** 185–90.

Effects on sexual function. There have been reports of *erectile dysfunction* in some men receiving statins. Five men receiving simvastatin developed impotence,[1] which resolved when fluvastatin was substituted in 4 of them. In another case,[2] impotence occurred in a patient receiving lovastatin, and recurred when therapy was changed to pravastatin. Up to 1995, the Australian Adverse Drug Reactions Advisory Committee[3] had received 28 reports of impotence associated with simvastatin, which had recurred on rechallenge in 4 cases. A report[4] from the French and Spanish drug monitoring systems, and an observational study[5] in high-risk cardiovascular patients, supported the association between statins and erectile dysfunction, and a systematic review[6] came to similar conclusions. However, it has been pointed out[7] that the increased risk of sexual dysfunction with statins in the Scandinavian Simvastatin Survival Study was not statistically significant, and there has also been a small study[8] suggesting that atorvastatin may improve erectile function in men with hyperlipidaemia as the only risk factor.

Decreased libido has also been reported with statins. Serum-testosterone concentrations were measured in 2 of 8 patients reported to the Netherlands Pharmacovigilance Centre and were found to be low;[9] they rose after the statin was stopped.

Testicular pain has been reported[10] in a 54-year-old patient 7 months after starting lovastatin. The pain resolved when lovastatin was stopped, but recurred with both simvastatin and atorvastatin. The mechanism for the reaction was unclear.

There has also been a report[11] of a *low sperm count* in a patient receiving lovastatin.

Gynaecomastia occurred in a patient 6 months after changing from simvastatin to atorvastatin.[12] Symptoms improved when atorvastatin was stopped and did not recur when treatment with simvastatin was restarted.

1. Jackson G. Simvastatin and impotence. *BMJ* 1997; **315:** 31.
2. Halkin A, *et al*. HMG-CoA reductase inhibitor-induced impotence. *Ann Pharmacother* 1996; **30:** 192.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Simvastatin and adverse endocrine effects in men. *Aust Adverse Drug React Bull* 1995; **14:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/05/08)
4. Carvajal A, *et al*. HMG Co A reductase inhibitors and impotence: two case series from the Spanish and French drug monitoring systems. *Drug Safety* 2006; **29:** 143–9.
5. Solomon H, *et al*. Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract* 2006; **60:** 141–5.
6. Rizvi K, *et al*. Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; **19:** 95–8.
7. Pedersen TR, Færgeman O. Simvastatin seems unlikely to cause impotence. *BMJ* 1999; **318:** 192.
8. Saltzman EA, *et al*. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol (Baltimore)* 2004; **172:** 255–8.
9. de Graaf L, *et al*. Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? *Br J Clin Pharmacol* 2004; **58:** 326–8.
10. Linnebur AS, Hiatt WH. Probable statin-induced testicular pain. *Ann Pharmacother* 2007; **41:** 138–42.
11. Hildebrand RD, Hepperlen TW. Lovastatin and hypospermia. *Ann Intern Med* 1990; **112:** 549–50.
12. Hammons KB, *et al*. Golf-inhibiting gynecomastia associated with atorvastatin therapy. *Pharmacotherapy* 2006; **26:** 1165–8.

Effects on skeletal muscle. The association between muscle disorders and statins is well known.[1-9] Mild *myalgia* is relatively common, but *myositis* and *myopathy*, with elevation of creatine kinase, may also occur. *Rhabdomyolysis*,[10,11] which involves severe muscle damage, substantial elevation of creatine kinase and myoglobinuria leading to renal impairment, occurs more rarely, but has resulted in fatalities. Muscle toxicity is dose-related and the risk appears to be broadly similar with all of the currently-marketed statins;[5,6,12] the incidence with cerivastatin was found to be considerably higher and this led to its withdrawal worldwide in 2001. Patients with complex medical problems, including renal impairment and possibly endocrine disorders such as hypothyroidism, may be at increased risk of muscle toxicity; drug interactions may also contribute (see p. 1494.2). Myopathy has been reported with other lipid regulating drugs, particularly fibrates, and the risk may be increased in patients with severe hyperlipidaemia who require combination therapy; careful monitoring is required if statins and fibrates are used together.[6,13] The UK CSM[1] and a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute,[6] have both advised that patients treated with statins should consult their doctor if they develop muscle pain, tenderness, or weakness and that treatment should be stopped if muscle toxicity occurs or is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising. If continued therapy is required, the dose may be reduced or another statin or alternative lipid regulating drug may be tried, although the risk of recurrent muscle problems appears quite high.[11] An algorithm for diagnosis and management of statin-associated myalgia has been suggested.[14]

The mechanism by which statins cause muscle toxicity is not clear, but it has been suggested that depletion of ubidecarenone concentrations may be involved.[15] Although positive results have been reported with ubidecarenone supplementation[16] evidence of benefit is limited and it is not generally recommended.[17]

Other muscular disorders that have been reported in patients receiving statins include *dermatomyositis* and *polymyositis*,[18] and *myasthenia gravis*.[19-21]

1. CSM/MCA. HMG CoA reductase inhibitors (statins) and myopathy. *Current Problems* 2002; **28:** 8–9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Fluvastatin and muscle disorders—a class effect. *Aust Adverse Drug React Bull* 1997; **16:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 30/05/08)
3. Ucar M, *et al*. HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety* 2000; **22:** 441–57.
4. Omar MA, *et al*. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001; **35:** 1096–1107.
5. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002; **36:** 288–95.
6. Pasternak RC, *et al*. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Circulation* 2002; **106:** 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 30/05/08)
7. Adverse Drug Reactions Advisory Committee (ADRAC). Risk factors for myopathy and rhabdomyolysis with the statins. *Aust Adverse Drug React Bull* 2004; **23:** 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0402.pdf (accessed 30/05/08)
8. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004; **116:** 408–16.
9. Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med* 2009; **150:** 858–68.
10. Graham DJ, *et al*. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004; **292:** 2585–90.
11. Antons KA, *et al*. Clinical perspectives of statin-induced rhabdomyolysis. *Am J Med* 2006; **119:** 400–9.
12. Staffa JA, *et al*. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002; **346:** 539–540.
13. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; **35:** 908–917.
14. Jacobson TA. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc* 2008; **83:** 687–700.
15. Hargreaves IP, *et al*. The effect of HMG-CoA reductase inhibitors on coenzyme Q_{10}: possible biochemical/clinical implications. *Drug Safety* 2005; **28:** 659–76.
16. Walravens PA, *et al*. Lovastatin, isoprenes, and myopathy. *Lancet* 1989; **ii:** 1097–8.
17. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q_{10} during statin therapy. *Ann Pharmacother* 2006; **40:** 290–4.
18. Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007; **21:** 17–24.
19. Parmar B, *et al*. Statins, fibrates, and ocular myasthenia. *Lancet* 2002; **360:** 717.
20. Cartwright MS, *et al*. Statin-associated exacerbation of myasthenia gravis. *Neurology* 2004; **63:** 2188.
21. Purvin V, *et al*. Statin-associated myasthenia gravis: report of 4 cases and review of the literature. *Medicine (Baltimore)* 2006; **85:** 82–5.

Effects on sleep patterns. Changes to sleep patterns have been reported with lipophilic statins such as lovastatin[1-3] and simvastatin,[4] but appear to be less common with pravastatin,[1] possibly because it is hydrophilic and less likely to cross the blood-brain barrier. However, a large placebo-controlled study[5] found that simvastatin had no effect on sleep patterns, and smaller studies that assessed sleep using questionnaires[6] or polysomnography[7-9] found no significant effects with any of the statins, although some patients appeared to have underlying sleep disorders.

Nightmares and sleep disturbances in a patient taking simvastatin and metoprolol resolved when treatment was changed to pravastatin and atenolol.[10] There has been a report of nightmares with atorvastatin, which resolved when the drug was stopped but recurred on rechallenge.[11]

1. Schaefer EJ. HMG-CoA reductase inhibitors for hypercholesterolemia. *N Engl J Med* 1988; **319:** 1222.
2. Rosenson RS, Goranson NL. Lovastatin-associated sleep and mood disturbances. *Am J Med* 1993; **95:** 548–9.
3. Sinzinger H, *et al*. Sleep disturbance and appetite loss after lovastatin. *Lancet* 1994; **343:** 973.

4. Barth JD, *et al.* Inhibitors of hydroxymethylglutaryl coenzyme A reductase for treating hypercholesterolaemia. *BMJ* 1990; **301:** 669.
5. Keech AC, *et al.* Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. *Br J Clin Pharmacol* 1996; **42:** 483–90.
6. Black DM, *et al.* Sleep disturbances and HMG CoA reductase inhibitors. *JAMA* 1990; **264:** 1105.
7. Eckernäs S-Å, *et al.* The effects of simvastatin and pravastatin on objective and subjective measures of nocturnal sleep: a comparison of two structurally different HMG CoA reductase inhibitors in patients with primary moderate hypercholesterolaemia. *Br J Clin Pharmacol* 1993; **35:** 284–9.
8. Kostis JB, *et al.* Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J Clin Pharmacol* 1994; **34:** 989–96.
9. Ehrenberg BL, *et al.* Comparison of the effects of pravastatin and lovastatin on sleep disturbance in hypercholesterolemic subjects. *Sleep* 1999; **22:** 117–21.
10. Boriani G, *et al.* Nightmares and sleep disturbances with simvastatin and metoprolol. *Ann Pharmacother* 2001; **35:** 1292.
11. Gregoor PJHS. Atorvastatin may cause nightmares. *BMJ* 2006; **332:** 950.

Precautions

Statins should not be given to patients with active liver disease (but see also Hepatic Impairment, below). Liver function should be assessed before starting treatment and subsequently when clinically indicated; additional assessment after 3 months and before and after dosage increases has been advised for some statins, particularly when high doses are given. Statins should not be used in patients who already have unexplained persistently raised serum-aminotransferase concentrations and should be stopped if marked or persistent increases in serum-aminotransferase concentrations occur. They should be avoided during pregnancy since there is a possibility that they could interfere with fetal sterol synthesis; there have been reports of congenital abnormalities associated with statins (see Pregnancy, below).

All statins may cause myopathy and rhabdomyolysis, especially at higher doses. High doses of statins should therefore be limited to those patients with severe hypercholesterolaemia and high cardiovascular risk, who do not achieve their target cholesterol concentration at lower doses, provided benefits outweigh the potential risk. They should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking drugs that increase plasma concentrations of the statin (see Interactions, below); the statin should be stopped if creatine phosphokinase increases significantly or if myopathy is diagnosed.

Statins should be used with caution in patients with renal impairment as the risk of myopathy is increased. Dose reduction may be required for statins that are excreted by the kidney and for those with a particularly high risk of myopathy (see Administration in Renal Impairment under Uses of the individual drugs for further details).

Children. For discussion of concerns relating to the use of statins in children, see Administration in Children under Uses, p. 1490.2.

Hepatic impairment. Although licensed product information contra-indicates the use of statins in patients with active liver disease, there is some interest in the possibility of using them in selected patients with chronic liver disease such as non-alcoholic fatty liver disease or non-alcoholic steatohepatitis.[1-3] The Liver Expert Panel of the National Lipid Association in the USA assessed the safety of statins, and concluded that although they should remain contra-indicated in patients with decompensated cirrhosis or acute liver failure (in whom, given the gravity of their illness, they were unlikely to be a relevant option in any case), there was no reason to do so in patients with chronic liver disease or compensated cirrhosis.[1]

A subsequent comment by UK experts[2] noted that use in patients with chronic liver disease and elevated transaminase values remained contentious. Those with AST and ALT concentrations less than 3 times above the normal upper limit could be offered statin therapy but at the lowest possible dose, and liver enzymes should be reassessed within 4 weeks; if no major change occurred, treatment could continue and values be monitored every 6 weeks for the next 3 months, and every 3 months thereafter. If values doubled from their original readings, treatment should be stopped, although rechallenge was possible once they returned to normal baseline values. They recommended that treatment should not be given to the following groups:

- those with transaminase values more than 3 times above the normal upper limit (although this was an arbitrary limit rather than an evidence-based one)
- those with evidence of impaired liver synthesis, e.g. low serum albumin or increased prothrombin time
- those with acute hepatitis of any cause
- those with Child B or C cirrhosis

It was noted that patients with end-stage liver disease often have low total cholesterol due to poor hepatic synthesis, and as such rarely require statin therapy.[2]

1. Cohen DE, *et al.* National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. *Am J Cardiol* 2006; **97:** 77C–81C.
2. Cash J, *et al.* Statin safety and chronic liver disease. *Int J Clin Pract* 2008; **62:** 1831–5.
3. Tandra S, Vuppalanchi R. Use of statins in patients with liver disease. *Curr Treat Options Cardiovasc Med* 2009; **11:** 272–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies simvastatin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. Statins are generally contra-indicated in pregnancy since there is a possibility that they might affect fetal sterol synthesis whereas the risk to the mother from stopping treatment temporarily is usually very low. Evidence that statins have adverse effects on the fetus, however, is limited. Studies based on postmarketing surveillance[1,2] or pregnancy registry data[3] have generally found that the frequency and range of congenital anomalies reported was similar to that expected in the general population. However, reviews of case reports[4,5] found that the incidence of CNS defects and limb anomalies was higher than expected, suggesting a possible adverse effect of statin exposure; 1 of the 5 cases reported as a CNS defect was later found to have cardiac anomalies only.[6]

1. Manson JM, *et al.* Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. *Reprod Toxicol* 1996; **10:** 439–46.
2. Pollack PS, *et al.* Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol* 2005; **73:** 888–96.
3. Ofori B, *et al.* Risk of congenital anomalies in pregnant users of statin drugs. *Br J Clin Pharmacol* 2007; **64:** 496–509.
4. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *N Engl J Med* 2004; **350:** 1579–82.
5. Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *Am J Med Genet* 2004; **131A:** 287–98.
6. Edison RJ, Muenke M. Gestational exposure to lovastatin followed by cardiac malformation misclassified as holoprosencephaly. *N Engl J Med* 2005; **352:** 2759.

Interactions

The most serious consequence of drug interactions with simvastatin and other statins is the development of myopathy or rhabdomyolysis. Drugs that can cause myopathy when given alone increase the risk of myopathy with all statins; these drugs include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by drugs that increase the plasma concentrations of statins, by inhibiting their metabolism or by inhibiting their uptake into the liver. Since the statins have different metabolic pathways, these interactions depend on the individual drug concerned. Simvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4, as are atorvastatin and lovastatin, and interactions may occur with drugs that inhibit this enzyme, including ciclosporin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, danazol, amiodarone, amlodipine, diltiazem, ranolazine, and verapamil; there may also be a similar interaction with grapefruit juice. Such combinations should be used with caution, if at all, and dose reduction may be advised (see Uses and Administration, p. 1489.3); UK licensed product information contra-indicates the use of simvastatin in patients receiving potent CYP3A4 inhibitors. Fluvastatin is metabolised mainly by CYP2C9 and pitavastatin by glucuronidation, while pravastatin and rosuvastatin are not significantly metabolised; interactions specific to these statins are discussed on p. 1385.2, p. 1471.2, p. 1473.2, and p. 1488.3, respectively.

Statins may also have effects on other drugs. Bleeding and increases in prothrombin time have been reported in patients taking simvastatin or other statins with coumarin anticoagulants.

General reviews.

1. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002; **41:** 343–70.
2. Martin J, Krum H. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant? *Drug Safety* 2003; **26:** 13–21.
3. CSM/MHRA. Statins and cytochrome P450 interactions. *Current Problems* 2004; **30:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
4. Rätz Bravo AE, *et al.* Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Safety* 2005; **28:** 263–75.
5. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006; **97** (suppl 8A): 27C–31C.
6. Neuvonen PJ, *et al.* Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006; **80:** 565–81.
7. Frishman WH, Horn J. Statin-drug interactions: not a class effect. *Cardiol Rev* 2008; **16:** 205–12.

Antiarrhythmics. *Amiodarone* is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations of statins metabolised by this enzyme, increasing the risk of toxicity. There have been reports[1-3] of myopathy and rhabdomyolysis in patients taking amiodarone and simvastatin (in some cases with other CYP3A4 inhibitors), and a pharmacokinetic study[4] found that amiodarone increased plasma-simvastatin concentrations in healthy subjects. High doses of simvastatin are not recommended in patients taking amiodarone (see Uses and Administration, p. 1489.3).

An asymptomatic increase in serum aminotransferases in a patient receiving rosuvastatin and amiodarone may have been the result of an interaction between the drugs.[5]

1. Roten L, *et al.* Rhabdomyolysis in association with simvastatin and amiodarone. *Ann Pharmacother* 2004; **38:** 978–81.
2. Chouhan UM, *et al.* Simvastatin interaction with clarithromycin and amiodarone causing myositis. *Ann Pharmacother* 2005; **39:** 1760–1.
3. Ricaurte B, *et al.* Simvastatin–amiodarone interaction resulting in rhabdomyolysis, azotemia, and possible hepatotoxicity. *Ann Pharmacother* 2006; **40:** 753–7.
4. Becquemont L, *et al.* Amiodarone interacts with simvastatin but not with pravastatin disposition kinetics. *Clin Pharmacol Ther* 2007; **81:** 679–84.
5. Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. *Am J Health-Syst Pharm* 2007; **64:** 1818–21.

Antibacterials. *Erythromycin* and other *macrolides* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Increased plasma concentrations of simvastatin have been reported with erythromycin,[1] and increased plasma concentrations of atorvastatin have been found with erythromycin[2] and *clarithromycin*,[3] but not with *azithromycin*.[3] There have been reports of myopathy or rhabdomyolysis in patients receiving simvastatin with clarithromycin,[4] and in patients receiving lovastatin with azithromycin,[5] clarithromycin,[5] or erythromycin.[6]

Rifampicin, an inducer of CYP2C9 and CYP3A4, may reduce the bioavailability of fluvastatin, and has also been reported to reduce the plasma concentration of simvastatin[7] and atorvastatin.[8]

There have been reports of rhabdomyolysis in patients receiving atorvastatin[9] or simvastatin[10] with *fusidic acid*.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64:** 177–82.
2. Siedlik PH, *et al.* Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol* 1999; **39:** 501–4.
3. Amsden GW, *et al.* A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002; **42:** 444–9.
4. Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001; **35:** 26–31.
5. Grunden JW, Fisher KA. Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 1997; **31:** 859–63.
6. Ayanian JZ, *et al.* Lovastatin and rhabdomyolysis. *Ann Intern Med* 1988; **109:** 682–3.
7. Kyrklund C, *et al.* Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 2000; **68:** 592–7.
8. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; **78:** 154–67.
9. Wenisch C, *et al.* Acute rhabdomyolysis after atorvastatin and fusidic acid therapy. *Am J Med* 2000; **109:** 78.
10. Yuen SLS, McGarity B. Rhabdomyolysis secondary to interaction of fusidic acid and simvastatin. *Med J Aust* 2003; **179:** 172.

Anticoagulants. For reports of bleeding and increased prothrombin time in patients receiving oral anticoagulants with statins, see Lipid Regulating Drugs, p. 1534.3.

Antidepressants. Myositis and rhabdomyolysis, with raised liver enzyme values, have been reported[1-4] in patients given simvastatin with *nefazodone*; in one case[3] the reaction appeared to be precipitated by the addition of azithromycin. Increased creatine kinase concentrations also occurred in a patient given pravastatin with nefazodone.[5]

A study[6] in healthy subjects found that *St John's wort* reduced the plasma concentration of simvastatin but had no effect on pravastatin.

1. Jacobson RH, *et al.* Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. *JAMA* 1997; **277:** 296.
2. Thompson M, Samuels S. Rhabdomyolysis with simvastatin and nefazodone. *Am J Psychiatry* 2002; **159:** 1607.
3. Skrabal MZ, *et al.* Two cases of rhabdomyolysis associated with high-dose simvastatin. *Am J Health-Syst Pharm* 2003; **60:** 578–81.
4. Karnik NS, Maldonado JR. Antidepressant and statin interactions: a review and case report of simvastatin and nefazodone-induced rhabdomyolysis and transaminitis. *Psychosomatics* 2005; **46:** 565–8.
5. Alderman CP. Possible interaction between nefazodone and pravastatin. *Ann Pharmacother* 1999; **33:** 871.
6. Sugimoto K-i, *et al.* Different effects of St John's Wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001; **70:** 518–24.

All cross-references refer to entries in Volume A

Antidiabetics. Rhabdomyolysis and acute renal failure developed about 6 weeks after *sitagliptin* was started in an elderly patient already stabilised on several drugs including simvastatin.[1] The condition resolved when both were stopped and did not recur when lovastatin was started. In this case, the patient already had chronic renal impairment, and it was noted that the dose of sitagliptin was double that recommended for his renal function. In another patient taking lovastatin, rhabdomyolysis developed after about 2 weeks of sitagliptin treatment, and recovery occurred after the statin was stopped.[2] In this case, although the patient was 75 years old, she was reported to have a calculated renal function within normal limits. The possible mechanism of an interaction between sitagliptin and statins is unclear. In a study in healthy young subjects, steady-state sitagliptin achieved after 5 days had no significant effect on the pharmacokinetics of a single dose of simvastatin.[3]

1. Kao DP, *et al.* Renal failure and rhabdomyolysis associated with sitagliptin and simvastatin use. *Diabet Med* 2008; **25:** 1229–30.
2. DiGregorio RV, Pasikhova Y. Rhabdomyolysis caused by a potential sitagliptin-lovastatin interaction. *Pharmacotherapy* 2009; **29:** 352–6.
3. Bergman AJ, *et al.* Effect of sitagliptin on the pharmacokinetics of simvastatin. *J Clin Pharmacol* 2009; **49:** 483–8.

Antifungals. *Itraconazole* and *ketoconazole* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Raised plasma concentrations of simvastatin,[1,2] lovastatin,[3,4] and atorvastatin[5] have been reported with itraconazole, whereas the effect on pravastatin,[1] rosuvastatin,[6] or fluvastatin[4] appears to be minimal. Myopathy and rhabdomyolysis have been reported with simvastatin and itraconazole[2,7] or ketoconazole,[8] and with lovastatin and itraconazole.[9] *Fluconazole* inhibits CYP2C9 and has been reported[10] to increase the plasma concentration of fluvastatin. There has also been a report[11] of rhabdomyolysis in a patient taking fluconazole and simvastatin.

1. Neuvonen PJ, *et al.* Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998; **63:** 332–41.
2. Segaert MF, *et al.* Drug-interaction-induced rhabdomyolysis. *Nephrol Dial Transplant* 1996; **11:** 1846–7.
3. Neuvonen PJ, Jalava K-M. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996; **60:** 54–61.
4. Kivistö KT, *et al.* Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998; **46:** 49–53.
5. Kantola T, *et al.* Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998; **64:** 58–65.
6. Cooper KJ, *et al.* Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2003; **73:** 322–9.
7. Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol* 1996; **132:** 1254.
8. Gilad R, Lampl Y. Rhabdomyolysis induced by simvastatin and ketoconazole treatment. *Clin Neuropharmacol* 1999; **22:** 295–7.
9. Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. *N Engl J Med* 1995; **333:** 664–5.
10. Kantola T, *et al.* Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000; **56:** 225–9.
11. Shaukat A, *et al.* Simvastatin–fluconazole causing rhabdomyolysis. *Ann Pharmacother* 2003; **37:** 1032–5.

Antineoplastics. For mention of a potential reduction of cytotoxic effect when *rituximab* is given with statins, see p. 855.1.

Antiplatelet drugs. For discussion of a possible interaction between statins and clopidogrel, see p. 1344.3

Antivirals. *HIV-protease inhibitors* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may affect the metabolism of simvastatin and other statins. Studies have shown increased plasma concentrations of both simvastatin and atorvastatin with *nelfinavir*,[1] and with *ritonavir-boosted saquinavir*,[2] whereas the plasma concentration of pravastatin was reduced with ritonavir-boosted saquinavir.[2] Rhabdomyolysis has been reported[3] in a patient taking simvastatin when ritonavir was added to her therapy. Although rosuvastatin is not significantly metabolised, increased plasma concentrations have been reported with *ritonavir-boosted lopinavir*.[4,5]

There has also been a report[6] of rhabdomyolysis in a patient receiving atorvastatin with the non-nucleoside reverse transcriptase inhibitor *delavirdine*.

Efavirenz is an inducer of CYP3A4 and a study in healthy subjects[7] found that it could reduce plasma concentrations of atorvastatin and simvastatin; plasma concentrations of pravastatin were also reduced, although it is not metabolised by CYP3A4.

1. Hsyu P-H, *et al.* Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother* 2001; **45:** 3445–50.
2. Fichtenbaum CJ, *et al.* Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002; **16:** 569–77.
3. Cheng CH, *et al.* Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. *Am J Health-Syst Pharm* 2002; **59:** 728–30.
4. van der Lee M, *et al.* Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. *Antivir Ther* 2007; **12:** 1127–32.
5. Kiser JJ, *et al.* Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2008; **47:** 570–8.
6. Castro JG, Gutierrez L. Rhabdomyolysis with acute renal failure probably related to the interaction of atorvastatin and delavirdine. *Am J Med* 2002; **112:** 505.
7. Gerber JG, *et al.* Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; **39:** 307–12.

Calcium-channel blockers. Calcium-channel blockers may increase plasma concentrations of some statins, probably by inhibition of the cytochrome P450 isoenzyme CYP3A4. Pharmacokinetic studies have reported increased plasma concentrations of simvastatin with *verapamil*,[1] and with *diltiazem*,[2] and of lovastatin with diltiazem;[3] the small increase with simvastatin and *lacidipine* was not considered clinically relevant.[4]

The interaction between statins and diltiazem has also been reported in patients. A retrospective study[5] found that the cholesterol-lowering effect of simvastatin was greater in patients who were also receiving diltiazem, and there have also been reports[6-8] of rhabdomyolysis, associated with hepatitis in 1 case,[6] in patients receiving simvastatin and diltiazem together. Rhabdomyolysis[8,9] and hepatitis[9] have also been reported in patients receiving atorvastatin with diltiazem.

For reference to increased bioavailability of verapamil with lovastatin see p. 1525.3.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64:** 177–82.
2. Mousa O, *et al.* The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000; **67:** 267–74.
3. Azie NE, *et al.* The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther* 1998; **64:** 369–77.
4. Ziviani L, *et al.* The effects of lacidipine on the steady/state plasma concentrations of simvastatin in healthy subjects. *Br J Clin Pharmacol* 2001; **51:** 147–52.
5. Yeo KR, *et al.* Enhanced cholesterol reduction by simvastatin in diltiazem-treated patients. *Br J Clin Pharmacol* 1999; **48:** 610–615.
6. Kanathur N, *et al.* Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. *Tenn Med* 2001; **94:** 339–41.
7. Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron* 2001; **89:** 117–118.
8. Gladding P, *et al.* Potentially fatal interaction between diltiazem and statins. *Ann Intern Med* 2004; **140:** W31. Available at: http://www.annals.org/cgi/reprint/140/8/W-31.pdf (accessed 14/11/07)
9. Lewin JJ, *et al.* Rhabdomyolysis with concurrent atorvastatin and diltiazem. *Ann Pharmacother* 2002; **36:** 1546–9.

Colchicine. For reports of additive muscle toxicity with statins and colchicine, see Cardiovascular Drugs under Interactions of Colchicine, p. 606.2.

Danazol. Rhabdomyolysis has been reported[1] in a patient receiving lovastatin with several other drugs; it was considered that an interaction with danazol was the most likely cause. A similar reaction has been reported[2] with simvastatin.

1. Dallaire M, Chamberland M. Rhabdomyolyse sévère chez un patient recevant lovastatine, danazol et doxycycline. *Can Med Assoc J* 1994; **150:** 1991–4.
2. Andreou ER, Ledger S. Potential drug interaction between simvastatin and danazol causing rhabdomyolysis. *Can J Clin Pharmacol* 2003; **10:** 172–4.

Endothelin receptor antagonists. *Bosentan* is an inducer of the cytochrome P450 isoenzyme CYP3A4 and has been reported[1] to reduce plasma-simvastatin concentrations in healthy subjects.

1. Dingemanse J, *et al.* Investigation of the mutual pharmacokinetic interactions between bosentan, a dual endothelin receptor antagonist, and simvastatin. *Clin Pharmacokinet* 2003; **42:** 293–301.

Fruit juices. *Grapefruit juice* inhibits the cytochrome P450 isoenzyme CYP3A4 and studies using concentrated grapefruit juice have reported increased plasma concentrations of simvastatin,[1] lovastatin,[2] and atorvastatin.[3] A study[4] using less concentrated grapefruit juice found only minimal effect on the activity of lovastatin, but the conclusions of this study have been criticised;[5] studies using normal strength grapefruit juice have found considerable increases in plasma concentrations of atorvastatin[6] and simvastatin.[7] There is also a case report[8] of a woman receiving simvastatin who developed symptoms of rhabdomyolysis 4 days after she started eating one grapefruit each day. Statins that are not significantly metabolised by CYP3A4, such as pitavastatin[6] and pravastatin,[3,9] do not appear to be affected.

Rhabdomyolysis has also been reported[10] in a patient taking rosuvastatin and ezetimibe when he started drinking *pomegranate juice* regularly.

1. Lilja JJ, *et al.* Grapefruit juice–simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998; **64:** 477–83.
2. Kantola T, *et al.* Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1998; **63:** 397–402.
3. Lilja JJ, *et al.* Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999; **66:** 118–27.
4. Rogers JD, *et al.* Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Clin Pharmacol Ther* 1999; **66:** 358–66.
5. Bailey DG, Dresser GK. Grapefruit juice–lovastatin interaction. *Clin Pharmacol Ther* 2000; **67:** 690.
6. Ando H, *et al.* Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *Br J Clin Pharmacol* 2005; **60:** 494–7.
7. Lilja JJ, *et al.* Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. *Br J Clin Pharmacol* 2004; **58:** 56–60.
8. Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. *Neurology* 2004; **62:** 670.
9. Fukazawa I, *et al.* Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br J Clin Pharmacol* 2004; **57:** 448–55.
10. Sorokin AV, *et al.* Rhabdomyolysis associated with pomegranate juice consumption. *Am J Cardiol* 2006; **98:** 705–6.

Immunosuppressants. Myopathy and rhabdomyolysis have been reported in patients receiving atorvastatin,[1] lovastatin,[2-4] or simvastatin[5-7] with immunosuppressant regimens including *ciclosporin*. The mechanism of the interaction may be additive toxicity, since both statins and ciclosporin are known to cause myopathy, but effects on plasma concentrations may also be involved. Pharmacokinetic studies have shown that ciclosporin increases the plasma concentrations of atorvastatin,[8,9] fluvastatin,[10,11] lovastatin,[12] pravastatin,[12,13] rosuvastatin,[14] and simvastatin.[15] For the effects of statins on blood-ciclosporin concentrations, see p. 1958.1.

1. Maltz HC, *et al.* Rhabdomyolysis associated with concomitant use of atorvastatin and cyclosporine. *Ann Pharmacother* 1999; **33:** 1176–9.
2. Norman DJ, *et al.* Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med* 1988; **318:** 46–7.
3. East C, *et al.* Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. *N Engl J Med* 1988; **318:** 47–8.
4. Corpier CL, *et al.* Rhabdomyolysis and renal injury with lovastatin use: report of two cases in cardiac transplant recipients. *JAMA* 1988; **260:** 239–41.
5. Blaison G, *et al.* Rhabdomyolyse causée par la simvastatine chez un transplanté cardiaque sous ciclosporine. *Rev Med Interne* 1992; **13:** 61–3.
6. Meier C, *et al.* Rhabdomyolyse bei mit Simvastatin und Ciclosporin behandelten Patienten: Rolle der aktivität des Cytochrom-P450-Enzymsystems der Leber. *Schweiz Med Wochenschr* 1995; **125:** 1342–6.
7. Gumprecht J, *et al.* Simvastatin-induced rhabdomyolysis in a CsA-treated renal transplant recipient. *Med Sci Monit* 2003; **9:** CS89–CS91.
8. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; **1:** 382–6.
9. Hermann M, *et al.* Substantially elevated levels of atorvastatin and metabolites in cyclosporine-treated renal transplant recipients. *Clin Pharmacol Ther* 2004; **76:** 388–91.
10. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; **62:** 1559–64.
11. Park J-W, *et al.* Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. *J Cardiovasc Pharmacol Ther* 2001; **6:** 351–61.
12. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; **62:** 311–21.
13. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; **25:** 2732–4.
14. Simonson SG, *et al.* Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004; **76:** 167–77.
15. Arnadottir M, *et al.* Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron* 1993; **65:** 410–13.

Levothyroxine. For reference to the effect of lovastatin and simvastatin in patients receiving levothyroxine, see Lipid Regulating Drugs, p. 2342.1.

Lipid regulating drugs. Myopathy and myositis are recognised adverse effects of both statins and fibric acid derivatives, including *fibrates* and *gemfibrozil*, and the risk is increased if they are given together. There has also been a report[1] of both hepatotoxicity and rhabdomyolysis in a patient given a statin and gemfibrozil together. The interaction between gemfibrozil and statins may also have a pharmacokinetic basis; studies have shown increased plasma concentrations of atorvastatin,[2] lovastatin,[3] pravastatin,[4] rosuvastatin,[5] and simvastatin[6] when given with gemfibrozil.

Myopathy has also been reported[7,8] in patients given statins with *nicotinic acid*, although a study[9] of adverse effects reported to the FDA found no increase in reports for lovastatin given with nicotinic acid compared with either drug alone.

For reports of increased hepatotoxicity when statins were given with *ezetimibe* see Effects on the Liver, p. 1380.1.

1. Akoglu H, *et al.* Combined organ failure with combination antihyperlipidemic treatment: a case of hepatic injury and acute renal failure. *Ann Pharmacother* 2007; **41:** 143–7.
2. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; **78:** 154–67.
3. Kyrklund C, *et al.* Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001; **69:** 340–5.
4. Kyrklund C, *et al.* Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003; **73:** 538–44.
5. Schneck DW, *et al.* The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004; **75:** 455–63.
6. Backman JT, *et al.* Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000; **68:** 122–9.

7. Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med* 1988; **109:** 597–8.
8. Hill MD, Bilbao JM. Case of the month: February 1999—54 year oldman with severe muscle weakness. *Brain Pathol* 1999; **9:** 607–8.
9. Alsheikh-Ali AA, Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration adverse event reporting system). *Am J Cardiol* 2007; **99:** 379–81.

Proton pump inhibitors. There is a report[1] of rhabdomyolysis causing AV block in a patient receiving atorvastatin when *esomeprazole* and clarithromycin were added to her treatment. As symptoms started before the introduction of clarithromycin, it was thought that a possible contributory mechanism for the interaction was a reduction in the first-pass metabolism of atorvastatin due to the inhibition of p-glycoprotein by esomeprazole.

1. Sipe BE, *et al*. Rhabdomyolysis causing AV blockade due to possible atorvastatin, esomeprazole, and clarithromycin interaction. *Ann Pharmacother* 2003; **37:** 808–11.

Ranolazine. A study[1] in healthy subjects showed that ranolazine moderately increased plasma concentrations of simvastatin but it was not thought that the interaction would be clinically significant.

1. Jerling M, *et al*. Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects. *J Clin Pharmacol* 2005; **45:** 422–33.

Pharmacokinetics

Simvastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Other active metabolites have been detected and several inactive metabolites are also formed. Simvastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action. Less than 5% of the oral dose has been reported to reach the circulation as active metabolites. Both simvastatin and its β-hydroxyacid metabolite are about 95% bound to plasma proteins. Simvastatin is mainly excreted in the faeces via the bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms. The half-life of the active β-hydroxyacid metabolite is 1.9 hours.

General reviews.

1. Mauro VF. Clinical pharmacokinetics and practical applications of simvastatin. *Clin Pharmacokinet* 1993; **24:** 195–202.
2. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; **31:** 348–71.
3. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; **32:** 403–25.
4. Neuvonen PJ, *et al*. Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; **47:** 463–74.

Genetic variation. The pharmacokinetics of statins are influenced not only by metabolising enzymes but also by their affinity for organ-specific transporter proteins responsible for their uptake and efflux from cells, in particular in the intestine and liver.[1,2] Statins differ not only in their affinity for cytochrome P450 isoenzymes, but also in their affinity for transporter proteins such as organic anion transporting polypeptides (OATPs) and P-glycoprotein (multidrug resistance 1; MDR1). Both metabolising enzymes and transporter proteins may be subject to ethnic and genetic variation, and it has been suggested that this may explain some of the variability in the efficacy and the risk of adverse effects in different populations.

1. Kim RB. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and genetic variability (single nucleotide polymorphisms) in a hepatic drug uptake transporter: what's it all about? *Clin Pharmacol Ther* 2004; **75:** 381–5.
2. Tirona RG. Ethnic differences in statin disposition. *Clin Pharmacol Ther* 2005; **78:** 311–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Coleflux; Colesterminol; Dosavastatin; Gemistatin; Klonastin; Labistatin; Lipimibe†; Lipoblock; Lipomax; Lisac; Nivelipol; Nosterol; Redusterol; Salvaxil; Sevacol; Several; Simvastec; Sistatin; Tanavat; Vasotenal; Zocor; ***Austral.***: Invast; Lipex; Ransim; Simvabell†; Simvahexal; Simvar; Zimstat; Zocor; ***Austria***: Gerosim; Nyzoc; Simvarcana; Simvastad; Simvatin; Zocord; ***Belg.***: Cholemed; Docsimvasta†; Simvafour; Simvastamed†; Zocor; ***Braz.***: Androlip; Clinfar; Lipistatina; Lipotex†; Liptrat; Menocol; Mivalen; Revastin; Sinvalip; Sinvane†; Sinvascor; Sinvastacor; Sinvastamed; Sinvaston; Sinvatrox; Sinvax; Vaslip; Vastatil; Zocor; ***Canad.***: Zocor; ***Chile***: Nimicor; Simvass; Vasomed; Vasotenal†; Zocor; ***China***: Bo Zhan Tong (博占同); Jian Zhi Ting (剑之亭); Jie Zhi (捷芝); Ka Di Ke (卡地克); Li Shu Da (理舒达); Lizhishu (利之舒); Luoqi (罗奇); Mi Xi Lun (米希伦); Sai Fu Ding (赛夫丁); Simcor (辛可); Su Zhi (苏之); Xi Sai (希赛); Xi Zhi Da (西之达); Xin Da Su (新达苏); Xin You Zhi (辛优旨); Xing Lu (幸露); Yixin (忆辛); Zheng Zhi (正支); Zhi Tai (旨泰); Zocor (舒降之); ***Cz.***: Apo-Simva; Coralip; Corsim; Egilipid; Gensi; Sim; Simbela†; Simgal; Simirex; Simva†; Simvacard; Simvax; Simvor; Vabadin; Vasilip; Zocor; ***Denm.***: Perichol; Simar; Simvacop†; Simvahall†; Simvahot†; Simvaklein; Simvanidda; Statstad; Vasilip; Zocor; ***Fin.***: Lipcut; Zocor; ***Fr.***: Lodales; Zocor; ***Ger.***: BeL; Simva; SimvaAPS†; Simvabeta; Simvacard†; Simvadoc†; Simvagamma; Simvahexal†; Simvalip; Zocor; ***Gr.***: Antichol; Arstatin; Avatratin; Bevostatin; Christatin; Doctiverine; Extrastatin; Glipal; Goldastatin; Iamastatin; Ipramid; Kymazol; Lepur; Lip-Down; Lipexal; Lipomin; Lipopress; Liporex; Lipozid; Lowcholid; Lusimva; Medistatin; Nezatin; Nitastin; Normotherin; Placol; Prelon; Priacin; Prizelip; Raptor; Ravostan; Redusterol; Simplaqor; Simvachol; Simvacor; Simvalark; Simvalid; Simvanox; Simvaprol; Simvasterol; Simvastil; Simvatin; Sivinar; Soneto; Sotovastin; Starezin; Stasiva; Statinal; Statinum; Stativer; Statosan; Stazor; Sterylip; Tremital; Vassor; Vastatin; Velkastatin; Veristin; Veritrat; Zocor; Zurocid; ***Hong Kong***: Avastinee; Corstat; Covastin; Qualicor; Simcard; Simplaqor; Simtin; Simvacor†; Simvell; Simvor; Stavid; Vasilip; Vick-Zocostatin; Vidastat; Zocor; ***Hung.***: Andever; Awestatin; Sicor; Simvacol; Simvagamma; Simvep; Simvor; Vasilip; Zocor; ***India***: Biosim; Simcard; Simchol; Simlo; Simvotin; ***Indon.***: Cholestat; Cholexin; Detrovel; Esvat; Ethicol; Lesvatin; Lipinorm; Mersivas; Normofat; Phalol; Pontizoc; Preschol; Rechol; Rendapid; Rocoz; Selvim; Simbado; Simchol; Simcor†; Sinova; Sintrol; Valemia; Vaster; Vazim†; Vidastat; Zaptrol; Zocor; Zovast; ***Irl.***: Ritechol; Simator; Simcovas; Simtan; Simzor; Sivatin; Zocor; ***Israel***: Simovil; Simvacor; Simvaxon; ***Ital.***: Alpheus; Krustat; Lipenil; Liponorm; Medipo; Omistat; Quibus; Setorilin; Simbatrix; Sinvacor; Sinvat; Sivastin; Vastgen; Xipocol; Zocor; ***Malaysia***: Covastin; Lipaco; Simcard†; Simtin; Simvacor; Simvor; Stavid; Vascor; Zocor; ***Mex.***: Apomastina; Colesken; Cotritev; Diskolestina; Fansia†; Imbistad; Nafatab; Nodolip; Pulsar-AT Dual; Ranvor†; Simplaqor; Sinccord; Sitatinal; Tulip†; Xintilan; Zeid; Zocor; Zorced; ***Neth.***: Marsim†; Simvalip; Simvastad; Simvastaine†; Vabadin†; Zocor; ***Norw.***: Zocor; ***NZ***: Lipex; SimStatin; Simva; SimvaRex; ***Philipp.***: Afordel; Altovast; Astin; Avastat; Buztin†; Cardiosim; Cholestad; Cholevas; Cholevast; Cholevist; Ecosta; Endovaz; Eurocor; Euvasten; Forcad; Ivast; Lipitin-S; Lipivas; Lipix; Lochol; Normastin; Orovas; Qualistat; Reduscole; Regumet; Saveor; Simbathree; Simlip; Simtin; Simvacor; Simvahex; Simvastin; Simvasyn; Simvaz; Simvoget; Sivatin; Stadex; Stavid; Stilz; Uni-Per; Vamstat; Vastat; Vastichol; Vastilan; Vazz; Vidastat; Vivastin; Wilsim; Ximvast; Zimcor; Zimvacor; Zivas; Zocor; Zolestat; Zolvastin; Zostatin; Zovast; ***Pol.***: Apo-Simva; Cardin; Egilipid; Simcovas; Simgal; Simratio; Simredin†; Simvacard; Simvachol; Simvacor; Simvagen; Simvahexal; Simvalip; Simvasterol; Simvor; Vasilip; Vastan; Ximve; Zifam; Zocor; ***Port.***: Actalipid†; Biolipe; Ceabisin; Ceasin†; Colvastina; Dislipina; Jabastatina; Lipaz; Simvacol; Simvasim; Sinpor; Sinvastil; Vascorim; Zapil; Zera; Zocor; ***Rus.***: Actalipid (Акталипид); Aterostat (Атеростат); Cholvasim (Холвасим); Levomir (ЛевОМИР); Simgal (Симгал); Simlo (Симло); Simplacor (Симплакор); Simvacard (Симвакард); Simvacol (Симвакол); Simvahexal (Симвагексал); Simvalimit (Симвалимит); Simvastol (Симвастол); Simvor (Симвор); Synkard (Синкард); Vasilip (Вазилип); Zocor (Зокор); Zorstat (Зорстат); Zovatin (Зоватин); ***S.Afr.***: Choleste; Lipidex; Michol; Redicor; Simaspen†; Simcard; Simvacor; Simvotin; Simzor; Zocor; Zysim; ***Singapore***: Cholestat; Covastin; Ifistatin; Priacin; Simtin; Simvacor; Simvas; Simvor; Simzal; Vascor; Vasilip; Zocor; ***Spain***: Alcosin; Arudel†; Belmalip; Colemin; Glutasey; Histop; Lipociden; Pantok; Zocor; ***Swed.***: Simidon; Vabadin; Zocord; ***Switz.***: Simcora; Simvasine; Simvast†; Simvastin; Zocor; ***Thai.***: Bestatin; Eucor; Lochol; Simvas; Simvor; Torio; Vascor; Zimmex; Zimva; Zocor; ***Turk.***: Lipovas; Simacor; Simastinteva; Simvakol; Zocor; Zovatin; ***UAE***: Simvast; ***UK***: Simvador; Zocor; ***Ukr.***: Simgal (Симгал); Simstat (Симстат); Simvachol (Симвахол); Simvacor (СимваКОР); Simvahexal (Симвагексал)†; Simvastat (Симвастат); Simvatin (Симватин); Vabadin (Вабадин); Vasilip (Вазилип); Vasostat (Вазостат)†; Zosta (Зоста); ***USA***: Zocor; ***Venez.***: Cynt; Kavelor; Simplaqor; Sinvaz; Tavor; Tinasin; Vasotenal; Vastan; Zocor.

Multi-ingredient Preparations. ***Arg.***: Alipas Duo; Coleflux Duo; Labistatin Duo; Redusterol Duo; Salvaxil Plus; Sinterol Compuesto; Vasotenal EZ; Vytorin; Zimetek; ***Austral.***: Vytorin; ***Austria***: Inegy; ***Belg.***: Inegy; ***Braz.***: Diocomb SI; Prevencor; Vytorin; Zetsim; ***Chile***: Adacai; Vytorin; Zintrepid; ***China***: Vytorin (葆至能); ***Cz.***: Inegy; ***Denm.***: Inegy; ***Fin.***: Inegy; ***Fr.***: Inegy; Vytorin; ***Ger.***: Inegy; ***Gr.***: Inegy; Vytorin; ***Hong Kong***: Vytorin; ***Hung.***: Inegy; ***Indon.***: Vytorin; ***Irl.***: Inegy; ***Israel***: Inegy; ***Ital.***: Goltor; Inegy; Vytorin; Zeklen; ***Malaysia***: Vytorin; ***Mex.***: Amlidual; Vytorin; Zintrepid; ***Neth.***: Inegy; ***Norw.***: Inegy; ***NZ***: Vytorin; ***Philipp.***: SafeStat; Vytorin; ***Port.***: Inegy; Vytorin; ***Rus.***: Inegy (Инеджи); ***Singapore***: Vytorin; ***Spain***: Inegy; Vytorin; ***Swed.***: Inegy; ***Switz.***: Inegy; ***Thai.***: Vytorin; ***Turk.***: Inegy; ***UK***: Inegy; ***USA***: Juvisync; Simcor; Vytorin; ***Venez.***: Adacai; Vytorin; Zintrepid.

Pharmacopoeial Preparations
BP 2014: Simvastatin Tablets;
USP 36: Simvastatin Tablets.

Sitaxentan Sodium *(USAN, rINNM)*

Natrii Sitaxentanum; Sitaxentán sódico; Sitaxentan Sodique; Sitaxsentan Sodium; TBC-11251 (sitaxentan or sitaxentan sodium); TBC-11251-z; Натрий Ситаксентан.

N-(4-Chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-o-tolyl]acetyl]-3-thiophenesulfonamide sodium.

$C_{18}H_{14}ClN_2NaO_6S_2$=476.9

CAS — 184036-34-8 (sitaxentan); 210421-74-2 (sitaxentan sodium).
UNII — 6V9JH46E20.

Uses and Administration

Sitaxentan is an endothelin receptor antagonist (p. 1245.1) with similar actions to bosentan (p. 1327.1), although it has a higher selectivity for the endothelin ET_A-receptor. It was used in the management of pulmonary hypertension functional class III (p. 1278.2) in an oral dose of 100 mg once daily, but was withdrawn due to reports of fatal liver toxicity.

Reviews.

1. Wittbrodt ET, Abubakar A. Sitaxsentan for treatment of pulmonary hypertension. *Ann Pharmacother* 2007; **41:** 100–105.
2. Benedict NJ. Sitaxsentan in the management of pulmonary arterial hypertension. *Am J Health-Syst Pharm* 2007; **64:** 363–8.
3. Scott LJ. Sitaxentan: in pulmonary arterial hypertension. *Drugs* 2007; **67:** 761–70.

Adverse Effects

As for Bosentan, p. 1327.3. Liver toxicity, while a known adverse effect of all endothelin receptor antagonists, has been more severe with sitaxentan and it has consequently been withdrawn worldwide—see below. Increases in INR and prolongation of the prothrombin time have also been reported.

Sitaxentan is teratogenic in *rats*.

Effects on the liver. Rare, idiosyncratic and severe liver toxicity, which sometimes worsened despite stopping the drug, has been reported with sitaxentan,[1,2] and after 3 fatal cases it was withdrawn worldwide.[3,4] The EMEA announced that it would review the hepatotoxicity of the other endothelin receptor antagonists (see under Bosentan, p. 1327.3).

1. Hoeper MM, *et al*. Severe hepatitis associated with sitaxentan and response to glucocorticoid therapy. *Eur Respir J* 2009; **33:** 1518–19.
2. Lavelle A, *et al*. Sitaxentan-induced hepatic failure in two patients with pulmonary arterial hypertension. *Eur Respir J* 2009; **34:** 770–1.
3. EMEA. Thelin (sitaxentan) to be withdrawn due to cases of unpredictable serious liver injury (issued 10/12/10). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/l (accessed 13/01/11)
4. EMEA. Update on the withdrawal of Thelin (issued 16/12/2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/12/WC500099940.pdf (accessed 13/01/11)

Precautions

As for Bosentan, p. 1327.3. Sitaxentan is contra-indicated in patients with mild to severe hepatic impairment (Child-Pugh Class A to C).

Although, like bosentan, sitaxentan is teratogenic in *rats* and similar precautions apply, its effects on combined oral contraceptives may differ (see Interactions below).

Interactions

Sitaxentan is both an inhibitor of and a substrate for the cytochrome P450 isoenzyme CYP2C9 and interactions may therefore occur with other drugs that are either metabolised by, or inhibit, this isoenzyme. Plasma concentrations of oral anticoagulants such as warfarin may be increased.

Use with ciclosporin is contra-indicated as plasma concentrations of sitaxentan are greatly increased (see below).

Sitaxentan has increased exposure to ethinylestradiol and norethisterone in those taking oral contraceptives and may possibly increase the associated risk of thromboembolism.

Ciclosporin. Licensed product information for sitaxentan stated that its concentration was increased sixfold when given with ciclosporin 3.5 mg/kg twice daily. Although the mechanism of action is unknown, it has been postulated that sitaxentan sodium is a substrate for the organic anion transporting polypeptide (OATP) transporter protein and should therefore be used with caution with other, more potent, OATP inhibitors.

Pharmacokinetics

Peak plasma concentrations occur within 1 to 4 hours of an oral dose of sitaxentan sodium. Its absolute bioavailability is 70 to 100%. A high-fat meal delays the rate of absorption but does not affect the extent. Sitaxentan is more than 99% bound to plasma proteins, mainly albumin.

Sitaxentan is highly metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 to weakly active metabolites. About 50 to 60% of a dose is excreted in the urine with the remainder appearing in the faeces; less than 1% is excreted unchanged. Sitaxentan has a terminal elimination half-life of 10 hours and steady state is achieved within about 6 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Thelin†; ***Austria***: Thelin†; ***Belg.***: Thelin†; ***Canad.***: Thelin†; ***Cz.***: Thelin†; ***Denm.***: Thelin†; ***Fr.***: Thelin†; ***Ger.***: Thelin†; ***Gr.***: Thelin†; ***Irl.***: Thelin†; ***Ital.***: Thelin†; ***Neth.***: Thelin†; ***Port.***: Thelin†; ***Spain***: Thelin†; ***Swed.***: Thelin†; ***UK***: Thelin†.

Sodium Apolate *(BAN, rINN)*

Apolate de Sodium; Apolato de sodio; Lyapolate Sodium (USAN); Natrii Apolas; Natriumapolaatti; Natriumapolat; Sodium Lyapolate; Натрия Аполат.

Poly(sodium ethylenesulphonate).

$(C_2H_3NaO_3S)_n$

CAS — 25053-27-4.

ATC — C05BA02.

ATC Vet — QC05BA02.

UNII — 9461405D9F.

Profile

Sodium apolate is a synthetic heparinoid anticoagulant. It has been used in the topical treatment of haematomas and superficial thromboses and for the relief of sprains and contusions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pergalen.

Sodium Nitroprusside

Disodium (*OC*-6-22)-Pentakis(cyano-*C*)nitrosylferrate Dihydrate; Natrii Nitroprussias; Natrii Nitroprussias Dihydricus; Natrii Nitroprussicum; Natrio nitroprusidas; Natriumnitroprussid; Natriumnitroprussidi; Nitroprusiato sódico; Nitroprussid sodný dihydrát; Nitroprussidnatrium; Nitroprusszidnátrium; Sodium Nitroferricyanide Dihydrate; Sodium Nitroprussiate; Sodium, nitroprussiate de; Sodu nitroprusydek; Sodyum Nitroprusid; Нитропруссид Натрия.

Sodium nitrosylpentacyanoferrate(III) dihydrate.

$Na_2Fe(CN)_5NO,2H_2O$=298.0

CAS — 14402-89-2 (anhydrous sodium nitroprusside); 13755-38-9 (sodium nitroprusside dihydrate).

ATC — C02DD01.

ATC Vet — QC02DD01.

UNII — EAO03PE1TC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Sodium Nitroprusside). Reddish-brown crystals or powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Sodium Nitroprusside). Reddish-brown, practically odourless crystals or powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; insoluble in benzene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Sodium nitroprusside has been reported to be visually incompatible with cisatracurium besilate[1] and with levofloxacin[2] during simulated Y-site administration.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
2. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability in solution. Solutions of sodium nitroprusside decompose when exposed to light and must be protected during infusion by wrapping the container with aluminium foil or some other light-proof material. Nitroprusside will react with minute quantities of organic and inorganic substances forming highly coloured products. If this occurs the solution should be discarded. Solutions should not be used more than 24 hours after preparation.

The instability of sodium nitroprusside solutions has been the subject of considerable investigation. Although stated to be more stable in acid than in alkaline solution,[1] a later study[2] found that whereas the initial light-induced darkening of a 1% solution was independent of pH, further degradation leading to the development of a blue precipitate required an acid pH. If protected from light by wrapping in aluminium foil, sodium nitroprusside 50 or 100 micrograms/mL was found to be stable in 5% glucose, lactated Ringer's, and normal saline solutions for 48 hours.[3] In clinical practice the infusion container should be opaque or protected with foil, but an amber giving set may be used, to allow visual monitoring.[4,5]

Various substances have been reported to increase the stability of nitroprusside solutions, including dimethyl sulfoxide,[6] glycerol,[1] sodium citrate,[1] and other salts with anionic chelating potential such as sodium acetate or phosphate.[1] In contrast sodium bisulfite and the hydroxybenzoates are reported to reduce stability.[1]

1. Schumacher GE. Sodium nitroprusside injection. *Am J Hosp Pharm* 1966; **23:** 532.
2. Hargrave RE. Degradation of solutions of sodium nitroprusside. *J Hosp Pharm* 1974; **32:** 188–91.
3. Mahony C, *et al.* In vitro stability of sodium nitroprusside solutions for intravenous administration. *J Pharm Sci* 1984; **73:** 838–9.
4. Davidson SW, Lyall D. Sodium nitroprusside stability in light-protective administration sets. *Pharm J* 1987; **239:** 599–601.
5. Lyall D. Sodium nitroprusside stability. *Pharm J* 1988; **240:** 5.
6. Asker AF, Gragg R. Dimethyl sulfoxide as a photoprotective agent for sodium nitroprusside solutions. *Drug Dev Ind Pharm* 1983; **9:** 837–48.

Uses and Administration

Sodium nitroprusside is a short-acting hypotensive drug with a duration of action of 1 to 10 minutes. It produces peripheral vasodilatation and reduces peripheral resistance by a direct action on both veins and arterioles. It has been termed a nitrovasodilator because it releases nitric oxide *in vivo*. Its effects appear within a few seconds of intravenous infusion. Sodium nitroprusside is used in the treatment of hypertensive crises (p. 1251.1) and to produce controlled hypotension during general anaesthesia. It has also been used to reduce preload and afterload in severe heart failure (p. 1262.3) including that associated with myocardial infarction (p. 1257.1).

It is given by continuous intravenous infusion of a solution containing 50 to 200 micrograms/mL. A controlled infusion device must be used. The solution should be prepared immediately before use by dissolving sodium nitroprusside in glucose 5% and then diluting with glucose 5%; the solution must be protected from light during infusion. Blood pressure should be monitored closely and care should be taken to prevent extravasation. In general, treatment should not continue for more than 72 hours. If required for several days, concentrations of cyanide should be monitored; the blood concentration should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. Thiocyanate concentrations in blood should also be measured if infusion continues for more than 72 hours and should not exceed 100 micrograms/mL. Since rebound hypertension has been reported when sodium nitroprusside is withdrawn, the infusion should be tailed off gradually over 10 to 30 minutes.

For **hypertensive crises** in patients not receiving antihypertensive drugs, an initial dose of 0.3 to 1.5 micrograms/kg per minute may be given, increasing gradually under close supervision until the desired reduction in blood pressure is achieved. The average dose required to maintain the blood pressure 30 to 40% below the pretreatment diastolic blood pressure is 3 micrograms/kg per minute and the usual dose range is 0.5 to 6 micrograms/kg per minute. Lower doses should be used in patients already receiving other antihypertensives. The maximum recommended rate is about 8 micrograms/kg per minute in the UK, and 10 micrograms/kg per minute in the USA; infusions at these rates should be used for no longer than 10 minutes and should be stopped after 10 minutes if there is no response. If there is a response, sodium nitroprusside should ideally be given for only a few hours to avoid the risk of cyanide toxicity. Treatment with an oral antihypertensive should be introduced as soon as possible.

For the **induction of hypotension** during anaesthesia a maximum dose of 1.5 micrograms/kg per minute is recommended.

In **heart failure** an initial dose of 10 to 15 micrograms/minute has been used, increasing by 10 to 15 micrograms/minute every 5 to 10 minutes according to response. The usual dosage range is 10 to 200 micrograms/minute.

Sodium nitroprusside has also been used as a reagent for detecting ketones in urine.

Administration in children. Although experience is more limited than with adults, sodium nitroprusside has been successfully used in infants and children. Continuous infusion of nitroprusside at a rate of 2 to 4 micrograms/kg per minute for 28 days was reported[1] in an 11-year-old child with refractory hypertension, without any signs of thiocyanate toxicity. In a series of 58 neonates with cardiovascular disorders or respiratory distress syndrome,[2] sodium nitroprusside was given in a usual initial dose of 250 to 500 nanograms/kg per minute, and the rate was then repeatedly doubled at intervals of 15 to 20 minutes until the desired effect was achieved, adverse effects supervened, or it was judged ineffective. The maximum rate did not exceed 6 micrograms/kg per minute. Infusion of sodium nitroprusside in doses of 0.5 to 8 micrograms/kg per minute to produce controlled reduction of blood pressure has also been reported[3] in 28 children with hypertensive crises; 16 had also received labetalol.[3] The risks of toxicity in paediatric patients have been reviewed.[4,5] One review[4] of sodium nitroprusside use in paediatric surgical patients found that infusions of 1.8 micrograms/kg or more per minute were associated with a greater risk of cyanide toxicity.

Although sodium nitroprusside is unlicensed in the UK for use in children, the *BNFC* suggests that neonates, infants, and children may be given an initial continuous intravenous infusion of 500 nanograms/kg per minute, which may be increased in steps of 200 nanograms/kg per minute to a maximum of 8 micrograms/kg per minute (or a maximum of 4 micrograms/kg per minute if given for longer than 24 hours).

For the use of inhaled sodium nitroprusside in neonates with pulmonary hypertension see below.

1. Luderer JR, *et al.* Long-term administration of sodium nitroprusside in childhood. *J Pediatr* 1977; **91:** 490–1.
2. Benitz WE, *et al.* Use of sodium nitroprusside in neonates: efficacy and safety. *J Pediatr* 1985; **106:** 102–10.
3. Deal JE, *et al.* Management of hypertensive emergencies. *Arch Dis Child* 1992; **67:** 1089–92.
4. Moffett BS, Price JF. Evaluation of sodium nitroprusside toxicity in pediatric cardiac surgical patients. *Ann Pharmacother* 2008; **42:** 1600–4.
5. Thomas C, *et al.* Sodium-nitroprusside-induced cyanide toxicity in pediatric patients. *Expert Opin Drug Safety* 2009; **8:** 599–602.

Ergotamine poisoning. For the use of sodium nitroprusside in the treatment of cyanosis of the extremities due to ergotamine overdosage, see Cardiovascular Effects, p. 674.3.

Pulmonary hypertension. Inhaled sodium nitroprusside has been used[1,2] as an alternative to inhaled nitric oxide in the treatment of hypoxic neonates with pulmonary hypertension (p. 1278.2).

1. Palhares DB, *et al.* Endotracheal inhalatory sodium nitroprusside in severely hypoxic newborns. *J Perinat Med* 1998; **26:** 219–24.
2. Mestan KKL, *et al.* Cardiopulmonary effects of nebulized sodium nitroprusside in term infants with hypoxic respiratory failure. *J Pediatr* 2003; **143:** 640–3.

Adverse Effects

Sodium nitroprusside rapidly reduces blood pressure and is converted in the body to cyanide and then thiocyanate. Its adverse effects can be attributed mainly to excessive hypotension and excessive cyanide accumulation; thiocyanate toxicity may also occur, especially in patients with renal impairment. Intravenous infusion of sodium nitroprusside may produce nausea and vomiting, apprehension, headache, dizziness, restlessness, perspiration, palpitations, retrosternal discomfort, abdominal pain, and muscle twitching, but these effects may be reduced by slowing the infusion rate.

An excessive amount of cyanide in plasma (more than 80 nanograms/mL), because of overdosage or depletion of endogenous thiosulfate (which converts cyanide to thiocyanate *in vivo*), may result in tachycardia, sweating, hyperventilation, arrhythmias, and profound metabolic acidosis. Metabolic acidosis may be the first sign of cyanide toxicity. Methaemoglobinaemia may also occur.

Adverse effects attributed to thiocyanate include headache, tinnitus, miosis, arthralgia, muscle cramps, and hyperreflexia; confusion, hallucinations, and convulsions have also been reported.

Other adverse effects include thrombocytopenia and phlebitis.

Effects on the blood. *THROMBOCYTOPENIA.* Platelet counts decreased in 7 of 8 patients with heart failure 1 to 6 hours after intravenous infusion of nitroprusside was started.[1] The counts began to return to normal 24 hours after the infusion was stopped.

1. Mehta P, *et al.* Nitroprusside lowers platelet count. *N Engl J Med* 1978; **299:** 1134.

Effects on the gastrointestinal tract. Five out of 38 patients who were given sodium nitroprusside intravenously for controlled hypotension during surgery developed symptoms of adynamic ileus postoperatively.[1] The symptoms could have been secondary to intestinal ischaemia due to diminished mesenteric arterial blood flow. However, other explanations have been proposed including sympathetic stimulation[2,3] or the concomitant use of opioid analgesics.[4]

1. Chen JW, *et al.* Adynamic ileus following induced hypotension. *JAMA* 1985; **253:** 633.
2. Gelman S. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.
3. Lampert BA. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.
4. Lemmo J, Karnes J. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.

Effects on intracranial pressure. A significant increase in intracranial pressure while the mean blood pressure was 80 or 90% of initial values was reported[1] in 14 normocapnic patients given an infusion of sodium nitroprusside to

produce controlled hypotension before neurosurgery; values reverted towards normal at mean blood pressures of 70% of controls. A similar but insignificant trend occurred in 5 hypocapnic patients. In another report[2] a rise in intracranial pressure was noted after the use of nitroprusside in a patient with Reye's syndrome.

1. Turner JM, *et al.* Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 1977; **49:** 419–24.
2. Griswold WR, *et al.* Nitroprusside-induced intracranial hypertension. *JAMA* 1981; **246:** 2679–80.

Phlebitis. Acute transient phlebitis has occurred after infusion of sodium nitroprusside.[1]

1. Miller R, Stark DCC. Acute phlebitis from nitroprusside. *Anesthesiology* 1978; **49:** 372.

Treatment of Adverse Effects

Adverse effects due to excessive hypotension may be treated by slowing or stopping the infusion.

For details of the treatment of cyanide poisoning see Hydrocyanic Acid, p. 2156.2. Thiocyanate can be removed by dialysis.

Precautions

Sodium nitroprusside should not be used in the presence of compensatory hypertension (for example, in arteriovenous shunts or coarctation of the aorta). It should be used with caution, if at all, in patients with hepatic impairment, and in patients with low plasma-cobalamin concentrations or Leber's optic atrophy. It should also be used with caution in patients with impaired renal or pulmonary function and with particular caution in patients with impaired cerebrovascular circulation. Thiocyanate, a metabolite of sodium nitroprusside, inhibits iodine binding and uptake and sodium nitroprusside should be used with caution in patients with hypothyroidism. The blood-thiocyanate concentration should be monitored if treatment continues for more than 3 days and should not exceed 100 micrograms/mL although toxicity may be apparent at lower thiocyanate concentrations. Thiocyanate concentrations do not reflect cyanide toxicity and cyanide concentrations should also be monitored; the blood concentration of cyanide should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. The acid–base balance should also be monitored. Care should be taken to ensure that extravasation does not occur. Sodium nitroprusside should not be withdrawn abruptly due to the risk of rebound effects.

Aortic stenosis. Vasodilators such as sodium nitroprusside are usually contra-indicated in conditions where cardiac outflow is obstructed since cardiac output cannot increase to compensate for the fall in blood pressure. However, a study[1] in patients with aortic stenosis and severe left ventricular dysfunction found that sodium nitroprusside was well tolerated and that it rapidly and markedly improved cardiac function.

1. Khot UN, *et al.* Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003; **348:** 1756–63.

Pregnancy. Although there are concerns that nitroprusside given to the mother might produce cyanide toxicity in the fetus, a systematic review[1] was unable to find sufficient evidence to determine the risk.

1. Sass N, *et al.* Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J* 2007; **125:** 108–11.

Tachyphylaxis. Tachyphylaxis to sodium nitroprusside was associated with high plasma concentrations of cyanide without metabolic acidosis in 3 patients undergoing hypotensive anaesthesia.[1]

1. Cottrell JE, *et al.* Nitroprusside tachyphylaxis without acidosis. *Anesthesiology* 1978; **49:** 141–2.

Withdrawal. Rebound haemodynamic changes, including hypertension and increased heart rate, occurred 10 to 30 minutes after stopping intravenous sodium nitroprusside infusion in 20 patients with heart failure.[1] The changes generally resolved spontaneously within 1 to 3 hours and produced only minimal exacerbation of symptoms in most patients, although 3 developed pulmonary oedema 20 to 30 minutes after stopping the infusion, needing restarting of nitroprusside in 2 cases. A study[2] investigating a possible mechanism for this effect found that plasma-renin concentrations were increased during infusion of nitroprusside and remained elevated for 30 minutes after the infusion was stopped. It was suggested that this persistence of elevated plasma-renin concentrations after clearance of short-lived nitroprusside may be responsible for the rebound effects.

1. Packer M, *et al.* Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. *N Engl J Med* 1979; **301:** 1193–7.
2. Cottrell JE, *et al.* Rebound hypertension after sodium nitroprusside-induced hypotension. *Clin Pharmacol Ther* 1980; **27:** 32–6.

Interactions

Enhanced hypotension should be expected if sodium nitroprusside is used with other antihypertensives or drugs that produce hypotension.

Alteplase. Sodium nitroprusside infusion prolonged the fibrinolytic activity of alteplase when given to *animals*; use of nitrovasodilators with alteplase may be responsible for the enhanced bleeding tendency seen in some patients on thrombolytic therapy.[1]

1. Korbut R, *et al.* Prolongation of fibrinolytic activity of tissue plasminogen activator by nitrovasodilators. *Lancet* 1990; **335:** 669.

Pharmacokinetics

Sodium nitroprusside is rapidly metabolised to cyanide in erythrocytes and smooth muscle and, *in vivo*, this is followed by the release of nitric oxide, the active metabolite. Cyanide is further metabolised in the liver to thiocyanate, which is slowly excreted in the urine; this metabolism is mediated by the enzyme rhodanase and requires the presence of thiosulfate. The plasma half-life of thiocyanate is reported to be about 3 days, but may be much longer in patients with renal impairment.

Reviews.

1. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet* 1984; **9:** 239–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Doketrol; Niprusodio; Nitroprus; ***Braz.***: Nipride; Nitropresabbott; Nitroprus; ***Canad.***: Nipride; ***Cz.***: Nipruss; ***Fr.***: Nitriate; ***Ger.***: Nipruss; ***Gr.***: Nitriate; ***India***: Nipress; Sonide; ***Israel***: Nipruss; ***Jpn***: Nitopro; ***Rus.***: Naniprus (Нанипрус); ***S.Afr.***: Hypoten; SNP†; ***Spain***: Nitroprussiat; ***Turk.***: Nipruss; ***USA***: Nitropress.

Pharmacopoeial Preparations
BP 2014: Sodium Nitroprusside Infusion;
USP 36: Sodium Nitroprusside for Injection.

Sotalol Hydrochloride

(BANM, USAN, rINNM) ⊗

d,l-Sotalol Hydrochloride; Hidrocloruro de sotalol; MJ-1999; Sotalol, chlorhydrate de; Sotalol, hidrocloruro de; Sotalol Hidroklorür; Sotalolhydrochlorid; Sotalol-hydrochlorid; Sotalolhydroklorid; Sotaloli Hydrochloridum; Sotalolihydrokloridi; Sotalolio hidrochloridas; Szotalol-hidroklorid; Соталола Гидрохлорид.

4′-(1-Hydroxy-2-isopropylaminoethyl)methanesulphonanilide hydrochloride.

$C_{12}H_{20}N_2O_3S,HCl$=308.8

CAS — 3930-20-9 (sotalol); 959-24-0 (sotalol hydrochloride).
ATC — C07AA07.
ATC Vet — QC07AA07.
UNII — HEC37C70XX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sotalol Hydrochloride). A white or almost white powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Sotalol Hydrochloride). A white to off-white powder. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform.

Stability. Suspensions of sotalol hydrochloride 5 mg/mL made using either commercially available or extemporaneously prepared vehicles were found[1] to be stable for up to 3 months when stored at 4 degrees or 25 degrees. Prolonged storage at 25 degrees was not recommended, however, because of the risk of microbial growth.

1. Nahata MC, Morosco RS. Stability of sotalol in two liquid formulations at two temperatures. *Ann Pharmacother* 2003; **37:** 506–9.

Uses and Administration

Sotalol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack both intrinsic sympathomimetic and membrane-stabilising properties. In addition to the class II antiarrhythmic activity of beta blockers, sotalol lengthens the duration of the action potential resulting in class III antiarrhythmic activity. For a classification and explanation of antiarrhythmic activity, see p. 1243.1.

Sotalol is used in the management of ventricular and supraventricular arrhythmias (p. 1266.1). Because of its proarrhythmic effects, it is usually reserved for severe or life-threatening arrhythmias, and it should not be used in patients with asymptomatic ventricular arrhythmias. Although it was formerly used for its beta-blocking effects in the management of angina pectoris, hypertension, and myocardial infarction, it is no longer recommended for these indications because of the risk of precipitating arrhythmias.

Sotalol is given as the hydrochloride. Treatment should be started in hospital with suitable monitoring facilities. The QT interval should be assessed before the start of treatment and whenever the dosage is adjusted (see Precautions p. 1499.2); plasma-electrolyte concentrations and renal function should also be monitored. The dose should be reduced in patients with renal impairment (see p. 1499.1).

The usual initial oral dose of sotalol hydrochloride is 80 mg daily, as a single dose or in two divided doses. The dosage is then individualised according to response, and doses are increased gradually allowing 2 or 3 days between increments. US licensed product information recommends a higher initial dose of 80 mg twice daily and this should not be increased for at least 3 days. Most patients respond to doses of 160 to 320 mg daily (usually given in two divided doses). Some patients with ventricular arrhythmias may require doses as high as 640 mg daily.

Sotalol may be given intravenously to control acute arrhythmias, to substitute for oral therapy, and for programmed electrical stimulation. To control acute arrhythmias, sotalol hydrochloride is given in a dose of 20 to 120 mg (500 to 1500 micrograms/kg) intravenously over 10 minutes. This dose may be repeated every 6 hours if necessary. To substitute for oral therapy an intravenous infusion of 200 to 500 micrograms/kg per hour may be used. The total daily dose should not exceed 640 mg. (In the USA, a dose of 75 mg infused over 5 hours is recommended to replace an oral dose of 80 mg.) For programmed electrical stimulation (to test antiarrhythmic efficacy) an initial dose of 1.5 mg/kg is given over 10 to 20 minutes, followed by an intravenous infusion of 200 to 500 micrograms/kg per hour.

Sotalol is used as a racemic mixture; *d*-sotalol (dexsotalol; (+)-sotalol) has also been investigated as an antiarrhythmic but development was stopped when it was found to increase mortality (see Action, below).

General references.

1. Fitton A, Sorkin EM. Sotalol: an updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. *Drugs* 1993; **46:** 678–719.
2. Nappi JM, McCollam PL. Sotalol: a breakthrough antiarrhythmic? *Ann Pharmacother* 1993; **27:** 1359–68.
3. Zanetti LAF. Sotalol: a new class III antiarrhythmic agent. *Clin Pharm* 1993; **12:** 883–91.
4. Hohnloser SH, Woosley RL. Sotalol. *N Engl J Med* 1994; **331:** 31–8.
5. Anderson JL, Prystowsky EN. Sotalol: an important new antiarrhythmic. *Am Heart J* 1999; **137:** 388–409.
6. Chaki AL, *et al.* Sotalol as adjunctive therapy to implantable cardioverter-defibrillators in heart failure patients. *Congest Heart Fail* 2009; **15:** 144–7.

Action. Sotalol is used as the racemic mixture of the two stereoisomers, *d*-sotalol (dexsotalol; (+)-sotalol) and *l*-sotalol ((-)-sotalol). A comparison of the effects of *d*-sotalol and racemic sotalol in 6 healthy subjects[1] showed that the beta-blocking activity resided almost entirely in the *l*-isomer, while the effects on the QT interval, which are consistent with type III antiarrhythmic activity, appear to be due to both isomers. A study in 8 healthy subjects also showed a lack of beta blockade by *d*-sotalol.[2] This would suggest that the electrophysiological effects of sotalol are unrelated to its beta-blocking properties. *d*-Sotalol has been investigated as an antiarrhythmic.[3] However, a preliminary placebo-controlled study in patients with myocardial infarction at high risk of arrhythmia due to impaired left ventricular function was terminated early when increased mortality was seen in the treatment group.[4,5]

1. Johnston GD, *et al.* A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers. *Br J Clin Pharmacol* 1985; **20:** 507–10.
2. Yasuda SU, *et al.* d-Sotalol reduces heart rate in vivo through a β-adrenergic receptor-independent mechanism. *Clin Pharmacol Ther* 1993; **53:** 436–42.
3. Advani SV, Singh BN. Pharmacodynamic, pharmacokinetic and antiarrhythmic properties of d-sotalol, the dextro-isomer of sotalol. *Drugs* 1995; **49:** 664–79.
4. Choo V. SWORD slashed. *Lancet* 1994; **344:** 1358.
5. Waldo AL, *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; **348:** 7–12. Correction. *ibid.*; 416.

Administration. Reference to the development of an intravenous dosage regimen for sotalol.[1]

1. Somberg JC, *et al.* Developing a safe intravenous sotalol dosing regimen. *Am J Ther* 2010; **17:** 365–72.

Administration in children. Sotalol has been used to treat both ventricular and supraventricular arrhythmias in children aged from newborn to adolescent;[1-3] it appears to be effective and well-tolerated, although proarrhythmic effects may occur. Neonates may be more sensitive to the QT-prolonging effects of sotalol[3] and lower doses may be appropriate. In the UK, the *BNFC* recommends the following oral doses of sotalol hydrochloride:

- Neonates: initial dose 1 mg/kg twice daily, increased as necessary every 3 to 4 days to a maximum of 4 mg/kg twice daily

- Children aged 1 month to 12 years: initial dose 1 mg/kg twice daily, increased as necessary every 2 to 3 days to a maximum of 4 mg/kg twice daily (maximum total dose 80 mg twice daily)

Licensed product information in the USA recommends doses of sotalol hydrochloride based on body surface area. Children aged 2 years and over may be given an initial dose of 30 mg/m² three times daily, increased as necessary at intervals of at least 36 hours to a maximum of 60 mg/m² three times daily. For children under 2 years of age the dose should be further reduced, and nomograms are available providing age-specific recommendations.

In children with refractory supraventricular tachycardia, sotalol has been given with flecainide; in a study[4] in children aged under 1 year, doses used ranged from 100 to 250 mg/m² daily of sotalol and from 40 to 150 mg/m² daily of flecainide.

Sotalol has also been used transplacentally to treat fetal tachycardias, including atrial flutter and supraventricular tachycardia. It may be effective as second-line therapy in addition to digoxin,[5] and has also been used first-line.[6,7] However, one retrospective study[6] of 21 fetuses given sotalol transplacentally found that it was more effective in atrial flutter than in supraventricular tachycardia; mortality was also higher in fetuses with supraventricular tachycardia, and the authors therefore suggested that sotalol should only be used in resistant cases.

1. Çeliker A, *et al*. Sotalol in treatment of pediatric cardiac arrhythmias. *Pediatr Int* 2001; **43:** 624–30.
2. Beaufort-Krol GCM, Bink-Boelkens MTE. Effectiveness of sotalol for atrial flutter in children after surgery for congenital heart disease. *Am J Cardiol* 1997; **79:** 92–4.
3. Läer S, *et al*. Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. *J Am Coll Cardiol* 2005; **46:** 1322–30.
4. Price JF, *et al*. Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39:** 517–20.
5. Sonesson S-E, *et al*. Foetal supraventricular tachycardia treated with sotalol. *Acta Paediatr* 1998; **87:** 584–7.
6. Oudijk MA, *et al*. Sotalol in the treatment of fetal dysrhythmias. *Circulation* 2000; **101:** 2721–6.
7. Rebelo M, *et al*. Sotalol in the treatment of fetal tachyarrhythmia. *Rev Port Cardiol* 2006; **25:** 477–81.

Administration in renal impairment. Sotalol is excreted mainly unchanged by the kidneys and may accumulate in renal impairment. The usual daily dosage (see Uses and Administration, p. 1498.2) should therefore be reduced, either by decreasing the size of each dose, or by increasing the interval between doses. UK licensed product information for oral or intravenous sotalol recommends the following doses based on creatinine clearance (CC):

- CC 30 to 60 mL/minute: half usual dose
- CC 10 to 30 mL/minute: quarter usual dose
- CC less than 10 mL/minute: not recommended

Oral dosage recommendations in the USA depend on both the indication and CC, and incremental increases should not be made until 5 or 6 doses have been given. In the treatment of ventricular arrhythmias, licensed product information recommends that in renal impairment doses should be given at the following intervals:

- CC 30 to 59 mL/minute: every 24 hours
- CC 10 to 29 mL/minute: every 36 to 48 hours
- CC less than 10 mL/minute: dosage should be individualised

For the treatment of atrial fibrillation, the same dosage intervals are recommended but sotalol is contra-indicated if CC is less than 40 mL/minute.

In patients who require intravenous sotalol hydrochloride, US recommendations are that the dosage frequency be reduced to once daily in those with CC between 60 and 40 mL/minute; a recommended initial dose is 75 mg daily, infused over 5 hours. It should be avoided completely (regardless of indication) in those with CC less than 40 mL/minute.

In a study of 10 hypertensive patients with varying degrees of renal impairment,[1] the apparent first-order elimination rate constant and plasma clearance of oral sotalol correlated with glomerular filtration rate. Another study[2] compared the kinetics of oral sotalol in patients with normal renal function, renal impairment, and renal failure. Elimination half-lives of 8.1 and 24.2 hours were reported in patients with CC above 39 mL/minute and between 8 and 38 mL/minute, respectively. It was suggested that an increase in the dosage interval to 48 or 72 hours may be necessary to compensate for longer half-lives. Caution is required when sotalol is used in patients on dialysis; a half-life of 33.9 hours was reported in patients with renal failure but this fell to 5.8 hours during dialysis which removed about 43% of sotalol.

1. Berglund G, *et al*. Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. *Eur J Clin Pharmacol* 1980; **18:** 321–6.
2. Blair AD, *et al*. Sotalol kinetics in renal insufficiency. *Clin Pharmacol Ther* 1981; **29:** 457–63.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Torsade de pointes has been reported in patients given sotalol, usually due to prolongation of the QT interval. The QT interval should be monitored: extreme caution is required if the QT interval exceeds 500 milliseconds and sotalol should be stopped or the dose reduced if the QT interval exceeds 550 milliseconds. As hypokalaemia or hypomagnesaemia may predispose patients to arrhythmias, serum-electrolyte concentrations should be monitored before and during treatment with sotalol.

Sotalol should be used with caution in renal impairment (see under Uses and Administration, above) and is contra-indicated in patients whose creatinine clearance is less than 10 mL/minute.

Breast feeding. Sotalol is distributed into breast milk and milk to serum ratios have been reported[1-3] to range from 2.2 to 8.8. In one report[2] it was calculated that a breast-fed infant might ingest 20 to 23% of a maternal dose; however, no bradycardia was noted in the infant in this study. The American Academy of Pediatrics states[4] that there have been no reports of clinical effects in breast-fed infants whose mothers were receiving sotalol and that therefore it may be considered to be usually compatible with breast feeding.

1. O'Hare MF, *et al*. Sotalol as a hypotensive agent in pregnancy. *Br J Obstet Gynaecol* 1980; **87:** 814–20.
2. Hackett LP, *et al*. Excretion of sotalol in breast milk. *Br J Clin Pharmacol* 1990; **29:** 277–8.
3. Wagner X, *et al*. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119:** 700–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sotalol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

There is an increased risk of precipitating ventricular arrhythmias if sotalol is given with other drugs that prolong the QT interval, and use with the following drugs is therefore not recommended: class Ia antiarrhythmics (including disopyramide, procainamide, and quinidine), amiodarone, phenothiazine antipsychotics, tricyclic antidepressants, certain antihistamines (astemizole or terfenadine), cisapride, erythromycin, halofantrine, pentamidine, quinolones, sultopride, and vincamine. Caution is required if sotalol is given with drugs that cause electrolyte disturbances, such as diuretics, since this also increases the risk of arrhythmias.

Other interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Sotalol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 4 hours after a dose. The plasma elimination half-life is about 10 to 20 hours. Sotalol has low lipid solubility. Very little is metabolised and it is excreted unchanged in the urine. Binding to plasma proteins is reported to be low. It crosses the placenta and is distributed into breast milk; concentrations in milk may be higher than those in maternal serum (see Breast Feeding, above). Only small amounts are reported to cross the blood-brain barrier and enter the CSF. Sotalol is removed by dialysis.

General references.

1. Singh BN, *et al*. Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs* 1987; **34:** 311–49.

Pregnancy. The systemic clearance of sotalol in 6 healthy women after an intravenous dose was significantly higher during pregnancy than in the postnatal period, and the mean elimination half-life was shorter (6.6 versus 9.3 hours), although the latter difference was not significant.[1] Clearance after an oral dose was also higher during pregnancy than afterwards, but half-lives (10.9 versus 10.3 hours) and mean bioavailability were similar. The changes were probably due to alterations in renal function in the antenatal period.

In a study[2] of transplacental therapy, sotalol was found to cross the placenta easily and completely, with steady-state plasma concentrations similar in mother and fetus. Sotalol accumulated in the amniotic fluid but not in the fetus; it was not associated with fetal growth restriction.

1. O'Hare MF, *et al*. Pharmacokinetics of sotalol during pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 521–4.
2. Oudijk MA, *et al*. Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. *J Am Coll Cardiol* 2003; **42:** 765–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sotacor; ***Austral.***: Cardol; Solavert; Sotacor; Sotahexal†; ***Austria***: Sotacor; Sotahexal; Sotamed; Sotastad; ***Belg.***: Sotalex; ***Braz.***: Sotacor; Sotahexal; ***Canad.***: Rylosol; ***Chile***: Hipecor; ***China***: Ji Di (济迪); Jin Lv Xin (金绿欣); Sotacor (施太可); Tan Shi (坦释); Wei Te (伟特); Xi An Lin (喜安林); Yi Huan (伊缓); Yuan Qi (元齐); ***Cz.***: Sotahexal; Sotalex†; ***Fin.***: Sotacor; Sotalin†; ***Fr.***: Sotalex; ***Ger.***: Darob†; Jutalex†; Rentibloc; Sota-Puren†; Sota-saar†; Sota†; Sotabeta; Sotagamma; Sotahexal†; Sotalex; Sotalodoc†; Sotastad†; ***Gr.***: Sotalex; ***Hong Kong***: Sotacor†; ***Hung.***: Sotahexal; Sotalex; ***Irl.***: Sotacor; Sotoger; ***Ital.***: Rytmobeta; Sotalex; ***Jpn***: Sotacor; ***Malaysia***: Sotacor; ***Mex.***: Sotaper; ***Neth.***: Sotacor†; ***Norw.***: Sotacor†; ***NZ***: Sotacor; Sotahexal†; ***Philipp.***: Sotalex†; ***Pol.***: Biosotal; Darob; Sotahexal; ***Port.***: Darob; ***Rus.***: Sotahexal (Сотагексал); Sotalex (Соталекс); ***S.Afr.***: Sotacor; Sotahexal; ***Singapore***: Sotacor; SotaHexal; ***Spain***: Sotapor; ***Swed.***: Sotacor; ***Switz.***: Sotalex; ***Turk.***: Darob; Sotarit; Talozin; ***UK***: Beta-Cardone; Sotacor; ***Ukr.***: Soritmik (Соритмік); Sotahexal (Сотагексал)†; ***USA***: Betapace.

Multi-ingredient Preparations. ***S.Afr.***: Sotazide†.

Pharmacopoeial Preparations

BP 2014: Sotalol Injection; Sotalol Tablets;
USP 36: Sotalol Hydrochloride Oral Suspension; Sotalol Hydrochloride Tablets.

Spirapril Hydrochloride *(BANM, USAN, rINNM)*

Espirapril, hidrocloruro de; Hidrocloruro de espirapril; Sch-33844; Spiraprilihydrokloridi; Spirapril, Chlorhydrate de; Spirapril-hydrochlorid; Spiraprilhydroklorid; Spiraprili hydrochloridum; Spiraprilio hidrochloridas; TI-211-950; Спираприла Гидрохлорид.

(*S*)-7-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid hydrochloride.

$C_{22}H_{30}N_2O_5S_2$,HCl=503.1

CAS — 83647-97-6 (spirapril); 94841-17-5 (spirapril hydrochloride).

ATC — C09AA11.

ATC Vet — QC09AA11.

UNII — OCC25LM897.

Pharmacopoeias. *Eur.* (see p. vii) includes the monohydrate.

Ph. Eur. 8: (Spirapril Hydrochloride Monohydrate). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in acetonitrile; practically insoluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Spirapril is an ACE inhibitor (p. 1282.2) that is used in the management of hypertension (p. 1251.1). It owes its activity to the diacid spiraprilat, to which it is converted after oral doses. It is given orally as the hydrochloride in a usual maintenance dose of 6 mg once daily.

References.

1. Noble S, Sorkin EM. Spirapril: a preliminary review of its pharmacology and therapeutic efficacy in the treatment of hypertension. *Drugs* 1995; **49:** 750–66.
2. Widimský J, *et al*. Czech and Slovak spirapril intervention study (CASSIS): a randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur J Clin Pharmacol* 1995; **49:** 95–102.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Quadropril; ***Cz.***: Renpress; ***Ger.***: Quadropril; ***Hung.***: Quadropril†; ***Ital.***: Renormax; Setrilan; ***Rus.***: Quadropril (Квадроприл); ***Spain***: Renormax†; Renpress†; ***Ukr.***: Quadropril (Квадроприл).

Spironolactone *(BAN, rINN)* ⊗

Espironolactona; SC-9420; Spirolactone; Spironolacton; Spironolactonum; Spironolakton; Spironolaktonas; Spironolaktoni; Спиронолактон.

7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone; (7α,17α)-7-(Acetylthio)-17-hydroxy-3-oxo-pregn-4-ene-21-carboxylic acid γ-lactone.

$C_{24}H_{32}O_4S$=416.6

CAS — 52-01-7.

ATC — C03DA01.

ATC Vet — QC03DA01.
UNII — 27O7W4T232.

NOTE. Compounded preparations of spironolactone may be represented by the following names:
- Co-flumactone (*BAN*)—spironolactone and hydroflumethiazide in equal parts (w/w)
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Spironolactone). A white or yellowish-white powder. Practically insoluble in water; soluble in alcohol. It exhibits polymorphism. Protect from light.

USP 36: (Spironolactone). A light cream-coloured to light tan, crystalline powder with a faint to mild mercaptan-like odour. Practically insoluble in water; soluble in alcohol and in ethyl acetate; freely soluble in chloroform and in benzene; slightly soluble in methyl alcohol and in fixed oils.

Stability. There was no appreciable loss of spironolactone from extemporaneously prepared suspensions of spironolactone, 2.5, 5 and 10 mg/mL, in a cherry syrup after storage for 2 weeks at 5 degrees or 30 degrees or at ambient room temperature under intense fluorescent light.[1] Degradation was less than 5% for samples stored for 4 weeks, but was more noticeable in suspensions with a higher initial concentration. There were no changes in colour or odour. Bacterial and fungal counts were well within acceptable limits after 4 weeks at 30 degrees.

1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm* 1989; **46:** 2040–2.

Uses and Administration

Spironolactone, a steroid with a structure resembling that of the natural adrenocortical hormone aldosterone, acts on the distal portion of the renal tubule as a competitive antagonist of aldosterone. It acts as a potassium-sparing diuretic, increasing sodium and water excretion and reducing potassium excretion.

Spironolactone is reported to have a relatively slow onset of action, requiring 2 or 3 days for maximum effect, and a similarly slow diminishment of action over 2 or 3 days on stopping.

Spironolactone is used in the management of heart failure, both to treat refractory oedema and in lower doses as an adjunct to standard therapy (see below). It is also used for refractory oedema associated with cirrhosis of the liver (with or without ascites, p. 1276.2), or the nephrotic syndrome, and in ascites associated with malignancy. It is frequently given with the thiazides, furosemide, or similar diuretics, where it adds to their natriuretic but diminishes their kaliuretic effects, hence conserving potassium in those at risk from hypokalaemia. Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics, is discussed under Effects on the Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p. 1404.2. It has been used in the treatment of essential hypertension (in lower doses than for oedema), but in the UK is no longer recommended for use in either essential hypertension or idiopathic oedema; doubts have been expressed over its safety during long-term administration.

Spironolactone is also used in the diagnosis and treatment of primary hyperaldosteronism (p. 1501.1).

Other conditions in which spironolactone has been tried on the basis of its anti-androgenic properties include hirsutism, particularly in the polycystic ovary syndrome.

In the treatment of **oedema**, spironolactone is usually given in an initial oral dose of 100 mg daily, subsequently adjusted as necessary; some patients may require doses of up to 400 mg daily. In hepatic cirrhosis with ascites and oedema, patients with a urinary sodium/potassium ratio greater than 1 may be given an initial dose of spironolactone 100 mg daily while patients with a ratio of less than 1 may be given initial doses of 200 to 400 mg daily.

Spironolactone is given in doses of 400 mg daily in the presumptive diagnosis of primary **hyperaldosteronism**; in doses of 100 to 400 mg daily for the pre-operative management of hyperaldosteronism; and in the lowest effective dosage for long-term maintenance therapy in the absence of surgery.

For doses in children, see below.

Potassium supplements should not be given with spironolactone.

References and reviews.
1. Skluth HA, Gums JG. Spironolactone: a re-examination. *DiCP Ann Pharmacother* 1990; **24:** 52–9.
2. Doggrell SA, Brown L. The spironolactone renaissance. *Expert Opin Invest Drugs* 2001; **10:** 943–54.
3. Sica DA. Spironolactone: an old friend rediscovered. *J Clin Hypertens (Greenwich)* 2006; **8:** 467–9.
4. Dorrance AM. Stroke therapy: is spironolactone the Holy Grail? *Endocrinology* 2008; **149:** 3761–3.
5. de Souza F, *et al.* Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension* 2010; **55:** 147–52.
6. Williams JS. Hypertension: spironolactone and resistant hypertension. *Nat Rev Endocrinol* 2010; **6:** 248–50.

Administration in children. Spironolactone may be given to neonates, infants, and children for the treatment of heart failure, oedema, and ascites. The *BNFC* recommends the following oral doses, based on age:
- neonates: 1 to 2 mg/kg daily in 1 or 2 divided doses; up to 7 mg/kg daily may be given in resistant ascites
- 1 month to 12 years: 1 to 3 mg/kg daily in 1 or 2 divided doses; up to 9 mg/kg daily may be given in resistant ascites
- 12 to 18 years: 50 to 100 mg daily in 1 or 2 divided doses; up to 9 mg/kg (maximum 400 mg) daily may be given in resistant ascites

The *BNFC* also suggests that these doses may be given for the reduction of hypokalaemia induced by diuretics or amphotericin.

References.
1. Buck ML. Clinical experience with spironolactone in pediatrics. *Ann Pharmacother* 2005; **39:** 823–8.

Acne. Spironolactone has been used for its anti-androgenic properties in some cases of acne (p. 1682.2) where standard therapy is unsuccessful. Beneficial responses to oral therapy have been reported in patients with acne from both open[1] and placebo-controlled[2,3] studies, although a systematic review[4] considered that there was insufficient evidence for its efficacy. Topical application has been tried[5,6] but response has been variable. It is possible that the vehicle may affect the response. In women, spironolactone may be useful when treatment with an oestrogen is contra-indicated.

1. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; **112:** 124–5.
2. Goodfellow A, *et al.* Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol* 1984; **111:** 209–14.
3. Muhlemann MF, *et al.* Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol* 1986; **115:** 227–32.
4. Brown J, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 26/02/10).
5. Messina M, *et al.* A new therapeutic approach to acne: an antiandrogen percutaneous treatment with spironolactone. *Curr Ther Res* 1983; **34:** 319–24.
6. Walton S, *et al.* Lack of effect of topical spironolactone on sebum excretion. *Br J Dermatol* 1986; **114:** 261–4.

Alopecia. Anti-androgens have a role in the treatment of hirsutism (see below) but have also been used in patients with androgenetic alopecia (p. 1682.3), and there is some evidence that spironolactone may be effective.[1-3]

1. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; **152:** 466–73.
2. Hoedemaker C, *et al.* Treatment of female pattern hair loss with a combination of spironolactone and minoxidil. *Australas J Dermatol* 2007; **48:** 43–5.
3. Yazdabadi A, *et al.* Successful treatment of female-pattern hair loss with spironolactone in a 9-year-old girl. *Australas J Dermatol* 2009; **50:** 113–14.

Bartter's syndrome. Spironolactone may be used to reduce potassium wasting in patients with Bartter's syndrome (p. 1779.3).

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p. 1602.1) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p. 1387.3); results with hydrochlorothiazide or spironolactone have been more ambiguous (p. 1403.3).

Heart failure. Drug therapy of heart failure (p. 1262.3) is based on the use of diuretics, ACE inhibitors, cardiac glycosides, beta blockers, and vasodilators. Spironolactone has been used as a diuretic for refractory oedema, but it also has an additional role as an aldosterone antagonist.[1,2] Although the precise neurohormonal mechanisms leading to the development of heart failure are still not clear, there is evidence that raised levels of aldosterone may contribute to the pathophysiology.[3,4] ACE inhibitor therapy suppresses aldosterone production but this effect is not complete and the use of spironolactone with ACE inhibitors has therefore been studied. In the Randomized Aldactone Evaluation Study (RALES)[5] in patients with severe heart failure, addition of spironolactone in a dose of 25 to 50 mg daily to therapy with ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation.[5] The use of spironolactone may be considered in patients with moderate to severe heart failure.[6-9] The benefit may be a class effect: a systematic review[10] found a 20% reduction in all-cause mortality when spironolactone, eplerenone, or canrenone were given to patients with left-ventricular dysfunction or after myocardial infarction. A small study[11] has also shown benefit in patients with less milder heart failure. However, use of spironolactone with ACE inhibitors may lead to hyperkalaemia and careful monitoring of potassium concentrations is required[12,13] (see Interactions, p. 1502.2). Retrospective analyses[14,15] of heart failure patients found that some 10 to 15% had to stop spironolactone because of hyperkalaemia, and a similar proportion stopped because of worsening renal function. Risk factors were advanced age and higher baseline plasma-potassium concentrations.

1. Tang WHW, *et al.* Aldosterone receptor antagonists in the medical management of chronic heart failure. *Mayo Clin Proc* 2005; **80:** 1623–30.
2. Marcy TR, Ripley TL. Aldosterone antagonists in the treatment of heart failure. *Am J Health-Syst Pharm* 2006; **63:** 49–58.
3. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol* 1999; **47:** 479–82.
4. Rocha R, Williams GH. Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs* 2002; **62:** 723–31.
5. Pitt B, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341:** 709–17.
6. Jessup M, *et al.* 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119:** 1977–2016. Correction. *ibid.*; **121:**e258. Also published in *J Am Coll Cardiol* 2009; **53:** e1–e90. Correction. *ibid.*; **54:** 2464 Also available at: http://circ.ahajournals.org/cgi/reprint/119/14/1977.pdf (accessed 11/10/10) and at: http://content.onlinejacc.org/cgi/reprint/53/15/e1.pdf (accessed 11/10/10)
7. Dickstein K, *et al.* Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; **29:** 2388–2442. Correction. *ibid.* 3069. [dose] Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf (accessed 14/10/08)
8. Scottish Intercollegiate Guidelines Network. Management of chronic heart failure (February 2007). Available at: http://www.sign.ac.uk/pdf/sign95.pdf (accessed 07/05/08)
9. NICE. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf (accessed 13/10/10)
10. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J* 2009; **30:** 469–77.
11. Macdonald JE, *et al.* Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* 2004; **90:** 765–70.
12. Georges B, *et al.* Spironolactone and congestive heart-failure. *Lancet* 2000; **355:** 1369–70.
13. Juurlink DN, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351:** 543–51.
14. Witham MD, *et al.* Tolerability of spironolactone in patients with chronic heart failure—a cautionary message. *Br J Clin Pharmacol* 2004; **58:** 554–7.
15. Lopes RJ, *et al.* Safety of spironolactone use in ambulatory heart failure patients. *Clin Cardiol* 2008; **31:** 509–13.

High-altitude disorders. Acetazolamide is generally the drug of choice for prophylaxis of high-altitude disorders (p. 1276.2). Anecdotal reports[1-4] and a small-scale double-blind study[5] suggested that spironolactone could be useful in preventing acute mountain sickness, although a deterioration in pulmonary function despite spironolactone prophylaxis has been noted in a patient.[6]

1. Currie TT, *et al.* Spironolactone and acute mountain sickness. *Med J Aust* 1976; **2:** 168–70.
2. Snell JA, Cordner EP. Spironolactone and acute mountain sickness. *Med J Aust* 1977; **1:** 828.
3. Turnbull G. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **280:** 1453.
4. Rutter LD. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **281:** 618.
5. Brown GV, *et al.* Spironolactone in acute mountain sickness. *Lancet* 1977; **1:** 855.
6. Meyers DH. Spironolactone prophylaxis of mountain sickness. *BMJ* 1980; **281:** 1569.

Hirsutism. Hirsutism (p. 2262.1) is frequently treated with anti-androgens, usually cyproterone or spironolactone. Spironolactone in doses of 50 to 200 mg daily has produced both subjective and objective improvement in hirsutism in patients with idiopathic hirsutism or polycystic ovary syndrome,[1-4] and its use has been reviewed.[5] It is preferably used with oral contraceptives,[6,7] to improve efficacy and menstrual irregularity and to avoid the risk of feminisation to a male fetus. Most studies have involved premenopausal women and it has been suggested[4,8] that spironolactone would be useful in women in whom cyproterone is contra-indicated or not tolerated. A randomised study (not placebo-controlled) found spironolactone 100 mg daily and cyproterone 100 mg daily to be equally effective,[9] while a systematic review[10] of the use of spironolactone in hirsutism concluded that it was significantly more effective than both cyproterone and finasteride for up to 12 months after treatment.

For reference to the use of spironolactone in alopecia, see above.

1. Cumming DC, *et al.* Treatment of hirsutism with spironolactone. *JAMA* 1982; **247:** 1295–8.
2. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; **112:** 124–5.
3. Evans DJ, Burke CW. Spironolactone in the treatment of idiopathic hirsutism and the polycystic ovary syndrome. *J R Soc Med* 1986; **79:** 451–3.

4. Barth JH, *et al.* Spironolactone therapy for hirsute women. *Br J Dermatol* 1988; **119** (suppl 33): 17.
5. Christy NA, *et al.* Spironolactone for hirsutism in polycystic ovary syndrome. *Ann Pharmacother* 2005; **39:** 1517–21. Correction. *ibid.*; 1765.
6. Chapman MG, *et al.* Spironolactone in combination with an oral contraceptive: an alternative treatment for hirsutism. *Br J Obstet Gynaecol* 1985; **92:** 983–5.
7. Rittmaster RS. Hirsutism. *Lancet* 1997; **349:** 191–5.
8. West TET. Does spironolactone have a place in treating facial hirsutism in women? *BMJ* 1988; **296:** 1456.
9. O'Brien RC, *et al.* Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *J Clin Endocrinol Metab* 1991; **72:** 1008–13.
10. Brown J, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 26/02/10).

Hyperaldosteronism. Hyperaldosteronism (aldosteronism) [1-6] is a disorder of mineralocorticoid excess characterised by high circulating levels of aldosterone. It is a common cause of secondary hypertension, and is frequently diagnosed in those with resistant hypertension. The cardiovascular risks associated with hyperaldosteronism are far greater than for those with primary hypertension,[7] therefore correct identification and treatment is important.

Hyperaldosteronism may be primary or secondary, the latter resulting from conditions in which there is activation of the renin-angiotensin-aldosterone system, including diuretic therapy, and oedematous conditions such as heart failure, hepatic cirrhosis, and nephrotic syndrome. Bartter's syndrome (p. 1779.3) also results in hyperaldosteronism. Primary hyperaldosteronism is less common, and is usually caused by either bilateral adrenal hyperplasia or unilateral aldosterone-producing adenoma (Conn's syndrome). Rarer causes of primary hyperaldosteronism include aldosterone-secreting adrenal carcinoma and familial forms such as glucocorticoid-remediable aldosteronism.

The classic presentation of hyperaldosteronism is of hypertension, hypokalaemia, and alkalosis, but most patients are normokalaemic, with symptomatic hypokalaemia present only in the most severe cases or in those taking diuretics. In general, those with severe or resistant hypertension, spontaneous or diuretic-induced hypokalaemia, or juvenile hypertension or stroke should be screened for primary hyperaldosteronism.[2,4] This is usually done by measuring the plasma aldosterone:renin ratio. In primary hyperaldosteronism the aldosterone concentration is raised but renin is suppressed, although this does not necessarily prove the **diagnosis**; in secondary hyperaldosteronism both are raised. The test may be confounded by circadian rhythm, posture, and drugs. Hypokalaemia should first be corrected, sodium intake increased, and spironolactone or eplerenone therapy stopped for at least 4 to 6 weeks beforehand. Antihypertensives that may be continued with a minimal effect on the aldosterone:renin ratio are the alpha-blockers and calcium-channel blockers. The diagnosis must be confirmed with suppression testing, either with volume expansion using sodium or fludrocortisone, or by blocking the renin-angiotensin-aldosterone system with an ACE inhibitor, usually captopril. Computed tomography imaging and adrenal vein sampling are used to identify adenoma from hyperplasia, and exclude carcinoma.

Unilateral laparoscopic adrenalectomy is the preferred **treatment** for unilateral adenoma,[1,3-6] improving hypertension and hypokalaemia in most patients although about half will need to continue antihypertensive therapy. An aldosterone antagonist such as spironolactone may be given pre-operatively to lower the blood pressure and normalise the serum potassium. In those not suitable for surgery, lifelong drug therapy is indicated. Bilateral hyperplasia is not surgically correctable and is also managed medically. There is most experience with spironolactone and it is the treatment of choice,[1,4,5] initially in high doses, reduced to the lowest effective dose for maintenance; eplerenone is an alternative if adverse effects are a problem. Amiloride has also been used, but high doses are required. A thiazide may be added to therapy to maximise the antihypertensive effect and minimise hyperkalaemia.[4]

Glucocorticoid-remediable hyperaldosteronism (GRA), also known as familial hyperaldosteronism type I (FH-I),[8] is a rare autosomal dominant form. It has been diagnosed using a dexamethasone-suppression test, but direct identification with genetic testing is now preferred. It is treated with a long-acting glucocorticoid such as dexamethasone or prednisone, with the addition of spironolactone, eplerenone, or amiloride if hypertension remains uncontrolled.

In secondary hyperaldosteronism the underlying condition should be treated, but diuretics such as spironolactone may be of benefit as part of the therapy.

1. Pimenta E, Calhoun DA. Primary aldosteronism: diagnosis and treatment. *J Clin Hypertens (Greenwich)* 2006; **8:** 887–93.
2. Rossi GP, *et al.* Primary aldosteronism - part I: prevalence, screening, and selection of cases for adrenal vein sampling. *J Nephrol* 2008; **21:** 447–54.
3. Rossi GP, *et al.* Primary aldosteronism: part II: subtype differentiation and treatment. *J Nephrol* 2008; **21:** 455–62.
4. Funder JW, *et al.* Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; **93:** 3266–81.
5. Carey RM. Primary aldosteronism. *Horm Res* 2009; **71** (suppl 1): 8–12.
6. Schirpenbach C, *et al.* The diagnosis and treatment of primary hyperaldosteronism in Germany: results on 555 patients from the German Conn Registry. *Dtsch Arztebl Int* 2009; **106:** 305–11.
7. Catena C, *et al.* Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med* 2008; **168:** 80–5.
8. McMahon GT, Dluhy RG. Glucocorticoid-remediable aldosteronism. *Arq Bras Endocrinol Metabol* 2004; **48:** 682–6.

Kidney disorders. There is evidence that aldosterone may play a role in the development of chronic kidney disease; although patients must be carefully monitored because of the risk of hyperkalaemia (see also Precautions, p. 1502.1) low-dose spironolactone has been investigated for its potential as an adjunct to reduce proteinuria and potentially retard the development of renal impairment in both diabetic and non-diabetic patients.[1-4]

1. Furumatsu Y, *et al.* Effect of renin-angiotensin-aldosterone system triple blockade on non-diabetic renal disease: addition of an aldosterone blocker, spironolactone, to combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. *Hypertens Res* 2008; **31:** 59–67.
2. Saklayen MG, *et al.* Effects of additive therapy with spironolactone on proteinuria in diabetic patients already on ACE inhibitor or ARB therapy: results of a randomized, placebo-controlled, double-blind, crossover trial. *J Investig Med* 2008; **56:** 714–19.
3. Sengul E, *et al.* Effect of spironolactone on urinary protein excretion in patients with chronic kidney disease. *Ren Fail* 2009; **31:** 928–32.
4. Bomback AS, *et al.* Renal aspirin: will all patients with chronic kidney disease one day take spironolactone? *Nat Clin Pract Nephrol* 2009; **5:** 74–5.

Precocious puberty. Spironolactone (as an anti-androgen) and testolactone were given to boys with familial precocious puberty (p. 2254.1) for periods of up to 18 months. Rates of growth and bone maturation were restored to normal during combination therapy but not with either drug given alone.[1] However, after further treatment for 2 to 4.2 years there was a diminishing response manifested by the recurrence of clinical features of puberty and an increase in the bone maturation rate.[2] Addition of deslorelin appeared to restore the control of puberty,[2] and in a long-term study[3] growth rate remained normal for 6 years.

1. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
2. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
3. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Premenstrual syndrome. Spironolactone has been used for its diuretic and anti-androgenic properties in premenstrual syndrome (p. 2272.3).

Adverse Effects

Spironolactone may give rise to headache and drowsiness, and gastrointestinal disturbances, including cramp and diarrhoea. Ataxia, mental confusion, and rashes have been reported as adverse effects. Gynaecomastia is not uncommon and in rare cases breast enlargement may persist. Other endocrine disorders include hirsutism, deepening of the voice, menstrual irregularities, and impotence. Transient increases in blood-urea-nitrogen concentrations may occur and mild acidosis has been reported. Spironolactone has been shown to cause tumours in *rats*.

Spironolactone may cause hyponatraemia and hyperkalaemia.

Incidence of adverse effects. A survey found that of 788 patients given spironolactone 164 developed adverse effects.[1] These included hyperkalaemia in 8.6%, dehydration in 3.4%, hyponatraemia in 2.4%, gastrointestinal disorders in 2.3%, neurological disorders in 2%, rash, and gynaecomastia. Hyperkalaemia was associated with renal impairment and the use of potassium supplements: only 2.8% of nonuraemic patients not receiving potassium chloride developed hyperkalaemia, while 42.1% of those with marked uraemia and treated with potassium chloride became hyperkalaemic.

In a study[2] of 54 patients (53 female, 1 male) taking spironolactone 200 mg daily for hirsutism or acne adverse effects were reported in 91%.[2] Menstrual disturbances occurred in 72% of patients, breast tenderness in 39%, dry skin in 39%, and breast enlargement in 24%. Other adverse effects included nausea and vomiting, dizziness, headache, drowsiness, and rashes. Two patients developed a chloasma-like pigmentation of the face. The gynaecological effects were reduced in patients taking oral contraceptives.

1. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.
2. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Carcinogenicity. Breast cancer was reported in 5 patients taking spironolactone and hydrochlorothiazide for prolonged periods[1] although it was suggested[2] that the association with spironolactone therapy was unlikely to be causal.

Although the *rat* may not be an appropriate model for determining long-term safety in man,[3,4] evidence of carcinogenicity in this species prompted the UK CSM to limit the product licences of spironolactone-containing products to exclude use in essential hypertension or idiopathic oedema.[5]

1. Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone. *Lancet* 1975; **i:** 1428–9.
2. Jick H, Armstrong B. Breast cancer and spironolactone. *Lancet* 1975; **ii:** 368–9.
3. Lumb G, *et al.* Effects in animals of chronic administration of spironolactone—a review. *J Environ Pathol Toxicol* 1978; **i:** 641–60.
4. Wagner BM. Long-term toxicology studies of spironolactone in animals and comparison with potassium canrenoate. *J Drug Dev* 1987; **1** (suppl 2): 7–11.
5. CSM. Spironolactone. *Current Problems* 1988; 21. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)

Effects on the blood. Agranulocytosis has been reported[1,2] in association with the use of spironolactone.

1. Stricker BHC, Oei TT. Agranulocytosis caused by spironolactone. *BMJ* 1984; **289:** 731.
2. Whitling AM, *et al.* Spironolactone-induced agranulocytosis. *Ann Pharmacother* 1997; **31:** 582–5.

Effects on electrolyte balance. *CALCIUM.* A report[1] suggested that spironolactone may have a calcium-sparing effect, in addition to its well known potassium-sparing properties.

1. Puig JG, *et al.* Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. *J Clin Pharmacol* 1991; **31:** 455–61.

POTASSIUM. There have been reports[1-3] of severe hyperkalaemia in patients taking spironolactone, including patients with renal impairment and those with a high potassium intake from either dietary sources or potassium supplements. In the Boston Collaborative Drug Surveillance Program[4] hyperkalaemia was reported in 42.1% of patients with uraemia taking spironolactone and receiving potassium supplements compared with 2.8% of those without uraemia and not receiving potassium supplements. Two deaths were attributed to hyperkalaemia in patients taking spironolactone and potassium chloride. Potassium supplements should be avoided in patients receiving spironolactone, and plasma-potassium concentrations should be carefully monitored in those with renal impairment. An analysis[5] of spironolactone prescriptions in a Scottish population between 1994 and 2007, however, noted that despite an increase in prescription after 1999 following the results of the RALES study, there was no concomitant increase in hospital admissions for hyperkalaemia, and instances of measured hyperkalaemia in outpatients actually fell, suggesting that careful monitoring enabled successful use of the drug.

1. Pongpaew C, *et al.* Hyperkalemic cardiac arrhythmia secondary to spironolactone. *Chest* 1973; **63:** 1023–5.
2. Udezue EO, Harrold BP. Hyperkalaemic paralysis due to spironolactone. *Postgrad Med J* 1980; **56:** 254–5.
3. O'Reilly PH, *et al.* Life-threatening hyperkalaemia after bladder decompression for high pressure chronic retention. *Lancet* 1987; **ii:** 859.
4. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.
5. Wei L, *et al.* Spironolactone use and renal toxicity: population based longitudinal analysis. *BMJ* 2010; **340:** c1768.

Effects on endocrine function. Spironolactone has been associated with disturbances of endocrine function. The most prominent in men is gynaecomastia which appears to be related to both dose and duration of treatment. Incidences of 62%[1] and 100%[2] have been reported. Gynaecomastia has also been accompanied by impotence.[3,4] The effects are generally reversible on stopping treatment. Reversal of male-pattern baldness has also been reported.[5]

In women symptoms include breast enlargement and tenderness.[6] The incidence of menstrual abnormalities may be high: unspecified disturbances have been reported in 33 of 53 women,[6] secondary amenorrhoea in 6 of 9,[7] and secondary and primary amenorrhoea in 1 and 2 patients, respectively.[8] The incidence of gynaecological disturbances has been found to be lower in women taking oral contraceptives.[6]

The mechanism of the effects of spironolactone on the endocrine system is unclear. Some workers[9] suggested that although spironolactone affects testosterone synthesis, the more likely explanation was its anti-androgenic action, and reduction in 17-hydroxylase activity. Others[10] found an alteration in the testosterone/oestrogen ratio due to an increase in testosterone clearance and increased peripheral conversion to estradiol. In addition, spironolactone is reported to inhibit binding of dihydrotestosterone to receptors.

1. Huffman DH, *et al.* Gynecomastia induced in normal males by spironolactone. *Clin Pharmacol Ther* 1978; **24:** 465–73.

2. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i:** 626.
3. Greenblatt DJ, Koch-Weser J. Gynecomastia and impotence complications of spironolactone therapy. *JAMA* 1973; **223:** 82.
4. Greenlaw C. Spironolactone induced gynecomastia: a case report. *Drug Intell Clin Pharm* 1977; **11:** 70–3.
5. Thomas PS. Hair: wanted and unwanted. *BMJ* 1986; **293:** 698.
6. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.
7. Levitt JI. Spironolactone therapy and amenorrhea. *JAMA* 1970; **211:** 2014–15.
8. Potter C, *et al*. Primary and secondary amenorrhea associated with spironolactone therapy in chronic liver disease. *J Pediatr* 1992; **121:** 141–3.
9. Loriaux DL, *et al*. Spironolactone and endocrine dysfunction. *Ann Intern Med* 1976; **85:** 630–6.
10. Rose LI, *et al*. Pathophysiology of spironolactone-induced gynecomastia. *Ann Intern Med* 1977; **87:** 398–403.

Effects on the gastrointestinal tract. Population-based studies[1-3] have identified a dose-dependent increased risk of gastrointestinal bleeding and ulcers in those taking spironolactone. The mechanism was thought to be inhibition of aldosterone-induced formation of fibrous tissue, thus impairing the healing of gastric and duodenal erosion.

1. Verhamme KMC, *et al*. Spironolactone and risk of upper gastrointestinal events: population based case-control study. Abridged version: *BMJ* 2006; **333:** 330–333. Full version: http://www.bmj.com/cgi/reprint/333/7563/330.pdf (accessed 20/05/10)
2. Russo A, *et al*. Spironolactone and gastrointestinal bleeding: a population based study. *Pharmacoepidemiol Drug Safety* 2008; **17:** 495–500.
3. Gulmez SE, *et al*. Spironolactone use and the risk of upper gastrointestinal bleeding: a population-based case-control study. *Br J Clin Pharmacol* 2008; **66:** 294–9.

Effects on lipid metabolism. Unlike thiazide diuretics, spironolactone appeared not to increase serum-cholesterol concentrations in a study of 23 patients.[1]

1. Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. *Arch Intern Med* 1984; **144:** 710–14.

Effects on the liver. Hepatotoxicity characterised by cholestatic lesions has been reported in a patient receiving spironolactone.[1] Only one other published case of spironolactone-associated hepatotoxicity was known to the authors.

1. Renkes P, *et al*. Spironolactone and hepatic toxicity. *JAMA* 1995; **273:** 376–7.

Effects on the skin. Lichen-planus-like skin eruptions developed in a 62-year-old woman who was taking digoxin, propranolol, diazepam, spironolactone, and iron tablets.[1] Flares of the lichen-planus-like eruption seemed to be associated with use of spironolactone and there was evidence of resolution when spironolactone was withdrawn. Cutaneous vasculitis was associated with spironolactone on 3 occasions in an 80-year-old man.[2] A chloasma-like pigmentation of the face was reported in 2 patients receiving spironolactone for hirsutism or acne.[3]

1. Downham TF. Spironolactone-induced lichen planus. *JAMA* 1978; **240:** 1138.
2. Phillips GWL, Williams AJ. Spironolactone induced vasculitis. *BMJ* 1984; **288:** 368.
3. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Hypersensitivity. Eosinophilia and a rash developed in 2 patients with alcoholic cirrhosis while taking spironolactone.[1] A report of the DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has also been associated[2] with spironolactone.

1. Wathen CG, *et al*. Eosinophilia associated with spironolactone. *Lancet* 1986; **i:** 919–20.
2. Ghislain PD, *et al*. Drug-induced eosinophilia and multisystemic failure with positive patch-test reaction to spironolactone: DRESS syndrome. *Acta Derm Venereol* 2004; **84:** 65–8.

Precautions

Spironolactone should not be used in patients with hyperkalaemia or severe renal impairment. It should be used with care in patients who are at increased risk of developing hyperkalaemia; such patients include the elderly, those with diabetes mellitus, and those with some degree of renal or hepatic impairment. It should also be given with care to patients likely to develop acidosis. Serum electrolytes and blood-urea-nitrogen should be measured periodically.

Breast feeding. The concentration of canrenone was measured[1] in the serum and milk of a breast-feeding woman taking 25 mg of spironolactone four times daily. The milk to serum concentration ratios of canrenone at 2 and 14.5 hours after a dose of spironolactone were 0.72 and 0.51 respectively, and it was estimated that the amount of canrenone ingested by the infant would be 0.2% of the mother's daily dose of spironolactone. The serum potassium and sodium levels of the infant were in the normal range. The American Academy of Pediatrics[2] considers that spironolactone is therefore usually compatible with breast feeding.

1. Phelps DL, Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci* 1977; **66:** 1203.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Diabetes mellitus. Severe hyperkalaemia was reported in a type 1 diabetic woman with hyporeninaemic hypoaldosteronism given spironolactone.[1]

1. Large DM, *et al*. Hyperkalaemia in diabetes mellitus—potential hazards of coexisting hyporeninaemic hypoaldosteronism. *Postgrad Med J* 1984; **60:** 370–3.

Interference with laboratory estimations. Spironolactone and canrenoate can interfere with some assays for plasma-digoxin concentrations.[1-3] However, spironolactone may also produce actual changes in digoxin concentrations (see p. 1357.2) and results of assays should be interpreted with caution.

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–87.
2. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12:** 82–4.
3. Steimer W, *et al*. Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354:** 1176–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies spironolactone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

There is an increased risk of hyperkalaemia if spironolactone is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may occur as well in patients also given ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients given spironolactone with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may reduce the excretion of lithium and increase the risk of lithium toxicity. Hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients given chlorpropamide. Spironolactone may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, spironolactone may enhance the effects of other antihypertensive drugs and may reduce vascular responses to noradrenaline.

ACE inhibitors and angiotensin II receptor antagonists. Severe hyperkalaemia has been reported in patients given spironolactone with ACE inhibitors or angiotensin II receptor antagonists and fatalities have occurred. In a study[1] of 44 patients taking such combinations for heart failure who were admitted to hospital with life-threatening hyperkalaemia, 37 required haemodialysis and 2 developed fatal complications. In another group[2] of 25 patients given spironolactone with ACE inhibitors who were admitted with severe hyperkalaemia, 2 died and 4 others developed severe cardiac arrhythmias. Advanced age, renal impairment or diabetes mellitus were risk factors for hyperkalaemia in both studies. It was suggested that combinations of spironolactone with ACE inhibitors or angiotensin II receptor antagonists should be used with caution in such patients and that they should not be given doses of spironolactone above 25 mg daily.

1. Wrenger E, *et al*. Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. *BMJ* 2003; **327:** 147–9.
2. Schepkens H, *et al*. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; **110:** 438–41.

Aspirin. Aspirin has been shown to produce substantial reductions in sodium excretion[1] in healthy subjects taking spironolactone and to reduce the excretion of spironolactone's active metabolite, canrenone.[2] However, use of aspirin in hypertensive patients[3] did not alter the effect of spironolactone on blood pressure, serum electrolytes, blood urea nitrogen, or plasma-renin activity.

1. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. *N Engl J Med* 1973; **289:** 198–200.
2. Ramsay LE, *et al*. Influence of acetylsalicylic acid on the renal handling of a spironolactone metabolite in healthy subjects. *Eur J Clin Pharmacol* 1976; **10:** 43–8.
3. Hollifield JW. Failure of aspirin to antagonize the antihypertensive effect of spironolactone in low-renin hypertension. *South Med J* 1976; **69:** 1034–6.

Cardiac glycosides. For discussions of the effects of spironolactone on *digoxin* and *digitoxin*, see p. 1357.2 and p. 1353.3, respectively. See also Interference with Laboratory Estimations, under Precautions, above.

Mitotane. For a report of the inhibition of the action of mitotane by spironolactone, see p. 833.1.

Warfarin. For reference to the interaction between warfarin and spironolactone, see p. 1533.3.

Pharmacokinetics

Spironolactone is well absorbed from the gastrointestinal tract, with a bioavailability of about 90%. It is about 90% bound to plasma proteins.

Spironolactone is metabolised extensively to several metabolites including canrenone and 7α-thiomethylspirolactone, both of which are pharmacologically active. The major metabolite may be 7α-thiomethylspirolactone, although it is uncertain to what extent the actions of spironolactone are dependent on the parent compound or its metabolites.

Spironolactone is excreted mainly in the urine and also in the faeces, in the form of metabolites. Spironolactone or its metabolites may cross the placental barrier, and canrenone is distributed into breast milk.

References.

1. Overdiek HWPM, Merkus FWHM. The metabolism and biopharmaceutics of spironolactone in man. *Rev Drug Metab Drug Interact* 1987; **5:** 273–302.
2. Gardiner P, *et al*. Spironolactone metabolism: steady-state serum levels of the sulfur-containing metabolites. *J Clin Pharmacol* 1989; **29:** 342–7.
3. Sungaila I, *et al*. Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. *Gastroenterology* 1992; **102:** 1680–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aldactone; Drimux A; Espimax; Expal; Lanx; Modulactone; Normital; Osiren; Rediun-E; ***Austral.***: Aldactone; Spiractin; ***Austria***: Aldactone; Spirobene; Spirohexal; Spirono; ***Belg.***: Aldactone; Docspirono†; Spirotop†; ***Braz.***: Aldactone; Diacqua; Espirolona; Spiroctan; ***Canad.***: Aldactone; Novo-Spiroton†; ***Chile***: Alizar; Cardactona; ***China***: Shi Er Tong (使尔通); ***Cz.***: Verospiron; ***Denm.***: Hexalacton; Spirix; Spiron; ***Fin.***: Spiresis†; Spirix; ***Fr.***: Aldactone; Flumach†; Practon†; Spiroctan; Spirononе†; ***Ger.***: Aldactone; Jenaspiron; Osyrol†; Spiro; Spirobeta; Spirogamma; Spirono†; Verospiron; ***Gr.***: Aldactone; Rocanol; Spinoral; Uridactone; ***Hong Kong***: Aldactone; Spiractin†; ***Hung.***: Huma-Spiroton; Spiron; Verospiron; ***India***: Aldactone; ***Indon.***: Aldactone; Carpiaton; Letonal; Spirola; Spirolacton; ***Irl.***: Aldactone; ***Israel***: Aldactone; Aldospirone†; Spironol; ***Ital.***: Aldactone; Spirolang; Uractone; ***Malaysia***: Spirolon; ***Mex.***: Aldactone; Biolactona; Nolasque; Vivitar; ***Norw.***: Aldactone; Spirix; ***NZ***: Spirotone; ***Philipp.***: Aldactone; ***Pol.***: Spironol; Verospiron; ***Port.***: Aldactone; Aldonar†; ***Rus.***: Verospilactone (Верошпилактон); Verospiron (Верошпирон); ***S. Afr.***: Aldactone; Spiractin; ***Singapore***: Aldactone; Spirolon; Uractonum; ***Spain***: Aldactone; ***Swed.***: Aldactone; ***Switz.***: Aldactone; Primacton†; Xenalon; ***Thai.***: Aldactone; Altone; Hyles; Pondactone; Spironex; ***Turk.***: Aldactone; ***UK***: Aldactone; ***Ukr.***: Verospiron (Верошпирон); ***USA***: Aldactone; ***Venez.***: Aldactone.

Multi-ingredient Preparations. ***Arg.***: Aldactone HCT; Aldactone-D; Aldazida; Lasilacton; ***Austria***: Aldactone Saltucin; Furo-Spirobene; Lasilacton; Sali-Aldopur; Spirono comp; ***Belg.***: Aldactazine; Docspirochlor†; ***Braz.***: Aldazida; Lasilactona; ***Canad.***: Aldactazide; Apo-Spirozide†; Novo-Spirozine†; ***Fr.***: Aldactazine; Aldalix; Practazin†; Spirоctazine; ***Ger.***: Furo-Aldopur†; Furorese Comp†; Osyrol Lasix†; Spiro comp; Spiro-D†; Spironothiazid; ***Gr.***: Aldactazide; Aldactazine; ***India***: Aldactide; Aldostix; Amifru-S; Aquamide; Dyamide Plus; Dytor Plus; Fruselac; Lasilactone; Minilacton; Spiromide; ***Indon.***: Aldazide; ***Irl.***: Aldactide†; ***Ital.***: Aldactazide; Lasitone; Spiridazide; Spirofur; ***Mex.***: Aldazida; Lasilacton; ***Philipp.***: Aldazide; ***Port.***: Aldactazine; Ondolen; ***S.Afr.***: Aldazide; ***Spain***: Aldactacine; Aldoleo; ***Switz.***: Aldozone†; Furospir; Lasilactone; ***Turk.***: Aldactazide; ***UK***: Aldactide; Lasilactone; ***USA***: Aldactazide; ***Venez.***: Aldactazida.

Pharmacopoeial Preparations

BP 2014: Spironolactone Oral Suspension; Spironolactone Tablets;

USP 36: Spironolactone and Hydrochlorothiazide Oral Suspension; Spironolactone and Hydrochlorothiazide Tablets; Spironolactone Oral Suspension; Spironolactone Tablets.

Staphylokinase

Estafilocinasa; Estafilokinasa; Estafiloquinasa; Staphylokinasa.

Profile

Staphylokinase is a thrombolytic derived from *Staphylococcus aureus*. Recombinant and modified forms are under investigation for the treatment of thromboembolic disorders, including acute myocardial infarction.

References.
1. Vanderschueren S, *et al*. Thrombolytic therapy of peripheral arterial occlusion with recombinant staphylokinase. *Circulation* 1995; **92:** 2050–57.
2. Vanderschueren S, *et al*. Randomized coronary patency trial of double-bolus recombinant staphylokinase versus front-loaded alteplase in acute myocardial infarction. *Am Heart J* 1997; **134:** 213–19.
3. Armstrong PW, *et al*. Collaborative angiographic patency trial of recombinant staphylokinase (CAPTORS II). *Am Heart J* 2003; **146:** 484–8.
4. Verhamme P, *et al*. A dose-finding clinical trial of staphylokinase SY162 in patients with long-term venous access catheter thrombotic occlusion. *J Thromb Thrombolysis* 2007; **24:** 1–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Shi Ai Ke (施爱克); Yi Li Tong (依力通).

Streptokinase *(BAN, rINN)*

Estreptokinasa; Estreptoquinasa; Plasminokinase; Sterptokinasum; Streptokinaasi; Streptokinas; Streptokinasum; Sztreptokináz; Стрептокиназа.

CAS — 9002-01-1.
ATC — B01AD01.
ATC Vet — QB01AD01.
UNII — 8X1OXL3SNU.

Pharmacopoeias. *Eur.* (see p. vii) includes a concentrated solution.

Ph. Eur. 8: (Streptokinase Concentrated Solution; Streptokinasi Solutio Concentrata). A preparation of a protein obtained from culture filtrates of certain strains of haemolytic *Streptococcus* group C. It has the property of combining with human plasminogen to form plasminogen activator. The potency is not less than 510 international units per microgram of nitrogen. A clear, colourless liquid. pH 6.8 to 7.5. Store in airtight containers at a temperature of -20 degrees. Protect from light.

Stability. The incorporation of albumin in commercial preparations of streptokinase has reduced the incidence of flocculation with streptokinase solutions. However, flocculation has occurred with small volumes prepared with sodium chloride 0.9% in sterilised glass containers apparently because of residual acid buffers that remain in empty evacuated containers after sterilisation.[1]

1. Thibault L. Streptokinase flocculation in evacuated glass bottles. *Am J Hosp Pharm* 1985; **42:** 278.

Units

The potency of streptokinase is expressed in international units and preparations are assayed using the third International Standard (2001).

The Christensen unit is the quantity of streptokinase that will lyse a standard blood clot completely in 10 minutes and is equivalent to the international unit.

Uses and Administration

Streptokinase is a thrombolytic drug derived from various streptococci. It rapidly converts endogenous plasminogen, indirectly by means of a streptokinase-plasminogen complex, to its active form plasmin (see Fibrinolysin, p. 1382.3), resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Streptokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p. 1245.3).

Streptokinase is given by intravenous or sometimes intra-arterial infusion in the treatment of thromboembolic disorders such as myocardial infarction (p. 1257.1), peripheral arterial thromboembolism (p. 1504.1), and venous thromboembolism (deep-vein thrombosis and pulmonary embolism) (p. 1274.1). It has also been tried in ischaemic stroke (p. 1504.2), although alteplase is generally preferred. Streptokinase may be used to clear cannulas and shunts and is used topically with streptodornase to clear clots and purulent matter.

In acute **myocardial infarction** streptokinase is usually given intravenously as a single dose of 1.5 million units infused over 1 hour as soon as possible after the onset of symptoms. Streptokinase has also been given in a suitable dose by intracoronary infusion but coronary catheterisation with the aid of angiography is required, thus restricting use to suitably equipped centres.

In the treatment of **pulmonary embolism** and other **arteriovenous occlusions** an initial loading dose of streptokinase, normally 250 000 units infused intravenously over 30 minutes, is given to overcome any resistance due to circulating antibodies. This is followed by infusion of a maintenance dose of 100 000 units/hour for 24 to 72 hours, depending on the condition to be treated; for central retinal thrombosis, 12 hours may be adequate. Treatment should be controlled by monitoring the thrombin clotting time, which should be maintained at 2 to 4 times normal values. Since thrombolytic activity rapidly fades when the infusion stops, streptokinase treatment is generally followed after 3 to 4 hours by intravenous heparin infusion, and then oral anticoagulation, to prevent re-occlusion.

Streptokinase, as a solution containing 250 000 units in 2 mL is used to clear occluded **cannulas**.

For doses in children, see below.

General references.
1. Fears R. Biochemical pharmacology and therapeutic aspects of thrombolytic agents. *Pharmacol Rev* 1990; **42:** 201–21.
2. Stringer KA. Beyond thrombolysis: other effects of thrombolytic drugs. *Ann Pharmacother* 1994; **28:** 752–6.
3. Ludlam CA, *et al*. Guidelines for the use of thrombolytic therapy. *Blood Coag Fibrinol* 1995; **6:** 273–85.
4. Bell WR. Present-day thrombolytic therapy: therapeutic agents—pharmacokinetics and pharmacodynamics. *Rev Cardiovasc Med* 2002; **3** (suppl 2): S34–S44.

Administration in children. There are limited data on the use of systemic thrombolytic therapy for arterial or venous thromboembolism in children and various dosage regimens have been used, based on case studies. The most widely used drugs are streptokinase and alteplase. For streptokinase, the Eighth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy[1] suggests a loading dose of 2000 units/kg to be given intravenously, followed by continuous infusion of 2000 units/kg per hour for 6 to 12 hours. In the UK, for children aged from 1 month to 12 years, the *BNFC* suggests a loading dose of 2500 to 4000 units/kg over 30 minutes, followed by infusion of 500 to 1000 units/kg per hour, continued until reperfusion occurs, up to a maximum of 3 days. Children aged 12 years and over may be given the usual adult dose (see above).

Alteplase may be preferred because of its fibrin specificity and low immunogenicity. The dose of alteplase suggested by the ACCP is 100 to 600 micrograms/kg per hour by continuous intravenous infusion over 6 hours. In the UK, for neonates and children up to 18 years of age, the dose recommended by the *BNFC* is 100 to 500 micrograms/kg per hour for 3 to 6 hours (maximum total daily dose of 100 mg). The use of alteplase to clear occluded catheters in children is discussed on p. 1297.2.

1. Monagle P, *et al*. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S. Also available at: http://chestjournal.chestpubs.org/content/133/6_suppl/887S.full.pdf (accessed 23/10/09)

Empyema and pleural effusion. Thoracic empyema is treated with antibacterials and pleural drainage. Efficient removal of fluid may be impaired by fibrinous clots within the pleural cavity. Intrapleural instillation of streptokinase (100 000 to 750 000 units in up to 100 mL of sodium chloride 0.9%) has been reported to be effective in small series of patients[1-4] and there have been reports of the successful use of alteplase[5-7] and urokinase.[4,8] However, a double-blind study[9] involving 454 patients found no benefit with streptokinase, and the role of thrombolytics remains unclear. A meta-analysis[10] found no evidence of benefit, although a systematic review[11] suggested that thrombolytics may reduce the need for surgical intervention. Intrapleural streptokinase has also been used successfully in a few patients with malignant multiloculated pleural effusion resistant to standard pleural drainage.[12]

Intrapericardial instillation of thrombolytics has been tried in a few patients with pericardial empyema to prevent the development of constrictive pericarditis.[13,14]

For reports of haemorrhage associated with intrapleural use of streptokinase, see Haemorrhage, under Adverse Effects, p. 1505.3.

1. Temes RT, *et al*. Intrapleural fibrinolytics in management of empyema thoracis. *Chest* 1996; **110:** 102–6.
2. Bouros D, *et al*. Role of streptokinase in the treatment of acute loculated parapneumonic pleural effusions and empyema. *Thorax* 1994; **49:** 852–5.
3. Davies RJO, *et al*. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. *Thorax* 1997; **52:** 416–21.
4. Bouros D, *et al*. Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. *Am J Respir Crit Care Med* 1997; **155:** 291–5.
5. Bishop NB, *et al*. Alteplase in the treatment of complicated parapneumonic effusion: a case report. Abstract: *Pediatrics* 2003; **111:** 423. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/2/e188 (accessed 16/06/04)
6. Walker CA, *et al*. Intrapleural alteplase in a patient with complicated pleural effusion. *Ann Pharmacother* 2003; **37:** 376–9.
7. Weinstein M, *et al*. Effectiveness and safety of tissue plasminogen activator in the management of complicated parapneumonic effusions. Abstract: *Pediatrics* 2004; **113:** 610. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/3/e182 (accessed 30/04/08)
8. Thomson AH, *et al*. Randomised trial of intrapleural urokinase in the treatment of childhood empyema. *Thorax* 2002; **57:** 343–7.
9. Maskell NA, *et al*. U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005; **352:** 865–74. Correction. *ibid.*; 2146.
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Intracardiac thrombosis. Thrombosis of prosthetic heart valves (see p. 1264.3) is usually treated surgically, but thrombolytics have also been used. In a study[1] of patients with left-sided prosthetic valve thrombosis, thrombolytic therapy was found to be more successful than surgery, especially in those who were critically ill; most patients were given streptokinase. Another retrospective study[2] in which patients were given streptokinase, urokinase, or alteplase, concluded that thrombolytics were effective but embolic and haemorrhagic complications might limit their use. Treatment with tenecteplase[3] has successfully resolved intracardiac thrombosis in a patient implanted with a ventricular assist device.

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Ischaemic heart disease. Thrombolytics such as alteplase, streptokinase, and urokinase have an established role in the early management of acute myocardial infarction (p. 1257.1). Myocardial infarction is caused by coronary artery occlusion, usually due to thrombosis, and thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium. Reduction of ECG abnormalities and modification of ventricular remodelling may also contribute to their effect. Other antithrombotics, in particular aspirin and heparin, are given as adjunctive therapy.

Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and 1-year mortality figures;[1,2] benefit has been maintained in 5-year[3] and 10-year[4,5] follow-up studies. Benefit is greatest with early treatment. Studies such as GISSI-1[6] and ISIS-2[7] helped to establish that mortality is reduced if thrombolytics are given within 6 hours of the onset of symptoms[8] and further studies provided evidence[9,10] that patients presenting within 12 hours should receive a thrombolytic. Use after 12 hours has been associated with an increase in adverse effects,[8] and is usually reserved for patients with evidence of ongoing ischaemia. Prehospital thrombolysis is feasible and reduces the time to thrombolysis and short-term mortality.[11] Five-year follow-up of one study[12] has suggested that there is also a beneficial effect on long-term mortality.

Choice of thrombolytic depends on factors such as cost, method of administration, and contra-indications. Although streptokinase has been the most widely used, several large studies have compared clinical benefit in terms of improved left ventricular function and mortality and have shown no difference between streptokinase and other thrombolytics, including saruplase,[13] the tissue plasminogen activator alteplase,[14] anistreplase,[15] and reteplase[16] in overall efficacy. In the GUSTO-I study,[17] accelerated or 'front loaded' alteplase (that is, rapid intravenous dosage over 1½ hours rather than the conventional 3 hours) was more effective than streptokinase, although the study was criticised for not comparing like with like. On the other hand, alteplase might be associated with a greater risk of stroke than streptokinase.[18] Studies comparing bolus injections of reteplase with accelerated alteplase (GUSTO-III)[19] and tenecteplase with alteplase (ASSENT-2)[20] have also found no difference in mortality rate.

The overall efficacy of thrombolytics is limited by persistent coronary occlusion, re-occlusion, and bleeding complications. Different thrombolytic regimens, such as bolus injections of reteplase, and combinations of thrombolytics, for example alteplase with streptokinase and alteplase with saruplase, have been investigated in attempts to improve patency rates. However, there has been concern that adverse effects may be higher with bolus injection. A study[21] comparing double-bolus alteplase with accelerated alteplase was terminated early when excess deaths were found in the group receiving bolus injections, and a subsequent meta-analysis[22] found a higher incidence of intracranial haemorrhage associated with bolus doses of various thrombolytics. Although use of thrombolytics before percutaneous coronary intervention (PCI) does not appear to be beneficial, a small study[23] has suggested that intracoronary streptokinase given immediately after PCI

may improve microvascular reperfusion; subsequent results[24] have suggested this may produce clinical benefit.

Thrombolytics have also been tried in other acute coronary syndromes, including unstable angina and non-ST elevation myocardial infarction (p. 1254.3). Although small-scale studies reported some benefit the results were variable, and an overview[8] of studies in patients with suspected myocardial infarction, which included some patients with unstable angina, found that there was no mortality benefit in patients without ST elevation. In 2 studies that investigated alteplase (the TIMI-IIIB study[25] with 1473 patients) and anistreplase (the UNASEM study[26] involving 159 patients), thrombolysis failed to improve outcome and was associated with an excess of bleeding complications. Thrombolytic therapy is therefore not recommended for patients with unstable angina or non-ST elevation myocardial infarction.

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Peripheral arterial thromboembolism. Although surgery has been the first-line therapy for peripheral arterial thromboembolism (p. 1273.3), thrombolytics have an increasingly important role, either alone or as an adjunct to surgery or percutaneous interventions.[1] Streptokinase, given intravenously, effectively restores arterial patency in acute occlusion, but the high rate of bleeding complications limits use of this route.[2] Direct intra-arterial infusion (catheter-directed thrombolysis) appears to be more effective, particularly when the catheter is placed directly into the thrombus, and this technique is now preferred. Alternatively, intra-arterial thrombolytics may be used as adjunctive therapy to reduce the clot burden before or during surgical or percutaneous intervention or to treat distal clots.[1] The *intravenous* dose generally used is 250 000 units over 30 minutes followed by 100 000 units/hour. A lower dose of 5000 units/hour has been used *intra-arterially* directly into the clot,[3] and for removal of distal clots during surgery streptokinase has been given intra-arterially in a dose of 100 000 units over 30 minutes or as five bolus doses of 20 000 units at 5-minute intervals.[4]

Other thrombolytics are now more widely used than streptokinase, although relative efficacy of the different drugs is unclear.[5] Alteplase and urokinase are both used, and clinical practice now favours them over streptokinase;[3,6,7] positive results have also been reported with reteplase and tenecteplase.[7]

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CENTRAL RETINAL ARTERY OCCLUSION. Central retinal artery occlusion may result in severe and permanent visual loss in the affected eye. The use of thrombolytics has been investigated for treatment, with variable results.

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Stroke. Stroke (p. 1269.2) is normally considered a contra-indication to the use of thrombolytics, and clearly they would be inappropriate in acute haemorrhagic stroke. However, when stroke is associated with thrombotic occlusion there is evidence, as with myocardial infarction, that a degree of neuronal recovery is possible if the occlusion is reversed sufficiently quickly, and thrombolytics may therefore have a role in some patients with acute ischaemic stroke.

Early studies with intravenous thrombolytics in acute *ischaemic stroke* suggested a reduction in early death, although subsequent randomised trials produced disappointing results, with the exception of one with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial).[1] The studies using streptokinase—MAST-E (Multicentre Acute Stroke Trial-Europe),[2] ASK (Australian Streptokinase Trial),[3] and MAST-I (Multicentre Acute Stroke Trial-Italy)[4,5]—were terminated before completion because of adverse outcomes (intracranial bleeding and increased mortality) in the treatment groups, particularly in those receiving therapy more than 3 hours after stroke onset.[3] The study investigating alteplase given within 6 hours of the onset of symptoms (ECASS I—European Cooperative Acute Stroke Study)[6] reported that, although some patients might benefit, overall alteplase was associated with higher mortality rates and an increase in some intracranial bleeding (parenchymal haemorrhage). In the NINDS randomised study,[1] alteplase given within 3 hours of the onset of ischaemic stroke appeared to improve clinical outcome despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[1] and this benefit was maintained at 12 months.[7] However, there was no difference in mortality or rate of recurrence of stroke. A second ECASS study (ECASS II)[8] that hoped to confirm the early findings of the NINDS study failed to confirm a statistical benefit for alteplase over placebo and found no significant differences between patients who received alteplase within 3 hours or between 3 and 6 hours. A review[9] of several studies confirmed that alteplase needed to be given early, and preferably within 90 minutes, if it was to be effective.

On the basis of the NINDS study, alteplase given within 3 hours of the onset of ischaemic stroke is now recommended for selected patients in most guidelines on stroke management.[10-15] Despite their own disappointing results, the ECASS II investigators reached a similar conclusion. However, these recommendations have been criticised.[16,17]

It has been pointed out[18,19] that very few patients will be eligible for treatment with alteplase, since the time of onset of symptoms is often uncertain and in many patients more than 3 hours elapses before a definite diagnosis of ischaemic stroke is made. A later analysis of results from 6 major controlled studies found that benefits of alteplase treatment were greater than risks (in terms of number needed to treat versus number needed to harm) up to 4.5 hours after symptom onset; there was no evidence of net benefit in the period from 4.5 to 6 hours after onset.[20]

In addition, the NINDS study[1] excluded patients with severe stroke and those taking anticoagulants. The rationale for exclusion of patients with severe stroke is that haemorrhagic transformation is more likely to occur with large areas of infarction.[18] However, size of infarct is difficult to identify by CT scanning.[18] Anticoagulants or antiplatelets are also contra-indicated in the first 24 hours after use of alteplase. The poor results obtained in studies using streptokinase have led to recommendations that streptokinase should be avoided in ischaemic stroke,[13] although an overview of thrombolytic studies[19] suggested that it may not be worse than alteplase and that the apparent hazards of streptokinase may be accounted for by differences in trial design (for example use with anticoagulants) and in patient population.

A systematic review[21] therefore concluded that further large studies are required to establish more clearly the overall role of thrombolytics in acute ischaemic stroke. Studies of the use of alteplase outside the setting of a clinical trial have had mixed results.[22-24] However, an observational study[25] found that alteplase was safe and effective when used in accordance with guidelines, while another study[26] found that it could be used in elderly patients (80 years-of-age and older), a group normally excluded from clinical trials. Another observational study[27] suggested (in line with the analysis of numbers needed to treat[20] referred to above) that alteplase was safe given up to 4.5 hours after stroke onset, and a randomised study[28] found that alteplase also improved outcomes when given after 3 to 4.5 hours, although the authors stressed that treatment within 3 hours was still preferred.

Intra-arterial thrombolytics may have advantages over intravenous use and may be used in selected patients.[12-14] Studies with nasaruplase[29] and urokinase[30] have suggested benefit up to 6 hours after stroke due to middle cerebral artery occlusion, and use of intra-arterial thrombolytics may therefore be considered in such patients.[12-14] Intra-arterial thrombolytics are also used in basilar artery occlusion, although evidence to support this is limited;[12,13,31] intravenous alteplase may be an alternative.[32] Combined use of intravenous and intra-arterial alteplase,[33] as well as use of adjunctive therapies such as therapeutic ultrasound[34] or antithrombotics, are under investigation but do not yet have an established role.[13]

Intravenous thrombolytics have no role in the management of acute *haemorrhagic stroke*, but they have been given locally to facilitate the aspiration of haematomas in both intracerebral[35] and subarachnoid haemorrhage. Small studies with urokinase have shown benefit in patients with intraventricular haemorrhage.

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Adverse Effects

In common with other thrombolytics streptokinase may cause haemorrhage, particularly from puncture sites; severe internal bleeding has occurred and may be difficult to control. Streptokinase is antigenic, and allergic reactions ranging from rashes to rarer anaphylactoid and serum-sickness-like symptoms have occurred. Fever, sometimes high, and associated symptoms such as chills and back or abdominal pain are quite frequent. Nausea and vomiting may occur. There have been a few reports of Guillain-Barré syndrome.

Streptokinase infusion may be associated with hypotension, both direct or as a result of reperfusion; bradycardia and arrhythmias may also occur due to reperfusion. The break-up of existing clots may occasionally produce emboli elsewhere; pulmonary embolism and acute renal failure due to cholesterol embolisation have been reported.

Back pain. Streptokinase infusion has been associated with the development of very severe low back pain, which resolves within a few minutes of stopping the infusion, and may be severe enough to warrant opioid analgesia.[1-4] The back pain may represent a hypersensitivity reaction. Providing that the pain is controlled and that dissecting aortic aneurysm is not suspected, it may still be possible to complete the streptokinase infusion.[4,5] Alternatively, immediate substitution with a different thrombolytic has been suggested.[6]

There have also been a few reports of low back pain associated with anistreplase infusion.[7,8]

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8. Lear J, Rajapakse R. Low back pain associated with anistreplase. *BMJ* 1993; **306:** 896.

Effects on the blood. Although falls in the haemoglobin value of patients receiving thrombolytics are most likely to be due to blood loss from haemorrhage, there has been a report of a patient who had signs of haemolytic anaemia after intravenous infusion of streptokinase.[1] In a subsequent test *in vitro* the patient's serum caused strong agglutination of streptokinase-treated red blood cells, supporting the view that streptokinase was responsible for the haemolysis.

1. Mathiesen O, Grunnet N. Haemolysis after intravenous streptokinase. *Lancet* 1989; **i:** 1016–17.

Effects on the eyes. Acute uveitis[1,2] and iritis,[3,4] associated with transient renal impairment in one patient,[3] have followed treatment of myocardial infarction with intravenous streptokinase. In one case uveitis was associated with serum sickness[2] and in all of them hypersensitivity to streptokinase was suspected.

1. Kinshuck D. Bilateral hypopyon and streptokinase. *BMJ* 1992; **305:** 1332.
2. Proctor BD, Joondeph BC. Bilateral anterior uveitis: a feature of streptokinase-induced serum sickness. *N Engl J Med* 1994; **330:** 576–7.
3. Birnbaum Y, *et al*. Acute iritis and transient renal impairment following thrombolytic therapy for acute myocardial infarction. *Ann Pharmacother* 1993; **27:** 1539–40.
4. Gray MY, Lazarus JH. Iritis after treatment with streptokinase. *BMJ* 1994; **309:** 97.

Effects on the kidneys. Transient proteinuria has been reported after use of streptokinase. In some patients proteinuria and renal impairment have developed about 7 days after thrombolytic therapy and have been associated with a syndrome resembling serum sickness,[1,2] suggesting a delayed hypersensitivity reaction; a similar case in a patient receiving anistreplase was associated with Henoch-Schönlein-like vasculitis.[3] These delayed reactions should be distinguished from the transient and apparently self-limiting proteinuria that has been reported in some patients in the first 24 to 72 hours after beginning streptokinase.[4,5] Proteinuria within the first 24 hours has been attributed to deposition of an immune complex in the glomeruli,[6] although haemodynamic and neurohormonal changes associated with acute myocardial infarction may be responsible since proteinuria has occurred in patients not receiving thrombolytic therapy.[7,8]

Streptokinase infusion has also been associated with acute oliguric renal failure due to acute tubular necrosis, apparently as a result of hypotension during the infusion, in a patient with existing renovascular narrowing.[9] Interestingly, it has been pointed out that a variant streptokinase may be the pathogenic agent in glomerulonephritis occurring after *Streptococcus pyogenes* infection.[10]

Renal failure has developed as a consequence of streptokinase-induced cholesterol embolism, see under Embolism, below.

1. Payne ST, *et al*. Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; **ii:** 1398.
2. Callan MFC, *et al*. Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
3. Ali A, *et al*. Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106–7.
4. Argent N, Adams PC. Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
5. More RS, Peacock F. Haematuria and proteinuria after thrombolytic therapy. *Lancet* 1990; **336:** 1454.
6. Lynch M, *et al*. Proteinuria with streptokinase. *Lancet* 1993; **341:** 1024.
7. Pickett TM, Hilton PJ. Proteinuria and streptokinase. *Lancet* 1993; **341:** 1538.
8. von Eyben FE, *et al*. Albuminuria with or without streptokinase. *Lancet* 1993; **342:** 365–6.
9. Kalra PA, *et al*. Acute tubular necrosis induced by coronary thrombolytic therapy. *Postgrad Med J* 1991; **67:** 212.
10. Barnham M. Hypersensitivity and streptokinase. *Lancet* 1990; **335:** 535.

Effects on the liver. Raised serum-alanine aminotransferase values, and in some cases raised aspartate aminotransferase activity, were seen more frequently in 95 patients who received streptokinase than in 94 given placebo as part of a study in patients with myocardial infarction.[1] The mechanism for the raised aminotransferase activity was not clear; a concomitant rise in γ-glutamyltransferase activity and bilirubin concentration suggested an hepatic source. Overt jaundice has been reported rarely.[2]

For references to rupture of the liver occurring during treatment with streptokinase, see Haemorrhage, below.

1. Maclennan AC, *et al*. Activities of aminotransferases after treatment with streptokinase for acute myocardial infarction. *BMJ* 1990; **301:** 321–2.
2. Gómez Guindal JA, *et al*. Ictericia inducida por estreptocinasa. *Rev Esp Cardiol* 1999; **52:** 1025–7.

Effects on the nervous system. There have been a few reports of Guillain-Barré syndrome after treatment with streptokinase.[1-4] Whether streptokinase was the cause is not certain although its antigenic properties do suggest that induction of an immunological reaction might be responsible.[3]

For discussion of cerebrovascular effects of streptokinase, see Haemorrhage, below.

1. Eden KV. Possible association of Guillain-Barré syndrome with thrombolytic therapy. *JAMA* 1983; **249:** 2020–1.
2. Leaf DA, *et al*. Streptokinase and the Guillain-Barré syndrome. *Ann Intern Med* 1984; **100:** 617.
3. Barnes D, Hughes RAC. Guillain-Barré syndrome after treatment with streptokinase. *BMJ* 1992; **304:** 1225.
4. Taylor BV, *et al*. Guillain-Barré syndrome complicating treatment with streptokinase. *Med J Aust* 1995; **162:** 214–15.

Effects on the respiratory system. Fatal acute respiratory distress syndrome occurred in a patient given streptokinase for pulmonary embolism.[1] It was suggested that streptokinase may have caused the pulmonary injury by altering vascular permeability due to generation of fibrinolytic products or via reperfusion oedema.

1. Martin TR, *et al*. Adult respiratory distress syndrome following thrombolytic therapy for pulmonary embolism. *Chest* 1983; **83:** 151–3.

Effects on the skin. Rashes may occur as an allergic reaction to streptokinase. For a report of skin necrosis possibly associated with cholesterol embolisation, see Embolism, below.

Embolism. Thrombolytic therapy has occasionally and paradoxically been associated with further embolism. This may be due to clots that break away from the treated thrombus, or to cholesterol crystals released after removal of fibrin from atheromatous plaques by thrombolysis.

Fatal pulmonary embolism has been reported,[1] apparently due to breakaway from a deep-vein thrombus under treatment. However, comparative studies have suggested that there is no evidence of a higher rate of such complications with streptokinase than with heparin.[2] When they do occur a good clinical response is usually seen to continued streptokinase.[2] Complications due to multiple microemboli were reported[3] in 7 of 475 consecutive patients treated with streptokinase or anistreplase for acute myocardial infarction. The sites of embolism were the legs (in 4) and brain (in 3); one patient apparently had systemic effects with skin infarction and renal impairment. Five of the 7 patients died. There has also been a report[4] of acute peripheral arterial thromboembolism in a patient given alteplase for ischaemic stroke.

Cholesterol embolisation can have many clinical manifestations depending on the location of the emboli. A classic presentation is livedo reticularis, gangrenous lower extremities, and acute renal failure.[5,6] Symptoms may appear within a few hours of starting thrombolytic treatment,[7] although in some cases they may not become evident for several days.[8-11]

1. Hill LN. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; **90:** 411–12.
2. Rogers LQ, Lutcher CL. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; **90:** 412–13.
3. Stafford PJ, *et al*. Multiple microemboli after disintegration of clot during thrombolysis for acute myocardial infarction. *BMJ* 1989; **299:** 1310–12.
4. Gomez-Beldarrain M, *et al*. Peripheral arterial embolism during thrombolysis for stroke. *Neurology* 2006; **67:** 1096–7.
5. Blankenship JC. Cholesterol embolisation after thrombolytic therapy. *Drug Safety* 1996; **14:** 78–84.
6. Wong FKM, *et al*. Acute renal failure after streptokinase therapy in a patient with acute myocardial infarction. *Am J Kidney Dis* 1995; **26:** 508–10.
7. Pochmalicki G, *et al*. Cholesterol embolisation syndrome after thrombolytic therapy for myocardial infarction. *Lancet* 1992; **339:** 58–9.
8. Ridker PM, Michel T. Streptokinase therapy and cholesterol embolization. *Am J Med* 1989; **87:** 357–8.
9. Pirson Y, *et al*. Cholesterol embolism in a renal graft after treatment with streptokinase. *BMJ* 1988; **296:** 394–5.
10. Dass H, Fescharek R. Skin necrosis induced by streptokinase. *BMJ* 1994; **309:** 1513–14.
11. Penswick J, Wright AL. Skin necrosis induced by streptokinase. *BMJ* 1994; **309:** 378.

Haemorrhage. Haemorrhage is a common adverse effect of thrombolytic therapy, and the problem and its management have been reviewed.[1] Thrombolytics are used to lyse pathological thrombi, but can also produce a 'lytic state' due to depletion of the natural plasmin inhibitor α_2-antiplasmin by excess plasmin production, thus predisposing to severe bleeding; they may also cause lysis of thrombi required for haemostasis.

Haemorrhage is a particular risk where there is existing or concomitant trauma. More than 70% of bleeding

episodes occur at vascular puncture sites,[1] so invasive procedures should be avoided if possible; if catheterisation is considered essential meticulous care of the vascular puncture site is necessary. Bleeding or severe bruising in patients receiving thrombolytic therapy have also been associated with intramuscular injection of analgesics,[2] the use of an automatic blood-pressure measuring machine,[3] a pre-existing prosthetic abdominal aortic graft,[4] and recent dental extraction.[5] Other disease states may also contribute: haemospermia has been reported after thrombolysis in a patient with mild prostatic symptoms,[6] haemorrhagic bullae have been reported in a patient with lichen sclerosus et atrophicus,[7] and diabetic patients are at risk of retinal haemorrhage if they have diabetic retinopathy,[8] although any increase in risk seems to be small.[9] A review of the GUSTO-I Study[10] (40 903 patients) identified older age, low body-weight, female sex, and African ancestry as other factors that increased the risk of haemorrhage.

Intracranial haemorrhage leading to stroke is the most serious bleeding complication with thrombolytics, and has a high mortality. Assessment of data from national registries and large-scale studies has identified several risk factors for intracranial haemorrhage, including those mentioned above for overall haemorrhage, hypertension on admission, a history of stroke, and thrombolysis with current alteplase regimens.[11-14] The benefits and risks must be assessed for each patient and thrombolytic therapy should still be given to the elderly and to those with hypertension if the expected benefits are great. Intracranial haemorrhage is a particular concern with the use of thrombolytics for the treatment of ischaemic stroke. In the NINDS study, using alteplase, clinical outcome appeared to be improved despite an increased incidence of symptomatic intracerebral haemorrhage. Subgroup analysis[15] suggested that severe neurological deficit, brain oedema, and mass effect, before treatment, were risks associated with the increased incidence of haemorrhage.

Fibrin-specific thrombolytics such as alteplase were developed in the hope that they would have less systemic effect than fibrin-nonspecific thrombolytics such as streptokinase and therefore cause less bleeding. However, studies that have assessed comparative bleeding rates have failed to confirm this, although the use of adjunctive antithrombotics and different dose regimens makes comparison difficult. In GUSTO-I,[10] the bleeding rate with alteplase plus intravenous heparin was lower than with streptokinase plus intravenous heparin, but was similar to that with streptokinase plus subcutaneous heparin. However, the rate of intracranial haemorrhage was higher with alteplase.[16] In ASSENT-2,[17] which compared bolus doses of the highly fibrin-specific thrombolytic tenecteplase with front-loaded alteplase, tenecteplase produced fewer major non-cerebral bleeds than alteplase but the rates of intracranial haemorrhage were nearly identical. Although a meta-analysis[18] suggested that rates of intracranial haemorrhage may be higher with bolus thrombolytics, others have suggested that this may not be a problem with newer bolus regimens.[19]

Other bleeding complications reported with thrombolytics include rupture of the spleen[20,21] and liver,[22] and rupture of a follicle has been reported in a menstruating woman.[23] Rupture of the heart with fatal consequences has been reported, although thrombolytics do not appear to increase the overall risk of cardiac rupture following myocardial infarction,[24] except possibly for early rupture in women.[25]

Diffuse alveolar haemorrhage,[26] ventricular wall haematoma,[27] and spinal epidural haematoma[28] have been reported in patients treated with streptokinase after myocardial infarction. Intrapleural use was associated with life-threatening haemorrhage in empyema after cardiac surgery,[29] and with fatal haemorrhage in a case of aortic dissection misdiagnosed as empyema.[30]

1. Sane DC, *et al.* Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med* 1989; **111:** 1010–22.
2. Morris GC, Sterry MJG. case report]. *BMJ* 1991; **302:** 246.
3. Gibson P. case report]. *BMJ* 1991; **302:** 1412.
4. London NJM, *et al.* Systemic thrombolysis causing haemorrhage around a prosthetic abdominal aortic graft. *BMJ* 1993; **306:** 1530–1.
5. Lustig JP, *et al.* Thrombolytic therapy for acute myocardial infarction after oral surgery. *Oral Surg Oral Med Oral Pathol* 1993; **75:** 547–8.
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7. Dunn HM, Fulton RA. Haemorrhagic bullae in a patient with lichen sclerosus et atrophicus treated with streptokinase. *Heart* 1996; **76:** 448.
8. Caramelli B, *et al.* Retinal haemorrhage after thrombolytic therapy. *Lancet* 1991; **337:** 1356–7.
9. Ward H, Yudkin JS. Thrombolysis in patients with diabetes. *BMJ* 1995; **310:** 3–4.
10. Berkowitz SD, *et al.* Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 1997; **95:** 2508–16.
11. Simoons ML, *et al.* Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993; **342:** 1523–8.
12. Aylward PE, *et al.* Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction: a randomized trial. *Ann Intern Med* 1996; **125:** 891–900.
13. Bovill EG, *et al.* Hemorrhagic events during therapy with recombinant tissue plasminogen activator, heparin, and aspirin for unstable angina (Thrombolysis in Myocardial Ischemia, Phase IIIB trial). *Am J Cardiol* 1997; **79:** 391–6.
14. Gurwitz JH, *et al.* Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. *Ann Intern Med* 1998; **129:** 597–604.
15. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997; **28:** 2109–18.
16. Gore JM, *et al.* Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. *Circulation* 1995; **92:** 2811–18.
17. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
18. Mehta SR, *et al.* Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000; **356:** 449–54.
19. Armstrong PW, *et al.* Bolus fibrinolysis: risk, benefit, and opportunities. *Circulation* 2001; **103:** 1171–3.
20. Wiener RS, Ong LS. Streptokinase and splenic rupture. *Am J Med* 1989; **86:** 249.
21. Blankenship JC, Indeck M. Spontaneous splenic rupture complicating anticoagulant or thrombolytic therapy. *Am J Med* 1993; **94:** 433–7.
22. Eklöf B, *et al.* Spontaneous rupture of liver and spleen with severe intra-abdominal bleeding during streptokinase treatment of deep venous thrombosis. *Vasa* 1977; **6:** 369–71.
23. Müller C-H, *et al.* Near-fatal intra-abdominal bleeding from a ruptured follicle during thrombolytic therapy. *Lancet* 1996; **347:** 1697.
24. Massel DR. How sound is the evidence that thrombolysis increases the risk of cardiac rupture? *Br Heart J* 1993; **69:** 284–7.
25. Becker RC, *et al.* Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study. *J Am Coll Cardiol* 1999; **33:** 479–87.
26. Yigla M, *et al.* Diffuse alveolar hemorrhage following thrombolytic therapy for acute myocardial infarction. *Respiration* 2000; **67:** 445–8.
27. Mohamed HA, *et al.* Right ventricular wall hematoma due to thrombolytic therapy presenting as cardiac tamponade: a case report and review of literature. *Can J Cardiol* 2003; **19:** 581–4.
28. Ozgocmen S, *et al.* Spinal epidural hematoma associated with streptokinase treatment for myocardial infarction. *Spinal Cord* 2004; **42:** 374–7.
29. Porter J, Banning AP. Intrapleural streptokinase. *Thorax* 1998; **53:** 720.
30. Srivastava P, *et al.* Fatal haemorrhage from aortic dissection following instillation of intrapleural streptokinase. *Scott Med J* 2000; **45:** 86–7.

Hypersensitivity. Streptokinase is a bacterial protein and has antigenic activity. The formation of streptokinase-neutralising antibodies may reduce the efficacy of subsequent doses and increase the risk of hypersensitivity reactions.

In a series of 25 patients given intravenous streptokinase for myocardial infarction, titres of streptokinase-neutralising antibodies rose from a mean neutralisation capacity of 0.16 millionunits before treatment to a mean of 25.54 million units 2 weeks after treatment, the highest individual titre being 93 million units. After 12 weeks the neutralisation capacity was still sufficient in 24 patients to have neutralised a standard 1.5-million unit dose of streptokinase. After 17 to 34 weeks titres were still high enough in 18 of 20 patients examined to neutralise at least half a standard dose.[1] As these results indicate, giving standard doses of streptokinase within several months of a previous course may lead to reduced effect. Thus, the recommended period in which it should not be repeated is usually between 5 days and 1 year after the initial dose (see Precautions, below). However, high titres of neutralising antibodies persisting for up to 7.5 years after use of streptokinase have been reported.[2-4] Since repeated dosage also increases the risk of hypersensitivity reactions, it has been suggested[2,5] that repeat courses should not be given within 4 or more years, and that if a repeat course is needed a non-antigenic thrombolytic such as alteplase or urokinase should be used until it is known whether or not high *in-vitro* titres affect efficacy. Increased titres of streptokinase-neutralising antibodies have also been measured in patients given topical streptokinase for wounds.[6]

Anistreplase also appears susceptible to neutralisation by streptokinase antibodies.[7]

Plasmacytosis,[8,9] serum-sickness,[8,10,11] rhabdomyolysis,[12] renal impairment (see Effects on the Kidneys, p. 1505.2), uveitis and iritis (see Effects on the Eyes, p. 1505.2), arthritis,[13] and anaphylaxis[14-17] have been reported in patients given streptokinase and are thought to represent hypersensitivity reactions, in some cases perhaps due to previous exposure to streptococcal antigens during infection. Back pain (see p. 1505.1) may also represent a hypersensitivity reaction. In some patients there may be a delay of between 1 and 10 days before the reaction appears.[18] The incidence of severe hypersensitivity reactions is probably fairly low, however; in the GISSI study anaphylaxis was reported in only 7 of 5860 patients although other hypersensitivity reactions leading to withdrawal of streptokinase were reported in 99 patients, with a further 42 such reactions after completion of the infusion.[15] Some episodes of apparent anaphylaxis seen with streptokinase may be fibrinolysin-mediated rather than antibody-antigen reactions. Alteplase, which is considered non-antigenic, has produced an anaphylactoid reaction in patients with a history of atopy.[19,20] Angioedema also occurred[21] in a patient with a history of SLE and penicillin allergy who was given alteplase for deep-vein thrombosis. Fibrinolysin, which activates complement cascade and the kinin system, is formed in quantity after the use of a thrombolytic. In most patients these effects are clinically insignificant, but the possibility of precipitating an anaphylactoid reaction exists, especially in those who are strongly atopic. The risk of angioedema with alteplase may also be increased in those taking ACE inhibitors—see under Interactions of Alteplase, p. 1298.1.

1. Jalihal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990; **335:** 184–5.
2. Elliott JM, *et al.* Neutralizing antibodies to streptokinase four years after intravenous thrombolytic therapy. *Am J Cardiol* 1993; **71:** 640–5.
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4. Squire IB, *et al.* Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J* 1999; **20:** 1245–52.
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12. Montgomery HE, *et al.* Rhabdomyolysis and multiple system organ failure with streptokinase. *BMJ* 1995; **311:** 1472.
13. Kelly MP, Bielawska C. Recurrence of a reactive arthritis following streptokinase therapy. *Postgrad Med J* 1991; **67:** 402.
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19. Purvis JA, *et al.* Anaphylactoid reaction after injection of alteplase. *Lancet* 1993; **341:** 966–7.
20. Massel D, *et al.* Anaphylactoid reaction during an infusion of recombinant tissue-type plasminogen activator for acute myocardial infarction. *Can J Cardiol* 1991; **7:** 298–302.
21. Francis CW, *et al.* Angioedema during therapy with recombinant tissue plasminogen activator. *Br J Haematol* 1991; **77:** 562–3.

Treatment of Adverse Effects

Allergic reactions to streptokinase may require treatment with antihistamines and corticosteroids, which have sometimes been given prophylactically. Anaphylaxis requires the use of adrenaline (for further details, see p. 1293.2).

Severe haemorrhage not controlled by local pressure requires the streptokinase infusion to be stopped. Tranexamic acid, aminocaproic acid, or aprotinin may be of benefit. Packed red blood cells may be preferable to whole blood for replacement therapy; factor VIII preparations may also be given. Volume expansion may be necessary, but the use of dextrans should be avoided because of their platelet-inhibiting properties.

Precautions

Streptokinase should be used with great care, if at all, in patients at increased risk of bleeding, or those in whom haemorrhage is likely to prove particularly dangerous. It should thus be avoided in patients with active internal bleeding or a recent history of peptic ulcer disease, oesophageal varices, ulcerative colitis or other bleeding gastrointestinal lesions, in patients with pancreatitis, in patients with subacute bacterial endocarditis, in patients with coagulation defects including those due to liver or kidney disease, or after recent surgery, childbirth, or trauma. It should not be given to patients at increased risk of cerebral bleeding including those with severe hypertension, haemorrhage or recent stroke, or to patients with cerebral neoplasm. It should not be given in pregnancy, particularly in the first 18 weeks because of the risk of placental separation and it has been suggested that it should not be used during heavy vaginal bleeding.

Invasive procedures, including intramuscular injections, should be avoided during, and immediately before and after, streptokinase therapy as they may increase the risk of bleeding; care should be taken when physically handling patients. Streptokinase should also be used with care in elderly patients. Patients with mitral stenosis associated with atrial fibrillation are more likely to have left heart thrombus which may lead to cerebral embolism after thrombolytic therapy. Although there is a theoretical risk of retinal bleeding in patients with diabetic retinopathy the benefits of treatment generally outweigh the risk.

Anti-streptokinase antibodies are formed after streptokinase use, with antibody titres rising abruptly after about 5 days. These antibodies may cause resistance or hypersensitivity to subsequent doses of streptokinase. Therefore,

further doses of streptokinase should not be given in the period between 5 days and 12 months after the initial dose (even longer periods have been suggested, see Hypersensitivity, under Adverse Effects, p. 1506.2); if thrombolytic therapy is required in this period an alternative non-antigenic drug should be used. High titres of anti-streptokinase antibodies may also occur in patients after some streptococcal infections such as streptococcal pharyngitis or acute rheumatic fever or in those with acute glomerulonephritis secondary to streptococcal infections; in such patients there may be resistance to streptokinase or a reduced effect.

Administration. Overinfusion of streptokinase may occur if a drop-counting infusion pump is used.[1] This arises as a result of flocculation of the streptokinase solution producing translucent fibres that affect the drop-forming mechanism so increasing the drop size.

For a comment on the incidence of flocculation in streptokinase solutions, see Stability, p. 1503.1.

1. Schad RF, Jennings RH. Overinfusions of streptokinase. *Am J Hosp Pharm* 1982; **39:** 1850.

Aortic dissection. A report of 4 cases of the inappropriate use of streptokinase in patients with aortic dissection misdiagnosed as myocardial infarction.[1] Thrombolytics are likely to extend aortic dissection and adversely affect the outcome. Of the 2 patients who died, one, who would have been suitable for early operation, died through the delay caused by impaired clotting. Although early intervention with thrombolytics may be of major benefit in acute myocardial infarction it is important that accurate differential diagnosis takes place to exclude conditions such as aortic dissection and prevent avoidable deaths.

For a report of fatal haemorrhage with streptokinase used in aortic dissection misdiagnosed as empyema, see Haemorrhage under Adverse Effects, p. 1505.3.

1. Butler J, *et al.* Streptokinase in acute aortic dissection. *BMJ* 1990; **300:** 517–19.

Cardiopulmonary resuscitation. Thrombolytics are not recommended after prolonged or traumatic cardiopulmonary resuscitation because of the risk of haemorrhage. However, studies[1,2] in patients given cardiopulmonary resuscitation for cardiac arrest associated with acute myocardial infarction have suggested that thrombolytics are generally safe and that any increase in bleeding complications is outweighed by the benefits of thrombolysis.

1. Cross SJ, *et al.* Safety of thrombolysis in association with cardiopulmonary resuscitation. *BMJ* 1991; **303:** 1242.
2. Kurkciyan I, *et al.* Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. *J Intern Med* 2003; **253:** 128–35.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies streptokinase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pregnancy. Thrombolytics are generally contra-indicated in pregnancy. However there are a few reports of their use and these have been briefly reviewed.[1] In most cases, thrombolytics were given at 28 weeks of pregnancy or later to patients with deep-vein thrombosis, pulmonary embolism, or prosthetic valve thrombosis. There were some reports of favourable maternal and fetal outcomes although therapy was associated with maternal haemorrhage, including spontaneous abortion and minor vaginal bleeding, especially when given near the time of delivery. There was one report of placental abruption with fetal death. A later review[2] noted about 200 successful cases of thrombolytic treatment in pregnancy, with a maternal mortality of about 1%, fetal mortality of about 6%, and premature delivery of about 6%. US guidelines[3] recommend reserving thrombolytic therapy in pregnant patients for life-threatening instances of thromboembolism.

1. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med* 1996; **125:** 751–62.
2. Ahearn GS, *et al.* Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of treatment options. *Arch Intern Med* 2002; **162:** 1221–7.
3. Bates SM, *et al.* American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133** (suppl): 844S–886S. Also available at: http://www.chestjournal.org/content/133/6_suppl/844S.full.pdf (accessed 14/10/09)

Interactions

Oral anticoagulants, heparin, and antiplatelet drugs such as aspirin are often used with streptokinase, but may increase the risk of haemorrhage. The risk may also be increased with dextrans, and with other drugs that affect coagulation or platelet function.

References.

1. Harder S, Klinkhardt U. Thrombolytics: drug interactions of clinical significance. *Drug Safety* 2000; **23:** 391–9.

Pharmacokinetics

Streptokinase is rapidly cleared from the circulation after intravenous use. Clearance is biphasic with the initial and more rapid phase being due to specific antibodies. A half-life of 23 minutes has been reported for the streptokinase-activator complex.

References.

1. Grierson DS, Bjornsson TD. Pharmacokinetics of streptokinase in patients based on amidolytic activator complex activity. *Clin Pharmacol Ther* 1987; **41:** 304–13.
2. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; **31:** 143–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Streptase; ***Austral.***: Streptase†; ***Belg.***: Streptase†; ***Braz.***: Solustrep; Streptase; Streptokin; Streptonase†; ***Canad.***: Streptase†; ***Chile***: Thromboflux; ***China***: Sikaitong (思凯通); Streptase (德链); Xin Tong (欣通); ***Cz.***: Streptase; ***Denm.***: Streptase; ***Fr.***: Streptase; ***Ger.***: Streptase; ***Gr.***: Kabikinase; Streptase; ***Hong Kong***: Streptase; ***Hung.***: Streptase; ***India***: Cardiostrep; Eskinase; Fibrokinase; Haemokinase; Icikinase; Kabikinase; Myokinase; Niskinase; STpase; Streptase; Zykinase; ***Indon.***: Streptase; ***Israel***: Streptase; ***Mex.***: Streptase; ***Neth.***: Streptase; ***NZ***: Streptase; ***Philipp.***: ST-Pase; Streptokin; Thromboflux; ***Pol.***: Streptase; ***Port.***: Streptase; ***Rus.***: Streptase (Стрептаза); Thromboflux (Тромбофлюкс); ***S.Afr.***: Streptase; ***Singapore***: Streptase; ***Spain***: Streptase†; ***Swed.***: Streptase; ***Switz.***: Streptase†; ***Thai.***: Streptase; Thromboflux; ***Turk.***: Kabikinase; Streptase; ***UK***: Streptase; ***Ukr.***: Farmakinase (Фармакиназа); ***USA***: Streptase; ***Venez.***: Streptase.

Multi-ingredient Preparations. ***Austria***: Varidase; ***Fin.***: Varidase†; ***Ger.***: Varidase; ***Mex.***: Varidasa; ***Norw.***: Varidase†; ***Pol.***: Biostreptaza; Distreptaza; ***Spain***: Ernodasa; Varidasa; ***Ukr.***: Biostrepta (Биострепта); Distreptaza (Дистрептаза).

Pharmacopoeial Preparations
BP 2014: Streptokinase Injection.

Strophanthin-K

Estrofantina; Kombé Strophanthin; Strophanthin; Strophanthoside-K; Строфантин-К.
CAS — 11005-63-3.

NOTE. Do not confuse with K-strophanthin-α which is Cymarin.

Pharmacopoeias. In *Chin.*

Profile

Strophanthin-K is a cardiac glycoside or a mixture of cardiac glycosides from strophanthus, the seeds of *Strophanthus kombe* (Apocynaceae) or other spp., adjusted by admixture with a suitable diluent such as lactose so as generally to possess 40% of the activity of anhydrous ouabain.

Strophanthin-K is a positive inotrope with general properties similar to those of digoxin (p. 1353.3). It is poorly absorbed from the gastrointestinal tract but may be given intravenously in maintenance doses of 125 to 250 micrograms daily in the management of heart failure (p. 1262.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Kombetin.

Homoeopathic Preparations. ***Austria***: Barium Med Complex; Corasan; Lakrima; ***Fr.***: Soludor; ***Ger.***: Cor Plus; Cor; Corvipas SL; Habstal-Cor N; Myonasan.

Suleparoid *(rINNM)*

Heparan Sulfate; Heparan Sulphate; Heparansulfat; Heparitin Sulfate; Siarczan Heparanu; Suleparoide; Suléparoïde; Suleparoidum; Sulfate d'Héparane; Сулепароид.
CAS — 9050-30-0.
UNII — 47959853R5.

Suleparoid Sodium *(rINN)*

Heparan Sulfate Sodium; Sodium Heparitin Sulphate; Suleparoide sódico; Suléparoïde Sodique; Suleparoidum Natricum; Сулепароид Натрий.
CAS — 57459-72-0.

Profile

Suleparoid is a naturally occurring glycosaminoglycan used topically in the management of haematomas and superficial thromboses, and for the relief of sprains and contusions. It has also been given orally. Suleparoid sodium is a component of danaparoid sodium (p. 1349.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Aremin; Clarema; Hemovasal; Vas†.

Multi-ingredient Preparations. ***Ital.***: Osmogel.

Sulodexide *(rINN)*

KRX-101; Sulodeksyd; Sulodexida; Sulodexidum; Сулодексид.
Glucurono-2-amino-2-deoxyglucoglucan sulfate.
CAS — 57821-29-1.
ATC — B01AB11.
ATC Vet — QB01AB11.

Profile

Sulodexide is a heparinoid consisting of a mixture of low-molecular-weight heparin and dermatan sulfate. It is used as a hypolipidaemic and antithrombotic and has been given orally and parenterally for peripheral vascular disease and cerebrovascular disease. It is also included in preparations used topically for local vascular inflammation and soft-tissue disorders. Sulodexide has also been investigated for other disorders including the treatment of diabetic nephropathy.

References.

1. Ofosu FA. Pharmacological actions of sulodexide. *Semin Thromb Hemost* 1998; **24:** 127–38.
2. Weiss R, *et al.* The role of sulodexide in the treatment of diabetic nephropathy. *Drugs* 2007; **67:** 2681–96.
3. Neri G, *et al.* Management of tinnitus: oral treatment with melatonin and sulodexide. *J Biol Regul Homeost Agents* 2009; **23:** 103–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Vessel Due F (伟素); ***Cz.***: Vessel Due F; ***Hung.***: Vessel Due F; ***Ital.***: Angioflux; Clarens; Provenal; Ravenol; Treparin; Vessel; ***Malaysia***: Vessel Due F; ***Philipp.***: Vessel Due F; ***Pol.***: Vessel Due F; ***Port.***: Vessel; ***Rus.***: Angioflux (Ангиофлюкс); Vessel Due F (Вессел Дуэ Ф); ***Spain***: Aterina; ***Thai.***: Vessel; ***Turk.***: Anjioflux; ***Venez.***: Vessel Due.

Sympathomimetics ⊗

Actions and Uses

Sympathomimetics have actions that mimic the effects of stimulation of postganglionic (adrenergic) nerves. They include the endogenous catecholamines adrenaline, noradrenaline, and dopamine, and other drugs that directly stimulate adrenergic receptors, as well as drugs that have an indirect action by stimulating the release of noradrenaline from storage vesicles in adrenergic nerve endings. Phenylephrine is an example of a direct-acting sympathomimetic, whereas ephedrine and many other sympathomimetics have both direct and indirect effects.

The endogenous sympathomimetics are catecholamines, consisting of a catechol portion (characterised by hydroxy groups at adjacent positions on a benzene ring) and an aliphatic amine portion. Adrenaline and noradrenaline both have direct actions on adrenergic receptors, whereas dopamine has direct and indirect actions, as well as stimulating specific dopamine receptors. Although sympathetic nerves are generally termed adrenergic, the principal neurotransmitter is actually noradrenaline; it also acts as a neurotransmitter in the CNS. The major physiological role of adrenaline is metabolic. Dopamine is an important neurotransmitter within the CNS, but also has a role peripherally within the renal, mesenteric, and coronary vasculature.

Adrenergic receptors are classified as either alpha or beta receptors, and these are subdivided into several types. Dopamine receptors are a distinct group of receptors that are mainly found in the CNS, and at least 5 subtypes are known (see p. 889.1); D_1 receptors also occur in some vascular beds. The effects of adrenergic stimulation depend on the location and activity of the receptors:

- $alpha_1$ receptors are found mainly in blood vessels, as well as in the skin, eye, bladder, uterus, and liver. Stimulation leads to vasoconstriction, particularly in the vessels of the skin and mucosa, abdominal viscera, and kidney; this results in an increase in blood pressure, sometimes with compensatory reflex bradycardia. $Alpha_1$ stimulation also results in contraction of other smooth muscle, including the urinary sphincter and the uterus, and induces mydriasis in the eye

- $alpha_2$ receptors are mainly found presynaptically. Stimulation appears to play a role in feedback inhibition of neurotransmitter release and may be involved in the inhibition of intestinal activity; it also plays a role in the inhibition of insulin secretion
- $beta_1$ receptors are found mainly in the heart. Stimulation produces an increase in the rate and force of contraction, increased conduction velocity, and greater automaticity
- $beta_2$ receptors are mainly found in blood vessels and the lung, as well as in the uterus, the gastrointestinal tract, the liver, and the ciliary body of the eye. Stimulation leads to vasodilatation, bronchodilatation, uterine relaxation, and a decrease in gastrointestinal motility; it also results in release of insulin and enhances gluconeogenesis and glycogenolysis
- $beta_3$ receptors are found in fat cells and are thought to have a role in lipolysis and thermogenesis; they have also been found in the heart, uterus, and bladder but their role is not clear
- D_1 receptors are found in the renal, mesenteric, and coronary vascular beds. Stimulation leads to vasodilatation

Sympathomimetics differ in their relative affinity for each type of receptor, and also in whether they have direct or indirect actions (see Table 5, below). Their effects generally reflect these characteristics, although both may depend on the dose. Feedback mechanisms and the homoeostatic response of the body are also important. The specific effects of the different sympathomimetics are described in more detail in the individual monographs.

The endogenous catecholamines all have a very short action and are inactive orally; they are also highly polar and do not cross the blood-brain barrier. Other sympathomimetics are analogues of catecholamines but generally have a longer duration of action and are orally active; many also cross the blood-brain barrier and have central effects. For example, dexamfetamine has marked central stimulant effects, while the seemingly paradoxical antihypertensive action of $alpha_2$ agonists such as clonidine may be due to central effects that outweigh their effects in vascular smooth muscle.

The differing characteristics of the sympathomimetics mean that they are used in a wide range of disorders. Those with $alpha_1$-agonist effects are mainly used to increase the blood pressure in hypotensive disorders and in shock (p. 1279.3). Some alpha agonists, such as phenylephrine (p. 1672.2), are also applied topically to produce vasoconstriction of mucosal surfaces and are used for the symptomatic relief of nasal congestion and in eye disorders; they may also be used as mydriatics. $Alpha_2$ agonists are used as central antihypertensives (see Clonidine, p. 1339.1), or in the treatment of glaucoma (see Apraclonidine, p. 2003.3). $Beta_1$ agonists are mainly used for their inotropic actions in acute heart failure and shock, while $beta_2$ agonists such as salbutamol (p. 1220.2) are used for their bronchodilator effects and as uterine relaxants in premature labour. Sympathomimetics with mainly CNS effects may be used as central stimulants (see Dexamfetamine, p. 2319.1).

Adverse Effects

Sympathomimetics may produce a wide range of adverse effects, generally resembling the effect of excessive stimulation of the sympathetic nervous system. These effects are mediated by the different types of adrenergic receptor, and the effects of individual drugs depend to a large extent on their relative activity at the different receptors, as well as the body's homoeostatic response. While many sympathomimetics are relatively selective for specific receptors, this depends on the dose, and at higher doses most have effects on all receptors.

Central effects may occur with all sympathomimetics and include anxiety, fear, restlessness, insomnia, confusion, irritability, headache, and psychotic states; dyspnoea, weakness, anorexia, nausea, and vomiting are also common. Although some sympathomimetics have direct effects, others do not cross the blood-brain barrier and their central effects appear to be a somatic response.

The most important adverse effects of the sympathomimetics are those that affect the cardiovascular system. Palpitations, tachycardia, and arrhythmias mainly result from stimulation of cardiac beta receptors, and there is also an increase in cardiac contractility; this may result in angina or cardiac arrest.

The effects on blood vessels depend on the relative effects at alpha and beta receptors, since most blood vessels have both. Stimulation of alpha receptors produces vasoconstriction, with resultant hypertension, and this may be severe enough to lead to cerebral haemorrhage or pulmonary oedema, particularly in overdosage. There may also be reflex bradycardia. Conversely, hypotension, with dizziness and fainting, and flushing, may occur due to $beta_2$-induced vasodilatation, and may contribute to tachycardia.

Alpha-mediated vasoconstriction causes cold extremities, since blood vessels supplying the skin and mucosa have only alpha receptors; this may lead to gangrene, particularly when sympathomimetics are infiltrated into digits. Extravasation similarly may cause tissue necrosis and sloughing. Topical application to mucosal surfaces also causes vasoconstriction, pain, and irritation; hypoxia may lead to rebound mucosal congestion.

Other effects include mydriasis, difficulty in micturition and urinary retention, piloerection, sweating, and increased salivation, all of which result from $alpha_1$ stimulation. Hypokalaemia and muscle tremor may occur as a result of $beta_2$ stimulation, although tremor may also occur as a somatic response. Effects on the uterus are complex and depend on the stage of the menstrual cycle; labour may be inhibited by $beta_2$ stimulation. Hyperglycaemia may occur due to complex metabolic effects, and lactic acidosis has also been reported.

Effects on the heart. The heart has mainly $beta_1$ adrenoceptors and cardiac arrhythmias are most likely with $beta_1$ agonists; increased mortality has been reported with the use of beta agonists in heart failure (see Ibopamine, p. 1407.2). A review[1] of vasopressor sympathomimetics, which are mainly used for their alpha-agonist properties, concluded that dopamine and adrenaline were associated with the highest risk, mainly of dose-related sinus tachycardia and ventricular arrhythmias. However, the clinical significance of most arrhythmias occurring with dopamine was considered questionable; supraventricular or ventricular arrhythmias with adrenaline were most likely in patients receiving general anaesthesia or with underlying disorders of cardiac conduction. The risk with noradrenaline was uncertain, though there are few clinical reports, while phenylephrine and methoxamine were thought unlikely to cause problems. Overall the frequency of serious problems with this class of drugs did not seem to be high, and benefits outweighed the risks in most patients.

Sympathomimetics may cause myocardial ischaemia, particularly in patients with ischaemic heart disease, and severe cardiovascular effects have occurred with the use of dobutamine for cardiac stress testing (see Diagnosis and Testing, p. 1366.2). In addition, myocardial infarction has been reported in an 11-year-old boy treated with nebulised racepinefrine for symptoms of croup,[2] and there have also been reports of myocardial ischaemia associated with adrenaline overdosage (see p. 1294.2).

1. Tisdale JE, *et al.* Proarrhythmic effects of intravenous vasopressors. *Ann Pharmacother* 1995; **29:** 269–81.
2. Butte MJ, *et al.* Pediatric myocardial infarction after racemic epinephrine administration. Abstract: *Pediatrics* 1999; **104:** 103–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e9 (accessed 07/10/05)

Topical use. Systemic effects may occasionally follow the local or topical use of sympathomimetics, for example as eye drops for the treatment of glaucoma.[1] Psychiatric effects including hallucinations and paranoia have also occurred after both proper and improper use of sympathomimetics in decongestant preparations.[2]

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
2. Anonymous. Drugs that cause psychiatric symptoms. *Med Lett Drugs Ther* 1993; **35:** 65–70.

Treatment of Adverse Effects

Most sympathomimetics have a short duration of action and treatment of adverse effects is mainly supportive; if given by infusion, stopping it or reducing the rate will be sufficient in many cases. A rapidly-acting alpha blocker, such as phentolamine, may be given to reverse $alpha_1$-mediated effects such as hypertension, while a beta blocker may be given for $beta_1$-mediated effects such as cardiac arrhythmias. In severe hypertension, rapidly-acting vasodilators such as glyceryl trinitrate have also been used.

In the case of extravasation of an alpha agonist, or injection into a digit, an alpha blocker such as phentolamine should be given as soon as possible to prevent tissue necrosis and ischaemic damage.

Non-catecholamine sympathomimetics may have a longer duration of action and adverse effects, particularly hypertension, may be prolonged.

Precautions

Sympathomimetics should be used with caution in patients with cardiovascular disorders, who may have an increased susceptibility to their effects. Particular care is needed in patients with cardiac arrhythmias, ischaemic heart disease, or hypertension. All sympathomimetics should generally be avoided in severe hypertension, although alpha agonists are particularly hazardous; they should also be used with caution in patients with occlusive vascular disease, who are at increased risk of peripheral ischaemia. $Beta_1$ agonists are a particular hazard in tachycardia. Sympathomimetics with $beta_2$ effects should be used with caution in obstructive cardiomyopathy and other disorders where a reduction in total peripheral resistance could be harmful.

Sympathomimetics should be avoided in phaeochromocytoma. Caution is also needed in patients with hyperthyroidism, who may be at increased risk of effects on the heart; elevated thyroid hormone concentrations may also enhance adrenoceptor sensitivity. Diabetics and elderly patients have a high incidence of atherosclerotic disease and may also be at higher risk; the effects of sympathomimetics on blood glucose should also be considered.

Alpha agonists in particular should be used with caution in angle-closure glaucoma, as well as in patients with prostate disorders, who may be at increased risk of urinary retention. Sympathomimetics with vasoconstrictor effects may reduce placental perfusion and should possibly be avoided in pregnancy; adrenaline and others with $beta_2$-mediated effects may also inhibit labour.

If sympathomimetics are used for circulatory support, hypovolaemia, metabolic acidosis, and hypoxia or hypercapnia should be corrected either before starting the sympathomimetic or while it is being given. Blood pressure should be monitored regularly during treatment.

Interactions

Interactions with sympathomimetics are complex and may be hazardous; they result mainly from their pharmacological actions at alpha and beta receptors.

Table 5. Actions of sympathomimetics.

	Action		Receptor specificity			
	Direct	Indirect	α	β_1	β_2	DA*
Adrenaline	+		+	+	+	
Dobutamine	+		+	+	+	
Dopamine	+	+	+	+		+
Dopexamine	+	+			+	+
Ephedrine	+	+	+	+	+	
Etilefrine	+		+	+	+	
Ibopamine		+	+	+	+	+
Isoprenaline	+			+	+	
Mephentermine	+	+	+	+		
Metaraminol	+	+	+	+		
Methoxamine	+		+			
Midodrine	+		+			
Noradrenaline	+		+	+		
Phenylephrine	+		+			

* = Dopaminergic

Increased cardiac effects may occur with drugs that increase the sensitivity of the myocardium to $beta_1$ agonists; hazardous arrhythmias may occur with volatile anaesthetics, particularly cyclopropane or halothane. Caution is also required with thyroid hormones, and with drugs that affect cardiac conduction, such as cardiac glycosides and antiarrhythmics.

All sympathomimetics affect blood pressure and should be used with caution with antihypertensive drugs or drugs that cause hypotension, particularly those whose action involves the sympathetic nervous system. Direct-acting sympathomimetics with alpha-agonist actions specifically reverse the hypotensive effect of adrenergic neurone blockers such as guanethidine, and severe hypertension may result. There are also complex interactions between both alpha and beta blockers and sympathomimetics, particularly those that have actions at both types of receptor. Alpha blockers antagonise the effects at alpha receptors but leave the beta-mediated effects unopposed, leading to an increased risk of hypotension and tachycardia. Beta blockers, especially those that are non-selective, antagonise the effects at beta receptors but leave the alpha-mediated effects unopposed, increasing the risk of hypertension and reflex bradycardia. They also antagonise the bronchodilating effects of $beta_2$ agonists. Severe anaphylaxis in patients taking non-cardioselective beta blockers may not respond to adrenaline (see below).

Hazardous interactions resulting in severe hypertension may occur with MAOIs (including RIMAs) and sympathomimetics, especially those that have indirect actions, since MAOIs increase the amount of noradrenaline stored in adrenergic nerve endings. Sympathomimetics for which the risk is particularly high include dexamfetamine, dopamine, dopexamine, ephedrine, isometheptene, mephentermine, metaraminol, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, and pseudoephedrine. The effects of direct-acting sympathomimetics such as adrenaline and noradrenaline may also be slightly enhanced. For additional warnings see under Phenelzine (p. 445.1) and Moclobemide (p. 438.1).

Tricyclic antidepressants block the inactivation of adrenaline and noradrenaline by uptake into the nerve endings and may increase their effect; hypertension and arrhythmias may occur. Conversely, the effect of indirectly-acting sympathomimetics could theoretically be reduced by tricyclics, although there is little clinical evidence that this occurs. There is also no evidence that an interaction occurs when local anaesthetic solutions containing adrenaline or noradrenaline are used in patients taking MAOIs or tricyclics, although great care needs to be taken to avoid inadvertent intravenous injection of these local anaesthetic preparations.

Interactions may also occur between sympathomimetics and drugs that have similar or opposing effects through non-adrenergic mechanisms. Sympathomimetics with central actions may potentiate the effects of CNS stimulants, while the vasoconstrictor and pressor effects of alpha agonists may be enhanced by drugs with similar effects, such as ergot alkaloids or oxytocin. $Beta_2$-mediated hypokalaemia may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, and aminophylline or theophylline; patients given high doses of $beta_2$ agonists with such drugs should have their plasma-potassium concentration monitored (see Interactions of Salbutamol, p. 1223.1). Hypokalaemia may also contribute to the increased susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides.

Antiparkinsonian drugs. Additive cardiovascular toxicity may occur when some sympathomimetics are given with antiparkinsonian drugs such as *levodopa* (see p. 908.1) and *bromocriptine* (see p. 899.1). Severe hypertension may also occur with some sympathomimetics and *selegiline* (see p. 916.2), possibly due to inhibition of peripheral monoamine oxidase.

Beta blockers. The interactions between beta blockers and sympathomimetics are complex and depend on the selectivity of both drugs. Patients given adrenaline (including the low doses used with local anaesthetics) while taking non-selective beta blockers such as *propranolol* can develop raised blood pressure due to alpha-mediated vasoconstriction, followed by reflex bradycardia, and occasionally cardiac arrest;[1] the bronchodilator effects of adrenaline and other $beta_2$ agonists are also inhibited. In contrast, cardioselective beta blockers such as *metoprolol*, have minimal effects on blood pressure and heart rate since they only inhibit the $beta_1$- mediated effects, leaving the $beta_2$-mediated vasodilatation to balance the vasoconstrictor effect. However, beta blockers that also have alpha-blocking effects, such as *carvedilol*, may cause hypotension since only the $beta_2$-induced vasodilatation remains; such an interaction has been reported with dobutamine.[2] Low doses of cardioselective beta blockers do not appear to interfere with sympathomimetic (isoprenaline)-induced bronchodilatation,[3] although the effect of larger doses is uncertain.

Propranolol has also been shown to inhibit the favourable pressor and bronchodilator responses to adrenaline when given for anaphylaxis.[4] Thus, patients on long-term treatment with some non-cardioselective beta blockers who develop anaphylaxis may be relatively refractory to adrenaline.

1. Jay GT, Chow MSS. Interaction of epinephrine and β -blockers. *JAMA* 1995; **274:** 1830–2.
2. Lindenfeld J, *et al*. Hypotension with dobutamine: β -adrenergic antagonist selectivity at low doses of carvedilol. *Ann Pharmacother* 1999; **33:** 1266–9.
3. Decalmer PBS, *et al*. Beta blockers and asthma. *Br Heart J* 1978; **40:** 184–9.
4. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981; **47:** 35–7.

General anaesthetics. Anaesthesia may sensitise the myocardium to the effects of sympathomimetics, increasing the risk of arrhythmias, and fatalities have been attributed to the use of adrenaline with *halothane* anaesthesia.[1] It has been suggested[2] that the use of adrenaline for haemostasis during surgery is a particular risk, although use of a low dose may be safe in patients anaesthetised with *cyclopropane*, *halothane*, or similar volatile anaesthetics; other factors likely to increase the irritability of the myocardium, such as carbon-dioxide retention, hypoxia, or the use of cocaine, should be avoided.[2,3] For *halothane* or *trichloroethylene* anaesthesia a maximum strength for the adrenaline solution of 1 in 100 000, given at a rate not exceeding 10 mL in any 10-minute period or 30 mL in 1 hour, has been recommended;[3] this may also apply for cyclopropane, although the risk of arrhythmias is higher.[3] Other volatile anaesthetics generally appear to carry less risk.

1. Buzik SC. Fatal interaction? Halothane, epinephrine and tooth implant surgery. *Can Pharm J* 1990; **123:** 68–9 and 81.
2. Anonymous. Anaesthetics and the heart. *Lancet* 1967; **i:** 484–5.
3. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. *Anesthesiology* 1968; **29:** 763.

Theophylline. For discussion of possible interactions between sympathomimetics with beta-agonist actions and theophylline, see p. 1236.3.

Vasodilators. Paradoxical hypotension may occur when sympathomimetics with both alpha-and beta-agonist properties are given with *tolazoline*, and there has been a report[1] of fatal hypotension in a patient given tolazoline and dopamine together. The mechanism of the interaction appears to be antagonism of the alpha-mediated vasoconstrictor effect of the sympathomimetic by the alpha-blocking effects of tolazoline, leaving the vasodilator effects unopposed.

1. Carlon GC. Fatal association of tolazoline and dopamine. *Chest* 1979; **76:** 336.

Talinolol *(rINN)* ⊗

Talinololum; Талинолол.
(±)-1-{*p*-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl}-3-cyclohexylurea.
$C_{20}H_{33}N_3O_3$=363.5
CAS — 57460-41-0.
ATC — C07AB13.
ATC Vet — QC07AB13.
UNII — 3S82268BKG.

Profile

Talinolol is a cardioselective beta blocker (p. 1316.3). It is given orally in the management of hypertension (p. 1251.1) and other cardiovascular disorders, in doses of up to 300 mg daily. It has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Cordanum; ***Rus.***: Cordanum (Корданум).

Teclothiazide Potassium *(BANM, rINNM)* ⊗

Kalii Teclothiazidum; Téclothiazide Potassique; Teclotiazida potásica; Tetrachlormethiazide Potassium; Калия Теклотиазид.
6-Chloro-3,4-dihydro-3-trichloromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide potassium.
$C_8H_7Cl_4N_3O_4S_2K$=454.2
CAS — 4267-05-4 (teclothiazide); 5306-80-9 (teclothiazide potassium).
UNII — SO5Y2RV80F.

Profile

Teclothiazide potassium is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) used in the treatment of oedema.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain.*** Quimodril.

Tedisamil *(BAN, USAN, rINN)*

KC-8857; Tédisamil; Tedisamilum; Тедизамил.
3′,7′-Bis(cyclopropylmethyl)spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane].
$C_{19}H_{32}N_2$=288.5
CAS — 90961-53-8.
ATC — C01BD06.
ATC Vet — QC01BD06.
UNII — A5VAY2U3R8.

Profile

Tedisamil is an antiarrhythmic under investigation for the treatment of atrial arrhythmias.

References.

1. Hohnloser SH, *et al*. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Coll Cardiol* 2004; **44:** 99–104.
2. Krishnamoorthy S, Lip GY. Novel antiarrhythmic drugs in atrial fibrillation: focus on tedisamil. *Expert Opin Invest Drugs* 2009; **18:** 1191–6.

Telmisartan *(BAN, USAN, rINN)*

BIBR-277; BIBR-277-SE; Telmisartaani; Telmisartán; Telmisartanum; Тельмизартан.
4′-{[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl}-2-biphenylcarboxylic acid.
$C_{33}H_{30}N_4O_2$=514.6
CAS — 144701-48-4.
ATC — C09CA07.
ATC Vet — QC09CA07.
UNII — U5SYW473RQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Telmisartan). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane. it dissolves in 1M sodium hydroxide. It exhibits polymorphism.

USP 36: (Telmisartan). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane; it dissolves in 1M sodium hydroxide. Store in airtight containers. Protect from light.

Uses and Administration

Telmisartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1) and for the prophylaxis of cardiovascular events in patients with certain risk factors (see Cardiovascular Risk Reduction, p. 1246.1).

Telmisartan is given orally. After a dose the hypotensive effect peaks within 3 hours and persists for at least 24 hours. The maximum hypotensive effect occurs within about 4 to 8 weeks after starting therapy.

In **hypertension**, telmisartan is given in an initial dose of 40 mg once daily. This may be adjusted, if necessary, within the range of 20 to 80 mg once daily. Low doses should be considered in patients with hepatic or renal impairment (see p. 1510.1).

For **cardiovascular risk reduction**, telmisartan may be given in a dose of 80 mg once daily.

The hydrochloride salt has also been used.

Reviews.

1. Sharpe M, *et al*. Telmisartan: a review of its use in hypertension. *Drugs* 2001; **61:** 1501–29.
2. Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. *Drugs* 2006; **66:** 51–83.
3. Gosse P. A review of telmisartan in the treatment of hypertension: blood pressure control in the early morning hours. *Vasc Health Risk Manag* 2006; **2:** 195–201.
4. Yamagishi S, *et al*. Potential utility of telmisartan, an angiotensin II type 1 receptor blocker with peroxisome proliferator-activated receptor-γ (PPAR-γ)-modulating activity for the treatment of cardiometabolic disorders. *Curr Mol Med* 2007; **7:** 463–9.
5. Francischetti EA, *et al*. Treatment of hypertension in individuals with the cardiometabolic syndrome: role of an angiotensin II receptor blocker, telmisartan. *Expert Rev Cardiovasc Ther* 2008; **6:** 289–303.
6. Rosario BH, Hendra TJ. Telmisartan in the treatment of hypertension. *Expert Opin Drug Metab Toxicol* 2008; **4:** 485–92.
7. Xi GL, *et al*. Meta-analysis of randomized controlled trials comparing telmisartan with losartan in the treatment of patients with hypertension. *Am J Hypertens* 2008; **21:** 546–52.
8. Baumhäkel M, Böhm M. Telmisartan prevents cardiovascular events in a broad group of at-risk patients. *Expert Opin Pharmacother* 2009; **10:** 3113–17.

9. Burnier M. Telmisartan: a different angiotensin II receptor blocker protecting a different population? *J Int Med Res* 2009; **37:** 1662–79.
10. Galzerano D, *et al*. New standards in hypertension and cardiovascular risk management: focus on telmisartan. *VascHealth Risk Manag* 2010; **6:** 113–33.
11. Zheng Z, *et al*. A systematic review and meta-analysis of telmisartan versus valsartan in the management of essential hypertension. *J Clin Hypertens (Greenwich)* 2010; **12:** 414–21.

Administration in hepatic or renal impairment. Doses of telmisartan may need to be adjusted in patients with hepatic or renal impairment.

- Giving telmisartan to patients with *hepatic impairment* resulted in an increase in bioavailability and a reduction in clearance compared with healthy subjects.[1] Although telmisartan was well tolerated, it was suggested that lower doses should be considered. In the UK telmisartan is contra-indicated in severe hepatic impairment and a maximum dose of 40 mg once daily is recommended for patients with mild to moderate impairment.
- Telmisartan appears to be well tolerated in patients with *renal impairment*, including those on dialysis.[2] However, in the UK, an initial dose of 20 mg once daily is recommended for patients with severe renal impairment or on haemodialysis.

1. Stangier J, *et al*. Pharmacokinetics and safety of intravenous and oral telmisartan 20 mg and 120 mg in subjects with hepatic impairment compared with healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1355–64.
2. Sharma AM, *et al*. Telmisartan in patients with mild/moderate hypertension and chronic kidney disease. *Clin Nephrol* 2005; **63:** 250–7.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1. Telmisartan should be used with caution in patients with hepatic impairment or biliary obstruction.

References.
1. Michel MC, *et al*. Safety of telmisartan in patients with arterial hypertension: an open-label observational study. *Drug Safety* 2004; **27:** 335–44.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies telmisartan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Digoxin. Telmisartan may increase serum concentrations of digoxin (see Angiotensin II Receptor Antagonists under Interactions of Digoxin, p. 1356.1) but the interaction is probably not clinically significant.

Pharmacokinetics

Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% after a 40-mg dose and 58% after a 160-mg dose. Peak plasma concentrations of telmisartan are reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the faeces via bile, mainly as unchanged drug. The terminal elimination half-life of telmisartan is about 24 hours.

References.
1. Stangier J, *et al*. Absorption, metabolism, and excretion of intravenously and orally administered [^{14}C]telmisartan in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1312–22.
2. Deppe S, *et al*. Telmisartan: a review of its pharmacodynamic and pharmacokinetic properties. *Expert Opin Drug Metab Toxicol* 2010; **6:** 863–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Deprevex; Gliosartan; Micardis; ***Austral.***: Micardis; ***Austria***: Micardis; ***Belg.***: Kinzalmono; Micardis; ***Braz.***: Micardis; Pritor; ***Canad.***: Micardis; ***Chile***: Cordiax; Micardis; Samertan†; ***China***: An Ya (安亚); An Yi Ning (安怡宁); Bang Tan (邦坦); Bei Di Ning (倍迪宁); Bo Xin Shu (博欣舒); Chang Ping (常平); Da Shu Ya (达舒亚); Di Sai Ping (迪赛平); Di Yi Ning (蒂益宁); Fan Tan (凡坦); Heng Bei (恒贝); Heng Xue Su (恒雪素); Huo Ping (获平); Jia Se Yi (嘉瑟宜); Kang Chu (康楚); Li Lai Ke (利来客); Li Wen (立文); Long Shu Ya (隆舒雅); Luo Ge Le (洛格乐); Luo Sha Ning (洛莎宁); Mei Si (美斯); Micardis (美卡素); Nideshu (尼德舒); Nuo Jin Ping (诺金平); Nuo Shi Mei (诺适美); Ou Mei Ning (欧美宁); Ping Ke Ya Xin (平克亚欣); Pu Mei Te (浦美特); Qu Ya (曲亚); Sai Ka (赛卡); Saitan (赛坦); Sha Tai Qi (沙泰齐); Sha Ting Ning (沙汀宁); Shang Er Ning (尚尔宁); Shi Ji (施吉); Shu Luo Ning (舒洛宁); Si Tai Le (斯泰乐); Sonia (舒尼亚); Su Ding (素定); Tan Xin Suo (坦芯素); Te Li Kang (特立康); Ti Yu (提愈); Tian He Heng (天禾恒); TianYi (天易); Xin Rui (欣蕊); Xin Yi Er (欣益尔); Xue Ying Ping (雪盈平); Ya Ping (雅屏); Ya Tan (亚坦); Yaweiyi (亚维伊); Yi Ya Ping (益亚平); Yu Le Ning (毓乐宁); Zhi Xin Feng (至信风); ***Cz.***: Dinortes; Kinzalmono; Micardis; Mirpresoc; Pritor; Tezeo; Tolura; Zanacodar; ***Denm.***: Micardis; Pritor†; ***Fin.***: Kinzalmono; Micardis; ***Fr.***: Micardis; Pritor; ***Ger.***: Kinzalmono; Micardis; ***Gr.***: Micardis; Pritor; ***Hong Kong***: Micardis; ***Hung.***: Micardis; Pritor; ***India***: Anzitel; Arbitel; Cortel; Cresar; Etela; Hytel; Lovetel; Mistra; Mytel; Newtel; Oditel; Telma; Telpres; ***Indon.***: Micardis; ***Irl.***: Actelsar; Dinortes; Kinzalmono; Micardis; Mirpresoc; Pritor; Telma; Tolura; Zanacodar; ***Israel***: Micardis†; ***Ital.***: Micardis; Pritor; ***Jpn***: Micardis; ***Malaysia***: Micardis; ***Mex.***: Micardis; Predxal; ***Neth.***: Dinortes; Kinzalmono; Micardis; Mirpresoc; Pritor; Telma; Tolura; Zanacodar; ***Norw.***: Micardis; ***NZ***: Micardis†; ***Philipp.***: Micardis; Pritor; ***Pol.***: Kinzalmono; Micardis; Pritor; Tolura; ***Port.***: Kinzalmono; Micardis; Pritor; ***Rus.***: Micardis (Микардис); Pritor (Прайтор); ***S. Afr.***: Micardis; Pritor; ***Singapore***: Micardis; ***Spain***: Micardis; Pritor; ***Swed.***: Micardis; ***Switz.***: Kinzal; Micardis; ***Thai.***: Micardis; ***Turk.***: Micardis; Pritor; ***UK***: Micardis; ***Ukr.***: Micardis (Микардис); Pritor (Прайтор); ***USA***: Micardis; ***Venez.***: Micardis; Pritor.

Multi-ingredient Preparations. ***Arg.***: Gliosartan Plus; Micardis Amlo; Micardis Plus; ***Austral.***: Micardis Plus; Twynsta; ***Austria***: MicardisPlus; ***Belg.***: Kinzalkomb; Micardis Plus; Twynsta; ***Braz.***: Micardis Anlo; Micardis HCT; Pritor HCT†; ***Canad.***: Micardis Plus; Twynsta; ***Chile***: Cordiax D; Micardis Plus; ***China***: Micardis Plus (美嘉素); ***Cz.***: Kinzalkomb; MicardisPlus; PritorPlus; Twynsta; ***Denm.***: MicardisPlus; PritorPlus; ***Fin.***: Kinzalkomb; MicardisPlus; ***Fr.***: MicardisPlus; PritorPlus; Twynsta; ***Ger.***: Kinzalkomb; MicardisPlus; Twynsta; ***Gr.***: Micardis Plus; Pritor Plus; Twynsta; ***Hong Kong***: Micardis Plus; ***Hung.***: MicardisPlus; PritorPlus; ***India***: Anzitel-H; Arbitel-H; Cortel-A; Cortel-H; Etela-H; Hytel-H; Lovetel-H; Mytel-H; Newtel-H; Oditel-H; Telma-H; Telpres-H; ***Indon.***: Micardis Plus; ***Irl.***: Kinzalkomb; MicardisPlus; Onduarp; PritorPlus; Twynsta; ***Ital.***: Micardis Plus; PritorPlus; ***Malaysia***: Micardis Plus; ***Mex.***: Micardis Plus; Predxal Plus; ***Neth.***: Kinzalkomb; Micardis Plus; Onduarp; PritorPlus; Tardipan; Twynsta; ***Norw.***: MicardisPlus; ***Philipp.***: Micardis Plus; PritorPlus; ***Pol.***: Kinzalkomb; Micardis Plus; Pritor Plus; Twynsta; ***Port.***: Kinzalkomb; Micardis Plus; PritorPlus; Twynsta; ***Rus.***: MicardisPlus (МикардисПлюс); ***S.Afr.***: Co-Micardis; ***Singapore***: Micardis Plus; Twynsta; ***Spain***: Micardis Plus; Pritor Plus; Twynsta; ***Swed.***: Micardis Plus; ***Switz.***: Kinzalplus; Micardis Amlo; MicardisPlus; ***Thai.***: Micardis Plus; Twynsta; ***Turk.***: Micardis Plus; Pritor Plus; ***UK***: MicardisPlus; ***Ukr.***: MicardisPlus (МикардисПлюс); ***USA***: Micardis HCT; ***Venez.***: Micardis Plus; Pritor Plus.

Pharmacopoeial Preparations
USP 36: Telmisartan and Hydrochlorothiazide Tablets; Telmisartan Tablets.

Temocapril Hydrochloride *(BANM, USAN, rINNM)*

CS-622; Hidrocloruro de temocapril; Témocapril, Chlorhydrate de; Temocapril, hidrocloruro de; Temocaprili Hydrochloridum; Темокаприла Гидрохлорид.

(+)-(2*S*,6*R*)-6-[[(1*S*)-1-Ethoxycarbonyl-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5*H*)-acetic acid hydrochloride.

$C_{23}H_{28}N_2O_5S_2$,HCl=513.1

CAS — 111902-57-9 (temocapril); 110221-44-8 (temocapril hydrochloride).

ATC — C09AA14.

ATC Vet — QC09AA14.

UNII — 8G820195VP.

Profile

Temocapril is an ACE inhibitor (p. 1282.2) that has been used in the treatment of hypertension (p. 1251.1). It owes its activity to the diacid temocaprilat to which it is converted after oral doses.

References.
1. Nakashima M, *et al*. Pharmacokinetics of temocapril hydrochloride, a novel angiotensin converting enzyme inhibitor, in renal insufficiency. *Eur J Clin Pharmacol* 1992; **43:** 657–9.
2. Oguchi H, *et al*. Pharmacokinetics of temocapril and enalapril in patients with various degrees of renal insufficiency. *Clin Pharmacokinet* 1993; **24:** 421–7.
3. Furuta S, *et al*. Pharmacokinetics of temocapril, an ACE inhibitor with preferential biliary excretion, in patients with impaired liver function. *Eur J Clin Pharmacol* 1993; **44:** 383–5.
4. Arakawa M, *et al*. Pharmacokinetics and pharmacodynamics of temocapril during repeated dosing in elderly hypertensive patients. *Eur J Clin Pharmacol* 2001; **56:** 775–9.
5. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; **41:** 207–24.
6. Yasunari K, *et al*. Pharmacological and clinical studies with temocapril, an angiotensin converting enzyme inhibitor that is excreted in the bile. *Cardiovasc Drug Rev* 2004; **22:** 189–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Acecol.

Tenecteplase *(BAN, USAN, rINN)*

Tenecteplasa; Ténectéplase; Tenecteplasum; TNK-tPA; Тенектеплаз.

[103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanine]plasminogen activator (human tissue-type).

CAS — 191588-94-0.

ATC — B01AD11.

ATC Vet — QB01AD11.

UNII — WGD229O42W.

Description. Tenecteplase is a 527 amino acid glycoprotein produced by recombinant DNA technology. It is a modified form of human tissue plasminogen activator.

Uses and Administration

Tenecteplase is a thrombolytic drug. It converts plasminogen to its active form plasmin, resulting in fibrinolysis and dissolution of blood clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Tenecteplase is a fibrin-specific thrombolytic (see p. 1245.3).

Tenecteplase is used similarly to streptokinase (p. 1503.1) in acute myocardial infarction (p. 1257.1). It is given intravenously as a single bolus dose over 5 to 10 seconds as soon as possible after the onset of symptoms. The dose is based on body-weight and ranges from 30 mg in patients less than 60 kg to a maximum of 50 mg in those 90 kg or above.

References.
1. Cannon CP, *et al*. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation* 1998; **98:** 2805–14.
2. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
3. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358:** 605–13.
4. Melzer C, *et al*. Fibrinolysis of acute peripheral arterial occlusion with tenecteplase—a new weight-optimized treatment regimen. *J Thromb Thrombolysis* 2004; **18:** 43–6.
5. Spöhr F, *et al*. International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. *Eur J Clin Invest* 2005; **35:** 315–23.
6. Kelly RV, *et al*. Safety of adjunctive intracoronary thrombolytic therapy during complex percutaneous coronary intervention: initial experience with intracoronary tenecteplase. *Catheter Cardiovasc Interv* 2005; **66:** 327–32.
7. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; **367:** 569–78.
8. Hull JE, *et al*. Tenecteplase in acute lower-leg ischemia: efficacy, dose, and adverse events. *J Vasc Interv Radiol* 2006; **17:** 629–36.
9. Kline JA, *et al*. Tenecteplase to treat pulmonary embolism in the emergency department. *J Thromb Thrombolysis* 2007; **23:** 101–5.
10. Johnson KK, *et al*. Tenecteplase for malignant pericardial effusion. *Pharmacotherapy* 2007; **27:** 303–5.
11. Melandri G, *et al*. Review of tenecteplase (TNKase) in the treatment of acute myocardial infarction. *Vasc Health Risk Manag* 2009; **5:** 249–56.
12. Becattini C, *et al*. TIPES Study Group. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res* 2010; **125:** e82–e86.
13. Tumlin J, *et al*. A phase III, randomized, double-blind, placebo-controlled study of tenecteplase for improvement of hemodialysis catheter function: TROPICS 3. *Clin J Am Soc Nephrol* 2010; **5:** 631–6.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tenecteplase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Streptokinase, p. 1507.1

Pharmacokinetics

After intravenous injection in patients with acute myocardial infarction, tenecteplase has a biphasic clearance from plasma with an initial half-life of 20 to 24 minutes and a terminal phase half-life of 90 to 130 minutes. It is cleared mainly by hepatic metabolism.

Reviews.
1. Tanswell P, *et al*. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet* 2002; **41:** 1229–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Metalyse; ***Austria***: Metalyse; ***Belg.***: Metalyse; ***Braz.***: Metalyse; ***Canad.***: TNKase; ***Chile***: Metalyse; ***Cz.***: Metalyse; ***Denm.***: Metalyse; ***Fin.***: Meta-

lyse; ***Fr.***: Metalyse; ***Ger.***: Metalyse; ***Gr.***: Metalyse; ***Hong Kong***: Metalyse; ***Hung.***: Metalyse; ***Irl.***: Metalyse; ***Ital.***: Metalyse; ***Malaysia***: Metalyse; ***Mex.***: Metalyse; ***Neth.***: Metalyse; ***Norw.***: Metalyse; ***NZ***: Metalyse; ***Pol.***: Metalyse; ***Port.***: Metalyse; ***Rus.***: Metalyse (Метализе); ***S.Afr.***: Metalyse; ***Singapore***: Metalyse; ***Spain***: Metalyse; ***Swed.***: Metalyse; ***Switz.***: Metalyse; ***Thai.***: Metalyse; ***Turk.***: Metalyse; ***UK***: Metalyse; ***Ukr.***: Metalize (Метализе); ***USA***: TNKase.

Terazosin Hydrochloride

(BANM, USAN, rINNM)

Abbott-45975; Hidrocloruro de terazosina; Teratsosiinihydrokloridi; Terazosin Hidroklorür; Terazosina, hidrocloruro de; Térazosine, chlorhydrate de; Terazosinhydroklorid; Terazosini Hydrochloridum; Теразозина Гидрохлорид.

1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(tetrahydro-2-furoyl)piperazine hydrochloride dihydrate; 6,7-Dimethoxy-2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]quinazolin-4-ylamine hydrochloride dihydrate.

$C_{19}H_{25}N_5O_4$,HCl,$2H_2O$=459.9

CAS — 63590-64-7 (terazosin); 63074-08-8 (anhydrous terazosin hydrochloride); 70024-40-7 (terazosin hydrochloride dihydrate).

ATC — G04CA03.

ATC Vet — QG04CA03.

UNII — D32S14F082 (terazosin hydrochloride); 8QOP8Z9955 (anhydrous terazosin hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Terazosin Hydrochloride Dihydrate). White or slightly yellow, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol; practically insoluble in acetone. A 2% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 36: (Terazosin Hydrochloride). A white to pale yellow, crystalline powder. soluble in water and in methyl alcohol; freely soluble in isotonic saline solution; slightly soluble in alcohol and in 0.1N hydrochloric acid; practically insoluble in acetone and in hexanes; very slightly soluble in chloroform. Store in airtight containers at a temperature between 20 degrees and 25 degrees.

Uses and Administration

Terazosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1), but a longer duration of action.

It is used in the management of hypertension (p. 1251.1) and in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction.

Terazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Terazosin hydrochloride 1.2 mg is equivalent to about 1 mg of terazosin. After oral doses its hypotensive effects are seen within 15 minutes and may last for up to 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose the initial dose for both hypertension and benign prostatic hyperplasia is 1 mg of terazosin at bedtime, increasing gradually at intervals of 7 days according to the patient's response. For **hypertension** the usual maintenance dose is 2 to 10 mg once daily and the usual maximum dose is 20 mg daily in a single dose or two divided doses. For **benign prostatic hyperplasia** the usual maintenance dose is 5 to 10 mg once daily.

Reviews.

1. Titmarsh S, Monk JP. Terazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. *Drugs* 1987; **33:** 461–77.
2. Achari R, Laddu A. Terazosin: a new alpha adrenoceptor blocking drug. *J Clin Pharmacol* 1992; **32:** 520–3.
3. Wilt TJ, *et al.* Terazosin for benign prostatic hyperplasia. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 01/02/06).

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3.

Overdosage. A report of sinus bradycardia and hypotension associated with ingestion of 300 mg of terazosin with suicidal intent.[1] The patient recovered with no sequelae after supportive treatment with atropine and intravenous fluids.

1. Seak C-J, Lin C-C. Acute intoxication with terazosin. *Am J Emerg Med* 2008; **26:** 117.e5–117.e6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terazosin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Urinary incontinence. For reference to urinary incontinence associated with terazosin, see under Adverse Effects of Prazosin Hydrochloride, p. 1475.1.

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Pharmacokinetics

Terazosin is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses; the bioavailability is reported to be about 90%. Peak plasma concentrations are achieved in about 1 hour. Terazosin is 90 to 94% protein bound. It is metabolised in the liver; one of the metabolites is reported to possess antihypertensive activity. The half-life in plasma is about 12 hours. Terazosin is excreted in faeces via the bile, and in the urine, as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Andrin; Benaprost; Blavin; Eglidon; Flumarc; Fosfomik; Geriprost; Isontyn; Panaprost; Proxatan; Rotiaz†; Teril; ***Austral.***: Hytrin; ***Austria***: Urocard; Uroflo; Vicard; ***Belg.***: Hytrin; Terazosabb; Uro-Hytrin†; ***Braz.***: Hytrin; ***Canad.***: Hytrin; ***Chile***: Adecur; Hytrin; ***China***: Hytrin (高特灵); Jun Yi (均益); Ke Pai (可派); Luo Di Er (罗迪尔); Mei Li Chang (美沥畅); Ou De Man (欧得曼); Pai Su (派速); Shi Ai Te (施艾特); Tai Le (泰乐); Yue Ke (悦克); Zheng Shu (正舒); ***Cz.***: Hytrin; Kornam; ***Denm.***: Sinalfa; ***Fr.***: Dysalfa; Hytrine; ***Ger.***: Flotrin; Heitrin; Tera; Terablock; Teranar; Terazid†; Terazoflo†; ***Gr.***: Hytrin; Vlanodrin; ***Hong Kong***: Hytrin; ***Hung.***: Hytrin; Setegis; ***India***: Gotera; Hytrin; Olyster; Zytrin; ***Indon.***: Hytrin; ***Irl.***: Benph; Hytrin; ***Israel***: Hytrin; ***Ital.***: Extersin; Ezosina; Itrin; Prostatil; Terafluss; Teraprost; Unoprost; Urodie; ***Malaysia***: Conmy; Hytrin; Ralsin; Terasin; ***Mex.***: Adecur; Hytrin; Romaken; ***Neth.***: Hytrin; ***Norw.***: Sinalfa; ***NZ***: Hytrin; ***Philipp.***: Conmy; Hykor; Hytrin; Hyzin; Lotencin; ***Pol.***: Hytrin; Kornam; Setegis; Tesin†; ***Port.***: Hytrin; ***Rus.***: Kornam (Корнам); Setegis (Сетегис); ***S.Afr.***: Hytrin; ***Singapore***: Hytrin; Terasin; ***Spain***: Alfaprost; Deflox; Magnurol; Mayul; Sutif; Teraumon; Zayasel; ***Swed.***: Hytrinex; Sinalfa; ***Switz.***: Hytrin BPH; ***Thai.***: Hytrin; ***Turk.***: Hytrin; Teranar; Teraumon; Tezoteva; ***UK***: Hytrin; ***Ukr.***: Alfater (Альфатер); Kornam (Корнам)†; Setegis (Сетегис); ***USA***: Hytrin; ***Venez.***: Adecur; Hytrin.

Pharmacopoeial Preparations

USP 36: Terazosin Capsules; Terazosin Tablets.

Tertatolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tertatolol; S-2395 (tertatolol or tertatolol hydrochloride); SE-2395 (tertatolol or tertatolol hydrochloride); Tertatolol, Chlorhydrate de; Tertatolol, hidrocloruro de; Tertatololi Hydrochloridum; Тертатолола Гидрохлорид.

(±)-1-(*tert*-Butylamino)-3-(thiochroman-8-yloxy)propan-2-ol hydrochloride.

$C_{16}H_{25}NO_2S$,HCl=331.9

CAS — 34784-64-0 (tertatolol); 33580-30-2 (tertatolol hydrochloride).

ATC — C07AA16.

ATC Vet — QC07AA16.

Profile

Tertatolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity.

Tertatolol is given orally as the hydrochloride in the management of hypertension (p. 1251.1) in a dose of 5 mg tertatolol hydrochloride once daily, increased to 10 mg once daily if required.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Artex; ***Gr.***: Artexal†; ***Irl.***: Artexal†; ***Neth.***: Artex; ***Port.***: Artex.

Tezosentan *(BAN, rINN)*

Tezosentán; Tézosentan; Tezosentanum; Тезозентан.

N-(6-(2-Hydroxyethoxy)-5-(*o*-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)-4-pyridyl]-4-pyrimidinyl)-5-isopropyl-2-pyridinesulfonamide.

$C_{27}H_{27}N_9O_6S$=605.6

CAS — 180384-57-0.

UNII — 64J9J55263.

Profile

Tezosentan is an endothelin receptor antagonist that has been studied in acute heart failure.

References.

1. Torre-Amione G, *et al.* Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure. *Circulation* 2001; **103:** 973–80.
2. Tovar JM, Gums JG. Tezosentan in the treatment of acute heart failure. *Ann Pharmacother* 2003; **37:** 1877–83.
3. Cotter G, *et al.* The hemodynamic and neurohormonal effects of low doses of tezosentan (an endothelin A/B receptor antagonist) in patients with acute heart failure. *Eur J Heart Fail* 2004; **6:** 601–9.
4. McMurray JJV, *et al.* Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007; **298:** 2009–19.

Tiadenol *(rINN)*

LL-1558; Tiadénol; Tiadenolum; Тиаденол.

2,2′-(Decamethylenedithio)diethanol.

$C_{14}H_{30}O_2S_2$=294.5

CAS — 6964-20-1.

ATC — C10AX03.

ATC Vet — QC10AX03.

UNII — 22251270CX.

Profile

Tiadenol is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 1.6 to 2.4 g daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mon.***: Fonlipol.

Ticagrelor *(BAN, USAN, rINN)*

AR-C126532XX; AZD-6140; Ticagrélor; Ticagrelorum; Тикагрельор.

(1*S*,2*S*,3*R*,5*S*)-3-(7-{[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

$C_{23}H_{28}F_2N_6O_4S$=522.6

CAS — 274693-27-5.

ATC — B01AC24.

ATC Vet — QB01AC24.

UNII — GLH0314RVC.

Uses and Administration

Ticagrelor is an adenosine triphosphate analogue and acts as a reversible purinoreceptor P2Y$_{12}$-antagonist in a similar manner to clopidogrel (p. 1342.3), inhibiting adenosine diphosphate-mediated platelet aggregation. It is given orally, usually with low-dose aspirin, for the prevention of thromboembolism in patients with acute coronary syndromes. A single loading dose of 180 mg is given, followed by a maintenance dose of 90 mg twice daily.

References.

1. Wallentin L, *et al.* PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–57.
2. Anderson SD, *et al.* Efficacy and safety of ticagrelor: a reversible P2Y12 receptor antagonist. *Ann Pharmacother* 2010; **44:** 524–37.
3. Gurbel PA, *et al.* Ticagrelor for the treatment of arterial thrombosis. *Expert Opin Pharmacother* 2010; **11:** 2251–9.
4. Abergel E, Nikolsky E. Ticagrelor: an investigational oral antiplatelet treatment for reduction of major adverse cardiac events in patients with acute coronary syndrome. *Vasc Health Risk Manag* 2010; **6:** 963–77.
5. Nawarskas JJ, Clark SM. Ticagrelor: a novel reversible oral antiplatelet agent. *Cardiol Rev* 2011; **19:** 95–100.
6. James SK, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ* 2011; **342:** d3527.
7. NICE. Ticagrelor for the treatment of acute coronary syndromes (issued October 2011). Available at: http://www.nice.org.uk/guidance/TA236/Guidance/pdf (accessed 08/03/12)

Adverse Effects and Precautions

The most common adverse effect associated with the use of ticagrelor (as with other reversible purinoreceptor P2Y$_{12}$-antagonist) is bleeding disorders (see Effects on the Blood, under Adverse Effects and Precautions of Ticlopidine, p. 1512.3). Ticagrelor should not be given to patients with haematopoietic disorders such as neutropenia or thrombocytopenia, haemorrhagic diathesis or other haemorrhagic disorders associated with a prolonged bleeding time, or condition with an increased risk of bleeding such as peptic ulcer disease, intracranial haemorrhage, or moderate to severe liver dysfunction. To avoid excessive bleeding, treatment with ticagrelor should be stopped 5 to 7 days before elective surgery. Treatment should not otherwise be prematurely stopped or interrupted; however, if this is necessary because of bleeding, ticagrelor should be restarted as soon as possible to avoid the risk of stent thrombosis, cardiovascular death, or myocardial infarction.

Mild to moderate dyspnoea, that often resolved without the need for treatment, was also commonly associated with

the use of ticagrelor. It should be used with caution in patients with a history of asthma or chronic obstructive pulmonary disease; no specific treatment is suggested for those who develop new, prolonged, or worsened dyspnoea, however, if dyspnoea is not tolerated UK licensed product information recommends that treatment with ticagrelor be stopped.

Asymptomatic ventricular pauses have been reported from early clinical studies and ticagrelor should be used with caution in patients with an increased risk of bradycardic events and in those taking drugs known to induce bradycardia (see below).

Serum creatinine levels may increase during treatment with ticagrelor; renal function should be checked one month after starting treatment and thereafter at appropriate intervals. Serum uric acid levels may also increase and ticagrelor should be used with caution in patients with a history of hyperuricaemia or gouty arthritis; use in uric acid nephropathy is not recommended.

References.
1. Gaglia MA, Waksman R. Overview of the 2010 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting regarding ticagrelor. *Circulation* 2011; **123:** 451–6.

Interactions

Ticagrelor is mainly metabolised by cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP3A5. The use of both strong inhibitors and inducers of CYP3A should therefore be avoided at the same time as ticagrelor use. Ticagrelor, itself, is a mild inhibitor of CYP3A4 and as such should not be given with CYP3A4 substrates that have a narrow therapeutic index, such as cisapride or ergot alkaloids. It also inhibits the p-glycoprotein transporter system and thus digoxin and ciclosporin levels should be monitored if starting or changing ticagrelor therapy.

UK product information advises caution in the use of ticagrelor with drugs known to cause bradycardia, such as beta blockers, calcium-channel blockers, and digoxin. Additionally, caution is needed when used with drugs known to alter haemostasis. Due to reports of cutaneous bleeding with SSRIs, caution is advised when giving these antidepressants with ticagrelor.

Pharmacokinetics

Ticagrelor is rapidly absorbed from the gastrointestinal tract with a mean absolute bioavailability of about 36%. Both ticagrelor and its active metabolite are extensively bound to plasma proteins (> 99.7%). The systemic exposure to the active metabolite is about 30 to 40% of the exposure to ticagrelor. The steady state volume of distribution for ticagrelor is about 88 litres and the mean half-life is about 7 hours for ticagrelor and 8.5 to 9 hours for the active metabolite. Ticagrelor is mainly metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and, to a lesser extent, CYP3A5. The primary route of elimination of the major metabolite of ticagrelor is likely to be biliary secretion. Recovery of ticagrelor and its major metabolite in the urine were less than 1% of the dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Brilique; ***Braz.***: Brilinta; ***Denm.***: Brilique; ***Fr.***: Brilique; ***Ger.***: Brilique; ***Gr.***: Brilique; ***Irl.***: Brilique; Possia; ***Israel***: Brilinta; ***Neth.***: Brilique; ***Norw.***: Brilique; ***Pol.***: Brilique; Possia; ***Port.***: Brilique; Possia; ***Singapore***: Brilinta; ***Spain***: Brilique; ***Swed.***: Brilique; ***Switz.***: Brilique; ***Thai.***: Brilinta; ***UK***: Brilique; ***USA***: Brilinta.

Ticlopidine Hydrochloride

(BANM, USAN, rINNM)

53-32C; 4-C-32; Hidrocloruro de ticlopidina; Ticlopidina, hidrocloruro de; Ticlopidine, Chlorhydrate de; Ticlopidinhydrochlorid; Ticlopidini Hydrochloridum; Tiklopidiinihydrokloridi; Tiklopidin Hidroklorür; Tiklopidinhidroklorid; Tiklopidin-hydrochlorid; Tiklopidinhydroklorid; Tiklopidino hidrochloridas; Тиклопидина Гидрохлорид.

5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride.

$C_{14}H_{14}ClNS,HCl$=300.2

CAS — 55142-85-3 (ticlopidine); 53885-35-1 (ticlopidine hydrochloride).

ATC — B01AC05.

ATC Vet — QB01AC05.

UNII — A1L4914FMF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ticlopidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; very slightly soluble in ethyl acetate. A 2.5% solution in water has a pH of 3.5 to 4.0.

USP 36: (Ticlopidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in ethyl acetate. Store in airtight containers at a temperature below 30 degrees.

Uses and Administration

Ticlopidine hydrochloride is a thienopyridine antiplatelet drug used in thromboembolic disorders (p. 1273.2). It is a platelet $P2Y_{12}$-receptor antagonist that acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It may be given prophylactically as an alternative to aspirin in patients at risk of thrombotic stroke (p. 1269.2) and in the management of intermittent claudication (see Chronic Occlusive Peripheral Arterial Disease, p. 1272.3) and ischaemic heart disease. It is also licensed as an adjunct to aspirin for the prevention of subacute stent occlusion after intracoronary stenting (but see Reperfusion and Revascularisation Procedures, below). Ticlopidine may also be used to prevent occlusion and platelet loss during extracorporeal circulatory procedures.

In the prevention of thrombotic **stroke**, and in **intermittent claudication**, ticlopidine hydrochloride is given orally in a dose of 250 mg twice daily, with meals. For the prevention of subacute stent occlusion after **intracoronary stenting** ticlopidine hydrochloride is given in a dose of 250 mg twice daily for 4 weeks, starting at the time of stent placement.

Regular haematological monitoring is required during ticlopidine therapy (see Adverse Effects and Precautions, below).

References.
1. McTavish D, *et al.* Ticlopidine: an updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs* 1990; **40:** 238–59.
2. Flores-Runk P, Raasch RH. Ticlopidine and antiplatelet therapy. *Ann Pharmacother* 1993; **27:** 1090–8.
3. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129:** 394–405.
4. Wallentin L. $P2Y_{12}$ inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009; **30:** 1964–77.

Reperfusion and revascularisation procedures. Coronary stents are widely used as an adjunct to angioplasty to prevent acute vessel closure and to reduce restenosis (see Reperfusion and Revascularisation Procedures, p. 1259.2). Subacute thrombosis is a major complication of their use and patients were initially treated with an aggressive combination of anticoagulants and antiplatelets. However, it is now generally recognised that antiplatelet drugs alone are adequate in most patients.

Early studies[1-4] found that ticlopidine for 4 to 6 weeks after stenting, given with long-term aspirin, was at least as effective as an oral anticoagulant with aspirin, with some studies showing benefit in terms of thrombosis[1,4] or bleeding complications.[1] However, the risk of neutropenia limits the use of ticlopidine, and clopidogrel is now generally preferred, although there is some evidence[5] that shorter courses of ticlopidine (2 weeks) may be acceptable.

Ticlopidine has also been reported[6] to improve the long-term patency of saphenous vein bypass grafts used to treat peripheral vascular disease in the legs.

1. Schömig A, *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; **334:** 1084–9.
2. Kastrati A, *et al.* Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. *Circulation* 1997; **96:** 462–7.
3. Bertrand ME, *et al.* Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation* 1998; **98:** 1597–1603.
4. Leon MB, *et al.* A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998; **339:** 1665–71.
5. Berger PB, *et al.* Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. *Circulation* 1999; **99:** 248–53.
6. Becquemin J-P. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. *N Engl J Med* 1997; **337:** 1726–31.

Adverse Effects and Precautions

Bleeding is the most commonly reported adverse effect with thienopyridines; skin rashes may also occur, and gastrointestinal disturbances are common with ticlopidine. Blood dyscrasias, including neutropenia, thrombotic thrombocytopenic purpura, and aplastic anaemia, have occurred. There have been reports of hepatitis and cholestatic jaundice. Blood-lipid concentrations may increase during long-term therapy.

Ticlopidine and other thienopyridines should not be given to patients with haematopoietic disorders such as neutropenia or thrombocytopenia, haemorrhagic diathesis or other haemorrhagic disorders associated with a prolonged bleeding time, or conditions with an increased risk of bleeding such as peptic ulcer disease, acute cerebral haemorrhage, or severe liver dysfunction. Full blood counts should be performed before starting treatment with ticlopidine and every 2 weeks during the first 3 months of therapy. If ticlopidine is stopped during this period, a full blood count should be performed within 2 weeks of stopping treatment. Consideration should be given to stopping ticlopidine therapy 10 to 14 days before elective surgery.

Effects on the blood. Severe *neutropenia* or *agranulocytosis* may occur in about 1% of patients given ticlopidine[1] and fatal infection has been reported.[2] Neutropenia usually develops within the first 3 months of therapy and is reversible on stopping ticlopidine, but there has been a report[3] of a delayed reaction that occurred 18 days after ticlopidine was stopped. Isolated *thrombocytopenia* occurs in about 0.4% of patients and *thrombotic thrombocytopenic purpura* (TTP), sometimes fatal, has occurred.[1,4-8] The rate of TTP associated with ticlopidine use in patients with stents has been estimated at between 1 in 1600 and 1 in 5000.[8] Conversely, good results have been achieved with ticlopidine as a treatment for thrombotic thrombocytopenic purpura,[9,10] but it should only be used with extreme caution.[11] Aplastic anaemia has also occurred rarely with ticlopidine.[1,12]

Clopidogrel has also been associated with blood dyscrasias. Up to August 2004, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[13] had received 80 reports of blood dyscrasias associated with clopidogrel, although ticlopidine was associated with a much higher rate of reports. Individual cases of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome,[8,14-17] aplastic anaemia,[18] leucopenia,[19] and acquired haemophilia A,[20] have also been reported. However the most frequently reported adverse effect of clopidogrel, as with other antithrombotics such as prasugrel and ticagrelor, is bleeding, particularly when given with other drugs affecting coagulation; ADRAC had received 130 reports of haemorrhagic events, leading to fatalities in 18 cases following the use of clopidogrel.[13] The rate of major bleeding events with ticagrelor is similar to that with clopidogrel.[21]

1. Love BB, *et al.* Adverse haematological effects of ticlopidine: prevention, recognition and management. *Drug Safety* 1998; **19:** 89–98.
2. Carlson JA, Maesner JE. Fatal neutropenia and thrombocytopenia associated with ticlopidine. *Ann Pharmacother* 1994; **28:** 1236–8.
3. Farver DK, Hansen LA. Delayed neutropenia with ticlopidine. *Ann Pharmacother* 1994; **28:** 1344–6.
4. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med* 1998; **128:** 541–4.
5. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura after stenting and ticlopidine. *Lancet* 1998; **352:** 1036–7.
6. Steinhubl SR, *et al.* Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. *JAMA* 1999; **281:** 806–10.
7. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Intern Med* 1999; **159:** 2524–8.
8. Zakarija A, *et al.* Ticlopidine- and clopidogrel-associated thrombotic thrombocytopenic purpura (TTP): review of clinical, laboratory, epidemiological, and pharmacovigilance findings (1989-2008). *Kidney Int* 2009; **75** (suppl 112s): S20–S24.
9. Vianelli N, *et al.* Thrombotic thrombocytopenic purpura and ticlopidine. *Lancet* 1991; **337:** 1219.
10. Bobbio-Pallavicini E, *et al.* Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP): results of a randomized multicenter trial by the Italian Cooperative Group for TTP. *Haematologica* 1997; **82:** 429–35.
11. Rock G, *et al.* Thrombotic thrombocytopenic purpura treatment in year 2000. *Haematologica* 2000; **85:** 410–19.
12. Symeonidis A, *et al.* Ticlopidine-induced aplastic anemia: two new case reports, review, and meta-analysis of 55 additional cases. *Am J Hematol* 2002; **71:** 24–32.
13. Adverse Drug Reactions Advisory Committee (ADRAC). Clopidogrel—haemorrhage and haematological disorders. *Aust Adverse Drug React Bull* 2004; **23:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0408.htm (accessed 17/08/05)
14. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000; **342:** 1773–7.
15. Oomen PHN, *et al.* Hemolytic uremic syndrome in a patient treated with clopidogrel. *Ann Intern Med* 2000; **132:** 1006.
16. Andersohn F, *et al.* Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome associated with clopidogrel: report of two new cases. Abstract: *Heart* 2004; **90:** e57. Full version: http://heart.bmjjournals.com/cgi/content/full/90/9/e57 (accessed 17/08/05)
17. von Mach M-A, *et al.* Subacute coronary stent thrombosis in a patient developing clopidogrel associated thrombotic thrombocytopenic purpura. Abstract: *Heart* 2005; **91:** e14. Full version: http://heart.bmjjournals.com/cgi/content/full/91/2/e14 (accessed 17/08/05)
18. Trivier J-M, *et al.* Fatal aplastic anaemia associated with clopidogrel. *Lancet* 2001; **357:** 446.
19. McCarthy MW, Kockler DR. Clopidogrel-associated leukopenia. *Ann Pharmacother* 2003; **37:** 216–19.
20. Haj M, *et al.* Acquired haemophilia A may be associated with clopidogrel. *BMJ* 2004; **329:** 323.
21. Gaglia MA, Waksman R. Overview of the 2010 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting regarding ticagrelor. *Circulation* 2011; **123:** 451–6.

Effects on the gastrointestinal tract. Diarrhoea is a common adverse effect of ticlopidine therapy; it usually occurs during the first few months of therapy and resolves within 1 to 2 weeks without stopping therapy. However, there has been a report[1] of diarrhoea and weight loss of 2 months duration that first presented 2 years after ticlopi-

dine was started; diarrhoea resolved when ticlopidine was withdrawn.

1. Mansoor GA, Aziz K. Delayed chronic diarrhea and weight loss possibly due to ticlopidine therapy. *Ann Pharmacother* 1997; **31:** 870–2.

Effects on the joints. Acute arthritis associated with a diffuse rash developed in a patient shortly after starting treatment with ticlopidine.[1] Both the rash and the arthritis resolved on withdrawal, and it was suggested that a hypersensitivity reaction might be involved. One case of polyarthritis and 3 cases of arthralgia associated with ticlopidine had been reported to the UK CSM up to March 2001. Two cases of acute arthritis have also been reported[2] with clopidogrel; symptoms developed 2 to 3 weeks after starting treatment and resolved after stopping.

1. Dakik HA, *et al.* Ticlopidine associated with acute arthritis. *BMJ* 2002; **324:** 27.
2. Garg A, *et al.* Clopidogrel associated with acute arthritis. *BMJ* 2000; **320:** 483.

Effects on the kidneys. A reversible deterioration in renal function has been reported in patients given ticlopidine after coronary stent implantation.[1,2] There has also been a report[3] of membranous nephropathy with nephrotic syndrome in a patient receiving clopidogrel.

1. Elsman P, Zijlstra F. Ticlopidine and renal function. *Lancet* 1996; **348:** 273–4.
2. Virdee M, *et al.* Ticlopidine and renal function. *Lancet* 1996; **348:** 1031–2.
3. Tholl U, *et al.* Clopidogrel and membranous nephropathy. *Lancet* 1999; **354:** 1443–4.

Effects on the liver. Cholestatic hepatitis has been reported in patients receiving ticlopidine and is usually reversible when ticlopidine is stopped.[1-3] However, there have been reports of persistent cholestasis after ticlopidine withdrawal.[4,5] A case of granulomatous hepatitis has also been reported.[6] Clopidogrel was substituted for ticlopidine in a patient who had developed raised liver enzymes during ticlopidine treatment;[7] liver enzyme values returned to normal during continued clopidogrel therapy. However, there has been a report[8] of hepatotoxicity with clopidogrel.

1. Cassidy LJ, *et al.* Probable ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 1995; **29:** 30–2.
2. Pérez-Balsa AM, *et al.* Hepatotoxicity due to ticlopidine. *Ann Pharmacother* 1998; **32:** 1250–1.
3. Skurnik YD, *et al.* Ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 2003; **37:** 371–5.
4. Colivicchi F, *et al.* Ticlopidine-induced chronic cholestatic hepatitis: a case report. *Curr Ther Res* 1994; **55:** 929–31.
5. Mambelli E, *et al.* Severe ticlopidine-induced cholestatic syndrome. *Blood Purif* 2007; **25:** 441–5.
6. Ruiz-Valverde P, *et al.* Ticlopidine-induced granulomatous hepatitis. *Ann Pharmacother* 1995; **29:** 633–4.
7. Zeolla MM, Carson JJ. Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33:** 939–41.
8. Willens HJ. Clopidogrel-induced mixed hepatocellular and cholestatic liver injury. *Am J Ther* 2000; **7:** 317–18.

Effects on the lungs. Bronchiolitis obliterans-organising pneumonia developed in a 76-year-old woman receiving ticlopidine and prednisone for temporal arteritis.[1] The condition resolved over several months when ticlopidine was withdrawn.

1. Alonso-Martinez JL, *et al.* Bronchiolitis obliterans-organizing pneumonia caused by ticlopidine. *Ann Intern Med* 1998; **129:** 71–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ticlopidine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Ticlopidine should be used with caution in patients receiving other drugs, such as anticoagulants and antiplatelet drugs, that increase the risk of bleeding. Ticlopidine is an inhibitor of cytochrome P450, including the isoenzymes CYP2C19, CYP2D6, and CYP2B6, and may inhibit the metabolism of other drugs that are metabolised by this route. The clearance of ticlopidine may be reduced by cimetidine. Corticosteroids may antagonise the effect of ticlopidine on bleeding time.

Anticoagulants. Use of ticlopidine with anticoagulants may increase the risk of bleeding. However, ticlopidine has been reported to antagonise the effect of *acenocoumarol* (see Antiplatelets under Interactions of Warfarin, p. 1532.3).

Antiepileptics. For a report of acute *phenytoin* toxicity in a well-stabilised patient following addition of ticlopidine, see p. 545.1.

Codergocrine. A study[1] in healthy subjects found that codergocrine mesilate reduced the plasma concentration of ticlopidine, probably by inhibiting its uptake from the gastrointestinal tract by organic anion transporting polypeptide (OATP)-B.

1. Lu W-J, *et al.* The effects of ergoloid mesylates and ginkgo biloba on the pharmacokinetics of ticlopidine. *J Clin Pharmacol* 2006; **46:** 628–34.

Xanthines. For reference to the effect of ticlopidine on *theophylline* half-life and plasma clearance, see p. 1236.3.

Pharmacokinetics

Ticlopidine is rapidly and almost completely absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins. The terminal half-life during chronic dosing is reported to be about 30 to 50 hours. Ticlopidine is extensively metabolised in the liver. About 60% of a dose is excreted in the urine as metabolites and 25% in the faeces.

References.

1. Desager J-P. Clinical pharmacokinetics of ticlopidine. *Clin Pharmacokinet* 1994; **26:** 347–55.
2. Buur T, *et al.* Pharmacokinetics and effect of ticlopidine on platelet aggregation in subjects with normal and impaired renal function. *J Clin Pharmacol* 1997; **37:** 108–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dosier; Ticlid; Trombenal; ***Austral.***: Ticlid†; Tilodene; ***Austria***: Thrombodine; Tiklid; ***Belg.***: Ticlid; ***Braz.***: Desagreg; Plaketar; Plavasc; Ticlid; Ticlobal; ***Chile***: Ateroclar; Plaquetil; Ticlid†; ***China***: Ban Su (板苏); Bang Jie Qing (邦解清); Cisen (辰欣); LiDe (力得); Qi Luo (齐洛); Tailuda (泰禄达); Tian Xin Li Bo (天新利博); Ticlid (抵克立得); Yu Chuan Tong (玉川通); ***Cz.***: Apo-Tic; Ipaton; Tagren; Ticlid†; ***Fr.***: Ticlid; ***Ger.***: Tiklyd; ***Gr.***: Anghostan; Etfariol; Iriflexin; Labortina; Neo Fulvigal; Neo-omnipen; Ruxicolan; Ticlid; Ticlodone; ***Hong Kong***: Aplaket; Ticlid; Tipidin; ***Hung.***: Aclotin; Aplatic; Ipaton; Placor; Ticlid; Ticlogal; ***India***: Aplaket; Ticlobest; Ticlop; Ticlopid; Tikleen; Tyklid; ***Indon.***: Agulan; Cartrilet; Goclid; Nufaclapide; Piclodin; Platidine; Ticard; Ticlid; Ticlon; Ticlophar; Ticuring; ***Ital.***: Antigreg; Aplaket; Chiaro; Clox; Fluilast; Flupid; Fluxidin; Klodin; Opteron; Ticlodone; Tiklid; ***Jpn***: Panaldine; ***Malaysia***: Antigreg; Aplaket; Strokan; Ticlid; Ticlopine†; Tipidin; ***Mex.***: Ticlid†; ***Norw.***: Ticlid; ***Philipp.***: Clotidone†; Ticlid; Tikpid; Vasopid; ***Pol.***: Aclotin; Apo-Clodin; Iclopid; Ifapidin; Ticlid; Ticlo; ***Port.***: Aplaket; Betlife; Klodipin†; Movin; Plaquetal; Previta; Ticlodix; Ticlopat; Tiklyd; Tiropa; Trombopat; ***Rus.***: Ticlid (Тиклид); Ticlo (Тиклo); Tikleen (Тиклин)†; ***Singapore***: Antigreg; Aplaket; Ticlid; Tiodin; Tipidin; ***Spain***: Ticlodone; Tiklid; ***Swed.***: Ticlid†; ***Thai.***: Aplaket; Cenpidine; Siclot†; Ticlid; Ticlo; Ticlodin; Ticlopine; Tilopin; Tipidine; Viladil†; ***Turk.***: Agretik; Ticlid; Ticlocard; ***UAE***: Ticopar; ***Ukr.***: Aclotin (Аклютин); Ipaton (Ипатон)†; ***USA***: Ticlid; ***Venez.***: Ticlid.

Multi-ingredient Preparations. ***India***: Astic.

Pharmacopoeial Preparations

USP 36: Ticlopidine Hydrochloride Tablets.

Tilisolol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de tilisolol; N-696; Tilisolol, Chlorhydrate de; Tilisololi Hydrochloridum; Тилизолола Гидрохлорид.

(±)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-2-methylisocarbostyril hydrochloride.

$C_{17}H_{24}N_2O_3$,HCl=340.8

CAS — 85136-71-6 (tilisolol); 62774-96-3 (tilisolol hydrochloride).

Profile

Tilisolol hydrochloride is a non-cardioselective beta blocker (p. 1316.3) with direct vasodilator activity. It is used in the management of angina pectoris (p. 1254.3) and hypertension (p. 1251.1) in oral doses of 10 to 20 mg once daily; up to a maximum of 30 mg once daily may be used if necessary.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Selecal.

Timolol Maleate *(BANM, USAN, rINNM)* ⊗

Maleato de timolol; MK-950; Timolol Maleat; Timolol, maléate de; Timolol, maleato de; Timolol maleinát; Timololi Maleas; Timololimaleaatti; Timololio maleatas; Timololmaleat; Timolol-maleát; Тимолола Малеат.

(*S*)-1-*tert*-Butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate.

$C_{13}H_{24}N_4O_3S$,$C_4H_4O_4$=432.5

CAS — 26839-75-8 (timolol); 91524-16-2 (timolol hemihydrate); 26921-17-5 (timolol maleate).

ATC — C07AA06; S01ED01.

ATC Vet — QC07AA06; QS01ED01.

UNII — P8Y54F701R.

NOTE. TIM is a code approved by the BP 2014 for use on single unit doses of eye drops containing timolol maleate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Timolol Maleate). A white or almost white, crystalline powder or colourless crystals. Soluble in water and in alcohol. A 2% solution in water has a pH of 3.8 to 4.3. Protect from light.

USP 36: (Timolol Maleate). A white to practically white, odourless or practically odourless powder. Soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform and in propylene glycol; insoluble in cyclohexane and in ether. A 2% solution in water has a pH of 3.8 to 4.3.

Uses and Administration

Timolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Timolol is used as the maleate in the management of glaucoma (p. 1999.1), hypertension (p. 1251.1), angina pectoris (p. 1254.3), and myocardial infarction (p. 1257.1). It is also used in the prophylactic treatment of migraine (p. 670.3). The hemihydrate is also used.

Eye drops containing timolol maleate or hemihydrate equivalent to 0.25 and 0.5% of timolol are instilled twice daily to reduce **raised intra-ocular pressure** in open-angle **glaucoma** and ocular hypertension. Once-daily use may suffice when the intra-ocular pressure has been controlled. Gel-forming eye drops are also available that are instilled once daily.

For other indications timolol is given orally. In **hypertension** timolol maleate is usually given in initial doses of 10 mg daily, increased according to response at intervals of 7 or more days. Usual maintenance doses are 10 to 40 mg daily, but doses up to 60 mg daily may be required in some patients; doses above 30 mg daily should be given in 2 equally divided doses.

In **angina pectoris** the initial dose is 5 mg twice daily, increased at intervals of 3 or more days by 10 mg daily. Most patients respond to 35 to 45 mg daily in divided doses, but some patients may require up to 60 mg daily.

In patients who have had a **myocardial infarction** timolol maleate is given in initial doses of 5 mg twice daily for 2 days, starting 7 to 28 days after infarction, and increased subsequently in the absence of any contra-indicating adverse effects, to 10 mg twice daily.

Doses of 10 to 20 mg daily of timolol maleate are used in the prophylaxis of **migraine**.

Reduced doses may be required in renal or hepatic impairment.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Timolol is distributed into breast milk. After instillation of timolol 0.5% eye drops twice daily, concentrations of timolol in breast milk of a woman were about 6 times greater than those in serum, the values being 5.6 and 0.93 nanograms/mL respectively.[1] In a study[2] in patients given oral timolol 5 mg three times daily, the mean concentration in breast milk was 15.9 nanograms/mL, and the ratio of milk to plasma concentrations was 0.8; a similar ratio was found at higher doses, and the authors considered that the amount ingested by an infant would not be important. No adverse effects were seen in these studies and the American Academy of Pediatrics considers[3] that timolol is therefore usually compatible with breast feeding.

1. Lustgarten JS, Podos SM. Topical timolol and the nursing mother. *Arch Ophthalmol* 1983; **101:** 1381–2.
2. Fidler J, *et al.* Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; **90:** 961–5.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010.] Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies timolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of timo-

lol and that the dose of timolol may need to be reduced if used together.

Pharmacokinetics

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged timolol. Timolol is not removed by haemodialysis.

Absorption. Reference to the systemic absorption of ophthalmic timolol.[1]

1. Nieminen T, *et al*. Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. *Scand J Clin Lab Invest* 2007; **67:** 237–45.

Metabolism. Timolol appears to be metabolised[1] by the cytochrome P450 isoenzyme CYP2D6 and studies[2-4] have shown that it is influenced by genetic polymorphism.

1. Volotinen M, *et al*. Timolol metabolism in human liver microsomes is mediated principally by CYP2D6. *Drug Metab Dispos* 2007; **35:** 1135–41.
2. McGourty JC, *et al*. Pharmacokinetics and beta-blocking effects of timolol in poor and extensive metabolizers of debrisoquin. *Clin Pharmacol Ther* 1985; **38:** 409–13.
3. Lewis RV, *et al*. Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1985; **19:** 329–33.
4. Lennard MS, *et al*. Timolol metabolism and debrisoquine oxidation polymorphism: a population study. *Br J Clin Pharmacol* 1989; **27:** 429–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atiglauc; Glatim; Ingetim†; Klonalol; Ofal; Plostim; Poentimol; Proflax; Protevis; Timed; Timoler†; Timolpres; Timoptic; Zopirol; ***Austral.***: Nyogel; Tenopt; Timoptol; ***Austria***: Dispatim; Tim-Ophtal; Timabak†; Timo-COMOD†; Timoftal; Timogel; Timohexal; Timoptic; ***Belg.***: Geltim; Nyogel; Nyolol; Timabak; Timo-POS; Timoptol; Timoptolgel; ***Braz.***: Glaucotrat; Glautimol; Nyolol; Tenoftal; Timabak; Timoneo; Timoptol; ***Canad.***: Apo-Timol; Apo-Timop; Novo-Timol; Tim-Ak; Timoptic; ***Chile***: Glausolets; Nyolol; Oculix; Timabak†; Timop†; Timoptol-XE; Tiof; ***China***: Chengrui (诚瑞); Di Li Jian (迪立见); Timoptol (添慕宁); ***Cz.***: Arutimol; Oftan; Ophthalmo-Timogal†; Timo-COMOD; Timohexal; Timoptol; Uni Timolol; ***Denm.***: Aquanil†; Nyogel; Optimol; Timacar; Timogel; Timoptol; Timosan; ***Fin.***: Betimol†; Blocanol; Timosan; ***Fr.***: Digaol†; Geltim; Nyogel; Ophtim; Timabak; Timacor; Timo-COMOD; Timoptol; ***Ger.***: Arutimol; Chibro-Timoptol; Dispatim; Nyogel†; Tim-Ophtal; Timo-COMOD; Timo-Stulln; Timo-Vision; TimoEDO; Timohexal†; Timomann; ***Gr.***: Betim; Dacrysoline; Flumetol; Geltim; Glafemak; Lithimole; Noval; Nyogel; Nyolol; Temserin; Thilotim; Tim-Alcon; Timabak; Timodose; Waucosin; Yesan; ***Hong Kong***: Nyolol; Oftan; Ophtamolol; Optimol†; Timabak; Timoptol; ***Hung.***: Arutimol; Cusimolol; Nyolol†; Oftan Timolol; ***India***: Glucomol; Glucotim; Iotim; Lopres; Nyolol; O'Clean; Ocobar; Ocu-Lol; Oculan; Ocupres; Ocutim; Optilax; Timolo†; ***Indon.***: Isotic Adretor; Kentimol†; Nyolol; Opthil; Tim-Ophtal; Ximex Opticom; ***Irl.***: Nyogel; Timofluid; Timoptol; Zanopro Plus; ***Israel***: Nyolol; Tiloptic; V-Optic; ***Ital.***: Blocadren; Cusimolol; Droptimol; Ialutim; Nyogel; Oftimolo; Timod; Timogel; Timolabak; Timolux; Timoptol; ***Jpn***: Timoptol; ***Malaysia***: Cusimolol; Optimol; Timo-COMOD; Timolast; Timoptol; ***Mex.***: Blocadren; Horex; Imot; Jertz; Nyolol; Shemol; Tenglamol; Timoptol; Timozzard; ***Mon.***: Gaoptol; Nyolol; ***Neth.***: Nyogel; Timo-COMOD; Timogel; Timoptol; ***Norw.***: Blocadren; Oftan; Timosan; ***NZ***: Apo-Timol; Apo-Timop; Hypermol†; Tilmat; Timolux; Timoptol; ***Philipp.***: Elevex; Glaucare; Glocure-Opta; I-Supres; Normopres; Nyolol; Ocuper; Oftan; Optamol; Timabak; Timoptol; ***Pol.***: Cusimolol; Nyolol; Oftan†; Oftensin; Timo-COMOD†; Timohexal†; Timoptic; ***Port.***: Nyogel; Nyolol; Timabak; Timogel; Timoglau; Timolen; Timoptol; ***Rus.***: Arutimol (Арутимол); Glautam (Глаутам); Glymol (Глимол); Nyolol (Ниолол); Ocucer (Окукэр); Ocumed (Окумед); Ocumol (Окумол); Ocupres-E (Окупрес-Е); Oftan Timolol (Офтан Тимолол); Optimol (Оптимол); Timadren (Тимадрен); Timo-Komod (Тимо-Комод); Timohexal (Тимогексал); ***S.Afr.***: Glaucosan; Nyogel; Timoptol; ***Singapore***: Nyolol; Tiamol; Timabak; Timo-COMOD; Timoptol; ***Spain***: Cusimolol; Timabak; Timoftol; Timogel; ***Swed.***: Blocadren; Optimol; Timosan; ***Switz.***: Nyolol; Timisol; Timo-COMOD; Timogel; Timoptic; ***Thai.***: Archimol; Glauco-Oph; Nyolol†; Opsartimol; Timo-optal; Timodrop; Timolast†; Timoptol; Timosil; ***Turk.***: Cusimolol†; Nyolol; Timabak; Timo-COMOD; Timoftal; Timoptic; Timosol; Timotem; ***UK***: Betim; Nyogel†; Timoptol; Tiopex; ***Ukr.***: Arutimol (Арутимол); Normatin (Норматин); Nyolol (Ниолол)†; Ocumed (Окумед); ***USA***: Betimol; Blocadren; Isatol; Istalol; Timoptic; ***Venez.***: Globitan; Matigel; Matilol; Nyolol; Timoptol.

Multi-ingredient Preparations. ***Arg.***: Aliviapres; Azarga; Combigan; Cosopt; Dor-Timolol; Dorlamida T; DuoTrav; Ganfort; Glaucostat T; Glaucotensil TD; Glaucotensil; Latimodorf; Louten T; Ocuprostim; Pilotim; Timed D; Timobrim; Xalacom; Zopirol DM; ***Austral.***: Azarga; Combigan; Cosopt; Ganfort; Timpilo†; Xalacom; ***Austria***: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Moducrin†; Xalacom; ***Belg.***: Azarga; Combigan; Cosopt; DuoTrav; Xalacom; ***Braz.***: Combigan; Cosopt; Ganfort; Glaucoftal; Xalacom; ***Canad.***: Azarga; Combigan; Cosopt; DuoTrav; Xalacom; ***Chile***: Azarga; Combigan; Cosopt; Dorsof T; Dorzine; DuoTrav; Gaax T; Ganfort; Glaucotensil T; Glausolets Plus; Latof-T; Tiof Plus; Xalacom; ***China***: Xalacom (适利加); ***Cz.***: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Xalacom; ***Denm.***: Alatopran; Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Latanostad Comp; Latiotim; Timosopt†; Xalacom†; Xalcom; ***Fin.***: Combigan; Cosopt; Fotil; Glaukostad; Latiotim; Oftastad Comp; Xalcom; ***Fr.***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Moducren; Pilobloq†; Xalacom; ***Ger.***: Azarga; Combigan; Cosopt; Dorzo Plus T; Dorzolamid comp; DuoTrav; Fotil; Ganfort; Moducrin; TP-Ophtal; Xalacom; ***Gr.***: Azarga; Combigan; Cosopt; Dorzoptic Plus; Dorzotim; Dotiz; Dropiltim; DuoTrav; Fotil; Ganfort; Optodrop-Co; T+P; Tesol; Timpilo; Tinoprost; Xalacom; Yvano; ***Hong Kong***: Combigan; Cosopt; DuoTrav; Ganfort; Moducren†; Timpilo†; Xalacom; ***Hung.***: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Glamzolid; Xalacom; ***India***: Brimochek-T; Brimocom; Brimolol; Careprost Plus; Combigan; Ganfort; Iotim-Plus; Laprost Plus; Latim; Latochek-T; Latocom; Misopt; Ocudor-T; ***Indon.***: Xalacom; ***Irl.***: Azarga; Claropt; Codalux; Combigan; Cosopt; Dortim; DuoTrav; Ganfort; Glaucotima; Lataneau Plus; Moducren†; Prestim; Timlatan; Xalacom; Xaloptic Combi; ***Israel***: Combigan; Cosopt; DuoTrav; Ganfort; Timpilo†; Xalacom; ***Ital.***: Azarga; Combigan; Cosopt; DuoTrav; Equiton; Ganfort; Glautimol; Pilobloc; Tavu; Timicon; Xalacom†; ***Malaysia***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; ***Mex.***: Anhigot; Combigan-D; Cosopt; Ganforti; Krytantek; Trovost; Xalacom; ***Neth.***: Azarga; Combigan; Cosopt; Dortim; DuoTrav; Fotil†; Ganfort; Latim-POS; Xalacom; ***Norw.***: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Latiotim; Xalcom; ***NZ***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Timpilo; Xalacom; ***Philipp.***: Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Xalacom; ***Pol.***: Azarga; Combigan; Cosopt; Dotiteva; DuoTrav; Fotil†; Ganfort; Rozacom; Xalacom; ***Port.***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Tavu; Timoglau Plus†; Timosopt†; Xalacom; ***Rus.***: Azarga (Азарга); Cosopt (Косопт); Fotil (Фотил); Pilotimol (Пилотимол); Xalacom (Ксалаком); ***S.Afr.***: Combigan; Cosopt; DuoTrav; Moducren†; Servatrin; Xalacom; ***Singapore***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; ***Spain***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Latimvista; Xalacom; ***Swed.***: Azarga; Combigan; Cosopt; Costad; DuoTrav; Fotil; Ganfort; Latiotim; Xalcom; ***Switz.***: Azarga; Co-Dorzolamid; Co-Latanoprost; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; ***Thai.***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; ***Turk.***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; ***UK***: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Prestim; Xalacom; ***Ukr.***: Combigan (Комбиган); Ganfort (Ганфорт); Lanotan T (Ланотан Т); Xalacom (Ксалаком); ***USA***: Combigan; Cosopt; Timolide†; ***Venez.***: Cosopt; Dobet; Glaucotensil T; Xalacom.

Pharmacopoeial Preparations
BP 2014: Dorzolamide and Timolol Eye Drops; Timolol Eye Drops; Timolol Tablets;
USP 36: Timolol Maleate and Hydrochlorothiazide Tablets; Timolol Maleate Ophthalmic Solution; Timolol Maleate Tablets.

Tinzaparin Sodium *(BAN, USAN, rINN)*

Tintsapariininatrium; Tinzaparin-Natrium; Tinzaparin sodná sůl; Tinzaparin Sodyum; Tinzaparina sódica; Tinzaparine Sodique; Tinzaparinnatrium; Tinzaparin-nátrium; Tinzaparino natrio druska; Tinzaparinum Natricum; Тинзапарин Натрий.

CAS — 9041-08-1.
ATC — B01AB10.
ATC Vet — QB01AB10.
UNII — 3S182ET3UA.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tinzaparin Sodium). It is prepared by enzymatic depolymerisation, using heparinase from *Flavobacterium heparinum*, of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5500 and 7500, with a characteristic value of about 6500. The mass percentage of chains lower than 2000 is not more than 10%. The degree of sulfation is 1.8 to 2.5 per disaccharide unit.

The potency is not less than 70 units and not more than 120 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 2.5.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Tinzaparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the prevention and treatment of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation.

For *prophylaxis* of **venous thromboembolism** tinzaparin sodium is given by subcutaneous injection in a variety of dosage regimens. In each case, the duration of treatment is 7 to 10 days.

- For patients at low or intermediate risk, such as those undergoing general surgical procedures, 3500 units of tinzaparin sodium are given 2 hours before the procedure, followed by 3500 units once daily.
- In patients at high risk, such as those undergoing orthopaedic surgery, an initial dose is either 50 units/kg given 2 hours before surgery, or a fixed dose of 4500 units given 12 hours before surgery. The same dose is then given as a once-daily maintenance dose. Alternatively, prophylaxis may be started after surgery at a dose of 75 units/kg once daily.

For the *treatment* of venous thromboembolism tinzaparin sodium is given in a dose of 175 units/kg by subcutaneous injection once daily for at least 6 days and until adequate oral anticoagulation is established. (In pregnant patients, early-pregnancy body-weight should be used to calculate doses.)

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, tinzaparin sodium may be given into the arterial side of the dialyser or intravenously. The dialyser may be primed with 500 to 1000 mL sodium chloride 0.9% containing 5000 units tinzaparin sodium/litre. For dialysis sessions lasting less than 4 hours a single dose of 2000 to 2500 units tinzaparin sodium is given; for longer sessions an initial dose of 2500 units is followed by an infusion of 750 units/hour.

For doses in children, see below.

References.
1. Friedel HA, Balfour JA. Tinzaparin: a review of its pharmacology and clinical potential in the prevention and treatment of thrombo-embolic disorders. *Drugs* 1994; **48:** 638–60.
2. Neely JL, *et al*. Tinzaparin sodium: a low-molecular-weight heparin. *Am J Health-Syst Pharm* 2002; **59:** 1426–36.
3. Nutescu EA, *et al*. Tinzaparin: considerations for use in clinical practice. *Ann Pharmacother* 2003; **37:** 1831–40.
4. Cheer SM, *et al*. Tinzaparin sodium: a review of its pharmacology and clinical use in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2004; **64:** 1479–502.
5. Hoy SM, *et al*. Tinzaparin sodium: a review of its use in the prevention and treatment of deep vein thrombosis and pulmonary embolism, and in the prevention of clotting in the extracorporeal circuit during haemodialysis. *Drugs* 2010; **70:** 1319–47.

Administration in children. Although tinzaparin is not licensed for use in children in the UK, the *BNFC* suggests that it may be given to children by subcutaneous injection for the prophylaxis and treatment of venous thromboembolism.

For *prophylaxis* of venous thromboembolism, children aged 1 month to 18 years may be given a dose of 50 units/kg once daily.

For *treatment* of venous thromboembolism, the following suggested doses are given according to age:

- 1 to 2 months: 275 units/kg once daily
- 2 months to 1 year: 250 units/kg once daily
- 1 to 5 years: 240 units/kg once daily
- 5 to 10 years: 200 units/kg once daily
- 10 years and over: 175 units/kg once daily

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Tinzaparin should be avoided in elderly patients with renal failure (see below).

Severe bleeding with tinzaparin sodium may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of about 100 units of tinzaparin sodium.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tinzaparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Use in the elderly. An increase in all-cause mortality was seen in patients aged 70 years or older with impaired renal function who were given tinzaparin for the treatment of deep-vein thrombosis or pulmonary embolism. As a result, the FDA recommended that alternatives be considered in these patients while the review of data continued.[1]

1. FDA. Communication about an ongoing safety review of Innohep (tinzaparin sodium injection) (issued 2nd December 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm136254.htm (accessed 03/08/10)

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Tinzaparin sodium is absorbed after subcutaneous injection with a bioavailability of about 90%. Peak plasma activity occurs within 4 to 6 hours. The elimination half-life is about 90 minutes but detectable anti-factor Xa activity may persist for up to 24 hours.

General references.
1. Kuhle S, *et al.* Dose-finding and pharmacokinetics of therapeutic doses of tinzaparin in pediatric patients with thromboembolic events. *Thromb Haemost* 2005; **94:** 1164–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Innohep; ***Canad.***: Innohep; ***Denm.***: Innohep; ***Fin.***: Innohep; ***Fr.***: Innohep; ***Ger.***: Innohep; ***Gr.***: Innohep; Logiparin; ***Hong Kong***: Innohep; ***India***: Logiparin; ***Irl.***: Innohep; ***Malaysia***: Innohep; ***Neth.***: Innohep; ***Norw.***: Innohep; ***NZ***: Innohep; ***Philipp.***: Innohep; ***Port.***: Innohep; ***Singapore***: Innohep; ***Spain***: Innohep; ***Swed.***: Innohep; ***Thai.***: Innohep; ***Turk.***: Innohep; ***UK***: Innohep; ***USA***: Innohep†.

Pharmacopoeial Preparations
BP 2014: Tinzaparin Sodium Injection.

Tirilazad Mesilate *(BANM, rINNM)*

Mesilato de tirilazad; Tirilatsadiinimesilaatti; Tirilazad, Mésilate de; Tirilazad, mesilato de; Tirilazad Mesylate (USAN); Tirilazadi Mesilas; Tirilazadini Mesilas; Tirilazadinmesilat; U-74006F (tirilazad or tirilazad mesilate); Тирилазада Мезилат.

21-[4-(2,6-Di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate hydrate.

$C_{38}H_{52}N_6O_2.CH_4O_3S.xH_2O$=721.0 (anhydrous)

CAS — 110101-66-1 (tirilazad); 111793-42-1 (tirilazad mesilate); 149042-61-5 (tirilazad mesilate).

ATC — N07XX01.

ATC Vet — QN07XX01.

UNII — HXS259UWKW (tirilazad mesylate hydrate); 19B418DV39 (anhydrous tirilazad mesylate).

Profile

Tirilazad, a lazaroid, is an inhibitor of lipid peroxidation thought to have a cytoprotective effect against radicals produced in response to tissue trauma. It has been used in the prevention of secondary tissue damage in subarachnoid haemorrhage. It has also been investigated in spinal cord injuries, head injuries, and ischaemic stroke.

References.
1. The Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/06/05).
2. Jang YG, *et al.* Metaanalysis of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2009; **10:** 141–7.
3. Zhang S, *et al.* Tirilazad for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 20/04/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Freedox (ФРИДОКС).

Tirofiban Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tirofibán; L-700462; MK-0383; MK-383; Tirofiban, Chlorhydrate de; Tirofibán, hidrocloruro de; Tirofiban Hidroklorür; Tirofibani Hydrochloridum; Тирофибана Гидрохлорид.

N-(Butylsulfonyl)-4-[4-(4-piperidyl)butoxy]-L-phenylalanine hydrochloride monohydrate.

$C_{22}H_{36}N_2O_5S.HCl.H_2O$=495.1

CAS — 144494-65-5 (tirofiban); 142373-60-2 (anhydrous tirofiban hydrochloride); 150915-40-5 (tirofiban hydrochloride monohydrate).

ATC — B01AC17.

ATC Vet — QB01AC17.

UNII — 6H925F8O5J.

Uses and Administration

Tirofiban hydrochloride is an antiplatelet drug that reversibly inhibits binding of fibrinogen to the glycoprotein IIb/IIIa receptors of platelets. It is given with heparin and aspirin for the management of unstable angina, both in patients managed medically and in those undergoing percutaneous coronary procedures. Tirofiban is used as the hydrochloride, but the dose is expressed in terms of the base; 110 nanograms of tirofiban hydrochloride monohydrate is equivalent to 100 nanograms of tirofiban base.

Tirofiban is given intravenously, at an initial rate of 400 nanograms/kg per minute for 30 minutes, and then continued at 100 nanograms/kg per minute. The recommended duration of treatment is at least 48 hours. Tirofiban infusion may be continued during coronary angiography, and should be maintained for 12 to 24 hours after angioplasty or atherectomy. The entire duration of treatment should not exceed 108 hours.

The dose of tirofiban should be reduced in patients with renal impairment (see below).

General references.
1. McClellan KJ, Goa KL. Tirofiban: a review of its use in acute coronary syndromes. *Drugs* 1998; **56:** 1067–80.
2. Menozzi A, *et al.* Tirofiban in acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2005; **3:** 193–206.
3. Shanmugam G. Tirofiban and emergency coronary surgery. *Eur J Cardiothorac Surg* 2005; **28:** 546–50.
4. Bukow SC, *et al.* Tirofiban for the treatment of ischaemic stroke. *Expert Opin Pharmacother* 2006; **7:** 73–9.
5. Mukherjee D, Roffi M. Current strategies with high-dose tirofiban. *Expert Opin Drug Metab Toxicol* 2007; **3:** 275–80.
6. Winter JP, Juergens CP. The role of tirofiban in the management of coronary artery disease. *Cardiovasc Hematol Disord Drug Targets* 2008; **8:** 138–46.
7. van 't Hof AWJ, Valgimigli M. Defining the role of platelet glycoprotein receptor inhibitors in STEMI: focus on tirofiban. *Drugs* 2009; **69:** 85–100.
8. Juwana YB, *et al.* Tirofiban for myocardial infarction. *Expert Opin Pharmacother* 2010; **11:** 861–6.

Administration in renal impairment. Patients with renal impairment (creatinine clearance less than 30 mL/minute) should receive half the usual infusion dose of tirofiban.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. Tirofiban, given with heparin and aspirin, has been tried as adjunctive therapy. A study[1] comparing tirofiban with heparin in the *medical management* of unstable angina (p. 1254.3) or non-Q-wave myocardial infarction reported an initial benefit, at 2 days, of reduced risk of refractory ischaemia, myocardial infarction, or death with tirofiban. This benefit was not maintained at 7 or 30 days after treatment, although a further analysis[2] found that the risk of death or myocardial infarction at 30 days was reduced in patients with raised troponin I concentrations who received tirofiban. In another study,[3] the combination of heparin and tirofiban also reduced the risk of refractory ischaemia, myocardial infarction, or death, compared with heparin alone, and benefit was maintained at 6 months. About half of these patients also underwent revascularisation procedures or surgery if required.

Tirofiban has also been studied in patients undergoing *interventional therapy* (see Reperfusion and Revascularisation Procedures, p. 1259.2), but results have been mixed. The RESTORE study[4] found short-term benefit with tirofiban as an adjunct to heparin in patients undergoing angioplasty or atherectomy for acute coronary syndromes (unstable angina or myocardial infarction), but this was not maintained at 30 days and there was no effect on restenosis after 6 months. However, an observational study[5] in patients with acute myocardial infarction found improved outcomes and studies[6-8] using a higher bolus dose of 25 micrograms/kg have been more promising, including on longer-term follow-up.[6] Pretreatment with tirofiban for 24 to 48 hours before intervention was found to improve angiographic outcomes compared with periprocedural treatment,[9] but there was no difference in clinical events at 30 days. In patients undergoing planned interventions, tirofiban was found to improve outcomes compared with placebo;[10] another study found that it was less effective than abciximab at 30 days,[11] although this difference was no longer apparent after 6 months.[12]

1. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; **338:** 1498–1505.
2. Heeschen C, *et al.* Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999; **354:** 1757–62.
3. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; **338:** 1488–97.
4. Gibson CM, *et al.* Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. *J Am Coll Cardiol* 1998; **32:** 28–34.
5. De Luca G, *et al.* Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. *Thromb Haemost* 2005; **93:** 820–3.
6. Valgimigli M, *et al.* The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004; **44:** 14–19.
7. Valgimigli M, *et al.* Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA* 2008; **299:** 1788–99.
8. van't Hof AWJ, *et al.* Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008; **372:** 537–46.
9. van 't Hof AWJ, *et al.* A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. *Eur Heart J* 2003; **24:** 1401–5.
10. Bonz AW, *et al.* Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol* 2002; **40:** 662–8.
11. Topol EJ, *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; **344:** 1888–94.
12. Moliterno DJ, *et al.* Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 2002; **360:** 355–60.

Adverse Effects

Bleeding is the most common adverse effect of tirofiban; others include nausea, headache, fever, rashes and other hypersensitivity reactions, and thrombocytopenia.

Effects on the blood. References to tirofiban-associated thrombocytopenia[1-9] and anaemia.[8]

1. Mulot A, *et al.* Practical approach to the diagnosis and management of thrombocytopenia associated with tirofiban treatment. *Am J Hematol* 2004; **77:** 67–71.
2. Patel S, *et al.* Profound thrombocytopenia associated with tirofiban: case report and review of literature. *Angiology* 2005; **56:** 351–5.
3. Dunkley S, *et al.* Two distinct subgroups of tirofiban-induced thrombocytopenia exist due to drug dependent antibodies that cause platelet activation and increased ischaemic events. *Platelets* 2005; **16:** 462–8.
4. Tuhta AG, *et al.* Tirofiban-associated acute thrombocytopenia. *Acta Cardiol* 2006; **61:** 577–9.
5. Clofent-Sanchez G, *et al.* A case of profound and prolonged tirofiban-induced thrombocytopenia and its correction by intravenous immunoglobulin G. *J Thromb Haemost* 2007; **5:** 1068–70.
6. Agnelli D, Ottani F. Trombocitopenia grave associata a tirofiban: approccio clinico alla diagnosi e alla gestione terapeutica. *G Ital Cardiol* 2008; **9:** 137–43.
7. Beiras-Fernandez A, *et al.* Acute profound thrombocytopenia after treatment with tirofiban and off-pump coronary artery bypass grafting. *Ann Thorac Surg* 2009; **87:** 629–31.
8. Sakellariou D, *et al.* First report of tirofiban-induced anemia (found in combination with severe thrombocytopenia). *Tex Heart Inst J* 2009; **36:** 55–7.
9. Rahman N, Jafary FH. Vanishing platelets: rapid and extreme tirofiban-induced thrombocytopenia after percutaneous coronary intervention for acute myocardial infarction. *Tex Heart Inst J* 2010; **37:** 109–12.

Precautions

As for Abciximab, p. 1282.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tirofiban as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

After stopping an infusion of tirofiban, the antiplatelet effect persists for about 4 to 8 hours. The plasma half-life is about 2 hours. Tirofiban is not highly bound to plasma proteins; the unbound fraction in plasma is about 35%. Tirofiban is eliminated largely unchanged in the urine, with some biliary excretion in the faeces. Tirofiban is removed by haemodialysis.

Reviews.
1. Kondo K, Umemura K. Clinical pharmacokinetics of tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist: comparison with the monoclonal antibody abciximab. *Clin Pharmacokinet* 2002; **41:** 187–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agrastat; ***Austral.***: Aggrastat; ***Austria***: Aggrastat; ***Belg.***: Aggrastat; ***Braz.***: Agrastat; ***Canad.***: Aggrastat; ***Chile***: Agrastat; ***China***: Aggrastat (艾卡特); Xin Wei Ning (欣维宁); ***Cz.***: Aggrastat†; ***Fin.***: Aggrastat; ***Fr.***: Agrastat; ***Ger.***: Aggrastat; ***Gr.***: Aggrastat; Avastar; ***Hung.***: Aggrastat; ***India***: Aggramed; Aggrastat; Aggribloc; Aggritor; GP-2 Ban; ***Irl.***: Aggrastat; ***Israel***: Aggrastat; ***Ital.***: Aggrastat; ***Malaysia***: Aggrastat†; ***Mex.***: Agrastat; ***Neth.***: Aggrastat; ***Norw.***: Aggrastat†; ***NZ***: Aggrastat; ***Philipp.***: Aggrastat; ***Pol.***: Aggrastat; ***Port.***: Aggrastat; ***S.Afr.***: Aggrastet; ***Singapore***: Aggrastat; ***Spain***: Agrastat; ***Swed.***: Aggrastat; ***Switz.***: Aggrastat; ***Thai.***: Aggrastat; ***Turk.***: Aggrastat; ***UK***: Aggrastat; ***USA***: Aggrastat; ***Venez.***: Agrastat.

Tocainide *(BAN, USAN, rINN)*

Tocainida; Tocaïnide; Tocainidum; Tokainid; Tokainidi; W-36095; Токаинид.

2-Aminopropiono-2′,6′-xylidide.

$C_{11}H_{16}N_2O$=192.3

CAS — 41708-72-9.

ATC — C01BB03.

ATC Vet — QC01BB03.
UNII — 27DXO59SAN.

Tocainide Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tocainida; Tocainida, hidrocloruro de; Tocaïnide, Chlorhydrate de; Tocainidi Hydrochloridum; Токаинида Гидрохлорид.

$C_{11}H_{16}N_2O,HCl$=228.7

CAS — 35891-93-1.
ATC — C01BB03.
ATC Vet — QC01BB03.
UNII — 2K7I38CKN5.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Tocainide Hydrochloride). A fine, white, odourless powder. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Profile

Tocainide is a class Ib antiarrhythmic (p. 1243.1) with similar properties to mexiletine (p. 1436.2); like mexiletine it is structurally related to lidocaine (p. 1992.1). Tocainide hydrochloride has been given orally and intravenously in the management of ventricular arrhythmias but severe haematological and pulmonary toxicity limit its use.

General references.

1. Holmes B, *et al.* Tocainide: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1983; **26:** 93–123.

Preparations

Pharmacopoeial Preparations
USP 36: Tocainide Hydrochloride Tablets.

Tocoferil Nicotinate

Tocoferilo, nicotinato de; Tocopherol Nicotinate; Tocopheryl Nicotinate; Vitamin E Nicotinate; Токоферола Никотинат.

(±)-α-Tocopherol nicotinate.

$C_{35}H_{53}NO_3$=535.8

CAS — 51898-34-1; 16676-75-8.
UNII — WI1J5UCY5C.

NOTE. The names Kenton, NE, Nichi E nate, Nico200, Nicobita-E, Toconijust, Vanarl N, and VE-nicotinate have been used as trade marks for tocoferil nicotinate.

Pharmacopoeias. In *Jpn.*

Profile

Tocoferil nicotinate is a lipid regulating drug and a vasodilator. It is used in the treatment of hyperlipidaemias (p. 1248.1), and in peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2). The usual oral dose is 100 to 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ding Rong (顶荣); Qing Zhi Wei (清之维); Wei Er Xin (维尔新); Wei Mai Xin (维麦欣); Weishike (威氏克); ***Hong Kong***: Hijuven†; ***Indon.***: Enico; ***Jpn***: Juvela; ***Malaysia***: Hijuven; ***Philipp.***: Hijuven†; ***Port.***: Reoferol.

Multi-ingredient Preparations. ***Arg.***: Anaphase; ***Chile***: Anaphase; Anastim; ***Fr.***: Anaphase; ***Ital.***: Evitex; ***Singapore***: Pedimed Foot Care Cream; ***Spain***: Evitex A E Fuerte; ***Venez.***: Anaphase; Anastim.

Todralazine Hydrochloride *(BANM, pINNM)*

BT-621; CEPH; Ecarazine Hydrochloride; Hidrocloruro de todralazina; Todralazina, hidrocloruro de; Todralazine, Chlorhydrate de; Todralazini Hydrochloridum; Todralazyny chlorowodorek; Тодралазина Гидрохлорид.

Ethyl 3-(phthalazin-1-yl)carbazate hydrochloride monohydrate.

$C_{11}H_{12}N_4O_2,HCl,H_2O$=286.7

CAS — 14679-73-3 (todralazine); 3778-76-5 (anhydrous todralazine hydrochloride).
UNII — 5998D60YO0.

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Todralazine hydrochloride is an antihypertensive structurally related to hydralazine (p. 1401.2) and with similar properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Apiracohl†; ***Pol.***: Binazin†.

Tolazoline Hydrochloride *(BANM, rINNM)*

Benzazoline Hydrochloride; Hidrocloruro de tolazolina; Tolazol. Hydrochlor.; Tolazolina, hidrocloruro de; Tolazoline, Chlorhydrate de; Tolazolini Hydrochloridum; Tolazolinium Chloratum; Толазолина Гидрохлорид.

2-Benzyl-2-imidazoline hydrochloride.

$C_{10}H_{12}N_2,HCl$=196.7

CAS — 59-98-3 (tolazoline); 59-97-2 (tolazoline hydrochloride).
ATC — C04AB02; M02AX02.
ATC Vet — QC04AB02; QM02AX02; QV03AB94.
UNII — E669Z6S1JG.

NOTE. Do not confuse with benazoline, which is a sympathomimetic vasoconstrictor, or with benazolin, which is a herbicide.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Tolazoline Hydrochloride). A white to off-white, crystalline powder. Its solutions are slightly acid to litmus. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 3 of chloroform, and 1 in 10 000 of ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Tolazoline hydrochloride is a vasodilator that has a direct dilator action on the peripheral blood vessels. It has some alpha-adrenoceptor blocking activity and also stimulates smooth muscle in the gastrointestinal tract, increases gastrointestinal secretion, can cause mydriasis, and has a stimulant effect on the heart.

Tolazoline hydrochloride has been used intravenously to reduce pulmonary artery pressure in persistent pulmonary hypertension in neonates with persistent fetal circulation (see below). It has been used orally and by subcutaneous, intramuscular, intravenous, or slow intra-arterial injection in the treatment of peripheral vascular disease. It has also been given in some ophthalmic conditions.

Adverse effects of tolazoline include piloerection, headache, flushing, tachycardia, cardiac arrhythmias, tingling, chilliness, shivering, sweating, nausea, vomiting, diarrhoea, and epigastric pain. Orthostatic hypotension or marked hypertension may occur, especially with large doses. Tolazoline stimulates gastric acid and may exacerbate peptic ulcer disease. Oliguria, haematuria, myocardial infarction, gastrointestinal haemorrhage, thrombocytopenia and other blood dyscrasias have been reported.

Interactions. Tolazoline should not be used with sympathomimetics such as *adrenaline* since the hypotensive effect may be potentiated due to unopposed beta-adrenoceptor stimulation. For a report of fatal hypotension associated with the use of tolazoline with *dopamine*, see Vasodilators under the Interactions of Sympathomimetics, p. 1509.2.

Pulmonary hypertension. Tolazoline and other vasodilators have been tried in persistent pulmonary hypertension in the newborn (p. 1278.2) in an attempt to induce selective pulmonary vasodilatation and improve gas exchange. The response is variable and often unsuccessful due to concomitant systemic hypotension, a failure to achieve or sustain pulmonary vasodilatation, and adverse effects, and other therapies such as high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, and inhaled nitric oxide are now more widely used.

The dose for pulmonary hypertension in neonates that was recommended by licensed product information was an intravenously infused loading dose of 1 to 2 mg/kg, followed by an infusion of 1 to 2 mg/kg per hour. The high incidence of adverse effects, however, led to several studies investigating the use of lower doses. One group suggested that a loading dose of 500 micrograms/kg given intravenously followed by a continuous infusion of 500 micrograms/kg per hour was more appropriate and safer than standard doses.[1] In a retrospective study[2] of extremely preterm infants (mean gestational age 24 weeks) with severe hypoxaemia (possibly attributable to persistent pulmonary hypertension), tolazoline was given as a slow bolus infusion, with most patients receiving a dose of 0.5 to 1 mg/kg; some required further doses.

Tolazoline has also been given via the endotracheal route,[3,4] although as it is acid in solution it may contribute to alveolar injury. In a study[4] of 12 neonates with gestational age ranging from 25 to 42 weeks, endotracheal tolazoline at doses from 1 to 2.5 mg/kg was found to cause no adverse systemic effects.

The *BNFC* gives a dose of 1 mg/kg by slow intravenous injection, followed by 200 micrograms/kg per hour by infusion if necessary. It warns that doses in excess of 300 micrograms/kg per hour are associated with cardiotoxicity and renal failure. A suggested dose for endotracheal use is 200 micrograms/kg diluted in 0.5 to 1 mL of sodium chloride 0.9%.

1. Monin P, *et al.* Treatment of persistent fetal circulation syndrome of the newborn: comparison of different doses of tolazoline. *Eur J Clin Pharmacol* 1987; **31:** 569–73.
2. Nuntnarumit P, *et al.* Efficacy and safety of tolazoline for treatment of severe hypoxemia in extremely preterm infants. *Pediatrics* 2002; **109:** 852–6.
3. Welch JC, *et al.* Endotracheal tolazoline for severe persistent pulmonary hypertension of the newborn. *Br Heart J* 1995; **73:** 99–100.
4. Parida SK, *et al.* Endotracheal tolazoline administration in neonates with persistent pulmonary hypertension. *J Perinatol* 1997; **17:** 461–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Divascol.

Multi-ingredient Preparations. ***Switz.***: Lunadon†.

Pharmacopoeial Preparations
USP 36: Tolazoline Hydrochloride Injection.

Torasemide *(BAN, rINN)* ⊗

AC-4464; BM-02015; Torasemid; Torasemid bezvodý; Torasemid, vattenfri; Torasemida; Torasémide; Torasémide anhydre; Torasemidi; Torasemidi, vedetön; Torasemidum; Torasemidum Anhydricum; Torazemidas, bevandenis; Torsemide (USAN); Торасемид.

1-Isopropyl-3-(4-*m*-toluidinopyridine-3-sulphonyl)urea.

$C_{16}H_{20}N_4O_3S$=348.4

CAS — 56211-40-6 (torasemide); 72810-59-4 (torasemide sodium).
ATC — C03CA04.
ATC Vet — QC03CA04.
UNII — W31X2H97FB.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Torasemide, Anhydrous). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol. It is sparingly soluble in dilute solutions of alkali hydroxides and slightly soluble in dilute acids. Protect from light.

USP 36: (Torsemide). A white to off-white, crystalline powder. Practically insoluble in water and in ether; slightly soluble in alcohol, in methyl alcohol, in 0.1N sodium hydroxide, and in 0.1N hydrochloric acid; very slightly soluble in acetone and in chloroform.

Uses and Administration

Torasemide is a loop diuretic with actions similar to those of furosemide (p. 1387.1).

Torasemide is used for oedema associated with heart failure (p. 1262.3), including pulmonary oedema, and with renal and hepatic disorders. It is also used in the treatment of hypertension (p. 1251.1), either alone or with other antihypertensives.

Diuresis after oral use starts within 1 hour, reaches a peak in about 1 to 2 hours, and lasts for up to 8 hours; after intravenous injection its effects are evident within 10 minutes but like oral use can last up to 8 hours.

In the treatment of **oedema** the usual oral dose is 5 mg once daily increased according to response to 20 mg once daily; doses of up to 40 mg daily have been required in some patients. Torasemide may also be given intravenously in usual initial doses of 10 to 20 mg daily. Higher doses may sometimes be necessary, especially in oedema of renal origin; the dose should be increased stepwise as necessary to a maximum of 200 mg daily, although doses should not exceed 40 mg daily in patients with hepatic cirrhosis.

In the treatment of **hypertension** torasemide is given in initial oral doses of 2.5 to 5 mg daily; US licensed product information allows the dose to be increased to 10 mg daily if required, although UK licensed product information suggests that doses above 5 mg are unlikely to produce additional benefit.

Reviews.[1-5] A comparative review of the loop diuretics[5] concluded that torasemide might be more effective and safer than furosemide in the treatment of patients with heart failure, although there was little evidence to support one loop diuretic over another in other oedematous disease states.

1. Blose JS, *et al.* Torsemide: a pyridine-sulfonylurea loop diuretic. *Ann Pharmacother* 1995; **29:** 396–402.
2. Dunn CJ, *et al.* Torasemide: an update of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; **49:** 121–42.
3. Brater DC. Benefits and risks of torasemide in congestive heart failure and essential hypertension. *Drug Safety* 1996; **14:** 104–120.
4. Ishido H, Senzaki H. Torasemide for the treatment of heart failure. *Cardiovasc Hematol Disord Drug Targets* 2008; **8:** 127–32.

5. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? *Ann Pharmacother* 2009; **43:** 1836–47.

Administration in children. Oral torasemide was shown[1] to be safe and effective in a group of children with heart failure, 62 of whom were newly diagnosed and 40 of whom were switched from furosemide. The children were aged from 3 weeks to 17 years and doses ranged from 180 to 800 micrograms/kg. In those who switched therapy, 1 mg of furosemide was replaced with 200 micrograms of torasemide.

1. Senzaki H, *et al.* Efficacy and safety of torasemide in children with heart failure. *Arch Dis Child* 2008; **93:** 768–71.

Adverse Effects and Precautions

As for Furosemide, p. 1388.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies torasemide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Furosemide, p. 1389.3.

Anticoagulants. For a report of an interaction between torasemide and *warfarin*, see Diuretics under Interactions of Warfarin, p. 1533.3.

Pharmacokinetics

Torasemide is well absorbed from the gastrointestinal tract. Peak serum concentrations occur within 1 hour of oral doses. Torasemide is metabolised by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. Metabolism takes place in the liver and inactive metabolites are excreted in the urine. The elimination half-life of torasemide is about 3.5 hours. Torasemide is extensively bound to plasma proteins. In patients with heart failure both hepatic and renal clearance are reduced. In patients with renal impairment, the renal clearance is reduced but total plasma clearance is not significantly altered.

References.
1. Knauf H, Mutschler E. Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clin Pharmacokinet* 1998; **34:** 1–24.
2. Vormfelde SV, *et al.* CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. *Clin Pharmacol Ther* 2004; **76:** 557–66.
3. Werner D, *et al.* Determinants of steady-state torasemide pharmacokinetics: impact of pharmacogenetic factors, gender and angiotensin II receptor blockers. *Clin Pharmacokinet* 2008; **47:** 323–32.

Gender. An open-label study[1] in 90 patients found that the area under the concentration-time curve for torasemide was significantly higher, and oral clearance significantly lower, in females compared with males.

1. Werner U, *et al.* Gender is an important determinant of the disposition of the loop diuretic torasemide. *J Clin Pharmacol* 2010; **50:** 160–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Torem; ***Belg.***: Torrem; ***China***: Li Quan (丽泉); Li Zhi (丽芝); Te Su Min (特苏敏); Te Su Ni (特苏尼); Tuosai (拓赛); Unat (益耐); Yi Mai Ge (伊迈格); Ze Tong (泽通); ***Cz.***: Diuver†; ***Ger.***: Toracard†; Toragamma†; Torasid†; Torem; Unat; ***Gr.***: Unat; ***Hong Kong***: Unat; ***India***: Demator; Diurator; Dyamide; Dytor; Dytro-Kem; Edeto; ***Ital.***: Diuremid; Diuresix; Toradiur; ***Jpn***: Luprac; ***Pol.***: Diured; Diuver; Trifas; ***Rus.***: Diuver (Диувер); Trigrim (Тригрим); ***S.Afr.***: ToraHexal; Unat†; ***Spain***: Dilutol; Filantor†; Isodiur; Sutril; Tadegan†; ***Swed.***: Torem; ***Switz.***: Toramide†; Torasem; Torasis†; Torem; ***Thai.***: Unat†; ***UK***: Torem; ***Ukr.***: Britomar (Бритомар); Diuver (Диувер); Torixal (Ториксал); Torsid (Торсид); Trifas (Трифас); Trigrim (Тригрим); ***USA***: Demadex.

Multi-ingredient Preparations. ***India***: Dyamide Plus; Dytor Plus.

Pharmacopoeial Preparations
USP 36: Torsemide Tablets.

Torcetrapib *(USAN, rINN)*

CP-529414; Torcétrapib; Torcetrapibum; Торцетрапиб.
Ethyl (2*R*,4*S*)-4-{[3,5-bis(trifluoromethyl)benzyl](methoxycarbonyl)amino}-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate.
$C_{26}H_{25}F_9N_2O_4$=600.5
CAS — 262352-17-0.
UNII — 4N4457MV2U.

Profile

Torcetrapib is a cholesteryl ester transfer protein inhibitor. It increases plasma concentrations of high-density lipoprotein (HDL)-cholesterol and has been investigated in the management of lipid disorders. Development was stopped after the finding of increased mortality associated with torcetrapib in randomised, controlled studies.

References.
1. Funder JW. The off-target effects of torcetrapib. *Endocrinology* 2009; **150:** 2024–6.

Trandolapril *(BAN, rINN)*

RU-44570; Trandolapriili; Trandolaprilum; Trandolapryl; Трандолаприл.
Ethyl (2*S*,3a*R*,7a*S*)-1-{(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl]alanyl}hexahydro-2-indolinecarboxylate; (2*S*,3a*R*,7a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}perhydroindole-2-carboxylic acid.
$C_{24}H_{34}N_2O_5$=430.5
CAS — 87679-37-6.
ATC — C09AA10.
ATC Vet — QC09AA10.
UNII — 1T0N3G9CRC.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Trandolapril). A white or almost white powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Trandolapril). A white or almost white powder. Practically insoluble in water; sparingly soluble in absolute alcohol; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Trandolapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and in left ventricular dysfunction following myocardial infarction (p. 1257.1).

Trandolapril owes its activity to trandolaprilat to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after 8 to 12 hours. The haemodynamic action lasts for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** the initial oral dose is 500 micrograms once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. In patients already taking a diuretic, the diuretic should be stopped, if possible, 2 to 3 days before starting trandolapril and resumed later if necessary. In patients with co-existing heart failure treatment with trandolapril should begin under close medical supervision. The usual maintenance dose for hypertension is 1 to 2 mg once daily, although up to 4 mg daily may be given, as a single dose or in 2 divided doses.

In **myocardial infarction**, treatment with trandolapril may be started 3 days after the infarction in an initial dose of 500 micrograms once daily, gradually increased to a maximum of 4 mg once daily.

A reduction in dosage may be necessary in patients with renal impairment (see below).

References.
1. Zannad F. Trandolapril: How does it differ from other angiotensin converting enzyme inhibitors? *Drugs* 1993; **46** (suppl 2): 172–82.
2. Wiseman LR, McTavish D. Trandolapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in essential hypertension. *Drugs* 1994; **48:** 71–90.
3. Køber L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; **333:** 1670–6.
4. Peters DC, *et al.* Trandolapril: an update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 1998; **56:** 871–93.
5. Diaz A, Ducharme A. Update on the use of trandolapril in the management of cardiovascular disorders. *Vasc Health Risk Manag* 2008; **4:** 1147–58.
6. Ruggenenti P, *et al.* Effect of trandolapril on regression of retinopathy in hypertensive patients with type 2 diabetes: a prespecified analysis of the Benedict trial. *J Ophthalmol* 2010; **2010:** 106384.

Administration in renal impairment. The initial dose of trandolapril in patients with renal impairment should not exceed 500 micrograms daily. UK licensed product information states that the maximum maintenance dose should be 2 mg daily in patients with a creatinine clearance of less than 10 mL/minute.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trandolapril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Trandolapril acts as a prodrug of the diacid trandolaprilat, its active metabolite. After oral doses of trandolapril the bioavailability of trandolaprilat is 40 to 60%. Trandolapril is metabolised in the liver to trandolaprilat and to some inactive metabolites. Peak plasma concentrations of trandolaprilat occur 4 to 6 hours after an oral dose of trandolapril. Trandolaprilat is more than 80% bound to plasma proteins. About 33% of an oral dose of trandolapril is excreted in the urine, mainly as trandolaprilat; the rest is excreted in the faeces. The effective half-life for accumulation of trandolaprilat is 16 to 24 hours after multiple doses of trandolapril.

Impaired renal function decreases the excretion of trandolaprilat. Trandolaprilat is removed by haemodialysis.

References.
1. Bevan EG, *et al.* Effect of renal function on the pharmacokinetics and pharmacodynamics of trandolapril. *Br J Clin Pharmacol* 1993; **35:** 128–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dolapril; Gopten; Odrik; Tranalpha; ***Braz.***: Gopten; ***Canad.***: Mavik; ***Cz.***: Fezzor; Gopten; Tanap†; ***Denm.***: Fezzor; Odrik; Prilotrand; ***Fr.***: Odrik; ***Ger.***: Udrik; ***Gr.***: Afenil; Daman; Odrik; ***Hung.***: Gopten; ***Indon.***: Gopten; ***Irl.***: Gopten; Odrik; ***Ital.***: Gopten; ***Jpn***: Odric; Preran; ***Neth.***: Gopten; ***Norw.***: Gopten; ***NZ***: Gopten; Odrik†; ***Pol.***: Gopten; Tensotrand; TrandoGen; ***Port.***: Gopten; Odrik; ***Rus.***: Gopten (Гоптен); ***S.Afr.***: Mavik; ***Spain***: Gopten; Odrik†; ***Switz.***: Gopten; ***Turk.***: Gopten; ***UK***: Gopten; ***USA***: Mavik.

Multi-ingredient Preparations. ***Austral.***: Tarka; ***Canad.***: Tarka; ***Cz.***: Tarka; ***Denm.***: Tarka; ***Fr.***: Tarka; ***Ger.***: Tarka; ***Gr.***: Tarka; Ziaxel; ***Hong Kong***: Tarka; ***Hung.***: Tarka; ***Indon.***: Tarka; ***Ital.***: Tarka; ***Mex.***: Tarka; ***Neth.***: Tarka; Ziaxel; ***NZ***: Ziaxel†; ***Philipp.***: Tarka; ***Pol.***: Tarka; ***Port.***: Tarka; Ziaxel; ***Rus.***: Tarka (Тарка); ***S. Afr.***: Tarka; ***Spain***: Tarka; Tricen†; ***Swed.***: Tarka†; ***Switz.***: Tarka; ***Turk.***: Tarka; ***UK***: Tarka; ***Ukr.***: Tarka (Тарка); ***USA***: Tarka; ***Venez.***: Tarka.

Pharmacopoeial Preparations
BP 2014: Trandolapril Capsules;
USP 36: Trandolapril Tablets.

Trapidil *(BAN, rINN)*

AR-12008; Tarpidil; Trapidiili; Trapidilis; Trapidilum; Трапидил.
7-Diethylamino-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine.
$C_{10}H_{15}N_5$=205.3
CAS — 15421-84-8.
ATC — C01DX11.
ATC Vet — QC01DX11.
UNII — EYG5Y6355E.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Trapidil). A white or almost white crystalline powder. Freely soluble in water; soluble in dehydrated alcohol and in dichloromethane. Protect from light.

Profile

Trapidil is a vasodilator and an inhibitor of platelet aggregation. It is also an antagonist of platelet-derived growth factor. It is used orally in the management of ischaemic heart disease (p. 1254.2) in doses of 400 to 600 mg daily, in divided doses; doses of up to 600 mg daily may be used to prevent restenosis after angioplasty (but see below). Trapidil-eluting stents have also been developed.

References to anti-platelet activity.
1. Yasue H, *et al.* Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction: Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. *Am J Cardiol* 1999; **83:** 1308–13.

References to pharmacokinetics.
1. Harder S, *et al.* Pharmacokinetics of trapidil, an antagonist of platelet derived growth factor, in healthy subjects and in patients with liver cirrhosis. *Br J Clin Pharmacol* 1996; **42:** 443–9.

Angioplasty and stenting. Although angiographic studies[1-3] have found that trapidil reduces the rate of restenosis after balloon angioplasty (see Reperfusion and Revascularisation Procedures, p. 1259.2), no effect on clinical outcomes[3] has been shown. Studies investigating the use of trapidil after coronary stenting[3,4] have shown no benefit in terms of restenosis or clinical events, and it was concluded that trapidil is not indicated for this purpose. Trapidil-eluting stents have been developed, with some sugges-

tion of benefit in preventing restenosis,[5] although robust evidence is scanty and studies are ongoing.[5,6]

1. Okamoto S, *et al.* Effects of trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, in preventing restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J* 1992; **123:** 1439–44.
2. Maresta A, *et al.* Trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty: results of the randomized, double-blind STARC study. *Circulation* 1994; **90:** 2710–15.
3. Maresta A, *et al.* Starc II, a multicenter randomized placebo-controlled double-blind clinical trial of trapidil for 1-year clinical events and angiographic restenosis reduction after coronary angioplasty and stenting. *Catheter Cardiovasc Interv* 2005; **64:** 375–82.
4. Serruys PW, *et al.* The TRAPIST study: a multicentre randomized placebo controlled clinical trial of trapidil for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound. *Eur Heart J* 2001; **22:** 1938–47.
5. Khan M, *et al.* Intrepide; Trapidil eluting stent. *EuroIntervention* 2008; **4:** 405–11.
6. Iaccarino D, *et al.* Rationale and study design of the OISTER trial: Optical coherence tomography evaluation of stent struts re-endothelialization in patients with non-ST-elevation acute coronary syndromes—a comparison of the intrEpide tRapidil eluting stent vs. taxus drug-eluting stent implantation. *J Cardiovasc Med (Hagerstown)* 2010; **11:** 536–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Travisco; ***Ger.***: Rocornal; ***Ital.***: Travisco; ***Jpn***: Rocornal.

Treprostinil *(USAN, rINN)*

15AU81; BW-15AU; BW-15AU81; LRX-15; Tréprostinil; Treprostinilo; Treprostinilum; Treprostinol; U-62840; UT-15; Трепростинил.

((1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy)acetic acid.

$C_{23}H_{34}O_5$=390.5

CAS — 81846-19-7.

ATC — B01AC21.

ATC Vet — QB01AC21.

UNII — RUM6K67ESG.

Treprostinil Sodium *(rINNM)*

Natrii Treprostinilum; Tréprostinil Sodique; Treprostinilo sódico; Натрий Трепростинил.

$C_{23}H_{33}NaO_5$=412.5

CAS — 289480-64-4.

ATC — B01AC21.

ATC Vet — QB01AC21.

UNII — 7JZ75N2NT6.

Uses and Administration

Treprostinil, a vasodilator and platelet aggregation inhibitor, is an analogue of the prostaglandin epoprostenol (prostacyclin; p. 1374.3) and is given in the treatment of pulmonary hypertension (p. 1278.2). Treprostinil sodium is given by continuous subcutaneous *infusion*; if this route cannot be tolerated, treprostinil sodium may be given by continuous infusion through a central venous catheter. Doses are calculated in terms of treprostinil: treprostinil sodium 1.32 nanograms is equivalent to about 1.25 nanograms of treprostinil. The infusion is started with a dose equivalent to treprostinil 1.25 nanograms/kg per minute; if this is not tolerated the dose should be halved. The infusion rate can be increased according to patient response, by increments of up to 1.25 nanograms/kg per minute each week for the first 4 weeks, followed by increases of up to 2.5 nanograms/kg per minute each week. There is limited experience with doses above 40 nanograms/kg per minute.

Treprostinil may also be given by *inhalation* in an initial dose of 18 micrograms inhaled 4 times daily, reduced to 6 or 12 micrograms inhaled 4 times daily if the higher dose is not tolerated. Dosage should then be increased in increments of 18 micrograms every 1 to 2 weeks as tolerated, to a maximum maintenance dose of 54 micrograms inhaled 4 times daily.

The dose of treprostinil should be reduced in hepatic impairment, see below.

Intravenous treprostinil has been investigated for intermittent claudication.

References.

1. Moller ER, *et al.* Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication. *Vasc Med* 2000; **5:** 231–7.
2. Simonneau G, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2002; **165:** 800–804.
3. Vachiéry J-L, *et al.* Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. *Chest* 2002; **121:** 1561–5.
4. Oudiz RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004; **126:** 420–7.
5. Gomberg-Maitland M, *et al.* Efficacy and safety of sildenafil added to treprostinil in pulmonary hypertension. *Am J Cardiol* 2005; **96:** 1334–6.
6. Fernandez B, Strootman D. The prostacyclin analog, treprostinil sodium, provides symptom relief in severe Buerger's disease—a case report and review of literature. *Angiology* 2006; **57:** 99–102.
7. Voswinckel R, *et al.* Inhaled treprostinil for treatment of chronic pulmonary arterial hypertension. *Ann Intern Med* 2006; **144:** 149–50.
8. Channick RN, *et al.* Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol* 2006; **48:** 1433–7.
9. Voswinckel R, *et al.* Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. *J Am Coll Cardiol* 2006; **48:** 1672–81.
10. Skoro-Sajer N, Lang I. Treprostinil for the treatment of pulmonary hypertension. *Expert Opin Pharmacother* 2008; **9:** 1415–20.
11. Voswinckel R, *et al.* Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension. *Pulm Pharmacol Ther* 2009; **22:** 50–6.
12. Hiremath J, *et al.* TRUST Study Group. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant* 2010; **29:** 137–49.
13. McLaughlin VV, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol* 2010; **55:** 1915–22.

Administration. A study[1] in 23 patients with pulmonary hypertension who were treated with subcutaneous infusion of treprostinil found that a rapid dose-escalation regimen (weekly or twice-weekly increments of 2.5 nanograms/kg per minute) lowered infusion-site pain and improved 12-week exercise outcomes without increasing adverse events when compared with a slower dose-escalation regimen (weekly increments of 1.25 to 2 nanograms/kg per minute).

1. Skoro-Sajer N, *et al.* A clinical comparison of slow- and rapid-escalation treprostinil dosing regimens in patients with pulmonary hypertension. *Clin Pharmacokinet* 2008; **47:** 611–18.

Administration in hepatic impairment. Clearance of treprostinil is reduced in patients with hepatic impairment. Licensed product information recommends that the initial dose of the *infusion* should be 0.625 nanograms/kg per minute, and should be increased cautiously, in mild to moderate impairment. No licensed dosage recommendations are given for severe hepatic impairment. However, intravenous treprostinil infusion was reported[1] to be safe and effective in 3 patients with end-stage liver disease, including 1 patient who was given 106 nanograms/kg per minute for 2 years.

Caution is also advocated when titrating upwards from the initial dose of *inhaled* treprostinil in patients with mild to moderate hepatic impairment.

1. Sakai T, *et al.* Initial experience using continuous intravenous treprostinil to manage pulmonary arterial hypertension in patients with end-stage liver disease. *Transpl Int* 2009; **22:** 554–61.

Peripheral vascular disease. Prostaglandins have been used for their vasodilating effect in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3) that is complicated by ulceration, and subcutaneous treprostinil was used[1] successfully to treat severe refractory digital necrosis in a patient with Raynaud's disease and scleroderma.

1. Engel G, Rockson SG. Treprostinil for the treatment of severe digital necrosis in systemic sclerosis. *Vasc Med* 2005; **10:** 29–32.

Adverse Effects and Precautions

As for Epoprostenol, p. 1375.3; infusion-site reactions are common. Inhaled treprostinil has been associated with signs of local irritation including haemoptysis (fatal in one case), and pneumonia. Treprostinil should be used with caution in hepatic impairment.

Interactions

Since treprostinil is a vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants.

Pharmacokinetics

Treprostinil sodium is rapidly and completely absorbed after subcutaneous injection. It is metabolised by the liver and eliminated with a terminal half-life of about 4 hours. About 80% of a dose is excreted in the urine, mainly as metabolites. The systemic absolute bioavailability of inhaled treprostinil is about 64% after an 18 microgram dose and about 72% after a 36 microgram dose.

References.

1. Wade M, *et al.* Absolute bioavailability and pharmacokinetics of treprostinil sodium administered by acute subcutaneous infusion. *J Clin Pharmacol* 2004; **44:** 83–8.
2. Wade M, *et al.* Pharmacokinetics of treprostinil sodium administered by 28-day chronic continuous subcutaneous infusion. *J Clin Pharmacol* 2004; **44:** 503–9.
3. Laliberte K, *et al.* Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. *J Cardiovasc Pharmacol* 2004; **44:** 209–14.
4. McSwain CS, *et al.* Dose proportionality of treprostinil sodium administered by continuous subcutaneous and intravenous infusion. *J Clin Pharmacol* 2008; **48:** 19–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Remodulin; ***Austral.***: Remodulin; ***Austria***: Remodulin; ***Belg.***: Remodulin; ***Canad.***: Remodulin; ***Chile***: Remodulin; ***Cz.***: Remodulin; ***Denm.***: Remodulin; ***Fin.***: Remodulin; ***Fr.***: Remodulin; ***Ger.***: Remodulin; ***Gr.***: Remodulin; ***Israel***: Remodulin; Tyvaso; ***Ital.***: Remodulin; ***Neth.***: Remodulin; ***Norw.***: Remodulin; ***Port.***: Remodulin; ***Swed.***: Remodulin; ***Switz.***: Remodulin; ***USA***: Remodulin; Tyvaso.

Triamterene *(BAN, USAN, rINN)* ⊗

NSC-77625; SKF-8542; Triamtereeni; Triamteren; Triamterén; Triamterenas; Triamtérène; Triamtereno; Triamterenum; Triantereno; Триамтерен.

6-Phenylpteridine-2,4,7-triamine; 2,4,7-Triamino-6-phenylpteridine.

$C_{12}H_{11}N_7$=253.3

CAS — 396-01-0.

ATC — C03DB02.

ATC Vet — QC03DB02.

UNII — WS821Z52LQ.

NOTE. Compounded preparations of triamterene may be represented by the following names:

- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Triamterene). A yellow, crystalline powder. Very slightly soluble in water and in alcohol. Protect from light.

USP 36: (Triamterene). A yellow, odourless, crystalline powder. Practically insoluble in water, in chloroform, in ether, in benzene, and in dilute alkali hydroxides; very slightly soluble in alcohol, in acetic acid, and in dilute mineral acids; soluble 1 in 30 of formic acid and 1 in 85 of 2-methoxyethanol. Store in airtight containers. Protect from light.

Uses and Administration

Triamterene is a weak diuretic with potassium-sparing properties which has actions and uses similar to those of amiloride (p. 1299.1). It produces a diuresis in about 2 to 4 hours, with a duration of 7 to 9 hours. The full therapeutic effect may be delayed until after several days of treatment.

Triamterene adds to the natriuretic but diminishes the kaliuretic effects of other diuretics. It is mainly used, as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the treatment of refractory oedema associated with hepatic cirrhosis, heart failure (p. 1262.3), and the nephrotic syndrome. It is also used with other diuretics in the treatment of hypertension (p. 1251.1).

When triamterene is given alone in the treatment of **oedema**, the oral dosage range is 150 to 250 mg daily, given in 2 divided doses, after breakfast and lunch. Doses may be given on alternate days for maintenance therapy. More than 300 mg daily should not be given.

Smaller doses are used initially when other diuretics are also given. When used with hydrochlorothiazide, for example, in the treatment of **hypertension**, an initial dose of 50 mg of triamterene daily may be used.

Potassium supplements should not be given.

Adverse Effects

As for Amiloride Hydrochloride, p. 1299.2. Triamterene has also been reported to cause photosensitivity reactions, increases in uric acid concentrations, and blood dyscrasias. Renal calculi may occur in susceptible patients, and megaloblastic anaemia has been reported in patients with depleted folic acid stores such as those with hepatic cirrhosis. Reversible renal failure, due either to acute interstitial nephritis or to an interaction with NSAIDs (see under Interactions, p. 1519.2) has occurred.

Incidence of adverse effects. In a postmarketing surveillance study of 70 898 patients[1] taking triamterene with hydrochlorothiazide the most common adverse effects were fatigue, dizziness, and nausea. Adverse effects necessitated withdrawal in 8.1% of patients. A subgroup analysis of 21 731 patients[2] indicated that hyperkalaemia was

more common in elderly patients and in those with diabetes mellitus.

1. Hollenberg NK, Mickiewicz CW. Postmarketing surveillance in 70,898 patients treated with a triamterene/hydrochlorothiazide combination (Maxzide). *Am J Cardiol* 1989; **63:** 37B–41B.
2. Hollenberg NK, Mickiewicz CW. Hyperkalemia in diabetes mellitus: effect of a triamterene-hydrochlorothiazide combination. *Arch Intern Med* 1989; **149:** 1327–30.

Effects on the blood. There have been case reports of pancytopenia associated with triamterene therapy.[1,2] Some patients had hepatic cirrhosis and the antifolate activity of triamterene was considered responsible.[2]

1. Castellano G, *et al.* Pancitopenia aguda y megaloblastosis medular durante el tratemiento con triamterene de la ascitis causada por cirrosis hepática: aportación de dos casos. *Gastroenterol Hepatol* 1983; **6:** 540–4.
2. Remacha A, *et al.* Triamterene-induced megaloblastosis: report of two new cases, and review of the literature. *Biol Clin Hematol* 1983; **5:** 127–34.

Effects on the kidneys. There have been reports[1-4] of renal calculi containing triamterene or its metabolites, generally in patients also taking hydrochlorothiazide. An abnormal urinary sediment, which was thought to represent precipitated triamterene, was described.[5] These observations were expanded in a crossover study:[6] abnormal urinary sediment was seen in 14 of 26 patients taking triamterene but in none taking amiloride. Triamterene and its metabolites were identified by others in 181 of 50 000 renal calculi.[7] Triamterene either formed the nucleus of the stone or was deposited with calcium oxalate or uric acid. One-third of the 181 stones were entirely or mainly composed of triamterene and its metabolites and it was suggested that supersaturation of the urine with these substances could provide suitable nuclei for the crystallisation of calcium oxalate.[8] However, other workers were unable to confirm this and suggested that triamterene and its metabolites could become incorporated into the protein matrix of existing stones.[9] In addition, an epidemiological study[10] found no evidence that triamterene use was associated with an increased incidence of renal stones. Some authors[11] have therefore considered that there was not enough evidence to contra-indicate the drug in patients with a history of recurrent renal calculi.

Deposition of triamterene in the urine may also play a part in the development of interstitial nephritis, which was diagnosed in 4 patients also taking hydrochlorothiazide, over a period of 4 years.[6]

Triamterene has also been associated with transient decline in renal function and the development of renal failure.[12,13] Several mechanisms may be responsible including interstitial nephritis, intrarenal obstruction by crystalline deposits, and an interaction with NSAIDs (see under Interactions, below).[13] Elderly patients may be particularly at risk.[12]

1. Ettinger B, *et al.* Triamterene-induced nephrolithiasis. *Ann Intern Med* 1979; **91:** 745–6.
2. Socolow EL. Triamterene-induced nephrolithiasis. *Ann Intern Med* 1980; **92:** 437.
3. Gault MH, *et al.* Triamterene urolithiasis. *Can Med Assoc J* 1981; **124:** 1556–7.
4. Grunberg RW, Silberg SJ. Triamterene-induced nephrolithiasis. *JAMA* 1981; **245:** 2494–5.
5. Fairley KF, *et al.* Abnormal urinary sediment in patients on triamterene. *Lancet* 1983; **i:** 421–2.
6. Spence JD, *et al.* Effects of triamterene and amiloride on urinary sediment in hypertensive patients taking hydrochlorothiazide. *Lancet* 1985; **ii:** 73–5.
7. Ettinger B, *et al.* Triamterene nephrolithiasis. *JAMA* 1980; **244:** 2443–5.
8. White DJ, Nancollas GH. Triamterene and renal stone formation. *J Urol (Baltimore)* 1982; **127:** 593–7.
9. Werness PG, *et al.* Triamterene urolithiasis: solubility, pK, effect on crystal formation, and matrix binding of triamterene and its metabolites. *J Lab Clin Med* 1982; **99:** 254–62.
10. Jick H, *et al.* Triamterene and renal stones. *J Urol (Baltimore)* 1982; **127:** 224–5.
11. Woolfson RG, Mansell MA. Does triamterene cause renal calculi? *BMJ* 1991; **303:** 1217–18.
12. Lynn KL, *et al.* Renal failure with potassium-sparing diuretics. *N Z Med J* 1985; **98:** 629–33.
13. Sica DA, Gehr TWB. Triamterene and the kidney. *Nephron* 1989; **51:** 454–61.

Effects on the skin. Photodermatitis has been reported in a patient taking triamterene.[1] Pseudoporphyria, possibly associated with exposure to sunlight, occurred in a patient with vitiligo during treatment with triamterene and hydrochlorothiazide.[2]

1. Fernández de Corres L, *et al.* Photodermatitis from triamterene. *Contact Dermatitis* 1987; **17:** 114–15.
2. Motley RJ. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; **300:** 1468.

Precautions

As for Amiloride Hydrochloride, p. 1299.3. Triamterene should also be given with caution to patients with hyperuricaemia or gout, or a history of renal calculi. Patients with depleted folic acid stores such as those with hepatic cirrhosis may be at increased risk of megaloblastic anaemia.

Triamterene may interfere with the fluorescent measurement of quinidine. It may slightly colour the urine blue.

Interactions

As for Amiloride Hydrochloride, p. 1299.3.

Digoxin. For a report of the effect of triamterene on digoxin concentrations, see p. 1357.2.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p. 892.2.

NSAIDs. There have been several reports of renal failure in patients taking triamterene and NSAIDs.[1,2] Both types of drug are nephrotoxic and in combination the effect appears to be additive.[3-5] It has been suggested that the suppression of urinary prostaglandins by NSAIDs could potentiate the nephrotoxic effects of triamterene.[1]

NSAIDs may also antagonise the diuretic action of triamterene.[6]

1. Favre L, *et al.* Reversible acute renal failure from combined triamterene and indomethacin: a study in healthy subjects. *Ann Intern Med* 1982; **96:** 317–20.
2. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; **293:** 698–9.
3. Bailey RR. Adverse renal reactions to non-steroidal anti-inflammatory drugs and potassium-sparing diuretics. *Adverse Drug React Bull* 1988; (Aug.): 492–5.
4. Lynn KL, *et al.* Renal failure with potassium-sparing diuretics. *N Z Med J* 1985; **98:** 629–33.
5. Sica DA, Gehr TWB. Triamterene and the kidney. *Nephron* 1989; **51:** 454–61.
6. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Pharmacokinetics

Triamterene is variably but fairly rapidly absorbed from the gastrointestinal tract. The bioavailability has been reported to be about 50%. The plasma half-life has been reported to be about 2 hours. It is estimated to be about 60% bound to plasma proteins. It is extensively metabolised, apparently via the cytochrome P450 isoenzyme CYP1A2, and is mainly excreted in the urine in the form of metabolites with some unchanged triamterene. Triamterene crosses the placenta and may be distributed into breast milk.

References.

1. Pruitt AW, *et al.* Variations in the fate of triamterene. *Clin Pharmacol Ther* 1977; **21:** 610–19.
2. Gundert-Remy U, *et al.* Plasma and urinary levels of triamterene and certain metabolites after oral administration to man. *Eur J Clin Pharmacol* 1979; **16:** 39–44.
3. Gilfrich HJ, *et al.* Pharmacokinetics of triamterene afteriv administration to man: determination of bioavailability. *Eur J Clin Pharmacol* 1983; **25:** 237–41.
4. Sörgel F, *et al.* Oral triamterene disposition. *Clin Pharmacol Ther* 1985; **38:** 306–12.
5. Fuhr U, *et al.* Rate-limiting biotransformation of triamterene is mediated by CYP1A2. *Int J Clin Pharmacol Ther* 2005; **43:** 327–34.

Hepatic impairment. Triamterene clearance was markedly decreased in 7 patients with alcoholic cirrhosis and ascites.[1] The diuretic effect lasted for up to 48 hours in cirrhotic patients compared with 8 hours in healthy controls.

1. Villeneuve JP, *et al.* Triamterene kinetics and dynamics in cirrhosis. *Clin Pharmacol Ther* 1984; **35:** 831–7.

Renal impairment. Urinary excretion of triamterene and its metabolite, hydroxytriamterene sulfate, was significantly reduced in patients with renal impairment[1] and in the elderly whose renal function was reduced.[2] Accumulation of the active metabolite was possible in patients with renal impairment.[1]

1. Knauf H, *et al.* Delayed elimination of triamterene and its active metabolite in chronic renal failure. *Eur J Clin Pharmacol* 1983; **24:** 453–6.
2. Williams RL, *et al.* Absorption and disposition of two combination formulations of hydrochlorothiazide and triamterene: influence of age and renal function. *Clin Pharmacol Ther* 1986; **40:** 226–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Dytac; ***UK***: Dytac†; ***USA***: Dyrenium.

Multi-ingredient Preparations. ***Austral.***: Hydrene; ***Austria***: Confit; Dytide H; Triamteren comp; Triastad HCT; ***Belg.***: Dyta-Urese; Dytenzide; ***Braz.***: Diurana; Iguassina; ***Canad.***: Apo-Triazide; Novo-Triamzide†; Nu-Triazide†; Pro-Triazide; Riva-Zide; ***Chile***: Drinamil; Hidroronol T; Uren; ***China***: No 0 (0号); ***Fin.***: Furesis comp; Uretren Comp; ***Fr.***: Isobar; Prestole; ***Ger.***: Beta-Turfa†; dehydro sanol tri; Diu Venostasin; Diucomb; Diuretikum Verla; Dociteren; Dytide H; Neotri; Nephral; Propra comp; Tri-Thiazid; Triampur Compositum; Triamteren comp; Triamteren HCT†; Triamteren tri-comp†; Triarese†; Turfa; Veratide†; ***Gr.***: Dyberzide; ***Hong Kong***: Apo-Triazide; Dyazide; ***India***: Ditide; Frusemene; ***Irl.***: Dyazide; ***Ital.***: Fluss; ***Mex.***: Dyazide†; ***Neth.***: Dyta-Urese; Dytenzide; ***NZ***: Triamizide†; ***Port.***: Dyazide; Triam Tiazida R; ***Rus.***: Apo-Triazide (Апо-триазид); Triam-Co (Триам-ко)†; Triampur Compositum (Триампур Композитум); Triamtel (Триамтел); ***S.Afr.***: Dyazide; Renezide; ***Singapore***: Apo-Triazide; ***Spain***: Salidur; ***Switz.***: Dyrenium compositum†; ***Thai.***: Dinazide; Dyazide; ***Turk.***: Triamteril; ***UK***: Dyazide; Dytide†; Frusene; Kalspare; Triamco; ***Ukr.***: Triampur Compositum (Триампур Композитум); ***USA***: Dyazide; Maxzide.

Pharmacopoeial Preparations
BP 2014: Co-triamterzide Tablets; Triamterene Capsules;
USP 36: Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Triamterene Capsules.

Trichlormethiazide *(rINN)* ⊗

Trichlorméthiazide; Trichlormethiazidum; Triclormetiazida; Trikloorimetiatsidi; Triklormetiazid; Трихлорметиазид.

6-Chloro-3-dichloromethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_8H_8Cl_3N_3O_4S_2$=380.6

CAS — 133-67-5.
ATC — C03AA06.
ATC Vet — QC03AA06.
UNII — Q58C92TUN0.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Trichlormethiazide). A white or practically white, crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 1100 of water, 1 in 48 of alcohol, 1 in 5000 of chloroform, 1 in about 4 of dimethylformamide, 1 in about 9 of dioxan, and 1 in 1400 of ether; freely soluble in acetone; soluble in methyl alcohol.

Profile

Trichlormethiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1404.2). It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis begins about 2 hours after an oral dose, and lasts about 24 hours.

In the treatment of oedema a usual dose has been 1 to 4 mg daily or intermittently. In the treatment of hypertension a usual dose has been 2 to 4 mg daily, either alone, or with other antihypertensives. In some patients 1 mg daily has been adequate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fin.***: Uretren Comp; ***Gr.***: Tensiplex; ***Jpn***: Irtra.

Pharmacopoeial Preparations
USP 36: Trichlormethiazide Tablets.

Triflusal *(BAN, rINN)*

Triflusaali; Triflusalis; Triflusalum; Trifluzál; UR-1501; Трифлусал.

2-Acetoxy-4-trifluoromethylbenzoic acid; *O*-Acetyl-4-(trifluoromethyl)salicylic acid.

$C_{10}H_7F_3O_4$=248.2

CAS — 322-79-2.
ATC — B01AC18.
ATC Vet — QB01AC18.
UNII — 1Z0YFI05OO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Triflusal). A white or almost white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 25 degrees.

Profile

Triflusal reduces platelet aggregation by inhibiting cyclooxygenase-1 and phosphodiesterases. It is used in the management of thromboembolic disorders (p. 1273.2) in usual oral doses of 300 to 900 mg daily.

References.

1. Murdoch D, Plosker GL. Triflusal: a review of its use in cerebral infarction and myocardial infarction, and as thromboprophylaxis in atrial fibrillation. *Drugs* 2006; **66:** 671–92.
2. González-Correa JA, De La Cruz JP. Triflusal: an antiplatelet drug with a neuroprotective effect? *Cardiovasc Drug Rev* 2006; **24:** 11–24.
3. Gómez-Isla T, *et al.* TRIMCI Study Group. A randomized, double-blind, placebo controlled-trial of triflusal in mild cognitive impairment: the TRIMCI study. *Alzheimer Dis Assoc Disord* 2008; **22:** 21–9.
4. Anninos H, *et al.* Triflusal: an old drug in modern antiplatelet therapy. Review of its action, use, safety and effectiveness. *Hellenic J Cardiol* 2009; **50:** 199–207.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Disgren; ***Braz.***: Disgren; ***Gr.***: Aflen; Reoflen; ***Hung.***: Disgren; ***Indon.***: Grendis; ***Ital.***: Triflux; ***Malaysia***: Grendis; ***Mex.***: Disgren; ***Philipp.***: Grendis; T-Bren; ***Port.***: Tecnosal; ***Spain***: Anpeval†; Disgren; ***Thai.***: Grendis; ***Ukr.***: Disgren (ДИСГРЕН); ***Venez.***: Disgren.

Trimetazidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimetazidina; Trimetatsidiinidihydrokloridi; Trimetazidin Hidroklorür; Trimetazidina, hidrocloruro de; Trimetazidindihidroklorid; Trimetazidindihydrochlorid; Trimetazidin-dihydrochlorid; Trimetazidindihydroklorid; Trimétazidine, Chlorhydrate de; Trimétazidine, dichlorhydrate de; Trimetazidine Dihydrochloride; Trimetazidini dihydrochloridum; Trimetazidini Hydrochloridum; Trimetazidino hidrochloridas; Trimetazine Hydrochloride; Триметазидина Гидрохлорид.

1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride.

$C_{14}H_{22}N_2O_3$,2HCl=339.3

CAS — 5011-34-7 (trimetazidine); 13171-25-0 (trimetazidine hydrochloride).

ATC — C01EB15.

ATC Vet — QC01EB15.

UNII — 48V6723Z1P.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Trimetazidine Dihydrochloride; Trimetazidine Hydrochloride BP 2014). A slightly hygroscopic, white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Trimetazidine hydrochloride is used in angina pectoris (p. 1254.3); however, following concerns over its questionable efficacy and reports of movement disorders such as parkinsonism, restless legs syndrome, tremor, and gait instability (see Effects on the Nervous System, below), the EMEA in Europe has recommended that trimetazidine should only be used as second-line, add-on therapy in the treatment of stable angina pectoris. The usual dose is 40 to 60 mg given daily in divided oral doses, although higher doses have been used in some countries (as modified-release preparations). It should be given with caution to the elderly and to patients with renal impairment. Therapy should be stopped permanently in patients who develop movement disorders and neurological consultation sought if such adverse effects persist for more than 4 months after stopping the drug.

Trimetazidine has also been used in the symptomatic treatment of vertigo, tinnitus, and Ménière's disease. However, its benefit in these indications has not been shown and the EMEA recommends against such use.

References.

1. McClellan KJ, Plosker GL. Trimetazidine: a review of its use in stable angina pectoris and other coronary conditions. *Drugs* 1999; **58:** 143–57.
2. Ciapponi A, *et al.* Trimetazidine for stable angina. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/06).
3. Danchin N. Clinical benefits of a metabolic approach with trimetazidine in revascularized patients with angina. *Am J Cardiol* 2006; **98** (suppl): 8J–13J.
4. Banach M, *et al.* The role of trimetazidine after acute myocardial infarction. *Curr Vasc Pharmacol* 2008; **6:** 282–91.
5. Di Napoli P, Taccardi AA. Trimetazidine: the future of cardiac function? *Future Cardiol* 2009; **5:** 421–4.
6. Gao D, *et al.* Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. *Heart* 2011; **97:** 278–86.
7. Zhang L, *et al.* Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol* 2012; **59:** 913–22.

Effects on the nervous system. Eight elderly patients aged between 72 and 94 years were reported[1] to have developed signs of parkinsonism while taking trimetazidine; the parkinsonism regressed completely when the drug was stopped. A retrospective study[2] found that adverse effects on motor function, including parkinsonism, gait disorders, and tremor, occurred in 56 of 130 patients taking trimetazidine and were more common in older patients.

In June 2012, the EMEA in Europe recommended new contra-indications and warnings to reduce the risk of movement disorders with trimetazidine.[3] The agency was aware of reports of movement disorders such as Parkinsonian symptoms, restless legs syndrome, tremor, and abnormal gait with trimetazidine and advised against its use in patients with a history of such disorders. It was also recommended that treatment with trimetazidine be permanently stopped in those who develop movement disorders.

1. Martí Massó JF. Parkinsonismo por trimetazidina. *Neurologia* 2004; **19:** 392–5.
2. Martí Massó J-F, *et al.* Trimetazidine induces parkinsonism, gait disorders and tremor. *Therapie* 2005; **60:** 419–22.
3. EMEA. European Medicines Agency recommends restricting use of trimetazidine-containing medicines (issued 22nd June, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/06/WC500129070.pdf (accessed 11/10/12)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vastarel; ***Austria***: Vastarel†; ***Braz.***: Vastarel; ***Chile***: Vastarel; ***China***: Aiyiling (爱怡令); Vasorel (万爽力); Ze Wei Er (泽维尔); ***Cz.***: Adexor†; Portora; Preductal; Zilutra; ***Denm.***: Vastarel; ***Fr.***: Vastarel; ***Gr.***: Atanol; Imovexil; Intervein; Latrimet; Liomagen; Novazidine; Trimedin; Trimedor; Trimevert; Vastarel; Zidin; ***Hong Kong***: Matenol; Trivedon; Vastarel; ***Hung.***: Adexor; Mezitan; Moduxin; Preductal; ***India***: Cardimax; Carvidon; Cytogard; Flavedon; Invidon; Isvedon; Kardin; Mayozest; Metacard†; Metagard; Myovedon; Trivedon; ***Indon.***: Trizedon; ***Irl.***: Vastarel; ***Ital.***: Vastarel; ***Malaysia***: Metagard†; Metazine; Vastarel; ***Philipp.***: Angimax; Angirel; Carvidon; Longity†; Tazinet†; Tazz; Trimerel; Vassapro; Vastarel; Vestar; ***Pol.***: Cyto-Protectin; Metazydyna; Preductal; Protevasc; Setal; Trimetaratio; ***Port.***: Tacirel; Trimepharma†; Vastarel; ***Rus.***: Angiozil (Ангиозил); Angital (Ангитал); Antisten (Антистен); Carditrim (Кардитрим); Deprenorm (Депренорм); Medarum (Медарум); Metagard (Метагард); Prebructal (ПреБРуктал); Predizin (Предизин); Preductal (Предуктал); Rimecor (Римекор); Trimektal (Триметкал); Trimet (Тримет); Trimetazide (Триметазид); ***Singapore***: Mejadin; Metagard; Vastarel; ***Spain***: Idaptan; ***Thai.***: Matenol; Metagem; Trizidine; Vastarel; Vastinol; ***Turk.***: Sitorel; Vastarel; ***Ukr.***: Cardimax (Кардимакс)†; Carductal (Кардуктал); Energoton (Энерготон); Metazidin (Метазидин); Predizin (Предизин); Preductal (Предуктал); Tricard (Трикард); Triductan (Тридуктан); ***Venez.***: Vastarel.

Multi-ingredient Preparations. ***Ukr.***: Cardasin (Кардазин).

Tripamide *(USAN, rINN)* ⊗

ADR-033; E-614; Tripamida; Tripamidum; Трипамид.

4-Chloro-*N*-(*endo*-hexahydro-4,7-methanoisoindolin-2-yl)-3-sulphamoylbenzamide.

$C_{16}H_{20}ClN_3O_3S$=369.9

CAS — 73803-48-2.

UNII — G36A0E9CVT.

Profile

Tripamide is a diuretic structurally related to indapamide. It is used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Normonal; ***Thai.***: Normonal.

Urapidil *(BAN, rINN)*

B-66256M; Urapidiili; Urapidilum; Урапидил.

6-[3-(4-o-Methoxyphenylpiperazin-1-yl)propylamino]-1,3-dimethyluracil.

$C_{20}H_{29}N_5O_3$=387.5

CAS — 34661-75-1.

ATC — C02CA06.

ATC Vet — QC02CA06.

UNII — A78GF17HJS.

Pharmacopoeias. In *Jpn*.

Urapidil Hydrochloride *(BANM, rINNM)*

Hidrocloruro de urapidil; Urapidil, Chlorhydrate d'; Urapidil, hidrocloruro de; Urapidili Hydrochloridum; Урапидила Гидрохлорид.

$C_{20}H_{29}N_5O_3$,HCl=423.9

CAS — 64887-14-5.

ATC — C02CA06.

ATC Vet — QC02CA06.

Uses and Administration

Urapidil is an antihypertensive drug that is reported to block peripheral alpha$_1$ adrenoceptors (see Alpha Blockers, p. 1243.1) and to have central actions. It produces a reduction in peripheral resistance and a fall in systolic and diastolic blood pressure, usually without reflex tachycardia.

Urapidil is used in the management of hypertension (p. 1251.1), including hypertensive crises.

Urapidil is given orally as the base and intravenously as the hydrochloride, but doses are usually expressed in terms of the base. Urapidil hydrochloride 10.94 mg is equivalent to about 10 mg of urapidil. Urapidil fumarate has also been given orally.

In hypertension oral doses of 30 to 90 mg are given twice daily. In hypertensive crises a suggested regimen is to give an initial dose of 25 mg by slow intravenous injection over 20 seconds, repeated if necessary after 5 minutes. This may be followed by a dose of 50 mg after a further 5 minutes if the response is still inadequate. Treatment should continue with a maintenance infusion of 9 to 30 mg/hour once the blood pressure is sufficiently reduced.

Reviews.

1. Dooley M, Goa KL. Urapidil: a reappraisal of its use in the management of hypertension. *Drugs* 1998; **56:** 929–55.
2. Buch J. Urapidil, a dual-acting antihypertensive agent: current usage considerations. *Adv Therapy* 2010; **27:** 426–43.

Adverse Effects and Precautions

Urapidil is reported to be well-tolerated, with adverse effects generally transient and most frequent at the beginning of therapy. Dizziness, nausea, headache, fatigue, orthostatic hypotension, palpitations, nervousness, pruritus, and allergic skin reactions have been reported.

It should be used with care in elderly patients and those with severe hepatic impairment. Intravenous urapidil should not be used in patients with aortic stenosis.

Urinary incontinence. Enuresis in 2 elderly patients was reported[1] to be associated with the use of urapidil.

1. Jonville A-P, *et al.* Urapidil and enuresis. *Lancet* 1992; **339:** 688.

Pharmacokinetics

After oral doses urapidil is rapidly absorbed with a reported bioavailability of 70 to 80%. It is reported to be about 80% bound to plasma proteins. Urapidil is extensively metabolised in the liver, mainly by hydroxylation, and excreted mostly in urine, as metabolites and 10 to 20% of unchanged drug. The elimination half-life is reported to be about 4.7 hours when given orally as capsules and about 2.7 hours after intravenous dosage.

Reviews.

1. Kirsten R, *et al.* Clinical pharmacokinetics of urapidil. *Clin Pharmacokinet* 1988; **14:** 129–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ebrantil; Hypotrit; ***Belg.***: Ebrantil; ***China***: Ebrantil (亚宁定); Jie Ping (捷平); Jie Tong (捷通); Lao Mai Na (劳麦纳); Lixiding (利喜定); LuoHao (罗浩); Ya Li Di (亚利敌); Yu You Ding (裕优定); ***Cz.***: Ebrantil; ***Fr.***: Eupressyl; Mediatensyl; ***Ger.***: Ebrantil; ***Hung.***: Ebrantil; ***Ital.***: Ebrantil; ***Neth.***: Ebrantil; ***Pol.***: Ebrantil; ***Port.***: Ebrantil; ***Rus.***: Ebrantil (Эбрантил); ***Spain***: Elgadil; ***Switz.***: Ebrantil; ***Ukr.***: Ebrantil (Эбрантил).

Urokinase *(BAN, USAN, rINN)*

Urokinaasi; Urokinas; Urokinasa; Urokinasum; Ürokinaz; Urokinazė; Urokináz; Uroquinasa; Урокиназа.

CAS — 9039-53-6.

ATC — B01AD04.

ATC Vet — QB01AD04.

UNII — 83G67E21XI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Urokinase). An enzyme isolated from human urine that activates plasminogen. It consists of a mixture of low (33 000) and high (54 000) molecular mass forms, the high molecular mass form being predominant. The potency is not less than 70 000 international units per mg of protein. A white or almost white, amorphous powder. Soluble in water. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Stability. Solutions of urokinase containing 2500 to 25 000 units/mL were found to be stable in single-use syringes when stored at -30 degrees for 30 days and also when stored frozen for 7 days, thawed, and refrozen for a further 23 days.[1]

1. Dedrick SC, Ramirez-Rico J. Potency and stability of frozen urokinase solutions in syringes. *Am J Health-Syst Pharm* 2004; **61:** 1586–9.

Units

The potency of urokinase is expressed in international units. Preparations are assayed using the first International Reference Preparation (1968), a mixture of low-molecular-weight and high-molecular-weight urokinases. The first International Standard for high-molecular-weight urokinase was established in 1989 for use with preparations of this type of urokinase.

Potency used to be expressed in Ploug or Plough units or in CTA units, but these now appear to be obsolete.

Uses and Administration

Urokinase is a thrombolytic produced by the kidney and found in human urine. It directly converts plasminogen to its active form plasmin, resulting in fibrinolysis and dissolution of blood clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on

p. 1124.3. Urokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p. 1245.3).

Urokinase is used similarly to streptokinase (p. 1503.1) in the management of thromboembolic disorders including venous thromboembolism (pulmonary embolism and deep-vein thrombosis; p. 1274.1) and peripheral arterial thromboembolism (p. 1273.3). It is also used to clear occluded catheters and cannulas. Urokinase has been used in myocardial infarction and for clearing clots after haemorrhage within the eye.

In the treatment of **venous thromboembolism**, urokinase is given by intravenous infusion in an initial dose of 4400 units/kg given over 10 to 20 minutes. This is followed by maintenance of 4400 units/kg per hour for 12 hours in pulmonary embolism, and for 12 to 24 hours in deep-vein thrombosis; 100 000 units/hour for 2 to 3 days is an alternative maintenance dose for deep-vein thrombosis. Patients with pulmonary embolism may be given urokinase by bolus injection instead, in a dose of 15 000 units/kg into the pulmonary artery. The injection may be given, with the dose adjusted according to plasma-fibrinogen concentration, up to 3 times in 24 hours.

In the treatment of **peripheral arterial thromboembolism**, a solution containing urokinase 2000 units/mL is infused into the clot via a catheter at a rate of 4000 units/minute for 2 hours. Angiography should then be performed and, if flow has not resumed, the catheter should be advanced into the occluded vessel and the infusion continued at the same rate for a further 2 hours. The procedure may be repeated, if necessary, up to 4 times. Once blood flow is re-established, the catheter should be partially withdrawn and infusion continued at a rate of 1000 units/minute until the remaining clot has lysed; a dose of 500 000 units given over 8 hours is usually sufficient.

For **clearing occluded intravenous catheters or cannulas**, 5000 to 25 000 units of urokinase is dissolved in the volume of sodium chloride 0.9% that will completely fill the catheter or cannula, which is then clamped off for 20 to 60 minutes; the lysate is then aspirated and the procedure repeated if necessary. Alternatively, up to 250 000 units may be infused into the device over a period of 90 to 180 minutes using a solution of 1000 to 2500 units/mL in sodium chloride 0.9%.

For doses in children, see below.

Administration in children. Urokinase may be used to clear occluded intravenous catheters and central lines in children in the same dose as for adults, see Uses and Administration, p. 1520.3.

Catheters and cannulas. For reference to the use of urokinase to maintain patency of long-term venous access devices, see under Uses for Alteplase, p. 1297.2.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Serious allergic reactions may be less likely to occur with urokinase than with streptokinase.

Hypersensitivity. Allergic reactions are considered to be less frequent with urokinase than with streptokinase. However, in a series of 6 patients who had previously been treated with streptokinase,[1] thrombolytic therapy with urokinase for recurrent myocardial infarction was associated with rigors in 4 patients, 2 of whom also developed bronchospasm. None of the patients had any history of atopy.

1. Matsis P, Mann S. Rigors and bronchospasm with urokinase after streptokinase. *Lancet* 1992; **340:** 1552.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies urokinase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Transmission of infection. Some preparations of urokinase are produced in cultures of human cells and there is a risk of transmission of infection associated with their use.

Interactions

As for Streptokinase, p. 1507.1.

Pharmacokinetics

After intravenous infusion urokinase is cleared rapidly from the circulation by the liver. A plasma half-life of up to 20 minutes has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Actosolv; ***China***: LuoXin (络欣); Sairong (赛溶); Youkai (优凯); ***Cz.***: Rheotromb†; ***Fr.***: Actosolv; Ukidan; ***Ger.***: Corase†; Rheotromb; ***Gr.***: Abbokinase; Syner-Kinase; Ukidan; Urochinasi; ***Hung.***: Rheotromb; ***India***: Dukinase; KD-Unase; Medinase; Solokinase; Uni-Kinase; ***Israel***: Abbokinase†; ***Jpn***: Uronase; ***Neth.***: Medacinase; ***Singapore***: Abbokinase; ***Spain***: Uroquidan†; ***UK***: Syner-Kinase.

Valsartan *(BAN, USAN, rINN)*

CGP-48933; Valsartaani; Valsartán; Valsartanum; Вальзартан.

N-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine; *N*-Pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-L-valine.

$C_{24}H_{29}N_5O_3$=435.5

CAS — 137862-53-4.

ATC — C09CA03.

ATC Vet — QC09CA03.

UNII — 80M03YXJ7I.

Pharmacopoeias. In *US*.

USP 36: (Valsartan). A white or almost white, hygroscopic powder. Practically insoluble in water; freely soluble in anhydrous ethanol; sparingly soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Suspension. The US licensed product information provides the following method for making 160 mL of a suspension containing valsartan 4 mg/mL:

- add 80 mL of *Ora-Plus* (*Paddock, USA*) to an amber glass bottle containing eight 80-mg tablets (*Diovan, Novartis*) and shake for at least 2 minutes
- allow to stand for at least 1 hour then shake again for at least 1 minute
- add 80 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and shake for at least 10 seconds

The suspension can be stored for 30 days at or below 30 degrees or for up to 75 days at 2 degrees to 8 degrees.

In the UK a licensed oral solution of valsartan 3 mg/mL is available.

Uses and Administration

Valsartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1), to reduce cardiovascular mortality in patients with left ventricular dysfunction after myocardial infarction (p. 1257.1), and in the management of heart failure (see under Losartan Potassium, p. 1423.2).

Valsartan is given orally. After a dose the hypotensive effect occurs within 2 hours, reaches a peak within 4 to 6 hours, and persists for over 24 hours. The maximum hypotensive effect is achieved within 2 to 4 weeks. The doses given below are for tablet and capsule formulations of valsartan; oral liquids are also available (either as a commercial preparation or an extemporaneous preparation) for use in children who have difficulty swallowing tablets (see Administration in Children, below). The bioavailabilities of solid and liquid formulations are not equivalent.

In **hypertension**, valsartan is given in an initial dose of 80 mg once daily. This may be increased, if necessary, to 160 mg once daily; the maximum dose is 320 mg once daily.

In **heart failure,** valsartan is given in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.

In patients who have had **myocardial infarction**, valsartan may be started as early as 12 hours after the infarction in clinically stable patients, in an initial dose of 20 mg twice daily; the dose may be doubled at intervals over the next few weeks up to 160 mg twice daily if tolerated.

For doses in children, see below.

Valsartan should be used with caution in patients with renal or hepatic impairment and dose reduction may be required in the latter (see below).

Reviews.

1. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54:** 299–311.
2. Ripley TL. Valsartan in chronic heart failure. *Ann Pharmacother* 2005; **39:** 460–9.
3. Mistry NB, *et al*. The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother* 2006; **7:** 575–81.
4. Bissessor N, White H. Valsartan in the treatment of heart failure or left ventricular dysfunction after myocardial infarction. *Vasc Health Risk Manag* 2007; **3:** 425–30.
5. Black HR, *et al*. Valsartan: more than a decade of experience. *Drugs* 2009; **69:** 2393–2414.

Administration in children. Valsartan may be used for hypertension in children aged 6 years and older.

UK licensed product information for tablet formulations includes an initial oral dose of 40 mg once daily for children weighing less than 35 kg, which may be increased to a maximum of 80 mg once daily if necessary. For children weighing 35 kg and over, the suggested initial dose is 80 mg once daily; recommended maximum doses for those weighing 35 to 80 kg are 160 mg once daily, while those weighing 80 kg and over may be given 320 mg once daily. An oral liquid formulation is also available; because of its higher bioavailability this formulation should be started at half the equivalent tablet dose in valsartan-naive patients. If switching from tablets to the oral solution is necessary then the dose should be halved; if switching from the solution to tablets the same dose should be used initially. The dose should be titrated further according to patient response.

US licensed product information for valsartan tablets recommends an initial dose of 1.3 mg/kg once daily (up to a maximum of 40 mg). The dose should be adjusted according to response, but doses above 2.7 mg/kg daily have not been studied. An extemporaneous suspension formulation may be used (see Suspension, above) in children who have difficulty swallowing tablets but exposure to valsartan may be higher with the suspension than with tablets.

There is no experience with valsartan in children with renal impairment (creatinine clearance below 30 mL/minute per 1.73 m^2) and it should therefore not be used in such children.

Administration in hepatic impairment. The elimination of valsartan may be reduced in patients with hepatic impairment or biliary obstruction and it should be used with caution, if at all, in such patients. In the UK, valsartan is contra-indicated in patients with severe hepatic impairment, cirrhosis, or biliary obstruction. In mild to moderate hepatic impairment, the total daily dose should not exceed 80 mg.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1. Valsartan should not be used in those with severe hepatic impairment or when creatinine clearance is less than 10 mL/min, and should be used with caution in patients with mild or moderate renal or hepatic impairment, in cirrhosis, and in biliary obstruction.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valsartan as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23% when given as a tablet and about 39% when given as an oral solution. Peak plasma concentrations of valsartan occur 2 to 4 hours after tablets and 1 to 2 hours after oral solution. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolised and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 6 hours. Following an oral dose about 83% is excreted in the faeces and 13% in urine.

References.

1. Brookman LJ, *et al*. Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997; **62:** 272–8.
2. Prasad PP, *et al*. Pharmacokinetics of multiple doses of valsartan in patients with heart failure. *J Cardiovasc Pharmacol* 2002; **40:** 801–7.
3. Blumer J, *et al*. Pharmacokinetics of valsartan in pediatric and adolescent subjects with hypertension. *J Clin Pharmacol* 2009; **49:** 235–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alpertan; Corosan; Diovan; Medicoran; Racorval; Sarval; Simultan; ***Austral.***: Diovan; ***Austria***: Diovan; ***Belg.***: Diovane; ***Braz.***: Angio II; Brasart; Diovan; Valsacor; ***Canad.***: Diovan; ***Chile***: Banyass; Dosara; Tareg; Valacor; Valaplex; Valax; Vartalan; Veralpres; ***China***: Da Le (达乐); Diovan (代文); Jia Fei (佳菲); Lizhu Weike (丽珠维可); Ping Xin (平欣); Sui Yue (缬悦); Tuo Ping (托平); Wei Er Tan (维尔坦); Xie Ke (缬克); Yi Fang (怡方); ***Cz.***: Blessin; Cezoryn; Diovan; Kylotan; Valaric; Valmed; Valsacor; Valsanorm; Valsargamma; Valzap; Vanatex; ***Denm.***: Cuenca†; Diovan; Diovane†; Salarvant; Saldanar; Tareg; ValHelen; Valsartamyl†; Valsavil; ***Fin.***: Diovan; Valsarstad; ***Fr.***: Nisis; Tareg; ***Ger.***: Cordinate; Diovan; Provas; Valsacor; ***Gr.***: Avalsan; Dalzad; Diovan; ***Hong Kong***: Diovan; ***Hung.***: Alvastran; Diovan; Nortivan; Tensart; Valsacor; Valsotens; Varexan†; Vezuran; ***India***: Diovan; Starval; ***Indon.***: Diovan; ***Irl.***: Cuenca; Diotev†; Diovan; Saldanar; Valsotens†; Valtan; Vamadrid; Vatan; ***Israel***: Diovan; Vector; ***Ital.***: Alsartan; Cortan; Rixil; Tareg; Valpression; Valsacor; ***Jpn***: Diovan; ***Malay-***

sia: Diovan; ***Mex.***: Diovan; ***Neth.***: Diovan; Lartavan; Saldanar; Simaldoz; Tifival; Vagrecor; Valcatuna; Valsabio†; Valsanorm; Valsartamib†; Valsavil†; Vamadrid; ***Norw.***: Diovan; ***Philipp.***: Diovan; ***Pol.***: Anartan; Bespres; Diovan; Nortivan; Tensart; Valsacor; Valsotens; Valtap; Valzek; Vanatex; Zelvartan; ***Port.***: Diovan; Talsare†; Tanvalir†; Tareg; Varirtan†; Vasanter†; Vatan†; ***Rus.***: Diovan (Диован); Nortivan (Нортиван); Valsacor (Вальсакор); Valsaforce (Валсафорс); Valz (Валз); ***S.Afr.***: Diovan; Migroben; Tareg; Zomevek; ***Singapore***: Diovan; ***Spain***: Aralter; Diovan; Kalpress; Miten; Vals; ***Swed.***: Diovan; ***Switz.***: Diovan; ***Thai.***: Diovan; Valatan; ***Turk.***: Cardopan; Diovan; Premium; Tamgard; ***UK***: Diovan; ***Ukr.***: Diocor Solo (Диокор Соло); Diovan (Диован); Valsacor (Вальсакор); Valzap (Валзап); Vasar (Вазар); ***USA***: Diovan; ***Venez.***: Alsart; Diovan; Vasaten.

Multi-ingredient Preparations. ***Arg.***: Alpertan D; Diovan A; Diovan D; Diovan Triple; Exforge D; Exforge; Racorval D; Sarval D; Simultan A; Simultan D; ***Austral.***: Co-Diovan; Exforge HCT; Exforge; ***Austria***: Co-Angiosan†; Co-Diovan; Exforge HCT; Exforge; ***Belg.***: Co-Diovane; Exforge HCT; Exforge; ***Braz.***: Diocomb SI; Diovan Amlo; Diovan HCT; Diovan Triplo; ***Canad.***: Diovan HCT; ***Chile***: Dosara-D; Exforge; Tareg-D; Valacor D; Valaplex-D; Valaxam; Vartalan AM; Vartalan D; Veralpres D; ***China***: Co-Diovan (复代文); Exforge (倍博特); Feng Hai Tan (丰海坦); FuTan (福坦); FuXin (复欣); Jia Ze (佳择); Jinxieke (金缬克); Lan Pu (兰普); ***Cz.***: Blessin Plus H; Co-Diovan†; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT; Imprida; Janartan; Kylotan Plus H; Teval Plus H†; Valsacombi; Valsaratio Plus H; Valzap Combi; Vanatex HCT; Zelvartancombo; ***Denm.***: Co-Diovan; Corixil; Cotareg; Diovan Comp; Exforge HCT; Exforge; Tevavaltan comp; Valsavil HCT; Valtension comp; ***Fin.***: Diovan Comp; Valsarstad Comp; ***Fr.***: Cotareg; Exforge HCT; Exforge; Nisisco; ***Ger.***: Co-Diovan; Cordinate plus; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Provas comp; Valsacor comp; Valsartan comp; Valsartan plus HCT; Valsartan/HCT; ***Gr.***: Co-Dalzad; Co-Diovan; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; ***Hong Kong***: Co-Diovan; Exforge; ***Hung.***: Alvastran HCT; Co-Valsacor; Diovan HCT; Exforge; Nortivan HCT; Tensart HCT; Valsartan HCT; Valsotens HCT; Varexan HCT†; ***India***: Nebicard-V; ***Indon.***: Co-Diovan; Exforge; ***Irl.***: Co-Diovan; Co-Vatan; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT; Imprida; Valsol Plus; Valtan comp; ***Israel***: Co-Diovan; Exforge; Vector Plus; ***Ital.***: Combisartan; Corixil; Cotareg; Valbacomp; Validroc; ***Malaysia***: Co-Diovan; Exforge; ***Mex.***: Co-Diovan; ***Neth.***: Co-Diovan; Copalia HCT; Copalia; Cotareg; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT†; Imprida; Valsacell HCT; ***Norw.***: Diovan Comp; Exforge HCT; Exforge; ***Philipp.***: Co-Diovan; Exforge; ***Pol.***: Anartan HCT; Co-Bespres; Co-Diovan; Co-Nortivan; Co-Valsacor; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT; Imprida; Tensart HCT; Valtap HCT; ***Port.***: Co-Angiosan; Co-Diovan; Co-Novasan; Co-Tareg; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Higo†; Imprida HCT; Imprida; ***Rus.***: Co-Diovan (Ко-Диован); Exforge (Эксфорж); Valsacor H (Вальсакор Н); Valsacor HD (Вальсакор НД); Valz H (Валз Н); ***S.Afr.***: Co-Diovan; Co-Migroben; Co-Tareg; Co-Zomevek; Exforge; ***Singapore***: Co-Diovan; Exforge HCT; Exforge; ***Spain***: Aralter Plus; Co-Diovan; Co-Vals; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida; Kalpress Plus; Lefluartil; Miten Plus; ***Swed.***: Diovan Comp; Exforge; ***Switz.***: Co-Diovan; Exforge HCT; Exforge; ***Thai.***: Co-Diovan; Exforge HCT; Exforge; ***Turk.***: Cardolex; Cardopan Plus; Co-Diovan; Co-Tamgard; Exforge HCT; Exforge; Premium Plus; ***UK***: Co-Diovan; Exforge; ***Ukr.***: Co-Diovan (Ко-Диован); Diocor (Диокор); Exforge (Эксфорж); Valsacor H (Вальсакор Н); Valsacor HD (Вальсакор НД); Valzap Plus (Валзап Плюс); Vasar H (Вазар Н); ***USA***: Diovan HCT; Exforge HCT; Exforge; ***Venez.***: Diovan HCT; Diovan/Amlibon; Vasaten HCT.

Pharmacopoeial Preparations

USP 36: Valsartan and Hydrochlorothiazide Tablets; Valsartan Tablets.

Verapamil Hydrochloride

(BANM, USAN, rINNM)

CP-16533-1 (verapamil); D-365 (verapamil); Hidrocloruro de verapamilo; Iproveratril Hydrochloride; Verapamiilihydrokloridi; Vérapamil, Chlorhydrate de; Verapamil Hidroklorür; Verapamil-hidroklorid; Verapamilhydrochlorid; Verapamil-hydrochlorid; Verapamilhydroklorid; Verapamili hydrochloridum; Verapamilio hidrochloridas; Verapamilo, hidrocloruro de; Верапамила Гидрохлорид.

S-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

$C_{27}H_{38}N_2O_4$,HCl=491.1

CAS — 52-53-9 (verapamil); 152-11-4 (verapamil hydrochloride).

ATC — C08DA01.

ATC Vet — QC08DA01.

UNII — V3888OEY5R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. & (Verapamil Hydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Verapamil Hydrochloride). A white or practically white, practically odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Verapamil hydrochloride will precipitate in alkaline solutions. There have been reports of incompatibility with solutions of aminophylline,[1] nafcillin sodium,[2] and sodium bicarbonate.[3]

1. Johnson CE, *et al.* Compatibility of aminophylline and verapamil in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 97–100.
2. Tucker R, Gentile JF. Precipitation of verapamil in an intravenous line. *Ann Intern Med* 1984; **101:** 880.
3. Cutie MR. Verapamil precipitation. *Ann Intern Med* 1983; **98:** 672.

Uses and Administration

Verapamil is a phenylalkylamine calcium-channel blocker (p. 1244.2) and a class IV antiarrhythmic (p. 1243.1). It slows conduction through the AV node, and thus slows the increased ventricular response rate that occurs in atrial fibrillation and flutter. Its anti-anginal effect is mainly due to coronary and peripheral vasodilatation, although it also inhibits coronary artery spasm; the decrease in peripheral vascular resistance reduces the work of the heart, which has a sparing effect on myocardial intracellular oxygen consumption. The decrease in peripheral vascular resistance may also explain its antihypertensive effect. Verapamil is used in the control of supraventricular arrhythmias and in the management of angina pectoris and hypertension. It may also be used in the management of myocardial infarction.

Verapamil may be given intravenously or orally, as the hydrochloride; doses are expressed in terms of verapamil hydrochloride.

In the acute management of supraventricular **arrhythmias** it is given intravenously, preferably under continuous ECG and blood pressure monitoring. The initial dose is 5 to 10 mg by slow intravenous injection over 2 to 3 minutes. If necessary, licensed product information in the UK allows a second dose of 5 mg to be given 5 to 10 minutes after the first; in the USA, a second dose of 10 mg may be given after 30 minutes.

Oral doses for the treatment of supraventricular arrhythmias are 120 to 480 mg daily in 3 or 4 divided doses, according to the severity of the condition and the patient's response.

In the management of **angina pectoris,** the usual oral dose is 120 mg three times daily; some patients with angina of effort may respond to 80 mg three times daily, but this lower dose is not likely to be effective in angina at rest or Prinzmetal's variant angina. Modified-release preparations may be given in doses of up to 480 mg daily.

In **hypertension** the usual initial oral dose is 240 mg daily, in 2 or 3 divided doses, adjusted according to response; doses of up to 480 mg daily have been used. Modified-release preparations may be given in similar daily doses.

In the secondary prevention of **myocardial infarction**, verapamil hydrochloride is given as a modified-release oral preparation, started at least 1 week after acute infarction (in patients without heart failure), in a dose of 360 mg daily in divided doses.

Doses of verapamil should be reduced in patients with hepatic impairment (see below).

For doses of verapamil in children with supraventricular arrhythmias or hypertension, see below.

The *R*-enantiomer of verapamil, arverapamil, is under investigation for the treatment of diarrhoea.

General reviews.

1. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. *Drugs* 1996; **51:** 792–819.
2. Prisant LM. Verapamil revisited: a transition in novel drug delivery systems and outcomes. *Heart Dis* 2001; **3:** 55–62.

Administration in children. Verapamil may be used for the treatment of supraventricular arrhythmias and hypertension in children, although great care is needed, especially in infants (see Precautions, p. 1524.3).

Intravenous doses of verapamil hydrochloride for supraventricular arrhythmias are as follows:

- children up to 1 year of age, 100 to 200 micrograms/kg
- 1 to 15 years, 100 to 300 micrograms/kg (to a maximum dose of 5 mg)

The dose should be given over at least 2 minutes and may be repeated after 30 minutes if necessary; doses at the lower end of the range may be adequate and the injection should be stopped when a response has been obtained.

Oral doses for supraventricular arrhythmias or for hypertension are:

- children up to 2 years of age, 20 mg two or three times daily
- 2 years and over, 40 to 120 mg two or three times daily according to age and response

Administration in the elderly. For a discussion of the effects of increasing age on verapamil, see under Pharmacokinetics, p. 1526.1.

Administration in hepatic impairment. Verapamil is extensively metabolised in the liver and should be used with caution in hepatic impairment; US licensed product information recommends that oral doses for patients with severe hepatic impairment should be reduced to about one-third of the usual dose (see Uses and Administration, above).

In a study[1] of patients with liver cirrhosis steady-state plasma concentrations of verapamil were double those seen in patients with normal liver function after intravenous doses and 5 times the normal concentration when given orally. The elimination half-life was prolonged about fourfold after oral or intravenous doses, suggesting that steady-state plasma concentration will not be reached in patients with liver cirrhosis until about 56 hours after therapy has started.

1. Somogyi A, *et al.* Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br J Clin Pharmacol* 1981; **12:** 51–60.

Administration in renal impairment. The pharmacokinetics and pharmacodynamic effects of verapamil are not significantly altered by renal impairment[1] and dosage adjustment is not considered to be necessary. The elimination of verapamil is not altered by haemodialysis,[1,2] haemofiltration,[2] or peritoneal dialysis[2] and no dosage supplement is required in patients undergoing these procedures.

1. Mooy J, *et al.* Pharmacokinetics of verapamil in patients with renal failure. *Eur J Clin Pharmacol* 1985; **28:** 405–10.
2. Beyerlein C, *et al.* Verapamil in antihypertensive treatment of patients on renal replacement therapy—clinical implications and pharmacokinetics. *Eur J Clin Pharmacol* 1990; **39** (suppl 1): S35–S37.

Amaurosis fugax. For a report of the use of verapamil in patients with amaurosis fugax, see under Uses and Administration of Nifedipine, p. 1448.1.

Bipolar disorder. Although lithium and valproate are the mainstays of therapy in bipolar disorder (p. 397.2) many other drugs have been tried, including verapamil.[1] Beneficial responses to verapamil at doses up to 480 mg daily have been reported,[2-4] although a review[5] concluded that there is limited support for its use. Verapamil has also been used with lithium, but there may be an increased risk of neurotoxicity (see under Interactions, p. 1525.3).

1. Höschl C. Do calcium antagonists have a place in the treatment of mood disorders? *Drugs* 1991; **42:** 721–29.
2. Dubovsky SL, *et al.* Calcium antagonists in mania: a double-blind study of verapamil. *Psychiatry Res* 1986; **18:** 309–20.
3. Giannini AJ, *et al.* Verapamil and lithium in maintenance therapy of manic patients. *J Clin Pharmacol* 1987; **27:** 980–2.
4. Wisner KL, *et al.* Verapamil treatment for women with bipolar disorder. *Biol Psychiatry* 2002; **51:** 745–52.
5. Levy NA, Janicak PG. Calcium channel antagonists for the treatment of bipolar disorder. *Bipolar Disord* 2000; **2:** 108–19.

Box jellyfish sting. Stings by the box jellyfish (*Chironex fleckeri*) (p. 2397.1) can be fatal because of the effects of the venom on the cardiovascular and respiratory systems and on the kidneys. Studies in *rodents* have reported a beneficial effect of intravenous verapamil in the treatment of box jellyfish envenomation, and use in patients with serious box-jellyfish stings has been recommended.[1] However, it has also been suggested[2] that the lack of evidence for benefit and the potential for adverse effects means that use of verapamil should be limited to extreme cases only.

1. Burnett JW. The use of verapamil to treat box-jellyfish stings. *Med J Aust* 1990; **153:** 363.
2. Bailey PM, *et al.* Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. *Med J Aust* 2003; **178:** 34–7.

Cardiac arrhythmias. Verapamil has an established role in the management of supraventricular cardiac arrhythmias (p. 1266.1). It is used for rate control in atrial fibrillation and flutter, and may also be used in paroxysmal supraventricular tachycardia. It has been successfully used with digoxin for transplacental therapy in fetal atrial flutter or supraventricular tachycardia,[1,2] although caution is necessary if it is used in infants since they may be particularly susceptible to its adverse effects (see Precautions, p. 1524.3).

1. Maxwell DJ, *et al.* Obstetric importance, diagnosis, and management of fetal tachycardias. *BMJ* 1988; **297:** 107–10.
2. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.

Cardiomyopathies. Verapamil has an established role as a negative inotrope in the management of patients with *hypertrophic cardiomyopathy*,[1,2] although it is usually reserved for patients in whom beta blockers either fail to control symptoms or are not tolerated. It may improve symptoms and exercise tolerance; although a crossover study[3] failed to show an improvement in exercise capacity

with verapamil or the beta blocker nadolol, most patients preferred drug treatment to placebo and there was an apparent improvement in quality of life with verapamil. Verapamil may also be useful for rate control in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. However, there is no evidence that it reduces the incidence of sudden cardiac death, and serious adverse effects have been reported,[4] especially in patients with severe outflow obstruction. Patients with hypertrophic cardiomyopathy appear to be particularly susceptible to conduction disturbances associated with verapamil, and this may worsen hypotension and outflow obstruction.

Dilated cardiomyopathy is treated similarly to heart failure and calcium-channel blockers are not usually used, although some benefit has been reported with diltiazem (see p. 1359.3).

For a discussion of the management of cardiomyopathies in general, see p. 1261.3.

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002; **287:** 1308–20.
2. Maron BJ, *et al*. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; **42:** 1687–713. Also published in *Eur Heart J* 2003; **24:** 1965–91. Also available at: http://eurheartj.oxfordjournals.org/content/24/21/1965.full.pdf+html (accessed 28/07/10) and at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HCM-FT.pdf (accessed 14/08/08)
3. Gilligan DM, *et al*. A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993; **21:** 1672–9.
4. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circulation* 1981; **64:** 437–41.

Epilepsy. There are reports[1-3] of the successful use of verapamil in drug-resistant epilepsy (p. 506.1). The mechanism is unknown: modulation of calcium may play a role, although evidence for other calcium-channel blockers as adjuncts in epilepsy has been unconvincing (see under Flunarizine, p. 630.1). An alternative suggestion, that inhibition of P-glycoprotein by verapamil boosts the effect of antiepileptics, remains to be confirmed.

1. Summers MA, *et al*. Use of verapamil as a potential P-glycoprotein inhibitor in a patient with refractory epilepsy. *Ann Pharmacother* 2004; **38:** 1631–4.
2. Iannetti P, *et al*. Calcium-channel blocker verapamil administration in prolonged and refractory status epilepticus. *Epilepsia* 2005; **46:** 967–9.
3. Iannetti P, *et al*. Addition of verapamil in the treatment of severe myoclonic epilepsy in infancy. *Epilepsy Res* 2009; **85:** 89–95.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p. 1449.1), although studies with verapamil have suggested that it is less effective than the ACE inhibitor trandolapril in patients with non-diabetic renal disease,[1] and that it does not prevent the development of renal disease in type 2 diabetics.[2] There is some evidence that verapamil may reduce the nephrotoxicity associated with certain drugs, including ciclosporin (see Transplantation, below), and the aminoglycoside gentamicin.[3]

1. Hemmelder MH, *et al*. Antiproteinuric efficacy of verapamil in comparison to trandolapril in non-diabetic renal disease. *Nephrol Dial Transplant* 1999; **14:** 98–104.
2. Ruggenenti P, *et al*. for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; **351:** 1941–51.
3. Kazierad DJ, *et al*. The effect of verapamil on the nephrotoxic potential of gentamicin as measured by urinary enzyme excretion in healthy volunteers. *J Clin Pharmacol* 1995; **35:** 196–201.

Malignant neoplasms. Verapamil has been shown to reverse multidrug resistance to antineoplastics in cultured cells and in *animal* studies,[1] but studies in which verapamil was added to therapy for small cell lung cancer[2] or multiple myeloma[3] failed to show any benefit. See p. 734.2 for a discussion of resistance to antineoplastics.

1. Ford JM, Hait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 1990; **42:** 155–99.
2. Milroy R, *et al*. A randomised clinical study of verapamil in addition to combination chemotherapy in small cell lung cancer. *Br J Cancer* 1993; **68:** 813–18.
3. Dalton WS, *et al*. A phase III randomized study of oral verapamil as a chemosensitizer to reverse drug resistance in patients with refractory myeloma: a Southwest Oncology Group Study. *Cancer* 1995; **75:** 815–20.

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including verapamil, in the management of migraine and cluster headache, see under Nifedipine, p. 1449.1.

Movement disorders. Verapamil has been associated with the development of various movement disorders (see Extrapyramidal Disorders under Adverse Effects of Nifedipine, p. 1452.2) but there have also been case reports[1,2] of its successful use in refractory movement disorders, including severe tardive dyskinesia. However, a systematic review[3] concluded that evidence for the use of verapamil or other calcium-channel blockers in tardive dyskinesia is limited and they are not generally recommended.

The usual management of tardive dyskinesia is discussed under the Adverse Effects of Chlorpromazine, p. 1049.3.

1. Abad V, Ovsiew F. Treatment of persistent myoclonic tardive dystonia with verapamil. *Br J Psychiatry* 1993; **162:** 554–6.
2. Ovsiew F, *et al*. Verapamil for severe hyperkinetic movement disorders. *Mov Disord* 1998; **13:** 341–4.
3. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/03/07).

Myocardial infarction. Calcium-channel blockers are not routinely used in either the acute or long-term treatment of myocardial infarction (p. 1257.1), although some benefit has been reported with non-dihydropyridines. Diltiazem, started within 24 to 72 hours of the onset of infarction and continued for up to 14 days, has been reported to protect against re-infarction and refractory angina in patients recovering from acute non-Q-wave infarction.[1] A pilot study[2] of intravenous diltiazem as an adjunct to thrombolysis in acute myocardial infarction also suggested a reduction in recurrent ischaemia; diltiazem was given intravenously for 48 hours, beginning at the same time as the thrombolytic, then continued orally for 4 weeks. However, a study[3] with verapamil, started on admission to hospital, found no effect on mortality at 6 months, and there was a suggestion that very early use (within 6 hours of symptom onset) was detrimental. A later study[4] reported that early use of verapamil in patients receiving thrombolysis improved outcome at 90 days. Benefit has also been shown[5] with use of intracoronary verapamil to terminate post-reperfusion arrhythmias. For use of verapamil in patients receiving percutaneous coronary intervention see Reperfusion and Revascularisation Procedures, below.

Although they are not standard therapy, diltiazem and verapamil may be used for long-term management in selected patients without heart failure. In a study by the Multicenter Diltiazem Postinfarction Trial (MDPIT) research group,[6] diltiazem (target dose 240 mg daily) reduced 1-year mortality and re-infarction rates in patients without left ventricular dysfunction, but increased such adverse events in those with left ventricular dysfunction. Re-analysis of the study provided further evidence that diltiazem should be avoided in postinfarction patients with left ventricular dysfunction.[7] Another study[8] in patients with acute myocardial infarction treated with thrombolysis found no reduction in mortality with diltiazem started 36 to 96 hours after infarction and continued for up to 6 months, although the incidence of non-fatal cardiac events was reduced. Patients with heart failure were excluded from the study. In the DAVIT II study[9] late intervention with verapamil (started in the second week after admission) reduced overall mortality, cardiac events, and re-infarction although another study[10] found only a benefit in re-infarction rate and not in overall mortality.

1. Gibson RS, *et al*. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986; **315:** 423–9.
2. Théroux P, *et al*. Intravenous diltiazem in acute myocardial infarction: diltiazem as adjunctive therapy to activase (DATA) trial. *J Am Coll Cardiol* 1998; **32:** 620–8.
3. The Danish Study Group on Verapamil in Myocardial Infarction. The Danish studies on verapamil in acute myocardial infarction. *Br J Clin Pharmacol* 1986; **21:** 197S–204S.
4. Marangelli V, *et al*. Early administration of verapamil after thrombolysis in acute anterior myocardial infarction: effect on left ventricular remodeling and clinical outcome. *Ital Heart J* 2000; **1:** 336–43.
5. Kato M, *et al*. Intracoronary verapamil rapidly terminates reperfusion tachyarrhythmias in acute myocardial infarction. *Chest* 2004; **126:** 702–8.
6. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319:** 385–92.
7. Goldstein RE, *et al*. Diltiazem increases late-onset congestive heart failure in post-infarction patients with early reduction in ejection fraction. *Circulation* 1991; **83:** 52–60.
8. Boden WE, *et al*. Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. *Lancet* 2000; **355:** 1751–6.
9. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II–DAVIT II). *Am J Cardiol* 1990; **66:** 779–85.
10. Rengo F, *et al*. A controlled trial of verapamil in patients after acute myocardial infarction: results of the calcium antagonist reinfarction Italian study (CRIS). *Am J Cardiol* 1996; **77:** 365–9.

Peyronie's disease. Verapamil has been used by intraplaque injection for the treatment of Peyronie's disease.[1,2] Pain, curvature, and erectile dysfunction were all improved. A systematic review[2] of 19 studies involving plaque injection therapy for Peyronie's disease, of which 4 used verapamil, noted that although the results of these suggested that injection was safe and effective in mild to moderate Peyronie's disease, the quality of studies was generally poor and its efficacy needed to be verified. Verapamil has also been given by iontophoresis, but again benefits remain unclear. A study[3] comparing verapamil and dexamethasone with lidocaine reported considerable improvement in plaque volume, penile curvature, and pain in the group given verapamil and dexamethasone, while patients given lidocaine had a transient improvement in pain but no change in plaque volume or curvature. However, a study[4] comparing verapamil with sodium chloride as placebo reported some improvement with both treatments, with no difference between the groups.

1. Levine LA, *et al*. Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol (Baltimore)* 2002; **168:** 621–5.
2. Russell S, *et al*. Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. *Eur Urol* 2007; **51:** 640–7.
3. Di Stasi SM, *et al*. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol (Baltimore)* 2004; **171:** 1605–8.
4. Greenfield JM, *et al*. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol (Baltimore)* 2007; **177:** 972–5.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention is widely used in the management of patients with acute myocardial infarction and angina pectoris, and adjunctive drug treatment has an important role in reducing complications and improving outcome (see p. 1259.2). Intracoronary verapamil may be used to treat vasospasm[1] and has also been used to treat[2,3] and prevent[4,5] the 'no-reflow' phenomenon. However, transient heart block occurred in some patients given verapamil prophylactically,[5] and this may limit its use.

There is also some evidence that verapamil may reduce the incidence of restenosis after coronary[6] or peripheral[7] percutaneous interventions.

1. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005; **26:** 804–47. Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf (accessed 14/08/08)
2. Piana RN, *et al*. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; **89:** 2514–18.
3. Demir I, *et al*. Treatment of no-reflowphenomenon with verapamil after primary stent deployment during myocardial infarction. *Jpn Heart J* 2002; **43:** 573–80.
4. Hang C-L, *et al*. Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. *Chest* 2005; **128:** 2593–8.
5. Vijayalakshmi K, *et al*. Prospective, randomised, controlledtrial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; **92:** 1278–84.
6. Bestehorn H-P, *et al*. Evaluation of the effect of oral verapamil on clinical outcome and angiographic restenosis after percutaneous coronary intervention: the randomized, double-blind, placebo-controlled, multicenter Verapamil Slow-Release for Prevention of Cardiovascular Events After Angioplasty (VESPA) Trial. *J Am Coll Cardiol* 2004; **43:** 2160–5.
7. Schweizer J, *et al*. Effect of high dose verapamil on restenosis after peripheral angioplasty. *J Am Coll Cardiol* 1998; **31:** 1299–1305.

Transplantation. Ciclosporin is widely used in transplantation to prevent rejection but its use is limited by its nephrotoxicity. Dihydropyridine calcium-channel blockers (see under Uses of Nifedipine, p. 1450.2) and diltiazem (p. 1360.1) have been reported to reduce ciclosporin-associated nephrotoxicity, and there is some evidence that verapamil may have a similar effect. Studies in renal[1,2] and heart or lung[3] transplant recipients suggested that verapamil can improve outcomes in patients receiving ciclosporin. Most studies have found that verapamil prevents ciclosporin-induced deterioration in renal function, despite increasing plasma-ciclosporin concentrations,[1,2] and there is also evidence[2] that graft survival may be improved. The beneficial effect of verapamil may be related to its ability to protect cells from ischaemia, selective vasodilatation of the afferent renal arterioles, or inherent immunosuppressive properties; its effect on plasma-ciclosporin concentrations may also be involved, either directly[1,2] or by allowing reduction of the ciclosporin dose.[3] However, one study[4] found that use of verapamil with ciclosporin resulted in higher serum-creatinine concentrations in patients given verapamil, with no reduction in the incidence of rejection, and careful monitoring is necessary if the drugs are used together. A higher incidence of severe infections has also been reported[5] in renal transplant patients given verapamil and ciclosporin; the authors suggested that if a rapid increase in plasma-ciclosporin concentrations was required, improved formulations of ciclosporin should be used rather than verapamil.

1. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: a review. *Am J Med* 1991; **90** (suppl 5A): 37S–41S.
2. Dawidson I, *et al*. Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; **2:** 983–90.
3. Chan C, *et al*. A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. *Transplantation* 1997; **63:** 1435–40.
4. Pirsch JD, *et al*. A controlled, double-blind, randomized trial of verapamil and cyclosporine in cadaver renal transplant patients. *Am J Kidney Dis* 1993; **21:** 189–95.
5. Nanni G, *et al*. Increased incidence of infection in verapamil-treated kidney transplant recipients. *Transplant Proc* 2000; **32:** 551–3.

Adverse Effects

Treatment with verapamil is generally well tolerated, but adverse effects connected with its pharmacological effects on cardiac conduction can arise and may be particularly severe in patients with previous myocardial damage or hypertrophic cardiomyopathies. Adverse effects on the heart include bradycardia, AV block, worsening heart

failure, and transient asystole. These effects are more common with parenteral than with oral therapy.

The most troublesome non-cardiac adverse effect is constipation. Nausea may occur but is less frequently reported. Other adverse effects include hypotension, dizziness, flushing, headaches, fatigue, dyspnoea, and peripheral oedema. There have been reports of skin reactions and some cases of abnormal liver function and hepatotoxicity. Gingival hyperplasia has occurred. Gynaecomastia has been reported rarely.

In overdosage there may be severe cardiotoxicity and profound hypotension.

Carcinogenicity. See under Adverse Effects of Nifedipine, p. 1450.3.

Effects on the cardiovascular system. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see Effects on Mortality, under Adverse Effects of Nifedipine, p. 1450.2.

Verapamil has vasodilating properties and negative inotropic activity and may cause adverse cardiovascular effects with worsening of arrhythmias. As discussed under Precautions (below) certain cardiac disorders put the patient at risk of severe toxicity.

Some references.

1. Radford D. Side effects of verapamil in infants. *Arch Dis Child* 1983; **58:** 465–6.
2. Perrot B, *et al.* Verapamil: a cause of sudden death in a patient with hypertrophic cardiomyopathy. *Br Heart J* 1984; **51:** 352–4.
3. Kirk CR, *et al.* Cardiovascular collapse after verapamil in supraventricular tachycardia. *Arch Dis Child* 1987; **62:** 1265–6.
4. Mohindra SK, Udeani GO. Long-acting verapamil and heart failure. *JAMA* 1989; **261:** 994.
5. Garratt C, *et al.* Degeneration of junctional tachycardia to pre-excited atrial fibrillation after intravenous verapamil. *Lancet* 1989; **ii:** 219.
6. Stajer D, *et al.* Cardiogenic shock following a single therapeutic oral dose of verapamil. *Int J Clin Pract* 2001; **55:** 69–70.
7. Shiraishi H, *et al.* Two cases of polymorphic ventricular tachycardia induced by the administration of verapamil against paroxysmal supraventricular tachycardia. *Intern Med* 2002; **41:** 445–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the endocrine system. Hyperprolactinaemia has been reported[1-4] in patients receiving verapamil, and in a few cases[2,3] patients have also had galactorrhoea.

Hyperglycaemia, metabolic acidosis, hyperkalaemia, and bradycardia have occurred[5] after a single dose of modified-release verapamil in a non-diabetic patient who had previously tolerated regular verapamil.

Verapamil has been reported not to affect the release of calcitonin,[6] thyroxine, tri-iodothyronine, thyrotrophin (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), or testosterone when given orally;[1] however, intravenous use has been reported to have an inhibitory effect on the release of FSH, LH, and TSH.[7]

1. Semple CG, *et al.* Calcium antagonists and endocrine status: lack of effect of oral verapamil on pituitary-testicular and pituitary-thyroid function. *Br J Clin Pharmacol* 1984; **17:** 179–82.
2. Gluskin LE, *et al.* Verapamil-induced hyperprolactinemia and galactorrhea. *Ann Intern Med* 1981; **95:** 66–7.
3. Fearrington EL, *et al.* Hyperprolactinemia-galactorrhea induced by verapamil. *Am J Cardiol* 1983; **51:** 1466–7.
4. Romeo JH, *et al.* Hyperprolactinaemia and verapamil: prevalence and potential association with hypogonadism in men. *Clin Endocrinol (Oxf)* 1996; **45:** 571–5.
5. Roth A, *et al.* Slow-release verapamil and hyperglycemic metabolic acidosis. *Ann Intern Med* 1989; **110:** 171–2.
6. Amado JA, *et al.* No effect of verapamil on calcium stimulated calcitonin release. *Postgrad Med J* 1987; **63:** 23–4.
7. Barbarino A, De Marinis L. Calcium antagonists and hormone release II: effects of verapamil on basal, gonadotrophin-releasing hormone- and thyrotrophin-releasing hormone-induced pituitary hormone release in normal subjects. *J Clin Endocrinol Metab* 1980; **51:** 749–53.

Effects on the gastrointestinal tract. For a report of intestinal pseudo-obstruction related to verapamil use, see under Adverse Effects of Diltiazem, p. 1360.2.

Effects on the liver. Elevated serum concentrations of liver enzymes and bilirubin have been reported during verapamil therapy.[1-5] Clinical symptoms of hepatotoxicity such as abdominal pain, fever, darkened urine, and malaise have also occurred.[2-5] These reactions might have been due to a hypersensitivity reaction and were reversible on stopping verapamil.

1. Brodsky SJ, *et al.* Hepatotoxicity due to treatment with verapamil. *Ann Intern Med* 1981; **94:** 490–1.
2. Stern EH, *et al.* Possible hepatitis from verapamil. *N Engl J Med* 1982; **306:** 612–13.
3. Nash DT, Feer TD. Hepatic injury possibly induced by verapamil. *JAMA* 1983; **249:** 395–6.
4. Guarascio P, *et al.* Liver damage from verapamil. *BMJ* 1984; **288:** 362–3.
5. Kumar KL, Colley CA. Verapamil-induced hepatotoxicity. *West J Med* 1994; **160:** 485–6.

Effects on the mouth. Gingival hyperplasia[1] and oral mucosal injury[2] have been associated with verapamil therapy. A study involving 115 patients who had received nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers in general.[3]

1. Pernu HE, *et al.* Verapamil-induced gingival overgrowth: a clinical, histologic, and biochemic approach. *J Oral Pathol Med* 1989; **18:** 422–5.
2. Guttenberg SA. Chemical injury of the oral mucosa from verapamil. *N Engl J Med* 1990; **323:** 615.
3. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.

Effects on the nervous system. There has been a report[1] of 3 patients who complained of unusual perceptual symptoms, described as painful coldness and numbness or bursting feelings, especially in the legs, while taking oral verapamil.

1. Kumana CR, Mahon WA. Bizarre perceptual disorder of extremities in patients taking verapamil. *Lancet* 1981; **i:** 1324–5.

Effects on the peripheral circulation. Secondary erythermalgia, a vasospastic arterial disorder that may be caused by vasoactive drugs, has been reported[1,2] in patients taking verapamil. Symptoms included burning pain, swelling, and erythema of the hands[2] and feet,[1,2] and resolved when verapamil was stopped. Similar reactions have been reported with nifedipine and other calcium-channel blockers (see p. 1452.1).

1. Drenth JPH, *et al.* Verapamil-induced secondary erythermalgia. *Br J Dermatol* 1992; **127:** 292–4.
2. Hart JJ. Painful, swollen, and erythematous hands and feet. *Arthritis Rheum* 1996; **39:** 1761–2.

Effects on the respiratory tract. A patient with a history of bronchial asthma developed symptoms of acute asthma after use of a modified-release verapamil preparation;[1] it was possible that excipients, notably alginate, may have been responsible for the reaction.

1. Ben-Noun L. Acute asthma associated with sustained-release verapamil. *Ann Pharmacother* 1997; **31:** 593–5.

Effects on sexual function. In a group of 14 men taking verapamil, 3 reported impotence;[1] in 1 patient normal sexual function returned when verapamil was stopped, but impotence recurred on rechallenge.

1. King BD, *et al.* Impotence during therapy with verapamil. *Arch Intern Med* 1983; **143:** 1248–9.

Effects on the skin and hair. The commonest skin reactions to verapamil have been rash, pruritus, alopecia, and urticaria;[1] there have been a few reports of erythema multiforme, the Stevens-Johnson syndrome, and exfoliative dermatitis.[1] Hypertrichosis, over many parts of the body, has been reported in a male patient within about 1 month of starting verapamil therapy.[2] In a female patient who had been prematurely grey for about 40 years use of verapamil caused portions of the hair to regrow in its original natural black colour.[3]

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
2. Sever PS. Hypertrichosis and verapamil. *Lancet* 1991; **338:** 1215–16.
3. Read GM. Verapamil and hair colour change. *Lancet* 1991; **338:** 1520.

Extrapyramidal disorders. Extrapyramidal disorders have been reported with calcium-channel blockers, particularly verapamil (see Nifedipine, p. 1452.2); however, see also p. 1523.1 for reports of the successful use of verapamil in refractory movement disorders.

Haemorrhage. See Effects on the Blood under Adverse Effects of Nifedipine, p. 1450.3.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p. 1452.3, but see also below.

Verapamil is not removed by dialysis.

Overdosage. The consequences and treatment of overdosage with verapamil are similar to those with other calcium-channel blockers (see Treatment of Adverse Effects under Nifedipine, p. 1452.3), although death and life-threatening complications may be more common with non-dihydropyridines such as verapamil; several fatalities have occurred.[1]

Individual reports of overdosage with verapamil have included:

- A patient[2] who took 3.2 g of verapamil developed bradycardia and hypotension, which responded to intravenous calcium gluconate injection. A continuous infusion of calcium gluconate was given for 12 hours to maintain sinus rhythm. The blood-verapamil concentration measured 5 hours after ingestion was 4 micrograms/mL.
- A patient[3] presented with loss of consciousness, severe hypotension, and bradycardia up to 18 hours after taking at least 1.2 g of verapamil. Treatment with glucagon, prenalterol, and atropine was unsuccessful, and there was a minimal response to intravenous calcium gluconate. Dobutamine and isoprenaline were given to maintain the blood pressure and mechanical ventilation was required for 24 hours, during which time metabolic acidosis and hyperglycaemia developed. The patient survived with cerebral anoxic damage.
- A patient[4] who had taken an unknown amount of verapamil developed cyanosis, undetectable blood pressure, and complete heart block. There was some response to sympathomimetics and calcium gluconate, although pacing was necessary to reverse the bradycardia. However, hypotension unresponsive to sympathomimetics developed after an episode of asystole and the patient died 19 hours after admission. The serum-verapamil concentration 12 hours after admission was 3 micrograms/mL.
- Haematemesis occurred in a patient[5] who took 3.2 g of verapamil; gastric ulceration was found on gastroscopy 12 hours after admission.

Overdosage with modified-release preparations of verapamil may result in prolonged toxicity of delayed onset.[6] Intravenous infusion of a fat emulsion, which can attenuate the cardiotoxicity of lipophilic drugs (see Soya Oil, p. 2093.1), was of benefit in a patient with refractory shock after a multidrug overdose including 13.44 g of verapamil in a modified-release formulation.[7] Conventional-release preparations may also produce prolonged toxicity; elimination half-life was reported to be prolonged to 15 hours and peak plasma concentrations delayed to 6 to 7 hours in a 59-year-old man after ingestion of 2.4 g of verapamil.[8] Rate-limiting absorption at high doses was considered to be the cause.

Although severe toxicity usually relates to acute verapamil overdosage, similar symptoms have also been reported with chronic toxicity. Long-term treatment with verapamil 240 mg daily[9] in a patient with cirrhosis of the liver led to loss of consciousness, cardiogenic shock, cyanosis, hypotension, severe acidosis, hyperkalaemia, hypothermia, and renal failure. The patient recovered after treatment with high doses of dopamine, noradrenaline, sodium bicarbonate, and sodium chloride.

1. Hofer CA, *et al.* Verapamil intoxication: a literature review of overdoses and discussions of therapeutic options. *Am J Med* 1993; **95:** 431–8.
2. Perkins CM. Serious verapamil poisoning: treatment with intravenous calcium gluconate. *BMJ* 1978; **2:** 1127.
3. Crump BJ, *et al.* Lack of response to intravenous calcium in severe verapamil poisoning. *Lancet* 1982; **ii:** 939–40.
4. Orr GM, *et al.* Fatal verapamil overdose. *Lancet* 1982; **ii:** 1218–19.
5. Miller ARO, Ingamells CJ. Gastrointestinal haemorrhage associated with an overdose of verapamil. *BMJ* 1984; **288:** 1346.
6. Barrow PM, *et al.* Overdose of sustained-release verapamil. *Br J Anaesth* 1994; **72:** 361–5.
7. Young AC, *et al.* Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. *Resuscitation* 2009; **80:** 591–3.
8. Buckley CD, Aronson JK. Prolonged half-life of verapamil in a case of overdose: implications for therapy. *Br J Clin Pharmacol* 1995; **39:** 680–3.
9. Stehle G, *et al.* Cardiogenic shock associated with verapamil in a patient with liver cirrhosis. *Lancet* 1990; **336:** 1079.

Precautions

Verapamil is contra-indicated in hypotension, cardiogenic shock, marked bradycardia, and uncompensated heart failure. It is also contra-indicated in second- or third-degree AV block, and in the sick-sinus syndrome, unless a pacemaker is fitted. There is an increased incidence of adverse cardiac effects in patients with hypertrophic cardiomyopathy. In patients with atrial flutter or fibrillation and an accessory pathway with anterograde conduction, for example Wolff-Parkinson-White syndrome, verapamil may induce severe ventricular tachycardia and it is usually contra-indicated in such patients.

Special care is required in using verapamil as an antiarrhythmic in infants as they may be more susceptible to verapamil-induced arrhythmias.

Doses of verapamil should be reduced in patients with hepatic impairment.

Sudden withdrawal of verapamil might be associated with exacerbation of angina.

Breast feeding. Verapamil concentrations in breast milk similar to those found in plasma have been reported[1] in a woman taking verapamil 80 mg four times daily. The maximum concentration measured in breast milk was 300 nanograms/mL. However, the average concentration in milk in another woman[2] taking 80 mg three times daily was 23% of that in serum. The serum concentration of verapamil in the breast-fed child was 2.1 nanograms/mL during treatment and undetectable 38 hours after the last maternal dose. In another patient[3] taking the same dose, the average steady-state concentrations of verapamil and norverapamil in milk were, respectively, 60% and 16% of the concentration in plasma, with the ratio between milk and plasma varying during a dosage interval. It was esti-

mated that the infant received less than 0.01% of the mother's dose, and no verapamil or norverapamil could be detected in the plasma of the infant. No adverse effects have been seen in breast-feeding infants, and the American Academy of Pediatrics considers[4] that verapamil is therefore usually compatible with breast feeding.

1. Inoue H, *et al.* Level of verapamil in human milk. *Eur J Clin Pharmacol* 1984; **26:** 657–8.
2. Andersen HJ. Excretion of verapamil in human milk. *Eur J Clin Pharmacol* 1983; **25:** 279–80.
3. Anderson P, *et al.* Verapamil and norverapamil in plasma and breast milk during breast feeding. *Eur J Clin Pharmacol* 1987; **31:** 625–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Muscular disorders. Sudden respiratory failure was believed to have been precipitated by intravenous verapamil therapy in a patient with Duchenne's muscular dystrophy.[1]

1. Zalman F, *et al.* Acute respiratory failure following intravenous verapamil in Duchenne's muscular dystrophy. *Am Heart J* 1983; **105:** 510–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies verapamil as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Wolff-Parkinson-White Syndrome. Patients with atrial flutter or fibrillation and an accessory pathway, such as those with Wolff-Parkinson-White syndrome, may be at increased risk of developing ventricular tachycardia if AV-blocking drugs such as verapamil are used, since conduction across the anomalous pathway may be increased. Ventricular fibrillation and severe hypotension have been reported[1] after the use of intravenous verapamil 5 to 10 mg in patients with the Wolff-Parkinson-White syndrome.

1. McGovern B, *et al.* Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. *Ann Intern Med* 1986; **104:** 791–4.

Interactions

Verapamil should be used with caution with drugs that have antiarrhythmic or beta-blocking effects; the use of intravenous verapamil with a beta blocker is especially hazardous (see below). Verapamil is extensively metabolised in the liver and interactions may occur with drugs that inhibit or enhance hepatic metabolism. Grapefruit juice may cause increased plasma concentrations of verapamil. Verapamil can itself affect the pharmacokinetics of other drugs, particularly by inhibition of the cytochrome P450 isoenzyme CYP3A4 and by effects on P-glycoprotein. Drugs affected include carbamazepine, ciclosporin, digoxin, midazolam, simvastatin, and theophylline; the plasma concentration of alcohol may also be increased. For details of these interactions, see under the individual drug monographs.

Analgesics. For a possible interaction of verapamil with *aspirin*, see under Antiplatelets, below.

Antiarrhythmics. Verapamil may have pharmacodynamic and pharmacokinetic interactions with other antiarrhythmics. Cardiogenic shock and asystole occurred in 2 patients receiving *flecainide* when verapamil was added to their therapy.[1] Verapamil given intravenously has been reported to cause severe hypotension in patients also receiving oral *quinidine*;[2] both drugs block alpha-adrenoceptors and verapamil may also increase the plasma concentration of quinidine.

1. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; **340:** 546.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil: possible additive competition at alpha-adrenergic receptors. *N Engl J Med* 1985; **312:** 167–70.

Antibacterials. Acute verapamil toxicity manifested by complete heart block has been reported in a patient after the use of *ceftriaxone* and *clindamycin*.[1] Displacement of verapamil from binding sites was postulated as the probable mechanism of action. *Rifampicin* is an enzyme-inducing drug and has been reported[2,3] to reduce plasma-verapamil concentrations. A verapamil dose of 1.92 g was required to control supraventricular tachycardia in a patient also taking rifampicin[3] and when rifampicin was withdrawn the plasma-verapamil concentration 9 days later was almost four times higher. A patient taking propranolol and verapamil developed symptomatic bradycardia a few days after starting treatment with *clarithromycin* and on another occasion after starting treatment with *erythromycin*.[4] Inhibition of verapamil metabolism by the antibacterials was proposed as the mechanism for the interaction. A further case of severe hypotension and bradycardia has also been reported[5] in a patient shortly after beginning therapy with clarithromycin and verapamil, and similar effects were seen[6] in a patient 2 days after starting *telithromycin*. A case of complete heart block has been reported[7] in a patient aged 79 taking verapamil, one week after erythromycin was added to her therapy, probably due to mutual inhibition of hepatic metabolism of both drugs.

1. Kishore K, *et al.* Acute verapamil toxicity in a patient with chronic toxicity: possible interaction with ceftriaxone and clindamycin. *Ann Pharmacother* 1993; **27:** 877–80.
2. Rahn KH, *et al.* Reduction of bioavailability of verapamil by rifampin. *N Engl J Med* 1985; **312:** 920–1.
3. Barbarash RA. Verapamil-rifampin interaction. *Drug Intell Clin Pharm* 1985; **19:** 559–60.
4. Steenbergen JA, Stauffer VL. Potential macrolide interaction with verapamil. *Ann Pharmacother* 1998; **32:** 387–8.
5. Kaeser YA, *et al.* Severe hypotension and bradycardia associated with verapamil and clarithromycin. *Am J Health-Syst Pharm* 1998; **55:** 2417–18.
6. Reed M, *et al.* Verapamil toxicity resulting from a probable interaction with telithromycin. *Ann Pharmacother* 2005; **39:** 357–60.
7. Goldschmidt N, *et al.* Compound cardiac toxicity of oral erythromycin and verapamil. *Ann Pharmacother* 2001; **35:** 1396–9.

Antiepileptics. *Phenobarbital* is a hepatic enzyme-inducing drug and has been reported[1] to increase the clearance of oral and intravenous verapamil and to reduce oral bioavailability in healthy subjects. Plasma protein binding of verapamil was also reduced. Dosage adjustment of verapamil may be needed in patients also taking phenobarbital. Marked reduction in verapamil concentrations has also occurred with *phenytoin*.[2]

For a report of neurotoxicity in patients given verapamil with *carbamazepine*, see Calcium-channel Blockers, under Interactions of Carbamazepine, p. 517.2.

1. Rutledge DR, *et al.* Effects of chronic phenobarbital on verapamil disposition in humans. *J Pharmacol Exp Ther* 1988; **246:** 7–13.
2. Woodcock BG, *et al.* A reduction in verapamil concentrations with phenytoin. *N Engl J Med* 1991; **325:** 1179.

Antiplatelet drugs. Calcium-channel blockers can inhibit platelet function (see Effects on the Blood under Adverse Effects of Nifedipine, p. 1450.3). Use of verapamil and *aspirin* in an 85-year-old man was considered to be the cause of ecchymoses and retroperitoneal bleeding that developed about 3 weeks after starting treatment with the combination.[1]

1. Verzino E, *et al.* Verapamil-aspirin interaction. *Ann Pharmacother* 1994; **28:** 536–7.

Benzodiazepines. For the effects of verapamil on the pharmacokinetics of *midazolam*, see Calcium-channel Blockers, p. 1069.3.

Beta blockers. Oral verapamil and beta blockers have been used together in the treatment of angina and hypertension but both drugs have cardiodepressant activity and the combination, if used at all, must be used with extreme caution; bradycardia, heart block, and left ventricular failure have been reported.[1-4] Bradycardia has also been reported[5] in a patient treated with *timolol* eye drops and oral verapamil. Patients with severe ischaemic heart disease or heart failure are particularly at risk.[6] The risks are increased with intravenous verapamil, and it has been suggested[6] that treatment with beta blockers should be stopped at least 24 hours before giving verapamil by this route; the interaction is particularly hazardous when both verapamil and beta blockers are given intravenously, and such combinations are not recommended.

Verapamil may also affect the pharmacokinetics of some beta blockers (see Calcium-channel Blockers, under Interactions of Beta Blockers, p. 1322.1).

1. Eisenberg JNH, Oakley GDG. Probable adverse interaction between oral metoprolol and verapamil. *Postgrad Med J* 1984; **60:** 705–6.
2. Hutchison SJ, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 659–60.
3. Findlay IN, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 1074.
4. McGourty JC, Silas JH. β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 1624.
5. Pringle SD, MacEwen CJ. Severe bradycardia due to interaction of timolol eye drops and verapamil. *BMJ* 1987; **294:** 155–6.
6. McInnes GT. Interactions that matter: calcium blockers. *Prescribers' J* 1988; **28:** 60–4.

Calcium salts. Calcium salts antagonise the pharmacological response to verapamil and other calcium-channel blockers and are given intravenously to treat their adverse effects (see Treatment of Adverse Effects under Nifedipine, p. 1452.3). Recurrence of atrial fibrillation has occurred[1] during maintenance verapamil treatment when calcium adipinate and calciferol were given orally.

1. Bar-Or D, Yoel G. Calcium and calciferol antagonise effect of verapamil in atrial fibrillation. *BMJ* 1981; **282:** 1585–6.

Everolimus. For the effect of verapamil on everolimus, see p. 1963.2.

General anaesthetics. For a recommendation that verapamil should not be used in patients anaesthetised with *halothane* or *enflurane*, see under Interactions of Diltiazem, p. 1361.3.

Histamine H_2-antagonists. Studies in healthy subjects using single doses of verapamil after pretreatment with *cimetidine* for up to 8 days have produced conflicting results. The pharmacokinetics of intravenous verapamil were unaltered by cimetidine in some studies,[1,2] but a 21% reduction in clearance and a 50% increase in the elimination half-life were also reported.[3] The pharmacokinetics of oral verapamil were unchanged in one study[2] but two others[1,4] reported a significant increase in bioavailability. Although one of these studies[1] found the interaction had no clinical effects, the other[4] reported an increased clinical effect in 5 of 6 subjects. The interaction with cimetidine appears to be stereoselective since the oral bioavailability of the *S*-enantiomer increased by 35% and that of the *R*-enantiomer by 15%.[4] The clinical significance of this interaction in patients and during long-term verapamil treatment is unknown, but cimetidine should be used with caution in patients receiving verapamil.

1. Smith MS, *et al.* Influence of cimetidine on verapamil kinetics and dynamics. *Clin Pharmacol Ther* 1984; **36:** 551–4.
2. Abernethy DR, *et al.* Lack of interaction between verapamil and cimetidine. *Clin Pharmacol Ther* 1985; **38:** 342–9.
3. Loi C-M, *et al.* Effect of cimetidine on verapamil disposition. *Clin Pharmacol Ther* 1985; **37:** 654–7.
4. Mikus G, *et al.* Interaction of verapamil and cimetidine: stereochemical aspects of drug metabolism, drug disposition and drug action. *J Pharmacol Exp Ther* 1990; **253:** 1042–8.

Lithium. Verapamil may have effects on neuromuscular function (see Extrapyramidal Disorders, p. 1524.2) and neurotoxicity has occurred[1-4] in patients receiving lithium after the addition of verapamil to their therapy, despite serum-lithium concentrations (where reported[1,2,4]) remaining in the therapeutic range. Verapamil has also been reported to decrease serum-lithium concentrations.[5]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26:** 717–19.
2. Price WA, Shalley JE. Lithium-verapamil toxicity in the elderly. *J Am Geriatr Soc* 1987; **35:** 177–8.
3. Helmuth D, *et al.* Choreoathetosis induced by verapamil and lithium treatment. *J Clin Psychopharmacol* 1989; **9:** 454–5.
4. Wright BA, Jarrett DB. Lithium and calcium channel blockers: possible neurotoxicity. *Biol Psychiatry* 1991; **30:** 635–6.
5. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108:** 1378–80.

St John's wort. A study in healthy subjects[1] found that repeated doses of St John's wort significantly reduced the plasma concentrations of both the *R*- and *S*-isomers of verapamil, probably due to induction of the cytochrome P450 isoenzyme CYP3A4.

1. Tannergren C, *et al.* St John's wort decreases the bioavailability of *R*- and *S*-verapamil through induction of the first-pass metabolism. *Clin Pharmacol Ther* 2004; **75:** 298–309.

Statins. A small crossover study[1] in healthy subjects suggested that oral *lovastatin* 20 mg produced marked increases in exposure and peak plasma concentrations of verapamil (about 60 and 30% respectively); the total increase in verapamil bioavailability was calculated at around 76%, and was thought to be due to inhibition of P-glycoprotein and first-pass metabolism of verapamil.

For mention of the effects of verapamil on a statin, see under Simvastatin, p. 1495.2.

1. Choi D-H, *et al.* Pharmacokinetic interaction between oral lovastatin and verapamil in healthy subjects: role of P-glycoprotein inhibition by lovastatin. *Eur J Clin Pharmacol* 2010; **66:** 285–90.

Theophylline. For the effects of verapamil on the pharmacokinetics of theophylline, see Calcium-channel Blockers, p. 1235.3.

Tolvaptan. For the effect of verapamil on tolvaptan concentrations, see p. 2633.1.

Pharmacokinetics

Verapamil is about 90% absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism in the liver and the bioavailability is only about 20%.

Verapamil has bi- or tri-phasic elimination kinetics and is reported to have a terminal plasma half-life of 2 to 8 hours after a single oral dose or after intravenous dosage. With repeated oral doses half-life increases to 4.5 to 12 hours. Verapamil acts within 5 minutes when given intravenously and within 1 to 2 hours when given orally; peak plasma concentrations occur 1 to 2 hours after an oral dose. There is considerable interindividual variation in plasma concentrations.

Verapamil is about 90% bound to plasma proteins. It is extensively metabolised in the liver to at least 12 metabolites of which norverapamil has been shown to have some activity. About 70% of a dose is excreted by the kidneys in the form of its metabolites but about 16% is excreted in the bile into the faeces. Less than 4% is excreted

unchanged. Verapamil crosses the placenta and is distributed into breast milk.

Reviews.

1. Hamann SR, *et al.* Clinical pharmacokinetics of verapamil. *Clin Pharmacokinet* 1984; **9:** 26–41.
2. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.
3. Kang D, *et al.* Population analyses of sustained-release verapamil in patients: effects of sex, race, and smoking. *Clin Pharmacol Ther* 2003; **73:** 31–40.

The elderly. Studies[1-3] comparing the pharmacokinetics and pharmacodynamics of verapamil in elderly (61 years and older) and young subjects have found that clearance and elimination half-life are increased in older subjects, and increased plasma concentrations have also been reported. However, there may also be changes in the response to verapamil in older subjects that are not directly related to the plasma concentration.

1. Abernethy DR, *et al.* Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: altered electrocardiographic and hypotensive responses. *Ann Intern Med* 1986; **105:** 329–36.
2. Gupta SK, *et al.* Age and gender related changes in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *Br J Clin Pharmacol* 1995; **40:** 325–31.
3. Abernethy DR, *et al.* Verapamil metabolite exposure in older and younger men during steady-state oral verapamil administration. *Drug Metab Dispos* 2000; **28:** 760–5.

Metabolism. Verapamil is extensively metabolised in the liver to several metabolites, and several cytochrome P450 isoenzymes appear to be involved. An *in-vitro* study[1] has suggested that the main isoenzymes responsible for the metabolism of both enantiomers of verapamil are CYP3A4, CYP3A5, and CYP2C8, and that the same isoenzymes are involved in the further metabolism of norverapamil. However, since CYP2C8 generally makes up only a small part of the cytochrome P450 content of the liver, it was considered that this would have little significance for potential drug interactions. In contrast to some previous reports, the isoenzymes CYP1A2 and CYP2C9 were not found to be involved to any great extent.

1. Tracy TS, *et al.* Cytochrome P450 isoforms involved in metabolism of the enantiomers of verapamil and norverapamil. *Br J Clin Pharmacol* 1999; **47:** 545–52.

Stereospecificity. Verapamil is used as a racemic mixture. It has been shown[1] that *S*-verapamil is 3.3 times more potent than the racemic mixture and 11 times more potent than *R*-verapamil. Thus it was concluded that the cardiac effects of verapamil are related not to the total plasma-verapamil concentration but to the concentration of the *S*-isomer, and conventional plasma concentration monitoring will be of little value in establishing therapeutic plasma concentrations during multiple oral dosing.

A series of studies have been carried out to determine whether differences in the pharmacokinetics of the *R*- and *S*-isomers of verapamil could account for the differences in the plasma concentration-response curve after oral and intravenous doses. When given intravenously, there were pronounced differences in the pharmacokinetics and protein binding of the 2 isomers;[2] the volume of distribution and total systemic clearance of *S*-verapamil were much higher than those of the *R*-isomer although the terminal half-life was similar. After oral doses of a mixture of *R*- and *S*-verapamil, plasma concentrations of the *R*-isomer were found to be substantially higher than those of the more potent *S*-isomer,[3] suggesting stereospecific first-pass hepatic metabolism and accounting for the apparent lower potency of verapamil when given orally. The proportion of *S*-isomer also depends on the oral formulation; modified-release formulations produce lower proportions of *S*-isomer in plasma than conventional formulations.[4]

1. Echizen H, *et al.* Effects of d,l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. *Clin Pharmacol Ther* 1985; **38:** 71–6.
2. Eichelbaum M, *et al.* Pharmacokinetics of (+)-, (-)- and (±)-verapamil after intravenous administration. *Br J Clin Pharmacol* 1984; **17:** 453–8.
3. Vogelgesang B, *et al.* Stereoselective first-pass metabolism of highly cleared drugs: studies of the bioavailability of L- and D-verapamil examined with a stable isotope technique. *Br J Clin Pharmacol* 1984; **18:** 733–40.
4. Karim A, Piergies A. Verapamil stereoisomerism: enantiomeric ratios in plasma dependent on peak concentrations, oral input rate, or both. *Clin Pharmacol Ther* 1995; **58:** 174–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Isoptino; Veral; Verapal; ***Austral.***: Anpec; Cordilox; Isoptin; Veracaps; Verahexal†; ***Austria***: Isoptin; Verapabene; Veroptinstada; ***Belg.***: Isoptine; Lodixal; ***Braz.***: Cordilat; Coronaril; Dilacor; Dilacoron; Multicor†; Neo Verpamil; Vasoton; Veramil; Verapress†; Veraval; ***Canad.***: Apo-Verap; Covera†; Isoptin; Novo-Veramil; Nu-Verap; Verelan; ***Chile***: Cardiolen; Isoptina; Presocor†; ***China***: Ao Di Mai Er (奥地迈尔); Ba Ping Te Jia (巴平特佳); Gai Heng (盖衡); Isoptin (异搏定); Novopressan (诺富生); Shida (释达); ***Cz.***: Isoptin; Lekoptin; Verahexal; Verogalid; ***Denm.***: Hexasoptin; Isoptin; Veraloc; ***Fin.***: Isoptin; Vermin†; Verpamil; ***Fr.***: Isoptine; ***Ger.***: Falicard; Isoptin; Vera-Lich†; Vera; Verabeta; Veragamma; Verahexal†; Veramex†; Veranorm†; Verasal†; Veroptinstada†; ***Gr.***: Brovicarpine; Elanver; Isoptin; Ranil; ***Hong Kong***: Anpec†; Apo-Verap; Isoptin; Verpamil†; ***Hung.***: Chinopamil; Isoptin; ***India***: Calaptin; Veramil; ***Indon.***: Cardiover; Isoptin; ***Irl.***: Isoptin; Veramil; Verap; Verisop; ***Israel***: Ikacor; Ikapress; Verapress; ***Ital.***: Cardinorm; Isoptin; Kata; Veraptin; ***Jpn***: Vasolan; ***Malaysia***: Akilen†; Isoptin; Verpamil; ***Mex.***: Cronovera; Dilacoran; Europave†; Serriten; Vepiltax; Veraken; Verdilac; ***Neth.***: Isoptin; ***Norw.***: Isoptin; Verakard; ***NZ***: Isoptin; Verpamil; ***Philipp.***: Isoptin; Verelan; ***Pol.***: Isoptin; Lekoptin†; Novo-Veramil; Staveran; ***Port.***: Fibrocard†; Isoptin; ***Rus.***: Finoptin (Финоптин); Isoptin (Изоптин); Lekoptin (Лекоптин)†; Verogalid (Верогалид); Veromil (Веромил)†; ***S.Afr.***: Calcicard; Isoptin; Ravamil; Vasomil; Verahexal; ***Singapore***: Beaptin; Isoptin; Verpamil; ***Spain***: Manidon; ***Swed.***: Isoptin; ***Switz.***: Flamon; Isoptin; Verapam†; ***Thai.***: Caveril; Isoptin; Sopmil; Verapin†; Vermine; ***Turk.***: Fibrocard; Isoptin; Ormil; Veroptin; ***UK***: Cordilox; Half Securon; Securon; Univer; Verapress; Vertab; Zolvera; ***Ukr.***: Finoptin (Финоптин); Lekoptin (Лекоптин); Veratard (Вератард); Verogalid (Верогалид); ***USA***: Calan; Covera; Isoptin; Verelan; ***Venez.***: Cronovera; Manidon; Veracor.

Multi-ingredient Preparations. ***Austral.***: Tarka; ***Austria***: Confit; Veracapt; ***Canad.***: Tarka; ***Cz.***: Tarka; ***Denm.***: Tarka; ***Fr.***: Tarka; ***Ger.***: Cordichin; Isoptin plus; Tarka; Veratide†; ***Gr.***: Tarka; Ziaxel; ***Hong Kong***: Tarka; ***Hung.***: Tarka; ***Indon.***: Tarka; ***Ital.***: Tarka; ***Mex.***: Tarka; ***Neth.***: Tarka; Ziaxel; ***NZ***: Ziaxel†; ***Philipp.***: Tarka; ***Pol.***: Tarka; ***Port.***: Tarka; Ziaxel; ***Rus.***: Tarka (Тарка); ***S.Afr.***: Tarka; ***Spain***: Tarka; Tricen†; ***Swed.***: Tarka†; ***Switz.***: Tarka; ***Turk.***: Tarka; ***UK***: Tarka; ***Ukr.***: Tarka (Тарка); ***USA***: Tarka; ***Venez.***: Tarka.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Verapamil Capsules; Prolonged-release Verapamil Tablets; Verapamil Injection; Verapamil Tablets;

USP 36: Verapamil Hydrochloride Extended-Release Capsules; Verapamil Hydrochloride Extended-release Tablets; Verapamil Hydrochloride Injection; Verapamil Hydrochloride Oral Solution; Verapamil Hydrochloride Oral Suspension; Verapamil Hydrochloride Tablets.

Vernakalant Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de vernakalant; RSD-1235; Vernakalant, Chlorhydrate de; Vernakalanti Hydrochloridum; Вернакаланта Гидрохлорид.

(3*R*)-1-{(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl}pyrrolidin-3-ol hydrochloride.

$C_{20}H_{31}NO_4$,HCl=385.9

CAS — 794466-70-9 (vernakalant); 748810-28-8 (vernakalant hydrochloride).

ATC — C01BG11.

ATC Vet — QC01BG11.

UNII — 7G4J1ZD9UQ.

NOTE. The name Kynapid has been used as a trademark for vernakalant hydrochloride.

Uses and Administration

Vernakalant hydrochloride is an antiarrhythmic drug used for the rapid conversion of recent-onset atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1). It acts by selective inhibition of atrial sodium and potassium repolarising currents and can therefore be classified as both a class I and class III antiarrhythmic.

Vernakalant hydrochloride may be given to non-surgical patients up to 7 days after onset of atrial fibrillation, or to surgical patients up to 3 days after onset. It is given by intravenous infusion at a dose of 3 mg/kg (maximum dose of 339 mg) over 10 minutes. If conversion to sinus rhythm does not occur within 15 minutes of this infusion, a second 10-minute infusion of 2 mg/kg (maximum dose of 226 mg) may be given. A cumulative dose of 5 mg/kg per 24 hours should not be exceeded. If conversion to sinus rhythm occurs during either infusion, the infusion should be continued to completion.

An oral formulation is also under investigation.

References.

1. Roy D, *et al.* A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; **44:** 2355–61.
2. Cheng JWM. Vernakalant in the management of atrial fibrillation. *Ann Pharmacother* 2008; **42:** 533–42.
3. Kozlowski D, *et al.* Vernakalant hydrochloride for the treatment of atrial fibrillation. *Expert Opin Invest Drugs* 2009; **18:** 1929–37.
4. Kowey PR, *et al.* Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009; **2:** 652–9.
5. Finnin M. Vernakalant: A novel agent for the termination of atrial fibrillation. *Am J Health-Syst Pharm* 2010; **67:** 1157–64.

Adverse Effects

Vernakalant hydrochloride often causes bradycardia, particularly at the time of conversion to sinus rhythm. Atrial flutter is also common, but usually converts to sinus rhythm with ongoing infusion. Less common cardiovascular adverse effects include heart block, ventricular tachycardia, and prolongation of the QRS complex or QT interval.

Other adverse effects include sneezing, taste disturbances, hypotension, dry mouth, hyperhidrosis, and pruritus.

Precautions

Vernakalant is contra-indicated in those with severe aortic stenosis, a systolic blood pressure of less than 100 mmHg, prolonged QT interval, severe bradycardia, sinus node dysfunction, or second- or third-degree heart block in the absence of a pacemaker. It should not be used within 4 hours of intravenous administration of a class I or III antiarrhythmic, nor within 30 days of an acute coronary syndrome. It is contra-indicated in moderate or severe heart failure (NYHA class III or IV), but may be used with caution in stable class I or II heart failure.

The infusion should be stopped if clinically significant bradycardia, hypotension, or ECG changes occur.

Interactions

Vernakalant should be used with caution in patients taking other antiarrhythmic drugs (see also Precautions, above). Vernakalant may prolong the QT interval, and there is a theoretical risk of serious ventricular arrhythmias when it is given with other QT-interval-prolonging drugs.

Pharmacokinetics

The pharmacokinetics of vernakalant are linear. It undergoes *O*-demethylation in the liver via the cytochrome P450 isoenzyme CYP2D6, followed by glucuronide conjugation. It has a mean elimination half-life of 3 hours in extensive metabolisers, and 5.5 hours in poor metabolisers.

References.

1. Mao ZL, *et al.* Pharmacokinetics of novel atrial-selective antiarrhythmic agent vernakalant hydrochloride injection (RSD1235): influence of CYP2D6 expression and other factors. *J Clin Pharmacol* 2009; **49:** 17–29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Brinavess; ***Cz.***: Brinavess; ***Denm.***: Brinavess; ***Ger.***: Brinavess; ***Gr.***: Brinavess; ***Irl.***: Brinavess; ***Israel***: Brinavess; ***Neth.***: Brinavess; ***Norw.***: Brinavess; ***Pol.***: Brinavess; ***Port.***: Brinavess; ***Spain***: Brinavess; ***Swed.***: Brinavess; ***Switz.***: Brinavess.

Vorapaxar *(USAN, rINN)*

SCH-530348 (vorapaxar sulfate); Vorapaxarum; Ворапаксар.

Ethyl [(1*R*,3a*R*,4a*R*,6*R*,8a*R*,9*S*,9a*S*)-9-[(1*E*)-2-[5-(3-fluorophenyl)pyridin-2-yl]ethen-1-yl]-1-methyl-3-oxododecahydronaphtho[2,3-*c*]furan-6-yl]carbamate.

$C_{29}H_{33}FN_2O_4$=492.6

CAS — 618385-01-6 (vorapaxar); 705260-08-8 (vorapaxar sulfate).

UNII — ZCE93644N2.

NOTE. Vorapaxar Sulfate is *USAN*.

Profile

Vorapaxar is a protease activated receptor-1 (PAR-1) antagonist that blocks thrombin-mediated platelet activation. It is given orally and is under investigation for the prevention and treatment of thrombosis; however, there have been concerns about a possible increased risk of stroke.

References.

1. Leonardi S, *et al.* Thrombin receptor antagonists for the treatment of atherothrombosis: therapeutic potential of vorapaxar and E-5555. *Drugs* 2010; **70:** 1771–83.

Warfarin *(BAN, rINN)*

Coumaphène; Hydroxyoxophenylbutylcoumarin; Varfariini; Varfarin; Varfarina; Warfarina; Warfarine; Warfarinum; Warfaryna; Варфарин.

(*RS*)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)coumarin.

$C_{19}H_{16}O_4$=308.3

CAS — 81-81-2.

ATC — B01AA03.

ATC Vet — QB01AA03.

UNII — 5Q7ZVV76EI.

Warfarin Potassium *(BANM, rINNM)*

Kalii Warfarinum; Potassium Warfarin; Warfarina potasica; Warfarine Potassique; Warfarinum Kalicum; Калия Варфарин.

$C_{19}H_{15}KO_4$=346.4

CAS — 2610-86-8.

ATC — B01AA03.

ATC Vet — QB01AA03.
UNII — I47IU4FOCO.

Pharmacopoeias. In *Jpn.*

Warfarin Sodium *(BANM, rINNM)*

Natrii Warfarinum; Sodium Warfarin; Varfariininatrium; Varfarin Sodyum; Varfarino natrio druska; Warfarin-Natrium; Warfarin sodná sůl; Warfarina sódica; Warfarine Sodique; Warfarinnatrium; Warfarin-nátrium; Warfarinum natricum; Натрий Варфарин.

$C_{19}H_{15}NaO_4$=330.3

CAS — 129-06-6.
ATC — B01AA03.
ATC Vet — QB01AA03.
UNII — 6153CWM0CL.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate. *Eur.* has a separate monograph for warfarin sodium clathrate (see below).

Ph. Eur. 8: (Warfarin Sodium). A white or almost white, hygroscopic, amorphous powder. Very soluble in water and in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.

USP 36: (Warfarin Sodium). A white, odourless, amorphous solid or a crystalline clathrate which is discoloured by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether. A 1% solution in water has a pH of 7.2 to 8.3. Protect from light.

Adsorption. Studies carried out for periods of 24 hours to 3 months found some adsorption of warfarin sodium by PVC when dissolved in 0.9% sodium chloride solution[1,2] or in 5% glucose solution.[3] In one of these studies,[1] adsorption was decreased by buffering the solution from its initial pH of 6.7 to a pH of 7.4. The second study[2] found no adsorption onto polyethylene-lined or glass infusion containers.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
3. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags: part i: sorption studies on 17 drugs. *Am J Hosp Pharm* 1974; **31:** 72–8.

Incompatibility. Solutions of warfarin sodium have been reported to be incompatible with adrenaline hydrochloride, amikacin sulfate, metaraminol tartrate, oxytocin, promazine hydrochloride, and tetracycline hydrochloride. Visual incompatibility has been reported[1] with solutions of warfarin sodium mixed with solutions of aminophylline, bretylium tosilate, ceftazidime, cimetidine hydrochloride, ciprofloxacin lactate, dobutamine hydrochloride, esmolol hydrochloride, gentamicin sulfate, labetalol hydrochloride, metronidazole hydrochloride, or vancomycin hydrochloride. Haze was also reported after 24 hours with sodium chloride 0.9%.

1. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Warfarin Sodium Clathrate *(BANM)*

Varfariininatriumklatraatti; Varfarino natrio druskos klatratas; Warfarin-Natrium-Clathrat; Warfarin sodná sůl klatrát; Warfarina sódica, clatrato de; Warfarine sodique clathrate; Warfarinnatriumklatrat; Warfarin-nátrium-klatrát; Warfarinum Natricum Clathratum.

The clathrate of warfarin sodium with isopropyl alcohol in the molecular proportions 2 to 1 respectively.

ATC — B01AA03.
ATC Vet — QB01AA03.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Eur.* (see p. vii).

Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate.

Ph. Eur. 8: (Warfarin Sodium Clathrate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.

Warfarin sodium clathrate contains about 92% of warfarin sodium.

Uses and Administration

Warfarin is a coumarin anticoagulant used in the treatment and prophylaxis of thromboembolic disorders (p. 1273.2). It acts by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p. 1124.3. Since warfarin acts indirectly, it has no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is seen. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Warfarin is used in the prevention and treatment of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p. 1274.1). If an immediate effect on blood coagulation is required, heparin should be given intravenously or subcutaneously to cover at least the first 5 days. Warfarin therapy may be begun with, or shortly after, initial heparin treatment. Warfarin is also used for the prevention of systemic thromboembolism and ischaemic stroke in some patients with atrial fibrillation (p. 1266.1), prosthetic heart valves (see Valvular Heart Disease, p. 1264.3), or who have suffered a myocardial infarction (p. 1257.1). It may also have a role in the prevention of myocardial infarction and in the management of stroke or transient ischaemic attacks (p. 1269.2). Antiplatelet drugs may be given concomitantly.

Warfarin may be used as a rodenticide, but resistance is common in *mice* and is developing in *rats*.

Administration and dosage. Warfarin is usually given orally but is equally effective given intravenously. Dosage must be determined individually as discussed below under Control of Anticoagulant Therapy. When rapid anticoagulation is required, an initial dose of warfarin sodium 10 mg may be given on the first day, although in many cases an initial dose of 5 mg daily is adequate; initial doses of less than 5 mg daily may be used in elderly patients and in those at increased risk of bleeding (see Precautions, p. 1529.2). Subsequent doses depend on the results of coagulation tests, but maintenance doses usually range from 3 to 9 mg daily. If necessary the same dose may be given by slow intravenous injection. Doses of warfarin sodium should be given at the same time each day. Theoretically, stopping warfarin abruptly may result in rebound hypercoagulability with risk of thrombosis. Therefore some clinicians have tailed off long-term treatment over several weeks. However, small studies suggest that a hypercoagulable state may persist for 8 to 9 weeks, regardless of the strategy used for stopping warfarin. The *American College of Chest Physicians* also considers that gradually stopping therapy may be confusing and inconvenient for the patient, and suggests that treatment may be stopped abruptly. Anticoagulant treatment booklets should be carried by patients.

Warfarin has also been given as the potassium salt; warfarin-deanol has been tried.

Control of oral anticoagulant therapy. Treatment with oral anticoagulants must be monitored to ensure that the dose is providing the required effect on the vitamin-K-dependent clotting factors; too small a dose provides inadequate anticoagulation, too large a dose puts the patient at risk of haemorrhage. This monitoring is commonly carried out by checking the clotting property of the patient's plasma using a suitable preparation of thromboplastin and a source of calcium. The time taken for the clot to form due to the effect of the thromboplastin preparation on prothrombin is known as the prothrombin time (PT). The prothrombin time ratio (PTR) is the prothrombin time of the patient's plasma divided by that for a standard plasma sample.

So that there is some consistency in prothrombin time ratios measured at different times or at different laboratories, it is now common practice for the manufacturer or control laboratory to calibrate their batches of thromboplastin against the international reference preparation. This calibration produces an international sensitivity index (ISI) appropriate to that thromboplastin. The laboratory measuring the clotting capacity of a sample of plasma is thus able to convert the prothrombin time ratio to an international normalised ratio (INR) using the sensitivity index through the formula

$$INR = PTR^{(ISI)}$$

Thus a PTR of 2.0 obtained with a thromboplastin with a declared ISI of 1.5 would be converted to an INR of 2.8. An INR is therefore equivalent to a PTR carried out using the primary international reference preparation of thromboplastin.

This method of standardisation has taken over from methods involving use of a standard reagent such as the British or Manchester comparative thromboplastin. Preparations of thromboplastin derived from *rabbit* brain have superseded or are superseding those from human brain because of the dangers of viral transmission; a recombinant human form is also available.

Recommended target values or ranges of INR for patients receiving anticoagulant treatment or cover for various conditions or procedures are given by the *British Society for Haematology* and the *American College of Chest Physicians*. These are given in Table 6, below. An INR within 0.5 units of the target value in the UK is generally considered satisfactory. In the USA it is recommended that the INR be maintained at the mid-level of the range. An INR less than 2.0 generally represents inadequate anticoagulation and an INR above 4.5 represents greater risk of haemorrhage.

Measurements should be carried out before treatment and then daily or on alternate days in the early stages of treatment. Once the dose has been established and the patient well stabilised the measurement can be made at greater but regular intervals, for example every 8 weeks; allowances should be made for any events that might influence the activity of the anticoagulant. Self-monitoring may be appropriate in some patients.

General references.

1. Le DT, *et al.* The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relation to other monitoring methods. *Ann Intern Med* 1994; **120:** 552–8.
2. Hirsh J, *et al.* American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation* 2003; **107:** 1692–1711. Also available at: http://circ.ahajournals.org/cgi/reprint/107/12/1692.pdf (accessed 25/02/05)
3. Fitzmaurice DA, *et al.* British Society of Haematology Taskforce for Haemostasis and Thrombosis. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. *Br J Haematol* 2005; **131:** 156–65. Correction. *ibid.* 2006; **132:** 118. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05739.x/pdf (accessed 21/10/11)

Table 6. Recommended International Normalised Ratios (INR).

	INR	Condition or procedure
UK	2.5	Treatment of venous thromboembolism; thromboembolism associated with antiphospholipid syndrome; atrial fibrillation, mural thrombus, valvular heart disease, cardiomyopathy, and following myocardial infarction; acute peripheral arterial embolism proceeding to embolectomy; bioprosthetic heart valves.
	2.5 or 3.0	Cardioversion (higher INR may be appropriate before procedure); some mechanical prosthetic heart valves.
	3.5	Recurrence of venous thromboembolism when on warfarin; some mechanical prosthetic heart valves.
US	2.0 to 3.0	Treatment of venous thrombosis and pulmonary embolism; secondary prophylaxis of thromboembolism associated with antiphospholipid syndrome; patients with anterior myocardial infarction and left ventricular thrombus or high risk of thrombus; left ventricular dysfunction with thrombus; and for prophylaxis of systemic embolism in patients with atrial fibrillation (depending on risk factors for stroke), cardioversion, valvular heart disease, bioprosthetic heart valves or some mechanical prosthetic heart valves.
	2.5 to 3.5	Prophylaxis in patients with some mechanical prosthetic heart valves.

4. Keeling D, *et al.* British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin -fourth edition. *Br J Haematol* 2011; **154:** 311–24. Correction. *ibid.;* **156:** 150–2. Also available at: http://www.bcshguidelines.com/documents/warfarin_4th_ed.pdf (accessed 27/02/12)
5. Bloomfield HE, *et al.* Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med* 2011; **154:** 472–82.
6. Guyatt GH, *et al.* American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): 7S–47S. Correction. *ibid.;* 1129. [dose] Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/1412S3.pdf (accessed 21/09/12)
7. Holbrook A, *et al.* American College of Chest Physicians. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): e152S–84S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112295.pdf (accessed 04/10/12)
8. Ageno W, *et al.* American College of Chest Physicians. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): e44S–88S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112292.pdf (accessed 21/09/12)

Administration and dosage. Algorithms and guidelines have been developed for beginning anticoagulant therapy, based on the method of Fennerty *et al.*[1] Although a loading dose of 10 mg daily for 2 days (depending on the INR) has been widely used, lower doses may be more appropriate, especially in hospitalised patients at greater risk of over-anticoagulation. Studies[2-4] comparing warfarin loading doses of 5 and 10 mg found that for both groups a therapeutic INR in the range of 2.0 to 3.0 was reached in most patients by day 5 of treatment. Although a study of outpatients with venous thromboembolism[5] found that a therapeutic INR was achieved 1.4 days sooner with the larger loading dose, the nomogram used was not designed for inpatients.

In situations where rapid anticoagulation is not necessary, loading doses may not be required and treatment should begin with the estimated maintenance dose. Studies[6,7] have found that the maintenance dose decreases with age and is lower in women than in men, and lower initial doses are therefore recommended in the elderly. Regimens that have been suggested include warfarin in a dose of 4 mg daily for 3 days, then adjusted according to the INR,[8] or, for patients requiring anticoagulation prophylaxis, 2 mg daily for 2 weeks followed by weekly adjustment using an algorithm until the target INR is reached.

1. Fennerty A, *et al.* Flexible induction dose regimen for warfarin and prediction of maintenance dose. *BMJ* 1984; **288:** 1268–70.
2. Harrison L, *et al.* Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; **126:** 133–6.
3. Crowther MA, *et al.* Warfarin: less may be better. *Ann Intern Med* 1997; **127:** 333.
4. Crowther MA, *et al.* A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999; **159:** 46–8.
5. Kovacs MJ, *et al.* Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. *Ann Intern Med* 2003; **138:** 714–19.
6. Singla DL, Morrill GB. Warfarin maintenance dosages in the very elderly. *Am J Health-Syst Pharm* 2005; **62:** 1062–6.
7. Garcia D, *et al.* Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest* 2005; **127:** 2049–56.
8. Siguret V, *et al.* Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med* 2005; **118:** 137–42.

DOSE ADJUSTMENT IN SURGERY. The management of patients receiving vitamin K antagonist anticoagulants who require surgery has been reviewed.[1-4] Warfarin dose adjustment should take into account several factors including the risks of both perioperative arterial thromboembolism and bleeding associated with different types of surgery, as well as the initial indication for anticoagulation.

Guidance from the USA[2,4] suggests that where the risk of bleeding is low, warfarin may be continued uninterrupted; local haemostatic measures may be required for minor dental and dermatological procedures. When the bleeding risk is higher, warfarin should be stopped about 5 days before surgery. On the day before surgery, corrective oral vitamin K may be given if the INR is still above 1.5. Warfarin may be restarted about 12 to 24 hours after surgery and when there is adequate haemostasis. It has also been suggested that bridging anticoagulation should be used when warfarin is being withheld and there is a high risk of perioperative thromboembolism. A therapeutic dose regimen of low-molecular-weight heparin is generally used, starting about 3 days before surgery. The final pre-operative dose is given about 24 hours before surgery and treatment is restarted 48 to 72 hours after surgery depending on the bleeding risk and when haemostasis is achieved. If intravenous unfractionated heparin is used, it is stopped 4 to 6 hours before surgery. The role of bridging in moderate risk of perioperative thromboembolism is less clear, and its use depends on individual patient and surgical risk factors. When it is used, it might be considered possible to restart 24 hours after surgery.

In cases of emergency surgery,[2,3] warfarin is stopped and intravenous or oral vitamin K is given. Prothrombin complex concentrate is also used if anticoagulant reversal is needed in less than 24 hours. Fresh frozen plasma may be used if concentrate is not available, but the required dose may risk volume overload.

1. Thachil J, *et al.* Management of surgical patients receiving anticoagulation and antiplatelet agents. *Br J Surg* 2008; **95:** 1437–48.
2. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. *Blood* 2011; **117:** 5044–9.
3. Vang ML, *et al.* Urgent reversal of vitamin K antagonist therapy. *Acta Anaesthesiol Scand* 2011; **55:** 507–16.
4. Douketis JD, *et al.* American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): e326S–50S. Correction. *ibid.;* 1129. [dose] Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112298.pdf (accessed 25/09/12)

Administration in children. Increasing numbers of infants and children are receiving anticoagulants for prophylaxis and treatment of thromboembolism. Doses of warfarin and therapeutic INR ranges have been adapted from adult therapy but cohort studies[1,2] of paediatric patients have found that warfarin requirements may be affected by several factors including age, and the use of infant formulas supplemented with vitamin K. Recommendations[3] for the use of oral anticoagulants in children have been published.

The *BNFC* suggests that neonates, children, and adolescents aged up to 18 years may be given an initial single oral dose of 200 micrograms/kg (maximum 10 mg) on the first day, adjusted over the next 3 days according to INR:

- INR < 1.4: 200 micrograms/kg (maximum 10 mg) once daily
- INR 1.4 to 3: 100 micrograms/kg (maximum 5 mg) once daily
- INR 3 to 3.5: 50 micrograms/kg (maximum 2.5 mg) once daily
- INR > 3.5: omit dose

The usual maintenance dose is 100 to 300 micrograms/kg once daily, adjusted according to INR. Up to 400 micrograms/kg may be needed in certain patients.

1. Tait RC, *et al.* Oral anticoagulation in paediatric patients: dose requirements and complications. *Arch Dis Child* 1996; **74:** 228–31.
2. Streif W, *et al.* Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999; **94:** 3007–14.
3. Monagle P, *et al.* American College of Chest Physicians. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): e737S–801S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112308.pdf (accessed 21/09/12)

Catheters and cannulas. For mention of the use of oral anticoagulants to prevent thrombosis in patients with indwelling infusion devices, see Heparin Sodium, p. 1398.1.

Connective tissue and muscular disorders. Warfarin has been proposed to treat subcutaneous calcium deposition (calcinosis cutis) in patients with dermatomyositis, but its value is disputed, see Polymyositis and Dermatomyositis, p. 1611.1.

Adverse Effects

The major risk from warfarin therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia. Although good control of warfarin anticoagulation is essential in preventing haemorrhage, bleeding has occurred at therapeutic international normalised ratio (INR) values. In such cases the possibility of an underlying cause such as renal or alimentary tract disease should be investigated. Skin necrosis, and purple discoloration of the toes (due to cholesterol embolisation) have occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with haemorrhage include alopecia, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Warfarin is a recognised teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterised by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop after use in any trimester but appear most likely when used in the second or third trimester. Use of warfarin during pregnancy has been associated with an increased rate of abortion and still-birth, although this may, in part, be the consequence of an underlying maternal condition. Use in the late stages of pregnancy is associated with fetal haemorrhage. Reported incidences of the above complications have varied considerably with maternal indications, doses, and treatment durations; analyses of reported cases have indicated that if a coumarin is taken throughout pregnancy, up to 30% of cases may result in spontaneous abortion or still-birth, and around 5% may result in an abnormal liveborn infant.

Effects on the blood. The incidence and risk of haemorrhage during long-term oral anticoagulation has been studied in patients in clinical studies[1,2] and in population-based studies.[1,3-7] The risk of bleeding was generally higher with more intense anticoagulation and in the presence of other risk factors, but the relationship with age was less clear. Some studies have shown higher rates of bleeding in elderly patients, but others have not; the risk of intracranial bleeding, however, does seem to be higher in the elderly.[2,6,7] Although cumulative risk of bleeding was related to duration of anticoagulation therapy, risk may be highest early in the course.[2]

Withdrawal of warfarin therapy may lead to rebound hypercoagulability and it has been suggested[8] that warfarin should be withdrawn gradually, although there is no clinical evidence to support this.

1. Reynolds MW, *et al.* Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest* 2004; **126:** 1938–45.
2. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
3. Gitter MJ, *et al.* Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. *Mayo Clin Proc* 1995; **70:** 725–33.
4. Fihn SD, *et al.* The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996; **124:** 970–9.
5. Palareti G, *et al.* Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; **348:** 423–8.
6. Palareti G, *et al.* Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. *Arch Intern Med* 2000; **160:** 470–8.
7. Fang MC, *et al.* Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 2004; **141:** 745–52.
8. Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet* 1996; **30:** 300–13.

Effects on the bones. Vitamin K is involved in bone metabolism and vitamin K deficiency is associated with an increased risk of osteoporotic fractures. It has been suggested, therefore, that patients on long-term treatment with those oral anticoagulants that are vitamin K antagonists may be at increased risk of osteoporosis and fractures. However, two large observational studies in older women have produced conflicting results. A prospective study[1] of both users and nonusers of warfarin found that warfarin was not associated with decrease in bone density or increase in fracture rates. A retrospective study[2] reported an association between long-term anticoagulant use and increased risk of vertebral and rib fractures, compared with the general population. Overall, however, the risk of any fracture was not significantly increased.

1. Jamal SA, *et al.* Warfarin use and risk for osteoporosis in elderly women. *Ann Intern Med* 1998; **128:** 829–32.
2. Caraballo PJ, *et al.* Long-term use of oral anticoagulants and the risk of fracture. *Arch Intern Med* 1999; **159:** 1750–6.

Effects on the fetus. Fetal complications of coumarin anticoagulants during pregnancy have been reviewed.[1-4]

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68:** 122–40.
2. Chan WS, *et al.* Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; **160:** 191–6.
3. Blickstein D, Blickstein I. The risk of fetal loss associated with warfarin anticoagulation. *Int J Gynaecol Obstet* 2002; **78:** 221–5.
4. Bates SM, *et al.* VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): e691S–736S.

Effects on the liver. There have been a few isolated reports of cholestatic liver damage in patients taking warfarin sodium,[1-3] which resolved on withdrawal.

1. Rehnqvist N. Intrahepatic jaundice due to warfarin therapy. *Acta Med Scand* 1978; **204:** 335–6.
2. Jones DB, *et al.* Jaundice following warfarin therapy. *Postgrad Med J* 1980; **56:** 671.
3. Adler E, *et al.* Cholestatic hepatic injury related to warfarin exposure. *Arch Intern Med* 1986; **146:** 1837–9.

Effects on sexual function. There have been reports[1-5] of priapism in patients taking oral anticoagulants such as warfarin. As with warfarin-induced skin necrosis (see p. 1529.1), priapism appears to be associated with protein C deficiency, and the two conditions have frequently occurred together.

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
2. Daryanani S, Wilde JT. Priapism in a patient with protein C deficiency. *Clin Lab Haematol* 1997; **19:** 213–14.
3. Zimbelman J, *et al.* Unusual complications of warfarin therapy: skin necrosis and priapism. *J Pediatr* 2000; **137:** 266–8.
4. Mahapatra M, *et al.* Priapism: an unusual manifestation of warfarin-induced skin necrosis with protein C deficiency. *J Assoc Physicians India* 2006; **54:** 963–4.
5. Abu Sham'a RA, *et al.* Stuttering priapism complicating warfarin therapy in a patient with protein C deficiency. *Int J Lab Hematol* 2008; **30:** 339–43.

Effects on the skin and hair. Skin and soft-tissue necrosis is a rare but well-established adverse effect of coumarin anticoagulants.[1-4] It is characterised by a localised, painful skin lesion, initially erythematous or haemorrhagic in appearance, that becomes bullous and eventually culminates in gangrenous necrosis. Fatalities have occurred. Areas of increased subcutaneous fat such as breast, thigh, and buttocks have most often been involved. The aetiology appears to be thrombotic but the exact pathophysiology is unknown. Patients with protein C deficiency appear to be at highest risk. Treatment with coumarin anticoagulants should be stopped if skin lesions appear and vitamin K should be given to reverse their effect. Heparin should be given to provide anticoagulation. Fresh frozen plasma or protein C concentrates may also have a role in reversing the condition. Surgical intervention is usually required if necrosis does develop.

Other skin reactions have also been reported with coumarins. Vasculitis affecting both legs developed in a 74-year-old woman a few weeks after starting treatment with acenocoumarol for deep-vein thrombosis and pulmonary embolism.[5] Acenocoumarol treatment was stopped and the skin lesions steadily improved over 15 days. However, the skin lesions reappeared a few hours after re-exposure to a single dose of acenocoumarol. The patient had also been taking amiodarone which may have contributed to the reaction. Henoch-Schönlein purpura was reported[6] in a 76-year-old woman 2 months after she started treatment with acenocoumarol; it resolved rapidly after the drug was withdrawn.

Increased shedding of telogen hair has been stated to occur in patients given coumarin anticoagulants.[7]

1. Cole MS, *et al*. Coumarin necrosis—a review of the literature. *Surgery* 1988; **103:** 271–7.
2. Comp PC. Coumarin-induced skin necrosis: incidence, mechanisms, management and avoidance. *Drug Safety* 1993; **8:** 128–35.
3. Chan YC, *et al*. Warfarin induced skin necrosis. *Br J Surg* 2000; **87:** 266–72.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Warfarin-induced skin necrosis. *Aust Adverse Drug React Bull* 2005; **24:** 23. Also available at: http://www.tga.gov.au/pdf/aadrb-0512.pdf (accessed 21/10/11)
5. Susano R, *et al*. Hypersensitivity vasculitis related to nicoumalone. *BMJ* 1993; **306:** 973.
6. Borrás-Blasco J, *et al*. Acenocoumarol-induced Henoch-Schönlein purpura. *Ann Pharmacother* 2004; **38:** 261–4.
7. Smith AG. Drug-induced disorders of hair and nails. *Adverse Drug React Bull* 1995 (173); 655–8.

Treatment of Adverse Effects

The methods used to manage bleeding and/or excessive anticoagulation during warfarin therapy, or after warfarin overdosage, depend upon the degree of bleeding, the value of the international normalised ratio (INR), and the degree of thromboembolic risk.

For patients **over-anticoagulated** on warfarin, the *British Society for Haematology* recommends the following:

- in non-bleeding patients with an INR over 5.0, withhold 1 or 2 doses of warfarin and reduce the maintenance dose
  - oral phytomenadione (vitamin K_1) may be considered if the INR is 5.0 to 8.0 and the patient is thought to be at high risk of bleeding
  - if the INR is over 8.0, give an oral dose of phytomenadione 1 to 5 mg
- in non-major bleeding, withhold or reduce the dose of warfarin and give intravenous phytomenadione 1 to 3 mg; tranexamic acid mouthwash may be useful for bleeding in the oral cavity
- in major bleeding, give a prothrombin complex concentrate infusion containing factors II, VII, IX, and X, at a dose of 25 to 50 units/kg, and intravenous phytomenadione 5 mg; fresh frozen plasma 15 to 30 mL/kg may be used if no concentrate is available but it will be less effective. Higher doses of phytomenadione have been used (see Over-anticoagulation, p. 2123.1); however phytomenadione takes several hours to act and large doses may reduce the response to resumed therapy with anticoagulants for a week or more.

US guidelines from the *American College of Chest Physicians* are as follows:

- if the INR is no more than 0.5 above the therapeutic range in a patient with previously stable therapeutic INRs, continue the current warfarin dose and test the INR within 1 to 2 weeks
- in non-bleeding patients, measures include withholding and adjusting the dose of warfarin; oral phytomenadione may be given when the INR is over 10.0
- in major bleeding, give a prothrombin complex concentrate and phytomenadione 5 to 10 mg by slow intravenous injection.

If bleeding occurs unexpectedly at therapeutic INR values, the possibility of an underlying cause such as renal or alimentary tract disease should be investigated.

See under Effects on the Skin and Hair, above, for the management of skin and soft tissue necrosis.

For **poisoning** in individuals not taking anticoagulant therapy, the *UK National Poisons Information Service* recommends that those who have ingested more than 250 micrograms/kg of warfarin or who have an INR greater than 4.0, should be given phytomenadione 10 to 20 mg orally. Infusion of prothrombin complex concentrate 30 to 50 units/kg should be given if there is active bleeding, and the dose of phytomenadione may be given by slow intravenous injection. Fresh frozen plasma 15 mL/kg may be used if concentrate is not available.

References.

1. Makris M, *et al*. Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. *J Thromb Thrombolysis* 2010; **29:** 171–81.
2. Goodnough LT, Shander A. How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage. *Blood* 2011; **117:** 6091–9.
3. Keeling D, *et al*. British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin -fourth edition. *Br J Haematol* 2011; **154:** 311–24. Correction. *ibid.*; **156:** 150–2. Also available at: http://www.bcshguidelines.com/documents/warfarin_4th_ed.pdf (accessed 27/02/12)
4. Holbrook A, *et al*. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 suppl): e152S–84S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112295.pdf (accessed 11/09/12)

Precautions

Warfarin should not be given to patients who are haemorrhaging. In general it should not be given to patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, peptic ulcer disease, severe wounds (including surgical wounds), cerebrovascular disorders, and bacterial endocarditis. Caution is also advised in patients with hepatic or renal impairment, and in those with uncontrolled hypertension. Consideration should be given to stopping warfarin a few days before an invasive procedure and using an alternative form of antithrombotic therapy. Pregnancy is generally considered to be a contra-indication, especially in the first trimester and during the late stages of pregnancy (see Adverse Effects, p. 1528.2). Warfarin should not be given to patients with heparin-induced thrombocytopenia until the platelet count has recovered.

Many factors may affect anticoagulant control with warfarin. These include vitamin K status, thyroid status, renal function, bioavailability differences between warfarin preparations, factors affecting absorption of warfarin, genetic variation in warfarin metabolism (see below), and drug interactions. Such factors may be responsible for apparent resistance to warfarin and a few patients have displayed hereditary resistance. Dosage alterations should be guided by regular monitoring of oral anticoagulant therapy and clinical status. Patients should carry anticoagulant treatment booklets.

A discussion of factors affecting the anticoagulant effect of warfarin sodium.[1]

1. Shetty HGM, *et al*. Clinical pharmacokinetic considerations in the control of oral anticoagulant therapy. *Clin Pharmacokinet* 1989; **16:** 238–53.

Breast feeding. Drug concentrations were measured[1] in the plasma and milk of 13 women given 2 to 12 mg of warfarin daily. Plasma concentrations varied from 1.6 to 8.5 micromoles/litre but were below the limit of detection of 0.08 micromoles/litre in the breast milk or in the plasma of the 7 infants who were breast fed. No anticoagulant effect was found in the 3 breast-fed infants tested. In another report[2] of 2 women (dose of warfarin not specified), no evidence of the drug was found in the milk of one mother, and no anticoagulant effect was found in either infant. Last available guidance from the American Academy of Pediatrics considered[3] that warfarin is therefore usually compatible with breast feeding.

1. Orme ML'E, *et al*. May mothers given warfarin breast-feed their infants? *BMJ* 1977; **1:** 1564–5.
2. McKenna R, *et al*. Is warfarin sodium contraindicated in the lactating mother? *J Pediatr* 1983; **103:** 325–7.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Genetic variation. The response to warfarin and dosing requirements vary widely between individuals and between different racial groups.[1,2] Factors involved include age, indication for anticoagulation, diet, and use of interacting drugs, but much of the variability appears to be related to genetic polymorphism.[3] Two genes appear to be particularly important: the gene for the cytochrome P450 isoenzyme CYP2C9, the major enzyme involved in warfarin metabolism; and the gene for vitamin K epoxide reductase (VKOR), which is involved in the synthesis of clotting factors and is the major target for warfarin and other coumarin anticoagulants.[4,5] Although polymorphisms in either gene may affect dose requirements, patients with variant alleles for both genes appear to be particularly sensitive to warfarin;[6] initial variability in response may be more strongly associated with VKOR.[7] Identification of affected patients by genetic testing may be used to guide initial warfarin dosage, and dosage algorithms have been suggested, although they require validation.[8-13] Similar effects have also been noted with other coumarins, including acenocoumarol[14,15] and phenprocoumon.[15,16]

1. Dang M-TN, *et al*. The influence of ethnicity on warfarin dosage requirement. *Ann Pharmacother* 2005; **39:** 1008–12.
2. Lam MPS, Cheung BMY. The pharmacogenetics of the response to warfarin in Chinese. *Br J Clin Pharmacol* 2012; **73:** 340–7.
3. Kamali F, Wynne H. Pharmacogenetics of warfarin. *Annu Rev Med* 2010; **61:** 63–75.
4. Schwarz UI, Stein CM. Genetic determinants of dose and clinical outcomes in patients receiving oral anticoagulants. *Clin Pharmacol Ther* 2006; **80:** 7–12.
5. Takeuchi F, *et al*. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS Genet* 2009; **5:** e1000433.
6. Aquilante CL, *et al*. Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. *Clin Pharmacol Ther* 2006; **79:** 291–302.
7. Schwarz UI, *et al*. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008; **358:** 999–1008.
8. Stehle S, *et al*. Pharmacogenetics of oral anticoagulants: a basis for dose individualization. *Clin Pharmacokinet* 2008; **47:** 565–94.
9. Wadelius M, *et al*. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009; **113:** 784–92.
10. Klein TE, *et al*. International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; **360:** 753–64. Correction. *ibid.*; **361:** 1613.
11. Lenzini P, *et al*. Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther* 2010; **87:** 572–8.
12. Johnson JA, *et al*. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther* 2011; **90:** 625–9.
13. Avery PJ, *et al*. EU-PACT Study Group. A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. *Clin Pharmacol Ther* 2011; **90:** 701–6.
14. Schalekamp T, *et al*. VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. *Clin Pharmacol Ther* 2006; **80:** 13–22.
15. Cadamuro J, *et al*. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. *Eur J Clin Pharmacol* 2010; **66:** 253–60.
16. Schalekamp T, *et al*. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. *Clin Pharmacol Ther* 2007; **81:** 185–93.

Macular degeneration. Intra-ocular haemorrhage leading to loss of vision has been reported[1,2] in patients with neovascular (wet) age-related macular degeneration receiving warfarin, and caution has been advised[3] in such patients.

1. Tilanus MAD, *et al*. Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2000; **238:** 482–5.
2. Ung T, *et al*. Long term warfarin associated with bilateral blindness in a patient with atrial fibrillation and macular degeneration. *Heart* 2003; **89:** 985.
3. Kowal LM, Harper CA. Visual complications of warfarin. *Med J Aust* 2002; **176:** 351.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies warfarin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Spinal anaesthesia. Spinal haematomas have occurred after spinal or epidural anaesthesia or analgesia in patients taking warfarin. The optimum perioperative management of warfarinised patients receiving central nerve blocks remains controversial, but US guidelines[1] make the following recommendations:

- warfarin should be stopped ideally 4 to 5 days before the procedure to normalise the INR before giving a central nerve block. Other medicines that increase the risk of bleeding should not be given concurrently
- if warfarin is restarted postoperatively, indwelling catheters are most safely removed while the INR is below 1.5
- if the INR is between 1.5 and 3, catheter removal should be done with caution
- if the INR is greater than 3, the warfarin dose should be withheld or reduced in patients with indwelling catheters. The safety of removing a catheter at this level of INR is uncertain

1. Horlocker TT, *et al*. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35:** 64–101.

Interactions

Many compounds interact with warfarin and its related oral anticoagulants. Details of their drug interactions are given below; if the anticoagulant is other than warfarin, then its identity is specified. The major interactions are summarised in Table 7, p. 1530.1. Interactions of a pharmacodynamic nature occurring with one anticoagulant may well apply to

another but this may not be the case with pharmacokinetic interactions. Many food and herbal preparations also have the potential to interact with oral anticoagulants; some are discussed below.

An interaction may be due to increased or decreased anticoagulant metabolism; with warfarin some interacting drugs such as cimetidine, co-trimoxazole, or phenylbutazone have a selective effect on its stereo-isomers. Altered absorption may sometimes play a part, as with colestyramine. Displacement of oral anticoagulants from plasma protein binding sites has been reported with many drugs, including some analgesics. Not all reports that have recorded an alteration in the pharmacokinetics of the anticoagulant have, however, shown a corresponding change in clinical response.

Interference with the coagulation process may be responsible for the increased risk of haemorrhage when aspirin, clofibrate, or thyroid hormones are used with anticoagulants. Many other compounds, such as asparaginase, some contrast media, epoprostenol, streptokinase, and urokinase also carry this risk; while interactions between these compounds and anticoagulants are not discussed further below, the possibility of an increased risk of haemorrhage should be considered when they are used together.

Table 7. Summary of major interactions of warfarin and its related oral anticoagulants.

Drugs generally recognised as diminishing the effects of oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

acetomenaphthone	dichloralphenazone
alcohol (chronic ingestion without liver impairment)	ethchlorvynol
aminoglutethimide	griseofulvin
barbiturates	nafcillin
bosentan	phytomenadione
carbamazepine	rifampicin
	St John's wort

Drugs recognised or generally reported as enhancing oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

alcohol (acute ingestion or chronic ingestion with liver impairment)	ethylestrenol
	fluconazole
	glucagon
allopurinol	itraconazole
amiodarone	ketoconazole
aspirin	metronidazole
cefamandole	miconazole
chloramphenicol	norethandrolone
cimetidine	NSAIDs
clofibrate	oxymetholone
cloral hydrate	quinidine
co-trimoxazole	stanozolol
danazol	sulfinpyrazone
dextropropoxyphene	tamoxifen
dextrothyroxine	telithromycin
dipyridamole	thyroid agents
disulfiram	tramadol
erythromycin	triclofos sodium
etacrynic acid	

Where there is a risk of serious haemorrhage from an interaction, then use of both drugs is best avoided. In other instances the anticoagulant activity should be carefully monitored so as to increase or decrease the anticoagulant dose as required. Critical periods are when patients stabilised on an anticoagulant start treatment with an interacting drug, or when patients stabilised on a regimen of an interacting drug and anticoagulant have the interacting drug withdrawn. Depending on the mechanism of the interaction, the clinical response to the interaction may be rapid or may take some days. Interactions involving displacement from plasma protein binding sites are often transient. Some interacting drugs do not produce predictable effects; there have for instance been reports of increased as well as decreased anticoagulant activity with disopyramide, phenytoin, quinidine, and oral contraceptives. Another problem occurs with dipyridamole; it can cause bleeding when given to patients taking anticoagulants but without any alteration in prothrombin times.

Reviews.

1. Harder S, Thürmann P. Clinically important drug interactions with anticoagulants: an update. *Clin Pharmacokinet* 1996; **30:** 416–44.
2. Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. *J Clin Pharmacol* 2005; **45:** 127–32.

Alcohol. Alcohol has a variable effect on warfarin. Heavy regular drinkers may have a diminished effect, perhaps through enzyme induction, although the effect of warfarin may be increased in the presence of liver impairment; acute ingestion has enhanced the effect of warfarin. A moderate alcohol intake is generally not considered to cause problems.

Analgesics and NSAIDs. All NSAIDs should be used with caution or not at all in patients on warfarin. Many NSAIDs inhibit platelet function to some extent and have an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage. Furthermore, some NSAIDs increase the hypoprothrombinaemic effect of warfarin, possibly by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein-binding sites. Many studies have compared the relative displacing action of a range of NSAIDs *in vitro*, but such studies cannot easily be extrapolated to the clinical situation. Changes in plasma concentration of unbound warfarin resulting from displacement from plasma protein-binding sites are usually transient and are most likely to occur in the first few weeks after an NSAID is added to or withdrawn from warfarin therapy; monitoring of anticoagulant therapy is, therefore, most critical during this period.

High doses of *aspirin* and some other *salicylates* enhance the hypoprothrombinaemic effect of warfarin and should generally be avoided in patients on oral anticoagulant therapy. Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. The possibility of an interaction with topical salicylates should also be considered.[1,2]

Use of *phenylbutazone* with warfarin has led to serious haemorrhage and should be avoided. Phenylbutazone affects the metabolism of the *R*- and *S*- isomers of warfarin in complex and different ways with the net effect of enhancing its anticoagulant activity.[3] Related drugs such as *oxyphenbutazone*, *azapropazone*,[4-6] and *feprazone*[7] behave similarly and should also be avoided.

For the following NSAIDs there are a few studies or isolated reports suggesting that they may enhance the hypoprothrombinaemic effect of warfarin or other specified oral anticoagulant: *diflunisal* (with acenocoumarol[8] or warfarin[9]), *flurbiprofen* (with acenocoumarol),[10] *indometacin*,[11,12] *ketoprofen*,[13] *meclofenamate sodium*,[14] *mefenamic acid*,[15] *piroxicam*, (with warfarin[16] or acenocoumarol[17]), *sulindac*,[18,19] *tiaprofenic acid* (with acenocoumarol),[20] and *tolmetin sodium*.[21] In many cases the result of concomitant therapy was an increased prothrombin time which may or may not be clinically significant; in other cases haemorrhage occurred. It should also be noted that for many of the above NSAIDs, perhaps particularly indometacin, there are studies (not cited) in which no enhancement of warfarin activity was found. NSAIDs with an apparently minimal effect on warfarin activity include *etodolac*, *ibuprofen*, and *naproxen*.

Interactions have also been reported with NSAIDs that are selective inhibitors of cyclo-oxygenase-2. As with other NSAIDs, some studies (not cited) have shown a lack of interaction between warfarin and *celecoxib*, but there have been several reports[22-25] of an increase in the INR with concomitant therapy and bleeding has occurred in some patients.[24] Increases in INR were also reported in studies[25,26] of warfarin with *rofecoxib*; and there were reports of bleeding.[27] A small increase in INR was also reported[28] with *etoricoxib* in healthy subjects but was thought unlikely to be of clinical significance in most patients.

In view of the above considerations, *paracetamol* is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon)[29-31] and isolated reports[32,33] have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported[34,35] in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol regularly.

Opioid analgesics do not generally cause problems. However, there have been reports of enhanced anticoagulant activity in patients given *tramadol* with warfarin[36,37] including 2 deaths from haemorrhagic stroke,[37] and also with phenprocoumon,[38] although a randomised, double-blind, placebo-controlled study[39] in 19 patients failed to find evidence of an interaction between phenprocoumon and tramadol. *Co-proxamol*, a combination of *dextropropoxyphene* and paracetamol, has increased the effect of warfarin.[40-42] *Co-codamol*, a combination of *codeine* and paracetamol, has also enhanced warfarin activity.[43]

Amongst other analgesics, *glafenine* has been reported to possibly enhance the activity of phenprocoumon.[44] *Phenazone*, an inducer of enzyme metabolism, reduces plasma concentrations of warfarin and, in contrast with most other analgesics, may necessitate an increase in warfarin dosage.[45]

1. Chow WH, *et al*. Potentiation of warfarin anticoagulation by topical methylsalicylate ointment. *J R Soc Med* 1989; **82:** 501–2.
2. Littleton F. Warfarin and topical salicylates. *JAMA* 1990; **263:** 2888.
3. Banfield C, *et al*. Phenylbutazone-warfarin interaction in man: further stereochemical and metabolic considerations. *Br J Clin Pharmacol* 1983; **16:** 669–75.
4. Powell-Jackson PR. Interaction between azapropazone and warfarin. *BMJ* 1977; **1:** 1193–4.
5. Green AE, *et al*. Potentiation of warfarin by azapropazone. *BMJ* 1977; **1:** 1532.
6. Win N, Mitchell DC. Azapropazone and warfarin. *BMJ* 1991; **302:** 969–70.
7. Chierichetti S, *et al*. Comparison of feprazone and phenylbutazone interaction with warfarin in man. *Curr Ther Res* 1975; **18:** 568–72.
8. Tempero KF, *et al*. Diflunisal: a review of pharmacokinetic and pharmacodynamic properties, drug interactions, and special tolerability studies in humans. *Br J Clin Pharmacol* 1977; **4** (suppl 1): 31S–36S.
9. Serlin MJ, *et al*. The effect of diflunisal on the steady state pharmacodynamics and pharmacokinetics of warfarin. *Br J Clin Pharmacol* 1980; **9:** 287P–8P.
10. Stricker BHC, Delhez JL. Interaction between flurbiprofen and coumarins. *BMJ* 1982; **285:** 812–13.
11. Koch-Weser J. Hemorrhagic reactions and drug interactions in 500 warfarin-treated patients. *Clin Pharmacol Ther* 1973; **14:** 139.
12. Self TH, *et al*. Drug enhancement of warfarin activity. *Lancet* 1975; **ii:** 557–8.
13. Flessner MF. Prolongation of prothrombin time and severe gastrointestinal bleeding associated with combined use of warfarin and ketoprofen. *JAMA* 1988; **259:** 353.
14. Baragar FD, Smith TC. Drug interaction studies with sodium meclofenamate (Meclomen). *Curr Ther Res* 1978; **23** (suppl 4): S51–S59.
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16. Rhodes RS, *et al*. A warfarin-piroxicam drug interaction. *Drug Intell Clin Pharm* 1985; **19:** 556–8.
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37. Adverse Drug Reactions Advisory Committee (ADRAC). Tramadol-warfarin interaction. *Aust Adverse Drug React Bull* 2004; **23:** 16. Also available at: http://www.tga.gov.au/pdf/aadrb-0408.pdf (accessed 21/10/11)
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Antiarrhythmics. *Amiodarone* has been shown in several studies to increase the activity of warfarin[1-7] and aceno-

coumarol,[8,9] probably through inhibition of metabolism. The potentiating effect of amiodarone has been reported to persist for up to 4 months after its withdrawal.[1] Phenprocoumon has been reported to be either unaffected[10] or potentiated[11] by amiodarone. Isolated reports with *disopyramide*[12] and *quinidine*[13] have suggested that these drugs can enhance the anticoagulant effect of warfarin. In 7 patients on warfarin or dicoumarol treated with disopyramide or quinidine, however, all but one needed a small increase in the weekly anticoagulant dose suggesting that the antiarrhythmic had reduced the anticoagulant effect.[14] Since the effect was seen after conversion of atrial fibrillation to sinus rhythm an involvement of haemodynamic factors was postulated. Several studies (not cited) have failed to show an effect of quinidine on warfarin. There are also reports indicating that *dronedarone*,[15] *propafenone*,[16] and *moracizine*[17] can enhance warfarin.

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2. Almog S, *et al*. Mechanism of warfarin potentiation by amiodarone: dose—and concentration—dependent inhibition of warfarin elimination. *Eur J Clin Pharmacol* 1985; **28:** 257–61.
3. Watt AH, *et al*. Amiodarone reduces plasma warfarin clearance in man. *Br J Clin Pharmacol* 1985; **20:** 707–9.
4. O'Reilly RA, *et al*. Interaction of amiodarone with racemic warfarin and its separated enantiomorphs in humans. *Clin Pharmacol Ther* 1987; **42:** 290–4.
5. Kerin NZ, *et al*. The incidence, magnitude, and time course of the amiodarone-warfarin interaction. *Arch Intern Med* 1988; **148:** 1779–81.
6. Lu Y, *et al*. Characteristics of the amiodarone–warfarin interaction during long-term follow-up. *Am J Health-Syst Pharm* 2008; **65:** 947–52.
7. Edwin SB, *et al*. An evaluation of the early pharmacodynamic response after simultaneous initiation of warfarin and amiodarone. *J Clin Pharmacol* 2010; **50:** 693–8.
8. Arboix M, *et al*. The potentiation of acenocoumarol anticoagulant effect by amiodarone. *Br J Clin Pharmacol* 1984; **18:** 355–60.
9. Richard C, *et al*. Prospective study of the potentiation of acenocoumarol by amiodarone. *Eur J Clin Pharmacol* 1985; **28:** 625–9.
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14. Sylvén C, Anderson P. Evidence that disopyramide does not interact with warfarin. *BMJ* 1983; **286:** 1181.
15. Pogge EK, Haber SL. Elevated international normalized ratio associated with use of dronedarone and warfarin. *Ann Pharmacother* 2011; **45:** e46.
16. Kates RE, *et al*. Interaction between warfarin and propafenone in healthy volunteer subjects. *Clin Pharmacol Ther* 1987; **42:** 305–11.
17. Serpa MD, *et al*. Moricizine—warfarin: a possible drug interaction. *Ann Pharmacother* 1992; **26:** 127.

Antibacterials. Several antibacterials have been involved in interactions with warfarin. Only a few reports are of serious effects and it is unlikely that any of the drugs need to be contra-indicated with warfarin; careful control should suffice.

Most of the drugs enhance the effects of warfarin. Apart from possible effects on the metabolism or plasma-protein binding of warfarin, some antibacterials may interfere with platelet function or with the bacterial synthesis of vitamin K in the gastrointestinal tract and thus have an anticoagulant effect of their own. This is generally considered unlikely to be of clinical significance except, perhaps, in patients with an inadequate vitamin K intake. Fever itself may increase the catabolism of clotting factors and exaggerate a potential antibacterial-warfarin interaction.

There are many reports of an enhanced warfarin response with *co-trimoxazole* and a significant association with increased bleeding has been confirmed;[1] stereospecific inhibition of warfarin metabolism is probably responsible.[2] The interaction is generally attributed to the *sulfamethoxazole* moiety and there are isolated reports suggesting that the activity of warfarin (or other specified oral anticoagulant) may be enhanced by other sulfonamides including *sulfafurazole*,[3] *sulfamethizole*,[4] and *sulfaphenazole* (with phenindione).[5]

There are several reports of potentiation of the effects of warfarin by *erythromycin* or its salts; inhibition of warfarin metabolism probably occurs. Although no clinically-significant increase in prothrombin time was found in 8 non-infected patients, the potential for an interaction was recognised.[6] An enhanced response to warfarin has also been reported with *azithromycin*,[7,8] with *roxithromycin*,[9] which included reports of spontaneous bleeding, and with *telithromycin*,[10,11] including a case of mild haemoptysis.[10] *Clarithromycin* may potentiate the effect of acenocoumarol[12] and of warfarin,[13] although other factors may also have been involved in this case.

Cefamandole has been reported to enhance the hypoprothrombinaemic response to warfarin.[14,15] Interference with vitamin K synthesis in the gastrointestinal tract and/or liver has been implicated. Related cephalosporins with an *N*-methylthiotetrazole side-chain such as *cefmetazole*, *cefmenoxime*, *cefoperazone*, and *latamoxef* may be expected to behave similarly although there appear to be no reports of an interaction. *Cefazolin*, which has a similar side-chain, may also enhance the effect of warfarin to some extent.[15] An elevated INR in a patient taking warfarin occurred on 2 separate occasions after the use of *ceftriaxone*.[16]

There have been reports of increased activity of warfarin (or other specified oral anticoagulant) by quinolone antibacterials including *nalidixic acid* (with warfarin[17,18] or acenocoumarol[19]), *ciprofloxacin*,[20-22] *gatifloxacin*,[22,23] *levofloxacin*,[22,24] *moxifloxacin*,[22,25] *norfloxacin*,[22,26] and *ofloxacin*,[27,28] although for some of these there are also studies indicating no effect (not cited). *Enoxacin* has been reported to decrease the clearance of *R*-warfarin but not *S*-warfarin; no prolongation of prothrombin time occurred.[29]

There are isolated reports suggesting an enhanced effect of warfarin (or other specified oral anticoagulant) with *aminosalicylic acid*,[30] *benzylpenicillin*,[31] *chloramphenicol* (with dicoumarol),[32] *doxycycline*,[33] *isoniazid*,[34] and *neomycin*.[35] Prothrombin times might be prolonged by broad-spectrum antibacterials such as *ampicillin*. There has been a report[36] of an increased INR and haematuria in a patient taking warfarin with *amoxicillin* and clavulanic acid, however, a randomised study[37] in 12 patients found no interaction between warfarin and amoxicillin with clavulanic acid. Warnings in licensed product information of potentiation of warfarin by *aztreonam*, *trimethoprim*, and *tetracyclines* other than doxycycline appear to have only a theoretical basis. The effect of *metronidazole* is discussed under Antiprotozoals, p. 1532.3.

Rifampicin diminishes the effect of warfarin by induction of metabolising enzymes in the liver. There are several reports of a similar effect with *nafcillin*[38-40] and with *dicloxacillin sodium*.[41,42]

When used for the treatment of traveller's diarrhoea, *rifaximin* is not expected to interact with warfarin because of its poor systemic bioavailability. However, a case of reduced effect of warfarin has been attributed to rifaximin used for the treatment of small bowel bacterial overgrowth. It was suggested that increased intestinal permeability, with the longer course and higher dose of rifaximin, enabled sufficient absorption of the antibacterial to result in liver enzyme induction.[43]

1. Fischer HD, *et al*. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. *Arch Intern Med* 2010; **170:** 617–21.
2. O'Reilly RA. Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. *N Engl J Med* 1980; **302** 33–5.
3. Sioris LJ, *et al*. Potentiation of warfarin anticoagulation by sulfisoxazole. *Arch Intern Med* 1980; **140:** 546–7.
4. Lumholtz B, *et al*. Sulfamethizole-induced inhibition of diphenylhydantoin, tolbutamide, and warfarin metabolism. *Clin Pharmacol Ther* 1975; **17:** 731–4.
5. Varma DR, *et al*. Prothrombin response to phenindione during hypoalbuminaemia. *Br J Clin Pharmacol* 1975; **2:** 467–8.
6. Weibert RT, *et al*. Effect of erythromycin in patients receiving long-term warfarin therapy. *Clin Pharm* 1989; **8:** 210–14.
7. Lane G. Increased hypoprothrombinemic effect of warfarin possibly induced by azithromycin. *Ann Pharmacother* 1996; **30:** 884–5.
8. Woldtvedt BR, *et al*. Possible increased anticoagulation effect of warfarin induced by azithromycin. *Ann Pharmacother* 1998; **32:** 269–70.
9. Anonymous. Interaction of warfarin with macrolide antibiotics. *Aust Adverse Drug React Bull* 1995; **14:** 11. Also available at: http://www.tga.gov.au/hp/aadrb-9508.htm (accessed 21/10/11)
10. Kolilekas L, *et al*. Potential interaction between telithromycin and warfarin. *Ann Pharmacother* 2004; **38:** 1424–7.
11. Health Canada. Telithromycin (Ketek) and warfarin: suspected interaction. *Can Adverse React News* 2005; **15** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n1-eng.pdf (accessed 21/10/11)
12. Grau E, *et al*. Interaction between clarithromycin and oral anticoagulants. *Ann Pharmacother* 1996; **30:** 1495–6.
13. Recker MW, Kier KL. Potential interaction between clarithromycin and warfarin. *Ann Pharmacother* 1997; **31:** 996–8.
14. Angaran DM, *et al*. The influence of prophylactic antibiotics on the warfarin anticoagulation response in the postoperative prosthetic cardiac valve patient. *Ann Surg* 1984; **199:** 107–11.
15. Angaran DM, *et al*. The comparative influence of prophylactic antibiotics on the prothrombin response to warfarin in the postoperative prosthetic cardiac valve patient: cefamandole, cefazoline, vancomycin. *Ann Surg* 1987; **206:** 155–61.
16. Clark TR, Burns S. Elevated international normalized ratio values associated with concomitant use of warfarin and ceftriaxone. *Am J Health-Syst Pharm* 2011; **68:** 1603–5.
17. Hoffbrand BI. Interaction of nalidixic acid and warfarin. *BMJ* 1974; **2:** 666.
18. Leor J, *et al*. Interaction between nalidixic acid and warfarin. *Ann Intern Med* 1987; **107:** 601.
19. Potasman I, Bassan H. Nicoumalone and nalidixic acid interaction. *Ann Intern Med* 1980; **92:** 571.
20. Mott FE, *et al*. Ciprofloxacin and warfarin. *Ann Intern Med* 1989; **111:** 542–3.
21. Kamada AK. Possible interaction between ciprofloxacin and warfarin. *DICP Ann Pharmacother* 1990; **24:** 27–8.
22. Health Canada. Fluoroquinolones and warfarin: suspected interaction. *Can Adverse React News* 2004; **14** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n3-eng.pdf (accessed 21/10/11)
23. Chock AWY, Stading JA. Indeterminable international normalized ratio with concurrent use of warfarin and gatifloxacin. *Am J Health-Syst Pharm* 2006; **63:** 1539–42.
24. Jones CB, Fugate SE. Levofloxacin and warfarin interaction. *Ann Pharmacother* 2002; **36:** 1554–7.
25. Elbe DHT, Chang SW. Moxifloxacin-warfarin interaction: a series of five case reports. *Ann Pharmacother* 2005; **39:** 361–4.
26. Linville T, Matanin D. Norfloxacin and warfarin. *Ann Intern Med* 1989; **110:** 751–2.
27. Leor J, Matetzki S. Ofloxacin and warfarin. *Ann Intern Med* 1988; **109:** 761.
28. Baciewicz AM, *et al*. Interaction of ofloxacin and warfarin. *Ann Intern Med* 1993; **119:** 1223.
29. Toon S, *et al*. Enoxacin-warfarin interaction: pharmacokinetic and stereochemical aspects. *Clin Pharmacol Ther* 1987; **42:** 33–41.
30. Self TH. Interaction of warfarin and aminosalicylic acid. *JAMA* 1973; **223:** 1285.
31. Brown MA, *et al*. Interaction of penicillin-G and warfarin? *Can J Hosp Pharm* 1979; **32:** 18–19.
32. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
33. Westfall LK, *et al*. Potentiation of warfarin by tetracycline. *Am J Hosp Pharm* 1980; **37:** 1620 and 1625.
34. Rosenthal AR, *et al*. Interaction of isoniazid and warfarin. *JAMA* 1977; **238:** 2177.
35. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; **77** (Aug.): 20–5.
36. Davydov L, *et al*. Warfarin and amoxicillin/clavulanate drug interaction. *Ann Pharmacother* 2003; **37:** 367–70.
37. Zhang Q, *et al*. Amoxicillin/clavulanic acid-warfarin drug interaction: a randomized controlled trial. *Br J Clin Pharmacol* 2011; **71:** 232–6.
38. Qureshi GD, *et al*. Warfarin resistance with nafcillin therapy. *Ann Intern Med* 1984; **100:** 527–9.
39. Fraser GL, *et al*. Warfarin resistance associated with nafcillin therapy. *Am J Med* 1989; **87:** 237–8.
40. Davis RL, *et al*. Warfarin-nafcillin interaction. *J Pediatr* 1991; **118:** 300–3.
41. Krstenansky PM, *et al*. Effect of dicloxacillin sodium on the hypoprothrombinemic response to warfarin sodium. *Clin Pharm* 1987; **6:** 804–6.
42. Mailloux A, *et al*. Potential interaction between warfarin and dicloxacillin. *Ann Pharmacother* 1996; **30:** 1402–7.
43. Hoffman JT, *et al*. Probable interaction between warfarin and rifaximin in a patient treated for small intestine bacterial overgrowth. *Ann Pharmacother* 2011; **45:** e25.

Antidepressants. *Amitriptyline* and *nortriptyline* have been reported to prolong the half-life of dicoumarol in healthy subjects.[1,2] The few reports investigating the effect of tricyclic antidepressants on warfarin have not been able to conclude that a significant interaction exists. *Mianserin* and phenprocoumon have been reported not to interact.[3]

The *BNF* considers that there is a possible risk of increased coumarin activity with *SSRIs*; increased warfarin activity has been reported in a few patients taking *fluoxetine*[4] and in a patient taking *fluvoxamine*.[5] The SNRI *duloxetine* has also been reported[6] to increase warfarin activity, although a study in healthy subjects was unable to confirm this effect.[7] There have also been reports of increased anticoagulant activity in patients taking acenocoumarol and *citalopram*,[8] fluvoxamine, or *venlafaxine*.[9]

An increase in the dose of warfarin has been required by patients also taking *trazodone*.[10,11]

See also St John's Wort, p. 1535.2.

1. Vesell ES, *et al*. Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; **283:** 1484–8.
2. Pond SM, *et al*. Effects of tricyclic antidepressants on drug metabolism. *Clin Pharmacol Ther* 1975; **18:** 191–9.
3. Kopera H, *et al*. Phenprocoumon requirement, whole blood coagulation time, bleeding time and plasma γ-GT in patients receiving mianserin. *Eur J Clin Pharmacol* 1978; **13:** 351–6.
4. Woolfrey S, *et al*. Fluoxetine-warfarin interaction. *BMJ* 1993; **307:** 241.
5. Limke KK, *et al*. Fluvoxamine interaction with warfarin. *Ann Pharmacother* 2002; **36:** 1890–2.
6. Glueck CJ, *et al*. Interaction of duloxetine and warfarin causing severe elevation of international normalized ratio. *JAMA* 2006; **295:** 1517–18.
7. Chappell J, *et al*. Effects of duloxetine on the pharmacodynamics and pharmacokinetics of warfarin at steady state in healthy subjects. *J Clin Pharmacol* 2009; **49:** 1456–66.
8. Borrás-Blasco J, *et al*. Probable interaction between citalopram and acenocoumarol. *Ann Pharmacother* 2002; **36:** 345.
9. Teichert M, *et al*. Selective serotonin re-uptake inhibiting antidepressants and the risk of overanticoagulation during acenocoumarol maintenance treatment. *Br J Clin Pharmacol* 2011; **72:** 798–805.
10. Hardy J-L, Sirois A. Reduction of prothrombin and partial thromboplastin times with trazodone. *Can Med Assoc J* 1986; **135:** 1372.
11. Small NL, Giamonna KA. Interaction between warfarin and trazodone. *Ann Pharmacother* 2000; **34:** 734–6.

Antidiabetics. There have been a few early instances of *tolbutamide* enhancing the activity of dicoumarol.[1] However, this effect has not been seen in later studies involving dicoumarol,[1-3] warfarin,[2] and phenprocoumon,[4] although one study did find altered dicoumarol pharmacokinetics.[3] An absence of effect has been documented for phenprocoumon and *insulin*, *glibenclamide*, or *glibornuride*,[4] but there is a report of glibenclamide enhancing the effect of warfarin.[5]

There has been an isolated report of bleeding in a patient taking *phenformin* and warfarin.[6] *Metformin* has been reported to diminish phenprocoumon activity.[7]

A study in healthy subjects found no pharmacokinetic interaction between *exenatide* and single-dose warfarin, and an insignificant reduction in INR.[8] However, licensed product information for exenatide warns that there have been reported cases of an increase in INR with this combination, sometimes associated with bleeding.

Coumarin anticoagulants may increase the hypoglycaemic effect of *sulfonylureas* (see p. 503.3).

An enhanced response to warfarin has been reported in a patient receiving *troglitazone*.[9]

1. Chaplin H, Cassell M. Studies on the possible relationship of tolbutamide to dicumarol in anticoagulant therapy. *Am J Med Sci* 1958; **235:** 706–16.
2. Poucher RL, Vecchio TJ. Absence of tolbutamide effect on anticoagulant therapy. *JAMA* 1966; **197:** 1069–70.
3. Jähnchen E, *et al*. Pharmacokinetic analysis of the interaction between dicoumarol and tolbutamide in man. *Eur J Clin Pharmacol* 1976; **10:** 349–56.
4. Heine P, *et al*. The influence of hypoglycaemic sulphonylureas on elimination and efficacy of phenprocoumon following a single oral dose in diabetic patients. *Eur J Clin Pharmacol* 1976; **10:** 31–6.
5. Jassal SV. *BMJ* 1991; **303:** 789.

6. Hamblin TJ. Interaction between warfarin and phenformin. *Lancet* 1971; **i:** 1323.
7. Ohnhaus EE, *et al*. The influence of dimethylbiguanide on phenprocoumon elimination and its mode of action: a drug interaction study. *Klin Wochenschr* 1983; **61:** 851–8.
8. Soon D, *et al*. Effect of exenatide on the pharmacokinetics and pharmacodynamics of warfarin in healthy Asian men. *J Clin Pharmacol* 2006; **46:** 1179–87.
9. Plowman BK, Morreale AP. Possible troglitazone—warfarin interaction. *Am J Health-Syst Pharm* 1998; **55:** 1071.

Antiepileptics. Barbiturates such as *phenobarbital* and *primidone* diminish the activity of warfarin and other coumarins through increased metabolism. *Carbamazepine* is reported to have a similar effect.[1,2] Reports of the effect of *phenytoin* on anticoagulants do not provide a clear picture. There are reports of phenytoin enhancing the effects of warfarin[3,4] and of acenocoumarol,[5] and a report of initial enhancement of warfarin followed by decreased anticoagulant action.[6] Phenytoin has been reported to diminish the effect of dicoumarol.[7] Addition of *felbamate* has been reported[8] to necessitate a reduction in warfarin dosage. In another patient there was a transient increase in response to warfarin when *valproic acid* was started.[9] Valproate also inhibits platelet function and caution is required with warfarin and other anticoagulants.

For the effect of oral anticoagulants on phenytoin, see p. 543.1.

1. Hansen JM, *et al*. Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12:** 539–43.
2. Ross JRY, Beeley L. Interaction between carbamazepine and warfarin. *BMJ* 1980; **280:** 1415–16.
3. Nappi JM. Warfarin and phenytoin interaction. *Ann Intern Med* 1979; **90:** 852.
4. Panegyres PK, Rischbieth RH. Fatal phenytoin warfarin interaction. *Postgrad Med J* 1991; **67:** 98.
5. Jose L, *et al*. Acenocoumarol and phenytoin toxicity in the presence of CYP2C9 mutation. *J Assoc Physicians India* 2008; **56:** 250–2.
6. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm* 1984; **3:** 200–3.
7. Hansen JM, *et al*. Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta Med Scand* 1971; **189:** 15–19.
8. Tisdel KA, *et al*. Warfarin—felbamate interaction: first report. *Ann Pharmacother* 1994; **28:** 805.
9. Guthrie SK, *et al*. Hypothesized interaction between valproic acid and warfarin. *J Clin Psychopharmacol* 1995; **15:** 138–9.

Antifungals. *Griseofulvin* has been reported to diminish the activity of warfarin.[1-3] There are several reports indicating that *miconazole*, given either systemically or topically as the oral gel, may enhance the activity of oral anticoagulants (warfarin, ethyl biscoumacetate, acenocoumarol, and phenindione).[4-11] Absorption of miconazole after intravaginal use may have enhanced the activity of acenocoumarol in 2 patients;[12] it enhanced the activity of warfarin[13] in another. Studies in healthy subjects given a single warfarin dose[14,15] support case reports[16-18] suggesting that *fluconazole* may increase the anticoagulant activity of warfarin. There are isolated reports of the potentiation of warfarin by *itraconazole*[19] and *ketoconazole*,[20] and of unspecified coumarins by topical *bifonazole* or *econazole*.[21] A case-control study[22] in a cohort of warfarin users over 65 years old showed an increased risk of bleeding associated with the use of azole antifungals.

There has been a case report of a reduction in the effect of warfarin by *terbinafine*,[23] although a study[24] in healthy subjects found no clinically significant interaction, and others[25] considered that no interaction usually occurs. A case of potentiation of warfarin by terbinafine has also been reported;[26] the authors speculate that concomitant cimetidine may have contributed to the interaction by increasing plasma-terbinafine concentrations.

1. Cullen SI, Catalano PM. Griseofulvin-warfarin antagonism. *JAMA* 1967; **199:** 582–3.
2. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; **77** (Aug.): 20–5.
3. Okino K, Weibert RT. Warfarin-griseofulvin interaction. *Drug Intell Clin Pharm* 1986; **20:** 291–3.
4. Loupi E, *et al*. Interactions médicamenteuses et miconazole: a propos de 10 observations. *Therapie* 1982; **37:** 437–41.
5. Watson PG, *et al*. Drug interaction with coumarin derivative anticoagulants. *BMJ* 1982; **285:** 1045–6.
6. Colquhoun MC, *et al*. Interaction between warfarin and miconazole oral gel. *Lancet* 1987; **i:** 695–6.
7. Bailey GM, *et al*. Miconazole and warfarin interaction. *Pharm J* 1989; **242:** 183.
8. Ariyaratnam S, *et al*. Potentiation of warfarin anticoagulant activity by miconazole oral gel. *BMJ* 1997; **314:** 349.
9. Evans J, *et al*. Treating oral candidiasis: potentially fatal. *Br Dent J* 1997; **182:** 452.
10. Pemberton MN, *et al*. Derangement of warfarin anticoagulation by miconazole oral gel. *Br Dent J* 1998; **184:** 68–9.
11. Ortín M, *et al*. Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; **33:** 175–7.
12. Lansdorp D, *et al*. Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; **47:** 225–6.
13. Thirion DJG, Farquhar Zanetti LA. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. *Pharmacotherapy* 2000; **20:** 98–9.
14. Lazar JD, Wilner KD. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12** (suppl 3): S327–S333.
15. Black DJ, *et al*. Warfarin–fluconazole II: a metabolically based drug interaction: in vivo studies. *Drug Metab Dispos* 1996; **24:** 422–8.
16. Seaton TL, *et al*. Possible potentiation of warfarin by fluconazole. *DICP Ann Pharmacother* 1990; **24:** 1177–8.
17. Gericke KR. Possible interaction between warfarin and fluconazole. *Pharmacotherapy* 1993; **13:** 508–9.
18. Baciewicz AM, *et al*. Fluconazole—warfarin interaction. *Ann Pharmacother* 1994; **28:** 1111.
19. Yeh J, *et al*. Potentiation of action of warfarin by itraconazole. *BMJ* 1990; **301:** 669.
20. Smith AG. Potentiation of oral anticoagulants by ketoconazole. *BMJ* 1984; **288:** 188–9. Correction. *ibid.*; 608.
21. Alexandra J-F, *et al*. Overanticoagulation with coumarin and cutaneous azole therapy. *Ann Intern Med* 2008; **148:** 633–5.
22. Baillargeon J, *et al*. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* 2012; **125:** 183–9.
23. Warwick JA, Corrall RJ. Serious interaction between warfarin and oral terbinafine. *BMJ* 1998; **316:** 440.
24. Guerret M, *et al*. Evaluation of effects of terbinafine on single oral dose pharmacokinetics and anticoagulant actions of warfarin in healthy volunteers. *Pharmacotherapy* 1997; **17:** 767–73.
25. Stockley IH. Terbinafine and warfarin mystery. *Pharm J* 1998; **260:** 408.
26. Gupta AK, Ross GS. Interaction between terbinafine and warfarin. *Dermatology* 1998; **196:** 266–7.

Antigout drugs. The drugs in this group most commonly implicated in interactions with anticoagulants are allopurinol and sulfinpyrazone.

With *allopurinol* there are conflicting reports of no interaction or an enhanced anticoagulant effect with dicoumarol,[1] phenprocoumon,[2] or warfarin.[3,4]

Interactions with *sulfinpyrazone* have usually involved warfarin and, apart from a case of a mixed response,[5] have involved increased anticoagulant activity, sometimes with haemorrhage, so calling for careful control. It is still not clear how sulfinpyrazone exerts its effect, but studies point to a stereoselective effect on warfarin metabolism where the *S*-isomer's metabolic clearance is inhibited;[6] sulfinpyrazone also affects platelets. Sulfinpyrazone has also enhanced the anticoagulant activity of acenocoumarol.[7] A significant interaction with phenprocoumon appears unlikely.[8]

Probenecid has accelerated the elimination of a single dose of phenprocoumon without effect on the prothrombin time.[9]

A study[10] of *benzbromarone* concluded that it enhanced the effect of warfarin by inhibition of the cytochrome P450 isoenzyme CYP2C9, leading to a stereoselective inhibition of the metabolism of warfarin.

1. Vesell ES, *et al*. Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; **283:** 1484–8.
2. Jähnchen E, *et al*. Interaction of allopurinol with phenprocoumon in man. *Klin Wochenschr* 1977; **55:** 759–61.
3. Rawlins MD, Smith SE. Influence of allopurinol on drug metabolism in man. *Br J Pharmacol* 1973; **48:** 693–8.
4. Pond SM, *et al*. The effects of allopurinol and clofibrate on the elimination of coumarin anticoagulants in man. *Aust N Z J Med* 1975; **5:** 324–8.
5. Nenci GG, *et al*. Biphasic sulphinpyrazone-warfarin interaction. *BMJ* 1981; **282:** 1361–2.
6. Toon S, *et al*. The warfarin-sulfinpyrazone interaction: stereochemical considerations. *Clin Pharmacol Ther* 1986; **39:** 15–24.
7. Michot F, *et al*. Über die Beeinflussung der gerinnungshemmenden Wirkung von Acenocoumarol durch Sulfinpyrazon. *Schweiz Med Wochenschr* 1981; **111:** 255–60.
8. Heimark LD, *et al*. The effect of sulfinpyrazone on the disposition of pseudoracemic phenprocoumon in humans. *Clin Pharmacol Ther* 1987; **42:** 312–19.
9. Mönig H, *et al*. The effects of frusemide and probenecid on the pharmacokinetics of phenprocoumon. *Eur J Clin Pharmacol* 1990; **39:** 261–5.
10. Takahashi H, *et al*. Potentiation of anticoagulant effect of warfarin caused by enantioselective metabolic inhibition by the uricosuric agent benzbromarone. *Clin Pharmacol Ther* 1999; **66:** 569–81.

Antihistamines. There has been a report[1] of a raised INR and severe epistaxis in a patient after the addition of *cetirizine* to long-term acenocoumarol.

1. Berod T, Mathiot I. Probable interaction between cetirizine and acenocoumarol. *Ann Pharmacother* 1997; **31:** 122.

Antimalarials. The ingestion of large amounts of tonic water by 2 patients necessitated a reduction in warfarin dosage. The enhanced effect was attributed to the *quinine* content of the tonic water.[1] A woman stabilised on warfarin developed haematuria and a high prothrombin ratio after taking *proguanil* for malaria prophylaxis.[2]

For an interaction with *atovaquone*, see Antiprotozoals, below.

1. Clark DJ. Clinical curio: warfarin and tonic water. *BMJ* 1983; **286:** 1258.
2. Armstrong G, *et al*. Warfarin potentiated by proguanil. *BMJ* 1991; **303:** 789.

Antimuscarinics. Cases of *tolterodine* enhancing the effect of warfarin have been reported.[1,2] In one,[1] it was stated that the manufacturers of tolterodine were aware of 6 reports of a possible interaction with warfarin. However, a study[3] in 20 healthy subjects found that tolterodine did not have a clinically significant effect on warfarin activity.

1. Colucci VJ, Rivey MP. Tolterodine–warfarin drug interaction. *Ann Pharmacother* 1999; **33:** 1173–6.
2. Taylor JR. Probable interaction between tolterodine and warfarin. *Pharmacotherapy* 2006; **26:** 719–21.
3. Rahimy M, *et al*. Effect of tolterodine on the anticoagulant actions and pharmacokinetics of single-dose warfarin in healthy volunteers. *Arzneimittelforschung* 2002; **52:** 890–5.

Antineoplastics. There have been several reports of interactions between warfarin and antineoplastics. No clear picture emerges from these reports which is not surprising considering that antineoplastics are often given in combination and that they can exert their own haematological effects. *Cyclophosphamide* for instance has been associated with an increase in warfarin's activity when given with *methotrexate* and *fluorouracil*,[1] but with a decrease when given with non-antineoplastic drugs.[2] Fluorouracil and its prodrug *capecitabine* have elevated the prothrombin time and INR of patients taking warfarin, causing bleeding in some.[3] Licensed product information for capecitabine states that altered coagulation parameters and bleeding have also occurred with phenprocoumon. An increase in the effect of warfarin has been reported when given with fluorouracil and levamisole (see Levamisole, p. 1534.2). There have been 2 cases reported[4] where *trastuzumab* enhanced the effect of warfarin. *Etoposide* with *vindesine*[5] or with *carboplatin*,[6] *cisplatin*,[7] *ifosfamide* with *mesna*,[8] and *tamoxifen*[9] have all produced an increased anticoagulant effect. *Aminoglutethimide* has led to decreased activity of warfarin or acenocoumarol,[10,11] probably due to increased coumarin metabolism. Licensed product information for the anti-androgen *flutamide* states that increases in prothrombin time have been reported after starting flutamide therapy in patients on long-term warfarin. *In vitro* data indicate a similar reaction is likely with *bicalutamide*. *Mercaptopurine*[12] and *mitotane*[13] have also decreased warfarin activity. Licensed product information for *vorinostat* states that prolongation of prothrombin time has been seen when the drug is given with coumarin derivatives. Isolated cases of elevated INR and bleeding events have been reported when *erlotinib*,[14] *gefitinib*,[15] and *sorafenib*[16] were used with warfarin.

1. Seifter EJ, *et al*. Possible interactions between warfarin and antineoplastic drugs. *Cancer Treat Rep* 1985; **69:** 244–5.
2. Tashima CK. Cyclophosphamide effect on coumarin anticoagulation. *South Med J* 1979; **72:** 633–4.
3. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. *Clin Colorectal Cancer* 2005; **5:** 175–80.
4. Nissenblatt MJ, Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment. *JAMA* 1999; **282:** 2299–2300.
5. Ward K, Bitran JD. Warfarin, etoposide, and vindesine interactions. *Cancer Treat Rep* 1984; **68:** 817–18.
6. Le AT, *et al*. Enhancement of warfarin response in a patient receiving etoposide and carboplatin chemotherapy. *Ann Pharmacother* 1997; **31:** 1006–8.
7. Yano R, *et al*. Transient elevation of international normalized ratio during cisplatin-based chemotherapy in patients who are taking warfarin. *Ann Pharmacother* 2011; **45:** e55.
8. Hall G, *et al*. Intravenous infusions of ifosfamide/mesna and perturbation of warfarin anticoagulant control. *Postgrad Med J* 1990; **66:** 860–1.
9. Givens CB, *et al*. Safety of concomitant tamoxifen and warfarin. *Ann Pharmacother* 2009; **43:** 1867–71.
10. Lønning PE, *et al*. The influence of a graded dose schedule of aminoglutethimide on the disposition of the optical enantiomers of warfarin in patients with breast cancer. *Cancer Chemother Pharmacol* 1986; **17:** 177–81.
11. Bruning PF, Bonfrèr JGM. Aminoglutethimide and oral anticoagulant therapy. *Lancet* 1983; **ii:** 582.
12. Spiers ASD, Mibashan RS. Increased warfarin requirement during mercaptopurine therapy: a new drug interaction. *Lancet* 1974: **ii:** 221–2.
13. Cuddy PG, *et al*. Influence of mitotane on the hypoprothrombinemic effect of warfarin. *South Med J* 1986; **79:** 387–8.
14. Thomas KS, *et al*. Elevated international normalized ratio associated with concomitant warfarin and erlotinib. *Am J Health-Syst Pharm* 2010; **67:** 1426–9.
15. Onoda S, *et al*. Drug interaction between gefitinib and warfarin. *Jpn J Clin Oncol* 2005; **35:** 478–82.
16. Moretti LV, Montalvo RO. Elevated international normalized ratio associated with concurrent use of sorafenib and warfarin. *Am J Health-Syst Pharm* 2009; **66:** 2123–5.

Antiplatelets. The interaction between anticoagulants and *dipyridamole* is unusual as bleeding can occur without any alteration in prothrombin times; special care is therefore required. This interaction has involved a small number of patients taking dipyridamole and warfarin or phenindione;[1] inhibition of platelet function by dipyridamole has been implicated. However, in general it does not appear to increase the risk of bleeding.[2]

Paradoxically, addition of *ticlopidine* was found to significantly increase acenocoumarol requirements.[3]

See also under Analgesics and NSAIDs (p. 1530.2).

1. Kalowski S, Kincaid-Smith P. Interaction of dipyridamole with anticoagulants in the treatment of glomerulonephritis. *Med J Aust* 1973; **2:** 164–6.
2. Levine MN, *et al*. Hemorrhagic complications of long-term anticoagulant therapy. *Chest* 1989; **95** (suppl): 26S–36S.
3. Salar A, *et al*. Ticlopidine antagonizes acenocoumarol treatment. *Thromb Haemost* 1997; **77:** 223–4.

Antiprotozoals. *Metronidazole* enhances the activity of warfarin[1,2] through selective inhibition of the metabolism of its *S*-isomer.[3]

A raised INR has been reported[4] in a patient taking warfarin after *atovaquone* was added to therapy.

1. Kazmier FJ. A significant interaction between metronidazole and warfarin. *Mayo Clin Proc* 1976; **51:** 782–4.
2. Dean RP, Talbert RL. Bleeding associated with concurrent warfarin and metronidazole therapy. *Drug Intell Clin Pharm* 1980; **14:** 864–6.
3. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. *N Engl J Med* 1976; **295:** 354–7.
4. Hidalgo K, *et al*. A potential interaction between warfarin and atovaquone. *Ann Pharmacother* 2011; **45:** e3.

Antithyroid drugs. See Thyroid and Antithyroid Drugs, p. 1535.2.

Antivirals. Reductions in dosage of either warfarin[1] or acenocoumarol[2] were necessary in 2 patients receiving *interferon alfa* for hepatitis C. The interactions may have been due to decreased metabolism of the anticoagulant. A similar need for a reduced warfarin dose had also been noted in other patients taking *interferon alfa-2b* or *interferon beta*.[1] However, in a patient taking interferon alfa-2b with *ribavirin*,[3] the warfarin dose needed to be increased, probably due to the interaction between ribavirin and warfarin.

A literature review[4] found that among the antiretrovirals, those most likely to interact with warfarin were the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the HIV-protease inhibitors (HIV-PIs). Of the NNRTIs, there were 4 reported cases in which *nevirapine* reduced the effect of warfarin, and one in which *efavirenz* increased it. From reports involving HIV-PIs, *saquinavir* appeared to inhibit warfarin's metabolism, while *darunavir*, *nelfinavir*, *ritonavir*, and *ritonavir-boosted lopinavir* appeared to induce it. (Ritonavir has also been reported[5] to decrease the response to acenocoumarol.) One conflicting report was noted in which ritonavir inhibited warfarin's metabolism; inconsistent ritonavir adherence was suggested as a possible reason.

Up to October 2005 there had been 19 reports[6] received by the Canadian health authorities (Health Canada) of enhanced response to warfarin between 1 and 11 days after starting *oseltamivir*. The increased INR ranged from 3.2 to 10.9; however, there was not enough information to be certain of causality. In 3 other cases there was a decrease in INR on the addition of oseltamivir. A retrospective study[7] also showed increases in INR after the use of oseltamivir in 7 of 15 patients who had been previously stabilised on warfarin for at least 3 months; bleeding was recorded in 3 patients. However, a prospective study[8] of 20 subjects stabilised on warfarin but without a clinical indication for oseltamivir found that it had no effect on either the pharmacodynamics or pharmacokinetics of warfarin. It was suggested that the influenza virus might alter the response to warfarin,[8] but this has been questioned.[7]

1. Adachi Y, *et al*. Potentiation of warfarin by interferon. *BMJ* 1995; **311:** 292.
2. Serratrice J, *et al*. Interferon-alpha 2b interaction with acenocoumarol. *Am J Hematol* 1998; **57:** 89.
3. Schulman S. Inhibition of warfarin activity by ribavirin. *Ann Pharmacother* 2002; **36:** 72–4.
4. Liedtke MD, Rathbun RC. Warfarin-antiretroviral interactions. *Ann Pharmacother* 2009; **43:** 322–8.
5. Llibre JM, *et al*. Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002; **36:** 621–3.
6. Health Canada. Oseltamivir (Tamiflu) and warfarin: suspected increase in INR. *Can Adverse React News* 2006; **16** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v16n1-eng.pdf (accessed 19/08/08)
7. Lee S-H, *et al*. Effect of oseltamivir on bleeding risk associated with warfarin therapy: a retrospective review. *Clin Drug Investig* 2012; **32:** 131–7.
8. Davies BE, *et al*. Effect of oseltamivir treatment on anticoagulation: a cross-over study in warfarinized patients. *Br J Clin Pharmacol* 2010; **70:** 834–43.

Anxiolytic sedatives, hypnotics, and antipsychotics. *Barbiturates*, by inducing liver metabolism, can reduce the activity of anticoagulants. The *benzodiazepines* do not generally have any effect although there is the rare report of increased or decreased activity.

Although there is a report suggesting that *cloral hydrate* may decrease the effect of dicoumarol by enzyme induction,[1] other studies and experience indicate an increase in the anticoagulant activity of warfarin.[2-4] However, the increase is only transient and is probably the result of displacement of warfarin from plasma protein binding sites by the metabolite trichloroacetic acid.[2] *Triclofos sodium* appears to increase the activity of warfarin in a similar way.[5]

Reduced anticoagulant activity has been reported with *dichloralphenazone*,[6,7] *ethchlorvynol* (with dicoumarol),[8] and *haloperidol* (with phenindione).[9] Compounds such as *meprobamate* and *methaqualone* appear to have no effect.

1. Cucinell SA, *et al*. The effect of chloral hydrate on bishydroxycoumarin metabolism: a fatal outcome. *JAMA* 1966; **197:** 366–8.
2. Sellers EM, Koch-Weser J. Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. *Ann N Y Acad Sci* 1971; **179:** 213–25.
3. Boston Collaborative Drug Surveillance Program. Interaction between chloral hydrate and warfarin. *N Engl J Med* 1972; **286:** 53–5.
4. Udall JA. Warfarin-chloral hydrate interaction: pharmacological activity and clinical significance. *Ann Intern Med* 1974; **81:** 341–4.
5. Sellers EM, *et al*. Enhancement of warfarin-induced hypoprothrombinemia by triclofos. *Clin Pharmacol Ther* 1972; **13:** 911–15.
6. Breckenridge A, Orme M. Clinical implications of enzyme induction. *Ann N Y Acad Sci* 1971; **179:** 421–3.
7. Whitfield JB, *et al*. Changes in plasma α-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; **1:** 316–18.
8. Johansson S-A. Apparent resistance to oral anticoagulant therapy and influence of hypnotics on some coagulation factors. *Acta Med Scand* 1968; **184:** 297–300.
9. Oakley DP, Lautch H. Haloperidol and anticoagulant treatment. *Lancet* 1963; **ii:** 1231.

Beta blockers. Beta blockers, particularly those with a high lipid solubility such as propranolol, may inhibit the metabolism of warfarin.[1] Although several studies have shown pharmacokinetic interactions between some beta blockers and oral anticoagulants, no effect on anticoagulant activity has generally been found. However, possible potentiation of the effect of warfarin by *propranolol*[2] has been reported.

1. Mantero F, *et al*. Effect of atenolol and metoprolol on the anticoagulant activity of acenocoumarin. *Br J Clin Pharmacol* 1984; **17:** 94S–96S.
2. Bax NDS, *et al*. Inhibition of drug metabolism by β-adrenoceptor antagonists. *Drugs* 1983; **25** (suppl 2): 121–6.

Cannabis. Cannabis smoking was reported[1] to significantly increase the INR of a patient taking warfarin, resulting in bruising, epistaxis, and gastrointestinal bleeding.

1. Yamreudeewong W, *et al*. Probable interaction between warfarin and marijuana smoking. *Ann Pharmacother* 2009; **43:** 1347–53.

Central stimulants. *Methylphenidate* has been reported both to increase the half-life of ethyl biscoumacetate,[1] and to have no effect on its half-life or anticoagulant activity.[2] *Prolintane* had no effect.[2]

1. Garrettson LK, *et al*. Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate: a new action of methylphenidate. *JAMA* 1969; **207:** 2053.
2. Hague DE, *et al*. The effect of methylphenidate and prolintane on the metabolism of ethyl biscoumacetate. *Clin Pharmacol Ther* 1971; **12:** 259–62.

Chamomile. A 70-year-old woman stabilised on warfarin developed multiple internal haemorrhages after she increased her use of chamomile lotion and consumption of chamomile tea to 4 or 5 times daily.[1] The interaction was considered to be due to the coumarin constituent of chamomile.

1. Segal R, Pilote L. Warfarin interaction with Matricaria chamomilla. *Can Med Assoc J* 2006; **174:** 1281–2.

Chinese herbal remedies. There have been reports of increased anticoagulation in patients taking Chinese herbal remedies with warfarin.[1-7] The remedies have ranged from single ingredient herbal preparations to complex multi-ingredient products, sometimes sold under the same brand name but with very different compositions.

1. Yu CM, *et al*. Chinese herbs and warfarin potentiation by 'Danshen'. *J Intern Med* 1997; **241:** 337–9.
2. Izzat MB, *et al*. A taste of Chinese medicine! *Ann Thorac Surg* 1998; **66:** 941–2.
3. Page RL, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* 1999; **19:** 870–6.
4. Chan TYK. Interaction between warfarin and danshen (Salvia miltiorrhiza). *Ann Pharmacother* 2001; **35:** 501–4.
5. Lam AY, *et al*. Possible interaction between warfarin and Lycium barbarum L. *Ann Pharmacother* 2001; **35:** 1199–1201.
6. Wong ALN, Chan TYK. Interaction between warfarin and the herbal product Quilinggao. *Ann Pharmacother* 2003; **37:** 836–8.
7. Su Q, Li Y. Interaction between warfarin and the herbal product Shengmai-yin: a case report of intracerebral hematoma. *Yonsei Med J* 2010; **51:** 793–6.

Corticosteroids and corticotropin. Corticosteroids are associated with an increase in blood coagulability, but their extensive use with anticoagulants, and very few reports of interaction, suggests that any problems are rare. However, there are some reports of corticosteroids or corticotropin either enhancing[1-3] or diminishing[4] the effects of anticoagulants. A retrospective study[5] in patients on long-term warfarin therapy given short courses of oral corticosteroids found that in most cases (29 of 32) there was an increase in INR, suggesting that careful monitoring is required.

1. Van Cauwenberge H, Jaques LB. Haemorrhagic effect of ACTH with anticoagulants. *Can Med Assoc J* 1958; **79:** 536–40.
2. Costedoat-Chalumeau N, *et al*. Potentiation of vitamin K antagonists by high-dose intravenous methylprednisolone. *Ann Intern Med* 2000; **132:** 631–5.
3. Stading JA, *et al*. Effects of prednisone on the international normalized ratio. *Am J Health-Syst Pharm* 2006; **63:** 2354–6. Correction. *ibid*. 2007; **64:** 130.
4. Chatterjea JB, Salomon L. Antagonistic effect of ACTH and cortisone on the anticoagulant activity of ethyl biscoumacetate. *BMJ* 1954; **2:** 790–2.
5. Hazlewood KA, *et al*. Effect of oral corticosteroids on chronic warfarin therapy. *Ann Pharmacother* 2006; **40:** 2101–6.

Cough suppressants. An increase in the activity of warfarin has been reported in patients taking *noscapine*[1,2] or *oxolamine*.[3] A subsequent study[3] suggested that the dose of warfarin should be reduced by 50% if oxolamine was started.

See also Menthol, p. 1535.1.

1. Scordo MG, *et al*. Warfarin–noscapine interaction: a series of four case reports. *Ann Pharmacother* 2008; **42:** 448–50.
2. Ohlsson S, *et al*. Noscapine may increase the effect of warfarin. *Br J Clin Pharmacol* 2008; **65:** 277–8.
3. Min KA, *et al*. Effect of oxolamine on anticoagulant effect of warfarin. *Am J Health-Syst Pharm* 2006; **63:** 153–6.

Cranberry. Between 1999 and 2003 the UK CSM[1] had received 5 reports suggesting an interaction between warfarin and cranberry juice. In 3 patients the activity of warfarin had been potentiated and one of them had died. In the other patients the INR was either reduced or unstable. By 2004 there had been 7 further reports of suspected interactions and the CSM advised[2] patients to avoid cranberry juice and other cranberry products while taking warfarin. However, despite case reports suggesting an increase in warfarin activity, the potential for a pharmacokinetic effect has been questioned,[3] and pharmacokinetic and pharmacodynamic studies[4-8] (some funded by producers of cranberry products) have failed to confirm an interaction.

1. CSM/MHRA. Possible interaction between warfarin and cranberry juice. *Current Problems* 2003; **29:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
2. CSM/MHRA. Interaction between warfarin and cranberry juice: new advice. *Current Problems* 2004; **30:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
3. Pham DQ, Pham AQ. Interaction potential between cranberry juice and warfarin. *Am J Health-Syst Pharm* 2007; **64:** 490–4.
4. Li Z, *et al*. Cranberry does not affect prothrombin time in male subjects on warfarin. *J Am Diet Assoc* 2006; **106:** 2057–61.
5. Lilja JJ, *et al*. Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam—probes of CYP2C9, CYP1A2, and CYP3A4. *Clin Pharmacol Ther* 2007; **81:** 833–9.
6. Ansell J, *et al*. The absence of an interaction between warfarin and cranberry juice: a randomized, double-blind trial. *J Clin Pharmacol* 2009; **49:** 824–30.
7. Mellen CK, *et al*. Effect of high-dose cranberry juice on the pharmacodynamics of warfarin in patients. *Br J Clin Pharmacol* 2010; **70:** 139–42.
8. Ngo N, *et al*. The warfarin-cranberry juice interaction revisited: A systematic in vitro-in vivo evaluation. *J Exp Pharmacol* 2010; **2010:** 83–91.

Dermatological drugs. A patient's warfarin dose had to be increased when he started treatment with *etretinate*.[1]

1. Ostlere LS, *et al*. Reduced therapeutic effect of warfarin caused by etretinate. *Br J Dermatol* 1991; **124:** 505–10.

Dietary supplements. There have been reports of an increased INR in patients taking warfarin and dietary supplements containing *glucosamine* with or without *chondroitin*,[1-3] and the UK CHM advises[4] that patients on warfarin should not take glucosamine. A similar effect has been reported[5] with *poliglusam*.

1. Rozenfeld V, *et al*. Possible augmentation of warfarin effect by glucosamine-chondroitin. *Am J Health-Syst Pharm* 2004; **61:** 306–7.
2. Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. *Pharmacotherapy* 2008; **28:** 540–8.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Interaction between glucosamine and warfarin. *Aust Adverse Drug React Bull* 2008; **27:** 3. Also available at: http://www.tga.gov.au/pdf/aadrb-0802.pdf (accessed 21/10/11)
4. CHM/MHRA. Glucosamine adverse reactions and interactions. *Current Problems* 2006; **31:** 8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
5. Huang S-S, *et al*. Chitosan potentiation of warfarin effect. *Ann Pharmacother* 2007; **41:** 1912–14.

Disulfiram. Two reports suggesting that disulfiram enhances the activity of warfarin[1,2] were confirmed by a study in 8 healthy subjects.[3] Although inhibition of liver enzymes by disulfiram was considered responsible,[3] a later study[4] suggested that disulfiram acts directly on the liver to increase hypoprothrombinaemia. This interaction is complicated by the variable effects of alcohol on warfarin (see p. 1530.2). Special care is therefore called for when these drugs are used together.

1. Rothstein E. Warfarin effect enhanced by disulfiram. *JAMA* 1968; **206:** 1574–5.
2. Rothstein E. Warfarin effect enhanced by disulfiram (Antabuse). *JAMA* 1972; **221:** 1052–3.
3. O'Reilly RA. Interaction of sodium warfarin and disulfiram (Antabuse) in man. *Ann Intern Med* 1973; **78:** 73–6.
4. O'Reilly RA. Dynamic interaction between disulfiram and separated enantiomorphs of racemic warfarin. *ClinPharmacol Ther* 1981; **29:** 332–6.

Diuretics. *Etacrynic acid* has been reported to enhance the activity of warfarin.[1] *Chlortalidone*[2] and *spironolactone*[3] have both been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. A case of an interaction between warfarin and *potassium canrenoate*, leading to a marked INR increase (10.8) and bruising, has been reported.[4] It was suggested that warfarin bioavailability was increased because potassium canrenoate can displace warfarin from serum albumin and because both drugs undergo hepatic metabolism via CYP3A. However, it is not uncommon to use these two drugs together and it was suggested that this patient was more susceptible to a clinically significant interaction because she was homozygous for the warfarin-sensitive genotype VKORC1-1639AA.

Torasemide has been reported to enhance the activity of warfarin,[5] possibly by competing for metabolism through the cytochrome P450 isoenzyme CYP2C9 and by displacement of warfarin from protein-binding sites. However, *bumetanide*, *furosemide*, and the *thiazides* appear to have no effect on warfarin.

1. Petrick RJ, *et al*. Interaction between warfarin and ethacrynic acid. *JAMA* 1975; **231:** 843–4.

2. O'Reilly RA, *et al.* Impact of aspirin and chlorthalidone on the pharmacodynamics of oral anticoagulant drugs in man. *Ann N Y Acad Sci* 1971; **179:** 173–86.
3. O'Reilly RA. Spironolactone and warfarin interaction. *Clin Pharmacol Ther* 1980; **27:** 198–201.
4. Maggini V, *et al.* A severe case of warfarin-canrenoate interaction: a role for genetic predisposition? *Br J Haematol* 2010; **150:** 482–3.
5. Bird J, Carmona C. Probable interaction between warfarin and torsemide. *Ann Pharmacother* 2008; **42:** 1893–8.

Endothelin receptor antagonists. A study in healthy subjects[1] showed that *bosentan* decreased the anticoagulant effect of warfarin; individual cases have also been reported.[2,3]

1. Weber C, *et al.* Effect of the endothelin-receptor antagonist bosentan on the pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol* 1999; **39:** 847–54.
2. Murphey LM, Hood EH. Bosentan and warfarin interaction. *Ann Pharmacother* 2003; **37:** 1028–31.
3. Spangler ML, Saxena S. Warfarin and bosentan interaction in a patient with pulmonary hypertension secondary to bilateral pulmonary emboli. *Clin Ther* 2010; **32:** 53–6.

Gastrointestinal drugs. Antacids may or may not interact with warfarin. *Bismuth carbonate* and *magnesium trisilicate* for example have been reported to reduce warfarin's absorption,[1] but *aluminium hydroxide* has been found to have no effect on warfarin or dicoumarol.[2] *Magnesium hydroxide*[2] has also been reported to have no effect on warfarin, but has increased the plasma concentrations of dicoumarol.[2]

There have been occasional reports of *sucralfate* diminishing the effect of warfarin.[3-5]

Histamine H_2-antagonists have been widely studied. There are several reports indicating that *cimetidine* can enhance the anticoagulant effect of warfarin and haemorrhage has occurred. Several studies show that cimetidine can increase the plasma concentration and half-life of warfarin and that there is a selective inhibitory effect on the metabolism of its *R*-isomer.[6-9] Not all these studies have, however, found an increase in prothrombin time. The effect of cimetidine on warfarin appears to be dose-dependent[6] and to be subject to interindividual variation;[8,9] careful monitoring is needed. Limited evidence suggests that cimetidine has a similar effect on the metabolism of acenocoumarol[10,11] and phenindione[10] but not of phenprocoumon.[12] Studies with *ranitidine* have generally been unable to show an effect on the metabolism of warfarin,[9,13] although in one study warfarin clearance was reduced.[6] There is a case report suggesting that potentiation of warfarin by ranitidine may occasionally occur.[14]

One study has suggested that the **proton pump inhibitor** *omeprazole* could inhibit the metabolism of *R*-warfarin although a clinically significant effect was unlikely.[15] While no evidence of an interaction was found in a retrospective study[16] of patients on acenocoumarol and omeprazole, an observational study suggested a risk of overanticoagulation when acenocoumarol is combined with *esomeprazole* or *lansoprazole*.[17] However, *pantoprazole* appears to have no effect on the pharmacokinetics or pharmacodynamics of warfarin[18] or phenprocoumon.[19]

The bulk **laxative** *psyllium* has been reported[20] to have no effect on warfarin, but in a retrospective cohort study, the use of *lactulose* in patients taking acenocoumarol or phenprocoumon was associated with raised INRs.[21]

Among **other** gastrointestinal drugs, a marked increase in the effect of warfarin has been reported in a patient when *cisapride* was added.[22]

A study[23] in healthy subjects found that *aprepitant* caused a small decrease in plasma concentration of the more active *S*-isomer of warfarin and there was also a decrease in INR.

A reduction in the response to warfarin with development of venous thrombosis has been reported in a patient receiving *mesalazine*,[24] and in another patient receiving *sulfasalazine*.[25]

1. McElnay JC, *et al.* Interaction of warfarin with antacid constituents. *BMJ* 1978; **2:** 1166.
2. Ambre JJ, Fischer LJ. Effect of coadministration of aluminum and magnesium hydroxides on absorption of anticoagulants in man. *Clin Pharmacol Ther* 1973; **14:** 231–7.
3. Mungall D, *et al.* Sucralfate and warfarin. *Ann Intern Med* 1983; **98:** 557.
4. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; **25:** 745–6.
5. Parrish RH, *et al.* Sucralfate-warfarin interaction. *Ann Pharmacother* 1992; **26:** 1015–16.
6. Desmond PV, *et al.* Decreased oral warfarin clearance after ranitidine and cimetidine. *Clin Pharmacol Ther* 1984; **35:** 338–41.
7. Choonara IA, *et al.* Stereoselective interaction between the R enantiomer of warfarin and cimetidine. *Br J Clin Pharmacol* 1986; **21:** 271–7.
8. Sax MJ, *et al.* Effect of two cimetidine regimens on prothrombin time and warfarin pharmacokinetics during long-term warfarin therapy. *Clin Pharm* 1987; **6:** 492–5.
9. Toon S, *et al.* Comparative effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of warfarin in man. *Eur J Clin Pharmacol* 1987; **32:** 165–72.
10. Serlin MJ, *et al.* Cimetidine: interaction with oral anticoagulants in man. *Lancet* 1979; **ii:** 317–19.
11. Gill TS, *et al.* Cimetidine-nicoumalone interaction in man: stereochemical considerations. *Br J Clin Pharmacol* 1989; **27:** 469–74.
12. Harenberg J, *et al.* Cimetidine does not increase the anticoagulant effect of phenprocoumon. *Br J Clin Pharmacol* 1982; **14:** 292–3.
13. Serlin MJ, *et al.* Lack of effect of ranitidine on warfarin action. *Br J Clin Pharmacol* 1981; **12:** 791–4.
14. Baciewicz AM, Morgan PJ. Ranitidine-warfarin interaction. *Ann Intern Med* 1990; **112:** 76–7.
15. Sutfin T, *et al.* Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther Drug Monit* 1989; **11:** 176–84.
16. Vreeburg EM, *et al.* Lack of effect of omeprazole on oral acenocoumarol anticoagulant therapy. *Scand J Gastroenterol* 1997; **32:** 991–4.
17. Teichert M, *et al.* Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment. *Br J Haematol* 2011; **153:** 379–85.
18. Duursema L, *et al.* Lack of effect of pantoprazole on the pharmacodynamics and pharmacokinetics of warfarin. *Br J Clin Pharmacol* 1995; **39:** 700–3.
19. Ehrlich A, *et al.* Lack of pharmacodynamic and pharmacokinetic interaction between pantoprazole and phenprocoumon in man. *Eur J Clin Pharmacol* 1996; **51:** 277–81.
20. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; **12:** 491–5.
21. Visser LE, *et al.* Overanticoagulation associated with combined use of lactulose and acenocoumarol or phenprocoumon. *Br J Clin Pharmacol* 2004; **57:** 522–4.
22. Darlington MR. Hypoprothrombinemia induced by warfarin sodium and cisapride. *Am J Health-Syst Pharm* 1997; **54:** 320–1.
23. Depré M, *et al.* Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *Eur J Clin Pharmacol* 2005; **61:** 341–6.
24. Marinella MA. Mesalamine and warfarin therapy resulting in decreased warfarin effect. *Ann Pharmacother* 1998; **32:** 841–2.
25. Teefy AM, *et al.* Warfarin resistance due to sulfasalazine. *Ann Pharmacother* 2000; **34:** 1265–8.

Ginkgo biloba. There is a report[1] of a woman stabilised on warfarin for 5 years who suffered an intracerebral haemorrhage 2 months after starting *Ginkgo biloba*, possibly due to the additive effect of the latter's antiplatelet activity. However, a study[2] in healthy subjects found no evidence that ginkgo affected warfarin pharmacokinetics or coagulation.

1. Matthews MK. Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology* 1998; **50:** 1933–4.
2. Jiang X, *et al.* Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 425–32.

Ginseng. A reduction in the response to warfarin was reported[1] in a patient after taking a ginseng preparation. A study[2] in healthy subjects also found a small reduction in response, although another study[3] in 31 patients found no significant effect.

1. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health-Syst Pharm* 1997; **54:** 692–3.
2. Yuan C-S, *et al.* American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. *Ann Intern Med* 2004; **141:** 23–7.
3. Lee YH, *et al.* Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. *Int J Cardiol* 2010; **145:** 275–6.

Glucagon. A dose-dependent enhancement of warfarin's anticoagulant activity has been reported with glucagon.[1]

1. Koch-Weser J. Potentiation by glucagon of the hypoprothrombinemic action of warfarin. *Ann Intern Med* 1970; **72:** 331–5.

Glucosamine. See Dietary Supplements, p. 1533.3.

Immunosuppressants. Severe bleeding occurred in a patient on long-term warfarin after stopping *azathioprine*,[1] while others[2,3] have needed an increased dose of warfarin when given with azathioprine.

There have been a few case reports of interaction between warfarin or acenocoumarol and *ciclosporin*, in which the dose of the anticoagulant or ciclosporin or both needed to be altered (see Anticoagulants under Interactions of Ciclosporin, p. 1957.3).

There has been a report[4] of *leflunomide* enhancing the effects of warfarin, causing gross haematuria after the second loading dose; the patient's INR rose from 3.4 to 11. It was stated that the UK CSM had received 4 reports of increased INR with leflunomide up to the end of 2002. In contrast, *teriflunomide* has been reported to decrease INR by 25% when given with warfarin.

1. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interaction. *Am J Med* 1992; **92:** 217.
2. Rotenberg M, *et al.* Effect of azathioprine on the anticoagulant activity of warfarin. *Ann Pharmacother* 2000; **34:** 120–2.
3. Vazquez SR, *et al.* Azathioprine-induced warfarin resistance. *Ann Pharmacother* 2008; **42:** 1118–23.
4. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. *BMJ* 2002; **325:** 1333. Correction. *ibid.* 2003; **326:** 432.

Leukotriene antagonists. *Zafirlukast* is reported to decrease the clearance of *S*-warfarin.[1] Licensed product information for zafirlukast states that it probably inhibits the cytochrome P450 isoenzyme CYP2C9 which is involved in the metabolism of warfarin. Prothrombin time may be significantly prolonged when zafirlukast is added and warfarin dosage should be adjusted accordingly.

A study[2] of *montelukast* and warfarin found no significant interaction between the two drugs.

1. Suttle AB, *et al.* Effect of zafirlukast on the pharmacokinetics of R- and S-warfarin in healthy men. *Clin Pharmacol Ther* 1997; **61:** 186.
2. Van Hecken, *et al.* Effect of montelukast on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol* 1999; **39:** 495–500.

Levamisole. An increased INR has been reported[1] in a patient taking chronic warfarin therapy after addition of *levamisole* and fluorouracil, possibly due to inhibition of warfarin metabolism. Interactions between warfarin and other fluorouracil-containing regimens have been reported (see Antineoplastics, p. 1532.2) but levamisole might also be involved. In a second patient, a similar reaction was reported[2] after levamisole and fluorouracil and an episode of bleeding subsequently occurred after levamisole alone.

1. Scarfe MA, Israel MK. Possible drug interaction between warfarin and combination of levamisole and fluorouracil. *Ann Pharmacother* 1994; **28:** 464–7.
2. Wehbe TW, Warth JA. A case of bleeding requiring hospitalization that was likely caused by an interaction between warfarin and levamisole. *Clin Pharmacol Ther* 1996; **59:** 360–2.

Lipid regulating drugs. Fibrates have been reported to interact with coumarin anticoagulants, sometimes to the point of haemorrhage. *Bezafibrate* has been reported to enhance the effect of phenprocoumon[1] and warfarin,[2] and *fenofibrate*[3] and *gemfibrozil*[4,5] have been reported to enhance the effect of warfarin, although a study[6] in healthy subjects found that gemfibrozil slightly decreased plasma-warfarin concentrations. The mechanism of any interaction between coumarins and fibrates is not clear; a combination of pharmacokinetic and pharmacodynamic factors has been suggested.[5]

Interactions may also occur between statins and coumarin anticoagulants, and small studies and case reports have described increased warfarin activity, and sometimes bleeding, with *fluvastatin*,[7-9] *lovastatin*,[10] *rosuvastatin*[11,12] (also with acenocoumarol[13]), and *simvastatin*[14,15] (also with acenocoumarol[16]), although there are also reports in which no effect was seen.[17-19] Licensed product information for *pravastatin* states that no change in warfarin activity has been seen in patients given both drugs, although there has been a report[20] of bleeding in a patient taking fluindione when pravastatin was added. An epidemiological study[21] in patients stabilised on warfarin found that risk of hospitalisation from gastrointestinal bleeding was raised when *atorvastatin*, fluvastatin, or simvastatin, but not pravastatin, was added to therapy. A suggested mechanism was inhibition of warfarin metabolism via the cytochrome P450 isoenzyme CYP3A4, with pravastatin being noted as the only statin among these not significantly metabolised by cytochrome P450 isoenzymes. In the case of simvastatin, inhibition of both CYP2C9 and CYP3A4 has elsewhere been suggested[22] as a mechanism. A study[23] of health subjects showed no interaction between *pitavastatin* and warfarin.

Dextrothyroxine increases the anticoagulant effect of warfarin sodium[24,25] and dicoumarol.[26]

Colestyramine has reduced warfarin's serum concentration[27] and half-life[28] as well as its activity.[27,28] The mechanisms of this interaction include binding of warfarin to colestyramine and reduced absorption;[27] the enterohepatic recycling of warfarin may also be interrupted.[28] Phenprocoumon's activity has also been reduced by colestyramine.[29] However, colestyramine can also reduce vitamin K absorption, and this may result in hypoprothrombinaemia and bleeding.

Use of *omega-3 fatty acids* (as fish oil preparations) in patients taking warfarin and other antithrombotics has been associated with INR elevation[30] and subdural haematoma.[31] However, controlled studies in patients taking fish oil and warfarin[32,33] have failed to show an effect on bleeding episodes or bleeding time.

Benfluorex[34] and *colestipol*[35] have been reported not to interact with phenprocoumon.

1. Zimmermann R, *et al.* The effect of bezafibrate on the fibrinolytic enzyme system and the drug interaction with racemic phenprocoumon. *Atherosclerosis* 1978; **29:** 477–85.
2. Beringer TRO. Warfarin potentiation with bezafibrate. *Postgrad Med J* 1997; **73:** 657–8.
3. Ascah KJ, *et al.* Interaction between fenofibrate and warfarin. *Ann Pharmacother* 1998; **32:** 765–8.
4. Ahmad S. Gemfibrozil interaction with warfarin sodium (Coumadin). *Chest* 1990; **98:** 1041–2.
5. Dixon DL, Williams VG. Interaction between gemfibrozil and warfarin: case report and review of the literature. *Pharmacotherapy* 2009; **29:** 744–8.
6. Lilja JJ, *et al.* Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 433–9.
7. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy* 2004; **24:** 285–90.
8. Trilli LE, *et al.* Potential interaction between warfarin and fluvastatin. *Ann Pharmacother* 1996; **30:** 1399–1402.
9. Kline SS, Harrell CC. Potential warfarin-fluvastatin interaction. *Ann Pharmacother* 1997; **31:** 790–1.
10. Ahmad S. Lovastatin: warfarin interaction. *Arch Intern Med* 1990; **150:** 2407.
11. Simonson SG, *et al.* Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol* 2005; **45:** 927–34.
12. Barry M. Rosuvastatin–warfarin drug interaction. *Lancet* 2004; **363:** 328.
13. Mondillo S, *et al.* Rosuvastatin–acenocoumarol interaction. *Clin Ther* 2005; **27:** 782–4.
14. Hickmott H, *et al.* The effect of simvastatin co-medication on warfarin anticoagulation response and dose requirements. *Thromb Haemost* 2003; **89:** 949–50.
15. Westergren T, *et al.* Probable warfarin–simvastatin interaction. *Ann Pharmacother* 2007; **41:** 1292–5.
16. Grau E, *et al.* Simvastatin-oral anticoagulant interaction. *Lancet* 1996; **347:** 405–6.

17. Jindal D, *et al.* Pharmacodynamic evaluation of warfarin and rosuvastatin co-administration in healthy subjects. *Eur J Clin Pharmacol* 2005; **61:** 621–5.
18. Gaw A, Wosornu D. Simvastatin during warfarin therapy in hyperlipoproteinaemia. *Lancet* 1992; **340:** 979–80.
19. Enajat M, *et al.* Safety of the combination of intensive cholesterol-lowering therapy with oral anticoagulation medication in elderly patients with atrial fibrillation: a randomized, double-blind, placebo-controlled study. *Drugs Aging* 2009; **26:** 585–93.
20. Trenque T, *et al.* Pravastatin: interaction with oral anticoagulant? *BMJ* 1996; **312:** 886.
21. Schelleman H, *et al.* Fibrate/Statin initiation in warfarin users and gastrointestinal bleeding risk. *Am J Med* 2010; **123:** 151–7.
22. Sconce EA, *et al.* The impact of simvastatin on warfarin disposition and dose requirements. *J Thromb Haemost* 2006; **4:** 1422–4.
23. Inagaki Y, *et al.* Drug-drug interaction study to assess the effects of multiple-dose pitavastatin on steady-state warfarin in healthy adult volunteers. *J Clin Pharmacol* 2011; **51:** 1302–9.
24. Owens JC, *et al.* Effect of sodium dextrothyroxine in patients receiving anticoagulants. *N Engl J Med* 1962; **266:** 76–9.
25. Solomon HM, Schrogie JJ. Change in receptor site affinity: a proposed explanation for the potentiating effect of D-thyroxine on the anticoagulant response to warfarin. *Clin Pharmacol Ther* 1967; **8:** 797–9.
26. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; **8:** 70–7.
27. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; **12:** 491–5.
28. Jähnchen E, *et al.* Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol* 1978; **5:** 437–40.
29. Meinertz T, *et al.* Interruption of the enterohepatic circulation of phenprocoumon by cholestyramine. *Clin Pharmacol Ther* 1977; **21:** 731–5.
30. Buckley MS, *et al.* Fish oil interaction with warfarin. *Ann Pharmacother* 2004; **38:** 50–3.
31. McClaskey EM, Michalets EL. Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: case report and review of the literature. *Pharmacotherapy* 2007; **27:** 152–60.
32. Eritsland J, *et al.* Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coag Fibrinol* 1995; **6:** 17–22.
33. Bender NK, *et al.* Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. *J Thromb Thrombolysis* 1998; **5:** 257–61.
34. De Witte P, Brems HM. Co-administration of benfluorex with oral anticoagulant therapy. *Curr Med Res Opin* 1980; **6:** 478–80.
35. Harvengt C, Desager JP. Effect of colestipol, a new bile acid sequestrant, on the absorption of phenprocoumon in man. *Eur J Clin Pharmacol* 1973; **6:** 19–21.

Menthol. Significant decreases in INR have been reported[1,2] in patients stabilised on warfarin when menthol cough preparations were taken.

1. Kassebaum PJ, *et al.* Possible warfarin interaction with menthol cough drops. *Ann Pharmacother* 2005; **39:** 365–7.
2. Coderre K, *et al.* Probable warfarin interaction with menthol cough drops. *Pharmacotherapy* 2010; **30:** 110.

Pesticides. Chlorinated insecticides diminished the activity of warfarin in a patient.[1]

1. Jeffery WH, *et al.* Loss of warfarin effect after occupational insecticide exposure. *JAMA* 1976; **236:** 2881–2.

Piracetam. Piracetam caused an increase in prothrombin time in a patient who had been stabilised on warfarin.[1]

1. Pan HYM, Ng RP. The effect of Nootropil in a patient on warfarin. *Eur J Clin Pharmacol* 1983; **24:** 711.

Sex hormones. There have been reports of steroids with anabolic or androgenic properties enhancing the activity of anticoagulants to the point of haemorrhage. Reports have covered *oxymetholone* and warfarin[1-3] or acenocoumarol;[4] *stanozolol* and warfarin[5,6] or dicoumarol;[7] *ethylestrenol* and phenindione;[8] *norethandrolone* and dicoumarol;[9] *methyltestosterone* and phenprocoumon;[10] and *danazol* and warfarin.[11-13] The manufacturer of *oxandrolone* states that an 80 to 85% reduction in warfarin dose was needed when oxandrolone was added to treatment. The mechanism of this interaction is not clear although it is considered that it is not caused by altered pharmacokinetics. Steroids with a 17-α-alkyl substituent appear to be most involved, but there has been a report of topically applied testosterone, which does not have such a substituent, enhancing warfarin.[14]

A retrospective study[15] of women receiving anticoagulant therapy who were started on *HRT* found that *tibolone* enhanced the effect of warfarin and of phenindione, possibly due to its androgenic properties. Tibolone again had a similar effect on warfarin in a prospective study in 16 healthy women.[16]

Oral contraceptives have also been implicated in interactions. However, while the effects of dicoumarol were diminished by a combined oral contraceptive,[17] those of acenocoumarol were enhanced by other preparations.[18] Combined oral contraceptives have increased the clearance of phenprocoumon without altering the anticoagulant effect.[19] There has also been a report[20] of a single course of *levonorgestrel* for emergency contraception increasing the effect of warfarin.

1. Robinson BHB, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **i:** 1356.
2. Longridge RGM, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **ii:** 90.
3. Edwards MS, Curtis JR. Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **ii:** 221.
4. de Oya JC, *et al.* Decreased anticoagulant tolerance with oxymetholone in paroxysmal nocturnal haemoglobinuria. *Lancet* 1971; **ii:** 259.
5. Acomb C, Shaw PW. A significant interaction between warfarin and stanozolol. *Pharm J* 1985; **234:** 73–4.
6. Shaw PW, Smith AM. Possible interaction of warfarin and stanozolol. *Clin Pharm* 1987; **6:** 500–2.
7. Howard W, *et al.* Anabolic steroids and anticoagulants. *BMJ* 1977; **1:** 1659–60.
8. Vere DW, Fearnley GR. Suspected interaction between phenindione and ethyloestrenol. *Lancet* 1968; **ii:** 281.
9. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; **8:** 70–7.
10. Husted S, *et al.* Increased sensitivity to phenprocoumon during methyltestosterone therapy. *Eur J Clin Pharmacol* 1976; **10:** 209–16.
11. Goulbourne IA, Macleod DAD. An interaction between danazol and warfarin: case report. *Br J Obstet Gynaecol* 1981; **88:** 950–1.
12. Meeks ML, *et al.* Danazol increases the anticoagulant effect of warfarin. *Ann Pharmacother* 1992; **26:** 641–2.
13. Booth CD. A drug interaction between danazol and warfarin. *Pharm J* 1993; **250:** 439–40.
14. Lorentz SMcQ, Weibert RT. Potentiation of warfarin anticoagulation by topical testosterone ointment. *Clin Pharm* 1985; **4:** 332–4.
15. McLintock LA, *et al.* Interaction between hormone replacement therapy preparations and oral anticoagulant therapy. *Br J Obstet Gynaecol* 2003; **110:** 777–9.
16. Elbers J, *et al.* Tibolone (Livial) enhances warfarin-induced anticoagulation in postmenopausal women. *Maturitas* 2007; **56:** 94–100.
17. Schrogie JJ, *et al.* Effect of oral contraceptives on vitamin K-dependent clotting activity. *Clin Pharmacol Ther* 1967; **8:** 670–5.
18. de Teresa E, *et al.* Interaction between anticoagulants and contraceptives: an unsuspected finding. *BMJ* 1979; **2:** 1260–1.
19. Mönig H, *et al.* Effect of oral contraceptive steroids on the pharmacokinetics of phenprocoumon. *Br J Clin Pharmacol* 1990; **30:** 115–18.
20. Ellison J, *et al.* Apparent interaction between warfarin and levonorgestrel used for emergency contraception. *BMJ* 2000; **321:** 1382.

St John's wort. St John's wort has been reported to reduce the anticoagulant effect of warfarin.[1]

1. Yue Q-Y, *et al.* Safety of St John's wort (Hypericum perforatum). *Lancet* 2000; **355:** 576–7.

Thyroid and antithyroid drugs. Since response to oral anticoagulants is dependent on thyroid status an interaction between oral anticoagulants and thyroid or antithyroid drugs might be expected. Thyroid compounds do enhance the activity of oral anticoagulants possibly by increased metabolism of clotting factors. The effect of *dextrothyroxine* is discussed under Lipid Regulating Drugs, p. 1534.3. Antithyroid compounds have not, however, been reported to diminish the effect of anticoagulants and paradoxically *propylthiouracil* has been reported to have caused hypoprothrombinaemia (see Effects on the Blood, under Carbimazole, p. 2335.2). However, in a patient given *thiamazole* for Graves' disease, the response to warfarin varied depending on his thyroid status and thiamazole dose.[1]

1. Busenbark LA, Cushnie SA. Effect of Graves' disease and methimazole on warfarin anticoagulation. *Ann Pharmacother* 2006; **40:** 1200–3.

Tobacco. A systematic review and meta-analysis of 13 studies of the effects of smoking on warfarin[1] concluded that smoking can increase warfarin clearance, leading to reduced warfarin effects, thus smokers may need slightly higher doses; smoking cessation could therefore, conversely, enhance warfarin effects. Close monitoring of smoking status during warfarin therapy is advised.

1. Nathisuwan S, *et al.* Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. *Chest* 2011; **139:** 1130–9.

Ubidecarenone. Decreased INR values and reduced effect of warfarin have been reported[1] in 3 patients given ubidecarenone.

1. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; **344:** 1372–3.

Vaccines. There have been a few reports of increased prothrombin time and bleeding in warfarin-stabilised patients after *influenza vaccination;* in 1 case a fatal intracranial bleed was possibly due to such an interaction.[1] However, studies have found only a small or inconsistent increase in warfarin activity[2,3] on vaccination, or no effect.[4-7] One study suggested that influenza vaccine decreased rather than increased the prothrombin time.[8] In a group of patients on long-term acenocoumarol therapy, influenza vaccination had no effect on acenocoumarol activity.[9]

1. Carroll DN, Carroll DG. Fatal intracranial bleed potentially due to a warfarin and influenza vaccine interaction. *Ann Pharmacother* 2009; **43:** 754–60.
2. Kramer P, *et al.* Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* 1984; **35:** 416–18.
3. Weibert RT, *et al.* Effect of influenza vaccine in patients receiving long-term warfarin therapy. *Clin Pharm* 1986; **5:** 499–503.
4. Lipsky BA, *et al.* Influenza vaccination and warfarin anticoagulation. *Ann Intern Med* 1984; **100:** 835–7.
5. Scott AK, *et al.* Lack of effect of influenza vaccination on warfarin in healthy volunteers. *Br J Clin Pharmacol* 1985; **19:** 144P–145P.
6. Gomolin IH. Lack of effect of influenza vaccine on warfarin anticoagulation in the elderly. *Can Med Assoc J* 1986; **135:** 39–41.
7. Iorio A, *et al.* Influenza vaccination and vitamin K antagonist treatment: a placebo-controlled, randomized, double-blind crossover study. *Arch Intern Med* 2010; **170:** 609–16.
8. Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. *Drug Intell Clin Pharm* 1988; **22:** 198–201.
9. Souto JC, *et al.* Lack of effect of influenza vaccine on anticoagulation by acenocoumarol. *Ann Pharmacother* 1993; **27:** 365–8.

Vitamins. Since vitamin K reverses the effects of oral anticoagulants, it is not surprising that there have been reports of *acetomenaphthone* and *phytomenadione* reducing anticoagulant activity, or of foods or nutritional preparations containing vitamin K compounds doing the same.

Occasional reports of *ascorbic acid* reducing the activity of warfarin[1,2] have not been confirmed in subsequent studies.[3,4] There have also been isolated reports suggesting that *vitamin E* may enhance the activity of warfarin[5] or dicoumarol,[6] although no effect was found in a study[7] of patients receiving warfarin and vitamin E. There has also been a report of elevated INR (greater than 12.3) in a patient on warfarin following the use of modified-release *nicotinamide*.[8]

1. Rosenthal G. Interaction of ascorbic acid and warfarin. *JAMA* 1971; **215:** 1671.
2. Smith EC, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; **221:** 1166.
3. Hume R, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; **219:** 1479.
4. Feetam CL, *et al.* Lack of a clinically important interaction between warfarin and ascorbic acid. *Toxicol Appl Pharmacol* 1975; **31:** 544–7.
5. Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* 1974; **230:** 1300–1.
6. Schrogie JJ. Coagulopathy and fat-soluble vitamins. *JAMA* 1975; **232:** 19.
7. Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol* 1996; **77:** 545–6.
8. Christopher A. Critically elevated INR in a patient on warfarin after increase in extended-release niacin dose. *Ann Pharmacother* 2011; **45:** e58.

Pharmacokinetics

Warfarin sodium is readily absorbed from the gastrointestinal tract; it can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half-life is about 40 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is used as a racemic mixture; the *S*-isomer is more potent. The *R*- and *S*-isomers are both metabolised in the liver. The *S*-isomer is metabolised more rapidly than the *R*-isomer, mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; other isoenzymes are also involved in the metabolism of the *R*-isomer. The stereoisomers may be affected differently by other drugs (see Interactions, p. 1529.3). Metabolites, with negligible or no anticoagulant activity, are excreted in the urine following reabsorption from the bile.

References.

1. Mungall DR, *et al.* Population pharmacokinetics of racemic warfarin in adult patients. *J Pharmacokinet Biopharm* 1985; **13:** 213–27.
2. Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin: understanding the dose-effect relationship. *Clin Pharmacokinet* 1986; **11:** 483–504.
3. Takahashi H, Echizen H. Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmacokinet* 2001; **40:** 587–603.
4. Lane S, *et al.* The population pharmacokinetics of R- and S-warfarin: effect of genetic and clinical factors. *Br J Clin Pharmacol* 2012; **73:** 66–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Circuvit; Coumadin; ***Austral.***: Coumadin; Marevan; ***Belg.***: Marevan; ***Braz.***: Coumadin; Marevan; Marfarin†; ***Canad.***: Coumadin; ***Chile***: Coumadin; ***Cz.***: Lawarin; ***Denm.***: Marevan; Waran; ***Fin.***: Marevan; ***Fr.***: Coumadine; ***Ger.***: Coumadin; ***Gr.***: Marevan; Panwarfin; ***Hung.***: Marfarin; ***India***: Uniwarfin; Warf; ***Indon.***: Simarc-2; ***Irl.***: Warfant; ***Israel***: Coumadin; ***Ital.***: Coumadin; ***Jpn***: Arefarin; Warlin; ***Malaysia***: Coumadin†; Orfarin; ***Mex.***: Coumadin; ***Norw.***: Marevan; ***NZ***: Coumadin; Marevan; ***Philipp.***: Coumadin; Warik; Zyfarin; ***Pol.***: Warfin; ***Port.***: Varfine; ***Rus.***: Marevan (Маревan); Warfarex (Варфарекс); ***Singapore***: Coumadin†; Marevan; Orfarin†; ***Spain***: Aldocumar; ***Swed.***: Waran; ***Thai.***: Befarin; Cogulax; Fargem; Maforan; Morfarin; Orfarin; Tufam†; Zydarin; ***Turk.***: Coumadin; Orfarin; ***UK***: Marevan; ***USA***: Coumadin; Jantoven; ***Venez.***: Anasmol; Coumadin; Cumar.

Pharmacopoeial Preparations

BP 2014: Warfarin Oral Suspension; Warfarin Tablets;
USP 36: Warfarin Sodium for Injection; Warfarin Sodium Tablets.

Xantinol Nicotinate *(BAN, rINN)*

Ksantinolinikotinaatti; Ksantynolu nikotynian; Nicotinato de xantinol; SK-331A; Xanthinol Niacinate (USAN); Xanthinol Nicotinate; Xanthinol nikotinát; Xantinol Nicotinate de; Xantinol, nicotinato de; Xantinoli Nicotinas; Xantinolnikotinat; Ксантинона Никотинат.

7-[2-Hydroxy-3-[(2-hydroxyethyl)methylamino]propyl]theophylline nicotinate.

$C_{13}H_{21}N_5O_4.C_6H_5NO_2$=434.5

CAS — 437-74-1.

ATC — C04AD02.

ATC Vet — *QC04AD02.*
UNII — *8G60H12X2D.*

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Xantinol nicotinate is a vasodilator with general properties similar to those of nicotinic acid (p. 2083.1), to which it is slowly hydrolysed. Xantinol nicotinate is used in the management of peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2) and in hyperlipidaemias (p. 1248.1). Oral doses of up to 3 g daily may be given. It has also been given by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Li Ao (奥利澳); Chang Long Qing (长龙清); Er Fu Mai (尔复迈); Fei Ke Mai Kang (菲克麦康); Fu Tong (孚通); Hai Fu Wei (海夫维); Hai Si Bi Da (海斯必达); He Xing (河星); Jingkang (靖康); Ni Fen Sa (尼芬萨); Qia Ke (恰克); Sai Tong (赛潼); Tai Wei Tong (太韦通); Tian Nuo Xin (天诺欣); Vedrin (麦全冬定); Xi Mei Xin (希美欣); Xin Pu Lu Tong (欣普路通); Yan Bi Er (延比尔); Yi Mei (怡玫); Yi Ting (怡汀); Zuo Nuo (左诺); ***Cz.***: Xanidil†; ***Ger.***: Complamin spezial†; ***Hung.***: Xavin†; ***India***: Complamina; ***Neth.***: Complamin; ***Pol.***: Sadamin†; ***Rus.***: Xatinate (Ксатинат); ***Switz.***: Complamin†.

Xemilofiban Hydrochloride *(USAN, rINNM)*

Hidrocloruro de xemilofibán; SC-54684A; Xémilofiban, Chlorhydrate de; Xemilofibán, hidrocloruro de; Xemilofibani Hydrochloridum; Ксемилофибана Гидрохлорид.

Ethyl (3*S*)-3-{3-[(*p*-amidinophenyl)carbamoyl]propionamido}-4-pentynoate monohydrochloride.

$C_{18}H_{22}N_4O_4$,HCl=394.9

CAS — *149820-74-6 (xemilofiban); 156586-91-3 (xemilofiban hydrochloride).*

UNII — *HIU55WBI80.*

Profile

Xemilofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug for the management of thromboembolic disorders such as unstable angina, and after angioplasty, but results have been disappointing.

References.

1. O'Neill WW, *et al.* Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. *N Engl J Med* 2000; **342:** 1316–24.
2. Brugts JJ, *et al.* Relation of periprocedural bleeding complications and long-term outcome in patients undergoing percutaneous coronary revascularization (from the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events [EXCITE] Trial). *Am J Cardiol* 2009; **103:** 917–22.

Xipamide *(BAN, USAN, rINN)* ⊗

Be-1293; Ksipamidi; MJF-10938; Xipamid; Xipamida; Xipamidum; Ксипамид.

4-Chloro-5-sulphamoylsalicylo-2′,6′-xylidide; 5-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethylphenyl)-2-hydroxy-benzamide.

$C_{15}H_{15}ClN_2O_4S$=354.8

CAS — *14293-44-8.*

ATC — *C03BA10.*

ATC Vet — *QC03BA10.*

UNII — *459EY0NUEC.*

Uses and Administration

Xipamide is a diuretic, structurally related to indapamide, with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2). It is given orally for hypertension (p. 1251.1), and for oedema, including that associated with heart failure (p. 1262.3).

Diuresis begins about 1 or 2 hours after an oral dose, reaches a peak at 4 to 6 hours, and lasts for about 12 hours.

In the treatment of **hypertension** the usual dose is 20 mg daily as a single morning dose, either alone, or with other antihypertensives. In some patients a dose of 10 mg daily may be adequate. In the treatment of **oedema** the usual initial dose is 40 mg daily, subsequently reduced to 20 mg daily, according to response; in resistant cases 80 mg daily may be required.

References.

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.
2. Knauf H, Mutschler E. Zur Wirkungsweise von Xipamid und seiner Klassifizierung als "Low-ceiling-Diuretikum": pharmakodynamische und pharmakokinetische Untersuchungen an gesunden Probanden sowie bei Nieren- und Leberkranken. *Arzneimittelforschung* 2005; **55:** 1–14.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Effects on electrolyte balance. Although reductions in plasma-potassium concentrations with xipamide have been shown to be on average comparable with those produced by thiazide and loop diuretics at equipotent doses,[1] there have been several reports of marked hypokalaemia in individual patients. Asymptomatic hypokalaemia was reported in 4 of 5 patients[2] (serum-potassium concentrations of less than 3.4 mmol/litre) and in 3 of 13 patients[3] (serum-potassium concentrations of less than 3.0 mmol/litre). Severe hypokalaemia resulting in ventricular arrhythmias has been reported after xipamide used alone[4] or with indapamide.[5] Profound electrolyte disturbances with altered consciousness and ventricular extrasystoles occurred in a patient taking digoxin after the addition of xipamide for 10 days.[6] A case of hypokalaemic periodic paralysis associated with xipamide use has also been reported.[7]

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.
2. Weissberg P, Kendall MJ. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
3. Raftery EB, *et al.* A study of the antihypertensive action of xipamide using ambulatory intra-arterial monitoring. *Br J Clin Pharmacol* 1981; **12:** 381–5.
4. Altmann P, Hamblin JJ. Ventricular fibrillation induced by xipamide. *BMJ* 1982; **284:** 494.
5. Boulton AJM, Hardisty CA. Ventricular arrhythmias precipitated by treatment with non-thiazide diuretics. *Practitioner* 1982; **226:** 125–8.
6. Bentley J. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
7. Boulton AJM, Hardisty CA. Hypokalaemicperiodic paralysis precipitated by diuretic therapy and minor surgery. *Postgrad Med J* 1982; **58:** 106–7.

Hepatic impairment. For a recommendation that xipamide should be given with caution to patients with liver disease, see under Pharmacokinetics, below.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Xipamide has been reported to be well absorbed from the gastrointestinal tract. Absorption is fairly rapid and peak plasma concentrations occur within 1 or 2 hours of oral doses. It is 99% bound to plasma proteins, and is excreted in the urine, partly unchanged and partly in the form of the glucuronide metabolite. It is reported to have a plasma half-life of about 5 to 8 hours. In patients with renal impairment excretion in the bile becomes more prominent.

References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Hepatic impairment. Xipamide was present in the plasma and in ascitic fluid in patients with liver cirrhosis in proportion to the protein content of the respective compartments.[1] The amount of drug excreted into the urine was much greater in patients with liver disease than in healthy control subjects. This was attributed to a diminution in hepatic elimination, which could result in significant effects on the clinical response to xipamide. Thus patients with cholestasis could have an enhanced response to xipamide. On the other hand cirrhotic patients with the hepatorenal syndrome may be resistant to diuretics. Xipamide should be used with caution in patients with liver disease.

1. Knauf H, *et al.* Xipamide disposition in liver cirrhosis. *Clin Pharmacol Ther* 1990; **48:** 628–32.

Renal impairment. After single oral and intravenous doses of xipamide 20 mg the drug appeared to be completely absorbed from the gastrointestinal tract.[1] The mean elimination half-life in healthy subjects was 7 hours and two-thirds of the clearance was by extrarenal routes. There was some accumulation in patients with chronic renal failure, with a calculated elimination half-life of 9 hours in end-stage renal disease.

1. Knauf H, Mutschler E. Pharmacodynamics and pharmacokinetics of xipamide in patients with normal and impaired kidney function. *Eur J Clin Pharmacol* 1984; **26:** 513–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Aquaphoril; ***Ger.***: Aquaphor; Aquex†; Xipa-Isis†; Xipa; Xipagamma; ***India***: Xipamid; ***Port.***: Diurexan; ***Spain***: Diurex; ***UK***: Diurexan; ***Ukr.***: Xipagamma (Ксипогамма).

Multi-ingredient Preparations. ***Ger.***: Neotri.

Zofenopril Calcium *(BANM, USAN, rINNM)*

Calcii Zofenoprilum; SQ-26991; Zofenopril cálcico; Zofénopril Calcique; Кальций Зофеноприл.

Calcium salt of (4*S*)-1-[(2*S*)-3-(Benzylthio)-2-methylpropionyl]-4-(phenylthio)-L-proline.

$C_{44}H_{44}CaN_2O_6S_4$=897.2

CAS — *81872-10-8 (zofenopril); 81938-43-4 (zofenopril calcium).*

ATC — *C09AA15.*

ATC Vet — *QC09AA15.*

UNII — *88ZQ329PU2.*

Profile

Zofenopril is an ACE inhibitor (p. 1282.2) that is used in the management of hypertension (p. 1251.1) and myocardial infarction (p. 1257.1). It owes its activity to the active metabolite zofenoprilat (SQ-26333) to which it is converted after oral doses. It is given orally in a usual daily maintenance dose of 30 to 60 mg of the calcium salt, as a single dose or in two divided doses.

References.

1. Ambrosioni E, *et al.* The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995; **332:** 80–5.
2. Borghi C, *et al.* Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension: SMILE study investigators: Survival of Myocardial Infarction Long-term Evaluation. *Am J Hypertens* 1999; **12:** 665–72.
3. Borghi C, *et al.* A review of the angiotensin-converting enzyme inhibitor, zofenopril, in the treatment of cardiovascular diseases. *Expert Opin Pharmacother* 2004; **5:** 1965–77.
4. Buikema H. Use of the ACE inhibitor zofenopril in the treatment of ischemic heart disease. *Expert Rev Cardiovasc Ther* 2006; **4:** 631–47.
5. Ambrosioni E. Defining the role of zofenopril in the management of hypertension and ischemic heart disorders. *Am J Cardiovasc Drugs* 2007; **7:** 17–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bifril; Zofenil; ***Belg.***: Zopranol; ***Chile***: Bifril†; ***Fin.***: Bifril†; Zofenil; ***Fr.***: Teoula; Zofenil; ***Gr.***: Zofepril; Zopranol; ***Irl.***: Zofenil; ***Ital.***: Bifril; Zantipres; Zopranol; ***Neth.***: Zofil; Zopranol; ***Port.***: Zofenil; Zopranol; ***Rus.***: Zocardis (Зокардис); ***Singapore***: Bifril; ***Switz.***: Zofenil†; ***Turk.***: Zoprotec; ***Ukr.***: Zocardis (Зокардис)†.

Multi-ingredient Preparations. ***Austria***: Bifril Plus; Zofenil Plus; ***Belg.***: Zopranol Plus; ***Denm.***: Zofenil Comp; ***Fin.***: Bifril Comp†; Zofenil Comp; ***Fr.***: Coteoula; Zofenilduo; ***Gr.***: Zofepril Plus; Zopranol Plus; ***Irl.***: Zofenil Plus; ***Ital.***: Bifrizide; Zantipride; Zoprazide; ***Neth.***: Zofil HCTZ; Zopranol HCTZ; ***Port.***: Zofenil Plus; Zopranol Plus; ***Spain***: Zofenil Diu†; Zopranol Diu†; ***Switz.***: Zofenil Plus†; ***Turk.***: Zoprotec Plus; ***Ukr.***: Zocardis Plus (Зокардис Плюс)†.

Chelators Antidotes and Antagonists

The drugs included in this chapter act in a variety of ways to counter the toxic effects of exogenous and endogenous substances in the body. They are therefore used in the management of poisoning and overdosage, to protect against the toxicity of drugs such as antineoplastics, and in the management of metabolic disorders such as Wilson's disease where toxic substances accumulate.

The main groups of drugs used include:

- antagonists, such as the opioid antagonist naloxone, that compete with the poison for receptor sites. Other antagonists act by blocking substances that mediate the effects of the toxin; atropine (p. 1310.2) acts in this way
- chelators and other drugs that form complexes with the toxin. This may reduce absorption of the toxin from the gastrointestinal tract, inactivate or reduce the activity of the toxin, or increase its elimination
- drugs that affect the metabolism of the toxin. Some antidotes, such as fomepizole in methyl alcohol poisoning, act by reducing the rate of metabolism to a toxic metabolite; alcohol (p. 1733.1) has a similar action. Others, such as methionine and glutathione, promote the formation of inactive metabolites; acetylcysteine (p. 1652.2) also acts in this way
- drugs that protect against the adverse effects of the toxin. Calcium folinate (p. 2066.3) is used for this purpose in methotrexate overdosage.

Acute poisoning

In the management of suspected acute poisoning it is often impossible to determine the identity of the poison or the size of the dose received with any certainty. Symptoms of acute poisoning are frequently non-specific, particularly in the early stages. Moreover, few poisons have specific antidotes or methods of elimination, and the mainstay of treatment for patients with suspected acute poisoning is therefore symptomatic and **supportive therapy**; in many cases nothing further is required. Supportive care in poisoning may include:

- maintenance of the airway, if necessary by intubation
- ensuring adequate ventilation
- managing shock or hypotension, mainly with intravenous fluids
- assessing consciousness and mental status and managing any immediate precipitating causes. Patients who are unconscious or who have respiratory depression may be given naloxone, particularly if opioid overdosage is a possibility. Some centres also recommend the routine administration of glucose to all unconscious patients since hypoglycaemia may be a cause of unconsciousness, although blood glucose measurements should be obtained first where facilities are immediately available
- monitoring for and controlling arrhythmias (although use of antiarrhythmic drugs may not be appropriate)
- monitoring for and controlling convulsions, usually with a benzodiazepine such as diazepam or lorazepam in the first instance
- managing hyper- or hypothermia with cooling measures or warming
- managing acidosis and fluid and electrolyte imbalances

Specific **antidotes** are available for several poisons and are the primary treatment where there is severe poisoning with a known toxin. They may be life-saving in such cases but their use is not without hazard and in many situations they are not necessary; their use should not preclude relevant supportive treatment.

Measures to reduce or **prevent absorption** of the poison are widely advocated. For inhalational poisoning the victim is removed from the source of poisoning. Some toxins, in particular pesticides, may be absorbed through the skin, and contaminated clothing should be removed and the skin thoroughly washed to avoid continued absorption. Caustic substances are removed from the skin or eyes with copious irrigation. However, for orally ingested poisons the best method for gastrointestinal decontamination remains controversial.

- *Activated charcoal* adsorbs various toxins and is often given to reduce absorption from the gastrointestinal tract.[1,2] A single dose is most likely to be effective if given as soon as possible after ingestion of a toxin, ideally within 1 hour.[1] Charcoal is generally well tolerated, although there is a risk of aspiration if the airway is not adequately protected. Repeated doses may be of use to eliminate some substances even after systemic absorption has occurred, such as those that undergo enterohepatic or enteroenteric recycling.[2]
- Active removal of poisons from the stomach by *induction of emesis* or *gastric lavage* has been widely used, but there is little evidence to support its role and there is potential for complications.[3-5]

  Induction of emesis with an emetic such as syrup of ipecacuanha has been used but is no longer recommended for either the home or hospital situation since there is no evidence that it improves outcomes, there are hazards associated with its use such as an increased risk of aspiration,[3,4] and it may delay the use or reduce the efficacy of activated charcoal, oral antidotes, and whole bowel irrigation.[3] If used at all, it should only be in fully conscious patients, where a potentially toxic amount has been ingested within the previous hour, and where other measures are unavailable or inappropriate. Emesis should not be induced if the poison is corrosive or petroleum based, if the toxin ingested is likely to alter mental status or cause seizures, or if the patient's condition may be adversely affected by vomiting.[3,4]

  Gastric lavage is also not recommended,[5] but may occasionally be considered for potentially life-threatening ingestion of non-caustic poisons that are not absorbed by activated charcoal, but only if less than one hour has elapsed since ingestion; it should not be attempted if the airway is not adequately protected or for petroleum-based toxins.
- *Cathartics* such as sorbitol or osmotic laxatives (such as magnesium citrate, magnesium sulfate, and sodium sulfate) have sometimes been used, but data do not support their use, either as the sole method of gut decontamination or routinely with activated charcoal.[6]
- *Whole-bowel irrigation* using a non-absorbable osmotic agent such as a macrogol has been used, particularly for substances that pass beyond the stomach before being absorbed, such as iron preparations or enteric-coated or modified-release formulations, but its role is not established.[7]
- Techniques intended to promote the elimination of poisons from the body, such as *haemodialysis* or *haemoperfusion*, are only of value for a limited number of poisons in a few severely poisoned patients.[8] *Forced diuresis* is no longer recommended, although *alkalinisation of the urine* using sodium bicarbonate infusion may have a role for selected poisons.[9]

Poisons Information Centres exist in many countries and should be consulted for more detailed information in specific situations; the International Programme on Chemical Safety has compiled a world directory of poisons centres (Yellow Tox).[10]

1. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *Clin Toxicol* 2005; **43:** 61–87. Also available at: http://www.clintox.org/documents/positionpapers/SingleDoseActivatedCharcoal.pdf (accessed 12/04/11)
2. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999; **37:** 731–51. Also available at: http://www.clintox.org/documents/positionpapers/MultipleDoseActivatedCharcoal.pdf (accessed 12/04/11)
3. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: ipecac syrup. *J Toxicol Clin Toxicol* 2004; **42:** 133–43. Also available at: http://www.clintox.org/documents/positionpapers/IpecacSyrup.pdf (accessed 12/04/11) Correction. *ibid.*; 1000.
4. Manoguerra AS, Cobaugh DJ. Guidelines for the Management of Poisoning Consensus Panel. Guideline on the use of ipecac syrup in the out-of-hospital management of ingested poisons. *Clin Toxicol* 2005; **43:** 1–10. Also available at: http://www.aapcc.org/archive/FinalizedPMGdlns/Ipecac%20Guideline%20-%20final%20for%20JTCT.pdf (accessed 12/04/11)
5. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. *J Toxicol Clin Toxicol* 2004; **42:** 933–43. Also available at: http://www.clintox.org/documents/positionpapers/GastricLavage.pdf (accessed 12/04/11)
6. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: cathartics. *J Toxicol Clin Toxicol* 2004; **42:** 243–53. Also available at: http://www.clintox.org/documents/positionpapers/Cathartics.pdf (accessed 12/04/11) Correction. *ibid.*; 1000.
7. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: whole bowel irrigation. *J Toxicol Clin Toxicol* 2004; **42:** 843–54. Also available at: http://www.clintox.org/documents/positionpapers/WholeBowelIrrigation.pdf (accessed 12/04/11) Correction. *ibid.*; 1000. [dose]
8. Greene SL, *et al.* Acute poisoning: understanding 90% of cases in a nutshell. *Postgrad Med J* 2005; **81:** 204–16.
9. Proudfoot AT, *et al.* American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position Paper on urine alkalinization. *J Toxicol Clin Toxicol* 2004; **42:** 1–26. Also available at: http://www.clintox.org/documents/positionpapers/UrineAlkalinization.pdf (accessed 12/04/11)
10. International Programme on Chemical Safety. World directory of poisons centres (Yellow Tox). Available at: http://www.who.int/ipcs/poisons/centre/directory/en/ (accessed 05/05/11)

Activated Charcoal

Actieve Kool; A-Kohle; Aktif Kömür; Aktiivihiili; Aktiivsüsi; Aktivált szén; Aktivkohle; Aktivt Kull; Aktyvintosios anglys; Carbó Actiu; Carbo Activatus; Carbo Medicinalis; Carbón activado; Carbone Attivo; Carvão Ativado; Charbon activé; Decolorising Charcoal; Kol, aktivt; Medicinal Charcoal; Uhlí aktivní; Węgiel leczniczy; Активен въглен; Активированный Уголь.

CAS — 16291-96-6 (charcoal).
ATC — A07BA01.
ATC Vet — QA07BA01.
UNII — 2P3VWU3H10.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Charcoal, Activated). It is obtained from vegetable matter by suitable carbonisation processes intended to confer a high adsorption power. A black, light powder free from grittiness. Practically insoluble in all usual solvents. It adsorbs not less than 40% of its own weight of phenazone, calculated with reference to the dried substance. Store in airtight containers.

USP 36: (Activated Charcoal). The residue from the destructive distillation of various organic materials, treated to increase its adsorptive power. A fine, black, odourless, tasteless powder, free from gritty matter. The USP 36 has tests for adsorptive power in respect of alkaloids and dyes.

Uses and Administration

Activated charcoal can adsorb many plant and inorganic poisons including drugs such as salicylates, paracetamol, barbiturates, and tricyclic antidepressants; when given orally it reduces their systemic absorption from the gastrointestinal tract and is therefore used in the treatment of acute oral poisoning (p. 1538.1). It is of little value for poisoning with strong acids, alkalis, or other corrosive substances, alcohols, cyanides, clofenotane, malathion, petroleum distillates, and metals including iron, lithium, lead, sodium, potassium, magnesium, and mercury salts. Adsorption characteristics can be influenced by the charcoal's particle size, thus different responses may be obtained with different preparations.

Activated charcoal is given orally or via a nasogastric tube usually as a slurry in water. A usual dose for reduction of absorption is 50 g, but higher doses (100 g) have been used. For maximum efficacy, activated charcoal should be given as soon as possible (within 1 hour) after ingestion of the toxic compound. For some drugs such as those that undergo enterohepatic or enteroenteric recycling (e.g. phenobarbital and theophylline) *repeated doses* of activated charcoal are of value in enhancing faecal elimination. Doses for repeated administration in active elimination have varied but typically 50 g may be given every 4 hours; 25 g every 2 hours or 12.5 g hourly may be better tolerated, but efficacy may be affected. For doses in children, see p. 1538.1.

Mixtures such as 'universal antidote', which contained activated charcoal, magnesium oxide, and tannic acid, should not be used; activated charcoal alone is more effective and tannic acid may cause hepatotoxicity.

In treatment of poisoning using charcoal haemoperfusion, activated charcoal is used to remove drugs from the bloodstream. Where available, it may be of value in acute severe poisoning by drugs such as the barbiturates, carbamazepine or theophylline when other intensive measures fail to improve the condition of the patient.

Activated charcoal is used in dressings for ulcers and suppurating wounds (p. 1690.1) to absorb bacteria and reduce malodour.

Activated charcoal has been used as a marker of intestinal transit and has also been tried in the treatment of flatulence. Both activated charcoal and vegetable charcoal (wood charcoal; carbo ligni) are included in preparations for various gastrointestinal disorders.

Up to 1 mL of a suspension of activated charcoal 40 mg/mL may be injected subcutaneously after stereotactic or ultrasonic localisation of breast lesions to aid excision in subsequent surgery (within 60 days).

Technical grades of activated charcoal have been used as purifying and decolorising agents, for the removal of residual gases in low-pressure apparatus, and in respirators as a protection against toxic gases.

Administration. Activated charcoal is most commonly given as a slurry in water but this is often unpalatable because of the colour, gritty taste, lack of flavour, and dif-

ficulty in swallowing.[1] Flavourings and other excipients are often added in an attempt to improve palatability, although the effect of any additives on the adsorptive capacity of charcoal needs to be considered. Studies *in vitro* or in healthy subjects indicated that some foods such as ice cream, milk, and cocoa might inhibit the adsorptive capacity of activated charcoal, whereas starches and jams appeared to have no effect.[2,3] Carmellose has improved palatability although it might also reduce adsorptive capacity.[4-6] Saccharin sodium, sucrose, or sorbitol may be suitable additives,[7] although there may be problems associated with sorbitol-containing products (see under Poisoning, below). Chocolate syrup has also been used but the sweetness and flavour may disappear after a few minutes of contact with the activated charcoal.[1] The *BNFC* suggests that activated charcoal suspension may be mixed with soft drinks such as caffeine-free diet cola or fruit juices to mask the taste. A more recent study[8] of charcoal use in children with suspected poisoning found no evidence that use of flavourings improved the success of administration.

1. Scholtz EC, *et al.* Evaluation of five activated charcoal formulations for inhibition of aspirin absorption and palatability in man. *Am J Hosp Pharm* 1978; **35:** 1355–9.
2. Levy G, *et al.* Inhibition by ice cream of the antidotal efficacy of activated charcoal. *Am J Hosp Pharm* 1975; **32:** 289–91.
3. De Neve R. Antidotal efficacy of activated charcoal in presence of jam, starch and milk. *Am J Hosp Pharm* 1976; **33:** 965–6.
4. Mathur LK, *et al.* Activated charcoal–carboxymethylcellulose gel formulation as an antidotal agent for orally ingested aspirin. *Am J Hosp Pharm* 1976; **33:** 717–19.
5. Manes M. Effect of carboxymethylcellulose on the adsorptive capacity of charcoal. *Am J Hosp Pharm* 1976; **33:** 1120, 1122.
6. Mathur LK, *et al.* Effect of carboxymethylcellulose on the adsorptive capacity of charcoal. *Am J Hosp Pharm* 1976; **33:** 1122.
7. Cooney DO. Palatability of sucrose-, sorbitol-, and saccharin-sweetened activated charcoal formulations. *Am J Hosp Pharm* 1980; **37:** 237–9.
8. Osterhoudt KC, *et al.* Activated charcoal administration in a pediatric emergency department. *Pediatr Emerg Care* 2004; **20:** 493–8.

Administration in children. Activated charcoal is used in children for the treatment of acute oral poisoning. For the reduction of absorption of poisons, a usual dose is 1 g/kg (to a maximum of 50 g) given orally or via a nasogastric tube. This dose may be repeated every 4 hours for the active elimination of poisons. If vomiting is a problem, smaller amounts of charcoal given hourly or every 2 hours may cause less gastric irritation. The *BNFC* recommends these doses for neonates and children up to 12 years of age; thereafter usual adult doses may be used, see Uses and Administration, p. 1537.3.

Poisoning. The management of acute poisoning is discussed on p. 1537.1. The use of a *single oral dose* of activated charcoal has become a widespread method of preventing the absorption of ingested compounds and may be superior to gastric emptying. The American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) consider[1] that activated charcoal may be used if a patient presents within 1 hour of ingesting a potentially toxic amount of a poison known to be adsorbed by charcoal. There are insufficient data to support general use beyond 1 hour after ingestion.[1-3] A meta-analysis[4] of studies in healthy subjects found that although the reduction in drug exposure was optimal when activated charcoal was given immediately after drug intake, there was still some reduction in drug exposure when activated charcoal was given up to 4 hours after drug intake. It has been suggested that activated charcoal may be given several hours after poisoning with modified-release formulations or drugs that slow gastrointestinal transit such as antimuscarinics; however, the *National Poisons Information Service* in the UK considers that there is little evidence to support such use.

Multiple oral doses of activated charcoal have been found to enhance the elimination of some drugs and toxic substances even after systemic absorption. Mechanisms by which activated charcoal may increase drug elimination from the body include interruption of the enterohepatic circulation of drugs excreted into the bile, reduction of the reabsorption of drugs which diffuse or are actively secreted into the intestines, and increased elimination of the drug via the gastrointestinal tract when given with a laxative to decrease gastrointestinal transit time, although the practice of using charcoal with a laxative has been questioned.[5-7] Repeated oral doses of activated charcoal may therefore be considered for compounds that undergo enterohepatic or enteroenteric circulation, have a small volume of distribution, are not extensively bound to plasma proteins, and have a low endogenous clearance. A large study[8] in Sri Lanka found that routine treatment with multiple-dose activated charcoal was no better than no charcoal or just a single dose in reducing mortality from acute self-poisoning; the nature of the poison (mostly pesticides or oleander), time to presentation, or severity of symptoms did not alter the findings. However, it is unclear to what extent these results apply in other settings.[9] After a review of the literature[7] the AACT and EAPCCT recommended that multiple doses of charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Anecdotal reports and studies in acutely poisoned patients indicate that a technique of giving multiple doses of charcoal may offer an alternative to charcoal haemoperfusion or haemodialysis. However, while activated charcoal is generally well tolerated, major complications do occasionally occur, including pulmonary aspiration and bowel obstruction.[10] Also, use of multiple doses of charcoal preparations containing sorbitol or sodium bicarbonate can result in increased vomiting[11] or in electrolyte disturbances.[5,12,13]

1. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *J Toxicol Clin Toxicol* 2005; **43:** 61–87. Also available at: http://www.clintox.org/documents/positionpapers/SingleDoseActivatedCharcoal.pdf (accessed 10/05/11)
2. Green R, *et al.* How long after drug ingestion is activated charcoal still effective? *J Toxicol Clin Toxicol* 2001; **39:** 601–5.
3. Cooper GM, *et al.* A randomized clinical trial of activated charcoal for the routine management of oral drug overdose. *Q J Med* 2005; **98:** 655–60.
4. Jürgens G, *et al.* The effect of activated charcoal on drug exposure in healthy volunteers: a meta-analysis. *Clin Pharmacol Ther* 2009; **85:** 501–5.
5. Neuvonen PJ, Olkkola KT. Oral activated charcoal in the treatment of intoxications: role of single and repeated doses. *Med Toxicol* 1988; **3:** 33–58.
6. Neuvonen PJ, Olkkola KT. Effect of purgatives on antidotal efficacy of oral activated charcoal. *Hum Toxicol* 1986; **5:** 255–63.
7. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999; **37:** 731–51. Also available at: http://www.clintox.org/documents/positionpapers/MultipleDoseActivatedCharcoal.pdf (accessed 12/08/10)
8. Eddleston M, *et al.* Ox-Col Poisoning Study collaborators. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet* 2008; **371:** 579–87.
9. Eyer P, Eyer F. Is this the epitaph for multiple-dose activated charcoal? *Lancet* 2008; **371:** 538–9.
10. Palatnick W, Tenenbein M. Activated charcoal in the treatment of drug overdose: an update. *Drug Safety* 1992; **7:** 3–7.
11. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; **27:** 358–61.
12. McLuckie A, *et al.* Role of repeated doses of oral activated charcoal in the treatment of acute intoxications. *Anaesth Intensive Care* 1990; **18:** 375–84.
13. Tenenbein M. Multiple doses of activated charcoal: time for reappraisal? *Ann Emerg Med* 1991; **20:** 529–31.

HAEMOPERFUSION. Haemoperfusion involves the passage of blood through an adsorbent material such as activated charcoal or synthetic hydrophobic polystyrene resins that can retain certain drugs and toxic agents. Early problems with charcoal haemoperfusion such as charcoal embolism, marked thrombocytopenia, fibrinogen loss, and pyrogen reactions have been largely overcome by purification procedures and by coating the carbon with biocompatible polymers. However, transient falls in platelet count, leucocyte count, and circulatory concentrations of clotting factors, calcium, glucose, urea, creatinine, and urate have been reported during haemoperfusion. While there is no substitute for supportive measures, haemoperfusion can significantly reduce the body burden of certain compounds with a low volume of distribution within 4 to 6 hours in some severely poisoned patients; haemoperfusion is not effective for drugs or poisons with very large volumes of distribution. Use of haemoperfusion has declined in recent years in favour of improved haemodialysis techniques.

References.

1. Winchester JF. Dialysis and hemoperfusion in poisoning. *Adv Ren Replace Ther* 2002; **9:** 26–30.
2. Holubek WJ, *et al.* Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int* 2008; **74:** 1327–34.
3. Gil HW, *et al.* Clinical outcome of hemoperfusion in poisoned patients. *Blood Purif* 2010; **30:** 84–8.

Porphyria. Activated charcoal may be used as part of the management of erythropoietic protoporphyria, one of the non-acute porphyrias (p. 1556.1). It acts as a sorbent in the gut lumen, interrupting the enterohepatic recycling of protoporphyrin. It may also have a role in congenital erythropoietic porphyria, a very rare porphyria. In a patient[1] with photomutilation due to this condition, activated charcoal 30 g given orally every 3 hours for 36 hours reduced the plasma-porphyrin concentration to normal values by 20 hours and was more effective than colestyramine or red cell transfusion. After stopping activated charcoal, plasma-porphyrin concentrations rose rapidly to near pretreatment levels within 10 days. Long-term treatment with oral charcoal over a 9-month period, at an optimal dose of 60 g three times daily, produced clinical remission with low concentrations of plasma and skin porphyrin and an absence of photocutaneous activity. However, exacerbation after an initial period of remission has been reported in another patient[2] and total lack of efficacy in a third.[3]

Activated charcoal has also been tried in variegate porphyria, but a study[4] in 8 patients found that oral charcoal led to clinical and biochemical deterioration with an increase in skin lesions and in urinary and plasma porphyrins.

1. Pimstone NR, *et al.* Therapeutic efficacy of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1987; **316:** 390–3.
2. Hift RJ, *et al.* The effect of oral activated charcoal on the course of congenital erythropoietic porphyria. *Br J Dermatol* 1993; **129:** 14–17.
3. Minder EI, *et al.* Lack of effect of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1994; **330:** 1092–4.
4. Hift RJ, *et al.* Administration of oral activated charcoal in variegate porphyria results in a paradoxical clinical and biochemical deterioration. *Br J Dermatol* 2003; **149:** 1266–9.

Pruritus. Activated charcoal has been tried in pruritus (p. 1687.3) associated with renal failure. In a double-blind crossover study,[1] activated charcoal 6 g daily orally for 8 weeks was more effective than placebo in relieving generalised pruritus in 11 patients undergoing maintenance haemodialysis. Another study[2] found that activated charcoal completely relieved pruritus in 10 of 23 haemodialysis patients, with a partial response in a further 10; treatment was generally well tolerated.

1. Pederson JA, *et al.* Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med* 1980; **93:** 446–8.
2. Giovannetti S, *et al.* Oral activated charcoal in patients with uremic pruritus. *Nephron* 1995; **70:** 193–6.

Tumour localisation. References to the use of injectable charcoal suspensions to localise lesions in the breast[1-4] and thyroid[5] for surgery.

1. Mullen DJ, *et al.* The use of carbon marking after stereotactic large-core-needle breast biopsy. *Radiology* 2001; **218:** 255–60.
2. Ko K, *et al.* The value of ultrasound-guided tattooing localization of nonpalpable breast lesions. *Korean J Radiol* 2007; **8:** 295–301.
3. Mathieu MC, *et al.* Tattooing breast cancers treated with neoadjuvant chemotherapy. *Ann Surg Oncol* 2007; **14:** 2233–8.
4. Ruiz-Delgado ML, *et al.* Abnormal mammography and sonography associated with foreign-body giant-cell reaction after stereotactic vacuum-assisted breast biopsy with carbon marking. *Acta Radiol* 2008; **49:** 1112–18.
5. Kang TW, *et al.* Preoperative ultrasound-guided tattooing localization of recurrences after thyroidectomy: safety and effectiveness. *Ann Surg Oncol* 2009; **16:** 1655–9.

Adverse Effects and Precautions

Activated charcoal is relatively non-toxic when given orally but gastrointestinal disturbances such as vomiting, constipation, or diarrhoea have been reported. It may colour the faeces, tongue, and mucous membranes black. Activated charcoal should be used with caution in patients at risk of gastrointestinal obstruction as it may reduce gastrointestinal motility. It has been associated with intestinal obstruction and perforation after multiple dosing.

Care is needed if activated charcoal is used in patients receiving specific oral antidotes such as methionine (see Interactions, p. 1539.1). As with any treatment given orally for poisoning the risk of aspiration should be considered in drowsy or comatose patients.

The adverse effects of haemoperfusion with activated charcoal are similar to those of haemodialysis (see p. 1779.2); additionally, patients often develop thrombocytopenia, leucopenia, and hypocalcaemia. Charcoal embolism has also occurred. See also Haemoperfusion, above.

There may be local pain and stinging with subcutaneous use, and injection of volumes greater than 1 mL may result in leakage and spread into surrounding tissues. Granuloma and foreign body reactions have been reported occasionally when particles of activated charcoal were left in subcutaneous tissue for more than 6 months.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are the main complication of oral activated charcoal. Vomiting may occur and is a risk factor for pulmonary aspiration (see Effects on the Lungs, p. 1539.1). Although some preparations may cause diarrhoea, activated charcoal may reduce gastrointestinal motility and multiple doses have been associated with intestinal obstruction or faecal impaction,[1-4] in some cases leading to ulceration[5] or perforation;[6] overdosage with drugs that reduce gastrointestinal motility may increase the risk.[2,3,6] Perforation has occurred after a single dose in a patient with diverticular disease.[7] Two cases of pseudo-obstruction, one of which was fatal, have also been reported[8] after the use of activated charcoal and sorbitol with opioid sedation for theophylline poisoning. In another report,[9] severe peritonitis developed in a patient given oral activated charcoal after gastric lavage; charcoal was found in the peritoneum, although the site of perforation could not be detected. Acute appendicitis has also been reported after multiple doses of activated charcoal.[10]

1. Watson WA, *et al.* Gastrointestinal obstruction associated with multiple-dose activated charcoal. *J Emerg Med* 1986; **4:** 401–7.
2. Anderson IM, Ware C. Syrup of ipecacuanha. *BMJ* 1987; **294:** 578.
3. Ray MJ, *et al.* Charcoal bezoar: small-bowel obstruction secondary to amitriptyline overdose therapy. *Dig Dis Sci* 1988; **33:** 106–7.
4. Atkinson SW, *et al.* Treatment with activated charcoal complicated by gastrointestinal obstruction requiring surgery. *BMJ* 1992; **305:** 563.
5. Mizutani T, *et al.* Rectal ulcer with massive haemorrhage due to activated charcoal treatment in oral organophosphate poisoning. *Hum Exp Toxicol* 1991; **10:** 385–6.

6. Gomez HF, *et al.* Charcoal stercolith with intestinal perforation in a patient treated for amitriptyline ingestion. *J Emerg Med* 1994; **12:** 57–60.
7. Green JP, McCauley W. Bowel perforation after single-dose activated charcoal. *CJEM* 2006; **8:** 358–60.
8. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7:** 74–7.
9. Mariani PJ, Pook N. Gastrointestinal tract perforation with charcoal peritoneum complicating orogastric intubation and lavage. *Ann Emerg Med* 1993; **22:** 606–9.
10. Eroglu A, *et al.* Multiple dose-activated charcoal as a cause of acute appendicitis. *J Toxicol Clin Toxicol* 2003; **41:** 71–3.

Effects on the lungs. Vomiting after oral activated charcoal for acute poisoning has been associated with pulmonary aspiration of gastric contents, sometimes with fatal results.[1-3] Vomiting may be related to the formulation used and may be increased with sorbitol-containing preparations,[4] although a study in children[5] failed to confirm this. The use of a cuffed endotracheal tube has been recommended for any patient with impaired laryngeal reflexes to prevent aspiration;[3] however, there have been reports of aspiration despite a protected airway, including a case of obstructive laryngitis in a child.[6] Acute[7] and chronic[8] pulmonary toxicity has also been reported after accidental instillation of charcoal into the lung due to misplacement of the nasogastric tube.

1. Harsch HH. Aspiration of activated charcoal. *N Engl J Med* 1986; **314:** 318.
2. Menzies DG, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; **297:** 459–60.
3. Rau NR, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; **297:** 918–19.
4. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; **27:** 358–61.
5. Osterhoudt KC, *et al.* Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. *Pediatrics* 2004; **113:** 806–10.
6. Donoso A, *et al.* Activated charcoal laryngitis in an intubated patient. *Pediatr Emerg Care* 2003; **19:** 420–1.
7. Harris CR, Filandrinos D. Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med* 1993; **22:** 1470–3.
8. Graff GR, *et al.* Chronic lung disease after activated charcoal aspiration. *Pediatrics* 2002; **109:** 959–61.

Porphyria. Activated charcoal may be used in the management of some porphyrias (see p. 1538.2). The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies activated charcoal as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Activated charcoal has the potential to reduce the absorption of many drugs from the gastrointestinal tract and simultaneous oral therapy should therefore be avoided. In the management of acute poisoning, concurrent medication should be given parenterally. Care is needed if a specific oral antidote such as methionine is given since adsorption of the antidote may decrease its efficacy; it has been recommended that activated charcoal should be cleared from the stomach or avoided if oral antidotes are to be used. The adsorptive capacity of activated charcoal may be reduced by food, see Administration, p. 1537.3. Larger doses of activated charcoal may be needed if a large meal was eaten before treatment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mamograf; Minicam Carb; ***Austral.***: Ad-Sorb†; Carbonet; Carbosorb X; Charcocaps; Charcotabs; Charcotrace; ***Austria***: Norit-Carbomix; Norit; ***Belg.***: Carboflex; Carbonet; Charbogir; Charbon de Belloc; Norit-Carbomix; Norit; ***Braz.***: Carverol; ***Canad.***: Adsorba; Charac; Charcodote Aqueous; ***Cz.***: Carbosorb; Norit†; ***Denm.***: Norit Carbomix; ***Fin.***: Adsorba C; Carbomix; ***Fr.***: Carbactive; Carbomix; Carbonet; Charbon de Belloc; Colocarb†; Formocarbine; Splenocarbine; Toxicarb; ***Ger.***: Adsorba C; Kohle-Compretten; Kohle-Hevert; Kohle-Pulvis; Kohle-Tabletten; Ultracarbon; ***Gr.***: Carbomix†; Norit; Toxicarb; Ultracarbon; ***Hong Kong***: Charcodote; ***Hung.***: Cralex; ***Indon.***: Bekarbon; ***Irl.***: Carbomix; Carbonet; Liqui-Char; ***Israel***: Norit; ***Ital.***: Carbomix; ***Malaysia***: Biocarbon; Ultracarbon; ***Mex.***: Carbotural; ***Neth.***: Norit; ***Norw.***: Carbomix†; Kohle-Compretten; Kull; Medikol†; ***NZ***: Carbosorb X; ***Port.***: Carbomix; Norit; ***Rus.***: Carbopekt (Карбопект); Ultra-Adsorb (Ультра-Адсорб); ***Singapore***: Aqueous Charcodote; Norit†; Ultracarbon; ***Spain***: Arkocapsulas Carbon Vegetal; Carboliq; Ultra Adsorb; ***Swed.***: Carbomix; Kolsuspension; Medikol†; ***Switz.***: Norit; ***Thai.***: Ca-R-Bon; Deltacarbon; Ultracarbon; ***Turk.***: Charflo Aqua; Farmacarbon; ***UK***: Actidose-Aqua Advance; Adsorba C; Bragg's Medicinal Charcoal; Carbomix; Carbonet; Charcodote; Clinisorb; Legius; Lyofoam C; Modern Herbals Trapped Wind & Indigestion; Norit; ***Ukr.***: Allocholum (Аллохол); Sorbex (Сорбекс); ***USA***: Actidose-Aqua; Charcoaid†; Charcoal Plus; Charcocaps; EZ Char; Kerr Insta-Char; Liqui-Char.

Multi-ingredient Preparations. ***Arg.***: Actisorb Plus; Carbogasol; Carbon Tabs; Diarrocalmol; Estreptocarbocaftiazol; Estreptocarbocaftiazol; Karbonetas†; Neoastrin; Opocarbon; ***Austral.***: Carbosorb XS; ***Austria***: Eucarbon; Intestinol†; ***Belg.***: Carbobel; Carbolactanose; ***Canad.***: Carboflex; Carbosylane; Charac Tol; Charcodote; ***Chile***: Carbon Sulfaguanidina; ***Cz.***: Carbocit; Carbotox; Eucarbon; ***Fr.***: Acticarbine; Actisorb Ag+; Carbolevure; Carbophos; Carbosylane; Carbosymag; Notgaz†; Stomargil; ***Ger.***: Mepilex Ag; ***Gr.***: Carbosylane; ***Hung.***: Eucarbon; ***India***: Distenil; Enzolact; Gasnil; Intazyme; Jayzyme; Laxzyme; Medizyme; Nutrozyme; Papytazyme; Unienzyme; ***Irl.***: Actisorb Silver; Carbosylane; ***Israel***: Carbosylane; Charcodote; Eucarbon; Kaltocarb; Novicarbon†; ***Ital.***: Actisorb; Carbone Composto†; Carbonesia; Carboyoghurt; Eucarbon; No-Gas; ***Malaysia***: Eucarbon Herbal; Eucarbon; ***Mex.***: Acilin; Dipecfur; ***NZ***: Carbosorb XS; ***Pol.***: Rapacholin AC†; Rapacholin C; ***Rus.***: Unienzyme с MPS (Юниэнзим с МПС); ***S.Afr.***: Eucarbon†; ***Singapore***: Charcodote; ***Switz.***: Carbolevure; Carboticon; Carvon; ***Thai.***: Belacid; Bicobon; Biodan; Carbomint; Carbonpectate; Delta Charcoal; Pepsitase; Polyenzyme-I†; Pro ABS; ***Turk.***: Charflo Sorbitol†; Eucarbon; Intestinol; Karboseptin; ***UK***: Acidosis; Actisorb Silver; Carbellon; Thickhead; ***Ukr.***: Eucarbon (Эукарбон); Huato Pills (Болюсы Хуато); ***USA***: Actidose with Sorbitol; Flatulex†; Poison Antidote Kit; ***Venez.***: Carbargal con Atropina; Carbargal; Guanicar.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; IBS Eze; Stomach Calm; Vitatona Energy†; ***Austria***: Gastricumeel; Katerex; ***Canad.***: Bioactiv N†; Cocyntal; Cruroheel S†; Endoteel†; Erysidoron 2†; Formula ES 211; Formula Homeo QR 209†; Gastrosine†; Hylands Upset Stomach; Ikoplex 11 Digestion Aid†; Ind Complex†; ***Chile***: Bioactiv N; Similibus; ***Cz.***: Gastrocynesine; ***Fr.***: Abbe Chaupitre no 44†; Cina Compose; Dermo-Drainol†; Gastro-Drainol†; Gastrocynesine; Veino-Drainol†; Voxpax; ***Ger.***: Carminativum Hevert; Derivatio H; Dcrivatio; EAP-61; gastri-loges N; Gastritis Complex; Gastro Magentabletten; Infi-Camphora; Infihepan; Lowe-Komplex Nr 6; Nuxal comp; Nuxal H; Sinuselect N; Stoma-Gastreu S R5; ***Neth.***: Chavita 1; Gastricumeel; Gastrocynesine†; Okugest; ***Port.***: Gastrocynesine; ***Rus.***: Capsicum-Plus (Капсикум-Плюс); ***Switz.***: Exsepta; Gastricumeel; Omida comprimes homeopathiques pour la gorge; Regenaplex Nr. 59b.

Amifostine *(BAN, USAN, rINN)*

Amifostini; Amifostin; Amifostina; Amifostinum; Ethiofos; Gammaphos; NSC-296961; WR-2721; Амифостин.

S-[2-(3-Aminopropylamino)ethyl] dihydrogen phosphorothioate.

$C_5H_{15}N_2O_3PS$=214.2

CAS — 20537-88-6 (amifostine); 63717-27-1 (amifostine monohydrate); 112901-68-5 (amifostine trihydrate).

ATC — V03AF05.

ATC Vet — QV03AF05.

UNII — 1LA426L95O (amifostine); L693H6MM64 (amifostine monohydrate); M487QF2F4V (amifostine trihydrate).

Pharmacopoeias. *US* includes the trihydrate.

USP 36: (Amifostine). The trihydrate is a white crystalline powder. Freely soluble in water. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Incompatibility. Amifostine has been reported[1] to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, chlorpromazine hydrochloride, cisplatin, ganciclovir sodium, hydroxyzine hydrochloride, miconazole, minocycline hydrochloride, and prochlorperazine edisilate during simulated Y-site administration.

1. Trissel LA, Martinez JF. Compatibility of amifostine with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2208–12.

Uses and Administration

Amifostine, an aminothiol compound, is a cytoprotective agent (see also below). It is converted in the body to its active metabolite WR-1065, which protects noncancerous cells against the toxic effects of antineoplastics and ionising radiation. It is used to reduce neutropenia-related infection associated with cyclophosphamide and cisplatin therapy and to reduce the cumulative renal toxicity associated with repeated cisplatin use. It is also used to reduce the incidence of xerostomia (dry mouth) in patients undergoing radiation therapy for head and neck cancer. Licensing details may vary between countries. Amifostine is under investigation in ameliorating the adverse effects of other antineoplastics and in the treatment of myelodysplasia.

In chemotherapy, amifostine is given by intravenous infusion over 15 minutes starting no more than 30 minutes before the antineoplastic therapy at a usual dose of 910 mg/m^2 once daily. Subsequent doses should be reduced to 740 mg/m^2 (or 728 mg/m^2 in some countries) in patients unable to tolerate the full dose. A dose of 740mg/m^2 is recommended for the reduction of cisplatin toxicity if doses of cisplatin of less than 100 mg/m^2 are used.

In the prevention of xerostomia, amifostine is given in a dose of 200 mg/m^2 daily as a 3-minute intravenous infusion starting 15 to 30 minutes before radiotherapy.

For use in children, see below.

Administration in children. Amifostine has been investigated as a cytoprotectant in children with variable results. In children from 3 years of age given a high-dose cisplatin regimen for medulloblastoma, intravenous amifostine 600 mg/m^2 given over 1 minute before and 3 hours into each cisplatin infusion significantly reduced grade 3 and 4 ototoxicity without altering outcomes after 1 year.[1] Earlier studies have also reported successful use of adult doses of amifostine (see above) in children on platinum regimens for solid tumours.[2,3] However, a reduction in cisplatin toxicity has not been seen in some other studies in osteosarcoma[4] and germ-cell tumours.[5]

Amifostine has also been tried subcutaneously as a radioprotectant in small numbers of children.[6]

1. Fouladi M, *et al.* Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma. *J Clin Oncol* 2008; **26:** 3749–55.
2. Stolarska M, *et al.* Cytoprotective effect of amifostine in the treatment of childhood neoplastic diseases—a clinical study including the pharmacoeconomic analysis. *Pharmacol Rep* 2006; **58:** 30–4.
3. Sidi V, *et al.* Use of amifostine in the treatment of recurrent solid tumours in children. *Hippokratia* 2007; **11:** 25–9.
4. Gallegos-Castorena S, *et al.* Toxicity prevention with amifostine in pediatric osteosarcoma patients treated with cisplatin and doxorubicin. *Pediatr Hematol Oncol* 2007; **24:** 403–8.
5. Marina N, *et al.*; Children's Oncology Group. Amifostine does not protect against the ototoxicity of high-dose cisplatin combined with etoposide and bleomycin in pediatric germ-cell tumors: a Children's Oncology Group study. *Cancer* 2005; **104:** 841–7.
6. Anacak Y, *et al.* Daily subcutaneous amifostine administration during irradiation of pediatric head and neck cancers. *Pediatr Blood Cancer* 2007; **48:** 579–81.

Cytoprotection. WR-1065, the active metabolite of amifostine, readily enters non-malignant cells where it deactivates cytotoxics such as alkylating and platinum-containing antineoplastics and protects against the effects of ionising radiation.[1-3] The cytoprotective effects of amifostine are reported to be selective for normal cells and not to interfere with the cytotoxic effects of antineoplastics and radiation on malignant cells. Several factors contribute to this selectivity, including the lower alkaline phosphatase content of malignant cells compared with normal cells, and the lower pH of malignant tissues, both of which decrease the formation and uptake of WR-1065 by malignant cells.[2,3]

Benefit has been reported with amifostine in various malignancies and the American Society of Clinical Oncology currently recommends[4] that its use may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy, as a treatment option for the reduction of severe neutropenia associated with chemotherapy, or to decrease the incidence of xerostomia in patients receiving radiotherapy alone for head and neck cancer. However, a systematic review[5] of 2 studies found amifostine had no radioprotective effect on the salivary glands in patients with differentiated thyroid cancer treated with high-dose radio-iodine.

Amifostine has been tried for mucositis and may be effective at preventing radiation proctitis in those receiving standard-dose radiotherapy for rectal cancer;[6] a dose of at least 340 mg/m^2 has been suggested, given before radiotherapy (see also Mucositis, p. 732.1).

Although amifostine is licensed for intravenous use, other routes have been tried.[7] The subcutaneous route is frequently tried, most often in a dose of 500 mg before radiotherapy, and has generally been found to be effective and associated with fewer adverse effects. Although it may offer advantages over intravenous use in terms of ease of administration and compliance, this has been contested by some.[7,8] Amifostine has also been tried rectally and as orally-active modified-release nanoparticles.[7]

Amifostine has also been used in children, see Administration in Children, above.

1. Foster-Nora JA, Siden R. Amifostine for protection from antineoplastic drug toxicity. *Am J Health-Syst Pharm* 1997; **54:** 787–800.
2. Mabro M, *et al.* A risk-benefit assessment of amifostine in cytoprotection. *Drug Safety* 1999; **21:** 367–87.
3. Culy CR, Spencer CM. Amifostine: an update on its clinical status as a cytoprotectant in patients with cancer receiving chemotherapy or radiotherapy and its potential therapeutic application in myelodysplastic syndrome. *Drugs* 2001; **61:** 641–84.
4. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; **27:** 127–45. Also available at: http://jco.ascopubs.org/cgi/reprint/27/1/127.pdf (accessed 13/05/11)
5. Ma C, *et al.* Amifostine for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 13/05/11).
6. Keefe DM, *et al.* Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; **109:** 820–31.
7. Praetorius NP, Mandal TK. Alternate delivery route for amifostine as a radio-/chemo-protecting agent. *J Pharm Pharmacol* 2008; **60:** 809–15.
8. Bardet E, *et al.* Subcutaneous compared with intravenous administration of amifostine in patients with head and neck cancer receiving radiotherapy: final results of the GORTEC 2000-02 phase III randomized trial. *J Clin Oncol* 2011; **29:** 127–33.

Adverse Effects, Treatment, and Precautions

Amifostine may cause a transient reduction, usually in systolic, or, less frequently, in diastolic blood pressure. However, more pronounced reductions in blood pressure may occur and transient loss of consciousness has been reported very rarely. To minimise hypotension, patients should be adequately hydrated before treatment begins and should be in a supine position. Amifostine should not be used in patients who are hypotensive or dehydrated. Patients taking antihypertensive drugs should stop treatment 24 hours before starting amifostine. Arterial blood pressure must be monitored during the amifostine infusion and if systolic blood pressure decreases significantly, the infusion must stop. Hypotension should be managed with infusion of sodium chloride 0.9% and postural management. Amifostine may be continued if blood pressure returns to normal within 5 minutes. If the full dose cannot be given, a reduced dose of amifostine is used for subsequent chemotherapy cycles, see Uses and Administration, p. 1539.2.

Tachycardia or bradycardia, arrhythmias, chest pain, myocardial ischaemia, myocardial infarction, cardiac arrest, convulsions, dyspnoea, apnoea, hypoxia, respiratory arrest, and renal failure have occurred rarely, and may be associated with hypotension. Caution is required in patients with cardiovascular or cerebrovascular disease, in elderly patients, and in those at risk of renal impairment.

Nausea and vomiting are common and use with an antiemetic is recommended.

Amifostine reduces serum-calcium concentrations, although clinical hypocalcaemia has occurred only very rarely. Serum-calcium concentrations should be monitored in patients at risk of hypocalcaemia and calcium supplements given if needed.

Other adverse effects include flushing, chills, fever, dizziness, somnolence, hiccups, and sneezing. Hypersensitivity reactions and anaphylactoid reactions have been reported including pruritus, urticaria, chest tightness, and laryngeal oedema. Amifostine should be immediately and permanently stopped if a severe acute allergic reaction occurs. Rashes may occur and there have been reports of more severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and bullous toxicity; fatalities have occurred. Most reactions developed after 10 or more days of amifostine treatment as a radioprotectant. Amifostine should be withheld if a cutaneous reaction occurs, and stopped permanently for serious or severe reactions, or if the reaction is associated with other symptoms such as fever.

Giving amifostine over a longer period than 15 minutes is associated with a higher incidence of adverse effects.

References.

1. Boccia R, *et al.* Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). *Int J Radiat Oncol Biol Phys* 2004; **60:** 302–9.

Effects on the musculoskeletal system. Shortly after an amifostine injection into the upper arm, a patient reported severe pain radiating from the injection site to the shoulders, neck, back, and waist, with numbness of the upper arms.[1]

1. Norales G, *et al.* Amifostine-induced back pain: a case report. *Am J Health-Syst Pharm* 2006; **63:** 381–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amifostine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Antihypertensives may potentiate hypotension caused by amifostine and it is therefore recommended that they be stopped 24 hours before starting amifostine treatment.

Pharmacokinetics

Amifostine is rapidly cleared from the plasma after intravenous doses and is dephosphorylated by alkaline phosphatase to the active metabolite WR-1065, a free thiol compound. This is further metabolised to a less active disulfide metabolite (WR-33278). The elimination half-life of amifostine after a 15-minute infusion is less than 10 minutes. Renal excretion of amifostine and its metabolites is minimal.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Erifostine; ***Austral.***: Ethyol; ***Belg.***: Ethyol; ***Braz.***: Ethyol; ***Chile***: Ethyol†; ***China***: An Fu Ding (安福定); Cytofos (采福); Tian Di Da (天地达); ***Cz.***: Ethyol; ***Fin.***: Ethyol; ***Fr.***: Ethyol; ***Ger.***: Ethyol†; ***Gr.***: Ethyol; ***India***: Amfos; Amiphos; Cytofos; Ethyol; M-Fost; Naprofos; ***Israel***: Ethyol†; ***Ital.***: Ethyol; ***Mex.***: Ethyol; ***Neth.***: Ethyol; ***NZ***: Ethyol; ***Philipp.***: Ethyol; ***Pol.***: Ethyol†; ***Port.***: Ethyol; ***Rus.***: Ethyol (Этиол); ***S. Afr.***: Ethyol; ***Spain***: Ethyol; ***Swed.***: Ethyol; ***Switz.***: Ethyol; ***Thai.***: Cytofos; Ethyol; ***Turk.***: Ethyol; ***UK***: Ethyol; ***USA***: Ethyol; ***Venez.***: Ethyol.

Pharmacopoeial Preparations

USP 36: Amifostine for Injection.

Ammonium Tetrathiomolybdate

Tetratiomolibdato de amonio.

$(NH_4)_2MoS_4$=260.3

CAS — 15060-55-6.

UNII — 4V6I63LW1E.

NOTE. The name Coprexa has been used as a trade mark for ammonium tetrathiomolybdate.

Profile

Ammonium tetrathiomolybdate is a chelator that aids the elimination of copper from the body. It is under investigation in the treatment of Wilson's disease and pulmonary fibrosis. There is also some interest in its use in the treatment of malignant neoplasms.

References.

1. Medici V, Sturniolo GC. Tetrathiomolybdate, a copper chelator for the treatment of Wilson disease, pulmonary fibrosis and other indications. *IDrugs* 2008; **11:** 592–606.
2. Brewer GJ. The use of copper-lowering therapy with tetrathiomolybdate in medicine. *Expert Opin Invest Drugs* 2009; **18:** 89–97.
3. Khan G, Merajver S. Copper chelation in cancer therapy using tetrathiomolybdate: an evolving paradigm. *Expert Opin Invest Drugs* 2009; **18:** 541–8.

Wilson's disease. Ammonium tetrathiomolybdate forms a complex with protein and copper. When it is taken with food it blocks the intestinal absorption of copper, and when given between meals it combines with albumin- and caeruloplasmin-bound copper. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels in patients with Wilson's disease (p. 1567.3); it may be particularly suitable for patients with neurological symptoms.[1] Bone marrow depression[1,2] and raised liver enzymes[1] have been reported; both have responded to temporary withdrawal or dose reduction.

1. Brewer GJ, *et al.* Treatment of Wilson disease with ammonium tetrathiomolybdate III: initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003; **60:** 379–85.
2. Harper PL, Walshe JM. Reversible pancytopenia secondary to treatment with tetrathiomolybdate. *Br J Haematol* 1986; **64:** 851–3.

Amyl Nitrite

Amile Nitrito; Amil-nitrit; Amyli Nitris; Amylis Nitris; Amylium Nitrosum; Amylnitrit; Amylnitritt; Amyylinitriitti; Azotito de Amilo; Azotyn Amylu; Dusitan Amylnatý; Isoamyl Nitrite; Isoamylnitriet; Isoamyylinitriitti; Isopentyl Nitrite; Isopentylnitrit; Nitrite d'amyle; Nitrito de Amila; Nitrito de amilo; Nitrito di Amile; Pentanolis Nitris; Нитрит Амила; Амилнитрит; Амілнітрит.

$C_5H_{11}NO_2$=117.1

ATC — V03AB22.

ATC Vet — QV03AB22.

UNII — 22T8Z09XAK (amyl nitrite); 5N0U5TUC9Z (3-methyl-1-butanol).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of amyl nitrite:

60 second trip; Aimes; Aimies; Ames; Amys; Boppers; Hard on; Pearls; Poppers; Sixty second trip; Snappers; Whiffenpoppers.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Amyl Nitrite). A mixture of the nitrite esters of 3-methyl-1-butanol and 2-methyl-1-butanol. A clear, yellowish liquid having a peculiar, ethereal, fruity odour. It is very flammable. It is volatile even at low temperatures. B.p. about 96 degrees. Practically insoluble in water; miscible with alcohol and with ether. Store in a cool place in airtight containers. Protect from light.

Stability. Amyl nitrite is liable to decompose with evolution of nitrogen, particularly if it has become acid in reaction.

Uses and Administration

Amyl nitrite is rapidly absorbed on inhalation and is used in the immediate treatment of patients with definite cyanide poisoning (p. 2156.2) to induce the formation of methaemoglobin, which combines with the cyanide to form non-toxic cyanmethaemoglobin. Other mechanisms such as nitric oxide formation, vasodilatation, and improved hepatic blood flow may also contribute to its mode of action. A suggested procedure is to give amyl nitrite by inhalation for up to 30 seconds every minute until intravenous treatment with sodium nitrite (p. 1574.3) and sodium thiosulfate (p. 1576.2) can be started. It has also been suggested for use in the management of hydrogen sulfide poisoning (p. 1799.2).

Amyl nitrite has an action similar to that of glyceryl trinitrate (p. 1391.3) and used to be given by inhalation for the relief of acute attacks of angina pectoris but is seldom used now.

Homoeopathy

Amyl nitrite has been used in homoeopathic medicines under the following names: Amyl nitrosum; Am. nit.; Amyl nit.

Uterine relaxation. Amyl nitrite relaxes uterine smooth muscle. While it is no longer used as a tocolytic, amyl nitrite inhalation has been used during labour to facilitate preterm caesarean section,[1] with general anaesthesia to relax uterine constriction rings,[2] or with epidural anaesthesia in the management of shoulder dystocia.[3]

1. Hendricks SK, *et al.* Amyl nitrite: use as a smooth muscle relaxant in difficult preterm cesarean section. *Am J Perinatol* 1992; **9:** 289–92.
2. El-Mowalfi DM. Geneva Foundation for Medical Education and Research. Obstetrics simplified: abnormal uterine action. Available at: http://www.gfmer.ch/Obstetrics_simplified/abnormal_uterine_action.htm (accessed 11/01/11)
3. Hepner DL, *et al.* The Zavanelli maneuver does not preclude regional anesthesia. *Anesth Analg* 1997; **84:** 1145–6.

Adverse Effects, Treatment, and Precautions

Amyl nitrite inhalation commonly causes flushing, headache, and dizziness; nausea and vomiting, hypotension, restlessness, pallor, sweating, urinary and faecal incontinence, and tachycardia may also occur. Overdosage may result in cyanosis, syncope, dyspnoea, and muscular weakness, due to vasodilatation and methaemoglobinaemia. Methylthioninium chloride may be required for severe methaemoglobinaemia but should not be used if cyanide poisoning is suspected since cyanide may be displaced. Respiratory depression, metabolic acidosis, convulsions, coma, and cardiovascular collapse can occur in severe toxicity; deaths are very rare.

Amyl nitrite may increase intra-ocular and intracranial pressure and should be used with caution in patients with glaucoma, recent head trauma, or cerebral haemorrhage.

Tolerance to nitrites can develop with chronic use.

Abuse. Volatile alkyl nitrites (commonly known as 'poppers'), including amyl, butyl, or isobutyl nitrite, have been abused in the belief that they expand creativity, stimulate music appreciation, promote a sense of abandon in dancing, and intensify sexual experience.[1,2]

Inhalation causes headache, tachycardia, syncope, acute psychosis, increased intra-ocular pressure, transient hemiparesis, methaemoglobinaemia, coma, and, rarely, sudden death. Haemolytic anaemia has also been reported[3-7] and may be more likely in those with glucose-6-phosphate deficiency;[5,7] in some subjects, Heinz body formation has been detected.[3,6] Methaemoglobinaemia may be severe,[8] and has also been reported after ingestion of volatile nitrites.[9-12] Symptoms are similar to those of hypoxia[11] and may be reversed by methylthioninium chloride.[8-12] Bilateral vision loss has been reported due to damage to the foveal photoreceptors; in some patients symptoms improved over several weeks.[13,14]

Inhalation of volatile nitrites has led to severe and extensive contact dermatitis around the face with secondary spread elsewhere on the body.[15,16]

1. Sigell LT, *et al.* Popping and snorting volatile nitrites: a current fad for getting high. *Am J Psychiatry* 1978; **135:** 1216–18.
2. Lockwood B. Poppers: volatile nitrite inhalants. *Pharm J* 1996; **257:** 154–5.
3. Romeril KR, Concannon AJ. Heinz body haemolytic anaemia after sniffing volatile nitrites. *Med J Aust* 1981; **1:** 302–3.
4. Brandes JC, *et al.* Amyl nitrite-induced hemolytic anemia. *Am J Med* 1989; **86:** 252–4.
5. Graves TD, Mitchell S. Acute haemolytic anaemia after inhalation of amyl nitrite. *J R Soc Med* 2003; **96:** 594–5.
6. Shortt J, *et al.* Oxidative haemolysis due to 'poppers'. *Br J Haematol* 2008; **142:** 328.
7. Neuberger A, *et al.* Hemolytic anemia in a G6PD-deficient man after inhalation of amyl nitrite ('poppers'). *Isr Med Assoc J* 2002; **4:** 1085–6.
8. Modarai B, *et al.* Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. *Emerg Med J* 2002; **19:** 270–1.
9. Laaban JP, *et al.* Amyl nitrite poppers and methemoglobulinemia. *Ann Intern Med* 1985; **103:** 804–5.
10. Osterloh J, Olson K. Toxicities of alkyl nitrites. *Ann Intern Med* 1986; **104:** 727.
11. Pierce JMT, Nielsen MS. Acute acquired methaemoglobinaemia after amyl nitrite poisoning. *BMJ* 1989; **298:** 1566.
12. Forsyth RJ, Moulden A. Methaemoglobinaemia after ingestion of amyl nitrite. *Arch Dis Child* 1991; **66:** 152.
13. Pece A, *et al.* Transient visual loss after amyl isobutyl nitrite abuse. *Semin Ophthalmol* 2004; **19:** 105–6.
14. Vignal-Clermont C, *et al.* Poppers-associated retinal toxicity. *N Engl J Med* 2010; **363:** 1583–5.

15. Bos JD, *et al.* Allergic contact dermatitis to amyl nitrite ('poppers'). *Contact Dermatitis* 1985; **12:** 109.
16. Foroozan M, *et al.* Dermatose faciale aux poppers. *Ann Dermatol Venereol* 2009; **136:** 298–9.

Handling and storage. Amyl nitrite is very flammable and must not be used where it may be ignited. It should be protected from light.

Pregnancy. Licensed product information warns that maternal use of amyl nitrite during pregnancy reduces blood pressure in the mother and blood flow across the placenta.

Interactions

Like organic nitrates, amyl nitrite and other inhaled volatile nitrites may potentiate the hypotensive effects of phosphodiesterase type-5 inhibitors, see Interactions, under Sildenafil, p. 2366.3.

Pharmacokinetics

Amyl nitrite is absorbed via the skin, lungs, mucous membranes, and the gastrointestinal tract. Therapeutic effects are seen within 1 minute of inhalation. It is metabolised rapidly in the liver by hydrolytic denitration and excreted as both metabolites and unchanged drug in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Tripac-Cyano; ***USA***: Cyanide Antidote Package; Emergent-Ez.

Homoeopathic Preparations. ***Austral.***: Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; ***Canad.***: Menopause.

Pharmacopoeial Preparations
USP 36: Amyl Nitrite Inhalant.

Asoxime Chloride

Asoxima, cloruro de; Chlorek Azoksymu; HI-6.
1-({[4-(Aminocarbonyl)pyridinio]methoxy}methyl)-2-[(hydroxyimino)methyl]pyridinium dichloride.
$C_{14}H_{16}Cl_2N_4O_3$=359.2
CAS — 34433-31-3.
UNII — HUV88P6SJS.

Profile

Asoxime chloride is a cholinesterase reactivator that has been tried in the treatment of poisoning by organophosphorus pesticides and related compounds, including nerve agents.

References.
1. Jovanović D, *et al.* A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; **9:** 49–51.
2. Kušić R, *et al.* HI-6 in man: efficacy of the oxime in poisoning by organophosphorus insecticides. *Hum Exp Toxicol* 1991; **10:** 113–18.
3. Lundy PM, *et al.* Development of the bisquaternary oxime HI-6 toward clinical use in the treatment of organophosphate nerve agent poisoning. *Toxicol Rev* 2006; **25:** 231–43.

AST-120

CAS — 90597-58-3.

Profile

AST-120 is a form of activated charcoal (p. 1537.3) consisting of spherical microcrystalline carbonaceous particles with oxygen complex including surface oxides. It is given orally as an adsorbent to delay the progression of chronic renal failure by removing uraemic toxins and their precursors from the gastrointestinal tract. It is also under investigation in hepatic encephalopathy and gastrointestinal disorders.

References.
1. Takahashi N, *et al.* Therapeutic effects of long-term administration of an oral adsorbent in patients with chronic renal failure: two-year study. *Int J Urol* 2005; **12:** 7–11.
2. Ueda H, *et al.* AST-120, an oral adsorbent, delays the initiation of dialysis in patients with chronic kidney diseases. *Ther Apher Dial* 2007; **11:** 189–95.
3. Fukuda Y, *et al.* Oral spherical adsorptive carbon for the treatment of intractable anal fistulas in Crohn's disease: a multicenter, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2008; **103:** 1721–9.
4. Shen B, *et al.* The efficacy and tolerability of AST-120 (spherical carbon adsorbent) in active pouchitis. *Am J Gastroenterol* 2009; **104:** 1468–74.
5. Akizawa T, *et al.* CAP-KD Study Group. Effect of a carbonaceous oral adsorbent on the progression of CKD: a multicenter, randomized, controlled trial. *Am J Kidney Dis* 2009; **54:** 459–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Kremezin; Kyucal.

Atipamezole *(BAN, USAN, rINN)*

Atipamezol; Atipamézole; Atipamezolum; MPV-1248; Атипамезол.
4-(2-Ethyl-2-indanyl)imidazole.
$C_{14}H_{16}N_2$=212.3
CAS — 104054-27-5.
ATC Vet — QV03AB90.
UNII — 03N9U5JAF6.

Atipamezole Hydrochloride *(BANM, rINNM)*

Atipametsolihydrokloridi; Atipamezol, hidrocloruro de; Atipamézole, Chlorhydrate d'; Atipamezolhydroklorid; Atipamezoli Hydrochloridum; Hidrocloruro de atipamezol; Атипамезола Гидрохлорид.
$C_{14}H_{16}N_2$,HCl=248.8
CAS — 104075-48-1.
UNII — 2W4279571X.

Profile

Atipamezole is a selective alpha$_2$-adrenergic receptor antagonist that is used as the hydrochloride in veterinary medicine to reverse the sedative effects of medetomidine.

References.
1. Pertovaara A, *et al.* Pharmacological properties, central nervous system effects, and potential therapeutic applications of atipamezole, a selective alpha2-adrenoceptor antagonist. *CNS Drug Rev* 2005; **11:** 273–88.

Bixalomer *(USAN, rINN)*

AMG-223; ASP-1585; Bixalomère; Bixalómero; Bixalomerum; Биксаломер.
N,N,N′,N′-Tetrakis(3-aminopropyl)butane-1,4-diamine polymer with 2-(chloromethyl)oxirane.
$(C_{16}H_{40}N_6)_x(C_3H_5ClO)_y$
CAS — 851373-13-2.
UNII — 3160WY51LV.

Profile

Bixalomer is a phosphate binder used for hyperphosphataemia (p. 1776.3) in patients with chronic renal failure. It is given orally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Kiklin.

Calcium Polystyrene Sulfonate

Calcium Polystyrene Sulphonate; Poliestirenosulfonato cálcico; Polistiren Sülfonat Kalsiyum; Полистирен Сульфонат Кальция.
CAS — 37286-92-3.
ATC — V03AE01.
ATC Vet — QV03AE01.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2014: (Calcium Polystyrene Sulfonate). A cream to light brown, fine powder. The calcium content is not less than 6.5% and not more than 9.5%, calculated with reference to the dried substance. Each g exchanges not less than 1.3 mmol and not more than 2.0 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water and in alcohol. Store in airtight containers.

Uses and Administration

Calcium polystyrene sulfonate, the calcium salt of sulfonated styrene polymer, is a cation-exchange resin that exchanges calcium ions for potassium ions and other cations in the gastrointestinal tract. It is used similarly to sodium polystyrene sulfonate (p. 1575.2) to enhance potassium excretion in the treatment of hyperkalaemia (p. 1777.1) associated with anuria or severe oliguria, and in dialysis patients. It may be preferred to the sodium resin in patients who cannot tolerate an increase in their sodium load. It is estimated that 1 g of calcium polystyrene sulfonate could bind 1.3 to 2 mmol of potassium but it is unlikely that such figures could be achieved in practice.

It is given orally or via a nasogastric tube in a usual dose of 15 g three or four times daily, as a suspension in water or syrup or as a sweetened paste. About 3 to 4 mL of vehicle has been suggested for each gram of resin. It should not be given in fruit juices that have a high potassium content.

When oral administration is difficult, calcium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 150 mL of water or glucose 10%, or 100 mL of 2% methylcellulose plus 100 mL of water, and retained, if possible, for at least 9 hours. Initial therapy may involve both oral and rectal routes. Following retention of the enema the colon should be irrigated to remove the resin.

For doses in children, see below.

Administration in children. Calcium polystyrene sulfonate is used in neonates and children to enhance potassium excretion in the treatment of hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients. Use is not recommended in neonates with reduced gut motility. It may be given orally as a suspension or paste, or rectally; calcium polystyrene sulfonate to be given rectally is mixed with water or glucose 5 or 10%, diluted in the same ratio as that for adults, see above. Care is needed with rectal use in children as excessive dosage or inadequate dilution can result in impaction of the resin; however, the oral route is not recommended in neonates. Licensed product information recommends a dose of 1 g/kg daily in divided doses, reduced to a maintenance dose of 500 mg/kg daily in divided doses. The *BNFC* suggests the same doses (to a daily maximum of 60 g orally, or 30 to 40 g rectally).

Adverse Effects and Precautions

As for Sodium Polystyrene Sulfonate, p. 1575.3. Sodium overloading is not a problem with calcium polystyrene sulfonate, but calcium overloading and hypercalcaemia may occur. It should therefore be avoided in patients with conditions such as hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma. Patients should be monitored for electrolyte disturbances, especially hypokalaemia and hypercalcaemia.

Effects on the gastrointestinal tract. Intestinal necrosis has been reported after oral use of calcium polystyrene sulfonate in a patient with acute colonic pseudo-obstruction,[1] and after oral and rectal use in a uraemic patient;[2] neither patient was given sorbitol.

1. Goutorbe P, *et al.* Intestinal necrosis associated with orally administered calcium polystyrene sulfonate without sorbitol. *Ann Pharmacother* 2011; **45:** 278.
2. Joo M, *et al.* Colonic mucosal necrosis following administration of calcium polystyrene [sic] sulfonate (Kalimate) in a uremic patient. *J Korean Med Sci* 2009; **24:** 1207–11.

Effects on the lungs. An elderly man who died from cardiac arrest was found at autopsy to have bronchopneumonia associated with inhalation of calcium polystyrene sulfonate;[1] the resin had been given orally to treat hyperkalaemia.

1. Chaplin AJ, Millard PR. Calcium polystyrene sulphonate: an unusual cause of inhalation pneumonia. *BMJ* 1975; **3:** 77–8.

Interactions

As for Sodium Polystyrene Sulfonate, p. 1576.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Resincalcio; RIC Calcio; ***Austral.***: Calcium Resonium; ***Austria***: CPS Pulver; Sorbisterit; ***Belg.***: Kayexalate; Sorbisterit; ***Braz.***: Sorcal; ***Canad.***: Resonium Calcium; ***Chile***: Sorbisterit; ***China***: Calcium Resonium (盖利生); ***Cz.***: Calcium Resonium; Resical; ***Denm.***: Resonium Calcium; Sorbisterit; ***Fin.***: Sorbisterit; ***Fr.***: Calcium-Sorbisterit†; Resikali; ***Ger.***: Calcium Resonium†; CPS Pulver; Elutit-Calcium; Sorbisterit; ***Gr.***: Calcium Resonium; ***Hong Kong***: Calcium Resonium; ***India***: Calcium Resonium; K-Bind; Kapstat; ***Indon.***: Kalitake; ***Irl.***: Calcium Resonium; Sorbisterit†; ***Jpn***: Kalimate; ***Malaysia***: Kalimate; ***Neth.***: Sorbisterit; ***Norw.***: Resonium Calcium; ***NZ***: Calcium Resonium; ***Philipp.***: Kalimate; ***Pol.***: Calcium Resonium; ***Port.***: Resical; ***Spain***: Resincalcio; Sorbisterit; ***Swed.***: Resonium Calcium; Sorbisterit; ***Switz.***: Sorbisterit; ***Thai.***: Kalimate; Resincalcio; ***Turk.***: Anti-potasium; ***UK***: Calcium Resonium; Sorbisterit.

Deferasirox *(USAN, rINN)*

CGP-72670; Deferasiroks; Déférasirox; Deferasiroxum; ICL-670; ICL-670A; Деферазирокс.
4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid.
$C_{21}H_{15}N_3O_4$=373.4
CAS — 201530-41-8.
ATC — V03AC03.
ATC Vet — QV03AC03.
UNII — V8G4MOF2V9.

Uses and Administration

Deferasirox is an orally active selective iron chelator that is used in the management of chronic iron overload (p. 1545.2) due to blood transfusion or non-transfusion dependent thalassaemia syndromes. Two moles of deferasirox bind with one mole of ferric ion to form a water-soluble iron complex; theoretically 100 mg of deferasirox can bind about 7.5 mg of iron, but in practice oral doses of 20 mg/kg daily are thought to result in iron losses of about 330 micrograms/kg each day. Deferasirox is available as tablets that may be dispersed in water, orange juice, or apple juice immediately before use. It should be taken on an empty stomach at least 30 minutes before food.

The usual initial dose for transfusional iron overload is 20 mg/kg once daily. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary, in steps of 5 to 10 mg/kg. Treatment should be withheld if serum-ferritin concentrations consistently fall below 500 micrograms/litre. Doses above 40 mg/kg daily are not recommended.

In iron overload of non-transfusion dependent thalassaemia syndromes, the usual initial dose is 10 mg/kg once daily. If the baseline liver-iron concentration is more than 15 mg of iron per gram of liver dry weight, the dose may be increased to 20 mg/kg daily after 4 weeks. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary, in steps of 5 to 10 mg/kg. Doses above 20 mg/kg daily (10 mg/kg daily in children) are not recommended. Treatment should be stopped when a satisfactory body-iron level has been achieved (serum-ferritin concentration below 300 micrograms/litre or liver-iron concentration below 3 mg of iron per gram of liver dry weight).

When deferasirox needs to be used with potent uridine diphosphate glucuronosyltransferase (UGT) inducers such as carbamazepine, rifampicin, phenytoin, phenobarbital, and ritonavir, or with colestyramine, the initial dose may be increased by 50% and adjusted according to serum-ferritin concentrations and response. For doses in children and in those with hepatic or renal impairment, see below.

References.

1. VanOrden HE, Hagemann TM. Deferasirox--an oral agent for chronic iron overload. *Ann Pharmacother* 2006; **40:** 1110–17.
2. Stumpf JL. Deferasirox. *Am J Health-Syst Pharm* 2007; **64:** 606–16.
3. Yang LPH, *et al.* Deferasirox: a review of its use in the management of transfusional chronic iron overload. *Drugs* 2007; **67:** 2211–30.
4. Vichinsky E. Clinical application of deferasirox: practical patient management. *Am J Hematol* 2008; **83:** 398–402.
5. Cappellini MD, Taher A. Long-term experience with deferasirox (ICL670), a once-daily oral iron chelator, in the treatment of transfusional iron overload. *Expert Opin Pharmacother* 2008; **9:** 2391–2402.
6. McLeod C, *et al.* Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation. *Health Technol Assess* 2009; **13:** 1–121.
7. Jabbour E, *et al.* Managing iron overload in patients with myelodysplastic syndromes with oral deferasirox therapy. *Oncologist* 2009; **14:** 489–96.
8. Kontoghiorghes GJ. Introduction of higher doses of deferasirox: better efficacy but not effective iron removal from the heart and increased risks of serious toxicities. *Expert Opin Drug Safety* 2010; **9:** 633–41.
9. Meerpohl JJ, *et al.* Deferasirox for managing transfusional iron overload in people with sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 12/11/10).
10. Ladis V, *et al.* Deferasirox administration for the treatment of non-transfusional iron overload in patients with thalassaemia intermedia. *Br J Haematol* 2010; **151:** 504–8. Correction. *ibid.*; **152:** 124.
11. Vichinsky E, *et al.* Long-term safety and efficacy of deferasirox (Exjade) for up to 5 years in transfusional iron-overloaded patients with sickle cell disease. *Br J Haematol* 2011; **154:** 387–97.
12. Cappellini MD, *et al.* Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. *Blood* 2011; **118:** 884–93.
13. Taher AT, *et al.* Deferasirox reduces iron overload significantly in nontransfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study. *Blood* 2012; **120:** 970–7.

Administration in children. Deferasirox is used for the management of chronic iron overload due to blood transfusion in children from 2 years of age, and for overload due to non-transfusion dependent thalassaemia syndromes in patients aged 10 years and older. It can generally be given in adult doses, see above. For dose adjustments in renal impairment, see below.

Administration in hepatic impairment. Deferasirox is not recommended in those with severe hepatic impairment (Child-Pugh class C). Those with mild or moderate (Child-Pugh class A or B, respectively) hepatic impairment should be monitored closely and the dose titrated as necessary. US licensed product information recommends that patients with moderate impairment be given 50% of the suggested starting dose (see Uses and Administration above). In the UK product information it is recommended that, in patients with moderate hepatic impairment, the deferasirox dose is considerably reduced, followed by progressive increases up to a maximum of 50% of the suggested starting dose.

Deferasirox therapy should be interrupted and/or the dose reduced if severe or persistent increases in liver enzymes or bilirubin occur during treatment.

Administration in renal impairment. Deferasirox doses should be adjusted in renal impairment (for monitoring requirements, see Adverse Effects and Precautions, below). Licensed product information varies between countries but recommended indicators for dose adjustment include a fall in estimated creatinine clearance (CC) to below 90 mL/minute, an increase in serum-creatinine concentration of more than 33% above average pretreatment values, and, particularly in children, a rise of serum-creatinine concentration above the age-appropriate upper limit of normal.

In patients being treated for chronic iron overload due to blood transfusion, the daily dose should be reduced by 10 mg/kg. If renal function deteriorates further then treatment with deferasirox should be stopped. Treatment may be restarted if individual circumstances allow. In patients being treated for non-transfusion dependent thalassaemia syndromes, adult doses should be reduced by 50% or stopped if the dose is 5 mg/kg daily; in children the dose may be reduced by 5 mg/kg.

In the USA, deferasirox is contra-indicated in patients with a CC of less than 40 mL/minute or a serum creatinine more than twice the age-appropriate upper limit of normal, whereas in the UK it is contra-indicated in those with an estimated CC of less than 60 mL/minute.

Mucormycosis. Deferasirox has been used successfully as an adjunct to antifungal therapy in the treatment of mucormycosis (p. 566.3),[1-3] although some treatment failures have also been reported.[2,4] Oral doses of about 15 to 20 mg/kg daily have been used,[1,2] usually with liposomal amphotericin B with which it is reported to be synergistic.[3] Deferasirox starves mucormycetes of the iron required for growth, unlike desferrioxamine which enhances iron uptake by the fungus (see p. 1547.2). Deferasirox may also enhance the inflammatory response to the infection.[4]

1. Reed C, *et al.* Deferasirox, an iron-chelating agent, as salvage therapy for rhinocerebral mucormycosis. *Antimicrob Agents Chemother* 2006; **50:** 3968–9.
2. Spellberg B, *et al.* Safety and outcomes of open-label deferasirox iron chelation therapy for mucormycosis. *Antimicrob Agents Chemother* 2009; **53:** 3122–5.
3. Busca A, *et al.* Combined antifungal therapy, iron chelation and surgical resection as treatment of hepatic zygomycosis in a patient with haematological malignancy. *Mycoses* 2010; **53:** 275–8.
4. Soummer A, *et al.* Failure of deferasirox, an iron chelator agent, combined with antifungals in a case of severe zygomycosis. *Antimicrob Agents Chemother* 2008; **52:** 1585–6.

Adverse Effects and Precautions

The commonest adverse effects with deferasirox are dose-related gastrointestinal disorders, such as nausea, vomiting, diarrhoea, and abdominal pain; diarrhoea may be more common in young children and the elderly. Upper gastrointestinal ulceration and haemorrhage, sometimes fatal, have been reported; fatal haemorrhages were more common in elderly patients with advanced malignancies and/or low platelet counts. Rashes are common and may respond to a reduction in dose; erythema multiforme has been reported. Serious hypersensitivity reactions such as anaphylaxis and angioedema have been reported, usually within the first month of deferasirox treatment. Other adverse effects include headache, pyrexia, pruritus, anxiety, sleep disorders, fatigue, dizziness, skin pigmentation disorders, infections, pharyngolaryngeal pain, and oedema. Leucocytoclastic vasculitis, urticaria, and alopecia have occurred.

Dose-dependent increases in serum creatinine are common and proteinuria may also occur. There have been reports of acute renal failure, including fatalities; renal tubulopathy, has occurred, mainly in children and adolescents with β-thalassaemia.

US licensed product information recommends that renal function is measured before starting therapy, and at least monthly thereafter. In high-risk patients, such as those with pre-existing renal impairment or at increased risk of acute renal failure, renal function should be measured weekly during the first month of treatment or after adjusting the dose, and monthly thereafter. Deferasirox should not be used in patients with a CC below 40 mL/minute or with a serum-creatinine more than twice the upper limit of normal.

In the UK, where deferasirox is not recommended in those with a CC below 60 mL/minute, all patients should have their renal function measured at baseline, weekly during the first month of treatment or after adjusting the dose, and monthly thereafter.

Tests for proteinuria should also be performed monthly. The dose should be reduced or treatment stopped if persistent increases in serum creatinine occur, see Administration in Renal Impairment, above.

Liver enzyme values may increase in patients receiving deferasirox, and cases of hepatitis and hepatic failure, sometimes fatal, have occurred. Gallstones have also been reported. Liver enzymes and bilirubin should be measured before starting deferasirox, every 2 weeks during the first month, and monthly thereafter. The dose of deferasirox may need to be modified in those with pre-existing hepatic impairment, or if increases in liver enzymes or bilirubin occur during treatment, see Administration in Hepatic Impairment, above.

As with other iron chelators, hearing loss and visual disorders, including cataracts, have occurred. Audiological and ophthalmological tests should be performed before starting deferasirox and then every 12 months. In children, annual assessment of growth and development is also recommended.

Serum ferritin should be measured monthly to assess patient response and avoid overchelation of iron. Treatment should be withheld if the value is consistently below 500 micrograms/litre in patients being treated for transfusional iron overload, or below 300 micrograms/litre in those with non-transfusion dependent thalassaemia syndromes.

There have been rare reports of blood disorders, some of which have been fatal, including agranulocytosis, neutropenia, and thrombocytopenia, in patients taking deferasirox. Blood counts should be monitored regularly. Deferasirox should be used with caution, if at all, when platelet counts are less than 50 000 cells/mm^3.

Serious adverse effects, including fatalities, were more often reported in elderly patients, in those with comorbidities such as pre-existing renal or hepatic impairment, or in those with advanced disease; deferasirox is therefore contra-indicated in those with a poor performance status, high-risk myelodysplastic syndromes, or advanced malignancies.

Hyperferritinaemia. Although serum-ferritin concentrations are generally considered to be a proxy measure for iron overload in patients with thalassaemia, there has been a report[1] of a patient in whom switching from desferrioxamine to oral deferasirox chelation therapy was associated with progressive rises in serum ferritin which were not paralleled by increases in body-iron as measured by MRI. After six months of therapy with deferasirox, serum ferritin had increased from about 600 to over 2700 ng/mL, despite progressive increases in deferasirox dosage from 10 to 30 mg/kg daily. On stopping the drug and resuming desferrioxamine the ferritin values returned to baseline.

1. Ricchi P, *et al.* Paradoxically increased ferritin level in a beta-thalassemia major patient following the start of deferasirox chelation therapy. *Acta Haematol (Basel)* 2010; **123:** 117–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies deferasirox as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. A report[1] of a successful birth after use of deferasirox during pregnancy.

1. Ricchi P, *et al.* A case of well-tolerated and safe deferasirox administration during the first trimester of a spontaneous pregnancy in an advanced maternal age thalassemic patient. *Acta Haematol (Basel)* 2011; **125:** 222–224.

Interactions

Deferasirox should not be given with aluminium-containing antacids since there is a possibility that it may chelate aluminium. The metabolism of deferasirox depends on uridine diphosphate glucuronosyltransferase (UGT) enzymes, and use with potent inducers of these enzymes such as carbamazepine, rifampicin, phenytoin, phenobarbital, and ritonavir may decrease exposure to deferasirox. The dose of deferasirox may need to be increased and the serum ferritin monitored (see also Uses and Administration, above).

Exposure to deferasirox was reduced when it was given with colestyramine, and their use together should be avoided. An increased initial dose of deferasirox should be considered if treatment with both drugs is necessary (see Uses and Administration, above).

Deferasirox inhibits cytochrome P450 isoenzymes CYP1A2 and CYP2C8, and may induce CYP3A4. Caution is advised when deferasirox is given with drugs which are metabolised by these isoenzymes.

References.

1. Skerjanec A, *et al.* Investigation of the pharmacokinetic interactions of deferasirox, a once-daily oral iron chelator, with midazolam, rifampin, and repaglinide in healthy volunteers. *J Clin Pharmacol* 2010; **50:** 205–13.

Pharmacokinetics

Deferasirox is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1.5 to 4 hours after ingestion. The absolute bioavailability is about 70% but is increased in the presence of food. Deferasirox is about 99% bound to plasma proteins, mainly albumin. Metabolism of deferasirox is mainly glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes. Cytochrome P450 isoenzyme-mediated metabolism appears to be minor. Deconjugation of the glucuronidates in the intestine and subsequent enterohepatic recycling are likely to occur. It is excreted mainly in the faeces via bile, as metabolites and as unchanged drug. About 8% of a dose is excreted in the urine. The mean elimination half-life is about 8 to 16 hours.

Children and adolescents have a lower exposure to deferasirox than adults; in children under 6 years of age exposure was about 50% lower. Men have a higher clearance of deferasirox than women.

References.

1. Galanello R, *et al*. Effect of food, type of food, and time of food intake on deferasirox bioavailability: recommendations for an optimal deferasirox administration regimen. *J Clin Pharmacol* 2008; **48:** 428–35.
2. Séchaud R, *et al*. Absolute oral bioavailability and disposition of deferasirox in healthy human subjects. *J Clin Pharmacol* 2008; **48:** 919–25.
3. Chirnomas D, *et al*. Deferasirox pharmacokinetics in patients with adequate versus inadequate response. *Blood* 2009; **114:** 4009–13.
4. Waldmeier F, *et al*. Pharmacokinetics, metabolism, and disposition of deferasirox in beta-thalassemic patients with transfusion-dependent iron overload who are at pharmacokinetic steady state. *Drug Metab Dispos* 2010; **38:** 808–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Exjade; ***Austral.***: Exjade; ***Austria***: Exjade; ***Belg.***: Exjade; ***Braz.***: Exjade; ***Canad.***: Exjade; ***Chile***: Exjade; ***China***: Exjade (恩瑞格); ***Cz.***: Exjade; ***Denm.***: Exjade; ***Fr.***: Exjade; ***Ger.***: Exjade; ***Gr.***: Exjade; ***Hong Kong***: Exjade; ***Hung.***: Exjade; ***Indon.***: Exjade; ***Irl.***: Exjade; ***Israel***: Exjade; ***Ital.***: Exjade; ***Malaysia***: Exjade; ***Neth.***: Exjade; ***Norw.***: Exjade; ***NZ***: Exjade; ***Philipp.***: Exjade; ***Pol.***: Exjade; ***Port.***: Exjade; ***Rus.***: Exjade (Эксиджад); ***S.Afr.***: Exjade; ***Singapore***: Exjade; ***Spain***: Exjade; ***Swed.***: Exjade; ***Switz.***: Exjade; ***Thai.***: Exjade; ***Turk.***: Exjade; ***UK***: Exjade; ***Ukr.***: Exjade (Эксиджад); ***USA***: Exjade.

Deferiprone *(BAN, USAN, rINN)*

APO-066; APO-66; CP-20; Deferipron; Deferiprona; Défériprone; Deferiproni; Deferipronum; Deferypron; Dimethylhydroxypyridone; DN-180-01-AF; L-1; L1; PL-1; Деферипрон.

1,2-Dimethyl-3-hydroxypyrid-4-one; 3-Hydroxy-1,2-dimethyl-4-pyridone.

$C_7H_9NO_2$=139.2

CAS — 30652-11-0.

ATC — V03AC02.

ATC Vet — QV03AC02.

UNII — 2BTY8KH53L.

Uses and Administration

Deferiprone is an orally active iron chelator used in the treatment of iron overload in patients with thalassaemia for whom desferrioxamine is unsuitable or ineffective. Three moles of deferiprone bind with one mole of ferric ion to form a stable water-soluble iron complex; theoretically 100 mg of deferiprone can bind about 13.4 mg of iron, but as with other iron chelators, it is unlikely that such a figure could be achieved in practice. Deferiprone may be given in oral doses of 25 mg/kg three times daily. Doses above 100 mg/kg daily are not recommended. For use in children, see Administration in Children, below.

Reviews.

1. Hoffbrand AV. Deferiprone therapy for transfusional iron overload. *Best Pract Res Clin Haematol* 2005; **18:** 299–317.
2. Piga A, *et al*. Deferiprone: new insight. *Ann N Y Acad Sci* 2005; **1054:** 169–74.
3. Kattamis A. Combined therapy with deferoxamine and deferiprone. *Ann N Y Acad Sci* 2005; **1054:** 175–82.
4. Roberts D, *et al*. Oral deferiprone for iron chelation in people with thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 29/07/10).
5. Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. *Acta Haematol (Basel)* 2009; **122:** 155–64.
6. Cappellini MD, *et al*. Overview of iron chelation therapy with desferrioxamine and deferiprone. *Hemoglobin* 2009; **33** (suppl 1): S58–S69.

Administration in children. UK licensed product information states that there are limited data on the use of deferiprone in children between 6 and 10 years of age, and no data on use in children below 6. Australian licensed product information states that limited data exist for children between the ages of 2 and 10 but that the effects of deferiprone on growth are unknown. Licensed doses in children are calculated by weight on the same basis as adults (see Uses and Administration, above).

A study evaluating an oral liquid formulation in 100 children aged between 1 and 10 years with transfusion-dependent anaemia found that an oral dose of deferiprone 50 to 100 mg/kg daily in three divided doses reduced serum-ferritin concentrations. Adverse effects were similar to those reported in adults, although an increase in serum-creatinine concentration was seen in 2 children during treatment, which resolved at the end of the 6-month study.[1]

In a retrospective study in 17 paediatric haematology or oncology patients with iron overload, rather lower doses of 20 to 40 mg/kg [daily] as tablets were found to be effective.[2]

1. El Alfy M, *et al*. The safety, tolerability, and efficacy of a liquid formulation of deferiprone in young children with transfusional iron overload. *J Pediatr Hematol Oncol* 2010; **32:** 601–5.
2. Won SC, *et al*. Efficacy and safety of deferiprone (Ferriprox), an oral iron-chelating agent, in pediatric patients. *Korean J Hematol* 2010; **45:** 58–61.

Iron distribution. Deferiprone has been investigated as a therapeutic strategy for relocating iron in disorders with defective iron distribution such as anaemia of chronic disease, or the neurodegenerative disorders Friedreich's ataxia, Alzheimer's disease, or Parkinson's disease.[1,2]

1. Kakhlon O, *et al*. Iron redistribution as a therapeutic strategy for treating diseases of localized iron accumulation. *Can J Physiol Pharmacol* 2010; **88:** 187–96.
2. Kakhlon O, *et al*. Cell functions impaired by frataxin deficiency are restored by drug-mediated iron relocation. *Blood* 2008; **112:** 5219–27.

Malaria. Deferiprone has been investigated for the treatment of malaria, see Malaria, under Desferrioxamine, p. 1546.1.

Thalassaemia. Patients with thalassaemia receiving regular blood transfusions commonly develop iron overload requiring use of iron chelators. Deferiprone was developed as an oral alternative to desferrioxamine, but its role has been controversial. See Thalassaemia under Uses of Desferrioxamine, p. 1545.2, for further information.

Adverse Effects, Treatment, and Precautions

Deferiprone commonly causes neutropenia, agranulocytosis, and thrombocytopenia and should not be used in neutropenic patients or in those with a history of agranulocytosis or recurrent neutropenia. The neutrophil count should be monitored weekly and treatment permanently stopped if neutropenia develops. Supportive treatment such as granulocyte colony-stimulating factor is recommended in those with severe neutropenia. Patients should be advised to seek immediate medical attention if symptoms indicative of infection such as fever, sore throat, or flu-like symptoms occur. Deferiprone should be withheld if an infection develops and the neutrophil count monitored more frequently.

Gastrointestinal disorders such as diarrhoea, nausea, vomiting, and abdominal pain are common during initial treatment with deferiprone. Most cases resolve with continued treatment, but some may require a temporary reduction in dose. A reddish-brown discoloration of the urine commonly occurs due to excretion of the iron-deferiprone complex. Other common adverse effects include headache, an increase or decrease in appetite, asthenia, musculoskeletal pain, peripheral oedema, dizziness, somnolence, pruritus, and urticaria. Arthropathy also occurs and can range from mild arthralgia to severe arthritis.

Serum ferritin should be measured every 2 or 3 months; treatment may need to be withheld if concentrations fall below 500 micrograms/litre. Deferiprone may reduce plasma-zinc concentrations and these should also be monitored and zinc supplements started if required.

Deferiprone is teratogenic in *animals* and should not be used during pregnancy. Women of child-bearing potential should be advised to use contraceptive measures during treatment with deferiprone.

Caution is advised in patients with hepatic or renal impairment and organ function should be monitored during therapy. Increased serum concentrations of alanine aminotransferase (ALT) have occurred; therapy may be withheld for persistent increases in ALT. For mention of an increase in serum-creatinine concentrations in some children treated with deferiprone, see Administration in Children, above.

A total daily dose above 100 mg/kg is not recommended due to the potential increased risk of adverse effects. Neurological disorders have been reported in children treated with higher than recommended doses of deferiprone, see Overdosage, below.

Auto-immune disorders. Deferiprone has been associated with isolated reports of auto-immune disorders such as Henoch-Schönlein purpura,[1] systemic vasculitis,[2] and a fatal case of SLE;[3] arthritic reactions are common. Although some thalassaemia patients treated with deferiprone had small increases in autoantibodies associated with SLE, no other symptoms were seen. Monitoring for autoantibodies and other immune abnormalities has been suggested.[4]

1. Unal S, *et al*. Severe Henoch-Schönlein purpura in a thalassemic patient under deferiprone treatment. *Am J Hematol* 2008; **83:** 165–6.
2. Castriota-Scanderbeg A, Sacco M. Agranulocytosis, arthritis and systemic vasculitis in a patient receiving the oral iron chelator L1 (deferiprone). *Br J Haematol* 1997; **96:** 254–5.
3. Mehta J, *et al*. Fatal systemic lupus erythematosus in patient taking oral iron chelator L1. *Lancet* 1991; **337:** 298.
4. Mehta J, *et al*. Oral iron chelator L1 and autoimmunity. *Blood* 1993; **81:** 1970–2.

Effects on the blood. Agranulocytosis, in some cases fatal, has been associated with deferiprone use.[1-3]

1. Henter J-I, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood* 2007; **109:** 5157–9.
2. Tewari S, *et al*. Necrotizing stomatitis: a possible periodontal manifestation of deferiprone-induced agranulocytosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; **108:** e13–e19.
3. Pontikoglou C, Papadaki HA. Idiosyncratic drug-induced agranulocytosis: the paradigm of deferiprone. *Hemoglobin* 2010; **34:** 291–304.

Effects on the ears and eyes. Like other iron chelators, adverse effects on the ears and eyes have been reported with deferiprone, including subclinical auditory and visual impairment,[1] and a higher incidence of retinal pigment epithelial degeneration.[2] In 2 reported cases of posterior subcapsular opacity the opacities were associated with reddish-brown deposits suggestive of iron accumulation.[3]

Hearing loss associated with desferrioxamine therapy remained stable or worsened when treatment was changed to deferiprone in 5 of 16 adults, although it was unclear if this reflected progression or irreversibility of the desferrioxamine damage or if deferiprone caused additional ototoxicity.[4]

1. Marciani MG, *et al*. Subclinical auditory and visual involvement during oral deferiprone therapy. *Am J Hematol* 1996; **51:** 179–80.
2. Taneja R, *et al*. Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. *Indian J Ophthalmol* 2010; **58:** 125–30.
3. Mehdizadeh M, Nowroozzadeh MH. Posterior subcapsular opacity in two patients with thalassaemia major following deferiprone consumption. *Clin Exp Optom* 2009; **92:** 392–4.
4. Chiodo AA, *et al*. Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; **26:** 116–22.

Hepatic fibrosis. Hepatic fibrosis was reported to have progressed in 5 patients with thalassaemia treated with deferiprone,[1] although other studies have found no evidence to suggest that deferiprone exacerbated liver fibrosis.[2-4]

1. Olivieri NF, *et al*. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; **339:** 417–23.
2. Wu S-F, *et al*. Liver fibrosis and iron levels during long-term deferiprone treatment of thalassemia major patients. *Hemoglobin* 2006; **30:** 215–18.
3. Chen A-C, *et al*. Effect of deferiprone on liver iron overload and fibrosis in hepatitis-C-virus-infected thalassemia. *Hemoglobin* 2006; **30:** 209–14.
4. Wanless IR, *et al*. Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. *Blood* 2002; **100:** 1566–9. Correction. *ibid*. 2003; **101:** 2460.

Overdosage. Neurological disorders were reported by the manufacturer and the French pharmacovigilance authorities in 2 children aged 7 and 9 who had been treated with deferiprone doses at 2½ times the highest recommended dose of 100 mg/kg daily. The children were treated for 1 and 2 years, respectively, and developed nystagmus, gait disorders, ataxia, dystonia, and, in one case, psychomotor retardation. These disorders gradually improved after deferiprone was stopped.[1]

Cerebellar syndrome was also reported in 2 children given deferiprone at higher than recommended doses.[2] The first patient was treated for more than 3 years before developing dizziness, axial hypotonia, nystagmus, diplopia, and obsessive-compulsive disorder. The second developed impaired motor coordination, dystonia, nystagmus, and the inability to walk in a straight line after 2 months of high-dose treatment. Again, symptoms in both patients gradually improved once deferiprone was stopped.

1. Agence française de sécurité sanitaire des produits de santé/Laboratoires Chiesi, France. Risque d'agranulocytoses fatales et de troubles neurologiques lors de l'utilisation de Ferriprox(déférirprone) (issued 1st September, 2006). Available at: http://www.afssaps.fr/content/download/12879/156735/version/1/file/lp060901.pdf (accessed 12/08/10)
2. Beau-Salinas F, *et al*. High doses of deferiprone may be associated with cerebellar syndrome. *BMJ* 2009; **338:** a2319.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies deferiprone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Interactions

Deferiprone chelates trivalent metal ions and could interact with aluminium-containing preparations; it should not be given with aluminium-containing antacids. Due to the risk

of additive toxicity, use with drugs that may cause neutropenia or agranulocytosis is not recommended.

Pharmacokinetics

Deferiprone is rapidly absorbed from the gastrointestinal tract and peak serum concentrations occur 45 to 60 minutes after an oral dose; absorption may be slowed in the presence of food and peak serum concentrations may be reduced. Protein binding is low (less than 10%). Deferiprone is metabolised to an inactive glucuronide metabolite and is excreted mainly in the urine as the metabolite and the iron-deferiprone complex, with a small amount of unchanged drug. The elimination half-life is about 2 to 3 hours.

References.

1. Limenta LMG, *et al.* Pharmacokinetics of deferiprone in patients with β-thalassaemia: impact of splenectomy and iron status. *Clin Pharmacokinet* 2011; **50:** 41–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ferriprox; ***Austral.***: Ferriprox; ***Austria***: Ferriprox; ***Belg.***: Ferriprox; ***Braz.***: Ferriprox; ***China***: Ferriprox (奥贝安可); ***Cz.***: Ferriprox; ***Denm.***: Ferriprox; ***Fin.***: Ferriprox; ***Fr.***: Ferriprox; ***Ger.***: Ferriprox; ***Gr.***: Ferriprox; Kelfer; ***Hong Kong***: Ferriprox; ***India***: Kelfer; ***Indon.***: Ferriprox; ***Irl.***: Ferriprox; ***Israel***: Ferriprox; ***Ital.***: Ferriprox; ***Malaysia***: Ferriprox; Kelfer; ***Neth.***: Ferriprox; ***Norw.***: Ferriprox; ***NZ***: Ferriprox; ***Pol.***: Ferriprox; ***Port.***: Ferriprox; ***Singapore***: Ferriprox; Kelfer; ***Spain***: Ferriprox; ***Swed.***: Ferriprox; ***Switz.***: Ferriprox; ***Thai.***: Ferriprox; GPO-L-One; Kelfer; ***Turk.***: Ferriprox; ***UK***: Ferriprox; ***USA***: Ferriprox.

Desferrioxamine Mesilate *(BANM)*

Ba-29837 (desferrioxamine hydrochloride); Ba-33112; Deferoksamiinimesilaatti; Deferoksamin Mezilat; Deferoksamino mesilatas; Deferoxamina, mesilato de; Deferoxamine Mesilate (pINNM); Déferoxamine, Mésilate de; Déféroxamine, mésilate de; Deferoxamine Mesylate (USAN); Deferoxamini Mesilas; Deferoxaminmesilat; Deferoxamin-mesylát; Deferoxamin-mezilát; Desferrioksamin Mesilat; Desferrioxamine Mesylate; Desferrioxamine Methanesulphonate; Mesilato de deferoxamina; NSC-527604 (desferrioxamine); Дефероксамина Мезилат.

30-Amino-3,14,25-trihydroxy-3,9,14,20,25-penta-azatriacontane-2,10,13,21,24-pentaone methanesulphonate; *N'*-{5-[(4-{[5-(Acetylhydroxyamino)pentyl]amino}-1,4-dioxobutyl) hydroxyamino]pentyl}-*N*-(5-aminopentyl)-*N*-hydroxy-butanediamide monomethanesulphonate.

$C_{25}H_{48}N_6O_8.CH_3SO_3H$=656.8

CAS — 70-51-9 (desferrioxamine); 138-14-7 (desferrioxamine mesilate); 1950-39-6 (desferrioxamine hydrochloride).

ATC — V03AC01.

ATC Vet — QV03AC01.

UNII — V9TKO7EO6K.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Deferoxamine Mesilate; Desferrioxamine Mesilate BP 2014). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol. A freshly prepared 10% solution in water has a pH of 3.7 to 5.5. Store at 2 degrees to 8 degrees. Protect from light.

USP 36: (Deferoxamine Mesylate). A white to off-white powder. Freely soluble in water; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Incompatibility. Licensed product information states that desferrioxamine solutions are incompatible with heparin.

Uses and Administration

Desferrioxamine is a chelator that has a high affinity for ferric iron. It appears to remove both free iron and iron bound to haemosiderin and ferritin but not iron bound to haemoglobin, transferrin, or cytochromes. One mole of desferrioxamine mesilate binds with one mole of ferric ion to form a stable complex, so theoretically 100 mg of desferrioxamine mesilate could bind about 8.5 mg of iron but it is unlikely that such a figure could be achieved in practice. Desferrioxamine also has an affinity for aluminium; one mole of desferrioxamine mesilate binds with one mole of aluminium to form a stable complex, so theoretically 100 mg of the mesilate could bind about 4.1 mg of aluminium.

Desferrioxamine increases the excretion of iron from the body and is used in the treatment of acute iron poisoning (see p. 1546.1) and for conditions associated with chronic iron overload; these include the treatment and diagnosis of the iron storage disorders haemochromatosis (when phlebotomy cannot be used) and haemosiderosis resulting from repeated blood transfusions as in thalassaemia. Desferrioxamine also increases the excretion of aluminium from the body and is used in the treatment and diagnosis of aluminium overload in patients with end-stage renal failure on maintenance dialysis. For further discussion of aluminium or iron overload, see below and p. 1545.2. Desferrioxamine is used in the diagnosis of some chronic anaemias such as sideroblastic anaemia (p. 1123.1) and auto-immune haemolytic anaemia (p. 1122.2).

Desferrioxamine is used as the mesilate and may be given by subcutaneous or intravenous infusion, by intramuscular injection, or intraperitoneally.

In the treatment of **acute iron poisoning**, desferrioxamine is usually given by intravenous infusion, particularly in patients who are symptomatic. However, US licensed product information advises intramuscular injection unless the patient is in shock, due to the risk of adverse effects with the intravenous route. The dose should be adjusted according to the severity of the poisoning, preferably as indicated by the serum-iron concentration and total iron binding capacity, if available, although chelation therapy should be started in patients with significant symptoms without waiting for the results of blood concentrations. In the UK, the usual initial dose of desferrioxamine mesilate is 15 mg/kg per hour by slow intravenous infusion, reducing after 4 to 6 hours to provide a total dose not exceeding 80 mg/kg in 24 hours, although larger doses may be tolerated. Alternatively, it may be given intramuscularly as a single dose of 2 g. In the USA, an initial dose of 1 g is given, either intravenously at a maximum rate of 15 mg/kg per hour, or by intramuscular injection. Subsequent doses of 500 mg may be given intravenously, at a rate not exceeding 125 mg/hour, or intramuscularly, every 4 hours for 2 doses, then every 4 to 12 hours according to response. A maximum dose of 6 g in 24 hours is recommended.

In the treatment of **chronic iron overload**, the dosage and route of administration should be determined for each patient by monitoring urinary iron excretion, with the aim of normalising serum-ferritin concentrations. Doses may be given by subcutaneous infusion, via an infusion pump, or by continuous intravenous infusion in those unable to have subcutaneous infusions or those with cardiac problems secondary to iron overload. An initial dose of 500 mg has been suggested, which may then be adjusted until a plateau of iron excretion is reached or with the aim of keeping the therapeutic index (the daily dose in mg/kg divided by the serum-ferritin concentration in micrograms/litre) below 0.025. The usual effective dose range is 20 to 60 mg/kg daily. Subcutaneous infusions are given 3 to 7 times a week depending on the degree of iron overload, usually over 8 to 12 hours, but infusion over 24 hours may be necessary in some patients. Although the UK considers subcutaneous infusion more effective, US licensed product information suggests an initial intramuscular dose of 0.5 to 1 g daily; a maximum dose of 1 g daily is recommended in the absence of a blood transfusion. Additional doses of desferrioxamine may be given at the time of blood transfusion; up to 2 g of desferrioxamine mesilate by intravenous infusion for each unit of blood transfused, at a rate of not more than 15 mg/kg per hour. Desferrioxamine should be given separately from the blood. In the USA the total dose from intramuscular injections plus intravenous infusions with blood transfusions should not exceed desferrioxamine mesilate 6 g daily. Ascorbic acid supplements (see Uses and Administration, under Vitamin C Substances, p. 2111.1) can enhance the excretion of iron, but, to reduce the risk of toxicity, should not be started until 1 month after starting desferrioxamine treatment (see under Interactions, p. 1547.3).

Desferrioxamine has been used as a *diagnostic test* for iron storage disease or some chronic anaemias in patients with normal renal function by injecting 500 mg of the mesilate intramuscularly and measuring the iron excreted in the urine over the next 6 hours. More than 1 mg of iron is suggestive of iron overload and more than 1.5 mg can be regarded as pathological.

In the treatment of **aluminium overload** in patients with end-stage renal failure, those undergoing maintenance haemodialysis or haemofiltration may be given desferrioxamine mesilate 5 mg/kg once a week by slow intravenous infusion during the last hour of a dialysis session, or 5 hours before dialysis in patients with more severe overload. Patients on peritoneal dialysis (CAPD or CCPD) may be given desferrioxamine mesilate 5 mg/kg once a week, by slow intravenous infusion, subcutaneously, intramuscularly, or intraperitoneally (the recommended route) before the final exchange of the day. For the *diagnosis* of aluminium overload, desferrioxamine mesilate 5 mg/kg is given by slow intravenous infusion during the last hour of haemodialysis. An increase in serum-aluminium concentration above baseline of more than 150 nanograms/mL (measured at the start of the next dialysis session) suggests aluminium overload.

For doses in children, see Administration in Children, below.

Administration. Compliance may be a problem with standard parenteral desferrioxamine regimens in patients with chronic iron overload. The oral,[1-3] rectal,[4] and intranasal[5] routes have therefore been tried as alternatives, but results have generally been disappointing. Twice-daily subcutaneous bolus injection has also been reported,[6-9] although the volume of the injection may be a limiting factor.[9]

Intraperitoneal desferrioxamine may be used to reduce aluminium levels in patients receiving peritoneal dialysis for chronic renal failure. Good results have also been reported[10] in a patient with haemochromatosis complicated by cirrhosis and cardiomyopathy, in whom a chronic peritoneal dialysis catheter was used to control ascites and to give desferrioxamine.

1. Callender ST, Weatherall DJ. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii:** 689.
2. Jacobs A, Chang Ting W. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii:** 794.
3. Kattamis C, *et al.* Oral desferrioxamine in young patients with thalassaemia. *Lancet* 1981; **i:** 51.
4. Kontoghiorghes G, *et al.* Desferrioxamine suppositories. *Lancet* 1983; **ii:** 454.
5. Gordon GS, *et al.* Intranasal administration of deferoxamine to iron overloaded patients. *Am J Med Sci* 1989; **297:** 280–4.
6. Borgna-Pignatti C, Cohen A. Evaluation of a new method of administration of the iron chelating agent deferoxamine. *J Pediatr* 1997; **130:** 86–8.
7. Franchini M, *et al.* Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload. *Blood* 2000; **95:** 2776–9.
8. Di Gregorio F, *et al.* An alternative to continuous subcutaneous infusion of desferrioxamine in thalassaemic patients. *Br J Haematol* 1997; **98:** 601–2.
9. Franchini M, *et al.* Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload: an update. *Blood* 2004; **103:** 747–8.
10. Swartz RD, Legault DJ. Long-term intraperitoneal deferoxamine for hemochromatosis. *Am J Med* 1996; **100:** 308–12.

Administration in children. Desferrioxamine is used in children to treat conditions associated with chronic iron overload (such as occurs in refractory anaemias as a result of repeated blood transfusions) and acute iron poisoning. It is also used to treat aluminium overload in children on dialysis.

For **acute iron poisoning** in children, desferrioxamine mesilate is usually given by continuous intravenous infusion in similar doses to those used in adults (see Uses and Administration, above). Alternatively, it may be given by intramuscular injection; UK licensed product information recommends a single dose of 1 g. In the USA, subsequent intramuscular dosage is suggested, as for adults.

For **chronic iron overload** in children, desferrioxamine mesilate is given to achieve iron balance and prevent haemosiderosis. The dosage should be determined by monitoring urinary iron excretion with the aim of normalising serum-ferritin concentrations. Doses are similar to those used in adults, although the *BNFC* suggests the initial dose should not exceed 30 mg/kg. In children under 3 years of age, the mean daily dose should not exceed 40 mg/kg to avoid growth retardation, see Precautions, p. 1546.2. Ascorbic acid (see p. 2111.2) can be given to enhance iron excretion.

Desferrioxamine mesilate is also given for **aluminium overload** in children on dialysis in the same dose as that used in adults.

Aluminium overload. Desferrioxamine is an effective aluminium chelator and may have a role in both acute and chronic aluminium toxicity. Accumulation of aluminium may be a particular problem in patients with chronic renal failure and has been implicated in renal osteodystrophy and dialysis dementia, as well as in other conditions, see Aluminium p. 2439.2. Acute aluminium toxicity is less common, but may occur following exposure to soluble aluminium salts.

Use of alternative phosphate binders (see Renal Osteodystrophy, p. 1170.1) and limits on the aluminium concentration of dialysis fluids reduce the exposure to aluminium in patients with chronic renal failure, but desferrioxamine may also be used to remove aluminium that has already accumulated. The desferrioxamine-aluminium chelate (aluminoxamine) is removed by haemoperfusion and by haemodialysis,[1] and also by peritoneal dialysis (although the amount removed may be much less), and desferrioxamine has been used successfully to treat aluminium overload in dialysis patients. It has also been used with dialysis in acute toxicity.

In patients with *dialysis encephalopathy*, increased aluminium excretion and clinical improvement has been reported[2,3] in patients given desferrioxamine in doses of up to 6 g once a week via the arterial line during the first 2 hours of haemodialysis.[2,3] A study[4] of 11 patients with dialysis encephalopathy found that 5 patients who were treated with deionised or reverse-osmosis water alone died, whereas of 6 who were also given desferrioxamine 6 to 10 g intravenously each week at dialysis, 4 showed clinical improvement. Substantial improvement in early aluminium encephalopathy has been achieved in a patient on

continuous ambulatory peritoneal dialysis by using intraperitoneal desferrioxamine.[5] Another small study[6] found that desferrioxamine improved psychomotor function in haemodialysis patients with impaired cerebral function but no clinical encephalopathy, who had only mildly elevated plasma-aluminium concentrations; desferrioxamine was given 3 times weekly during dialysis. Improvement in acute encephalopathy related to alum bladder irrigation has also been reported.[7] However, use of desferrioxamine may also exacerbate encephalopathy and caution is required (see Aluminium Encephalopathy, under Adverse Effects, Treatment, and Precautions, p. 1546.2).

Desferrioxamine has produced rapid clinical improvement in patients with *dialysis-related bone disease*.[8-10] In some studies[9,10] this has been associated with a reduction in the aluminium content of bone; others[8] have reported clinical improvement with no apparent effect on bone aluminium. Lower doses than those licensed for treatment (see Uses and Administration, p. 1544.1) have been evaluated; a once weekly intravenous dose of 2.5 mg/kg showed similar efficacy to the standard dose of 5 mg/kg in one study.[11] Diagnosis of aluminium-related bone disease may require bone biopsy, but some studies have suggested that measurement of plasma-aluminium concentrations after a desferrioxamine infusion may also be used. Some studies reporting positive results[9,12] have used relatively high doses of desferrioxamine (40 mg/kg) with plasma-aluminium measured 24 to 44 hours later, but there have been concerns about desferrioxamine toxicity.[13] A study[10] using a lower dose of desferrioxamine (28.5 mg/kg) and measuring plasma aluminium 5 hours later found similar increases in patients both with and without bone-aluminium accumulation. However, others have reported[14] that lower doses of desferrioxamine (5 or 10 mg/kg) are adequate when combined with measurement of serum-parathyroid hormone concentrations. The *National Kidney Foundation* guidelines[13] for bone metabolism and disease in chronic kidney disease suggest that when aluminium toxicity is suspected, a test dose of desferrioxamine 5 mg/kg is infused during the last hour of the dialysis session. Serum-aluminium concentrations are measured at baseline and 2 days later, before the next dialysis session; the test is considered positive if the aluminium concentration increases by 50 nanograms/mL or more. Aluminium bone disease is diagnosed when there is a positive desferrioxamine test and serum-parathyroid concentrations below 150 picograms/mL. Desferrioxamine is used to treat aluminium toxicity in symptomatic patients with aluminium concentrations of 60 to 200 nanograms/mL or a positive desferrioxamine test. To avoid desferrioxamine-induced neurotoxicity, patients with a baseline serum-aluminium concentration above 200 nanograms/mL should not have a desferrioxamine test or treatment.

Desferrioxamine therapy has also produced beneficial results in *dialysis patients with anaemia*[15-17] and has also been found to reverse aluminium-induced resistance to erythropoietin.[18,19]

Prurigo nodularis in chronic aluminium overload has responded to desferrioxamine, with resolution of itch and skin lesions.[20]

1. Chang TMS, Barre P. Effect of desferrioxamine on removal of aluminium and iron by coated charcoal haemoperfusion and haemodialysis. *Lancet* 1983; **ii:** 1051–3.
2. Ackrill P, *et al*. Successful removal of aluminium from patient with dialysis encephalopathy. *Lancet* 1980; **ii:** 692–3.
3. Arze RS, *et al*. Reversal of aluminium dialysis encephalopathy after desferrioxamine treatment. *Lancet* 1981; **ii:** 1116.
4. Milne FJ, *et al*. Low aluminium water, desferrioxamine, and dialysis encephalopathy. *Lancet* 1982; **ii:** 502.
5. Payton CD, *et al*. Successful treatment of aluminium encephalopathy by intraperitoneal desferrioxamine. *Lancet* 1984; **i:** 1132–3.
6. Altmann P, *et al*. Disturbance of cerebral function by aluminium in haemodialysis patients without overt aluminium toxicity. *Lancet* 1989; **ii:** 7–12.
7. Nakamura H, *et al*. Acute encephalopathy due to aluminum toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; **40:** 296–300.
8. Brown DJ, *et al*. Treatment of dialysis osteomalacia with desferrioxamine. *Lancet* 1982; **ii:** 343–5.
9. McCarthy JT, *et al*. Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 1990; **74:** 257–76.
10. Malluche HH, *et al*. The use of deferoxamine in the management of aluminum accumulation in bone in patients with renal failure. *N Engl J Med* 1984; **311:** 140–4.
11. Kan W-C, *et al*. Comparison of low-dose deferoxamine versus standard-dose deferoxamine for treatment of aluminium overload among haemodialysis patients. *Nephrol Dial Transplant* 2010; **25:** 1604–8.
12. Milliner DS, *et al*. Use of deferoxamine infusion test in the diagnosis of aluminium-related osteodystrophy. *Ann Intern Med* 1984; **101:** 775–80.
13. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; **42** (suppl 3): S1–S201. Also available at: http://www.kidney.org/professionals/kdoqi/guidelines_bone/pdf/boneguidelines.pdf (accessed 07/01/11)
14. D'Haese PC, *et al*. Use of the low-dose desferrioxamine test to diagnose and differentiate between patients with aluminium-related bone disease, increased risk for aluminium toxicity, or aluminium overload. *Nephrol Dial Transplant* 1995; **10:** 1874–84.
15. de la Serna F-J, *et al*. Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. *Lancet* 1988; **i:** 1009–11.
16. Altmann P, *et al*. Aluminium chelation therapy in dialysis patients: evidence for inhibition of haemoglobin synthesis by low levels of aluminium. *Lancet* 1988; **i:** 1012–15.
17. Padovese P, *et al*. Desferrioxamine versus erythropoietin for treatment of dialysis anaemia. *Lancet* 1990; **335:** 1465.
18. RosenlöfK, *et al*. Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; **335:** 247–9.
19. Zachée P, *et al*. Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; **335:** 1038–9.
20. Brown MA, *et al*. Prurigo nodularis and aluminium overload in maintenance haemodialysis. *Lancet* 1992; **340:** 48.

Iron overload. Chronic iron overload can be caused by inappropriately increased gastrointestinal absorption, by grossly excessive oral intake over long periods, or by parenteral administration of iron, for example from transfused blood.[1,2] Excess iron is stored in the form of ferritin and haemosiderin. The term **haemosiderosis** is applied to the accumulation of haemosiderin in body tissues without associated tissue damage; **haemochromatosis** refers to a chronic disease state in which iron overload leads to tissue damage, mainly in the heart, liver, and pancreas.

Primary or hereditary haemochromatosis is caused by a genetic defect in iron metabolism that results in excessive gastrointestinal absorption of iron. The treatment of choice for primary haemochromatosis is phlebotomy,[1-7] but chelation therapy may be needed in patients with anaemia, hypoproteinaemia, or severe cardiac disease. Other management strategies include dietary modification to reduce iron absorption; gastric-acid suppressing drugs such as proton pump inhibitors have been investigated as a means of reducing gastrointestinal absorption of iron.[5]

Neonatal haemochromatosis is a rare condition of unknown cause and results in fetal death or severe liver injury. Antioxidants and iron chelators may improve prognosis,[8] but many infants require liver transplantation. Maternal treatment with normal immunoglobulins has been reported[9] to reduce the severity of recurrent neonatal haemochromatosis, and normal immunoglobulin with exchange transfusion has been used successfully in a small number of neonates on the first day of life, reducing the need for liver transplantation.[10]

Secondary or acquired haemochromatosis is commonly associated with chronic anaemias, in particular thalassaemia, in which excessive iron uptake due to disordered erythropoiesis and excess iron from repeated blood transfusions contribute to iron overload.[1,2] These patients generally require iron chelation, usually with parenteral desferrioxamine although oral iron chelators such as deferasirox and deferiprone have also been used (see below).

1. Porter JB. Practical management of iron overload. *Br J Haematol* 2001; **115:** 239–52.
2. Barton JC. Optimal management strategies for chronic iron overload. *Drugs* 2007; **67:** 685–700.
3. Yen AW, *et al*. Revisiting hereditary hemochromatosis: current concepts and progress. *Am J Med* 2006; **119:** 391–9.
4. Adams PC, Barton JC. Haemochromatosis. *Lancet* 2007; **370:** 1855–60.
5. Adams PC, Barton JC. How I treat hemochromatosis. *Blood* 2010; **116:** 317–25.
6. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. *Gastroenterology* 2010; **139:** 393–408.
7. Franchini M. Hereditary iron overload: update on pathophysiology, diagnosis, and treatment. *Am J Hematol* 2006; **81:** 202–9.
8. Flynn DM, *et al*. Progress in treatment and outcome for children with neonatal haemochromatosis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F124–F127.
9. Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. *Lancet* 2004; **364:** 1690–8.
10. Rand EB, *et al*. Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. *J Pediatr* 2009; **155:** 566–71.

THALASSAEMIA. Patients homozygous for β-thalassaemia (p. 1124.1) have severe anaemia requiring regular blood transfusions. As a consequence of this treatment iron overload develops and the excessive deposition of iron in the myocardium usually results in these patients dying in their second or third decade from arrhythmias or cardiac failure. Iron chelators such as desferrioxamine are therefore used to retard the accumulation of iron.

Desferrioxamine has been shown to prevent complications and improve survival in thalassaemic patients given regular systemic therapy.[1-5] There is also some evidence that impaired organ function might improve with intensive therapy. The liver is the main site of iron accumulation in iron overload, and a reduction in liver-iron concentrations and improvement in liver function has been reported[6] in patients with transfusional iron overload treated with desferrioxamine 2 to 4 g by slow subcutaneous infusion over 12 hours on 6 nights a week. However, in another study[7] improvement in the degree of hepatic fibrosis was seen after 3 to 5 years in only 2 of 7 patients given desferrioxamine up to 85 mg/kg daily by subcutaneous injection, despite reductions in iron concentrations. Preservation or possibly improvement in cardiac function has also been reported,[8-10] although cardiac disease continues to be the main cause of death in patients with thalassaemia. Although initial studies used intramuscular treatment, increased iron excretion is seen with continuous subcutaneous infusion, and this is usually the preferred route. However, compliance may be a problem, and is a major determinant of the efficacy of treatment.[2] Intensive intravenous therapy, using continuous infusion devices, has been used successfully[11] in patients inadequately treated with subcutaneous desferrioxamine, and good results have also been reported[12,13] with intermittent intravenous infusions. Subcutaneous bolus injection has also been used (see Administration, p. 1544.3) although it may not be tolerated in all patients. Better iron excretion may be achieved if patients are given daily supplements of oral ascorbic acid in addition to desferrioxamine (but see under Interactions, p. 1547.3). The most appropriate time to start desferrioxamine is not clear. Beginning chelation therapy before puberty could help to ensure normal sexual development in patients with thalassaemia major.[14] Other studies[1,2] have reported that starting therapy before severe iron overload develops, and maintaining low serum-ferritin concentrations, prevents cardiac disease and improves prognosis, suggesting that chelation therapy should be started as early as possible, to prevent organ damage developing. However, desferrioxamine has been associated with adverse effects on growth (see Effects on Growth Rate, p. 1547.1) and it is usual to delay therapy until children are about 3 years of age, when iron overload becomes significant, although earlier treatment may be required in some cases.[3]

Alternatives to desferrioxamine have also been investigated. Deferiprone, which is given orally, effectively reduces iron overload,[5,15] but its long-term benefits are controversial. A study[16] in patients with thalassaemia reported progression of hepatic fibrosis in patients given deferiprone, although another study[17] was unable to confirm these findings. Other studies[18-20] have suggested that deferiprone may be superior to desferrioxamine in reducing cardiac complications. A systematic review[21] found no evidence to change treatment recommendations that indicate deferiprone for use in those for whom desferrioxamine is contra-indicated or ineffective; the authors acknowledged that there was a need for more research. It has been suggested that treatment with desferrioxamine and deferiprone may have an additive effect, and it has been widely studied.[22-25] One study reported a reduction in myocardial iron and an improvement in ejection fraction and endothelial function with the combination compared with desferrioxamine alone;[22] increased survival has also been seen with intensive combined treatment.[26] However, despite the increased chelating ability of the combination, another study did not find sequential use to improve survival.[27] Deferasirox, another oral iron chelator, is also used;[28] it may, however, be less effective than deferiprone in reducing cardiac complications.[20] Deferasirox has also been combined with desferrioxamine in the hope of improved efficacy.[29]

1. Olivieri NF, *et al*. Survival in medically treated patients with homozygous β-thalassemia. *N Engl J Med* 1994; **331:** 574–8.
2. Brittenham GM, *et al*. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med* 1994; **331:** 567–73.
3. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood* 1997; **89:** 739–61.
4. Roberts D, *et al*. Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/12/09).
5. Maggio A. Light and shadows in the iron chelation treatment of haematological diseases. *Br J Haematol* 2007; **138:** 407–21.
6. Hoffbrand AV, *et al*. Improvement in status and liver function in patients with transfusional iron overload with long-term subcutaneous desferrioxamine. *Lancet* 1979; **i:** 947–9.
7. Maurer HS, *et al*. A prospective evaluation of iron chelation therapy in children with severe β-thalassemia: a six-year study. *Am J Dis Child* 1988; **142:** 287–92.
8. Freeman AP, *et al*. Early left ventricular dysfunction and chelation therapy in thalassemia major. *Ann Intern Med* 1983; **99:** 450–4.
9. Marcus RE, *et al*. Desferrioxamine to improve cardiac function in iron-overloaded patients with thalassaemia major. *Lancet* 1984; **i:** 392–3.
10. Wolfe L, *et al*. Prevention of cardiac disease by subcutaneous deferoxamine in patients with thalassemia major. *N Engl J Med* 1985; **312:** 1600–3.
11. Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk β-thalassemia. *Blood* 2000; **95:** 1229–36.
12. Hagège I, *et al*. Long-term administration of high-dose deferoxamine 2 days per week in thalassemic patients. *Eur J Haematol* 2001; **67:** 230–1.
13. Miskin H, *et al*. Reversal of cardiac complications in thalassemia major by long-term intermittent daily intensive iron chelation. *Eur J Haematol* 2003; **70:** 398–403.
14. Bronspiegel-Weintrob N, *et al*. Effect of age at the start of iron chelation therapy on gonadal function in β-thalassemia major. *N Engl J Med* 1990; **323:** 713–19.
15. Addis A, *et al*. Meta-analytic review of the clinical effectiveness of oral deferiprone (L_1). *Eur J Clin Pharmacol* 1999; **55:** 1–6.
16. Olivieri NF, *et al*. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; **339:** 417–23.
17. Wanless IR, *et al*. Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. *Blood* 2002; **100:** 1566–9.
18. Anderson LJ, *et al*. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet* 2002; **360:** 516–20.
19. Piga A, *et al*. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003; **88:** 489–96.
20. Pepe A, *et al*. Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison

determined by quantitative magnetic resonance imaging. *Haematologica* 2011; **96:** 41–7.
21. Roberts D, *et al.* Oral deferiprone for iron chelation in people with thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 22/08/07).
22. Tanner MA, *et al.* A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation* 2007; **115:** 1876–84.
23. Tsiapras D, *et al.* Effect of combined chelation therapy with deferiprone and deferoxamine on left ventricular diastolic function in adult β-thalassemia major patients. *Hemoglobin* 2010; **34:** 210–20.
24. Ricchi P, *et al.* Combined chelation therapy in thalassemia major with deferiprone and desferrioxamine: a retrospective study. *Eur J Haematol* 2010; **85:** 36–42.
25. Drakonaki EE, *et al.* Deferoxamine versus combined therapy for chelating liver, spleen and bone marrow iron in β-thalassemic patients: a quantitative magnetic resonance imaging study. *Hemoglobin* 2010; **34:** 95–106.
26. Lai ME, *et al.* Increased survival and reversion of iron-induced cardiac disease in patients with thalassemia major receiving intensive combined chelation therapy as compared to desferoxamine alone. *Blood Cells Mol Dis* 2010; **45:** 136–9.
27. Maggio A, *et al.* Long-term sequential deferiprone-deferoxamine versus deferiprone alone for thalassaemia major patients: a randomized clinical trial. *Br J Haematol* 2009; **145:** 245–54.
28. Pennell DJ, *et al.* Efficacy of deferasirox in reducing and preventing cardiac iron overload in β-thalassemia. *Blood* 2010; **115:** 2364–71.
29. Jetsrisuparb A, *et al.* Retrospective study on the combination of desferrioxamine and deferasirox for treatment of iron-overloaded thalassemic patients: first evidence of more than 2 years. *J Pediatr Hematol Oncol* 2010; **32:** 400–3.

Iron poisoning. Diagnosis of acute iron poisoning relies on the history, clinical symptoms, and serum-iron concentrations. An intramuscular desferrioxamine challenge test has also been used; if free iron is present, ferrioxamine will be excreted in the urine imparting a classic 'vin rosé' colour. However, interpretation is difficult and a negative result does not rule out toxicity; the test is no longer generally recommended.

The management of acute iron poisoning (see Treatment of Adverse Effects, under Iron, p. 2074.2) involves supportive care and parenteral desferrioxamine for severe toxicity. Although addition of desferrioxamine to gastric lavage fluid has been suggested there is little evidence of efficacy and some concern over possible toxic effects of ferrioxamine.

Malaria. Following the suggestion that iron-deficiency anaemia may offer some protection against infections (see Infections in the Precautions for Iron, p. 2074.3), desferrioxamine was tried in a few patients with malaria.[1,2] Any antimalarial effect of desferrioxamine was thought to be as a result of chelation of parasite-associated iron rather than reduction in body-iron concentrations in the patient. Desferrioxamine given intravenously was reported[3] to shorten the time to regain consciousness in children with cerebral malaria receiving standard therapy with intravenous quinine and oral pyrimethamine-sulfadoxine. However, in another study[4] there was no evidence of a beneficial effect on mortality when desferrioxamine was added to an antimalarial treatment regimen that included a loading dose of quinine. Deferiprone has also been studied,[5,6] with mixed results. A systematic review[7] considered that although there were some positive results with desferrioxamine and deferiprone, there were insufficient data to draw conclusions about efficacy. The potential for adverse effects and the need for parenteral administration of desferrioxamine was also deemed likely to limit their use for malaria. The use of desferrioxamine in the treatment of malaria is not recommended by WHO.[8]

1. Gordeuk VR, *et al.* Iron chelation as a chemotherapeutic strategy for falciparum malaria. *Am J Trop Med Hyg* 1993; **48:** 193–7.
2. Thompson DF. Deferoxamine treatment of malaria. *Ann Pharmacother* 1994; **28:** 602–3.
3. Gordeuk V, *et al.* Effect of iron chelation therapy on recovery from deep coma, in children with cerebral malaria. *N Engl J Med* 1992; **327:** 1473–7.
4. Thuma PE, *et al.* Effect of iron chelation therapy on mortality in Zambian children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 214–18.
5. Thuma PE, *et al.* Assessment of the effect of the oral iron chelator deferiprone on asymptomatic Plasmodium falciparum parasitemia in humans. *Am J Trop Med Hyg* 1998; **58:** 358–64.
6. Mohanty D, *et al.* Deferiprone (L1) as an adjuvant therapy for Plasmodium falciparum malaria. *Indian J Med Res* 2002; **115:** 17–21.
7. Smith HJ, Meremikwu MM. Iron chelating agents for treating malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 11/01/11).
8. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 31/08/10)

Porphyria. The management of various forms of porphyria is discussed on p. 1556.1. Desferrioxamine has been used to reduce serum-iron concentrations in porphyria cutanea tarda and may have a role if phlebotomy is contra-indicated. In a study of 25 patients with porphyria cutanea tarda,[1] subcutaneous infusion of desferrioxamine was found to be as effective as repeated phlebotomies in normalising porphyrin excretion and iron storage. Intravenous desferrioxamine was also used successfully to treat porphyria cutanea tarda,[2] including haemodialysis-related disease;[3-5] however, intramuscular use was ineffective.[6]

1. Rocchi E, *et al.* Iron removal therapy in porphyria cutanea tarda: phlebotomy versus slow subcutaneous desferrioxamine infusion. *Br J Dermatol* 1986; **114:** 621–9.
2. Rocchi E, *et al.* High weekly intravenous doses of desferrioxamine in porphyria cutanea tarda. *Br J Dermatol* 1987; **117:** 393–6.
3. Praga M, *et al.* Treatment of hemodialysis-related porphyria cutanea tarda with deferoxamine. *N Engl J Med* 1987; **316:** 547–8.
4. Labidi J. Porphyria cutanea tarda in a chronic hemodialysis patient. *Saudi J Kidney Dis Transpl* 2010; **21:** 919–22.
5. Pitche P, *et al.* Porphyrie cutanée tardive chez l'hémodialysé. Un cas sévère traité efficacement par déféroxamine. *Ann Dermatol Venereol* 2003; **130:** 37–9.
6. Muñoz JJ, *et al.* Desferrioxamine in the treatment of porphyria cutanea tarda: ineffectiveness of intramuscular administration. *J Dermatol* 1990; **17:** 329–31.

Stroke. Desferrioxamine has been investigated[1,2] for its potential value in reducing local neurotoxicity after intracerebral haemorrhage (p. 1269.2).

1. Hua Y, *et al.* Deferoxamine therapy for intracerebral hemorrhage. *Acta Neurochir Suppl* 2008; **105:** 3–6.
2. Selim M. Deferoxamine mesylate: a new hope for intracerebral hemorrhage: from bench to clinical trials. *Stroke* 2009; **40** (3 suppl): S90–S91.

Adverse Effects, Treatment, and Precautions

Rapid intravenous injection of desferrioxamine may cause flushing, urticaria, tachycardia, hypotension, and shock. Injection-site reactions include pain, swelling, pruritus, and erythema, and may be associated with systemic adverse effects including arthralgia, myalgia, fever, headache, bronchospasm, and gastrointestinal disorders. Other allergic reactions include rash, angioedema, and anaphylaxis.

Blood dyscrasias such as thrombocytopenia, leucopenia, and aplastic anaemia have occurred, as have hepatic dysfunction and increases in liver enzymes. Acute respiratory distress syndrome has been reported after treatment with high-dose intravenous desferrioxamine. Desferrioxamine treatment of aluminium overload has resulted in hypocalcaemia and aggravation of hyperparathyroidism,

Bone disorders such as metaphyseal dysplasia and impaired growth have been seen in young children or those given inappropriately high doses of desferrioxamine and regular checks on height and weight are recommended for children. A reduction in dose may restore growth rate. Muscle spasms and bone pain can also occur.

Nervous system disorders include dizziness, peripheral neuropathy, and paraesthesia. Desferrioxamine may exacerbate aluminium-related encephalopathy and precipitate seizures. Prophylactic treatment with antiepileptics such as clonazepam has been suggested for patients judged to be at risk. Visual and auditory disturbances have been reported, usually when desferrioxamine is given at high doses, for prolonged periods, or in patients with low ferritin concentrations. Hearing loss and tinnitus are uncommon and visual disturbances (including retinal changes, cataracts, optic neuritis, and impaired peripheral, colour, and night vision) are rare; these disturbances are usually reversible if desferrioxamine is withdrawn. Regular ophthalmological and audiological examinations are recommended for patients on long-term therapy.

Caution is required when using desferrioxamine in patients with renal impairment as the metal complex is excreted by the kidneys. The desferrioxamine-iron complex may colour the urine red or brown. Dysuria, increases in serum-creatinine, renal tubular disorders, and acute renal failure have been reported during treatment.

An increased susceptibility to infection, particularly with *Yersinia* species, has been reported in patients with iron overload; desferrioxamine therapy may sometimes exacerbate this. Severe fungal infections, including some fatalities, have also been reported, mainly in patients undergoing dialysis. If infection is suspected, treatment with desferrioxamine should be stopped and appropriate antimicrobial treatment given. Desferrioxamine may be restarted once the infection has been cleared.

The adverse effects of desferrioxamine generally respond to dosage reduction. In acute overdosage desferrioxamine may be removed by haemodialysis. The urinary excretion of iron should be measured regularly during treatment for iron overload, and the serum concentration of aluminium monitored during the management of aluminium overload. Monitoring of cardiac function is also recommended in those receiving combined treatment with ascorbic acid (see also Interactions, p. 1547.3).

Aluminium encephalopathy. Desferrioxamine may be used in the management of aluminium-associated encephalopathy, but has also been associated with precipitation or exacerbation of dementia,[1-3] with some fatal outcomes,[1] in dialysis patients with aluminium overload. It has been suggested[2] that the effect could be dose related. Desferrioxamine mobilises stored aluminium and may therefore increase plasma-aluminium concentrations, leading to toxicity. Use of a low dose of desferrioxamine (for example, 10 mg/kg) shortly before dialysis, in addition to charcoal haemoperfusion, has been recommended.[1] However, exacerbation of aluminium encephalopathy has also been reported[3] after the low dose of 500 mg twice weekly.

1. Sherrard DJ, *et al.* Precipitation of dialysis dementia by deferoxamine treatment of aluminum related bone disease. *Am J Kidney Dis* 1988; **12:** 126–30.
2. McCauley J, Sorkin I. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; **4:** 110–14.
3. Lillevang ST, Pedersen FB. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; **4:** 676.

Breast feeding. It is unknown whether desferrioxamine is excreted in breast milk. There are case reports describing the use of desferrioxamine in breast-feeding mothers,[1,2] without significant disturbance of iron metabolism in the infant.[1] However, data are scarce and licensed product information recommends that the drug should only be used if the benefits of treatment are considered to outweigh the risks.

1. Surbek DV, *et al.* Pregnancy and lactation in homozygous β-thalassemia major. *J Perinat Med* 1998; **26:** 240–3.
2. Pafumi C, *et al.* Pregnancy outcome of a transfusion-dependent thalassemic woman. *Ann Hematol* 2000; **79:** 571–3.

Diagnostic tests. *In vitro* and *animal* studies[1] have suggested that desferrioxamine could interfere with estimations of total iron-binding capacity. It may also interfere with colorimetric iron assays.

Desferrioxamine also binds gallium and has been reported[2-4] to distort the results of gallium-67 imaging studies. Licensed product information recommends stopping desferrioxamine 48 hours before scintigraphy.

1. Bentur Y, *et al.* Misinterpretation of iron-binding capacity in the presence of deferoxamine. *J Pediatr* 1991; **118:** 139–42.
2. Nagamachi S, *et al.* Gallium-67 scintigraphy in patients with hemochromatosis treated by deferoxamine. *Ann Nucl Med* 1988; **2:** 35–9.
3. Baker DL, Manno CS. Rapid excretion of gallium-67 isotope in an iron-overloaded patient receiving high-dose intravenous deferoxamine. *Am J Hematol* 1988; **29:** 230–2.
4. Brown SJ, *et al.* Altered biodistribution of gallium-67 in a patient with aluminum toxicity treated with desferoxamine. *J Nucl Med* 1990; **31:** 115–17.

Effects on the blood. A patient with end-stage renal disease developed reversible thrombocytopenia on 3 separate occasions after intravenous infusions of desferrioxamine for dialysis osteomalacia.[1] Acute fatal aplastic anaemia occurred in a 16-year-old girl with thalassaemia after high intravenous doses of desferrioxamine (80 mg/kg daily) for 20 days.[2]

1. Walker JA, *et al.* Thrombocytopenia associated with intravenous desferrioxamine. *Am J Kidney Dis* 1985; **6:** 254–6.
2. Sofroniadou K, *et al.* Acute bone marrow aplasia associated with intravenous administration of deferoxamine (desferrioxamine). *Drug Safety* 1990; **5:** 152–4.

Effects on the ears and eyes. Lens opacities, optic neuropathy, retinal pigmentary changes and other retinal abnormalities, and ocular disturbances including loss of colour vision, night blindness, decreased visual acuity, and field defects, have been reported in patients receiving long-term or high-dose treatment with desferrioxamine.[1-4] Irreversible ocular toxicity has also occurred after a single intravenous dose to test for aluminium overload in a patient with chronic renal failure on dialysis.[5] Studies have reported widely differing rates; in 2 studies long-term use of desferrioxamine was associated with symptomatic or asymptomatic ocular changes in 4% (2 of 52)[1] and 66% (10 of 15)[6] of patients respectively.

Sensorineural hearing impairment has also been reported,[1,7] and in one study[8] was attributed to desferrioxamine in 29% of patients (22 of 75).

The mechanism by which desferrioxamine causes neurotoxicity is unclear. Some studies[3,6] have suggested that depletion of trace metals, particularly zinc or copper, may be involved; other studies[7,9] have found an association with dose, suggesting a direct toxic effect of desferrioxamine. Low serum-ferritin concentrations may be a risk factor for ototoxicity, and it has been suggested that the risk may be minimised by adjusting the desferrioxamine dose according to serum-ferritin concentrations, to achieve a therapeutic index below 0.025 (calculated by dividing the daily dose in mg/kg by the serum-ferritin concentration in micrograms/litre);[9] this therapeutic index has also been used in patients with ocular toxicity.[4] Reported risk factors for visual loss in desferrioxamine retinopathy include blood-retinal barrier breakdown associated with diabetes and rheumatoid arthritis, metabolic encephalopathy, and renal failure.[2] Both ophthalmic and auditory abnormalities can improve when desferrioxamine is withdrawn,[1,2,6] although sometimes the effects may be irreversible[4] or recovery may only be partial.[2] Hearing loss associated with desferrioxamine therapy remained stable or worsened in some patients when treatment was changed to deferiprone, see Effects on the Ears and Eyes, under Deferiprone, p. 1543.3.

There has also been a report[10] of improvement following use of zinc supplements.

1. Cohen A, *et al.* Vision and hearing during deferoxamine therapy. *J Pediatr* 1990; **117:** 326–30.
2. Haimovici R, *et al.* Deferoxamine Retinopathy Study Group. The expanded clinical spectrum of deferoxamine retinopathy. *Ophthalmology* 2002; **109:** 164–71.
3. Genead MA, *et al.* Macular vitelliform lesion in desferrioxamine-related retinopathy. *Doc Ophthalmol* 2010; **121:** 161–6.
4. Lai TYY, *et al.* Rapid development of severe toxic retinopathy associated with continuous intravenous deferoxamine infusion. *Br J Ophthalmol* 2006; **90:** 243–4.
5. Bene C, *et al.* Irreversible ocular toxicity from single "challenge" dose of deferoxamine. *Clin Nephrol* 1989; **31:** 45–8.
6. De Virgiliis S, *et al.* Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia. *Arch Dis Child* 1988; **63:** 250–5.
7. Karimi M, *et al.* Evaluation of the incidence of sensorineural hearing loss in beta-thalassemia major patients under regular chelation therapy with desferrioxamine. *Acta Haematol (Basel)* 2002; **108:** 79–83.
8. Chiodo AA, *et al.* Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; **26:** 116–22.
9. Porter JB, *et al.* Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. *Br J Haematol* 1989; **73:** 403–9.
10. Pinna A, *et al.* Rapid recovery with oral zinc sulphate in deferoxamine-induced presumed optic neuropathy and hearing loss. *J Neuroophthalmol* 2001; **21:** 32–3.

Effects on growth rate. Growth retardation has been noted in thalassaemic children undergoing desferrioxamine therapy,[1-3] and bone dysplasia has occurred even with subcutaneous doses of no more than 50 mg/kg daily, with the metaphysis of the distal ulna commonly affected.[3] Growth retardation was related to dose[1,2] and inversely related to iron stores.[1] It was greater in those who started receiving desferrioxamine at the start of transfusion therapy at about 9 months old than in those who started desferrioxamine once iron accumulation was established, after about 3 years. A sharp increase in growth velocity was reported in 15 patients with low ferritin levels after a 50% reduction in desferrioxamine dose.[1]

1. Piga A, *et al.* High-dose desferrioxamine as a cause of growth failure in thalassaemic patients. *Eur J Haematol* 1988; **40:** 380–1.
2. De Virgiliis S, *et al.* Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr* 1988; **113:** 661–9.
3. Chan YL, *et al.* Desferrioxamine-induced long bone changes in thalassaemic patients — radiographic features, prevalence and relations with growth. *Clin Radiol* 2000; **55:** 610–14.

Effects on the kidneys. Intensive treatment with intravenous infusions of desferrioxamine has been associated[1,2] with acute decreases in renal function, and it has been suggested[3] that nephrotoxicity could be related to the high doses used; acute renal failure has also been reported[4,5] after intravenous overdosage of desferrioxamine. However, other studies[6-9] have also found reductions in renal function associated with more usual subcutaneous dosage regimens. Renal function generally improved once desferrioxamine was stopped. Two mechanisms have been proposed for desferrioxamine-induced kidney damage: inhibition of prostaglandin synthesis causing an acute decrease in renal perfusion in the absence of systemic blood pressure changes, or inhibition of tubular resorption resulting in solute diuresis.[2]

1. Batey R, *et al.* Acute renal insufficiency occurring during intravenous desferrioxamine therapy. *Scand J Haematol* 1979; **22:** 277–9.
2. Koren G, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1989; **143:** 1077–80.
3. Li Volti S, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1990; **144:** 1069–70.
4. Cianciulli P, *et al.* Acute renal failure occurring during intravenous desferrioxamine therapy: recovery after haemodialysis. *Haematologica* 1992; **77:** 514–15.
5. Prasannan L, *et al.* Acute renal failure following deferoxamine overdose. *Pediatr Nephrol* 2003; **18:** 283–5.
6. Koren G, Bentur Y. Acute changes in renal function associated with deferoxamine. *Am J Dis Child* 1990; **144:** 1070.
7. Cianciulli P, *et al.* Early detection of nephrotoxic effects in thalassemic patients receiving desferrioxamine therapy. *Kidney Int* 1994; **46:** 467–70.
8. Clajus C, *et al.* Acute kidney injury due to deferoxamine in a renal transplant patient. *Nephrol Dial Transplant* 2008; **23:** 1061–4.
9. Hamed EA, ElMelegy NT. Renal functions in pediatric patients with beta-thalassemia major: relation to chelation therapy: original prospective study. *Ital J Pediatr* 2010; **36:** 39.

Effects on the lungs. Pulmonary complications, including fatal acute respiratory distress syndrome, have been reported in patients given prolonged or high-dose intravenous desferrioxamine. A pulmonary syndrome with tachypnoea, hypoxaemia, reduced pulmonary function, and evidence of diffuse interstitial fibrosis and inflammation, has been reported[1-4] with high doses for thalassaemia or acute iron poisoning. There has also been a report[5] of fatal acute respiratory distress syndrome in 4 patients given intravenous desferrioxamine for 65 to 92 hours for acute iron poisoning; toxicity was attributed to the prolonged infusion since no pulmonary complications had been noted with desferrioxamine given for less than 24 hours. Subsequent correspondence, however, suggested alternative explanations for the pulmonary injury such as the use of doses above the daily maximum,[6] or a direct effect of acute iron intoxication following inadequate desferrioxamine therapy.[7] Other proposed mechanisms for the pulmonary injury include generation of free radicals leading to oxidative damage,[3-5,8] or a hypersensitivity reaction,[1,2] although some patients who had pulmonary symptoms with intravenous therapy tolerated subcutaneous treatment.[1,3]

1. Freedman MH, *et al.* Pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine infusions. *Am J Dis Child* 1990; **144:** 565–9.
2. Scanderbeg AC, *et al.* Pulmonary syndrome and intravenous high-dose desferrioxamine. *Lancet* 1990; **336:** 1511.
3. Rego EM, *et al.* Dose-dependent pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine. *Am J Hematol* 1998; **58:** 340–1.
4. Ioannides AS, Panisello JM. Acute respiratory distress syndrome in children with acute iron poisoning: the role of intravenous desferrioxamine. *Eur J Pediatr* 2000; **159:** 158–9.
5. Tenenbein M, *et al.* Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; **339:** 699–701.
6. Macarol V, Yawalkar SJ. Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1601.
7. Shannon M. Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1601.
8. Helson L, *et al.* Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1602–3.

Effects on the skin. Desferrioxamine may be used in the management of porphyria cutanea tarda (see p. 1556.1). However, lesions resembling porphyria cutanea tarda developed in 3 patients during long-term therapy with desferrioxamine for aluminium toxicity.[1] The lesions worsened on exposure to sun and resolved when treatment was completed. It was also possible that the lesions were associated with aluminium accumulation. Alopecia was noted in 1 patient but an association with desferrioxamine could not be established.

1. McCarthy JT, *et al.* Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 1990; **74:** 257–76.

Hypersensitivity. Individual cases of anaphylactoid reactions have been reported with desferrioxamine given by various parenteral routes, and desensitisation has been carried out successfully in some patients.[1-5] Immunological studies have suggested that the reaction may be pseudoallergic in nature;[2-4] 4 patients who were unable to tolerate subcutaneous desferrioxamine due to severe hypersensitivity reactions were successfully treated with high-dose intravenous therapy.[6]

Effects on the lungs have also been attributed to hypersensitivity (see above).

1. Miller KB, *et al.* Rapid desensitisation for desferrioxamine anaphylactic reaction. *Lancet* 1981; **i:** 1059.
2. Bousquet J, *et al.* Rapid desensitisation for desferrioxamine anaphylactoid reactions. *Lancet* 1983; **ii:** 859–60.
3. Patriarca G, *et al.* Successful desensitization of a child with desferrioxamine hypersensitivity. *J Investig Allergol Clin Immunol* 1995; **5:** 294–5.
4. La Rosa M, *et al.* Desensitization treatment for anaphylactoid reactions to desferrioxamine in a pediatric patient with thalassemia. *J Allergy Clin Immunol* 1996; **97:** 127–8.
5. Gülen F, *et al.* Successful desensitization of a case with desferrioxamine hypersensitivity. *Minerva Pediatr* 2006; **58:** 571–4.
6. Lombardo T, *et al.* High-dose intravenous desferrioxamine (DFO) delivery in four thalassemic patients allergic to subcutaneous DFO administration. *Am J Hematol* 1996; **51:** 90–2.

Infection susceptibility. *Yersinia enterocolitica* is one of the most iron-dependent of all microbes and the risk of infection is increased in patients with iron overload. Use of exogenous iron-binding compounds (siderophores) such as desferrioxamine, may increase the ability of *Y. enterocolitica* to take up iron and may contribute to the increased risk of infection. Infections due to *Y. enterocolitica* (p. 186.2) have been reported in patients receiving desferrioxamine for acute iron overdosage[1] or for chronic iron overload.[2-5] Severe infection with *Y. pseudotuberculosis* has also been reported in a thalassaemic patient on long-term desferrioxamine therapy.[6]

Treatment with desferrioxamine may also increase susceptibility to mucormycosis. Infections have occurred both in patients with iron overload disorders[7-10] and in those who do not have excessive iron stores.[11-13] A review[8] of 26 cases of mucormycosis in patients undergoing treatment revealed that 23 patients died; in 19 cases the diagnosis was only made at necropsy and only 9 patients received potentially effective treatment (surgery and/or amphotericin B). The organisms responsible were *Rhizopus* species in 13 cases and *Cunninghamella bertholletiae* in 3. In another review of 24 cases of mucormycosis in patients on dialysis,[14] at least 21 were receiving desferrioxamine; infection was fatal in 21 of the 24 patients.

In view of the serious nature of these infections it is important that they should be recognised and treated promptly. It has been suggested that a short course of a suitable antibacterial could be given as prophylaxis to young children from areas with a high incidence of yersiniosis who require treatment with desferrioxamine.[15]

1. Melby K, *et al.* Septicaemia due to Yersinia enterocolitica after oral overdoses of iron. *BMJ* 1982; **285:** 467–8.
2. Scharnetzky M, *et al.* Prophylaxis of systemic yersinosis in thalassaemia major. *Lancet* 1984; **i:** 791.
3. Chiu HY, *et al.* Infection with Yersinia enterocolitica in patients with iron overload. *BMJ* 1986; **292:** 97.
4. Kelly D, *et al.* Yersinia and iron overload. *BMJ* 1986; **292:** 413.
5. Gallant T, *et al.* Yersinia sepsis in patients with iron overload treated with deferoxamine. *N Engl J Med* 1986; **314:** 1643.
6. Gordts B, *et al.* Yersinia pseudotuberculosis septicaemia in thalassaemia major. *Lancet* 1984; **i:** 41–2.
7. Sane A, *et al.* Deferoxamine treatment as a risk factor for zygomycete infection. *J Infect Dis* 1989; **159:** 151–2.
8. Daly AL, *et al.* Mucormycosis: association with deferoxamine therapy. *Am J Med* 1989; **87:** 468–71.
9. Kubota N, *et al.* A massive intraventricular thrombosis by disseminated mucormycosis in a patient with myelodysplastic syndrome during deferoxamine therapy. *Haematologica* 2003; **88:** 117–18.
10. Reyes HM, *et al.* Pulmonary invasive mucormycosis in a patient with secondary iron overload following deferoxamine therapy. *Proc (Bayl Univ Med Cent)* 2008; **21:** 378–81.
11. Goodill JJ, Abuelo JG. Mucormycosis–a new risk of deferoxamine therapy in dialysis patients with aluminum or iron overload? *N Engl J Med* 1987; **316:** 54.
12. Windus DW, *et al.* Fatal rhizopus infections in hemodialysis patients receiving deferoxamine. *Ann Intern Med* 1987; **107:** 678–80.
13. Boelaert JR, *et al.* Mucormycosis infections in dialysis patients. *Ann Intern Med* 1987; **107:** 782–3.
14. Boelaert JR, *et al.* Mucormycosis among patients on dialysis. *N Engl J Med* 1989; **321:** 190–1.
15. Hadjiminas JM. Yersiniosis in acutely iron-loaded children treated with desferrioxamine. *J Antimicrob Chemother* 1988; **21:** 680–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desferrioxamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] Indeed, desferrioxamine may be used in the management of porphyria cutanea tarda to reduce iron concentrations (see p. 1546.1).

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/09/11)

Pregnancy. Desferrioxamine has been associated with fetal abnormalities in some *animal* studies, and licensed product information recommends use in pregnancy only if the benefits are considered to outweigh the risks. A review[1] of pregnancy outcome after iron overdose found that of 66 patients reported to the UK Teratology Information Service, 35 of whom had received desferrioxamine, 7 gave birth to infants with malformations (severe in one). However, in each case overdosage had occurred after the first trimester and the malformations therefore could not be directly related to either iron or desferrioxamine. It was concluded that treatment of iron overdose with desferrioxamine should not be withheld solely on the grounds of pregnancy. Long-term use of desferrioxamine has also been reported in pregnant patients with thalassaemia; a case report[2] and review of the literature found no evidence of teratogenicity despite use at various stages of gestation, suggesting that desferrioxamine may be given to the mother if necessary.

1. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; **12:** 579.
2. Singer ST, Vichinsky EP. Deferoxamine treatment during pregnancy: is it harmful? *Am J Hematol* 1999; **60:** 24–6.

Interactions

Ascorbic acid is often given in addition to desferrioxamine to patients with iron overload to achieve better iron excretion. However, in early treatment, when there is excess tissue iron, there is some evidence that ascorbic acid may worsen iron toxicity, particularly to the heart. It is therefore recommended that a maximum daily oral dose of 200 mg of ascorbic acid should be used in adults, that vitamin C should not be given within the first month of desferrioxamine treatment or to those with heart failure, and that cardiac function should be monitored during combined use.

Desferrioxamine binds to gallium and may distort gallium-67 imaging results, see Diagnostic Tests, p. 1546.3.

Phenothiazines. Neurological symptoms including loss of consciousness occurred in 2 patients given *prochlorperazine* during desferrioxamine therapy,[1] possibly due to synergistic effects on iron mobilisation. UK licensed product information therefore advises that they should not be used together.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; **56:** 345–55.

Pharmacokinetics

Desferrioxamine mesilate is poorly absorbed from the gastrointestinal tract but rapidly absorbed after intramuscular injection or subcutaneous infusion. Peak plasma concentrations occur about 30 minutes after an intramuscular dose. When given parenterally it forms chelates with iron and aluminium ions to form ferrioxamine and aluminoxamine, respectively. The chelates are excreted in the urine and faeces via the bile. Desferrioxamine is metabolised, mainly in the plasma. Elimination of desferrioxamine and ferrioxamine is biphasic after intramuscular injection, with an initial half-life of 1 hour for desferrioxamine and 2.4 hours for ferrioxamine, and a terminal half-life of 6 hours for both compounds. Desferrioxamine is absorbed during peritoneal dialysis if added to the dialysis fluid. It is also removed by dialysis.

References.
1. Allain P, *et al.* Pharmacokinetics and renal elimination of desferrioxamine and ferrioxamine in healthy subjects and patients with haemochromatosis. *Br J Clin Pharmacol* 1987; **24:** 207–12.
2. Porter JB. Deferoxamine pharmacokinetics. *Semin Hematol* 2001; **38** (Suppl 1): 63–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Desferal; ***Austral.***: Desferal; ***Austria***: Desferal; ***Belg.***: Desferal; ***Braz.***: Desferal; ***Canad.***: Desferal; ***Chile***: Desferal; ***China***: Desferal (得斯芬); ***Cz.***: Desferal; ***Denm.***: Desferal; Desferin; ***Fin.***: Desferal; ***Fr.***: Desferal; ***Ger.***: Desferal; ***Gr.***: Desferal; ***Hong Kong***: Desferal; ***Hung.***: Desferal; ***India***: Desferal; ***Indon.***: Desferal; ***Irl.***: Desferal; ***Israel***: Desferal; ***Ital.***: Desferal; ***Malaysia***: Desferal; ***Mex.***: Desferal; ***Neth.***: Desferal; ***Norw.***: Desferal; ***Philipp.***: Desferal; ***Pol.***: Desferal; ***Port.***: Desferal; ***Rus.***: Desferal (Десферал); ***S.Afr.***: Desferal; ***Singapore***: Desferal; ***Spain***: Desferin; ***Swed.***: Desferal; ***Switz.***: Desferal; ***Thai.***: Desferal; Talifer; ***Turk.***: Desferal; ***UK***: Desferal; ***Ukr.***: Desferal (Десферал); ***USA***: Desferal; ***Venez.***: Desferal.

Pharmacopoeial Preparations
BP 2014: Desferrioxamine Injection;
USP 36: Deferoxamine Mesylate for Injection.

Dexrazoxane *(BAN, USAN, rINN)*

ADR-529; Deksrazoksan; Dexrazoxano; Dexrazoxanum; ICRF-187; NSC-169780; Дексразоксан.

(+)-(*S*)-4,4′-Propylenebis(piperazine-2,6-dione).

$C_{11}H_{16}N_4O_4$=268.3

CAS — 24584-09-6.

ATC — V03AF02.

ATC Vet — QV03AF02.

UNII — 048L81261F.

Uses and Administration

Dexrazoxane is the *S*-(+)-enantiomer of the antineoplastic drug razoxane and is a cytoprotective agent that is used to reduce the cardiotoxicity of doxorubicin and other anthracyclines (see Effects on the Heart, p. 784.1); it is also used in the management of anthracycline extravasation. Dexrazoxane and its active metabolites chelate iron within the cells and appear to prevent the formation of the anthracycline-iron complex that is thought to be responsible for cardiotoxicity.

Dexrazoxane is used to prevent chronic cumulative cardiomyopathy associated with doxorubicin or epirubicin in patients with advanced or metastatic cancer who have previously received anthracyclines; in many countries use is restricted to adults who have received a minimum cumulative dose of doxorubicin 300 mg/m² or epirubicin 540 mg/m². It is given by intravenous infusion over 15 minutes usually starting about 30 minutes before the anthracycline, as the hydrochloride, although doses are expressed as the base. The dose is calculated on a 10:1 ratio of dexrazoxane to doxorubicin or epirubicin, for instance 500 mg/m² of dexrazoxane is given for every 50 mg/m² of doxorubicin. A reduction in dose may be required in patients with renal impairment (see below).

In patients with anthracycline extravasation, dexrazoxane is given intravenously into a large vein in an area other than that affected by the extravasation. It is given once daily for 3 days, by intravenous infusion over 1 to 2 hours, starting within 6 hours of extravasation; the dose should be given at about the same time each day. The usual dose is 1 g/m² (maximum 2 g) on the first and second days, and 500 mg/m² (maximum 1 g) on the third day.

References.
1. Links M, Lewis C. Chemoprotectants: a review of their clinical pharmacology and therapeutic efficacy. *Drugs* 1999; **57:** 293–308.
2. Cvetković RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. *Drugs* 2005; **65:** 1005–24.
3. Langer SW. Dexrazoxane for anthracycline extravasation. *Expert Rev Anticancer Ther* 2007; **7:** 1081–8.
4. Hasinoff BB. The use of dexrazoxane for the prevention of anthracycline extravasation injury. *Expert Opin Invest Drugs* 2008; **17:** 217–23.
5. Jones RL. Utility of dexrazoxane for the reduction of anthracycline-induced cardiotoxicity. *Expert Rev Cardiovasc Ther* 2008; **6:** 1311–17.
6. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; **27:** 127–45. Also available at: http://jco.ascopubs.org/cgi/reprint/27/1/127.pdf (accessed 04/09/09)

Administration in children. Doxorubicin has been used in the treatment of acute lymphoblastic leukaemia in children but cardiotoxicity may be a problem. A randomised study[1] in 206 children found that those given dexrazoxane with doxorubicin had fewer elevations of cardiac troponin T, a marker of myocardial damage, than those given doxorubicin alone, but longer follow-up was needed to assess effects on cardiac function and survival. Longer-term follow-up in this group[2] found that adding dexrazoxane to doxorubicin seemed to have a cardioprotectant effect up to 5 years after treatment, as indicated by ECG measurements of left ventricular structure and function, and this effect was more pronounced in girls than in boys. No adverse effects on relapse risk, frequency of secondary malignancies, or survival were noted. Nonetheless, in June 2011, the EMEA restricted the use of dexrazoxane due to the increased risk of secondary malignancies such as acute myeloid leukaemia and myelodysplastic syndrome (see Carcinogenicity, below), contra-indicating its use in patients under the age of 18 years.

1. Lipshultz SE, *et al.* The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004; **351:** 145–53.
2. Lipshultz SE, *et al.* Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. *Lancet Oncol* 2010; **11:** 950–61.

Administration in renal impairment. Dexrazoxane is mainly excreted in the urine and clearance is reduced in patients with renal impairment.[1] Licensed product information recommends a dose reduction of 50% for patients with a creatinine clearance below 40 mL/minute.

1. Brier ME, *et al.* Pharmacokinetics of dexrazoxane in subjects with impaired kidney function. *J Clin Pharmacol* 2011; **51:** 731–8.

Adverse Effects and Precautions

Dexrazoxane may add to the bone-marrow depression caused by antineoplastics and frequent complete blood counts are recommended during therapy. At high doses of chemotherapy, where the dexrazoxane dose exceeds 1 g/m², bone-marrow suppression may increase significantly. Leucopenia and thrombocytopenia generally reverse quickly upon stopping dexrazoxane treatment. Anaemia and bone marrow aplasia occur rarely. Although dexrazoxane protects against the cardiotoxic effects of anthracyclines, cardiac function should continue to be monitored when dexrazoxane is used. Other adverse effects reported include gastrointestinal disorders, infection, neurotoxicity, alopecia, fever, pain on injection, and injection site reactions. There may also be an increased risk of thromboembolism when dexrazoxane is given with chemotherapy. Dexrazoxane may increase the urinary clearance of iron and zinc; transient increases in the serum concentrations of triglycerides and amylase can occur, and a transient decrease in serum calcium concentration has been seen.

Dexrazoxane is cytotoxic, and may increase the risk of secondary malignancies when combined with antineoplastic regimens, see Carcinogenicity, below. Teratogenic effects have been seen in *animal* studies, and effective contraception is recommended throughout treatment in both women and men; men should continue with contraceptive measures for at least 3 months after stopping dexrazoxane treatment. There is also some evidence that dexrazoxane may reduce the efficacy of the FAC antineoplastic regimen (fluorouracil, doxorubicin, and cyclophosphamide). Due to the risks associated with dexrazoxane therapy, use in many countries is restricted to adult patients who have received a minimum cumulative dose of doxorubicin 300 mg/m² or epirubicin 540 mg/m².

Liver dysfunction has occasionally occurred in patients treated with dexrazoxane. Patients with known liver function disorders should have their liver function assessed before receiving dexrazoxane for anthracycline extravasation. Clearance of dexrazoxane and its active metabolites may be reduced in patients with renal impairment, see also Administration in Renal Impairment, above.

Carcinogenicity. Dexrazoxane has been associated with an increased incidence of secondary acute myeloid leukaemia or myelodysplastic syndrome in children with Hodgkin's disease or acute lymphoblastic leukaemia (ALL) given dexrazoxane with antineoplastic therapy.[1] Dexrazoxane is the (+)-enantiomer of razoxane, which has also been associated with secondary malignancies, and has topoisomerase II inhibitory activity; it has been suggested the occurrence of secondary malignancies could be attributed to the effect of combining dexrazoxane with multiple antineoplastics, particularly topoisomerase II inhibitors.[2] However, results from studies have been conflicting. Although one study[3] in children with Hodgkin's disease reported an increased incidence of secondary malignancies when dexrazoxane was used with other topoisomerase II inhibitors, it was not designed to assess this effect. An analysis of long-term outcomes of paediatric studies in ALL,[4] included one study in which the 10-year cumulative incidence of secondary malignancies was 4.2% in patients who had received dexrazoxane versus 1.3% in those who had not. However, an analysis of a study[5] in children with leukaemia did not find any association between dexrazoxane and the incidence of secondary malignancies. Nonetheless, the use of dexrazoxane in patients less than 18 years of age is considered contra-indicated in the EU.

1. MHRA. Dexrazoxane: increased risk of secondary malignancies in children with haematological malignancies. *Drug Safety Update* 2010; **4** (2): A1. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con093878.pdf (accessed 16/05/11)
2. Novartis UK. Important safety information on Cardioxane (dexrazoxane) (issued 22/07/10). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0907936&RevisionSelectionMethod=Latest (accessed 04/08/10)
3. Tebbi CK, *et al.* Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol* 2007; **25:** 493–500.
4. Salzer WL, *et al.* Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: a report from the children's oncology group. *Leukemia* 2010; **24:** 355–70.
5. Barry EV, *et al.* Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *J Clin Oncol* 2008; **26:** 1106–11.

Effects on the skin. Severe cutaneous and subcutaneous necrosis has been reported[1] in a patient who received dexrazoxane by infusion into a peripheral forearm vein, followed by intravenous injection of doxorubicin at a different site in the same arm. Local pain occurred during the dexrazoxane infusion but there was no evidence of extravasation.

1. Lossos IS, Ben-Yehuda D. Cutaneous and subcutaneous necrosis following dexrazoxane-CHOP therapy. *Ann Pharmacother* 1999; **33:** 253–4.

Pharmacokinetics

After intravenous infusion dexrazoxane is rapidly distributed mainly in the total body water, with high concentrations in the liver and kidneys; there is no significant entry into the CSF. Plasma protein binding is low (2%). Dexrazoxane undergoes intracellular hydrolysis to active metabolites. Dexrazoxane is mainly excreted in the urine as unchanged drug and metabolites. The elimination half-life is reported to be about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Cardioxane; Savene; ***Belg.***: Savene; ***Braz.***: Cardioxane; ***Canad.***: Zinecard; ***Chile***: Cardioxane; ***China***: Ao Nuo Xian (奥诺先); ***Cz.***: Cardioxane; Cyrdanax; Procard; Savene; ***Denm.***: Cardioxane; Savene; ***Fin.***: Cardioxane†; ***Fr.***: Cardioxane; Savene; ***Ger.***: Cardioxane; ***Gr.***: Cardioxane; Savene; Zinecard; ***Hung.***: Cardioxane; ***Irl.***: Cardioxane; Savene; ***Israel***: Cardioxane; ***Ital.***: Cardioxane; Savene; ***Mex.***: Cardioxane; ***Neth.***: Cardioxane; Savene; ***Norw.***: Savene; ***Pol.***: Cardioxane; Savene; ***Port.***: Cardioxane; Savene; ***Rus.***: Cardioxane (Кардиоксан); ***Spain***: Cardioxane; Savene; ***Swed.***: Savene; ***UK***: Cardioxane; Savene; ***USA***: Totect; Zinecard; ***Venez.***: Cardioxane.

Dicobalt Edetate *(BAN, rINN)*

Cobalt Edetate; Cobalt EDTA; Cobalt Tetracemate; Dicobalti Edetas; Dicobalto, edetato de; Dikobalt Edetat; Édétate Dicobaltique; Edetato de dicobalto; Edetato dicobaltio; Дикобальта Эдетат.

Cobalt [ethylenediaminetetra-acetato(4-)-*N*,*N*′,*O*,*O*′]cobalt(II).

$C_{10}H_{12}Co_2N_2O_8$=406.1

CAS — 36499-65-7.

UNII — UKC6GH80QR.

Uses and Administration

Dicobalt edetate is a chelator used in the treatment of severe cyanide poisoning (p. 2156.2). It forms a relatively non-toxic stable ion-complex with cyanide. Owing to its toxicity, dicobalt edetate should be used only in confirmed cyanide poisoning and never as a precautionary measure. A suggested dose is 300 mg given by intravenous injection over about 1 minute, repeated if the response is inadequate; a further dose of 300 mg may be given 5 minutes later if required. For less severe poisoning injections may be given over 5 minutes. Each injection of dicobalt edetate may be followed immediately by 50 mL of glucose 50% intravenously to reduce toxicity. For doses in children, see below.

Administration in children. Although unlicensed in the UK for use in children, the *National Poisons Information Service* suggests an intravenous injection of dicobalt edetate 4 mg/kg given over 1 minute for the treatment of severe cyanide poisoning. This is followed immediately by an intravenous injection of glucose 25%; 25 mL for children aged under 2 years, and 50 mL in those from 2 years.

Adverse Effects, Treatment, and Precautions

Dicobalt edetate may cause vomiting, diarrhoea, and headache. Anaphylactic reactions have occurred and include hypotension, tachycardia, chest pain, urticaria, rash, sweating, and severe facial, laryngeal, and pulmonary oedema. Other reported adverse effects include convulsions and arrhythmias. Hypertonic glucose solution (which appeared to reduce toxicity in early *animal* studies) may be injected after dicobalt edetate for this purpose, see Uses and Administration, above.

The adverse effects of dicobalt edetate are more severe in the absence of cyanide. Therefore, dicobalt edetate should not be given unless cyanide poisoning is confirmed and poisoning is severe such as when consciousness is impaired.

Oedema. A patient with cyanide toxicity developed severe facial and pulmonary oedema after treatment with dicobalt edetate.[1] It has been suggested that when dicobalt edetate is used, facilities for intubation and resuscitation should be immediately available.

1. Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. *BMJ* 1985; **291:** 785–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Kelocyanor; ***Gr.***: Kelocyanor.

Digoxin-specific Antibody Fragments

Digoxin Immune Fab (Ovine); F(ab); Fragmentos de anticuerpos específicos antidigoxina; Fragmentos Fab de anticuerpos antidigoxina; Антидигоксин.

ATC — V03AB24.
ATC Vet — QV03AB24.
UNII — YB12NQZ1YN.

Uses and Administration

Digoxin-specific antibody fragments are derived from antibodies produced in sheep immunised to digoxin. Digoxin has greater affinity for the antibodies than for tissue-binding sites, and the digoxin-antibody complex is then excreted in the urine. Digoxin-specific antibody fragments are used to treat severe digoxin or digitoxin intoxication (p. 1355.1) in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

It is estimated that 38 or 40 mg (depending on the preparation) of antibody fragments can bind about 500 micrograms of digoxin or digitoxin; the dose is thus calculated using the steady-state plasma concentration or the amount of glycoside ingested. Doses are diluted in sodium chloride 0.9% and given by intravenous infusion over 30 minutes via a 0.22-micrometre in-line filter. If cardiac arrest is imminent the dose may be given as a bolus. In the case of incomplete reversal or recurrence of toxicity a further dose can be given after several hours.

After acute ingestion of an unknown amount of digoxin or digitoxin a dose of 760 or 800 mg is suggested; alternatively an initial dose of 380 or 400 mg can be given with an additional 380 or 400 mg if required. For toxicity during chronic therapy when the steady-state plasma concentration is unknown, a dose of 228 or 240 mg is suggested.

For doses in children, see Administration in Children, below.

Digoxin-specific antibody fragments are being investigated for the treatment of hypertension, particularly in eclampsia and pre-eclampsia.

Administration. It has been suggested[1] that giving digoxin-specific antibody fragments by infusion over 7 hours, after an initial loading dose, could be useful in ensuring adequate antibody concentrations are maintained to bind digoxin as it is released from tissue stores over a prolonged period.

1. Schaumann W, *et al.* Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; **30:** 527–33.

Administration in children. Digoxin-specific antibody fragments are licensed in children to treat severe digoxin or digitoxin intoxication in which conventional treatment is ineffective. The dose is calculated using the steady-state plasma concentration or the amount of glycoside ingested, as for adults, see Uses and Administration, above. For acute ingestion of an unknown amount of glycoside, children may also be given the adult dose, although smaller children (20 kg and under) should be individually assessed and monitored for volume overload. For toxicity during chronic therapy when the steady-state plasma concentration is unknown, children weighing over 20 kg may be given the adult dose; for those weighing 20 kg and under a dose of 38 or 40 mg is usually sufficient.

There are reports of successful use in children with cardiac glycoside poisoning.[1,2]

1. Laurent G, *et al.* Anticorps antidigoxine au cours d'une intoxication digitalique sévère chez un nouveau-né de 11 jours. Revue de la littérature. *Ann Cardiol Angeiol (Paris)* 2001; **50:** 274–84.
2. Camphausen C, *et al.* Successful treatment of oleander intoxication (cardiac glycosides) with digoxin-specific Fab antibody fragments in a 7-year-old child: case report and review of literature. *Z Kardiol* 2005; **94:** 817–23.

Administration in renal impairment. In renal impairment, elimination of antibody-bound digoxin or digitoxin is delayed[1-3] and antibody fragments can be detected in the plasma for 2 to 3 weeks after treatment.[1] The rebound in free-digoxin concentrations that has been reported after treatment with digoxin-specific antibody fragments (see Poisoning, below), occurred much later in patients with renal impairment than in those with normal renal function. Those with severe renal impairment may need to be observed for longer after treatment with antibody fragments, and monitoring of free (unbound) plasma-digoxin concentrations may be useful.[1]

1. Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 2004; **27:** 1115–33.
2. Allen NM, *et al.* Clinical and pharmacokinetic profiles of digoxin immune Fab in four patients with renal impairment. *DICP Ann Pharmacother* 1991; **25:** 1315–20.
3. Ujhelyi MR, *et al.* Disposition of digoxin immune Fab in patients with kidney failure. *Clin Pharmacol Ther* 1993; **54:** 388–94.

Poisoning. Digoxin-specific antibody fragments can reverse severe digitalis toxicity with an initial response usually seen within 30 minutes of the end of the infusion. Haemodynamic status normally improves, but in those with heart failure withdrawal of the inotropic support provided by digoxin may produce a decline in cardiac function. Plasma potassium concentrations may fall rapidly after reversal of toxicity. Glycoside toxicity has been reported to recur within 24 hours after treatment with antibody fragments. The reason for this is unclear, although it has been suggested that changes in the distribution of glycoside and antibody fragments may play a role.[1,2] It has been suggested that for either acute or chronic toxicity, half the calculated loading dose (see Uses and Administration, above) should be given initially, with further doses given only if response is inadequate or if toxicity recurs.[3] Digoxin-specific antibody fragments are usually reserved for severe or life-threatening digitalis toxicity, such as that associated with significant hyperkalaemia, arrhythmias, or bradycardia;[3] however they have also been used in patients with less severe toxicity but with poor prognostic features such as underlying cardiac disease or age over 55 years.[4]

Digoxin-specific antibody fragments have also been used to reverse toxicity from cardiac glycosides present in other plants such as common or yellow oleander (p. 2574.3) and in poisoning due to preparations containing toad venom.[5]

1. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; **28:** 483–93.
2. Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 2004; **27:** 1115–33.
3. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev* 2004; **23:** 135–43.
4. Lapostolle F, *et al.* Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med* 2008; **36:** 3014–18.
5. Brubacher JR, *et al.* Treatment of toad venom poisoning with digoxin-specific Fab fragments. *Chest* 1996; **110:** 1282–8.

Adverse Effects and Precautions

Allergic reactions to digoxin-specific antibody fragments have been reported rarely. A pruritic rash, facial flushing and swelling, and chills in the absence of fever have occurred on the day of treatment, and urticaria and thrombocytopenia have been reported up to 16 days after treatment.

Patients known to be allergic to sheep protein and those previously given digoxin-specific antibody fragments may be at greater risk of developing an allergic reaction. An intradermal or skin scratch test may be used to test for sensitivity in those considered to be at high risk.

Blood pressure, ECG, and potassium concentrations should be monitored closely during and after use. Digoxin-specific antibody fragments can interfere with digitalis immunoassay measurements; after treatment, total serum concentrations of digoxin will represent free plus bound digoxin and so can be misleading.

Pregnancy. Although data are scarce, there are reports of the use of digoxin-specific antibody fragments in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Pharmacokinetics

Digoxin-specific antibody fragments bind digoxin to form an inactive complex. These complexes accumulate in the blood before being excreted via the kidneys and the reticuloendothelial system. Digoxin-specific antibody fragments are excreted in the urine with an elimination half-life between 15 and 23 hours. In renal impairment the half-life is increased up to tenfold.

References.

1. Schaumann W, *et al.* Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; **30:** 527–33.
2. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; **28:** 483–93.
3. Renard C, *et al.* Pharmacokinetics of digoxin-specific Fab: effects of decreased renal function and age. *Br J Clin Pharmacol* 1997; **44:** 135–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Digibind; ***Canad.***: Digibind†; DigiFab; ***Fr.***: Digibind†; ***Gr.***: Digibind; DigiFab; ***Hong Kong***: Digitalis Antidote; ***UK***: Digibind; DigiFab; ***USA***: Digibind†; DigiFab.

Dimercaprol *(BAN, rINN)*

BAL; British Anti-Lewisite; Dimercaprolum; Dimerkaprol; Dimerkaproli; Dimerkaprolis; Димеркапрол.

2,3-Dimercaptopropan-1-ol.

$C_3H_8OS_2$=124.2

CAS — 59-52-9.
ATC — V03AB09.
ATC Vet — QV03AB09.
UNII — 0CPP32S55X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Dimercaprol). A clear colourless or slightly yellow liquid. Soluble in water and in arachis oil; miscible with alcohol and with benzyl benzoate. Store at 2 degrees to 8 degrees in well-filled airtight containers. Protect from light.

USP 36: (Dimercaprol). A colourless or practically colourless liquid, having a disagreeable, mercaptan-like odour. Soluble 1 in 20 of water; soluble in alcohol, in benzyl benzoate, and in methyl alcohol. Store at a temperature not exceeding 8 degrees in airtight containers. Protect from light.

Uses and Administration

Dimercaprol is a chelator that has been used in the treatment of acute poisoning by arsenic (p. 2449.1), gold (p. 131.3), and mercury (p. 2556.3). It may also be used in the treatment of poisoning by other heavy metals such as antimony and bismuth, and, with sodium calcium edetate, in acute lead poisoning (p. 2542.1). However, other chelators may be preferred for systemic use. Dimercaprol has been used in refractory Wilson's disease (p. 1567.3). Dimercaprol 5% has been applied as an ointment for skin lesions or as eye drops for ocular symptoms of arsenic toxicity.

The sulfhydryl groups on dimercaprol compete with endogenous sulfhydryl groups on proteins such as enzymes to combine with these metals; chelation by dimercaprol therefore prevents or reverses any inhibition of the sulfhydryl enzymes by the metal and the dimercaprol-metal complex formed is readily excreted by the kidney. Since the complex may dissociate, particularly at acid pH, or be oxidised, the aim of treatment is to provide an excess of dimercaprol in body fluids until the excretion of the metal is complete.

Dimercaprol should be given by deep intramuscular injection in the treatment of heavy metal poisoning. The individual dose is determined by severity of symptoms and the causative agent. Single doses should not generally exceed 3 mg/kg but single doses of up to 5 mg/kg may be required initially in patients with severe acute poisoning. Various dosage schedules are in use.

In the UK, 400 to 800 mg is given on the first day of treatment, 200 to 400 mg on the second and third days, and 100 to 200 mg on the fourth and subsequent days, all in divided doses. (For a 70-kg adult, this would correspond to a daily dose of about 5.7 to 11.4 mg/kg on the first day.)

Dimercaprol dosage schedules in the USA depend on the causative heavy metal. A recommended regimen for severe *arsenical* or *gold* poisoning is dimercaprol 3 mg/kg given at 4-hourly intervals throughout the first 2 days, 4 times daily on the third day, and then twice daily for 10 days or until recovery. In milder cases, 2.5 mg/kg is given 4 times daily on each of the first 2 days, twice daily on the third day, and then once daily for 10 days. In severe gold dermatitis the *American Hospital Formulary Service* recommends a dose of dimercaprol 2.5 mg/kg every 4 hours for 2 days, then twice daily for about 1 week, and for gold-induced thrombocytopenia, 100 mg of dimercaprol has been given twice daily for 15 days.

For *mercury* poisoning, an initial dose of dimercaprol 5 mg/kg is followed by 2.5 mg/kg one or two times daily for 10 days.

Dimercaprol is also used with sodium calcium edetate (p. 1573.3) for *lead* poisoning, particularly when there are symptoms of lead encephalopathy. Dimercaprol is usually

started first, since sodium calcium edetate may cause mobilisation of stored lead in symptomatic toxicity. A suggested regimen is to give dimercaprol intramuscularly in an initial dose of 4 mg/kg, followed at 4-hourly intervals by dimercaprol 3 to 4 mg/kg intramuscularly and sodium calcium edetate; the sodium calcium edetate may be given either intravenously, or intramuscularly at a different site from the dimercaprol. Treatment may be continued for 2 to 7 days depending on the clinical response; in patients with lead encephalopathy, combined therapy should be continued until the patient is stable. In severe lead poisoning, a minimum of 2 days without treatment should elapse before a second course of therapy with either combined dimercaprol and sodium calcium edetate or sodium calcium edetate alone is considered.

Administration in children. Dimercaprol has been used in children in the treatment of acute poisoning by heavy metals such as arsenic, gold, mercury, antimony, and bismuth. It can also be used with sodium calcium edetate for acute lead poisoning. After the second or third injection of dimercaprol, about 30% of children develop a fever that may persist until treatment is stopped. Doses are the equivalent per unit body-weight to those used in adults, see p. 1549.3. In the UK, the *BNFC* states that the use of dimercaprol in heavy metal poisoning has been superseded by other chelators. However, the *American Hospital Formulary Service* states that infants and children with mercury poisoning have been treated with an intramuscular dose of dimercaprol 3 mg/kg, given every 4 hours for the first 2 days, then every 6 hours for 1 day, then every 12 hours for a further 7 or 8 days.

Adverse Effects and Treatment

The most consistent adverse effects produced by dimercaprol are hypertension and tachycardia. Other adverse effects include nausea, vomiting, headache, burning sensation of the lips, mouth, throat, eyes, and penis, lachrymation and salivation, tingling of the extremities, a sensation of constriction in the throat and chest, muscle pains and muscle spasm, rhinorrhoea, conjunctivitis, sweating, anxiety, weakness, and abdominal pain. Transient reductions in the leucocyte count have also been reported. High doses have produced hypertensive encephalopathy with convulsions and coma. Pain may occur at the injection site and sterile abscesses occasionally develop. In children, fever commonly occurs and persists during therapy.

Adverse effects are dose-related, relatively frequent, and usually reversible. It has been suggested that ephedrine sulfate 30 to 60 mg, given orally 30 minutes before each injection of dimercaprol, may reduce adverse effects; antihistamines may alleviate some of the symptoms.

Precautions

Dimercaprol should be used with care in patients with hypertension or renal impairment. It should be stopped, or continued with extreme caution, if acute renal insufficiency develops during therapy. Alkalinisation of the urine may protect the kidney during therapy by stabilising the dimercaprol-metal complex. Dimercaprol should not be used in patients with hepatic impairment unless due to arsenic poisoning. It should not be used in the treatment of poisoning due to cadmium, iron, or selenium as the dimercaprol-metal complexes formed are more toxic than the metals themselves. Dimercaprol injection is usually formulated in arachis oil, which should be avoided in those with peanut allergy.

G6PD deficiency. Haemolysis has been reported[1] during chelation therapy with dimercaprol and sodium calcium edetate for high blood-lead concentrations in 2 children with a deficiency of G6PD.

1. Janakiraman N, *et al.* Hemolysis during BAL chelation therapy for high blood lead levels in two G6PD deficient children. *Clin Pediatr (Phila)* 1978; **17:** 485–7.

Pregnancy. Although data are scarce, there are reports of the use of dimercaprol for poisoning in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1,2]

1. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; **3:** 37–9.
2. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Interactions

Iron supplements should not be given during dimercaprol therapy as the dimercaprol-iron complex formed is toxic.

Pharmacokinetics

After intramuscular injection, peak plasma concentrations of dimercaprol occur within 30 to 60 minutes. It is widely distributed but is concentrated in the kidney, liver, and small intestine. Dimercaprol is rapidly metabolised and the metabolites and dimercaprol-metal chelates are excreted in the urine and bile. Elimination is essentially complete within 4 hours of a single dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Zorex (Зорекс).

Multi-ingredient Preparations. ***Ukr.***: Zorex (Зорекс).

Pharmacopoeial Preparations
BP 2014: Dimercaprol Injection;
USP 36: Dimercaprol Injection.

4-Dimethylaminophenol Hydrochloride

Dimetamfenol Hydrochloride; 4-Dimetilaminofenol, hidrocloruro de; 4-DMAP; 4-Диметиламинофенола Гидрохлорид.

$C_8H_{11}NO,HCl$=173.6

CAS — 619-60-3 (4-dimethylaminophenol); 5882-48-4 (4-dimethylaminophenol hydrochloride).

ATC — V03AB27.

ATC Vet — QV03AB27.

UNII — 0Q0F93G1TR.

Profile

4-Dimethylaminophenol hydrochloride is reported to oxidise haemoglobin to methaemoglobin and has been used with sodium thiosulfate as an alternative to sodium nitrite (p. 1574.3) in the treatment of cyanide poisoning. Doses of 3 to 4 mg/kg have been given intravenously.

References.

1. Weger NP. Treatment of cyanide poisoning with 4-dimethylaminophenol (DMAP)--experimental and clinical overview. *Fundam Appl Toxicol* 1983; **3:** 387–96.
2. Weger NP. Treatment of cyanide poisoning with 4-dimethylaminophenol (DMAP)—experimental and clinical overview. *Middle East J Anesthesiol* 1990; **10:** 389–412.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: 4-DMAP; ***Neth.***: 4-DMAP†.

Diprenorphine Hydrochloride *(BANM, rINNM)*

Diprenorfina, hidrocloruro de; Diprénorphine, Chlorhydrate de; Diprenorphinhydrochlorid; Diprenorphini Hydrochloridum; Hidrocloruro de diprenorfina; M-5050; Дипренорфина Гидрохлорид.

(6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-(1-hydroxy-1-methylethyl)-6-*O*-methyl-6,14-ethano-17-normorphine hydrochloride; 2-[(-)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]propan-2-ol hydrochloride.

$C_{26}H_{35}NO_4,HCl$=462.0

CAS — 14357-78-9 (diprenorphine); 16808-86-9 (diprenorphine hydrochloride).

ATC Vet — QV03AB92.

UNII — WBS7IEP4SN.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Diprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Diprenorphine hydrochloride is an opioid antagonist used as a radioligand in positron-emission tomography to image opiate receptors. It is also used in veterinary medicine to reverse the effects of etorphine hydrochloride.

Ditiocarb Sodium *(rINN)*

DDC; DDTC; DEDC; DeDTC; Dithiocarb Sodium; Ditiocarbe Sodique; Ditiocarbo sódico; Ditiocarbum Natricum; DTC; Sodium Diethyldithiocarbamate; Sodu dietyloditiokarbaminian; U-14624; Дитиокарб Натрий.

$C_5H_{10}NNaS_2$=171.3

CAS — 148-18-5.

UNII — A5304YEB5E.

NOTE. The code DDC has also been used as a synonym for Zalcitabine, p. 1023.2.

Profile

Ditiocarb sodium is a chelator that has been used in nickel carbonyl poisoning. Disulfiram (p. 2495.3), which is rapidly metabolised to ditiocarb, has been used as an alternative. Ditiocarb has also been used in the destruction of cisplatin wastes (see Handling and Disposal, p. 768.2).

Edetic Acid *(BAN, rINN)*

Acide Édétique; Ácido edético; Ácido etilendiaminotetraacético; Acido Etilendiamminotetraacetico; Acidum Edeticum; Edathamil; Edético, ácido; Edetiinihappo; Edetinsäure; Edetinsyra; Edeto rūgštis; EDTA; Ethyleendiaminetetraazijnzuur; Ethylendiamintetraessigsäure; Etiléndiamintetraecetsav; Etilén-diamin-tetraecetsav; Kwas edetynowy; Kyselina edetová; Tetracemic Acid; Эдетовая Кислота.

Ethylenediaminetetra-acetic acid.

$C_{10}H_{16}N_2O_8$=292.2

CAS — 60-00-4.

UNII — 9G34HU7RV0.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Edetic Acid). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Edetic Acid). A white crystalline powder. Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Sodium Edetate

Monosodium Edetate; Sodu edetynian; Эдетат Натрия.

CAS — 17421-79-3 (monosodium edetate).

ATC — S01XA05.

ATC Vet — QS01XA05.

NOTE. The name sodium edetate has been used in the literature for various sodium salts of edetic acid. Do not confuse with sodium calcium edetate (p. 1573.2) or etomidate (p. 1901.1); see also Inappropriate Administration, p. 1551.2.

Disodium Edetate *(BAN)*

Dinatrii Edetas; Dinatrii Edetas Dihydricus; Dinatrio edetatas; Dinatriumedetaatti; Dinatriumedetat; Disodium Edathamil; Disodium EDTA; Disodium Tetracemate; Disodu edetynian; Edetan disodný dihydrát; Édétate disodique; Edetate Disodium; Edetato disódico; Edetynian disodu; EDTA disódico; Natrii Edetas; Natriumedetat; Nátrium-edetát; Sodium Versenate.

Disodium dihydrogen ethylenediaminetetra-acetate dihydrate .

$C_{10}H_{14}N_2Na_2O_8.2H_2O$=372.2

CAS — 139-33-3 (anhydrous disodium edetate); 6381-92-6 (disodium edetate dihydrate).

ATC — S01XA05.

ATC Vet — QS01XA05.

UNII — 8NLQ36F6MM (anhydrous disodium edetate); 7FLD91C86K (disodium edetate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Disodium Edetate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 36: (Edetate Disodium). A white crystalline powder. Soluble in water. pH of a 5% solution in water is between 4.0 and 6.0.

Trisodium Edetate

Edetate Trisodium (USAN); Edetato trisódico.

Trisodium hydrogen ethylenediaminetetra-acetate .

$C_{10}H_{13}N_2Na_3O_8$=358.2

CAS — 150-38-9.

ATC — S01XA05.

ATC Vet — QS01XA05.

UNII — 420IP921MB.

Tetrasodium Edetate

Edetate Sodium (USAN).

$C_{10}H_{12}N_2Na_4O_8$=380.2

CAS — 64-02-8.

ATC — S01XA05.

ATC Vet — QS01XA05.

UNII — MP1J8420LU.

Incompatibility. Edetic acid and its salts chelate bivalent and trivalent metals and may affect the activity of drugs

such as zinc insulin that contain such ions. Additives stabilised with disodium edetate may chelate trace metals in TPN solutions. Although edetates may enhance the antimicrobial efficacy of some disinfectants (see Chloroxylenol, p. 1748.2), other preservatives may be inactivated. For reference to the inactivation of phenylmercuric salts by disodium edetate, see Incompatibility, under Phenylmercuric Nitrate, p. 1765.2. For a report of edetates reducing the antimicrobial efficacy of thiomersal, see Incompatibility, p. 1771.3.

Uses and Administration

Edetic acid and its salts are chelators; sodium edetate has a high affinity for calcium, with which it forms a stable, soluble complex that is readily excreted by the kidneys. It is given intravenously in the emergency treatment of hypercalcaemia (p. 1776.1). It has also been used to control digitalis-induced cardiac arrhythmias, although less toxic agents are generally preferred (p. 1355.1). It has also been applied topically to the eyes as a collagenase inhibitor or to treat calcium deposits such as in band keratopathy or after calcium hydroxide burns.

Sodium edetate also chelates other polyvalent metals but, unlike sodium calcium edetate, which is saturated with calcium, it is not used for the treatment of heavy metal poisoning since hypocalcaemia rapidly develops.

In the treatment of hypercalcaemia, injections containing varying amounts of disodium edetate are used, diluted with 500 mL of sodium chloride 0.9% or glucose 5% and infused over at least 3 hours. A daily dose of 50 mg/kg up to a maximum of 3 g may be given for 5 days; repeated if necessary after 2 drug-free days, up to a total of 15 doses. However, it is generally recommended that other measures to lower calcium concentrations should also be used, and disodium edetate therapy restricted to 48 hours. The trisodium salt has also been used.

Edetates are also used in pharmaceutical manufacturing as well as having other industrial applications and as anticoagulants for blood taken for haematological investigations. Sodium edetates are used in cleaners for contact lenses and as antoxidant synergists in cosmetic and pharmaceutical preparations. Other salts of edetic acid that are used clinically include sodium calcium edetate (p. 1573.2), dicobalt edetate (p. 1548.3), and sodium feredetate (p. 2088.3).

Atherosclerosis. Calcium is thought to be necessary for several steps in atherogenesis and removal of calcium from atherosclerotic plaques using a chelator such as disodium edetate has been tried in patients with atherosclerosis (p. 1250.2). However, reports of beneficial clinical responses are largely anecdotal or from small, short-term, or uncontrolled clinical studies; a meta-analysis[1] of controlled studies concluded that there was insufficient evidence of benefit or harm, and a further randomised study[2] in patients with coronary heart disease found no benefit with sodium edetate treatment. In addition, adverse effects are common with chelation therapy, and fatalities have been reported;[3] literature reviews[4,5] considering both uncontrolled and controlled studies have concluded that in view of the potential toxicity of such treatment it should be considered obsolete.

1. Dans AL, *et al.* Chelation therapy for atherosclerotic cardiovascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 04/10/05).
2. Knudtson ML, *et al.* Chelation therapy for ischemic heart disease: a randomized controlled trial. *JAMA* 2002; **287:** 481–6.
3. Magee R. Chelation treatment of atherosclerosis. *Med J Aust* 1985; **142:** 514–15.
4. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. *Circulation* 1997; **96:** 1031–3.
5. Ernst E. Chelation therapy for coronary heart disease: an overview of all clinical investigations. *Am Heart J* 2000; **140:** 139–41.

Gallstones. Edetic acid has been suggested as a possible solvent for non-cholesterol gallstones (p. 2639.1).

Adverse Effects and Treatment

Edetic acid, used as a pharmaceutical excipient, is generally well tolerated. It chelates calcium, and hypocalcaemia has occurred with prolonged use or rapid infusion; when included in preparations for the mouth, calcium may be leached from the teeth. Adverse effects have been reported after inhalation of solutions containing edetic acid, and when used as an excipient in topical formulations, it has rarely caused skin sensitisation.

With sodium edetate, adverse effects are similar to Sodium Calcium Edetate, p. 1574.1. Sodium edetate may also cause hypokalaemia or hypomagnesaemia, and blood glucose concentrations may be reduced. Rapid intravenous infusion or high serum concentrations of sodium edetate may cause a sudden drop in serum-calcium concentrations, and tetany, convulsions, respiratory arrest, and cardiac arrhythmias may result. Calcium supplements may be given intravenously for hypocalcaemia but should be used with extreme caution in patients with tetany, particularly in digitalised patients since the effect of the digitalis may be reversed.

References.

1. Morgan BW, *et al.* Adverse effects in 5 patients receiving EDTA at an outpatient chelation clinic. *Vet Hum Toxicol* 2002; **44:** 274–6.
2. Prabha A, *et al.* Chelation therapy for coronary heart disease. *Am Heart J* 2002; **144:** E10.

Effects on the respiratory tract. Inhalation of an ipratropium nebuliser solution that contained edetic acid as one of the preservatives caused bronchoconstriction in 6 of 22 patients with asthma.[1] Inhalation of edetic acid alone produced dose-related bronchoconstriction that persisted for more than 1 hour.

1. Beasley CRW, *et al.* Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ* 1987; **294:** 1197–8.

Inappropriate administration. There have been fatalities in both children and adults when they were given sodium edetate instead of *sodium calcium edetate* (p. 1573.2), which is a chelator used for the treatment of lead poisoning.[1,2] The FDA had received reports[3] of 11 deaths associated with the use of sodium edetate over the period 1971 to 2007; in 5 cases, sodium edetate was given instead of sodium calcium edetate, and in 2 cases, sodium edetate was given instead of *etomidate* (p. 1901.1). In some cases, confusion had arisen due to the use of the term EDTA in prescribing the drug. The FDA recommended that the full product name be used, and that prescribers should consider including the indication for use on the prescription.[2] Subsequently, sodium edetate products were withdrawn in the USA.

1. CDC. Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003-2005. *MMWR* 2006; **55:** 204–7. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5508.pdf (accessed 12/08/10)
2. FDA Public Health Advisory. Edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051138.htm (accessed 12/08/10)
3. FDA. Questions and answers on edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm113738.htm (accessed 12/08/10)

Precautions

Sodium edetate should be used with caution, if at all, in patients with renal impairment or anuria. Caution is also required in patients with hypocalcaemia, hypokalaemia, tuberculosis, impaired cardiac function, diabetes mellitus, or a history of seizures. Renal, hepatic, and cardiac function should be monitored regularly, along with blood pressure and serum and urinary electrolytes, particularly calcium, magnesium, and potassium; daily urinalysis is also recommended. Sodium edetate is irritant to the tissues and must be diluted before infusion; the recommended rate should not be exceeded. There may be an increased risk of nephrotoxicity when using sodium edetate to treat hypercalcaemia associated with metastatic bone disease.

Interference with laboratory tests. Disodium edetate may interfere with serum-calcium determination using the oxalate method giving lower concentrations than expected. Sampling just before the next dose or acidifying the sample will minimise the effect.

BLOOD TESTING. Pseudothrombocytopenia due to platelet clumping is a recognised complication of the use of edetates as anticoagulants for blood sampling and may lead to diagnostic errors.[1] The mechanism appears to be antibody-mediated. Alternative anticoagulants have been suggested.[1,2]

1. Bizzaro N. EDTA-dependent pseudothrombocytopenia: a clinical and epidemiological study of 112 cases, with 10-year follow-up. *Am J Hematol* 1995; **50:** 103–9.
2. Lippi U, *et al.* EDTA-induced platelet aggregation can be avoided by a new anticoagulant also suitable for automated complete blood count. *Haematologica* 1990; **75:** 38–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Chelatran†; ***Irl.***: Limclair†; ***Venez.***: Edetil.

Multi-ingredient Preparations. ***Canad.***: Largal Ultra; Mylan-Eti-Cal; ***Ger.***: Urgosan; ***India***: Fairgenol-H; ***Israel***: Claritone; ***Mex.***: Adapettes; ***UK***: Uriflex G; Uriflex R; ***USA***: Clear Eyes Contact Lens Relief; Summer's Eve Post-Menstrual; Triv; Zonite.

Pharmacopoeial Preparations

BP 2014: Disodium Edetate Eye Drops; Trisodium Edetate Infusion;

USP 36: Edetate Disodium Injection.

Ferric Citrate

Ferrum Citricum Oxidatum; Ferrum Citricum Oxydatum; KRX-0502.

CAS — 2338-05-8; 28633-45-6; 3522-50-7.

ATC — B03AB06.

ATC Vet — QB03AB06.

UNII — 63G354M39Z.

NOTE. The name Zerenex has been used as a trade mark for ferric citrate.

Profile

Ferric citrate is an oral, iron-based compound that binds to phosphate to form a non-absorbable complex. It is under investigation for the treatment of hyperphosphataemia in patients with end-stage renal disease.

Homoeopathy

Ferric citrate is used in homoeopathic medicines under the following names: Citrate ferrique; Ferric citrate; Ferrum cit; Ferrum citricum.

Flumazenil *(BAN, USAN, rINN)*

Flumatseniili; Flumazénil; Flumazenilis; Flumazenilo; Flumazenilum; Flumazepil; Ro-15-1788; Ro-15-1788/000; Флумазенил.

Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

$C_{15}H_{14}FN_3O_3$=303.3

CAS — 78755-81-4.

ATC — V03AB25.

ATC Vet — QV03AB25.

UNII — 40P7XK9392.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Flumazenil). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in dichloromethane; sparingly soluble in methyl alcohol.

USP 36: (Flumazenil). A white to off-white powder. Practically insoluble in water; slightly soluble in acidic aqueous solutions. Store in airtight containers.

Uses and Administration

Flumazenil is a benzodiazepine antagonist that acts competitively at CNS benzodiazepine receptors. It is used in anaesthesia and intensive care to reverse benzodiazepine-induced sedation; it may also be used to treat benzodiazepine overdosage (but see warnings in Precautions, p. 1552.3, and under Benzodiazepine Antagonism: Overdosage, p. 1552.1).

Flumazenil should be given by slow intravenous injection or infusion. Reversal of benzodiazepine-induced sedation usually starts within 1 to 2 minutes of the end of the injection, with the peak effect occurring after 6 to 10 minutes.

The usual initial dose for the **reversal of benzodiazepine-induced sedation** is 200 micrograms, followed at intervals of 60 seconds by further doses of 100 to 200 micrograms if required, to a maximum total dose of 1 mg or occasionally 2 mg (usual range, 0.3 to 1 mg); each dose should be given over 15 seconds, and further doses should only be given if an adequate response has not occurred 45 seconds after completion of the injection. If drowsiness recurs an intravenous infusion may be used, at a rate of 100 to 400 micrograms/hour, adjusted according to response. Alternatively, further doses of up to 1 mg, in boluses of 200 micrograms as above, may be given at 20-minute intervals to a maximum of 3 mg in one hour. Patients at risk from the effects of benzodiazepine reversal, such as those dependent on benzodiazepines, should receive smaller bolus injections of 100 micrograms. For doses in children, see p. 1552.1.

The usual initial dose for the management of **benzodiazepine overdose** is 200 micrograms given intravenously over 30 seconds. A further dose of 300 micrograms can be given after another 30 seconds and can be followed by doses of 500 micrograms at one-minute intervals if required, to a total dose of 3 mg or occasionally 5 mg. If a dose of up to 5 mg produces no response then further doses are unlikely to be effective. If symptoms of intoxication recur, repeated doses may be given at 20-minute intervals; not more than 1 mg, in boluses of 500 micrograms as above, should be given at any one time and not more than 3 mg in one hour. Alternatively, an intravenous infusion may be given at a usual rate of 100 to 500 micrograms/hour and adjusted according to response.

If signs of overstimulation occur during the use of flumazenil, then diazepam or midazolam may be given by slow intravenous injection.

Flumazenil labelled with carbon-11 (p. 2223.1) has been used for studying GABA receptors by positron emission tomography.

Flumazenil is being investigated for hypersomnia, obsessive-compulsive disorder, and alcohol dependence.

General references.

1. Brogden RN, Goa KL. Flumazenil: a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991; **42:** 1061–89.
2. Hoffman EJ, Warren EW. Flumazenil: a benzodiazepine antagonist. *Clin Pharm* 1993; **12:** 641–56.
3. Krenzelok EP. Judicious use of flumazenil. *Clin Pharm* 1993; **12:** 691–2.
4. Seger DL. Flumazenil—treatment or toxin. *J Toxicol Clin Toxicol* 2004; **42:** 209–16.

Administration. Flumazenil is usually used intravenously, but has also been given by intramuscular injection,[1] orally,[1,2] rectally,[1] and via an endotracheal tube.[3] Intranasal administration has been found to be effective in children.[1,4,5]

1. McGlone R, *et al.* A comparison of intramuscular ketamine with high dose intramuscular midazolam with and without intranasal flumazenil in children before suturing. *Emerg Med J* 2001; **18:** 34–8.
2. Girdler NM, *et al.* A randomised, controlled trial of cognitive and psychomotor recovery from midazolam sedation following reversal with oral flumazenil. *Anaesthesia* 2002; **57:** 868–76.
3. Palmer RB, *et al.* Endotracheal flumazenil: a new route of administration for benzodiazepine antagonism. *Am J Emerg Med* 1998; **16:** 170–2.
4. Heard C, *et al.* Intranasal flumazenil and naloxone to reverse oversedation in a child undergoing dental restorations. *Paediatr Anaesth* 2009; **19:** 795–7.
5. Scheepers LD, *et al.* Plasma concentration of flumazenil following intranasal administration in children. *Can J Anaesth* 2000; **47:** 120–4.

Administration in children. In children, flumazenil is used to reverse benzodiazepine-induced sedation. UK and US licensed product information recommend initial doses of flumazenil 10 micrograms/kg (maximum single dose 200 micrograms) by intravenous injection over 15 seconds to reverse the effects of benzodiazepines given for conscious sedation in children from 1 to 17 years of age. If necessary this can be repeated 45 seconds after completion of the previous injection, up to a maximum of 4 additional times to a total dose of 50 micrograms/kg or 1 mg, whichever is lower. The *BNFC* suggests that this dose may also be used to reverse the sedative effects of benzodiazepines in neonates and children under 12 months of age. If drowsiness recurs after the initial injection the *BNFC* recommends giving subsequent flumazenil doses by intravenous infusion. Neonates and children up to 18 years of age may be given 2 to 10 micrograms/kg per hour (to a maximum of 400 micrograms/hour in those aged 1 month and over), adjusted according to response.

Although flumazenil is not licensed in the UK for benzodiazepine overdose in children, it may be useful in those who are naive to benzodiazepines, or for preventing the need for ventilation, particularly in children with severe respiratory disorders. The *National Poisons Information Service* suggests an initial dose of 10 micrograms/kg given by intravenous injection over 30 seconds in children over 4 years of age. This can be repeated once if required, 30 seconds after completion of the initial injection; no more than 2 doses may be given in 24 hours. Alternatively, an intravenous infusion of 10 micrograms/kg per hour may be used.

Benzodiazepine antagonism. Flumazenil is a specific benzodiazepine antagonist that binds competitively with benzodiazepine receptors, reversing the centrally mediated effects of benzodiazepines. Its effects are evident within a few minutes of intravenous injection, even after substantial doses of benzodiazepines, and last for up to 3 hours depending on the dose and on the characteristics of the benzodiazepine intoxication. In patients who have taken benzodiazepines for prolonged periods, flumazenil may precipitate withdrawal symptoms.

SEDATION. Flumazenil reduces sedation and amnesia after the use of benzodiazepines for induction or maintenance of general anaesthesia, and in patients undergoing minor surgery or diagnostic procedures who are given benzodiazepines for conscious sedation.[1] Sedation may recur, particularly if long-acting benzodiazepines have been used, and there have been reports of increased analgesic requirements and anxiety after use of flumazenil. Although flumazenil may antagonise the obvious effects of sedation, higher cognitive functions may still be impaired[2,3] and the patient may be unfit to be discharged unless accompanied. Although experience with flumazenil in children is limited, it appears to be well tolerated and effective when used to reverse conscious sedation.[4] Flumazenil has also been used in intensive care to reverse sedation and assist in weaning from mechanical ventilation, but is not routinely recommended.

OVERDOSAGE. Flumazenil may be used as an adjunct in the management of benzodiazepine overdose including overdose involving multiple agents. However, its use may unmask the effects of other intoxicants,[5] and since benzodiazepine overdose is rarely lethal and may even protect against the toxicity of other drugs,[6] flumazenil is not recommended in mixed overdose,[7] particularly when involving tricyclic antidepressants. Repeated doses of flumazenil may be needed to maintain consciousness depending on the benzodiazepine responsible and the magnitude of the overdose; continuous infusion has also been used.[8,9]

1. Brogden RN, Goa KL. Flumazenil: a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991; **42:** 1061–89.
2. Sanders LD, *et al.* Reversal of benzodiazepine sedation with the antagonist flumazenil. *Br J Anaesth* 1991; **66:** 445–53.
3. Girdler NM, *et al.* A randomised crossover trial of post-operative cognitive and psychomotor recovery from benzodiazepine sedation: effects of reversal with flumazenil over a prolonged recovery period. *Br Dent J* 2002; **192:** 335–9.
4. Shannon M, *et al.* Safety and efficacy of flumazenil in the reversal of benzodiazepine-induced conscious sedation. *J Pediatr* 1997; **131:** 582–6.
5. Weinbroum AA, *et al.* A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Safety* 1997; **17:** 181–96.
6. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness: controversies in the use of a 'coma cocktail'. *JAMA* 1995; **274:** 562–9.
7. Carvalho C, Walker DA. Coma cocktail: a role for flumazenil? *Br J Hosp Med* 2007; **68:** 112.
8. Brammer G, *et al.* Continuous intravenous flumazenil infusion for benzodiazepine poisoning. *Vet Hum Toxicol* 2000; **42:** 280–1.
9. Chern C-H, *et al.* Continuous flumazenil infusion in preventing complications arising from severe benzodiazepine intoxication. *Am J Emerg Med* 1998; **16:** 238–41.

Hepatic encephalopathy. Flumazenil has been tried in hepatic encephalopathy (p. 1808.2) because of the suspected role of benzodiazepine-like agonists in the pathogenesis of the disorder.[1,2] However, benefits have generally been modest, and a meta-analysis[3] concluded that flumazenil did produce short-term improvement of hepatic encephalopathy but had no effect on recovery or survival; it might be considered for patients with chronic liver disease and hepatic encephalopathy but routine clinical use was not recommended.

1. Grimm G, *et al.* Improvement of hepatic encephalopathy treated with flumazenil. *Lancet* 1988; **ii:** 1392–4.
2. Basile AS, *et al.* The pathogenesis and treatment of hepatic encephalopathy: evidence for the involvement of benzodiazepine receptor ligands. *Pharmacol Rev* 1991; **43:** 27–71.
3. Als-Nielsen B, *et al.* Benzodiazepine receptor antagonists for hepatic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 04/10/05).

Non-benzodiazepine antagonism. Although flumazenil is a specific benzodiazepine antagonist, it may also block the effects of other drugs that act via the benzodiazepine receptor. In a double-blind study[1] in healthy subjects, flumazenil rapidly antagonised clinical sedation induced by zolpidem, and a rapid response to flumazenil has been reported[2] in a patient who presented in a coma following mixed overdosage with zolpidem, alcohol, and prothipendyl (although use of flumazenil in mixed overdosage is generally contra-indicated). A retrospective analysis[3] similarly noted recovery in 17 of 20 patients with zopiclone overdose who were treated with flumazenil. Flumazenil has also been tried in zaleplon toxicity.[4] Although unlicensed in the UK, the *National Poisons Information Service* suggests that flumazenil can be used to treat severe toxicity from other sedatives that act via the benzodiazepine receptor such as zolpidem, zopiclone, and zaleplon; it is rarely required but may be useful in children who are naive to benzodiazepines, or for preventing the need for ventilation, particularly in those with severe respiratory disorders. It is given in the same doses as those used for benzodiazepine overdose, see Uses, p. 1551.3.

There have also been reports of flumazenil reversing coma associated with antihistamines,[5,6] carisoprodol,[7] and gabapentin.[8] Several other drugs are reported[7] to be reversed by flumazenil including baclofen, cannabis, carbamazepine, cloral hydrate, chlorzoxazone, and meprobamate; however, efficacy has not been established. Although reversal of alcohol-induced sedation has also been suggested, a controlled study[9] found no effect with flumazenil at a dose comparable to that used for benzodiazepine overdosage.

1. Patat A, *et al.* Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther* 1994; **56:** 430–6.
2. Lheureux P, *et al.* Zolpidem intoxication mimicking narcotic overdose: response to flumazenil. *Hum Exp Toxicol* 1990; **9:** 105–7.
3. Yang C-C, Deng J-F. Utility of flumazenil in zopiclone overdose. *Clin Toxicol* 2008; **46:** 920–1.
4. Höjer J, *et al.* Zaleplon-induced coma and bluish-green urine: possible antidotal effect by flumazenil. *J Toxicol Clin Toxicol* 2002; **40:** 571–2.
5. Lassaletta A, *et al.* Reversal of an antihistamine-induced coma with flumazenil. *Pediatr Emerg Care* 2004; **20:** 319–20.
6. Plant JR, MacLeod DB. Response of a promethazine-induced coma to flumazenil. *Ann Emerg Med* 1994; **24:** 979–82.
7. Roberge RJ, *et al.* Flumazenil reversal of carisoprodol (Soma) intoxication. *J Emerg Med* 2000; **18:** 61–4.
8. Butler TC, *et al.* Flumazenil and dialysis for gabapentin-induced coma. *Ann Pharmacother* 2003; **37:** 74–6.
9. Lheureux P, Askenasi R. Efficacy of flumazenil in acute alcohol intoxication: double blind placebo-controlled evaluation. *Hum Exp Toxicol* 1991; **10:** 235–9.

Adverse Effects and Precautions

Adverse effects after use of flumazenil may be due to the reversal of benzodiazepine effects or benzodiazepine withdrawal syndrome (p. 1065.1). Adverse effects most frequently reported with flumazenil alone are dizziness, increased sweating, pain at injection site, headache, and abnormal or blurred vision. Nausea, vomiting, fatigue, cutaneous vasodilatation, dry mouth, tremor, chills, dyspnoea, cough, nasal congestion, hiccups, and injection site reactions such as thrombophlebitis and rash have occurred. Hypersensitivity reactions including anaphylaxis have been seen. Palpitations have been reported after rapid injection; other cardiovascular adverse effects include tachycardia or bradycardia, extrasystole, hypotension or hypertension, and chest pain.

Anxiety, fear, agitation, and emotional lability have occurred with flumazenil, and care is required in patients with a history of anxiety or panic attacks. Other nervous system adverse effects include confusion, drowsiness or insomnia, and paraesthesia. Seizures have occurred, particularly in patients with epilepsy or severe hepatic impairment, or those who have been taking benzodiazepines for long-term sedation. Eye disorders include visual field defects, diplopia, strabismus, increased lachrymation, and ear disorders include transient hearing impairment, hyperacusis, and tinnitus. Speech disorders include dysphonia. Patients who have taken benzodiazepines for prolonged periods are particularly at risk of developing withdrawal symptoms and rapid injection of flumazenil should be avoided in such patients. Flumazenil should not be used to treat benzodiazepine dependence or benzodiazepine withdrawal syndrome, and caution is required in patients with other drug dependencies.

Because of its short duration of action, patients given flumazenil to reverse benzodiazepine-induced sedation should be kept under close observation; further doses of flumazenil may be necessary. Flumazenil is contra-indicated in patients who are receiving benzodiazepines to control potentially life-threatening conditions and should not be given to epileptic patients who have been receiving benzodiazepines for a prolonged period to control seizures. Use after cardiac arrest is also contra-indicated.

In cases of mixed overdose, flumazenil may unmask adverse effects of other psychoactive drugs. In particular, it should not be used in the presence of severe intoxication with tricyclic and related antidepressants as convulsions, arrhythmias, and cardiac arrest can be precipitated.

Flumazenil should not be given to patients who have received neuromuscular blockers until the effects of neuromuscular blockade have fully cleared. Dosage should be adjusted individually; in high-risk or anxious patients, and after major surgery, it may be preferable to maintain some sedation during the early postoperative period. Flumazenil should be used with caution in patients with head injury since it may precipitate seizures or alter cerebral blood flow and increase intracranial pressure.

Careful titration of dosage is recommended in hepatic impairment.

Cardiac arrhythmias,[1] sometimes preceded by tonic-clonic (grand mal) seizures[2,3] and occasionally fatal,[2] have been reported in several patients after the use of flumazenil for mixed overdoses with benzodiazepines and other psychotropics. Heart block has also been reported[4] after flumazenil use in a patient who had taken benzodiazepines, paracetamol, nifedipine, and atenolol. Death from refractory tonic-clonic seizures has been reported in a patient[5] after the use of flumazenil for a mixed overdose with a benzodiazepine and a tricyclic antidepressant.

Death from respiratory failure occurred in an 83-year-old woman after sedation with midazolam[6] despite use of flumazenil, although some[7] considered that this did not represent a failure by flumazenil to reverse the depressive effects on respiration of midazolam. Ventricular fibrillation followed by asystole and death has been reported in a patient given flumazenil during weaning from assisted ventilation (a period during which diazepam had been given).[8]

1. Short TG, *et al.* Ventricular arrhythmia precipitated by flumazenil. *BMJ* 1988; **296:** 1070–1.
2. Burr W, *et al.* Death after flumazenil. *BMJ* 1989; **298:** 1713.
3. Marchant B, *et al.* Flumazenil causing convulsions and ventricular tachycardia. *BMJ* 1989; **299:** 860.
4. Herd B, Clarke F. Complete heart block after flumazenil. *Hum Exp Toxicol* 1991; **10:** 289.
5. Haverkos GP, *et al.* Fatal seizures after flumazenil administration in a patient with mixed overdose. *Ann Pharmacother* 1994; **28:** 1347–9.
6. Lim AG. Death after flumazenil. *BMJ* 1989; **299:** 858–9. Correction. *ibid.*: 1531.
7. Birch BRP, Miller RA. Death after flumazenil? *BMJ* 1990; **300:** 467–8.
8. Katz Y, *et al.* Cardiac arrest associated with flumazenil. *BMJ* 1992; **304:** 1415.

Effects on mental function. Although flumazenil is considered to lack agonist properties, a study[1] in healthy subjects found that intravenous flumazenil resulted in impairment of some measures of cognition and alertness. A severe

acute psychotic disorder, which developed during treatment with flumazenil in a patient with hepatic encephalopathy, resolved when flumazenil was discontinued.[2]

1. Neave N, *et al.* Dose-dependent effects of flumazenil on cognition, mood, and cardio-respiratory physiology in healthy volunteers. *Br Dent J* 2000; **189:** 668–74.
2. Seebach J, Jost R. Flumazenil-induced psychotic disorder in hepatic encephalopathy. *Lancet* 1992; **339:** 488–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flumazenil as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. Although data are scarce, there are reports of the use of flumazenil in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Pharmacokinetics

Flumazenil is absorbed from the gastrointestinal tract but undergoes extensive first-pass hepatic metabolism and has a systemic bioavailability of about 20%. It is about 50% bound to plasma proteins, mostly albumin. It is metabolised in the liver, mainly to the inactive carboxylic acid form. Intake of food during an intravenous infusion results in a 50% increase in clearance, probably due to the postprandial increase in liver perfusion. Flumazenil is excreted as metabolites, mainly in the urine, with a small amount in the faeces. The terminal elimination half-life is about 40 to 80 minutes. In patients with hepatic impairment the clearance of flumazenil is decreased with a resultant increase in half-life.

References.

1. Klotz U, *et al.* Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *Eur J Clin Pharmacol* 1984; **27:** 115–17.
2. Roncari G, *et al.* Pharmacokinetics of the new benzodiazepine antagonist Ro 15-1788 in man following intravenous and oral administration. *Br J Clin Pharmacol* 1986; **22:** 421–8.
3. Breimer LTM, *et al.* Pharmacokinetics and EEG effects of flumazenil in volunteers. *Clin Pharmacokinet* 1991; **20:** 491–6.
4. Jones RDM, *et al.* Pharmacokinetics of flumazenil and midazolam. *Br J Anaesth* 1993; **70:** 286–92.
5. Roncari G, *et al.* Flumazenil kinetics in the elderly. *Eur J Clin Pharmacol* 1993; **45:** 585–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fadaflumaz; Flumage; Flumanovag; Flumazen; Fluxifarm†; ***Austral.***: Anexate; ***Austria***: Anexate; ***Belg.***: Anexate; ***Braz.***: Flumazen; Flumazil; Flunexil; Lanexat; ***Canad.***: Anexate†; ***Chile***: Fluoxem; Lanexat; ***China***: Anexate (安易行); Lai Yi (莱意); ***Cz.***: Anexate; ***Fin.***: Lanexat†; ***Fr.***: Anexate; ***Ger.***: Anexate; ***Gr.***: Anexate; Demoxate; Flumexate; ***Hong Kong***: Anexate; ***Hung.***: Anexate; ***Indon.***: Anexate†; ***Irl.***: Anexate; ***Israel***: Anexate; ***Ital.***: Anexate; ***Malaysia***: Anexate; Antabenz; ***Mex.***: Lanexat; ***Neth.***: Anexate; ***Norw.***: Anexate; ***NZ***: Anexate; ***Philipp.***: Anexate; ***Pol.***: Anexate; ***Port.***: Anexate; ***Rus.***: Anexat (Анексат); ***S.Afr.***: Anexate; ***Singapore***: Anexate; ***Spain***: Anexate; ***Swed.***: Lanexat; ***Switz.***: Anexate; ***Thai.***: Anexate; ***Turk.***: Anexate; ***UK***: Anexate†; ***USA***: Romazicon; ***Venez.***: Lanexat.

Pharmacopoeial Preparations

USP 36: Flumazenil Injection.

Fomepizole *(BAN, USAN, rINN)*

Fomepitsoli; Fomepizol; Fomépizole; Fomepizolum; 4-Methylpyrazole; 4-MP; Фомепизол.

4-Methyl-1*H*-pyrazole.

$C_4H_6N_2$=82.11

CAS — 7554-65-6.

ATC — V03AB34.

ATC Vet — QV03AB34.

UNII — 83LCM6L2BY.

Uses and Administration

Fomepizole is a competitive inhibitor of alcohol dehydrogenase. It is used for the treatment of poisoning by ethylene glycol (p. 2500.3) or methyl alcohol (p. 2196.3), which are converted to toxic metabolites by alcohol dehydrogenase. Fomepizole is given in a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 4 doses; the dose should then be increased to 15 mg/kg every 12 hours until serum concentrations of ethylene glycol or methyl alcohol are less than 20 mg per 100 mL. All doses should be given by intravenous infusion over 30 minutes in at least 100 mL of sodium chloride 0.9% or glucose 5%. In patients who also require haemodialysis, doses of fomepizole should be given every 4 hours during haemodialysis sessions. Alternatively, the *National Poisons Information Service* in the UK suggests that a loading dose of 15 mg/kg can be infused over 30 to 45 minutes, followed by a continuous infusion of 1 mg/kg per hour for the duration of the haemodialysis.

Fomepizole has also been given similarly as the sulfate and the hydrochloride.

References.

1. Baum CR, *et al.* Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics* 2000; **106:** 1489–91.
2. Brent J, *et al.* Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; **344:** 424–9.
3. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother* 2002; **36:** 1085–9.
4. Mycyk MB, Leikin JB. Antidote review: fomepizole for methanol poisoning. *Am J Ther* 2003; **10:** 68–70.
5. Brent J. Fomepizole for ethylene glycol and methanol poisoning. *N Engl J Med* 2009; **360:** 2216–23.
6. Brent J. Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings. *Clin Toxicol* 2010; **48:** 401–6.

Administration. It has been suggested[1] that the evidence for rapid autoinduction of fomepizole metabolism, and the consequent need for an increase in dosage after the first 4 maintenance doses, is capable of more than one interpretation, and that an alternative regimen of 20 mg/kg intravenously every 12 hours throughout treatment might be equally effective and more convenient. However, further study in the relevant patient groups is needed before any change in regimen can be recommended.

1. Bestic M, *et al.* Fomepizole: a critical assessment of current dosing recommendations. *J Clin Pharmacol* 2009; **49:** 130–7.

Adverse Effects and Precautions

Fomepizole is generally well tolerated. The most frequent adverse effects associated with fomepizole are headache, nausea, dizziness, drowsiness, and taste disturbances. Other less common adverse effects include abdominal or back pain, fever, rash and other hypersensitivity reactions, gastrointestinal disturbances, hypotension, tachycardia or bradycardia, shock, anuria, multi-organ system failure, disseminated intravascular coagulation, anaemia, lymphangitis, pharyngitis, and hiccups. Nervous system reactions include seizures, lightheadedness, agitation, anxiety, vertigo, flushing, nystagmus, abnormal smell, and speech or visual disturbances.

Injection site reactions have been reported; fomepizole should not be given undiluted or by bolus injection. Transient increases in hepatic enzyme values and eosinophilia have been noted with repeated dosing, and liver function tests and blood counts should be monitored.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fomepizole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Fomepizole inhibits alcohol dehydrogenase and thus reduces the rate of elimination of alcohol by about 40%; similarly alcohol reduces the rate of elimination of fomepizole by about 50%. Fomepizole also induces cytochrome P450 isoenzymes and could potentially interact with other drugs that affect this enzyme system.

Pharmacokinetics

Fomepizole is absorbed from the gastrointestinal tract but is usually given intravenously. It is metabolised in the liver, mainly to 4-carboxypyrazole; the metabolites are excreted in the urine, with only a small amount of unchanged drug. After multiple doses, fomepizole induces its own metabolism by the cytochrome P450 enzyme system, significantly increasing the rate of elimination. Fomepizole is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Antizol; ***Israel***: Antizol; ***UK***: Antizol; ***USA***: Antizol.

Fuller's Earth

Argile Smectique; Argilla Smectica; Bleicherde; Terra Fullonica; Terre à Foulon; Tierra de Fuller; Фуллерова Земля.

CAS — 8031-18-3.

Profile

Fuller's earth is a clay-like substance (smectite) related to kaolin (p. 1850.1) and bentonite (p. 2170.3) that has the ability to adsorb impurities or colouring from fats, grease, or oils. It consists mainly of hydrated aluminium silicates that contain exchangeable metal cations such as magnesium, sodium, and calcium within their structure. Clay minerals that occur in varying amounts in Fuller's earth include montmorillonite, kaolinite, attapulgite or palygorskite, and halloysite. Fuller's earth has been used in the management of paraquat poisoning (p. 2159.2), although activated charcoal is now generally preferred. It has also been used for its adsorbent properties in various dermatological preparations, as a cat litter, as a stain remover, and in industry as a refining, filtering, or decolorising medium.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Camomila.

Fytic Acid *(rINN)*

Acide Fytique; Ácido fítico; Acidum Fyticum; Inositol Hexaphosphate; Inositolhexaphosphoric Acid; Phytic Acid; Фэитовая Кислота.

1,2,3,4,5,6-Cyclohexanehexolphosphoric acid; *Myo*-inositolhexakis(dihydrogen phosphate).

$C_6H_{18}O_{24}P_6$=660.0

CAS — 83-86-3.

UNII — 7IGF0S7R8I.

Calcium Magnesium Fytate *(rINNM)*

Calcii Magnesii Fytas; Calcium Magnesium Inositol Hexaphosphate; Calcium Magnesium Phytate; Fitato de calcio y magnesio; Fitina; Fytate de Calcium Magnésium; Inositocalcium; Phytin; Кальция Магния Фэитат.

CAS — 3615-82-5.

UNII — N1DEP08LNK.

Pharmacopoeias. In *Viet.*

Sodium Fytate *(rINNM)*

Fitato de sodio; Fitato sódico; Fytate de Sodium; Natrii Fytas; Phytate Sodium (USAN); Sodium cyclohexanehexyl(hexaphosphate); Sodium Phytate; SQ-9343; Натрий Фэитат.

$C_6H_9Na_9O_{24}P_6$=857.9

CAS — 7205-52-9.

UNII — 88496G1ERL.

Profile

Fytic acid is a phosphorus compound with chelating actions. It occurs naturally in plants as the insoluble calcium magnesium salt and is a major source of phosphate in the diet, although there is debate about its bioavailability. Excess intake of fytate has been associated with deficiencies of elements such as calcium, iron, and zinc.

Fytic acid has been used in topical preparations for the treatment of skin hyperpigmentation, where it is claimed to reduce the action of enzymes involved in melanogenesis. Calcium magnesium fytate has been used as a tonic. Sodium fytate reacts with calcium in the gastrointestinal tract to form non-absorbable calcium fytate which is excreted in the faeces. Sodium fytate has been used in a similar manner to sodium cellulose phosphate (p. 1574.2) to reduce the absorption of calcium from the gut in the treatment of hypercalciuria. It also binds other metals.

Sodium fytate labelled with technetium-99m (p. 2228.1) has been used intravenously for imaging of the liver.

References.

1. Zhou JR, Erdman JW. Phytic acid in health and disease. *Crit Rev Food Sci Nutr* 1995; **35:** 495–508.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Phytat DB†; ***Hung.***: Fyton; ***Singapore***: Nu-Derm Exfoderm.

Multi-ingredient Preparations. ***Braz.***: Libiplus; ***Fr.***: Vitathion; ***Ital.***: Lightening; Phytic Acid; ***Port.***: Cebrotex Forte†; Relavit Fosforo; ***Spain***: Fosgluten Reforzado†; ***Turk.***: Calcidine; ***Ukr.***: Quadevit (Квадевит).

Glucagon *(BAN, rINN)*

Gliukagonas; Glucagó; Glucagón; Glucagone; Glucagonum; Glukagon; Glukagoni; HGF; Глюкагон.

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr.

$C_{153}H_{225}N_{43}O_{49}S$=3482.8

CAS — 16941-32-5.

ATC — H04AA01.

ATC Vet — QH04AA01.

UNII — 76LA80IG2G.

Pharmacopoeias. In *US.*

USP 36: (Glucagon). A polypeptide hormone obtained from porcine and bovine pancreas glands. A fine, white or faintly coloured, practically odourless, crystalline powder. Soluble in dilute alkali and acid solutions; insoluble in most organic solvents. Store under nitrogen in airtight glass containers at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Glucagon is an endogenous polypeptide hormone that is produced by the alpha cells of the pancreatic islets of Langerhans. It is a hyperglycaemic that mobilises glucose by activating hepatic glycogenolysis. Glucagon for therapeutic use may be derived from animal sources but is now more commonly produced using recombinant DNA techniques. It is usually given as the hydrochloride, but doses are expressed as glucagon (note that 1 unit is equivalent to 1 mg of glucagon).

Glucagon is used in the treatment of severe hypoglycaemic reactions when the patient cannot take glucose orally and intravenous glucose is not feasible. It is given by subcutaneous, intramuscular, or intravenous injection in a dose of 1 mg. If there is no response within 10 minutes, intravenous glucose should be given, although there is no contra-indication to repeating the dose of glucagon. Once the patient has responded sufficiently to take carbohydrate orally this should be given to restore liver glycogen stores and prevent relapse of hypoglycaemia.

As glucagon reduces the motility of the gastrointestinal tract it is used as a diagnostic aid in gastrointestinal examinations. The route of administration and dose is dependent upon the diagnostic procedure. A dose of 1 to 2 mg intramuscularly has an onset of action of 4 to 15 minutes and a duration of effect of 10 to 40 minutes; 0.2 to 2 mg intravenously produces an effect within 1 minute that lasts for 5 to 25 minutes. A usual dose for relaxation of the stomach, duodenum, and small bowel is 200 to 500 micrograms intravenously or 1 mg intramuscularly. To relax the colon 500 to 750 micrograms is given intravenously or 1 to 2 mg intramuscularly.

For doses in children, see below.

Glucagon possesses positive cardiac inotropic activity but is not generally considered suitable for heart failure. However, it is used in the treatment of beta-blocker overdosage, see Cardiovascular Effects, below.

Action. References.

1. Habegger KM, *et al.* The metabolic actions of glucagon revisited. *Nat Rev Endocrinol* 2010; **6:** 689–97.
2. Taborsky GJ. The physiology of glucagon. *J Diabetes Sci Technol* 2010; **4:** 1338–44.

Administration. Glucagon is licensed for use by subcutaneous, intramuscular, and intravenous injection for hypoglycaemia, but intranasal[1] and rectal[2] formulations have also been investigated.

1. Teshima D, *et al.* Nasal glucagon delivery using microcrystalline cellulose in healthy volunteers. *Int J Pharm* 2002; **233:** 61–6.
2. Parker DR, *et al.* Glucagon is absorbed from the rectum but does not hasten recovery from hypoglycaemia in patients with type 1 diabetes. *Br J Clin Pharmacol* 2008; **66:** 43–9.

Administration in children. Glucagon is used in children for the treatment of severe hypoglycaemia associated with diabetes. It can be given by subcutaneous, intramuscular, or intravenous injection, usually as the hydrochloride, although doses are expressed as glucagon. A dose of 500 micrograms is recommended for children weighing less than 25 kg or younger than 6 to 8 years of age. Older patients or those weighing more than 25 kg should be given the adult dose, see above. The *BNFC* suggests a dose of 20 micrograms/kg in neonates. Intravenous glucose is required if there is no response within 10 minutes, and oral carbohydrates should be given once the patient has responded to prevent relapse.

Glucagon is used as a diagnostic aid in gastrointestinal examinations as it reduces the motility of the gastrointestinal tract. The dose depends on the procedure, see Uses and Administration, above.

The *BNFC* also suggests glucagon doses for treatment of endogenous hyperinsulinaemia in young children, although unlicensed for this indication in the UK. Neonates may be given a single dose of 200 micrograms/kg (to a maximum of 1 mg), and children from 1 month to 2 years of age a dose of 1 mg, by intravenous or intramuscular injection. Alternatively, doses may be given by continuous intravenous infusion:

- neonate: 1 to 18 micrograms/kg per hour adjusted according to response, to a maximum of 50 micrograms/kg per hour
- 1 month to 2 years: 1 to 10 micrograms/kg per hour, increased if necessary

For further discussion of glucagon use for hypoglycaemia, see below. Glucagon can also be used in children for management of beta-blocker overdose, see Cardiovascular Effects, below, or to measure growth hormone secretion, see Diagnosis and Testing, below.

Cardiovascular effects. Glucagon has chronotropic and inotropic effects due to its ability to raise cyclic AMP concentrations independently of a response to catecholamines.[1] It is used in the management of beta-blocker overdosage (p. 1320.2), although evidence of benefit is mainly anecdotal;[2] doses of 2 to 10 mg (or 50 to 150 micrograms/kg in children, to a maximum of 10 mg) by intravenous injection, followed by an infusion of 50 micrograms/kg per hour, have been suggested.

Glucagon may also have a role in anaphylactic shock (see under Adrenaline, p. 1293.2), particularly in patients receiving beta blockers, in whom adrenaline may be less effective. A dramatic improvement in refractory hypotension during an anaphylactic reaction to contrast media was described in a 75-year-old man receiving beta blockers after intravenous glucagon.[3]

There has also been a report[4] of benefit with intravenous glucagon after calcium-channel blocker overdosage, but evidence from controlled studies is not available[2] and glucagon is not generally regarded as standard treatment for such patients.

1. White CM. A review of potential cardiovascular uses of intravenous glucagon administration. *J Clin Pharmacol* 1999; **39:** 442–7.
2. Bailey B. Glucagon in β-blocker and calcium channel blocker overdoses: a systematic review. *J Toxicol Clin Toxicol* 2003; **41:** 595–602.
3. Zaloga GP, *et al.* Glucagon reversal of hypotension in a case of anaphylactic shock. *Ann Intern Med* 1986; **105:** 65–6.
4. Walter FG, *et al.* Amelioration of nifedipine poisoning associated with glucagon therapy. *Ann Emerg Med* 1993; **22:** 1234–7.

Diagnosis and testing. Glucagon stimulates secretion of growth hormone and cortisol (hydrocortisone) and has been used as a test of pituitary function in adults,[1-3] and in children.[4-7] It may be particularly suitable when first-line tests such as the insulin-tolerance test are contra-indicated.[3,8] Although unlicensed in the UK for this indication, the *BNFC* suggests glucagon 100 micrograms/kg (to a maximum of 1 mg) as a single intramuscular dose in children from 1 month to 18 years of age. It has also been given by subcutaneous injection in a dose of 50 micrograms/kg.[9] The glucagon stimulation test should be used with caution in young children;[5] severe secondary hypoglycaemia and death has been reported[10] in a 2-year-old child after a glucagon test for growth hormone secretion.

1. Gómez JM, *et al.* Growth hormone release after glucagon as a reliable test of growth hormone assessment in adults. *Clin Endocrinol (Oxf)* 2002; **56:** 329–34.
2. Abs R. Update on the diagnosis of GH deficiency in adults. *Eur J Endocrinol* 2003; **148:** S3–S8.
3. Ho KKY. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol* 2007; **157:** 695–700. Also available at: http://www.ghresearchsociety.org/files/2007_Consensus_AGHD.pdf (accessed 18/07/08)
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
5. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 04/10/05)
6. di Iorgi N, *et al.* The accuracy of the glucagon test compared to the insulin tolerance test in the diagnosis of adrenal insufficiency in young children with growth hormone deficiency. *J Clin Endocrinol Metab* 2010; **95:** 2132–9.
7. Secco A, *et al.* The glucagon test in the diagnosis of growth hormone deficiency in children with short stature younger than 6 years. *J Clin Endocrinol Metab* 2009; **94:** 4251–7.
8. Cook DM, *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients—2009 update: executive summary of recommendations. *Endocr Pract* 2009; **15:** 580–6.
9. Kappy MS, *et al.* Assessing adrenal function in primary care settings with a single sample subcutaneous glucagon test. *J Pediatr* 2006; **149:** 682–6.
10. Shah A, *et al.* Hazards of pharmacologic tests of growth hormone secretion in childhood. *BMJ* 1992; **304:** 173–4.

Gastrointestinal disorders. The relaxant effect of glucagon on smooth muscle has been used to facilitate passage of swallowed foreign bodies[1] and impacted food boluses[2] that have become lodged in the lower oesophagus. However, a controlled study[3] in children with impacted oesophageal coins found that glucagon was not effective and it has been suggested that it should not be used as first-line therapy.[4]

1. Cooke MW, Glucksman EE. Swallowed coins. *BMJ* 1991; **302:** 1607.
2. Farrugia M, *et al.* Radiological treatment of acute oesophageal food impaction. *Br J Hosp Med* 1995; **54:** 410–11.
3. Mehta D, *et al.* Glucagon use for esophageal coin dislodgment in children: a prospective, double-blind, placebo-controlled trial. *Acad Emerg Med* 2001; **8:** 200–3.
4. Arora S, Galich P. Myth: glucagon is an effective first-line therapy for esophageal foreign body impaction. *CJEM* 2009; **11:** 169–71.

Hypoglycaemia. Hypoglycaemia most commonly occurs in diabetic patients, particularly those receiving insulin therapy. Other rare causes include alcohol ingestion and tumours such as insulinomas. Neonatal hypoglycaemia occurs in small-for-gestational-age infants or infants of diabetic mothers. Persistent or recurrent hypoglycaemia in neonates is usually due to an endocrine or metabolic disorder, such as nesidioblastosis.

Glucose is the treatment of choice for **acute** hypoglycaemia since it corrects the problem at source. In patients who are unconscious or unable to take glucose orally, it may need to be given intravenously. Glucagon is an alternative in such situations, and first-line use has been suggested[1] since it is more convenient and easier to give than parenteral glucose, particularly in emergency situations. However, glucagon has a slower onset and may not always be effective, particularly where hepatic glycogen stores are depleted, such as in patients with alcohol-induced hypoglycaemia or with insulinoma. Low doses of glucagon have also been given prophylactically[2] in diabetic children at risk of developing hypoglycaemia due to gastrointestinal disorders or reduced oral intake.

Hypoglycaemia in neonates is usually managed by adjusting the enteral feeds or by giving parenteral glucose in symptomatic infants. Glucagon may be used if parenteral glucose is not effective or cannot be given.[3,4] In infants with persistent hyperinsulinaemic hypoglycaemia, continuous infusion of glucagon has been used, although oral treatments such as diazoxide plus chlorothiazide are usually preferred. Nifedipine has been added in resistant cases.[5] Pancreatectomy is often required in infants who are not responsive to diazoxide, although subcutaneous octreotide and frequent feeds have been used to manage symptoms in some infants with diffuse disease.[6]

Intractable hypoglycaemia (such as that resulting from excessive endogenous insulin production from islet cell tumours or hyperplasia) is usually treated with diazoxide, but continuous infusion of glucagon has been used in patients with tumour-associated hypoglycaemia.[7,8]

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; **306:** 600–1.
2. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care* 2001; **24:** 643–5.
3. Carter PE, *et al.* Glucagon for hypoglycaemia in infants small for gestational age. *Arch Dis Child* 1988; **63:** 1264.
4. Williams AF. Hypoglycaemia of the newborn: a review. *Bull WHO* 1997; **75:** 261–90.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.
6. Kapoor RR, *et al.* Hyperinsulinaemic hypoglycaemia. *Arch Dis Child* 2009; **94:** 450–7.
7. Samaan NA, *et al.* Successful treatment of hypoglycemia using glucagon in a patient with an extrapancreatic tumor. *Ann Intern Med* 1990; **113:** 404–6.
8. Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. *Cancer* 1998; **82:** 1585–92.

Adverse Effects

Nausea and vomiting may occur after use of glucagon. Hypersensitivity reactions (including rash and anaphylactic shock), abdominal pain, hypotension or hypertension, tachycardia or bradycardia, and hypokalaemia have also been reported.

Precautions

Glucagon should generally not be given to patients with phaeochromocytoma since it can cause a release of catecholamines producing marked hypertension. Glucagon should be given with care to patients with insulinoma as the increase in blood glucose may stimulate insulin secretion. Glucagon was formerly used to diagnose phaeochromocytoma and insulinoma but this use has been largely abandoned. Caution is also required when it is being used as a diagnostic aid in glucagonoma, or in diabetic patients or elderly patients with heart disease.

Glucagon is not effective in patients with marked depletion of liver glycogen stores, as in starvation, adrenal insufficiency, alcohol-induced hypoglycaemia, or chronic hypoglycaemia. Oral carbohydrates should be given after glucagon to prevent relapse of hypoglycaemia.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glucagon as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. Although data are scarce, there are reports of the use of glucagon during pregnancy for hypoglycaemia or as an inotrope, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Interactions

The hyperglycaemic effect of glucagon is antagonised by insulin, and caution is needed when using glucagon as a diagnostic agent in diabetic patients. Beta blockers and indometacin may also reduce glucagon's hyperglycaemic effect. Glucagon inhibits gastrointestinal motility and an additive effect may be seen with antimuscarinic drugs.

Warfarin. For a report of glucagon enhancing the anticoagulant effect of warfarin, see p. 1534.2.

Pharmacokinetics

Glucagon has a plasma half-life of about 3 to 6 minutes but longer values have been reported in diabetics (see Bioavailability, below). It is inactivated in the liver, kidneys, and plasma.

Bioavailability. In a study[1] in healthy subjects and diabetic patients the bioavailability of glucagon given intranasally was about 30% of that after intramuscular injection. However, the mean value for the apparent half-life after intramuscular injection was 28.6 and 31.4 minutes respectively in the two groups, compared with 6.6 and 11.9 minutes for intravenous infusion, and 5.5 and 13.8 minutes when given intranasally, possibly due to slow release of glucagon from the injection site.

1. Pontiroli AE, *et al.* Pharmacokinetics of intranasal, intramuscular and intravenous glucagon in healthy subjects and diabetic patients. *Eur J Clin Pharmacol* 1993; **45:** 555–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: GlucaGen; ***Austral.***: GlucaGen; ***Austria***: GlucaGen; ***Belg.***: GlucaGen; ***Braz.***: GlucaGen; ***Canad.***: GlucaGen; ***Chile***: GlucaGen; ***China***: GlucaGen; ***Cz.***: GlucaGen; ***Denm.***: GlucaGen; ***Fin.***: GlucaGen; ***Fr.***: GlucaGen; ***Ger.***: GlucaGen; ***Gr.***: GlucaGen; ***Hong Kong***: GlucaGen; ***Hung.***: GlucaGen; ***India***: GlucaGen; Glugon; ***Irl.***: GlucaGen; ***Israel***: GlucaGen; ***Ital.***: GlucaGen; ***Malaysia***: GlucaGen; ***Neth.***: GlucaGen; ***NZ***: GlucaGen; ***Pol.***: GlucaGen; ***Port.***: GlucaGen; ***Rus.***: GlucaGen (Глюкаген); ***S.Afr.***: GlucaGen; ***Singapore***: GlucaGen; ***Spain***: GlucaGen; ***Switz.***: GlucaGen; ***Turk.***: GlucaGen; ***UK***: GlucaGen; ***Ukr.***: GlucaGen (ГлюкаГен); ***USA***: GlucaGen.

Pharmacopoeial Preparations
BP 2014: Human Glucagon for Injection;
USP 36: Glucagon for Injection.

Glucarpidase *(rINN)*

Carboxypeptidase G_2; Glucarpidasa; Glucarpidasum; Глюкарпидаз.
CAS — 9074-87-7.
ATC — V03AF09.
ATC Vet — QV03AF09.
UNII — 2GFP9BJD79.

Uses and Administration

Glucarpidase is a recombinant glutamate carboxypeptidase that hydrolyses methotrexate to inactive metabolites; it is used in the management of methotrexate toxicity (plasma concentrations of >1 micromol/litre) in patients with delayed methotrexate clearance due to impaired renal function (p. 826.3). A single intravenous bolus injection of glucarpidase 50 units/kg is given over 5 minutes.

Treatment with folinic acid rescue should be continued when glucarpidase is given (but see Interactions, below). For the first 48 hours after glucarpidase, the dose of folinic acid should be based on the patient's methotrexate concentration before glucarpidase was given; thereafter, the dose is based on measured methotrexate concentrations. *Methotrexate concentrations within 48 hours of a dose of glucarpidase can only be reliably measured by a chromatographic method. Measurement of methotrexate using immunoassays during this time period is unreliable as an inactive metabolite of methotrexate (with a half-life of about 9 hours) interferes with the measurement resulting in an overestimation of the methotrexate concentration.* For further information on folinic acid rescue, see under Sodium Folinate, p. 2067.1.

References.

1. Widemann BC, *et al.* Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G2. *J Natl Cancer Inst* 2004; **96:** 1557–9.
2. Buchen S, *et al.* Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer* 2005; **92:** 480–7.
3. Schwartz S, *et al.* Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. *Oncologist* 2007; **12:** 1299–1308.
4. Phillips M, *et al.* Pharmacokinetics of glucarpidase in subjects with normal and impaired renal function. *J Clin Pharmacol* 2008; **48:** 279–84.
5. Patterson DM, Lee SM. Glucarpidase following high-dose methotrexate: update on development. *Expert Opin Biol Ther* 2010; **10:** 105–11.
6. Widemann BC, *et al.* Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. *J Clin Oncol* 2010; **28:** 3979–86.

Adverse Effects and Precautions

The most common adverse effects associated with the use of glucarpidase may include paraesthesias, flushing, nausea and/or vomiting, hypotension, and headache. Less commonly it may also cause serious allergic reactions including anaphylaxis.

Interactions

Treatment with folinic acid rescue should be continued when glucarpidase is given. However, because folinic acid is a substrate for glucarpidase, it should not be given within 2 hours before or after a dose of glucarpidase. Similarly, glucarpidase may also interact with reduced folates and folate inhibitors.

Pharmacokinetics

The mean elimination half-life of glucarpidase, in the absence of methotrexate, is 5.6 hours; in severe renal impairment (creatinine clearance less than 30 mL/min) this rises to 8.2 hours. The mean volume of distribution is 3.6 litres indicating that glucarpidase is mostly found in the plasma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Voraxaze.

Glutathione *(BAN)*

Glutathion; Glutathionum; Glutatión; Glutation; Glutationas; Glutationi; GSH; Глутатион.
N-(*N*-L-γ-Glutamyl-L-cysteinyl)glycine.
$C_{10}H_{17}N_3O_6S$=307.3
CAS — 70-18-8.
ATC — V03AB32.
ATC Vet — QV03AB32.
UNII — GAN16C9B8O.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn.* and *US.*

Ph. Eur. 8: (Glutathione). Fermentation product. A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Glutathione). Store in airtight containers.

Profile

Glutathione is an endogenous peptide with antioxidant and other metabolic functions. Glutathione and glutathione sodium are used to prevent neurotoxicity associated with cisplatin and other platinum derivatives; they have also been tried to prevent other adverse effects of antineoplastic and radiation therapy, as well as being promoted for a very broad range of disorders including heavy metal poisoning, skin pigmentation disorders, liver disorders, dyspepsia, hypersensitivity reactions, and pre-eclampsia. It has been added to nutritional supplements and eye irrigation solutions, sometimes as the disulfide, oxiglutatione. Glutathione has also been investigated for lung disorders (see below). A liposomal formulation of glutathione has been tried as a replacement therapy in patients with inborn errors of glutathione metabolism.

Antineoplastic toxicity. Glutathione has been reported to reduce the incidence of neurotoxicity induced by cisplatin therapy. In a double-blind, randomised study[1] in 50 patients receiving cisplatin for advanced gastric cancer, glutathione significantly reduced the incidence of neuropathy assessed within one week of completing cisplatin therapy. There did not appear to be any reduction in cytotoxic activity. Benefit has also been seen in small randomised studies in patients receiving oxaliplatin.[2,3]

1. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. *J Clin Oncol* 1995; **13:** 26–32.
2. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2002; **20:** 3478–83.
3. Milla P, *et al.* Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. *Anticancer Drugs* 2009; **20:** 396–402.

Lung disorders. Glutathione is an important extracellular antioxidant in the lung and high concentrations are found in lung epithelial lining fluid. A deficiency of glutathione may contribute to the epithelial damage that occurs in various lung disorders, and treatment with nebulised glutathione has therefore been investigated. Small studies have found beneficial biochemical results in patients with idiopathic pulmonary fibrosis[1] and in cystic fibrosis,[2] but the clinical effects of these changes are not clear. Another study in cystic fibrosis[3] found no effect on oxidative markers after treatment for 2 weeks, but there was a small improvement in lung function, an effect also noted in another small study.[4]

Benefit has also been reported[5] with glutathione in a patient with emphysema. However, in a study[6] of patients with mild asthma, inhalation of glutathione solution was associated with bronchoconstriction, leading to cough or breathlessness in some patients, possibly due to sulfite formation.

1. Borok Z, *et al.* Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis. *Lancet* 1991; **338:** 215–16.
2. Roum JH, *et al.* Glutathione aerosol suppresses lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis. *J Appl Physiol* 1999; **87:** 438–43.
3. Griese M, *et al.* Improvement of alveolar glutathione and lung function but not oxidative state in cystic fibrosis. *Am J Respir Crit Care Med* 2004; **169:** 822–8.
4. Bishop C, *et al.* A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis. *Chest* 2005; **127:** 308–17.
5. Lamson DW, Brignall MS. The use of nebulized glutathione in the treatment of emphysema: a case report. *Altern Med Rev* 2000; **5:** 429–31.
6. Marrades RM, *et al.* Nebulized glutathione induces bronchoconstriction in patients with mild asthma. *Am J Respir Crit Care Med* 1997; **156:** 425–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: A Tuo Mo Lan (阿拓莫兰); Gan Zhi (甘志); Ge La Da Xin (格拉达欣); Lv Ting Nuo (绿汀诺); Neuthione (乃奇安); Song Tai Si (松泰斯); Tad (泰特); Tian Yi (天亿); ***Hong Kong***: Glu-tathion; TAD; ***India***: Glutasoz; Gluton; ***Ital.***: Gluthion; Ridutox; Rition; TAD; Tationil; ***Jpn***: Glutathin†; Tathion; ***Philipp.***: Gluta; ***Rus.***: Glutoxim (Глутоксим); ***USA***: Cachexon.

Multi-ingredient Preparations. ***Austral.***: BSS Plus†; ***Canad.***: BSS Plus; Vitathion-ATP†; ***Fr.***: BSS Compose†; ***Ger.***: BSS Plus; ***Hung.***: BSS Plus†; ***India***: Basol Plus; DSN; I-Site; Imunolife; Macuchek; Oxyeye; ***Indon.***: nutrivision; ***Israel***: BSS Plus; ***Ital.***: Biotad; Endoepatox; Preastig; Puraflor; Riduton Ergo; ***Malaysia***: BSS Plus; ***Mex.***: Avitil; ***Philipp.***: Illumina; Nutrof†; ***S.Afr.***: BSS Plus; Vita-Thion; ***Singapore***: BSS Plus; Essentials†; Nutrivision†; ***Spain***: Tomevit†; ***Thai.***: BSS Plus; ***Turk.***: BSS Plus; ***UK***: Neurozan; ***USA***: BSS Plus; PowerMate; Sucrets Defense Kids Formula.

Haem Derivatives

Heme Derivatives; Hemo, derivados del grupo; Производные Гема.
ATC — B06AB01 (Haematin).
ATC Vet — QB06AB01 (haematin).

Profile

Haem is the iron protoporphyrin constituent of haemoglobin and is responsible for its colour and oxygen-carrying capacity. It is used in the management of porphyrias (p. 1556.1). Haem is given intravenously as its derivatives, although there is some confusion over their terminology. The names haematin (hematin) and haemin (hemin) have been used interchangeably although chemically haematin is the hydroxy derivative, formed by the reaction of haemin and sodium carbonate in solution. The arginine salt (haem arginate; haemin arginate; heme arginate) is reported to be more stable.

Haem arginate is used in the treatment of acute hepatic porphyrias, including acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria. It is given by slow intravenous infusion in a dose of 3 mg/kg daily for 4 days, infused over at least 30 minutes. The maximum recommended dose is 250 mg daily. The course may be repeated, with close monitoring, in patients with an inadequate response.

Haematin (haemin formulated for injection with sodium carbonate) is used intravenously for recurrent attacks of acute intermittent porphyria associated with the menstrual cycle in patients unresponsive to other therapy. It is given in a usual dose of 1 to 4 mg/kg daily for 3 to 14 days as an intravenous infusion over 10 to 15 minutes. In severe cases the dose may be repeated after 12 hours, but no more than 6 mg/kg should be given in any 24 hour period.

Injection site reactions may occur after infusion of haem derivatives and they should be given into a large arm vein or central vein which is then flushed with sodium chloride 0.9%. Use of a filter is recommended due to the colour of

the infusion. Increased serum ferritin concentrations have been reported after prolonged use of haem derivatives, and transient mild anticoagulant effects have been noted with haematin.

Administration. Lyophilised formulations of haematin, formulated as haemin with sodium carbonate, are usually reconstituted with water. However, in order to maximise stability and prevent the formation of degradation products that can cause adverse effects it has been suggested that it may be given as haem albumin by reconstituting with an equimolar amount of albumin 25% instead.[1]

1. Anderson KE, *et al.* Reconstitution of hematin for intravenous infusion. *Ann Intern Med* 2006; **144:** 537–8.

Administration in children. Attacks of porphyria are uncommon in children, but UK licensed product information for haem arginate notes that limited experience in tyrosinaemia suggests that a dose of not more than 3 mg/kg daily may safely be given for 4 days.

Porphyrias. The porphyrias are a group of inherited and acquired disorders of haem biosynthesis in which defects in specific enzymes lead to the accumulation of haem precursors, including aminolevulinic acid, porphobilinogen, and porphyrins.[1-12] They are generally classified as acute or non-acute, reflecting their clinical presentation, or as hepatic or erythropoietic, depending on the site of the enzyme defect. The three most common forms are acute intermittent porphyria, porphyria cutanea tarda, and erythropoietic protoporphyria.

ACUTE PORPHYRIAS. These are inherited disorders characterised by the accumulation of porphyrin precursors, leading to acute attacks of neurovisceral symptoms. The most common form is ***acute intermittent porphyria*** (acute hepatic porphyria); ***variegate porphyria*** and ***hereditary coproporphyria*** are generally less common forms in which there is accumulation of both porphyrin precursors and porphyrins, leading to acute attacks with cutaneous symptoms similar to those seen in non-acute porphyrias (see below).

In acute porphyrias, some enzyme activity is present and the defect only becomes apparent when demand for hepatic haem is increased. Attacks are rare before puberty and the disorder may remain latent in many patients. The presenting symptom is most commonly severe abdominal pain; other gastrointestinal symptoms such as nausea and vomiting also occur, along with autonomic effects including hypertension, tachycardia, sweating, pallor, and pyrexia. Convulsions may occur at the peak of an attack and may persist between attacks. Neuropathy leads to weakness and paralysis and may progress rapidly to respiratory distress. Psychiatric symptoms are also common, particularly agitation, anxiety, and behavioural disturbances. Various factors can increase the demand for haem and attacks are usually precipitated by drugs, alcohol, smoking, steroid hormones, reduced caloric intake, or infection. They typically last for several days and are followed by complete recovery, although in some patients chronic abdominal pain may persist without other symptoms.

The primary management of an attack is to remove precipitants and to provide intensive support. **Symptomatic treatment** is complicated by the wide range of drugs that may precipitate porphyria. High doses of parenteral opioids may be required for pain; there is a danger of addiction occurring, but this is rare unless attacks are frequent or pain persists between attacks. Phenothiazines such as chlorpromazine are useful to control nausea and agitation and their sedative effect may also be beneficial. High doses of propranolol may be required for cardiovascular symptoms. Assisted ventilation may be necessary. Convulsions usually disappear as the attack resolves; management of patients who have convulsions between attacks is a therapeutic problem since many antiepileptics are porphyrinogenic (see Porphyria, p. 512.1). **Specific therapy** is aimed at suppressing the haem biosynthetic pathway, to prevent further accumulation of precursors. Haem, given as either haematin or haem arginate, is the most effective treatment and should be given as soon as possible after onset of the attack; it produces feedback suppression of the biosynthetic pathway. Tin-protoporphyrin, a haem oxygenase inhibitor, has been given with haem to prolong its action but is not commercially available. A high carbohydrate intake may also suppress haem precursor production and should be ensured in all patients, especially if haem is not immediately available; it is usually given orally to prevent fluid overload and exacerbation of hyponatraemia, but intravenous glucose may be required in patients who are vomiting. **Prevention** of attacks involves avoiding drugs that precipitate porphyria and maintaining an adequate carbohydrate intake. Gonadorelin analogues, such as buserelin, may have a role in preventing attacks related to the menstrual cycle. Long-term treatment with haem has been tried in patients with frequent attacks.

NON-ACUTE PORPHYRIAS. These are characterised by the accumulation of porphyrins and usually present with cutaneous symptoms, although porphyrins also accumulate in the liver and liver damage commonly occurs. ***Porphyria cutanea tarda*** (cutaneous hepatic porphyria) is the most common form of porphyria. It is usually an acquired disorder and there is an association with moderate or heavy alcohol intake and hepatitis C. There is usually a raised serum-iron concentration and use of oestrogen has also been implicated. The main clinical symptom is cutaneous photosensitivity leading to bullous dermatosis, pruritus, and skin fragility, in areas exposed to sunlight. **Management** involves protecting the skin from sunlight and trauma and avoiding causative agents such as alcohol and iron. Sunscreen preparations must be based on zinc oxide or titanium dioxide to be effective. Reduction of serum-iron concentrations by phlebotomy restores enzyme function and is effective in most patients; it should be carried out every 1 to 2 weeks until remission occurs, and may be required periodically for maintenance. Chloroquine and hydroxychloroquine have also been used and may be effective where phlebotomy is contra-indicated; they appear to act by complexing with porphyrins and increasing their excretion, but low doses are necessary to avoid exacerbating the condition. An alternative method of reducing serum-iron is with the iron chelator desferrioxamine, although it may be less effective than phlebotomy; it is usually reserved for patients unable to tolerate phlebotomy. In patients with renal failure who are too anaemic for phlebotomy and who cannot excrete chloroquine, erythropoietin may be used, and may be combined with desferrioxamine or low-volume phlebotomy.

Erythropoietic protoporphyria is a less common non-acute porphyria and is an inherited disorder leading to accumulation of protoporphyrin. Symptoms are cutaneous and there is an acute reaction to sunlight leading to urticaria, pruritus, swelling, redness, and a severe burning sensation; liver damage may also occur. **Management** involves protection of the skin, as for porphyria cutanea tarda. Betacarotene is widely used to increase tolerance to sunlight, although its efficacy is not established; canthaxanthin, another carotenoid, has also been used. Haem administration, as haematin or haem arginate, may be beneficial in suppressing protoporphyrin production. Colestyramine and activated charcoal reduce protoporphyrin levels by interrupting enterohepatic recycling; they also bind other porphyrins and may have a role in rare forms of porphyria such as ***congenital erythropoietic porphyria***.

1. Thadani H, *et al.* Diagnosis and management of porphyria. *BMJ* 2000; **320:** 1647–51.
2. Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001; **26:** 225–32.
3. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. *Int J Clin Pract* 2002; **56:** 272–8.
4. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther* 2003; **16:** 57–64.
5. Lecha M, *et al.* Diagnosis and treatment of the hepatic porphyrias. *Dermatol Ther* 2003; **16:** 65–72.
6. Anderson KE, *et al.* Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; **142:** 439–50. Correction. *ibid.*; **143:** 316.
7. Sassa S. Modern diagnosis and management of the porphyrias. *Br J Haematol* 2006; **135:** 281–92.
8. Puy H, *et al.* Porphyrias. *Lancet* 2010; **375:** 924–37.
9. American Porphyria Foundation. Information available at: http://www.porphyriafoundation.com (accessed 27/05/11)
10. European Porphyria Initiative. Information available at: http://www.porphyria-europe.org (accessed 27/05/11)
11. Porphyria South Africa. Information available at: http://web.uct.ac.za/depts/porphyria/index.htm (accessed 27/05/11)
12. Norwegian Porphyria Centre (NAPOS). Information available at: http://www.drugs-porphyria.org (accessed 27/05/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Panhematin; ***Austria***: Normosang; ***Belg.***: Normosang; ***Canad.***: Proferrin; ***Denm.***: Normosang; ***Fin.***: Normosang; ***Fr.***: Normosang; ***Ger.***: Normosang; ***Gr.***: Normosang; ***Irl.***: Normosang; ***Ital.***: Normosang; ***Jpn***: Normosang; ***Neth.***: Normosang; ***Port.***: Normosang; ***Spain***: Normosang; ***Swed.***: Normosang; ***Switz.***: Normosang; ***UK***: Normosang; ***USA***: Duofer; Panhematin.

Multi-ingredient Preparations. ***Cz.***: Normosang; ***India***: Hembit.

Lanthanum Carbonate *(USAN)*

Carbonato de lantano; Lanthaan(III)carbonaat; Lanthancarbonat; Lanthaniumcarbonaat; Карбонат Лантана; Углекислый Лантан.

Lanthanum carbonate (2:3) hydrate.

$La_2(CO_3)_3.xH_2O$=457.8 (anhydrous lanthanum carbonate)

CAS — 54451-24-0.

ATC — V03AE03.

ATC Vet — QV03AE03.

UNII — 490D9F069T.

NOTE. The names Lambda and Phosbloc have been used as trade marks for lanthanum carbonate.

Uses and Administration

Lanthanum carbonate is a phosphate binder used for hyperphosphataemia (p. 1776.3) in patients with chronic renal failure. It is given orally as the hydrate, but doses are expressed in terms of elemental lanthanum. The usual initial daily dose is 0.75 to 2.25 g of elemental lanthanum, given in divided doses with meals. The dose should be adjusted every 2 to 3 weeks until an acceptable serum-phosphate concentration is achieved; the usual maintenance dose is 1.5 to 3 g daily in divided doses, but up to 3.75 g daily has been given. The tablets should be chewed thoroughly before swallowing.

Reviews.

1. Joy MS, *et al.* Lanthanum carbonate. *Ann Pharmacother* 2006; **40:** 234–40.
2. de Freitas D, *et al.* Lanthanum carbonate—a first line phosphate binder? *Semin Dial* 2007; **20:** 325–8.
3. Drüeke TB. Lanthanum carbonate as a first-line phosphate binder: the "cons". *Semin Dial* 2007; **20:** 329–32.
4. Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. *Curr Med Res Opin* 2007; **23:** 3167–75. Correction. *ibid.* 2008; **24:** 708.
5. Barton Pai A, *et al.* Therapeutic use of the phosphate binder lanthanum carbonate. *Expert Opin Drug Metab Toxicol* 2009; **5:** 71–81.
6. Curran MP, Robinson DM. Lanthanum carbonate: a review of its use in lowering serum phosphate in patients with end-stage renal disease. *Drugs* 2009; **69:** 2329–49.

Adverse Effects and Precautions

The most common adverse effects with lanthanum carbonate are gastrointestinal disturbances, including nausea, vomiting, constipation, diarrhoea, dyspepsia, and abdominal pain. There have been reports of gastrointestinal obstruction, ileus, and faecal impaction; tablets should be chewed thoroughly before swallowing. Caution is required when using lanthanum in patients with altered gastrointestinal anatomy or reduced gastrointestinal motility, including those taking medication that slows the digestive tract. Only small amounts of lanthanum are absorbed from the gastrointestinal tract but some accumulation of lanthanum in bone has been reported; the clinical significance of this is unknown.

Ingestion of lanthanum carbonate may produce a radiopaque appearance on abdominal radiography.

Interactions

Lanthanum carbonate may increase gastric pH, reducing the absorption of other drugs such as chloroquine or ketoconazole which should be given at least 2 hours apart from lanthanum. Lanthanum carbonate releases lanthanum ions in the gastrointestinal tract, forming a complex with some drugs and reducing their absorption, see Antacids and Metal Ions under Ciprofloxacin, p. 265.1, and Chelators and Antidotes under Levothyroxine, p. 2342.1; tetracyclines may also be affected in this way.

Pharmacokinetics

Lanthanum carbonate is poorly absorbed from the gastrointestinal tract, with an absolute oral bioavailability of less than 1%. The small fraction that is absorbed is more than 99% bound to plasma proteins and is widely distributed in the tissues, particularly the bones, the liver, and the gastrointestinal tract. The plasma elimination half-life is reported to be about 36 hours in healthy subjects and 56 hours in those on dialysis. Lanthanum is excreted mainly in the faeces.

References.

1. Damment SJP, Pennick M. Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet* 2008; **47:** 553–63.
2. Bronner F, *et al.* A model of the kinetics of lanthanum in human bone, using data collected during the clinical development of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet* 2008; **47:** 543–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fosrenol; ***Austria***: Fosrenol; ***Belg.***: Fosrenol; ***Canad.***: Fosrenol; ***Cz.***: Fosrenol; ***Denm.***: Fosrenol; ***Fin.***: Fosrenol; ***Fr.***: Fosrenol; ***Ger.***: Fosrenol; ***Gr.***: Fosrenol; ***Hong Kong***: Fosrenol; ***Hung.***: Fosrenol; ***India***: Fosbait; Lanthonate; ***Indon.***: Fosrenol; ***Irl.***: Foznol; ***Israel***: Fosrenol; ***Ital.***: Foznol; ***Neth.***: Fosrenol; ***Norw.***: Fosrenol; ***Philipp.***: Fosrenol; ***Port.***: Fosrenol; ***S.Afr.***: Fosrenol; ***Spain***: Fosrenol; ***Swed.***: Fosrenol; ***Switz.***: Fosrenol; ***Thai.***: Fosrenol; ***UK***: Fosrenol; ***USA***: Fosrenol.

Lofexidine Hydrochloride

(BANM, USAN, rINNM)

Ba-168; Hidrocloruro de lofexidina; Lofeksidin Hidroklorür; Lofexidina, hidrocloruro de; Lofexidine, Chlorhydrate de; Lofexidini Hydrochloridum; MDL-14042; MDL-14042A; RMI-14042A; Лофексидина Гидрохлорид.

2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline hydrochloride.

$C_{11}H_{12}Cl_2N_2O,HCl$=295.6
CAS — 31036-80-3 (lofexidine); 21498-08-8 (lofexidine hydrochloride).
ATC — N07BC04.
ATC Vet — QN07BC04.
UNII — V47G1SDI1B.

Pharmacopoeias. In *Chin.*

Uses and Administration

Lofexidine is an alpha$_2$-adrenoceptor agonist structurally related to clonidine (p. 1339.1). It has antihypertensive activity, but is used mainly in the control of opioid withdrawal symptoms.

In opioid withdrawal, lofexidine is given as the hydrochloride in an initial oral dose of 800 micrograms daily in divided doses. The dose may be increased gradually by 400 to 800 micrograms daily to a maximum of 2.4 mg daily; the maximum single dose should not exceed 800 micrograms. After 7 to 10 days, or longer in some cases, treatment is withdrawn gradually over at least 2 to 4 days.

Opioid dependence. The use of lofexidine has been reviewed.[1] A systematic review[2] of the use of alpha$_2$-adrenoceptor agonists in the management of opioid dependence (p. 109.2) concluded that they were as effective as methadone, although patients stayed in treatment for longer with methadone and there were fewer adverse effects with methadone than with clonidine. Lofexidine was associated with less hypotension than clonidine and may therefore be preferred, particularly for outpatient treatment.

1. Gish EC, *et al.* Lofexidine, an α_2-receptor agonist for opioid detoxification. *Ann Pharmacother* 2010; **44:** 343–51.
2. Gowing L, *et al.* Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 12/08/10).

Adverse Effects

Lofexidine has central alpha-adrenergic effects and may cause drowsiness, dizziness, dryness of the mouth, throat, and nose, hypotension, and bradycardia; prolongation of the QT interval has also been reported. Sedation may occur following overdosage.

Sudden withdrawal of lofexidine may produce rebound hypertension.

Precautions

Lofexidine should be used with caution in patients with cerebrovascular disease, cardiovascular disease including recent myocardial infarction, bradycardia, renal impairment, or a history of depression. It should be avoided in those at risk of QT prolongation.

It may cause drowsiness and if affected, patients should not drive or operate machinery.

Withdrawal of lofexidine therapy should be gradual over 2 to 4 days or more to reduce the risk of rebound hypertension.

Interactions

Lofexidine may enhance the central depressant effects of sedatives, including alcohol. It may also enhance the effects of antihypertensives. Lofexidine should not be used with other drugs which prolong the QT interval. Tricyclic antidepressants may reduce the efficacy of lofexidine.

Methadone. A 44-year-old opioid-dependent female receiving methadone had prolongation of the QT interval after a single 400-microgram dose of lofexidine.[1] The patient had previously had a normal QT while receiving methadone and it was suggested the effect might have been caused by the combination of the 2 drugs.

1. Schmittner J, *et al.* QT interval increased after single dose of lofexidine. *BMJ* 2004; **329:** 1075.

Pharmacokinetics

Lofexidine is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 3 hours. It is extensively metabolised in the liver and excreted mainly in the urine. The elimination half-life is 11 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kai Er Ding (凯尔丁); ***UK***: Britlofex.

Mesna *(BAN, USAN, rINN)*

D-7093; Mesnum; NSC-113891; UCB-3983; Месна.
Sodium 2-mercaptoethanesulphonate.
$C_2H_5NaO_3S_2$=164.2
CAS — 19767-45-4.
ATC — R05CB05; V03AF01.
ATC Vet — QR05CB05; QV03AF01.
UNII — NR7O1405Q9.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mesna). A white or slightly yellow, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

USP 36: (Mesna). A white or slightly yellow crystalline hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. Store in airtight containers. pH 4.5 to 6.0.

Dimesna *(rINN)*

BNP-7787; Dimesnum; Mesna Disulfide; Димесна.
Disodium 2,2′-dithiodiethanesulfonate.
$C_4H_8Na_2O_6S_4$=326.3
CAS — 16208-51-8.
UNII — 230R951Y4D.

NOTE. The name Tavocept has been used as a trade mark for dimesna.

Incompatibility and stability. There was no evidence of degradation of mesna when stored in solution with ifosfamide in polyethylene infusion bags at room temperature for 7 hours[1] or in polypropylene syringes at room temperature or at 4 degrees for 4 weeks.[2] However, in the latter study ifosfamide concentrations fell by about 3% after 7 days and 12% after 4 weeks at both temperatures. Another study[3] found that mixtures of mesna with cyclophosphamide in polyethylene infusion bags were stable for 48 hours at 4 degrees and for 6 hours at room temperature.

Mesna has been reported to be incompatible with platinum compounds such as carboplatin and cisplatin.

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i:** 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii:** 468.
3. Menard C, *et al.* Stability of cyclophosphamide and mesna admixtures in polyethylene infusion bags. *Ann Pharmacother* 2003; **37:** 1789–92.

Uses and Administration

Mesna is used for the prevention of urothelial toxicity in patients being treated with the antineoplastics ifosfamide or cyclophosphamide. In the kidney, dimesna, the inactive metabolite of mesna, is reduced to free mesna. This has thiol groups that react with the metabolites of ifosfamide and cyclophosphamide, including acrolein, which are considered to be responsible for the toxic effects on the bladder.

The aim of mesna therapy is to ensure adequate levels of mesna in the urine throughout the period during which these toxic metabolites are present. The duration of mesna treatment should therefore equal that of the antineoplastic treatment plus the time taken for the concentration of antineoplastic metabolites in the urine to fall to non-toxic concentrations. Urinary output should be maintained and the urine monitored for haematuria and proteinuria throughout the treatment period. However, frequent emptying of the bladder should be avoided.

Mesna may be given intravenously or orally for the prevention of urothelial toxicity, the dosage and frequency depending on the antineoplastic regimen used. After oral use, availability of mesna in urine is about 50% of that after intravenous use and excretion in urine is delayed up to 2 hours and is more prolonged. The intravenous preparation may be given orally added to a flavoured drink; this mixture may be stored in a sealed container in a refrigerator for up to 24 hours. Alternatively, tablets are available.

Intravenous bolus antineoplastic regimens.

- If ifosfamide or cyclophosphamide is given as an intravenous bolus, the *intravenous dose of mesna* is 20% of the dose of the antineoplastic on a weight for weight basis given on 3 occasions over 15 to 30 minutes at intervals of 4 hours beginning at the same time as the antineoplastic injection; thus the total dose of mesna is equivalent to 60% of the antineoplastic given.
  This regimen is repeated each time the antineoplastic is used. Each individual dose of mesna may be increased to 40% of the dose of the antineoplastic and given 4 times at intervals of 3 hours in patients at high risk of urotoxicity; in such cases the total dose of mesna is equivalent to 160% of the antineoplastic given.
- The *oral dose of mesna* is 40% of the intravenous bolus dose of the antineoplastic given on 3 occasions at intervals of 4 hours beginning 2 hours before the antineoplastic injection; thus a total dose of mesna equivalent to 120% of the antineoplastic is given. In patients at high-risk of urothelial toxicity a shorter interval may be left between oral mesna doses, or the number of doses increased, or both.
- Alternatively, the initial dose of mesna (20% of the dose of the antineoplastic) may be given *intravenously* at the same time as the antineoplastic, followed by two *oral doses* (each 40% of the dose of the antineoplastic) given 2 and 6 hours after the intravenous dose.

Any of these regimens may be used if **cyclophosphamide** is given **orally**.

Intravenous infusion antineoplastic regimens.

- If the antineoplastic is given as a continuous intravenous infusion, an initial bolus intravenous injection of mesna (20% of the first 24-hour antineoplastic dose) is given at the start of the antineoplastic regimen, followed by a continuous infusion of mesna given concurrently with the antineoplastic infusion at the same total dose (100%). A further 12-hour infusion of mesna (60% of the final 24-hour antineoplastic dose) is started when the antineoplastic regimen finishes; thus a total dose of mesna equivalent to 180% of the antineoplastic dose is given.
  The final 12-hour infusion may be replaced either by 3 intravenous injections each of 20% of the final 24-hour antineoplastic dose at intervals of 4 hours, the first injection being given 4 hours after the infusion has been stopped, or by *oral mesna* given in 3 doses each of 40% of the final 24-hour antineoplastic dose, the first dose being given when the infusion is stopped, and the second and third doses being given 2 and 6 hours later.

Mesna has also been used as a **mucolytic** in the management of some respiratory-tract disorders. A dose of 600 mg to 1.2 g is inhaled up to 4 times daily via a nebuliser; the drug may also be given by direct endotracheal instillation in a dose of 200 to 400 mg/hour. For sinusitis, 400 to 600 mg can be instilled into the sinuses and repeated every 2 or 3 days if needed.

For doses in children, see below.

Dimesna is under investigation as an antineoplastic and a chemoprotectant.

General references.

1. Schoenike SE, Dana WJ. Ifosfamide and mesna. *Clin Pharm* 1990; **9:** 179–91.
2. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6:** 144–54.
3. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; **27:** 127–45. Also available at: http://jco.ascopubs.org/cgi/reprint/27/1/127.pdf (accessed 15/01/10)

Administration in children. Mesna is used for the prevention of urothelial toxicity in children being treated with the antineoplastics ifosfamide and cyclophosphamide. Doses are similar to those used in adults (see above), although it may be necessary to use a more intensive dose schedule as children generally micturate more frequently than adults. Some parenteral formulations of mesna contain the preservative benzyl alcohol which has been associated with a fatal toxic syndrome in neonates and infants, see Neonates, under Benzyl Alcohol, p. 1740.1. Such formulations should not be used in children aged 12 years of age or less.

Mesna has also been used as a mucolytic in children with cystic fibrosis. Although unlicensed for such use in the UK, the *BNFC* suggests 3 to 6 mL of a 20% solution of mesna, nebulised twice daily.

Hyperhomocysteinaemia. Mesna has been tried for hyperhomocysteinaemia, implicated in the pathogenesis of some cardiovascular diseases (see Atherosclerosis, p. 1250.2, and Ischaemic Heart Disease, p. 1254.2, Venous Thrombosis, p. 1274.1, and Stroke, p. 1269.2), with variable results.[1,2]

1. Urquhart BL, *et al.* Mesna as a nonvitamin intervention to lower plasma total homocysteine concentration: implications for assessment of the homocysteine theory of atherosclerosis. *J Clin Pharmacol* 2007; **47:** 991–7.
2. Urquhart BL, *et al.* Mesna for treatment of hyperhomocysteinemia in hemodialysis patients: a placebo-controlled, double-blind, randomized trial. *Clin J Am Soc Nephrol* 2008; **3:** 1041–7.

Adverse Effects and Precautions

Adverse effects that may occur after use of mesna include gastrointestinal disturbances, headache, fatigue, depression, irritability, hypotension (but see p. 1558.1), tachycardia, rash, musculoskeletal pain, hyperaesthesia, rhinitis, pharyngitis, cough, flu-like symptoms, injection-site reactions, flushing, dizziness, and drowsiness. Bronchospasm has been reported after nebulisation and endotracheal use.

Hypersensitivity or pseudo-hypersensitivity reactions have been reported rarely, and include skin and mucous membrane reactions, a transient rise in liver enzyme values, thrombocytopenia, and general symptoms such as fever;

sudden hypotension and tachycardia occasionally occur. Such reactions appear to be more common in patients with auto-immune disorders.

Mesna may produce a false positive result in diagnostic tests for urinary ketones and may produce a false positive or false negative result in diagnostic tests for urinary erythrocytes.

Some parenteral formulations of mesna contain the preservative benzyl alcohol which has been associated with a fatal toxic syndrome in neonates and infants, see Neonates, under Benzyl Alcohol, p. 1740.1. Such formulations should not be used in children aged 12 years of age or less.

Effects on blood pressure. Hypotension may occur with mesna; however, severe hypertension has also been reported[1] after use of mesna, either alone or with ifosfamide.

1. Gilleece MH, Davies JM. Mesna therapy and hypertension. *DICP Ann Pharmacother* 1991; **25:** 867.

Effects on the nervous system. For reports of severe encephalopathy in patients receiving mesna and ifosfamide, see p. 806.3.

Hypersensitivity. Hypersensitivity reactions including rash, fever, nausea, facial and periorbital oedema, ulceration of mucous membranes, and tachycardia have been attributed to mesna.[1-4] Reactions may be more common in patients with auto-immune disorders; drug eruptions developed in 7 of 16 patients receiving mesna and cyclophosphamide for auto-immune disorders.[5] Five of these patients had a rash, with angioedema in 2 cases, and a pseudo-hypersensitivity reaction was diagnosed.

1. Lang E, Goos M. Hypersensitivity to mesna. *Lancet* 1985; **ii:** 329.
2. Seidel A, *et al*. Allergic reactions to mesna. *Lancet* 1991; **338:** 381.
3. Gross WL, *et al*. Allergic reactions to mesna. *Lancet* 1991; **338:** 381–2.
4. D'Cruz D, *et al*. Allergic reactions to mesna. *Lancet* 1991; **338:** 705–6.
5. Zonzits E, *et al*. Drug eruptions from mesna: after cyclophosphamide treatment of patients with systemic lupus erythematosus and dermatomyositis. *Arch Dermatol* 1992; **128:** 80–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mesna as probably not porphyrinogenic when used for the prevention of urothelial toxicity in patients given antineoplastics; it may be used as a drug of first choice and no precautions are needed. When used as a mucolytic, mesna is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

Mesna is absorbed from the gastrointestinal tract. It is rapidly metabolised to the disulfide, dimesna, after oral or intravenous dosage and is excreted in the urine as both metabolite and unchanged drug; dimesna is reduced back to mesna, which is the active form, in the kidney. After an intravenous dose the half-lives of mesna and dimesna are reported to be about 20 minutes and 70 minutes, respectively, but after repeated dosing (intravenous followed by oral) the half-life of mesna is reported to be up to 8 hours. Mesna is about 70% bound to plasma proteins.

References.

1. Burkert H, *et al*. Bioavailability of orally administered mesna. *Arzneimittelforschung* 1984; **34:** 1597–1600.
2. James CA, *et al*. Pharmacokinetics of intravenous and oral sodium 2-mercaptoethane sulphonate (mesna) in normal subjects. *Br J Clin Pharmacol* 1987; **23:** 561–8.
3. El-Yazigi A, *et al*. Pharmacokinetics of mesna and dimesna after simultaneous intravenous bolus and infusion administration in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1997; **37:** 618–24.
4. Verschraagen M, *et al*. Pharmacokinetics of BNP7787 and its metabolite mesna in plasma and ascites: a case report. *Cancer Chemother Pharmacol* 2003; **51:** 525–9.
5. Boven E, *et al*. Phase I and pharmacokinetic study of the novel chemoprotector BNP7787 in combination with cisplatin and attempt to eliminate the hydration schedule. *Br J Cancer* 2005; **92:** 1636–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Delinar†; Mestian; Neper; Varimesna; ***Austral.***: Uromitexan; ***Austria***: Mistabron†; Uromitexan; ***Belg.***: Mistabron; Uromitexan; ***Braz.***: Mitexan; Tevamesna; ***Canad.***: Uromitexan; ***Chile***: Mucofluid†; Uromitexan; Uroprot; ***China***: Mei An (美安); Uromitexan (优美善); ***Cz.***: Mistabron; Uromitexan; ***Denm.***: Uromitexan; ***Fin.***: Uromitexan; ***Fr.***: Mucofluid†; Uromitexan; ***Ger.***: Uromitexan; ***Gr.***: Mucofluid; Uromitexan; ***Hong Kong***: Mistabron†; Uromitexan; ***Hung.***: Uromitexan; ***India***: Mistabron; Uromitexan; ***Indon.***: Uromitexan; ***Irl.***: Uromitexan; ***Israel***: Mexan†; ***Ital.***: Uromitexan; ***Jpn***: Uromitexan; ***Mex.***: Mescryo; Mesnil; Mesodal; Uromes; Uroprot; Ziken†; ***Neth.***: Mistabron†; Uromitexan; ***Norw.***: Uromitexan; ***NZ***: Uromitexan; ***Philipp.***: Mistabron; Uromitexan†; ***Pol.***: Anti-Uron; Mistabron†; Mucofluid; Uromitexan; ***Port.***: Uromitexan; ***Rus.***: Uromitexan (Уромитексан); ***S.Afr.***: Mistabron; Uromitexan; ***Singapore***: Mistabron†; Uromitexan; ***Spain***: Mucofluid; Uromitexan; ***Swed.***: Uromitexan; ***Switz.***: Uromitexan; ***Thai.***: Uromitexan; Uroprot; ***Turk.***: Uromitexan; ***USA***: Mesnex.

Multi-ingredient Preparations. ***India***: Holoxan Uromitexan; Ifex-M; Ifomid-M; Ifoxan with Mesna; Ipamide with Mesna†; Isoxan.

Methionine *(BAN, USAN, rINN)*

L-Metionina; M; Methionin; L-Methionine; Méthionine; *S*-Methionine; Methioninum; Metioniini; Metionin; Metionín; Metionina; Metioninas; Metiyonin; Метионин; Метіонін.

L-2-Amino-4-(methylthio)butyric acid.

$C_5H_{11}NO_2S$=149.2

CAS — 63-68-3.

ATC — V03AB26.

ATC Vet — QA05BA90; QG04BA90; QV03AB26.

UNII — AE28F7PNPL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Methionine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. A 2.5% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 36: (Methionine). White crystals having a characteristic odour. Soluble in water, in warm dilute alcohol, and in dilute mineral acids; insoluble in dehydrated alcohol, in acetone, in ether, and in benzene. pH of a 1% solution in water is between 5.6 and 6.1.

DL-Methionine

Methionin racemický; DL-Méthionine; DL-Methioninum; Methioninum Racemicum; DL-Metioniini; DL-Metionin; DL-Metionina; DL-Metioninas; Racemethionine (USAN); DL-Метионин.

DL-2-Amino-4-(methylthio)butyric acid.

$C_5H_{11}NO_2S$=149.2

CAS — 59-51-8.

ATC — V03AB26.

ATC Vet — QV03AB26.

UNII — 73JWT2K6T3.

NOTE. The name methionine is often applied to DL-methionine.

Compounded preparations of DL-methionine may be represented by the following names:

- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol respectively.

Pharmacopoeias. In *Eur.* (see p. vii), Also in *USNF*. *Int*., and *Viet*.

Ph. Eur. 8: (DL-Methionine). An almost white crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol; dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 5.4 to 6.1. Protect from light.

USNF 31: (Racemethionine). An almost white, crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. pH of a 2% solution in water is 5.4 to 6.1. Protect from light.

Uses and Administration

L-Methionine is an essential amino acid that is included in oral dietary supplements and amino-acid solutions used for parenteral nutrition (p. 2044.1). It enhances the synthesis of glutathione and has been used as an alternative to acetylcysteine in the treatment of paracetamol poisoning to prevent hepatotoxicity; however, the use of methionine as an antidote has been largely superseded by acetylcysteine (see p. 116.2). It also lowers urinary pH and is used as an adjunct in the management of urinary-tract infections, to treat renal calculi, and to reduce irritation of the skin caused by urine. Methionine is also used as an adjunct in the treatment of liver disorders, and high oral doses have been given as a loading test in the assessment of hyperhomocysteinaemia (below).

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the usual dose of methionine is 2.5 g orally every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol. For doses in children, see below. Preparations containing both methionine and paracetamol have been formulated for use in situations where overdosage may occur.

To lower the urinary pH during chronic urinary-tract infections or to treat renal calculi, a usual oral dose of L-methionine 0.5 to 1 g is given 3 times daily.

Acetylmethionine has also been used.

Administration in children. Methionine is included in amino-acid solutions used for parenteral nutrition in children; it has also been used as an antidote in the treatment of paracetamol poisoning, but has been largely superseded by acetylcysteine.

For paracetamol overdose, children under 6 years of age can be given an oral dose of 1 g methionine every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol. Children aged 6 years or over can be given the adult dose, see above.

Hyperhomocysteinaemia. Methionine is metabolised to homocysteine and an oral methionine-loading test is used in the assessment of hyperhomocysteinaemia which has been implicated in the development of several disorders including cardiovascular disease (see p. 2063.3) and psychiatric conditions such as Alzheimer's disease and depression (see p. 2046.3). Although fasting homocysteine measurements can be used to diagnosis hyperhomocysteinaemia, about half of patients have normal fasting homocysteine but an elevated concentration after a methionine-loading test,[1] which could indicate vitamin B_6 deficiency or a genetic mutation in the enzyme involved in the metabolism of homocysteine.[2] An oral dose of L-methionine 100 mg/kg is given and plasma homocysteine concentrations measured about 6 hours post-dose.[1,2]

1. van der Griend R, *et al*. Postmethionine-load homocysteine determination for the diagnosis hyperhomocysteinaemia and efficacy of homocysteine lowering treatment regimens. *Vasc Med* 2002; **7:** 29–33.
2. Herrmann W, *et al*. Hyperhomocysteinaemia: a critical review of old and new aspects. *Curr Drug Metab* 2007; **8:** 17–31.

Adverse Effects and Precautions

Methionine may cause nausea, vomiting, drowsiness, and irritability. Methionine can cause acidification of the urine and blood. It should not be used in patients with acidosis, hyperuricaemia or hyperuricosuria, uric acid- or cystine-containing renal calculi, or metabolic disorders such as oxalosis, homocystinuria, or hypermethioninaemia. Methionine may aggravate hepatic encephalopathy in patients with established liver damage; it should be used with caution in patients with severe liver disease.

High-dose regimens. High doses of oral methionine (5 to 40 g daily for up to 2 months) have precipitated psychotic symptoms in schizophrenic patients, although doses of 10 g have been given to healthy subjects without significant adverse effects. Dizziness, drowsiness, polyuria, and changes in blood pressure were reported in a controlled study of patients with cardiovascular disease given the methionine-loading test (see Hyperhomocysteinaemia, above). A fatality has been reported after a methionine-loading test in which the subject was thought to have been given about 10 times the intended dose.

Methionine is metabolised to homocysteine, high levels of which have been associated with cardiovascular disease (see p. 2063.3) and psychiatric conditions such as Alzheimer's disease and depression (see p. 2046.3). There is no evidence to suggest that dietary intake of methionine causes vascular damage, and although the high doses used in the methionine-loading test result in endothelial dysfunction, this effect is acute and so a single test is therefore deemed unlikely to be harmful.[1]

1. Garlick PJ. Toxicity of methionine in humans. *J Nutr* 2006; **136** (suppl 6): 1722S–1725S.

Interactions

Methionine may be adsorbed by activated charcoal and the effect of oral methionine may be reduced if they are given together. Methionine is an urinary acidifier and may increase exposure to drugs that undergo tubular reabsorption in acidic urine, such as some antibacterials.

Dopaminergics. For reference to the antagonism of the antiparkinsonian effect of *levodopa* by methionine, see Nutritional Agents, under Interactions of Levodopa, p. 907.3.

Pharmacokinetics

Methionine is well absorbed from the gastrointestinal tract. It is metabolised in the liver to *S*-adenosylmethionine (ademetionine, p. 2429.3) and then homocysteine. Homocysteine is then either remethylated to methionine or forms taurine and cysteine (a precursor of glutathione). Methionine has a half-life of about 1 to 1.5 hours. About 5 to 10% of a dose is excreted unchanged in the urine and about 80% is excreted as an inorganic sulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Methnine†; ***Austria***: Acimethin; ***China***: Bai Fu Li (百扶力); Qi Cun (齐存); Xin Yuan

Da (欣源达); ***Ger.***: Acimethin†; Acimol; Methiotrans†; Urol methin; ***Gr.***: Urosamine; ***Rus.***: Eslidine (Эслидин); ***Switz.***: Acimethin; ***USA***: M-Caps; Uracid.

Multi-ingredient Preparations. ***Arg.***: Cistidac; Cistimax; Dial-ND; Gastricur; Levantol Procaina; Piel Vital; Tricomax; Triconal; Valcatil Max; Valcatil Plus; Valcatil; ***Austral.***: Berberis Complex†; PM Syrin; ***Braz.***: Abcler; Anekron; Biohepax†; Chofrafig; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Hepalin; Hepatox; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B6; Panvitrop; Regenom; Silimalon; Xantinon B12; Xantinon Complex; ***Canad.***: Betagard; Emulsi Factors; Formula AO†; Formula IC†; Formula VIR†; Hepaticol; Right Choice PM†; ***Chile***: Vantux Plus; Vantux; ***China***: Bao Jia Wei (保甲维); Bei Xin (倍辛); Bo Shi Duo An (博仕多安); Fu Er Jian (孚尔健); Gan Du Xin (甘度欣); Neo-Minophagen C (美能); Tian Qi (天芪); Wei Bi Lai (维必莱); Wei Ding Xi (维定喜); Wei Li (维力); Xi Bi Kang (西比康); Yi Wei (异维); ***Fr.***: Anacaps tri-Activ; Anacaps†; Forcapil; Lobamine-Cysteine; Nivabetol†; Verrulyse-Methionine; ***Ger.***: Merz Spezial Dragees N†; ***Hong Kong***: Lipochol; Pilfood; Revicon; Super Vita Vim; ***Hung.***: Forcapil; Revalid; ***India***: Alnacer; Beminal; Delage; Dexia; Enerjex; Fevastin Plus; Fibrotin; Furtipil-L; Gardian; Inpro; Livobion; Livobion; Lycostar-CM; Namsafe; Neutrosec; Pamela; Parasafe; ***Indon.***: BIO-EPL†; Carni Plus; DFM; Lipagent; Methicol; Methioson; Vionin NF; Vionin; ***Irl.***: Antox; ***Ital.***: Biomineral One; Biomineral Plus; Biophase Complex†; Chiton; Detoxicon; Lipoenergy; Vitreolux; ***Malaysia***: Revicon; Revital; ***Mex.***: Lipovitasi-Or; ***Philipp.***: ALAnerv; Arcostrong†; Biomix; Energel; Rejuvenex; Revicon Forte (Improved); ***Pol.***: Methiovit†; Revalid; ***Rus.***: Decamevit (Декамевит); Remaxol (Ремаксол); Selmevit (Селмевит); ***S.Afr.***: Hepavite†; ***Singapore***: Revicon; Vitiron; ***Spain***: Dertrase; Epitelizante; ***Switz.***: Mechovit†; Vitiron; ***Thai.***: Lipochol; Liporon; Revicon†; Vita Multicap; Vitop; ***UK***: Antox; Lipotropic Factors; Paradote†; Pilfood; ***Ukr.***: Decamevit (Декамевит); Detoxil (Детоксил); Hepahealth (Гепахелс); PM Sirin (ПМ Сирин); Quadevit (Квадевит); Revalid (Ревалид); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Amino-Cerv; Geritol; Liponol; Methatropic.

Methylthioninium Chloride

(BAN, rINN)

Azul de Metileno; Bleu de Méthylène; Błękit metylenowy; Blu di Metilene; CI Basic Blue 9; Cloruro de metiltioninio; Colour Index No. 52015; Methyleenblauw; Methylenblått; Methylenblau; Methylene Blue; Methylenii Caeruleum; Methylthioninii Chloridum; Methylthioninii Chloridum Hydricum; Méthylthionin, Chlorure de; Methylthioniniumchlorid; Methylthionin-chlorid hydrát; Metilen Mavisi; Metiltioninio chloridas; Metiltioninio Clorure; Metiltioninio, cloruro de; Metiltionin-klorid; Metyleenisininen; Metylenblått; Metylenblått; Metylotioniniowy chlorek; Metyltioniniumklorid; Metyylitioniniumkloridi; Schultz No. 1038; Tetramethylthionine Chloride Trihydrate; Метилтиониния Хлорид; Метиленовый Синий; Метиленовий Синій.

3,7-Bis(dimethylamino)phenazathionium chloride trihydrate.

$C_{16}H_{18}ClN_3S,3H_2O$=373.9

CAS — 61-73-4 (anhydrous methylthioninium chloride); 7220-79-3 (methylthioninium chloride trihydrate).

ATC — V03AB17; V04CG05.

ATC Vet — QV03AB17; QV04CG05.

UNII — T42P99266K (methylthioninium chloride trihydrate); 8NAP7826UB (anhydrous methylthioninium chloride).

NOTE. *Commercial methylthioninium chloride may consist of the double chloride of tetramethylthionine and zinc, and is not suitable for medicinal use.*

The name Rember has been used as a trade mark for methylthioninium chloride.

Pharmacopoeias. In *Chin.* and *US*; in *Eur.* (see p. vii) (as xH_2O); in *Int.* (as anhydrous or $3H_2O$).

Ph. Eur. 8: (Methylthioninium Chloride). A dark blue, crystalline powder with a copper-coloured sheen, or green crystals with a bronze-coloured sheen. Soluble in water; slightly soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Methylene Blue). Dark green crystals or crystalline powder with a bronze-like lustre. Is odourless or practically so. Solutions in water or alcohol are deep blue in colour. Soluble 1 in 25 of water and 1 in 65 of alcohol; soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Methylthioninium chloride is a thiazine dye that is used in the treatment of methaemoglobinaemia. It is also used as an antiseptic, as a bacteriological stain, as a dye in diagnostic procedures or surgery, to prevent urolithiasis, and for viral photoinactivation in some plasma products.

Methylthioninium chloride is given intravenously or orally. The 1% solution for injection can be given orally after dilution; 5 to 10 mL is diluted in 100 to 200 mL of water. It can also be applied topically; the blue colour can be removed from the skin with hypochlorite solution.

In patients with methaemoglobinaemia, therapeutic doses of methylthioninium chloride can lower the levels of methaemoglobin in the red blood cells. It activates a normally dormant reductase enzyme system, which reduces the methylthioninium chloride to leucomethylene blue that in turn is able to reduce methaemoglobin to haemoglobin. However, in large doses methylthioninium chloride can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Methylthioninium chloride is not effective for the treatment of methaemoglobinaemia in patients with G6PD deficiency and is potentially harmful (see p. 1560.2).

In the treatment of acute methaemoglobinaemia, such as in nitrite poisoning, methylthioninium chloride is given intravenously as a 1% solution in doses of 1 to 2 mg/kg injected over several minutes. A repeat dose may be given after 30 to 60 minutes if required. A maximum total dose of 7 mg/kg has been suggested. Doses are calculated from lean body-weight. It may also be used for the maintenance of chronic or inherited methaemoglobinaemia in oral doses of up to 300 mg daily.

When methylthioninium chloride is used as a diagnostic aid for fistula detection, 1 to 3 mL of a 1% solution is injected into the opening and the appearance of blue discoloration in the surrounding tissues noted. Similar or more dilute solutions have been used to aid sentinel lymph-node biopsy (see below). To stain the parathyroid glands, a dose of 5 mg/kg is diluted in 500 mL of sodium chloride 0.9% or glucose 5% and infused intravenously over 1 hour.

Methylthioninium chloride has a mildly antiseptic action and has been given orally in minor urinary-tract infections and to prevent urolithiasis. It is also included in some preparations intended for application to the eye, mouth and pharynx, and skin.

Methylthioninium chloride has been used in the diagnosis of ruptured amniotic membranes (but see Pregnancy under Adverse Effects and Precautions, p. 1560.3). It was formerly used in a renal-function test.

Administration in children. Methylthioninium chloride is used in children for the treatment of methaemoglobinaemia in the same doses as adults, see Uses and Administration, above. It has been suggested that the metabolism of methylthioninium chloride to leucomethylene blue is likely to be less efficient in neonates, and some countries do not recommend use in infants under 4 months of age.

Dementia. The aggregation of tau protein filaments in the brain is believed to be associated with the development of cognitive symptoms in Alzheimer's disease (see Dementia, p. 388.1). Methylthioninium chloride, which is thought to dissolve and prevent such aggregations, is under investigation in the management of Alzheimer's disease.

References.

1. Oz M, *et al.* Methylene blue and Alzheimer's disease. *Biochem Pharmacol* 2009; **78:** 927–32.

Glutaric aciduria. Glutaric aciduria type II is a metabolic disorder associated with a deficiency of electron-transferring flavoproteins involved in the metabolism of amino acids and fatty acids. Treatment may involve diets low in fats and protein, and some success has been reported with riboflavin. Methylthioninium chloride may also be of benefit since it may act as an electron acceptor, and a response has been seen in an infant[1] with neonatal glutaric aciduria type II. An association has also been noted between encephalopathy due to ifosfamide neurotoxicity (see Effects on the Nervous System under Adverse Effects of Ifosfamide, p. 806.3) and glutaric aciduria, possibly due to inhibition of electron transport by a metabolite of ifosfamide. Methylthioninium chloride has therefore been tried for both treatment and prevention of ifosfamide neurotoxicity; however, conflicting results have been reported[2-6] and its role remains unclear.[7]

1. Harpey J-P, *et al.* Methylene-blue for riboflavine-unresponsive glutaricaciduria type II. *Lancet* 1986; **i:** 391.
2. Küpfer A, *et al.* Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. *Lancet* 1994; **343:** 763–4.
3. Zulian GB, *et al.* Methylene blue for ifosfamide-associated encephalopathy. *N Engl J Med* 1995; **332:** 1239–40.
4. Pelgrims J, *et al.* Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer* 2000; **82:** 291–4.
5. Brunello A, *et al.* Ifosfamide-related encephalopathy in elderly patients: report of five cases and review of the literature. *Drugs Aging* 2007; **24:** 967–73.
6. Sweiss KI, *et al.* Encephalopathy after high-dose ifosfamide: a retrospective cohort study and review of the literature. *Drug Safety* 2008; **31:** 989–96.
7. Patel PN. Methylene blue for management of ifosfamide-induced encephalopathy. *Ann Pharmacother* 2006; **40:** 299–303.

Hypotension. Excess nitric oxide production leading to peripheral vasodilatation may be involved in the pathogenesis of hypotension associated with several conditions and it has been suggested that methylthioninium chloride, which is a guanylate cyclase inhibitor, may block the effects of nitric oxide and increase blood pressure in such cases. Studies[1,2] in patients with septic shock, including 5 neonates[3] with refractory hypotension assumed to be due to sepsis, have suggested that methylthioninium chloride increases blood pressure and improves tissue oxygenation, although no mortality benefit has been found. A subsequent systematic review[4] noted that although there was evidence of improvement in haemodynamic parameters it was mainly from observational studies, and that there was a risk of worsening respiratory function. If such treatment were to be used, an initial intravenous bolus dose of 2 mg/kg was probably appropriate.

There have also been reports of the successful use of methylthioninium chloride in patients with anaphylactic shock,[5] hypotension associated with haemodialysis,[6] vasoplegia after cardiac surgery,[7] and severe hepatopulmonary syndrome,[8] all of which may involve increased nitric oxide production. However, the role of methylthioninium chloride in these conditions is not established.[9]

The usual management of shock is discussed on p. 1279.3; anaphylactic shock should be treated with adrenaline, as discussed on p. 1293.2.

1. Preiser J-C, *et al.* Methylene blue administration in septic shock: a clinical trial. *Crit Care Med* 1995; **23:** 259–64.
2. Kirov MY, *et al.* Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med* 2001; **29:** 1860–7.
3. Driscoll W, *et al.* Effect of methylene blue on refractory neonatal hypotension. *J Pediatr* 1996; **129:** 904–8.
4. Paciullo CA, *et al.* Methylene blue for the treatment of septic shock. *Pharmacotherapy* 2010; **30:** 702–15.
5. Oliviera Neto AM, *et al.* Methylene blue: an effective treatment for contrast medium-induced anaphylaxis. *Med Sci Monit* 2003; **9:** CS102–CS106.
6. Peer G, *et al.* Methylene blue, a nitric oxide inhibitor, prevents haemodialysis hypotension. *Nephrol Dial Transplant* 2001; **16:** 1436–41.
7. Levin RL, *et al.* Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg* 2004; **77:** 496–9.
8. Schenk P, *et al.* Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; **133:** 701–6.
9. Stawicki SP, *et al.* Methylene blue and vasoplegia: who, when, and how? *Mini Rev Med Chem* 2008; **8:** 472–90.

Ifosfamide encephalopathy. See Glutaric Aciduria, above.

Lymph node biopsy. Methylthioninium chloride is used as an alternative to other blue dyes as an adjunct in the identification and biopsy of sentinel lymph nodes in cancer patients, particularly in breast cancer[1-4] but also in those with gastrointestinal tumours,[5] or malignant melanoma.[6]

Typically, the dye has been injected as up to 5 mL of a 1% solution, but in breast cancer patients infiltration into the subareolar area of a more dilute solution, such as a 0.125% solution is effective and may be associated with fewer complications.[2,3] (For mention of necrosis associated with use in sentinel node biopsy see p. 1560.3.)

1. Masannat Y, *et al.* Properties and characteristics of the dyes injected to assist axillary sentinel node localization in breast surgery. *Eur J Surg Oncol* 2006; **32:** 381–4.
2. Zakaria S, *et al.* Safety and technical success of methylene blue dye for lymphatic mapping in breast cancer. *Am J Surg* 2008; **196:** 228–33.
3. Mathelin C, *et al.* Methylene blue dye, an accurate dye for sentinel lymph node identification in early breast cancer. *Anticancer Res* 2009; **29:** 4119–25.
4. East JM, *et al.* Sentinel lymph node biopsy for breast cancer using methylene blue dye manifests a short learning curve among experienced surgeons: a prospective tabular cumulative sum (CUSUM) analysis. *BMC Surg* 2009; **9:** 2.
5. Soni M, *et al.* A prospective trial comparing 1% lymphazurin vs 1% methylene blue in sentinel lymph node mapping of gastrointestinal tumors. *Ann Surg Oncol* 2009; **16:** 2224–30.
6. Liu Y, *et al.* A randomized study comparing the effectiveness of methylene blue dye with lymphazurin blue dye in sentinel lymph node biopsy for the treatment of cutaneous melanoma. *Ann Surg Oncol* 2008; **15:** 2412–17.

Methaemoglobinaemia. Methaemoglobinaemia is a rare disorder of the blood in which there is an increase in the proportion of haemoglobin present in the oxidised form. Inherited methaemoglobinaemia may be due either to a deficiency of methaemoglobin reductase or to a structural abnormality of haemoglobin.[1] Acquired methaemoglobinaemia may be caused by drugs[1,2] or chemicals that oxidise haemoglobin, including nitrates and nitrites, sodium nitroprusside, dapsone, sulfonamides, phenacetin, and some local anaesthetics such as prilocaine; it may occur as a result of direct administration or occupational[3] or environmental exposure. Exposure to low doses over long periods may lead to chronic methaemoglobinaemia whereas large doses may lead to an acute effect.

Methaemoglobinaemia has a profound effect on oxygen transport by the blood; there is an increase in oxygen affinity leading to reduced tissue delivery and varying degrees of cyanosis. The presence of symptoms depends upon the degree and rapidity of methaemoglobin formation. Chronic mild methaemoglobinaemia is generally well tolerated although patients may appear cyanotic. Acute methaemoglobinaemia, particularly where methaemoglobin levels exceed 20%, is associated with dyspnoea, headache, malaise, giddiness, and altered mental state; methaemoglobin levels above 50% may lead to vascular collapse, coma, and death.

Patients with inherited methaemoglobinaemia are usually asymptomatic but treatment may be given for cosmetic purposes to reduce the cyanotic skin colour. Patients with reductase deficiency generally respond to oral therapy with drugs that promote the reduction of methaemoglobin to haemoglobin, such as ascorbic acid, riboflavin, or methylthioninium chloride; methylthioninium chloride may also be given intravenously. Patients with structural abnormalities of haemoglobin do not respond. In acquired methaemoglobinaemia the causative agent should be identified and removed. Chronic or mild cases may not require treatment but acute symptomatic methaemoglobinaemia may be life-threatening and patients should be given intravenous methylthioninium chloride, along with oxygen and other supportive therapy as required. Toxicity is uncommon with methylthioninium chloride but it should not be used for methaemoglobinaemia due to the use of nitrites for cyanide poisoning since increased toxicity may result (for debate about its use after chlorate poisoning, see Adverse Effects and Precautions, below). Severe methaemoglobinaemia may require exchange transfusion; exchange transfusion with haemodialysis is the treatment of choice in patients with acute methaemoglobinaemia and haemolysis. Hyperbaric oxygen therapy has also been suggested in severe cases. Ascorbic acid is not useful in the acute situation since it acts too slowly but it may be of benefit where maintenance therapy is required.

1. do Nascimento TS, *et al.* Methemoglobinemia: from diagnosis to treatment. *Rev Bras Anestesiol* 2008; **58:** 657–64.
2. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia: treatment issues. *Drug Safety* 1996; **14:** 394–405.
3. Bradberry SM. Occupational methaemoglobinaemia: mechanisms of production, features, diagnosis and management including the use of methylene blue. *Toxicol Rev* 2003; **22:** 13–27.

ADMINISTRATION. In acute methaemoglobinaemia, methylthioninium chloride is usually given by intravenous bolus injection, but repeated doses may be needed and continuous intravenous infusion has also been used. Methylthioninium chloride was given at a dose of 7.5 to 10 mg/hour for 43 hours to control methaemoglobinaemia after dapsone poisoning.[1] The patient had responded to two bolus doses of 100 mg but methaemoglobinaemia had subsequently increased again owing to the long half-life of dapsone. Additional therapy included repeated doses of activated charcoal. A dosing schedule for methylthioninium chloride of 1 to 2 mg/kg as a bolus followed by a continuous infusion at an initial rate of 100 to 150 micrograms/kg per hour was suggested. Others have found that continuous infusion of methylthioninium chloride was more effective than intermittent infusion in a small number of children with dapsone-induced methaemoglobinaemia.[2]

Methylthioninium chloride has also been given successfully by intraosseous infusion for acute methaemoglobinaemia in an infant in whom attempted intravenous access failed.[3]

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; **4:** 387–92.
2. Prasad R, *et al.* Dapsone induced methemoglobinemia: intermittent vs continuous intravenous methylene blue therapy. *Indian J Pediatr* 2008; **75:** 245–7.
3. Herman MI, *et al.* Methylene blue by intraosseous infusion for methemoglobinemia. *Ann Emerg Med* 1999; **33:** 111–13.

Photodynamic therapy. Methylthioninium chloride is a photosensitiser and, as well as being used for bacterial, fungal, and viral photoinactivation,[1] has also been tried in photodynamic therapy (PDT) for various refractory conditions. It has been applied topically for PDT of oral lichen planus,[2,3] plaque psoriasis,[4] acne vulgaris,[5] and herpes simplex.[6] It has also been injected into lesions for PDT of Kaposi's sarcoma[7] (for further discussion of PDT and its use in malignancy, see p. 849.1).

1. Biel MA. Photodynamic therapy of bacterial and fungal biofilm infections. *Methods Mol Biol* 2010; **635:** 175–94.
2. Aghahosseini F, *et al.* Treatment of oral lichen planus with photodynamic therapy mediated methylene blue: a case report. *Med Oral Patol Oral Cir Bucal* 2006; **11:** E126–E129.
3. Aghahosseini F, *et al.* Methylene blue-mediated photodynamic therapy: a possible alternative treatment for oral lichen planus. *Lasers Surg Med* 2006; **38:** 33–8.
4. Salah M, *et al.* Methylene blue mediated photodynamic therapy for resistant plaque psoriasis. *J Drugs Dermatol* 2009; **8:** 42–9.
5. Fadel M, *et al.* Liposomal methylene blue hydrogel for selective photodynamic therapy of acne vulgaris. *J Drugs Dermatol* 2009; **8:** 983–90.
6. Marotti J, *et al.* Photodynamic therapy can be effective as a treatment for herpes simplex labialis. *Photomed Laser Surg* 2009; **27:** 357–63.
7. Tardivo JP, *et al.* New photodynamic therapy protocol to treat AIDS-related Kaposi's sarcoma. *Photomed Laser Surg* 2006; **24:** 528–31.

Priapism. Priapism is usually treated with corporal aspiration or intracavernosal vasoconstrictors (see under Uses of Metaraminol, p. 1430.2). There have been reports[1-5] of the successful use of intracavernosal methylthioninium chloride, particularly in patients with drug-induced priapism; it is thought to act by blocking the vasodilator effects of nitric oxide. However, penile necrosis has occurred[6] after the use of methylthioninium chloride and it should probably be avoided in patients with corporal fibrosis; aspiration of methylthioninium chloride about 5 minutes after injection has been suggested.[2,3]

1. Steers WD, Selby JB. Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1991; **146:** 1361–3.
2. deHoll JD, *et al.* Alternative approaches to the management of priapism. *Int J Impot Res* 1998; **10:** 11–14.
3. Martínez Portillo FJ, *et al.* Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol* 2001; **39:** 20–3.
4. Hübler J, *et al.* Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol* 2003; **35:** 519–21.
5. Passavanti G, *et al.* From methylene blue (methylthionine chloride) to Al-Ghorab procedure: the therapy of priapism (our experience). *Arch Ital Urol Androl* 2009; **81:** 242–4.
6. Mejean A, *et al.* Re: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1993; **149:** 1149.

Adverse Effects and Precautions

After high intravenous doses, methylthioninium chloride may cause nausea, vomiting, abdominal and chest pain, headache, dizziness, mental confusion, profuse sweating, dyspnoea, and hypertension; methaemoglobinaemia and haemolysis may occur. Haemolytic anaemia and hyperbilirubinaemia have been reported in neonates after intra-amniotic injection.

Oral use may cause gastrointestinal disturbances and dysuria. Rash and a burning sensation have been reported with intravenous use and large doses are irritant to the urinary tract. Necrosis, abscesses, ulceration, and thrombophlebitis have also occurred after injection; subcutaneous use is not recommended. It should also not be given by intrathecal injection as neural damage has occurred. Intra-articular injection has resulted in effusion in the joint.

Anaphylactic reactions have occurred with methylthioninium. Other adverse effects include hypotension and arrhythmias.

The drug imparts a blue colour to saliva, urine, faeces, and skin, which may hinder a diagnosis of cyanosis. Use may result in an underestimation of the oxygen saturation reading in pulse oximetry. Methylthioninium chloride may also cause a false positive result in the phenolsulfonphthalein excretion test. Effects on the nervous system may impair the patient's ability to drive or operate machinery.

Methylthioninium chloride should be used with caution in patients with renal impairment and is not recommended in patients with G6PD deficiency (see below). Methylthioninium chloride is used to treat methaemoglobinaemia but in large doses it can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Haemoglobin concentrations should also be monitored with long-term use as anaemia may occur. Methylthioninium chloride should not be used to treat methaemoglobinaemia induced by sodium nitrite during the treatment of cyanide poisoning, since cyanide binding will be reduced with resultant increased toxicity. Caution is required in methaemoglobinaemia due to chlorate poisoning as chlorate inactivates G6PD reducing the efficacy of treatment; there is also a risk of methylthioninium chloride catalysing chlorate to chlorite, increasing the production of methaemoglobin.

Aniline poisoning. It has been suggested[1] that methylthioninium chloride should be used with caution in the treatment of aniline-induced methaemoglobinaemia since it may precipitate Heinz body formation and haemolytic anaemia. Methylthioninium chloride may reduce methaemoglobin concentrations, but repeated doses could aggravate haemolysis without further reducing methaemoglobinaemia.

1. Harvey JW, Keitt AS. Studies of the efficacy and potential hazards of methylene blue therapy in aniline-induced methaemoglobinaemia. *Br J Haematol* 1983; **54:** 29–41.

Effects on mental function. For reports of encephalopathy and CNS toxicity associated with the use of methylthioninium chloride see Interactions, p. 1561.1.

G6PD deficiency. Methylthioninium chloride is not effective for the treatment of methaemoglobinaemia in patients with G6PD deficiency as they have a diminished capacity to reduce methylthioninium chloride to leucomethylene blue (which in turn reduces methaemoglobin to haemoglobin); treatment is also potentially harmful as these patients are particularly susceptible to the haemolytic anaemias induced by methylthioninium chloride. Although most data support a risk of haemolytic anaemia, there have been reports of use in African men with G6PD deficiency without haemolysis.[1]

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.

Hypersensitivity. There are reports of anaphylactic reactions, including anaphylactic shock, with methylthioninium chloride.[1-4]

1. Rzymski P, *et al.* Anaphylactic reaction to methylene blue dye after laparoscopic chromopertubation. *Int J Gynaecol Obstet* 2003; **81:** 71–2.
2. Dewachter P, *et al.* Severe anaphylactic shock with methylene blue instillation. *Anesth Analg* 2005; **101:** 149–50.
3. Jangjoo A, *et al.* Anaphylaxis reaction of a breast cancer patient to methylene blue during breast surgery with sentinel node mapping. *Acta Oncol* 2010; **49:** 877–8.
4. Nubret K, *et al.* Anaphylactic shock to fresh-frozen plasma inactivated with methylene blue. *Transfusion* 2011; **51:** 125–8.

Necrosis. Necrosis has occurred in patients with breast cancer after methylthioninium chloride injection for sentinel lymph node biopsy, with skin and parenchymal necrosis after subdermal injection,[1] and skin and fat necrosis followed by dry gangrene after injection around the tumour.[2]

Penile necrosis has been reported after intracavernosal injection of methylthioninium chloride for priapism, see above.

1. Reyes FJ, *et al.* Complications of methylene blue dye in breast surgery: case reports and review of the literature. *J Cancer* 2011; **2:** 20–5.
2. Salhab M, *et al.* Skin and fat necrosis of the breast following methylene blue dye injection for sentinel node biopsy in a patient with breast cancer. *Int Semin Surg Oncol* 2005; **2:** 26.

Pregnancy. Although *intra-amniotic* injection of methylthioninium chloride has been used to diagnose premature rupture of fetal membranes or to identify separate amniotic sacs in twin pregnancies, there have been several reports of haemolytic anaemia (Heinz-body anaemia) and hyperbilirubinaemia in neonates who had been exposed to methylthioninium chloride in the amniotic cavity.[1-7] In most cases, exchange transfusions and/or phototherapy were required to control the jaundice; in 2 cases phototherapy led to a phototoxic reaction.[5,7] It has therefore been suggested[3,8] that the use of methylthioninium chloride for detecting premature rupture of the membranes should be avoided.

Multiple ileal occlusions have been reported in babies born to mothers who had twin pregnancies and who had received methylthioninium chloride by amniocentesis;[4,9,10] in some cases it was possible to determine that methylthioninium chloride had been injected into the amniotic sac of the affected twin. Analysis of data from the EUROCAT registries[11] for 1980 to 1988, which surveyed pregnancy outcomes in 11 countries, found a slightly higher risk of ileal and jejunal atresia or stenosis in twins regardless of whether they had received methylthioninium chloride, but the use of methylthioninium chloride was rare and no increased risk could be shown in babies exposed to it. Results from a retrospective cohort study[12] also suggested that there was a higher risk of fetal death after methylthioninium chloride for midtrimester amniocentesis in twin pregnancies. A review[8] from the CDC concluded that the epidemiological evidence for the teratogenicity of methylthioninium chloride was quite strong and advised that it should not be used for midtrimester amniocentesis.

A further difficulty in using methylthioninium chloride by amniocentesis for the diagnosis of premature rupture of the membranes is that the resultant staining of the skin and mucous membranes of the neonate hinders assessment of hypoxia, including the use of pulse oximetry.[13]

Although data on first trimester exposure to *intra-uterine* methylthioninium chloride are limited, there have been case reports with normal pregnancy outcomes.[14]

Oral methylthioninium chloride was not associated with an increased risk of malformations during the first trimester in 9 cases, or after the first trimester in 37 others.[15]

1. Cowett RM, *et al.* Untoward neonatal effect of intraamniotic administration of methylene blue. *Obstet Gynecol* 1976; **48** (suppl): 74s–75s.
2. Serota FT, *et al.* The methylene-blue baby. *Lancet* 1979; **ii:** 1142–3.
3. Crooks J. Haemolytic jaundice in a neonate after intra-amniotic injection of methylene blue. *Arch Dis Child* 1982; **57:** 872–3.
4. Nicolini V, Monni G. Intestinal obstruction in babies exposed in utero to methylene blue. *Lancet* 1990; **336:** 1258–9.
5. Porat R, *et al.* Methylene blue-induced phototoxicity: an unrecognized complication. *Pediatrics* 1996; **97:** 717–21.
6. Gauthier TW. Methylene blue-induced hyperbilirubinemia in neonatal glucose-6-phosphate dehydrogenase (G6PD) deficiency. *J Matern Fetal Med* 2000; **9:** 252–4.
7. George M. Methylene-blue-induced hyperbilirubinemia and phototoxicity in a neonate. *Clin Pediatr (Phila)* 2000; **39:** 659–61.
8. Cragan JD. Teratogen update: methylene blue. *Teratology* 1999; **60:** 42–8.
9. van der Pol JG, *et al.* Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins. *Br J Obstet Gynaecol* 1992; **99:** 141–3.
10. Lancaster PAL, *et al.* Intra-amniotic methylene blue and intestinal atresia in twins. *J Perinat Med* 1992; **20** (suppl 1): 262.
11. Dolk H. Methylene blue and atresia or stenosis of ileum and jejunum. *Lancet* 1991; **338:** 1021–2.
12. Kidd SA, *et al.* Fetal death after exposure to methylene blue dye during mid-trimester amniocentesis in twin pregnancy. *Prenat Diagn* 1996; **16:** 39–47.
13. Troche BT. The methylene blue baby. *N Engl J Med* 1989; **320:** 1756–7.
14. Gerli S, *et al.* Laparoscopy and methylene blue intrauterine injection immediately after undiagnosed conception: effect on pregnancy and neonatal outcome. *Eur J Obstet Gynecol Reprod Biol* 2004; **112:** 102–3.
15. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Interactions

Serotonergic drugs. Methylthioninium chloride has been associated with reports of encephalopathy and CNS toxicity.[1-6] These generally occurred when given intravenously as a visualising agent for thyroid or parathyroid surgery or for the management of uncontrolled hypotension during cardiac surgery; all patients had recently received serotonergic drugs such as *bupropion, buspirone, clomipramine, mirtazapine, SSRIs,* or *venlafaxine*,[4,5] and symptoms were consistent with serotonin syndrome.[7] The MHRA in the UK therefore recommends that methylthioninium chloride should be avoided in patients recently treated with such drugs.

1. Khan MAS, *et al.* Prolonged postoperative altered mental status after methylene blue infusion during parathyroidectomy: a case report and review of the literature. *Ann R Coll Surg Engl* 2007; **89:** W9–W11.
2. Sweet G, Standiford SB. Methylene-blue-associated encephalopathy. *J Am Coll Surg* 2007; **204:** 454–8.
3. Ng BK, *et al.* Serotonin syndrome following methylene blue infusion during parathyroidectomy: a case report and literature review. *Can J Anaesth* 2008; **55:** 36–41.
4. MHRA/CHM. Methylthioninium chloride (methylene blue): CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; **1** (6): 5–6. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033510&RevisionSelectionMethod=LatestReleased (accessed 19/07/08)
5. MHRA/CHM. Methylthioninium chloride (methylene blue): update on CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; **2** (9): 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON043810&RevisionSelectionMethod=LatestReleased (accessed 08/09/09)
6. Pollack G, *et al.* Parathyroid surgery and methylene blue: a review with guidelines for safe intraoperative use. *Laryngoscope* 2009; **119:** 1941–6.
7. Ng BKW, Cameron AJD. The role of methylene blue in serotonin syndrome: a systematic review. *Psychosomatics* 2010; **51:** 194–200.

Pharmacokinetics

Methylthioninium chloride is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after an oral dose. It is extensively distributed in the tissues where it is reduced to leucomethylene blue (leucomethylthioninium chloride). Most of a dose is excreted in the urine, mainly as leucomethylene blue with smaller amounts of unchanged drug; there is also excretion via the bile. It has a half-life of about 5 to 6.5 hours. Metabolism may be reduced in neonates (see Administration in Children, p. 1559.2).

References.
1. Peter C, *et al.* Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharmacol* 2000; **56:** 247–50.
2. Pruthi S, *et al.* Pharmacokinetics of methylene blue dye for lymphatic mapping in breast cancer—implications for use in pregnancy. *Am J Surg* 2011; **201:** 70–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Metilenkek; ***UK***: Proveblue; ***USA***: Urolene Blue†.

Multi-ingredient Preparations. ***Arg.***: Mictasol Azul; Muelita; ***Braz.***: Acridin; Cystex; Mictasol; Sepurin; Vislin; Visodin; ***Canad.***: Blue Collyrium; Collyre Bleu Laiter; ***Fr.***: Collyre Bleu; Pastilles Monleon†; ***Hong Kong***: Clear Blue; ***Israel***: Pronestin; ***Ital.***: Visustrin; ***Pol.***: Ginjal; Mibalin†; ***Rus.***: Neo-Anusol (Нео-анузол); ***Spain***: Centilux; Ojosbel Azul†; ***Switz.***: Collyre Bleu Laiter; ***Turk.***: Buco Bleu; Helmo-Blue; Helmobleu; ***USA***: Atrosept; Darpaz†; Hyophen; MHP-A; MSP-Blu; Phosphasal; Prosed/DS; UAA; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Urogesic Blue; Uryl; Ustell; Uticap; Utira; Utrona-C.

Pharmacopoeial Preparations
BP 2014: Methylthioninium Injection;
USP 36: Methylene Blue Injection.

Milk Thistle

Armurariul; Card burral; Card lleter; Card marià; Cardo Mariano; Chardon marie (milk-thistle fruit); Lady's Thistle; Maarianohdakkeenhedelmä (milk-thistle fruit); Margainių vaisiai (milk-thistle fruit); Mariadistel; Marian Thistle; Mariatistelfrukt (milk-thistle fruit); Mariendistel; Ostropest Plamisty; Ostropestřec Mariánský; Pegasti Badelj; Plod ostropestřece mariánského (milk-thistle fruit); Silybi mariani fructus (milk-thistle fruit); St Mary's Thistle; Tikrasis Margainis; Молочный Чертополох; Марьин Чертополох; Бял Трън.

CAS — 84604-20-6 (milk thistle extract).
*ATC Herb — HA05BA5002 (*Silybum marianum*: fruit); HA05BA5003 (*Silybum marianum*: herb).*
*UNII — U946SH95EE (*Silybum marianum *seed); 8Z2I9LEJ7S (*Silybum marianum *extract).*

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Milk-Thistle Fruit). The mature fruit, devoid of the pappus, of *Silybum marianum*. It contains not less than 1.5% of silymarin expressed as silibinin (dried drug).

USP 36: (Milk Thistle). The dried ripe fruit of *Silybum marianum* (Asteraceae), the pappus having been removed. It contains not less than 2% of silymarin, calculated as silibinin, on the dried basis. Store in airtight containers. Protect from light.

Silibinin *(rINN)*

Silibinina; Silibinine; Silibininum; Silybin; Silybum Substance E_6; Sylibina; Sylibinina; Szilibinin; Силибинин.
3,5,7-Trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl]-4-chromanone.
$C_{25}H_{22}O_{10}$=482.4
CAS — 22888-70-6.
UNII — 4RKY41TBTF.

NOTE. The name silymarin has been used for both a mixture of silibinin, silicristin, and silidianin, and for silibinin alone.

Silicristin *(rINN)*

Silicristina; Silicristine; Silicristinum; Silikrystyna; Silychristin; Силикристин.
2-[2,3-Dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuranyl]-3,5,7-trihydroxy-4-chromanone.
$C_{25}H_{22}O_{10}$=482.4
CAS — 33889-69-9.
UNII — LK279ER14X.

Silidianin *(rINN)*

Silidianina; Silidianine; Silidianinum; Silydianin; Силидианин.
(+)-2,3α,3aα,7a-Tetrahydro-7aα-hydroxy-8(*R*)-(4-hydroxy-3-methoxyphenyl)-4-(3α,5,7-trihydroxy-4-oxo-2β-chromanyl)-3,6-methanobenzofuran-7(6a*H*)-one.
$C_{25}H_{22}O_{10}$=482.4
CAS — 29782-68-1.
UNII — 7P89L7W179.

Silymarin

Silimarina; Silymarinum.
A mixture of the isomers silibinin, silicristin, and silidianin..
CAS — 65666-07-1.
ATC — A05BA03.
ATC Vet — QA05BA03.

Profile

Milk thistle (*Silybum marianum*; *Carduus marianus*) is used in herbal medicine, mainly for gastrointestinal and hepatobiliary disorders. The fruit contains the active principle silymarin, a mixture of flavonolignans including the isomers silibinin, silicristin, and silidianin, of which silibinin is the major component. Silymarin is claimed to be a free radical scavenger and to have hepatoprotectant properties; it has been used in various liver disorders, as well as to prevent hepatotoxicity associated with poisoning. In *Amanita phalloides* mushroom poisoning (p. 2565.3) silibinin (as the disodium dihemisuccinate salt) is used.

Milk thistle is usually given as a standardised extract from the fruit containing mainly silymarin, although the herb has also been used; the strength of the extract is expressed in terms of silymarin or silibinin, although the exact equivalence is not always clear. It is usually given orally since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A typical oral dose of up to 140 mg of silymarin two or three times daily has been suggested for hepatic disorders. An oral dose of 108 mg silymarin up to twice daily has been given as a traditional remedy to relieve symptoms associated with overindulgence of food and drink, such as headache and upset stomach. Disodium silibinin dihemisuccinate is water-soluble and is given intravenously; 350 mg silibinin is equivalent to about 529 mg of the disodium dihemisuccinate. It is given, usually with beta-lactam antibacterials, in *Amanita phalloides* poisoning in a dose equivalent to silibinin 20 mg/kg daily, given in 4 divided doses, each by intravenous infusion over 2 hours.

References.
1. Saller R, *et al.* An updated systematic review with meta-analysis for the clinical evidence of silymarin. *Forsch Komplementmed* 2008; **15:** 9–20.
2. Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. *Cancer Lett* 2008; **269:** 352–62.
3. Wu J-W, *et al.* Drug-drug interactions of silymarin on the perspective of pharmacokinetics. *J Ethnopharmacol* 2009; **121:** 185–93.

Adverse effects. A report of acute generalised exanthematous pustulosis,[1] with extensive skin and oral lesions and raised serum creatinine, in a patient who had been drinking milk thistle tea for dyspepsia. Symptoms responded to treatment with oral prednisone. Subsequent skin tests confirmed hypersensitivity to an aqueous extract of milk thistle.

1. Ramírez-Santos A, *et al.* Pustulosis exantemática generalizada aguda debida a una infusión de cardo mariano (*Silybum marianum*). *Actas Dermosifiliogr* 2011. Available at: http://www.elsevier.es/sites/default/files/elsevier/eop/S0001-7310(11)00220-1.pdf (accessed 17/08/11)

Amanita poisoning. Silymarin and silibinin have been found to be effective in preventing hepatotoxicity after amanita poisoning.[1-3]

1. Lorenz D. Über die anwending von silibinin bei der knollenblätterpilzvergiftung. *Dtsch Arzt* 1982; **79:** 43–5.
2. Hruby K, *et al.* Chemotherapy of Amanita phalloides poisoning with intravenous silibinin. *Hum Toxicol* 1983; **2:** 183–90.
3. Enjalbert F, *et al.* Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40:** 715–57.

Liver disorders. Milk thistle or silymarin has been used for various liver disorders including viral hepatitis, alcoholic liver disease, and cirrhosis.[1,2] Although some beneficial effects have been noted in individual studies, a systematic review considered most studies to be of poor quality and a significant effect on mortality or the complications of liver disease was not shown.[3]

1. Saller R, *et al.* The use of silymarin in the treatment of liver diseases. *Drugs* 2001; **61:** 2035–63.
2. Abenavoli L, *et al.* Milk thistle in liver diseases: past, present, future. *Phytother Res* 2010; **24:** 1423–32.
3. Rambaldi A, *et al.* Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 13/07/11).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Laragon; ***Austral.***: Legalon; Liver-Vite†; ***Austria***: Apihepar; Ardeyhepan; Legalon; ***Belg.***: Legalon SIL; Legalon; ***Braz.***: Forfig; Legalon; Siliver; ***Chile***: Legalon; ***China***: Legalon (利加隆); Shui Lin Jia (水林佳); ***Cz.***: Flavobion; Lagosa; Legalon; Silygal†; ***Fr.***: Legalon; ***Ger.***: Alepa†; Alepafort; Ardeyhepan; Biocellfax†; Cefasilymarin; Hegrimarin†; Hepa-Loges; HepaBesch; Hepar-Pasc; Hepatos; Heplant; Lagosa; Legalon SIL; Legalon; Phytohepar; Silibene†; Silicur†; Silimarit; Silvaysan; ***Gr.***: Legalon; ***Hong Kong***: Legalon; ***Hung.***: Hegrimarin; Legalon SIL; Legalon; Silegon; ***India***: Alrin-B; Hepasil; Levalon; Limarin; Livosil; Marisil; Nitoliv; Silybon; ***Indon.***: Liparin; ***Ital.***: Legalon; Silimarin; Silirex; Silmar; Synchrorose; ***Malaysia***: Cefasily; Legalon; ***Mex.***: Etagerin†; Legalon; ***Philipp.***: Hepavit; Heprotec; Legalon; Liver Plus; Liveraide; Livermate; ***Pol.***: Flexiderm†; Lagosa; Legalon; Silimax; Sylicaps†; Sylimarol; Sylimarynal; Syliverin; ***Port.***: Legalon SIL; Legalon; ***Rus.***: Carsil (Карсил); Legalon (Легалон); Naturcarsevt (Натуркарсевт); Silimar (Силимар); ***S.Afr.***: Legalon; ***Singapore***: Legalon; ***Spain***: Legalon SIL; Legalon; Silarine; ***Switz.***: Legalon SIL; Legalon; ***Thai.***: Legalon; Leveron; Liverin; Marina; Miltis; Pharmarin; Samarin; Sivylar†; ***UK***: Digestive Relief; Indulgeze; Silamarie; Thisilyn; ***Ukr.***: Carsil (Карсил); Darsil (Дарсил); Heparsil (Гепарсил)†; Legalon (Легалон); Legalon SIL (Легалон SIL); Silarsil (Силарсил); ***Venez.***: Legalon.

Multi-ingredient Preparations. ***Arg.***: Bibol Leloup; Quelodin F; ***Austral.***: Antioxidant Forte Tablets†; Bio ACE Excell; Bupleurum Complex†; Bupleurum Compound; ChelaCo; Daily Plus Max†; Detox Program; DiGest; Extralife Liva-Care†; HerbaVital; Joint Ease; LivCo; Liver Detox; Liver Tonic Complex; Livton Complex; Mens Performance Multi; PM Syrin; St Mary's Thistle Plus†; Women's Vitality Multi; ***Austria***: Hepabene†; Iberogast; ***Braz.***: Silimalon; ***Canad.***: Gallexier†; Milk Thistle Extract Formula; Milk Thistle†; Para-Gone; ***Cz.***: Iberogast; Simepar; ***Ger.***: Bilisan Duo†; Cholhepan N; Gallexier; Heumann Verdauungstee Solu-Lipar; Iberogast; ***Hong Kong***: Hepatofalk Planta†; Simepar; ***Hung.***: Hepabene; Iberogast; Majvedo es Detoxikalo; ***India***: Alcohep; Alisia; Alrin-B; Arosi; Cancon; Denafed; Good Liver; Hepa; Hepasil-B; Hepawin Plus; Hosliv; Lecivit-S; Levalon; Livasa; Livasa; Livbel; Livbel; Liveril; Livopill; Livosil-B; Nitlor Plus; Palron; ***Indon.***: Aptivium Liver Support†; Bio-Curliv; Curliv Plus; Curliv Plus; Cursil; Hepa-Q; Hepagard; Hepamax; Heparviton; Hepasil; Hepatin; Hepatofalk Planta†; Letrosil; Livercare; Naturliver; Proliva; Proliver; Verona; Vionin NF; ***Ital.***: Berart; Depatox; Endoepatox; Legalon Plus; Legalon Plus; Linfoguard†; Liverton; ***Malaysia***: Hepavite; Simepar; ***Mon.***: Romarinex Chrome; ***Neth.***: Iberogast; ***Philipp.***: Hepamin; Hepavite; Liverine; Livermin; Liverpro; Liverton; ***Pol.***: Artecholin†; Artecholwex†; Gastrobonisol; Iberogast; Sylicynar; Sylifex; Sylivit; Tabletki Przeciw Niestrawnosci; ***Port.***: Synchrorose Intensivo; ***Rus.***: Bonjigar (Бонджигар); Hepabene (Гепабене); Phosphonciale (Фосфонциале); Sibectan (Сибектан); ***Singapore***: Hepasil DTX†; Hepatofalk Planta†; Hepavite; Simepar; ***Spain***: Iberogast; ***Swed.***: Iberogast; ***Switz.***: Iberogast; Simepar; Tisane hepatique et biliaire; ***UK***: Cypar; Digestisan; Milk Thistle Complex; ***Ukr.***: Hepabene (Гепабене); Hepahealth (Гепахелс); Iberogast (Иберогаст); Levasil (Левасил); Livonorm (Ливонорм); Memory Booster (Мемори Бустер); PM Sirin (ПМ Сирин); Simepar (Симепар); ***Venez.***: Hepasil.

Homoeopathic Preparations. ***Austria***: Galstena; Gracil; Hamamelis-Homaccord; Lymphdiaral; Taraxacum Med Complex; Venodril; Vensa; ***Canad.***: Carduus Plex†; Chelidonium Plex†; Cynara Complex†; Dandelion Combination†; Digestion; Formula FV 213; Hepar Compositum; Nixotinex; ***Chile***: Calcarea fluor Compuesta; Formula II Especial; Variplant; ***Cz.***: Hepeel; ***Fr.***: Boripharm No 15†; Boripharm No 1†; Chelidonium Compose; Cholesterolum Complexe No 112†; Hepatodrainol; Homeodose

20†; L 114; L 28; Vascodran; Vascoflor; Yucca Complexe No 110; ***Ger.***: Bomagall; Chelidonium comp; Chol-Do; Chola-Plantin N†; Chole-cyl L Ho-Len-Complex; Cholo 2-injektopas; Derivatio H; Derivatio; Galloselect; Gastro-Plantin N†; HanoHepan; Hepa-Gastreu N R7; Hepar comp; Hepar-Hevert N; Hepar-Hevert; Hepar-Hevert; Heparanox H; Infihepan; Lithias-cyl L Ho-Len-Complex; Marianon Hepar; Mariendistel Curarina; Ossidal; Phonix Silybum spag; phono Ven; Phyto-L; Rufebran heparo†; Spasmo-Bomaleb†; veno-loges N; Wibotin HM; ***Hung.***: Hepeel; ***Neth.***: Acidolite; Ailgeno spag; Dolilite; Hepa-Gastreu R7; Hepalite; Hepatodrainol†; Hepeel H; Lymphdiaral; ***Port.***: Hepatodrainol; ***Rus.***: Galstena (Галстена); Vensa (Венза); ***Switz.***: Hepeel; metaheptachol; Regenaplex Nr. 35b; Regenaplex Nr. 80aN; ***Ukr.***: Choledius (Холедиус); Galstena (Галстена); ***USA***: Preferred Remedies Detoxin.

Pharmacopoeial Preparations
USP 36: Milk Thistle Capsules; Milk Thistle Tablets.

Nalmefene *(BAN, USAN, rINN)*

6-Desoxy-6-methylene-naltrexone; JF-1; Nalmefeeni; Nalmefen; Nalméfène; Nalmefeno; Nalmefenum; Nalmetrene; ORF-11676; Налмефен.
17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol.
$C_{21}H_{25}NO_3$=339.4
CAS — 55096-26-9.
UNII — TOV02TDP9I.

Nalmefene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalmefeno; Nalméfène, Chlorhydrate de; Nalmefeni Hydrochloridum; Nalmefeno, hidrocloruro de; Nalmetrene Hydrochloride; Налмефена Гидрохлорид.
$C_{21}H_{25}NO_3$,HCl=375.9
CAS — 58895-64-0 (anhydrous nalmefene hydrochloride); 1228646-70-5 (nalmefene hydrochloride dihydrate).
UNII — K7K69QC05X (anhydrous nalmefene hydrochloride); 52Z0G7QVJX (nalmefene hydrochloride dihydrate).

Uses and Administration

Nalmefene is a derivative of naltrexone and is a specific opioid antagonist with actions similar to those of naloxone (p. 1563.1), but with a longer duration of action. It is given orally, as the hydrochloride dihydrate, as an adjunct in the management of alcohol dependence (p. 1734.1). Nalmefene is thought to act by modulating the activity of opioid receptors, which are involved in addiction, to reduce the urge to drink; it is used to help reduce the level of alcohol consumption in adult patients who have a high drinking risk, without physical withdrawal symptoms and who do not require immediate detoxification.

The patient's clinical status, alcohol dependence, and level of alcohol consumption should be evaluated before starting treatment with nalmefene; it should only be used in those who continue to have a high drinking risk level 2 weeks after the initial assessment. Nalmefene should be used on an as-required, rather than regular, basis; a single dose of 18 mg is taken preferably 1 to 2 hours before the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, a dose should be taken as soon as possible; no more than a single dose of 18 mg should be taken daily. Patients should be monitored regularly and the need for continued treatment evaluated on a regular basis; there are no clinical data for treatment longer than 1 year.

Anhydrous nalmefene hydrochloride has been given intravenously for the reversal of postoperative central depression due to the use of opioids and in the management of known or suspected opioid overdosage.

References.
1. Karhuvaara S, *et al.* Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 2007; **31:** 1179–87.
2. Soyka M, Rösner S. Nalmefene for treatment of alcohol dependence. *Expert Opin Invest Drugs* 2010; **19:** 1451–9.
3. Gual A, *et al.* ESENSE 2 Study Group. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *Eur Neuropsychopharmacol* 2013; **23:** 1432–42.
4. Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence. *CNS Drugs* 2013; **27:** 761–72.

Gambling. For mention of the use of nalmefene in the treatment of gambling, see under Naltrexone, p. 1565.3.

Pruritus. It has been suggested that because central opioid receptors modulate itch, an opioid antagonist might be useful in pruritus (p. 1687.3).[1] A systematic review[2] found that opioid antagonists are effective in opioid-induced pruritus, and a number have also been reported to be of benefit in pruritus of other causes; some[1] recommend opioid antagonists as a treatment option for refractory cholestatic pruritus. Tachyphylaxis, loss of efficacy despite unchanged therapy, has been reported with long-term opioid antagonist treatment (from 1 to 9 months), and may be due to up-regulation of opioid receptors. An increase in dose or interruption in treatment for 2 to 3 weeks may restore the antipruritic effect.[1]

Rapid improvement of severe pruritus was reported after a single oral dose of *nalmefene* 10 or 20 mg in a double-blind study of 80 patients with either chronic urticaria or atopic dermatitis.[3] Pruritus was almost completely eliminated in up to 60% of patients receiving nalmefene. Adverse effects occurred in 67% of patients and included dizziness or lightheadedness, fatigue, and nausea. In another study,[4] 14 patients with resistant pruritus secondary to cholestatic liver disease were treated with oral nalmefene for 2 to 26 months. The initial dose was 2 mg twice daily and the dose was increased gradually as necessary. Although 13 of the patients reported some amelioration of pruritus, 5 found that increasing doses were required to produce any benefit, and in 3 tolerance appeared to develop.

Continuous infusion of *naloxone* 200 nanograms/kg per minute was reported to reduce perception of pruritus and scratching activity in a double-blind study of 29 patients with pruritus due to cholestasis,[5] although the role of continuous infusion in long-term management may be limited. A literature review[6] of opioid antagonists in the management of opioid-induced pruritus found most evidence supporting the use of continuous infusions of low-dose naloxone (range: 0.25 to 3 micrograms/kg per hour) for prevention in adults and children; however, doses above 2 micrograms/kg per hour are not generally recommended due to the risk of reversal of analgesia. Naloxone lotion is being investigated for the topical treatment of pruritus associated with cutaneous T-cell lymphoma such as mycosis fungoides.

Benefit has been reported with oral *naltrexone* 50 mg daily in pruritus of various origins,[7] as well as in patients with cholestatic pruritus.[8,9] In uraemic pruritus, conflicting results have been reported;[10,11] a subsequent study[12] suggested that naltrexone might be of benefit in selected patients.

1. Phan NQ, *et al.* Antipruritic treatment with systemic μ-opioid receptor antagonists: a review. *J Am Acad Dermatol* 2010; **63:** 680–8.
2. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; **18:** 346–57.
3. Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; **21:** 135–6.
4. Bergasa NV, *et al.* Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; **27:** 679–84.
5. Bergasa NV, *et al.* Effects of naloxone infusions in patients with the pruritus of cholestasis. *Ann Intern Med* 1995; **123:** 161–7.
6. Miller JL, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. *Am J Health-Syst Pharm* 2011; **68:** 1419–25.
7. Metze D, *et al.* Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999; **41:** 533–9.
8. Wolfhagen FH, *et al.* Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology* 1997; **113:** 1264–9.
9. Terg R, *et al.* Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. *J Hepatol* 2002; **37:** 717–22.
10. Peer G, *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348:** 1552–4.
11. Pauli-Magnus C, *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11:** 514–9.
12. Legroux-Crespel E, *et al.* A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; **208:** 326–30.

Adverse Effects and Precautions

For general adverse effects and precautions of opioid antagonists, see Naloxone, p. 1564.2 and p. 1564.3, respectively.

When used in the management of alcohol dependence, the most common adverse effects of nalmefene are nausea, dizziness, insomnia, and headache; most of these are mild or moderate and of short duration, and occur at the start of treatment. Confusional state and, rarely, hallucinations and dissociation have also been reported.

Therapeutic use of opioids should be avoided during nalmefene treatment. When analgesia is required, larger than usual doses of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects; close monitoring may be necessary. Nalmefene should be stopped 1 week before elective surgery involving opioid analgesia.

Nalmefene should be used with caution in patients with mild or moderate hepatic or renal impairment; it is contra-indicated in those with severe impairment.

Pharmacokinetics

Nalmefene is absorbed after oral doses but bioavailability is only about 40% owing to significant first-pass metabolism. Peak plasma concentrations occur about 1.5 hours after oral dosing; around 45% is bound to plasma proteins. It is metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine. Some of the dose is excreted in the faeces and it may undergo enterohepatic recycling. The terminal elimination half-life after an intravenous or oral dose is reported to be about 10 or 12.5 hours, respectively.

References.
1. Dixon R, *et al.* Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; **39:** 49–53.
2. Dixon R, *et al.* Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. *J Clin Pharmacol* 1987; **27:** 233–9.
3. Frye RF, *et al.* The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. *Br J Clin Pharmacol* 1996; **42:** 301–6.
4. Frye RF, *et al.* Effects of liver disease on the disposition of the opioid antagonist nalmefene. *Clin Pharmacol Ther* 1997; **61:** 15–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Lemeng (乐萌); Shuna (扦纳); ***Mex.***: Nocarex†; ***UK***: Selincro.

Nalorphine *(BAN, rINN)*

Nalorfiini; Nalorfin; Nalorfina; Nalorphin; Nalorphinum; Налорфин.
(-)-(5*R*,6*S*)-9a-Allyl-4,5-epoxymorphin-7-en-3,6-diol; 17-Allyl-17-normorphine.
$C_{19}H_{21}NO_3$=311.4
CAS — 62-67-9.
ATC — V03AB02.
ATC Vet — QV03AB02.
UNII — U59WB2WRY2.

Nalorphine Hydrobromide *(BANM, rINNM)*

Hidrobromuro de nalorfina; Nalorphine, Bromhydrate de; Nalorphini Hydrobromidum; Налорфина Гидробромид.
$C_{19}H_{21}NO_3$,HBr=392.3
CAS — 1041-90-3.
ATC — V03AB02.
ATC Vet — QV03AB02.
UNII — 1OLB66508A.

Pharmacopoeias. In *Chin.*

Nalorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalorfina; Nalorfina, hidrocloruro de; Nalorphine, Chlorhydrate de; Nalorphini Hydrochloridum; Nalorphinium Chloride; Налорфина Гидрохлорид.
$C_{19}H_{21}NO_3$,HCl=347.8
CAS — 57-29-4.
ATC — V03AB02.
ATC Vet — QV03AB02.
UNII — 9FPE56Z2TW.

Pharmacopoeias. In *US.*

USP 36: (Nalorphine Hydrochloride). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Nalorphine is an opioid antagonist with properties similar to those of naloxone (p. 1563.1); in addition it also possesses some agonist properties and adverse effects such as drowsiness, respiratory depression, miosis, dysphoria, and lethargy may occur if it is given to patients who have not received opioids. It has been used as the hydrobromide or hydrochloride to reverse opioid-induced respiratory depression, but may exacerbate respiratory depression induced by alcohol or other non-opioid central depressants.

Preparations

Pharmacopoeial Preparations
USP 36: Nalorphine Hydrochloride Injection.

Naloxone Hydrochloride

(BANM, USAN, rINNM)

N-Allylnoroxymorphone Hydrochloride; Cloridrato de Naloxona; EN-15304; Hidrocloruro de naloxona; Nalokson Hidroklorür; Naloksonihydrokloridi; Naloksono hidrochloridas; Naloksonu chlorowodorek dwuwodny; Naloxona, hidrocloruro de; Naloxone, Chlorhydrate de; Naloxone (chlorhydrate de) dihydraté; Naloxon-hidroklorid; Naloxonhydrochlorid; Naloxonhydrochlorid; Naloxonhydroklorid; Naloxoni Hydrochloridum; Naloxoni hydrochloridum dihydricum; Налоксона Гидрохлорид.
17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate; (-)-(5*R*,14*S*)-9a-Allyl-4,5-

epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate.
$C_{19}H_{21}NO_4,HCl,2H_2O$=399.9
CAS — 465-65-6 (naloxone); 357-08-4 (anhydrous naloxone hydrochloride); 51481-60-8 (naloxone hydrochloride dihydrate).
ATC — V03AB15.
ATC Vet — QV03AB15.
UNII — F850569PQR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*. Forms specified may be anhydrous, dihydrate, or both.

Ph. Eur. 8: (Naloxone Hydrochloride Dihydrate; Naloxone Hydrochloride BP 2014). It contains two molecules of water of hydration. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.

USP 36: (Naloxone Hydrochloride). It is anhydrous or contains two molecules of water of hydration. A white to slightly off-white powder. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its aqueous solution is acidic. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Infusions of naloxone hydrochloride should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high-molecular-weight anions, or solutions with an alkaline pH.

Uses and Administration

Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It is an antagonist of opioids that possess agonist or mixed agonist-antagonist activity although larger doses may be needed for compounds with the latter activity. It is used to reverse opioid central depression, including respiratory depression, induced by natural or synthetic opioids, in the management of known or suspected opioid overdosage, postoperatively after the use of opioids during surgery, and in neonates when opioid analgesics have been given to the mother during labour.

Naloxone hydrochloride is usually given intravenously for the most rapid action, with onset within 2 minutes. The onset of action is only slightly less rapid when it is given intramuscularly or subcutaneously. Other routes, including the endotracheal, have also been used. The duration of action of naloxone is dependent on the dose and route, but is generally in the range of 1 to 4 hours. An intravenous infusion may be used for a sustained response; commonly, 2 mg of naloxone hydrochloride is added to 500 mL of sodium chloride 0.9% or glucose 5% to obtain a concentration of 4 micrograms/mL.

In the management of known or suspected **opioid overdosage**, the initial dose of naloxone hydrochloride is 0.4 to 2 mg given intravenously and repeated if necessary at intervals of 2 to 3 minutes. If no response has been seen after a total dose of 10 mg then the diagnosis of overdosage with drugs other than opioids should be considered. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used. When sustained opioid antagonism is needed, an intravenous infusion may be used. Dosage regimens have not been well established, and the rate of infusion must be titrated according to the patient's response. Some have recommended an infusion of 60% of the initial dose per hour given via an infusion pump, either undiluted, or diluted to a concentration of 200 micrograms/mL in glucose. Others have suggested an initial intravenous loading dose of 400 micrograms, followed by a continuous infusion at an initial rate of 400 micrograms/hour. Alternatively, an intravenous loading dose of 5 micrograms/kg has been suggested, followed by a continuous infusion of 2.5 micrograms/kg per hour.

Naloxone hydrochloride may also be used **postoperatively** to reverse central depression resulting from the use of opioids during surgery. A dose of 100 to 200 micrograms (corresponding to 1.5 to 3 micrograms/kg) may be given intravenously at intervals of 2 to 3 minutes, titrated for each patient in order to obtain an optimum respiratory response while maintaining adequate analgesia. If further doses are needed after 1 to 2 hours, they may be given by intramuscular injection or intravenous infusion for a sustained effect; infusions should be titrated according to response.

All patients receiving naloxone should be closely monitored as the duration of action of many opioids exceeds that of naloxone and repeated doses may be required.

For doses in children, see Administration in Children, below.

Naloxone hydrochloride is included in some oral opioid formulations to reduce the potential for parenteral abuse, or to counteract opioid-induced constipation. Naloxone hydrochloride has also been used cautiously in small doses to diagnose opioid dependence by precipitating the withdrawal syndrome (see p. 1564.2 and under Naltrexone, p. 1565.2).

Administration. Naloxone is usually given intravenously in opioid overdosage but may also be given intramuscularly or subcutaneously if intravenous access is not available. Alternative routes have also been tried; a study[1] using intranasal naloxone found that it was effective for prehospital management of suspected opioid overdosage, although response was slower than with intramuscular injection.

See also Administration in Children, below.

1. Kelly A-M, *et al.* Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 2005; **182:** 24–7.

Administration in children. In the **management of known or suspected opioid overdosage** in children, licensed product information recommends a usual initial dose of naloxone hydrochloride 10 micrograms/kg intravenously; if this does not result in the desired degree of clinical improvement, a subsequent dose of 100 micrograms/kg may be given. If the intravenous route is not feasible, naloxone can be given intramuscularly or subcutaneously in divided doses. The *BNFC* concurs with these doses for neonates and children up to the age of 12 years; those aged 12 years or older can be given the adult dose (see Uses and Administration, above). The *BNFC* also states that naloxone can be given by continuous intravenous infusion using an infusion pump, diluted to a concentration of 4 micrograms/mL in glucose 5% or sodium chloride 0.9%. Doses are recommended according to age:

- neonate to 12 years: 5 to 20 micrograms/kg per hour, adjusted according to response
- 12 to 18 years: 0.24 to 1.2 mg infused over 1 hour, then adjusted according to response

For **respiratory depression induced by opioid overdose**, the Committee on Drugs of the American Academy of Pediatrics[1] recommends initial naloxone doses as follows:

- neonates, and children under 5 years of age, or in those weighing less than 20 kg: 100 micrograms/kg
- children 5 years of age or older, or those weighing 20 kg or more: 2 mg

The American Heart Association[2] gives similar doses. Doses can be repeated as needed to maintain opiate reversal. Doses can be given by the intravenous,[1,2] intraosseous,[1,2] intramuscular, subcutaneous,[1] or endotracheal routes.[2] However, the American Academy of Pediatrics states that the endotracheal route is not recommended for neonates, and recommends intravenous or intramuscular use.[1] Intramuscular injection produces a more gradual and prolonged effect than intravenous administration but absorption may be erratic. The use of injections containing 20 micrograms/mL of naloxone hydrochloride is no longer recommended because of the fluid load involved at these doses, especially in small neonates.[3]

The American Academy of Pediatrics states that lower initial doses of 1 to 15 micrograms/kg may be considered for other clinical situations such as **respiratory depression associated with therapeutic opioid use**.[1] For complete or partial reversal of CNS depression caused by opioids, UK licensed product information for one preparation (*Hameln, UK*) suggests an initial intravenous dose of 10 to 20 micrograms/kg given at intervals of 2 to 3 minutes until satisfactory respiration and consciousness are obtained. Additional doses may be required at 1- to 2-hour intervals depending on the opioid and individual response. US licensed product information states that for **postoperative use**, initial doses of 5 to 10 micrograms may be given intravenously at 2- to 3-minute intervals until the desired response is obtained. In the UK, the *BNFC* suggests doses by intravenous injection according to age:

- neonate up to 12 years: 1 microgram/kg, repeated every 2 to 3 minutes if needed
- 12 to 18 years: 1.5 to 3 micrograms/kg, followed by a subsequent dose of 100 micrograms if needed

Opioid-induced depression in **neonates** resulting from the use of opioid analgesics in the mother during labour may be reversed by giving naloxone hydrochloride 10 micrograms/kg to the infant by intravenous, intramuscular, or subcutaneous injection, repeated at intervals of 2 to 3 minutes if necessary. Alternatively, a single intramuscular dose of 60 micrograms/kg may be given at birth for a more prolonged action. Naloxone should be given with caution to the infants of opioid-dependent mothers since withdrawal symptoms can result.

1. Hegenbarth MA. American Academy of Pediatrics Committee on Drugs. Preparing for pediatric emergencies: drugs to consider. *Pediatrics* 2008; **121:** 433–43. Also available at: http://pediatrics.aappublications.org/cgi/reprint/pediatrics;121/2/433.pdf (accessed 09/09/09)
2. Kleinman ME, *et al.* Part 14: pediatric advanced life support. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; **122** (suppl 3): S876–S908. Available at: http://circ.ahajournals.org/cgi/reprint/122/18_suppl_3/S876 (accessed 09/02/11)
3. American Academy of Pediatrics. Emergency drug doses for infants and children and naloxone use in newborns: clarification. *Pediatrics* 1989; **83:** 803. Also available at: http://pediatrics.aappublications.org/cgi/reprint/83/5/803.pdf (accessed 17/08/10)

Administration in hepatic or renal impairment. Licensed product information for parenteral naloxone states that safety and efficacy have not been established in patients with hepatic or renal impairment, and caution is required. Naloxone plasma concentrations were reported to be about 6 times higher in patients with liver cirrhosis than those without liver disease.

A pharmacokinetic study[1] of an oral naltrexone plus opioid formulation in patients with severe hepatic impairment found that there were only minor differences in the bioavailability and elimination of total naloxone in those with hepatic impairment compared with healthy subjects. However, high concentrations of unconjugated naloxone were noted in those with hepatic impairment (in healthy subjects oral naloxone is inactivated during hepatic first-pass metabolism and unconjugated naloxone is usually undetectable), and the authors of the study theorised that systemically available naloxone might antagonise the analgesic effect of the opioid.

1. Brennscheidt U, *et al.* Pharmacokinetics of tilidine and naloxone in patients with severe hepatic impairment. *Arzneimittelforschung* 2007; **57:** 106–11.

Administration with buprenorphine. Buprenorphine is a mixed opioid agonist/antagonist that dissociates slowly from opioid receptors (p. 31.1); naloxone may not completely reverse respiratory depression caused by buprenorphine. A pharmacokinetic study[1] found that a continuous intravenous infusion was the most effective way to give naloxone to prevent the recurrence of respiratory depression; a rate of 4 mg per 70 kg per hour was suggested.

Low-dose naloxone has been reported to increase the analgesic effect of buprenorphine.[2] This effect was dependent on the dose ratio of the 2 drugs, with a significant effect at a ratio of 15:1 buprenorphine to naloxone, but not at ratios above or below this. An increase in adverse effects was not seen. UK licensed product information also reports that naloxone may increase buprenorphine analgesia, and suggests that this may be the result of naloxone inhibiting the reduced analgesia sometimes seen with high doses of buprenorphine.

Naloxone is added to some sublingual formulations of buprenorphine used for opioid dependence to discourage parenteral abuse.

1. Yassen A, *et al.* Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers. *Clin Pharmacokinet* 2007; **46:** 965–80.
2. La Vincente SF, *et al.* Enhanced buprenorphine analgesia with the addition of ultra-low-dose naloxone in healthy subjects. *Clin Pharmacol Ther* 2008; **83:** 144–52.

Eating disorders. Opioid antagonists including naloxone have been tried in the management of eating disorders, see Naltrexone, p. 1565.3.

Non-opioid overdosage. Naloxone antagonises the action of exogenous and endogenous opioids. This may explain the varying responses reported to naloxone used in the treatment of overdosage with non-opioids, some of which may modulate endogenous opioids.

Benefit has been reported[1] with naloxone in valproate overdosage, although the evidence is based on case reports. There have also been case reports suggesting benefit in overdosage with camylofin,[2] chlorpromazine,[3] and ibuprofen.[4] A study[5] with midazolam in healthy subjects found that naloxone did not reverse respiratory depression, although there had been earlier reports of benefit in coma due to benzodiazepines.

Naloxone has been used for clonidine intoxication, but retrospective reviews[6,7] have concluded that responses are inconsistent, and there have been reports of hypertension. The value of naloxone in brimonidine overdosage is also uncertain; although it has been used, a retrospective study in children found little evidence that it has any effect on outcomes.[8] There has been a report[9] of the successful use of naloxone after captopril overdosage.

Naloxone may also be of benefit in overdosage with drugs that are structurally related to opioids, including apomorphine,[10] dextromethorphan,[11] and loperamide.[12]

1. Roberge RJ, Francis EH. Use of naloxone in valproic acid overdose: case report and review. *J Emerg Med* 2002; **22:** 67–70.
2. Schvartsman S, *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; **ii:** 1246.
3. Chandavasu O, Chatkupt S. Central nervous system depression from chlorpromazine poisoning: successful treatment with naloxone. *J Pediatr* 1985; **106:** 515–6.
4. Easley RB, Altemeier WA. Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. *Pediatr Emerg Care* 2000; **16:** 39–41.

5. Forster A, *et al.* Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study. *Anesth Analg* 1983; **62:** 920–4.
6. Fiser DH, *et al.* Critical care for clonidine poisoning in toddlers. *Crit Care Med* 1990; **18:** 1124–8.
7. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; **116:** 654–8.
8. Lai Becker M, *et al.* Brimonidine tartrate poisoning in children: frequency, trends, and use of naloxone as an antidote. Abstract: *Pediatrics* 2009; **123:** 590–1. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/2/e305.pdf (accessed 11/09/09)
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; **20:** 1125–7.
10. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; **14:** 442–9.
11. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; **9:** 237–8.
12. Friedli G, Haenggeli C-A. Loperamide overdose managed by naloxone. *Lancet* 1980; **i:** 1413.

Pruritus. For reference to the use of opioid antagonists, including naloxone, in the management of pruritus, see under Nalmefene, p. 1562.1

Reversal of opioid effects. Naloxone is used postoperatively to reverse central depression resulting from the use of opioids during surgery. However, the beneficial analgesic effects of the opioids may also be reversed, and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use.

In patients receiving longer-term opioids, low doses of naloxone have been reported to alleviate some of their adverse effects without loss of therapeutic efficacy, although results of studies have been inconsistent. Continuous intravenous infusion of naloxone reduced the incidence of adverse effects in patients receiving morphine by patient-controlled analgesia (PCA) for postoperative pain.[1] Pain control was not compromised and the lower dose of naloxone used (250 nanograms/kg hourly as opposed to 1 microgram/kg hourly) appeared to have an opioid-sparing effect. Adverse effects associated with intravenous tramadol were also reduced with a low-dose intravenous infusion of naloxone (50 to 200 nanograms/kg per hour) in one study[2]; analgesia was not affected. Additionally, naloxone reversed respiratory depression in a patient given intrathecal morphine,[3] without reversing analgesia. However, other studies have found neither improvement in morphine-induced adverse effects[4,5] nor any difference in analgesic requirements with use of intravenous naloxone, and a small study[6] in patients receiving extradural fentanyl found that naloxone failed to relieve urinary retention but pain scores rapidly increased. (A slightly larger study, however,[7] noted lower postoperative urinary residuals, more frequent voiding, fewer catheterisations, and comparable analgesia in patients who received intravenous naloxone with morphine PCA.)

Naloxone has been tried specifically to reduce pruritus associated with opioid therapy, again with variable effect. A subcutaneous dose of naloxone 400 micrograms did not prevent pruritus in women undergoing elective caesarean section;[8] however, when naloxone was added to a morphine and bupivacaine epidural post-hysterectomy, pruritus and nausea were reduced and analgesia maintained.[9]

Improvements in gastrointestinal adverse effects have been noted when naloxone was given with opioid analgesia. Intravenous naloxone has been shown to reverse the delay in gastric emptying induced by opioid analgesics in healthy subjects[10] and in women during labour.[11] Adding naloxone to a postoperative epidural was shown to reduce morphine-induced gut hypomotility without affecting analgesia,[12] and nausea and vomiting caused by epidural sufentanil were reduced when naloxone was included;[13] pain scores were also lower with naloxone. Naloxone has been given enterally to counteract constipation induced by opioid infusions in intensive care.[14] It has been reported to improve bowel function without compromising analgesia,[15] and is included in some oral prolonged-release opioid formulations. In patients receiving long-term oral opioids, oral naloxone in a daily dose equivalent to 20 to 40% of the daily opioid dose relieved opioid-induced constipation without compromising analgesic control.[16,17] Doses equivalent to 10% or less of the opioid dose were ineffective.[18] However, other studies[19] have found adverse effects even at low doses of naloxone, and the optimum dose remains unclear.

It has been suggested that naloxone may limit opioid tolerance; however, an intravenous infusion of naloxone 250 nanograms/kg per hour did not reduce fentanyl requirements in critically-ill children.[20]

Methylnaltrexone, a related opioid antagonist is used for the reversal of opioid-induced constipation (see p. 1861.3).

1. Gan TJ, *et al.* Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology* 1997; **87:** 1075–81.
2. Jia D-L, *et al.* A small-dose naloxone infusion alleviates nausea and sedation without impacting analgesia via intravenous tramadol. *Chin Med J (Engl)* 2010; **123:** 1695–8.
3. Jones RDM, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. *BMJ* 1980; **281:** 645–6.
4. Sartain JB, *et al.* Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. *Anesthesiology* 2003; **99:** 148–51.
5. Greenwald PW, *et al.* Low-dose naloxone does not improve morphine-induced nausea, vomiting, or pruritus. *Am J Emerg Med* 2005; **23:** 35–9.
6. Wang J, *et al.* Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia. *Br J Anaesth* 1998; **80:** 565–6.
7. Gallo S, *et al.* A study of naloxone effect on urinary retention in the patient receiving morphine patient-controlled analgesia. *Orthop Nurs* 2008; **27:** 111–15.
8. Lockington PF, Fa'aea P. Subcutaneous naloxone for the prevention of intrathecal morphine induced pruritus in elective Caesarean delivery. *Anaesthesia* 2007; **62:** 672–6.
9. Choi JH, *et al.* Epidural naloxone reduces pruritus and nausea without affecting analgesia by epidural morphine in bupivacaine. *Can J Anaesth* 2000; **47:** 33–7.
10. Nimmo WS, *et al.* Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *BMJ* 1979; **2:** 1189.
11. Frame WT, *et al.* Effect of naloxone on gastric emptying during labour. *Br J Anaesth* 1984; **56:** 263–5.
12. Lee J, *et al.* Epidural naloxone reduces intestinal hypomotility but not analgesia of epidural morphine. *Can J Anaesth* 2001; **48:** 54–8.
13. Kim MK, *et al.* Epidural naloxone reduces postoperative nausea and vomiting in patients receiving epidural sufentanil for postoperative analgesia. *Br J Anaesth* 2007; **99:** 270–5.
14. Arpino PA, Thompson BT. Safety of enteral naloxone for the reversal of opiate-induced constipation in the intensive care unit. *J Clin Pharm Ther* 2009; **34:** 171–5.
15. Löwenstein O, *et al.* Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol* 2010; **10:** 12.
16. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **337:** 1475.
17. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 582.
18. Robinson BA, *et al.* Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 581–2.
19. Thomas MC, Erstad BL. Safety of enteral naloxone and i.v. neostigmine when used to relieve constipation. *Am J Health-Syst Pharm* 2003; **60:** 1264–7.
20. Darnell CM, *et al.* Effect of low-dose naloxone infusion on fentanyl requirements in critically ill children. *Pediatrics* 2008; **121:** e1363–e1371. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/e1363 (accessed 14/02/11)

DIAGNOSTIC USE. Naloxone is used to reverse opioid effects in the diagnosis of opioid overdose, although some workers have recommended that it should only be used in patients with clinical signs of opioid overdose.[1]

Naloxone has also been used in the diagnosis of opioid dependence. It has been given intravenously to precipitate withdrawal symptoms, but methods that do not induce acute withdrawal have also been investigated. Pupillary dilatation in response to topical naloxone solution (naloxone eye drops) has been suggested as a useful method, but varying results have been reported depending on the strength of the solution used. A study[2] using naloxone hydrochloride solution 1 mg/mL distinguished patients with a physical dependence from non-dependent patients who had received opioids on a single occasion as pre-operative medication, but this response was not confirmed in another study[3] using naloxone 400 micrograms/mL solution. Another study[4] reported that a 2 mg/mL solution of naloxone hydrochloride gave useful results in an outpatient setting. However, there has been a report[5] of withdrawal syndrome and pupillary dilatation in 4 opioid dependent subjects after instillation of naloxone solution 40 mg/mL.

1. Hoffman JR, *et al.* The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med* 1991; **20:** 246–52.
2. Creighton FJ, Ghodse AH. Naloxone applied to conjunctiva as a test for physical opiate dependence. *Lancet* 1989; **i:** 748–50.
3. Loimer N, *et al.* Conjunctival naloxone is no decision aid in opioid addiction. *Lancet* 1990; **335:** 1107–8.
4. Ghodse AH, *et al.* Evaluation of the opioid addiction test in an outpatient drug dependency unit. *Br J Psychiatry* 1999; **175:** 158–62.
5. Sanchez-Ramos JR, Senay EC. Ophthalmic naloxone elicits abstinence in opioid-dependent subjects. *Br J Addict* 1987; **82:** 313–15.

Shock. Endogenous opioids may have a role in the pathophysiology of shock but studies investigating naloxone for the treatment of shock have produced contradictory results. A systematic review[1] concluded that naloxone does increase blood pressure in various forms of shock, but no significant effect on mortality was shown. US licensed product information has noted that the optimal dose and duration of therapy with naloxone have not been established, and that caution should be exercised before its use, particularly in patients with underlying pain or who have previously received opioids and may have developed opioid tolerance.

1. Boeuf B, *et al.* Naloxone for shock. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 04/10/05).

Adverse Effects

Opioid antagonists are generally considered to have little, if any, intrinsic action. When they are given in the absence of opioids, or to reverse the effects of opioids in non-opioid dependent patients, adverse effects are generally mild.

Adverse effects associated with competitive opioid antagonists may be caused by the reversal of opioid effects such as opioid withdrawal symptoms (see Dependence and Withdrawal under Opioid Analgesics, p. 109.1). Other reported effects on the nervous system include dizziness, headache, hallucinations, and excitement; seizures have occurred rarely. Effects on the cardiovascular system include hypertension or hypotension, tachycardia or bradycardia, ventricular fibrillation, myocardial infarction, and heart failure. Opioid antagonists may stimulate the release of some hormones such as those from the pituitary. Hypersensitivity reactions such as anaphylactic shock, urticaria, dyspnoea, and angioedema have been reported with parenteral use.

Other adverse effects reported with naloxone include arrhythmias, pulmonary oedema, coma, and encephalopathy, usually with postoperative use; fatalities have occurred. There are rare reports of erythema multiforme. Large doses of naloxone and rapid reversal of opioid effects may contribute to the development of adverse effects.

Effects on the cardiovascular system. Hypertension,[1,2] pulmonary oedema,[3] and cardiac arrhythmias including ventricular tachycardia and fibrillation[4] have been reported after the postoperative use of naloxone, generally in patients with pre-existing heart disease undergoing cardiac surgery. However, there have also been reports in healthy patients,[5,6] including some fatalities.[5]

Hypotension, bradycardia, and precipitation of focal seizures have been reported in patients given high-dose naloxone for acute ischaemic stroke.[7]

Ventricular fibrillation has been seen in an opioid addict given naloxone to reverse the effects of diamorphine.[8] However, this patient was later shown to have hepatic cirrhosis and alcoholic cardiomyopathy and the UK *National Poisons Information Service* noted that it had never been informed of such a suspected adverse reaction despite being contacted in about 800 cases of opioid poisoning each year.[9] In a later report severe adverse effects were noted in 6 of 453 subjects given naloxone to reverse diamorphine intoxication.[10] The effects were: asystole (1 case), generalised convulsions (3 cases), pulmonary oedema (1 case), and violent behaviour (1 case).

1. Tanaka GY. Hypertensive reaction to naloxone. *JAMA* 1974; **228:** 25–6.
2. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979; **58:** 524–5.
3. Flacke JW, *et al.* Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; **47:** 376–8.
4. Michaelis LL, *et al.* Ventricular irritability associated with the use of naloxone hydrochloride: two case reports and laboratory assessment of the effects of the drug on cardiac excitability. *Ann Thorac Surg* 1974; **18:** 608–14.
5. Wride SRN, *et al.* A fatal case of pulmonary oedema in a healthy young male following naloxone administration. *Anaesth Intensive Care* 1989; **17:** 374–7.
6. Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; **59:** 576–7.
7. Barsan WG, *et al.* Use of high dose naloxone in acute stroke: possible side effects. *Crit Care Med* 1989; **17:** 762–7.
8. Cuss FM, *et al.* Cardiac arrest after reversal of effects of opiates with naloxone. *BMJ* 1984; **288:** 363–4.
9. Barret L, *et al.* Cardiac arrest following naloxone. *BMJ* 1984; **288:** 936.
10. Osterwalder JJ. Naloxone—for intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Clin Toxicol* 1996; **34:** 409–16.

Precautions

Naloxone should be used with caution in patients physically dependent on opioids, or who have received large doses of opioids, as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p. 109.1). A withdrawal syndrome may be precipitated in neonates of opioid-dependent mothers when naloxone is used in the neonate, or when it is given during pregnancy, as it crosses the placenta. Analgesia may be reversed when naloxone is used postoperatively.

Caution is required in patients with cardiac disease or those receiving cardiotoxic drugs.

The duration of action of some opioids exceeds that of naloxone; patients should therefore be carefully monitored after use in case of relapse. Reversal of respiratory depression due to partial opioid agonists or mixed agonists/antagonists such as buprenorphine may be incomplete, see also Administration with Buprenorphine, p. 1563.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naloxone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pharmacokinetics

Naloxone is absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism. It is extensively distributed into body tissues and fluids, particularly the brain as it is highly lipophilic. Protein binding is about 32 to 45%. It is metabolised in the liver,

mainly by glucuronide conjugation, with naloxone-3-glucuronide as the major metabolite. It is excreted in the urine as metabolites. It has a plasma half-life of about 1 to 1.5 hours after parenteral doses in adults, and around 3 hours in neonates. Naloxone crosses the placenta.

Pregnancy and the neonate. A study in 30 mothers given a single intravenous dose of naloxone during the second stage of labour, indicated that naloxone rapidly crossed the placental barrier so that some therapeutic effect might be anticipated in most neonates.[1] Placental transfer in 7 further mothers given naloxone intramuscularly was considered to be too variable for therapeutic purposes.

In 12 neonates given naloxone hydrochloride 35 or 70 micrograms intravenously via the umbilical vein, the mean plasma half-life was 3.53 or 2.65 hours respectively.[2] These half-lives were 2 to 3 times longer than those reported for adults, possibly due to a diminished ability of the newborn to metabolise drugs by conjugation with glucuronic acid. Mean peak plasma concentrations of 8.2 nanograms/mL or 13.7 nanograms/mL in those given 35 or 70 micrograms respectively, were reached within 40 minutes but this time was very variable, and in 5 neonates peak concentrations were reached within 5 minutes. Naloxone hydrochloride 200 micrograms intramuscularly in 17 further neonates produced peak concentrations of 7.4 to 34.6 nanograms/mL at 0.5 to 2 hours.

1. Hibbard BM, *et al*. Placental transfer of naloxone. *Br J Anaesth* 1986; **58:** 45–8.
2. Moreland TA, *et al*. Naloxone pharmacokinetics in the newborn. *Br J Clin Pharmacol* 1980; **9:** 609–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antiopiaz†; Grayxona; Narcanti†; Narxona; ***Austral.***: Narcan†; ***Braz.***: Narcan; ***China***: Feng Du (风度); Fu Er Xin (富尔欣); Jian Tian Neng (健天能); Jin Er Lun (金尔伦); Kawin Nuotong (凯因诺彤); Na Le Shu (纳乐枢); Rui Luo Jian (瑞络健); Sai Xian (赛先); Su Nuo (苏诺); Xin Pu Ao (欣浦澳); Xinqing (欣晴); ***Cz.***: Intrenon; Nexodal; ***Denm.***: Nexodal; ***Fin.***: Nexodal; ***Fr.***: Nalone†; Narcan; ***Gr.***: Narcan; ***Hong Kong***: Mapin†; ***India***: Nalox; Narcotan; Nex; ***Indon.***: Nokoba; ***Irl.***: Narcan†; Nexodal†; ***Ital.***: Narcan; ***Malaysia***: Mapin; ***Neth.***: Nexodal†; ***Norw.***: Nexodal; ***NZ***: Narcan; ***Philipp.***: Narcotan; Narlox; ***Port.***: Naxan; Naxolan; Nexodal; ***Rus.***: Naloxon (Налоксон); ***S.Afr.***: Narcan; Zynox†; ***Singapore***: Mapin; Narcan; ***Swed.***: Nexodal; ***Thai.***: Narcan; ***UK***: Prenoxad; ***Venez.***: Narcan; Oxogina.

Multi-ingredient Preparations. ***USA***: Zubsolv.

Used as an adjunct in:. ***Austral.***: Suboxone; Targin; ***Austria***: Suboxone; Targin; ***Belg.***: Suboxone; Targinact; Tinalox; Valtran; ***Canad.***: Suboxone; Targin; ***Cz.***: Suboxone; Targin; ***Denm.***: Suboxone; Targin; ***Fin.***: Targiniq; ***Fr.***: Suboxone; Targinact; ***Ger.***: Andolor†; Celldolor†; Nalidin†; Suboxone; Targin; Tili Comp†; Tili-Puren†; Tilicomp; Tilidin comp†; Tilidin N†; Tilidin plus; Tilidin-saar†; Tilidin; Tilnalox†; Valoron N; ***Gr.***: Suboxone; ***Hong Kong***: Suboxone; ***Hung.***: Suboxone; ***Indon.***: Suboxone; ***Irl.***: Suboxone; Targin; ***Israel***: Targin; ***Ital.***: Suboxone; Targin; ***Jpn***: Peltazon; Pentagin; Sosegon; ***Malaysia***: Suboxone; ***Neth.***: Suboxone; Targinact; ***Norw.***: Suboxone; Targiniq; ***NZ***: Suboxone; Targin; ***Pol.***: Suboxone; ***Port.***: Suboxone; ***Singapore***: Targin; ***Spain***: Suboxone; Targin; ***Swed.***: Suboxone; Targiniq; ***Switz.***: Targin; ***Turk.***: Suboxone; ***UK***: Suboxone; Targinact; ***USA***: Suboxone; Talwin NX†.

Pharmacopoeial Preparations
BP 2014: Naloxone Injection; Neonatal Naloxone Injection;
USP 36: Naloxone Hydrochloride Injection; Pentazocine and Naloxone Tablets.

Naltrexone *(BAN, USAN, rINN)*

Naltrekson; Naltreksoni; Naltrexon; Naltrexona; Naltrexonum; Налтрексон.

(5*R*)-9a-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one; 17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

$C_{20}H_{23}NO_4$=341.4

CAS — 16590-41-3.

ATC — N07BB04.

ATC Vet — QN07BB04; QV03AB30.

UNII — 5S6W795CQM.

Naltrexone Hydrochloride *(BANM, rINNM)*

EN-1639A; Hidrocloruro de naltrexona; Naltreksonihydrokloridi; Naltreksono hidrochloridas; Naltrexona, hidrocloruro de; Naltrexone, Chlorhydrate de; Naltrexonhydrochlorid; Naltrexon-hydrochlorid; Naltrexonhydroklorid; Naltrexoni Hydrochloridum; Налтрексона Гидрохлорид.

$C_{20}H_{23}NO_4$,HCl=377.9

CAS — 16676-29-2.

ATC — N07BB04.

ATC Vet — QN07BB04.

UNII — Z6375YW9SF.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Naltrexone Hydrochloride). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Naltrexone Hydrochloride). Store in airtight containers.

Uses and Administration

Naltrexone is a specific opioid antagonist with actions similar to those of naloxone (p. 1563.1); however, it is more potent than naloxone and has a longer duration of action. It is used in the management of opioid dependence and alcohol dependence.

Naltrexone hydrochloride is used as an aid to maintaining abstinence after opioid withdrawal in detoxified, formerly **opioid-dependent** patients. Naltrexone treatment should not be started until the patient has been detoxified and abstinent from opioids for at least 7 to 10 days because of the risk of acute withdrawal; abstinence should be verified by analysis of the patient's urine. A *naloxone challenge test* may then be used to confirm the absence of opioids, as follows: naloxone hydrochloride 200 micrograms is given intravenously and the patient monitored for 30 seconds for evidence of withdrawal symptoms; if none occur, a further dose of 600 micrograms is given and the patient monitored for 20 to 30 minutes. A confirmatory rechallenge with naloxone hydrochloride 1.6 mg intravenously may be considered if results are ambiguous. US licensed product information suggests a naloxone challenge test with a single dose of 800 micrograms given subcutaneously as an alternative to the intravenous route.

Once a negative naloxone challenge test has been obtained, naltrexone hydrochloride is given to maintain abstinence. An oral dose of 25 mg may be given initially. If no signs of opioid withdrawal occur subsequent doses may be increased to 50 mg daily. The usual maintenance dose of naltrexone hydrochloride is 350 mg weekly given as 50 mg daily, but the dosing interval may be lengthened to improve compliance; for example, doses of 100 mg on Monday and Wednesday and 150 mg on Friday may be effective, and various other intermittent dosage regimens have been used. Alternatively, naltrexone (as the base) may be given as a long-acting modified-release intramuscular injection in a dose of 380 mg once every 4 weeks. Patients should be carefully counselled and warned that attempts to overcome the opioid blockade with large doses of opioids could result in fatal opioid intoxication.

Naltrexone hydrochloride is also used as an adjunct in the management of **alcohol dependence** at a recommended oral dose of 50 mg daily. Alternatively, naltrexone (as the base) may be given as a modified-release intramuscular injection in a dose of 380 mg once every 4 weeks.

Naltrexone hydrochloride is included in some oral opioid formulations to reduce the potential for parenteral abuse.

Alcohol withdrawal and abstinence. Naltrexone may be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p. 1734.1).[1,2] Two systematic reviews have concluded that oral naltrexone is safe and effective for treatment of alcohol dependence,[2,3] although there is less evidence for long-term benefit.[3] However, since the risk of relapse is particularly high early after alcohol withdrawal, treatment for at least 6 months has been recommended.[4] Compliance with oral naltrexone may be a problem,[2,3] and promising results[2,5-7] have been reported with a long-acting intramuscular injection given monthly.

Although it has been suggested that there may be a difference in response to naltrexone treatment for alcohol dependency depending on gender, results from studies have been conflicting. Some have reported little effect on drinking in women treated with naltrexone and cognitive behaviour therapy,[8] while others have reported either a greater effect in women than men,[9] or less effect in women than men (in those with alcohol plus cocaine dependence).[10] In contrast, women and men had a similar response to naltrexone in an analysis of data from a larger study,[11] and naltrexone was suggested as a viable treatment option for both sexes.

Naltrexone appears to be more effective at reducing the amount of alcohol consumed than producing complete abstinence;[3] reports[12] from patients who continued to drink during therapy suggest that naltrexone may reduce the pleasure associated with drinking, possibly by blocking the effect of endorphins released as a result of alcohol consumption.

Although naltrexone does not appear to be hepatotoxic at the oral dosage of 50 mg daily used for alcohol dependence, caution is recommended in patients with liver disease;[4] careful monitoring is recommended if it is given with disulfiram since hepatotoxicity could potentially be increased.

Nalmefene, a derivative of naltrexone, is also used as an adjunct in the management of alcohol dependence (for details see under Nalmefene, p. 1562.1).

1. Anton RF. Naltrexone for the management o f alcohol dependence. *N Engl J Med* 2008; **359:** 715–21.
2. Rösner S, *et al*. Opioid antagonists for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 10/02/11).
3. Bouza C, *et al*. Efficacy and safety o f naltrexone and acamprosate i n the treatment of alcohol dependence: a systematic review. *Addiction* 2004; **99:** 811–28.
4. Berg BJ, *et al*. A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. *Drug Safety* 1996; **15:** 274–82.
5. Garbutt JC, *et al*. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293:** 1617–25. Correction. *ibid.*: 1978.
6. Swainston Harrison T, *et al*. Extended-release intramuscular naltrexone. *Drugs* 2006; **66:** 1741–51.
7. Ciraulo DA, *et al*. Early treatment response i n alcohol dependence with extended-release naltrexone. *J Clin Psychiatry* 2008; **69:** 190–5.
8. O'Malley SS, *et al*. Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. *Alcohol Clin Exp Res* 2007; **31:** 625–34.
9. Kiefer F, *et al*. A neuroendocrinological hypothesis on gender effects of naltrexone in relapse prevention treatment. *Pharmacopsychiatry* 2005; **38:** 184–6.
10. Pettinati HM, *et al*. Gender differences with high-dose naltrexone in cocaine and alcohol dependence. *J Subst Abuse Treat* 2008; **34:** 378–90.
11. Greenfield SF, *et al*. Gender differences in alcohol treatment: an analysis of outcome from the COMBINE study. *Alcohol Clin Exp Res* 2010; **34:** 1803–12.
12. Volpicelli JR, *et al*. Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995; **152:** 613–15.

Autism. Autistic disorders have been linked with abnormalities in the endogenous opioid system and there is some evidence[1] that naltrexone may be of benefit in children with autism, especially in those with self-injurious behaviour.

1. ElChaar GM, *et al*. Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. *Ann Pharmacother* 2006; **40:** 1086–95.

Eating disorders. Endogenous opioids may have a role in the pathophysiology of eating disorders,[1] thus opioid antagonists such as naloxone and naltrexone have been tried in their management. Naltrexone is under investigation, combined with bupropion, in the management of obesity.[2-7] In one study[6] mean weight loss in participants taking oral naltrexone 32 mg plus bupropion for up to 56 weeks was 6.1 kg compared with 1.4 kg in those taking placebo.

Naltrexone has also been tried in anorexia and other eating disorders.[8,9]

1. de Zwaan M, Mitchell JE. Opiate antagonists and eating behavior in humans: a review. *J Clin Pharmacol* 1992; **32;** 1060–72.
2. Lee MW, Fujioka K. Naltrexone for the treatment of obesity: review and update. *Expert Opin Pharmacother* 2009; **10:** 1841–5.
3. Greenway FL, *et al*. NB-201 Study Group. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J Clin Endocrinol Metab* 2009; **94:** 4898–4906.
4. Plodkowski RA, *et al*. Bupropion and naltrexone: a review of their use individually and in combination for the treatment of obesity. *Expert Opin Pharmacother* 2009; **10:** 1069–81.
5. Padwal R. Contrave, a bupropion a nd naltrexone combination therapy for the potential treatment of obesity. *Curr Opin Investig Drugs* 2009; **10:** 1117–25.
6. Greenway FL, *et al*. COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; **376:** 595–605. Corrections. *ibid.*; 594 and 1392.
7. Wadden TA, *et al*. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)* 2011; **19:** 110–20.
8. Gade K, *et al*. Atypical anorexia in a male patient accompanied by strong obsessive-compulsive symptoms successfully treated with naltrexone. *Pharmacopsychiatry* 2009; **42:** 164–5.
9. Kmoch V, *et al*. Two patients with eating disorders treated by naltrexone. *Neuro Endocrinol Lett* 2009; **30:** 327–30.

Gambling. Naltrexone has been tried for pathological gambling with some success.[1] Nalmefene has also been investigated, but with variable results.[2,3]

1. Grant JE, *et al*. A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J Clin Psychiatry* 2008; **69:** 783–9.
2. Grant JE, *et al*. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. *Am J Psychiatry* 2006; **163:** 303–12.
3. Grant JE, *et al*. Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. *Br J Psychiatry* 2010; **197:** 330–1.

Opioid dependence. *MAINTENANCE.* Naltrexone is a long-acting, non-addictive oral opioid antagonist. It is considered effective in maintaining abstinence in opioid addicts after detoxification, although a systematic review[1] noted that evidence of superiority to other treatments (including placebo) was lacking, and compliance with therapy is difficult to maintain because although naltrexone blocks the euphoriant effects of opioids it does not block the craving

for them. It is thus most effective in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1-4] Modified-release injectable naltrexone may be used for maintenance, and may increase adherence to treatment,[5] although evidence of efficacy is limited.[6] Complications have been reported with depot injections, including opioid withdrawal[7] and ineffective analgesia after surgery.[7] There is a risk of overdose if opioids are used to overcome the antagonist effect of naltrexone; although there are rare reports of deaths after opioid and non-opioid overdoses in patients with naltrexone implants,[8] it is not clear if the risk is different than might be expected in such patients.[9,10] Precautions relating to naloxone use should be noted, see below.

For a discussion of the management of opioid dependence, see p. 109.2.

1. Minozzi S, *et al.* Oral naltrexone maintenance treatment for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 03/03/11).
2. George S, Ekhtiari H. Naltrexone in the treatment of opioid dependence. *Br J Hosp Med* 2010; **71:** 568–70.
3. NICE. Naltrexone for the management of opioid dependence: Technology Appraisal Guidance 115 (issued January 2007). Available at: http://guidance.nice.org.uk/TA115/guidance/pdf/English (accessed 02/05/07)
4. Adi Y, *et al.* Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. *Health Technol Assess* 2007; **11:** iii–iv, 1–85. Also available at: http://www.hta.ac.uk/fullmono/mon1106.pdf (accessed 15/02/11)
5. Comer SD, *et al.* Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006; **63:** 210–18.
6. Lobmaier P, *et al.* Sustained-release naltrexone for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).
7. Lintzeris N, *et al.* Unplanned admissions to two Sydney public hospitals after naltrexone implants. *Med J Aust* 2008; **188:** 441–4.
8. Gibson AE, *et al.* Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; **186:** 152–3.
9. Hulse GK, Tait RJ. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; **187:** 54.
10. Sim MG-B. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; **187:** 54.

RAPID DETOXIFICATION. Naltrexone has been used in various regimens for rapid detoxification;[1,2] opioid withdrawal may be achieved in only a few days, although benefits for long-term outcome are not yet established. It has also been used for ultrarapid detoxification under anaesthesia, although a systematic review[3] concluded that the risks outweighed the benefits of using opioid antagonists in such procedures. A later study[4] also failed to support the use of such a regimen.

Use of a subcutaneous implant of naltrexone for rapid opioid detoxification has been associated with complications, including pulmonary oedema, prolonged withdrawal, variceal rupture, and aspiration pneumonia; fatalities have occurred.[5] Modified-release injectable formulations of naltrexone are generally reserved for maintaining abstinence, see Maintenance, p. 1565.3.

1. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA* 1998; **279:** 229–34.
2. Gowing L, *et al.* Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 12/08/10).
3. Gowing L, *et al.* Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 12/08/10).
4. Collins ED, *et al.* Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA* 2005; **294:** 903–13.
5. Hamilton RJ, *et al.* Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med* 2002; **9:** 63–8.

Pruritus. For reference to the use of opioid antagonists, including naltrexone, in pruritus, see under Nalmefene, p. 1562.1.

Adverse Effects

For general adverse effects of opioid antagonists, see Naloxone, p. 1564.2.

Other adverse effects reported with naltrexone include oedema, increased or decreased appetite, ejaculatory difficulties and reduced potency, toothache, and depression and suicidal ideation. There have been reports of respiratory, urinary, and gastrointestinal infections. Nasopharyngitis, nasal congestion or bleeding, sneezing, hoarseness, cough, pupillary constriction, and tinnitus have been associated with naltrexone, as have rash, pruritus, acne, alopecia, and speech disorders. Reversible idiopathic thrombocytopenia purpura has been reported rarely.

High doses of naltrexone may cause hepatocellular injury. Hepatitis, abnormalities in hepatic function, and increases in liver enzymes or bilirubin have been reported. Urinary retention, increased frequency, or discomfort during urination have occurred.

Injection site reactions, including abscesses and tissue necrosis, have been reported with intramuscular naltrexone. There have also been rare reports of eosinophilic pneumonia.

Effects on the liver. Increased liver enzyme values were reported in 6 of 40 obese patients given naltrexone 50 or 100 mg daily for 8 weeks.[1] Five of the 6 patients had minimally abnormal liver function before naltrexone was given and liver function tests returned to baseline values or better on stopping naltrexone.

Raised transaminase levels were noted in 5 of 26 obese patients after 3 weeks of treatment with naltrexone 300 mg daily; transaminase activity returned to normal when treatment was stopped.[2]

1. Atkinson RL, *et al.* Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; **38:** 419–22.
2. Mitchell JE. Naltrexone and hepatotoxicity. *Lancet* 1986; **i:** 1215.

Effects on the muscles. Asymptomatic rhabdomyolysis has been reported[1] in a patient receiving naltrexone; the condition resolved when naltrexone was withdrawn.

1. Zaim S, *et al.* Rhabdomyolysis associated with naltrexone. *Ann Pharmacother* 1999; **33:** 312–3.

Precautions

Naltrexone should be avoided in patients physically dependent on opioids as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p. 109.1). Withdrawal symptoms may develop within 5 minutes and last up to 48 hours. Patients should be warned that attempting to overcome opioid antagonism may result in opioid intoxication or overdose; they may also be more sensitive to lower doses of opioids after treatment with naltrexone. For further precautions when using naltrexone as an adjunct in the treatment of opioid dependence, see Uses and Administration, p. 1565.2.

Therapeutic use of opioids should be avoided during naltrexone treatment. When analgesia is required, larger than usual doses of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects. Naltrexone should be stopped 48 to 72 hours before elective surgery involving opioid analgesia.

Naltrexone should be used with caution in patients with hepatic impairment and is contra-indicated in patients with acute hepatitis or hepatic failure. Regular monitoring of hepatic function is recommended. Caution is also advised in renal impairment.

Naltrexone may cross-react with some immunoassay methods for the detection of opioids in the urine.

Breast feeding. Naltrexone and its metabolite, 6-β-naltrexol, were detected in the breast milk of a mother taking oral naltrexone for opioid addiction. The total relative infant dose over 24 hours was calculated as 1.06%. A very low concentration of 6-β-naltrexol was found in the plasma of the infant, who was healthy and showed no adverse effects at 6 weeks.[1]

1. Chan CF, *et al.* Transfer of naltrexone and its metabolite 6,beta-naltrexol into human milk. *J Hum Lact* 2004; **20:** 322–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naltrexone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. There are reports[1] of naltrexone use in pregnant women, either orally or as an implant. Although follow-up of the infants was not always undertaken, delivery of healthy infants was described in many cases.

1. Farid WO, *et al.* The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. *Curr Neuropharmacol* 2008; **6:** 125–50.

Pharmacokinetics

Naltrexone is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism and may undergo enterohepatic recycling. It is extensively metabolised in the liver and the major metabolite, 6-β-naltrexol, may also possess weak opioid antagonist activity. Peak plasma concentrations of naltrexone and 6-β-naltrexol occur about 1 hour after oral dosing. The elimination half-life of oral naltrexone is around 4 hours and that of 6-β-naltrexol about 13 hours. Plasma concentrations of a modified-release formulation of naltrexone (*Vivitrol, USA*) peak about 2 hours after intramuscular injection. This is followed by another peak around 2 to 3 days later, and then a slow decline in concentrations from about 14 days post-dose to at least 1 month. The elimination half-life of both naltrexone and 6-β-naltrexol from this formulation is about 5 to 10 days. Naltrexone is about 20% bound to plasma proteins at therapeutic doses. Naltrexone and its metabolites are excreted mainly in the urine, with a small fraction in the faeces. Less than 2% of an oral dose of naltrexone is excreted unchanged.

Hepatic impairment. A study[1] in 11 patients with hepatic cirrhosis found that the systemic availability of naltrexone was significantly increased, particularly in those with decompensated disease.

1. Bertolotti M, *et al.* Effect of liver cirrhosis on the systemic availability of naltrexone in humans. *J Hepatol* 1997; **27:** 505–511.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Revez; ***Austral.***: Revia; ***Austria***: Dependex; Ethylex; Naltrexin†; Nemexin†; Revia; ***Belg.***: Nalorex; ***Braz.***: Revia; ***Canad.***: Revia; ***Chile***: Nalerona; ***China***: Narcoral (纳克莱); Nuo Xin Sheng (诺欣生); ***Cz.***: Adepend; Nemexin†; Revia; ***Denm.***: Adepend; ***Fin.***: Revia; ***Fr.***: Nalorex†; Revia; ***Ger.***: Adepend; Nemexin; ***Gr.***: Nalorex; ***Hong Kong***: Revia†; ***Hung.***: Antaxon; Nemexin†; Revia†; ***India***: Naltima; Nodict; ***Indon.***: Nutrexon; Phaltrexia†; ***Irl.***: Ethylex; Nalorex; Revia†; ***Ital.***: Antaxone; Nalorex; Narcoral; ***Malaysia***: Narpan; ***Mex.***: Revia†; ***Neth.***: Nalorex†; Revia; ***Norw.***: Revia†; ***NZ***: Naltraccord; Revia; ***Port.***: Antaxone; Basinal; Destoxican; Nalorex†; ***Rus.***: Antaxone (Антаксон); Prodetoxon (Продетоксон); Vivitrol (Вивитрол); ***Singapore***: Trexan; ***Spain***: Antaxone; Celupan†; Revia; ***Swed.***: Revia†; ***Switz.***: Naltrexin; Nemexin†; ***Thai.***: Revia; ***Turk.***: Ethylex; ***UK***: Adepend; Nalorex; Opizone; ***Ukr.***: Antaxone (Антаксон); ***USA***: Revia; Trexan; Vivitrol.

Multi-ingredient Preparations.

Used as an adjunct in:. ***USA***: Embeda.

Pharmacopoeial Preparations
USP 36: Naltrexone Hydrochloride Tablets.

Obidoxime Chloride *(USAN, rINN)*

Chlorek Obidoksymu; Cloruro de obidoxima; LüH6; Obidoxim Chlorid; Obidoxima, cloruro de; Obidoximchlorid; Obidoxime, Chlorure d'; Obidoximi Chloridum; Обидоксима Хлорид.

1,1′-[Oxybis(methylene)]bis[4-(hydroxyimino)methyl]pyridinium dichloride.

$C_{14}H_{16}Cl_2N_4O_3$=359.2

CAS — 7683-36-5 (obidoxime); 114-90-9 (obidoxime chloride).

ATC — V03AB13.

ATC Vet — QV03AB13.

UNII — 3HXR312Z9M.

Profile

Obidoxime chloride is a cholinesterase reactivator with similar actions and uses to pralidoxime (p. 1571.1). It is given with atropine in the treatment of organophosphorus poisoning in a usual initial dose of 250 mg (4 mg/kg) by slow intravenous injection or by intramuscular injection. This may be followed by intravenous infusion of 750 mg over 24 hours, continued until the concentration of organophosphate is below critical levels; alternatively, repeated doses of 4 to 8 mg/kg by intravenous injection may be given at intervals of 2 to 4 hours. For doses in children, see below.

References.

1. Thiermann H, *et al.* Cholinesterase status, pharmacokinetics and laboratory findings during obidoxime therapy in organophosphate poisoned patients. *Hum Exp Toxicol* 1997; **16:** 473–80.
2. Eyer F, *et al.* Obidoxime in acute organophosphate poisoning: 1—clinical effectiveness. *Clin Toxicol* 2009; **47:** 798–806.
3. Thiermann H, *et al.* Obidoxime in acute organophosphate poisoning: 2—PK/PD relationships. *Clin Toxicol* 2009; **47:** 807–13.
4. Thiermann H, *et al.* Pharmacokinetics of obidoxime in patients poisoned with organophosphorus compounds. *Toxicol Lett* 2010; **197:** 236–42.

Administration in children. Obidoxime chloride is used with atropine to treat children with organophosphorus poisoning. An initial dose of 4 to 8 mg/kg (maximum 250 mg) by slow intravenous injection or by intramuscular injection is followed by either a continuous intravenous infusion of 10 mg/kg daily, or repeated doses of 4 to 8 mg/kg by intravenous injection at intervals of 2 to 4 hours.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies obidoxime as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Toxogonin†; ***Chile***: Toxogonin; ***Cz.***: Toxogonin; ***Ger.***: Toxogonin; ***Neth.***: Toxogonin; ***S. Afr.***: Toxogonin; ***Switz.***: Toxogonine.

Penicillamine *(BAN, USAN, rINN)*

Penicilamin; Penicilamina; Penicilaminas; Penicillamin; Penicillamina; D-Penicillamine; Pénicillamine; Penicillaminum; Penicylamina; Penisilamin; Penisillamiini; Пеницилламин.

D-3,3-Dimethylcysteine; D-3-Mercaptovaline.

$C_5H_{11}NO_2S$=149.2

CAS — 52-67-5 (penicillamine); 2219-30-9 (penicillamine hydrochloride).

ATC — M01CC01.

ATC Vet — QM01CC01.

UNII — GNN1DV99GX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Penicillamine). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 36: (Penicillamine). A white or practically white, crystalline powder having a slight characteristic odour. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store in airtight containers.

Uses and Administration

Penicillamine is a chelator that aids the elimination from the body of certain heavy-metal ions, including copper, lead, and mercury, by forming stable water-soluble complexes with them that are readily excreted by the kidney. It is used in the treatment of Wilson's disease (below) to promote the excretion of copper, in heavy-metal poisoning such as lead poisoning (p. 2542.1), in cystinuria (below) to reduce urinary concentrations of cystine, in severe active rheumatoid arthritis (p. 13.2), and in chronic active hepatitis.

Penicillamine is given orally and should be taken on an empty stomach. To reduce toxicity, the lowest effective dose should be used.

In the treatment of **Wilson's disease**, the optimal dosage to achieve a negative copper balance should be determined initially by measuring 24-hour urinary copper excretion; a 24-hour cupriuresis of over 2 mg should be sustained for about 3 months. Subsequently, free copper in the serum is monitored; adequately treated patients will usually have free-copper serum values of less than 10 micrograms per 100 mL. In the UK, an initial dose of 1.5 to 2 g daily in divided doses is suggested; a maintenance dose of 0.75 to 1 g daily may be adequate once control is achieved and should be continued indefinitely. A maintenance dose of 2 g daily should not be continued for more than a year. A dose of 20 mg/kg daily in divided doses is suggested for the elderly. In the USA, a usual initial dose of 0.75 to 1.5 g daily is suggested; it is seldom necessary to exceed 2 g daily. In those who cannot tolerate such doses an initial dose of 250 mg daily, increased gradually, may provide better control and reduce adverse effects.

In the management of **lead poisoning**, penicillamine may be given in doses of 1 to 1.5 g daily in divided doses until urinary lead is stabilised at less than 500 micrograms/day. Elderly patients may be given 20 mg/kg daily in divided doses.

In **cystinuria**, doses of penicillamine are adjusted according to cystine concentrations in the urine. For the *treatment* of cystinuria and cystine calculi, the dose is usually in the range of 1 to 4 g daily in divided doses to achieve a urinary cystine concentration of not more than 200 mg/litre. An initial dose of 250 mg daily increased gradually may provide good control and reduce adverse effects. For the *prevention* of cystine calculi, doses of 0.5 to 1 g at bedtime may be given to achieve a urinary cystine concentration of not more than 300 mg/litre. An adequate fluid intake is essential to maintain urine flow when penicillamine is used for cystinuria.

In the treatment of **severe active rheumatoid arthritis**, an initial dose of penicillamine 125 to 250 mg daily is increased gradually by the same amount at intervals of 4 to 12 weeks. Remission is usually achieved with maintenance doses of 500 to 750 mg daily in divided doses, but up to 1.5 g daily may be required. Improvement may not occur for several months; US licensed product information suggests that penicillamine should be stopped if there is no response after treatment for 3 to 4 months with 1 to 1.5 g daily; in the UK, treatment should be stopped if there is no benefit within 12 months. After remission has been sustained for 6 months an attempt may be made to gradually reduce the dose by 125 to 250 mg daily every 3 months but relapse may occur. Lower doses may be required in the elderly who may be more susceptible to developing adverse effects. Initial doses of 125 mg daily are recommended, gradually increased by this amount every 4 to 12 weeks to a maximum of 1 g daily if necessary.

In the management of **chronic active hepatitis**, penicillamine may be given after liver function tests have indicated that the disease has been controlled by corticosteroids. The initial dose is 500 mg daily in divided doses, increased gradually over 3 months to 1.25 g daily, while at the same time reducing the corticosteroid dose.

For doses in children, see below.

Acetylpenicillamine has been used in mercury poisoning.

Administration in children. Penicillamine is used in children for the treatment of Wilson's disease, for poisoning by heavy metals such as lead, for cystinuria, and for severe active juvenile rheumatoid arthritis.

For the treatment of **Wilson's disease**, an oral dose of 20 mg/kg daily in 2 or 3 divided doses is recommended. Children from 12 years may be given the adult maintenance dose, see above.

For **lead poisoning**, the recommended daily oral dose is 15 to 20 mg/kg in 2 or 3 divided doses in children whose blood lead concentrations are less than 45 micrograms/100 mL.

In **cystinuria**, the penicillamine dose should be adjusted to maintain the urinary cystine concentration below 200 mg/litre and adequate fluid intake ensured. An oral dose of 20 to 30 mg/kg daily in 2 or 3 divided doses has been suggested.

For **juvenile idiopathic arthritis**, UK licensed product information recommends an initial oral dose of penicillamine 2.5 to 5 mg/kg daily before food, increased every 4 weeks over 3 to 6 months to a usual maintenance dose of 15 to 20 mg/kg daily, although the *BNFC* advises that penicillamine is no longer used as a disease-modifying antirheumatic drug.

Chronic active hepatitis. Penicillamine has been tried in chronic active hepatitis (p. 1602.3) as an alternative to prolonged corticosteroid maintenance therapy once control of the disease is achieved. The dose of penicillamine is increased over several months to a suitable maintenance dose and, at the same time, the corticosteroid dose is decreased.

Cystinuria. Cystinuria is an inherited disorder of renal amino-acid excretion in which there is excessive excretion of cystine (cysteine disulfide), along with ornithine, lysine, and arginine. The low solubility of cystine leads to the formation of cystine stones in the urinary tract, resulting in pain, haematuria, renal obstruction, infection, and renal impairment.[1,2] Treatment is mainly aimed at reducing the urinary concentration of cystine to below its solubility limit of about 300 mg/litre at urinary pH (5 to 7). Patients with cystinuria excrete 400 to 1200 mg cystine daily and should be advised to drink at least 3 litres of water daily, including at night, to maintain a dilute urine. Cystine is more soluble in alkaline urine (above 7.5) and urinary alkalinisers such as potassium bicarbonate or potassium citrate may be used; sodium-based alkalinisers are not generally recommended. Penicillamine may also be used, particularly in patients where these measures are ineffective or not tolerated; it complexes with cystine to form more soluble compounds, thereby preventing cystine stone formation, and promoting the gradual dissolution of existing stones. Adverse effects are common and tiopronin, which has a similar action, may be used as an alternative. Captopril may increase the solubility of cystine and has been used in some patients such as those with hypertension, although evidence of efficacy is inconsistent. Dietary restrictions have also been used: a reduction in sodium reduces urinary cystine excretion and a low-salt diet is recommended. Restriction of protein, to reduce methionine, a precursor of cystine, has also been suggested, but is not generally recommended as it is difficult to maintain. Urological interventions may be necessary to remove established stones.[1-3]

1. Ahmed K, *et al.* Cystine calculi: challenging group of stones. *Postgrad Med J* 2006; **82:** 799–801.
2. Knoll T, *et al.* Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol* 2005; **20:** 19–24.
3. Türk C, *et al.* European Association of Urology. Guidelines on urolithiasis (updated April 2010). Available at: http://www.uroweb.org/gls/pdf/Urolithiasis%202010.pdf (accessed 18/03/11)

Primary biliary cirrhosis. Copper accumulation in the liver has been noted in patients with primary biliary cirrhosis (see under Ursodeoxycholic Acid,p. 2638.3) and therapy with penicillamine to reduce liver-copper concentrations has been studied. Despite good preliminary results, most studies have found it to be ineffective and any benefit appears to be offset by the high incidence of adverse effects.[1,2]

1. James OFW. D-Penicillamine for primary biliary cirrhosis. *Gut* 1985; **26:** 109–13.
2. Gong Y, *et al.* D-penicillamine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 18/03/11).

Retinopathy of prematurity. Penicillamine has been investigated for the prophylaxis of retinopathy of prematurity (p. 2120.3) in infants considered to be at risk, and a systematic review of 2 such studies considered that there was evidence for a reduced incidence of acute retinopathy.[1] Further studies were considered justified, with careful attention to possible adverse effects.

1. Phelps D, *et al.* D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 18/03/11).

Rheumatoid arthritis. Penicillamine is one of a diverse group of disease-modifying antirheumatic drugs that have been used in rheumatoid arthritis (p. 13.2) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease. However, early enthusiasm for penicillamine has been tempered by a high incidence of adverse effects.[1] During long-term therapy as many as 50% of patients taking penicillamine have been reported to stop treatment because of adverse effects.[2] Low doses of penicillamine to reduce the incidence of adverse effects have been tried and while doses as low as 125 mg daily have been claimed to be effective in some patients, a 36-week multicentre double-blind study[3] involving 225 patients concluded that a dose of penicillamine 500 mg daily was only slightly more effective than placebo. A dose of 125 mg daily was not significantly different from either the 500-mg dose or placebo. However, a 5-year open study[4] comparing penicillamine in doses up to 500 mg daily with hydroxychloroquine, sodium aurothiomalate, or auranofin found penicillamine to be as effective as the other drugs and well tolerated, with 53% of the patients randomised to penicillamine still receiving it at 5 years, as opposed to about 30 to 35% of those randomised to other drugs.

1. Suarez-Almazor ME, *et al.* Penicillamine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 31/03/11).
2. Moens HJB, *et al.* Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14:** 1115–19.
3. Williams HJ, *et al.* Low-dose D-penicillamine therapy in rheumatoid arthritis: a controlled, double-blind clinical trial. *Arthritis Rheum* 1983; **26:** 581–92.
4. Jessop JD, *et al.* A long-term five-year randomized controlled trial of hydroxychloroquine, sodium aurothiomalate, auranofin and penicillamine in the treatment of patients with rheumatoid arthritis. *Br J Rheumatol* 1998; **37:** 992–1002.

Scleroderma. Penicillamine affects the cross-linking of collagen,[1] and observational studies[2,3] have suggested that it may be of benefit in scleroderma (p. 1938.3), and perhaps in some visceral manifestations of systemic sclerosis. A randomised study[4] comparing a conventional dose of penicillamine (up to 1 g daily) with a very low dose (125 mg on alternate days) found no difference in outcome, but there were more adverse effects with the higher dose. Although the lower dose was not expected to be effective, the skin score improved significantly in both groups; however, there was insufficient evidence to attribute this to use of penicillamine, and its role in scleroderma remains to be established.

For a report of sclerodermatous lesions in a patient taking penicillamine for Wilson's disease, see Scleroderma, under Effects on the Skin, p. 1569.2.

1. Herbert CM, *et al.* Biosynthesis and maturation of skin collagen in scleroderma, and effect of D-penicillamine. *Lancet* 1974; **i:** 187–92.
2. Steen VD, *et al.* D-Penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982; **97:** 652–9.
3. Derk CT, *et al.* A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset. *Br J Dermatol* 2008; **158:** 1063–8.
4. Clements PJ, *et al.* High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999; **42:** 1194–1203.

Wilson's disease. Wilson's disease, or hepatolenticular degeneration, is a rare autosomal disorder of copper accumulation.[1-7] Excretion of excess copper, which normally occurs via the bile, is impaired and total body copper progressively increases. The excess copper accumulates in the liver, brain, and other organs including the kidneys and corneas, and eventually causes tissue damage.

Effective treatment of Wilson's disease involves the use of copper-reducing drugs to establish a negative copper balance. This prevents deposition of more copper and also mobilises excess copper that has already been deposited making it available for excretion. Once negative copper balance has been achieved, maintenance treatment must be continued lifelong. Dietary restriction of copper is not generally considered to be an important part of the treatment of Wilson's disease, although patients may be advised to avoid copper-rich foods, such as liver and shellfish, during the first year of treatment and to restrict their consumption thereafter. Symptomatic recovery from copper overload occurs slowly, but is usually complete if treatment is started early enough, and a normal life expectancy can be achieved. However, once irreversible

organ damage such as liver cirrhosis has occurred, treatment can only prevent further deterioration; those presenting with end-stage liver disease do not benefit from copper-reducing therapy, and liver transplantation is necessary (although successful medical treatment has been reported in children). The drugs used to reduce copper concentrations in the treatment of Wilson's disease are penicillamine, trientine, and zinc. Dimercaprol has been used with penicillamine in refractory patients. Ammonium tetrathiomolybdate, an investigational drug, may also be used.

- *Penicillamine* reduces copper concentrations in several ways. Its main action is to chelate circulating copper, which is then excreted in the urine. In addition, penicillamine reduces the affinity of copper for proteins and polypeptides, allowing removal of copper from tissues. It also induces hepatic synthesis of metallothionein, a protein that combines with copper to form a non-toxic product.
- *Trientine* is a less potent copper chelator than penicillamine; it competes for copper bound to serum albumin and increases copper excretion.
- *Zinc* induces synthesis of metallothionein in the intestine so that absorption of copper from the gastrointestinal tract is blocked. It is usually given as the acetate as this form is less irritating to the stomach than the sulfate.
- *Ammonium tetrathiomolybdate* forms a complex with protein and copper. When it is given with food it blocks the intestinal absorption of copper, and when taken between meals it combines with albumin- and caeruloplasmin-bound copper.
- *Dimercaprol* may accelerate the removal of copper from brain tissue as it is not electrically charged and therefore crosses vascular and cellular membranes more readily than penicillamine, which has charged carboxyl and amino groups.

CHOICE OF DRUG. Penicillamine is generally regarded as the drug of choice for the initial management of Wilson's disease as it produces a rapid reduction in copper levels. However, it may initially exacerbate neurological symptoms (possibly due to transiently increased brain and blood copper concentrations) and some practitioners therefore suggest starting with zinc; zinc is less suitable in those requiring rapid reduction of copper levels as it has a slow onset of action. Trientine, which may also exacerbate neurological symptoms, is mainly used in patients intolerant of penicillamine, although it is also used for initial treatment as there is less toxicity. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels; it may be particularly suitable for patients with neurological symptoms. Dimercaprol can be used with penicillamine in patients who remain symptomatic or deteriorate on penicillamine alone. Because it must be given intramuscularly it is usually used in acute disease to improve control.

Once a negative copper balance is achieved, maintenance therapy must be continued for life. Penicillamine, trientine, and zinc are all used for maintenance treatment. Patients taking penicillamine are also given pyridoxine to prevent deficiency (see Precautions, p. 1569.3). The adverse effects of penicillamine may be a problem during long-term use and zinc, which has low toxicity, is often preferred. Zinc is also used in patients in the asymptomatic stage of the disease.

1. Brewer GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc Soc Exp Biol Med* 2000; **223:** 39–46.
2. Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *Hepatology* 2003; **37:** 1475–92.
3. El-Youssef M. Wilson disease. *Mayo Clin Proc* 2003; **78:** 1126–36.
4. Merle U, *et al*. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut* 2007; **56:** 115–20.
5. Ala A, *et al*. Wilson's disease. *Lancet* 2007; **369:** 397–408.
6. Lee V, *et al*. Wilson's disease: a complex picture. *Clin Pharmacist* 2009; **1:** 239–41.
7. Lorincz MT. Neurologic Wilson's disease. *Ann N Y Acad Sci* 2010; **1184:** 173–87.

Adverse Effects and Treatment

Adverse effects occur frequently with penicillamine and may be severe. Gastrointestinal disturbances including anorexia, nausea, and vomiting may occur; oral ulceration and stomatitis have been reported, as has transient loss or impairment of taste.

Rashes occurring early in treatment are commonly allergic and may be associated with pruritus, urticaria, and fever; they are usually transient but temporary withdrawal or dose reduction and use of corticosteroids or antihistamines may be required. Penicillamine treatment should be permanently stopped if a rash develops with fever, arthralgia, and lymphadenopathy. Dermatomyositis, lupus erythematosus, and pemphigus have been reported. Stevens-Johnson syndrome and toxic epidermal necrolysis have been seen during penicillamine treatment. Prolonged use of high doses may affect skin collagen and elastin, resulting in increased skin friability, extravasation of blood, pseudoxanthoma elasticum, and eruptions resembling elastosis perforans serpiginosa. A late rash or acquired epidermolysis bullosa (penicillamine dermatopathy) has occurred and may require doses to be reduced or stopped.

Haematological adverse effects have included thrombocytopenia, neutropenia, and leucopenia; these are usually reversible, but agranulocytosis and aplastic anaemia have occurred and fatalities have been reported. Treatment may need to be withheld or withdrawn if leucopenia or thrombocytopenia occur, or if there are 3 successive falls in the white blood cell or platelet count while still within the usual range. Other adverse effects on the blood include haemolytic or sideroblastic anaemia, thrombotic thrombocytopenia purpura, red cell aplasia, monocytosis, leucocytosis, eosinophilia, and thrombocytosis.

Proteinuria occurs frequently and in some patients may progress to glomerulonephritis or nephrotic syndrome; renal failure has been reported, and Goodpasture's syndrome (glomerulonephritis associated with intra-alveolar haemorrhage) has been fatal. Treatment should be immediately withdrawn if there are abnormal urinary findings with haemoptysis and pulmonary infiltrates. Penicillamine-induced haematuria is rare; treatment may need to be withdrawn for increasing or persistent proteinuria or haematuria.

Effects on the nervous system include psychiatric disturbances, agitation, anxiety, visual disturbances, tinnitus, optic neuritis, and sensory or motor peripheral neuropathies including Guillain Barré syndrome; muscular weakness may occur with the peripheral neuropathies.

Other adverse effects associated with penicillamine include breast-enlargement, alopecia, yellow nail syndrome, reactivated peptic ulcer, hypoglycaemia associated with anti-insulin antibodies, myasthenic syndrome that is usually reversible but has progressed to fatal myasthenia gravis, polymyositis, increases in liver enzyme values, intrahepatic cholestasis and toxic hepatitis, pancreatitis, vasculitis including fatal renal vasculitis, thyroiditis, migratory polyarthralgia, rheumatoid arthritis, or septic arthritis in those with pre-existing rheumatoid arthritis, pulmonary fibrosis, allergic alveolitis, obliterative bronchiolitis, interstitial pneumonitis, and asthma.

Incidence of adverse effects. References describing the range and incidence of adverse effects associated with of D-penicillamine.[1-3] The L- or DL-forms are much more toxic.[4]

1. Kean WF, *et al*. Efficacy and toxicity of D-penicillamine for rheumatoid disease in the elderly. *J Am Geriatr Soc* 1982; **30:** 94–100.
2. Steen VD, *et al*. The toxicity of D-penicillamine in systemic sclerosis. *Ann Intern Med* 1986; **104:** 699–705.
3. Munro R, Capell HA. Penicillamine. *Br J Rheumatol* 1997; **36:** 104–9.
4. Kean WF, *et al*. Chirality in antirheumatic drugs. *Lancet* 1991; **338:** 1565–8.

Effects on the blood. Of the 18 deaths ascribed to penicillamine reported to the UK CSM between January 1964 and December 1977, 14 were apparently due to blood disorders, at least 7 of them being marrow aplasias. The myelotoxicity of penicillamine was reviewed in 10 patients with confirmed or suspected marrow depression during penicillamine treatment for rheumatoid arthritis or scleroderma; 6 died.[1]

An incidence of 12 to 27% has been reported for penicillamine-induced thrombocytopenia in patients with rheumatoid arthritis, possibly due to bone-marrow suppression and a reduced platelet-production rate.[2]

There have been isolated reports[3-5] of thrombotic thrombocytopenic purpura attributed to the use of penicillamine, with some fatalities.

1. Kay AGL. Myelotoxicity of D-penicillamine. *Ann Rheum Dis* 1979; **38:** 232–6.
2. Thomas D, *et al*. Thrombokinetics in patients with rheumatoid arthritis treated with D-penicillamine. *Ann Rheum Dis* 1984; **43:** 402–6.
3. Ahmed F, *et al*. Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1978; **138:** 1292–3.
4. Speth PAJ, *et al*. Thrombotic thrombocytopenic purpura associated with D-penicillamine treatment in rheumatoid arthritis. *J Rheumatol* 1982; **9:** 812–13.
5. Trice JM, *et al*. Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. *Arch Intern Med* 1983; **143:** 1487–8.

Effects on the breasts. Breast enlargement has been reported both in women[1-5] and in men[6] taking penicillamine and may be a rare adverse effect. In some patients breast enlargement was prolonged with poor resolution and others required surgery. Danazol has been used successfully to treat penicillamine-induced breast gigantism.[2-4]

1. Thew DCN, Stewart IM. D penicillamine and breast enlargement. *Ann Rheum Dis* 1980; **39:** 200.
2. Taylor PJ, *et al*. Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282:** 362–3.
3. Rooney PJ, Cleland J. Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282:** 1627–8.
4. Craig HR. Penicillamine induced mammary hyperplasia: report of a case and review of the literature. *J Rheumatol* 1988; **15:** 1294–7.
5. Tchebiner JZ. Breast enlargement induced by D-penicillamine. *Ann Pharmacother* 2002; **36:** 444–5.
6. Reid DM, *et al*. Reversible gynaecomastia associated with D-penicillamine in a man with rheumatoid arthritis. *BMJ* 1982; **285:** 1083–4.

Effects on endocrine function. Congenital goitrous hypothyroidism was reported in 2 siblings whose mother took penicillamine during pregnancy for Wilson's disease. Subclinical hypothyroidism was also noted in a further 5 children with Wilson's disease, 4 of whom had taken penicillamine for 3 to 3.5 years and then changed to zinc therapy; zinc was the sole treatment in 1 patient. During penicillamine therapy, thyroid-stimulating hormone concentrations were significantly higher than those during zinc treatment. The authors suggested hypothyroidism could have been the result of inhibition of thyroperoxidase activity by penicillamine.[1]

1. Hanukoglu A, *et al*. Hypothyroidism and dyshormonogenesis induced by D-penicillamine in children with Wilson's disease and healthy infants born to a mother with Wilson's disease. *J Pediatr* 2008; **153:** 864–6.

Effects on the gastrointestinal tract. There have been isolated reports of acute colitis in patients taking penicillamine.[1,2] Ileal ulceration and stenosis in a patient with Wilson's disease was considered to be related to elastosis probably resulting from long-term penicillamine therapy.[3]

1. Hickling P, Fuller J. Penicillamine causing acute colitis. *BMJ* 1979; **2:** 367.
2. Grant GB. Penicillamine causing acute colitis. *BMJ* 1979; **2:** 555.
3. Wassef M, *et al*. Unusual digestive lesions in a patient with Wilson's disease treated with long-term penicillamine. *N Engl J Med* 1985; **313:** 49.

Effects on the heart. For reports of heart block, Stokes-Adams syndrome, and fatal myocarditis in patients taking penicillamine, see Polymyositis under Effects on the Muscles and the Neuromuscular System, p. 1569.1.

Effects on the kidneys. Proteinuria associated with penicillamine[1,2] has usually occurred within 4 to 18 months of starting therapy, although onset can be later. A greater incidence has been found in patients with rheumatoid arthritis and cystinuria than in those with Wilson's disease. The severity varies; proteinuria of nephrotic proportions usually develops rapidly but resolves on drug withdrawal. Minimal change, mesangioproliferative, and membranous nephropathy have all been associated with penicillamine; progressive glomerulonephritis has been seen in a few patients with features of Goodpasture's syndrome (see Effects on the Respiratory System, p. 1569.1).

Although there is some evidence of a relationship between nephropathy and penicillamine dose and its rate of increase,[1] a study of 33 rheumatoid arthritis patients with penicillamine-induced nephropathy found no correlation with the dose or duration of treatment.[3] Appreciable proteinuria could still be detected 12 months after stopping penicillamine in 40% of these patients, but subsequently resolved in those whose proteinuria was solely related to penicillamine.

Penicillamine was successfully reintroduced and continued for at least 13 months in 5 patients with rheumatoid arthritis who had developed proteinuria during the first course of therapy. Proteinuria did not recur.[4] Another study[5] in 8 patients with proteinuria but no oedema suggested that penicillamine could be safely continued; proteinuria resolved in 5 of the patients during continued therapy.

Corticosteroids have been used in patients developing rapidly progressive glomerulonephritis[6] but may be unnecessary and potentially hazardous in patients who develop nephrotic syndrome.[3]

1. Anonymous. Penicillamine nephropathy. *BMJ* 1981; **282:** 761–2.
2. Habib GS, *et al*. Penicillamine and nephrotic syndrome. *Eur J Intern Med* 2006; **17:** 343–8.
3. Hall CL, *et al*. Natural course of penicillamine nephropathy: a long term study of 33 patients. *BMJ* 1988; **296:** 1083–6.
4. Hill H, *et al*. Resumption of treatment with penicillamine after proteinuria. *Ann Rheum Dis* 1979; **38:** 229–31.
5. DeSilva RN, Eastmond CJ. Management of proteinuria secondary to penicillamine therapy in rheumatoid arthritis. *Clin Rheumatol* 1992; **11:** 216–9.
6. Ntoso KA, *et al*. Penicillamine-induced rapidly progressive glomerulonephritis in patients with progressive systemic sclerosis: successful treatment of two patients and a review of the literature. *Am J Kidney Dis* 1986; **8:** 159–63.

Effects on the liver. Penicillamine has been associated with hepatotoxicity. A case report and review of the literature[1] described 9 patients, all of whom had liver function profiles consistent with intrahepatic cholestasis; 1 patient died of acute renal failure but the others improved rapidly after drug withdrawal. In a later report,[2] a 72-year-old man with rheumatoid arthritis developed jaundice about 4 weeks after starting penicillamine therapy. Liver biopsy indicated a slight degree of cholangitis with eosinophils in the portal tracts and severe predominantly intrahepatocellular cholestasis. Jaundice cleared within 3 weeks of stopping penicillamine and liver enzyme values approached normal after 6 weeks. However, in another case[3] cholestasis persisted despite withdrawal of penicillamine and the patient died of sepsis 14 months later. Monitoring of

liver function and eosinophil counts in the early weeks of penicillamine therapy has been recommended.[1]

1. Seibold JR, *et al*. Cholestasis associated with D-penicillamine therapy: case report and review of the literature. *Arthritis Rheum* 1981; **24:** 554–6.
2. Devogelaer JP, *et al*. A case of cholestatic hepatitis associated with D-penicillamine therapy for rheumatoid arthritis. *Int J Clin Pharmacol Res* 1985; **5**: 35–8.
3. Jacobs JWG, *et al*. Fatal cholestatic hepatitis caused by D-penicillamine. *Br J Rheumatol* 1994; **33:** 770–3.

Effects on the muscles and the neuromuscular system. Neuromyotonia,[1] and profound sensory and motor neuropathy that responded to pyridoxine supplementation,[2] have occurred in patients taking penicillamine. Low back pain with fever and rash has also been reported;[3] back pain and fever recurred on rechallenge. It was suggested that an allergic mechanism was involved.

1. Reeback J, *et al*. Penicillamine-induced neuromyotonia. *BMJ* 1979; **1:** 1464–5.
2. Pool KD, *et al*. Penicillamine-induced neuropathy in rheumatoid arthritis. *Ann Intern Med* 1981; **95:** 457–8.
3. Bannwarth B, *et al*. Low back pain associated with penicillamine. *BMJ* 1991; **303:** 525.

MYASTHENIA. Myasthenia gravis is a well recognised, though uncommon, complication of long-term penicillamine therapy, particularly in patients with rheumatoid arthritis or other auto-immune disorders.[1-5] Symptoms are similar to those seen with spontaneous myasthenia gravis and include ptosis and diplopia, and generalised weakness, occasionally affecting the respiratory muscles. The onset of symptoms usually occurs within 6 to 7 months but may be delayed for several years. Myasthenic symptoms usually resolve spontaneously once penicillamine is withdrawn, but some patients require anticholinesterase therapy. Acetylcholine receptor antibodies have been reported in 75% or more of affected patients.[2,3] Several reports have suggested a genetic tendency to penicillamine-induced myasthenia, and an association with HLA antigens DR1 and Bw35 has been found in some studies,[1,4,6] although others[5] have not replicated these findings.

1. Delamere JP, *et al*. Penicillamine-induced myasthenia in rheumatoid arthritis: its clinical and genetic features. *Ann Rheum Dis* 1983; **42:** 500–4.
2. Carter H, *et al*. La myasthénie au cours du traitement de la polyarthrite rhumatoïde par la D-pénicillamine. *Therapie* 1984; **39:** 689–95.
3. Katz LJ, *et al*. Ocular myasthenia gravis after D-penicillamine administration. *Br J Ophthalmol* 1989; **73:** 1015–18.
4. Garlepp MJ, *et al*. HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286:** 338–40.
5. Drosos AA, *et al*. D-penicillamine induced myasthenia gravis: clinical, serological and genetic findings. *Clin Exp Rheumatol* 1993; **11:** 387–91.
6. Hill M, *et al*. T cell responses to D-penicillamine in drug-induced myasthenia gravis: recognition of modified DR1:peptide complexes. *J Neuroimmunol* 1999; **97:** 146–53.

POLYMYOSITIS. Penicillamine therapy has been associated rarely with polymyositis and dermatomyositis.[1-7] Cardiac complications may occur: at least 2 deaths have resulted from myocarditis,[1] and complete heart block[1,3,8] and severe Stokes-Adams attacks[3] have been reported. It is possible that some patients may have a genetically determined susceptibility to this complication.[4]

1. Doyle DR, *et al*. Fatal polymyositis in D-penicillamine-treated rheumatoid arthritis. *Ann Intern Med* 1983; **98:** 327–30.
2. Renier JC, *et al*. Polymyosite induite par la D-pénicillamine. *Therapie* 1984; **39:** 697–703.
3. Christensen PD, Sørensen KE. Penicillamine-induced polymyositis with complete heart block. *Eur Heart J* 1989; **10:** 1041–4.
4. Carroll GJ, *et al*. Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14:** 995–1001.
5. Aydintug AO, *et al*. Polymyositis complicating D-penicillamine treatment. *Postgrad Med J* 1991; **67:** 1018–20.
6. Jan V, *et al*. Pemphigus, polymyosite et myasthénie induits par la D-pénicillamine. *Ann Dermatol Venereol* 1999; **126:** 153–6.
7. Dourmishev LA, *et al*. D-penicillamine induced polymyositis and morphea in a woman with Hashimoto thyroiditis. *J Eur Acad Dermatol Venereol* 2002; **16:** 538–9.
8. Wright GD, *et al*. D-penicillamine induced polymyositis causing complete heart block. *Clin Rheumatol* 1994; **13:** 80–2.

Effects on the respiratory system. Pulmonary haemorrhage associated with progressive renal failure has been reported[1,2] with penicillamine and has generally been classified as Goodpasture's syndrome, although patients usually lack anti-glomerular basement membrane antibodies; an immune-complex mechanism has also been suggested.[1] There have been rare reports of obliterative bronchiolitis in patients with rheumatoid arthritis treated with penicillamine.[3-6]

Upper respiratory tract disorders have also been reported. A 76-year-old patient taking penicillamine developed rhinitis, bilateral blepharitis, and pemphigus foliaceus;[7] the rhinitis and blepharitis resolved when penicillamine was withdrawn. In addition, 2 patients with lower respiratory symptoms also developed persistent sinusitis,[6] which required surgery.

1. Turner-Warwick M. Adverse reactions affecting the lung: possible association with D-penicillamine. *J Rheumatol* 1981; **8** (suppl 7): 166–8.
2. Derk CT, Jimenez SA. Goodpasture-like syndrome induced by D-penicillamine in a patient with systemic sclerosis: report and review of the literature. *J Rheumatol* 2003; **30:** 1616–20.
3. Lyle WH. D-Penicillamine and fatal obliterative bronchiolitis. *BMJ* 1977; **1:** 105.
4. Epler GR, *et al*. Bronchiolitis and bronchitis in connective tissue disease: a possible relationship to the use of penicillamine. *JAMA* 1979; **242:** 528–32.
5. Murphy KC, *et al*. Obliterative bronchiolitis in two rheumatoid arthritis patients treated with penicillamine. *Arthritis Rheum* 1981; **24:** 557–60.
6. Wolfe F, *et al*. Upper and lower airway disease in penicillamine treated patients with rheumatoid arthritis. *J Rheumatol* 1983; **10:** 406–10.
7. Presley AP. Penicillamine induced rhinitis. *BMJ* 1988; **296:** 1332.

Effects on the skin. Penicillamine-induced skin lesions have been reviewed.[1] Reactions include those resulting from interference with collagen and elastin (see below); those associated with auto-immune mechanisms such as pemphigus, pemphigoid, lupus erythematosus, and dermatomyositis; and those classified as acute sensitivity reactions including macular or papular eruptions and urticaria. The effects on collagen and elastin tend to occur only after prolonged use of high doses, as in patients with Wilson's disease or cystinuria, whereas patients with diseases characterised by altered immune systems, such as rheumatoid arthritis, are more prone to develop the antibody-related adverse skin reactions. Acute hypersensitivity reactions tend to occur early in treatment, usually within the first 7 to 10 days, and appear not to be dose-related. Lichenoid reactions, stomatitis, nail changes, and adverse effects on hair have also occurred.

1. Levy RS, *et al*. Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8:** 548–58.

INTERFERENCE WITH COLLAGEN AND ELASTIN. Long-term, high-dose treatment with penicillamine can interfere with elastin and collagen production giving rise to increased skin friability, haemorrhagic lesions, miliary papules, and excessive wrinkling and laxity of the skin.[1] Penicillamine dermatopathy, characterised by wrinkling and purpura over bony prominences, has been described.[2] In addition, lesions resembling pseudoxanthoma elasticum have been reported.[3,4]

Abnormal elastic tissue has also been reported in patients taking low doses of penicillamine (less than 1 g daily), not only in the skin but also in joint capsules,[5] and elastosis perforans serpiginosa (normally described after long-term, higher dose therapy[6,7]) has been reported.[8]

In all these cases, histological findings generally show damage to elastic fibres giving them a typical appearance described as 'lumpy-bumpy' or 'bramble-bush'.

For reports of cutis laxa in neonates, see Pregnancy under Precautions, p. 1570.1.

1. Levy RS, *et al*. Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8:** 548–58.
2. Sternlieb I, Scheinberg IH. Penicillamine therapy for hepatolenticular degeneration. *JAMA* 1964; **189:** 748–54.
3. Thomas RHM, *et al*. Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1984; **77:** 794–8.
4. Bentley-Phillips B. Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1985; **78:** 787.
5. Dalziel KL, *et al*. Elastic fibre damage induced by low-dose D-penicillamine. *Br J Dermatol* 1990; **123:** 305–12.
6. Hill VA, *et al*. Penicillamine-induced elastosis perforans serpiginosa and cutis laxa in Wilson's disease. *Br J Dermatol* 2000; **142:** 560–1.
7. Atzori L, *et al*. D-penicillamine elastosis perforans serpiginosa: description of two cases and review of the literature. *Dermatol Online J* 2011; **17:** 3.
8. Sahn EE, *et al*. D-Penicillamine-induced elastosis perforans serpiginosa in a child with juvenile rheumatoid arthritis. *J Am Acad Dermatol* 1989; **20:** 979–88.

LICHEN PLANUS. There have been rare reports of lichen planus in patients with primary biliary cirrhosis taking penicillamine,[1,2] although the role of penicillamine has been questioned. Oral lichen planus associated with penicillamine has also been reported[3] in patients with rheumatoid arthritis.

1. Powell FC, Rogers RS. Primary biliary cirrhosis, penicillamine, and lichen planus. *Lancet* 1981; **ii:** 525.
2. Powell FC, *et al*. Lichen planus, primary biliary cirrhosis and penicillamine. *Br J Dermatol* 1982; **107:** 616.
3. Blasberg B, *et al*. Lichenoid lesions of the oral mucosa in rheumatoid arthritis patients treated with penicillamine. *J Rheumatol* 1984; **11:** 348–51.

PEMPHIGUS. Bullous skin disorders are established adverse effects of penicillamine and appear to have an autoimmune basis.[1] Pemphigus-spectrum disorders have been most commonly reported, including pemphigus vulgaris, pemphigus foliaceus, herpetiform pemphigus, pemphigus erythematosus, benign mucous membrane pemphigoid, cicatricial pemphigoid, and combined pemphigus and pemphigoid features.

1. Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; **35:** 732–42.

PSORIASIFORM ERUPTIONS. Two patients with rheumatoid arthritis developed psoriasiform eruptions during penicillamine treatment.[1] In 1 patient the eruption resolved when penicillamine was stopped but worsened when treatment was restarted.

1. Forgie JC, Highet AS. Psoriasiform eruptions associated with penicillamine. *BMJ* 1987; **294:** 1101.

SCLERODERMA. Penicillamine has been used in the treatment of scleroderma and systemic sclerosis (see under Uses, p. 1567.3). However, scleroderma, with evidence of pulmonary involvement, developed in a 14-year-old boy with Wilson's disease who had been treated with penicillamine for 11 years[1] and the suitability of penicillamine for this indication has therefore been questioned.

1. Miyagawa S, *et al*. Systemic sclerosis-like lesions during long-term penicillamine therapy for Wilson's disease. *Br J Dermatol* 1987; **116:** 95–100.

TOXIC EPIDERMAL NECROLYSIS. A 56-year-old woman developed agranulocytosis and toxic epidermal necrolysis 7 weeks after starting therapy with penicillamine 250 mg daily for primary biliary cirrhosis.[1] Severe toxic epidermal necrolysis has also been reported[2] in a woman taking penicillamine for Wilson's disease.

1. Ward K, Weir DG. Life threatening agranulocytosis and toxic epidermal necrolysis during low dose penicillamine therapy. *Ir J Med Sci* 1981; **150:** 252–3.
2. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol* 1984; **10:** 973–8.

Genetic factors. There is evidence that some patients may have a genetically determined increased susceptibility to the adverse effects of penicillamine. Several studies have suggested that rheumatoid arthritis patients with a poor capacity for producing sulfoxides may be more susceptible to the toxic effects of penicillamine.[1,2] Patients with primary biliary cirrhosis also appear to have poor sulfoxidation capacity,[3] and this may contribute to their high incidence of adverse reactions to penicillamine, although no association between penicillamine toxicity and sulfoxidation status was found in a study of 20 such patients.[4]

Several studies have also suggested that certain histocompatibility antigens may increase susceptibility to penicillamine toxicity. An increased incidence of adverse reactions was noted[2] in patients with HLA-DR3, while other studies have shown associations between proteinuria and HLA antigens B8 and DR3,[5,6] myasthenia gravis and Bw35 and DR1,[7] thrombocytopenia and HLA antigens DR4,[5,6] A1,[5] and C4BQO,[5] and polymyositis or dermatomyositis and HLA antigens B18, B35, and DR4.[8] However, not all studies have reported the same associations, and the clinical usefulness of sulfoxidation testing or HLA-typing is not established.[6,9]

1. Panayi GS, *et al*. Deficient sulphoxidation status and D-penicillamine toxicity. *Lancet* 1983; **i:** 414.
2. Emery P, *et al*. D-Penicillamine induced toxicity in rheumatoid arthritis: the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; **11:** 626–32.
3. Olomu A, *et al*. Poor sulphoxidation in primary biliary cirrhosis. *Lancet* 1985; **i:** 1504.
4. Mitchison HC, *et al*. D-penicillamine-induced toxicity in primary biliary cirrhosis (PBC): the role of sulphoxidation status. *Gut* 1986; **27:** A622.
5. Stockman A, *et al*. Genetic markers in rheumatoid arthritis: relationship to toxicity from D-penicillamine. *J Rheumatol* 1986; **13:** 269–73.
6. Moens HJB, *et al*. Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14:** 1115–19.
7. Garlepp MJ, *et al*. HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286:** 338–40.
8. Carroll GJ, *et al*. Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14:** 995–1001.
9. Hall CL. Penicillamine nephropathy. *BMJ* 1988; **297:** 137.

Systemic lupus erythematosus. A syndrome resembling SLE developed in 6 women with long-standing severe rheumatoid arthritis while taking penicillamine;[1] this represented a frequency of penicillamine-induced lupus erythematosus of about 2%. All 6 had developed previous cutaneous reactions to gold therapy. A case of bullous SLE associated with penicillamine has also been reported.[2]

1. Chalmers A, *et al*. Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; **97:** 659–63.
2. Condon C, *et al*. Penicillamine-induced type II bullous systemic lupus erythematosus. *Br J Dermatol* 1997; **136:** 474–5.

Precautions

Penicillamine is contra-indicated in patients with lupus erythematosus or a history of penicillamine-induced agranulocytosis, aplastic anaemia, or severe thrombocytopenia. It is also contra-indicated in patients with moderate or severe renal impairment, and should be used with care in those with mild impairment; a reduced dose may be necessary. Penicillamine is a degradation product of penicillin and patients who are allergic to penicillin may show cross-sensitivity to penicillamine although this appears to be rare.

Patients need to be carefully monitored for adverse effects; elderly patients may be at increased risk of toxicity. In all patients, full blood counts and renal function should be assessed before starting treatment. During therapy full blood counts and urinalysis should be carried out periodically. Liver function tests at 6-monthly intervals have also been recommended.

Therapy should ideally be continuous for cystinuria or Wilson's disease as interruptions to treatment for even a few days have been followed by sensitivity reactions when restarting penicillamine.

Oral pyridoxine 25 mg daily may be given to patients on long-term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.

A reduced dose of penicillamine has been suggested for patients undergoing surgery (see Anaesthesia and Surgery, below).

Anaesthesia and surgery. Penicillamine may delay wound healing due to its effects on collagen and elastin and US licensed product information suggests that the dose should be reduced to 250 mg daily for 6 weeks before surgery and during the postoperative period until healing has taken place.

The effects of penicillamine on muscle function should also be considered in patients requiring anaesthesia; a 57-year-old woman[1] with penicillamine-induced myasthenia developed prolonged postoperative apnoea, necessitating artificial ventilation.

1. Fried MJ, Protheroe DT. D-Penicillamine induced myasthenia gravis: its relevance for the anaesthetist. *Br J Anaesth* 1986; **58:** 1191–3.

Breast feeding. Although data are scarce, a review reported no adverse effects in the infants of nursing mothers taking penicillamine for Wilson's disease; the concentration of zinc and copper in the breast milk was reduced in one study.[1]

1. Sternlieb I. Wilson's disease and pregnancy. *Hepatology* 2000; **31:** 531–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies penicillamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pregnancy. Penicillamine teratogenicity has been reviewed.[1] Evidence of the embryotoxicity of maternal penicillamine exposure in *animal* studies had been confirmed in humans by 5 reports of cutis laxa in neonates of mothers who had taken penicillamine during pregnancy; 3 further reports of intra-uterine brain injury were less characteristic. Nevertheless most pregnancy outcomes were normal. No birth defects had been reported when penicillamine was stopped in early pregnancy. In conditions where there are safer treatment options, it is advisable to stop penicillamine during pregnancy; however, it is generally recommended that women taking penicillamine for Wilson's disease should continue throughout pregnancy since the benefits outweigh the risks. Of 153 pregnancies in 111 women with Wilson's disease treated with penicillamine, there were 144 normal neonates (1 premature), 4 elective abortions, 1 miscarriage, and 4 infants with birth defects: mannosidosis (1), cleft lip and palate (1), and transient cutis laxa (2).[2] A reduced dose of penicillamine 0.75 to 1 g daily has been used during the first 2 trimesters in women with well-controlled Wilson's disease, reducing to 500 mg daily during the last trimester. If a caesarean section is planned, the dose should be reduced as described for surgery, see above.

For a report of congenital hypothyroidism associated with use of penicillamine during pregnancy, see Effects on Endocrine Function, p. 1568.3.

1. Rosa FW. Teratogen update: penicillamine. *Teratology* 1986; **33:** 127–31.
2. Sternlieb I. Wilson's disease and pregnancy. *Hepatology* 2000; **31:** 531–2.

Interactions

Penicillamine forms chelates with metal ions and oral absorption may be reduced if it is given with iron or other metals, antacids, or food. Penicillamine should be taken on an empty stomach and it has been recommended that there should be an interval of at least 2 hours between taking penicillamine and iron supplements or antacids. Mineral supplements should be avoided. It has also been suggested that digoxin should not be given within 2 hours of penicillamine, see Interactions of Digoxin, p. 1358.1. Additive toxicity may occur if penicillamine is given with drugs that have adverse renal or haematological effects.

Antacids or food. In a single-dose study in 6 healthy subjects, penicillamine given orally immediately after food or a dose of an antacid mixture (aluminium hydroxide, magnesium hydroxide, and simeticone), resulted in plasma concentrations of penicillamine that were 52% and 66%, respectively, of those obtained in a fasting state. Results suggested that the reduction in plasma-penicillamine concentrations was associated with decreased absorption.[1] Another study[2] showed that the reduction of penicillamine plasma concentrations produced by aluminium- and magnesium-containing antacids did not occur with sodium bicarbonate, and thus the interaction was probably a result of chelation rather than a pH effect.

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulphate. *Clin Pharmacol Ther* 1983; **33:** 465–70.
2. Ifan A, Welling PG. Pharmacokinetics of oral 500 mg penicillamine: effect of antacids on absorption. *Biopharm Drug Dispos* 1986; **7:** 401–5.

Diazepam. For a report of re-activation of intravenous diazepam-induced phlebitis by oral penicillamine, see under Diazepam, p. 1070.3.

Gold. There have been conflicting reports on the effect of previous gold therapy on the subsequent development of penicillamine toxicity in patients with rheumatoid arthritis.

Some studies[1,2] have suggested that adverse effects with penicillamine may be more common in patients who have previously reacted adversely to gold, but others[3,4] have found no correlation. One study[5] found that although the overall incidence of adverse effects with penicillamine appeared unaffected by prior gold therapy, bone-marrow depression and rashes were more common in those previously given gold. It has been suggested[2] that the interaction occurs due to mobilisation of gold from the tissues by penicillamine, and an interval of at least 6 months between gold and penicillamine in patients with prior gold toxicity was recommended. However, another report[6] found that the interval between gold and penicillamine had no influence on the development of toxicity and suggested that there might be a common genetic susceptibility in certain patients. A patient who had developed myasthenia with penicillamine had a recurrence with gold therapy,[7] but another study[4] found no evidence that the adverse effects of gold were increased in those with prior penicillamine toxicity.

1. Hill H. Penicillamine and previous treatment with gold. *BMJ* 1978; **2:** 961.
2. Dodd MJ, *et al.* Adverse reactions to D-penicillamine after gold toxicity. *BMJ* 1980; **280:** 1498–1500.
3. Multi-centre Trial Group. Absence of toxic or therapeutic interaction between penicillamine and previously administered gold in a trial of penicillamine in rheumatoid disease. *Postgrad Med J* 1974; **50** (suppl 2): 77–8.
4. Steven MM, *et al.* Does the order of second-line treatment in rheumatoid arthritis matter? *BMJ* 1982; **284:** 79–81.
5. Webley M, Coomes EN. Is penicillamine therapy in rheumatoid arthritis influenced by previous treatment with gold? *BMJ* 1978; **2:** 91.
6. Smith PJ, *et al.* Influence of previous gold toxicity on subsequent development of penicillamine toxicity. *BMJ* 1982; **285:** 595–6.
7. Moore AP, *et al.* Penicillamine induced myasthenia reactivated by gold. *BMJ* 1984; **288:** 192–3.

Insulin. Unexplained hypoglycaemia in 2 patients with type 1 diabetes occurred 6 to 8 weeks after penicillamine treatment for rheumatoid arthritis was started.[1] Both patients required a reduction in their insulin dose. A possible immunological mechanism has been proposed.[1,2]

1. Elling P, Elling H. Penicillamine, captopril, and hypoglycemia. *Ann Intern Med* 1985; **103:** 644–5.
2. Becker RC, Martin RG. Penicillamine-induced insulin antibodies. *Ann Intern Med* 1986; **104:** 127–8.

Iron. Plasma-penicillamine concentrations were reduced to 35% when penicillamine was given after a dose of ferrous sulfate in healthy subjects.[1] Patients stabilised on penicillamine while on oral iron therapy were considered unlikely to respond fully to penicillamine and would be exposed to a large increase in penicillamine absorption with possible adverse reactions if the iron was stopped.[2]

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulfate. *Clin Pharmacol Ther* 1983; **33:** 465–70.
2. Harkness JAL, Blake DR. Penicillamine nephropathy and iron. *Lancet* 1982; **ii:** 1368–9.

Probenecid. Probenecid may reduce the beneficial effects of penicillamine in cystinuria, and it has been suggested[1] that hyperuricaemic cystinuric patients should not be given both drugs.

1. Yu T-F, *et al.* Studies on the metabolism of D-penicillamine and its interaction with probenecid in cystinuria and rheumatoid arthritis. *J Rheumatol* 1984; **11:** 467–70.

Pharmacokinetics

Penicillamine is rapidly but variably absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 3 hours. It is reported to be more than 80% bound to plasma proteins, particularly albumin. Penicillamine undergoes some metabolism in the liver, to *S*-methyl penicillamine. It is mainly excreted in the urine as disulfides, along with some *S*-methyl penicillamine and unchanged drug; a small amount may be excreted in the faeces. Elimination is biphasic with an initial elimination half-life of about 1 to 3 hours followed by a slower phase, suggesting gradual release from tissues.

Reviews.

1. Netter P, *et al.* Clinical pharmacokinetics of D-penicillamine. *Clin Pharmacokinet* 1987; **13:** 317–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cuprimine; Cupripen; ***Austral.***: D-Penamine; ***Austria***: Artamin; ***Braz.***: Cuprimine; ***Canad.***: Cuprimine; ***Cz.***: Metalcaptase; ***Denm.***: Atamir; ***Fr.***: Trolovol; ***Ger.***: Metalcaptase; ***Gr.***: Cupripen†; ***India***: Artamin; Cilamin; Distamin; ***Irl.***: Distamine; ***Ital.***: Pemine; ***Jpn***: Metalcaptase; ***Malaysia***: Artamin; ***Mex.***: Adalken; Sufortan; ***Neth.***: Gerodyl; ***NZ***: D-Penamine; ***Pol.***: Cuprenil; ***Port.***: Kelatine; Trolovol; ***Rus.***: Cuprenil (Купренил); ***S.Afr.***: Metalcaptase†; ***Spain***: Cupripen; ***Switz.***: Mercaptyl†; ***Thai.***: Cuprimine; ***UK***: Distamine; ***USA***: Cuprimine; Depen.

Pharmacopoeial Preparations

BP 2014: Penicillamine Tablets;
USP 36: Penicillamine Capsules; Penicillamine Tablets.

Pentetic Acid *(BAN, USAN, rINN)*

Acide Pentétique; Ácido pentético; Acidum Penteticum; Diethylentriaminpentaessigsäure; DTPA; Pentético, ácido; Pentetinezuur; ZK-43649; Пентетовая Кислота.

Diethylenetriamine-*NNN′N″N″*-penta-acetic acid.

$C_{14}H_{23}N_3O_{10}$=393.3

CAS — 67-43-6.

UNII — 7A314HQM0I.

Pharmacopoeias. In *US*.

USP 36: (Pentetic Acid). A white odourless or almost odourless powder.

Calcium Trisodium Pentetate *(BAN, rINN)*

Ca-DTPA; Calcii Trinatrii Pentetas; Calcium Trisodium DTPA; NSC-34249; Pentetate Calcium Trisodium (USAN); Pentétate de Calcium Trisodique; Pentetato cálcico trisódico; Pentetato calcio y trisodio; Trisodium Calcium Diethylenetriaminepentaacetate; Кальция Тринатрия Пентетат.

$C_{14}H_{18}CaN_3Na_3O_{10}$=497.4

CAS — 12111-24-9.

UNII — G79YN26H5B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pentetate Sodium Calcium for Radiopharmaceutical Preparations). A starting material for the preparation of technetium (^{99m}Tc) pentetate injection. A white or almost white, hygroscopic powder or crystals. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 8.0 to 9.5. Store in airtight containers. Protect from light.

Zinc Trisodium Pentetate *(rINNM)*

Pentétate de Zinc Trisodique; Pentetate Zinc Trisodium; Pentetato zinc y trisodio; Trisodium Zinc Diethylenetriaminepentaacetate; Zinci Trinatrii Pentetas; Zn-DTPA (zinc pentetate or zinc trisodium pentetate); Цинка Тринатрия Пентетат.

$C_{14}H_{18}N_3Na_3O_{10}Zn$=522.7

CAS — 65229-17-6 (zinc pentetate); 125833-02-5 (zinc trisodium pentetate).

UNII — NXU65IC8PG.

Uses and Administration

Pentetic acid and its salts are chelators with the general properties of the edetates (see Edetic Acid, p. 1550.3). Calcium trisodium pentetate and zinc trisodium pentetate are used in the treatment of poisoning by radioactive metals such as plutonium, americium, and curium. Calcium trisodium pentetate is more effective within the first 24 hours and is preferred for the initial dose; however, zinc depletion may occur and if further chelation is required treatment should be continued with zinc trisodium pentetate if possible.

The usual dose is 1 g of either calcium or zinc trisodium pentetate once daily, by slow intravenous injection over 3 to 4 minutes or by intravenous infusion over 30 minutes diluted in 100 to 250 mL of sodium chloride 0.9%, glucose 5%, or lactated Ringer's solution. Treatment is continued according to the estimated radioactive body burden. For patients poisoned solely by inhalation calcium trisodium pentetate or zinc trisodium pentetate may be given by nebulisation.

For doses in children, see below.

Pentetates, labelled with metallic radionuclides, are used in nuclear medicine (see Indium-111, p. 2224.3, and Technetium-99m, p. 2228.3).

Administration in children. Calcium trisodium pentetate and zinc trisodium pentetate are chelators that may be used in children for the treatment of poisoning by radioactive metals such as plutonium, americium, and curium, in the same way as for adults (see above). The usual starting and maintenance dose of either calcium or zinc trisodium pentetate is 14 mg/kg (to a maximum of 1 g) once daily, by slow intravenous injection or by intravenous infusion.

The safety and efficacy of calcium trisodium pentetate and zinc trisodium pentetate given by nebulisation has not been established for children.

Thalassaemia. Iron overload in patients with thalassaemia (p. 1124.1) is usually treated with desferrioxamine, but auditory toxicity can result. Calcium pentetic acid has been used as an alternative. A study[1] in 5 patients in whom desferrioxamine had to be withdrawn because of high-tone deafness found that the pentetate was as effective as desferrioxamine and hearing improved during treatment. Oral zinc supplements were necessary to maintain adequate plasma-zinc concentrations.

1. Wonke B, *et al.* Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; **64:** 77–82.

Adverse Effects and Precautions

Adverse effects that have been reported with calcium or zinc trisodium pentetate include headache and lightheadedness. Pentetates chelate trace metals and supplements may be needed with long-term use. Trace metals and serum-electrolytes should be monitored during use.

Other adverse effects reported with calcium trisodium pentetate include nausea and diarrhoea, injection-site reactions, chest pain, allergic reactions, dermatitis, and a metallic taste. Bronchospasm has occurred after inhalation. It should be used with caution in patients with severe haemochromatosis since fatalities have been reported when high doses were used.

Pharmacokinetics

Pentetates are rapidly distributed throughout the extracellular space and eliminated by glomerular filtration, with most of a dose excreted in the urine within 24 hours. Only a small amount (less than 3%) is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Ditripentat; ***Ger.***: Ditripentat-Heyl; ***Israel***: DTPA; Frosstimage Kit (DTPA).

Pralidoxime *(BAN, rINNM)*

2-PAM; Pralidoksiimi; Pralidoksyna; Pralidossima; Pralidoxim; Pralidoxima; Pralidoximum; Пралидоксим.

2-Hydroxyiminomethyl-1-methylpyridinium.

$C_7H_9N_2O$=137.2

CAS — 6735-59-7; 495-94-3.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — P7MU9UTP52.

Pralidoxime Chloride *(BANM, USAN, rINNM)*

2-Formyl-1-methylpyridinium Chloride Oxime; 2-PAM; 2-PAM Chloride; 2-PAMCl; Pralidoxim Chlorid; Pralidoxima, cloruro de; Pralidoxime, Chlorure de; Pralidoximi Chloridum; 2-Pyridine Aldoxime Methochloride; Пралидоксима Хлорид.

$C_7H_9ClN_2O$=172.6

CAS — 51-15-0.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — 38X7XS076H.

Pharmacopoeias. In *US*.

USP 36: (Pralidoxime Chloride). A white to pale yellow, odourless, crystalline powder. Freely soluble in water.

Pralidoxime Iodide *(BANM, USAN, rINN)*

Ioduro de pralidoxima; NSC-7760; 2-PAM Iodide; 2-PAMI; Pralidoxim Iodid; Pralidoxima, ioduro de; Pralidoxime, Iodure de; Pralidoximi Iodidum; Yoduro de pralidoxima; Пралидоксима Йодид.

$C_7H_9IN_2O$=264.1

CAS — 94-63-3.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — 7H254VC0NT.

Pharmacopoeias. In *Chin.*

Pralidoxime Mesilate *(BANM, rINNM)*

Mesilato de pralidoxima; P2S; 2-PAMM; Pralidoksiimimesilaatti; Pralidoksim Mezilat; Pralidoxim Mesilat; Pralidoxima, mesilato de; Pralidoxime, Mésilate de; Pralidoxime Mesylate (USAN); Pralidoxime Methanesulphonate; Pralidoximi Mesilas; Pralidoximmesilat; Пралидоксима Мезилат.

$C_7H_9N_2O,CH_3O_3S$=232.3

CAS — 154-97-2.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — 45CO7XIN2K.

Pralidoxime Metilsulfate *(BANM, rINNM)*

Pralidoxima, metilsulfato de; Pralidoxime Methylsulphate; Pralidoxime, Métilsulfate de; Pralidoximi Metilsulfas; Пралидоксима Метилсульфат.

$C_7H_9N_2O,CH_3SO_4$=248.3

CAS — 1200-55-1.

ATC — V03AB04.

ATC Vet — QV03AB04.

Pharmacopoeias. In *It.*

Uses and Administration

Pralidoxime is a cholinesterase reactivator. It is used as an adjunct to, but *not* as a substitute for, atropine in the treatment of poisoning by certain cholinesterase inhibitors. Its main indication is in poisoning due to organophosphorus insecticides or related compounds (see p. 2158.3). These compounds phosphorylate and consequently inactivate cholinesterase, causing acetylcholine accumulation and muscle paralysis. Pralidoxime reactivates cholinesterase, restoring the enzymatic destruction of acetylcholine at the neuromuscular junction and relieving muscle paralysis. Use with atropine is required to counteract the adverse effects of acetylcholine accumulation, particularly at the respiratory centre. Its ability to antagonise different organophosphorus anticholinesterases varies, as reactivation is dependent on the nature of the phosphoryl group and the rate at which inhibition becomes irreversible. It is not effective in the treatment of poisoning due to phosphorus, inorganic phosphates, or organophosphates without anticholinesterase activity. Its use in the treatment of poisoning by carbamate insecticides (p. 2150.1) is controversial, see Carbamate Poisoning, below. In some countries pralidoxime is used for the treatment of overdosage by anticholinesterase drugs used to treat myasthenia gravis such as neostigmine, pyridostigmine, and ambenonium, although caution is advised when using pralidoxime in patients with myasthenia gravis, see Precautions, below.

Pralidoxime is usually given as the chloride but the mesilate, iodide, and metilsulfate salts have also been used. In severe poisoning pralidoxime is usually given as an intravenous infusion over 15 to 30 minutes, or as a slow intravenous injection over at least 5 minutes if infusion is not practicable or there is pulmonary oedema. Alternatively, for less severe toxicity or when the intravenous route is not feasible, pralidoxime can be given by intramuscular or subcutaneous injection; it has also been given orally.

In the treatment of **organophosphorus poisoning** pralidoxime should be given as soon as possible. After about 36 hours it becomes less effective since cholinesterase inactivation usually becomes irreversible after this time; however, patients with severe poisoning may occasionally respond up to 48 hours or longer after exposure, depending on the organophosphate involved. Injections of *atropine* should be given intravenously or intramuscularly and repeated as necessary until muscarinic effects disappear or signs of atropine toxicity are seen; atropinisation should then be maintained for 48 hours or more. Large amounts of atropine may be required. See under Atropine Sulfate, p. 1311.3, for details of dosages. As soon as the effects of atropine become apparent, 1 to 2 g of *pralidoxime* chloride should be given intravenously and repeated after 1 hour and then every 10 to 12 hours if necessary. Alternatively, the *BNF* recommends pralidoxime chloride in an initial dose of 30 mg/kg given by intravenous infusion or injection; the initial dose is then followed by intravenous infusion at a rate of 8 mg/kg per hour to a usual maximum dose of 12 g in 24 hours. Pralidoxime treatment is continued until the patient has not required atropine for 12 hours.

Intramuscular dosing of pralidoxime is based on the severity of poisoning; for mild symptoms a dose of pralidoxime chloride 600 mg is given by intramuscular injection, and repeated once or twice at 15 minute intervals as needed. For more severe symptoms pralidoxime chloride 1.8 g is given intramuscularly, as 3 injections of 600 mg in rapid succession. For persistent symptoms, up to 3 further doses of 600 mg at 15 minute intervals may be given as needed, starting 1 hour after the last injection. Auto-injectors for intramuscular injection are available for emergency use, and contain pralidoxime alone, pralidoxime with atropine, or pralidoxime with atropine plus avizafone. In some countries, an oral dose of pralidoxime 1 to 3 g, as the metilsulfate, is given every 5 hours for milder toxicity.

For **antimyasthenic overdose** an initial dose of pralidoxime chloride 1 to 2 g is given by intravenous infusion, followed by an intravenous infusion of 0.5 to 1 g/hour; alternatively, the initial dose can be repeated after 1 hour and then every 3 to 8 hours if needed.

The dose of pralidoxime may need to be reduced in patients with renal impairment.

Treatment may be monitored by the determination of blood-cholinesterase concentrations and clinical symptoms.

Other oximes with cholinesterase-reactivating properties that have been used similarly include asoxime chloride (p. 1541.1), obidoxime chloride (p. 1566.3), and trimedoxime bromide (p. 1579.1).

Administration in children. Pralidoxime chloride is used in children as an adjunct to atropine in the treatment of organophosphorus poisoning; the *BNFC* recommends the same dose as that recommended by the *BNF* for adults, see above.

Carbamate poisoning. The use of pralidoxime for poisoning due to carbamate insecticides is controversial. Licensed product information states that pralidoxime should not be used to treat poisoning by carbamate pesticides as it may increase toxicity, and it has been suggested that as carbamate-induced cholinesterase inhibition is spontaneously reversible, oxime therapy is not necessary. However, there are reports of successful use of pralidoxime in carbamate poisoning,[1-3] and it is suggested, with atropine, as a treatment option by some authorities.

1. Burgess JL, *et al.* Aldicarb poisoning: a case report with prolonged cholinesterase inhibition and improvement after pralidoxime therapy. *Arch Intern Med* 1994; **154:** 221–4.
2. Tracqui A, *et al.* Repeated measurements of aldicarb in blood and urine in a case of nonfatal poisoning. *Hum Exp Toxicol* 2001; **20:** 657–60.
3. Hoffman RS, *et al.* Use of pralidoxime without atropine in rivastigmine (carbamate) toxicity. *Hum Exp Toxicol* 2009; **28:** 599–602.

Organophosphorus poisoning. Oximes such as pralidoxime are widely used in poisoning with organophosphate *pesticides*. Although benefit has been shown in *animal* studies, reviews[1,2] have pointed out that there is little good evidence from human studies to support their use and that randomised controlled studies are needed to confirm their efficacy and safety, as well as the optimum regimens to use. A randomised study[3] in patients with moderately severe poisoning with organophosphorus pesticides found that a continuous infusion of pralidoxime iodide 1 g/hour for 48 hours was more effective than a dose of 1 g every 4 hours. However, another controlled study[4] found that the WHO-recommended regimen of pralidoxime chloride 2 g as a loading dose, followed by constant infusion of 500 mg/hour, was of no benefit in patients self-poisoned with organophosphorus insecticides, despite clear evidence of reactivation of red cell acetylcholinesterase.

Cholinesterase reactivators such as the oximes have also been used for poisoning with organophosphate *nerve agents*. Studies in *animals* have suggested that the efficacy of the different oximes depends on the organophosphate involved; asoxime (p. 1541.1) and HLö-7 may be more effective than pralidoxime or obidoxime for poisoning with nerve agents, particularly for soman poisoning.[5]

1. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003; **22:** 165–90.
2. Buckley NA, *et al.* Oximes for acute organophosphate pesticide poisoning. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 01/03/11).
3. Pawar KS, *et al.* Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet* 2006; **368:** 2136–41.
4. Eddleston M, *et al.* Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med* 2009; **6:** e1000104. Available at: http://www.plosmedicine.org/article/fetchObjectAttachment.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.1000104&representation=PDF (accessed 18/12/09)
5. Kassa J. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J Toxicol Clin Toxicol* 2002; **40:** 803–16.

Adverse Effects

Use of pralidoxime may be associated with drowsiness, dizziness, disturbances of vision, nausea, hypertension, tachycardia, headache, hyperventilation, and muscular weakness. Impaired renal function and increases in liver enzymes have been reported, as have transient increases in creatine phosphokinase. Hypertension, tachycardia, laryngospasm, and muscle rigidity have been attributed to giving pralidoxime intravenously at too rapid a rate. Large doses of pralidoxime may cause transient neuromuscular blockade.

Precautions

Pralidoxime should be used cautiously in patients with renal impairment; a reduction in dosage may be necessary. Caution is also required in giving pralidoxime to patients with myasthenia gravis as it may precipitate a myasthenic crisis. The use of pralidoxime for poisoning due to carbamate insecticides is controversial, see Carbamate Poisoning, above.

When atropine and pralidoxime are given together, the signs of atropinisation may occur earlier than might be expected when atropine is used alone.

Pregnancy. Although data are scarce, there are reports of the use of pralidoxime for poisoning in the second or third

trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Pharmacokinetics

Peak plasma concentrations of pralidoxime occur about 5 to 15 minutes after an intravenous dose. Absorption from the gastrointestinal tract is poor. It is not bound to plasma proteins and has limited distribution into the CNS. Pralidoxime is metabolised in the liver and excreted by renal tubular secretion; within 12 hours 80% of a dose is recovered unchanged in the urine, with the remainder as a metabolite. The elimination half-life is about 1 to 3 hours.

References.

1. Sidell FR, Groff WA. Intramuscular and intravenous administration of small doses of 2-pyridinium aldoxime methochloride to man. *J Pharm Sci* 1971; **60:** 1224–8.
2. Siddell FR, *et al.* Pralidoxime methanesulfonate: plasma levels and pharmacokinetics after oral administration to man. *J Pharm Sci* 1972; **61:** 1136–40.
3. Swartz RD, *et al.* Effects of heat and exercise on the elimination of pralidoxime in man. *Clin Pharmacol Ther* 1973; **14:** 83–9.
4. Schexnayder S, *et al.* The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *J Toxicol Clin Toxicol* 1998; **36:** 549–55.
5. Abbara C, *et al.* Pharmacokinetic analysis of pralidoxime after its intramuscular injection alone or in combination with atropine-avizafone in healthy volunteers. *Br J Pharmacol* 2010; **161:** 1857–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Contrathion; ***Braz.***: Contrathion; ***Fr.***: Contrathion; ***Gr.***: Contrathion; ***India***: Aldopam; CBC-PAM; Clopam; Lyphe; Neopam; Nispam; Pam-A Korea; ***Ital.***: Contrathion; ***Malaysia***: Pampara; ***Singapore***: Pam-A; ***Turk.***: Contrathion†; ***USA***: Protopam.

Multi-ingredient Preparations. ***Fr.***: Ineurope; ***UK***: Nerve Agent Antidote L4A1; ***USA***: DuoDote.

Pharmacopoeial Preparations
USP 36: Pralidoxime Chloride for Injection.

Protamine *(rINNM)*

Protamin; Protamina; Protaminum; Protammina; Протамин.
CAS — 9012-00-4.
ATC — V03AB14.
ATC Vet — QV03AB14.
UNII — 72G3UY6T4N.

Protamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Protamina; Hidrocloruro de protamina; Protamiinihydrokloridi; Protamina, hidrocloruro de; Protamine, chlorhydrate de; Protamin-hidroklorid; Protaminhydrochlorid; Protaminhydroklorid; Protamini Hydrochloridum; Protamino hidrochloridas; Протамина Гидрохлорид.
ATC — V03AB14.
ATC Vet — QV03AB14.
UNII — 5URD19Y60H.

Protamine Sulfate *(BAN, rINN)*

Protamiinisulfaatti; Protamin Sulfat; Protamina Solfato; Protamina, sulfato de; Protamine, Sulfate de; Protamine Sulphate; Protamini Sulfas; Protamino sulfatas; Protaminsulfat; Protamin-sulfát; Protamin-szulfát; Protaminy siarczan; Solfato di Protamina; Sulfato de protamina; Протамина Сульфат.
CAS — 9009-65-8.
ATC — V03AB14.
ATC Vet — QV03AB14.
UNII — 0DE9724IHC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Protamine Sulfate). A mixture of the sulfates of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Protamine Sulfate). A purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish. Store at 2 degrees to 8 degrees in airtight containers.

Uses and Administration

Protamine is a basic protein that combines with heparin to form a stable inactive complex. Protamine is used to neutralise the anticoagulant action of heparin in the treatment of haemorrhage resulting from severe heparin or low-molecular-weight heparin overdosage. It is also used to neutralise the effect of heparin given before surgery and during extracorporeal circulation as in dialysis or cardiac surgery. Protamine is usually given as the sulfate, although the hydrochloride may also be used.

Protamine sulfate is usually given by slow intravenous injection over about 10 minutes. The dose is dependent on the amount and type of heparin to be neutralised and ideally should be titrated against the coagulability of the patient's blood. Protamine has weak anticoagulating properties and if given in excess its anticoagulant action could be significant. Not more than 50 mg of protamine sulfate should be injected for any one dose; patients should be carefully monitored as further doses may be required.

For *unfractionated heparin* the Ph. Eur. 8 specifies that 1 mg of either protamine hydrochloride or protamine sulfate precipitates not less than 100 units of heparin, assayed against a specific reference batch of heparin sodium. UK licensed product information states that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous). US licensed product information states that each mg of protamine sulfate neutralises not less than 100 USP units of heparin. As heparin is being continuously excreted the dose should be reduced if more than 15 minutes have elapsed since intravenous heparin injection; for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Alternative regimens may be necessary if heparin has been given subcutaneously or by continuous intravenous infusion. To neutralise heparin given by intravenous infusion, the heparin infusion should be stopped and 25 to 50 mg protamine sulfate given by slow intravenous injection. If heparin was given subcutaneously, 1 mg of protamine sulfate should be given for each 100 units of mucous heparin, as a slow intravenous injection of protamine sulfate 25 to 50 mg with the remainder infused over 8 to 16 hours.

For *low-molecular-weight heparins*, protamine neutralises the anti-thrombin activity but only partially neutralises the anti-factor-Xa effect; 1 mg of a protamine salt is stated to inhibit the effects of about:

- 71 units of bemiparin sodium
- 80 to 120 units of certoparin sodium
- 100 units of dalteparin sodium
- 1 mg (100 units) of enoxaparin sodium
- 82 units of reviparin sodium
- 100 units of tinzaparin sodium

The dose of protamine may need to be reduced if time has elapsed since the last dose of low-molecular-weight heparin. There may be prolonged absorption from subcutaneous injection of low-molecular-weight heparins and intermittent injection or continuous infusion of protamine sulfate may be useful.

Protamine is used in some insulin preparations to prolong the effects of insulin.

Haemorrhagic disorders. Endogenous production of heparin-like substances may, rarely, be responsible for some bleeding disorders. It has been suggested that protamine could be useful as a diagnostic aid *in vitro* and could be given intravenously for transient control of bleeding in such patients.[1,2]

1. Tefferi A, *et al.* Circulating heparin-like anticoagulants: report of five consecutive cases and a review. *Am J Med* 1990; **88:** 184–8.
2. Bayly PJM, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73:** 840–2.

Adverse Effects and Precautions

Intravenous injection of protamine, particularly if given rapidly, may cause hypotension and bradycardia. Dyspnoea, a sensation of warmth, transient flushing, nausea and vomiting, back pain, and lassitude may also occur. Anaphylactoid reactions have been reported including circulatory collapse and myocardial infarction, capillary leak, pulmonary and systemic hypertension, angioedema, and respiratory distress syndrome. Fatal anaphylaxis has occurred. Reactions are more likely after rapid injection, large doses, or repeated dosing. Patients at risk include diabetics who have received protamine-insulin preparations, those who have previously received protamine (including those who have undergone procedures such as coronary angioplasty or cardiopulmonary bypass surgery where protamine is frequently used), and those allergic to fish. Men who are infertile or who have had a vasectomy may be at increased risk since they may have antibodies to protamine. Severe left ventricular dysfunction and abnormal pulmonary haemodynamics may also be risk factors.

Protamine has an anticoagulant effect when given in the absence of heparin or at doses in excess of those required to neutralise heparin.

When repeated doses of protamine are used to neutralise large doses of heparin, rebound bleeding which responds to further doses of protamine, may occur. Clotting parameters should be closely monitored in patients receiving such prolonged therapy.

Effects on the cardiovascular system. In a review of the toxicity of protamine,[1] adverse cardiovascular responses were considered to be of 3 types: transient hypotension related to rapid drug administration, occasional anaphylactoid responses, and rarely, catastrophic pulmonary vasoconstriction. Severe adverse reactions including marked hypotension, vascular collapse, and pulmonary oedema were described in 4 patients given protamine sulfate after cardiac surgery.[2] Previous reports of similar reactions to protamine were reviewed. A total of 17 patients had immediate anaphylactic reactions; a complement-dependent IgG antibody-mediated reaction had been found in 1 patient and 3 patients tested for allergy to protamine had positive skin tests. In 15 of these 17 patients there was evidence of previous exposure to protamine. Suspected reactions to protamine occurred in a further 10 patients after cardiac surgery. However, these reactions were characterised by severe vascular damage, manifested as noncardiogenic pulmonary oedema or persistent hypotension, and onset was delayed for 30 minutes to several hours. Evidence suggested that these reactions were not antibody mediated; only 2 of 7 evaluable patients had previous exposure. All patients required aggressive therapy. A systematic review[3] noted that serious anaphylactic reactions to protamine appeared to be rare (fewer than 1% of treated patients) although evidence was patchy and largely anecdotal; the most common predisposing factor appeared to be treatment with protamine-containing insulin preparations.

1. Horrow JC. Protamine: a review of its toxicity. *Anesth Analg* 1985; **64:** 348–61.
2. Holland CL, *et al.* Adverse reactions to protamine sulfate following cardiac surgery. *Clin Cardiol* 1984; **7:** 157–62.
3. Nybo M, Madsen JS. Serious anaphylactic reactions due to protamine sulfate: a systematic literature review. *Basic Clin Pharmacol Toxicol* 2008; **103:** 192–6.

Pregnancy. Although data are scarce, there are reports of the use of protamine in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Denpru; ***Hong Kong***: Prosulf; ***India***: Neutrahep; Newtain; Prota; ***Israel***: Prosulf; ***UK***: Prosulf†.

Pharmacopoeial Preparations
BP 2014: Protamine Sulphate Injection;
USP 36: Protamine Sulfate for Injection; Protamine Sulfate Injection.

Prussian Blue

Albastru de Berlin; Azul da Prússia; Azul de Prusia; Berlin Blue; Berliner Blau; Berlinerblått; Blau de Prússia; Bleu de Prusse; Błękit Pruski; Blu di Prussia; CI Pigment Blue 27; Colour Index No. 77510; Ferric Ferrocyanide; Ferric Hexacyanoferrate (II); Hexacianoferrato férrico; Insoluble Prussian Blue; Karaliaučiaus Mėlis; Preussinsininen; Pruisisch Blauw; Prussian Blue Insoluble (USAN); Prøyssisk Blå; Прусская Лазурь; Прусская Синь.
$Fe_4[Fe(CN)_6]_3$=859.2
CAS — 14038-43-8 (insoluble Prussian blue); 12240-15-2 (soluble Prussian blue); 25869-00-5 (soluble Prussian blue).
ATC — V03AB31.
ATC Vet — QV03AB31.
UNII — TLE294X33A.

NOTE. Prussian blue is available in several forms and it is not always clear from the literature which form is being referred to. CI Pigment Blue 27 has been used for both insoluble ferric hexacyanoferrate (II) (Colour Index No. 77510) and the soluble potassium, sodium, or ammonium ferric hexacyanoferrate (II) salts

Profile

Prussian blue is used in the treatment of thallium poisoning (see p. 2628.3) and for known or suspected internal contamination with radiocaesium. When given orally it forms a non-absorbable complex with thallium or caesium in the gastrointestinal tract and increases their elimination from the body; it may also bind other elements and patients should be monitored for electrolyte imbalances. Prussian blue may cause constipation and a fibre-based laxative is

recommended; mannitol is also used. Prussian blue may be mixed with food or liquid when given orally, but this may result in blue discoloration of the mouth and teeth.

The usual dose of Prussian blue is 250 to 300 mg/kg daily, or about 20 g daily given in divided doses either orally or by nasogastric tube. In the USA, a lower oral dose of 3 g three times daily is recommended; in radiocaesium contamination this can be reduced to 1 or 2 g three times daily once the internal radioactivity has been substantially decreased, which may improve gastrointestinal tolerance. For thallium poisoning, treatment should continue until the urinary excretion of thallium falls to 500 micrograms or less per 24 hours, the urine or blood concentration is less than 10 micrograms/L, or no thallium can be detected in the faeces. For radiocaesium contamination, a minimum of 30 days treatment should be given. For doses in children, see Administration in Children, below.

References.
1. Thompson DF, Church CO. Prussian blue for treatment of radiocesium poisoning. *Pharmacotherapy* 2001; **21:** 1364–7.
2. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22:** 29–40.
3. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; **38:** 1509–14.

Administration in children. Prussian blue is used in the treatment of children with thallium poisoning or for known or suspected internal contamination with radiocaesium. The usual dose of prussian blue is 250 to 300 mg/kg daily given in divided doses either orally or by nasogastric tube. In the USA, an oral dose of 1 g three times daily is recommended for children aged 2 to 12 years of age.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Radiogardase-Cs; ***Ger.***: Antidotum Thallii-Heyl; Radiogardase-Cs; ***Rus.***: Ferrocin (Ферроцин); ***USA***: Radiogardase.

Sevelamer *(BAN, rINN)*

Sevelameeri; Sévélamer; Sevelámero; Sevelamerum; Севеламер.

Allylamine polymer with 1-chloro-2,3-epoxypropane.

CAS — 52757-95-6.
ATC — V03AE02.
ATC Vet — QV03AE02.
UNII — 941N5DUU5C.

Sevelamer Carbonate *(BANM, USAN, rINNM)*

Carbonato de sevelámero; GT-335-012; Sévélamer Carbonate; Sevelameri Carbonas; Севеламера Карбонат.

Allylamine polymer with 1-chloro-2,3-epoxypropane carbonate.

CAS — 845273-93-0.
ATC — V03AE02.
ATC Vet — QV03AE02.
UNII — 9YCX42I8IU.

Sevelamer Hydrochloride *(BANM, USAN, rINNM)*

GT16-026A; Hidrocloruro de sevelámero; Sévélamer, Chlorhydrate de; Sevelameri Hydrochloridum; Sevelámero, hidrocloruro de; Севеламера Гидрохлорид.

Allylamine polymer with 1-chloro-2,3-epoxypropane hydrochloride.

CAS — 182683-00-7.
ATC — V03AE02.
ATC Vet — QV03AE02.
UNII — GLS2PGI8QG.

NOTE. The name sevelamer has been used for both sevelamer and sevelamer hydrochloride.

Uses and Administration

Sevelamer is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure. It is given orally as either the carbonate or the hydrochloride in patients on haemodialysis or peritoneal dialysis; sevelamer carbonate is also used in patients with chronic kidney disease and a high serum-phosphate concentration but not requiring dialysis. The initial dose is 0.8 to 1.6 g of sevelamer carbonate or sevelamer hydrochloride three times daily with each meal, depending on the severity of hyperphosphataemia. Doses should then be adjusted according to serum-phosphate concentrations; the usual maintenance dose is from 0.8 to 4 g with each meal.

References.
1. Tonelli M, *et al.* Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007; **22:** 2856–66.
2. Goldsmith DR, *et al.* Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. *Drugs* 2008; **68:** 85–104.
3. Raggi P, *et al.* Ten-year experience with sevelamer and calcium salts as phosphate binders. *Clin J Am Soc Nephrol* 2010; **5** (suppl 1): S31–S40.
4. Zhang Q, *et al.* Meta-analysis comparing sevelamer and calcium-based phosphate binders on cardiovascular calcification in hemodialysis patients. *Nephron Clin Pract* 2010; **115:** c259–c267.
5. Fishbane S, *et al.* A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. *Am J Kidney Dis* 2010; **55:** 307–15.
6. Barna MM, *et al.* Sevelamer carbonate. *Ann Pharmacother* 2010; **44:** 127–34.
7. Assimon MM, *et al.* The effect of sevelamer hydrochloride and calcium-based phosphate binders on mortality in hemodialysis patients: a need for more research. *Consult Pharm* 2010; **25:** 41–54.
8. Biggar P, Ketteler M. Sevelamer carbonate for the treatment of hyperphosphatemia in patients with kidney failure (CKD III–V). *Expert Opin Pharmacother* 2010; **11:** 2739–50.

Adverse Effects and Precautions

The most common adverse effects associated with sevelamer are gastrointestinal disturbances including constipation; dysphagia and oesophageal tablet retention, intestinal obstruction and perforation, ileus, and diverticulitis have been reported. Other adverse effects include rash and pruritus.

Sevelamer is contra-indicated in patients with hypophosphataemia and in bowel obstruction. Caution is recommended in patients with gastrointestinal disorders such as dysphagia, severe motility disorders, active inflammatory bowel disease, or in those who have had major gastrointestinal surgery as there is limited experience with sevelamer in these patients. A suspension may be preferred to tablet formulations in patients with a history of swallowing disorders.

When switching from other phosphate binders to sevelamer hydrochloride, worsening of metabolic acidosis has occurred, see also below. Sevelamer hydrochloride contains about 180 mg of chloride per gram, and serum chloride may increase during treatment as chloride may be exchanged for phosphorus in the gut. Close monitoring of both chloride and bicarbonate is recommended with sevelamer hydrochloride.

Effects on acid/base balance. Sevelamer hydrochloride has been associated with metabolic acidosis as indicated by reductions in serum-bicarbonate concentrations; this does not seem to be a problem with sevelamer carbonate.[1]

1. Pai AB, Shepler BM. Comparison of sevelamer hydrochloride and sevelamer carbonate: risk of metabolic acidosis and clinical implications. *Pharmacotherapy* 2009; **29:** 554–61.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sevelamer as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Sevelamer has been reported to reduce the bioavailability of ciprofloxacin (see p. 265.2), ciclosporin (see p. 1955.1), mycophenolate (see p. 1965.1), tacrolimus (see p. 1973.3), and levothyroxine (p. 2342.1). It may also affect the bioavailability of other drugs and should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Renagel; ***Austria***: Renagel; Renvela; ***Belg.***: Renagel; Renvela; ***Braz.***: Renagel; ***Canad.***: Renagel; ***Chile***: Renvela; ***Cz.***: Renagel; Renvela; ***Denm.***: Renagel; Renvela; ***Fin.***: Renagel†; ***Fr.***: Renagel; Renvela; ***Ger.***: Renagel; Renvela; ***Gr.***: Renagel; Renvela; ***Hong Kong***: Renagel; ***Hung.***: Renagel; Renvela; ***India***: Foseal; ***Irl.***: Renagel; Renvela; ***Israel***: Renagel; Renvela; ***Ital.***: Renagel; ***Jpn***: Phosblock; Renagel; ***Neth.***: Renagel; Renvela; ***Norw.***: Renagel; Renvela; ***NZ***: Renagel; ***Pol.***: Renagel; ***Port.***: Renagel; Renvela; ***Rus.***: Renagel (Ренагель); ***S.Afr.***: Renagel; ***Singapore***: Renvela; ***Spain***: Renagel; Renvela; ***Swed.***: Renagel; Renvela; ***Switz.***: Renagel; Renvela; ***Thai.***: Renvela; ***Turk.***: Renagel; ***UK***: Renagel; Renvela; ***USA***: Renagel; Renvela.

Sodium Calcium Edetate *(BAN, rINN)*

Calcioedetato de sodio; Calcium Disodium Edathamil; Całcium Disodium Edetate; Calcium Disodium Ethylenediaminetetra-acetate; Calcium Disodium Versenate; Calcium édétate de sodium; Calcium EDTA; Disodium Calcium Tetracemate; E385; Edetan sodno-vápenatý hydrát; Edetate Calcium Disodium (USAN); Edetato cálcico disódico; Edetato de calcio y sodio; Kalcium-nátrium-edetát; Natrii Calcii Edetas; Natrii Calcii Edetas Hydricus; Natrio-kalcio edetatas; Natriumcalciumedetat; Natriumkalciumedetat; Natriumkalsiumedetaatti; Sodium, calcium édétate de; Sodium Calciumedetate; Sodu wapnia edetynian; Sodyum Kalsiyum Edetat; Wapniowo-disodowy edetynian; Натрия Кальция Эдетат.

The calcium chelate of disodium ethylenediaminetetraacetate; Disodium[(ethylenedinitrilo)tetraacetato]calciate(2-) hydrate.

$C_{10}H_{12}CaN_2Na_2O_8.xH_2O$=374.3 (anhydrous)

CAS — 62-33-9 (anhydrous sodium calcium edetate); 23411-34-9 (sodium calcium edetate hydrate).
UNII — 25IH6R4SGF (sodium calcium edetate); 8U5D034955 (anhydrous sodium calcium edetate).

NOTE. Do not confuse with sodium edetate; see Inappropriate Administration under Sodium Edetate, p. 1551.2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Calcium Edetate). A white or almost white, hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 6.5 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Edetate Calcium Disodium). White, slightly hygroscopic, odourless, crystalline powder or granules. Freely soluble in water. pH of a 20% solution in water is between 6.5 and 8.0. Store in airtight containers.

Incompatibility. See under Edetic Acid, p. 1550.3. Sodium calcium edetate solution is also incompatible with the following solutions for injection:

- amphotericin B
- glucose 10%
- hydralazine hydrochloride
- invert sugar 10% in sodium chloride 0.9%
- Ringer's solution and lactated Ringer's solution
- sodium lactate 1.9%

Uses and Administration

Sodium calcium edetate is the calcium chelate of disodium edetate and is a chelator used in the treatment of lead poisoning (p. 2542.1). It mobilises lead from bone and tissues and aids elimination from the body by forming a stable, water-soluble, lead complex which is readily excreted by the kidneys. It may be used as a diagnostic test for lead poisoning but measurement of blood-lead concentrations is generally preferred.

Sodium calcium edetate is also a chelator of other heavy-metal polyvalent ions, including chromium, and has been used in the treatment of poisoning by radioactive metals such as plutonium.

Sodium calcium edetate is also used as a pharmaceutical excipient and as a food additive.

In the treatment of lead poisoning, sodium calcium edetate may be given by intramuscular injection or by intravenous infusion. Although the intravenous route is generally preferred, intramuscular injection may be considered for patients with lead encephalopathy and cerebral oedema as rapid infusion can increase intracranial pressure. Sodium calcium edetate may initially aggravate the symptoms of lead toxicity due to mobilisation of stored lead and it has often been given with dimercaprol (p. 1549.3) in patients who are symptomatic; the first dose of dimercaprol should preferably be given at least 4 hours before the sodium calcium edetate.

For intravenous infusion, sodium calcium edetate should be diluted with glucose 5% or sodium chloride 0.9% to a concentration of not more than 3%. Alternatively, sodium calcium edetate may be given intramuscularly in equally divided doses 8 to 12 hours apart. Intramuscular injection of sodium calcium edetate is painful and lidocaine or procaine should be added to a final concentration of 0.5% to minimise pain.

In the UK, the usual dose of sodium calcium edetate for severe toxicity or encephalopathy is 80 mg/kg daily in 2 divided doses, or 75 mg/kg once daily, by intravenous infusion over at least 1 hour. In the USA and some other countries, a dose of 1 g/m^2 daily by intravenous infusion over 8 to 12 hours or by intramuscular injection is suggested for asymptomatic patients; a daily dose of 1.5 g/m^2 given intramuscularly in divided doses may be used with dimercaprol in patients with symptomatic poisoning. Treatment is given for up to 5 days, repeated if necessary usually after an interval of at least 2 days. Any further treatment with sodium calcium edetate should then not be given for at least 7 days.

As excretion is mainly renal, an adequate urinary flow must be established and maintained during treatment. For administration in renal impairment or when there is lead nephropathy, see p. 1574.1.

Administration in children. Sodium calcium edetate is used in children as a chelator in the treatment of lead

poisoning. Children absorb considerably more ingested lead than adults and are at greater risk of developing toxicity such as encephalopathy. Some recommend intramuscular injection as the preferred route (the intravenous route has been associated with fatalities in some young children); however, it is painful and others recommend the intravenous route where possible. Last available guidance from the *American Academy of Pediatrics* considered that intravenous administration was safe and more appropriate than the intramuscular route in children; slow infusion over several hours or a continuous infusion were recommended.[1] Doses are similar to those used in adults, see p. 1573.3.

1. Anonymous. Treatment guidelines for lead exposure in children. American Academy of Pediatrics Committee on Drugs. *Pediatrics* 1995; **96:** 155–60. [Retired October 2007] Also available at: http://pediatrics.aappublications.org/cgi/reprint/96/1/155 (accessed 31/08/10)

Administration in renal impairment. The dose of sodium calcium edetate should be reduced in patients with mild renal impairment and it should not be used in patients with active renal disease or during periods of anuria. In adults with lead nephropathy, the following daily intravenous or intramuscular doses have been suggested, according to serum-creatinine concentrations:

- 20 to 30 micrograms/mL: 500 mg/m² daily for 5 days
- 30 to 40 micrograms/mL: 500 mg/m² every 48 hours for 3 doses
- above 40 micrograms/mL: 500 mg/m² once weekly

These regimens may be repeated at one month intervals.

Adverse Effects

Sodium calcium edetate is nephrotoxic and glycosuria, proteinuria, and microscopic haematuria may occur; renal proximal tubular necrosis has resulted in fatal nephrosis. Glomerular changes occur rarely. Nephrotoxicity appears to be dose dependent. Thrombophlebitis has followed intravenous infusion, particularly if given rapidly or if a concentrated solution is used. Pain at the intramuscular injection site has been reported. Other adverse effects that have been reported include gastrointestinal disturbances such as nausea and diarrhoea, abdominal pain, chills, fever, malaise, headache, myalgia, arthralgia, histamine-like responses such as sneezing, nasal congestion, and lachrymation, transient hypotension, cardiac rhythm irregularities, mild increases in hepatic enzyme values, tremor, numbness, tingling, cheilosis, rash, transient bone marrow depression, anaemia, and excessive thirst.

Sodium calcium edetate chelates trace metals such as zinc within the body and zinc deficiency has been reported. Displacement of calcium from sodium calcium edetate may lead to hypercalcaemia.

Effects on the kidneys. Of 130 children with lead poisoning who received chelation therapy with sodium calcium edetate (25 mg/kg intramuscularly every 12 hours) and dimercaprol (3 mg/kg intramuscularly every 4 hours) for a total of 5 days, 21 developed clinical evidence of nephrotoxicity and in 4 severe oliguric acute renal failure began 1 or 2 days after chelation therapy was discontinued.[1] Nephrotoxicity was probably attributable to the use of sodium calcium edetate.

1. Moel DI, Kumar K. Reversible nephrotic reactions to a combined 2,3-dimercapto-l-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels. *Pediatrics* 1982; **70:** 259–62.

Precautions

Sodium calcium edetate should be used with caution, if at all, in patients with renal impairment (see also Administration in Renal Impairment, above). It is also not recommended in those with hepatitis. Urinalysis, serum electrolytes, and renal and hepatic function should be monitored frequently during treatment. ECG monitoring is recommended during intravenous therapy.

Sodium calcium edetate can chelate several endogenous metals, including zinc, and may increase their excretion; therapy should be intermittent to prevent severe deficiency developing and monitoring of zinc levels may be required (see below).

Sodium calcium edetate should not be given orally in the treatment of lead poisoning as it has been suggested that absorption of lead may be increased as a result.

Pregnancy. Although data are scarce, there are reports of the use of sodium calcium edetate for poisoning in the second or third trimester of pregnancy, without adverse effects on the neonate.[1,2]

1. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; **3:** 37–9.
2. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Trace metal depletion. Sodium calcium edetate 500 mg/m² was given by deep intramuscular injection every 12 hours for 5 days to 10 children with asymptomatic lead poisoning.[1] As well as reducing blood-lead concentrations, sodium calcium edetate also produced a marked fall in the mean plasma-zinc concentration but this rebounded rapidly after the end of treatment. Mean urinary-zinc excretion increased about seventeenfold during the first 24 hours of therapy. Sodium calcium edetate had little effect on the plasma concentrations or urinary excretion of copper. The results suggested that careful monitoring of zinc was required during treatment with sodium calcium edetate.

1. Thomas DJ, Chisolm JJ. Lead, zinc and copper decorporation during calcium disodium ethylenediamine tetraacetate treatment of lead-poisoned children. *J Pharmacol Exp Ther* 1986; **239:** 829–35.

Pharmacokinetics

Sodium calcium edetate is poorly absorbed from the gastrointestinal tract. It distributes mainly to the extracellular fluid and does not penetrate cells. It is not significantly metabolised but is excreted by the kidneys. The half-life is about 20 to 60 minutes, with about 50% of a dose is excreted in the urine in 1 hour and over 95% in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Ledclair; ***India***: Ledcure; ***Irl.***: Ledclair†; ***Turk.***: Libenta; ***UK***: Ledclair.

Multi-ingredient Preparations. ***Arg.***: Calcium C.

Pharmacopoeial Preparations
BP 2014: Sodium Calcium Edetate Infusion;
USP 36: Edetate Calcium Disodium Injection.

Sodium Cellulose Phosphate

Cellulose Sodium Phosphate (USAN); Celulosa, fosfato sódico de; Целлюлозы Фосфат Натрия.
CAS — 9038-41-9; 68444-58-6.
ATC — V03AG01.
ATC Vet — QV03AG01.
UNII — E6S1NJ4Y5Q.

Pharmacopoeias. In *US.*

USP 36: (Cellulose Sodium Phosphate). It is prepared by the phosphorylation of alpha cellulose. A free-flowing, cream-coloured, odourless, powder. Insoluble in water, in dilute acids, and in most organic solvents. The pH of a filtrate of a 5% mixture in water is between 6.0 and 9.0. The inorganic bound phosphate content is not less than 31.0% and not more than 36.0%; the free phosphate content is not more than 3.5%; and the sodium content is not less than 9.5% and not more than 13.0%, all calculated on the dried basis. The calcium binding capacity, calculated on the dried basis, is not less than 1.8 mmol per g.

Profile

Sodium cellulose phosphate, the sodium salt of the phosphate ester of cellulose, is a cation-exchange resin that exchanges sodium ions for calcium and other divalent cations. When given orally, it binds calcium ions within the stomach and intestine to form a non-absorbable complex which is excreted in the faeces. Theoretically a 5-g dose will bind about 350 mg calcium. It has been used in the treatment of absorptive hypercalciuria with recurrent formation of calcium-containing renal calculi (p. 2350.3), and in hypercalcaemia associated with osteopetrosis, sarcoidosis, idiopathic hypercalcaemia of infancy, and vitamin D intoxication.

Diarrhoea and other gastrointestinal disturbances have been reported with sodium cellulose phosphate. It should not be given to patients with primary or secondary hyperparathyroidism, hypomagnesaemia, hypocalcaemia, bone disease, or enteric hyperoxaluria, and it should be used cautiously in pregnant women and children, since they have high calcium requirements. Patients should be monitored for electrolyte disturbances.

Interactions. Sodium cellulose phosphate binds with calcium and other cations. Use with calcium or magnesium salts, including cation-donating antacids or laxatives, may reduce its efficacy. Magnesium supplements are often required in patients receiving sodium cellulose phosphate but should be given at least one hour before or after any dose of the resin since the absorption of the magnesium may otherwise be impaired.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Calcibind†.

Pharmacopoeial Preparations
USP 36: Cellulose Sodium Phosphate for Oral Suspension.

Sodium Nitrite

Azotan(III) Sodu; Dusitan sodný; E250; Natrii nitris; Natrio nitritas; Natrium Nitrit; Natrium Nitrosum; Natriumnitriet; Natriumnitriitti; Natriumnitrit; Nátrium-nitrit; Natriumnitritt; Nitrit de Sodi; Nitrit de Sodiu; Nitrito de Sódio; Nitrito de Sodio; Nitrito di Sodio; Nitrito sódico; Sodio Nitrito; Sodium, nitrite de; Sodu azotyn; Sodyum Nitrit; Нитрит Натрия; Азотистокислый Натрий.
$NaNO_2$=68.99
CAS — 7632-00-0.
ATC — V03AB08.
ATC Vet — QV03AB08.
UNII — M0KG633D4F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8 (Sodium Nitrite). Hygroscopic, colourless crystals or mass, or yellowish rods. Freely soluble in water; soluble in alcohol. Store in airtight containers.

USP 36: (Sodium Nitrite). A white to slightly yellow granular powder, or white or practically white, opaque fused masses or sticks. It is deliquescent in air. Soluble 1 in 1.5 of water; sparingly soluble in alcohol. Its solutions are alkaline to litmus. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Sodium nitrite is used with sodium thiosulfate in the treatment of severe cyanide poisoning (p. 2156.2). Sodium nitrite produces methaemoglobin which preferentially combines with cyanide ions to form cyanmethaemoglobin, thereby displacing cyanide from cytochrome oxidase and restoring aerobic metabolism. As cyanide dissociates from methaemoglobin, it is converted to relatively non-toxic thiocyanate which is excreted in the urine; sodium thiosulfate is given as a sulfur donor, accelerating the conversion of cyanide to thiocyanate. Sodium nitrite may also enhance cyanide clearance by vasodilatation.

The usual dosage regimen is 300 mg of sodium nitrite (10 mL of a 3% solution) given intravenously over 2 to 20 minutes followed by 12.5 g of sodium thiosulfate (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over 10 minutes. The methaemoglobin concentration should not be allowed to exceed 30 to 40%. If symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses. However, the *UK National Poisons Information Service* considers the risk of methaemoglobinaemia to be excessive with a second dose of sodium nitrite and recommends that only the sodium thiosulfate be repeated if necessary. In patients with anaemia, the sodium nitrite dose should be reduced according to the haemoglobin concentration.

For doses in children, see below.

Sodium nitrite has also been suggested in the treatment of hydrogen sulfide poisoning (see p. 1799.2).

Sodium nitrite is used as a rust inhibitor, for example in instrument disinfectants. It is also used as a preservative in foods such as cured meats. Potassium nitrite is also used as a food preservative.

Sodium nitrite generates nitric oxide and is being investigated for the treatment of vaso-occlusive crisis in sickle-cell disease, myocardial ischaemic-reperfusion injury, and cerebral vasospasm.

Administration in children. Sodium nitrite is used in children with sodium thiosulfate for the treatment of cyanide poisoning. The usual regimen for children from 1 month to 18 years is sodium nitrite 4 to 10 mg/kg to a maximum of 300 mg (0.13 to 0.33 mL/kg of a 3% solution, maximum 10 mL) by intravenous injection over 5 to 20 minutes, followed by sodium thiosulfate 400 mg/kg to a maximum of 12.5 g (as a 25 or 50% solution) by intravenous injection over 10 minutes. US licensed product information suggests a lower dose of sodium thiosulfate 250 mg/kg (as a 25% solution), and warns that neonates and infants under 6 months of age may be particularly susceptible to methaemoglobinaemia with sodium nitrite. As in adults (see Uses, above), doses may need to be reduced in children with anaemia.

Adverse Effects and Precautions

Sodium nitrite may cause nausea and vomiting, abdominal pain, dizziness, headache, cyanosis, tachypnoea, and dyspnoea. Blurred vision, confusion, anxiety, diaphoresis, fatigue, and generalised numbness or tingling have also been reported. Vasodilatation has resulted in syncope, hypotension, and tachycardia; arrhythmias, cardiovascular collapse, coma, convulsions, and death have occurred in overdose.

Nitrites readily oxidise haemoglobin to methaemoglobin, causing methaemoglobinaemia. Methaemoglobin concentrations should be monitored and oxygen given during sodium nitrite treatment. Caution is needed when sodium nitrite is given with other drugs that may cause methaemoglobinaemia such as procaine and sodium nitroprusside, and when used in patients with, or at high risk of, methaemoglobinaemia including those with congenital methaemoglobin reductase deficiency, neonates and infants under 6 months of age, and those with pre-existing anaemia; dose reductions should be considered in anaemic patients, see Uses and Administration, p. 1574.3. Care is also required in patients with diminished oxygen or cardiovascular reserves such as those with smoke inhalation or substantial blood loss. Patients with G6PD deficiency may be at increased risk of haemolysis with sodium nitrite.

Blood pressure should be monitored when giving sodium nitrite as rapid injection can cause hypotension. It should be used cautiously with other drugs that reduce blood pressure or volume, or that cause vasodilatation, such as antihypertensives, diuretics, and phosphodiesterase type-5 inhibitors. Sodium nitrite is excreted by the kidneys and care is needed when using in patients with renal impairment.

Carcinogenicity. Sodium nitrite is a precursor for the formation of *N*-nitroso compounds such as nitrosamines, many of which are carcinogenic in *animals*. However, data in humans are limited. Occupational exposure to sodium nitrite has been associated with a higher incidence of oesophageal cancer. Sodium nitrite was used as an anticorrosive and coolant fluid in the production of screws, and workers were required to blow excess sodium nitrite solution from screws and so their faces, respiratory tract and alimentary tract were directly exposed; their hands were also soaked in sodium nitrite solution for 8 hours each day. A cohort of 160 workers were exposed for between 16 and 23 years with 21 developing cancer, including 11 cases of oesophageal cancer, in the 30 years of follow-up; there were no malignancies in a cohort of other unexposed workers from the same factory.[1]

1. Xie T-P, *et al*. Long-term exposure to sodium nitrite and risk of esophageal carcinoma: a cohort study for 30 years. *Dis Esophagus* 2011; **24:** 30–2.

Methaemoglobinaemia. Severe methaemoglobinaemia has been reported after consumption of nitrite-contaminated meat,[1-3] inadvertent ingestion of sodium nitrite,[4-8] and intentional overdose.[9]

1. Walley T, Flanagan M. Nitrite-induced methaemoglobinaemia. *Postgrad Med J* 1987; **63:** 643–44.
2. Kennedy N, *et al*. Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; **76:** 367–8.
3. Khan A, *et al*. Deadly meatballs—a near fatal case of methaemoglobinaemia. *N Z Med J* 2006; **119:** U2107. Available at: http://www.nzma.org.nz/journal/119-1239/2107/content.pdf (accessed 26/01/11)
4. Finan A, *et al*. Methaemoglobinaemia associated with sodium nitrite in three siblings. *BMJ* 1998; **317:** 1138–9.
5. Anonymous. Methemoglobinemia following unintentional ingestion of sodium nitrite—New York, 2002. *MMWR* 2002; **51:** 639–42.
6. Chui JSW, *et al*. Nitrite-induced methaemoglobinaemia—aetiology, diagnosis and treatment. *Anaesthesia* 2005; **60:** 496–500.
7. Tung S-P, *et al*. Methaemoglobinaemia secondary to the ingestion of sodium nitrite in mistake for common salt. *Resuscitation* 2006; **70:** 168–9.
8. Maric P, *et al*. Methaemoglobinaemia following ingestion of a commonly available food additive. *Med J Aust* 2008; **188:** 156–8.
9. Harvey M, *et al*. Fatal methaemoglobinaemia induced by self-poisoning with sodium nitrite. *Emerg Med Australas* 2010; **22:** 463–5.

Treatment of Adverse Effects

When toxicity results from the ingestion of nitrites, treatment is supportive and symptomatic; oxygen and methylthioninium chloride may be required for methaemoglobinaemia although methylthioninium chloride should not be given if cyanide poisoning is suspected since cyanide may be displaced. Exchange transfusion may be considered for severe or refractory methaemoglobinaemia.

Pharmacokinetics

Sodium nitrite is rapidly absorbed after oral dosing. In the blood nitrite reacts with haemoglobin, producing methaemoglobin; the peak effect is seen about 30 to 70 minutes after an intravenous dose. About 40% of a dose of sodium nitrite is excreted unchanged in the urine, with the remaining 60% metabolised to ammonia and similar small molecules. Elimination half-life ranges from 21 minutes (intravenous dosing) to 35 minutes (oral ingestion).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Gr.***: Cyanide Antidote Package; ***Ital.***: Citrosil Alcolico Azzuro; ***S.Afr.***: Tripac-Cyano; ***USA***: Cyanide Antidote Package; Nithiodote.

Pharmacopoeial Preparations
USP 36: Sodium Nitrite Injection.

Sodium Polystyrene Sulfonate

Natrii polystyrenesulfonas; Natrii Polystyrensulfonas; Natrio polistirensulfonatas; Natriumpolystyreenisulfonaatti; Natriumpolystyrensulfonat; Natrium-polystyrensulfonát; Natriumpolystyrolsulfonat; Poliestirenosulfonato sódico; Polystyrène sulfonate sodique; Sodium Polystyrene Sulphonate; Sulfonato sódico de poliestireno; Полистирен Сулфонат Натрия.

CAS — 9003-59-2; 9080-79-9; 25704-18-1.
ATC — V03AE01.
ATC Vet — QV03AE01.
UNII — 1699G8679Z.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sodium Polystyrene Sulfonate). An almost white to light brown powder. It contains 9.4 to 11.0% of sodium, calculated with reference to the dried substance. Each g exchanges 2.8 mmol to 3.4 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USP 36: (Sodium Polystyrene Sulfonate). A golden brown, fine, odourless powder containing not more than 10% of water. The sodium content is not less than 9.4% and not more than 11.5%, calculated on the anhydrous basis. Each g exchanges not less than 110 mg and not more than 135 mg of potassium, calculated on the anhydrous basis. Insoluble in water.

Uses and Administration

Sodium polystyrene sulfonate, the sodium salt of sulfonated styrene copolymer with divinylbenzene, is a cation-exchange resin that exchanges sodium ions for potassium ions and other cations in the gastrointestinal tract when given orally or rectally. The exchanged resin is then excreted in the faeces. Each gram of resin exchanges about 3 mmol of potassium *in vitro*, and about 1 mmol *in vivo*.

Sodium polystyrene sulfonate is used to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria, and in dialysis patients (caution is required due to the sodium content). An effect may not be evident for several hours or longer, and in severe hyperkalaemia, where a rapid effect is required, other measures must also be considered (see p. 1777.1).

Serum-electrolyte concentrations should be monitored throughout treatment and doses given according to response.

The usual oral dose is 15 g up to four times daily as a suspension in water or syrup or as a sweetened paste. It should not be given in fruit juices that have a high potassium content.

When oral use is difficult, sodium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 150 mL of water or glucose 10%. The enema should be retained, if possible, for at least 9 hours; higher doses, shorter retention times, and alternative vehicles have also been used. After retention of the enema the colon should be irrigated to remove the resin. Initial therapy may involve both oral and rectal routes.

For doses in children, see below.

Other polystyrene sulfonate resins include calcium polystyrene sulfonate (p. 1541.2), which is used similarly to the sodium resin and potassium polystyrene sulfonate, which has been used in the treatment of hypercalciuria. Aluminium polystyrene sulfonate, ammonium polystyrene sulfonate, and magnesium polystyrene sulfonate have all occasionally been used.

Administration in children. Sodium polystyrene sulfonate is used in neonates and children to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria, and in dialysis patients. It may be given orally as a suspension or paste (see above), or rectally. Each 1 g of sodium polystyrene sulfonate to be given rectally is mixed with 5 to 10 mL of a methylcellulose solution; 5 mL water or glucose 10% may also be used but retention is more difficult. With rectal use the enema should be retained as long as possible and the colon then irrigated to remove the resin. Care is needed with rectal use in children as excessive dosage or inadequate dilution can result in impaction of the resin; however, the oral route is not recommended in neonates.

UK licensed product information recommends a dose of 1 g/kg daily in divided doses, reduced to a maintenance dose of 500 mg/kg daily in divided doses. Alternatively, the *BNFC* suggests doses of 125 to 250 mg/kg three or four times daily; the maximum single dose via the oral route is 15 g. In the USA, licensed product information suggests 1 g of sodium polystyrene sulfonate for each mmol of potassium.

Adverse Effects and Treatment

Gastric irritation, anorexia, nausea, vomiting, constipation, and occasionally diarrhoea may develop during treatment with sodium polystyrene sulfonate. Constipation may be severe; large doses in elderly patients, and rectal use, particularly in children, may result in faecal impaction. Gastrointestinal concretions have occurred after oral use. Intestinal necrosis, which may be fatal, and other serious gastrointestinal effects including bleeding, ulceration, ischaemic colitis, and perforation have also occurred. If constipation develops, sodium polystyrene sulfonate treatment should be stopped until normal bowel function returns (see also Precautions, below).

Serious potassium deficiency can occur with sodium polystyrene sulfonate and signs of severe hypokalaemia may include irritability, confusion, ECG abnormalities, cardiac arrhythmias, and severe muscle weakness. Like other cation-exchange resins, sodium polystyrene sulfonate is not totally selective and its use may result in other electrolyte disturbances such as hypocalcaemia and hypomagnesaemia. Significant sodium retention may also occur.

Effects on the gastrointestinal tract. Colonic necrosis, including some fatalities, has been reported[1-3] after use of enemas containing sodium polystyrene sulfonate in sorbitol. Studies in *animals*[1] suggested that the use of sorbitol was a contributory factor, although failure to irrigate the colon adequately, as recommended by the manufacturer, was also suggested[4,5] as a possible cause. Both colonic[6,7] and upper gastrointestinal necrosis[8] have also been reported after oral or nasogastric sodium polystyrene sulfonate with sorbitol, and there have also been reports of colonic necrosis with oral[9] or rectal[10] sodium polystyrene sulfonate alone.

1. Lillemoe KD, *et al*. Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 1987; **101:** 267–72.
2. Wootton FT, *et al*. Colonic necrosis with Kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989; **111:** 947–9.
3. Rogers FB, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: case report and review of the literature. *J Trauma* 2001; **51:** 395–7.
4. Burnett RJ. Sodium polystyrene-sorbitol enemas. *Ann Intern Med* 1990; **112:** 311–12.
5. Shepard KV. Cleansing enemas after sodium polystyrene sulfonate enemas. *Ann Intern Med* 1990; **112:** 711.
6. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* 1997; **21:** 60–9.
7. McGowan CE, *et al*. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. *South Med J* 2009; **102:** 493–7.
8. Abraham SC, *et al*. Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 2001; **25:** 637–44.
9. Cheng ES, *et al*. Colonic necrosis and perforation following oral sodium polystyrene sulfonate (Resonium A/Kayexelate) in a burn patient. *Burns* 2002; **28:** 189–90.
10. Rugolotto S, *et al*. Necrotizing enterocolitis in a 850 gram infant receiving sorbitol-free sodium polystyrene sulfonate (Kayexalate): clinical and histopathologic findings. *J Perinatol* 2007; **27:** 247–9.

Effects on the lungs. Particles of sodium polystyrene sulfonate were found at autopsy in the lungs of 3 patients who had taken the resin orally and were associated with acute bronchitis and bronchopneumonia in 2 and with early bronchitis in the third.[1] It was suggested that, where possible, it may be preferable to give sodium polystyrene sulfonate rectally, but if it has to be given orally the patient should be positioned carefully to avoid aspiration.

1. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. *Arch Intern Med* 1982; **142:** 379–81.

Precautions

Sodium polystyrene sulfonate should not be given orally to neonates, and is contra-indicated by any route in those with reduced gut motility or obstructive bowel disease. Care is also needed with rectal use in neonates and children in order to avoid impaction of the resin. Treatment should be stopped if clinically significant constipation develops. Although sorbitol has been recommended for the prophylaxis and treatment of constipation, there have been reports of colonic necrosis, including fatalities, in patients given this combination (see Effects on the Gastrointestinal Tract, above) and most licensed product information advises against the use of sorbitol with polystyrene sulfonates. Magnesium-containing laxatives are also contra-indicated (see Interactions, p. 1576.1).

Patients receiving sodium polystyrene sulfonate should be monitored for electrolyte disturbances, especially hypokalaemia. Since serum concentrations may not always reflect intracellular potassium deficiency, symptoms of hypokalaemia should also be watched for and the decision to stop treatment assessed individually.

Use of sodium polystyrene sulfonate can result in sodium overloading and it should be used cautiously in patients with renal failure or conditions requiring a restricted sodium intake, such as heart failure and severe hyper-

tension; calcium polystyrene sulfonate (p. 1541.2) may be preferred in these patients.

After use of sodium polystyrene sulfonate retention enemas, the colon should be irrigated to ensure removal of the resin.

Interactions

Sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, competition for binding sites may reduce the potassium-lowering effect of the resin. In addition, metabolic alkalosis may develop due to binding of the cation by the resin preventing neutralisation of bicarbonate ions in the small intestine. Seizures have been reported due to metabolic alkalosis in a patient with chronic hypocalcaemia of renal failure given magnesium hydroxide with sodium polystyrene sulfonate and use of magnesium-containing laxatives should therefore be avoided.

Ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine (see p. 2342.1) and lithium salts.

Hypokalaemia may exacerbate the adverse effects of digoxin and sodium polystyrene sulfonate should be used with caution in patients receiving cardiac glycosides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Resonium A; ***Austria***: Resonium A; ***Belg.***: Kayexalate; ***Canad.***: K-Exit; Kayexalate; ***Denm.***: Resonium; ***Fin.***: Resonium; ***Fr.***: Kayexalate; ***Ger.***: Anti-Kalium Na; Elutit-Natrium; Resonium A; ***Gr.***: Kayexalate; ***Hong Kong***: Resonium A; ***Hung.***: Resonium A; ***Israel***: Kayexalate; ***Ital.***: Kayexalate; ***Neth.***: Resonium A; ***NZ***: Resonium A; ***Pol.***: Resonium A; ***Port.***: Resonium; ***S.Afr.***: Kexelate; ***Singapore***: Resinsodio; ***Spain***: Resinsodio; ***Swed.***: Resonium; ***Switz.***: Resonium A; ***Thai.***: Kayexalate; Resinsodio†; Resonium A; ***UK***: Resonium A; ***USA***: Kayexalate; Kionex; SPS; ***Venez.***: Kayexalate.

Pharmacopoeial Preparations
USP 36: Sodium Polystyrene Sulfonate Suspension.

Sodium Thiosulfate

Disodium Thiosulfate Pentahydrate; Hiposulfito sódico; Natrii thiosulfas; Natrii Thiosulfas Pentahydricus; Nātrija Tiosulfāts; Natrio tiosulfatas; Natrium Thiosulfuricum; Natriumthiosulfaat; Natriumthiosulfat; Natriumtiosulfaatti; Natriumtiosulfat; Nátrium-tioszulfát; Sodium Hyposulphite; Sodium, thiosulfate de; Sodium Thiosulphate; Sodu tiosiarczan; Sodyum Tiyosülfat; Thiosíran Sodný; Thiosíran sodný pentahydrát; Tiosiarczan Sodu; Tiosíran Sodný; Tiosolfato di Sodio; Tiossulfato de Sódio; Tiosulfat de Sodi; Tiosulfat de Sodiu; Tiosulfato sódico; Тиосульфат Натрия.

$Na_2S_2O_3,5H_2O$=248.2

CAS — 7772-98-7 (anhydrous sodium thiosulfate); 10102-17-7 (sodium thiosulfate pentahydrate).

ATC — V03AB06.

ATC Vet — QV03AB06.

UNII — HX1032V43M (sodium thiosulfate); L0IYT1O31N (anhydrous sodium thiosulfate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Thiosulfate). Colourless transparent crystals; efflorescent in dry air. It dissolves in its own water of crystallisation at about 49 degrees. Very soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH of 6.0 to 8.4. Store in airtight containers.

USP 36: (Sodium Thiosulfate). Large, colourless crystals, or a coarse, crystalline powder. Is deliquescent in moist air and effloresces in dry air at temperatures exceeding 33 degrees. Soluble 1 in 0.5 of water; insoluble in alcohol. Its solutions are neutral or faintly alkaline to litmus. Store in airtight containers.

Incompatibility. Sodium thiosulfate may reduce the activity of some preservatives, including bronopol (p. 1740.3), phenylmercuric salts (see Phenylmercuric Nitrate, p. 1765.2), and thiomersal (p. 1771.3).

Stability. Solutions of sodium thiosulfate 50% stored in air developed cloudiness or a deposit after autoclaving.[1] Addition of sodium phosphate 0.5% or 1.2% improved stability but solutions became cloudy or developed a deposit after 12 and 6 weeks respectively at 25 degrees. Solutions containing sodium bicarbonate 0.5% became cloudy or developed a deposit after 12 weeks at 25 degrees. No significant improvement in stability was obtained when the concentration of sodium thiosulfate was reduced to 30% or 15%, or when the injection was sealed under nitrogen.

1. Anonymous. Sodium thiosulphate injection–effect of additives on stability. *PSGB Lab Rep* P/75/3 1975.

Uses and Administration

Sodium thiosulfate is used in the treatment of cyanide poisoning (p. 2156.2). Sodium thiosulfate may be effective alone in less severe cases of cyanide poisoning or in acrylonitrile poisoning, but it is often used with sodium nitrite (p. 1574.3). Sodium thiosulfate has also been used to prevent cyanide poisoning induced by sodium nitroprusside.

Sodium thiosulfate acts as a sulfur donor for the enzyme rhodanese, which catalyses the conversion of cyanide to relatively non-toxic thiocyanate, and thus accelerates the detoxification of cyanide.

The usual dosage regimen is 300 mg of sodium nitrite (10 mL of a 3% solution) given intravenously over 2 to 20 minutes followed by 12.5 g of sodium thiosulfate (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over 10 minutes. If symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses. However, the *UK National Poisons Information Service* only recommends a further dose of sodium thiosulfate if necessary, since it considers the risk of methaemoglobinaemia to be excessive with a second dose of sodium nitrite. For doses in children, see below.

Sodium thiosulfate is used as an isotonic 4% solution in the management of extravasation of chlormethine and has been tried in the management of extravasation of some other antineoplastics (but see below).

Sodium thiosulfate has been used for its antifungal properties. Sodium thiosulfate and magnesium thiosulfate are included in mixed preparations for a variety of disorders.

Administration in children. Sodium thiosulfate is used in children in the treatment of cyanide poisoning. It may be effective alone in less severe cases of cyanide poisoning or in acrylonitrile poisoning, but it is often used with sodium nitrite. The usual regimen for children from 1 month to 18 years is sodium nitrite 4 to 10 mg/kg to a maximum of 300 mg (0.13 to 0.33 mL/kg of a 3% solution, maximum 10 mL) by intravenous injection over 5 to 20 minutes, followed by sodium thiosulfate 400 mg/kg to a maximum of 12.5 g (as a 25 or 50% solution) by intravenous injection over 10 minutes. However, US licensed product information suggests a lower dose of sodium thiosulfate 250 mg/kg (as a 25% solution).

Antineoplastic toxicity. Sodium thiosulfate may be used in the management of extravasation of chlormethine and some other antineoplastics (although this is a contentious area, see p. 731.3). It is also used to inactivate some antineoplastics before disposal.

Sodium thiosulfate, given by intravenous infusion, has also been investigated for reducing the systemic toxicity of some antineoplastics. It has been reported to reduce the incidence of nephrotoxicity associated with intraperitoneal cisplatin (see Prophylaxis under Effects on the Kidneys, p. 767.3) and to reduce hearing loss associated with carboplatin (see Effects on the Ears, p. 760.1).

Bromate poisoning. Sodium thiosulfate has been used in the treatment of bromate poisoning[1,2] although its clinical efficacy is unclear;[3] it is thought to act by reducing bromate to the less toxic bromide ion, but evidence is lacking.[3,4] Although it has been given orally, this is no longer recommended since toxic sulfide may be formed.[4] However, intravenous sodium thiosulfate may have a role in some clinical circumstances.[4,5]

1. Lue JN, *et al.* Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; **7:** 66–70.
2. Lichtenberg R, *et al.* Bromate poisoning. *J Pediatr* 1989; **114:** 891–4.
3. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 570, 572.
4. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.
5. Johnson CE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 572.

Calciphylaxis. Sodium thiosulfate has been used successfully to treat patients with calcification of skin, soft-tissues, and arterioles (calcific uraemic arteriolopathy). However, controlled studies are lacking.

References.

1. Hayden MR, *et al.* Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. *Cardiovasc Diabetol* 2005; **4:** 4. Available at: http://www.cardiab.com/content/pdf/1475-2840-4-4.pdf (accessed 22/12/09)
2. Bruccueri M, *et al.* Long-term intravenous sodium thiosulfate in the treatment of a patient with calciphylaxis. *Semin Dial* 2005; **18:** 431–4.
3. Araya CE, *et al.* Sodium thiosulfate treatment for calcific uremic arteriolopathy in children and young adults. *Clin J Am Soc Nephrol* 2006; **1:** 1161–6.
4. Baker BL, *et al.* Calciphylaxis responding to sodium thiosulfate therapy. *Arch Dermatol* 2007; **143:** 269–70.
5. Ackermann F, *et al.* Sodium thiosulfate as first-line treatment for calciphylaxis. *Arch Dermatol* 2007; **143:** 1336–7.
6. Subramaniam K, *et al.* Complete resolution of recurrent calciphylaxis with long-term intravenous sodium thiosulfate. *Australas J Dermatol* 2008; **49:** 30–4.
7. Hayden MR, *et al.* Calciphylaxis: calcific uremic arteriolopathy and the emerging role of sodium thiosulfate. *Int Urol Nephrol* 2008; **40:** 443–51.
8. Musso CG, *et al.* Oral sodium thiosulfate solution as a secondary preventive treatment for calciphylaxis in dialysis patients. *Saudi J Kidney Dis Transpl* 2008; **19:** 820–1.
9. Hackett BC, *et al.* Calciphylaxis in a patient with normal renal function: response to treatment with sodium thiosulfate. *Clin Exp Dermatol* 2009; **34:** 39–42.
10. Kalisiak M, *et al.* Calcific uremic arteriolopathy (calciphylaxis): successful treatment with sodium thiosulfate in spite of elevated serum phosphate. *J Cutan Med Surg* 2009; **13** (suppl 1): S29–34.
11. Schlieper G, *et al.* Sodium thiosulfate in the treatment of calcific uremic arteriolopathy. *Nat Rev Nephrol* 2009; **5:** 539–43.
12. Musso CG, *et al.* Use of sodium thiosulfate in the treatment of calciphylaxis. *Saudi J Kidney Dis Transpl* 2009; **20:** 1065–8.
13. Hayden MR, Goldsmith DJ. Sodium thiosulfate: new hope for the treatment of calciphylaxis. *Semin Dial* 2010; **23:** 258–62.
14. Miceli S, *et al.* Sodium thiosulfate not always resolves calciphylaxis: an ambiguous response. *Ren Fail* 2011; **33:** 84–7.

Adverse Effects and Precautions

The toxicity of sodium thiosulfate is low. Hypernatraemia, hypotension, nausea and vomiting, diarrhoea, diuresis, and metabolic acidosis have been reported and are thought to be due to both the intrinsic osmotic properties of sodium thiosulfate, and from thiocyanate which is formed when sodium thiosulfate is used to treat cyanide poisoning. An increased clotting time has occurred 1 to 3 days after use of sodium thiosulfate. A salty taste in the mouth and a warm sensation over the body have also been reported.

Sodium thiosulfate may exacerbate hypertension or oedema and should be used with caution in patients who may have these symptoms such as those with congestive heart failure, liver cirrhosis, renal impairment, and toxaemia of pregnancy.

For other adverse effects associated with the production of thiocyanate, see Adverse Effects, under Sodium Nitroprusside, p. 1497.3.

Pharmacokinetics

Sodium thiosulfate is poorly absorbed from the gastrointestinal tract. After intravenous injection it is distributed throughout the extracellular fluid, and the thiosulfate is oxidised to sulfate or incorporated into endogenous sulfur compounds. Sodium thiosulfate is excreted in the urine with the reported elimination half-life ranging from about 20 minutes to 3 hours.

An intravenous infusion of sodium thiosulfate 12 g/m^2 was given over 6 hours to 8 patients receiving intraperitoneal antineoplastic therapy.[1] The thiosulfate was rapidly eliminated, 95% being excreted within 4 hours of stopping the infusion; on average only 28.5% of the dose was recovered unchanged in the urine. The mean plasma elimination half-life was 80 minutes.

1. Shea M, *et al.* Kinetics of sodium thiosulfate, a cisplatin neutralizer. *Clin Pharmacol Ther* 1984; **35:** 419–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Azufracid; ***Austria***: Schwefelbad Dr Klopfer; ***Canad.***: Adasept; ***Cz.***: Carbotox; ***Fr.***: Desintex Infantile†; Desintex-Choline†; Desintex; Rhino-Sulfuryl; Vagostabyl; ***Ger.***: Lento Nit K; Schwefelbad Dr Klopfer†; ***Gr.***: Cyanide Antidote Package; Efalan; ***Hung.***: Schwefelbad Dr Klopfer†; ***India***: Histaglobulin; ***Ital.***: Antimicotica Solforata†; ***S. Afr.***: Tripac-Cyano; ***USA***: Cyanide Antidote Package; Nithiodote; Tinver; Versiclear.

Pharmacopoeial Preparations
BP 2014: Sodium Thiosulphate Injection;
USP 36: Sodium Thiosulfate Injection.

Succimer *(BAN, USAN, rINN)*

Acide Dimercaptosuccinique; Ácido dimercaptosuccínico; Dimercaptobernsteinsäure; Dimerkaptoravsyre; DIM-SA; DMSA; Kwas Dimerkaptobursztynowy; Succimère; Succimero; Succímero; Succimerum; Suksimeeri; Сукцимер.

meso-2,3-Dimercaptosuccinic acid; (*R**,*S**)-2,3-Dimercaptobutanedioic acid.

$C_4H_6O_4S_2$=182.2

CAS — 304-55-2.

UNII — DX1U2629QE.

Pharmacopoeias. In *Chin.*

Uses and Administration

Succimer is a chelator structurally related to dimercaprol (p. 1549.3). It forms water-soluble chelates with heavy metals and is used in the treatment of lead poisoning (see

p. 1577.1). It has also been used in the treatment of poisoning with other heavy metals such as mercury.

Succimer, labelled with a radionuclide such as technetium-99m (p. 2228.1), is used in nuclear medicine.

In the treatment of lead poisoning, succimer is given orally in a dose of 10 mg/kg or 350 mg/m^2 every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks unless blood-lead concentrations indicate the need for more prompt treatment. For further information on use in children, see below.

Administration in children. Succimer is used in children for the treatment of lead poisoning, see below. It is given orally in the same doses as those used in adults, see p. 1576.3. For young children, succimer capsules can be opened and the succimer beads taken from a spoon or sprinkled on a small amount of soft food and swallowed.

Lead poisoning. Succimer is an effective lead chelator[1,2] and is used in the management of lead poisoning (p. 2542.1). Succimer is also used in children with chronic lead exposure, and various dosage regimens have been studied.[3] It has also been used to lower lead concentrations in neonates with congenital exposure.[4,5]

Treatment is generally only indicated if blood-lead concentrations are greater than 45 micrograms per 100 mL;[6] although short-term studies[7] in children with lower concentrations have shown effective reduction of blood lead, no effect on neurodevelopmental outcome has been shown in follow-up studies[8,9] and treatment of such children remains controversial.

1. Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin Pharm* 1991; **10:** 914–22.
2. Bradberry S, Vale A. Dimercaptosuccinic acid (succimer; DMSA) in inorganic lead poisoning. *Clin Toxicol* 2009; **47:** 617–31.
3. Farrar HC, *et al*. A comparison of two dosing regimens of succimer in children with chronic lead poisoning. *J Clin Pharmacol* 1999; **39:** 180–3.
4. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; **3:** 37–9.
5. Powell ST, *et al*. Succimer therapy for congenital lead poisoning from maternal petrol sniffing. *Med J Aust* 2006; **184:** 84–5.
6. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; **116:** 1036–46. [Re-affirmed Nov 2008] Also available at: http://pediatrics.aappublications.org/cgi/reprint/116/4/1036.pdf (accessed 11/10/05)
7. Besunder JB, *et al*. Short-term efficacy of oral dimercaptosuccinic acid in children with low to moderate lead intoxication. *Pediatrics* 1995; **96:** 683–7.
8. Rogan WJ, *et al*. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001; **344:** 1421–6.
9. Dietrich KN, *et al*. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. *Pediatrics* 2004; **114:** 19–26.

Mercury poisoning. Succimer, given orally, increases the renal excretion of mercury and may be used in mercury poisoning (p. 2556.3). In patients with renal impairment, the succimer-mercury chelate may accumulate, and alternative methods have been tried. Extracorporeal infusion of succimer into the arterial blood line during haemodialysis, a procedure known as extracorporeal regional complexing haemodialysis, produced a substantial clearance of mercury in an anuric patient following intoxication with inorganic mercury.[1] Clearance was about ten times greater than that achieved with haemodialysis after intramuscular dimercaprol.

A study[2] using blood samples from children being treated for lead exposure suggested that succimer had limited efficacy against low-level organic mercury exposure.

1. Kostyniak PJ, *et al*. Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Toxicol* 1990; **9:** 137–41.
2. Cao Y, *et al*. Efficacy of succimer chelation of mercury at background exposures in toddlers: a randomized trial. *J Pediatr* 2011; **158:** 480.e1–485.e1.

Adverse Effects and Precautions

The most commonly reported adverse effects with succimer are gastrointestinal disorders and increases in serum transaminases; flu-like symptoms, drowsiness, and dizziness have also occurred. Mild to moderate neutropenia has been reported in some patients and regular full blood counts are recommended; treatment should be stopped or withheld if severe neutropenia occurs. Rash may also require succimer to be stopped; rechallenge may be considered if continued treatment is necessary. Other adverse effects include headache, a metallic taste, sensorimotor neuropathy, musculoskeletal pain, arrhythmias, proteinuria, rhinitis, and cough. An allergic mucocutaneous reaction has occurred rarely.

Succimer should be used with caution in patients with renal impairment or a history of hepatic disease. Liver function should be measured before starting and at least every week during treatment.

G6PD deficiency. Haemolysis followed use of succimer in one patient with G6PD deficiency, although lead poisoning may have contributed to the reaction. Additionally, succimer did not provoke haemolysis in two G6PD-deficient children. A review concluded that although data were scarce, succimer could probably be given safely to G6PD-deficient patients.[1]

1. Youngster I, *et al*. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33:** 713–26.

Pregnancy. Although data are scarce, there are reports of the use of succimer for poisoning in the second or third trimester of pregnancy, without adverse effects on the neonate.[1,2]

1. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; **3:** 37–9.
2. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; **67:** 133–40.

Pharmacokinetics

Succimer is rapidly but variably absorbed after oral doses. It undergoes rapid and extensive metabolism and is excreted mainly in the urine as metabolites. The succimer-lead chelate is eliminated in the urine and the bile, and undergoes enterohepatic recycling.

References.

1. Dart RC, *et al*. Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. *J Pediatr* 1994; **125:** 309–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Succicaptal; ***Gr.***: Succicaptal; ***USA***: Chemet.

Sucroferric Oxyhydroxide *(USAN)*

PA-21.

Polynuclear iron(III) oxyhydroxide stabilised with sucrose and starches.

$FeHO_2.xC_{12}H_{22}O_{11}.y\ (C_6H_{10}O_5)_n$

CAS — 12134-57-5.

ATC — V03AE05.

Profile

Sucroferric oxyhydroxide is a polynuclear iron (III)-oxyhydroxide stabilised with sucrose and starches. It is used as a phosphate binder for hyperphosphataemia in patients with chronic renal failure requiring haemodialysis. Doses are usually expressed in terms of the iron content; each tablet contains 500 mg of iron, equivalent to about 2.5 g of sucroferric oxyhydroxide. It is given orally in a usual initial dose of one tablet 3 times daily with meals, and then adjusted according to serum-phosphate concentrations in steps of one tablet daily at weekly intervals. The usual daily dose is 3 or 4 tablets. Gastrointestinal adverse effects have occurred, consistent with those commonly seen with oral iron preparations, see Adverse Effects of Iron, p. 2074.1.

References.

1. GeisserP, Philipp E. PA21: a novel phosphate binder for the treatment of hyperphosphatemia in chronic kidney disease. *Clin Nephrol* 2010; **74:** 4–11.
2. Wüthrich RP, *et al*. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; **8:** 280–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Velphoro.

Sugammadex Sodium

(BANM, USAN, rINNM)

Natrii Sugammadexum; Org-25969; Sugammadex sódico; Sugammadex Sodique; Натрий Сугаммадекс.

$C_{72}H_{104}Na_8O_{48}S_8$=2178.0

CAS — 343306-79-6.

ATC — V03AB35.

ATC Vet — QV03AB35.

UNII — ERJ6X2MXV7.

Uses and Administration

Sugammadex sodium is a modified gamma cyclodextrin that is a selective relaxant binding agent used for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. Sugammadex is given via an intravenous injection as the sodium salt, although doses are expressed in terms of the base. Sugammadex 100 mg is equivalent to about 108.78 mg sugammadex sodium.

For routine reversal of rocuronium- or vecuronium-induced blockade, a dose of 2 to 4 mg/kg sugammadex is recommended, depending on the depth of neuromuscular blockade. If re-occurrence of blockade occurs postoperatively, a repeat dose of 4 mg/kg sugammadex may be given.

For immediate reversal of rocuronium-induced blockade, a dose of 16 mg/kg sugammadex is recommended.

For doses in children, see below.

Reviews.

1. Nicholson WT, *et al*. Sugammadex: a novel agent for the reversal of neuromuscular blockade. *Pharmacotherapy* 2007; **27:** 1181–8.
2. Welliver M, *et al*. Discovery, development, and clinical application of sugammadex sodium, a selective relaxant binding agent. *Drug Des Devel Ther* 2008; **2:** 49–59.
3. Yang LPH, Keam SJ. Sugammadex: a review of its use in anaesthetic practice. *Drugs* 2009; **69:** 919–42.
4. Plaud B. Le sugammadex: une nouveauté qui s'inscrit dans le cadre de l'amélioration de la sécurité des patients ou un simple gadget? *Ann Fr Anesth Reanim* 2009; **28** (suppl 2): S64–S69.
5. Kovac AL. Sugammadex: the first selective binding reversal agent for neuromuscular block. *J Clin Anesth* 2009; **21:** 444–53.
6. Abrishami A, *et al*. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 14/12/09).

Administration in children. Sugammadex sodium is used for the routine reversal of rocuronium-induced neuromuscular blockade in children and adolescents aged 2 to 17 years. Intravenous injection of 2 mg/kg sugammadex is recommended once recovery reaches an appropriate stage. For paediatric administration, sugammadex sodium can be diluted in sodium chloride 0.9%, to a concentration of 10 mg/mL.

Adverse Effects and Precautions

The most commonly reported adverse effect after use of sugammadex sodium is dysgeusia, which was mainly seen after high doses. Hypersensitivity reactions, including anaphylaxis, have occurred; reported symptoms include urticaria, erythematous rash, hypotension, tachycardia, and swelling of the tongue and pharynx. Bronchospasm has been reported rarely in patients with pulmonary complications.

Return of neuromuscular blockade has been reported, usually with suboptimal doses; respiratory function should be monitored until adequate spontaneous respiration is restored. If neuromuscular blockade is reversed during continued anaesthesia, additional doses of anaesthetic or opioid may be required if signs of inadequate anaesthesia occur.

Sugammadex is not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) due to a reduced clearance. Use is also not recommended in haemodialysis patients as clearance can be erratic. Patients with severe hepatic impairment should be treated with caution, as sugammadex has not been studied in this population.

Sugammadex should not be used to reverse block induced by nonsteroidal neuromuscular blockers such as suxamethonium chloride or benzylisoquinolinium compounds.

Activated partial thromboplastin time and prothrombin time may be slightly increased with sugammadex and caution is required in patients taking anticoagulants or those with pre-existing coagulopathies (see also Interactions, below).

Interactions

Although no interaction studies have been carried out, theoretically rocuronium or vecuronium could be displaced from the complex formed with sugammadex, resulting in re-occurrence of neuromuscular blockade. Toremifene may delay recovery if given on the same day as the operation. Fusidic acid may delay recovery if given pre-operatively, but is not expected to do so when given postoperatively. Rocuronium or vecuronium may also be displaced by flucloxacillin in intravenous doses of 500 mg or more, delaying recovery when given pre-operatively; such doses should be avoided for 6 hours postoperatively. When these drugs must be used within 6 hours of sugammadex, close monitoring for signs of neuromuscular blockade is recommended.

After reversal of blockade, rocuronium or vecuronium should not be given again for up to 16 hours, depending on the dose of sugammadex used and the intended dose of neuromuscular blocker (UK licensed product information recommends 24 hours). Patients with mild or moderate renal impairment require longer waiting times.

Sugammadex may slightly increase the activated partial thromboplastin time and the prothrombin time, and an additive effect has been noted *in vitro* with vitamin K antagonists, unfractionated heparin, low-molecular-weight heparins, rivaroxaban, and dabigatran. This interaction is not considered clinically relevant in patients on routine postoperative prophylactic anticoagulation, but caution is required in patients on therapeutic anticoagulants or those with pre-existing coagulopathies. If neuromuscular block-

ade is needed again within the recommended waiting time a nonsteroidal neuromuscular blocker should be used.

Sugammadex may interfere with serum progesterone assays.

Hormonal contraceptives. For information on the potential interaction between sugammadex and hormonal contraceptives, see Sugammadex, under Hormonal Contraceptives, p. 2244.1.

Pharmacokinetics

Neither sugamrnadex nor the complex it forms with rocuronium bind to plasma proteins or erythrocytes. Sugammadex is excreted by the kidneys, with 96% of a dose appearing in the urine, mainly as unchanged sugammadex. The elimination half-life in adults is about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bridion; ***Austria***: Bridion; ***Belg.***: Bridion; ***Braz.***: Bridion; ***Chile***: Bridion; ***Cz.***: Bridion; ***Denm.***: Bridion; ***Fr.***: Bridion; ***Ger.***: Bridion; ***Gr.***: Bridion; ***Hung.***: Bridion; ***Irl.***: Bridion; ***Israel***: Bridion; ***Malaysia***: Bridion; ***Neth.***: Bridion; ***Norw.***: Bridion; ***NZ***: Bridion; ***Pol.***: Bridion; ***Port.***: Bridion; ***Rus.***: Bridan (Брай дан); ***Spain***: Bridion; ***Swed.***: Bridion; ***Switz.***: Bridion; ***Turk.***: Bridion; ***UK***: Bridion; ***Ukr.***: Bridion (Брайдан).

Tiopronin *(rINN)*

Thiopronine; Thioproninum; Tioproniini; Tiopronina; Tiopronine; Тиопронин.

N-(2-Mercaptopropionyl)glycine.

$C_5H_9NO_3S$=163.2

CAS — 1953-02-2.

ATC — R05CB12.

ATC Vet — QG04BC90; QR05CB12.

UNII — C5W04GO61S.

Uses and Administration

Tiopronin is a sulfhydryl compound and chelator with properties similar to those of penicillamine (p. 1567.1). It is given orally in the management of cystinuria (below), along with adequate hydration and alkalinisation of the urine, in usual doses of 0.8 to 1 g daily in divided doses. The dose should be adjusted according to the urinary cystine concentration; up to 2 g daily has been given. Tiopronin should be given on an empty stomach. Tiopronin is used in similar doses in rheumatoid arthritis. It has also been used in hepatic disorders and heavy-metal poisoning (including haemosiderosis and Wilson's disease) and formerly as a mucolytic. Tiopronin is being investigated as a neuroprotective agent in subarachnoid haemorrhage.

Cystinuria. Tiopronin may be used as an alternative to penicillamine in the management of cystinuria (p. 1567.2). A multicentre study[1] in 66 patients with cystine nephrolithiasis found that addition of tiopronin in doses of up to 2 g daily (mean 1.193 g) to standard alkali and fluid therapy significantly reduced urinary-cystine concentrations and the rate of new stone formation. Adverse effects were similar to those reported with penicillamine. In the 49 patients previously given penicillamine, it had produced adverse effects in 41, forcing therapy to be stopped in 34, whereas 37 had adverse effects with tiopronin, requiring drug withdrawal in 15. In the remaining 17 patients, 11 had adverse effects with tiopronin and 1 stopped treatment because of proteinuria. However, of the 34 patients who had been unable to tolerate penicillamine, 22 were able to continue treatment with tiopronin.

1. Pak CYC, *et al.* Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol (Baltimore)* 1986; **136:** 1003–8.

Rheumatoid arthritis. Tiopronin has been reported to have activity comparable to that of gold salts[1] and penicillamine[2] in patients with rheumatoid disease, and has been used to treat rheumatoid arthritis (p. 13.2), particularly in patients intolerant of penicillamine.

1. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; **7:** 577–81.
2. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; **57:** 105–11.

Adverse Effects and Precautions

Tiopronin has similar adverse effects and precautions to those of penicillamine (p. 1568.1 and p. 1569.3) but reactions are generally fewer and less severe. Patients who have previously shown toxicity to penicillamine are more likely to develop adverse effects to tiopronin.

Unlike penicillamine, vitamin B_6 deficiency has occurred uncommonly with tiopronin.

Incidence of adverse effects. In a study of 140 patients[1] with rheumatoid arthritis receiving long-term treatment with tiopronin, adverse effects necessitated withdrawal of treatment in 56 patients (40%). The majority of adverse effects occurred within the first 6 months of treatment. The most common were those affecting the skin and mucous membranes (46 patients) including stomatitis, pruritus, erythema, and 1 case of pemphigus. Proteinuria developed in 5 patients and nephrotic syndrome in 3. Haematological disorders developed in 13 patients. Gastrointestinal disorders and ageusia were also reported.

In another study of 74 patients[2] with rheumatoid arthritis adverse effects were reported in 32 patients (43%) and necessitated withdrawal in 24%. The most common adverse effects were ageusia (21%), mucocutaneous lesions (16%), and gastrointestinal disturbances (14%). Haematological disorders occurred in 5 patients and proteinuria in 3 patients.

In a comparative study in 200 patients,[3] treatment was withdrawn due to toxicity in 27% of patients taking tiopronin and 21% of patients treated with gold.

1. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; **57:** 105–11.
2. Ehrhart A, *et al.* Effets secondaires dus au traitement par la tiopronine de 74 polyarthrites rhumatoïdes. *Rev Rhum* 1991; **58:** 193–7.
3. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; **7:** 577–81.

Effects on the blood. Haematological disorders including leucopenia or thrombocytopenia have been reported during long-term studies of tiopronin. Isolated cases of agranulocytosis[1] and bone marrow aplasia[2] have also occurred.

See also Incidence of Adverse Effects, above.

1. Corda C, *et al.* Thiopronin-induced agranulocytosis. *Therapie* 1990; **45:** 161.
2. Taillan B, *et al.* Aplasie médullaire au cours d'une polyarthrite rhumatoïde traitée par tiopronine. *Rev Rhum* 1990; **57:** 443–4.

Effects on the kidneys. Proteinuria developed in 3 patients 4 to 14 months after starting treatment with tiopronin for cystinuria.[1] None of the patients had clinical symptoms of nephrotic syndrome. Renal biopsies in 2 patients showed membranous glomerulonephritis. Proteinuria disappeared in all 3 patients 4 to 5 months after tiopronin was discontinued. However, there was histological evidence of irreversible changes and signs of progressive glomerular lesions in 1 patient.

1. Lindell A, *et al.* Membranous glomerulonephritis induced by 2-mercaptopropionylglycine (2-MPG). *Clin Nephrol* 1990; **34:** 108–15.

Effects on the skin. Mucocutaneous lesions are among the most common adverse effects of tiopronin (see Incidence of Adverse Effects, above). Reversible lichenoid eruptions have been reported[1] in a patient after treatment with tiopronin for 2 years, and may have been due to an immunological reaction to the sulfhydryl group. Lesions resembling pemphigus have also been reported in a few patients[2,3] and may require treatment with a corticosteroid or other immunosuppressant.

1. Kurumaji Y, Miyazaki K. Tiopronin-induced lichenoid eruption in a patient with liver disease and positive patch test reaction to drugs with sulfhydryl group. *J Dermatol* 1990; **17:** 176–81.
2. Trotta F, *et al.* Thiopronine-induced pemphigus vulgaris in rheumatoid arthritis. *Scand J Rheumatol* 1984; **13:** 93–5.
3. Verdier-Sevrain S, *et al.* Thiopronine-induced herpetiform pemphigus: report of a case studied by immunoelectron microscopy and immunoblot analysis. *Br J Dermatol* 1994; **130:** 238–40.

Pharmacokinetics

Tiopronin is absorbed from the gastrointestinal tract; peak plasma concentrations occur 3 to 6 hours after an oral dose. Up to 48% of the dose is reported to be excreted in the urine during the first 4 hours and up to 78% by 72 hours.

References.

1. Carlsson SM, *et al.* Pharmacokinetics of intravenous 2-mercaptopropionylglycine in man. *Eur J Clin Pharmacol* 1990; **38:** 499–503.
2. Carlsson MS, *et al.* Pharmacokinetics of oral tiopronin. *Eur J Clin Pharmacol* 1993; **45:** 79–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Chen Ji Ge (辰吉格); Ding Shu (丁舒); Hai Nuo Xin (海诺欣); Kai Na (凯纳); KaiXiLai (凯西莱); Kang Tong Su (康酮索); Libiqi (力比奇); Nuo Bai Li (诺百力); Nuoning (诺宁); Qie Ling Bao (切灵宝); Tong Da Rui (同达瑞); Wei Chun (维春); ***Fr.***: Acadione; ***Ger.***: Captimer; ***Gr.***: Acadione; Thiola; ***Ital.***: Thiola; Thiosol†; ***USA***: Thiola.

Trientine Dihydrochloride *(BAN, rINNM)*

Cuprid; Dihidrocloruro de trientina; MK-0681; TECZA (base or dihydrochloride); TETA (base or dihydrochloride); TJA-250; Trien Hydrochloride; Trientin Dihidroklorür; Trientina, dihidrocloruro de; Trientine, Dichlorhydrate de; Trientine Hydrochloride (USAN); Trientini Dihydrochloridum; Triethylenetetramine Dihydrochloride; Триентина Дигидрохлорид.

2,2′-Ethylenedi-iminobis(ethylamine) dihydrochloride; *N,N′*-bis(2-Aminoethyl)-1,2-ethanediamine dihydrochloride.

$C_6H_{18}N_4.2HCl$=219.2

CAS — 112-24-3 (trientine); 38260-01-4 (trientine dihydrochloride).

UNII — HC3NX54582.

Pharmacopoeias. In *US.*

USP 36: (Trientine Hydrochloride). A white to pale yellow crystalline powder. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store under an inert gas in airtight containers at 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Trientine is a copper chelator used in the treatment of Wilson's disease (p. 1567.3). It tends to be used in patients intolerant of penicillamine.

Trientine dihydrochloride is given orally, preferably on an empty stomach. In the USA, the usual initial dose is 0.75 to 1.25 g daily in 2 to 4 divided doses; this may be increased to a maximum of 2 g daily if required. In the UK, a dose of 1.2 to 2.4 g daily, in 2 to 4 divided doses, has been recommended. For doses in children, see below.

Trientine is being studied in the prevention of macular oedema after eye procedures, and as an adjunct in cancer chemotherapy.

References.

1. Lu J. Triethylenetetramine pharmacology and its clinical applications. *Mol Cancer Ther* 2010; **9:** 2458–67.

Administration in children. Trientine dihydrochloride is used in children for the treatment of Wilson's disease, particularly in those intolerant to penicillamine.[1] The initial oral dose in the USA is 500 or 750 mg daily in divided doses, increased if necessary to a maximum of 1.5 g daily. Doses are similar in the UK; for children aged 2 to 12 years, the *BNFC* suggests an oral dose of trientine dihydrochloride 600 mg to 1.5 g daily in 2 to 4 divided doses adjusted according to response. Older children can be given the usual adult dose (see above). The dose may be reduced and the frequency of dosing increased if nausea is a problem.

1. Taylor RM, *et al.* EuroWilson Consortium. Triethylene tetramine dihydrochloride (trientine) in children with Wilson disease: experience at King's College Hospital and review of the literature. *Eur J Pediatr* 2009; **168:** 1061–8.

Adverse Effects and Precautions

Trientine may cause headache, dystonia, muscular spasm, myasthenia gravis, gastrointestinal disturbances, rash, and very rarely, anaemia, duodenitis, colitis, and rhabdomyolysis. Trientine can cause excessive excretion of trace metals such as zinc and iron; iron deficiency may occur, see also Interactions, below. Symptoms of SLE have recurred in a patient who had previously reacted to penicillamine. Hypersensitivity reactions including bronchospasm and dermatitis have occurred after prolonged environmental exposure in workers.

Pregnancy. Of 11 pregnancies in 7 women with Wilson's disease treated with trientine, 8 resulted in the delivery of a normal infant. One infant was premature and had a chromosomal defect, isochromosome X, there was one miscarriage associated with a contraceptive coil, and one elective termination. The average duration of treatment with trientine at the time of conception was almost 5 years and treatment was continued throughout pregnancy in most women. There was no significant copper depletion in the infants, and the 8 healthy infants developed normally during follow-up over 3 months to 9 years.[1]

1. Walshe JM. The management of pregnancy in Wilson's disease treated with trientine. *Q J Med* 1986; **58:** 81–7.

Interactions

Trientine may be inactivated in the gastrointestinal tract by binding with metallic ions, and the absorption of iron may be impaired. Iron supplements should be taken at least 2 hours before or after trientine. Other mineral supplements may be similarly affected, and they should generally be avoided. It is recommended that trientine is taken on an empty stomach at least 1 hour apart from any other drug, food, or milk.

Pharmacokinetics

Trientine is rapidly but poorly absorbed from the gastrointestinal tract. Peak plasma concentrations occur up to about 2 hours after an oral dose. There is modest accumulation of trientine and its metabolites after repeated dosing, but it is not expected to be clinically significant. Trientine is extensively metabolised by acetylation with the majority of a dose excreted in the urine as metabolites. The average half-life is estimated to be around 2 to 4 hours.

References.
1. Cho H-Y, *et al.* Pharmacokinetic and pharmacodynamic modeling of a copper-selective chelator (TETA) in healthy adults. *J Clin Pharmacol* 2009; **49:** 916–28.
2. Lu J, *et al.* Pharmacokinetics, pharmacodynamics, and metabolism of triethylenetetramine in healthy human participants: an open-label trial. *J Clin Pharmacol* 2010; **50:** 647–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Singapore***: Syprine; ***USA***: Syprine.

Pharmacopoeial Preparations
USP 36: Trientine Hydrochloride Capsules.

Trimedoxime Bromide *(rINN)*

Bromuro de trimedoxima; Dipyroxime; TMB-4; Trimédoxime, Bromure de; Trimedoximi Bromidum; Тримедоксима Бромид.

1,1′- Trimethylenebis[4-formylpyridinium bromide]dioxime.

$C_{15}H_{18}Br_2N_4O_2$=446.1

CAS — 56-97-3.

UNII — ED0GXI9825.

NOTE. Do not confuse with Trimedoxine, a range of veterinary antibacterial preparations.

Profile

Trimedoxime bromide is a cholinesterase reactivator given with atropine in the treatment of organophosphorus poisoning.

References.
1. Kozer E, *et al.* Pediatric poisoning from trimedoxime (TMB4) and atropine automaticinjectors. *J Pediatr* 2005; **146**: 41–4.
2. Bentur Y, *et al.* Civilian adult self injections of atropine-trimedoxime (TMB4) auto-injectors. *Clin Toxicol* 2006; **44:** 301–6.

Unithiol

DMPS; Unithiolum; Unitiol; Unitioli; Унитиол.

Sodium 2,3-dimercaptopropanesulfonate .

$C_3H_7NaO_3S_3$=210.3

CAS — 4076-02-2.

UNII — 690VN2L7TK.

Profile

Unithiol is a chelator structurally related to dimercaprol (p. 1549.3). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, and inorganic and organic mercury compounds (see below).

In acute mercury poisoning an oral dose of unithiol 1.2 to 2.4 g daily is used. Oral doses are given in 100 to 200 mg portions evenly spaced over 24 hours. When unithiol cannot be given orally, intramuscular or slow intravenous injection can be used; a dose of 250 mg is given every 3 or 4 hours initially and then the frequency reduced daily to 250 mg every 8 to 24 hours from day 5 onwards. In chronic lead or mercury poisoning unithiol is given orally in a dose of 100 mg three or four times daily, increasing if required for severe toxicity.

The *National Poisons Information Service* in the UK prefers intravenous unithiol for the treatment of acute or chronic mercury poisoning, as the bioavailability of the oral formulation is low (about 40%); however, oral use may still be considered in less severe poisoning. A 5-day course of unithiol 30 mg/kg daily is recommended, given intravenously or orally in divided doses. A further treatment course may be considered if necessary based on blood- and urine-mercury concentrations. The same dose is recommended intravenously for the initial treatment of acute and chronic arsenic poisoning; treatment can be continued with oral unithiol once the patient has stabilised.

Reviews.
1. Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; **2:** 317–23.
2. Aposhian HV, *et al.* Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology* 1995; **97:** 23–38.

Arsenic poisoning. Complete recovery, without renal or neurological sequelae, has been reported[1,2] after use of unithiol in patients with potentially lethal acute arsenic poisoning; haemodialysis was also used in 1 patient.[2] Increased urinary arsenic excretion, with some improvement in clinical symptoms, has also been reported[3,4] with unithiol in chronic arsenic toxicity.

1. Moore DF, *et al.* Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). *J Neurol Neurosurg Psychiatry* 1994; **57:** 1133–5.
2. Kruszewska S, *et al.* The use of haemodialysis and 2,3 propanesulphonate (DMPS) to manage acute oral poisoning by lethal dose of arsenic trioxide. *Int J Occup Med Environ Health* 1996; **9:** 111–115.
3. Wax PM, Thornton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. *J Toxicol Clin Toxicol* 2000; **38:** 777–80.
4. Guha Mazumder DN, *et al.* Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *J Toxicol Clin Toxicol* 2001; **39:** 665–74.

Lead poisoning. Unithiol may be used in lead poisoning,[1] although other chelators are generally preferred (p. 2542.1). In a study of 12 children[2] it reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma, although the urinary excretion of lead, copper, and zinc was increased during treatment.

1. Aaseth J, *et al.* Treatment of mercury and lead poisonings with dimercaptosuccinic acid and sodium dimercaptopropanesulfonate: a review. *Analyst* 1995; **120:** 853–4.
2. Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; **235:** 665–9.

Mercury poisoning. Unithiol is used in poisoning with mercury and mercury salts (p. 2556.3) and has been given by various routes. In 7 patients with poisoning due to mercury vapour or mercuric oxide, oral unithiol 100 mg given twice daily for up to 15 days enhanced urinary elimination of mercury;[1] the urinary elimination of copper and zinc was also increased in most patients and 2 developed rashes. A dose of 5 mg/kg intramuscularly three times daily, reduced to once daily by the third day of treatment, effectively reduced the half-life of mercury in the blood after poisoning with methylmercury.[2] A patient with severe mercuric chloride poisoning was treated successfully with unithiol given intravenously for 4 weeks, then orally for 3 weeks.[3] Unithiol has also been used with haemofiltration in patients with inorganic mercury poisoning and acute renal failure.[4,5] It has also proved useful in reversing the neurological symptoms associated with exposure to mercury vapour.[6]

1. Mant TGK. Clinical studies with dimercaptopropane sulphonate in mercury poisoning. *Hum Toxicol* 1985; **4:** 346.
2. Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; **218:** 74–83.
3. Toet AE, *et al.* Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS). *Hum Exp Toxicol* 1994; **13:** 11–16.
4. Pai P, *et al.* Treatment of a case of severe mercuric salt overdose with DMPS (dimercapo-1-propane sulphonate [sic]) and continuous haemofiltration. *Nephrol Dial Transplant* 2000; **15:** 1889–90.
5. Dargan PI, *et al.* Case report: severe mercuric sulphate poisoning treated with 2,3-dimercaptopropane-1-sulphonate and haemodiafiltration. *Crit Care* 2003; **7:** R1–R6.
6. Bradberry SM, *et al.* DMPS can reverse the features of severe mercury vapor-induced neurological damage. *Clin Toxicol* 2009; **47:** 894–8.

Wilson's disease. Unithiol 200 mg twice daily[1] was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease (p. 1567.3) after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride. Unithiol was started in 2 similar patients[1] but both withdrew from treatment, one because of fever and a fall in leucocyte count after a test dose and the other because of intense nausea and taste impairment.

1. Walshe JM. Unithiol in Wilson's disease. *BMJ* 1985; **290:** 673–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Dimaval; ***Ger.***: Dimaval.

Contrast Media

Contrast media are widely used as adjuncts to diagnostic visualisation techniques such as radiography, magnetic resonance imaging, and ultrasound imaging. Although the techniques vary, they are all based on the fact that different tissues within the body have different physical properties, for example their ability to absorb radiation, or their density. These differences can be detected and used to produce images. Contrast media act in varying ways to accentuate the differences between tissues, and enhance the images obtained. There are different types of contrast medium, and choice depends upon the visualisation technique being used, as well as the properties of the individual media. The main groups described below are magnetic resonance contrast media, radiographic contrast media, and ultrasound contrast media.

Magnetic Resonance Contrast Media

Magnetic resonance imaging uses a combination of radiofrequency energy and magnetic fields to produce sectional images of the body. The technique is based on the property of hydrogen nuclei (protons) to absorb energy when aligned in a magnetic field; the energy is then released as the protons relax, generating a signal. Tissues differ in their proton content and factors affecting relaxation, and therefore produce different signals, which can be detected and analysed to produce an image.

Contrast media may be used to enhance magnetic resonance images. The media used are *paramagnetic* or *superparamagnetic* agents that develop magnetic properties when placed in a magnetic field. These properties affect the relaxation of adjacent protons during magnetic resonance imaging, and thus modify the signals produced. Paramagnetic compounds contain gadolinium or manganese and act by increasing relaxation and enhancing the signal. They are used as complexes or chelates to reduce their toxicity; gadopentetic acid is a typical gadolinium chelate, while mangafodipir is the only manganese chelate currently available. Superparamagnetic contrast media, such as ferucarbotran and ferumoxides, contain coated particles of iron compounds and act by interfering with the magnetic field to reduce the signal from proton relaxation.

References.

1. Sands MJ, Levitin A. Basics of magnetic resonance imaging. *Semin Vasc Surg* 2004; **17:** 66–82.
2. Gibby WA. Basic principles of magnetic resonance imaging. *Neurosurg Clin N Am* 2005; **16:** 1–64.
3. McGowan JC. Basic principles of magnetic resonance imaging. *Neuroimaging Clin N Am* 2008; **18:** 623–36.

Radiographic Contrast Media

Radiography (including X-ray imaging, computed tomography, and fluoroscopy) is based on the difference between tissues in the extent to which they absorb X-rays. This depends largely on the density of the tissue, and increasing the difference, or contrast, between specific tissues can enhance the images produced. *Positive contrast* imaging is achieved by introducing a contrast medium into the area of interest to increase the density and enhance absorption of the X-rays. Alternatively, in *negative contrast* imaging, a gas (air, oxygen, or carbon dioxide) may be used to allow the X-rays to penetrate more easily. *Double contrast* uses both a gas and contrast medium together.

Radiographic contrast media are based on elements with high atomic numbers that absorb X-rays. The agents most commonly used are *iodinated organic compounds*, particularly tri-iodinated benzene compounds, and their degree of opacity or radiodensity is directly proportional to their iodine content. *Barium* is another element that absorbs X-rays, and barium sulfate has long been used in radiography. Other heavy atoms have been investigated but acute or chronic toxicity makes most of them unsuitable for use.

Iodinated contrast media may be classified as ionic or nonionic, and as monomeric or dimeric, and there are important differences between them that affect their use. The most important requirements for a contrast medium are that it absorbs X-rays efficiently, that it can be introduced into the area of the body to be visualised, and that it is safe. For iodinated contrast media, the radiodensity depends solely on the iodine concentration, whereas adverse effects are largely dependent on the osmolality of the solution (the number of particles present in a given weight of solution), with low-osmolality solutions being better tolerated. Distribution within the body depends on the pharmacokinetic and physical properties of the contrast medium.

Ionic monomeric media, such as the amidotrizoates, generally have a very high osmolality when given in concentrations suitable for radiographic visualisation, and therefore tend to be associated with a relatively high incidence of adverse effects. Osmolality may be reduced by using an *ionic dimeric* medium, such as adipiodone, which has twice the number of iodine atoms per molecule, or by using a *nonionic monomer*, such as iohexol, which does not dissociate into a cation and anion. *Nonionic dimeric* media, such as iodixanol, are also available and have the best ratio of radiodensity to osmolality; however, they also tend to be more viscous, and this may make them hard to use and affect distribution within the body.

References.

1. Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; **209:** 185–7.
2. Barrs TJ. X-rays and radiopaque drugs. *Am J Health-Syst Pharm* 2005; **62:** 2026–30.

Ultrasound Contrast Media

Ultrasound imaging uses the acoustic properties of different tissues to produce images. Reflection of sound waves (echo) occurs at the interface between tissues with different acoustic properties, particularly where this difference is large, and this can be detected and analysed to produce images. Contrast agents are generally used to enhance the echogenicity of blood and therefore to enable measurement of blood flow in different parts of the body.

Ultrasound contrast media increase echogenicity by providing an interface that reflects sound. Although usually referred to as ultrasound contrast media or *echocontrast* media, the increase in echogenicity may in fact reduce contrast between tissues, and *echo-enhancers* may be a better term. Most ultrasound contrast media consist of microbubbles and provide a gas-liquid interface that reflects sound more effectively than blood alone, allowing blood flow to be more easily detected. The microbubbles may be air or another inert gas, such as perflutren or another perfluorocarbon, and may be either preformed or made at the time of injection. Agitated saline has been used as a simple ultrasound contrast medium, but is only suitable for cardiac imaging since the bubbles lack stability. Microbubbles of air formed during the dissolution of galactose are also used, and may be stabilised by addition of palmitic acid. Other stabilisers may be used, or the microbubbles may be encapsulated to increase the duration of their effect. Substances used for encapsulation include albumin (p. 1130.2) and phospholipids; polycyanoacrylates have also been investigated.

References.

1. Blomley MJK, *et al.* Microbubble contrast agents: a new era in ultrasound. *BMJ* 2001; **322:** 1222–5.
2. Liang H-D, Blomley MJK. The role of ultrasound in molecular imaging. *Br J Radiol* 2003; **76** (special issue): S140–S150.
3. Dijkmans PA, *et al.* Microbubbles and ultrasound: from diagnosis to therapy. *Eur J Echocardiogr* 2004; **5:** 245–56.
4. Dayton PA, Rychak JJ. Molecular ultrasound imaging using microbubble contrast agents. *Front Biosci* 2007; **12:** 5124–42.
5. Klibanov AL. Ultrasound molecular imaging with targeted microbubble contrast agents. *J Nucl Cardiol* 2007; **14:** 876–84.
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Choice of Contrast Medium

Radiography, with and without the use of contrast, has been one of the most widely used diagnostic techniques and remains of great importance. However, concerns about the adverse effects of X-rays, and limitations of the images produced, have led to the increasing use of alternative methods such as ultrasound and magnetic resonance imaging. Choice of technique and use of contrast depends on the area to be visualised, the facilities available, and any patient characteristics affecting the likelihood of adverse effects, such as age and morbidity. Some imaging procedures and the factors affecting choice of technique and use of contrast, including adverse effects, are discussed below.

Uses of contrast media. For **urography** (visualisation of the kidneys and urinary tract) ultrasound is generally the most widely used technique, but radiography still has an important role. Contrast media that are excreted in the urine are used to enhance the images. Suitable media contain small, highly water-soluble molecules, with low protein-binding, that undergo rapid glomerular filtration and passage into the urinary tract. High plasma concentrations are needed to achieve adequate urinary concentrations for visualisation, so they are generally given intravenously. Most ionic iodinated media are suitable and the amidotrizoates have often been used, but lower-osmolality media are usually preferred since they have a lower incidence of adverse effects.

For **angiography** (visualisation of the circulatory system) radiography is still frequently used, particularly to produce dynamic images (fluoroscopy) during invasive procedures, although magnetic resonance angiography may be an alternative. Iodinated contrast media for angiography are similar to those used for urography; the main requirement is for a water-soluble molecule that will be rapidly distributed through the blood vessels. In addition, the solution should be of low viscosity to facilitate rapid injection and of high radiodensity to counteract the diluting effects of the blood. Low cardiotoxicity is particularly important for procedures that require a high concentration of contrast medium, such as angiocardiography or digital subtraction angiography, and low-osmolality media are now generally preferred for all angiographic procedures. Another widely used method for visualising the heart is echocardiography, which uses ultrasound imaging, and microbubble contrast media such as galactose or encapsulated gases (perfluorocarbons or sulfur hexafluoride) may be used to improve the images.

For **gastrointestinal imaging** endoscopy is often the preferred technique, but radiography also has a role. Positive, negative, and double contrast techniques are used. For positive contrast the contrast medium should not be absorbed but should form an even, homogeneous coat on the gastrointestinal mucosa, without interacting with gut secretions or producing misleading radiographic artefacts. The chief contrast medium for this purpose is barium sulfate, and much effort has been devoted to the production of suitable formulations to improve its coating properties and reduce the formation of bubbles, cracks, and other radiographic artefacts. Iodinated contrast media may be used as an alternative, but images tend to be inferior.

For **cholecystography** and **cholangiography** (visualisation of the gallbladder and biliary tract) ultrasound techniques have generally replaced radiography. Where radiography is used, choice of contrast medium depends on the intended procedure and the route. For intra-operative or endoscopic procedures, water-soluble contrast media may be used, but for non-invasive imaging the contrast medium used must be excreted in the bile. This requires a molecule with a free carboxy or other acidic group, since the biliary active transport mechanism is an anion transfer process; the molecule also needs to be large or highly protein-bound to prevent rapid excretion by the kidney. Suitable intravenous media include adipiodone and iotroxic acid. For oral use, absorption from the gastrointestinal tract is also required, and suitable media tend to be smaller molecules that are conjugated with glucuronic acid within the body before excretion in the bile, such as iopanoic acid. For visualisation of lesions within the liver itself, magnetic resonance imaging may be used; contrast media used to enhance the images include ferucarbotran and ferumoxides, as well as gadolinium or manganese chelates.

For **myelography** (visualisation of the structures of the spinal cord) and imaging of other parts of the CNS, magnetic resonance imaging is generally preferred, often with the use of gadolinium chelates such as gadopentetic acid as contrast media. Where radiography is used, the most important requirement for contrast media is low toxicity, and nonionic media are most common.

For **arthrography** (visualisation of the joint capsule) many radiographic contrast media are suitable provided they are well-diluted before use. Magnetic resonance imaging with gadolinium chelates may also have a role.

Bronchography (examination of the bronchial tree) has been performed with oily or aqueous media, such as iopydol or iopydone, instilled through a catheter or bronchoscope to coat the airways; however, other visualisation techniques are generally preferred.

For **hysterosalpingography** (visualisation of the uterus and fallopian tubes) ultrasound and endoscopic techniques are generally used, and microbubble contrast media such as galactose may be used to improve ultrasound images. If radiography is performed, water-soluble iodinated contrast media may be used.

For **lymphography** or **lymphangiography** (visualisation of the lymphatic system) a high radiodensity is required and the contrast medium must be retained within the lymphatic system for long enough to be visualised, requiring particulate, water-insoluble media, or very large molecules. Iodised oil has been most widely used, but adverse effects and limited distribution within the lymphatic system restrict its use.

Adverse effects of contrast media. Although contrast media are generally considered to be very safe, with most adverse effects being mild and transient, more severe and

even life-threatening reactions are possible, and the risk of adverse effects may influence the choice of contrast medium or imaging technique in a particular patient.

Iodinated **radiographic contrast media** all have a similar range of adverse effects (see under Amidotrizoic Acid, p. 1582.1) but the incidence and severity varies. Many of the adverse effects are related to the osmolality of the preparation, and the incidence tends to be lower with those that have low osmolality. Osmolality depends on the number of particles present in the solution; for a given iodine content, this is highest for the ionic monomers and lowest for nonionic dimers, and this is reflected in the incidence of adverse effects. Immediate hypersensitivity reactions also tend to be less frequent with nonionic media (see under Amidotrizoic Acid, p. 1583.1), although these reactions are not directly related to osmolality. However, low-osmolality media tend to be more expensive; while nonionics and dimers are preferred, ionic monomers may still have a role in patients at low risk of adverse effects. Ionic contrast media may also carry a lower risk of thromboembolism (see Effects on the Blood, p. 1582.1).

Magnetic resonance contrast media tend to be safer than iodinated contrast media, although similar general effects may occur. Ionic and nonionic media are available, but this tends to have little influence on the incidence of adverse effects. All gadolinium chelates have similar adverse effects (see under Gadopentetic Acid, p. 1586.2); there is a theoretical risk of gadolinium toxicity due to instability of the chelates and most preparations also contain free chelating agent to reduce this risk. The adverse effects of superparamagnetic iron compounds are described under ferumoxides (p. 1584.2) and ferumoxsil (p. 1584.3).

Ultrasound contrast media are generally safe; minor and transient adverse effects have been reported, but may be due to the procedure rather than to the contrast medium used. Some microbubble ultrasound contrast media such as perflutren (p. 1595.2) and sulfur hexafluoride (p. 1595.3) have been associated with more severe cardiopulmonary reactions.

References.

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8. Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. *Drug Safety* 2006; **29:** 133–41.
9. European Society of Urogenital Radiology. ESUR guidelines on contrast media, version 7.0 (issued August 2008). Available at: http://www.esur.org/Guidelines_gallery.46.0.html (accessed 01/06/09)

Adipiodone *(BAN, rINN)*

Adipiodon; Adipiodona; Adipiodoni; Adipiodonum; Iodipamide; Адипиодон.

3,3′-Adipoyldiaminobis(2,4,6-tri-iodobenzoic acid).

$C_{20}H_{14}I_6N_2O_6$=1139.8

CAS — 606-17-7.

ATC — V08AC04.

ATC Vet — QV08AC04.

UNII — TKQ858A3VW.

Description. Adipiodone contains about 66.8% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Iodipamide). A white, practically odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Meglumine Adipiodone *(rINNM)*

Adipiodona de meglumina; Adipiodone Meglumine (BANM); Adipiodone Méglumine; Dimeglumine Iodipamide; Iodipamide Meglumine; Meglumine Iodipamide; Meglumini Adipiodonum; Меглумина Адипиодон.

The di(*N*-methylglucamine) salt of adipiodone.

$C_{20}H_{14}I_6N_2O_6.(C_7H_{17}NO_5)_2$=1530.2

CAS — 3521-84-4.

ATC — V08AC04.

ATC Vet — QV08AC04.

UNII — X064O0Y1A4.

Description. Meglumine adipiodone contains about 49.8% of I.

Pharmacopoeias. *US* includes only as an injection.

Incompatibility. Incompatibilities have been reported between meglumine adipiodone and some antihistamines.

Uses and Administration

Adipiodone is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1); it is taken up by the liver and excreted in bile, and is used in cholangiography and cholecystography.

Adipiodone is given intravenously as a solution containing 52% of the meglumine salt. The usual dose is about 10 g of meglumine adipiodone, given by slow intravenous injection over about 10 minutes.

A solution of meglumine adipiodone with meglumine diatrizoate is given by intra-uterine instillation for hysterosalpingography.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1. Rapid injection may increase the incidence of adverse effects.

Adipiodone may show some uricosuric activity.

Effects on the liver. Of 149 patients given the recommended dose of adipiodone, 13 developed elevated serum aspartate aminotransferase (SGOT) values; of 126 who received twice the dose, 23 developed elevated values.[1] Hepatotoxicity has also been reported[2-4] on isolated occasions in patients given meglumine adipiodone.

1. Scholz FJ, *et al*. Hepatotoxicity in cholangiography. *JAMA* 1974; **229:** 1724.
2. Stillman AE. Hepatotoxic reaction to iodipamide meglumine injection. *JAMA* 1974; **228:** 1420–1.
3. Sutherland LR, *et al*. Meglumine iodipamide (Cholografin) hepatotoxicity. *Ann Intern Med* 1977; **86:** 437–9.
4. Imoto S. Meglumine hepatotoxicity. *Ann Intern Med* 1978; **88:** 129.

Pharmacokinetics

Meglumine adipiodone is rapidly distributed in extracellular fluid after intravenous injection and is reported to be extensively bound to plasma proteins. It appears in the bile ducts within about 10 to 15 minutes after injection, with peak opacity at about 20 to 30 minutes, and reaches the gallbladder by about 1 hour, peak opacification occurring after about 2 hours. About 80 to 95% is excreted unchanged in the faeces; small amounts are excreted unchanged in urine. A terminal half-life of about 2 hours has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Cholografin; ***USA***: Cholografin.

Multi-ingredient Preparations. ***Canad.***: Sinografin; ***USA***: Sinografin.

Pharmacopoeial Preparations

BP 2014: Meglumine Iodipamide Injection;
USP 36: Iodipamide Meglumine Injection.

Amidotrizoic Acid *(BAN, rINNM)*

Acide Amidotrizoïque; Ácido amidotrizoico; Acidum Amidotrizoicum; Acidum Diatrizoicum; Amidotritsoiinihappo; Amidotrizoesäure-Dihydrat; Amidotrizoesav; Amidotrizoico, ácido; Amidotrizoinė rūgštis; Amidotrizoinsyra; Diatritsoiinihappo; Diatrizoic Acid (USAN); Diatrizoinsyra; Kyselina amidotrizoová; NSC-262168; Амидотризоевая Кислота.

3,5-Diacetamido-2,4,6-tri-iodobenzoic acid.

$C_{11}H_9I_3N_2O_4.2H_2O$=649.9

CAS — 117-96-4 (anhydrous amidotrizoic acid); 50978-11-5 (amidotrizoic acid dihydrate).

ATC — V08AA01.

ATC Vet — QV08AA01.

UNII — 5UVC90J1LK.

Description. Amidotrizoic acid contains about 62% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Amidotrizoic Acid Dihydrate). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Diatrizoic Acid). It is anhydrous or contains two molecules of water of hydration. A white, odourless, powder. Very slightly soluble in water and in alcohol; soluble in dimethylformamide and in alkali hydroxide solutions.

Meglumine Amidotrizoate *(BANM, rINNM)*

Amidotrizoate de Méglumine; Amidotrizoato de meglumina; Diatrizoate Meglumine; Meglumine Diatrizoate; Meglumini Amidotrizoas; Methylglucamine Diatrizoate; Меглумина Амидотризоат.

N-Methylglucamine 3,5-diacetamido-2,4,6-tri-iodobenzoate.

$C_{11}H_9I_3N_2O_4.C_7H_{17}NO_5$=809.1

CAS — 131-49-7.

ATC — V08AA01.

ATC Vet — QV08AA01.

UNII — 3X9MR4N98U.

Description. Meglumine amidotrizoate contains about 47.1% of I.

Pharmacopoeias. In *US.*

USP 36: (Diatrizoate Meglumine). A white, odourless, powder. Freely soluble in water. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Sodium Amidotrizoate *(BANM, rINN)*

Amidotrizoate de Sodium; Amidotrizoato de sodio; Diatrizoate Sodium; Natrii Amidotrizoas; Natrio amidotrizoatas; Natriumamidotritsoaatti; Natriumamidotrizoat; Natrium-amidotrizoát; Nátrium-amidotrizoát; NSC-61815; Sodium, amidotrizoate de; Sodium Diatrizoate; Sodu amidotrizoat; Натрия Амидотризоат.

Sodium 3,5-diacetamido-2,4,6-tri-iodobenzoate.

$C_{11}H_8I_3N_2NaO_4$=635.9

CAS — 737-31-5.

ATC — V08AA01.

ATC Vet — QV08AA01.

UNII — V5403H8VG7.

Description. Sodium amidotrizoate contains about 59.9% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Chin. includes the injection.

Ph. Eur. 8: (Sodium Amidotrizoate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 50% solution in water has a pH of 7.5 to 9.5. Protect from light.

USP 36: (Diatrizoate Sodium). A white, odourless, powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether.

Incompatibility. Incompatibilities of sodium amidotrizoate with some antihistamines have been reported.

Uses and Administration

The amidotrizoates are ionic monomeric iodinated radiographic contrast media (p. 1580.1). Both the sodium and the meglumine salt have been widely used in diagnostic radiography; however, adverse effects may be reduced by using a mixture of both salts, and this is often preferred. Preparations are available containing a wide range of strengths. Mixtures containing sodium amidotrizoate 10% w/v with meglumine amidotrizoate 66% w/v, or sodium amidotrizoate 4% with meglumine amidotrizoate 26%, are commonly used. For use alone, preparations containing sodium amidotrizoate 25 to 50% w/v, or meglumine amidotrizoate 60% w/v, may be appropriate.

The amidotrizoates are used in an extensive range of procedures, although in many cases lower osmolality contrast media are now preferred. The dose and route depend on the procedure and the degree and extent of contrast required. They are given intravenously for urography, for venography, and in computed tomography; for urography, they have also been given by intramuscular or subcutaneous injection, but these routes are not generally recommended. They may be given intra-arterially for angiography, by intra-articular injection for arthrography, or by intra-osseous injection for imaging of the vasculature of the bones. For other procedures they may be instilled into body cavities, or injected into the gallbladder, biliary ducts, or spleen. Amidotrizoates have also been given orally or rectally for imaging of the gastrointestinal tract.

Solutions of amidotrizoates have also been given as an enema in the treatment of uncomplicated meconium ileus.

Calcium amidotrizoate and lysine amidotrizoate have also been used as contrast media.

Gastrointestinal obstruction. Amidotrizoates and other water-soluble contrast media have been given rectally as osmotic agents in the management of gastrointestinal obstruction due to meconium ileus;[1] however, adverse effects have been reported in neonates (see p. 1583.2). They have also been used as an alternative to barium sulfate enemas in the management of intussusception (see under Barium Sulfate, p. 1583.3). Amidotrizoates given orally have been used in the management of adhesive

small bowel obstruction;[2] they allow identification of patients who require surgery and, although they have not been shown to relieve obstruction, they may reduce length of hospital stay in patients treated without surgery.

1. Murshed R, *et al.* Meconium ileus: a ten-year review of thirty-six patients. *Eur J Pediatr Surg* 1997; **7:** 275–7.
2. Abbas S, *et al.* Oral water soluble contrast for the management of adhesive small bowel obstruction. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 14/07/08).

Adverse Effects and Treatment

Amidotrizoates and other iodinated contrast media may cause adverse effects due to direct toxicity, which tends to be dose-related and predictable, but use often leads to unpredictable or anaphylactoid reactions. Most reactions occur within 5 to 10 minutes and are mild and transient; however, severe, life-threatening reactions may also occur, and delayed reactions have been reported.

Direct toxic effects of iodinated contrast media are related to the osmolality of the solutions used and are most common with the amidotrizoates and other ionic monomeric compounds, which have a high osmolality. The route, the speed with which it is given, and the volume, concentration, and viscosity of the solution, also affect the incidence of adverse effects. For ionic media, the cation is also important: meglumine salts are generally better tolerated, but sodium salts have a lower viscosity and may produce fewer arrhythmias, and preparations containing a mixture of the salts are therefore often used. Anaphylactoid reactions are also more common with high-osmolality, ionic contrast media.

The most frequent direct adverse reaction to iodinated contrast media is flushing or a sensation of heat and caused by vasodilatation in response to the osmolality of the solution. Pain at the injection site is also common and extravasation may lead to tissue damage or thrombophlebitis.

General symptoms such as nausea, vomiting, headache, and dizziness may be related to patient anxiety or similar factors, or may be due to a mild anaphylactoid reaction. Urticaria, pruritus, pallor, sweating, a metallic taste, weakness, coughing, rhinitis, sneezing, lachrymation, and visual disturbances may also occur. Cardiovascular effects may also be due to direct toxicity, notably after intracoronary injection, or anaphylactoid response; they include hypotension, tachycardia, bradycardia, transient ECG abnormalities, and haemodynamic disturbances. More severe anaphylactoid reactions may lead to dyspnoea, bronchospasm, angioedema, severe urticaria, and eventually to profound hypotension, pulmonary oedema, respiratory arrest, ventricular fibrillation, circulatory failure, and cardiac arrest; fatalities have occurred.

CNS effects may result from direct toxicity, particularly after intrathecal use of ionic media or use in patients with a compromised blood-brain barrier, and can lead to severe neurotoxicity. Convulsions are more common in patients with epilepsy or brain tumours, but may also result from anaphylactoid reactions; paraesthesia, paralysis, and coma have also been reported.

Acute renal failure is an established adverse effect of contrast media, particularly in patients with predisposing factors such as dehydration (see Effects on the Kidneys (below), and Precautions, p. 1583.1). It appears to be related to the osmolality of the solution and is usually reversible, but deaths have occurred.

Iodinated contrast media also have direct effects on the blood, inhibiting blood coagulation and platelet aggregation. However, thromboembolism may also occur (see below). Disseminated intravascular coagulation and thrombocytopenia have also been reported.

Hyperthyroidism has been reported with use of iodinated contrast media, particularly in patients with goitre, and thyroid storm may be precipitated in patients with thyrotoxicosis. This is probably due to the small amounts of iodine present as a contaminant or released by any breakdown of the medium in the body. For the effects of iodine on the thyroid gland, see p. 2338.2.

Mild diarrhoea may follow the oral or rectal use of amidotrizoates for gastrointestinal examinations. Aspiration of oral solutions has caused fatal pulmonary oedema.

Adverse effects are treated symptomatically; adequate resuscitative facilities should be available when radiographic procedures are undertaken, and patients should be kept under observation for a suitable period after the procedure.

Effects on the blood. Iodinated contrast media affect blood coagulation to differing degrees.[1,2] Amidotrizoates and other ionic contrast media have inhibitory effects on blood coagulation and platelet aggregation, whereas nonionic media lack these effects. In procedures such as angiography, which are associated with a risk of thromboembolism, there may therefore be an advantage in using ionic media. However, the better overall tolerability of nonionic media means that they are still generally preferred to ionic media for angiography, particularly in patients at high risk of non-thromboembolic adverse effects.

Other effects on the blood that have been reported with amidotrizoates and other iodinated contrast media include disseminated intravascular coagulation,[3,4] haemolysis,[5] thrombocytopenia,[6,7] and thrombotic microangiopathy.[8]

1. Husted SE, Kanstrup H. Thrombotic complications in coronary angioplasty—ionic versus non-ionic low-osmolar contrast media. *Acta Radiol* 1998; **39:** 340–3.
2. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; **25:** 1079–98.
3. Lucas LM, *et al.* Case report: multisystem failure following intravenous iopamidol. *Clin Radiol* 1992; **45:** 276–7.
4. Shigyo M, *et al.* A rare case of disseminated intravascular coagulation caused by the nonionic contrast medium iohexol. *J Urol (Baltimore)* 1995; **153:** 1901–3.
5. Catterall JR, *et al.* Intravascular haemolysis with acute renal failure after angiocardiography. *BMJ* 1981; **282:** 779–80.
6. Shojania AM. Immune-mediated thrombocytopenia due to an iodinated contrast medium (diatrizoate). *Can Med Assoc J* 1985; **133:** 123.
7. Ural AU, *et al.* Thrombocytopenia following intravenous iopamidol. *Eur J Clin Pharmacol* 1998; **54:** 575–6.
8. Fairley S, Ihle BU. Thrombotic microangiopathy and acute renal failure associated with arteriography. *BMJ* 1986; **293:** 922–3.

Effects on the kidneys. Contrast nephropathy or contrast-induced nephrotoxicity is a well-established adverse effect of iodinated contrast media.[1-10] Estimates of the incidence vary depending on the type and amount of contrast medium used, the definition of nephropathy, and the population of patients being studied, but is about 1 to 6% overall. In the majority of patients who develop contrast-medium-induced renal impairment the condition develops within about 24 hours of the procedure, is asymptomatic, and resolves completely within about 10 days. However, the condition may occasionally be severe, producing oliguria and renal failure that requires dialysis; fatalities have occurred. A retrospective analysis[11] found that the development of contrast nephropathy was associated with increased 30-day mortality, and that this risk was higher in those given the contrast medium intravenously rather than intra-arterially.

The **mechanism** of nephrotoxicity is not certain, but is thought to involve both medullary hypoxia due to reduced renal blood flow, and direct toxicity. The osmolality of the contrast medium solution appears to be an important factor and most studies have shown that high-osmolality media increase the risk compared with low-osmolality media. There is also some evidence that use of media that are iso-osmolar with plasma may reduce the risk even further. The volume of contrast solution used is also important, and risk increases with higher volumes. The use of ionic or nonionic media appears to have less influence, except that nonionic media generally have a lower osmolality and may therefore be preferred.

The most important patient characteristic that increases the risk of nephrotoxicity is pre-existing renal impairment, especially in patients with diabetes mellitus. Other **risk factors** include conditions where there is reduced renal blood flow, such as heart failure and dehydration. Old age, repeated exposure (over a short period of time), multiple myeloma, and use with other nephrotoxic drugs, are also risk factors.

Various methods have been tried for **prophylaxis** of contrast medium-induced nephropathy.[1,3-10,12-14] All patients should be assessed for risk factors and those at high risk should be given a small volume of a low-osmolality or iso-osmolar nonionic medium if possible. *Hydration* before and after the procedure is of established benefit and is recommended in all patients, although the optimum route and fluid to use remains unclear. Oral hydration may be adequate in low risk patients, but most patients are given sodium chloride 0.45% or 0.9% intravenously. Sodium bicarbonate may be an alternative but the evidence is conflicting. Several studies have appeared to show an advantage for the use of sodium bicarbonate over sodium chloride in preventing contrast-induced nephropathy,[15-18] and a meta-analysis including these studies appeared to confirm the benefit.[19] However, it noted the risk of publication bias and study heterogeneity,[19] and others have found no advantage[20,21] or in one retrospective study even an increased risk[22] compared with no prophylaxis. Thus, although some protocols have suggested the use of bicarbonate-based hydration to prevent nephropathy,[23] further studies are needed to confirm its role.

Antoxidants have been suggested as a way of reducing the direct toxicity of contrast media. Acetylcysteine is widely used,[24] but again, evidence of benefit is conflicting. Some studies have produced promising results, but others have been less positive and, although reviews and meta-analyses have shown benefit[25,26] or a trend towards benefit,[27-29] this may reflect publication bias,[30] and most have concluded[24,26-29,31] that the wide variation between the studies included means that the efficacy of acetylcysteine remains uncertain. Later randomised studies have also reported conflicting results.[32,33] An observational study[34] found that there was no difference in the incidence of contrast nephropathy before and after the introduction of acetylcysteine prophylaxis, while a follow-up study[35] found that acetylcysteine had no effect on overall outcomes over 9 months. However, some authors[4,7,24] recommend the use of acetylcysteine in particularly high-risk patients. Ascorbic acid has also been tried and showed benefit in one study,[36] and promising results have been reported with trimetazidine, an anti-anginal drug with antoxidant properties,[37] but further confirmation is needed.

Other approaches have generally produced disappointing results.[1,3-7,10,12] The use of diuretics may increase the risk of nephropathy and is not recommended. Vasodilators have been tried, including atrial natriuretic peptide, calcium-channel blockers, low-dose dopamine, and alprostadil, but benefit has not been established and they are not generally used. Although positive results have been reported[38] with fenoldopam, which has preferential effects on renal blood flow, a large randomised study[39] failed to confirm any benefit. Studies with theophylline have produced conflicting results, although a meta-analysis[40] concluded that it might be of benefit. Use of dialysis to remove contrast medium from the circulation has also been suggested; some benefit has also been found with haemofiltration started before the procedure,[41] but not with haemodialysis immediately after the procedure.[42]

1. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; **25:** 1079–98.
2. Rudnick MR, Goldfarb S. Pathogenesis of contrast-induced nephropathy: experimental and clinical observations with an emphasis on the role of osmolality. *Rev Cardiovasc Med* 2003; **4** (suppl 5): S28–S33.
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33. Marenzi G, *et al*. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006; **354:** 2773–82.
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36. Spargias K, *et al*. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; **110:** 2837–42.
37. Onbasili AO, *et al*. Trimetazidine in the prevention of contrast-induced nephropathy after coronary procedures. *Heart* 2007; **93:** 698–702.
38. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; **35:** 1278–82. Correction. *ibid*.; 1677.
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42. Vogt B, *et al*. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med* 2001; **111:** 692–8.

Hypersensitivity. Anaphylactoid reactions to iodinated contrast media are more common with the ionic agents than the nonionic media of lower osmolality. Patients at increased risk are those with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to a contrast medium, and those receiving beta blockers or interleukin-2 therapy. In such patients, nonionic media are preferred. Stopping treatment with beta blockers should be considered in patients with other risk factors.

Pretreatment with corticosteroids may be considered for preventing anaphylactoid reactions in high-risk patients, and an antihistamine may also be given. However, reactions may still occur and the value of premedication remains controversial.

Patients may also experience delayed type-IV hypersensitivity reactions, usually manifesting as mild to moderate maculopapular rash, urticaria, and angioedema. For unknown reasons, unlike immediate reactions, these may be more common with nonionic dimeric contrast media.

References.

1. Canter LM. Anaphylactoid reactions to radiocontrast media. *Allergy Asthma Proc* 2005; **26:** 199–203.
2. Idée J-M, *et al*. Allergy-like reactions to iodinated contrast agents: a critical analysis. *Fundam Clin Pharmacol* 2005; **19:** 263–81.
3. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; **78:** 686–93.
4. Tramèr MR, *et al*. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. Abridged version: *BMJ* 2006; **333:** 675–8. Full version: http://www.bmj.com/cgi/reprint/333/7570/675 (accessed 05/09/08)
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Precautions

The risk of anaphylactoid reactions with amidotrizoates and other iodinated contrast media is increased in patients with asthma or a history of allergies and they should be used with great caution in such patients; they should not be used in patients with a previous reaction to contrast media or iodine. Test doses have been given but are not generally recommended since they do not predict hypersensitivity with certainty and may cause severe or fatal reactions. Pretreatment with corticosteroids may be considered in patients considered at high risk of reactions, but the value of this is uncertain (see Hypersensitivity, above). An antihistamine may be given with the corticosteroid.

Iodinated contrast media should be used with caution in patients with severe hepatic or renal impairment, diabetics with renal impairment, and others who may be at increased risk of renal failure. Dehydration should be avoided, and any fluid or electrolyte imbalance should be corrected before contrast media are given. Particular care is needed in patients with multiple myeloma since dehydration resulting from use of contrast media may cause precipitation of protein in the renal tubules, leading to anuria and fatal renal failure.

Caution is also necessary in patients with severe hypertension, advanced cardiac disease, phaeochromocytoma, sickle-cell disease, or hyperthyroidism or epilepsy, and in debilitated, severely ill, very old, or very young patients.

Amidotrizoates and other hypertonic contrast media are neurotoxic and should not be given intrathecally; patients with subarachnoid haemorrhage may be at risk with any intravascular use. Intravascular contrast media should also be used with caution in any patient with occlusive vascular disease. Iodinated contrast media should not be used for hysterosalpingography in the presence of infection or inflammation of the pelvic cavity, nor during menstruation or in pregnancy (although any abdominal radiography should be avoided during pregnancy because of the risks of radiation to the fetus).

Iodine-containing contrast media may interfere with thyroid function tests. There may also be interference with blood coagulation tests and certain urine tests.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving amidotrizoates and the American Academy of Pediatrics considers[1] that they are therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Neonates. Although amidotrizoates may be used in the management of some forms of intestinal obstruction (see p. 1581.3), meglumine amidotrizoate was considered[1] a possible contributory factor in the deaths of 2 infants who developed bowel necrosis, perforation, and peritonitis after its use for meconium ileus.

1. Leonidas JC, *et al*. Possible adverse effects of methylglucamine diatrizoate compounds on the bowel of newborn infants with meconium ileus. *Radiology* 1976; **121:** 693–6.

Pharmacokinetics

Amidotrizoates are very poorly absorbed from the gastrointestinal tract. Amidotrizoates in the circulation are not significantly bound to plasma proteins. If renal function is not impaired, unchanged amidotrizoate is rapidly excreted by glomerular filtration; over 95% of an intravascular dose is reported to be excreted in urine within 24 hours, and about 1 to 2% of a dose may be excreted in faeces. Trace amounts may be detected in other body fluids including tears and saliva. Faecal excretion may increase to 10 to 50% in severe renal impairment. The half-life of amidotrizoates has been reported to be 30 to 60 minutes, which can increase to 20 to 140 hours in severe renal impairment. They are removed by haemodialysis and peritoneal dialysis.

The amidotrizoates cross the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Angiografina; Densopax; Gastropaque Iodo; MD-76; MD-Gastroview; Plenigraf; Temistac; Tomoray 76C; Triyosom; Urografina; Urovisona; X-Graf C; X-Graf; ***Austral.***: Gastrografin; MD-76†; MD-Gastroview; Urografin; ***Austria***: Gastrografin; Peritrast; ***Belg.***: Gastrografin; Urografine; ***Braz.***: Hypaque-M; Hypaque; Urografina; ***Canad.***: Gastrografin; Hypaque-M†; Hypaque†; MD-76†; Reno-Dip†; Reno†; Renocal†; ***Chile***: Angiovist†; Reliev 76%; Reliev; ***China***: Angiografin (格纳芬); ***Denm.***: Urografin; ***Fin.***: Gastrografin; ***Fr.***: Gastrografine; Radioselectan; ***Ger.***: Ethibloc†; Gastrografin; Gastrolux; Peritrast; Urolux Retro; ***Gr.***: Gastrografin; Urografin; ***Hung.***: Gastrografin; Peritrast; ***India***: Angiografin; Urografin; ***Irl.***: Urografin; ***Ital.***: Gastrografin; ***Neth.***: Gastrografin; Urografin; ***Norw.***: Gastrografin; ***NZ***: Gastrografin; Urografin; ***Port.***: Gastrografina; Urografina; ***Rus.***: Trazograph (Тразограф); Triombrast (Триомбраст); Urografin (Урографин); ***S.Afr.***: Gastrografin; Urografin; ***Spain***: Gastrografin; Pielograf†; Plenigraf; Radialar 280; Trazograf†; Uro Angiografin†; Urografin; ***Swed.***: Gastrografin; Urografin†; ***Switz.***: Gastrografin; Gastrolux; ***Turk.***: Urografin; Urovideo; Urovist-Angiografin; ***UK***: Gastrografin; Hypaque; Urografin 150; ***Ukr.***: Trazograph (Тразограф)†; ***USA***: Cystografin; Gastrografin; Hypaque-M, Hypaque-76†; Hypaque†; MD-76; MD-Gastroview; Reno-M†; Renografin†.

Multi-ingredient Preparations. ***Canad.***: Sinografin; ***India***: Contrastin; ***Irl.***: Gastrografin; ***USA***: Sinografin.

Pharmacopoeial Preparations

BP 2014: Meglumine Amidotrizoate Injection;
USP 36: Diatrizoate Meglumine and Diatrizoate Sodium Injection; Diatrizoate Meglumine and Diatrizoate Sodium Solution; Diatrizoate Meglumine Injection; Diatrizoate Sodium Injection; Diatrizoate Sodium Solution.

Barium Sulfate

Barii sulfas; Barii Sulphas; Bario sulfatas; Barium Sulfuricum; Barium Sulphate; Bariumsulfaatti; Bariumsulfat; Báriumszulfát; Baru siarczan; Baryum (Sulfate de); Baryum, sulfate de; Síran barnatý; Sulfato de bario; Сульфат бария.

$BaSO_4$=233.4

CAS — 7727-43-7.

ATC Vet — QV08BA02.

UNII — 25BB7EKE2E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Barium Sulfate). A fine, white powder, free from gritty particles. Practically insoluble in water and in organic solvents; very slightly soluble in acids and in solutions of alkali hydroxides.

USP 36: (Barium Sulfate). A fine, white, odourless, bulky powder, free from grittiness. Practically insoluble in water, in organic solvents, and in solutions of acids and of alkalis. pH of a 10% w/w aqueous suspension is between 3.5 and 10.0.

Uses and Administration

Barium sulfate is used as a radiographic contrast medium (p. 1580.1) for X-ray examination of the gastrointestinal tract involving single- or double-contrast techniques or computed tomography.

The dose of barium sulfate is dependent upon the type of examination and technique used. In the UK typical doses and concentrations used for examination are:

- oesophagus: up to 150 mL of a 50 to 200% w/v suspension given orally
- stomach and duodenum: up to 300 mL of a 30 to 200% w/v suspension given orally
- small intestine: 100 to 300 mL of a 30 to 150% w/v suspension given orally
- colon: 200 mL to 2 litres of a 20 to 130% w/v suspension given as an enema

A suspension containing 1.2 to 2.2% may be used in gastrointestinal computed tomography.

In the USA, suspensions containing up to 230% w/v barium sulfate may be used; lower concentrations are available for use in computed tomography and usually contain about 1 to 2% w/v.

For double-contrast examination, gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide; separate gas-producing preparations based on sodium bicarbonate are also available. Air given via a tube may be used as an alternative to carbon dioxide.

Reviews.

1. Nolan DJ, Traill ZC. The current role of the barium examination of the small intestine. *Clin Radiol* 1997; **52:** 809–20.
2. Mendelson RM. The role of the barium enema in the diagnosis of colorectal neoplasia. *Australas Radiol* 1998; **42:** 191–6.
3. de Zwart IM, *et al*. Barium enema and endoscopy for the detection of colorectal neoplasia: sensitivity, specificity, complications and its determinants. *Clin Radiol* 2001; **56:** 401–9.
4. Rubesin SE, Maglinte DD. Double-contrast barium enema technique. *Radiol Clin North Am* 2003; **41:** 365–76.
5. O'Connor SD, Summers RM. Revisiting oral barium sulfate contrast agents. *Acad Radiol* 2007; **14:** 72–80.
6. Canon CL. Is there still a role for double-contrast barium enema examination? *Clin Gastroenterol Hepatol* 2008; **6:** 389–92.

Intussusception. Contrast media enemas and ultrasound are both used in the diagnosis of intussusception, a condition in infants where part of the intestine prolapses into the lumen of an adjacent part causing an obstruction.[1-3] However, some consider ultrasound to be superior for diagnosis and reserve enemas for the therapeutic reduction of intussusception. Reduction is achieved as a result of the hydrostatic pressure of the enema pushing the intestine back into its natural position. Although there is extensive experience using barium enemas for reduction some centres prefer to use water-soluble contrast media so as to minimise the risk of chemical peritonitis if perforation of the bowel occurs. Other agents used instead of barium for reduction include air enemas or ultrasound guided saline enemas, both of which avoid or reduce radiographic exposure. Surgery is indicated when enema therapy fails or is considered unsuitable.

1. del-Pozo G, *et al*. Intussusception in children: current concepts in diagnosis and enema reduction. *Radiographics* 1999; **19:** 299–319.
2. Sorantin E, Lindbichler F. Management of intussusception. *Eur Radiol* 2004; **14** (suppl 4): L146–L154.
3. Waseem M, Rosenberg HK. Intussusception. *Pediatr Emerg Care* 2008; **24:** 793–800.

Adverse Effects

Because barium sulfate is almost insoluble it lacks the severe toxicity characteristic of the barium ion; deaths have occurred in patients given the more soluble barium sulfide in error for the sulfate.

Constipation may occur after oral or rectal barium sulfate; impaction, obstruction, and appendicitis have occurred. Surgical removal of faecaliths has sometimes been necessary. Cramping or diarrhoea have also been reported. Venous intravasation has led to the formation of emboli; deaths have occurred. Perforation of the bowel has led to peritonitis, adhesions, granulomas, and a high mortality rate.

ECG abnormalities have occurred during the use of barium sulfate enemas.

Accidental aspiration into the lungs has led to pneumonitis or granuloma formation.

Hypersensitivity. A survey of hypersensitivity reactions to barium preparations found that although barium is inert many of the additives used in formulation have the potential to cause reactions.[1] Of 106 reactions reported or found

in the literature, 61% involved the skin and only 8% the respiratory tract; unconsciousness was reported in 8% of cases. In view of the frequency of use of barium preparations, such adverse reactions must be very rare, but radiologists should be aware that they might be somewhat more common than was usually appreciated. A number of severe reactions associated with the use of barium enemas supplied with an inflatable latex cuff may have been due to leaching of components from the latex.[2]

1. Janower ML. Hypersensitivity reactions after barium studies of the upper and lower gastrointestinal tract. *Radiology* 1986; **161:** 139–40.
2. Nightingale SL. Severe adverse reactions to barium enema procedures. *JAMA* 1990; **264**: 2863.

Precautions

Barium sulfate should not be given to patients with intestinal obstruction and care is needed in those with conditions such as pyloric stenosis or lesions that may predispose to obstruction. Adequate hydration should be ensured after the procedure to prevent severe constipation.

It is contra-indicated in patients with gastrointestinal perforation, and should be avoided, particularly when given rectally, in those at risk of perforation, such as patients with acute ulcerative colitis or diverticulitis and after rectal or colonic biopsy, sigmoidoscopy, or radiotherapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies barium sulfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Barigraf; Bario; Bariofarma; Barosperse†; E-Z-Cat; Entero VU; Gastropaque; Novopac; Opti-Up; Scheribar; Tixobar; Top-Cat; ***Austral.***: Medebar†; Medescan†; ***Austria***: Micropaque; Prontobario; Scannotrast; ***Belg.***: E-Z-Paque; Micropaque; Microtrast; Polibar; ***Braz.***: Bariogel; ***Canad.***: Anatrast†; Baricon†; Barobag†; Barocat†; Barosperse†; Cheetah†; Enhancer†; Enterovu†; Entrobar†; Entroease†; Esobar†; Esopho-Cat†; Flo-Coat†; Intropaste†; Liqui-Coat HD†; Medebar Plus†; Polibar Liquid†; Polibar Plus†; Polibar Rapid†; Prepcat†; Readi-Cat†; Ultra-R†; Unibar†; ***China***: Bei Ying (倍颖); ***Cz.***: E-Z-Cat; E-Z-HD; Micropaque; Microtrast†; Polibar; ***Denm.***: Micropaque†; Microtrast; Mixobar; Unicat; ***Fin.***: Mixobar; ***Fr.***: Micropaque; Microtrast; ***Ger.***: Barilux; Micropaque; Microtrast; ***Gr.***: Barilux; Micropaque; Polibar ACB; Unibaryt-R; ***Hung.***: E-Z-Cat; E-Z-HD; Micropaque; Microtrast; Polibar Rapid†; Polibar; ***Irl.***: Baricat; Maxibar; Polibar; ***Israel***: E-Z-Cat; E-Z-HD; E-Z-Paque; Entero VU; Polibar ACB; Polibar Plus†; ***Ital.***: Prontobario; TAC Esofago; ***Neth.***: Baricol; E-Z-Cat; E-Z-HD; Micropaque; Polibar; ***Norw.***: Mixobar; ***Port.***: E-Z-Cat; E-Z-HD; Gastrobario; Micropaque; Microtrast; Polibar; ***Rus.***: Bar-VIPS (Бар-ВИПС); ***Spain***: Barigraf; Barilux; Bario Dif†; Disperbarium†; ***Swed.***: Mixobar; ***Switz.***: CAT-Barium (E-Z-CAT); Microbar-HD (E-Z-HD); Micropaque; Polibar ACB; ***Thai.***: Solotop; ***Turk.***: Bar-X-Ray; E-Z-Cat; E-Z-HD; Opti-Up; Polibar; R-X; Radyobarit; Ultrabarit; ***UK***: Baritop; E-Z-Cat; E-Z-HD; E-Z-Paque; Polibar Rapid; Polibar; ***USA***: Anatrast†; Baricon†; Barocat; Barobag†; Barosperse†; Bear-E-Yum; CheeTah†; Digibar; E-Z-HD; E-Z-Paque; E-Z-Paste; Enecat; Enemark; Enhancer†; Entero VU; Entrobar†; Epi-C; Flo-Coat†; HD 200 Plus†; HD 85†; Intropaste†; Liqui-Coat HD†; Liquipake; Medebar†; Medescan; Polibar; Prepcat†; Readi-Cat; Scan C†; Tomocat†; Tonojug†; Tonopaque†; Varibar; ***Venez.***: Barin.

Multi-ingredient Preparations. ***Turk.***: Radyobarit-Double Contrast.

Pharmacopoeial Preparations
BP 2014: Barium Sulphate for Suspension; Barium Sulphate Oral Suspension;
USP 36: Barium Sulfate for Suspension; Barium Sulfate Paste; Barium Sulfate Suspension; Barium Sulfate Tablets.

Ferristene *(BAN, USAN)*

Ferristeno; Ферристен.
$C_8H_{11}NO_3S_x(Fe_2O_3)_{0.725}$
CAS — 155773-56-1.
ATC — V08CB02.
ATC Vet — QV08CB02.

Description. Ferristene contains about 23.4% of Fe.

Profile

Ferristene consists of iron ferrite crystals carried on monosized spheres of cross-linked poly(ammonium styrenesulfonate). It has superparamagnetic properties and has been used orally as a magnetic resonance contrast medium (p. 1580.1) for imaging of the abdomen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Abdoscan.

Ferucarbotran *(BAN, USAN)*

Ferrixan; Ferucarbotrano; SHU-555A; ZK-132281.

Profile

Ferucarbotran is a colloidal aqueous suspension of iron oxide (magnetite and maghemite) particles coated with carboxydextran. It has superparamagnetic properties and is used similarly to ferumoxides (below) as a magnetic resonance contrast medium (p. 1580.1) for imaging of the liver; the particles are taken up by the reticuloendothelial system of the liver and spleen and provide contrast enhancement. It is given intravenously as a solution containing 28 mg/mL of iron. The usual dose is 0.9 mL for patients weighing less than 60 kg and 1.4 mL for patients weighing 60 kg and over.

References.

1. Reimer P, Balzer T. Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. *Eur Radiol* 2003; **13:** 1266–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Resovist; ***Belg.***: Resovist†; ***Cz.***: Resovist†; ***Fr.***: Cliavist†; ***Ger.***: Resovist†; ***Gr.***: Resovist; ***Ital.***: Resovist; ***Neth.***: Resovist†; ***Norw.***: Resovist†; ***Port.***: Resovist†; ***Spain***: Resovist†; ***Swed.***: Resovist†; ***Switz.***: Resovist†.

Ferumoxides *(BAN, USAN)*

AMI-25; Ferumóxidos.
$(Fe_2O_3)_m(FeO)_n$
CAS — 119683-68-0.
UNII — G6N3J05W84.

Uses and Administration

Ferumoxides consists of colloidal particles of magnetite (iron oxide). It has superparamagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1) for imaging of the liver; the particles are taken up by the reticuloendothelial system of the liver and spleen and provide contrast enhancement. It is available as a suspension containing 11.2 mg/mL of iron, which should be diluted in 100 mL of glucose 5% before use and given intravenously over at least 30 minutes. The dose is expressed in terms of iron. In Europe, the usual dose is 840 micrograms/kg; in the USA, a dose of 560 micrograms/kg is used.

Reference to the use of ferumoxides followed by a gadolinium-based contrast medium.[1]

1. Qayyum A, *et al.* Detection of hepatocellular carcinoma by ferumoxides-enhanced MR imaging in cirrhosis: incremental value of dynamic gadolinium-enhancement. *J Magn Reson Imaging* 2006; **23:** 17–22.

Adverse Effects and Precautions

The most common adverse effects with ferumoxides are pain, vasodilatation, and hypotension; paraesthesia may also occur. Hypersensitivity reactions have developed. Extravasation may lead to discoloration of the skin around the injection site. Ferumoxides should not be used in patients with known hypersensitivity to iron and should be used with caution in patients with iron overload disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Endorem; ***Belg.***: Endorem†; ***Denm.***: Endorem†; ***Fin.***: Endorem†; ***Fr.***: Endorem†; ***Ger.***: Endorem†; ***Gr.***: Endorem; ***Irl.***: Endorem; ***Ital.***: Endorem; ***Jpn***: Feridex†; ***Neth.***: Endorem†; ***Norw.***: Endorem†; ***Port.***: Endorem; ***Spain***: Endorem†; ***Swed.***: Endorem†; ***Switz.***: Endorem†; ***Turk.***: Endorem; ***USA***: Feridex.

Pharmacopoeial Preparations
USP 36: Ferumoxides Injection.

Ferumoxsil *(BAN, USAN)*

AMI-121; Ferumoksiili; Ferumoxil; Férumoxsil; Ferumoxsilum; Ферумоксил.
CAS — 171544-35-7.
ATC — V08CB01.
ATC Vet — QV08CB01.
UNII — 6HJV9H13XS.

Uses and Administration

Ferumoxsil consists of a silicone polymer bonded to colloidal particles of magnetite (iron oxide). It has superparamagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1) for imaging of the gastrointestinal tract; the particles remain in the stomach and intestine when given orally or rectally and provide contrast enhancement. It is given as a suspension containing 175 micrograms/mL of iron. The usual dose is 600 to 900 mL orally, or 300 to 600 mL rectally.

Adverse Effects and Precautions

The most common adverse effects with ferumoxsil are diarrhoea, nausea, vomiting, and abdominal pain; oral paraesthesia has also been reported. Ferumoxsil should be used with caution in patients with iron overload disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lumirem; ***Denm.***: Lumirem; ***Fin.***: Lumirem; ***Fr.***: Lumirem; ***Ger.***: Lumirem; ***Ital.***: Lumirem; ***Neth.***: Lumirem; ***Port.***: Lumirem; ***Swed.***: Lumirem; ***USA***: Gastromark.

Pharmacopoeial Preparations
USP 36: Ferumoxsil Oral Suspension.

Ferumoxtran-10 *(USAN)*

AMI-227; BMS-180549; Code 7227.
CAS — 189047-99-2.

Profile

Ferumoxtran-10 consists of colloidal particles of magnetite (iron oxide) coated with a low-molecular-weight dextran. It has superparamagnetic properties and has been investigated as a magnetic resonance contrast medium for imaging of the lymphatic system.

Gadobenic Acid *(BAN, rINN)*

Acide Gadobénique; Ácido gadobénico; Acidum Gadobenicum; B-19036; Gadobénico, ácido; Gd-BOPTA; Гадобеновая Кислота.
Dihydrogen [(±)-4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)]gadolinate(2-).
$C_{22}H_{28}GdN_3O_{11}$=667.7
CAS — 113662-23-0.
ATC — V08CA08.
ATC Vet — QV08CA08.

Meglumine Gadobenate *(BANM, rINNM)*

B-19036/7; Gadobenaattidimeglumiini; Gadobenatdimeglumin; Gadobénate de Méglumine; Gadobenate Dimeglumine (USAN); Gadobenato de meglumina; Gadobenatum Dimegluminum; Meglumini Gadobenas; Меглумина Гадобенат.
$C_{22}H_{28}GdN_3O_{11}.2C_7H_{17}NO_5$=1058.2
CAS — 127000-20-8.
ATC — V08CA08.
ATC Vet — QV08CA08.
UNII — 3Q6PPC19PO.

Uses and Administration

Gadobenic acid is an ionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of the liver and CNS, and in magnetic resonance angiography to detect narrowing or obstruction of the abdominal or peripheral arteries.

Gadobenic acid is given intravenously as the meglumine salt. It is available as a solution containing meglumine gadobenate 529 mg/mL (0.5 mmol/mL). Usual doses by body-weight for imaging are:

- liver: 0.1 mL/kg (0.05 mmol/kg)
- brain or spine: 0.2 mL/kg (0.1 mmol/kg)
- angiography: 0.2 mL/kg (0.1 mmol/kg)

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

References.

1. Kirchin MA, *et al.* Safety assessment of gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance. *J Magn Reson Imaging* 2001; **14:** 281–94.

2. Shellock FG, *et al*. Safety of gadobenate dimeglumine (MultiHance): summary of findings from clinical studies and postmarketing surveillance. *Invest Radiol* 2006; **41:** 500–9.

Pharmacokinetics

Gadobenate is rapidly distributed into the extracellular space after intravenous injection. An elimination half-life of about 1.2 to 1.7 hours has been reported. It is not metabolised and about 78 to 94% of a dose is excreted in the urine within 24 hours; about 2 to 4% is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: MultiHance; ***Austria***: MultiHance; ***Belg.***: MultiHance; ***Canad.***: MultiHance; ***China***: MultiHance (莫迪司); ***Cz.***: MultiHance; ***Denm.***: MultiHance; ***Fin.***: MultiHance; ***Fr.***: MultiHance; ***Ger.***: MultiHance; ***Gr.***: MultiHance; ***Hung.***: MultiHance; ***Irl.***: MultiHance; ***Israel***: MultiHance; ***Ital.***: MultiHance; ***Neth.***: MultiHance; ***Norw.***: MultiHance; ***NZ***: MultiHance; ***Port.***: MultiHance; ***Singapore***: MultiHance; ***Spain***: MultiHance; ***Swed.***: MultiHance; ***Switz.***: MultiHance; ***Turk.***: MultiHance; ***UK***: MultiHance; ***USA***: MultiHance.

Gadobutrol *(USAN, rINN)*

Gadobutrolum; ZK-135079; Гадобутрол.

{10-[(1*RS*,2*SR*)-2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)}gadolinium.

$C_{18}H_{31}GdN_4O_9$=604.7

CAS — 138071-82-6; 770691-21-9.

ATC — V08CA09.

ATC Vet — QV08CA09.

UNII — 1BJ477IO2L.

NOTE. Protovist is a trade mark that has been used for gadobutrol.

Uses and Administration

Gadobutrol is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of the CNS, kidneys, and liver, and in magnetic resonance angiography.

Gadobutrol is available as a solution containing 605 mg/mL (1 mmol/mL). It is given intravenously. Usual doses for adults by body-weight are:

- cranial and spinal imaging: 0.1 mL/kg (0.1 mmol/kg). A second dose of up to 0.2 mL/kg (0.2 mmol/kg) may be given within 30 minutes if required
- kidneys and liver: 0.1 mL/kg (0.1 mmol/kg)
- angiography: 0.1 to 0.3 mL/kg (0.1 to 0.3 mmol/kg)

Children aged 7 years and older and adolescents may be given 0.1 mL/kg (0.1 mmol/kg) for all the above indications. This dose may also be given to children aged 2 years and older in CNS imaging.

A solution containing 302.5 mg/mL (0.5 mmol/mL) has also been used.

References.

1. Huppertz A, Rohrer M. Gadobutrol, a highly concentrated MR-imaging contrast agent: its physicochemical characteristics and the basis for its use in contrast-enhanced MR angiography and perfusion imaging. *Eur Radiol* 2004; **14** (suppl 5): M12–M18.

Administration in children. Gadobutrol is licensed in the UK for imaging of the CNS, kidneys, and liver, and in magnetic resonance angiography, in children aged 7 years and older. In the USA, gadobutrol may be used for CNS imaging in children aged 2 years and older. For doses, see Uses and Administration, above.

See also under Pharmacokinetics, below.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2. Gadobutrol may prolong cardiac repolarisation and should not be used in patients with uncorrected hypokalaemia. Caution is required in patients with severe cardiovascular disease, and in those with congenital long QT syndrome or a history of drug-induced arrhythmias.

General references.

1. Forsting M, Palkowitsch P. Prevalence of acute adverse reactions to gadobutrol—a highly concentrated macrocyclic gadolinium chelate: review of 14,299 patients from observational trials. *Eur J Radiol* 2010; **74:** e186–e192.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gadobutrol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Gadodiamide *(BAN, USAN, rINN)*

Gadodiamid; Gadodiamida; Gadodiamidi; Gadodiamidum; GdDTPA-BMA; S-041; Гадодиамид.

[*N*,*N*-Bis(2-{(carboxymethyl)[(methylcarbamoyl)methyl]amino}ethyl)glycinato(3-)]gadolinium; a complex of gadolinium with diethylenetriamine penta-acetic acid bismethylamide.

$C_{16}H_{26}GdN_5O_8$=573.7

CAS — 131410-48-5 (anhydrous gadodiamide); 122795-43-1 (gadodiamide hydrate).

ATC — V08CA03.

ATC Vet — QV08CA03.

UNII — 84F6U3J2R6.

Pharmacopoeias. In *US.*

USP 36: (Gadodiamide). A white, odourless, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Store in airtight containers.

Uses and Administration

Gadodiamide is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures, imaging of the whole body, angiography and evaluation of cardiac perfusion (stress/rest testing and late enhancement), and mammography.

Gadodiamide is available as a solution containing 287 mg/mL (0.5 mmol/mL). Usual intravenous doses by body-weight are:

- cranial and spinal imaging: for adults and children, 0.2 mL/kg (0.1 mmol/kg). Adults may be given a second dose of 0.4 mL/kg (0.2 mmol/kg) within 20 minutes if required
- whole body imaging: for adults and children, 0.2 mL/kg (0.1 mmol/kg)
- kidneys: for adults and children, 0.1 mL/kg (0.05 mmol/kg) may be adequate
- angiography: for adults, 0.2 mL/kg (0.1 mmol/kg)
- cardiac perfusion in coronary artery disease: for adults, 0.3 mL/kg (0.15 mmol/kg). For stress/rest testing, this is given rapidly in 2 equally divided doses 10 minutes or more apart, the first dose being accompanied by a pharmacological stress agent given via a separate intravenous line
- mammography: 0.2 to 0.4 mL/kg (0.1 to 0.2 mmol/kg)

Liposomal gadodiamide is under investigation for the adjunctive treatment of glioma, by aiding visualisation of the distribution of the antineoplastic topotecan.

Administration in children. Gadodiamide is licensed for use in children from 2 years of age in both the EU and the USA; it is used for cranial and spinal imaging and whole body imaging. For doses see Uses and Administration, above.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2. Inadvertent intrathecal use of gadodiamide has resulted in convulsions, coma, and deficits of sensory and motor nerve function.

Effects on the pancreas. Acute pancreatitis developed in a patient shortly after injection of gadodiamide for hepatic imaging.[1] Another patient[2] developed both acute pancreatitis and acute renal failure after use of gadodiamide for angiography.

1. Terzi C, Sökmen S. Acute pancreatitis induced by magnetic-resonance-imaging contrast agent. *Lancet* 1999; **354:** 1789–90. Correction. *ibid.* 2000; **355:** 660.
2. Schenker MP, *et al*. Gadolinium arteriography complicated by acute pancreatitis and acute renal failure. *J Vasc Interv Radiol* 2001; **12:** 393.

Interference with diagnostic tests. Gadodiamide may interfere with colorimetric methods for measuring serum calcium concentrations, resulting in falsely low measurements. Severe pseudohypocalcaemia has been reported[1-3] after the use of gadodiamide, particularly in patients with renal impairment.[2] There is also *in vitro* evidence that a similar interference may occur with gadoversetamide.[2]

1. Doorenbos CJ, *et al*. Severe pseudohypocalcemia after gadolinium-enhanced magnetic resonance angiography. *N Engl J Med* 2003; **349:** 817–18.
2. Prince MR, *et al*. Gadodiamide administration causes spurious hypocalcemia. *Radiology* 2003; **227** 639–46.
3. Williams SF, *et al*. Spurious hypocalcemia after gadodiamide administration. *Mayo Clin Proc* 2005; **80:** 1655–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gadodiamide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Renal impairment. For the view that gadodiamide may carry a particular risk of the development of nephrogenic systemic fibrosis in patients with renal impairment, see p. 1586.3.

Pharmacokinetics

Gadodiamide is rapidly distributed into extracellular fluid. About 96% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 70 minutes has been reported. Gadodiamide is not bound to plasma proteins. It is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Omniscan; ***Austral.***: Omniscan; ***Austria***: Omniscan; ***Belg.***: Omniscan; ***Canad.***: Omniscan; ***Chile***: Omniscan; ***China***: Omniscan (欧乃影); ***Cz.***: Omniscan; ***Denm.***: Omniscan; ***Fin.***: Omniscan; ***Fr.***: Omniscan; ***Ger.***: Omniscan; ***Gr.***: Omniscan; ***Hung.***: Omniscan; ***Irl.***: Omniscan; ***Israel***: Omniscan; ***Ital.***: Omniscan; ***Jpn***: Omniscan; ***Neth.***: Omniscan; ***Norw.***: Omniscan; ***NZ***: Omniscan; ***Port.***: Omniscan; ***Rus.***: Omniscan (Омнискан); ***Spain***: Omniscan; ***Swed.***: Omniscan; ***Switz.***: Omniscan; ***Turk.***: Omniscan; ***UK***: Omniscan; ***Ukr.***: Omniscan (Омнискан); ***USA***: Omniscan.

Pharmacopoeial Preparations

USP 36: Gadodiamide Injection.

Gadofosveset Trisodium *(BANM, USAN, rINNM)*

Gadofosveset trisódico; Gadofosvéset Trisodique; Gadofosvesetum Trinatricum; MS-325 (gadofosveset); MS-32520; Тринатрий Гадофосвезет.

Trisodium (*N*-[2-[bis(carboxymethyl)amino]ethyl]-*N*-{(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl}glycine 4,4-diphenylcyclohexyl hydrogen phosphato(6-))gadolinate(3-).

$C_{33}H_{38}GdN_3Na_3O_{14}P$=957.9

CAS — 201688-00-8 (gadofosveset); 193901-90-5 (gadofosveset trisodium).

ATC — V08CA11.

ATC Vet — QV08CA11.

UNII — XM33Q67UVH (gadofosveset trisodium); 9430ZR8ZAN (anhydrous gadofosveset trisodium).

Profile

Gadofosveset is a gadolinium chelate used as a paramagnetic contrast medium (p. 1580.1) in magnetic resonance angiography. It binds to plasma proteins, particularly albumin, and therefore acts as a blood pool agent, allowing visualisation of the vasculature.

Gadofosveset is given by intravenous injection as the trisodium salt. It is available as a solution containing gadofosveset trisodium 244 mg/mL (0.25 mmol/mL). The usual dose is 0.12 mL/kg (0.03 mmol/kg).

References.

1. Henness S, Keating GM. Gadofosveset. *Drugs* 2006; **66:** 851–7.
2. Goyen M. Gadofosveset-enhanced magnetic resonance angiography. *Vasc Health Risk Manag* 2008; **4:** 1–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ablavar; ***Belg.***: Vasovist†; ***Canad.***: Ablavar; Vasovist; ***Cz.***: Ablavar; ***Denm.***: Vasovist†; ***Fr.***: Vasovist†; ***Ger.***: Ablavar†; ***Gr.***: Ablavar†; ***Hung.***: Vasovist; ***Ital.***: Vasovist†; ***Neth.***: Ablavar†; ***Norw.***: Ablavar†; ***Pol.***: Vasovist; ***Port.***: Ablavar; ***Spain***: Ablavar†; ***Swed.***: Ablavar†; ***Switz.***: Vasovist†; ***Turk.***: Vasovist; ***UK***: Ablavar; ***USA***: Ablavar.

Gadopentetic Acid *(BAN, rINN)*

Acide Gadopentétique; Ácido gadopentético; Acidum Gadopenteticum; Gadolinium-DTPA; Gadopentético, ácido; Гадопентетовая Кислота.

Dihydrogen (*N*,*N*-bis{2-[bis(carboxymethyl)amino]ethyl}glycinato(5-))gadolinate(2-); a complex of gadolinium with diethylenetriamine penta-acetic acid.

$C_{14}H_{20}GdN_3O_{10}$=547.6

CAS — 80529-93-7.

ATC — V08CA01.

ATC Vet — QV08CA01.

UNII — K2I13DR72L.

Meglumine Gadopentetate *(BANM, rINNM)*

Dimeglumine Gadopentetate; Gadopentétate de Méglumine; Gadopentetate Dimeglumine (USAN); Gadopentetate Meglumine; Gadopentétate méglumine; Gadopentetato de meglumina; Meglumini Gadopentetas; SH-L-451-A; Мегглумина Гадопентетат.

$C_{14}H_{20}GdN_3O_{10}.(C_7H_{17}NO_5)_2$=938.0

CAS — 86050-77-3.

ATC — V08CA01.

ATC Vet — QV08CA01.

UNII — RH248G8V27.

Pharmacopoeias. *Chin.* and *US* include only as an injection.

Uses and Administration

Gadopentetic acid is an ionic gadolinium chelate used as a contrast medium in magnetic resonance imaging (p. 1580.1). Gadolinium has paramagnetic properties that affect the relaxivity of hydrogen ions, increasing the signal intensity and therefore enhancing the contrast between tissues. Chelation of gadolinium reduces its toxicity while retaining its paramagnetic properties; it also affects distribution within the body. Most gadolinium chelates distribute freely into extracellular fluid but do not cross the blood-brain barrier, and they are particularly useful for imaging the brain and associated structures.

Gadopentetic acid is given intravenously as meglumine gadopentetate for contrast enhancement in magnetic resonance imaging of cranial and spinal structures, and of the whole body, it has also been used for evaluation of renal function. It is given by intra-articular injection for arthrography, and has been used orally and rectally in imaging of the gastrointestinal tract.

For cranial, spinal, and whole body imaging, a solution containing meglumine gadopentetate 469.01 mg/mL (0.5 mmol/mL) is used in the following usual doses by body-weight:

- cranial and spinal imaging: for adults and children aged over 1 month, 0.2 mL/kg (0.1 mmol/kg) (but see also Precautions, below). A further dose of 0.2 mL/kg (0.1 mmol/kg) may be given within 30 minutes to adults and children aged over 1 year if necessary; in adults this second dose may be 0.4 mL/kg (0.2 mmol/kg). In special circumstances a dose of 0.6 mL/kg (0.3 mmol/kg) may be used in adults.
- whole body imaging: for adults and children aged over 1 month, 0.2 mL/kg (0.1 mmol/kg); in adults and children aged over 1 year a dose of 0.4 mL/kg (0.2 mmol/kg) may be needed in some cases to produce adequate contrast and in special circumstances a dose of 0.6 mL/kg (0.3 mmol/kg) may be used in adults.

For arthrography a solution containing meglumine gadopentetate 1.876 mg/mL (0.002 mmol/mL) is given to adults by intra-articular injection. The dose depends on the joint being imaged; the usual range is from 1 to 20 mL although up to 50 mL may be given into the knee.

For imaging of the gastrointestinal tract a solution containing meglumine gadopentetate 9.38 mg/mL has been used, diluted further before use.

Administration in children. Gadopentetate is licensed in the UK for use in cranial and spinal imaging and whole body imaging in children (but see also Precautions, below). For doses, see Uses and Administration, above.

Adverse Effects

There may be headache, nausea, vomiting, dizziness, and transient sensations of heat or cold or taste disturbances on injection of gadopentetate or other gadolinium chelates. Rarely, convulsions, hypotension, allergic or anaphylactoid reactions, and shock may occur. Paraesthesias and localised pain have also been reported. Transient elevations of serum iron and bilirubin values have been observed. Nephrogenic systemic fibrosis may occur rarely in patients with renal impairment (see under Precautions, below).

General references.

1. Nelson KL, *et al.* Clinical safety of gadopentetate dimeglumine. *Radiology* 1995; **196:** 439–43.

Effects on the nervous system. Subacute encephalopathy has been reported[1] in a woman who was given repeated doses of a gadolinium chelate for magnetic resonance imaging. It was suggested that renal impairment may have contributed to retention of gadolinium, with subsequent diffusion into the CSF.

1. Maramattom BV, *et al.* Gadolinium encephalopathy in a patient with renal failure. *Neurology* 2005; **64:** 1276–8.

Hypersensitivity. Although rare, anaphylactoid reactions have occurred with a number of gadolinium chelates.[1] Severe reactions have been reported with gadopentetate,[2] gadoterate,[3,4] and gadoteridol,[5] including a fatal reaction with gadopentetate.[6] There has also been a report[7] of a severe reaction with gadoteridol in a patient who had previously tolerated gadopentetate. Reactions may occur despite premedication with antihistamines and corticosteroids.[8] Since such reactions are unpredictable, UK licensed product information for gadolinium chelates recommends that facilities for resuscitation should be readily available when they are used.

1. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 2000; **12:** 205–13.
2. Tardy B, *et al.* Anaphylactic shock induced b y intravenous gadopentetate dimeglumine. *Lancet* 1992; **339:** 494.
3. Meuli RA, Maeder P. Life-threatening anaphylactoid reaction after IV injection of gadoterate meglumine. *Am J Roentg* 1996; **166:** 729.
4. Beaudouin E, *et al.* Anaphylactic shock induced by gadoterate meglumine (DOTAREM). *Allerg Immunol (Paris)* 2003; **35:** 382–5.
5. Shellock FG, *et al.* Adverse reaction to intravenous gadoteridol. *Radiology* 1993; **189:** 151–2.
6. Jordan RM, Mintz RD. Fatal reaction to gadopentetate dimeglumine. *Am J Roentg* 1995; **164:** 743–4.
7. Witte RJ, Anzai LL. Life-threatening anaphylactoid reaction after intravenous gadoteridol administration in a patient who had previously received gadopentetate dimeglumine. *Am J Neuroradiol* 1994; **15:** 523–4.
8. Dillman JR, *et al.* Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *Am J Roentg* 2008; **190:** 187–90.

Precautions

Gadopentetate and other gadolinium chelates should not be used in patients with severe renal impairment (GFR less than 30 mL/minute per 1.73 m^2) or with acute renal impairment associated with hepato-renal syndrome or liver transplantation (see Renal Impairment, below). It should be given with care to patients with moderate renal impairment, epilepsy, hypotension, or a history of hypersensitivity, asthma, or other allergic respiratory disorders. Although, with the exception of neonates, gadopentetate is licensed in the UK for use in infants under 1 year of age, it should be used with caution because of their immature renal function (see also Children, below). US licensed product information considers that safety and efficacy have not been demonstrated in those under 2 years of age. Some other gadolinium chelates may not be licensed for use in children (see under the individual monographs). Studies *in vitro* suggest a theoretical risk that enhancement of magnetic moment by gadolinium chelates might induce vaso-occlusive symptoms in patients with sickle-cell disease, but clinical evidence is lacking. Care should be taken to avoid extravasation. Gadopentetate may interfere with tests of serum iron or bilirubin concentrations.

Breast feeding. Studies[1-3] have shown that gadopentetate is distributed into breast milk in very small amounts; the total amount excreted in the milk within 24 hours was less than 0.04% of the intravenous dose in all cases. No adverse effects have been seen in breast-feeding infants whose mothers were receiving gadopentetic acid and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding. However, to minimise the risk of nephrogenic systemic fibrosis associated with gadolinium chelates in breast-feeding infants, the EMEA's Committee for Medicinal Products for Human Use[5] (CHMP) advises mothers to stop breast feeding for at least 24 hours after the use of high-risk agents (gadodiamide, gadopentetate, and gadoversetamide). The decision of whether to continue or suspend breast feeding for 24 hours after the use of medium- (gadobenate, gadofosveset, and gadoxetate) or low-risk agents (gadobutrol, gadoterate, and gadoteridol) should be made in consultation with the mother.

1. Schmiedl U, *et al.* Excretion of gadopentetate dimeglumine in human breast milk. *Am J Roentg* 1990; **154:** 1305–6.
2. Rofsky NM, *et al.* Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. *J Magn Reson Imaging* 1993; **3:** 131–2.
3. Kubik-Huch RA, *et al.* Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology* 2000; **216:** 555–8.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)
5. MHRA/CHM. Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis. *Drug Safety Update* 2010; **3** (6): 3–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON068297 (accessed 22/03/10)

Children. After reviewing the risk of nephrogenic systemic fibrosis associated with gadolinium chelates, the EMEA's Committee for Medicinal Products for Human Use[1] (CHMP) contra-indicated the use of high-risk agents (gadodiamide, gadopentetate, and gadoversetamide) in neonates. Furthermore, when medium- (gadobenate, gadofosveset, and gadoxetate) or low-risk agents (gadobutrol, gadoterate, and gadoteridol) are used in neonates, or when any gadolinium chelate is used in infants, a single lowest possible dose should be given and not repeated for at least 7 days.

1. MHRA/CHM. Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis. *Drug Safety Update* 2010; **3** (6): 3–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON068297 (accessed 27/04/10)

Myasthenia gravis. Acute deterioration of myasthenia gravis has been reported[1] in a patient after imaging of the brain using gadopentetate.

1. Nordenbo AM, Somnier FE. Acute deterioration of myasthenia gravis after intravenous administration of gadolinium-DTPA. *Lancet* 1992; **340:** 1168.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gadopentetic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Renal impairment. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) is a rare condition that has been reported in patients with renal impairment. Use of gadolinium-containing contrast media appears to be a risk factor;[1-3] most cases have occurred with gadodiamide given in high doses for magnetic resonance angiography, but there have also been reports with other gadolinium-containing contrast media and with lower doses. It has been suggested that the mechanism involves release of free gadolinium ions into the tissues, and that the potential for this varies between the different gadolinium-based contrast media available, with gadodiamide and gadoversetamide more likely to do so.[4] The macrocyclic structure of gadoteridol and gadoterate was thought to be less prone to this effect, but further research is needed. A number of regulatory authorities including the FDA,[5] the MHRA,[6] Health Canada,[7] and the Therapeutic Goods Administration[8] (TGA) in Australia, advise that use of gadolinium-containing contrast media should be restricted in patients with severe renal impairment (GFR less than 30 mL/minute per 1.73 m^2). The TGA contra-indicates the use of gadodiamide, gadopentetate, and gadoversetamide in such patients, whereas the FDA and Health Canada advise that all gadolinium-containing contrast media should be avoided unless the diagnostic information is essential and cannot be obtained another way. The FDA gives a similar warning for use in patients with acute renal failure associated with hepato-renal syndrome or around the time of liver transplantation. More recently, the MHRA reported[9] that, after further review, the EMEA's Committee for Medicinal Products for Human Use (CHMP) contra-indicated the use of high-risk agents (gadodiamide, gadopentetate, and gadoversetamide) in those with severe renal impairment; furthermore, if use of a medium- (gadobenate, gadofosveset, and gadoxetate) or low-risk agent (gadobutrol, gadoterate, and gadoteridol) is necessary, a single lowest possible dose should be given and not repeated for at least 7 days (similar advice is also given for patients in the perioperative liver-transplantation period). For those with moderate impairment (GFR 30 to 59 mL/minute per 1.73 m^2), the CHMP advises that if use of a high-risk agent is necessary, a single lowest possible dose should be given and not repeated for at least 7 days. The value of haemodialysis to remove gadolinium-containing contrast media after use is unknown. The CHMP also advises that renal function should be tested in all patients receiving high-risk agents, and is generally advisa-

ble for those receiving medium- or low-risk agents, particularly patients aged 65 years or older.

1. Perazella MA, Rodby RA. Gadolinium-induced nephrogenic systemic fibrosis in patients with kidney disease. *Am J Med* 2007; **120:** 561–2.
2. Health Canada. Gadolinium-containing contrast agents and nephrogenic systemic fibrosis: update. *Can Adverse React News* 2007; **17** (4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n4-eng.pdf (accessed 25/08/10)
3. Moreno-Romero JA, *et al*. Nephrogenic systemic fibrosis: a case series suggesting gadolinium as a possible aetiological factor. *Br J Dermatol* 2007; **157:** 783–7.
4. Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? *Semin Dial* 2008; **21:** 129–34.
5. FDA. Gadolinium-containing contrast agents for magnetic resonance imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance (issued 8th June 2006, updated 22nd December, 2006 and 23rd May, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142884.htm (accessed 24/08/10)
6. MHRA/CHM. Gadolinium-containing MRI contrast agents: nephrogenic systemic fibrosis. *Drug Safety Update* 2007; **1** (1): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FIL E&dDocName=-CON2031801&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
7. Health Canada. Association of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD) with the use of gadolinium-containing contrast agents (issued 9th March, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/gadolinium_nth-aah-eng.pdf (accessed 18/03/09)
8. Adverse Drug Reactions Advisory Committee (ADRAC). MRI scans with gadolinium-containing contrast agents and the risk of nephrogenic systemic fibrosis—caution in patients with renal impairment. *Aust Adverse Drug React Bull* 2008; **27:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0802.pdf (accessed 18/03/09)
9. MHRA/CHM. Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis. *Drug Safety Update* 2010; **3** (6): 3–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON068297 (accessed 22/03/10)

Pharmacokinetics

Gadopentetate is rapidly distributed into the extracellular space after intravenous injection. An elimination half-life of 1.6 hours has been reported. It is not metabolised and about 90% of a dose is excreted in the urine within 24 hours. It does not appear to bind to plasma proteins. A small amount is distributed into breast milk. Gadopentetate is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Magnevist; Opacite; Viewgam; ***Austral.***: Magnevist; ***Austria***: Magnegita; Magnevist; ***Belg.***: Magnegita; Magnevist; ***Braz.***: Magnevistan; ***Canad.***: Magnevist; ***Chile***: Magnevistan†; ***Cz.***: Magnegita; Magnetolux; Magnevist; ***Denm.***: Magnegita†; Magnevist; Magnograf; ***Fin.***: Magnevist; ***Fr.***: Magnegita; Magnevist; ***Ger.***: Magnegita; Magnevist; MR-Lux; ***Gr.***: Magnevist; ***Hung.***: Magnevist; ***India***: Magnevist; ***Irl.***: Magnegita; Magnetolux; Magnevist; ***Israel***: Gado-MRI; Magnetol; ***Ital.***: Magnevist; ***Mex.***: Viewgam†; ***Neth.***: Magnegita; Magnevist†; Magnograf†; ***Norw.***: Magnevist; ***NZ***: Magnevist; ***Philipp.***: Gadomin; ***Port.***: Ceacont; Magnegita; Magnevist; ***Rus.***: Magnevist (Магневист); ***S.Afr.***: Magnevist; ***Spain***: Magnetolux; Magnevist; Magnograf†; ***Swed.***: Magnevist; ***Switz.***: Magnevist; Magnograf; MR-Lux; ***Turk.***: Magnevist; ***UK***: Magnevist; ***Ukr.***: Magnilek (Магнилек); Tomovist (Томовист); ***USA***: Magnevist; ***Venez.***: Magnevistan.

Pharmacopoeial Preparations
USP 36: Gadopentetate Dimeglumine Injection.

Gadoteric Acid *(BAN, rINN)*

Acide Gadotérique; Ácido gadotérico; Acidum Gadotericum; Gadoteerihappo; Gadotérico, ácido; Gadotersyra; Gd-DOTA; ZK-112004; Гадотеровая Кислота.

Hydrogen [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)]gadolinate(1-); Hydrogen [1,4,7,10-tetrakis(carboxylatomethyl)-1,4,7,10-tetra-azacyclododecane-κ^4*N*]gadolinate (1-).

$C_{16}H_{25}GdN_4O_8$=558.6
CAS — 72573-82-1.
ATC — V08CA02.
ATC Vet — QV08CA02.
UNII — QVF9Y6955W.

Meglumine Gadoterate *(BANM, rINNM)*

Gadotérate de Méglumine; Gadoterate Meglumine (USAN); Gadoterato de meglumina; Meglumini Gadoteras; P-449; Меглумина Гадотерат.

$C_{16}H_{25}N_4O_8.C_7H_{17}NO_5Gd$=753.9
CAS — 92943-93-6.
ATC — V08CA02.
ATC Vet — QV08CA02.

Uses and Administration

Gadoteric acid is an ionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body, and in magnetic resonance angiography.

Gadoteric acid is given intravenously as the meglumine salt. It is available as a solution containing meglumine gadoterate 376.9 mg/mL (0.5 mmol/mL). The usual dose in adults and children is 0.2 mL/kg (0.1 mmol/kg) by intravenous injection. A second dose of up to 0.4 mL/kg (0.2 mmol/kg) may be given within 30 minutes if necessary. For angiography, a dose of 0.1 to 0.2 mL/kg (0.05 to 0.1 mmol/kg) may be given, repeated if required.

Administration in children. For doses of gadoteric acid in children, see Uses and Administration, above.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

Hypersensitivity. For reports of anaphylactoid reactions with gadoterate, see under Adverse Effects of Gadopentetic Acid, p. 1586.2.

Pharmacokinetics

Gadoterate is distributed into the extracellular space after intravenous injection. It is not bound to plasma proteins. A plasma half-life of about 1.5 hours has been reported. It is not metabolised and about 90% of a dose is excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dotarem; ***Austral.***: Dotarem; ***Austria***: Artirem; Dotarem; ***Belg.***: Artirem; Dotarem; ***Chile***: Dotarem; ***Cz.***: Dotarem; ***Denm.***: Dotarem; ***Fin.***: Dotarem; ***Fr.***: Artirem; Dotarem; ***Ger.***: Artirem; Dotarem; ***Gr.***: Dotarem; ***Hung.***: Dotarem; ***Irl.***: Dotarem; ***Israel***: Dotarem; ***Ital.***: Dotarem; ***Neth.***: Artirem; Dotarem; ***Norw.***: Dotarem; ***NZ***: Dotarem; ***Port.***: Dotarem; ***Rus.***: Dotarem (Дотарем); ***Spain***: Dotarem; ***Swed.***: Dotarem; ***Switz.***: Artirem; Dotarem; ***Thai.***: Dotarem; ***Turk.***: Dotarem; ***USA***: Dotarem; ***Venez.***: Dotarem.

Gadoteridol *(BAN, USAN, rINN)*

Gadotéridol; Gadoteridoli; Gadoteridolum; Gd-HP-DO3A; SQ-32692; Гадотеридол.

(±)-[10-(2-Hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)]gadolinium.

$C_{17}H_{29}GdN_4O_7$=558.7
CAS — 120066-54-8.
ATC — V08CA04.
ATC Vet — QV08CA04.
UNII — 0199MV609F.

Pharmacopoeias. In *US.*

USP 36: (Gadoteridol). A white to off-white, odourless, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in isopropyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Gadoteridol is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body.

Gadoteridol is available as a solution containing 279.3 mg/mL (0.5 mmol/mL). The usual adult dose is 0.2 mL/kg (0.1 mmol/kg) intravenously; for CNS imaging, an additional dose of up to 0.4 mL/kg (0.2 mmol/kg) may be given up to 30 minutes after the first if necessary. A single dose of 0.2 mL/kg (0.1 mmol/kg) is used in children from 6 months of age (see also below).

Administration in children. In some countries, gadoteridol is licensed for use in children from 6 months of age; UK licensed product information notes that experience is limited in children between 6 months and 2 years of age, and advises particular caution if it is to be used in this age group. US licensed product information considers that safety and efficacy have not been demonstrated in this age group, and only indicates the product for imaging cranial and spinal structures in those aged 2 years and over. For doses see Uses and Administration, above.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2 and p. 1586.2, respectively.

Reviews.
1. Runge VM, Parker JR. Worldwide clinical safety assessment of gadoteridol injection: an update. *Eur Radiol* 1997; **7** (suppl 5): 243–5.

Hypersensitivity. For a report of an anaphylactoid reaction with gadoteridol, see under Adverse Effects of Gadopentetic Acid, p. 1586.2.

Pharmacokinetics

Gadoteridol is distributed into extracellular fluid after intravenous injection. About 94% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 1.57 hours has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Prohance; ***Austria***: Prohance; ***Belg.***: Prohance; ***Canad.***: ProHance; ***Cz.***: Prohance; ***Denm.***: Prohance; ***Fin.***: Prohance; ***Fr.***: Prohance; ***Ger.***: Prohance; ***Irl.***: Prohance; ***Ital.***: Prohance; ***Jpn***: Prohance; ***Neth.***: Prohance; ***Norw.***: Prohance; ***Spain***: Prohance; ***Swed.***: Prohance; ***Switz.***: Prohance; ***UK***: Prohance; ***USA***: Prohance.

Pharmacopoeial Preparations
USP 36: Gadoteridol Injection.

Gadoversetamide *(BAN, USAN, rINN)*

Gadoversetamida; Gadoversétamide; Gadoversetamidum; MP-1177; Гадоверсетамид.

{*N*,*N*-Bis[2-({[carboxymethyl][(2-methoxyethyl)carbamoyl]methyl}amino)ethyl]glycinato(3-)}gadolinium.

$C_{20}H_{34}GdN_5O_{10}$=661.8
CAS — 131069-91-5.
ATC — V08CA06.
ATC Vet — QV08CA06.
UNII — RLM74T3Z9D.

Pharmacopoeias. In *US.*

USP 36: (Gadoversetamide). A white odourless powder. Freely soluble in water. Store in airtight containers. Protect from light.

Uses and Administration

Gadoversetamide is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body (particularly to visualise the liver).

Gadoversetamide is available as a solution containing 330.9 mg/mL (0.5 mmol/mL). The usual dose is 0.2 mL/kg (0.1 mmol/kg) intravenously.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

Interference with diagnostic tests. Like gadodiamide (see p. 1585.3), gadoversetamide may interfere with colorimetric methods for measuring serum-calcium concentrations.

Gadoversetamide may also interfere with measurement of serum-copper, iron, and zinc concentrations.

Renal impairment. For the view that gadoversetamide may carry an increased risk of the development of nephrogenic systemic fibrosis in patients with renal impairment, see p. 1586.3.

Pharmacokinetics

Gadoversetamide is distributed into the extracellular space after intravenous injection. It is not bound to plasma proteins. An elimination half-life of about 1.7 hours has been reported. It is not metabolised and about 95.5% of a dose is excreted in the urine within 24 hours. Gadoversetamide is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Optimark; ***Austral.***: Optimark; ***Austria***: Optimark; ***Belg.***: Optimark; ***Canad.***: Optimark; ***Cz.***: Optimark; ***Denm.***: Optimark†; ***Gr.***: Optimark; ***Hung.***: Optimark; ***Irl.***: Optimark; ***Neth.***: Optimark; ***Norw.***: Optimark; ***Pol.***:

Optimark; ***Port.***: Optimark; ***Rus.***: Optimark (Оптимарк); ***Spain***: Optimark; ***Swed.***: Optimark; ***USA***: Optimark.

Pharmacopoeial Preparations
USP 36: Gadoversetamide Injection.

Gadoxetic Acid *(rINN)*

Acide Gadoxétique; Ácido gadoxético; Acidum Gadoxeticum; Gadoxético, ácido; Gd-EOB-DTPA; Гадоксетовая Кислота.
Dihydrogen [*N*-{(2*S*)-2-[bis(carboxymethyl)amino]-3-(*p*-ethoxyphenyl)propyl}-*N*-[2-[bis(carboxymethyl)amino]ethyl] glycinato(5-)]gadolinate(2-).
$C_{23}H_{30}GdN_3O_{11}$=681.8
CAS — *135326-11-3 (gadoxetic acid).*
ATC — *V08CA10.*
ATC Vet — *QV08CA10.*
UNII — *3QJA87N40S.*

Sodium Gadoxetate *(rINNM)*

Gadoxétate de Sodium; Gadoxetate Disodium (USAN); Gadoxetate Sodium; Gadoxetato de sodio; Natrii Gadoxetas; ZK-139834; Натрий Гадоксетат.
$C_{23}H_{28}GdN_3Na_2O_{11}$=725.7
CAS — *135326-22-6.*
ATC — *V08CA10.*
ATC Vet — *QV08CA10.*
UNII — *HOY74VZE0M.*

Uses and Administration

Gadoxetic acid is an ionic gadolinium chelate with actions similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It is taken up by the liver and excreted in bile and is used in imaging of the liver.

Gadoxetic acid is given intravenously as the sodium salt. It is available as a solution containing sodium gadoxetate 181.4 mg/mL (0.25 mmol/mL). The usual dose is 0.1 mL/kg (0.025 mmol/kg).

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

Pharmacokinetics

Gadoxetate is distributed into the extracellular space after intravenous injection and is also taken up by the liver. It is less than 10% bound to plasma proteins. It is excreted in about equal amounts in the bile and in the urine. An elimination half-life of about 1 hour has been reported. Gadoxetate is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Primovist; ***Austria***: Primovist; ***Belg.***: Primovist; ***Canad.***: Primovist; ***China***: Primovist (普美显); ***Cz.***: Primovist; ***Fin.***: Primovist; ***Ger.***: Primovist; ***Gr.***: Primovist; ***Hung.***: Primovist; ***Irl.***: Primovist; ***Ital.***: Primovist; ***Neth.***: Primovist; ***Norw.***: Primovist; ***Port.***: Primovist; ***Rus.***: Primovist (Примовист); ***Spain***: Primovist; ***Swed.***: Primovist; ***Switz.***: Primovist; ***Turk.***: Primovist; ***UK***: Primovist; ***USA***: Eovist.

Galactose *(USAN)*

D-Galactopyranose; α-D-Galactopyranose; Galactosa; D-Galactose; Galactosum; Galaktaosi; Galaktos; Galaktosa; Galaktozė; Galaktóz; Galaktoza; Галактоза.
$C_6H_{12}O_6$=180.2
CAS — *59-23-4 (D-galactose); 3646-73-9 (α-D-galactose).*
ATC — *V04CE01; V08DA02 (microparticles of galactose).*
ATC Vet — *QV04CE01; QV08DA02 (microparticles of galactose).*
UNII — *X2RN3Q8DNE.*

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8 (Galactose). A white or almost white, crystalline or finely granulated powder. Freely soluble or soluble in water; very slightly soluble in alcohol.

USNF 31: (Galactose). A white, crystalline or finely granulated powder. Soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Profile

Galactose is a naturally occurring monosaccharide used as an ultrasound contrast medium (p. 1580.2); dissolution of galactose microparticles releases microbubbles of air that provide echo-enhancement.

Galactose may be given as a microbubble-microparticle suspension prepared immediately before use by suspending 3 g of galactose microparticles in 13.5 mL of a solution containing 200 mg/mL galactose. When given transcervically to enhance ultrasound imaging of the female genital tract, the usual dose is 2 to 5 mL, with additional doses of 1 to 2 mL as required, to a maximum of 30 mL. When given intravenously in echocardiography, the usual dose is 4 to 10 mL; infants and children may be given the following doses according to age: neonates to 4 weeks, 0.5 mL; 4 weeks to 12 months, 1 to 2 mL; 1 to 5 years, 2 mL. Adults and children, including infants, may be given the maximum of 5 injections.

Similar suspensions of galactose, with palmitic acid to stabilise the microbubbles, prepared immediately before use by suspending galactose microparticles in water for injection to concentrations of 200, 300, and 400 mg/mL are also used. When given intravenously to enhance ultrasound imaging of blood vessels and in echocardiography, the dose and strength used varies depending on the procedure. When given as a bladder instillation for diagnosis of vesicoureteral reflux in children, the 300 mg/mL suspension is recommended; the volume used in infants is 5 mL and in older children 10% of the measured bladder volume.

The clearance of galactose given intravenously has been used as a measure of liver function. Galactose labelled with carbon-13 (p. 2470.3) has also been used.

Administration in children. Galactose is licensed for use in infants and children in echocardiography and for diagnosis of vesicoureteral reflux. For doses, see Uses and Administration, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies galactose as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Precautions. Preparations that contain, or are metabolised to, galactose may interfere with the results from glucose tests (p. 2516.3). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2] Licensed product information warns that galactose should not be used for visualisation in patients with galactosaemia.

1. MHRA Medical device alert: ref MDA/2007/058 issued 19th July, 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 24/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Levovist; ***Austria***: Echovist; ***Fr.***: Echovist†; Levovist†; ***Ger.***: Echovist; Levovist†; ***Gr.***: L-Vist; Levovist; ***Hung.***: Echovist†; ***Israel***: Echovist; ***Ital.***: Levovist; ***NZ***: Levovist†; ***Spain***: Levovist†; ***Swed.***: Echovist†; ***Switz.***: Levovist†; ***UK***: Echovist†.

Multi-ingredient Preparations. ***India***: Osmowin; ***Ital.***: Reumilase.

Iobitridol *(BAN, rINN)*

Iobitridolum; Jobitridol; Jobitridoli; Йобитридол.
N,N'-Bis(2,3-dihydroxypropyl)-5-[2-(hydroxymethyl)hydracrylamido]-2,4,6-triiodo-*N,N'*-dimethylisophthalamide.
$C_{20}H_{28}I_3N_3O_9$=835.2
CAS — *136949-58-1.*
ATC — *V08AB11.*
ATC Vet — *QV08AB11.*
UNII — *182ECH14UH.*

Profile

Iobitridol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, or by instillation into body cavities and is used in a wide range of procedures including angiography, arthrography, cholangiopancreatography, and hysterosalpingography. It is also used for contrast enhancement in computed tomography.

It is usually available as solutions containing 54.84 to 76.78% of iobitridol (equivalent to 250 to 350 mg/mL of iodine). The dose and strength used varies depending on the procedure and route.

References.

1. Petersein J, *et al.* Results of the safety and efficacy of iobitridol in more than 61,000 patients. *Eur Radiol* 2003; **13:** 2006–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iobitridol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Xenetic†; Xenetix; ***Austria***: Xenetix; ***Belg.***: Xenetix; ***Chile***: Xenetix; ***Cz.***: Xenetix; ***Denm.***: Xenetix; ***Fin.***: Xenetix; ***Fr.***: Xenetix; ***Ger.***: Xenetix; ***Gr.***: Xenetix; ***Hung.***: Xenetix; ***Irl.***: Xenetix; ***Israel***: Xenetix; ***Ital.***: Xenetix; ***Neth.***: Xenetix; ***Norw.***: Xenetix; ***Port.***: Xenetix; ***Rus.***: Xenetix (Ксенетикс); ***Spain***: Xenetix; ***Swed.***: Xenetix; ***Switz.***: Xenetix; ***Thai.***: Xenetix; ***Turk.***: Xenetix; ***Venez.***: Xenetix.

Iocetamic Acid *(BAN, USAN, pINN)*

Acide Iocétamique; Ácido iocetámico; Acidum Iocetamicum; DRC-1201; Iocetámico, ácido; Jocetamsyra; Josetaamihappo; MP-620; Йоцетамовая Кислота.
N-Acetyl-*N*-(3-amino-2,4,6-tri-iodophenyl)-2-methyl-β-alanine; 2-[*N*-(3-Amino-2,4,6-tri-iodophenyl)acetamidomethyl]-propionic acid.
$C_{12}H_{13}I_3N_2O_3$=614.0
CAS — *16034-77-8.*
ATC — *V08AC07.*
ATC Vet — *QV08AC07.*
UNII — *FA675Q0E3E.*

Description. Iocetamic acid contains about 62% of I.

Profile

Iocetamic acid is an ionic monomeric iodinated radiographic contrast medium with similar properties to iopanoic acid (p. 1591.1). It is absorbed from the gastrointestinal tract and excreted in bile and has been given orally for cholecystography.

Iodamide *(BAN, USAN, rINN)*

Ametriodinic Acid; B-4130; Iodamida; Iodamidum; Jodamid; Jodiamidi; SH-926; Йодамид.
α,5-Diacetamido-2,4,6-tri-iodo-*m*-toluic acid; 3-Acetamido-5-acetamidomethyl-2,4,6-tri-iodobenzoic acid.
$C_{12}H_{11}I_3N_2O_4$=627.9
CAS — *440-58-4.*
ATC — *V08AA03.*
ATC Vet — *QV08AA03.*
UNII — *4RII332O0R.*

Description. Iodamide contains about 60.6% of I.

Pharmacopoeias. In *Jpn*.

Meglumine Iodamide *(BANM, rINNM)*

Iodamida de meglumina; Iodamide Meglumine (USAN); Iodamide Méglumine; Meglumini Iodamidum; Меглумина Йодамид.
The *N*-methylglucamine salt of iodamide.
$C_{12}H_{11}I_3N_2O_4.C_7H_{17}NO_5$=823.2
CAS — *18656-21-8.*
ATC — *V08AA03.*
ATC Vet — *QV08AA03.*
UNII — *6X283535A3.*

Description. Meglumine iodamide contains about 46.3% of I.

Sodium Iodamide *(BANM, rINNM)*

Iodamida sódica; Iodamide Sodique; Iodamide Sodium; Natrii Iodamidum; Натрий Йодамид.
$C_{12}H_{10}I_3N_2NaO_4$=649.9
CAS — *10098-82-5.*
ATC — *V08AA03.*
ATC Vet — *QV08AA03.*

Description. Sodium iodamide contains about 58.6% of I.

Profile

Iodamide is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It is used in many procedures and may be given intravenously or by other routes, for example by instillation into the bladder or uterus; it has also been used for computed tomography.

It has been given as a 24 to 65% solution of the meglumine salt, or as a mixture of the sodium and meglumine salts; solutions of the sodium salt have also been used. The dose varies according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Uromiro; ***Venez.***: Uromiron.

Iodised Oil

Aceite yodado; Ethiodized Oil; Этиловые Эфиры Йодированных Жирных Кислот.

CAS — 8001-40-9 (iodised oil); 8008-53-5 (ethiodized oil injection).
ATC — V08AD01.
ATC Vet — QV08AD01.
UNII — KZW0R0686Q.

Description. Iodised oil is an iodine addition product of the ethyl esters of the fatty acids obtained from poppy-seed oil. It contains about 35 to 39% of combined iodine.

Incompatibility. Because of its solvent action on polystyrene, iodised oil injection should not be given in syringes made with polystyrene.

Uses and Administration

Iodised oil is an iodinated radiographic contrast medium (p. 1580.1) that is used mainly for lymphography. It has been used for hysterosalpingography but water-soluble agents are preferred. Although some preparations have been used in bronchography, the fluid injection of iodised oil is unsuitable for such use. Doses are dependent upon the procedure.

Because it is slowly metabolised to release iodine, iodised oil is used in the management of iodine deficiency (p. 2337.3).

Infertility. For reference to the use of iodised oil in the management of infertility, see Hysterosalpingography under Adverse Effects and Precautions, below.

Malignant neoplasms. Intra-arterial injection of iodised oil has been used in both the diagnosis and management of malignant neoplasms of the liver (p. 709.3). After injection into the hepatic artery, iodised oil is selectively retained by hepatic carcinomas and may have a role as an adjunct to computed tomography for both diagnosis and monitoring.[1-3] It has also been used in the management of hepatic carcinoma,[2,4] either to increase the retention of antineoplastics (chemoembolisation),[5] or to provide targeted delivery of radioactive iodine.[6]

1. Dalla Palma L. Diagnostic imaging and interventional therapy of hepatocellular carcinoma. *Br J Radiol* 1998; **71:** 808–18.
2. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003; **52** (suppl): iii1–iii8. Also available at: http://www.bsg.org.uk/pdf_word_docs/hcc.pdf (accessed 27/03/06)
3. Zheng X-H, *et al.* Detection of hypervascular hepatocellular carcinoma: comparison of multi-detector CT with digital subtraction angiography and Lipiodol CT. *World J Gastroenterol* 2005; **11:** 200–203.
4. Trinchet JC, *et al.* Review article: intra-arterial treatments in patients with hepatocellular carcinoma. *Aliment Pharmacol Ther* 2003; **17** (suppl 2): 111–18.
5. Group d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; **332:** 1256–61.
6. Lau WY, *et al.* Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; **353:** 797–801.

Adverse Effects and Precautions

The risk of hypersensitivity reactions or iodism is greater after the use of iodised oil than after water-soluble iodinated contrast media such as the amidotrizoates. Pulmonary oil embolism is reported to be relatively frequent after lymphography but is not usually severe; however, hypotension, tachycardia, and pulmonary oedema and infarction may occur rarely and deaths have been reported in patients with pulmonary disease. Chemical pneumonitis, oedema, granuloma formation, and goitre have occurred.

Great care must be taken to avoid vascular structures, because of the danger of oil embolism; it should therefore not be used in areas affected by haemorrhage or local trauma. Iodised oil should be used with care in patients with thyroid dysfunction or a history of allergic reactions. Use may interfere with thyroid-function tests for several months.

Hysterosalpingography. The use of oily contrast media such as iodised oil for hysterosalpingography has been associated with serious adverse effects, including tubal occlusion,[1] and cerebral and pulmonary oil embolism,[2,3] and water-soluble contrast media are usually preferred. However, diagnostic hysterosalpingography using iodised oil has been associated with an increase in fertility[4] and randomised trials[5,6] using iodised oil for treatment in patients with unexplained infertility have found a similar effect.

1. Wright FW, Stallworthy J. Female sterility produced by investigation. *BMJ* 1973; **3:** 632.
2. Dan U, *et al.* Cerebral embolization and coma after hysterosalpingography with oil-soluble contrast medium. *Fertil Steril* 1990; **53:** 939–40.
3. Uzun O, *et al.* Pulmonary and cerebral oil embolism after hysterosalpingography with oil soluble contrast medium. *Respirology* 2004; **9:** 134–6.
4. Johnson NP. A review of the use of lipiodol flushing for unexplained infertility. *Treat Endocrinol* 2005; **4:** 233–43.
5. Nugent D, *et al.* A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. *Fertil Steril* 2002; **77:** 173–5.
6. Johnson NP, *et al.* The FLUSH trial—flushing with lipiodol for unexplained (and endometriosis-related) subfertility by hysterosalpingography: a randomized trial. *Hum Reprod* 2004; **19:** 2043–51.

Pharmacokinetics

Iodised oil may persist in the body for several weeks or months. It is only slowly absorbed from most body sites, although absorption from the peritoneal cavity is stated to be relatively rapid. It is reported to be slowly metabolised to fatty acids and iodine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lipiodol; ***Austral.***: Lipiodol; ***Austria***: Lipiodol; ***Belg.***: Lipiodol; ***Canad.***: Lipiodol; ***Chile***: Lipiodol; ***Cz.***: Lipiodol; ***Denm.***: Lipiodol; ***Fr.***: Lipiodol; ***Ger.***: Lipiodol; ***Gr.***: Lipiodol; ***Hung.***: Lipiodol; ***Irl.***: Lipiodol; ***Israel***: Lipiodol; ***Ital.***: Lipiodol; ***Neth.***: Lipiodol; ***NZ***: Lipiodol; ***Port.***: Lipiodol; ***Switz.***: Lipiodol; ***Thai.***: Lipiodol Ultra-Fluide; ***Turk.***: Lipiodol; ***UK***: Lipiodol; ***USA***: Ethiodol†; ***Venez.***: Lipiodol.

Pharmacopoeial Preparations
BP 2014: Iodised Oil Fluid Injection;
USP 36: Ethiodized Oil Injection.

Iodixanol *(BAN, USAN, rINN)*

2-5410-3A; Iodixanolum; Jodiksanoli; Jodixanol; Йодиксанол.

5,5′-[(2-Hydroxytrimethylene)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide].

$C_{35}H_{44}I_6N_6O_{15}$=1550.2
CAS — 92339-11-2.
ATC — V08AB09.
ATC Vet — QV08AB09.
UNII — HW8W27HTXX.

Description. Iodixanol contains about 49.1% of I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Iodixanol). A white or almost white, hygroscopic powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Iodixanol). A white to off-white, amorphous, odourless, hygroscopic powder. Freely soluble in water. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Iodixanol is a nonionic dimeric iodinated radiographic contrast medium (p. 1580.1); it is iso-osmolar with blood. It may be given intravenously, intra-arterially, intrathecally, orally, or by instillation into body cavities, and is used in procedures including angiography, arthrography, cholangiopancreatography, hysterosalpingography, myelography, and urography, as well as for imaging of the upper gastrointestinal tract and for contrast enhancement during computed tomography.

Iodixanol is usually available as a solution containing between 30.5 and 65.2% of iodixanol (equivalent to between 150 and 320 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

References.

1. Spencer CM, Goa KL. Iodixanol: a review of its pharmacodynamic and pharmacokinetic properties and diagnostic use as an x-ray contrast medium. *Drugs* 1996; **52:** 899–927.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1. For adverse effects relating to the use of nonionic contrast media such as iodixanol for myelography, see under Iohexol (p. 1590.2).

References.

1. McCullough PA. Renal safety of iodixanol. *Expert Rev Cardiovasc Ther* 2006; **4:** 655–61.
2. Heinrich MC, *et al.* Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology* 2009; **250:** 68–86.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iodixanol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

Iodixanol is rapidly distributed into extracellular fluid after intravenous injection. It is not bound to plasma proteins. It is not metabolised and about 97% of a dose is excreted in the urine within 24 hours. A terminal elimination half-life of about 2 hours has been reported. Iodixanol is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Visipaque; ***Austral.***: Visipaque; ***Austria***: Visipaque; ***Belg.***: Visipaque; ***Canad.***: Visipaque; ***Chile***: Visipaque; ***China***: Visipaque (威视派克); ***Cz.***: Visipaque; ***Denm.***: Visipaque; ***Fin.***: Visipaque; ***Fr.***: Visipaque; ***Ger.***: Visipaque; ***Gr.***: Visipaque; ***Hung.***: Visipaque; ***Irl.***: Visipaque; ***Israel***: Visipaque; ***Ital.***: Visipaque; ***Neth.***: Visipaque; ***Norw.***: Visipaque; ***NZ***: Visipaque; ***Port.***: Visipaque; ***Rus.***: Visipaque (Визипак); ***Spain***: Visipaque; ***Swed.***: Visipaque; ***Switz.***: Visipaque; ***Turk.***: Visipaque; ***UK***: Visipaque; ***Ukr.***: Visipaque (Визипак); ***USA***: Visipaque.

Pharmacopoeial Preparations
USP 36: Iodixanol Injection.

Iodoxamic Acid *(BAN, USAN, rINN)*

Acide Iodoxamique; Ácido iodoxámico; Acidum Iodoxamicum; B-10610; Iodoxámico, ácido; Jodoksaamihappo; Jodoxamsyra; SQ-21982; Йодоксамовая Кислота.

3,3′-(4,7,10,13-Tetraoxahexadecanedioyldiamino)bis(2,4,6-tri-iodobenzoic acid).

$C_{26}H_{26}I_6N_2O_{10}$=1287.9
CAS — 31127-82-9.
ATC — V08AC01.
ATC Vet — QV08AC01.
UNII — NS1Y283HW4.

Description. Iodoxamic acid contains about 59.1% of I.

Meglumine Iodoxamate *(BANM, rINNM)*

Dimeglumine Iodoxamate; Iodoxamate de Méglumine; Iodoxamate Meglumine (USAN); Iodoxamato de meglumina; Meglumini Iodoxamas; Меглумина Йодоксамат.

The di(*N*-methylglucamine) salt of iodoxamic acid.

$C_{26}H_{26}I_6N_2O_{10}.(C_7H_{17}NO_5)_2$=1678.4
CAS — 51764-33-1.
ATC — V08AC01.
ATC Vet — QV08AC01.
UNII — CIX5G6J9R1.

Description. Meglumine iodoxamate contains about 45.4% of I.

Profile

Iodoxamic acid is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1) that has been used intravenously as the meglumine salt for cholecystography and cholangiography.

Iofendylate *(BAN, rINN)*

Ethyl Iodophenylundecylate; Iodophendylate; Iofendilato; Iofendylatum; Iophendylate; Jofendylaatti; Jofendylat; Йофендилат.

A mixture of stereoisomers of ethyl 10-(4-iodophenyl) undecanoate.

$C_{19}H_{29}IO_2$=416.3
CAS — 99-79-6; 1320-11-2.
ATC — V08AD04.
ATC Vet — QV08AD04.
UNII — 2990I809YH (iophendylate); 6V3I57K9UL (ethyl 10-(4-iodophenyl)undecanoate).

Description. Iofendylate contains about 30.5% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Iophendylate). A colourless to pale yellow, viscous liquid, darkening on long exposure to air. Is odourless or has a faintly ethereal odour. Very slightly soluble in water; freely soluble in alcohol, in chloroform, in ether, and in benzene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Iofendylate is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It was formerly used for

myelography, but was associated with serious adverse effects, including allergy, arachnoiditis, and aseptic meningitis, and has now been superseded by nonionic media. Residues of iofendylate remaining years after myelography have been associated with adverse effects. Other former uses included ventriculography, and visualisation of the fetus in the amniotic sac.

Preparations

Pharmacopoeial Preparations
BP 2014: Iofendylate Injection;
USP 36: Iophendylate Injection.

Ioglicic Acid *(BAN, USAN, rINN)*

Acide Ioglicique; Ácido Ioglícico; Acidum Ioglicicum; Ioglícico, ácido; Joglicinsyra; Joglisiinihappo; SH-H-200-AB; Йоглициевая Кислота.

5-Acetamido-2,4,6-tri-iodo-*N*-(methylcarbamoylmethyl)isophthalamic acid.

$C_{13}H_{12}I_3N_3O_5$=671.0

CAS — 49755-67-1.
ATC — V08AA06.
ATC Vet — QV08AA06.
UNII — 3LGR5S8101.

Description. Ioglicic acid contains about 56.7% of I.

Meglumine Ioglicate *(BANM, rINNM)*

Ioglicate de Méglumine; Ioglicate Meglumine; Ioglicato de meglumina; Meglumini Ioglicas; Меглумина Йоглицият.

The *N*-methylglucamine salt of ioglicic acid.

$C_{13}H_{12}I_3N_3O_5$,$C_7H_{17}NO_5$=866.2

ATC — V08AA06.
ATC Vet — QV08AA06.
UNII — FK97TOF9G0.

Description. Meglumine ioglicate contains about 44.0% of I.

Sodium Ioglicate *(BANM, rINNM)*

Ioglicate de Sodium; Ioglicate Sodium; Ioglicato sódico; Natrii Ioglicas; Натрий Йоглицият.

$C_{13}H_{11}I_3N_3NaO_5$=693.0

ATC — V08AA06.
ATC Vet — QV08AA06.
UNII — YS85R4Y0EA.

Description. Sodium ioglicate contains about 54.9% of I.

Profile

Ioglicic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) that has been used, as the meglumine and sodium salts, for diagnostic procedures.

Iohexol *(BAN, USAN, rINN)*

Iohexolum; Joheksoli; Joheksolis; Johexol; Win-39424; Йогексол.

N,N′-Bis(2,3-dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-tri-iodoisophthalamide.

$C_{19}H_{26}I_3N_3O_9$=821.1

CAS — 66108-95-0.
ATC — V08AB02.
ATC Vet — QV08AB02.
UNII — 4419T9MX03.

Description. Iohexol contains about 46.4% of I.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Iohexol). A white or greyish-white, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Iohexol). A white to off-white, hygroscopic, odourless powder. Very soluble in water and in methyl alcohol; practically insoluble or insoluble in chloroform and in ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Iohexol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, intrathecally, orally, rectally, or by instillation into body cavities and is used in diagnostic procedures including myelography, angiography, urography, arthrography, and visualisation of the gastrointestinal tract and body cavities. Iohexol is also used to produce contrast enhancement during computed tomography.

Iohexol is usually available as solutions containing 30.2 to 75.5% of iohexol (equivalent to 140 to 350 mg/mL of iodine) and the dose and strength used vary according to the procedure and the route.

Adverse Effects, Treatment, and Precautions

Iohexol and other nonionic iodinated contrast media have similar adverse effects and precautions to ionic media but the effects tend to be less severe and the incidence is generally lower; see under the amidotrizoates, p. 1582.1 and p. 1583.1 for details.

Additional neurological adverse effects may occur when nonionic media such as iohexol are used for myelography. These include severe headache, backache, neck stiffness, dizziness, and leg or sciatic-type pain. Convulsions, aseptic meningitis, and mild and transitory perceptual aberrations, such as visual and speech disturbances, and confusion, may occur occasionally; rarely, more severe mental disturbances have occurred. Urinary retention has also been reported.

Breast feeding. Iohexol is distributed into breast milk in very small quantities[1] but no adverse effects have been seen in breast-feeding infants whose mothers were receiving iohexol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Nielsen ST, *et al.* Excretion of iohexol and metrizoate in human breast milk. *Acta Radiol* 1987; **28:** 523–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Effects on the nervous system. Encephalopathy developed in a 48-year-old man with sciatica within 9 hours of iohexol for lumbar myelography but had largely resolved 48 hours after the myelogram; complete resolution took 4 days.[1] However, recovery was slow in a patient who developed paraplegia and areflexia in the legs after a similar procedure. Five months later the patient still complained of paraesthesia in her legs and could not stand without support.[2] Encephalopathy has also been reported in association with use of iohexol for coronary angiography.[3]

1. Donaghy M, *et al.* Encephalopathy after iohexol myelography. *Lancet* 1985; **ii:** 887.
2. Noda K, *et al.* Prolonged paraplegia after iohexol myelography. *Lancet* 1991; **337**: 681.
3. Sawaya RA, *et al.* Contrast-induced encephalopathy following coronary angioplasty with iohexol. *South Med J* 2007; **100:** 1054–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iohexol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Antiarrhythmics. A small retrospective study[1] found that concurrent use of iohexol and *amiodarone* resulted in significant prolongation of the QT_c interval compared with iohexol alone. Caution was advised in the use of iohexol in patients taking antiarrhythmics that prolong QT interval.

1. Goernig M, *et al.* Iohexol contrast medium induces QT prolongation in amiodarone patients. *Br J Clin Pharmacol* 2004; **58:** 96–8.

Pharmacokinetics

After intravascular use, 90% or more of a dose of iohexol is eliminated unchanged in the urine within 24 hours. An elimination half-life of about 2 hours in patients with normal renal function has been reported. Protein binding in blood is reported to be very low.

Pregnancy. Contrast material was detected[1] in the intestines of twin neonates who were born 17 hours after iohexol was given to their mother for angiography, suggesting that transplacental transfer had taken place.

1. Moon AJ, *et al.* Transplacental passage of iohexol. *J Pediatr* 2000; **136:** 548–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Omnipaque; ***Austral.***: Omnipaque; ***Austria***: Accupaque; Omnipaque; ***Belg.***: Omnipaque; ***Canad.***: Omnipaque; ***Chile***: Omnipaque; ***China***: Omnipaque (欧乃派克); Ou Su (欧苏); Shuang Bei (双北); ***Cz.***: Omnipaque; ***Denm.***: Omnipaque; ***Fin.***: Omnipaque; ***Fr.***: Omnipaque; ***Ger.***: Accupaque; Iohexagita; Omnipaque; ***Gr.***: Accupaque; Omnipaque; ***Hung.***: Omnipaque; ***India***: Radiopaque; ***Irl.***: Omnipaque; ***Israel***: Omnipaque; ***Ital.***: Omnipaque; ***Neth.***: Omnipaque; ***Norw.***: Omnipaque; ***NZ***: Omnipaque; ***Port.***: Omnipaque; ***Rus.***: Omnipaque (Омнипак); Unihexol (Юнигексол); ***Spain***: Nitigraf; Omnipaque; Omnitrast†; ***Swed.***: Omnipaque; ***Switz.***: Accupaque; Omnipaque†; ***Thai.***: Iobrix; ***Turk.***: Kopaq; Omnipaque; ***UK***: Omnipaque; ***Ukr.***: Omnipaque (Омнипак); Tomohexol (Томогексол); Unipak (Юнипак); ***USA***: Omnipaque.

Pharmacopoeial Preparations
USP 36: Iohexol Injection.

Iomeprol *(BAN, USAN, rINN)*

Iomérprol; Iomeprolum; Jomeprol; Jomeproli; Йомепрол.

N,N′-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(*N*-methylglycolamido)-isophthalamide.

$C_{17}H_{22}I_3N_3O_8$=777.1

CAS — 78649-41-9.
ATC — V08AB10.
ATC Vet — QV08AB10.
UNII — 17E17JBP8L.

Description. Iomeprol contains about 49% of I.

Uses and Administration

Iomeprol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, intrathecally, or by instillation into body cavities, and is used in radiographic procedures including myelography, angiography, urography, and arthrography. It is also used to produce contrast enhancement during computed tomography.

Iomeprol is usually available as solutions containing 30.62 to 81.65% of iomeprol (equivalent to 150 to 400 mg/mL of iodine) and the dose and strength used vary according to the procedure and the route.

Reviews.

1. Dooley M, Jarvis B. Iomeprol: a review of its use as a contrast medium. *Drugs* 2000; **59:** 1169–86.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1. For adverse effects relating to the use of nonionic contrast media such as iomeprol for myelography, see under Iohexol (above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iomeprol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

After intravascular use, iomeprol is rapidly eliminated unchanged in the urine, with a terminal elimination half-life of 1.9 hours. It is not significantly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Iomeron; ***Austria***: Iomeron; ***Belg.***: Iomeron; ***China***: Iomeron (典迈伦); ***Cz.***: Iomeron; ***Denm.***: Iomeron; ***Fin.***: Iomeron; ***Fr.***: Iomeron; ***Ger.***: Imeron; ***Gr.***: Iomeron; ***Hong Kong***: Iomeron†; ***Hung.***: Iomeron; ***Irl.***: Iomeron; ***Israel***: Iomeron; ***Ital.***: Iomeron; ***Jpn***: Iomeron; ***Neth.***: Iomeron; ***Norw.***: Iomeron; ***NZ***: Iomeron; ***Port.***: Iomeron; ***Spain***: Iomeron; ***Swed.***: Iomeron; ***Switz.***: Iomeron; ***Turk.***: Iomeron; ***UK***: Iomeron.

Iopamidol *(BAN, USAN, rINN)*

B-15000; Iopamidolum; Jopamidol; Jopamidoli; Jopamidolis; SQ-13396; Йопамидол.

(*S*)-*N,N′*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-5-lactamidoisophthalamide.

$C_{17}H_{22}I_3N_3O_8$=777.1

CAS — 60166-93-0; 62883-00-5.
ATC — V08AB04.
ATC Vet — QV08AB04.
UNII — JR13W81H44.

Description. Iopamidol contains about 49% of I.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Iopamidol). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane; very slightly soluble in methyl alcohol. Protect from light.

USP 36: (Iopamidol). A white to off-white, practically odourless, powder. Very soluble in water; practically insoluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Iopamidol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, intrathecally, intra-articularly, orally, or rectally and is used in radiographic procedures including angiography, arthrography, myelography, urography, and imaging of the gastrointestinal tract. Iopamidol is also used for contrast enhancement during computed tomography.

Iopamidol is usually available as solutions containing 30.62 to 75.5% of iopamidol (equivalent to 150 to 370 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Gastrointestinal obstruction. Enemas of iopamidol were considered safe and effective in the management of meconium ileus in extremely low-birth-weight infants.[1]

1. Nakaoka T, *et al.* Iopamidol enema treatment for meconium obstruction of prematurity in extremely low-birth weight inlants: a safe and effective method. *Pediatr Surg Int* 2009; **25:** 273–6.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1. For the adverse effects relating to the use of nonionic contrast media such as iopamidol for myelography, see under Iohexol, p. 1590.2; for specific references, see below.

Effects on the nervous system. Reports[1-6] of serious neurological sequelae to lumbar myelography with iopamidol.

1. Wallers K, *et al.* Severe meningeal irritation after intrathecal injection of iopamidol. *BMJ* 1985; **291:** 1688.
2. Robinson C, Fon G. Adverse reaction to iopamidol. *Med J Aust* 1986; **144:** 553.
3. Bell JA, McIlwaine GG. Postmyelographic lateral rectus palsy associated with iopamidol. *BMJ* 1990; **300:** 1343–4.
4. Mallat Z, *et al.* Aseptic meningoencephalitis after iopamidol myelography. *Lancet* 1991; **338:** 252.
5. Bain PG, *et al.* Paraplegia after iopamidol myelography. *Lancet* 1991; **338:** 252–3.
6. Klein KM, *et al.* Status epilepticus and seizures induced by iopamidol myelography. *Seizure* 2004; **13:** 196–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iopamidol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

On intravascular use, iopamidol is rapidly eliminated, with up to 50% of the dose recovered unchanged in the urine within 2 hours; the elimination half-life is about 2 hours. It is not significantly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hemoray; Iopamiron; Opacrile; ***Austral.***: Isovue†; ***Austria***: Gastromiro; Jopamiro; Scanlux; ***Braz.***: Iopamiron; ***Canad.***: Isovue; ***Chile***: Radiomiron; ***China***: Ioparnro (典比乐); ***Cz.***: Iopamigita; Scanlux; ***Fr.***: Iopamiron; ***Ger.***: Iopamigita; Iopathek; Solutrast; Unilux; ***Gr.***: Iopamiro; Radoso; Scanlux; ***Hong Kong***: Iopamiro†; ***Hung.***: Iopamiro; Scanlux; ***Irl.***: Gastromiro; Niopam; ***Israel***: Iopamiro; ***Ital.***: Gastromiro; Iopamiro; Iopasen; Scanlux; ***Mex.***: Pamiray†; ***Neth.***: Gastromiro; Iopamigita; Iopamiro; Scanlux†; ***NZ***: Iopamiro†; Isovue; ***Port.***: Gastromiro; Iopamiro; Scanlux; ***Rus.***: Iopamiro (Йопамиро); ***Singapore***: Iopamiro; ***Spain***: Iopamiro; Scanlux: ***Switz.***: Iopamiro; Scanlux; ***Turk.***: Iopamiro; Minotriyod; Pamiray; ***UK***: Gastromiro; Niopam; Scanlux; ***USA***: Isovue; ***Venez.***: Iopamiron.

Pharmacopoeial Preparations
BP 2014: Iopamidol Injection; Iopamidol Oral Solution;
USP 36: Iopamidol Injection.

Iopanoic Acid *(BAN, rINN)*

Acide iopanoïque; Ácido iopanoico; Acidum Iopanoicum; Iodopancic Acid; Iopanoico, ácido; Iopansäure; Jopaanihappo; Jopano rūgštis; Jopánsav; Jopansyra; Kyselina jopanoová; Йопаноевая Кислота

2-(3-Amino-2,4,6-tri-iodobenzyl)butyric acid.

$C_{11}H_{12}I_3NO_2$=570.9

CAS — 96-83-3.
ATC — V08AC06.
ATC Vet — QV08AC06.
UNII — FE9794P71J.

Description. Iopanoic acid contains about 66.7% of I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Iopanoic Acid). A white or yellowish-white powder. Practically insoluble in water; soluble in dehydrated alcohol and in methyl alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Iopanoic Acid). A cream-coloured powder, with a faint characteristic odour. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in solutions of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

Profile

Iopanoic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It has been given orally for cholecystography and cholangiography in usual doses of 3 g, with plenty of water, about 10 to 14 hours before X-ray examination.

Iopanoic acid has also been used in the management of hyperthyroidism (see below).

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving iopanoic acid and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Hyperthyroidism. Iopanoic acid and other iodinated oral cholecystographic agents reduce conversion of thyroxine to tri-iodothyronine, as well as inhibiting release of thyroid hormones from the thyroid gland,[1] and they have been used in the management of hyperthyroidism (p. 2332.2). Iopanoic acid has been used successfully for pre-operative preparation in severe hyperthyroidism,[2-4] and for control of hyperthyroidism before radio-iodine treatment.[5] It has a rapid effect but rebound hyperthyroidism may occur and it is not generally suitable for long-term use.[1]

1. Braga M, Cooper DS. Oral cholecystographic agents and the thyroid. *J Clin Endocrinol Metab* 2001; **86:** 1853–60.
2. Pandey CK, *et al.* Rapid preparation of severe uncontrolled thyrotoxicosis due to Graves' disease with iopanoic acid--a case report. *Can J Anesth* 2004; **51:** 38–40.
3. Dhillon KS, *et al.* Treatment of hyperthyroidism associated with thyrotropin-secreting pituitary adenomas with iopanoic acid. *J Clin Endocrinol Metab* 2004; **89:** 708–11.
4. Panzer C, *et al.* Rapid preoperative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab* 2004; **89:** 2142–4.
5. Bal CS, *et al.* Effect of iopanoic acid on radioiodine therapy of hyperthyroidism: long-term outcome of a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90:** 6536–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Iopac; ***Spain***: Colegraf†.

Pharmacopoeial Preparations
BP 2014: Iopanoic Acid Tablets;
USP 36: Iopanoic Acid Tablets.

Iopentol *(BAN, USAN, rINN)*

Compound 5411; Iopentolum; Jopentol; Jopentoli; Йопентол

N,N'-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxy-3-methoxypropyl)acetamido]-2,4,6-tri-iodoisophthalamide.

$C_{20}H_{28}I_3N_3O_9$=835.2

CAS — 89797-00-2.
ATC — V08AB08.
ATC Vet — QV08AB08.
UNII — 7D6XWX0767.

Description. Iopentol contains about 45.6% of I.

Profile

Iopentol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, orally, or by instillation into body cavities, and is used in procedures including angiography, arthrography, endoscopic retrograde cholangiopancreatography, hysterosalpingography, urography, and visualisation of the gastrointestinal tract. It is also used for contrast enhancement in computed tomography.

Iopentol is usually available as solutions containing 32.9 to 76.8% of iopentol (equivalent to 150 to 350 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Imagopaque†; ***Fr.***: Ivepaque†; ***Gr.***: Imagopaque.

Iopodic Acid *(BANM, rINNM)*

Acide Iopodique; Ácido Iopodico; Acidum Iopodicum; Iopódico, ácido; Ipodic Acid; Йоподовая Кислота

3-(3-Dimethylaminomethyleneamino-2,4,6-tri-iodophenyl) propionic acid.

$C_{12}H_{11}I_3N_2O_2$=598.0

CAS — 5587-89-3.
ATC — V08AC08; V08AC10.
ATC Vet — QV08AC08; QV08AC10.
UNII — F604ZKI910.

Calcium Iopodate *(BANM, rINNM)*

Calcii Iopodas; Calcium Ipodate; Iopodate Calcique; Iopodato cálcico; Ipodate Calcium; Kalciumjopodat; Kalsiumjopodaatti; Кальций Йоподат

$(C_{12}H_{10}I_3N_2O_2)_2Ca$=1234.0

CAS — 7151-11-7.
ATC — V08AC10.
ATC Vet — QV08AC10.
UNII — 505TW5M9ZZ.

Description. Calcium iopodate contains about 61.7% of I.

Sodium Iopodate *(BAN, rINN)*

Iopodate de Sodium; Iopodato de sodio; Ipodate Sodium (USAN); Natrii Iopodas; Natriumjopodaatti; Natriumjopodat; NSC-106962; Sodium Ipodate; Натрий Йоподат

$C_{12}H_{11}I_3N_2NaO_2$=619.9

CAS — 1221-56-3.
ATC — V08AC08.
ATC Vet — QV08AC08.
UNII — F316LLW9WW.

Description. Sodium iopodate contains about 61.4% of I.

Pharmacopoeias. In *US.*

USP 36: (Ipodate Sodium). A fine, white or off-white, odourless, crystalline powder. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 2 of dimethylacetamide, and 1 in 3.5 of dimethylformamide and of dimethyl sulfoxide; very slightly soluble in chloroform; freely soluble in methyl alcohol. Store in airtight containers.

Profile

Iopodic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It has similar properties to iopanoic acid (above) and has been used orally as the sodium or calcium salt for cholecystography and cholangiography. It has also been tried in the management of hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Biloptin.

Pharmacopoeial Preparations
USP 36: Ipodate Sodium Capsules.

Iopromide *(BAN, USAN, rINN)*

Iopromid; Iopromida; Iopromidum; Jopromid; Jopromidi; ZK-35760; Йопромид

N,N'-Bis(2,3-dihydroxypropyl)-2,4,6-tri-iodo-5-(2-methoxyacetamido)-*N*-methylisophthalamide.

$C_{18}H_{24}I_3N_3O_8$=791.1

CAS — 73334-07-3.
ATC — V08AB05.
ATC Vet — QV08AB05.
UNII — 712BAC33MZ.

Description. Iopromide contains about 48.1% of I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Iopromide). Iopromide is a mixture of diastereoisomers and atropisomers. A white or slightly yellowish powder. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in alcohol and in acetone. Protect from light.

USP 36: (Iopromide). A white to slightly yellow powder. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in alcohol, in acetone, and in ether. Protect from light.

Uses and Administration

Iopromide is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, or by instillation into body cavities, and is used in procedures including angiography, arthrography, hysterosalpingography, urography, and assessment of dialysis shunt patency. It is also used for contrast enhancement during computed tomography.

Iopromide is usually available as solutions containing 31.2 to 76.9% of iopromide (equivalent to 150 to 370 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1. Crystallisation and precipitation of iopromide has occurred from concentrated solutions; any preparation so affected should not be used.

References.
1. Kopp AF, *et al*. Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. *Acta Radiol* 2008; **49:** 902–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iopromide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

On intravascular use, iopromide is rapidly distributed in the extracellular fluid. It is not metabolised and is eliminated unchanged in the urine; about 2% of a dose is excreted in faeces. An elimination half-life of about 2 hours has been reported; about 60% of a dose is excreted in urine within 3 hours and about 92% within 24 hours. Iopromide is not significantly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clarograf; ***Austral.***: Ultravist; ***Austria***: Ultravist; ***Belg.***: Ultravist; ***Canad.***: Ultravist; ***China***: Ultravist (优维显); ***Cz.***: Ultravist; ***Denm.***: Ultravist; ***Fin.***: Ultravist; ***Fr.***: Ultravist; ***Ger.***: Ultravist; ***Gr.***: Ultravist; ***Hung.***: Ultravist; ***Irl.***: Ultravist; ***Israel***: Ultravist; ***Ital.***: Ultravist; ***Jpn***: Proscope; ***Neth.***: Ultravist; ***Norw.***: Ultravist; ***NZ***: Ultravist; ***Port.***: Ultravist; ***Rus.***: Ultravist (Ультравист); ***S.Afr.***: Ultravist; ***Spain***: Clarograf†; Ultravist; ***Swed.***: Ultravist; ***Switz.***: Ultravist; ***Turk.***: Ultravist; ***UK***: Ultravist; ***USA***: Ultravist.

Pharmacopoeial Preparations
USP 36: Iopromide Injection.

Iopydol *(BAN, USAN, pINN)*

Iopidol; Iopydolum; Jopydol; Jopydoli; Йопидол.
1-(2,3-Dihydroxypropyl)-3,5-di-iodo-4-pyridone.
$C_8H_9I_2NO_3$=421.0
CAS — 5579-92-0.
ATC — V08AD02.
ATC Vet — QV08AD02.
UNII — T4661K682A.

Description. Iopydol contains about 60.3% of I.

Profile

Iopydol is an iodinated radiographic contrast medium (p. 1580.1) that has been used with iopydone for bronchography.

Iopydone *(BAN, USAN, rINN)*

Iopidona; Iopydonum; Йопидон.
3,5-Di-iodo-4-pyridone.
$C_5H_3I_2NO$=346.9
CAS — 5579-93-1.
UNII — J6B56XB19T.

Description. Iopydone contains about 73.2% of I.

Profile

Iopydone is an iodinated radiographic contrast medium (p. 1580.1) that has been used with iopydol for bronchography.

Iosarcol *(pINN)*

Iosarcolum; Йозаркол.
3,5-Diacetamido-2,4,6-triiodo-*N*-methyl-*N*-{[methyl(D-*gluco*-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]methyl}benzamide.
$C_{21}H_{29}I_3N_4O_9$=862.2
CAS — 97702-82-4.
UNII — 4DSD895OGC.

Description. Iosarcol contains about 44.2% of I.

Profile

Iosarcol is an iodinated nonionic monomeric contrast medium (p. 1580.1) used for a wide range of radiographic imaging procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Melitrast†; ***Ger.***: Melitrast.

Iotalamic Acid *(BAN, rINN)*

Acide Iotalamique; Ácido iotalámico; Acidum Iotalamicum; Iotalámico, ácido; Iotalaminsäure; Iothalamic Acid (USAN); Iothalamic Acid; Jotalaamihappo; Jotalaminsav; Jotalamo rūgštis; Jotalamsyra; Kyselina jotalamová; Methalamic Acid; MI-216; Йоталамовая Кислота.
5-Acetamido-2,4,6-tri-iodo-*N*-methylisophthalamic acid.
$C_{11}H_9I_3N_2O_4$=613.9
CAS — 2276-90-6.
ATC — V08AA04.
ATC Vet — QV08AA04.
UNII — 16CHD79MIX.

Description. Iotalamic acid contains about 62% of I.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Iothalamic Acid). A white, odourless, powder. Slightly soluble in water and in alcohol; soluble in solutions of alkali hydroxides. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Meglumine Iotalamate *(BANM, rINNM)*

Iotalamate de Méglumine; Iotalamato de meglumina; Iothalamate Meglumine; Meglumine Iothalamate; Meglumini Iotalamas; Меглумина Йоталамат.
The *N*-methylglucamine salt of iotalamic acid.
$C_{11}H_9I_3N_2O_4.C_7H_{17}NO_5$=809.1
CAS — 13087-53-1.
ATC — V08AA04.
ATC Vet — QV08AA04.
UNII — XUW72GOP7W.

Description. Meglumine iotalamate contains about 47.1% of I.

Pharmacopoeias. *US* includes only as various injections.

Sodium Iotalamate *(BANM, rINNM)*

Iotalamate de Sodium; Iotalamato de sodico; Iotalamato de sodio; Iothalamate Sodium; Natrii Iotalamas; Sodium Iothalamate; Натрий Йоталамат.
$C_{11}H_8I_3N_2NaO_4$=635.9
CAS — 17692-74-9; 1225-20-3.
ATC — V08AA04.
ATC Vet — QV08AA04.
UNII — KDN276D83N.

Description. Sodium iotalamate contains about 59.9% of I.

Pharmacopoeias. *US* includes only as various injections.

Uses and Administration

Iotalamic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to the amidotrizoates (p. 1581.3). It may be given intravenously, intra-arterially, or by instillation into the bladder or uterus, and is used in procedures including angiography, arthrography, cholangiography, urography and hysterosalpingography. It is also used for contrast enhancement in computed tomography. Iotalamates have also been given orally or rectally for imaging of the gastrointestinal tract.

Iotalamic acid is usually available as solutions containing up to 54% of sodium iotalamate or up to 60% of meglumine iotalamate. The dose and strength used vary according to the procedure and route. A mixture of the two salts has been given to minimise adverse effects.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1.

Incidence of adverse effects. In 40 patients who underwent phlebography with 60% meglumine iotalamate minor adverse reactions were common despite the use of saline flushing and muscle contraction to clear the veins after examination.[1] The commonest effect was pain at the site of injection, or in the calf and foot; 15 patients of those who had pain in the calf or foot were found to have venous thrombosis. Major complications of phlebography appear to be rare but can cause serious morbidity; examination of 200 case notes and a retrospective study involving 3060 patients revealed 4 cases of necrosis in the skin of the foot and gangrene of the foot in 2.

1. Thomas ML, MacDonald LM. Complications of ascending phlebography of the leg. *BMJ* 1978; **ii:** 317–18.

Pharmacokinetics

On intravascular use the iotalamates are rapidly distributed; suitable concentrations for urography reach the urinary tract within 3 to 8 minutes of a bolus intravenous injection. Protein binding is reported to be low. The iotalamates are eliminated by the kidneys. In patients with normal renal function more than 90% of the dose injected is excreted in urine within 24 hours; an elimination half-life of about 90 minutes has been reported. Small amounts are reported to be excreted via the bile in the faeces. The iotalamates are removed by peritoneal dialysis and haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Conray; Cysto-Conray; ***Austral.***: Conray; ***Canad.***: Conray; Cysto-Conray; Vascoray†; ***Irl.***: Conray; ***UK***: Conray; ***USA***: Conray; Cysto-Conray.

Pharmacopoeial Preparations
USP 36: Iothalamate Meglumine and Iothalamate Sodium Injection; Iothalamate Meglumine Injection; Iothalamate Sodium Injection.

Iotrolan *(BAN, USAN, rINN)*

Iotrol; Iotrolán; Iotrolane; Iotrolanum; Iotrolum; Jotrolaani; Jotrolan; ZK-39482; Йотролан.
N,N′,N″,N‴-Tetrakis(2,3-dihydroxy-1-hydroxymethylpropyl)-2,2′,4,4′,6,6′-hexaiodo-5,5′-(*N,N′*-dimethylmalonyldi-imino) di-isophthalamide.
$C_{37}H_{48}I_6N_6O_{18}$=1626.2
CAS — 79770-24-4.
ATC — V08AB06.
ATC Vet — QV08AB06.
UNII — 16FL47B687.

Description. Iotrolan contains about 46.8% of I.

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Iotrolan). A white or yellowish-white, hygroscopic powder. Very soluble in water; practically insoluble in alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers. Protect from light.

Uses and Administration

Iotrolan is a nonionic dimeric iodinated radiographic contrast medium (p. 1580.1). It is given intrathecally for myelography and for contrast enhancement in computed tomography, and by instillation into body ducts or cavities for procedures including lymphography, arthrography, hysterosalpingography, cholangiopancreatography, and for visualisation of the mammary ducts. It may also be given orally for imaging of the gastrointestinal tract.

Iotrolan is usually available as solutions containing 51.3% or 64.1% of iotrolan (equivalent to 240 or 300 mg/mL of iodine, respectively) and the dose and strength used vary according to the procedure and route.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1. For the adverse effects relating to the use of nonionic contrast media such as iotrolan for myelography, see under Iohexol, p. 1590.2.

Pharmacokinetics

Iotrolan is excreted unchanged in the urine. After intrathecal injection, about 80% is excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Osmovist†; ***China***: Isovist (伊索显); ***Ger.***: Isovist; ***Gr.***: Isovist; ***Hung.***: Isovist†; ***Neth.***: Isovist†; ***NZ***: Isovist†; ***S.Afr.***: Isovist†; ***Switz.***: Isovist†; ***UK***: Isovist†.

Iotroxic Acid *(BAN, USAN, rINN)*

Acide Iotroxique; Ácido iotróxico; Acidum Iotroxicum; Iotróxico, ácido; Jotroksihappo; Jotroxsyra; SH-213AB; Йотроксовая Кислота.
3,3′-(3,6,9-Trioxaundecanedioyldi-imino)bis(2,4,6-tri-iodobenzoic acid).
$C_{22}H_{18}I_6N_2O_9$=1215.8
CAS — 51022-74-3.

ATC — V08AC02.
ATC Vet — QV08AC02.
UNII — 84C5PTP9X6.

Description. Iotroxic acid contains about 62.6% of I.

Pharmacopoeias. In *Int.* and *Jpn.*

Meglumine Iotroxate *(BANM, rINNM)*

Dimeglumine Iotroxate; Iotroxate de Méglumine; Iotroxate Meglumine; Iotroxato de meglumina; Meglumine Iotroxinate; Meglumini Iotroxas; Меглумина Йотроксат.

The di(*N*-methylglucamine)salt of iotroxic acid.

$C_{22}H_{18}I_6N_2O_9.2C_7H_{17}NO_5$=1606.2

CAS — 68890-05-1.
ATC — V08AC02.
ATC Vet — QV08AC02.
UNII — 389136RRO0.

Description. Meglumine iotroxate contains about 47.4% of I.

Uses and Administration

Iotroxic acid is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1); it is taken up by the liver and excreted in bile, and is used in cholecystography and cholangiography.

Iotroxic acid is given intravenously as a solution containing 10.5% of the meglumine salt. The usual dose is 10.5 g of meglumine iotroxate (equivalent to about 5 g of iodine), given by infusion over at least 30 minutes. Alternatively, a solution containing 22.8% of meglumine iotroxate may be used.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Pharmacokinetics

After intravenous injection, iotroxic acid binds to plasma proteins and is taken up by the liver; plasma-protein binding is about 60 to 90%. It is excreted primarily unchanged in the bile; a small amount is metabolised and excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Biliscopin; ***Austria***: Biliscopin; ***Ger.***: Biliscopin†; ***Gr.***: Biliscopin; ***NZ***: Biliscopin†; ***Switz.***: Biliscopin†; ***UK***: Biliscopin.

Ioversol *(BAN, USAN, rINN)*

Ioversolum; Joversol; Joversoli; MP-328; Йоверсол.

N,N′-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl)glycolamido]-2,4,6-tri-iodoisophthalamide.

$C_{18}H_{24}I_3N_3O_9$=807.1

CAS — 87771-40-2.
ATC — V08AB07.
ATC Vet — QV08AB07.
UNII — N3RIB7X24K.

Description. Ioversol contains about 47.2% of I.

Pharmacopoeias. In *US.*

USP 36: (Ioversol). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Ioversol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1) that is given intra-arterially or intravenously for angiography and urography. It is also used for contrast enhancement during computed tomography. It is usually available as a solution containing 34 to 74% of ioversol (equivalent to 160 to 350 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

References.

1. Floriani I, *et al.* Clinical profile of ioversol: a metaanalysis of 57 randomized, double-blind clinical trials. *Invest Radiol* 1996; **31:** 479–91.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Hypersensitivity. A report[1] of a fatal anaphylactoid reaction to ioversol.

1. Jansman FGA, *et al.* Fatal anaphylactoid reaction following ioversol administration. *Pharm World Sci* 2007; **29:** 584–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ioversol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

When given intravascularly, ioversol is rapidly eliminated unchanged in the urine, with a half-life of about 1.5 hours; more than 95% of a dose is eliminated within 24 hours. Binding to plasma or serum proteins is very low.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Optiray; ***Austral.***: Optiray; ***Austria***: Optiray; ***Belg.***: Optiject; Optiray; ***Canad.***: Optiray; ***Cz.***: Optiray; ***Denm.***: Optiray; ***Fin.***: Optiray; ***Fr.***: Optiject; Optiray; ***Gr.***: Optiray; ***Hung.***: Optiray; ***Irl.***: Optiray; ***Ital.***: Optiray; ***Neth.***: Optiray; ***Norw.***: Optiray; ***Port.***: Optiray; ***Rus.***: Optiray (Оптирей); ***Spain***: Optiray; ***Swed.***: Optiray; ***Switz.***: Optiray; ***UK***: Optiray; ***USA***: Optiray.

Pharmacopoeial Preparations
USP 36: Ioversol Injection.

Ioxaglic Acid *(BAN, USAN, rINN)*

Acide Ioxaglique; Ácido ioxáglico; Acidum Ioxaglicum; Ioxáglico, ácido; Ioxaglinsäure; Joksagliinihappo; Joksagliko rūgštis; Joxaglinsav; Joxaglinsyra; Kyselina joxaglová; P-286; Йоксагловая Кислота.

N-(2-Hydroxyethyl)-2,4,6-tri-iodo-5-[2′,4′,6′-tri-iodo-3′-(*N*-methylacetamido)-5′-methylcarbamoylhippuramido]isophthalamic acid.

$C_{24}H_{21}I_6N_5O_8$=1268.9

CAS — 59017-64-0.
ATC — V08AB03.
ATC Vet — QV08AB03.
UNII — Z40X7EI2AF.

Description. Ioxaglic acid contains about 60% of I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ioxaglic Acid). A white or almost white hygroscopic powder. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Ioxaglic Acid). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Meglumine Ioxaglate *(BANM, rINNM)*

Ioxaglate de Méglumine; Ioxaglate Meglumine (USAN); Ioxaglato de meglumina; Meglumini Ioxaglas; MP-302 (meglumine ioxaglate with sodium ioxaglate); Меглумина Йоксаглат.

The *N*-methylglucamine salt of ioxaglic acid.

$C_{24}H_{21}I_6N_5O_8.C_7H_{17}NO_5$=1464.1

CAS — 59018-13-2.
ATC — V08AB03.
ATC Vet — QV08AB03.
UNII — 75JR975T11.

Description. Meglumine ioxaglate contains about 52% of I.

Sodium Ioxaglate *(BANM, rINNM)*

Ioxaglate de Sodium; Ioxaglate Sodium (USAN); Ioxaglato sódico; MP-302 (sodium ioxaglate with meglumine ioxaglate); Natrii Ioxaglas; Natriumjoksaglaatti; Natriumjoxaglat; Натрий Йоксаглат.

$C_{24}H_{20}I_6N_5NaO_8$=1290.9

CAS — 67992-58-9.
ATC — V08AB03.
ATC Vet — QV08AB03.
UNII — HQ43CN02U9.

Description. Sodium ioxaglate contains about 59% of I.

Uses and Administration

Ioxaglic acid is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1). It is given intravenously, intra-arterially, intra-articularly, or by instillation into body ducts and cavities and is used in diagnostic procedures including angiography, arthrography, hysterosalpingography, and urography. It is also used for contrast enhancement during computed tomography.

Ioxaglic acid is usually available as solutions containing a mixture of the sodium and meglumine salts. Commonly used solutions contain 39.3% of meglumine ioxaglate and 19.6% of sodium ioxaglate (equivalent to 320 mg/mL of iodine) or 24.6% of meglumine ioxaglate and 12.3% of sodium ioxaglate (equivalent to 200 mg/mL of iodine). The dose and strength used depend upon the procedure and route.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ioxaglic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

On intravascular use, ioxaglates are rapidly distributed throughout the extracellular fluid. Protein binding is reported to be very low. They are mainly excreted unchanged in the urine, although biliary excretion may predominate in renal impairment. With normal renal function, about 90% of a dose is excreted in the urine within 24 hours; an elimination half-life of about 90 minutes has been reported. Ioxaglates cross the placenta and are distributed into breast milk. They are removed by haemodialysis and peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hexabrix; ***Austral.***: Hexabrix; ***Austria***: Hexabrix; ***Belg.***: Hexabrix; ***Canad.***: Hexabrix; ***Chile***: Hexabrix; ***Cz.***: Hexabrix; ***Denm.***: Hexabrix†; ***Fin.***: Hexabrix; ***Fr.***: Hexabrix; ***Ger.***: Hexabrix; ***Gr.***: Hexabrix; ***Hung.***: Hexabrix; ***Irl.***: Hexabrix; ***Israel***: Hexabrix; ***Ital.***: Hexabrix; ***Neth.***: Hexabrix; ***Norw.***: Hexabrix; ***NZ***: Hexabrix; ***Port.***: Hexabrix; ***Spain***: Hexabrix; ***Swed.***: Hexabrix; ***Switz.***: Hexabrix; ***Turk.***: Hexabrix; ***UK***: Hexabrix; ***USA***: Hexabrix; ***Venez.***: Hexabrix.

Multi-ingredient Preparations. ***Thai.***: Hexabrix.

Pharmacopoeial Preparations
USP 36: Ioxaglate Meglumine and Ioxaglate Sodium Injection.

Ioxilan *(USAN, rINN)*

Ioxilán; Ioxilane; Ioxilanum; Ioxitol; Йоксилан.

N-(2,3-Dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-*N′*-(2-hydroxyethyl)-2,4,6-triidoisophthalamide.

$C_{18}H_{24}I_3N_3O_8$=791.1

CAS — 107793-72-6.
ATC — V08AB12.
ATC Vet — QV08AB12.
UNII — A4YJ7J11TG.

Description. Ioxilan contains about 48.1% of I.

Pharmacopoeias. In *US.*

USP 36: (Ioxilan). A white to off-white, practically odourless, powder. Soluble in water and in methyl alcohol. pH of a 10% solution in water is between 5.0 and 7.5. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Ioxilan is a nonionic monomeric iodinated radiographic contrast medium (see p. 1580.1). It is given intra-arterially or intravenously for procedures including angiography and urography; it is also used for contrast enhancement during computed tomography.

Ioxilan is usually available as solutions containing 62.3 or 72.7% of ioxilan (equivalent to 300 or 350 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Pharmacokinetics

After intravascular use, ioxilan is rapidly eliminated unchanged in the urine; about 94% of a dose is excreted within 24 hours. Protein binding is reported to be very low. Ioxilan is dialysable.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Imagenil; ***Turk.***: Oxilan; ***USA***: Oxilan.

Pharmacopoeial Preparations
USP 36: Ioxilan Injection.

Ioxitalamic Acid *(rINN)*

Acide Ioxitalamique; Ácido ioxitalámico; Acidum Ioxitalamicum; AG-58107; Ioxitalámico, ácido; Ioxithalamic Acid; Joksitalaamihappo; Joxitalamsyra; Йокситаламовая Кислота.

5-Acetamido-*N*-(2-hydroxyethyl)-2,4,6-tri-iodoisophthalamic acid.

$C_{12}H_{11}I_3N_2O_5$=643.9

CAS — 28179-44-4.

ATC — V08AA05.

ATC Vet — QV08AA05.

UNII — 967RDI7Z6K.

Description. Ioxitalamic acid contains about 59.1% of I.

Pharmacopoeias. In *Fr.*

Meglumine Ioxitalamate *(rINNM)*

Ioxitalamate de Méglumine; Ioxitalamate Meglumine; Ioxitalamato de meglumina; Meglumini Ioxitalamas; Меглумина Йокситаламат.

The *N*-methylglucamine salt of ioxitalamic acid.

$C_{12}H_{11}I_3N_2O_5.C_7H_{17}NO_5$=839.2

CAS — 29288-99-1.

ATC — V08AA05.

ATC Vet — QV08AA05.

Description. Meglumine ioxitalamate contains about 45.4% of I.

Sodium Ioxitalamate *(rINNM)*

Ioxitalamate de Sodium; Ioxitalamate Sodium; Ioxitalamato sódico; Natrii Ioxitalamas; Натрий Йокситаламат.

$C_{12}H_{10}I_3N_2NaO_5$=665.9

CAS — 33954-26-6.

ATC — V08AA05.

ATC Vet — QV08AA05.

Description. Sodium ioxitalamate contains about 57.2% of I.

Profile

Ioxitalamic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to those of the amidotrizoates (p. 1582.1). It is given intravenously or by instillation into body cavities for procedures including angiography, cholangiography, cystography, hysterosalpingography, and urography; it may be given orally or rectally for imaging of the gastrointestinal tract. It is also used for contrast enhancement in computed tomography.

Ioxitalamic acid is usually available as a solution containing 21% of the sodium salt (equivalent to 120 mg/mL of iodine), 55.1 to 66% of the meglumine salt (equivalent to 250 to 300 mg/mL of iodine), or as a mixture of both salts. The dose and strength used vary according to the procedure and route.

Monoethanolamine ioxitalamate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Telebrix 30; Telebrix 38; Telebrix Coronario; Telebrix Hystero; ***Belg.***: Telebrix Gastro; Telebrix Hystero; Telebrix; ***Canad.***: Telebrix; ***Chile***: Telebrix 30; Telebrix 35; ***Cz.***: Telebrix 30; Telebrix 35; Telebrix Gastro; ***Fr.***: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Ger.***: Telebrix Gastro; Telebrix N 180 and 300; ***Gr.***: Telebrix 30; Telebrix Gastro; Telebrix Hystero; Telebrix; ***Hung.***: Telebrix Gastro†; Telebrix†; ***Israel***: Telebrix Gastro; Telebrix; ***Mex.***: Telebrix†; ***Neth.***: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Port.***: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Switz.***: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Thai.***: Telebrix 35; ***Turk.***: Telebrix; ***Venez.***: Telebrix 30; Telebrix 35; Telebrix Hystero.

Mangafodipir Trisodium *(BANM, USAN, rINNM)*

Mangafodipir trisódico; Mangafodipir Trisodique; Mangafodipirum Trinatricum; MnDPDP (mangafodipir); S-095 (mangafodipir); Win-59010-2 (mangafodipir); Win-59010; Тринатрий Мангафодипир.

Trisodium trihydrogen (*OC*-6-13)-{[*N*,*N*′-ethylenebis(*N*-[[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methyl}glycine) 5,5′-bis(phosphato)](8^-)} manganate(6-); Trisodium trihydrogen (*OC*-6-13)-*N*,*N*′-ethane-1,2-diylbis{N-[2-methyl-3-oxido-κ*O*-5-(phosphonatooxymethyl)-4-pyridylmethyl]glycinato(*O*,*N*)}manganate(II).

$C_{22}H_{27}MnN_4Na_3O_{14}P_2$=757.3

CAS — 155319-91-8 (mangafodipir); 140678-14-4 (mangafodipir trisodium).

ATC — V08CA05.

ATC Vet — QV08CA05.

UNII — 129FW80TG4.

Pharmacopoeias. In *US.*

USP 36: (Mangafodipir Trisodium). Pale yellow crystals or crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in acetone; slightly soluble in chloroform; sparingly soluble in methyl alcohol. pH of a 1% solution in water is between 5.5 and 7.0. Store at a temperature not exceeding 8 degrees.

Uses and Administration

Mangafodipir is a manganese chelate that is used as a magnetic resonance contrast medium (p. 1580.1) for imaging of the liver and pancreas. Manganese has paramagnetic properties that increase the relaxivity of hydrogen ions, leading to signal enhancement. Free manganese is released from mangafodipir in the body and is taken up by normal liver and pancreatic tissue, increasing the degree of contrast.

Mangafodipir is given intravenously as the trisodium salt.

In the UK, a solution containing mangafodipir trisodium 7.57 mg/mL (10 micromol/mL) is used. Usual doses for imaging are:

- liver: 0.5 mL/kg (5 micromol/kg) given by intravenous infusion at a rate of 2 to 3 mL/minute
- pancreas: 0.5 mL/kg (5 micromol/kg) given by intravenous infusion at a rate of 4 to 6 mL/minute

In the USA, a more concentrated preparation is used, containing mangafodipir trisodium 37.9 mg/mL (50 micromol/mL). Usual doses are:

- liver: 0.1 mL/kg (5 micromol/kg), given by slow intravenous injection to a maximum dose of 15 mL

Adverse Effects and Precautions

The most common adverse effects of mangafodipir are injection site discomfort, feelings of warmth or flushing, headache, nausea, vomiting, abdominal pain, and taste disturbances. Hypersensitivity reactions, including anaphylactoid reactions, may occur. Transient increases in bilirubin and liver transaminase concentrations and decreases in plasma-zinc concentrations have been reported.

Mangafodipir should be used with caution in patients with hepatic or renal impairment and should be avoided if impairment is severe. It should not be given to patients with phaeochromocytoma.

References.

1. Federle MP, *et al.* Safety and efficacy of mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: results of the U.S. multicenter phase III clinical trials (safety). *J Magn Reson Imaging* 2000; **12:** 186–97.

Pharmacokinetics

After intravenous injection, mangafodipir is dephosphorylated and manganese is exchanged for zinc leading to the release of free manganese ions and the formation of 2 inactive metabolites. Manganese is rapidly taken up by the liver, pancreas, kidney and spleen; about 15 to 20% is excreted in the urine within 24 hours, with most of the remainder excreted in the faeces over about 4 days. The metabolites are almost entirely excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Teslascan†; ***Belg.***: Teslascan†; ***Canad.***: Teslascan; ***Cz.***: Teslascan†; ***Fr.***: Teslascan†; ***Ger.***: Teslascan†; ***Gr.***: Teslascan†; ***Hung.***: Teslascan†; ***Irl.***: Teslascan†; ***Ital.***: Teslascan†; ***Neth.***: Teslascan†; ***Norw.***: Teslascan†; ***NZ***: Teslascan; ***Pol.***: Teslascan†; ***Port.***: Teslascan†; ***Rus.***: Teslascan (Тесласкан); ***Spain***: Teslascan†; ***Swed.***: Teslascan†; ***Switz.***: Teslascan†; ***Turk.***: Teslascan; ***UK***: Teslascan†; ***USA***: Teslascan†.

Pharmacopoeial Preparations
USP 36: Mangafodipir Trisodium Injection.

Metrizamide *(BAN, USAN, rINN)*

Metritsamidi; Metrizamid; Metrizamida; Métrizamide; Metrizamidum; Win-39103; Метризамид.

2-[3-Acetamido-2,4,6-tri-iodo-5-(*N*-methylacetamido)benzamido]-2-deoxy-D-glucose.

$C_{18}H_{22}I_3N_3O_8$=789.1

CAS — 31112-62-6 (metrizamide); 55134-11-7 (metrizamide, glucopyranose form).

ATC — V08AB01.

ATC Vet — QV08AB01.

UNII — RHH3W8F1CO.

Description. Metrizamide contains about 48.2% of I.

Profile

Metrizamide is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1) that has been used in myelography, angiography, intravenous urography, and arthrography, and also for contrast enhancement during computed tomography.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving metrizamide and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Metrizoic Acid *(BANM, rINNM)*

Acide Métrizoïque; Ácido metrizoico; Acidum Metrizoicum; Metritsoiinihappo; Metrizoico, ácido; Metrizoinsyra; Метризоевая Кислота.

3-Acetamido-2,4,6-tri-iodo-5-(*N*-methylacetamido)benzoic acid.

$C_{12}H_{11}I_3N_2O_4$=627.9

CAS — 1949-45-7.

ATC — V08AA02.

ATC Vet — QV08AA02.

UNII — CM1N99QR1M.

Description. Metrizoic acid contains about 60.6% of I.

Meglumine Metrizoate *(BANM, rINNM)*

Meglumini Metrizoas; Métrizoate de Méglumine; Metrizoate Meglumine; Metrizoato de meglumina; Меглумина Метризоат.

The *N*-methylglucamine salt of metrizoic acid.

$C_{12}H_{11}I_3N_2O_4.C_7H_{17}NO_5$=823.2

CAS — 7241-11-4.

ATC — V08AA02.

ATC Vet — QV08AA02.

UNII — RJY6JR42WQ.

Description. Meglumine metrizoate contains about 46.3% of I.

Sodium Metrizoate *(BAN, rINN)*

Métrizoate de Sodium; Metrizoate Sodium (USAN); Metrizoato de sodio; Natrii Metrizoas; NSC-107431; Натрия Метризоат.

$C_{12}H_{10}I_3N_2NaO_4$=649.9

CAS — 7225-61-8.

ATC — V08AA02.

ATC Vet — QV08AA02.

UNII — O65Q227UIC.

Description. Sodium metrizoate contains about 58.6% of I.

Profile

Metrizoic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to those of the amidotrizoates (p. 1582.1). It has been used as the meglumine and sodium salts, often with calcium metrizoate and magnesium metrizoate, for a variety of diagnostic procedures including angiography, cholangiography, and hysterosalpingography.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving metrizoate and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Perflenapent *(USAN, rINN)* ⊗

Dodecafluoropentanum; Dodekafluoropentaani; Dodekafluoropentan; Perflénapent; Perflenapentum; Перфленапент.

Dodecafluoropentane.

C_5F_{12}=288.0

CAS — 678-26-2.

ATC — V08DA03.

ATC Vet — QV08DA03.

UNII — 483AU1Y5CZ.

Profile

Perflenapent is a liquid perfluorocarbon that has been used as an ultrasound contrast medium (p. 1580.2) for echocardiography. It has been given intravenously as an emulsion containing droplets of perflenapent; on warming to body temperature the droplets form microbubbles of perflenapent gas that provide echo-enhancement. A small amount of perflisopent (below) was also included in the formulation.

References.

1. Robbin ML, Eisenfeld AJ. Perflenapent emulsion: a US contrast agent for diagnostic radiology—multicenter, double-blind comparison with a placebo. *Radiology* 1998; **207:** 717–22.
2. Kitzman DW, Wesley DJ. Safety assessment of perflenapent emulsion for echocardiographic contrast enhancement in patients with congestive heart failure or chronic obstructive pulmonary disease. *Am Heart J* 2000; **139:** 1077–80.

Perflexane *(USAN, rINN)* ⊗

Perflexano; Perflexanum; Перфлексан.

Tetradecafluorohexane.

C_6F_{14}=338.0

CAS — 355-42-0.

UNII — FX3WJ41CMX.

Profile

Perflexane is a perfluorocarbon gas that has been used as an ultrasound contrast medium (p. 1580.2) for echocardiography. Dry microspheres containing the gas are reconstituted immediately before use, leading to the formation of microbubbles of perflexane that provide echo-enhancement; lipids are included in the microspheres to stabilise the bubbles when they form.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Imagent.

Perflisopent *(USAN, rINN)* ⊗

Perflisopentum; Перфлизопент.

Nonafluoro-2-(trifluoromethyl)butane.

C_5F_{12}=288.0

CAS — 594-91-2.

UNII — 40FAQ8ON24.

Profile

Perflisopent is a perfluorocarbon that has been used as an ultrasound contrast medium (p. 1580.2) with perflenapent (above) for echocardiography.

Perflubutane *(USAN, rINN)*

AI-700; Perflubutano; Perflubutanum; Perfluorobutane; Перфлубутан.

Decafluorobutane.

C_4F_{10}=238.0

CAS — 355-25-9.

UNII — SE4TWR0K2C.

NOTE. The name Imagify has been used as a trade mark for perflubutane.

Profile

Perflubutane is a perfluorocarbon ultrasound contrast medium (p. 1580.2) that is used as microspheres in the detection of focal liver lesions. It is under investigation in the assessment of myocardial perfusion.

References.

1. Senior R. Imagify® (perflubutane polymer microspheres) injectable suspension for the assessment of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007; **5:** 413–21.
2. Moriyasu F, Itoh K. Efficacy of perflubutane microbubble-enhanced ultrasound in the characterization and detection of focal liver lesions: phase 3 multicenter clinical trial. *Am J Roentg* 2009; **193:** 86–95.
3. Takahashi M, *et al.* Contrast-enhanced ultrasound with perflubutane microbubble agent: evaluation of differentiation of hepatocellular carcinoma. *Am J Roentg* 2011; **196:** W123–W131.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Sonazoid.

Perflutren *(BAN, USAN, rINN)* ⊗

DMP-115; FS-069; MRX-115; Octafluoropropanum; Oktafluoropropaani; Oktafluoropropan; Perfluoropropane; Perflutrène; Perflutreno; Perflutrenum; Перфлутрен.

Octafluoropropane.

C_3F_8=188.0

CAS — 76-19-7.

UNII — CK0N3WH0SR.

Profile

Perflutren is a perfluorocarbon gas used as either albumin- or lipid-coated microspheres as an ultrasound contrast medium (p. 1580.2) for echocardiography.

- The *albumin-coated microspheres* are suspended in 1% albumin solution immediately before use and are given in a dose of 0.5 to 3 mL by intravenous injection, repeated if necessary up to a total dose of 8.7 mL.
- The *lipid-coated microsphere* suspension is formed by agitating the gas with a lipid solution immediately before use and is given in a dose of 10 microlitre/kg by intravenous injection, repeated once after 30 minutes if required, or as intravenous injections of 100 to 400 microlitres repeated as required up to a maximum total dose of 1.6 mL. Alternatively, 1.3 mL of the suspension may be diluted in 50 mL of sodium chloride 0.9% or glucose 5% and given by intravenous infusion at an initial rate of 4 mL/minute, adjusted as required, to a maximum rate of 10 mL/minute.

Serious cardiopulmonary reactions, including fatalities, have been reported with perflutren and it should be used with extreme caution and appropriate monitoring in patients with pulmonary hypertension or unstable cardiopulmonary conditions. The safety of perflutren has not been established in patients with right-to-left cardiac shunts; as it can enter the arterial circulation directly via such shunts, it should also be used with extreme caution or avoided in such patients.

Perflutren has been given by intra-ocular injection to provide tamponade in the management of retinal detachment.

Adverse effects. After reports of serious cardiopulmonary events, including several deaths, during or within 30 minutes of use of a microbubble contrast agent, in October 2007 the FDA required warnings and contra-indications to be added to the US licensed product information for perflutren. Contra-indications included worsening or unstable heart failure, acute myocardial infarction or coronary syndromes, serious ventricular arrhythmias, and conditions predisposing to pulmonary hypertension. Although 5 further fatalities associated with perflutren use had been reported as of July 2008, along with a further 60 reports of serious non-fatal adverse events, the FDA considered it appropriate to remove most of these contra-indications in the light of subsequent evidence.[1] The contrast medium continued to be contra-indicated in patients with right-to-left or bidirectional shunts, and intensive monitoring was considered indicated in patients with pulmonary hypertension or unstable cardiopulmonary conditions for 30 minutes after use. UK licensed product information notes the absence of safety data in patients with right-to-left shunts, and in those on mechanical ventilation, and advises caution in such patients.

Retrospective analyses of data from patients undergoing echocardiography[2-4] found no evidence that the incidence of adverse effects or death was increased in patients given perflutren.

1. FDA. Information for healthcare professionals: micro-bubble contrast agents (marketed as Definity (perflutren lipid microsphere) injectable suspension and Optison (perflutren protein-type A microspheres for injection)) (issued 17th July, 2008). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm092270.htm (accessed 24/08/10)
2. Herzog CA. Incidence of adverse events associated with use of perflutren contrast agents for echocardiography. *JAMA* 2008; **299:** 2023–5.
3. Kusnetzky LL, *et al.* Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. *J Am Coll Cardiol* 2008; **51:** 1704–6.
4. Dolan MS, *et al.* Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography: a multicenter experience. *J Am Coll Cardiol* 2009; **53:** 32–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Optison; ***Canad.***: Definity; ***Chile***: Definity; ***Cz.***: Luminity†; Optison; ***Denm.***: Optison; ***Fr.***: Luminity†; ***Ger.***: Optison; ***Gr.***: Optison; ***Hung.***: Optison; ***Irl.***: Luminity†; Optison; ***Israel***: Definity; ***Ital.***: Luminity†; Optison; ***Neth.***: Luminity†; Optison; ***Norw.***: Optison; ***NZ***: Definity; ***Pol.***: Luminity†; ***Port.***: Luminity†; Optison; ***Spain***: Luminity†; ***Swed.***: Luminity†; Optison; ***UK***: Luminity†; Optison; ***USA***: Definity; Optison.

Pharmacopoeial Preparations

USP 36: Perflutren Protein-Type A Microspheres Injectable Suspension.

Propyliodone *(rINN)*

Propiliodona; Propyliodonum; Propyljodon; Propyylijodoni; Пропилиодон.

Propyl 1,4-dihydro-3,5-di-iodo-4-oxo-1-pyridylacetate.

$C_{10}H_{11}I_2NO_3$=447.0

CAS — 587-61-1.

ATC — V08AD03.

ATC Vet — QV08AD03.

UNII — 5NPJ6BPX36.

Description. Propyliodone contains about 56.8% of I.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Propyliodone). A white or almost white, crystalline powder. Is odourless or has a faint odour. Practically insoluble in water; soluble in alcohol, in acetone, and in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Propyliodone is an iodinated radiographic contrast medium (p. 1580.1) that has been used for bronchography as either an aqueous or oily suspension.

Preparations

Pharmacopoeial Preparations

USP 36: Propyliodone Injectable Oil Suspension.

Sodium Tyropanoate *(BAN, rINN)*

Natrii Tyropanoas; NSC-107434; Tiropanoato de sodio; Tyropanoate de Sodium; Tyropanoate Sodium (USAN); Win-8851-2; Натрия Тиропаноат.

Sodium 2-(3-butyramido-2,4,6-tri-iodobenzyl)butyrate.

$C_{15}H_{17}I_3NNaO_3$=663.0

CAS — 27293-82-9 (tyropanoic acid); 7246-21-1 (sodium tyropanoate).

ATC — V08AC09.

ATC Vet — QV08AC09.

UNII — XRJ0P5FAYO.

Description. Sodium tyropanoate contains about 57.4% of I.

Profile

Sodium tyropanoate is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to those of iopanoic acid (p. 1591.1) and has been used for cholecystography and cholangiography.

Sulfur Hexafluoride *(USAN)*

BRI; Hexafluouro de azufre; Sulphur Fluoride; Sulphur Hexafluoride; Серы Гексафторид.

F_6S=146.1

CAS — 2551-62-4.

ATC — V08DA05.

ATC Vet — QV08DA05.

UNII — WS7LR3I1D6.

Profile

Sulfur hexafluoride is a gas with little biological activity that is used as an ultrasound contrast medium (p. 1580.2) for imaging of the blood vessels and for echocardiography. Microbubbles of sulfur hexafluoride are formed on reconstitution of the preparation and provide echo-enhancement; phospholipids and surfactants are included to stabilise the microbubbles. It is given intravenously as a suspension containing 45 micrograms/mL, in a usual dose of 2 mL for echocardiography, or 2.4 mL for imaging blood vessels; the dose may be repeated once if necessary.

Sulfur hexafluoride has been associated with hypersensitivity reactions; patients should be monitored for at least 30 minutes after use, and resuscitation equipment should be available. Particular care is advised in patients with ischaemic heart disease, in whom serious and occasionally fatal cardiac events have occurred: sulfur hexafluoride is contra-indicated in patients with recent acute coronary syndrome or clinically unstable ischaemic heart disease. It should also not be given to patients with severe pulmonary hypertension, uncontrolled hyper-

tension, acute respiratory distress syndrome, or right-to-left shunts. Care is advised in patients with lung disorders.

Sulfur hexafluoride has also been used as an adjunct in eye surgery for retinal detachment.

References.
1. Kim SS, *et al*. Outcomes of sulfur hexafluoride (SF6) versus perfluoropropane (C3F8) gas tamponade for macular hole surgery. *Retina* 2008; **28:** 1408–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulfur hexafluoride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: SonoVue; ***Belg.***: SonoVue; ***China***: SonoVue (声诺维); ***Cz.***: SonoVue; ***Denm.***: SonoVue; ***Fin.***: SonoVue; ***Fr.***: SonoVue; ***Gr.***: SonoVue; ***Hung.***: SonoVue; ***Irl.***: SonoVue; ***Ital.***: SonoVue; ***Neth.***: SonoVue; ***Norw.***: SonoVue; ***Pol.***: SonoVue; ***Port.***: SonoVue; ***Singapore***: SonoVue; ***Spain***: SonoVue; ***Swed.***: SonoVue; ***Switz.***: SonoVue; ***UK***: SonoVue.

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The adrenal cortex synthesises both corticosteroids, based on a 21-carbon nucleus, and some sex hormones, mainly androgens, based on a 19-carbon nucleus. The corticosteroids are traditionally divided into those with mainly glucocorticoid actions, of which cortisol (hydrocortisone) is the most important endogenous example, and those that are mainly mineralocorticoid, of which aldosterone is much the most important.

The endogenous glucocorticoids are under regulatory control from the hypothalamus and pituitary, via the releasing hormones corticorelin (p. 1628.1) and corticotropin or ACTH (p. 1628.3). In return the glucocorticoids act to inhibit production and release of these releasing hormones by a negative feedback mechanism. The system is known collectively as the hypothalamic-pituitary-adrenal (HPA) axis. Aldosterone secretion, by contrast, is under the control of the renin-angiotensin system.

The main **mineralocorticoid** actions are on fluid and electrolyte balance. They enhance sodium reabsorption in the kidney and hence expand the extracellular fluid volume, and they enhance renal excretion of potassium and H^+.

The **glucocorticoid** actions are wide-ranging. They have potent anti-inflammatory and immunosuppressive effects, at least partly through inhibition of the release of various cytokines, and it is mainly these that are made use of clinically (see below). They also have profound metabolic effects: blood glucose concentrations are maintained or increased by a decrease in peripheral glucose utilization and an increase in gluconeogenesis; glycogen deposition, protein breakdown, and lipolysis are increased, and effects on calcium uptake and excretion lead to a decrease in body calcium stores. Glucocorticoids facilitate the action of many other active endogenous substances, and affect the function of cardiovascular system, kidneys, skeletal muscle and CNS.

Many synthetic congeners and derivatives of the corticosteroids are available. The main corticosteroids used systemically are hydroxy compounds (alcohols). They are relatively insoluble in water and the sodium salt of the phosphate or succinate ester is generally used to provide water-soluble forms for injections or solutions. Such esters are readily hydrolysed in the body.

Various structure-activity relationships are understood for the corticosteroids and have been made use of in the development of new compounds. The presence of a hydroxyl group at position 11 seems to be essential for glucocorticoid activity, while a hydroxyl at position 21 is required for mineralocorticoid activity. Fluorination at position 9 enhances both mineralocorticoid and glucocorticoid activity. Substitution at carbon 16 (as in betamethasone, dexamethasone, or triamcinolone) virtually eliminates mineralocorticoid activity. Esterification of corticosteroids at the 17 or 21 positions with fatty acids generally increases the topical activity. The formation of cyclic acetonides at the 16 and 17 positions further increases topical anti-inflammatory activity, usually without increasing systemic glucocorticoid activity. Figure 1 (below) shows the basic steroidal skeleton structure.

Figure 1. Steroidal skeleton.

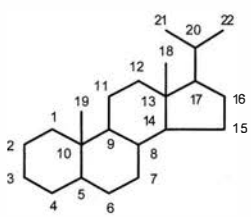

In the medical and pharmacological literature the names of unesterified corticosteroids have frequently been used indiscriminately for both the unesterified and esterified forms and it is not always apparent to which form reference is being made. The unesterified form is sometimes qualified by the phrase 'free alcohol'.

Uses and Administration of Corticosteroids

The corticosteroids are used in physiological doses for replacement therapy in adrenal insufficiency. Pharmacological doses are used when palliative anti-inflammatory or immunosuppressant effects are required. Before instituting therapy the benefits and risks of corticosteroids should be considered; where appropriate, local rather than systemic therapy should be used. The lowest effective dose should be used for the shortest possible time; high doses may be needed for life-threatening situations.

The effects of different corticosteroids vary qualitatively as well as quantitatively, and it may not be possible to substitute one for another in equal therapeutic amounts without provoking adverse effects. Thus, whereas cortisone and hydrocortisone have very appreciable mineralocorticoid (or sodium-retaining) properties relative to their glucocorticoid (or anti-inflammatory) properties, prednisolone and prednisone have considerably less, and others, such as betamethasone and dexamethasone, have none or virtually none. In contrast, the mineralocorticoid properties of fludrocortisone are so pronounced that its glucocorticoid effects are considered to have no clinical significance.

As a rough guide, the approximate **equivalent doses** of the main corticosteroids in terms of their glucocorticoid (or anti-inflammatory) properties alone, are:

- betamethasone 750 micrograms
- cortisone acetate 25 mg
- dexamethasone 750 micrograms
- hydrocortisone 20 mg
- methylprednisolone 4 mg
- prednisolone 5 mg
- prednisone 5 mg
- triamcinolone 4 mg

However, esterification generally alters potency and compounds given at equivalent glucocorticoid doses may not have equivalent clinical effect.

The mineralocorticoid properties of corticosteroids (see above) are rarely used. Exceptions include the treatment of

primary adrenocortical insufficiency, in which both mineralocorticoid and glucocorticoid replacement is necessary, usually in the form of fludrocortisone with hydrocortisone (for details, see p. 1600.2). The mineralocorticoid properties of fludrocortisone are also used to maintain blood pressure in patients with orthostatic hypotension (see p. 1634.3).

The anti-inflammatory and immunosuppressant glucocorticoid properties of corticosteroids (see p. 1597.1) are used to suppress the clinical manifestations of disease in many disorders considered to have inflammatory or immunological components. For these purposes, the synthetic analogues with their considerably reduced mineralocorticoid properties linked with enhanced glucocorticoid properties, are preferred. Despite the existence of very powerful synthetic glucocorticoids with virtually no mineralocorticoid activity, the hazards of inappropriately high glucocorticoid therapy are such that the less powerful prednisolone and prednisone are the glucocorticoids of choice for most conditions, since they allow for a greater margin of safety. There is little to choose between prednisolone and prednisone; prednisolone is usually recommended in the UK since it exists in a metabolically active form, whereas prednisone is inactive and must be converted into its active form by the liver; hence, particularly in some liver disorders, bioavailability of prednisone is less reliable (but see Hepatic Impairment under Precautions of Prednisolone, p. 1646.3).

Because the therapeutic effects of corticosteroids seem to be of longer duration than the metabolic effects, intermittent treatment with corticosteroids has been used to allow the metabolic rhythm of the body to become re-established while maintaining the therapeutic effects. Regimens of intermittent therapy have usually consisted of short courses of treatment or of the use of single doses on alternate days. Such alternate-day therapy, however, is only appropriate for corticosteroids with a relatively short duration of action and small mineralocorticoid effect, such as prednisolone, and only in certain disease states. Corticosteroids are also given in single daily doses at times coinciding with maximum or minimum output of the adrenal cortex in order to obtain the desired effect on the adrenals (see Diurnal Effect under Administration, below).

Doses of corticosteroids higher than those required for physiological replacement will eventually lead to some degree of adrenal suppression, the extent depending on the dose given, and the route, frequency, time, and duration of treatment. The adrenal glands are considered to have a daily output equivalent to about 10 or 20 mg of hydrocortisone (cortisol), but individual blood-cortisol concentrations may vary widely, and can increase up to tenfold or more during stress. Therefore, during periods of stress or trauma, such as during and after surgery and when suffering from infections, the corticosteroid dosage of patients must be increased. In patients on long-term corticosteroid therapy undergoing surgery this is usually provided by parenteral hydrocortisone; graduated regimens tailored to the severity of surgery (see p. 1640.3) are now preferred to the former high-dose standard regimens tapered over 5 days, whose use has been questioned (see Surgery, under Administration, p. 1599.1).

Although the empirical use of a corticosteroid is appropriate in a life-threatening situation, generally it is advisable not to begin corticosteroid therapy until a definite diagnosis has been made, for otherwise symptoms may be masked to such an extent that a true diagnosis becomes extremely difficult to make and the disease may reach an advanced stage before detection.

Systemic therapy is indicated in many conditions. Where possible the oral route is preferred but parenteral doses may be used if the disease is severe or an emergency arises. Intravenous therapy is generally used for intensive emergency treatment as the onset of action is relatively fast although intramuscular injections, often formulated as longer-acting depot preparations, may also be used to provide subsequent cover. Examples of conditions treated with systemic corticosteroids include:

- as an adjunct to adrenaline in life-threatening allergic reactions such as angioedema or anaphylaxis (see p. 1293.2)
- some blood disorders, including auto-immune haemolytic anaemia (p. 1122.2) and immune thrombocytopenia (p. 1606.1)
- selected connective tissue and muscle disorders, such as Behçet's syndrome (p. 1601.1), polymyalgia rheumatica (p. 1610.3), polymyositis (p. 1611.1), SLE (p. 1613.3), and the vasculitic syndromes (p. 1615.2)
- some inflammatory eye disorders, particularly those affecting the posterior chamber such as uveitis (p. 1615.1)
- inflammatory gastrointestinal disorders, such as Crohn's disease and ulcerative colitis, although local administration by the rectal route may be preferred in some circumstances (see p. 1808.3)
- infections accompanied by a severe inflammatory component provided that appropriate anti-infective drugs are also given and that the benefits of corticosteroid therapy outweigh the possible risk of disseminated infection; examples of conditions where corticosteroid may be considered include helminthic infections, the Jarisch-Herxheimer reaction, and tuberculous meningitis (p. 1614.3)
- selected kidney disorders including lupus nephritis (see Systemic Lupus Erythematosus, p. 1613.3) and various glomerular disorders (p. 1604.3)
- selected liver disorders, including auto-immune chronic active hepatitis (p. 1602.3)
- some neurological disorders such as infantile spasms (see Epilepsy, p. 1604.1) and subacute demyelinating polyneuropathy (p. 1611.2); also in cerebral oedema (p. 1602.3), including that associated with malignancy
- some respiratory disorders, such as asthma (p. 1600.3, although inhaled corticosteroids are preferred to oral therapy for prophylaxis), interstitial lung disease (p. 1607.1), pulmonary sarcoid (p. 1612.2), and neonatal respiratory distress syndrome (p. 1608.3)
- some cases of rheumatoid arthritis, where recent evidence suggests there may be value in early treatment of active disease (see p. 1612.1)
- severe skin disorders such as pemphigus and pemphigoid (p. 1687.1)

Glucocorticoids are also used with antineoplastics in regimens for the management of malignant disease. They are also given to reduce immune responses after organ transplantations, often with other immunosuppressants (see p. 1932.2).

Corticosteroids are not now considered useful in patients with aspiration syndromes or stroke.

Intra-articular injection, in the absence of infection and with full aseptic precautions, may be used, for example, in the treatment of rheumatoid arthritis (p. 13.2), osteoarthritis (p. 12.3), and ankylosing spondylitis (see Spondyloarthropathies, p. 14.3). Either hydrocortisone acetate or one of the esters of the synthetic corticosteroids is used. It should be noted that there have been several reports of joint damage after the intra-articular injection of corticosteroids into load-bearing joints.

Topical application often produces dramatic suppression of skin diseases in which inflammation is a prominent feature, such as eczema (p. 1684.1), seborrhoeic dermatitis (p. 1689.1), and some forms of psoriasis (p. 1688.1). However, the disease may return or be exacerbated when corticosteroids are withdrawn and this appears to be a particular problem in some of the forms of psoriasis. Occasionally, corticosteroids may be used with the addition of a suitable antimicrobial, such as neomycin, in the treatment of infected skin. For comments on the topical application of preparations containing a corticosteroid and neomycin, see Adverse Effects of Neomycin, p. 330.2.

Intralesional injection sometimes hastens the resolution of chronic skin lesions such as lichen planus (p. 1685.2), alopecia areata (p. 1682.3), and keloids.

Topical application to the eye in inflammatory and traumatic disorders has led to dramatic results, but the occurrence of herpetic and fungal infections of the cornea and other serious complications are considerable obstacles, and eye drops containing corticosteroids should be used under strict ophthalmic supervision with regular checks of intra-ocular pressure. Care is also required when corticosteroids are given by **subconjunctival injection** in inflammatory eye disorders.

Ear drops containing corticosteroids are used in the treatment of otitis externa (see p. 195.1).

Inhalational therapy is widely used in the prophylaxis of asthma (p. 1600.3).

Nasal application is used in the prophylaxis and treatment of allergic and non-allergic rhinitis (see p. 612.1) and nasal polyps (p. 1608.2).

Rectal administration, by either suppository or enema, may be used for some corticosteroids, notably in the treatment of inflammatory bowel disease (p. 1808.3).

Administration

Diurnal effect. The diurnal rhythm of the adrenal cortex leads to about 70% of the daily secretion being made between midnight and 9 am.[1] In the treatment of adrenal cortical hyperplasia a dose of hydrocortisone given at night will be nearly twice as suppressive as the same dose given during the day. However, in treating allergic or collagen disease when suppression of adrenal cortical activity is best avoided a dose of hydrocortisone at about 8 am is indicated. When reducing corticosteroid dosage after treatment, a single dose given at 8 am will be most beneficial and will not inhibit corticotropin secretion. Also, for similar reasons,[2] when used for replacement therapy corticosteroids are given in unequal doses during the day (two-thirds of the daily dose in the morning, and one-third at night).

1. Demos CH, *et al.* A modified (once a day) corticosteroid dosage regimen. *Clin Pharmacol Ther* 1964; **5:** 721–7.
2. Aronson JK. Chronopharmacology: reflections on time and a new text. *Lancet* 1990; **335:** 1515–16.

Epidural route. Although epidural injections of corticosteroids have been widely used in the treatment of sciatica and chronic low back pain (p. 9.2), evidence of efficacy is lacking or conflicting, and guidelines do not recommend them for routine use.[1,2] Others have also reviewed epidural corticosteroid use.[3-6]

It should be noted that inadvertent intrathecal injection of corticosteroids has resulted in severe neurological complications.

1. Armon C, *et al.* Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007; **68:** 723–9. Also available at: http://www.neurology.org/cgi/reprint/68/10/723.pdf (accessed 24/03/10)
2. Airaksinen O, *et al.* COST B13 Working Group on Guidelines for Chronic Low Back Pain. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; **15** (suppl 2): S192–S300. Also available at: http://www.backpaineurope.org/web/files/WG2_Guidelines.pdf (accessed 24/03/10)
3. Abdi S, *et al.* Epidural steroids in the management of chronic spinal pain: a systematic review. *Pain Physician* 2007; **10:** 185–212.
4. Young IA, *et al.* The use of lumbar epidural/transforaminal steroids for managing spinal disease. *J Am Acad Orthop Surg* 2007; **15:** 228–38.
5. Stafford MA, *et al.* Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. *Br J Anaesth* 2007; **99:** 461–73.
6. Valat JP, Rozenberg S. Local corticosteroid injections for low back pain and sciatica. *Joint Bone Spine* 2008; **75:** 403–7.

Inhalational therapy. Corticosteroids are given by inhalation, particularly in the maintenance therapy of asthma, in order to deliver the drug directly to the lungs, at smaller doses than are needed orally, and minimise systemic adverse effects. Different inhaled corticosteroids differ in their potency, though there is little evidence of a difference in efficacy at recommended doses.[1] Of those widely available by inhalation, beclometasone dipropionate and budesonide have been considered to have similar potency, while flunisolide is less potent, and ciclesonide, fluticasone propionate, and mometasone furoate are considered to be more potent. However, formulation may affect drug availability; the replacement of chlorofluorocarbon propellants with a hydrofluoroalkane has increased the drug availability from some products, necessitating the use of lower doses[2,3] (see also Reformulation, under Beclometasone Dipropionate, p. 1622.3).

Efficient delivery to the bronchial tree is crucial and several different devices are available, including pressurised aerosol inhalers, breath-actuated aerosol inhalers, and dry powder inhalers. These devices appear to be equally effective for the delivery of corticosteroids.[4] However, many patients, especially children, find that inhalation is made much easier by fitting a spacer device to the inhaler.[5] Such a device is recommended when high doses are to be inhaled, to prevent oropharyngeal deposition and subsequent systemic absorption. However, the type of spacer used and the method of use may dramatically alter the amount of drug available for inhalation. The drug should be introduced into the spacer by single actuations, each followed by inhalation, with the delay between actuation of the inhaler and inhalation from the spacer kept to a minimum. In some spacers static electricity accumulates, and the build up of charge reduces drug delivery: this can be controlled by washing and drying the spacer in air once a month. Considerable differences in the dose delivered to the airways may also be seen between different types of nebuliser, and between nebulisers and spacer devices.[6]

It should be borne in mind that apparent differences in the dose supplied from inhaler devices in different countries may in some cases be artefacts, due to variations in the way the dose is measured or expressed. In the UK, for example, the dose supplied from a metered-dose inhaler is generally quoted as the amount released into the mouthpiece from the valve. In the USA, however, doses may be stated in terms of the amount of drug emitted from the mouthpiece, which due to drug deposition will be slightly less than the amount released from the valve.

1. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother* 2009; **43:** 519–27.
2. Newman SP. Deposition and effects of inhaled corticosteroids. *Clin Pharmacokinet* 2003; **42:** 529–44.
3. MHRA/CHM. Inhaled products that contain corticosteroids. *Drug Safety Update* 2008; **1** (12): 6–7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Brocklebank D, *et al.* Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma. *BMJ* 2001; **323:** 896–900.
5. O'Callaghan C, Barry PW. How to choose delivery devices for asthma. *Arch Dis Child* 2000; **82:** 185–7.
6. O'Callaghan C, Barry P. Delivering inhaled corticosteroids to patients. *BMJ* 1999; **318:** 410–11.

Intra-articular route. Intra-articular and periarticular injection of corticosteroids is an established treatment for a variety of joint and soft-tissue lesions.[1-4] Pain and

Table 1. Guide to potencies of topical corticosteroids.

Very potent	Potent	Moderately potent	Mild
Clobetasol propionate 0.05%	Amcinonide 0.1%	Alclometasone dipropionate 0.05%	Fluocinolone acetonide 0.0025%
Diflucortolone valerate 0.3%	Beclometasone dipropionate 0.025%	Betamethasone valerate 0.025%	Hydrocortisone 0.5% and 1%
Fluocinolone acetonide 0.2%	Betamethasone benzoate 0.025%	Clobetasone butyrate 0.05%	Hydrocortisone acetate 1%
Halcinonide 0.1%	Betamethasone dipropionate 0.05%	Desonide 0.05%	Methylprednisolone acetate 0.25%
Ulobetasol propionate 0.05%	Betamethasone valerate 0.1%	Desoximetasone 0.05%	
	Budesonide 0.025%	Fludroxycortide 0.0125%	
	Desoximetasone 0.25%	Flumetasone pivalate 0.02%	
	Diflorasone diacetate 0.05%	Fluocinolone acetonide 0.00625% and 0.01%	
	Diflucortolone valerate 0.1%	Fluocortin butyl 0.75%	
	Fluclorolone acetonide 0.025%	Fluocortolone preparations (caproate with pivalate, each 0.1%	
	Fluocinolone acetonide 0.025%	and caproate with either free alcohol or pivalate, each 0.25%)	
	Fluocinonide 0.05%	Hydrocortisone aceponate 0.1%	
	Fluprednidene acetate 0.1%	Hydrocortisone buteprate 0.1%	
	Fluticasone propionate 0.005% and 0.05%	Prednicarbate 0.25%	
	Hydrocortisone butyrate 0.1%		
	Methyprednisolone aceponate 0.1%		
	Mometasone furoate 0.1%		
	Triamcinolone acetonide 0.1%		

inflammation associated with rheumatoid and juvenile idiopathic arthritis, crystal arthropathies such as gout, and osteoarthritis can be alleviated by injection of a suitable corticosteroid, and in some cases the benefits may be quite prolonged. The longer-acting esters methylprednisolone acetate, triamcinolone acetonide, and triamcinolone hexacetonide are generally preferred. In some cases these may be combined with a local anaesthetic and a short-acting soluble corticosteroid for more rapid relief and to reduce the risk of a post-injection flare.

The risks associated with this technique have been reviewed.[5] Accurate injection technique is essential, and vigorous skin cleansing and an aseptic technique are required to avoid the introduction of infection into the joint; pre-existing joint infection is a contra-indication to corticosteroid injection. Intra-articular injections may be repeated if necessary but it has been suggested that a single joint should not be injected more than 3 or 4 times a year.

Periarticular injection is also used in various soft tissue disorders such as bursitis, capsulitis (painful shoulder syndromes), epicondylitis, tenosynovitis, and carpal tunnel syndrome. Particular care is required to avoid injection directly into a tendon, as this may cause the tendon to rupture. A shorter-acting corticosteroid such as hydrocortisone acetate may be more suitable for extra-articular lesions.

1. Anonymous. Articular and periarticular corticosteroid injections. *Drug Ther Bull* 1995; **33:** 67–70.
2. Caldwell JR. Intra-articular corticosteroids: guide to selection and indications for use. *Drugs* 1996; **52:** 507–14.
3. Pullar T. Routes of drug administration: intra-articular route. *Prescribers' J* 1998; **38:** 123–6.
4. Schumacher HR, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. *Am J Med* 2005; **118:** 1208–14.
5. Hunter JA, Blyth TH. A risk-benefit assessment of intra-articular corticosteroids in rheumatic disorders. *Drug Safety* 1999; **21:** 353–65.

Intranasal route. In the management of allergic rhinitis corticosteroids are given intranasally in order to deliver the drug directly to the affected area, to use lower doses than are needed orally, and reduce the risk of systemic adverse effects. They are usually given by metered dose pump spray. The extent of local effect versus systemic effect may be influenced by the drug's molecular weight, lipophilicity, metabolism in nasal tissue, and type of delivery device.[1] In practice, however, when intranasal corticosteroid sprays are used as recommended there is little evidence that they have a significant systemic effect, and their local adverse effects are similar.[2,3] For details of systemic effects associated with inappropriately prolonged use of corticosteroid nasal drops, see Intranasal Administration under Precautions, p. 1619.1.

1. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. *Drug Safety* 2000; **23:** 11–33.
2. Waddell AN, *et al*. Intranasal steroid sprays in the treatment of rhinitis: is one better than another? *J Laryngol Otol* 2003; **117:** 843–5.
3. Meltzer EO. Intranasal steroids: managing allergic rhinitis and tailoring treatment to patient preference. *Allergy Asthma Proc* 2005; **26:** 445–51.

Surgery. In the light of what was known in 1994 about the adrenal stress response to surgery, a discussion on the appropriate glucocorticoid supplementation for patients receiving corticosteroids who undergo surgery concluded that some recommendations were excessive.[1] (At this time in the UK recommended regimens consisted of the equivalent of 100 mg of hydrocortisone, usually as the sodium succinate, intravenously or intramuscularly before surgery, repeated every 8 hours, with the dose being tapered over 5 days to 20 or 30 mg daily.) It was suggested that for minor surgery 25 mg of hydrocortisone or its equivalent pre-operatively was adequate; where surgical stress was likely to be moderate, 50 to 75 mg of hydrocortisone or its equivalent daily in divided doses for 1 to 2 days was suggested. For major surgical stress, a target of 100 to 150 mg of hydrocortisone or its equivalent should be given daily in divided doses for 2 to 3 days, although less might be given if the patient's pre-operative glucocorticoid dose was low. It was also considered that the practice of gradually reducing postoperative coverage over several days was not supported by evidence except in cases of high-dose glucocorticoid use for prolonged periods.

Another review[2] of this subject also concluded that for minor surgery, 25 mg of hydrocortisone, or the patient's usual dose of corticosteroid, given pre-operatively, was appropriate. However, the authors argued that for surgery causing greater stress, it was preferable to avoid the increases in plasma-cortisol associated with intermittent bolus doses. They suggested that for moderate surgery an intravenous dose of hydrocortisone 25 mg at induction should be followed by an infusion of 100 mg over 24 hours; for major surgery the infusion should be continued for 48 to 72 hours after surgery. The usual oral corticosteroid dose may be resumed once these infusions have been completed, providing the postoperative course is uncomplicated and gastrointestinal function has returned.

A subsequent systematic review[3] found that there was still little data from controlled studies of this common practice. Based on this limited information, it was concluded that patients being treated with therapeutic doses of corticosteroids would not routinely need additional stress doses when undergoing surgical procedures, provided they were given their usual daily dose of corticosteroid. However, they should be monitored carefully in the perioperative period, and stress doses of hydrocortisone may be needed in patients with volume-refractory hypotension; a serum-cortisol measurement was recommended in these patients before starting therapy. Patients receiving physiological replacement doses of corticosteroids for primary disease of the hypothalamic-pituitary-adrenal axis would require supplemental corticosteroid doses in the perioperative period.

For currently recommended regimens see Uses and Administration of Hydrocortisone, p. 1640.3.

1. Salem M, *et al*. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg* 1994; **219:** 416–25.
2. Nicholson G, *et al*. Peri-operative steroid supplementation. *Anaesthesia* 1998; **53:** 1091–1104.
3. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Arch Surg* 2008; **143:** 1222–6.

Topical application. Guidelines[1,2] for the correct use of topical corticosteroids recommend that an appropriately potent preparation to bring the skin disorder under control should be used. Some recommend use of the lowest potency that will control the disorder, while others have advocated starting treatment with a more potent preparation, treatment may then be continued with a less potent preparation and with less frequent application, once control is obtained. The most potent topical corticosteroids are generally reserved for recalcitrant dermatoses. Once the skin has healed, treatment should be tailed off. Particular care is necessary in the use of topical corticosteroids in children, and the more potent preparations are contra-indicated in infants under 1 year of age, although potent preparations may be needed briefly in older children. It has been suggested that a 'steroid holiday' of at least 2 weeks be considered in children after each 2 or 3 weeks of daily topical therapy to allow thinned epidermis to restore itself and maintain its barrier function.[3]

Care is also necessary in applying corticosteroids to certain anatomical sites such as the face and flexures; some advocate using only hydrocortisone 0.5 or 1% on the face. Advice should be given that topical corticosteroids should be applied sparingly in thin layers, by smoothing gently into the skin preferably after a bath, and that no benefit is gained from more frequent than twice daily application or by vigorous rubbing.

In a study to determine the requirement of topical corticosteroids,[4] 16 adult patients with eczema were treated with a variety of topical preparations until substantial clearing had occurred (up to 10 days). Results indicated that the mean requirement of preparation, regardless of potency or vehicle, was 6.86 g/m^2. Using this value the calculated quantities of topical corticosteroid to the nearest 5 g required for twice daily application for one week for the whole body, arms and legs only, and trunk only respectively were as follows:

- 6 months of age, 35 g, 20 g, and 15 g
- 1 year, 45 g, 25 g, and 15 g
- 4 years, 60 g, 35 g, and 20 g
- 8 years, 90 g, 50 g, and 35 g
- 12 years, 120 g, 65 g, and 45 g
- 16 years, 155 g, 85 g, and 55 g
- adult (70-kg male), 170 g, 90 g, and 60 g

Calculated quantities for the same application schedule for an adult (70-kg male) for individual portions of the body were:

- face and neck, 10 g
- one arm, 15 g
- one leg, 30 g
- hands and feet, 10 g

Table 1 (above) is a guide to the potency of topical corticosteroids. There may be some degree of overlap between these groups and, not surprisingly, there are minor variations to this classification. For example, some authorities consider fluocinolone acetonide 0.2% to be potent rather than very potent and halcinonide 0.1% to be potent rather than very potent.

It has been suggested, however, that the advent of nonfluorinated double esters such as hydrocortisone and methylprednisolone aceponates, or prednicarbate, has resulted in corticosteroids whose topical anti-inflammatory potency is not as closely related to their potential atrophic effects on skin, and that a classification taking both into account would be desirable.[5,6]

1. Miller JA, Munro DD. Topical corticosteroids: clinical pharmacology and therapeutic use. *Drugs* 1980; **19:** 119–34.
2. Savin JA. Some guidelines to the use of topical corticosteroids. *BMJ* 1985; **290:** 1607–8.
3. Hepburn D, *et al*. Topical steroid holiday. *Pediatrics* 1995; **95:** 455.
4. Maurice PDL, Saihan EM. Topical steroid requirement in inflammatory skin conditions. *Br J Clin Pract* 1985; **39:** 441–2.
5. Mori M, *et al*. Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; **10:** 406–12.
6. Schäfer-Korting M, *et al*. Topical glucocorticoids with improved risk-benefit ratio: rationale of a new concept. *Drug Safety* 1996; **14:** 375–85.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is characterised by areas of lung damage leading to decreased pulmonary compliance, pulmonary oedema associated with increased capillary and alveolar permeability, and refractory hypoxaemia. Diffuse pulmonary infiltrates are seen on radiography, and patients have dyspnoea, tachypnoea, or both. Diagnosis is mainly clinical, and there has been some disagreement as to what should be included in the syndrome;[1] it is now seen as forming the most severe end of a spectrum of symptoms due to lung inflammation and increased permeability known as acute lung injury.[1-3] ARDS is sometimes considered to refer to 'adult respiratory distress syndrome' but it is not confined to adult patients.[1,2]

ARDS may be caused by a variety of pulmonary or systemic insults but is particularly frequent in patients with

sepsis;[4] because of an association with failure of other organs it has been suggested that it represents the pulmonary component of multiple organ failure syndrome.[5] Many inflammatory mediators have been implicated in its pathogenesis but evidence suggests that recruitment of neutrophils by interleukins plays an important role.[1]

Management. Therapy for ARDS is essentially supportive. Mechanical ventilation is necessary in most cases, and circulatory support may require fluids, cardiac inotropes, and vasodilators. Optimum management may include diuretics and fluid restriction provided that cardiac output and oxygen delivery are maintained.[6] Because of the association with sepsis antibacterial therapy may be important, but studies of anti-endotoxin antibodies have produced disappointing results.[3] Improvements in supportive care and mechanical ventilation are considered to have reduced the mortality rate.[1,7] Partial liquid ventilation with perfluorocarbons has been tried, but good evidence to support this intervention is not available.[8]

Many drugs have been proposed for the management of ARDS, but, although case reports are often encouraging, none has been conclusively shown to improve mortality in controlled studies,[9] or in systematic review.[10] Corticosteroids do not appear to reduce acute mortality,[3,5] and may increase mortality rates in persistent ARDS if started 14 or more days after the onset of the condition.[11] Good results have been reported with inhaled epoprostenol,[12,13] but these results await confirmation from larger controlled studies.

There is evidence that ketoconazole may prevent development of ARDS in patients considered at risk,[14,15] but it does not appear to be effective as a treatment for ARDS or acute lung injury.[16] Among the drugs that have proved disappointing are acetylcysteine,[17,18] alprostadil,[19,20] and nitric oxide[21] (which may, however, improve oxygenation to some degree). Studies[22,23] of pulmonary surfactants in ARDS have generally shown no survival benefit; however, calfactant significantly decreased mortality when given to infants, children, and adolescents.[24]

A high-fat, low-carbohydrate diet has been advocated for patients with ARDS. Supplementation with eicosapentaenoic acid and gamolenic acid has been reported to benefit oxygenation, but with no significant effect on mortality.[7,25]

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; **342:** 1334–49. Correction. *ibid.*; **343:** 520.
2. Bernard GR, *et al*. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149:** 818–24.
3. Bigatello LM, Zapol WM. New approaches to acute lung injury. *Br J Anaesth* 1996; **77:** 99–109.
4. Piantadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med* 2004; **141:** 460–70.
5. Weinberger SE. Recent advances in pulmonary medicine (part 2). *N Engl J Med* 1993; **328:** 1462–70.
6. Elsasser S, *et al*. Adjunctive drug treatment in severe hypoxic respiratory failure. *Drugs* 1999; **58:** 429–46.
7. Hite RD, Morris PE. Acute respiratory distress syndrome: pharmacological treatment options in development. *Drugs* 2001; **61:** 897–907.
8. Davies MW, Fraser JF. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 05/05/05).
9. Jain R, DalNogare A. Pharmacological therapy for acute respiratory distress syndrome. *Mayo Clin Proc* 2006; **81:** 205–12.
10. Adhikari N, *et al*. Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 05/05/05).
11. Steinberg KP, *et al*. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; **354:** 1671–84.
12. Walmrath D, *et al*. Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342:** 961–2.
13. Walmrath D, *et al*. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153:** 991–6.
14. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; **21:** 1635–42.
15. Sinuff T, *et al*. Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; **14:** 1–6.
16. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; **283:** 1995–2002.
17. Jepsen S, *et al*. Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; **20:** 918–23.
18. Domenighetti G, *et al*. Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; **12:** 177–82.
19. Bone RC, *et al*. Randomized double-blind, multicenter study of prostaglandin E_1 in patients with the adult respiratory distress syndrome. *Chest* 1989; **96:** 114–19.
20. Abraham E, *et al*. Liposomal prostaglandin E_1, in acute respiratory distress syndrome: a placebo-controlled, randomized, double-blind, multicenter clinical trial. *Crit Care Med* 1996; **24:** 10–15.
21. Sokol J, *et al*. Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 05/05/05).
22. Anzueto A, *et al*. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996; **334:** 1417–21.
23. Spragg RG, *et al*. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004; **351:** 884–92.
24. Willson DF, *et al*. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA* 2005; **293:** 470–6. Correction. *ibid.*; **294:** 900.
25. Cranshaw J, *et al*. The pulmonary physician in critical care 9: non-ventilatory strategies in ARDS. *Thorax* 2002; **57:** 823–9.

Adrenal hyperplasia, congenital

See Congenital Adrenal Hyperplasia, p. 1603.2.

Adrenocortical insufficiency

The major function of the adrenal cortex is the production of glucocorticoid and mineralocorticoid hormones, of which cortisol (hydrocortisone) and aldosterone respectively are the most important. Glucocorticoid production is regulated by the hypothalamic-pituitary-adrenal axis, being stimulated by the release of ACTH (adrenocorticotrophic hormone; corticotropin) from the pituitary, while mineralocorticoid production is mainly controlled by the renin-angiotensin system.

Adrenocortical insufficiency is defined as inadequate production of endogenous corticosteroids. It may be primary (Addison's disease), due to destruction of the adrenal cortex; or secondary, due to hypothalamic or pituitary disease, or corticosteroid therapy which suppresses ACTH release.[1,2] Diagnosis can be difficult, even with the aid of hormone tests such as the tetracosactide stimulation test.[3]

Clinical manifestations of adrenocortical insufficiency are usually seen once about 90% of the adrenal cortex is destroyed. Weight loss, anorexia, weakness, and fatigue may be accompanied by gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhoea, as well as electrolyte abnormalities (hyponatraemia, hyperkalaemia), salt craving, and orthostatic hypotension. In acute cases, abdominal pain and rigidity, fever, volume depletion, hypotension, and shock may occur. Hyperpigmentation, especially of skin creases, exposed areas, and scars is a distinguishing feature of primary, but not secondary, insufficiency. Hypoglycaemia is more likely in secondary deficiency due to lack of growth hormone, and failure of other pituitary hormones usually accompanies secondary adrenocortical insufficiency.

Treatment for acute insufficiency should be with intravenous hydrocortisone as the sodium succinate, sodium phosphate or other readily soluble ester: the usual dose is the equivalent of 100 mg every 6 to 8 hours for 24 hours. Volume depletion, dehydration, hypotension and hypoglycaemia should be corrected with intravenous saline and glucose, and precipitating factors, such as infection, should be dealt with appropriately. Provided no complications occur, the dosage of hydrocortisone can be tapered over 4 or 5 days to oral maintenance therapy.

For chronic insufficiency the usual oral dosage of **maintenance** or **replacement therapy** is hydrocortisone 20 to 30 mg, preferably divided unequally, e.g. 30 mg as 20 mg in the morning and 10 mg in the evening, in an attempt to mimic the natural pattern of secretion. Other corticosteroids have been used, including cortisone acetate, prednisolone, prednisone, and dexamethasone, but offer no advantage over hydrocortisone. Patients with primary insufficiency also require additional mineralocorticoid replacement with fludrocortisone, usually in a dose of 100 micrograms daily. Mineralocorticoid replacement is not usually necessary in secondary insufficiency. There has been some evidence of benefit from studies of adjunctive oral use of prasterone, another steroidal compound secreted by the adrenal glands, in patients with primary or secondary adrenal insufficiency.

Corticosteroid cover. An increase in replacement therapy is required during periods of stress. In mild infection, a doubling of the maintenance dose of hydrocortisone may be appropriate but for major infection, or severe stress such as surgery, parenteral therapy is required. It is generally considered safer to overestimate rather than underestimate the appropriate cover. For regimens used to provide cover in patients with secondary insufficiency due to corticosteroid therapy see Uses and Administration of Hydrocortisone, p. 1640.3.

1. Arlt W, Allolio B. Adrenal insufficiency. *Lancet* 2003; **361:** 1881–93.
2. Chakera AJ, Vaidya B. Addison disease in adults: diagnosis and management. *Am J Med* 2010; **123:** 409–13.
3. Dorin RI, *et al*. Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; **139:** 194–204.

AIDS

For the use of corticosteroids in AIDS patients with pneumocystis pneumonia, see p. 1610.2.

Alopecia

The management of alopecia (p. 1682.3) is often difficult. In alopecia areata intralesional corticosteroids, most commonly triamcinolone, will induce hair growth although they are not suitable when more than 50% of the scalp is involved.[1] Regrowth is confined to the site of injection and therefore patchy, although soon concealed by spontaneous growth from uninjected regions. Some atrophy of the scalp is inevitable. Topical corticosteroids are mostly reported to be ineffective although some consider them beneficial; the use of systemic corticosteroids is controversial, given their adverse effects and a lack of evidence that they alter the long-term prognosis.

1. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; **61:** 53–69.

Anaemias

For the use of corticosteroids in haemolytic anaemias, including cold haemagglutinin disease, see p. 1122.2.

Anaphylaxis

Anaphylaxis (p. 1293.2) is a medical emergency and prompt treatment with adrenaline is required. Corticosteroids have little place in the immediate management of anaphylaxis since their beneficial effects are delayed for several hours. However, in severely ill patients early use of intramuscular or slow intravenous hydrocortisone may avert late sequelae and help prevent or shorten protracted reactions, although it is doubtful whether they prevent biphasic attacks. Corticosteroids may be particularly useful in patients with an asthmatic component.

Aspiration syndromes

For a review of the management of aspiration syndromes, including reference to the probable lack of value of corticosteroids, see p. 1804.2.

Asthma

The cornerstones of current asthma therapy, as discussed in more detail on p. 1195.2, are the $beta_2$-adrenoceptor agonists and the corticosteroids. Drug therapy for **chronic asthma** is managed by a stepwise approach. Patients requiring only occasional relief from symptoms may be managed with an inhaled short-acting $beta_2$ agonist as required. An inhaled corticosteroid such as beclometasone dipropionate, budesonide, or fluticasone may be added to therapy if symptomatic relief is needed more than three times a week but regular use is important since corticosteroids take several hours to exert an effect in asthma. If control is still inadequate, a long-acting $beta_2$ agonist is added. The dose of inhaled corticosteroid may be increased if further control is needed, and other additional therapies include anti-leukotrienes or theophylline. Severe asthma requires regular bronchodilator therapy as well as high-dose inhaled corticosteroids, while in the most severe cases, regular oral corticosteroids may also be required. A short 'rescue' course of oral corticosteroid may be needed at any stage for an acute exacerbation. Corticosteroids should be used cautiously in children because of possible adverse effects on growth.

Guidelines vary slightly in their definition of low, moderate and high inhaled corticosteroid doses. In ***UK*** guidelines,[1] the reference inhaled corticosteroid was beclometasone dipropionate (p. 1621.2) given via a chlorofluorocarbon (CFC)-containing metered-dose inhaler (MDI) as this is the formulation used in most of the evidence-base that supports current asthma management. However, CFC-containing MDIs are being phased out and adjustments to doses may be required for other formulations and corticosteroids. Differences in CFC-free beclometasone dipropionate formulations available in the UK mean they are not dose equivalent (see Reformulation, under Beclometasone Dipropionate, p. 1622.3).

- For **adults**, doses in the range 200 to 800 micrograms daily of beclometasone dipropionate or equivalent are considered *low* initial doses, with 400 micrograms daily being an appropriate starting dose for most patients
- a dose of 800 micrograms daily is considered *moderate*
- doses greater than 800 up to 2000 micrograms daily are *high*
- For **children** aged 5 to 12 years, doses in the range 200 to 400 micrograms daily are considered *low* initial doses, with 200 micrograms daily being an appropriate starting dose for most patients
- a dose of 400 micrograms daily is considered *moderate*
- doses over 400 up to 800 micrograms daily are *high*

The definition in ***global*** guidelines[2] vary slightly.

- For **adults**, doses in the range 200 to 500 micrograms daily of beclometasone dipropionate via a CFC-containing MDI are considered *low* initial doses
- doses over 500 up to 1000 micrograms daily are considered *moderate*
- doses over 1000 up to 2000 micrograms daily are *high*
- For **children** aged over 5 years, doses in the range 100 to 200 micrograms daily are considered *low* initial doses
- doses over 200 up to 400 micrograms daily are considered *moderate*
- doses over 400 micrograms daily are *high*

In the ***USA*** CFC-containing beclometasone dipropionate MDIs have been phased out and replaced with MDIs containing hydrofluoroalkane (HFA). The recommended US dose of beclometasone dipropionate HFA MDI, relative to a CFC-containing MDI formulation, is lower due to differences in delivery characteristics between the products; however, a definitive comparative therapeutic ratio has not been found. In addition, doses are given as the amount delivered *from* the mouthpiece in the USA, instead of the amount delivered *into* the mouthpiece. For one product, Qvar (*Teva, USA*), each 100 micrograms of beclometasone dipropionate delivered *into* the mouthpiece equates to 80 micrograms delivered *from* the mouthpiece. Doses in the US guidelines[3] will therefore seem somewhat lower, although in practical terms there is probably little difference.

- For **adults**, US guidelines consider doses in the range 80 to 240 micrograms daily of beclometasone dipropionate via a HFA-containing MDI to be *low* initial doses
- doses greater than 240 up to 480 micrograms daily are considered *moderate*
- doses above 480 micrograms daily are *high*
- For **children** aged 5 to 12 years, doses in the range 80 to 160 micrograms daily are considered *low* initial doses
- doses greater than 160 up to 320 micrograms daily are considered *moderate*
- doses above 320 micrograms daily are considered *high*

Acute severe asthma (status asthmaticus) is potentially life-threatening and is treated with inhaled oxygen and $beta_2$ agonists, as well as systemic corticosteroids; inhaled ipratropium bromide, and intravenous magnesium sulfate, xanthine, or $beta_2$ agonist may need to be added. Once lung function is stabilised the patient can be discharged on a regimen of oral and inhaled corticosteroids, and bronchodilators.

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Behçet's syndrome

Behçet's syndrome (or Behçet's disease) is a recurrent multifocal disorder most prevalent in the Far East and countries of the Mediterranean and Middle East.

The clinical features include oral and genital ulceration, skin lesions, arthritis, vasculitis leading to thromboembolic disorders and aneurysms, ocular lesions (including uveitis, hypopyon, and iridocyclitis leading eventually to blindness), and CNS involvement (meningomyelitis, dementia, extrapyramidal symptoms, and paralysis, sometimes fatal). Gastrointestinal disturbances and involvement of other body systems have been reported. However, the complete gamut of symptoms is unlikely in a single patient, and the disease has been classified into mucocutaneous, arthritic, neurological, and ocular forms depending on the predominant symptoms. Diagnosis can be difficult, but oral ulceration, with recurrent genital ulceration, ocular involvement, and skin lesions or a positive pathergy test are considered the major diagnostic criteria.[1,2]

Treatment of Behçet's syndrome is essentially symptomatic and empirical. Controlled studies are mostly lacking, which has hindered meta-analysis.[3] Where possible, topical treatment of **mucocutaneous** lesions should be attempted before embarking on systemic therapy. Topical application of a potent corticosteroid, such as triamcinolone acetonide, or a tetracycline solution may be tried for oral ulceration.[1,2] Genital ulcers can be treated topically with betamethasone ointment.[2] Sucralfate suspension used topically has also been reported to be effective in oral and genital ulceration,[4] and topical mesalazine has been tried.[5] Systemically, colchicine is reportedly beneficial in the treatment of mucocutaneous lesions,[1,2] although a review failed to find any evidence of benefit from colchicine treatment.[3] Systemic corticosteroids are advocated for severe mucocutaneous disease;[4] oral prednisolone has been given for erythema nodosum.[1,2] Thalidomide is also effective for mucocutaneous symptoms,[2,4] although relapses occur on cessation of therapy. Other drugs with reported efficacy for mucocutaneous symptoms include azathioprine,[4] benzathine benzylpenicillin (sometimes with colchicine),[4] dapsone,[1,2,4,6] interferon alfa,[4,6] levamisole,[4] pentoxifylline,[1] and rebamipide.[4,6]

The use of NSAIDs in the treatment of **arthritis** in patients with Behçet's disease is controversial,[4] although indometacin is used.[2] Colchicine is also used,[2,4] and sulfasalazine may be beneficial in patients who do not respond to NSAIDs.[1] Corticosteroids used with azathioprine are effective,[2,4] as are interferon alfa,[1,2,4] and benzathine benzylpenicillin.[3]

Short courses of intravenous methylprednisolone or high-dose oral prednisolone with subsequent tapering are used in the acute phase of **neurological** involvement, and may be followed by chlorambucil, cyclophosphamide, or methotrexate.[2] Chronic CNS disease is generally resistant to therapy.[2]

Ocular involvement in Behçet's disease leads to blindness in about a quarter of patients.[1,2] For acute attacks of anterior uveitis, topical mydriatics such as tropicamide, or corticosteroid drops may be sufficient. Local injections of corticosteroids are used to treat acute attacks of posterior uveitis, and systemic use may also be required.[2] Oral corticosteroid therapy does not improve visual prognosis, however, and may lead to secondary retinal thrombosis or cataracts;[2] good evidence of its benefit is lacking.[3] Colchicine is used for prophylaxis of both anterior and posterior uveitis;[2] ciclosporin is considered more effective at controlling acute ocular attacks[1] but its efficacy appears to gradually decline.[2,4] Other drugs deemed effective in preventing ocular inflammation include azathioprine,[1-4] chlorambucil,[2,4] and cyclophosphamide.[2,4] There are reports of benefit with benzathine benzylpenicillin, interferon alfa, levamisole, methotrexate, pentoxifylline, sulfasalazine, and thalidomide.[4] Tacrolimus has also been beneficial in cases of refractory uveitis.[1,4] Combinations of the above drugs are also used, such as corticosteroids with immunosuppressants, or corticosteroids with cytotoxics.[4]

In patients with **vasculitis**, arteritis is treated with systemic corticosteroids and cyclophosphamide, either orally or pulsed monthly boluses.[1,2] Deep-vein thrombosis has been treated with anticoagulants, such as warfarin or heparin, but caution is advised in those with pulmonary arteritis because of the risk of potentially fatal haemoptysis,[2] and their use is generally not recommended.[1,4] Aspirin is used with immunosuppressants, particularly azathioprine.[4] Stanozolol has also been used to treat the vascular symptoms of Behçet's disease.

Corticosteroids and sulfasalazine are the main drugs used for **gastrointestinal** lesions;[2] thalidomide has also been beneficial.[1]

Infliximab has been found to reduce acute ocular inflammation,[7] and heal gastrointestinal ulceration;[8] it has also proved effective in controlling neurological manifestations of the disease.[9]

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Bell's palsy

Bell's palsy is a condition that may be caused[1,2] by herpes simplex virus 1. It affects the facial nerves and results in facial muscle weakness and paralysis. It is often accompanied by pain and lachrymation. Untreated, over 80% of all patients recover completely or almost so, while in a smaller number facial weakness persists; complete failure of motor recovery is very rare.

Corticosteroids dramatically relieve pain associated with Bell's palsy,[3] and their use in treatment is widely accepted.[4] A meta-analysis has confirmed that early corticosteroid treatment increases the frequency of full recovery of facial motor function.[5] A short course of oral therapy is usually given, such as prednisolone 25 mg twice daily for 10 days starting within 72 hours of the onset of symptoms.[6]

It has been suggested that aciclovir or valaciclovir might be effective in treating Bell's palsy. However, systematic reviews and meta-analyses have found them to be of no benefit when given alone.[7,8] Reviews of studies that added these antivirals to corticosteroid therapy have found either no additional benefit[9] or a reduction in risk of unsatisfactory recovery of only borderline significance.[7]

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Bites and stings

Corticosteroids (prednisone 100 mg daily) have been recommended for the stabilisation of erythrocyte membranes in the management of systemic envenomation by the brown recluse spider (*Loxosceles reclusa*).[1] They have also been given after stings by some species of scorpion, although their value is not certain.[1] Corticosteroids are considered to have no place in snake venom poisoning.[2] Topical corticosteroids may be useful for mild itching of healing skin after some types of jelly fish sting, while systemic corticosteroids have been used for delayed hypersensitivity reactions.[3]

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Bone cysts

Intralesional corticosteroid injection (usually methylprednisolone) has been used as an alternative to surgical or other methods for the treatment of bone cysts.[1-6] An early report indicated that methylprednisolone acetate 40 to 200 mg injected into unicameral bone cysts under brief general anaesthesia stimulated bone formation to obliterate the cyst or promoted sufficient healing to prevent further fractures.[1] A single injection was sufficient for healing in 10 to 25% of cysts; only rarely were more than 4 injections needed. Treatment of an aneurysmal bone cyst with methylprednisolone and calcitonin has also been reported.[7] (Systemic corticosteroids are, of course, generally associated with bone loss rather than bone formation—see Effects on the Bones and Joints, p. 1616.2).

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Brain injury

See Spinal Cord and Head Injury, p. 1613.2.

Bronchiolitis

Acute bronchiolitis is usually caused by RSV infection (p. 961.3) in infants and young children, and may contribute to the subsequent development of asthma. Supportive therapy, where necessary, may involve the use of oxygen and bronchodilators (see also p. 1221.2). Many studies have failed to show a benefit from corticosteroid therapy, and it has generally been considered that corticosteroids have no role in the management of the condition.[1] Although one study did find that oral prednisolone might be of benefit,[2] it was suggested that the results might be due to inclusion of children with asthma among the study population.[3] A systematic review[4] found little benefit in terms of length of hospital stay or admission rate and no evidence of improvement in clinical scores, respiratory rate, or oxygen saturation when compared with placebo. However, a study[5] found that a 3-day course of oral prednisolone given to children aged 6 to 35 months with respiratory distress reduced disease severity, length of hospital stay, and the duration of symptoms. Inhaled corticosteroids seem to be of little value[6] and a systematic review concluded that they did not prevent post-bronchiolitic wheezing when given during the initial acute phase of bronchiolitis.[7]

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disease: a randomized, placebo-controlled trial. *J Pediatr* 2003; **143:** 725–30.
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Bronchopulmonary dysplasia

Bronchopulmonary dysplasia is the major cause of chronic lung disease (defined as the need for supplementary oxygen more than 28 days after birth) in neonates. It has also been defined as oxygen dependency beyond a corrected gestational age of 36 weeks.[1] It is considered to comprise 4 radiographically distinct stages, of which stage 1 is effectively indistinguishable from neonatal respiratory distress syndrome (see p. 1608.3), with which it is usually associated. A 'bubbly' appearance of the lung is seen in radiographs of advanced disease. Bronchopulmonary dysplasia is invariably associated with prolonged mechanical ventilation, but it is uncertain whether it plays a causative role, or whether the disease develops anyway in infants with respiratory failure severe enough to need prolonged ventilation.[2] Other risk factors include prematurity, low birth-weight, pulmonary oedema, inflammation due to infection or other causes, and adrenal insufficiency.[1]

Treatment. Corticosteroids, usually in the form of systemic dexamethasone, have been widely used in premature infants with bronchopulmonary dysplasia,[1] or who are considered to be at high risk of it (the borderline between treatment and prophylaxis in studies in these mechanically ventilated infants is not always clear[3]). Dexamethasone has been reported to improve pulmonary outcome, allowing more rapid weaning from mechanical ventilation, and in some studies was reported to improve neurological outcome as well.[4] However, some investigators consider its benefits in the long term inadequately established.[3,5,6]

There also remains some concern about possible adverse effects of dexamethasone, especially on long-term development.[1,7,8] One meta-analysis suggested that use was associated with a high incidence of cerebral palsy and neurodevelopmental impairment, and should be abandoned.[9] Infants requiring mechanical ventilation and given intravenous dexamethasone or placebo in a study were followed up about 8 years later. Children in the dexamethasone group were shorter, had smaller head circumferences, poorer motor skills and coordination, lower IQ scores, and a higher frequency of clinically significant disabilities.[10] However, a 15-year follow-up of preterm infants given dexamethasone at 2 weeks of age, showed that those given a 42-day course had significantly better neurological outcomes than those given an 18-day course, or saline placebo.[11]

Many studies have favoured an initial dexamethasone dose of 500 micrograms/kg daily intravenously, tapered over a period of days to weeks, but it is not always clear if this is expressed in terms of the base or one of its esters,[12] and in any case regimens have varied between studies. Despite suggestions that starting therapy shortly after birth might minimise lung injury, evidence suggests that early therapy offers no advantage,[6,13] and may be more hazardous.[6,8,14-16] Meta-analysis has suggested that while beginning dexamethasone at any time between birth and 14 days of age reduced the risk of chronic lung disease, mortality was only reduced in the group who began treatment between 7 and 14 days of age.[17] However, a subsequent systematic review concluded that the benefits of therapy started between 7 to 14 days may not outweigh the adverse effects.[14]

In an attempt to propose guidelines, a review of the available evidence concluded that there was no role for corticosteroid use in the first 4 days of life and that use should be limited to exceptional clinical circumstances such as ventilator dependency in an infant after the second week of life. When used, the lowest effective dose was recommended for the shortest possible duration; dexamethasone 200 micrograms/kg daily (in two divided doses) for 3 days, then 100 micrograms/kg daily for 3 days, then 50 micrograms/kg daily for 3 days was suggested.[1]

Inhaled corticosteroids have also been investigated. A systematic review did not find any reduction in the incidence of chronic lung disease or the need for systemic corticosteroids.[18] Another systematic review of controlled studies found that inhaled corticosteroids may improve the rate of extubation in infants.[19]

Additional therapy is essentially supportive, including fluid restriction, nutritional supplementation, bronchodilators, and diuretics. Routine use of bronchodilators for prevention of bronchopulmonary dysplasia is not recommended, and studies of use in treatment are limited.[2] UK guidelines (issued in 1998 but not subsequently updated) considered that diuretics were indicated for episodes of associated cardiac failure but their long-term value was uncertain; if used, consideration should be given to a calcium-sparing regimen.[20] Improved pulmonary status has been reported with furosemide in established dysplasia,[21,22] although routine or sustained use cannot be recommended at present. Results with hydrochlorothiazide and spironolactone are more ambiguous.[23,24] Anaemia in infants with bronchopulmonary dysplasia has benefited from erythropoietin.[25] Although vitamin A deficiency has been implicated in the pathogenesis of bronchopulmonary dysplasia, studies of vitamin A supplementation have produced conflicting results. However, differences in patient population, postnatal therapies, and dosage of vitamin A could explain these results,[26] and some recommend supplementation to reduce the incidence of chronic lung disease.[2,26] Despite promising preliminary results,[27] treatment with alpha$_1$-proteinase inhibitor has not been shown to reduce the incidence of chronic lung disease.[2] Similarly, although there is evidence suggesting that early use of sudismase may reduce development of chronic lung disease (but not bronchopulmonary dysplasia),[28] routine use is not recommended.[2]

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Cachexia

For mention of the use of corticosteroids in cancer-related cachexia see under Uses and Administration of Megestrol, p. 2289.3.

Cardiac arrhythmias

Atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1) is common after cardiothoracic surgery, and although it is usually self-limiting, it may be associated with increased morbidity and mortality. Cardiopulmonary bypass used during surgery provokes an inflammatory response that may contribute to atrial fibrillation, and there has been some investigation of the effect of prophylactic corticosteroids. Dexamethasone, hydrocortisone, methylprednisolone, and prednisolone have been tried, in single doses or short courses; studies have been small and results mixed.[1-3] A systematic review[3] of 9 studies found that corticosteroids may reduce the incidence of atrial fibrillation and shorten hospital stay, but the effect may depend on the dose, and larger studies are required.

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Cerebral oedema

Corticosteroids (usually dexamethasone) play an important role in the treatment of cerebral oedema caused by malignancy and dexamethasone is advocated for the cerebral oedema associated with high-altitude disorders (see p. 1276.2). The management of raised intracranial pressure and the usual drugs used to treat it are discussed on p. 1271.3.

Corticosteroids have also been used for the management of raised intracranial pressure in patients with head injuries or stroke, but despite earlier small studies showing them to be beneficial in some patients, current opinion is that corticosteroids are not useful in head injuries (see Spinal Cord and Head Injury, p. 1613.2) or stroke, and that their adverse effects may outweigh any possible benefit.

Chronic active hepatitis

Chronic hepatitis is characterised by liver cell necrosis and inflammation that persists for more than 6 to 12 months. Probably the most serious form is chronic active hepatitis in which inflammatory infiltrates (mononuclear and plasma cells) are found within and around the portal areas, with piecemeal necrosis of adjacent liver cells, and in severe cases bands of necrotic tissue between portal tracts or to the central vein (bridging necrosis). Symptoms are essentially non-specific and include fatigue, malaise, fever, anorexia, jaundice, and raised serum aminotransferase values; biopsy is required for accurate diagnosis. The causes of chronic active hepatitis vary and may include: infection with hepatitis viruses; adverse effects of drugs such as isoniazid, methyldopa, or nitrofurantoin; or, particularly in women, an apparently idiopathic form, auto-immune hepatitis.

Treatment with corticosteroids is widely used in patients with auto-immune hepatitis.[1,2] A moderate initial oral dose of 20 to 30 mg of prednisolone or prednisone daily or a higher dose of 60 mg daily may be used,[3-5] and is then slowly tapered over several months to the minimum required for maintenance. Daily maintenance therapy appears more effective than alternate-day regimens. Patients who respond (as shown by a return of serum aminotransferase values to the normal or near normal range and a reduction in the inflammatory processes on biopsy) usually require prolonged treatment; although some patients remain in remission for months to years after withdrawal, relapse generally occurs, and therapy should be reinstated when the disease becomes active again.[1]

Combined treatment including azathioprine is frequently given and may be the preferred initial treatment in some patients;[4,5] such treatment is at least as effective as a corticosteroid alone,[2] can produce[6,7] and maintain[8,9] remission, and permits a reduction in corticosteroid dosage in a group of patients who will require long-term drug treatment.[1] There has been some dispute about the value of azathioprine alone, but combined therapy has generally been found to be superior.[6] However, azathioprine has been used alone in high doses to maintain remission.[5,9]

In contrast to the fairly extensive experience with azathioprine, ciclosporin is little used in this condition; once started it appears to be required indefinitely.[4] It may be an alternative in severe disease where corticosteroids alone or with azathioprine cannot suffice. Mycophenolate mofetil may offer an alternative to azathioprine.[5] Some investiga-

tors have also used cyclophosphamide successfully,[3] and tacrolimus has been reported to be of benefit.[10]

Penicillamine has been tried as an alternative to prolonged use of corticosteroid maintenance therapy, the dose of penicillamine being gradually increased over several months to a suitable maintenance dose as the dosage of corticosteroid is tapered off.

It is generally agreed that immunosuppression is not suitable in patients with viral chronic active hepatitis.[11] However, combination therapy has been reported to produce benefit in patients positive for HBsAg,[6] and it has been reported[12] that patients with chronic active hepatitis of unknown cause, at least some of whom may have hepatitis C,[11] respond as well to corticosteroids or combined therapy as patients with proven auto-immune disease. Liver transplantation (p. 1936.3) may be necessary in patients who are refractory to or intolerant of immunosuppressive therapy, and in whom end-stage liver disease develops.[1]

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Chronic obstructive pulmonary disease

Corticosteroids play some part in the symptomatic and palliative management of chronic obstructive pulmonary disease (COPD—p. 1199.1). Inhaled corticosteroids can reduce exacerbation rates, although their effect on long-term outcome is less clear. There has also been some concern about increased rates of pneumonia reported in patients treated with inhaled corticosteroids. Guidelines on the management of COPD generally recommend that regular treatment with inhaled corticosteroids should be combined with a long-acting beta$_2$ agonist for symptomatic patients with moderate to severe disease and repeated exacerbations. Short courses of systemic corticosteroids may be used in the management of acute exacerbations of COPD.

Churg-Strauss syndrome

The Churg-Strauss syndrome is sometimes classified with polyarteritis nodosa (see p. 1610.2), although, unlike the latter, pulmonary manifestations are relatively common in Churg-Strauss syndrome. Patients commonly have a history of allergic disease (rhinitis, sinusitis, and asthma); intractable asthma and eosinophilia with granulomatous vasculitis characterise the syndrome.

Treatment is similar to that of polyarteritis nodosa, being based on systemic corticosteroids and, where necessary, cyclophosphamide.[1-4] When cyclophosphamide is used, intravenous pulse therapy is often preferred to continuous oral dosage,[2,4] as it has been shown to reduce adverse effects and allows for a lower total dose.[3,4] Substitution of cyclophosphamide with azathioprine or mycophenolate mofetil after 4 to 6 months can also allow for reduced overall doses of cyclophosphamide to be given,[3,4] although azathioprine is not as effective as cyclophosphamide for primary treatment.[3] In patients with haemorrhagic cystitis, there is some suggestion that mycophenolate mofetil may be more effective than azathioprine.[3] Interferon alfa may also be of benefit.[4,5] In patients refractory to corticosteroids and cyclophosphamide, there are reports of benefit with antilymphocyte immunoglobulins or intravenous immunoglobulins.[3]

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Cogan's syndrome

Corticosteroids are useful in the treatment of Cogan's syndrome, a condition characterised by non-syphilitic interstitial keratitis and audiovestibular symptoms including deafness.[1-3] The deafness, although often irreversible, may respond to systemic corticosteroids begun within 2 weeks of onset of symptoms (prednisolone or prednisone, at least 1.5 mg/kg daily for 2 weeks is advised) and ocular involvement benefits from topical corticosteroid therapy (e.g. prednisolone 1% at a rate of 1 drop every hour for 1 to 2 weeks).[3] Improvement in ocular symptoms has also been seen with sodium cromoglicate eye drops.[4] For patients with severe Cogan's syndrome including large-vessel vasculitis, corticosteroids have been used with other immunosuppressants such as azathioprine, ciclosporin and cyclophosphamide.[5] Methotrexate has also been tried.[6]

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Congenital adrenal hyperplasia

Congenital adrenal hyperplasia comprises a heterogeneous group of disorders due to inherited defects of steroid synthesis in the adrenal gland, the most frequent of which are defects involving 21-hydroxylase or 11-β-hydroxylase. Defective enzyme production blocks the formation of cortisol and aldosterone; the pituitary produces increased amounts of ACTH in an attempt to compensate, but this results in excessive adrenal androgen production. Presentation varies from virilisation and abnormal genital formation at birth to mild cryptic forms that may be detected only later in life. Salt-losing forms (due to lack of aldosterone or the accumulation of precursors with antagonist activity) may lead to hyperkalaemia, acidosis, and dehydration. Patients with 11-β-hydroxylase defect are also prone to hypertension.

Neonates with **salt-losing forms** of congenital adrenal hyperplasia require urgent treatment. Treatment usually consists of a mineralocorticoid, fludrocortisone, and a glucocorticoid (usually hydrocortisone) in regimens similar to those for adrenocortical insufficiency (see p. 1600.2).[1-5] Saline infusion or addition of salt to the feed is required initially.

Even where salt-losing symptoms are not overt or marked, control is reportedly better with a mineralocorticoid added to therapy, rather than with hydrocortisone alone,[4] and it has been recommended that children with salt-losing congenital adrenal hyperplasia should continue to receive combined therapy at least until adult life.[1] Careful titration of dosage is important to avoid growth retardation and toxicity, and potent synthetic glucocorticoids such as betamethasone and dexamethasone may be inappropriate in infants and children with the condition, even in the non-salt-losing form. An alternative approach is the use of flutamide and testolactone to block androgenic effects, with a reduced dose of hydrocortisone.[4,6] However, studies suggest that normal growth is possible with regular glucocorticoid therapy.[7,8]

Patients with **non-salt-losing congenital adrenal hyperplasia** may be adequately managed with glucocorticoids alone, and in mild late-onset forms a single dose daily in the late evening (when its suppressive effect on ACTH production is greatest) may be sufficient. In adults who do not require mineralocorticoid treatment betamethasone or dexamethasone may be useful because of their lack of mineralocorticoid actions.

Surgical correction may be necessary in females with masculinised external genitalia. Giving a glucocorticoid to pregnant women whose offspring are considered at risk has been tried in an attempt to prevent virilisation:[3] dexamethasone is preferred to hydrocortisone because of a lack of placental degradation.[4]

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Corneal graft rejection

Corticosteroids are the mainstay of postoperative prophylaxis and treatment of corneal graft rejection.[1] Topical and subconjunctival corticosteroids are widely used, but in acute rejection episodes involving the endothelium systemic therapy is usually necessary. A single 500-mg intravenous pulse of methylprednisolone appears to be as effective as up to 2 weeks of treatment with oral prednisolone 60 to 80 mg daily for the management of severe endothelial rejection.[2] However, another study found that addition of a single intravenous pulse of 500 mg methylprednisolone to local corticosteroid treatment with betamethasone and dexamethasone gave no benefit over local therapy alone.[3]

In high-risk patients corticosteroids alone provide insufficient immunosuppression and systemic immunosuppression has been tried, although the evidence base is limited,[1] mainly relating to the use of ciclosporin, and with inconsistent results. Mycophenolate mofetil has also been tried,[1,4] and has been reported to be as effective as ciclosporin in preventing acute rejection after high-risk corneal transplantation.[4] However, because most patients are healthy and transplantation is not life-saving, the risks of systemic immunosuppression may be hard to justify.[1] Topical ciclosporin has also been investigated.[5]

Corticosteroids have also been used to reduce inflammation after corneal reconstruction using tissue engineered from autologous oral mucosal epithelium.[6]

For discussions of the role of corticosteroids in other forms of organ and tissue grafting, see Organ and Tissue Transplantation, p. 1932.2.

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Croup

Croup is an acute childhood syndrome of upper respiratory tract inflammation (laryngotracheobronchitis) associated with viral infection, usually by parainfluenza virus although other viruses may also produce the syndrome. It is characterised by harsh, barking cough, stridor, and hoarseness, most usually occurring at night.[1-3]

Traditional home management has revolved around the inhalation of steam, despite a lack of evidence for efficacy, but symptoms may be sufficiently alarming to result in presentation to a hospital.

In severe croup there is clear evidence that treatment with a systemic corticosteroid reduces symptoms and decreases the need for intubation.[4-6] Oral dexamethasone is as effective as intramuscular,[7] and while dexamethasone 600 micrograms/kg is commonly prescribed, lower doses of 300 micrograms/kg and 150 micrograms/kg appear to be equally effective.[2] Nebulised budesonide has also been reported to be effective,[8-10] and of similar efficacy to inhalation of nebulised adrenaline.[11] However despite the theoretical attraction of this route, studies have failed to find any significant difference in efficacy between nebulised budesonide 2 mg and oral dexamethasone 600 micrograms/kg,[12] or combination therapy with both,[13] and another study found 600 micrograms/kg of dexamethasone given intramuscularly to be more effective than 4 mg of nebulised budesonide.[14] In contrast, others have found that addition of nebulised budesonide to oral dexamethasone produced more rapid improvement than the latter alone.[15] Studies have also shown a significant benefit from corticosteroids in children with mild to moderate croup,[12,16-18] and although the use of such potent drugs in children with a mild, largely self-limiting condition has been questioned,[19] a review of the risks and benefits concluded that oral dexamethasone 150 micrograms/kg, or nebulised budesonide 2 mg were the treatment of choice in mild to moderate croup while oral prednisolone 1 mg/kg should be given for croup requiring intubation.[1] However, nebulised adrenaline is probably the initial drug of choice where rapid relief of obstructive symptoms is required.[2,3] Oxygen is given to those children with upper airway obstruction and significant oxygen desaturation.[3] Heliox, a mixture of helium and oxygen, may be used as adjunctive therapy to

glucocorticoids, for short-term treatment of refractory croup.[2]

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Cystic fibrosis

Corticosteroids have been used orally or by inhalation in the management of the inflammatory response of the lungs in cystic fibrosis (see p. 177.2) but do not form part of standard management.

Deafness

For references to the use of corticosteroids in the treatment of deafness associated with Cogan's syndrome, see p. 1603.2.

Dermatomyositis

For references to the treatment of dermatomyositis with corticosteroids, see Polymyositis and Dermatomyositis, p. 1611.1.

Eaton-Lambert myasthenic syndrome

Corticosteroids have been tried in the treatment of Eaton-Lambert myasthenic syndrome (p. 684.1).

Eczema

Topical corticosteroids have an important role in the management of atopic eczema (p. 1684.1). The least potent preparation that is effective should be used, combined with regular use of an emollient; in mild to moderate disease the topical corticosteroid is only given for 1 to 2 weeks at a time. Most patients with mild to moderate eczema respond to treatment with a mildly potent preparation such as 1% hydrocortisone ointment. For older children and adults with refractory disease, a more potent topical corticosteroid should be considered for long enough to bring the disease under control, followed by a weaker preparation as the condition improves.

The use of systemic corticosteroids is a treatment of last resort in resistant severe eczema, usually for short periods to control the disease, and very rarely for maintenance.

Eosinophilic oesophagitis

For mention of the use of corticosteroids in eosinophilic oesophagitis, see p. 1807.1.

Epidermolysis bullosa

High-dose oral corticosteroids may be tried to control blistering in severe forms of epidermolysis bullosa (p. 1684.3).

Epilepsy

Corticosteroids and corticotropin have been commonly used to treat **infantile spasms,** which are generally unresponsive to conventional antiepileptics. There is, however, limited evidence for the efficacy of oral corticosteroids.[1] Corticotropin appears to be effective for short-term treatment, and one study[2] indicated that high-dose corticotropin was preferable to prednisone, but the optimum dose and duration of therapy have not been determined.[1,3] In addition, corticotropin and corticosteroids are associated with frequent and severe adverse effects, and as discussed on p. 506.1, some now prefer newer antiepileptics such as vigabatrin. A short-term study of infants with spasms of non-tuberous sclerosis origin found that tetracosactide or prednisolone were superior to vigabatrin.[4] However, vigabatrin is preferred for the treatment of spasms due to tuberous sclerosis,[3,4] and data are insufficient for recommendations regarding the use of any drug to improve the long-term outcome of children with infantile spasms.[1,3]

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Erythema multiforme

In the management of erythema multiforme (p. 1684.3) systemic corticosteroids may be considered in severe reactions but there has been controversy about their value.

Giant cell arteritis

Giant cell arteritis (temporal arteritis; cranial arteritis) is a vasculitic disorder that is frequently associated with polymyalgia rheumatica (p. 1610.3). It occurs mainly in persons over 50 years of age of European, particularly Scandinavian, extraction and is more common in women than men. It is characterised by inflammatory, granulomatous lesions with giant mononuclear cell infiltrates affecting large and medium sized arteries, particularly those supplying the neck and extracranial structures of head and arms. Symptoms vary but may include headache, scalp tenderness, claudication of the jaw, swelling and absence of pulse in the temporal artery, fever, weight loss, malaise, anaemia, visual disturbances, and irreversible blindness. About a third of all patients also have polymyalgia rheumatica.

Treatment is with corticosteroids,[1-8] and early diagnosis and treatment is desirable to reduce the risk of sudden blindness. Most regimens have involved high initial doses of corticosteroid to control the disease followed by reduction to a maintenance dose, but both initial and maintenance doses have varied considerably. Oral prednisone or prednisolone 40 to 60 mg daily initially is generally considered adequate in uncomplicated cases without visual symptoms;[1,4-6] this can then be reduced gradually according to the patient's response. Some, however, recommend[2] lower initial doses of about 20 mg daily.

While it is suggested that patients presenting with visual symptoms should receive 80 mg daily or 1 mg/kg daily of prednisone or prednisolone,[2,7,8] some ophthalmologists[9] recommend that all patients with giant cell arteritis receive these doses, as visual loss may be sudden and profound. Initial 1-g doses of pulsed intravenous methylprednisolone have also been used.[3,5,7,9]

Maintenance treatment is usually required and while a small number require indefinite treatment, most patients should be able to stop treatment within 5 years; however, relapses are not uncommon.[8]

Because of the need for prolonged corticosteroid therapy, adverse effects are common,[8] and their management difficult. Azathioprine has been added to corticosteroid therapy for its modest 'steroid-sparing' effect,[10] whereas results with methotrexate have been conflicting.[4,6,11] Other immunosuppressants have been tried,[4,6] but are not routinely used. Dapsone has been reported to be of benefit, but its use is limited by haematological toxicity.[4] Infliximab has been tried.[7]

The prognosis is excellent in adequately-treated patients, as the life expectancy of patients with giant cell arteritis is the same as the general population.[12]

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Glomerular kidney disease

Glomerular disease accounts for a considerable proportion of all kidney disease. Various forms of primary glomerular disease (glomerulopathy) are known, and are discussed below; in addition, many systemic diseases (connective tissue disorders such as SLE as well as malignancy and conditions such as diabetes), may result in secondary glomerular disorders. Despite the various potential causes it is thought that many of these diseases act by common immunological mechanisms to damage the glomerulus, either by accumulation of antigen-antibody complexes (immune-complex nephritis) or more rarely by the formation of antibodies to the glomerular basement membrane (anti-GBM nephritis).[1]

Since the kidney can respond in only a limited number of ways to glomerular damage, certain common presentations are seen regardless of aetiology, including **acute glomerulonephritis** (acute nephritis syndrome), which is marked by haematuria and proteinuria of abrupt onset, usually with renal impairment (a decrease in glomerular filtration rate), salt and water retention, and hypertension; and the **nephrotic syndrome**, which is marked by severe proteinuria, hypoalbuminaemia, and oedema. Other, less dramatic presentations of glomerular disease are asymptomatic proteinuria or microscopic haematuria; alternatively, glomerular disease may be one of the many potential causes of chronic renal failure. Appropriate management of these conditions depends to a considerable extent on the underlying disease.

• MANAGEMENT OF PRIMARY GLOMERULAR DISEASE.

Minimal change nephropathy (MCN; minimal change disease). This condition occurs mainly in children, the highest incidence being at 2 to 4 years, and is the main cause of childhood nephrotic syndrome. It also accounts for about 20% of adult cases of nephrotic syndrome.[2] It is treated with a corticosteroid. Regimens vary somewhat but a suggested oral regimen for adults has been 60 mg prednisolone daily for 4 days, reduced to 40 mg daily until remission occurs (which in 90% of patients will be within 3 weeks) and then tapered off.[2] In children, initial doses of 60 mg/m^2 of prednisolone or prednisone daily have been used,[3] which may be given for 4 weeks before switching to 40 mg/m^2 given on alternate days for a further 4 weeks, and then tapered off.[4] Lower relapse rates have been reported with 60 mg/m^2 prednisone given daily for 6 weeks, followed by 40 mg/m^2 on alternate days for 6 weeks; this 12-week course may be preferable to the standard 8-week course.[3] A modification to the children's dose is to give 60 mg/m^2 of prednisolone daily until there is a response when the dose is reduced to 40 mg/m^2 on alternate days for the next 4 weeks. If there is no response within 4 weeks of treatment with the 60 mg/m^2 dose then the drug should be withdrawn and the child considered to be corticosteroid resistant.[5] A systematic review of treatment regimens found that children with their first episode of nephropathy should be treated with prednisone for at least 3 months, and possibly up to 7, to reduce the risk of relapse.[6]

Relapse is common and occurs in about 60% of cases; relapses usually respond to a further course of corticosteroids, but if a third relapse occurs cyclophosphamide 2 to 3 mg/kg daily for 8 to 12 weeks may be added to a course of corticosteroid therapy.[2,3] Deflazacort may also be effective in corticosteroid-sensitive patients who do not respond to prednisone.[6] Cytotoxics or immunosuppressants are reserved for frequently relapsing or corticosteroid-dependent cases because of their potential for severe toxicity, including carcinogenesis; cyclophosphamide appears to be preferred to chlorambucil because it is perceived as entailing a somewhat lower risk, although both are effective.[3,7] Ciclosporin has been used long-term to achieve and maintain remission, although renal biopsies are advised to screen for nephrotoxicity.[3,7] Levamisole has also been reported to be of benefit.[3,7]

Focal glomerulosclerosis. Focal glomerulosclerosis is a sclerosing lesion affecting parts of the glomeruli which occurs in some patients who otherwise have symptoms characteristic of minimal change nephropathy, and some authorities do not regard it as a distinct disease. It is common in abusers of diamorphine and has also been linked with the nephropathy that can occur in patients with AIDS. Treatment is similar to that for minimal change nephropathy but only about 20% of cases respond to corticosteroids; addition of a cytotoxic immunosuppressant such as cyclophosphamide may improve the prospect of

remission. Responses to ciclosporin have been seen in both adults and children with corticosteroid-resistant disease.[3,8] Prolonged treatment may be necessary and relapse is common when ciclosporin is stopped.[7] Tacrolimus has been reported to be successful after ciclosporin failure,[3,8] and mycophenolate mofetil has been tried with conflicting results.[8] High-dose pulsed methylprednisolone, given in a tapering schedule over 6 years, has been reported to show high response rates in focal glomerulosclerosis.[3] In patients who fail to respond, progression to renal failure may occur over several years, but renal transplantation may not be helpful as disease can recur in the transplanted kidney.

Membranous nephropathy (membranous glomerulonephritis). This is a disease mainly of adults, in whom it is the single most important cause of the nephrotic syndrome, accounting for about 50% of cases. It is characterised by diffuse thickening of the glomerular basement membrane after subepithelial deposition of immune complexes. The course of disease is variable and often slow, with some spontaneous remissions, which makes it difficult to show the benefits of treatment and the use of potentially toxic drugs difficult to justify. Cyclophosphamide or chlorambucil combined with a corticosteroid appear to produce some clinical improvement, and stabilisation of progressive disease, but corticosteroids alone do not appear to be of benefit.[9-11] Cyclophosphamide may be preferred as it seems to be better tolerated.[11] Ciclosporin is an alternative but therapy may need to be continued for 6 months or more before remission occurs[9,10] and a systematic review found it to be no better than placebo.[11] Other immunosuppressants under investigation in this condition include mycophenolate mofetil[10] and rituximab. Recent studies have also emphasised the control of blood pressure and proteinuria using ACE inhibitors and angiotensin II receptor antagonists.[10]

Mesangiocapillary glomerulonephritis (MCGN; membranoproliferative glomerulonephritis; MPGN). Mesangiocapillary glomerulonephritis comprises 2 separate diseases, known as type I and type II, which both occur in children and young adults and usually result in nephrotic syndrome, although about 20% of cases present with acute glomerulonephritis. Both forms show proliferation of mesangial cells and thickening of glomerular walls with formation of deposits (in type I disease due to immune complexes) in capillary walls and basement membranes. There is no established treatment regimen: some improvement or stabilisation of renal function may occur with corticosteroids and cytotoxic immunosuppressants, but about half of all patients develop end-stage renal failure within 15 to 20 years (type I disease) or 6 to 10 years (type II disease). Antiplatelet drugs and anticoagulants have also been tried but as with other therapies there is little evidence of benefit, and some centres do not recommend any specific therapy, although prednisolone and cyclophosphamide may be offered to those with a rapidly progressive course.[12]

IgA nephropathy (Berger's disease) is the commonest cause of primary glomerular disease, and is most common in young men. It results in focal, segmental proliferative glomerulonephritis associated with mesangial formation of immune deposits largely composed of IgA. The usual presentation is acute glomerulonephritis with gross haematuria, often during or just after viral upper-respiratory-tract infection. Some patients develop rapidly progressive disease similar to idiopathic rapidly progressive glomerulonephritis, with renal failure within 6 months, but in many others the syndrome is benign, and requires only observation. No form of therapy has been unequivocally shown to be of value, but control of associated hypertension, usually with ACE inhibitors, is considered important. Corticosteroids and cytotoxic immunosuppressants may be tried in severe rapidly progressive disease.[13-17] Promising results have been seen with the use of n-3 fatty acids from fish oil, and there are also reports of benefit with normal immunoglobulin, and mycophenolate mofetil.[16]

Idiopathic rapidly progressive glomerulonephritis (RPGN). Although rapidly progressive glomerulonephritis (crescentic glomerulonephritis) may be a feature of other forms of glomerular disease such as IgA nephropathy (see above) or Goodpasture's syndrome (see below) it also occurs in an idiopathic form. The disease is characterised by the formation of glomerular crescents associated with leakage of fibrin from damaged capillaries, and loss of renal function is very rapid, sometimes with renal failure within weeks. Oral corticosteroids are of little value alone, but pulsed intravenous methylprednisolone followed by oral prednisone or prednisone and cyclophosphamide over several months has produced some impressive responses;[18,19] an alternative is the use of intensive plasma exchange with a corticosteroid and cytotoxic immunosuppressants.[20] Controlled studies of these therapies are mostly lacking, although a small prospective study[21] found lymphocytapheresis to be more effective than pulsed methylprednisolone as an addition to prednisolone and cyclophosphamide therapy for reduction of glomerular injury.

Goodpasture's syndrome. Goodpasture's syndrome is a form of anti-GBM nephritis in which rapidly progressive glomerulonephritis is accompanied by pulmonary haemorrhage (because the antibody responsible for the renal symptoms also reacts with the membranes of the alveoli). It is a disease mainly of young males. Pulmonary haemorrhage responds to high dose oral prednisolone or prednisone, or pulsed intravenous methylprednisolone, but corticosteroids are of little value in controlling renal lesions, which requires vigorous plasma exchange therapy with corticosteroids and cyclophosphamide on a daily or alternate-day basis for several weeks, until antibody is no longer detectable and disease progression has halted; it is important to begin therapy before renal damage becomes irreversible.[22]

• MANAGEMENT OF SECONDARY GLOMERULAR DISEASE.

Post-infectious glomerulonephritis. The classical form of post-infectious glomerulonephritis is post-streptococcal glomerulonephritis, which produces an immune-complex-mediated acute glomerulonephritis, but glomerular disease may follow other bacterial infections, as well as protozoal infections such as malaria (malaria-associated nephrotic syndrome is familiar in endemic regions) and viral infections such as AIDS (see Focal Glomerulosclerosis, above). In most cases no additional treatment beyond appropriate management of infection and general supportive care is warranted, and corticosteroids and cytotoxic immunosuppressants are not generally used and may in some cases be harmful.[23] Nonetheless, delayed progressive renal disease may occur in a minority of patients, and has prompted efforts to treat.[22]

Other secondary glomerulopathies. Where glomerular disease is secondary to other diseases (connective tissue disorders such as SLE, the vasculitides, Henoch-Schönlein purpura, thrombotic thrombocytopenic purpura, or others such as rheumatoid arthritis, amyloidosis, neoplasia, sickle-cell disease, gout, or diabetes mellitus) most treatment is directed at the underlying disease. In addition, symptomatic management such as the use of sodium restriction for the oedema of nephrotic syndrome may be appropriate; diuretics should be used cautiously because of the risk of hypovolaemia.[24] Proteinuria of various causes may respond to the use of ACE inhibitors or NSAIDs,[2,24] although care is required in patients with renal artery stenosis or renal failure respectively. Associated hypertension and hypercholesterolaemia should be treated, and anticoagulants such as heparin may be required for associated coagulation disorders.[24] Renal toxicity can arise from various drug treatments and this should also be treated symptomatically.

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Gout

Systemic corticosteroids have been used as a second-line alternative to NSAIDs or colchicine in the treatment of acute gout (p. 600.1). A systematic review including 3 small studies of intramuscular or oral corticosteroids found that the evidence of benefit was inconclusive, although there seemed to be few adverse effects from such short-term treatment.[1] Subsequently, the same group carried out a small comparative double-blind study of oral prednisolone or naproxen for 5 days in patients with confirmed gout,[2] which concluded that the drugs were equally effective, and suggested that corticosteroids might be considered as a first-line option.

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Graves' ophthalmopathy

Patients with moderate to severe ophthalmopathy as a result of hyperthyroidism (p. 2332.2) may be treated with corticosteroids or with orbital radiotherapy. There is evidence of a synergistic effect when these therapies are combined. If orbital radiotherapy is contra-indicated, glucocorticoids may be combined with ciclosporin. There is some suggestion that intravenous pulse therapy is more effective than oral glucocorticoids.[1] Giving a corticosteroid with radio-iodine therapy may prevent transient exacerbation of Graves' ophthalmopathy.[2]

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Haemangioma

Haemangiomas are benign vascular neoplasms of the skin that may enlarge dramatically before regressing spontaneously. Although no treatment is normally required, occasional complications due to ocular or visceral involvement, or associated thrombocytopenia due to platelet trapping (the Kasabach-Merritt syndrome), may merit treatment, generally with corticosteroids. Oral prednisone or prednisolone is usually given; intravenous high-dose methylprednisolone has been used for life-threatening haemangiomas.[1] Response is variable.[1-3] Another common technique is intralesional injection of a mixture of triamcinolone with betamethasone.[4] There has been a report of 2 infants responding to vincristine after corticosteroids had failed.[5] Interferon alfa has been used for corticosteroid-refractory lesions.[1] Improvements in haemangioma have also been reported in infants treated with propranolol.[6,7] Phototherapy with a pulsed dye laser has also been reported to be effective;[8] a randomised study of this method found no benefit compared with observation only,[9] but treatment is still recommended by some[10] for problematic lesions.

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Headache

Corticosteroids have a limited role in the management of some types of headache. Although their long-term use is not considered desirable, short courses of a corticosteroid can be effective in the prevention of cluster headache attacks during cluster periods (p. 670.1). Prednisolone may be started at an oral dose of 60 to 100 mg once daily for 2 to 5 days, then reduced by 10 mg every 2 or 3 days so that treatment is stopped after 2 to 3 weeks.[1] Prednisolone has also been given to manage the aggravation of symptoms associated with the withdrawal of analgesics in medication-

overuse headache (p. 670.2). Corticosteroids have also been used for the emergency treatment of prolonged severe attacks of migraine (status migrainosus) (p. 670.3) refractory to other drugs.

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Herpes infections

Although corticosteroids alone are contra-indicated for most forms of ocular herpes simplex infection (p. 955.2), which should be treated with a topical antiviral, a combination of corticosteroid and antiviral may be indicated for herpes simplex stromal keratitis. For discussion of the use of corticosteroids in Bell's palsy, which may be associated with herpes simplex virus, see p. 1601.2, and for discussion of their role in postherpetic neuralgia, see p. 10.3.

Hypercalcaemia

For a description of the treatment of hypercalcaemia, including the specific role of corticosteroids, see p. 1775.3 and p. 1167.2.

Hypersensitivity vasculitis

Hypersensitivity vasculitis is usually associated with an antigenic stimulus, either exogenous (e.g. a drug[1] or microbe), or endogenous (e.g. an immune complex associated with connective tissue disease). The term covers a heterogeneous group of disorders, many of which are associated with some underlying disease process (including infections, malignant neoplasms and disorders such as rheumatoid arthritis or SLE), as well as vasculitis of less clear aetiology such as Henoch-Schönlein purpura, a disease typically seen in prepubertal males. There is a suggestion that such a broad grouping is inappropriate, and that the term 'hypersensitivity vasculitis' should not be used;[2] however, it continues to be found in the literature.

Hypersensitivity vasculitis is characterised by small vessel involvement (arterioles and venules), particularly of the skin, and skin manifestations such as purpura, rashes, and urticaria predominate. Neutrophil debris is typically present around the vessel (**leucocytoclastic vasculitis**). However other organ systems may also be involved: in **Henoch-Schönlein purpura**, the skin lesions are associated with arthralgia, abdominal pain and other gastrointestinal symptoms, and glomerulonephritis.[3] Although not always immediately apparent, renal impairment may be delayed, and progress to end-stage renal failure.[4]

The prognosis is typically much better in hypersensitivity vasculitis than in the other major vasculitic syndromes, and most cases resolve spontaneously. Where a recognised antigenic stimulus is present it should be removed if possible, e.g. by withdrawal of a drug[1] or by appropriate therapy of infection. Hypersensitivity vasculitis generally responds less well to conventional drug therapy than other vasculitic syndromes. Nonetheless, where disease persists or results in organ dysfunction, a corticosteroid should be given, typically oral prednisone or prednisolone 60 mg, or 1 mg/kg daily, tapered rapidly until therapy can be stopped. Plasmapheresis has also been used, but the use of cytotoxic immunosuppressants is less well established. However azathioprine[4] and cyclophosphamide[5] have been used successfully with corticosteroids. Anecdotal reports of excellent responses to dapsone in Henoch-Schönlein purpura exist.[6] Other drugs that have been tried include danazol,[7] pentoxifylline,[8] the latter sometimes with dapsone,[8] and normal immunoglobulin.[9]

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Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an immune-mediated disorder characterised by increased destruction and impaired production of platelets, resulting in low platelet counts and an increased risk of bruising and bleeding. Primary ITP has no obvious underlying cause. This condition has been commonly called idiopathic thrombocytopenic purpura, and also known as auto-immune thrombocytopenic purpura, but immune thrombocytopenia has been advocated as the preferred term because symptoms of bleeding are absent or minimal in many patients. It has also been described as having acute and chronic phases, but an alternative categorisation of newly-diagnosed, persistent (3 to 12 months after diagnosis), and chronic (lasting more than 12 months), has been proposed. A platelet count of less than 150×10^9 cells/litre has generally been used as a threshold for diagnosis. However, a lower threshold of 100×10^9 cells/litre has been suggested, to account for population variation and physiological pregnancy-related thrombocytopenia.[1] Secondary ITP may be associated with auto-immune diseases, viral infections, and exposure to certain drugs.

Treatment. Consensus documents,[2] guidelines,[3] and reviews[4,5] of the management of primary ITP have been published. The main goal of therapy is to maintain a platelet count that prevents major bleeding, rather than attempting to normalise counts. Treatment is generally considered when counts have fallen to 30 to 50×10^9 cells/litre. Corticosteroids are the mainstay of initial treatment for adults with newly-diagnosed primary ITP, usually given as oral prednisone or prednisolone 0.5 to 2 mg/kg daily for 2 to 4 weeks, then tapered. A response usually occurs within several days to weeks. High-dose parenteral methylprednisolone has also been used, and there is limited evidence of benefit from pulsed high-dose oral dexamethasone. Intravenous normal immunoglobulin may be used when corticosteroids are contra-indicated, or added to corticosteroid therapy when a more rapid response is needed. Anti-D immunoglobulin is an alternative for rhesus-positive non-splenectomised patients.

A range of treatments have been used for second-line therapy in adults who have not responded to, or have relapsed after, first-line treatment.[2,3] Splenectomy can provide sustained remission in the majority of patients, but a delay in surgery for at least 6 months should be considered because spontaneous improvement or late remission can occur 6 to 12 months after diagnosis. Vaccination against meningococcal, pneumococcal, and *Haemophilus influenzae* type b infection are recommended in patients who undergo splenectomy, because of the lifelong risks of uncontrolled infection. Opinions differ about the value of lifelong antibacterial prophylaxis (see also Spleen Disorders, p. 207.3). A range of second-line medical options may be considered, but none has a clear advantage and so choice for the individual patient depends on bleeding history, comorbidities, adverse effects of long-term therapy, and compliance. Immunosuppressive drugs that may be considered include azathioprine, ciclosporin, cyclophosphamide, mycophenolate mofetil, and vinca alkaloids (vinblastine or vincristine); response rates of at least 50% are possible but an effect may take several weeks to occur. Benefit from a 4-week course of rituximab has also been reported, but remission is not sustained in many patients and re-treatment may be needed. Dapsone has been used for its corticosteroid-sparing effect; it may delay splenectomy but splenectomised patients have a low response rate. The attenuated androgen danazol appears to be more effective in older women and splenectomised patients, but response can be slow (3 to 6 months). The thrombopoietin receptor agonists eltrombopag and romiplostim stimulate platelet production and may be used second-line; however, continuous therapy is needed and thrombocytopenia can become worse if treatment is stopped.

A rapid increase in platelet count may be needed by patients at high risk of bleeding, those with active CNS, gastrointestinal, or genito-urinary bleeding, and those needing surgery. Management may include a combination of corticosteroid (such as intravenous methylprednisolone) with normal immunoglobulin, platelet infusions, and antifibrinolytics (such as aminocaproic acid and tranexamic acid). Menstrual bleeding can be reduced by a progestogen-containing intra-uterine contraceptive device or oral contraceptive.[2]

Gestational thrombocytopenia is typical in normal *pregnancy* and may exacerbate or cause the relapse of pre-existing primary ITP. Although some experts believe that there is insufficient evidence to recommend platelet thresholds for treatment,[3] others suggest that in the first two trimesters treatment should be given when the patient is symptomatic, has a platelet count below 20 to 30×10^9 cells/litre, or when an increase in platelet count is considered necessary to be safe for procedures.[2] Evidence for recommending safe platelet counts is lacking, but some have suggested thresholds of at least 75×10^9 cells/litre for spinal or epidural anaesthesia, and at least 50×10^9 cells/litre for caesarean section.[2] Treatment of maternal ITP is similar to that used in non-pregnant women, based on corticosteroids and normal immunoglobulin or anti-D immunoglobulin.[2,3] However, other treatments such as cytotoxics, rituximab, and thrombopoietin receptor agonists are generally avoided in pregnancy. If splenectomy is necessary, it should be performed in the second trimester; it may increase the risk of pregnancy loss in the first trimester and becomes technically difficult in the third trimester.

Neonatal thrombocytopenia may occur secondary to maternal ITP and last for months.[2] Although treatment is rarely needed, neonates may be given normal immunoglobulin to manage haemorrhage or if platelet counts are below 20×10^9 cells/litre.

Serious bleeding does not occur in most *children* with primary ITP, despite very low platelet counts. At least two-thirds of young patients will improve spontaneously within 6 months of diagnosis, and remissions are generally durable. Newly-diagnosed primary ITP can therefore be managed initially by observation, regardless of platelet count, with drug therapy reserved for patients with moderate to severe bleeding, or at significant risk of bleeding. First-line therapy is similar to that recommended for adults, consisting of intravenous normal immunoglobulin or anti-D immunoglobulin, and short courses of prednisone or prednisolone. For children with persistent or chronic ITP, first-line treatments may be repeated, but in unresponsive disease options include high-dose dexamethasone, high-dose methylprednisolone, or rituximab. Experience with other treatments is more limited. Long-term corticosteroid treatment and cytotoxics should be used with extreme care because of their adverse effects in children. Splenectomy is generally deferred for as long as possible because of the high rates of spontaneous remission in children, and because the risk of death from ITP is extremely low and significantly less than that from postsplenectomy sepsis.[2,3]

Secondary ITP is generally managed by treating the underlying condition or withdrawing the offending drug.

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Infections

Although long-term corticosteroid therapy has an adverse effect on the body's response to infection (see Effects on Immune Response, under Adverse Effects, p. 1617.2), the judicious use of corticosteroids, usually on a short-term basis, with appropriate anti-infective drugs, may have a beneficial effect on the symptoms of selected acute infections, and may on occasions be life-saving.

For further comment on the use of corticosteroids in ocular herpes infections, infectious mononucleosis, leishmaniasis, leprosy, meningitis, pneumocystis pneumonia in AIDS patients, septic shock, and tuberculosis, see under the relevant headings in this section.

Infectious mononucleosis

Discussions on the use of corticosteroids in infectious mononucleosis (glandular fever—see Epstein-Barr Virus Infections, p. 955.1) usually consider that although all cases would respond promptly to therapy, only patients with an unduly prolonged infection and those with an exceptionally severe sore throat that interferes with respiratory function should be treated with a corticosteroid.[1,2] Some may consider using corticosteroids in patients with aplastic anaemia, thrombocytopenia, haemolytic anaemia, encephalitis, pericarditis, or myocarditis associated with infection by the Epstein-Barr virus. The corticosteroid used, dosage, route, and duration of treatment is variable. Dexamethasone, methylprednisolone, and prednisolone have all been tried in infectious mononucleosis. While corticosteroid treatment is considered relatively safe in infectious mononucleosis, impaired immunity might theoretically increase the risk of Epstein-Barr virus-related tumours in later life.

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Inflammatory bowel disease

Corticosteroids with aminosalicylates form the mainstay of treatment for active ulcerative colitis and Crohn's disease (see Inflammatory Bowel Disease, p. 1808.3). In moderate to severe acute disease systemic corticosteroids are indicated for initial management, either orally or in the most severe cases intravenously. Doses are high initially and are gradually reduced as symptoms resolve. In patients with

disease confined to the distal colon or rectum, local topical therapy with suppositories, rectal foams, or enemas of corticosteroids may be appropriate. Oral or rectal formulations of poorly absorbed or rapidly metabolised corticosteroids such as beclometasone, budesonide, or tixocortol have been developed in the hope of producing local improvement without systemic effects.

Interstitial lung disease

Interstitial lung disease (diffuse parenchymal lung disease) represents a large and heterogeneous group of inflammatory disorders that have in common a thickening of the interstitial walls between alveoli. In some cases, particularly in the early stages, this is due to accumulation of inflammatory cells in the interstitium, and control of inflammation can reverse the changes; however, when fibrotic changes to the alveolar walls take place these are usually irreversible. The causes of chronic interstitial lung disease are numerous and include pneumoconioses due to inhalation of inorganic dusts (as in asbestosis and silicosis); extrinsic allergic alveolitis due to inhalation of, usually, organic antigens (as in farmers' lung, bird fanciers' lung, and many similar occupational disorders); idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis); adverse effects of drugs such as bleomycin; sarcoidosis; lung disease associated with collagen vascular disorders such as rheumatoid arthritis and SLE, or with the vasculitides; histiocytic syndromes; and pulmonary eosinophilic syndromes. Idiopathic pulmonary fibrosis (below) and sarcoidosis (p. 1612.2) are probably the most common chronic interstitial lung diseases.[1]

The symptoms of interstitial lung disease are usually insidious and non-specific, and may include dyspnoea of varying severity, usually first noticed on exertion, cough, and fatigue; fine crackling sounds (rales) on breathing and finger clubbing occur in some forms. If the disease progresses, respiratory failure becomes more severe, and eventually may prove fatal.

Where a causative agent can be identified, initial treatment is to prevent exposure but where inflammation persists, or where the causation is uncertain, corticosteroids are the mainstay of treatment (despite a lack of controlled studies for efficacy),[1] in an attempt to control inflammation and preserve as much normal tissue as possible. The management of idiopathic pulmonary fibrosis is discussed in more detail below.

Idiopathic pulmonary fibrosis is one of the idiopathic interstitial pneumonias, a subgroup of interstitial lung disease. The terminology used for the idiopathic interstitial pneumonias has been confusing, but improved diagnostic methods have facilitated the development of an internationally accepted classification system.[2] The terms idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis are now synonymous, and are used for a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause. It is associated with a specific histologic pattern known as usual interstitial pneumonia, in which there is interstitial inflammation, fibrosis, and honeycomb changes. The clinical course is generally of gradual deterioration, occasionally with periods of rapid decline, and a median length of survival after diagnosis of between 2.5 and 3.5 years. Idiopathic pulmonary fibrosis should be distinguished from the other forms of idiopathic interstitial pneumonia, which may differ in prognosis and response to corticosteroid therapy; these are non-specific interstitial pneumonia, cryptogenic organising pneumonia (bronchiolitis obliterans organising pneumonia), acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and lymphoid interstitial pneumonitis.

Guidelines and reviews state that pharmacologic therapy for idiopathic pulmonary fibrosis has no definitive, proven benefit.[1,3,4] Corticosteroids have traditionally been used, based on observational reports of a symptomatic response to treatment in about 50% of patients, and an improvement in lung function in up to 25%. However, these early reports were likely to have included a heterogeneous mix of patients that included other types of idiopathic interstitial pneumonias.[1,5] Although randomised placebo-controlled studies have not been done, several retrospective studies found no evidence of benefit from high-dose corticosteroids, and they are not recommended as monotherapy in patients with definite idiopathic pulmonary fibrosis.[1,3] The use of a corticosteroid with an immunosuppressive or cytotoxic drug, particularly azathioprine or cyclophosphamide, has also been tried but these dual-therapy combinations are not recommended.[1,3] However, there was some evidence from a randomised study that the addition of acetylcysteine to prednisone and azathioprine slowed the rate of decline in lung function.[6] Triple oral therapy has been recommended by the British Thoracic Society, consisting of prednisolone (500 micrograms/kg daily, tapering over 3 months to 125 micrograms/kg daily) with azathioprine (2 to 3 mg/kg daily, to a maximum of 150 mg daily) and acetylcysteine (600 mg three times daily).[1] However, further study is required to confirm the benefits of this combination. Joint guidelines (from America, Europe, Japan and Latin America)[3] have also suggested that this combination, as well as acetylcysteine monotherapy, may be of use in a minority of patients. There is limited evidence to suggest that the antifibrotic pirfenidone may improve pulmonary function and progression-free survival,[7] and it too has been proposed as a reasonable choice in a minority of patients.[3]

Microvascular thrombosis may be an important pathogenic process in idiopathic pulmonary fibrosis,[1] and anticoagulation might have a beneficial effect on survival but further studies are needed.[1,3]

Many other drugs have been tried in patients with idiopathic pulmonary fibrosis.[1,3,4,7] Ciclosporin has been used adjunctively and also as a corticosteroid-sparing treatment, but data are too limited to support its use.[3,4] Colchicine has been suggested to be as effective as corticosteroids, however, studies have generally shown no evidence of survival benefit, and it is not recommended.[3,4] There are reports of response to penicillamine, but controlled studies are lacking, and in view of its adverse effects, its use is generally not recommended.[4] Despite promising preliminary results, a large controlled study of interferon gamma found no significant effects on mortality compared with placebo.[8] Experimental strategies include the use of relaxin, suramin, sildenafil, endothelin receptor antagonists, angiotensin II receptor antagonists, and gene therapy.[3,4]

In patients in whom other options fail, lung transplantation (p. 1937.3) should be considered.[1,3]

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8. King TE, *et al*. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; **374:** 222–8.

Leishmaniasis

Corticosteroids may be required to control severe inflammation in patients with mucocutaneous leishmaniasis (p. 923.1), although pentavalent antimony is usually the drug used for initial treatment.

Leprosy

Type I lepra (reversal) reactions in patients with leprosy (p. 188.3) frequently respond to high-dose corticosteroids (for example 40 to 60 mg of prednisolone daily) started immediately and given for several days.[1] Doses may be reduced over several weeks or months. Corticosteroids may also be used for type II reactions.

It has been considered that corticosteroid treatment of nerve function impairment should be started within 6 months of onset, as the earlier that treatment was started, the more likely it was that function would be restored. A standardised regimen in which the usual adult dose was 40 mg daily of prednisolone for 4 weeks, tapered over the next 12 weeks, has been reported to be successful in the field management of acute nerve function impairment,[2] as has a regimen consisting of 30 mg of prednisone for 2 weeks tapered down with a minimum duration of 10 weeks.[3] However, a subsequent study[4] in patients with mild nerve impairment for less than 6 months, and another in patients with established sensory impairment[5] both failed to show any benefit from a tapered corticosteroid regimen. There was evidence that sensory impairment may undergo some degree of spontaneous recovery, which casts doubt on previous reports of benefit from uncontrolled studies of corticosteroids. The use of a lower dose prophylactic regimen has also been studied, starting with prednisolone 20 mg daily for 3 months then tapering in the fourth month.[6] Although the incidence of new leprosy-related reactions and associated nerve function impairment in all patients was reduced during corticosteroid treatment, there appeared to be a rebound after this was stopped and the initial beneficial effect was not sustained at 1 year. Interestingly, however, subgroup analysis suggested that existing nerve function impairment at diagnosis may affect the outcome; after 4 months of prophylaxis, a significant reduction in acute reactions or new nerve function impairment was seen only in those without initial evidence of impairment although, as before, this was not sustained.

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Lichen

Lichen planus (p. 1685.2) is generally controlled with corticosteroids applied topically or, occasionally, injected intralesionally; systemic corticosteroids (usually prednisone or prednisolone) are used for severe erosive lichen planus, generalised cutaneous disease, and acute exacerbations.[1,2] Prednisone has generally been used in oral doses of 30 to 60 mg daily, for courses of 4 to 6 weeks.[1] Shorter courses may be of value: prednisolone (30 mg daily for 10 days) was reported to be effective and safe for mild or moderately severe lichen planus.[3]

Topically applied corticosteroids form the mainstay of treatment of lichen sclerosus (p. 1685.2). UK guidelines recommend clobetasol propionate 0.05% ointment, usually applied once daily at night for 4 weeks, then on alternate nights for 4 weeks, then twice weekly for 4 weeks, after which the patient should be reviewed. Once the condition is under control, the frequency of application may be increased as necessary when symptoms recur.[4] Another review has suggested that after inducing remission with a potent topical corticosteroid, hydrocortisone 1% may be applied once daily for long-term control of the condition in children.[5]

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Liver disorders

Corticosteroids are considered to be useful in chronic active hepatitis (p. 1602.3). There is some disagreement over the benefit from corticosteroid therapy in alcoholic liver disease with hepatic encephalopathy,[1-4] and they do not appear to be of benefit in acute hepatic failure.[5] Corticosteroid therapy may however be of benefit in sclerosing cholangitis.[6]

No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p. 2638.3). Corticosteroids are one of a number of drugs for which reports of benefit exist, but their use has been restricted as they may exacerbate bone disease.

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2. Ramond M-J, *et al*. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; **326:** 507–12.
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6. Lindor KD, *et al*. Advances in primary sclerosing cholangitis. *Am J Med* 1990; **89:** 73–80.

Male infertility

Immunosuppressive treatment with corticosteroids has been given for male infertility (p. 2253.1) due to low-grade auto-immune orchitis.[1] Corticosteroids have also been used in men with autoantibodies to spermatozoa. Various regimens have been tried, such as giving the man a corticosteroid for a set number of days during the partner's menstrual cycle, or giving a continuous low-dose for several months.[2] However, there is a lack of evidence of benefit from substantial controlled studies and the use of corticosteroids is not generally recommended. They might,

however, be considered for men with autoantibodies who have failed assisted reproductive techniques.[1]

1. Haidl G. Management strategies for male factor infertility. *Drugs* 2002; **62:** 1741–53.
2. Lombardo F, *et al*. Antisperm immunity in natural and assisted reproduction. *Hum Reprod Update* 2001; **7:** 450–6.

Malignant neoplasms

Corticosteroids are extensively prescribed in malignant disease for the relief of pain, nerve compression, or raised intracranial pressure; to alleviate dyspnoea, effusion, or hypercalcaemia; to counteract adverse effects of other therapies such as antineoplastic-induced nausea and vomiting or radiation-induced inflammation; and in the management of cachexia and to improve mood and sense of well-being.[1] In addition they form an important part of multidrug anticancer regimens used for various haematological malignancies such as acute lymphoblastic leukaemia (p. 692.3) and Hodgkin's disease (p. 696.1). In contrast, it has been postulated that the use of corticosteroids in patients with solid, non-haematological tumours might induce resistance in cancer cells to cytotoxic therapy, and increase the risk of treatment failure, although clinical evidence for this is lacking.[2]

1. Twycross R. The risks and benefits of corticosteroids in advanced cancer. *Drug Safety* 1994; **11:** 163–78.
2. Rutz HP. Effects of corticosteroid use on treatment of solid tumours. *Lancet* 2002; **360:** 1969–70.

Meningitis

Corticosteroids may be given as adjuncts to antibacterial therapy in bacterial meningitis (p. 191.1), in the hope of moderating any neurological sequelae; there is some evidence that dexamethasone, especially if given early, may reduce the risk of deafness in children and reduce mortality in adults.

Mouth ulceration

Local treatment of mouth ulcers (p. 1811.2) often involves a topical corticosteroid for symptomatic relief. Systemic corticosteroids have occasionally been given where there is severe underlying disease.

Multiple sclerosis

Corticosteroids are often used in the management of multiple sclerosis (p. 996.3). Corticosteroid therapy reduces the duration of the relapse and accelerates recovery, but it is unknown whether it alters the course of the disease in the long term.[1,2] Methylprednisolone has superseded corticotropin and prednisolone as the drug of choice. Methylprednisolone is usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days, sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g of methylprednisolone daily have been tried.[3] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis[4] although the effect was not sustained beyond 2 years.[5] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[6] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[7]

In patients with primary progressive disease, the benefits of short-course methylprednisolone lasted no longer than 3 months[8] although, in patients with secondary progressive disease, a preliminary study has suggested that progression may be delayed by intermittent high-dose methylprednisolone therapy.[9]

1. Rudick RA, *et al*. Management of multiple sclerosis. *N Engl Med J* 1997; **337:** 1604–11.
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3. Oliveri RL, *et al*. Randomized trial comparing two different high doses of methylprednisolone in MS: a clinical and MRI study. *Neurology* 1998; **50:** 1833–6.
4. Beck RW, *et al*. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* 1993; **329:** 1764–9.
5. Beck RW, *et al*. The optic neuritis treatment trial: three-year follow-up results. *Arch Ophthalmol* 1995; **113:** 136–7.
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7. Barnes D, *et al*. Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. *Lancet* 1997; **349:** 902–6.
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Muscular dystrophies

Muscular dystrophies are a range of inherited myopathies in which there is progressive degeneration of muscle fibres and associated muscle weakness. They may be classified according to the mode of inheritance. The most common type is the fatal recessive X-linked **Duchenne muscular dystrophy** (DMD) in which there is a deficiency in the structural muscle protein dystrophin. There is no effective therapy that affects the ultimate outcome of the various muscular dystrophies. Management is mainly through the use of physiotherapy, supports, and surgery. Drug treatment has been tried for symptomatic management, but generally the number of patients studied has been small. However, corticosteroids have been shown to be effective in increasing muscle strength and function in children for 6 months to 2 years;[1] prednisone or prednisolone 750 micrograms/kg daily is considered to be the most effective dose,[1-3] with gradual tapering to doses as low as 300 micrograms/kg daily if necessary.[2] Improvement does not appear to be sustained to the same degree with alternate-day therapy;[4] some benefit in terms of motor function preservation has been reported with intermittent prednisone (750 micrograms/kg daily for 10 days of each month).[5] Benefit has also been seen with deflazacort[1-3,6] in doses of 900 micrograms/kg daily. It has been suggested that the failure of azathioprine to produce any beneficial effect when used alone or added to prednisone treatment might indicate that prednisone's efficacy is not due to immunosuppression.[7] There have also been reports of benefit in small numbers of patients given ciclosporin or oxandrolone; evidence to support the use of most other drugs is either conflicting or unconvincing. A small study found that supplementation with creatine monohydrate (100 mg/kg daily) significantly increased handgrip strength in the dominant hand compared with placebo; results were independent of corticosteroid use.[8] Future prospects for treatment include gene therapy, haematopoietic stem-cell therapy, or upregulation of the protein utrophin (related to dystrophin) to try to ameliorate the dystrophy.[9,10]

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2. Moxley RT, *et al*. Practice parameter: corticosteroid treatment of Duchenne dystrophy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2005; **64:** 13–20. Also available at: http://www.aan.com/professionals/practice/guidelines/pda/Duchenne_Muscular_Dystrophy.pdf (accessed 26/08/08)
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6. Bigger WD, *et al*. Deflazacort treatment of Duchenne muscular dystrophy. *J Pediatr* 2001; **138:** 45–50.
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Myasthenia gravis

Corticosteroids are the main immunosuppressants used in the management of myasthenia gravis (p. 684.1).

Nasal polyps

Nasal polyps[1-3] are outgrowths of the nasal mucosa, typically pale, smooth, translucent, and round or pear-shaped. They are often associated with a history of rhinitis or asthma; the triad of nasal polyps, asthma, and hypersensitivity to aspirin may occur. Patients typically present with obstruction, loss of smell, and often rhinorrhoea and postnasal drip.

Corticosteroids are extremely effective in reducing polyp size, either by the intranasal[4,5] or systemic route.[5,6] In the former case beginning with betamethasone sodium phosphate nasal drops, and then maintaining the reduction with an intranasal spray such as beclometasone, budesonide, or fluticasone, has been suggested.[1] Alternatively prednisone, prednisolone, or dexamethasone can be given orally: suggested regimens have included prednisone 60 mg daily, tapered over 10 or 14 days and followed by intranasal corticosteroids,[2] or dexamethasone 12, 8, and 4 mg daily, each for 3 days.[1] Surgery may be necessary where there is marked obstruction, and most patients require it at some point,[1] although polyps usually recur. Pre-operative use of systemic corticosteroids may help reduce recurrence.[2] Continued use of topical corticosteroids may reduce the frequency of relapses.[4] Antibacterials may be indicated for superimposed bacterial infection. Antihistamines, although not extensively studied, have been reported to be of benefit in nasal obstruction. Leukotriene antagonists have shown promising results, although large-scale studies are lacking; they may be indicated in patients with aspirin hypersensitivity.[5]

1. Lund VJ. Diagnosis and treatment of nasal polyps. *BMJ* 1995; **311:** 1411–14.
2. Slavin RG. Nasal polyps and sinusitis. *JAMA* 1997; **278:** 1849–54.
3. Drake-Lee AB. Nasal polyps. *Hosp Med* 2004; **65:** 264–7.
4. Badia L, Lund V. Topical corticosteroids in nasal polyposis. *Drugs* 2001; **61:** 573–8.
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Nausea and vomiting

Corticosteroids, usually in the form of dexamethasone, play an important role in antiemetic regimens (see p. 1811.3) used to combat the effects of moderately to severely emetogenic cancer chemotherapy: they have been shown to enhance the effects of both metoclopramide- and 5-HT_3 antagonist-based regimens. Dexamethasone is a well-established treatment for delayed emesis. It is also used in palliative care and in the prophylaxis of postoperative nausea and vomiting. A study of corticosteroid treatment in refractory hyperemesis gravidarum showed improvements in appetite, weight gain, and well-being, and suggested that corticosteroids might improve nausea and vomiting but was too small to provide conclusive evidence.[1]

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Neonatal intraventricular haemorrhage

For the suggestion that antenatal corticosteroids may reduce the incidence of intraventricular haemorrhage in neonates, see p. 1128.3.

Neonatal respiratory distress syndrome

Neonatal respiratory distress syndrome is a condition of increasing respiratory distress occurring at, or shortly after, birth. It is marked by cyanosis, tachypnoea, expiratory grunting and sternal retraction. Symptoms increase in severity with progressive collapse of the lung (atelectasis), leakage of plasma into alveolar spaces, and the formation of hyaline membranes, until death occurs or slow recovery takes place from about the 2nd to 4th day. The syndrome affects mainly premature infants and its incidence increases with the degree of prematurity; severe problems are most likely in those delivered before 30 weeks of gestation. Symptoms are thought to be at least partly due to inadequate amounts of surfactant in the premature lung resulting in high internal surface tension and increased risk of alveolar collapse, but in very immature infants other factors, possibly including impaired sodium and fluid absorption from the lung, may play a role.[1]

Treatment. The optimum treatment is prevention, and previous[2] and more recent[3] UK guidelines recommend betamethasone 12 mg daily by intramuscular injection for 2 days in women in whom delivery before 34 weeks of gestation is likely. Similar recommendations apply elsewhere. In the USA, for example, antenatal corticosteroid treatment (with betamethasone or dexamethasone) is recommended for women between 24 and 34 weeks of pregnancy who show signs of premature delivery.[4] Results from a large study suggest that babies born after 37 weeks by elective caesarean section also benefit from antenatal betamethasone.[5] Betamethasone may be preferable to dexamethasone, as the latter appears to have a deleterious effect on neurodevelopment.[6] Long-term follow-up of those exposed antenatally to betamethasone showed no deleterious effects on psychological functioning[7] or on cardiovascular risk factors;[8] however, small increases in insulin resistance, albeit clinically insignificant, were noted in those exposed to the glucocorticoid. An overview of studies of antenatal corticosteroid therapy suggests that it may reduce the risk of respiratory distress syndrome by about 50% overall;[9] the risk of death, and of periventricular haemorrhage and necrotising enterocolitis is also reduced. Whether repeat courses should be considered is uncertain, although the practice has become widespread. A systematic review[10] indicated that repeat doses did reduce the occurrence and severity of neonatal lung disease and risk of serious health problems in the first few weeks of life. However, these benefits were associated with a reduction in some measures of weight and head circumference at birth and there was insufficient evidence on the long-term benefits and risks. Some have recommended that repeat doses be restricted to patients in clinical studies.[6,11] Delaying delivery with a tocolytic (see Premature Labour, p. 2131.1) may be considered to increase the time available for management with antenatal corticosteroids.[2,3] Reported benefit from adding protirelin to antenatal corticosteroids has not been borne out by 2 large multicentre studies.[12-14] The earlier of these studies actually found neonatal outcome

and maternal morbidity to be worse in those who also received protirelin,[12,13] but this conclusion has been questioned.[15,16]

In infants born with the syndrome rapid supportive care is required, which may include correction of metabolic acidosis, circulatory support, oxygen supplementation, and assisted ventilation, although there has been a lack of consensus about the most appropriate method for these.[2] Ventilation using a helium-oxygen mixture may give better results than a nitrogen-oxygen mix.[17] Another alternative is the use of partial liquid ventilation with the fluorocarbon compound perflubron.[18] Meta-analysis suggests that inhaled nitric oxide improves outcomes in infants born at or near term who are hypoxaemic,[19] but evidence of benefit in preterm infants has not been shown.[20] The majority of infants survive the acute episode with careful management, although associated complications may subsequently develop, including bronchopulmonary dysplasia (p. 1602.1), retinopathy of prematurity (p. 2120.3), and cerebral palsy. There is evidence that supplementation with inositol can significantly reduce the incidence of adverse outcomes in preterm infants.[21]

Since deficiency of surfactant is considered to play an important role in the neonatal respiratory distress syndrome, the use of surfactant replacement therapy has been intensively investigated, and is now accepted as reducing the risk of death from the disease and the development of pneumothorax and other lung complications.[2,22,23] Both natural and synthetic surfactants have been used and although both are effective results have tended to be better with the preparations of natural origin.[24-26] Natural surfactants of differing origins may also vary in their properties: poractant,[27] or calfactant,[28] have both been reported to give better responses than beractant. Surfactant is given as a suspension by endotracheal tube directly into the infant's lung, although other devices, such as nebulisers, have been investigated. Most surfactants are given in recommended doses of 100 to 200 mg/kg phospholipids. Repeat doses may be given if necessary, and a meta-analysis[29] of data from two randomised controlled studies using preparations of natural surfactant extract in neonates with established disease found a more favourable clinical outcome, including a decreased risk of pneumothorax, with multiple rather than single doses. However, in clinical practice the number of doses and the dosage interval varies. One large study[30] found that a dose of 100 mg/kg, repeated twice, was as effective as 200 mg/kg followed by up to four further doses of 100 mg/kg. Another found that 3 doses, given at 12-hour intervals with the first dose shortly after birth were more effective than the first dose alone in improving physiological findings and mortality rates in low birth-weight infants.[31] One large multicentre randomised controlled study[32] investigated the difference between giving repeat doses of a surfactant (calfactant) at a low threshold of respiratory support, as recommended by the manufacturer, versus a higher threshold. The conclusion was that efficacy was not compromised by delaying surfactant re-treatment in infants with uncomplicated respiratory distress syndrome until they had reached a higher level of respiratory support than is currently recommended, but infants with complications should continue to be treated by the currently recommended low-threshold strategy.

There has been debate whether 'prophylactic' early therapy, given immediately after birth to all infants deemed at risk of the syndrome, or delayed therapy given 2 or more hours after birth to intubated infants who have developed symptoms, is the more appropriate,[33] but the large OSIRIS study,[34] and later systematic reviews,[35-37] found in favour of early intervention, and this strategy is recommended in the UK guidelines.[2,3] However, two subsequent studies undertaken when maternal antenatal corticosteroid prophylaxis and nasal continuous positive airway pressure (CPAP) had become routine found that early stabilisation on CPAP, with surfactant only given to infants needing intubation, was associated with a reduced risk of chronic lung disease or death when compared with prophylactic surfactant.[38]

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Optic neuropathies

Causes of optic neuropathies are diverse, and they may be classified by their aetiology.[1,2] Ischaemic optic neuropathies, of which the acute anterior form is most common, may be caused by vasculitic syndromes (p. 1615.2) such as giant cell arteritis (p. 1604.2).[3] Inflammatory optic neuropathies (optic neuritis) may be caused by infectious disease, immune-mediated disorders such as Behçet's disease (p. 1601.1), sarcoidosis (p. 1612.2), or demyelination of the optic nerve such as occurs with multiple sclerosis (p. 996.3).[4,5] Other causes include hereditary disorders, trauma, or compression. Vitamin or nutritional deficiency (often due to alcohol abuse) or toxicity (due to drugs such as amiodarone, digoxin, or isoniazid) may also lead to optic neuropathy.[1,2] Clinical features such as pattern of visual field loss and pain can aid diagnosis.[2]

Management will depend on the type of neuropathy and any underlying disease. Individual studies have reported benefit with corticosteroids. Improvement in vision was reported in patients with auto-immune optic neuropathy after 5 to 7 days of treatment with high doses of intravenous methylprednisolone (1 to 2 g daily) or oral prednisolone (80 to 400 mg daily).[6] In some patients, recurrent visual loss required repeated high-dose intravenous methylprednisolone, an increase in oral prednisolone dosage, or additional immunosuppressants, but in many patients visual benefits were maintained even when treatment was withdrawn. Visual recovery has also been reported in patients with optic neuritis of unknown aetiology given intravenous methylprednisolone 250 or 500 mg every 6 hours for 3 to 7 days.[7] Another study found oral prednisone alone (1 mg/kg daily for 14 days) to be ineffective whereas intravenous methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days) was beneficial in the treatment of acute optic neuritis.[8] Unexpectedly, there was an increased risk of new episodes in patients treated with oral prednisone alone,[8] and this regimen should be avoided.[9] A review of corticosteroid use in optic neuritis concluded that high-dose oral or parenteral methylprednisolone, or corticotropin, were of value in the treatment of acute disease. However, their long-term benefit could not be determined.[10] In contrast, a systematic review of 5 studies found no evidence of benefit from intravenous or oral corticosteroid therapy at the doses used.[11]

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Organ and tissue transplantation

For a discussion of organ and tissue transplantation, including the role of corticosteroids, see p. 1932.2.

Osteoarthritis

Systemic corticosteroids are not considered to have a place in the management of osteoarthritis (p. 12.3); however, intra-articular injection may be useful for acute exacerbations of joint pain and inflammation. Such injections should be given only infrequently and as adjunctive therapy.

Osteopetrosis

Osteopetrosis is a rare set of heterogeneous disorders characterised by an increase in bone density, generally due to a failure of the osteoclasts to resorb mineralised bone. In the severe infantile malignant form there is reduction in the bone marrow space, leading to anaemia, hepatosplenomegaly, and nerve compression that may produce blindness and deafness; early death often results. The adult form is benign; patients typically present with fractures, back and bone pain, but no haematological abnormalities, and generally have a full life expectancy.[1]

Bone marrow transplantation may be curative for the infantile malignant form if a suitable donor can be found.[1,2] Corticosteroids are used palliatively. Benefit has been reported in 3 of 4 children treated with oral prednisone 1 mg/kg daily, with phosphate supplements and a low-calcium diet.[3] Some patients have also benefited from the use of high-dose calcitriol, again with a low-calcium diet.[4]

Another study, in 14 patients, found that treatment with interferon gamma-1b increased bone resorption.[5] In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

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Pain

Corticosteroids have produced improvement, often substantial, in neuropathic pain, including pain due to nerve damage and sympathetically maintained pain, and are widely used in conditions such as cancer pain. Dexamethasone, methylprednisolone, and prednisolone have been used for pain management, sometimes in the form of long-acting depot injections administered locally. The exact mechanism of action of corticosteroids in analgesia is not clear but may involve relief of pressure on nervous tissue by reduction of inflammation and oedema.

For discussions of pain and its management, see p. 4.1.

Pancreatitis

Although corticosteroids are generally ineffective for pancreatitis (p. 2580.2), auto-immune pancreatitis is one form of the disease that does respond well to corticosteroid therapy. An oral dose of prednisolone (or prednisone) 30 to 40 mg daily may be used for control of the initial inflammatory phase.[1,2] The dose is then gradually reduced, although the optimal duration of treatment and the role of low-dose maintenance therapy is not yet clear.[2] Responses to corticosteroids have also been reported[3,4] in patients with acute episodes of pancreatitis caused by sarcoidosis (p. 1612.2).

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Pemphigus and pemphigoid

Systemic corticosteroids are the mainstay of management of pemphigus and pemphigoid (p. 1687.1). Initially, high doses are used to control blistering, which may take weeks. The optimum dose has not yet been established and suggestions have varied enormously; very high doses of oral prednisolone have been used in the past. The usual starting dose for widespread disease is about 1 mg/kg daily of prednisolone, continued until new blisters stop forming, then gradually decreased. However, doses above 750 micrograms/kg daily may have no additional benefit in bullous pemphigoid, and lower starting doses have been suggested for some patients: 300 micrograms/kg daily in localised or mild disease, 600 micrograms/kg daily in moderate disease, and 0.75 to 1 mg/kg daily in severe disease.[1] Doses of 40 to 60 mg daily for mild pemphigus vulgaris and 60 to 100 mg daily for more severe disease have been recommended.[2] Pulsed intravenous corticosteroids such as methylprednisolone (0.25 to 1 g given for up to 5 consecutive days) may be considered for severe or refractory disease, particularly if there has been no response to high oral doses.[2] Other immunosuppressants may be added once remission is achieved and the condition has stabilised, with the aim of tapering the corticosteroid and eventually withdrawing treatment. Maintenance treatment must be individualised; one suggested regimen for tapering the corticosteroid is to reduce the dose of prednisolone by 50% every 2 weeks; alternatively, the dose is reduced by 5 to 10 mg weekly then more slowly below 20 mg daily.[2]

A very potent topical corticosteroid such as clobetasol propionate can be sufficient to control localised or mild to moderate disease in some patients, particularly in bullous pemphigoid, and can be a useful adjunct to systemic treatment in pemphigus and pemphigoid.[1,2] A large randomised study[3] found that topical application of 40 g of clobetasol propionate cream 0.05% daily to the entire body had a similar efficacy to oral prednisone 500 micrograms/kg daily for moderate bullous pemphigoid and was better than 1 mg/kg daily for severe disease. Blistering and ulceration of the oral mucous membranes may be treated with topical corticosteroid preparations such as mouthwashes, adhesive pastes, lozenges, or aerosols.[2,4] Intralesional injections have also been used for isolated lesions of the oral mucosa.[4] Topical corticosteroids do not control ocular disease on their own but may be added to initial systemic therapy to control acute ocular inflammation; they should not be used as long-term therapy.[5]

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Pneumocystis pneumonia

The management of pneumocystis pneumonia (p. 567.2) is mainly with co-trimoxazole. In patients with severe infection who are hypoxic, adjuvant therapy with high-dose oral or intravenous corticosteroids reduces both the risk of respiratory failure and the risk of death.[1,2] Concerns about the potential for further immunosuppression with such adjuvant therapy in patients with HIV infection[3] do not seem to have been borne out: a comparative study noted no increase in mortality or the risk of developing other opportunistic infections.[4]

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Polyarteritis nodosa and microscopic polyangiitis

Polyarteritis nodosa is considered the prototype of systemic necrotising vasculitis. It may occur at any age but is more common in white patients and in men. It is characterised by inflammation throughout the arterial wall with fibrinoid necrosis of the arterial media, particularly in medium-sized vessels, partial occlusion of the vessel due to proliferation of the intima (possibly leading to thrombosis and infarction), fibrosis, and the formation of aneurysms. Microscopic polyangiitis, in which small vessels are mainly involved, with frequent renal and pulmonary involvement, has been seen as part of the spectrum of polyarteritis nodosa but is now considered an entity in its own right, although patients may have features of both. Antineutrophil cytoplasmic antibodies (ANCA) are common in patients with microscopic polyangiitis, which has many similarities to Wegener's granulomatosis (p. 1615.2), but not in classic polyarteritis nodosa.

Symptoms depend on the vessels affected but most patients have fever, weight loss, myalgia, and arthralgia. Those associated with gastrointestinal involvement include mouth ulceration, diarrhoea, visceral pain, haemorrhage, or sometimes infarction of the bowel, while involvement of liver can lead to hepatomegaly or hepatic necrosis and pancreatic involvement may simulate pancreatitis. Renal involvement may present as acute glomerulonephritis and renal failure or as nephrotic syndrome; like pulmonary involvement it is a feature particularly of microscopic polyangiitis, and associated with a poor prognosis. Skin lesions, peripheral neuropathies, alterations in mental function, convulsions, episcleritis or scleritis and retinal vasculitis, ischaemic heart disease, heart failure, Raynaud's phenomenon, and hypertension are among other potential symptoms. If untreated, death, usually due to renal or cardiac involvement, occurs in about 90% of patients within 5 years.

Classic polyarteritis nodosa may respond to treatment with a corticosteroid given alone, typically prednisone or prednisolone in a dose of 40 to 60 mg daily; however, although the benefits of adding a cytotoxic to the regimen have been queried,[1,2] a combined regimen with cyclophosphamide is often preferred.[1,3-5] Some reserve combined therapy for patients with evidence of more severe disease.[6] In patients with microscopic polyangiitis a combined regimen is recommended.[6,7] One suggested oral regimen is prednisone or prednisolone 1 mg/kg with cyclophosphamide 2 mg/kg, both daily, for initial induction of remission.[8] Pulsed intravenous methylprednisolone has also been used, followed by a tapering dose of corticosteroid. There is a trend towards giving shorter courses of cyclophosphamide, and to using intravenous pulsed cyclophosphamide rather than oral dosage, in an attempt to reduce adverse effects.[5,8,9] Treatment with corticosteroids and cyclophosphamide should not exceed 1 year.[9] Azathioprine has been substituted for cyclophosphamide to maintain remission, and mycophenolate mofetil has been tried in a few patients as an alternative to cyclophosphamide in combination therapy after initial induction.[6,10] Rituximab plus corticosteroids has been reported to have similar efficacy to cyclophosphamide plus corticosteroids, with some suggestion that rituximab may be more effective in relapsing disease.[11]

Polyarteritis nodosa may be associated with hepatitis B infection; the vasculitis responds in most cases to treatment with antiviral drugs and plasma exchange.[3,9] Prolonged treatment with corticosteroids and cyclophosphamide should be avoided in these patients because of the risks of enhanced viral replication. However, corticosteroids may be given initially to rapidly control severe life-threatening vasculitis. The corticosteroid is stopped abruptly after 2 weeks to enhance immunological clearance of hepatocytes infected by hepatitis B virus and to favour seroconversion, and plasma exchange and antiviral drug therapy are started.[5]

Plasma exchange with cyclophosphamide may also be useful in patients with microscopic polyangiitis, particularly those with acute renal failure or severe pulmonary haemorrhage.[7] Another therapy that has been tried in this group, but with ambiguous results, is high dose intravenous normal immunoglobulin.[8]

Vasodilators such as calcium-channel blockers, inhibitors of platelet activation, or drugs that improve blood flow may be useful to improve local ischaemia.[12] Skin lesions in a patient with cutaneous polyarteritis nodosa have reportedly responded to oral pentoxifylline.[13]

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Polychondritis

Relapsing polychondritis is a rare systemic disease that results in inflammation and destruction of cartilage in various parts of the body, most seriously in the respiratory system (e.g. nose, larynx, and trachea). Airway narrowing and obstruction due to loss of cartilaginous support results, and may be complicated by pneumonia; fatalities have resulted. Cardiovascular involvement, ocular manifestations, skin disorders, and renal disease may occur; it may also be associated with other diseases such as the vasculitic syndromes. Mild inflammation is usually treated with dapsone, colchicine, or NSAIDs. Relatively high doses of corticosteroid may improve symptoms in active disease, but do not appear to retard progression. Acute airway obstruction may be treated with high-dose intravenous pulse corticosteroids.[1,2] Methotrexate,[3] azathioprine,[1] or ciclosporin[2] may be of value in reducing corticosteroid requirements. CD4 antibodies have also been tried in refractory disease but did not prove particularly useful in clinical practice.[2] Newer biological therapies such as infliximab or etanercept have been reported to be of benefit in a few cases, but their role in the management of the disease remains to be determined.[2]

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Polymyalgia rheumatica

Polymyalgia rheumatica is a rheumatic disorder of uncertain aetiology. It occurs mainly in persons over 50 years of age of European, especially Scandinavian, extraction and is more common in women than in men. The disease is characterised by myalgia and severe morning stiffness in the neck and shoulder girdle and in the hips and pelvic girdle, which may spread in more advanced cases to the muscles of the thighs, chest, and arms. Stiffness and pain are worse after periods of inactivity. There may be some joint involvement; other symptoms include fatigue, weight loss, and fever, and anaemia and raised erythrocyte sedimentation rate are seen. In some patients polymyalgia rheumatica is associated with giant cell arteritis (p. 1604.2).

Treatment. Although NSAIDs may improve the symptoms of polymyalgia rheumatica they do not control the disease process, and corticosteroids are preferred;[1-5] in particular, corticosteroid therapy is essential where giant cell arteritis is present.

The usual initial oral dose is prednisolone or prednisone 10 to 20 mg daily, depending on the severity of symptoms; higher doses are needed where giant cell arteritis is also present, particularly if there are ophthalmic symptoms.[4,6] After 1 to 2 months a reduction in dosage is usually possible

provided symptoms are well controlled. Dosage reduction should be gradual;[4-6] mean maintenance dose at one year is about 5 or 6 mg daily.[1,5,6]

Maintenance therapy may need to be prolonged. Although about a third to a half of all patients may be able to have corticosteroids withdrawn within about 2 years,[2] maintenance can be required for considerably longer periods.[5,6] Intramuscular methylprednisolone has also been found to be effective in polymyalgia rheumatica; because the cumulative dose with prolonged therapy is lower it has been suggested that this has advantages over the use of oral corticosteroids.[7] Intravenous pulse methylprednisolone has also been used.[5] Relapse is not uncommon and is most likely within one year of corticosteroid withdrawal.[2,3,5] It may be associated with arteritic symptoms, but arteritic relapses are unusual in patients whose original presentation was pure polymyalgia.[2] Methotrexate or azathioprine may be used for their corticosteroid-sparing effect in patients in whom withdrawal is difficult.[2-4]

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Polymyositis and dermatomyositis

The term polymyositis has been used to describe several types of rare idiopathic inflammatory muscle disorders (myopathies).

The cardinal symptom of polymyositis is symmetrical progressive muscle weakness, usually starting in the shoulder girdle and neck, and pelvic girdle. Onset is usually gradual over a period of months, and accompanied by mild pain and tenderness, although more rapidly evolving disease with intense muscle pain is known. With progression, weakness may prevent the patient from moving their limbs, and muscle atrophy and contracture can develop. Dysphagia, pulmonary aspiration, and hypoventilation may occur, and some patients develop fibrosing alveolitis; pulmonary involvement, especially aspiration pneumonia, can be fatal. ECG abnormalities, usually asymptomatic, are common, and some patients develop Raynaud's syndrome. Primary disease may be associated with rashes, in which case it is known as dermatomyositis. Purplish scaly rashes on knees, elbows, and knuckles, and a characteristic purplish ('heliotrope') coloration and oedema of the eyelids may occur. A childhood form known as juvenile dermatomyositis exists, in which additional signs include vasculitis and subcutaneous calcium deposition (calcinosis cutis), and gastrointestinal haemorrhage and perforation may occur.

Treatment. Patients with active disease require bed rest, with the head elevated in patients at risk of aspiration. Physiotherapy to maintain muscle tone and avoid the development of contractures may be required.

Initial drug therapy is based on corticosteroids.[1-5] The usual choice is oral prednisone or prednisolone 40 to 60 mg or more, or 1 to 2 mg/kg daily. This usually produces improvement within 1 to 2 months. The dose may then be gradually tapered off to the minimum required for disease control;[1-3] some patients with well controlled disease may be satisfactorily maintained on an alternate-day regimen.[2,3] In patients with severe disease or extramuscular manifestations such as lung involvement, pulse intravenous methylprednisolone may be preferred initially, to gain more rapid disease control.[1,2,4] Maintenance therapy may need to be prolonged and a reduction in corticosteroid dosage to the minimum is therefore desirable, but too early or too rapid a reduction may lead to relapse.

Up to 30% of patients do not respond to corticosteroids,[2] or develop unacceptable adverse effects, and in these cases the second-line drugs are cytotoxic immunosuppressants.[1-3] There is considerable experience with the use of methotrexate, orally, subcutaneously, intramuscularly, or intravenously, usually at weekly intervals; it may be used with corticosteroids, permitting a reduction in their dose. Azathioprine may also be given with corticosteroids, again permitting a reduction in corticosteroid dosage, and the combination has also been shown to be superior to a corticosteroid alone for long-term maintenance (although this was only apparent after more than a year of therapy).[6] There is some evidence that methotrexate may be superior to azathioprine in patients unresponsive to prednisone alone.[7] Combining methotrexate and azathioprine has also been suggested.[2,4]

Some consider that corticosteroid therapy should be combined with a cytotoxic immunosuppressant such as azathioprine or methotrexate from the outset of treatment.

The role of other drugs is less well defined. Cyclophosphamide may be of use in patients with lung disease,[1,3,5] while chlorambucil and tacrolimus have produced benefit in individual cases but have not been formally assessed.[4] There have been reports of ciclosporin producing a response in refractory disease.[2,4] Normal immunoglobulin has also produced responses; it is usually reserved for refractory cases, or as an add-on therapy in patients inadequately controlled on corticosteroids and immunosuppressants, or for whom immunosuppressants are contra-indicated.[2,3] Promising results have been obtained with fludarabine[1] and mycophenolate mofetil;[2,3] there are preliminary reports of success with etanercept, and infliximab, and interferon beta has been investigated.[2]

Cutaneous symptoms in patients with dermatomyositis do not always respond satisfactorily to corticosteroids, but hydroxychloroquine is reputed to be of benefit in patients with rash,[8] probably due to a photoprotective effect.[9] Calcinosis, which can cause considerable morbidity, is particularly difficult to treat but some cases have responded to treatment with aluminium hydroxide, alendronate, diltiazem, or magnesium sulfate.[4] Warfarin therapy has been used,[10,11] but its value for calcinosis is disputed.[12]

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12. Ansell B. Is there a treatment for the calcinosis of juvenile dermatomyositis? *Br J Rheumatol* 1990; **29:** 263.

Polyneuropathies

Ten patients with subacute demyelinating polyneuropathy obtained a beneficial response to corticosteroid therapy.[1] In one patient the response was initially slight, but became dramatic when azathioprine was added. Prednisone was given in initial single daily doses of 40 to 150 mg, until definite clinical improvement was obtained, and followed by a single-dose alternate-day regimen. Corticosteroids are generally considered to be of little use in Guillain-Barré syndrome (see under Musculoskeletal and Nerve Disorders, p. 2406.1), which usually occurs due to an acute inflammatory polyradiculoneuropathy. In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), corticosteroids are reported to be beneficial,[1,2] although a review[2] found weak evidence to support this. Subacute demyelinating neuropathy appeared to be a distinct and clinically identifiable entity in which corticosteroid therapy is indicated.[1]

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Postoperative ocular inflammation

Corticosteroid eye drops are used to control the inflammatory response commonly seen after cataract surgery; prednisolone is usually used but dexamethasone may be necessary if the inflammation is severe.

Corticosteroids should only be used with care and for short periods for topical control of postoperative ocular inflammation, as discussed on p. 103.3.

Pregnancy

Although some adverse effects have been recorded and certain precautions need to be observed, the use of corticosteroids during pregnancy (see under Precautions, p. 1619.1) is appropriate to promote fetal maturation where there is a risk of premature delivery (see Neonatal Respiratory Distress Syndrome, p. 1608.3). In addition, in those maternal conditions serious enough to require systemic corticosteroids the risk to both mother and offspring of discontinuing therapy is often greater than that of corticosteroid use during pregnancy.

Psoriasis

The management of psoriasis is described on p. 1688.1 where topical corticosteroids are mentioned among first-line treatments. Combination therapy using corticosteroids with other topical treatments, such as calcipotriol or tazarotene, may be used to reduce adverse effects and improve efficacy of both drugs.[1]

Intralesional injection of corticosteroids has been used for small, localised, recalcitrant plaques of psoriasis but caution is required to avoid skin atrophy or depigmentation.[2] Systemic corticosteroids are not generally recommended, but have been used for short periods in extreme or rare cases; there is a risk of systemic adverse effects and of rebound psoriasis occurring on stopping therapy.

Topical corticosteroids remain the mainstay of treatment in scalp psoriasis, although long-term treatment is not recommended; the more potent corticosteroids are reserved for adult use.[3]

1. Trozak DJ. Topical corticosteroid therapy in psoriasis vulgaris: update and new strategies. *Cutis* 1999; **64:** 315–18.
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Pyoderma gangrenosum

A systemic corticosteroid is one of the treatments that is usually tried in pyoderma gangrenosum (p. 1688.3). High-dose oral treatment or intravenous pulse therapy may be needed initially to induce remission.[1,2] Response is usually rapid, but maintenance doses vary considerably. Healing of superficial granulomatous pyoderma has occurred after intralesional injection of triamcinolone,[3,4] oral doses of prednisolone,[3,4] and after long-term topical corticosteroids.[4]

1. Reichrath J, *et al*. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53:** 273–83.
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Respiratory disorders

Although corticosteroids have been used in the management of many forms of respiratory disorder, this use has frequently been on an empirical and uncontrolled basis, and evidence of benefit is often somewhat mixed. Thus, while an established role exists for corticosteroids in the management of asthma (p. 1600.3), the antenatal prevention of neonatal respiratory distress syndrome (p. 1608.3), and probably in croup (p. 1603.3) they are no longer used in aspiration syndromes (p. 1804.2) and their role in interstitial lung disorders (see p. 1607.1 and under Sarcoidosis, p. 1612.2) and in acute respiratory distress syndrome (p. 1599.3) is uncertain. Other disorders in which they have been tried with varying success include bronchiolitis (p. 1601.3), chronic obstructive pulmonary disease (p. 1603.1), fat embolism syndrome,[1] acute eosinophilic pneumonia[2] and pulmonary eosinophilia,[3] diffuse alveolar haemorrhage,[4] and 'ice hockey lung' (due to nitrogen dioxide).[5]

1. Van Besouw J-P, Hinds CJ. Fat embolism syndrome. *Br J Hosp Med* 1989; **42:** 304–11.
2. Anonymous. Acute eosinophilic pneumonia. *Lancet* 1990; **335:** 947.
3. Anonymous. Pulmonary eosinophilia. *Lancet* 1990; **335:** 512.
4. Metcalf JP, *et al*. Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. *Am J Med* 1994; **96:** 327–34.
5. Anonymous. Ice hockey lung: NO_2 poisoning. *Lancet* 1990; **335:** 1191.

Retinal vasculitis

Inflammation of the retinal blood vessels (retinal vasculitis) usually occurs as a feature of ocular disorders such as Eales disease; systemic inflammatory conditions such as Behçet's disease (p. 1601.1), sarcoidosis (p. 1612.2), and multiple sclerosis (p. 996.3); or infections such as herpes (p. 955.2), tuberculosis (p. 210.2), syphilis (p. 205.2), and toxoplasmosis (p. 924.2). Vascular sheathing, occlusion, macular oedema, and retinal haemorrhage can occur, and symptoms of retinal vasculitis include painless loss of vision, blurred vision, floaters, and scotoma.[1,2]

In the treatment of non-infectious retinal vasculitis, corticosteroids are used to control inflammation and prevent long-term vision loss. Local treatment by periocular injection may be used in unilateral disease or moderate inflammation; improvement usually occurs in 2 to 3 weeks and may last for up to 3 months. Oral corticosteroids may be required for moderate to severe bilateral disease with a marked reduction in visual acuity, and improvement may take 3 to 4 weeks to appear.[1] Other immunosuppressants may be needed for vasculitis that is unresponsive or inadequately controlled by corticosteroids, and may be used for their corticosteroid-sparing effect when long-term therapy is required. Azathioprine and ciclosporin are most

commonly used, but cyclophosphamide, methotrexate, and mycophenolate have also been tried.[1,2] Appropriate anti-infective therapy can clear retinal vasculitis associated with infection, but corticosteroids may be needed where there is residual vasculitis.[1]

1. Walton RC, Ashmore ED. Retinal vasculitis. *Curr Opin Ophthalmol* 2003; **14:** 413–19.
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Retroperitoneal fibrosis

Retroperitoneal fibrosis[1-4] is a rare disease that is idiopathic in most cases, but may be secondary to other causes, such as malignancy, infection, retroperitoneal injury, or as an adverse effect of a drug. Fibrosis and inflammation develop in the retroperitoneum resulting in a peri-aortic mass; organ involvement can cause urinary-tract obstruction, bowel dysfunction, and venous compression. Most patients present with dull, poorly localised pain in the back, flank, or abdomen. Physical manifestations include hypertension, lower extremity oedema, and venous thromboembolism.

Treatment involves removal of any external cause, preservation of renal function, and suppression of the inflammatory process. Surgery is used to confirm diagnosis and also to relieve cases with severe ureteral obstruction.

Corticosteroids are the mainstay of medical therapy, although the optimal dose and duration remain to be established. Typical regimens start with a high initial dose of prednisone or prednisolone (40 to 60 mg daily) which is then gradually tapered over 2 to 3 months to a maintenance dose of 5 to 10 mg daily, and then stopped after 1 to 2 years.[1-4] Disease relapse is common after stopping corticosteroids.[1]

Immunosuppressive drugs have been used either in unresponsive cases, or as part of a corticosteroid-sparing regimen;[1,2] while no controlled studies have been done, there are anecdotal reports of efficacy using azathioprine, ciclosporin, cyclophosphamide, methotrexate, and mycophenolate mofetil.[1-4] Colchicine with a low- to moderate-dose corticosteroid for a prolonged period has been reported to be of benefit.[4] Tamoxifen monotherapy has also been reported to be effective, although results have been mixed.[1] While some have stated that its place in therapy has yet to be defined,[1,2] others consider reports of benefit to be convincing and that it is a relatively safe choice.[4] Despite a lack of data, some have advocated that the use of imatinib or rituximab be considered when other treatments have failed or prove problematic.[4]

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Rheumatoid arthritis

Systemic corticosteroids can play an important role in the management of juvenile idiopathic arthritis (p. 12.1); they may be given by intra-articular injection in oligoarthritis, and to control disease flares, or systemically in more widespread and severe disease.

Similarly, in adult rheumatoid arthritis (p. 13.2). corticosteroids may be added to DMARD therapy to control synovitis or provide cover when changing therapies, since they provide rapid symptomatic control. They have been shown to reduce the development of joint erosions, and in the short-term this beneficial effect outweighs their adverse effects on bone. Short- to moderate-term use of systemic corticosteroids (in doses not exceeding the equivalent of 15 mg of prednisolone daily) is therefore considered valuable. However, their adverse effects mean that longer term use cannot be justified. Intra-articular injection is recommended for acute disease flares, particularly when combined with aggressive DMARD therapy.

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Rhinitis

For a brief description of rhinitis and a discussion of its management including the use of corticosteroids, see p. 612.1. Reviews[1,2] including a systematic review,[1] found that intranasal corticosteroids produced greater relief of the nasal symptoms of allergic rhinitis than oral antihistamines, and there was no difference between the two treatments in relief of eye symptoms. Commonly used nasal sprays appear to have similar efficacy and adverse effect profiles,[3] and choice of therapy is probably influenced by other factors including cost[3] and patient preference.[4]

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Sarcoidosis

Sarcoidosis is a disorder involving the development of multiple granulomas in a variety of organs, which may subsequently resolve or progress to chronic fibrosis.[1] The disease is frequently asymptomatic, and since it usually regresses spontaneously estimating the incidence is difficult, but it appears to vary considerably in different countries. It is most often seen in young adults and is slightly more common in female than male and in black than white patients.

Almost any organ can be affected, but manifestations in lymph nodes, lungs, skin, joints, and eyes are common. Lymphadenopathy, some decrease in pulmonary function, dyspnoea, and cough may mark lung and lymph node involvement. Skin manifestations include erythema nodosum, macular or papular lesions due to granuloma formation in the skin, and violaceous plaques on fingers, nose, ears, and cheeks known as lupus pernio. Arthropathy, with painful joint swellings, may be associated with erythema nodosum and fever in acute presentations; bone lesions are most common in fingers and toes. Involvement of the nervous system may be particularly difficult to diagnose because of its protean manifestations. Involvement of the eyes is usually manifest as uveitis although other symptoms include keratoconjunctivitis sicca. Symptomatic disease involving the gastrointestinal tract, liver, pancreas, heart, or kidneys is rare, although asymptomatic involvement may occur.

In addition to symptoms directly due to the disease, sarcoidosis is often associated with hypercalcaemia (p. 1776.1) and hypersensitivity to the effects of vitamin D. Other biochemical abnormalities include raised serum concentrations of angiotensin-converting enzyme (ACE), and there are abnormalities of some aspects of immune function.

Diagnosis of sarcoidosis is problematic because of its multiple manifestations and the fact that it is so often clinically silent. It is often detected by accident, when radiography is performed for other reasons, but biopsy is often needed to help confirm the disease. The Kveim test, in which an antigen derived from patients with sarcoidosis (see p. 2538.3) is given intradermally and produces a delayed reaction in patients with the disease, is now rarely used because of its perceived lack of precision, although some still consider it useful.[2]

Treatment. Asymptomatic disease requires no therapy, and since spontaneous remission can occur, corticosteroids, which are the usual therapy,[1,3] are generally reserved for patients in whom the disease affects the function of a vital organ or for patients with hypercalcaemia. NSAIDs alone may be adequate to control the fever and arthropathy of acute disease. Where corticosteroids are called for a typical oral regimen is prednisolone or prednisone 30 to 40 mg daily, the dose being reduced after several weeks as the patient improves.[3-6] Therapy should be continued (at the minimum effective maintenance dose) for 6 to 24 months before any attempt is made to withdraw it.[3] Alternate-day dosage has been suggested, with 40 mg every other day as initial therapy,[7] and 5 to 10 mg every other day as maintenance.[8] There is some evidence[9] that relapse may be more likely after withdrawal of corticosteroids than in patients who do not receive corticosteroid therapy, but this may simply reflect the natural course of disease in this group. Higher initial doses of 60 to 80 mg daily of prednisone are generally used in cardiac sarcoidosis, although controversy exists as to the clinical efficacy and optimal dose and duration of corticosteroids. Treatment halts progression and improves survival, but it does not reduce the incidence of ventricular arrhythmias.[10] In pulmonary disease, oral corticosteroids can have beneficial effects on symptoms, chest X-ray, and spirometry results in the short term (up to about 2 years) and may be used in patients with progressive disease or significant symptoms. However, there is little evidence of improved lung function and the long-term effects on disease progression are uncertain.[3,11] Inhaled corticosteroids have also been investigated for both initial and maintenance therapy in pulmonary sarcoidosis; they are not considered to be of significant benefit, although they may have a role in symptomatic relief of cough in a subgroup of patients.[3] In patients with ocular disease corticosteroid drops and ointment are used for anterior uveitis; resistant cases, or patients with posterior uveitis, require systemic corticosteroids.[1] Skin lesions usually respond to corticosteroids but the high doses that may be required for suppression of lupus pernio may produce changes in appearance as disfiguring as the disease.[4]

Other drugs have occasionally been used in sarcoidosis but are very much second-line. In patients in whom corticosteroids are not effective or not tolerated cytotoxic immunosuppressants have been given, with variable results.[1,3,4,6,8] Methotrexate has perhaps been most useful, having been found to be effective in low oral doses (up to 15 mg weekly) in refractory disease;[1,3,12] corticosteroid-sparing effects may be evident after 6 months.[8] Azathioprine has been used for severe refractory cases.[6] Results with ciclosporin have been variable,[8] although there are reports of response in refractory skin lesions and optic neuropathy.[1] Toxicity and concerns about carcinogenesis limit the use of chlorambucil and cyclophosphamide.[1,6] The antimalarials have also been tried as adjuncts or alternatives to corticosteroid therapy,[6] and may be useful for skin disease and hypercalcaemia.[8] Potential ocular toxicity is a concern, however, and although hydroxychloroquine may be less oculotoxic than chloroquine,[8] regular ophthalmological assessment is recommended.[6] Other reports of benefit in cutaneous sarcoidosis have involved allopurinol,[13] thalidomide,[14] and tranilast,[15] while there is report of response to melatonin in 2 patients with refractory sarcoidosis.[16] Infliximab and pentoxifylline have also shown promising results.[8]

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11. Paramothayan NS, *et al*. Corticosteroids for pulmonary sarcoidosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 12/07/05).
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16. Cagnoni ML, *et al*. Melatonin for treatment of chronic refractory sarcoidosis. *Lancet* 1995; **346:** 1229–30.

Sciatica

For mention of the use of epidural corticosteroid injections to treat sciatica, and doubts about the extent of benefit, see Administration, Epidural Route, p. 1598.3.

Scleritis

Scleritis and episcleritis are inflammatory diseases of the sclera often associated with various systemic diseases. Episcleritis tends to be a benign superficial condition but treatment can be difficult and it tends to recur. The use of topical corticosteroids and topical NSAIDs are sometimes of temporary benefit. Scleritis is a rarer more deep-seated inflammation. Initial treatment of non-necrotising scleritis is with NSAIDs; high dose systemic corticosteroids (usually oral prednisone or prednisolone 60 to 80 mg daily) have been used successfully in many patients unresponsive to NSAIDs.[1,2] If necessary, to reduce any attendant adverse effects, corticosteroids have been given by orbital floor injection (methylprednisolone acetate 40 mg)[1] or at a reduced systemic dosage with an additional immunosuppressant such as ciclosporin, methotrexate, cyclophosphamide, or azathioprine.[3] Immunosuppressants may also be of value alone in severe or unresponsive disease.[4] It has been suggested that immunosuppressant therapy should be the initial choice in necrotising scleritis, as therapeutic failure is very common with less aggressive regimens.[4]

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Scleroderma

Corticosteroids may be useful for the management of scleroderma (p. 1938.3), but must be used with care because of the risk of exacerbating renal and other problems.

Seborrhoeic dermatitis

Topical corticosteroids are used with an imidazole antifungal in the management of seborrhoeic dermatitis (p. 1689.1).

Septic shock

The role of corticosteroids in septic shock (see under Septicaemia, p. 203.2) has been controversial. Early studies reported both beneficial[1] and detrimental[2] effects, but corticosteroids were considered ineffective[2,3] and likely to worsen secondary infection.[4-6] More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who have adrenal insufficiency.[7] However, their routine use in septic shock is not recommended[8] and a systematic review[9] concluded that short-course high-dose corticosteroids did not alter mortality rates in severe sepsis and septic shock, and that current evidence did not support their use. However, meta-analyses and reviews[9-11] suggest that longer courses (5 to 11 days) of low-dose corticosteroids might reduce mortality, especially in those with vasopressor-dependent septic shock.

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Sickle-cell disease

A study[1] has suggested that a short course of high-dose methylprednisolone might be a useful adjunct in controlling pain in sickle-cell crisis (p. 11.1). However, the use of corticosteroids in sickle-cell disease is problematic; apart from the usual adverse effects, including the risk of exacerbating underlying infection, corticosteroid therapy has been reported to provoke sickle-cell crisis in patients with sickle C disease—see under Precautions, p. 1619.2.

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Skin disorders

For some guidelines to the use of topical application of corticosteroids in skin disorders, see under Administration, p. 1599.2. For discussion of the use of corticosteroids in individual skin disorders see under the relevant headings in this section.

Soft-tissue rheumatism

Soft-tissue rheumatism (p. 14.2) includes several conditions affecting tendons, ligaments, muscles, fascia, and joint capsules; some lesions may respond to local injections of corticosteroid, often given with a local anaesthetic. In the treatment of shoulder pain, intra-articular injection of triamcinolone acetonide was considered to be superior to physiotherapy for reducing pain in the short-term.[1] Injection of corticosteroids below the point where the clavicle joins the shoulder blade (subacromial injection) may be superior to placebo for rotator cuff disease, as may intra-articular injection for adhesive capsulitis.[2] One meta-analysis[3] found that subacromial injection produced dose dependent benefit for up to 9 months in shoulder pain associated with rotator cuff tendinitis, with a number-needed-to-treat of between 1.4 and 2.2; there was some evidence that higher doses (50 mg equivalent of prednisone or greater) were more effective. However, there has been concern over accuracy of needle placement, and the scanty evidence to guide treatment.[2,4] There is also limited evidence that oral corticosteroids may produce improvement in pain and mobility in patients with adhesive capsulitis (frozen shoulder), but this improvement may not last beyond 6 weeks.[5] In lateral epicondylitis (tennis elbow), local injections of triamcinolone acetonide with local anaesthetic improved short-term outcomes such as pain and disability, although long-term results favoured physiotherapy.[6] Another study found that short-term benefit with corticosteroid injection for epicondylitis was paradoxically reversed after 6 weeks, implying the need for caution.[7] Evidence appears to support the use of corticosteroids such as betamethasone and methylprednisolone, with local anaesthetic, in trigger finger.[4] In contrast, no benefit has been found in Achilles' tendinopathy.[4] In carpal tunnel syndrome, injection of corticosteroids produces short term benefit but has not been shown to produce better results than other treatments such as splinting in the longer term.[8] Concerns have been expressed about the lack of good studies to support the use of corticosteroids,[2,4] and some have suggested that in tendinopathies, they be reserved for chronic injuries, and that short- or moderate-acting, soluble preparations be used.[4] Tendon rupture after local corticosteroid injection may occur.[4]

See also Administration, Intra-articular Route, p. 1598.3

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Spinal cord and head injury

Spinal cord injury usually causes significant disability arising from either partial or total paralysis. The degree of disability and organ dysfunction is determined by the spinal level of the injury, and whether severance of the cord is complete or not. Patients with lesions at the level of the fourth cervical vertebra and above will almost certainly have respiratory problems or diaphragm paralysis, requiring ventilation. Spinal shock occurs almost invariably, resulting in hypotension and reduced renal perfusion, which may cause renal failure. Patients are also at risk for acute respiratory distress syndrome (p. 1599.3) and thromboembolism (p. 1273.2). Lesions above the fifth thoracic vertebra may cause autonomic dysreflexia which results in a potentially life-threatening rise in blood pressure, requiring the use of antihypertensives.[1]

Neural tissue in the spinal cord cannot regenerate and damage is considered permanent; however, some lessening of disability is possible with rehabilitation. One of the main aims in the management of spinal cord injuries is to minimise secondary damage from hypoxia, hypoperfusion and inflammation. Results of a multicentre placebo-controlled study in the USA[2] indicated that high-dose intravenous corticosteroids resulted in improvements in neurological function if given within 8 hours of spinal cord injury. Methylprednisolone was given in an initial dose of 30 mg/kg followed by 5.4 mg/kg per hour for 23 hours. A subsequent study found that although this regimen was adequate if begun within 3 hours of injury, better results were obtained by continuing methylprednisolone for 48 hours in patients in whom therapy commenced 3 to 8 hours after injury.[3,4] The lazaroid tirilazad, given for 48 hours, had some benefit in this study, although it was less effective than 48 hours of treatment with methylprednisolone in the doses used. In contrast, a systematic review found that high-dose methylprednisolone did not improve neurological function in patients, and might potentially have a deleterious effect.[5] Another review failed to find any benefit from the use of gangliosides.[6]

The longer-term management of spinal cord injuries has been reviewed.[7]

Management of traumatic head injury poses similar problems and risks to those of spinal cord trauma. The effects of corticosteroids on mortality in acute traumatic head injury had been unclear, until an international randomised study in 10 008 adults found that the risk of death from all causes within 2 weeks[8] or 6 months[9] of significant head injury was higher in the group given methylprednisolone compared with placebo. There is little evidence that tirilazad is of any value in acute traumatic brain injury,[10,11] nor for other interventions that have been suggested for this, including barbiturates,[12] calcium-channel blockers such as nimodipine (other than perhaps in a subgroup of patients with subarachnoid haemorrhage—see also p. 1455.3),[13] central stimulants such as methylphenidate or the amfetamines,[14] inhibitors of glutamate neurotransmission,[15] or hyperventilation or hyperbaric oxygen therapy.[16,17] Progesterone is under investigation.[18,19] Mannitol is widely used after severe head injury to reduce intracranial pressure (p. 1271.3), but evidence from randomised studies is limited and it is unclear whether mannitol therapy has any effect on death or disability.[20]

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Spondyloarthropathies

Intra-articular injections of corticosteroids have been given in ankylosing spondylitis (see Spondyloarthropathies, p. 14.3).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an auto-immune disease of complex aetiology characterised by autoantibodies that participate in the mediation of tissue damage affecting joints, skin, kidney, CNS, and other organs. It is far more common in women than in men, the evidence suggesting that male hormones have a protective effect, and peak onset is usually in women in their 20s and 30s.

The commonest symptom in patients with SLE is arthralgia or arthritis; fatigue, fever, weight loss, rashes (characteristically a so-called 'butterfly rash' on the cheeks and bridge of the nose), CNS involvement including personality changes, anaemia, nephritis, and pulmonary symptoms (notably pleurisy) are also frequent, while other symptoms include myalgia, alopecia, Raynaud's syndrome, convulsions, coma, stroke, pneumonitis, pericarditis, myocarditis with tachycardia, leucopenia, thrombocytopenia, coagulation disorders (both thrombosis and haemorrhage), hepatomegaly, splenomegaly, and lymphadenopathy. Thrombotic symptoms and recurrent miscarriage may represent an 'antiphospholipid antibody syndrome'

due to antibodies against phospholipids, which occurs in about a third of all patients with SLE but may also occur independently.[1,2]

Management. SLE is characterised by exacerbation and remission so individualised management with careful monitoring and appropriate and timely symptomatic treatment is required. Treatment is largely empirical and there have been few controlled studies.

In addition to any specific treatment, patients require emotional support, extensive rest, and avoidance where possible of stimuli that may provoke disease exacerbation, including ultraviolet light, certain drugs or foods rich in psoralens, infections, and psychological stress.

Mild disease may require no treatment, or may be managed simply with NSAIDs for muscular and joint symptoms.[3] In more severe, but non-life-threatening disease chloroquine or, more often, hydroxychloroquine is effective, particularly for cutaneous and joint manifestations,[4-6] although disease flare may occur on withdrawal.[7] Retinoids such as acitretin have also been shown to be of use in some patients.[8]

Many patients require treatment with corticosteroids at some point, although in such patients they can be a major cause of morbidity.[6,9] It is usual to use a corticosteroid when treatment with NSAIDs or antimalarials has failed, or when life or vital organs are threatened.[3] They are usually given in high doses (1 mg/kg or more of prednisone or prednisolone daily, sometimes preceded by a course of intravenous methylprednisolone)[3] for life-threatening manifestations such as high fever, severe thrombocytopenia, coma, seizures, or involvement of a major organ such as the kidney (see also Lupus Nephritis, below). Non-life-threatening symptoms that fail to respond to other measures will usually respond to lower corticosteroid doses (not more than 500 micrograms/kg daily of prednisolone or prednisone).[3] Once a response is achieved the dose should be tapered to the lowest required to control symptoms, sometimes in the form of alternate-day dosage, although disease may relapse.[3] Complete withdrawal is optimal, although some patients may need long-term maintenance on about 5 mg daily.[3] One study found that raising the maintenance corticosteroid dose temporarily to counteract any increases in the concentration of antibodies to double-stranded DNA may reduce the number of relapses,[10] but the design and conclusions of this study are open to criticism.

Prolonged corticosteroid therapy, particularly at the higher doses, is associated with adverse effects such as aseptic bone necrosis and an increased susceptibility to infection, and other drugs have been added to corticosteroid therapy in an attempt to lower the corticosteroid dose but maintain disease control. In particular the immunosuppressant azathioprine has been used for its corticosteroid-sparing effect.[3] Oral or intravenous pulse cyclophosphamide has been used with some success to treat severe organ involvement although toxicity may be of concern.[3,6] Low-dose weekly methotrexate may also be helpful in patients with cutaneous or joint involvement.[11] Leflunomide and tacrolimus are sometimes used in patients who are intolerant or resistant to other immunosuppressants,[6] and belimumab appears to be of benefit.[12] The antimalarials may also be combined with corticosteroid therapy, and in addition to a corticosteroid-sparing effect there is a suggestion that hydroxychloroquine may counter the adverse effects of corticosteroids on serum-lipid profiles.[3,13] Prasterone is under investigation for the treatment of severe disease.[14] Thalidomide has been investigated for treating cutaneous manifestations of SLE.[15] Remission has been reported in a few patients with refractory disease given rituximab.[5]

Thrombotic symptoms due to antiphospholipid antibodies require adequate long-term anticoagulation with warfarin or low-dose aspirin, and it should be borne in mind that stroke and related CNS symptoms will not respond to corticosteroids. In patients with other severe CNS symptoms that fail to respond to corticosteroids intravenous cyclophosphamide may be helpful,[16,17] but response is unpredictable. Intravenous immunoglobulin has been used as an adjunct in CNS lupus,[5] although its role is unclear; it may also be used in the management of thrombocytopenic symptoms.[18]

In patients with severe and potentially fatal symptoms plasma exchange may provide temporary benefit by removing circulating antibodies.

Lupus nephritis. Renal disease is probably the best studied symptom of SLE. Almost all patients develop some renal involvement,[19] with clinical nephritis in up to 50%.[20,21] Usual manifestations of renal disease include hypertension, oedema, proteinuria or frank nephrotic syndrome, and oliguria; more severe disease is usually associated with focal or diffuse proliferative glomerulonephritis on biopsy.[20,21]

Patients with active disease (worsening renal function, proteinuria, and urinary sediment) require aggressive treatment to prevent irreversible renal damage. It is generally accepted that the use of a cytotoxic immunosuppressant with a corticosteroid is more effective than the use of corticosteroids alone in controlling nephritis and the risk of end-stage renal failure,[19,20] although corticosteroids alone may be used for less severe disease.[18]

One suggested outline for treatment in severe active disease is to begin with pulsed intravenous methylprednisolone as 3 doses of 1g daily, or prednisone or prednisolone orally (initially 0.5 to 1 mg/kg daily, gradually reduced) accompanied if necessary by cyclophosphamide or azathioprine.[21] An alternative approach is to begin therapy with intermittent intravenous cyclophosphamide,[22] which appears to be more effective than pulsed methylprednisolone[23,24] and then to maintain patients with low-dose oral prednisone plus pulsed intravenous cyclophosphamide. Azathioprine may be a useful alternative for patients who cannot tolerate cyclophosphamide;[20,21] it may be used as maintenance after cyclophosphamide induction in an attempt to reduce toxicity.[19,21] Ciclosporin has also been investigated, with preliminary results suggestive of benefit,[25,26] but has been viewed with caution because of its nephrotoxicity.[20,21] Mycophenolate mofetil has shown promising results;[27,28] some suggest it may come to replace cyclophosphamide.[5] Other drugs that have been reported to be of benefit include intravenous immunoglobulins,[20] cladribine, and fludarabine.[19] Autologous haematopoietic stem-cell transplantation (p. 1933.1) is considered feasible in SLE.[20,29]

Pregnancy. Although symptoms of SLE do not appear to be exacerbated in most patients during pregnancy,[30,31] it is considered advisable that pregnancy be deferred until the disease is in remission or controlled by therapy, since complications are more likely in active disease.[15,30] Cyclophosphamide or methotrexate are contra-indicated in pregnancy because of the risk of teratogenesis but corticosteroids, azathioprine, and hydroxychloroquine may be used if necessary:[3,4,6,32] the risks of miscarriage, still-birth, growth retardation, or preterm delivery due to the disease are considered greater than the risks to the fetus of continued therapy. The use of low-dose aspirin (75 mg daily) has been recommended in women with renal involvement or a history of pre-eclampsia or fetal growth retardation;[32] in women with antiphospholipid antibodies, low-dose aspirin with subcutaneous heparin or low-molecular-weight heparin markedly improves the live-birth rate.[1,2,15,33] The use of high-dose prednisone, with or without aspirin, to suppress antiphospholipid antibodies, while reportedly effective in some women with bad obstetric histories,[34,35] has been found by others to be of no benefit,[36] and is associated with unacceptable maternal morbidity.[37] Warfarin prophylaxis, which appears effective in other patients with the antiphospholipid antibody syndrome,[38] is unsuited to pregnant women because of the teratogenic effects of warfarin.[39]

Postpartum exacerbation is well recognised,[30,32] and some workers favour prophylactic corticosteroid cover during the puerperium. A small proportion of neonates born to mothers with lupus have a neonatal lupus syndrome,[40] manifesting most seriously as heart block which may require a permanent pacemaker.

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Takayasu's arteritis

Takayasu's arteritis is a vasculitis of the aorta and its branches seen particularly in young women and in Oriental patients. It is characterised by vasculitis followed by fibrosis, leading to stenosis or occlusion of the vessel. Symptoms vary depending on the anatomical site, but include constitutional symptoms such as fever, malaise, and arthralgia, syncope, dyspnoea, palpitations, loss of pulses, intermittent claudication, and visual disturbances.

Active inflammatory disease may respond to corticosteroids: doses of 1 mg/kg daily of prednisone or prednisolone, tapered after one month in patients who respond, have been suggested.[1,2] In patients who do not respond, azathioprine, cyclophosphamide, or methotrexate have been added, although opinions vary as to the necessity of cytotoxic agents in these patients.[1-3] Ciclosporin[4] and mycophenolate mofetil[5] have also been used. A preliminary report[6] suggests that the use of etanercept or infliximab to inhibit the actions of tumour necrosis factor may be useful in patients who are refractory to other treatments. Widely varying estimates of mortality and aggressiveness exist for Takayasu's arteritis, and in the absence of large controlled studies it is difficult to assess the benefits of drug therapy. The course may be very prolonged, and minimising the maintenance dosage (e.g. by alternate-day corticosteroid therapy) is important to avoid adverse effects.[7]

Surgical reconstruction of affected vessels has been carried out in patients at risk of ischaemic compromise.[8] Angioplasty has been tried.

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Tuberculosis

The use of corticosteroids in tuberculosis (p. 210.2) is controversial. They should never be given to patients with active disease without protective chemotherapy cover, and must be used with caution in patients with dormant disease as it may be reactivated. Use of corticosteroids in pulmonary tuberculosis is to be avoided except in life-threatening disease. WHO suggests that corticosteroids may be useful adjuvants to antituberculous therapy in selected conditions including tuberculous meningitis, pericarditis, pleural effusion, or laryngitis, or tuberculosis of the renal tract, adrenocortical insufficiency due to adrenal gland tuber-

culosis, massive lymph node enlargement, or to control drug hypersensitivity. They are also likely to be of benefit in patients with HIV infection and the above conditions.[1] Similar recommendations have been made by NICE[2] and the CDC[3] with regard to tuberculous meningitis and pericarditis. However, systematic reviews of tuberculous pleurisy[4] and pericarditis[5] have concluded that there is insufficient evidence to support the use of corticosteroids in these conditions.

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Urticaria and angioedema

Oral antihistamines are the mainstay of treatment for urticaria (p. 1689.2). Severe attacks refractory to standard therapy may require a short course of oral corticosteroid therapy.

When angioedema affecting the larynx (laryngeal oedema) is present, the patients should be treated with adrenaline as an allergic emergency (see Anaphylaxis and Anaphylactic Shock, p. 1293.2).

Uveitis

Uveitis is inflammation of the uveal tract of the eye, which comprises the choroid, ciliary body, and the iris. It is usually idiopathic but may be secondary to infection, allergy, or inflammatory disorders with an auto-immune component.

In anterior uveitis, also referred to as iridocyclitis, there is inflammation of the iris (iritis) and the ciliary body (cyclitis). It tends to be acute and self-limiting and is likely to be associated with infection. The iris becomes spongy and hyperaemic and exudates may result in adhesions between the iris and the lens (posterior synechiae). Chronic anterior uveitis is associated with formation of cataracts and glaucoma. Posterior uveitis can be acute or chronic and may just affect the choroid (choroiditis) or may also involve the retina (chorioretinitis). It is more likely to be an auto-immune condition.

The treatment of uveitis has been reviewed.[1-4]

Corticosteroids given topically and, when necessary, systemically are the mainstay of treatment for acute anterior uveitis.[5] Cycloplegics and mydriatics such as atropine, cyclopentolate, and homatropine are used adjunctively to rest the ciliary body and iris, diminish hyperaemia, and to prevent the formation of posterior synechiae. Antibacterials should be used to treat any infection. In children with chronic anterior uveitis associated with juvenile idiopathic arthritis, corticosteroids are supplemented with chronic use of an oral NSAID if inflammation persists after 90 days of treatment and attempted corticosteroid withdrawal.[6] In the 30% or so of cases that do not respond to corticosteroids and NSAIDs, low-dose weekly methotrexate (with folic acid supplements daily) is advocated, with other immunosuppressants being substituted or used adjunctively when methotrexate fails or is not tolerated.

Treatment of posterior uveitis is less satisfactory than that of acute anterior uveitis since gross damage to the retina often occurs before the condition can be controlled. Corticosteroids are usually required given either as periocular injections or as high-dose systemic therapy.[5] A suggested protocol[2] involves the use of high-dose systemic corticosteroids to control active disease; long-term control is then maintained mainly with low-dose ciclosporin, corticosteroids being tapered to a low dose or eventually withdrawn. Certain patients may require an additional immunosuppressant, usually azathioprine, although methotrexate, cyclophosphamide, ciclosporin, or chlorambucil may be considered. Other immunosuppressants being studied include tacrolimus, and there are reports of improvement with mycophenolate mofetil.[4,5]

Visual impairment in chronic uveitis is often the result of macular oedema and is not necessarily prevented by immunosuppressants. Short-term treatment with acetazolamide is considered to have produced some encouraging results in reducing chronic uveitic macular oedema but its long-term efficacy or efficacy with low-dose corticosteroids remains to be determined.[7] Although systemic and topical NSAIDs have been shown to reduce cystoid macular oedema in post cataract extraction (see Postoperative Inflammatory Ocular Disorders, p. 103.3) their role in the treatment of macular oedema associated with uveitis is less clear.

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Vasculitic syndromes

Vasculitis may be defined as inflammation of the blood vessel wall, and the term has been applied in describing a wide range of diseases involving blood vessels of various sizes and types. Vasculitis may occur as part of a systemic disease such as rheumatoid arthritis or SLE, or may itself be the primary disorder, and symptoms may vary from superficial cutaneous disease, with purpura and urticaria, to progressive and fatal systemic vasculitides such as Wegener's granulomatosis. In some forms of vasculitis, such as giant cell arteritis, mononuclear giant cells may be seen, while in granulomatous vasculitis the mononuclear cells form granulomata adjacent to the damaged vessel wall. Necrotising vasculitis is used to describe inflammation associated with necrosis of the media, the middle part of the vessel wall, while polyarteritis implies inflammation of the full thickness of an arterial wall.

Because of the heterogeneous nature of this group of diseases and the degree of overlap which exists between some of them, and between them and other diseases, classification has been difficult. Classification has often been based on the size of the affected vessel, as well as the presence or absence of granulomata and antineutrophil cytoplasmic antibodies (ANCA), and whether the vasculitis is primary or secondary. Of the major primary vasculitic syndromes, giant cell arteritis (p. 1604.2) and Takayasu's arteritis (p. 1614.3) are examples of large vessel disease; classic polyarteritis nodosa (p. 1610.2) affects medium-sized vessels; Churg-Strauss syndrome (p. 1603.1), microscopic polyangiitis (p. 1610.2), and Wegener's granulomatosis (below) are diseases of small or medium-sized vessels; the so-called 'hypersensitivity vasculitides' (p. 1606.1), including Henoch-Schönlein purpura, are small vessel diseases, though usually limited in extent.

Treatment depends on the type of vasculitis, its severity, and prognosis. Treatment of the systemic vasculitides has revolved around corticosteroids and cyclophosphamide; other cytotoxic immunosuppressants, normal immunoglobulins, NSAIDs, anticoagulants, dapsone, and colchicine have been tried in various forms of disease.

Vitiligo

Topical corticosteroids are sometimes effective in inducing repigmentation in patients with vitiligo (p. 1687.2 under Pigmentation Disorders).

Wegener's granulomatosis

Wegener's granulomatosis is a form of granulomatous vasculitis that occurs more frequently in men and in white patients. It is characterised by necrotising vasculitis of small arteries and veins, accompanied by granuloma formation, and affecting particularly the respiratory tract and kidneys. It is usually associated with antineutrophil cytoplasmic antibodies (ANCA). Symptoms include rhinorrhoea, sinusitis, cough and dyspnoea (signs of pulmonary infiltration which is seen in the majority of patients at presentation); renal manifestations include haematuria, proteinuria, uraemia, and oedema of the lower limbs due to a focal glomerulonephritis which can progress to crescentic glomerulonephritis and rapidly progressive renal failure. Other organ systems may be involved, with effects similar to those of microscopic polyangiitis (see p. 1610.2). If untreated, the disease is fatal.

Treatment is with a combination regimen based on cyclophosphamide with a corticosteroid. A standard regimen has been low-dose (1 to 2 mg/kg daily) oral cyclophosphamide, with prednisolone or prednisone 1 mg/kg daily by mouth initially, subsequently tapered to an alternate-day regimen and eventually stopped.[1-3] Cyclophosphamide is usually continued for at least a year before considering gradual withdrawal but there is a trend in Europe towards the use of shorter courses of cyclophosphamide.[4] Standard treatment regimens produce improvement or remissions in about 90% of patients.[1,5] Relapses may subsequently occur in about half, and require re-treatment; prompt intensification of treatment when serum ANCA concentrations begin to rise may avert relapse.[6] There is evidence from one controlled study that addition of co-trimoxazole to maintenance regimens reduces the incidence of relapse,[7] although another suggested that it might actually increase the risk of relapse.[8]

Despite the success of regimens based on low-dose oral cyclophosphamide there is considerable concern about their toxicity, particularly since prolonged use may be necessary. Intermittent high-dose intravenous ('pulse') cyclophosphamide has been suggested as an alternative to the oral regimen with fewer adverse effects,[9] but results in practice seem to have been variable.[10,11] Regimens similar to the standard regimen, but substituting azathioprine for cyclophosphamide once remission is achieved (usually after 3 to 6 months) and continuing with low-dose corticosteroids concomitantly have been used.[12] Rituximab plus corticosteroids has been reported to have similar efficacy to cyclophosphamide plus corticosteroids, with some suggestion that rituximab may be more effective in relapsing disease.[13] Other drugs, such as methotrexate, have been tried and addition of low-dose weekly methotrexate to a corticosteroid may be a possible treatment option.[8,14-16] Ciclosporin has been reported to reverse acute renal failure in 2 patients with Wegener's granulomatosis, as well as controlling fulminant symptoms unresponsive to cyclophosphamide and corticosteroids in one of them,[17] but others have found ciclosporin plus a corticosteroid to be ineffective in suppressing disease activity.[18] Etoposide[19] and infliximab[20] have also been successfully used to induce remission in cyclophosphamide-resistant disease, but etanercept has proved ineffective in maintaining remission.[21] Other drugs that have been investigated include high-dose intravenous immunoglobulin[22] and mycophenolate mofetil.[23] While anti-CD4 monoclonal antibodies have proved useful in patients with microscopic polyangiitis, which has some similarities to Wegener's granulomatosis, the role of such investigational regimens remains to be determined.

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Adverse Effects of Corticosteroids and their Treatment

The adverse effects of corticosteroids may result from unwanted mineralocorticoid or glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis.

Mineralocorticoid adverse effects are manifest in the retention of sodium and water, with oedema and hypertension, and in the increased excretion of potassium

with the possibility of hypokalaemic alkalosis. In susceptible patients, cardiac failure may be induced. Disturbances of electrolyte balance are common with the naturally occurring corticosteroids, such as cortisone and hydrocortisone, but are less frequent with many synthetic glucocorticoids, which have little or no mineralocorticoid activity.

Adverse **glucocorticoid** effects lead to mobilisation of calcium and phosphorus, with osteoporosis and spontaneous fractures; muscle wasting and nitrogen depletion; and hyperglycaemia with accentuation or precipitation of the diabetic state. The insulin requirements of diabetic patients are increased. Increased appetite is often reported.

Impaired tissue repair and immune function can lead to delayed wound healing, and increased susceptibility to infection. Increased susceptibility to all kinds of infection, including septicaemia, tuberculosis, fungal infections, and viral infections, has been reported in patients on corticosteroid therapy. Infections may also be masked by the anti-inflammatory, analgesic, and antipyretic effects of glucocorticoids. The increased severity of varicella and measles may lead to a fatal outcome in non-immune patients receiving systemic corticosteroid therapy.

Other adverse effects include menstrual irregularities, amenorrhoea, hyperhidrosis, skin thinning, ocular changes including development of glaucoma and cataract, mental and neurological disturbances, benign intracranial hypertension, acute pancreatitis, and avascular necrosis of bone. An increase in the coagulability of the blood may lead to thromboembolic complications. Peptic ulceration has been reported but reviews of the literature do not always agree that corticosteroids are responsible for an increased incidence.

The negative feedback effects of glucocorticoids on the hypothalamic-pituitary-adrenal (HPA) axis may lead to adrenal atrophy, in some cases after therapy for as little as 7 days. This produces secondary adrenocortical insufficiency, which may become manifest after overly rapid withdrawal of treatment or be precipitated by some stress such as infection or trauma. Patients vary considerably in the degree and duration of adrenal suppression after a given course of corticosteroid, but adrenal atrophy may persist for months or years, and withdrawal should be gradual in those who have been treated for any length of time (see also Withdrawal, p. 1618.1). High doses of corticosteroids given during pregnancy may cause fetal or neonatal adrenal suppression. Although the precise mechanism is uncertain, growth retardation may follow the use of even relatively small doses of corticosteroids in children.

Large doses of corticosteroids, or of corticotropin, may produce Cushingoid symptoms typical of hyperactivity of the adrenal cortex, with moon-face, sometimes with hirsutism, buffalo hump, flushing, increased bruising, ecchymoses, striae, and acne (see also Cushing's Syndrome, p. 2559.1). Giving large intravenous doses of corticosteroids too rapidly may cause cardiovascular collapse.

Hypersensitivity reactions have occurred with corticosteroids, mainly when applied topically.

Adverse effects occur, in general, fairly equally with all systemic corticosteroid preparations and their incidence rises steeply if dosage increases much above physiological values, traditionally considered to be about 7.5 mg daily of prednisolone or its equivalent (see Uses and Administration, p. 1597.3, for equivalent doses of other corticosteroids). Short courses at high dosage for emergencies appear to cause fewer adverse effects than prolonged courses with lower doses.

Most topically applied (including inhaled) corticosteroids may, under certain circumstances, be absorbed in sufficient amounts to produce systemic effects. The topical application of corticosteroid preparations to the eyes has produced corneal ulcers, raised intra-ocular pressure, and reduced visual function. Application of corticosteroids to the skin has led to loss of skin collagen and subcutaneous atrophy; local hypopigmentation of deeply pigmented skins has been reported after both the intradermal injection and topical application of potent corticosteroids. Dryness, irritation, epistaxis, and rarely ulceration or perforation of the nasal septum have followed intranasal use; smell and taste disturbances may also occur. Hoarseness and candidiasis of the mouth or throat may occur in patients receiving inhaled corticosteroids.

Intrathecal dosage (including inadvertent intrathecal dosage after attempted epidural injection) has been associated with arachnoiditis.

Adverse effects should be treated symptomatically, with the corticosteroid dosage reduced or slowly withdrawn where possible.

Reviews.

1. Fardet L, *et al*. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. *Drug Safety* 2007; **30:** 861–81.

Adrenal suppression. The inhibition of hypothalamic-pituitary-adrenocortical function associated with corticosteroid use may persist for a year or more after treatment is withdrawn and may cause acute adrenocortical insufficiency with circulatory collapse during stress. The degree of suppression depends on several factors, including length of treatment, time of day treatment is given, type of corticosteroid preparation used, route, dose used, and dosing interval. In general, suppression of secretion of adrenocorticotrophic hormone and atrophy of the adrenal gland become progressively more definite as doses of corticosteroid exceed physiological amounts (see Uses and Administration, p. 1597.3), and as the duration of therapy increases (significant suppression is likely in patients receiving more than 3 weeks of therapy). It is less when the corticosteroid is given as a single dose in the morning, and even less if this morning dose is given on alternate days or less frequently. In patients taking high enough doses of corticosteroids to suppress the adrenals the dose should be increased during any form of stress (for example, illness or surgery); similarly those treated with such doses within the last 2 or 3 months should be restarted on therapy. Where the interval since treatment is greater than 3 months, resumption of treatment depends on clinical assessment of signs of adrenocortical insufficiency.

To avoid precipitating acute adrenocortical insufficiency, withdrawal of corticosteroid treatment should be carried out gradually, differing regimens being used according to the disease being treated and the duration of therapy. Examples of withdrawal regimens that have been used are described under Withdrawal, p. 1618.1.

Adrenal suppression may occur after very short courses of high-dose therapy and since many patients undergoing such therapy will be under continuing stress when the drugs are stopped, gradual withdrawal of corticosteroids over 5 to 7 days is preferable.

It should also be remembered that corticosteroid-induced adrenal suppression has been associated not only with systemic therapy, but has followed topical application of corticosteroid preparations, particularly those containing potent corticosteroids. Some degree of adrenal suppression is also associated with the use of high dose inhalants and nasal preparations, and has followed the topical application of eye drops and eye ointments.

Effects on the bones and joints. Corticosteroid-induced **avascular necrosis** of bone is an uncommon but disabling complication of therapy.[1-3] The incidence may vary in patients with different disease states; alcoholics, and patients with connective tissue disease (especially SLE) may have increased susceptibility.[3,4] There may be a relationship with corticosteroid dose: even short courses of high-dose corticosteroids may be associated with its development.[1-3] Avascular necrosis has also been associated with topical application of corticosteroids.[5]

Corticosteroids may also produce **osteoporosis.** A review[6] of data obtained from studies published between 1970 and 1990 established that osteoporosis is a common consequence of long-term treatment with corticosteroids, occurring in about 50% of patients. Bone loss is more rapid during the early stages of therapy and is most rapid in areas of the skeleton containing the greatest proportion of trabecular bone such as the spine, hip, distal radius, pelvis, and ribs.

Reviews and guidelines[7-11] on the prevention and management of corticosteroid-induced osteoporosis suggest that the dose should be minimised, as oral doses above 7.5 mg of prednisolone or prednisone (or the equivalent) daily are associated with more significant bone loss and increased fracture risk.[12] Alternate-day therapy, although desirable for its reduced effect on the hypothalamic-pituitary-adrenal axis, does not reduce the risk of bone loss. It should be borne in mind that long-term use of inhaled corticosteroids may also reduce bone mineral density. Patients should maintain an adequate intake of calcium and vitamin D (prophylactic therapy with both has been advocated in all patients starting corticosteroids[13]), should take regular exercise, and avoid smoking and excessive alcohol intake. HRT has been advocated in postmenopausal women but recent re-evaluation of the risks and benefits of HRT may render this option unattractive. Bisphosphonates may be used in high-risk patients as they are effective at preventing and treating corticosteroid-induced bone loss[14] and may reduce fracture rates.[8-10] There is some evidence to suggest that calcitonin has a beneficial effect on bone mass, and it may be considered as an alternative when bisphosphonates cannot be used. Fluoride has been studied in corticosteroid-induced osteoporosis, but although it was found to increase bone density, there is concern about the resultant bone structure and a possible increase in fracture rates. There are reports of benefit from anabolic therapy, but evidence is limited. A thiazide diuretic may be helpful in controlling hypercalciuria in patients not receiving calcitriol.[8] Whether some corticosteroids have reduced effects on the bone is unclear.[9]

There is a risk of **tendinopathies** with the use of corticosteroids, especially of the Achilles and patellar tendons; ruptures have been reported.[15] Most reports have concerned oral or intra-articular use, but there have been occasional cases in patients receiving inhaled or topical corticosteroids.

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15. Blanco I, *et al*. Corticosteroid-associated tendinopathies: an analysis of the published literature and spontaneous pharmacovigilance data. *Drug Safety* 2005; **28:** 633–43.

Effects on carbohydrate and protein metabolism. Corticosteroids produce glucose intolerance[1-4] and protein catabolism.[5,6] A population study found that *oral* corticosteroid therapy may be associated with up to 2% of incident cases of diabetes mellitus in primary care.[7] Although mainly associated with systemic use, there is a report of deterioration in diabetic control associated with high-dose *inhaled* corticosteroid treatment.[8] A study in diabetic patients also found that use of inhaled corticosteroids was associated with increased serum-glucose concentrations in a dose-response manner.[9] The risk of new-onset diabetes mellitus might also be increased with long term use of high-dose *topical* corticosteroids applied to the skin.[10]

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Effects on the cardiovascular system. Adverse effects of glucocorticoids include hypertension, hyperglycaemia, obesity, and dyslipidaemia,[1-3] which are independent risk factors for cardiovascular disease. However, glucocorticoids also have anti-inflammatory effects[1,2] which may exert an anti-atherosclerotic effect. Cohort studies[2,3] established that oral glucocorticoid use was associated with an increased risk for heart failure, and that high-dose therapy was associated with an increased risk for cardiovascular disease, including myocardial infarction.

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3. Wei L, *et al*. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004; **141:** 764–70.

Effects on the cerebrovascular system. Despite being used in high doses to treat benign intracranial hypertension, corticosteroids may also occasionally cause this disorder. Children receiving long-term therapy are mainly affected, an increase in dosage often being responsible. Symptoms usually subside when dosage is reduced.[1]

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Effects on the eyes. During ophthalmic use of corticosteroids about one-third of patients will develop **raised intraocular pressure**, usually within a few weeks of treatment with potent corticosteroids, or within months with weaker ones.[1] The effects on children are variable, but they may

be at risk of a greater and more rapid response to ophthalmic corticosteroids.[1] Raised intra-ocular pressure and glaucoma can also be caused by topical use of corticosteroids on the face, particularly with prolonged use.[2] There is evidence of an increased risk in patients receiving prolonged high-dose inhaled corticosteroids.[3] Increases in intra-ocular pressure appear to be less common with systemic corticosteroids,[4] but a study in elderly patients showed that the risk of raised intra-ocular pressure or open-angle glaucoma increased with the dose and duration of oral use.[5]

Topical application of corticosteroids in patients with bacterial, fungal, or viral **eye infection** can alleviate the symptoms but allow the infection to develop.[1,6] In ocular herpes simplex infection there is the risk of corneal ulceration and scarring that may lead to loss of vision.

Cataract formation is associated with systemic corticosteroid use. It has also been reported after ophthalmic[1,4] and topical[2,7] use. There is evidence that cataract formation may also be associated with prolonged use of high-dose inhaled corticosteroids.[8-10] The intranasal use of corticosteroids, however, does not appear to increase the risk.[11] It has been suggested that the lens in children might be more sensitive than in adults, but this may be due to the large doses of corticosteroids, relative to body size, given orally in these cases. Evidence of an increased risk in children from inhaled corticosteroids is limited, but is probably outweighed by the benefits of asthma control.[12]

Systemic corticosteroid use has also been associated with damage to the retinal pigment epithelial barrier, predisposing the patient to serous **retinal detachment**.[13]

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7. Costagliola C, *et al.* Cataracts associated with long-term topical steroids. *Br J Dermatol* 1989; **120:** 472–3.
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12. Cumming RG, Mitchell P. Inhaled corticosteroids and cataract: prevalence, prevention and management. *Drug Safety* 1999; **20:** 77–84.
13. Polak BCP, *et al.* Diffuse retinal pigment epitheliopathy complicating systemic corticosteroid treatment. *Br J Ophthalmol* 1995; **79:** 922–5.

Effects on the gastrointestinal tract. It has long been considered that treatment with corticosteroids might lead to peptic ulcers. Some years ago a review of the data then available suggested that since an ulcer developed in 1% of control patients not receiving corticosteroids, the 2% incidence for patients receiving corticosteroids did not warrant the prophylactic use of anti-ulcer drugs in all patients.[1] Others have found little evidence of an increased risk of peptic ulcer produced by corticosteroids alone although there is some increased risk when using them with NSAIDs.[2] A later cohort study[3] found a modest increase in risk of gastrointestinal bleeding with current use of corticosteroids, which increased when NSAIDs were also used. It has been suggested that it might be prudent to avoid such combination therapy whenever possible.[4]

Doubt has therefore been cast on the prophylactic value of anti-ulcer therapy given with corticosteroids.[1,5] If an ulcer does develop and there is good reason to continue treatment then corticosteroids may be continued along with some form of ulcer therapy.[1]

There have been several reports of corticosteroids being associated with gastrointestinal perforation.[6-9] There is a risk that the anti-inflammatory properties of corticosteroids may mask the signs of perforation and delay diagnosis with potentially fatal results.

1. Spiro HM. Is the steroid ulcer a myth? *N Engl J Med* 1983; **309:** 45–7.
2. Piper JM, *et al.* Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991; **114:** 735–40.
3. Nielsen GL, *et al.* Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med* 2001; **111:** 541–5.
4. Guslandi M, Tittobello A. Steroid ulcers: a myth revisited. *BMJ* 1992; **304:** 655–6.
5. Marcus P, McCauley DL. Steroid therapy and H_2-receptor antagonists: pharmacoeconomic implications. *Clin Pharmacol Ther* 1997; **61:** 503–8.
6. Arsura EL. Corticosteroid-associated perforation of colonic diverticula. *Arch Intern Med* 1990; **150:** 1337–8.
7. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; **66:** 1164–6.
8. O'Neil EA, *et al.* Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications. *Arch Dis Child* 1992; **67:** 10–11.
9. Epstein A, *et al.* Perforation of colon diverticula during corticosteroid therapy for pemphigus vulgaris. *Ann Pharmacother* 1993; **27:** 979–80.

Effects on growth. Corticosteroids impair normal growth in children when given systemically,[1-3] and although alternate-day therapy may reduce the effect on growth it does not abolish it. There has been some concern about possible effects of inhaled corticosteroids on growth.[1,4] Some studies have not found an effect of inhaled corticosteroids on growth if doses are modest, even when treatment is prolonged.[1,5,6] Others have found that inhaled corticosteroids, particularly in high doses, do have some effect on growth parameters,[5,7-10] but it is unclear whether this has long-term effects on the child's ultimate height, and the alternative in children requiring such high-dose therapy is likely to be an oral corticosteroid, with its consequent effects. Some studies,[11,12] in children with mild to moderate asthma, have suggested that a small reduction in growth velocity may occur in the first year of treatment, but that it then normalises and adult height is not adversely affected. Nonetheless, in the light of the increasing number of studies suggesting some effects of inhaled or intranasal corticosteroids on growth the FDA has required the inclusion of a warning in US labelling that such products may slow growth rates. For a suggestion that inhalation of a single dose of budesonide in the morning had less effect on growth than twice daily dosage, see Administration, p. 1625.2.

1. Allen DB, *et al.* A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994; **93:** 967–76.
2. Lai H-C, *et al.* Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *N Engl J Med* 2000; **342:** 851–9.
3. Mushtaq T, Ahmed SF. The impact of corticosteroids on growth and bone health. *Arch Dis Child* 2002; **87:** 93–6.
4. Hanania NA, *et al.* Adverse effects of inhaled corticosteroids. *Am J Med* 1995; **98:** 196–208.
5. Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992; **89:** 839–42.
6. Volovitz B, *et al.* Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med* 1993; **329:** 1703–8.
7. Wolthers OD, Pedersen S. Short term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. *Arch Dis Child* 1993; **68:** 673–6.
8. Todd G, *et al.* Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996; **348:** 27–9.
9. McCowan C, *et al.* Effect of asthma and its treatment on growth: four year follow up of cohort of children from general practices in Tayside, Scotland. *BMJ* 1998; **316:** 668–72.
10. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Abstract: *Pediatrics* 2000; **106:** 129. Full version: http://pediatrics.aappublications.org/cgi/content/full/106/1/e8 (accessed 27/04/04)
11. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; **343:** 1054–63.
12. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000; **343:** 1064–9.

Effects on immune response. Owing to their immunosuppressant effect, giving corticosteroids in doses greater than those required for physiological replacement therapy is associated with increased susceptibility to infection, aggravation of existing infection, and activation of latent infection. An additional problem is that the anti-inflammatory effect of corticosteroids may mask symptoms until the infection has progressed to an advanced stage; the altered response of the body may also permit the bizarre spread of infections, frequently in aberrant forms, such as disseminated parasitic infections. The risk is greater in patients receiving high doses, or associated therapy with other immunosuppressants such as cytotoxic drugs, and in those who are already debilitated. Children receiving high doses of corticosteroids are at special risk from childhood diseases, such as chickenpox, but vaccination with living organisms is contra-indicated since infection may be induced (killed vaccines or toxoids can be given but the response may be reduced).

This increased susceptibility to infection and masking of symptoms may also be caused by topical or local corticosteroid therapy. Thus, topical application to the skin has led to unusual changes such as atypical ringworm infection. Fungal infections (particularly candidiasis), generally restricted to the mouth and throat, are associated with corticosteroid inhalations. Severe damage to the eye has followed the ocular use of corticosteroids in herpetic infections, and a generalised spread of herpes infection may follow application to the mouth in the presence of herpes infection.

Conversely, the effect of corticosteroids on the symptoms and course of some infections may be life-saving (see Infections, under Uses and Administration, p. 1606.3). Before embarking on a long-term course of corticosteroid therapy general measures for the reduction of risk of infection include a diligent search for active or quiescent infection and, where appropriate, prevention or eradication of the infection before starting, or giving chemoprophylaxis during corticosteroid treatment.

Effects on lipid metabolism. Glucocorticoids have potent effects on lipid metabolism, facilitating the effects of growth hormone and endogenous stimulants of lipolysis. As a result they increase both high- and low-density lipoprotein cholesterol concentrations in the blood.

On prolonged use glucocorticoids also have a dramatic effect on body fat distribution, resulting in the characteristic Cushingoid appearance of moon face, and increased fat at the back of the neck and supraclavicular area.

Effects on mental state. Mental disturbances caused by corticosteroids include depression, mania, euphoria, and delirium.[1,2] Psychotic symptoms, insomnia, and hyperactivity have also been reported in children and adolescents treated with inhaled,[3,4] oral, and intravenous corticosteroids.[3] The risk of adverse effects appears to be dose-related, but there are reports of cases associated with very low dosages. Reversible impairment of memory has been associated with intravenous methylprednisolone.[5-7]

1. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. *Drug Safety* 2000; **22:** 111–22.
2. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006; **81:** 1361–7.
3. Stuart FA, *et al.* Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child* 2005; **90:** 500–506.
4. de Vries TW, *et al.* Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. *Eur J Clin Pharmacol* 2006; **62:** 343–6.
5. Oliveri RL, *et al.* Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing-remitting multiple sclerosis. *Acta Neurol Scand* 1998; **97:** 366–9.
6. Brunner R, *et al.* Effect of corticosteroids on short-term and long-term memory. *Neurology* 2005; **64:** 335–7.
7. Uttner I, *et al.* Reversible impaired memory induced by pulsed methylprednisolone in patients with MS. *Neurology* 2005; **64:** 1971–3.

Effects on the neonate. Various adverse effects have been reported in premature neonates given corticosteroids, see under Dexamethasone, p. 1633.1.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with intravenous use of dexamethasone sodium phosphate[1-4] and hydrocortisone sodium phosphate,[5] but not with hydrocortisone sodium succinate.[5] Descriptions of this reaction include itching, burning, tingling, and severe pain. It can begin within seconds of giving the injection, and clear within minutes of stopping. This reaction appears to be caused by the corticosteroid phosphate ester itself, and clears in the time it takes for the drug to be hydrolysed. It has been suggested that the reaction can be abolished or avoided by giving the drug as a dilute solution, over at least 5 to 15 minutes.[2-4]

Epidural lipomatosis (fat deposition around the spinal cord) is a rare complication of systemic corticosteroids.[6] It has been associated with both high daily doses (more than 30 mg prednisone daily) and lower doses given over several years. The onset of symptoms is usually gradual, ranging from 6 months to more than 20 years after beginning corticosteroid use. Spinal cord compression causes back pain radiating to the lower limbs, and severe neurological complications can develop. The lipomatosis may regress or disappear after the corticosteroid is withdrawn or the dose is lowered, but patients with myelopathy or rapidly progressive neurological deficit may need emergency surgery.

1. Czerwinski AW, *et al.* Effects of a single, large, intravenous injection of dexamethasone. *Clin Pharmacol Ther* 1972; **13:** 638–42.
2. Allan SG, Leonard RCF. Dexamethasone antiemesis and side-effects. *Lancet* 1986; **i:** 1035.
3. Neff SPW, *et al.* Excruciating perineal pain after intravenous dexamethasone. *Anaesth Intensive Care* 2002; **30:** 370–1.
4. Perron G, *et al.* Perineal pruritus after i v dexamethasone administration. *Can J Anesth* 2003; **50:** 749–50.
5. Novak E, *et al.* Anorectal pruritus after intravenous hydrocortisone sodium succinate and sodium phosphate. *Clin Pharmacol Ther* 1976; **20:** 109–12.
6. Hierholzer J, *et al.* Epidural lipomatosis: case report and literature review. *Neuroradiology* 1996; **38:** 343–8.

Effects on the pancreas. Acute pancreatitis has been associated with corticosteroid use,[1-3] although evidence supporting the association has been challenged on several grounds, both clinical and experimental.[2]

1. Nakashima Y, Howard JM. Drug-induced acute pancreatitis. *Surg Gynecol Obstet* 1977; **145:** 105–9.
2. Banerjee AK, *et al.* Drug-induced acute pancreatitis: a critical review. *Med Toxicol Adverse Drug Exp* 1989; **4:** 186–98.
3. Felig DM, Topazian M. Corticosteroid-induced pancreatitis. *Ann Intern Med* 1996; **124:** 1016.

Effects on the skin and hair. Topical corticosteroids are associated with several local adverse effects on the skin, mainly due to their antiproliferative effects on keratinocytes and fibroblasts (leading to skin thinning and atrophy), and to possible interference with the skin flora (leading to increased risk of superinfection or opportunistic infection).[1] Skin thinning is more likely if corticosteroids are applied under occlusion (this is especially true of halogenated corticosteroids, which are more resistant to inactivation by enzymes in the epidermis). Striae, which occur usually in intertriginous areas such as axillae and groin where skin is thin, moist, and occluded, are the most readily appreciable manifestation of skin atrophy,

and are irreversible, unlike more minor degrees of atrophy. Other local adverse effects include telangiectasias and purpura.[1] Acneform pustules at the site of application have occurred.

The balance between benefit and the likelihood of local or systemic adverse effects on topical application of corticosteroids will depend on the chemical structure of the drug (i.e. its lipophilicity and resistance to enzymic degradation), the formulation of the vehicle, the way in which it is applied, and the nature of the skin to be treated.[1]

Skin thinning, bruising, and purpura have also been reported in patients receiving inhaled corticosteroids.[2-4] There have been a few case reports of eczematous and erythematous lesions of the face and body, and urticaria, following inhalation or intranasal use.[5]

The adverse skin effects arising from systemic corticosteroids also include striae and skin thinning as well as acneform eruptions. Somewhat counter-intuitively a case-control study has suggested an increased risk of Stevens-Johnson syndrome or toxic epidermal necrolysis in patients receiving corticosteroids, particularly in the period shortly after beginning therapy.[6]

Hypertrichosis has occurred in patients given inhaled corticosteroid therapy, including children.[7] The risk may be increased with excessive dosage, and in some cases additional corticosteroid therapy was being given by other routes, such as intranasally or applied topically to the skin. The effect usually improved when the corticosteroid was stopped, but in some cases the excessive hair remained.

1. Mori M, *et al.* Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; **10:** 406–12.
2. Shuttleworth D, *et al.* Inhaled corticosteroids and skin thinning. *Br J Dermatol* 1990; **122:** 268.
3. Capewell S, *et al.* Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990; **300:** 1548–51.
4. Tashkin DP, *et al.* Skin manifestations of inhaled corticosteroids in COPD patients: results from Lung Health Study II. *Chest* 2004; **126:** 1123–33.
5. Isaksson M. Skin reactions to inhaled corticosteroids: incidence, avoidance and management. *Drug Safety* 2001; **24:** 369–73.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.
7. de Vries TW, *et al.* Hypertrichosis as a side effect of inhaled steroids in children. *Pediatr Pulmonol* 2007; **42:** 370–3.

Effects on the voice. Dysphonia is associated with inhaled corticosteroids.[1] Although oropharyngeal candidiasis and dysphonia may occur at the same time, many patients with dysphonia do not have candidiasis, and the two conditions do not appear to be directly related. The cause of this dysphonia has not been fully explained, but clinical investigations have found changes including bowing of the vocal cords due to bilateral adductor myopathy, mucosal changes, and supraglottic hyperfunction.

1. Lavy JA, *et al.* Dysphonia associated with inhaled steroids. *J Voice* 2000; **14:** 581–8.

Hypersensitivity and anaphylaxis. There have been occasional reports of hypersensitivity reactions, and sometimes anaphylaxis, caused by corticosteroids.[1,2] Reactions have occurred with any route, although the topical route is mainly involved. It has been noted that the incidence of hypersensitivity is increasing[3] and it has been suggested that a lack of response in chronic eczema might be due to a reaction to the corticosteroid treatment.[3] Fluorinated corticosteroids may be less likely to induce a contact hypersensitivity reaction than non-fluorinated compounds.[4]

1. Kamm GL, Hagmeyer KO. Allergic-type reactions to corticosteroids. *Ann Pharmacother* 1999; **33:** 451–60.
2. Torres MJ, Canto G. Hypersensitivity reactions to corticosteroids. *Curr Opin Allergy Clin Immunol* 2010; **10:** 273–9.
3. Dooms-Goossens A. Sensitivity to corticosteroids: consequences for anti-inflammatory therapy. *Drug Safety* 1995; **13:** 123–9.
4. Thomson KF, *et al.* The prevalence of corticosteroid allergy in two U.K. centres: prescribing implications. *Br J Dermatol* 1999; **141:** 863–6.

Tumour lysis syndrome. There have been reports of corticosteroid-induced tumour lysis syndrome.[1-4]

1. Sparano J, *et al.* Increasing recognition of corticosteroid-induced tumour lysis syndrome in non-Hodgkin's lymphoma. *Cancer* 1990; **65:** 1072–3.
2. Smith RE, Stoiber TR. Acute tumor lysis syndrome in prolymphocytic leukemia. *Am J Med* 1990; **88:** 547–8.
3. Haller C, Dhadly M. The tumor lysis syndrome. *Ann Intern Med* 1991; **114:** 808–9.
4. Tsao Y-T, *et al.* Steroids for acute spinal cord injury: revealing silent pathology. *Lancet* 2009; **374:** 500.

Withdrawal of Corticosteroids

The use of pharmacological doses of corticosteroids suppresses the endogenous secretion of corticotropin by the anterior pituitary, with the result that the adrenal cortex becomes atrophied. Sudden withdrawal or reduction in dosage, or an increase in corticosteroid requirements associated with the stress of infection or accidental or surgical trauma, may then precipitate acute adrenocortical insufficiency; deaths have followed the abrupt withdrawal of corticosteroids. Adrenocortical insufficiency has also occurred after the effective reduction in systemic corticosteroid concentrations produced by overly rapid transfer from oral to inhaled corticosteroid therapy. For the emergency treatment of acute adrenocortical insufficiency caused by abrupt withdrawal of corticosteroids, see Adrenocortical Insufficiency, p. 1600.2.

In some instances, withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment. Other effects that may occur during withdrawal or change of corticosteroid therapy include fever, myalgia, arthralgia, weight loss, benign intracranial hypertension with headache and vomiting, and papilloedema caused by cerebral oedema. Latent rhinitis or eczema may be unmasked.

Duration of treatment and dosage are important factors in determining suppression of the pituitary-adrenal response to stress on cessation of corticosteroid treatment, and individual liability to suppression is also important.

After short courses at moderate doses it may be appropriate to withdraw corticosteroids without tapering the dose (see below). However, after high-dose or prolonged therapy, withdrawal should be gradual, the rate depending upon the individual patient's response, the dose, the disease being treated, and the duration of therapy. Recommendations for initial reduction, stated in terms of prednisolone, have varied from as little as steps of 1 mg monthly to 2.5 to 5 mg every 2 to 7 days. Provided the disease is unlikely to relapse the dose of systemic corticosteroid may be reduced rapidly to physiological values; dose reduction should then be slower to allow recovery of pituitary-adrenal function. Symptoms attributable to over-rapid withdrawal should be countered by resuming a higher dose and continuing the reduction at a slower rate. Giving corticotropin does not help to re-establish adrenal responsiveness.

This gradual withdrawal of corticosteroid therapy permits a return of adrenal function adequate for daily needs, but years may sometimes be required for the return of function necessary to meet the stress of infection, surgery, or trauma. On such occasions patients with a history of recent corticosteroid withdrawal should be protected by means of supplementary corticosteroid therapy as described under Precautions, below.

The UK CSM recommends that moderate dosage with corticosteroids (up to 40 mg daily of prednisolone, or equivalent), for up to 3 weeks, may be stopped without tapering provided that the original disease is unlikely to relapse, although prophylactic cover may be required for any stress within a week of finishing the course.[1] However, it should be borne in mind that individuals vary widely in their response to corticosteroids and their ability to tolerate withdrawal. Gradual withdrawal should be considered, even after shorter courses, if higher doses are given, or in patients with other risk factors for adrenocortical insufficiency, including those who have had repeated courses of systemic corticosteroids, those who receive a course within one year of finishing long-term corticosteroid therapy, or those who regularly take doses in the evening, when their suppressive effect is greater. Withdrawal should not be abrupt in any patient who receives systemic corticosteroids for more than 3 weeks.[1]

How dose reduction is carried out depends largely on the likelihood of relapse of the original disease. If this is unlikely, the dose of systemic corticosteroid may be reduced rapidly to physiological values (traditionally considered to be 7.5 mg of prednisolone daily or equivalent). It should then be reduced more slowly to allow the hypothalamic-pituitary-adrenal axis to recover.[1] Where disease relapse is a possibility even the initial reduction may need to be more cautious. Long-term treatment may require withdrawal over many months (such as a reduction of 1 mg in the daily dose of prednisolone every 3 to 4 weeks).

In reviews of the inhibition of hypothalamic-pituitary-adrenocortical function associated with corticosteroid use, further regimens for corticosteroid withdrawal are described.[2-4] For example, patients who have been treated for weeks or months may have their daily dose of prednisolone reduced by 2.5 to 5 mg every 2 or 3 days, or, for those on longer-term treatment, the reduction may be more gradual at a rate of 2.5 mg every 1 to 3 weeks and possibly less. When the dose has reached 10 mg daily decrements may be made with 1-mg tablets. Another approach may be to convert daily therapy gradually into alternate-day therapy by progressively reducing the amount of corticosteroid received on every second day, and once alternate-day therapy is established the dose may be further reduced until, for example, a dose of 1 mg on alternate days for one week is attained.

1. CSM/MCA. Withdrawal of systemic corticosteroids. *Current Problems* 1998; **24:** 5–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
2. Anonymous. Corticosteroids and hypothalamic-pituitary-adrenocortical function. *BMJ* 1980; **280:** 813–14.
3. Helfer EL, Rose LI. Corticosteroids and adrenal suppression: characterising and avoiding the problem. *Drugs* 1989; **38:** 838–45.
4. Page RC. How to wean a patient off corticosteroids. *Prescribers' J* 1997; **37:** 11–16.

Precautions for Corticosteroids

Systemic corticosteroids should be used with great caution in the presence of heart failure, recent myocardial infarction, or hypertension, in patients with diabetes mellitus, epilepsy (but see p. 1604.1 for use in infantile spasms), glaucoma, hypothyroidism, hepatic failure, osteoporosis, peptic ulceration, psychoses or severe affective disorders, and renal impairment. Children may be at increased risk of some adverse effects; in addition, corticosteroids may cause growth retardation, and prolonged use is rarely justified. The elderly too may be at greater risk from adverse effects.

Corticosteroids are usually contra-indicated in the presence of acute infections uncontrolled by appropriate antimicrobial therapy. Similarly, patients already receiving corticosteroids are more susceptible to infection, the symptoms of which, moreover, may be masked until an advanced stage has been reached. Patients with active or doubtfully quiescent tuberculosis should not be given corticosteroids except, very rarely, as adjuncts to treatment with antitubercular drugs. Patients with quiescent tuberculosis should be observed closely and should receive chemoprophylaxis if corticosteroid therapy is prolonged.

The risks of chickenpox and probably of severe herpes zoster are increased in non-immune patients receiving therapeutic doses of systemic corticosteroids, and patients should avoid close personal contact with either infection. Passive immunisation is recommended for non-immune patients who do come into contact with chickenpox. Similar precautions apply to measles. Live vaccines should not be given to patients receiving high-dose systemic corticosteroid therapy nor for at least 3 months afterwards; killed vaccines or toxoids may be given although the response may be attenuated.

During prolonged courses of corticosteroid therapy, patients should be examined regularly. Sodium intake may need to be reduced and calcium and potassium supplements may be necessary. Monitoring of the fluid intake and output, and daily weight records may give early warning of fluid retention. Back pain may signify osteoporosis. Children are at special risk from raised intracranial pressure. Patients should carry cards (and preferably also wear bracelets) giving full details of their corticosteroid therapy; they and their relatives should be fully conversant with the implications of their therapy and the precautions to be taken.

Measures to compensate for the adrenals' inability to respond to stress (see Withdrawal, above) include increasing the dose to cover minor intercurrent illnesses or trauma such as surgery (with intramuscular doses to cover vomiting). For details of dosages used, see Uses and Administration, p. 1597.3.

Rapid intravenous injection of massive doses of corticosteroids may sometimes cause cardiovascular collapse and injections should therefore be given slowly or by infusion.

Many drugs have been reported to interfere with certain assay procedures for corticosteroids in body fluids and corticosteroids themselves may interfere with or alter the results of assays for some endogenous substances or drugs.

The risk of systemic absorption should always be considered when applying corticosteroids topically. They should not be applied with an occlusive dressing to large areas of the body. Long-term topical use is best avoided, especially in children. Also they should not be used for the treatment of ulcerative conditions, nor of rosacea, and should not be used indiscriminately for pruritus. Occasionally they may be used with the addition of a suitable antimicrobial substance in the treatment of infected skin but there is a risk of sensitivity reactions occurring.

Height should be monitored in children receiving prolonged therapy with inhaled or nasal corticosteroids. High doses of inhaled corticosteroids should preferably be inhaled using large-volume spacer devices to reduce oropharyngeal deposition and hence the incidence of candidiasis; rinsing the mouth with water after inhalation may also be helpful. In addition the use of spacer devices may reduce systemic absorption (see also Inhalation Therapy, under Uses and Administration, p. 1598.3). Paradoxical bronchospasm has occurred with inhaled corticosteroids and may require therapy to be stopped, although if mild it may be prevented by inhalation of a $beta_2$ adrenoceptor agonist, or by transfer from an aerosol to a dry powder formulation.

Caution is required when corticosteroids are used locally to treat eye disorders (see p. 1619.1).

Contraception. There are some isolated case reports of contraceptive failure in women using intra-uterine devices and receiving corticosteroid therapy.[1-3]

1. Zerner J, *et al.* Failure of an intrauterine device concurrent with administration of corticosteroids. *Fertil Steril* 1976; **27:** 1467–8.
2. Inkeles DM, Hansen RI. Unexpected pregnancy in a woman using an intrauterine device and receiving steroid therapy. *Ann Ophthalmol* 1982; **14:** 975.

3. Buhler M, Papiernik E. Successive pregnancies in women fitted with intrauterine devices who take anti-inflammatory drugs. *Lancet* 1983; **i:** 483.

Eye disorders. Topical corticosteroids have transformed the management of inflammatory disease of the anterior segment of the eye and it should be noted that while their proper use may be sight-saving their inappropriate use is potentially blinding.[1] The dangers include the conversion of a simple dendritic herpes simplex epithelial lesion into an extensive amoeboid ulcer with the likelihood of permanent corneal scarring and loss of vision and also the risk of potentiation of bacterial and fungal infections. Other dangers include the development of open-angle glaucoma and cataracts. Topical corticosteroids are used by ophthalmologists in herpes simplex keratitis but always under appropriate antiviral cover and their use requires considerable experience. They should never be given for an undiagnosed red eye and many consultant ophthalmic surgeons believe that general practitioners should never begin therapy without an ophthalmic opinion.

Further studies and discussions on the inappropriate use of corticosteroids to treat eye disorders are listed below.[2-10]

1. St Clair Roberts D. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1414–15.
2. Lavin MJ, Rose GE. Use of steroid eye drops in general practice. *BMJ* 1986; **292:** 1448–50.
3. Claoué CMP, Stevenson KE. Incidence of inappropriate treatment of herpes simplex keratitis with topical steroids. *BMJ* 1986; **292:** 1450–1.
4. Livingstone A. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1737.
5. Lawrence M. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1737–8.
6. Trevor-Roper P. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1738.
7. Jay B. Steroids, the eye, and general practitioners. *BMJ* 1986; **293:** 205.
8. Rose GE, Lavin MJ. Steroids, the eye, and general practitioners. *BMJ* 1986; **293:** 205.
9. O'Day DM. Corticosteroids: an unresolved debate. *Ophthalmology* 1991; **98:** 845–6.
10. Stern GA, Buttross M. Use of corticosteroids in combination with antimicrobial drugs in the treatment of infectious corneal disease. *Ophthalmology* 1991; **98:** 847–53.

Intranasal administration. Local adverse effects from intranasal corticosteroids include irritation, epistaxis, and smell and taste disturbances (see also p. 1615.3). Ulceration, septal perforation, and hypersensitivity reactions have occurred.[1]

There have been cases of Cushing's syndrome associated with inappropriately prolonged use of corticosteroid nasal drops in children.[2,3] Such drops should not be prescribed on a repeat prescription basis; where treatment is contemplated for more than 6 weeks appropriate monitoring has been recommended. See also Adrenal Suppression, under Adverse Effects, p. 1616.1.

1. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. *Drug Safety* 2003; **26:** 863–93.
2. Findlay CA, *et al.* Childhood Cushing's syndrome induced by betamethasone nose drops, and repeat prescriptions. *BMJ* 1998; **317:** 739–40.
3. Perry RJ, *et al.* Cushing's syndrome, growth impairment, and occult adrenal suppression associated with intranasal steroids. *Arch Dis Child* 2002; **87:** 45–8.

Porphyria. Corticosteroids have generally been considered to be safe in patients with porphyria although there is conflicting evidence of porphyrinogenicity. In a review[1] of drug-induced porphyrias it was noted that a report suggesting that corticosteroids may have a role in treating the acute attack together with many reports attesting to their safety, contrasted with their repeated incrimination as the offending agent in producing such episodes. It was considered that as corticosteroids may be life-saving, they should be used if really indicated.

For classification of porphyrinogenicity by The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, of specific drugs, see under the individual monographs.

1. Moore MR, Disler PB. Drug-induction of the acute porphyrias. *Adverse Drug React Acute Poisoning Rev* 1983; **2:** 149–89.

Pregnancy. Studies have shown that corticosteroid use in pregnant women did not have adverse effects on the fetus in terms of psychological development[1] or growth and general health factors.[2] However, in an isolated report[3] the topical use of triamcinolone in a pregnant woman for treatment of eczema was considered to have caused fetal growth retardation. In another study[4] of 11 women with placenta praevia given intramuscular betamethasone 12 mg repeated 24 hours later, there were 2 cases of constriction of the ductus arteriosus; neither case was severe.

Early studies in *animals* showed an increase in fetal cleft palate after maternal ingestion of high corticosteroid doses, and cortisone has been used widely as a tool for the investigation of mechanisms responsible for cleft lip and palate. With doses used in clinical practice, however, the risk appears to be low. In an analysis of several hundred cases reported in the literature[5] it was concluded that the incidence of cleft palate in exposed children was slightly higher than in a random sample, but that in the small selected group studied, this higher incidence might be fallacious. Although an increased incidence of malformations in the children of asthmatic mothers given prednisolone 2.5 to 30 mg daily during pregnancy was noted,[6] others[7] have suggested that the outcome might have been worse in untreated asthmatic mothers. Moreover, no significant increase in the risk of fetal or maternal complications was found in a study of asthmatic mothers given prednisolone 2.5 to 20 mg daily.[8] Subsequently, no evidence of a teratogenic effect for corticosteroids was noted in a comparison of the maternal drug histories of the mothers of 764 infants born with anomalies of the CNS and 764 controls,[9] and in another study[10] there were no striking differences in birth-weight and frequency of 'small for dates' infants born to mothers who received systemic corticosteroids during pregnancy for pemphigoid gestationis and those who did not.

Fears concerning the use of corticosteroids during late pregnancy relate to their direct adverse effects on the fetus. These involve the known adverse effects of corticosteroids, such as increased risk of infection and adrenal insufficiency. No such adverse effects were noted in the infants of 70 exposed pregnancies,[8] although there have been individual reports.[11,12] The potential dangers of maternal diabetogenic effects have been shown in a study of metabolic changes induced in diabetic women by salbutamol (used in the prevention of premature labour) which could be exacerbated by use of dexamethasone (to promote maturation of the fetal lung) with consequent danger to the fetus.[13]

A review[14] by the UK CSM concluded that there was no convincing evidence that corticosteroids caused an increased incidence of congenital abnormality. Prolonged or repeated use during pregnancy did increase the risk of intra-uterine growth retardation but this did not seem to be a problem following short-term treatment. It was noted that the ability of different corticosteroids to cross the placenta varied very markedly.

1. Schmand B, *et al.* Psychological development of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome. *Pediatrics* 1990; **86:** 58–64.
2. Doyle LW, *et al.* Antenatal steroid therapy and 5-year outcome of extremely low birth weight infants. *Obstet Gynecol* 1989; **73:** 743–6.
3. Katz VL, *et al.* Severe symmetric intrauterine growth retardation associated with the topical use of triamcinolone. *Am J Obstet Gynecol* 1990; **162:** 396–7.
4. Wasserstrum N, *et al.* Betamethasone and the human fetal ductus arteriosus. *Obstet Gynecol* 1989; **74:** 897–900.
5. Popert AJ. Pregnancy and adrenocortical hormones: some aspects of their interaction in rheumatic diseases. *BMJ* 1962; **1:** 967–72.
6. Warrell DW, Taylor R. Outcome for the foetus of mothers receiving prednisolone during pregnancy. *Lancet* 1968; **i:** 117–18.
7. Scott JK. Foetal risk with maternal prednisolone. *Lancet* 1968; **i:** 208.
8. Schatz M, *et al.* Corticosteroid therapy for the pregnant asthmatic patient. *JAMA* 1975; **233:** 804–7.
9. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
10. Holmes RC, Black MM. The fetal prognosis in pemphigoid gestationis (herpes gestationis). *Br J Dermatol* 1984; **110:** 67–72.
11. Grajwer LA, *et al.* Neonatal subclinical adrenal insufficiency: result of maternal steroid therapy. *JAMA* 1977; **238:** 1279–80.
12. Evans TJ, *et al.* Congenital cytomegalovirus infection after maternal renal transplantation. *Lancet* 1975; **i:** 1359–60.
13. Gündoğdu AS, *et al.* Comparison of hormonal and metabolic effects of salbutamol infusion in normal subjects and insulin-requiring diabetics. *Lancet* 1979; **ii:** 1317–21.
14. CSM/MCA. Systemic corticosteroids in pregnancy and lactation. *Current Problems* 1998; **24:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Septic shock. Some manufacturers recommend that corticosteroids should not be given to patients with septic shock and references to the controversial use of high-dose corticosteroids are given under Septic Shock, in Uses and Administration, p. 1613.1.

Sickle-cell disease. Sickle-cell crisis was reported to have been precipitated by corticosteroids in 2 patients with sickle C disease.[1] The crises in these patients were considered to have started with ischaemic necrosis of the bone marrow leading to fat embolism, cerebral hypoxia, and coma.

For mention of the use of corticosteroids in sickle-cell crisis, see under Sickle-cell Disease, in Uses and Administration, p. 1613.1.

1. Huang JC, *et al.* Sickling crisis, fat embolism, and coma after steroids. *Lancet* 1994; **344:** 951–2.

Tooth erosion. The increased incidence of tooth erosion seen in patients with asthma might be related to the pH of inhaled powder (but not aerosol) formulations.[1] Beclometasone dipropionate and fluticasone had pHs of 4.76 as powder formulations, whereas the pHs of the aerosols were well above the pH of 5.5 at which tooth substance begins to dissolve. Budesonide was less acidic in its powder formulation (pH 6.47).

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; **317:** 820.

Varicella. Several cases of fatal or near fatal chickenpox have been reported in patients receiving corticosteroids.[1-3] Although mostly associated with systemic use, severe disseminated varicella and staphylococcal pericarditis have been reported in an infant following a single application of a potent topical corticosteroid cream.[4] Guidelines issued by the UK CSM state that all patients taking systemic corticosteroids for purposes other than replacement, and who have not had chickenpox, should be regarded as being at risk of severe chickenpox, irrespective of the dose or duration of treatment.[2,5] Passive immunisation with varicella-zoster immunoglobulin should be given to non-immune patients who are receiving corticosteroids, or who have received them within the last 3 months, if they are exposed to chickenpox. Passive immunisation should preferably be given within 3 days and not later than 10 days from exposure.[2] The CSM considered that there was no good evidence that topical, inhaled, or rectal corticosteroids were associated with an increased risk of severe chickenpox.

1. Rice P, *et al.* Near fatal chickenpox during prednisolone treatment. *BMJ* 1994; **309:** 1069–70.
2. CSM/MCA. Severe chickenpox associated with systemic corticosteroids. *Current Problems* 1994; **20:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 19/03/10)
3. Dowell SF, Breese JS. Severe varicella associated with steroid use. *Pediatrics* 1993; **92:** 223–8.
4. Brumund MR, *et al.* Disseminated varicella and staphylococcal pericarditis after topical steroids. *J Pediatr* 1997; **131:** 162–3.
5. Ellender D, *et al.* Severe chickenpox during treatment with corticosteroids. *BMJ* 1995; **310:** 327.

Interactions of Corticosteroids

Concurrent use of barbiturates, carbamazepine, phenytoin, primidone, or rifampicin may enhance the metabolism and reduce the effects of systemic corticosteroids. Conversely oral contraceptives or ritonavir may increase plasma concentrations of corticosteroids. Use of corticosteroids with potassium-depleting diuretics, such as thiazides or furosemide, may cause excessive potassium loss. There is also an increased risk of hypokalaemia with concurrent amphotericin B or bronchodilator therapy with xanthines or beta$_2$ agonists. There may be an increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. Response to anticoagulants may be altered by corticosteroids and requirements of antidiabetic drugs and antihypertensives may be increased. Corticosteroids may decrease serum concentrations of salicylates and may decrease the effect of anticholinesterases in myasthenia gravis. The antiglucocorticoid effect of mifepristone will antagonise the effects of corticosteroids.

Analgesics. For the effect of corticosteroids on *salicylates*, see Aspirin, Interactions, p. 26.3.

Antibacterials. *Rifampicin* reduces the activity of corticosteroids[1-8] by accelerating their metabolism, and a similar effect would be expected with other rifamycins. There is limited evidence that the macrolide antibacterials *troleandomycin*,[9-11] and perhaps *erythromycin*,[12] may inhibit the metabolism of methylprednisolone, but not of prednisolone.[10] Dosage reduction should be made as necessary if troleandomycin and methylprednisolone are used together. There is no evidence of a clinically significant interaction between these macrolides and other corticosteroids.

For reference to corticosteroids lowering plasma concentrations of *isoniazid* and enhancing its renal clearance, see p. 313.2.

1. Edwards OM, *et al.* Changes in cortisol metabolism following rifampicin therapy. *Lancet* 1974; **ii:** 549–51.
2. Maisey DN, *et al.* Rifampicin and cortisone replacement therapy. *Lancet* 1974; **ii:** 896–7.
3. Steenbergen GJ, Pfaltzgraff RE. Treatment of neuritis in borderline leprosy with rifampicin and corticosteroids—a pilot trial. *Lepr Rev* 1975; **46:** 115–18.
4. Buffington GA, *et al.* Interaction of rifampin and glucocorticoids: adverse effect on renal allograft function. *JAMA* 1976; **236:** 1958–60.
5. Hendrickse W, *et al.* Rifampicin-induced non-responsiveness to corticosteroid treatment in nephrotic syndrome. *BMJ* 1979; **1:** 306.
6. van Marle W, *et al.* Concurrent steroid and rifampicin therapy. *BMJ* 1979; **1:** 1020.
7. Jopline WH, Pettit JHS. Interaction between rifampicin, steroids and oral contraceptives. *Lepr Rev* 1979; **50:** 331–2.
8. McAllister WAC, *et al.* Rifampicin reduces effectiveness and bioavailability of prednisolone. *BMJ* 1983; **286:** 923–5.
9. Szefler SJ, *et al.* The effect of troleandomycin on methylprednisolone elimination. *J Allergy Clin Immunol* 1980; **66:** 447–51.
10. Szefler SJ, *et al.* Steroid-specific and anticonvulsant interaction aspects of troleandomycin-steroid therapy. *J Allergy Clin Immunol* 1982; **69:** 455–60.
11. Kamada AK, *et al.* Glucocorticoid reduction with troleandomycin in chronic severe asthmatic children: implication for future trials and clinical application. *J Allergy Clin Immunol* 1992; **89:** 285.
12. LaForce CF, *et al.* Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. *J Allergy Clin Immunol* 1983; **72:** 34–9.

Anticoagulants. For the various effects of corticosteroids on anticoagulants, see under Warfarin Sodium, p. 1533.2.

Antiepileptics. Reduced efficacy of corticosteroids has been noted in asthmatic, arthritic, renal transplant, and other patients who also received *phenytoin* or *phenobarbital*,[1-3] and the clearance of corticosteroids has also been reported to be markedly increased by *carbamazepine*.[3] Hypoadrenalism occurred when *topiramate* was started in a patient who had been stabilised on corticosteroid replace-

ment therapy for congenital adrenal hyperplasia.[4] Induction of microsomal liver enzymes by the antiepileptic, resulting in enhanced metabolism of the corticosteroid is believed to be the underlying mechanism. Different corticosteroids appear to be affected to different degrees, but the disease state, doses, and other determinants such as diet, sex, and other drugs used may also be contributory factors. An increase in the dosage of the corticosteroids may be necessary in order to maintain the desired therapeutic response.[1]

1. Brooks SM, *et al.* Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N Engl J Med* 1972; **286:** 1125–8.
2. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; **18:** 131–50.
3. Bartoszek M, *et al.* Prednisolone and methylprednisolone kinetics in children receiving anticonvulsant therapy. *Clin Pharmacol Ther* 1987; **42:** 424–32.
4. Jacob K, Trainer PJ. Topiramate can induce hypoadrenalism in patients taking oral corticosteroid replacement. *BMJ* 2009; **338:** 1076.

Antifungals. *Ketoconazole*[1,2] and *itraconazole*[3,4] increase serum-methylprednisolone concentrations and enhance methylprednisolone's adrenal suppressive effects. A 50% reduction in intravenous methylprednisolone dose was suggested during ketoconazole therapy.[2] A similar effect was not evident with oral prednisone[4,5] although some workers[6] found that ketoconazole reduced the total clearance of prednisolone given intravenously and of prednisone given orally. Itraconazole can also reduce the clearance of dexamethasone; in a study[7] of 8 healthy subjects, the area under the concentration-time curve (AUC) for both intravenous and oral dexamethasone was increased about 3.5-fold, and the morning plasma-cortisol concentration was suppressed for at least 2 days longer. A study[8] of healthy subjects found that ketoconazole increased the AUC for oral budesonide more than sixfold when they were given together, but only about fourfold when the doses were given 12 hours apart. Systemic exposure to inhaled budesonide is increased by itraconazole, which probably reduces the metabolism of budesonide.[9] Adrenal suppression was found in 11 of 25 patients with cystic fibrosis who were treated with this combination; one patient developed Cushing's syndrome.[10] A similar interaction may have been the cause of significant adrenal suppression in a patient with cystic fibrosis who was treated with itraconazole and inhaled fluticasone propionate.[11]

1. Glynn AM, *et al.* Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion. *Clin Pharmacol Ther* 1986; **39:** 654–9.
2. Kandrotas RJ, *et al.* Ketoconazole effects on methylprednisolone disposition and their joint suppression of endogenous cortisol. *Clin Pharmacol Ther* 1987; **42:** 465–70.
3. Varis T, *et al.* Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. *Clin Pharmacol Ther* 1998; **64:** 363–8.
4. Lebrun-Vignes B, *et al.* Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol* 2001; **51:** 443–50.
5. Ludwig EA, *et al.* Steroid-specific effects of ketoconazole on corticosteroid disposition: unaltered prednisolone elimination. *DICP Ann Pharmacother* 1989; **23:** 858–61.
6. Zürcher RM, *et al.* Impact of ketoconazole on the metabolism of prednisolone. *Clin Pharmacol Ther* 1989; **45:** 366–72.
7. Varis T, *et al.* The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther* 2000; **68:** 487–94.
8. Seidegård J. Reduction of the inhibitory effect of ketoconazole on budesonide pharmacokinetics by separation of their time of administration. *Clin Pharmacol Ther* 2000; **68:** 13–17.
9. Raaska K, *et al.* Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. *Clin Pharmacol Ther* 2002; **72:** 362–9.
10. Skov M, *et al.* Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. *Eur Respir J* 2002; **20:** 127–33.
11. Parmar JS, *et al.* Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 2002; **57:** 749–50.

Antineoplastics. For reference to single doses of prednisone inhibiting the activation of *cyclophosphamide* (but longer-term treatment increasing its activation), see Cyclophosphamide, p. 773.3.

Antivirals. For a possible effect of corticosteroids on the metabolism of HIV-protease inhibitors, see p. 988.1.

Ritonavir can greatly increase plasma concentrations of fluticasone, through inhibition of cytochrome P450 isoenzyme CYP3A4, leading to systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.[1-3] There have been reports of osteoporosis, with fractures in one case, associated with Cushing's syndrome due to this interaction.[2] Similar interactions are expected with other HIV-protease inhibitors.

1. GlaxoSmithKline, Canada. Important safety information regarding a drug interaction between fluticasone propionate (Flonase/Flovent/Advair) and ritonavir (Norvir/Kaletra), issued 22 January, 2004. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/fluticasone_ritonavir_hpc-cps-eng.pdf (accessed 22/08/08)
2. Samaras K, *et al.* Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005; **90:** 4394–8.
3. Johnson SR, *et al.* Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006; **148:** 386–8.

Calcium-channel blockers. Studies in healthy subjects have found that *diltiazem* reduces the clearance of methylprednisolone.[1,2]

1. Varis T, *et al.* Diltiazem and mibefradil increase the plasma concentrations and greatly enhance the adrenal-suppressant effect of oral methylprednisolone. *Clin Pharmacol Ther* 2000; **67:** 215–21.
2. Booker BM, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and methylprednisolone in healthy volunteers. *Clin Pharmacol Ther* 2002; **72:** 370–82.

Gastrointestinal drugs. *Aprepitant* increased plasma concentrations of dexamethasone and methylprednisolone in a pharmacokinetic study.[1] Licensed product information for aprepitant recommends that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. For the appropriate regimen when these drugs are given together for nausea and vomiting, see Administration under Aprepitant, p. 1819.3.

1. McCrea JB, *et al.* Effects of the neurokinin$_1$ receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003; **74:** 17–24.

Growth hormone. Somatropin (growth hormone) therapy may impair the conversion of cortisone and prednisone to their active metabolites, cortisol and prednisolone, respectively. This occurs through the inhibition of the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 in hepatic and adipose tissues. Licensed product information suggests that patients should be monitored for the need to increase doses of cortisone or prednisone after somatropin is started. Studies of cortisone acetate in hypopituitary patients receiving growth hormone replacement have reached different conclusions; some concluded that the effect may be insignificant,[1] while others suggested that dose adjustments may be needed.[2,3]

Somatropin may increase the clearance of corticosteroids that are metabolised by the cytochrome P450 isoenzyme CYP3A4, although the clinical significance of this is unknown.

High doses of corticosteroids may inhibit the growth promoting effects of somatropin.

1. Beentjes JAM, *et al.* Effects of growth hormone replacement on cortisol metabolism in hypopituitary patients treated with cortisone acetate. *Scand J Clin Lab Invest* 2001; **61:** 277–86.
2. Swords FM, *et al.* The effects of growth hormone deficiency and replacement on glucocorticoid exposure in hypopituitary patients on cortisone acetate and hydrocortisone replacement. *Clin Endocrinol (Oxf)* 2003; **59:** 613–20.
3. Sigurjonsdottir HA, *et al.* Lack of regulation of 11 β-hydroxysteroid dehydrogenase type 1 during short-term manipulation of GH in patients with hypopituitarism. *Eur J Endocrinol* 2009; **161:** 375–80.

Histamine. For the effect of systemic corticosteroids on histamine given exogenously, see p. 2525.3.

Immunosuppressants. It has been suggested that mutual inhibition of metabolism occurs between *ciclosporin* and corticosteroids, and may increase the plasma concentrations of either drug.[1,2] A review[3] cited studies supporting this conclusion but also mentioned studies that showed that ciclosporin did not significantly decrease clearance of prednisolone[4] and that corticosteroids either did not change, or decreased, ciclosporin concentrations.[5,6] Some of these conflicting results may be due to differences in the methods used to measure ciclosporin concentrations.

1. Ost L. Effects of cyclosporin on prednisolone metabolism. *Lancet* 1984; **i:** 451.
2. Klintmalm G, Säwe J. High dose methylprednisolone increases plasma cyclosporin levels in renal transplant recipients. *Lancet* 1984; **i:** 731.
3. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (part II). *Clin Pharmacokinet* 1990; **19:** 400–15.
4. Frey FJ, *et al.* Evidence that cyclosporine does not affect the metabolism of prednisolone after renal transplantation. *Transplantation* 1987; **43:** 494–8.
5. Ptachcinski RJ, *et al.* Cyclosporine - high-dose steroid interaction in renal transplant recipients: assessment by HPLC. *Transplant Proc* 1987; **19:** 1728–9.
6. Hricik DE, *et al.* Association of the absence of steroid therapy with increased cyclosporine blood levels in renal transplant recipients. *Transplantation* 1990; **49:** 221–3.

Leukotriene antagonists. Severe peripheral oedema occurred in a patient treated with *montelukast* and prednisone for asthma, but not when either drug was used alone.[1] Montelukast may have potentiated sodium and fluid retention caused by the corticosteroid.

1. Geller M. Marked peripheral edema associated with montelukast and prednisone. *Ann Intern Med* 2000; **132:** 924.

Lipid regulating drugs. Giving *colestipol* to a patient with hypopituitarism taking oral hydrocortisone maintenance therapy resulted in headaches, ataxia, and lethargy.[1] Mental status returned to normal within hours of an intravenous dose of hydrocortisone 100 mg, and colestipol was subsequently withdrawn uneventfully.

1. Nekl KE, Aron DC. Hydrocortisone-colestipol interaction. *Ann Pharmacother* 1993; **27:** 980–1.

Neuromuscular blockers. For reference to corticosteroids antagonising the effects of *competitive neuromuscular blockers*, see under Atracurium, p. 2032.3.

Sex hormones. There have been reviews[1,2] discussing several reports of an enhanced effect of corticosteroids in women also receiving *oestrogens* or *oral contraceptives* and commenting that the dose of corticosteroids in some cases may need to be reduced. There is some evidence that budesonide may be less affected by use with oral contraceptives than prednisolone.[3]

1. Shenfield GM. Drug interactions with oral contraceptive preparations. *Med J Aust* 1986; **144:** 205–10.
2. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; **18:** 472–84.
3. Seidegård J, *et al.* Effect of an oral contraceptive on the plasma levels of budesonide and prednisolone and the influence on plasma cortisol. *Clin Pharmacol Ther* 2000; **67:** 373–81.

Smoking. There was a report of an appreciable and consistent increase in plasma corticosteroids after cigarette smoking.[1] However, a review concerning the clinical importance of smoking and drug interactions[2] concluded that in the majority of examples, including corticosteroids, there was little evidence of a recognisable hazard from the interaction.

1. Kershbaum A, *et al.* Effect of smoking and nicotine on adrenocortical secretion. *JAMA* 1968; **203:** 275–8.
2. D'Arcy PF. Tobacco smoking and drugs: a clinically important interaction? *Drug Intell Clin Pharm* 1984; **18:** 302–7.

Sympathomimetics. Studies in 21 asthmatic patients suggested that the plasma half-life of dexamethasone was decreased by *ephedrine*.[1] More importantly use of corticosteroids with *beta$_2$ agonists* may potentiate any hypokalaemic effects.[2]

1. Brooks SM, *et al.* The effects of ephedrine and theophylline on dexamethasone metabolism in bronchial asthma. *J Clin Pharmacol* 1977; **17:** 308–18.
2. CSM. β_2 agonists, xanthines and hypokalaemia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 23/03/10)

Thalidomide. In a double-blind crossover study of thalidomide in the treatment of severe chronic erythema nodosum leprosum,[1] the dose of prednisolone necessary to suppress symptoms was considerably reduced in 9 of 10 patients while they were receiving thalidomide; there has been a comment[2] that prednisolone should not be given with thalidomide.

For reference to a possible interaction between thalidomide and dexamethasone, see Effects on the Skin under Adverse Effects of Thalidomide, p. 870.2.

1. Waters MFR. An internally-controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Lepr Rev* 1971; **42:** 26–42.
2. WHO, Regional Office for the Western Pacific. Final report on the first regional working group on leprosy, Manila, Philippines, 7–12 December, 1978. *Lepr Rev* 1979; **50:** 326–9.

Xanthines. For the effect of corticosteroids on *aminophylline* and *theophylline*, see p. 1235.3.

Pharmacokinetics of Corticosteroids

Corticosteroids are, in general, readily absorbed from the gastrointestinal tract. They are also absorbed when given locally. After topical use, particularly under an occlusive dressing or when the skin is broken, or use rectally as an enema, sufficient corticosteroid may be absorbed to give systemic effects; this is also a possibility with other local routes such as inhalation. Water-soluble forms of corticosteroids are given by intravenous injection for a rapid response; more prolonged effects are achieved using lipid-soluble forms of corticosteroids by intramuscular injection.

Corticosteroids are rapidly distributed to all body tissues. They cross the placenta to varying degrees and may be distributed in small amounts into breast milk.

Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding globulin (transcortin) has high affinity but low binding capacity, while albumin has low affinity but large binding capacity. The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol). They also tend to have longer half-lives.

Corticosteroids are metabolised mainly in the liver but also in other tissues, and are excreted in the urine. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

Reviews.

1. Begg EJ, *et al.* The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987; **146:** 37–41.
2. McGhee CNJ. Pharmacokinetics of ophthalmic corticosteroids. *Br J Ophthalmol* 1992; **76:** 681–4.
3. Jusko WJ. Pharmacokinetics and receptor-mediated pharmacodynamics of corticosteroids. *Toxicology* 1995; **102:** 189–96.
4. Derendorf H, *et al.* Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol* 1998; **101** (suppl 2): S440–6.
5. Czock D, *et al.* Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* 2005; **44:** 61–98.

Alclometasone Dipropionate

(BANM, USAN, rINNM) ⊗

Alclometasona, dipropionato de; Alclométasone, Dipropionate d'; Alclometasoni Dipropionas; Alklometasondipropionat; Alklometasonidipropionaatti; Dipropionato de alclometasona; Sch-22219; Альклометазона Дипропионат.

7α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

$C_{28}H_{37}ClO_7$=521.0

CAS — 67452-97-5 (alclometasone); 66734-13-2 (alclometasone dipropionate).

ATC — D07AB10; S01BA10.

ATC Vet — QD07AB10; QS01BA10.

UNII — 5S6PQL4N1V.

Pharmacopoeias. In *US.*

USP 36: (Alclometasone Dipropionate). Store in airtight containers.

Profile

Alclometasone dipropionate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see Topical Application, p. 1599.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alclometasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Afloderm; ***Ger.***: Delonal†; ***Gr.***: Lomesone; ***Hong Kong***: Perderm†; ***Indon.***: Cloderm; Perderm; ***Irl.***: Modrasone; ***Ital.***: Legederm; ***Mex.***: Logoderm†; ***Pol.***: Afloderm; ***Port.***: Miloderme; ***Rus.***: Afloderm (Афлодерм); ***UK***: Modrasone; ***USA***: Aclovate; ***Venez.***: Demiderm.

Pharmacopoeial Preparations

USP 36: Alclometasone Dipropionate Cream; Alclometasone Dipropionate Ointment.

Aldosterone *(BAN, rINN)*

Aldosteron; Aldosterona; Aldostérone; Aldosteroni; Aldosteronum; Electrocortin; Альдостерон.

11β,18-Epoxy-18,21-dihydroxypregn-4-ene-3,20-dione.

$C_{21}H_{28}O_5$=360.4

CAS — 52-39-1.

ATC — H02AA01.

ATC Vet — QH02AA01.

UNII — 4964P6T9RB.

Uses and Administration

Aldosterone is the main mineralocorticoid (p. 1597.1) secreted by the adrenal cortex. It has no significant glucocorticoid (anti-inflammatory) properties.

Aldosterone has been given by intramuscular or intravenous injection, with a glucocorticoid, in the treatment of primary adrenocortical insufficiency (p. 1600.2) but synthetic mineralocorticoids such as fludrocortisone (p. 1634.3), which can be given orally, are usually preferred. It has also been used as the sodium succinate.

Adverse Effects

Aldosterone has very pronounced mineralocorticoid actions and little effect on carbohydrate metabolism. It may therefore have the mineralocorticoid adverse effects described for the corticosteroids in general (p. 1615.3).

Amcinonide *(BAN, USAN, rINN)* ⊗

Amcinónida; Amcinonidum; Amcinopol; CL-34699; Амцинонид.

16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{28}H_{35}FO_7$=502.6

CAS — 51022-69-6.

ATC — D07AC11.

ATC Vet — QD07AC11.

UNII — 423W026MA9.

Pharmacopoeias. In *US.*

Profile

Amcinonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, lotion, or ointment containing 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Amicla; ***Canad.***: Cyclocort; ***Fr.***: Penticort†; ***Ger.***: Amciderm; ***Mex.***: Visderm H; ***Thai.***: Amciderm†; Visderm.

Pharmacopoeial Preparations

USP 36: Amcinonide Cream; Amcinonide Ointment.

Beclometasone Dipropionate

(BANM, rINNM) ⊗

Beclometasona, dipropionato de; Béclométasone, dipropionate de; Beclometasoni dipropionas; Beclometasoni Diproprionas; Beclomethasone Dipropionate (USAN); Beclomethasone Dipropionate; Beklometasondipropionat; Beklometason-dipropionát; Beklometasonidipropionaatti; Beklometazon Dipropiyonat; Beklometazon-diproprionát; Beklometazono dipropionatas; Beklometazonu dipropionian; 9α-Chloro-16β-methylprednisolone Dipropionate; Dipropionato de beclometasona; Sch-18020W; Беклометазона Дипропионат.

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

$C_{28}H_{37}ClO_7$=521.0

CAS — 4419-39-0 (beclometasone); 5534-09-8 (beclometasone dipropionate).

ATC — A07EA07; D07AC15; R01AD01; R03BA01.

ATC Vet — QA07EA07; QD07AC15; QR01AD01; QR03BA01.

UNII — 5B307S63B2 (beclomethasone dipropionate); 4H7L9AI22I (beclomethasone dipropionate monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.*

US allows either the anhydrous or monohydrate form. *Eur.* also includes a separate monograph for the monohydrate.

Ph. Eur. 8: (Beclometasone Dipropionate, Anhydrous). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

Ph. Eur. 8: (Beclometasone Dipropionate Monohydrate). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

USP 36: (Beclomethasone Dipropionate). It is anhydrous or contains one molecule of water of hydration. A white to cream white, odourless powder. Very slightly soluble in water; freely soluble in alcohol and in acetone; very soluble in chloroform.

Uses and Administration

Beclometasone dipropionate is a corticosteroid with mainly glucocorticoid activity (p. 1597.1).

It is stated to exert a topical effect on the lungs without significant systemic activity at recommended doses (but see Adrenal Suppression under Adverse Effects, p. 1622.2), and is used by inhalation for the prophylaxis of **asthma** (see below). Many formulations are now available, with differing dosage regimens, and the appropriate product literature should be consulted before starting therapy or changing to another formulation. Furthermore, in the UK the doses of beclometasone dipropionate for asthma are expressed in terms of the amount supplied into the mouthpiece per actuation, whereas in the USA doses are expressed in terms of the amount emitted from the mouthpiece; recommended doses therefore appear somewhat lower in the USA than the UK doses given below, although in practical terms there is probably no difference.

In the UK the initial dose of most aerosol and dry powder inhalers is generally 200 to 400 micrograms daily for mild asthma, and 600 to 1600 micrograms daily for moderate to severe asthma. The dose should be adjusted according to response, and reduced to the lowest effective dose for maintenance. The usual maintenance dose is in the region of 400 to 800 micrograms daily, but up to 2 mg daily may be necessary in severe asthma. Therapy is usually given in 2 divided doses, although high-dose therapy may be given in 4 divided doses. Owing to differences in the relative bioavailability to the lungs, some powder inhalation delivery systems may be licensed for higher initial doses, although maximum doses are similar to those above. In contrast, some hydrofluoroalkane (CFC-free) inhalers must be used in lower doses: typical UK doses for one product (*Qvar; Ivax, UK*) range from 100 to 200 micrograms daily in mild asthma to 400 to 800 micrograms daily in severe asthma, given as 2 divided doses. See also Reformulation, p. 1622.3.

Beclometasone dipropionate is also used as a nasal spray and, like inhalation formulations used for asthma (see above), doses may appear to vary between countries depending on whether the dose is expressed in terms of the amount of drug supplied into, or emitted from, the nasal adaptor per actuation. In the prophylaxis and treatment of allergic and non-allergic **rhinitis** (p. 612.1), usual doses are 100 micrograms in each nostril twice daily or 50 micrograms in each nostril 3 or 4 times daily; a total of 400 micrograms daily should not generally be exceeded. A dose of 50 micrograms in each nostril twice daily may be sufficient for prophylaxis. The nasal spray is also used to prevent recurrence of **nasal polyps** after surgical removal (p. 1608.2).

Locally-acting formulations of beclometasone dipropionate are used in the management of **inflammatory bowel disease** (see p. 1622.1). In mild to moderate ulcerative colitis, a modified-release oral tablet is given in a dose of 5 mg once daily in the morning, before or after breakfast. Ulcerative colitis affecting the distal colon or rectum may be treated locally with a retention enema, usually in a dose of 3 mg daily at bedtime, or 1 mg once or twice daily. Treatment is usually given for 3 to 4 weeks.

Beclometasone dipropionate is also used topically in the treatment of various **skin disorders**. It is generally applied as a cream or ointment containing 0.025%. Beclometasone salicylate has also been used topically. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

For doses used in children, see below.

Administration in children. Beclometasone dipropionate, given by inhalation, is used in children in the prophylaxis of **asthma**. The appropriate product information should be consulted before starting therapy or changing to another formulation because of the range of products available and the different ways in which doses may be expressed (see Uses, above). In the UK the dose of most aerosol and dry powder inhalers for children aged 6 years and older is generally 100 micrograms given 2 to 4 times daily. The dose should be adjusted according to response, and reduced to the lowest effective dose for maintenance. In the USA, a hydrofluoroalkane (CFC-free) inhaler (*Qvar; Ivax, USA*), is licensed for use in children aged 5 years and older. Expressed in terms of the amount of drug delivered from the mouthpiece, the initial dose is 40 micrograms twice daily, which is then adjusted according to response; the recommended maximum dose is 80 micrograms twice daily.

In the treatment and prophylaxis of **rhinitis**, children over 6 years of age may be given adult doses (see above).

Adenoidal hypertrophy. Although normally managed by surgery (or if less severe simply by symptomatic relief) adenoidal hypertrophy in children was reported to respond to aqueous nasal beclometasone 336 micrograms daily in an 8-week crossover study.[1] Improvements in adenoidal obstruction and symptom scores were enhanced in a subsequent 16-week follow-on study using 168 micrograms daily. Another similar study,[2] of an initial 4-week crossover period followed by 24 weeks of open-label treatment, found symptomatic improvements in about half of the patients, and at 100 weeks there was a decrease in the rate of adenotonsillectomy in children who had responded to beclometasone compared with nonresponders.

1. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. *Pediatrics* 1995; **95:** 355–64.
2. Criscuoli G, *et al.* Frequency of surgery among children who have adenotonsillar hypertrophy and improve after treatment with nasal beclomethasone. Abstract: *Pediatrics* 2003; **111:** 663. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/3/e236 (accessed 27/04/04)

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

High-dose regimens may pose problems of compliance if beclometasone must be inhaled several times daily.

However, one study[1] found once-daily inhalation to be as effective as the same dose divided into 2 daily inhalations in short-term control of moderate asthma. Also there have been doubts that increasing the dose of inhaled beclometasone brings about increased benefits,[2] but guidelines and clinical practice suggest that improved control can often be achieved by increasing the dose. A systematic review[3] noted that while there was little evidence of an effect of dose titration above 400 micrograms daily in those with mild to moderate asthma, evidence was lacking in patients with more severe disease (who are more likely to be given high-dose therapy), and studies were needed to resolve the question.

Inhalation of beclometasone dipropionate as a nebulised solution has been found to be useful in the management of severe asthma in children aged 2 years or under previously unresponsive to other drugs.[4] Nebulised beclometasone dipropionate was also effective in the management of recurrent episodes of bronchopulmonary obstruction after bronchiolitis in children under 2 years of age.[5] However, in other reports nebulised beclometasone dipropionate, although more effective than saline in pre-school children, produced a response less than that usually seen with inhalation of beclometasone from an aerosol or capsules,[6] or no benefit at all.[7] This may have been due to beclometasone somehow failing to reach the lungs.[8] In pre-school children able to use a spacer device with a metered aerosol, intermittent therapy with high-dose beclometasone dipropionate, given at the first sign of symptoms, reduced the severity of acute episodic asthma.[9]

1. Gagnon M, *et al.* Comparative safety and efficacy of single or twice daily administration of inhaled beclomethasone in moderate asthma. *Chest* 1994; **105:** 1732–7.
2. Boe J, *et al.* High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal axis. *Eur Respir J* 1994; **7:** 2179–84.
3. Adams NP, *et al.* Beclomethasone versus placebo for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 22/08/08).
4. Pedersen W, Prahl P. Jet-nebulized beclomethasone dipropionate in the management of bronchial asthma: topical steroids for asthmatic children younger than 4 years. *Allergy* 1987; **42:** 272–5.
5. Carlsen KH, *et al.* Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch Dis Child* 1988; **63:** 1428–33.
6. Storr J, *et al.* Nebulised beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986; **61:** 270–3.
7. Webb MSC, *et al.* Nebulised beclomethasone dipropionate suspension. *Arch Dis Child* 1986; **61:** 1108–10.
8. Clarke SW. Nebulised beclomethasone dipropionate suspension: commentary. *Arch Dis Child* 1986; **61:** 1110.
9. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; **65:** 407–10.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1).

Cough. In children with recurrent cough inhalation of beclometasone 200 micrograms twice daily from a conventional aerosol or salbutamol 200 micrograms twice daily had no effect on cough frequency or severity.[1] However, in another study of 200 adults, use of beclometasone, salbutamol, or sodium cromoglicate (all in aerosol formulation) given 15 minutes before anaesthesia, significantly decreased coughing caused by fentanyl when compared with placebo. Of the 50 patients given beclometasone, none experienced coughing.[2]

1. Chang AB, *et al.* A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Arch Dis Child* 1998; **79:** 6–11.
2. Agarwal A, *et al.* Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. *Can J Anesth* 2003; **50:** 297–300.

Graft-versus-host disease. Beclometasone is under investigation for its topical effect in the treatment of intestinal graft-versus-host disease (GVHD) that can develop after haematopoietic stem cell transplantation (p. 1933.1). A few small studies have suggested that oral beclometasone dipropionate, given with an induction course of oral prednisone for systemic effect, can increase caloric intake, improve gastrointestinal symptoms, and provide an overall survival advantage in acute GVHD.[1] Promising results have also been reported in chronic intestinal GVHD.[2] Repeated courses may be needed in some patients to achieve and maintain response, but prolonged therapy appears to be feasible.[3]

1. Doan PL, Chao NJ. The role of oral beclometasone dipropionate in the treatment of gastrointestinal graft-versus-host disease. *Drugs* 2009; **69:** 1339–50.
2. Villanueva FN, *et al.* Oral beclomethasone dipropionate for the treatment of gastrointestinal chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2009; **15:** 1331–6.
3. Iyer RV, *et al.* Long-term use of oral beclomethasone dipropionate for the treatment of gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant* 2005; **11:** 587–92.

Inflammatory bowel disease. Beclometasone dipropionate 500 micrograms given nightly as an enema was as effective as betamethasone phosphate 5 mg enemas in the treatment of acute attacks of distal ulcerative colitis.[1] Although betamethasone produced slightly superior histological improvement and faster disappearance of blood from the stools, systemic adverse effects noted with betamethasone therapy were absent in patients treated with beclometasone.

Comparisons of beclometasone dipropionate enemas (3 mg) with prednisolone sodium phosphate enemas[2] (30 mg) or mesalazine enemas[3] (1 g) found them to be equally effective. Treatment was well tolerated. Beclometasone dipropionate has also been studied for the oral treatment of ulcerative colitis.[4,5]

For a review of the management of inflammatory bowel disease, including the role of corticosteroids, see p. 1808.3.

1. Halpern Z, *et al.* A controlled trial of beclomethasone versus betamethasone enemas in distal ulcerative colitis. *J Clin Gastroenterol* 1991; **13:** 38–41.
2. Campieri M, *et al.* Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis. *Aliment Pharmacol Ther* 1998; **121:** 361–6.
3. Gionchetti P, *et al.* Italian BDP Study Group. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial. *J Clin Gastroenterol* 2005; **39:** 291–7.
4. Rizzello F, *et al.* Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002; **16:** 1109–16.
5. Campieri M, *et al.* Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003; **17:** 1471–80.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Adrenal suppression may occur in some patients treated with high-dose long-term inhalation therapy for asthma. It has been stated that in the majority of patients no significant suppression is likely to occur when total daily doses of less than 1.5 mg are used (but see Adrenal Suppression, below).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Systemic absorption may also follow nasal use, particularly after high doses or prolonged treatment.

Adrenal suppression. The problem of adrenal suppression with corticosteroids is discussed on p. 1616.1. Listed below are some references and correspondence concerning adrenal suppression due to beclometasone inhalation therapy,[1-8] in some cases occurring with doses below 1.5 mg daily.[6] However, one study found that function of the hypothalamic-pituitary-adrenal axis remained normal in most patients at beclometasone doses below 3 mg daily.[9]

1. Grant IWB, Crompton GK. Becloforte inhaler. *BMJ* 1983; **286:** 644–5.
2. Slessor IM. Becloforte inhaler. *BMJ* 1983; **286:** 645.
3. Ebden P, Davies BH. High-dose corticosteroid inhalers for asthma. *Lancet* 1984; **ii:** 576.
4. Law CM, *et al.* Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. *Lancet* 1986; **i:** 942–4.
5. Brown HM. Nocturnal adrenal suppression in children inhaling beclomethasone dipropionate. *Lancet* 1986; **i:** 1269.
6. Maxwell DL, Webb J. Adverse effects of inhaled corticosteroids. *BMJ* 1989; **298:** 827–8.
7. Priftis K, *et al.* Adrenal function in asthma. *Arch Dis Child* 1990; **65:** 838–40.
8. Tabachnik E, Zadik Z. Diurnal cortisol secretion during therapy with inhaled beclomethasone dipropionate in children with asthma. *J Pediatr* 1991; **118:** 294–7.
9. Brown PH, *et al.* Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. *Thorax* 1993; **48:** 233–8.

Candidiasis. Results of a study involving 229 asthmatic children indicated that the presence of a sore throat or a hoarse voice was not related to the presence of *Candida* or to treatment with inhaled beclometasone.[1] The occurrence of only one clinical case of oral candidiasis in 129 of the children receiving beclometasone confirmed previous observations that it is an uncommon finding in children compared with the reported incidence of between 4.5 and 13% in adults. The incidence of colonisation with *Candida* was greater in those children who received corticosteroids than in those who did not but was not affected by either the dose or type of inhaler used.

1. Shaw NJ, Edmunds AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986; **61:** 788–90.

Effects on the bones. The adverse effects of corticosteroids in general on bones are discussed on p. 1616.2.

Studies in healthy subjects have shown that inhaled beclometasone dipropionate can suppress bone metabolism.[1-3] These studies measured biochemical markers such as serum-osteocalcin concentrations, serum alkaline phosphatase activity, and urinary hydroxyproline-creatinine ratio, over short periods of time. Another study found that markers of collagen turnover, but not osteocalcin, were reduced by beclometasone or budesonide 800 micrograms daily in mildly asthmatic children.[4] Results are difficult to interpret since osteocalcin concentrations are reduced in patients with asthma regardless of treatment,[5] and it is uncertain whether significant bone loss does occur in practice. One 12-month study[6] in adults with asthma found that biochemical markers showed suppressed bone formation from inhaled beclometasone, and that there was some loss of bone mineral density from the hip. This study also found that inhaled fluticasone, in equivalent therapeutic doses, may have less adverse effect on bone. Another, smaller, study[7] found no adverse effects from beclometasone or fluticasone on bone mass or metabolism. In a study[8] of asthmatic children, comparing those treated with inhaled budesonide with those who received no corticosteroids, an average daily dose of about 500 micrograms budesonide for 3 to 6 years did not adversely affect bone density and mineral measures.

1. Pouw EM, *et al.* Beclomethasone inhalation decreases serum osteocalcin concentrations. *BMJ* 1991; **302:** 627–8.
2. Ali N, *et al.* Beclomethasone and osteocalcin. *BMJ* 1991; **302:** 1080.
3. Teelucksingh S, *et al.* Inhaled corticosteroids, bone formation and osteocalcin. *Lancet* 1991; **338:** 60–1.
4. Birkebæk NH, *et al.* Bone and collagen turnover during treatment with inhaled dry powder budesonide and beclomethasone dipropionate. *Arch Dis Child* 1995; **73:** 524–7.
5. König P, *et al.* Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. *J Pediatr* 1993; **122:** 219–26.
6. Pauwels RA, *et al.* Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. *Am J Respir Crit Care Med* 1998; **157:** 827–32.
7. Medici TC, *et al.* Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax* 2000; **55:** 375–82.
8. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998; **157:** 178–83.

Effects on growth. Meta-analysis of 3 eligible studies (out of 92 examined) concluded that inhaled beclometasone therapy at a dose of 400 micrograms daily may cause a 1.54 cm/year decrease in growth in children with mild to moderate asthma.[1] The long-term effects of treatment are unknown, and therefore it is not clear whether catch-up growth will occur on stopping therapy. The lowest possible dose of corticosteroid therapy should be used in asthma, and growth should be monitored.[1] There is also evidence[2] that long-term intranasal beclometasone for the treatment of allergic rhinitis can slow growth in children; the effect on final height is unknown. For further details of the effects of corticosteroids on growth, see p. 1617.2.

1. Sharek PJ, *et al.* Beclomethasone for asthma in children: effects on linear growth. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).
2. Skoner DP, *et al.* Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Abstract: *Pediatrics* 2000; **105:** 415–16. Full version: http://pediatrics.aappublications.org/cgi/content/full/105/2/e23 (accessed 27/04/04)

Effects on the lungs. Pulmonary eosinophilia has occurred in patients treated with inhaled beclometasone.[1-4]

1. Paterson IC, *et al.* Pulmonary eosinophilia after substitution of aerosol for oral corticosteroid therapy. *Br J Dis Chest* 1975; **69:** 217–22.
2. Hudgel DW, Spector SL. Pulmonary infiltration with eosinophilia: recurrence in an asthmatic patient treated with beclomethasone dipropionate. *Chest* 1977; **72:** 359–60.
3. Klotz LR, *et al.* The use of beclomethasone dipropionate inhaler complicated by the development of an eosinophilic pneumonia reaction. *Ann Allergy* 1977; **39:** 133–6.
4. Mollura JL, *et al.* Pulmonary eosinophilia in a patient receiving beclomethasone dipropionate aerosol. *Ann Allergy* 1979; **42:** 326–9.

Hypersensitivity. There have been reports of asthmatic reactions to beclometasone dipropionate inhalations, possibly associated with materials used in their formulation, or with the containers.[1-4]

1. Maddern PJ, *et al.* Adverse reaction after aerosol inhalation. *Med J Aust* 1978; **1:** 274.
2. Godin J, Malo JL. Acute bronchoconstriction caused by Beclovent and not Vanceril. *Clin Allergy* 1979; **9:** 585–9.
3. Clark RJ. Exacerbation of asthma after nebulised beclomethasone dipropionate. *Lancet* 1986; **ii:** 574–5.
4. Beasley R, *et al.* Benzalkonium chloride and bronchoconstriction. *Lancet* 1986; **ii:** 1227.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies beclometasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Reformulation. Reformulation of some metered-dose inhalers to use a chlorofluorocarbon (CFC)-free propellant has resulted in a change of efficacy. One CFC-free product (*Qvar, UK*) was reported to be effective at about half the dose[1] required with the CFC-containing product (see Uses and Administration, p. 1621.2) and the UK CSM issued a reminder of the need for dosage reduction when converting from the conventional formulation to this product.[2] An open-label, crossover study in healthy subjects also found higher beclomethasone plasma concentrations after use of another brand (*Beclazone, Eire*) of CFC-free product.[3]

However, this dose reduction does not apply to all CFC-free formulations of beclometasone,[4] and the UK MHRA has advised that such products should be prescribed by trade name.[5] A review[6] concluded that good studies on the bioequivalence between the reference beclometasone preparation and the newer CFC-free formulations were not available.

1. Davies RJ, *et al*. Hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol provides equivalent asthma control to chlorofluorocarbon beclomethasone dipropionate at approximately half the total daily dose. *Respir Med* 1998; **92** (suppl): 23–31.
2. CSM/MCA. Dose of CFC-free inhaled beclomethasone (Qvar). *Current Problems* 1999; **25**: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 06/07/06)
3. Lipworth BJ, Jackson CM. Pharmacokinetics of chlorofluorocarbon and hydrofluoroalkane metered-dose inhaler formulations of beclomethasone dipropionate. *Br J Clin Pharmacol* 1999; **48**: 866–8.
4. Anonymous. Switching to CFC-free beclometasone for asthma. *Drug Ther Bull* 2008; **46**: 46–8.
5. MHRA. Beclometasone dipropionate pressurised metered dose inhaler (issued 8th August 2006). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024433&RevisionSelectionMethod=LatestReleased (accessed 15/03/10)
6. Derom E, Pauwels RA. Pharmacokinetic and pharmacodynamic properties of inhaled beclometasone dipropionate delivered via hydrofluoroalkane-containing devices. *Clin Pharmacokinet* 2005; **44**: 815–36.

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Beclometasone is stated to be readily absorbed from sites of local application, and rapidly distributed to all body tissues. It is metabolised mainly in the liver, but also in other tissues including gastrointestinal tract and lung; enzymatic hydrolysis rapidly produces the monopropionate (which has some glucocorticoid activity), and, more slowly, the free alcohol, which is virtually devoid of activity. Only a small proportion of an absorbed dose is excreted in urine, the remainder being excreted in the faeces mainly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Airbeclosona†; Menaderm Simple; Propavent; Rectomenaderm; Rinosol; ***Austral.***: Beconase Allergy & Hayfever 12 Hour; Beconase†; Becotide†; Qvar; ***Austria***: Aerocortin; Beclomet; Becotide; ***Belg.***: Beclometatop†; Beclophar; Beconase†; Clipper; Qvar; ***Braz.***: Alerfin; Beclort; Beclosol; Clenil; Miflasona; ***Canad.***: Gen-Beclo†; Mylan-Beclo; Propaderm; Qvar; Rivanase; ***Chile***: Beclosema†; Destap; Filair†; Flumates†; ***China***: Beconase (伯克纳); Becotide (必可酮); Beikele (贝可乐); ***Cz.***: Aldecin†; Becloforte; Beclomet; Becodisks†; Beconase†; Becotide†; Clenil; Ecobec; Nasobec; ***Denm.***: AeroBec; Beclomet; Beconase; Fostair; ***Fin.***: AeroBec; Beclomet; Beclonasal; Beconase; ***Fr.***: Asmabec; Beclo-Rhino; Beclojet; Beclone†; Beclospin; Beclospray; Beconase; Becotide; Bemedrex; Ecobec; Humex Rhume des Foins; Miflasone; Qvar; Qvarspray; Rhinomaxil; Rinoclenil; ***Ger.***: AeroBec†; Beclo†; Beclohexal†; Beclomet; Beclorhinol; Beconase Aquosum†; Bronchocort; Junik; Livocab direkt mit Beclometason†; ratioAllerg; Rhinivict; Sanasthmax; Sanasthmyl†; Ventolair; ***Gr.***: Beclomet; Becloneb; Beclospin; Becolex; Becotide; Bidiclin; Breathline; Clenil Forte Jet; Clenil Rino†; Clenil; Dermolate; Iriniozol; Qvar; Respocort; Rinosol; ***Hong Kong***: Beclate; Beclazone; Beconase; Cycloson†; Nasobec; Qvar†; ***Hung.***: Beclonasal; ***India***: Becderm; Beclasone; Beclate; Becloair; Becloderm; Becoride; Belar; Cortisone-BM; Econase; ***Indon.***: Beclomet†; Beconase†; Becotide†; Cleniderm; ***Irl.***: Asmabec; Beclazone; Beclo-Rhino†; Becloneb; Beclospin; Beconase Hayfever; Beconase; Becotide; Nasobec; Qvar; ***Israel***: Qvar; Viarex†; ***Ital.***: Becotide; Bemedrex; Clenil; Clenilexx; Clipper; Inalone; Klostenal; Menaderm Simplex; Prontinal; Rino Clenil; Topster; Turbinal; ***Jpn***: Propaderm; Rhinocort; Salcoat; ***Malaysia***: Beclate; Beclazone; Beclomet; Beconase; Belax; Clenil; Qvar; ***Mex.***: Beclazone†; Beconase; Becotide†; Dobipro; Riferina; ***Neth.***: Beclodin†; Beclofort†; Qvar; ***Norw.***: AeroBec; Beclomet; Becotide†; ***NZ***: Alanase; Atomase; Beclazone; Beconase Hayfever; Qvar; Respocort; ***Philipp.***: Qvar†; ***Pol.***: Beclonasal; Becodisk†; Cortare; Nasobec†; ***Port.***: Beclotaide; Beconase; Clenil†; Ecobec; Qvar; ***Rus.***: Aldecin (Альдецин); Beclate (Беклат); Beclazone (Беклазон); Becloforte (Беклофорте)†; Beclojet (Бекложет)†; Beclospir (Беклоспир); Becodisk (Бекодиск)†; Beconase (Беконазе)†; Becotide (Бекотид); Clenil (Кленил); Cycloson (Циклозон); Nasobec (Насобек); Rhinoclenil (Ринокленил); ***S.Afr.***: Beceze; Beclate; Beclofort†; Beconase; Becotide†; Ciplanaze; Clenil; Qvar; Ventnaze; ***Singapore***: Beclo Asma; Beclomet; Decomit; ***Spain***: Beclo Asma†; Beclo Rino; Becloenema; Becloforte; Beclosona†; Beconase; Becotide; Bidiclin; Clipper; Dereme†; Menaderm Simple; Recto Menaderm NF; ***Swed.***: AeroBec; Beclomet; Becotide; ***Switz.***: BECeco; Beclonarin†; Becodisk†; Beconase; Beconasol†; Qvar; ***Thai.***: Atomase†; Beclocip; Beclomet; Beconase; Bemase; Clenil; Qvar; Rino Clenil; ***Turk.***: Becloforte; Becodisks; Becotide†; Beklamet; Beklazon; Clenil; Filair; Rinoclenil; ***UAE***: Beclohale; ***UK***: AeroBec†; Asmabec; Beceze; Beclazone†; Beclogen; Becodisks†; Beconase; Clenil; Clipper; Filair; Hayfever Relief; Nasobec; Pollenase Nasal; Pulvinal Beclometasone Dipropionate; Qvar; Vivabec; ***Ukr.***: Beclazone (Беклазон); ***USA***: Beclovent; Beconase; Qnasl; Qvar; ***Venez.***: Beclofortil; Beclorino; Beclosil; Beconase; Biobeclasona; Biobeclod; Genbeclo; Nasair.

Multi-ingredient Preparations. ***Arg.***: Beclasma; Biotaer Nebulizable; Butocort; Butosol†; Menaderm N; Salbutol Beclo; Ventide; ***Austria***: Formodual; Foster; ***Belg.***: Inuvair; ***Braz.***: Aerocort S; Aerotide; Clenil Compositum; Fostair; ***Chile***: AeroPlus; Aerosoma†; Asmavent-B; Belomet; Butocort; Butotal B; Herolan Aerosol; Ventide; ***Cz.***: Combair; Formodual†; ***Denm.***: Innovair; ***Fin.***: Innovair; ***Fr.***: Formodual; Innovair; ***Ger.***: Foster; Inuvair; ***Gr.***: Beclomycin; Foster; Inuvair; ***Hong Kong***: Ventide†; ***Hung.***: Foster; ***India***: Adcort; Advin-NC; Aerocort; Aerotide; Aerovent; Anocream; Arima; Atasol; Baclasia-CG; Baclasia-CN; BC-Zole; Becderm-N; Beciosal; Beclasone-C; Beclasone-GM; Beclate-C; Beclate-N; Beclocid-G; Beclocid; Beclocin-O; Becloderm-C; Becloderm-N; Beclolab-CG; Beclolab-NC; Beclomin; Beclomin; Beclotis-C; Beclotis-CG; Beclozen; Becmet-CG; Becmet-CG; Becmet-G; Becmet-GM; Becmet-N; Becmet-S; Bectop; Becze-N; Belar-G; Benda; Bestec; Bestonim C; Bestonim N; Bestopic-N; Bestopic; Bugderm; Candasia-B; Candibiotic; Candid B; Candiderma +; Candiderma; Candikit-N; Candivate; Canesten-S; Canison-B; Canison-BN; Canoderma; Cazol-B; CBL; CLCD; Cloben-G; Cloben; Clobiotic; Clocip B; Clocip NB; Clofung GM; Clofung-G; Clofung-N; Clofung; Clomax BN; Clomax-B; Clomax-BG; Clorid-B; CNB; Corge-C; Cuticare; Cutigard; Decand B; Decand BG; Derbec-N; Derisone; Dermaspan; Derminol; Diprogen; Drep; Durabec; Eclospan; Ecodax-G; Elderm; Eligao; Everbate; Evergum; Excan; Fubac; Fucin-B; Fudec-B; Fungi-BC; Fusiwal-B; Fuson-B; GCB; Gemiderm; Gentalene Plus; Gentalene-C; Ifyclo-G; Imidil B; Imidil Plus; Infabact; Itchicos; Itchicure; Itchipol; Lamonte-BG; LBC; Leobet-GM; Leobet-NC; Leozole-B; Lotril-B; Lotril-BG; Mycoderm; Mycotic; Naderm RF; NC Derm; Neobate; Nifugal-B; Nivate-NC; Nuforce-GM; Olotic; Onderm; Otek-AC Plus; Otichek; Otiden; Otiderm; Otiflox; Otocin-O; Otocin; Otocos; Otosym; Pilovate; Sigmaderm; Stecort-NM†; Translipo-Triple; ***Indon.***: Ventide†; ***Ital.***: Clenil Compositum; Formodual; Foster; Inuver; Menaderm; ***Malaysia***: Aerocort; ***Mex.***: Ventide; ***Neth.***: Formodual; Foster; ***Norw.***: Inuxair; ***Philipp.***: Candibec; Combiderm; ***Pol.***: Fostex; ***Port.***: Formodual; Foster; ***Rus.***: Candibiotic (Кандибиотик); Candid B (Кандид Б); Candiderm (Кандидерм); Foster (Фостер); ***Spain***: Butosol; Formodual; Foster; Menaderm Clio; Menaderm Neomicina; Menaderm Otologico; ***Swed.***: Innovair; ***Thai.***: Beclosal; Clenil Compositum†; ***Turk.***: Belogent; Clenil Kompoze; Foster; Innovair; Ventide; ***UK***: Fostair; ***Ukr.***: Candibiotic (Кандибиотик); Candid B (Кандид-Б); Candiderm (Кандидерм); ***Venez.***: Aerocort; Beclosal; Butosol; Venticort; Ventide.

Pharmacopoeial Preparations

BP 2014: Beclometasone Aqueous Nasal Spray; Beclometasone Cream; Beclometasone Inhalation Powder, pre-dispensed; Beclometasone Inhalation Powder; Beclometasone Ointment; Beclometasone Pressurised Inhalation.

Betamethasone *(BAN, USAN, rINN)* ⊗

Beetametasoni; Betadexamethasone; Betametason; Betametasona; Betametazon; Betametazonas; Betamethason; Bétaméthasone; Betamethasonum; Flubenisolone; Flubenisolonum; 9α-Fluoro-16β-methylprednisolone; β-Methasone; NSC-39470; Sch-4831; Бетаметазон.

9α-Fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_5$=392.5

CAS — 378-44-9.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QD07XC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS01CB04; QS02BA07; QS03BA03.

UNII — 9842X06Q6M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Betamethasone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 36: (Betamethasone). A white to practically white, odourless, crystalline powder. Soluble 1 in 5300 of water, 1 in 65 of alcohol, 1 in 15 of warm alcohol, 1 in 325 of chloroform, and 1 in 3 of methyl alcohol; sparingly soluble in acetone and in dioxan; very slightly soluble in ether. Store in airtight containers at a temperature between 2 degrees and 30 degrees.

Betamethasone Acetate *(BANM, rINNM)* ⊗

Acetato de betametasona; Beetametasoniasetaatti; Betametasona, acetato de; Betametasonacetat; Betametazon Asetat; Betametazon-acetát; Betametazono acetatas; Betamethasonacetat; Betamethason-acetát; Bétaméthasone, Acétate de; Betamethasoni Acetas; Бетаметазона Ацетат.

Betamethasone 21-acetate.

$C_{24}H_{31}FO_6$=434.5

CAS — 987-24-6.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — TI05AO53L7.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Betamethasone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in dichloromethane; freely soluble in acetone. It shows polymorphism. Protect from light.

USP 36: (Betamethasone Acetate). A white to creamy-white, odourless powder. Soluble 1 in 2000 of water, 1 in 9 of alcohol, and 1 in 16 of chloroform; freely soluble in acetone. Store in airtight containers at a temperature between 2 degrees and 30 degrees.

Betamethasone Benzoate

(BANM, USAN, rINNM) ⊗

Benzoato de betametasona; Betametasona, benzoato de; Bétaméthasone, Benzoate de; Betamethasoni Benzoas; W-5975; Бетаметазона Бензоат.

Betamethasone 17α-benzoate.

$C_{29}H_{33}FO_6$=496.6

CAS — 22298-29-9.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — 877K0XW47A.

Pharmacopoeias. In *US*.

USP 36: (Betamethasone Benzoate). A white to practically white, practically odourless, powder. Insoluble in water; soluble in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers at a temperature between 2 degrees and 30 degrees.

Betamethasone Dipropionate

(BANM, USAN, rINNM) ⊗

Beetametasonidipropionaatti; Betametasona, dipropionato de; Betametasondipropionat; Betametazon Dipropiyonat; Betametazon-dipropionát; Betametazono dipropionatas; Betametazonu dipropionian; Betamethasondipropionat; Betamethason-dipropionát; Bétaméthasone, Dipropionate de; Betamethasoni Dipropionas; Dipropionato de betametasona; Sch-11460; Бетаметазона Дипропионат.

Betamethasone 17α,21-dipropionate.

$C_{28}H_{37}FO_7$=504.6

CAS — 5593-20-4.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — 826Y60901U.

NOTE. Compounded preparations of betamethasone dipropionate may be represented by the following names:

- Co-climasone (*PEN*)—clotrimazole and betamethasone dipropionate.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Betamethasone Dipropionate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Betamethasone Dipropionate). A white to cream-white, odourless powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in chloroform. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Betamethasone Sodium Phosphate

(BANM, rINNM) ⊗

Beetametasoninatriumfosfaatti; Betametasona, fosfato sódico de; Betametasonnatrifosfatum; Betametazon Disodyum Fosfat; Betametazon-nátrium-foszfát; Betametazono natrio fosfatas; Betamethasondihydrogenphosphat-Dinatrium; Betamethasone Disodium Phosphate; Bétaméthasone, phosphate sodique de; Betamethason-fosfát sodná sůl; Betamethasoni natrii phosphas; Fosfato sódico de betametasona; Natrii Betamethasoni Phosphas; Натрия Бетаметазона Фосфат.

Betamethasone 21-(disodium phosphate).

$C_{22}H_{28}FNa_2O_8P$=516.4

CAS — 360-63-4 (betamethasone phosphate); 151-73-5 (betamethasone sodium phosphate).

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.
ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.
UNII — 7BK02SCL3W.

NOTE. BET is a code approved by the BP 2014 for use on single unit doses of eye drops containing betamethasone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Betamethasone Sodium Phosphate). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.5 to 9.0. Store in airtight containers. Protect from light.

USP 36: (Betamethasone Sodium Phosphate). A white to practically white, odourless, hygroscopic, powder. Soluble 1 in 2 of water and 1 in 470 of alcohol; freely soluble in methyl alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers.

Betamethasone Valerate

(BANM, USAN, rINNM) ⊗

Betametasonivaleraatti; Betametasona, valerato de; Betametasonvalerat; Betametazon Valerat; Betametazono valeratas; Betametazonu walerianian; Betametazon-valerát; Béta-méthasone, valérate de; Betamethasoni Valeras; Betamethasonvalerat; Betamethason-valerát; Valerato de betametasona; Бетаметазона Валерат.

Betamethasone 17α-valerate.

$C_{27}H_{37}FO_6$=476.6

CAS — 2152-44-5.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.
ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.
UNII — 9IFA5XM7R2.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Betamethasone Valerate). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Betamethasone Valerate). A white to practically white, odourless, powder. Practically insoluble in water; soluble 1 in 16 of alcohol, 1 in less than 10 of chloroform, and 1 in 400 of ether; freely soluble in acetone; slightly soluble in benzene. Store in airtight containers.

Uses and Administration

Betamethasone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); the anti-inflammatory activity of 750 micrograms of betamethasone is equivalent to about 5 mg of prednisolone. It has been used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (p. 1597.3), except adrenal-deficiency states for which hydrocortisone with supplementary fludrocortisone is preferred. Its virtual lack of mineralocorticoid properties makes betamethasone particularly suitable for treating conditions in which water retention would be a disadvantage.

The dose is usually expressed in terms of the base, and the following are each equivalent to about 1 mg of betamethasone:

- betamethasone acetate 1.1 mg
- betamethasone benzoate 1.3 mg
- betamethasone dipropionate 1.3 mg
- betamethasone sodium phosphate 1.3 mg
- betamethasone valerate 1.2 mg

However, esterification generally alters potency and compounds with equivalent betamethasone content may not have equivalent clinical effect.

When given **orally** betamethasone or betamethasone sodium phosphate are used; the usual dose, expressed in terms of betamethasone, ranges from 0.5 to 5 mg daily.

For **parenteral** use the sodium phosphate ester may be given intravenously by injection or infusion or intramuscularly by injection in doses equivalent to 4 to 20 mg of betamethasone. Doses may be repeated 3 or 4 times in 24 hours if necessary, depending on the condition being treated and the clinical response. It may also be given by local injection into soft tissues in doses equivalent to 4 to 8 mg of betamethasone. The dose may be repeated on 2 or 3 occasions, according to patient response. The sodium phosphate ester is also sometimes used with the acetate or dipropionate esters, which have a slower and more prolonged action. These suspensions may be given by intramuscular injection for a systemic effect, or by intra-articular, soft-tissue, or intralesional injection for local therapy.

For doses used in children, see below.

Betamethasone sodium phosphate is also used in the **topical** treatment of allergic and inflammatory conditions of the eyes, ears, or nose, usually as drops or ointment containing 0.1%.

For topical application in the treatment of various skin disorders the dipropionate and valerate esters of betamethasone are extensively used in creams, ointments, lotions, and scalp applications. The usual concentrations available are the equivalent of 0.05% of betamethasone as the dipropionate, and 0.025 or 0.1% as the valerate. A medicated plaster containing betamethasone valerate is also available. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Betamethasone valerate has also been used by **inhalation** for the prophylaxis of asthma.

Other esters of betamethasone which have occasionally been used include the benzoate, butyrate propionate, phosphate, salicylate (cortobenzolone), and valero-acetate.

Betamethasone adamantoate has been used in veterinary practice.

Administration in children. For **parenteral** use betamethasone sodium phosphate may be given intravenously by injection or infusion. It may be given to provide the following doses equivalent to betamethasone:

- infants aged up to 1 year: 1 mg
- 1 to 5 years: 2 mg
- 6 to 12 years: 4 mg
- 12 years and older: adult doses (see above)

Doses may be repeated 3 or 4 times in 24 hours if necessary, depending on the condition being treated and the clinical response.

Haemangioma. For reference to the use of a mixture of betamethasone and triamcinolone for the intralesional injection of haemangiomas, see p. 1605.3.

Inflammatory bowel disease. For a comparison of betamethasone and beclometasone enemas in the treatment of ulcerative colitis, see under Beclometasone, p. 1622.1. Corticosteroids are one of the mainstays of treatment of inflammatory bowel disease, the general management of which is discussed on p. 1808.3.

Neonatal respiratory distress syndrome. For a discussion on the antenatal use of betamethasone to prevent neonatal respiratory distress syndrome, see p. 1608.3.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Betamethasone has little or no effect on sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Anosmia. Complete anosmia was reported in 2 patients after the use of nasal drops containing betamethasone and neomycin sulfate[1] and, in one patient, showed no sign of resolving 1 year later. The reaction was thought to be due to the preservative thiomersal present in the drops, although it was noted that neomycin could exert a toxic effect on the olfactory mucosa and that there have been several reports of anosmia associated with the use of betamethasone alone.

1. Whittet HB, *et al.* Anosmia due to nasal administration of corticosteroid. *BMJ* 1991; **303:** 651.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies betamethasone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Betamethasone crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bactisona; Betacort; Betacort; Betacort; Betasone-G 12 Horas; Betasone-G; Betatopic; Betnovate Capilar; Betnovate; Biocur; Blacor; Butasona RL; Butasona; Celestone Cronodose; Celestone; Cevicort NC; Cevicort; Coid; Corteroid Retard; Corteroid; Corticas Retard; Corticas; Cortiderma; Cortimar†; Crono Corticas; Cronobetacort; Cronocorteroid; Cronodicasone Depot; Cronodicasone; Cronolevel; Deltalaf; Depocort Crono; Depocort Retard; Depocort; Dermizol; Dicasone; Difenac Forte; Diprosone; Lazar-Cort; Metamar; Micosep B; Quiacort; Rapi-Betacort; Transderma B; Valederm; Vitacortil B; ***Austral.***: Antroquoril; Betnovate; Celestone Chronodose; Celestone M; Cortival; Diprosone; Eleuphrat; ***Austria***: Betnesol; Betnovate; Celestan; Diproderm; Diproforte; Diprophos; Solu-Celestan; ***Belg.***: Betnelan-V; Betnesol; Celestone Chronodose; Celestone; Diprolene; Diprosone; ***Braz.***: Beclonato; Benevat; Beta Long; Betaderm; Betametagen; Betaprospan; Betaspan; Betatrinta; Betnelan; Betnolon; Betnovate; Betrat B; Betrospam; Betsona; Celestone Soluspan; Celestone; Dermatisan; Diprobeta; Diprocort; Diprosen; Diprosone; Diprospan; Duoflam; Koide; Sensitex†; Valbet; ***Canad.***: Betaderm, Betaject; Betnesol; Celestoderm; Celestone Soluspan; Diprolene; Diprosone; Luxiq; Prevex B; ratio-Ectosone; ratio-Topilene; ratio-Topisone; Rivasone; Rolene; Rosone; Taro-Sone; Valisone; ***Chile***: Cidoten Rapilento; Cidoten V; Cidoten; Coritex; Cremirit; Cronolevel; Dacam RL; Dacam; Diprolene†; Diprospan; Diprospan; Disopranil; Esancort; Konicortil; Labosona; Oftasona P; Spel†; ***China***: Bei Shi Li (贝施利); Beisong (倍松); Diprospan (得宝松); Li Yan Jia (力言佳); Zheng Tuo (正妥); ***Cz.***: Beloderm; Betesil; Betnovate; Diprophos; Diprosone; Kuterid; ***Denm.***: Betnovat; Betnovate; Bettamousse; Celeston; Celeston; Diproderm; Diprofos; Diprolen; Diprospan; ***Fin.***: Bemetson; Betapred; Betnovat; Bettamousse; Celestoderm; Celeston Chronodose; Diproderm; Diprolen; ***Fr.***: Betesil; Betnesol; Betneval; Buccobet; Celestene Chronodose; Celestene; Celestoderm†; Diprolene; Diprosone; ***Ger.***: Bemon; Beta-Creme†; Betagalen; BetaLotio†; BetaSalbe†; Betnesalic mono†; Betnesol-V; Betnesol; Celestamine N; Celestan Depot; Celestan solubile; Celestan-V; Cordes Beta; Deflatop; Diprosis; Diprosone Depot; Diprosone; Linolacort Beta; Soderm; ***Gr.***: Alo-Haar; Bagoco†; Betamatic; Betatape; Betnesol; Betnovate; Celestene; Celestoderm-V; Celestone Chronodose; Celestone; Flogozyme; Galinocort; Helpoderm; Iracliton†; Locason-N†; Locason; Movithiol; Osmoran; Propiochrone; Propioform; Sanorvil; ***Hong Kong***: Beprogel; Beprosone; Betasone; Betnovate; Betowel†; CP-Betasone†; Derzid; Diprocel; Diprosone; Diprospan; Synmethasone†; Uniflex†; ***Hung.***: Betesil; Diprophos; ***India***: Acticard; Belar; Belsone; Ben; Benicort; Betacortril; Betafoam; Betagel; Betalar; Betamil; Betamine; Betariv; Betawin; Betnecip; Betnecort; Betnederm; Betnelan; Betnesol; Betni; Betnovate; Betsone; Bevent; Celestone; Cortiderm; Cortil; Diplene; Diprovate; Glosone; Lupiderm; Milbeta; Ocusone; Topicasone; Valbet; Walacort; ***Indon.***: Benoson; Betam-Ophtal; Betason; Betnovate†; Betodermin; Betopic; Celestoderm-V; Celestone; Corsaderm; Diprosone-OV; Exabet†; Mesonta†; Metonate; Molason; Oviskin; Proson†; Protocort; Scanderma; Skizon†; Vason†; ***Irl.***: Betacap; Betnelan†; Betnesol; Betnovate; Bettamousse; Diprosone; ***Israel***: Betacap; Betacorten; Betnesol; Betnovate; Bettamousse; Celestone Chronodose; Diprolene†; Diprosone†; Diprospan; ***Ital.***: Beben; Bentelan; Beta 21; Betamesol; Betesil; Bettamousse; Celestone Cronodose; Celestone; Cortiflam; Diprosone; Ecoval; ***Malaysia***: Beavate; Benosone; Beprogel; Beprosone; Besone; Beta; Betamet; Betasone; Betnosone†; Betnovate; Bufencon; Daivobet; Dibetasol†; Diprocel; Diprosone; Diprospan; Uniflex; ***Mex.***: Betnovate; Celestone Soluspan; Celestone; Cronolevel; Dermoval; Diprofast; Diprovate†; Diprosone†; Diprospan; Disons Dex; Erispan; Reubaxona; ***Neth.***: Betnelan; Betnesol; Celestoderm†; Celestone Chronodose; Celestone; Diprolene; Diprosone; ***Norw.***: Betnovat; Bettamousse; Celeston; Diproderm; ***NZ***: Beta; Betnesol; Betnovate; Bivate; Celestone Chronodose; Diprolene†; Diprosone; ***Philipp.***: Beprosone; Beta-D; Beta; Betaderm; Betnelan; Betnovate; Celestone; Diprolene; Diprosone; Diprospan; Hoebenate; Innodesone; Steroderm; ***Pol.***: Beloderm; Celestone; Diprolene; Diprophos; Diprosone†; Kuterid; ***Port.***: Betnovate; Celesdepot; Celestone; Cilestoderme; Diprofos; Diprosone; Soluderme; ***Rus.***: Akriderm (Акридерм); Beloderm (Белодерм); Betasone (Бетазон); Celestoderm-V (Целестодерм-В); Celestone (Целестон); Diprospan (Дипроспан); Flosteron (Флостерон); ***S.Afr.***: Betanoid; Betnesol; Betnovate; Celestone Soluspan; Celestone; Diprosone; Lenasone; Lenovate; Persivate; Repivate; Steromien; Topivate; ***Singapore***: Beprogel; Beprosone; Besone; Betacorten†; Betasone; Betnovate; Camnovate; Dermasone; Derzid; Dibetasol; Diprocel; Diprosone; Diprospan; HD-Betasone; Medobeta; SP-Betasone; Synmethasone; Uniflex; ***Spain***: Betnovate; Bettamousse; Celestoderm-V; Celestone Cronodose; Diproderm; ***Swed.***: Betapred; Betnoderm†; Betnovat; Bettamousse; Celeston bifas; Celeston valerat†; Diproderm; Diprolen; ***Switz.***: Betnesol; Betnovate; Celestoderm-V†; Celestone Chronodose; Celestone†; Diprolene; Diprosone; ***Thai.***: Beprogel; Bepronate; Beprosone; Besone; Bessasone†; Beta; Betacort; Betama; Betameth; Bethasone; Betnovate; Betosone; Bipro†; Clinivate; Derzid; Diprobet; Diprosone; Diprospan; Diprotop; Hofra B; Polynovate; Sebo; TM Bet; Valbet; Valerbet; ***Turk.***: Betnovate; Celestoderm-V; Celestone Chronodose; Dermabel; Dermakord; Diprolene; Diprospan; Novovate; Seroderm; ***UAE***: Betasone; Betasone; ***UK***: Betacap; Betesil; Betnelan†; Betnesol; Betnovate RD (Ready Diluted); Betnovate; Bettamousse; Diprosone; Vista-Methasone; ***Ukr.***: Betaspan

(Бетаспан); Celestoderm (Целестодерм); Celeston (Целестон); Diprospan (Дипроспан); Flosteron (Флостерон); Mesoderm (Мезодерм); ***USA***: Beta-Val; Cel-U-Jec; Celestone Soluspan; Celestone; Diprolene; Diprosone†; Luxiq; Maxivate; Valisone; ***Venez.***: Beprospen; Betacort; Betaderm; Betagen Solspen; Betagen; Betnovate; Celestoderm; Celestone Soluspan; Celestone; Diprocel; Diprosone; Diprospan; Itisona.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Betamethasone Eye Drops; Betamethasone Injection; Betamethasone Sodium Phosphate Tablets; Betamethasone Tablets; Betamethasone Valerate Cream; Betamethasone Valerate Lotion; Betamethasone Valerate Ointment; Betamethasone Valerate Scalp Application;

USP 36: Betamethasone Benzoate Gel; Betamethasone Cream; Betamethasone Dipropionate Cream; Betamethasone Dipropionate Lotion; Betamethasone Dipropionate Ointment; Betamethasone Dipropionate Topical Aerosol; Betamethasone Oral Solution; Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension; Betamethasone Sodium Phosphate Injection; Betamethasone Syrup; Betamethasone Tablets; Betamethasone Valerate Cream; Betamethasone Valerate Lotion; Betamethasone Valerate Ointment; Clotrimazole and Betamethasone Dipropionate Cream.

Budesonide *(BAN, USAN, rINN)* ⊗

Budesonid; Budesónida; Budésonide; Budesonidi; Budesonidum; Budezonid; Budezonidas; S-1320; Будезонид.

An epimeric mixture of the α- and β-propyl forms of 16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

$C_{25}H_{34}O_6$=430.5

CAS — 51333-22-3 (11β,16α); 51372-29-3 (11β,16α(R)); 51372-28-2 (11β,16α(S)).

ATC — A07EA06; D07AC09; H02AB16; R01AD05; R03BA02.

ATC Vet — QA07EA06; QD07AC09; QR01AD05; QR03BA02.

UNII — Q3OKS62Q6X (11β,16α(RS)); 168L5HT37P (11β,16α(S)).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Budesonide). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

USP 36: (Budesonide). A white to off-white, odourless, crystalline powder. Practically insoluble in water and in heptane; sparingly soluble in alcohol; freely soluble in chloroform. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Budesonide is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It is used by inhalation in the management of **asthma** (below), in usual doses of 400 micrograms daily in 2 divided doses from a metered-dose aerosol; in severe asthma the dosage may be increased up to a total of 1.6 mg daily, and guidelines for the management of asthma permit up to 2 mg daily. Maintenance doses may be less than 400 micrograms daily but should not be below 200 micrograms daily. Budesonide is also available for the management of asthma in the form of a dry powder inhaler; doses are 200 to 800 micrograms daily, as 2 divided doses or a single daily dose; up to 800 micrograms twice daily may be given if necessary. Patients for whom budesonide from a pressurised inhaler or dry powder formulation is unsatisfactory may use a nebulised solution. The usual starting dose when asthma is severe, or while reducing or stopping oral corticosteroids, is 1 to 2 mg inhaled twice daily. This may be increased if asthma is very severe. Maintenance doses are 0.5 to 1 mg inhaled twice daily.

Budesonide is used intranasally for the prophylaxis and treatment of **rhinitis** (p. 612.1). In the UK, two nasal spray preparations are available, one containing 100 micrograms per metered spray, and one containing 64 micrograms per metered spray. The initial recommended dose is either 2 sprays into each nostril once daily in the morning, or 1 spray into each nostril twice daily. This may be subsequently reduced to 1 spray into each nostril once daily; treatment can be continued for up to 3 months. In the USA, a nasal spray delivering 32 micrograms of budesonide per actuation is available. The recommended initial dose is 1 spray into each nostril once daily, increasing as necessary up to a maximum of 4 sprays in each nostril once daily. The dose should then be reduced to the lowest effective dose that maintains control of symptoms.

Budesonide is also used as a nasal spray in the management of **nasal polyps** (p. 1608.2). In the UK, 1 spray (containing 64 or 100 micrograms, as above) is given into each nostril twice daily for up to 3 months. As an alternative, some preparations containing doses of 64 micrograms may be given as 2 sprays into each nostril once daily.

Locally-acting formulations of budesonide are used in the management of **inflammatory bowel disease** (see below). In mild to moderate Crohn's disease affecting the ileum or ascending colon it is given orally as modified-release capsules intended for a topical effect on the gastrointestinal tract. The recommended dose is 9 mg daily for active disease, as either a single dose before breakfast or in 3 divided doses about 30 minutes before meals, depending on the preparation. Treatment is given for up to 8 weeks, and the dosage should be reduced 2 to 4 weeks before discontinuing therapy. For recurring episodes of active Crohn's disease, an 8-week course may be repeated. After an 8-week course for active disease, budesonide 6 mg once daily is recommended for maintenance of clinical remission, for up to 3 months; thereafter, doses are tapered and therapy stopped, as continued treatment has not shown substantial clinical benefit. There is some absorption of budesonide from the gastrointestinal tract, and the dose may need to be reduced in patients with hepatic impairment, especially those with cirrhosis (see also Hepatic Impairment, p. 1626.2). Ulcerative colitis affecting the rectum and sigmoid colon may be treated locally with budesonide. A retention enema providing a dose of 2 mg in 100 mL is given daily at bedtime for 4 weeks, which may be extended to 8 weeks if the patient is not in remission after the initial 4-week course. Alternatively, a rectal foam can be used in a dose of 2 mg once daily, usually for 6 to 8 weeks. The dose may be given in the morning or the evening, but treatment is more effective if the bowel is emptied before a dose is given.

Locally-acting formulations of budesonide are also used in the management of **collagenous colitis** (see Microscopic Colitis, p. 1626.1). It is given orally as modified-release capsules in a dose of 3 mg three times daily for up to 8 weeks. The dosage should be reduced gradually during the last 2 weeks of therapy.

A viscous oral formulation of budesonide is under investigation for the local treatment of **eosinophilic oesophagitis** (p. 1807.1).

Budesonide is used topically in the treatment of various **skin disorders**, as a cream, lotion, or ointment containing 0.025%. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

For doses used in children, including the use of budesonide in childhood **croup**, see below.

General reviews.

1. Brogden RN, McTavish D. Budesonide: an updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 1992; **44:** 375–407 and 1012.
2. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. *Drugs* 2000; **60:** 1141–78.
3. Stanaland BE. Once-daily budesonide aqueous nasal spray for allergic rhinitis: a review. *Clin Ther* 2004; **26:** 473–92.

Administration. *INHALATIONAL ROUTE.* One study in 6 children aged up to 30 months found that about 75% of the nominal dose of nebulised budesonide was deposited in the nebuliser system,[1] while a study in 126 older children indicated that maintenance doses of budesonide could be halved when the dose was given by dry powder inhaler rather than nebuliser, without any loss of asthma control.[2] Although oropharyngeal deposition is thought to play a role in the systemic effects of inhaled corticosteroids, another study[3] indicated that only about 20% of the systemically available drug appeared to be derived from oropharyngeal deposition after inhalation from a dry powder inhaler.

There is evidence that the timing of inhaled therapy might influence some systemic effects. A study[4] in children with mild asthma found that 800 micrograms of budesonide inhaled in the morning had less effect on measurements of short-term growth and collagen turnover than inhalation of 400 micrograms twice daily.

1. Carlsen KCL, *et al*. How much nebulised budesonide reaches infants and toddlers? *Arch Dis Child* 1992; **67:** 1077–9.
2. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993; **69:** 130–3.
3. Pedersen S, *et al*. The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbuhaler. *Br J Clin Pharmacol* 1993; **36:** 211–14.
4. Heuck C, *et al*. Adverse effects of inhaled budesonide (800 micrograms) on growth and collagen turnover in children with asthma: a double-blind comparison of once-daily versus twice-daily administration. *J Pediatr* 1998; **133:** 608–12.

Administration in children. Budesonide is used by inhalation in the management of **asthma** in children. Using a metered-dose aerosol, children aged from 2 to 12 years old may be given 200 to 800 micrograms daily, in divided doses. A dry powder inhaler, which is breath-actuated, may be used in children aged 5 years and older in doses of 200 to 800 micrograms daily in 2 divided doses. Daily doses of up to 400 micrograms may be given as a single daily dose. If these methods of delivery are unsatisfactory, a nebulised solution may be used. For children between 3 months and 12 years of age, an initial dose of 0.5 to 1 mg twice daily may be given. The maintenance dose is usually 250 to 500 micrograms twice daily, but a dose of 250 micrograms once daily may be adequate.

Budesonide is also given by inhalation as a nebulised solution in the management of childhood **croup** (p. 1603.3). The usual dose is 2 mg, as a single inhaled dose or as 2 doses of 1 mg given 30 minutes apart.

Budesonide may be used intranasally in the prophylaxis and treatment of allergic **rhinitis** in children aged 6 years and older. In the UK, a nasal spray containing 64 micrograms per metered spray may be used in similar doses to those used in adults (see Uses and Administration, above). In the USA, the recommended initial dose of a spray delivering 32 micrograms per actuation is 1 spray into each nostril once daily, increasing as necessary to a maximum of 2 sprays into each nostril once daily. The dose should then be reduced to the lowest effective dose that maintains control of symptoms.

In the UK, a nasal spray containing 64 micrograms per metered spray may also be given in similar doses to those used in adults (see Uses and Administration, above) for the management of **nasal polyps** in children aged 6 years and older.

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

References to the use of budesonide in asthma.[1-7] Its use as a fixed-dose combination with formoterol has also been reviewed.[8-10]

1. Baker JW, *et al*. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999; **103:** 414–21.
2. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; **343:** 1054–63.
3. Leflein JG, *et al*. Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. *Pediatrics* 2002; **109:** 866–72.
4. Pauwels RA, *et al*. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; **361:** 1071–6.
5. FitzGerald JM, *et al*. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004; **59:** 550–6.
6. Berger WE, *et al*. Safety of budesonide inhalation suspension in infants aged six to twelve months with mild to moderate persistent asthma or recurrent wheeze. *J Pediatr* 2005; **146:** 91–5.
7. Berger WE. Budesonide inhalation suspension for the treatment of asthma in infants and children. *Drugs* 2005; **65:** 1973–89.
8. Goldsmith DR, Keating GM. Budesonide/formoterol: a review of its use in asthma. *Drugs* 2004; **64:** 1597–1618.
9. McCormack PL, Lyseng-Williamson KA. Budesonide/formoterol: a review of its use as maintenance and reliever inhalation therapy in asthma. *Drugs* 2007; **67:** 2407–31.
10. Lyseng-Williamson KA, Simpson D. Budesonide/formoterol pressurized metered-dose inhaler. *Drugs* 2008; **68:** 1855–64.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1). The use of a fixed-dose combination of budesonide and formoterol has been reviewed.[1,2]

1. Reynolds NA, *et al*. Budesonide/formoterol: in chronic obstructive pulmonary disease. *Drugs* 2004; **64:** 431–41.
2. Lyseng-Williamson KA. Budesonide/formoterol pressurized metered-dose inhaler: in chronic obstructive pulmonary disease. *Drugs* 2009; **69:** 1459–70.

Cystic fibrosis. Cystic fibrosis (p. 177.2) is associated with bronchial hyper-responsiveness; a small study[1] has suggested that inhalation of budesonide 1.6 mg daily for 6 weeks improves hyper-responsiveness slightly and leads to improvement in cough and dyspnoea. A larger study[2] of budesonide given for two successive 3-month treatment periods found improved hyper-responsiveness and a trend towards slower decline in lung function.

1. Van Haren EHJ, *et al*. The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995; **89:** 209–14.
2. Bisgaard H, *et al*. Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med* 1997; **156:** 1190–6.

Inflammatory bowel disease. Budesonide has been given as an enema for the treatment of distal ulcerative colitis, in which context its potency and low systemic availability are advantageous.[1] A rectal foam has also been developed, which may be easier to use, and retain in the bowel, than an enema.[2] Budesonide is available as a modified-release oral dosage form for the management of active Crohn's disease.[1,3] Ileal-release preparations of budesonide have been indicated as first-line therapy in the treatment of mild to moderate ileal and right-sided colonic Crohn's disease.[4] Systematic review[5] has suggested that it is slightly less effective than conventional corticosteroid therapy, but is associated with fewer adverse effects. Budesonide has also been effective in delaying relapse in quiescent disease.[6-8] However, the benefit appears to be short-term (3 months)[4] and it has been concluded that oral modified-release budesonide is not effective in long-term (12

months) maintenance of remission.[4,9] Similarly, oral budesonide was ineffective in preventing postoperative recurrence after resection for Crohn's disease.[10]

For a discussion of inflammatory bowel disease, see p. 1808.3.

1. Spencer CM, McTavish D. Budesonide: a review of its pharmacological properties and therapeutic efficacy in inflammatory bowel disease. *Drugs* 1995; **50:** 854–72.
2. Gross V, *et al.* Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 2006; **23:** 303–12.
3. McKeage K, Goa KL. Budesonide (Entocort EC capsules): a review of its therapeutic use in the management of active Crohn's disease in adults. *Drugs* 2002; **62:** 2263–82.
4. Lichtenstein GR, *et al.* American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; **130:** 935–9. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508506000734.pdf (accessed 22/09/06)
5. Seow CH, *et al.* Budesonide for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 22/08/08).
6. Greenberg GR, *et al.* Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled dose-ranging study. *Gastroenterology* 1996; **110:** 45–51.
7. Löfberg R, *et al.* Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease: a placebo controlled one year study. *Gut* 1996; **39:** 82–6.
8. Gross V, *et al.* Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. *Gut* 1998; **42:** 493–6.
9. Benchimol EI, *et al.* Budesonide for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 12/03/10).
10. Hellers G, *et al.* Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. *Gastroenterology* 1999; **116:** 294–300.

Microscopic colitis. Budesonide has been studied in the treatment of microscopic colitis (p. 1811.1). It has been used in a few small controlled studies[1-5] of the management of collagenous colitis. Treatment courses given orally for 6 or 8 weeks were found to improve symptoms and histology, and the short-term benefits have been confirmed by meta-analysis,[6] although high rates of relapse after stopping treatment have been reported.[3,5] Treatment for up to 6 months has been reported to maintain remission,[7,8] but the risk of relapse is still high after therapy is stopped.[8]

Oral budesonide has also been studied with some success in a small number of patients with lymphocytic colitis.[9]

1. Baert F, *et al.* Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 2002; **122:** 20–5.
2. Miehlke S, *et al.* Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Gastroenterology* 2002; **123:** 978–84.
3. Bonderup OK, *et al.* Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut* 2003; **52:** 248–51.
4. Madisch A, *et al.* Oral budesonide therapy improves quality of life in patients with collagenous colitis. *Int J Colorectal Dis* 2005; **20:** 312–16.
5. Miehlke S, *et al.* Long-term follow-up of collagenous colitis after induction of clinical remission with budesonide. *Aliment Pharmacol Ther* 2005; **22:** 1115–19.
6. Feyen B, *et al.* Meta-analysis: budesonide treatment for collagenous colitis. *Aliment Pharmacol Ther* 2004; **20:** 745–9.
7. Miehlke S, *et al.* Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2008; **135:** 1510–16.
8. Bonderup OK, *et al.* Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gut* 2009; **58:** 68–72.
9. Miehlke S, *et al.* Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. *Gastroenterology* 2009; **136:** 2092–2100.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Inhalation of high doses of budesonide is associated with some adrenal suppression. Systemic absorption may follow nasal use, particularly after high doses or prolonged treatment. The dose of oral budesonide may need to be reduced in hepatic impairment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Reviews.

1. Christensson C, *et al.* Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. *Drug Safety* 2008; **31:** 965–88.

Effects on the bones. For mention of the effects of inhaled budesonide on markers of collagen turnover and bone density in asthmatic children, see under Adverse Effects of Beclometasone, p. 1622.2. For the suggestion that inhalation once-daily in the morning may have less marked effects on growth and collagen turnover than twice-daily inhalation, see Administration, p. 1625.2.

Effects on the nervous system. Psychotic behaviour has been reported after use of inhaled budesonide.[1-3]

1. Lewis LD, Cochrane GM. Psychosis in a child inhaling budesonide. *Lancet* 1983; **ii:** 634.
2. Meyboom RHB, de Graff-Breederveld N. Budesonide and psychic side effects. *Ann Intern Med* 1988; **109:** 683.
3. Connett G, Lenney W. Inhaled budesonide and behavioural disturbances. *Lancet* 1991; **338:** 634–5.

Hepatic impairment. In a study[1] of patients with primary biliary cirrhosis the clearance of oral budesonide was significantly reduced in those with cirrhosis (stage IV) compared with milder disease (stage I/II). Elevated budesonide concentrations were sufficient to suppress cortisol production, and believed to be associated with the development of portal vein thrombosis in 2 cirrhotic patients.

1. Hempfling W, *et al.* Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. *Hepatology* 2003; **38:** 196–202.

Hypersensitivity. Contact dermatitis has been reported to topical or intranasal budesonide.[1] An anaphylactoid reaction occurred 5 minutes after the first dose of oral budesonide in a patient who had previously reacted in a similar way to mesalazine.[2]

1. Quintiliani R. Hypersensitivity and adverse reactions associated with the use of newer intranasal corticosteroids for allergic rhinitis. *Curr Ther Res* 1996; **57:** 478–88.
2. Heeringa M, *et al.* Anaphylactic-like reaction associated with oral budesonide. *BMJ* 2000; **321:** 927.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies budesonide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Budesonide is rapidly and almost completely absorbed after oral administration, but has poor systemic availability (about 10%) due to extensive first-pass metabolism in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolites, 6-β-hydroxybudesonide and 16-α-hydroxyprednisolone have less than 1% of the glucocorticoid activity of unchanged budesonide. Budesonide is reported to have a terminal half-life of about 2 to 4 hours.

General references.

1. Donnelly R, Seale JP. Clinical pharmacokinetics of inhaled budesonide. *Clin Pharmacokinet* 2001; **40:** 427–40.
2. Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort® EC) capsules for Crohn's disease. *Clin Pharmacokinet* 2004; **43:** 803–21.
3. Kraft WK, *et al.* The pharmacokinetics of nebulized nanocrystal budesonide suspension in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 67–72.
4. Lähelmä S, *et al.* Equivalent lung deposition of budesonide in vivo: a comparison of dry powder inhalers using a pharmacokinetic method. *Br J Clin Pharmacol* 2005; **59:** 167–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerovent; Aerovial; Airbude†; Budeson; Budezonil; Cuteral; Entocort; Exudrol-Bude; Hypersol B; Inflammide; Infliplus†; Nastizol Hidrospray; Neumocort; Neumotex; Proetzonide; Pulmo Lisoflam; Rino-B; Spirocort; ***Austral.***: Budamax; Entocort; Pulmicort; Rhinocort; ***Austria***: Budenobronch; Budiair; Budo-san; Entocort; Giona; Miflonide; Pulmicort; Rhinocort; ***Belg.***: Budenofalk; Docbudeso†; Entocort; Miflonide; Pulmicort; Rhinobudesonide†; Rhinocort; ***Braz.***: Budecort; Budiair; Busonid; Entocort; Miflonide; Noex; Pulmicort; ***Canad.***: Entocort; Pulmicort; Rhinocort; ***Chile***: Aero-Bud; Aerovial Aqua; Aerovial; Budasmal; Budenofalk; Clebudan; Inflammide; Neumocort; Pulmicort†; Rhinocort; Rino-B; ***China***: Ji Shu (吉舒); Pulmicort (普米克); Rhinocort (雷诺考特); ***Cz.***: Budenofalk; Budiair; Entocort; Giona; Miflonid; Pulmax†; Pulmicort; Rhinocort; Ribuspir†; Tafen; Tinkair; ***Denm.***: Budenofalk; Endoprol†; Entocord; Entocort; Giona; Intestifalk; Miflonide; Pulmicort; Rhinocort; Rhinosol†; Spirocort; ***Fin.***: Budenofalk; Entocort; Novopulmon; Pulmicort; Rhinocort; ***Fr.***: Entocort; Miflonil; Mikicort; Novopulmon; Pulmicort; Rafton; Rhinocort; ***Ger.***: Budapp; Budecort; Budenobronch; Budenofalk; Budes†; Budiair; Entocort; Miflonide; Novopulmon; Pulmax†; Pulmicort; ***Gr.***: Abelitan; Aldesonit; Arsicort; Astrocast; Aurid; Axelovert; Beysonit; Biosonide; Budecol; Budemar; Budenite; Budenofalk; Budeprol; Buderen; Budesan; Budesoderm; Budesonal; Budiair; Busonal; Butekont; Buyamin; Dedostryl; Dexalocal; Eolan; Esonide; Etrafonil; Farlidone; Ixor†; Labetasol; Lisobron; Lydenal; Miflonide; Minalerg; Nalator; Obecirol; Obusonid; Olfo; Olfosonide; Olyspal; Pimoftal; Pulmicort; Pulmiver; Pulmovance; Resata; Rhinobros; Rhinoside; Ribuspir; Rinoster; Serbo; Sonidal; Talgan; Therasonid; Udesogel; Udesospray; Velorium; Vericort; Vernoral; Vinecort; Zefecort; Zymacter; Zyolaif; Zytual; ***Hong Kong***: Budena; Budenase; Budenofalk; Butacort†; Cycortide; Entocort; Pulmicort; Rhinocort; ***Hung.***: Aerox; Budenofalk; Budesogen; Entocort; Miflonide; Neplit†; Pulmax†; Pulmicort; Rhinocort; ***India***: Budate; Budecort; Budenase; Budez; Budvent; Buovent DP; Derinide; Pulmicort; Rhinocort; ***Indon.***: Budenofalk; Inflammide; Obucort; Pulmicort; Rhinocort; ***Irl.***: Budenofalk; Budesitan; Entocort; Pulmicort; Rhinocort; ***Israel***: Budeson; Budicort; Entocort; Miflonide; Nasocort; ***Ital.***: Aircort; Bidien; Bodinet; Bodix; Budexan; Budiair; Budineb; Busosed; Desonax; Eltair; Entocir; Kesol; Marxide; Miflo; Miflonide; Pulmaxan; Rafton; Rhinocort; Spirocort; Xavin; ***Malaysia***: Besonin; Budecort; Budenase; Budenide; Budiair; Butacort; Eltair; Giona; Inflammide†; Pulmicort; Rhinocort; ***Mex.***: Aerosial†; Budosan†; Entocort; Miflonide; Numark; Pulmicort; Rhinocort; ***Neth.***: Budenofalk; Entocort; Larbex; Pulmicort; Rhinocort; Ribuspir†; ***Norw.***: Entocort; Giona; Pulmicort; Rhinocort; ***NZ***: Budenocort; Butacort; Eltair; Entocort; Pulmicort; ***Philipp.***: Asmavent; Bronex; Budecort; Budenofalk; Denecort; Obucort; Primavent; ***Pol.***: Budenofalk; Buderhin; Budiair; Entocort; Horacort†; Miflonide; Neplit; Pulmicort; Rhinocort; Tafen; ***Port.***: Aeromax; Budiair; Budo-san; Entocort; Miflonide; Neo Rinactive†; Pulmax†; Pulmicort; ***Rus.***: Benacort (Бенакорт); Benarin (Бенарин); Budenofalk (Буденофальк); Budiair (Будиэйр); Cycortide (Цикортид); Pulmicort (Пульмикорт); Tafen (Тафен); ***S.Afr.***: Budeflam; Entocord; Inflammide; Inflanaze; Pulmicort; Rhinocort; ***Singapore***: Budenofalk; Eltair; Esonide; Frenolyn; Giona; Inflammide†; Pulmicort; Rhinocort; ***Spain***: Budena†; Demotest†; Entocord; Intestifalk; Miflonide; Neo Rinactive†; Novopulm; Olfex; Pulmicort; Pulmictan; Rhinocort; Ribujet; ***Swed.***: Budenofalk; Desonix; Entocort; Giona; Novopulmon; Pulmicort; Rhinocort; ***Switz.***: Budenid; Budenofalk; Cortinasal; Entocort; Miflonide; Pulmicort; Rhinocort; ***Thai.***: Aeronide; Besonin; Budecort; BudeSpray; Budiair; Bunase; Eltair†; Giona; Obucort; Pulmicort; Rhinocort; ***Turk.***: Budenofalk; Budiair; Entocort; Giona; Inflacort; Miflonide; Neo Rinactive; Neo-Rinactive; Pulmicort; Rhinocort; ***UAE***: Sonidar; ***UK***: Budelin; Budenofalk; Entocort; Pulmicort; Rhinocort; ***Ukr.***: Budenofalk (Буденофальк); Novopulmon (Новопульмон); Pulmicort (Пульмикорт); Tafen (Тафен); ***USA***: Entocort; Pulmicort; Rhinocort; Uceris; ***Venez.***: Biosonida; Bronklast; Budecort; Budenas; Miflonide; Pulmicort; Pulmolet; Rhinocort; Rinolet.

Multi-ingredient Preparations. ***Arg.***: Frevia; Neumoterol; Symbicort; ***Austral.***: Symbicort; ***Austria***: Symbicort; ***Belg.***: Symbicort; ***Braz.***: Alenia; Foraseq; Symbicort; Vannair; ***Canad.***: Symbicort; ***Chile***: Symbicort; Vannair; ***China***: Symbicort (信必可); ***Cz.***: Budfor; Edoflo; Symbicort; ***Denm.***: Assieme; Rilast; Sinestic; Symbicort; ***Fin.***: Symbicort; ***Fr.***: Symbicort; ***Ger.***: Symbicort; ***Gr.***: Symbicort; ***Hong Kong***: Symbicort; ***Hung.***: Symbicort; ***India***: Budamate; Budesal; Fomtide; Foracort; Formonide; ***Indon.***: Symbicort; ***Irl.***: Budfor; Edoflo; Symbicort; ***Israel***: Symbicort; ***Ital.***: Assieme; Assiememite; Sinestic; Sinesticmite†; Symbicort; ***Jpn***: Symbicort; ***Malaysia***: Foracort; Symbicort; ***Mex.***: Symbicort; ***Neth.***: Assieme; Budfor; Edoflo†; Sinestic; Symbicort; ***Norw.***: Symbicort; ***NZ***: Symbicort; Vannair; ***Philipp.***: Symbicort; ***Pol.***: Symbicort; ***Port.***: Assieme; Symbicort; ***Rus.***: Biasten (Биастен); Foradil Combi (Форадил Комби); Simbicort (Симбикорт)†; Symbicort (Симбикорт); ***S.Afr.***: Symbicord; ***Singapore***: Symbicort; ***Spain***: Rilast; Symbicort; ***Swed.***: Symbicort; ***Switz.***: Symbicort; Vannair; ***Thai.***: Symbicort; ***Turk.***: Combipack; Foradil Combi; Symbicort; Ventofor-Combi; ***UK***: Symbicort; ***Ukr.***: Simbicort (Симбикорт); ***USA***: Symbicort; ***Venez.***: Foraseq; Symbicort.

Pharmacopoeial Preparations

BP 2014: Budesonide Aqueous Nasal Spray; Budesonide Inhalation Powder, pre-dispensed; Budesonide Inhalation Powder; Budesonide Nebuliser Suspension; Budesonide Pressurised Inhalation.

Ciclesonide *(USAN, rINN)* ⊗

BY-9010; Ciclesonida; Ciclésonide; Ciclesonidum; RPR-251526; Циклезонид.

(*R*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate.

$C_{32}H_{44}O_7$=540.7

CAS — 126544-47-6; 141845-82-1.

ATC — R01AD13; R03BA08.

ATC Vet — QR01AD13; QR03BA08.

UNII — S59502J185.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ciclesonide). A white or yellowish-white, crystalline powder. Practically insoluble in water; freely soluble to soluble in acetone and in dehydrated alcohol.

Uses and Administration

Ciclesonide is a corticosteroid with glucocorticoid activity (p. 1597.1). It is used by inhalation in the management of **asthma** (see p. 1627.1). The usual dose is 160 micrograms daily from a metered-dose aerosol, given either once daily or in 2 divided doses. In severe asthma, a dose of 320 micrograms twice daily may be used. The dose may be reduced to 80 micrograms once daily for maintenance. Ciclesonide is given intranasally for the treatment of

seasonal and perennial allergic **rhinitis** (p. 612.1) in adults and adolescents 12 years of age and older; children 6 years of age and older may be treated for seasonal allergic rhinitis. A dose of 200 micrograms once daily is given as 2 sprays of 50 micrograms into each nostril.

Administration in children. Ciclesonide may be given intranasally for the treatment of seasonal allergic rhinitis in children aged 6 years and older, in the same dose used in adults (see p. 1626.3).

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

Reviews of ciclesonide.

1. Deeks ED, Perry CM. Ciclesonide: a review of its use in the management of asthma. *Drugs* 2008; **68:** 1741–70.
2. Manning P, *et al.* Ciclesonide versus placebo for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 10/03/10).
3. Manning P, *et al.* Ciclesonide versus other inhaled steroids for chronic asthma in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 10/03/10).

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p. 612.1.

Reviews of ciclesonide.

1. Dhillon S, Wagstaff AJ. Ciclesonide nasal spray: in allergic rhinitis. *Drugs* 2008; **68:** 875–83.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Systemic absorption may follow inhalation of ciclesonide, particularly if high doses are used for prolonged periods.

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Ciclesonide is hydrolysed to its biologically active metabolite, desciclesonide, by esterase enzymes in the lung and nasal mucosa. The systemic bioavailability for desciclesonide is reported to be more than 50% when ciclesonide is given by metered-dose inhaler; desciclesonide has also been found in the serum of some patients after nasal use. Oral bioavailability is less than 1%. Ciclesonide and desciclesonide are extensively bound to plasma proteins. It is further metabolised to inactive metabolites mainly via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6. The mean elimination half-life of desciclesonide is about 6 to 7 hours after inhalation of ciclesonide. After oral or intravenous dosage, ciclesonide is mainly excreted via the faeces.

Reviews.

1. Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. *J Clin Pharmacol* 2007; **47:** 782–9.
2. Nave R. Clinical pharmacokinetic and pharmacodynamic profile of inhaled ciclesonide. *Clin Pharmacokinet* 2009; **48:** 243–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alvesco; Cicletex; Omnaris; ***Austral.***: Alvesco; Omnaris; ***Austria***: Alvesco; ***Belg.***: Alvesco; ***Braz.***: Alvesco; Omnaris; ***Canad.***: Alvesco; Omnaris; ***Chile***: Alvesco†; ***Cz.***: Alvesco; ***Denm.***: Alvesco; ***Fin.***: Alvesco; ***Fr.***: Alvesco; ***Ger.***: Alvesco; ***Gr.***: Alvesco; Amavio; Freathe; ***Hong Kong***: Alvesco; Omnaris; ***Hung.***: Alvesco; ***India***: Ciclohale; Osonide†; ***Irl.***: Alvesco; ***Israel***: Alvesco; ***Jpn***: Alvesco; ***Malaysia***: Alvesco; Omnaris; ***Mex.***: Alvesco; Omnaris; ***Neth.***: Alvesco; ***Norw.***: Alvesco; ***Philipp.***: Omnaris; ***Pol.***: Alvesco; ***Port.***: Alvesco; ***S.Afr.***: Alvesco; ***Singapore***: Alvesco; ***Spain***: Alvesco; ***Swed.***: Alvesco; ***Switz.***: Alvesco; ***Turk.***: Alvesco; ***UK***: Alvesco; ***USA***: Alvesco; Omnaris; Zetonna; ***Venez.***: Alvesco.

Clobetasol Propionate *(BANM, USAN, rINNM)* ⊗

CCI-4725; Clobétasol, Propionate de; Clobetasol, propionato de; Clobetasoli Propionas; Clobetasolpropionat; GR-2/925; Klobetasol-propionát; Klobetazol Propiyonat; Klobetazolu propionian; Propionato de clobetasol; Клобетазола Пропионат.

21-Chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

$C_{25}H_{32}ClFO_5$=467.0

CAS — 25122-41-2 (clobetasol); 25122-46-7 (clobetasol propionate).

ATC — D07AD01.

ATC Vet — QD07AD01.

UNII — 779619577M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clobetasol Propionate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

USP 36: (Clobetasol Propionate). A white to cream crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone, in chloroform, in dimethyl sulfoxide, in dioxan, and in methyl alcohol; slightly soluble in benzene and in ether. Store in airtight containers. Protect from light.

Profile

Clobetasol propionate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, ointment, gel, scalp application, shampoo, or foam containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Clobetasol butyrate has also been used similarly.

References.

1. Campisi G, *et al.* A new delivery system of clobetasol-17-propionate (lipid-loaded microspheres 0.025%) compared with a conventional formulation (lipophilic ointment in a hydrophilic phase 0.025%) in topical treatment of atrophic/erosive oral lichen planus: a phase IV, randomized, observer-blinded, parallel group clinical trial. *Br J Dermatol* 2004; **150:** 984–90.
2. Jarratt M, *et al.* Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. *J Drugs Dermatol* 2004; **3:** 367–73.
3. Reygagne P, *et al.* Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatol Treat* 2005; **16:** 31–6.
4. Breneman D, *et al.* Clobetasol propionate 0.05% lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation versus clobetasol propionate emollient cream. *J Drugs Dermatol* 2005; **4:** 330–6.
5. Lowe N, *et al.* Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. *J Dermatol Treat* 2005; **16:** 158–64.
6. Reid DC, Kimball AB. Clobetasol propionate foam in the treatment of psoriasis. *Expert Opin Pharmacother* 2005; **6:** 1735–40.
7. Sanchez Regana M, *et al.* Treatment of nail psoriasis with 8% clobetasol nail lacquer: positive experience in 10 patients. *J Eur Acad Dermatol Venereol* 2005; **19:** 573–7.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; **154:** 139–45.
9. Vena GA, *et al.* Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006; **154:** 353–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clobetasol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clob-X; Clobefar; Clobesol; Dermaclob; Dermadex; Dermexane Capilar; Dermexane; Perfracort; Ribatra; Salac; ***Austria***: Clarelux; Clobex; Dermovate; ***Belg.***: Clarelux; Clobex; Dermovate; ***Braz.***: Clob-X; Clobesol; Cortalen C; Dermacare; Propiosol; Psorex; Psorin†; Therapsor; ***Canad.***: Clobex; Dermovate; ***Chile***: Alticort†; Balsan; Clob-X; Clodavan; Cortopic†; Dermovate; Koniderm; Xinder; ***China***: Dermovate (特美夫); En Fu Shuang (恩肤霜); Eurobetsol (欧博士); Xian Ke Xin (显克欣); ***Cz.***: Clobex; Clovate; Dermovate; Hoziac†; ***Denm.***: Clobex; Dermovat; ***Fin.***: Clarelux; Clobex; Dermovat; ***Fr.***: Clarelux; Clobex; Dermoval; ***Ger.***: Clarelux; Clobegalen; Clobex; Dermoxin; Dermoxinale; Karison; ***Gr.***: Butavate; Clarelux; Clobex; Rubocord; Yugofin; ***Hong Kong***: Clobasol; Clobesol; Clobetaderm†; Clobex; Cloderm; Dermo†; Dermovate; Dermowel†; Dhabesol; Eurobetsol; Medodermone; Uni-Dermo†; Uniderm; Univate†; ***Hung.***: Clobex; Closanasol; Dermovate; ***India***: Betanate; Clobaderm; Clobetamil; Clobetavate; Cloderm; Clodip; Clofoam; Clomic; Clonate; Clop-E; Clop; Clorap; Cortaz; Cortisol; Cosvate; Cotrimax; Cutivate; Dermotyl; Diplene-AF; Ecziclo; Enderm; Eumosone; Excel; Kloryl; Lobate; Lobesol; Magclo; Tenovate; Topifort; ***Indon.***: Bersol; Clobesan; Clofalam; Cloflam; Clonaderm; Closol†; Dermovate; Elopro; Forderm; Hercum; Ikaderm; Kloderma; Klonat†; Lamodex; Lotasbat; Primaderm†; Psoriderm; Tempovate; ***Irl.***: Clarelux; Dermovate; Etrivex; ***Israel***: Dermovate; ***Ital.***: Clobesol; Olux; ***Malaysia***: Clobet; Clobex; Cloderm; Dermosol; Dermovate; Dhabesol; Uniderm; Univate; ***Mex.***: Clobesol; Clobexpro; Clobixfoam; Dermatovate; Lobevat; ***Neth.***: Clarelux; Clobex; Dermovate; ***Norw.***: Clobex; Dermovat; ***NZ***: Clobex; Dermol; ***Philipp.***: Cleovate; Clobex; Clobison; Clonate; Closderm; Dermosol; Dermovate; Eurobel; Glevate; Probelin; ***Pol.***: Clobederm; Clobex; Dermklobal; Dermovate; Novate; ***Port.***: Clarelux; Dermovate; Etrivex; ***Rus.***: Clovate (Кловейт); Dermovate (Дермовейт); Powercort (Пауэркорт); ***S.Afr.***: Clobex; Dermovate; Dovate; Xenovate; ***Singapore***: Clobex; Cloderm; Clonovate; Dermosol; Dermovate; Dhabesol; Lobesol; Medodermone; Powercort; SP-Clobesol; Steriderm-S; Uniderm; Univate; ***Spain***: Clarelux; Clobex; Clovate; Decloban; ***Swed.***: Clobex; Dermovat; ***Switz.***: Clarelux; Clobex; Dermovate; ***Thai.***: Betasol; Chinovate; Clinoderm; Clobasone; Clobet; Clobetate; Clobex; Cloderm; Clodermis; Clonovate; Clotasol; Cobesol; Cotaso; Delacor; Dergemate; Dermaman; Dermovate; Kaltazone; Klobecort; P-Vate; Selma; Stivate; Tacosol; Uniderm; ***Turk.***: Dermovate; Psoderm; Psovate; ***UAE***: Gamavate; ***UK***: Clarelux; ClobaDerm; Dermovate; Etrivex; ***Ukr.***: Clovate (Кловейт); Delor (Делор); Dermovate (Дермовейт); ***USA***: Clobex; Cormax; Olux; Temovate; ***Venez.***: Dermovate.

Multi-ingredient Preparations. ***Arg.***: Clobeplus; Clobesol LA; Dermadex NN; Dermexane; ***China***: Baolongkang (保龙慷); Compound Ketoconazole (复方酮康唑); Dapule (达普乐); Jin Niu Er (金纽尔); ***Hong Kong***: Clobert-G†; Clonetin†; Neoclobet†; Uni-Quaderm†; ***India***: Alclos-GM; Betalic; Betanate G; Betanate GM; Betanate M; Betaspi-GM; CGM; Clobact-GM; Clobaderm-GM; Clobasia-GM; Clobecos-GM; Cloberis-GM; Clobesym-GM; Clobeta-CF; Clobetamil-G; Clobquad; Cloby; Cloderm-GM; Clodip-GM; Clogem; Clogem; Clomic-M; Clomic-S; Clomic-ZM; Clonate-F; Clonate-G; Clonate-GM; Clop-G; Clop-M; Clop-MG; Clop-S; Clorap-S; Clos-GM; Clotof-G; Clotof-GM; Clotof-M; Cortaz-S; Cortisol-G; Cosvate-G; Cosvate-GM; Cutasol-GM; Cutivate-GT; Cutivate-MF; Cutivate-S; Dermocrat Plus; Dermonit; Dermotel; Dermotriad; Dermotyl-M; Dipgenta Plus; Dipsalic-F; Ecziclo-G; Ecziclo-GM; Ecziclo-M; Enderm-GM; Etan-G; Etan-GM; Excel-M; Fungifite; Hyton; Kloryl-G; Kloryl-M; Labosol-GM; Leobet-GZ; Leta-GM; Lobate-G; Lobate-GM; Lobate-GN; Lobate-M; Lobate-S; Magclo-G; Miclogenta; Micogram; Nadicin-C; Nadoxin-C; Tenovate G; Tenovate M; ***Philipp.***: Dermovate-NN; ***UK***: Dermovate-NN†.

Pharmacopoeial Preparations

BP 2014: Clobetasol Cream; Clobetasol Ointment;

USP 36: Clobetasol Propionate Cream; Clobetasol Propionate Ointment; Clobetasol Propionate Topical Solution.

Clobetasone Butyrate *(BANM, USAN, rINNM)* ⊗

Butirato de clobetasona; CCI-5537; Clobetasona, butirato de; Clobetasonbutyrat; Clobétasone, Butyrate de; Clobetasoni Butiras; Clobetasoni Butyras; GR-2/1214; Klobetasonbutyrat; Klobetason-butyrát; Klobetasonibutyraatti; Klobetazon Bütirat; Klobetazon-butirát; Klobetazono butiratas; Клобетазона Бутират.

21-Chloro-9α-fluoro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione 17-butyrate.

$C_{26}H_{32}ClFO_5$=479.0

CAS — 54063-32-0 (clobetasone); 25122-57-0 (clobetasone butyrate).

ATC — D07AB01; S01BA09.

ATC Vet — QD07AB01; QS01BA09.

UNII — 8U0H6X16EO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clobetasone Butyrate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Profile

Clobetasone butyrate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Clobetasone butyrate is also used for inflammatory eye disorders, as eye drops containing 0.1%. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clobetasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Eumovate; ***Austral.***: Becoderm-C†; Eumovate; ***Austria***: Emovate; ***Belg.***: Eumovate; ***Braz.***: Eumovate; ***Canad.***: Spectro Eczemacare; ***Denm.***: Emovat; ***Fin.***: Emovat; ***Ger.***: Emovate; ***Gr.***: Rettavate; ***Hong Kong***: Eumovate; ***Irl.***: Eumovate; ***Israel***: Eumovate; ***Ital.***: Clobet; Eumovate; Solderma; Visucloben; ***Malaysia***: Eumovate; U-Closone; ***Neth.***: Emovate; ***NZ***: Becoderm-C†; Eumovate; ***Port.***: Emovate; ***S.Afr.***: Eumovate†; ***Singapore***: Amisol; Eumovate; ***Spain***: Emovate; ***Swed.***: Emovat; ***Switz.***: Emovate; ***Thai.***: U-Closone; ***Turk.***: Eumovate; ***UK***: Eumovate; ***Venez.***: Eumovate.

Multi-ingredient Preparations. ***India***: Clobequad; Eumosone-G; Eumosone-M; Lozee-GM; Lozee-M; Lozee; ***Israel***: Cicloderm-C; ***Ital.***: Visucloben Antibiotico; Visucloben Decongestionante; ***UK***: Trimovate.

Pharmacopoeial Preparations
BP 2014: Clobetasone Cream; Clobetasone Ointment.

Clocortolone Pivalate *(USAN, rINNM)* ⊗

CL-68; Clocortolona, pivalato de; Clocortolone, Pivalate de; Clocortoloni Pivalas; Pivalato de clocortolona; SH-863; Клокортолона Пивалат.

9α-Chloro-6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-pivalate.

$C_{27}H_{36}ClFO_5$=495.0

CAS — 4828-27-7 (clocortolone); 34097-16-0 (clocortolone pivalate).

ATC — D07AB21.

ATC Vet — QD07AB21.

UNII — QBL8IZH14X.

Pharmacopoeias. In *US*.

USP 36: (Clocortolone Pivalate). A white to yellowish-white, odourless powder. Sparingly soluble in alcohol; soluble in acetone; freely soluble in chloroform and in dioxan; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clocortolone pivalate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1), as a 0.1% cream or ointment, in the treatment of various skin disorders. Clocortolone caproate has been used with the pivalate.

When applied topically, particularly to large areas, where the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Kaban†; Kabanimat†; ***USA***: Cloderm.

Pharmacopoeial Preparations
USP 36: Clocortolone Pivalate Cream.

Cloprednol *(BAN, USAN, rINN)* ⊗

Cloprednolum; RS-4691; Клопреднол.

6-Chloro-11β,17α,21-trihydroxypregna-1,4,6-triene-3,20-dione.

$C_{21}H_{25}ClO_5$=392.9

CAS — 5251-34-3.

ATC — H02AB14.

ATC Vet — QH02AB14.

UNII — SYP56O3GJG.

Profile

Cloprednol is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); the anti-inflammatory activity of 2.5 mg of cloprednol is equivalent to about 5 mg of prednisolone. Cloprednol is given orally in various disorders for which corticosteroid therapy is helpful (p. 1597.3), in usual doses ranging from 1.25 to 12.5 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Syntestan.

Corticorelin *(rINN)* ⊗

Corticoliberin; Corticorelina; Corticoréline; Corticorelinum; Corticotrophin-releasing Hormone HLC; Corticotropin-releasing Factor; CRF; CRH; Hormona liberadora de corticotropina; Кортикорелин.

$C_{208}H_{344}N_{60}O_{63}S_2$ = 4757.5 (human); $C_{205}H_{339}N_{59}O_{63}S$ = 4670.3 (ovine)

CAS — 86784-80-7 (corticorelin (human)); 79804-71-0 (corticorelin (ovine)).

ATC — V04CD04.

ATC Vet — QV04CD04.

UNII — Y124TZ0513 (corticorelin ovine); 305OE8862Y (corticorelin human).

Corticorelin Triflutate *(rINNM)* ⊗

Corticorelin Trifluoroacetate; Corticorelina, triflutato de; Corticoréline, Triflutate de; Corticorelini Triflutas; Triflutato de corticorelina; Кортикорелина Трифлутат.

$C_{205}H_{339}N_{59}O_{63}S_xC_2HF_3O_2$(ovine)

CAS — 121249-14-7 (corticorelin ovine triflutate).

ATC — V04CD04.

ATC Vet — QV04CD04.

UNII — 56X54T817Q (corticorelin ovine triflutate).

NOTE. Corticorelin Ovine Triflutate is *USAN*.

Uses and Administration

Corticorelin is a polypeptide hypothalamic releasing hormone that stimulates the release of corticotropin (below) from the anterior pituitary. It is used in the differential diagnosis of Cushing's syndrome (see Diagnosis and Testing, below) and other adrenal disorders. Corticorelin is usually given as the triflutate, but doses are expressed in terms of corticorelin (human or ovine). A single dose of 100 micrograms, or of 1 microgram/kg, is given by intravenous injection over 30 seconds. Higher and more rapid doses have been used but may be associated with an increased risk of adverse effects (see below).

Corticorelin acetate is under investigation for the treatment of cerebral oedema associated with brain tumours.

Administration. Corticorelin was well absorbed after subcutaneous injection and bioavailability was calculated to be about 60 to 70%; absorption was slower with high doses, suggesting that it may be a saturable process. Given the retention of bioactivity, the subcutaneous route was considered an attractive alternative to intravenous use.[1]

1. Angst MS, *et al.* Pharmacokinetics, cortisol release, and hemodynamics after intravenous and subcutaneous injection of human corticotropin-releasing factor in humans. *Clin Pharmacol Ther* 1998; **64:** 499–510.

Diagnosis and testing. Corticorelin may be used in the diagnosis of adrenal disorders including Cushing's syndrome (p. 2559.1). In the initial diagnosis of Cushing's syndrome, a dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism in patients with mild hypercortisolism and equivocal results on other diagnostic tests. This combination is reportedly more accurate than either alone,[1] but it is cumbersome and difficult to carry out on an ambulatory basis.[2]

When a diagnosis of ACTH-dependent Cushing's syndrome has been established, corticorelin may be used for differential diagnosis of the subtype. Patients with pituitary Cushing's syndrome have an exaggerated increase in plasma-corticotropin and plasma-cortisol concentrations in response to corticorelin, whereas those with adrenal or ectopic syndrome generally have no response.[3,4] The corticorelin stimulation test is of comparable diagnostic efficacy to the dexamethasone suppression test,[5,6] although false results have been obtained with both tests.[2,5,7] Again, a combination of the dexamethasone and corticorelin tests is reportedly more accurate than either alone.[6] The most reliable test to distinguish between pituitary and nonpituitary forms of Cushing's syndrome is to measure the difference between central and peripheral concentrations of ACTH after giving corticorelin.[2] However, this requires sampling of central (petrosal) venous blood, an invasive procedure needing considerable expertise.

1. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; **269:** 2232–8.
2. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
3. Chrousos GP, *et al.* The corticotropin-releasing factor stimulation test: an aid in the evaluation of patients with Cushing's syndrome. *N Engl J Med* 1984; **310:** 622–6.
4. Newell-Price J, *et al.* Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 2002; **87:** 1640–5.
5. Hermus AR, *et al.* The corticotropin-releasing-hormone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. *Lancet* 1986; **ii:** 540–4.
6. Nieman LK, *et al.* The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **105:** 862–7.
7. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.

Adverse Effects

Flushing of the face, neck, and upper chest, and mild dyspnoea may follow intravenous injection of corticorelin, and last for about 3 to 5 minutes. Prolonged flushing, tachycardia, hypotension, and chest tightness have been reported after large doses.

Effects on the cardiovascular system. Loss of consciousness, lasting for 10 seconds to 5 minutes, occurred in 3 patients, 2 of whom had Cushing's disease and one who had secondary adrenal insufficiency, after intravenous injection of corticorelin 200 micrograms.[1] The 2 patients with Cushing's disease had a slight accompanying fall in blood pressure. In a fourth patient, receiving corticosteroid and thyroid hormone replacement therapy, injection of corticorelin was associated with a sharp fall in systolic blood pressure and subsequent asystole. These serious adverse effects were not noted by others[2,3] and were variously attributed to impurities,[2] high dosage,[2] vasovagal syncope,[3] or to the fact that the corticorelin used in the study was of ovine rather than human origin.[3] The authors of the original study[1] have since stated[4] that lowering of the dose from 200 micrograms given intravenously over 10 seconds to 100 micrograms over 60 seconds has stopped serious adverse effects but that ovine corticorelin was still preferred because of its longer duration of action and lower incidence of hypotensive adverse effects. There has, however, been a further report of chest pain accompanied by a fall in blood pressure in a patient receiving corticorelin at a dose of 100 micrograms.[5]

1. Hermus A, *et al.* Serious reactions to corticotropin-releasing factor. *Lancet* 1983; **i:** 776.
2. Schulte HM, *et al.* Safety of corticotropin-releasing factor. *Lancet* 1983; **i:** 1222.
3. Oppermann D. Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; **ii:** 1031–2.
4. Hermus ARMM, *et al.* Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; **ii:** 1032–3.
5. Paloma VC, *et al.* Chest pain after intravenous corticotropin-releasing hormone. *Lancet* 1989; **i:** 222.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: CRH; ***Fr.***: Stimu-ACTH; ***Ger.***: Cortirel†; CRH; ***Neth.***: CRH; ***USA***: Acthrel.

Corticotropin *(BAN, rINN)* ⊗

ACTH; Adrenocorticotrofina; Adrenocorticotrophic Hormone; Adrenocorticotrophin; Corticotrofina; Corticotrophin; Corticotropina; Corticotropine; Corticotropinum; Hormona adrenocorticotropa; Kortikotropiini; Kortikotropin; Кортикотропин.

CAS — 9002-60-2 (corticotropin); 9050-75-3 (corticotropin zinc hydroxide); 8049-55-6 (corticotropin zinc hydroxide).

ATC — H01AA01.

ATC Vet — QH01AA01.

UNII — K0U68Q2TXA (corticotropin); 0480S42OTR (corticotropin bovine/ovine); FP33F50XKB (corticotropin porcine).

Pharmacopoeias. In *US* as preparations for injection.

Units

5 units of porcine corticotropin for bioassay are contained in about 50 micrograms (with lactose 5 mg) in one ampoule of the third International Standard (1962).

Uses and Administration

Corticotropin is a naturally occurring hormone of the anterior lobe of the pituitary gland. It stimulates the adrenal glands to secrete adrenocortical hormones, especially cortisol (hydrocortisone), some mineralocorticoids such as corticosterone, and, to a lesser extent, androgens. It has little effect on aldosterone secretion, which proceeds independently.

Secretion of corticotropin by the functioning pituitary gland is controlled by the release of corticorelin from the hypothalamus and is also regulated by a negative feedback mechanism involving concentrations of circulating glucocorticoids. Conditions of stress may also stimulate secretion.

Corticotropin may be used diagnostically to investigate adrenocortical insufficiency. It has also been used therapeutically in most of the conditions (with the exception of the adrenal deficiency states and adrenocortical overactivity) for which systemic corticosteroid therapy is indicated (p. 1597.3). Such use is now fairly limited. However, corticotropin may be used in certain neurological disorders such as infantile spasms and multiple sclerosis. The synthetic polypeptide tetracosactide (p. 1648.1), which has the same amino-acid sequence as the first 24 residues of human corticotropin, may be used as an alternative.

Tosactide is another polypeptide analogue of corticotropin; it has the same sequence as the first 28 residues.

Corticotropin has been available for injection in two forms. One form is a plain injection that may be given by the subcutaneous, intramuscular, or intravenous routes. The other form is a long-acting depot preparation in which the viscosity is increased by the addition of gelatin, and which is given subcutaneously or intramuscularly; it must not be given intravenously. Individual responses to therapeutic corticotropin vary considerably and doses must be adjusted accordingly.

For *diagnostic purposes* the corticotropin test is based on the measurement of plasma-cortisol concentrations before and after injection. The plain preparation is used in doses of 10 to 25 units in 500 mL of glucose 5% infused intravenously over 8 hours.

For *therapeutic purposes* typical doses for the depot preparation have been about 40 to 80 units every 24 to 72 hours by the subcutaneous or the intramuscular route. As soon as possible the dosage should be reduced gradually to the minimum necessary to control symptoms.

A depot preparation of corticotropin combined with zinc hydroxide for intramuscular injection has been used in the past.

Epilepsy. The use of corticotropin in the management of infantile spasms is referred to under Epilepsy in Corticosteroids, p. 1604.1.

Multiple sclerosis. Short-term courses of corticotropin have been used to speed recovery from acute exacerbations of multiple sclerosis (p. 996.3) but corticosteroids, usually methylprednisolone, are now preferred.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or tetracosactide, but a controlled study of tetracosactide use found no benefit (see p. 1648.2).

Adverse Effects

Corticotropin stimulates the adrenals to produce cortisol (hydrocortisone) and mineralocorticoids; it therefore has the potential to produce similar adverse glucocorticoid and mineralocorticoid effects to those of the corticosteroids (see p. 1615.3). In particular, its mineralocorticoid properties can produce marked sodium and water retention; considerable potassium loss may also occur.

Corticotropin can induce sensitisation, and severe hypersensitivity reactions, including anaphylaxis, may occur. This is generally considered to be due to the porcine component of the peptide.

Whereas corticosteroids replace endogenous cortisol (hydrocortisone) and thereby induce adrenal atrophy, corticotropin's stimulant effect induces hypertrophy. Nevertheless, the ability of the hypothalamic-pituitary-adrenal axis to respond to stress is still reduced, and abrupt withdrawal of corticotropin may result in symptoms of adrenal insufficiency (see Withdrawal, below).

Reports of adverse effects in children given corticotropin for infantile spasms.

1. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. *Arch Dis Child* 1980; **55:** 664–72.
2. Hanefeld F, *et al.* Renal and pancreatic calcification during treatment of infantile spasms with ACTH. *Lancet* 1984; **i:** 901.
3. Riikonen R, *et al.* Disturbed calcium and phosphate homeostasis during treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; **61:** 671–6.
4. Perheentupa J, *et al.* Adrenocortical hyporesponsiveness after treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; **61:** 750–3.

Withdrawal

Corticotropin use may depress the hypothalamic-pituitary-adrenal axis. Abrupt withdrawal of corticotropin may therefore produce adrenocortical and pituitary unresponsiveness, and therapy should be stopped gradually. An increase in corticosteroid requirements associated with the stress of infection, or accidental or surgical trauma, may also precipitate acute adrenocortical insufficiency. See also Withdrawal under Corticosteroids, p. 1618.1.

Precautions

As for Corticosteroids, p. 1618.3.

Phaeochromocytoma. A hypertensive crisis in a patient given intravenous tetracosactide led to the discovery of an adrenaline-secreting phaeochromocytoma.[1] It was suggested that corticotropin should be used with caution in patients with orthostatic hypotension in whom the diagnosis of phaeochromocytoma has not been excluded.

1. Jan T, *et al.* Epinephrine-producing pheochromocytoma with hypertensive crisis after corticotropin injection. *Am J Med* 1990; **89:** 824–5.

Interactions

Interactions seen with corticotropin are liable to be similar to those with corticosteroids (p. 1619.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acthelea; ***India***: Acton Prolongatum; ***USA***: Acthar.

Pharmacopoeial Preparations
USP 36: Corticotropin for Injection; Corticotropin Injection; Corticotropin Zinc Hydroxide Injectable Suspension; Repository Corticotropin Injection.

Cortisone Acetate *(BANM, rINNM)* ⊗

Acetato de cortisona; Compound E Acetate; Cortisona, acetato de; Cortisonacetat; Cortisone, Acétate de; Cortisoni Acetas; 11-Dehydro-17-hydroxycorticosterone Acetate; Kortisonacetat; Kortison-acetát; Kortisoniasetaatti; Kortizon-acetát; Kortizono acetatas; Kortyzonu octan; Кортизона Ацетат.

17α,21-Dihydroxypregn-4-ene-3,11,20-trione 21-acetate.

$C_{23}H_{30}O_6$=402.5

CAS — 53-06-5 (cortisone); 50-04-4 (cortisone acetate).

ATC — H02AB10; S01BA03.

ATC Vet — QH02AB10; QS01BA03.

UNII — 883WKN7W8X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cortisone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; freely soluble in dichloromethane; soluble in dioxan. Protect from light.

USP 36: (Cortisone Acetate). A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 350 of alcohol, 1 in 75 of acetone, 1 in 4 of chloroform, and 1 in 30 of dioxan. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Cortisone is a corticosteroid secreted by the adrenal cortex. It has glucocorticoid activity (p. 1597.1), as well as appreciable mineralocorticoid activity; 25 mg of cortisone acetate is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

Cortisone acetate is rapidly effective when given orally, and more slowly by intramuscular injection.

Cortisone acetate has been used mainly for replacement therapy in adrenocortical insufficiency (p. 1600.2), but hydrocortisone (p. 1640.1) is generally preferred since cortisone itself is inactive and must be converted by the liver to hydrocortisone, its active metabolite; hence, in some liver disorders the activity of cortisone may be less reliable. Doses of cortisone acetate for oral replacement therapy are 12.5 to 37.5 mg daily in divided doses, with fludrocortisone if additional mineralocorticoid activity is required.

Cortisone acetate has been used in the treatment of many of the allergic and inflammatory disorders for which corticosteroid therapy is helpful (p. 1597.3) but prednisolone or other synthetic glucocorticoids are generally preferred. Oral doses of cortisone acetate have generally ranged from about 25 to 300 mg daily. It has also been given by intramuscular injection.

Homoeopathy

Cortisone has been used in homoeopathic medicines.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cortisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Cortisone acetate is readily absorbed from the gastrointestinal tract and the cortisone is rapidly converted in the liver to its active metabolite, hydrocortisone (cortisol). The biological half-life of cortisone itself is only about 30 minutes. Absorption of cortisone acetate from intramuscular sites is considerably slower than after oral doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cortate; ***Ital.***: Cortone; ***UK***: Cortisyl; ***USA***: Cortone†.

Multi-ingredient Preparations. ***Braz.***: Corciclen; ***Spain***: Blefaridа†; Gingilone.

Homoeopathic Preparations. ***Ger.***: Cortirell†; Cortisorell; ***Neth.***: Pulsatilla comp.

Pharmacopoeial Preparations
BP 2014: Cortisone Tablets;
USP 36: Cortisone Acetate Injectable Suspension; Cortisone Acetate Tablets.

Cortivazol *(USAN, pINN)* ⊗

Cortivazolum; H-3625; MK-650; NSC-80998; Кортивазол.

11β,17α,21-Trihydroxy-6,16α-dimethyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazol-20-one 21-acetate.

$C_{32}H_{38}N_2O_5$=530.7

CAS — 1110-40-3.

ATC — H02AB17.

ATC Vet — QH02AB17.

UNII — YM183K0H63.

Profile

Cortivazol is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 300 micrograms of cortivazol is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is given in the treatment of musculoskeletal and joint disorders by intra-articular, periarticular, or epidural injection in doses of about 1.25 to 3.75 mg, according to the size of the joint, usually at intervals of 1 to 3 weeks. It has also been given orally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Altim; ***Gr.***: Altim.

Deflazacort *(BAN, USAN, rINN)* ⊗

Azacort; Deflatsakorti; Déflazacort; Deflazacortum; Deflazakort; DL-458-IT; L-5458; MDL-458; Oxazacort; Дефлазакорт.

11β,21-Dihydroxy-2′-methyl-5′β*H*-pregna-1,4-dieno[17,16-*d*]oxazole-3,20-dione 21-acetate.

$C_{25}H_{31}NO_6$=441.5

CAS — 14484-47-0.

ATC — H02AB13.

ATC Vet — QH02AB13.

UNII — KR5YZ6AE4B.

Profile

Deflazacort is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 6 mg of deflazacort is reportedly equivalent in anti-inflammatory activity to about 5 mg of prednisolone (but see Action, below).

Deflazacort is used for its anti-inflammatory and immunosuppressant properties in conditions responsive to corticosteroid therapy (p. 1597.3). It is given in initial oral doses of up to 120 mg daily; usual maintenance doses are 3 to 18 mg daily. For doses used in children, see p. 1630.1.

References.

1. Markham A, Bryson HM. Deflazacort: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; **50:** 317–33.
2. Mignogna MD, *et al.* Oral pemphigus: long term behaviour and clinical response to treatment with deflazacort in sixteen cases. *J Oral Pathol Med* 2000; **29:** 145–52.
3. Campbell C, Jacob P. Deflazacort for the treatment of Duchenne dystrophy: a systematic review. *BMC Neurol* 2003; **3:** 7. Available at: http://www.biomedcentral.com/1471-2377/3/7 (accessed 20/06/06)
4. Biggar WD, *et al.* Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. *Neuromuscul Disord* 2006; **16:** 249–55.

Action. Although it has been suggested that deflazacort produces fewer adverse effects than some conventional corticosteroids such as prednisolone, a study in healthy subjects found that the ratio of efficacy for deflazacort compared with prednisolone was higher than the 1.2 : 1 previously assumed,[1] implying that lower effective doses of deflazacort had been used in such comparisons. A review[2] of clinical studies of patients treated with deflazacort concluded that it was slightly less potent than prednisolone, and that many of the data on adverse effects

were inconsistent. All systemic corticosteroids may produce clinically significant adverse reactions (see also p. 1615.3), which are mainly dependent on dose and duration of use.

1. Babadjanova G, *et al.* Comparison of the pharmacodynamic effects of deflazacort and prednisolone in healthy subjects. *Eur J Clin Pharmacol* 1996; **51:** 53–7.
2. Anonymous. Deflazacort – an alternative to prednisolone? *Drug Ther Bull* 1999; **37:** 57–8.

Administration in children. Deflazacort is used in children for its anti-inflammatory and immunosuppressant properties in conditions responsive to corticosteroid therapy. Oral doses of 0.25 to 1.5 mg/kg daily may be used. The *BNFC* suggests that this dose may be given once daily or on alternate days in children aged from 1 month up to 12 years, and states that up to 2.4 mg/kg (to a maximum of 120 mg) daily has been used in emergency situations. Older children may be given adult doses (see p. 1629.3).

Renal calculi. Deflazacort has been given with nifedipine to ease the spontaneous passage of renal calculi and stone fragments (see under Nifedipine, p. 1450.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Azacortid; Cordefla; Defas; Flamirex; ***Braz.***: Calcort; Cortax; Deflaimmun; Deflanil; Denacen; Flaz-Cort; Flazal; ***Chile***: Azacortid; Dezartal; ***Ger.***: Calcort; ***Gr.***: Deflan; Flantadin; ***India***: Alnacort; Cincort; Core; Cortimax; Defcort; Defglu; Defjee; Deflar; Defocart; Defza; Dezert; DFZ; Ducort; Emzacort; Flazlar; Flozamin; Flozastar; Laza; Lazoc; MDCort; Medipred; MP Next; Nayacort; New Premisol; Nuradef; ***Irl.***: Calcort†; ***Ital.***: Deflan; Flantadin; ***Mex.***: Calcort; Carzoflep; Setatrep; ***Port.***: Desay; Rosilan; ***Spain***: Dezacor; Zamene; ***Switz.***: Calcort; ***Turk.***: Flantadin; ***UK***: Calcort; ***Venez.***: Calcort.

Deprodone *(BAN, rINN)* ⊗

Deprodona; Déprodone; Deprodonum; Desolone; RD-20000 (deprodone propionate); Депродон.

11β,17α-Dihydroxypregna-1,4-diene-3,20-dione.

$C_{21}H_{28}O_4$=344.5

CAS — 20423-99-8 (deprodone); 20424-00-4 (deprodone propionate).

UNII — Z380L7N00P.

NOTE. The names Allomidon and Eclar have been used as trade marks for deprodone propionate.

Profile

Deprodone is a corticosteroid that has been used topically as the propionate.

Desonide *(BAN, USAN, rINN)* ⊗

D-2083; Desfluorotriamcinolone Acetonide; Desonid; Desonida; Désonide; Desonidi; Desonidum; 16-Hydroxyprednisolone 16,17-Acetonide; Prednacinolone Acetonide; Дезонид.

11β,21-Dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

$C_{24}H_{32}O_6$=416.5

CAS — 638-94-8.

ATC — D07AB08; S01BA11.

ATC Vet — QD07AB08; QS01BA11.

UNII — J280872D1O.

Profile

Desonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, ointment, lotion, gel, or foam containing 0.05%. The pivalate ester has also been used.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Desonide sodium phosphate has been used in preparations for ocular use.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desonide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Desoplus; DesOwen; Locatop; ***Austral.***: DesOwen; ***Braz.***: Dermatol; Desonol; ***Canad.***: Desocort; Tridesilon; Verdeso; ***Chile***: DesOwen; ***China***: DesOwen (莱索文); Li Yan Zhuo (力言卓); ***Cz.***: Locatop†; ***Fin.***: Apolar; ***Fr.***: Locapred; Locatop; Tridesonit; ***Hong Kong***: DesOwen; ***India***: DesOwen; ***Indon.***: Apolar; Dermades; Dermanide; Desolex; Nufapolar; ***Israel***: Locatop; ***Ital.***: Prenacid; Reticus; Sterades; ***Mex.***: Dersupril; DesOwen; ***Norw.***: Apolar; ***Philipp.***: DesOwen; ***Pol.***: Locatop; ***Port.***: Locapred†; Zotinar; ***Rus.***: Prenacid (Пренацид); ***Singapore***: DesOwen; ***Switz.***: Locapred; Locatop†; ***Turk.***: Prenacid; ***USA***: Desonate; DesOwen; LoKara†; Verdeso; ***Venez.***: Dermosupril; DesOwen; Erilon.

Multi-ingredient Preparations. ***Fr.***: Cirkan a la Prednacinolone; ***Indon.***: Apolar-N; Desolex-N; ***Norw.***: Apolar med dekvalin; ***Port.***: Zotinar-N; ***Venez.***: Dermosupril C.

Desoximetasone *(BAN, USAN, rINN)* ⊗

A-41-304; Desoksimetasoni; Desoximetason; Desoximetasona; Désoximétasone; Desoximetasonum; Desoxymethasone; Hoe-304; R-2113; Дезоксиметазон.

9α-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_4$=376.5

CAS — 382-67-2.

ATC — D07AC03.

ATC Vet — QD07AC03; QD07XC02.

UNII — 4E07GXB7AU.

Pharmacopoeias. In *US*.

USP 36: (Desoximetasone). A white to practically white, odourless, crystalline powder. Insoluble in water; freely soluble in alcohol, in acetone, and in chloroform.

Profile

Desoximetasone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, or ointment; concentrations used range from 0.05 to 0.25%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Adverse effects. A photosensitivity reaction occurred in a patient treated for psoriasis with topical desoximetasone; rechallenge led to a recurrence.[1] The patient was also receiving propranolol hydrochloride.

1. Stierstorfer MB, Baughman RD. Photosensitivity to desoximetasone emollient cream. *Arch Dermatol* 1988; **124:** 1870–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desoximetasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Esperson; ***Canad.***: Desoxi; Topicort; ***Denm.***: Ibaril†; ***Fin.***: Ibaril; ***Ger.***: Topisolon; ***Indon.***: Dercason; Desomex†; Dexigen; Dexocort; Dexosyn; Esperson; Inerson; Lerskin; Pyderma; Soderma†; Topcort; ***Ital.***: Flubason; ***Neth.***: Ibaril; Topicorte; ***Norw.***: Ibaril; ***Spain***: Flubason; ***Switz.***: Topisolon†; ***Thai.***: Cendexsone†; Esperson; TO Corte; Topicorte; Topoxy; ***USA***: Topicort.

Multi-ingredient Preparations. ***Braz.***: Esperson N; ***Indon.***: Denomix; ***Thai.***: Topifram.

Pharmacopoeial Preparations

USP 36: Desoximetasone Cream; Desoximetasone Gel; Desoximetasone Ointment.

Desoxycortone *(BAN, rINN)*

Decortone; Deoxycortone; Desoksikortoni; Desoxicortona; Desoxikorton; Desoxycorticosterone; Désoxycortone; Desoxycortonum; Дезоксикортон.

21-Hydroxypregn-4-ene-3,20-dione.

$C_{21}H_{30}O_2$=314.5

CAS — 64-85-7.

ATC — H02AA03.

ATC Vet — QH02AA03.

UNII — 40GP35YQ49.

Desoxycortone Acetate *(BANM, rINNM)*

Acetato de desoxicortona; Cortin; Decortone Acetate; 11-Deoxycorticosterone Acetate; Deoxycortone Acetate; Desoksikortoniasetaatti; Desoxicortona, acetato de; Desoxikortonacetat; Desoxycorticosterone Acetate; Desoxycortonacetat; Désoxycortone, acétate de; Desoxycortoni Acetas; Desoxykorton-acetát; Dezoksikortono acetatas; Dezoksykortonu octan; Dezoxikorton-acetát; Дезоксикортона Ацетат.

Desoxycortone 21-acetate.

$C_{23}H_{32}O_4$=372.5

CAS — 56-47-3.

ATC — H02AA03.

ATC Vet — QH02AA03.

UNII — 6E0A168O88.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Desoxycortone Acetate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; slightly soluble in propylene glycol and in fatty oils. Protect from light.

USP 36: (Desoxycorticosterone Acetate). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in dioxan; slightly soluble in vegetable oils. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Desoxycortone Pivalate *(BANM, rINNM)*

Deoxycorticosterone Pivalate; Deoxycorticosterone Trimethylacetate; Deoxycortone Pivalate; Deoxycortone Trimethylacetate; Desoxicortona, pivalato de; Desoxycorticosterone Pivalate; Desoxycorticosterone Trimethylacetate; Désoxycortone, Pivalate de; Desoxycortoni Pivalas; Pivalato de desoxicortona; Дезоксикортона Пивалат.

Desoxycortone 21-pivalate.

$C_{26}H_{38}O_4$=414.6

CAS — 808-48-0.

ATC — H02AA03.

ATC Vet — QH02AA03.

UNII — 16665T4A2X.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Desoxycorticosterone Pivalate). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Desoxycortone is a corticosteroid secreted by the adrenal cortex and has mainly mineralocorticoid activity (p. 1597.1). It has no significant glucocorticoid action.

Desoxycortone acetate has been used in the treatment of adrenocortical insufficiency (p. 1600.2) as an adjunct to cortisone or hydrocortisone. For this purpose, however, fludrocortisone given orally is now usually preferred.

Desoxycortone acetate is given by intramuscular injection as an oily solution, in doses of up to 10 mg once or twice daily.

Desoxycortone has also been used as its enantate, phenylpropionate, and sodium hemisuccinate esters. Desoxycortone pivalate is used in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Syncortyl; ***Ital.***: Cortiron.

Multi-ingredient Preparations. ***Gr.***: Docabolin†.

Pharmacopoeial Preparations

USP 36: Desoxycorticosterone Acetate Injection; Desoxycorticosterone Acetate Pellets.

Dexamethasone *(BAN, rINN)* ⊗

Deksametasoni; Deksametazon; Deksametazonas; Desamethasone; Dexametason; Dexametasona; Dexametasone; Dexametazon; Dexamethason; Dexaméthasone; Dexamethasonum; 9α-Fluoro-16α-methylprednisolone; Hexadecadrol; Дексаметазон.

9α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_5$=392.5

CAS — 50-02-2.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QD07XB05; QD10AA03; QH02AB02; QR01AD03; QS01BA01; QS01CB01; QS02BA06; QS03BA01.
UNII — 7S5I7G3JQL.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Dexamethasone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Dexamethasone). A white to practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol, in acetone, in dioxan, and in methyl alcohol; slightly soluble in chloroform; very slightly soluble in ether.

Dexamethasone Acetate

(BANM, USAN, rINNM) ⊗

Acetato de dexametasona; Deksametasoniasetaatti; Deksametazono acetatas; Dexametasona, acetato de; Dexametasonacetat; Dexametazon-acetát; Dexamethasonacetat; Dexamethason-acetát; Dexaméthasone, acétate de; Dexamethasoni Acetas; Дексаметазона Ацетат.

Dexamethasone 21-acetate.

$C_{24}H_{31}FO_6$=434.5

CAS — 1177-87-3 (anhydrous dexamethasone acetate); 55812-90-3 (dexamethasone acetate monohydrate).
ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.
ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.
UNII — E2287TKU04 (dexamethasone acetate); K7V8P532WP (anhydrous dexamethasone acetate); DWN2WN457X (dexamethasone acetate monohydrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Viet.*

Int. and *US* allow the anhydrous form or the monohydrate.

Ph. Eur. 8: (Dexamethasone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Dexamethasone Acetate). It contains one molecule of water of hydration or is anhydrous. A clear, white to off-white, odourless powder. Practically insoluble in water; freely soluble in acetone, in dioxan, and in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Dexamethasone Isonicotinate

(BANM, rINNM) ⊗

Deksametasoniisonikotinaatti; Deksametazonu izonikotynian; Dexametasona, isonicotinato de; Dexametasonisonikotinat; Dexaméthasone, Isonicotinate de; Dexamethasoni Isonicotinas; Dexamethasonisonicotinat; Dexamethasonisonikotinát; Isonicotinato de dexametasona; Дексаметазона Изоникотинат.

Dexamethasone 21-isonicotinate.

$C_{28}H_{32}FNO_6$=497.6

CAS — 2265-64-7.
ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.
ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.
UNII — 8LGC0BOA71.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dexamethasone Isonicotinate). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in acetone.

Dexamethasone Phosphate *(BANM, rINNM)* ⊗

Dexametasona, fosfato de; Dexaméthasone, Phosphate de; Dexamethasoni Phosphas; Fosfato de dexametasona; Дексаметазона Фосфат.

Dexamethasone 21-(dihydrogen phosphate).

$C_{22}H_{30}FO_8P$=472.4

CAS — 312-93-6.
ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.
ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.
UNII — 2BP70L44PR.

Dexamethasone Sodium Metasulfobenzoate *(rINNM)* ⊗

Dexametasona, metasulfobenzoato sódico de; Dexaméthasone Métasulfobenzoate Sodique; Dexamethasone Sodium Metasulphobenzoate (BANM); Dexamethasone Sodium Metasulphobenzoate; Metasulfobenzoato sódico de dexametasona; Natrii Dexamethasoni Metasulfobenzoas; Натрий Метасульфобензоат Дексаметазон.

Dexamethasone 21-(sodium *m*-sulphobenzoate).

$C_{29}H_{32}FNaO_9S$=598.6

CAS — 3936-02-5.
ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.
ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.
UNII — 4T1RAI19H8.

Dexamethasone Sodium Phosphate

(BANM, rINNM) ⊗

Deksametasoninatriumfosfaatti; Deksametazon Sodyum Fosfat; Deksametazono natrio fosfatas; Dexametasona, fosfato sódico de; Dexametasonnatriumfosfat; Dexametazon-nátrium-foszfát; Dexamethasondihydrogenphosphat-Dinatrium; Dexaméthasone, phosphate sodique de; Dexamethasone Phosphate Sodium; Dexamethason-fosfát sodná sůl; Dexamethasoni Natrii Phosphas; Fosfato sódico de dexametasona; Natrii Dexamethasoni Phosphas; Sodium Dexamethasone Phosphate; Натрия Дексаметазона Фосфат.

Dexamethasone 21-(disodium orthophosphate).

$C_{22}H_{28}FNa_2O_8P$=516.4

CAS — 2392-39-4.
ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.
ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.
UNII — AI9376Y64P.

NOTE. DSP is a code approved by the BP 2014 for use on single unit doses of eye drops containing dexamethasone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US,* and *Viet.*

Ph. Eur. 8: (Dexamethasone Sodium Phosphate). A white or almost white, very hygroscopic, powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.5 to 9.5. Store in airtight containers. Protect from light.

USP 36: (Dexamethasone Sodium Phosphate). A white or slightly yellow, crystalline powder. Is odourless or has a slight odour of alcohol, and is exceedingly hygroscopic. Soluble 1 in 2 of water; slightly soluble in alcohol; insoluble in chloroform and in ether; very slightly soluble in dioxan. pH of a 1% solution in water is between 7.5 and 10.5. Store in airtight containers.

Uses and Administration

Dexamethasone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 750 micrograms of dexamethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

It has been used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (p. 1597.3), except adrenocortical insufficiency for which hydrocortisone with supplementary fludrocortisone is preferred. Its lack of mineralocorticoid properties makes dexamethasone particularly suitable for treating conditions where water retention would be a disadvantage.

The dose may be expressed in terms of the base, and the following are each equivalent to about 1 mg of dexamethasone:

- dexamethasone acetate 1.1 mg
- dexamethasone isonicotinate 1.3 mg
- dexamethasone phosphate 1.2 mg
- dexamethasone sodium metasulfobenzoate 1.5 mg
- dexamethasone sodium phosphate 1.3 mg

However, esterification generally alters potency and compounds with equivalent dexamethasone content may not have equivalent clinical effect.

Dexamethasone sodium phosphate 1.1 mg is equivalent to about 1 mg of dexamethasone phosphate.

For **oral** administration dexamethasone is given in usual doses of 0.5 to 10 mg daily. Dexamethasone is also used orally in the dexamethasone suppression tests for the diagnosis of Cushing's syndrome (for further details see under Diagnosis and Testing, p. 1632.1).

For **parenteral administration** in *intensive therapy* or in *emergencies*, the sodium phosphate ester may be given intravenously by injection or infusion or intramuscularly by injection; doses are sometimes expressed in terms of the free alcohol, the phosphate, or the sodium phosphate and confusion has sometimes arisen in the literature because of these variations. Initial doses used, expressed in terms of dexamethasone phosphate, range from about 0.5 to 24 mg daily (about 0.4 to 20 mg of dexamethasone). Intravenous doses equivalent to 2 to 6 mg/kg of dexamethasone phosphate given slowly over a minimum period of several minutes have been suggested for the treatment of severe shock. These high doses may be repeated within 2 to 6 hours and this treatment should be continued only until the patient's condition is stable and usually for no longer than 48 to 72 hours. Alternatively, the initial intravenous injection may be followed by a continuous intravenous infusion of 3 mg/kg per 24 hours.

Dexamethasone sodium phosphate is also used in the treatment of *cerebral oedema* caused by malignancy. An initial intravenous dose equivalent to 10 mg of dexamethasone phosphate is followed by 4 mg intramuscularly every 6 hours until the symptoms of oedema subside. A response is usually obtained after 12 to 24 hours and dosage may be reduced after 2 to 4 days, then gradually stopped over 5 to 7 days. A much higher dosage schedule has also been suggested for use in acute life-threatening cerebral oedema. An initial intravenous dose equivalent to 50 mg of dexamethasone phosphate is followed by 8 mg intravenously every 2 hours for the first 3 days of treatment. The dose is then reduced to 4 mg every 2 hours on day 4, followed by 4 mg every 4 hours on days 5 to 8 of treatment. Thereafter, the dose is gradually reduced by 4 mg daily. A maintenance dose of 2 mg given by intravenous or intramuscular injection 2 or 3 times daily has been used in patients with recurrent or inoperable neoplasms.

Dexamethasone is given intravenously and orally for the prevention of *nausea and vomiting* induced by cancer chemotherapy (see p. 1632.3).

The sodium phosphate ester is given by **intra-articular, intralesional**, or **soft-tissue injection**. For intra-articular injection doses equivalent to 0.8 to 4 mg of dexamethasone phosphate are used depending upon the size of the joint. For soft-tissue injection doses of 2 to 6 mg are used. Injections are repeated every 3 to 5 days to every 2 to 3 weeks. Dexamethasone acetate has also been given by intramuscular, intra-articular, soft-tissue, and intralesional injection.

For **topical** application in the treatment of various *skin disorders*, either dexamethasone or its esters may be used. Concentrations may be expressed in terms of dexamethasone, commonly in the range of 0.02 to 0.1% in preparations such as creams, ointments, and lotions. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Dexamethasone is also used topically in various *eye and ear disorders*, and preparations may contain either dexamethasone or one of its esters. Concentrations are often expressed in terms of dexamethasone or dexamethasone phosphate and are commonly 0.05 to 0.1% for eye or ear drops and eye ointments.

For allergic rhinitis (p. 612.1) and other allergic or inflammatory *nasal conditions*, a nasal spray containing dexamethasone isonicotinate is available; the acetate, phosphate, sodium phosphate, and sodium metasulfobenzoate have also been used.

A biodegradable **intravitreal implant** containing dexamethasone is used for the treatment of macular oedema after branch or central retinal vein occlusion.

Other esters of dexamethasone that have occasionally been used include the hemisuccinate, linoleate, palmitate, pivalate, propionate, sodium succinate, tebutate, and valerate.

The phenpropionate and troxundate esters have been used in veterinary medicine.

Dexamethasone-releasing stents may be used to reduce restenosis after coronary artery stent placement.

Alcohol withdrawal syndrome. Dexamethasone was reported to be effective in a patient with benzodiazepine-resistant delirium tremens[1] and resolved symptoms of alcohol withdrawal syndrome resistant to other treatments in another 110 patients.[2] However, a subsequent small study found no evidence that dexamethasone was effective.[3]

1. Fischer DK, *et al.* Efficacy of dexamethasone in benzodiazepine-resistant delirium tremens. *Lancet* 1988; **i:** 1340–1.
2. Pol S, *et al.* Dexamethasone for alcohol withdrawal. *Ann Intern Med* 1991; **114:** 705–6.
3. Adinoff B, Pols B. Dexamethasone in the treatment of the alcohol withdrawal syndrome. *Am J Drug Alcohol Abuse* 1997; **23:** 615–22.

Amyloidosis. For mention of the use of dexamethasone in patients with amyloidosis, see p. 819.3.

Blood disorders. High-dose pulsed dexamethasone therapy has been found useful in some patients with immune thrombocytopenia (p. 1606.1).

Cerebral oedema. Corticosteroids, usually dexamethasone, play an important role in the treatment of cerebral oedema in malignancy (see Raised Intracranial Pressure, p. 1271.3), and dexamethasone is advocated for

the cerebral oedema associated with high-altitude disorders (see below).

Congenital adrenal hyperplasia. Because of its lack of mineralocorticoid properties, dexamethasone has little advantage in the salt-losing form of congenital adrenal hyperplasia (p. 1603.2), in which mineralocorticoid therapy must be given, and its potency means that dose titration to avoid toxicity can be difficult in infants and children, even with the non-salt-losing form. However, it may be useful in adults with forms of the syndrome that do not require mineralocorticoid replacement. It has also been given antenatally to the mother to prevent virilisation of female fetuses.

Diagnosis and testing. *CUSHING'S SYNDROME.* Dexamethasone has been used to differentiate Cushing's disease (adrenal hyperplasia caused by defects of pituitary origin) from other forms of Cushing's syndrome (caused by ectopic ACTH secretion from non-pituitary tumours or by cortisol secretion from adrenal tumours). The dexamethasone suppression test as first proposed[1] involved giving oral dexamethasone in low doses of 500 micrograms four times daily for 8 doses followed by higher doses of 2 mg four times daily for 8 doses. In the low-dose tests the urinary excretion of cortisol and 17-hydroxycorticosteroids is suppressed in healthy persons but not in patients and in the high-dose tests the excretion is still not suppressed in those with Cushing's syndrome but is partially suppressed in those with Cushing's disease. Because this test usually involves patients being admitted to hospital for urine collection over several days and because false-negative responses are reported to be fairly frequent, more rapid and reliable tests have been sought. The low-dose test plus measurement of serum-cortisol concentrations and the excretion of free cortisol in urine over 24 hours has been suggested[2] to be a reliable method for screening for Cushing's syndrome. In the UK a single dose of 1 mg of dexamethasone given at night is often used and is considered sufficient to inhibit corticotropin secretion for 24 hours in most subjects. In another variation[3] a single dose of dexamethasone 8 mg has been given at night and plasma-cortisol concentrations measured the next day; this test (known as the overnight high-dose dexamethasone suppression test) has again been said to be a practical and reliable alternative for the differential diagnosis of Cushing's syndrome.

Further variations in the dexamethasone suppression test have included giving a continuous intravenous infusion of dexamethasone at a rate of 1 mg/hour for 7 hours, with hourly measurement of blood-cortisol concentrations.[4] Initial results indicate that this variation produces a lower number of false-positive diagnoses than the test using oral dexamethasone. Other alternatives are a combined low-dose dexamethasone suppression test and corticotropin-releasing hormone (corticorelin) test,[5] or combination of a dexamethasone suppression test with a metyrapone test.[6]

Reviews[7,8] of diagnostic tests for Cushing's syndrome have outlined both the advantages and disadvantages of tests using dexamethasone. These suggested that where there is suspicion of Cushing's syndrome, the overnight low-dose dexamethasone suppression test may be used as part of a range of measures, and that the dexamethasone-corticorelin test may be useful when there are equivocal results from initial screening. In a study to assess the efficacy of low-dose dexamethasone, some patients were found to suppress plasma or urinary steroid concentrations to levels previously thought to exclude a diagnosis of Cushing's syndrome. The authors concluded that these low-dose tests should not be used as the sole criterion for diagnosis, and that a much lower value for serum cortisol should be used to achieve adequate sensitivity.[9] In the differentiation of ACTH-dependent and ACTH-independent forms of Cushing's syndrome, one review[7] suggested that the high-dose dexamethasone suppression test cannot be recommended because of poor specificity.

For further discussion of the various methods used for the diagnosis of Cushing's syndrome and details of its management, see p. 2559.1. Various drugs may interfere with the dexamethasone suppression test.

1. Liddle GW. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1960; **20:** 1539–60.
2. Kennedy L, *et al.* Serum cortisol concentrations during low dose dexamethasone suppression test to screen for Cushing's syndrome. *BMJ* 1984; **289:** 1188–91.
3. Tyrrell JB, *et al.* An overnight high-dose dexamethasone suppression test for rapid differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **104:** 180–6.
4. Biemond P, *et al.* Continuous dexamethasone infusion for seven hours in patients with the Cushing syndrome: a superior differential diagnostic test. *Ann Intern Med* 1990; **112:** 738–42.
5. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; **269:** 2232–8.
6. Avgerinos PC, *et al.* The metyrapone and dexamethasone suppression tests for the differential diagnosis of the adrenocorticotropin-dependent Cushing syndrome: a comparison. *Ann Intern Med* 1994; **121:** 318–27.
7. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
8. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.
9. Findling JW, *et al.* The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. *J Clin Endocrinol Metab* 2004; **89:** 1222–6.

DEPRESSION. The Health and Public Policy Committee of the American College of Physicians noted that the dexamethasone suppression test for depression (p. 398.1) was based on the premise that endogenously depressed patients have shown pituitary-adrenal axis abnormalities but had been found to have a low sensitivity for detecting depression. It was of unproven value and was not recommended as a screening test.[1] Nonetheless, interest remains; studies[2-6] have shown conflicting results.

1. Young M, Schwartz JS. The dexamethasone suppression test for the detection, diagnosis, and management of depression. *Ann Intern Med* 1984; **100:** 307–8.
2. Coryell W. DST abnormality as a predictor of course in major depression. *J Affect Disord* 1990; **19:** 163–9.
3. Płocka-Lewandowska M, *et al.* Dexamethasone suppression test and suicide attempts in schizophrenic patients. *Eur Psychiatry* 2001; **16:** 428–31.
4. Coryell W, Schlesser M. The dexamethasone suppression test and suicide prediction. *Am J Psychiatry* 2001; **158:** 748–53.
5. Black DW, *et al.* The relationship between DST results and suicidal behavior. *Ann Clin Psychiatry* 2002; **14:** 83–8.
6. Yerevanian BI, *et al.* The dexamethasone suppression test as a predictor of suicidal behavior in unipolar depression. *J Affect Disord* 2004; **83:** 103–8.

High-altitude disorders. Dexamethasone is effective in the prevention of symptoms of acute mountain sickness (p. 1276.2), for which mild cerebral oedema may be a contributing factor, but it is not generally considered suitable for routine prophylaxis because of concern about its adverse effects. In the treatment of acute severe mountain sickness, which may involve the development of pulmonary and cerebral oedema, the mandatory treatment is immediate descent, and drug therapy is mainly adjunctive, to facilitate descent or maintain the patient until descent is possible. Under these circumstances dexamethasone and oxygen form the mainstays of treatment.

References.
1. Ferrazzini G, *et al.* Successful treatment of acute mountain sickness with dexamethasone. *BMJ* 1987; **294:** 1380–2.
2. Ellsworth AJ, *et al.* A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med* 1987; **83:** 1024–30.
3. Montgomery AB, *et al.* Effects of dexamethasone on the incidence of acute mountain sickness at two intermediate altitudes. *JAMA* 1989; **261:** 734–6.
4. Levine BD, *et al.* Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med* 1989; **321:** 1707–13.
5. Keller H-R, *et al.* Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *BMJ* 1995; **310:** 1232–5.
6. Dumont L, *et al.* Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; **321:** 267–72.

Hirsutism. Unbound testosterone concentrations were consistently elevated in 32 hirsute women; when concentrations were suppressed to normal by dexamethasone 0.5 to 1 mg at night hirsutism was generally improved or ceased to progress after 8 to 10 months of treatment.[1] Other studies have shown only a modest improvement[2] or no improvement at all[3] in hirsutism when treated with dexamethasone. Addition of dexamethasone to anti-androgen therapy appeared to prolong the duration of remission in a later study.[4]

The mainstay of drug treatment for hirsutism tends to be an anti-androgen such as cyproterone or spironolactone (p. 2262.1). Although low dose corticosteroids can suppress adrenal androgen production, careful consideration of the risks and benefits is advisable, especially since therapy for hirsutism may have to be given long-term.

1. Paulson JD, *et al.* Free testosterone concentration in serum: elevation is the hallmark of hirsutism. *Am J Obstet Gynecol* 1977; **128:** 851–7.
2. Carmina E, Lobo RA. Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. *Obstet Gynecol* 1991; **78:** 845.
3. Rittmaster RS, Thompson DL. Effect of leuprolide and dexamethasone on hair growth and hormone levels in hirsute women: the relative importance of the ovary and the adrenal in the pathogenesis of hirsutism. *J Clin Endocrinol Metab* 1990; **70:** 1096–1102.
4. Carmina E, Lobo RA. The addition of dexamethasone to antiandrogen therapy for hirsutism prolongs the duration of remission. *Fertil Steril* 1998; **69:** 1075–9.

Malaria. Corticosteroids, especially dexamethasone, have been used in cerebral malaria (p. 644.1) in the belief that their anti-inflammatory effect would reduce cerebral oedema. However, studies have shown that cerebral oedema does not play a significant role in the pathophysiology of cerebral malaria and, indeed, double-blind studies using both moderate doses (2 mg/kg) and high doses (11 mg/kg) of dexamethasone intravenously over 48 hours found no reduction in death rates. Thus it is now considered that corticosteroids have no place in the treatment of cerebral malaria.[1]

1. Prasad K, Garner P. Steroids for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).

Malignant neoplasms. Dexamethasone has been used in some regimens for the treatment of malignancy, for example in acute lymphoblastic leukaemia (p. 692.3) and multiple myeloma (p. 699.2).

Meningitis. The role of corticosteroids in the adjuvant treatment of bacterial meningitis (p. 191.1) has been the subject of considerable debate. Studies have shown conflicting results.[1-3] However, a systematic review[4] concluded that there was evidence of benefit, particularly in reducing deafness and short-term neurological sequelae in children and adults in high-income countries; mortality and long-term neurological sequelae were not reduced. No beneficial effect was seen in low-income countries. It has been suggested[4] that a 4-day regimen of dexamethasone (0.6 mg/kg daily) be given to adults and children in high-income countries, preferably before or with the first dose of antibacterial. Implementation of a nationwide policy to give routine adjunctive intravenous dexamethasone (10 mg every 6 hours for 4 days) with or before the first dose of parenteral antibacterial for the treatment of adults with pneumococcal meningitis in a European country resulted in a 10% decrease in mortality (from 30 to 20%); adjunctive dexamethasone treatment appeared to be more effective in those 55 years of age and older.[5]

1. Molyneux EM, *et al.* Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002; **360:** 211–18.
2. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; **347:** 1549–56.
3. Thwaites GE, *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; **351:** 1741–51.
4. Brouwer MC, *et al.* Corticosteroids for acute bacterial meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2010 (accessed 08/03/12).
5. Brouwer MC, *et al.* Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology* 2010; **75:** 1533–9.

Nausea and vomiting. Dexamethasone has antiemetic properties, particularly against acute and delayed vomiting induced by cancer chemotherapy[1] (p. 1811.3). It may be used alone for prevention of acute symptoms associated with moderately-emetogenic treatment and is combined with a 5-HT_3 antagonist for highly-emetogenic treatment. Typical dosage regimens have been dexamethasone 4 to 8 mg orally immediately before moderately-emetogenic chemotherapy and 20 mg by intravenous injection for more severely emetogenic chemotherapy. Dexamethasone is the drug of choice for prevention of delayed symptoms, given alone or with other antiemetics. A typical oral dose is 8 mg twice daily for 2 to 4 days. Dexamethasone is also effective for the prevention of postoperative nausea and vomiting,[2] and may be used to manage nausea and vomiting in palliative care.

1. Ioannidis JPA, *et al.* Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *J Clin Oncol* 2000; **18:** 3409–22.
2. Henzi I, *etal.* Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2000; **90:** 186–94.

Opportunistic mycobacterial infections. Dexamethasone in doses of 1 to 4 mg daily was associated with weight gain, reduction in fever, and an improved sense of well-being in 5 patients with HIV and disseminated *Mycobacterium avium* complex infection.[1] Combination antimycobacterial therapy for nontuberculous mycobacterial infections (p. 194.1) was also given. Similar results have been noted by others.[2]

1. Wormser GP, *et al.* Low-dose dexamethasone as adjunctive therapy for disseminated Mycobacterium avium complex infections in AIDS patients. *Antimicrob Agents Chemother* 1994; **38:** 2215–17.
2. Dorman SE, *et al.* Adjunctive corticosteroid therapy for patients whose treatment for disseminated Mycobacterium avium complex infection has failed. *Clin Infect Dis* 1998; **26:** 682–6.

Respiratory disorders. Corticosteroids such as dexamethasone have been given antenatally to mothers at risk of premature delivery in order to hasten fetal lung maturation and help prevent *neonatal respiratory distress syndrome* (p. 1608.3) and *bronchopulmonary dysplasia* (p. 1602.1). Neonatal dexamethasone has been reported to improve pulmonary outcome and assist weaning from mechanical ventilation in infants that have developed bronchopulmonary dysplasia.

Dexamethasone is also one of the drugs of choice for the management of severe *croup* (see p. 1603.3). However, as with other corticosteroids (p. 1601.3) it appears to be of little value in *bronchiolitis*.[1-3]

1. Roosevelt G, *et al.* Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet* 1996; **348:** 292–5.
2. Klassen TP, *et al.* Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized controlled trial. *J Pediatr* 1997; **130:** 191–6.
3. Corneli HM, *et al.* A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007; **357:** 331–9.

Retinopathy of prematurity. For a suggestion that antenatal dexamethasone might be helpful in the prophylaxis of retinopathy of prematurity, see p. 2120.3. For mention of

the uncertain effect of neonatal dexamethasone on retinopathy of prematurity, see Effects on the Neonate, under Adverse Effects below.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Dexamethasone has little or no effect on sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Effects on the neonate. The adverse effects of corticosteroids on the fetus are discussed under Pregnancy on p. 1619.1.

Adverse effects noted in premature neonates with bronchopulmonary dysplasia (p. 1602.1) receiving dexamethasone treatment to enable weaning from assisted ventilation have included hypertension[1-4] often accompanied by bradycardia,[1,2] gastroduodenal perforation,[4-6] ulceration and thinning of the gastric wall,[5] development of a catabolic state,[4,7] renal calcification,[8,9] and transient myocardial hypertrophy.[10-13] There is some evidence of a suppressive effect on motor activity and spontaneous movement.[14] It has been postulated that neonatal dexamethasone may both increase[15] and decrease[16] retinopathy of prematurity; its true effect is uncertain.[17]

There is also a concern that longer term development of the child may be adversely affected.[18,19] Although data are scanty, a meta-analysis[20] has concluded that postnatal use of corticosteroids to treat or prevent bronchopulmonary dysplasia is associated with dramatic increases in the incidence of cerebral palsy and neurodevelopmental impairment, and suggested that such use should be abandoned.

Pulsed dosage may reduce the adverse effects but may also reduce efficacy.[21]

1. Ohlsson A, Heyman E. Dexamethasone-induced bradycardia. *Lancet* 1988; **ii:** 1074.
2. Puntis JWL, *et al.* Dexamethasone-induced bradycardia. *Lancet* 1988; **ii:** 1372.
3. Marinelli KA, *et al.* Effects of dexamethasone on blood pressure in premature infants with bronchopulmonary dysplasia. *J Pediatr* 1997; **130:** 594–602.
4. Stark AR, *et al.* Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344:** 95–101.
5. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; **66:** 1164–6.
6. Smith H, Sinha S. Gastrointestinal complications associated with dexamethasone treatment. *Arch Dis Child* 1992; **67:** 667.
7. Macdonald PD, *et al.* A catabolic state in dexamethasone treatment of bronchopulmonary dysplasia. *Arch Dis Child* 1990; **65:** 560–1.
8. Kamitsuka MD, Peloquin D. Renal calcification after dexamethasone in infants with bronchopulmonary dysplasia. *Lancet* 1991; **337:** 626.
9. Narendra A, *et al.* Nephrocalcinosis in preterm babies. *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F207–F213.
10. Werner JC, *et al.* Hypertrophic cardiomyopathy associated with dexamethasone therapy for bronchopulmonary dysplasia. *J Pediatr* 1992; **120:** 286–91.
11. Bensky AS, *et al.* Cardiac effects of dexamethasone in very low birth weight infants. *Pediatrics* 1996; **97:** 818–21.
12. Skelton R, *et al.* Cardiac effects of short course dexamethasone in preterm infants. *Arch Dis Child* 1998; **78:** F133–F137.
13. Zecca E, *et al.* Cardiac adverse effects of early dexamethasone treatment in preterm infants: a randomized clinical trial. *J Clin Pharmacol* 2001; **41:** 1075–81.
14. Bos AF, *et al.* Qualitative assessment of general movements in high-risk preterm infants with chronic lung-disease requiring dexamethasone therapy. *J Pediatr* 1998; **132:** 300–6.
15. Batton DG, *et al.* Severe retinopathy of prematurity and steroid exposure. *Pediatrics* 1992; **90:** 534–6.
16. Sobel DB, Philip AGS. Prolonged dexamethasone therapy reduces the incidence of cryotherapy for retinopathy of prematurity in infants of less than 1 kilogram birth weight with bronchopulmonary dysplasia. *Pediatrics* 1992; **90:** 529–33.
17. Ehrenkranz RA. Steroids, chronic lung disease, and retinopathy of prematurity. *Pediatrics* 1992; **90:** 646–7.
18. Greenough A. Gains and losses from dexamethasone for neonatal chronic lung disease. *Lancet* 1998; **352:** 835–6.
19. Shinwell ES, *et al.* Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. *Arch Dis Child Fetal Neonatal Ed* 2000; **83:** F177–F181.
20. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr* 2001; **1:** 1. Available at: http://www.biomedcentral.com/1471-2431/1/1 (accessed 27/04/04)
21. Bloomfield FH, *et al.* Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease: a randomized trial. *J Pediatr* 1998; **133:** 395–400.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with the intravenous use of dexamethasone sodium phosphate (see p. 1617.3).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexamethasone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3. Various drugs may interfere with the dexamethasone suppression test.

Antiepileptics. As mentioned on p. 544.2, dexamethasone may decrease or increase plasma concentrations of *phenytoin*. Like other enzyme-inducing drugs, phenytoin also has the potential to increase the metabolism of dexamethasone. There have been reports of false positive dexamethasone suppression tests (see Diagnosis and Testing, p. 1632.1) in patients taking *carbamazepine*.[1]

1. Ma RCW, *et al.* Carbamazepine and false positive dexamethasone suppression tests for Cushing's syndrome. *BMJ* 2005; **330:** 299–300.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Dexamethasone is readily absorbed from the gastrointestinal tract. Its biological half-life in plasma is about 190 minutes. Binding of dexamethasone to plasma proteins is about 77%, which is less than for most other corticosteroids. Up to 65% of a dose is excreted in urine within 24 hours. Clearance in premature neonates is reported to be proportional to gestational age, with a reduced elimination rate in the most premature. It readily crosses the placenta with minimal inactivation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Decadron; Degabina†; Dexalaf; Dexalergin; Dexameral; Dexatotal; Duo-Decadron; Fadametasona; Gotabiotic D; Ingedex†; Isopto Maxidex; Lormine; Nexadron; Rapi-Dexacort; Rupedex; Sedesterol; Trofinan; ***Austral.***: Dexmethsone; Maxidex; ***Austria***: Dexabene; Fortecortin; Monodex; ***Belg.***: Aacidexam; Dexa-Sine†; Maxidex; ***Braz.***: Bexeton; Cetadex; Cortitop; Decadron; Decadronal; Deflaren; Dexacilin†; Dexaden; Dexadermil; Dexaglos; Dexagreen; Dexameson; Dexametax; Dexaminor; Dexanil; Dexason; Dexazona; Lisoderme; Maxidex; Metadex; Metaxon; Minidex; Neodex; Topidexa†; Uni Dexa; ***Canad.***: Ak-Dex; Dexasone; Diodex; Maxidex; Ozurdex; ***Chile***: Cortyk; Maxidex; Oradexon; ***China***: 999 Piyanping (999 皮炎平); Di Da (迪达); Duo Ta Ke Mei (多他可美); Ge Da Li (戈达利); Limethason (利美达松); Surodex (思诺迪清); Xi Luo An (息洛安); Yi Ke Tie (意可贴); You Nuo Ping (优诺平); Zhong Yi Mei Song (众益美松); ***Cz.***: Baycuten†; Dexaltin†; Dexamed; Fortecortin; Ozurdex; ***Denm.***: Maxidex; Ozurdex; ***Fin.***: Kaarmepakkaus†; Oftan Dexa; Oradexon; ***Fr.***: Dectancyl; Dexafree; Maxidex; Neodex; Ozurdex; ***Ger.***: afpred-DEXA†; Axidexa†; Cortidexason; Dexa Loscon mono; dexaclinit; Dexa-Effekton; Dexa-Ophtal; Dexa-ratiopharm; Dexa-Rhinospray Mono†; Dexa-Rhinospray N; Dexa-sine; Dexa; Dexabene; Dexabeta†; DexaEDO; Dexaflam†; Dexagalen; Dexagel; Dexahexal†; Dexapos; Fortecortin; InfectoDexaKrupp; Isopto Dex; Lipotalon; Monodex; Ozurdex; Solupen; Solutio Cordes Dexa N; Spersadex; Totocortin†; Tuttozem N; ***Gr.***: Decadron; Dexa-Sine; Dexacollyre; Dexafar; Dexamed†; Dexaton; Dexatopic†; Maxidex; Oradexon; Soldesanil; Thilodexine; ***Hong Kong***: CP-Dexa†; Dexaltin; Dexamed; Dexasone; Dexmetha†; Dexmethsone; Limethason†; Maxidex; ***Hung.***: Dexa; Maxidex; Oradexon†; ***India***: Decdak ST; Decdan; Decolite; Decrina; Dedron; Deksa; Demisone; Deosone; Dex-V; Dex; Dexacip; Dexaject; Dexalab; Dexamac; Dexamag; Dexamine; Dexane; Dexar; Dexariv; Dexasia; Dexasone; Dexona; Idizone; Intradex; Losone; Low-Dex; Mexa; Millicortenol; Wymesone; ***Indon.***: Camidexon; Cetadexon†; Corsona; Cortidex; Danasone†; Decilone†; Dellamethasone†; Dexa-M; Etason; Fortecortin†; Indexon; Inthesa-5†; Kalmethasone; Lanadexon; Licodexon; Molacort; Nufadex; Oradexon; Prodexon; Pycameth; Pyradexon†; Scandexon; ***Irl.***: Dexsol; Maxidex; Ozurdex; ***Israel***: Dexacort; Maxidex; Ozurdex; Sterodex; ***Ital.***: Capital; Decadron; Dermadex; Dexamono; Etacortilen; Luxazone; Megacort; Soldesam; Visumetazone; ***Jpn***: Limethason; Methaderm; Voalla; ***Malaysia***: Decan; Dexalone; Dexaltin; Dexasone; Maxidex; Penatone; Roximeth; ***Mex.***: Adrecort; Alin; Azona; Beminex; Bexine†; Cortidex; Cryometasona; Decadron; Decadronal; Decorex; Dexafrin; Dexagrin; Dexal; Dexamilan; Dexicart†; Dexilal; Dexona†; Dibasona; Etacortilen; Examsa†; Indarzona-N†; Lergosin; Maxidex; Metax; Pardex; Reusan; Taprodex†; Taxyl; Wiserdex; ***Neth.***: Dexa-POS; Dexsol; Oradexon; Ozurdex; ***Norw.***: Isopto Maxidex; Ozurdex; Spersadex; ***NZ***: Maxidex; ***Philipp.***: Adrecort; Cordex; Dabrin; Decan; Decilone; Dexamet; Dexticort; Drenex; Isodexam; Maxidex; Midexone†; Oradexon; Penodex; Santeson; Scancortin; Vexamet; ***Pol.***: Dexafree; Dexapolcort; Dexaven; Ozurdex; ***Port.***: Decadron; Dexafree; Dexaval; Oradexon; Ozurdex; Ronic; ***Rus.***: Detametazon (Детаметажон); Dexacort (Дексакорт); Dexafar (Дексафар); Dexamed (Дексамед); Dexapos (Дексапос); Dexason (Дексазон); Dexaven (Дексавен); Dexona (Дексона Д); Maxidex (Максидекс); Oftan Dexametason (Офтан Дексаметазон); ***S. Afr.***: Decadron†; Decasone; Dexagel; Dexona; Maxidex; Spersadex; ***Singapore***: Decan; Decordex; Dexaltin; Dexamed; Dexasone; Dexmetha; Dextrasone; Erladexone; Maxidex; Roximeth; SP-Cordexa; SW-Dexasone; ***Spain***: Dexafree; Fortecortin; Maxidex; Ozurdex; ***Swed.***: Dexacortal†; Isopto Maxidex; Opnol; Ozurdex; ***Switz.***: Dexacortin†; Dexafree; Dexalocal; Fortecortin; Maxidex; Mephamesone; Ozurdex; Spersadex; ***Thai.***: B Dexol; Decadron†; Dexa ANB; Dexa-O; Dexa-P; Dexa-Y; Dexa; Dexagel†; Dexaltin; Dexano; Dexapro; Dexasone; Dexion; Dexon; Dexone; Dexthasol; Dexthasone; Dexton; Lodexa; Oradexon; Phenodex; ***Turk.***: Cebedex; Dekort; Deksalon; Deksamet; Dexa-Sine; Kordexa; Maxidex; Onadron; Spersadex; ***UK***: Dexsol; Dropodex; Maxidex; Ozurdex; ***Ukr.***: Dexagel (Дексагель)†; Farmadex (Фармадекс); Maxidex (Максидекс); Medexol (Медексол)†; Ozurdex (Озурдекс); ***USA***: Aeroseb-Dex; Baycadron; Dalalone; Decadron†; Decaspray†; Dexasone; Dexone†; DexPak; Hexadrol†; Maxidex; Ozurdex; Zema; ***Venez.***: Decalona; Decobel; Dexacort; Dexamin; Maradex.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Dexamethasone and Neomycin Ear Spray; Dexamethasone Eye Drops, Suspension; Dexamethasone Sodium Phosphate Eye Drops, Solution; Dexamethasone Sodium Phosphate Injection; Dexamethasone Sodium Phosphate Oral Solution; Dexamethasone Tablets;

USP 36: Ciprofloxacin and Dexamethasone Otic Suspension; Dexamethasone Acetate Injectable Suspension; Dexamethasone Elixir; Dexamethasone Gel; Dexamethasone Ophthalmic Suspension; Dexamethasone Oral Solution; Dexamethasone Sodium Phosphate Cream; Dexamethasone Sodium Phosphate Inhalation Aerosol; Dexamethasone Sodium Phosphate Injection; Dexamethasone Sodium Phosphate Ophthalmic Ointment; Dexamethasone Sodium Phosphate Ophthalmic Solution; Dexamethasone Tablets; Dexamethasone Topical Aerosol; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution; Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension.

Dichlorisone Acetate *(rINNM)* ⊗

Acetato de diclorisona; Dichlorisone, Acétate de; Dichlorisoni Acetas; Diclorisona, acetato de; Diclorisone Acetate; Дихлоризона Ацетат.

9α,11β-Dichloro-17α,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{23}H_{28}Cl_2O_5$=455.4

CAS — 7008-26-6 (dichlorisone); 79-61-8 (dichlorisone acetate).

UNII — 64FTA4579H.

Profile

Dichlorisone acetate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream containing 0.25 or 1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Dermaren; Dicloderm Forte†.

Diflorasone Diacetate *(BANM, USAN, rINNM)* ⊗

Diacetato de diflorasona; Diflorasona, diacetato de; Diflorasone, Diacetate de; Diflorasoni Diacetas; U-34865; Дифлоразона Диацетат.

6α,9α-Difluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-diacetate.

$C_{26}H_{32}F_2O_7$=494.5

CAS — 2557-49-5 (diflorasone); 33564-31-7 (diflorasone diacetate).

ATC — D07AC10.

ATC Vet — QD07AC10.

UNII — 7W2J095CWX.

Pharmacopoeias. In *US.*

USP 36: (Diflorasone Diacetate). A white to pale yellow, crystalline powder. Insoluble in water; soluble in acetone and in methyl alcohol; very slightly soluble in ether;

sparingly soluble in ethyl acetate; slightly soluble in toluene. Store in airtight containers.

Profile

Diflorasone diacetate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Florone; ***Gr.***: Florone; ***India***: Diflorate; ***Mex.***: Diasorane; ***Spain***: Murode; ***USA***: Apexi-Con; Florone; Maxiflor; Psorcon.

Multi-ingredient Preparations. ***Arg.***: Filoderma Plus; Filoderma; Griseocrem.

Pharmacopoeial Preparations

USP 36: Diflorasone Diacetate Cream; Diflorasone Diacetate Ointment.

Diflucortolone *(BAN, USAN, rINN)* ⊗

Diflucortolona; Diflucortolonum; Diflukortolon; Diflukortoloni; Дифлукортолон.

6α,9α-Difluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{28}F_2O_4$=394.5

CAS — 2607-06-9.

ATC — D07AC06.

ATC Vet — QD07AC06; QD07XC04.

UNII — K253365DXI.

Diflucortolone Pivalate *(BANM, USAN, rINNM)* ⊗

Diflucortolona, pivalato de; Diflucortolone, Pivalate de; Diflucortoloni Pivalas; Pivalato de diflucortolona; SH-968; Дифлукортолона Пивалат.

Diflucortolone 21-pivalate.

$C_{27}H_{36}F_2O_5$=478.6

CAS — 15845-96-2.

ATC — D07AC06.

ATC Vet — QD07AC06.

UNII — ZR05N78276.

Diflucortolone Valerate *(BANM, rINNM)* ⊗

Diflucortolona, valerato de; Diflucortolone, Valérate de; Diflucortoloni Valeras; Diflukortolon Valerat; Valerato de diflucortolona; Дифлукортолона Валерат.

Diflucortolone 21-valerate.

$C_{27}H_{36}F_2O_5$=478.6

CAS — 59198-70-8.

ATC — D07AC06.

ATC Vet — QD07AC06.

UNII — 1A63Z067C8.

Pharmacopoeias. In *Br.*

BP 2014: (Diflucortolone Valerate). A white to creamy white crystalline powder. Practically insoluble in water; freely soluble in dichloromethane and in dioxan; sparingly soluble in ether; slightly soluble in methyl alcohol. Protect from light.

Profile

Diflucortolone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.1 or 0.3% of the valerate.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nerisona; ***Austria***: Neriforte; Nerisona; ***Belg.***: Nerisona; ***Braz.***: Nerisona; ***Canad.***: Nerisone; ***Fr.***: Nerisone; ***Ger.***: Nerisona; ***Gr.***: Nerisona; ***Hong Kong***: Nerisone; ***Indon.***: Nerilon; Nerisona; Valeron†; ***Israel***: Neriderm; ***Ital.***: Cortical; Dermaval; Dervin; Flu-Cortanest; Nerisona; Temetex; ***Mex.***: Nerisona; ***Neth.***: Nerisona; ***NZ***: Nerisone; ***Philipp.***: Nerisona; ***Port.***: Nerisona; ***S.Afr.***: Nerisone; ***Spain***: Claral; ***Turk.***: Temetex; ***UK***: Nerisone.

Multi-ingredient Preparations. ***Arg.***: Diflunazol; Nerisona C; Scheriderm; ***Austria***: Travocort; ***Belg.***: Travocort; ***Braz.***: Bi-Nerisona; ***Canad.***: Nerisalic†; ***Chile***: Bi-Nerisona†; ***Fr.***: Nerisalic; Nerisone C; ***Ger.***: Travocort; ***Gr.***: Nerisona C; Travocort; ***Hong Kong***: Nerisone C; Travocort; ***Indon.***: Nerisona Combi; Travocort; ***Irl.***: Travocort; ***Israel***: Isocort; Multiderm; Tevaderm; ***Ital.***: Corti-Fluoral; Dermaflogil; Impetex; Nerisalic; Nerisona C; Travocort; ***Malaysia***: Isoradin; Travocort; ***Mex.***: Bi-Nerisona; Scheriderm; ***NZ***: Nerisone C; ***Philipp.***: Nerisona Combi; Travocort; ***Pol.***: Travocort; ***Port.***: Nerisona C; Travocort; ***Rus.***: Travocort (Травокорт); ***S.Afr.***: Maxaderm; Travocort; ***Singapore***: Travocort; ***Spain***: Claral Plus; ***Switz.***: Travocort; ***Thai.***: Travocort; ***Turk.***: Impetex; Nerisona C; Travazol; Travocort; ***Ukr.***: Travocort (Травокорт); ***Venez.***: Binerisona.

Pharmacopoeial Preparations

BP 2014: Diflucortolone Cream; Diflucortolone Oily Cream; Diflucortolone Ointment.

Difluprednate *(USAN, rINN)* ⊗

CM-9155; Difluprednato; Difluprednatum; W-6309; Дифлупреднат.

6α,9α-Difluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate.

$C_{27}H_{34}F_2O_7$=508.6

CAS — 23674-86-4.

ATC — D07AC19.

ATC Vet — QD07AC19.

UNII — S8A06QG2QE.

Profile

Difluprednate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or gel; concentrations used are 0.02 or 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Difluprednate is used topically as a 0.05% ophthalmic emulsion for the treatment of inflammation and pain following ocular surgery.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Epitopic; ***Jpn***: Myser; ***USA***: Durezol.

Fluclorolone Acetonide *(BAN, rINN)* ⊗

Acetónido de fluclorolona; Fluclorolona, acetónido de; Fluclorolone, Acétonide de; Flucloroloni Acetonidum; Flucloronide (USAN); Fluklorolonacetonid; Fluklorolоniasetonidi; RS-2252; Флуклоролона Ацетонид.

9α,11β-Dichloro-6α-fluoro-21-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

$C_{24}H_{29}Cl_2FO_5$=487.4

CAS — 3693-39-8.

ATC — D07AC02.

ATC Vet — QD07AC02.

UNII — MG258KTA37.

Profile

Fluclorolone acetonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream containing 0.2%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Cutanit.

Fludrocortisone Acetate

(BANM, rINNM) ⊗

Acetato de fludrocortisona; Fludrocortisona, acetato de; Fludrocortisonacetat; Fludrocortisone, acétate de; Fludrocortisoni Acetas; Fludrokortison acetát; Fludrokortisonacetat; Fludrokortisoniasetaatti; Fludrokortizon-acetát; Fludrokortizono acetatas; Fludrokortyzonu octan; 9α-Fluorohydrocortisone 21-Acetate; Флудрокортизона Ацетат.

9α-Fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate.

$C_{23}H_{31}FO_6$=422.5

CAS — 127-31-1 (fludrocortisone); 514-36-3 (fludrocortisone acetate).

ATC — H02AA02.

ATC Vet — QH02AA02.

UNII — V47IF0PVH4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Fludrocortisone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol.

USP 36: (Fludrocortisone Acetate). White to pale yellow, odourless or practically odourless, hygroscopic, crystals or crystalline powder. Insoluble in water; sparingly soluble in alcohol and in chloroform; slightly soluble in ether. Protect from light.

Uses and Administration

Fludrocortisone is a corticosteroid with glucocorticoid and highly potent mineralocorticoid activity (p. 1597.1).

Fludrocortisone acetate is given orally to provide mineralocorticoid replacement in primary adrenocortical insufficiency (p. 1600.2), with glucocorticoids. It is used in a dose range of 50 to 300 micrograms daily.

Fludrocortisone acetate may also be given with glucocorticoid therapy in doses of up to 200 micrograms daily in the salt-losing form of congenital adrenal hyperplasia (p. 1603.2).

It is also given in the management of severe orthostatic hypotension (see below).

Fludrocortisone acetate is applied topically for its glucocorticoid actions in the treatment of various disorders. It is used as an ingredient of eye ointment or ear drops, usually in a concentration of 0.1%. Fludrocortisone acetate has also been included in topical preparations used for skin disorders. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Administration. A study of fludrocortisone requirements in 10 patients with Addison's disease indicated that dosage was often inadequate.[1] Nine were initially on fludrocortisone 50 to 100 micrograms daily in addition to cortisone or hydrocortisone; 5 were also taking levothyroxine for an associated auto-immune thyroid disease; one, who had detectable levels of aldosterone, was not initially receiving fludrocortisone. All the patients had evidence of sodium and water depletion and fludrocortisone was started at 300 micrograms daily, with downwards adjustments. Most patients required 200 micrograms daily; 2 patients elected to remain on 300 micrograms daily, but in most this dose caused pronounced sodium and water retention. The patient with detectable aldosterone levels required 50 micrograms daily. Eight of the 10 patients felt better on the higher fludrocortisone doses while 2 felt no change.

1. Smith SJ, *et al.* Evidence that patients with Addison's disease are undertreated with fludrocortisone. *Lancet* 1984; **i:** 11–14.

Neurally mediated hypotension. Fludrocortisone may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p. 1277.2) but there is limited evidence to support its use.

Orthostatic hypotension. Orthostatic (postural) hypotension[1-8] is a fall in blood pressure that occurs upon rising abruptly to an erect position, although it may also occur after a period of prolonged standing. Characteristic symptoms include lightheadedness, dizziness, blurred vision, weakness in the limbs, and syncope.

The causes of orthostatic hypotension are wide-ranging and include autonomic dysfunction, such as in the Shy-Drager syndrome, diabetes mellitus, and Parkinson's disease, circulating volume depletion, phaeochromocytoma, and Addison's disease. Orthostatic hypotension may also occur following a period of prolonged bed rest or after meals.

Orthostatic hypotension may result from the adverse effects of a range of drugs, such as antihypertensives, diuretics, tricyclic antidepressants, phenothiazines, and MAOIs.

In mild cases **nonpharmacological treatment** alone may be adequate. This includes increasing salt intake if not contra-indicated, maintaining adequate hydration, the use

of elastic stockings to improve venous return and increase cardiac output, and elevating the head of the bed to reduce early morning symptoms. Drug-induced orthostatic hypotension should be treated by withdrawing the drug or by dose reduction.

Pharmacological treatment. No pharmacological treatment is entirely satisfactory: responses and tolerance vary greatly between patients. Fludrocortisone acetate is usually tried first; it increases sodium retention and thus plasma volume. Most reports indicate some response in about 80% of patients, but hypokalaemia, fluid retention, and supine hypertension may limit its use. In patients who fail to respond adequately an NSAID (usually indometacin) may be tried, alone or with fludrocortisone. In patients with overt autonomic failure a beta blocker with some partial agonist activity, such as pindolol, may be tried although they are potentially dangerous.

Sympathomimetics may be useful in some patients with autonomic failure; the direct acting drugs such as phenylephrine or midodrine are usually more consistently effective than the indirect such as ephedrine, but even so, responses tend to vary with the degree of denervation. Ambulatory noradrenaline infusion therapy is under investigation for severe refractory orthostatic hypotension. Patients with central neurological abnormalities may respond to desmopressin, while drugs such as ergotamine or dihydroergotamine may be useful for resistant disease.

Other drugs that have been tried include metoclopramide, which may be useful for autonomic symptoms in patients with diabetes mellitus, fluoxetine, octreotide, yohimbine, clonidine, and in patients with concurrent anaemia, erythropoietin. Caffeine has been tried in postprandial hypotension but its value in all but the mildest cases is dubious.[5] The use of MAOIs (which given alone can induce orthostatic hypotension) with a sympathomimetic to induce a pressor reaction is controversial. Most of these drugs have potentially serious adverse effects and few are well evaluated.

1. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39:** 74–85.
2. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153:** 474–85.
3. Schoenberger JA. Drug-induced orthostatic hypotension. *Drug Safety* 1991; **6:** 402–7.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51:** 648–60.
5. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; **35:** 124–32.
6. Frishman WH, *et al.* Drug treatment of orthostatic hypotension and vasovagal syncope. *Heart Dis* 2003; **5:** 49–64.
7. Freeman R. Treatment of orthostatic hypotension. *Semin Neurol* 2003; **23:** 435–42.
8. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007; **120:** 841–7.

Adverse Effects, Treatment, Withdrawal, and Precautions

Fludrocortisone acetate has glucocorticoid actions about 10 times as potent as hydrocortisone and mineralocorticoid effects more than 100 times as potent. Adverse effects are mainly those due to mineralocorticoid activity, as described on p. 1615.3. Withdrawal effects of corticosteroids and precautions for their use are discussed on p. 1618.1 and p. 1618.3, respectively.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fludrocortisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Fludrocortisone is readily absorbed from the gastrointestinal tract. The plasma half-life is about 3.5 hours or more, but fludrocortisone has a more prolonged biological half-life of 18 to 36 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lonikan; ***Austral.***: Florinef; ***Austria***: Astonin H; ***Braz.***: Florinefe; ***Canad.***: Florinef; ***Chile***: Florinef; ***Denm.***: Florinef; ***Fin.***: Florinef; ***Fr.***: Adixone; ***Ger.***: Astonin H; ***Gr.***: Florinef; ***Hong Kong***: Florinef; ***Hung.***: Astonin H; ***India***: Floricot; ***Irl.***: Florinef; ***Malaysia***: Florinef; ***Mex.***: Florinef; ***Neth.***: Florinef; ***Norw.***: Florinef; ***NZ***: Florinef; ***Pol.***: Cortineff; ***Rus.***: Cortineff (Кортинефф); ***S.Afr.***: Florinef; ***Singapore***: Florinef; ***Spain***: Astonin; ***Swed.***: Florinef; ***Switz.***: Florinef; ***Thai.***: Florinef; ***UK***: Florinef; ***Ukr.***: Cortineff (Кортинефф); ***USA***: Florinef.

Multi-ingredient Preparations. ***Belg.***: Panotile; ***Braz.***: Panotil; ***Fr.***: Panotile; ***Gr.***: Paroticin; ***Indon.***: Nelicort; Otilon; Otopain; Otopraf; ***Neth.***: Panotile; ***Pol.***: Dicortineff; ***Spain***: Fludronef†; Panotile†; ***Switz.***: Panotile; ***Thai.***: Otosamthong†; SM Oto.

Pharmacopoeial Preparations
BP 2014: Fludrocortisone Tablets;
USP 36: Fludrocortisone Acetate Tablets.

Fludroxycortide *(BAN, rINN)* ⊗

33379; Fludroksikortidi; Fludroxicortida; Fludroxikortid; Fludroxycortidum; Fluorandrenolone; 6α-Fluoro-16α-hydroxyhydrocortisone 16,17-Acetonide; Flurandrenolide (USAN); Flurandrenolone; Флудроксикортид.
6α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.
$C_{24}H_{33}FO_6$=436.5
CAS — 1524-88-5.
ATC — D07AC07.
ATC Vet — QD07AC07.
UNII — 8EUL29XUQT.

Pharmacopoeias. In *US*.

USP 36: (Flurandrenolide). A white to off-white, fluffy, odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 72 of alcohol, 1 in 10 of chloroform, and 1 in 25 of methyl alcohol. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Profile

Fludroxycortide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, lotion, or ointment containing 0.0125% or 0.05%. It is also used as an adhesive polyethylene tape impregnated with fludroxycortide 4 micrograms/cm^2.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Drenison; ***UK***: Haelan; ***USA***: Cordran.

Multi-ingredient Preparations. ***Braz.***: Dreniformio; Drenison N.

Pharmacopoeial Preparations
USP 36: Flurandrenolide Cream; Flurandrenolide Lotion; Flurandrenolide Ointment; Flurandrenolide Tape; Neomycin Sulfate and Flurandrenolide Cream; Neomycin Sulfate and Flurandrenolide Lotion; Neomycin Sulfate and Flurandrenolide Ointment.

Flumetasone Pivalate *(BANM, rINNM)* ⊗

Flumetason pivalát; Flumetasona, pivalato de; Flumétasone, Pivalate de; Flumetasoni Pivalas; Flumetasonipivalaatti; Flumetasonpivalat; Flumetasonum Pivalas; Flumetazon Pivalat; Flumetazono pivalatas; Flumetazon-pivalát; Flumetazonu piwalan; Flumethasone Pivalate (USAN); Flumethasone Trimethylacetate; NSC-107680; Pivalato de flumetasona; Флуметазона Пивалат.
Flumethasone 21-pivalate.
$C_{27}H_{36}F_2O_6$=494.6
CAS — 2002-29-1.
ATC — D07AB03.
ATC Vet — QD07AB03.
UNII — 0DV09X6F21.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Flumetasone Pivalate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in acetone. Protect from light.

USP 36: (Flumethasone Pivalate). A white to off-white crystalline powder. Insoluble in water; soluble 1 in 89 of alcohol, 1 in 350 of chloroform, and 1 in 2800 of ether; slightly soluble in methyl alcohol; very slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Flumetasone pivalate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a 0.02% cream, ointment, or lotion. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Flumetasone pivalate is also used in ear drops in a concentration of 0.02% with clioquinol 1%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Locacortene; ***Ger.***: Cerson; Locacorten; ***Gr.***: Locacorten; ***Neth.***: Locacorten; ***Pol.***: Lorinden†; ***Switz.***: Locacorten.

Multi-ingredient Preparations. ***Arg.***: Tresite F; ***Austral.***: Locacorten Vioform; ***Belg.***: Locasalen; ***Braz.***: Locorten Vioformio; Losalen; ***Canad.***: Locacorten Vioform; ***Denm.***: Locacorten Vioform; ***Fin.***: Locacorten Vioform; ***Fr.***: Alkocortenbioform†; Alkosalen†; Alkotar†; Locacortene Vioforme†; Locasalene†; Psocortene†; ***Ger.***: DuoGalen; Locacorten Vioform; Locasalen; ***Gr.***: Locacorten Tar; Locacorten Vioform; Locacorten with Neomycin; Locasalene; ***Hong Kong***: Locasalen; ***Hung.***: Lorinden A; Lorinden C; ***Indon.***: Locasalen; ***Israel***: Topisalen; ***Ital.***: Locorten Vioformio†; Locorten; Locorten; Losalen; Vasosterone Oto†; ***Neth.***: Locacorten Vioform; Locasalen; ***NZ***: Locacorten Vioform; Locorten Vioform; ***Philipp.***: Locasalen; ***Pol.***: Lorinden A; Lorinden C; Lorinden N; ***Rus.***: Lorinden A (Лоринден А); Lorinden C (Лоринден С); ***S.Afr.***: Locacorten Vioform; ***Spain***: Losalen†; ***Swed.***: Locacorten Vioform; ***Switz.***: Locasalen; ***Thai.***: Flumasalen†; Locasalen; ***Turk.***: Locacortene Vioform; Locasalene; ***UK***: Locorten Vioform; ***Ukr.***: Lorinden A (Лоринден А); Lorinden C (Лоринден С); ***Venez.***: Locasalen; Locorten Vioformo.

Pharmacopoeial Preparations
USP 36: Flumethasone Pivalate Cream.

Flunisolide *(BAN, USAN, rINN)* ⊗

Flunisolid; Flunisolida; Flunisolidi; Flunisolidum; RS-1320 (flunisolide acetate); RS-3999; Флунизолид.
6α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.
$C_{24}H_{31}FO_6$=434.5
CAS — 3385-03-3 (flunisolide); 77326-96-6 (flunisolide hemihydrate); 4533-89-5 (flunisolide acetate).
ATC — R01AD04; R03BA03.
ATC Vet — QR01AD04; QR03BA03.
UNII — QK4DYS664X.

Pharmacopoeias. In *US* which specifies the hemihydrate.

USP 36: (Flunisolide). A white to creamy-white crystalline powder. Practically insoluble in water; soluble in acetone; sparingly soluble in chloroform; slightly soluble in methyl alcohol.

Uses and Administration

Flunisolide is a corticosteroid with glucocorticoid activity (p. 1597.1) used as a nasal spray for the prophylaxis and treatment of allergic **rhinitis** (p. 612.1). In the UK a formulation containing 25 micrograms per metered spray is available; in the USA each metered spray of some preparations contains 29 micrograms flunisolide hemihydrate. The recommended starting dose is 2 sprays into each nostril twice daily, increased if necessary to three times daily, and then reduced for maintenance. In the USA a maximum dose of 8 sprays into each nostril daily has been established.

Like some other corticosteroids, flunisolide is also used by inhalation from metered-dose aerosols in the management of **asthma** (see p. 1600.3). The usual dosage of flunisolide from an aerosol using chlorofluorocarbon (CFC) propellants is 500 micrograms inhaled twice daily. In severe asthma the dosage may be increased but should not exceed a total of 2 mg daily. A hydrofluoroalkane (CFC-free) aerosol, which is also available in some countries, has a lower dose because of different delivery characteristics. The usual dose, expressed as flunisolide hemihydrate, is

160 micrograms twice daily, which may be increased after 3 to 4 weeks but should not exceed 320 micrograms twice daily.

For doses used in children, see below.

Administration in children. Flunisolide may be used in children as a nasal spray for the prophylaxis and treatment of allergic **rhinitis**. In the UK a formulation containing 25 micrograms per metered spray is available; in the USA each metered spray of some preparations contains 29 micrograms flunisolide hemihydrate. In the UK, for children aged from 5 to 14 years, a starting dose of 1 spray into each nostril may be given up to a maximum of 3 times daily. Children in the USA aged 6 to 14 years old may be treated with this dose, or an initial 2 sprays into each nostril twice daily (which is also the recommended maximum of 4 sprays into each nostril daily).

Flunisolide is also used by inhalation from metered-dose aerosols in the management of **asthma** in children. The dosage of flunisolide from an aerosol using chlorofluorocarbon (CFC) propellants for children of 6 to 15 years of age is 500 micrograms inhaled twice daily, which should not be exceeded. A hydrofluoroalkane (CFC-free) aerosol, which is also available in some countries, has a lower dose because of different delivery characteristics. In children aged 6 to 11 years of age a dose of flunisolide hemihydrate 80 micrograms twice daily may be used, increased after 3 to 4 weeks to a maximum of 160 micrograms twice daily if necessary.

For both indications, the dose should be reduced to the lowest effective for maintenance. Older children may be given adult doses (see p. 1635.3).

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Flunisolide is reported to undergo extensive first-pass metabolism, with only 20% of the dose available systemically if it is given orally. The major metabolite, 6β-hydroxyflunisolide has some glucocorticoid activity; it has a half-life of about 4 hours. Only small amounts of flunisolide are absorbed after intranasal doses.

References.
1. Chaplin MD, *et al*. Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980; **27:** 402–13.
2. Möllmann H, *et al*. Pharmacokinetic/pharmacodynamic evaluation of systemic effects of flunisolide after inhalation. *J Clin Pharmacol* 1997; **37:** 893–903.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Syntaris†; ***Canad.***: Rhinalar; ***Cz.***: Syntaris†; ***Fr.***: Nasalide†; ***Ger.***: Syntaris; ***Gr.***: Bronalide; ***Ital.***: Aerflu; Aerolid; Asmaflu; Assolid; Careflu; Charlyn; Citiflux; Desaflu; Doricoflu; Eliosid; Euroflu; Fluminex; Flunitop; Forbest; Givair; Inalcort†; Kaimil; Levonis; Lunibron; Lunis; Multinebulgen; Nambrol; Nebulcort; Nebulgen; Nereflun; Nisolid; Nisoran; Plaudit; Pulmist; saflineb; Syntaris; Turm; Ventoflu; ***Neth.***: Syntaris†; ***Norw.***: Lokilan†; ***UK***: Syntaris; ***USA***: AeroBid; AeroSpan; Nasarel.

Multi-ingredient Preparations. ***Ital.***: Plenaer.

Pharmacopoeial Preparations
USP 36: Flunisolide Nasal Solution.

Fluocinolone Acetonide *(BANM, USAN, rINN)* ⊗

Acetónido de fluocinolona; 6α,9α-Difluoro-16α-hydroxyprednisolone Acetonide; Fluocinolon acetonid; Fluocinolona, acetónido de; Fluocinolon-acetonid; Fluocinolonacetonid; Fluocinolone, acétonide de; Fluocinoloni Acetonidum; Fluocinolono acetonidas; Fluocynolonu acetonid; Fluosinoloniasetonidi; NSC-92339; Флуоцинолона Ацетонид.

6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

$C_{24}H_{30}F_2O_6$=452.5

CAS — 67-73-2.

ATC — C05AA10; D07AC04; S01BA15; S02BA08.

ATC Vet — QC05AA10; QD07AC04; QS01BA15; QS02BA08.

UNII — 0CD5FD6S2M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet. Br.* and *Viet.* have a separate monograph for the dihydrate; *US* allows either the anhydrous form or the dihydrate.

Ph. Eur. 8: (Fluocinolone Acetonide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol and in acetone. Protect from light.

BP 2014: (Fluocinolone Acetonide Dihydrate). A white or almost white, crystalline powder. Practically insoluble in water and in hexane; soluble in dehydrated alcohol; freely soluble in acetone; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 36: (Fluocinolone Acetonide). It is anhydrous or contains two molecules of water of hydration. A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 45 of alcohol, 1 in 25 of chloroform, and 1 in 350 of ether; soluble in methyl alcohol.

Profile

Fluocinolone acetonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, ointment, or scalp application; concentrations normally range from 0.0025 to 0.025% although higher-strength preparations may be available. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Fluocinolone acetonide is also used topically with an antibacterial in the treatment of infective inflammatory eye, ear, and nose disorders. Ear drops containing fluocinolone acetonide 0.01% may be used in eczematous external otitis. A sterile implant of fluocinolone acetonide is used intravitreally for the treatment of chronic non-infectious posterior uveitis. Another intravitreal implant is used in the treatment of diabetic macular oedema, and is under investigation in age-related macular degeneration and retinal vein occlusion. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

References.
1. Mohammad DA, *et al*. Retisert: is the new advance in treatment of uveitis a good one? *Ann Pharmacother* 2007; **41:** 449–54.
2. Sanford M. Fluocinolone acetonide intravitreal implant (Iluvien): in diabetic macular oedema. *Drugs* 2013; **73:** 187–93.
3. Haritoglou C, *et al*. Fluocinolone acetonide and its potential in the treatment of chronic diabetic macular edema. *Clin Ophthalmol* 2013; **7:** 503–9.

Formulation. The potency of fluocinolone acetonide varied with the formulation in a study[1] involving different *Synalar* topical preparations, the gel, ointment, and cream. The cream was the most potent followed by the gel, and then the ointment. A comparison of topical vasoconstrictor activity (used as an index of potency) unexpectedly found that the commercial dilutions of the cream (containing 0.00625% and 0.0025%) were indistinguishable in their effects from the full-strength (0.025%) cream.

1. Gao HY, Li Wan Po A. Topical formulations of fluocinolone acetonide: are creams, gels and ointments bioequivalent and does dilution affect activity? *Eur J Clin Pharmacol* 1994; **46:** 71–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluocinolone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duoflu; Flulone; ***Belg.***: Synalar†; ***Canad.***: Capex; Derma-Smoothe/FS; DermOtic; Fluoderm; Synalar; ***Chile***: Adermina; ***Cz.***: Flucinar; Gelargin; ***Denm.***: Synalar; ***Fr.***: Synalar†; ***Ger.***: Flucinar; Jellin; ***Gr.***: Synalar Simple; ***Hong Kong***: Aplosyn†; Synaderm†; Synalar; Synalone†; Synfulin†; Uni-Fluocin†; ***Hung.***: Flucinar; ***India***: Emderm; Flucin; Flucocin; Flucort-H; Flucort; Luci; ***Indon.***: Cinolon; Dermasolon; Esinol; Inoderm; Licosolon; ***Israel***: Dermalar†; ***Ital.***: Dermolin; Fluocit†; Fluomix Same; Fluovitef; Localyn SV†; Localyn; Omniderm; Sterolone; Ultraderm; ***Malaysia***: Fluciderm; ***Mex.***: Cortifung-S; Cortilona; Cremisona; Farmacorti; Flumicin†; Fluomex; Fusalar†; Lonason; Naflucen; Synalar; ***Norw.***: Synalar; ***NZ***: Synalar; ***Philipp.***: Aplosyn; Cynozet; Flucin; Synalar; Syntopic; ***Pol.***: Flucinar; ***Port.***: Oto-Synalar N; Synalar; ***Rus.***: Flucinar (Флуцинар); Sinaflan (Синафлан); Sinoderm (Синодерм); ***S.Afr.***: Cortoderm; Fluoderm†; Synalar; ***Singapore***: Fluciderm; Flunolone-V; Synalar; Synfulin; ***Spain***: Co Fluocin Fuerte†; Cortiespec†; Fluocid Forte†; Fluodermo Fuerte†; Flusolgen†; Gelidina; Synalar Rectal Simple; Synalar; ***Swed.***: Synalar; ***Switz.***: Synalar; ***Thai.***: Cervicum†; Flunolone-V†; Fulone†; Supralan†; Synalar†; ***UK***: Iluvien; Synalar; ***Ukr.***: Flucar (Флуцар); Flucinar (Флуцинар); Synaflan (Синафлан); ***USA***: Capex; Derma-Smoothe/FS; DermOtic; Fluonid; Retisert; Synalar; Synemol; ***Venez.***: Bratofil; Neo-Synalar.

Multi-ingredient Preparations. ***Arg.***: Neoblanc; Tri-Luma; Trimegtante; ***Belg.***: Procto-Synalar; Synalar Bi-Otic; ***Braz.***: Dermoxin†; Elotin; Fluo-Vaso; Hormoskin; Neocinolon; Otomixyn; Otosynalar; Suavicid; Tri-Luma; Triderm; Vitacid Plus; ***Chile***: Otoseptil; Tri-Luma; ***Denm.***: Synalar med Chinoform; ***Fin.***: Cetraxal Comp; ***Fr.***: Antibio-Synalar; ***Ger.***: Jellin-Neomycin; ***Gr.***: Myco-Synalar; Otospon; Procto Synalar-N; Procto-Synalar N; Synalar; ***Hong Kong***: Aplosyn-C†; Aplosyn-N†; Aplosyn-Otic; Flunolone; Fluonid-N; Fusodic†; Synaderm-N†; Synalar N; Synalone-N†; Synco-CFN†; Syneolona†; Tri-Luma; ***Hung.***: Flucinar N; ***India***: Atderm; Ceflox-CF; Ciprobiotic-FC; Ciprolar-F; Ciprolar-FC; E-Derm; Eczo-Wokadine; Flual-M; Flucocin-N; Flucocip; Flucort-C; Flucort-MZ; Flucort-N; Flucreme-NM; Fungitop-F; Gentacort-FC; Gentacort-MF; GMF; Luci-N; Mediron; Micogel F; Mictop-F; Nazo-F; Neocip FC; Olamin-F; Zole-F; ***Indon.***: Bravoderm-N; Cinogenta; Cinolon-N; Fasolon; Fluocort-N; Genolon; Gentasolon; Kalcinol-N; Neosinol; Ociderm-N; Refaquin; Sinobiotik†; Synalten; Zumaderm-N†; ***Ital.***: Cortanest Plus; Doricum; Lauromicina; Localyn-Neomicina; Localyn; Localyn; Mecloderm F; Nefluan; Proctolyn; ***Malaysia***: Flumicin†; Tri-Luma; ***Mex.***: Acenil; Bentix; Cetoquina Y; Cortifung-N; Cortifung-Y; Cortilona Compuesta; Dermatofin; Farmacorti YC; Fluccinol N; Fluo Grin†; Gynoclin-V; Lasalar-Y; Luzolona Y; Neoderm-F; Nysmosons-V; Promibasol-Plus†; Synalar C; Synalar N; Synalar Neo; Synalar O; Synalar Oftalmico†; Tri-Luma; Vagitrol-V; Yderm; ***Neth.***: Synalar; ***Norw.***: Synalar med Chinoform; ***Philipp.***: Aceflo; Aplosyn C; Aplosyn N; Aplosyn-Otic; Neo-Synalar; Synalar Otic; Tri-Luma; ***Pol.***: Flucinar N; ***Port.***: Synalar N; Synalar Rectal; ***Rus.***: Flucinar N (Флуцинар Н); Nefluan (Нефлуан); Simetrid (Симетрид); ***S.Afr.***: Cortoderm-C†; Synalar C; Synalar N; ***Singapore***: Flunolone; Syneolona; Tri-Luma; ***Spain***: Abrasone Rectal; Abrasone; Aceoto Plus; Alergical; Artrodesmol Extra; Cetraxal Plus; Creanolona; Flodermol; Midacina; Otomidrin; Synalar Nasal; Synalar Otico; Synalar Rectal; Synalotic; Ultramicina Plus; Vinciseptil Otico; ***Switz.***: Procto-Synalar N; Synalar N; ***Thai.***: Flunobate-N; Flunolone; Fluo-Neo; Fluocort-N; Fluonid-N†; Gental-F; Supralan-N; Synalar N; Tri-Luma; ***UK***: Synalar C; Synalar N; ***Ukr.***: Cetraxal Plus (Цетраксал Плюс); Flucinar N (Флуцинар N); ***USA***: Tri-Luma; ***Venez.***: Bratofil c Neomicina; Neo-Synalar con Neomicina; Tri-Luma.

Pharmacopoeial Preparations
BP 2014: Fluocinolone Cream; Fluocinolone Ointment;
USP 36: Fluocinolone Acetonide Cream; Fluocinolone Acetonide Ointment; Fluocinolone Acetonide Topical Solution; Neomycin Sulfate and Fluocinolone Acetonide Cream.

Fluocinonide *(BAN, USAN, rINN)* ⊗

Fluocinolide; Fluocinolone Acetonide 21-Acetate; Fluocinonid; Fluocinónida; Fluocinonidum; Fluosinonidi; NSC-101791; Флуоциноníд.

6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{26}H_{32}F_2O_7$=494.5

CAS — 356-12-7.

ATC — C05AA11; D07AC08.

ATC Vet — QC05AA11; QD07AC08.

UNII — 2W4A77YPAN.

Pharmacopoeias. In *Br., Chin., Jpn*, and *US*.

BP 2014: (Fluocinonide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in chloroform. Protect from light.

USP 36: (Fluocinonide). A white to cream-coloured, crystalline powder having not more than a slight odour. Practically insoluble in water; slightly soluble in alcohol, in methyl alcohol, and in dioxan; sparingly soluble in acetone and in chloroform; very slightly soluble in ether.

Profile

Fluocinonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, ointment, or scalp application containing 0.05%. A cream containing 0.1% may also be available.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Lidemol; Lidex; Lyderm; Tiamol; Topactin†; Topsyn†; ***Denm.***: Metosyn; ***Ger.***: Topsym; ***Gr.***: Lamagramm; Lidex; ***Ital.***: Flu-21; Topsyn; ***Mex.***: Topsyn;

Norw.: Metosyn; ***Philipp.***: Dermadex; Lidemol; Lidex; ***Spain***: Novoter; ***Switz.***: Topsym; ***UK***: Metosyn; ***USA***: Lidex; Vanos.

Multi-ingredient Preparations. ***Ger.***: Jelliproct; ***Israel***: Comagis; ***Mex.***: Topsyn-Y; ***Philipp.***: Lidex NGN; ***Spain***: Novoter Gentamicina; ***Switz.***: Mycolog N; Topsym polyvalent; ***UK***: Vipsogal; ***Ukr.***: Cremgen (Кремген).

Pharmacopoeial Preparations
BP 2014: Fluocinonide Cream; Fluocinonide Ointment;
USP 36: Fluocinonide Cream; Fluocinonide Gel; Fluocinonide Ointment; Fluocinonide Topical Solution.

Fluocortin Butyl *(BAN, USAN, rINNM)* ⊗

Butil éster de la fluocortina; Butylis Fluocortinas; Fluocortina, butil éster de la; Fluocortine Butyle; SH-K-203; Флуокортин Бутил.

Butyl 6α-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-oate.

$C_{26}H_{35}FO_5$=446.6

CAS — 33124-50-4 (fluocortin); 41767-29-7 (fluocortin butyl).
ATC — D07AB04.
ATC Vet — QD07AB04.
UNII — 6N7OA9MO7O.

Profile

Fluocortin butyl is a corticosteroid that has been used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.75%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Fluocortin butyl has also been used in the form of a dry powder nasal inhalation for the management of allergic rhinitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Vaspit; ***Spain***: Vaspit.

Fluocortolone *(BAN, USAN, rINN)* ⊗

Fluocortolona; Fluocortolonum; Fluokortolon; Fluokortoloni; 6α-Fluoro-16α-methyl-1-dehydrocorticosterone; SH-742; Флуокортолон.

6α-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_4$=376.5

CAS — 152-97-6.
ATC — C05AA08; D07AC05; H02AB03.
ATC Vet — QC05AA08; QD07AC05; QH02AB03.
UNII — 65VXC1MH0J.

Fluocortolone Caproate *(USAN, rINNM)* ⊗

Caproato de fluocortolona; Fluocortolona, caproato de; Fluocortolone, Caproate de; Fluocortolone Hexanoate (BANM); Fluocortoloni Caproas; Fluokortolon Kaproat; Fluokortolon Kapronat; SH-770; Флуокортолона Капроат.

Fluocortolone 21-hexanoate.

$C_{28}H_{39}FO_5$=474.6

CAS — 303-40-2.
ATC — C05AA08; D07AC05; H02AB03.
ATC Vet — QC05AA08; QD07AC05; QH02AB03.
UNII — 90893P8662.

Pharmacopoeias. In *Br.*

BP 2014: (Fluocortolone Hexanoate). A white or creamy-white, odourless or almost odourless, crystalline powder. It exhibits polymorphism. Practically insoluble in water and in ether; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone and in dioxan; sparingly soluble in chloroform. Protect from light.

Fluocortolone Pivalate *(BANM, rINNM)* ⊗

Fluocortolona, pivalato de; Fluocortolone, Pivalate de; Fluocortolone Trimethylacetate; Fluocortoloni Pivalas; Fluokortolon Pivalat; Fluokortolonipivalaatti; Fluokortolono pivalatas; Fluokortolonpivalat; Fluokortolon-pivalát; Pivalato de fluocortolona; Флуокортолона Пивалат.

Fluocortolone 21-pivalate.

$C_{27}H_{37}FO_5$=460.6

CAS — 29205-06-9.
ATC — C05AA08; D07AC05; H02AB03.
ATC Vet — QC05AA08; QD07AC05; QH02AB03.
UNII — 9J8AL6K50Q.

Pharmacopoeias. In *Eur.* (see p. vii)

Ph. Eur. 8: (Fluocortolone Pivalate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dioxan. Protect from light.

Profile

Fluocortolone and its esters are corticosteroids mainly used topically for their glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. They are usually used as a cream or ointment; concentrations usually used are 0.25% of the caproate with 0.25% of either the free alcohol or pivalate ester. The pivalate and caproate esters have also been used together in ointments or suppositories for the treatment of anorectal disorders.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Fluocortolone free alcohol is sometimes given orally for its systemic effects in conditions for which corticosteroids are indicated (p. 1597.3), in usual doses of 5 to 100 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ultracur S; ***Austria***: Ultralan; Ultralan; ***Ger.***: Ultralan; ***Gr.***: Imiprom†; Ultralanum; ***Hong Kong***: Ultralan; ***Israel***: Ultralan; ***Ital.***: Ultralan; Ultralan; ***Philipp.***: Ultralan†; ***Spain***: Ultralan M; ***Turk.***: Ultralan; Ultralan; ***UK***: Ultralanum Plain.

Multi-ingredient Preparations. ***Arg.***: Ultraproct; ***Austral.***: Ultraproct†; ***Austria***: Doloproct; Pilison; ***Belg.***: Doloproct; Ultraproct; ***Braz.***: Ultraproct; ***Chile***: Ultraproct; ***Denm.***: Doloproct; Doloproct; ***Fin.***: Neoproct; ***Fr.***: Ultralan†; Ultraproct; ***Ger.***: Doloproct; ***Gr.***: Doloproct; ***Hong Kong***: Ultraproct N; ***Hung.***: Doloproct; ***Indon.***: Ultraproct N; Ultraproct†; ***Irl.***: Ultraproct; ***Ital.***: Doloproct; Ultraproct; ***Mex.***: Ultraproct; ***NZ***: Doloproct; Ultraproct; ***Philipp.***: Doloproct; Ultraproct; ***Port.***: Ultraproct; ***Rus.***: Doloprokt (Долопрокт); Ultraproct (Ультрапрокт); ***Spain***: Doloproct; ***Swed.***: Doloproct; ***Thai.***: Scheriproct N; ***Turk.***: Doloproct; Ultralan Crinale; Ultraproct; ***UK***: Ultraproct; ***Ukr.***: Doloproct (Долопрокт); Ultraproct (Ультрапрокт).

Pharmacopoeial Preparations
BP 2014: Fluocortolone Cream.

Fluorometholone *(BAN, rINN)* ⊗

Fluorométholone; Fluorometholonum; Fluorometolon; Fluorometolona; Fluorometoloni; Флуорометолон.

9α-Fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_4$=376.5

CAS — 426-13-1.
ATC — C05AA06; D07AB06; S01BA07.
ATC Vet — QC05AA06; QD07AB06; QD07XB04; QD10AA01; QS01BA07; QS01CB05.
UNII — SV0CSG527L.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Fluorometholone). A white to yellowish white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in ether.

USP 36: (Fluorometholone). A white to yellowish-white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 2200 of chloroform; very slightly soluble in ether. Store in airtight containers. Protect from light.

Fluorometholone Acetate

(BANM, USAN, rINNM) ⊗

Acetato de fluorometolona; Fluorométholone, Acétate de; Fluorometholoni Acetas; Fluorometolon Asetat; Fluorometolona, acetato de; U-17323; Флуорометолона Ацетат.

Fluorometholone 17-acetate.

$C_{24}H_{31}FO_5$=418.5

CAS — 3801-06-7.
ATC — C05AA06; D07AB06; S01BA07.
ATC Vet — QC05AA06; QD07AB06; QS01BA07.
UNII — 9I50C3I3OK.

Pharmacopoeias. In *US.*

USP 36: (Fluorometholone Acetate).

Profile

Fluorometholone is a corticosteroid used for its glucocorticoid activity (p. 1597.1), usually as eye drops containing 0.1%, in the treatment of allergic and inflammatory conditions of the eye. Fluorometholone acetate is used similarly.

Fluorometholone is also used topically in the treatment of various skin disorders.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemiceffects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flarex; FML; ***Austral.***: Flarex; Flucon; FML; ***Belg.***: Fluacort; Flucon; FML; ***Braz.***: Florate; Flumex; Flutinol; ***Canad.***: Flarex; FML; ***Chile***: Aflarex; Fluforte; Flumetol N; ***China***: Flarex (拂雷); Flumetholon (氟美童); FML (艾氟龙); ***Cz.***: Efflumidex; Flarex; Flucon; Fluoropos; ***Denm.***: Flurolon; ***Fin.***: FML; ***Fr.***: Flucon; ***Ger.***: Efflumidex; Fluoro-Ophtal†; Fluoropos; ***Gr.***: Facocinerin; Florate; Flucon; Fluxinam; FML; Talirax; Toscacort; ***Hong Kong***: Flarex; Flucon†; Flumetholon; FML; ***Hung.***: Efflumidex; Flarex†; Flucon; ***India***: F-Lone; Flarex; Flomex; Flomon; Flosef; Flurisone; FML; FML; Mep-Fluron; ***Indon.***: Flumetholon; Ocuflam; ***Irl.***: FML; ***Israel***: Flarex; FML; ***Ital.***: Flarex; Fluaton; Flumetol; ***Malaysia***: Flarex; FML; ***Mex.***: Flarex; Fluforte; Flumetol NF; ***Neth.***: FML; ***NZ***: Flucon; FML; ***Philipp.***: Flarex; Flulon; FML; ***Pol.***: Flarex; Flucon; ***Port.***: Flurop; FML; ***Rus.***: Flarex (Флаpекс); ***S.Afr.***: Flucon; FML; ***Singapore***: FML; ***Spain***: FML; Isopto Flucon; ***Switz.***: FML; ***Thai.***: Flarex; Flu Oph; Flucon; FML; ***Turk.***: Flarex; Fluoropos; FML; ***UK***: FML; ***USA***: Eflone; Flarex; FML; ***Venez.***: Aflarex; Flumetol.

Multi-ingredient Preparations. ***Arg.***: Delisan; Efemolina; FML Neo; Larsimal; Nesbiler; ***Belg.***: Infectoflam†; ***Braz.***: Flumex N; ***Canad.***: FML Neo†; ***China***: Infectoflam (易妥芬); ***Ger.***: Cibaflam†; Efemolin†; ***Gr.***: Efemoline; Fluorocort; FML Neo; Helpometil; Indo-Cort; Luzin; ***Hong Kong***: Efemoline; ***India***: Flomex N; FML Neo; FML-T; LT-Cin; Nutob-F; Obra-F; ***Irl.***: FML Neo†; ***Ital.***: Efemoline; Flumeciclina†; Flumezina; Gentacort†; ***Mex.***: Fluforte N; Fluorometil; ***Philipp.***: Efemoline; Infectoflam; ***Port.***: FML Neo; ***S.Afr.***: Efemoline; FML Neo; ***Singapore***: Efemoline; Infectoflam; ***Spain***: Bexicortil†; Cortisdin Urea†; Flugen†; Fluorvas; ***Switz.***: Efemoline; FML Neo; Infectoflam†; ***Thai.***: Efemoline; FML Neo; Infectoflam†; ***Turk.***: Efemoline; Flumetol†; ***USA***: FML-S†.

Pharmacopoeial Preparations
BP 2014: Fluorometholone Eye Drops;
USP 36: Fluorometholone Cream; Fluorometholone Ophthalmic Suspension; Neomycin Sulfate and Fluorometholone Ointment; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension.

Fluprednidene Acetate *(BANM, rINNM)* ⊗

Acetato de fluprednideno; Fluprednidène, Acétate de; Fluprednideni Acetas; Fluprednideno, acetato de; Fluprednylidene 21-Acetate; Флупреднидена Ацетат.

9α-Fluoro-11β,17α,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione 21-acetate.

$C_{24}H_{29}FO_6$=432.5

CAS — 2193-87-5 (fluprednidene); 1255-35-2 (fluprednidene acetate).
ATC — D07AB07.
ATC Vet — QD07AB07.
UNII — GE65DV564S.

Profile

Fluprednidene acetate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a 0.1% cream, or as an ointment containing 0.05% or 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluprednidene as

not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Decoderm; ***Belg.***: Decoderm; ***Ger.***: Decoderm; ***Indon.***: Decoderm.

Multi-ingredient Preparations. ***Austria***: Decoderm Compositum; Decoderm trivalent†; Vobaderm; ***Belg.***: Decoderm Compositum†; ***Ger.***: Candio-Hermal Plus; Crinohermal fem; Decoderm Comp; Decoderm tri; Sali-Decoderm; Vobaderm; ***Gr.***: Antimycotic; Catrigel; Combi; Conazol; Decoderm Trivalente-N; Domycotin; Edmudo; Expectein; Feminella; Finicort; Flenazole; Flumicomplex; Fluniprol; Flunovon; Fosemyk; Fumicon; Iflerit; Micoflup; Micogen; Mifler†; Milfer; Oxigon; Panderm; Panmyk; Sarmel; Verdal; ***Indon.***: Decoderm 3; Gentacortin†; ***Ital.***: Decoder Micoflu; ***Switz.***: Decoderm bivalent; ***UK***: Acorvio Plus.

Fluticasone *(BAN, rINN)* ⊗

Fluticasona; Fluticasonum; Флутиказон.

S-(Fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate.

$C_{22}H_{27}F_3O_4S$=444.5

CAS — 90566-53-3.

ATC — D07AC17; R01AD08; R03BA05.

ATC Vet — QD07AC17; QR01AD08; QR03BA05.

UNII — CUT2W21N7U.

Fluticasone Furoate *(BANM, USAN, rINN)* ⊗

Fluticasonum Furoas; Furoate de Fluticasone; Furoato de fluticasona; GW-685698X; Флутиказон фуроат.

6α,9-Difluoro-17-{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate.

$C_{27}H_{29}F_3O_6S$=538.6

CAS — 397864-44-7.

ATC — D07AC17; R01AD08; R01AD12; R03BA05.

ATC Vet — QD07AC17; QR01AD08; QR01AD12; QR03BA05.

UNII — JS86977WNV.

Fluticasone Propionate *(BANM, USAN, rINNM)* ⊗

CCI-18781; Fluticasona, propionato de; Fluticasone, propionate de; Fluticasoni Propionas; Fluticasonpropionat; Flutikasonipropionaatti; Flutikasonpropionat; Flutikason-propionát; Flutikazon Propiyonat; Flutikazono propionatas; Propionato de fluticasona; Флутиказона Пропионат.

S-Fluoromethyl 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate 17-propionate.

$C_{25}H_{31}F_3O_5S$=500.6

CAS — 80474-14-2.

ATC — D07AC17; R01AD08; R03BA05.

ATC Vet — QD07AC17; QR01AD08; QR03BA05.

UNII — O2GMZ0LF5W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fluticasone Propionate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Fluticasone Propionate). Micronised fluticasone propionate is a fine white powder. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Uses and Administration

Fluticasone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It is given as the propionate or furoate ester; the latter is reported to have enhanced affinity for the glucocorticoid receptor. Fluticasone is stated to exert a topical effect on the lungs without significant systemic effects at usual doses, due to its low systemic bioavailability (but see Adrenal Suppression, p. 1639.1).

Fluticasone propionate is used by powder or aerosol inhalation for the prophylaxis of **asthma** (below). Typical initial doses in the UK range from 100 micrograms twice daily in mild asthma up to 500 micrograms twice daily in severe asthma, adjusted according to response; some patients may benefit from doses up to 1 mg twice daily under specialist supervision. The drug may also be given via a nebuliser in severe chronic asthma. Usual doses are 0.5 to 2 mg twice daily. In the USA, doses by powder inhalation are similar to those in the UK. The aerosol inhalation formulations contain 50, 125, or 250 micrograms of fluticasone propionate in each metered spray, which delivers 44, 110, or 220 micrograms, respectively from the actuator. Doses are therefore expressed in these units; dosage ranges from 88 micrograms twice daily to 880 micrograms twice daily, depending on previous therapy.

Fluticasone furoate is also given by dry powder inhalation in asthma prophylaxis; it is available in combination inhalers that also contain vilanterol trifenatate (p. 1239.3). The dose of fluticasone furoate may be expressed as the amount in each available dose (100 micrograms) or as the delivered dose leaving the mouthpiece (92 micrograms). A delivered dose of 92 micrograms is inhaled once daily; this may be increased to 184 micrograms once daily if necessary.

Fluticasone is used, usually with a long-acting beta$_2$ agonist, for the treatment of **chronic obstructive pulmonary disease** (below). Fluticasone propionate is given as a powder or aerosol inhalation in doses of 500 micrograms twice daily. Fluticasone furoate is given by dry powder inhalation in a delivered dose of 92 micrograms once daily.

Fluticasone is administered by nasal spray in the prophylaxis and treatment of **allergic rhinitis** (p. 1639.1). The usual dose of fluticasone propionate is 100 micrograms into each nostril once daily, increased if necessary to 100 micrograms into each nostril twice daily. A maintenance dose of 50 micrograms in each nostril once daily may be effective. Fluticasone furoate is also used in the management of allergic rhinitis, and is given in a starting dose of 55 micrograms into each nostril once daily. When the maximum benefit has been achieved and symptoms controlled, the dose should be reduced to the minimum effective dose; 27.5 micrograms into each nostril once daily may be sufficient to maintain control of symptoms.

Fluticasone propionate drops are used in the treatment of **nasal polyps**, 200 micrograms should be instilled into each nostril once or twice daily for at least 4 to 6 weeks.

Fluticasone propionate is applied topically in the treatment of various **skin disorders**. Creams and ointments containing 0.05% and 0.005%, respectively are available. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

For doses used in children, see below.

Administration in children. Fluticasone propionate is used by powder or aerosol inhalation for the prophylaxis of **asthma** in children. The typical initial dose in the UK for children aged 4 to 16 years old is 50 to 100 micrograms twice daily, increased to 200 micrograms twice daily if necessary. The drug may also be given via a nebuliser in the management of acute exacerbations of asthma in children; those aged 4 to 16 years may be given 1 mg twice daily. In the USA, doses by powder inhalation are similar to those in the UK, at 50 to 100 micrograms twice daily in children aged from 4 to 11 years old. The aerosol inhalation formulation licensed for use in children contains 50 micrograms of fluticasone propionate in each metered spray, which delivers 44 micrograms from the actuator. Doses are therefore expressed in multiples of this amount and children aged 4 to 11 years are given 88 micrograms twice daily.

Fluticasone is administered by nasal spray in the prophylaxis and treatment of **allergic rhinitis**. For children aged 4 to 11 years old, the usual dose of fluticasone propionate is 50 micrograms into each nostril once daily, increased if necessary to 50 micrograms into each nostril twice daily. Fluticasone furoate is also used in the management of allergic rhinitis. Children aged 2 to 11 years may be started on 27.5 micrograms into each nostril once daily, which may be increased to 55 micrograms into each nostril once daily if necessary to control symptoms. The dose may then be reduced to 27.5 micrograms into each nostril once daily to maintain control.

Older children and adolescents may be given adult doses for asthma and rhinitis (see above).

In the treatment of **nasal polyps**, fluticasone propionate may be given to children aged 16 years and older using adult doses (see above).

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

Some references to the use of fluticasone propionate for asthma are given below,[1-14] including one to a study indicating that increasing the dose of inhaled fluticasone did not produce increased benefit.[1]

1. Boe J, *et al.* High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. *Eur Respir J* 1994; **7:** 2179–84.
2. Jarvis B, Faulds D. Inhaled fluticasone propionate: a review of its therapeutic efficacy at dosages ≤ 500 micrograms/day in adults and adolescents with mild to moderate asthma. *Drugs* 1999; **57:** 769–803.
3. Bisgaard H, *et al.* The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999; **160:** 126–31.
4. ZuWallack R, *et al.* Long-term efficacy and safety of fluticasone propionate powder administered once or twice daily via inhaler to patients with moderate asthma. *Chest* 2000; **118:** 303–312.
5. Holt S, *et al.* Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001; **323:** 253–6.
6. Purucker ME, *et al.* Inhaled fluticasone propionate by diskus in the treatment of asthma: a comparison of the efficacy of the same nominal dose given either once or twice a day. *Chest* 2003; **124:** 1584–93.
7. Masoli M, *et al.* Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax* 2004; **59:** 16–20.
8. Masoli M, *et al.* Systematic review of the dose-response relation of inhaled fluticasone propionate. *Arch Dis Child* 2004; **89:** 902–7.
9. Lasserson TJ, *et al.* Fluticasone versus 'extrafine' HFA-beclomethasone dipropionate for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/10).
10. Guilbert TW, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; **354:** 1985–97.
11. Adams N, *et al.* Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 22/08/08).
12. Adams NP, *et al.* Fluticasone versus placebo for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 11/03/10).
13. Adams NP, *et al.* Fluticasone at different doses for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 11/03/10).
14. McKeage K, Keam SJ. Salmeterol/fluticasone propionate: a review of its use in asthma. *Drugs* 2009; **69:** 1799–1828.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1).

References and reviews.

1. Fenton C, Keating GM. Inhaled salmeterol/fluticasone propionate: a review of its use in chronic obstructive pulmonary disease. *Drugs* 2004; **64:** 1975–96.
2. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; **67:** 2383–2405.
3. Martinez FJ, *et al.* Fluticasone furoate/vilanterol (100/25; 200/25 micrograms) improves lung function in COPD: a randomised trial. *Respir Med* 2013; **107:** 550–9.

Cough. A small study in children with persistent nocturnal cough compared fluticasone propionate 1 mg twice daily for 3 nights, followed by 500 micrograms twice daily for 11 nights, given by metered-dose inhaler, with placebo. Coughs reduced significantly by nights 15 and 16 in the children given the corticosteroid. However, both groups improved significantly compared to baseline, leading the authors to conclude that inhaled corticosteroids should not be given at the time of presentation of persistent nocturnal cough. If they are given, then a 2-week course of high dose corticosteroids may benefit some children.[1] In a controlled crossover study in adult patients with chronic cough, inhaled fluticasone 500 micrograms twice daily for 14 days significantly improved certain measurements of cough, although overall reduction in cough severity was modest.[2] In adults with a cough lasting more than 2 weeks, fluticasone 500 micrograms twice daily for 2 weeks decreased cough scores from day 5 onwards in non-smokers.[3]

1. Davies MJ, *et al.* Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. *Arch Dis Child* 1999; **81:** 38–44.
2. Chaudhuri R, *et al.* Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. *J Allergy Clin Immunol* 2004; **113:** 1063–70.
3. Ponsioen BP, *et al.* Efficacy of fluticasone on cough: a randomised controlled trial. *Eur Respir J* 2005; **25:** 147–52.

Eczema. In a study in patients with moderate to severe eczema (p. 1684.1), fluticasone propionate 0.05% cream or 0.005% ointment was applied once or twice daily for 4 weeks; if eczema stabilised, either the cream, the ointment, or an emollient placebo was then applied on 2 days per week, for up to 16 weeks. Fluticasone cream reduced the risk of relapse to about one-sixth of that of placebo, whereas the ointment formulation reduced the risk to about half; median times to relapse were similar for both fluticasone formulations. The formulations were originally expected to be of similar potency.[1] Others have commented[2] that caution should be exercised in generalising these results to primary care settings where most cases of eczema are likely to be mild, and relapses infrequent.

1. Berth-Jones J, *et al.* Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003; **326:** 1367.
2. Williams HC. Twice-weekly topical corticosteroid therapy may reduce atopic dermatitis relapses. *Arch Dermatol* 2004; **140:** 1151–2.

Inflammatory bowel disease. Fluticasone propionate, given orally, has produced variable results in the treatment of Crohn's disease[1] and ulcerative colitis;[2,3] some benefit was also reported in coeliac disease.[4] The dose was 5 mg four times daily but some consider[2] higher doses necessary.

For a review of the management of inflammatory bowel disease, including the role of corticosteroids, see p. 1808.3.

1. Carpani de Kaski M, *et al.* Fluticasone propionate in Crohn's disease. *Gut* 1991; **32:** 657–61.
2. Hawthorne AB, *et al.* Double blind trial of oral fluticasone propionate v prednisolone in the treatment of active ulcerative colitis. *Gut* 1993; **34:** 125–8.
3. Angus P, *et al.* Oral fluticasone propionate in active distal ulcerative colitis. *Gut* 1992; **33:** 711–14.
4. Mitchison HC, *et al.* A pilot study of fluticasone propionate in untreated coeliac disease. *Gut* 1991; **32:** 260–5.

Nasal polyps. For discussion of the value of corticosteroids in the treatment of nasal polyps, including reference to the use of fluticasone, see p. 1608.2.

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p. 612.1. Some further references to the use of fluticasone in rhinitis are given below.

1. Wiseman LR, Benfield P. Intranasal fluticasone propionate: a reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs* 1997; **53:** 885–907.
2. McCormack PL, Scott LJ. Fluticasone furoate: intranasal use in allergic rhinitis. *Drugs* 2007; **67:** 1905–15.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively). Hypersensitivity reactions have occurred with fluticasone. Eosinophilic conditions, including Churg-Strauss syndrome, have been reported rarely, in most cases after a transfer from oral corticosteroid therapy.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Inhalation or nasal use of large amounts of fluticasone may produce systemic effects also (see below).

Adrenal suppression. Despite the fact that inhaled fluticasone is generally thought to lack systemic effects at therapeutic doses, a study in 25 healthy subjects[1] indicated that fluticasone propionate as single inhaled doses of 250, 500, and 1000 micrograms did produce a reduction in plasma cortisol, indicating suppression of the hypothalamic-pituitary-adrenal axis to some degree. Others have also found evidence of adrenal suppression with fluticasone,[2-5] particularly at high doses and in children,[6] and the effect may be more marked with repeated than with single doses.[4,6-8] Several cases of adrenal crisis have been associated with high-dose inhaled fluticasone,[9,10] including at least one fatality.[6] It has been recommended that children using inhaled fluticasone at doses above 400 micrograms daily should have adrenal function monitoring and a written plan for emergency corticosteroid replacement therapy.[6]

1. Grahnén A, *et al.* An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994; **38:** 521–5.
2. Clark DJ, *et al.* Comparative systemic bioactivity of inhaled budesonide and fluticasone propionate in asthmatic children. *Br J Clin Pharmacol* 1996; **42:** 264P.
3. Rohatagi S, *et al.* Dynamic modeling of cortisol reduction after inhaled administration of fluticasone propionate. *J Clin Pharmacol* 1996; **36:** 938–41.
4. Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. *Thorax* 1997; **52:** 55–8.
5. Eid N, *et al.* Decreased morning serum cortisol levels in children with asthma treated with inhaled fluticasone propionate. *Pediatrics* 2002; **109:** 217–21.
6. Paton J, *et al.* Adrenal responses to low dose synthetic ACTH (Synacthen) in children receiving high dose inhaled fluticasone. *Arch Dis Child* 2006; **91:** 808–13.
7. Lönnebo A, *et al.* An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers. *Eur J Clin Pharmacol* 1996; **49:** 459–63.
8. Wilson AM, *et al.* Adrenal suppression with high doses of inhaled fluticasone propionate and triamcinolone acetonide in healthy voluteers. *Eur J Clin Pharmacol* 1997; **53:** 33–7.
9. Todd GRG, *et al.* Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002; **87:** 457–61.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Fluticasone and adrenal crisis. *Aust Adverse Drug React Bull* 2003; **22:** 6. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0304.htm (accessed 06/05/04)

Aspergillosis. The fungal infection aspergillosis has been reported in patients receiving inhaled[1,2] and intranasal[3] fluticasone.

1. Fairfax AJ, *et al.* Laryngeal aspergillosis following high dose inhaled fluticasone therapy for asthma. *Thorax* 1999; **54:** 860–1.
2. Leav BA, *et al.* Invasive pulmonary aspergillosis associated with high-dose inhaled fluticasone. *N Engl J Med* 2000; **343:** 586.
3. Bratton RL, *et al.* Aspergillosis related to long-term nasal corticosteroid use. *Mayo Clin Proc* 2002; **77:** 1353–7.

Effects on the bones. For studies of the effects on bone of inhaled fluticasone, compared with beclometasone, see p. 1622.2.

Effects on the muscles. Proximal myopathy has been reported in children receiving high-dose inhaled fluticasone;[1] the patients recovered after replacement of fluticasone with alternative corticosteroid therapy.

1. De Swert LF, *et al.* Myopathy in children receiving high-dose inhaled fluticasone. *N Engl J Med* 2004; **350:** 1157–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluticasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Fluticasone propionate is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism; oral bioavailability is reported to be only about 1%.

References.
1. Mackie AE, *et al.* Pharmacokinetics of intravenous fluticasone propionate in healthy subjects. *Br J Clin Pharmacol* 1996; **41:** 539–42.
2. van Boxtel CJ, Sheffer AL, eds. The pharmacokinetics of fluticasone propionate. *Clin Pharmacokinet* 2000; **39** (suppl): 1–54.
3. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol* 2001; **51:** 103–5.
4. Allen A, *et al.* Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin Ther* 2007; **29:** 1415–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alenys; Balivent; Crivanil; Cutivate; Flixonase; Flixotide; Fluti-K; Fluticort; Inhalan; Lidil Cort; Lirtodac; Proair; Rinisona; ***Austral.***: Avamys; Flixonase Allergy & Hayfever 24 Hour; Flixonase; Flixotide; ***Austria***: Avamys; Cutivate; Flixonase; Flixotide; ***Belg.***: Avamys; Cutivate; Flixonase; Flixotide; ***Braz.***: Avamys; Flixonase; Flixotide; Flutican; Fluticaps; Flutivate; Plurair; ***Canad.***: Avamys; Cutivate; Flonase; Flovent; ***Chile***: Albeoler; Alenys; Avamys; Brexonase; Brexovent†; Flixonase; Flixotide; Flucomix; Flusona; Fluticort; Flutivate; Nebulex; Raffonin; ***China***: Cutivate (克廷肤); Flixonase (辅舒良); Flixotide (辅舒酮); ***Cz.***: Alergonase†; Alisade; Avamys; Cutivate; Flixonase†; Flixotide; Nasofan; ***Denm.***: Avamys; Cutivat; Flixonase; Flixotide; Flutide; ***Fin.***: Flixonase; Flixotide; Flutide; Nasofan; ***Fr.***: Avamys; Flixonase; Flixotide; Flixovate; ***Ger.***: Atemur†; Avamys; Flutica†; Flutide; Flutivate; ***Gr.***: Alerxem; Avamys; Bocacort-S; Cortixide; Dermocort; Flicazen; Flihaler; Flixocort; Flixoderm; Flixonase; Flixotide; Flixotide; Flucortis; Flutarzole; Fluticapen; Flutikrem; Flutinasal; Flutizal; Nasofan; Salenga; Ybecor; ***Hong Kong***: Avamys; Cutivate; Dalman; Dermcasone; Flixonase; Flixotide; Lutisone; Nasofan; ***Hung.***: Avamys; Cutivate; Flixonase; Flixotide; Flutirin; ***India***: Flixonase; Floease; Flohale; Flomist; Flucasia; Fluster; Flute; Fluticare; Fluticone; Flutiflo; Flutivate; Flutopic; Moliderm; Nezaflo; Otrivin-C; Zoflut; ***Indon.***: Avamys; Cutivate†; Flixonase; Flixotide; Medicort; ***Irl.***: Avamys; Flixonase; Flixotide; Nasofan; ***Israel***: Allegro; Avamys; Flixonase; Flixotide; Flutitrim; ***Ital.***: Avamys; Flixoderm; Flixonase; Flixotide; Fluspiral; Fluticrem; Nasofan; Ticavent; ***Jpn***: Flonase†; ***Malaysia***: Avamys; Cutivate; Flixonase; Flixotide; Flomist; ***Mex.***: Avamys; Caneti†; Cutivate; Flixonase; Flixotide; ***Neth.***: Avamys; Cortifil; Cutivate; Flixonase; Flixotide; Fluticrem; Flutide; ***Norw.***: Avamys; Flutide; Flutivate; ***NZ***: Flixonase; Flixotide; Nasaclear†; ***Philipp.***: Avamys; Cutivate; Flixotide; Nasoflo; ***Pol.***: Alisade; Avamys; Cutivate; Fanipos; Flixonase; Flixotide; ***Port.***: Asmatil; Asmo-Lavi; Avamys; Brisovent; Cutivate; Eustidil; Flixotaide; Flutaide; Rontilona; Ubizol; ***Rus.***: Avamys (Авамис); Cutivate (Кутивейт); Flixonase (Фликсоназе); Flixotide (Фликсотид); Nazarel (Назарел); ***S.Afr.***: Avamys; Cutivate; Flixonase; Flixotide; Flohale DP; Flomist; Flonase; ***Singapore***: Avamys; Cutivate; Flixonase; Flixotide; Flutitrim; ***Spain***: Avamys; Cutivate; Flixonase; Flixotide; Fluinol; Flunutrac; Flusonal; Fluticrem; Inalacor; Nasofan†; Rinosone; Trialona; ***Swed.***: Avamys; Flutide; Flutivate; ***Switz.***: Avamys; Axotide; Cutivate; Flutinase; Nasofan; ***Thai.***: Avamys; Flixonase; Flixotide; ***Turk.***: Avamys; Brethal; Cutivate; Dalman; Flixonase; Flixotide; ***UAE***: Potencort; ***UK***: Avamys; Cutivate; Flixotide; Nasofan; Pirinase; ***Ukr.***: Avamis (Авамис); Cutivate (Кутивейт); Flixonase (Фликсоназе); Flixotide (Фликсотид); Nasofan (Назофан); ***USA***: Cutivate; Flonase; Flovent; Veramyst; ***Venez.***: Cutivate; Flixonase; Flixotide; Fluticort.

Multi-ingredient Preparations. ***Arg.***: Crivanil Plus; Flutivent; Lirtodac Plus; Neumotide; Proair Bronquial; Seretide; ***Austral.***: Seretide; ***Austria***: Seretide; Viani; ***Belg.***: Flutiform; Seretide; Viani†; ***Braz.***: Seretide; ***Canad.***: Advair; ***Chile***: Aerometrol Plus; Aurituss; Brexotide; Flunacross-S; Fluxamol; Seretide; ***China***: Seretide (舒利迭); ***Cz.***: Duaspir†; Seretide; ***Denm.***: Aliflus†; Seretaide; Seretide; ***Fin.***: Dymista; Flutiform; Seretide; Viani; ***Fr.***: Seretide; ***Ger.***: Atmadisc; Viani; ***Gr.***: Byany; Rolenium; Seretide; Viani; ***Hong Kong***: Seretide; ***Hung.***: Seretide; Thoreus; ***India***: Avessa; Azeflo; Combihale-FF; Combitide; Duonase; Esiflo; Flutibact; Fluticare-C; Fluticare-N; Forair; Nezalast; Seretide; Seroflo; ***Indon.***: Seretide; ***Irl.***: Seretide; Viani; ***Israel***: Seretide; ***Ital.***: Aliflus; Seretide; ***Malaysia***: Seretide; ***Mex.***: Flixovent; Seretide; ***Neth.***: Aliflus; Brisair†; Flutiform; Iffeza; Seretide; ***Norw.***: Flutiform; Seretide; ***NZ***: Seretide; ***Philipp.***: Salmeflo; Seretide; ***Pol.***: Seretide; ***Port.***: Brisomax; Maizar; Seretaide; Veraspir; ***Rus.***: Seretide (Серетид); Tevacomb (Тевакомб); ***S.Afr.***: Foxair; Sereflo; Seretide; ***Singapore***: Seretide; ***Spain***: Anasma; Brisair; Inaladuo; Plusvent; Seretide; ***Swed.***: Seretide; ***Switz.***: Seretide; ***Thai.***: Seretide; Seroflo; ***Turk.***: Respiro; Seretide; ***UK***: Dymista; flutiform; Relvar Ellipta; Seretide; ***Ukr.***: Seretide (Серетид); ***USA***: Advair; Breo Ellipta; Dymista; ***Venez.***: Seretide.

Pharmacopoeial Preparations

BP 2014: Fluticasone Cream; Fluticasone Inhalation Powder, pre-dispensed; Fluticasone Inhalation Powder; Fluticasone Nasal Drops; Fluticasone Nasal Spray; Fluticasone Ointment; Fluticasone Pressurised Inhalation;

USP 36: Fluticasone Propionate Cream; Fluticasone Propionate Inhalation Aerosol; Fluticasone Propionate Inhalation Powder; Fluticasone Propionate Nasal Spray; Fluticasone Propionate Ointment.

Halcinonide *(BAN, USAN, rINN)* ⊗

Alcinonide; Halcinonid; Halcinónida; Halcinonidum; Halsinonid; Halsinonidi; SQ-18566; Гальциноид.

21-Chloro-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.

$C_{24}H_{32}ClFO_5$=455.0

CAS — 3093-35-4.

ATC — D07AD02.

ATC Vet — QD07AD02.

UNII — SI86V6QNEG.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Halcinonide). A white to off-white, odourless, crystalline powder. Insoluble in water and in hexanes; slightly soluble in alcohol and in ether; soluble in acetone and in chloroform.

Profile

Halcinonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a 0.1% cream, lotion, or ointment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Halog; ***Canad.***: Halog†; ***China***: Ha Le Te (哈乐特); ***Cz.***: Betacorton†; ***Gr.***: Ascochrom; Hamiltoderm-D; ***Hong Kong***: Halog†; ***India***: Cortilate; ***Indon.***: Halog†; ***Ital.***: Halciderm; ***Mex.***: Dermalog; ***Switz.***: Betacortone; ***Turk.***: Volog; ***USA***: Halog; ***Venez.***: Halog.

Multi-ingredient Preparations. ***Braz.***: Halog Capilar; ***Cz.***: Betacorton S†; Betacorton U†; ***India***: Cobederm-H†; Cortilate-N; Cortilate-S; Halog-E; Orkid-S; ***Ital.***: Halciderm Combi; Halciderm; ***Mex.***: Dermalog-C; ***Switz.***: Betacortone S; Betacortone; ***Turk.***: Betacorton; ***Venez.***: Halcicomb; Halog.

Pharmacopoeial Preparations

USP 36: Halcinonide Cream; Halcinonide Ointment; Halcinonide Topical Solution.

Halometasone *(rINN)* ⊗

C-48401-Ba; Halometason; Halometasona; Halométasone; Halometasoni; Halometasonum; Halometazon; Halomethasone; Галометазон.

2-Chloro-6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{27}ClF_2O_5$=444.9

CAS — 50629-82-8.

ATC — D07AC12.

ATC Vet — QD07AC12.

UNII — J69Z9UU41Z.

Profile

Halometasone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream containing 0.05% of halometasone monohydrate.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Aoneng (澳能); Sicorten (适确得); Sicorten Plus (新适确得); ***Hong Kong***: Sicorten; ***Spain***: Sicorten†; ***Switz.***: Sicorten†; ***Turk.***: Sicorten.

Multi-ingredient Preparations. ***Ger.***: InfectoCortiSept; Sicorten Plus†; ***Spain***: Sicorten Plus†; ***Switz.***: Sicorten Plus.

Hydrocortisone *(BAN, rINN)* ⊗

Anti-inflammatory Hormone; Compound F; Cortisol; Hidrocortisona; Hidrokortizon; Hidrokortizonas; Hydrocortison; Hydrocortisonum; Hydrokortison; Hydrokortisoni; Hydrokortyzon; 17-Hydroxycorticosterone; NSC-10483; Гидрокортизон.

11β,17α,21-Trihydroxypregn-4-ene-3,20-dione.

$C_{21}H_{30}O_5$=362.5

CAS — 50-23-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QD07XA01; QH02AB09; QS01BA02; QS01CB03; QS02BA01.

UNII — WI4X0X7BPJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Hydrocortisone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; slightly soluble in dichloromethane. Protect from light.

USP 36: (Hydrocortisone). A white to practically white, odourless, crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 40 of alcohol and 1 in 80 of acetone; slightly soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Hydrocortisone Acetate *(BANM, rINNM)* ⊗

Acetato de hidrocortisona; Cortisol Acetate; Hidrocortisona, acetato de; Hidrokortizon Asetat; Hidrokortizon-acetát; Hidrokortizono acetatas; Hydrocortisonacetat; Hydrocortisone, Acétate d'; Hydrocortisoni Acetas; Hydrokortisonacetat; Hydrokortison-acetát; Hydrokortisoniasetaatti; Hydrokortyzonu octan; Гидрокортизона Ацетат.

Hydrocortisone 21-acetate.

$C_{23}H_{32}O_6$=404.5

CAS — 50-03-3.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 3X7931PO74.

NOTE. HCOR is a code approved by the BP 2014 for use on single unit doses of eye drops containing hydrocortisone acetate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Hydrocortisone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 36: (Hydrocortisone Acetate). A white to practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 230 of alcohol and 1 in 200 of chloroform.

Hydrocortisone Buteprate *(BANM, rINNM)* ⊗

Buteprato de hidrocortisona; Hidrocortisona, buteprato de; Hydrocortisone, Butéprate d'; Hydrocortisone Butyrate Propionate; Hydrocortisone Probutate (USAN); Hydrocortisoni Butepras; TS-408; Гидрокортизона Бутепрат.

Hydrocortisone 17-butyrate 21-propionate.

$C_{28}H_{40}O_7$=488.6

CAS — 72590-77-3.

ATC — D07AB11.

ATC Vet — QD07AB11.

UNII — O6550D6K3A.

Hydrocortisone Butyrate

(BANM, USAN, rINNM) ⊗

Butirato de hidrocortisona; Cortisol Butyrate; Hidrocortisona, butirato de; Hidrokortizon Bütirat; Hydrocortisone, Butyrate d'; Hydrocortisoni Butiras; Гидрокортизона Бутират.

Hydrocortisone 17α-butyrate.

$C_{25}H_{36}O_6$=432.6

CAS — 13609-67-1.

ATC — D07AB02.

ATC Vet — QD07AB02.

UNII — 05RMF7YPWN.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Hydrocortisone Butyrate). A white to practically white, practically odourless crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; freely soluble in chloroform; slightly soluble in ether.

Hydrocortisone Cipionate *(BANM, rINNM)* ⊗

Cipionato de hidrocortisona; Cortisol Cypionate; Hidrocortisona, cipionato de; Hydrocortisone, Cipionate d'; Hydrocortisone Cyclopentylpropionate; Hydrocortisone Cypionate; Hydrocortisoni Cipionas; Гидрокортизона Ципионат.

Hydrocortisone 21-(3-cyclopentylpropionate).

$C_{29}H_{42}O_6$=486.6

CAS — 508-99-6.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 4XDY25L70B.

Hydrocortisone Hydrogen Succinate

(BANM, rINNM) ⊗

Cortisol Hemisuccinate; Hidrocortisona, hidrogenosuccinato de; Hidrogenosuccinato de hidrocortisona; Hidrokortizon-hidrogén-szukcinát; Hidrokortizono hemisukcinatas; Hydrocortisone Hemisuccinate; Hydrocortisone, Hémisuccinate d'; Hydrocortisone, hydrogénosuccinate d'; Hydrocortisone Succinate; Hydrocortisonhydrogensuccinat; Hydrocortisoni Hemisuccinas; Hydrocortisoni hydrogenosuccinas; Hydrokortison-hydrogen-sukcinát; Hydrokortisonivetysuksinaatti; Hydrokortisonvätesuccinat; Гидрокортизона Гемисукцинат.

Hydrocortisone 21-(hydrogen succinate).

$C_{25}H_{34}O_8$=462.5

CAS — 2203-97-6 (anhydrous hydrocortisone hydrogen succinate); B3784-20-7 (hydrocortisone hydrogen succinate monohydrate).

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — LIU00Z1Z84.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. *US* allows the anhydrous form or the monohydrate.

Ph. Eur. 8: (Hydrocortisone Hydrogen Succinate). A white or almost white, hygroscopic powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone; dissolves in dilute solutions of alkali carbonates and alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Hydrocortisone Hemisuccinate). It contains one molecule of water of hydration or is anhydrous. Store in airtight containers.

Hydrocortisone Sodium Phosphate

(BANM, rINNM) ⊗

Cortisol Sodium Phosphate; Fosfato sódico de hidrocortisona; Hidrocortisona, fosfato sódico de; Hydrocortisone, Phosphate Sodique d'; Natrii Hydrocortisoni Phosphas; Натрия Гидрокортизона Фосфат.

Hydrocortisone 21-(disodium orthophosphate).

$C_{21}H_{29}Na_2O_8P$=486.4

CAS — 6000-74-4.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 0388G963HY.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Hydrocortisone Sodium Phosphate). A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 7.5 to 9.0. Protect from light.

USP 36: (Hydrocortisone Sodium Phosphate). A white to light yellow, odourless or practically odourless, exceedingly hygroscopic, powder. Soluble 1 in 1.5 of water; slightly soluble in alcohol; practically insoluble in chloroform, in dioxan, and in ether. Store in airtight containers.

Hydrocortisone Sodium Succinate

(BANM, rINNM) ⊗

Cortisol Sodium Succinate; Hidrocortisona, succinato sódico de; Hydrocortisone, Succinate Sodique d'; Hydrocortisoni Natrii Succinas; Hydrokortyzonu bursztynianu sól sodowa; Succinato sódico de hidrocortisona; Гидрокортизона Натрия Сукцинат.

Hydrocortisone 21-(sodium succinate).

$C_{25}H_{33}NaO_8$=484.5

CAS — 125-04-2.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 50LQB69S1Z.

Pharmacopoeias. In *Chin.*, *Int.*, *It.*, *Jpn.*, *Pol.*, and *US*.

USP 36: (Hydrocortisone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Very soluble in water and in alcohol; very slightly soluble in acetone; insoluble in chloroform. Store in airtight containers. Protect from light.

Hydrocortisone Valerate

(BANM, USAN, rINNM) ⊗

Cortisol Valerate; Hidrocortisona, valerato de; Hydrocortisone, Valérate d'; Hydrocortisoni Valeras; Valerato de hidrocortisona; Гидрокортизона Валерат.

Hydrocortisone 17-valerate.

$C_{26}H_{38}O_6$=446.6

CAS — 57524-89-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 68717P8FUZ.

Pharmacopoeias. In *US*.

Uses and Administration

Hydrocortisone is a corticosteroid with both glucocorticoid and to a lesser extent mineralocorticoid activity (p. 1597.1); 20 mg of hydrocortisone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. As cortisol it is the most important of the mainly glucocorticoid corticosteroids secreted by the adrenal cortex. Hydrocortisone is used, usually with a more potent mineralocorticoid, for replacement therapy in adrenocortical insufficiency (p. 1600.2). It may also be used for its glucocorticoid properties in other conditions for which corticosteroid therapy is indicated (p. 1597.3) but drugs with fewer mineralocorticoid effects tend to be preferred for the long-term systemic therapy of auto-immune and inflammatory disease.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of hydrocortisone:

- hydrocortisone acetate 112 mg
- hydrocortisone buteprate 135 mg
- hydrocortisone butyrate 119 mg
- hydrocortisone cipionate 134 mg
- hydrocortisone hydrogen succinate 128 mg
- hydrocortisone sodium phosphate 134 mg
- hydrocortisone sodium succinate 134 mg
- hydrocortisone valerate 123 mg

However, esterification generally alters potency and compounds with equivalent hydrocortisone content may not have equivalent clinical effect.

When given **orally** hydrocortisone free alcohol is usually used; the cipionate ester is used in some formulations. For *replacement therapy* in acute or chronic adrenocortical insufficiency the normal requirement is 20 to 30 mg daily (usually taken in 2 doses, the larger in the morning and the smaller in the early evening, to mimic the circadian rhythm of the body). Additional sodium chloride may be required if there is defective aldosterone secretion, but mineralocorticoid activity is usually supplemented by fludrocortisone acetate orally. Similar regimens have also been used to correct glucocorticoid deficiency in the salt-losing form of congenital adrenal hyperplasia (p. 1603.2).

Hydrocortisone may be given **intravenously**, by slow injection or infusion, in the form of a water-soluble derivative such as hydrocortisone sodium succinate or hydrocortisone sodium phosphate when a rapid effect is required in *emergencies*: such conditions are acute adrenocortical insufficiency caused by Addisonian or post-adrenalectomy crises, by the abrupt accidental withdrawal of therapy in corticosteroid-treated patients, or by the inability of the adrenal glands to cope with increased stress in such patients; certain allergic emergencies such as anaphylaxis; acute severe asthma (status asthmaticus—see

also p. 1195.2); and shock. The usual dose is the equivalent of 100 to 500 mg of hydrocortisone, repeated 3 or 4 times in 24 hours, according to the severity of the condition and the patient's response. Fluids and electrolytes should be given as necessary to correct any associated metabolic disorder. Similar doses to those specified above may also be given **intramuscularly** but the response is likely to be less rapid than that seen after intravenous doses. Corticosteroids are considered to be of secondary value in anaphylactic shock because of their relatively slow onset of action, but intravenous hydrocortisone may be a useful adjunct to adrenaline to prevent further deterioration in severely affected patients.

For doses used in children, see below.

In patients with adrenal deficiency states supplementary corticosteroid therapy may be necessary during some *surgical operations* and hydrocortisone sodium succinate or sodium phosphate may be given intramuscularly or intravenously before surgery. Various regimens have been proposed (see also Surgery, p. 1599.1). In patients taking more than 10 mg of oral prednisolone or its equivalent daily, the *BNF* recommends the following regimen:

- *minor surgery under general anaesthesia*, either the usual oral corticosteroid dose on the morning of surgery *or* hydrocortisone 25 to 50 mg (usually as the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is resumed after surgery
- *moderate or major surgery*, the usual oral corticosteroid dose on the morning of surgery, *plus* hydrocortisone 25 to 50 mg intravenously at induction, and followed by similar doses of hydrocortisone 3 times daily, for 24 hours after moderate surgery and 48 to 72 hours after major surgery; the usual corticosteroid dose is resumed once hydrocortisone injections are stopped

For **local injection** into soft tissues hydrocortisone is usually used in the form of the sodium phosphate or sodium succinate esters; doses in terms of hydrocortisone are usually 100 to 200 mg. For intra-articular injection hydrocortisone acetate is usually used in doses of 5 to 50 mg depending upon the size of the joint.

For **topical application** in the treatment of various skin disorders hydrocortisone and the acetate, buteprate, butyrate, and valerate esters are normally employed in creams, ointments, or lotions. Concentrations usually used have ranged from 0.1 to 2.5%. Although it is considered that hydrocortisone has fewer adverse effects on the skin and is less liable to cause adrenal suppression than the more potent topical corticosteroids (see p. 1599.2 for a rough guide to the clinical potencies of topical corticosteroids), it should be borne in mind that this property may be considerably modified both by the type of formulation or vehicle used and by the type of esterification present; other factors that may also influence the degree of absorption include the site of application, use of an occlusive dressing, the degree of skin damage, and the size of the area to which the preparation is applied.

Hydrocortisone or its esters are also available in a variety of other dosage forms including those for ophthalmic, aural, dental, and rectal application, for use in allergic and inflammatory disorders.

Other esters of hydrocortisone that have occasionally been used include the aceponate, caproate, glycyrrhetinate, and propionate. Esters such as the aceponate may show modified topical activity.

Administration in children. When given **orally** as *replacement therapy* in adrenocortical insufficiency, the *BNFC* suggests that neonates and children aged from 1 month to 18 years of age may be given hydrocortisone in usual doses of 8 to 10 mg/m^2 daily in 3 divided doses, although higher doses may be needed. Larger portions of the daily dose are given in the morning and smaller portions in the evening. In congenital adrenal hyperplasia, initial oral doses of 9 to 15 mg/m^2 daily in 3 divided doses may be used; again, higher doses may be needed and the dose should be adjusted according to response.

When used **intravenously** for *emergencies* such as acute adrenocortical insufficiency, the following doses may be given:

- neonates: initially 10 mg as a slow injection, then 100 mg/m^2 daily as a continuous infusion or in divided doses every 6 to 8 hours; the dose should be adjusted according to response and, when stable, reduced over 4 to 5 days to an oral maintenance dose
- 1 month to 12 years old: initially 2 to 4 mg/kg as a slow injection or infusion, then 2 to 4 mg/kg every 6 hours; the dose should be adjusted according to response and, when stable, reduced over 4 to 5 days to an oral maintenance dose
- 12 to 18 years old: 100 mg every 6 to 8 hours by slow injection or infusion

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Effects on fluid and electrolyte balance. A report of marked hypokalaemia and hypomagnesaemia associated with high-dose intravenous hydrocortisone therapy in an alcoholic patient with suspected immune thrombocytopenia.[1] Cardiac arrhythmias developed, and prolonged infusion of magnesium and potassium was required to restore normal plasma concentrations.

1. Ramsahoye BH, *et al*. The mineralocorticoid effects of high dose hydrocortisone. *BMJ* 1995; **310:** 656–7.

Effects on the nervous system. For reports and comments on paraesthesia or perineal irritation associated with hydrocortisone sodium phosphate given intravenously, see p. 1617.3.

Hypersensitivity and anaphylaxis. References to hypersensitivity reactions and anaphylaxis associated with the intravenous use of hydrocortisone;[1-7] topical application can also result in hypersensitivity.[8]

1. Chan CS, *et al*. Hydrocortisone-induced anaphylaxis. *Med J Aust* 1984; **141:** 444–6.
2. Seale JP. Anaphylactoid reaction to hydrocortisone. *Med J Aust* 1984; **141:** 446.
3. Corallo CE, Sosnin M. Bronchospasm, tachycardia following intravenous hydrocortisone. *Aust J Hosp Pharm* 1985; **15:** 103–4.
4. Al Mahdy H, Hall M. Anaphylaxis and hydrocortisone. *Ann Intern Med* 1988; **108:** 487–8.
5. Fulcher DA, Katelaris CH. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review. *Med J Aust* 1991; **154:** 210–14.
6. Kawane H. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate. *Med J Aust* 1991; **154**: 782.
7. Currie GP, *et al*. An unexpected response to intravenous hydrocortisone succinate in an asthmatic patient. *Br J Clin Pharmacol* 2005; **60:** 342.
8. Wilkinson SM, *et al*. Hydrocortisone: an important cutaneous allergen. *Lancet* 1991; **337:** 761–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydrocortisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief account of the pharmacokinetics of corticosteroids, see p. 1620.3.

Hydrocortisone is readily absorbed from the gastrointestinal tract and peak blood concentrations occur in about an hour. The plasma half-life is about 100 minutes. It is more than 90% bound to plasma proteins. Following intramuscular injection, the absorption of the water-soluble sodium phosphate and sodium succinate esters is rapid, while absorption of hydrocortisone free alcohol and its lipid-soluble esters is slower. Absorption of hydrocortisone acetate after intra-articular or soft-tissue injection is also slow. Hydrocortisone is absorbed through the skin, particularly in denuded areas.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol. These are excreted in the urine, mainly conjugated as glucuronides, with a very small proportion of unchanged hydrocortisone. Hydrocortisone readily crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfacort; Anusol-HC; Azuthidrona; Demacort; Fridalit; Hidrotisona; Lactid HC; Locoid; Medrocil; Microsona; Oralsone; Proavenal H; Schericur†; Sirotamicin HC; Stiefcortil; Transderma H; ***Austral.***: Colifoam; Cortef; Cortic; Derm-Aid; DermAid; Egocort; Hycor; Hysone; Sigmacort; Siguent Hycor; Solu-Cortef; ***Austria***: Colifoam; Ekzemsalbe F; Hydoftal sine neomycino†; Hydrocortone; Hydroderm; Locoidon†; ***Belg.***: Azacortine; Cremicort-H; Locoid; Pannocort; Solu-Cortef; ***Braz.***: Androcortil; Ariscorten; Benzenil; Berlison; Cortisonal; Cortiston; Cortizol; Cortizon†; Hicortin†; Hidrocortex; Hidyn H; Locoid; Nutracort; Solu-Cortef; Stiefcortil; Therasona; Westcort†; ***Canad.***: Barriere-HC; Claritin Skin Itch Relief; Cortamed; Cortate; Cortef; Cortenema; Cortifoam; Cortoderm; Dermaflex HC; Emo-Cort; Hycort; Hyderm; Hydrosone; HydroVal; Neo-HC†; Novo-Hydrocort; Prevex HC; Sarna HC; Solu-Cortef; Soothing Cream; Westcort†; ***Chile***: Aquanil HC†; Calmurid; Cortisol; Efficort; Hipoge; Locoid; Nutracort; Pandel; Solu-Cortef; ***China***: Efficort (益芙可); Locoid (来可得); Youzhouer (尤卓尔); ***Cz.***: Locoid; ***Denm.***: Colifoam; Hyderm; Locoid; Mildison; Plenadren; Solu-Cortef; ***Fin.***: Ampikyy; Apocort; Bucort; Colifoam; Hyderm; Kyypakkaus; Locoid; Solu-Cortef; ***Fr.***: Aphilan; Calmicort; Colofoam; Cortapaisyl; Cortisedermyl; Dermaspraid Demangeaison†; Dermofenac; Efficort; Hydracort†; Locoid; Mitocortyl†; ***Ger.***: Alfason; Colifoam; Ebenol; Fenistil Hydrocort†; Ficortril; Hydrocutan mild†; Hydrocutan; Hydrogalen; Hydroson; Laticort; Linola Akut; Linolacort Hydro; Muni; Munitren†; Neuroderm Akut; Pandel†; Posterisan cort; Retef†; Sanatison Mono†; Soventol HydroCort; Soventol HydroSpray; Systral Hydrocort†; ***Gr.***: Colifoam; Filocot; Lyo-Cortin; Nutracort; Rolak; Solu-Cortef; ***Hong Kong***: BF-Hycort†; Cortef; Cortosone†; Derm-Aid; Dhacort; Egocort; Hydrosone; Hytisone; Sigmacort; Solu-Cortef; Uni-Cort†; ***Hung.***: Cortef; Laticort; Locoid; Solu-Cortef; ***India***: Arvisone; Cardol; Cipcorlin; Cort-H; Cort-S; Cortygard; Cutisoft; Efcorlin; Eldercoid; Entofoam; Geocort; H-Cort; Hisone; Hobutide; HS; Hy-Sone; Hycort; Hycoson; Hyss; Hyver; Intacorlin; Irays; Labocort; Lacticare-HC; Locoid; Lycor; Lycortin-S; M-Cort; Multicort; Niscort; Novacort; Wycort; ***Indon.***: Berlicort; Calacort†; Enkacort; Lexacorton; Locoid†; Steroderm†; ***Irl.***: Colifoam; Corlan; Cortopin; Dioderm; Emucream HC†; Hc45; Hydrocortisyl; Hydrocortone; Locoid; Plenadren; Solu-Cortef; ***Israel***: Cortifoam; Cortizone; Efficort†; Lanacort; Solu-Cortef; ***Ital.***: Colifoam; Cortidro; Cortop; Dermirit; Dermocortal; Flebocortid; Foille Insetti; Idracemi; Lanacort; Lenirit; Locoidon; Sintotrat; Solu-Cortef; ***Jpn***: Pandel; Saxizon; ***Malaysia***: Derm-Aid; Efficort; Egocort; H-Cort; Hycort; Hydrocort; Solu-Cortef; ***Mex.***: Aquanil HC; Collicort†; Efficort; Fadol†; Flebocortid; Flemex; Icorsan; Lacticare-HC; Locoid; Microsona; Nositrol; Nutracort; Solhidrol; Westcort; ***Neth.***: Buccalsone†; Cremicort; Locoid; Mildison†; Plenadren; Solu-Cortef; Zure oordruppels met hydrocortison; ***Norw.***: Colifoam†; Locoid; Mildison; Plenadren; Solu-Cortef; ***NZ***: BK HC; Colifoam; Derm-Aid; DP Hydrocortisone†; Egocort; Lemnis Fatty Cream HC; Lipocort; Locoid; Mildison; Skincalm; Solu-Cortef; ***Philipp.***: Biocort; Clovisone; Cortin; Cortizan; Costeron-H; Droxiderm; Efficort; Hovicor; Hycort; Hycortil; Hydrotopic; Lacticare-HC; Ocecor; Pharmacort; Primacort; Solu-Cortef; Sorvilor; Stericort; Syntesor; ***Pol.***: Corhydron; Hydrocort; Laticort; Locoid; Procortin; ***Port.***: Colifoam; Hidalone; Hydrocortone; Lactisona; Locoid; Pandel; Pandermil; Rapicort; Solu-Cortef; ***Rus.***: Cortef (Кортеф); Laticort (Латикорт); Locoid (Локоид); Sopolcort N (Сополькорт Н)†; ***S.Afr.***: Biocort; Covocort; Dilucort; Locoid; Mezzoderm; Mylocort; Procutan; Skincalm; Solu-Cortef; Stopitch; ***Singapore***: Cortisone; Derm-Aid; Dhacort; Efficort; Egocort; H-Cort; Hydrocort; Hydroderm; Nu-Derm Tolereen†; Solu-Cortef; ***Spain***: Actocortina; Aftasone; Calmiox; Ceneo; Dermosa Hidrocortisona; Hemodren; Hemorrane; Hidroaltesona; Hidrocisdin; Isdinium; Lactisona; Nutrasona; Oralsone; Scalpicin Capilar†; Schericur; Suniderma; ***Swed.***: Colifoam; Ficortril; Hyderm; Locoid; Mildison; Solu-Cortef; Uniderm†; ***Switz.***: Alfacortone; Hydrocortone; Locoid; Sanadermil; Solu-Cortef; ***Thai.***: H-Cort; HC; Hytisone; Lacticare-HC; Prevex HC†; Solu-Cortef; ***Turk.***: Cortimycine; Hipokort; Locoid; ***UAE***: Alfacort; ***UK***: Colifoam; Corlan†; Cortopin; Cortropin; Dermacort; Dioderm; Efcortelan†; Efcortesol; Exe-Cort; Hc45; Hydrocortistab; Hydrocortone†; Lanacort; Locoid; Mildison; Plenadren; Solu-Cortef; Zenoxone; ***Ukr.***: Laticort (Латикорт); Locoid (Локоид); Solu-Cortef (Солу-Кортеф); ***USA***: A-Hydrocort; Acticort; Ala-Cort; Anucort-HC; Aquanil HC; Aveeno Active Naturals Hydrocortisone; Bactine; CaldeCort; Carmol HC; Cetacort; Colocort; Cort-Dome; Cortaid; Cortef Feminine Itch; Cortef; Corticaine†; Corticool; Cortifoam; Cortizone; Dermarest Dri-Cort; Dermol HC; Dermolate; EarSol-HC; Gynecort; Hemril-HC; Hi-Cor; Hydrocortone; HydroSkin; Hytone; Itch-X; Lacticare-HC†; Lanacort; Locoid; Massengill Medicated; Neutrogena T/Scalp; Noble Formula HC; NuCort; Nutracort; Orabase HCA; Pandel; Penecort; Procort†; Proctocort; Proctocream HC 2.5%†; Recort Plus; Rectacort-HC; Scalacort DK; Solu-Cortef; Synacort; Tegrin-HC; Texacort; U-Cort; Westcort; Xerese; ***Venez.***: Corticina; Efficort; Hidrocort; Hidrozona; Liocort; Nutracort; Solu-Cortef; Stricort.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Gentamicin and Hydrocortisone Acetate Ear Drops; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injection; Hydrocortisone Acetate Ointment; Hydrocortisone Acetate Oral Suspension; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment; Hydrocortisone and Neomycin Cream; Hydrocortisone Cream; Hydrocortisone Ointment; Hydrocortisone Oromucosal Tablets; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Phosphate Oral Solution; Hydrocortisone Sodium Succinate Injection; Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment;

USP 36: Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone

Ointment; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injectable Suspension; Hydrocortisone Acetate Lotion; Hydrocortisone Acetate Ointment; Hydrocortisone Acetate Ophthalmic Ointment; Hydrocortisone Acetate Ophthalmic Suspension; Hydrocortisone and Acetic Acid Otic Solution; Hydrocortisone Butyrate Cream; Hydrocortisone Cream; Hydrocortisone Gel; Hydrocortisone Injectable Suspension; Hydrocortisone Lotion; Hydrocortisone Ointment; Hydrocortisone Rectal Suspension; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Succinate for Injection; Hydrocortisone Tablets; Hydrocortisone Valerate Cream; Hydrocortisone Valerate Ointment; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Lotion; Neomycin Sulfate and Hydrocortisone Acetate Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin Sulfate and Hydrocortisone Cream; Neomycin Sulfate and Hydrocortisone Ointment; Neomycin Sulfate and Hydrocortisone Otic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Acetate Ophthalmic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Ointment; Polymyxin B Sulfate and Hydrocortisone Otic Solution.

Isoflupredone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de isoflupredona; 9α-Fluoroprednisolone Acetate; Isoflupredona, acetato de; Isofluprédone, Acétate d'; Isoflupredoni Acetas; U-6013; Изофлупредона Ацетат.

9α-Fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{23}H_{29}FO_6$=420.5

CAS — 338-95-4 (isoflupredone); 338-98-7 (isoflupredone acetate).

UNII — 55P9TUL75S.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Isoflupredone Acetate). Protect from light.

Profile

Isoflupredone acetate is a corticosteroid that has been used for its topical glucocorticoid activity (p. 1597.1) in allergic rhinitis.

Isoflupredone is also employed in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Israel:*** Proaft.

Loteprednol Etabonate *(BANM, USAN, rINNM)* ⊗

CDDD-5604; Etabonato de loteprednol; HGP-1; Lotéprednol, Etabonate de; Loteprednol, etabonato de; Loteprednol Ethyl Carbonate; Loteprednoli Etabonas; P-5604; Лотепреднола Этабонат.

(11β,17α)-17-[(Ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester.

$C_{24}H_{31}ClO_7$=467.0

CAS — 129260-79-3 (loteprednol); 82034-46-6 (loteprednol etabonate).

ATC — S01BA14.

ATC Vet — QS01BA14.

UNII — YEH1EZ96K6.

Profile

Loteprednol etabonate is a corticosteroid used for its glucocorticoid activity (p. 1597.1) in the topical management of inflammatory and allergic disorders of the eye. It is usually used as eye drops containing 0.2 or 0.5%.

Prolonged application to the eye of preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

References.

1. Noble S, Goa KL. Loteprednol etabonate: clinical potential in the management of ocular inflammation. *BioDrugs* 1998; **10:** 329–39.
2. Pavesio CE, DeCory HH. Treatment of ocular inflammatory conditions with loteprednol etabonate. *Br J Ophthalmol* 2008; **92:** 455–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Alrex; Lopred; Lotemax; Lotesoft; Talof; ***Austria:*** Lotemax; ***Braz.:*** Alrex; Loteprol; ***Canad.:*** Alrex; Lotemax; ***Chile:*** Oftol; ***China:*** Lotemax (露达舒); ***Ger.:*** Lotemax; ***Gr.:*** Lotemax; ***Hong Kong:*** Alrex; Lotemax; ***India:*** Loteflam; Lotepred; ***Irl.:*** Lotemax; ***Israel:*** Lotemax; ***Ital.:*** Lotemax; ***Mex.:*** Loterex; Lotesoft; ***Pol.:*** Lotemax; ***Singapore:*** Lotemax; ***Thai.:*** Lotemax; ***Turk.:*** Lotemax; ***UK:*** Lotemax; ***USA:*** Alrex; Lotemax; ***Venez.:*** Lotesoft.

Multi-ingredient Preparations. ***Arg.:*** Lotemicin; Zylet; ***Braz.:*** Zylet; ***Israel:*** Zylet; ***Mex.:*** Zyleth; ***Singapore:*** Zylet; ***Thai.:*** Zylet; ***USA:*** Zylet.

Mazipredone *(rINN)* ⊗

Mazipredona; Maziprédone; Mazipredonum; Мазипредон.

11β,17-Dihydroxy-21-(4-methyl-1-piperazinyl)pregna-1,4-diene-3,20-dione.

$C_{26}H_{38}N_2O_4$=442.6

CAS — 13085-08-0.

UNII — QN0W2YSW63.

Profile

Mazipredone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1). It is used as the hydrochloride with miconazole in the treatment of fungal infections of the skin.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.:*** Depersolon (Деперзолон).

Multi-ingredient Preparations. ***Hung.:*** Mycosolon; ***Pol.:*** Mycosolon; ***Rus.:*** Mycosolon (Микозолон); ***Ukr.:*** Mycosolon (Микозолон)†.

Meprednisone *(USAN, rINN)* ⊗

Meprednisona; Méprednisone; Meprednisonum; 16β-Methylprednisone; NSC-527579; Sch-4358; Менпреднизон.

17α,21-Dihydroxy-16β-methylpregna-1,4-diene-3,11,20-trione.

$C_{22}H_{28}O_5$=372.5

CAS — 1247-42-3.

ATC — H02AB15.

ATC Vet — QH02AB15.

UNII — 67U96J8P35.

Pharmacopoeias. In *US*.

USP 36: (Meprednisone). Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Meprednisone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It has been given orally as either the free alcohol or the acetate and by injection as the sodium hemisuccinate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Cortipyren B; Deltisona B; Latisona B†; Prednisonal; Prenolone; Rupesona B; ***Mex.:*** Lectan.

Methylprednisolone *(BAN, rINN)* ⊗

Meilprednizolon; Methylprednisolon; 6α-Methylprednisolone; Méthylprednisolone; Methylprednisolonum; Metilprednisolona; Metilprednizolon; Metilprednizolonas; Metylprednisolon; Metyylipredniisoloni; NSC-19987; Метилпреднизолон.

11β,17α,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{30}O_5$=374.5

CAS — 83-43-2.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QD10AA02; QH02AB04.

UNII — X4W7ZR7023.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Methylprednisolone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in acetone and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Methylprednisolone). A white to practically white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 100 of alcohol, and in 1 in 800 of chloroform and of ether; slightly soluble in acetone; sparingly soluble in dioxan and in methyl alcohol. Store in airtight containers. Protect from light.

Methylprednisolone Acetate *(BANM, rINNM)* ⊗

Acetato de metilprednisolona; Methylprednisolonacetat; Methylprednisolon-acetát; Méthylprednisolone, acétate de; Methylprednisoloni Acetas; Metilprednisolona, acetato de; Metilprednizolon Asetat; Metilprednizolon-acetát; Metilprednizolono acetatas; Metylprednisolonacetat; Metyylipredniisoloniasetaatti; Метилпреднизолона Ацетат.

Methylprednisolone 21-acetate.

$C_{24}H_{32}O_6$=416.5

CAS — 53-36-1.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QH02AB04.

UNII — 43502P7F0P.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Methylprednisolone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

USP 36: (Methylprednisolone Acetate). A white or practically white, odourless, crystalline powder. Soluble 1 in 1500 of water, 1 in 400 of alcohol, 1 in 250 of chloroform, and 1 in 1500 of ether; sparingly soluble in acetone and in methyl alcohol; soluble in dioxan. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Methylprednisolone Hydrogen Succinate

(BANM, rINNM) ⊗

Hidrogenosuccinato de metilprednisolona; Methylprednisolone Hemisuccinate; Méthylprednisolone, Hémisuccinate de; Méthylprednisolone, Hydrogénosuccinate de; Methylprednisolonhydrogensuccinat; Methylprednisolon-hydrogensukcinát; Methylprednisoloni Hemisuccinas; Methylprednisoloni Hydrogenosuccinas; Metilprednisolona, hidrogenosuccinato de; Metilprednizolon-hidrogén-szukcinát; Metilprednizolono-vandenilio sukcinatas; Metylprednisolonvätesuccinat; Metyylipredniisolonivetysuksinaatti; Метилпреднизолона Гемисукцинат.

Methylprednisolone 21-(hydrogen succinate).

$C_{26}H_{34}O_8$=474.6

CAS — 2921-57-5.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QH02AB04.

UNII — 5GMR90S4KN.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Methylprednisolone Hydrogen Succinate). A white or almost white, hygroscopic powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in acetone; dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Methylprednisolone Hemisuccinate). A white or nearly white, odourless or nearly odourless, hygroscopic solid. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone. Store in airtight containers.

Methylprednisolone Sodium Succinate

(BANM, rINNM) ⊗

Methylprednisolone Sodium Hemisuccinate; Méthylprednisolone, Succinate Sodique de; Methylprednisoloni Natrii Succinas; Metilprednisolona, succinato sódico de; Metilprednizolon Sodyum Süksinat; Succinato sódico de metilprednisolona; Метилпреднизолона Натрия Сукцинат.

Methylprednisolone 21-(sodium succinate).

$C_{26}H_{33}NaO_8$=496.5

CAS — 2375-03-3.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QH02AB04.

UNII — LEC9GKY20K.

Pharmacopoeias. In *US*.

USP 36: (Methylprednisolone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Soluble 1 in 1.5 of water and 1 in 12 of alcohol; very slightly soluble in acetone; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Methylprednisolone sodium succinate injection (*Solu-Medrol, USA*) was considered to be stable for 7 days when diluted in water for injection and stored in glass vials at 4 degrees. When stored under similar conditions at 22 degrees, it was considered to be stable for 24 hours.[1] The manufacturers state that the prepared solution should be stored at 20 to 25 degrees and used within 48 hours of mixing.

1. Nahata MC, *et al.* Stability of diluted methylprednisolone sodium succinate injection at two temperatures. *Am J Hosp Pharm* 1994; **51:** 2157–9.

Uses and Administration

Methylprednisolone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 4 mg of methylprednisolone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

It is used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (see p. 1597.3) except adrenocortical-deficiency states, for which hydrocortisone with supplementary fludrocortisone is preferred.

The dose is usually expressed in terms of the base, and the following are each equivalent to about 40 mg of methylprednisolone:

- methylprednisolone acetate 44 mg
- methylprednisolone hydrogen succinate 51 mg
- methylprednisolone sodium succinate 53 mg

However, esterification generally alters potency and compounds with equivalent methylprednisolone content may not have equivalent clinical effect.

When given **orally**, methylprednisolone usually has an initial dosage range of 4 to 48 mg daily but higher initial doses of up to 100 mg or more daily may be used in acute severe disease.

For **parenteral use** in *intensive* or *emergency therapy*, methylprednisolone sodium succinate may be given by intramuscular or intravenous injection or by intravenous infusion. The intravenous route is preferred for its more rapid effect in emergency therapy. The usual initial intramuscular or intravenous dose ranges from the equivalent of 10 to 500 mg of methylprednisolone daily. Large intravenous doses (over 250 mg) should normally be given slowly over at least 30 minutes; doses up to 250 mg should be given over at least 5 minutes. High doses should generally not be given for prolonged periods; emergency treatment should only be used until the patient is stabilised. High doses given intermittently for a limited period have sometimes been known as 'pulse therapy' (see Administration, below) and in *graft rejection* (see Organ and Tissue Transplantation, p. 1932.2) up to 1 g has been given daily for up to 3 days. In intensive therapy of acute *spinal cord injury* (p. 1613.2) initial doses of the equivalent of 30 mg/kg of methylprednisolone have been given by bolus intravenous injection over 15 minutes and followed, after a 45-minute pause, by intravenous infusion of 5.4 mg/kg per hour over 24 hours or longer. For slow intravenous infusion methylprednisolone sodium succinate is dissolved in an appropriate volume of glucose 5% or sodium chloride 0.9% or sodium chloride 0.9% and glucose 5%.

For doses used in children, see below.

Methylprednisolone acetate may be given as an aqueous suspension by intramuscular injection for a prolonged systemic effect, the dose varying from 40 mg every 2 weeks to 120 mg weekly.

For **intra-articular injection** and for **injection into soft tissues** methylprednisolone acetate aqueous suspension is used. The dose by intra-articular injection varies from 4 to 80 mg according to the size of the affected joint. The acetate may also be given by intralesional injection in doses of 20 to 60 mg.

For use in the treatment of various skin disorders methylprednisolone acetate may be applied **topically**, usually in concentrations of 0.25%. The aceponate, which may show modified topical activity, has also been applied as a 0.1% cream, lotion, or ointment. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Other esters of methylprednisolone that have occasionally been used include the cipionate and the suleptanate.

General references.

1. Cronstein BN. Clinical use of methylprednisolone sodium succinate: a review. *Curr Ther Res* 1995; **56:** 1–15.

Administration. For short-term intensive corticosteroid therapy or in certain emergency situations a technique known as 'pulse therapy' has been used. Methylprednisolone has often been used in this manner. Typically, high doses of about 1 g intravenously have been given, daily or on alternate days or weekly, for a limited number of doses; the most common regimen appears to be 1 g daily for 3 days.

Administration in children. Doses of methylprednisolone in children have varied considerably, depending on the condition being treated.

The *BNFC* suggests that an **oral** dose of 0.5 to 1.7 mg/kg daily in 2 to 4 divided doses may be used for inflammatory and allergic disorders in children aged from 1 month to 18 years old.

Methylprednisolone sodium succinate has been given **parenterally** by the intravenous route. The *BNFC* suggests that inflammatory and allergic disorders may be treated intravenously, by either injection or infusion, in equivalent doses to those used orally. High intravenous doses providing 10 to 30 mg/kg (maximum 1 g) of methylprednisolone, given once daily or on alternate days for up to 3 doses, may be used in 'pulse therapy' in children aged from 1 month to 18 years old for conditions such as severe erythema multiforme (Stevens-Johnson syndrome), lupus nephritis, and systemic onset juvenile idiopathic arthritis. In graft rejection, a dose of 10 to 20 mg/kg (maximum 1 g) once daily may be given for up to 3 days.

Blood disorders. Methylprednisolone is one of the corticosteroids that have been used in the management of haemangioma (p. 1605.3) and the Kasabach-Merritt syndrome.[1] There are also reports of benefit from very high-dose therapy in a few patients with refractory primary acquired pure red cell aplasia,[2] or aplasia due to Blackfan-Diamond anaemia.[3]

1. Özsoylu Ş, *et al.* Megadose methylprednisolone therapy for Kasabach-Merritt syndrome. *J Pediatr* 1996; **129:** 947.
2. Kadikoylu G, *et al.* High-dose methylprednisolone therapy in pure red cell aplasia. *Ann Pharmacother* 2002; **36:** 55–8.
3. Bernini JC, *et al.* High-dose intravenous methylprednisolone therapy for patients with Diamond-Blackfan anemia refractory to conventional doses of prednisone. *J Pediatr* 1995; **127:** 654–9.

IMMUNE THROMBOCYTOPENIA. High-dose intravenous methylprednisolone may be used as part of the emergency management of immune thrombocytopenia (p. 1606.1), for example when major acute bleeding or intracranial haemorrhage supervene. There is some evidence that methylprednisolone is less effective than normal immunoglobulins. Methylprednisolone has also been used orally or intravenously in the management of the chronic form, although prednisolone or prednisone are more frequently used for oral therapy and good controlled studies are scanty.

References.

1. von dem Borne AEGKR, *et al.* High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. *BMJ* 1988; **296:** 249–50.
2. Özsoylu S, *et al.* Megadose methylprednisolone for chronic idiopathic thrombocytopenic purpura. *Lancet* 1990; **336:** 1078–9.
3. Akoğlu T, *et al.* Megadose methylprednisolone pulse therapy in adult idiopathic thrombocytopenic purpura. *Lancet* 1991; **337:** 56.
4. Özsoylu S. Mega-dose methylprednisolone for chronic idiopathic thrombocytopenic purpura. *Lancet* 1991; **337:** 1611–12.
5. Rosthøj S, *et al.* Randomized trial comparing intravenous immunoglobulin with methylprednisolone pulse therapy in acute idiopathic thrombocytopenic purpura. *Acta Paediatr* 1996; **85:** 910–15.
6. Alpdoğan Ö, *et al.* Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. *Br J Haematol* 1998; **103:** 1061–3.
7. Godeau B, *et al.* Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; **359:** 23–9.

Rheumatoid arthritis. Methylprednisolone given in intravenous pulses has been reported[1-7] to be effective in the treatment of rheumatoid arthritis (p. 13.2) including juvenile idiopathic arthritis. Some studies have shown this treatment to be of greatest benefit when given with a disease-modifying antirheumatic drug (DMARD),[1,2,4] although others showed the addition of methylprednisolone to existing therapy to have no extra benefit.[6] A comparatively low dose of 100 mg was found to be as effective as 1 g in one study.[3] Monthly doses of methylprednisolone by deep intramuscular injection were also an effective adjunct to gold therapy.[8]

A preliminary study in children has found intravenous pulses of methylprednisolone 30 mg/kg to be effective treatment for systemic flares of juvenile idiopathic arthritis.[7]

1. Walters HT, Cawley MID. Combined suppressive drug treatment in severe refractory rheumatoid disease: an analysis of the relative effects of parenteral methylprednisolone, cyclophosphamide and sodium aurothiomalate. *Ann Rheum Dis* 1988; **47:** 924–9.
2. Smith MD, *et al.* The clinical and immunological effects of pulse methylprednisolone therapy in rheumatoid arthritis I: clinical effects. *J Rheumatol* 1988; **15:** 229–32.
3. Igelhart IW, *et al.* Intravenous pulsed steroids in rheumatoid arthritis: a comparative dose study. *J Rheumatol* 1990; **17:** 159–62.
4. Smith MD, *et al.* Pulse methylprednisolone therapy in rheumatoid arthritis: unproved therapy, unjustified therapy, or effective adjunctive treatment? *Ann Rheum Dis* 1990; **49:** 265–7.
5. Kapisinszky N, Keszthelyi B. High dose intravenous methylprednisolone pulse therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 1990; **49:** 567–8.
6. Hansen TM, *et al.* Double blind placebo controlled trial of pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. *BMJ* 1990; **301:** 268–70.
7. Adebajo AO, Hall MA. The use of intravenous pulsed methylprednisolone in the treatment of systemic-onset juvenile chronic arthritis. *Br J Rheumatol* 1998; **37:** 1240–2.
8. Corkill MM, *et al.* Intramuscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. *Br J Rheumatol* 1990; **29:** 274–9.

Systemic lupus erythematosus. Methylprednisolone has been widely used to treat disease flares or severe manifestations of SLE (p. 1613.3).

References.

1. Badsha H, Edwards CJ. Intravenous pulses of methylprednisolone for systemic lupus erythematosus. *Semin Arthritis Rheum* 2003; **32:** 370–7.
2. Danowski A, *et al.* Flares in lupus: Outcome Assessment Trial (FLOAT), a comparison between oral methylprednisolone and intramuscular triamcinolone. *J Rheumatol* 2006; **33:** 57–60.
3. Trevisani VF, *et al.* Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 20/06/06).

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively). Rapid intravenous injection of large doses has been associated with cardiovascular collapse.

Methylprednisolone may be slightly less likely than prednisolone to cause sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

References to various adverse effects associated with intravenous methylprednisolone in high-dose pulse therapy[1-11] and to adverse effects after intra-articular[12,13] and intranasal injection.[14] Epidural dosage (or more particularly inadvertent intrathecal dosage during attempted epidural placement) may be associated with serious adverse effects including arachnoiditis and aseptic meningitis, although the degree of risk is uncertain.[15]

1. Newmark KJ, *et al.* Acute arthralgia following high-dose intravenous methylprednisolone therapy. *Lancet* 1974; **ii:** 229.
2. Bailey RR, Armour P. Acute arthralgia after high-dose intravenous methylprednisolone. *Lancet* 1974; **ii:** 1014.
3. Bennett WM, Strong D. Arthralgia after high-dose steroids. *Lancet* 1975; **i:** 332.
4. Moses RE, *et al.* Fatal arrhythmia after pulse methylprednisolone therapy. *Ann Intern Med* 1981; **95:** 781–2.
5. Oto A, *et al.* Methylprednisolone pulse therapy and peritonitis. *Ann Intern Med* 1983; **99:** 282.
6. Suchman AL, *et al.* Seizure after pulse therapy with methyl prednisolone. *Arthritis Rheum* 1983; **26:** 117.
7. Ayoub WT, *et al.* Central nervous system manifestations after pulse therapy for systemic lupus erythematosus. *Arthritis Rheum* 1983; **26:** 809–10.
8. Williams AJ, *et al.* Disseminated aspergillosis in high dose steroid therapy. *Lancet* 1983; **i:** 1222.
9. Barrett DF. Pulse methylprednisolone therapy. *Lancet* 1983; **ii:** 800.
10. Baethge BA, Lidsky MD. Intractable hiccups associated with high-dose intravenous methylprednisolone therapy. *Ann Intern Med* 1986; **104:** 58–9.
11. Gardiner PVG, Griffiths ID. Sudden death after treatment with pulsed methylprednisolone. *BMJ* 1990; **300:** 125.
12. Black DM, Filak AT. Hyperglycemia with non-insulin-dependent diabetes following intraarticular steroid injection. *J Fam Pract* 1989; **28:** 462–3.
13. Pollock B, *et al.* Chronic urticaria associated with intra-articular methylprednisolone. *Br J Dermatol* 2001; **144:** 1228–30.
14. Johns KJ, Chandra SR. Visual loss following intranasal corticosteroid injection. *JAMA* 1989; **261:** 2413.
15. Rodgers PT, Connelly JF. Epidural administration of methylprednisolone for back pain. *Am J Hosp Pharm* 1994; **51:** 2789–90.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methylprednisolone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Methylprednisolone is fairly rapidly distributed after oral doses, with a plasma half-life of 3.5 hours or more. The tissue half-life is reported to range from 18 to 36 hours.

Methylprednisolone acetate is absorbed from joints over a week but is more slowly absorbed following deep intramuscular injection. The sodium succinate ester is rapidly absorbed after intramuscular doses, and peak plasma concentrations occur in 2 hours.

Methylprednisolone crosses the placenta.

References.

1. Tornatore KM, *et al.* Repeated assessment of methylprednisolone pharmacokinetics during chronic immunosuppression in renal transplant recipients. *Ann Pharmacother* 1995; **29:** 120–4.
2. Rohatagi S, *et al.* Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997; **37:** 916–25.

3. Tornatore KM, *et al*. Pharmacokinetics and pharmacodynamic response of methylprednisolone in premenopausal renal transplant recipients. *J Clin Pharmacol* 2004; **44:** 1003–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Advantan; Cipridanol; Cortisolona; Solu-Medrol; Totalsolona; ***Austral.***: Advantan; Depo-Medrol; Depo-Nisolone; Methylpred; Solu-Medrol; ***Austria***: Advantan; Solu-Medrol; Urbason; ***Belg.***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Braz.***: Advantan; Alergolon; Depo-Medrol; Predi-Medrol; Predmetil; Solu-Medrol; Solupren; Unimedrol; ***Canad.***: Depo-Medrol; Medrol; Solu-Medrol; ***Chile***: Depo-Medrol; Medrol; Solu-Medrol; ***China***: Medrol (美卓乐); Mi Le Song (米乐松); Solu-Medrol (甲强龙); You Jin (尤金); ***Cz.***: Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***Denm.***: Depo-Medrol; Medrol; Solu-Medrol; ***Fin.***: Advantan; Depo-Medrol; Medrol; Solomet; Solu-Medrol; ***Fr.***: Depo-Medrol; Medrol; Solu-Medrol; ***Ger.***: Advantan; M-PrednisHexal; Metypred; Metysolon; Predni M; Urbason; ***Gr.***: Advantan; Depo-Medrol; Depo-Medrone†; Fodier; Lyo-drol; Medrol; Solu-Medrol; Veriderm Medrol; ***Hong Kong***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Hung.***: Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***India***: Acto-Pred; Aricort M; Avpred; Biolone; Cecort; Depo-Medrol; Depomax; Depopred; Deposet; Dispred; Elpred M; Geopred; Happisone; Hosicort; Ivepred; Lumi-M; Lupus; MB Sole; Medicort; Medrol; Mega-Pred; Melpred; Melsone; Mepred; Meprosol; Mepsonate; Methyl-Pred; MPA; MPSS; MSLone; Mypred; Nayapred; Neo-Drol; Neodrol-AS; Nicord; Nicort; Nispred; Omnacortil; Solu-Medrol; ***Indon.***: Advantan; Comedrol; Depo-Medrol; Flason; Glomeson; Hexilon; Intidrol; Lameson; Lexcomet; Medixon; Medrol; Meprilon; Meproson; Mesol; Metcor; Methylon; Metidrol†; Metisol; Metrison; Nichomedson; Phadilon; Prednicort; Prednox; Pretilon; Prolon 8; Rhemafar; Sanexon; Solu-Medrol; Somerol; Sonicor; Stenirol; Thimelon; Tisolon; Tison; Toras; Tropidrol; Urbason; Xilon; Yalone; ***Irl.***: Advantan; Depo-Medrone; Solu-Medrone; ***Israel***: Depo-Medrol; Medrol; Solu-Medrol; ***Ital.***: Advantan; Asmacortone†; Avancort†; Depo-Medrol; Medrol; Metilbetasone Solubile†; Solu-Medrol; Supresol; Urbason; ***Malaysia***: Depo-Medrol; Solu-Medrol; ***Mex.***: Advantan; Cryosolona; Depo-Medrol; Metisona; Prednilem†; Radilem†; Solipred; Solu-Medrol; ***Neth.***: Depo-Medrol; Solu-Medrol; ***Norw.***: Depo-Medrol; Medrol; Solu-Medrol; ***NZ***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Philipp.***: Adrena; Advantan; Depo-Medrol; Medixon; Medrol; Mepresone; Prednox; Solu-Medrol; Solu-Ped; Solucin; ***Pol.***: Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***Port.***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Rus.***: Advantan (Адвантан); Depo-Medrol (Депо-медрол); Lemod (Лемод); Medrol (Медрол); Metypred (Метипред); Solu-Medrol (Солу-медрол); ***S.Afr.***: Advantan; AP Methylpred; Depo-Medrol; Medrol; Metypresol†; Solu-Medrol; ***Singapore***: Solu-Medrol; ***Spain***: Adventan; Lexxema; Solu-Moderin; Urbason; ***Swed.***: Depo-Medrol; Medrol; Solu-Medrol; ***Switz.***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Thai.***: Depo-Medrol; Solu-Medrol; ***Turk.***: Advantan; Depo-Medrol; Depometikort; Precort; Prednol; Urbason; ***UK***: Depo-Medrone; Medrone; Solu-Medrone; ***Ukr.***: Advantan (Адвантан); Depo-Medrol (Депо-Медрол); Medrol (Медрол); Metypred (Метипред); Solu-Medrol (Солу-Медрол); Sterocort (Стерокорт); ***USA***: A-Methapred; dep-Medalone; Depo-Medrol; Medrol; Solu-Medrol; ***Venez.***: Advantan; Depo-Medrol; Medrol; Prednicort; Solu-Medrol.

Multi-ingredient Preparations. ***Austral.***: Neo-Medrol†; ***Belg.***: Depo-Medrol + Lidocaine; ***Canad.***: Depo-Medrol with Lidocaine; Medrol Acne Lotion; Neo-Medrol Acne; ***Fin.***: Depo-Medrol cum Lidocain; Solomet c bupivacain hydrochlorid; ***Gr.***: Medrol Acne Lotion; Neo-Medrol; Veriderm-Neo Medrol; ***Hong Kong***: Depo-Medrol with Lidocaine; Neo-Medrol Acne; ***Irl.***: Depo-Medrone with Lidocaine; ***Israel***: Depo-Medrol with Lidocaine; Neo-Medrol; ***Ital.***: Depo-Medrol + Lidocaina; ***Malaysia***: Neo-Medrol; ***Neth.***: Depo-Medrol + Lidocaine; ***Norw.***: Depo-Medrol cum Lidocain; ***NZ***: Depo-Medrol with Lidocaine; ***Pol.***: Depo-Medrol z Lidokaina; ***Port.***: Depo-Medrol com Lidocaina; ***S.Afr.***: Depo-Medrol with Lidocaine; Neo-Medrol†; ***Singapore***: Neo-Medrol; ***Swed.***: Depo-Medrol cum Lidocain; ***Switz.***: Depo-Medrol Lidocaine; ***Thai.***: Neo-Medrol; ***UK***: Depo-Medrone with Lidocaine.

Pharmacopoeial Preparations

BP 2014: Methylprednisolone Acetate Injection; Methylprednisolone Tablets;

USP 36: Methylprednisolone Acetate Cream; Methylprednisolone Acetate Injectable Suspension; Methylprednisolone Sodium Succinate for Injection; Methylprednisolone Tablets; Neomycin Sulfate and Methylprednisolone Acetate Cream.

Mometasone Furoate

(BANM, USAN, rINNM) ⊗

Furoato de mometasona; Mometasona, furoato de; Mométasone, furoate de; Mometasonfuroat; Mometasonfuroát; Mometasoni Furoas; Mometasonifuroaatti; Mometazon Furoat; Mometazon-furoát; Mometazono furoatas; Mometazonu furoinian; Sch-32088; Мометазона Фуроат.

9α,21-Dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate).

$C_{27}H_{30}Cl_2O_6$=521.4

CAS — 105102-22-5 (mometasone); 83919-23-7 (mometasone furoate).

ATC — D07AC13; R01AD09; R03BA07.

ATC Vet — QD07AC13; QR01AD09; QR03BA07.

UNII — 04201GDN4R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Mometasone Furoate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone and in dichloromethane.

USP 36: (Mometasone Furoate). A white to off-white powder. Soluble in acetone and in dichloromethane.

Uses and Administration

Mometasone furoate is a corticosteroid used for its glucocorticoid activity (see p. 1597.1).

Mometasone furoate is used by dry powder inhaler for the prophylaxis of **asthma** (below). Doses may differ between countries and dosage units may be expressed differently, as either the amount of drug released per actuation or the amount delivered from the mouthpiece. UK licensed product information includes an initial dose of 400 micrograms inhaled once daily in the evening for mild to moderate asthma in adults and adolescents aged 12 years and older. This may be adjusted to a maintenance dose of 200 micrograms once or twice daily. In severe asthma, an initial dose of 400 micrograms twice daily is used, then titrated to the lowest effective dose once symptoms are controlled. US doses are provided in terms of the amount of drug released per actuation (an actuation that releases 110 micrograms delivers 100 micrograms from the mouthpiece). An initial dose of 220 micrograms once daily in the evening is used in adults and adolescents, aged 12 years and older, who have been treated with inhaled therapy only (bronchodilators or corticosteroids); this may be increased to a maximum of 440 micrograms daily as a single dose or 2 divided doses. Patients receiving oral corticosteroids may be started on 440 micrograms twice daily.

A nasal suspension of mometasone furoate 0.05%, as the monohydrate, is given in the treatment and prophylaxis of the symptoms of **allergic rhinitis** (below). The usual dose is the equivalent of 100 micrograms of mometasone furoate in each nostril once daily, increased if necessary to 200 micrograms in each nostril daily. Once symptoms are controlled a dose of 50 micrograms in each nostril daily may be effective for maintenance.

The nasal suspension is also given for the treatment of **nasal polyps** (below) in patients 18 years and older; the recommended initial dose in the UK is 100 micrograms into each nostril once daily, increased after 5 to 6 weeks to twice daily if needed. In the USA the recommended initial dose is 100 micrograms in each nostril twice daily, although once daily administration may be sufficient in some patients.

Mometasone furoate is used topically in the treatment of various **skin disorders** (below). It is usually used as a cream, ointment, lotion, or scalp application containing 0.1%. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

For doses used in children, see below.

Administration in children. Mometasone furoate may be used in the management of **asthma** in children. In the USA, a dry powder inhaler is licensed for use in children aged 4 to 11 years in a dose of 110 micrograms once daily in the evening, regardless of prior therapy; this is the maximum recommended daily dose.

A nasal suspension of mometasone furoate 0.05%, as the monohydrate, is given in the treatment of the symptoms of **allergic rhinitis**. In the UK, the dose for children aged between 6 and 11 years is the equivalent of 50 micrograms in each nostril once daily. In the USA, similar doses may be given to children as young as 2 years of age.

Older children are given adult doses for these indications (see above).

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3). Reviews of the use of mometasone furoate.

1. Sharpe M, Jarvis B. Inhaled mometasone furoate: a review of its use in adults and adolescents with persistent asthma. *Drugs* 2001; **61:** 1325–50.
2. McCormack PL, Plosker GL. Inhaled mometasone furoate: a review of its use in persistent asthma in adults and adolescents. *Drugs* 2006; **66:** 1151–68.

Nasal polyps. For discussion of the value of corticosteroids in the treatment of nasal polyps, see p. 1608.2. References to the use of mometasone furoate.

1. Stjärne P, *et al*. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2006; **132:** 179–85.
2. Stjärne P, *et al*. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2006; **126:** 606–12.
3. Small CB, *et al*. Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis. *J Allergy Clin Immunol* 2008; **121:** 928–32.
4. Stjärne P, *et al*. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg* 2009; **135:** 296–302.

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p. 612.1. Some further references to the use of mometasone furoate in rhinitis are given below.

1. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 1998; **56:** 725–45.
2. Lundblad L, *et al*. Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a Nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2001; **121:** 505–9.
3. Schenkel E. Features of mometasone furoate nasal spray and its utility in the management of allergic rhinitis. *Expert Opin Pharmacother* 2003; **4:** 1579–91.
4. van Drunen C, *et al*. Nasal allergies and beyond: a clinical review of the pharmacology, efficacy, and safety of mometasone furoate. *Allergy* 2005; **60** (suppl 80): 5–19. Correction. *ibid.*; 1335.
5. Zitt M, *et al*. Mometasone furoate nasal spray: a review of safety and systemic effects. *Drug Safety* 2007; **30:** 317–26.
6. Baldwin CM, Scott LJ. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 2008; **68:** 1723–39.

Skin disorders. References.

1. Prakash A, Benfield P. Topical mometasone: a review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. *Drugs* 1998; **55:** 145–63.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Adrenal suppression may occur in some patients treated with high-dose long-term inhalation of mometasone furoate for asthma. Systemic absorption may also follow nasal use, particularly after high doses or prolonged treatment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mometasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Mometasone furoate is poorly absorbed after inhalation, intranasal use, and topical application. It undergoes hepatic metabolism mainly by the cytochrome P450 isoenzyme CYP3A4. The terminal elimination half-life is about 5 hours; metabolites are excreted mainly in the faeces and to a lesser extent in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Derimod; Elocon; Fenisona; Hexaler Bronquial; Hexaler Nasal; Metason; Momeplus; Mometax; Nasonex; Novasone; Uniclar; ***Austral.***: Elocon; Nasonex; Novasone; ***Austria***: Asmanex; Elocon; Nasonex; ***Belg.***: Elocom; Nasonex; ***Braz.***: Dermotil; Elocom; Nasonex; Oximax; Topison; Topliv; ***Canad.***: Asmanex; Elocom; Nasonex; ***Chile***: Dermaten; Dermosona; Elocom; Flogocort; Lisoder; Metacross; Momelab; Nasonex; Rinoval; Uniclar; ***China***: Eloson (艾洛松); Fu Mei Song (芙美松); Nasonex (内舒拿); Suqi (速奇); ***Cz.***: Asmanex; Elocom; Eztom; Momerid; Nasonex; ***Denm.***: Asmanex; Elocom; Elocon; Nasomet; Nasonex; ***Fin.***: Asmanex; Demoson; Elocon; Nasonex; ***Fr.***: Nasonex; ***Ger.***: Asmanex; Ecural; Momegalen; Nasonex; ***Gr.***: Asmanex; Bioelementa; Ecelecort; Elocon; Elovent; Esine; F-Din; Fremomet; Logren; Makiren; Metason; Mofur; Molken; Momecort; Movesan; Mozeton; Nasamet; Nasonex; Pharmecort; Prospiril; Yperod; ***Hong Kong***: Elisone; Elomet; Elosone; Nasonex; Topcort; ***Hung.***: Elocom; Momegen; Nasonex; ***India***: Aquamet; Cratisone; Cumef; Cutizone; Dermanex; Elocon; Ezoma; Femcort; HHSone; M-Fact; Metacon; Metacort; Metaspray; Mezo; MMS; Moco; Momate; Momecon; Momeflo; Momoz; Momtas; Most; Topcort; ***Indon.***: Dermovel; Elocon; Eloskin; Elox; Iflacort; Intercon; Mefurosan; Mesone; Metaflam; Mofacort; Mofulex; Momet; Motaderm; Moteson†; Nasonex; ***Irl.***: Asmanex; Elocon; Monovo; Nasonex; ***Israel***: Elocom; Nasonex; ***Ital.***: Altosone; Elocon; Nasonex; Rinelon; ***Jpn***: Nasonex; ***Malaysia***: Elomet; Elosone; Melomet; Momate; Nasonex; Vizomet; ***Mex.***: Elica; Elomet; Elovent; Rinelon; Uniclar; ***Neth.***: Asmanex; Elocon; Elovent†; Monovo; Nasonex; ***Norw.***: Asmanex; Elocon; Nasonex; ***NZ***: Asmanex†; Bronconex;

Elocon; Nasonex; ***Philipp.***: Elica; Elocon; Mezo; Momate; Mosone; Nasonex; Rinelon; ***Pol.***: Asmanex; Elocom; Elosone; Momarid; Momederm; Nasonex; ***Port.***: Asmanex; Desdek; Elocom; Elomet; Elovent; Nasomet; Prospiril; ***Rus.***: Elocom (Элоком); Momat (Момат); Nasonex (Назонекс); Uniderm (Унидерм); ***S.Afr.***: Elocon; Mometagen; Nasonex; Nexomist; Rinelon; ***Singapore***: Asmanex; Elomet; Elosone; Nasonex; ***Spain***: Asmanex; Elica; Elocom; Konex; Nasonex; Pinarsina†; Rinelon†; ***Swed.***: Asmanex; Demoson; Elocon; Nasonex; ***Switz.***: Asmanex; Elocom; Monovo; Nasonex; ***Thai.***: Elomet; Nasonex; Novasone; Rinelon; ***Turk.***: Asmanex; Codermo; Elocon; M-Furo; Momecon; Mometix; Nasonex; Nazofix; Nazoster; Rinose; Risonel; ***UK***: Asmanex; Elocon; Nasonex; ***Ukr.***: Elocom (Элоком); Eloson (Элозон); Momederm (Момедерм); Nasonex (Назонекс); ***USA***: Asmanex; Elocon; Momexin; Nasonex; Propel; ***Venez.***: Asmanex; Cortynase; Dergentil; Elocon; Elomet; Nasonex.

Multi-ingredient Preparations. ***Canad.***: Zenhale; ***Chile***: Velosalic†; ***Cz.***: Momesalic; ***Ger.***: Elosalic; ***Gr.***: Elosalic; Momesalic; ***Hong Kong***: Elosalic; ***Hung.***: Elosalic; ***India***: Cortimax-S; Cutizone-T; Depig-TM; Eveglow; Fudec-M; Furomet; M-Lite; Mecloma-F; Mecloma-T; Melacare; Melacut; Melalite-XL; Metazole; Mezo-T; Momate-S; Momoz-F; Momoz-S; Momoz-T; Motoso; Multi-HTM; ***Indon.***: Elosalic; ***Pol.***: Elosalic; ***Port.***: Monsalic; ***Rus.***: Elocom-S (Элоком-С); Momat-S (Момат-С); ***S.Afr.***: Elosalic†; ***Singapore***: Elosalic; ***Spain***: Elocom Plus; ***Swed.***: Elosalic; ***Turk.***: Elosalic; Momesalic; ***Ukr.***: Elocom-S (Элоком-С); ***USA***: Dulera; ***Venez.***: Elosalic.

Pharmacopoeial Preparations
BP 2014: Mometasone Aqueous Nasal Spray; Mometasone Cream; Mometasone Ointment; Mometasone Scalp Application; **USP 36:** Mometasone Furoate Cream; Mometasone Furoate Ointment; Mometasone Furoate Topical Solution.

Paramethasone Acetate

(BANM, USAN, rINNM) ⊗

Acetato de parametasona; 6α-Fluoro-16α-methylprednisolone 21-Acetate; Parametasona, acetato de; Parametazon Asetat; Paraméthasone, Acétate de; Paramethasoni Acetas; Параметазона Ацетат.

6α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate.

$C_{24}H_{31}FO_6$=434.5

CAS — 53-33-8 (paramethasone); 1597-82-6 (paramethasone acetate).

ATC — H02AB05.

ATC Vet — QH02AB05.

UNII — 8X50N88ZDP.

Pharmacopoeias. In *Fr.*

Profile

Paramethasone acetate is a corticosteroid that has been used systemically for its mainly glucocorticoid activity (p. 1597.1); 2 mg of paramethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. The disodium phosphate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Dilar; ***Mex.***: Dilar†; ***Turk.***: Depo-Dilar.

Multi-ingredient Preparations. ***Mex.***: Dilarmine†.

Prednicarbate *(BAN, USAN, rINN)* ⊗

Hoe-777; Prednicarbat; Prednicarbato; Prednicarbatum; Prednikarbaatti; Prednikarbat; Prednikarbát; Prednikarbatas; S-77-0777; Предникарбат.

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 17-(ethyl carbonate) 21-propionate.

$C_{27}H_{36}O_8$=488.6

CAS — 73771-04-7.

ATC — D07AC18.

ATC Vet — QD07AC18.

UNII — V901LV1K7D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Prednicarbate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol and in acetone; sparingly soluble in propylene glycol. Protect from light.

USP 36: (Prednicarbate). A white to almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; sparingly soluble in propylene glycol. Protect from light.

Profile

Prednicarbate is a corticosteroid used topically for its glucocorticoid activity (see p. 1597.1) in the treatment of various skin disorders. It has usually been used as a cream, ointment, or lotion, containing 0.1 to 0.25%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

References.

1. Schäfer-Korting M, *et al.* Prednicarbate activity and benefit/risk ratio in relation to other topical glucocorticoids. *Clin Pharmacol Ther* 1993; **54:** 448–56.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prednicarbate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Prednitop; ***Braz.***: Dermatop; Invex; ***Canad.***: Dermatop; ***Chile***: Dermatop; ***Cz.***: Dermatop; ***Ger.***: Dermatop†; Prednitop; ***India***: Dermatop; ***Indon.***: Dermatop; ***Ital.***: Dermatop; ***Mex.***: Alisyd; ***Spain***: Batmen; Peitel; ***Switz.***: Prednicutan; Prednitop; ***Thai.***: Dermatop; ***Turk.***: Dermatop; ***USA***: Dermatop.

Pharmacopoeial Preparations
USP 36: Prednicarbate Cream; Prednicarbate Ointment.

Prednisolone *(BAN, rINN)* ⊗

1,2-Dehydrohydrocortisone; Deltahydrocortisone; Metacortandralone; NSC-9120; Prednisolon; Prednisolona; Prednisoloni; Prednisolonum; Prednizolon; Prednizolonas; Преднизолон.

11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione.

$C_{21}H_{28}O_5$=360.4

CAS — 50-24-8 (anhydrous prednisolone); 52438-85-4 (prednisolone sesquihydrate).

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QD07XA02; QH02AB06; QR01AD02; QS01BA04; QS01CB02; QS02BA03; QS03BA02.

UNII — 9PHQ9Y1OLM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.*

US allows the anhydrous form or the sesquihydrate.

Ph. Eur. 8: (Prednisolone). A white or almost white, hygroscopic, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Prednisolone). It is anhydrous or contains one and one-half molecules of water of hydration. A white to practically white, odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 30 of alcohol, 1 in 50 of acetone, and 1 in 180 of chloroform; soluble in dioxan and in methyl alcohol.

Prednisolone Acetate *(BANM, rINNM)* ⊗

Acetato de prednisolona; Prednisolona, acetato de; Prednisolonacetat; Prednisolon-acetát; Prednisolone, acétate de; Prednisoloni Acetas; Prednisoloniasetaatti; Prednizolon Asetat; Prednizolon-acetát; Prednizolono acetatas; Prednizolonu octan; Преднизолона Ацетат.

Prednisolone 21-acetate.

$C_{23}H_{30}O_6$=402.5

CAS — 52-21-1.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — 8B2807733D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Prednisolone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Prednisolone Acetate). A white to practically white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 120 of alcohol; slightly soluble in acetone and in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Prednisolone Caproate *(rINNM)* ⊗

Caproato de prednisolona; Prednisolona, caproato de; Prednisolone, Caproate de; Prednisolone Hexanoate (BANM); Prednisoloni Caproas; Преднизолона Капроат.

Prednisolone 21-hexanoate.

$C_{27}H_{38}O_6$=458.6

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Prednisolone Hydrogen Succinate

(BANM, rINNM) ⊗

Hidrogenosuccinato de prednisolona; Prednisolona, hidrogenosuccinato de; Prednisolone Hemisuccinate; Prednisolone, Hémisuccinate de; Prednisoloni Hemisuccinas; Преднизолона Гемисукцинат.

Prednisolone 21-(hydrogen succinate).

$C_{25}H_{32}O_8$=460.5

CAS — 2920-86-7.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — G7080T74ON.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Prednisolone Hemisuccinate). A fine, creamy-white, practically odourless, powder with friable lumps. Soluble 1 in 4170 of water, 1 in 6.3 of alcohol, 1 in 1064 of chloroform, and 1 in 248 of ether; soluble in acetone. Store in airtight containers.

Prednisolone Metasulfobenzoate Sodium

(rINNM) ⊗

ATL-2502; Metasulfobenzoato sódico de prednisolona; Natrii Prednisoloni Metasulfobenzoas; Prednisolona, metasulfobenzoato sódico de; Prednisolone Métasulfobenzoate Sodique; Prednisolone Metasulphobenzoate Sodium (BANM); Prednisolone Sodium Metasulphobenzoate; Prednisolone Sodium Metazoate (USAN); R-812; Натрий Метасульфобензоат Преднизолон.

Prednisolone 21-(sodium *m*-sulphobenzoate).

$C_{28}H_{31}NaO_9S$=566.6

CAS — 630-67-1.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — D345THM53T.

Prednisolone Pivalate *(BANM, rINNM)* ⊗

Pivalato de prednisolona; Prednisolona, pivalato de; Prednisolone, Pivalate de; Prednisolone Trimethylacetate; Prednisoloni Pivalas; Prednisolonipivalaatti; Prednisolonpivalat; Prednisolon-pivalát; Prednizolono pivalatas; Prednizolon-pivalát; Prednizolonu piwalan; Преднизолона Пивалат.

Prednisolone 21-pivalate.

$C_{26}H_{36}O_6$=444.6

CAS — 1107-99-9.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — 24W6S37NXU.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Prednisolone Pivalate). A white, or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. Protect from light.

Prednisolone Sodium Phosphate

(BANM, rINNM) ⊗

Fosfato sódico de prednisolona; Natrii Prednisoloni Phosphas; Prednisolona, fosfato sódico de; Prednisolondihydrogenphosphat-Dinatrium; Prednisolone, Phosphate Sodique de; Prednisolonfosfát sodná sůl; Prednisoloni Natrii Phosphas; Prednisoloninatriumfosfaatti; Prednisolonnatriumfosfat; Prednizolon Sodyum Fosfat; Prednizolonnárium-foszfát; Prednizolono natrio fosfatas; Натрия Преднизолона Фосфат.

Prednisolone 21-(disodium orthophosphate).

$C_{21}H_{27}Na_2O_8P$=484.4

CAS — 125-02-0.
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — IV021NXA9J.

NOTE. PRED is a code approved by the BP 2014 for use on single unit doses of eye drops containing prednisolone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Prednisolone Sodium Phosphate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Protect from light.

USP 36: (Prednisolone Sodium Phosphate). A white or slightly yellow friable granules or powder. Is odourless or has a slight odour. Is slightly hygroscopic. Soluble 1 in 4 of water and 1 in 13 of methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone and in dioxan. pH of a 1% solution in water is between 7.5 and 10.5. Store in airtight containers.

Prednisolone Sodium Succinate

(BANM, rINNM) ⊗

Prednisolona, succinato sódico de; Prednisolone Sodium Hemisuccinate; Prednisolone, Succinate Sodique de; Prednisoloni Natrii Succinas; Succinato sódico de prednisolona; Преднизолона Натрия Сукцинат.

11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(sodium succinate).

$C_{25}H_{31}NaO_8$=482.5

CAS — 1715-33-9.
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — 8223RR9DWF.

Pharmacopoeias. *Jpn* and *US* include Prednisolone Sodium Succinate for Injection.

USP 36: (Prednisolone Sodium Succinate for Injection). A creamy white powder with friable lumps, having a slight odour.

Prednisolone Steaglate *(BAN, rINN)* ⊗

Esteaglato de prednisolona; Prednisolona, esteaglato de; Prednisolone, Stéaglate de; Prednisoloni Steaglas; Преднизолона Стеарлат.

Prednisolone 21-stearoylglycolate.

$C_{41}H_{64}O_8$=685.0

CAS — 5060-55-9.
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — OZQ2XN817F.

Prednisolone Tebutate *(BANM, rINNM)* ⊗

Prednisolona, tebutato de; Prednisolone Butylacetate; Prednisolone, Tébutate de; Prednisolone 21-*tert*-Butylacetate; Prednisolone Tertiary-butylacetate; Prednisoloni Tebutas; Tebutato de prednisolona; Преднизолона Тебутат.

Prednisolone 21-(3,3-dimethylbutyrate).

$C_{27}H_{38}O_6.H_2O$=476.6

CAS — 7681-14-3 (anhydrous prednisolone tebutate).
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — 1V7A1U282K.

Pharmacopoeias. In *US.*

USP 36: (Prednisolone Tebutate). A white to slightly yellow, hygroscopic, free-flowing powder, which may show some soft lumps. Is odourless or has not more than a moderate characteristic odour. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in chloroform and in dioxan. Store in airtight containers sealed under nitrogen at a temperature not exceeding 8 degrees.

Uses and Administration

Prednisolone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 5 mg of prednisolone is equivalent in anti-inflammatory activity to about 25 mg of cortisone acetate. In general, prednisolone, either in the form of the free alcohol or in one of the esterified forms, is the drug of choice in the UK for conditions in which routine systemic corticosteroid therapy is indicated (see p. 1597.3), except adrenocortical-deficiency states for which hydrocortisone with supplementary fludrocortisone is preferred. The more potent pituitary-suppressant properties of a glucocorticoid such as dexamethasone may, however, be required for the diagnosis and management of conditions associated with adrenal hyperplasia.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of prednisolone:

- prednisolone acetate 110 mg
- prednisolone caproate 127 mg
- prednisolone hydrogen succinate 128 mg
- prednisolone metasulfobenzoate sodium 157 mg
- prednisolone pivalate 123 mg
- prednisolone sodium phosphate 135 mg
- prednisolone sodium succinate 134 mg
- prednisolone steaglate 190 mg
- prednisolone tebutate 132 mg

However, esterification generally alters potency and compounds with equivalent prednisolone content may not have equivalent clinical effect.

When given **orally** prednisolone is usually used although the acetate, sodium phosphate, and steaglate are also given; the usual dose, expressed in terms of prednisolone, is about 2.5 to 60 mg daily in divided doses, as a single daily dose after breakfast, or as a double dose on alternate days. Alternate-day early-morning dosage regimens produce less suppression of the hypothalamic-pituitary axis but may not always provide adequate control. Enteric-coated tablets of prednisolone are also available (for the view that these should not be used in patients with inflammatory bowel disease, see below).

For **parenteral use** the sodium phosphate ester has been given either intravenously by injection or infusion, or intramuscularly by injection. An aqueous suspension of prednisolone acetate is also used intramuscularly for a prolonged effect, in doses of 25 to 100 mg once or twice weekly. The sodium succinate ester has also been given parenterally.

For **intra-articular injection** suggested doses are 5 to 25 mg of prednisolone acetate. The sodium phosphate and tebutate esters have been given by intra-articular injection, intralesional injection, and by injection into soft tissue.

Prednisolone acetate and prednisolone sodium phosphate are also used in the **topical treatment** of allergic and inflammatory conditions of the eyes or ears, usually as drops containing 0.5 or 1%. Prednisolone has also been used topically as the free alcohol and as the hemisuccinate, pivalate, metasulfobenzoate sodium, and sodium acetate esters.

For **rectal use** prednisolone metasulfobenzoate sodium or prednisolone sodium phosphate are often given. Retention enemas containing the equivalent of 20 mg of prednisolone per 100 mL, rectal foam containing the equivalent of 20 mg of prednisolone per dose, or suppositories containing the equivalent of 5 mg of prednisolone are available. Prednisolone has also been used rectally as the free alcohol and as the acetate and caproate esters.

Other esters of prednisolone that have occasionally been used include the farnesil, palmitate, sodium tetrahydrophthalate, and valeroacetate.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Owing to its less pronounced mineralocorticoid activity prednisolone is less likely than cortisone or hydrocortisone to cause sodium retention, electrolyte imbalance, and oedema. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Breast feeding. Concentrations of prednisone and prednisolone in breast milk from a woman 120 minutes after prednisone 10 mg orally were found to be 26.7 nanograms and 1.6 nanograms/mL respectively.[1] In another 7 women given a single 5-mg oral dose of tritium-labelled prednisolone, a mean of 0.14% of the radioactivity from the dose was recovered per litre of milk in the next 48 to 61 hours.[2] In a study of 3 women, only about 0.025% of a single intravenous dose of prednisolone phosphate 50 mg was found in breast milk over 6 hours.[3] During maintenance therapy with prednisolone in daily doses of 10 to 80 mg in 6 women, the milk to serum concentration ratio of prednisolone ranged from 0.2, for doses of 30 mg or more, to 0.1 for lower doses.[4] The authors estimated that a breast-fed infant would receive less than 0.1% of the maternal dose of prednisolone, and that this would be a negligible addition to the infant's endogenous cortisol production. They also concluded that exposure could be minimised by breast feeding at least 4 hours after the dose.

A review[5] by the UK CSM remarked that prednisolone was distributed into breast milk in small amounts and recommended that infants of mothers receiving 40 mg or more daily should be monitored for signs of adrenal suppression. The American Academy of Pediatrics considers[6] that the use of prednisone or prednisolone is usually compatible with breast feeding.

1. Katz FH, Duncan BE. Entry of prednisone into human milk. *N Engl J Med* 1975; **293:** 1154.
2. McKenzie SA, *et al.* Secretion of prednisolone into breast milk. *Arch Dis Child* 1975; **50:** 894–6.
3. Greenberger PA, *et al.* Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993; **53:** 324–8.
4. Öst L, *et al.* Prednisolone excretion in human milk. *J Pediatr* 1985; **106:** 1008–11.
5. CSM/MCA. Systemic corticosteroids in pregnancy and lactation. *Current Problems* 1998; **24:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 20/06/06)
6. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/04/04)

Hepatic impairment. Conversion of prednisone to prednisolone has been reported to be impaired in chronic active liver disease.[1,2] However, although plasma-prednisolone concentrations were found to be more predictable after prednisolone than prednisone in a group of healthy subjects,[3] no difference was noted in patients with chronic active hepatitis, in whom impaired elimination of prednisolone compensated for any impaired conversion of prednisone. A review of the pharmacokinetics of prednisone and prednisolone[4] concluded that fear of inadequate conversion of prednisone into prednisolone was not justified.

1. Powell LW, Axelsen E. Corticosteroids in liver disease: studies on the biological conversion of prednisone to prednisolone and plasma protein binding. *Gut* 1972; **13:** 690–6.
2. Madsbad S, *et al.* Impaired conversion of prednisone to prednisolone in patients with liver cirrhosis. *Gut* 1980; **21:** 52–6.
3. Davis M, *et al.* Prednisone or prednisolone for the treatment of chronic active hepatitis? A comparison of plasma availability. *Br J Clin Pharmacol* 1978; **5:** 501–5.
4. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990; **19:** 126–46.

Inflammatory bowel disease. Symptoms recurred in a patient with Crohn's disease on changing from conventional to enteric-coated tablets of prednisolone.[1] This was not an isolated occurrence in the authors' unit, and it was advocated that only non-enteric-coated prednisolone tablets should be used in Crohn's disease, and that the enteric-coated form be used with caution in any condition characterised by diarrhoea or a rapid transit time.

1. Beattie RM, Walker-Smith JA. Use of enteric coated prednisolone in Crohn's disease. *Arch Dis Child* 1994; **71:** 282.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prednisolone, when given by most routes, as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. However, NAPOS also suggests that prednisolone rectal ointment and suppositories are possibly porphyrinogenic and as such it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/11/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Prednisolone and prednisone are both readily absorbed from the gastrointestinal tract, but whereas prednisolone already exists in a metabolically active form, prednisone must be converted in the liver to its active metabolite, prednisolone. In general, this conversion is rapid so this difference is of little consequence when seen in the light of intersubject variation in the pharmacokinetics of prednisolone itself; bioavailability also depends on the dissolution rates of the tablet formulations. As discussed under Hepatic Impairment, above, reduced corticosteroid concentrations when giving prednisone to patients with liver disease do not seem to be a problem in practice. After intramuscular doses the sodium phosphate ester of prednisolone is rapidly absorbed whereas the acetate, in the suspension form, is only slowly absorbed.

Peak plasma concentrations of prednisolone occur 1 or 2 hours after an oral dose, and it has a usual plasma half-life of 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food.

Prednisolone is extensively bound to plasma proteins, although less so than hydrocortisone (cortisol). The volume of distribution, and also the clearance are reported to increase with an increase from low to moderate doses; at very high doses, clearance appears to become saturated.

Prednisolone is excreted in the urine as free and conjugated metabolites, with an appreciable proportion of unchanged prednisolone. Prednisolone is largely inactivated as it crosses the placenta; small amounts are excreted in breast milk.

Prednisolone has a biological half-life lasting several hours, intermediate between those of hydrocortisone (cortisol) and the longer-acting glucocorticoids, such as dexamethasone. It is this intermediate duration of action that makes it suitable for the alternate-day dosage regimens which have been found to reduce the risk of adrenocortical insufficiency, yet provide adequate corticosteroid coverage in some disorders.

General reviews of the pharmacokinetics of prednisolone[1,2] and some references to its pharmacokinetics in healthy subjects[3] and in various disease states.[4-8]

1. Begg EJ, *et al*. The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987; **146:** 37–41.
2. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990; **19:** 126–46.
3. Rohatagi S, *et al*. Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997; **37:** 916–25.
4. Berghouse LM, *et al*. Plasma prednisolone levels during intravenous therapy in acute colitis. *Gut* 1982; **23:** 980–3.
5. Shaffer JA, *et al*. Absorption of prednisolone in patients with Crohn's disease. *Gut* 1983; **24:** 182–6.
6. Reece PA, *et al*. Prednisolone protein binding in renal transplant patients. *Br J Clin Pharmacol* 1985; **20:** 159–62.
7. Frey FJ, *et al*. Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. *Clin Pharmacol Ther* 1988; **44:** 510–21.
8. Miller PFW, *et al*. Pharmacokinetics of prednisolone in children with nephrosis. *Arch Dis Child* 1990; **65:** 196–200.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cortizul†; Ultracortenol; ***Austral.***: Panafcortelone; Predmix; Predsol; Predsolone; Redipred; Solone; Sterofrin†; ***Austria***: Aprednislon; Kuhlprednon; Rectopred; Solu-Dacortin; Ultracortenol; ***Belg.***: Pred Forte; Ultracortenol†; ***Braz.***: Oftpred; Oralpred; Pred Fort; Pred Mild; Predsim; Prelone; Ster; ***Canad.***: Diopred; Pediapred; Pred Forte; Pred Mild; ***Chile***: Pred Forte; Predsolets; Sophipren; ***China***: Pred Forte (百力特); ***Cz.***: Linola-H-Fett N†; Predni-POS; Ultracortenol; ***Denm.***: Pred-Clysma; Ultracortenol; ***Fin.***: Di-Adreson-F; Pred Forte; Ultracortenol; ***Fr.***: Hydrocortancyl; Solupred; ***Ger.***: Decortin H; Dermosolon; Dontisolon D; hefasolon; Infectocortikrupp; Inflanefran; Klismacort; Linola-H N; Linola-H-Fett N; Lygal Kopftinktur N; Predni H; Predni-Ophtal; Predni-POS; Predni; Prednigalen; Prednihexal†; Prednisolut; Solu-Decortin H; Ultracortenol; ***Gr.***: Adelcort; Adelone; Deltacortril; Prezolon; Solupred; ***Hong Kong***: Delcorlon†; Desolon†; Dhasolone; Di-Adreson-F†; Panafcortelone; Pred Forte; Pred Mild; Predenema†; Predfoam; Redipred; Ultracortenol†; Xepasone†; ***Hung.***: Di-Adreson-F†; Linola-H N†; Linola-H-Fett N†; Ultracortenol†; ***India***: Acticort; Anesolin; Aquapred; Delsone; Deltacortril; Dispred DPS; Elpred; Emsolone; GB-Pred AC; Hostacortin H; Immupress; Kidpred; Nisolone; Nucort-P; Nucort; Omnacortil; Predone; Wysolone; ***Irl.***: Deltacortril; Pred Forte; Pred Mild; Predenema†; Predfoam†; Prednesol; Predsol; ***Israel***: Danalone; Pred Forte; Ultracortenol†; ***Ital.***: Deltacortenesol; ***Jpn***: Farnerate†; Farnezone; Lidomex; Livimex; Predonema; ***Malaysia***: Dhasolone; Econopred; Nisolon; Pred Forte; Pred Mild; Predon; Zoralone; ***Mex.***: Cetapred; Delta Corti; Delta-Diona; Desnisol; Fisopred; Meticortelone; Pred-NF; Pred; Prednefrin SF; Sophipren; ***Neth.***: Di-Adreson-F; Pred Forte; Ultracortenol; ***Norw.***: Pred-Clysma; Ultracortenol; ***NZ***: Pred Forte; Pred Mild; Redipred; ***Philipp.***: Histacort; Ilocet; Inflastat; Ipredniz; Isolone; Liquipred; Liquisone; Medsone; Optipred; Pred Forte; Predisyr; Prednecort; Romamed; Syrupred†; Vistapred; ***Pol.***: Encortolon; Fenicort; Mecortolon; ***Port.***: Frisolona; Lepicortinolo; Predniocil; Solu-Dacortina; ***Rus.***: Medopred (Медопред); ***S.Afr.***: Aspelone; Capsoid; Lenisolone; Pred Forte; Pred Mild; Preflam; Prelone; ***Singapore***: Delcorlon; Deltasolone; Dhasolone; Econopred; Pred; Prelone-3; SP-Cortil; Walesolone; Xepasone; ***Spain***: Estilsona; Pred Forte; ***Swed.***: Precortalon aquosum; Pred-Clysma; Ultracortenol; ***Switz.***: Hexacortone; Pred Forte; Premandol; Spiricort; Ultracortenol; ***Thai.***: Clinipred; Di-Adreson-F; Fortisone; Inf-Oph; Neosolone; Opredsone; Polypred; Pred Forte; Pred Mild; Predcap; Predi; Predisole; Predman; Prednersone; Prednisil†; Predsomed; Presoga; ***Turk.***: Codelsol†; Codelton†; Deltacortril; Hexacorton; Neocorten; Norsol; Pred Forte; Predni-POS; Prednol; Prozolon; ***UAE***: Gupisone; ***UK***: Deltacortril; Deltastab; Precortisyl; Pred Forte; Predenema†; Predfoam†; Predsol; ***USA***: AsmalPred Plus; Flo-Pred; Key-Pred-SP; Millipred; Omnipred; Orapred; Pediapred; Pred Forte; Pred Mild; Pred-Phosphate; Pred; Predcor; Prednisol†; Prelone; Veripred; ***Venez.***: Meticortelone; Ocupred; Sintisone; Sophipren.

Multi-ingredient Preparations. ***Arg.***: Afluhist Plus; Bactio Rhin Prednisolona; Blefamide; Cortizul†; Delta Tomanil B12; Deltar; Efecoryl Forte; Esodar; Fenipred; Neocortizul†; Oftaldrop; Otidrops; Prednefrin; Prednifarma; Prednifarma; Procto Venart; Relefrina†; Rucaten Prednisolona; Scheriproct; Solupred†; ***Austral.***: Prednefrin; Scheriproct; ***Austria***: Delta-Hadensa; Scheriproct; ***Belg.***: Hemosedan; Predmycin P; Scheriproct; Sofrasolone; ***Braz.***: Colutoide; Fonergin; Isopto Cetapred; Polipred; Predmicin; Rifocort; Rinisone; Zypred; ***Canad.***: Akcide; Blephamide; Dioptimyd; ***Chile***: Banedif Oftalmico con Prednisolona†; Blefamide†; Blefamide; Deltamid; Gemitin con Prednisolona; Scheriproct; Sintoftona; ***China***: Poly Pred (帕利百); ***Cz.***: Alpicort F; Alpicort; Imacort; ***Fin.***: Scheriproct; ***Fr.***: Cortisal; Deliproct; Derinox; Deturgylone; ***Ger.***: Alpicort F; Alpicort; Aquapred†; Bismolan H Corti; Blephamide; Imazol comp; Inflanegent; Leioderm P; Linoladiol-H N; ***Gr.***: Blephamide; Blikosan; Dermol; Hemorrocort; Isopto Cetapred; Precortivit; Scheriproct Neo; ***Hong Kong***: Pilelife†; ***Hung.***: Alpicort F; Alpicort; Aurobin; Prednisolon J†; Rheosolon; ***India***: Atrisolon; Chloramsone; Exopred; Ocepred; Ofelder-PA; Oflacin-P; Perfocyn†; ***Indon.***: Borraginol-S; Chloramphecort-H; Klorfeson; ***Irl.***: Predmycin-P; Scheriproct; ***Israel***: Aflumycin; Blephamide; Threolone; ***Ital.***: Bio-Delta Cortilen; Deltamidrina; Solprene; ***Mex.***: Artrilan†; Blefamide-F; Blefamide; Dartrizon; Deltamid; Deltron; Isopto Cetapred; Obrypre; Otalgan; Premid; Scheriproct; ***Norw.***: Scheriproct; ***NZ***: Blephamide†; ***Philipp.***: Cetapred†; Exopred; Histacort; Isopto Cetapred†; Lonace; Predmycin-P; Sterilid-V; ***Pol.***: Alpicort E; Alpicort; Mecortolon N; ***Port.***: Anacal; Conjunctilone-S; Meocil; Neo-Davisolona; Predniftalmina; Scheriproct; ***Rus.***: Aurobin (Ауробин); Dermosolon (Дермозолон); Gyterna (Гитерна); Hepatrombin H (Гепатромбин Г); Hepazolon (Гепазолон); Insanovin (Инсановин); Tergynan (Тержинан); ***S.Afr.***: Scheriproct; ***Singapore***: Blephamide†; Predmycin-P†; ***Spain***: Alergical; Antigrietun; Kanapomada†; Nasopomada†; Poly Pred; Rinobanedif; Rinovel†; Ruscus; Teolixir Compositum†; ***Swed.***: Scheriproct N; ***Switz.***: Alpicort F; Blephamide; Imacort; Locaseptil-Neo; Mycinopred†; Scheriproct; ***Thai.***: Denson†; Exopred; Farakil; Levoptin; Mysolone-N; Neozolone; Pred Oph; Predmycin P; Prednisil-N†; Prednisolone-N; Unipred; ***Turk.***: Blephamide; Kortisetin; Otimisin; Prednol-A; Suprenil; ***UK***: Predsol-N†; Scheriproct; ***Ukr.***: Aurobin (Ауробин); Dermosolon (Дермозолон)†; Hepathrombin H (Гепатромбин Г); Imacort (Имакорт); Neotrizol (Неотризол); Prednicarb (Предникарб); Tergynan (Тержинан); ***USA***: Blephamide; Metimyd†; Poly-Pred†; Pred G; Sulfamide; Vasocidin; Vasocine; ***Venez.***: Clorasona; Permucal; Scheriproct; Sulfacort.

Homoeopathic Preparations. ***Ger.***: NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Prednisolone Tablets; Prednisolone Acetate Injection; Prednisolone Enema; Prednisolone Sodium Phosphate Ear Drops; Prednisolone Sodium Phosphate Eye Drops; Prednisolone Tablets;

USP 36: Chloramphenicol and Prednisolone Ophthalmic Ointment; Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Acetate Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Prednisolone Acetate Injectable Suspension; Prednisolone Acetate Ophthalmic Suspension; Prednisolone Cream; Prednisolone Sodium Phosphate Injection; Prednisolone Sodium Phosphate Ophthalmic Solution; Prednisolone Sodium Succinate for Injection; Prednisolone Syrup; Prednisolone Tablets; Prednisolone Tebutate Injectable Suspension; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Suspension.

Prednisone *(BAN, rINN)* ⊗

1,2-Dehydrocortisone; Deltacortisone; Deltadehydrocortisone; Metacortandracin; NSC-10023; Prednison; Prednisona; Prednisoni; Prednisonum; Prednizon; Prednizonas; Преднизон.

17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione.

$C_{21}H_{26}O_5$=358.4

CAS — 53-03-2.

ATC — A07EA03; H02AB07.

ATC Vet — QA07EA03; QH02AB07.

UNII — V80R961HZT.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows the anhydrous form or the monohydrate.

Ph. Eur. 8: (Prednisone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Prednisone). It contains one molecule of water of hydration or is anhydrous. A white to practically white, odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 150 of alcohol and 1 in 200 of chloroform; slightly soluble in dioxan and in methyl alcohol.

Prednisone Acetate *(BANM, rINNM)* ⊗

Acetato de prednisona; Prednisona, acetato de; Prednisone, Acétate de; Prednisoni Acetas; Prednizonu octan; Преднизона Ацетат.

Prednisone 21-acetate.

$C_{23}H_{28}O_6$=400.5

CAS — 125-10-0.

ATC — A07EA03; H02AB07.

ATC Vet — QA07EA03; QH02AB07.

UNII — OU93QEL83U.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Prednisone is a biologically inert corticosteroid that is converted in the liver to the mainly glucocorticoid corticosteroid prednisolone. It has the same chemical relationship to prednisolone as cortisone has to hydrocortisone. The indications and dosage of prednisone for oral use are exactly the same as those for prednisolone (see p. 1646.1, and the chapter introduction, p. 1597.3).

In the UK prednisolone has historically been preferred to prednisone, on the grounds that it does not require conversion to the active substance, but in practice this is rarely significant (see Hepatic Impairment, under Prednisolone, p. 1646.3), and in some countries, such as the USA, prednisone is the drug of choice for many of the conditions in which routine systemic corticosteroid therapy is indicated.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prednisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Meticorten; Metilpres; Prednipirine; ***Austral.***: Panafcort; Predsone; Sone; ***Austria***: Lodotra; ***Belg.***: Lodotra; ***Braz.***: Artinizona; Becortem; Corticorten; Flamacorten; Meticorten; Precortil; Predison†; Prednax; Prednis; Predson; Predval; ***Canad.***: Winpred; ***Chile***: Bersen; Cortiprex; Meticorten; Procion; ***Cz.***: Rectodelt; ***Denm.***: Lodotra; ***Fin.***: Lodotra; ***Fr.***: Cortancyl; ***Ger.***: Decortin; Lodotra; Predni Tablinen; Rectodelt; ***Gr.***: Chrocort; ***Hung.***: Rectodelt; ***Indon.***: Inflason; Nufapredson; Pehacort; ***Israel***: Lodotra; ***Ital.***: Deltacortene; Lodotra; ***Mex.***: Artrinol-On; Ednapron†; Losinon; Meprosona-F; Meticorten; Norapred; Prednidib; ***Neth.***: Lodotra; ***Norw.***: Lodotra; ***Philipp.***: Biosone; Bioster†; Endosone; Oracort†; Orasone; Pred; Predoral; Predsone; Prolix; Qualisone; Steerometz†; ***Pol.***: Encorton; Lodotra; ***Port.***: Lodotra; Meticorten; Nocasio†; ***S.Afr.***: Meticorten; Panafcort; Predeltin†; Pulmison; Trolic; ***Spain***: Dacortin; ***Swed.***: Deltison; Lodotra; ***Switz.***: Lodotra; ***UK***: Lodotra; ***Ukr.***: Rectodelt (Ректодельт); ***USA***: Deltasone; Liquid Pred; Meticorten; Panasol-S; Rayos; Sterapred†; ***Venez.***: Meticorten.

Multi-ingredient Preparations. ***Arg.***: Peganix; ***Austria***: Fluorex Plus; Oleomycetin-Prednison†; ***Chile***: Alerzona†; ***Mex.***: Barigesic†; Pre Clor; ***Spain***: Coliriocilina Prednisona†; Fiacin†; Kanafosal Predni†; Prednisona Neomicina.

Pharmacopoeial Preparations

USP 36: Prednisone Oral Solution; Prednisone Tablets.

Rimexolone *(BAN, USAN, rINN)* ⊗

Org-6216; Rimeksolon; Rimeksoloni; Rimexolon; Rimexolona; Rimexolonum; Trimexolone; Римексолон.

11β-Hydroxy-16α,17α-dimethyl-17β-propionylandrosta-1,4-dien-3-one.

$C_{24}H_{34}O_3$=370.5

CAS — 49697-38-3.

ATC — H02AB12; S01BA13.

ATC Vet — QH02AB12; QS01BA13.

UNII — O7M2E4264D.

Pharmacopoeias. In *US.*

USP 36: (Rimexolone). A white to off-white powder. Freely soluble in chloroform; sparingly soluble in methyl alcohol.

Profile

Rimexolone is a corticosteroid applied topically to the eye for its glucocorticoid activity (see p. 1597.1) in the treatment of inflammatory eye disorders including uveitis (p. 1615.1) and postoperative inflammation. It is used as a 1% suspension.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rimexolone as not

porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Vexol; ***Belg.***: Vexolon; ***Braz.***: Vexol; ***Canad.***: Vexol; ***Denm.***: Vexol; ***Fin.***: Vexol; ***Fr.***: Vexol; ***Ger.***: Vexol; ***Gr.***: Vexol; ***Hong Kong***: Vexol; ***Irl.***: Vexol; ***Ital.***: Vexol; ***Mex.***: Vexol; ***Neth.***: Vexol; ***Norw.***: Vexol; ***NZ***: Vexol; ***Port.***: Vexol; ***Singapore***: Vexol; ***Spain***: Vexol; ***Swed.***: Vexol; ***Switz.***: Vexol; ***Turk.***: Vexol; ***UK***: Vexol; ***USA***: Vexol.

Pharmacopoeial Preparations
USP 36: Rimexolone Ophthalmic Suspension.

Suprarenal Cortex ⊗

Corteza suprarrenal.

Profile

Suprarenal cortex contains a number of steroid compounds the most active of which are corticosterone, dehydrocorticosterone, hydrocortisone, cortisone, and aldosterone. It has been prepared from the adrenal glands of oxen. Suprarenal cortex was formerly used intramuscularly for the treatment of adrenocortical insufficiency but it has been superseded by hydrocortisone and other corticosteroids (see p. 1600.2).

Suprarenal cortex is an ingredient of a wide range of preparations, often with other organ extracts or vitamins, promoted for indications ranging from asthenia to liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Mobilat; ***Belg.***: Mobilat; ***Braz.***: Mobilat; ***Chile***: Mobilat†; ***Cz.***: Mobilat; ***Fin.***: Mobilat; ***Philipp.***: Mobilat; ***Pol.***: Mobilat; ***Thai.***: Mobilat.

Homoeopathic Preparations. ***Neth.***: Chavita 2; Emvita 6; Emvita 7.

Tetracosactide *(BAN, rINN)* ⊗

Cosintropina; Cosyntropin (USAN); Tetracosactid; Tetracosactida; Tétracosactide; Tetracosactido; Tetracosactidum; Tetracosactrin; Tetracosactrina; Tetrakosaktid; Tetrakosaktidi; Tetrakosaktrin; Tetrakozaktidas; Тетракозактид.

Corticotrophin-(1–24)-tetracosapeptide; Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro.

$C_{136}H_{210}N_{40}O_{31}S$=2933.5

CAS — 16960-16-0 (tetracosactide); 22633-88-1 (tetracosactide hexa-acetate); 60189-34-6 (tetracosactide x acetate).

ATC — H01AA02.

ATC Vet — QH01AA02.

UNII — 72YY86EA29.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tetracosactide). A synthetic tetracosapeptide in which the sequence of amino acids is the same as that of the first 24 residues of human corticotropin. It is available as an acetate. It increases the rate at which corticoid hormones are secreted by the adrenal gland. By convention, 1 microgram of tetracosactide is equivalent to 1 unit of tetracosactide. A white or yellow, amorphous powder. Sparingly soluble in water. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Tetracosactide is a synthetic polypeptide with general properties similar to those of corticotropin (p. 1628.3). Tetracosactide is used diagnostically to investigate adrenocortical insufficiency (p. 1600.2).

Although tetracosactide, like corticotropin, has also been used therapeutically for most of the conditions in which systemic corticosteroid therapy is indicated, it is now rarely used for such indications.

Tetracosactide is usually used in the form of the acetate although doses are often expressed in terms of tetracosactide itself.

For *diagnostic purposes* tetracosactide acetate is used intramuscularly or intravenously as a plain injection in the first instance then, if results are inconclusive, intramuscularly as a long-acting depot injection. The initial test using the plain injection is based on the measurement of plasma-cortisol concentrations immediately before and exactly 30 minutes after an intramuscular or intravenous injection equivalent to 250 micrograms of tetracosactide; adrenocortical function may be regarded as normal if there is a rise in the cortisol concentration of at least 200 nanomoles/litre (70 micrograms/litre). In some cases the dose may be given by intravenous infusion over 6 hours to provide a greater stimulus of the adrenal glands, with cortisol concentrations measured before and at the end of the infusion. A low-dose test using 1 microgram has also been used (see Diagnostic Use, below).

If the results of this test are equivocal, or where functional reserve of the adrenal cortex is to be determined, the long-acting depot preparation may be used, the dose being 1 mg of tetracosactide acetate given intramuscularly. Adrenocortical function is regarded as normal if plasma-cortisol concentrations have steadily increased to 1000 to 1800 nanomoles/litre 5 hours after the injection. A 3-day test, for example with 1 mg of the depot preparation given each morning, is also used to differentiate between primary and secondary adrenocortical insufficiency; this is preceded on the first day and followed on the fourth day by the test using the plain injection. A marked improvement in the second assessment suggests secondary adrenocortical insufficiency.

For *therapeutic purposes* tetracosactide acetate has been given by intramuscular injection as the long-acting depot preparation. The usual initial dose of tetracosactide acetate has been 1 mg daily (or 1 mg every 12 hours in acute cases), reduced after the acute symptoms have been controlled to 0.5 to 1 mg every 2 or 3 days or 1 mg weekly.

For doses used in children, see below.

Administration in children. For diagnostic use, children may be given an intravenous or intramuscular dose of the plain injection of tetracosactide 145 micrograms/m^2, to a maximum of 250 micrograms. The *BNFC* also includes a low-dose test of 300 nanograms/m^2.

Tetracosactide acetate in a long-acting depot preparation has been given intramuscularly for therapeutic use in conditions requiring systemic corticosteroid therapy. For children aged 3 to 5 years old, an initial dose of 250 to 500 micrograms has been given daily, and then every 2 to 8 days for maintenance. A dose of 0.25 to 1 mg has been used similarly in children aged 5 to 12 years.

Tetracosactide has also been used to manage infantile spasms (see Epilepsy, p. 506.1). For children aged 1 month and older, the *BNFC* suggests using the depot preparation in a dose of 500 micrograms by intramuscular injection, given on alternate days and adjusted according to response.

Diagnostic use. Tetracosactide is widely used in the diagnosis of adrenal insufficiency (p. 1600.2). It is usually given by intramuscular or intravenous injection in a dose of 250 micrograms, with plasma-cortisol concentrations measured before and 30 minutes after the injection. The sensitivity of this test has been questioned, as such a high dose may produce a cortisol response in patients with partial adrenal gland atrophy, resulting in a missed diagnosis of secondary adrenal insufficiency. A low-dose test using an intravenous dose of 1 microgram has been proposed as a more sensitive test.

A meta-analysis[1] concluded that high- and low-dose tests performed similarly in the diagnosis of secondary adrenal insufficiency. However, the high-dose test was favoured because of the lack of a commercially available low-dose preparation. A later review[2] advocated the use of the low-dose test for diagnosing secondary insufficiency, but recommended the high-dose test for diagnosis of suspected primary adrenal insufficiency. Both considered that more study was needed of the use of these tests in critically ill patients.[1,2]

1. Dorin RI, *et al.* Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; **139:** 194–204.
2. Magnotti M, Shimshi M. Diagnosing adrenal insufficiency: which test is best—the 1-microgram or the 250-microgram cosyntropin stimulation test? *Endocr Pract* 2008; **14:** 233–8.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or, more recently, tetracosactide.[1-5] Intramuscular injection and intravenous infusion have both been used, but a controlled study[6] in 18 women found that a single intramuscular dose of tetracosactide 1 mg was no more beneficial than sodium chloride 0.9%. As discussed on p. 1979.1, many patients respond to conservative measures.

1. Collier BB. Treatment for post dural puncture headache. *Br J Anaesth* 1994; **72:** 366–7.
2. Foster P. ACTH treatment for post-lumbar puncture headache. *Br J Anaesth* 1994; **73:** 429.
3. Kshatri AM, Foster PA. Adrenocorticotropic hormone infusion as a novel treatment for postdural puncture headache. *Reg Anesth* 1997; **22:** 432–4.
4. Carter BL, Pasupuleti R. Use of intravenous cosyntropin in the treatment of postdural puncture headache. *Anesthesiology* 2000; **92:** 272–4.
5. Cánovas L, *et al.* Use of intravenous tetracosactin in the treatment of postdural puncture headache: our experience in forty cases. *Anesth Analg* 2002; **94:** 1369.
6. Rucklidge MWM, *et al.* Synacthen Depot for the treatment of postdural puncture headache. *Anaesthesia* 2004; **59:** 138–41.

Adverse Effects, Withdrawal, and Precautions

As for Corticotropin, p. 1629.1. Although hypersensitivity reactions, including anaphylaxis, may occur with the use of tetracosactide, it is reported to be less immunogenic than corticotropin; US licensed product information suggests that patients with a history of hypersensitivity to corticotropin may tolerate tetracosactide. In the UK, however, previous hypersensitivity to corticotropin or to tetracosactide is considered a contra-indication to tetracosactide use. Tetracosactide is also contra-indicated in patients with a history of allergic disorders such as asthma.

Since hypersensitivity reactions may occur up to 1 hour after injection, sufficient time should be allowed for recovery after use at the hospital or surgery. Self-administration is not recommended.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetracosactide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Corticosteroids, p. 1619.3.

Pharmacokinetics

On intravenous injection tetracosactide has triphasic pharmacokinetics. It is rapidly eliminated from plasma, mostly by distribution to the adrenal glands and kidneys. It is metabolised by serum endopeptidases into inactive oligopeptides, and then by aminopeptidases into free amino acids. Most of a dose is excreted in urine within 24 hours. The terminal half-life of tetracosactide is about 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Synacthen; ***Austria***: Synacthen; ***Belg.***: Synacthen; ***Canad.***: Cortrosyn; Synacthen Depot; ***Chile***: Synacthen; ***Denm.***: Synacthen; ***Fr.***: Synacthene; ***Ger.***: Synacthen Depot; Synacthen; ***Gr.***: Cortrosyn; Nuvacthen; Synacthene; ***Hong Kong***: Cortrosyn†; ***Irl.***: Synacthen; ***Israel***: Synacthen; ***Ital.***: Synacthen; ***Neth.***: Synacthen; ***NZ***: Synacthen; ***Port.***: Synacthen; ***Rus.***: Synacthen (Синактен)†; Synacthen Depot (Синактен Депо); ***S.Afr.***: Synacthen Depot; ***Spain***: Nuvacthen Depot; ***Swed.***: Synacthen; ***Switz.***: Synacthen Depot; Synacthen; ***Thai.***: Cortrosyn; ***Turk.***: Synacthen Depot; ***UK***: Synacthen Depot; Synacthen; ***USA***: Cortrosyn; ***Venez.***: Synacthen.

Pharmacopoeial Preparations
BP 2014: Tetracosactide Injection; Tetracosactide Zinc Injection.

Tixocortol Pivalate *(BANM, USAN, rINNM)* ⊗

JO-1016; Pivalato de tixocortol; Tixocortol, Pivalate de; Tixocortol, pivalato de; Tixocortoli Pivalas; Тиксокортола Пивалат.

11β,17α-Dihydroxy-21-mercaptopregn-4-ene-3,20-dione 21-pivalate.

$C_{26}H_{38}O_5S$=462.6

CAS — 61951-99-3 (tixocortol); 55560-96-8 (tixocortol pivalate).

ATC — A07EA05; R01AD07.

ATC Vet — QA07EA05; QR01AD07.

UNII — 6K28E35M3B.

Profile

Tixocortol pivalate is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It is used as buccal, nasal, throat, and rectal preparations. It is reported to undergo rapid first-pass metabolism, primarily in the liver, and to have minimal systemic effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Pivalone; ***Singapore***: Pivalone; ***Switz.***: Pivalone†.

Multi-ingredient Preparations. ***Fr.***: Thiovalone; ***Switz.***: Pivalone compositum.

Triamcinolone *(BAN, rINN)* ⊗

9α-Fluoro-16α-hydroxyprednisolone; Fluoxiprednisolonum; Triamcinolon; Triamcinolona; Triamcinolonas; Triamcinolonum; Triamcynolon; Triamsinoloni; Триамцинолон.

9α-Fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione.
$C_{21}H_{27}FO_6$=394.4
CAS — 124-94-7.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QD07XB02; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — 1ZK20VI6TY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Triamcinolone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water and in dichloromethane; slightly soluble in methyl alcohol. Protect from light.

USP 36: (Triamcinolone). A white or practically white, odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol.

Triamcinolone Acetonide *(BANM, rINNM)* ⊗

Acetónido de triamcinolona; Triamcinolon acetonid; Triamcinolona, acetónido de; Triamcinolonacetonid; Triamcinolone, Acétonide de; Triamcinoloni acetonidum; Triamcinolono acetonidas; Triamcynolonu acetonid; Triamsinolon Asetonid; Triamsinoloniasetonidi; Триамцинолона Ацетонид.
9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.
$C_{24}H_{31}FO_6$=434.5
CAS — 76-25-5.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — F446C597KA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Chin. also includes Triamcinolone Acetonide Acetate.

Ph. Eur. 8: (Triamcinolone Acetonide). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Triamcinolone Acetonide). A white to cream-coloured crystalline powder, having not more than a slight odour. Practically insoluble in water; sparingly soluble in dehydrated alcohol, in chloroform, and in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Triamcinolone Acetonide Sodium Phosphate *(BANM, USAN, rINNM)* ⊗

CL-61965; CL-106359; Fosfato de sodio del acetónido de triamcinolona; Triamcinolona, acetónido de, fosfato de sodio del; Triamcinolone Acétonide, Phosphate Sodique de; Triamcinoloni Acetonidi Natrici Phosphas; Триамцинолона Ацетонида Натрия Фосфат.
Triamcinolone acetonide 21-disodium phosphate.
$C_{24}H_{30}FNa_2O_9P$=558.4
CAS — 1997-15-5.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

Triamcinolone Diacetate *(BANM, rINNM)* ⊗

Diacetato de triamcinolona; Triamcinolona, diacetato de; Triamcinolone, Diacetate de; Triamcinoloni Diacetas; Триамцинолона Диацетат.
Triamcinolone 16α,21-diacetate.
$C_{25}H_{31}FO_8$=478.5
CAS — 67-78-7.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — A73MM2Q32P.

Pharmacopoeias. In *US*.

USP 36: (Triamcinolone Diacetate). A fine, white to off-white, crystalline powder, having not more than a slight odour. Practically insoluble in water; soluble 1 in 13 of alcohol, 1 in 80 of chloroform, and 1 in 40 of methyl alcohol; slightly soluble in ether.

Triamcinolone Hexacetonide

(BAN, USAN, rINNM) ⊗

CL-34433; Hexacetónido de triamcinolona; TATBA; Triamcinolona, hexacetónido de; Triamcinolone Acetonide 21-(3,3-Dimethylbutyrate); Triamcinolone, Hexacétonide de; Triamcinolon-hexacetonid; Triamcinolonhexacetonid; Triamcinoloni Hexacetonidum; Triamcinolono heksacetonidas; Triamsinoloniheksasetonidi; Триамцинолона Гексацетонид.
9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-(3,3-dimethylbutyrate).
$C_{30}H_{41}FO_7$=532.6
CAS — 5611-51-8.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — I7GT1U99Y9.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Triamcinolone Hexacetonide). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol. Protect from light.

USP 36: (Triamcinolone Hexacetonide). A white to cream-coloured powder. Practically insoluble in water; soluble in chloroform; slightly soluble in methyl alcohol.

Uses and Administration

Triamcinolone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 4 mg of triamcinolone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (see p. 1597.3), except adrenocortical insufficiency for which hydrocortisone with supplementary fludrocortisone is preferred.

The dose may be expressed in terms of the base, and the following are each equivalent to about 10 mg of triamcinolone:
- triamcinolone acetonide 11 mg
- triamcinolone acetonide sodium phosphate 14 mg
- triamcinolone diacetate 12 mg
- triamcinolone hexacetonide 14 mg

However, esterification generally alters potency and compounds with equivalent triamcinolone content may not have equivalent clinical effect.

For **oral dosage** triamcinolone is used in doses ranging from 4 to 48 mg daily.

For parenteral use the acetonide ester is given in doses of about 40 to 80 mg by **intramuscular injection**. It is usually given as a suspension to provide a prolonged systemic effect. A single dose of 40 to 100 mg of the acetonide may provide symptomatic control throughout the pollen season for hay fever sufferers (but see Rhinitis, p. 1650.1). The diacetate ester has also been given intramuscularly.

For **intra-articular injection** triamcinolone acetonide, diacetate, and hexacetonide have all been used. Doses for these esters have typically been in the range of 2.5 to 40 mg, depending upon the size of the joint injected.

For **topical application** in the treatment of various skin disorders triamcinolone acetonide is used, usually in creams, lotions, or ointments containing 0.1% although concentrations ranging from 0.025 to 0.5% have been employed. Several topical preparations also contain an antimicrobial drug. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Triamcinolone esters are also commonly used by **intralesional** or **intradermal injection** in the treatment of some inflammatory skin disorders such as keloids. Suggested doses for the various esters have been:
- acetonide: 1 to 3 mg per site with no more than 5 mg injected into any one site or not more than 30 mg in total if several sites of injection are used
- diacetate: a total of 5 to 25 mg, injected as no more than 100 micrograms/cm² of skin surface area
- hexacetonide: up to 500 micrograms per square inch (about 80 micrograms/cm²) of affected skin

In the treatment of allergic rhinitis (p. 1650.1) triamcinolone acetonide may be given by a **nasal spray** in a usual initial dose of 2 sprays (110 micrograms) into each nostril once daily, reduced to 1 spray (55 micrograms) into each nostril once daily when control is achieved.

Preservative-free suspensions of triamcinolone acetonide are available for **intravitreal injection** (see Eye Disorders, below). A dose of 4 mg is used for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions that are unresponsive to topical corticosteroids. Further doses may be given as needed during the course of treatment. A dose of 1 to 4 mg may be used for visualisation during vitrectomy.

For doses used in children, see below.

Other esters of triamcinolone that have occasionally been used include the acetonide dipotassium phosphate, acetonide hemisuccinate, aminobenzal benzamidoisobutyrate, and benetonide. Flupamesone (triamcinolone acetonide metembonate) has also been used.

Administration in children. Triamcinolone acetonide and hexacetonide have been used for **intra-articular injection** in children. Although unlicensed in the UK for use in children under 6 years of age, the *BNFC* includes doses for injection into larger joints in those aged from 1 to 18 years. A dose of triamcinolone acetonide 2 mg/kg may be used, to a usual maximum of 40 mg, or triamcinolone hexacetonide 1 mg/kg to a usual maximum of 20 mg. However, higher doses have been used. Treatment may be repeated for relapse if necessary, although each joint should usually be treated no more than 3 or 4 times in a year.

In the treatment of allergic rhinitis triamcinolone acetonide may be given by a **nasal spray**. Children aged 6 to 12 years may be given 1 spray (55 micrograms) into each nostril once daily. This dose may be increased to 2 sprays (110 micrograms) into each nostril once daily for control of severe symptoms. The lowest effective dose should be used once symptoms have been controlled. In children aged from 2 to 5 years, the recommended and maximum dose is 55 micrograms into each nostril once daily.

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

Intramuscular triamcinolone acetonide has been reported to be more effective than oral low-dose prednisone in controlling exacerbations in patients with severe, chronic, life-threatening asthma,[1] although this conclusion is controversial.[2-7]

1. Ogirala RG, *et al*. High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. *N Engl J Med* 1991; **324:** 589–9. Correction. *ibid.*; 1380.
2. Salmeron S, *et al*. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 429–30.
3. Nicholas SS. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 430.
4. Kidney JC, *et al*. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 430.
5. Capewell S, McLeod DT. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 430.
6. Ogirala RG, *et al*. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 431.
7. Capewell S, McLeod D. Injected corticosteroids in refractory asthma. *Lancet* 1991; **338:** 1075–6.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1).

Eye disorders. Intravitreal injection of triamcinolone acetonide has been tried in the management of eye disorders characterised by oedema and the abnormal proliferation of intra-ocular cells. Promising results have been reported in diabetic macular oedema,[1,2] cystoid macular oedema, and oedema associated with retinal vein occlusion.[2-5] It has also been used in age-related macular degeneration (p. 880.2; better results being seen when it is combined with photodynamic therapy), in proliferative diabetic retinopathy, and in the management of some forms of cataract and non-infectious uveitis.[2,3] Complications of treatment may include raised intra-ocular pressure (IOP)[6] and both infectious and non-infectious endophthalmitis.[2] Patients with a baseline IOP greater than 16 mmHg or receiving a second injection should be carefully monitored, as they may be at greater risk of an increase; monitoring should continue beyond 6 months.[6]

Dissolved drugs are not retained in the eye for prolonged periods, and early studies and off-label treatment have used injectable suspensions to achieve long-lasting concentrations of triamcinolone in the vitreous body.[7] However, these commercial products were intended for intramuscular and intra-articular use and not licensed for intravitreal injection, and there has been concern about the potential ocular toxicity of their preservative, benzyl alcohol.[2,7] Various techniques, such as sedimentation, centrifugation, and filtration, have been used extemporaneously to reduce the benzyl alcohol content of such products, but the quantity of triamcinolone in the final preparation may be altered depending on the technique used.[8] More recently, preservative-free products have been licensed in the USA for intravitreal use (*Triesence; Alcon, USA* and *Trivaris; Allergan, USA*—see Uses and Administration, above).

1. Ip MS. Intravitreal injection of triamcinolone: an emerging treatment for diabetic macular edema. *Diabetes Care* 2004; **27:** 1794–7.
2. Jonas JB. Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand* 2005; **83:** 645–63.

3. van Kooij B, *et al*. The pros and cons of intravitreal triamcinolone injections for uveitis and inflammatory cystoid macular edema. *Ocul Immunol Inflamm* 2006; **14:** 73–85.
4. Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. *Ophthalmic Res* 2006; **38:** 218–45.
5. Sivaprasad S, *et al*. Intravitreal steroids in the management of macular oedema. *Acta Ophthalmol Scand* 2006; **84:** 722–33.
6. Rhee DJ, *et al*. Intraocular pressure alterations following intravitreal triamcinolone acetonide. *Br J Ophthalmol* 2006; **90:** 999–1003.
7. Jonas JB. Effects of triamcinolone acetonide injections with and without preservative. *Br J Ophthalmol* 2007; **91:** 1099–1101.
8. García-Arumí J, *et al*. Comparison of different techniques for purification of triamcinolone acetonide suspension for intravitreal use. *Br J Ophthalmol* 2005; **89:** 1112–14.

Haemangioma. For reference to the use of a mixture of triamcinolone and betamethasone for intralesional injection of haemangioma, see p. 1605.3.

Rhinitis. Triamcinolone is used[1,2] in the management of allergic rhinitis (p. 612.1). However, the use of depot injections of triamcinolone to manage seasonal allergic rhinitis has been deemed unacceptable by some.[3]

1. Jeal W, Faulds D. Triamcinolone acetonide: a review of its pharmacological properties and therapeutic efficacy in the management of allergic rhinitis. *Drugs* 1997; **53:** 257–80.
2. Gawchik SM, Saccar CL. A risk-benefit assessment of intranasal triamcinolone acetonide in allergic rhinitis. *Drug Safety* 2000; **23:** 309–22.
3. Anonymous. Any place for depot triamcinolone in hay fever? *Drug Ther Bull* 1999; **37:** 17–18.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively). High doses of triamcinolone may have a greater tendency to produce proximal myopathy. Its effects on sodium and water retention are less than those of prednisolone.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Effects on the eye. For complications and precautions associated with intravitreal use of triamcinolone see under Eye Disorders, p. 1649.3.

Hypersensitivity. Local reactions to topical triamcinolone preparations have been attributed to the content of ethylenediamine.[1,2] However, there have also been reports of anaphylactic shock after intra-articular[3] or intramuscular[4] injection of triamcinolone acetonide.

1. Wright S, Harman RRM. Ethylenediamine and piperazine sensitivity. *BMJ* 1983; **287:** 463–4.
2. Freeman S. Allergy to Kenacomb cream. *Med J Aust* 1986; **145:** 361.
3. Larsson L. Anaphylactic shock after ia administration of triamcinolone acetonide in a 35-year-old female. *Scand J Rheumatol* 1989; **18:** 441–2.
4. Gonzalo FE, *et al*. Anaphylactic shock caused by triamcinolone acetonide. *Ann Pharmacother* 1994; **28:** 1310.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies triamcinolone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Triamcinolone is reported to have a half-life in plasma of about 2 to over 5 hours. It is bound to plasma albumin to a much smaller extent than hydrocortisone.

The acetonide, diacetate, and hexacetonide esters of triamcinolone are only very slowly absorbed from injection sites.

Triamcinolone crosses the placenta.

References to the pharmacokinetics of triamcinolone and its esters.

1. Möllmann H, *et al*. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985; **29:** 85–9.
2. Derendorf H, *et al*. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. *Clin Pharmacol Ther* 1986; **39:** 313–17.
3. Derendorf H, *et al*. Pharmacokinetics of triamcinolone acetonide after intravenous, oral, and inhaled administration. *J Clin Pharmacol* 1995; **35:** 302–5.
4. Argenti D, *et al*. A mass balance study to evaluate the biotransformation and excretion of [^{14}C]-triamcinolone acetonide following oral administration. *J Clin Pharmacol* 2000; **40:** 770–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fortcinolona; Glytop; Kenacort-A; Kenacort; Ledercort; Nasacort; Triamciterap; Triampoen; ***Austral.***: Aristocort; Kenacort-A; Kenalog in Orabase; Telnase; Tricortone; ***Austria***: Nasacort; Solu-Volon A; Volon A; Volon; ***Belg.***: Albicort; Delphi; Kenacort-A; ***Braz.***: Airclin; Azmacort†; Nasacort; Omcilon-A Orabase; Oncicrem-A; Oncileg A; Theracort; Triancil; ***Canad.***: Aristocort; Aristospan; Kenalog; Nasacort; Oracort; Triaderm; ***Chile***: Kenacort-A†; Nasacort; ***China***: A Sai Song (阿赛松); Kenacort-A (康宁克通-A); Kenalog (康宁乐); Nincort (宁康); Xing Rui Ke (星瑞克); Zhen De (珍德); ***Cz.***: Nasacort†; Triamcinolon; ***Denm.***: Kenalog; Lederspan; Nasacort; ***Fin.***: Aftab; Kenacort-T†; Lederspan; Nasacort; ***Fr.***: Hexatrione; Kenacort; Nasacort; ***Ger.***: Aftab; Delphicort; Kortikoid-ratiopharm; Lederlon; Linolacort Triam; Nasacort†; Polcortolon N; Rhinisan; Triam; TriamCreme; Triamgalen; Triamhexal†; TriamSalbe†; Volon A; Volon; Volonimat N; Volonimat; ***Gr.***: Forlion; Kenacort-A; Kenacort; Nasacort; Nasatrim; Senciderm; Triamcinal; ***Hong Kong***: Aftach; Aristo; Dermacort; Kenacort-A†; Kenalog in Orabase†; Nasacort; Oramedy; Shincort; Syncort†; Triam†; ***Hung.***: Ftorocort; Kenalog; Polcortolone; ***India***: Av Cort; Avcort; Comcort; Cortrima; D-Cort; Hicort; Hylone; Hynot; Kenacort; Ledercort; Nixcort; Tess; Tricort; ***Indon.***: Amtocort; Flamicort; Kenacort-A; Kenacort; Kenalog in Orabase; Ketricin; Nasacort; Sinocort; Triamcort; Tridez†; Trilac; Trinolon; ***Irl.***: Adcortyl in Orabase†; Adcortyl; Kenalog†; Nasacort; ***Israel***: Oracort; Sterocort; Steronase Aq; ***Ital.***: Aftab; Kenacort; Nasacort; Triamvirgi; ***Jpn***: Aftach; MaQaid; ***Malaysia***: Dermacort; Kanolone; Kenalog in Orabase; Metoral; Nasacort AQ; Orrepaste; Shincort; Sivkort; Tramsone; ***Mex.***: ATLC; Azucort†; Intralon; Kenacort; Kenalog Dental; Nasacort; Softram; Triamsicort; Zamacort†; ***Neth.***: Kenacort-A; Nasacort; Zure oordruppels met triamcinolonacetonide; ***Norw.***: Kenacort-T; Lederspan; Nasacort; Triesence; ***NZ***: Aristocort; Kenacort-A; Kenalog in Orabase; Oracort; Telnase; ***Philipp.***: Actonaze; Kanosole; Kenacort-A†; Kenacort†; Shincort; Tricin; Tricort; ***Pol.***: Polcortolon; ***Port.***: Aftach; Nasacort; ***Rus.***: Berlicort (Берликорт)†; Ftorocort (Фторокорт); Kenalog (Кеналог); Polcortolon (Полькортолон); Polcortolon (Полькортолон); Polcortolon TC (Полькортолон ТС); Triacort (Триакорт); ***S.Afr.***: Kenalog in Orabase; Nasacor; ***Singapore***: Dermacort†; Kenalog in Orabase; Keno; Nasacort; Oral-T; Oramedy; Orrepaste; Shincort; Tramsone; Triamnone; Trinolone; ***Spain***: Flutenal†; Nasacort; Proctosteroid; Trigon Depot; ***Swed.***: Kenacort-T; Lederspan; Nasacort; ***Switz.***: Kenacort-A Solubile; Kenacort-A; Kenacort; Nasacort; Triamcort; ***Thai.***: Actyl; Aristocort; Betji-Cort; Centocort; Curran; Dynacort; Facort; Ftorocort†; Generlog; Kanolone; Kela; Kelamild; Kemzid; Kena-Lite; Kenacort-A†; Kenalog in Orabase†; Keno; Lala; Laver; Lenicort; Lonna; M-Divate; Manolone; Metoral; Milanolone†; Musaral; Nasacort; Oracortia; Oral-T; Oralog†; Oralpac; Orapaste; Orcilone; Paloc; Risto; Shincort; Simacort; T-1†; T-Ora; TA Osoth; Tacinol; Thainocort; Topilone; Tram; Tramsilone; Triama; Trilosil; Trim; Trinoman; TV Lone; Unif†; V Nolone; V-Nolone; Vacinolone; Zyno; ***Turk.***: Artropan; Kenacort-A; Nasacort; Sinakort-A; Triaver; ***UK***: Adcortyl in Orabase†; Adcortyl; Kenalog; Nasacort; ***Ukr.***: Focort (Фокорт); Ftorocort (Фторокорт); Kenalog (Кеналог); Polcortolon (Полькортолон); ***USA***: AllerNaze; Aristospan; Atolone; Azmacort†; Flutex†; Kenalog in Orabase; Kenalog; Kenonel; Nasacort; Oralone Dental†; pediaderm TA; Tac; Tri-Kort; Triacet; Triam-A; Triamonide; Trianex; Triderm; Triesence; Trilog; Trivaris; ***Venez.***: Kenacort; Nasacort.

Multi-ingredient Preparations. ***Arg.***: Bagovit A Plus; Biotaer Nasal†; Kenacomb; Mantus; Sorsis; ***Austral.***: Kenacomb; Otocomb Otic; ***Austria***: Aureocort; Pevisone; Volon A antibiotikahaltig†; Volon A Tinktur; ***Belg.***: Mycolog; Pevisone†; Trianal; ***Braz.***: Londerm-N†; Mud; Neolon D; Omcilon-A M; Oncibel; Oncileg; Onciplus†; ***Canad.***: ratio-Triacomb; Viaderm-KC; ***China***: An Long (安隆); Fu Yan Ning (扶严宁); Ji Bai Fu (吉伯芙); Kenacomb (复方康纳乐霜); Pevisone (派瑞松); YiFuQing (益富清); Zhaohuile (朝晖乐); ***Cz.***: Triaderm†; Triamcinolon E; Triamcinolon S; Triamcinolon; ***Denm.***: Kenalog Comp med Mycostatin†; Pevison; Pevisone†; ***Fin.***: Pevisone; ***Fr.***: Cidermex†; Kenalcol†; Localone; Pevisone; ***Ger.***: Epipevisone; Ledermix; Moronal V†; Mykoproct sine†; Volon A Tinktur N; Volon A-Schuttelmix; Volonimat Plus N†; ***Gr.***: Bioderm; Biofiloderm; Dermochrom; Kenacomb; Olamyc; Pevison; ***Hong Kong***: Anso; Antiderm†; Centacomb; Clotrinolon; Dermawell†; Ecocort; Inquadeicren; Kenacomb†; Ledermix; Oragesic; Pevisone; Tri-Gel†; Triacomb†; Triamecon; Triconazole; Triditol-G; ***Hung.***: Alkcema; Polcortolon TC†; ***India***: Daktarin-T; Exsora; Kenacomb; Kenalog-S; Ledercort-N; Micolon; ***Indon.***: Kenantist†; New Kenacomb†; ***Irl.***: Kenacomb†; Ledermix; ***Israel***: Dermacombin; Ledermix; Oracort E; Pevisone†; ***Ital.***: Assocort†; Aureocort; Dermomycin Cort; Dirahist; Kataval; Pevisone; ***Malaysia***: Aecoras; Ecocort; Econazine; Endix; Kenacomb; Kifugan; Oral-Aid; ***Mex.***: Bidrozil†; Biotriamin†; Kenacomb; Softramc; ***Neth.***: Mycolog†; Trianal; Will-Anal; ***Norw.***: Pevisone; ***NZ***: Kenacomb; Viaderm-KC; ***Philipp.***: Kenacomb†; Nizolex; Oticom; Pevisone; ***Pol.***: Pevisone; Polcortolon TC; Triacomb; ***Port.***: Localone; Pevisone; ***S.Afr.***: Kenacomb†; Pevisone; Trialone†; ***Singapore***: Ecocort; Econazine; Epiderm; Oracort E; Oral Aid; Pevisone; ***Spain***: Aldoderma; Anasilpiel†; Anso; Cemalyt; Cremsol†; Flutenal Gentamicina†; Flutenal Sali†; Interderm; Nesfare; Positon; ***Swed.***: Kenacombin Novum†; Kenacort-T comp†; Pevisone; ***Switz.***: Kenacort-A; Ledermix; Pevisone; ***Thai.***: Dermacombin; Ecocort; Ecoderm; Econazine; Fungisil-T; KA-Cilone†; Kelaplus; Kenacomb†; Lymarin; Tara-Plus; Timi; Tricozole; Trimicon; ***Turk.***: Aftogel; Ekze-Mant; ***UAE***: Panderm; ***UK***: Aureocort; Ledermix; ***Ukr.***: Trimistin (Тримистин); ***USA***: Myco-Biotic II; Myco-Triacet II; Mycogen II; Mycolog-II; Myconel; NGT; Tri-Statin II; ***Venez.***: Kenacomb; Kenalog.

Used as an adjunct in:. ***Rus.***: Prodetoxon (Продетоксон).

Pharmacopoeial Preparations

BP 2014: Triamcinolone Acetonide Injection; Triamcinolone Acetonide Nasal Spray; Triamcinolone Cream; Triamcinolone Hexacetonide Injection; Triamcinolone Ointment; Triamcinolone Oromucosal Paste; Triamcinolone Tablets;

USP 36: Neomycin Sulfate and Triamcinolone Acetonide Cream; Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment; Nystatin and Triamcinolone Acetonide Cream; Nystatin and Triamcinolone Acetonide Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment; Triamcinolone Acetonide Cream; Triamcinolone Acetonide Dental Paste; Triamcinolone Acetonide Injectable Suspension; Triamcinolone Acetonide Lotion; Triamcinolone Acetonide Ointment; Triamcinolone Acetonide Topical Aerosol; Triamcinolone Diacetate Injectable Suspension; Triamcinolone Diacetate Syrup; Triamcinolone Hexacetonide Injectable Suspension; Triamcinolone Tablets.

Ulobetasol Propionate *(rINNM)* ⊗

BMY-30056; CGP-14458; 6-α-Fluoroclobetasol Propionate; Halobetasol Propionate (USAN); Propionato de ulobetasol; Ulobétasol, propionate d'; Ulobetasol, propionato de; Ulobetasoli Propionas; Улобетазола Пропионат.

21-Chloro-6α,9-difluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

$C_{25}H_{31}ClF_2O_5$=485.0

CAS — 98651-66-2 (ulobetasol); 66852-54-8 (ulobetasol propionate).

ATC — D07AC21.

ATC Vet — QD07AC21.

UNII — 91A0K1TY3Z.

Pharmacopoeias. In *US.*

USP 36: (Halobetasol Propionate). A white to off-white powder. Practically insoluble in water; freely soluble in acetone and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Ulobetasol propionate is a corticosteroid that is used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Ultravate; ***India***: Halobeta; Halostrol; Halovate; Hobs; ***USA***: Halonate; Ultravate.

Multi-ingredient Preparations. ***India***: Halostrol-F; Halostrol-M; Halovate-F; Halovate-S; Hobs-S; ***USA***: Halac Kit.

Cough Suppressants Expectorants Mucolytics and Nasal Decongestants

This chapter describes drugs that are used mainly as cough suppressants, expectorants, or mucolytics, and also those sympathomimetics primarily used for the relief of nasal congestion. Other drugs used in cough include antihistamines (p. 610.1), bronchodilators (p. 1195.1), and local anaesthetics (p. 1976.1). Compounds with a demulcent action such as glycerol (p. 2517.2) and sucrose (p. 2096.3) are also used, as are various hydrating inhalations.

Cough suppressants

Cough suppressants have either a central or a peripheral action on the cough reflex or a combination of both. Centrally acting cough suppressants increase the threshold of the cough centre in the brain to incoming stimuli whereas those acting peripherally decrease the sensitivity of the receptors in the respiratory tract. Some drugs have an indirect peripheral mechanism of action and may alter mucociliary factors, exert a local analgesic or anaesthetic action on the receptors, protect the receptors from irritant stimuli, or act as bronchodilators.

Those centrally acting cough suppressants structurally related to morphine that are included in this chapter, such as dextromethorphan, have little or no analgesic action. Those that also have an important analgesic action, such as codeine or diamorphine, are described in the chapter on Analgesics, p. 3.1.

Described in this chapter are

- Acetyldihydrocodeine, p. 1654.3
- Benproperine, p. 1656.2
- Benzonatate, p. 1656.2
- Bibenzonium, p. 1656.3
- Butamirate, p. 1657.3
- Butetamate, p. 1658.1
- Clobutinol, p. 1658.3
- Clofedanol, p. 1659.1
- Cloperastine, p. 1659.2
- Dextromethorphan, p. 1660.1
- Dimemorfan, p. 1661.3
- Dimethoxanate, p. 1661.3
- Dropropizine, p. 1662.2
- Elecampane, p. 1662.3
- Ethyl Orthoformate, p. 1665.3
- Fedrilate, p. 1665.3
- Fominoben, p. 1665.3
- Glaucine, p. 1666.1
- Helicidine, p. 1667.1
- Isoaminile, p. 1668.2
- Morclofone, p. 1669.2
- Nepinalone, p. 1670.2
- Nicocodine, p. 1670.3
- Normethadone, p. 1670.3
- Noscapine, p. 1670.3
- Oxeladin, p. 1671.2
- Oxolamine, p. 1671.2
- Pentoxyverine, p. 1672.1
- Pholcodine, p. 1675.1
- Pipazetate, p. 1675.2
- Poppy Capsule, p. 1675.3
- Prenoxdiazine, p. 1675.3
- Promolate, p. 1676.1
- Sodium Dibunate, p. 1677.3
- Thebacon, p. 1679.1
- Tipepidine, p. 1679.1
- Zipeprol, p. 1680.3

Expectorants

Expectorants are considered to increase the volume of secretions in the respiratory tract thereby facilitating their removal by ciliary action and coughing. Many traditional expectorants, including ipecacuanha, squill, ammonium salts, some volatile oils, and various iodide compounds, have been considered to achieve this by a reflex irritant effect on the gastric mucosa.

Described in this chapter are

- Ammonium Salts, p. 1655.3
- Calcium Iodide, p. 1658.1
- Cocillana, p. 1659.2
- Coltsfoot, p. 1659.2
- Creosote, p. 1659.3
- Elecampane, p. 1662.3
- Eprazinone, p. 1664.3
- Eprozinol, p. 1665.1
- Eriodictyon, p. 1665.2
- Fudosteine, p. 1666.1
- Guacetisal, p. 1666.1
- Guaiacol, p. 1666.1
- Guaietolin, p. 1666.2
- Guaifenesin, p. 1666.2
- Guaimesal, p. 1667.1
- Iodinated Glycerol, p. 1667.2
- Ipecacuanha, p. 1667.2
- Marrubium, p. 1668.3
- Senega Root, p. 1677.2
- Squill, p. 1677.3
- Sulfogaiacol, p. 1678.1
- Terpin Hydrate, p. 1678.2
- Tolu Balsam, p. 1679.2

Mucolytics

Mucolytics alter the structure of mucus to decrease its viscosity thereby facilitating its removal by ciliary action or expectoration.

Acetylcysteine, carbocisteine, and mecysteine all have thiol groups; if this group is free, as in acetylcysteine, it may be substituted for disulfide bonds in mucus and therefore break the mucus chains. However, drugs such as carbocisteine with 'protected' thiol groups cannot act by this mechanism and their exact mode of action is unclear. Thiol groups are also involved in the mechanism of action of some of these drugs when they are used in the treatment of poisoning.

Deoxyribonucleases such as dornase alfa act as mucolytics by hydrolysing the accumulated extracellular DNA from decaying neutrophils that contributes to the viscous respiratory secretions of cystic fibrosis.

Drugs with **mucoregulatory** actions, typically affecting mucin and chloride secretion by acting on ion channels in the respiratory tract, are also being developed; examples under investigation include denufosol and talniflumate.

Described in this chapter are

- Acetylcysteine, p. 1652.2
- Ambroxol, p. 1654.3
- Bromhexine, p. 1656.3
- Brovanexine, p. 1657.3
- Carbocisteine, p. 1658.1
- Dembrexine, p. 1659.3
- Denufosol, p. 1660.1
- Dornase Alfa, p. 1662.1
- Eprazinone, p. 1664.3
- Eprozinol, p. 1665.1
- Erdosteine, p. 1665.1
- Ethyl Cysteine Hydrochloride, p. 1665.2
- Mecysteine, p. 1669.1
- Methyl Dacisteine, p. 1669.2
- Neltenexine, p. 1670.2
- Sobrerol, p. 1677.2
- Talniflumate, p. 1678.2
- Telmesteine, p. 1678.2

Sympathomimetics

Sympathomimetics described in this chapter may be used systemically (such as phenylephrine) or locally (such as naphazoline), for their alpha agonist actions to produce vasoconstriction of the nasal mucosa, thus relieving congestion. Others such as ephedrine have both alpha and beta agonist actions. The beta agonist actions confer upon them bronchodilating properties, but they have been superseded as bronchodilators by the more selective $beta_2$ agonists such as salbutamol. The value of bronchodilators in non-asthmatic cough has not been confirmed.

Described in this chapter are

- Amidefrine, p. 1655.3
- Clonazoline, p. 1659.1
- Ephedra, p. 1663.1
- Ephedrine, p. 1663.1
- Etafedrine, p. 1665.2
- Fenoxazoline, p. 1665.3
- Indanazoline, p. 1667.1
- Levmetamfetamine, p. 1668.3
- Methoxyphenamine, p. 1669.1
- Methylephedrine, p. 1669.2
- Naphazoline, p. 1669.3
- Oxymetazoline, p. 1671.3
- Phenylephrine, p. 1672.2
- Phenylpropanolamine, p. 1674.1
- Pseudoephedrine, p. 1676.1
- Tetryzoline, p. 1678.3
- Tramazoline, p. 1679.3
- Tuaminoheptane, p. 1679.3
- Tymazoline, p. 1679.3
- Xylometazoline, p. 1680.1

Cough

Cough is an important physiological protective mechanism, but may also occur as a symptom of an underlying disorder such as asthma, gastro-oesophageal reflux disease, and postnasal drip. Treatment of the disorder often alleviates the cough, but there are times when symptomatic treatment is appropriate. The treatment chosen depends on whether the cough is productive or non-productive.[1-11]

A **non-productive cough** such as that often seen with the common cold serves no useful purpose for the patient, and cough suppressants may provide some relief, particularly if given at night.

- Of the commonly used *cough suppressants*, pholcodine and dextromethorphan are considered to have fewer adverse effects than codeine. However, there is little evidence that these drugs are effective in severe cough.
- Sedating *antihistamines* such as diphenhydramine are frequently used as cough suppressants in compound preparations. Suggested mechanisms of action have included reduction in cholinergic nerve transmission, or cough suppression as a result of their sedative effects. Antihistamines reduce nasal secretions and may be of value in treating cough caused by postnasal drip, particularly if associated with allergic rhinitis (see p. 612.1). However, they should not be used to treat a productive cough because they may cause formation of viscid mucus plugs. Their sedative effects are a disadvantage for daytime use but may be a short-term advantage for night coughs.
- *Demulcents* probably act as indirect peripherally acting cough suppressants by providing a protective coating over sensory receptors in the pharynx. Demulcents include glycerol, honey, liquorice, and sucrose syrups.

A potent cough suppressant such as morphine is needed for the relief of **intractable cough** in terminal illness. The use of such a potent opioid is not otherwise considered appropriate for cough.

- *Local anaesthetics* such as lidocaine or bupivacaine have been inhaled in severe intractable cough, including cough caused by malignant neoplasms. Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, such treatment should be used with care. There may also be temporary loss of the swallowing reflex.

A **productive cough** is characterised by the presence of sputum and may be associated with conditions such as chronic bronchitis, bronchiectasis, or cystic fibrosis. Cough suppressants are inappropriate, since the cough serves the purpose of clearing the airways, but expectorants have been used on the grounds that increasing the volume of secretions in the respiratory tract facilitates removal by ciliary action and coughing. However, clinical evidence of efficacy is lacking, and many authorities consider expectorants to be of no value other than as a placebo.

- Commonly used *expectorants* include ammonium salts, guaifenesin, ipecacuanha, and sodium citrate. Iodides have also been used but there has been concern over their safety for prolonged use in respiratory disorders and because of their potential for thyroid suppression; in particular, it has been recommended that they should not be given to children, adolescents, pregnant women, or patients with goitre.
- *Mucolytics* have been shown to affect sputum viscosity and structure and patients have reported alleviation of their symptoms, but no consistent improvement in lung function has been found. Commonly used mucolytics include acetylcysteine, bromhexine, carbocisteine, and mecysteine. Dornase alfa is also available, in particular for patients with cystic fibrosis. In theory mucolytics may disrupt the gastric mucosal barrier and caution has been recommended in patients with a history of peptic ulcer disease.
- *Hydrating agents* liquefy mucus and also have a demulcent effect. Hydration may be achieved simply by inhaled warm moist air. The addition of substances such as menthol, benzoin, or volatile oils is unlikely to provide any additional benefit but may encourage the use of such inhalations. Inhaled aerosols of water, sodium bicarbonate, sodium chloride, surfactants such as tyloxapol, osmotic agents such as mannitol, and proteolytic enzymes such as chymotrypsin and trypsin, have also been used for their reported hydrating or mucolytic effects on respiratory secretions.

Cough may sometimes be associated with **bronchospasm** in patients with asthma.

- *Bronchodilators* such as salbutamol (a $beta_2$ agonist) or ipratropium (an antimuscarinic) alleviate cough associated with bronchospasm. However, they are not generally considered of benefit in other forms of cough, and hence are not recommended other than in asthma or selected patients with chronic obstructive pulmonary disease.

Cough and cold preparations containing various combinations of cough suppressants and/or expectorants, with sympathomimetics, antihistamines, or analgesics are available. Some combinations, such as a cough suppressant and an expectorant, seem illogical and have little evidence to support their efficacy. As with many combinations, doses of individual drugs may be inadequate or inappropriate, and the large number of ingredients may expose the patient to unnecessary adverse effects. In particular, concern has been expressed about the safety in *children* of cough and cold preparations that contain antihistamines, cough suppressants, expectorants, and sympathomimetic decongestants, either alone or in combination. A systematic review[12] has found no good evidence for or against the efficacy of over-the-counter (OTC) preparations in acute cough. The British Thoracic Society considers that OTC medications are as effective as placebo for acute cough with head colds in children.[13] In early 2008, the FDA[14] and MHRA[15] both advised that OTC cough and cold preparations should not be given to children under 2 years of age. They warned of the potential for serious and potentially life-threatening adverse effects and that such preparations provided only symptomatic relief, at best. They also advised that if these products were to be used in children older than 2 years of age, the recommended dose should be followed carefully and measured accurately, and that only one preparation should be used to avoid overdosage of the same drug or similar drugs. A review by the FDA of the use of such preparations in older children (2 to 11 years of age) is ongoing. However, in October 2008, most US manufacturers voluntarily revised the labelling of OTC cough and cold preparations to state not for use in children aged under 4 years.[16] In early 2009, after further review, the MHRA[17] advised that OTC cough and

cold preparations should not be given to children under 6 years of age as there was no robust evidence of their efficacy and because they can cause adverse effects such as allergic reactions, sleep disturbances, and hallucinations. In those aged from 6 to 12 years, such preparations should only be used as second-line therapy and for no more than 5 days; the MHRA also considered that further research is warranted in this age group. Subsequently, additional restrictions have been imposed on the use of OTC cough and cold preparations containing codeine in those aged 18 years and under (see Cough under Codeine, p. 41.1).

To alleviate symptoms of coughs and colds in children aged under 6 years, the MHRA[17] recommends using single-constituent paracetamol or ibuprofen, simple cough preparations (such as those containing glycerol or honey and lemon), vapour rubs and inhalant decongestants (that can be applied to clothing), and, particularly in infants, sodium chloride nasal drops.

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4. Fontana GA, Pistolesi M. Chronic cough and gastro-oesophageal reflux. *Thorax* 2003; **58:** 1092–5.
5. Dicpinigaitis PV. Cough in asthma and eosinophilic bronchitis. *Thorax* 2004; **59:** 71–2.
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7. Morice AH, *et al*. The diagnosis and management of chronic cough. *Eur Respir J* 2004; **24:** 481–92.
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10. Morice AH, *et al*. British Thoracic Society Cough Guideline Group. BTS Guidelines: Recommendations for the management of cough in adults. *Thorax* 2006; **61** (suppl): i1–i24. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/coughguidelinesaugust06.pdf (accessed 15/07/08)
11. Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008; **371:** 1375–84.
12. Smith SM, *et al*. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/04/08).
13. Shields MD, *et al*. British Thoracic Society Cough Guideline Group. BTS guidelines: Recommendations for the assessment and management of cough in children. *Thorax* 2008; **63** (suppl III): iii1–iii15. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/cough_in_children.pdf (accessed 15/07/08)
14. FDA. FDA releases recommendations regarding use of over-the-counter cough and cold products (issued 17th January, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116839.htm (accessed 17/08/10)
15. MHRA/CHM. Updated advice—over-the-counter cough and cold medicines for children. *Drug Safety Update* 2008; **1** (9): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 15/04/08)
16. FDA. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children (issued 8th October, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm (accessed 17/08/10)
17. MHRA. Press release: better medicines for children's coughs and colds (issued 28th February, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON038902 (accessed 06/04/09) See also: MHRA/CHM. Over-the-counter cough and cold medicines for children. *Drug Safety Update* 2009; **2** (9): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON043810&RevisionSelectionMethod=LatestReleased (accessed 17/08/10)

Nasal congestion

Nasal congestion is frequently a symptom of conditions such as rhinitis (p. 612.1), treatment of which can include the use of antihistamines, sympathomimetics, corticosteroids, antimuscarinics, and cromoglicate or nedocromil.

Sympathomimetics are also widely used as nasal decongestants to provide symptomatic relief of the common cold (p. 951.1). They are used for the vasoconstriction produced by their alpha-adrenergic effects; redistribution of local blood flow reduces oedema of the nasal mucosa, thus improving ventilation, drainage, and nasal stuffiness. Sympathomimetics such as ephedrine, phenylephrine, naphazoline, oxymetazoline, and xylometazoline can be used topically as nasal drops or sprays. Those such as pseudoephedrine are given orally. Over-the-counter cough and cold preparations containing sympathomimetic decongestants should be used with caution in children and generally avoided in young children, for details see p. 1651.2.

Topical use, particularly if prolonged, may lead to rebound congestion as vasodilatation becomes prominent and the effects of vasoconstriction subside. Use is therefore restricted to periods of not more than 7 consecutive days. Oral use is not associated with such rebound congestion, but is more likely to be associated with systemic adverse effects and a higher risk of drug interactions. A systematic review found no difference in efficacy between oral and topical decongestants from the limited evidence available.[1]

The benefits of *antihistamines* in nasal congestion other than that associated with allergic rhinitis are doubtful, particularly by topical application.

Inhalations of warm moist air are also useful in the treatment of nasal congestion associated with the common cold. As in the case of cough (see p. 1651.2) the addition of substances such as menthol, benzoin, or volatile oils may encourage the use of such inhalations. Sodium chloride nasal drops may also be effective, particularly in infants and young children.

1. Taverner D, Latte GJ. Nasal decongestants for the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 [Withdrawn] (accessed 14/08/10).

Acetylcysteine *(BAN, USAN, rINN)*

5052; Acetilcisteína; Acetilcisteinas; Acetilcisztein; Acetylcystein; Acétylcystéine; Acetylcysteinum; Asetilsistein; Asetyylikysteiini; NSC-111180; Ацетилцистеин.

N-Acetyl-L-cysteine.

$C_5H_9NO_3S$=163.2

CAS — 616-91-1.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

UNII — WYQ7N0BPYC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Acetylcysteine). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 2.8. Protect from light.

USP 36: (Acetylcysteine). A white crystalline powder having a slight acetic odour. Soluble 1 in 5 of water and 1 in 4 of alcohol; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 2.8. Store in airtight containers.

Incompatibility. Acetylcysteine is incompatible with some metals, including iron and copper, with rubber, and with oxygen and oxidising substances. Some antimicrobials including amphotericin B, ampicillin sodium, erythromycin lactobionate, and some tetracyclines are either physically incompatible with, or may be inactivated on mixture with, acetylcysteine.

Stability. A change in colour of solutions of acetylcysteine to light purple does not indicate significant impairment of safety or efficacy.

Acetylcysteine Sodium *(BANM, rINNM)*

Acetilcisteína sódica; Acétylcystéine Sodique; Natrii Acetylcysteinum; Натрий Ацетилцистеин.

$C_5H_8NNaO_3S$=185.2

CAS — 19542-74-6.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

UNII — NRD80R06FB.

Uses and Administration

Acetylcysteine is a mucolytic that reduces the viscosity of secretions probably by the splitting of disulfide bonds in mucoproteins. Since this action is greatest at a pH of 7 to 9, commercial preparations may have had their pH adjusted with sodium hydroxide. It is sometimes stated that acetylcysteine sodium is used, although the dose is expressed in terms of acetylcysteine.

Acetylcysteine is also able to promote the detoxification of an intermediate paracetamol metabolite, and has a key role in the management of paracetamol overdosage.

Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough (p. 1653.3). It can be given by nebulisation of 3 to 5 mL of a 20% solution or 6 to 10 mL of a 10% solution through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution or 2 to 20 mL of a 10% solution may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour. Mechanical suction of the liquefied secretions may be necessary, and nebulisers containing iron, copper, or rubber components should not be used.

Acetylcysteine as a mucolytic is also given orally, as lozenges, or as granules or effervescent tablets dissolved in water, in a usual dose of 600 mg daily as a single dose or in 3 divided doses.

In the treatment of **dry eye** (p. 2190.1) associated with abnormal mucus production, acetylcysteine, usually as a 5% solution with hypromellose, is given topically 3 or 4 times daily. Higher concentrations have been used in some centres.

Acetylcysteine is given by intravenous infusion or orally in the treatment of **paracetamol poisoning** (p. 1653.2).

- If given intravenously: 150 mg/kg (maximum of 16.5 g) of acetylcysteine in 200 mL of glucose 5% is given initially over 60 minutes. This is followed by infusion of 50 mg/kg (maximum of 5.5 g) in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg (maximum of 11 g) in one litre of glucose 5% over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable.
- If given orally: an initial dose of 140 mg/kg as a 5% solution is followed by 70 mg/kg every 4 hours for an additional 17 doses.

Acetylcysteine is reported to be most effective when given within 8 hours of paracetamol overdosage, with the protective effect diminishing after this time. However, starting treatment with acetylcysteine later (up to and beyond 24 hours) may still be of benefit.

Acetylcysteine may be used for the treatment of idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1653.1).

For doses in children, see below.

Reviews.

1. Atkinson MC. The use of N-acetylcysteine in intensive care. *Crit Care Resusc* 2002; **4:** 21–7.
2. Dekhuijzen PNR. Antioxidant properties of *N*-acetylcysteine: their relevance in relation to chronic obstructive pulmonary disease. *Eur Respir J* 2004; **23:** 629–36.
3. Guerin J-C, *et al*. Le stress oxydatif en pathologie broncho-pulmonaire: apport de la N-acétyl-cystéine (NAC). *Rev Pneumol Clin* 2005; **61:** 16–21.
4. Aitio M-L. N-acetylcysteine—passe-partout or much ado about nothing? *Br J Clin Pharmacol* 2006; **61:** 5–15.
5. Dekhuijzen PN. Acetylcysteine in de behandeling van ernstige COPD. *Ned Tijdschr Geneeskd* 2006; **150:** 1222–6.

Administration in children. Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough. Doses in children are similar to adults; 3 to 5 mL of a 20% solution, or 6 to 10 mL of a 10% solution, may be nebulised through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution, or 2 to 20 mL of a 10% solution, may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour.

Acetylcysteine has also been given orally in a variety of dosage forms. Licensed doses and age ranges vary somewhat from country to country and even from preparation to preparation. For example, in France, children may be given the following doses:

- 1 month to 2 years: 100 mg twice daily
- 2 to 7 years: 200 mg twice daily
- 7 years and over: 200 mg 3 times daily (adult dose)

In Germany and Switzerland, however, a more typical dose for children under 2 years of age is 50 mg two or three times daily.

Acetylcysteine has been used to treat meconium ileus in neonates and distal obstruction syndrome in children with **cystic fibrosis**, although the *BNFC* states that evidence of its efficacy is lacking. Such use is not licensed in the UK, but if it is to be used the *BNFC* suggests an oral dose of acetylcysteine 200 to 400 mg up to 3 times daily if necessary for meconium ileus in neonates. For the *treatment* of distal intestinal obstruction syndrome in children with cystic fibrosis, a single oral dose is recommended as follows:

- 1 month to 2 years: 0.4 to 3 g
- 2 to 7 years: 2 to 3 g
- 7 to 18 years: 4 to 6 g

For the *prevention* of distal intestinal obstruction syndrome, it is recommended to be given orally as follows:

- 1 month to 2 years: 100 to 200 mg 3 times daily
- 2 to 12 years: 200 mg 3 times daily
- 12 to 18 years: 200 to 400 mg 3 times daily

The injection may be used orally, diluted to a concentration of 50 mg/mL; orange or black currant juice or cola may be used as diluents to mask the bitter taste.

In the treatment of **dry eye** associated with tear deficiency, or impaired or abnormal mucus production, acetylcysteine 5% eye drops with hypromellose may be applied, as in adults, 3 or 4 times daily.

Acetylcysteine is given by intravenous infusion or orally in the treatment of **paracetamol poisoning**. Doses for children, including neonates, are similar to adults (see also Uses and Administration, above and Overdosage on p. 116.2), although the volume of intravenous fluid is modified. The *BNFC* suggests the following *intravenous* doses, according to body-weight:

- under 20 kg: initially 150 mg/kg in 3 mL/kg glucose 5% given over 60 minutes, followed by 50 mg/kg in 7 mL/kg glucose 5% given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% given over 16 hours
- 20 to 40 kg: initially 150 mg/kg in 100 mL glucose 5% given over 60 minutes, followed by 50 mg/kg in 250 mL glucose 5% given over 4 hours, then 100 mg/kg in 500 mL glucose 5% given over 16 hours
- over 40 kg: adult dose

In the USA, the following *oral* dose is licensed for use in children: 140 mg/kg initially, followed by 70 mg/kg every 4 hours for an additional 17 doses.

Anxiety disorders. In a small 12-week double-blind study,[1] oral acetylcysteine (range 1.2 to 2.4 g daily) produced greater improvement in symptoms of hair-pulling than placebo in patients with trichotillomania.

1. Grant JE, *et al.* N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 2009; **66:** 756–63.

Aspergillosis. Although it is not one of the standard therapies discussed on p. 563.1, local instillation of acetylcysteine into the cavity containing the fungus ball has been used to treat aspergilloma.[1] There is some evidence *in vitro* that acetylcysteine has inhibitory properties against *Aspergillus* and *Fusarium* spp.[2]

1. Kauffman CA. Quandary about treatment of aspergillomas persists. *Lancet* 1996; **347:** 1640.
2. De Lucca AJ, *et al.* N-Acetylcysteine inhibits germination of conidia and growth of Aspergillus spp. and Fusarium spp. *Antimicrob Agents Chemother* 1996; **40:** 1274–6.

Burns. Children with smoke inhalation injury (p. 1683.1) who were treated with aerosolised heparin 5000 units alternating with 3 mL of 20% acetylcysteine solution, inhaled every 2 hours for the first 7 days after injury, appeared to have significantly reduced mortality and reintubation rates compared with historical controls.[1]

1. Desai MH, *et al.* Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [sic] therapy. *J Burn Care Rehabil* 1998; **19:** 210–12. Correction. *ibid.* 1999; **20:** 49.

Cystic fibrosis. Mucolytics such as acetylcysteine are generally not considered[1] to be effective in treating the pulmonary manifestations of cystic fibrosis (p. 177.2).

Meconium ileus equivalent (bowel obstruction due to abnormally viscid contents of the terminal ileum and right colon[2]) in patients with cystic fibrosis has largely disappeared with the use of pancreatic enzymes but may occur when insufficient doses are given;[3] mild cases may be treated with acetylcysteine.[3] Doses of 10 mL of a 20% solution of acetylcysteine have been given orally 4 times daily with 100 mL of a 10% solution of acetylcysteine given as an enema up to 4 times daily depending on the degree of the obstruction.[2]

For suggested children's doses in meconium ileus and distal obstruction syndrome, see Administration in Children, p. 1652.3.

1. Duijvestijn YC, Brand PL. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatr* 1999; **88:** 38–41.
2. Hanly JG, Fitzgerald MX. Meconium ileus equivalent in older patients with cystic fibrosis. *BMJ* 1983; **286:** 1411–13.
3. David TJ. Cystic fibrosis. *Arch Dis Child* 1990; **65:** 152–7.

Interstitial lung disease. Acetylcysteine with prednisolone and azathioprine is a recommended option for the treatment of idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1607.1). In a randomised controlled study, adjunctive oral treatment with acetylcysteine 600 mg three times daily slowed the loss of vital lung capacity compared with standard therapy with azathioprine and prednisone.[1]

1. Demedts M, *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; **353:** 2229–42.

Kidney disorders. Acetylcysteine has been reported to improve kidney function in patients with the hepatorenal syndrome and may offer a potential bridging therapy in such patients awaiting liver transplantation.[1] It has also been used in the prevention of contrast media-induced nephrotoxicity in patients with chronic renal impairment, but evidence of benefit is conflicting and its role remains to be established; see Effects on the Kidney under Amidotrizoic Acid (p. 1582.2) for further details.

1. Holt S, *et al.* Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* 1999; **353:** 294–5.

Liver disorders. Although benefit has been reported from studies of acetylcysteine in acute liver failure,[1] and some have suggested that it may be useful in preventing tissue hypoxia in patients with acute liver failure receiving vasopressors,[2] studies have mainly been small and clinical outcomes are not well studied.[1] It does not appear to be of benefit in patients undergoing orthotopic liver transplantation.[3,4]

For reference to use in the hepatorenal syndrome, see Kidney Disorders, above. For use in paracetamol-induced liver damage, see Overdosage, under Paracetamol, p. 116.2.

1. Sklar GE, Subramaniam M. Acetylcysteine treatment for non-acetaminophen-induced acute liver failure. *Ann Pharmacother* 2004; **38:** 498–501.
2. Caraceni P, Van Thiel DH. Acute liver failure. *Lancet* 1995; **345:** 163–9.
3. Bromley PN, *et al.* Effects of intraoperative N-acetylcysteine in orthotopic liver transplantation. *Br J Anaesth* 1995; **75:** 352–4.
4. Steib A, *et al.* Does N-acetylcysteine improve hemodynamics and graft function in liver transplantation? *Liver Transpl Surg* 1998; **4:** 152–7.

Meconium ileus. For the use of acetylcysteine in infants with meconium ileus, see Cystic Fibrosis, above.

Myocardial infarction. Some studies suggest that addition of intravenous acetylcysteine to thrombolytic therapy in patients with acute myocardial infarction (p. 1257.1) may be of benefit.[1,2] The value of acetylcysteine as an adjunct in patients with or at risk of myocardial infarction has been reviewed.[3,4]

1. Arstall MA, *et al.* N-Acetylcysteine in combination with nitroglycerin and streptokinase for the treatment of evolving acute myocardial infarction: safety and biochemical effects. *Circulation* 1995; **92:** 2855–62.
2. Šochman J, *et al.* Infarct size limitation: acute N-acetylcysteine defense (ISLAND trial): preliminary analysis and report after the first 30 patients. *Clin Cardiol* 1996; **19:** 94–100.
3. Marchetti G, *et al.* Use of N-acetylcysteine in the management of coronary artery diseases. *Cardiologia* 1999; **44:** 633–7.
4. Sochman J. N-acetylcysteine in acute cardiology: 10 years later: what do we know and what would we like to know?! *J Am Coll Cardiol* 2002; **39:** 1422–8.

Nitrate tolerance. Acetylcysteine appears to be able to potentiate the peripheral and coronary effects of glyceryl trinitrate.[1] While some studies[2-5] have suggested that acetylcysteine can reverse tolerance to nitrates in patients with coronary heart disease or heart failure, others have failed to find any benefit,[6] although there may be a specific subgroup of responders.[5] The various attempts at overcoming nitrate tolerance are discussed on p. 1394.1.

1. Horowitz JD, *et al.* Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris. *Circulation* 1988; **77:** 787–94.
2. Packer M, *et al.* Prevention and reversal of nitrate tolerance in patients with congestive heart failure. *N Engl J Med* 1987; **317:** 799–804.
3. May DC, *et al.* In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. *N Engl J Med* 1987; **317:** 805–9.
4. Boesgaard S, *et al.* Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris. *Circulation* 1992; **85:** 143–9.
5. Pizzulli L, *et al.* N-acetylcysteine attenuates nitroglycerin tolerance in patients with angina pectoris and normal left ventricular function. *Am J Cardiol* 1997; **79:** 28–33.
6. Hogan JC, *et al.* Chronic administration of N-acetylcysteine fails to prevent nitrate tolerance in patients with stable angina pectoris. *Br J Clin Pharmacol* 1990; **30:** 573–7.

Poisoning and toxicity. Acetylcysteine has been studied for the potential treatment of many forms of toxicity,[1] but only treatment of acute paracetamol poisoning is widely accepted.

1. Chyka PA, *et al.* Utility of acetylcysteine in treating poisonings and adverse drug reactions. *Drug Safety* 2000; **22:** 123–48.

CARBON TETRACHLORIDE. The treatment of carbon tetrachloride poisoning is discussed on p. 2175.1. Reports suggest that prompt intravenous therapy with acetylcysteine may help to minimise hepatorenal damage in acute poisoning with carbon tetrachloride.[1,2] When added to supportive therapy the initial dosage regimen should be the same as that used for paracetamol poisoning but as carbon tetrachloride has a much longer half-life than paracetamol, the duration of treatment may need to be increased.[3]

1. Ruprah M, *et al.* Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. *Lancet* 1985; **i:** 1027–9.
2. Mathieson PW, *et al.* Survival after massive ingestion of carbon tetrachloride treated by intravenous infusion of acetylcysteine. *Hum Toxicol* 1985; **4:** 627–31.
3. Meredith TJ, *et al.* Diagnosis and treatment of acute poisoning with volatile substances. *Hum Toxicol* 1989; **8:** 277–86.

PARACETAMOL. Acetylcysteine is usually the antidote of choice for paracetamol overdosage (p. 116.2). The intravenous route is favoured in the UK, despite possible anaphylactic reaction, mainly because of concerns over the effects of vomiting and activated charcoal on oral absorption.[1] In the USA the oral route has conventionally been used, despite the unpleasant odour and taste of acetylcysteine solutions, with no evident reduction in effect by charcoal.[2,3] The intravenous route is now also licensed in the USA. Oral and intravenous formulations appear to be equally effective.[4] A disadvantage of the oral route is therapeutic failure in those patients who develop nausea and vomiting, which occurs in most patients with severe poisoning; delays in absorption may also be of concern especially when the end of the critical 8-hour interval is approaching. However, with oral doses, the whole absorbed dose passes through the liver, producing high local concentrations at the site of toxicity.[5] Some consider the intravenous route to be more reliable, and to require fewer doses and a shorter duration of treatment.[6] The major disadvantage of intravenous use is possible anaphylactic reaction. Although these reactions are considered uncommon in patients with paracetamol poisoning, rare fatalities have been reported, and patients with asthma appear to be at particular risk (see also under Precautions, p. 1654.1).[5] Some infuse the first dose of acetylcysteine over 60 minutes instead of 15 minutes[6] in order to reduce the incidence and severity of reactions. However, a multicentre, randomised study found no reduction in adverse outcomes with a 60-minute infusion compared with an infusion period of 15 minutes.[7] It has been suggested that intravenous acetylcysteine may be preferred in those patients with severe poisoning, who present late, who have nausea and vomiting, or who have problems with absorption. Oral use might be preferred in those who present early with uncomplicated mild to moderate poisoning, or who have asthma.[5,8] Whichever route is given, the interval is considered the single most important factor for the prevention of severe hepatic damage.[4,5]

1. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; **346:** 547–52.
2. Bowden CA, Krenzelok EP. Clinical applications of commonly used contemporary antidotes: a US perspective. *Drug Safety* 1997; **16:** 9–47.
3. Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med* 2008; **359:** 285–92.
4. Brok J, *et al.* Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/10/06).
5. Prescott L. Oral or intravenous *N*-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med* 2005; **45:** 409–13.
6. Anonymous. Acetylcysteine (Acetadote) for acetaminophen overdosage. *Med Lett Drugs Ther* 2005; **47:** 70–1.
7. Kerr F, *et al.* The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 2005; **45:** 402–8.
8. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; **63:** 1821–7.

Respiratory disorders. Acetylcysteine has been used as a mucolytic in a variety of respiratory disorders associated with productive cough (p. 1651.2). Although there is controversy over the benefits of mucolytics in treating chronic bronchitis or chronic obstructive pulmonary disease (COPD), there is some evidence that they may reduce exacerbations (see p. 1199.1). However, a double-blind multicentre study in patients with COPD failed to find evidence that oral acetylcysteine 600 mg daily reduced exacerbations;[1] as with most other interventions in this condition, it could also not be shown to reduce the rate of decline in lung function.

For the use of aerosolised heparin and acetylcysteine to treat smoke inhalation injury, see Burns, above. It has been suggested that intravenous acetylcysteine might also be of use in acute respiratory distress syndrome (ARDS—p. 1599.3),[2] possibly due to its action as a free radical scavenger,[2,3] but controlled studies in established ARDS failed to show benefit.[4,5]

Acetylcysteine may be used in idiopathic pulmonary fibrosis (see Interstitial Lung Disease, above). See also above for the use of acetylcysteine in the management of cystic fibrosis.

1. Decramer M, *et al.* Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; **365:** 1552–60.
2. Bernard GR. Potential of N-acetylcysteine as treatment for the adult respiratory distress syndrome. *Eur Respir J* 1990; **3** (suppl 11): 496S–498S.
3. Skolnick A. Inflammation-mediator blockers may be weapons against sepsis syndrome. *JAMA* 1990; **263:** 930–1.
4. Jepsen S, *et al.* Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; **20:** 918–23.
5. Domenighetti G, *et al.* Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; **12:** 177–82.

Scleroderma. Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome resulting from scleroderma (see p. 1938.3).

Adverse Effects

Hypersensitivity reactions have been reported in patients receiving acetylcysteine, including bronchospasm, angioedema, rashes and pruritus; hypotension, or occasionally hypertension, may occur. Other adverse effects reported with acetylcysteine include flushing, nausea and vomiting, fever, syncope, sweating, arthralgia, blurred vision, disturbances of liver function, acidosis, convulsions, and cardiac or respiratory arrest. Haemoptysis, rhinorrhoea, and stomatitis have been associated with inhalation of acetylcysteine.

Reviews.

1. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol* 2009; **47:** 81–8.

Hypersensitivity. The most common symptoms of patients with **anaphylactoid** reactions after the intravenous use of acetylcysteine in the treatment of paracetamol poisoning are rash and pruritus; other features have included flushing, nausea or vomiting, angioedema, tachycardia, bronchospasm, hypotension, and hypertension;[1-3] ECG abnormalities associated with an anaphylactoid reaction have also been reported in a patient.[4] Anaphylactoid reactions to intravenous acetylcysteine appear to be dose-related.[5] One group estimated that when acetylcysteine was given correctly the **frequency** of the anaphylactoid response was between 0.3 and 3%, whereas 11 of 15 patients who had received an overdose had a n anaphylactoid reaction.[6] Intradermal testing and study of plasma-acetylcysteine concentrations in patients who developed

reactions to acetylcysteine suggests a 'pseudo-allergic' rather than an immunological reaction,[7,8] although symptoms consistent with a serum sickness-like illness developed after exposure to acetylcysteine in one patient.[9] It has been suggested that generalised reactions to acetylcysteine can be **treated** with intravenous injection of an antihistamine;[5,10] infusion of acetylcysteine should be temporarily stopped but can usually be restarted at a slower rate without further reaction.[3] Life-threatening respiratory or cardiovascular symptoms require first-line treatment with adrenaline.

Symptoms after **overdosage** with acetylcysteine have been more severe. Hypotension appears to be especially prominent;[6] additional symptoms have included respiratory depression, haemolysis, disseminated intravascular coagulation, and renal failure, but some of these may have been due to paracetamol poisoning.[1] Death occurred in 3 patients who received an overdose of acetylcysteine while being treated for paracetamol poisoning,[1,11] but in 2 of them the role of acetylcysteine in this outcome was unclear.

1. Mant TGK, *et al.* Adverse reactions to acetylcysteine and effects of overdose. *BMJ* 1984; **289:** 217–19.
2. Dawson AH, *et al.* Adverse reactions to N-acetylcysteine during treatment for paracetamol poisoning. *Med J Aust* 1989; **150:** 329–31.
3. Pizon AF, LoVecchio F. Adverse reaction from use of intravenous N-acetylcysteine. *J Emerg Med* 2006; **31:** 434–5.
4. Bonfiglio MF, *et al.* Anaphylactoid reaction to intravenous acetylcysteine associated with electrocardiographic abnormalities. *Ann Pharmacother* 1992; **26:** 22–5.
5. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998; **31:** 710–15.
6. Sunman W, *et al.* Anaphylactoid response to intravenous acetylcysteine. *Lancet* 1992; **339:** 1231–2.
7. Bateman DN, *et al.* Adverse reactions to N-acetylcysteine. *Hum Toxicol* 1984; **3:** 393–8.
8. Donovan JW, *et al.* Adverse reactions of N-acetylcysteine and their relation to plasma levels. *Vet Hum Toxicol* 1987; **29:** 470.
9. Mohammed S, *et al.* Serum sickness-like illness associated with N-acetylcysteine therapy. *Ann Pharmacother* 1994; **28:** 285.
10. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; (Dec.): 496–9.
11. Anonymous. Death after N-acetylcysteine. *Lancet* 1984; **i:** 1421.

Precautions

Acetylcysteine should be used with caution in asthmatic patients. It should also be used with caution in patients with a history of peptic ulcer disease, both because drug-induced nausea and vomiting may increase the risk of gastrointestinal haemorrhage in patients predisposed to the condition, and because of a theoretical risk that mucolytics may disrupt the gastric mucosal barrier. The volume of intravenous fluid required when acetylcysteine is given for the treatment of paracetamol overdosage may increase the risk of fluid overload. This may result in hyponatraemia, seizures, and death, in certain patients including children, those requiring fluid restriction, or those who weigh less than 40 kg.

Asthma. Bronchospasm precipitated in 2 asthmatic patients[1] and severe asthma and respiratory arrest in another[2] have been reported after intravenous treatment with acetylcysteine. There is also a report of a patient with brittle asthma who had a similar reaction and subsequently died after receiving intravenous treatment with acetylcysteine.[3] The increased risk does not justify delaying or withholding acetylcysteine in asthmatic patients with paracetamol poisoning, but consideration might be given to initial intravenous infusion over 30 to 60 minutes rather than the conventional 15 minutes.[4] However, a large multicentre study found no benefit from the more prolonged infusion—see Paracetamol under Poisoning and Toxicity, p. 1653.2.

1. Ho SW-C, Beilin LJ. Asthma associated with N-acetylcysteine infusion and paracetamol poisoning: report of two cases. *BMJ* 1983; **287:** 876–7.
2. Reynard K, *et al.* Respiratory arrest after N-acetylcysteine for paracetamol overdose. *Lancet* 1992; **340:** 675.
3. Appelboam AV, *et al.* Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. *Emerg Med J* 2002; **19:** 594–5.
4. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 2001; **51:** 87–91.

Hepatic impairment. The total clearance of acetylcysteine in patients with cirrhosis was found to be markedly impaired, and the elimination half-life almost twice that of healthy controls.[1] Since some of the more serious adverse effects of acetylcysteine occur when plasma concentrations are high, the authors considered that increased vigilance for untoward anaphylactoid reactions and other adverse effects was necessary in patients with cirrhosis receiving acetylcysteine, and further studies to determine the optimum dosage regimen in such patients were required.

1. Jones AL, *et al.* Pharmacokinetics of N-acetylcysteine are altered in patients with chronic liver disease. *Aliment Pharmacol Ther* 1997; **11:** 787–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acetylcysteine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Acetylcysteine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5 to 1 hour after oral doses of 200 to 600 mg.[1] Some studies indicate dose-dependent pharmacokinetics with peak concentrations, the time taken to reach peak concentrations, and bioavailability increasing with increasing doses.[2] Acetylcysteine may be present in plasma as the parent compound or as various oxidised metabolites such as *N*-acetylcystine, *N*,*N*-diacetylcystine, and cysteine either free or bound to plasma proteins by labile disulfide bonds or as a fraction incorporated into protein peptide chains.[3] In a study about 50% was in a covalently protein-bound form 4 hours after a dose.[4] Oral bioavailability is low and mean values have ranged from 4 to 10% depending on whether total acetylcysteine or just the reduced forms are measured.[4,5] It has been suggested that acetylcysteine's low oral bioavailability may be due to metabolism in the gut wall and first-pass metabolism in the liver.[4,5] Renal clearance may account for about 30% of total body clearance.[5] On intravenous dosage mean terminal half-lives have been calculated to be 1.95 and 5.58 hours for reduced and total acetylcysteine, respectively; the terminal half-life of total acetylcysteine was 6.25 hours after oral doses.[4]

For reference to altered pharmacokinetics in patients with hepatic impairment, see above.

1. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. *Clin Pharmacokinet* 1991; **20:** 123–34.
2. Borgström L, Kågedal B. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing to man. *Biopharm Drug Dispos* 1990; **11:** 131–6.
3. De Caro L, *et al.* Pharmacokinetics and bioavailability of oral acetylcysteine in healthy volunteers. *Arzneimittelforschung* 1989; **39:** 383–6.
4. Olsson B, *et al.* Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. *Eur J Clin Pharmacol* 1988; **34:** 77–82.
5. Borgström L, *et al.* Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol* 1986; **31:** 217–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: AC Lan; ACC; Acemuk; Broncolium; ***Austral.***: Acetadote; Mucomyst†; Parvolex†; ***Austria***: ACC; Aeromuc; Fluimucil; Husten ACC; Hustenloser; Mucobene; ***Belg.***: Bronchocil; Docacetyl†; Lysomucil; Lysox; Nactop; Pectomucil; ***Braz.***: Aires; Bromuc; Cisteil; Flucistein; Fluicis; Fluimucil Solucao Nasal; Fluimucil; Fluiteina; Mucocetil; NAC; ***Canad.***: Mucomyst; Parvolex; ***Chile***: Fluimucil; Mucolitico; ***China***: Asixintai (阿思欣泰); Fluimucil (富露施); Mucosof (麦可素); Yi Wei Shi (易维适); ***Cz.***: ACC; Fluimucil; Mucobene; NAC; Solmucol; ***Denm.***: Granon; Kuril; Mucolysin; Mucomyst; ***Fin.***: Mucomyst; Mucoporetta†; ***Fr.***: Broncoclar†; Codotussyl Expectorant; Euronac; Exomuc; Fluimucil; Genac; Humex Expectorant; Mucolator†; Mucomyst; Mucomystendo; Mucospire†; Solmucol; ***Ger.***: ACC†; Acemuc; Acetabs†; Acetyst†; Fluimucil; Myxofat; NAC; Tussamag NAC†; ***Gr.***: Bioscal; Chricetyl; Cross; Elicor; Fluimucil; Flumil Antidoto; Flustaren; Hevox; Kantrenol; Mucomyst; Neocof; Ovoctil; Panfaco; Parvolex; Saloril; Spacyl; Trebon-N; Vaden; Vedilan-T; Vlenolys; ***Hong Kong***: Exomuc; Fluimucil; Hidonac; Madame Pearl's Mucolytic; Mutamso; Parvolex†; Solmucol; ***Hung.***: ACC; Fluimucil; NAC†; Solmucol; Sputopur; ***India***: Cilol; Fluimucil; Flumucil; Gluton; Mucare; Mucinac; Mucohelp; Mucomelt; Mucomix; Mucosys; Mucotyle; Mucyst; Nacel; Nacfil; ***Indon.***: Fluimucil; Hidonac; Mucylin; Nytex; Pectocil; Simucil; ***Irl.***: Parvolex; ***Israel***: Reolin; RheuNAC†; Siran; Tiran†; ***Ital.***: Altersol; Brunac; Fluimucil; Hidonac; Mucisol; Mucofial; Mucofrin; Mucoxan; Solmucol; Tirocular; Ultraflu; ***Malaysia***: Acetin; Fluimucil; Hidonac; Mucolator; Parvolex†; ***Mex.***: ACC; ***Neth.***: Bisolbruis; Fluimucil; Kruidvat Hoesttabletten Acetylcysteine; Solmucol†; ***Norw.***: Bronkyl; Mucomyst; ***NZ***: Acetadote; Parvolex; ***Philipp.***: Broncoflem; Fluimucil; Hidonac; Pharcetil; Solmucol†; ***Pol.***: ACC; Fluimucil; Syntemucol†; Tussicom; ***Port.***: Bluval; Cetussin; Fluimucil; Flumil†; Mucolator†; Pulmosal; Tirocular; ***Rus.***: ACC (АЦЦ); Exomuc (Экзомюк)†; Fluimucil (Флуимуцил); Muconex (Муконекс); NAC (Н-АЦ); ***S.Afr.***: ACC; Amuco; Mucolator; Parvolex; Solmucol; ***Singapore***: ACC; Codotussyl; Fluimucil; L-Cimexyl†; Parvolex†; Solmucol; Spatam; ***Spain***: Fluimucil; Flumil Antidoto; Flumil; Flumonac†; Frenacil†; Iniston Mucus; Mucoaliv; Ratiomucol; ***Swed.***: Viskoferm; ***Switz.***: ACC; Acemucol; DemoLibral†; Dynamucil; Ecomucyl; Fluimucil toux grasse; Fluimucil; Helvetussin; Muco-Mepha; Muco-X; Mucofluid; Mucomed; Mucostop; NeoCitran Expectorant; Secresol†; Solmucol; ***Thai.***: Acetin; Alistine; Cystaline; Flemex-AC; Flucil; Fluimucil; Hidonac; Mucil; Muclear; Mucocil; Mucolid; Mucolise; Mucotic; Mucoza†; Mysoven; NAC; Simucin; Stenac; ***Turk.***: Act; Asist; Brunac; Extal; Mentopin; Miratta; Mucolator; Muconex; Mukolatin; Mukosetil; NAC; Oxxa; ***UK***: Parvolex; ***Ukr.***: ACC (АЦЦ); Acestad (Ацестад); Acetal C (Ацетал С); Fluimucil (Флуимуцил); ***USA***: Acetadote; Mucomyst†.

Multi-ingredient Preparations. ***Arg.***: Acemuk Biotic; Acemuk L; ***Braz.***: Accuvit; Rinofluimucil; ***Fr.***: Rhinofluimucil; ***Hong Kong***: Rinofluimucil†; ***Hung.***: Rinofluimucil; ***India***: D-Gard; Fourts-B; Horac; Koxcure; L-Nit; Mucomelt Forte; Mucomelt-A; Mucovent; Nefrosave; Oximet; Oxydex; ***Indon.***: Dorbigot; nutrivision; Proview; Sistenol; ***Irl.***: Ilube†; ***Ital.***: Broncosulfur; Dicotuss; Migel; Rinofluimucil; ***Philipp.***: Lungcaire Plus; ***Port.***: Rinofluimucil; ***Rus.***: Rinofluimucil (Ринофлуимуцил); ***Singapore***: Hidonac; ***Spain***: Fluimucil Complex; Rinoflumil; ***Switz.***: Fluimucil Grippe Day & Night; Rinofluimucil; Solmucaine; Solmucalm; ***Thai.***: Fluimucil Antibiotic†; Rinofluimucil; ***UK***: Ilube; ***Ukr.***: Helpex Breathe (Хелпекс Бриз); Livonorm (Ливонорм); Rinofluimucil (Ринофлуимуцил); ***USA***: ALZ-NAC; Cerefolin NAC; Diabetiks; PowerMate.

Pharmacopoeial Preparations

BP 2014: Acetylcysteine Eye Drops; Acetylcysteine Injection;
USP 36: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Acetylcysteine Solution.

Acetyldihydrocodeine Hydrochloride

Acetildihidrocodeína, hidrocloruro de; Ацетилдигидрокодеина Гидрохлорид.

4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-yl acetate hydrochloride.

$C_{20}H_{25}NO_4$,HCl=379.9

CAS — 3861-72-1 (acetyldihydrocodeine).
ATC — R05DA12.
ATC Vet — QR05DA12.
UNII — HFF29F23AG.

Profile

Acetyldihydrocodeine hydrochloride is an opioid derivative related to dihydrocodeine (p. 52.2) that has been used as a centrally acting cough suppressant for non-productive cough (p. 1651.2) in a usual oral daily dose of 20 to 50 mg; no more than 20 mg should be taken as a single dose.

Ambroxol Hydrochloride *(BANM, rINNM)*

Ambroksolihydrokloridi; Ambroksolio hidrochloridas; Ambroxol, Chlorhydrate d'; Ambroxol, hidrocloruro de; Ambroxol hydrochlorid; Ambroxol-hidroklorid; Ambroxolhydrochlorid; Ambroxolhydroklorid; Ambroxoli Hydrochloridum; Hidrocloruro de ambroxol; NA-872 (ambroxol); Амброксола Гидрохлорид.

trans-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol hydrochloride.

$C_{13}H_{18}Br_2N_2O$,HCl=414.6

CAS — 18683-91-5 (ambroxol); 15942-05-9 (ambroxol hydrochloride); 23828-92-4 (ambroxol hydrochloride).
ATC — R05CB06.
ATC Vet — QR05CB06.
UNII — CC995ZMV90.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Ambroxol Hydrochloride). A white or yellowish crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Ambroxol is a metabolite of bromhexine (p. 1656.3) and is used similarly as a mucolytic. It has also been stated to have local anaesthetic properties. It is given in a usual oral daily dose of 60 to 120 mg of the hydrochloride in 2 divided doses. Ambroxol has also been given by inhalation, injection, or rectally. It is also available as lozenges for the symptomatic relief of sore throat.

References.

1. Schutz A, *et al.* Local anaesthetic properties of ambroxol hydrochloride lozenges in view of sore throat: clinical proof of concept. *Arzneimittelforschung* 2002; **52:** 194–9.
2. Beeh KM, *et al.* Antiinflammatory properties of ambroxol. *Eur J Med Res* 2008; **13:** 557–62.
3. Malerba M, Ragnoli B. Ambroxol in the 21st century: pharmacological and clinical update. *Expert Opin Drug Metab Toxicol* 2008; **4:** 1119–29.
4. de Mey C, *et al.* Efficacy and safety of ambroxollozenges in the treatment of acute uncomplicated sore throat: EBM-based clinical documentation. *Arzneimittelforschung* 2008; **58:** 557–68.

Adverse effects. *HYPERSENSITIVITY.* Ambroxol-induced contact dermatitis has been reported;[1,2] in one case tested, the patient was not cross-sensitive to the chemically similar bromhexine.

1. Mancuso G, Berdondini RM. Contact allergy to ambroxol. *Contact Dermatitis* 1989; **20:** 154.
2. Monzón S, *et al.* Ambroxol-induced systemic contact dermatitis confirmed by positive patch test. *Allergol Immunopathol (Madr)* 2009; **37:** 167–8.

Pharmacokinetics. References to pharmacokinetic studies of ambroxol.

1. Hammer R, *et al.* Speziesvergleich in Pharmakokinetik und Metabolismus von NA 872 Cl Ambroxol bei Ratte, Kaninchen, Hund und Mensch. *Arzneimittelforschung* 1978; **28:** 899–903.

2. Jauch R, *et al*. Ambroxol, Untersuchungen zum Stoffwechsel beim Menschen und zum quantitativen Nachweis in biologischen Proben. *Arzneimittelforschung* 1978; **28:** 904–11.
3. Vergin H, *et al*. Untersuchungen zur Pharmakokinetik und Bioäquivalenz unterschiedlicher Darreichungsformen von Ambroxol. *Arzneimittelforschung* 1985; **35:** 1591–5.

Respiratory disorders. Mixed results[1-3] were obtained when ambroxol was used in chronic bronchitis or chronic obstructive pulmonary disease (COPD—p. 1199.1); in a randomised study, it was no better than placebo in preventing acute exacerbations of COPD; however, in a subset of patients with more severe disease, ambroxol therapy reduced the number of exacerbations.[4] It was ineffective[5] when given to mothers for the prophylaxis of neonatal respiratory distress syndrome (p. 1608.3), although it may be of modest benefit in the early treatment of established disease in infants.[6,7]

Inhalation of ambroxol aerosol has also produced beneficial effects in a patient with alveolar proteinosis who refused alveolar lavage.[8]

For the use of mucolytics in productive cough, see p. 1651.2.

1. Olivieri D, *et al*. Ambroxol for the prevention o f chronic exacerbations: long-term multicenter trial: protective effect of ambroxol against winter semester exacerbations: a double-blind study versus placebo. *Respiration* 1987; **51** (suppl 1): 42–51.
2. Guyatt GH, *et al*. A controlled trial o f ambroxol i n chronic bronchitis. *Chest* 1987; **92:** 618–20.
3. Alcozer G, *et al*. Prevention of chronic bronchitis exacerbations with ambroxol (Mucosolvan Retard): an open, long-term, multicenter study in 5,635 patients. *Respiration* 1989; **55** (suppl 1): 84–96.
4. Malerba M, *et al*. Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD: double-blind, randomized, multicenter, placebo-controlled study (the AMETHIST Trial). *Pulm Pharmacol Ther* 2004; **17:** 27–34.
5. Dani C, *et al*. Antenatal ambroxol treatment does not prevent the respiratory distress syndrome in premature infants. *Eur J Pediatr* 1997; **156:** 392–3.
6. Wauer RR, *et al*. Randomized double blind trial of Ambroxol for the treatment of respiratory distress syndrome. *Eur J Pediatr* 1992; **151:** 357–63.
7. Schmalisch G, *et al*. Changes in pulmonary function in preterm infants recovering from RDS following early treatment with ambroxol: results of a randomized trial. *Pediatr Pulmonol* 1999; **27:** 104–12.
8. Diaz JP, *et al*. Response to surfactant activator (ambroxol) in alveolar proteinosis. *Lancet* 1984; **i:** 1023.

Uricosuric action. A study[1] was carried out in 48 young male healthy subjects to examine the uricosuric effect of ambroxol. The minimum effective dose for lowering plasma-uric acid concentrations was found to be between 250 and 500 mg daily given in 2 divided doses. Although these doses are much higher than those used to treat bronchopulmonary disease, doses as high as 1 g daily were well tolerated.

1. Oosterhuis B, *et al*. Dose-dependent uricosuric effect of ambroxol. *Eur J Clin Pharmacol* 1993; **44:** 237–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ambril; Antitusivo; Apracur Expectorante; Branzol; Bronquisedan Ninos; Cortos; Expectosan Novo Te Caliente; Mucosolvon; Tavinex Expectorante; Tavinex Expectotabs; Teosona Expectorante; Tosambrex; Tosedrin Jarabe; ***Austria***: Ambrobene; Ambrohexal; Mucoangin; Mucosan; Mucosolvan; ***Belg.***: Mucoangin; Surbronc; ***Braz.***: Ambroflux; Ambrol; Ambroten†; Ambroxmel; Anabron; Broncoflux; Bronxol; Expectuss; Fluibron; Fluidin; Fluisolvan; Mucibron; Mucoangin; Mucoclean; Mucolin; Mucosolvan; Mucoxolan; Neossolvan; Spectoflux; ***Chile***: Broncot; Esanflu; Fluibron; Fluomit; Mintamox; Mucosolvan; Muxol; Tocalm; ***China***: Ai Mu (艾沐); Ambrohexal (安普索); Ao Gu Li (奥古丽); Bei Lai (贝莱); BiYu (必与); Bromussyl (百沫舒); En Jiu Ping (恩久平); Fei De Xing (菲得欣); Gei Xin (给欣); Hai Tian Xin (海天欣); Jinxin (津欣); Kai Shun (开顺); Kao Fu Ke (考夫克); Lansu (兰苏); Losolvan (乐舒凡); Mucosolvan (沐舒坦); NaiBang (耐邦); Nuo Jian (诺健); Pingtan (平坦); Rui Tian (瑞田); Run Jing (润津); Shu Tan Qing (抒坦清); Shuai Ke Tan (帅克坦); Shuang Chang (双倡); Tan Jing (坦静); Tan Ke Shu (坦刻抒); Wei Ke Lai (维可莱); Xin De Sheng (欣得生); Yi Nuo Shu (伊诺舒); ***Cz.***: Ambex; Ambrobene; Ambrosan; Ambrospray; Dr Rentschler Hustenloser†; Flavamed; Halixol; Mucosin; Mucosolvan; Neo-Bronchol; Solvolan; ***Denm.***: Flavamed; Mucoangin; ***Fin.***: Flavamed; ***Fr.***: Lysopadol; Muxol; Surbronc; ***Ger.***: Ambrobeta; Ambrohexal†; Expit; frenopect†; Larylin Husten-Loser Pastillen†; Lindoxyl†; Mucoangin; Mucosolvan; Padiamuc†; Wick Hustenloser; ***Gr.***: Abrobion; Abrolen; Afrodor; Amboral; Ambri-Xil; Ambromyc; Anavix; Apochralen; Aprinol; Auroxidol; Auroxol; Broxol; Bunafon; Celibron; Dolcevin; Ebertuss; Effercet; Erosil; Famucosolv; Fluibrox; Grenovix; Hivotex; Kriolen; Lextarol; Lisopulm; Mavixan; Mucolin; Mucosolvan; Mucovix; Nabelon; Nibren; Olbenorin; Pharmaprol; Provixen-N; Puntol; Respirol; Saribal; Stefolant; Strubelin; Tevoril; Tosse; Tussefar; Zyrantol; ***Hong Kong***: Amxol; Lambroxol†; Marbroxol†; Max; Mucobrox†; Mucosolvan; Qualisolvon; ***Hung.***: Ambrobene; Ambrohexal†; Halixol; Mucoangin; Solvolan†; ***India***: Acocontin†; Acolyt†; Ambril; Ambrodil; Ambrolite; Amsol; Coscoril; Inhalex; Kofarest; Liquidix; Mucolite; Mucoresp; ***Indon.***: Ambril; Berea; Brommer; Bronchopront; Broncozol; Broxal; Cystelis; Epexol; Extropect; Gunapect†; Interpec; Lapimuc; Limoxin; Molapect; Mucera; Mucolica; Mucopect; Mucos; Mucoxol; Nufanibrox; Promuxol; Roverton; Silopect; Sohopec†; Transbroncho; Transmuco; ***Ital.***: Ambrofluid; Ambrotus; Amobronc; Atus; Broxol; Brufix; Fluibron; Fluixol; Gammaxol; Lintos; Muciclar; Mucoaricodil; Mucobron†; Mucosolvan; Secretil; Surfactal; Tauxolo; Viscomucil; Zerinol Gola; ***Jpn***: Mucosal; Mucosolvan; ***Malaysia***: Amtuss; Amxol; Axol; Mucosolvan; Shinoxol; Strepsils Chesty Cough; ***Mex.***: Ambrofur; Amocol; Axol; Balsibron; Bicronux; Bionoxol; Boxolam†; Brogal; Bronolban; Brosolan†; Broxaquim; Broxofar; Broxoffler; Broxol; Broxolim; Cloxan; Ebromin; Euroxol; Expeflen; Ital-Ultra; Loexom; Loxibrin†; Mucibron; Mucoangin; Mucosolvan; Mucovibrol; Mucoxol; Musalten; Musvan; Oxolvan; Prospec; Protitus; Randex; Sekretovit; Septacin; Seraxol-S; Solpat; Tobrin; Trimexine; Tunitol-BX; Tusibron; Ulax-F; Viaxol; Weiscal; ***Neth.***: Bisolangin; Mucoangin; Rexambro; ***Philipp.***: AMB; Ambroday; Ambrolex; Ambromax; Atrivex; Brocof; Bromace; Bromacef; Broxan; Broxifil; Broxil-M; Broxitrol; Broxolvan†; Exolpen; Expel; Genox; Medibron; Mepebrox†; Mucosolin; Mucosolvan; Mucovis; Mucusurf; Myracof; Phlemasol; Pontef†; Pulmobrol; Relicof; Resbron; Sinecod Exp; Sobromer; Strepsils Chesty Cough; Sybron; Venteze; Voxoll; Zircam; Zobrixol; ***Pol.***: Aflegan; Ambro†; Ambrohexal; Ambroksol; Ambrosan; Ambrosol; Deflegmin; Entus; Flavamed; Mucoangin; Mucosolvan; Mukobron†; Tussal Expectorans; ***Port.***: Benflux; Bromax; Broncoliber; Bronxol; Drenoxol; Fluidox; Fluidrenol; Hipotosse; Lactucol; Mucodrenol; Mucosolvan; Mucotosse; ***Rus.***: Ambrobene (Амбробене); Ambrohexal (Амброгексал); Ambrosan (Амбросан); Ambrosol (Амбросол)†; Bronchorus (Бронхорус); Bronchowern (Бронховерн); Bronhoxol (Бронхоксол); Flavamed (Флавамед); Halixol (Халиксол); Lasolvan (Лазолван); Medovent (Медовент)†; Medox (Медокс); Neo-Bronchol (Нео-Бронхол); Suprima-Kof (Суприма-Коф); ***Singapore***: Amxol; Axol; Max; Mucoclear; Mucosolvan; Shinoxol; Strepsils Chesty Cough; ***Spain***: Ambrolitic†; Dinobroxol; Lizipadol; Motosol; Mucibron; Mucosan; Naxpa; ***Swed.***: Mucoangin; ***Switz.***: Bisolvon Ambroxol; Lysopaine dol Ambroxol; Mucabrox; Mucoangin; Mucosolvon; ***Thai.***: Ambixol; Ambrocin; Ambrolex; Ambrolytic; Ambrox; Ambroxan; Ampromed; Amtuss; Amxol; Bro-Am; Broncol†; Broxol; Max†; Medovent†; Misovan; Movent; Mubroxol; Muco; Mucobrox; Mucodic; Mucolan†; Mucolax; Mucolid; Mucolyse; Mucomed; Mucopec; Mucosal; Mucosolvan; Mucovon; Mucoxine; Mucozan†; Musocan; Mybroxol; Nucobrox; Polibroxol; Secretin; Simusol; Strepsils Chesty Cough; Streptuss-AX; ***Turk.***: Ambreks; Ambrol; Cofitus; Fluibron; Mukoral; Pulmor; Sekrol; Tusilin; Tusol; Tusulin; ***UAE***: Mucum; ***Ukr.***: Ambrobene (Амбробене); Ambrohexal (Амброгексал); Ambrosan (Амбросан); Ambrotard (Амбротард); Bronchoval (Бронховал); Flavamed (Флавамед); Lasolvan (Лазолван); Medox (Медокс); ***Venez.***: Ambril; Ambromuco; Ambrox; Benflux; Brocantol; Bronchopront; Litusix; Misulvan; Mucoangin; Mucorama; Mucosolvan; Muxen; Xolvax.

Multi-ingredient Preparations. ***Arg.***: Aliviatos; Amoxidal Respiratorio Duo; Amoxidal Respiratorio; Amoxigrand Bronquial; Amoxipenil Bronquial; Antitusivo L; Aseptobron Respiratorio; Bronquisedan Mucolitico; Bronquisedan; Cefacilina Bronquial; Grinsil Respiratorio Duo; Grinsil Respiratorio NF; Ideobron; Letondal; Lorabrox; Muco Dosodos Biotic; Muco Dosodos; Mucoprednibron; Mucosolvon Compositum; No-Tos Biotic; Nobactam Bronquial; Oxibron NF; Oximar Respiratorio†; Pulmonix Plus; Toraxan; Trifamox Bronquial Duo; ***Austria***: Mucospas; ***Chile***: Ambrotos; ***China***: Ambrocol (易坦静); ***Cz.***: Doxycyclin Al Comp; ***Ger.***: Ambrodoxy†; Ambroxol AL comp†; Ambroxol comp; Broncho-Euphyllin; Doxy Comp†; Doxy Plus†; Spasmo-Mucosolvan; ***India***: Abcet; Acolate Plus; Airitis Plus; Airtis Plus; Alcetra Plus; Aldine-D; Alkarex-PD; Alnacet-AL; Altec; Ambcet; Ambicet; Amborex-GS; Ambrex; Ambril-S; Ambril-SG; Ambro PD; Ambro S; Ambro TS; Ambrodex; Ambrodil Plus; Ambrodil-S; Ambrogen-S; Ambrol Plus; Ambrol-AM; Ambrol-C; Ambrol-GPC; Ambrol-TG; Ambrolax-PD; Ambrolax; Ambrolite-2S; Ambrolite-S; Ambrolite-ST; Ambros-GM; Ambrosin-T; Ambrosol; Ambroter; Ambrowin; Ambroxit; Amcare; Amcof; Amcold; Amgat; Amlee-P; Amox-AR; Amriz; Amrolite 2S; Amven-C; Amy; Amyrcl; Arbid-A; Arcuf Plus; Arid-D; Arid; Arikof-P; Arolin-XN; Asthalin AX; Atoril; Aurox 50; Avirox-AM; Axalin Expectorant; Axalin-AX†; Axalin; Axol Plus; Axol-XL; Azintra-AX; Azithral Jun; Azro AM; Azyxin Plus; Bluetus; Borox-L; Bricarex A; Brocin; Brocoter-A; Brodil; Brofentol Plus; Bromcough; Broncodil; Broncozone; Bronq; Brox; Broxter; Calscot-AX; Canrox-A; Car-OD; Cedbrox; Ceftas AL; Cetliv A; Cetmet TCF; Cetry Plus; Cetzine-A; Cez-A; Clamoxy A; Clear Chest; Cleded-AT; Cledex-AT; Cobury-AX; Codril-AT; Codril-P; Cofaid-EX; Coftex-AG; Coftex-DMR; Cogof-A; Coldastat-LX; Coldman; Combicold; Cope-D; Corico-CS; Corid-B; Coriminic X; Corophen-A; Coscopin-BR; Cosome-A; Cosyp-E; Covil-A; Cozy-AM; Cozy-AM; Cratex; Cufdex-EX; Decofed-X; Deletus-BX; Dilevocet-Plus; Dilo-BM; DM; Dox-M-A; DYL-AX; Ecogat A; Elcet-P; Elcy-A; Elsol-S; Elsol-T; Euphomin Plus; Ex-GTM; Exituss; Exol; Exolit; Expectus; Festa; Finecef AM; Floxigat M; Fluzet X; Gatikind-AM; Gatrich; Gatus; Hicet-AX; His-P; Historil; Idalez Plus; Indikof-B; Instaryl-P; Intacof-S; Intragat-AM; Kafban; Kazibrox; Kefdil-AX; Kevrox-SA; Kickkof; Kofarest Expectorant; Kofarest; Kofban-EX; Kofrid Plus; Koxcure; Kufgen-X; Kufnil-A; L-Cin-A; L-Triz Plus; L-Triz-A; Laveta-A; Laz-AX; Lazine Plus; LCF; LCZ-Plus; LCZ-XP; Le Zyncet-A; Lebact-AM; Lecope-AD; Leczine-A; Lenex; Lepit-A; Lepit-AM; Leverest-AM; Levocet Plus; Levogo Plus; Levoriz-AM; Levostar Plus Exp; Levostar Plus; Levostar-AM; Levotan; Levotra-A; Levzed-A; Lezo-AM; LFast-AM; LG Plus; LG-Plus; Litcoff-P; Litcoff; Livbest-AM; Lorex-AP; Lorfast-AM; Lorfast-AM; Luzer-A; Mags; Marex; Medirox-A; Microdox; Mituss-AX; Mucaryl-AX; Mucobar-S; Mucoclav; Mucomelt-A; Mucomox; Mucopen; Mucoresp Plus; Mucoresp-CT; Mucoresp-CZ; Mucoresp; Mucovent; Munorm; Muscarin; Mutech; Nam Cold-SR; NBLcet Plus; Nizla Plus; Norvent; Novamox AX; Nozik; NT-Kuf-AM; Nucope-AD; Nutuss-A; Oox-LC; Oox-P; Oox; Optex-AT; Roxeptin-ME; Suprivent-A; ***Mex.***: Acimox-Ex; Aeroflux; Alerfin Ex; Alexing; Ambodil-C; Aminoefedrison; Apomuxol; Balsibron-C; Biovicam Ex; Bisincof; Brogal Compositum; Brogal-T; Brogamax; Brominol-C†; Bronar; Bronolban-M; Broquixol; Brosolan C†; Broxofar Compuesto; Broxol Air; Broxol Plus; Broxolim-C; Brumax; Cefabroxil; Cibronal; Cobadex; Connex; Coricidin Expec; Dexbrolex; Dexol; Dexoltryn; Dinolan; Dizolvin-Flux; Dofaxil; Doralan-Ax; Ebromin P; Faribrox; Ferlex; Flamebin; Fludexol-CL; Fluvicil; Fluxibit; Fluxol; Fultac; Gelamxol; Gimabrol†; Histiacil NF; Laritol Ex; Linfarden; Loexom FC; Loexom FS; Loxorol; Mucoflux; Mucosolvan Compositum; Mucovibrol Amoxi; Mucovibrol C; Musaldox; Neumyn-AS; Pentibroxil; Plexus; Ravotaf; Removil; Rezplen; Rombox; Salamflux; Sekretovit Amoxi; Sekretovit Ex; Sensibit XP; Septacin Amoxi; Septacin Ex; Seraxol; Serbol; Sermoxol; Sibilex; Solbotex; Solcibrol; Tadinar-C; Tavexyl; Tesalon Tenalif; Tesofan Ex; TheraFlu Tenalif; Torva; Toxol; Ulax-C; Vanmoxol†; ***Port.***: Clembroxol; Mucospas; Ventoliber; ***Rus.***: Codelac Broncho (Коделак Бронхо); Codelac Broncho with Thymus Serpyllum (Коделак Бронхо с Чабрецом Обусловлено); Coldact Broncho (Колдакт Бронхо); Rinicold-Broncho (Риниколд Бронхо); ***Ukr.***: Coldact Broncho (Колдакт Бронхо)†; Helpex Breathe (Хелпекс Бриз); Milistan Cough (Мілістан Кашлю); Milistan Cough Hot Tea (Мілістан Гарячий Чай Від Кашлю); Pectolvan C (Пектолван Ц); Pulmolor (Пульмолор); Salbroxol (Сальброксол); ***Venez.***: Aeroflux; Ambroclar; Ambromuco Compositum; Arbixil; Clenbuxol; Litusix Compositum; Mucolin; Mucosolvan Compositum.

Amidefrine Mesilate *(BANM, rINN)* ⊗

5190; Amidefrina, mesilato de; Amidéfrine, Mésilate d'; Amidefrini Mesilas; Amidephrine Mesylate (USAN); Amidephrine Mesylate; Mesilato de amidefrina; MJ-5190; Амидефрина Мезилат.

3-(1-Hydroxy-2-methylaminoethyl)methanesulphonanilide methanesulphonate.

$C_{10}H_{16}N_2O_3S,CH_4O_3S$=340.4

CAS — 3354-67-4 (amidefrine); 1421-68-7 (amidefrine mesilate).

UNII — S3IG39T94B.

Profile

Amidefrine mesilate is a sympathomimetic with alpha-adrenergic activity similar to that of phenylephrine (p. 1672.2). It is used for its vasoconstrictor properties in the local treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Fentrinol.

Ammonium Acetate

Amonio, acetato de; Amonowy octan; Ацетат Аммония; Уксуснокислый Аммоний.

$CH_3CO_2NH_4$=77.08

CAS — 631-61-8 (ammonium acetate); 8013-61-4 (ammonium acetate solution).

UNII — RRE756S6Q2.

Pharmacopoeias. *Br.* includes Strong Ammonium Acetate Solution.

Ammonium Bicarbonate *(BAN)*

Ammonii hydrogenocarbonas; Ammonium, bicarbonate d'; Ammónium-hidrogén-karbonát; Ammoniumvätekarbonat; Ammoniumvetykarbonaatti; Amonio, bicarbonato de; Amonio-vandenilio karbonatas; E503; Hydrogenuhličitan amonný; Бикарбонат Аммония; Гидрокарбонат Аммония; Двууглекислый Аммоний.

Ammonium hydrogen carbonate.

NH_4HCO_3=79.06

CAS — 1066-33-7.

UNII — 45JP4345C9.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ammonium Hydrogen Carbonate; Ammonium Bicarbonate BP 2014). A fine, white or almost white, slightly hygroscopic, crystalline powder or white or almost white crystals. It volatilises rapidly at 60 degrees; volatilisation takes place slowly at ambient temperatures if slightly moist. It is in a state of equilibrium with ammonium carbamate. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

The BP 2014 directs that when Ammonium Carbonate is prescribed or demanded Ammonium Bicarbonate shall be dispensed or supplied.

Ammonium Carbonate

Amonio, carbonato de; Amonowy węglan; Carbonato de Amonio; E503; Карбонат Аммония; Углекислый Аммоний.
CAS — 8000-73-5.
UNII — NJ5VT0FKLJ.

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 31: (Ammonium Carbonate). A white powder, or hard, white or translucent masses having a strong odour of ammonia, without empyreuma. It consists of ammonium bicarbonate and ammonium carbamate, in varying proportions. It yields 30 to 34% of NH_3. On exposure to air it loses ammonia and carbon dioxide, becoming opaque, and is finally converted into friable porous lumps or a white powder of ammonium bicarbonate. Soluble 1 in 4 of water. It is decomposed by hot water. Its solutions are alkaline to litmus. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

NOTE. The BP 2014 directs that Ammonium Bicarbonate shall be dispensed or supplied when Ammonium Carbonate is prescribed or demanded.

Ammonium Chloride

510; Ammonii chloridum; Ammonium Chloratum; Ammonium, chlorure d'; Ammoniumchlorid; Ammónium-klorid; Ammoniumklorid; Ammoniumkloridi; Amonio chloridas; Amonio, cloruro de; Amonowy chlorek; Chlorid amonný; Cloruro de Amonio; Muriate of Ammonia; Sal Ammoniac; Хлорид Аммония; Хлористый Аммоний.
NH_4Cl=53.49
CAS — 12125-02-9.
ATC — B05XA04; G04BA01.
ATC Vet — QB05XA04; QG04BA01.
UNII — 01Q9PC255D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Ammonium Chloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water.

USP 36: (Ammonium Chloride). Colourless crystals or white, fine or course, crystalline powder. Is somewhat hygroscopic. Freely soluble in water and in glycerol, and even more so in boiling water; sparingly soluble in alcohol. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers.

Uses and Administration

Ammonium chloride is used as an expectorant in productive cough (p. 1651.2). Other ammonium salts that have been used similarly include the acetate, bicarbonate, camphorate, carbonate, citrate (p. 2441.3), and glycyrrhizate (p. 2520.3).

Giving ammonium chloride produces a transient diuresis and acidosis. It may be used in the treatment of severe metabolic alkalosis (p. 1775.3). Each g of ammonium chloride represents 18.69 mmol of chloride. It is usually given as a 1 to 2% solution by slow intravenous infusion, in a dosage depending on the severity of the alkalosis. A concentrated solution of ammonium chloride may be diluted by sodium chloride injection.

Ammonium chloride may also be used to maintain the urine at an acid pH in the treatment of some urinary-tract disorders. It is usually given orally, often as enteric-coated tablets, in a dose of 1 to 2 g every four to six hours. Higher doses were sometimes used in forced acid diuresis procedures to aid the excretion of basic drugs, such as amfetamines, in severe cases of overdosage (but see p. 2320.1).

Ammonium chloride has been promoted for self administration as a diuretic, for example in premenstrual water retention; an oral dose of 650 mg three times daily for up to 6 days has been suggested, but such use is generally considered inappropriate.

Adverse Effects and Treatment

Ammonium salts are irritant to the gastric mucosa and may produce nausea and vomiting particularly in large doses. Large doses of ammonium chloride may cause a profound acidosis and hypokalaemia which should be treated symptomatically. Intravenous ammonium chloride can cause pain and irritation at the site of injection, which may be decreased by slowing the rate of infusion.

Excessive doses of ammonium salts, particularly if given by rapid intravenous injection, may give rise to hepatic encephalopathy due to the inability of the liver to convert the increased load of ammonium ions to urea.

Precautions

Ammonium salts are contra-indicated in patients with hepatic or renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ammonium chloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Ammonium chloride is absorbed from the gastrointestinal tract. The ammonium ion is converted into urea in the liver; the anion thus liberated into the blood and extracellular fluid causes a metabolic acidosis and decreases the pH of the urine; this is followed by transient diuresis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nyal Bronchitis Cough; ***Ger.***: Extin N; ***Singapore***: Lin So Peppermint Cough.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austria***: Cranagil; Tonsan chronisch; ***Canad.***: Nareel†; ***Chile***: Rinoplex; ***Fr.***: Vinicard†; ***Ger.***: Muco-cyl L Ho-Len-Complex; ***Hung.***: Naso-Heel S; ***Switz.***: Regenaplex Nr 28b; Regenaplex Nr. 79.

Pharmacopoeial Preparations
BP 2014: Ammonium Chloride Mixture; Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Strong Ammonium Acetate Solution; White Liniment;
USP 36: Ammonium Chloride Delayed-release Tablets; Ammonium Chloride Injection; Aromatic Ammonia Spirit; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution.

Benproperine *(rINN)*

ASA-158/5 (benproperine phosphate); Benproperiini; Benproperin; Benproperina; Benpropérine; Benproperinum; Бенпроперин.
1-[2-(2-Benzylphenoxy)-1-methylethyl]piperidine.
$C_{21}H_{27}NO$=309.5
CAS — 2156-27-6.
ATC — R05DB02.
ATC Vet — QR05DB02.
UNII — 3AA6IZ48YK.

Pharmacopoeias. *Chin.* includes the phosphate.

Profile

Benproperine is used as a cough suppressant in non-productive cough (p. 1651.2). It is reported to have a peripheral and central action and has been given in usual oral doses of 25 to 50 mg two to four times daily as the phosphate. Benproperine embonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fa Si Te (法思特); Fu Song (服松); Ke Pai Ning (咳哌宁); Ke Te (科特); KeLiTing (可立停); Pai Xin (哌欣); Shan Qing (山清); ***Ger.***: Tussafug; ***Hong Kong***: Cofrel; ***Jpn***: Flaveric.

Benzonatate *(BAN, rINN)*

Bensonatat; Bentsonataatti; Benzonatato; Benzonatatum; Benzononatine; KM-65; Бензонатат.
3,6,9,12,15,18,21,24,27-Nonaoxaoctacosyl 4-butylaminobenzoate.
$C_{13}H_{18}NO_2(OCH_2CH_2)_nOCH_3$, where *n* has an average value of 8
CAS — 104-31-4 (where n = 8).
ATC — R05DB01.
ATC Vet — QR05DB01.
UNII — 5P4DHS6ENR.

Pharmacopoeias. In *US.*

USP 36: (Benzonatate). A clear, pale yellow, viscous liquid having a faint characteristic odour. Soluble 1 in less than 1 of water, of alcohol, of chloroform, and of ether; freely soluble in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Benzonatate is a cough suppressant used in non-productive cough (p. 1651.2); it is stated to act peripherally. It is related to tetracaine (p. 1996.3) and has a local anaesthetic action on mucosa. It is given to adults and children over the age of 10 years in an oral dose of 100 or 150 mg three times daily; up to 600 mg daily in divided doses may be given if necessary. Benzonatate is reported to act within about 20 minutes and its effects are reported to last for 3 to 8 hours.

Administration in children. For doses of benzonatate in children, see Uses and Administration, above.

Adverse Effects

Headache, dizziness, sedation, confusion, and visual hallucinations have been reported with benzonatate use. Other adverse effects include gastrointestinal disturbances, nasal congestion, an ocular burning sensation, pruritus, and rashes. Local anaesthetic properties can produce numbness of the mouth, tongue, and pharynx if oral preparations are chewed or sucked instead of being swallowed whole. Hypersensitivity reactions, possibly related to local anaesthesia, have included bronchospasm, laryngospasm, and cardiovascular collapse. CNS stimulation and convulsions, followed by CNS depression, may occur in overdosage; cardiac arrhythmias have also been recorded.

Overdosage. A review[1] of 2172 cases of benzonatate toxicity found moderate or major effects reported in 116 (5%). Cardiac and CNS effects were most frequently reported, including tachycardia, ventricular arrhythmia, cardiac arrest, asystole, hypotension, agitation, seizures, and coma. This included 4 deaths due to dysrhythmias. Based on 676 cases, the authors suggested that an oral dose of 200 mg or more has the potential to cause serious adverse effects in children less than 6 years old. The FDA[2] has warned that in children less than 10 years of age, signs and symptoms of overdosage can occur within 15 to 20 minutes, and that deaths have been reported within hours of accidental benzonatate ingestion.

1. Winter ML, *et al.* Benzonatate ingestion reported to the National Poison Center Database System (NPDS). *J Med Toxicol* 2010; **6**: 398–402.
2. FDA. FDA drug safety communication: death resulting from overdose after accidental ingestion of Tessalon (benzonatate) by children under 10 years of age (issued 14/12/10). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm236651.htm (accessed 20/12/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Benz; ***Mex.***: Beknol; Benzonal; Bronpax†; Capsicof; D-Tato; Lemtosid†; Nafatosin; Novapsyl; Pebegal; Pharben; Supracof; Tesalon; Tesopen†; Texoven; Tusical†; Tusitato; Tuzzil; Velpro; ***USA***: Tessalon; Zonatuss.

Pharmacopoeial Preparations
USP 36: Benzonatate Capsules.

Bibenzonium Bromide *(BAN, rINN)*

Bibenzonii Bromidum; Bibenzonio, bromuro de; Bibenzonium, Bromure de; Bromuro de bibenzonio; Diphenetholine Bromide; ES-132; Бибензония Бромид.
[2-(1,2-Diphenylethoxy)ethyl]trimethylammonium bromide.
$C_{19}H_{26}BrNO$=364.3
CAS — 59866-76-1 (bibenzonium); 15585-70-3 (bibenzonium bromide).
ATC — R05DB12.
ATC Vet — QR05DB12.
UNII — 4455J9277Q.

Profile

Bibenzonium bromide is a cough suppressant used in non-productive cough (p. 1651.2) which is stated to have a central action; it has been given orally.

Bromhexine *(BAN, rINN)*

Bromexina; Bromhexin; Bromhexina; Bromhexinum; Bromiheksiini; Butamirat; Бромгексин.
2-Amino-3,5-dibromobenzyl(cyclohexyl)methylamine.
$C_{14}H_{20}Br_2N_2$=376.1
CAS — 3572-43-8.
ATC — R05CB02.
ATC Vet — QR05CB02.
UNII — Q1J152VB1P.

Bromhexine Hydrochloride

(BANM, USAN, rINNM)

Bromheksino hidrochloridas; Bromhexina, hidrocloruro de; Bromhexine, chlorhydrate de; Brómhexin-hidroklorid; Bromhexinhydrochlorid; Bromhexin-hydrochlorid; Bromhexinhydroklorid; Bromhexini hydrochloridum; Bromiheksiinihydrokloridi; Bromoheksyny chlorowodorek; Cloridrato de Bromexina; Hidrocloruro de bromhexina; NA-274; Бромгексина Гидрохлорид.

$C_{14}H_{20}Br_2N_2,HCl$=412.6
CAS — 611-75-6.
ATC — R05CB02.
ATC Vet — QR05CB02.
UNII — YC2ZOM3Z8V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Bromhexine Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Uses and Administration

Bromhexine is a mucolytic used in the treatment of respiratory disorders associated with productive cough (p. 1651.2). Bromhexine is usually given orally in a dose of 8 to 16 mg of the hydrochloride three times daily. It has also been given by deep intramuscular or slow intravenous injection or inhaled as an aerosol solution.

Bromhexine has also been used orally and topically in the treatment of dry eye syndromes associated with abnormal mucus production (see below).

Dry eye. Bromhexine has been used orally in the treatment of dry eye (p. 2190.1) in Sjögren's syndrome but results have been conflicting; it appears to have no effect on tear secretion in healthy subjects.[1] It has also been tried topically.

1. Avisar R, *et al.* Oral bromhexine has no effect on tear secretion in healthy subjects. *Ann Pharmacother* 1996; **30:** 1498.

Respiratory-tract infection. *USE WITH AN ANTIBACTERIAL.* Bromhexine has been shown to enhance the penetration of erythromycin into bronchial secretions.[1] Although bromhexine is used as an adjuvant in the treatment of respiratory infections, few controlled studies appear to have been conducted to determine if any additional benefit is obtained. However, some studies have found improved responses with cefalexin[2] and amoxicillin.[3]

1. Bergogne-Berezin E, *et al.* Etude de l'influence d'un agent mucolytique (bromhexine) sur le passage de l'érythromycine dans les sécrétions bronchiques. *Therapie* 1979; **34:** 705–11.
2. Boraldi F, Palmieri B. Antibiotic and mucolytic therapy in elderly patients with different cases of bronchopulmonary diseases. *Curr Ther Res* 1983; **33:** 686–91.
3. Roa CC, Dantes RB. Clinical effectiveness of a combination of bromhexine and amoxicillin in lower respiratory tract infection: a randomized controlled trial. *Arzneimittelforschung* 1995; **45:** 267–72.

Adverse Effects

Gastrointestinal adverse effects may occur occasionally with bromhexine and a transient rise in serum aminotransferase values has been reported. Other reported adverse effects include headache, dizziness, sweating, and skin rashes. Inhalation of bromhexine has occasionally produced cough or bronchospasm in susceptible subjects.

Precautions

Since mucolytics may disrupt the gastric mucosal barrier bromhexine should be used with care in patients with a history of peptic ulcer disease. Care is also advisable in asthmatic patients. Clearance of bromhexine or its metabolites may be reduced in patients with severe hepatic or renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bromhexine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations occur after about 1 hour. Bromhexine undergoes extensive first-pass metabolism in the liver: its oral bioavailability is stated to be only about 20%. It is widely distributed to body tissues. About 85 to 90% of a dose is excreted in the urine mainly as metabolites. Ambroxol (p. 1654.3) is a metabolite of bromhexine. Bromhexine is highly bound to plasma proteins. It has a terminal elimination half-life of 13 to 40 hours. Bromhexine crosses the blood-brain barrier and small amounts cross the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Amiorel; Aseptobron Expectorante; Balsasulf; Bisolvon; Bromexidril; Bromhetos; Broncocalmine; Brondilax; Bronquisedan Max; Bronquisedan Pediatrico; Catarrosine; Expectosan Extra Forte; Fadatos NF; Funciobron B; Lisi-Tos; Lorbi-Bis; Lorbi; Medex; Namir; Nastizol Expectorante; No-Tos Mucolitico; Pulmonix; Pulmosan; Qura Plus; Sandival†; Toscalmin; Tostop; ***Austral.***: Bisolvon Chesty; Duro-Tuss Chesty Cough; Duro-Tuss Mucolytic Cough Liquid†; ***Austria***: Bisolvon; ***Belg.***: Bisolvon; Bromex; Bronchi-Mereprine†; ***Braz.***: Bisolphar; Bisolvon; Bispect; Bisuran; Bronxina; ***Chile***: Bisolvon; Bropavol; Flumed†; Noremine; ***China***: Ao Qun (傲群); Fei Li Xing (菲力星); Fu Zhi (伏枝); HeKeDiSi (赫克迪思); Ka Bei (卡贝); Pu Ni Ke Si (普尼克斯); Sai Wei (赛维); ***Cz.***: Mucohex†; Paxirasol; ***Denm.***: Bisolvon; ***Fin.***: Bisolvon; Medipekt; Mucovin; ***Fr.***: Bisolvon; ***Ger.***: Bisolvon; ***Gr.***: Bisolvon; Bolisegna; Bromiramin; Bron-Hal; Bronchotussine; Butilen; Diamelitus; Neo-Pulmolysine; Seltak; ***Hong Kong***: Bisofan; Bromoson; Bromxine; Duro-Tuss Mucolytic; Ekxine; Exolit†; Extovon†; Hosolvon†; Uni-Hexine†; Vasican; ***Hung.***: Paxirasol; ***India***: Bisolvon; Bromex; ***Indon.***: Bisolvon; Bromika; Dexolut; Ethisolvan; Exovon†; Farmavon; Hexon; Hustab P; Lexavon; Mucobron; Mucohexin; Mucosolvan; Poncosolvon; Solvinex; Thephidron; Yavon; ***Irl.***: Bisolvon; ***Israel***: Movex; Mucoless; Solvex; ***Ital.***: Bisolvon; ***Jpn***: Bisolvon; ***Malaysia***: Beacolytic; Bislan; Bromxine; Disol†; Mucolex; Mucolix; Mucoxin; Vasican; ***Mex.***: Bisolvon; Bromicof; Fluexin; Meroxan†; Nastizol Ex; Normoflex; Tesacof; Toridran-N; ***Neth.***: Bisolvon; Darolan Slijmoplossende†; Kruidvat Hoestdrank Broomhexine; Kruidvat Hoestelixer†; Kruidvat Hoesttabletten Broomhexine; Otrivin; Trekpleister Hoesttabletten; ***Norw.***: Bisolvon; ***NZ***: Bisolvon; Duro-Tuss Chesty Cough; ***Philipp.***: Bidocsol; Bisolvex; Bisolvon; Broxol; Dur-Elix†; Easepex†; Extruss; Fleminate; Mucolyptus; Muconix; Mucosform; Xinebrom; ***Pol.***: Flegamina; ***Port.***: Basiflux; Bisolvon; Bromocal†; Broncoral; Lisomucin; Tosseque; ***Rus.***: Flegamin (Флегамин)†; Solvin (Солвин); ***S.Afr.***: Bisolvon; Bronkese†; ***Singapore***: Asthmaxine; Bislan; Bisolvon†; Bromxine; Duro-Tuss Chesty Cough; Duro-Tuss Chesty Cough; Exolit; Hosolvon; Mucolix; Mucosol; Vasican; ***Spain***: Bisolmed; Bisolvon; ***Swed.***: Bisolvon; Bromhex; ***Switz.***: Bisolvon; ***Thai.***: Asovon; Axistal; Belen; Bioxine; Bisoltab; Bisolvon; Bomexin†; Bromcolex; Bromex; Bromhex; Bromoson; Bromso; Bromtussin; Bromxin; Bromxine; Bronclear; Bronkase; Bronmucon; Brovol; Buzetin; Cohexine; Disol; Dutross; Extovon; Ida; Jimax; Manovon; Mihexine†; Mucine; Mucocin; Mucola; Mucopac; Mucoxin†; Musovon; Ohexine; Romulin; St Luke's Cough; Tromadil†; Usovan; ***Turk.***: Bromek; Bromeksin; Viscol; ***UAE***: Mucolyte; ***Venez.***: Bedena; Bexilon; Bisectron; Bisolvon; Bromedrina; Bromexol; Bromox; Inquixol; Kecnitril; Lisomucin; Mucobrol; Reosil; Teraflem.

Multi-ingredient Preparations. ***Arg.***: Agrip; Amiorel Compuesto; Amox-G Bronquial; Amoxidal Respiratorio; Amplibenzatin Bronquial; Aseptobron Bromexina; Bio Grip Classic; Bisolvon Compositum; Cofron; Cor-Tagrip; Coris Grip; Dosulfin Bronquial; Duflegrip; Eritrobron; Espectocural; Factor Antigripal; Farintos; Finagrip Forte; Frenotos Muc; Grinsil Respiratorio; Gripaben; Matrix Grip†; Nastizol Compositum; Neumobacticel; Nexogrip; No-Tos NF; Notozen†; Panotos NF; Panotos; Paracetamol Grip NF; Pectoral Hebert; Piritos; Pulmocler; Pulmonix Grip; Qura; Refrianex Compuesto; Refrianex; Rupediol; Selectus FN; Selectus; Termogrip; Toxam; Toxambay; ***Austral.***: Benadryl Chesty Forte; Bisolvon Sinus†; Chemists Own Chesty Cough; Chemists Own Chesty Mucus Cough; Dimetapp Chesty Cough; Duro-Tuss Chesty Cough Forte; Duro-Tuss Chesty Cough Plus Nasal Decongestant; Duro-Tuss Expectorant; Duro-Tuss Sinus†; Robitussin Chesty Cough Forte; Tussinol Expectorant†; ***Braz.***: Broncatar; Bronco-Polimoxil; ***Chile***: Bauxol; Brontal; Diadicon; Esantuss; Mucobrol; Plus-Tos; ***China***: An Bu (安卜); Bi Li (毕利); Cha Xin Na Min (茶新那敏); Pu Kuai (浦快); Xi Meng (熙蒙); Xiaoke (消刻); Zheng Da Su Ke (正大素克); ***Cz.***: Bronchosan†; ***Hong Kong***: America†; Barlodin†; Bromcolin†; Bronco-DM†; Broncodin†; Cofetal†; Coltalin-GP Extra; Coughlin†; Decaugh II†; DF Multi-Symptom†; Duro-Tuss Expectorant; Fastolin†; Fusta†; Futalin†; Futara†; Mecostop†; Methor-Co†; Metoplex; Nosbrom†; Robitussin ME; Vida Cough†; Vidatapp Forte†; ***Hung.***: Nasopax; ***India***: Adcold-BR; Adcold-SBG; Aeromox; Albutamol; Alernyl-B; Alerpect; Alpha-Zedex; Ambitus; Amexine; Anacuf; Ascodex Plus; Ascodryl; Ascoril Expectorant; Ascoril; Asi-Ril; Asma-ZED; Asmatide-BR; Asmotone Plus; Ast-Ex; Asthakind; Asthavent-BR; Asthos; Atus-D; Benituss; Benylin E; Bex; Blast; Brachy; Brex-S; Brex; Brex; Bro-Zedex; Brofentol; Bromolin; Bronchosolvin; Broncorex; Bronkex; Bronkosyrup-EX; Bronmix; Bronsim; Browin Junior; Browin-TG; Brozeet; C-Cold; Capex-Bron Exp; Carecof; CC-Koff; Cefel-B; Celar; Cep-Bro; Chescare; Cheston DT; Cheston Exp; Cheston; Cinkof; Cleartuss-D; Cleartuss-T; Cof Q; Cof QX; Cofal; Cofdex Forte; Cofdex-P; Cofdex; Cofpet-DX; Cofsym; Coftex-BT; Cofvyn; Cor-4; Corinite; Cos-P; Coscoril; Cosome Exp; Cufokin; DCol-BR; Deletus P; Dolar; Dr Koff; Eascof Exp; Eascof; Edomox-B; Efelin-X; Efelin; Eledyl; Elite-P; Elkof; Elkuf; Eltocin-BR; Ep-Koff; Ero-B; Esma-PD; Estharil Plus; Eto-Salbetol; Etoxin-B Exp; Etoxin-B; Exiplon-BR; Expect-T; Flemnil; Flu-4-BR; Flu-4; Gocold; Grilinctus-BM; Hanex; Heximox; Himox-B; Ingahist-X; Ingahist; Instaryl; Intenoal; Kalzibrox-BT; Kno-OL; Kofend-X; Kofkul; Koforil; Kofryl-P; Kuff-Q; Kuff-Q; Kuff-X; Kufkair; Kufnil-A; Labocof; Lamoxy-BX; Lemo Linctus; Lemohist-BG; Libitus Plus; Medkof; Megaril; Megatuss-P; Mexol-G; Mituss-BR; Monamox-BR; Moxbro; Moxind BR; Muco Asthalin; Mucolinc; Mucomelt-XP; Mucorid; Mucosol; Mulitmix; Multimix; Mycocin; Neorex; New Zephrol; Nomorcuf; NSI-Ril; NT-Kuf-M; Nutuss-BR; Okaril Plus; Okaril; Otymox; Oxybro; Pulmo-Rest Expectorant†; Pulmo-Rest; Respimox; Sedosolvin; Siokof-P; Solvin; Suprivent; Terpect; Terpect; Terphylate; Toscof; Tuspel Plus; Zedex-P; Zedex; Zeecof; Zeet; Zeet; ***Indon.***: Bisolvon Extra; Bisolvon Flu; Bodrex Flu & Batuk Berdahak; Bodrexin Flu & Batuk; Brolexan†; Fortusin; Halmezin; Hustab; Mucotussan†; Nufadipect; Oskadon Flu & Batuk Berdahak; Woods' Peppermint Expectorant; ***Irl.***: Alupent Expectorant†; ***Ital.***: Tauglicolo; ***Malaysia***: Duro-Tuss Expectorant; Duro-Tuss Sinus†; Hosolvan DM; ***Mex.***: Acroxil-C; Ambrexin†; Amoxibron; Arlexen B; Berosolvon; Bisolpent Ex; Bisolvon A; Bisolvon E; Bremoxiral; Bromel†; Bromixen; Bromoxil; Brupen Compuesto; Ceclordox; Cepobrom; Duracef Expec; Eriwest; Fasinat; Fluxedan; Hidramox-M; Kodel; Lumoxbron S; Mucocef; Mucoxina; Pantobron; Penamox M; Penbritin Ex; Pentibrom; Pentrexyl Expec; Quimobrom; ***NZ***: Benadryl Chesty Forte; Duro-Tuss Expectorant; Robitussin ME; ***Philipp.***: Bisolpent; Mucosform; Pecof; ***Pol.***: Flegatussin†; ***Rus.***: Ascoril Expectorant (Аскорил Экспекторант); Bronchosan (Бронхосан); Jocet (Джосет); Kasnol (Кашнол); Zedex (Зедекс)†; ***S.Afr.***: Adco-Linctopent; Benylin Chesty; Bisolvon Linctus DA; Bronkese Compound; Duro-Tuss†; Flemeze; ***Singapore***: Duro-Tuss Expectorant; Robitussin ME; SP-Brom; ***Spain***: Bactopumon; Balsoprim; Bisolvon Compositum†; Bronco Aseptilex Fuerte†; Bronco Tonic†; Bronquidiazina CR; Clamoxyl Mucolitico; Pulmo Borbalan†; ***Swed.***: Mollipect; ***Thai.***: Bisolvon EX; Bromso-Ex; Bromsuno; Bronchoprex Expectorant; Dexbroxine; Dutross-P; Ida-D; Kupa; Mucolate; Nasorest Expectorant; Pabron Cough; Presco; Robitussin ME; Tauglicolo; Tusno; ***Ukr.***: Ascoril Expectorant (Аскорил Экспекторант)†; Bro-Zedex (Бро-Зедекс)†; Bronchosan (Бронхосан)†; Helpex Anticold Syrup (Хелпекс Антиколд Сироп); Joset (Джосет); Zedex (Зедекс); ***Venez.***: Broxodin; Opilina Compuesta; Oxolavin Compuesto; Tolmex.

Brovanexine Hydrochloride *(rINNM)*

Brovanexina, hidrocloruro de; Brovanexine, Chlorhydrate de; Brovanexini Hydrochloridum; Hidrocloruro de brovanexina; Брованексина Гидрохлорид.

4-(Acetyloxy)-*N*-[2,4-dibromo-6-[(cyclohexylmethylamino)methyl]phenyl]-3-methoxybenzamide monohydrochloride.

$C_{24}H_{29}Br_2ClN_2O_4$=604.8

CAS — 54340-61-3 (brovanexine); 54340-60-2 (brovanexine hydrochloride).

UNII — 5114I50SMG.

Profile

Brovanexine is a derivative of bromhexine (p. 1656.3) and is given orally as the hydrochloride, usually as an adjunct to antibacterials in preparations for the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Bronquimucil†; ***Spain***: Broncimucil.

Multi-ingredient Preparations. ***Arg.***: Trifamox Bronquial.

Butamirate Citrate *(BANM, USAN, rINNM)*

Abbott-36581; Butamirát-citrát; Butamirate, Citrate de; Butamirati Citras; Butamirato, citrato de; Butamyrate Citrate; Citrato de butamirato; HH-197; Бутамирата Цитрат.

2-(2-Diethylaminoethoxy)ethyl 2-phenylbutyrate dihydrogen citrate.

$C_{18}H_{29}NO_3,C_6H_8O_7$=499.6

CAS — 18109-80-3 (butamirate); 18109-81-4 (butamirate citrate).

ATC — R05DB13.

ATC Vet — QR05DB13.

UNII — 67HP51L98R.

Profile

Butamirate citrate is a cough suppressant used in non-productive cough (p. 1651.2) and stated to have a central action. The usual oral dose is up to 30 mg daily in 3 or 4 divided doses; some countries permit up to 90 mg daily in divided doses. Modified-release tablets containing 50 mg have been given 2 or 3 times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dosodos; Proking NF; Talasa NF; Tossec; ***Belg.***: Sinecod; ***Cz.***: Sinecod; Tussin; ***Gr.***: Antis; Antitoss; Bartil; Betavix; Boutavixal; Bronchofyl; Butacodin; Butagan; Butamir; Butrin; Buvastin; Chemisolv; Chributan; Codexine-R; Codimin; Devix; Doctamine; Drosten; Ellisek-S; Gertotus; Leogumil; Lotrecin; Mebronol; Minatuss; Nontoss; Novamir; Oaxen; Pandigal; Pintal; Roctylan; Rondover; Safarol; Sinecod; Siroflex; Stilex; Velkacet; Verocod; Vilvom; Zeleven; Zetapron; ***Hung.***: NeoCitran Antitussive†; Sinecod; ***Ital.***: Butiran; Lenistar†; Lexosedin; Sinecod Tosse Sedativo; ***Neth.***: Sinecod; ***Philipp.***: Sinecod; ***Pol.***: Sinecod; Supremin; ***Port.***: Sinecod; ***Rus.***: Omnitus (Омнитус); Panatus (Панатус); Sinecod (Синекод); ***Switz.***: DemoTussol; NeoCitran Antitussif; Sinecod;

The symbol † denotes a preparation no longer actively marketed

Thai.: Sinecod; ***Turk.***: Butamcod; Butirol; Kreval; Sinecod; Solmirat; Tusamol; Tussia.

Multi-ingredient Preparations. ***Arg.***: Muco Dosodos; ***Cz.***: Stoptussin; ***Rus.***: Stoptussin (Стоптуссин); ***Switz.***: Hicoseen†; ***Ukr.***: Pectolvan Stop (Пектолван Стоп); Stoptussin (Стоптуссин).

Butetamate Citrate *(BANM, rINNM)*

Butétamate, Citrate de; Butetamati Citras; Butetamato, citrato de; Butethamate Citrate; Butethamate Dihydrogen Citrate; Citrato de butetamato; Бутетамата Цитрат.

2-Diethylaminoethyl 2-phenylbutyrate citrate.

$C_{16}H_{25}NO_2,C_6H_8O_7$=455.5

CAS — 14007-64-8 (butetamate); 13900-12-4 (butetamate citrate).

UNII — 70430R0X79.

Profile

Butetamate citrate is reported to be an antispasmodic and bronchodilator and has been used alone or in combination preparations for the symptomatic treatment of coughs and other associated respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Heliphenicol.

Multi-ingredient Preparations. ***Arg.***: Apracur Antigripal; Bio Grip 4; Bronquisedan; Febrigrip; Fugafebril; Kiper; Matrix Grip Antigripal; Mejoral Grip; Mucoprednibron; No-Tos NF; Piritos; Pulmocler; Refenax Jarabe; Tavinex Antigripal; ***Austria***: Influbene†; ***Switz.***: Bronchotussine†.

Calcium Iodide

Calcii Iodidum; Calciumjodid; Ioduro de calcio; Kalcio jodidas; Kalsiumjodidi; Йодид Кальция.

CaI_2=293.9

CAS — 10102-68-8.

UNII — 8EKI9QEE2H (calcium iodide); 4B9QO6S58D (calcium iodide hexahydrate).

Pharmacopoeias. *Eur.* (see p. vii) includes the tetrahydrate for homoeopathic preparations.

Ph. Eur. 8: (Calcium Iodide Tetrahydrate for Homoeopathic Preparations; Calcii Iodidum Tetrahydricum ad Praeparationes Homoeopathicas). A white or almost white, very hygroscopic, powder. Very soluble to freely soluble in water and in alcohol. Store in airtight containers.

Profile

Calcium iodide has been used orally in expectorant mixtures. The limitations of iodides as expectorants are discussed under Cough, p. 1651.2. The actions of the iodides are discussed under Iodine (p. 2336.3).

Homoeopathy

Calcium iodide has been used in homoeopathic medicines under the following names: Calcium iodatum; Calcium jodatum; Calcarea iodata; Cal. iod.; Calc iod.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Calcidrine; Norisodrine with Calcium Iodide.

Homoeopathic Preparations. ***Austria***: Exangina†; ***Canad.***: Barijodeel†; Minerals+; Rexorubia†; ***Fr.***: Rexorubia; Scrofularia Compose; ***Ger.***: Angina-Gastreu S R1; Lymphaden Lymphdrusentabletten; Mullersche Tabletten; Otimed; ***Switz.***: Sinusin; Strumeel N; ***Venez.***: Strumeel T.

Carbocisteine *(BAN, rINN)*

AHR-3053; Carbocistein; Carbocisteína; Carbocistéine; Carbocisteinum; Carbocysteine (USAN); Karbocistein; Karbocisteinas; Karbocisztein; Karbocystein; Karbocysteina; Karbosisteiini; Karbosistein; LJ-206; Карбоцистеин.

S-Carboxymethyl-L-cysteine.

$C_5H_9NO_4S$=179.2

CAS — 2387-59-9; 638-23-3 (carbocisteine, L-form).

ATC — R05CB03.

ATC Vet — QR05CB03.

UNII — 740J2QX53R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Carbocisteine). A white or almost white, crystalline powder. Practically insoluble in water and in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. A 1% suspension in water has a pH of 2.8 to 3.0. Protect from light.

Incompatibility. UK licensed product information states that mixing carbocisteine with pholcodine linctus causes precipitation of carbocisteine from solution but no information is given on whether this incompatibility is with the pholcodine or some component of the formulation used.

Carbocisteine Lysine *(BANM, rINNM)*

Carbocisteína lisina; Carbocistéine Lysine; Carbocisteinum Lysinum; Carbocysteine Lysine; Карбоцистеина Лизин.

CAS — 49673-81-6.

ATC — R05CB03.

ATC Vet — QR05CB03.

UNII — 1D1Y95PXXA.

Carbocisteine Sodium *(BANM, rINNM)*

Carbocisteína sódica; Carbocistéine Sodique; Carbocysteine Sodium; Natrii Carbocisteinum; Натрий Карбоцистеин.

CAS — 49673-84-9 (carbocisteine sodium, L-form).

ATC — R05CB03.

ATC Vet — QR05CB03.

UNII — 2UZV9PEJ2N.

Uses and Administration

Carbocisteine is used for its mucolytic activity in respiratory disorders associated with productive cough (p. 1651.2). It is given orally in a dose of 750 mg three times daily, reduced by one-third when a response is obtained. Carbocisteine is also given orally as the sodium or lysine salts.

For doses in children, see below.

Reviews.

1. Macciò A, *et al*. Carbocysteine: clinical experience and new perspectives in the treatment of chronic inflammatory diseases. *Expert Opin Pharmacother* 2009; **10:** 693–703.

Administration in children. Children aged from 2 to 5 years may be given oral carbocisteine 62.5 to 125 mg four times daily and those aged 5 to 12 years 250 mg three times daily.

Chronic obstructive pulmonary disease. The value of mucolytic therapy in chronic obstructive pulmonary disease (COPD—p. 1199.1) is controversial. Two studies have reported some improvements in lung function in patients with chronic bronchitis given carbocisteine for up to 6 months,[1,2] but it appeared to have no effect on the number of acute exacerbations.[1] However, later studies[3-5] have reported reductions in the number of acute exacerbations; the number of common colds was also lower in the carbocisteine group in one of the studies.[4] Carbocisteine may also produce some beneficial effects on sputum rheology.[2,6]

1. Grillage M, Barnard-Jones K. Long-term oral carbocisteine therapy in patients with chronic bronchitis: a double blind trial with placebo control. *Br J Clin Pract* 1985; **39:** 395–8.
2. Aylward M, *et al*. Clinical evaluation of carbocisteine (Mucolex) in the treatment of patients with chronic bronchitis: a double-blind trial with placebo control. *Clin Trials J* 1985; **22:** 36–44.
3. Allegra L, *et al*. Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: a multicenter, double-blind, placebo-controlled trial. *Respiration* 1996; **63:** 174–80.
4. Yasuda H, *et al*. Carbocisteine reduces frequency of common colds and exacerbations in patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc* 2006; **54:** 378–80.
5. Zheng J-P, *et al*. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet* 2008; **371:** 2013–18.
6. Braga PC, *et al*. Identification of subpopulations of bronchitic patients for suitable therapy by a dynamic rheological test. *Int J Clin Pharmacol Res* 1989; **IX:** 175–82.

Adverse Effects and Precautions

Nausea and gastric discomfort, and gastrointestinal bleeding have occasionally occurred with carbocisteine. Skin rashes have also been reported.

Carbocisteine should be used with caution in patients with a history of peptic ulcer disease because of the risk that mucolytics may disrupt the gastric mucosal barrier.

Effects on endocrine function. Transient hypothyroidism associated with the use of carbocisteine developed in a patient with compromised thyroid function.[1]

1. Wiersinga WM. Antithyroid action of carbocisteine. *BMJ* 1986; **293:** 106.

Pharmacokinetics

Carbocisteine is rapidly and well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after an oral dose. It appears to penetrate into lung tissue and respiratory mucus. Carbocisteine is excreted in the urine as unchanged drug and metabolites. Acetylation, decarboxylation, and sulfoxidation have been identified as the major metabolic pathways. Sulfoxidation may be governed by genetic polymorphism.

References.

1. Karim EFIA, *et al*. An investigation of the metabolism of S-carboxymethyl-L-cysteine in man using a novel HPLC-ECD method. *Eur J Drug Metab Pharmacokinet* 1988; **13:** 253–6.
2. Brockmoller J, *et al*. Evaluation of proposed sulphoxidation pathways of carbocysteine in man by HPLC quantification. *Eur J Clin Pharmacol* 1991; **40:** 387–92.
3. Steventon GB. Diurnal variation in the metabolism of S-carboxymethyl-L-cysteine in humans. *Drug Metab Dispos* 1999; **27:** 1092–7.
4. Jovanovic D, *et al*. A comparative bioavailability study of a generic capsule formulation containing carbocysteine. *Pharmazie* 2006; **61:** 446–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mucolitic; Pectox; Salvitos; ***Belg.***: Balsoclase Mucolyticum; Broncho-pectoralis Carbocisteine; Muco Rhinathiol; Romilar Mucolyticum†; Siroxyl; Soludril Expectorans; ***Braz.***: Carbocin; Carbofan; Carbotoss; Certuss†; Fluilitic; Fluitoss; Mucocis†; Mucocistein; Mucofan; Mucoflux; Mucolab; Mucolisil; Mucolitic; Mucolix†; Mucotoss; Santoss; ***Chile***: Broncotusilan; Carbotos; Coldin; ***China***: Bai Yue (百越); Baling (霸灵); Kang Pu Li (康普利); ***Cz.***: Fenorin; Pectodrill; Sinecosin; ***Fin.***: Reodyn; ***Fr.***: Bronchathiol; Bronchokod; Broncoclar; Bronkirex†; Clarix Expectorant; Drill Expectorant; Ergix Expectorant; Exotoux; Fluditec; Fluvic†; Humex Expectorant; Medibronc; Muciclar†; Pharmakod expectorant†; Rhinathiol; Tussilene†; ***Ger.***: Transbronchin; ***Gr.***: Allstam; Bronchiole; Ceflavit; Chilvax; Convenil; Divalio; Drizak; Duxil; Dynax; Ectofus; Estival; Grossenel; Methovix; Mucopront; Mucorem; Mucothiol; Neo-Adinal; Nystetrin; Pneumol; Pulmoclase; Santamex-Expectorant; Siroxyl; Trusil; ***Hong Kong***: Fluifort; Mucosin; Mucospect; Purasol†; Rhinathiol; Solmux; ***Hung.***: Drill Expectorant; Drill; Fenorin; Mucopront; NeoCitran Expectorant†; Rhinathiol; Solucis†; ***India***: Mucodyne; ***Indon.***: Broncholit; Mucocil†; Solmux†; ***Irl.***: Benylin Mucus Relief; Exputex; Mucodyne; Mucogen†; Mucolex†; PectoDrill; Pulmoclase†; Unicough Chesty; Viscolex; ***Israel***: Mical; Muco-Treat; Mucolit; Mucomed; Mucosol†; ***Ital.***: Broncomucil†; Fluicare; Fluifort; Lisomucil; Mucocis; Mucolase; Mucostar; Mucotreis; Polimucil; Recofluid; Sinecod Tosse Fluidificante; Solucis; ***Jpn***: Mucodyne; ***Malaysia***: Fluifort; Kastipron; Pabron Cough; Rhinathiol; SCMC; ***Mex.***: Arbistin; Expelin; Mucolin Pediatrico; ***Neth.***: Dampo Solvopect†; Mucodyne; Rami Slijmoplossende†; Rhinathiol; ***Philipp.***: Abluent†; Aflem; Ameustyn; Bromycil; Broncocent; Broxytone; Bysbalon; Carboflem; Carbomed; Carbosol†; Ceascol; CRB; Cysdexpel; Emuxel†; Esboxyl; Fayerex; Flemsol; Fluralex; Genecar; Lofenin; Loviscol; Mediphlegm; Nivicof; Pediaplex; Pertussin; Phlegmol; Pulmin-CMC; S-Muxine; Solmux; Solplem†; Trimulex; Viscodec; Westcarbox; Zylotin; Zymelytic; ***Pol.***: Mukolina; PectoDrill; ***Port.***: Drill Mucolitico; Finatux; Griflux; Mucolex†; Mucorespiral; Mucorhinathiol Infantil†; Mucorhinathiol Mucoral; Pulmiben; ***Rus.***: Bronchobos (Бронхобос); Fluditec (Флюдитек); Fluifort (Флуифорт); Libexin Muco (Либексин Муко); Mucodin (Мукодин); Mucosol (Мукосол); ***S.Afr.***: Acuphlem†; Betaphlem; Bronchette; Co-Flem; Dis-chem; Flemex; Flemgo; Flemlite; Flutex; Lessmusec; Medphlem†; Mucoflem†; Mucoless; Mucolinct†; Mucopan; Mucosol; Mucospect; ***Singapore***: Mucodin; Mucon; Rhinathiol; Robitussin CM; SCMC; Solmux; SP-Mucoplex; ***Spain***: Actithiol; Anatac; Cinfamucol; Cisbedal; Fluidin Mucolitico; Frimuce; Iniston Mucolitico; Mucovital; Pectodrill; Pectox; Viscoteina; ***Switz.***: MAKU Mucolytique†; Mephathiol; Mucogeran†; Muco-septal; Pectorex Mucolytique; Pectox; Rhinathiol; Rhinatussol; Rotpunkt Apotheke Mucolytique Sirop†; Tussantiol; ***Thai.***: Amicof; Bocytin; Carbocter; Carbocys; Carbomed; Carbopect; Carsemex; Cisteine; Copharmex; Exflem; Expetan; Flemex; Fluifort; I-Cof; Mucolex; Mucomex; Muflex; Murhinol; Rhinamex; Rhinathiol; Rhinatol; Rhinex; Siflex; Solmux†; Throatsil-CBS; ***Turk.***: Mucobron; Mucosis; Mukoliz; Mukotik; ***UK***: Mucodyne; ***Ukr.***: Fluditec (Флюдитек); Langes (Лангес); ***Venez.***: Broxolflem; Gulaper; Loganil; Loviscol; Mucofar; Mucopront.

Multi-ingredient Preparations. ***Arg.***: Mucolitic Antitusivo; ***China***: Bang Ao Shu (邦奥舒); Kai Yin (凯茵); ***Fr.***: Rhinathiol Promethazine; ***Gr.***: Carbozor; Flemagon; Grupozil; Gutman; Mucostein; Pneumol Plus; Polimucil; Respinorm; Sevlenyl; Sobrein; Sorbexyl; Tussifren; Vanesin; ***Hong Kong***: Mucoprom; Rhinathiol Promethazine; ***India***: Caceff; Carbasma; Carbicef; Carbomox; Carlymox; Carmox; Cecarb; Cidoresp; Cismox; Cystamox; Moxycarb; Mucobron; Muconal; ***Ital.***: Keraflex; Libexin Mucolitico; ***Malaysia***: CP Cough Syrup; Mucoease Plus; Mucoprom; Rhinathiol Promethazine; ***Mex.***: Mucolin; ***Philipp.***: Solmux-Broncho (Reformulated); ***Port.***: Bronquial; Niflux; ***Singapore***: Rhinathiol Promethazine; ***Spain***: Actithiol Antihist; Bronquicisteina†; Eduprim Mucolitico†; ***Switz.***: Rhinathiol Promethazine†; Triofan Rhume; ***Ukr.***: Milistan Cough (Мілістан Кашлю); Pectolvan C (Пектолван Ц).

Clobutinol Hydrochloride *(rINNM)*

Clobutinol, Chlorhydrate de; Clobutinol, hidrocloruro de; Clobutinoli Hydrochloridum; Hidrocloruro de clobutinol; KAT-256; Клобутинола Гидрохлорид.

2-(4-Chlorobenzyl)-3-(dimethylaminomethyl)butan-2-ol hydrochloride.

$C_{14}H_{22}ClNO,HCl$=292.2

CAS — 14860-49-2 (clobutinol); 1215-83-4 (clobutinol hydrochloride).

ATC — R05DB03.

ATC Vet — QR05DB03.
UNII — N2U6799DZQ.

Profile

Clobutinol hydrochloride is a centrally acting cough suppressant for non-productive cough (p. 1651.2) that has been given orally in doses of 40 to 80 mg three times daily; it has also been given by subcutaneous, intramuscular, or intravenous injection. However, the EMEA has recommended for its withdrawal due to the risk of QT interval prolongation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Proking; ***Chile***: Broncodual; Calfetos; Clobotil; Cloval; Pulbronc Simple; ***Gr.***: Silomat.

Multi-ingredient Preparations. ***Arg.***: Bronquisedan Mucolitico; ***Braz.***: Hytos Plus; ***Chile***: Broncodual Compuesto; Cloval Compuesto; Pulbronc; Solvanol; Tusabron†; Vapoflu; ***Gr.***: Silomat Compositum; ***Indon.***: Silomat Compositum†; ***UAE***: Orcinol†.

Clofedanol Hydrochloride *(BANM, rINNM)*

Chlophedianol Hydrochloride (USAN); Clofédanol, Chlorhydrate de; Clofedanol, hidrocloruro de; Clofedanoli Hydrochloridum; Hidrocloruro de clofedanol; SL-S01; Клофеданола Гидрохлорид.
2-Chloro-α-(2-dimethylaminoethyl)benzyl alcohol hydrochloride.
$C_{17}H_{20}ClNO,HCl$=326.3
CAS — 791-35-5 (clofedanol); 511-13-7 (clofedanol hydrochloride).
ATC — R05DB10.
ATC Vet — QR05DB10.
UNII — 69QQ5B99BY.

Pharmacopoeias. In *Jpn*.

Profile

Clofedanol hydrochloride is a centrally acting cough suppressant for non-productive cough (p. 1651.2) that has been given in oral doses of 25 mg three or four times daily. For doses in children, see below.

Administration in children. The following oral doses of clofedanol hydrochloride have been recommended for children:

- 2 to 6 years: 12.5 mg 3 or 4 times daily
- 6 to 12 years: 12.5 to 25 mg 3 or 4 times daily

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Ulone.

Multi-ingredient Preparations. ***Arg.***: Causalon Bronquial; Cofron; Notozen†; Pectoral Hebert; Selectus FN; Toxam; Toxambay; ***Chile***: Bauxol; Brontal; Diadicon; Esantuss; Kolibel; Mucobrol; Plus-Tos; ***USA***: Biclora-D; Biclora; Certuss-D; Chlo Tuss EX; Clofera; Dicel CD; Donatussin; DryMax AF; Prohist CF; Vanacof APE; Vanacof DX; Vanacof GPE; Vanacof-8.

Clonazoline Hydrochloride *(rINNM)* ⊗

Clonazoline, Chlorhydrate de; Clonazolini Hydrochloridum; Hidrocloruro de clonazolina; Клоназолина Гидрохлорид.
2-[(4-Chloro-1-naphthyl)methyl]-2-imidazoline hydrochloride.
$C_{14}H_{13}ClN_2,HCl$=281.2
CAS — 17692-28-3 (clonazoline); 23593-08-0 (clonazoline hydrochloride).

Profile

Clonazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3) used for its vasoconstrictor activity in the local treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Localyn.

Cloperastine *(rINN)*

Cloperastina; Clopérastine; Cloperastinum; HT-11; Клоперастин.
1-[2-[(*p*-Chloro-α-phenylbenzyl)oxy]ethyl]piperidine.
$C_{20}H_{24}ClNO$=329.9
CAS — 3703-76-2 (cloperastine); 132301-89-4 (levocloperastine).
ATC — R05DB21.
ATC Vet — QR05DB21.
UNII — 69M5L7BXEK.

Cloperastine Fendizoate *(rINNM)*

Cloperastina, fendizoato de; Clopérastine, Fendizoate de; Cloperastine Hydroxyphenylbenzoyl Benzoic Acid; Cloperastine Phendizoate; Cloperastini Fendizoas; Fendizoato de cloperastina; Клоперастина Фендизоат.
$C_{20}H_{24}ClNO,C_{20}H_{14}O_4$=648.2
CAS — 85187-37-7 (cloperastine fendizoate); 220329-19-1 (levocloperastine fendizoate).
ATC — R05DB21.
ATC Vet — QR05DB21.
UNII — 2M1053055U.

Cloperastine Hydrochloride *(rINNM)*

Cloperastina, hidrocloruro de; Clopérastine, Chlorhydrate de; Cloperastini Hydrochloridum; Hidrocloruro de cloperastina; Клоперастина Гидрохлорид.
$C_{20}H_{24}ClNO,HCl$=366.3
CAS — 14984-68-0.
ATC — R05DB21.
ATC Vet — QR05DB21.
UNII — PI4N7C63ND.

Pharmacopoeias. In *Jpn*.

Profile

Cloperastine is primarily a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It also has some antihistaminic action. The hydrochloride has been given orally as tablets in usual doses of 10 to 20 mg three times daily. Cloperastine fendizoate is used in oral liquid preparations in equivalent doses. Cloperastine fendizoate 17.7 mg is equivalent to about 10 mg of cloperastine hydrochloride. Levocloperastine fendizoate has been used similarly.

References.

1. Alíprandi P, *et al.* Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. *Drugs Exp Clin Res* 2004; **30:** 133–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Lysotossil; Sekin; ***Braz.***: Seki; Tilugen; ***Hong Kong***: Uncough; ***Ital.***: Cloel; Clofend; Mitituss; Nitossil; Novotossil; Politosse; Privituss; Quik; Seki; ***Jpn***: Hustazol; ***Malaysia***: Copastin; ***Mex.***: Privituss; Sekisan; ***Port.***: Tecnofox; ***Spain***: Flutox; Sekisan.

Multi-ingredient Preparations. ***Thai.***: Hustazol-C.

Cocillana

Grape Bark; Guapi Bark; Huapi Bark; Коккилана.
CAS — 1398-77-2.
*ATC Herb — HR05WA5017 (*Guarea guidonia*: bark).*

Profile

Cocillana is the dried bark of *Guarea guidonia* (*G. rusbyi*, *Sycocarpus rusbyi*, *G. trichilioides*) (Meliaceae), a South American tree. It is used as an expectorant similarly to ipecacuanha (p. 1667.2). It has been used in large doses as an emetic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Codetabs.

Multi-ingredient Preparations. ***Canad.***: Sirop Cocillana Codeine; ***Fin.***: Codesan Comp; ***Hong Kong***: Co-Epherine†; Coci-Fedra-C†; Coci-Fedra†; Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Compound Cocillana†; Coolding†; Dextrocilla; Eurocilana; ***Ital.***: Broncosedina; Broncosedina; ***S. Afr.***: Adco-Cocillana Co; Corbar; ***Swed.***: Cocillana-Etyfin; ***Venez.***: Cerylana.

Coltsfoot

Coughwort; Fárfara; Huflattich; Tusílago; Tussilage; Камчужная Трава.
*ATC Herb — HR05WA5060 (*Tussilago farfara: *flower); HR05WA5061 (*Tussilago farfara: *leaf); HR05WA5062 (*Tussilago farfara: *whole plant).*
*UNII — 6177A89GA2 (*Tussilago farfara*); UEE27X2Q2M (*Tussilago farfara *flower); 6WBB6U5V2Q (*Tussilago farfara *flower bud); 0JXZ63016V (*Tussilago farfara *flowering); G2GH7V846Z (*Tussilago farfara *leaf); F02X1126ZN (*Tussilago farfara *root).*

Pharmacopoeias. *Chin.* and *Fr.* include Coltsfoot Flower.

Profile

The leaves and flowers of coltsfoot (*Tussilago farfara*) have been used for their demulcent and supposed expectorant properties in the treatment of cough and other mild respiratory disorders. However, there has been some concern about potential hepatotoxicity and carcinogenicity due to the content of pyrrolizidine alkaloids.

A review[1] of the actions and uses of coltsfoot pointed out that given the potential risks of its use long-term or in pregnancy, and the availability of other demulcent herbs, the use of coltsfoot preparations to treat throat irritations can no longer be considered appropriate.

1. Berry M. Coltsfoot. *Pharm J* 1996; **256:** 234–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Farfaron.

Multi-ingredient Preparations. ***Arg.***: Arceligasol; Negacne; ***Canad.***: Herbal Cough Syrup†; ***Cz.***: Species Pectorales Planta; ***Fr.***: Mediflor Pectorale d'Alsace no 8†; ***Ital.***: Lozione Same Urto; ***Pol.***: Mucosit; Pyrosal; ***Rus.***: Fitantis (Фитантис); Pectorales Species No 1 (Грудной Сбор 1); Pectorales Species No 2 (Грудной Сбор 2); ***UK***: Antibron; Chesty Cough Relief.

Homoeopathic Preparations. ***Fr.***: Hamamelis Compose; Poconeol no 24; Poconeol no 55; ***Ger.***: Jsostoma S; Roth's RKT Tropfen.

Creosote

Creasote; Creosota; Creosotal (creosote carbonate); Wood Creosote; Древесный Креозот.
CAS — 8021-39-4 (creosote); 8001-59-0 (creosote carbonate).
ATC — R05CA08.
ATC Vet — QR05CA08.
UNII — 3JYG22FD73.

Pharmacopoeias. In *Jpn*.

Profile

Creosote is a liquid consisting of a mixture of guaiacol, cresol, and other phenols obtained from wood tar. It possesses disinfectant properties and has been used as an expectorant. It has also been used as the carbonate and as lactocreosote.

Adverse effects are similar to those of Phenol, p. 1764.2.

Commercial creosote used for timber preservation is obtained from coal tar.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Compound Inhalation of Menthol†; ***Austria***: Famel cum Codein†; Famel cum Ephedrin†; ***Braz.***: Rhum Creosotado†; ***Fr.***: Pulperyl; Sedapulpe†; Yranol Eugenole; ***Hong Kong***: Nisshin Seirogan†; ***India***: Mynberrys Compound; Pulm-Cod (C & G); ***Ital.***: Creosoto Composto; ***UK***: Famel Original.

Homoeopathic Preparations. ***Austral.***: Teething Relief; ***Austria***: Bronchalis-Heel; ***Canad.***: Bronkeel†; Hylands Vaginitis†; ***Cz.***: Bronchalis-Heel; Lamioflur†; ***Fr.***: Boripharm No 11†; Conium Complexe No 36†; Diabene; Hedera Complexe No 120; Homeodose 8†; Kreosotum Complexe No 62; ***Ger.***: Aletris Oligoplex†; Arte-cyl Ho-Len-Complex; Hewelymphon N†; Mucosa compositum; Prostata-Entoxin N; Sinupas; Ulco-cyl L Ho-Len-Complex; ***Hung.***: Bronchalis-Heel; ***Neth.***: Bronchalis; Mucosa comp H; Ricura; ***Rus.***: Plantago-Plus (Плантаго-Плюс); ***Switz.***: Bronchalis-Heel; Regenaplex Nr. 59b.

Dembrexine *(BAN, rINN)*

Dembreksiini; Dembrexin; Dembrexina; Dembrexinum; Dembroxol; Дембрексин.
trans-4-[(3,5-Dibromosalicyl)amino]cyclohexanol.
$C_{13}H_{17}Br_2NO_2$=379.1
CAS — 83200-09-3 (dembrexine); 52702-51-9 (dembrexine hydrochloride).
UNII — 4F61F502T5.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Dembrexine Hydrochloride Monohydrate for Veterinary Use; Dembrexine Hydrochloride Monohydrate

BP(Vet) 2014). A white or almost white, crystalline powder. Slightly soluble in water and in anhydrous ethanol; freely soluble in methyl alcohol.

Profile

Dembrexine is a mucolytic used as the hydrochloride in veterinary medicine.

Denufosol Tetrasodium *(USAN, rINNM)*

Denufosol tetrasódico; Dénufosol tetrasodique; Denufosolum tetranatricum; INS-37217; Денуфозол Тетранатрий.

2′-Deoxycytidine(5′)tetraphospho(5′)uridine tetrasodium.

$C_{18}H_{23}N_5Na_4O_{21}P_4$=861.3

CAS — 211448-85-0 (denufosol); 318250-11-2 (denufosol tetrasodium).

UNII — 82M942WZ4A.

Profile

Denufosol tetrasodium is a selective $P2Y_2$-receptor agonist that stimulates chloride and water secretion from respiratory tract epithelial cells, and increases mucosal hydration and mucociliary clearance. An inhaled preparation is under investigation for the treatment of cystic fibrosis.

References.
1. Cole P, *et al.* Denufosol tetrasodium. *Drugs Of The Future* 2008; **33:** 668–72.

Dextromethorphan *(BAN, pINN)*

Dekstrometorfaani; Dextrométhorphane; Dextromethorphanum; Dextrometorfan; Dextrometorfano; Декстрометорфан.

(+)-3-Methoxy-9a-methylmorphinan; (9*S*,13*S*,14*S*)-6,18-Dideoxy-7,8-dihydro-3-*O*-methylmorphine.

$C_{18}H_{25}NO$=271.4

CAS — 125-71-3.

ATC — R05DA09.

ATC Vet — QR05DA09.

UNII — 7355X3ROTS.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dextromethorphan:

Bromage; Brome; Candy; CCC; C-C-C; Dex; Dextro; DM; Dmx; Drex; DXM; Red Devils; Robo; Rojo; Rowbowing; Skittles; Skittling; Snurf; Triple C; Triple C's; Tussin; Velvet; Vitamin D.

Pharmacopoeias. In *US.*

USP 36: (Dextromethorphan). A practically white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; freely soluble in chloroform. Store in airtight containers.

Dextromethorphan Hydrobromide

(BANM, pINNM)

Dekstrometorfaanihydrobromidi; Dekstrometorfan Hidrobromür; Dekstrometorfano hidrobromidas; Dekstrometorfanu bromowodorek; Dextromethorfan-hydrobromid monohydrát; Dextrométhorphane, Bromhydrate de; Dextromethorphanhydrobromid; Dextromethorphani hydrobromidum; Dextromethorphani Hydrobromidum Monohydricum; Dextrometorfán-hidrobromid; Dextrometorfanhydrobromid; Dextrometorfano, hidrobromuro de; Hidrobromuro de dextrometorfano; Декстрометорфана Гидробромид.

Dextromethorphan hydrobromide monohydrate.

$C_{18}H_{25}NO,HBr,H_2O$=370.3

CAS — 125-69-9 (anhydrous dextromethorphan hydrobromide); 6700-34-1 (dextromethorphan hydrobromide monohydrate).

ATC — R05DA09.

ATC Vet — QR05DA09.

UNII — 9D2RTI9KYH (dextromethorphan hydrobromide); Z0CG3115FG (anhydrous dextromethorphan hydrobromide).

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Dextromethorphan Hydrobromide). An almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Dextromethorphan Hydrobromide). Practically white crystals or crystalline powder having a faint odour. Soluble 1 in 65 of water; freely soluble in alcohol and in chloroform; insoluble in ether. pH of a 1% solution in water is between 5.2 and 6.5. Store in airtight containers.

Uses and Administration

Dextromethorphan hydrobromide is a cough suppressant used for the relief of non-productive cough (below); it has a central action on the cough centre in the medulla. It is also an antagonist of *N*-methyl-D-aspartate (NMDA) receptors and a σ-receptor agonist. Although structurally related to morphine, dextromethorphan has no classical analgesic properties (but see Pain, below) and little sedative activity.

As a cough suppressant dextromethorphan hydrobromide is reported to act within half an hour of an oral dose and to exert an effect for up to 6 hours. It is given orally in doses of 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to a usual maximum of 120 mg in 24 hours.

Dextromethorphan polistirex (a dextromethorphan and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release oral preparations. The dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, is the equivalent of 60 mg every 12 hours.

Dextrorphan (p. 2492.3), the *O*-demethylated metabolite of dextromethorphan, also has cough suppressant properties.

For doses in children, see below.

Dextromethorphan is also used in the treatment of pseudobulbar affect associated with amyotrophic lateral sclerosis and multiple sclerosis (see Neurological Disorders, below). It is given with low-dose quinidine which increases the bioavailability of dextromethorphan by inhibiting its metabolism. It is given as a fixed oral dose combination of dextromethorphan hydrobromide 20 mg and quinidine sulfate 10 mg. The dextromethorphan is given at a starting dose of 20 mg daily for 7 days followed by a maintenance dose of 20 mg twice daily.

Administration in children. Although dextromethorphan hydrobromide is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in young children, for details see p. 1651.2 and also Cough, below.

In the USA, the following oral doses have been given according to age:

- 4 to 6 years: 2.5 to 5 mg every 4 hours, or 7.5 mg every 6 to 8 hours, to a maximum of 30 mg in 24 hours
- 6 to 12 years: 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours, to a maximum of 60 mg in 24 hours

Dextromethorphan polistirex is used in modified-release oral preparations. The following dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, has been given to children:

- 2 to 6 years: 15 mg every 12 hours
- 6 to 12 years: 30 mg every 12 hours

Cough. Equal doses of dextromethorphan hydrobromide and codeine phosphate were of similar efficacy in reducing the frequency of chronic cough (p. 1651.2) in a double-blind crossover study in adults, but dextromethorphan had a greater effect than codeine on cough intensity.[1] However, these drugs were little more effective than placebo in suppressing night-time cough in children.[2-4] The American Academy of Pediatrics has commented[5] that there is no good evidence for the antitussive efficacy of dextromethorphan in children, that dosage guidelines are derived from (possibly inappropriate) extrapolation from effects in adults, and that adverse effects have been reported. Furthermore, in 2008, the FDA and the MHRA advised that over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in those under 2 years of age. In 2009, after further review, the MHRA advised that such preparations should also be avoided in children aged under 6 years. For further details, see p. 1651.2.

There is also some evidence that genetic polymorphism in the cytochrome P450 isoenzyme CYP2D6, and hence variations in metabolism, may have a significant influence on the antitussive efficacy of dextromethorphan.[6]

1. Matthys H, *et al.* Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983; **11:** 92–100.
2. Gadomski A, Horton L. The need for rational therapeutics in the use of cough and cold medicine in infants. *Pediatrics* 1992; **89:** 774–6.
3. Taylor JA, *et al.* Efficacy of cough suppressants in children. *J Pediatr* 1993; **122:** 799–802.
4. Paul IM, *et al.* Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004; **114:** e85–e90.
5. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics* 1997; **99:** 918–20. [Re-affirmed October 2006] Also available at: http://pediatrics.aappublications.org/cgi/reprint/99/6/918.pdf (accessed 11/05/07)
6. Wright CE, *et al.* CYP2D6 polymorphism and the anti-tussive effect of dextromethorphan in man. *Thorax* 1997; **52** (suppl 6): A73.

Neurological disorders. Dextromethorphan appears to have anticonvulsant activity and may have neuroprotective effects in cerebral ischaemia.[1] These effects may be related to its activity as an antagonist of *N*-methyl-D-aspartate (NMDA) receptors or to interaction with σ-receptors. It has been studied in Parkinson's disease for treatment[2] or for management of levodopa-induced dyskinesias,[3] and for its potential protective action in stroke and acute brain injury.

Dextromethorphan has also been studied for the management of amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) but was not found to be of benefit.[4-6] However, studies indicated that the combination of dextromethorphan and quinidine was effective in treating pseudobulbar affect (emotional lability) associated with amyotrophic lateral sclerosis[7,8] and multiple sclerosis[8,9] The addition of quinidine inhibits the metabolism of the dextromethorphan increasing its bioavailability.[10]

The NMDA-antagonist properties of dextromethorphan have also been investigated for the treatment[11,12] of nonketotic hyperglycinaemia (p. 2623.2).

1. Tortella FC, *et al.* Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends Pharmacol Sci* 1989; **10:** 501–7.
2. Bonuccelli U, *et al.* Dextromethorphan and parkinsonism. *Lancet* 1992; **340:** 53.
3. Verhagen Metman L, *et al.* Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. *Neurology* 1998; **51:** 203–6.
4. Askmark H, *et al.* A pilot trial of dextromethorphan in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1993; **56:** 197–200.
5. Blin O, *et al.* A controlled one-year trial of dextromethorphan in amyotrophic lateral sclerosis. *Clin Neuropharmacol* 1996; **19:** 189–92.
6. Gredal O, *et al.* A clinical trial of dextromethorphan in amyotrophic lateral sclerosis. *Acta Neurol Scand* 1997; **96:** 8–13.
7. Brooks BR, *et al.* Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology* 2004; **63:** 1364–70.
8. Pioro EP, *et al.* Safety, Tolerability, and Efficacy Results Trial of AVP-923 in PBA Investigators. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol* 2010; **68:** 693–702.
9. Panitch HS, *et al.* Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol* 2006; **59:** 780–7.
10. Rosen H. Dextromethorphan/quinidine sulfate Zenvia for pseudobulbar affect. *Drugs Today* 2008; **44:** 661–8.
11. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97:** 924–6.
12. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132:** 709–13.

Pain. Dextromethorphan has a potential role in the blockade of pain. It has been investigated[1-3] in the management of neuropathic pain with promising results in diabetic neuropathy (p. 8.2), although pain was not reduced in postherpetic neuralgia (p. 10.3). High doses of dextromethorphan may be needed for an effect, or combination with quinidine, which inhibits dextromethorphan metabolism.[4] However, the use of dextromethorphan in diabetic neuropathy remains investigational.[5]

A systematic review[6] of 28 studies of dextromethorphan as an adjunct for postoperative pain found that despite a tendency for patients to report less pain than with placebo, and to use less opioid analgesia postoperatively, the differences tended to be inconsistent and of questionable clinical significance. There was some suggestion that parenteral dextromethorphan was more effective than oral.

1. Nelson KA, *et al.* High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997; **48:** 1212–18.
2. Sang CN, *et al.* Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology* 2002; **96:** 1053–61.
3. Carlsson KC, *et al.* Analgesic effect of dextromethorphan in neuropathic pain. *Acta Anaesthesiol Scand* 2004; **48:** 328–36.
4. Thisted RA, *et al.* Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study. *Clin Ther* 2006; **28:** 1607–18.
5. Criner TM, Perdun CS. Dextromethorphan and diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 1221–3.
6. Duedahl TH, *et al.* A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* 2006; **50:** 1–13.

Adverse Effects and Treatment

Adverse effects with dextromethorphan appear to be rare and may include dizziness and gastrointestinal disturbances. Excitation, confusion, and respiratory depression may occur after overdosage. Dextromethorphan has been subject to abuse, but there is little evidence of dependence of the morphine type.

General references.
1. Bem JL, Peck R. Dextromethorphan: an overview of safety issues. *Drug Safety* 1992; **7:** 190–9.

Hypersensitivity. A fixed-drug reaction developed in a patient after ingestion of dextromethorphan 30 mg.[1] Oral provocation with dextromethorphan produced a positive reaction but the results of topical application tests were negative. Urticaria, angioedema, and shortness of breath were reported in another patient;[2] symptoms recurred on oral challenge, but no skin test was performed. Similar symptoms were reported in a third patient;[3] skin testing

provoked a positive reaction. On oral rechallenge, the patient developed urticaria initially, followed by generalised erythema and pruritus and decreased blood pressure after a second dose.

1. Stubb S, Reitamo S. Fixed-drug eruption due to dextromethorphan. *Arch Dermatol* 1990; **126:** 970–1.
2. Knowles SR, Weber E. Dextromethorphan anaphylaxis. *J Allergy Clin Immunol* 1998; **102:** 316–17.
3. Robledo T, *et al*. Adverse reaction to dextromethorphan. *Allergy* 2004; **59:** 890.

Overdosage. There have been reports[1-7] of overdosage or accidental poisoning (usually in children) due to dextromethorphan, including rare fatalities. Naloxone may be effective in reversing toxicity. Extrapyramidal reactions were seen in a child who ingested dextromethorphan.[6] Overdosage has also been associated with abuse (see below).

1. Shaul WL, *et al*. Dextromethorphan toxicity: reversal by naloxone. *Pediatrics* 1977; **59:** 117–19.
2. Katona B, Wason S. Dextromethorphan danger. *N Engl J Med* 1986; **314:** 993.
3. Rammer L, *et al*. Fatal intoxication by dextromethorphan: a report on two cases. *Forensic Sci Int* 1988; **37:** 233–6.
4. Schneider SM, *et al*. Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; **9:** 237–8.
5. Pender ES, Parks BR. Toxicity with dextromethorphan-containing preparations: a literature review and report of two additional cases. *Pediatr Emerg Care* 1991; **7:** 163–5.
6. Warden CR, *et al*. Dystonic reaction associated with dextromethorphan ingestion in a toddler. *Pediatr Emerg Care* 1997; **13:** 214–15.
7. Roberge RJ, *et al*. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; **17:** 285–8.

Precautions

Dextromethorphan should not be given to patients at risk of developing respiratory failure. Caution is needed in patients with a history of asthma and it should not be given during an acute attack. Care is also advisable in patients with bronchitis, emphysema, or in other conditions where chronic or persistent cough occurs.

Abuse. Dextromethorphan has been abused,[1-11] alone or with other drugs in over-the-counter preparations or as a powder sold under the name DXM. There have been a few reports of dependence,[1,2,10] but evidence of classical opioid dependence is generally considered to be lacking.

1. Fleming PM. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; **293:** 597.
2. Orrell MW, Campbell PG. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; **293:** 1242–3.
3. Walker J, Yatham LN. Benylin (dextromethorphan) abuse and mania. *BMJ* 1993; **306:** 896.
4. Wolfe TR, Caravati EM. Massive dextromethorphan ingestion and abuse. *Am J Emerg Med* 1995; **13:** 174–6.
5. Nordt SP. DXM: a new drug of abuse? *Ann Emerg Med* 1998; **31:** 794–5.
6. Cranston JW, Yoast R. Abuse of dextromethorphan. *Arch Fam Med* 1999; **8:** 99–100.
7. Price LH, Lebel J. Dextromethorphan-induced psychosis. *Am J Psychiatry* 2000; **157:** 304.
8. Noonan WC, *et al*. Dextromethorphan abuse among youth. *Arch Fam Med* 2000; **9:** 791–2.
9. Banerji S, Anderson IB. Abuse of Coricidin HBP cough and cold tablets: episodes recorded by a poison center. *Am J Health-Syst Pharm* 2001; **58:** 1811–14.
10. Desai S, *et al*. Chronic addiction to dextromethorphan cough syrup: a case report. *J Am Board Fam Med* 2006; **19:** 320–3.
11. Bryner JK, *et al*. Dextromethorphan abuse in adolescence: an increasing trend: 1999-2004. *Arch Pediatr Adolesc Med* 2006; **160:** 1217–22.

Children. For doubts about the use of dextromethorphan as an antitussive in children see Cough, under Uses and Administration, p. 1660.2.

Interactions

Severe and sometimes fatal reactions have been reported after use of dextromethorphan in patients receiving MAOIs. Dextromethorphan is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6; the possibility of interactions with inhibitors of this enzyme, including amiodarone, haloperidol, propafenone, quinidine, SSRIs, and thioridazine, should be borne in mind.

Antiarrhythmics. *Quinidine* can increase serum concentrations of dextromethorphan markedly, and some patients have had symptoms of dextromethorphan toxicity when the two drugs have been used together.[1,2] Based on this interaction, the combination has been studied for its therapeutic effect in amyotrophic lateral sclerosis and pseudobulbar affect (see Neurological Disorders, p. 1660.3). *Amiodarone* also appears to be able to increase serum concentrations of dextromethorphan.[3]

1. Zhang Y, *et al*. Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmacol Ther* 1992; **51:** 647–55.
2. Pope LE, *et al*. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol* 2004; **44:** 1132–42.
3. Funck-Brentano C, *et al*. Influence of amiodarone on genetically determined drug metabolism in humans. *Clin Pharmacol Ther* 1991; **50:** 259–66.

Antibacterials. Serotonin syndrome-like symptoms have occurred when dextromethorphan has been taken with *linezolid*.

Antidepressants. A patient receiving *fluoxetine* had visual hallucinations after she began taking dextromethorphan.[1] The hallucinations were similar to those she had had 12 years earlier with lysergide. She had previously taken dextromethorphan alone without any adverse reactions. A serotonin syndrome (p. 443.2) has been reported in a patient who took a cold-remedy containing dextromethorphan while receiving *paroxetine*.[2]

1. Achamallah NS. Visual hallucinations after combining fluoxetine and dextromethorphan. *Am J Psychiatry* 1992; **149:** 1406.
2. Skop BP, *et al*. The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* 1994; **12:** 642–4.

Pharmacokinetics

Dextromethorphan is rapidly absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites including dextrorphan (p. 2492.3), which has some cough suppressant activity.

Genetic polymorphism. The *O*-demethylation of dextromethorphan and the hydroxylation of debrisoquine are under common polymorphic control, involving the cytochrome P450 isoenzyme CYP2D6, and dextromethorphan has been used as an alternative to debrisoquine (p. 1350.1) for the phenotyping of oxidative metabolism.[1,2] Non-invasive determinations can be made using samples of urine or saliva.[3,4] Dextromethorphan has also been suggested as a tool to investigate *N*-demethylation, an alternate metabolic pathway for this drug.[5]

1. Belec L, *et al*. Extensive oxidative metabolism of dextromethorphan in patients with almitrine neuropathy. *Br J Clin Pharmacol* 1989; **27:** 387–90.
2. Streetman DS, *et al*. Dose dependency of dextromethorphan for cytochrome P450 2D6 (CYP2D6) phenotyping. *Clin Pharmacol Ther* 1999; **66:** 535–41.
3. Hildebrand M, *et al*. Determination of dextromethorphan metabolizer phenotype in healthy volunteers. *Eur J Clin Pharmacol* 1989; **36:** 315–18.
4. Hou Z-Y, *et al*. Salivary analysis for determination of dextromethorphan metabolic phenotype. *Clin Pharmacol Ther* 1991; **49:** 410–19.
5. Jones DR, *et al*. Determination of cytochrome P450 3A4/5 activity in vivo with dextromethorphan N-demethylation. *Clin Pharmacol Ther* 1996; **60:** 374–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dextrotos; Romilar; ***Austral.***: Benadryl Dry Forte; Bisolvon Dry; Robitussin Dry Cough Forte; Strepsils Cough Relief†; Vicks Formula 44 Dry Cough†; ***Austria***: Tussastopp; Wick Formel 44 Husten-Pastillen; Wick Formel 44 Hustenstiller; ***Belg.***: Actifed New; Balsoclase Dextromethorphan; Bisoltussin; Bronchosedal; Dexir; Humex†; Nortussine Mono; Romilar Antitussivum†; Soludril Antiussivum; Toux-San; Touxium Antitussivum; Tussipect†; Tusso Rhinathiol; Vicks Vaposyrup Antitussif; ***Braz.***: Trimedal Tosse; ***Canad.***: Balminil DM; Benylin DM-D-E-A Cold and Sinus; Benylin DM; Benylin Tickly Throat Cough; Bronchophan DM; Buckley's DM; Childrens Cough†; Cold and Flu-in-One; Cough Syrup DM; Delsym; DM Children's Cough Syrup; DM Cough Syrup; DM Sans Sucre; Dry Cough Syrup; Jack & Jill Thin Strips Cough†; Koffex DM; Neocitran Cough; Robitussin Childrens†; Robitussin DM CoughGels; Sedatuss DM; Sucrets Cough Control; Sucrets DM; Triaminic Cough; Triaminic DM; Triaminic Long Acting Cough; Vicks Custom Care Dry Cough; Vicks DayQuil Cough; Vicks Formula 44†; Vicks Pediatric Formula 44; ***Chile***: Pectobronc; Tusminal; ***China***: Bei Ke Er (倍克尔); Bei Tai (贝泰); Dekesi (德可思); Jiang Ke (降克); Kang Yu Deng Tong (康裕登通); Ke Le Er (可乐尔); Ke Li Ting (克立停); KeDi (可迪); Kening (科宁); Luo Shun (洛顺); Pusiran (普西兰); Rui Kai Ping (瑞凯平); Shu De (舒得); Shuang Hong Ling (双红灵); Xian Luo Ke (先罗可); Xiaomei (小眉); ***Cz.***: Dr Rentschler Hustenstiller†; Humex Pro Deti; Robitussin Antitussicum; Robitussin Junior; Stopex; Tussidrill; ***Denm.***: Dexofan; ***Fin.***: Resilar; Rometor; ***Fr.***: Atuxane; Capsyl†; Dexir†; Dextrocidine; Drill toux seche; Ergix Toux Seche; Euphonyl Toux Seche; Fluditec toux seche; Humex Toux Seche Dextromethorphane; Nodex; Pulmodexane; Tussidane; Tuxium; Vicks Toux Seche; ***Ger.***: Hustenstiller; NeoTussan†; Silomat DMP; Wick Husten-Pastillen gegen Reizhusten mit Honig; Wick Husten-Sirup gegen Reizhusten mit Honig; ***Gr.***: Vaposyrup; ***Hong Kong***: Depan-F; Dexcophan†; Dextrome; Dextrophen†; Eifcof-G†; Pusiran; Robitussin DX; Robitussin Maximum Strength Cough†; Robitussin Paediatric Cough†; Tussils; Uni-DM†; ***Hung.***: Drill†; Methor†; Rhinathiol; Robitussin Antitussicum; Robitussin Junior; Tussopront; ***India***: Alex; Chericof; DM; Kofend-D; Kofgard; Lastuss; Lexcof; Omnitus; ***Indon.***: Bisoltussin; Romilar; ***Irl.***: Benylin Non-Drowsy Dry Cough; Delsym†; Robitussin Dry Cough; Robitussin Junior†; ***Israel***: Kofli†; Kuffex DM; Tarodex; ***Ital.***: Aricoditosse; Bechilar; Bisolvon Tosse Sed; Bronchenolo Tosse; Bronchetab; Broncofama; Formitrol; Lisomucil Tosse Sedativo; Metorfan; Tossoral; Tussycalm; Vicks Tosse Pastiglie; Vicks Tosse Sedativo; ***Malaysia***: Depan-F; Dexcophan†; Nospan; Pusiran; Tussidex Forte; Tussils; Upha Dextrophan; ***Mex.***: Atassol; Athos; Balbek†; Balsedrina; Bekesina-S; Bekidiba Dex†; Bioquidan; Brocolan; Bromelip; Debequin; Dontuxin; Flex Metak; Jarabe Garde; Neo-Ulcoid; Protan; Quimofan; Romilar; Tosifan; ***Neth.***: Bisoltussin; Dampo bij droge hoest†; Daro Retard; Darolan Hoestprikkeldempende†; Daromefan†; Dexal; Pectofree; Rami-Dextromethorfan†; Tussipect; Vicks Hoestsiroop; Vicks Hoesttabletten; ***NZ***: Benadryl Dry Forte†; Robitussin DX; Strepsils Dry Cough; ***Philipp.***: Cofles; Decormin; Dexof; Extendryl DM; Flemonex-DXM; Mytusan DM; Pulmodex; Strepsils Dry Cough; Streptuss; Suprekof DM†; ***Pol.***: Acodin; Dexatussin; Robitussin Antitussicum; Robitussin Junior; Tussal Antitussicum; Tussidex; TussiDrill; ***Port.***: Bisoltussin; Diacol; Drill Tosse Seca; Rhinathiol; Setustop; Tussilene; Vicks Pastihas; Vicks Xarope Antitussico; ***S.Afr.***: Benylin Dry Cough; Dilinct Dry Cough; ***Singapore***: Beathorphan; Dexcophan; Metophan; Nospan; Pusiran; Robitussin Honey Cough; Tussidex; Tussils; ***Spain***: Aquitos†; Bexatus; Bicasan; Bisolvon Antitusivo; Cinfatos; Couldetos; Formulatus; Frenatus†; Fritusil; Iniston Antitusivo; Laitos; Normotus; Notus; Novag Tuss; Parlatos; Pastillas Dr Andreu; Romilar; Serratos†; Streptuss†; Tip; Tusorama†; Tussidrill; ***Switz.***: Bexine; Bexomed; Calmerphan-L; Calmesine; Dextro-Med; Emedrin N; Hicoseen N; Irotussin; Pulmofor; Tossa-X; Tussalpront†; Vicks Formule 44 Calmine†; Vicks Toux Seche; ***Thai.***: A-Tussin; Antus; Cetussin; Cortuss; Dec; Depan-F†; Dex; Dextramet; Dextro-5; Dextrocough; Dextrodon; Dextromed; Dextropac; Dextroral; Dextrosia; Eifcof; Icolid Plus; Icolid; KB Dextro; Lohak; Manodextro; Methorphan; MLM-Dex†; Polydex; Potussan; Pusiran; Romilar; Strepsils Dry Cough; Throatsil Dex; Tusacdon; Tusco; Tussanyl; Tussils; ***UAE***: Exedexe; Sedofan P†; ***UK***: Adult Dry Cough; Benylin Dry Coughs Non-Drowsy; Dry Cough Syrup; Robitussin Dry Cough; Vicks Cough Lozenges with Honey; Vicks Cough Syrup with Honey for Dry Coughs; Vicks Vaposyrup for Dry Coughs; ***Ukr.***: Daleron Cold 3 (Далерон Колд 3); ***USA***: AeroTuss 12; Buckleys Cough; Creo-Terpin; Creomulsion; Delsym; DexAlone; Diabe-Tuss DM; ElixSure Childrens Cough; Hold DM; Little Colds Cough Formula; Long-Acting Cough Suppressant; PediaCare Childrens Long-Acting Cough; PediaCare Infants Long-Acting Cough; Robitussin Adult Lingering Cold Long-Acting Cough; Robitussin Children's Cough Long-Acting; Robitussin CoughGels; Robitussin Pediatric; Scot-Tussin Diabetes; Scot-Tussin DM Cough Chasers; Silphen DM; Simply Cough; Sucrets DM; Theraflu Cough; Triaminic Long Acting Cough; Trocal†; Vicks 44 Cough Relief; Vicks Nature Fusion Cough; ***Venez.***: Libolar; Promedin; Tilodrin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

USP 36: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Dextromethorphan Hydrobromide Syrup; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Dimemorfan Phosphate *(rINNM)*

AT-17; Dimémorfane, Phosphate de; Dimemorfani Phosphas; Dimemorfano, fosfato de; Fosfato de dimemorfano; Димеморфана Фосфат.

(+)-3,9a-Dimethylmorphinan phosphate.

$C_{18}H_{25}N,H_3PO_4$=353.4

CAS — 36309-01-0 (dimemorfan); 36304-84-4 (dimemorfan phosphate).

ATC — R05DA11.

ATC Vet — QR05DA11.

UNII — S203Y5Y1QP.

Pharmacopoeias. In *Jpn*.

Profile

Dimemorfan phosphate is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It is given orally in doses of 20 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Tusben; ***Jpn***: Astomin; ***Spain***: Dastosin.

Dimethoxanate Hydrochloride *(BANM, rINNM)*

Diméthoxanate, Chlorhydrate de; Dimethoxanati Hydrochloridum; Dimetoxanato, hidrocloruro de; Hidrocloruro de dimetoxanato; Диметоксаната Гидрохлорид.

2-(2-Dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate hydrochloride.

$C_{19}H_{22}N_2O_3S,HCl$=394.9

CAS — 477-93-0 (dimethoxanate); 518-63-8 (dimethoxanate hydrochloride).

ATC — R05DB28.

ATC Vet — QR05DB28.

UNII — N5I6SR31GJ.

Profile

Dimethoxanate hydrochloride is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It has been given orally in usual doses of 37.5 mg three or four times daily.

Dornase Alfa (BAN, USAN, rINN)

Deoxyribonuclease; Desoxyribonuclease; DNase I; Dornasa alfa; Dornasum Alfa; Dornaz Alfa; rhDNase; Дорназа Альфа.
Deoxyribonuclease I (human recombinant).
$C_{1321}H_{1995}N_{339}O_{396}S_9$=29250.0
CAS — 9003-98-9 (bovine deoxyribonuclease); 143831-71-4 (human deoxyribonuclease); 132053-08-8 (human deoxyribonuclease).
ATC — B06AA10; R05CB13.
ATC Vet — QB06AA10; QR05CB13.
UNII — 08E71HM000 (bovine); 953A26OA1Y (human).

Description. Dornase alfa is a recombinant enzyme having the same amino acid sequence and glycosylation pattern as human deoxyribonuclease I.

Uses and Administration

Dornase alfa acts as a mucolytic by hydrolysing DNA that has accumulated in sputum from decaying neutrophils. It is used as a nebulised solution in patients with cystic fibrosis (below); in the UK its indication is limited to patients with a forced vital capacity (FVC) greater than 40% of predicted value and to patients over 5 years of age, but in the USA it may also be given for advanced disease (FVC less than 40%) and to younger children. The usual dose is 2500 units (2.5 mg) of dornase alfa given once daily via a jet nebuliser. This dose may be given twice daily to patients over 21 years of age.

Bovine deoxyribonuclease has been used similarly. It has also been used topically, often with fibrinolysin, as a debriding agent for inflammatory and infected lesions. Bovine deoxyribonuclease has also been given by injection.

Administration in children. Although in some countries dornase alfa is not recommended for use in children under 5 years of age (for details of doses, see Uses and Administration, above), a study[1] to assess the delivery of dornase alfa to the lungs of children with cystic fibrosis aged between 3 months and 5 years, showed that the amounts present in the lower airways were comparable to those in older children. It also appeared to be safe in these younger patients during the 2-week study period.

1. Wagener JS, *et al.* Aerosol delivery and safety of recombinant human deoxyribonuclease in young children with cystic fibrosis: a bronchoscopic study. *J Pediatr* 1998; **133:** 486–91.

Asthma. There are reports of the use of dornase alfa to liquefy mucus plugs and relieve an attack of acute severe asthma (p. 1195.2) in children.[1-3] However, a randomised controlled study[4] found that adding a single dose of nebulised dornase alfa to standard emergency treatment has no benefits in children with moderate to severe acute asthma.

1. Greally P. Human recombinant DNase for mucus plugging in status asthmaticus. *Lancet* 1995; **346:** 1423–4.
2. Patel A, *et al.* Intratracheal recombinant human deoxyribonuclease in acute life-threatening asthma refractory to conventional treatment. *Br J Anaesth* 2000; **84:** 505–7.
3. Durward A, *et al.* Resolution of mucus plugging and atelectasis after intratracheal rhDNase therapy in a mechanically ventilated child with refractory status asthmaticus. *Crit Care Med* 2000; **28:** 560–2.
4. Boogaard R, *et al.* Recombinant human deoxyribonuclease for the treatment of acute asthma in children. *Thorax* 2008; **63:** 141–6.

Chronic obstructive pulmonary disease. A large phase III study in patients hospitalised for acute exacerbations of chronic bronchitis (p. 1199.1) was halted prematurely because of a non-significant trend to increased mortality in patients given dornase alfa.[1]

1. Hudson TJ. Dornase in treatment of chronic bronchitis. *Ann Pharmacother* 1996; **30:** 674–5.

Cystic fibrosis. There is good evidence that inhalation therapy with dornase alfa can produce modest but useful improvement in lung function in some patients with cystic fibrosis (p. 177.2). Most studies have concentrated on patients with mild or moderate disease (forced vital capacity at least 40% of the predicted value) in whom FEV_1 and forced vital capacity have shown improvements generally of the order of 5 to 10%,[1-3] and in whom more prolonged therapy (24 weeks) has been shown to reduce the risk of exacerbations of respiratory infections, and hence the need for intravenous antibacterial therapy.[3] There is also evidence that benefit may occur in patients with more severe disease.[4] A systematic review[5] of studies concluded that there is evidence to show that dornase alfa therapy over a 1-month period is associated with improved lung function. Furthermore, a randomised, multicentre, placebo-controlled study[6] in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a period of 96 weeks. However, only a minority of patients, perhaps about one-third,[7] benefit from the drug, and at present there is no way of identifying those who will respond other than by a therapeutic trial.[8,9]

Given the high cost of therapy, which is not entirely recouped by savings in acute care, there has been some controversy about the appropriate use of dornase alfa:[10-13] it seems to be generally felt that it should be reserved for specialist use in cystic fibrosis clinics, but that patients should not be denied a trial where appropriate. Most responders with mild to moderate impairment of lung function will show improvements within 2 weeks, although in more severely affected patients a 6-week trial is advocated.[8] A review of the use of dornase alfa in cystic fibrosis concluded that dosing on alternate days would be as effective as daily dosing, and would reduce costs and treatment time.[14]

1. Ramsey BW, *et al.* Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis* 1993; **148:** 145–51.
2. Ranasinha C, *et al.* Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993; **342:** 199–202.
3. Fuchs H, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994; **331:** 637–42.
4. McCoy K, *et al.* Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996; **110:** 889–95.
5. Jones AP, Wallis C. Dornase alpha for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 17/05/10).
6. Quan JM, *et al.* A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001; **139:** 813–20.
7. Davis PB. Evolution of therapy for cystic fibrosis. *N Engl J Med* 1994; **331:** 672–3.
8. Conway SP, Littlewood JM. rhDNase in cystic fibrosis. *Br J Hosp Med* 1997; **57:** 371–2.
9. Ledson MJ, *et al.* Targeting of dornase alpha therapy in adult cystic fibrosis. *J R Soc Med* 1998; **91:** 360–4.
10. Anonymous. Dornase alfa for cysticfibrosis. *Drug Ther Bull* 1995; **33:** 15–16.
11. Spencer D, Weller P. Dornase-alfa for cystic fibrosis. *Lancet* 1995; **345:** 1307.
12. Bush A, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; **310:** 1533.
13. Robert G, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; **311:** 813.
14. Suri R. The use of human deoxyribonuclease (rhDNase) in the management of cystic fibrosis. *BioDrugs* 2005; **19:** 135–44.

Adverse Effects and Precautions

Common adverse effects with dornase alfa aerosol include pharyngitis, hoarseness of the voice, and chest pain. Occasionally laryngitis, conjunctivitis, and skin rashes and urticaria have been reported. There may be a transient decline in pulmonary function on beginning therapy with dornase alfa.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dornase alfa as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pulmozyme; ***Austral.***: Pulmozyme; ***Austria***: Pulmozyme; ***Belg.***: Pulmozyme; ***Braz.***: Pulmozyme; ***Canad.***: Pulmozyme; ***Chile***: Viscozyme; ***Cz.***: Pulmozyme; ***Denm.***: Pulmozyme; ***Fin.***: Pulmozyme; ***Fr.***: Pulmozyme; ***Ger.***: Pulmozyme; ***Gr.***: Pulmozyme; ***Hung.***: Pulmozyme; ***Irl.***: Pulmozyme; ***Israel***: Pulmozyme; ***Ital.***: Pulmozyme; ***Jpn***: Pulmozyme; ***Mex.***: DNSM; Pulmozyme; ***Neth.***: Pulmozyme; ***Norw.***: Pulmozyme; ***NZ***: Pulmozyme; ***Pol.***: Pulmozyme; ***Port.***: Pulmozyme; ***Rus.***: Pulmozyme (Пульмозим); ***S.Afr.***: Pulmozyme; ***Spain***: Pulmozyme; ***Swed.***: Pulmozyme; ***Switz.***: Pulmozyme; ***Turk.***: Pulmozyme; ***UK***: Pulmozyme; ***Ukr.***: Pulmozyme (Пульмозим); ***USA***: Pulmozyme.

Multi-ingredient Preparations. ***Arg.***: Clorfibrase; ***Austria***: Fibrolan; ***Braz.***: Cauterex; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino Cauterex; Gino Fibrase; ***Chile***: Elase; ***Cz.***: Fibrolan†; ***Fr.***: Elase; ***Hung.***: Fibrolan; ***Malaysia***: Elase; ***Mex.***: Fibrase SA; Fibrase; Ridasa; ***Pol.***: Fibrolan; ***Switz.***: Fibrolan.

Dropropizine (BAN, rINN)

Dropropitsiini; Dropropizin; Dropropizina; Dropropizinum; UCB-1967; Дропропизин.
3-(4-Phenylpiperazin-1-yl)propane-1,2-diol.
$C_{13}H_{20}N_2O_2$=236.3
CAS — 17692-31-8.
ATC — R05DB19.
ATC Vet — QR05DB19.
UNII — U0K8WHL37U.

Levodropropizine (BAN, rINN)

DF-526; Levdropropizine; Levodropropitsiini; Levodropropizin; Levodropropizina; Levodropropizinas; Lévodropropizine; Levodropropizinum; Леводропропизин.
The (-)-(*S*)-isomer of dropropizine.
$C_{13}H_{20}N_2O_2$=236.3
CAS — 99291-25-5.
ATC — R05DB27.
ATC Vet — QR05DB27.
UNII — 3O31P6T4G3.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Levodropropizine). A white or almost white powder. Slightly soluble in water and in alcohol; freely soluble in dilute acetic acid and in methyl alcohol. A 2.5% solution in water has a pH of 9.2 to 10.2. Protect from light.

Profile

Dropropizine is a cough suppressant reported to have a peripheral action in non-productive cough (p. 1651.2). It is given orally usually in a dose of 30 mg three or four times daily. Levodropropizine, the (-)-(*S*)-isomer of dropropizine, is claimed to produce fewer CNS effects and is used similarly in an oral dose of 60 mg up to three times daily.

References.

1. Catena E, Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough: comparison with dextromethorphan. *Pulm Pharmacol Ther* 1997; **10:** 89–96.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Perlatos; ***Belg.***: Catabex; Levotuss; ***Braz.***: Antux; Atossion; Ecos; Eritos; Flextoss; Neotoss; Percof; Tussiflex D; Vibral; Vibrazin; Zyplo; ***Chile***: Broncard; Broncatox; ***China***: JiShu (及舒); Kao Fu Ting (考孚亭); Ke Chang (可畅); Ke Li Yu (可莉俞); Run Hui (润汇); Shu Chang (抒畅); Zuo Pai Xin (佐派欣); ***Cz.***: Ditustat; Levopront; ***Ger.***: Larylin Husten-Stiller; Quimbo; ***Gr.***: Dropavix; Levotuss; ***Hong Kong***: Bronal; ***Hung.***: Levopront; ***Indon.***: Levopront; ***Ital.***: Actiribex; Danka; Domutussina; Levotuss; Salvituss; Tau-Tux; ***Mex.***: Kastovin; Levocof; Troferit; Velatuss; Zyplo; ***Neth.***: Levotuss; ***Philipp.***: Levopront; ***Pol.***: Levopront; ***Port.***: Catabina; Levotuss; ***Rus.***: Levopront (Левопронт); ***Spain***: Levotuss; Tautoss; ***Thai.***: Bronal; Ivorin; Levopront; ***Turk.***: Lavenil; Levopront; Pulmorest; ***Venez.***: Antux; Levopront.

Multi-ingredient Preparations. ***Braz.***: Notuss; ***Ital.***: Actiribexen; Elisir Terpina; Guaiacalcium Complex; Tiocalmina; Tussamag Complex; ***Mex.***: Dizolvin-Flux.

Elecampane

Ala; Alant; Aunée; Énula; Énula campana; Helenio; Inula; Ínula; Девясил Высокий.
CAS — 97676-35-2 (elecampane oil).
UNII — 3VD070DG5G (Inula helenium); E55SMD6DA8 (Inula helenium root); VN35VNS0OO (Inula helenium root oil).

Pharmacopoeias. In *Chin.* (which also includes various other species of *Inula*) and *Fr.*

Profile

Elecampane is the root of *Inula helenium* (Compositae). It has been used in herbal preparations for the treatment of cough for its supposed expectorant and cough suppressant properties. It is also used as a flavouring in foods and alcoholic beverages.

Elecampane contains sesquiterpene lactones including alantolactone (alant camphor; elecampane camphor; inula camphor; helenin), which was formerly used in the treatment of worm infections, and has also been an ingredient of some cough preparations.

Elecampane oil has been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: HRF; ResCo; ***Austria***: Brust- und Hustentee St Severin; Klosterfrau Melissengeist; Pervivo; ***Canad.***: Herbal Cough Syrup†; Honey Blend Herbal Cough Syrup; ***Cz.***: Klosterfrau Melisana; Species Cholagogae Planta†; ***Fr.***: Mediflor Digestive No 3; ***Ger.***: Klosterfrau Melissengeist; ***Hung.***: Antipoll; Bittner; Klosterfrau Melisana; ***Pol.***: Pectosol; Pervivo; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Sodecor (Содекор); ***S.Afr.***: Wonderkroonessens; ***Switz.***: Hederix; Padmed Laxan; ***UK***: Catarrh-eeze; Cough Soother Herbal Syrup; Cough-eeze; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Vegetable Cough Remover; ***Ukr.***: Pectolvan Phyto (Пектолван Фито).

Homoeopathic Preparations. ***Ger.***: Drosera-Weliplex†; ***Neth.***: Drosinula.

Ephedra ⊗

Efedra; Ma-huang; Эфедра хвощевая (*Ephedra equisetina*); Хвойник.

*UNII — 2E31ONF9M5 (*Ephedra intermedia *stem); 55L3XLO37E (*Ephedra sinica *stem).*

Pharmacopoeias. In *Chin.*, *Eur.*, (see p. vii) *Ger.*, and *Jpn*.

Chin. also includes the roots of *Ephedra sinica* or *E. intermedia*.

Ph. Eur. 8: (Ephedra Herb); Ephedrae Herba. The dried herbaceous stem of *Ephedra sinica*, *E. intermedia*, or *E. equisetina*. It contains a minimum of 1% of ephedrine.

Profile

Ephedra consists of the dried young branches of *Ephedra sinica*, *E. equisetina*, and *E. gerardiana* (including *E. nebrodensis*) (Ephedraceae), containing not less than 1.25% of alkaloids, calculated as ephedrine.

The action of ephedra is due to the presence of ephedrine (below) and pseudoephedrine (p. 1676.1). It has been used chiefly as a source of these alkaloids. The FDA states that ephedra-containing dietary supplements are unsafe and the sale of these products is banned in the USA. Other countries have also banned the sale of ephedra-containing dietary supplements.

For reference to the adverse effects of herbal products containing ephedra, see Abuse, under Ephedrine, p. 1664.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Formula S/E†; Sinueaze†.

Multi-ingredient Preparations. ***Ger.***: Cefadrin†; ***Hong Kong***: Sesoforte†; ***Jpn***: Bofutsushosan; Colgen Maoto; Eppikajutsuto; Gokoto; Goshakusan; Kakkonto; Kakkontokasenkyushin'i; Makyokansekito; Makyoyokukanto; Maobushisaishinto; Maoto; Shimpito; Shoseiryuto; Yokuininto.

Homoeopathic Preparations. ***Fr.***: Santaherba; ***Rus.***: Sambucus-Plus (Самбукус-Плюс).

Ephedrine *(BAN)* ⊗

Efedriini; Efedrin; Efedrina; Efedrinas; Ephedrina; (-)-Ephedrine; Éphédrine; Ephedrinum; Эфедрин.

(1*R*,2*S*)-2-Methylamino-1-phenylpropan-1-ol.

$C_{10}H_{15}NO$=165.2

CAS — 299-42-3 (anhydrous ephedrine); 50906-05-3 (ephedrine hemihydrate).

ATC — C01CA26; R01AA03; R01AB05; S01FB02.

ATC Vet — QG04BX90; QR01AA03; QR01AB05; QR03CA02; QS01FB02.

UNII — GN83C131XS.

Description. Ephedrine is an alkaloid obtained from species of *Ephedra*, or prepared synthetically. It may exist in a hemihydrate form or as the anhydrous substance.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of ephedrine:

Trucker's Speed.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*, which have specifications, in either the same monograph or in separate monographs, for the anhydrous form and for the hemihydrate.

Ph. Eur. 8: (Ephedrine, Anhydrous). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very soluble in alcohol. It melts at about 36 degrees. Protect from light.

Ph. Eur. 8: (Ephedrine Hemihydrate; Ephedrine BP 2014). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very soluble in alcohol. It melts at about 42 degrees, determined without previous drying. Protect from light.

USP 36: (Ephedrine). It is anhydrous or contains not more than one-half molecule of water of hydration. It is an unctuous, practically colourless solid or white crystals or granules. It gradually decomposes on exposure to light. M.p. between 33 degrees and 40 degrees, the variability being the result of differences in the moisture content, anhydrous ephedrine having a lower melting-point than the hemihydrate. Soluble 1 in 20 of water and 1 in 0.2 of alcohol; soluble in chloroform and in ether; moderately and slowly soluble in liquid paraffin, the solution becoming turbid if the ephedrine contains more than about 1% of water. Its solutions are alkaline to litmus. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Ephedrine Hydrochloride *(BANM)* ⊗

Efedriinihydrokloridi; Efedrin Hidroklorür; Efedrin hydrochlorid; Efedrina, hidrocloruro de; Efedrin-hidroklorid; Efedrinhydroklorid; Efedrino hidrochloridas; Efedryny chlorowodorek; Ephedrinae Hydrochloridum; Éphédrine, chlorhydrate d'; Ephedrine Chloride; Ephedrinhydrochlorid; Ephedrini Hydrochloridum; Ephedrinium Chloratum; *l*-Ephedrinum Hydrochloricum; Эфедрина Гидрохлорид.

$C_{10}H_{15}NO,HCl$=201.7

CAS — 50-98-6.

ATC — C01CA26; R01AA03; R01AB05; S01FB02.

ATC Vet — QR01AA03; QR01AB05; QR03CA02; QS01FB02.

UNII — NLJ6390P1Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. It melts at about 219 degrees. Protect from light.

USP 36: (Ephedrine Hydrochloride). Fine, white, odourless crystals or powder. Soluble 1 in 3 of water and 1 in 14 of alcohol; insoluble in ether. Protect from light.

Ephedrine Sulfate *(BANM)* ⊗

Efedrina, sulfato de; Ephedrine Sulphate; Эфедрина Сульфат.

$(C_{10}H_{15}NO)_2,H_2SO_4$=428.5

CAS — 134-72-5.

ATC — C01CA26; R01AA03; R01AB05; S01FB02.

ATC Vet — QR01AA03; QR01AB05; QR03CA02; QS01FB02.

UNII — U6X61U5ZEG.

Pharmacopoeias. In *Int.* and *US*.

USP 36: (Ephedrine Sulfate). Fine, white, odourless crystals or powder. It darkens on exposure to light. Soluble 1 in 1.3 of water and 1 in 90 of alcohol. Protect from light.

Racephedrine Hydrochloride

(BANM, USAN, rINNM) ⊗

dl-Ephedrine Hydrochloride; *dl*-Ephedrinium Chloride; Efedriinihydrokloridi, raseeminen; Efedrinhydroklorid, racemisk; Efedrino (raceminio) hidrochloridas; Éphédrine (chlorhydrate d') racémique; Ephedrini racemici hydrochloridum; Hidrocloruro de racefedrina; Racém efedrin-hidroklorid; Racemic Ephedrine Hydrochloride; Racéphédrine, Chlorhydrate de; Racephedrini Hydrochloridum; Рацефедрина Гидрохлорид.

(±)-2-Methylamino-1-phenylpropan-1-ol hydrochloride.

$C_{10}H_{15}NO,HCl$=201.7

CAS — 90-81-3 (racephedrine); 134-71-4 (racephedrine hydrochloride).

UNII — 43SK4LAO7D.

Pharmacopoeias. In *Eur.*

Ph. Eur. 8: (Ephedrine Hydrochloride, Racemic; Racephedrine Hydrochloride BP 2014). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol; practically insoluble in ether. It melts at about 188 degrees. Protect from light.

Uses and Administration

Ephedrine is a sympathomimetic (p. 1507.3) with direct and indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity and has pronounced stimulating effects on the CNS. It has a more prolonged though less potent action than adrenaline. In therapeutic doses it raises the blood pressure by increasing cardiac output and also by inducing peripheral vasoconstriction. Tachycardia may occur but is less frequent than with adrenaline. Ephedrine also causes bronchodilatation, reduces intestinal tone and motility, relaxes the bladder wall while contracting the sphincter muscle but relaxes the detrusor muscle of the bladder and usually reduces the activity of the uterus. It has a stimulant action on the respiratory centre. It dilates the pupil but does not affect the light reflexes. After ephedrine has been used for a short while, tachyphylaxis may develop.

Ephedrine salts are used, either alone or in combination preparations, in the symptomatic relief of nasal congestion (p. 1652.1). They may be given orally, or topically as nasal drops or sprays. Ephedrine salts have sometimes been used in motion sickness in combination preparations with hyoscine or an antihistamine and have been tried for postoperative nausea and vomiting (p. 1811.3).

Ephedrine salts have been given parenterally to combat a fall in blood pressure during spinal or epidural anaesthesia (below). Ephedrine is of little value in hypotensive crises produced by shock, circulatory collapse, or haemorrhage. It is no longer generally advocated for orthostatic hypotension.

Ephedrine salts have been used as bronchodilators, but the more $beta_2$-selective sympathomimetics, such as salbutamol, are now preferred.

Other uses of ephedrine salts include diabetic neuropathic oedema, in which they may provide marked relief. They have also been used in micturition disorders.

Nasal drops or sprays usually containing ephedrine 0.5 or 1% are used in the treatment of **nasal congestion**. Ephedrine salts have also been given by oral inhalation.

To reverse **hypotension** induced by spinal or epidural anaesthesia, a solution containing ephedrine hydrochloride 3 mg/mL is given by slow intravenous injection in doses of 3 to 6 mg (or at most 9 mg) repeated every 3 to 4 minutes as required; the maximum total dose is 30 mg. Ephedrine salts have also been given by intramuscular or subcutaneous injection.

The *BNF* suggests an oral dose of 30 to 60 mg of ephedrine hydrochloride three times daily in the treatment of **diabetic neuropathic oedema**.

Several other salts of ephedrine have been given including the camsilate, the levulinate, the tannate, and the thiocyanate. Racephedrine hydrochloride has also been used.

For doses in children, see below.

Administration in children. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including ephedrine) should be used with caution in children and generally avoided in young children, for details see p. 1651.2. The *BNFC* suggests that ephedrine nasal drops may be used in children aged 6 years and over for the short-term treatment of severe **nasal congestion** that has not responded to sodium chloride nasal drops or inhalation of warm moist air. Nasal drops containing ephedrine hydrochloride 0.5% may be instilled into each nostril up to 3 or 4 times daily for a maximum of 5 days in children aged 6 to 12 years or 7 days in those over 12 years.

Ephedrine is rarely needed in children for reversal of **hypotension** induced by spinal or epidural anaesthesia, but if it is used the *BNFC* suggests the following doses of a solution containing ephedrine hydrochloride 3 mg/mL, given by slow intravenous injection via a central line:

- 1 to 12 years: 500 to 750 micrograms/kg or 17 to 25 mg/m^2 every 3 to 4 minutes according to response up to a maximum total dose of 30 mg
- 12 to 18 years: 3 to 7.5 mg (maximum 9 mg) repeated every 3 to 4 minutes according to response up to a maximum total dose of 30 mg

Congenital myasthenia. Ephedrine has been shown to be of benefit in certain types of congenital myasthenia (p. 685.1).

Micturition disorders. Ephedrine salts have been used in nocturnal enuresis, although other treatments are usually preferred, and have been tried in patients with stress incontinence but the value of such treatment is not clear.

Spinal anaesthesia. Parenteral sympathomimetics such as ephedrine and phenylephrine have been advocated for the correction of hypotension associated with local anaesthesia. The risk of hypotension with spinal or epidural block is greater than many other forms of nerve block (see Adverse Effects of Central Block, p. 1978.1). Ephedrine has been used[1,2] although not always successfully[3] for the correction of such hypotension. It has also been used prophylactically,[4,5] although prophylactic use during labour has been associated with fetal tachycardia,[5] and adequate hydration of the patient beforehand is more important in minimising hypotension.

1. Hall PA, *et al.* Spinal anaesthesia for Caesarean section: comparison of infusions of phenylephrine and ephedrine. *Br J Anaesth* 1994; **73:** 471–4.
2. Thomas DG, *et al.* Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. *Br J Anaesth* 1996; **76:** 61–5.
3. Critchley LAH, *et al.* Hypotension during subarachnoid anaesthesia: haemodynamic effects of ephedrine. *Br J Anaesth* 1995; **74:** 373–8.
4. Sternlo J-E, *et al.* Prophylactic im ephedrine in bupivacaine spinal anaesthesia. *Br J Anaesth* 1995; **74:** 517–20.
5. Cleary-Goldman J, *et al.* Prophylactic ephedrine and combined spinal epidural: maternal blood pressure and fetal heart rate patterns. *Obstet Gynecol* 2005; **106:** 466–72.

Adverse Effects

As for Sympathomimetics, p. 1508.2. Ephedrine has both alpha- and beta-agonist effects and its commonest adverse effects are tachycardia, anxiety, restlessness, and insomnia. Tremor, dry mouth, impaired circulation to the extremities, hypertension, and cardiac arrhythmias may also occur.

Ephedrine may be used in labour to maintain blood pressure during spinal anaesthesia but can cause fetal tachycardia.

Paranoid psychosis, delusions, and hallucinations may also follow ephedrine overdosage. Prolonged use has no cumulative effect, but tolerance with dependence has been reported.

For a discussion of the toxicity reported from the self-administration of ephedrine-containing dietary supplements or herbal stimulants, see Abuse, below.

Precautions

As for Sympathomimetics, p. 1508.3. Ephedrine should be given with care to patients with hyperthyroidism, diabetes mellitus, ischaemic heart disease, hypertension, renal impairment, or angle-closure glaucoma. In patients with prostatic enlargement, ephedrine may increase difficulty with micturition.

Irritability and disturbed sleep have been reported in breast-fed infants.

Abuse. Although illicit use of ephedrine is mainly in the manufacture of street stimulants such as metamfetamine (p. 2324.2), there is increasing evidence of the abuse of ephedrine preparations in some countries,[1] and the public health and social problems associated with its abuse appear to be significant, particularly in certain African countries. Ephedrine is also sold as a street substitute for 'Ecstasy' (Methylenedioxymethamfetamine, p. 2325.2).

Adverse effects reported with illicit ephedrine use include cardiovascular toxicity[2,3] and chest pain.[4]

There is controversy over the abuse liability of over-the-counter (OTC) stimulants such as ephedrine:[5] some studies have indicated that ephedrine is, overall, a relatively weak reinforcer whereas others have suggested that the abuse potential may be high. Examination of the characteristics of 5 patients who had been taking ephedrine-containing OTC preparations in high doses for periods ranging from 8 months to 2 years, emphasised the reinforcing and, therefore, addictive potential of ephedrine; similar observations were made for 2 patients who had ingested phenylpropanolamine long term, combined with pseudoephedrine in one of these cases. The authors suggested that, for most people, OTC preparations containing weaker sympathomimetics will not be reinforcing at the recommended doses. However, these cases strengthen the research findings that high-dose use of an OTC stimulant increases its potency, and thus its effects become more like amfetamine (p. 2316.1).

Toxicity has also been reported[6-8] from the self-administration of ephedrine-containing dietary supplements or herbal stimulants, usually based on ephedra (mahuang) and marketed for a variety of purposes including weight loss and as an alternative to illegal drugs of abuse. Not all cases of ephedrine toxicity have arisen as a result of overt abuse but rather because of inadequate labelling of content and dosage instructions on some unlicensed products. A small study found that combinations of herbal caffeine and ephedra alkaloids taken in recommended amounts resulted in plasma ephedrine concentrations that exceeded the usual therapeutic range. Significant increases occurred in blood pressure and heart rate, and unfavourable effects on glucose and potassium homoeostasis were noted.[9] The use of ephedra-containing dietary supplements is now banned in the USA and some other countries.

Adverse effects from ingestion of ephedrine-containing OTC preparations, including herbal products (usually in high doses and/or long term) have included coronary artery thrombosis,[10] myocardial infarction, seizures,[11] psychotic reactions,[12] nephrolithiasis,[13-15] and myocarditis;[16] some fatalities have been reported. Frank dependence has been reported in female weightlifters following long-term use of high doses.[17]

For a report of urinary calculi developing in a patient who had ingested a preparation containing guaifenesin and ephedrine, see Abuse, under Guaifenesin, p. 1666.3.

1. WHO. Recommendations from the Expert Committee on Drug Dependence. *WHO Drug Inf* 1998; **12:** 227–9.
2. Cockings JGL, Brown MA. Ephedrine abuse causing acute myocardial infarction. *Med J Aust* 1997; **167:** 199–200.
3. Zahn KA, *et al*. Cardiovascular toxicity after ingestion of "herbal ecstacy" [sic]. *J Emerg Med* 1999; **17:** 289–91.
4. James LP, *et al*. Sympathomimetic drug use in adolescents presenting to a pediatric emergency department with chest pain. *J Toxicol Clin Toxicol* 1998; **36:** 321–8.
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17. Gruber AJ, Pope HG. Ephedrine abuse among 36 female weightlifters. *Am J Addict* 1998; **7:** 256–61.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ephedrine, when used as a bronchodilator, as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Ephedrine has direct and indirect actions and may cause a hypertensive crisis in patients receiving an MAOI (including a RIMA); the possibility of such an interaction after intranasal use of ephedrine should also be borne in mind. See also under Phenelzine (p. 445.1) and Moclobemide (p. 438.1). Since ephedrine has both alpha- and beta-agonist properties it should be avoided or used with care in patients undergoing anaesthesia with cyclopropane, halothane, or other volatile anaesthetics. An increased risk of arrhythmias may occur if given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants, and there is an increased risk of vasoconstrictor or pressor effects in patients receiving ergot alkaloids or oxytocin. The rate of metabolism of some other drugs is increased by ephedrine. For mention of the potential additive stimulant effects seen with caffeine and ephedrine, see Sympathomimetics, under Caffeine, p. 1206.2. For the effect of ephedrine on histamine given exogenously, see p. 2525.3.

Pharmacokinetics

Ephedrine is readily and completely absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine, with small amounts of metabolites produced by hepatic metabolism. Ephedrine has been variously reported to have a plasma half-life ranging from 3 to 6 hours depending on urinary pH; elimination is enhanced and half-life accordingly shorter in acid urine.

References.

1. Welling PG, *et al*. Urinary excretion of ephedrine in man without pH control following oral administration of three commercial ephedrine sulfate preparations. *J Pharm Sci* 1971; **60:** 1629–34.
2. Sever PS, *et al*. The metabolism of (-)-ephedrine in man. *Eur J Clin Pharmacol* 1975; **9:** 193–8.
3. Pickup ME, *et al*. The pharmacokinetics of ephedrine after oral dosage in asthmatics receiving acute and chronic treatment. *Br J Clin Pharmacol* 1976; **3:** 123–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Muchan; ***Belg.***: Ephedronguent†; ***Braz.***: Unifedrine; ***Chile***: Efedrosan†; ***Gr.***: Neo Rhinovit; Rhinolex; ***Hong Kong***: Efmol†; ***Hung.***: Epherit; ***India***: Efipres; ***Mex.***: Tendrin†; ***Pol.***: Efrinol; ***Port.***: Spinefe; ***Turk.***: Rinitalmit†; ***UK***: CAM; ***USA***: Kondon's Nasal; ***Venez.***: Colirio Iris.

Multi-ingredient Preparations. ***Arg.***: Amiorel Compuesto; Aqua Lent Colirio; Bideon Free; Bisolvon Compositum; Clarisoft; Coliria; Efodil; Exudrol; Fadatos; Irix Clasico; Kalopsis; Neoefodil; No-Tos Adultos; Quemicetina Nasal Compuesta; Sintebron; Usualix; Vislus; ***Austria***: Coldargan; Famel cum Ephedrin†; Helopyrin; Novipec†; Pilka Forte; Piniment; Spirbon†; Wick Erkaltungs-Saft fur die Nacht†; Wick Erkaltungssirup fur die Nacht; ***Belg.***: Argyrophedrine†; Endrine Doux; Endrine; ***Braz.***: Beclase†; Franol; Inhalante Yatropan; Marax; Rinisone; Tonaton; ***Canad.***: Madame Pearl's Cough Syrup; Rhino-Vaccin†; ***Chile***: Broncodeina; Pulmagol; ***China***: Cofetol (奥亭); Compound Codeine (复方待因); Fufang Dan An Pian (复方胆氨片); Libang Zhikelu (联邦止咳露); ***Cz.***: Mukoseptonex E; Tussilen†; ***Fin.***: Codesan Comp; Sir. Ephedrin; ***Fr.***: Caustinerf Arsenical; Devitasol Arsenical†; Osmotol; Otylol; Rhinamide; Rhino-Sulfuryl; Transmer†; Yranicid Arsenical; ***Ger.***: Wick Medinait fur die Nacht; ***Gr.***: Evex; Neo-Bronchoton-R; Otil; Sival-B; Toryl; Torylet; ***Hong Kong***: Against Cough†; Amiton†; Antihist EC Expectorant†; Antipect†; Co-Epherine†; Coci-Fedra-C†; Coryl†; DEC†; Decofam Cough; Dhasedyl; Ephecol†; Ephedyl-DM†; Ephedyl†; Ephendyln†; Fendil†; Fendyl; Fritussin†; Marsedyl†; Methor-Co†; Methorsedyl; Metoplex; Neo-Tussin†; P.E. D.†; PEC; Pecolin†; Phensedyn; Promethazine Compound Linctus†; Prosedyl†; Sedral†; Sedylin†; Uni-Ramine CE; Uni-Theodal†; ***Hung.***: Coderetta N; Coderit N; Coldargan†; Hemorid; Hemorid; ***India***: Alergin; Asmapax; Bronolax; Cadiphylate; Cafona-E; Codoric; Cofton SF; Cortasthma; Dericip Plus; Elixir Efelin; Endrine Mild; Endrine; Gocold; Jiffy; Kufma; Marax; Mulitmix; Multimix; Multimix; Osdoril; ***Indon.***: Asmadex; Asmano; Asmasolon; Asthma Soho; Bronchitin; Cold Cap; Ersylan; Kafsir; Koffex for Children; Mixadin; Neo Napacin†; Oskadryl; Phenadex; Poncolin D; Poncolin; Prinasma†; Theochodil; Thymcal; ***Israel***: Pertussol; Proaf†; To-Care; Tucare; Tussophedrine NF; Tussosedan†; ***Ital.***: Argotone Rino; Deltarinolo; Fienamina; Pasta Arsenicale; Rinovit; ***Malaysia***: Asthma; Cofnil-N†; Dexcophan Cough†; Dhasedyl DM; Diprodin; Phensedyl Dry Cough; ***Mex.***: Alfan†; Broncofedrina; Coderit; Jarabe de Capulin†; Paliatil; ***Pol.***: Rubital Compositum; Syrop Prawoslazowy Zlozony; Tussipect; Tussipect; ***Port.***: Anti-Asmatico†; Ipesandrine†; Mebocatuss; Sedotusse†; ***Rus.***: Bronchitussin (Бронхитусен); Bronchocin (Бронхоцин); Broncholytin (Бронхолитин); Bronchoton (Бронхотон); Insanovin (Инсановин); Solutan (Солутан)†; Theophedrinum-N (Теофедрин-Н); ***S.Afr.***: Brunacod†; Codef†; Colcleer; Corbar; Coughcod†; Dequa-Coff; Docsed†; Flusin†; Genasma†; Grippon†; Lenazine Forte; Linctodyl†; Natrophylline Compound†; Oto-Phen Forte†; Phensedyl; Repasma†; Sinucon; Sinuend; Vicks Medinite†; ***Singapore***: Alcough; Ancolin; Anti-phlegm; Beacons Cough; Brecolin; Chlorsedyl; Cophadyl-E; Coughlax; Decofam Cough; Dexcophan Cough Linctus Plus; Dhasedyl DM; Dhasedyl; Diprodin; Ephedyl DM; Ephedyl; Pico's Children's Cough; Pico's Cough; PO-V-SU; Polins Cough; Promedyl; Robinson Cough; Sedilix; Semerin; SP-Brom; Sunamine; Sunny Children Cough; Sunsedyl; Veelanz's Cough Syrup; Vyling Anti-Cough Menthol; Williams Cough; ***Spain***: Bisolvon Compositum†; Brota Rectal Balsamico†; Cilinafosal Dihidroestreptomicina†; Cilinafosal Hidrocortisona†; Cilinafosal Neomicina†; Cilinafosal†; Fludren†; Hemoal; Kanafosal Predni†; Kanafosal†; Medinait; Pazbronquial; Tabletas Quimpe†; Vitavox†; Voxfor†; ***Swed.***: Lepheton; Lergigan comp; Mollipect; ***Switz.***: Demo Elixir pectoral N†; Haemolan†; Kemeol†; Pastilles pectorales du Dr. Welti; Pectocalmine N; Sano Tuss; Sanotussin; Vicks Medinait; ***Turk.***: Antibeksin; Artu; Brodil; Broksin; Defeks; Dorfan; Eupnase; Fenasthma; Fenokodin†; Hemoralgine; Latusin†; Neo Sedeks; Neofedrin; Pedrin; Pektodin†; Penikin†; Pereks; Radycodin; Radyokodin; Sulfarhin; ***UAE***: Codaphed Plus; Codaphed; ***UK***: Do-Do ChestEze; Dolvan; Haymine; Noradran; Paranorm; ***Ukr.***: Bronchobru (Бронхобрю); Broncholytin (Бронхолитин); ***USA***: Broncholate†; Bronkaid Dual Action†; Bronkotuss Expectorant; Hydrophed; KIE; Marax; Pazo; Primatene; Quadrinal; Quelidrine; Rentamine Pediatric; Rynatuss†; Tedrigen; Theodrine; Theomax DF; Tri-Tannate Plus Pediatric; Tuss-Tan; ***Venez.***: Amodion; Pi-Fedrin; Pidrol; Tabonuco.

Homoeopathic Preparations. ***Chile***: Ikoplex No 3.

Pharmacopoeial Preparations

BP 2014: Ephedrine Elixir; Ephedrine Hydrochloride Tablets; Ephedrine Injection; Ephedrine Nasal Drops;

USP 36: Ephedrine Sulfate Capsules; Ephedrine Sulfate Injection; Ephedrine Sulfate Nasal Solution; Ephedrine Sulfate Syrup; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Eprazinone Hydrochloride *(rINN/NM)*

CE-746; Eprazinona, hidrocloruro de; Éprazinone, Chlorhydrate d'; Eprazinoni Hydrochloridum; Hidrocloruro de eprazinona; Эпразинона Гидрохлорид.

3-[4-(β-Ethoxyphenethyl)piperazin-1-yl]-2-methylpropiophenone dihydrochloride.

$C_{24}H_{32}N_2O_2,2HCl$=453.4

CAS — 10402-90-1 (eprazinone); 10402-53-6 (eprazinone hydrochloride).

ATC — R05CB04.

ATC Vet — QR05CB04.

UNII — 394X1L8I9Y.

Profile

Eprazinone hydrochloride has been variously described as having mucolytic or expectorant properties as well as a direct relaxant action on bronchial smooth muscle. It is used for cough (p. 1651.2) and is given in oral doses of 50 to 100 mg three times daily. It has also been given rectally.

Effects on the skin. Skin eruptions have been associated with the oral use of eprazinone.[1,2]

1. Faber M, *et al*. Eprazinonexanthem mit subkornealer Pustelbildung. *Hautarzt* 1984; **35:** 200–3.
2. Tanabe K, *et al*. Non-pigmented fixed drug eruption induced by eprazinone hydrochloride. *Dermatol Online J* 2005; **11:** 25.

Overdosage. Symptoms in two 22-month-old children who received an overdose of 800 mg of eprazinone included somnolence, ataxia, and seizures.[1]

1. Merigot P, *et al*. Les convulsions avec trois antitussifs dérivés substitués de la pipérazine: (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; **32:** 504–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Isilung†; ***Fr.***: Mucitux; ***Jpn***: Resplen.

Eprozinol Hydrochloride *(rINNM)*

Éprozinol, Chlorhydrate d'; Eprozinoli Hydrochloridum; Hidrocloruro de eprozinol; Эпрозинола Гидрохлорид.
3-[4-(β-Methoxyphenethyl)piperazin-1-yl]-1-phenylpropan-1-ol dihydrochloride.
$C_{22}H_{30}N_2O_2.2HCl$=427.4
CAS — 32665-36-4 (eprozinol).
ATC — R03DX02.
ATC Vet — QR03DX02.
UNII — X9AMI360PI.

Profile

Eprozinol hydrochloride has been given orally for its mucolytic or expectorant properties.

Adverse effects. Convulsions and coma were reported in a 19-year-old patient after taking eprozinol.[1]

1. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués de la pipérazine: (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; **32:** 504–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Eupneron†.

Erdosteine *(BAN, rINN)*

Erdosteiini; Erdostein; Erdosteína; Erdostéine; Erdosteinum; Эрдостеин.
(±)-({[(Tetrahydro-2-oxo-3-thienyl)carbamoyl]methyl}thio) acetic acid.
$C_8H_{11}NO_4S_2$=249.3
CAS — 84611-23-4.
ATC — R05CB15.
ATC Vet — QR05CB15.
UNII — 76J0853EKA.

Uses and Administration

Erdosteine is a mucolytic that is used in the treatment of disorders of the respiratory tract characterised by productive cough (p. 1651.2). It is given in usual oral doses of 300 mg twice daily for a maximum of 10 days.

Doses may have to be reduced in hepatic impairment (see below).

Administration in hepatic and renal impairment. Exposure to erdosteine is increased in patients with hepatic impairment. UK licensed product information states that no increase in adverse effects has been seen in patients with mild hepatic impairment, but restricts the oral dose in these patients to a maximum of 300 mg daily. Erdosteine is contra-indicated in severe hepatic impairment as there is no experience of use in this group of patients.

Although no difference in absorption or elimination has been seen in patients with moderate renal impairment, the risk of accumulation of metabolites cannot be excluded. For this reason, use of erdosteine is contra-indicated in patients with a creatinine clearance of less than 25 mL/minute.

Chronic obstructive pulmonary disease. Erdosteine has been used[1-3] in the management of chronic obstructive pulmonary disease (p. 1199.1) but the value of mucolytics in this disorder is controversial and a recent review[4] considered the few published studies of erdosteine to be outdated and of poor quality.

1. Dechant KL, Noble S. Erdosteine. *Drugs* 1996; **52:** 875–81.
2. Marchioni CF, *et al.* Evaluation of efficacy and safety of erdosteine in patients affected by chronic bronchitis during an infective exacerbation phase and receiving amoxycillin as basic treatment (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study). *Int J Clin Pharmacol Ther* 1995; **33:** 612–18.
3. Moretti M, *et al.* The effect of long-term treatment with erdosteine on chronic obstructive pulmonary disease: the EQUALIFE Study. *Drugs Exp Clin Res* 2004; **30:** 143–52.
4. Anonymous. Erdosteine for COPD exacerbations. *Drug Ther Bull* 2008; **46:** 79–80.

Adverse Effects and Precautions

Gastrointestinal disturbances may occur with erdosteine. Headache, dyspnoea, taste alterations, urticaria, erythema, and dermatitis have been reported rarely. Erdosteine should not be used in patients with active peptic ulcer disease. For precautions when used in patients with hepatic or renal impairment, see under Uses and Administration, above.

Pharmacokinetics

Erdosteine is rapidly absorbed after oral use and peak plasma concentrations occur after about an hour; absorption is unaffected by food. Erdosteine undergoes first-pass metabolism to an active metabolite, *N*-thiodiglycolyl-homocysteine. Plasma protein binding is about 64.5%. The elimination half-life is about 1.46 hours for erdosteine, and about 1.62 hours for the metabolite. It is mainly excreted in the urine as metabolites; faecal elimination is negligible.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fluidasa; ***Austria***: Erdomed; ***Belg.***: Mucodox; ***Braz.***: Flusten; ***Chile***: Biopulmin; ***China***: A Duo Ting (阿多停); He Tan (和坦); Lu Chang (露畅); Tantong (坦通); ***Cz.***: Erdomed; ***Denm.***: Erdotin; ***Fin.***: Erdopect; ***Fr.***: Vectrine; ***Gr.***: Theovix; Tusselin; ***Hung.***: Erdomed; ***India***: Erdomac; Erdozet; ***Indon.***: Edotin; Mucotein; Recustein; Vectrine; ***Irl.***: Erdotin; ***Israel***: Erdotin; ***Ital.***: Erdotin; ***Mex.***: Dostein; Esteclin; ***Philipp.***: Ectrin; Zertin; ***Pol.***: Erdomed; ***Port.***: Erdotin†; ***Switz.***: Mucofor; ***Turk.***: Erdostin; Evosten; ***UK***: Erdotin.

Multi-ingredient Preparations. ***Mex.***: Esteclin Bac†.

Eriodictyon

Hierba santa; Mountain Balm; Yerba Santa; Эриодиктион калифорнийский.
CAS — 8013-08-9.
UNII — 2Y7TIQ135H.

NOTE. The name Hierba Santa (Yerba Santa) has been applied to many plants including *Artemesia absinthium* (p. 2426.1).

Profile

Eriodictyon consists of the dried leaves of *Eriodictyon californicum* (Hydrophyllaceae). It has been used as an expectorant. It has also been used in the treatment of dry mouth and to mask the taste of bitter drugs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Mouth Kote.

Multi-ingredient Preparations. ***Ger.***: Saliva natura; ***Ital.***: Broncosedina; Broncosedina; ***Switz.***: Hydro Santa†; ***UK***: Saliva Natura; ***USA***: Feminease; ***Venez.***: Yerba Santa.

Homoeopathic Preparations. ***Canad.***: Breathe More; ***Fr.***: Boripharm No 11†; Santaherba; ***Ger.***: A-Bomin; Broncho-Injektopas; Bronchopas; Pulmo Bronchialcomplex; Rufebran broncho†; Santa Flora S.

Etafedrine Hydrochloride

(BANM, USAN, rINNM) ⊗

Etafedrina, hidrocloruro de; Étafédrine, Chlorhydrate d'; Etafedrini Hydrochloridum; Ethylephedrine Hydrochloride; Hidrocloruro de etafedrina; Этафедрина Гидрохлорид.
(-)-2-(Ethylmethylamino)-1-phenylpropan-1-ol hydrochloride.
$C_{12}H_{19}NO.HCl$=229.7
CAS — 7681-79-0 (etafedrine); 48141-64-6 ((-)-etafedrine); 5591-29-7 (etafedrine hydrochloride).
UNII — Y134VQ304Y.

Profile

Etafedrine hydrochloride is a sympathomimetic related to ephedrine (p. 1663.1). It is used for its bronchodilator effects in combination preparations for the relief of cough and associated respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: EMS Expectorante; Revenil Dospan; Revenil Expectorante; Revenil; Xpe Expectorante; ***Canad.***: Dalmacol; ratio-Calmydone; ***Indon.***: Decolsin; ***S.Afr.***: Nethaprin Dospan†; Nethaprin Expectorant†; ***Thai.***: Brondil†.

Ethyl Cysteine Hydrochloride

Etilcisteína, hidrocloruro de; Этиловый Эфир Цистеина Гидрохлорида.
Ethyl L-2-amino-3-mercaptopropionate hydrochloride.
$C_5H_{11}NO_2S.HCl$=185.7
CAS — 3411-58-3 (ethyl cysteine); 868-59-7 (ethyl cysteine hydrochloride).

Pharmacopoeias. In *Jpn*.

Profile

Ethyl cysteine hydrochloride is a mucolytic that has been used in the treatment of disorders of the respiratory tract associated with productive cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cystanin.

Ethyl Orthoformate

Ether de Kay; Ortoformiato de etilo; Ortoformiato de trietilo; Triethoxymethane; Trietoximetano; Этиловый Эфир Ортомуравьиной Кислоты.
Triethyl orthoformate.
$C_7H_{16}O_3$=148.2
CAS — 122-51-0.

Pharmacopoeias. In *Fr*.

Profile

Ethyl orthoformate is a cough suppressant. It is reported to be a respiratory antispasmodic and has been given orally or rectally.

Fedrilate *(rINN)*

Fédrilate; Fedrilato; Fedrilatum; UCB-3928; Федрилат.
1-Methyl-3-morpholinopropyl perhydro-4-phenylpyran-4-carboxylate.
$C_{20}H_{29}NO_4$=347.5
CAS — 23271-74-1.
ATC — R05DB14.
ATC Vet — QR05DB14.
UNII — NT86R8M7J5.

Profile

Fedrilate is a cough suppressant used orally for non-productive cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Gotas Binelli.

Fenoxazoline Hydrochloride *(rINNM)* ⊗

Fénoxazoline, Chlorhydrate de; Fenoxazolini Hydrochloridum; Hidrocloruro de fenoxazolina; Феноксазолина Гидрохлорид.
2-(2-Isopropylphenoxymethyl)-2-imidazoline hydrochloride.
$C_{13}H_{18}N_2O.HCl$=254.8
CAS — 4846-91-7 (fenoxazoline); 21370-21-8 (fenoxazoline hydrochloride).
ATC — R01AA12.
ATC Vet — QR01AA12.
UNII — 6K28Y098S7.

Profile

Fenoxazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3) that has been used topically for its vasoconstrictor properties in the symptomatic treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nebulicina; ***Braz.***: Nasofelin; Rinigran.

Fominoben Hydrochloride *(rINNM)*

Fominobén, hidrocloruro de; Fominobène, Chlorhydrate de; Fominobeni Hydrochloridum; Hidrocloruro de fominobén; PB-89; Фоминобена Гидрохлорид.
3′-Chloro-2′-[*N*-methyl-*N*-(morpholinocarbonylmethyl)aminomethyl]benzanilide hydrochloride.
$C_{21}H_{24}ClN_3O_3.HCl$=438.3
CAS — 18053-31-1 (fominoben); 24600-36-0 (fominoben hydrochloride).
UNII — XCT2R4OS1G.

Profile

Fominoben hydrochloride is a centrally acting cough suppressant that is also reported to have respiratory stimulant properties. It is used for cough (p. 1651.2) and is given in oral doses of 160 mg up to three times daily; it has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Noleptan†; ***Mex.***: Noleptan.

Fudosteine *(rINN)*

Fudosteína; Fudostéine; Fudosteinum; SS-320A; Фудостеин.
(-)-3-[(3-Hydroxypropyl)thio]-L-alanine.
$C_6H_{13}NO_3S$=179.2
CAS — 13189-98-5.
UNII — UR9VPI71PT.

Profile

Fudosteine is an expectorant given orally in a dose of 400 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Zhong Chang (中畅); ***Jpn***: Cleanal; Spelear.

Glaucine

Boldine Dimethyl Ether; DL-832 (*dl*-glaucine phosphate); *dl*-Glaucine; Glaucina; MDL-832 (*dl*-glaucine phosphate); Глауцин.
DL-1,2,9,10-Tetramethoxyaporphine.
$C_{21}H_{25}NO_4$=355.4
CAS — 5630-11-5 (dl-glaucine); 73239-87-9 (dl-glaucine phosphate); 475-81-0 (d-glaucine); 5996-06-5 (d-glaucine hydrobromide).
UNII — NU19306XA7.

Profile

Glaucine is a centrally acting cough suppressant used in non-productive cough; it has been given as the phosphate.

d-Glaucine has also been used, as the hydrobromide and the hydrochloride. It has been obtained from *Glaucium flavum* (Papaveraceae).

Abuse. A 23-year-old woman developed nausea and vomiting within 30 minutes of taking 2 tablets described as "head candy" or as a BZP-free "herbal high".[1] This was followed by a period of dissociative-type symptoms and later by agitation, tachycardia, and tachypnoea. Analysis of serum and urine revealed the presence of glaucine.

1. Dargan PI, *et al.* Detection of the pharmaceutical agent glaucine as a recreational drug. *Eur J Clin Pharmacol* 2008; **64:** 553–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Glauvent (Глаувент).

Multi-ingredient Preparations. ***Rus.***: Bronchitussin (Бронхитусен); Bronchocin (Бронхоцин); Broncholytin (Бронхолитин); Bronchoton (Бронхотон); ***Ukr.***: Broncholytin (Бронхолитин).

Guacetisal *(rINN)*

Acetylsalicylic Acid Guaiacol Ester; Guacétisal; Guacetisalum; Гуацетисал.
o-Methoxyphenyl salicylate acetate.
$C_{15}H_{14}O_5$=286.3
CAS — 55482-89-8.
ATC — N02BA14.
ATC Vet — QN02BA14.
UNII — T6EKB9V2O2.

Profile

Guacetisal has been used in respiratory disorders as an expectorant. It has also been used as an antipyretic to reduce fever. It has been given orally and rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Suo Di Fei (索迪菲).

Guaiacol

Gaïacol; Guaiacolum; Guajacol; Guayacol; Gwajakol; Methyl Catechol; Гваякол.
2-Methoxyphenol.
$C_7H_8O_2$=124.1
CAS — 90-05-1 (guaiacol); 553-17-3 (guaiacol carbonate); 60296-02-8 (calcium guaiacolglycolate); 4112-89-4 (guaiacol phenylacetate).
UNII — 6JKA7MAH9C.

Pharmacopoeias. In *Eur.* (see p. vii). *Fr.* also includes guaiacol carbonate.

Ph. Eur. 8: (Guaiacol). A crystalline mass or colourless or yellowish hygroscopic liquid. Sparingly soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Guaiacol has disinfectant properties and has been used in dentistry and as an expectorant for productive cough.

In high concentrations, adverse effects are similar to, but less severe than, those of phenol (p. 1764.2).

Many salts and derivatives of guaiacol have been used similarly including the carbonate, cinnamate, ethylglycolate, calcium and sodium glycolates, phenylacetate, and phenylbutyrate. See also Guaifenesin, below and Sulfoguaicol, p. 1678.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Eucaliptine†.

Multi-ingredient Preparations. ***Arg.***: Aseptobron; Atomo Desinflamante Familiar; Atomo Desinflamante; ***Belg.***: Eucalyptine Pholcodine; Inopectol†; ***Braz.***: Ozonyl; Transpulmin Balsamo; Transpulmin; ***Canad.***: Creo-Rectal; Demo-Cineol†; ***Fr.***: Aldyzine; Bi-Qui-Nol; Bronchorectine au Citral; Essence Algerienne; Osomol; Pastiserol†; Pulmo Bailly; Pulmoserum; Rockles; Valda†; ***India***: Mynberrys Compound; ***Ital.***: Eugenol-Guaiacolo Composto; Fosfoguaiacol†; Lipobalsamo; ***Mex.***: Guayalin; ***Mon.***: Bronchodermine; Bronchodermine; ***Port.***: Algina; ***Spain***: Bronco Aseptilex Fuerte†; Tos Mai; ***UK***: Dragon Balm; Pulmo Bailly; ***USA***: Methagual.

Homoeopathic Preparations. ***Canad.***: Hylagesic APF.

Guaietolin *(rINN)*

Glycerylguethol; Glyguetol; Guaietolina; Guaïétoline; Guaietolinum; Guayetolina; Гвайэтолин.
3-(2-Ethoxyphenoxy)propane-1,2-diol.
$C_{11}H_{16}O_4$=212.2
CAS — 63834-83-3.
UNII — G9J54386JH.

Profile

Guaietolin is an analogue of guaifenesin (below) which is used as an expectorant. It has been given for cough (p. 1651.2) in oral doses of 300 to 600 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Guethural.

Guaifenesin *(BAN, USAN, rINN)*

Glicerilguayacol; Glyceryl Guaiacolate; Glycerylguayacolum; Guaiacol Glycerol Ether; Guaiacyl Glyceryl Ether; Guaifenesiini; Guaifenesina; Guaïfénésine; Guaifénésine; Guaifenesinum; Guaiphenesin; Guajacolum Glycerolatum; Gvajfenezin; Gvajfenezinas; Гвайфенезин.
(*RS*)-3-(2-Methoxyphenoxy)propane-1,2-diol.
$C_{10}H_{14}O_4$=198.2
CAS — 93-14-1.
ATC — R05CA03.
ATC Vet — QM03BX90; QR05CA03.
UNII — 495W7451VQ.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Guaifenesin). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol.

USP 36: (Guaifenesin). A white to slightly grey crystalline powder. May have a slight characteristic odour. Soluble 1 in 60 to 70 of water; soluble in alcohol, in chloroform, and in propylene glycol; sparingly soluble in glycerol. Store in airtight containers.

Uses and Administration

Guaifenesin is reported to increase the volume and reduce the viscosity of tenacious sputum and is used as an expectorant for productive cough (see Respiratory Disorders, below). It is given in oral doses of 200 to 400 mg every 4 hours. In the USA, a maximum of 6 doses daily is allowed; however, in the UK, it is more usual to give 4 times daily. Modified-release preparations, given every 12 hours, are also available. For doses in children, see below.

Guaifenesin has been used similarly as the calcium salt.

Guaifenesin is used as an adjunct to anaesthesia in veterinary medicine.

Administration in children. Guaifenesin is licensed for use as an expectorant in children. However, over-the-counter cough and cold preparations containing expectorants (including guaifenesin) should be used with caution in children and generally avoided in young children; for details, see Cough, p. 1651.2.

In the USA, typical licensed oral doses, given every 4 hours, according to age, are:

- 4 to 6 years, 50 to 100 mg
- 6 to 12 years, 100 to 200 mg

Modified-release preparations, given every 12 hours, are also available.

In the UK, licensed product information suggests that these doses may be given up to a maximum of 4 times daily.

Respiratory disorders. An FDA review of preparations available over-the-counter concluded that guaifenesin was an effective expectorant.[1] The use of expectorants for productive cough is discussed on p. 1651.2. A small study[2] found that guaifenesin also appeared to reduce cough reflex sensitivity in patients with upper respiratory-tract infections, which produce a transient increase in sensitivity, although it had no effect on cough reflex in healthy subjects. The mechanism for this effect was unclear.

1. Thomas J. Guaiphenesin—an old drug now found to be effective. *Aust J Pharm* 1990; **71:** 101–3.
2. Dicpinigaitis PV, Gayle YE. Effect of guaifenesin on cough reflex sensitivity. *Chest* 2003; **124:** 2178–81.

Adverse Effects and Precautions

Gastrointestinal discomfort, nausea, and vomiting have occasionally been reported with guaifenesin, particularly in very large doses.

Abuse. Urinary calculi have been reported in patients consuming large quantities of over-the-counter preparations containing guaifenesin.[1,2] Spectroscopic analysis[1] revealed that the stones were composed of a calcium salt of beta-(2-methoxyphenoxy)-lactic acid, which is a metabolite of guaifenesin. Small quantities of ephedrine were also present in the stones of one of several patients who had ingested preparations containing a combination of guaifenesin and ephedrine.[2]

1. Pickens CL, *et al.* Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis. *Urology* 1999; **54:** 23–7.
2. Assimos DG, *et al.* Guaifenesin- and ephedrine-induced stones. *J Endourol* 1999; **13:** 665–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies guaifenesin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Guaifenesin is well absorbed from the gastrointestinal tract. It is metabolised and then excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Guaifen; Omega 100 Bronquial; Plenum; Vick 44 Exp; Vickmiel; ***Austral.***: Actifed CC Chesty†; Robitussin Chesty Cough; Robitussin EX†; Vicks Cough Syrup for Chesty Cough; Vicks Formula 44 Chesty Cough†; ***Austria***: Resyl; ***Belg.***: Vicks Vaposyrup Expectorant; ***Braz.***: Broncofenil; Dimetapp Expectorante†; Expectovic; Transpulmin; Vick Xarope; Xarope Vick Mel; ***Canad.***: Balminil Expectorant; Benylin Chest Congestion; Benylin DM-D-E-A Cold and Sinus; Benylin E†; Bronchophan Expectorant; Cold and Flu-in-One; Cough Syrup Expectorant; Expectorant Cough Formula; Expectorant Syrup; Expectorant; Robitussin; Vicks Chest Congestion Relief; Vicks DayQuil Mucus Control; ***Cz.***: Coldrex Broncho; Guajacuran; Robitussin Expectorans; ***Fin.***: Tintus; ***Fr.***: Vicks Expectorant; ***Ger.***: Fagusan; Wick Husten-Loser; ***Gr.***: VP-Syrup; ***Hong Kong***: Breacol; G.G. Tab†; Glylate; Gufensin; Mucolex†; Neotussin†; Robitussin Chest Congestion†; Robitussin EX; Uni-Colex; ***Hung.***: Coldrex Broncho†; Relaxil-G; Robitussin Expectorans; ***India***: Barkeit; ***Indon.***: Probat; ***Irl.***: Benylin Childrens Chesty Cough; Lemsip Chesty Cough; Meltus Honey and Lemon†; Robitussin Chesty Cough; Tixylix Chesty Cough; ***Israel***: Kuffex DM; Resyl; Robitussin; Vitussin; ***Ital.***: Broncovanil; Resyl; Vicks Tosse Fluidificante; ***Malaysia***: Guafensin; Mucinex; ***Mex.***: Robitussin; Tukol†; Vick 44 Exp; ***Norw.***: Tussin; ***NZ***: Mucinex; Robitussin EX; ***Philipp.***:

Bena; Benadryl Expectorant; Flemonex; Guais†; Pharmachem; Robitussin Expectorant; Suprekof; Transpulmin G; Venalax XPT; ***Pol.***: Guajavis; Guajazyl; Robitussin Expectorans; ***Port.***: Vicks Xarope Expectorante; ***Rus.***: Coldrex Broncho (Колдрекс Бронхо); Novo-Passit (Ново-Пассит); Theraflu KV (Терафлю КВ); Tussin (Туссин); ***S.Afr.***: Actospect; Benylin Wet Cough; Borstol Linctus†; Broncholin; Chamberlains Cough Remedy Honey and Liquorice†; Chamberlains Cough Remedy Peppermint†; Dilinct Junior; Expelinct; Flemmi-Ped†; Med-Lemon Cough Syrup†; Vicks Acta Plus Expectorant†; ***Singapore***: Breacol; Cofen; Decosyn; Guardian Cough; Robitussin EX; Wood's Peppermint Cough Syrup; ***Spain***: Formulaexpec; Frispec; ***Swed.***: Resyl†; Theracough; ***Switz.***: Resyl; Vicks Sirop Expectorant; ***Thai.***: Fenesin; Genesin; Glycolate; Glyryl; Guaiacol; Kidkof; Mulade; Robitussin; Tussa†; ***Turk.***: Vicks Vapo Expectorant; Vicks VapoSyrup; ***UK***: Adult Chesty Cough Non Drowsy; Benylin Childrens Chesty Coughs; Benylin Mucus Cough Honey & Lemon; Benylin Mucus Cough Menthol; Boots Chesty Cough Syrup 6 Years Plus; CalCough Six Plus; Expectorant Cough Syrup; Hill's Balsam Chesty Cough; Jackson's All Fours; Jackson's Bronchial Balsam; Lemsip Cough & Cold Chesty Cough; Robitussin Chesty Cough; Tixylix Chesty Cough; Venos for Kids; Vicks Cough Syrup for Chesty Coughs; Vicks Vaposyrup for Chesty Coughs; ***USA***: Bidex; Buckleys Chest Congestion; Diabetic Tussin Mucus Relief; Ganidin NR†; Glycotuss; Guiatuss; Humavent; Humibid Maximum Strength; Iophen NR; Liquibid; Liquituss GG; Mucinex; MucusRelief; Naldecon Senior EX; Organ-I NR; Organidin NR; Refenesen; Robitussin Mucus & Chest Congestion; Scot-Tussin Expectorant; Siltussin; Tusibron; Vicks Dayquil Mucus Control; Xpect; ***Venez.***: Alivetos Pediatrico; Robitessin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

USP 36: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Guaifenesin and Codeine Phosphate Syrup; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin Capsules; Guaifenesin Syrup; Guaifenesin Tablets; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution.

Guaimesal *(rINN)*

Guaïmésal; Guaimesalum; Гваймесал.

(±)-2-(*o*-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-one.

$C_{16}H_{14}O_5$=286.3

CAS — 81674-79-5.

UNII — K43273G1CW.

Profile

Guaimesal is reported to have expectorant and antipyretic properties and has been given orally as an adjunct in the treatment of respiratory-tract disorders. It has also been given rectally in suppositories.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pak.***: Brontermil.

Helicidine

Helicidina; Helixinum; Гелицидин.

Profile

Helicidine is a mucoglycoprotein from the snail *Helix pomatia* that has been used as a cough suppressant.

References.

1. Pons F, *et al.* L'effect bronchorelaxant de l'helicidine, un extrait d'Helix pomatia, fait intervenir une liberation de prostaglandine E2. *Pathol Biol (Paris)* 1999; **47:** 73–80.

Indanazoline Hydrochloride *(rINNM)* ⊗

Hidrocloruro de indanazolina; Indanazolin Hidroklorür; Indanazolina, hidrocloruro de; Indanazoline, Chlorhydrate d'; Indanazolini Hydrochloridum; Инданазолина Гидрохлорид.

$C_{12}H_{15}N_3$,HCl=237.7

CAS — 56601-85-5.

UNII — Z364A90IV8.

Profile

Indanazoline is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3). It has been used as the hydrochloride for its vasoconstrictor effect in the management of nasal congestion (p. 1652.1). It has been given as nasal drops, a nasal gel, or a nasal spray in a concentration equivalent to indanazoline 0.1%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Farial.

Iodinated Glycerol *(BAN, USAN)*

Glicerol yodado; Iodopropylidene Glycerol; Глицерин Йодированный.

$C_6H_{11}IO_3$=258.1

CAS — 5634-39-9.

UNII — 34ON63CCO3.

Profile

Iodinated glycerol, a methyl derivative of domiodol, is an isomeric mixture of iodinated dimers of glycerol. It has been used as an expectorant. The limitations of iodides as expectorants are discussed in Cough on p. 1651.2. The actions of iodides and iodine compounds are discussed under Iodine p. 2336.3. Prolonged use of iodinated glycerol has been associated with thyroid dysfunction (see Effects on the Thyroid Gland, below) and severe skin eruptions; gastrointestinal disturbances and hypersensitivity reactions have also occurred. Malignant neoplasms have developed in *animals* given iodinated glycerol.

Chronic obstructive pulmonary disease. Studies[1-3] of the use of iodinated glycerol in patients with chronic bronchitis have produced conflicting results. The use of mucolytics or expectorants in chronic obstructive pulmonary disease (p. 1199.1) is controversial.

1. Petty TL. The National Mucolytic Study: results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990; **97:** 75–83.
2. Repsher LH. Treatment of stable chronic bronchitis with iodinated glycerol: a double-blind, placebo-controlled trial. *J Clin Pharmacol* 1993; **33:** 856–60.
3. Rubin BK, *et al.* Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest* 1996; **109:** 348–52.

Effects on the thyroid gland. Thyroid dysfunction (both hyperthyroidism and hypothyroidism) has developed after giving iodinated glycerol to previously euthyroid patients. It was recommended that baseline thyroid function tests should be carried out before starting treatment with iodinated glycerol;[1] it should be withdrawn if abnormal results are obtained during use.

1. Gittoes NJL, Franklyn JA. Drug-induced thyroid disorders. *Drug Safety* 1995; **13:** 46–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Iophen; Par Glycerol; R-Gen.

Ipecacuanha

Hlavěnkový kořen; Ipecac; Ipecacuana; Ipécacuanha, racine d'; Ipecacuanha Root; Ipecacuanhae Radix; Ipecacuanhawurzel; Ipekakuanų šaknys; Ipekakuána-gyökér; Ipekakuananjuuri (ipecacuanha root); Ipekakuanarot (ipecacuanha root); Korzeń ipekakuany; Raíz de ipecacuana; Ипекакуана.

CAS — 8012-96-2.

ATC — R05CA04; V03AB01.

ATC Vet — QR05CA04; QV03AB01.

*ATC Herb — HV03AB5002 (*Psychotria ipecacuanha: *root); HP01AW5001 (*Cephaelis acuminata: *root); HR05WA5048 (*Psychotria ipecacuanha: *root); HR05WA5002 (*Cephaelis acuminata: *root); HP01AW5002 (*Psychotria ipecacuanha: *root); HV03AB5001 (*Cephaelis acuminata: *root).*

UNII — 62I3C8233L.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Eur., *Jpn*, and *US* also include a monograph for Prepared Ipecacuanha or a similar standardised form.

Ph. Eur. 8: (Ipecacuanha Root; Ipecacuanha BP 2014). It consists of the fragmented and dried underground organs of *Cephaelis ipecacuanha* known as Matto Grosso ipecacuanha, or of *C. acuminata* known as Costa Rica ipecacuanha, or a mixture of both species. It contains not less than 2.0% of total alkaloids, calculated as emetine. It has a slight odour. Store in airtight containers. Protect from light.

The BP 2014 directs that when Ipecacuanha, Ipecacuanha Root, or Powdered Ipecacuanha is prescribed or demanded, Prepared Ipecacuanha shall be dispensed or supplied.

Ph. Eur. 8: (Ipecacuanha, Prepared; Ipecacuanhae Pulvis Normatus). It is ipecacuanha root powder adjusted to an alkaloidal content of 1.9 to 2.1% of total alkaloids, calculated as emetine. Store in airtight containers. Protect from light.

USP 36: (Ipecac). The dried rhizome and roots of *Cephaelis acuminata* or of *C. ipecacuanha* (Rubiaceae). It yields not less than 2% of ether-soluble alkaloids of which not less than 90% is emetine and cephaeline; the content of cephaeline varies from an amount equal to, to an amount not more than 2.5 times, that of emetine.

USP 36: (Powdered Ipecac). It contains 1.9 to 2.1% of ether-soluble alkaloids, with emetine and cephaeline content as for Ipecacuanha. It is pale brown, weak yellow, or light olive-grey powder that should be stored in airtight containers.

Uses and Administration

Ipecacuanha has been used as an **expectorant** in productive cough (p. 1651.2) in doses of up to about 1.4 mg of total alkaloids. Compound preparations of ipecacuanha, such as Desessartz syrup, have also been used in respiratory disorders.

Ipecacuanha may also be used in larger doses as an **emetic** but is of very limited value (see Poisoning, below). Vomiting usually occurs within 30 minutes of an oral emetic dose, due to an irritant effect on the gastrointestinal tract and a central action on the chemoreceptor trigger zone. Doses are usually followed by a copious drink of water or fruit juice. Adults have been given doses of about 42 mg of total alkaloids; each 5 mL of Ipecac Syrup (USP 36) supplies about 7 mg of total alkaloids. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred. For doses in children, see below.

Homoeopathy

Ipecacuanha has been used in homoeopathic medicines under the following names: Ipeca; Cephaelis ipecacuanha; Ipecac.

Administration in children. Over-the-counter cough and cold preparations containing expectorants (including ipecacuanha) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2.

In the UK, induction of emesis with ipecacuanha is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration (but see also Poisoning, below).

In the USA, children aged 6 months to 1 year have been given about 7 to 14 mg of total alkaloids and older children about 21 mg. Each 5 mL of Ipecac Oral Solution (USP 36) supplies about 7 mg of total alkaloids. Doses are usually followed by a copious drink of water or fruit juice; in young children this may be given before the dose. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred.

Poisoning. Measures to reduce absorption of the toxic substance, such as stomach emptying, have often been advocated in the management of acute poisoning (p. 1537.1). Ipecacuanha has been used to induce emesis, but is no longer routinely recommended. It may be considered in alert, conscious patients, if a potentially life-threatening amount of toxic substance has been ingested within the preceding hour, and where other measures are unavailable or inappropriate.

Adverse Effects

Large doses of ipecacuanha have an irritant effect on the gastrointestinal tract, and persistent bloody vomiting or bloody diarrhoea may occur. Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which is most likely if vomiting does not occur after emetic doses of ipecacuanha, may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, combined with dehydration due to vomiting may cause vasomotor collapse followed by death.

There have been several reports of chronic abuse of ipecacuanha to induce vomiting in eating disorders; cardiotoxicity and myopathy have occurred and may be a result of accumulation of emetine.

There have also been several reports of ipecacuanha poisoning due to the unwitting substitution of Ipecac Fluidextract (a former USP preparation) for Ipecac Syrup (USP); the fluidextract was about 14 times the strength of the syrup.

References.

1. Manno BR, Manno JE. Toxicology of ipecac: a review. *Clin Toxicol* 1977; **10:** 221–42.

Hypersensitivity. Allergy, characterised by rhinitis, conjunctivitis, and chest tightness, has occurred due to inhalation of ipecacuanha dust in packers of ipecacuanha tablets.[1]

1. Luczynska CM, *et al.* Occupational allergy due to inhalation of ipecacuanha dust. *Clin Allergy* 1984; **14:** 169–75.

Vomiting. Prolonged vomiting has been reported in 17% of patients given ipecacuanha in the treatment of poisoning and may lead to gastric rupture, Mallory-Weiss tears of the oesophagogastric junction, cerebrovascular events, and pneumomediastinum and pneumoperitoneum.[1]

1. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; **133:** (Dec.): 496–9.

Treatment of Adverse Effects

After acute overdose of ipecacuanha, activated charcoal is given to delay absorption followed if necessary by gastric lavage. Prolonged vomiting may be controlled by the injection of antiemetics. Fluid and electrolyte imbalance should be corrected and facilities should be available to correct any cardiac effects and subsequent shock.

When ipecacuanha is withdrawn after chronic abuse, recovery may be prolonged due to the slow elimination of emetine.

Precautions

The use of emetics is now rarely favoured; in particular, ipecacuanha should not be used as an emetic in patients who are unconscious or whose condition otherwise increases the risk of aspiration, nor in patients who have taken substances, such as corrosive compounds or petroleum products, that might be especially dangerous if aspirated. Ipecacuanha should not be given to patients in shock or to those at risk from seizures either as a result of their condition or from compounds, such as strychnine, that have been ingested. Patients with cardiovascular disorders are at risk if ipecacuanha is absorbed.

Abuse. Ipecac syrup has been abused by patients with eating disorders to induce vomiting.[1] Adverse effects of repeated vomiting, such as metabolic complications, aspiration pneumonitis, parotid enlargement, dental abnormalities, and oesophagitis or haematemesis due to mucosal lacerations (the Mallory-Weiss syndrome) may be seen. Cardiotoxicity may occur and fatalities have been reported including one patient who had ingested 90 to 120 mL of ipecac syrup daily for 3 months.[2] It has been suggested that cardiac effects and myopathy after the prolonged abuse of ipecac syrup may be due to the long-term accumulation of emetine[3,4] but some have expressed doubts.[5]

Cardiomyopathy has also been reported in children given ipecacuanha to produce factitious illness (Munchausen's syndrome by proxy);[6-8] fatalities have occurred.

1. Harris RT. Bulimarexia and related serious eating disorders with medical complications. *Ann Intern Med* 1983; **99:** 800–7.
2. Adler AG, *et al.* Death resulting from ipecac syrup poisoning. *JAMA* 1980; **243:** 1927–8.
3. Palmer EP, Guay AT. Reversible myopathy secondary to abuse of ipecac in patients with major eating disorders. *N Engl J Med* 1985; **313:** 1457–9.
4. Pope HG, *et al.* The epidemiology of ipecac abuse. *N Engl J Med* 1986; **314:** 245–6.
5. Isner JM. Effects of ipecac on the heart. *N Engl J Med* 1986; **314:** 1253.
6. Goebel J, *et al.* Cardiomyopathy from ipecac administration in Munchausen syndrome by proxy. *Pediatrics* 1993; **92:** 601–3.
7. Schneider DJ, *et al.* Clinical and pathologic aspects of cardiomyopathy from ipecac administration in Munchausen's syndrome by proxy. *Pediatrics* 1996; **97:** 902–6.
8. Carter KE, *et al.* Munchausen syndrome by proxy caused by ipecac poisoning. *Pediatr Emerg Care* 2006; **22:** 655–6.

Interactions

The action of ipecacuanha may be delayed or diminished if it is given with or after charcoal; antiemetics may also reduce its effect.

Food. *Milk* had been believed to impair the emetic efficacy of ipecacuanha but there was no significant difference in the time to onset of vomiting, the duration of vomiting, or the number of episodes in 250 children who were given ipecac syrup with milk compared with 250 given ipecac syrup with clear fluids.[1]

1. Klein-Schwartz W, *et al.* The effect of milk on ipecac-induced emesis. *J Toxicol Clin Toxicol* 1991; **29:** 505–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Ipecavom; ***UK***: Fennings Little Healers.

Multi-ingredient Preparations. ***Arg.***: No-Tos Infantil; No-Tos Infantil; ***Braz.***: Expec; Expectomel; Fenergan Expectorante; Iodesin; KI-Expectorante; Melagriao; Pilulas Ross; ***Chile***: Pectokast; ***Fr.***: Phytotux; ***Ger.***: Weleda Hustenelixier; ***Gr.***: Neo-Bronchoton-R; Torylet; ***Hong Kong***: Fritussin†; Uni-Cophedene†; ***Indon.***: Andonex; Koffex for Children; Promе; Promedex; Promethazine Ikapharmindo; ***Irl.***: Venos Honey & Lemon; ***Israel***: Doveri†; Laxative Compound; Promethazine Expectorants; Prothiazine Expectorant; ***Neth.***: Promethazine comp†; ***Port.***: Stodal; ***Rus.***: Prothiazine Expectorant (Протиазин Экспекторант); ***S.Afr.***: Chamberlains Cough Remedy Regular†; Cough Elixir†; Linctus Tussi Infans†; SB Cirogin Cough Mixture†; ***Singapore***: Beacons Cough; Pico's Children's Cough; PO-V-SU; Robinson Cough; Sunny Children Cough; Veelanz's Cough Syrup; Williams Cough; ***Spain***: Alofedina; Buco Regis; Fenergan Expectorante; ***Switz.***: Bromocod N†; Demo Elixir pectoral N†; DemoPectol; Elixir contre la toux†; Neo-Codion N; Pastilles pectorales du Dr. Welti; ***UK***: Allens Dry Tickly Cough; Allens Pine & Honey; Asthma & Catarrh Relief; Beehive Balsam; Buttercup Infant Cough Syrup; Buttercup Syrup (Blackcurrant flavour); Buttercup Syrup (Honey and Lemon flavour); Cough-eeze; Covonia Herbal Mucus Cough Syrup; Galloway's Cough Syrup; Hill's Balsam Chesty Cough for Children; Hill's Balsam Chesty Cough Pastilles; Hill's Balsam Extra Strong; Honey & Molasses; Jackson's Troublesome Coughs; Kilkof; Lockets Medicated Linctus; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Vegetable Cough Remover; ***USA***: Poison Antidote Kit; Quelidrine; ***Venez.***: Codebromil; Dromil Sauco; Novacodin; Tabonuco; Tessamag con Codeina.

Homoeopathic Preparations. ***Austral.***: Childrens Cough Relief; Respatona Chesty Cough & Nasal Congestion; ***Austria***: Nausyn; Nisylen†; Pertudoron†; Pulsatilla Med Complex; Tonsan chronisch; toxi-loges; ***Canad.***: Breathe More; Brocosin; Bronkeel†; Cough & Cold; Cough Syrup with Honey†; Diarrhea; Drosera Complex; Drosera Plex†; Homeo-Form G†; Homeo-Form R†; Hyalgesic HP†; Hylands Formula CS; Hylands Headache; Jet Lag; Pertudoron 1†; Phytotux H; Stodal; ***Chile***: Pertussin; Similibus; ***Cz.***: Bronchalis-Heel; Drosetux; Stodal; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Abbe Chaupitre no 67†; Abbe Chaupitre no 91†; Baudry; Boripharm No 15†; Cetraria Complexe No 61; Drosera Complexe No 64; Drosera Compose; Hepatocynesine†; Homeogene 14†; Homeogrippe†; Ipeca Complexe No 65; Ipeca Compose; L 107; Nux Vomica Complexe No 49; Pates Pectorales; Pertudoron; Poconeol no 48; Pulmo-Drainol†; Santaherba; Stodal; Stodal; Tabacum Compose; ***Ger.***: Bronchiselect; Broncho-Injektopas; Bronchopas; Gastro Magentabletten; Monapax; Mucosa compositum; Nisylen; Pertudoron 1; Procordal vertigo; toxi-loges; toxi-loges; Tussiflorin Hom; Tussisana; Tussistin S; Tussistin; Viropect; ***Hung.***: Stodal; ***Neth.***: Bronchalis; Drosinula; Gravifem†; Homeocare siroop; Kind 0-6 Nisykind; Kind 0-6 Tussikind; Kind 0-6 Tussikind; Mucosa comp H; Nectadyn H; Nisyleen; Stodal; Travelin; Tussistin; ***Rus.***: Influcid (Инфлюцид); Stodal (Стодаль); ***S.Afr.***: Pertudoron Drops†; ***Switz.***: Drosetux; Regenaplex Nr 38b; TussEx; ***UK***: Cough Elixir; Nausyn; ***Ukr.***: Influcid (Инфлюцид); Stodal (Стодаль).

Pharmacopoeial Preparations
BP 2014: Paediatric Ipecacuanha Emetic Mixture;
Ph. Eur.: Ipecacuanha Liquid Extract, Standardised; Ipecacuanha Tincture, Standardised;
USP 36: Ipecac Oral Solution.

Isoaminile *(BAN, rINN)*

Isoaminiili; Isoaminil; Isoaminilo; Isoaminilum; Изоаминил.
4-Dimethylamino-2-isopropyl-2-phenylpentanonitrile.
$C_{16}H_{24}N_2$=244.4
CAS — 77-51-0.
ATC — R05DB04.
ATC Vet — QR05DB04.
UNII — R4823W2PQL.

Isoaminile Citrate *(BANM, rINNM)*

Citrato de isoaminilo; Isoaminile, Citrate d'; Isoaminili Citras; Isoaminilo, citrato de; Изоаминила Цитрат.
4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile dihydrogen citrate.
$C_{16}H_{24}N_2,C_6H_8O_7$=436.5
CAS — 126-10-3; 28416-66-2.
ATC — R05DB04.
ATC Vet — QR05DB04.
UNII — 27K34XSD46.

Isoaminile Cyclamate *(rINNM)*

Ciclamato de isoaminilo; Isoaminile, Cyclamate d'; Isoaminili Cyclamas; Изоаминила Цикламат.
4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile cyclohexanesulfamate.
$C_{16}H_{24}N_2,C_6H_{13}NO_3S$=423.6
CAS — 10075-36-2.
ATC — R05DB04.
ATC Vet — QR05DB04.
UNII — 4055851484.

Profile

Isoaminile is a centrally acting cough suppressant that has been given orally; the citrate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Peracon; ***Indon.***: Peracon; ***Turk.***: Peracon.

Levmetamfetamine *(USAN, rINN)* ⊗

l-Deoxyephedrine; L-Desoxiefedrina; L-Desoxyephedrine; Lesoxyephedrine; Levmétamfétamine; Levmetamfetaminum; Levmetanfetamina; Levometanfetamina; *l*-Methamphetamine; *l*-Methylamphetamine; Левметамфетамин.
(*R*)-*N*,α-Dimethylbenzeneethanamine; (-)-(*R*)-*N*,α-Dimethylphenethylamine.
$C_{10}H_{15}N$=149.2
CAS — 33817-09-3.
UNII — Y24T9BT2Q2.

Pharmacopoeias. In *US*.

USP 36: (Levmetamfetamine). A clear, practically colourless, liquid. Store in airtight containers. Protect from light.

Profile

Levmetamfetamine is the *laevo* isomer of metamfetamine (p. 2324.2) and is used topically in the treatment of nasal congestion.

References.
1. Mendelson JE, *et al.* The clinical pharmacology of intranasal l-methamphetamine. *BMC Clin Pharmacol* 2008; **8:** 4. Available at: http://www.biomedcentral.com/content/pdf/1472-6904-8-4.pdf (accessed 02/07/09)

Abuse. Levmetamfetamine is a less potent central stimulant than metamfetamine, but it has been subject to occasional abuse.[1,2] In addition, as a stimulant, its use is prohibited in sport during competition.[3]

1. Halle AB, *et al.* Drug abuse with Vicks nasal inhaler. *South Med J* 1985; **78:** 761–2.
2. Ferrando RL, *et al.* Bizarre behavior following the ingestion of levodesoxyephedrine. *Drug Intell Clin Pharm* 1988; **22:** 214–17.
3. World Anti-Doping Agency. The world anti-doping code: the 2010 prohibited list international standard. Available at: http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/WADA_Prohibited_List_2010_EN.pdf (accessed 01/12/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Vicks Vapor Inhaler.

Marrubium

Andornkraut; Herba Marrubii; Hurtanminttu; Jablečníková nať; Juanrubio; Kransborre; Malva de sapo; Malvarrubia; Marrube blanc, parties aériennes fleuries de; Marrubii herba; Marrubio; Šantrų žolė; White Horehound; Шандра Обыкновенная.
*ATC Herb — HA09WA5016 (*Marrubium vulgare*: herb); HR05WA5028 (*Marrubium vulgare*: herb); HA05AW5012 (*Marrubium vulgare*: herb).*
*UNII — 7A72MUN24Z (*Marrubium vulgare *whole); K08036XEJV (*Marrubium vulgare *leaf).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (White Horehound). The whole or fragmented dried flowering aerial parts of *Marrubium vulgare*. It contains a minimum 0.7% of marrubiin ($C_{20}H_{28}O_4$ = 332.4), calculated as the dried drug.

Profile

Marrubium is the flower or leaf of *Marrubium vulgare* (Labiatae). It has been used for its supposed expectorant properties in herbal preparations for the treatment of cough. It has also been used as a flavouring.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Angocin Bronchialtropfen.

Multi-ingredient Preparations. ***Austral.***: Broncafect; ***Austria***: Asthmatee EF-EM-ES; Gallen- und Lebertee St Severin; Hustensaft Weleda; ***Canad.***: Echinamide Cold and Cough†; Honey Blend Herbal Cough Syrup; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; ***Cz.***: Original Schwedenbitter; Species Cholagogae Planta†; The Salvat; Zlucnikova Cajova Smes; ***Ger.***: Weleda Hustenelixier; ***Hung.***: Antipoll; ***Ital.***: Altuss; Broncosedina; Broncosedina; ***Pol.***: Amarosal; ***S.Afr.***: Cough Elixir†; ***Switz.***: Elixir contre la toux†; Hederix; ***UK***: Allens Chesty Cough; Asthma & Catarrh Relief; Catarrh-eeze; Chest Mixture; Cough Soother Herbal Syrup; Cough-eeze; Herb and Honey Cough Elixir; Honey & Molasses; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Modern Herbals Cough Mixture; Vegetable Cough Remover.

Homoeopathic Preparations. ***Canad.***: Infilex†; ***Neth.***: Infragil; ***UK***: Cough Elixir.

Mecysteine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mecisteína; Mecisteína, hidrocloruro de; Mécystéine, Chlorhydrate de; Mecysteini Hydrochloridum; Methyl Cysteine Hydrochloride; Methylcysteine Hydrochloride; Мецистеина Гидрохлорид.

Methyl L-2-amino-3-mercaptopropionate hydrochloride.

$C_4H_9NO_2S,HCl$=171.6

CAS — 2485-62-3 (mecysteine); 18598-63-5 (mecysteine hydrochloride); 5714-80-7 (mecysteine hydrochloride).

UNII — 33RG619160.

Uses and Administration

Mecysteine hydrochloride is used as a mucolytic in respiratory disorders associated with productive cough (p. 1651.2). It is given orally in a usual dose of 200 mg three times daily before meals reduced to 200 mg twice daily after 6 weeks. A rapid clinical effect can be achieved by giving 200 mg four times daily for the first 2 days. For doses in children, see below.

Mecysteine has also been given by inhalation.

Administration in children. The recommended oral dose of mecysteine hydrochloride in children aged 5 to 12 years is 100 mg 3 times daily.

Respiratory disorders. Mecysteine hydrochloride given orally has reduced symptoms of cough in patients with chronic bronchitis or other respiratory disorders, but its effect on sputum production and pulmonary function has been variable.[1,2] The use of mucolytics in chronic obstructive pulmonary disease (p. 1199.1) is controversial.

1. Aylward M, *et al.* Clinical therapeutic evaluation of methylcysteine hydrochloride in patients with chronic obstructive bronchitis: a balanced double-blind trial with placebo control. *Curr Med Res Opin* 1978; **5:** 461–71.
2. Sahay JN, *et al.* The effect of methyl cysteine (Visclair) in respiratory diseases: a pilot study. *Clin Trials J* 1982; **19:** 137–43.

Adverse Effects and Precautions

Nausea and heartburn have occasionally been reported. Since mucolytics may disrupt the gastric mucosal barrier mecysteine hydrochloride should be used with caution in patients with a history of peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Visclair†; ***UK***: Visclair.

Menglytate *(rINN)*

Menglitato; Menglytatum; Menthol Ethylglycolate; Менглитат.

p-Menth-3-yl ethoxyacetate.

$C_{14}H_{26}O_3$=242.4

CAS — 579-94-2.

UNII — C3B9R0E116.

Profile

Menglytate is an ingredient of some preparations promoted for the treatment of cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Coryfin C; Neo Borocillina Balsamica; Neo Borocillina Decong.

Methoxyphenamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metoxifenamina; Methoxiphenadrin Hydrochloride; Méthoxyphénamine, Chlorhydrate de; Methoxyphenamini Hydrochloridum; Metoxifenamina, hidrocloruro de; Mexyphamine Hydrochloride; Метоксифенамина Гидрохлорид.

2-Methoxy-*N*α-dimethylphenethylamine hydrochloride.

$C_{11}H_{17}NO,HCl$=215.7

CAS — 93-30-1 (methoxyphenamine); 5588-10-3 (methoxyphenamine hydrochloride).

ATC — R03CB02.

ATC Vet — QR03CB02.

UNII — 52V8BVV7FX.

Profile

Methoxyphenamine is a sympathomimetic with effects similar to those of ephedrine (p. 1663.1), given orally as the hydrochloride. It has been used as a bronchodilator mainly in combination preparations for the relief of cough and nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Cheracol; ***China***: Asmeton (阿斯美); Ke Zhi (克之); ***Hong Kong***: Asmeton; ***Irl.***: Casacol; ***Venez.***: Metoxifilin.

Methyl Dacisteine *(rINNM)*

Dacisteína de metilo; Dacistéine Méthyle; Dacisteinum Methylis; EL-1035 (dacisteine); Methyl Diacetylcysteinate; Дацистеин Метил.

Methyl *N,S*-diacetyl-L-cysteinate.

$C_8H_{13}NO_4S$=219.3

CAS — 18725-37-6 (dacisteine); 19547-88-7 (methyl dacisteine).

Profile

Like acetylcysteine (p. 1652.2), methyl dacisteine has been used as a mucolytic in respiratory disorders associated with productive cough (p. 1651.2). It has been given orally in a usual dose of 600 mg daily, divided into 3 or 4 doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Mucothiol.

Methylephedrine Hydrochloride *(BANM)* ⊗

dl-N-Methylephedrine Hydrochloride; *dl*-Methylephedrine Hydrochloride; Metilefedrina, hidrocloruro de; Метилэфедрина Гидрохлорид.

(1*RS*,2*RS*)-2-Dimethylamino-1-phenylpropan-1-ol hydrochloride.

$C_{11}H_{17}NO,HCl$=215.7

CAS — 552-79-4 ((-)-methylephedrine); 1201-56-5 ((±)-methylephedrine); 38455-90-2 ((-)-methylephedrine hydrochloride); 942-46-1 ((±)-methylephedrine hydrochloride); 18760-80-0 ((±)-methylephedrine hydrochloride).

UNII — 99214P83XM.

Pharmacopoeias. In *Jpn*.

Profile

Methylephedrine hydrochloride is a sympathomimetic with effects similar to those of ephedrine (p. 1663.1). It has been used as a bronchodilator and is given orally in combination preparations for the relief of cough and nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kang Yu Deng Tong (康裕登通).

Multi-ingredient Preparations. ***China***: Ai Kai Ping (爱凯平); Norpin A (纳尔平); Xi Er Ke (西尔克); ***Hong Kong***: Codaewon; ***Jpn***: Colgen Kowa IB; Lightgen; Sin Colgen Kowa Kaze†; ***S.Afr.***: Ilvico†; ***Switz.***: Tossamine plus; ***Thai.***: Hustazol-C; Methorcon; ***Venez.***: Ilvico.

Morclofone *(rINN)*

Dimeclofenone; Morclofona; Morclofonum; Morclophon; Морклофон.

4′-Chloro-3,5-dimethoxy-4-(2-morpholinoethoxy)benzophenone.

$C_{21}H_{24}ClNO_5$=405.9

CAS — 31848-01-8 (morclofone); 31848-02-9 (morclofone hydrochloride).

ATC — R05DB25.

ATC Vet — QR05DB25.

UNII — VY62TIB872.

Profile

Morclofone is a centrally acting cough suppressant used for non-productive cough (p. 1651.2); it is given orally in usual doses of 150 mg four or five times daily. It has also been given as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Nitux.

Naphazoline *(BAN, rINN)* ⊗

Nafatsoliini; Nafazolin; Nafazolina; Naphazolinum; Нафазолин.

2-(1-Naphthylmethyl)-2-imidazoline.

$C_{14}H_{14}N_2$=210.3

CAS — 835-31-4.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

UNII — H231GF11BV.

Naphazoline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de nafazolina; Nafatsoliinihydrokloridi; Nafazolin Hidroklorür; Nafazolina, hidrocloruro de; Nafazolin-hidroklorid; Nafazolin-hydrochlorid; Nafazolinhydroklorid; Nafazolino hidrochloridas; Naphazoline, Chlorhydrate de; Naphazolinhydrochlorid; Naphazolini Hydrochloridum; Нафазолина Гидрохлорид.

$C_{14}H_{14}N_2,HCl$=246.7

CAS — 550-99-2.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

UNII — MZ1131787D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Naphazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. Protect from light.

USP 36: (Naphazoline Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Naphazoline Nitrate *(BANM, rINNM)* ⊗

Nafatsoliininitraatti; Nafazolin Nitrat; Nafazolina, nitrato de; Nafazolinnitrat; Nafazolin-nitrát; Nafazolino nitratas; Nafazoliny azotan; Naphazoline, Nitrate de; Naphazolini nitras; Naphazolinium Nitricum; Naphazolinnitrat; Naphthizinum; Nitrato de nafazolina; Нафазолина Нитрат.

$C_{14}H_{14}N_2,HNO_3$=273.3

CAS — 5144-52-5.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

UNII — SC99GR1T5S.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet*.

Ph. Eur. 8: (Naphazoline Nitrate). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Protect from light.

Uses and Administration

Naphazoline is a sympathomimetic (p. 1507.3) with marked alpha-adrenergic activity. It is a vasoconstrictor with a rapid and prolonged action in reducing swelling and congestion when applied to mucous membranes.

Naphazoline and its salts are used for the symptomatic relief of nasal congestion (p. 1652.1). Solutions containing 0.05 to 0.1% of the hydrochloride or the nitrate may be applied topically as nasal drops or a spray usually up to once every 6 hours. For doses in children, see below.

Solutions containing up to 0.1% of naphazoline hydrochloride have been instilled into the eye as a conjunctival decongestant (see Conjunctivitis, p. 611.1).

Naphazoline has been used as a vasoconstrictor with local anaesthetics.

Naphazoline acetate has also been used in nasal preparations.

Administration in children. In some countries, solutions containing naphazoline nitrate 0.05% have been applied topically as nasal drops or a spray, usually 2 or 3 times daily, in children aged 7 years and over for the symptomatic relief of nasal congestion.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; naphazoline has mainly alpha-agonist effects. After local use, transient irritation may occur. Rebound congestion may occur after frequent or prolonged use. Systemic effects, including nausea, headache, and dizziness, have occurred after topical use. Overdosage or accidental oral use of naphazoline may cause CNS depression with marked reduction of body temperature and bradycardia, sweating, drowsiness, and coma, particularly in children; it should be used with great caution, if at all, in infants and young children. Use of naphazoline in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Hypertension may be

followed by rebound hypotension. Treatment of adverse effects is symptomatic.

Abuse. Ischaemic stroke that developed in a 46-year-old man was considered to have been precipitated by abuse of topical naphazoline.[1] The patient had used more than 20 nasal applications daily for several years.

1. Costantino G, *et al*. Ischemic stroke in a man with naphazoline abuse history. *Am J Emerg Med* 2007; **25**: 983.e1–983.e2.

Effects on the eyes. For mention of conjunctivitis induced by ophthalmic decongestant preparations containing naphazoline, see under Phenylephrine, p. 1673.2.

Intraoperative use. A report[1] of 2 cases of toxicity associated with intraoperative use of a naphazoline-soaked sponge to control excessive bleeding after adenoidectomy. Hypertension and reflex bradycardia, which evolved in one case into marked hypotension, were noted in both patients. There was evidence of CNS depression with a reduced respiration rate and prolonged recovery from anaesthesia.

1. Wenzel S, *et al*. Course and therapy of intoxication with imidazoline derivate naphazoline. *Int J Pediatr Otorhinolaryngol* 2004; **68**: 979–83.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naphazoline for ophthalmic use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Since naphazoline is absorbed through the nasal mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p. 1508.3.

Pharmacokinetics

Systemic absorption has been reported after topical use of solutions of naphazoline. It is not given systemically, but it is readily absorbed from the gastrointestinal tract. Naphazoline instilled into the eye causes conjunctival vasoconstriction within 10 minutes and effects can last for up to 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actifedrin Nasal; Afluhist; Bactio Rhin; Bano Ocular Agrand†; Dazolin; Disel; Fabozolina; Gentisyl NF; Gotabiotic D; Gotinal; Let-Nasal; Mirasan; Mirus-S; Nafazolex; Nasalex; Panoptic NF; Privina; Rhinal; ***Austral.***: Albalon; Murine Clear Eyes; Naphcon; ***Austria***: Aconex; Coldan; Rhinon; Rhinoperd; ***Belg.***: Deltarhinol-Mono; Naphcon; Neofenox Naphazoline†; Neusinol; Priciasol; Vasocedine; ***Braz.***: Claroft; Gotaliv; Multisoro; Narix; Nazicol†; Neosoro; Privina; Rinomax; Rinos-A; Sonarin (AD); Soroclim; ***Canad.***: Ak-Con; Albalon; Allergy Drops†; Clear Eyes; Diopticon; Naphcon Forte; Original Eye Drops; Refresh Redness Relief; ***Chile***: Clarimir; Red Off; ***China***: Hu Tai (乎泰); Runjie (润洁); ***Cz.***: Sanorin; ***Ger.***: Duraultra N; Privin†; Proculin†; Tele-Stulln†; Televis-Stulln; ***Gr.***: Coldan; Naphcon; ***Hong Kong***: Albalon; All Clear; ***Hung.***: Iridina; ***India***: Clearine; Ocucel; Ocustress; ***Indon.***: Optrine†; ***Irl.***: Albalon†; Murine Irritation and Redness Relief; ***Israel***: Naphcon Forte†; ***Ital.***: Collirio Alfa; Imidazyl; Iridina Due; Naftazolina; Pupilla; Rinazina; ***Malaysia***: Albalon†; ***Mex.***: Afazol; Alfazina; Alphadinal†; Celunaf; Fazolin; Gamatropin†; Gotinal; Nazil; Oftaseptik; ***Neth.***: Albalon†; ***NZ***: Clear Eyes; Naphcon; ***Philipp.***: Cosooth; Vasoclear; ***Pol.***: Rhinazin; ***Rus.***: Nafazol (Нафазол); Sanorin (Санорин); ***S.Afr.***: Murine Clear Eyes; Safyr Bleu; ***Spain***: Alfa†; Miraclar; Vasoconstrictor Pensa; ***Thai.***: Albalon; Naphcon†; ***Turk.***: Deltarhinol†; Enflucide†; ***UK***: Murine Irritation & Redness Relief; ***Ukr.***: Nasolin (Назолин)†; Sanorin (Санорин); ***USA***: Advanced Eye Relief Redness; Ak-Con; Albalon†; All Clear†; Clear Eyes Plus Redness Relief; Clear Eyes; Napha Forte; Naphcon; Privine; ***Venez.***: Clarasol; Clearize; Fazolan; Gotinal; Naphcon; Nas; Niazol; Ninazo.

Multi-ingredient Preparations. ***Arg.***: Afluhist Plus; Alvo Nasal; Antibiocort; Bactio Rhin Prednisolona; Bideon; Biotaer Nasal†; Dexalergin; Disel Hidrocortisona; Drynisan; Factioneye; Fadanasal; Gripace; Hyalcrom; Mira Klonal; Mirus; Nasojol; Nasomicina; Neo-Currino; Neodexa Plus†; Neoefodil; Neosona; Nexadron Compuesto; Nexadron Plus; Panoptic; Provacsin Nasal; Refenax Colirio; Refenax Gotas Nasales; Rinofilax AG M; Rinogel; Rinolabsa; Suavithiol†; Vistadex; Visuclar; ***Austral.***: Albalon-A; Antistine-Privine; Naphcon-A; Optrex Medicated†; Visine Allergy; ***Austria***: Coldistan; Coldophthal; Luuf-Nasenspray; Ophtaguttal; Rhinon; Rhinoperd comp; ***Belg.***: Minhavez; Naphcon-A; Sofraline; Sofrasolone; ***Braz.***: Clanistil; Claril; Colirio Legrand; Colirio Moura Brasil; Colirio Teuto; Conidrin; Cristalin; Fluo-Vaso; Hemodotti†; Hidrocin; Lerin; Maxibell; Naridrin; Nariflux; Nasomil; Neo Quimica Colirio†; Nitrileno; Novo Rino; Rhinosept†; Rinisone; Sinustrat Vasoconstritor; Sorine Adulto; Stilux; Visazul; Visiplex; Visolon; Visual; Zincolok; ***Canad.***: Albalon-A; Blue Collyrium; Clear Eyes Allergy; Clear Eyes for Dry Eyes Plus Redness Relief; Collyre Bleu Laiter; Diopticon A; Naphcon-A; Onrectal†; Opcon-A; Refresh Eye Allergy Relief; Visine Advance Allergy; Zincfrin-A†; ***Chile***: Clarimir F; Dessolets; Miral; Naphcon-A; Naphtears; Nico Drops; Novo-Tears; Oculosan†; Oftalirio; Red Off Aqua; Red Off Plus; ***China***: Naphcon-A (那素达); Xin Le Dun (新乐敦); ***Cz.***: Sanorin-Analergin; ***Denm.***: Ansal†; Antistina-Privin; Sesal; ***Fr.***: Collyre Bleu; Derinox; ***Ger.***: Antistin-Privin†; duraultra†; Oculosan N†; Siozwo†; ***Gr.***: Neo-Priphen; Oculosan; Septobore; Zabysept; Zincfrin-A; ***Hong Kong***: Clear Blue; Frazoline†; Konjunktival; Naphcon-A; Nazin; Oculosan; Opcon-A; Vista-Tone†; Visurex; ***India***: Andre-I-Kul†; Andre; Betnesol-N Nasal†; E-Norm; Efcorlin; Exxon; Fenox†; I-Boric; I-Top; Igardex; Mezol; Microsol; Mil; N-Cool; N-Zolin; Naflin; NCZ; Nefacool; Nilhist; NPBor; Ocucel-A; Ocuclear; Ocudecon; Ocurest-AH; Ocurest-Z; Ocurest; Ovisil; Proto-Boric†; ***Indon.***: Flamergi; Indofrin-A†; Isotic Azora; Naphcon-A; Oculosan; Zincopto; ***Irl.***: Optrex Clear Eyes; ***Israel***: Alnase; Optryl; Phenyphrine-Azol†; Proaf†; ***Ital.***: Alfaflor; Antisettico Astringente Sedativo; Antistin-Privina; Collirio Alfa Antistaminico; Deltarinolo; Fotofil; Genalfa†; Imidazyl Antistaminico; Indaco; Iristamina; Oftalmil; Pupilla Antistaminico; Rinocidina; Zinc-Imizol; ***Malaysia***: Alergoftal†; Napha A; Naphcon-A; ***Mex.***: Afazol Z; Biofrin; Biotarson O†; Eyrasil; Istasol; Midazol Ofteno; Mirus; Naphacel; Naphtears; Opcon-A; Poentobral D; Soltrictor con Lagrifilm; Solutina; Sulvi; Zincfrin-A; ***NZ***: Betnesol Aqueous; Clear Eyes ACR; Naphcon-A; Optrex Red-Eye Relief; Visine Allergy; ***Philipp.***: Decocon A; Irazol; Moisturizing All Clear; Naphcon-A; Oculosan; Optaphen; Vistallerg; ***Pol.***: Betadrin; Cincol; Dermophenazol; Mibalin†; Oculosan; Oftophenazol; Rhinophenazol; Sulfarinol; ***Port.***: Alergiftalmina; ***Rus.***: Betadrin (Бетадрин); Ocumethyl (Окуметил); Polynadim (Полинадим); Sanorin (Санорин); Sanorin-Analergin (Санорин-аналергин); ***S.Afr.***: Adco-Nasdro†; Antistin-Privin; Covomycin; Covosan†; ENT; Fenox; Oculosan; Universal Nasal Drops†; Zincfrin-A†; ***Singapore***: Antistin-Privin; Naphcon-A; Nazal Spray; ***Spain***: Alergoftal; Centilux; Cloram Zinc†; Colirio-cilina Adren Astr†; Epistaxol; Kanafosal Predni†; Kanafosal†; Oftalmol Ocular; Ojosbel Azul†; Ojosbel; Rinovel†; Zolina; ***Swed.***: Antasten-Privin†; ***Switz.***: Antistin-Privin†; Collyre Bleu Laiter; Oculosan; Spray nasal comp pour adultes†; ***Thai.***: Levoptin; Naphcon-A; Oculosan; ***Turk.***: Alergoftal; Sulfarhin; ***UK***: Eye Dew; Murine Bright & Moist Eyes; Optrex Red Eyes; ***Ukr.***: Sanorin-Analergin (Санорин-Аналергин); ***USA***: 4-Way Fast Acting; Antazoline-V; Clear Eyes Seasonal Relief; Maximum Strength Allergy Drops; Naphazoline Plus†; Naphcon-A; Naphoptic-A; Ocuhist; Opcon-A; VasoClear A; Vasocon-A; Visine-A; ***Venez.***: Camolyn Plus; Pinazo; Soltin; Soluclear.

Used as an adjunct in:. ***Fr.***: Xylocaine; ***Spain***: Anestesico.

Pharmacopoeial Preparations

USP 36: Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution; Naphazoline Hydrochloride Nasal Solution; Naphazoline Hydrochloride Ophthalmic Solution.

Neltenexine *(rINN)*

Neltenexina; Nelténexine; Neltenexinum; Нелтенексин.

4′,6′-Dibromo-α-[(*trans*-4-hydroxycyclohexyl)amino]-2-thiophene-carboxy-*o*-toluidide.

$C_{18}H_{20}Br_2N_2O_2S$=488.2

CAS — 99453-84-6.

ATC — R05CB14.

ATC Vet — QR05CB14.

UNII — U942DGM90X.

Profile

Neltenexine is a mucolytic that has been used in respiratory disorders associated with productive cough (p. 1651.2). It has been given orally as the monohydrate, in usual doses of 37.4 mg three times daily. Neltenexine has also been given rectally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Alveoten; Tenoxol†.

Nepinalone *(rINN)*

Nepinalona; Népinalone; Nepinalonum; Непиналон.

(±)-3,4-Dihydro-1-methyl-1-(2-piperidinoethyl)-2(1*H*)-napthalenone.

$C_{18}H_{25}NO$=271.4

CAS — 22443-11-4.

ATC — R05DB26.

ATC Vet — QR05DB26.

UNII — L9806LPR7G.

Profile

Nepinalone has been used as the hydrochloride as a cough suppressant in non-productive cough (p. 1651.2). Oral doses of nepinalone hydrochloride 10 mg have been given three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Nepituss; Placatus; Tussolvina.

Nicocodine *(BAN, rINN)*

Nicocodina; Nicocodinum; Никокодин.

6-Nicotinoylcodeine; 3-*O*-Methyl-6-*O*-nicotinoylmorphine.

$C_{24}H_{24}N_2O_4$=404.5

CAS — 3688-66-2.

UNII — DYX391P13E.

Profile

Nicocodine is an opioid related to codeine (p. 40.2). It has been used orally as the hydrochloride for its central cough suppressant effects in non-productive cough.

Normethadone Hydrochloride *(BANM, rINNM)*

Desmethylmethadone Hydrochloride; Hidrocloruro de normetadona; Hoechst-10582 (normethadone); Normetadona, hidrocloruro de; Norméthadone, Chlorhydrate de; Normethadoni Hydrochloridum; Phenyldimazone Hydrochloride; Норметадона Гидрохлорид.

6-Dimethylamino-4,4-diphenylhexan-3-one hydrochloride.

$C_{20}H_{25}NO,HCl$=331.9

CAS — 467-85-6 (normethadone); 847-84-7 (normethadone hydrochloride).

ATC — R05DA06.

ATC Vet — QR05DA06.

Profile

Normethadone is closely related to methadone (p. 88.3). The hydrochloride is given orally as a cough suppressant in preparations for non-productive cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Cophylac.

Noscapine *(BAN, rINN)*

L-α-Narcotine; Narcotine; Noscapin; Noscapina; Noscapinum; Noskapiini; Noskapin; Noskapinas; Noszkapin; NSC-5366; Носкапин.

(3*S*)-6,7-Dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide.

$C_{22}H_{23}NO_7$=413.4

CAS — 128-62-1.

ATC — R05DA07.

ATC Vet — QR05DA07.

UNII — 8V32U4AOQU.

Description. Noscapine is an alkaloid obtained from opium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Noscapine). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water at 20 degrees, very slightly soluble at 100 degrees; slightly soluble in alcohol; soluble in acetone; dissolves in strong acids although the base may be precipitated on dilution with water. Protect from light.

USP 36: (Noscapine). A fine, white or practically white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in ether; soluble in acetone; freely soluble in chloroform.

Noscapine Camsilate *(BANM, rINNM)*

Camphoscapine; Camsilato de noscapina; Noscapina, camsilato de; Noscapine, Camsilate de; Noscapine Camsylate; Noscapini Camsilas; Носкапина Камзилат.

Noscapine camphor-10-sulphonate.

$C_{22}H_{23}NO_7$, $C_{10}H_{16}O_4S$=645.7

CAS — 25333-79-3.

ATC — R05DA07.

ATC Vet — QR05DA07.

Noscapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de noscapina; Narcotine Hydrochloride; Noscapina, hidrocloruro de; Noscapine, Chlorhydrate de; Noscapinhydrochlorid-Monohydrat; Noscapini Hydrochlor-

idum; Noscapini Hydrochloridum Monohydricum; Noscapinium Chloride; Noskapiinihydrokloridi; Noskapin hydrochlorid monohydrát; Noskapinhydroklorid; Noskapino hidrochloridas; Noskapiny chlorowodorek; Noszkapinhidroklorid; Носкапина Гидрохлорид.

$C_{22}H_{23}NO_7$,HCl,H_2O=467.9

CAS — 912-60-7 (anhydrous noscapine hydrochloride).

ATC — R05DA07.

ATC Vet — QR05DA07.

UNII — TTN62ITH9I.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* (both with H_2O); in *Jpn* (with xH_2O).

Ph. Eur. 8: (Noscapine Hydrochloride). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water and in alcohol. Aqueous solutions are faintly acid; the base may be precipitated when the solutions are allowed to stand. A 2% solution in water has a pH of not less than 3.0. Protect from light.

Uses and Administration

Noscapine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p. 1660.2). It is given in an oral dose of up to 50 mg three times daily. It is also used rectally. Noscapine has also been given as the ascorbate, camsilate, embonate, and the hydrochloride.

Adverse Effects and Precautions

As for Dextromethorphan, p. 1660.3. Hypersensitivity reactions have been reported.

Breast feeding. Maximum concentrations of noscapine in the breast milk of 8 women given 100 or 150 mg of noscapine ranged[1] from 11 to 83 nanograms/mL. It was estimated that breast-fed infants of mothers receiving noscapine 50 mg three times daily would ingest at most 300 nanograms/kg of noscapine per feed, an amount considered unlikely to be a hazard. No adverse effects have been seen in breast-fed infants whose mothers were given noscapine, and the American Academy of Pediatrics[2] considers that it is therefore usually compatible with breast feeding.

1. Olsson B, *et al.* Excretion of noscapine in human breast milk. *Eur J Clin Pharmacol* 1986; **30:** 213–15.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 13/12/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies noscapine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. The UK CSM stood by their recommendation[1] that products containing noscapine should be contra-indicated in women of child-bearing potential (because of potential mutagenic effects[2]), after criticism that the decision was based solely on the results of *in-vitro* work.[3]

1. Asscher AW, Fowler LK. Papaveretum in women of childbearing potential. *BMJ* 1991; **303:** 648.
2. CSM. Genotoxicity of papaveretum and noscapine. *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 21/03/07)
3. Allen S, *et al.* Papaveretum in women of child bearing potential. *BMJ* 1991; **303:** 647.

Interactions

Noscapine should not be given with alcohol or other CNS depressants.

Anticoagulants. For mention of a possible interaction between noscapine and *warfarin,* see Cough Suppressants, p. 1533.2.

Pharmacokinetics

References.

1. Karlsson MO, *et al.* Pharmacokinetics of oral noscapine. *Eur J Clin Pharmacol* 1990; **39:** 275–9.
2. Karlsson MO, Dahlstrom B. Serum protein binding of noscapine: influence of a reversible hydrolysis. *J Pharm Pharmacol* 1990; **42:** 140–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Nosca-Mereprine; Noscaflex; ***Ger.***: Capval; ***Hong Kong***: Excopin†; Recoma†; ***Indon.***: Longatin; Mercotin; ***Neth.***: Fluitussin; Kruidvat Hoestdrank Noscapine; Natterman Noscasan; Otrivin; Roter Noscapect; ***S. Afr.***: Nitepax; ***Spain***: Tuscalman; ***Swed.***: Nipaxon; ***Switz.***: Tussanil N.

Multi-ingredient Preparations. ***Arg.***: Funciobron; Graneodin N; No-Tos Pocket; Tosedrin Compuesto†; Vi-Balsabron; ***Austria***: Tuscalman; Tuscalman; ***Belg.***: Noscaflex; ***Chile***: AB Antitusivo; Bucogerm Tos; Captus†; Congestex; Cotibin Flu Dia y Noche; Freshmel Tos; Geniol Compuesto; Geniol-P Compuesto con Clorfenamino†; Graneodin-Tos; Gripexin Limonada Caliente†; No-Flu; Tapsin Compuesto con Clorfenamina; Tapsin Compuesto Dia/Noche Plus; Tapsin Compuesto DN; Tapsin Compuesto; ***China***: Asmeton (阿斯美); Ke Zhi (克之); ***Fr.***: Tussisedal; ***Hong Kong***: Asmeton; Coldcap-A; Coldtab-2; Coltalin-GP Extra; Coughlin†; Decaugh II†; Dr Jacobson Cough Syrup†; Nosazine†; Nosbrom†; Noscaphylline†; Panadol Cold & Flu Extra; Wel-Coplex†; ***India***: Coscopin Plus; Coscopin; Coscopin; ***Indon.***: Dextrosin Anak; Flucodin; Flunadin†; Noscapax; Paratusin; Paratusin; Tilomix; ***Singapore***: New Tonin Troche; Tonin Cough; ***Swed.***: Spasmofen; ***Switz.***: DemoTussil; Hederix; Spasmosol†; Tossamine plus; Tossamine; Tuscalman; Tuscalman; ***Turk.***: Coldeks; Tusifon.

Oxeladin Citrate *(BANM, rINNM)*

Citrato de oxeladina; Okseladiinivetysitraatti; Okseladinovandenilio citratas; Oxeladina, citrato de; Oxeladin-citrát; Oxéladine, Citrate d'; Oxéladine, hydrogénocitrate d'; Oxeladini Citras; Oxeladini hydrogenocitras; Oxeladinvätecitrat; Окселадина Цитрат.

2-(2-Diethylaminoethoxy)ethyl 2-ethyl-2-phenylbutyrate dihydrogen citrate.

$C_{20}H_{33}NO_3$,$C_6H_8O_7$=527.6

CAS — 468-61-1 (oxeladin); 52432-72-1 (oxeladin citrate).

ATC — R05DB09.

ATC Vet — QR05DB09.

UNII — 5AEV5C340C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oxeladin Hydrogen Citrate). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly to very slightly soluble in ethyl acetate.

Profile

Oxeladin citrate has been given orally as a centrally acting cough suppressant for non-productive cough (p. 1651.2). Up to 50 mg daily in divided doses has been given orally. Higher doses of up to 120 mg daily have been given as a modified-release preparation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Elitos; Frenotos; Nadetos; Plardox; ***Fr.***: Paxeladine; ***Gr.***: Antivix; ***Ukr.***: Paxeladin (Пакселадин).

Multi-ingredient Preparations. ***Arg.***: Aseptobron Bromexina; Aseptobron C; Frenotos Muc; Pectoral Lafedar; ***Mex.***: Connex; Fluxedan; Tesalon Tenalif; TheraFlu Tenalif.

Oxolamine *(rINN)*

683-M; Oksolamiini; Oksolamin; Oxolamin; Oxolamina; Oxolaminum; Оксоламин.

5-[2-(Diethylamino)ethyl]-3-phenyl-1,2,4-oxadiazole.

$C_{14}H_{19}N_3O$=245.3

CAS — 959-14-8.

ATC — R05DB07.

ATC Vet — QR05DB07.

UNII — 90BEA145GY.

Oxolamine Citrate *(rINNM)*

AF-438; Citrato de oxolamina; Oxolamina, citrato de; Oxolamine, Citrate d'; Oxolamini Citras; SKF-9976; Оксоламина Цитрат.

$C_{14}H_{19}N_3O$,$C_6H_8O_7$=437.4

CAS — 1949-20-8.

ATC — R05DB07.

ATC Vet — QR05DB07.

UNII — K5X4XBR694.

Oxolamine Phosphate *(rINNM)*

Fosfato de oxolamina; Oxolamina, fosfato de; Oxolamine, Phosphate d'; Oxolamini Phosphas; Оксоламина Фосфат.

CAS — 1949-19-5.

ATC — R05DB07.

ATC Vet — QR05DB07.

Profile

Oxolamine is a cough suppressant with a mainly peripheral action that has been used for non-productive cough (p. 1651.2). It has been given as the citrate in usual oral doses of 100 to 200 mg three times daily. The phosphate has been used similarly. It has also been given as the tannate.

Hallucinations in children have been reported after oxolamine use.

References.

1. McEwen J, *et al.* Hallucinations in children caused by oxolamine citrate. *Med J Aust* 1989; **150:** 449–52.

Interactions. *ANTICOAGULANTS.* For mention of a possible interaction between oxolamine and *warfarin,* see Cough Suppressants, p. 1533.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Numosol; Perebron; Respibron; Teratos; Tulox; ***Gr.***: Goltuss; Perebron; ***Israel***: Symphocal; ***Ital.***: Tussibron; ***Mex.***: Aledron; Bredon; Contuxin†; Eumol; Expecmin; Oxathos; Oxobron†; Oxomar; Oxomifer; Oxotus†; Oxotusin; ***Turk.***: Kalamin; Oksabron; Oksalamin; Oxotuss; Perbrons; Perebron; Sekodin; Subitol; Tusebron; ***Venez.***: Broxol; Cafox; Calcimonio; Citralamina; Lexo; Opilina; Oxalcor; Oxotil; Perebron.

Multi-ingredient Preparations. ***Ital.***: Uniplus; ***Mex.***: Caltusine; Caobe; Guaxoquim; Otofen; ***Turk.***: Contex; Forza; Katarin Forte; Katarin; Oledro; ***Venez.***: Opilina Compuesta; Oxolavin Compuesto.

Oxymetazoline Hydrochloride

(BANM, USAN, rINNM) ⊗

H-990; Hidrocloruro de oximetazolina; Oksimetatsoliinihydrokloridi; Oksimetazolin Hidroklorür; Oksimetazolino hidrochloridas; Oximetazolina, hidrocloruro de; Oximetazolin-hidroklorid; Oximetazolinhydroklorid; Oxymetazolin hydrochlorid; Oxymétazoline, chlorhydrate d'; Oxymetazolinhydrochlorid; Oxymetazolini Hydrochloridum; Sch-9384; Оксиметазолина Гидрохлорид.

$C_{16}H_{24}N_2O$,HCl=296.8

CAS — 2315-02-8.

ATC — R01AA05; R01AB07; S01GA04.

ATC Vet — QR01AA05; QR01AB07; QS01GA04.

UNII — K89MJ055VY.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Oxymetazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol.

USP 36: (Oxymetazoline Hydrochloride). A white to practically white, fine, hygroscopic, crystalline powder. Soluble 1 in 6.7 of water, 1 in 3.6 of alcohol, and 1 in 862 of chloroform; practically insoluble in ether and in benzene. pH of a 5% solution in water is between 4.0 and 6.5. Store in airtight containers.

Uses and Administration

Oxymetazoline is a direct-acting sympathomimetic (p. 1507.3) with marked alpha-adrenergic activity. It is a vasoconstrictor and reduces swelling and congestion when applied to mucous membranes. It acts within a few minutes and the effect lasts for up to 12 hours. It is used as the hydrochloride for the symptomatic relief of nasal congestion (p. 1652.1). In adults and children aged over 6 years, a 0.05% solution of oxymetazoline hydrochloride is applied topically as nasal drops or a spray, usually 2 or 3 times daily to each nostril as required. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including oxymetazoline) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2.

A 0.025% solution of oxymetazoline hydrochloride may be instilled into the eye every 6 hours when necessary as a conjunctival decongestant in adults and children aged over 6 years (see Conjunctivitis, p. 611.1).

Administration in children. For details of the use of oxymetazoline hydrochloride in children, see Uses and Administration, above.

Adverse Effects, Treatment, and Precautions

As for Naphazoline, p. 1669.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxymetazoline for

nasal use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Since oxymetazoline is absorbed through the mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p. 1508.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Apracur Nasal; Lidil; Newclar; Rinox VX; Visine D; Yusin; ***Austral.***: Chemists Own Decongestant Nasal Spray; Dimetapp 12 Hour Nasal; Drixine Nasal; Logicin Rapid Relief; Sudafed Nasal Decongestant; Vicks Sinex; ***Austria***: Nasiben; Nasivin; ***Belg.***: Nesivine; Rhino Humex†; Vicks Sinex; ***Braz.***: Afrin; Aturgyl; Desfrin; Freenal; Nasivin; Oxifrin; Rinidal; ***Canad.***: Afrin†; Claritin Allergic Congestion Relief; Claritin Eye Allergy Relief†; Decongestant Nasal Mist; Dristan; Drixoral; Long Lasting Nasal Mist; Vicks Sinex; Visine Workplace; Zicam Congestion Relief†; Zicam Sinus Relief†; ***Chile***: Facimin; Iliadin; Oxilin; ***China***: Da Fen Lin (达芬霖); Dan Zhong Di Bi Ye (丹中滴鼻液); Di Li Tuo (迪立托); Feng Lang (风朗); Oxylin (欧斯啉); ***Cz.***: Nasivin; Oxamet; Sinex Vicks; ***Denm.***: Iliadin†; ***Fin.***: Vicks Sinex; ***Fr.***: Aturgyl; Pernazene; ***Ger.***: Nasivin Sanft†; Nasivin; Vistoxyn†; Wick Sinex; ***Gr.***: Ezixin; Iliadin; Narol; Ronal; Vicks Vapospray; ***Hong Kong***: Afrin; Duration†; Iliadin; Logicin Rapid Relief; Long Lasting Decongestant Nasal Mist; ***Hung.***: Afrin; Nasivin; ***India***: Naselin; Nasivion; Nazoden; Oxylin; Sinarest-PD; Sinarest; ***Indon.***: Afrin; Iliadin; Visine LR; ***Irl.***: Iliadin†; Oxylin†; Vicks Sinex; ***Israel***: Af-Tipa; Alrin; Nasivin; Rhinoclir; Sinulen; ***Ital.***: Actifed Nasale; Equimet; Ossimet; Oxilin; Rino Calyptol; ***Jpn***: Nasivin; ***Malaysia***: Afrin; Iliadin; Oxynase; ***Mex.***: Afrin†; Iliadin; Naztril; Oxylin; Sinex; Visine AD; ***Neth.***: Afrin; Nasivin; Oxylin; Vicks Sinex; ***Norw.***: Iliadin†; Rhinox; ***NZ***: At-Eze†; Dimetapp 12 Hour Nasal; ***Philipp.***: Drixine; Nasivin; ***Pol.***: Acatar; Afrin; Nasivin; Nosox; Oxalin; Resoxym; ***Port.***: Alerjon; Bisolspray; Nasarox; Nasex; Nasorhinathiol; Oxylin; Rinerge; Sinexsensi; Vicks Vapospray; ***Rus.***: Nasivin (Називин); Nazol (Назол); Nesopin (Несопин); Noksprey (Нокспрей); Sanorinchik (Саноринчик); ***S. Afr.***: Allergex; DriNasal; Dristan; Drixine; Iliadin; Oxylin; Sparkling White Eye Drops†; Vicks Decongestant†; ***Singapore***: Afrin; Iliadin; Nazolin; Oxy-Nase; Utabon†; ***Spain***: Alerfrin; Antirrinum; Corilisina†; Couldespir; Cuvenax; Friresp; Lairesp; Nasolina; Nebulicina; Novag Rino; Nuerel; Oftinal†; Respibien; Respir; Serranasal†; SinexSensi; Utabon; ***Swed.***: Iliadin; Nasin; Nezeril; Vicks Sinex; ***Switz.***: Nasivine; ***Thai.***: Iliadin; Metzodin; Oxymet; Pernazene Oxy; ***Turk.***: Burazin; Iliadin; Oksinazal; Rinidin; ***UAE***: Nasivin; ***UK***: Afrazine; Nasivin; Vicks Sinex; ***Ukr.***: Nasalong (Назалонг); Nasivin (Називин); Naso-Spray (Назо-Спрей); Nazol (Назол); Noxprey (Нокспрей); Oxamet (Оксамет)†; Rinazoline (Риназолин)†; Rint (Ринт); ***USA***: 4-Way Long Lasting; Afrin Extra Moisturizing; Afrin Sinus; Afrin; Allerest 12 Hour Nasal†; Chlorphed-LA; Dristan 12-hr Nasal Decongestant Spray; Dristan Long Lasting; Duramist Plus; Duration; Genasal; Nasal Relief; Nasal Spray; Neo-Synephrine 12 Hour; Nostrilla Complete Congestion Relief; Nostrilla; NTZ Long Acting Nasal; Twice-A-Day; Vicks Sinex 12-Hour; Visine LR; ***Venez.***: Afrin; Airfen; Clarix; Drixine; Nasin.

Multi-ingredient Preparations. ***Arg.***: Alosol; Panoxi; ***Austral.***: Nasex†; ***Austria***: Wick SinexAloe; ***Fr.***: Deturgylone; ***Ger.***: Nasivin Zink†; ***Hong Kong***: Bonjedex; ***Hung.***: Nasopax; ***Israel***: Sinaf†; ***Ital.***: Vicks Sinex; ***Mex.***: Grimal; Hyalox; ***NZ***: Vicks Sinex†; ***Rus.***: Nazol Advance (Назол Адванс); ***S.Afr.***: Nazene Z; ***Spain***: Respibien Antialergico; Seniospray†; Utabon Complex; Vicks Spray†; ***Switz.***: Vicks Sinex; ***Ukr.***: Nazol Advans (Назол Адванс).

Pharmacopoeial Preparations

USP 36: Oxymetazoline Hydrochloride Nasal Solution; Oxymetazoline Hydrochloride Ophthalmic Solution.

Pentoxyverine (BAN, rINN)

Carbetapentane; Pentoksiveriini; Pentoxiverin; Pentoxiverina; Pentoxyvérine; Pentoxyverinum; Пентоксиверин.

2-[2-(Diethylamino)ethoxy]ethyl 1-phenylcyclopentanecarboxylate.

$C_{20}H_{31}NO_3$=333.5

CAS — 77-23-6.

ATC — R05DB05.

ATC Vet — QR05DB05.

UNII — 32C726X12W.

Pentoxyverine Citrate (BANM, rINNM)

Carbetapentane Citrate; Citrato de pentoxiverina; Pentoksiveriinivetysitraatti; Pentoksiverino-vandenilio citratas; Pentoxiverina, citrato de; Pentoxiverin-hidrogén-citrát; Pentoxiverinvätecitrat; Pentoxyverincitrat; Pentoxyverin-citrát; Pentoxyvérine, Citrate de; Pentoxyverine Hydrogen Citrate; Pentoxyvérine, hydrogénocitrate de; Pentoxyverini Citras; Pentoxyverini Hydrogenocitras; UCB-2543; Пентоксиверина Цитрат.

$C_{20}H_{31}NO_3.C_6H_8O_7$=525.6

CAS — 23142-01-0.

ATC — R05DB05.

ATC Vet — QR05DB05.

UNII — 4SH0MFJ5HJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Pentoxyverine Hydrogen Citrate; Pentoxyverine Citrate BP 2014). A white or almost white crystalline powder. M.p. about 93 degrees. Freely soluble in water and in methyl alcohol; soluble in alcohol and in dichloromethane; very soluble in glacial acetic acid. A 10% solution in water has a pH of 3.3 to 3.7. Protect from light.

Pentoxyverine Hydrochloride (BANM)

Pentoksiverin Hidroklorür; Pentoxiverina, hidrocloruro de; Пентоксиверина Гидрохлорид.

$C_{20}H_{31}NO_3$,HCl=369.9

CAS — 1045-21-2.

ATC — R05DB05.

ATC Vet — QR05DB05.

UNII — MG7AT31IVT.

Profile

Pentoxyverine is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). Usual doses of up to 180 mg daily of the citrate or hydrochloride have been given orally in divided doses. The tannate is also given orally and the base has been given rectally.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pentoxyverine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nyal Dry Cough; ***Austria***: Sedotussin†; ***Belg.***: Balsoclase Antitussivum; ***Fin.***: Toclase†; ***Fr.***: Clarix Toux Seche; Codotussyl Toux Seche; Codotussyl Toux Seche; Toclase Toux Seche; Vicks Pectoral; ***Ger.***: Sedotussin; Silomat; ***Gr.***: Tuclase; ***Hong Kong***: Toclase†; ***Hung.***: Sedotussin†; ***Ital.***: Tuclase†; ***Neth.***: Balsoclase†; Tuclase†; ***Philipp.***: Toclase; ***Thai.***: Toclase†; ***Turk.***: Toclase; ***USA***: Solotuss†.

Multi-ingredient Preparations. ***Arg.***: Bio Grip Plus; Wilpan Antigripal; ***Austral.***: Vicks Cough Syrup†; ***Braz.***: Coldrin; Resprin; ***China***: Xiaoke (消刻); ***Fin.***: Toclase Expectorant†; ***Hong Kong***: Active Cough Syrup†; Against Cough†; Broncholax†; Coci-Fedra†; Cofetal†; Marflu-X†; Marsedyl II†; Vida Cough†; ***Neth.***: Balsoclase Compositum†; Balsoclase-E†; ***S.Afr.***: Vicks Acta Plus†; ***Turk.***: Gayaben; Seskadeks; ***USA***: Albatussin; Allres Pd†; AMBI 1000/5†; Aquatab C†; Aridex; BetaVent†; C-Tanna 12D; Carb Pseudo-Tan; Carbatab; Carbatuss; Corzall Plus; Corzall-PE; Corzall; D-Tann CD; Diphen Tann/ PE Tann/ CT Tann; Duratuss CS†; Dynex VR†; Dytan-AT; Dytan-CD†; Dytan-CS; Exall-D; Exall; Exratuss; Extendryl GCP; Gentex†; Levall 12; Levall; Oratuss; Pyrlex CB; Re-Tann; Rentamine Pediatric; Respi-Tann G†; Respi-Tann Pd; Rynatuss†; Tannic-12; Trexbrom; Tri-Tannate Plus Pediatric; Tuss-Tan; Tussi-12 D; Tussi-12; Tussi-12D S; Tussizone†; Tusso-ZMR†; Tusso-ZR†; Tustan 12S; V-Cof; Vazotan; XiraTuss; Xpect-AT; ***Venez.***: Resprin; Tolmex; Yerba Santa.

Phenylephrine (BAN, rINN)

Fenilefrin; Fenilefrina; Fenilefrinas; Fenylefrin; Fenyyliefriini; Phenylephrin; Phényléphrine; Phenylephrinum; *m*-Synephrine; Фенилэфрин.

(1*R*)-1-(3-Hydroxyphenyl)-2-methylaminoethanol.

$C_9H_{13}NO_2$=167.2

CAS — 59-42-7.

ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.

ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.

UNII — 1WS297W6MV.

NOTE. Synephrine has been used as a synonym for oxedrine (p. 1463.1). Care should be taken to avoid confusion with phenylephrine (*m*-synephrine).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Phenylephrine). A white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. It dissolves in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Phenylephrine Acid Tartrate

Bitartrato de fenilefrina; Fenilefrina, bitartrato de; Phenylephrine Bitartrate (rINNM); Phényléphrine, Bitartrate de; Phenylephrine Tartrate (BANM); Phenylephrini Bitartras; Tartrato ácido de fenilefrina; Фенилэфрина Битартрат.

$C_9H_{13}NO_2.C_4H_6O_6$=317.3

CAS — 13998-27-1.

ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.

ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.

UNII — 27O3Q5ML57.

Pharmacopoeias. In *US.*

USP 36: (Phenylephrine Bitartrate). A white or almost white powder or colourless crystals. Freely soluble in water. pH of a 10% solution in water is between 3.0 and 4.0. Store in airtight containers. Protect from light.

Phenylephrine Hydrochloride (BANM, rINNM)

Fenilefrin Hidroklorür; Fenilefrina, hidrocloruro de; Fenilefrin-hidroklorid; Fenilefrino hidrochloridas; Fenylefrin hydrochlorid; Fenylefrinhydroklorid; Fenylefryny chlorowodorek; Fenyyliefriinihydrokloridi; Hidrocloruro de fenilefrina; Mesatonum; Metaoxedrini Chloridum; Phényléphrine, Chlorhydrate de; Phenylephrinhydrochlorid; Phenylephrini Hydrochloridum; Фенилэфрина Гидрохлорид.

$C_9H_{13}NO_2$,HCl=203.7

CAS — 61-76-7.

ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.

ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.

UNII — 04JA59TNSJ.

NOTE. PHNL is a code approved by the BP 2014 for use on single unit doses of eye drops containing phenylephrine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PHNCYC is a similar code approved for eye drops containing phenylephrine hydrochloride and cyclopentolate hydrochloride.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Phenylephrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol.

USP 36: (Phenylephrine Hydrochloride). White or practically white, odourless, crystals. Freely soluble in water and in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Phenylephrine hydrochloride is a sympathomimetic (p. 1507.3) with mainly direct effects on adrenergic receptors. It has mainly alpha-adrenergic activity and is without significant stimulating effects on the CNS at usual doses. Its pressor activity is weaker than that of noradrenaline (p. 1458.3) but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys.

Phenylephrine and its salts are most commonly used, either topically or orally, for the symptomatic relief of **nasal congestion** (but see p. 1673.1). They are frequently included in preparations intended for the relief of cough and cold symptoms. For nasal congestion, a 0.25 to 1% solution may be instilled as nasal drops or a spray into each nostril every 4 hours as required, or phenylephrine hydrochloride may be given in usual oral doses of 10 mg every four hours (up to a maximum of 60 mg daily) or 12 mg up to four times daily.

In ophthalmology, phenylephrine hydrochloride is used as a **mydriatic** (p. 2000.2) in concentrations of up to 10%; generally solutions containing 2.5 or 10% are used but systemic absorption can occur (see Effects on the Cardiovascular System, p. 1673.2) and the 10% strength, in particular, should be used with caution. The mydriatic effect can last several hours. Solutions containing 2.5% or more may cause intense irritation and a local anaesthetic should be instilled into the eye a few minutes beforehand.

Ocular solutions containing lower concentrations (usually 0.12% phenylephrine hydrochloride) are used as a **conjunctival decongestant** (see Conjunctivitis, p. 611.1).

Phenylephrine has been used parenterally in the treatment of hypotensive states, such as those encountered during circulatory failure or spinal anaesthesia. Phenyleph-

rine has also been used in orthostatic hypotension (see under Fludrocortisone, p. 1634.3). For **hypotension**, an initial dose of phenylephrine hydrochloride 2 to 5 mg may be given as a 1% solution subcutaneously or intramuscularly with further doses of 1 to 10 mg if necessary, according to response. A dose of 100 to 500 micrograms by slow intravenous injection as a 0.1% solution, repeated as necessary after at least 15 minutes, has also been used. In severe hypotensive states, 10 mg in 500 mL of glucose 5% or sodium chloride 0.9% has been infused intravenously, initially at a rate of up to 180 micrograms/minute, reduced, according to the response, to 30 to 60 micrograms/minute.

For doses in children, see below.

Phenylephrine hydrochloride has been given by intravenous injection to stop **paroxysmal supraventricular tachycardia** but other drugs are preferred (see Cardiac Arrhythmias, p. 1266.1). The initial dose is usually not greater than 500 micrograms given as a 0.1% solution with subsequent doses gradually increased in increments of 100 to 200 micrograms up to 1 mg if necessary.

Phenylephrine hydrochloride has been used for its vasoconstrictor action as an **adjunct** to local anaesthetics.

Phenylephrine has also been used as the acid tartrate to prolong the bronchodilator effects of isoprenaline when given by inhalation. However, isoprenaline is now little used by this route.

Phenylephrine tannate has also been used.

Administration in children. Phenylephrine hydrochloride is used for the symptomatic relief of **nasal congestion**; however, over-the-counter cough and cold preparations containing sympathomimetic decongestants (including phenylephrine) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2. In the USA, phenylephrine hydrochloride may be used in children aged from 6 to 12 years; 2 or 3 drops, or 1 or 2 sprays, of a 0.25% solution may be instilled into each nostril every four hours as needed. In the UK, oral preparations for nasal congestion associated with colds and hay fever are not licensed in children under 12 years of age.

Phenylephrine hydrochloride is used for **mydriasis** in diagnostic or therapeutic procedures. Solutions containing 2.5% are used in children as the 10% strength is contra-indicated owing to the risk of systemic effects.

For acute **hypotension**, phenylephrine hydrochloride may be given subcutaneously or intramuscularly; the following doses, according to age, are suggested in the *BNFC*:

- 1 to 12 years: 100 micrograms/kg every 1 to 2 hours as needed (to a maximum dose of 5 mg)
- 12 to 18 years: 2 to 5 mg, followed if necessary by further doses of 1 to 10 mg (maximum initial dose 5 mg)

Although the intravenous route is not licensed in the UK for such use in children, intravenous injection is preferred to the other parenteral routes; the *BNFC* recommends the following doses given as a 0.1% solution:

- 1 to 12 years: 5 to 20 micrograms/kg (maximum 500 micrograms), repeated as needed after at least 15 minutes
- 12 to 18 years: 100 to 500 micrograms, repeated as needed after at least 15 minutes

For intravenous infusion, the solution is diluted with glucose 5% or sodium chloride 0.9% to a concentration of 20 micrograms/mL and given as a continuous infusion via a central venous catheter. The *BNFC* gives the following doses:

- 1 to 16 years: 100 to 500 nanograms/kg per minute, adjusted according to response
- 16 to 18 years: initially up to 180 micrograms/minute, reduced to 30 to 60 micrograms/minute according to response

Faecal incontinence. Topical application of phenylephrine gel has been shown to increase resting anal tone[1] and has been investigated in patients with faecal incontinence.[2] Although application of a 10% gel did not appear to be of clinical benefit in a double-blind crossover study in 36 patients with faecal incontinence caused by internal sphincter dysfunction,[3] continence was improved in another small study in patients with ileoanal pouches.[4]

1. Cheetham MJ, *et al.* Topical phenylephrine increases anal canal resting pressure in patients with faecal incontinence. *Gut* 2001; **48:** 356–9.
2. Cheetham MJ, *et al.* Drug treatment for faecal incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 04/01/07).
3. Carapeti EA, *et al.* Randomized controlled trial of topical phenylephrine in the treatment of faecal incontinence. *Br J Surg* 2000; **87:** 38–42.
4. Carapeti EA, *et al.* Randomized, controlled trial of topical phenylephrine for fecal incontinence in patients after ileoanal pouch construction. *Dis Colon Rectum* 2000; **43:** 1059–63.

Nasal congestion. A meta-analysis concluded that there was insufficient evidence that phenylephrine 10 mg was an effective oral decongestant (p. 1652.1).[1]

1. Hatton RC, *et al.* Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. *Ann Pharmacother* 2007; **41:** 381–90.

Priapism. Alpha agonists, including phenylephrine, may be used in the management of priapism (see under Metaraminol, p. 1430.2). For reference to phenylephrine in low dosage and dilute solution being given by intracavernosal injection to reverse priapism, see under Alprostadil, p. 2353.2.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; phenylephrine has mainly alpha-agonist effects. It has a longer duration of action than noradrenaline and an excessive vasopressor response may cause a prolonged rise in blood pressure. It induces tachycardia or reflex bradycardia and should therefore be avoided in severe hyperthyroidism and used with caution in severe ischaemic heart disease. Patients with diabetes mellitus or prostatic hyperplasia should also avoid phenylephrine.

Since phenylephrine is absorbed through the mucosa systemic effects may follow application to the eyes or the nasal mucosa. In particular, phenylephrine 10% eye drops can have powerful systemic effects. They should be avoided or only used with extreme caution in infants, the elderly, and in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis. Fatalities have been reported in patients with pre-existing cardiovascular disease.

Use of phenylephrine in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Ophthalmic solutions of phenylephrine are contra-indicated in patients with angle-closure glaucoma. Corneal clouding may occur if corneal epithelium has been denuded or damaged.

Excessive or prolonged use of phenylephrine nasal drops can lead to rebound congestion.

Phenylephrine hydrochloride is irritant and may cause local discomfort at the site of application; extravasation of the injection may even cause local tissue necrosis.

Effects on the cardiovascular system. Systemic adverse effects have occurred after the use of phenylephrine as eye drops (particularly at a strength of 10%), or nasal drops.

Hypertension[1] and hypertension with pulmonary oedema[2] have been described in infants and children after the use of phenylephrine 10% eye drops. Hypertension with arrhythmias has also been reported in an 8-year-old child[3] and in an adult[4] after phenylephrine 10% eye drops had been used. Details have also been published on a series of 32 patients who had systemic cardiovascular reactions, including fatal myocardial infarctions, after the use of phenylephrine 10% solutions in the eye.[5] Severe cardiovascular adverse reactions have also been reported with the use of phenylephrine as topical 10% ocular[6] or 0.25% nasal[7] pledgets.

Although the incidence of such reactions seems low,[8] the use of lower concentrations[1,5] and caution in susceptible patients such as those with cardiovascular disorders or the elderly,[5] have been advocated. A reduction in the eye-drop volume has been found to produce adequate mydriasis and may reduce systemic absorption and the risk of adverse cardiovascular effects.[9,10]

1. Borromeo-McGrail V, *et al.* Systemic hypertension following ocular administration of 10% phenylephrine in the neonate. *Pediatrics* 1973; **51:** 1032–6.
2. Baldwin FJ, Morley AP. Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops. *Br J Anaesth* 2002; **88:** 440–2.
3. Vaughan RW. Ventricular arrhythmias after topical vasoconstrictors. *Anesth Analg* 1973; **52:** 161–5.
4. Lai Y-K. Adverse effect of intraoperative phenylephrine 10%: case report. *Br J Ophthalmol* 1989; **73:** 468–9.
5. Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol* 1978; **85:** 447–53.
6. Fraunfelder FW, *et al.* Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol* 2002; **134:** 624–5.
7. Hecker RB, *et al.* Myocardial ischemia and stunning induced by topical intranasal phenylephrine pledgets. *Mil Med* 1997; **162:** 832–5.
8. Brown MM, *et al.* Lack of side effects from topically administered 10% phenylephrine eyedrops: a controlled study. *Arch Ophthalmol* 1980; **98:** 487–9.
9. Craig EW, Griffiths PG. Effect on mydriasis of modifying the volume of phenylephrine drops. *Br J Ophthalmol* 1991; **75:** 222–3.
10. Wheatcroft S, *et al.* Reduction in mydriatic drop size in premature infants. *Br J Ophthalmol* 1993; **77:** 364–5.

Effects on the eyes. Acute and chronic conjunctivitis has been reported[1] after use of over-the-counter ophthalmic decongestant preparations of phenylephrine, naphazoline, or tetryzoline. The conjunctival inflammation took several weeks to resolve in some cases. Dermatoconjunctivitis[2] has also been reported after use of phenylephrine eye drops.

1. Soparkar CN, *et al.* Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. *Arch Ophthalmol* 1997; **115:** 34–8.
2. Moreno-Ancillo A, *et al.* Allergic contact reactions due to phenylephrine hydrochloride in eyedrops. *Ann Allergy Asthma Immunol* 1997; **78:** 569–72.

Effects on mental function. Hallucinations and paranoid delusions have been reported[1] in a patient after excessive use of a nasal spray containing phenylephrine 0.5%. Mania has also followed the use of large oral doses.[2]

1. Snow SS, *et al.* Nasal spray 'addiction' and psychosis: a case report. *Br J Psychiatry* 1980; **136:** 297–9.
2. Waters BGH, Lapierre YD. Secondary mania associated with sympathomimetic drug use. *Am J Psychiatry* 1981; **138:** 837–40.

Hypersensitivity. Cross-sensitivity to phenylephrine has been reported in a patient hypersensitive to pseudoephedrine.[1] See also Effects on the Eyes, above.

1. Buzo-Sanchez G, *et al.* Stereoisomeric cutaneous hypersensitivity. *Ann Pharmacother* 1997; **31:** 1091.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenylephrine for cardiac or ophthalmic use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Phenylephrine has mainly direct alpha-agonist properties and is less liable than adrenaline or noradrenaline to induce ventricular fibrillation if used as a pressor agent during anaesthesia with inhalational anaesthetics such as cyclopropane and halothane; nevertheless, caution is necessary. Since phenylephrine is absorbed through the mucosa, interactions may also follow topical application, particularly in patients receiving an MAOI (including a RIMA). See also under Phenelzine (p. 445.1) and Moclobemide (p. 438.1).

Cardiovascular drugs. Hypertensive reactions have been reported in a patient stabilised on *debrisoquine* when given phenylephrine orally,[1] in patients receiving *reserpine* or *guanethidine* when given phenylephrine eye drops,[2] and a fatal reaction occurred in a patient receiving *propranolol* and *hydrochlorothiazide* also after the instillation of phenylephrine eye drops.[3]

1. Aminu J, *et al.* Interaction between debrisoquine and phenylephrine. *Lancet* 1970; **ii:** 935–6.
2. Kim JM, *et al.* Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervation. *Am J Ophthalmol* 1978; **85:** 862–8.
3. Cass E, *et al.* Hazards of phenylephrine topical medication in persons taking propranolol. *Can Med Assoc J* 1979; **120:** 1261–2.

Pharmacokinetics

Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscularly it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about 1 hour and up to about 2 hours, respectively. Intravenous injections are effective for about 20 minutes.

Systemic absorption follows topical application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fadalefrina; Poen Efrina; Prefrin; Qura Nasal; ***Austral.***: Actifed PE†; Albalon Relief; Codral Relief Decongestant; Dimetapp PE Nasal Decongestant; Neo-Synephrine; Nyal Cold + Flu; Nyal Decongestant; Nyal Nasal Decongestant PE; Nyal Sinus Relief PE; Prefrin; Sudafed PE; ***Austria***: Visadron; ***Belg.***: Spraydil; Visadron; ***Braz.***: Denason; ***Canad.***: Ak-Dilate; Dionephrine; Hemorrhoidal Relief; Little Noses Decongestant; Mydfrin; Neo-Synephrine; Prefrin†; Sudafed PE; Triaminic Thin Strips Nasal Congestion; ***Chile***: Mydfrin; ***China***: Wei Li Ang (维力昂); ***Cz.***: Humex Nosni; Neo-Synephrine; ***Fin.***: Oftan Metaoksedrin; ***Fr.***: Humoxal; ***Ger.***: Neosynephrin-POS; Otriven Baby†; Visadron; ***Gr.***: Ibition; Prefrin; ***Hong Kong***: Mydfrin; Prefrin†; Visopt†; ***India***: Drosyn; Fencel; Frenin; Lefrine; Nefrisol; ***Israel***: Efrin; Neo-Synephrine†; ***Ital.***: Isonefrine; Nasomixin CM; Neo-Synephrine; ***Malaysia***: Mydfrin; Prefrin; ***Mex.***: Actifed Advance; Dilufrin†; Lefrine†; Nefrin; Plegh; Rinolan; ***Mon.***: Neosynephrine; ***Neth.***: Boradrine†; Visadron; ***NZ***: Albalon Relief; Neosynephrine; Prefrin; Sudafed PE Nasal Decongestant; ***Philipp.***: Decolgen†; Mydfrin; Neo-Synephrine; ***Pol.***: Neosynephrin; ***Port.***: Davinefrina; Neo-Sinefrina; VibrocilFen; Visadron; ***Rus.***: Irifrin (Ирифрин); Mesaton (Мезатон); Nazol Baby (Назол Бэби); Nazol Kids (Назол Кидс); Rhinopront (Ринопронт); ***S.Afr.***: I-Glo; Naphensyl; Prefrin; ***Singapore***: Mydfrin†; Prefrin; ***Spain***: ADA†; Boraline†; Disneumon Mentol†; Disneumon Pernasal; Mirazul; Visadron; Vistafrin†; ***Switz.***: Neo-Synephrine; Rexophtal N†; Spray nasal pour enfants†; ***Turk.***: Mydfrin; ***UK***: Boots Decongestant Capsules; Fenox; Non-Drowsy Sudafed Congestion Relief; ***Ukr.***: Glycodin (Глікодин)†; Nasol Baby (Назол Беби); ***USA***: AH-chew D; Ak-Dilate; Anu-Med; Children's Nostril; Hemorrhoidal Suppositories; Lusonal; Mydfrin; Nasop†; Neo-Synephrine; Neofrin; Nostril; Ocu-Phrin; Pedia Care Childrens Decongestant; Phenyl-T†; Rectacaine; Relief†; Rhinall;

The symbol † denotes a preparation no longer actively marketed

Sinex; Sudafed PE; Triaminic Infant Thin Strips Decongestant†; Triaminic Thin Strips Cold; Tronolane.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. *Braz.*: Anestesico.

Pharmacopoeial Preparations
BP 2014: Phenylephrine Eye Drops; Phenylephrine Injection; **USP 36:** Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Phenylephrine Hydrochloride Injection; Phenylephrine Hydrochloride Nasal Jelly; Phenylephrine Hydrochloride Nasal Solution; Phenylephrine Hydrochloride Ophthalmic Solution.

Phenylpropanolamine *(BAN, rINN)*

Fenilpropanolamina; Fennylpropanolamin; Fenyylipropanoliamiini; Phénylpropanolamine; Phenylpropanolaminum; Фенилпропаноламин; (±)-Norephedrine.

(1*RS*,2*SR*)-2-Amino-1-phenylpropan-1-ol.

$C_9H_{13}NO$=151.2

CAS — 14838-15-4.

ATC — R01BA01.

ATC Vet — QG04BX91; QR01BA01.

UNII — 33RU150WUN.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phenylpropanolamine:

Pseudocaine.

Phenylpropanolamine Hydrochloride

(BANM, rINNM)

Fenilpropanolamina, hidrocloruro de; Fenilpropanolaminhidroklorid; Fenilpropanolamino hidrochloridas; Fenylpropanolamin hydrochlorid; Fenylpropanolaminhydroklorid; Fenyylipropanoliamiinihydrokloridi; Hidrocloruro de fenilpropanolamina; Mydriatin; Phénylpropanolamine, Chlorhydrate de; Phenylpropanolaminhydrochlorid; Phenylpropanolamini Hydrochloridum; Фенилпропаноламина Гидрохлорид.

$C_9H_{13}NO,HCl$=187.7

CAS — 154-41-6.

ATC — R01BA01.

ATC Vet — QG04BX91; QR01BA01.

UNII — 8D5I63UE1Q.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

US also includes phenylpropanolamine bitartrate.

Ph. Eur. 8: (Phenylpropanolamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane.

USP 36: (Phenylpropanolamine Hydrochloride). A white crystalline powder, having a slight aromatic odour. Soluble 1 in 1.1 of water, 1 in 7.4 of alcohol, and 1 in 4100 of chloroform; insoluble in ether. pH of a 3% solution in water is between 4.2 and 5.5. Store in airtight containers. Protect from light.

Uses and Administration

Phenylpropanolamine is a mainly indirect-acting sympathomimetic (p. 1507.3) with an action similar to that of ephedrine (p. 1663.2) but less active as a CNS stimulant.

Phenylpropanolamine has been given orally as the hydrochloride for the symptomatic treatment of **nasal congestion** (p. 1652.1). It has frequently been used in combination preparations for the relief of cough and cold symptoms.

In the management of nasal congestion, phenylpropanolamine hydrochloride has been given in oral doses of up to 50 mg twice daily as modified-release preparations.

Other uses of phenylpropanolamine have included the control of urinary incontinence in some patients and the management of some forms of priapism. Phenylpropanolamine has been used to suppress appetite in the management of obesity but the use of stimulants is no longer recommended.

Phenylpropanolamine polistirex (a phenylpropanolamine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has also been used, as have phenylpropanolamine bitartrate, phenylpropanolamine maleate, and phenylpropanolamine sulfate.

Adverse Effects and Precautions

As for Ephedrine, p. 1663.3 and p. 1664.1.

Severe hypertensive episodes have followed phenylpropanolamine ingestion (see below). As with other indirect-acting sympathomimetics, tolerance to the therapeutic effects of phenylpropanolamine has been reported with prolonged use.

An extensive and detailed review[1] of adverse effects attributed to phenylpropanolamine noted in 1990 that many of the adverse drug reactions reported in Europe described an alteration of mental status whereas those in North America were more often compatible with hypertension. The author suggested that this might be due to a difference in the isomers present in phenylpropanolamine preparations, based on earlier reports that *d*-norpseudoephedrine, the most potent of several isomeric forms as a stimulant of the CNS, was present in European preparations of phenylpropanolamine. However, later investigation suggests that currently the racemic mixture (±)-norephedrine (*d,l*-norephedrine) is the isomeric form present in commercial preparations in both Europe and the USA.[2]

The original review[1] concentrated on North American cases. The majority of products available were decongestants or cough or cold remedies; a small number were promoted as diet aids.

The data suggested that over-the-counter (OTC) products were more likely to be associated with an adverse reaction than a prescription medication; this may be because such OTC products were more likely to be overused and to be considered innocuous by the patient. It was also likely that drug interactions (below) rather than 'true overdosages' were involved in many of the adverse events, particularly as many OTC preparations contain other ingredients. (See also Abuse under Ephedrine, p. 1664.1, for further discussion about the consequences of use of OTC preparations containing sympathomimetics, including phenylpropanolamine.)

The adverse reactions varied widely ranging from headache and elevated blood pressure to cardiopulmonary arrest, intracranial haemorrhage, and death. Mild reactions included blurred vision, dizziness, anxiety, agitation, tremor, confusion, and hypersensitivity reaction. Severe reactions included hypertensive crisis with hypertensive encephalopathy, seizures, arrhythmias, psychosis, and acute tubular necrosis. One unifying theme of many of the severe cases was that high blood pressure or symptoms suggestive of this were the presenting feature; an acute, persistent, severe headache was also noted in many cases.

It was pointed out that overall phenylpropanolamine was relatively safe. Although billions of doses were consumed annually, few cases of adverse drug reactions had been reported.

It was believed that certain groups may be at particular risk of adverse reactions to phenylpropanolamine: persons with elevated blood pressure, overweight persons (who are likely to be both hypertensive and to use diet aids), patients with eating disorders (who tend to abuse substances including diet aids), and the elderly (who may be multiple drug takers and likely to be hypertensive and at risk already of a stroke).

Subsequently, after a large case-control study in the USA which found an increased risk of haemorrhagic stroke associated with the use of preparations containing phenylpropanolamine (and in particular in women who used phenylpropanolamine as an appetite suppressant),[3] the FDA took steps to remove phenylpropanolamine from all drug products in the USA and requested that it no longer be marketed. Products containing phenylpropanolamine have also been withdrawn in some other countries. However, this study and the FDA decision have been criticised[4-6] notably on the basis that there was no evidence of an increased risk with the amount of phenylpropanolamine normally present in decongestant preparations and the study may have been subject to confounding. The UK CSM[7] considered that the evidence of a link between UK products containing phenylpropanolamine and haemorrhagic stroke was weak (phenylpropanolamine is not licensed as an appetite suppressant in the UK and the maximum recommended dose of 100mg daily was lower than the 150mg daily recommended in the USA). It was therefore suggested by UK commentators that use of licensed doses, with appropriate precautions, posed no additional risk.[2] However, subsequently, UK preparations containing phenylpropanolamine have either been reformulated (mainly with pseudoephedrine) or withdrawn by the manufacturers.

1. Lake CR, *et al.* Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* 1990; **89:** 195–208.
2. Moffatt T, *et al.* Phenylpropanolamine: putting the record straight. *Pharm J* 2000; **265:** 817.
3. Kernan WN, *et al.* Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000; **343:** 1826–32.
4. Ernst ME, Hartz A. Phenylpropanolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344:** 1094.
5. Wolowich WR, *et al.* Phenylpropanolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344:** 1094–5.
6. Stier BG, Hennekens CH. Phenylpropanolamine and hemorrhagic stroke in the Hemorrhagic Stroke Project: a reappraisal in the context of science, the Food and Drug Administration, and the law. *Ann Epidemiol* 2006; **16:** 49–52.
7. CSM/MCA. Phenylpropanolamine and haemorrhagic stroke. *Current Problems* 2001; **27:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 04/01/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenylpropanolamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. For a comment that drug interactions were likely to have been involved in many adverse events associated with phenylpropanolamine see under Adverse Effects and Precautions, above. Due to its indirect action, hypertensive crisis is a particular risk in patients receiving MAOIs. For mention of the potential that phenylpropanolamine can increase plasma-caffeine concentrations, see Sympathomimetics, under Caffeine, p. 1206.2.

Amantadine. Severe psychosis has been reported[1] in a woman taking amantadine with phenylpropanolamine. In another report,[2] a 39-year-old man had intense and recurrent *déjà vu* experiences after taking amantadine with phenylpropanolamine for viral influenza. The effect ceased when he stopped both drugs. The authors suggested that his symptoms were due to increased dopamine activity caused by the combination.

1. Stroe AE, *et al.* Psychotic episode related to phenylpropanolamine and amantadine in a healthy female. *Gen Hosp Psychiatry* 1995; **17:** 457–8.
2. Taiminen T, Jääskeläinen SK. Intense and recurrent déjà vu experiences related to amantadine and phenylpropanolamine in a healthy male. *J Clin Neurosci* 2001; **8:** 460–2.

Antipsychotics. A 27-year-old woman with schizophrenia and T-wave abnormality of the heart, who had responded to *thioridazine* 100mg daily with procyclidine 2.5mg twice daily, died from ventricular fibrillation within 2 hours of taking a single dose of a preparation reported to contain chlorphenamine maleate 4mg with phenylpropanolamine hydrochloride 50mg (*Contac C*), concurrently with thioridazine.[1]

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; **119:** 729–31.

Antivirals. A patient taking an over-the-counter nasal decongestant preparation containing phenylpropanolamine and clemastine as well as a triple-drug HIV prophylactic regimen, had a hypertensive crisis 3 days after *stavudine* was substituted for *zidovudine*;[1] the other antivirals in the regimen were *indinavir* and *lamivudine*.

1. Khurana V, *et al.* Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106:** 118–19.

Bromocriptine. For a report of hypertension and life-threatening complications after use of phenylpropanolamine with bromocriptine, see Sympathomimetics, p. 899.1.

NSAIDs. A 27-year-old woman who had been taking D-phenylpropanolamine [sic] 85mg daily for some months, had severe hypertension when she also took *indometacin* 25 mg. It was considered that the inhibition of prostaglandin synthesis by indometacin might have caused enhancement of the sympathomimetic effect of phenylpropanolamine.[1]

1. Lee KY, *et al.* Severe hypertension after ingestion of an appetite suppressant (phenylpropanolamine) with indomethacin. *Lancet* 1979; **i:** 1110–11.

Pharmacokinetics

Phenylpropanolamine is readily and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 or 2 hours after oral doses. It undergoes some metabolism in the liver, to an active hydroxylated metabolite, but up to 80 to 90% of a dose is excreted unchanged in the urine within 24 hours. The half-life has been reported to be about 3 to 5 hours.

References.

1. Simons FER, *et al.* Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr* 1996; **129:** 729–34.
2. Chester N, *et al.* Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; **57:** 62–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Rinexin; ***Ger.***: Boxogetten S; Recatol mono; ***Norw.***: Rinexin; ***Philipp.***: Desotap†; Disudrin; Naldec; Nasadec; Nasaphen†; Nasathera P; Neo-Coldan; ***Swed.***: Rinexin.

Multi-ingredient Preparations. ***Chile***: Contac†; Matinor; Sinutab; ***Fin.***: Rinomar; ***Ger.***: Antiadipositum; Basoplex; Wick Daymed Erkaltungs; ***Gr.***: Dimetapp New; Dimetapp; Ornade-2; Rhino-

pront-S; ***Hong Kong***: Antamin†; Anticol†; B.P.P.†; BPP Cough Syrup†; Brom-PP; Brom-Ramine Compound; Corhisdin with codeine†; Coritussal†; CPP†; DM-Cordyl†; Eascold; Eurotapp; Fludane†; Neozep; Pholix†; Qualizep; Rhinopront†; Syncoldtab-M†; Tripe P; Tuseran; Uni-Vasin; Vidatapp†; ***India***: A-Cof; Abcof-DM; Aceper; Actifed DM; Actifed Plus; Actiflu Plus; Actiflu; Actioner-DX; Alerid Cold; Alerid D; Alernyl-DC; Allset; Altec Cough Formula; Altec-P; Ambrodex; Ambrodil Plus; Ambrol-GPC; Ascoril-D; Asisneez; Bactpar Plus; Biorex; Brick; Brick; Broncare; Broncos; Brontac-Plus; C-Cold; Calmcold; Calmcold; Calscot; Calscot; Capex-DMR; Carecof Exp; Carecof; CC Cap; CC-Koff; CCGO; Celar; Cetcip Cold; Cetcip-D; Cetin Cold; Cetin Kid; Cetin-D; Cetra; Cezcold; Chericold; Cheston Cold; Cheston DT; Cheston; Cindexa; Ciz Cold; Cledex; Cobury-DX; Codril-P; Cof QD; Cofal-D; Cofar-D; Cofdex Forte; Cofdex Forte; Cofdex-P; Cofdex; Cogof; Cold-CZ; Cold-Relief; Cold-War; Coldact Plus; Coldact; Coldant; Coldap; Coldargic; Coldastat-LX; Coldastat; Coldastat; Coldcure; Coldec; Coldfin; Coldgone; Coldilak; Coldoff; Coldtaur; Coldtaur; Coldwar; Coldy; Coldy; Colgin; Colrex Plus; Colsan; Contac-CC; Control; Contus Plus; Contus-650; Contus; Contus; Cor-4; Corophen-D; Cos-D; Coscopin-BR; Cosome Exp; Cosome; Covil-A; Cozy Cool; CPP; Cuf-Dex; Cufcalm; Cuffmol-P; Cufree; CZ-Cold; DCol-BR; Decold CP; Decomine; Delcon Plus; Delcon; Demine; Dencold; Dex-PC; Dexcof; Dexphen; Dextrotuss; Dolar; Dold; Dolo-Cold; DPC; Drynoz; DSQ; Dual Cold; Easicold; Elcold; Elgnil Cold; Ephact-XR; Ephedrex; Eskold Expectorant; Eskold; Est-Coff; Etric Plus; Evercold; Fenace Plus; Fevacold; Fincof; Fineorest; Flemnil; Flu-4-DMR; Flucold; Flucold; Flukuff; Fluzet; Fricold; Fricold; Grilinctus†; Idalez Plus; Ifycet; Incold; Incold; Incough-DX; Kaituss; Kazibrox; Kofrid-D; Kofryl-P; Koftame; Kol-DC; Kolderon; Kozifed; Kuff-D; Kuff-Q; Kuffdac-C; Kufgen-D; Kufkair-P; L-Cit Plus; L-Triz Plus; LCZ-Plus; Leday-CC; Lemohist-C; Lemohist; Lemohist; Lenex; Lenomol; Leverest Plus; Levogo Plus; Levoriz Plus; Levostar Plus; Levostar-D; Lexcof; LG-Plus; Libitus; Lincotuss-P; Linctus-DX; Littlekof-DM; Lorex-AP; Lucold; Marcold; Nicip Cold; Nocold; Nocold; Rinostat; Zeet Linctus; Zeet; ***Indon.***: Agrippin†; Allerin; Alpara; Anacetine; Anadex; Antiza; Benilin†; Bestocol; Bodrexin; Bronchophen†; Calorex†; Codecon; Colfin; Collerin Expectorant; Colza†; Combi Flu; Corsagrip; Cosyr†; Cough EN Expectorant; Cough EN Plus; Decolgen; Decolgen; Decolsin; Deconal; Dextral; Dextrosin Anak; Dextrosin; Extra-Flu; Farapon; Flu Stop; Flu-Tab; Flucadex†; Flucodin; Flucyl†; Fludane Plus; Fludane; Flunadin†; Flunax†; Flutamol-P; Flutamol; Fluzep; Fortaflu†; Frigrip; Gunacold†; Intunal; Kontrabat; Lacoldin; Lapisiv; Mixaflu; Mixagrip; Molexflu; Mucotussan†; Nalgestan; Neo Novapon Plus; Neo Novapon; Neozep; New Coldin†; Nodrof; Oskadon Flu & Batuk Berdahak; Paranomin; Paratusin; Pilexal; Ponflu; Protusif†; Pyridryl Plus; Recomint; Sanaflu Plus; Sanaflu; Stop Cold; Topras; Triadex; Tuseran Forte†; Tuseran†; Tuzalos; Ultragrip†; Ultragrip; ***Irl.***: Day & Night†; ***Mex.***: Graneodin D Mentol; Lentostamin†; Numonyl Jarabe†; ***Philipp.***: A-P-Histallin†; AC Nex; Allerin Reformulated; Coldrex Reformulated†; Colvan; Colvan; Congestril (Reformulated); Conotab; Cynosal; Decolsin Reformulated; Drinus; Drinus; Dynatussin; Dynatussin; Eleobron; Hisdec; Mucobron Forte; Mucotuss; Myracof-AF†; Myracof-T†; Nafarin A (Reformulated); Nagelin; Nasagesic; Nasatapp; Nasathera CPM; Nasathera; Neo-Bromexan Forte; Neo-Bromexan; Nostero†; Noxifen; Ornex; Pediatapp; Penbrosol; Plemerid†; PPB; Rhinodec; Rhinotapp; Sinutab Extra Strength; Solvamin; Tridecon; Tuseran (Reformulated)†; Zeditapp; ***S.Afr.***: Adco-Sinal Co; Betalix†; Colcaps†; Coldvico†; Eskornade†; Flustat†; Infacet†; Merck-Flu†; Nitecall†; Ornacol†; Rinex†; Si-Nade†; Sinuclear; Sinustat Flu†; Sinustat; Sinustop with Codeine†; Sinustop†; Sinutab ND; Sinutab with Codeine; Sinutab†; ***Spain***: Irritos†; Senioral; ***Swed.***: Rinomar; ***Thai.***: Aorinyl; Clinepect; ***Turk.***: Alfarol; Apex; Cetaflu-forte; Contex; Corsal; Ekorinol†; Parol Cold; Rhinopront; Rhinotussal; ***Ukr.***: Flucoldex (Флюколдекс).

Pharmacopoeial Preparations

USP 36: Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Tablets; Phenylpropanolamine Hydrochloride Capsules; Phenylpropanolamine Hydrochloride Extended-release Capsules; Phenylpropanolamine Hydrochloride Extended-release Tablets; Phenylpropanolamine Hydrochloride Oral Solution; Phenylpropanolamine Hydrochloride Tablets.

Pholcodine *(BAN, rINN)*

Folcodina; Folkodiini; Folkodin; Folkodin monohydrát; Folkodinas; Pholcodin; Pholcodinum; Pholcodinum Monohydricum; Фолкодин.

3-*O*-(2-Morpholinoethyl)morphine monohydrate.

$C_{23}H_{30}N_2O_4,H_2O$=416.5

CAS — 509-67-1 (anhydrous pholcodine).

ATC — R05DA08.

ATC Vet — QR05DA08.

UNII — LPP64AWZ7L.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Pholcodine). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; freely soluble in alcohol and in acetone; dissolves in dilute mineral acids.

Uses and Administration

Pholcodine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p. 1660.2). It is given orally in a usual dose of 5 to 10 mg three or four times daily. For doses in children, see below. The citrate has also been used. Pholcodine polistirex (a pholcodine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has been used in modified-release preparations.

Administration in children. Although pholcodine is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including pholcodine) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2. The *BNFC* suggests giving those aged 6 to 12 years 2 to 5 mg three or four times daily.

Adverse Effects and Precautions

As for Dextromethorphan, p. 1660.3. Constipation, drowsiness, and skin rashes have been reported occasionally.

Support for a hypothesis that consumption of pholcodine may sensitise individuals to hypersensitivity to neuromuscular blockers has resulted in one pholcodine preparation being taken off the Norwegian market in March 2007.[1] A subsequent retrospective analysis in Sweden, where pholcodine had not been available since mid 1989, of serum samples taken from patients who had had IgE-mediated allergy appeared to support this hypothesis.[2]

1. Florvaag E, Johansson SGO. The pholcodine story. *Immunol Allergy Clin North Am* 2009; **29:** 419–27.
2. Johansson SGO, *et al*. Pholcodine caused anaphylaxis in Sweden 30 years ago. *Allergy* 2009; **64:** 820–1.

Interactions

Use of pholcodine with alcohol or other CNS depressants may increase the effects on the CNS.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Actifed CC Dry†; Chemists Own Dry Cough; Duro-Tuss Dry Cough; Tussinol†; ***Belg.***: Cotrane Pholcodine; ***China***: Pholcotussin (欧博士福尔可定); ***Fin.***: Tuxi†; ***Fr.***: Atouxx Toux Seche†; Biocalyptol; Dimetane; Flucalyptol; Humex Toux Seche Pholcodine†; Pharmakod toux seche†; Respilene†; Rhinathiol Toux Seche Pholcodine†; Valda Toux Seche†; ***Hong Kong***: Duro-Tuss; Uni-Pholco; ***Irl.***: Expulin Dry Cough†; Pholcodex; Pholcolin†; ***Malaysia***: Dhacodine; Ducodin; Duro-Tuss; ***NZ***: Benadryl Dry Tickly Cough; Duro-Tuss Dry Cough; ***S.Afr.***: Pholcolinct†; Pholtex; ***Singapore***: Duro-Tuss; ***UK***: Benylin Childrens Dry Coughs; Boots Dry Cough Syrup 1 Year Plus; Galenphol; Hill's Balsam Dry Cough; Pavacol-D; Tixylix Dry Cough†.

Multi-ingredient Preparations. ***Austral.***: Chemists Own Kiddicol; Demazin Cough & Cold†; Difflam Anti-inflammatory Lozenges with Cough Suppressant; Duro-Tuss Decongestant†; Duro-Tuss Dry Cough Plus Nasal Decongestant; Duro-Tuss Dry Cough; Duro-Tuss Expectorant; Duro-Tuss PE Dry Cough plus Nasal Decongestant; Tixylix Night†; ***Belg.***: Broncho-pectoralis Pholcodine; Eucalyptine Pholcodine; Pholco-Mereprine; ***China***: Ao Si Ling (奥斯灵); Photifed-M (澳特斯); ***Fr.***: Atouxx†; Broncalene; Clarix Toux Seche†; Hexapneumine†; Hexapneumine; Pholcodyl†; Polery; Pulmosodyl; Trophires†; ***Hong Kong***: Double 'P' Syrup†; Duro-Tuss Decongestant; Duro-Tuss Expectorant; Hexapneumine; Pholix†; Tripe P; ***India***: Childryl; Lincotuss-P; Tixylix; ***Irl.***: Day Nurse; Expulin Childrens Cough†; Expulin†; Nirolex Day Cold & Flu; Solpadeine Cold & Flu; ***Malaysia***: Difflam Anti-Inflammatory Lozenges (with cough suppressant); Duro-Tuss Expectorant; Phensedyl Dry Cough; Promedyl Plus; Rhynacol†; Russedyl Plus; ***NZ***: Difflam Cough; Duro-Tuss Cough†; Duro-Tuss Expectorant; Duro-Tuss Lozenges; Tixylix; ***S.Afr.***: Contra-Coff†; Docsed†; Folcofen; Pholtex Linctus; Procof; Respinol Compound†; Tixylix†; ***Singapore***: Difflam Cough Lozenges; Duro-Tuss Cough Lozenges; Duro-Tuss Decongestant†; Duro-Tuss Expectorant; ***Spain***: Caltoson Balsamico†; ***Switz.***: Pecto-Baby†; Phol-Tussil; Phol-Tux; ***UK***: Boots Nightime Cough Syrup 1 Year Plus; Cough Nurse; Day & Night Nurse; Day Nurse; Nirolex Day Cold & Flu; Nirolex Night Cold & Flu; Tixylix Cough & Cold†; Tixylix Night-Time†; ***Ukr.***: Hexapneumine for Children (Гексапневмин Для Детей)†.

Pharmacopoeial Preparations

BP 2014: Pholcodine Linctus; Strong Pholcodine Linctus.

Pipazetate *(BAN, rINN)*

D-254; Pipazétate; Pipazetato; Pipazetatum; Pipazethate (USAN); SKF-70230-A; SQ-15874; Пипазетат.

2-(2-Piperidinoethoxy)ethyl pyrido[3,2-*b*][1,4]benzothiazine-10-carboxylate.

$C_{21}H_{25}N_3O_3S$=399.5

CAS — 2167-85-3.

ATC — R05DB11.

ATC Vet — QR05DB11.

UNII — M5EK1T5V2L.

Pipazetate Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipazetato; Pipazétate, Chlorhydrate de; Pipazetati Hydrochloridum; Pipazetato, hidrocloruro de; Pipazethate Hydrochloride; Piperestazine Hydrochloride; Пипазетата Гидрохлорид.

$C_{21}H_{25}N_3O_3S,HCl$=436.0

CAS — 6056-11-7.

ATC — R05DB11.

ATC Vet — QR05DB11.

UNII — 757GN3W2CZ.

Profile

Pipazetate hydrochloride is a centrally acting cough suppressant that also has some peripheral actions in non-productive cough. It has been given orally and rectally.

Overdosage. A healthy 4-year-old child became somnolent and agitated, with convulsions, followed by coma, after swallowing an unknown number of tablets containing pipazetate; cardiac arrhythmias also developed.[1] Fatal toxicity has also been reported in children.[2,3]

1. da Silva OA, Lopez M. Pipazethate—acute childhood poisoning. *Clin Toxicol* 1977; **11:** 455–8.
2. Bonavita V, *et al*. Accidental lethal pipazethate poisoning in a child. *Z Rechtsmed* 1982; **89:** 145–8.
3. Soto E, *et al*. Pipazethate lethality in a baby. *Vet Hum Toxicol* 1993; **35:** 41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Selvigon; ***Gr.***: Selvigon; ***Indon.***: Selvigon; ***Ital.***: Selvjgon; ***Mex.***: Selvigon.

Multi-ingredient Preparations. ***Indon.***: Transpulmin.

Poppy Capsule

Dormideiras; Fruit du Pavot; Fruto de adormidera; Mohnfrucht; Papaveris Capsula; Poppy Heads; Маковая Коробочка.

Pharmacopoeias. In *Chin.*

Profile

Poppy capsule consists of dried fruits of *Papaver somniferum* (Papaveraceae), collected before dehiscence has occurred, containing very small amounts of morphine with traces of other opium alkaloids. It is mildly sedative and has been used as a liquid extract or syrup in cough mixtures.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Sedemol; Sulfa-Sedemol; ***Braz.***: Malvodon†; ***Fr.***: Mediflor Pectorale d'Alsace no 8†.

Prenoxdiazine Hydrochloride *(rINNM)*

Hidrocloruro de prenoxdiazina; HK-256; Prenoxdiazin Hydrochloride; Prenoxdiazina, hidrocloruro de; Prénoxdiazine, Chlorhydrate de; Prenoxdiazini Hydrochloridum; Преноксдиазина Гидрохлорид.

3-(2,2-Diphenylethyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole hydrochloride.

$C_{23}H_{27}N_3O,HCl$=397.9

CAS — 47543-65-7 (prenoxdiazine); 37671-82-2 (prenoxdiazine hibenzate); 982-43-4 (prenoxdiazine hydrochloride).

ATC — R05DB18.

ATC Vet — QR05DB18.

Profile

Prenoxdiazine hydrochloride is a peripherally acting cough suppressant for non-productive cough that has been given orally. Prenoxdiazine hibenzate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Libexin; Rhinathiol Tusso; ***India***: Libexin; ***Rus.***: Libexin (Либексин); ***Ukr.***: Libexin (Либексин).

Multi-ingredient Preparations. ***Ital.***: Libexin Mucolitico.

Promolate *(rINN)*

Morphethylbutyne; Promolato; Promolatum; Промолат.
2-Morpholinoethyl 2-methyl-2-phenoxypropionate.
$C_{16}H_{23}NO_4$=293.4
CAS — 3615-74-5.
UNII — 5WGM277OKR.

Profile

Promolate is a cough suppressant that has been given rectally to infants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Atusil.

Pseudoephedrine *(BAN, rINN)* ⊗

d-Isoephedrine; Pseudoefedriini; Pseudoefedrin; Pseudoefedrina; Pseudoéphédrine; Pseudoephedrinum; *d*-Ψ-Ephedrine; Псевдоэфедрин.
(+)-(1S,2S)-2-Methylamino-1-phenylpropan-1-ol.
$C_{10}H_{15}NO$=165.2
CAS — 90-82-4.
ATC — R01BA02.
ATC Vet — QR01BA02.
UNII — 7CUC9DDI9F.

Description. Pseudoephedrine is an alkaloid obtained from *Ephedra* spp.

Pseudoephedrine Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de pseudoefedrina; Pseudoefedriinihydrokloridi; Pseudoefedrina, hidrocloruro de; Pseudoefedrin-hydrochlorid; Pseudoefedrinhydroklorid; Pseudoefedrino hidrochloridas; Pseudoéphédrine, Chlorhydrate de; Pseudoephedrinhydrochlorid; Pseudoephedrini hydrochloridum; Psödoefedrin Hidroklorür; Pszeudoefedrin-hidroklorid; Псевдоэфедрина Гидрохлорид.
$C_{10}H_{15}NO.HCl$=201.7
CAS — 345-78-8.
ATC — R01BA02.
ATC Vet — QR01BA02.
UNII — 6V9V2RYJ8N.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Pseudoephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Pseudoephedrine Hydrochloride). A fine, white to off-white crystalline powder, having a faint characteristic odour. Soluble 1 in 0.5 of water, 1 in 3.6 of alcohol, 1 in 91 of chloroform, and 1 in 7000 of ether. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers. Protect from light.

Pseudoephedrine Sulfate

(BANM, USAN, rINNM) ⊗

Pseudoefedrina, sulfato de; Pseudoéphédrine, Sulfate de; Pseudoephedrine Sulphate; Pseudoephedrini Sulfas; Sch-4855; Sulfato de pseudoefedrina; Псевдоэфедрина Сульфат.
$(C_{10}H_{15}NO)_2,H_2SO_4$=428.5
CAS — 7460-12-0.
ATC — R01BA02.
ATC Vet — QR01BA02.
UNII — Y9DL7QPE6B.

Pharmacopoeias. In *US*.

USP 36: (Pseudoephedrine Sulfate). Odourless, white crystals or crystalline powder. Freely soluble in alcohol. pH of a 5% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Uses and Administration

Pseudoephedrine is a direct- and indirect-acting sympathomimetic (p. 1507.3). It is a stereoisomer of ephedrine (p. 1663.1) and has a similar action, but has been stated to have less pressor activity and fewer CNS effects.

Pseudoephedrine and its salts are given orally for the symptomatic relief of nasal congestion (p. 1652.1). They are commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms.

Pseudoephedrine hydrochloride or sulfate are generally given orally in doses of 60 mg every 4 to 6 hours up to a maximum of 4 doses in 24 hours. For doses in children, see below. Modified-release preparations are also available; a usual adult dose is 120 mg every 12 hours or 240 mg every 24 hours.

Other uses of pseudoephedrine include the control of urinary incontinence in some patients and the management of some forms of priapism.

Pseudoephedrine polistirex (a pseudoephedrine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has also been used, as has pseudoephedrine tannate.

Administration in children. The *BNFC* states there is little evidence to support the use of systemic decongestants in children. However, a suggested oral dose of pseudoephedrine hydrochloride for the management of mucosal congestion of the upper respiratory tract in those aged 6 to 12 years is 30 mg 3 or 4 times daily.

Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including pseudoephedrine) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2.

Barotrauma. Results from a controlled study[1] suggest that pseudoephedrine given to adults at least 30 minutes before flying appears to decrease the incidence of ear pain associated with pressure changes.[1] However, a similar decrease in risk was not noted in children.[2]

1. Jones JS, *et al.* A double-blind comparison between oral pseudoephedrine and topical oxymetazoline in the prevention of barotrauma during air travel. *Am J Emerg Med* 1998; **16:** 262–4.
2. Buchanan BJ, *et al.* Pseudoephedrine and air travel-associated ear pain in children. *Arch Pediatr Adolesc Med* 1999; **153:** 466–8.

Adverse Effects and Precautions

As for Ephedrine, p. 1663.3 and p. 1664.1. The commonest adverse effects of pseudoephedrine include tachycardia, anxiety, restlessness, and insomnia; skin rashes and urinary retention have occasionally occurred. Hallucinations have been reported rarely, particularly in children.

Abuse. Acute psychosis and visual and tactile hallucinations have been reported[1] in an 18-year-old male after intravenous misuse of pseudoephedrine hydrochloride. Pseudoephedrine has also been used for the illicit manufacture of street stimulants such as metamfetamine (p. 2324.2).

For reference to toxic effects after long-term use of over-the-counter preparations containing sympathomimetics, such as pseudoephedrine, see under Ephedrine, p. 1664.1.

1. Sullivan G. Acute psychosis following intravenous abuse of pseudoephedrine: a case report. *J Psychopharmacol* 1996; **10:** 324–5.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers that contain pseudoephedrine with dexbrompheniramine maleate have resulted in crying, irritability, and poor sleep patterns in the infant.

The concentrations of pseudoephedrine and triprolidine in plasma and breast milk of 3 mothers for up to 48 hours after ingestion of a preparation containing pseudoephedrine hydrochloride 60 mg with triprolidine hydrochloride 2.5 mg have been studied.[2] Concentrations of pseudoephedrine in milk were consistently higher than in plasma; the half-life in both fluids was between 4.2 and 7.0 hours. Assuming a generous milk secretion of 500 mL over 12 hours it was calculated that the excreted dose was the equivalent of 250 to 330 micrograms of pseudoephedrine base, or 0.5 to 0.7% of the dose ingested by the mothers. Triprolidine did not appear to be concentrated in breast milk. The amounts of pseudoephedrine and triprolidine distributed into breast milk were probably not high enough to warrant cessation of breast feeding.

A small, randomised, crossover study concluded that a single dose of 60 mg pseudoephedrine hydrochloride decreased 24-hour milk production by 24%. The authors of the study suggested that pseudoephedrine might be of benefit for suppressing excess milk production.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/01/07)
2. Findlay JWA, *et al.* Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; **18:** 901–6.
3. Aljazaf K, *et al.* Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breastmilk. *Br J Clin Pharmacol* 2003; **56:** 18–24.

Convulsions. A child who suffered a generalised seizure after ingesting a large quantity of pseudoephedrine hydrochloride tablets was believed to be the first report of convulsions associated with overdose of a preparation containing the drug as a single ingredient.[1]

1. Clark RF, Curry SC. Pseudoephedrine dangers. *Pediatrics* 1990; **85:** 389–90.

Effects on the gastrointestinal tract. Ischaemic colitis has been reported[1-3] after acute or chronic use of pseudoephedrine in combination cold and allergy preparations. In one case[3] the authors suggested that use with tramadol may have contributed to adrenergic vasoconstriction by inhibition of noradrenaline reuptake.

1. Dowd J, *et al.* Ischemic colitis associated with pseudoephedrine: four cases. *Am J Gastroenterol* 1999; **94:** 2430–4.
2. Lichtenstein GR, Yee NS. Ischemic colitis associated with decongestant use. *Ann Intern Med* 2000; **132:** 682.
3. Traino AA, *et al.* Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. *Ann Pharmacother* 2004; **38:** 2068–70.

Effects on mental function. Adverse mental effects (particularly in children) have been associated with combination preparations containing pseudoephedrine.[1-5] See also Abuse, above.

1. Leighton KM. Paranoid psychosis after abuse of Actifed. *BMJ* 1982; **284:** 789–90.
2. Sankey RJ, *et al.* Visual hallucinations in children receiving decongestants. *BMJ* 1984; **288:** 1369.
3. Stokes MA. Visual hallucinations in children receiving decongestants. *BMJ* 1984; **288:** 1540.
4. Roberge RJ, *et al.* Dextromethorphan and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; **17:** 285–8.
5. Soutullo CA, *et al.* Psychosis associated with pseudoephedrine and dextromethorphan. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 1471–2.

Effects on the skin. Recurrent pseudo-scarlatina has been described in a female patient and attributed, on some occasions at least, to ingestion of pseudoephedrine.[1] Further fixed drug eruptions associated with pseudoephedrine have been reported.[2-4] In another woman, an erythematous macular rash developed 5½ hours after an oral challenge with pseudoephedrine 60 mg; other symptoms, which mimicked the effects of toxic shock syndrome, included nausea and vomiting, fever, orthostatic hypotension, light-headedness, fatigue, and desquamation of the skin on her palms and soles.[3] However, considering the frequent use of pseudoephedrine in over-the-counter medications, associated drug eruptions generally appear to be rare.[2]

1. Taylor BJ, Duffill MB. *Br J Dermatol* 1988; **118:** 827–9.
2. Camisa C. Fixed drug reactions to pseudoephedrine hydrochloride. *Br J Dermatol* 1989; **120:** 857–8.
3. Cavanah DK, Ballas ZK. Pseudoephedrine reaction presenting as recurrent toxic shock syndrome. *Ann Intern Med* 1993; **119:** 302–3.
4. Hauken M. Fixed drug eruption and pseudoephedrine. *Ann Intern Med* 1994; **120:** 442.

Paediatric mortality. In response to reports in the USA of overdosages associated with cough and cold medications, the CDC and the National Association of Medical Examiners investigated deaths in infants aged under 12 months associated with such use; 3 cases were identified. All 3 infants had high concentrations of pseudoephedrine in postmortem blood samples, 2 had detectable blood concentrations of dextromethorphan and paracetamol, and 1 was also found to have detectable concentrations of doxylamine. None of the deaths were determined to be intentional. Two infants had evidence of respiratory infection upon autopsy; no cardiac abnormalities were found in any of the infants.[1]

1. CDC. Infant deaths associated with cough and cold medications—two States, 2005. *MMWR* 2007; **56:** 1–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm (accessed 19/04/07)

Pregnancy. During pregnancy taking pseudoephedrine with paracetamol has been suggested to increase the risk of gastroschisis (defective closure of the abdominal wall) in newborns.[1] Although the evidence for this is weak, it is advisable that pseudoephedrine should be avoided during pregnancy because of the severity of the abnormality and the availability of alternatives to pseudoephedrine.

1. Werler MM, *et al.* Maternal medication use and risks of gastroschisis and small intestinal atresia. *Am J Epidemiol* 2002; **155:** 26–31.

Tolerance. In 34 healthy males given pseudoephedrine 120 or 150 mg twice daily for 7 days, as a modified-release preparation, mean plasma concentrations were about 450 or 510 nanograms/mL, respectively. Adverse effects (dry mouth, anorexia, insomnia, anxiety, tension, restlessness, tachycardia, palpitations) were common; there was some evidence of tachyphylaxis.[1]

1. Dickerson J, *et al.* Dose tolerance and pharmacokinetic studies of L(+) pseudoephedrine capsules in man. *Eur J Clin Pharmacol* 1978; **14:** 253–9.

Interactions

As for Ephedrine, p. 1664.2. Pseudoephedrine may cause a hypertensive crisis in patients receiving a MAOI (including a RIMA). For additional warnings see under phenelzine (p. 445.1) and moclobemide (p. 438.1). For mention of a possible interaction between pseudoephedrine and tramadol, see Effects on the Gastrointestinal Tract, above.

Antacids. The absorption rate of pseudoephedrine hydrochloride was increased by *aluminium hydroxide* mixture but

was decreased by *kaolin*; in the latter case adsorption may have competed with absorption.[1]

1. Lucarotti RL, *et al.* Enhanced pseudoephedrine absorption by concurrent administration of aluminium hydroxide gel in humans. *J Pharm Sci* 1972; **61:** 903–5.

Vaccines. A 21-year-old mildly obese man taking pseudoephedrine in an over-the-counter formulation for weight loss collapsed and died with a core temperature of 42.2 degrees while exercising, shortly after inoculation with *Japanese encephalitis vaccine* and *typhoid vaccine*.[1] The combined effects of the pseudoephedrine, activity, and the pyrogenic action of the vaccines appeared to have contributed to failure of the thermoregulatory system.

1. Franklin QJ. Sudden death after typhoid and Japanese encephalitis vaccination in a young male taking pseudoephedrine. *Mil Med* 1999; **164:** 157–9.

Pharmacokinetics

Pseudoephedrine is readily absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine with small amounts of its hepatic metabolite. It has a half-life of about 5 to 8 hours; elimination is enhanced and half-life accordingly shorter in acid urine. Small amounts are distributed into breast milk.

References.

1. Simons FER, *et al.* Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr* 1996; **129:** 729–34.
2. Chester N, *et al.* Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; **57:** 62–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aseptobron Descongestivo; Mex; Qura Plus; ***Austral.***: Chemists Own Sinus Relief; Dimetapp Sinus†; Logicin Sinus; Sudafed Sinus & Nasal Decongestant†; Sudafed†; ***Belg.***: Otrivine Nasa-Tab†; Rinomar†; Vasocedine Pseudoephedrine; ***Canad.***: Benylin D†; Benylin DM-D-E-A Cold and Sinus; Cold and Flu-in-One; Congest Aid†; Decon†; Drixoral ND†; Eltor; Non Drowsy Contac Cold 12 Hour†; Non Drowsy Regular Strength Contac Cold 12 Hour†; Pseudofrin; Sudafed Decongestant; Tantafed; ***Chile***: Dexan; ***China***: Ai Qing (艾清); De Li Tong (德力通); Long Sha (龙沙); Tong Shu (同舒); ***Cz.***: Nurofen Stopgrip; ***Fr.***: Sudafed; ***Hong Kong***: Logicin Sinus; Syncodrin†; Uni-Sufed†; Vicodrine†; Vidadrine†; ***India***: Dolcy; Sudafed; ***Indon.***: Alco; Disudrin; Neo Triaminic; Rhinos Neo; Sudafed†; ***Irl.***: Decongestant; Meltus Decongestant†; Sudafed Non-Drowsy Decongestant; Zirtek Plus; ***Israel***: Afalpi; Kalsinus; Sinufed; Tarophed†; ***Ital.***: Narixan; ***Mex.***: Dofedrin†; Sudafed†; ***NZ***: Sudafed 12 Hour Relief†; Sudafed Sinus & Nasal Decongestant†; Sudomyl; ***Pol.***: Sudafed; ***Port.***: Contact; Sudafed; ***S.Afr.***: Acunaso; Adco-Sufedrin; Adco-Symptofed; Drilix; Drinasal S†; Sinumed; Sudafed Sinus†; ***Singapore***: Contac Non Drowsy; Pseudorine; Sudafed; ***Spain***: Neo Durasina†; Reactine Plus†; ***Switz.***: Otrinol†; ***Turk.***: Dekoferin; Eksofed; Rinogest; Sudafed; ***UAE***: Sedofan II; ***UK***: Contac Non Drowsy; Galpseud; Meltus Decongestant; Non-Drowsy Sudafed Decongestant; ***Ukr.***: Daleron Cold 3 (Далерон Колд 3); ***USA***: Afrin; Allermed; Cenafed†; Childrens Sudafed Nasal Decongestant; Congestaid; Decofed†; DeFed; Dimetapp Decongestant†; Dorcol Children's Decongestant; Drixoral Non-Drowsy Formula†; Efidac 24 Pseudoepehdrine†; ElixSure Childrens Congestion; Genaphed; Halofed; Kid Kare Pediatric Nasal Decongestant; Medi-First Sinus Decongestant†; Mini Pseudo; Nasofed†; PediaCare Infant's Decongestant†; Pseudo-Gest; Pseudo; Seudotabs; Silfedrine†; Simply Stuffy; Sinustop Pro; Sudafed Non-Drowsy; SudoGest Non-Drowsy; Triaminic Allergy Congestion†; Unifed; Zephrex-D.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Pseudoephedrine Oral Solution; Pseudoephedrine Tablets;

USP 36: Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution; Diphenhydramine and Pseudoephedrine Capsules; Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Pseudoephedrine Hydrochloride Extended-Release Capsules; Pseudoephedrine Hydrochloride Extended-release Tablets; Pseudoephedrine Hydrochloride Syrup; Pseudoephedrine Hydrochloride Tablets; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution; Triprolidine and Pseudoephedrine Hydrochlorides Syrup; Triprolidine and Pseudoephedrine Hydrochlorides Tablets.

Senega Root

Észak-amerikai-szenegagyökér; Polígala Raíz; Polygala, racine de; Polygalae Radix; Putokšlių šaknys; Raíz de polígala; Rattlesnake Root; Seneca Snakeroot; Senega; Seneganjuuri; Senegarot; Senegawurzel; Vítodový kořen; Истод Сенега.

ATC — R05CA06.
ATC Vet — QR05CA06.
*ATC Herb — HR05WA5042 (*Polygala senega: *root).*
UNII — M7T6H7D4IF.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Jpn also describes the powdered root.

Ph. Eur. 8: (Senega Root). The dried and usually fragmented root and root crown of *Polygala senega* or certain closely related species of *Polygala* or a mixture of these. It has a faint, sweet odour, slightly rancid or reminiscent of methyl salicylate. Protect from light and humidity.

Profile

Senega root has been used as an expectorant in oral preparations for respiratory-tract disorders.

Polygala amara is a related species that is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Hebert Caramelos; Ixana; Ixana; No-Tos Adultos; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Pectobron; ***Austral.***: Asa Tones†; Nyal Night-Time Cough; Senega and Ammonia; ***Austria***: Eicebaer; Tussimont; ***Belg.***: Saintbois; ***Braz.***: Expectomel; Melagriao; ***Canad.***: Bronchial Cough; Sirop Cocillana Codeine; ***Fr.***: Neo-Codion; NurAiD; ***Hong Kong***: Coci-Fedra-C†; Coci-Fedra†; Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Coolding†; Dextrocilla; Eurocilana; Mist Expect Stim†; ***India***: Elixir Efelin; ***Ital.***: Altuss; ***Port.***: Stodal; ***Rus.***: Neo-Codion Babies (Нео-Кодион Для Младенцев)†; ***S.Afr.***: Borstol Cough Remedy†; ***Singapore***: NeuroAid; ***Spain***: Pastillas Pectorales Kely†; Pulmofasa; ***Swed.***: Cocillana-Etyfin; ***Switz.***: Hederix; Liberol Pastilles contre la toux†; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Pastilles pectorales du Dr. Welti; Pectocalmine N; Pectoral N; Phol-Tux; Siropectan; ***Thai.***: Mist Scill Ammon; Squill and Ammonia; ***UK***: Antibron; Chest Mixture; Chesty Cough Relief; Tickly Cough & Sore Throat Relief; ***Ukr.***: Pectoral (Пекторал); ***Venez.***: Acetoben; Dromil Sauco; Novacodin; Yerba Santa.

Homoeopathic Preparations. ***Austral.***: Respatona Chesty Cough & Nasal Congestion; ***Austria***: Globuli gegen Husten Nr 2; ***Canad.***: L52 Cough & Cold; ***Cz.***: Lehnigrip†; Stodal; ***Fr.***: Boripharm No 11†; Ipeca Complexe No 65; L 52; Stodal; ***Ger.***: Infigripp.

Sobrerol

Ciclidrol; Cyclidrol; Sobreroli; Sobrerolo; Sobrerolum; Соберол.

p-Menth-6-ene-2,8-diol.
$C_{10}H_{18}O_2$=170.3
CAS — 498-71-5.
ATC — R05CB07.
ATC Vet — QR05CB07.
UNII — AI0NX02O35.

Pharmacopoeias. In *It.*

Profile

Sobrerol is a mucolytic that has been used in respiratory disorders characterised by productive cough (p. 1651.2). Oral doses of up to 600 mg have been given daily in divided doses. Sobrerol has also been given by injection, inhalation, or rectally.

Pharmacokinetics. The pharmacokinetics of sobrerol after oral or intravenous doses has been studied in patients with acute exacerbations of chronic bronchitis.[1] Sobrerol was rapidly absorbed from the gastrointestinal tract and rapidly distributed. After intravenous and oral dosage, 13 and 23% of the dose respectively was excreted in the urine as unchanged drug, glucuronidated sobrerol, and hydrated carvone. Sobrerol was shown to accumulate in bronchial mucus.

1. Braga PC, *et al.* Pharmacokinetics of sobrerol in chronic bronchitis: comparison of serum and bronchial mucus levels. *Eur J Clin Pharmacol* 1983; **24:** 209–15.

Respiratory disorders. References.

1. Bellussi L, *et al.* Evaluation of the efficacy and safety of sobrerol granules in patients suffering from chronic rhinosinusitis. *J Int Med Res* 1990; **18:** 454–9.
2. Azzollini E, *et al.* Sobrerol (Sobrepim) administered dropwise to children with acute hypersecretory bronchopulmonary disease: a controlled trial v bromhexine. *Clin Trials J* 1990; **27:** 241–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Sobrepin; ***Hong Kong***: Mucoflux; ***Ital.***: Sobrepin; Sopulmin; ***Malaysia***: Mucoflux; ***Philipp.***: Mucoflux; ***Port.***: Mucodox; Pulmus; ***Singapore***: Mucoflux; ***Spain***: Sobrepin; ***Thai.***: Mucoflux.

Multi-ingredient Preparations. ***Gr.***: Carbozor; Flemagon; Grupozil; Gutman; Mucostein; Pneumol Plus; Polimucil; Respinorm; Sevlenyl; Sobrein; Sorbexyl; Tussifren; Vanesin; ***Ital.***: Fluental; ***Port.***: Bronquial; Niflux.

Sodium Dibunate *(BAN, rINN)*

Dibunate de Sodium; Dibunato de sodio; L-1633; Natrii Dibunas; Натрий Дибунат.

Sodium 2,6-di-*tert*-butylnaphthalene-1-sulphonate.
$C_{18}H_{23}NaO_3S$=342.4
CAS — 14992-59-7 (sodium dibunate).
ATC — R05DB16.
ATC Vet — QR05DB16.
UNII — FRS4SO3K8D.

Profile

Sodium dibunate is a cough suppressant given orally and rectally in non-productive cough. It is claimed to have central and peripheral actions. Chlorcyclizine dibunate (naftoclizine) has also been given similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Dibunafon; ***Port.***: Becantex.

Multi-ingredient Preparations. ***Braz.***: Beclase†; ***Ger.***: Ephepect-Blocker-Pastillen N; ***Hong Kong***: Ephepect Blocker; ***Mex.***: Broend; Neo-Brontyl†; ***Ukr.***: Bronchobru (Бронхобрю).

Squill

Bulbo de Escila; Cebolla Albarrana; Cila; Escila; Meerzwiebel; Scilla; Scillae bulbus; Scille; Scille, bulbe de; White Squill; Морской Лук.

Pharmacopoeias. In *Br.* and *Ger.*

BP 2014: (Squill). The dried sliced bulb of *Drimia maritima* with the membranous outer scales removed, and containing not less than 68% of alcohol (60%)-soluble extractive. Store at a temperature not exceeding 25 degrees in a dry place.

Indian Squill

Escila India; Urginea; Морской Лук Индийский.

*ATC Herb — HR05WA5006 (*Drimia maritima: *bulb); HG04BW5009 (*Drimia maritima: *bulb); HC01AB5001 (*Drimia maritima: *bulb).*

Pharmacopoeias. In *Br.*

BP 2014: (Indian Squill). The bulb of *Drimia indica*, with the outer membranous scales removed, usually sliced and dried. Store at a temperature not exceeding 25 degrees in a dry place.

Uses and Administration

Squill and Indian squill are used as expectorants in productive cough and have been given as the oxymel, elixir, tincture, or vinegar. Preparations containing squill are used in some countries in the treatment of cardiovascular disorders.

Red squill has been used as a rodenticide (p. 2161.2).

The historical use of squill has been reviewed.[1]

1. Aliotta G, *et al.* The diuretic use of Scilla from Dioscorides to the end of the 18th century. *J Nephrol* 2004; **17:** 342–7.

Adverse Effects, Treatment, and Precautions

The adverse effects of squill and Indian squill in large doses include nausea, vomiting, and diarrhoea. As squill and Indian squill contain cardiac glycosides they can cause similar adverse effects to digoxin (p. 1354.3).

Abuse. Reports of cardiac glycoside toxicity and myopathy associated with the abuse of linctuses that have contained opiates and squill.[1-5]

1. Kennedy M. Cardiac glycoside toxicity: an unusual manifestation of drug addiction. *Med J Aust* 1981; **2:** 686–9.
2. Kilpatrick C, *et al.* Myopathy with myasthenic features possibly induced by codeine linctus. *Med J Aust* 1982; **2:** 410.
3. Seow SSW. Abuse of APF linctus codeine and cardiac glycoside toxicity. *Med J Aust* 1984; **140:** 54.
4. Thurston D, Taylor K. Gee's Linctus. *Pharm J* 1984; **233:** 63.
5. Smith W, *et al.* Wenckebach's phenomenon induced by cough linctus. *BMJ* 1986; **292:** 868.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Ixana; ***Austral.***: Nyal Night-Time Cough; ***Canad.***: Bronco Asmol†; Herbal Cough Syrup†; Sirop Cocillana Codeine; ***Ger.***: Miroton†; ***Hong Kong***: Coci-Fedra-C†; Coci-Fedra†; Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Compound Cocillana†; Coolding†; Dextrocilla; Ephecol†; Eurocilana; Fritussin†; Mist Expect Stim†; ***Mex.***: Verisan Triplex; ***S.Afr.***: Adco-Cocillana Co; Contra-Coff†; Linctus Tussi Infans†; ***Thai.***: Mist Scill Ammon; Squill and Ammonia; ***UK***: Allens Chesty Cough; Allens Pine & Honey; Balm of Gilead†; Buttercup Syrup; Chest Mixture; Covonia Herbal Mucus Cough Syrup; Covonia Mentholated; Galloway's Cough Syrup; Honey & Molasses; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Potters Gees Linctus; Quitacoff; Sanderson's Throat Specific; Sanderson's Throat Specific.

Homoeopathic Preparations. ***Austria***: Homviocorin; ***Canad.***: Husteel†; Valerianaheel Comp†; ***Cz.***: Husteel; ***Ger.***: Confludin N; Cor-loges; Corvipas SL; Lowe-Komplex Nr 13; Lymphdiaral; Truw Gold; Uroselect; ***Hung.***: Husteel; ***Neth.***: Asthmakhell†; Husteel; ***Ukr.***: Homviocorin-N (Хомвиокорин-N).

Pharmacopoeial Preparations
BP 2014: Squill Liquid Extract; Squill Oxymel.

Sulfogaiacol *(rINN)*

Kalii Sulfoguajacolas; Kalium Guajacolsulfonicum; Kaliumsulfoguajakolaatti; Kaliumsulfoguajakolat; Potassium Guaiacolsulfonate; Potassium Guaiacolsulphonate; Sulfogaïacol; Sulfogaiacolum; Sulfoguayacol; Sulfogwajakol; Thiocol; Tiocol; Сульфогайякол.

Potassium hydroxymethoxybenzenesulphonate hemihydrate.

$C_7H_7KO_5S,½H_2O$=251.3

CAS — 1321-14-8 (anhydrous sulfogaiacol); 78247-49-1 (sulfogaiacol hemihydrate).

ATC — R05CA09.

ATC Vet — QR05CA09.

UNII — 713AJ00NPG (sulfogaiacol); TTK33Z47F1 (sulfogaiacol hemihydrate).

Pharmacopoeias. In *Pol.* and *US.* Also in *Fr.* and *Jpn*, both of which do not specify the hemihydrate.

USP 36: (Potassium Guaiacolsulfonate). Protect from light.

Profile

Sulfogaiacol is used as an expectorant for productive cough. Calcium guaiacolsulfonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pectoral Lafedar Ninos; ***Austria***: Pectosorin†; ***China***: Kang Yu Deng Tong (康裕登通); ***Israel***: Guaiacol; ***Ital.***: Tioguialina; ***Mex.***: Broncoserum; ***Pol.***: Apitussic; Diabetussic.

Multi-ingredient Preparations. ***Arg.***: Medex Rub; No-Tos Infantil; No-Tos Infantil; Pastillas De Ambay; Pectobron; Pectoral Lafedar; ***Austria***: Pneumopan†; ***Belg.***: Broncho-pectoralis Pholcodine; Eucalytux; Pholco-Mereprine; Saintbois; ***Braz.***: Broncatar; Expectil; Fenergan Expectorante; Iodetal; Trifedrin; ***China***: Ke Li An (克立安); Norpin A (纳尔平); Xin Tai Luo Qi (新泰洛其); ***Fr.***: Camphodionyl†; Ephydion†; Neo-Codion; Passedyl; Pneumaseptic†; ***Hong Kong***: Chrisracol; Ephecol†; ***Hung.***: Erigon; ***India***: Pulm-Cod (C & G); ***Indon.***: Benacol DTM; Benacol Expectorant; Febrinex; Phenacold; Phenadex; Prome; Promethazine Ikapharmindo; Sanadryl; ***Israel***: Cod-Guaiacol; Oxacatin; Pertussol; Promethazine Expectorants; To-Care; Tucare; Tussophedrine NF; ***Ital.***: Balsamina Kroner; Bronchenolo; Bronchiase; Donalg; Guaiacalcium Complex; Polised; Sciroppo Berta; Stenobronchial; Tauglicolo; Tiocalmina; Tiocosol†; ***Mex.***: Eucaliptine†; Exofil; Oxin; Pulmovital; ***Philipp.***: Cofrel; ***Pol.***: Apipulmol; Gwajatussin; Herbapect; Pastylki Wykrztusne; Thiocodin; ***Port.***: Codol; ***Rus.***: Neo-Codion (Нео-Кодион)†; ***Spain***: Bronco Medical; Broncovir; Brota Rectal Balsamico†; Fenergan Expectorante; Pastillas Pectorales Kely†; Pazbronquial; Pulmofasa; ***Switz.***: Neo-Codion N; Phol-Tux; ***Thai.***: Bisolvon EX; Bromso-Ex; Dutross-P; Hustazol-C; ***Turk.***: Antibeksin; Artu; Fenokodin†; Gayabeksin; Gayaben; Latusin†; Pektodin†; Seskadeks; ***Ukr.***: Tos-Mai (Тос-Май); ***USA***: Cypex; De-Chlor NX†; Entuss Expectorant; Humibid DM; Humibid; Hy-KXP†; Hydron EX†; Hydron KGS†; KGS-PE; Lemotussin-DM; Marcof†; Prolex DM†; Prolex DMX†.

Talniflumate *(USAN, rINN)*

BA-7602-06; Talniflumato; Talniflumatum; Тальнифлумат.

Phthalidyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.

$C_{21}H_{13}F_3N_2O_4$=414.3

CAS — 66898-62-2.

UNII — JFK78S0U9S.

NOTE. The name Lomucin has been used as a trade mark for talniflumate.

Profile

Talniflumate inhibits the human calcium-activated chloride channel protein hCLCA1, which is overexpressed in the lungs of patients with certain pulmonary diseases associated with excessive or abnormal mucus production. Talniflumate has been investigated for the management of cystic fibrosis, chronic obstructive pulmonary disease, and asthma. Talniflumate has also been used to treat inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Somalgen.

Telmesteine *(rINN)*

Telmesteína; Telmestéine; Telmesteinum; Тельместеин.

(-)-3-Ethyl hydrogen (*R*)-3,4-thiazolidinedicarboxylate.

$C_7H_{11}NO_4S$=205.2

CAS — 122946-43-4.

UNII — 124I3FE35T.

Profile

Telmesteine has been used as a mucolytic in the treatment of respiratory-tract disorders including cough (p. 1651.2) in oral doses of 300 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Reolase.

Multi-ingredient Preparations. ***Austral.***: Atopiclair†; ***Indon.***: Atopiclair; ***Israel***: Atopiclair; Xclair; ***Singapore***: Atopiclair; ***UK***: Atopiclair; Xclair; ***USA***: Atopiclair.

Terpin Hydrate *(BANM)*

Terpene Hydrate; Terpiinihydraatti; Terpina, hidrato de; Terpinhydrat; Terpini Hydras; Terpinol; Терпингидрат.

p-Menthane-1,8-diol monohydrate; 4-Hydroxy-α,α,4-trimethylcyclohexanemethanol monohydrate.

$C_{10}H_{20}O_2,H_2O$=190.3

CAS — 80-53-5 (anhydrous terpin); 2451-01-6 (terpin monohydrate).

UNII — S3V868548T.

Pharmacopoeias. In *Fr., Swiss, US,* and *Viet.*

USP 36: (Terpin Hydrate). Colourless lustrous crystals or white powder with a slight odour. It effloresces in dry air. Soluble 1 in 200 of water, 1 in 35 of boiling water, 1 in 13 of alcohol, 1 in 3 of boiling alcohol, and 1 in 140 of chloroform and of ether. A hot 1% solution is neutral to litmus. Store in airtight containers.

Stability. If crystals form in terpin hydrate elixir, they may be redissolved by warming the closed container of solution in warm water and then gently shaking it.

Profile

Terpin hydrate has been stated to increase bronchial secretion directly and has been given orally as an expectorant in productive cough.

Nausea, vomiting, or abdominal pain may follow the ingestion of terpin hydrate on an empty stomach.

Terpin hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Alma; ***India***: Haffkinol.

Multi-ingredient Preparations. ***Arg.***: Aseptobron; ***Braz.***: Ozonyl; Tetrapulmo†; ***Chile***: Broncodeina; ***Cz.***: Coldrex; ***Fin.***: Toclase Expectorant†; ***Fr.***: Bronchorectine au Citral; Euphonyl Expectorant; Pulmofluide Simple; Pulmoll†; Terpine Gonnon; Terpone; Thiopectol; ***Hong Kong***: Chrisracol; Codoplex; Coldcap-A; Coldtab-2; Panadol Cold & Flu Day; Panadol Cold & Flu Extra; Panadol Cold & Flu; ***Hung.***: Coldrex; ***India***: Benakof; Cadistin Exp; Glycodin; ***Ital.***: Elisir Terpina; Neo Borocillina Balsamica; ***Neth.***: Balsoclase Compositum†; ***Pol.***: Coldrex MaxGrip C; ***Rus.***: Alex Plus (Алекс Плюс); Coldrex (Колдрекс); Flucoldex Forte (Флюколдекс Форте); Glycodin (Гликодин); Tedein (Тедеин); Tercodin (Теркодин); Terpincod (Терпинкод); ***Spain***: Pastillas Pectorales Kely†; Terponil†; ***Switz.***: Bromocod N†; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; ***Thai.***: Antust; Codee-C; Cophartussin; CPM; D-Coate; Decofsin; Dexpin; Dextro Compound; Dextro; Dextussin; Dimophen; Fartussin; Glycoff; Icolid DX; Methopine; Mila-Tercon†; Muco-DX†; Rocal; Seco; Sinfussi; Stocof; Stocol; Terco-C; Terco-D; Terracol-A; Tusspac; ***Turk.***: Tusifon; ***UK***: Original Cabdrivers Expectorant; ***Ukr.***: Alex Plus (Алекс Плюс)†; Coldrex (Колдрекс); Glycodin (Глікодин).

Pharmacopoeial Preparations
USP 36: Terpin Hydrate and Codeine Elixir; Terpin Hydrate Elixir.

Tetryzoline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tetrahidrozolina; Hidrocloruro de tetrizolina; Tetrahydrozoline Hydrochloride; Tetrazolin Hidroklorür; Tetrizolina, hidrocloruro de; Tetrizolino hidrochloridas; Tetrytsoliinihydrokloridi; Tétryzoline, Chlorhydrate de; Tetryzolin-hydrochlorid; Tetryzolinhydrochlorid; Tetryzolinhydroklorid; Tetryzolini Hydrochloridum; Тетризолина Гидрохлорид.

2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-imidazoline hydrochloride.

$C_{13}H_{16}N_2,HCl$=236.7

CAS — 84-22-0 (tetryzoline); 522-48-5 (tetryzoline hydrochloride).

ATC — R01AA06; R01AB03; S01GA02.

ATC Vet — QR01AA06; QR01AB03; QS01GA02.

UNII — 0YZT43HS7D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tetryzoline Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dehydrated alcohol; practically insoluble in acetone.

USP 36: (Tetrahydrozoline Hydrochloride). A white odourless solid. Soluble 1 in 3.5 of water and 1 in 7.5 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Store in airtight containers.

Profile

Tetryzoline is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3). It is used as the hydrochloride for its vasoconstrictor effect in the symptomatic relief of nasal congestion (p. 1652.1). A 0.1% solution is instilled into each nostril as nasal drops or a spray as necessary, although not more often than every 3 hours. A lower strength solution of 0.05% is also available.

Solutions of tetryzoline hydrochloride containing 0.05% have been used as a conjunctival decongestant (see Conjunctivitis, p. 611.1).

Other salts of tetryzoline including the nitrate, phosphate, and sulfate have been used similarly.

Abuse. Tetryzoline ophthalmic solution 0.05% has been given orally in drug facilitated sexual assault to obtain an obtunded flaccid victim who is unable to resist or recall events.[1]

1. Spiller HA, *et al.* Drug facilitated sexual assault using an over-the-counter ocular solution containing tetrahydrozoline (Visine). *Leg Med (Tokyo)* 2007; **9:** 192–5.

Effects on the eyes. For mention of conjunctivitis induced by ophthalmic decongestant preparations containing tetryzoline, see under Phenylephrine, p. 1673.2.

Poisoning. A 17-year-old girl who ingested about 10 to 15 mL of a 0.05% solution of tetryzoline by mistake developed lethargy, slowed speech and ataxia.[1] She also complained of dizziness, headache, and sinus congestion. Drowsiness, bradycardia, and orthostatic hypotension were apparent up to 36 hours post-ingestion.

1. Spiller H, Griffith J. Prolonged cardiovascular effects after unintentional ingestion of tetrahydrozoline. *Clin Toxicol* 2008; **46:** 171–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bano Ocular; Chiosan; Irix; Ocudiafan; Piam; Visubril; ***Austral.***: Murine Sore Eyes; Visine Clear; ***Belg.***: Visine; ***Canad.***: Eye Drops; Original Eye Drops; Visine Original; ***Chile***: Visine; Visional Gotas; ***Cz.***: Rhinal†; Vasopos N; Visine; ***Denm.***: Visine Visiclear; ***Fin.***: Oftan Starine; Visclear; ***Ger.***: Ophtalmin N; Tetrilin; Vasopos N; Visine Yxin; ***Gr.***: Octilia; Ursa-Fin; Visine; Vispring; ***Hong Kong***: Murine Plus†; Optizoline; Visine Original†; ***Hung.***: Tyzine†; Visine; ***India***: Visine†; ***Indon.***: Braito†; Insto; Isotic Clearin†; Santo; Visine; Visolin†; Visto; ***Israel***: Azoline; Eye Relief; Stilla; V-

Zoline; View; Visine; ***Ital.***: Demetil; Eyedec; Octilia; Stilla Decongestionante; Stilla Unidose; Vasorinil; ***Jpn***: Narbel; ***Malaysia***: Allersine; Visine†; ***Mex.***: Eye-Mo; Tetrazol; ***NZ***: Visine; ***Philipp.***: Eye-Mo; Sinutab NS; Visine Advanced Relief†; Visine Cool†; Visine; Visol; ***Pol.***: Berberil; Starazolin; Tetryvil†; Visine; ***Port.***: Visine; ***Rus.***: Montevizin (Монтевизин); Octilia (Октилия); Tyzine (Тизин); Visine (Визин); Vizoptik (Визоптик); ***S.Afr.***: Visine; ***Singapore***: Optizoline; ***Spain***: Azulina; Vispring; ***Switz.***: Rhinopront Top†; Visine; ***Thai.***: Visine†; ***Turk.***: Burnil; Eye-Visol; Visine; Zenkain†; ***Ukr.***: Tyzine (Тизин); Vial (Виаль); Visine (Визин); ***USA***: Eye Drops; Eye-Zine; Optigene 3; Tyzine; Visine Original.

Multi-ingredient Preparations. ***Arg.***: Antiflogol; Efemolina; Larsimal; Provisual Compuesto; Toflam Plus; Visine Plus; ***Austral.***: Visine Advanced Relief; ***Braz.***: Fenidex; Mirabel; Vislin; Visodin; ***Canad.***: Allergy Eye Drops; Clear Eyes Triple; Visine Advance Triple Action; Visine Allergy; Visine Cool; ***Chile***: Spersallerg; ***Cz.***: Spersallerg; ***Ger.***: Allergopos N†; Berberil N; Efemolin†; Spersallerg†; ***Gr.***: Efemoline; Spersadexoline; Spersallerg; ***Hong Kong***: Efemoline; Murine Plus Natural†; Spersallerg; Visine AC†; Visine Moisturizing†; ***Hung.***: Spersallerg; ***India***: Optihist-Plus; ***Indon.***: Visine Extra; ***Israel***: Visine AC; ***Ital.***: Biorinil; Cromozil; Efemoline; Eta Biocortilen VC; Flumezina; Ischemol A; Stillergy; Tetramil; Visublefarite; Visucloben Decongestionante; Visumetazone Antibiotico; Visumetazone Decongestionante; Visustrin; ***Malaysia***: Gentadexa; Spersadexoline†; Spersallerg; ***Mex.***: Fluorometil; Visine Extra; ***Norw.***: Spersallerg; ***NZ***: Visine Advanced Relief; ***Philipp.***: Efemoline; Spersallerg; ***Pol.***: Spersallerg; ***Port.***: Gentadexa; ***Rus.***: Spersallerg (Сперсаллерг); ***S.Afr.***: Efemoline; Gemini; Oculerge; Spersadexoline†; Spersallerg; ***Singapore***: Efemoline; Murine Plus; Spersadexoline; Spersallerg; ***Spain***: Fluorvas; Gentadexa; Medrivas Antib; Medrivas; Tivitis†; Vasodexa; ***Switz.***: Collypan; Efemoline; Spersallerg; ***Thai.***: Allergis; Antazallerge; CD-Oph; Efemoline; Histaoph; Mano; Opsil-A; Spersadexoline†; Spersallerg; ***Turk.***: Efemoline; Flumetol†; ***USA***: Advanced Relief Visine; Geneye AC Allergy†; Murine Plus; Visine Maximum Redness Relief; Visine Totality Multi-Symptom Relief; ***Venez.***: Gentidexa.

Pharmacopoeial Preparations
USP 36: Tetrahydrozoline Hydrochloride Nasal Solution; Tetrahydrozoline Hydrochloride Ophthalmic Solution.

Thebacon Hydrochloride *(BANM, rINNM)*

Acethydrocodone Hydrochloride; Acetyldihydrocodeinone Hydrochloride; Dihydrocodeinone Enol Acetate Hydrochloride; Hidrocloruro de tebacón; Tebacón, hidrocloruro de; Thébacone, Chlorhydrate de; Thebaconi Hydrochloridum; Тебакона Гидрохлорид.

6-*O*-Acetyl-7,8-dihydro-3-*O*-methyl-6,7-didehydromorphine hydrochloride; (-)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphin-6-en-6-yl acetate hydrochloride.

$C_{20}H_{23}NO_4$,HCl=377.9

CAS — 466-90-0 (thebacon); 20236-82-2 (thebacon hydrochloride).

ATC — R05DA10.

ATC Vet — QR05DA10.

Profile

Thebacon hydrochloride is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It has actions similar to those of codeine (p. 40.2) but is stated to be about 4 times more potent. It is given orally in a usual daily dose of 10 mg in divided doses; the maximum daily dose should not exceed 20 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Acediconе†.

Tipepidine Hibenzate *(rINNM)*

AT-327 (tipepidine); CR-662 (tipepidine); Hibenzato de tipepidina; Tipepidina, hibenzato de; Tipépidine, Hibenzate de; Tipepidine Hybenzate; Tipepidini Hibenzas; Типепидина Гибензат.

3-[Di(2-thienyl)methylene]-1-methylpiperidine 2-(4-hydroxybenzoyl)benzoate.

$C_{15}H_{17}NS_2$,$C_{14}H_{10}O_4$=517.7

CAS — 5169-78-8 (tipepidine); 31139-87-4 (tipepidine hibenzate).

ATC — R05DB24.

ATC Vet — QR05DB24.

UNII — 78578GFU8W.

Pharmacopoeias. In *Jpn.*

Profile

Tipepidine hibenzate is a cough suppressant used for non-productive cough (p. 1651.2) which is claimed also to have an expectorant action. It is given orally as the hibenzate but doses are expressed as the citrate; tipepidine hibenzate 22.2 mg is equivalent to about 20 mg of tipepidine citrate. A usual dose is the equivalent of 20 to 40 mg of the citrate 3 times daily.

Epileptogenic effect. Generalised convulsions associated with therapeutic oral doses of tipepidine hibenzate have occurred in some patients.[1]

1. Cuomo RM. On the possible convulsive activity of an antitussive piperidinic derivative ('tipepidina ibenzato') in man. *Acta Neurol (Napoli)* 1982; **37:** 110–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Asverin†; ***Indon.***: Asvex; ***Jpn***: Asverin.

Multi-ingredient Preparations. ***Arg.***: Di-Neumobron; ***Indon.***: Neo Novapon Plus; Neo Novapon; ***Jpn***: Sin Colgen Kowa Kaze†.

Tolu Balsam

Bálsamo de Tolú; Balsamum Tolutanum; Baume de Tolu; Tolu balzamas; Toluánský balzám; Tolubalsam; Tolubalzsam; Tolupalsami; Толуанский Бальзам.

CAS — 9000-64-0; 8017-09-2.

*ATC Herb — HR05WA5031 (*Myroxylon balsamum *var.* balsamum*: balsam).*

UNII — TD2LE91MBE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tolu Balsam). Oleoresin obtained from the trunk of *Myroxylon balsamum* var. *balsamum*. It contains 25 to 50% of free or combined acids, expressed as cinnamic acid, calculated with reference to the dried drug. It occurs as a hard, friable, brownish to reddish-brown mass; thin fragments are brownish-yellow when examined against the light. It has an odour reminiscent of vanillin. Practically insoluble in water and in petroleum spirit; very soluble or freely soluble in alcohol. Do not store in powdered form.

USP 36: (Tolu Balsam). A balsam obtained from *Myroxylon balsamum* (Leguminosae). It is a brown or yellowish-brown plastic solid transparent in thin layers and brittle when old, dried, or exposed to cold temperatures. It has a pleasant aromatic odour, resembling that of vanilla. Practically insoluble in water and in petroleum spirit; soluble in alcohol, in chloroform, and in ether, sometimes with slight residue or turbidity. Store at a temperature not exceeding 40 degrees in airtight containers.

Profile

Tolu balsam is considered to have very mild antiseptic properties and some expectorant action but is mainly used in the form of a syrup to flavour cough mixtures. However, Tolu Syrup (BP 2014) is based on cinnamic acid (p. 1748.3) and no longer contains tolu balsam.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: No-Tos Adultos; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Pastillas Medex; Pastillas Pagliano; Pectobron; Refenax Caramelos Expectorantes; ***Austral.***: Camphor Linctus Compound; ***Belg.***: Saintbois; ***Braz.***: Expectomel; Frenotosse; Glycon; Inhalante Yatropan; Iodetal; Melagriao; Vick Pastilhas†; ***Canad.***: Bronco Asmol†; ***Chile***: Elitos ET; Fitotos; Flemex Jat; Jarabe Palto Compuesto con Miel Adulto; Pulmosina; ***Fr.***: Broncalene Nourisson†; Dinacode avec codeine; Hexapneumine†; Pastilles Medicinales Vicks; Pastilles Monleon†; Phytotux; Pulmosodyl; Terpine Gonnon; Thiopectol; Tussipax; ***Hong Kong***: Baby Cough with Antihistamine†; Hexapneumine†; ***India***: Cadistin Exp; ***Ital.***: Stenobronchial; ***Mex.***: Citos; Fen-y-Tos; ***Port.***: Broncodiazina†; Stodal; ***Rus.***: Solutan (Солутан)†; ***S.Afr.***: Choats Extract of Lettuce Cough Mixture†; Linctus Tussi Infans†; Puma Cough Balsam†; Turulington Tincture†; ***Spain***: Bactopumon; Bronquidiazina CR; Pulmofasa; ***Switz.***: Baume Zeller; DemoPectol; Neo-Codion N; Phol-Tussil; Pommade au Baume; Rotpunkt Apotheke pastilles pour les bronches avec codeine; Sano Tuss; Siropectan; ***Thai.***: Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; ***UK***: Allens Chesty Cough; Chesty Cough Relief; Modern Herbals Cold & Congestion; Sanderson's Throat Specific; ***Ukr.***: Bronchial Balsam Bells (Бронхиальный Бальзам Беллс); ***USA***: Tonsiline; Vicks Menthol Cough Drops; ***Venez.***: Yerba Santa.

Homoeopathic Preparations. ***Cz.***: Stodal; ***Fr.***: Stodal.

Pharmacopoeial Preparations
BPC 1954: Compound Iodoform Paint;
USNF 31: Tolu Balsam Syrup; Tolu Balsam Tincture;
USP 36: Compound Benzoin Tincture.

Tramazoline Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de tramazolina; Tramazolina, hidrocloruro de; Tramazoline, Chlorhydrate de; Tramazolin-hidroklorid; Tramazolin-hydrochlorid; Tramazolini hydrochloridum; Tramazolino hidrochloridas; Tramazoliny chlorowodorek; Трамазолина Гидрохлорид.

2-(5,6,7,8-Tetrahydro-1-naphthylamino)-2-imidazoline hydrochloride monohydrate.

$C_{13}H_{17}N_3$,HCl,H_2O=269.8

CAS — 1082-57-1 (tramazoline); 3715-90-0 (tramazoline hydrochloride).

ATC — R01AA09.

ATC Vet — QR01AA09.

UNII — 4DG710Q678.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tramazoline Hydrochloride Monohydrate). A white or almost white crystalline powder. Soluble in water and in alcohol. A 5% solution in water has a pH of 4.9 to 6.3.

Profile

Tramazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3). It is used to provide symptomatic relief of nasal congestion (p. 1652.1). Tramazoline hydrochloride is given as a solution containing about 0.12%, instilled into each nostril as nasal drops or a spray three or four times daily.

Solutions of tramazoline hydrochloride containing about 0.06% have also been used in eye drops as a conjunctival decongestant (see Conjunctivitis, p. 611.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Spray-Tish; ***Belg.***: Rhinospray; ***Cz.***: Muconasal Plus; ***Ger.***: Biciron; Ellatun; Rhinospray; ***Ital.***: Rinogutt; ***Neth.***: Bisolnasal; ***Port.***: Rhinospray; ***Rus.***: Rhinosprey (Риносprей); ***Spain***: Rhinospray Eucaliptus; Rhinospray.

Multi-ingredient Preparations. ***Arg.***: Dexa-Rhinospray N; ***Austral.***: Spray-Tish Menthol; ***Austria***: Rhinospray Plus; ***Belg.***: Dexa-Rhinospray; ***Ger.***: Dexa Biciron; Rhinospray Plus; ***Gr.***: Dexa-Rhinaspray-N; Dexa-Rhinaspray; ***Hung.***: Rhinospray Plus; ***Irl.***: Dexa-Rhinaspray Duo†; ***Ital.***: Rinogutt Antiallergico Spray; Rinogutt; ***Neth.***: Rhinospray met eucalyptus; ***Rus.***: Adrianol (Адрианол); ***Spain***: Rhinospray Antialergico.

Tuaminoheptane Sulfate *(BANM, rINNM)* ⊗

Sulfato de tuaminoheptano; Tuaminoheptane, Sulfate de; Tuaminoheptane Sulphate; Tuaminoheptani Sulfas; Tuaminoheptano, sulfato de; Туаминогептана Сульфат.

$(C_7H_{17}N)_2$,H_2SO_4=328.5

CAS — 6411-75-2.

ATC — R01AA11; R01AB08.

ATC Vet — QR01AA11; QR01AB08.

UNII — WZK5LN5CNW.

Profile

Tuaminoheptane is a volatile sympathomimetic (p. 1507.3) that has been used as the sulfate for the symptomatic relief of nasal congestion. Tuaminoheptane has also been used in the form of the carbonate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Rinofluimucil; ***Fr.***: Rhinofluimucil; ***Hong Kong***: Rinofluimucil†; ***Hung.***: Rinofluimucil; ***Ital.***: Rinofluimucil; ***Port.***: Rinofluimucil; ***Rus.***: Rinofluimucil (Ринофлуимуцил); ***Spain***: Rinofluimil; ***Switz.***: Rinofluimucil; ***Thai.***: Rinofluimucil; ***Ukr.***: Rinofluimucil (Ринофлуимуцил).

Tymazoline Hydrochloride *(BANM)* ⊗

2-Thymyloxymethyl-2-imidazoline Hydrochloride; Timazolina, hidrocloruro de; Tymazolini Hydrochloridum; Tymazoliny chlorowodorek; Тимазолина Гидрохлорид.

2-(2-Isopropyl-5-methylphenoxymethyl)-2-imidazoline hydrochloride.

$C_{14}H_{20}N_2O$,HCl=268.8

CAS — 24243-97-8 (tymazoline); 28120-03-8 (tymazoline hydrochloride).

ATC — R01AA13.

ATC Vet — QR01AA13.

Pharmacopoeias. In *Pol.*

Profile

Tymazoline is a sympathomimetic that has been used as the hydrochloride similarly to naphazoline (p. 1669.3) for its local vasoconstrictor effect in the symptomatic relief of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Thymazen†; ***Thai.***: Pernazene†.

Xylometazoline Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de xilometazolina; Ksilometazolin Hidroklorür; Ksilornetazolino hidrochloridas; Ksylometatsoliinihydroklori-idi; Ksylometazoliny chlorowodorek; Xilometazolina, hidrocloruro de; Xilometazolinhidroklorid; Xylométazoline, chlorhydrate de; Xylometazolinhydro; Xylometazolinhydrochlorid; Xylometazolinhydrochlorid; Xylometazolini Hydrochloridum; Ксилометазолина Гидрохлорид.

2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-2-imidazoline hydrochloride.

$C_{16}H_{24}N_2$,HCl=280.8

CAS — 526-36-3 (xylometazoline); 1218-35-5 (xylometazoline hydrochloride).

ATC — R01AA07; R01AB06; S01GA03.

ATC Vet — QR01AA07; QR01AB06; QS01GA03.

UNII — X5S84033NZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Xylometazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

USP 36: (Xylometazoline Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 35 of water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether and in benzene. pH of a 5% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Uses and Administration

Xylometazoline is a direct-acting sympathomimetic (p. 1507.3) with marked alpha-adrenergic activity. It is a vasoconstrictor which reduces swelling and congestion when applied to mucous membranes. The effect begins within 5 to 10 minutes of application and lasts for up to 10 hours.

Xylometazoline is used as the hydrochloride for the short-term symptomatic relief of nasal congestion (p. 1652.1). A 0.1% solution of xylometazoline hydrochloride is applied topically as nasal drops or a spray into each nostril two or three times daily. For doses in children, see below.

Xylometazoline hydrochloride solution is instilled into the eye as a conjunctival decongestant (see Conjunctivitis, p. 611.1). Preparations containing 0.05% xylometazoline hydrochloride with 0.5% antazoline sulfate are typical; 0.1% xylometazoline hydrochloride has also been used.

Administration in children. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including xylometazoline) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2. The *BNFC* suggests that xylometazoline nasal drops may be used in children aged 6 to 12 years for the short-term treatment of severe nasal congestion which has not responded to sodium chloride nasal drops or inhalation of warm moist air. A 0.05% solution of xylometazoline hydrochloride is licensed for such use; 1 or 2 drops are instilled into each nostril once or twice daily, for a maximum of 5 days.

Adverse Effects, Treatment, and Precautions

As for Naphazoline, p. 1669.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies xylometazoline for nasal use as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/10/11)

Interactions

Since xylometazoline is absorbed through the mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p. 1508.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nastizol; Otrivina; ***Austral.***: Otrivin; ***Austria***: Otrivin; RatioSoft; Xylo-COMOD; ***Belg.***: Nasa Rhinathiol; Nasasinutab; Nuso-San; Otrivine Anti-Rhinitis; ***Braz.***: Otrivina; ***Canad.***: Balminil Decongest; Balminil Nasal Decongestant; Certified Decongestant†; Cold and Allergy Decongestant†; Decongest; Decongestant Nasal Spray; Decongestant Nose Drops; Nasal Decongestant; Otrivin; Vaporisateur Nasal Decongestionnant; ***China***: TianCheng Nuo Er (天诚诺尔); ***Cz.***: Mar Rhino; Nasenspray AL; Nasentropfen AL†; Olynth; Otrivin; Rhino-Stas; Rinoxyl; Snup; Xylo-COMOD; Xylorin; ***Denm.***: Klarigen; Noxorin; Otrivin; Passagen†; Zymelin; ***Fin.***: Naso-Ratiopharm; Nasolin; Otrivin; ***Ger.***: Balkis†; Gelonasal; Hysan Schnupfenspray; Nasaltropfen axcount†; Nasengel AL; Nasengel; Nasenspray AL†; Nasenspray E†; Nasenspray K†; Nasenspray; Nasentropfen AL†; Nasentropfen Stada†; Nasentropfen-ratiopharm; Olynth; Otriven gegen Schnupfen†; Otriven†; Rapako xylo; schnupfen endrine; Siozwo; Snup; Tussamag Nasenspray†; Xylo-COMOD†; Xylo-POS†; ***Gr.***: Otrivin-Menthol; Otrivin; Silphin; ***Hong Kong***: Decongestant Nasal Spray; Otrivin; Xyloma; ***Hung.***: Nasan; Novorin; Otrivin; Rhinathiol; Rhino-Stas†; ***India***: Acolate DPS; Atrovin; Biomist; Birvine; Broflex; Caxyl; Cyfer; Decon; Diconal; Goair; Hynasal-XL; Loxzol; Mucoris; Nam Cold Nasal; Naso Wikoryl; Nasomet; Nasrea; Nazalin†; Nazle; Nazolin; Nomocon; Nos-Air; Nozin; Nozy; Opun; Ortinase; Ortinose; Otrinoz; Otrivin; ***Indon.***: Otrivin; ***Irl.***: Otrivine; Sudafed Non-Drowsy Decongestant; ***Israel***: Af-Care; Nazalet; Otrivin; Xylo-POS; Xylovit; ***Ital.***: Argotone Dec; Neo Rinoleina; Otrivin; ***Malaysia***: Otrivin; ***Neth.***: Kruidvat Neusdruppels†; Meralys; Mucorhinyl; Nasadur; Nasomaris; Nasonal; Otrivin; Xyladur; Xylo-COMOD†; Xylo-POS; Xylozolin; ***Norw.***: Naso; Nazaren; Otrivin; Xolin†; Zymelin; ***NZ***: Otrivine; ***Philipp.***: Otrivin; ***Pol.***: Otrivin; Xylogel; Xylorin; ***Port.***: Otrivina; Rinorex†; ***Rus.***: Dlianos (Длянос); Grippostad Rhino (Гриппостад Рино); Halazolin (Галазолин); Influrin (Инфлюрин); Olynth (Олинт)†; Otrivin (Отривин); Pharmazolin (Фармазолин); Rhinonorm (Ринонорм); Rhinorus (Ринорус); Rhinostop (Риностоп); Snup (Снуп); Suprima-Nos (Суприма-Нос); Tyzine Xylo (Тизин Ксило); Xilen (Ксилен); Xymelin (Ксимелин); ***S.Afr.***: Otrivin; Sinutab; ***Singapore***: Otrivin; ***Spain***: Amidrin; Frenasal; Idasal; Otrivin†; Rhinovin; Rinoblanco; ***Swed.***: Nasoferm; Olynth; Otrivin; ***Switz.***: Nasben†; Nasobol Xylo; Olynth†; Otrivin; Rhinostop; Rinosedin; Spray nasal neo; Xylo-Mepha; ***Thai.***: Otrivin; ***Turk.***: Berkolin; Naze; Otrivine; Rinizol; Xylo-COMOD; ***UAE***: Xylolin; ***UK***: Non-Drowsy Sudafed Decongestant Nasal Spray; Otradrops; Otrasprav; Otrivine; Tixycolds Cold and Allergy†; ***Ukr.***: Dr Theiss Nasal Spray (Спрей Назальный Др Тайсс)†; Eucazolin (Эвказолин); Galazolin (Галазолин); Meralys (Мералис); Otrivin (Отривин); Rinazal (Ріназал); Tyzine Xylo (Тизин Ксило); Xylo-Mepha (Ксило-Мефа); Xylohexal (Ксилогексал)†; ***USA***: 4-Way Moisturizing Relief; Otrivin.

Multi-ingredient Preparations. ***Austral.***: Murine Allergy; ***Austria***: Nasic; ***Belg.***: Otrivine Duo; ***Chile***: Bacitopic Compuesto†; Nasomin; Rinobanedif; ***Cz.***: Nasic; ***Denm.***: Otrivin Menthol; Zymelin Plus; ***Fin.***: Otrivin Comp; Otrivin Menthol; ***Ger.***: Nasic; ***Gr.***: Nasosyn; Otrivin Advance; ***Hung.***: Otrivin Duo; ***Irl.***: Otrivine-Antistin; ***Israel***: Otrivin Complete; ***Ital.***: Inalar; ***Mex.***: Rinadex Compuesto; ***Neth.***: Otrivin Duo; Otrivin Menthol; ***Norw.***: Otrivin Comp; Otrivin med mentol; Zycomb; ***NZ***: Otrivine Menthol; Otrivine-Antistin†; ***Pol.***: Otrivin Duo; ***Port.***: Otrifar; ***Rus.***: Xymelin Extra (Ксимелин Экстра); ***Spain***: Otriduo; ***Swed.***: Otrivin Comp; Otrivin Menthol; ZyComb†; ***Switz.***: Nasic; Triofan Rhume; ***Turk.***: Otrivine Mentol; Rynacrom Compound; ***UK***: Otrivine-Antistin; ***Ukr.***: Xymelin Extra (Ксимелин Экстра); Zycomb (Зикомб)†.

Pharmacopoeial Preparations

BP 2014: Xylometazoline Nasal Drops;

USP 36: Xylometazoline Hydrochloride Nasal Solution.

Zipeprol Hydrochloride *(rINNM)*

CERM-3024; Hidrocloruro de zipeprol; Zipéprol, Chlorhydrate de; Zipeprol, hidrocloruro de; Zipeproli Hydrochloridum; Зипепрола Гидрохлорид.

α-(α-Methoxybenzyl)-4-(β-methoxyphenethyl)-1-piperazineethanol dihydrochloride.

$C_{23}H_{32}N_2O_3$,2HCl=457.4

CAS — 34758-83-3 (zipeprol); 34758-84-4 (zipeprol hydrochloride).

ATC — R05DB15.

ATC Vet — QR05DB15.

UNII — U6WT9D8ASL.

Profile

Zipeprol is a centrally acting cough suppressant that is stated to have a peripheral action on bronchial spasm. It has been given as the hydrochloride in the treatment of cough, (p. 1651.2), typically in an oral dose of 150 to 300 mg daily in divided doses. There have been reports of abuse and overdosage producing neurological symptoms.

Abuse and overdosage. Severe neurological symptoms have been reported in young adults after habitual abuse of zipeprol for euphoria. Patients have presented with generalised seizures, followed by coma.[1] One patient who ingested 750 mg of zipeprol [over twice the maximum daily dose] had several opisthotonic crises and developed cerebral oedema.[2] Symptoms of overdosage in children have included restlessness, somnolence, ataxia, choreic movements, forced deviation of the head and eyes, generalised seizures, respiratory depression, and coma.[1,3] Fatalities have been reported.

Dependence and withdrawal symptoms similar to those produced by opioids have been reported.[4] WHO has assessed zipeprol to have a moderate potential for dependence and liability for abuse.[5] Although zipeprol is a weak opioid agonist at high doses its toxicity and hallucinogenic and other psychotropic effects constitute a significant element in its abuse, and the public health and social problems associated with such abuse were considered substantial.

1. Moroni C, *et al.* Overdosage of zipeprol, a non-opioid antitussive agent. *Lancet* 1984; **i:** 45.
2. Perraro F, Beorchia A. Convulsions and cerebral oedema associated with zipeprol abuse. *Lancet* 1984; **i:** 45–6.
3. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués dé la pipérazine (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; **32:** 504–11.
4. Mallaret MP, *et al.* Zipeprol: primary dependence in an unaddicted patient. *Ann Pharmacother* 1995; **29:** 540.
5. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_856.pdf (accessed 11/05/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Frenotos; ***Gr.***: Delaviral; Demetovix; Devixil; Dovavixin; Duo-Extolen; Jactuss; Sousibim; ***Mex.***: Tusigen.

Multi-ingredient Preparations. ***Gr.***: Extolen.

Dermatological Drugs and Sunscreens

Dermotological Drug Groups, p. 1681
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The skin is subject to a very wide range of lesions. Some may be characteristic of specific systemic diseases and fade as the disease regresses. Some are caused by specific local infections and are best treated by the appropriate antimicrobial (see Skin Infections in the chapters Antibacterials, p. 207.1, and Antifungals, p. 568.1). The skin is also subject to damage from environmental hazards. Excessive or prolonged exposure to solar radiation is associated with degenerative changes in the skin (premature ageing of the skin or photoageing, p. 1686.2), actinic (solar) keratoses (which are risk factors or precursors of skin cancers), and malignant neoplasms of the skin (p. 714.1). Some skin disorders are adverse effects of therapeutic and other agents, ranging from mild hypersensitivity to the life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis (see Drug-induced Skin Reactions, p. 1683.3, and Drug-induced Photosensitivity, p. 1686.1). There also remain skin disorders whose aetiology is poorly understood.

The distribution and morphological description of the skin lesion (its shape, colour, and surface characteristics) are important in the diagnosis of skin disorders. There are many terms used to describe skin lesions:

- abscess–a collection of pus in a cavity
- bulla (or blister)–a fluid-filled circumscribed lesion larger than 0.5 cm in diameter
- comedo–a plug of keratin and sebum in a pilosebaceous follicle
- ecchymosis (bruise)–an extravasation of blood into the skin
- erythema–red coloration due to vascular dilatation
- fissure–a slit through the whole thickness of the skin
- horn–a thickening of the skin that is taller than it is broad
- keratosis–a horny thickening of the skin
- lichenification–hard, thickened skin with increased markings
- macule–an area of altered colour or texture with no elevation above the surface of the surrounding skin
- nodule–a dome-shaped or spherical-shaped, solid lesion, usually more than 0.5 cm in diameter and depth
- papilloma–a nipple-like mass
- papule–a raised solid lesion, usually less than 0.5 cm in diameter
- petechia–a pinhead-sized macule of blood in the skin
- plaque–a raised, flat-topped, circumscribed lesion, usually larger than 2 cm in diameter but with no substantial depth
- purpura–a macule of blood in the skin, larger than a petechia
- pustule–an accumulation of pus in the skin
- scale–a flat plate or flake of stratum corneum
- stria–a streak-like, linear, atrophic lesion, pink, purple, or white in colour
- telangiectasia–a visible permanent dilatation of small cutaneous blood vessels
- ulcer–a loss of the whole thickness of dermis and epidermis produced by sloughing of necrotic tissue; healing results in a scar
- vesicle–a fluid-filled circumscribed lesion less than 0.5 cm in diameter
- wheal–an elevated, white, compressible area of oedema often surrounded by a red flare

Dermatological Drug Groups

Treatment of skin disorders may include topical and/or systemic drug therapy, although the pharmacology of many of the drugs used in dermatology is poorly understood. Physical methods such as cryotherapy, UV radiation, radiotherapy, and surgery also have a role. Some of the main drug groups used in dermatology are described below.

Antidandruff Drugs

Antidandruff drugs have antibacterial and antifungal properties and are used particularly in shampoos to manage dandruff and seborrhoeic dermatitis of the scalp.

Described in this chapter are

Dipyrithione, p. 1701.1
Piroctone Olamine, p. 1716.3
Pyrithione Zinc, p. 1718.1
Selenium Sulfide, p. 1719.3
Tars and Tar Oils, p. 1723.2

Corticosteroids

Corticosteroids are widely used for their anti-inflammatory (glucocorticoid) and immunosuppressant properties in the management of various skin conditions. Topical preparations are commonly used, but systemic treatment may be required for severe conditions or to control acute exacerbations. The actions and uses of the corticosteroids are discussed in much greater detail in the section beginning on p. 1597.1. See also below for other immunosuppressants used in dermatology.

Immune System Modifiers

Some immunosuppressants are used specifically in psoriasis or eczema, and are included in this chapter. Other immunosuppressants and antineoplastics with immunosuppressant properties that are used in dermatology and covered in other chapters include azathioprine (p. 1940.3), ciclosporin (p. 1945.2), methotrexate (p. 822.2), and tacrolimus (p. 1968.3). Corticosteroids are also widely used for their anti-inflammatory and immunosuppressant effects (see above). Adalimumab (p. 17.2), etanercept (p. 55.1), and infliximab (p. 74.2) are immunomodulators also used in the management of psoriasis.

Described in this chapter are

Alefacept, p. 1692.3
Efalizumab, p. 1702.2
Pimecrolimus, p. 1716.1
Ustekinumab, p. 1728.2

Keratolytics

Keratolytics help to soften and ease exfoliation of the horny layer of the epidermis, and are used in conditions such as acne, seborrhoeic dermatitis and dandruff, and hyperkeratotic disorders.

Described in this chapter are

Alcloxa, p. 1692.2
Aldioxa, p. 1692.2
Allantoin, p. 1693.1
Benzoyl Peroxide, p. 1696.1
Glycolic Acid, p. 1704.3
Keluamid, p. 1710.2
Resorcinol, p. 1718.3
Salicylic Acid, p. 1719.1
Salnacedin, p. 1719.3
Sulfur, p. 1721.1
Tioxolone, p. 1725.1
Urea, p. 1727.3

Photosensitisers

Psoralen photosensitisers markedly increase the skin's sensitivity to UVA light, and are used in photochemotherapy (PUVA) for the management of disorders such as psoriasis, vitiligo, cutaneous T-cell lymphoma, and polymorphic light eruption. For a discussion of photodynamic therapy, a form of light-activated treatment used in the management of malignant neoplasms, see under Porfimer Sodium, p. 849.1.

Described in this chapter are

Methoxsalen, p. 1711.3
5-Methoxypsoralen, p. 1714.1
Trioxysalen, p. 1727.2

Pigment Modifiers

Drugs such as hydroquinone that reduce pigmentation are used to lighten skin in hyperpigmentation conditions such as chloasma. Dihydroxyacetone is used to darken skin in vitiligo, and monobenzone is used to permanently depigment normal skin in extensive vitiligo. Erythrulose is used to darken skin, either alone or with dihydroxyacetone, in artificial suntan preparations. Photosensitisers (above) are also used in vitiligo.

Described in this chapter are

Arbutin, p. 1694.3
Azelaic Acid, p. 1695.1
Dihydroxyacetone, p. 1700.1
Erythrulose, p. 1703.3
Glycolic Acid, p. 1704.3
Hydroquinone, p. 1705.1
Kojic Acid, p. 1710.2
Mequinol, p. 1711.1
Monobenzone, p. 1714.2

Retinoids

Retinoids, and the retinoid analogue adapalene, are vitamin A analogues used in the management of various skin conditions including acne, psoriasis, and keratinisation disorders. Liarozole (p. 1710.3) increases retinoic acid concentrations in the body, and is under investigation for various skin disorders.

Described in this chapter are

Acitretin, p. 1690.3
Adapalene, p. 1692.1
Etretinate, p. 1703.3
Isotretinoin, p. 1706.2
Motretinide, p. 1714.3
Retinaldehyde, p. 1719.1
Tazarotene, p. 1724.2
Tretinoin, p. 1725.2

Sunscreens

Sunscreens are used to protect the skin against sunlight. There are 2 types: *physical* (reflective or inorganic) agents that are opaque and reflect both UVA and UVB radiation and *chemical* (absorbent or organic) agents that because of their chromophore groups absorb a particular range of wavelengths within the UV spectrum (for definitions, see Light-induced Skin Reactions, p. 1685.3). Physical sunscreens include titanium dioxide and zinc oxide. A classification of the chemical sunscreens included in this chapter is given in Table 1, below. Many products combine sunscreens from different groups in order to widen the protection afforded.

Table 1. Chemical sunscreens.

UVA absorbers	UVB absorbers
Anthranilates Meradimate	**Aminobenzoates** Aminobenzoic acid Lisadimate Padimate Padimate O
Camphorsulfonic acid derivatives Ecamsule	**Camphor derivatives** Enzacamene
Dibenzoylmethanes Avobenzone Dibenzoylmethane Isopropyldibenzoylmethane	**Cinnamates** Amiloxate Cinoxate Diolamine methoxycinnamate Octinoxate Octocrilene
UVA and UVB absorbers	**Salicylates** Homosalate Octisalate
Benzophenones Dioxybenzone Mexenone Oxybenzone Sulisobenzone	

Trolamine salicylate (p. 141.2) and salol (p. 129.3) are salicylic acid derivatives that have analgesic properties, but have also been used as sunscreens.

Described in this chapter are

Amiloxate, p. 1694.1
Aminobenzoic Acid, p. 1694.2
Avobenzone, p. 1695.1
Bemotrizinol, p. 1695.3
Bisoctrizole, p. 1697.1
Cinnamates, p. 1699.2
Cinoxate, p. 1699.2
Dibenzoylmethane, p. 1700.1
Diolamine Methoxycinnamate, p. 1700.2
Dioxybenzone, p. 1700.2
Drometrizole, p. 1702.1
Ecamsule, p. 1702.1
Ensulizole, p. 1703.1
Enzacamene, p. 1703.2
Homosalate, p. 1705.1
Iscotrizinol, p. 1706.1
Isopropyldibenzoylmethane, p. 1706.2
Lisadimate, p. 1710.3
Melanin, p. 1711.1
Meradimate, p. 1711.2
Methyl Anthranilate, p. 1714.2
Mexenone, p. 1714.2
Octil Triazone, p. 1715.1
Octinoxate, p. 1715.1
Octisalate, p. 1715.2
Octocrilene, p. 1715.2
Oxybenzone, p. 1715.3
Padimate, p. 1715.3
Padimate O, p. 1716.1
Sulisobenzone, p. 1722.1
Titanium Dioxide, p. 1725.1
Zinc Oxide, p. 1729.1

Vitamin D Derivatives

Some vitamin D derivatives are used in the treatment of psoriasis because they appear to induce differentiation and suppress proliferation of keratinocytes. Mention of other vitamin D derivatives that have been studied in psoriasis can be found under Vitamin D Substances, p. 2112.3.

Described in this chapter are

Calcipotriol, p. 1697.2
Tacalcitol, p. 1722.1

Wound Management Agents

Many compounds and dressings are used in the management of wounds and ulcers. Although some are included in this chapter, others can be found throughout *Martindale*, including white and yellow soft paraffins (p. 2211.3), alginates such as calcium alginate (p. 1136.3), proteolytic enzymes such as collagenase (p. 2484.1) and fibrinolysin (p. 1382.3), and fibrin glue (p. 1151.2).

Described in this chapter are

Becaplermin, p. 1695.2
Centella, p. 1698.3
Cerous Nitrate, p. 1699.1
Crilanomer, p. 1699.2
Dextranomer, p. 1699.3
Maggots, p. 1711.1
Polyphloroglucinol Phosphate, p. 1717.3
Polyurethane Foam, p. 1718.1
Prezatide Copper Acetate, p. 1718.1
Pyroxylin, p. 1718.2
Skin Substitutes, p. 1720.2
Trafermin, p. 1725.1

Topical Drug Administration

For drugs that are applied topically, the vehicle and formulation may be as important as the active drug. Indeed, some cream and ointment bases are used alone for their protective or emollient properties, while adverse effects of topical preparations are sometimes attributed to constituents of the vehicle such as stabilisers and preservatives. The choice of formulation depends on the skin condition being treated and the area affected. Lotions and gels are useful for hairy areas. Creams (oil-in-water emulsions) have cooling and emollient effects, are readily absorbed by the skin, and are used for acute and exudative conditions. Ointments (water-in-oil emulsions) are more occlusive than creams and are particularly suitable for dry lesions. Pastes (powder incorporated in an ointment basis) are also occlusive and are useful for their protective properties and for their use on circumscribed lesions. Less frequently used formulations include applications, collodions, and dusting powders. Typical quantities of preparations required per week for twice daily application to specific areas of an adult are given in Table 2, below.

Table 2. Typical quantities of preparations required per week for twice daily application to an adult.

	Creams and Ointments	Lotions
Face	15 to 30 g	100 mL
Both hands	25 to 50 g	200 mL
Scalp	50 to 100 g	200 mL
Both arms or both legs	100 to 200 g	200 mL
Trunk	400 g	500 mL
Groins and genitalia	15 to 25 g	100 mL

NOTE. These quantities do *not* apply to corticosteroid preparations.

Management of Dermatological Disorders

The management of some of the commoner skin conditions is discussed below.

Acne

Acne is a disorder of the pilosebaceous follicle; common features include increased sebum production, follicular keratinisation, colonisation by *Propionibacterium acnes*, and localised inflammation. Mild acne is characterised by open or closed comedones (blackheads and whiteheads), some of the latter developing into inflamed lesions such as papules and pustules. In moderate acne, the papules and pustules are more widespread, and there may be mild scarring. Severe acne is characterised by the presence of nodular abscesses or cysts in addition to widespread pustules and papules, and may lead to extensive scarring.

The most common form of acne is acne vulgaris. It is common in teenagers and while by their mid-20s the majority of cases have resolved, a few people still require treatment in their 30s and 40s. Skin areas typically affected are the face, shoulders, upper chest, and back. Acne may also occur in late middle age and in the elderly (late onset acne) and in infants (infantile acne). Certain drugs, including androgens, corticosteroids, corticotropin, hormonal contraceptives containing androgenic progestogens such as levonorgestrel, isoniazid, lithium, methoxsalen, and some antiepileptics may produce an acneform rash, as may substances such as tars, oils, and oily cosmetics.

Treatment aims to reduce the bacterial population of the pilosebaceous follicles, reduce the rate of sebum production, reduce inflammation, and remove the keratinised layer blocking the follicles. Drugs used include keratolytics, retinoids, and antibacterials. If topical preparations are not effective, oral preparations may be required. Response to therapy is commonly slow and long-term treatment is usually necessary.

Mild acne is treated topically, in particular with benzoyl peroxide, retinoids, and antibacterials. Abrasives have been used but their efficacy is doubtful, and preparations based on sulfur or salicylic acid are considered by some to be obsolete; irritating astringents, harsh cleansers, and antibacterial soaps should be avoided. Topical corticosteroids, despite their presence in some compound preparations, should not be used.

Benzoyl peroxide has an antimicrobial action and mild keratolytic properties, and both comedones and inflammation generally respond well. It is probably the most widely used drug in mild acne because of its ready availability. Azelaic acid is an alternative to benzoyl peroxide that may cause less local irritation, but be less effective. Topical retinoids are effective in both comedonal and inflammatory acne; tretinoin is widely used but isotretinoin and tazarotene are considered to be equally effective. Adapalene, a naphthoic acid derivative with retinoid activity, also has similar efficacy, but may be better tolerated. Topical antibacterials can be used particularly for inflammatory acne. Tetracycline, clindamycin, and erythromycin are generally used, and appear to be roughly equivalent in efficacy. However, development of resistance by the skin flora is an increasing problem. Nicotinamide has also been used topically in mild to moderate inflammatory acne.

Generally, benzoyl peroxide is used alone as a first-line therapy for mild inflammatory acne, and topical retinoids can be used when comedones predominate.[1,2] Topical antibacterials may be used in inflammatory acne but should not be used alone; the addition of a topical retinoid or benzoyl peroxide improves efficacy and reduces the risk of developing resistance. However, many patients have both comedonal and inflammatory acne to some degree, and a retinoid with benzoyl peroxide, or a retinoid with benzoyl peroxide and a topical antibacterial, can be used.[3] Once there is clinical improvement and inflammatory lesions are under control, which may take 8 to 12 weeks,[4] the antibacterial can be stopped and the retinoid continued as maintenance therapy.[3] If there is no improvement within 6 to 8 weeks with antibacterial therapy, treatment should be stopped.[5] Further courses of topical antibacterial may be needed for flare-ups.[3]

Moderate acne is best treated with oral rather than topical antibacterials, of which tetracyclines appear to be the drugs of first choice. Tetracycline, doxycycline, lymecycline, or oxytetracycline may be used. Minocycline has also been reported to be effective; however, it can cause skin pigmentation and may be associated rarely with immunologically mediated reactions. Alternatives to the tetracyclines include erythromycin, co-trimoxazole, and trimethoprim. Resistance is an important problem, especially with erythromycin, and benzoyl peroxide is therefore also used.[3,6] To further limit the development of resistance, antibacterials should be used for no longer than necessary, the same antibacterial should be used for subsequent courses if the patient relapses,[3,6] and oral and topical antibacterials should not be used together.[6] Oral antibacterials have to be used for at least 3 months.[3,6] A total course of up to 6 months may be needed; longer treatment should generally be avoided but may be warranted in some cases.[6] If there is no response after 6 to 8 weeks, the antibacterial should be changed.[3] A topical retinoid may also be used for additional comedolytic activity. After the course of antibacterial has finished, a topical retinoid alone or with benzoyl peroxide is continued as maintenance therapy.[3,6] Women with moderate acne who also require oral contraception may be treated additionally with a combined oral contraceptive containing a non-androgenic progestogen.[2,4]

Severe acne is usually treated with oral isotretinoin;[3] there are also reports of oral isotretinoin being used outside this licensed indication for less severe acne that is resistant to treatment or that is causing physical scarring or psychological distress.[1] Where it cannot be used, high doses of oral antibacterials with a topical retinoid and benzoyl peroxide may be considered.[6] In women with signs of hyperandrogenism,[2-4] adjunctive use of the combination of anti-androgenic cyproterone with ethinylestradiol may be considered (this is available as a combination preparation that also provides contraception). A combined (non-androgenic) contraceptive is an alternative. Spironolactone has been used for its anti-androgenic properties in women when oestrogens are contra-indicated.

There is evidence to suggest that photodynamic therapy with a photosensitiser, such as 5-aminolevulinic acid, may be beneficial in acne.[7-9]

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Alopecia

Alopecia (hair loss) has many causes but androgenetic alopecia is the most common form. Alopecia may also be congenital, be associated with systemic disorders, severe emotional and physical stress, or skin disorders, or be due to nutritional deficiencies. Some drugs may cause alopecia; examples include antineoplastics (see p. 730.3), beta blockers, diazoxide, heparin, verapamil, and warfarin. In cicatricial alopecia there is destruction of the hair follicles (scarring) resulting in permanent hair loss. Drug treatment may be tried in alopecia areata and androgenetic alopecia but it is often unsuccessful or has only a modest effect. Treatment of any other associated underlying condition causing alopecia, or removal of a suspected drug, may produce hair regrowth. Some treatments have also been tried in cicatricial alopecia in an attempt to stop the scarring process and permanent hair loss. Non-drug options include the use of wigs and hairpieces, cosmetic hair products, or hair transplantation surgery.

Alopecia areata is an auto-immune disorder in which there is a loss of hair in sharply defined areas of skin that normally bear hair. The affected area can vary in size from about 1 cm^2 to the whole scalp (alopecia totalis) or all body hair (alopecia universalis).

Small or isolated patches of alopecia areata may not need treatment and in many patients hair regrows within a few months. If loss of hair becomes a problem cosmetically, treatment may be offered but is often not totally satisfactory. Several treatment options have been tried.[1-3] Intralesional corticosteroids stimulate hair regrowth at the site of injection and may be of benefit for limited patchy hair loss. Oral pulsed or continuous corticosteroids may be used in severe progressive cases. Potent topical corticosteroids, topical dithranol, and minoxidil lotion may also be used, although their efficacy is debatable. Contact immunotherapy with diphencyprone has shown benefit in patients with extensive patchy hair loss, alopecia totalis and universalis. Photochemotherapy with ultraviolet A radiation (PUVA) with either systemic or topical psoralens such as methoxsalen has been tried, but potentially serious adverse effects and limited efficacy restrict its use.

Androgenetic alopecia is hereditary thinning of the hair induced by androgens in genetically susceptible men and women.[1] Over time, the growth phase of the hair cycle becomes shorter and hair follicles become smaller, producing shorter, finer hairs that cover the scalp poorly. *Male-pattern alopecia* (male-pattern baldness)[1,3,4] involves recession of the hairline in the frontal region of the scalp or

loss of hair at the vertex. It is usually associated with increasing age in men. Topical minoxidil is more effective in male-pattern alopecia than it is in the areata forms of alopecia, but is still, at best, only modestly effective. Because of the role of androgens in this condition anti-androgens and 5α-reductase inhibitors may also be tried. The 5α-reductase inhibitor finasteride has been shown to be of benefit in men with male-pattern alopecia. Alfatradiol, another 5α-reductase inhibitor, is available in some countries for topical use. To maintain effectiveness, minoxidil or finasteride must be used continuously as any benefit will be lost within months of stopping treatment. Androgenetic alopecia also occurs in women (*female-pattern alopecia*);[5] there is a similar pattern of hair loss although the thinning may be more diffuse and milder in women than men. Most women with androgenetic alopecia do not have elevated androgen concentrations and are treated with topical minoxidil. However, an anti-androgen such as cyproterone acetate or spironolactone might be considered for women with accompanying signs of hyperandrogenism such as hirsutism (p. 2262.1). Finasteride and dutasteride are also being investigated in women with alopecia.[6]

Cicatricial alopecia involves inflammation and replacement of the hair follicles by fibrous tissue and the aim of treatment is to stop this process before hair loss is permanent. As well as hair loss, there can be pustules, crusting, scaling, and itching. There are several different types of cicatricial alopecia and many treatments have been tried, but there is no standard therapy.[7-9] In those where the scalp biopsy shows mainly lymphocytic infiltration, topical and/or intralesional corticosteroids can be used alone for limited disease or added to systemic therapy. Systemic corticosteroids may be used and other oral treatments that have been tried for more extensive or progressive disease include hydroxychloroquine, isotretinoin, mycophenolate mofetil, and ciclosporin. There are also reports of benefit from other topical therapies such as pimecrolimus, tacrolimus, and tazarotene. In neutrophilic cicatricial alopecia, oral antibacterials are used to control follicular infection and suppuration. Oral isotretinoin has been used in patients with neutrophilic dissecting cellulitis.

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Burns

Burns may be caused by chemicals or heat. Initial treatment of burns is irrigation with cold or tepid water for at least 20 minutes; hypothermia should be avoided. This limits the skin damage in burns caused by heat and removes the causative agent in chemical burns. Sodium bicarbonate solution is then used on acid burns and acetic acid solution on alkaline burns. The extent of a burn injury is described by area and depth. The affected body-surface can be calculated, and the depth of the burn may be classified as superficial (first-degree); partial thickness (second-degree), which may be further classified as superficial or deep partial thickness; or full thickness (third-degree). The major problems associated with burns are hypovolaemic shock, inhalation injury, metabolic abnormalities, and infection. For burns affecting the eye, see p. 1782.1.

- After a burn, fluid accumulates rapidly in the wound area due to increased permeability of the microcirculation and this loss of fluid from the circulation may produce hypovolaemic shock (p. 1279.3) if burns involve at least 15 to 20% of the body-surface.
- Inhalation injury producing airway oedema is mainly a result of exposure to toxic gases. Endotracheal intubation is required until the oedema subsides. Oxygen therapy is used, and nebulised beta$_2$ agonists may be given to treat bronchospasm. Inhalation of heparin and acetylcysteine may be of benefit in reducing pulmonary failure.
- Hypermetabolism and marked catabolism can result from major burn injury. Protein breakdown and loss causes muscle wasting and weakness, impaired wound healing and skin breakdown, and impaired immunity. Other effects of metabolic disturbances include an increase in liver fat and hepatomegaly, osteopenia, tachycardia and increased myocardial oxygen consumption. Enteral feeding (p. 2044.1) to match nutrient requirements is essential for metabolic management. Other treatments that have been tried to reduce net catabolism include the amino acids arginine and glutamine, drugs with anabolic effects including insulin, oxandrolone, and somatropin (for concerns about the latter use see p. 1920.3), and catecholamine antagonism using beta blockers such as propranolol.
- Prevention of infection is an important part of burn wound management. Micro-organisms proliferate rapidly in burn wounds, especially those severe enough to impair immune function, and sepsis remains the major fatal complication of burns. Burn wounds should be cleansed with normal saline (see Wounds and Ulcers, p. 1690.1). This may be all that is required for very minor burn wounds; a non-adherent dressing, such as paraffin tulle, may be used if necessary. Topical antibacterials, such as chlorhexidine, sulfadiazine silver, silver nitrate, and mafenide acetate, may be applied as required. Sodium hypochlorite (Dakin's solution) may also be of value, although opinions differ as to its usefulness. Removal of devitalised tissue is also an essential element of management. Infections require aggressive systemic treatment (see under Skin Infections, p. 207.1).

Full thickness burn wounds require skin grafting. This is performed as soon as possible after stabilisation of the patient. Skin grafting may also be considered for deep partial thickness wounds. If the area to be grafted is very extensive, the grafting procedure may have to be in stages (at intervals of about a week) as sufficient autologous skin becomes available. Alternatively, temporary skin substitutes may be used to supplement autologous skin and allow wound closure in one stage. Cultured epidermal autografts may also be available to either supplement autologous skin, or to be used alone if necessary.

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Darier's disease

Darier's disease (keratosis follicularis) is an uncommon inherited keratinisation disorder (see p. 1685.2) and is characterised by groups of horny papules over the body. These may become irritated and/or infected, exudative, and crusted. Involvement of the nails is characteristic. Severity varies greatly; emollients, use of soap substitutes, and wearing cool clothing are important in controlling irritation in all patients, and may be sufficient in the mildest cases. More severe cases are treated by topical application of keratolytics such as salicylic acid or topical retinoids such as isotretinoin, tretinoin, or tazarotene. Topical corticosteroids are helpful in some patients to alleviate retinoid-induced irritation. Treatment with oral retinoids (acitretin, etretinate, or isotretinoin) is needed in more extensive disease, and has been combined with topical retinoids. Ciclosporin and topical fluorouracil have also been tried; some patients have been reported to respond to dietary supplementation with essential fatty acids. There is only anecdotal evidence to support the use of surgery or laser therapy, although these may be tried in refractory cases.

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Dermatitis herpetiformis

Dermatitis herpetiformis is a rare blistering disorder of the subepidermal tissue in which the vesicles and papules are intensely irritant and pruritic. The knees, elbows, buttocks, shoulders, and scalp are areas typically affected. The disease presents usually during early to middle adult life and is a chronic condition, although there may be periods of remission that last several months. In most patients there is also a mild gastrointestinal absorptive defect characterised by gluten hypersensitivity (gluten enteropathy or coeliac disease, see p. 2043.1). Skin lesions can be suppressed by dapsone; the sulfonamides sulfamethoxypyridazine or sulfapyridine have been used as alternatives to dapsone.[1-6] A gluten-free diet may improve both gastrointestinal symptoms and the skin disorder.[2,4-7]

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Drug-induced skin reactions

Drugs are a frequent cause of adverse skin reactions. The skin reaction may mimic a spontaneously occurring skin disorder and is therefore included in the differential diagnosis of most skin diseases. Alternatively, the drug may produce quite specific changes. The reaction can develop after the first dose or after a period of sensitisation. Pigmentation changes or effects on hair may take some months to become apparent. Drug-induced nail changes have also been reported.

Reactions range from mild rashes to severe life-threatening reactions including angioedema with urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Other serious skin reactions include hypersensitivity syndromes, serum sickness, and vasculitis.

Stevens-Johnson syndrome (see also Erythema Multiforme, p. 1684.3) is a severe, blistering skin reaction also affecting the mucous membranes of the oropharynx, eyes, and genitalia and accompanied sometimes by fever, pain, and malaise. **Toxic epidermal necrolysis** (Lyell's syndrome or scalded skin syndrome) as described on p. 1689.1, is a more severe form of the reaction where considerable amounts of the epidermis may be shed. Sulfonamides, carbamazepine, and allopurinol are among the many drugs that have been associated with both these reactions.

Hypersensitivity syndrome is a severe, idiosyncratic reaction which includes rash and fever, and often hepatitis, arthralgias, lymphadenopathy, and haematological abnormalities. It tends to have a relatively late and slow onset. Some antiepileptics and sulfonamides cause this syndrome, as well as allopurinol, dapsone, and gold salts. **Serum sickness** is manifest as rash, fever, arthralgia and arthritis and typically develops 8 to 14 days after doses of serum preparations and vaccines. **Vasculitic reactions** may occur 7 to 21 days after beginning therapy with drugs such as allopurinol, penicillins, and sulfonamides (see Hypersensitivity Vasculitis, p. 1606.1). The vasculitis usually affects small vessels of the lower extremities producing purpura, although it can also affect vessels in the kidney, liver, and gastrointestinal tract, in which case it may be life-threatening.

Maculopapular exanthematic eruptions are probably the most frequent drug-induced skin reaction. Drugs commonly causing these rashes include carbamazepine, chlorpromazine, nitrofurantoin, penicillins, and sulfonamides. **Urticaria** (p. 1689.2) is also frequently drug-induced. **Photosensitivity** rashes where the skin reaction is confined to light-exposed areas may be phototoxic or photoallergic in nature (see Drug-induced Photosensitivity, p. 1686.1). Amiodarone produces a phototoxic reaction in many patients. Some drugs cause **pigmentary changes** (see Pigmentation Disorders, p. 1687.2). Chlorpromazine can cause both photosensitivity and pigmentary changes. **Acneform eruptions** may be produced by many drugs (see Acne, p. 1682.2). Some drugs produce skin reactions resembling **pemphigus** and **pemphigoid** (see p. 1687.1). Most of the drugs implicated contain a thiol group or metabolism of the drug generates a thiol group. Examples include captopril, penicillamine, penicillins, piroxicam, and rifampicin. **Fixed-drug eruptions** are inflammatory patches that appear at the same sites each time the drug is taken, and may occur with many drugs including dapsone, sulfonamides, and tetracycline.

Drug-induced **nail changes** include onychomadesis, nail fragility, onycholysis, paronychia, pigmentation, and vascular changes. The effect is usually transient and disappears with drug withdrawal. Drugs reported to cause nail changes include antineoplastics, psoralens, retinoids, tetracyclines, and zidovudine.

The majority of drug-induced adverse skin reactions are mild. However, in severe reactions rapid withdrawal of the suspected drug is needed. In some cases, this may mean stopping several drugs. In most cases the skin reaction will be resolved by symptomatic treatment. Another dose of the offending drug may establish whether the skin eruption is

drug-induced, although reactions may be more severe and therefore rechallenge should not be performed after a serious reaction.

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Eczema

Eczema (often used synonymously with the term dermatitis) refers to a variety of skin conditions characterised by epidermal inflammation and itching. The areas of skin affected vary in the different types of eczema, but the skin lesions share certain common features. In acute eczema the skin is typically red and inflamed with papules, vesicles, and blisters. In chronic eczema the skin may show the same features but be more dry, scaly, pigmented, and thickened. Eczema may be categorised as exogenous (including allergic, irritant, and photosensitivity eczema) or endogenous (such as atopic, discoid/nummular, gravitational, and seborrhoeic eczema), but there may be multiple causes of eczema, both endogenous and exogenous, in an individual patient. Two of the most common forms of eczema are atopic eczema (see below) and seborrhoeic dermatitis (p. 1689.1).

Atopic eczema mainly affects infants and children although adults may also suffer. The skin is itchy and there is a chronic or relapsing dermatitis in which the face and neck and flexures of the elbows and knees are involved most often and are excoriated and lichenified.

General principles for the management of **atopic eczema** may also be applied to other eczematous skin disorders. Cure of atopic eczema is said to be unrealistic, but good control can be achieved with proper management. The objective of treatment should be to reduce signs and symptoms, to prevent or reduce recurrences, and to provide long-term management by preventing exacerbation. Guidelines have been issued by, among others, the Primary Care Dermatology Society with the British Association of Dermatologists,[1] the American Academy of Dermatology,[2] the International Consensus Conference on Atopic Dermatitis (ICCAD II),[3] and, in the UK, the National Collaborating Centre for Women's and Children's Health.[4] The management of eczema is also frequently reviewed.[5-8]

First-line treatment.
- Regular bathing using soap substitutes is important to *cleanse and hydrate* the skin; soaps and detergents should be avoided as these remove the natural lipid from the skin. Suitable bath oils should be used to maintain skin hydration. Emollients should be applied liberally to the whole body at least twice daily, especially after bathing, and more frequently throughout the day to hands and face. Although widely recommended, it has been noted that the use of bath emollients is not based on robust evidence and there is a need to evaluate the efficacy of such treatment.[9]
- Patients should be educated on the *avoidance of trigger factors*. These may include irritants, microbes, and psychological or allergic factors.

Acute control of pruritus and inflammation.
- Intermittent topical *corticosteroids* are the mainstay of treatment and are used for up to a week to manage acute flares of atopic eczema. Treatment for up to 6 weeks may be needed for initial control of chronic eczema. To minimise potential adverse effects the minimum strength preparation to control the disease should be used, and the age of patient, site of eczema, and extent of disease should be considered when selecting the appropriate preparation. Very potent preparations should be used in children only under specialist supervision.
- Topical *calcineurin inhibitors* (pimecrolimus or tacrolimus) may be used as alternative therapy when corticosteroids are contra-indicated, or as second-line therapy in patients who have not responded adequately to topical corticosteroids. Pimecrolimus is indicated for mild to moderate disease and tacrolimus for moderate to severe eczema. The main adverse effect is burning at the site of application. Once the condition settles the patient should revert to treatment with emollients.

Maintenance therapy.
- Topical corticosteroids may be used intermittently for acute exacerbations. Once the patient is back in remission emollients should be continued.
- For persistent disease or frequent flares, topical calcineurin inhibitors are effective and may be used at the earliest sign of recurrence. While these drugs prevent disease progression they do not have the adverse effects of corticosteroids and consequently may be used on all body areas (including sensitive areas like the face, eyelids, and neck) for extended periods. Studies so far suggest that these new drugs are safe in the short term. However, they do suppress T lymphocytes and although systemic absorption is minimal there may be a possibility of immunosuppression, skin cancers, or bacterial infection. There has been considerable debate about the possible risk of cancer associated with topical calcineurin inhibitors (see Carcinogenicity, under Tacrolimus, p. 1971.2). These concerns in particular prompted licensing authorities in Europe and the USA in 2006 to remind prescribers that these drugs should only be used intermittently as second-line treatments, and should not be used in children less than 2 years of age.[10-12]
- *Coal tar* preparations may be used occasionally for chronic atopic eczema, and *ichthammol* may be used as an ointment or paste bandages for chronic lichenified eczema.

Adjunctive therapy.
- Overt bacterial, fungal, or viral infections should be treated with an appropriate systemic drug (see Skin Infections under Antibacterials, p. 207.1, and under Antifungals, p. 568.1). Topical preparations are generally not used as they should be restricted to limited areas and patients with eczema often have widespread infections.
- A sedating *antihistamine* may be used short term for severe pruritus associated with relapse or at night-time if scratching disturbs sleep or occurs while asleep. Non-sedating antihistamines are generally ineffective in eczema but may be of benefit in atopic dermatitis and concomitant urticaria. Topical *doxepin* may provide short-term relief from pruritus, but drowsiness and contact dermatitis can occur.

Patients whose eczema fails to respond to these first-line treatments, even under specialist supervision, require further measures.

Severe refractory disease.
- *Phototherapy* with ultraviolet A or B, or in combination, may be useful, and photochemotherapy using a psoralen (generally methoxsalen) with ultraviolet A (PUVA) may be used in severe, widespread disease. However, potential long term effects such as premature ageing of the skin and skin malignancy need to be considered.
- Therapy with *more potent topical and oral corticosteroids* may be considered for short periods of time. In general, only mild corticosteroids (such as 1% hydrocortisone) should be used on the face and in flexures as absorption is increased in these areas.
- *Wet-wrap dressings* are sometimes used intermittently, particularly in children, for hydration and anti-inflammatory effects.[4,8,13,14] Different techniques have been described: wet bandages or dressings may be applied to skin already covered with an emollient or diluted corticosteroid cream, alternatively the dressing may be soaked in warm diluted cream before use; a dry outer dressing may be added. Dressings may be used only on affected parts of the body, or a whole-body suit may be used for extensive eczema, and left in place for up to 24 hours. Treatment can continue for several weeks, but should probably be limited to about 1 week when corticosteroids are used because of the risk of adverse effects from systemic absorption.[4,8,13] Wet-wrapping may not be appropriate in patients whose eczema has become infected.
- Various *other drugs* have been tried in resistant eczema. Azathioprine, ciclosporin, or methotrexate may be tried in selected patients.

Evening primrose oil and borage oil have also been tried although evidence in favour of a useful therapeutic effect is poor. Other drugs at an experimental stage include interferons, mycophenolate mofetil, and thymopentin. There has been much interest in the use of complementary and alternative therapies and herbal medicines, but serious adverse effects have occasionally occurred and although encouraging results have been reported the degree of benefit is still uncertain.[4,15,16]

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Epidermolysis bullosa

Epidermolysis bullosa consists of a group of similar congenital disorders characterised by severe blistering of the skin.[1,2] Sometimes the mucosae, especially of the mouth and oesophagus, are also affected. The blistering may be caused by various structural and metabolic defects and occurs at different levels in the skin in the different forms (simple, junctional, and dystrophic). Blistering can follow even minor trauma or can arise spontaneously. In some patients blistering and scarring can cause marked tissue loss of the affected areas and the most severe forms are fatal in early infancy because of infection of the blisters. Milder forms may be managed by avoiding trauma and keeping blisters clean and dry, but there is no truly effective treatment for the severe forms. High-dose oral corticosteroids may be needed. Phenytoin has been tried, but was unsuccessful in a controlled study. Thalidomide has also been tried, and oral tetracycline has reduced the number of lesions in a few cases.

There is also an acquired form of the disease, epidermolysis bullosa acquisita, and it too is difficult to treat;[3] corticosteroids and other immunosuppressants may be tried. Individual patients have responded to high-dose intravenous immunoglobulins or extracorporeal photochemotherapy (oral methoxsalen followed by removal of blood and UV irradiation of leucocytes outside the body before reinfusion).[4,5] There are individual case reports of successful treatment with monoclonal antibodies such as basiliximab (an interleukin-2 receptor antibody)[6] and rituximab (an anti-CD20 antibody).[7]

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Erythema multiforme

Erythema multiforme is an inflammatory reaction of the skin characterised by maculopapular lesions that may become annular and blister. Areas typically affected are the hands, forearms, elbows, knees, and feet. It is usually associated with a precipitating trigger such as infection (notably herpes simplex infection); it may also be associated with drug use, neoplastic disease, or collagen or inflammatory diseases. In severe forms there is also blistering of the mucous membranes (usually of the mouth). There is some overlap in the descriptions of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, and attempts have been made to classify them into distinct categories.[1-4] Erythema multiforme occurs mainly after infections, whereas the Stevens-Johnson syndrome is mainly a drug-induced reaction and seems to be part of a spectrum of skin reactions, with life-threatening toxic epidermal necrolysis being the more severe form (see Drug-induced Skin Reactions, p. 1683.3).

As erythema multiforme is usually an acute reaction of relatively short duration, symptomatic treatment as for

burns (see p. 1683.1) may be all that is required. If severe reactions occur systemic corticosteroids may be considered, although there has been controversy about their value. Erythema multiforme may become a recurrent disorder in some patients and various drugs have been tried for treatment and prophylaxis.[5] Aciclovir, given in short courses or continuously, has been used particularly when herpes simplex infection appeared to be a trigger factor. Other drugs that have been tried for recurrent erythema multiforme include dapsone, hydroxychloroquine, mepacrine, azathioprine, mycophenolate, and thalidomide.

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Hyperhidrosis

Hyperhidrosis (excessive sweating) can be generalised or focal, affecting the palms of the hands, soles of the feet, axillae, or less commonly the craniofacial region. No cause can usually be established although it may be secondary to an underlying endocrinological, neurological, or neoplastic disorder;[1,2] in some cases, it may be drug-induced.[3]

Drug therapy should be tried initially but is often ineffective in severe cases. Aluminium salts, such as aluminium chloride or aluminium chlorohydrate in alcoholic solvents applied topically, may be successful in milder forms of focal hyperhidrosis.[1,2,4,5] Topical antimuscarinics such as diphemanil metilsulfate, glycopyrronium bromide, or hyoscine hydrobromide may also provide some relief, particularly in craniofacial sweating.[2] Adverse effects of oral antimuscarinics generally preclude such use, although oral propantheline bromide has been used successfully to control excessive sweating in a few patients with spinal cord injuries. An intravenous infusion of phentolamine mesilate may be effective in some patients with generalised hyperhidrosis.[6] Tap water iontophoresis may be an alternative first-line option for palmar or plantar hyperhidrosis.[1,2,4] Intradermal injection of botulinum A toxin is used for focal hyperhidrosis when topical therapies are insufficient, although injections are painful and local or regional anaesthesia may be needed, especially for treatment of the hands and feet.[1,2,4,5] Formaldehyde and glutaral solutions have been used topically for hyperhidrosis affecting the feet but are not very effective and are not usually recommended.

When drug therapy fails to provide adequate relief surgery may be attempted.[1,2,4,5] Subcutaneous curettage or excision of skin bearing the eccrine glands has been used but minimally invasive techniques, notably endoscopic thoracic sympathectomy, are now available; the latter offers a simple and effective management for severe localised upper limb hyperhidrosis.

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Ichthyosis

Ichthyosis is a term used for generalised noninflammatory dry scaling or keratinisation disorders (see below). There are several different forms of ichthyosis and severity and incidence varies. They are generally inherited disorders. Emollients, including urea, are used to provide relief to the dry skin by coating the skin surface with an oily film thus preventing evaporation of water. If scaling is more severe topical keratolytics such as salicylic acid or urea are used. Topical retinoids such as tazarotene may be tried. In the severest forms of ichthyosis oral retinoids may be necessary. Acitretin, etretinate, and isotretinoin have all been used. A few patients have responded to topical calcipotriol or tacrolimus, but systemic absorption may be a problem. Liarozole, an oral inhibitor of retinoic acid catabolism, has been investigated.

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Keratinisation disorders

Keratinisation is the process whereby basal epidermal cells are transformed into dead cells of the stratum corneum from where they are shed. The process takes about 14 days and shedding normally balances production so that the thickness of the stratum corneum does not alter. Keratinisation disorders (keratoses) are characterised by reduced shedding and the formation of scale at the skin surface. A scale is an aggregate of horn cells that have failed to separate horizontally and hyperkeratosis is an exaggeration of this failure in which there is also a vertical build up of the horn cells. Keratinisation disorders include Darier's disease and ichthyosis (see p. 1683.2 and above, respectively). Certain inflammatory skin disorders, such as psoriasis (see p. 1688.1), also show enhanced epidermal proliferation.

Lichen planus

Lichen planus is an inflammatory skin disorder with itchy papular lesions arising usually on the extremities. The nails and oral or buccal mucosa, and rarely the genital mucosa, may also be affected. Its cause is uncertain although sufferers have a higher incidence of auto-immune disease than normal. Some drugs can produce lichenoid reactions; examples include mepacrine, methyldopa, penicillamine, and sodium aurothiomalate.

Evidence for the efficacy of the various treatments that have been tried is mostly scanty.[1-3] In most patients lichen planus remits spontaneously and, if mild and localised, little or no treatment is needed. Potent topical corticosteroids are often used for localised cutaneous disease when treatment is needed, and occlusive dressings may be used to enhance efficacy.[1,4] However, less potent corticosteroids should generally be used on the face, axillae, groin, or genitals. Intralesional corticosteroids, such as triamcinolone acetonide, can be used for hyperkeratotic or resistant localised plaques. Symptomatic mucosal disease is also treated with topical corticosteroids;[1,3-5] various dosage forms have been used including ointments, adhesive bases, pastes, lozenges, and mouthwashes. Other drugs that have been used topically, with variable results, include ciclosporin and the retinoids isotretinoin and tretinoin. Intralesional corticosteroids have also been used for resistant or erosive mucosal lesions.[1,5]

Systemic corticosteroids may be used in generalised cutaneous lichen planus and acute exacerbations of mucosal disease.[1,3-5] If the condition becomes resistant to corticosteroid therapy, an oral retinoid such as acitretin, etretinate, or isotretinoin, may be tried. Other oral treatments for which there are reports of benefit in small numbers of patients include ciclosporin, griseofulvin, chloroquine and hydroxychloroquine, and photochemotherapy using a psoralen with UVA (PUVA).[1,5] Topical tacrolimus and pimecrolimus have also been tried.[3]

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Lichen sclerosus

Lichen sclerosus is a chronic inflammatory skin condition that most commonly occurs in women, but is also seen in men and children.[1-6] It affects the anogenital area, causing itching, soreness, and urinary and sexual problems. Extragenital lesions may occur, but do not usually itch, and some patients may show no symptoms at all.[1,3,6] Lichen sclerosus runs a relapsing and remitting course and complications include secondary infection, most commonly with *Candida*, physical scarring, and vulvodynia. The most common complication seen in male patients is phimosis. Although the exact cause of the disease is unknown, there appears to be a strong association with auto-immune disorders and genetic factors have also been implicated. There is also an association between lichen sclerosus and squamous cell and verrucous carcinoma.[1,3,4,6]

Management of lichen sclerosus includes the control of symptoms, prevention and treatment of complications, and the early detection of malignancies.[1,3,4,6] Emollients and soap substitutes are recommended. Topical potent corticosteroids such as clobetasol propionate or betamethasone dipropionate 0.05% have been shown to be safe and effective for both genital and extragenital disease. Intralesional triamcinolone was found to be effective in a small study. The benefit and safety of other topical treatments, such as pimecrolimus, tacrolimus, retinoids, testosterone, and progesterone are not clear. However, recent reviews[7,8] concluded that pimecrolimus and tacrolimus may be useful second-line drugs for patients who are resistant to topical corticosteroids. Systemic retinoids may be useful in complicated disease that is not responding to topical corticosteroids. There have been reports of benefit for treatment with stanozolol, photochemotherapy using a psoralen with UVA (PUVA), photodynamic therapy using topical 5-aminolevulinic acid, and laser therapy. Surgical intervention is only indicated for complications of scarring or the development of malignancy.[1,3,4,6]

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Light-induced skin reactions

Light, although essential for many biological functions, may cause a variety of disorders, particularly due to the ultraviolet portion of the solar spectrum.

Ultraviolet (UV) light has different properties according to its wavelength.

- **UVA** (wavelengths 320 to 400 nm) produces immediate direct tanning of the skin with little erythema although it does contribute to the long-term harmful effects of photoageing and cancers. UVA has also been subdivided into UVA-I (340 to 400 nm) and UVA-II (320 to 340 nm); the effects of UVA-II are more like those of UVB.
- **UVB** (wavelengths 290 to 320 nm) is about 1000 times stronger than UVA in producing erythema and is that part of the sun's spectrum that is responsible for producing sunburn and it too contributes to long-term effects. UVB also produces tanning by indirect pigmentation.
- **UVC** (wavelengths 200 to 290 nm) produces erythema without tanning. The earth's surface is usually screened by the ozone layer from UVC radiation although UVC may be emitted by artificial sources such as bactericidal lamps and industrial welding arcs.

In normal healthy individuals **exposure to sunlight** (including reflected light from snow, white sand, or water) causes an increase in pigmentation (tanning). This is an adaptive mechanism to protect the skin from UV radiation. Immediate tanning results from the oxidation of melanin precursors in the uppermost layers of the skin. There may also be a delayed and indirect pigmentation due to the formation of new melanin. The ability of an individual to form a tan is genetically predetermined. Melanin provides some protection against further exposure, but the main protection is provided by thickening of the corneous layer. However, excessive exposure to strong sunlight causes erythema and sunburn, which is an inflammatory response to the damage caused by UV radiation.

Excessive and prolonged exposure to intense sunlight may lead to degenerative changes in the skin (premature ageing of the skin or photoageing, p. 1686.2), actinic (solar) keratoses (which are risk factors or precursors of skin cancers), immunosuppression, and some skin cancers such as basal cell or squamous cell carcinomas and malignant melanomas (see Malignant Neoplasms of the Skin, p. 714.1). Some patient groups are also at higher risk of adverse effects from sunlight exposure. Even brief exposure to sunlight can trigger a reaction in those with photosensitivity disorders (p. 1686.2), patients with hypopigmentation disorders such as vitiligo and albinism (see Pigmentation Disorders, p. 1687.2) are more susceptible to sunburn, and transplant patients receiving systemic immunosuppressants are at increased risk of skin cancers (see under Organ and Tissue Transplantation, p. 1932.2). Many drugs can cause a phototoxic or photoallergic reaction (see Drug-induced Photosensitivity, p. 1686.1).

Protection against sunlight is therefore beneficial, both in healthy people to prevent skin damage, and in patients at increased risk of adverse effects from sunlight exposure. Medical and scientific personnel exposed to ultraviolet lamps may need protection against the whole of the UV spectrum. This may be achieved by appropriate dress and through the use of **sunscreens** applied to the skin. Sunscreens may be of chemical or physical types (see p. 1681.3) and many products combine sunscreens of different types to maximise protection. A broad-spectrum sunscreen should be effective against both UVA and UVB, but UVA coverage can be variable. It may be difficult to formulate physical sunscreens in cosmetically acceptable ways.

The efficacy of a particular sunscreen preparation is often expressed as its **sun protection factor (SPF)**. This is a ratio of the time required for irradiation to produce minimal perceptible erythema (minimal erythemal dose; MED) with the skin protected with the sunscreen compared with the MED without protection, for a standard 2 mg/cm^2 dose of sunscreen. Thus the SPF is mainly an indication of efficacy against UVB light. Various systems have been suggested for classifying the relative efficacies of sunscreens against UVA light but none appears, as yet, to be universally accepted. The efficacy of a sunscreen is also highly dependent upon its correct application and studies have found that, in general, sunscreen preparations are applied haphazardly and in insufficient quantities to provide optimal protection.

Governmental authorities and dermatologists in many countries issue guidance to the public on sun protection, including sunscreen use. General measures include avoiding sunlight exposure when UV radiation is strongest (usually between 10 a.m. and 3 p.m.), seeking shade when outdoors in strong sunlight, using wrap-around sunglasses that conform to appropriate standards, and wearing a broad-brimmed hat and clothing that protect against sunlight. Sunscreens should be applied liberally and evenly to all exposed areas of skin at least 15 to 30 minutes before sunlight exposure, and re-applied at least every 2 hours and after swimming or perspiring. Broad-spectrum products are recommended; dermatologists in some countries such as the UK and USA advocate the use of preparations with at least SPF 15 (SPF 15+), while in Australia SPF 30+ is recommended.

Many treatments have been tried in the management of acute *sunburn*, but studies have been small and results often conflicting. There is a lack of strong evidence to show that any specific treatment reduces epidermal damage or the time to healing once the signs and symptoms of sunburn have developed. Emollients, cool compresses, paracetamol, and NSAIDs, are often used for symptomatic relief of erythema, pain, and pruritus; oral antihistamines, topical hydrocortisone, and topical anaesthetics might also be considered.

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Drug-induced photosensitivity. Photosensitivity can be produced by drugs either given systemically or applied topically, and the reaction can be phototoxic or photoallergic in nature.[1] In *phototoxicity*, a direct toxic effect on tissues occurs when the drug is energised by absorbing radiation. The reaction has a rapid onset (usually within 24 hours) and occurs on exposed skin areas. Resembling an exaggerated sunburn, the reaction can include erythema, oedema, hyperpigmentation causing a darker red than sunburn, pruritus, and urticaria. The response is dependent on the dose of the photosensitiser and the intensity of sunlight exposure. In *photoallergy*, the hypersensitivity reaction has an immunological basis requiring previous exposure to the photosensitising drug. The onset may be delayed until several days after exposure to sunlight and present as a papulovesicular eruption, pruritus, and eczematous dermatitis. Photoallergic reactions are less common than phototoxicity.

Systemic drug groups that have been reported to cause photosensitivity include:

- antibacterials (fluoroquinolones, sulfonamides, and tetracyclines)
- antidepressants (tricyclic antidepressants and St John's wort)
- antiepileptics (carbamazepine, lamotrigine, phenobarbital, and phenytoin)
- antihistamines (including cyproheptadine, diphenhydramine, and loratadine)
- antimalarials (chloroquine, quinine, pyrimethamine, and mefloquine)
- antineoplastics (including fluorouracil, methotrexate, and vinblastine)
- cardiovascular drugs (including ACE inhibitors, amiodarone, quinidine, thiazide diuretics, and simvastatin)
- corticosteroids
- NSAIDs
- phenothiazine antipsychotics
- sex hormones (oestrogens and progestogens)
- sulfonylurea antidiabetic drugs
- retinoids (isotretinoin)

Photocontact dermatitis occurs from the interaction between sunlight and topically applied substances, and can be either a phototoxic or photoallergic reaction. Implicated drugs have included antiseptics, antifungals, coal tar, corticosteroids, local anaesthetics, and retinoids.[1] Photosensitivity reactions have also occurred to the topical sunscreens intended to prevent them.[1,2] Photoallergic reactions have been reported for chemical sunscreens, particularly aminobenzoic acid and benzophenones (dioxybenzone, mexenone, oxybenzone, and sulisobenzone). Reactions to cinnamates seem to be less frequent.

Photosensitivity reactions are managed symptomatically as for sunburn (see Light-induced Skin Reactions, p. 1685.3); antihistamines and corticosteroids may be needed to treat photoallergic reactions. If the offending drug cannot be withdrawn or substituted, sun exposure should be minimised with appropriate clothing and sunscreens.[1]

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Photoageing. Exposure to sunlight induces changes in the skin in addition to the normal ageing process. This photoageing, or photodamage, can manifest as wrinkles, skin roughness and dryness, irregular pigmentation, telangiectasia, sallowness, and lentigines (sun or liver spots). Photoageing is also associated with increased risks of actinic keratoses and skin cancers (see Malignant Neoplasms of the Skin, p. 714.1).

Cosmetic treatments and procedures for the effects of photoageing have been extensively and widely promoted, but few have undergone rigorous scientific evaluation and there is a lack of data in general.[1] Measures to limit sunlight exposure, including the use of sunscreens, reduce the progression of photoageing.[2,3] Topical retinoids, such as isotretinoin, tazarotene, and tretinoin, can improve fine wrinkles, irregular pigmentation, roughness, and lentigines. However, the effect is dose-related and these drugs can cause irritation and photosensitivity.[1-4] Hydroxyacid keratolytics such as glycolic acid are also widely promoted for the reduction of photoageing effects. Low concentrations are used in nonprescription cosmetic preparations, and higher concentrations may be used as chemical peels. Overall, however, their effects are limited.[1,2] Local injection of botulinum A toxin to cause muscle paralysis is used for the cosmetic reduction of lines and wrinkles.[2,3] Injectable skin fillers such as bovine collagen and hyaluronic acid are also available to reduce lines and deep wrinkles.[2] Other procedures in use include dermabrasion to reduce wrinkles, and cryosurgery or electrosurgery for discrete pigmented lesions; lasers or other light therapies are also used for wrinkles, pigmented lesions, and benign vascular proliferations such as telangiectasia and angiomas.[2] Topical photodynamic therapy may have a role in photorejuvenation.[5] Oral and topical antoxidants have also been promoted for the treatment and prevention of photoageing, but there is a lack of data to support such claims.[2,3]

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Photosensitivity disorders. In some persons even brief exposure to sunlight can result in light-induced disorders of the skin.

Polymorphic light eruption is a common hypersensitivity reaction characterised by pruritic erythematous papulovesicular lesions that develop several hours after exposure to sunlight. The condition usually begins in adulthood and affects more women than men. For many patients the susceptibility to eruption starts in early spring and resolves by late summer as the skin becomes more tolerant to sunlight, but patients with severe forms may also be symptomatic in the winter. Mild forms can settle without scarring within days, by sun avoidance and use of a broad-spectrum sunscreen. Potent topical corticosteroids or a short course of oral prednisolone may be useful to control the acute rash. A gradual increase in exposure to sunlight may be sufficient for desensitisation in mild cases, but patients with more severe disease may need to undergo artificial hardening of the skin by UVB phototherapy or photochemotherapy using a psoralen with UVA (PUVA). However, this effect is temporary and usually needs to be repeated each spring.[1-4] Azathioprine may be considered in patients who are very sensitive to sunlight, for whom sunscreens are ineffective, and who cannot tolerate phototherapy.[2]

Chronic actinic dermatitis is manifested by a persistent, often lichenified, eczematous eruption that usually only affects the exposed areas although in a small number of patients larger areas can be affected. It mainly affects older men, and many patients may be unaware of the role that sunlight plays in the condition. These patients may also show clinically relevant allergy to many naturally occurring substances, as well as drugs and sunscreens.[3,5,6] Management is based on sunlight and allergen avoidance and the use of sunscreens, emollients, and topical or oral corticosteroids. Phototherapy or photochemotherapy may also be useful. Systemic immunosuppressants including azathioprine, ciclosporin, and mycophenolate mofetil have been used in resistant disease.[1,4-6] Interferon alfa and topical tacrolimus have also been used successfully in a few cases.[1,4]

Actinic prurigo is similar to polymorphic light eruption but less common, and is characterised by persistent pruritic papules on areas exposed to sunlight, often with extension to covered areas. Other features include scarring, cheilitis, and eye involvement. It is managed similarly with sunscreens, topical or oral corticosteroids, and phototherapy or photochemotherapy. Thalidomide has been used, but relapse frequently occurs when treatment is stopped.[1,4]

Solar urticaria is an uncommon condition that can often be managed with sunscreens alone, but non-sedating antihistamines such as loratadine may also be helpful. Phototherapy and photochemotherapy have also been used.[1,4]

Xeroderma pigmentosum is a rare autosomal recessive condition in which a defective DNA-repair system fails to repair UV-induced DNA damage.[7] The skin is hypersensitive to sunlight, resulting in serious sunburn after minimal exposure. From a very early age patients start to develop lentigines (sun or liver spots), spotty hypopigmentation, telangiectasias, calloused thickening, atrophy, scabbing, and scarring. Numerous actinic keratoses, precancerous lesions, and malignant neoplasms of the skin (p. 714.1) develop in childhood and many patients die before reaching adulthood. Other effects of the disease include motor impairment, mental retardation, ocular damage, leukaemia, and dental caries. Management involves strict avoidance of sunlight and use of broad-spectrum sunscreens. There is some evidence that systemic retinoids, such as acitretin and isotretinoin, may be useful in preventing the development of skin cancers, although adverse effects from long-term use may be of concern. Topical fluorouracil may be used on actinic keratoses and malignant skin cancers. A topical preparation containing recombinant T4 endonuclease V, a DNA-repair enzyme, is under investigation to reduce the incidence of actinic keratoses and skin cancers.

Other conditions that can be exacerbated by sunlight include the cutaneous porphyrias (p. 1556.1), lupus erythematosus (p. 1613.3), and sometimes herpes labialis (p. 955.2).

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Molluscum contagiosum

Molluscum contagiosum is a poxvirus infection that produces small (1 to 2 mm) pearly-white or flesh-coloured papules that are smooth and dome-shaped with central umbilication. The lesions are usually found on the skin but can appear in mucosal areas, mainly the genital mucosa and conjunctiva. The infection is highly contagious, being spread through physical contact and other modes such as shared bathtubs and towels, and is most prevalent in schoolchildren. Individual lesions tend to persist for only a few weeks, and in most children the natural course of infection is spontaneous clearance within 2 to 4 years of onset. However, immunocompromised patients are more likely to develop extensive disease.[1]

For most patients, no treatment is necessary and the condition will eventually clear, although symptomatic therapy including topical corticosteroids and antihistamines may be needed if there is pruritus, eczematous symptoms, or inflammation. Treatment of the lesions may be indicated in immunocompromised patients and in those with extensive lesions, who are at increased risk of scarring. Local destruction of individual lesions may be achieved using topical cantharidin, cryosurgery, or curettage.[1] In adults with genital molluscum contagiosum, piercing of the lesions with or without application of tincture of iodine or phenol may be considered; topical podophyllotoxin is another alternative for genital skin lesions in men.[2] Cimetidine and topical imiquimod have been tried as immunomodulators.[1] HAART used in patients with HIV

All cross-references refer to entries in Volume A

infection can promote clearance of molluscum contagiosum, and topical cidofovir has also been tried in patients with HIV infection.[1] However, clear evidence to support any form of treatment is lacking.[3]

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Pemphigus and pemphigoid

Pemphigus and pemphigoid are rare, disabling, and severe or potentially fatal blistering skin diseases. They are distinct disorders although both have an auto-immune basis. Some drugs might also trigger pemphigus or pemphigoid; implicated drugs have included penicillamine and ACE inhibitors.

- There are several types of pemphigus. In pemphigus vulgaris, the most common type, the blistering is intra-epidermal and can occur anywhere on the skin surface or present as ulceration of the mucous membranes. It is a chronic, progressive disorder requiring prolonged treatment.
- Pemphigoid is also known as bullous pemphigoid and occurs mainly in elderly persons. The blistering is subepidermal and affects the skin; mucous membranes can be affected in up to a half of all patients but it may be mild and not noticed by the patient. Pemphigoid is usually a self-limiting disorder and treatment can often be stopped after a couple of years.
- Mucous membrane pemphigoid (cicatricial pemphigoid) is a rare form that affects mainly the oral mucosa and conjunctiva, and may affect other mucosae, causing scarring.

The treatment of the blistering in both pemphigus and pemphigoid follows a similar pattern. Wet dressings and general treatment as for burns (see p. 1683.1) are commonly used. Corticosteroids are used initially to induce remission. Maintenance treatment often includes adjunctive therapies aimed at keeping control of the disease while tapering the corticosteroid dose, with the ultimate aim of complete treatment withdrawal.

High doses of systemic corticosteroids may be required to control the blistering, which may take weeks.[1-3] The optimum dose has not been established and suggestions have varied enormously (for more detail see Pemphigus and Pemphigoid, under Corticosteroids, p. 1610.1); very high doses of oral prednisolone have been used in the past.[2] Pulsed intravenous corticosteroids such as methylprednisolone may be considered for severe or refractory disease, particularly if there has been no response to high oral doses.[2,3] A very potent topical corticosteroid such as clobetasol propionate can be sufficient to control localised or mild to moderate disease in some patients, particularly in bullous pemphigoid.[1,3-5] Blistering and ulceration of the oral mucous membranes may be treated with topical corticosteroid preparations.[2,3,6] Intralesional injections have also been used for isolated lesions of the skin[3] and oral mucosa.[3,6] Topical corticosteroids may need to be added to initial systemic therapy to control acute ocular inflammation.[7]

Various therapies have been used as adjuncts or occasionally as alternatives to treatment with corticosteroids. However, given the rarity of the diseases, few controlled studies have been performed. Immunosuppressive therapy, usually with azathioprine, may be added to improve disease control and permit a reduction in corticosteroid dosage.[1,2,4,6] Cyclophosphamide and methotrexate have been used similarly although there is less information published about their use.[1,2,4,8] Oral or intravenous cyclophosphamide with a corticosteroid may be useful in severe or rapidly progressing mucous membrane pemphigoid.[6] Chlorambucil might be considered if other immunosuppressants cannot be used, but there is very limited evidence to support this.[1,2] Mycophenolate mofetil and ciclosporin have also been used in small numbers of patients with some reports of success.[1,2,4,6] Some patients with bullous pemphigoid respond to dapsone,[1,4] and it may be adequate for first-line treatment in mild to moderate inflammation in mucous membrane pemphigoid.[6,7] A tetracycline, alone or with nicotinamide, may be useful in controlling the lesions of various types of pemphigus and pemphigoid. They may be tried in patients with mild to moderate disease.[1,2,4] Intramuscular gold therapy has also been used for pemphigus vulgaris, and might be considered when other adjunctive drugs cannot be used.[2] High-dose intravenous immunoglobulin has been given to permit reduction of corticosteroid therapy in pemphigus and pemphigoid, and in some patients has produced prolonged remission.[9] It is usually reserved for severe disease that has not responded to other therapies.[2,4] Rituximab has induced remission in previously unresponsive pemphigus.[3,10-12] Plasmapheresis (plasma exchange) may be tried in severe, unresponsive disease,[1,2] but there is little evidence of benefit and its use can be limited by cost and adverse effects.[4]

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Pigmentation disorders

The pigment melanin is produced in melanocytes in the basal layer of the epidermis. It is a complex polymer synthesised from the amino acid, dihydroxyphenylalanine. Melanin production is under pituitary control but is also influenced by other endocrine secretions.

Decreased pigmentation (hypopigmentation) and excessive pigmentation (hyperpigmentation) can occur and may be either generalised or localised.

Albinism is a rare inherited disorder that can cause generalised **hypopigmentation**. Affected individuals are extremely sensitive to solar irradiation and must use sunscreens regularly.

A common form of localised hypopigmentation is **vitiligo**. Sharply defined areas of depigmentation are seen and may remain localised or spread so that total depigmentation eventually occurs. Depigmented areas are more susceptible to sunburn and all exposed areas, both normal and depigmented, should be protected from sunlight with clothing or sunscreens. Cosmetic camouflage of the depigmented area is commonly used, and may be sufficient for patients when only small affected areas are visible.[1] Dihydroxyacetone produces a brown staining of the skin that may be cosmetically acceptable. There is no totally effective repigmentation treatment, although some therapies may offer a degree of benefit. Topical corticosteroids are sometimes effective at inducing repigmentation,[2,3] and it is recommended that these be considered for a trial period of no more than 2 months.[1] Topical pimecrolimus has been suggested as an alternative to topical corticosteroids.[1] Narrowband UVB phototherapy or photochemotherapy with psoralens (PUVA) is recommended only in patients who cannot be managed with more conservative treatments, who have widespread vitiligo, or who have localised vitiligo with significant impact on their quality of life.[1] It is suggested that this treatment be reserved for patients with darker skin types.[1] Some consider UVB phototherapy to be superior to the use of UVA,[2,3] and the initial treatment of choice in moderate to severe disease,[4] or in non-segmental vitiligo.[1] Experimental drug therapy for re-inducing pigment has included UVA light therapy with either khellin or phenylalanine; oral levamisole, alone or with topical corticosteroids, has also been reported to be of benefit. There are a few small studies and case reports of benefit with the use of topical tacrolimus[4,5] and combinations of topical calcipotriol with either UV light therapy or a corticosteroid.[4] Various grafting techniques are recommended in patients for whom surgical treatment is appropriate.[1] Transplantation of autologous cultured melanocytes, ultrathin epidermal sheets, or basal cell layer suspension may be beneficial in some forms of vitiligo. The optimal transplant procedure is autologous epidermal suspension applied to laser-abraded lesions followed by narrow band UVB or PUVA therapy.[1] Transplantation is not suitable for progressive, widespread vitiligo vulgaris.[3,6] If the vitiligo affects a large proportion of the body (more than 50%), and if PUVA is ineffective at inducing repigmentation, an option is to consider inducing depigmentation in the remaining normal skin in order to match the lighter vitiligous areas.[1] Permanent depigmentation may be induced by monobenzone,[1] but patients must subsequently use topical sunscreens in order to avoid damage caused by solar exposure.

Hyperpigmentation can be caused by increased amounts of melanin, or by other substances such as iron in the skin. Generalised hyperpigmentation may be seen in Addison's disease, acanthosis nigricans, and primary haemochromatosis; other causes may include cirrhosis, chronic renal failure, and glycogen storage disease. Darkening of the skin can also occur in patients taking certain drugs due to a deposition of the drug-melanin complex in the skin. Notable examples include amiodarone, minocycline, and phenothiazines. Localised hyperpigmentation is seen in chloasma (melasma) in which there is facial involvement and is encountered most commonly in pregnancy; it may also be associated with hormonal contraceptive use. Several compounds have been used basically as bleaching agents in hyperpigmentary disorders, and of these hydroquinone has been used most often;[7,8] monobenzone is not recommended. A beneficial response to topical tretinoin and azelaic acid in patients with chloasma has been described. Combination preparations containing hydroquinone, tretinoin, and a corticosteroid are available in some countries. Laser therapy, or the use of chemical peels, has also been tried.[7,8]

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Pruritus

Pruritus (itching) is a common and distressing symptom of many skin disorders but may also have a systemic cause such as obstructive jaundice, chronic renal disease, endocrine disease, certain malignancies, or a drug hypersensitivity reaction. The exact pathophysiology of itching is unclear, and different inflammatory mediators may be associated with itching in different disorders; the CNS is also thought to play a role in the perception of itch.

Pruritus should be considered as symptomatic of the underlying disorder and treatment should focus on the removal of the offending trigger. However, symptomatic treatment of pruritus may also be necessary.

Emollients may be useful where dry skin is a contributory factor, and may be applied for **topical** management of pruritus. Calamine and crotamiton are often used topically, despite some uncertainty about their value, as are preparations containing phenol or agents such as menthol that cause capillary dilatation with a subsequent sensation of cold and analgesia. Topical capsaicin has also been used and topical corticosteroids may be used to relieve pruritus when there is associated inflammation. Local anaesthetics or antihistamines are only marginally effective for topical use and can very occasionally cause sensitisation. However, lauromacrogol 400 has proved of benefit. Doxepin, a tricyclic antidepressant with very potent antihistaminic activity, has been used topically for the relief of pruritus associated with dermatitis, but adverse effects from systemic absorption can limit its use.

Sedating antihistamines given **orally** are commonly used to relieve more generalised pruritus and are used to control the severe itching associated with dermatoses such as atopic eczema (see p. 1684.1). Mirtazapine, a noradrenergic and serotonergic antidepressant with a potent antihistamine effect, has been tried in various types of pruritus with reports of success. Bile-acid binding resins, such as colestyramine, are used to relieve pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction, primary biliary cirrhosis, or intrahepatic cholestasis of pregnancy. There are reports of cholestatic pruritus also responding to ondansetron although results from controlled studies have been mixed. Rifampicin has also been used. Pruritus caused by obstetric cholestasis has been treated with ursodeoxycholic acid, which also corrects the associated biochemical abnormalities. Central opioid receptors modulate itch and opioid antagonists such as nalmefene and naltrexone have been reported to relieve pruritus. Many other drugs, including cimetidine, gabapentin, and propofol, have been of benefit in some patients. Paroxetine has been useful in

some patients with cancer-related pruritus, but the effect tended to wear off after several weeks. PUVA (see under Methoxsalen, p. 1712.1) may be helpful in some pruritic skin conditions including aquagenic pruritus.

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Psoriasis

Psoriasis is a chronic inflammatory skin disorder characterised by enhanced epidermal proliferation leading to erythema, scaling, and thickening of the skin. It appears to be a T-cell mediated auto-immune disease. There are several types of psoriasis including guttate, flexural, pustular, and erythrodermic, but chronic plaque psoriasis (psoriasis vulgaris) is the most common form. In chronic plaque psoriasis the areas most commonly affected are the extensor sides of the knees, elbows, and hands, and the scalp and sacrum. There is no cure and treatment is designed to induce a remission or suppress disease to a tolerable level.

The treatment of psoriasis has been the subject of many reviews.[1-9]

Topical drugs are the treatment of first choice for chronic plaque psoriasis. Mild conditions may be managed with the use of emollients alone but dithranol, coal tar, calcipotriol, or tazarotene are the usual active treatments for mild to moderate forms. Patients unresponsive to one topical drug may respond to another and alternatives should be tried before considering more aggressive management. Topical drugs are often used in combination.

- Although effective, dithranol stains the skin and clothes and as it is irritant careful adjustment of the strength and duration of application needs to be made. It has traditionally been applied overnight in the form of ointments or pastes but newer short-contact regimens and creams are more suitable for home therapy.
- Coal tar is used either as crude extracts or refined products and although the refined products may be more aesthetically acceptable they may also be less effective.
- Salicylic acid enhances the rate of loss of surface scale and is included in many combination preparations with dithranol or coal tar.
- Calcipotriol and tacalcitol are vitamin D analogues, that have the advantage of being odourless and nonstaining. Maxacalcitol is another vitamin D analogue under investigation.
- Tazarotene, a retinoid, is also effective in psoriasis but significant irritation can limit its use and it should be avoided in pruritic psoriasis.
- Topical corticosteroids are also effective but they may lead to dermal atrophy, tachyphylaxis, systemic toxicity, and may precipitate unstable and pustular psoriasis. They are reported to be the most widely used treatment in the USA.[2]

Guttate psoriasis is strongly associated with streptococcal infection and patients may require antimicrobial treatment but firm evidence of a beneficial effect on the skin lesions[10] (or indeed of any intervention for guttate psoriasis[11]) is lacking.

Phototherapy with UVB light (290 to 320 nm) is effective when used alone for chronic plaque or guttate psoriasis but also enhances the efficacy of calcipotriol, coal tar, or dithranol. Studies have indicated that the therapeutic wavelengths are in the region of 311 to 313 nm. Consequently, narrowband UVB lamps (TL-01) have been developed to emit a spectrum that peaks at 311 nm.[12]

Photochemotherapy (PUVA) involves the use of oral or topical psoralens such as methoxsalen with UVA light and is generally considered to be the treatment of first choice for psoriasis that is resistant to topical therapies. Guidelines for PUVA have been published.[13,14] Psoralens have also been used with UVB light. Commercially available sunbeds, which emit UVA light, are not recommended as they are rarely effective and induce skin ageing and fragility.

Psoriasis refractory to topical therapy and PUVA may respond to **systemic drugs**. Systemic treatment may also be indicated for extensive chronic plaque psoriasis in elderly or infirm patients, for generalised pustular or erythrodermic psoriasis, or for severe psoriatic arthritis (see Spondyloarthropathies, p. 14.3).

- Immunosuppressants such as methotrexate are useful for severe refractory psoriasis, the aim of treatment being to bring psoriasis under control, enabling a return to other modes of treatment rather than to induce remission. Ciclosporin is also used in severe refractory psoriasis and may be used either to induce a remission or in low-dose maintenance therapy to prevent relapse. Tacrolimus, sirolimus, and mycophenolate are under investigation for both oral and topical use, and azathioprine has been tried.
- Systemic retinoids such as acitretin are also effective, and use with PUVA may allow a reduction in doses and associated toxicity for each therapy. Generalised pustular and palmoplantar pustular psoriasis are particularly responsive to acitretin. UVB therapy may also be used with acitretin.
- With the recognition that psoriasis is an auto-immune disease, immunomodulating drugs have been developed with an aim to provide selective immunotherapy, by either targeting T-cells or by cytokine modulation. Alefacept and efalizumab inhibit T-cell activation and show similar efficacy in the treatment of psoriasis. Cytokine modulating therapy includes blocking the action of tumour necrosis factor with adalimumab, etanercept, or infliximab, which have been found to be effective for psoriasis skin lesions and psoriatic arthritis. British[15] and American[16] guidelines endorse the use of biological treatments in appropriate patients.
  The British Association of Dermatologists recommends[15] that in chronic plaque psoriasis the biological therapies (adalimumab, etanercept, and infliximab) should be reserved for patients with severe disease that is unresponsive or refractory to standard therapies such as acitretin, ciclosporin, methotrexate, UVB, and PUVA, or when such therapies cannot be used. Adalimumab or etanercept are considered to be the first choice in stable disease. Adalimumab or infliximab may be useful when rapid disease control is needed; limited evidence suggests that infliximab may be first choice in unstable erythrodermic or generalised pustular psoriasis. Ustekinumab may also be used, but only if TNF therapy has failed or is contra-indicated. Also, it is worth considering a different TNF antagonist before trying ustekinumab. Methotrexate may be combined with either adalimumab, etanercept, or infliximab in certain circumstances e.g. associated arthropathy or to improve efficacy. American guidelines state that adalimumab, alefacept, or etanercept may be used in moderate to severe psoriasis but infliximab should be reserved for severe disease.[16] They also suggest the 3 cytokine modulators may be used in moderate to severe psoriatic arthritis and, like the British guidelines, support the combination of biological therapies with methotrexate in psoriatic arthritis.
- Hydroxycarbamide, fumarates, tioguanine, and sulfasalazine have also been tried. Many anecdotal reports note improvement of psoriasis when patients are given drug therapy for co-existing disease. The value of such drugs can be particularly difficult to establish because of the chronic relapsing and recurring nature of psoriasis.

The chronic nature of psoriasis has resulted in several different strategies being tried in order to maximise treatment efficacy and minimise toxicity.[5,6] Combinations of established drugs at lower doses can include methotrexate with either ciclosporin or acitretin, or acitretin with UV therapy. Sequential therapy uses a rapidly acting, potentially more toxic, drug to bring the condition under control initially, followed by a less toxic drug for maintenance; examples include using methotrexate or ciclosporin followed by acitretin. Rotational therapy may be used to minimise long-term toxicity by using each treatment for 1 to 2 years; methotrexate, acitretin, and UV therapy have been used in this way.[6] However, ciclosporin should not follow PUVA therapy in this way because of an increased risk of cutaneous squamous cell carcinoma.[5] There is limited experience with the use of newer immunomodulating drugs in these regimens.[6]

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Pyoderma gangrenosum

Pyoderma gangrenosum is a rare serious ulcerative skin disorder often associated with systemic diseases such as inflammatory bowel disease, rheumatoid arthritis, or myeloproliferative disorders. Initially an acutely inflamed nodule is present which progresses very rapidly to large painful ulcers. Any area of the body may be involved, but the face, legs, and buttocks are frequent sites.

Treatment essentially consists of cleansing and dressings for the ulcers and appropriate therapy for any underlying disease. When necessary high doses of systemic corticosteroids or treatment with ciclosporin may be given. There have also been reports in small numbers of patients of benefit with sulfasalazine, dapsone, azathioprine, tacrolimus, thalidomide, infliximab, colchicine, and nicotine chewing gum.

A related but less severe form of the disease, superficial granulomatous pyoderma, has responded to intralesional or oral corticosteroids.

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Rosacea

Rosacea is a chronic condition affecting the face; rarely, the trunk and limbs may be affected. Phases of this disorder include flushing episodes, persistent erythema and telangiectasia, an inflammatory papulopustular phase, and in advanced cases rhinophyma (nasal hypertrophy and deformity). Ocular involvement is also common and can cause conjunctivitis, keratitis, styes, and chalazia.[1-4] The precise cause of rosacea remains unclear. It has been suggested that *Helicobacter pylori* in the gastrointestinal tract may cause flushing by inducing the production of endogenous vasodilators, and that *Demodex folliculorum*, a mite found in human follicles, may have a role in papulopustular rosacea.[3]

The inflammatory episodes of rosacea (papules, swelling, and pustules) are responsive to treatment, but the underlying erythema and telangiectasia usually persist.

- Episodes of flushing may be limited by avoiding trigger factors such as alcoholic and hot drinks, and spicy foods.[1,4,5] Patients should use soap-free cleansers and high factor sunscreens.[1,3] In severe cases clonidine or a beta blocker such as atenolol, has been used.[3]
- Persistent erythema may be improved by *H. pylori* eradication (see Peptic Ulcer Disease, p. 1813.2) but the efficacy of such therapy has not been established.[3]
- Papulopustular rosacea is usually controlled effectively by oral antibacterials.[1,3-6] Tetracyclines (doxycycline, minocycline, oxytetracycline, tetracycline) have been widely used, but clarithromycin, erythromycin, and metronidazole are suitable alternatives. Improvement occurs over several weeks, and long-term treatment may be necessary. Systemic isotretinoin is also effective, but it is generally reserved for severe or resistant cases of rosacea.

  Topical therapies, particularly metronidazole and azelaic acid,[3-5,7,8] provide effective alternatives to oral drugs. Other topical therapies that may be useful include tetracyclines, clindamycin, erythromycin, retinoids, or a combination of sulfacetamide sodium with sulfur. Where infestations of *D. folliculorum* are suspected of aggravating the condition, topical treatments such as benzyl

benzoate, crotamiton, or permethrin may be tried. There are also anecdotal reports of the successful treatment of demodicidosis with oral ivermectin. Topical corticosteroids should not be used because they exacerbate rosacea.

- Ocular rosacea symptoms are managed with eyelid hygiene and artificial tears. Metronidazole gel can be applied to the eyelids but systemic antibacterials may be needed for more severe disease.[4,5]
- Rhinophyma requires conventional or laser surgery;[1,3-5] isotretinoin may be used for a few months preoperatively to shrink the bulbous portions.[1]

Non-drug therapies that have been advocated include facial massage;[1] however, as for many of the drug therapies[7] controlled studies are lacking. Laser therapy has been used to obliterate telangiectasia.[1,3,5]

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Seborrhoeic dermatitis

Seborrhoeic dermatitis is a common eczematous skin disorder (see Eczema p. 1684.1) in which erythematous pruritic patches of skin may become either scaly or exudative and crusted. Scaling lesions are the type most commonly seen. In some cases, known as seborrhoeic folliculitis, there may also be follicular papules or pustules. Seborrhoeic dermatitis occurs in regions of the body where sebaceous glands are plentiful, such as the scalp, face, and chest, although the condition is not associated with increased sebum production. The cause of seborrhoeic dermatitis is unknown, although it might be related to overgrowth with *Malassezia ovalis* (*Pityrosporum ovale*), a normal commensal yeast.

Treatment is suppressive rather than curative. Topical preparations containing antifungals such as ciclopirox olamine, terbinafine, or an imidazole (bifonazole, ketoconazole, miconazole), usually with hydrocortisone, are the main drugs used. If unsuccessful, keratolytics such as salicylic acid or tars may be used. Topical macrolactam immunosuppressants such as pimecrolimus and tacrolimus are being investigated as alternate therapy. Shampoos containing ketoconazole, pyrithione zinc, or selenium sulfide are commonly used for scalp involvement. Topical lithium succinate has been tried.

Dandruff due to normal shedding of scalp skin (pityriasis capitis) is treated similarly to seborrhoeic dermatitis of the scalp.

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Toxic epidermal necrolysis

Toxic epidermal necrolysis (Lyell's syndrome or scalded skin syndrome) is usually a drug-induced skin reaction. It has been described as a severe form of Stevens-Johnson syndrome, or as the most severe form of erythema multiforme (p. 1684.3), although such classifications have been debated. It generally begins with lesions of the mucous membranes of the oropharynx, eyes, and genitalia, and fever and pain. Subsequently, a macular rash, blisters, or diffuse erythema develop, and affected skin may detach irregularly, sometimes in large sheets. Toxic epidermal necrolysis is managed similarly to burns (p. 1683.1), but specific treatments have not been established. The use of systemic corticosteroids is controversial because of a higher risk of infection. Other treatments that have been tried with some reports of benefit include plasmapheresis, intravenous immunoglobulin, cyclophosphamide, ciclosporin, and infliximab.

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Urticaria and angioedema

Urticaria and angioedema are conditions caused by the release of inflammatory mediators from mast cells and basophils. **Urticaria** (also known as nettlerash or hives) is characterised by circumscribed, elevated, erythematous, and usually pruritic areas of oedema (wheals) involving the superficial portion of the dermis. Individual lesions arise suddenly, often within a few minutes, and may last up to 24 hours. In severe, acute urticaria, wheals may cover most of the skin surface. In chronic urticaria (continuous or recurrent lesions over at least 6 weeks) only a few wheals may develop each day. When subcutaneous or submucosal tissues are involved, causing swelling of the eyelids, lips, tongue, larynx, or genitalia, the condition is called **angioedema**. For hereditary angioedema, caused by complement C1 esterase inhibitor deficiency, see p. 2485.2.

Although urticaria may be caused by an allergy, it often has a non-allergic mechanism. Urticaria occurs as an adverse effect of many drugs, for example aspirin and many antibacterials. Other types of urticaria include dermographism (linear wheal formation on scratching or stroking) and cholinergic urticaria (evoked by such triggers as exercise, heat, and emotion and characterised by small papulous wheals surrounded by an erythematous flare). In **idiopathic anaphylaxis**, patients have attacks of urticaria or angioedema, sometimes with bronchospasm, hypotension, or syncope.

The **management** of urticaria and angioedema has been reviewed.[1-5] Avoidance of unnecessary exposure to known allergens or triggers is of prime importance in the management of urticaria, although in many chronic cases no trigger factor can be found. Severe, acute urticaria or angioedema requires urgent treatment as for anaphylaxis (p. 1293.2).

- Topical treatment of urticaria is rarely effective except for mild cases. Calamine, menthol, and crotamiton have cooling or antipruritic effects. Topical corticosteroids are of no value; topical antihistamines are not very effective and carry a slight risk of sensitisation.
- Most patients with urticaria derive some benefit from oral antihistamines (H_1-antagonists), especially in the relief of pruritus. A non-sedating antihistamine is the first line of treatment. If necessary, the dose may be increased after a few weeks or a different non-sedating antihistamine may be used. Combination with a leukotriene antagonist (see below) may also be tried.[4,5]
- Leukotriene antagonists such as montelukast and zafirlukast and the leukotriene inhibitor zileuton have been used alone and with antihistamines in the management of urticaria. Montelukast may add benefit to an antihistamine in chronic urticaria associated with hypersensitivity to aspirin or food additives, and in patients with evidence of histamine-releasing autoantibodies, but not in chronic idiopathic urticaria. There is some anecdotal evidence that antileukotrienes might be useful in primary cold urticaria, delayed pressure urticaria, and dermographism.[6]
- A short course of an oral corticosteroid may be indicated for control of acute urticaria in patients refractory to other measures.
- Severe disease difficult to treat with non-sedating antihistamines may respond to a combination with ciclosporin;[4,5] alternatively, omalizumab or dapsone may be considered in certain patients.[5] The combination of non-sedating antihistamines with H_2-antagonists such as ranitidine is sometimes used. However, some[5] consider this to be supported by weak evidence. Similarly, the use of drugs such as doxepin, which has H_1- and H_2-antagonist properties, and the calcium-channel blocker nifedipine, is based on weak evidence.[5] Although sedating antihistamines may be useful at bedtime, their use has been discouraged mainly because of the associated adverse effects.
- Addition of a sympathomimetic such as terbutaline has also been suggested for patients unresponsive to treatment with an H_1-antagonist alone, but results have varied.

It has been suggested that chronic urticaria may be associated with thyroid auto-immunity and that levothyroxine therapy may be of benefit in patients with antithyroid antibodies. Several other drugs including danazol, stanozolol, sulfasalazine, and intravenous immunoglobulin have reportedly produced benefit in limited numbers of patients, but such therapies are largely used empirically.

Patients with frequent attacks of idiopathic anaphylaxis have benefited from prophylaxis with a corticosteroid and antihistamine; once the condition is controlled the corticosteroid, and then the antihistamine, may be tapered and gradually withdrawn. Adjuvant ketotifen, cromoglicate, salbutamol, or montelukast may be helpful in permitting corticosteroid tapering in dependent patients. Adrenaline should be available for acute attacks.[7]

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Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Plantar warts on the soles of the feet are sometimes called verrucas. Anogenital warts are known as condylomata acuminata. Warts do disappear spontaneously but as they may not do so for months or years patients often seek treatment.

There is no specific antiviral therapy against the human papillomavirus,[1-6] although cidofovir has been tried (see below). Treatment usually relies on some form of local tissue destruction.

- Non-pharmacological techniques include surgical excision, electrocauterisation, or laser therapy. Photodynamic therapy using 5-aminolevulinic acid is also a possible treatment option.[7] Cryotherapy (tissue freezing) may be performed with liquid nitrogen or solid carbon dioxide.
- Chemical destruction with acids (acetic acid, lactic acid, nitric acid, salicylic acid, or trichloroacetic acid), silver nitrate, formaldehyde or glutaral, or podophyllum resin or its derivatives (podophyllotoxin) is another option. Podophyllum resin and podophyllotoxin are often used for anogenital warts.
- Intralesional injection of cytotoxics such as bleomycin or fluorouracil also destroys the wart and may be used in severe or resistant cases. Fluorouracil may also be applied topically.

Other treatments based on less destructive mechanisms have also been used.

- Tretinoin has been tried topically for its effect on epidermal growth.
- Imiquimod is an immune response modifier that is used topically to treat anogenital warts. There is also some evidence to suggest that it is effective for other cutaneous warts. Other drugs with immunomodulatory effects, such as cimetidine, have been tried in a few patients. There are also small studies of treatment with diphencyprone, a contact sensitiser.
- Interferons have antiviral, antiproliferative, and immunomodulatory actions and have thus been investigated in the management of warts; some studies, especially those involving intralesional administration, have showed benefit. Other routes of administration are under investigation; topical interferon alfa for anogenital warts, and an oral formulation for warts in the oral cavity of patients with HIV infection.
- Cidofovir is an antiviral that has activity against human papillomavirus. Investigational intravenous or topical use has been successful in a small number of patients with cutaneous or anogenital warts.
- Sinecatechins is a mixture of complex polyphenols extracted from green tea leaves. Although its mechanism of action is unclear, it is used in the treatment of external genital and perianal warts.

A quadrivalent recombinant human papillomavirus vaccine has recently been developed and is used to prevent anogenital warts, cervical cancer, and other pre-cancerous lesions caused by human papillomavirus types 6, 11, 16, and 18.

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Wounds and ulcers

Wounds (physical injuries of the skin and underlying structures) may be the result of mechanical trauma, burns, or chemical injury. Ulcers are often the result of various underlying disorders. Among the commonest types, *decubitus ulcers* (bedsores, pressure sores) occur in patients with extended immobility when prolonged pressure on the skin over a bony prominence produces localised ischaemia. *Leg ulcers* may result from venous incompetence (venous ulcers) or be ischaemic in origin (arterial ulcers), while patients with peripheral neuropathy, such as diabetics or those with leprosy, may develop *neuropathic ulcers* due to repetitive inadvertent injury. Wounds or ulcers may be described as superficial, partial thickness, or full thickness. Superficial wounds are limited to epithelial tissue and heal rapidly by regeneration of epithelial cells. Partial thickness wounds involve the dermis and include some blood vessel damage, and therefore wound repair is a longer process. Full thickness wounds extend at least to subcutaneous fat, and healing requires synthesis of new connective tissue.

Healing mechanisms are essentially the same regardless of the cause of the damage:

- immediate haemostatic processes involve formation of a platelet plug and fibrin clot, as described under Haemostasis and Fibrinolysis, p. 1124.3
- the early granulation and re-epithelialisation phase takes place up to about 21 days after injury depending on wound size and site. Platelet-derived growth factors stimulate fibroblasts to produce granulation tissue, comprising a collagen matrix well-supplied with capillary vessels, and growth of epidermal cells leading to re-epithelialisation of the wound surface
- during the final dermal repair and remodelling phase the collagen matrix undergoes strengthening and there is a reduction in vascularity. This phase can continue for up to 2 years after injury.

Several factors are important for efficient wound healing. Adequate supplies of nutrients, especially vitamin C and zinc (which are often given as supplements) and oxygen are needed. A good blood supply is thus essential. Clinical infection, either systemic or local, due to contamination by environmental microbes, causes tissue damage and delays healing. The process of wound repair requires many cellular and acellular factors, such as platelets and growth factors, and deficiencies in these may also be responsible for delayed healing. Thus, the patient's age, systemic conditions, concomitant drugs, nutritional status, and congenital deficiencies all influence the rate of healing.

Local **wound management** includes cleansing, removal of exudate, and prevention of microbial contamination. Choice of wound treatment preparation will depend on the size, location, type, and cause of the wound, on the presence of infection, and on the particular stage of healing.

Wound **cleansing** is required to remove any dirt or foreign bodies and to **remove exudate** and slough (pus and necrotic tissue). This helps to prevent infection and aids healing. Commonly used cleansing solutions are sodium chloride 0.9%, hypochlorite, hydrogen peroxide, povidone-iodine, and chlorhexidine. However, some antiseptics and hypochlorites might be associated with delayed wound healing, especially with prolonged use, as they delay collagen production and cause inflammation. Also, many antiseptics are inactivated by organic material. Sodium chloride solution may be all that is required for routine cleansing of non-infected wounds.

Many of the cleansing solutions also help to remove slough. Other wound management preparations more specifically directed at removing slough include dextranomer, hydrogels, hydrocolloids, and enzyme preparations such as a mixture of streptokinase and streptodornase. Dextranomer, hydrogels, and hydrocolloids cause debridement by their occlusive, rehydrating properties. Surgical debridement is a fast and efficient way of removing necrotic tissue. Larval therapy (the use of live sterile maggots of *Lucilia sericata*, the common greenbottle fly) has also been effective for debridement of infected or necrotic wounds, including diabetic foot ulceration.

Wounds may produce large volumes of exudate as a result of inflammatory reactions, especially during the first few days. Hydrocolloid and alginate preparations and foam dressings are effective moisture absorbers.

All wounds are colonised by bacteria to some extent and there is no evidence that this superficial **infection** affects healing. However, infection with *Pseudomonas aeruginosa* may delay healing. Topical antimicrobials may be considered, but short-term use is advisable; sulfadiazine silver is used, especially in burns. Acetic acid has also been used. Infections are treated systemically if there are indications of clinical infection such as sudden pain, cellulitis, and increased discharge; systemic management of bacterial skin infections is described on p. 207.1.

Wound **dressings** and packing preparations help to protect the wound and provide the correct environment for wound healing. Some also help by absorbing exudate. Superficial wounds usually only require a low-adherent dressing. Traditional dry dressings such as cotton wool, gauze, and lint are not used for partial or full thickness cavity wounds since they shed fibres, adhere to the wound, and cause wound dehydration. Hydrogels, hydrocolloids, polysaccharides, cadexomer-iodine, alginates, and foam dressings are all effective cavity wound preparations. Hyaluronic acid is incorporated into some dressings to promote wound healing.

Activated charcoal is very effective at reducing offensive odours from **malodorous wounds**, as are sugar (sucrose) pastes. Sucrose may exert its antibacterial effect by competing for water present in the cells of bacteria. Metronidazole is active against anaerobic bacteria that are associated with the pungent smell and is used topically for deodorising malodorous tumours. Metronidazole is not generally used on wounds because of the risk of inducing resistance but it is sometimes used to deodorise malodorous venous leg ulcers or decubitus ulcers.

In addition to the use of wound preparations, there may be other measures that aid healing of specific wounds or ulcers. Some wounds may require skin grafting. Skin substitutes, and growth factors, such as becaplermin, molgramostim, trafermin, and urogastrone, are being used or developed for non-healing ulcers and wounds. Autologous blood-derived platelet gels containing growth factors are available to aid and accelerate wound healing. Topical phenytoin has produced some encouraging results in promoting the healing of various types of ulcers. Measures that aid the return of fluid from the leg, such as flexing the ankles, elevation, and use of compression bandages are beneficial in **venous ulcers**. There is insufficient evidence to recommend one type of dressing in preference to another, including the use of hydrocolloid dressings instead of simple low adherent dressings. The bioflavonoids, given orally, may improve venous insufficiency and therefore also aid healing. Systemic drugs that improve the supply of oxygen to tissues, for example pentoxifylline, may be useful in ischaemic and venous ulcers. Topical and systemic ketanserin has been investigated in a few patients and may be beneficial in wounds and ulcers where there is impaired blood flow. Hyperbaric oxygen therapy has been tried in a range of chronic wounds; it might be useful in reducing amputation in patients with chronic diabetic foot ulcers. Vascular surgery may be necessary in the management of some ulcers caused by ischaemia or chronic venous insufficiency. In **decubitus ulcers**, relief of pressure is the most important measure in management. Support surfaces and the use of various products containing silicone may help protect fragile tissue. The management of **burns** and **chemical burns** is described on p. 1683.1.

General references.
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17. Palfreyman S, *et al.* Dressings for venous leg ulcers: systematic review and meta-analysis. *BMJ* 2007; **335:** 244–8.
18. Reddy M, *et al.* Treatment of pressure ulcers: a systematic review. *JAMA* 2008; **300:** 2647–62.
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Abrasive Agents

Abrasivos; Абразивные Вещества; Шлифовальные Средства.

Aluminium Oxide

Aliuminio oksidas; Alumiinioksidi; Aluminii Oxidum; Aluminio, óxido de; Aluminiumoxid; Alumínium-oxid; Aluminum Oxide; Glinu tlenek; Алюминия Оксид.

Al_2O_3=102.0

CAS — 1344-28-1.

ATC — D10AX04.

ATC Vet — QD10AX04.

UNII — LMI26O6933.

Pharmacopoeias. In *USNF.*

Eur. (see p. vii) includes the hydrated form (see Aluminium Hydroxide, p. 1817.2).

USNF 31: (Aluminum Oxide). It contains not less than 47.0% and not more than 60.0% of Al_2O_3. A white or almost white, amorphous powder. Practically insoluble in water; very slightly soluble in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers at a temperature not exceeding 30 degrees.

Pumice

Lapis Pumicis; Piedra pómez; Pierre Ponce Granulée; Pumex; Pumex Granulatus; Pumice Stone; Пемза.

CAS — 1332-09-8.

Pharmacopoeias. In *US.*

USP 36: (Pumice). Pumice is a substance of volcanic origin consisting chiefly of complex silicates of aluminium, potassium, and sodium. Odourless, very light, hard, rough, porous greyish masses or gritty, greyish powder. It is stable in air. Practically insoluble in water and not attacked by acids. Three grades of powdered pumice are recognised:

- superfine (=pumice flour)—not less than 97% passes through a No. 200 [US] sieve
- fine—not less than 95% passes through a No. 150 sieve and not more than 75% through a No. 200 sieve
- coarse—not less than 95% passes through a No. 60 sieve and not more than 5% through a No. 200 sieve

Profile

Abrasive agents such as fused synthetic aluminium oxide or powdered pumice have been used either as adjuncts in the treatment of acne (despite doubts about their value—see p. 1682.2) or for the removal of hard skin. Pumice has also been used as a dental abrasive and as a filtering medium. Other agents used as abrasives for acne include polyethylene granules.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abralux; Ionax Scrub; Puraclin Exfoliante; ***Austral.***: Brasivol†; ***Braz.***: Ionax Scrub; ***Chile***: Ionax Scrub; Podexine Exfoliante; Scrub-Atlas; ***Fr.***: Brasivol; ***Irl.***: Brasivol†; ***Malaysia***: Ionax Scrub; ***Mex.***: Betagranulos; Ionax Scrub; ***Philipp.***: Ionax Scrub; ***S.Afr.***: Brasivol†; ***Singapore***: Ionax Scrub; ***UK***: Brasivol; ***USA***: Brasivol; Ionax Scrub; ***Venez.***: Betagranulos; Ionax Scrub.

Multi-ingredient Preparations. ***Arg.***: Scrub-Atlas; ***Belg.***: Stomacid; ***Chile***: Podexine Durezas y Callosidades; ***Hung.***: Gastracid; ***Indon.***: Aludonna; ***Ital.***: Clarifex Scrub; ***Mex.***: Dermobras; ***S. Afr.***: Pedimed†; ***Switz.***: Cliniderm; ***Ukr.***: Altacid (Алтацид)†; ***USA***: Pernox; Zanfel; ***Venez.***: Exfoliderm.

Homoeopathic Preparations. ***Canad.***: Comp-Drops 3 Bowel Support†; Eczema; Headache & Migraine; Homeo-Form CO†; Homeo-Form MI†; Reneel†; ***Ger.***: Curare comp; Gastriselect N; Infifer N; Lowe-Komplex Nr 6; ***Neth.***: Colintest-Gastreu R37; Enulite; Gynaelite; ***Switz.***: Gastronol; Regenaplex Nr 38b.

Acitretin *(BAN, USAN, rINN)*

Acitretina; Acitretinas; Acitrétine; Acitretinum; Asitretiini; Asitretin; Etretin; Etretina; Ro-10-1670; Ro-10-1670/000; Ацитретин.

(*all-trans*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid; (2*E*,4*E*,6*E*,8*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid.

$C_{21}H_{26}O_3$=326.4

CAS — 55079-83-9.

ATC — D05BB02.

ATC Vet — QD05BB02.
UNII — LCH760E9T7.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Acitretin). A yellow or greenish-yellow, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in acetone; very slightly soluble in cyclohexane; sparingly soluble in tetrahydrofuran. It is sensitive to air, heat, and light, especially in solution. Store at 2 degrees to 8 degrees in airtight containers. Protect from light. It is recommended that the contents of an opened container be used as soon as possible and any unused part be protected by an atmosphere of inert gas.

USP 36: (Acitretin). A yellow or greenish, crystalline powder. Practically insoluble in water; slightly soluble in acetone and in alcohol; very slightly soluble in cyclohexane; sparingly soluble in tetrahydrofuran. Store in airtight containers at 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Acitretin is a retinoid and is a metabolite of etretinate (p. 1703.3). It is used orally in the treatment of severe psoriasis resistant to other forms of therapy, palmo-plantar pustular psoriasis, severe congenital ichthyosis and Darier's disease (keratosis follicularis), and in severe lichen planus.

In the UK, acitretin is given in an initial daily dose of 25 or 30 mg with food for 2 to 4 weeks; in the USA (where it is licensed only for use in psoriasis) initial doses up to 50 mg daily are permitted. The daily dosage is adjusted thereafter according to clinical response and adverse effects; optimal results are usually obtained with 25 to 50 mg given daily for a further 6 to 8 weeks but some patients may require up to 75 mg daily. For the treatment of Darier's disease a starting dose of 10 mg may be appropriate, adjusted thereafter according to response. In Darier's disease and congenital ichthyosis treatment may be required for more than 3 months but a daily dosage of 50 mg should not be exceeded. In the UK, licensed product information recommends that continuous treatment should not last longer than 6 months for any indication because of limited clinical data. For lichen planus, doses are similar to those used in the UK (see above).

For doses in children, see below.

Administration in children. Acitretin is not generally considered suitable for use in children. However, reviews[1,2] of its use in children with severe inherited disorders of keratinisation reported that acitretin was an effective and safe treatment provided that the minimal effective dose was used and that adverse effects were carefully monitored. UK licensed product information contra-indicates acitretin use in children unless the benefits significantly outweigh the risks, particularly premature epiphyseal closure and other skeletal effects associated with retinoids. However, if deemed necessary an oral dose of 500 micrograms/kg once daily (occasionally up to 1 mg/kg daily for limited periods) has been suggested, but the maximum daily dose should not exceed 35 mg. The *BNFC* suggests that these doses may be used under expert supervision for children aged 1 month to 12 years for the treatment of severe extensive psoriasis resistant to other forms of therapy, palmo-plantar pustular psoriasis, severe congenital ichthyosis, and Darier's disease. The adult dose (see above) is considered suitable for children from 12 years of age. The *BNFC* also includes a dose of 500 micrograms/kg daily (occasionally up to 1 mg/kg daily) for the management of harlequin ichthyosis in neonates.

1. Lacour M, *et al.* An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol* 1996; **134:** 1023–9.
2. Zhang X-B, *et al.* Clinical investigation of acitretin in children with severe inherited keratinization disorders in China. *J Dermatolog Treat* 2008; **19:** 221–8.

Eye disorders. A case report indicated that acitretin, given for psoriasis at an initial dose of 30 mg daily for one month and then reduced to 20 mg daily, improved corneal opacities in a patient with chronic tuberculosis-related interstitial keratitis.[1]

1. Labetoulle M, *et al.* Rapid improvement of chronic interstitial keratitis with acitretin. *Br J Ophthalmol* 2002; **86:** 1445–6.

Malignant neoplasms. Acitretin may be useful in preventing the development of skin neoplasms in high-risk individuals, such as solid organ transplant recipients.[1,2] However, long-term therapy is needed to maintain the effect and adverse effects can limit its use[2] (see also Malignant Neoplasms under Isotretinoin, p. 1707.1). Gradual dose escalation may help to minimise mucocutaneous effects, and one proposed schedule for oral acitretin starts with 10 mg on alternate days for 2 weeks, 10 mg daily for the next 2 weeks, then 20 mg daily for a month; the dose is then adjusted as tolerated. Maintenance regimens of 25 mg daily, or alternating daily doses of 10 mg and 20 mg, have been used.[3]

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Skin disorders. Acitretin is used alone or with PUVA (a psoralen with UVA irradiation, see p. 1712.1) or UVB in psoriasis[1-5] (p. 1688.1). Studies have shown that use with PUVA or UVB light may increase efficacy and allow a reduction in the exposure to radiation required. It is also used in keratinisation disorders such as severe forms of ichthyosis[1,5-8] (p. 1685.1) and Darier's disease (keratosis follicularis)[1,5,9] (p. 1683.2). Benefit has been reported in various other skin disorders including lichen planus (p. 1685.2), lichen sclerosus (p. 1685.2), and cutaneous lupus erythematosus (p. 1613.3).[1,5]

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7. Steijlen PM, *et al.* Acitretin in the treatment of lamellar ichthyosis. *Br J Dermatol* 1994; **130:** 211–14.
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Adverse Effects and Precautions

As for Isotretinoin, p. 1707.2 and p. 1709.2.

Acitretin has a relatively short half-life, but etretinate, which has a very prolonged half-life, has been detected in the plasma of some patients receiving acitretin. Recommendations vary slightly in different countries but pregnancy should be avoided for at least 2 to 3 years after treatment has been withdrawn (see also Pregnancy, below) and patients should not donate blood for at least 1 to 3 years after stopping therapy. Female patients should avoid alcohol during treatment with acitretin and for 2 months after stopping treatment (see under Interactions, below).

Breast feeding. Acitretin was distributed into the breast milk of a woman treated with oral acitretin for psoriasis. Although the estimated amount of acitretin that would be consumed by a breast-fed infant was only 1.5% of the maternal dose, the authors considered that the toxic potential of acitretin to the infant justified its avoidance. In this case, the infant was not breast-fed during acitretin therapy.[1] Licensed product information also recommends that breast-feeding women should not be given acitretin. The American Academy of Pediatrics, however, has found no mention of clinical effect on the infant, and considers the maternal use of acitretin to be usually compatible with breast feeding.[2]

1. Rollman O, Pihl-Lundin I. Acitretin excretion into human breast milk. *Acta Derm Venereol (Stockh)* 1990; **70:** 487–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/09/07)

Capillary leak syndrome. There are rare reports of capillary leak syndrome associated with acitretin. In one case, generalised oedema and weight gain, haemorrhagic lesions, and evidence of rhabdomyolysis were seen.[1] In another, there was oedema and weight gain, dyspnoea, pulmonary infiltrates, pleural effusion, hypotension, and oliguria.[2] These reactions may be related to the retinoic acid syndrome that can occur with tretinoin (see p. 1726.2). Generalised oedema has also been reported with etretinate (p. 1704.1).

1. Estival JL, *et al.* Capillary leak syndrome induced by acitretin. *Br J Dermatol* 2004; **150:** 150–2.
2. Vos LE, *et al.* Acitretin induces capillary leak syndrome in a patient with pustular psoriasis. *J Am Acad Dermatol* 2007; **56:** 339–42.

Effects on the blood. For reports of adverse effects on the blood by oral retinoids, including agranulocytosis associated with acitretin, see under Isotretinoin, p. 1707.3.

Effects on the eyes. For reference to maculopathy occurring during therapy with acitretin, and the ocular effects of benign intracranial hypertension caused by retinoids, see under Isotretinoin, p. 1707.3.

Effects on the musculoskeletal system. For reference to myopathy occurring during therapy with acitretin, and a discussion of hyperostosis and calcinosis that can occur with oral retinoid therapy, see under Isotretinoin, p. 1708.2.

Effects on the skin. For mention of the exacerbation of erythroderma by acitretin, see under Isotretinoin, p. 1709.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acitretin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. The risks of spontaneous abortion and malformations similar to those associated with isotretinoin (p. 1709.3) are high when acitretin or etretinate are given during pregnancy, particularly the first trimester.[1,2] Although the risks might be lower after stopping treatment, malformations have still been reported in infants and aborted fetuses conceived within 2 years of stopping acitretin[1,3] and up to 45 months after stopping etretinate.[1] In the UK licensed product information for acitretin recommends that pregnancy should be avoided during and for at least 2 years (3 years is recommended in the USA) after withdrawal of therapy because etretinate, which has a much longer half-life than acitretin, has been detected in the plasma of some patients given acitretin. It has been pointed out that plasma-etretinate concentrations are a poor indication of total body stores; a study[4] has indicated that there may be substantial concentrations of etretinate in the fatty tissues of women who have received acitretin.

For information on contraceptive choice in women taking oral retinoids, see under Isotretinoin, p. 1709.3.

1. Geiger J-M, *et al.* Teratogenic risk with etretinate and acitretin treatment. *Dermatology* 1994; **189:** 109–16.
2. Barbero P, *et al.* Acitretin embryopathy: a case report. *Birth Defects Res A Clin Mol Teratol* 2004; **70:** 831–3.
3. Maradit H, Geiger J-M. Potential risk of birth defects after acitretin discontinuation. *Dermatology* 1999; **198:** 3–4.
4. Sturkenboom MCJM, *et al.* Inability to detect plasma etretinate and acitretin is a poor predictor of the absence of these teratogens in tissue after stopping acitretin treatment. *Br J Clin Pharmacol* 1994; **38:** 229–35.

Interactions

As for Isotretinoin, p. 1710.1.

Etretinate has been detected in the plasma of some patients receiving acitretin and acitretin is also a metabolite of etretinate; therefore interactions associated with etretinate (see p. 1704.1) may also apply to acitretin. Taking acitretin with alcohol has been associated with etretinate formation.

For discussion of the potential interactions of retinoids with hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p. 2243.3.

Alcohol. The consumption of alcohol has been associated with the formation of etretinate in patients taking acitretin.[1,2] One study[2] found a trend suggesting that a higher alcohol intake was associated with a higher risk of etretinate formation and higher etretinate concentrations. However, the presence of alcohol is not essential for this transformation to take place and etretinate has also been detected in a patient taking acitretin who did not drink alcohol.[3] Consequently, licensed product information warns that alcohol must not be consumed by female patients during acitretin therapy and for 2 months after stopping, to avoid the formation of etretinate and associated prolonged risks of teratogenicity (see Pregnancy, above).

1. Larsen FG, *et al.* Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. *J Invest Dermatol* 1993; **100:** 623–7.
2. Larsen FG, *et al.* Acitretin is converted to etretinate only during concomitant alcohol intake. *Br J Dermatol* 2000; **143:** 1164–9.
3. Maier H, Hönigsmann H. Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 1996; **348:** 1107.

Pharmacokinetics

Acitretin is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 5 hours after oral doses. Bioavailability after a single dose is about 60 to 70%, but this can vary considerably; bioavailability may be increased by dosage with food. Acitretin is highly bound to plasma proteins. It is metabolised to 13-*cis*-acitretin. Etretinate (p. 1703.3) has also been detected in the plasma of some patients after doses of acitretin. The elimination half-life of acitretin is about 2 days but account should always be taken

of the fact that the half-life of etretinate is much longer, being about 120 days. Acitretin is excreted as metabolites in bile and urine, and is distributed into breast milk.

General references.

1. Larsen FG, *et al*. Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; **23:** 42–61.
2. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; **190** (suppl): 1–33.
3. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; **39** (suppl): S25–S33.

Renal impairment. The pharmacokinetics of acitretin are reported to be altered in patients with chronic renal failure but neither acitretin nor its 13-*cis* metabolite are removed by haemodialysis.[1]

1. Stuck AE, *et al*. Pharmacokinetics of acitretin and its 13-cis metabolite in patients on haemodialysis. *Br J Clin Pharmacol* 1989; **27:** 301–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Neotigason; ***Austral.***: Neotigason; ***Austria***: Neotigason; ***Belg.***: Neotigason; ***Braz.***: Neotigason; ***Canad.***: Soriatane; ***Chile***: Neotigason; ***China***: Fang Xi (方希); Neotigason (新体卡松); ***Cz.***: Neotigason; ***Denm.***: Neotigason; ***Fin.***: Neotigason; ***Fr.***: Soriatane; ***Ger.***: Neotigason; ***Gr.***: Neotigason; ***Hong Kong***: Neotigason; ***Hung.***: Neotigason; ***India***: Aceret; Acetec; Acitrin; ***Irl.***: Neotigason; ***Israel***: Neotigason; ***Ital.***: Neotigason; ***Malaysia***: Neotigason; ***Mex.***: Neotigason; ***Neth.***: Keraderm; Neotigason; Regioderm; ***Norw.***: Neotigason; ***NZ***: Neotigason; Novatretin; ***Philipp.***: Neotigason; ***Pol.***: Neotigason; ***Port.***: Neotigason; ***Rus.***: Neotigason (Неотигазон); ***S.Afr.***: Neotigason; ***Singapore***: Neotigason; ***Spain***: Neotigason; ***Swed.***: Neotigason; ***Switz.***: Acicutan; Neotigason; ***Thai.***: Neotigason; ***Turk.***: Neotigason; ***UK***: Neotigason; ***USA***: Soriatane; ***Venez.***: Neotigason.

Pharmacopoeial Preparations
BP 2014: Acitretin Capsules;
USP 36: Acitretin Capsules.

Adapalene *(BAN, USAN, rINN)*

Adapaleeni; Adapalen; Adapalène; Adapaleno; Adapalenum; CD-271; Адапален.

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

$C_{28}H_{28}O_3$=412.5

CAS — 106685-40-9.

ATC — D10AD03.

ATC Vet — QD10AD03.

UNII — 1L4806J2QF.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Adapalene). A white or almost white powder. Practically insoluble in water and in alcohol; sparingly soluble in tetrahydrofuran.

USP 36: (Adapalene). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in tetrahydrofuran. Store in airtight containers. Protect from light.

Uses and Administration

Adapalene is a naphthoic acid derivative and retinoid analogue with actions similar to those of tretinoin (p. 1725.2). Adapalene is used in topical treatment of mild to moderate acne (p. 1682.2) where comedones, papules, and pustules predominate.

Adapalene is usually applied once daily at night as a 0.1% solution, cream, or gel to skin that has been cleansed and dried; a 0.3% gel is also available. Some patients may require less frequent applications. Other topical preparations that may cause irritation should not be used concurrently. If treatment with topical antibacterials or benzoyl peroxide is required, these should be applied in the morning and adapalene applied at night. However, a formulation combining adapalene with benzoyl peroxide, allowing simultaneous application, is available in some countries.

There may be apparent exacerbations of the acne during early treatment and a consistent therapeutic response may not be evident for at least 8 weeks. However, if there is no response after 12 weeks, therapy should be reassessed.

For use in young children, see below.

References.

1. Brogden RN, Goa KL. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs* 1997; **53:** 511–19.
2. Waugh J, *et al*. Adapalene: a review of its use in the treatment of acne vulgaris. *Drugs* 2004; **64:** 1465–78.
3. Pariser DM, *et al*. Adapalene Study Group. The efficacy and safety of adapalene gel 0.3% in the treatment of acne vulgaris: a randomized, multicenter, investigator-blinded, controlled comparison study versus adapalene gel 0.1% and vehicle. *Cutis* 2005; **76:** 145–51.
4. Thiboutot D, *et al*. Adapalene Study Group. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol* 2006; **54:** 242–50.
5. Thiboutot DM, *et al*. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol* 2006; **142:** 597–602.
6. Gollnick HP, *et al*. Adapalene–BPO Study Group. Adapalene–benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol* 2009; **161:** 1180–9.

Administration in children. Although not licensed for young children in the UK the *BNFC* includes adapalene 0.1% cream and gel, applied thinly once daily at night, for neonatal and infantile acne.

Adverse Effects and Precautions

As for Tretinoin, p. 1726.1 and p. 1726.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adapalene as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Anophthalmia and agenesis of the optic chiasma were found in a fetus after termination of pregnancy in a woman who had applied adapalene 0.1% topically from the month before pregnancy until 13 weeks of gestation.[1]

1. Autret E, *et al*. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet* 1997; **350:** 339.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acnidazil; Adapne; Differin; Doniq; KM Gel; Panalene; Sinac; ***Austral.***: Differin; ***Austria***: Differin; ***Belg.***: Differin; ***Braz.***: Adacne; Adapel; Dalap; Deriva; Differin; ***Canad.***: Differin; ***Chile***: Adamed; Adiamil; Daplen†; Differin; Flamir; Nyskin; Zudenina; ***China***: Differin (达芙文); ***Cz.***: Differine; ***Denm.***: Redap; ***Fin.***: Differin; ***Fr.***: Differine; ***Ger.***: Differin; ***Gr.***: Adaferin; ***Hong Kong***: Aclear; Differin; Tifforly; ***Hung.***: Differin; ***India***: Aclene; Adaferin; Adapen; Adaple; Adaret; Adiff; Adlene-AD; Alangel; Alene; Apgel; Deriva; Difra; ***Indon.***: Evalen; ***Irl.***: Differin; ***Israel***: Adaferin; ***Ital.***: Differin; ***Malaysia***: Deriva; Differin; T3 ADA; ***Mex.***: Adaferin; Leneda; Trablene†; ***Neth.***: Differin; ***Norw.***: Differin; ***NZ***: Differin; ***Philipp.***: Differin; Klenzit; ***Pol.***: Differin; ***Port.***: Differin; ***Rus.***: Clenzit (Клензит); Differin (Дифферин); ***S.Afr.***: Differin; ***Singapore***: Differin; ***Spain***: Differine; ***Swed.***: Differin; ***Switz.***: Differin; ***Thai.***: Differin; ***Turk.***: Differin; Palexil; ***UK***: Differin; ***USA***: Differin; ***Venez.***: Differin.

Multi-ingredient Preparations. ***Arg.***: Epiduo; Panalene Duo; ***Austral.***: Epiduo; ***Belg.***: Epiduo; ***Braz.***: Adacne Clin; Epiduo; ***Canad.***: Tactuo; ***Denm.***: Epiduo; Tactuo†; ***Fin.***: Epiduo; ***Fr.***: Epiduo; ***Ger.***: Epiduo; ***Gr.***: Epiduo; ***Hong Kong***: Epiduo; ***India***: Acneris-AD; Adacin; Clindapene; Clinderm-A; Deriva-C; Deriva-CMS; Epilene C; Faceclin-A; Feiz; Labopene-C; ***Ital.***: Epiduo; ***Norw.***: Epiduo; ***NZ***: Epiduo; ***Philipp.***: Epiduo; ***Pol.***: Epiduo; ***Port.***: Epiduo; ***Rus.***: Clenzit-C (Клензит-С); ***Singapore***: Epiduo; ***Spain***: Epiduo; Tactuoben; ***Swed.***: Epiduo; ***Switz.***: Epiduo; ***Thai.***: Epiduo; ***UK***: Epiduo; ***USA***: Epiduo.

Pharmacopoeial Preparations
BP 2014: Adapalene Cream; Adapalene Gel.

Aldioxa *(USAN, rINN)*

ALCA; Alcloxum; Aluminium Chlorhydroxyallantoinate; Aluminum Chlorhydroxy Allantoinate; Clorohidroxialantoinato de aluminio; RC-173; Альклокса.

Chlorotetrahydroxy[(2-hydroxy-5-oxo-2-imidazolin-4-yl) ureato]dialuminium.

$C_4H_9Al_2ClN_4O_7$=314.6

CAS — 1317-25-5.

UNII — 1888O9DQA2.

Profile

Alcloxa is an astringent and keratolytic related to allantoin (p. 1693.1). It is present in multi-ingredient preparations intended for various skin and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Babysan Powder.

Multi-ingredient Preparations. ***Hong Kong***: Pilelife†; ***Malaysia***: Neo-Medrol; ***Thai.***: Neo-Medrol; ***UK***: Dermidex.

Aldioxa *(USAN, rINN)*

ALDA; Aldioxum; Aluminium Dihydroxyallantoinate; Aluminum Dihydroxy Allantoinate; Dihidroxialantoinato de aluminio; Dihydroxyaluminum Allantoinate; RC-172; Альдиокса.

Dihydroxy[(2-hydroxy-5-oxo-2-imidazolin-4-yl)ureato]aluminium.

$C_4H_7AlN_4O_5$=218.1

CAS — 5579-81-7.

UNII — 8T66I31YNK.

Pharmacopoeias. In *Jpn.*

Profile

Aldioxa is an astringent and keratolytic related to allantoin (p. 1693.1). It is present in multi-ingredient preparations intended for various skin and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Culmisa (卡尔萨); Ou Di Jia (欧迪佳); Xi Jing (悉景).

Multi-ingredient Preparations. ***Arg.***: ZeaSorb; ***Austral.***: ZeaSorb†; ***Canad.***: ZeaSorb; ***China***: CP Bright (正大维他); JieAn (捷安); ***Fr.***: ZeaSorb; ***Gr.***: Rikospray Silicone; ***Indon.***: ZeaSorb; ***Irl.***: ZeaSorb; ***Israel***: Aronal Forte; ***Ital.***: Rikospray; ***Mex.***: Dentsiblen†; ***Philipp.***: ZeaSorb; ***S.Afr.***: ZeaSorb†; ***Singapore***: ZeaSorb; ***Thai.***: ZeaSorb†; ***UK***: Cetanorm; ZeaSorb.

Alefacept *(BAN, USAN, rINN)*

Aléfacept; Alefaceptum; BG-9273; BG-9712; LFA3TIP; Recombinant Human LFA-3/1gG$_1$ Fusion Protein; Алефацепт.

A dimer of 1-92 antigen LFA-3 (human) fusion protein with human immunoglobulin G1 (hinge-C_H2-C_H3 γ1-chain).

CAS — 222535-22-0.

ATC — L04AA15.

ATC Vet — QL04AA15.

UNII — ELK3V90G6C.

Uses and Administration

Alefacept is a recombinant human fusion protein that binds to CD2 on memory T-lymphocytes, preventing their activation and reducing their number. It is used in the management of moderate to severe chronic plaque psoriasis (p. 1688.1) and is given in a dose of 15 mg once weekly by intramuscular injection, for 12 weeks. A second 12-week course may be given if necessary, starting not less than 12 weeks after the completion of the first.

General references.

1. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001; **345:** 248–55.
2. Krueger GG, *et al*. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002; **47:** 821–33.
3. Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. *Br J Dermatol* 2003; **148:** 784–8.
4. Lebwohl M, *et al*. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003; **139:** 719–27.
5. Korman NJ, Moul DK. Alefacept for the treatment of psoriasis: a review of the current literature and practical suggestions for everyday clinical use. *Semin Cutan Med Surg* 2005; **24:** 10–18.
6. Ortonne JP, *et al*. An open-label study of alefacept plus ultraviolet B light as combination therapy for chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 2005; **19:** 556–63.
7. Mease PJ, *et al*. Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006; **54:** 1638–45.
8. Strober BE, Menon K. Alefacept for the treatment of psoriasis and other dermatologic diseases. *Dermatol Ther* 2007; **20:** 270–6.
9. Landells I, *et al*. Efficacy outcomes in patients using alefacept in the AWARE study. *J Cutan Med Surg* 2009; **13** (suppl 3): S122–S130.
10. Dunn LK, Feldman SR. Alefacept treatment for chronic plaque psoriasis. *Skin Therapy Lett* 2010; **15:** 1–3.

Adverse Effects and Precautions

Chills are common on intravenous dosage of alefacept. Other adverse effects are cough, dizziness, headache, injection site pain and inflammation, myalgia, nausea, pharyngitis, and pruritus. More serious adverse reactions are cardiovascular events (including coronary artery disorder and myocardial infarction), hypersensitivity reactions, lymphopenia, and serious infections requiring hospitalisation. Cases of hepatotoxicity including asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis, and acute liver failure have occurred. Like other drugs with immunosuppressant actions, alefacept may increase the risk of malignancies, particularly basal or squamous cell cancers of the skin. It should not be given to patients with a history of malignancy.

Alefacept should also not be given to patients with pre-existing serious infections, and should be stopped if these develop. Its use should be considered carefully in patients with chronic infections or a history of recurrent infection.

Alefacept induces a dose-dependent reduction in circulating CD4+ and CD8+ T-lymphocyte counts. It is

therefore also contra-indicated in patients with HIV infection as the reduction in CD4+ T-lymphocytes could accelerate disease progression or increase complications of HIV infection. CD4+ T-lymphocyte counts should be monitored before starting alefacept therapy and then every 2 weeks during the 12-week treatment period. Treatment should not be started in patients with a CD4+ T-lymphocyte count below normal. Doses should be withheld and weekly monitoring started if the counts fall below 250 cells/microlitre, and treatment stopped if the counts remain below this level for one month.

Therapy should be stopped immediately, and appropriate treatment given, in patients who have anaphylaxis or serious hypersensitivity; it should not be restarted.

References.
1. Goffe B, *et al*. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. *Clin Ther* 2005; **27:** 1912–21.

Pharmacokinetics

Alefacept has a bioavailability of about 63% after intramuscular injection. After an intravenous dose it has an elimination half-life of about 11 to 12 days.

References.
1. Vaishnaw AK, TenHoor CN. Pharmacokinetics, biologic activity, and tolerability of alefacept by intravenous and intramuscular administration. *J Pharmacokinet Pharmacodyn* 2002; **29:** 415–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Amevive†; ***Canad.***: Amevive†; ***Israel***: Amevive; ***Switz.***: Amevive†; ***USA***: Amevive.

Allantoin *(BAN, USAN)*

Alantoin; Alantoína; Alantoinas; Allantoiini; Allantoïne; Allantoinum; Glioxildiureído; Glyoxyldiureide; 5-Ureidohidantoína; Кордианин; Аллантоин.

5-Ureidohydantoin; 5-Ureidoimidazolidine-2,4-dione; 2,5-Dioxoimidazolidin-4-ylurea.

$C_4H_6N_4O_3$=158.1

CAS — 97-59-6.

UNII — 344S277G0Z.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Allantoin). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol.

USP 36: (Allantoin). A white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol.

Profile

Allantoin is an astringent and keratolytic. It is present in multi-ingredient preparations intended for various skin disorders and is also used for its astringent properties in preparations for the treatment of haemorrhoids and other anorectal disorders.

Psoriasis. In the USA the FDA decided that allantoin should be removed from lotions indicated for psoriasis as it was considered to be ineffective.[1]

1. Anonymous. Nonprescription drug review gains momentum. *WHO Drug Inf* 1991; **5:** 62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Masse; ***Pol.***: Alantan.

Multi-ingredient Preparations. ***Arg.***: Abanta; Adermicina A Post Solar; Afonisan; Atomoderma A-E; Bushi; Contractubex; Crema Para Paspaduras†; Cremsor N; Cutidermin Emulsion Humectante†; Dermaloe; Esmedent con Fluor; Euroderm-A; Factor AE; Integrum; Lactocrem Bebe; Lociherp Liposomas Vitaminado; Masivol; Medic; Mencogrin AP; Mencogrin; Mencogrin; Novofarma; Pastillas Lorbi†; Pastillas Medex; Sebosoap; ***Austral.***: Alphosyl†; Blistex Medicated Lip Ointment†; FootSmart; Hemocane; Macro Natural Vitamin E Cream; Medi Creme; Medi Pulv; Paxyl; SoloSite; Triple Care Cream; ***Austria***: Contractubex; Rheumex†; ***Braz.***: Contractubex; Fisioativ; Lactrex; Vitaderme; ***Canad.***: Blistex Medicated Lip Ointment†; Polysporin Lip Treatment; ***Chile***: Adolex; Dermaglos; Diencil; Ncnegloss†; Pancrit; Queratopil; Sanoderm; Ureadin 30; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; ***China***: Contractubex (康瑞保); Zhongxin (中鑫); ***Cz.***: Contractubex; Jox; Panlid†; ***Fr.***: Calmobrul; Cicatryl; Eryginе†; Hydracuivre; Ilast Care; Ilast Hydra; Ilast O'Clean; Ilast Post-Op; Seborheane†; Spirial; Urgo Cicatrices; ***Ger.***: Contractubex; Hydro Cordes; Hylo-Vision HD Plus; Ilast Care; Lipo Cordes; ***Gr.***: Contractubex; Pisaveril; ***Hong Kong***: Alox†; Alphate†; Aselan†; Contractubex; Egoderm; Egopsoryl TA; Pyodontyl†; ***Hung.***: Contractubex; ***India***: Acnederma; Acneguard; Acnestal; Aloederm-B; Alorex; Alphosyl; Anaproct; Anomex; Clin-3; Clin-3; Clinagel; Contractubex; Diafoot; Dibi; Elure; Hexilak; Mint; New Eye Lotion†; Shield; ***Indon.***: Atopiclair; Mederma; Verile; ***Irl.***: Pedamed; ***Israel***: Atopiclair; Comfrey Plus; Proctozorin-N; Rekasitin†; Xclair; ***Ital.***: Angstrom Viso; Biolastic T5; Centella Complex; Cerosteril; Cue Soluzione Otologica; Ginoxil Ecoschiuma; Keraflex; Resvelife Sole; Resvelife; Sensigel; Sensiquell; Tial-Z; Xerial; ***Malaysia***: Dermaheal DeAkni; Dermaheal Post Laser Cream; Egoderm; Egopsoryl TA; ***Mex.***: Antaderm; Contractubex; Dealan; Glossderm; Hipoglos Cremoso; Hipoglos; Lactrex; Mederma; Sebryl Plus; Sebryl; Sebstopp; Unguento de la Madre; ***NZ***: Egoderm; Egopsoryl TA; Medipulv; ***Philipp.***: Contractubex; Dermablend Colloidal Oatmeal Lotion; Hiruscar; ***Pol.***: Alantan-Plus; Alantavit; Baikaderm; Cepan; Contractubex; Dernilan; Mucosit; Pupilek†; Septalan†; Tointex†; ***Rus.***: Contractubex (Контрактубекс); Hepatrombin (Гепатромбин); Jox (Йокс); ***S.Afr.***: Alphosyl†; Arola Rosebalm†; Blistex; Clearasil Medicated Facial Cleanser†; ***Singapore***: Atopiclair; Egoderm; Egopsoryl TA; Erase; Hiruscar; Nu-Derm Toner; Octenisan; Purifying Gel; ***Spain***: Alphosyl†; Antigrietun; Hepro; Polaramine Crema; ***Switz.***: Alphastria; Baume Dalet; Contractubex; Gorgonium; Keli-med; Lyman; Optrex compresses†; PC 30 V; Sportium; ***Thai.***: Opplin; ***Turk.***: Contractubex; ***UK***: Actinac†; Alphosyl HC†; Anodesyn; Atopiclair; Vesagex Heelbalm; ***Ukr.***: Contractubex (Контрактубекс); Hepathrombin (Гепатромбин); Jox (Йокс); ***USA***: Alasulf; Anbesol Cold Sore Therapy; Atopiclair; Blistex Lip Balm; Blistex; Deltavac; DIT1-2; Dr Dermi-Heal; Ionax Astringent; Orabase Lip; Tanac Dual Core; Tanac; ***Venez.***: Alantamida; Lactrex.

Aloe Vera

Aloe; Алоэ Вера; Алоэ Древовидное.

ATC Herb — HA06AB5002 (Aloe vera: *dry leaf juice); HD02WA5001* (Aloe vera: *leaf mucilage).*

UNII — KIZ4X2EHYX (Aloe vera); *ZY81Z83H0X* (Aloe vera *leaf); 575DY8C1ER* (Aloe vera *flower).*

Profile

Aloe vera gel is a mucilaginous preparation obtained from the leaves of *Aloe vera* (*A. barbadensis*). It does not include the sap of *Aloe vera*, which contains anthraquinones, and should not be confused with aloes (p. 1816.1).

Aloe vera gel is widely used in cosmetics and toiletries for a reported moisturising and revitalising action. Aloe vera oil, which is reported to be made by macerating aloe vera in soybean, almond or apricot oils, is also used in cosmetics and toiletries.

References.
1. WHO. Aloe Vera Gel. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO; 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/6.html (accessed 27/05/10)

Aloe vera is widely used in cosmetics and toiletries for a reported moisturising and revitalising action. There are also claims for the beneficial and even curative properties of aloe vera gel in the treatment of conditions such as acne, psoriasis, burns, wounds, arthritis, diabetes, hyperlipidaemia, peptic ulcer, and genital herpes.[1,2] Evidence to support these claims is lacking. There is also no strong evidence to support the use of aloe vera gel in the prevention or treatment of radiation-induced skin reactions in cancer patients.[3]

1. Marshall JM. Aloe vera gel: what is the evidence? *Pharm J* 1990; **244:** 360–2.
2. Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. *Br J Gen Pract* 1999; **49:** 823–8.
3. Richardson J, *et al*. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol)* 2005; **17:** 478–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aloedent†; Amenite Vera; Barrocutina; Biorevit Gel; Puraloe Post Solar; Solenil Post Solar Cool Gel; ***Braz.***: Aloax; Soapelle; ***Fr.***: Veraskin†; ***Ger.***: Pox-Clin†; Rinupret; ***India***: Aloven; Jula; ***Ital.***: Epitaloe; ***Singapore***: Curacao.

Multi-ingredient Preparations. ***Arg.***: Abanta; Acuaderm; Aftersun; Aloebel; Aristaloe; Aristaloe; Atomo Ordenador; Brunavera; Capson; Control Acne; Crema De Ordene; Cutidermin Crema Regeneradora†; Cutidermin Spray Humectante†; Dermaloe; Dermvien; Eurocolor Post Solar; Galenic Restaurador Capilar; KW; Maprosol Gel; Maternity Crema de Ordene; Mucobase; Negacne; Ocusun; Olamine; Omicohol A; Pervicol Toallas; Pervicol; Post Solar Nort; Puraloe Nutritiva; Puraloe; Recover Whitening; Refrane P; Refrane Plus; Repelente Zasu; Sadeltan F; Snella Vag; Solenil Post Solar; Talowin; Vera Plus; Xicanil Control NF Locion; Xyloprocto Toallas; ***Austral.***: Aloe Vera Gel; Aloe Vera Plus; Lipz Ointment; Percutane†; Psor-Asist; Rapaid Rash-Relief; Triple Care Cream; Vicks Baby Balsam; ***Austria***: Wick SinexAloe; ***Braz.***: Actine; Actine; Malvatricin Natural Soft†; ***Canad.***: Pure Gardens; ***Chile***: Ac-Sal†; Acniben Toallitas; Cellenergy; Fray Romano; Glicoisdin; Micodual; Nenegloss†; Solarcaine Aloe Vera Gel; Ureadin Rx DB; Ureadin Rx RD; ***Fr.***: Cicatridine; Rhinodoron; ***Ger.***: Rhinodoron; ***Hong Kong***: Pregnacare; ***Hung.***: After Burn; ***India***: Acnestal; Ale; Alo-E; Aloat NC; Alockin; Aloekin; Alogard; Alovit-AF; Alovit; Alv; Bioskin; Calosoft; Calvera; Cimfi; Coral; Dermamoist; Dew Derm; Dewsoft; Diabecon; Eelovit; Elovera-SPF; Elovera; Elovera; Evaren; Evecare; Evecare; Herr; Hidrate; Humidus; Ivan; Korisma; Moiste; Moisturex-AF; Nasoclear Aloegel; Sofderm; ***Indon.***: Jointfit; Oramin-G; Velostin; ***Israel***: Agisten with Aloe Vera; Aphtagone†; Aptha-X†; ***Ital.***: Capso; Ekotrofil; Faringel; Ginoxil Ecoschiuma; Ninfagin; Proctocella Complex; Sclerovis H Plus; Vulnopur; ***Malaysia***: A-Bruzzy; Elovera; Neo-Healar†; T3 Acne; TDF AHA Facial Wash for Oily/Acne Prone Skin; ***Mex.***: Aloemagnolia; Gelconordin; Hipoglos Cremoso; ***NZ***: Chap Stick; Lamisil Odor Eze†; Solarcaine Aloe; Vicks Baby Balsam; ***Philipp.***: Elovera; Enfacare; Hiruscar; Intima†; Nap; ***Port.***: Alkagin; ***Rus.***: Elovera (Эловера); ***Singapore***: A-Bruzzy; Aze; Desitin Creamy; Hiruscar; ***UK***: Antiac; Don't Bug Me; Sinose; ***Ukr.***: Ambovit (Амбовит); Bon-Apetit (Бон-Аппетит); Eve Care (Ив Кер)†; Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Aloe Grande; Biotene with Calcium; Bodi Kleen; Bodi Oil; Boudreaux's All Natural Butt Paste; Dermtex HC with Aloe; Duraflex Comfort; Entertainer's Secret; Geri-Lav Free; Gold Bond Medicated Triple Action Relief; Hawaiian Tropic Cool Aloe with I.C.E.; Hemorid For Women; Maximum Strength Flexall 454; Miaderm Radiation Relief; Mucotrol; Nasal-Ease; OraMagicRx; RadiaPlex Rx; Rx Support Heartburn & Acid Reflux Plus Aloe; Solarcaine Aloe Extra Burn Relief; Zim's Max Freeze; ***Venez.***: Andantol Jalea; Flucirac; Gameral; Gelsem; Jengimiel Sabila; Jengimiel.

Homoeopathic Preparations. *Canad.*: Hae 2 Complex†.

Aluminium Chloride

Aluminio chloridas heksahidratas; Alumiinikloridiheksahydraatti; Aluminii Chloridum Hexahydricum; Aluminio, cloruro de; Aluminium Chloratum; Aluminium (chlorure d') hexahydraté; Alumínium-klorid-hexahidrát; Aluminiumkloridhexahydrat; Aluminum Chloride; Chlorid hlinitý hexahydrát; Cloreto de Aluminio; Cloruro de aluminio; Glinu chlorek; Алюминия Хлорид.

Aluminium chloride hexahydrate.

$AlCl_3.6H_2O$=241.4

CAS — 7446-70-0 (anhydrous aluminium chloride); 7784-13-6 (aluminium chloride hexahydrate).

ATC — D10AX01.

ATC Vet — QD10AX01.

UNII — LIF1N9568Y (aluminium chloride); 3CYT62D3GA (aluminium chloride hexahydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Aluminium Chloride Hexahydrate). A deliquescent, white or slightly yellow, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; soluble in glycerol. Store in airtight containers.

USP 36: (Aluminum Chloride). Deliquescent, white or yellowish-white, practically odourless, crystalline powder. Its solutions are acid to litmus. Soluble 1 in 0.9 of water and 1 in 4 alcohol; soluble in glycerol. Store in airtight containers.

Uses and Administration

Aluminium chloride has astringent properties and is used in a 20% alcoholic solution as an antiperspirant in the treatment of hyperhidrosis (p. 1685.1). It is applied to dry skin, usually at bedtime, and is washed off in the morning before the sweat glands are fully active. Initially, it may be applied each night until sweating improves, then less frequently, as required, to maintain efficacy.

Homoeopathy

Aluminium chloride has been used in homoeopathic medicines under the following names: Aluminium muriaticum; Alumin mur.

References.
1. Scholes KT, *et al*. Axillary hyperhidrosis treated with alcoholic solution of aluminium chloride hexahydrate. *BMJ* 1978; **2:** 84–5.
2. Ellis H, Scurr JH. Axillary hyperhidrosis - topical treatment with aluminium chloride hexahydrate. *Postgrad Med J* 1979; **55:** 868–9.

Adverse Effects

Aluminium chloride may cause irritation especially if applied to damp skin; this is attributed to the formation of hydrochloric acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alumpak; Drysol; ***Austral.***: Driclor; ***Canad.***: Hemodent†; ***Chile***: Drysol; Xerac AC; ***Fr.***: Driclor; Etiaxil; ***Ger.***: Gargarisma zum Gurgeln; Mallebrin Konzentrat; ***Hong Kong***: Driclor; ***Irl.***: Anhydrol Forte; Driclor†; ***Israel***: Anhydrol Forte; ***Malaysia***: Driclor†; ***Mex.***: Drysol; ***NZ***: Hidrosol†; ***Philipp.***: Driclor; ***Pol.***: Antidral; ***S.Afr.***: Driclor; ***Singapore***: Driclor; ***Switz.***: Etiaxil; Racestyptine†; ***UK***: Anhydrol Forte; Driclor; Odaban; ***USA***: Drysol; Lumicain; Xerac AC.

Multi-ingredient Preparations. ***Arg.***: Carnot Topico; ***Canad.***: Racestyptine; ***Chile***: Hidrofugal Forte†; Hidrofugal†; ***Fr.***: Ephydrol; ***Mex.***: Prespir; ***Switz.***: Baume Dalet; ***USA***: Stypto-Caine.

Pharmacopoeial Preparations

BP 2014: Aluminium Chloride Solution.

Aluminium Chlorohydrate

Aluminio, clorohidróxido de; Aluminium Chlorhydrate; Aluminium Chloride Hydroxide Hydrate; Aluminum Chlorhydroxide; Aluminum Chloride Hydroxide Hydrate; Aluminum Chlorohydrate (USAN); Aluminum Hydroxychloride; Alüminyum Hidroksiklorür; Basic Aluminium Chloride; Clorohidrato de aluminio; Алюминия Хлорогидрат.

$Al_2(OH)_5Cl.xH_2O$

CAS — 1327-41-9 (anhydrous aluminium chlorohydrate).

ATC — D09AA08; M05BX02.

ATC Vet — QD09AA08; QM05BX02.

UNII — HPN8MZW13M.

Pharmacopoeias. In *US.*

US also includes a range of compounds based on aluminium chlorohydrate. These are:

- aluminium dichlorohydrate and sesquichlorohydrate
- the polyethylene glycol (macrogol) complexes and propylene glycol complexes of aluminium chlorohydrex, aluminium dichlorohydrex, and aluminium sesquichlorohydrex
- the tri-, tetra-, penta-, and octachlorohydrates of aluminium zirconium and their respective glycine derivatives.

USP 36: (Aluminum Chlorohydrate). A 15% w/w solution in water has a pH of 3.0 to 5.0

Profile

Aluminium chlorohydrate is used similarly to aluminium chloride in hyperhidrosis (p. 1685.1). Single-ingredient products for hyperhidrosis generally have a concentration in the range of 10 to 25%.

Aluminium chlorohydrate is also included in a variety of dermatological preparations for its astringent and antiperspirant properties.

Aluminium toxicity. Bone pain, extreme fatigue, and raised aluminium concentrations in a woman with normal renal function were attributed to the use of an antiperspirant cream containing aluminium chlorohydrate 20%. She had been applying about 1 g of cream to each underarm daily for 4 years. Within 8 months of stopping the antiperspirant, plasma-aluminium concentrations had returned to normal and symptoms had resolved.[1]

1. Guillard O, *et al.* Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. *Am J Med* 2004; **117:** 956–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bromhistop; Normoskin; Perspi; Sodorant; ***Austral.***: QV Naked Anti-Perspirant Deodorant; ***Canad.***: Avon Antiperspirant Deodorant†; Avon On Duty†; Creme Deodorant Multi-Soin Anti-Perspirant†; Hydrosal; Scholl Dry Antiperspirant Foot Aerosol Powder†; ***Chile***: Hansaplast Footcare†; Hidrofugal†; ***Fr.***: pM†; Spirial; ***Ger.***: Phosphonorm; ***India***: Aldry; ***Israel***: Aloxan Derma†; ***Ital.***: Spirial; ***Mex.***: Skin Dry; ***NZ***: Neat Effect; Neat Feat; Neat One; Neat Touch; ***Port.***: Dermagor Antitranspirante; Lambda; ***Switz.***: Gelsica†; Phosphonorm; ***Turk.***: Anti-Fosfat Al; Kursept; Terkur; ***UK***: Chiron Barrier Cream; ***USA***: Bromi-Lotion.

Multi-ingredient Preparations. ***Arg.***: Neobitiol; Sodorant; ***Austral.***: Neo-Medrol†; ***Austria***: Sulgan 99; ***Canad.***: Feet Athletes Foot and Antifungal†; Medrol Acne Lotion; Neo-Medrol Acne; ***Chile***: Hidrofugal Forte†; Hidrofugal†; Normaderm Stick Secante Camufu Imperfecciones; Uriage Desodorante Tri-Actif; ***Fr.***: Spirial; ***Gr.***: Medrol Acne Lotion; Neo-Medrol; ***Hong Kong***: Neo-Medrol Acne; ***India***: Hancid; ***Indon.***: Betiga†; ***Israel***: Fungimon; Neo-Medrol; Pedisol†; ***S.Afr.***: Neo-Medrol†; ***Singapore***: Neo-Medrol; ***Spain***: Hongosan†; ***Turk.***: Pers-Mant; ***USA***: Breezee Mist Foot Powder; Ostiderm.

Pharmacopoeial Preparations

USP 36: Aluminum Chlorohydrate Solution; Aluminum Dichlorohydrate Solution; Aluminum Sesquichlorohydrate Solution; Aluminum Zirconium Octachlorohydrex Gly Solution; Aluminum Zirconium Pentachlorohydrate Solution; Aluminum Zirconium Pentachlorohydrex Gly Solution; Aluminum Zirconium Tetrachlorohydrate Solution; Aluminum Zirconium Tetrachlorohydrex Gly Solution; Aluminum Zirconium Trichlorohydrate Solution; Aluminum Zirconium Trichlorohydrex Gly Solution.

Amiloxate *(USAN, rINN)*

Amiloxato; Amiloxatum; E-1000; Isoamyl *p*-Methoxycinnamate; Амилоксат.

Isopentyl *p*-methoxycinnamate; 3-(4-Methoxyphenyl)-2-propenoic acid 3-methylbutyl ester.

$C_{15}H_{20}O_3$=248.3

CAS — 71617-10-2.

UNII — 376KTP06K8.

NOTE. Neo-Heliopan E 1000 is a trade name that has been used for amiloxate.

Pharmacopoeias. In *US.*

USP 36: (Amiloxate). Store in airtight containers.

Profile

Amiloxate, a substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (p. 1715.1). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lelco.

Multi-ingredient Preparations. ***Arg.***: Fotoprotector Extrem; Fotoprotector; Lelco Labial; Lelco P Ultra; Lelco Spray; Lelco Ultrablock Extreme; Lelco Ultrablock†; Ozonosol; ***Austral.***: Sunsense; ***Braz.***: Fotoprotetor Spray Isdin†; ***Chile***: Ansolar; Emolan Gel Protector Solar; Emolan†; Fotoprotector Isdin Extrem†; Fotoprotector Isdin-25 Pediatrics†; ***Ger.***: Daylong actinica†; ***Hong Kong***: Sunsense†; ***Malaysia***: Sunsense Sport Gel†; Sunsense Sport†; ***Singapore***: Sunsense Sport†; ***Switz.***: Daylong actinica; ***UK***: Uvistat.

Aminobenzoic Acid

Acide 4-Aminobenzoïque; Acidum 4-Aminobenzoicum; Amben; 4-Aminobensoesyra; 4-Aminobentsoehappo; 4-aminobenzoesav; Aminobenzoico, ácido; 4-Aminobenzoinė rūgštis; Kwas 4-aminobenzoesowy; Kyselina 4-aminobenzoová; PAB; PABA; Pabacidum; Para-aminobenzoic Acid; Vitamin Bx; Vitamin H'; Аминобензойная Кислота.

4-Aminobenzoic acid.

$C_7H_7NO_2$=137.1

CAS — 150-13-0.

ATC — D02BA01.

ATC Vet — QD02BA01.

UNII — TL2TJE8QTX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (4-Aminobenzoic Acid; Aminobenzoic Acid BP 2014). White or slightly yellow crystalline powder. Slightly soluble in water; freely soluble in alcohol; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Aminobenzoic Acid). White or slightly yellow, odourless crystals or crystalline powder. It discolours on exposure to air or light. Slightly soluble in water and in chloroform; freely soluble in alcohol and in solutions of alkali hydroxides or carbonates; sparingly soluble in ether. Store in airtight containers. Protect from light.

Uses and Administration

Aminobenzoic acid is applied topically as a sunscreen (p. 1681.3). Aminobenzoic acid and its derivatives effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p. 1685.3). Aminobenzoate sunscreens may therefore be used to prevent sunburn, but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection against such photosensitivity.

Aminobenzoic acid has sometimes been included as a member of the vitamin-B group, but deficiency of aminobenzoic acid in man or *animals* has not been found.

Aminobenzoic acid has been used with bentiromide (p. 2454.3) in the PABA or BTPABA test of pancreatic function.

Adverse Effects and Precautions

Adverse skin reactions such as local irritation and contact dermatitis have been reported after the topical use of aminobenzoate sunscreens. Aminobenzoate sunscreens should not be used by those with a history of photosensitivity or hypersensitivity reactions to structurally related drugs such as sulfonamides, thiazide diuretics, and ester-type local anaesthetics.

Aminobenzoic acid may stain clothing.

Allergic and photoallergic contact dermatitis have been reported after topical use of aminobenzoic acid or its esters.[1] Early reports of such reactions led to the removal of these compounds from sunscreen preparations (many are now described as 'PABA-free'), although padimate O still appears to be widely used.[2] Patients allergic to aminobenzoic acid may also react to structurally related allergens such as para-aminobenzoic acid ester anaesthetics, sulfonamides, and paraphenylenediamine in hair dyes.[1,2]

Skin reactions (vitiligo) have also been reported with oral aminobenzoic acid[3] and the adverse effects associated with the former use of high oral doses for various conditions have been highlighted.[4]

1. Scheuer E, Warshaw E. Sunscreen allergy: A review of epidemiology, clinical characteristics, and responsible allergens. *Dermatitis* 2006; **17:** 3–11. Correction. *ibid.*; 162.
2. Mackie BS, Mackie LE. The PABA story. *Australas J Dermatol* 1999; **40:** 51–3.
3. Hughes CG. Oral PABA and vitiligo. *J Am Acad Dermatol* 1983; **9:** 770.
4. Worobec S, LaChine A. Dangers of orally administered para-aminobenzoic acid. *JAMA* 1984; **251:** 2348.

Pharmacokinetics

If given orally, aminobenzoic acid is absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Pabasun; Paraminan; ***India***: Pabalak; Pabatab; Paraminol; ***Rus.***: Actipol (Актипол); ***Spain***: Hachemina Fuerte†; ***Ukr.***: Actipol (Актипол).

Multi-ingredient Preparations. ***Arg.***: Biorevit Solar 15; ***Braz.***: Pantogar; ***Cz.***: Revalid; ***Hong Kong***: Pantogar; ***Hung.***: Revalid; ***India***: Melanocyl; Melonil; Menofit; Menopace Iso; Menopace; Pabatab-BZ; ***Indon.***: Pantogar; ***Mex.***: Pabafilm†; Pantogar; ***Rus.***: Pantovigar (Пантовигар); ***Singapore***: Pantogar; ***Spain***: Tri Hachemina†; ***Switz.***: Pantogar; Revalid†; ***Turk.***: Pantogar; ***Ukr.***: Pantogar (Пантогар); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: PowerVites.

Pharmacopoeial Preparations

USP 36: Aminobenzoic Acid Gel; Aminobenzoic Acid Topical Solution.

Ammonium Lactate *(USAN)*

Amonio, lactato de; BMS-186091; Аммония Лактат.

$C_3H_9NO_3$=107.1

CAS — 52003-58-4.

ATC Vet — QA16QA04.

UNII — 67M901L9NQ.

Profile

Ammonium lactate is a humectant applied as a cream or lotion containing 12% lactic acid neutralised with ammonium hydroxide. It is used in the treatment of dry scaly conditions of the skin including ichthyosis. Adverse effects of topical ammonium lactate preparations include transient erythema, burning, and stinging. Treated areas may be more sensitive to sunlight and exposure should be minimised.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lacto-Cev; Lactrex; Nutrafilm; ***Braz.***: Lac-Hydrin†; ***Fr.***: Kerapil; ***India***: Lak-Am-Lact; ***Malaysia***: Lanate; ***Mex.***: Lac-Hydrin; ***NZ***: Lac-Hydrin†; Lanate†; ***Singapore***: Lanate; ***USA***: al12; Amlactin; Geri-Hydrolac; Halonate; Kerasal AL; Lac-Hydrin; LAC-Lotion.

Multi-ingredient Preparations. ***Arg.***: Clobeplus; Clobesol LA; Dermexane; Lactiderm; Lacto-Cev Zn; ***Braz.***: Lactrex; ***Chile***: Queratopil; ***Fr.***: I-Soft; Zeniac LP Fort; Zeniac LP; Zeniac; ***Indon.***: Exfoliac†; ***Ital.***: Alfa Acid; Ipso Urea; ***Mex.***: Lactrex; ***USA***: Carb-O-Lac HP; Halac Kit; Kerasal Ultra; Ultralytic 2; ***Venez.***: Lactrex.

Arbutin

Arbutoside; Arbutyna; Beta-arbutin; Ursin; Арбутин.

4-Hydroxyphenyl-βD-glucopyranoside.

$C_{12}H_{16}O_7$=272.3

CAS — 497-76-7 (beta-arbutin); 84380-01-8 (alpha-arbutin).

UNII — C5INA23HXF.

Profile

Arbutin is a glycosylated derivative of hydroquinone (p. 1705.1) extracted from bearberry (p. 2453.2) and similar plants. It is used topically in concentrations of 1 to 5% as a depigmenting agent for the skin in hyperpigmentation disorders. The higher concentrations may lead to a paradoxical hyperpigmentation.

Alpha-arbutin has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cellskinlab Phyto Spot; Melasoft; ***Chile***: Phyto Corrective Gel†; Phyto Spot; Recover Ol; ***Fr.***: Effasun Depigmentante; ***India***: Carofit; Demelan; Kojivit; Niltan; ***Ital.***: Brunex; ***Port.***: Despigmentante†.

Avobenzone *(USAN, rINN)*

Avobenzona; Avobenzonum; Butylmethoxydibenzoylmethane; 4-*tert*-Butyl-4′-methoxydibenzoylmethane; Авобензон.

1-(*p*-*tert*-Butylphenyl)-3-(*p*-methoxyphenyl)-1,3-propanedione; 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-1,3-propanedione.

$C_{20}H_{22}O_3$=310.4

CAS — 70356-09-1.

UNII — G63QQF2NOX.

NOTE. Escalol 517, Eusolex 9020, Neo-Heliopan 357, and Parsol 1789 are trade names that have been used for avobenzone.

Pharmacopoeias. In *US.*

USP 36: (Avobenzone). Store in airtight containers. Protect from light.

Profile

Avobenzone is a substituted dibenzoylmethane used by topical application as a sunscreen (p. 1681.3). Dibenzoylmethanes absorb light in the UVA range (for definitions, see p. 1685.3) and may therefore be used with other sunscreens that absorb UVB light to prevent sunburn; they will also provide some protection against drug-related or other photosensitivity reactions associated with UVA light.

Contact and photocontact allergic dermatitis has occasionally been reported with the topical use of dibenzoylmethane sunscreens.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lelco; ***Canad.***: Clinique Skin Supplies; Coppertone Oil-Free Sunscreen; Silkies Enriche; ***Chile***: ROC Minesol Bronze.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Avotermin *(rINN)*

Avotermina; Avotermine; Avoterminum; Human Recombinant Transforming Growth Factor β3; TGF-β3; Авотермин.

CAS — 182212-66-4.

UNII — 2Q1GS25JWN.

NOTE. The name Juvista has been used as a trade mark for avotermin.

Profile

Avotermin is a human recombinant transforming growth factor β3 under investigation to improve scar tissue appearance following surgery. It is given as an intradermal injection around the margins of the wound site.

References.

1. Bush J, *et al.* Therapies with emerging evidence of efficacy: avotermin for the improvement of scarring. *Dermatol Res Pract* 2010. Available at: http://www.hindawi.com/journals/drp/2010/690613.html (accessed 25/10/10)
2. Occleston NL, *et al.* Avotermin for the improvement of scar appearance: a new pharmaceutical in a new therapeutic area. *Expert Opin Invest Drugs* 2009; **18:** 1231–9.
3. Ferguson MWJ, *et al.* Prophylactic administration of avotermin for improvement of skin scarring: three double-blind, placebo-controlled, phase I/II studies. *Lancet* 2009; **373:** 1264–74.

Azelaic Acid *(USAN, rINN)*

Acide azélaïque; Ácido anchoico; Ácido azelaico; Ácido lepargílico; Acidum Azelaicum; Anchoic acid; Atselaiinihappo; Azelaico, ácido; Azelaik Asit; Azelainsyra; Lepargylic acid; ZK-62498; Азелаиновая Кислота.

Nonanedioic acid; Heptane-1,7-dicarboxylic acid.

$C_9H_{16}O_4$=188.2

CAS — 123-99-9.

ATC — D10AX03.

ATC Vet — QD10AX03.

UNII — F2VW3D43YT.

Uses and Administration

Azelaic acid inhibits the growth of *Propionibacterium* spp. and reduces keratinisation. It is used in the topical treatment of mild to moderate inflammatory acne (p. 1682.2) and for the inflammatory papules and pustules of mild to moderate rosacea (p. 1688.3). It has also been tried in hyperpigmentary skin disorders such as melasma, and in malignant melanoma.

In the treatment of **acne** azelaic acid is applied twice daily for up to 6 months as a 20% cream or 15% gel. Improvement usually occurs within four weeks.

For the treatment of mild to moderate **rosacea**, a 15% gel should be applied to the affected area twice daily. Improvement usually occurs in 4 to 8 weeks; optimum results are usually seen after several months of treatment.

References.

1. Fitton A, Goa KL. Azelaic acid: a review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs* 1991; **41:** 780–98.
2. Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid, and other therapies. *Cutis* 1996; **57** (suppl): 36–45.
3. Elewski B, Thiboutot D. A clinical overview of azelaic acid. *Cutis* 2006; **77** (suppl): 12–16.
4. Del Rosso JQ. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. *Cutis* 2006; **77** (suppl): 22–4.
5. Liu RH, *et al.* Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized controlled trials. *Arch Dermatol* 2006; **142:** 1047–52.

Adverse Effects and Precautions

Topical application of azelaic acid may produce a transient skin irritation such as burning, stinging, pruritus, dryness, and scaling. It is usually mild and disappears on continued treatment, but in a few patients the irritation may persist, requiring reduced frequency of application or temporary suspension of treatment. There have been rare reports of hypopigmentation, rash, and photosensitivity. Azelaic acid should not be applied to the eyes, mouth, or other mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azelaic acid as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cutacelan; ***Austral.***: Azclear; Finacea; Skinoren†; ***Austria***: Skinoren; ***Belg.***: Skinoren; ***Braz.***: Azelan; Dermazelaic; Dermizan; ***Canad.***: Finacea; ***Cz.***: Aknoren; Skinoren; ***Denm.***: Finacea; Skinoren; ***Fin.***: Skinoren; ***Fr.***: Finacea; Skinoren; ***Ger.***: Skinoren; ***Gr.***: Alenzantyl; Arbonid; Azedose; Azelac; Azelaxine; Azelderm; Cevigen; Chemilaic; Exazen; Forcilen; Kenedril; Noreskin; Opilet; Prevolac; Skinoren; Sonalent; Zelicrema; Zorkenil; Zumilin; ***Hong Kong***: Qualicren; Qualilaic; Skinoren; ***Hung.***: Finacea; Skinoren; ***India***: Aziderm; ***Indon.***: Aza 20; Skinoren†; Zelface; Zeliris; ***Irl.***: Skinoren; ***Israel***: Skinoderm; ***Ital.***: Finacea; Neocutis; Skinoren; ***Malaysia***: Acnederm Lotion; Skinoren; ***Mex.***: Finacea; ***Neth.***: Finacea; ***Norw.***: Finacea; Skinoren; ***NZ***: Skinoren; ***Philipp.***: Skinoren†; ***Pol.***: Acne-Derm; Finacea; Hascoderm; Skinoren; ***Port.***: Dermazil†; Finacea; Skinoren; ***Rus.***: Skinoren (Скинорен); ***S.Afr.***: Skinoren; ***Singapore***: Skinoren; ***Spain***: Finacea; Skinoren; Zelaika†; Zelideram; ***Swed.***: Finacea; Skinoren; ***Switz.***: Skinoren; ***Thai.***: Skinoren; ***Turk.***: Azelderm; Finacea; Skinoren; ***UK***: Finacea; Skinoren; ***Ukr.***: Acnestop (Акнестоп); Azogel (Азогель); Skinoren (Скиноren); ***USA***: Azelex; Finacea; Finevin; ***Venez.***: Cutacelan.

Multi-ingredient Preparations. ***Fr.***: Melascreen Depigmentant; ***Hong Kong***: Acnederm; ***Ital.***: Zeroac; ***NZ***: Acnederm; ***Singapore***: Acnederm; Bio-Taches†; ***USA***: NicAzel Forte; Tri-zel; VP-Zel.

Becaplermin *(BAN, USAN, rINN)* ⊗

Becaplermina; Bécaplermine; Becaplerminum; Bekaplermiini; Bekaplermin; RWJ-60235; Бекаплермин.

Recombinant human platelet-derived growth factor BB.

CAS — 165101-51-9.

ATC — A01AD08; D03AX06.

ATC Vet — QA01AD08; QD03AX06.

UNII — 1B56C968OA.

Uses and Administration

Becaplermin is a recombinant human platelet-derived growth factor (rhPDGF-BB) that enhances the formation of granulation tissue and promotes wound healing (p. 1690.1).

Becaplermin is used in the management of full thickness neuropathic diabetic skin ulcers (see Diabetic Foot Disease, p. 464.2). It is applied topically as a 0.01% gel once daily, covered by a moist saline gauze dressing. If no meaningful healing process (decrease in ulcer size of about 30%) is evident after 10 weeks of therapy, or complete healing has not occurred in 20 weeks, treatment should be re-assessed.

Becaplermin is used with a resorbable synthetic calcium phosphate matrix in products which promote bone and tissue growth in the treatment of periodontal disease or in orthopaedic surgery for foot and ankle fusion. They are also under investigation in the treatment of osteonecrosis of the jaw, fractures, and osteoporosis, and in the repair of cartilage, ligament, and tendon injuries.

References.

1. Nagai MK, Embil JM. Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers. *Expert Opin Biol Ther* 2002; **2:** 211–18.
2. Nevins M, *et al.* Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. *J Periodontol* 2005; **76:** 2205–15.
3. McGuire MK, *et al.* rhPDGF-BB promotes healing of periodontal defects: 24-month clinical and radiographic observations. *Int J Periodontics Restorative Dent* 2006; **26:** 223–31. Correction. *ibid.* 2007; **27:** 88.
4. Fang RC, Galiano RD. A review of becaplermin gel in the treatment of diabetic neuropathic foot ulcers. *Biologics* 2008; **2:** 1–12.
5. Graham S, *et al.* Investigating the role of PDGF as a potential drug therapy in bone formation and fracture healing. *Expert Opin Invest Drugs* 2009; **18:** 1633–54.
6. Papanas N, Maltezos E. Benefit-risk assessment of becaplermin in the treatment of diabetic foot ulcers. *Drug Safety* 2010; **33:** 455–61.

Adverse Effects and Precautions

Becaplermin is contra-indicated if there is active infection at the application site, because adverse effects such as cellulitis, osteomyelitis, and deep wound infections have been reported, depending on the product used. If the site becomes infected during therapy, treatment should be stopped until the infection clears, or, if surgically used, consideration should be given to removing the grafting material containing becaplermin. Other adverse effects include application site reactions such as pain, erythema, or swelling.

The surgical use of becaplermin may also cause anaphylaxis, bleeding, haematoma, wound dehiscence, and local or peripheral neuralgia; caution is advised in patients with severe endocrine-induced diseases, or those receiving immunosuppressive therapy or conditions that may cause bleeding complications. When used orthopaedically, becaplermin should not be implanted in patients with metabolic disorders known to adversely affect the skeleton, such as renal osteodystrophy or hypercalcaemia.

Becaplermin should not be used if the patient has neoplasms at or near the site of topical application or periodontal use. Furthermore, some manufacturers have contra-indicated it in any known malignancy.

Carcinogenicity. Malignancies distant from the application site of topical becaplermin have been seen in a clinical study and in postmarketing use, according to licensed product information. Also, a review conducted by the EMEA, which included an epidemiological study, showed an increase in death rate from all cancers in patients treated with 3 or more tubes of becaplermin gel [tube size unspecified].[1] However, this review concluded that the overall risk of developing cancer was not significantly different between users and non-users. Based on these findings and acknowledging the study's limitations, the EMEA[1] and MHRA[2] have nonetheless recommended that becaplermin should not be used in patients with any form of cancer.

1. EMEA. Questions and answers on the review of Regranex (becaplermin). Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004 (issued 18th February 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/02/WC500074138.pdf (accessed 16/11/10)
2. MHRA/CHM. Becaplermin (Regranex) for diabetic ulcers: contra-indicated in patients with any known current cancer. *Drug Safety Update* 2010; **3** (9): 10. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON076501 (accessed 01/11/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Regranex†; ***Canad.***: Regranex†; ***Cz.***: Regranex†; ***Fr.***: Regranex†; ***Ger.***: Regranex†; ***Gr.***: Regranex; ***Irl.***: Regranex†; ***Israel***: Regranex†; ***Mex.***: Regranex; ***Neth.***: Regranex†; ***Port.***: Regranex†; ***Spain***: Regranex†; ***Switz.***: Regranex†; ***UK***: Regranex†; ***USA***: Regranex.

Multi-ingredient Preparations. ***Canad.***: Augment Bone Graft; ***USA***: GEM 21S.

Bemotrizinol *(USAN, rINN)*

Bémotrizinol; Bemotrizinolum; BEMT; Bis-ethylhexyloxyphenol Methoxyphenol Triazine; FAT-70884; Бемотрицинол.

2,2′-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis{5-[(2-ethylhexyl)oxy]phenol}.

$C_{38}H_{49}N_3O_5$=627.8

CAS — 187393-00-6.

UNII — PWZ1720CBH.

NOTE. Tinosorb S is a trade name that has been used for bemotrizinol.

Profile

Bemotrizinol is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Eucerin; ***Fr.***: Daylong Ultra; ***Singapore***: Sunsense Anti-Ageing.

Multi-ingredient Preparations. ***Arg.***: Cetaphil UV Defense; Eucerin Sun Protection 3D; Fotoprotector Extrem Pediatrics; Fotoprotector Extrem; Fotoprotector Pediatrics†; Fotoprotector Ultra; Polysianes; Protector Labial Extrem; ***Austral.***: Hamilton Family Sunscreen; Hamilton Toddler; Sunsense Anti Ageing Face; Sunsense Bronze Shield; Sunsense Lip Balm†; Sunsense Moisturising Face; ***Braz.***: Sundown Kids Colour; Sundown Kids Colour; Sundown Kids; Sundown Mousse; Sundown Spray; Sundown; Sundown; ***Canad.***: Anthelios; ROC Minesol Protect Ultra High; ROC Minesol Protect Very High†; Soleil Protexion Velvet Moisture; Soleil Protexion Velvet Moisture; ***Chile***: Ansolar; Avene Spray 50+; Eucerin Hydro-Protect; Eucerin Ninos; Eucerin Solar†; Eucerin; Eucerin; Eucerin; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Hyaluron; Nutraisdin; Photoscreen†; Protector Labial Extrem†; ROC Minesol Actif; ROC Minesol Protect; ROC Minesol Protect; ***Fr.***: Anthelios; Anthelios; Daylong; Melascreen solaire; Sun LEB; ***Ger.***: Daylong actinica†; ***Hong Kong***: Sunsense Anti-ageing Face Matte; ***Malaysia***: Cetaphil UVA/UVB Defense; SunSense Anti-Ageing Face; ***Mex.***: Eclipsol Clarity; Eclipsol Forte; Eclipsol Hydro; Eclipsol Ultra; ProZone Baby; ProZone Ultra Fluido; ***NZ***: Hamilton Toddler; ***Singapore***: Cetaphil UVA/UVB; Lipoderm; Sunsense Moisturising Face; ***Switz.***: Daylong actinica; ***Thai.***: Eucerin Sun Sensitive Skin†; Sebamed Multi Protect Suncream; ***UK***: Anthelios XL; Spotner; Uvistat Lipscreen.

Bentoquatam *(USAN)*

Quaternium 18-bentonite; Quaternium-18 bentonita; Бентокватам.

Bis(hydrogenated tallow alkyl)dimethylammonium complex with sodium bentonite.

CAS — 1340-69-8.

Profile

Bentoquatam, described as an organoclay compound, is a barrier preparation that is applied topically as a 5% lotion to prevent allergic contact dermatitis caused by poison ivy, poison oak, or poison sumac. The lotion is applied in a sufficient quantity to form a visible coating 15 minutes before possible contact with the plants. If continued protection is required the lotion may be re-applied every 4 hours or at any time if the visible coating is removed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Ivy Block.

Benzoyl Peroxide *(USAN)*

Bensoylperoxid; Bentsoyyliperoksidi; Benzoilo peroksidas; Benzoil-peroxid; Benzoyil Peroksit; Benzoylis Peroxidum; Benzoylperoxid; NSC-675; Peróxido de benzoílo; Peroxyde de benzoyle; Пероксид бензоила; Бензоил Пероксид.

Dibenzoyl peroxide.

$C_{14}H_{10}O_4$=242.2

CAS — 94-36-0 (anhydrous benzoyl peroxide).

ATC — D10AE01.

ATC Vet — QD10AE01; QD11AX90.

UNII — W9WZN9A0GM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Benzoyl Peroxide, Hydrous). It contains not less than 70% and not more than 77% of anhydrous benzoyl peroxide and not less than 20% of water. It rapidly loses water on exposure to air and may explode if the water content is too low. A white or almost white, amorphous or granular powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; soluble in dichloromethane with separation of water. Store at 2 degrees to 8 degrees in a container that has been treated to reduce static charges and that has a device for the release of excess pressure. Unused material should not be returned to its original container but should be destroyed by the addition of sodium hydroxide solution (10%). Destruction can be considered to be complete if the addition of a crystal of potassium iodide does not result in the release of free iodine after acidification with dilute hydrochloric acid. Protect from light.

USP 36: (Hydrous Benzoyl Peroxide). It contains a minimum of 20% of water for the purpose of reducing flammability and shock sensitivity. The hydrous form is a white granular powder with a characteristic odour. Sparingly soluble in water and in alcohol; soluble in acetone, in chloroform, and in ether. Store in the original container, treated to reduce static charges. Unused material should not be returned to its original container but should be destroyed by the addition of sodium hydroxide solution (10%). Destruction can be considered to be complete if the addition of a crystal of potassium iodide does not result in the release of free iodine.

Uses and Administration

Benzoyl peroxide has mild keratolytic properties. Its antimicrobial action is probably due to its oxidising effect and activity has been reported against *Staphylococcus epidermidis* and *Propionibacterium acnes*. It is used mainly in the treatment of acne (below), applied once or twice daily in topical preparations usually containing 2.5 to 10%, sometimes with other antimicrobials. For use in young children, see below. It has been used similarly in the treatment of fungal skin infections (p. 568.1), such as tinea pedis although other drugs are usually preferred. A 20% lotion has been applied every 8 to 12 hours in the treatment of decubitus or stasis ulcers. Strengths are expressed as anhydrous benzoyl peroxide although it is used in a hydrous form for safety (see Pharmacopoeias, above).

Benzoyl peroxide is also used as a bleaching agent in the food industry and as a catalyst in the plastics industry.

Acne. Benzoyl peroxide applied topically in concentrations of up to 10% is probably the most widely used first-line drug in the management of mild acne (p. 1682.2). Early studies in *animals* found benzoyl peroxide to be sebosuppressive[1] but later studies showed that sebum excretion rises during the first few months of treatment,[2,3] probably due to the comedolytic action of benzoyl peroxide, and remains at a stable level thereafter. Benzoyl peroxide has been shown to have a significant inhibitory effect on skin microflora, with reductions in surface and follicular microorganisms within 48 hours of beginning treatment, but clinical improvement took several more days to appear.[4] The combined use of benzoyl peroxide with topical clindamycin or erythromycin can inhibit the development of antibacterial resistance and bring about clinical improvement when resistance already exists.[5]

1. Gloor M, *et al.* Cytokinetic studies on the sebo-suppressive effect of drugs using the example of benzoyl peroxide. *Arch Dermatol Res* 1980; **267:** 97–9.
2. Cunliffe WJ, *et al.* Topical benzoyl peroxide increases the sebum excretion rate in patients with acne. *Br J Dermatol* 1983; **109:** 577–9.
3. Pierard-Franchimont C, *et al.* Topical benzoyl peroxide increases the sebum excretion rate. *Br J Dermatol* 1984; **110:** 506.
4. Bojar RA, *et al.* The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol* 1995; **132:** 204–8.
5. Taylor GA, Shalita AR. Benzoyl peroxide-based combination therapies for acne vulgaris: a comparative review. *Am J Clin Dermatol* 2004; **5:** 261–5.

Administration in children. In addition to its use in adolescents with acne, benzoyl peroxide has also been used topically in the treatment of neonatal and infantile acne; it may be applied once or twice daily starting with lower strength preparations of 2.5%.

Adverse Effects and Precautions

Topical application of benzoyl peroxide may produce skin irritation, particularly at the start of treatment. In some patients the irritation may require reduced frequency of application or temporary suspension of treatment. Skin dryness, peeling, rash, and transient local oedema may also occur. Contact sensitisation has been reported in some patients using preparations containing benzoyl peroxide. Caution is required when applying it near the eyes, the mouth and other mucous membranes, and to the neck and other sensitive areas. Patients should be alerted to benzoyl peroxide's bleaching property.

Body odour. An unusual unpleasant body odour in a patient was attributed to the topical use of benzoyl peroxide.[1]

1. Molberg P. Body odor from topical benzoyl peroxide. *N Engl J Med* 1981; **304:** 1366.

Carcinogenicity. There has been concern at the implications of some *animal* studies showing benzoyl peroxide to possess some tumour-promoting activity.[1] However, a retrospective survey in Canada concluded that there was no indication that the normal use of benzoyl peroxide in the treatment of acne was associated with an increased risk of facial cancer.[2] A comprehensive review[3] that included *in-vitro* and *animal* studies, as well as human data, also concluded that there was no evidence to associate the topical use of benzoyl peroxide with the development of skin cancer in humans. However, the International Agency for Research on Cancer[4] considers that there is inadequate evidence in humans and its overall evaluation is that benzoyl peroxide is not classifiable as to its carcinogenicity to humans.

1. Jones GRN. Skin cancer: risk to individuals using the tumour promoter benzoyl peroxide for acne treatment. *Hum Toxicol* 1985; **4:** 75–8.
2. Hogan DJ, *et al.* A study of acne treatments as risk factors for skin cancer of the head and neck. *Br J Dermatol* 1991; **125:** 343–8.
3. Kraus AL, *et al.* Benzoyl peroxide: an integrated human safety assessment for carcinogenicity. *Regul Toxicol Pharmacol* 1995; **21:** 87–107.
4. IARC/WHO. Benzoyl peroxide. *IARC monographs on the evaluation of carcinogenic risks to humans volume 71* 1999. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 27/09/07)

Handling. Benzoyl peroxide powder may explode if subjected to grinding, percussion, or heat. Hydrous benzoyl peroxide containing water to reduce the risk of explosion may still explode if exposed to temperatures higher than 60 degrees or cause fires in the presence of reducing substances.

Hypersensitivity. Benzoyl peroxide appears to induce contact hypersensitivity quite often when used to treat leg ulcers,[1] but it is unclear how often this occurs when used in the treatment of acne.[2] Patch testing[3,4] in some studies suggests that up to 76% of patients may be hypersensitive to benzoyl peroxide but this does not appear to correlate either with the clinical irritation produced during treatment, which usually resolves on continued use, or with the reported incidence of hypersensitivity.[2,4] In one study 25% of patients were considered to be hypersensitive from patch testing but only 2 of 44 patients developed clinical hypersensitivity.[4] Another study involving 204 patients with acne found that the incidence of false-positive irritant skin reactions to benzoyl peroxide was about 15% but only 1% of the patients had true allergic reactions to the drug on further testing.[5] However, there has been concern that hypersensitivity to benzoyl peroxide may be mistaken for irritation or worsening of the acne.[3]

1. Vena GA, *et al.* Contact dermatitis to benzoyl peroxide. *Contact Dermatitis* 1982; **8:** 338.
2. Cunliffe WJ, Burke B. Benzoyl peroxide: lack of sensitization. *Acta Derm Venereol (Stockh)* 1982; **62:** 458–9.
3. Leyden JJ, Kligman AM. Contact sensitization to benzoyl peroxide. *Contact Dermatitis* 1977; **3:** 273–5.
4. Rietschel RL, Duncan SH. Benzoyl peroxide reactions in an acne study group. *Contact Dermatitis* 1982; **8:** 323–6.
5. Balato N, *et al.* Acne and allergic contact dermatitis. *Contact Dermatitis* 1996; **34:** 68–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies benzoyl peroxide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pharmacokinetics

Work *in vitro* and in *animals*[1] suggests that although there is some absorption of benzoyl peroxide after topical application, any absorbed drug appears to be metabolised in the skin to benzoic acid and rapidly excreted in the urine.

1. Yeung D, *et al.* Benzoyl peroxide: percutaneous penetration and metabolic disposition II: effect of concentration. *J Am Acad Dermatol* 1983; **9:** 920–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acnepas; Acnesan; Benzihex; Eclaran; Ecnagel PB; Paracne; PB Gel; Solugel; Tiltis; Valucne PB; Vixiderm E; Xicanil; ***Austral.***: Benzac; Brevoxyl; Clearasil Ultra Acne Treatment Cream; Oxy; PanOxyl; ***Austria***: Akneroxid; Benzaknen; Brevoxyl; ***Belg.***: Akneroxid; Benzac; Brevoxyl; Pangel; ***Braz.***: Acnase; Acnezil; Benzac AC; Benzac; Dermesan; PanOxyl; Solugel; ***Canad.***: Acetoxyl†; Acne Solutions; Acne Vanishing Treatment; Acneban; Adasept BP; Benoxyl†; Benzac; Benzagel; Cetaphil Acne; Clean & Clear Continuous Control; Clean & Clear Persa Gel; Clear Acne†; Clear Pore On-The-Spot†; Clear Skin Treatment Repairing; Clear Zone†; Clearasil Daily Clear Acne B.P. Plus; Clearasil Stayclear BP Plus†; Clenziderm; Dermacne; Dermalogica Special Clearing Booster; Desquam-X†; Emergency Acne; Life Acne; Medicated Acne Gel†; Nature's Cure Acne; Overnight Acne Control; Oxy†; Oxyderm; PanOxyl; Pure Perfection Classic; Rodan & Fields Proactiv Renewing Cleanser; Rodan & Fields Proactiv Repairing; Shave Cream; Skin ID; Solugel; Spectro Acnecare; ***Chile***: Benzac; Pansulfox; Peroxiben Plus; Pirobac; Solugel; ***China***: Benzihex (班赛); Bi Ning (碧宁); ***Cz.***: Akneroxid; Basiron AC†; Eclaran; Oxy†; ***Denm.***: Basiron; ***Fin.***: Basiron; Brevoxyl; ***Fr.***: Brevoxyl; Curaspot; Cutacnyl; Eclaran; Effacne; Pannogel; PanOxyl; ***Ger.***: Aknefug-oxid; Akneroxid; Benzaknen; Benzoyt; Benzperox†; Brevoxyl; Cordes BPO; Klinoxid†; Marduk; PanOxyl; Sanoxit†; ***Gr.***: Benzac-W; Bioacne; Brevoxyl; ***Hong Kong***: Akneroxid; Benzac AC; Brevoxyl; Oxy†; Oxyderm†; PanOxyl; ***Hung.***: Aknefug-oxid; Akneroxid; Lubexyl; ***India***: Abenz; Actiben; Akneroxid; Benzac AC; Brevoxyl; Persol; ***Indon.***: Benzolac; Pimplex†; ***Irl.***: Acnecide; Brevoxyl; PanOxyl; ***Israel***: Acne Derm; Benzac; Clearex Benzoyl Peroxide; Clearex Cover Up; Oxy; PanOxyl; ***Ital.***: Benzac; Benzolait; PanOxyl; Reloxyl; ***Malaysia***: Akneroxid; Benzac AC; Brevoxyl; PanOxyl; ***Mex.***: Akeprul; Benoxyl; Benzac AC; Benzaderm; Solugel; ***Neth.***: Akneroxid†; Benzac; Kruidvat Hydrogel; Oxy†; Tendox†; ***Norw.***: Basiron; Brevoxyl†; PanOxyl†; ***NZ***: Benzac; Brevoxyl; Clearasil Ultra; PanOxyl; ***Phi-***

lipp.: Benoxyl†; Benzac AC; Brevoxyl†; PanOxyl; Ultra Clearasil†; ***Pol.***: Akneroxid; Benzacne; Benzapur†; Brevoxyl; Lubexyl; ***Port.***: Benoxygel; Benzac; Eclaran; PanOxyl; Peroxiben; ***Rus.***: Basiron (Базирон); Eclaran (Экларан); ***S.Afr.***: Benoxyl†; Benzac AC; Brevoxyl; Clearasil Benzoyl P; Dry & Clear†; PanOxyl; ***Singapore***: Acnacyl†; Akneroxid; Benzac; Brevoxyl; PanOxyl; ***Spain***: Benoxygel†; Oxiderma; PanOxyl†; Peroxacne; Peroxiben; Solucel; Stop Espinilla Normaderm†; ***Swed.***: Basiron; Brevoxyl; Stioxyl†; ***Switz.***: Acnefuge; Akneroxid; Aknex†; Benzac; Benzaknen; Lubexyl; ***Thai.***: Acnexyl; Aczee; Benzac; Brevoxyl; Enzoxid; PanOxyl; ***Turk.***: Aknefug BP; Aksil; Benzac AC; Neutrogena Acne Mask; ***UK***: Acnecide; Brevoxyl; Oxy; PanOxyl; ***USA***: Acne Clear; Acne Medication; Benzac; BenzE-Foam; Benziq; BP Gel; BP Wash; Brevoxyl; Clearasil; Clinac BPO; Del Aqua; Delos; Desquam; DesquamX; Fostex; Lavoclen; NeoBenz; OC8; On-the-Spot Acne Treatment; Oxy; Pacnex; PanOxyl; Riax; SE BPO; Soluclenz; Triaz; Zaclir; ***Venez.***: Acnex; Benzac AC; Ecuaderm; Neutrogena OnSpot.

Multi-ingredient Preparations. ***Arg.***: Acnepas E; Clidan B; Clindacur; Clindoxyl; CP-Acne Duo; Dermaclean†; Duo Clindacin; Epiduo; Erimicin; Panalene Duo; Pentoclave Combi; Perclin; Peroxiclin Duo; Peroximicina; ***Austral.***: ClindaBenz; Duac; Epiduo; ***Austria***: Acne Plus; Indoxyl; ***Belg.***: Acneplus; Benzadermine; Benzamycin†; Epiduo; ***Braz.***: Acnase; Clindoxyl; Epiduo; ***Canad.***: Benzaclin; Benzamycin; Clindoxyl; Tactuo; ***Chile***: Benzac Plus; Erimicin; Indoxyl; Klina; ***China***: Benzamycin (必麦森); ***Cz.***: Duac; ***Denm.***: Clindoxyl; Epiduo; Tactuo†; ***Fin.***: Clindoxyl; Epiduo; ***Fr.***: Epiduo; ***Ger.***: Acne Plus; Duac; Epiduo; ***Gr.***: Benzamycin; Epiduo; Erybenz; Indoxyl; Zarcad; ***Hong Kong***: Acnesol†; Benzolac Cl; Duac; Epiduo; ***Hung.***: Duac; ***India***: Acnebenz; Alesa; Persol Forte; ***Indon.***: Benzolac Cl; Feldixid†; ***Irl.***: Benzamycin†; Duac; Quinoderm; ***Israel***: Benzaclin†; Benzamycin; Duac; ***Ital.***: Acnidazil; Delta 80 Plus; Delta 80; Duac; Epiduo; Katoxyn; ***Malaysia***: Duac; ***Mex.***: Benzac Plus†; Benzaclin†; Benzamycin†; Clindapack; Indoxyl; ***Neth.***: Acnecare; Duac; ***Norw.***: Epiduo; ***NZ***: Duac; Epiduo; ***Philipp.***: Acne Plus†; Duac; Epiduo; ***Pol.***: Duac; Epiduo; ***Port.***: Duac; Epiduo; Zacne†; ***S.Afr.***: Acneclear†; Acnidazil†; Quinoderm†; ***Singapore***: Benzamycin†; Clindoxyl; Epiduo; ***Spain***: Duac; Epiduo; Tactuoben; ***Swed.***: Duac; Epiduo; ***Switz.***: Acne Creme Plus; Duac; Epiduo; ***Thai.***: Duac; Epiduo; ***Turk.***: Benzaclin; Benzamycin; Clindoxyl; ***UK***: Duac Once Daily; Epiduo; Quinoderm; ***Ukr.***: Duac (Дуак); ***USA***: Acanya; Bencort; Benzaclin; Benzamycin; Duac; Effaclar Duo; Epiduo; Inova Acne Control; Inova; NuOx; Sulfoxyl; Vanoxide-HC; Zacare Kit; Zoderm.

Pharmacopoeial Preparations
BP 2014: Benzoyl Peroxide Cream; Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream;
USP 36: Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Erythromycin and Benzoyl Peroxide Topical Gel.

Bisoctrizole *(USAN, rINN)*

Bisoctrizol; Bisoctrizolum; FAT-75634; MBBT; Methylene Bis-Benzotriazolyl Tetramethylbutylphenol; Бизоктризол.
2,2′-Methylenebis[6-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol].
$C_{41}H_{50}N_6O_2$=658.9
CAS — 103597-45-1.
UNII — 8NT850T0YS.

NOTE. Tinosorb M is a trade name that has been used for bisoctrizole.

Pharmacopoeias. In *US.*

USP 36: (Bisoctrizole). Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Bisoctrizole is used as a sunscreen (p. 1681.3). It is effective against UVB and UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lelco; ***Singapore***: Sunsense Anti-Ageing.

Multi-ingredient Preparations. ***Arg.***: Fotocrem 50; Fotoprotector Extrem Pediatrics; Fotoprotector Extrem UVA Plus†; Fotoprotector Extrem UVA†; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Pediatrics†; Fotoprotector Ultra; Fotosol Ultra 50; Fotosol Ultra Autobronceante; Fotosol Ultra; Fotosol; Lelco Ultrablock Extreme; Lelco Ultrablock†; Ocusun; Polysianes; Polysianes; Valublock V; Valublock; ***Austral.***: Sunsense Anti Ageing Face; Sunsense Bronze Shield; Sunsense Ultra; ***Braz.***: Fotoprotetor Isdin Extrem UVA†; Fotoprotetor Isdin Extrem; Fotoprotetor Isdin Extrem; ***Canad.***: ROC Minesol Protect Ultra High; ROC Minesol Protect Very High†; Soleil Protexion Velvet Moisture; Soleil Protexion Velvet Moisture; ***Chile***: Ansolar; Avene Spray 50+; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Extrem Plus†; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Fotosol Cassara†; Fotosol Ultra†; Fotosol Ultra; Fotosol; Nutraisdin; Photoderm AKN†; Photoderm AR†; Photoderm Kid†; Photoderm Max†; Photoderm Spot†; Photoscreen†; Photoscreen; ROC Minesol Actif; ROC Minesol Protect; ROC Minesol Protect; Uriage Crema Color; Uriage Crema Extra; Uriage Protector Solar†; ***Fr.***: Avene Antirougeurs; Daylong; Hyseke Solaire; Melascreen solaire; SVR 100†; ***Ger.***: Daylong actinica†; ***Hong Kong***: Spectraban Sensitive 30; SunSense Anti-ageing Face Matte; ***Malaysia***: SunSense Anti-Ageing Face; ***Mex.***: Dermaglos Solar†; Eclipsol Clarity; Eclipsol Forte; Eclipsol Hydro; Eclipsol Ultra; ProZone Ultra Fluido; Umbrella Plus; ***Singapore***: Protexio; ***Switz.***: Daylong actinica; ***UK***: Spotner; Uvistat; Uvistat; ***Venez.***: Photoderm Max; Photoderm Max; Photoderm.

Calamine

Calamina; Kalamin; Prepared Calamine; Каламин.

Pharmacopoeias. In *Br., Chin., Int.,* and *US.*

BP 2014: (Calamine). It is a basic zinc carbonate coloured with ferric oxide. It is an amorphous, impalpable, pink or reddish-brown powder, the colour depending on the variety and amount of ferric oxide present and the process by which it is incorporated. Practically insoluble in water; it dissolves with effervescence in hydrochloric acid.

USP 36: (Calamine). It is zinc oxide with a small proportion of ferric oxide. A pink, odourless, fine powder. Insoluble in water; practically completely soluble in mineral acids.

Profile

Calamine has mild astringent and antipruritic actions and is used as a dusting powder, cream, lotion, or ointment in a variety of skin conditions although its value is uncertain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Ducilamina; ***India***: Calak; Intracal; ***Spain***: Talquistina†; ***Thai.***: Cabana.

Multi-ingredient Preparations. ***Arg.***: Acuaderm; Caladryl; Calcusan; Dermithan; Irricutan; Labsacalm; Northicalm; Pinklot; Piracalamina; Prurisedan Rosa; Prurisedan; Urtikalma; ***Austral.***: Animine; Calaband†; Calamine Lotion; Dermalife Plus†; ***Belg.***: Caladryl; ***Braz.***: Caladryl; Calamed; Calamina†; Calamyn; Calsol; Dermamina; Solardril Composto; ***Canad.***: Aveeno Anti-Itch; Caladryl†; Calamine Antihistamine; Calmoseptine†; Lotion Calamine avec Antihistaminique; ***Chile***: Ivarest; Pruriced; ***Fr.***: Gel de Calamine; Pruriced; Pruriced; ***Hong Kong***: Aicadryl†; Bacamine†; Cadramine-V; DPH with Calamine†; Improved Versal†; Uni-Calmin†; Vasogen†; ***India***: Calacare; Caladryl; Calak; Calosoft; Calskin; Calvera; Cimfi; Siloderm; ***Indon.***: Caladine†; Caladryl†; Calamec†; Calarex†; Confortin; Minos†; Regata†; ***Irl.***: RBC†; Vasogen†; ***Israel***: Baby Paste + Chamomile†; Calamine Lotion; ***Malaysia***: Dermoplex Calamine; Norash; Twinkle Calamine†; ***Mex.***: Caladryl; Dermocare; Procicar; ***NZ***: Am-O-Lin†; ***Philipp.***: Caladryl; Calmoseptine; ***Port.***: Benaderma com Calamina; Caladryl; ***S.Afr.***: Adco-Biohist; Caladryl; Calasthetic; Histamed†; ***Singapore***: Acne Clear; Calamine and Menthol; Calamol; Norash; ***Thai.***: Allerdryl; Ancamin; Antipru; Cadinyl; Cadramine; Caladiph; Caladryl†; Calahyst Frx; Calakin; Calamine Lotion; Calamine Lotion; Calamine-D; Calanol; Calapro; Calarin; Caloryne; Canamine; Canerin; Clara; Fadril†; Hista; Kadryl; KB Calo; Lanol; M-D; Patar lotion; ***Turk.***: Caladryl†; Derivit; Diyenil†; Kalmosan; Tanol; ***UK***: Calaband; Lacto Calamine; Lacto Calamine; RBC; Swarm; Vasogen; ***USA***: Aveeno Anti-Itch†; Caladryl; Calagesic; Calamycin; Dome-Paste; Ivarest; RA Lotion; ***Venez.***: Borocanfor; Calaminol; Calasyl Original; Micofeet.

Pharmacopoeial Preparations
BP 2014: Aqueous Calamine Cream; Calamine and Coal Tar Ointment; Calamine Lotion; Calamine Ointment;
USP 36: Calamine Topical Suspension; Phenolated Calamine Topical Suspension.

Calcipotriol *(BAN, rINN)*

Calcipotriene (USAN); Calcipotriolum; Kalcipotriol; Kalcypotriol; Kalsipotriol; Kalsipotrioli; MC-903; Кальципотриол.
(5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol.
$C_{27}H_{40}O_3$=412.6
CAS — 112828-00-9; 112965-21-6.
ATC — D05AX02.
ATC Vet — QD05AX02.
UNII — 143NQ3779B.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the monohydrate.

Ph. Eur. 8: (Calcipotriol, Anhydrous; Calcipotriolum Anhydricum). A white or almost white, crystalline powder. It is sensitive to heat and light. A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers at a temperature of -20 degrees or below. Protect from light.

Ph. Eur. 8: (Calcipotriol Monohydrate; Calcipotriolum Monohydricum). A white or almost white, crystalline powder. It is sensitive to light. A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Calcipotriol is a vitamin D_3 derivative. *In vitro* it appears to induce differentiation and to suppress proliferation of keratinocytes.

Calcipotriol is used in a cream or ointment for the management of plaque psoriasis and as a solution in the management of scalp psoriasis; the concentration of calcipotriol used is 0.005%. Applications should be made once or twice daily. No more than 100 g of cream or ointment, or 60 mL of scalp solution, should be applied in one week. If both are used, the limit is 60 g of cream or ointment with 30 mL of scalp solution, or 30 g of cream or ointment with 60 mL of scalp solution.

For the use of calcipotriol in children, see below.

Administration in children. Topical calcipotriol may be used in the management of plaque psoriasis in children. In the UK, the ointment (0.005%) may be applied twice daily. The maximum applied in one week should be 50 g in children aged 6 to 12 years, and 75 g in children more than 12 years of age. The *BNFC* also suggests that under specialist supervision the scalp solution (0.005%) may be applied twice daily to children aged 6 years and over for the treatment of scalp psoriasis; no more than 30 mL of the solution should be applied in one week to those aged 6 to 12 years, with older children receiving a maximum of 45 mL in one week. When preparations are used together, the *BNFC* recommends a maximum total calcipotriol dose of 2.5 mg in any one week for children aged 6 to 12 years (e.g. 20 mL of the scalp solution with 30 g of the ointment); in older children, the maximum is 3.75 mg in any one week (e.g. 30 mL of the scalp solution with 45 g of the ointment). In the UK, the scalp solution is not licensed for use in children and the ointment is not licensed for use in children under 6 years; however, safety and efficacy have been reported in small 8-week studies that have included children as young as 2 years old.[1-3] There are also a few case reports of topical calcipotriol use in infants with psoriasis, aged 3 months[4] and 6 months.[5]

1. Darley CR, *et al.* Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; **135:** 390–3.
2. Oranje AP, *et al.* Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 1997; **36:** 203–8.
3. Patrizi A, *et al.* Topical calcipotriol in childhood psoriasis. *Acta Derm Venereol* 1999; **79:** 477.
4. Travis LB, Silverberg NB. Psoriasis in infancy: therapy with calcipotriene ointment. *Cutis* 2001; **68:** 341–4.
5. Choi YJ, *et al.* Infantile psoriasis: successful treatment with topical calcipotriol. *Pediatr Dermatol* 2000; **17:** 242–4.

Skin disorders. Topical drugs are the treatment of first choice for *chronic plaque psoriasis* (p. 1688.1). Calcipotriol, dithranol, and coal tar are commonly used for mild to moderate forms of the disorder. Calcipotriol inhibits cell proliferation and increases cell differentiation by binding to vitamin D receptors, thus inhibiting epidermal growth and returning some normality to the skin's structure. It is also possible that calcipotriol affects immunological and inflammatory processes in the skin.[1] Topical calcipotriol has been shown to be effective in mild to moderate chronic plaque psoriasis; it is at least as effective as dithranol, coal tar, and corticosteroids, and has been reported to be superior in several studies.[1,2] Calcipotriol is also more cosmetically acceptable than dithranol, which can stain, and coal tar, which can have an unpleasant smell. Benefits have been maintained with long-term use, and repeat courses are effective for the management of relapse. Although there are fewer studies in children, calcipotriol has been reported to be safe and effective in studies including children aged 2 to 15 years[1] (see also Administration in Children, above). Calcipotriol, applied as a topical solution, is also effective for *scalp psoriasis*.[3] When solutions of calcipotriol and betamethasone were compared for mild to moderate scalp psoriasis,[4] calcipotriol produced a satisfactory response, but betamethasone was more effective and was associated with less irritation of the scalp and face. Similar results were reported in a study comparing calcipotriol with clobetasol propionate in moderate to severe scalp psoriasis.[5] In a study of patients with *nail psoriasis* about half received benefit from calcipotriol ointment over a 3 to 5 month treatment period.[6] This result was similar to that found for patients treated with betamethasone and salicylic acid ointment.

Use of calcipotriol with other antipsoriatic drugs may be beneficial. The combination of calcipotriol with a topical corticosteroid is more effective than monotherapy with either of these.[1,7,8] Treatment for up to 4 weeks is usually effective and may be followed by maintenance calcipotriol monotherapy.[9] Topical calcipotriol with systemic therapies has also been tried. There is evidence that the response to oral ciclosporin or acitretin can be improved,[1] as can the response to phototherapy (UVB) or photochemotherapy (PUVA).[1,10] Combination therapy may also reduce the cumulative dose of acitretin, UVB, or PUVA required to achieve clearance or marked improvement of psoriasis, potentially reducing the risk of long-term adverse effects from these treatments.[1,10,11] However, because of the potential for the vehicle of topical calcipotriol preparations to block UV irradiation, they should be applied at least 2 hours before irradiation.[12] Despite promising reports from combination therapy using topical calcipotriol with systemic treatment, phototherapy, or photochemotherapy, a systematic review[13] found that although there can be a measurable additive effect, it may not be clinically significant in patients' own assessments.

A 2-week course of high-dose calcipotriol (up to 360 g of 0.005% ointment weekly) has been used for inpatient treatment of extensive psoriasis, followed by the usual recommended dose (up to 100 g weekly) for residual psoriasis.[14] Asymptomatic hypercalcaemia and hypercalciuria occurred in some patients, and the authors suggested that the monitoring of calcium homoeostasis is mandatory with this regimen (see also Effects on Calcium Homoeostasis, below). Relapse occurred in most patients within one year.

Beneficial results with calcipotriol have also been reported in small numbers of patients with various skin disorders[15] including *acrodermatitis continua of Hallopeau, confluent and reticulated papillomatosis, congenital ichthyosis, inflammatory linear verrucous epidermal nevus, lichen amyloidosis, morphea or linear scleroderma, pityriasis rubra pilaris, prurigo nodularis,* and *seborrhoeic dermatitis.* A small open study[16] has indicated that topical calcipotriol may be effective in the treatment of oral *leucoplakia* (see under Bleomycin, p. 750.3). It has also been tried, alone or with UVA or UVB, or a topical corticosteroid, in the treatment of *vitiligo*[17-21] (see Pigmentation Disorders, p. 1687.2), but results have been mixed.

1. Scott LJ, *et al.* Calcipotriol ointment: a review of its use in the management of psoriasis. *Am J Clin Dermatol* 2001; **2:** 95–120.
2. Ashcroft DM, *et al.* Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000; **320:** 963–7.
3. Thaçi D, *et al.* Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3,396 patients. *Dermatology* 2001; **203:** 153–6.
4. Klaber MR, *et al.* Comparative effects of calcipotriol solution (50 micrograms/mL) and betamethasone 17-valerate solution (1 mg/mL) in the treatment of scalp psoriasis. *Br J Dermatol* 1994; **131:** 678–83.
5. Reygagne P, *et al.* Clobetasolpropionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatol Treat* 2005; **16:** 31–6.
6. Tosti A, *et al.* Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol* 1998; **139:** 655–9.
7. Fenton C, Plosker GL. Calcipotriol/betamethasone dipropionate: a review of its use in the treatment of psoriasis vulgaris. *Am J Clin Dermatol* 2004; **5:** 463–78.
8. Kragballe K, van de Kerkhof PCM. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20:** 39–44.
9. White S, *et al.* Use of calcipotriene cream (Dovonex cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex): a randomized, parallel-group clinical trial. *Am J Clin Dermatol* 2006; **7:** 177–84.
10. Torras H, *et al.* A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. *J Dermatol Treat* 2004; **15:** 98–103.
11. Woo WK, McKenna KE. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *Br J Dermatol* 2003; **149:** 146–50.
12. De Rie MA, *et al.* Calcipotriol ointment and cream or their vehicles applied immediately before irradiation inhibit ultraviolet B-induced erythema. *Br J Dermatol* 2000; **142:** 1160–5.
13. Ashcroft DM, *et al.* Combination regimens of topical calcipotriene in chronic plaque psoriasis: systematic review of efficacy and tolerability. *Arch Dermatol* 2000; **136:** 1536–43.
14. Bleiker TO, *et al.* Long-term outcome of severe chronic plaque psoriasis following treatment with high-dose topical calcipotriol. *Br J Dermatol* 1998; **139:** 285–6.
15. Holm EA, Jemec GBE. The therapeutic potential of calcipotriol in diseases other than psoriasis. *Int J Dermatol* 2002; **41:** 38–43.
16. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; **30:** 402–6.
17. Ameen M, *et al.* Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo. *Br J Dermatol* 2001; **145:** 476–9.
18. Chiaverini C, *et al.* Treatment of vitiligo by topical calcipotriol. *J Eur Acad Dermatol Venereol* 2002; **16:** 137–8.
19. Kumaran MS, *et al.* Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20:** 269–73.
20. Goktas E, *et al.* Combination of narrow band UVB and topical calcipotriol for the treatment of vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20:** 553–7.
21. Arca E, *et al.* Narrow-band ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of vitiligo. *J Dermatol* 2006; **33:** 338–43.

Adverse Effects and Precautions

The most frequent adverse effect associated with calcipotriol is skin irritation and it should not therefore be applied to the facial area. Symptoms may include burning, itching, erythema, and dry skin, but stopping therapy is seldom necessary. Aggravation of psoriasis may occur. Hypercalcaemia has occurred during treatment with calcipotriol and although rapidly reversible on withdrawal, it should not be used in patients with disorders of calcium metabolism. Other rare adverse effects may include skin atrophy, hyperpigmentation, and photosensitivity. Patients should limit or avoid excessive exposure to both natural and artificial sunlight, because *animal* studies have suggested that topical calcipotriol may enhance the effect of UV radiation to induce skin tumours.

Effects on calcium homoeostasis. Calcipotriol is a vitamin D derivative and therefore has the potential to cause hypercalcaemia and hypercalciuria. Up to December 1993, when about 150 000 patients in the UK had been treated with calcipotriol, the UK CSM had received 6 reports of hypercalcaemia and 2 of hypercalciuria.[1] Three of the patients with hypercalcaemia either had used doses in excess of the recommended maximum (see Uses and Administration, p. 1697.3) or had pustular or exfoliative psoriasis. Hypercalcaemia and hypercalciuria were reversible on withdrawal of calcipotriol. A study[2] investigating the effect of calcipotriol on urine calcium excretion found that use of the maximum recommended dose for 4 weeks produced increased urine calcium excretion, and the authors suggested that patients requiring the maximum dose of calcipotriol should be monitored for hypercalciuria before and during treatment. A review[3] of the effects of vitamin D analogues on calcium homoeostasis concluded that patients with unstable psoriasis are at particular risk of toxicity from calcipotriol and that measurement of urine calcium excretion is a more sensitive indicator of toxicity than serum-calcium concentrations.

1. CSM/MCA. Dovonex ointment (calcipotriol). *Current Problems* 1994; **20:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 27/09/07)
2. Berth-Jones J, *et al.* Urine calcium excretion during treatment of psoriasis with topical calcipotriol. *Br J Dermatol* 1993; **129:** 411–14.
3. Bourke JF, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135:** 347–54.

Hyperpigmentation. Hyperpigmentation occurred at the site of calcipotriol application in 2 patients after use with PUVA-bath therapy (a topical psoralen with UVA irradiation) for psoriasis.[1] The effect persisted for at least 4 months in these patients. Hyperpigmentation of psoriatic plaques was also reported in a patient treated with topical calcipotriol and UVB phototherapy.[2] Abnormal lentiginous pigmentation of psoriatic plaques occurred in a patient treated with topical calcipotriol for psoriasis, which had worsened during chemotherapy for melanoma, and was still present 2 years after stopping chemotherapy and calcipotriol.[3] The authors also noted that melanoma can cause pigment changes and may have played a role in this case.

There has been some interest in the hyperpigmentary effects of calcipotriol for the possible treatment of vitiligo (see Skin Disorders, p. 1697.3).

1. Gläser R, *et al.* Hyperpigmentation due to topical calcipotriol and photochemotherapy in two psoriatic patients. *Br J Dermatol* 1998; **139:** 148–51.
2. Rütter A, Schwarz T. Ausgeprägte Hyperpigmentierung in psoriatischen Plaques als Folge einer Kombinationsbehandlung mit UVB-311 nm und Calcipotriol. *Hautarzt* 2000; **51:** 431–3.
3. Oláh J, *et al.* Pigment anomaly caused by calcipotriol in a subject with melanoma. *J Eur Acad Dermatol Venereol* 2004; **18:** 113–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcipotriol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daivonex; ***Austral.***: Daivonex; ***Austria***: Psorcutan; ***Belg.***: Daivonex; ***Braz.***: Daivonex; ***Canad.***: Dovonex; ***Chile***: Daivonex; ***China***: Aofuqing (澳夫青); Daivonex (达力士); ***Cz.***: Daivonex; ***Denm.***: Daivonex; Dovonex; ***Fin.***: Daivonex; ***Fr.***: Daivonex; ***Ger.***: Daivonex; Psorcutan; ***Gr.***: Cipocal; Dopotril; Dovonex; F-Psorin; Psoraffect; ***Hong Kong***: Cipotriol; Daivonex; ***Hung.***: Daivonex†; ***India***: Daivonex; Heximar; ***Indon.***: Daivonex; ***Irl.***: Calcil†; Dovonex; ***Israel***: Daivonex; ***Ital.***: Daivonex; Psorcutan; ***Jpn***: Dovonex; ***Malaysia***: Daivobet; Daivonex; ***Mex.***: Daivonex; Eukadar; ***Neth.***: Daivonex†; Fenipsorian†; ***Norw.***: Daivonex†; ***NZ***: Daivonex; ***Philipp.***: Daivonex; ***Pol.***: Daivonex; Sorel Plus; ***Port.***: Daivonex; ***Rus.***: Daivonex (Дайвонекс); ***S.Afr.***: Dovonex; ***Singapore***: Daivonex; ***Spain***: Daivonex; ***Swed.***: Daivonex†; ***Switz.***: Daivonex; ***Thai.***: Daivonex; ***Turk.***: Psorcutan; ***UK***: Dovonex; ***USA***: Dovonex; Sorilux.

Multi-ingredient Preparations. ***Arg.***: Taclonex; ***Austral.***: Daivobet; ***Austria***: Psorcutan Beta; Xamiol; ***Belg.***: Dovobet; Xamiol; ***Braz.***: Daivobet; ***Canad.***: Dovobet; Xamiol; ***China***: Daivobet (得肤宝); ***Cz.***: Daivobet; Xamiol; ***Denm.***: Daivobet; Xamiol; ***Fin.***: Daivobet; Xamiol; ***Fr.***: Daivobet; Xamiol; ***Ger.***: Daivobet; Psorcutan Beta; Xamiol; ***Gr.***: Dovobet; Xamiol; ***Hong Kong***: Daivobet; Xamiol; ***Hung.***: Daivobet; ***India***: Daivobet; Heximar-B; ***Indon.***: Daivobet; ***Irl.***: Dovobet; Xamiol; ***Israel***: Daivobet; Xamiol; ***Ital.***: Dovobet; Token; Xamiol; ***Mex.***: Daivobet; ***Neth.***: Dovobet; Xamiol; ***Norw.***: Daivobet; Xamiol; ***NZ***: Daivobet; ***Philipp.***: Daivobet; Xamiol; ***Pol.***: Daivobet; Xamiol; ***Port.***: Daivobet; Xamiol; ***Rus.***: Daivobet (Дайвобет); ***S.Afr.***: Dovobet; ***Singapore***: Daivobet; Xamiol; ***Spain***: Daivobet; Xamiol; ***Swed.***: Daivobet; Xamiol; ***Switz.***: Daivobet; Xamiol; ***Thai.***: Daivobet; Xamiol; ***Turk.***: Psorcutan Beta; ***UK***: Dovobet; Xamiol†; ***USA***: Taclonex.

Centella

Azijinės centelės žolė; Ázsiai gázlófű; Centellae Asiaticae Herba; Herba Centellae; Hidrocótilo; Hydrocotyle; Indian Pennywort; Nať centely asijské; Rohtosammakonputki; Sallatsspikblad; Wassernabelkraut, Asiatisches; Центелла Азиатская (*Centella asiatica*).

CAS — 464-92-6 (asiatic acid); 16830-15-2 (asiaticoside); 18449-41-7 (madecassic acid); 34540-22-2 (madecassoside).

ATC Herb — HM01AW5005 (Centella asiatica: *herb*); *HD03WB5001* (Centella asiatica: *herb*).

UNII — 7M867G6T1U (Centella asiatica); *6810070TYD* (Centella asiatica *extract*).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii) and *US*. *US* also includes a powdered form, a powdered extract, and Centella Asiatica Triterpenes.

Ph. Eur. 8: (Centella). The dried, fragmented aerial parts of *Centella asiatica*. It contains not less than 6% of total triterpenoid derivatives, expressed as asiaticoside, calculated with reference to dried drug. Protect from light.

USP 36: (Centella Asiatica). The dried aerial parts of *Centella asiatica* (*Hydrocotyle asiatica*) (Apiaceae). It is also known in commerce as gotu kola. It contains not less than 2.0% of triterpene derivatives. Protect from light and moisture.

USP 36: (Centella Asiatica Triterpenes). A fraction enriched in *Centella asiatica* triterpenes derivatives. It contains not less than 90.0% of triterpene derivatives. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Profile

Centella contains the triterpene acids madecassic acid, asiatic acid, and their glycosides asiaticoside and madecassoside. It has been used topically and orally in the management of wounds, ulcers, and keloid scars. Preparations containing asiaticoside and madecassoside have also been used.

The names gotu kola, gotu cola, and gota kola are used for *Centella asiatica* (=*Hydrocotyle asiatica*) in herbal medicine.

Homoeopathy

Centella has been used in homoeopathic medicines.

References.

1. WHO. Herba Centallae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO; 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/10.html (accessed 27/05/10)

Adverse effects. Contact dermatitis has been reported with the topical use of centella.[1] There is also a report of 3 cases of hepatotoxicity associated with ingestion of centella, all presenting with jaundice, painful hepatomegaly, and granulomatous hepatitis with areas of necrosis.[2]

1. Gonzalo Garijo MA, *et al.* Allergic contact dermatitis due to Centella asiatica: a new case. *Allergol Immunopathol (Madr)* 1996; **24:** 132–4.
2. Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of Centella asiatica. *Rev Esp Enferm Dig* 2005; **97:** 115–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pertusan; ***Belg.***: Madecassol; ***Braz.***: Centelax†; Centella-Vit†; ***Chile***: Celulase Plus; Celulase; Centabel; Escar T; Madecassol; ***Fr.***: Madecassol; ***Gr.***: Madecassol; ***Hong Kong***: Madecassol; ***India***: Iqmem; Learnol Plus; ***Indon.***: Fitocassol; Lanakeloid; Madecassol; Tekasol; ***Ital.***: Centellase; ***Malaysia***: Lanakeloid; ***Mex.***: Madecassol; ***Port.***: Madecassol; ***Singapore***: Centellase; Centica; Lanakeloid; ***Spain***: Blastoestimulina; Grail; ***Thai.***: Madecassol; ***Turk.***: Madecassol; ***Venez.***: Litonate; Madecassol.

Multi-ingredient Preparations. ***Arg.***: Adelgazar; Aftersun; Biocell; Cellasene Gold; Cellasene†; Celu-Atlas; Centella Asiatica Compuesta; Centella Asiatica Diates†; Centella Asiatica Plus; Centella Asiatica Spir; Centella Asiatica Vital; Centella Incaico; Centella Queen Complex; Centella Queen Complex; Centella Queen Reductora; Centellacrom; Centellase de Centella Queen; Cen-

All cross-references refer to entries in Volume A

tellase Gel; Clevosan; Clevosan; CVP Cellulite; CVP Cellulite; Desgras Piel Naranja; Doctor 10 Body; Durgel; Energizante Vital con ginseng; Estri-Atlas; Fangan Plus; Garcinol Max; Gentianella; Ginal Cent; Ginkan; Herbaccion Celfin; Indian Health - Centella; Indian Health - Garcinia; Linfol Cicatrizante; Lociherp Liposomas Antiage; Lociherp Liposomas Vitaminado; Mailen; Moragen; Natural Diet; Neo Pelvicillin; Nio Marine; No-Gras; Ovufem; Ovumix; Pentol; Redudiet; Septigyn; Vagicural Plus; Varicura; Venoful; VNS 45; ***Austral.***: Aesculus & Ruscus Compound; Arthro-Eze; Brahmi Super Learning Complex; Extralife Leg-Care†; For Women Active Woman Formula†; Mindac; ***Chile***: Cellenergy; Celu-Atlas; Celulase Con Neomicina; Cicaplast; Cicapost; Escar T-Neomicina; Estri-Atlas; Perfect Body; Redermic Piel; Redermic XL; Ruboril AI; Ureadin Rx DB; ***Fr.***: Cicaplast; Cicatridine; Fadiamone; Veganix; ***Ger.***: Ialunara; ***India***: Abana; Attentio; Dermec; Dermec; Geriforte; Geriforte; Memtone; Menosan; Mentat; Mulmin Plus; ***Indon.***: Lanakeloid-E; Venos; ***Ital.***: Angiorex Complex; Angioton; Angioton; Angiovein; Capill Venogel; Capill; Centella Complex; Centella Complex; Centeril H; Centeril H; Clebolider†; Criotonal; Dermilia Flebozin†; Emmenoiasi; Flavion; Flebo-Si†; Flebofort; Flebofort; Flebolider; Flebovis; Flebozin; Fraxiven; Gelovis; Idren; Levital Plus; Lik-Gel†; Neomyrt Plus; Osmogel; Pik Gel; Proctocella Complex; Slimmer Plus; Tractoven; Vaginol; Vasotonal; Venactive; Venoplant; Venoplant; Venoplant; Wasotonal†; ***Malaysia***: Lanakeloid-E; ***Mex.***: Madecassol C; Madecassol N; Nordibela; Varicyl; ***Mon.***: Akildia; Cicaleine; ***Philipp.***: Memory DD†; Memory Plus; Premium Memori Plus; Ruflex; ***Port.***: Antiestrias; ***Singapore***: Lanakeloid-E; Memomet; Ruflex; ***Spain***: Blastoestimulina†; Blastoestimulina; Blastoestimulina; Cemalyt; Nesfare; ***Ukr.***: Intellan (Интеллан); Osteoartisi Max (Остеоартизи Макс); Trypsidan (Трипсидан)†; ***USA***: Mucotrol; ***Venez.***: Celyth's.

Homoeopathic Preparations. ***Fr.***: Boripharm No 1†; Boripharm No 22†; Saponaria Compose; ***Ger.***: Allergo-Loges; Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Ekzevowen.

Ceramides

N-Acylsphingosines.
CAS — 104404-17-3 (ceramide); 100403-19-8 (ceramides).

Profile

Ceramides are a diverse group of sphingolipids found in the skin. They consist of a sphingoid base (sphingosine, phytosphingosine, or hydroxysphingosine) linked to a fatty acid by an amide bond; the fatty acid may be an alpha hydroxy acid, an esterified alpha hydroxy acid, or a nonhydroxy acid and the carbon chains vary in length but usually contain between 16 and 40 carbon atoms. The major ceramides present in human skin have been classified either by their characteristics on chromatography (ceramides 1 to 8) or by a code consisting of 1 or 2 letters defining the type of fatty acid (A, EO, or N) followed by a letter defining the sphingoid base (S, P, or H).

Ceramides have an important role in the structure and function of the stratum corneum and natural and synthetic ceramides and their precursors have been applied topically in skin disorders such as dry skin and eczema. They have also been given orally in nutritional supplements.

Reviews.
1. Coderch L, *et al.* Ceramides and skin function. *Am J Clin Dermatol* 2003; **4:** 107–29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Philipp.***: Ceraklin.

Multi-ingredient Preparations. ***Arg.***: Aminoterapia†; Lipiforce; Ureadin Facial; ***Chile***: Effaclar H; Ureadin Facial Antiarrugas; Ureadin Facial; Urealeti; ***Fr.***: Actipur 3 en 1; Actipur Antiimperfections; ***Hong Kong***: Physiogel; ***Malaysia***: Pynocare-white; ***Singapore***: Balneum Intensiv; Ceradan; ***UK***: Balneum.

Cerous Nitrate

Cerio, nitrato de; Cerium Nitrate; Ceru(III) azotan; Церия Нитрат.
$Ce(NO_3)_3$=326.1
CAS — 10108-73-3.
UNII — 7U25VKD7PW.

Profile

Cerous nitrate has been used topically, mainly with sulfadiazine silver, in the treatment of burns.

References.
1. Garner JP, Heppell PS. Cerium nitrate in the management of burns. *Burns* 2005; **31:** 539–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Flammacerium; ***Braz.***: Dermacerium; ***Fr.***: Flammacerium; ***Gr.***: Flammacerium; ***Hong Kong***: Flammacerium; ***Neth.***: Flammacerium; ***Philipp.***: Flammacerium; ***Pol.***: Flammacerium†; ***Spain***: Flammazine Cerio; ***UK***: Flammacerium.

Cinnamates

Cinnamate Esters.

Profile

Cinnamates are esters of cinnamic acid (p. 1748.3). Simple esters such as ethyl cinnamate (p. 2185.1) are used as flavours and perfumes. Substituted cinnamates, including *p*-methoxycinnamates such as octinoxate (p. 1715.1), are used as sunscreens.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Avene 20 Proteccion Total; Avene 20 Proteccion Total; Fotoprotectores; Fotoprotectores; Photoscreen†; Photoscreen; ***Fr.***: SVR 100†; ***Port.***: Uriage Extreme†.

Cinoxate *(USAN, rINN)*

Cinoxato; Cinoxatum; Циноксат.
2-Ethoxyethyl *p*-methoxycinnamate; 3-(4-Methoxyphenyl)-2-propenoic acid 2-ethoxyethyl ester.
$C_{14}H_{18}O_4$=250.3
CAS — 104-28-9.
UNII — 5437O7N5BH.

Profile

Cinoxate, a substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (p. 1715.1). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: RV Paque; ***Venez.***: Neutrogena Ultra Sheer.

Crilanomer *(rINN)*

Acrylonitrile-starch Copolymer; Crilanomère; Crilanómero; Crilanomerum; ZK-94006; Крилономер.
A starch polymer with acrylonitrile.
CAS — 37291-07-9.
ATC — D03AX09.
ATC Vet — QD03AX09.

Profile

Crilanomer is a starch copolymer used as a hydrogel wound dressing in the management of wounds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Intrasite.

Crotamiton *(BAN, rINN)*

Crotam; Crotamitón; Crotamitonum; Krotamiton; Krotamitonas; Krotamitoni; Кротамитон.
N-Ethyl-*N*-*o*-tolylcrotonamide; *N*-Ethylcrotono-*o*-toluidide; *N*-Ethyl-*N*-(2-methylphenyl)-2-butenamide.
$C_{13}H_{17}NO$=203.3
CAS — 483-63-6.
ATC Vet — QP53AX04.
UNII — D6S4O4XD0H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Crotamiton). A colourless or pale yellow oily liquid. It solidifies partly or completely at low temperatures. It is mainly the (*E*)-isomer, with not more than 15% of the (*Z*)-isomer. Slightly soluble in water; miscible with alcohol. Protect from light.

USP 36: (Crotamiton). A colourless to slightly yellowish oil with a faint amine-like odour. It is a mixture of *cis*- and *trans*-isomers. Soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Crotamiton is used as an antipruritic (p. 1687.3), although its value is considered uncertain (see also below). It is applied as a 10% cream or lotion 2 or 3 times daily; children aged less than 3 years may receive one application daily.

Crotamiton has also been used as an acaricide in the treatment of scabies but other more effective drugs are usually preferred (p. 2148.1). The 10% cream or lotion is applied, after first bathing and drying, to the whole of the body-surface below the chin, particular attention being paid to body folds and creases. A second application should be applied 24 hours later but it may need to be used once daily up to a total of 5 days to be effective.

Pruritus. A double-blind study in 31 patients[1] found that 10% crotamiton lotion was no more effective an antipruritic than its vehicle.
1. Smith EB, *et al.* Crotamiton lotion in pruritus. *Int J Dermatol* 1984; **23:** 684–5.

Adverse Effects and Precautions

Topical use of crotamiton occasionally causes irritation. There have been rare reports of hypersensitivity reactions. Crotamiton should not be used in patients with acute exudative dermatitis. It should not be applied near the eyes, mouth, or other mucous membranes or on excoriated skin.

Ingestion of crotamiton may cause burning and irritation of oral, oesophageal, and gastric mucosa with nausea, vomiting, and abdominal pain.

Overdosage. A 23-year-old woman developed tonic-clonic seizures, requiring treatment with diazepam, after ingestion of a crotamiton emulsion.[1] Other hospital treatment included gastric lavage, activated charcoal, and metoclopramide. Crotamiton was detected in serum at a concentration of 34 micrograms/mL and was also detectable with several metabolites in the urine. Reference was also made to a report of a 2½-month-old child who had developed pallor and cyanosis after excessive dermal application of a crotamiton cream.
1. Meredith TJ, *et al.* Crotamiton overdose. *Hum Exp Toxicol* 1990; **9:** 57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Eurax; ***Austria***: Eurax†; ***Belg.***: Eurax†; ***Canad.***: Eurax; ***Chile***: Eurax; ***China***: An Fu Kang (安夫康); Youlifu (优力肤); ***Fr.***: Eurax; ***Ger.***: Crotamitex†; Eraxil†; ***Gr.***: Eurax; ***Hong Kong***: Dermorax†; Eurax; Eurosin; Marax†; ***India***: Crotorax; ***Irl.***: Eurax; ***Israel***: Eurax; Scabicin; ***Ital.***: Eurax; ***Malaysia***: A-Bite; Crotorax†; Eurax; Moz-Bite; ***Mex.***: Acomexol; Eurax; ***Norw.***: Eurax; ***NZ***: Eurax; Itch-Soothe; ***Philipp.***: Congen; Eurax; Scabirax†; ***Port.***: Eurax; Scabicin; ***S. Afr.***: Eurax; ***Singapore***: Crotorax; Eurax; Moz-Bite; ***Switz.***: Eurax; ***UK***: Eurax; ***USA***: Eurax; ***Venez.***: Crotanol.

Multi-ingredient Preparations. ***Arg.***: Anastim; Empecid Pie; ***Chile***: Kertyol; ***Fr.***: Kelual DS; ***Hong Kong***: Uni-Rax-HC†; ***India***: Crotorax-HC; Kertyol-S; ***Irl.***: Eurax-Hydrocortisone; ***Israel***: Duo-Scabil; ***Jpn***: Una A Gel†; Una A; ***Malaysia***: Crotamiton H; ***Singapore***: Crotorax-HC; ***UK***: Eurax Hc; ***Venez.***: Kertyol.

Pharmacopoeial Preparations
BP 2014: Crotamiton Cream; Crotamiton Lotion;
USP 36: Crotamiton Cream.

Dextranomer *(BAN, rINN)*

Dekstranomeeri; Dextranomère; Dextranómero; Dextranomerum; Декстраномер.
Dextran cross-linked with epichlorohydrin (1-chloro-2,3-epoxypropane); Dextran 2,3-dihydroxypropyl 2-hydroxy-1,3-propanediyl ether.
CAS — 56087-11-7.
ATC — D03AX02.
ATC Vet — QD03AX02.
UNII — 30KXI0TVD3.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dextranomer). White or almost white, spherical beads. Practically insoluble in water. It swells in water and electrolyte solutions

Uses and Administration

The action of dextranomer as a wound dressing depends upon its ability to absorb up to 4 times its weight of fluid, including dissolved and suspended material of molecular weight up to about 5000.

Dextranomer is used for the cleansing of exudative and infected burns (p. 1683.1), wounds and ulcers (p. 1690.1), and for preparation for skin grafting.

The wound is cleansed with sterile water or saline and allowed to remain wet; dextranomer in the form of spherical beads is sprinkled on to a depth of at least 3 to 6 mm and covered with a sterile dressing. Occlusive dressings are not recommended as they may lead to maceration around the wound. The dextranomer should be removed when the

layer has become saturated with exudate; the old layer is washed off with a stream of sterile water or saline before renewal. The frequency of renewal will depend on the wound, ranging from once or twice daily to several times a day. All dextranomer must be removed before skin grafting. Dextranomer may also be applied as a paste (either ready-made or prepared by mixing dextranomer beads with glycerol).

Implants containing dextranomer microspheres in a stabilised hyaluronic acid carrier gel (NASHA/Dx) have been injected into the submucosa of the urethra in the management of female stress urinary incontinence (p. 2349.2). Connective tissue gradually surrounds the microspheres, and the resulting augmented tissue helps to restore urinary continence. In vesicoureteral reflux in children, implants containing up to 50 mg may be injected into the submucosa of the ureter, creating a bulge close to the ureteral orifice. The procedure may be repeated after 3 months if necessary.

References.
1. Stenberg ÅM, *et al*. Urethral injection for stress urinary incontinence: long-term results with dextranomer/hyaluronic acid copolymer. *Int Urogynecol J* 2003; **14:** 335–8.
2. van Kerrebroeck P, *et al*. Efficacy and safety of a novel system (NASHA/Dx copolymer using the Implacer device) for treatment of stress urinary incontinence. *Urology* 2004; **64:** 276–81.
3. Chapple CR, *et al*. An open, multicentre study of NASHA/Dx Gel (Zuidex®) for the treatment of stress urinary incontinence. *Eur Urol* 2005; **48:** 488–94.
4. Dean GE, Doumanian LR. The extended use of Deflux (dextranomer/hyaluronic acid) in pediatric urology. *Curr Urol Rep* 2006; **7:** 143–8.
5. Routh JC, *et al*. Single center experience with endoscopic management of vesicoureteral reflux in children. *J Urol (Baltimore)* 2006; **175:** 1889–93.
6. Yu RN, Roth DR. Treatment of vesicoureteral reflux using endoscopic injection of nonanimal stabilized hyaluronic acid/dextranomer gel: initial experience in pediatric patients by a single surgeon. *Pediatrics* 2006; **118:** 698–703.
7. Molitierno JA, *et al*. Endoscopic treatment of vesicoureteral reflux using dextranomer hyaluronic acid copolymer. *J Pediatr Urol* 2008; **4:** 221–8.

Adverse Effects and Precautions

Dextranomer can cause pain during dressing changes in some patients, and bleeding, blistering, and erythema have been reported occasionally. It should not be used in deep wounds or cavities from which it cannot be easily removed, nor should it be used on dry wounds. Care should be exercised when paste formulations of dextranomer are used near the eyes.

Spillage may render surfaces very slippery.

Viscous gel implants containing dextranomer, injected submucosally around the urethra, can cause transient urinary retention. Injection site reactions including mass, abscess, and pseudocyst formation have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Debrisan; ***Mex.***: Debrisan; ***Pol.***: Acudex†; ***S.Afr.***: Debrisan†; ***USA***: Debrisan†.

Multi-ingredient Preparations. ***UK***: Zuidex; ***USA***: Deflux; Solesta.

Dibenzoylmethane

Dibenzoilmetano; Дибензоилметан.
1,3-Diphenyl-1,3-propanedione.
$C_{15}H_{12}O_2$=224.3
CAS — 120-46-7.
UNII — ANS7ME8OKC.

Profile

Dibenzoylmethane is a sunscreen (p. 1681.3) with actions similar to those of avobenzone (p. 1695.1). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: RoC Sunscreen Stick.

Dihydroxyacetone

Cetotriosa; DHA; Dihidroxiacetona; Ketotriose; Дигидроксиацетон.
1,3-Dihydroxypropan-2-one.
$C_3H_6O_3$=90.08
CAS — 96-26-4.
UNII — O10DDW6JOO.

NOTE. DHA is also used as a synonym for docosahexaenoic acid (p. 1460.1).

Pharmacopoeias. In *US*.

USP 36: (Dihydroxyacetone). A white to off-white crystalline powder. The monomeric form is freely soluble in water, in alcohol, and in ether; the dimeric form is freely soluble in water, soluble in alcohol, and sparingly soluble in ether. A 5% solution in water has a pH between 4.0 and 6.0. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

Uses and Administration

Application to the skin of preparations containing dihydroxyacetone slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin.

A single application may give rise to a patchy appearance; progressive darkening of the skin results from repeated use until a point is reached when the maximum effect is achieved. If the treatment is stopped the colour starts to fade after about 2 days and disappears completely within 8 to 14 days as the external epidermal cells are lost by normal attrition.

Preparations usually contain 5% of dihydroxyacetone and have been used to camouflage vitiligo (see Pigmentation Disorders, p. 1687.2) or to produce an artificial suntan. Some preparations include sunscreens since the pigmentation produced gives no protection against sunburn.

Adverse Effects and Precautions

Skin irritation from dihydroxyacetone occurs rarely; rashes and allergic dermatitis have been reported. Contact with eyes, abraded skin, and clothing should be avoided.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Autohelios Bronz; DHA Autobronceante; Eurocolor Sin Sol; Ikx Autobronceante†; Lelco sin Sol; Maprosol Autobronceante; ***Austral.***: Tru Bronz; Vitadye†; ***Braz.***: Autohelios; ***Chile***: Fotoprotectores; Leche Autobronceante; Neutrogena Build a Tan; ROC Minesol Bronze; Uriage Bruma Autobronceante; ***Mex.***: Dermacrom; ***USA***: Chromelin Complexion Blender.

Multi-ingredient Preparations. ***Arg.***: Fotosol Ultra Autobronceante; Polysianes Autobronceante; ***Austral.***: Sunsense Self Tanning System Self Tan; ***Braz.***: Sunmax Autobronzeador; ***Chile***: Neutrogena Build a Tan; ***Fr.***: Autohelios; Viticolor; ***UK***: ViTicolor; ***USA***: QT.

Diolamine Methoxycinnamate

DEA-Methoxycinnamate; Diethanolamine Methoxycinnamate; Diolamina metoxicinnamato; Diolamine Méthoxycinnamate; Diolamine *p*-Methoxycinnamate (pINNM); Diolaminum Metoxicinnamatum; Диоламин Метоксисинамат.
p-Methoxycinnamic acid compound with 2,2′-iminodiethanol (1:1).
$C_{10}H_{10}O_3.C_4H_{11}NO_2$=283.3
CAS — 56265-46-4.
UNII — 1UFJ6AS9NX.

Profile

Diolamine methoxycinnamate, a compounded substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (p. 1715.1). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: President's Choice Sunblock.

Dioxybenzone *(USAN, rINN)*

Benzofenon-8; Benzophenone-8; Dioxibenzona; Dioxybenzonum; NSC-56769; Диоксибензон.
2,2′-Dihydroxy-4-methoxybenzophenone.
$C_{14}H_{12}O_4$=244.2
CAS — 131-53-3.
UNII — B762XZ551X.

Pharmacopoeias. In *US*.

USP 36: (Dioxybenzone). A yellow powder. Practically insoluble in water; freely soluble in alcohol and in toluene. Store in airtight containers. Protect from light.

Profile

Dioxybenzone, a substituted benzophenone, is a sunscreen (p. 1681.3) with actions similar to those of oxybenzone (p. 1715.3). It is effective against UVB and some UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Solaquin Forte; Spectraban; ***Canad.***: Solaquin Forte; ***Chile***: Clasifel; ***Mex.***: Clasifel; ***USA***: Solaquin Forte; Solaquin Forte.

Pharmacopoeial Preparations
USP 36: Dioxybenzone and Oxybenzone Cream.

Diphencyprone

Difenciprona; Дифенципрон.
2,3-Diphenylcyclopropenone-1.
$C_{15}H_{10}O$=206.2
CAS — 886-38-4.
UNII — I7G14NW5EC.

Profile

Diphencyprone has been applied as a contact sensitiser for the treatment of alopecia. It has also been tried in warts.

Adverse effects. Diphencyprone is considered to lack serious adverse effects but some patients may not be able to tolerate the induced hypersensitivity reaction. There have been reports of generalised urticaria and dermographism, sometimes severe, following the use of diphencyprone.[1-5] In another case, a severe reaction of urticaria and dermographism, which lasted several months, occurred after the initial sensitisation dose.[6] Allergy to diphencyprone has been reported in medical and nursing staff in spite of taking protective precautions during its application.[7] A patient who received diphencyprone treatment for warts developed a widespread pruritic rash and palpitations due to ventricular extrasystoles.[1] Vitiligo has also been reported in patients treated with diphencyprone[8-10] and it has been suggested that this might be due to unmasking of subclinical vitiligo.[8,9] Erythema multiforme-like eruptions have been associated with the topical application of diphencyprone.[11,12]

1. Lane PR, Hogan DJ. Diphencyprone. *J Am Acad Dermatol* 1988; **19:** 364–5.
2. Tosti A, *et al*. Contact urticaria during topical immunotherapy. *Contact Dermatitis* 1989; **21:** 196–7.
3. Skrebova N, *et al*. Severe dermographism after topical therapy with diphenylcyclopropenone for alopecia universalis. *Contact Dermatitis* 2000; **42:** 212–15.
4. Francomano M, Seidenari S. Urticaria after topical immunotherapy with diphenylcyclopropenone. *Contact Dermatitis* 2002; **47:** 310–11.
5. Short KA, Higgins EM. Urticaria as a side-effect of diphencyprone therapy for resistant viral warts. *Br J Dermatol* 2005; **152:** 583–5.
6. Alam M, *et al*. Severe urticarial reaction to diphenylcyclopropenone therapy for alopecia areata. *J Am Acad Dermatol* 1999; **40:** 110–12.
7. Shah M, *et al*. Hazards in the use of diphencyprone. *Br J Dermatol* 1996; **134:** 1153.
8. Hatzis J, *et al*. Vitiligo as a reaction to topical treatment with diphencyprone. *Dermatologica* 1988; **177:** 146–8.
9. Duhra P, Foulds IS. Persistent vitiligo induced by diphencyprone. *Br J Dermatol* 1990; **123:** 415–16.
10. Henderson CA, Ilchyshyn A. Vitiligo complicating diphencyprone sensitization therapy for alopecia universalis. *Br J Dermatol* 1995; **133:** 496–7.
11. Perret CM, *et al*. Erythema multiforme-like eruptions: a rare side effect of topical immunotherapy with diphenylcyclopropenone. *Dermatologica* 1990; **180:** 5–7.
12. Oh C-W, *et al*. Bullous erythema multiforme following topical diphenylcyclopropenone application. *Contact Dermatitis* 1998; **38:** 220–1.

Alopecia. Diphencyprone has been used as a contact sensitiser in the treatment of various forms of alopecia (p. 1682.3) including areata, totalis, and universalis. Case series reports generally describe treatment of adults, but some groups have also included adolescents and children, and some have reported solely on treatment in children.[1,2]

Initial sensitisation is usually achieved by applying a 2% solution of diphencyprone in acetone to a small area of scalp, which may be repeated if necessary beneath plastic occlusion if adequate sensitisation is not produced. Thereafter, weaker concentrations are applied once weekly and gradually increased in strength to produce erythema and pruritus for 36 to 48 hours post-therapy. Concentrations that have been used vary between reports and the first treatment application may be as dilute as 0.00001%, with further applications gradually increased to up to 2%. Only one side of the scalp is treated until the optimum concentration is found, in order to prevent a widespread adverse reaction. Once hair regrowth has started on the treated side the applications may be extended to the entire scalp.[1-8] As well as erythema and pruritus, patients usually have transient eczema and regional lymph node swelling.[2,5,7,8]

Hair regrowth may not start for several months,[4,6,8] and the required duration of therapy can vary considerably; at least 8 months of treatment may be required,[3,6] and up to 12 months[1,2] or more[4,6] has been reported. Not all patients will respond to treatment and reported response rates vary, although these have probably been influenced by the different definitions used for complete, partial, and no response. Overall, however, regrowth of hair can occur in

up to about 70% of patients, with around half of these having complete regrowth.[1,4,6-8] Some reports have attempted to determine which factors might be associated with clinical response to diphencyprone. There is disagreement between studies but some possible unfavourable prognostic factors include extensive involvement,[4,6,8] younger age at onset,[8] longer disease duration before treatment,[5,7] and a history of atopic eczema.[4,7] The need for high diphencyprone concentrations and prolonged therapy have also been associated with a less favourable outcome.[8]

Despite these rates of response a significant number of patients will relapse, either during or after stopping treatment, and re-treatment may be considered.[4,6,7] The time to relapse can be variable. Remission in a small group of complete responders ranged from 1 month to 2 years after stopping therapy.[4] Another group of patients who achieved total regrowth of hair were able to stop treatment with diphencyprone for a mean of 15 months without relapse[9] while a further group maintained satisfactory hair growth for a mean follow-up period of 19.8 months.[5]

1. MacDonald Hull S, *et al.* Alopecia areata in children: response to treatment with diphencyprone. *Br J Dermatol* 1991; **125:** 164–8.
2. Schuttelaar M-L, *et al.* Alopecia areata in children: treatment with diphencyprone. *Br J Dermatol* 1996; **135:** 581–5.
3. MacDonald Hull S, Cunliffe WJ. Successful treatment of alopecia areata using the contact allergen diphencyprone. *Br J Dermatol* 1991; **124:** 212–13.
4. Hoting E, Boehm A. Therapy of alopecia areata with diphencyprone. *Br J Dermatol* 1992; **127:** 625–9.
5. Gordon PM, *et al.* Topical diphencyprone for alopecia areata: evaluation of 48 cases after 30 months' follow-up. *Br J Dermatol* 1996; **134:** 869–71.
6. Pericin M, Trüeb RM. Topical immunotherapy of severe alopecia areata with diphenylcyclopropenone: evaluation of 68 cases. *Dermatology* 1998; **196:** 418–21.
7. Cotellessa C, *et al.* The use of topical diphenylcyclopropenone for the treatment of extensive alopecia areata. *J Am Acad Dermatol* 2001; **44:** 73–6.
8. Wiseman MC, *et al.* Predictive model for immunotherapy of alopecia areata with diphencyprone. *Arch Dermatol* 2001; **137:** 1063–8.
9. van der Steen PHM, *et al.* Topical immunotherapy for alopecia areata: re-evaluation of 139 cases after an additional follow-up period of 19 months. *Dermatology* 1992; **184:** 198–201.

Warts. Diphencyprone has been tried in the treatment of recalcitrant warts. The successful treatment of digital or plantar warts in 42 of 60 patients has been described.[1] The patients were initially sensitised with a 2% topical solution of diphencyprone in acetone, then the warts treated every 1 to 4 weeks with solutions ranging from 0.01 to 6%. In another series,[2] diphencyprone in a paraffin ointment was effective in the clearance of palmar, plantar, palmoplantar, and periungual warts in 135 of 154 patients. A concentration of diphencyprone 2% was used for the initial sensitisation, and concentrations of 0.5 to 4% were used for treatment once every 3 weeks. After initial sensitisation with diphencyprone 2% in acetone, a preparation of diphencyprone with salicylic acid in white soft paraffin applied every night as tolerated was reported to be successful in 44 of 50 patients treated for palmoplantar warts.[3] The concentration of diphencyprone in the ointment ranged from 0.01 to 0.2%, and the concentration of salicylic acid was 15%.

1. Buckley DA, *et al.* Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141:** 292–6.
2. Upitis JA, Krol A. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. *J Cutan Med Surg* 2002; **6:** 214–17.
3. Armour K, Orchard D. Treatment of palmoplantar warts with a diphencyprone and salicylic acid ointment. *Australas J Dermatol* 2006; **47:** 182–5.

Dipyrithione *(USAN, rINN)*

Bispiriyon; Bispyrithione; Dipiritiona; Dipyrithionum; OMDS; Piriyon Disülfit; Pyrithione Disulfide; Дипиритион.

2,2′-Dithiodipyridine 1,1′-dioxide.

$C_{10}H_8N_2O_2S_2$=252.3

CAS — 3696-28-4.

UNII — 9L87N86R9A.

Profile

Dipyrithione is reported to have antibacterial and antifungal properties and is included in preparations for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Perkapil.

Multi-ingredient Preparations. ***Canad.***: Dan-Tar Plus†; Polytar AF; ***Switz.***: Crimanex.

Dithiosalicylic Acid

Ditiosalicílico, ácido; Дитиосалициловая Кислота.

2-Hydroxybenzenecarbodithioic acid.

$C_7H_6OS_2$=170.2

CAS — 527-89-9.

UNII — 8LV29H49A3.

Profile

Dithiosalicylic acid has been used in multi-ingredient preparations used topically for the treatment of acne and seborrhoeic dermatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Sacnel.

Dithranol *(BAN, rINN)*

Anthralin; Antralin; Antralina; Dioxiantranol; Dioxyanthranol; Dithranolum; Ditranol; Ditranoli; Ditranolis; Lignolina; Дитранол.

1,8-Dihydroxyanthrone; 1,8-Dihydroxy-9(10*H*)-anthracenone.

$C_{14}H_{10}O_3$=226.2

CAS — 1143-38-0 (dithranol); 16203-97-7 (dithranol triacetate).

ATC — D05AC01.

ATC Vet — QD05AC01.

UNII — U8CJK0JH5M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Dithranol). A yellow or brownish-yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Anthralin). A yellowish-brown, odourless, crystalline powder. Insoluble in water; slightly soluble in alcohol, in ether, and in glacial acetic acid; soluble in acetone, in chloroform, in benzene, and in solutions of alkali hydroxides. The filtrate from a suspension in water is neutral to litmus. Store at a temperature of 8 degrees to 15 degrees in airtight containers. Protect from light.

Stability. The stability of dithranol has been studied in several bases and vehicles.[1-4] The weaker preparations of dithranol may be less stable.[1,3,4] Salicylic acid is included in dithranol preparations as an antoxidant and its inclusion in pastes also containing zinc oxide prevents their discoloration due to the inactivation of dithranol by zinc oxide.[5] However, zinc oxide or starch can be omitted from dithranol pastes without loss of efficacy provided stiffness is maintained.[5] Addition of ascorbic or oxalic acid may improve dithranol's stability in '*Unguentum Merck*' but salicylic acid appears to be ineffective.[1] The effect of salicylic acid on the instability of dithranol in yellow soft paraffin is variable[1,2] and its inclusion has been questioned as it can be irritant and percutaneous absorption can be significant.[1] Dithranol is relatively stable in white soft paraffin.[1]

The application of any type of heat and contact with metal spatulas should be avoided during the manufacture of dithranol pastes[6] and if milling facilities are not available dithranol can be incorporated into Lassar's paste by dissolving it first in chloroform.[5]

1. Green PG, *et al.* The stability of dithranol in various bases. *Br J Dermatol* 1985; **113** (suppl 29): 26.
2. Lee RLH. Stability of dithranol (anthralin) in various vehicles. *Aust J Hosp Pharm* 1987; **17:** 254–8.
3. Hiller C, *et al.* How stable is dithranol? An investigation into the degradation of different dithranol formulations. *Pharm Pract* 1995; **5:** 428–31.
4. Thoma K, Holzmann C. Stabilization of dithranol in topical formulations. *Acta Pharm Hung* 1998; **68:** 313–21.
5. Comaish S, *et al.* Factors affecting the clearance of psoriasis with dithranol (anthralin). *Br J Dermatol* 1971; **84:** 282–9.
6. *PSGB Lab Report P/79/1* 1979.

Uses and Administration

Dithranol is used in the treatment of subacute and chronic psoriasis, usually in one of two ways.

Conventional treatment is commonly started with an ointment or paste containing 0.1% dithranol (0.05% in very fair patients) applied for a few hours; the strength is gradually increased as necessary to 0.5%, occasionally to 1%, and the duration of contact extended to overnight periods or longer. The preparation is sparingly and accurately applied to the lesions only. If, on initial treatment, lesions spread or excessive irritation occurs, the concentration of dithranol or the frequency of application should be reduced; if necessary, treatment should be stopped. After each treatment period the patient should bathe or shower to remove any residual dithranol.

For *short-contact therapy* dithranol is usually applied in a soft basis to the lesions for up to 60 minutes daily, before being washed off. As with conventional treatment the strength used is gradually increased from 0.1 to 2% but strengths up to 5% have been used. Surrounding unaffected skin may be protected by white soft paraffin.

Treatment for psoriasis should be continued until the skin is entirely clear. Intermittent courses may be needed to maintain the response. Treatment schedules often involve coal tar and UV irradiation (preferably UVB) before the application of dithranol (see below). Salicylic acid is included in many topical preparations of dithranol.

A cream containing dithranol triacetate has been used similarly to dithranol in conventional treatment of psoriasis.

Alopecia. Dithranol cream (0.5 to 1%) applied for 20 to 60 minutes to the scalp and then washed off, has been found to be of benefit in the treatment of alopecia areata (p. 1682.3). However, at least 6 months of treatment may be required for a cosmetically acceptable result.[1] The response rate has, however, been difficult to evaluate because of the small number of reports, and although it has been widely prescribed for limited patchy alopecia areata, some guidelines conclude that there is no convincing evidence of efficacy.[2]

1. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; **61:** 53–69.
2. MacDonald Hull SP, *et al.* British Association of Dermatologists. Guidelines for the management of alopecia areata. *Br J Dermatol* 2003; **149:** 692–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Alopecia%20Areata.pdf (accessed 20/07/10)

Psoriasis. Dithranol used alone or with coal tar, (with or without ultraviolet light), continues to be one of the drugs of first-line treatment for psoriasis (p. 1688.1). It is particularly suited to the treatment of stable chronic plaque psoriasis but unlike coal tar, is irritant to healthy skin and care is required to ensure that it is only applied to lesions. Treatment with dithranol is therefore more feasible when the plaques are large, or few in number. Use with coal tar may help to reduce the irritant effects of dithranol without affecting efficacy. conventional treatment with dithranol is time consuming and more suitable for use on hospital inpatients. Dithranol formulated in stiff preparations such as Lassar's paste to minimise spreading to perilesional skin is left on overnight covered with a suitable dressing and washed off the next day. Treatment is usually started with a concentration of 0.1% (0.05% in fair-skinned patients) and gradually increased according to the response and irritation produced. Cream formulations may be less effective but are more suitable for domestic use. Short-contact therapy in which concentrations of up to 5% of dithranol are applied daily for up to 1 hour is more suitable for use on an outpatient basis and there appears to be little reduction in efficacy; irritation and staining may also be reduced.

Dithranol is also used with UVB phototherapy and there have been many modifications of the original Ingram's regimen in which dithranol is applied after bathing in a tar bath and exposure to ultraviolet light. Inpatient stays of up to 3 weeks may be required but long periods of remission can be obtained.

Reviews.

1. Mahrle G. Dithranol. *Clin Dermatol* 1997; **15:** 723–37.

Adverse Effects and Precautions

Dithranol may cause a burning sensation especially on perilesional skin. Patients with fair skin may be more sensitive than those with dark skin. It is irritant to the eyes and mucous membranes. Use on the face, skin flexures, and genitals should be avoided. Hands should be washed after use.

Dithranol should not be used for acute or pustular psoriasis or on inflamed skin. It stains skin, hair, some fabrics, plastics, and enamel. Staining of bathroom ware may be less of a problem with creams than ointments. Stains on skin and hair slowly disappear on cessation of treatment.

Handling. Dithranol is a powerful irritant and should be kept away from the eyes and tender parts of the skin.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dithranol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Micanol; ***Canad.***: Anthraforte; Anthranol; Anthrascalp; ***Ger.***: Micanol; ***India***: Psorinol†; ***Indon.***: Anthramed; ***Irl.***: Dithrocream; ***Israel***: Dithrocream; Micanol†; ***Ital.***: Psoriderm†; ***NZ***: Micanol; ***Port.***: Micanol; ***S.Afr.***: Anthranol†; ***Singapore***: Micanol; ***Spain***: Micanol; ***UK***: Dithrocream; Micanol; ***USA***: Dritho-Scalp; Psoriatec; Zithranol-RR.

Multi-ingredient Preparations. ***Austral.***: Dithrasal†; ***Fr.***: Anaxeryl; ***Ger.***: Psoradexan; Psoralon MT; ***Gr.***: Filorose; ***Hong Kong***: Dithrasal†; ***India***: Derobin-HC; Derobin; ***Singapore***: Dithrasal; ***Spain***: Lapices Epiderm Metadier†; ***Turk.***: Psoraks; ***UK***: Psorin; Psorin.

Pharmacopoeial Preparations
BP 2014: Dithranol and Salicylic Acid Ointment; Dithranol Cream; Dithranol Ointment; Dithranol Paste;
USP 36: Anthralin Cream; Anthralin Ointment.

Drometrizole *(USAN, rINN)*

Drometrizol; Drométrizol; Drometrizolum; Дрометризол.
2-(2*H*-Benzotriazol-2-yl)-*p*-cresol.
$C_{13}H_{11}N_3O$=225.3
CAS — 2440-22-4.
UNII — 5X93W9OFZL.

Drometrizole Trisiloxane

Дрометризола Трисилоксан.
2-(2*H*-Benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-{1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]-1-disiloxanyl}propyl)phenol.
$C_{24}H_{39}N_3O_3Si_3$=501.8
CAS — 155633-54-8.

NOTE. Mexoryl XL and Silatrizole are trade names that have been used for drometrizole trisiloxane.

Profile

Drometrizole trisiloxane is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Anthelios; Antherpos; Cetaphil UV Defense; ***Braz.***: Anthelios Helioblock Dermopediatrics; Anthelios Helioblock Spray; Anthelios Helioblock W40; Anthelios Helioblock; Antherpos; Helioblock†; Helioblock; Melani-D Maos; ***Canad.***: Anthelios XL; Anthelios XL; Anthelios; Antherpos†; Aqualia; Creme Visage; Face Multi-Protection; Face Multi-Protection; High Protection Cream; Lait Protecteur; Lip Protection; Ombrelle Cream; Ombrelle Kids; Ombrelle Stick; Rosaliac; Sun Protection; Sunscreen Cream; Ultra Protection Sunscreen; Ultra-Fluid Body Milk; Ultra-Fluid Sun Protection; ***Chile***: Anthelios AC; Anthelios AE; Anthelios Dermo-Pediatrics; Anthelios Extremo; Anthelios Spray; Anthelios W; Anthelios XL; Cetaphil Defense; Hydraphase XL; Melani-D; Redermic XL; ***Fr.***: Anthelios; Anthelios; Anthelios; Antherpos†; Capital Soleil; ***Irl.***: Anthelios†; ***Malaysia***: Cetaphil UVA/UVB Defense; ***Singapore***: Anthelios XL Extreme; Cetaphil UVA/UVB; ***UK***: Anthelios XL.

Ecamsule *(USAN, rINN)*

Ecamsul; Écamsule; Ecamsulum; Экамсул.
(±)-(3*E*,3′*E*)-3,3′-(*p*-Phenylenedimethylidyne)bis[2-oxo-10-bornanesulfonic acid]; Terephthalylidene-3,3′-dicamphor-10,10′-disulfonic acid.
$C_{28}H_{34}O_8S_2$=562.7
CAS — 92761-26-7.
UNII — M94R1PM439.

NOTE. Mexoryl SX is a trade name that has been used for ecamsule.

Pharmacopoeias. *US* includes a solution.

USP 36: (Ecamsule Solution). An aqueous solution containing 30 to 34% w/w of ecamsule. Store in airtight containers. Protect from light.

Profile

Ecamsule, a camphorsulfonic acid derivative, is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Anthelios; Antherpos; Cetaphil UV Defense; ***Braz.***: Anthelios Helioblock Dermopediatrics; Anthelios Helioblock Spray; Anthelios Helioblock W30; Anthelios Helioblock W40; Anthelios Helioblock; Antherpos; Helioblock; Melani-D Maos; ***Canad.***: Anthelios XL; Anthelios†; Anthelios; Aqualia; Baume Levres; Biotherm†; Creme Fondante†; Creme Visage; Face Multi-Protection; Face Multi-Protection; High Protection Cream; Hydraphase UV; Lait Ecran Enfants†; Lait Protecteur; Lotion Tres Douce; Lotion Vapo†; Multi Recharge; Ombrelle Cream; Ombrelle Kids; Ombrelle L'Oreal Suncare Research Kids; Ombrelle Lotion Extreme; Ombrelle Lotion; Ombrelle Lotion; Ombrelle Lotion; Ombrelle Sport Lotion; Protective Gel†; Rosaliac; Sun Protection; Sunscreen Cream; Thermal FIX UV†; Ultra-Fluid Body Milk; Ultra-Fluid Protection†; Ultra-Fluid Sun Protection; ***Chile***: Anthelios AC; Anthelios AE; Anthelios Dermo-Pediatrics; Anthelios Extremo; Anthelios Spray; Anthelios W; Anthelios XL; Cetaphil Defense; Hydraphase XL; Redermic XL; ***Fr.***: Anthelios; Anthelios; Anthelios; Antherpos†; Capital Soleil; ***Irl.***: Anthelios†; ***Malaysia***: Cetaphil UVA/UVB Defense; ***Singapore***: Anthelios XL Extreme; Cetaphil UVA/UVB; ***UK***: Ambre Solaire; Anthelios XL; ***USA***: Anthelios 40; Anthelios SX; Capital Soleil; UV Protective.

Efalizumab *(USAN, rINN)*

Anti-CD11a; Éfalizumab; Efalizumabum; Hu-1124; Эфализумаб.
Immunoglobulin G1, anti-(human antigen CD11a)(human-mouse monoclonal hu1124 γ1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer.
CAS — 214745-43-4.
ATC — L04AA21.
ATC Vet — QL04AA21.
UNII — XX2MN88N5D.

Uses and Administration

Efalizumab is a humanised monoclonal antibody that binds to human CD1 1a on leucocytes to inhibit the activation of T-lymphocytes. It has been used for the treatment of chronic moderate to severe plaque psoriasis (p. 1688.1) in patients aged 18 years and over. Efalizumab is given by subcutaneous injection. The initial dose is 700 micrograms/kg, followed by a weekly dose of 1 mg/kg; a single dose should not exceed 200 mg. Treatment is given for 12 weeks, then continued in those who have responded. However, in early 2009 both the FDA and the EMEA reviewed the safety of efalizumab, in response to case reports of progressive multifocal leukoencephalopathy, and the drug was subsequently withdrawn from many markets including Australia, Canada, the USA, and Europe.

References.

1. Lebwohl M, *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003; **349:** 2004–13.
2. Gordon KB, *et al.* Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003; **290:** 3073–80. Correction. *ibid.* 2004; **291:** 1070.
3. Menter A, *et al.* Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 2005; **141:** 31–8.
4. Leonardi CL, *et al.* Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. *J Am Acad Dermatol* 2005; **52:** 425–33.
5. Wellington K, Perry CM. Efalizumab. *Am J Clin Dermatol* 2005; **6:** 113–20.
6. Jordan JK. Efalizumab for the treatment of moderate to severe plaque psoriasis. *Ann Pharmacother* 2005; **39:** 1476–82.
7. Menter A, *et al.* Long-term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol* 2006; **54** (suppl 1): S182–S188.
8. Dubertret L, *et al.* Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol* 2006; **155:** 170–81.
9. Leonardi C, *et al.* Efalizumab: results of a 3-year continuous dosing study for the long-term control of psoriasis. *Br J Dermatol* 2008; **158:** 1107–16.

Adverse Effects and Precautions

The most common adverse affects associated with efalizumab are flu-like symptoms including chills, fever, headache, myalgia, and nausea. These reactions are dose-related in both incidence and severity and usually occur within two days after the first two injections. Other adverse effects include acne, back pain, and elevations in alkaline phosphatase concentrations and liver function values. More serious adverse effects of efalizumab include arthritis, interstitial pneumonitis, hypersensitivity reactions, inflammatory polyradiculoneuropathy, and thrombocytopenia. Treatment should be stopped in patients who develop such reactions. Other neurological adverse events have included facial palsy and transverse myelitis. Severe haemolytic anaemia, diagnosed 4 to 6 months after the start of efalizumab treatment, has been reported. Treatment should be stopped immediately if haemolytic anaemia occurs. Asymptomatic leucocytosis or lymphocytosis commonly occurs during treatment. Worsening of psoriasis or development of variant forms (pustular, erythrodermic, or guttate) have been reported during and after stopping efalizumab therapy.

As a result of immunosuppression, patients given efalizumab are at increased risk of infection. It should not be given to patients with a serious infection and should be used with care in those with chronic infection or a history of recurring infection. Serious bacterial, viral, fungal, and other opportunistic infections have occurred. Reports of progressive multifocal leukoencephalopathy associated with JC virus infection have prompted the withdrawal of efalizumab from many markets (see Effects on the Nervous System, p. 1703.1). Live and live-attenuated vaccines should not be given during efalizumab treatment because of the risk of infection; response to all vaccines may also be reduced. Efalizumab should be withheld from 8 weeks before until 2 weeks after vaccination. Immunosuppression caused by efalizumab might also increase the risk of developing malignancies, so it should be used with care or avoided in patients with a history, or at high risk, of malignancy. Based on studies in *mice*, efalizumab is not recommended for use in children because of the potential risk of permanent suppression of humoral immunity with repeated administration.

Assessment of the platelet count is advised before starting therapy and monthly during early treatment. Frequency of monitoring may be decreased with ongoing treatment.

Incidence of adverse effects. The safety data from 13 controlled and open-label studies of efalizumab in psoriasis have been analysed.[1] During the first 12 weeks of therapy the most common events in patients treated with efalizumab were headache, fever, chills, nausea, vomiting, or myalgia, starting within 48 hours of dosing. In 4 controlled studies that included 1620 patients treated with efalizumab and 715 with placebo, about a third of efalizumab-treated patients reported headache, while chills, nausea, and pain occurred in around 10%, and fever and myalgia in about 8%. These events usually occurred with the first 1 or 2 doses of efalizumab but by the third and subsequent doses the incidence was similar to that in the placebo group. Atypical or unusual worsening of psoriasis, and the development of variant forms, particularly guttate psoriasis, were reported in 3.2% of patients treated with efalizumab; other forms included psoriatic erythroderma, inverse psoriasis, palmoplantar psoriasis, and pustular psoriasis. In 5 studies of extended therapy for 13 to 60 weeks (1115 patients treated for 13 to 24 weeks and 228 for 60 weeks) the rate of adverse effects remained low, there was no new pattern of serious adverse effects, and there was no evidence of cumulative toxicity. An analysis of infection risk found similar rates of mild to moderate and serious infections in patients treated with either efalizumab or placebo. Nevertheless, efalizumab should not be used in patients with pre-existing serious infection. Anti-efalizumab antibodies were found in 67 of 1063 patients, but there was no apparent effect on efficacy, safety, or pharmacodynamics.

There have been infrequent reports of new onset or recurrent severe arthritis, including psoriatic arthritis, in patients treated with efalizumab. Separate analyses[1,2] of pooled study data both found that the incidence of arthropathy events was low (less than 4%) and similar for patients treated with either efalizumab or placebo. However, there was some suggestion[2] that patients with a history of arthropathy and those who have a poor clinical response to efalizumab may be at higher risk.

1. Papp KA, *et al.* Safety of efalizumab in patients with moderate to severe chronic plaque psoriasis: review of clinical data. *J Cutan Med Surg* 2005; **9:** 313–23.
2. Pincelli C, *et al.* The incidence of arthropathy adverse events in efalizumab-treated patients is low and similar to placebo and does not increase with long-term treatment: pooled analysis of data from phase III clinical trials of efalizumab. *Arch Dermatol Res* 2006; **298:** 329–38.

Carcinogenicity. Efalizumab is an immunosuppressant and as such might increase the risk of malignancy. An analysis[1] of pooled data from clinical studies that included 2980 patients given efalizumab found 51 patients (1.7%) with 67 malignancies. Most cases were of non-melanoma skin cancer (51 cases in 35 patients) and it was found that many had risk factors for skin cancer. Other cases included 3 lymphomas, 12 solid tumours at various sites, and 1 malignant melanoma. However, when compared with patients given placebo and data from 2 external cohorts of psoriasis patients (to allow for the increased risk of skin cancers seen in psoriasis patients compared with the general population) there was no evidence that efalizumab increased the risk of developing a malignancy. Nevertheless, further data are needed to determine whether efalizumab has any long-term effect on the development of malignancies.

1. Leonardi CL, *et al.* A review of malignancies observed during efalizumab (Raptiva) clinical trials for plaque psoriasis. *Dermatology* 2006; **213:** 204–14.

Effects on the blood. *Thrombocytopenia* has been described in 6 patients given efalizumab.[1] In 5 cases it started 8 to 12 weeks after starting weekly efalizumab. In all cases the platelet counts recovered quickly after efalizumab was stopped; in 5 cases corticosteroids were also given. In another case a woman presented with *pancytopenia* 4 weeks after starting efalizumab therapy.[2] Efalizumab was stopped and the patient treated with granulocyte colony-stimulating factor, normal immunoglobulin, oral prednisone, platelet transfusion, and darbepoetin alfa. Cell counts returned to normal limits within 4 weeks. Asymptomatic *thrombotic thrombocytopenic purpura* was diagnosed after 6 weeks of efalizumab therapy in a woman with psoriasis; the reaction was successfully managed with plasma exchange.[3]

1. Warkentin TE, Kwon P. Immune thrombocytopenia associated with efalizumab therapy for psoriasis. *Ann Intern Med* 2005; **143:** 761–3.

2. Tom WL, *et al*. Efalizumab-induced autoimmune pancytopenia. *Br J Dermatol* 2006; **155:** 1045–7.
3. Thachil J, Martlew V. Thrombotic thrombocytopenic purpura with the use of efalizumab for psoriasis. *Br J Dermatol* 2008; **158:** 1138–9.

Effects on the nervous system. In early 2009, efalizumab was withdrawn from the market in the USA[1] and Europe[2] after reports of progressive multifocal leukoencephalopathy; some of the cases were fatal. This rare neurological condition, caused by JC virus infection, had occurred in a small number of patients who had been using efalizumab for more than 3 years in the treatment of moderate to severe plaque psoriasis. (Efalizumab has since been withdrawn from other countries including Australia and Canada.)

Aseptic meningitis has been reported with efalizumab. Severe headache developed 48 hours after the first dose of efalizumab in 2 cases, which was followed after 12 to 24 hours by neck stiffness.[3,4] One of the patients also had photophobia and phonophobia.[3]

1. FDA. FDA statement on the voluntary withdrawal of Raptiva from the U.S. market (issued 8th April, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143347.htm (accessed 22/07/10)
2. EMEA. Public statement on Raptiva (efalizumab): withdrawal of the marketing authorisation in the European Union (issued 3rd August, 2009). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000060.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp&jsenabled=true (accessed 22/07/10)
3. Kluger N, *et al*. Efalizumab-induced aseptic meningitis. *Br J Dermatol* 2007; **156:** 189–91.
4. Rivas-Rodríguez R, *et al*. Efalizumab-induced aseptic meningitis. *Farm Hosp* 2007; **31:** 70–1.

Interactions

For a warning concerning the use of live vaccines in patients receiving efalizumab see Adverse Effects and Precautions, p. 1702.2.

Pharmacokinetics

Peak plasma concentrations of efalizumab occur about 1 to 2 days after subcutaneous injection, with a bioavailability of about 50%. Steady state is reached at week 4 of weekly dosing. Efalizumab is metabolised by intracellular degradation. It is cleared by non-linear saturable elimination and the time to elimination after the last dose is about 25 days.

References.

1. Mortensen DL, *et al*. Pharmacokinetics and pharmacodynamics of multiple weekly subcutaneous efalizumab doses in patients with plaque psoriasis. *J Clin Pharmacol* 2005; **45:** 286–98.
2. Sun Y-N, *et al*. Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. *J Clin Pharmacol* 2005; **45:** 468–76.
3. Joshi A, *et al*. An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis. *J Clin Pharmacol* 2006; **46:** 10–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Raptiva; ***Austral.***: Raptiva†; ***Austria***: Raptiva†; ***Braz.***: Raptiva†; ***Canad.***: Raptiva†; ***Cz.***: Raptiva†; ***Denm.***: Raptiva†; ***Fin.***: Raptiva†; ***Fr.***: Raptiva†; ***Ger.***: Raptiva†; ***Gr.***: Raptiva†; ***Hong Kong***: Raptiva†; ***Irl.***: Raptiva†; ***Israel***: Raptiva; ***Ital.***: Raptiva†; ***Malaysia***: Raptiva†; ***Mex.***: Raptiva†; ***Neth.***: Raptiva†; ***Norw.***: Raptiva†; ***NZ***: Raptiva; ***Port.***: Raptiva†; ***Rus.***: Raptiva (Раптива); ***Singapore***: Raptiva†; ***Spain***: Raptiva†; ***Swed.***: Raptiva†; ***Switz.***: Raptiva†; ***Turk.***: Raptiva; ***UK***: Raptiva†; ***USA***: Raptiva†.

Ensulizole *(USAN, rINN)*

Ensulizol; Ensulizolum; Phenylbenzimidazole Sulphonic Acid; Энсулизол.
2-Phenyl-1*H*-benzimidazole-5-sulphonic acid.
$C_{13}H_{10}N_2O_3S$=274.3
CAS — 27503-81-7.
UNII — 9YQ9DI1W42.

NOTE. Eusolex 232 and Neo-Heliopan Hydro are trade names that have been used for ensulizole.

Pharmacopoeias. In *US.*

USP 36: (Ensulizole). A white to ivory-coloured, odourless powder. Practically insoluble in water and in oily solvents; soluble in alcohol; its salts are freely soluble in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Ensulizole is used topically as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Coppertone Tan Magnifier; Hawaiian Tropic Dark Tanning.

Multi-ingredient Preparations. ***Arg.***: Fotocrem 50; Fotocrem 50; Fotoprotector Extrem Pediatrics; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Ultra; Lelco P Ultra; Lelco Ultrablock Extreme; Lelco Ultrablock†; Ozonosol; Ozonosol; Refrane Total; ***Austral.***: Sunsense Sport; ***Braz.***: Isotrexol; Neutrogena Healthy Skin Anti-rugas com FPS 15; Sunmax Acqua; ***Canad.***: Anti-Aging Moisturizing†; Aqua Fusion†; Aqua Soleil; Aqua Soleil; Bienfait Multi-vital†; Creme Haute Exigence; Creme Solaire Tres Haute Protection Special Intolerances; Creme Solaire Tres Haute Protection Special Peaux Sensibles; Dermaglow†; Dove Face†; Fluide Hydratant Quotidien; Future E; High Resolution†; Hydra-C; Hydrafresh; Kids Sunscreen; Lotion Sport; Marcelle Essentials; Marcelle Multi-Defense; Mesoestetic; Mesoestetic; Moisture Rescue; Multi Recharge; Neutrogena Anti-Wrinkle; Neutrogena Day Moisture; Neutrogena Healthy Defense†; Nivea Visage Q10 Advanced Wrinkle Reducer†; Nutitionist Regenerating Moisturizer†; Oil of Olay Total Effects†; Ombrelle Lotion; Ombrelle Lotion; Premium Sunscreen; Primordiale; Protective Gel†; Refinish†; Renergie Microlift RARE†; Renergie Microlift†; Revitalizing Q10 Moisturizer†; Shiseido Skincare Day Moisture Protection; Skin Clarifying; Skin Renew; Sun Defense; Sunscreen Lotion Ecran; Triple Protect; Ultra Protection Sunscreen; Ultra-Lift Anti-Wrinkle†; Vita Lift; ***Chile***: Emolan Bloqueador Solar; Eucerin Q10 Active; Eucerin Solar†; Eucerin; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Fotoprotector Isdin-25 Pediatrics†; Hidrafil†; Neutrogena Crema Humectante; Neutrogena Healthy Defense; Neutrogena Healthy Skin; Nutraisdin; ***Fr.***: Trio S; ***Hong Kong***: Sunsense Ultra; ***India***: Nuface; ***Malaysia***: Sunsense Ultra; ***Mex.***: Filtrosol; Hidrafil; ***Neth.***: Contralum Ultra; ***Singapore***: Sunsense Ultra; ***Thai.***: Eucerin Sun Sensitive Skin†; ***USA***: Durascreen; Eucerin Dry Skin Care Daily Facial; Eucerin Moisturizing Face; Hawaiian Tropic Protective Tanning Dry; Neutrogena Intensified; Nivea Sun; Oil of Olay; ***Venez.***: Filtrosol.

Enzacamene *(USAN, rINN)*

Enzacamène; Enzacameno; Enzacamenum; Methyl Benzylidene Camphor; 3-(4-Methylbenzylidene)bornan-2-one; 3-(4-Methylbenzylidene)camphor; Энзакамен.
1,7,7-Trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one.
$C_{18}H_{22}O$=254.4
CAS — 36861-47-9 (D,L-form); 38102-62-4 (form unspecified).
UNII — 8I3XWY40L9.

NOTE. Eusolex 6300, Neo-Heliopan MBC, and Parsol 5000 are trade names that have been used for enzacamene.

Pharmacopoeias. In *US.*

USP 36: (Enzacamene). A white, fine crystalline powder. M. p. between 66 degrees and 68 degrees. Practically insoluble in water; freely soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Enzacamene is a camphor derivative used as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Clear Zinke; ***NZ***: Hamilton Sunscreen†.

Multi-ingredient Preparations. ***Arg.***: Fotoprotector Extrem Pediatrics; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Ultra; Fotoprotector; Fotoprotector; Ureadin Facial; ***Austral.***: Hamilton Family Sunscreen; Hamilton Family Sunscreen; Hamilton Family Sunscreen; Hamilton Optimal; Hamilton Quadblock; Hamilton Quadblock; Hamilton Solastick; Hamilton Sportblock Broad Spectrum Milk†; Hamilton Toddler; Le Tan Sunscreen Lotion†; Lip-Eze; Sunsense Sport; Sunsense Sport; Sunsense Ultra; Sunsense; Sunsense; Superfade UV Hand Shield; UV Triplegard Kids; UV Triplegard Sports; Zinc Cream White; ***Braz.***: Fotoprotetor Isdin Extrem Infantil†; Fotoprotetor Isdin Extrem UVA†; Fotoprotetor Isdin Extrem; Fotoprotetor Isdin Extrem; Fotoprotetor Isdin Infantil†; Fotoprotetor Isdin†; Fotoprotetor Spray Isdin†; Sunmax 30; Sunmax Acqua; Uvless; ***Canad.***: Anthelios†; Biotherm†; Lotion Sport; Mesoestetic; Rejuva; ROC Minesol Protect Ultra High; ROC Minesol Protect Very High†; Soleil Protexion Velvet Moisture; Soleil Protexion Velvet Moisture; Sunscreen Lotion Ecran; ***Chile***: Emolan Bloqueador Solar; Emolan Gel Protector Solar; Emolan†; Eucerin Solar†; Fotoprotector Isdin Dry Oil†; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Extrem Plus†; Fotoprotector Isdin Extrem†; Fotoprotector Isdin Extrem; Fotoprotector Isdin Extrem; Fotoprotector Isdin F-15†; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Fotoprotector Isdin-25 Pediatrics†; Fotoprotector Isdin-50†; Photoderm AR†; Photoderm Max†; Photoderm Spot†; ROC Minesol Actif; ROC Minesol Protect; ROC Minesol Protect; ***Fr.***: SVR 100†; ***Hong Kong***: Spectraban 60; Sunsense Clear Mist†; Sunsense Milk Mist†; Sunsense Sport; Sunsense Ultra; Sunsense†; ***Indon.***: Intersun; Paranox†; ***Irl.***: Antherpos†; ***Ital.***: Photoderm Max; ***Malaysia***: Spectraban; Sunsense Clear Mist†; Sunsense Milk Mist†; Sunsense Sport Gel†; Sunsense Ultra; ***Mex.***: Eclipsol Hydro; Extreme Sun; Heliocare; ProZone Ultra Fluido; ProZone Ultra; Umbrella Plus; Umbrella; ***Neth.***: Contralum Ultra; ***NZ***: Hamilton Optimal; Hamilton Quadblock; Hamilton Quadblock; Hamilton Solastick; Hamilton Sunscreen; Hamilton Sunscreen; Hamilton Sunscreen; Hamilton Toddler; ***Singapore***: Spectraban 60; Sunsense Clear†; Sunsense Milk†; Sunsense Ultra; ***Switz.***: Keli-med; ***Thai.***: Eucerin Sun Sensitive Skin†; Sebamed Suncream 20; Sebamed Sunlotion 20†; Spectraban†; ***UK***: Ambre Solaire; E45 Sun†; ***Venez.***: Filtrosol; Photoderm Max.

Erythrulose

DL-Glycero-tetrulose; Эритрулаза.
1,3,4-Trihydroxy-2-butanone.
$C_4H_8O_4$=120.1
CAS — 40031-31-0 (DL-erythrulose); 496-55-9 (D-erythrulose); 533-50-6 (L-erythrulose).

Profile

Application to the skin of preparations containing L-erythrulose slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin. It is often used with dihydroxyacetone (p. 1700.1) in artificial suntan preparations. Recommended concentrations are usually 1 to 3% when used with dihydroxyacetone; concentrations of up to 5% have been applied when used alone.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Sunsense Self Tanning System Self Tan; ***Braz.***: Sunmax Autobronzeador; ***Fr.***: Viticolor; ***UK***: ViTicolor.

Etretinate *(BAN, USAN, rINN)*

Etretinaatti; Etretinat; Étrétinate; Etretinato; Etretinatum; Ro-10-9359; Этретинат.
Ethyl 3-methoxy-15-apo-φ-caroten-15-oate; Ethyl (*all-trans*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetra-enoate.
$C_{23}H_{30}O_3$=354.5
CAS — 54350-48-0.
ATC — D05BB01.
ATC Vet — QD05BB01.
UNII — 65M2UDR9AG.

Uses and Administration

Etretinate is a retinoid and is a derivative of tretinoin (p. 1725.2). It has been given orally for the treatment of severe, extensive psoriasis that has not responded to other treatment, especially generalised and palmo-plantar pustular psoriasis. It has also been used in severe congenital ichthyosis, severe Darier's disease (keratosis follicularis) as well as other disorders of keratinisation, and oral lichen planus. Acitretin (p. 1690.3) is now preferred to etretinate.

Therapy is generally started at doses of 0.75 to 1 mg/kg daily in divided oral doses. A maximum dose of 1.5 mg/kg daily should not be exceeded (some licensed product information has suggested a maximum of 75 mg daily). Erythrodermic psoriasis may respond to lower initial doses of 250 micrograms/kg daily, increased at weekly intervals by 250 micrograms/kg daily until optimal response occurs. After the initial response, generally after 8 to 16 weeks of therapy, maintenance doses of 500 to 750 micrograms/kg daily have been given. Therapy should be stopped once lesions have sufficiently resolved.

References.

1. Magis NLJ, *et al*. The treatment of psoriasis with etretinate and acitretin: a follow up of actual use. *Eur J Dermatol* 2000; **10:** 517–21.
2. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; **154:** 267–76.

Adverse Effects and Precautions

As for Isotretinoin, p. 1707.2 and p. 1709.2.

Donation of blood should be avoided for at least 2 years after cessation of treatment. The period of time during which pregnancy must be avoided after stopping treatment has not been determined; detectable plasma-etretinate concentrations have been reported nearly 3 years after the last dose.

In addition to the references cited below, further references to the adverse effects of etretinate can be found in Isotretinoin, under Effects on the Blood (p. 1707.3), Cardiovascular System (p. 1707.3), Eyes (p. 1707.3), Liver (p. 1708.1), Musculoskeletal System (p. 1708.2), Serum Lipids (p. 1708.3), and the Skin (p. 1709.1), as well as under Vasculitic Syndromes (p. 1709.2).

Carcinogenicity. A report of 2 patients who developed lymphomas while receiving etretinate[1] prompted a report of 3 other malignancies in patients taking etretinate.[2]

1. Woll PJ, *et al.* Lymphoma in patients taking etretinate. *Lancet* 1987; **ii:** 563–4.
2. Harrison PV. Retinoids and malignancy. *Lancet* 1987; **ii:** 801.

Effects on the kidneys. Rare cases of impaired renal function associated with etretinate have been described.[1,2] In one report[1] it was also noted that in manufacturer-sponsored studies the mean serum-creatinine concentration had been raised in patients receiving etretinate.

1. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii:** 1093.
2. Cribier B, *et al.* Renal impairment probably induced by etretinate. *Dermatology* 1992; **185:** 266–8.

Oedema. A report of generalised oedema after treatment with etretinate.[1] Five other cases had been reported in the literature and rechallenge in 4 patients had provoked a recurrence. Generalised oedema as part of the capillary leak syndrome has been reported with acitretin (p. 1691.2).

1. Allan S, Christmas T. Severe edema associated with etretinate. *J Am Acad Dermatol* 1988; **19:** 140.

Pregnancy. For further information on the teratogenicity of etretinate, see under Acitretin, p. 1691.3.

Interactions

As for Isotretinoin, p. 1710.1.

Anticoagulants. Etretinate has been reported to reduce the therapeutic efficacy of *warfarin* (see Dermatological Drugs, p. 1533.3).

Antiepileptics. Etretinate was ineffective and none of its characteristic mucocutaneous adverse effects occurred in a patient with pityriasis rubra pilaris who was already taking *carbamazepine* and *valproate* for epilepsy. However, there was a clinical response after the carbamazepine had been withdrawn, suggesting that it may have reduced the bioavailability or increased the metabolism of etretinate.[1]

1. Mohammed KN. Unresponsiveness to etretinate during anticonvulsant therapy. *Dermatology* 1992; **185:** 79.

Antineoplastics. The risk of developing hepatotoxicity may be increased when etretinate is used with *methotrexate* (see Retinoids, p. 828.3).

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p. 2243.3.

Pharmacokinetics

The mean bioavailability of etretinate is about 40% after oral doses but there is a large interindividual variation. Absorption can be increased if taken with milk or fatty food. Etretinate undergoes significant first-pass metabolism and plasma concentrations of the active carboxylic acid metabolite, acitretin (p. 1690.3), may be detected before those of the parent drug; acitretin may itself be metabolised to etretinate (see p. 1691.3). Both etretinate and acitretin are extensively bound to plasma protein. Etretinate appears to accumulate in adipose tissue after repeated dosing and has a prolonged elimination half-life of about 120 days; detectable serum concentrations have been noted up to 3 years after stopping therapy. Up to 75% of a dose is excreted in the faeces mainly as unchanged drug. Etretinate is also excreted in the urine as metabolites. Etretinate crosses the placenta. Although it is unknown whether etretinate is distributed into breast milk, this would be expected because of its lipophilicity; acitretin, a metabolite of etretinate, has been found in breast milk when it was given to a lactating woman (see Breast Feeding, p. 1691.2).

References.

1. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; **10:** 38–62.
2. DiGiovanna JJ, *et al.* Etretinate: persistent serum levels after long-term therapy. *Arch Dermatol* 1989; **125:** 246–51.
3. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; **190** (suppl): 1–33.
4. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; **39** (suppl): S25–S33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tigason.

Fumaric Acid

Ácido alomaleico; Ácido boleico; Acidum Fumaricum; Allomalenic Acid; Boletic Acid; E297; Fumárico, ácido; Kwas fumarowy; Фумаровая Кислота.

trans-Butenedioic acid.

$C_2H_2(CO_2H)_2$=116.1

CAS — 110-17-8.

ATC — D05AX01.

ATC Vet — QD05AX01.

UNII — 88XHZ13131.

Pharmacopoeias. In *Pol.* Also in *USNF.*

USNF 31: (Fumaric Acid). White, odourless granules or crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform.

Dimethyl Fumarate *(USAN)*

AZL-O-211089; BG-12; Dimethylfumarate; FAG-201.

Dimethyl (2*E*)-but-2-enedioate.

$C_6H_8O_4$=144.1

CAS — 624-49-7.

UNII — FO2303MNI2.

Uses and Administration

Fumaric acid and some of its derivatives have been used in the treatment of psoriasis and other skin disorders (see below).

Dimethyl fumarate is used in the treatment of relapsing forms of multiple sclerosis (see below). A modified-release preparation is given orally in an initial dose of 120 mg twice daily. After 7 days this should be increased to a maintenance dose of 240 mg twice daily.

Fumaric acid is also used as an acidifier and flavouring agent in foods.

Multiple sclerosis. Dimethyl fumarate, mainly via its active metabolite monomethyl fumarate, is reported to activate the nuclear factor (erythroid-derived 2)-like (Nrf2) pathway involved in cellular response to oxidative stress, and the potential immunomodulatory and neuroprotective effects of dimethyl fumarate have been studied in multiple sclerosis (p. 996.3). Compared with placebo, it has reduced relapse rates and improved some other outcome measures in patients with relapsing-remitting disease.[1,2]

1. Fox RJ, *et al.* CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; **367:** 1087–97. Correction. *ibid.*; 1673.
2. Gold R, *et al.* DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; **367:** 1098–1107.

Skin disorders. Fumaric acid, its sodium salts, and derivatives such as dimethyl fumarate, monoethyl fumarate (ethyl hydrogen fumarate), and octil hydrogen fumarate have been used, both topically and systemically, in the treatment of psoriasis (p. 1688.1) and other skin disorders. Dimethyl fumarate appears to be the most active compound given orally but combination with various salts of monoethyl fumarate has been claimed to improve efficacy.[1-6] However, there have been reports of acute renal failure associated with treatment and the German Federal Office of Health has expressed the opinion that the available evidence did not establish the value of fumaric acid derivatives in psoriasis or other skin disorders.[7] A subsequent retrospective analysis of 41 patients who received fumaric acid esters orally, for between 1 and 14 years, suggested that these drugs might be effective,[8] and a later review suggested that they may be of value in refractory psoriasis.[9]

1. van Loenen AC, *et al.* Fumaarzuurtherapie: van fictie tot werkelijkheid? *Pharm Weekbl* 1989; **124:** 894–900.
2. Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: a long-term retrospective study on the effect of fumaric acid combination (FAC-EC) therapy and dimethyl-fumaric acid ester (DMFAE) monotherapy. *Br J Dermatol* 1990; **123:** 534–5.
3. Nugteren-Huying WM, *et al.* Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990; **22:** 311–12.
4. Altmeyer PJ, *et al.* Antipsoriatic effect of fumaric acid derivatives: results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 1994; **30:** 977–81.
5. Mrowietz U, *et al.* Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. *Br J Dermatol* 1999; **141:** 424–9.
6. Ständer H, *et al.* Efficacy of fumaric acid ester monotherapy in psoriasis pustulosa palmoplantaris. *Br J Dermatol* 2003; **149:** 220–2.
7. Anonymous. Fumaric acid derivatives and nephrotoxicity. *WHO Drug Inf* 1990; **4:** 28.
8. Hoefnagel JJ, *et al.* Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; **149:** 363–9.
9. Harries MJ, *et al.* Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *Br J Dermatol* 2005; **153:** 549–51.

Adverse Effects and Precautions

Adverse effects of dimethyl fumarate and other fumaric acid derivatives include gastrointestinal disturbances, abdominal pain, raised hepatic transaminases, and skin reactions such as rash and pruritus. Flushing is common but may be reduced by giving the fumarate with food. The effect generally starts soon after beginning therapy and improves or resolves over time.

Lymphopenia commonly occurs in patients given fumarates. A complete blood count should be taken before starting and then annually during therapy. Transient eosinophilia has also been reported.

There have been reports of acute renal failure associated with fumarates (see Skin Disorders, above).

Reported adverse effects[1] with fumaric acid derivatives were generally mild in a retrospective study of 66 patients with psoriasis, with only 1 case of elevated serum creatinine; however, lymphocytopenia was common and resulted in treatment being stopped in 4 patients. Other adverse effects with oral therapy have included disturbances of liver function,[2] gastrointestinal effects,[2,3] and flushing.[2,3] There has been a report of exanthema in a patient receiving dimethyl fumarate for lichen planus.[4]

1. Hoefnagel JJ, *et al.* Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; **149:** 363–9.
2. Nieboer C, *et al.* Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. *J Am Acad Dermatol* 1989; **20:** 601–8.
3. Mrowietz U, *et al.* Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. *Br J Dermatol* 1998; **138:** 456–60.
4. Guenther CH, *et al.* Macular exanthema due to fumaric acid esters. *Ann Pharmacother* 2003; **37:** 234–6.

Pharmacokinetics

Dimethyl fumarate is rapidly hydrolysed to its active metabolite, monomethyl fumarate, by esterases in the gastrointestinal tract, blood, and tissues. There is a lag time in absorption from oral modified-release preparations so that peak plasma concentrations of monomethyl fumarate occur after about 2 to 2.5 hours. It is metabolised further through the citric acid cycle, with the exhalation of carbon dioxide being the main route of elimination; trace amounts of monomethyl fumarate are found in urine. The terminal half-life of monomethyl fumarate is about 1 hour.

References.

1. Litjens NHR, *et al.* Pharmacokinetics of oral fumarates in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 429–32.
2. Rostami-Yazdi M, *et al.* Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. *Arch Dermatol Res* 2010; **302:** 531–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ingepsor†; ***USA***: Tecfidera.

Multi-ingredient Preparations. ***Ger.***: Fumaderm; ***Indon.***: Diasulin; ***Venez.***: Diamel.

Homoeopathic Preparations. ***Ger.***: Hepar comp; Zitronensaure-zyklus-Heel.

Glycolic Acid

Ácido hidroxiacético; Glicólico, ácido; Hydroxyacetic Acid; Гидроксиуксусная Кислота; Гликолевая Кислота.

Hydroxyethanoic acid.

$C_2H_4O_3$=76.05

CAS — 79-14-1.

UNII — 0WT12SX38S.

Profile

Glycolic acid is an alpha hydroxy organic acid with keratolytic and humectant properties. It has been used in topical preparations for hyperpigmentation (see Pigmentation Disorders, p. 1687.2) and photodamaged skin (see Photoageing, p. 1686.2). Glycolic acid derivatives with similar properties and uses include ammonium glycolate and guanidine glycolate.

Other alpha hydroxy acids (fruit acids) that have been used similarly include citric acid (p. 2480.3), lactic acid (p. 2539.1), malic acid (p. 2549.2), and mandelic acid (p. 320.3). Preparations containing mixed alpha hydroxy acids from natural sources have also been used.

Sun protection is advised if topical alpha hydroxy acids are used.

Reviews.

1. Kornhauser A, *et al.* Applications of hydroxy acids: classification, mechanisms, and photoactivity. *Clin Cosmet Investig Dermatol* 2010; **3:** 135–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfabase 8; Geloforte; Glicoisdin; Gligel; Hidrofrut; Ikeriane; Lactrime; Lipomax; Loxidil; Vansame G; ***Braz.***: Demelan; ***Canad.***: Reversa; ***Chile***: Neosolets;

Scrub-Atlas; Unitone 4; ***Fr.***: Ikeriane; ***Ger.***: Dr Wolff's acne attack; ***Hong Kong***: Glyderm†; ***India***: Glyaha; Glyco-6; Glyco-A; Glylak; Golic; ***Indon.***: Exfoliac†; Glycare†; Glycore; ***Ital.***: NeoStrata; Shakti; ***Mex.***: Glicoderm; Glicolic; Nova Derm; ***Philipp.***: Teranex; ***Singapore***: Glyderm†.

Multi-ingredient Preparations. ***Arg.***: Cellskinlab C + AHA; Cleanance; Control Acne; Diacneal; Hidroskin; Keracnyl; Keracnyl; Lactocrem; Melacler; Negacne; Neoquin Forte; Neoquin; NeoStrata Gel Despigmentante; NeoStrata; Percutalfa; Puraplus; Purasoft; Recover Whitening; Revi-Atlas; Revital; Scrub-Atlas; Vansame GS; Vansame Plus; ***Austral.***: Elucent Skin Refining Day Cream; NeoStrata; Sunsense Anti Ageing Face; ***Braz.***: Glyquin; ***Canad.***: Biobase-G; Glyquin XM; NeoStrata Blemish Spot Gel†; NeoStrata†; Reversa UV; ***Chile***: Diacneal; Glicoisdin; Glicoisdin; Keracnyl Stop Bouton; Keracnyl; NeoStrata; Neutrogena Healthy Skin†; Neutrogena Healthy Skin; Neutrogena Limpiadora†; Normaderm Barra de Limpieza; Normaderm Exfoliante; Normaderm Gel de Limpieza; Normaderm Tonico Astringente; Photoderm AKN†; Revi-Atlas; Teen Derm K; Ureadin Forte; ***Fr.***: Aniospray 29†; Cleanance K; Day Peel†; Kelual DS; Keracnyl eau nettoyante†; Keracnyl stop bouton; Keracnyl; Keracnyl; Keracnyl; Kertyol PSO; Kertyol-S†; Melascreen Depigmentant; Night Peel†; Node K; Seborheane†; ***Hong Kong***: Glyquin†; SunSense Anti-ageing Face Matte; ***India***: Demelan; Glyaha-HQ; Glyaha-HQSP; Glyaha-KOJ; Glyaha-VIT; ***Indon.***: Exfoliac†; Interquin Plus; ***Ital.***: Acnesan; Biophase Shampoo; Lightening; Neoceuticals Spot Treatment†; Phytic Acid; Same-Seb Beta; ***Malaysia***: Exfoliac Sunblock; TDF AHA Facial Wash for Oily/Acne Prone Skin; TDF AHA Oily & Acne Solution; ***Mex.***: Glicolic H; Nova Derm Facial Lightening; ***Port.***: Bioclin Sebo Care†; U Lactin†; Ureadin Forte; Ureadin; ***Singapore***: Glyquin XM†; Glyquin†; Nu-Derm Exfoderm Forte; Percutalfa; Purifying Gel; ***Turk.***: NeoStrata Akne; NeoStrata Hiperpigmentasyon; NeoStrata; ***USA***: Glyquin XM; ***Venez.***: Diacneal; Photoderm AKN.

Homosalate *(USAN, rINN)*

Homomenthyl Salicylate; Homosalato; Homosalatum; Гомосалат.

3,3,5-Trimethylcyclohexyl salicylate.

$C_{16}H_{22}O_3$=262.3

CAS — 118-56-9.

UNII — V06SV4M95S.

NOTE. Eusolex HMS and Neo-Heliopan HMS are trade names that have been used for homosalate.

Pharmacopoeias. In *US.*

USP 36: (Homosalate). Store in airtight containers.

Profile

Homosalate, a substituted salicylate, is a sunscreen (p. 1681.3) with actions similar to those of octisalate (p. 1715.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Coppertone Oil-Free Sunscreen; ***USA***: Coppertone Moisturizing; Tropical Blend Dark Tanning; Tropical Blend Dry Oil.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Hydroquinone

Hidrokinon; Hidroquinol; Hidroquinona; Hydrochinon; Hydrochinonum; Quinol; Teequinol; Гидрохинон.

1,4-Benzenediol.

$C_6H_6O_2$=110.1

CAS — 123-31-9.

ATC — D11AX11.

ATC Vet — QD11AX11.

UNII — XV74C1N1AE.

NOTE. Do not confuse with Hydroquinine (p. 2529.2).

Pharmacopoeias. In *US.*

USP 36: (Hydroquinone). Fine white needles which darken on exposure to light and air. Soluble 1 in 17 of water, 1 in 4 of alcohol, 1 in 51 of chloroform, and 1 in 16.5 of ether. Store in airtight containers. Protect from light.

Uses and Administration

Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. Hydroquinone is used topically as a depigmenting agent for the skin in hyperpigmentation conditions (p. 1687.2) such as chloasma (melasma), freckles, and lentigines (liver spots). Concentrations of 2 to 4% are commonly used; higher concentrations may be very irritant and increase the risk of ochronosis. It may be several weeks before any effect is apparent but depigmentation may last for 2 to 6 months after stopping.

Application of hydroquinone should stop if there is no improvement after 2 months. Hydroquinone should be applied twice daily only to intact skin which should be protected from sunlight to reduce repigmentation. A preparation containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% may be applied once daily at night in the treatment of chloasma (melasma). Hydroquinone preparations often include a sunscreen or a sunblocking basis.

Hydroquinone is also used as an antoxidant in topical preparations and in photographic developers.

Adverse Effects, Treatment, and Precautions

Topical hydroquinone may cause transient erythema and a mild burning sensation. Occasionally hypersensitivity has occurred and US licensed product information recommends skin testing before use. Hydroquinone should not be applied to abraded or sunburnt skin. It should not be used to bleach eyelashes or eyebrows and contact with the eyes should be avoided as it may produce staining and corneal opacities. High concentrations or prolonged use may produce a blue-black hyperpigmentation (ochronosis) or pigmented colloid milium. The systemic effects of hydroquinone and their treatment are similar to those of phenol (see p. 1764.2) but tremors and convulsions may also occur.

Carcinogenicity. There is some evidence from *animal* studies that hydroquinone might be carcinogenic (see Effects on the Skin, below).

Effects on the liver. Toxic hepatitis in a radiographer was attributed to occupational exposure to hydroquinone fumes from the developing medium used in the darkroom.[1] However, it has been pointed out[2] that hydroquinone is not volatile under normal conditions of use and that surveillance of 879 people engaged in the manufacture and use of hydroquinone from 1942 to 1990 found no association between toxic hepatitis and hydroquinone exposure.

1. Nowak AK, *et al.* Darkroom hepatitis after exposure to hydroquinone. *Lancet* 1995; **345:** 1187.
2. O'Donaghue JL, *et al.* Hydroquinone and hepatitis. *Lancet* 1995; **346:** 1427–8.

Effects on the skin. The incidence of exogenous ochronosis (blue-black hyperpigmentation) in a survey of black South African patients was found to be 15% in males and 42% in females with 69% of affected individuals admitting to using hydroquinone-containing preparations.[1] This was considered to be more consistent with a toxic effect of a drug with a low therapeutic index, rather than an idiosyncratic reaction. The data revealed that even preparations with hydroquinone 2% or less with a sunscreen produced ochronosis. Ochronosis usually became apparent after about 6 months of use and, once established, was probably irreversible. Patients may initially use skin lighteners for cosmetic purposes but once ochronosis develops they may fall into the 'skin lightener trap' as they use other hydroquinone preparations to remove the disfigurement.[1] Treatment of exogenous ochronosis is based on stopping the use of hydroquinone, but it may take years for any improvement to be apparent. There are a few reports of benefit from topical tretinoin, dermabrasion, and laser therapy, but these are far from established therapies.[2] Reversible brown discoloration of the nails has also been reported after the use of skin lighteners containing hydroquinone.[3-5]

In addition to the risk of ochronosis it has been suggested that, based on *animal* studies, long-term use of hydroquinone might be carcinogenic.[6] In the USA, preparations containing up to 2% hydroquinone may be sold without prescription, but in 2006, based on data regarding potential carcinogenicity and reports of ochronosis, the FDA proposed to reclassify these products as drugs and make them available by prescription only.[7] In Europe the use of hydroquinone in cosmetic preparations for skin lightening is already banned, but it is still available for prescription as a medicine.[6]

1. Hardwick N, *et al.* Exogenous ochronosis: an epidemiological study. *Br J Dermatol* 1989; **120:** 229–38.
2. Levin CY, Maibach H. Exogenous ochronosis: an update on clinical features, causative agents and treatment options. *Am J Clin Dermatol* 2001; **2:** 213–17.
3. Mann RJ, Harman RRM. Nail staining due to hydroquinone skin-lightening creams. *Br J Dermatol* 1983; **108:** 363–5.
4. Ozluer SM, Muir J. Nail staining from hydroquinone cream. *Australas J Dermatol* 2000; **41:** 255–6.
5. Parlak AH, *et al.* Discolouration of the fingernails from using hydroquinone skin-lightening cream. *J Cosmet Dermatol* 2003; **2:** 199–201.
6. Kooyers TJ, Westerhof W. Toxicology and health risks of hydroquinone in skin lightening formulations. *J Eur Acad Dermatol Venereol* 2006; **20:** 777–80.
7. FDA. Skin bleaching drug products for over-the-counter human use: proposed rule. *Fed Regist* 2006; **71:** 51146–55. Available at: http://edocket.access.gpo.gov/2006/E6-14263.htm (accessed 23/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Claripel; ***Braz.***: Claquinona; Claripel; Cleankinol; Hidropeek; Solaquin; ***Canad.***: Active 4; Creme Blanchissante; Eldopaque; Eldoquin; Esoterica Regular; Esoterica Unscented†; Lustra; Nuderm; Palmer's Skin Success; Rodan & Fields Proactiv Skin Lightening†; Seequin; Ultraquin Plain; Vantex; ***Chile***: Etnoderm; Unitone 4; ***China***: Qian Bai (千白); ***Fr.***: Effasun Hydroquin; ***Gr.***: Eldopaque; ***Hong Kong***: Derma-Rx Lightener†; Domina; Eldopaque; Eldoquin; Solaquin†; ***India***: Claripel Plus; Depig; Eslite; Eukroma; Hyde; Hyne; Melalite Forte; Melanorm; ***Indon.***: Bioquin; Eqinon; Mediquin; Melanox; Melaskin†; Pigmet†; Pylaquin†; Qutifar†; Skinox; Vitaquin; ***Israel***: Esomed; ***Malaysia***: Eldopaque; Eldoquin†; Melashine; ***Mex.***: Crema Blanca; Eldopaque; Eldoquin; Hidroquin; Melanex; Quinoret Forte; ***NZ***: Eldoquin†; ***Port.***: Pigmentasa; ***Singapore***: Eldopaque; Eldoquin; Nu-Derm Blender; Nu-Derm Clear; Polyquin; Solaquin†; ***Spain***: Despigmental; Hidroquilaude; Licoforte; Licostrata; Melanasa; Nadona; Pigmentasa; Solumelan; ***Thai.***: Clariderm†; Delanin; Delet†; Persatina; ***Turk.***: Expigment; ***UK***: Eldopaque; Eldoquin; Solaquin; ***USA***: Aclaro; Claripel†; Eldopaque; Eldoquin; EpiQuin; Esoterica Regular; Lustra; Solaquin.

Multi-ingredient Preparations. ***Arg.***: Melacler; Melasmax; Neoblanc; Neoquin Forte; Neoquin; NeoStrata Gel Despigmentante; Solaquin Forte; Tri-Luma; Trimegtante; ***Austral.***: Superfade Original†; ***Braz.***: Glyquin; Hormoskin; Suavicid; Tri-Luma; Triderm; Vitacid Plus; ***Canad.***: Continuum Unifying; Drula Fade; Esoterica Facial; Esoterica Sunscreen Fade; Glyquin XM; Lustra-AF; NeoStrata HQ Plus; NeoStrata HQ†; Nuderm Sunfader; Solaquin Forte; Sunbalance; Ultraquin Hydroquinone with Sunscreens; ***Chile***: Clasifel; NeoStrata; Tri-Luma; ***Ger.***: Pigmanorm; ***Hong Kong***: Glyquin†; Superfade; Tri-Luma; ***India***: A-Ret HC; Acsolve-H; Brite; Depig-TM; Eukroma-SG; Eveglow; Glyaha-HQ; Glyaha-HQSP; Glyaha-KOJ; Hyclean; Lite-Up; M-Lite; Melacare; Melacut; Melalite Plus; Melalite-XL; Melalite; Melalong; Melanorm-HC; Multi-HTM; ***Indon.***: Hidrogel†; Interquin Plus; Interquin; Meladerm; Nu-Derm Sunblock†; Refaquin; ***Malaysia***: Solaquin Forte†; Tri-Luma; ***Mex.***: Clasifel; Glicolic H; Nova Derm Facial Lightening; Quinoret; Solaquin; Tri-Luma; ***Philipp.***: Tri-Luma; ***Singapore***: Glyquin XM†; Glyquin†; Nu-Derm Sunfader†; Tri-Luma; ***Switz.***: Pigmanorm; ***Thai.***: Tri-Luma; ***Turk.***: Metamorfoz; NeoStrata Hiperpigmentasyon; ***USA***: Esoterica Facial and Sunscreen; Esoterica Fade Cream; Glyquin XM; Solaquin Forte; Solaquin Forte; Tri-Luma; ***Venez.***: Tri-Luma.

Pharmacopoeial Preparations

USP 36: Hydroquinone Cream; Hydroquinone Topical Solution.

Ichthammol *(BAN)*

Ammonii Bituminosulfonas; Ammonii Sulfogyrodalas; Ammonio Sulfoittiolato; Ammonium Bithiolicum; Ammonium Bitumenosulfonicum; Ammonium Bituminosulphonate; Ammonium Ichthosulphonate; Ammonium Sulfobituminosum; Ammonium Sulpho-Ichthyolate; Ammoniumbituminosulfonat; Amonowy sulfobituminian; Bithiolate Ammonique; Bithyol; Bitiol; Bitiolato amónico; Bitomol; Bituminol; Ichtammol; Ichtamolis; Ichthammolum; Ichthamol; Ichthosulphol; Ichthyol; Ichthyolammonium; Ictamol; Ictiolsulfonato amónico; Ihtamol; Iktammol; Iktammoli; Sulfobituminato amónico; Sulfoictiolato amónico; Ихтаммол; Ихтиол.

CAS — 8029-68-3.

UNII — NQ14646378.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Ichthammol). A dense blackish-brown liquid. It is obtained by distillation of certain bituminous schists, sulfonation of the distillate, and neutralisation of the product with ammonia. It contains not less than 4.5% and not more than 7.0% of total ammonia, not less than 10.5% of organically combined sulfur, calculated with reference to the dried substance, and not more than 20% of the total sulfur in the form of sulfates.

Miscible with water and with glycerol; slightly soluble in alcohol, in fatty oils, and in liquid paraffin; forms homogeneous mixtures with wool fat and soft paraffin.

USP 36: (Ichthammol). A reddish-brown to brownish-black viscous fluid with a strong characteristic empyreumatic odour. It is obtained by the destructive distillation of a bituminous schist, sulfonation of the distillate, and neutralisation of the product with ammonia. It yields not less than 10.0% of total sulfur and not less than 2.5% of ammonia. Miscible with water, with glycerol, and with fixed oils and fats. Partially soluble in alcohol and in ether.

Incompatibility. Ichthammol is incompatible with wool alcohols.

Profile

Ichthammol has slight bacteriostatic properties and is used in many topical preparations, for a variety of skin disorders; it has also been used in suppositories for anorectal disorders.

Ichthammol is often used with zinc oxide in medicated bandages for chronic lichenified eczema (p. 1684.1). Ichthammol may be slightly irritant to the skin and there have been rare reports of hypersensitivity.

Light Ammonium Bituminosulfonate (Ammoniumbituminosulfonat Hell) is produced from the light distillate fraction of shale oil.

Ammoniumsulfobitol, an ammonium bituminosulfonate similar to ichthammol but with a low sulfur content, was commercially available as Tumenol Ammonium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Egoderm; ***Austria***: Ichtho-Bad; Ichtholan; ***Belg.***: Bithiol; Poudre Velours†; ***Cz.***: Ichtoxyl; ***Ger.***: Ichtho-Bad; Ichtholan spezial; Ichtholan; Ichthyol; Thiobitum; ***Indon.***: Ichtiyol-Zalf; ***Ital.***: Ittiolo; ***Neth.***: Daro Trekzalf; Trekzalf; ***Switz.***: Bitumol; Ichtho-Bad; Ichtholan; ***Turk.***: Ihtiyol; Pomat Ichthyole†; Pommade Ichthyole†; ***Ukr.***: Fitoval Antidandruff (Фитовал Против Перхоти).

Multi-ingredient Preparations. ***Arg.***: Cicatrina; ***Austral.***: Egoderm; Ichthopaste; ***Austria***: Aknemycin compositum; Delta-Hadensa; Hadensa; Hadensa; Inotyol; Inotyol; ***Belg.***: Antipiol†; Inotyol; ***Canad.***: Ichtopaste; ***Chile***: Kertyol; Selegel; ***Cz.***: Pityol; Saloxyl; ***Denm.***: Inotyol; ***Fin.***: Hadensa†; Hadensa; ***Fr.***: Anaxeryl; Gelictar Fort†; Inotyol; Node DS; Oxythyol; Phytheol Force†; Selegel†; Squaphane; ***Ger.***: Aknemycin†; ***Gr.***: Ichthocortex; ***Hong Kong***: Egoderm; Egoderm; ***India***: Exsora; Itchasia; ***Israel***: Aknemycin; Inotyol; ***Ital.***: Antiemorroidali†; Dermatar; Ichthopaste; Ityolate CE; Tricoderm F; ***Malaysia***: Egoderm; Egoderm; ***Norw.***: Inotyol; ***NZ***: Egoderm; ***Pol.***: Neo-Tormentil; Tormentile Forte; Tormentiol; ***Port.***: Efluvium Anti-caspa†; Efluvium Anti-seborreico†; Pansebase Composto; Secpel Composto†; ***Rus.***: Bethiol (Бетиол); ***S.Afr.***: Antipeol; ***Singapore***: Egoderm; Egoderm; ***Spain***: Hadensa; Ictiomen; ***Swed.***: Inotyol; ***Switz.***: Akne-Mycin†; Bain extra-doux; Furodermal†; Radix†; ***Turk.***: Hedensa; ***UK***: Antipeol; Ichthopaste; Icthaband; St James Balm; ***Ukr.***: Prostalin (Просталин); ***USA***: Boil Ease; Boyol Salve; ***Venez.***: Node DS.

Homoeopathic Preparations. ***Canad.***: Cutisitum†; ***Ger.***: Hewelymphon N†.

Pharmacopoeial Preparations
BP 2014: Zinc and Ichthammol Cream;
USP 36: Ichthammol Ointment.

Ictasol *(USAN)*

Ichtasol; Ichthyol-Natrium Hell; Light Sodium Bituminosulphonate; Natrium Sulfobituminosum Decoloratum; Sulfobituminato sódico; Sulfobituminato sódico decolorado.

$C_{28}H_{36}Na_2O_6S_3$=610.7

CAS — 12542-33-5; 1340-06-3.
ATC — D10BX01.
ATC Vet — QD10BX01.

Profile

Ictasol is a sodium bituminosulfonate produced from the light distillate fraction of shale oil. Sodium bituminosulfonate is obtained by the destructive distillation of certain bituminous schists, sulfonation of the distillate, and neutralisation of the product with sodium hydroxide.

Ictasol has similar properties to ichthammol (p. 1705.3) and is used in many preparations for a variety of skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Crino Cordes; Lavichthol†; Solutio Cordes; ***Ger.***: Aknichthol; Ichthoderm; Ichtholan T; Ichthosin; Ichthraletten; Leukichtan; Solutio Cordes.

Multi-ingredient Preparations. ***Arg.***: Selegel; ***Austria***: Aknichthol; Ichthalgan forte; Leukichtan; ***Fr.***: I-Soft; Kertyol PSO; Node DS+; Sebosquam†; ***Ger.***: Aknederm Neu†; Aknichthol; Ichthocortin; Ichthoseptal†; Pelvichthol N†; ***Switz.***: Aknichthol.

Iscotrizinol *(USAN)*

Diethylhexyl Butamido Triazone; Diethylhexylbutamido Triazone; Dioctylbutamidotriazone.

Bis(2-ethylhexyl) 4,4′-[(6-{[4-(*tert*-butylcarbamoyl)phenyl]amino}-1,3,5-triazine-2,4-diyl)diimino]dibenzoate.

$C_{44}H_{59}N_7O_5$=766.0

CAS — 154702-15-5.
UNII — 2UTZ0QC864.

NOTE. Uvasorb HEB is a trade name that has been used for iscotrizinol.

Profile

Iscotrizinol is used as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Eucerin Ninos; Eucerin Solar†; Eucerin; Fotoprotector Isdin Dry Oil†; Nutraisdin; ***Fr.***: Sun LEB; ***Thai.***: Eucerin Sun Sensitive Skin†; Sebamed Multi Protect Suncream.

Isopropyldibenzoylmethane

Isopropildibenzoilmetano; Изопропилдибензоилметан.

1-[4-(1-Methylethyl)phenyl]-3-phenyl-1,3-propanedione.

$C_{18}H_{18}O_2$=266.3

CAS — 63250-25-9.

Profile

Isopropyldibenzoylmethane, a substituted dibenzoylmethane, is a sunscreen (p. 1681.3) with actions similar to those of avobenzone (p. 1695.1). It is effective against UVA light (for definitions, see p. 1685.3).

Isotretinoin *(BAN, USAN, rINN)*

13-*cis*-Retinoic Acid; Isotretinoiini; Isotretinoína; Isotrétinoïne; Isotretinoinum; Izotretinoin; Izotretinoinas; Izotretynoina; Ro-4-3780; Изотретиноин.

(13*Z*)-15-Apo-β-caroten-15-oic acid; (2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid.

$C_{20}H_{28}O_2$=300.4

CAS — 4759-48-2.
ATC — D10AD04; D10BA01.
ATC Vet — QD10AD04; QD10BA01.
UNII — EH28UP18IF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Isotretinoin). A yellow or light orange, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. It is sensitive to air, heat, and light, especially in solution. Store in airtight containers under an inert gas. Protect from light. It is recommended that the contents of an opened container be used as soon as possible and that any unused part be protected by an atmosphere of an inert gas.

USP 36: (Isotretinoin). Yellow crystals. Practically insoluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in macrogol 400; soluble in chloroform. Store in airtight containers under an atmosphere of an inert gas. Protect from light.

Uses and Administration

Isotretinoin is a retinoid. It is the *cis* configuration of tretinoin (p. 1725.2), which is the acid form of vitamin A (p. 2098.3). Isotretinoin is given orally for the treatment of severe acne (below) that has not responded to other measures; it is also applied topically in milder forms of acne. It is not indicated for uncomplicated adolescent acne, and is not licensed for prepubertal acne (but see also Administration in Children, below, for use in infantile acne). Isotretinoin has also been tried in other skin disorders (p. 1707.2) and in some forms of neoplastic disease (p. 1707.1).

In the UK and several other countries the initial oral dose of isotretinoin for acne is 500 micrograms/kg daily, although in the USA initial doses of up to 1 mg/kg daily are permitted. The dose is given with food once daily or in two divided doses and adjusted if necessary up to 1 mg/kg daily according to response and adverse effects. Patients intolerant to the initial dose may be able to continue treatment at a lower dose, but there is a higher risk of relapse. Doses up to 2 mg/kg daily are permitted in the USA and some other countries for patients whose disease is very severe or mainly on the body instead of the face. A lower starting dose has been recommended for patients with severe renal impairment (see p. 1707.1).

Acute exacerbation of acne is occasionally seen during the initial period, but usually subsides within 7 to 10 days on continued treatment. Treatment should continue for 15 to 24 weeks or until the total cyst count has decreased by over 70%. Long-term remission and relapse rates are related to total dose, and additional benefit is not expected beyond a cumulative dose of 120 to 150 mg/kg. Improvement may continue for several months after stopping treatment; prolonged remissions can occur.

Repeat courses are not normally recommended but occasionally they may be required. However, since acne may continue to improve after stopping isotretinoin, there must be at least a 2-month drug-free period before starting repeat treatment.

For the topical treatment of acne a gel containing 0.05% of isotretinoin is applied sparingly once or twice daily. A therapeutic response may not be evident for 6 to 8 weeks.

General reviews.

1. DiGiovanna JJ. Systemic retinoid therapy. *Dermatol Clin* 2001; **19:** 161–7.
2. Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001; **45** (suppl): S150–S157.
3. Vivat-Hannah V, Zusi FC. Retinoids as therapeutic agents: today and tomorrow. *Mini Rev Med Chem* 2005; **5:** 755–60.
4. Njar VC, *et al*. Retinoids in clinical use. *Med Chem* 2006; **2:** 431–8.

Acne. The retinoids play an important role in the treatment of acne (p. 1682.2). Isotretinoin reduces sebum excretion with a subsequent reduction in growth of *Propionibacterium acnes*; it also normalises the differentiation of keratinocytes, which has a comedolytic effect, and appears to have a direct anti-inflammatory effect.[1-3] The main indication for oral isotretinoin therapy is severe forms of acne (such as conglobate or nodulocystic acne or acne at risk of permanent scarring) that is unresponsive to other therapy including systemic antibacterials. Some argue,[4,5] however, that oral isotretinoin should be considered for first-line treatment in other cases, such as less severe acne that has the potential to cause scarring or acne that is causing severe psychological distress. Most patients remain free of their disease after a single course of isotretinoin, or have a mild recurrence that responds to other treatments to which it was previously resistant. A minority will relapse and those at higher risk include patients less than 16 years of age, those with severe acne on the trunk, and adult women.[2] Cumulative dose, rather than daily dose, appears to be an important factor in achieving stable remission.[4] To avoid relapse, a course of therapy to a cumulative dose of 120 to 150 mg/kg is required.[2] This usually equates to a course of 5 to 6 months using daily doses of 0.5 to 1 mg/kg. One group suggests[4] that treatment should be continued for 2 months after complete clearing of acne to avoid recurrence, and that higher cumulative doses (up to 200 mg/kg) might be needed in some cases, such as those showing clear signs of ongoing improvement when a cumulative dose of 150 mg/kg has been reached. In patients who do relapse, repeat courses may be indicated.[2,3] However, improvement may continue for several months after withdrawal and at least 2 months should elapse before determining whether further treatment is necessary. There is evidence to suggest that patients who repeatedly relapse after stopping standard isotretinoin therapy may benefit from continuous use of very low doses of isotretinoin, such as 250 or 500 micrograms/kg daily taken every 4th week for 6 months, 100 micrograms/kg daily, or a single dose of 20 mg once or twice a week.[6] Low-dose regimens have also been tried instead of standard isotretinoin doses for persistent moderate or severe acne. A dose of 20 mg daily for 6 months has produced significant improvement or complete remission in moderate acne.[7] However, prolonged use of low-dose regimens is needed to achieve a cumulative dose of 120 mg/kg and reduce the risk of relapse.[8] Isotretinoin has also been used for the treatment of acne associated with immunosuppressive therapy in transplant recipients.[9,10]

Isotretinoin is also used topically for acne. Although it has no sebosuppressive effect and only a weak direct anti-inflammatory effect by this route[1] its comedolytic effect makes unplugged follicles less anaerobic, reducing *P. acnes* growth and associated inflammation.[11] Topical isotretinoin appears to have a similar efficacy to tretinoin, but may be better tolerated.[3]

Isotretinoin is not licensed for the treatment of prepubertal acne because of the risk of adverse effects including early epiphyseal closure, but see also Administration in Children, below.

1. Gollnick H. Current concepts of the pathogenesis of acne: implications for drug treatment. *Drugs* 2003; **63:** 1579–96.
2. James WD. Acne. *N Engl J Med* 2005; **352:** 1463–72.
3. Chivot M. Retinoid therapy for acne: a comparative review. *Am J Clin Dermatol* 2005; **6:** 13–19.
4. Cooper AJ. The Australian Roaccutane Advisory Board. Treatment of acne with isotretinoin: recommendations based on Australian experience. *Australas J Dermatol* 2003; **44:** 97–105.
5. Dréno B, *et al*. An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. *Eur J Dermatol* 2006; **16:** 565–71.
6. Palmer RA, *et al*. Microdose' isotretinoin. *Br J Dermatol* 2000; **143:** 205–6.
7. Amichai B, *et al*. Low-dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol* 2006; **54:** 644–6.
8. Mandekou-Lefaki I, *et al*. Low-dose schema of isotretinoin in acne vulgaris. *Int J Clin Pharmacol Res* 2003; **23:** 41–6.
9. Tam M, Cooper A. The use of isotretinoin in a renal transplant patient with acne. *Br J Dermatol* 1987; **116:** 463.
10. Bunker CB, *et al*. Isotretinoin treatment of severe acne in posttransplant patients taking cyclosporine. *J Am Acad Dermatol* 1990; **22:** 693–4.
11. Goulden V. Guidelines for the management of acne vulgaris in adolescents. *Pediatr Drugs* 2003; **5:** 301–13.

Administration in children. Oral isotretinoin is licensed in most countries for use from 12 years of age where appropriate, but it is not licensed for the treatment of prepuber-

tal acne because of the risk of adverse effects including early epiphyseal closure. However, it has been used orally with some success in nodulocystic infantile acne when topical preparations and antibacterial therapies have not been effective.[1-4] A range of doses have been used, sometimes influenced by the dosage form available, but in general doses have been similar to those used in older patients. For example, the *BNFC* considers that children aged 1 month to 2 years with severe infantile acne may be given 200 micrograms/kg once daily increased, if necessary, to 1 mg/kg daily (in 1 or 2 divided doses) for 16 to 24 weeks; the maximum cumulative dose per course is 150 mg/kg. As there are no suitable licensed oral products for children, isotretinoin liquid capsules have been opened and the contents mixed with a drink[1,2] or soft food[3] immediately before use to make administration easier. One report[3] described freezing the capsule so that it could be cut more easily to the required dose, which could then be concealed in food.

Topical isotretinoin is not licensed in the UK for use in children although the *BNFC* mentions use of the 0.05% gel applied once or twice daily for acne vulgaris.

For mention of the investigation of isotretinoin in children with neuroblastoma, see Malignant Neoplasms, below.

1. Mengesha YM, Hansen RC. Toddler-age nodulocystic acne. *J Pediatr* 1999; **134:** 644–8.
2. Sarazin F, *et al*. Treatment of an infantile acne with oral isotretinoin. *Eur J Dermatol* 2004; **14:** 71–2.
3. Barnes CJ, *et al*. A practical approach for the use of oral isotretinoin for infantile acne. *Pediatr Dermatol* 2005; **22:** 166–9.
4. Torrelo A, *et al*. Severe acne infantum successfully treated with isotretinoin. *Pediatr Dermatol* 2005; **22:** 357–9.

Administration in renal impairment. Although renal impairment does not affect the pharmacokinetics of isotretinoin, licensed UK product information suggests that patients with severe renal impairment being treated with oral isotretinoin for acne should be started at a lower dose, such as 10 mg daily. It may be gradually increased up to 1 mg/kg daily as tolerated.

Malignant neoplasms. Retinoids such as isotretinoin have been studied in the treatment of various neoplastic or preneoplastic disorders. Although oral tretinoin is used for remission induction in acute promyelocytic leukaemia (see p. 1725.3), other retinoids do not have an established role in the treatment of cancer. There may, however, be a place for the use of retinoids in the chemoprevention of some malignancies.

There has been particular interest in the potential for retinoids to prevent the formation of *skin cancers* (p. 714.1) in patients at increased risk. Maintenance immunosuppression may increase the incidence of pre-malignant and malignant skin lesions in solid organ transplant recipients; large numbers of lesions can develop and tend to be more aggressive than those in the general population.[1] Although there has been some investigation in cardiac transplant recipients, most case reports and some small studies have involved renal transplant patients. Oral acitretin has been reported to reduce the number of actinic keratoses and reduce the development of new basal and squamous cell carcinomas in these patients.[1-4] Other patients at increased risk of skin cancers who may benefit from prophylactic retinoid therapy include those with xeroderma pigmentosum and naevoid basal cell carcinoma syndrome; oral isotretinoin, rather than acitretin, has been tried in such patients.[5] Retinoids might also be considered in others who have already developed nonmelanoma skin cancers, such as those with conditions requiring maintenance immunosuppression, chronic lymphocytic leukaemia or non-Hodgkin's lymphoma, severe photodamage of the skin, and those with squamous cell carcinoma at high risk of metastasis or that has already metastasised.[5]

Since retinoids suppress rather than cure skin cancer, rebound occurs when the retinoid is stopped and long-term therapy is needed. There is some concern about the risks of such long-term use, particularly on plasma lipids and bone, and monitoring has been recommended.[1,4,5] The mucocutaneous adverse effects that commonly occur can affect patient acceptance during long-term use; mucocutaneous effects may be more severe with isotretinoin, but hair loss may be more extensive with acitretin.[4,5] Gradual dose escalation to an effective dose can be used to minimise these mucocutaneous effects. One example using isotretinoin starts with a dose of 250 micrograms/kg on alternate days for a month, increased to 250 micrograms/kg daily for the second month, then to 500 micrograms/kg daily for the third month; the dose is then adjusted as tolerated.[5] As there are risks of teratogenicity with retinoids, isotretinoin is preferred for women of child-bearing potential because of its shorter half-life.[4,5] For acitretin doses that have been used, see p. 1691.1.

Topical application of retinoids has also been tried for chemoprevention of skin cancers. Topical tretinoin has been used on actinic keratoses in organ transplant recipients, but results have been mixed and may depend on dose. If squamous cell carcinomas are present, however, systemic retinoids should be considered.[3]

Retinoids have been studied in the chemoprevention of primary disease recurrence and second primary tumours after treatment for *squamous cell carcinoma of the head and neck* (p. 708.1) but results have been mixed and limited by resistance and toxicity.[6] A large placebo-controlled study[7] has also reported that low-dose oral isotretinoin (30 mg daily for 3 years with an additional 4 years of follow-up) did not reduce the rate of second primary tumours or death in patients who had been treated for early stage head and neck squamous cell carcinoma. There has also been some interest in the use of retinoids, given orally (isotretinoin) or topically (isotretinoin or tretinoin), in the management of *oral leucoplakia*, which can be pre-malignant (see under Bleomycin, p. 750.3). However, despite reports of beneficial response, relapse frequently occurs on stopping retinoid therapy.[6,8]

Oral isotretinoin has been studied as continuation therapy in children with high-risk *neuroblastoma* that had responded to intensive chemotherapy. One study[9] found improved survival with 6 cycles of isotretinoin given for 14 days of each 28-day cycle. Long-term (5 year) follow-up results seem to confirm an improvement in overall survival in these patients.[10] However, another study[11] using a lower dose given daily for 4 years or until relapse found no additional benefit from isotretinoin.

1. Kovach BT, *et al*. Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; **19:** 726–34.
2. Chen K, *et al*. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; **152:** 518–23.
3. Neuhaus IM, Tope WD. Practical retinoid chemoprophylaxis in solid organ transplant recipients. *Dermatol Ther* 2005; **18:** 28–33.
4. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; **19:** 306–14.
5. Otley CC, *et al*. Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg* 2006; **32:** 562–8.
6. Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? *Crit Rev Oncol Hematol* 2005; **55:** 143–52.
7. Khuri FR, *et al*. Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst* 2006; **98:** 441–50.
8. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; **95:** 1258–64.
9. Matthay KK, *et al*. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999; **341:** 1165–73.
10. Matthay KK, *et al*. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *J Clin Oncol* 2009; **27:** 1007–13.
11. Kohler JA, *et al*. A randomized trial of 13-cis retinoic acid in children with advanced neuroblastoma after high-dose therapy. *Br J Cancer* 2000; **83:** 1124–7.

Skin disorders. Apart from its established role in the treatment of acne (p. 1706.3), isotretinoin has been tried in many other skin disorders not responding to usual therapy.[1,2] Clinical responses to oral isotretinoin have been reported[1] in small numbers of patients with anogenital warts (p. 1689.3), rosacea (p. 1688.3), and lichen planus (p. 1685.2). Benefit has also been reported for keratinisation disorders such as Darier's disease[2] (p. 1683.2), ichthyosis[1,2] (p. 1685.1), and pityriasis rubra pilaris.[1,2] Isotretinoin is less effective than other retinoids for psoriasis[1] (p. 1688.1). Oral isotretinoin may be used for chemoprevention of skin cancers (see Malignant Neoplasms, above).

Topical isotretinoin has been used to reduce some of the signs of photoageing[3] (p. 1686.2).

1. Akyol M, Özçelik S. Non-acne dermatologic indications for systemic isotretinoin. *Am J Clin Dermatol* 2005; **6:** 175–84.
2. Sehgal VN, *et al*. Isotretinoin – unapproved indications/uses and dosage: a physician's reference. *Int J Dermatol* 2006; **45:** 772–7.
3. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; **65:** 1061–72.

Adverse Effects

The adverse effects of isotretinoin and other oral retinoids are similar to those of vitamin A (see p. 2101.2) and are generally reversible and dose-related. The most common are dryness of the mucous membranes and skin, which can often progress to cheilitis, epistaxis, conjunctivitis, localised exfoliation including palmo-plantar exfoliation, pruritus, erythematous rash, and skin fragility. Less common effects have included hair thinning (occasionally irreversible), hirsutism, photosensitivity, changes in skin pigmentation, paronychia, nail dystrophy, pyogenic granuloma, and increased sweating. Acne can be exacerbated at the beginning of isotretinoin treatment, and there are very rare reports of acne fulminans occurring. Less common adverse effects on the eyes include corneal opacities, visual disturbances such as blurred vision and colour vision disorders, impaired night vision that may persist, photophobia, and keratitis. Papilloedema, visual disturbances, headache, and nausea and vomiting can be signs and symptoms of benign intracranial hypertension. Arthralgia, myalgia, and back pain are commonly reported, and there have been rare reports of arthritis, osteoporosis, and tendinitis. Hyperostosis and calcinosis have also occurred, particularly in patients treated with high doses of isotretinoin over long periods for keratinisation disorders. Premature closure of the epiphyses has occurred in children treated with isotretinoin. Elevation of serum triglycerides is common, and pancreatitis has occurred in patients with high concentrations; cholesterol concentrations may also be increased. Increases in hepatic enzymes, erythrocyte sedimentation rate, and blood glucose can also occur. Alterations in haematological measures are common; there have also been reports of anaemia, thrombocytopenia, and neutropenia, and very rare reports of agranulocytosis. Other effects that have been reported rarely include gastrointestinal symptoms, hepatitis, hearing impairment, drowsiness, seizures, vasculitis, and hypersensitivity reactions including anaphylaxis. Mood changes, psychotic symptoms, depression, and suicidal behaviour have occurred in patients treated with oral isotretinoin. There may also be an association with skin infections and an inflammatory bowel syndrome.

Isotretinoin and other retinoids are teratogenic.

When isotretinoin is applied topically the adverse effects are similar to those of tretinoin (see p. 1726.1).

General references.

1. Mills CM, Marks R. Adverse reactions to oral retinoids: an update. *Drug Safety* 1993; **9:** 280–90.
2. Keefe M. Adverse reactions profile: retinoids. *Prescribers' J* 1995; **35:** 71–6.
3. McLane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol* 2001; **45:** S188–S194.
4. Goodfield MJD, *et al*. British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010; **162:** 1172–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf (accessed 10/08/10)
5. Charakida A, *et al*. Safety and side effects of the acne drug, oral isotretinoin. *Expert Opin Drug Safety* 2004; **3:** 119–29.
6. Goldsmith LA, *et al*. American Academy of Dermatology consensus conference on the safe and optimal use of isotretinoin: summary and recommendations. *J Am Acad Dermatol* 2004; **50:** 900–906. Correction. *ibid.*; **51:** 348. [dose]

Effects on the blood. Serious adverse effects on the blood have been reported rarely with oral retinoids, and are thought to be idiosyncratic in nature. There have been reports of thrombocytopenia in patients taking isotretinoin[1] and etretinate.[2,3] A few cases of agranulocytosis have involved isotretinoin[4] and acitretin.[5] In contrast, there are also reports of transient and asymptomatic thrombocytosis associated with isotretinoin[6] and tretinoin.[7,8] Leucocytosis is often associated with the retinoic acid syndrome caused by tretinoin (p. 1726.2).

1. Moeller KE, Touma SC. Prolonged thrombocytopenia associated with isotretinoin. *Ann Pharmacother* 2003; **37:** 1622–4.
2. Naldi L, *et al*. Etretinate therapy and thrombocytopenia. *Br J Dermatol* 1991; **124:** 395.
3. Seishima M, *et al*. Thrombocytopenia possibly induced by etretinate in a psoriatic patient. *J Dermatol* 2005; **32:** 917–20.
4. Waisman M. Agranulocytosis from isotretinoin. *J Am Acad Dermatol* 1988; **18:** 395–6.
5. Chave TA, *et al*. Agranulocytosis and total scalp alopecia following acitretin. *Br J Dermatol* 2003; **148:** 1063–4.
6. Jansen T, Altmeyer P. Thrombocytosis induced by low-dose isotretinoin. *Int J Dermatol* 2000; **39:** 956–7.
7. Losada R, *et al*. Thrombocytosis in patients with acute promyelocytic leukaemia during all-trans retinoic acid treatment. *Br J Haematol* 1996; **95:** 704–5.
8. Kentos A, *et al*. All-trans retinoic acid induced thrombocytosis in a patient with acute promyelocytic leukaemia. *Br J Haematol* 1997; **97:** 685.

Effects on the cardiovascular system. From 1983 to the end of 2005, Health Canada had received 29 reports of adverse cardiovascular effects in patients treated with isotretinoin, including myocardial infarction, stroke, and pulmonary embolism.[1] Thrombotic stroke has also been attributed to the use of acitretin in a woman treated for psoriasis,[2] and rare cases of myocardial ischaemia and infarction have been reported with etretinate.[3] Thromboembolic disorders have also occurred in patients given tretinoin for remission induction in acute promyelocytic leukaemia (see p. 1726.1).

There are rare reports of isotretinoin causing cardiac arrhythmias, such as sinus tachycardia with right branch bundle block[4] and atrial tachycardia.[5]

1. Springuel P, Roy G. Health Canada. Isotretinoin (Accutane): myocardial infarction, cerebrovascular and thromboembolic disorders. *Can Adverse React News* 2006; **16:** 3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n2-eng.php (accessed 28/07/08)
2. Royer B, *et al*. Acitretin-associated thrombotic stroke. *Ann Pharmacother* 2002; **36:** 1879–82.
3. Anonymous. Reports from regulatory agencies: etretinate. *WHO Drug Inf* 1987; **1:** 29.
4. Charalabopoulos K, *et al*. Two new adverse effects of isotretinoin. *Br J Dermatol* 2003; **148:** 593.
5. Hasdemir C, *et al*. Isotretinoin (13-cis-retinoic acid) associated atrial tachycardia. *Pacing Clin Electrophysiol* 2005; **28:** 348–9.

Effects on the eyes. Ocular adverse effects reported with oral isotretinoin have been reviewed.[1,2] Using the WHO Causality Assessment Guide of Suspected Adverse Reactions, an analysis[3] of 2449 spontaneous reports found that

decreased dark adaptation, ocular sicca, and the ocular signs and symptoms of intracranial hypertension, accounted for most of the reports that were certainly associated with isotretinoin. In some cases of intracranial hypertension the patient had also been taking other drugs, such as tetracyclines, that have also been associated with this effect. There was also a certain association between isotretinoin and abnormal meibomian gland secretion and gland atrophy, blepharoconjunctivitis, corneal opacities, decreased vision, increased tear osmolarity, keratitis, myopia, ocular discomfort and decreased tolerance to contact lenses, and photophobia. There was a probable association with reversible decreased colour vision and permanent loss of dark adaptation. Other effects that had been reported, but only possibly associated with isotretinoin, included corneal ulcers, diplopia, eyelid oedema, optic neuritis, permanent sicca, and subconjunctival haemorrhage.

There are fewer reports of ocular adverse effects with other oral retinoids. Intracranial hypertension with papilloedema, blurred vision, and headache, has been reported with acitretin, etretinate, and tretinoin.[4-6] A 1-year follow-up failed to find any evidence of ocular toxicity attributable to etretinate in 4 patients who had received long-term treatment, including 1 patient who had toxic optic neuropathy due to methotrexate and who was able to continue treatment with etretinate.[7] Ectropion has been associated with etretinate therapy in a patient.[8] Maculopathy occurred in a patient after a year of treatment with acitretin for psoriasis.[9]

1. Fraunfelder FT, *et al.* Adverse ocular reactions possibly associated with isotretinoin. *Am J Ophthalmol* 1985; **100:** 534–7.
2. Fraunfelder FT, *et al.* Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol* 2001; **132:** 299–305.
3. Fraunfelder FW. Ocular side effects associated with isotretinoin. *Drugs Today* 2004; **40:** 23–7.
4. Colucciello M. Pseudotumor cerebri induced by all-trans retinoic acid treatment of acute promyelocytic leukemia. *Arch Ophthalmol* 2003; **121:** 1064–5.
5. Guirgis MF, Lueder GT. Intracranial hypertension secondary to all-trans retinoic acid treatment for leukemia: diagnosis and management. *J AAPOS* 2003; **7:** 432–4.
6. Fraunfelder FW, Fraunfelder FT. Evidence for a probable causal relationship between tretinoin, acitretin, and etretinate and intracranial hypertension. *J Neuroophthalmol* 2004; **24:** 214–16.
7. Pitts JF, *et al.* Etretinate and visual function: a 1-year follow-up study. *Br J Dermatol* 1991; **125:** 53–5.
8. Brenner S, *et al.* Ectropion: an adverse effect of etretinate therapy for psoriasis. *DICP Ann Pharmacother* 1990; **24:** 1007.
9. Lois N, White M. Acitretin-associated maculopathy. *Arch Ophthalmol* 2004; **122:** 928–30.

Effects on the gastrointestinal tract. A causal association has been suggested in cases of inflammatory bowel disease developing in patients taking oral isotretinoin.[1,2] Between 1997 and 2002 the FDA received 85 reports of Crohn's disease, ulcerative colitis, colitis, or haemorrhagic colitis attributed to isotretinoin;[3] the association was judged probable in 62 cases and possible in 23. Specific treatment, in addition to drug withdrawal, was required in 35 patients, 11 were hospitalised, and 7 underwent surgery. Rechallenge was positive in the 3 reported cases. The authors of this review suggested that isotretinoin should be used with caution in patients with a history of inflammatory bowel disease or symptoms suggestive of the condition and those who might be at increased risk because of a family history. Although there have been patients with inflammatory bowel disease who have received isotretinoin without adverse effect, there are some cases in which the condition may have been exacerbated by isotretinoin.[1,4]

1. Reniers DE, Howard JM. Isotretinoin-induced inflammatory bowel disease in an adolescent. *Ann Pharmacother* 2001; **35:** 1214–16.
2. Passier JLM, *et al.* Isotretinoin-induced inflammatory bowel disease. *Neth J Med* 2006; **64:** 52–4.
3. Reddy D, *et al.* Possible association between isotretinoin and inflammatory bowel disease. *Am J Gastroenterol* 2006; **101:** 1569–73.
4. Godfrey KM, James MP. Treatment of severe acne with isotretinoin in patients with inflammatory bowel disease. *Br J Dermatol* 1990; **123:** 653–5.

Effects on the liver. Transient slight elevations of serum concentrations of liver enzymes are common with etretinate, but there have been few reports of acute hepatitis[1,2] or cholestatic jaundice.[3] Acute hepatitis may progress to chronic active hepatitis, despite stopping etretinate therapy[4] but studies of serial liver biopsies from patients receiving long-term etretinate have failed to show any significant chronic liver damage.[5-7] Licensed product information has included reports of hepatic fibrosis, necrosis, and/or cirrhosis.

An overview considered that some form of hepatotoxicity may be seen in up to 20% of patients treated with etretinate and significant liver disease in 1%.[8]

Isotretinoin may also cause mild elevations of liver enzymes and licensed product information states that hepatitis has occurred rarely. There is also a report of fatty liver.[9]

1. Foged EK, Jacobsen FK. Side effects due to RO 10-9359 (Tigason). *Dermatologica* 1982; **164:** 395–403.
2. Weiss VC, *et al.* Hepatotoxic reactions in a patient treated with etretinate. *Arch Dermatol* 1984; **120:** 104–6.
3. Gavish D, *et al.* Cholestatic jaundice, an unusual side effect of etretinate. *J Am Acad Dermatol* 1985; **13:** 669–70.
4. Weiss VC, *et al.* Chronic active hepatitis associated with etretinate therapy. *Br J Dermatol* 1985; **112:** 591–7.
5. Glazer SD, *et al.* Ultrastructural survey and tissue analysis of human livers after a 6-month course of etretinate. *J Am Acad Dermatol* 1984; **10:** 632–8.
6. Foged E, *et al.* Histologic changes in the liver during etretinate treatment. *J Am Acad Dermatol* 1984; **11:** 580–3.
7. Roenigk HH, *et al.* Serial liver biopsies in psoriatic patients receiving long-term etretinate. *Br J Dermatol* 1985; **112:** 77–81.
8. Boyd AS. An overview of the retinoids. *Am J Med* 1989; **86:** 568–74.
9. Taylor AEM, Mitchison H. Fatty liver following isotretinoin therapy. *Br J Dermatol* 1991; **124:** 505–6.

Effects on mental function. Case reports provide evidence of depression, psychotic symptoms, suicide, and suicide attempts occurring as idiosyncratic adverse effects of isotretinoin. However, the high background prevalence of psychiatric illness among adolescents in general, and among patients with acne, are potentially confounding factors. Most retrospective studies have not shown a clear cause and effect mechanism and prospective studies have been limited by sample size and although one large case-crossover study found an association between isotretinoin and depression,[1] the findings were contested.[2] Systematic reviews have found no strong evidence for an association between isotretinoin use and depression or suicidal behaviour, but noted that the evidence was not sufficiently compelling to rule out a weak association,[3,4] although other factors were probably more important.[3] In the absence of better evidence, monitoring for depression and other psychiatric effects has been advised for all patients receiving isotretinoin.[1,5-8]

Two cases of sustained dreaming have also been reported. After 2 to 3 weeks of oral isotretinoin, both patients reported changes in their dreaming pattern with a feeling that they had been 'dreaming all night'. The dreams persisted for 4 to 5 weeks after which they subsided despite continued isotretinoin therapy.[9]

1. Azoulay L, *et al.* Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008; **69:** 526–32.
2. Thakrar BT, Robinson NJ. Isotretinoin and the risk of depression. *J Clin Psychiatry* 2009; **70:** 1475.
3. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg* 2005; **24:** 92–102.
4. Strahan JE, Raimer S. Isotretinoin and the controversy of psychiatric adverse effects. *Int J Dermatol* 2006; **45:** 789–99.
5. Ng CH, Schweitzer I. The association between depression and isotretinoin use in acne. *Aust N Z J Psychiatry* 2003; **37:** 78–84.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Acne, isotretinoin and suicidality. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0506.htm (accessed 27/09/07)
7. CHM/MHRA. Isotretinoin (Roaccutane): psychiatric adverse reactions. *Current Problems* 2006; **31:** 8–9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 27/09/07)
8. Goodfield MJD, *et al.* British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010; **162:** 1172–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf (accessed 27/05/10)
9. Gupta MA, Gupta AK. Isotretinoin use and reports of sustained dreaming. *Br J Dermatol* 2001; **144:** 919–20.

Effects on the musculoskeletal system. Hyperostotic changes (bone spurs) or calcification of tendons and ligaments, resembling *diffuse idiopathic skeletal hyperostosis* (DISH), have been reported with systemic retinoid therapy.[1,2] DISH-like hyperostotic changes are common in the general population and are associated with ageing; the use of chronic retinoid therapy may increase the risk of developing these changes. Reports have particularly involved patients with keratinisation disorders being treated with large doses of retinoids for prolonged periods, and radiographic changes can be found in most patients after long-term treatment. However, minimal bone changes have also been found in radiographic studies of patients treated with isotretinoin in the dose range usually used to treat acne. Changes were also reported in a study of very low doses of isotretinoin used over 3 years to investigate skin cancer prevention. There have been few reports on the skeletal adverse effects of chronic low-dose etretinate and acitretin and results so far have been equivocal;[2] further studies are needed to clarify any effects. *Premature closure of the epiphyses* in children treated with retinoids has also been described.[1] Again, high doses or prolonged therapy were often used. There is limited evidence to suggest that children might also be at increased risk of slender long bones. There have been rare reports of changes in bone mineral density and *osteoporosis* from retinoid therapy, but there is limited evidence to confirm this association.[1] Ongoing clinical surveillance and periodic radiographic skeletal surveys have been recommended during long-term therapy; symptomatic bone spurs may be treated surgically.[1]

There have also been individual reports of *hypercalciuria*[3] or *hypercalcaemia*[4-6] associated with oral retinoid therapy.

Muscular disorders such as myalgia are not uncommon in patients treated with oral isotretinoin. Reversible myopathy with muscle pain, weakness, and raised creatine kinase concentrations has been described in a few patients treated with isotretinoin,[7] etretinate,[8] and acitretin.[9] Asymptomatic muscle damage has also been found in a study of patients given etretinate for at least a year.[10] Rhabdomyolysis and myoglobinuria have been described in a patient given isotretinoin for acne.[11] Myositis, often affecting the lower limbs, has occurred in a few patients given tretinoin for remission induction in acute promyelocytic leukaemia.[12-15] In one case, cardiac myositis also occurred.[14] Symptoms usually had an onset of 2 to 4 weeks and responded to stopping tretinoin and being treated with a corticosteroid. In a few cases, subsequent courses of tretinoin were given without recurrence of symptoms.[14,15] A review[15] suggested that some cases of myositis might have been associated with the retinoic acid syndrome (see under Tretinoin, p. 1726.2) or Sweet's syndrome (see Effects on the Skin, under Tretinoin, p. 1726.2).

1. DiGiovanna JJ. Isotretinoin effects on bone. *J Am Acad Dermatol* 2001; **45:** S176–S182.
2. Halverstam CP, *et al.* Lack of significant skeletal changes after long-term, low-dose retinoid therapy: case report and review of the literature. *J Cutan Med Surg* 2006; **10:** 291–9.
3. Wilson DJ, *et al.* Skeletal hyperostosis and extraosseous calcification in patients receiving long-term etretinate (Tigason). *Br J Dermatol* 1988; **119:** 597–607.
4. Valentic JP, *et al.* Hypercalcemia associated with oral isotretinoin in the treatment of severe acne. *JAMA* 1983; **250:** 1899–1900.
5. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii:** 1093.
6. Akiyama H, *et al.* Hypercalcaemia due to all-trans retinoic acid. *Lancet* 1992; **339:** 308–9.
7. Hodak E, *et al.* Muscle damage induced by isotretinoin. *BMJ* 1986; **293:** 425–6.
8. Hodak E, *et al.* Etretinate-induced skeletal muscle damage. *Br J Dermatol* 1987; **116:** 623–6.
9. Lister RK, *et al.* Acitretin-induced myopathy. *Br J Dermatol* 1996; **134:** 989–90.
10. David M, *et al.* Electromyographic abnormalities in patients undergoing long-term therapy with etretinate. *J Am Acad Dermatol* 1988; **19:** 273–5.
11. Guttman-Yassky E, *et al.* Acute rhabdomyolysis and myoglobinuria associated with isotretinoin treatment. *Int J Dermatol* 2003; **42:** 499–500.
12. Miranda N, *et al.* Myositis with tretinoin. *Lancet* 1994; **334:** 1096.
13. Martínez-Chamorro C, *et al.* ATRA-induced myositis in induction therapy of acute promyelocytic leukemia. *Haematologica* 2002; **87:** ECR08.
14. Fabbiano F, *et al.* All-trans retinoic acid induced cardiac and skeletal myositis in induction therapy of acute promyelocytic leukaemia. *Br J Haematol* 2005; **129:** 444–5.
15. Chan KH, *et al.* A case of all-trans retinoic acid-induced myositis in the treatment of acute promyelocytic leukaemia. *Clin Lab Haematol* 2005; **27:** 399–401.

Effects on the nervous system. There has been a report[1] of Guillain-Barré syndrome in 2 patients taking oral isotretinoin; both patients required ventilatory support and recovered slowly after treatment with intravenous immunoglobulins. There had been 1 case reported previously to the UK CSM. Intracranial hypertension, causing headaches and papilloedema, can occur with retinoids, including isotretinoin (see Effects on the Eyes, p. 1707.3).

1. Pritchard J, *et al.* Guillain-Barré syndrome seen in users of isotretinoin. *BMJ* 2004; **328:** 1537.

Effects on the respiratory system. There have been reports of exercise-induced wheezing,[1] eosinophilic pleural effusion,[2] and worsening asthma[3,4] associated with isotretinoin therapy. The US manufacturers have records of adverse effects on the lung including worsening asthma, recurrent pneumothorax, interstitial fibrosis, and pulmonary granuloma.[5] A study of healthy subjects confirmed that lung function tests could deteriorate after treatment with isotretinoin.[5]

1. Fisher DA. Exercise-induced bronchoconstriction related to isotretinoin therapy. *J Am Acad Dermatol* 1985; **13:** 524.
2. Bunker CB, *et al.* Isotretinoin and eosinophilic pleural effusion. *Lancet* 1989; **i:** 435–6.
3. Sabroe RA, *et al.* Bronchospasm induced by isotretinoin. *BMJ* 1996; **312:** 886.
4. Kapur N, *et al.* Exacerbation of asthma by isotretinoin. *Br J Dermatol* 2000; **142:** 388–9.
5. Bunker CB, *et al.* Isotretinoin and the lung. *Br J Dermatol* 1991; **125** (suppl 38): 29.

Effects on serum lipids. The oral retinoids induce dose-dependent changes in serum lipids. There can be increases in very-low-density-lipoprotein cholesterol with smaller increases in low-density-lipoprotein cholesterol and reductions in high-density-lipoprotein cholesterol.[1,2] These effects appear to be unrelated to age or sex. They occur early during treatment and are usually reversible within a few weeks of withdrawal. Overall, the effect of isotretinoin is much greater than that of etretinate. Although the total cholesterol and triglyceride concentrations may remain within normal limits, types IIb and IV hyperlipidaemias are not uncommon among patients receiving oral retinoids. A large retrospective study[3] of patients treated with isotretinoin for acne found that of those who had normal concentrations before treatment, there was an increase in triglycerides in 44% and in total cholesterol in 31% of

patients. Pancreatitis may be associated with hypertriglyceridaemia in patients treated with isotretinoin.[4-7]

Retinoids should be used with caution in patients with pre-existing hypertriglyceridaemia or in those at risk of developing hypertriglyceridaemia.[1] Use of fish oil containing eicosapentaenoic acid has been reported to attenuate retinoid-induced increases in serum-cholesterol and serum-triglyceride concentrations.[2,8]

1. Henkin Y, *et al*. Secondary dyslipidemia: inadvertent effects of drugs in clinical practice. *JAMA* 1992; **267:** 961–8.
2. Mantel-Teeuwisse AK, *et al*. Drug-induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Safety* 2001; **24:** 443–56.
3. Zane LT, *et al*. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. *Arch Dermatol* 2006; **142:** 1016–22.
4. Flynn WJ, *et al*. Pancreatitis associated with isotretinoin-induced hypertriglyceridemia. *Ann Intern Med* 1987; **107:** 63.
5. McCarter TL, Chen YK. Marked hyperlipidemia and pancreatitis associated with isotretinoin therapy. *Am J Gastroenterol* 1992; **87:** 1855–8.
6. Jamshidi M, *et al*. Acute pancreatitis secondary to isotretinoin-induced hyperlipidemia. *J Okla State Med Assoc* 2002; **95:** 79–80.
7. Greene JP. An adolescent with abdominal pain taking isotretinoin for severe acne. *South Med J* 2006; **99:** 992–4.
8. Marsden JR. Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. *Hum Toxicol* 1987; **6:** 219–22.

Effects on sexual function. Ejaculatory failure has been reported in 3 men to be associated with isotretinoin treatment.[1] A possible mechanism could be an effect on the goblet cells of the seminal vesicles, an effect similar to the general reduction in body secretions which leads to dry mucous membranes.

1. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system. *Lancet* 1994; **344:** 198.

Effects on the skin, hair, and nails. Apart from the more common effects of oral retinoids on the skin and hair (see Adverse Effects, p. 1707.2), there have been isolated reports of various other reactions. Stickiness of the skin, particularly of the palms and soles, has been described with etretinate.[1,2] It has also occurred in a patient using topical tretinoin,[3] but not when he had previously taken a course of oral isotretinoin. Papules and pustules on the palms and soles have also been described with etretinate use.[4] In a series of 5 patients being treated for psoriasis, the lesions appeared 5 to 9 days after starting therapy and cleared spontaneously within a few weeks leaving a desquamation, despite continuing etretinate.

Granulomatous nodules or pyogenic granulomas have been reported with isotretinoin,[5,6] etretinate,[7,8] topical tretinoin,[9,10] and topical tazarotene.[11] Pyoderma gangrenosum has occurred in patients treated with isotretinoin.[12-14] Prurigo-like eruptions have been reported with etretinate.[15] Precipitation or exacerbation of erythroderma has been reported with isotretinoin,[16] etretinate,[17] and acitretin.[18]

Reversible chloasma (melasma) has been reported with isotretinoin.[19]

Acne fulminans is an uncommon complication of acne, developing as a sudden onset of ulcerative crusting acne with fever, weight loss, and musculoskeletal pain. Although isotretinoin may be used to treat this condition,[20] there have been reports of acne fulminans being precipitated by isotretinoin.[21,22] In some cases erythema nodosum has also developed,[23,24] but it has been suggested that this might be a manifestation of acne fulminans rather than an adverse effect of isotretinoin.[24] Erythema nodosum has also occurred in patients given oral tretinoin for remission induction in acute promyelocytic leukaemia. In a series of 4 cases, patients were successfully managed with a 5-day course of oral corticosteroid allowing the tretinoin course to be completed.[25]

There has been a report of fatal toxic epidermal necrolysis associated with etretinate.[26] Reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis are also mentioned in the licensed product information for isotretinoin.

For other reports of eruptions associated with vasculitic syndromes, see below. Painful scrotal ulcers and Sweet's syndrome (acute febrile neutrophilic dermatosis) are other reactions that have been reported with oral tretinoin (see p. 1726.2). Skin erosion after wax depilation has been reported in patients receiving retinoids (see Skin Fragility under Precautions, p. 1710.1).

Curling hair has been described in transplant recipients taking isotretinoin and azathioprine.[27] Oral retinoids have been associated with nail fragility, onycholysis,[28] paronychia, and other forms of nail dystrophy.[29,30]

1. Penneys NS, Hernandez D. A sticky problem with etretinate. *N Engl J Med* 1991; **325:** 521.
2. Higgins EM, Pembroke AC. Sticky palms—an unusual side-effect of etretinate therapy. *Clin Exp Dermatol* 1993; **18:** 389–90.
3. Lockridge J, *et al*. Tretinoin-induced sticky skin: a case report and review of the literature. *Cutis* 1999; **63:** 142–4.
4. David M, *et al*. Palmoplantar eruption associated with etretinate therapy. *Acta Derm Venereol (Stockh)* 1986; **66:** 87–9.
5. Lane PR, Hogan DJ. Granulomatous lesions appearing during isotretinoin therapy. *Can Med Assoc J* 1984; **130:** 550.
6. Türel A, *et al*. A rare side-effect of systemic isotretinoin treatment: pyogenic granuloma. *J Eur Acad Dermatol Venereol* 2003; **17:** 609–11.
7. Williamson DM, Greenwood R. Multiple pyogenic granulomata occurring during etretinate therapy. *Br J Dermatol* 1983; **109:** 615–17.
8. Kanoh H, *et al*. Granulomatous nodule on vocal cord possibly induced by etretinate therapy. *Br J Dermatol* 2000; **142:** 1258–60.
9. MacKenzie-Wood AR, Wood G. Pyogenic granuloma-like lesions in a patient using topical tretinoin. *Australas J Dermatol* 1998; **39:** 248–50.
10. Teknetzis A, *et al*. Pyogenic granulomas following topical application of tretinoin. *J Eur Acad Dermatol Venereol* 2004; **18:** 337–9.
11. Dawkins MA, *et al*. Pyogenic granuloma-like lesion associated with topical tazarotene therapy. *J Am Acad Dermatol* 2000; **43:** 154–5.
12. Hughes BR, Cunliffe WJ. Development of folliculitis and pyoderma gangrenosum in association with abdominal pain in a patient following treatment with isotretinoin. *Br J Dermatol* 1990; **122:** 683–7.
13. Gangaram HB, *et al*. Pyoderma gangrenosum following treatment with isotretinoin. *Br J Dermatol* 1997; **136:** 636–7.
14. Freiman A, Brassard A. Pyoderma gangrenosum associated with isotretinoin therapy. *J Am Acad Dermatol* 2006; **55** (suppl): S107–S108.
15. Boer J, Smeenk G. Nodular prurigo-like eruptions induced by etretinate. *Br J Dermatol* 1987; **116:** 271–4.
16. Wantzin GL, Thomsen K. A new cutaneous side effect of isotretinoin. *J Am Acad Dermatol* 1985; **13:** 665.
17. Levin J, Almeyda J. Erythroderma due to etretinate. *Br J Dermatol* 1985; **112:** 373.
18. Mahé E, *et al*. Acitretin-induced erythroderma in a psoriatic patient. *J Eur Acad Dermatol Venereol* 2006; **20:** 1133–4.
19. Burke H, Carmichael AJ. Reversible melasma associated with isotretinoin. *Br J Dermatol* 1996; **135:** 862.
20. Seukeran DC, Cunliffe WJ. The treatment of acne fulminans: a review of 25 cases. *Br J Dermatol* 1999; **141:** 307–9.
21. Huston NR, Mules R. Acne fulminans with severe myalgia precipitated by isotretinoin therapy. *N Z Med J* 1985; **36:** 821.
22. Choi EH, Bang D. Acne fulminans and 13-cis-retinoic acid. *J Dermatol* 1992; **19:** 378–83.
23. Kellett JK, *et al*. Erythema nodosum and circulating immune complexes in acne fulminans after treatment with isotretinoin. *BMJ* 1985; **290:** 820.
24. Tan BB, *et al*. Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. *Clin Exp Dermatol* 1997; **22:** 26–7.
25. Kuo MC, *et al*. All-trans-retinoic acid-induced erythema nodosum in patients with acute promyelocytic leukemia. *Ann Hematol* 2004; **83:** 376–80.
26. McIvor A. Fatal toxic epidermal necrolysis associated with etretinate. *BMJ* 1992; **304:** 548.
27. van der Pijl JW, *et al*. Isotretinoin and azathioprine: a synergy that makes hair curl? *Lancet* 1996; **348:** 622–3.
28. Önder M, *et al*. Isotretinoin-induced nail fragility and onycholysis. *J Dermatol Treat* 2001; **12:** 115–16.
29. Dharmagunawardena B, Charles-Holmes R. Median canaliform dystrophy following isotretinoin therapy. *Br J Dermatol* 1997; **137:** 658–9.
30. Yung A, *et al*. Isotretinoin-induced elkonyxis. *Br J Dermatol* 2005; **153:** 671–2.

Effects on taste. Almost complete loss of taste has been reported in a patient given oral isotretinoin 600 micrograms/kg daily for 20 weeks.[1] Sense of taste returned about 6 months after isotretinoin was stopped. Up to September 1994 the UK CSM knew of 5 cases of taste changes, including 4 reports of loss of taste.

1. Halpern SM, *et al*. Loss of taste associated with isotretinoin. *Br J Dermatol* 1996; **134:** 378.

Overdosage. Apart from vague abdominal discomfort there were no other symptoms or significant abnormalities in a 15-year-old who was treated with gastric lavage 1.5 hours after ingestion of 350mg of isotretinoin.[1] The authors noted a similar outcome in 2 other cases of isotretinoin overdosage reported in the literature at that time. In a subsequent report, mild headache, skin that was dry and peeling, and cheilitis occurred in a 29-year-old who ingested 900 mg of isotretinoin.[2]

1. Hepburn NC. Deliberate self-poisoning with isotretinoin. *Br J Dermatol* 1990; **122:** 840–1.
2. Aubin S, *et al*. Massive isotretinoin intoxication. *Clin Exp Dermatol* 1995; **20:** 348–50.

Vasculitic syndromes. The manufacturer of isotretinoin and etretinate has received isolated reports of vasculitis associated with the use of these oral retinoids; Wegener's granulomatosis has also been reported after the use of isotretinoin.[1,2] The precise mechanism underlying these effects is unknown; in some patients there may have been a direct toxic effect as symptoms developed shortly after the start of treatment, in other patients the onset was long-delayed and may have been triggered by the incidental use of antibacterials. Vasculitis, manifesting as fever and skin lesions, has been reported in patients given oral tretinoin for acute promyelocytic leukaemia.[3]

1. Dwyer JM, *et al*. Vasculitis and retinoids. *Lancet* 1989; **ii:** 494–6.
2. Anonymous. Retinoids and necrotizing vasculitis. *WHO Drug Inf* 1989; **3:** 187.
3. Paydas S, *et al*. Vasculitis associated with all trans retinoic acid (ATRA) in a case with acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 547–8.

Precautions

Isotretinoin and other oral retinoids are teratogenic and therefore contra-indicated in pregnant patients. It is advisable for female patients to begin using contraceptive measures 1 month before starting isotretinoin treatment. Pregnancy should be excluded before starting therapy and avoided during treatment and for 1 month after stopping treatment. Patients receiving isotretinoin should not donate blood during, or for 1 month after stopping therapy, because of the potential risk to the fetus of a pregnant transfusion recipient. *Pregnancy or blood donation must be avoided for much longer periods in patients taking acitretin or etretinate.* Isotretinoin is contra-indicated in patients with hepatic impairment, hyperlipidaemias, and hypervitaminosis A. Renal impairment does not affect the pharmacokinetics of isotretinoin but a lower starting dose has been suggested in severe impairment. It is unknown whether isotretinoin is distributed into breast milk but its lipophilicity makes this likely; isotretinoin use in breast-feeding women is therefore contra-indicated because of the potential for adverse effects in the infant. Isotretinoin should be used with care in patients with a history of depression and patients taking isotretinoin should be monitored for signs of depressive illness.

Liver function and fasting blood lipids should be measured at the start of therapy, after the first month (or every 1 to 2 weeks for the first 2 months for acitretin), and thereafter as appropriate. Blood glucose should be monitored throughout treatment in patients who either have, or are predisposed to, diabetes mellitus. Some recommend routine radiological evaluation in patients receiving long-term therapy (see under Effects on the Musculoskeletal System, p. 1708.2). Patients may have a reduced tolerance to contact lenses.

Excessive exposure to sunlight and UV light should be avoided.

Dizziness, drowsiness, and visual disturbances may occur rarely, and could affect the performance of skilled tasks such as driving.

When applied topically the precautions described under tretinoin (see p. 1726.3) should be considered.

Pregnancy. The problem of prescribing oral retinoids to women of child-bearing potential has been discussed.[1,2] Intra-uterine exposure to isotretinoin has caused spontaneous abortion and a characteristic pattern of fetal malformations involving craniofacial, cardiac, thymic, and CNS structures.[3,4] Some infants have also shown subnormal intelligence and other neuropsychological impairments.[5] The risk of malformation appears to be high at all therapeutic doses of isotretinoin even when the duration of exposure is short.[6] Despite warnings on the use of retinoids during pregnancy and the need for adequate contraception in women of child-bearing potential, and other strict guidelines on their use, intra-uterine exposure to retinoids has still occurred.[7-10]

Isotretinoin has a relatively short half-life and it has been recommended that conception should be avoided for at least one month after the end of treatment.[11] A survey of women who conceived after the use of isotretinoin (64% within one month of stopping treatment) suggested that the incidence of spontaneous abortion or congenital malformations was no greater than in the general population.[12]

Warnings to avoid conception are similar for oral tretinoin (see p. 1726.3). However, patients taking oral retinoids with longer half-lives must avoid conception for much longer periods; at least 2 years (3 years in the USA) is recommended if patients are taking acitretin although the period of time for patients taking etretinate has not been established (see also Pregnancy under Acitretin, p. 1691.3).

Unless otherwise contra-indicated, oral combined contraceptives have been recommended as the contraceptive method of choice for women undergoing retinoid treatment, starting at least 1 month before the retinoid.[13] Use of an additional form of contraception, such as a barrier method, is also recommended.[2,7,11] For further information on the use of hormonal contraceptives with retinoids, see p. 2243.3.

1. Mitchell AA. Oral retinoids: what should the prescriber know about their teratogenic hazards among women of child-bearing potential? *Drug Safety* 1992; **7:** 79–85.
2. Chan A, *et al*. Oral retinoids and pregnancy. *Med J Aust* 1996; **165:** 164–7.
3. Lammer EJ, *et al*. Retinoic acid embryopathy. *N Engl J Med* 1985; **313:** 837–41.
4. Rosa F. Isotretinoin dose and teratogenicity. *Lancet* 1987; **ii:** 1154.
5. Adams J. High incidence of intellectual deficits in 5-year-old children exposed to isotretinoin 'in utero'. *Teratology* 1990; **41:** 614.
6. Dai WS, *et al*. Epidemiology of isotretinoin exposure during pregnancy. *J Am Acad Dermatol* 1992; **26:** 599–606.
7. Atanackovic G, Koren G. Fetal exposure to oral isotretinoin: failure to comply with the Pregnancy Prevention Program. *Can Med Assoc J* 1999; **160:** 1719–20.
8. CDC. Accutane-exposed pregnancies—California, 1999. *MMWR* 2000; **49:** 28–31.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Avoiding fetal abnormalities with isotretinoin. *Aust Adverse Drug React Bull* 2005; **24:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.htm (accessed 27/09/07)
10. Abroms L, *et al*. What is the best approach to reducing birth defects associated with isotretinoin? *PLoS Med* 2006; **3:** e483. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0030483 (accessed 23/07/10)
11. Goodfield MJD, *et al*. British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010; **162:** 1172–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf (accessed 27/05/10)
12. Dai WS, *et al*. Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol* 1989; **125:** 362–5.
13. Lehucher Ceyrac D, *et al*. Retinoids and contraception. *Dermatology* 1992; **184:** 161–70.

Skin fragility. Wax depilation should be avoided in patients receiving retinoids since they cause increased skin fragility and facial and leg erosions have occurred.[1-3] Licensed UK product information also recommends that wax depilation should be avoided for at least 6 months after isotretinoin treatment because of the risk of epidermal stripping. Aggressive chemical dermabrasion and cutaneous laser treatment should also be avoided for a period of 5 to 6 months after treatment because of the risk of hypertrophic scarring in atypical areas and, more rarely, post-inflammatory hypo- or hyperpigmentation in treated areas.

1. Egido Romo M. Isotretinoin and wax epilation. *Br J Dermatol* 1991; **124:** 393.
2. Holmes SC, Thomson J. Isotretinoin and skin fragility. *Br J Dermatol* 1995; **132:** 165.
3. Woollons A, Price ML. Roaccutane and wax epilation: a cautionary tale. *Br J Dermatol* 1997; **137:** 839–40.

Interactions

Use of isotretinoin with vitamin A (including dietary supplements) should be avoided because of additive toxic effects. Tetracyclines should be avoided as their use with isotretinoin has been associated with the development of benign intracranial hypertension. Skin irritation may be increased if isotretinoin is given with topical keratolytic or exfoliative anti-acne treatments; such use should be avoided.

Antiepileptics. For the effect of isotretinoin on *carbamazepine*, see Dermatological Drugs, p. 517.3.

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p. 2243.3.

Pharmacokinetics

Isotretinoin is absorbed from the gastrointestinal tract and absorption may be increased by food. Minimal systemic absorption occurs after topical application. Peak plasma concentrations occur 1 to 4 hours after oral doses. Oral bioavailability is low, possibly due to metabolism in the gut wall and first-pass metabolism in the liver. Isotretinoin is highly bound to plasma proteins. It is metabolised in the liver to its major metabolite 4-oxo-isotretinoin; there is also some isomerisation of isotretinoin to tretinoin. Several cytochrome P450 isoenzymes are involved in isotretinoin metabolism, including CYP2C8, CYP2C9, CYP3A4, and CYP2B6. Isotretinoin, tretinoin, and their metabolites undergo enterohepatic recycling. The terminal elimination half-life of isotretinoin is 10 to 20 hours, while that of the 4-oxo metabolite may be up to 50 hours; return to physiological levels of retinoids takes about 2 weeks after stopping therapy. Equal amounts of a dose appear in the faeces, mainly as unchanged drug, and in the urine as metabolites.

Isotretinoin crosses the placenta. It is unknown whether isotretinoin is distributed into breast milk but its lipophilicity makes this likely.

References.

1. Colburn WA, *et al.* Food increases the bioavailability of isotretinoin. *J Clin Pharmacol* 1983; **23:** 534–9.
2. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; **10:** 38–62.
3. Kraft JC, *et al.* Embryonic retinoid concentrations after maternal intake of isotretinoin. *N Engl J Med* 1989; **321:** 262.
4. Larsen FG, *et al.* Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; **23:** 42–61.
5. Chen C, *et al.* Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol* 1997; **37:** 279–84.
6. Nulman I, *et al.* Steady-state pharmacokinetics of isotretinoin and its 4-oxo metabolite: implications for fetal safety. *J Clin Pharmacol* 1998; **38:** 926–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atlacne; Curacne; Isotrex; Retinide; Roaccutan; Zonatian; ***Austral.***: Accure†; Isohexal†; Isotrex; Oratane; Roaccutane; Rocta; Rocta; ***Austria***: Ciscutan; Lurantal; Roaccutan†; ***Belg.***: Isocural; Isosupra Lidose; Roaccutane; ***Braz.***: Acnil†; Cecnoin; Isofacet†; Isotrex; Lurantal; Roacutan; ***Canad.***: Accutane; Clarus; ***Chile***: Acneral; Acnotin; Isdiben; Isocross; Isotrex; Piplex; Roacnetan; ***China***: Ai Si Jie (爱思洁); Isotrex (安素丝); Tai Er Si (泰尔丝); Teweisi (特维丝); ***Cz.***: Aknenormin; Curacne; Isotretin†; Roaccutane; Stiefel Acne Gel; ***Denm.***: Accutin; Capsoderm†; Isotrex; Tretiosan; ***Fin.***: Roaccutan; ***Fr.***: Contracne; Curacne; Procuta; ***Ger.***: Aknefug Iso; Aknenormin; Isoderm; IsoGalen; Isotret†; Isotrex; ***Gr.***: A-Cnotren; Accuran; Acnogen; Acnotan; Aknesil; Curacne; Derminoin; Flitrion; Inotrin; Isodermal; Isogeril; Isoskin; Isotroin; Lyotret; Noitron; Noroseptan; Novacne; Opridan; Policano; Reducar; Roaccutan; Rocne; Stiefotrex; Trecifan; Tretin; ***Hong Kong***: Acnotin; Isotrex; Reducar; Roaccutane; ***Hung.***: Aknenormin; Isotrex; Roaccutan; Sotret; Tretinak†; ***India***: Acnex; Acno; Acutret; Cutret; Elvac; Iret; Isac; Iso-Aret; Isobest; Isofact; Isoret; Isotane; Isotin; Isotriz; Isotroin; Nextin; ***Indon.***: Isotrex; ***Irl.***: Isotrex; Roaccutane; ***Israel***: Curatane; Isotrex†; Roaccutane; ***Ital.***: Aisoskin; Isoriac; Isotrex; Roaccutan; ***Malaysia***: Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Mex.***: Isofacе; Isotrex; Neotrex; Oratane; Roaccutan; Sotrexe; Vastionin; ***Mon.***: Roaccutane; ***Neth.***: Curacne†; Roaccutane; ***Norw.***: Roaccutan†; ***NZ***: Isotane†; Isotrex; Oratane; ***Philipp.***: Acnetrex; Acutrex; Isotrex; Roaccutane; ***Pol.***: Aknenormin; Axotret; Curacne; Isotrex; Izotek; Izotziaja; Roaccutane†; Tretinex; ***Port.***: Isdiben; Isoprotil; Isotrex; Orotrex; ***Rus.***: Retasol (Ретасол); Retinoic Ointment (Ретиноевая Мазь); Roaccutane (Роаккутан); ***S.Afr.***: Acnetane; Isotrex; Oratane; Roaccutane; ***Singapore***: Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Spain***: Acnemin; Dercutane; Farmacne; Flexresan; Isdiben; Isoacne; Isotrex; Mayesta; Roacutan†; ***Switz.***: Curakne; Liderma†; Roaccutane; Tretinac; ***Thai.***: A-Cnotren; Acnotin; Isotane; Isotrex; Proacne; Roaccutane; Sotret; Tinoin; ***Turk.***: Actretin; Aknetrent; Roaccutane; Zoretanin; ***UK***: Isotrex; Roaccutane; ***Ukr.***: Acnetin (Акнетин); Roaccutane (Роаккутан); ***USA***: Absorica; Accutane†; Amnesteem; Claravis; Myorisan; Sotret; Zenatane; ***Venez.***: Cuticlin; Isofacе; Roaccutan.

Multi-ingredient Preparations. ***Austria***: Isotrex; Isotrexin; ***Braz.***: Isotrexin; Isotrexol; ***Cz.***: Isotrexin; ***Fr.***: Antibiotrex; ***Ger.***: Isotrexin; ***Hung.***: Isotrexin; ***Irl.***: Isotrexin; ***Ital.***: Isotrexin; ***Pol.***: Isotrexin; ***Port.***: Isotrexin; ***Rus.***: Isotrexin (Изотрексин); ***Singapore***: Isotrexin; ***Spain***: Isotrex Eritromicina; ***Thai.***: Isotrexin; ***Turk.***: Isotrexin; ***UK***: Isotrexin; ***Ukr.***: Isotrexin (Изотрексин).

Pharmacopoeial Preparations
BP 2014: Isotretinoin Capsules; Isotretinoin Gel;
USP 36: Isotretinoin Capsules.

Keluamid

Keluamida; Келуамид.

Profile

Keluamid has keratolytic properties and has been used in topical preparations for the treatment of seborrhoeic dermatitis and other scaling skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kelual; ***Fr.***: Kelual.

Multi-ingredient Preparations. ***Arg.***: Kelual Zinc; ***Fr.***: Kelual DS; Kelual DS; Kelual Zinc†; Kertyol-S†.

Kinetin

6-Furfurylaminopurine; N^6-Furfuryladenine; Кинетин.
$C_{10}H_9N_5O$=215.2
CAS — 525-79-1.
UNII — P39Y9652YJ.

NOTE. The name kinetin has also been used as a proprietary name for hyaluronidase (p. 2527.2).

Profile

Kinetin is a plant growth hormone that has been promoted in products for the management of photodamaged skin and hyperpigmentation but good evidence of efficacy appears to be lacking.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Kinerase; ***Hong Kong***: Kinerase; ***Mex.***: Kinerase; ***Singapore***: Kinerase; ***USA***: Kinerase.

Multi-ingredient Preparations. ***Philipp.***: Kinerase.

Kojic Acid

Kójico, ácido; Койевая Кислота.
5-Hydroxy-2-hydroxymethyl-4-pyrone.
$C_6H_6O_4$=142.1
CAS — 501-30-4.
UNII — 6K23F1TT52.

Profile

Kojic acid is reported to inhibit melanin production and is used in topical preparations for the treatment of hyperpigmentation disorders (p. 1687.2). Kojic acid is also used as a food additive.

References.

1. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg* 1999; **25:** 282–4.
2. Bentley R. From miso, saké and shoyu to cosmetics: a century of science for kojic acid. *Nat Prod Rep* 2006; **23:** 1046–62.
3. García-Gavín J, *et al.* Pigmented contact dermatitis due to kojic acid: a paradoxical side effect of a skin lightener. *Contact Dermatitis* 2010; **62:** 63–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Unitone 4.

Multi-ingredient Preparations. ***Arg.***: Cellskinlab Phyto Spot; Melasoft; Neoquin; ***Braz.***: Melani-D Maos; ***Chile***: Melani-D; NeoStrata; Phyto Spot; Recover Ol; ***India***: Biolite; Carofit; Clearz; Demelan; E-Cate; Glyaha-KOJ; KC-Lite; ***Indon.***: Hidrogel†; ***Ital.***: Brunex; ***Mex.***: Nova Derm Facial Lightening; ***Port.***: Despigmentante†; ***Singapore***: Disco.

Liarozole *(BAN, rINN)*

Liarozol; Liarozolum; Лиарозол.
(±)-5-(*m*-Chloro-α-imidazol-1-ylbenzyl)benzimidazole.
$C_{17}H_{13}ClN_4$=308.8
CAS — 115575-11-6; 145858-51-1.
UNII — K0Q29TGV9Y.

Liarozole Fumarate *(BANM, USAN, rINNM)*

Fumarato de liarozol; Liarozole, Fumarate de; Liarozoli Fumaras; R-85246; Лиарозола Фумарат.
$2C_{17}H_{13}ClN_4,3C_4H_4O_4$=965.8
CAS — 145858-52-2.
UNII — 91W7VLK7J3.

Liarozole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de liarozol; Liarozole, Chlorhydrate de; Liarozoli Hydrochloridum; R-75251; Лиарозола Гидрохлорид.
$C_{17}H_{13}ClN_4$, HCl=345.2
CAS — 145858-50-0.
UNII — 29T7S2IB97.

Profile

Liarozole, an imidazole analogue, increases plasma and cutaneous retinoic acid concentrations through inhibition of cytochrome P450 isoenzymes involved in retinoic acid catabolism. It is under investigation for the management of ichthyoses and psoriasis.

References.

1. Bhushan M, *et al.* Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; **145:** 546–53.
2. Lucker GPH, *et al.* Topical liarozole in ichthyosis: a double-blind, left-right comparative study followed by a long-term open maintenance study. *Br J Dermatol* 2005; **152:** 566–9.
3. Verfaille CJ, *et al.* Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. *Br J Dermatol* 2007; **156:** 965–73.

Lisadimate *(USAN, rINN)*

Glyceryl Aminobenzoate; Glyceryl PABA; Lisadimato; Lisadimatum; Лизадимат.
Glyceryl 1-(4-aminobenzoate).
$C_{10}H_{13}NO_4$=211.2
CAS — 136-44-7.
UNII — A886B5N5IM.

Profile

Lisadimate, a substituted aminobenzoate, is a sunscreen (see p. 1681.3) with actions similar to those of aminobenzoic acid (p. 1694.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Brite; ***USA***: Total Eclipse.

Lithium Succinate

Litio, succinato de; Лития Сукцинат.
$C_4H_6O_4.xLi$
CAS — 16090-09-8.
ATC — D11AX04.
ATC Vet — QD11AX04.
UNII — MD64P82Y28.

Profile

Lithium succinate is reported to have anti-inflammatory properties and is used as an 8% cream or ointment, usually with zinc sulfate. It is applied twice daily initially in the treatment of seborrhoeic dermatitis (p. 1689.1). It should be used with caution in patients with psoriasis as it may exacerbate their condition.

References.
1. Gould DJ, *et al*. A double-blind, placebo-controlled, multicenter trial of lithium succinate ointment in the treatment of seborrheic dermatitis. *J Am Acad Dermatol* 1992; **26:** 452–7.
2. Cuelenaere C, *et al*. Use of topical lithium succinate in the treatment of seborrhoeic dermatitis. *Dermatology* 1992; **184:** 194–7.
3. Langtry JA, *et al*. Topical lithium succinate ointment (Efalith) in the treatment of AIDS-related seborrhoeic dermatitis. *Clin Exp Dermatol* 1997; **22:** 216–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Efalith; ***Ger.***: Efadermin; ***Irl.***: Efalith†; ***Switz.***: Efalith.

Maggots

Larvas; Sterile Larvae; Личинки.

Profile

Maggots used in wound management are the live sterile larvae of *Lucilia sericata*, the common greenbottle fly. Larval therapy (sometimes called biosurgery) may be used for debridement of infected or necrotic wounds (p. 1690.1), including diabetic foot ulcers. Maggots produce a mixture of proteolytic enzymes that breaks down the necrotic tissue while leaving the healthy tissue unharmed, and kill or prevent the growth of micro-organisms, particularly Gram-positive bacteria. The movement of the maggots also appears to stimulate the growth of granulation tissue.

The maggots are applied to the surface of the wound and kept in place with dressings for up to 3 days. They are removed with the dressing, and the wound is irrigated with sodium chloride solution; any remaining maggots are removed with forceps.

Maggots should not be applied to wounds that have a tendency to bleed easily, or that communicate with a body cavity or any internal organ. Pain has been reported with larval therapy and some patients may require analgesics.

References.
1. Courtenay M, *et al*. Larva therapy in wound management. *J R Soc Med* 2000; **93:** 72–4.
2. Jukema GN, *et al*. Amputation-sparing treatment by nature: "surgical" maggots revisited. *Clin Infect Dis* 2002; **35:** 1566–71.
3. Sherman RA, Shimoda KJ. Presurgical maggot debridement of soft tissue wounds is associated with decreased rates of postoperative infection. *Clin Infect Dis* 2004; **39:** 1067–70.
4. Armstrong DG, *et al*. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc* 2005; **95:** 254–7.
5. Steenvoorde P, *et al*. Maggot debridement therapy: free-range or contained? An in-vivo study. *Adv Skin Wound Care* 2005; **18:** 430–5.
6. Dumville JC, *et al*. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. Abridged version: *BMJ* 2009; **338:** 1047–50. Full version: http://www.bmj.com/cgi/reprint/338/mar19_2/b773 (accessed 16/03/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: LarvE.

Melanin

Меланин.

Profile

Melanin is a group of natural pigments found in many plants and animals; they are present in human skin and hair. Natural and synthetic forms of melanin have been used in sunscreen preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fotobloc.

Multi-ingredient Preparations. ***Arg.***: Fotocrem Ultra; Melablock; ***Chile***: ProZone Face†; ProZone Gel; ***Mex.***: ProZone Baby; ProZone Body; ProZone Face; ProZone Gel; ProZone Ultra Fluido; ProZone Ultra.

Mequinol *(USAN, rINN)*

BMS-181158; Éter metílico de la hidroxiquinona; *p*-Guaiacol; 4-HA; 4-Hidroxianisol; HQMME; Hydroquinone Monomethyl Ether; *p*-Hydroxyanisole; Hydroxyquinone Methyl Ether; Méquinol; Mequinolum; Metoxifenol; *p*-Metoxifenol; Меквинол.

4-Methoxyphenol.

$C_7H_8O_2$=124.1

CAS — 150-76-5.

ATC — D11AX06.

ATC Vet — QD11AX06.

UNII — 6HTBU7K3AM.

Profile

Mequinol is used similarly to hydroquinone (p. 1705.1), in concentrations of up to 20%, in the treatment of hyperpigmentation (see Pigmentation Disorders, p. 1687.2). A preparation containing mequinol 2% with tretinoin 0.01% is used for the treatment of solar lentigines (liver spots).

Adverse effects. A report of severe reversible irregular hypopigmentation of the hands, arms, neck, and legs in a West Indian woman who applied a bleaching wax containing mequinol for 2 to 3 months to lighten the colour of her skin.[1]

1. Boyle J, Kennedy CTC. British cosmetic regulations inadequate. *BMJ* 1984; **288:** 1998–9.

Pigmentation disorders. References.
1. Fleischer AB, *et al*. The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol* 2000; **42:** 459–67.
2. Njoo MD, *et al*. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. *J Am Acad Dermatol* 2000; **42:** 760–9.
3. Ortonne JP, *et al*. Safety and efficacy of combined use of 4-hydroxyanisole (mequinol) 2%/tretinoin 0.01% solution and sunscreen in solar lentigines. *Cutis* 2004; **74:** 261–4.
4. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. *Cutis* 2004; **74:** 319–22.
5. Draelos ZD. The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin effectively improves the appearance of solar lentigines in ethnic groups. *J Cosmet Dermatol* 2006; **5:** 239–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Leucodin; ***Fr.***: Any; Clairodermyl; Creme des 3 Fleurs d'Orient†; Leucodinine B; ***Gr.***: Leucodinine-M; ***Spain***: Novo-Dermoquinona.

Multi-ingredient Preparations. ***Canad.***: Solage; ***USA***: Solage†.

Meradimate *(USAN, rINN)*

Menthyl *O*-Aminobenzoate; Menthyl Anthranilate; Méradimate; Meradimato; Meradimatum; Мерадимат.

5-Methyl-2-(1-methylethyl)-cyclohexyl 2-aminobenzoate.

$C_{17}H_{25}NO_2$=275.4

CAS — 134-09-8.

UNII — J9QGD60OUZ.

NOTE. Do not confuse with methyl anthranilate (p. 1714.2). Neo-Heliopan MA is a trade name that has been used for meradimate.

Pharmacopoeias. In *US*.

USP 36: (Meradimate). Store in airtight containers.

Profile

Meradimate is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Fotocrem Ultra; ***Austral.***: Blistex Ultra Lip Balm; ***Canad.***: Blistex Ultra Protection Lip Balm; Exact Lip Balm Year-Round Protection; Kids Sunscreen; Lip Conditioner Lip Balm; Marcelle Essentials; Marcelle Multi-Defense; Spray-on Sunscreen; Spray-on Sunscreen; Watkins Aloe Vera Botanical Lip Balm; Zoom Protective Lip Cream; ***Chile***: Proteccion Ultra; ***USA***: A-Fil; Blistex Ultra Protection; Catrix Correction; Hawaiian Tropic Baby Faces; Hawaiian Tropic Protective Tanning Dry; Hawaiian Tropic; Hawaiian Tropic; Hawaiian Tropic; Hawaiian Tropic; Herpecin-L; Lip Tone; Neutrogena; Neutrogena; Neutrogena.

Ammoniated Mercury

Aminomercuric Chloride; Hydrargyri Aminochloridum; Hydrargyrum Amidochloratum; Hydrargyrum Ammoniatum; Hydrargyrum Praecipitatum Album; Mercuric Amidochloride; Mercuric Ammonium Chloride; Mercurio amoniacal; Mercury Amide Chloride; Mercury Aminochloride; Precipitado blanco (de mercurio); White Precipitate; Хлористый Меркураммоний.

NH_2HgCl=252.1

CAS — 10124-48-8.

ATC — D08AK01.

ATC Vet — QD08AK01.

UNII — JD546Z56F0.

NOTE. 'White Precipitate' has also been used as a name for Precipitated Mercurous Chloride.

Pharmacopoeias. In *US*.

USP 36: (Ammoniated Mercury). A white amorphous powder or pulverulent pieces; odourless. It is stable in air, but darkens on exposure to light. Insoluble in water and in alcohol; readily soluble in warm hydrochloric, nitric, and acetic acids. Protect from light.

Profile

Ammoniated mercury was formerly used topically in the treatment of skin infections and psoriasis but the use of such mercurial preparations is generally deprecated. Frequent or prolonged application to large areas or to broken skin or mucous membranes can cause mercury poisoning (see p. 2556.1) and use on infants has produced acrodynia (pink disease). Ammoniated mercury is also a potent sensitiser and can produce allergic reactions.

Homoeopathy

Ammoniated mercury has been used in homoeopathic medicines under the following names: Mercurius praecipitatus albus; Merc praecip alb.

Effects on the kidneys. Of 60 patients who were found to have nephrotic syndrome, 32 had used skin-lightening creams containing 5 to 10% of ammoniated mercury.[1] Concentrations of mercury in the urine of these patients were up to 250 nanograms/mL compared with a usual upper limit of 80 nanograms/mL. Of 26 patients followed up for up to 2 years, 13 had no remission or response to treatment; 6 of these had used skin lighteners.

1. Barr RD, *et al*. Nephrotic syndrome in adult Africans in Nairobi. *BMJ* 1972; **2:** 131–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Cz.***: Homeogene 9; Homeovox.

Mesulphen *(BAN)*

Dimethyldiphenylene Disulphide; Dimethylthianthrene; Mesulfeeni; Mesulfen (pINN); Mesulfen; Mésulfène; Mesulfeno; Mesulfenum; Месульфен.

It consists mainly of 2,7-dimethylthianthrene.

$C_{14}H_{12}S_2$=244.4

CAS — 135-58-0.

ATC — D10AB05; P03AA03.

ATC Vet — QD10AB05; QP53AA01.

UNII — EG6V6W7WDD.

Pharmacopoeias. *Jpn* includes thianthol, a mixture of 2,7-dimethylthianthrene and ditolyl disulfide.

Profile

Mesulphen has been used as a parasiticide and antipruritic in a range of skin disorders including acne, scabies, and seborrhoea. Sensitivity to mesulphen has occasionally been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Soufrol.

Methoxsalen *(BAN)*

Ammoidin; Amoidina; Methoxalenum; 8-Methoxypsoralen; Metoksaleeni; Metoksalen; Metoxalen; Metoxaleno; Metoxipsoraleno; 8-MOP; Xanthotoxin; Xantotoxina; Метоксален.

9-Methoxyfuro[3,2-*g*]chromen-7-one; 9-Methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one.

$C_{12}H_8O_4$=216.2

CAS — 298-81-7.

ATC — D05AD02; D05BA02.

ATC Vet — QD05AD02; QD05BA02.

UNII — U4VJ29L7BQ.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Methoxsalen). White to cream-coloured, odourless, fluffy, needle-like crystals. Practically insoluble in water; sparingly soluble in boiling water and in ether; soluble in boiling alcohol, in acetone, in acetic acid, in propylene glycol, and in benzene; freely soluble in chloroform. Protect from light.

Uses and Administration

Methoxsalen, a psoralen, is a constituent of the seeds of *Ammi majus* and the roots of *Heracleum candicans*. It is a photosensitiser that markedly increases skin reactivity to long-wavelength ultraviolet radiation (320 to 400 nm), an effect used in photochemotherapy or PUVA [psoralen (P) and high-intensity long-wavelength UVA irradiation]. In the presence of UVA methoxsalen bonds with DNA, inhibiting DNA synthesis and cell division, and can lead to cell injury. Recovery from the cell injury may be followed by increased melanisation of the epidermis and thickening

of the stratum corneum. Methoxsalen may also increase pigmentation by an action on melanocytes.

PUVA is used to treat idiopathic vitiligo and severe, recalcitrant, disabling psoriasis not adequately responsive to conventional topical therapy. It may also be useful in selected cases of atopic eczema and polymorphic light eruptions and may be used in T-cell lymphomas such as mycosis fungoides.

Methoxsalen is given orally or applied topically in PUVA regimens. *Differing oral dosage forms of methoxsalen may have significantly varying bioavailabilities and times to onset of photosensitisation.* The UVA exposure dose should generally be based on prior measurement of the minimal phototoxic dose although it can be calculated with regard to the skin type of the patient if phototoxic dose testing cannot be carried out.

- To repigment **vitiliginous** areas, methoxsalen is given in a dose of 20 mg or up to 600 micrograms/kg *orally* 2 to 4 hours before measured periods of exposure to UVA, depending on the preparation. Treatment is usually given twice a week or on alternate days, but always at least 48 hours apart.
- Methoxsalen may also be applied *topically* to repigment small, well-defined vitiliginous lesions. Preparations containing up to 1% have been used but dilution to 0.1 or 0.01% may be necessary to avoid adverse cutaneous effects. The surrounding skin should be protected by an opaque sunscreen. Some suggest that the treated area should be exposed to UVA soon after application while others recommend waiting up to 2 hours. After exposure the lesions should be washed and protected from light; protection may be necessary for up to 48 hours or longer. Treatment is repeated usually once weekly. Significant repigmentation may not appear until after 6 to 9 months of treatment.
- For the treatment of **psoriasis** a dose of up to about 600 micrograms/kg *orally* is given 1.5 to 3 hours before UVA, depending on the preparation. Treatment is usually given twice a week although increased frequencies, but with at least 48-hour intervals between doses, have been suggested. If there is no response or only minimal response after the fifteenth PUVA treatment some suggest that the dosage may be increased by 10 mg and that this higher dose be used for the remainder of the course of treatment.
- Methoxsalen may also be used *topically* with UVA exposure for the treatment of psoriasis. For direct application to affected areas of skin a preparation containing about 0.15% (or diluted to 0.015% if necessary to avoid adverse cutaneous effects) is applied 15 minutes before UVA exposure. Alternatively the patient may take a whole body bath for 15 minutes in a methoxsalen solution, followed immediately by UVA exposure. UK guidelines (see also Skin Disorders, below) suggest a typical concentration of methoxsalen 2.6 mg/litre for such solutions although higher concentrations (up to about 3.7 mg/litre) have been used. Hand and foot soaks may be used to treat only those affected areas; a solution containing methoxsalen 3 mg/litre may be used with the affected areas immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. Baths or soaks are generally given twice a week.

Psoralen itself has also been used.

Administration. The dose of methoxsalen is usually calculated on the basis of body-weight. This method of dose calculation produces a considerable difference between the doses received by heavy and light patients. A study in 41 patients with psoriasis[1] suggested that using methoxsalen 25 mg/m^2 gave more consistent plasma concentrations and may reduce the potential for burning in heavy patients and prevent underdosing in light patients undergoing PUVA therapy.

1. Sakuntabhai A, *et al.* Calculation of 8-methoxypsoralen dose according to body surface area in PUVA treatment. *Br J Dermatol* 1995; **133:** 919–23.

PUVA. PUVA combines psoralens with UVA irradiation. The psoralens may be given directly to the patient, either orally or topically, and the patient is then exposed to UVA. In extracorporeal PUVA (extracorporeal photochemotherapy; photopheresis), an oral dose of a psoralen is given, after which the patient's leucocytes are isolated, exposed to UVA extracorporeally, and then reinfused. In another method of extracorporeal photopheresis methoxsalen is added directly to leucocytes that have already been removed from the patient. The mixture is then treated with UVA after which it is returned to the patient; the total dose of methoxsalen used by this method is lower than that used orally. PUVA has been used in many disorders including skin disorders, mycosis fungoides, and organ and tissue transplant rejection (below).

MYCOSIS FUNGOIDES. PUVA therapy is used in the treatment of the manifestations of cutaneous mycosis fungoides and Sèzary syndrome, two forms of cutaneous T-cell lymphoma (see p. 698.3). Extracorporeal PUVA therapy (photopheresis; see above) has also been used,[1-6] particularly for disease with erythrodermic features. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests a usual treatment cycle of 2 consecutive days, which is repeated every 2 to 4 weeks. More frequent treatment may be given to symptomatic patients and those with a high peripheral blood tumour burden. Response is assessed every 3 months and then, when complete or maximal response has occurred, treatment is tapered to every 6 to 12 weeks before stopping. Relapse may be treated with the same schedule. After the first 3 months of therapy, treatment should generally be continued for a further 3 months in patients with stable disease (no response). However, consideration should be given to stopping treatment, or using combination therapy (photopheresis with interferon alfa and/or bexarotene), if there is disease progression. At 6 months and beyond, treatment should be stopped, or combination therapy considered, in patients with stable or progressive disease, but for those already receiving combination therapy, photopheresis should be stopped.

1. Duvic M, *et al.* Photopheresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; **35:** 573–9.
2. Zic JA, *et al.* Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996; **35:** 935–45.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
4. Rubegni P, *et al.* Extracorporeal photochemotherapy in long-term treatment of early stage cutaneous T-cell lymphoma. *Br J Dermatol* 2000; **143:** 894–6.
5. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. *Dermatol Ther* 2003; **16:** 337–46.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154:** 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158:** 659–78.

ORGAN AND TISSUE TRANSPLANTATION. PUVA[1,2] and extracorporeal PUVA therapy[3-6] (photopheresis; see above) have been tried in both acute and chronic graft-versus-host disease (GVHD) that is unresponsive to usual treatment (see Haematopoietic Stem Cell Transplantation, p. 1933.1). As well as improvements in GVHD, particularly cutaneous manifestations, PUVA therapies have enabled the doses of corticosteroids and other immunosuppressants to be reduced. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests, for chronic GVHD, a usual treatment cycle of 2 consecutive days, repeated every 2 weeks. Response is assessed after 3 months and treatment reduced to once every 4 weeks if there has been a complete or partial response. Treatment is then re-assessed every 3 months and tapered or stopped when a complete or maximal response has occurred. It should be stopped if there is no response or disease progression.

Photopheresis has also been tried in treating rejection of solid organ transplants,[3,6,8] particularly after heart transplantation (p. 1934.2). It also showed promise in a study[9] of the prevention of heart transplant rejection.

1. Bonanomi S, *et al.* Bath PUVA therapy in pediatric patients with drug-resistant cutaneous graft-versus-host disease. *Bone Marrow Transplant* 2001; **28:** 631–2.
2. Furlong T, *et al.* Psoralen and ultraviolet A irradiation (PUVA) as therapy for steroid-resistant cutaneous acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; **8:** 206–12.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
4. Foss FM, *et al.* Extracorporeal photopheresis in chronic graft-versus-host disease. *Bone Marrow Transplant* 2002; **29:** 719–25.
5. Kanold J, *et al.* Extracorporeal photochemotherapy for graft versus host disease in pediatric patients. *Transfus Apheresis Sci* 2003; **28:** 71–80.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154:** 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158:** 659–78.
8. Dall'Amico R, Murer L. Extracorporeal photochemotherapy: a new therapeutic approach for allograft rejection. *Transfus Apheresis Sci* 2002; **26:** 197–204.
9. Barr ML, *et al.* Photopheresis for the prevention of rejection in cardiac transplantation. *N Engl J Med* 1998; **339:** 1744–51.

SKIN DISORDERS. PUVA has been used in many skin disorders and guidelines have been published by the British Photodermatology Group,[1,2] which are summarised as follows:

- Indications for PUVA in chronic plaque **psoriasis** include severe extensive psoriasis unresponsive to conventional topical therapies, relapse within 3 to 6 months of successful topical treatment, or patient refusal of topical treatment if UVB phototherapy has failed (see p. 1688.1 for a discussion of the various treatments of psoriasis). Initial UVA exposure should preferably be determined on the basis of prior measurement of the minimal phototoxic dose rather than on the skin type. Increases in UVA irradiation are then calculated as a percentage of previous doses.

  Methoxsalen in an oral dose of 600 micrograms/kg given 2 hours before UVA exposure is the widely accepted standard regimen. Alternatively, 5-methoxypsoralen 1.2 mg/kg, again 2 hours before UVA exposure, can be given and appears to be almost free of the adverse reactions such as nausea, pruritus, and erythema induced by methoxsalen. However, until the clinical efficacy of 5-methoxypsoralen has been clearly shown, methoxsalen should remain the psoralen of choice for most clinical situations.

  Alternatives to oral PUVA are baths or soaks using methoxsalen or trioxysalen. For whole body bathing a concentration of methoxsalen 2.6 mg/litre is typically utilised with the patient bathing for 15 minutes followed by immediate exposure to UVA. For hand and foot soaks a concentration of methoxsalen 3 mg/litre is used with the affected area immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. For trioxysalen a concentration of about 330 micrograms/litre is used for a 15-minute whole body bath or hand and foot soak followed by immediate UVA exposure for whole body therapy, or a 30 minute delay before hand and foot UVA exposure. Whole body baths or hand and foot soaks are given twice each week.

  Methoxsalen may also be applied topically to the affected areas. A concentration of about 0.15% (or 0.015% if erythema occurs) is used in an emulsion, or 0.005% in an aqueous gel, and applied 15 minutes before UVA exposure.

  PUVA treatment should be stopped as soon as disease clearance is achieved; maintenance PUVA should be avoided to minimise cumulative UVA exposure, but may be considered if there is rapid relapse. A combination of PUVA with acitretin (300 to 700 micrograms/kg orally) or etretinate (0.5 to 1 mg/kg orally) may be considered in patients who have reached 50 treatment sessions or relapsed within 6 months of PUVA. PUVA and methotrexate are also effective for severe psoriasis but should be reserved for such cases because of the possible increased risk of skin cancer
- Use of oral PUVA twice weekly with methoxsalen 600 micrograms/kg or 5-methoxypsoralen 1.2 mg/kg has been effective in many patients with **vitiligo** (see Pigmentation Disorders, p. 1687.2). If patches are well demarcated topical application of methoxsalen 0.15% may be preferable
- In **mycosis fungoides** PUVA is an effective symptomatic treatment for early disease and a useful adjunct for late-stage disease but optimal regimens have not been established (see above)
- PUVA is effective for atopic **eczema** (p. 1684.1) but clearance is less certain than for psoriasis, twice the number of treatments may be needed, and relapse is more frequent. It should therefore be reserved for severe disease unresponsive to conventional treatments. Optimal regimens have not been established
- In **polymorphic light eruptions** (see Photosensitivity Disorders, p. 1686.2) PUVA is effective in up to 90% of patients but is only indicated in those who are frequently or severely affected despite the regular use of high-protection broad-spectrum sunscreens. Several arbitrary regimens are in use
- Variable results have also been reported in a variety of other disorders but data has been insufficient to establish precise guidelines. Such disorders include actinic prurigo, alopecia areata, aquagenic pruritus, chronic actinic dermatitis, granuloma annulare, lichen planus, nodular prurigo, pityriasis lichenoides, localised scleroderma, solar urticaria, and urticaria pigmentosa. In most cases relapse occurs in the absence of maintenance therapy and PUVA should usually only be tried as a last resort.

Extracorporeal PUVA has been tried in patients with severe epidermolysis bullosa acquisita,[3,4] lichen planus,[5] and scleroderma.[6,7]

1. British Photodermatology Group. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; **130:** 246–55.
2. Halpern SM, *et al.* Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2000; **142:** 22–31. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Topical%20PUVA%20Therapy.pdf (accessed 23/07/10)
3. Miller JL, *et al.* Remission of severe epidermolysis bullosa acquisita induced by extracorporeal photochemotherapy. *Br J Dermatol* 1995; **133:** 467–71.
4. Gordon KB, *et al.* Treatment of refractory epidermolysis bullosa acquisita with extracorporeal photochemotherapy. *Br J Dermatol* 1997; **136:** 415–20.
5. Guyot AD, *et al.* Treatment of refractory erosive oral lichen planus with extracorporeal photochemotherapy: 12 cases. *Br J Dermatol* 2007; **156:** 553–6.
6. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
7. Knobler RM, *et al.* A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *J Am Acad Dermatol* 2006; **54:** 793–9.

Adverse Effects

Methoxsalen given orally commonly causes nausea and less frequently mental effects including insomnia, nervousness, and depression.

Photochemotherapy or PUVA (see under Uses and Administration, p. 1712.1) may cause pruritus and mild transient erythema. Other effects include oedema, dizziness, headache, vesiculation, bulla formation, acneform eruption, and severe skin pain. Overexposure to sunlight or UVA radiation may produce severe burns in patients being treated with psoralens. Hypertrichosis, pigmentation alterations of skin or nails, and onycholysis, have also been reported. PUVA can produce premature ageing of the skin, and may be associated with an increased risk of malignant cutaneous neoplasms.

Carcinogenicity. See under Effects on the Skin, below.

There has been concern about a possible increased risk of noncutaneous malignancies associated with PUVA. However, a long-term study of 1380 patients followed for 20 years reported no overall increase in solid malignancies, lymphoma, or leukaemia.[1]

1. Stern RS, Väkevä LH. PUVA Follow-up Study. Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. *J Invest Dermatol* 1997; **108:** 897–900.

Effects on the eyes. Free methoxsalen has been detected in the lens of the eye for at least 12 hours after oral doses.[1] It may become integrated into the structure of the lens if there is exposure to UV light, promoting cataract formation in patients who fail to wear suitable eye protection for 12 to 24 hours after methoxsalen ingestion.[2] However, provided that eye protection is used there appears to be no significant dose-dependent increase in the risk of cataract formation,[3] although a higher risk of developing nuclear sclerosis and posterior subcapsular opacities has been noted in patients who have received more than 100 treatments.[4] Other ocular effects include dose-related transient visual-field defects reported in 3 patients receiving PUVA therapy.[5] Psoralens may also increase the sensitivity of the retina to visible light.[6]

1. Lerman S, *et al*. Potential ocular complications from PUVA therapy and their prevention. *J Invest Dermatol* 1980; **74:** 197–9.
2. Woo TY, *et al*. Lenticular psoralen photoproducts and cataracts of a PUVA-treated psoriatic patient. *Arch Dermatol* 1985; **121:** 1307–8.
3. See J-A, Weller P. Ocular complications of PUVA therapy. *Australas J Dermatol* 1993; **34:** 1–4.
4. Stern RS, *et al*. Ocular findings in patients treated with PUVA. *J Invest Dermatol* 1985; **85:** 269–73.
5. Fenton DA, Wilkinson JD. Dose-related visual-field defects in patients receiving PUVA therapy. *Lancet* 1983; **i:** 1106.
6. Souêtre E, *et al*. 5-Methoxypsoralen increases the sensitivity of the retina to light in humans. *Eur J Clin Pharmacol* 1989; **36:** 59–61.

Effects on the hair. Hypertrichosis was noticed in 15 of 23 female patients receiving PUVA therapy compared with 2 of 14 patients treated with UVA alone.[1]

1. Rampen FHJ. Hypertrichosis in PUVA-treated patients. *Br J Dermatol* 1983; **109:** 657–60.

Effects on the immune system. PUVA therapy appears to have immunosuppressive effects and inhibits lymphocytes, polymorphonuclear leucocytes, and Langerhans' cells.[1-3] It is capable of inducing antinuclear antibody formation and a syndrome similar to systemic lupus syndrome has developed during treatment.[4,5] An immunological basis has also been suspected for the development of nephrotic syndrome in one patient who received PUVA therapy.[6]

See also Hypersensitivity, below.

1. Farber EM, *et al*. Long-term risks of psoralen and UV-A therapy for psoriasis. *Arch Dermatol* 1983; **119:** 426–31.
2. Morison WL, *et al*. Abnormal lymphocyte function following long-term PUVA therapy for psoriasis. *Br J Dermatol* 1983; **108:** 445–50.
3. Chang A, *et al*. PUVA and UVB inhibit the intra-epidermal accumulation of polymorphonuclear leukocytes. *Br J Dermatol* 1988; **119:** 281–7.
4. Bruze M, *et al*. Fatal connective tissue disease with antinuclear antibodies following PUVA therapy. *Acta Derm Venereol (Stockh)* 1984; **64:** 157–60.
5. Bruze M, Ljunggren B. Antinuclear antibodies appearing during PUVA therapy. *Acta Derm Venereol (Stockh)* 1985; **65:** 31–6.
6. Lam Thuon Mine LTK, *et al*. Nephrotic syndrome after treatment with psoralens and ultraviolet A. *BMJ* 1983; **287:** 94–5.

Effects on the skin. *MALIGNANT NEOPLASMS.* Squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, actinic keratosis, Bowen's disease, and malignant melanoma have all been reported during or after cessation of PUVA.[1-3] There have been several large long-term follow-up studies to assess the risk of **non-melanoma** skin cancer in patients receiving PUVA therapy. Early studies from Europe found no clear evidence that PUVA was independently carcinogenic but did find that previous treatment with arsenic, methotrexate, or ionising radiation increased the incidence of skin tumours.[4] Studies from the USA have found an increase in the incidence of basal cell carcinoma and squamous cell carcinoma independent of other treatment,[5] which was dose-related in some studies.[6] Male genitalia appeared to be particularly susceptible.[7] It has been suggested that the differences between the findings might be due to the fact that in Europe higher and fewer doses are used and the median total dose employed may be only 29% of that used in the USA.[8] However, further studies from northern Europe also found a dose-related increase in the risk of developing squamous cell carcinomas.[9-11] One small series suggested that about 50% of the recipients of high-dose PUVA went on to develop squamous cell carcinomas or premalignant lesions.[12] While some European workers have findings that confirm the increased susceptibility of the male genitalia[13] others have failed to find any such evidence.[14,15] Ongoing surveillance of patients is encouraged as US data[16,17] show the risk of skin cancers and genital tumours to persist long-term after stopping PUVA therapy. A few patients have gone on to develop metastatic disease.[18,19]

There are anecdotal reports of **malignant melanomas** occurring in patients who had received PUVA. A prospective study[20] in 1380 patients with psoriasis who were first treated with PUVA in 1975 or 1976 found that the risk of melanoma increases about 15 years after the first treatment with PUVA and that the risk was increased especially in patients who had received 250 treatments or more. The authors suggested that long-term PUVA should therefore be used with caution, especially in younger patients. Further follow-up of this group[21] found the incidence of melanoma to increase over time. However, a similar follow-up study[11] of 4799 patients treated with PUVA found no increase in the risk for malignant melanoma. Comparing their findings with the earlier study, the authors suggested that the results might differ because one-fifth of their cohort had received bath PUVA in which lower UVA doses are used. The comment has also been made[22] that patients receiving long-term therapy should be followed up carefully and that such therapy should not be used in patients at risk for melanoma.

A study[23] of follow-up data on patients who had received trioxysalen bath PUVA did not find an increase in risk of developing either squamous cell carcinoma or malignant melanoma, but the authors suggested that further study is needed to determine the carcinogenicity of trioxysalen PUVA.

1. Reshad H, *et al*. Cutaneous carcinoma in psoriatic patients treated with PUVA. *Br J Dermatol* 1984; **110:** 299–305.
2. Kemmett D, *et al*. Nodular malignant melanoma and multiple squamous cell carcinomas in a patient treated by photochemotherapy for psoriasis. *BMJ* 1984; **289:** 1498.
3. Suurmond D, *et al*. Skin cancer and PUVA maintenance therapy for psoriasis. *Br J Dermatol* 1985; **113:** 485–6.
4. Henseler T, *et al*. Skin tumors in the European PUVA study. *J Am Acad Dermatol* 1987; **16:** 108–16.
5. Forman AB, *et al*. Long-term follow-up of skin cancer in the PUVA-48 cooperative study. *Arch Dermatol* 1989; **125:** 515–19.
6. Stern RS, *et al*. Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 1988; **91:** 120–4.
7. Stern RS, *et al*. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; **322:** 1093–7.
8. Moseley H, Ferguson J. Photochemotherapy: a reappraisal of its use in dermatology. *Drugs* 1989; **38:** 822–37.
9. Bruynzeel I, *et al*. High single-dose' European PUVA regimen also causes an excess of non-melanoma skin cancer. *Br J Dermatol* 1991; **124:** 49–55.
10. Lindelöf B, *et al*. PUVA and cancer: a large-scale epidemiological study. *Lancet* 1991; **338:** 91–3.
11. Lindelöf B, *et al*. PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; **141:** 108–12.
12. Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. *Br J Dermatol* 1994; **131:** 215–19.
13. Perkins W, *et al*. Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; **336:** 1248.
14. Wolff K, Hönigsmann H. Genital carcinomas in psoriasis patients treated with photochemotherapy. *Lancet* 1991; **337:** 439.
15. Aubin F, *et al*. Genital squamous cell carcinoma in men treated by photochemotherapy: a cancer registry-based study from 1978 to 1998. *Br J Dermatol* 2001; **144:** 1204–6.
16. Stern RS, *et al*. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol* 2002; **47:** 33–9.
17. Nijsten TEC, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol* 2003; **121:** 252–8.
18. Lewis FM, *et al*. Metastatic squamous-cell carcinoma in patient receiving PUVA. *Lancet* 1994; **344:** 1157.
19. Stern RS. Metastatic squamous cell cancer after psoralen photochemotherapy. *Lancet* 1994; **344:** 1644–5.
20. Stern RS, *et al*. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 1997; **336:** 1041–5.
21. Stern RS. The PUVA Follow Up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; **44:** 755–61.
22. Wolff K. Should PUVA be abandoned? *N Engl J Med* 1997; **336:** 1090–1.
23. Hannuksela-Svahn A, *et al*. Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. *Br J Dermatol* 1999; **141:** 497–501.

NON-MALIGNANT SKIN DISORDERS. Toxic pustuloderma, marked by erythema and superficial pustular lesions, has been reported in a patient given PUVA therapy for mycosis fungoides.[1] Bullous pemphigoid occurring, or recurring, has been seen in patients treated with PUVA, usually for psoriasis.[2] A case of lichen planus pemphigoides has also been described in a woman treated with topical PUVA.[3] Another effect sometimes associated with PUVA is severe skin pain;[4,5] the pain may respond to treatment with topical capsaicin.[5] Long-term PUVA treatment accelerates ageing of the skin.[6]

1. Yip J, *et al*. Toxic pustuloderma due to PUVA treatment. *Br J Dermatol* 1991; **125:** 401–2.
2. Barnadas MA, *et al*. Bullous pemphigoid in a patient with psoriasis during the course of PUVA therapy: study by ELISA test. *Int J Dermatol* 2006; **45:** 1089–92.
3. Kuramoto N, *et al*. PUVA-induced lichen planus pemphigoides. *Br J Dermatol* 2000; **142:** 509–12.
4. Burrows NP, *et al*. PUVA-induced skin pain. *Br J Dermatol* 1993; **129:** 504.
5. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131:** 584–5.
6. Sator P-G, *et al*. Objective assessment of photoageing effects using high-frequency ultrasound in PUVA-treated psoriasis patients. *Br J Dermatol* 2002; **147:** 291–8.

Hypersensitivity. Hypersensitivity reactions to methoxsalen and PUVA therapy occur rarely but there have been reports of drug-induced fever,[1] bronchoconstriction,[2] and contact dermatitis.[3] Cases of anaphylaxis have also been attributed to methoxsalen[4] and 5-methoxypsoralen.[5]

1. Tóth Kása I, Dobozy A. Drug fever caused by PUVA treatment. *Acta Derm Venereol (Stockh)* 1985; **65:** 557–8.
2. Ramsay B, Marks JM. Bronchoconstriction due to 8-methoxypsoralen. *Br J Dermatol* 1988; **119:** 83–6.
3. Takashima A, *et al*. Allergic contact and photocontact dermatitis due to psoralens in patients with psoriasis treated with topical PUVA. *Br J Dermatol* 1991; **124:** 37–42.
4. Park JY, *et al*. Anaphylaxis to 8-methoxypsoralen during photochemotherapy. *Photodermatol Photoimmunol Photomed* 2003; **19:** 37–8.
5. Legat FJ, *et al*. Anaphylaxis to 5-methoxypsoralen during photochemotherapy. *Br J Dermatol* 2001; **145:** 821–2.

Precautions

Methoxsalen should not generally be given to patients with diseases associated with light sensitivity such as porphyria, although it may be used with care in some photosensitivity disorders to decrease sensitivity to sunlight. Other contra-indications include aphakia, melanoma or a history of melanoma, and invasive squamous cell carcinoma. It is generally recommended that PUVA therapy should not be used in children. Methoxsalen should be used with caution in patients with hepatic impairment.

Patients should not sunbathe for 24 hours before and 48 hours after PUVA treatment. They should avoid exposure to sunlight, even through glass or cloud cover for at least 8 hours after methoxsalen ingestion and should wear wrap-around UVA absorbing glasses for 24 hours after ingestion. Photosensitivity is more prolonged after topical application and treated skin should be protected from exposure to sunlight for at least 12 to 48 hours, and possibly for up to a week. Unless specific treatment is required male genitalia should be shielded during PUVA therapy. It has been recommended that patients undergo an ophthalmic examination before starting therapy and at regular intervals thereafter, especially those at increased risk of cataracts. Patients should also receive regular examinations for signs of premalignant or malignant skin lesions. Anti-nuclear antibody titre may be tested before starting therapy, particularly if there is a suggestion of connective tissue disease; frequent evaluation during treatment is probably not necessary for patients with uncomplicated psoriasis, an initial negative test, and no symptoms of connective tissue disease.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methoxsalen as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Methoxsalen should be used with caution with other drugs also known to cause photosensitivity. It inhibits the action of cytochrome P450 isoenzyme CYP2A6, and may increase plasma concentrations of drugs metabolised via this enzyme.

Antiepileptics. Failure of PUVA treatment due to abnormally low serum concentrations of methoxsalen in a patient with epilepsy was probably a result of induction of hepatic enzymes by *phenytoin*.[1]

1. Staberg B, Hueg B. Interaction between 8-methoxypsoralen and phenytoin. *Acta Derm Venereol (Stockh)* 1985; **65:** 553–5.

Emollients. Some emollient preparations may have a photoprotective effect, and if applied immediately before UVA irradiation could interfere with the efficacy of PUVA therapy.[1,2]

1. Hudson-Peacock MJ, *et al*. Photoprotective action of emollients in ultraviolet therapy of psoriasis. *Br J Dermatol* 1994; **130:** 361–5.
2. Otman SGH, *et al*. Modulation of ultraviolet (UV) transmission by emollients: relevance to narrowband UVB phototherapy and psoralen plus UVA photochemotherapy. *Br J Dermatol* 2006; **154:** 963–8.

Food. Some foods, for example, celery, parsnip, and parsley, contain psoralens and eating large quantities may increase the risk of phototoxicity with methoxsalen. A patient[1] who ate a large quantity of celery soup the evening before and 2 hours before undergoing PUVA therapy for atopic eczema developed severe phototoxicity after treatment, which was attributed to the additive effects of methoxsalen and psoralens contained in the celery.

1. Boffa MJ, *et al.* Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol* 1996; **135:** 334.

Melatonin. For the effect of methoxsalen on melatonin, see p. 2552.2.

Xanthines. For mention of the effect of systemic methoxsalen on the metabolism of theophylline, see Methoxsalen, under Interactions of Theophylline, p. 1236.2.

Pharmacokinetics

When taken orally methoxsalen is well but variably absorbed from the gastrointestinal tract and there is considerable interindividual variation in peak serum concentrations. Depending on the oral formulation used increased photosensitivity is present 1 hour after a dose, reaches a peak at about 1 to 4 hours, and disappears after about 8 hours. Methoxsalen is highly protein bound. It appears to be preferentially taken up by epidermal cells. It also diffuses into the lens of the eye. Methoxsalen is almost completely metabolised. About 95% of a dose is excreted in the urine within 24 hours. The photosensitising action of methoxsalen may persist for several days after topical application. The erythema induced by oral or topical PUVA is usually delayed and peaks after 2 to 3 days.

References.

1. de Wolff FA, Thomas TV. Clinical pharmacokinetics of methoxsalen and other psoralens. *Clin Pharmacokinet* 1986; **11:** 62–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Oxsoralen Ultra; ***Austral.***: Oxsoralen†; ***Austria***: Oxsoralen; ***Belg.***: Mopsoralen; ***Braz.***: Oxsoralen; ***Canad.***: Oxsoralen; Ultramop†; ***Chile***: Oxsoralen; ***China***: Meladinine (敏柏宁); ***Cz.***: Oxsoralen; Uvadex; ***Fr.***: Meladinine; Uvadex; ***Ger.***: Meladinine; Uvadex; ***Gr.***: Melaoline; Uvadex; ***Hong Kong***: Oxsoralen; ***Hung.***: Oxsoralen; ***India***: Manaderm†; Meladerm; Melanocyl; Melcyl; Melonil; ***Indon.***: Delsoralen; Oxsoralen; ***Irl.***: Deltasoralen†; ***Jpn***: Oxsoralen; ***Malaysia***: Oxsoralen†; ***Mex.***: Dermox; Meladinina; Oxsoralen; ***Neth.***: Geroxalen; Uvadex; ***NZ***: Oxsoralen†; ***Pol.***: Geralen†; Oxsoralen; ***Port.***: Uvadex; ***Rus.***: Oxsoralen (Оксорален); ***S.Afr.***: Oxsoralen†; ***Singapore***: Meladinine†; Oxsoralen; ***Spain***: Oxsoralen; ***Switz.***: Meladinine†; Uvadex†; ***Thai.***: Meladinine; ***Turk.***: Geroxalen; Vitpso; ***UK***: Puvasoralen; ***USA***: Oxsoralen; Uvadex.

Multi-ingredient Preparations. ***India***: Melanocyl; Melonil.

Pharmacopoeial Preparations
USP 36: Methoxsalen Capsules; Methoxsalen Topical Solution.

5-Methoxypsoralen

Bergapteeni; Bergapten; Bergapteno; Bergaptenum; 5-Metoxipsoraleno; 5-MOP; 5-Метоксипсорален.
4-Methoxy-7*H*-furo[3,2-*g*]chromen-7-one.
$C_{12}H_8O_4$=216.2
CAS — 484-20-8.
ATC — D05BA03.
ATC Vet — QD05BA03.
UNII — 4FVK84C92X.

Profile

5-Methoxypsoralen is a photosensitiser with actions similar to those of methoxsalen (p. 1711.3). It may be given orally in the PUVA therapy (see under Methoxsalen, p. 1712.1) of psoriasis and vitiligo.

5-Methoxypsoralen is included in some cosmetic suntan preparations to enhance tanning but because of its potential phototoxicity this is considered unwise by authorities in Europe and the USA. Photosensitivity caused by 5-methoxypsoralen is sometimes known as Berloque dermatitis.

5-Methoxypsoralen is an ingredient of bergamot oil (p. 2455.1).

References.

1. McNeely W, Goa KL. 5-Methoxypsoralen: a review of its effects in psoriasis and vitiligo. *Drugs* 1998; **56:** 667–90.

Hypersensitivity. For mention of anaphylaxis associated with the use of 5-methoxypsoralen, see Hypersensitivity, under Adverse Effects of Methoxsalen, p. 1713.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Geralen; ***UK***: Pentaderm.

Methyl Anthranilate

Metilo, antranilato de; Metylu antranilan; Метилантранилат.
Methyl 2-aminobenzoate.
$C_8H_9NO_2$=151.2
CAS — 134-20-3.
UNII — 981I0C1E5W.

NOTE. Do not confuse with menthyl anthranilate (see Meradimate, p. 1711.2).

Profile

Methyl anthranilate has been used in sunscreen preparations. It is a constituent of several essential oils.

Mexenone *(BAN, pINN)*

Benzofenon-10; Benzophenone-10; Mexenona; Mexénone; Mexenonum; Мексенон.
2-Hydroxy-4-methoxy-4′-methylbenzophenone.
$C_{15}H_{14}O_3$=242.3
CAS — 1641-17-4.
UNII — ET1UGF4A0B.

Pharmacopoeias. In *Br.*

BP 2014: (Mexenone). A pale yellow odourless or almost odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone.

Profile

Mexenone, a substituted benzophenone, is a sunscreen (p. 1681.3) with actions similar to those of oxybenzone (p. 1715.3). It is effective against UVB and some UVA light (for definitions, see p. 1685.3)

Preparations

Pharmacopoeial Preparations
BP 2014: Mexenone Cream.

Monobenzone *(rINN)*

Benoquina; Éter monobencílico de la hidroquinona; Hydroquinone Monobenzyl Ether; Monobenzona; Monobenzonum; Монобензон.
4-Benzyloxyphenol.
$C_{13}H_{12}O_2$=200.2
CAS — 103-16-2.
ATC — D11AX13.
ATC Vet — QD11AX13.
UNII — 9L2KA76MG5.

Pharmacopoeias. In *US.*

USP 36: (Monobenzone). Store at a temperature not exceeding 30 degrees in airtight containers. Protect from light.

Uses and Administration

Monobenzone has actions similar to those of hydroquinone (p. 1705.1) but in some patients it also produces extensive and selective destruction of melanocytes. It is used locally for final, permanent depigmentation of normal skin in extensive vitiligo (see Pigmentation Disorders, p. 1687.2). Monobenzone is not recommended for freckling, chloasma, or hyperpigmentation following skin inflammation or due to photosensitisation after the use of certain perfumes. It has no effect on melanomas or pigmented naevi.

For vitiligo a cream containing monobenzone 20% is applied to the affected areas two or three times daily until a satisfactory response is obtained, and thereafter as necessary, usually about twice weekly. Depigmentation only becomes apparent when the preformed melanin pigments have been lost with the normal sloughing of the stratum corneum and this may take several months. If, however, no improvement is noted after 4 months, treatment should be stopped. Excessive exposure to sunlight should be avoided during treatment. After depigmentation the skin will be sensitive for the rest of the patient's life and a sunscreen must be used during sun exposure.

Adverse Effects and Precautions

Monobenzone may cause skin irritation and sensitisation. In some patients this is transient and the drug need not be withdrawn. In others, an eczematous sensitisation may occur. Excessive depigmentation may occur even beyond the areas under treatment and may produce unsightly patches.

Monobenzone frequently produces permanent depigmentation and should not be used as a substitute for hydroquinone.

Interactions

Agalsidase. For the recommendation that monobenzone not be used with agalsidase alfa or beta, see p. 2438.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Benoquin; ***India***: Benoquin; ***USA***: Benoquin†.

Pharmacopoeial Preparations
USP 36: Monobenzone Cream.

Monochloroacetic Acid

Chloroacetic Acid; Kwas chlorooctowy; Monocloroacético, ácido; Монохлоруксусная Кислота.
$C_2H_3O_2Cl$=94.49
CAS — 79-11-8.
UNII — 5GD84Y125G.

Profile

Preparations containing 50% of monochloroacetic acid are used as a caustic for the removal of plantar warts (p. 1689.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Warzenmittel†; ***Switz.***: Acetocaustine; ***USA***: Monocete.

Multi-ingredient Preparations. ***Turk.***: IL-33.

Motretinide *(USAN, rINN)*

Motretinid; Motretinida; Motrétinide; Motretinidi; Motretinidum; Ro-11-1430; Мотретинид.
(*all-trans*)-*N*-Ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide.
$C_{23}H_{31}NO_2$=353.5
CAS — 56281-36-8.
ATC — D10AD05.
ATC Vet — QD10AD05.
UNII — W786807KL1.

Profile

Motretinide is a retinoid structurally related to acitretin (p. 1690.3). Motretinide is used topically in the treatment of acne (p. 1682.2). It is applied in preparations containing 0.1%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Tasmaderm.

Nalfurafine Hydrochloride *(USAN, rINNM)*

AC-820; Hidrocloruro de nalfurafina; Nalfurafine, Chlorhydrate de; Nalfurafini Hydrochloridum; TRK-820; Нальфурафина Гидрохлорид.
(*E*)-*N*-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide hydrochloride.
$C_{28}H_{32}N_2O_5$,HCl=513.0
CAS — 152657-84-6 (nalfurafine); 152658-17-8 (nalfurafine hydrochloride).
ATC — V03AX01; V03AX02.
ATC Vet — QV03AX02.
UNII — 25CC4N0P8J.

Profile

Nalfurafine hydrochloride is a selective κ-opioid receptor agonist that is used in the management of treatment-resistant pruritus (p. 1687.3) in haemodialysis patients. It is given orally in a dose of 2.5 micrograms once daily in the evening, which may be increased to 5 micrograms once daily if required.

References.

1. Wikström B, *et al.* κ -Opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005; **16:** 3742–7.

2. Nakao K, Mochizuki H. Nalfurafine hydrochloride: a new drug for the treatment of uremic pruritus in hemodialysis patients. *Drugs Today* 2009; **45:** 323–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Remitch.

Naphthalan Liquid

Naftalan; Naphthalanic Oil; Naphthalanum Liquidum; Нафталановое Масло.

CAS — 37229-16-6.

Profile

Naphthalan liquid is an oil-like complex mixture of naphthene hydrocarbons and tars obtained from the oil fields of Azerbaijan and Croatia. It has analgesic, anti-inflammatory, and emollient properties and is used in the treatment of conditions such as psoriasis and in various musculoskeletal disorders. It is usually applied locally in the form of the oil or as an ointment or alternatively patients may bath in the oil.

References.
1. Vržogić P, *et al.* Naphthalan – a natural medicinal product. *Acta Dermatovenerol Croat* 2003; **11:** 178–84.

Octil Triazone

Ethylhexyl Triazone; Octiltriazona; Octyl Triazone; Октилтриазон.

2,4,6-Trianilino-*p*-(carbo-2′-ethylhexyl-1′-oxy)-1,3,5-triazine.

$C_{48}H_{66}N_6O_6$=823.1

CAS — 88122-99-0.

NOTE. Uvinul T 150 is a trade name that has been used for octil triazone.

Profile

Octil triazone is used as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cetaphil UV Defense; Fotoprotector Extrem; Fotoprotector; Lelco Ultrablock Extreme; Lelco Ultrablock†; ***Austral.***: Hamilton Quadblock; Sunsense Daily Face; Sunsense Moisturising Face; Sunsense Toddler Milk; Sunsense; ***Braz.***: Anthelios Helioblock Spray; Anthelios Helioblock W30; Helioblock†; Sunmax 60; Sunmax Acqua; ***Chile***: Ansolar; Ansolar; Emolan Gel Protector Solar; Eucerin Solar†; Eucerin; Eucerin; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Extrem†; Hyaluron; Nutraisdin; Photoderm AR†; Photoderm Max†; Photoderm Spot†; Uriage Crema Color; Uriage Crema Extra; Uriage Protector Solar†; ***Fr.***: Anthelios; Anthelios; Anthelios; SVR 100†; ***Ger.***: Daylong actinica†; ***Hong Kong***: Sunsense Clear Mist†; Sunsense Daily Face; Sunsense Toddler Milk; ***Malaysia***: Cetaphil UVA/UVB Defense; Sunsense Clear Mist†; Sunsense Daily Face; Sunsense Toddler Milk; ***Mex.***: Dermaglos Solar†; ***NZ***: Aquasun; Hamilton Quadblock; ***Singapore***: Cetaphil UVA/UVB; Sunsense Clear†; Sunsense Daily Face; Sunsense Moisturising Face; Sunsense Toddler Milk; ***Switz.***: Daylong actinica; ***Thai.***: Eucerin Sun Sensitive Skin†; ***UK***: Anthelios XL; ***Venez.***: Photoderm Max; Photoderm.

Octinoxate *(USAN, rINN)*

Ocinoxate; Octinoxato; Octinoxatum; Octyl methoxycinnamate; Оциноксат.

2-Ethylhexyl-*p*-methoxycinnamate; 3-(4-Methoxylphenyl)-2-propenoic acid 2-ethylhexyl ester.

$C_{18}H_{26}O_3$=290.4

CAS — 5466-77-3.

ATC — D02BA02.

ATC Vet — QD02BA02.

UNII — 4Y5P7MUD51.

NOTE. Escalol 557, Eusolex 2292, Neo-Heliopan AV, Parsol MCX, Tinosorb OMC, Uvinul MC 80, and Uvinul MC 80 N are trade names that have been used for octinoxate.

Pharmacopoeias. In *US.*

USP 36: (Octinoxate). Pale yellow oil. Insoluble in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Octinoxate, a substituted cinnamate, is used by topical application as a sunscreen (p. 1681.3). Cinnamate sunscreens effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p. 1685.3). Cinnamate sunscreens may therefore be used to prevent sunburn but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection against such photosensitivity. Cinnamates may occasionally produce photosensitivity reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Blistex Lip Conditioning Balm; Clear Zinke; ***Braz.***: Solaquin; ***Canad.***: Almay Hydracolor Lipstick†; Almay TLC Truly Lasting†; Anti-Aging Foundation; Aqua Fusion Teinte†; Aquaradiance†; Aquasource; Avon Beyond; Avon Sun Self-Tanning†; Ceramide Time Complex; Clinique Skin Supplies; Diorskin Sculpt; Feel Naturale†; Finish†; Hawaiian Tropic Dark Tanning†; Hawaiian Tropic Oil; Healthy Makeup†; Lip Balm; Luxiva Sheer Defense; Mac Hyper Real†; Mac Mineralize; Mac Select Tint†; Marcelle Sheer Tint; Moisture Extreme†; Photogenic Lumessence; Prescriptives Incredible†; Revlon Lipgloss†; Revlon Super Lustrous†; Sense Matte†; Sheer Protection†; Shiseido Benefiance Daytime; Shiseido Benefiance Daytime; Silkies Enriche; Skin Caviar; Ultra Color Rich Cool Bliss†; Ultra Facial Tinted Moisturizer; Visible Lift†; Vitalumiere; ***Chile***: ROC Minesol Bronze; ***NZ***: Hamilton Sunscreen†; ***Singapore***: Sunsense Anti-Ageing; ***USA***: Coppertone Tan Magnifier; Neutrogena Glow; Neutrogena Moisture.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Octisalate *(USAN, rINN)*

Octisalato; Octisalatum; Octyl Salicylate; Октисалат.

2-Ethylhexyl salicylate; 2-Hydroxybenzoic acid 2-ethylhexyl ester.

$C_{15}H_{22}O_3$=250.3

CAS — 118-60-5.

UNII — 4X49Y0596W.

NOTE. Escalol 587, Eusolex OS, and Neo-Heliopan OS are trade names that have been used for octisalate.

Pharmacopoeias. In *US.*

USP 36: (Octisalate). Store in airtight containers.

Profile

Octisalate is a substituted salicylate used topically as a sunscreen (p. 1681.3). Salicylates effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p. 1685.3). Salicylate sunscreens may therefore be used to prevent sunburn, but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection.

Salicylates may occasionally produce photosensitivity reactions or contact dermatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lelco; ***Canad.***: Clinique Skin Supplies; Coppertone Oil-Free Sunscreen; ***Chile***: ROC Minesol Bronze.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Octocrilene *(rINN)*

2-Ethylhexyl α-cyano-β-phenylcinnamate; Octocrilène; Octocrileno; Octocrilenum; Octocrylene (USAN); Octocrylene; Октокрилен.

2-Ethylhexyl 2-cyano-3,3-diphenylacrylate.

$C_{24}H_{27}NO_2$=361.5

CAS — 6197-30-4.

UNII — 5A68WGF6WM.

NOTE. Escalol 597, Eusolex OCR, Neo-Heliopan 303, Parsol 340, and Uvinul N 539 T are trade names that have been used for octocrilene.

Pharmacopoeias. In *US.*

USP 36: (Octocrylene). Store in airtight containers.

Profile

Octocrilene, a substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (above). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Coppertone Oil-Free Sunscreen.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Oxybenzone *(USAN, rINN)*

Benzofenon-3; Benzophenone-3; Oxibenzona; Oxybenzonum; Оксибензон.

2-Hydroxy-4-methoxybenzophenone.

$C_{14}H_{12}O_3$=228.2

CAS — 131-57-7.

UNII — 95OOS7VE0Y.

NOTE. Escalol 567, Eusolex 4360, Neo-Heliopan BB, Tinosorb B3, and Uvinul M 40 are trade names that have been used for oxybenzone.

Pharmacopoeias. In *US.*

USP 36: (Oxybenzone). A pale yellow powder. Practically insoluble in water; freely soluble in alcohol and in toluene. Store in airtight containers. Protect from light.

Profile

Oxybenzone is a substituted benzophenone used topically as a sunscreen (p. 1681.3). Benzophenones effectively absorb light throughout the UVB range (wavelengths 290 to 320 nm) and also absorb some UVA light with wavelengths of 320 to about 360 nm and some UVC light with wavelengths of about 250 to 290 nm (for definitions, see p. 1685.3). Benzophenones may therefore be used to prevent sunburn and may also provide some protection against drug-related or other photosensitivity reactions associated with UVA light; in practice they are usually combined with a sunscreen from another group.

Photocontact allergic dermatitis can be caused by topical application of benzophenone sunscreens. Oxybenzone is widely used and often found to be a photo-allergen in patients with these reactions. Contact allergy reactions occur less frequently.

Hypersensitivity. Chemical sunscreens are known to cause photosensitivity and contact allergy reactions. Oxybenzone is widely used and reported to be the sunscreen photo-allergen most commonly detected in photopatch testing.[1,2] In a group of 5800 patients with suspected allergic contact dermatitis who were tested for contact allergens,[3] a positive reaction to oxybenzone was recorded in 0.6%. There have also been rare reports of severe allergic reactions to oxybenzone including anaphylaxis; sensitivity was confirmed by patch testing.[4,5] A history of atopy may predispose patients to such reactions.

1. Berne B, Ros A-M. 7 years experience of photopatch testing with sunscreen allergens in Sweden. *Contact Dermatitis* 1998; **38:** 61–4.
2. Bryden AM, *et al.* Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 2006; **155:** 737–47.
3. Marks JG, *et al.* North American Contact Dermatitis Group patch-test results, 1998 to 2000. *Am J Contact Dermat* 2003; **14:** 59–62.
4. Emonet S, *et al.* Anaphylaxis to oxybenzone, a frequent constituent of sunscreens. *J Allergy Clin Immunol* 2001; **107:** 556–7.
5. Yesudian PD, King CM. Severe contact urticaria and anaphylaxis from benzophenone-3 (2-hydroxy 4-methoxy benzophenone). *Contact Dermatitis* 2002; **46:** 55–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biorevit Labial; Lelco; ***Braz.***: Solaquin; ***Canad.***: Clinique Skin Supplies; Coppertone Oil-Free Sunscreen; Silkies Enriche.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

USP 36: Dioxybenzone and Oxybenzone Cream.

Padimate *(BAN, rINN)*

Amyl Dimethylaminobenzoate; Isoamyl Dimethylaminobenzoate; Padimate A (USAN); Padimate A; Padimato; Padimatum; Падимат.

A mixture of pentyl, isopentyl, and 2-methylbutyl 4-dimethylaminobenzoates .

$C_{14}H_{21}NO_2$=235.3

CAS — 14779-78-3 (pentyl 4-dimethylaminobenzoate); 21245-01-2 (isopentyl 4-dimethylaminobenzoate).

UNII — 77FU10423X.

Profile

Padimate, a substituted aminobenzoate, is a sunscreen (p. 1681.3) with actions similar to those of aminobenzoic acid (p. 1694.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Uvless; ***Canad.***: Solaquin Forte; ***USA***: Vaseline Intensive Care Blockout.

Padimate O *(BANM, USAN)*

Ethylhexyl Dimethyl PABA; Octyl Dimethyl PABA; Padimato O; Падимат О.

2-Ethylhexyl 4-(dimethylamino)benzoate.

$C_{17}H_{27}NO_2$=277.4

CAS — 21245-02-3.

UNII — Z11006CMUZ.

NOTE. Escalol 507 and Eusolex 6007 are trade names that have been used for padimate O.

Pharmacopoeias. In *US.*

USP 36: (Padimate O). A light yellow, mobile liquid with a faint aromatic odour. Practically insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in isopropyl alcohol, and in liquid paraffin. Store in airtight containers. Protect from light.

Profile

Padimate O, a substituted aminobenzoate, is a sunscreen (p. 1681.3) with actions similar to those of aminobenzoic acid (p. 1694.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Chapstick; Iluminoderm; Vunsu; Womosol; ***Austral.***: Chapstick†; ***Braz.***: Solaquin; ***Canad.***: Saving Face†; ***Chile***: Chapstick Mint; Emolan H.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
USP 36: Padimate O Lotion.

Pimecrolimus *(BAN, USAN, rINN)*

ASM-981; Pimécrolimus; Pimecrolimús; Pimecrolimusum; Pimekrolimus; Pimekrolimuusi; SDZ-ASM-981; Пимекролимус.

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-3-{(*E*)-2-[(1*R*,3*R*,4*S*)-4-Chloro-3-methoxycyclohexyl]-1-methylvinyl}-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone.

$C_{43}H_{68}ClNO_{11}$=810.5

CAS — 137071-32-0.

ATC — D11AH02.

ATC Vet — QD11AH02.

UNII — 7KYV510875.

Uses and Administration

Pimecrolimus is a macrolactam ascomycin derivative related to tacrolimus (p. 1968.3) that acts as a calcineurin inhibitor and has similar anti-inflammatory and immunosuppressant actions. It is used topically for short-term and intermittent long-term treatment of mild to moderate atopic eczema (p. 1684.1) in non-immunocompromised patients over the age of 2 years when conventional therapies are ineffective or unsuitable. Pimecrolimus is applied twice daily as a 1% cream until signs and symptoms clear. Treatment should be stopped if there is no improvement after 6 weeks or if eczema is exacerbated.

Oral forms of pimecrolimus are also being investigated for the treatment of psoriasis and atopic eczema.

Administration in infants. A review[1] of data from 10 studies that included 1133 infants between 3 and 23 months of age who were treated with topical pimecrolimus 1% cream for up to 2 years found that the level of systemic exposure to pimecrolimus was very low and comparable to that seen in older children and adults. Treatment was reported to be effective and there was no evidence of immunosuppression or an increase in the rate of infections. Licensed product information, however, does not recommend its use in patients under 2 years of age as the effect of pimecrolimus cream on the developing immune system in infants is unknown (for concerns about possible carcinogenicity see below).

1. Paul C, *et al.* Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. Abstract: *Pediatrics* 2006; **117:** 202–3. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/1/e118 (accessed 27/09/07)

Eczema. The use of topical pimecrolimus in eczema has been the subject of reviews and meta-analyses,[1-3] generally concluding that it is less effective than moderate or potent corticosteroids or tacrolimus;[2,3] there is also a lack of studies comparing efficacy with mild corticosteroids.[2,3] For the use of topical pimecrolimus specifically in infants, see above.

Oral use of pimecrolimus has also been the subject of one trial[4] although it was noted that further study was required.

1. Wellington K, Jarvis B. Topical pimecrolimus: a review of its clinical potential in the management of atopic dermatitis. *Drugs* 2002; **62:** 817–40.
2. Ashcroft DM, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; **330:** 516–22.
3. Ashcroft DM, *et al.* Topical pimecrolimus for eczema. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 12/04/10).
4. Wolff K, *et al.* Efficacy and tolerability of three different doses of oral pimecrolimus in the treatment of moderate to severe atopic dermatitis: a randomized controlled trial. *Br J Dermatol* 2005; **152:** 1296–1303.

Lichen. There are a few case reports[1,2] of benefit from pimecrolimus 1% cream in the management of oral *lichen planus* (p. 1685.2). In most cases it was applied twice daily, and in some cases adhesive gel or paste was also used. Improvement in oral lesions occurred within 2 to 4 weeks in 3 cases.[1] In 3 small randomised, placebo-controlled studies[1,3-5] of patients with erosive disease, pimecrolimus 1% cream was applied twice daily for about 4 weeks, with varying results. Although pain scores were reduced with pimecrolimus, the reduction in erythema was not maintained in one study.[3] There was also a trend towards an improvement in ulceration but changes in scores were not statistically significant. The other 2 studies noted more significant reductions in pain and extent of erosion, with one[5] suggesting a possible sustained remission seen after treatment was stopped, whilst the other[4] contradicts this. In some patients who did not respond in the first month of treatment therapy for another month did prove beneficial.[5] Topical pimecrolimus has also been tried in the management of genital lichen planus. In a series[6] of 11 women, 9 noted benefit after 4 to 6 weeks of treatment; with follow-up of up to 10 months, 6 of them had had a complete response and 3 a partial response.

The resolution of signs and symptoms of *lichen sclerosus* (p. 1685.2) has been reported in 7 female patients (aged 4 to 48 years) with the use of topical pimecrolimus 1% cream twice daily for 3 to 4 months.[7,8] A poor response was reported in a 62-year-old woman who used the cream less frequently because of burning and stinging.[7]

1. Esquivel-Pedraza L, *et al.* Treatment of oral lichen planus with topical pimecrolimus 1% cream. *Br J Dermatol* 2004; **150:** 771–3.
2. Dissemond J, *et al.* Pimecrolimus in an adhesive ointment as a new treatment option for oral lichen planus. *Br J Dermatol* 2004; **150:** 782–4.
3. Swift JC, *et al.* The effectiveness of 1% pimecrolimus cream in the treatment of oral erosive lichen planus. *J Periodontol* 2005; **76:** 627–35.
4. Passeron T, *et al.* Treatment of oral erosive lichen planus with 1% pimecrolimus cream: a double-blind, randomized, prospective trial with measurement of pimecrolimus levels in the blood. *Arch Dermatol* 2007; **143:** 472–6.
5. Volz T, *et al.* Pimecrolimus cream 1% in erosive oral lichen planus—a prospective randomized double-blind vehicle-controlled study. *Br J Dermatol* 2008; **159:** 936–41.
6. Lonsdale-Eccles AA, Velangi S. Topical pimecrolimus in the treatment of genital lichen planus: a prospective case series. *Br J Dermatol* 2005; **153:** 390–4.
7. Goldstein AT, *et al.* Pimecrolimus for the treatment of vulvar lichen sclerosus: a report of 4 cases. *J Reprod Med* 2004; **49:** 778–80.
8. Boms S, *et al.* Pimecrolimus 1% cream for anogenital lichen sclerosus in childhood. *BMC Dermatol* 2004; **4:** 14. Available at: http://www.biomedcentral.com/1471-5945/4/14 (accessed 27/09/07)

Psoriasis. Topical pimecrolimus may have some benefit[1] in the treatment of psoriasis (p. 1688.1). Although studies have generally found it to be less effective than topical corticosteroids or topical calcipotriol,[2-4] one study[2] in patients with chronic plaque psoriasis did report that pimecrolimus 1% ointment applied under occlusion had a similar efficacy to clobetasol propionate 0.05% ointment.

Oral pimecrolimus is also under investigation and has reduced disease severity in dose-finding studies in patients with chronic plaque psoriasis.[5,6]

1. Gribetz C, *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004; **51:** 731–8.
2. Mrowietz U, *et al.* The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol* 1998; **139:** 992–6.
3. Mrowietz U, *et al.* An experimental ointment formulation of pimecrolimus is effective in psoriasis without occlusion. *Acta Derm Venereol* 2003; **83:** 351–3.
4. Kreuter A, *et al.* 1% Pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a double-blind, randomized controlled study. *Arch Dermatol* 2006; **142:** 1138–43.
5. Rappersberger K, *et al.* Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol* 2002; **119:** 876–87.
6. Gottlieb AB, *et al.* Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double-blind, multicentre, randomized, dose-finding trial. *Br J Dermatol* 2005; **152:** 1219–27.

Seborrhoeic dermatitis. Small studies[1,2] suggest that topical pimecrolimus has a similar efficacy to topical corticosteroids in the treatment of seborrhoeic dermatitis (p. 1689.1). It has also been effective in a few cases that had not responded to topical corticosteroids.[3]

1. Rigopoulos D, *et al.* Pimecrolimus cream 1% vs. betamethasone 17-valerate 0.1% cream in the treatment of seborrhoeic dermatitis: a randomized open-label clinical trial. *Br J Dermatol* 2004; **151:** 1071–5.
2. Firooz A, *et al.* Pimecrolimus cream, 1%, vs hydrocortisone acetate cream, 1%, in the treatment of facial seborrheic dermatitis: a randomized, investigator-blind, clinical trial. *Arch Dermatol* 2006; **142:** 1066–7.
3. Cunha PR. Pimecrolimus cream 1% is effective in seborrhoeic dermatitis refractory to treatment with topical corticosteroids. *Acta Derm Venereol* 2006; **86:** 69–70.

Adverse Effects and Precautions

As for topical tacrolimus (p. 1971.1).

The most frequent adverse effects of topical pimecrolimus are a burning sensation, irritation, pruritus, erythema, and folliculitis at the application site. Uncommon effects include skin papilloma and various bacterial and viral skin infections. Rarely anaphylactic reactions, sometimes severe, have been reported.

Cases of lymphadenopathy have been reported in patients using pimecrolimus cream. Treatment with pimecrolimus should be stopped in patients who develop lymphadenopathy in the absence of a clear aetiology or in the presence of acute infectious mononucleosis. Patients should be monitored to ensure that the condition resolves.

Carcinogenicity. Carcinogenicity studies in *animals* and reports of malignancies in patients treated with topical calcineurin inhibitors prompted the FDA to issue an alert about the possible risk and to make recommendations about the appropriate use of topical pimecrolimus and tacrolimus (see under Tacrolimus, p. 1971.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pimecrolimus as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Alcohol intolerance, described as flushing, rash, burning, itching, or swelling, has occurred rarely after the consumption of alcohol by patients using topical pimecrolimus.

Pharmacokinetics

There is minimal systemic absorption and no accumulation from topical use of pimecrolimus. Studies in *animals* and *in vitro* have found no evidence of metabolism in the skin.

Pimecrolimus is absorbed from the gastrointestinal tract after oral doses, and is about 74 to 87% bound to plasma proteins. It is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A subfamily. About 78% of a single dose is eliminated in the faeces as metabolites and less than 1% as unchanged pimecrolimus. Only about 2.5% of a dose is eliminated in the urine, as metabolites.

References.

1. Van Leent EJM, *et al.* Low systemic exposure after repeated topical application of pimecrolimus (Elidel, SD Z ASM 981) in patients with atopic dermatitis. *Dermatology* 2002; **204:** 63–8.
2. Scott G, *et al.* Pharmacokinetics of pimecrolimus, a novel nonsteroid anti-inflammatory drug, after single and multiple oral administration. *Clin Pharmacokinet* 2003; **42:** 1305–14.
3. Zollinger M, *et al.* Pimecrolimus: absorption, distribution, metabolism, and excretion in healthy volunteers after a single oral dose and supplementary investigations in vitro. *Drug Metab Dispos* 2006; **34:** 765–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Elidel; ***Austral.***: Elidel; ***Austria***: Elidel; ***Belg.***: Elidel; ***Braz.***: Elidel; ***Canad.***: Elidel; ***Chile***: Elidel; ***China***: Elidel (爱宁达); ***Cz.***: Elidel; ***Denm.***: Elidel; ***Fin.***: Elidel; ***Ger.***: Elidel; ***Gr.***: Aregen; Elidel; ***Hong Kong***: Elidel; ***Hung.***: Elidel; ***India***: Elidel; Pacroma; ***Indon.***: Elidel; ***Israel***: Elidel; ***Ital.***: Elidel; ***Malaysia***: Elidel; ***Mex.***: Elidel; ***Neth.***: Elidel; ***Norw.***: Elidel; ***NZ***: Elidel; ***Philipp.***: Elidel; ***Pol.***: Elidel; ***Port.***: Aregen; Elidel; ***Rus.***: Elidel (Элидел); ***S.Afr.***: Elidel; ***Singapore***: Elidel†; ***Spain***: Elidel; Rizan; ***Swed.***: Elidel; ***Switz.***: Elidel; ***Thai.***: Elidel; ***Turk.***: Elidel; ***UK***: Elidel; ***Ukr.***: Elidel (Элидел); ***USA***: Elidel; ***Venez.***: Elidel.

Piroctone Olamine *(USAN, rINNM)*

Piroctona olamina; Piroctoni Olaminum; Пироктон Оламин.

1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1*H*)-pyridone compound with 2-aminoethanol (1:1).

$C_{14}H_{23}NO_2.C_2H_7NO$=298.4

CAS — 50650-76-5 (piroctone); 68890-66-4 (piroctone olamine).

UNII — A4V5C6R9FB.

Profile

Piroctone olamine has been used in shampoos for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Plusgel†; ***Braz.***: Soapex; ***Fr.***: Charlieu Antipelliculaire†; Evolith DS†; Topicrem Traitement PV†; ***Ital.***: Olamin P†; ***Mex.***: Betapirox; ***Venez.***: Betapirox.

Multi-ingredient Preparations. ***Arg.***: Micocert; Micodual; Pitiriax; ***Braz.***: Ortosol P; Pityval; Saliker; ***Chile***: Anastim; Eucerin Shampoo Anticaspa†; Eucerin Shampoo para el Tratamiento de la Caspa; Foltene Research Anticaspa†; Kerium Anticaspa - Caspa Grasa; Kerium Anticaspa -Caspa Seca; Kerium Anticaspa Intensivo; Micodual; NeoStrata; Node DS†; Pityval; Shampoo Anticaspa†; ***Fr.***: Ionax P†; Kelual DS; Kerium Intensive†; Kertyol Shampooing†; Node DS+; Node DS; Node P†; Novophane DS; Novophane K; Phytheol Force†; Phytosquame†; Pityval†; PSO†; Seborheane†; ***India***: Climdan; ***Irl.***: Effaclar AI; ***Israel***: Atopiclair; Xclair; ***Ital.***: Biophase Shampoo; Biothymus DS; Biothymus DS; Genisol; Nonak; Prurex; Sideck Shampoo Antiforfora; Tricoderm F; ***Port.***: Alpha Septol; Bioclin Sebo Care†; ***Singapore***: Atopiclair; Pedimed Foot Care Cream; ***Turk.***: Numis; ***UK***: Atopiclair; ***USA***: Atopiclair; ***Venez.***: Anastim; Kertyol; Node DS; Sensibio DS.

Podophyllum

American Mandrake; May Apple Root; Podófilo; Podofilum; Podoph.; Podophyllum Rhizome; Rizoma de podófilo; Подофилл щитовидный (*Podophyllum peltatum*).

ATC Herb — HA06AB5012 (Podophyllum peltatum: rhizome).
UNII — 5Y42EY8SM7 (Podophyllum peltatum); 25713A4VP3 (Podophyllum peltatum root).

Pharmacopoeias. In *US*.

USP 36: (Podophyllum). The dried rhizomes and roots of *Podophyllum peltatum* (Berberidaceae). It yields not less than 5% of resin. It has a slight odour.

Indian Podophyllum

Ind. Podoph.; Indian Podophyllum Rhizome; Podófilo indio; Подофилл гималайский (*Podophyllum emodi*).

Description. The dried fruits or rhizomes and roots of *Podophyllum hexandrum* (*P. emodi*) (Berberidaceae).

Podophyllum Resin

Podofilino; Podoph. Resin; Podophylli Resina; Podophyllin; Resina de podófilo; Подофиллин.

CAS — 8050-60-0.
ATC Herb — HD06BB5001 (Podophyllum peltatum: resin); HA06AB5011 (Podophyllum peltatum: resin).
UNII — 16902YVY2B.

Pharmacopoeias. In *Int.* and *US* (both from podophyllum only). In *Br.* from Indian podophyllum.

BP 2014: (Podophyllum Resin). The resin obtained from the rhizomes and roots of *Podophyllum hexandrum* (*P. emodi*). It contains not less than 50% of total aryltetralin lignans, calculated as podophyllotoxin.

An amorphous powder, varying in colour from light brown to greenish-yellow or brownish-grey masses, with a characteristic odour; caustic. On exposure to light or to temperatures above 25 degrees it becomes darker in colour.

Partly soluble in hot water but precipitated again on cooling; partly soluble in chloroform, in ether, and in dilute ammonia solution. Protect from light.

USP 36: (Podophyllum Resin). The powdered mixture of resins extracted from podophyllum (the rhizomes and roots of *Podophyllum peltatum*) by percolation with alcohol and subsequent precipitation with acidified water. It contains not less than 40% and not more than 50% of hexane-insoluble matter.

An amorphous caustic powder, varying in colour from light brown to greenish-yellow. On exposure to light or to temperatures above 25 degrees it becomes darker in colour.

Soluble in alcohol with a slight opalescence; partially soluble in chloroform and in ether. A solution in alcohol is acid to litmus. Store in airtight containers. Protect from light.

Podophyllotoxin *(BAN)*

Podofilotoxina; Podofilox (USAN); Podofyllotoksiini; Podofyllotoxin; Podophyllotoxinum; Подофиллотоксин.

(5*R*,5a*R*,8a*R*,9*R*)-5,5a,6,8,8a,9-Hexahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3′4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6-one.

$C_{22}H_{22}O_8$=414.4
CAS —518-28-5.
ATC —D06BB04.
ATC Vet — QD06BB04.
UNII —L36H50F353.

Uses and Administration

Podophyllum resin and podophyllotoxin have an antimitotic action and are used mainly as topical treatments for anogenital warts (condylomata acuminata). Podophyllum resin and podophyllotoxin may be used on external genital and perianal warts; podophyllum resin may also be used on urethral meatus warts. However, neither of these compounds should be used to treat warts on mucous membranes, including vaginal, cervical, intra-urethral, intra-anal, and rectal warts.

Podophyllum resin is usually formulated in compound benzoin tincture in strengths of 15% Indian podophyllum resin or 10 to 25% American podophyllum resin. Lower concentrations of American podophyllum resin in alcoholic solutions have been used. The solution is left on the warts for 1 to 4 hours, and then washed off. Only a small area or number of warts should be treated at any one time and care must be taken to avoid application to healthy tissue. This procedure is carried out once a week for up to 3 to 6 weeks. Preparations containing podophyllotoxin 0.5% in alcohol or alcoholic gel or podophyllotoxin 0.15% cream are used similarly. They are applied twice daily for 3 days but not washed off. Treatment may be repeated at weekly intervals for up to a total of 4 or 5 weeks of treatment. Podophyllum resin is also used with other keratolytics for the removal of plantar warts.

Although podophyllum resin and podophyllotoxin preparations are generally not used in children, see below.

When taken orally podophyllum resin is highly irritant to the intestinal mucosa and produces violent peristalsis resulting in a drastic purging action. It has been superseded by less toxic laxatives.

Homoeopathy

Podophyllum has been used in homoeopathic medicines under the following names: Podoph pelt; Podophyllum peltatum.

Podophyllum resin has been used in homoeopathic medicines under the following names: Podophyllinum.

Administration in children. The use of podophyllum resin and podophyllotoxin preparations in children is generally avoided because of the potential for severe local irritation and systemic toxicity. Nonetheless, some podophyllum resin-containing preparations are licensed in children for the treatment of plantar warts. Also, podophyllotoxin has been used for the treatment of symptomatic, persistent anogenital warts in children.[1] The *BNFC* suggests that, although not licensed for use in children, podophyllotoxin preparations may be used in regimens similar to those used in adults (see above) in children 2 years of age and older who are able to cooperate with treatment.

1. Bellew SG, *et al.* Childhood warts: an update. *Cutis* 2004; **73:** 379–84.

Anogenital warts. Podophyllum preparations are one of the treatment choices for anogenital warts caused by human papillomavirus infection (condylomata acuminata) (p. 1689.3). Podophyllum resin preparations have traditionally been applied by a healthcare provider because of the potential local and systemic toxicity associated with inappropriate or excessive use.[1] However, podophyllotoxin may be more effective[2,3] and less toxic[2] than podophyllum resin, and is suitable for self-treatment by the patient.[1,4]

1. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Correction. *ibid.* 2011; **60:** 18. [dose] Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 02/02/11)
2. von Krogh G, Longstaff E. Podophyllin office therapy against condyloma should be abandoned. *Sex Transm Infect* 2001; **77:** 409–12.
3. Lacey CJN, *et al.* Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sex Transm Infect* 2003; **79:** 270–5.
4. von Krogh G, *et al.* European Course on HPV Associated Pathology (ECHPV). European guideline for the management of anogenital warts. *Int J STD AIDS* 2001; **12** (suppl 3): 40–7. Also available at: http://www.iusti.org/sti-information/pdf/guidelines.pdf (accessed 27/09/07)

Adverse Effects

Podophyllum is very irritant, especially to the eyes and mucous membranes. It can also cause severe systemic toxicity after ingestion or topical application, which is usually reversible but has been fatal. Symptoms of toxicity include nausea, vomiting, abdominal pain, and diarrhoea; there may be thrombocytopenia, leucopenia, renal failure, and hepatotoxicity. Central effects are delayed in onset and prolonged in duration and include acute psychotic reactions, hallucinations, confusion, dizziness, stupor, ataxia, hypotonia, seizures, and coma. EEG changes may persist for several days. Peripheral and autonomic neuropathies develop later and may result in paraesthesias, reduced reflexes, muscle weakness, tachycardia, apnoea, orthostatic hypotension, paralytic ileus, and urinary retention. Neuropathy may persist for several months.

Poisoning. Reports and reviews of podophyllum toxicity.[1-7] A few of the cases followed consumption of herbal preparations containing podophyllum or the related plant bajiaolian (*Dysosma pleianthum*). Death has occurred after ingestion of 10 g of podophyllum.

1. Cassidy DE, *et al.* Podophyllum toxicity: a report of a fatal case and a review of the literature. *J Toxicol Clin Toxicol* 1982; **19:** 35–44.
2. Dobb GJ, Edis RH. Coma and neuropathy after ingestion of herbal laxative containing podophyllin. *Med J Aust* 1984; **140:** 495–6.
3. Holdright DR, Jahangiri M. Accidental poisoning with podophyllin. *Hum Exp Toxicol* 1990; **9:** 55–6.
4. Tomczak RL, Hake DH. Near fatal systemic toxicity from local injection of podophyllin for pedal verrucae treatment. *J Foot Surg* 1992; **31:** 36–42.
5. Kao W-F, *et al.* Podophyllotoxin intoxication: toxic effect of bajiaolian in herbal therapeutics. *Hum Exp Toxicol* 1992; **11:** 480–7.
6. Chan TYK, Critchley JAJH. Usage and adverse effects of Chinese herbal medicines. *Hum Exp Toxicol* 1996; **15:** 5–12.
7. Chu CC, *et al.* Sensory neuropathy due to bajiaolian (podophyllotoxin) intoxication. *Eur Neurol* 2000; **44:** 121–3.

Precautions

The risk of systemic toxicity after topical application of podophyllum is increased by the treatment of large areas with excessive amounts for prolonged periods, by the treatment of friable, bleeding, or recently biopsied warts, and by inadvertent application to normal skin or mucous membranes.

Podophyllum should not be used during pregnancy or breast feeding. There are few reports of use during pregnancy and a teratogenic risk cannot be ruled out. Adverse systemic effects in the mother would also be undesirable during pregnancy, and there are other non-drug treatments available for the treatment of anogenital warts. It is unknown whether podophyllum is distributed into breast milk.

Handling. Podophyllum resin is strongly irritant to the skin, eyes, and mucous membranes and requires careful handling.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies podophyllotoxin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Podoxin; ***Austral.***: Condyline; Wartec; ***Austria***: Condylox; ***Belg.***: Wartec; ***Braz.***: Wartec; ***Canad.***: Condyline; Podofilm; Wartec; ***China***: Condylox (慷定来); Podofilm (尤力青); Wartec (华特); You Tuo Xin (尤脱欣); ***Cz.***: Wartec; ***Denm.***: Condyline; Wartec; ***Fin.***: Condyline; Wartec; ***Fr.***: Condyline; ***Ger.***: Condylox; Wartec; ***Gr.***: Podofilox; Wartec; ***Hong Kong***: Podofilm; Wartec; ***Hung.***: Condyline; Wartec; ***India***: Condyline; ***Irl.***: Condyline; Warticon; ***Israel***: Condylox; ***Ital.***: Condyline; Wartec; ***Mex.***: Podofilia; Vipodo; Wartec; ***Neth.***: Condyline; Wartec; ***Norw.***: Condyline; Wartec; ***NZ***: Condyline; Wartec; ***Pol.***: Condyline; Wartec; ***Port.***: Condyline†; ***Rus.***: Condyline (Кондилин); Wartec (Вартек); ***S.Afr.***: Wartec; ***Singapore***: Podofilm; Wartec; ***Spain***: Wartec; ***Swed.***: Condyline; Wartec; ***Switz.***: Condyline; Warix; ***Turk.***: Podofilm; ***UK***: Condyline; Warticon; ***Ukr.***: Wartec (Вартек); ***USA***: Condylox; Pod-Ben-25; Podocon; Podofin.

Multi-ingredient Preparations. ***Austral.***: Posalfilin†; ***Canad.***: Canthacur-PS; Cantharone Plus; ***Ger.***: Unguentum lymphaticum†; ***Hong Kong***: F-Podofim†; ***Irl.***: Posalfilin; ***Neth.***: Diarrheel S; ***NZ***: Posalfilin; ***Port.***: Doce Alivio; ***S.Afr.***: Posalfilin†; ***Spain***: Alofedina; ***Turk.***: Canthacur-PS; ***UK***: Posalfilin†; ***Venez.***: Linfoderm.

Homoeopathic Preparations. ***Austral.***: IBS Eze; Stomach Calm; ***Austria***: Daram; Zahnkugelchen; ***Canad.***: Carduus Plex†; Diarrex; Indigestion†; Vegetal Tonic; ***Fr.***: Aloe Compose; Basilicum Complexe No 96; Bilinum Complexe No 113; Billerol; Diaralia; Hepatopan†; L 114; Ricinus Compose; Tonique Vegetal; ***Ger.***: Cefaspasmon N†; Chola-Plantin N†; ***Rus.***: Berberis-Plus (Берберис-Плюс); ***Switz.***: Diarrheel S; ***Ukr.***: Choledius (Холедиус).

Pharmacopoeial Preparations
BP 2014: Compound Podophyllin Paint;
USP 36: Podophyllum Resin Topical Solution.

Polyphloroglucinol Phosphate

Polifloroglucinol, fosfato de; Polyphloroglucin Phosphate; Полифлороглюцина Фосфат.

Poly[benzene-1,3,5-triol mono(dihydrogen phosphate)].
$(C_6H_7O_6P)_n$
CAS — 51202-77-8.

Profile

Polyphloroglucinol phosphate has an inhibitory effect on hyaluronidase and has been applied topically in the treatment of wounds and pruritic skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dealyd.

Polyurethane Foam *(USAN)*

Полиуретановая Пена; Пенополиуретан.
CAS — 9009-54-5.

Profile

Polyurethane foam is a urethane polymer that is used in wound dressings.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Allevyn; Opsite; ***Belg.***: Allevyn; Askina Transorbent†; Biatain; Combiderm; Duoderm E; Mepilex; Permafoam; Tegaderm Foam; Tielle; ***Canad.***: Tegaderm Foam; ***Chile***: Epi Foam; ***Fr.***: Allevyn; Clip Blessurest†; Clip Derm†; Clip Strip†; Opsite; Optiskin†; Permafoam; Suprasorb; Tielle†; ***Ger.***: Allevyn; Biatain Ag; Biatain-Ibu; Biatain; DracoFoam; Opsite; ***Irl.***: Allevyn; ***Ital.***: Allevyn; Bioclusive; Cutinova Hydro; Opsite Flexigrid; Suprasorb F, M, P; ***S.Afr.***: Opsite; ***UK***: Allevyn; Cutinova; Lyofoam; Opsite.

Multi-ingredient Preparations. ***Ital.***: Biopatch; Silverdres.

Prezatide Copper Acetate *(USAN, rINN)*

Acetato de prezatida cúprica; Acetato de prezatida de cobre; PC-1020 (prezatide copper); Prezatida cúprica, acetato de; Prézatide Cuprique, Acétate de; Prezatidi Cuprici Acetas; Презатида Меди Ацетат.
Hydrogen [N^2-(*N*-glycyl-L-histidyl)-L-lysinato][N^2-(*N*-glycyl-L-histidyl)-L-lysinato(2−)]cuprate(1−) diacetate.
$C_{28}H_{46}CuN_{12}O_8.2C_2H_4O_2$=862.4
CAS — 130120-57-9.
UNII — A3LEI4P1NB.

Profile

Prezatide copper acetate is a copper-containing tripeptide that is used topically as a wound-healing agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Iamin†; ***USA***: Iamin Hydrating Gel.

Pyrithione Zinc *(BAN, USAN, rINN)*

Çinko Pirition; Piritiona cíncica; Piritiona de zinc; Pyrithione Zincique; Pyrithionum Zincicum; Zinc 2-Pyridinethiol 1-Oxide; Zinc Pyridinethione; Пиритион Цинк.
Bis[1-hydroxypyridine-2(1*H*)-thionato]zinc.
$C_{10}H_8N_2O_2S_2Zn$=317.7
CAS — 13463-41-7.
ATC — D11AX12.
ATC Vet — QD11AX12.
UNII — R953O2RHZ5.

Profile

Pyrithione zinc has bacteriostatic and fungistatic properties. It is used similarly to selenium sulfide (p. 1720.1) in usual concentrations of 1 to 2% in the control of seborrhoeic dermatitis and dandruff (p. 1689.1). It is an ingredient of some proprietary shampoos. It has also been used in the treatment of pityriasis versicolor.

Pyrithione magnesium has also been used.

Effects on the nervous system. Peripheral neuritis with paraesthesia and muscle weakness in a patient was associated with the prolonged use of a shampoo containing pyrithione zinc 2%.[1] The muscle weakness had disappeared 3 months after stopping the shampoo and 2 years later the paraesthesia had improved by about 75%.

Studies in *animals* had found signs of neurotoxicity after oral doses of pyrithione zinc but whereas absorption after topical application was found to be 13% for pyrithione sodium it was less than 1% for pyrithione zinc.[2]

1. Beck JE. Zinc pyrithione and peripheral neuritis. *Lancet* 1978; **i:** 444.
2. Parekh CK. Zinc pyrithione and peripheral neuritis. *Lancet* 1978, **i:** 940.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aeroseb; Amenite Cap; Antiminth; Dermazinc; Hairplus; Min Huil; Molnia; Skin-Cap; ***Austral.***: Dan-Gard†; Dandruff Control Pert 2 in 1; ***Austria***: Desquaman; ***Braz.***: ZN Shampoo; ***Canad.***: Active Control†; Actrol†; American Crew Classic; Axe Armour; Axe Freeze†; Biolage Scalptherapie; Brylcreem Anti-Dandruff†; Chill Blast†; Dan-Gard; Dandruff Conditioner; Dandruff Shampoo; Dandruff; Denorex Everyday; Dermazinc; Essaim†; Fructis Anti-Dandruff; Head & Shoulders; Herbal Essences No Flakin Way Antidandruff†; Herbal Shampoo and Scalp Treatment†; Intense Clear; KMS; Life Dandruff; Normal Dandruff Treatment†; Out of Africa†; Pantene Anti-Dandruff†; Pert Plus; Power Clear†; Purete†; Retaliate; Rodan & Fields Proactiv Antidandruff†; Satinique Dandruff Control; Scalp Relief; Selsun Blue Anti-Dandruff; Shampoo Control; Shampooing Anti-Pelliculaire; Sprayzinc; T/Gel Daily Control; Vive Men†; Zinc Zap; ZNP†; ***Chile***: Biolane; DHS Zinc; Skin Cap; ZNP†; ***China***: Skin-Cap (适今可); ***Fr.***: Skin Cap; ZNP†; ***Gr.***: Daohair-S; Desquaman; ***Hung.***: Freederm pH Balance Shampoo; Freederm Zinc Shampoo; ***Indon.***: Blue Cap; Blue Cap; Blue Cap; ***Israel***: Desquaman; ***Ital.***: Rivescal ZPT; SDE Zinc; ZNP; ***Mex.***: Pirimed; ZNP; ***Port.***: ZP Dermil; ***Rus.***: Cinocap (Цинокап); Freederm Zinc (Фридерм Цинк); Skin-Cap (Скин-Кап); ***Spain***: Zincation†; ***Turk.***: Zetion; Zintion; ***Ukr.***: Psoricap (Псорикап); ***USA***: DermaZinc; DHS Zinc; Head & Shoulders; Noble Formula; Skin Cure; Zincon; ZNP; ***Venez.***: Albepir; Blue Caps; Pirimed.

Multi-ingredient Preparations. ***Arg.***: Aeroseb; Zinc-S Plus; ***Austral.***: Fongitar†; ***Braz.***: Fisohex II; ***Canad.***: Herbal Multi-Tar Plus; Mild Multi-Tar Plus; Multi-Tar Plus†; Regular Multi-Tar Plus; X-Seb Plus; Z-Plus; ***Chile***: Node DS†; ***Cz.***: Polytar AF; ***Fr.***: Kelual DS; Node DS+; Node DS; Node P†; Novophane DS; Novophane K; ***Hong Kong***: Fongitar; Multi-Tar†; ***Hung.***: Polytar AF†; Squa-med; ***India***: Apodruff; Clinhair; Danclear; Dancure; Emvate; Everzple; Flakefree; Fungicide; Hyphoral; Kekona; Ketosis; Ketz; Koiz; KTC; Nazcare; Nazz; Nuforce Shampoo; Ocona-Z; Scalpe; ***Ital.***: Biothymus DS; Keto Z; Ketomousse; Kevis; ***Malaysia***: Ketoplus; ***Philipp.***: Fongitar; Scalpex; ***Pol.***: Polytar AF; ***Port.***: Alpha Septol; Fongitar; ***Rus.***: Keto Plus (Кето Плюс); ***S.Afr.***: Fongitar; ***Singapore***: Fongitar; ***Spain***: Zincation Plus; ***Switz.***: Sebo-Soufrol†; Squa-med; ***Thai.***: Fongitar†; ***Turk.***: Pirdolin; Seboreks; Sedolin†; ***UK***: Polytar AF†; ***Ukr.***: Keto Plus (Кето Плюс); ***USA***: Denorex Dual Force; X-Seb Plus; Xolegel Duo; ***Venez.***: Node DS; Pelset Plus.

Pyrogallol

1,2,3-Bencenotriol; Pirogálico, ácido; Pirogałol; Pyrogallic Acid; Pyrogallolum; Пирогаллол.
Benzene-1,2,3-triol.
$C_6H_6O_3$=126.1
CAS — 87-66-1.
UNII — 01Y4A2QXY0.

Pharmacopoeias. In *Fr.* and *Pol.*

Profile

Pyrogallol was formerly used topically in the treatment of psoriasis and parasitic skin diseases, but application over large areas or denuded surfaces is dangerous and may produce systemic effects similar to phenol poisoning (see p. 1764.2); methaemoglobinaemia, haemolysis, and kidney damage may also occur.

Pyrogallol stains the skin and hair black.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Pyrogallic.

Pyroxylin *(rINN)*

Algodão-Polvora; Algodón pólvora; Cellulose Nitrate; Celulosa decanítrica; Colloxylinum; Fulmicoton; Gossypium Collodium; Kollodiumwolle; Nitrato de celulosa; Piroxilina; Pyroxyline; Pyroxylinum; Soluble Guncotton; Пироксилин.
CAS — 9004-70-0.
UNII — KYR8BR2X6O.

Pharmacopoeias. In *Br., Jpn, Pol.*, and *US.*

BP 2014: (Pyroxylin). A nitrated cellulose obtained by the action of a mixture of nitric and sulfuric acids on wood pulp or cotton linters that have been freed from fatty matter. It must be damped with not less than 25% of isopropyl alcohol or of industrial methylated spirit. White or almost white cuboid granules or fibrous material resembling absorbent cotton but harsher to the touch and more powdery. It is highly flammable. Soluble in acetone and in glacial acetic acid. Store in well-closed containers, loosely packed, protected from light, and at a temperature not exceeding 15 degrees, remote from fire. The container should be suitably designed to disrupt should the internal pressure reach or exceed 1400 kPa. The amount of damping fluid must not be allowed to fall below 25% w/w; should this happen, the material should be either rewetted or used immediately for the preparation of Collodion.

USP 36: (Pyroxylin). Pyroxylin is obtained by the action of a mixture of nitric and sulfuric acids on cotton and consists chiefly of cellulose tetranitrate $(C_{12}H_{16}N_4O_{18})_n$. It occurs as a light yellow, matted mass of filaments resembling raw cotton but harsher to the touch. It is highly flammable. Store loosely packed, protected from light. When kept in well-closed containers and exposed to light, it decomposes with the evolution of nitrous vapours, leaving a carbonaceous residue.

Profile

Pyroxylin is used in the preparation of collodions which are applied to the skin for the protection of small cuts and abrasions. Collodions are also used as vehicles for the application of drugs when prolonged local action is required.

Handling. Dry pyroxylin is explosive and sensitive to ignition by impact or friction and should be handled carefully.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Callicida; ***Neth.***: Duofilm; ***UK***: Dispello; ***Venez.***: Kayivis.

Pharmacopoeial Preparations
BP 2014: Collodion; Flexible Collodion;
USP 36: Collodion; Flexible Collodion.

Resorcinol

m-Dihidroxibenceno; *m*-Dihydroxybenzene; Dioxybenzolum; Resorcin; Resorcina; Résorcinol; Resorcinolum; Resorsinoli; Rezorcin; Rezorcinolis; Rezorcynol; Резорцинол.
Benzene-1,3-diol.
$C_6H_6O_2$=110.1
CAS — 108-46-3.
ATC — D10AX02; S01AX06.
ATC Vet — QD10AX02; QS01AX06.
UNII — YUL4LO94HK.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Resorcinol). Colourless or slightly pinkish-grey crystals or crystalline powder. M.p. 109 degrees to 112 degrees. It becomes red on exposure to air and light. Very soluble in water and in alcohol. Protect from light.

USP 36: (Resorcinol). White or practically white, needle-shaped crystals or powder with a faint characteristic odour. M.p. 109 degrees to 111 degrees. It acquires a pink tint on exposure to air and light. Soluble 1 in 1 of water and of alcohol; slightly soluble in chloroform; freely soluble in ether and in glycerol. A 5% solution in water is neutral or acid to litmus. Protect from light.

Incompatibility. Resorcinol is incompatible with ferric salts.

Resorcinol Monoacetate

Acetato de resorcina; Resorcin Acetate; Resorcinol, monoacetato de; Резорцинола Моноацетат.
3-Acetoxyphenol.
$C_8H_8O_3$=152.1
CAS — 102-29-4.
ATC — D10AX02; S01AX06.
ATC Vet — QD10AX02; QS01AX06.
UNII — YL6O37RD1S.

Pharmacopoeias. In *US.*

USP 36: (Resorcinol Monoacetate). A pale yellow or amber, viscous liquid with a faint characteristic odour. Sparingly soluble in water; soluble in alcohol and in most organic solvents. A saturated solution in water is acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Resorcinol has keratolytic properties and has been used, usually with sulfur, in topical preparations for the treatment of acne (p. 1682.2) and seborrhoeic skin conditions (p. 1689.1), although other treatments are generally preferred.

Resorcinol has also been used in preparations for the treatment of anorectal disorders often complexed with bismuth compounds (see Haemorrhoids, p. 1808.1).

Resorcinol monoacetate has been used similarly but may provide a milder action with a longer duration.

Dentistry. Resorcinol powder added incrementally to a few drops of formaldehyde 40% solution to saturation and polymerised using 1 or 2 drops of sodium hydroxide 10% solution produces a hard red material, known as "Russian Red". This resin has been used in dentistry in eastern Europe, Russia, and China. Zinc oxide or barium sulfate is

often added to the mixture before polymerisation to make it radio-opaque.[1]

1. Schwandt NW, Gound TG. Resorcinol-formaldehyde resin "Russian Red" endodontic therapy. *J Endod* 2003; **29:** 435–7.

Adverse Effects, Treatment, and Precautions

Resorcinol is a mild irritant and may result in skin sensitisation. It should not be applied to large areas of the body, for prolonged periods, or in high concentrations, especially in children, as it is absorbed through intact skin as well as broken skin and may interfere with thyroid function or produce methaemoglobinaemia. Resorcinol may produce hyperpigmentation in patients with dark skins and may darken light-coloured hair. Systemic toxic effects of resorcinol are similar to those of phenol and are treated accordingly (see p. 1764.3) but convulsions may occur more frequently.

Abnormal coloration. Resorcinol could cause green discoloration of the urine.[1]

1. Karlstrand J. The pharmacist and the ostomate. *J Am Pharm Assoc* 1977; **NS17:** 735–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Dermobarrina; ***USA***: Castel.

Multi-ingredient Preparations. ***Arg.***: Acnoxin; Astriluge; Bifena; Callicida; Control Acne; Cutidermin Bebe Polvo†; Dermacne; Dermo Vagisil Crema; Ecnagel E; Ecnagel; Farmigras; Merbenloc; Nemegel; Pinklot; Suffisance; Ukase Dermo; Xicanil Control†; ***Austral.***: Eskamel†; ***Braz.***: Pantevit; ***Canad.***: Acnomel†; Clearasil Acne Control†; Clearasil Acne Cream†; Clearasil Stayclear†; Hemo-Pic†; Lanacane Medicated Cream; Mazon Medicated Cream; Sebo Concept D/A; Vagisil; ***Chile***: Dermac Crema; ***Fr.***: Anaxeryl; Bain de Bouche Lipha†; Gelictar Fort†; Nestosyl; Osmotol; Paracamf; Paradentose†; Squaphane S; Synthol; ***Gr.***: Creme Phyllis de Jeunesse; Neo Akmine; Rysolone; ***Hong Kong***: Acne-Aid†; ***Hung.***: Glycosept; ***Indon.***: Bioacne; Rosal; Verile; ***Irl.***: Anusol-HC; ***Israel***: Pitrisan†; ***Ital.***: Blefarolin; Fucsina Fenica; Labocaina; ***Malaysia***: Acne-Aid†; ***Mex.***: Acnomel; Axel; Dermac; Dermocare; Dermoscalp; Jabon del Tio Nacho; Shampoo del Tio Nacho†; ***NZ***: Lanacane; ***Pol.***: Afronis; Hemorectal; ***Port.***: Resodermil†; ***Rus.***: Fucaseptol (Фукасептол); Fucorcin (Фукорцин); Neo-Anusol (Нео-анузол); ***S.Afr.***: Anugesic†; Eskamel†; ***Singapore***: Acne Clear; Acne-Aid†; Castellani's Paint; ***Spain***: Dermomycose Liquido; Milrosina; Resorborina; ***Switz.***: Clabin; Eau Precieuse; Lotio decapans; ***Thai.***: Anusol†; Zema; ***Turk.***: Buco Bleu; Pilo Cura; ***USA***: Acnomel; Bensulfoid; Bicozene†; Castaderm; Dermarest; Fungi-Nail; Heal Aid Plus; RA Lotion; Rezamid; Sulforcin; Unguentine Maximum Strength; Vagisil; ***Venez.***: Klenyl.

Homoeopathic Preparations. ***Canad.***: ClearAc Cleanser†.

Pharmacopoeial Preparations
BPC 1973: Magenta Paint;
USP 36: Carbol-Fuchsin Topical Solution; Compound Resorcinol Ointment; Resorcinol and Sulfur Topical Suspension.

Retinaldehyde

Retinal; Retinene; Vitamin A Aldehyde; Ретинальдегид.
$C_{20}H_{28}O$=284.4
CAS — 116-31-4.
UNII — RR725D715M.

Profile

Retinaldehyde is a derivative of vitamin A (p. 2098.3) that has been used in preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ystheal; ***Chile***: Ystheal.

Multi-ingredient Preparations. ***Arg.***: Diacneal; Diroseal; Eluage; ***Chile***: Diacneal; Diroseal; ***Fr.***: Diroseal†; ***Venez.***: Diacneal.

Salicylic Acid

Acide salicylique; Acido Ortóxibenzoico; Acidum salicylicum; Kwas salicylowy; Kyselina salicylová; Salicílico, ácido; Salicilo rūgštis; Salicylsäure; Salicylsyra; Salisilik Asit; Salisyylihappo; Salizylsäure; Szalicilsav; Салициловая Кислота.
2-Hydroxybenzoic acid.
$C_7H_6O_3$=138.1
CAS — 69-72-7.
ATC — D01AE12; S01BC08.
ATC Vet — QD01AE12; QS01BC08.
UNII — O414PZ4LPZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Salicylic Acid). White or colourless acicular crystals or a white or almost white, crystalline powder. Slightly soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Salicylic Acid). White crystals, usually in fine needles or a white, fluffy, crystalline powder. The synthetic form is white and odourless but if prepared from natural methyl salicylate it may have a slightly yellow or pink tint, and a faint, mint-like odour. Soluble 1 in 460 of water, 1 in 15 of boiling water, 1 in 3 of alcohol, 1 in 45 of chloroform, 1 in 3 of ether, and 1 in 135 of benzene.

Uses and Administration

Salicylic acid has **keratolytic** properties and is applied topically in the treatment of hyperkeratotic and scaling skin conditions such as dandruff and seborrhoeic dermatitis (p. 1689.1), ichthyosis (p. 1685.1), psoriasis (p. 1688.1), and acne (p. 1682.2). Preparations usually contain between 2 and 6% salicylic acid, but a wider range of concentrations has been used. It is often used with other drugs, notably coal tar.

Preparations containing up to 60% salicylic acid have been used as a **caustic** for the removal of plantar warts (p. 1689.3), corns, or calluses; surrounding healthy skin should be protected (see below).

Salicylic acid also possesses **fungicidal** properties and is used topically in the treatment of dermatophyte skin infections (see p. 568.1); propyl salicylate and bromosalicylic acid have been used similarly.

Zinc salicylate has been used similarly to salicylic acid in the treatment of seborrhoeic dermatitis and acne.

Adverse Effects and Precautions

Salicylic acid is a mild irritant and application of salicylic acid preparations to the skin may cause dermatitis. Preparations containing high concentrations of salicylic acid can cause skin ulceration or erosion; healthy skin surrounding warts, corns, and calluses should be protected with soft paraffin or specially designed plasters when such preparations are being used. Salicylic acid should be used with care on the extremities of patients with impaired peripheral circulation or diabetes; caution has also been suggested if caustic preparations are used in patients with significant peripheral neuropathy. The drug is readily absorbed through the skin, and symptoms of acute systemic salicylate poisoning (see Aspirin, p. 24.2) have been reported after excessive use; deaths have occurred, mainly in children. To minimise absorption after topical application salicylic acid should not be used for prolonged periods, in high concentrations, on large areas of the body, or on inflamed or broken skin. Contact with mouth, eyes, and other mucous membranes should be avoided. In the UK, the MHRA has recommended that topical oral pain relief preparations containing salicylates should not be used in children under 16 years of age (for details, see Reye's Syndrome, p. 39.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Callicida; Callicida; Duofilm; Duoforte; Effaclar K; Koal; Neo A-V; Renovate; Salpad; Verrutopic AS; Verrutrix; ***Austral.***: Clearasil Blackhead Control; Clearasil DailyClear; Clearasil Medicated Wipes†; Clearasil Ultra Overnight; Clearasil Ultra Rapid; Duofilm; Egozite Cradle Cap; Ionil; John Plunketts Sunspot Cream; ***Austria***: Squamasol; ***Belg.***: Anticors Diable Vert†; Duofilm; Sicombyl; ***Braz.***: A Curitybina; Clean & Clear Gel Secativo; Clean & Clear Hidratante; Clean & Clear Locao Adstringente; Ionil; Kalloplast; Neutrogena Antiacne; ***Canad.***: Acnopur†; Almay Clear Complexion†; Artistry Blemish Control†; Aveda Balancing; Avon Clearskin Invisible Blemish Corrector†; Avon Clearskin Purifying Gel Cleanser†; Blemish Control; Carnation; Clearasil Cleanser†; Dermarest; Duofilm; Duoforte; Formula P6†; Medicated Callus Removers†; Medicated Corn Removers†; Neutrogena Acne Wash; Neutrogena Clear Pore†; Neutrogena T/Gel Conditioner†; Noxzema Triple Clean†; Occlusal†; pHisoDerm Acne Mask†; Scholl 2-Drop Corn Remedy; Scholl Callus Remover; Scholl Corn Remover; Sebcur; Sensitive Skin Facial Astringent†; Shiseido Pureness Anti-Shine†; Soluver Plus; Soluver; Trans-Plantar†; Trans-Ver-Sal†; X-Seb; Zap-It†; ***Chile***: DHS Sal; Duoplant Gel; Eucerin Piel Grasa†; Eucerin Reductor de Sebo/Grasa; Mediklin; Neutrogena Deep Clean Limpiador Facial; Neutrogena Gel Control Brillo†; Neutrogena Linea Acne†; Neutrogena T/Gel Acondicionador; Quitacallos; ***Cz.***: Callous†; Sophtal-POS N; Spofaplast†; Urgocor; Verruca Removal†; ***Fin.***: Cornina Hansaplast; ***Fr.***: Ciella; Coricide le Diable; Feuille de Saule; Ikeriane; Pommade Mo Cochon; Sanitos; Septisol†; Sophtal; Transvercid; Tricosteril Coripel†; Urgocor†; ***Ger.***: Aknefug-liquid; Collomack; Gehwol Huhneraugen-Pflaster extra stark; Gehwol Schalpaste; Gothaplast Hornhautpflaster; Gothaplast Huhneraugenpflaster; Lygal Kopfsalbe N†; Psorimed; Schrundensalbe Dermi-cyl; Sophtal-POS N; Squamasol; Urgocor†; Verrucid; ***Gr.***: Abadasol†; Adaptoplast; Apsoderm; Asalid; Astemil; Callifugo; Fungiheal; Hansaplast Callous; Opsor; Opsorad; Psorimed; Salicyd; Salipsor; Saronic; Solimed; Zino; ***Hong Kong***: Duofilm; Egozite Cradle Cap; ***Hung.***: Seal & Heal; ***India***: Dersol; Eremis; Keracnyl; ***Indon.***: Topix†; Yodsaben†; ***Irl.***: Acnisal; Callous Removal Pads; Carnation; Compound W†; Corn Removal Pads; Corn Removers; Occlusal; Pickles; Soft-Corn†; Thwart; Vericaps†; Verrugon; Wartex; ***Israel***: Carnation; Clearex for Sensitive Skin; Salikaren; Scholl Corn/Callous Removers; Trans-Ver-Sal; ***Ital.***: Keranon; Salicil; Trans-Ver-Sal; ***Malaysia***: Clearasil 3 in 1 Deep Cleansing Wash†; Clearasil Ice Wash†; Clearasil Ultra Deep Pore†; Clearasil; Egozite Cradle Cap; Ellgy Corns & Warts; Palmer's Skin Success Acne Medication; ***Mex.***: Duoplant; Excelsior; Ionil Plus†; Trans-Ver-Sal; ***Mon.***: Antalyre; ***Neth.***: Formule W; Psorimed†; ***NZ***: Duofilm; Egozite Cradle Cap; ***Philipp.***: Ionil†; Wart-Off†; ***Pol.***: Callous; Corn and Callous; Corn; Keratolysin†; Masc przeciw Odciskom i Zgrubieniom Skory; Saliderm; Seal & Heal; Soft Corn; Urgo Cor†; ***Port.***: Calicida Moreno; Transvercid; Urgocor; Verrufilm; ***Rus.***: Urgocor Coricide (Уpокор Мозольный); ***S.Afr.***: Compound W†; Cross Brand Corn Plasters†; Emzaclear; Freezone†; Jiffy Medi+ Plus†; Piccadilly Foot Ointment; SB Unola Corn Remover†; Trans-Ver-Sal†; Yalta Corn Salve†; ***Singapore***: Anti-White Spot; Centa Skin; Clearasil 3 in 1; Clearasil Deep Cleansing; Clearasil Ice Wash; Clearasil Oil Free Gel Wash; Clearasil Skin Perfecting Wash; Clearasil Ultra Acne Clearing; Clearasil Ultra Deep Pore; Clearasil Ultra Rapid Action; Clearasil Ultra Spot Clearing Scrub; Duofilm; FST; Panau Salap; Pineapple Brand Lotion; Senkon White Spot; Toh Skin; White Spot; ***Spain***: Callicida Gras†; Callicida Kendu; Callicida Salve†; Callofin†; Unguento Morry; Urgocall†; Verrupatch; Verruplan; ***Swed.***: Salsyvase; ***Switz.***: Scholl Warzenfilm†; Wurzeltod; ***Turk.***: Nasiral; Salsil; Scholl Callous†; ***UK***: Acnisal; Carnation; Clearasil Double Action Pads; Compound W; Occlusal; Pickles Foot Ointment; Scholl Callus Removal; Scholl Corn Removal; Scholl Verucca Removal; SCR; Snufflebabe Cradle Cap; Verrugon; Wartex; ***USA***: Clearasil Clearstick; Compound W; Dr Scholl's Callus Removers; Dr Scholl's Clear Away; Dr Scholl's Corn Removers; Dr Scholl's Corn/Callus Remover; Dr Scholl's Wart Remover; Duofilm; Duoplant; Fostex Acne Medication Cleansing; Freezone; Gordofilm; Hydrisalic; Ionil Plus†; Ionil; Keralyt; Mediplast; MG217 Sal-Acid; Mosco; Occlusal; Off-Ezy; Oxy Night Watch; P & S; Panscol; PropapH; Psor-a-set; Psoriasin Medicated Wash; SA; Sal-Acid†; Sal-Plant; Salac†; Salactic Film; Salacyn; Salex; Salkera; Salvax; Stri-Dex Clear; Trans-Ver-Sal AdultPatch; Trans-Ver-Sal PediaPatch; Trans-Ver-Sal PlantarPatch; Virasal; Wart Remover; Wart-Off; X-Seb; ***Venez.***: Acnil; Neutrogena T-Sal.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Fr.***: Billerol.

Pharmacopoeial Preparations
BP 2014: Coal Tar and Salicylic Acid Ointment; Compound Benzoic Acid Ointment; Dithranol and Salicylic Acid Ointment; Dithranol Paste; Salicylic Acid Collodion; Salicylic Acid Cream; Salicylic Acid Ointment; Zinc and Salicylic Acid Paste;
BPC 1973: Salicylic Acid and Sulphur Ointment;
USP 36: Benzoic and Salicylic Acids Ointment; Salicylic Acid Collodion; Salicylic Acid Gel; Salicylic Acid Plaster; Salicylic Acid Topical Foam; Zinc Oxide and Salicylic Acid Paste.

Salnacedin *(USAN, rINN)*

G-201; Salnacedina; Salnacédine; Salnacedinum; SCY; Сальнацедин.
N-Acetyl-L-cysteine salicylate.
$C_{12}H_{13}NO_5S$=283.3
CAS — 87573-01-1.
UNII — 02X9QIP2NU.

Profile

Salnacedin has anti-inflammatory and keratolytic properties and is applied topically in the treatment of seborrhoeic dermatitis and acne.

Sebacic Acid

Ácido decanodioico; Sebácico, ácido; Себациновая Кислота.
Decanedioic acid; Octane-1,8-dicarboxylic acid.
$C_{10}H_{18}O_4$=202.2
CAS — 111-20-6.
UNII — 97AN39ICTC.

Profile

Sebacic acid may be used as a buffering agent in cosmetic preparations. Some of its esters, such as diethyl sebacate ($C_{14}H_{26}O_4$ = 258.4) and diisopropyl sebacate ($C_{16}H_{30}O_4$ = 286.4) may be used as emollients.

Selenium Sulfide

Seleenidisulfidi; Selendisulfid; Seleni Disulfidum; Selenii disulfidum; Selenio, sulfuro de; Sélénium, disulfure de;

Selenium Disulphide; Selenium Sulphide; Seleno disulfidas; Sulfid seleničitý; Szelén-diszulfd; Сульфид Селения.

SeS_2=143.1

CAS — 7488-56-4.

ATC — D01AE13.

ATC Vet — QD01AE13.

UNII — Z69D9E381Q.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Selenium Disulfide; Selenium Sulfide BP 2014). A bright orange to reddish-brown powder. Practically insoluble in water.

USP 36: (Selenium Sulfide). A bright orange to reddish-brown powder with not more than a faint odour. Practically insoluble in water and in organic solvents; soluble 1 in 161 of chloroform and 1 in 1667 of ether.

Uses and Administration

Selenium sulfide has antifungal and antiseborrhoeic properties. It is used topically in the treatment of dandruff (pityriasis capitis) and seborrhoeic dermatitis of the scalp (p. 1689.1). Five to 10 mL of a lotion or shampoo containing 2.5% of selenium sulfide is applied to the wet scalp; the hair is rinsed and the application repeated; the preparation should remain in contact with the scalp for 2 to 3 minutes each time. The hair should be well rinsed after the treatment and all traces of the preparation removed from the hands and nails. Applications are usually made twice weekly for 2 weeks, then once weekly for 2 weeks and then only when necessary. Shampoos and lotions containing 1% are also used.

Selenium sulfide is also used as a 2.5% lotion in the treatment of pityriasis versicolor (see Skin Infections, p. 568.1). The lotion may be applied to the affected areas with a small amount of water and allowed to remain for 10 minutes before thorough rinsing. This procedure is repeated once daily for about 7 days. Alternatively undiluted 2.5% lotion has been applied at bedtime and washed off in the morning on 3 separate occasions at 3-day intervals.

Selenium sulfide has also been used as an adjunct to the systemic treatment of tinea capitis (see Dermatophytoses under Skin Infections, p. 568.1).

Adverse Effects, Treatment, and Precautions

Topical application of selenium sulfide can produce irritation of the scalp and skin, especially in the genital area and skin folds. Treated areas should be rinsed thoroughly to reduce inflammation, and contact with the eyes should be avoided. Oiliness or dryness of the scalp or hair, hair discoloration, and hair loss have been reported. Selenium sulfide shampoos should not be used within 48 hours of applying hair colours or straightening or waving preparations. Selenium sulfide may discolour metals.

Only traces of selenium sulfide are absorbed through intact skin but prolonged use on broken skin has resulted in systemic toxicity. To minimise absorption it should not be applied to mucous membranes or to skin that is inflamed or damaged. Toxicity is expected to be low from the ingestion of shampoos containing selenium sulfide. Nausea, vomiting, and diarrhoea may occur and gastrointestinal decontamination is generally considered unnecessary, but systemic absorption and toxicity, particularly neurological effects, might develop if large amounts are retained in the gut.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies selenium sulfide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Systemic toxicity. A woman with excoriated eruptions on her scalp developed weakness, anorexia, abdominal pain, vomiting, tremors, sweating, a metallic taste in her mouth, and a garlic-like smell on her breath after using a shampoo containing selenium sulfide 2 or 3 times weekly for 8 months.[1] All symptoms subsided 10 days after the shampoo was stopped.

1. Ransone JW, *et al.* Selenium sulfide intoxication. *N Engl J Med* 1961; **264:** 384–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Selsun; ***Austria***: Selsun; Selukos; ***Belg.***: Selsun; ***Braz.***: Caspacil; Selsun; ***Canad.***: Versel; ***Chile***: Selsun; ***China***: Xi Er Sheng (希尔生); ***Denm.***: Selsun†; ***Fin.***: Selsun†; Selukos; ***Fr.***: Selsun; Vichy Dercos Shampooing Antipelliculaire; ***Ger.***: Selsun; Selukos†; ***Gr.***: Selsun; ***Hong Kong***: Sellon; Selsun†; ***Indon.***: Selsun; Topisel†; ***Irl.***: Selsun; ***Israel***: Sebosel; Selsun; ***Ital.***: Selsun Blu; ***Malaysia***: Sellon; ***Neth.***: Selsun; ***Norw.***: Selsun; Selukos; ***NZ***: Selsun; ***Phil.ipp.***: Selsun Blue†; ***Pol.***: Selsun; ***Port.***: Finitor; Selenix; ***S.Afr.***: Selsun; ***Singapore***: Seldron; Selsun; ***Spain***: Bioselenium; Caspiselenio†; ***Swed.***: Selsun; Selukos; ***Switz.***: Selsun; ***Thai.***: Sebosel; Selfide; Sellon; Selsun; ***Turk.***: Selsun; ***UK***: Selsun; ***USA***: Head & Shoulders Intensive Treatment; Selenos; SelRx; Selsun; ***Venez.***: Selegel.

Multi-ingredient Preparations. ***Arg.***: Selegel; ***Chile***: Selegel; Shampoo Anti Caspa Fortificante; Shampoo Anti-Caspa; ***Fr.***: Selegel†; ***India***: Candid-TV; Dandruff Plus; ***Spain***: Sebumselen; ***Switz.***: Ektoselene; ***Venez.***: Selenil.

Pharmacopoeial Preparations

BP 2014: Selenium Sulphide Scalp Application;
USP 36: Selenium Sulfide Topical Suspension.

Sinecatechins *(USAN)*

Kunecatechins.

A mixture whose major constituents are (-)-epicatechin, (-)-epigallocatechin, the corresponding 3-gallate esters, and their corresponding epimers..

CAS — 811420-59-4 (sinecatechins); 490-46-0 ((-)-epicatechin); 1257-08-5 ((-)-epicatechin 3-O-gallate); 970-74-1 ((-)-epigallocatechin); 989-51-5 ((-)-epigallocatechin 3-O-gallate).

UNII — W2ZU1RY8B0 (green tea leaf); T432289GYZ (sinecatechins).

NOTE. The name Polyphenon E has been used as a trade mark for sinecatechins-containing preparations.

Profile

Sinecatechins is a mixture of complex polyphenols extracted from green tea leaves. Although its mechanism of action is unclear, sinecatechins is used in the treatment of external genital and perianal warts (p. 1689.3). A 15% ointment is applied 3 times daily until complete clearance of all warts, but for no longer than 16 weeks. Local adverse effects are common with the topical application of sinecatechins and include erythema, pruritus, burning, pain or discomfort, erosion or ulceration, oedema, induration, and vesicular rash. Less common effects include urethritis, pigmentation changes, and hyperaesthesia.

References.

1. Gross G, *et al.* A randomized, double-blind, four-arm parallel-group, placebo-controlled phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. *J Eur Acad Dermatol Venereol* 2007; **21:** 1404–12.
2. Anonymous. Veregen: a botanical for treatment of genital warts. *Med Lett Drugs Ther* 2008; **50:** 15–16.
3. Gross G. Polyphenon E: Eine neue topische Therapie für Condylomata acuminata. *Hautarzt* 2008; **59:** 31–5.
4. Stockfleth E, *et al.* Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. *Br J Dermatol* 2008; **158:** 1329–38.
5. Tatti S, *et al.* Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol* 2008; **111:** 1371–9.
6. Tatti S, *et al.* Polyphenon E: a new treatment for external anogenital warts. *Br J Dermatol* 2010; **162:** 176–184.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Veregen; ***Ital.***: Epinerve; ***USA***: Veregen.

Multi-ingredient Preparations. ***Indon.***: Liproqy; Vipro-G; Vipro-G; ***Ital.***: Legalon Plus; ***USA***: Dexatrim Max Daytime Appetite Control.

Skin Substitutes

Sustitutos de la piel.

Profile

Biological and semisynthetic materials have been developed for use as temporary dressings in burns, ulcers, and other injuries associated with skin loss. The rationale is to prevent fluid and heat loss, to reduce infection, to protect exposed structures, to reduce pain, and to prepare the site for grafting (see Burns, p. 1683.1, and Wounds and Ulcers, p. 1690.1).

Denatured porcine and bovine skin, consisting of the dermal and/or epidermal layers, have been used. More recently bioengineered human skin equivalents have been produced which more closely mimic human skin, as well as human, living dermal replacement products.

Reviews.

1. Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol* 2005; **23:** 403–12.
2. Braye F, *et al.* Les substituts cutanés reconstruits en laboratoire: application au traitement des brûlés. *Pathol Biol (Paris)* 2005; **53:** 613–17.
3. Bar-Meir E, *et al.* Skin substitutes. *Isr Med Assoc J* 2006; **8:** 188–91.
4. Hrabchak C, *et al.* Biological skin substitutes for wound cover and closure. *Expert Rev Med Devices* 2006; **3:** 373–85.
5. Blozik E, Scherer M. Skin replacement therapies for diabetic foot ulcers: systematic review and meta-analysis. *Diabetes Care* 2008; **31:** 693–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kytinon Hemostatico; Kytinon Kit; Kytinon Lamina; Kytinon Q4; ***S.Afr.***: Dermagraft†; ***UK***: Dermagraft; Myskin; TransCyte; ***USA***: Apligraf; Dermagraft; Orcel; TransCyte.

Multi-ingredient Preparations. ***Arg.***: Kytinon ABC; Kytinon ATM.

Sodium Ascorbyl Phosphate

Ascorbil Fosfato de Sodio; Sodium Ascorbyl Monophosphate; Trisodium Ascorbate-2-phosphate.

$C_6H_6Na_3O_9P$=322.0

CAS — 66170-10-3.

UNII — 836SJG51DR.

Profile

Sodium ascorbyl phosphate is a derivative of vitamin C (p. 2110.3) with antoxidant properties. It is used topically in preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Probio-C; ***Mex.***: Cetopic; ***Venez.***: Cepin.

Sodium Pidolate *(pINNM)*

NaPCA; Natrii Pidolas; Pidolate de Sodium; Pidolato sódico; Piroglutamato sódico; Pirrolidona carboxilato de sodio; Sodium Pyroglutamate; Sodium Pyrrolidone Carboxylate; Натрий Пидолат.

Sodium 5-oxopyrrolidine-2-carboxylate.

$C_5H_7NNaO_3$=152.1

CAS — 28874-51-3 (DL-sodium pidolate); 54571-67-4 (L-sodium pidolate).

UNII — 1V74VH163T (L-sodium pidolate); 469OTG57A2 (DL-sodium pidolate).

Profile

Sodium pidolate is used as a humectant. It is applied topically as a cream or lotion, often in multi-ingredient preparations, in the treatment of dry skin disorders.

Copper and zinc pidolate are used similarly; they have also been used as nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Effaclar; Nicozinc; ***Hong Kong***: DermaVeen†.

Multi-ingredient Preparations. ***Arg.***: Lacticare; Nicozinc; ***Austral.***: Dermadrate; FootSmart; Papulex; ***Braz.***: Effaclar; Lacticare; ***Chile***: Effaclar Agua Desmaquillante Purificante; Effaclar Hidratante Matificante Activa; Effaclar K; Kerium Anticaspa -Caspa Grasa; Normaderm Barra de Limpieza; Uriage Cu-Zn; ***Fr.***: Bio-Zinc†; Cu-Zn; Effaclar K; Forcapil; Hydracuivre; Hyseke; Lacticare†; Mycogel†; Papulex; ***Hong Kong***: Dermadrate; DS Emulsion†; Mycogel†; ***Hung.***: Forcapil; ***India***: Aloederm-B; Efaderm; Efatop-PE; ***Indon.***: Lacticare†; ***Irl.***: Effaclar K; Effaclar; Hydromol; Lacticare†; ***Ital.***: Angstrom Viso; ***Malaysia***: Aqua Care; Lacticare; ***Mex.***: Lacticare; ***NZ***: Dermadrate†; ***Philipp.***: Lacticare; ***S.Afr.***: Lacticare†; ***Singapore***: Dermadrate; Dermavive; Effaclar K; Lacticare; Papulex Isocorrexion; Papulex Oil-Free; Stop-Itch Plus; ***Thai.***: Lacticare; ***UK***: Hydromol.

Squaric Acid Dibutylester

Éster dibutílico del ácido escuárico; Quadratic Acid Dibutylester; SADBE; Дибутиловый Эфир Скваториковой Кислоты.

The dibutyl ester of 3,4-dihydroxy-3-cyclobutene-1,2-dione; 3,4-Dibutoxy-3-cyclobutene-1,2-dione.

$C_{12}H_{18}O_4$=226.3

CAS — 2892-62-8 (squaric acid dibutylester); 2892-51-5 (squaric acid).

UNII — 4RTO57VG65.

Profile

Squaric acid dibutylester has been tried similarly to diphencyprone (p. 1700.3) as a contact sensitiser in the treatment of alopecia. It has also been tried in warts.

References.

1. Tosti A, *et al.* Long-term results of topical immunotherapy in children with alopecia totalis or alopecia universalis. *J Am Acad Dermatol* 1996; **35:** 199–201.

All cross-references refer to entries in Volume A

2. Micali G, *et al*. Treatment of alopecia areata with squaric acid dibutylester. *Int J Dermatol* 1996; **35:** 52–6.
3. Lee AN, Mallory SB. Contact immunotherapy with squaric acid dibutylester for the treatment of recalcitrant warts. *J Am Acad Dermatol* 1999; **41:** 595–9.
4. Silverberg NB, *et al*. Squaric acid immunotherapy for warts in children. *J Am Acad Dermatol* 2000; **42:** 803–8.
5. Micali G, *et al*. Use of squaric acid dibutylester (SADBE) for cutaneous warts in children. *Pediatr Dermatol* 2000; **17:** 315–18.
6. Dall'Oglio F, *et al*. Adult and paediatric contact immunotherapy with squaric acid dibutylester (SADBE) for recurrent, multiple, resistant, mucocutaneous anogenital warts. *Sex Transm Infect* 2002; **78:** 309–10.
7. Dall'Oglio F, *et al*. Topical immunomodulator therapy with squaric acid dibutylester (SADBE) is effective treatment for severe alopecia areata (AA): results of an open-label, paired-comparison, clinical trial. *J Dermatol Treat* 2005; **16:** 10–14.
8. Ajith C, *et al*. Efficacy and safety of the topical sensitizer squaric acid dibutyl ester in alopecia areata and factors influencing the outcome. *J Drugs Dermatol* 2006; **5:** 262–6.
9. Hama N, *et al*. Usefulness of topical immunotherapy with squaric acid dibutylester for refractory common warts on the face and neck. *J Dermatol* 2009; **36:** 660–2.

Sulfur

Azufre; Enxôfre; Kén; Kükürt; Rikki; Schwefel; Siarka; Síra; Soufre; Sulphur; Sulphurium; Svavel; Cepa.

S=32.06

CAS — 7704-34-9.

ATC — D10AB02.

ATC Vet — QD10AB02.

UNII — 70FD1KFU70.

Pharmacopoeias. In *Chin.*, *Eur*. (see p. vii), *Jpn*, and *US*. Some have monographs for Precipitated Sulfur (Milk of Sulfur), Sublimed Sulfur (Flowers of Sulfur), or both. Some specify it is only for external use.

Eur. also includes for homoeopathic preparations.

Ph. Eur. 8: (Sulfur for External Use). A yellow powder. The size of most of the particles is not greater than 20 micrometres and that of almost all the particles is not greater than 40 micrometres. Practically insoluble in water; soluble in carbon disulfide; slightly soluble in vegetable oils. Protect from light.

Ph. Eur. 8: (Sulfur for Homoeopathic Preparations; Sulfur ad Praeparationes Homoeopathicas). A yellow powder. Practically insoluble in water; soluble in carbon disulfide; slightly soluble in vegetable oils. Protect from light.

USP 36: (Precipitated Sulfur). A very fine, pale yellow, odourless, amorphous or microcrystalline powder. Practically insoluble in water; very slightly soluble in alcohol; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; soluble 1 in 100 of olive oil.

USP 36: (Sublimed Sulfur). A fine, yellow, crystalline powder with a faint odour. Practically insoluble in water and in alcohol; sparingly soluble in olive oil.

Uses and Administration

Sulfur is a keratolytic, a mild antiseptic, a mild antifungal, and a parasiticide.

Colloidal sulfur has a smaller particle size than either precipitated or sublimed sulfur. It is sulfur in an aqueous medium containing a colloid such as albumin or gelatin.

Sulfur has been widely used in lotions, creams, or ointments, usually combined with other agents, in concentrations of up to 10% in the treatment of acne, dandruff, seborrhoeic conditions, scabies, and superficial fungal infections, although there are more convenient and effective preparations.

Lotions of precipitated sulfur with lead acetate have been used to darken grey hair.

Sulfur was also formerly used as a mild irritant laxative.

Homoeopathy

Sulfur has been used in homoeopathic medicines under the following names: Sulphur.

General references.

1. Lin AN, *et al*. Sulfur revisited. *J Am Acad Dermatol* 1988; **18:** 553–8.
2. Gupta AK, Nicol K. The use of sulfur in dermatology. *J Drugs Dermatol* 2004; **3:** 427–31.

Adverse Effects and Precautions

Topical application of sulfur can cause skin irritation and dermatitis has been reported after repeated application. Contact with the eyes, mouth, and other mucous membranes should be avoided. Contact with sulfur can discolour certain metals such as silver, and application of sulfur with topical mercurial compounds can lead to the generation of hydrogen sulfide which has a foul odour and may stain the skin black.

Handling. Sulfur has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulfur as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Macbirs Sulphur; Molnia; ***Canad.***: Aloepure; Rodan & Fields Proactiv Refining Mask†; ***India***: Dermosol; ***Indon.***: Acne Feldin; JF Sulfur†; ***Ital.***: Acqua Sirmione; Eudermal Sapone Allo Zolfo pH 5; Misurid; ***Malaysia***: JF Sulfur; ***Neth.***: Schwef-Heel; ***Philipp.***: Erasul; Sulderm†; ***Port.***: Acnederma†; ***Turk.***: Capila Savon; ***USA***: Acne Lotion 10; Liquimat; Sulfoam; Sulmasque.

Multi-ingredient Preparations. ***Arg.***: Azufracid; Bentophyto; Bifena; Farmigras; Medicatex; Merbenloc; Nemegel; Novofarma; Novofarma; Onelacne; Pinklot; Sastid; Suffisance; Ukase Dermo; Xicanil Control†; ***Austral.***: Clearasil Pimple Treatment Cream†; EgoPsoryl TA; Eskamel†; Neo-Medrol†; Psor-Asist; Psor-Asist; ***Austria***: Aknichthol; Eucarbon; Herposicc; Schwefelbad Dr Klopfer; ***Braz.***: Acnase; Actine; Dermax; Dermic†; Dermolimp; Salder S; Salisoap; Salisoap; Sastid; ***Canad.***: Acnomel†; Clearasil Acne Control†; Clearasil Acne Cream†; Clearasil Stayclear†; Mazon Medicated Shampoo; Medrol Acne Lotion; Meted†; Neo-Medrol Acne; Sebo Concept D/A; Sebulex†; Sterex Plus†; Sterex†; Sulfacet-R; ***Chile***: Dermac Crema; Sastid Jabon; ***Cz.***: Eucarbon; ***Fr.***: Dermo-Sulfuryl; Kertyol PSO; Kertyol PSO; Notrino†; Paps†; Selso; Solacy; Sulfuryl; Zeniac; ***Ger.***: Schwefelbad Dr Klopfer†; ***Gr.***: Creme Phyllis de Jeunesse; Medrol Acne Lotion; Neo Akmine; Neo-Medrol; Rysolone; ***Hong Kong***: Acne-Aid†; BF-2-4-2†; Egopsoryl TA; Neo-Medrol Acne; Sastid; ***Hung.***: Bolus Laxans; Eucarbon; Schwefelbad Dr Klopfer†; ***India***: Acnil; Coalsyl-S; Persol Forte; ***Indon.***: Bioacne; Feldixid†; Salicyl-Zwavelzalf; Sastid†; ***Irl.***: Cocois; Meted; Pragmatar†; Skin Clear†; ***Israel***: Duo-Scabil; Eucarbon; Neo-Medrol; ***Ital.***: Acnesan; Anti-Acne; Eucarbon; Geroderm Zolfo; Lenirose; Sacnel; Same-Seb; Saugella Solido Zolfo; Troca Flu Spray Nasale; ***Jpn***: Circanetten; ***Malaysia***: Acne-Aid†; Clearasil Pimple Treatment; Egopsoryl TA; Eucarbon; Neo-Medrol; Nixoderm; Panoff; Sastid; ***Mex.***: Acnomel; Axel; Axel; Dermac; Jabon del Tio Nacho; Sastid; ***NZ***: Clearasil; Coco-Scalp; Egopsoryl TA; ***Philipp.***: Dermalin†; Sastid; ***Pol.***: Acne Sulf†; Balsulphur; Cocois; Dermaknel†; Zdroj; ***Port.***: Resodermil†; ***Rus.***: Sulfodecortem (Сульфодекортэм); ***S.Afr.***: Balsem Sulphuris; Clearasil T†; Eskamel†; Haarlemensis; Neo-Medrol†; Sastid; Zeel; Zeel; ***Singapore***: Acne Clear; Acne-Aid†; Clearasil Pimple Treatment; Cocois Co; Cocois; Egopsoryl TA; Neo-Medrol; Nixoderm; Panoff; Poly-N; Sastid; Veelanz's Ointment; ***Spain***: Crisiaxo; Laxante Sanatorium†; ***Swed.***: Sevorex; ***Switz.***: Acne Creme; Acne Gel; Ektoselene; Sebo-Soufrol†; ***Thai.***: Circanetten; Neo-Medrol; Sastid†; ***Turk.***: Eucarbon; Karboseptin; Wilkinson†; ***UK***: Actinac†; Balto Foot Balm; Clearasil Active Treatment Cream; Cocois; Herbheal Ointment; Meted; Psorasolv; Sebco; Simpsons; Skin Clear; TCP; ***Ukr.***: Eucarbon (Эукарбон); ***USA***: Acno; Acnomel; Acnotex; Ala seb T; ala seb; Avar; Aveeno Cleansing Bar†; Bensulfoid; Boil Ease; BP Cleansing Wash; Cerisa; Chigg Away; Claris; Clenia†; Exoderm; Finac; Fostex Medicated; Garimide; Meted; MG217 Medicated Tar-Free; MG400; Nicosyn; NuOx; Pazol XS; Pernox; Plexion; Rezamid; Rosac†; Rosaderm; Rosanil; Rosula†; Sastid; SE SS; Seale's Lotion; Sebasorb; Sebex-T; Sebex; Sebulex; SSS; Sulfacet-R; SulfaCleanse; Sulforcin; Sulfoxyl; Sulpho-Lac; SulZee†; Sumadan; Sumaxin; Suphera; Virti-Sulf; Zencia; Zetacet†; ***Venez.***: Klenyl; Klenyl; Niosilin; Selenil.

Homoeopathic Preparations. ***Austral.***: Echine†; Homoderma; ***Austria***: Acidum picrinicum Med Complex†; Engystol; Erbiode Akne; Erysidoron Nr 2; Mandragora Med Complex; Ohrentropfen Similasan; Sulfur Med Complex; ***Canad.***: Adrisin†; Art Complex†; Arthflex; Backache with Arnica†; Berberis-Homaccord†; Calendula +; Calms Forte 4 Kids; Calsom†; Cutisitum†; Earache; Echinacea Compositum; Echinacea L40†; Eczema L87; Endoteel†; Engystol; Erysidoron 2†; Euphorbium Compositum; Euphorbium Compositum; Execalm†; Formula DE 226†; Formula PC 223†; Hae 1 Complex†; Hepar Compositum; Homeo-Form G†; Hyalgesic LBP†; Ikoplex 12†; Indigestion†; Luffeel Nasal Spray; SK Complex†; Sorinoheel; Ubicoenzyme; Urarthone†; Zeel Comp; ***Chile***: Grippakit; Ikoplex No 12; ***Cz.***: Engystol; Luffeel; Paragrippe; Zeel Compositum; Zeel Salbe†; ***Fr.***: Abbe Chaupitre no 19†; Abbe Chaupitre no 1†; Abbe Chaupitre no 22†; Abbe Chaupitre no 35†; Abbe Chaupitre no 79†; Abbe Chaupitre no 82†; Abbe Chaupitre no 83†; Abbe Chaupitre no 88†; Abbe Chaupitre no 91†; Aesculus Complexe No 103; Basilicum Complexe No 96; Cholesterolum Complexe No 112†; Echinacea Complexe No 40; Euphorbium Complexe No 88; Geranium Complexe No 108†; grippe†; Hypophysis Complexe No 31†; Jenoverine†; Millefolium Complexe No 7†; Nux Vomica Complexe No 49; Paragrippe; Pulsatilla Complexe No 60†; Rhododendron Complexe No 42†; Scabiosa Complexe No 87; Sclerocalcine; Staphysagria Complexe No 92†; Sulfur Complexe No 12; Symphytum Complexe No 48†; Urarthone; ***Ger.***: Asthmakhell N; BN dolo†; Cefalymphat†; Cefasulfon N†; Chamoca M; Colchicum Complex; Colintest-Gastreu; Cysto-cyl L Ho-Len-Complex; Derma-Plantin†; Dermi-cyl L Ho-Len-Complex; Engystol; Erysidoron 2; Gastro-Plantin N†; Genu-cyl L Ho-Len-Complex; Haemorrhoid-Gastreu N; Hepar comp; Hewerheum N†; Hexacyl; Luffeel Comp; Lymphaden Complex; Lymphaden; metabiarex; Mucosa compositum; Regenaplex Haut G; Rufebran rheumo†; Sulfurell; Toxiselect; Zeel comp; ***Hung.***: Klimakt-Heel; Luffeel; Zeel; ***Neth.***: Aesculus Comp; Asakell; Asthmakhell†; Auriculite; Bronchilite; Dermafleur; Dermalite; Echinacea comp; Engystol; Hemorrolite; Homeocare Revito; Jenoverine†; Luffeel H; Lymfelite; Paragrippe†; Prurilite; Pulsatilla comp; Thuyalite; Urtizon complex; Zeel comp N; ***Port.***: Paragrippe; ***Rus.***: Tabacum-Plus (Табакум-Плюс); Urtica-Plus (Уртика-Плюс); Zeel T (Цель Т); ***S.Afr.***: Engystol N; Erysidoron 2†; ***Switz.***: Engystol; Regenaplex Nr. 25a; Regenaplex Nr. 31b; Regenaplex Nr. 49a; Regenaplex Nr. 71b; ***UK***: Erysidoron 2; ***Ukr.***: Engystol (Энгистол); ***USA***: Eczemol.

Pharmacopoeial Preparations

BPC 1973: Salicylic Acid and Sulphur Ointment;

USP 36: Resorcinol and Sulfur Topical Suspension; Sulfur Ointment.

Sulfurated Lime

Cal sulfurada; Calcium Sulphide; Calx Sulphurata; Sulfuro cálcico; Sulphurated Lime; Сульфид Кальция (calcium sulfide); Сернистый Кальций (calcium sulfide).

CAS — 8028-82-8 (sulfurated lime solution); 20548-54-3 (calcium sulfide); 1344-81-6 (calcium polysulfide).

Profile

Sulfurated lime is a mixture containing calcium sulfide (CaS) and not more than 50% of calcium sulfate (p. 2173.1); it is prepared by heating calcium sulfate with carbonaceous matter. Sulfurated lime solution (Vleminckx's solution) is an aqueous solution containing calcium polysulfides and calcium thiosulfate prepared by boiling sublimed sulfur with calcium hydroxide in water.

Sulfurated lime has been used topically as sulfurated lime solution for acne, scabies, seborrhoeic dermatitis, and pustular infections such as boils and carbuncles. A similar solution known as 'lime-sulphur' (lime sulfur) is used as a fungicide in horticulture.

Homoeopathy

An impure grade of calcium sulfide has been used in homoeopathic medicines under the following names: Hepar sulfuris; Hepar sulfuris calcareum; Hepar Sulphuris; Hepar Sulph.; Hepar sulphuris calcareum; Hepar sulph calc.

NOTE. The name Hepar Sulfuris is also applied to Sulfurated Potash (see below).

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Childrens Cough Relief; Childrens Runny Nose Relief; Earache Relief†; Respatona Chesty Cough & Nasal Congestion; Respatona Head Cold; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; ***Austria***: Echinacea-Cosmoplex; Euphorbium Compositum; Globuli gegen Kopfschmerzen; Globuli gegen Schlafstorungen; Nebenhohlen-Tropfen Nr 26†; Rhododendroneel; Tonsiotren; Traumeel; ***Canad.***: Angeel†; Calnor†; ClearAc†; Crou Complex†; Echinacea Compositum; Euphorbium Compositum; Euphorbium Compositum; Homeo-Form SI†; Homeovox; Hylands Cough; Hylands Formula CA; Larydol†; Nareel†; Rhinar†; Sinus Ease; Sinus; Sinuspax†; Traumeel; ***Cz.***: Angin-Heel S; Euphorbium Compositum; Homeovox; Traumeel; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Abbe Chaupitre no 48†; Abbe Chaupitre no 91†; Boripharm No 10†; Boripharm No 22†; Homeovox; Sinuspax; Voxpax; ***Ger.***: Dermi-cyl L Ho-Len-Complex; Entzundungstropfen; Euphorbium comp SN; Gastritis Complex; Haut-Gastreu R60; Hevertotox; Immunorell; Infihepan; Odonton-Echtroplex; Otofren; Roth's RKT Tropfen; Rufebran broncho†; Schworosin; Sinusitis Hevert SL; Sinusitis Hevert†; Tonsiotren H; toxi-loges; Traumeel S; ***Hung.***: Homeovox; Traumeel; ***Neth.***: Emvita 10; Emvita 3; Habifac; Hemorrolite; Homeovox; Kind 0-3 Chamodent; Lergilite; Mercurius-Heel; Prurilite; Sabal-Homaccord; Thuyalite; Tonsiotreen; Traumeel S; ***Port.***: Homeovox; ***Rus.***: Homeovox (Гомеовокс); Sabal-Homaccord (Сабаль-Гомаккорд); Tonsilotren (Тонзилотрен); ***S.Afr.***: Euphorbium Compositum S†; Traumeel S; ***Switz.***: Homeovox; Regenaplex Nr. 50b; Sinuspax†; Traumeel; TussEx; ***Ukr.***: Dentokind (Дентокинд); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); Traumeel S (Траумель С); ***USA***: Traumeel; ***Venez.***: Traumeel.

Sulfurated Potash

Foie de Soufre; Hepar Sulfuris; Hígado de azufre; Kalii Sulfidum; Liver of Sulphur; Potasa sulfurada; Potassa Sulphurata; Schwefelleber; Sulphurated Potash; Сернаа Печень.

CAS — 39365-88-3.

NOTE. The title Hepar Sulphuris is used in homoeopathic medicine for an impure grade of calcium sulfide—see Sulfurated Lime, above.

Pharmacopoeias. In *US*.

USP 36: (Sulfurated Potash). A mixture composed chiefly of potassium polysulfides and potassium thiosulfate, containing not less than 12.8% of sulfur as sulfide. Irregular, liver-brown pieces when freshly made, changing to greenish-yellow. It has an odour of hydrogen sulfide. Soluble 1 in 2 of water, usually leaving a slight residue. Alcohol dissolves

only the sulfides. A 10% solution is light brown in colour and alkaline to litmus. Store in small, airtight containers.

Incompatibility. Sulfurated potash is incompatible with acids.

Profile

Sulfurated potash has been used in the treatment of acne and other skin disorders usually in the form of a lotion with zinc sulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Cz.***: Lamioflur†; ***Ger.***: Sinasal; ***Hung.***: Angin-Heel; ***Rus.***: Belladonna-Plus (Белладонна-Плюс); Pharyngomed (Фарингомед); Phytolacca-Plus (Фитолакка-Плюс); Rhus-Plus (Рус-Плюс); Traumeel S (Траумель С).

Pharmacopoeial Preparations
USP 36: Zinc Sulfide Topical Suspension.

Sulisobenzone *(USAN, rINN)*

Benzofenon-4; Benzophenone-4; NSC-60584; Sulisobenzona; Sulisobenzonum; Сулизобензон.
5-Benzoyl-4-hydroxy-2-methoxybenzenesulphonic acid.
$C_{14}H_{12}O_6S$=308.3
CAS — 4065-45-6.
UNII — 1W6L629B4K.

NOTE. Escalol 577 and Uvinul MS 40 are trade names that have been used for sulisobenzone.

Pharmacopoeias. In *US.*

USP 36: (Sulisobenzone). Light tan powder. M.p. about 145 degrees. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in ethyl acetate. Store in airtight containers. Protect from light.

Profile

Sulisobenzone, a substituted benzophenone, is a sunscreen (p. 1681.3) with actions similar to those of oxybenzone (p. 1715.3). It is effective against UVB and some UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Nubevital BB; Nubevital Sunblock Ultra; Refrane Plus; ***Braz.***: Sunmax Acqua; ***Chile***: Hidrafil†; Spectraban 55; ***Mex.***: Hidrafil; Spectraban 55; ***USA***: Hawaiian Tropic Protective Tanning Dry.

T4 Endonuclease V

Bacteriophage T4 Endodeoxyribonuclease V; T4 Эндонуклеаза V; T4N5.
Coliphage T4 endodeoxyribonuclease V.
CAS — 52227-85-7.

NOTE. The name Dimericine has been used as a trade mark for T4 endonuclease V.

Profile

T4 endonuclease V is a DNA-repair enzyme that is reported to remove DNA damaged by UV radiation. It is under investigation to reduce the incidence of actinic keratosis and basal cell carcinoma in patients with xeroderma pigmentosum (see Photosensitivity Disorders, p. 1686.2).

References.
1. Wolf P, *et al.* Topical treatment with liposomes containing T4 endonuclease V protects human skin in vivo from ultraviolet-induced upregulation of interleukin-10 and tumor necrosis factor-α. *J Invest Dermatol* 2000; **114:** 149–56.
2. Yarosh D, *et al.* Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet* 2001; **357:** 926–9.
3. Cafardi JA, Elmets CA. T4 endonuclease V: review and application to dermatology. *Expert Opin Biol Ther* 2008; **8:** 829–38.

Tacalcitol *(BAN, rINN)*

1α,24-Dihydroxycholecalciferol; 1α,24-Dihydroxyvitamin D_3; Tacalcitolum; Takalsitol; Такальцитол.
(+)-(5*Z*,7*E*,24*R*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,24-triol monohydrate.
$C_{27}H_{44}O_3.H_2O$=434.7
CAS — 57333-96-7 (anhydrous tacalcitol); 93129-94-3 (tacalcitol monohydrate).
ATC — D05AX04.
ATC Vet — QD05AX04.
UNII — C2W72OJ5ZU.

Uses and Administration

Tacalcitol is a vitamin D_3 derivative, with actions and uses similar to those of calcipotriol (p. 1697.3).

Tacalcitol is applied topically in the management of plaque psoriasis (p. 1688.1). It is used as the monohydrate, as either a lotion or an ointment, in a concentration equivalent to 4 micrograms/g (0.0004%) of anhydrous tacalcitol. Applications are made sparingly, once daily, preferably at bedtime. No more than 10 mL of lotion or 10 g of ointment should be applied each day. When used together, the total weekly dose of anhydrous tacalcitol should not exceed 280 micrograms (e.g. 30 mL of lotion plus 40 g of ointment). Duration of treatment depends on the severity of the lesions; continuous and intermittent treatments for up to 8 weeks have been used with the lotion, and up to 18 months with the ointment.

Tacalcitol may be degraded by UV radiation and therefore if combined with UV therapy, the radiation should be given in the morning and tacalcitol applied at bedtime.

References.
1. Peters DC, Balfour JA. Tacalcitol. *Drugs* 1997; **54:** 265–71.
2. Gollnick H, Menke T. Current experience with tacalcitol ointment in the treatment of psoriasis. *Curr Med Res Opin* 1998; **14:** 213–18.
3. Harrison PV. Topical tacalcitol treatment for psoriasis. *Hosp Med* 2000; **61:** 402–5.
4. Van de Kerkhof PCM, *et al.* Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. *Br J Dermatol* 2002; **146:** 414–22.
5. Lecha M, *et al.* Tacalcitol in the treatment of psoriasis vulgaris: the Spanish experience. *J Eur Acad Dermatol Venereol* 2005; **19:** 414–17.

Adverse Effects and Precautions

As for Calcipotriol, p. 1698.2. Paraesthesia may also occur. Tacalcitol may be applied to the face, but care should be taken to avoid the eyes. Tacalcitol may be degraded by UV radiation (see Uses and Administration, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Curatoderm; ***Belg.***: Curatoderm; ***Chile***: Bonalfa†; ***China***: Bonalfa (萌尔夫); ***Cz.***: Curatoderm; ***Fr.***: Apsor; ***Ger.***: Curatoderm; ***Hung.***: Curatoderm; ***Israel***: Curatoderm; ***Ital.***: Ticlapsor; Vellutan; ***Jpn***: Bonalfa; ***Mex.***: Bonalfa†; ***Pol.***: Curatoderm; ***Port.***: Bonalfa; ***Spain***: Bonalfa; ***Switz.***: Curatoderm; ***UK***: Curatoderm.

Purified Talc

E553(b); Mastek; Powdered Talc; Purified French Chalk; Talc; Talco (esteatita); Talco purificado; Talcum; Talcum Purificatum; Talk; Talkas; Talkki; Talkum; Очищенный Тальк.
CAS — 14807-96-6.
UNII — 7SEV7J4R1U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Talc; Purified Talc BP 2014). A powdered, selected, natural, hydrated, magnesium silicate. Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$; it may contain varying amounts of associated minerals. A light, homogeneous, white or almost white powder, greasy to the touch (non-abrasive). It should be free from asbestos. Practically insoluble in water, in alcohol, and in dilute solutions of acids and of alkali hydroxides.

USP 36: (Talc). A powdered, selected, natural, hydrated magnesium silicate. It may contain variable amounts of associated minerals among which chlorites (hydrated aluminium and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate) are predominant. A very fine, white or greyish-white, unctuous crystalline powder, which adheres readily to the skin, and is free from grittiness.

Uses and Administration

Purified talc is used in massage and as a dusting powder to allay irritation and prevent chafing. It is usually mixed with starch, to increase absorption of moisture, and zinc oxide. Talc used in dusting powders should be sterilised. Purified talc is used as a lubricant and diluent in making tablets and capsules and to clarify liquids.

Sterile purified talc is also used as a sclerosant after drainage of malignant pleural effusion and for recurrent spontaneous pneumothorax. It is administered into the pleural cavity as a slurry or by aerosol (insufflation). Doses of about 5 g may be used for pleural effusion and 2 g for pneumothorax.

Pleural effusions. Talc is used as a sclerosant to achieve pleurodesis in the management of benign and malignant pleural effusions (p. 700.1) and recurrent spontaneous pneumothorax.[1-4] It is generally given into the pleural space as a slurry via intercostal tube, or by insufflation (talc poudrage) at thoracoscopy. Most reports have used a dose of 2 to 5 g, but doses have ranged from 1 to 10 g. A study[5] of talc pleurodesis in patients with malignant pleural effusion found both slurry and insufflation to be equally effective. The most common adverse effects associated with this use of talc are pain and fever. Other reported effects have included local infection and empyema, cardiovascular complications, and respiratory failure (see also Effects on the Lungs, p. 1723.1).

1. Kennedy L, Sahn SA. Talc pleurodesis for the treatment of pneumothorax and pleural effusion. *Chest* 1994; **106:** 1215–22.
2. de Campos JRM, *et al.* Thoracoscopy talc poudrage: a 15 year experience. *Chest* 2001; **119:** 801–6.
3. Antunes G, *et al.* British Thoracic Society. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003; **58** (suppl 2): ii29–ii38. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pleural%20Disease/Guidelines/PleuralDiseaseMalignantPE.pdf (accessed 28/07/08)
4. Henry M, *et al.* British Thoracic Society. BTS guidelines for the management of spontaneous pneumothorax. *Thorax* 2003; **58** (suppl 2): ii39–ii52. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pleural%20Disease/Guidelines/PleuralDiseaseSpontaneous.pdf (accessed 28/07/08)
5. Dresler CM, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; **127:** 909–15.

Adverse Effects and Precautions

Contamination of wounds or body cavities with talc is liable to cause granulomas and it should not be used for dusting surgical gloves.

Inhalation of talc can cause respiratory irritation; prolonged exposure may produce pneumoconiosis.

The most common adverse effects of talc pleurodesis are chest pain and fever. More serious complications that can occur include empyema, pneumonitis, dyspnoea, hypoxaemia, pulmonary oedema, pulmonary embolism, acute respiratory distress syndrome, and respiratory failure. Cardiovascular complications such as tachycardia, myocardial infarction, hypotension, hypovolaemia, and asystolic arrest have also occurred in patients treated with talc pleurodesis. However, the role of talc in serious complications is not always clear as the underlying condition of patients with malignant pleural effusion and the procedure itself are likely to be contributing factors.

Talc is liable to be heavily contaminated with bacteria, including *Clostridium tetani*, *Cl. welchii*, and *Bacillus anthracis*. When used in dusting powders or to treat pneumothorax and pleural effusions, it should be sterilised.

Abuse. Adverse pulmonary and ocular effects have been associated with the presence of talc in abused substances. It may be present as an excipient in oral medications that are crushed then dissolved and injected, or it may have been purposely added as a filler to the abused substance. When injected intravenously, the insoluble talc particles can embolise in small pulmonary vessels causing occlusion and pulmonary hypertension. The particles may also then migrate into the pulmonary interstitium, inducing a foreign-body reaction and fibrosis. Irregular nodules can develop in the lungs, which may coalesce to form conglomerate masses.[1] Talc retinopathy is described as deposits of crystalline talc embolising in the retinal microvasculature after intravenous injection.[2-4] Pulmonary granulomas[5] and talc retinopathy[6] have also been described after nasal inhalation of abused substances containing talc.

1. Gotway MB, *et al.* Thoracic complications of illicit drug use: an organ system approach. *Radiographics* 2002; **22** (suppl): S119–S135.
2. Martidis A, *et al.* Talc embolism: a static retinopathy. *Am J Ophthalmol* 1997; **124:** 841–3.
3. Fraser-Bell S, Capon M. Talc retinopathy. *Clin Experiment Ophthalmol* 2002; **30:** 432–3.
4. El-Jabali F, Cohen S. Talc retinopathy. *N Engl J Med* 2006; **354:** e11. Available at: http://content.nejm.org/cgi/reprint/354/12/e11.pdf (accessed 27/09/07)
5. Johnson DC, *et al.* Foreign body pulmonary granulomas in an abuser of nasally inhaled drugs. *Pediatrics* 1991; **88:** 159–61.
6. Kumar RL, *et al.* Crystalline retinopathy from nasal ingestion of methamphetamine. *Retina* 2006; **26:** 823–4.

Carcinogenicity. A review by a working group of the International Agency for Research on Cancer concluded that there was inadequate evidence to confirm whether purified talc was carcinogenic in humans but there was sufficient evidence to confirm that talc containing asbestiform fibres was carcinogenic to man.[1] There have been suggestions of a link between the use of talc and ovarian cancer[2] but although a case-controlled study suggested an approximate doubling of the risk among women after perineal use of talc the working group noted that information was not available on the asbestos content of the talcs.[1] Further case-controlled studies have also reported a positive association between perineal talc use and ovarian cancer, although others have found no association. A large prospective cohort study[3] that included 78 630 women found little support for an association overall, although from an analysis by histological subtype there appeared to be a modest increase in the risk for serous

invasive cancer. A meta-analysis[4] that included this cohort study and 15 case-controlled studies did find a positive association between any exposure to perineal talc and the risk of developing ovarian cancer (relative risk 1.33; 95% confidence interval 1.16 to 1.45). However, the authors highlighted possible selection bias and confounding factors that may have resulted in a false-positive association. There was a lack of a clear dose-response relationship, different results for hospital-based and population-based patients, and the timing of exposure to talc in relation to cancer diagnosis was not always known.

An analysis of epidemiological studies in workers involved in milling the raw mineral (not containing asbestos-like fibres) found no evidence of an increased risk of lung cancer; there was some evidence of an excess among miners or other industrial workers exposed to talc, but these populations were also exposed to other potential carcinogens.[5]

1. IARC/WHO. Silica and some silicates. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 42* 1987. Available at: http://monographs.iarc.fr/ENG/Monographs/vol42/volume42.pdf (accessed 27/09/07)
2. Longo DL, Young RC. Cosmetic talc and ovarian cancer. *Lancet* 1979; **ii:** 349–51.
3. Gertig DM, *et al*. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000; **92:** 249–52.
4. Huncharek M, *et al*. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res* 2003; **23:** 1955–60.
5. Wild P. Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence. *Occup Environ Med* 2006; **63:** 4–9.

Effects on the lungs. Acute respiratory failure has occurred in patients treated with talc pleurodesis, given either as a slurry or by insufflation. In a series of 338 patients treated with insufflation, 4 developed acute respiratory failure and 3 of them died.[1] In another series[2] of 78 patients who underwent 89 procedures using slurry or insufflation, respiratory complications developed after 24 procedures including acute respiratory distress syndrome after 8 procedures in 7 patients of whom 1 died. In a debate based on these and other reports, including some series in which there were no respiratory complications, it was argued[3] that although the risk of acute respiratory distress is small the use of talc for pleurodesis should be abandoned in favour of other drugs such as tetracyclines or bleomycin, or mechanical abrasion of the pleura. The opposing view[4] was that there were many possible causes for acute respiratory distress in these cases, and that talc was still the best pleurodesis agent available. In a prospective randomised comparison in patients with malignant pleural effusion,[5] respiratory complications were more common with insufflation than slurry. The authors noted that the role of talc in causing acute respiratory complications of pleurodesis is unclear and further study is needed.

It has been suggested that acute respiratory distress syndrome after talc pleurodesis may be related to the talc particle size. There were no such reactions in a study[6] of 558 patients given large-particle (mean size 24.5micrometres) talc insufflation, and the authors suggested that reported cases appeared to occur in countries where talc products contained higher concentrations of small particles (less than 5micrometres).

For other effects on the lungs, see under Abuse, p. 1722.3 and Infant Skin Care, below.

1. Campos JRM, *et al*. Respiratory failure due to insufflated talc. *Lancet* 1997; **349:** 251–2.
2. Rehse DH, *et al*. Respiratory failure following talc pleurodesis. *Am J Surg* 1999; **177:** 437–40.
3. Light RW. Talc should not be used for pleurodesis. *Am J Respir Crit Care Med* 2000; **162:** 2024–6.
4. Sahn SA. Talc should be used for pleurodesis. *Am J Respir Crit Care Med* 2000; **162:** 2023–4.
5. Dresler CM, *et al*. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; **127:** 909–15.
6. Janssen JP, *et al*. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. *Lancet* 2007; **369:** 1535–9.

Infant skin care. The routine use of non-medicated powders in the skin care of infants can be hazardous and their use should be discouraged.[1,2] Talc acts as a pulmonary irritant and inhalation of baby-powders by infants has caused severe respiratory difficulties and several deaths have been reported. Careful respiratory monitoring is indicated in children suspected of inhaling talcum powder as the onset of symptoms may be delayed for several hours.[1] There have also been reports of umbilical granulomas resulting from contamination of umbilical stumps with talcum powder used for skin care.[2]

1. Pairaudeau PW, *et al*. Inhalation of baby powder: an unappreciated hazard. *BMJ* 1991; **302:** 1200–1.
2. Sparrow SA, Hallam LA. Talc granulomas. *BMJ* 1991; **303:** 58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Sclerosol.

Multi-ingredient Preparations. ***Arg.***: Dr Selby; Talquisedan; ***Austral.***: ZSC; ***Austria***: Cutimix; Herposicc; Prurimix; Rombay; ***Belg.***: Aloplastine†; ***Braz.***: Pomaderme; ***Chile***: Talquisedan; ***Fr.***: Aloplastine; Poudre du Marcheur†; Supro; ***India***: Derby Cool; ***Indon.***: Minos†; Yanthi Baby & Bath Powder†; ***Israel***: Pedisol†; ***Jpn***: Bofutsushosan; Choreito; Choreitogoshimotsuto; Gorinsan; ***Malaysia***: Rowarolan; ***Mex.***: Hipoglos; ***NZ***: Grans Remedy; Lamisil Odor Eze†; ***Philipp.***: Johnson's Baby Double Protection Powder; ***Pol.***: Pedipur; ***Port.***: Cuidaderma; ***Rus.***: Teimurov (Теймурова); ***Spain***: Amniolina; Ictiomen; ***Switz.***: Tanno-Hermal; ***Turk.***: Cinkos; ***USA***: Caldesene; Columbia Antiseptic Powder.

Pharmacopoeial Preparations
BP 2014: Talc Dusting Powder;
USP 36: Nystatin Topical Powder.

Tars and Tar Oils

Breas y aceites de brea.

Birch Tar Oil

Aceite de abedul; Aceite de brea de abedul; Birkenteer; Goudron de Bouleau; Oleum Betulae Albae; Oleum Betulae Empyreumaticum; Oleum Betulae Pyroligneum; Oleum Rusci; Pix Betulae; Pyroleum Betulae; Масло Берестового Дёгтя.

Description. Birch tar oil is obtained by the destructive distillation of the wood and bark of the silver birch, *Betula verrucosa* (*B. pendula*; *B. alba*), and the birch, *B. pubescens* (Betulaceae); the distillate is allowed to stand and the oily upper layer separated from the residual tar.

Cade Oil

Alquitrán de Enebro; Ardıç Katranı; Brea de enebro; Goudron de Cade; Juniper Tar; Juniper Tar Oil; Kad Yağı; Kadeöl; Oleum Cadinum; Oleum Juniperi Empyreumaticum; Pix Cadi; Pix Juniperi; Pix Oxycedri; Pyroleum Juniperi; Pyroleum Oxycedri; Wacholderteer; Можжевеловый Дёготь.
ATC Herb — HD05AA5001 (Juniperus oxycedrus: *tar*).
UNII — 1Q84T0P2G3.

Description. Cade oil contains guaiacol, ethylguaiacol, creosol, and cadinene.

Pharmacopoeias. In *US*.

USP 36: (Juniper Tar). The empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* (Pinaceae). It is a dark brown, clear, thick liquid with a tarry odour. Very slightly soluble in water; soluble 1 in 9 of alcohol; soluble 1 in 3 of ether leaving only a slight flocculent residue; partially soluble in petroleum spirit; miscible with amyl alcohol, with chloroform, and with glacial acetic acid. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Coal Tar

Alcatrão Mineral; Alquitrán de hulla; Brea de hulla; Crude Coal Tar; Goudron de Houille; Kamenouhelný dehet; Katran; Oleum Lithanthracis; Pix Carbon.; Pix Carbonis; Pix Lithanthracis; Pix Mineralis; Pyroleum Lithanthracis; Steinkohlenteer; Каменноугольная Смола.
UNII — R533ESO2EC.

Description. Prepared coal tar is commercial coal tar heated at 50 degrees for 1 hour.

Alcoholic solutions of coal tar or prepared coal tar prepared with the aid of polysorbate have been referred to as Liquor Picis Carbonis and Liquor Carbonis Detergens.

Pharmacopoeias. In *Br*., *Fr*., *Int*., and *US*.

BP 2014: (Coal Tar). A product obtained by the destructive distillation of bituminous coal at a temperature of about 1000 degrees. A nearly black, viscous liquid with a strong characteristic penetrating odour. On exposure to air it gradually becomes more viscous. It burns in air with a luminous sooty flame. Slightly soluble in water; partly soluble in absolute alcohol, in chloroform, in ether, and in volatile oils. A saturated solution is alkaline to litmus.

USP 36: (Coal Tar). The tar obtained by the destructive distillation of bituminous coal at temperatures in the range of 900 degrees to 1100 degrees. It may be processed further either by extraction with alcohol and suitable dispersing agents and maceration times or by fractional distillation with or without the use of suitable organic solvents.

A nearly black, viscous liquid with a characteristic naphthalene-like odour. Slightly soluble in water to which it imparts an alkaline reaction; partially soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in ether, in methyl alcohol, and in petroleum spirit; more soluble in benzene; almost completely soluble in nitrobenzene. Store in airtight containers.

Tar

Alquitrán Vegetal; Brea; Brea de Pino; Brea vegetal; Goudron Végétal; Nadelholzteer; Pine Tar; Pix Abietinarum; Pix Liquida; Pix Pini; Pyroleum Pini; Wood Tar; Древесная Смола; Древесный Дёготь.
ATC Herb — HD08AW5002 (Pinus spp.: *tar*).
UNII — YFH4WC535J.

Pharmacopoeias. In *Br*.

BP 2014: (Tar). A bituminous liquid obtained from the wood of various trees of the family Pinaceae by destructive distillation. It is known in commerce as Stockholm Tar. A dark brown or nearly black semi-liquid with a characteristic empyreumatic odour; it is heavier than water. Soluble in alcohol (90%), in chloroform, in ether, and in fixed and volatile oils. The aqueous liquid obtained by shaking 1 g with 20 mL of water for 5 minutes is acidic to litmus paper.

Storage. When stored for some time tar separates into a layer which is granular in character due to minute crystallisation of catechol, resin acids, etc. and a surface layer of a syrupy consistence.

Uses and Administration

Tars and tar oils can reduce the thickness of the epidermis. They are antipruritic and may be weakly antiseptic. They are used topically in eczema (p. 1684.1), psoriasis (below), dandruff, seborrhoeic dermatitis (p. 1689.1), and other skin disorders. Coal tar preparations have largely replaced the use of wood tars. Ultraviolet (UVB) light increases the efficacy of coal tar in the treatment of psoriasis.

Some wood tars, including creosote (p. 1659.3) have been used in expectorant preparations.

Nonprescription use. After a review of products for safety and efficacy the FDA ruled that cade oil or tar should not be used in nonprescription shampoos[1] and that tar should no longer be included in nonprescription expectorants.[2]

1. Anonymous. Nonprescription drug review gains momentum. *WHO Drug Inf* 1991; **5:** 62.
2. Anonymous. FDA announces standards for nonprescription sleep-aid products and expectorants. *Clin Pharm* 1989; **8:** 388.

Psoriasis. Coal tar has long been employed in the treatment of psoriasis (p. 1688.1), and used alone or with dithranol and/or ultraviolet light it continues to be a first-line option, although its use is declining. It is particularly suited to the treatment of stable chronic plaque psoriasis. Its mode of action is unknown but it is considered to have antiproliferative and anti-inflammatory activity, producing a reduction in the thickness of viable epidermis. Crude tar preparations are rather messy and unpleasant; refined products may be more aesthetically acceptable and less likely to stain skin, hair, and clothing although some consider them to be less effective.

Treatments usually start with concentrations equivalent to 0.5 to 1% of crude coal tar with the concentration being increased as necessary every few days up to a maximum of 10%. The higher strength preparations may be required for the management of thicker patches of psoriasis but the British Association of Dermatologists considers that coal tar preparations of between 1 and 5% in white or yellow soft paraffin are as effective as higher concentrations, and that the use of higher concentrations, which has been traditionally advocated, has no evidence-based foundation and is best avoided, especially as it restricts outpatient use.

Coal tar may not clear psoriasis as fast as other agents but extended periods of remission can be obtained with its use. The Goeckerman regimen utilises the enhanced efficacy obtained when coal tar is applied before exposure to ultraviolet (UVB) light. The mechanism for this effect is unknown but it does not appear to be due to the photosensitising action of coal tar. In most regimens the coal tar is applied 2 hours before exposure to UVB light. In Ingram's regimen and its modifications the use of coal tar and UVB light is followed by topical treatment with dithranol. It has been suggested that the irritant effects of dithranol treatment can be reduced without loss of efficacy if coal tar is also used.

References.
1. Rotstein H, Baker C. The treatment of psoriasis. *Med J Aust* 1990; **152:** 153–64.
2. Arnold WP. Tar. *Clin Dermatol* 1997; **15:** 739–44.
3. Thami GP, Sarkar R. Coal tar: past, present and future. *Clin Exp Dermatol* 2002; **27:** 99–103.
4. British Association of Dermatologists. Psoriasis – general management. Available at: http://www.bad.org.uk/site/769/Default.aspx (accessed 25/05/10)

Adverse Effects and Precautions

Tars and tar oils may cause irritation and acne-like eruptions of the skin and should not be applied to inflamed or broken skin, mucosa, or the anogenital area. They should be used with caution on the face and skin flexures. Hypersensitivity reactions are rare but wood tars are more likely to cause

sensitisation than coal tar. However, unlike wood tars, coal tar has a photosensitising action. Preparations of refined tar products appear to be less likely than crude tars to stain the skin, hair, and clothing.

Depending on their composition the systemic effects of tars and tar oils are similar to those for phenol (see p. 1764.2).

Carcinogenicity. Coal tar and coal tar distillates contain several known and potential carcinogens including benzene, naphthalene, and other polycyclic aromatic hydrocarbons.[1] Studies of occupational exposure (for example, during coke production, coal gasification, and aluminium production) have found systemic absorption of significant amounts of polycyclic aromatic hydrocarbons,[2] and increases in the risks of developing a range of cancers.[1,2] Systemic absorption of polycyclic aromatic hydrocarbons has also been measured after the application of coal tar preparations used in the treatment of skin conditions.[2] However, although an increased risk of skin carcinoma was found[3] in 59 patients with psoriasis who had had very high exposures to tar and/or UV radiation, other cohort studies[4-6] found no increase in the risk of developing cancers from coal tar, even after long-term use.

1. National Toxicology Program. Coal tars and coal tar pitches. *Rep Carcinog* 2002; **10:** 68–70.
2. van Schooten F-J, Godschalk R. Coal tar therapy: is it carcinogenic? *Drug Safety* 1996; **15:** 374–7.
3. Stern RS, *et al.* Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1980; **i:** 732–5.
4. Pittelkow MR, *et al.* Skin cancer in patients with psoriasis treated with coal tar. *Arch Dermatol* 1981; **117:** 465–8.
5. Jones SK, *et al.* Further evidence of the safety of tar in the management of psoriasis. *Br J Dermatol* 1985; **113:** 97–101.
6. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73:** 2759–64.

Extemporaneous preparation. Concern about the possible carcinogenic potential of coal tar (see above) led the Health and Safety Executive in the UK to recommend that gloves for chemical protection, as opposed to disposable surgeon's gloves, should be worn during the extemporaneous preparation of formulations containing coal tar.[1]

1. Anonymous. Chemical protection gloves recommended for coal tar ointments. *Pharm J* 1997; **259:** 757.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alcoderm; Fijacid; Ingeshamp†; Luxofar; Soriacur; Sorial; Sutrico Tar; Targel; ***Austral.***: Alphosyl†; Linotar†; Neutrogena T/Gel; Pinetarsol; Polytar Plus; ***Braz.***: Tarflex; Theratar; ***Canad.***: Balnetar†; Doak-Oil; Exorex; Mazon Medicated Soap; Neutrogena T/Gel Therapeutic; Neutrogena T/Gel†; Pentrax; Psoriasin; T/Gel Therapeutic; Targel; Tersa-Tar; ***Chile***: DHS Tar Gel; Neutrogena Shampoo Neutar†; Tarmed; Tigel Coaltar; ***Cz.***: Delatar†; ***Fr.***: Caditar; ***Ger.***: Lorinden Teersalbe; Tarmed; Teer-Linola-Fett; ***Gr.***: Exorex; Ionil; Neutrogena T/Gel; Tarmed; ***Hong Kong***: Pinetarsol; Zetar†; ***Hung.***: Freederm Tar Shampoo; ***India***: Cotar; Exorex; ***Irl.***: Exorex; Neutrogena T/Gel; Pentrax; Pinetarsol†; Psoriderm; ***Israel***: Alphosyl 2 in 1; T/Gel†; ***Ital.***: Konor; SDE Tar; ***Malaysia***: Baby Shield Medicated Cleanser; Pin-Xol; Pinetarsol; ***Mex.***: Ionil-T Plus†; Tarmed; ***Neth.***: Exorex; ***NZ***: Pinetarsol; ***Pol.***: Delatar†; Freederm Tar†; Polytar; ***Port.***: Neutar†; Tarmed; ***Rus.***: Freederm Tar (Фридерм Деготь); ***S.Afr.***: Alphosyl†; Denorex; Exarex; Linotar†; ***Singapore***: Hi-Tar; Pinetarsol; Polytar Plus; ***Spain***: Alfitar; Alphosyl†; Exorex; Piroxgel; Tar Isdin Champu†; Tarmed; ***UK***: Alphosyl 2 in 1; Carbo-Dome; Clinitar†; Exorex; Pentrax; Pinetarsol†; Psoriderm; T/Gel; ***USA***: Balnetar; DHS Tar; Fototar; Grandpas Wonder Pine Tar Conditioner; Ionil-T Plus†; MG217 Medicated; Neutrogena T/Gel; Oxipor VHC; PC-Tar; Pentrax; Polytar; Psorent; Taraphilic; Tegrin; Tera-Gel; Zetar; ***Venez.***: Neutrogena T-Gel.

Multi-ingredient Preparations. ***Arg.***: Acnetrol; Aeroseb; Champuacid; Cidermex; Cremsor N; Eurocoal; Farm-X; Hyaluron; Ingemet†; Ionil-T; Laurinol Plus; Medic; Mencogrin AP; Mencogrin; Mencogrin; Novofarma; Novofarma; Novofarma; Oilalfo Compuesto; Salpad T; Sequals G; Sorsis Beta; Sorsis; Sorsis; ***Austral.***: Alphosyl†; Eczema Cream; EgoPsoryl TA; Fongitar†; Hamilton Pine Tar with Menthol; Ionil-T; Pinetarsol; Pinetarsol; Polytar; Psor-Asist; Sebitar; ***Braz.***: Hebrin; Ionil-T; Polytar; ***Canad.***: Dan-Tar Plus†; Denorex Medicated; Herbal Multi-Tar Plus; Mazon Medicated Cream; Mazon Medicated Shampoo; Medi-Dan; Mild Multi-Tar Plus; Multi-Tar Plus†; Oxiport†; P & S Plus†; Polytar AF; Polytar; Regular Multi-Tar Plus; Sebcur-T; SJ Liniment†; Sterex Plus†; Sterex†; Tardan; Targel SA; X-Seb T Plus; X-Seb T; X-Tar†; ***Chile***: Ionil-T; ***Cz.***: Polytar AF; Polytar; Suspensio Visnevski cum Pice Liquida HBF; ***Fr.***: Alkotar†; Laccoderme a l'huile de cade†; Node DS+; Node DS; Node K; Node P†; Novophane K; Psocortene†; Sebosquam†; Squaphane E; Squaphane P; Squaphane S; Squaphane; Squaphane; ***Gr.***: Locacorten Tar; Pisaveril; ***Hong Kong***: BF-2-4-2†; Egopsoryl TA; Fongitar; Ionil-T; Multi-Tar†; Polytar Emollient; Polytar; Sebitar; ***Hung.***: Polytar AF†; Polytar†; ***India***: Alphosyl; Carel; Coalsyl-S; Coalsyl-S; Cotar-K; Cotar-S; Dermatar; Derobin-HC; Derobin; Ionax T; Ketotar; Ocona-CT; ***Indon.***: Polytar†; ***Irl.***: Capasal; Cocois; Denorex†; Polytar Emollient; Polytar; Pragmatar†; ***Israel***: Capasal; Polytar; ***Ital.***: Listerine Tartar Control; Pentrax; Rivescal Tar; ***Malaysia***: Egopsoryl TA; Mentar; Polytar; Sebitar; ***Mex.***: Antaderm; Dariseb; Dealan; Dermoscalp; Ionil-T†; Jabon del Tio Nacho; Polytar; Sebryl Plus; Sebryl; Sebstopp; Shampoo del Tio Nacho†; ***Mon.***: Dermagor Betacade; ***Neth.***: Denorex; ***NZ***: Coco-Scalp; Egopsoryl TA; Ionil-T; Polytar Emollient†; Polytar Plus; Polytar; Sebitar; ***Philipp.***: Fongitar; Ionil-T†; Polytar; ***Pol.***: Cocois; Polytar AF; Psorisan†; ***Port.***: Alpha Cade; Banholeum Composto; Betacade; Fongitar; Polytar; ***S.Afr.***: Alphosyl†; Fongitar; Haarlemensis; Oxipor VHC†; Polytar; SB Universal Ointment†; Tritar; ***Singapore***: Cocois Co; Cocois; Egopsoryl TA; Fongitar; Ionil-T; Polytar; Sebitar; ***Spain***: Alphosyl†; Emolytar†; Ionil Champu; Polytar†; Tar Isdin Plus†; Zincation Plus; ***Thai.***: Fongitar†; Polytar; ***Turk.***: Kadolin; Wilkinson†; ***UK***: Alphosyl HC†; Capasal; Cocois; Polytar AF†; Polytar Emollient; Polytar Liquid; Polytar Plus; Psorin; Sebco; Snowfire; Varicose Ointment; ***Ukr.***: Olesan (Олесан)†; ***USA***: Ala seb T; Boil Ease; Ionil-T; Medotar; Neutrogena T/Sal; Pazol XS; Sal-Oil-T; Sebex-T; Tarlene; Tarsum; X-Seb T Plus; X-Seb T.

Homoeopathic Preparations. ***Canad.***: Adrisin†.

Pharmacopoeial Preparations

BP 2014: Calamine and Coal Tar Ointment; Coal Tar and Salicylic Acid Ointment; Coal Tar and Zinc Ointment; Coal Tar Paste; Coal Tar Solution; Strong Coal Tar Solution; Zinc and Coal Tar Paste; **USP 36:** Coal Tar Ointment; Coal Tar Topical Solution; Compound Resorcinol Ointment.

Tazarotene *(BAN, USAN, rINN)*

AGN-190168; Tatsarroteeni; Tazaroten; Tazarotène; Tazarotenо; Tazarotenum; Тазаротен.

Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate.

$C_{21}H_{21}NO_2S$=351.5

CAS — 118292-40-3.

ATC — D05AX05.

ATC Vet — QD05AX05.

UNII — 818DR9Y8PS.

Uses and Administration

Tazarotene is a retinoid used for the topical treatment of mild to moderate acne and plaque psoriasis, and to treat signs of photoageing. Tazarotene is a prodrug that is de-esterified in the skin to its active form, tazarotenic acid. The mode of action is unknown but it appears to modulate cell proliferation and differentiation.

In the treatment of **psoriasis**, tazarotene 0.05% cream or gel is used initially and increased to 0.1% if necessary. It is applied once daily in the evening. In the UK tazarotene is licensed for use in patients with psoriasis affecting up to 10% of the body-surface; in the USA, it may be used on psoriasis involving up to 20% of the body-surface.

In the treatment of **acne**, tazarotene is applied as a 0.1% gel or cream once daily in the evening.

There may be exacerbation of acne during early treatment or of psoriasis at any time during treatment. The treatment period is usually up to 12 weeks, although tazarotene has been used for up to 12 months in the treatment of psoriasis.

A 0.1% cream is used in the topical treatment of certain signs of **photoageing** (facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines). It is applied once daily at bedtime to lightly cover the entire face.

Reviews.

1. Foster RH, *et al.* Tazarotene. *Drugs* 1998; **55:** 705–11.
2. Tang-Liu DD-S, *et al.* Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. *Clin Pharmacokinet* 1999; **37:** 273–87.
3. Guenther LC. Optimizing treatment with topical tazarotene. *Am J Clin Dermatol* 2003; **4:** 197–202.

Malignant neoplasms. There has been some interest in the use of topical tazarotene in the treatment of neoplasms affecting the skin. Preliminary studies have reported some lesion regression or clearance in basal cell[1] and squamous cell carcinomas[2] (p. 714.2), and mycosis fungoides[3] (p. 698.3).

1. Bianchi L, *et al.* Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. *Br J Dermatol* 2004; **151:** 148–56.
2. Bardazzi F, *et al.* A pilot study on the use of topical tazarotene to treat squamous cell carcinoma in situ. *J Am Acad Dermatol* 2005; **52:** 1102–4.
3. Apisarnthanarax N, *et al.* Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. *J Am Acad Dermatol* 2004; **50:** 600–607.

Skin disorders. Tazarotene is used for the topical treatment of mild to moderate acne[1,2] (p. 1682.2) and plaque psoriasis[3,4] (p. 1688.1); benefit has also been reported for psoriasis of the nails.[5,6] Improvement has been reported too in keratinisation disorders such as Darier's disease[7,8] (p. 1683.2) and congenital ichthyosis[9-11] (p. 1685.1). Topical tazarotene can also improve some signs of photoageing (p. 1686.2), including fine wrinkling, mottled hyperpigmentation, and lentigines (liver spots).[12-14]

1. Leyden JJ. Meta-analysis of topical tazarotene in the treatment of mild to moderate acne. *Cutis* 2004; **74** (4 suppl): 9–15.
2. Shalita AR, *et al.* Effects of tazarotene 0.1% cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. *Clin Ther* 2004; **26:** 1865–73.
3. Weinstein GD, *et al.* Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 2003; **48:** 760–7.
4. Dando TM, Wellington K. Topical tazarotene: a review of its use in the treatment of plaque psoriasis. *Am J Clin Dermatol* 2005; **6:** 255–72.
5. Scher RK, *et al.* Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis* 2001; **68:** 355–8.
6. Bianchi L, *et al.* Tazarotene 0.1% gel for psoriasis of the fingernails and toenails: an open, prospective study. *Br J Dermatol* 2003; **149:** 207–9.
7. Oster-Schmidt C. The treatment of Darier's disease with topical tazarotene. *Br J Dermatol* 1999; **141:** 603–4.
8. Brazzelli V, *et al.* Linear Darier's disease successfully treated with 0.1% tazarotene gel "short-contact" therapy. *Eur J Dermatol* 2006; **16:** 59–61.
9. Hofmann B, *et al.* Effect of topical tazarotene in the treatment of congenital ichthyosis. *Br J Dermatol* 1999; **141:** 642–6.
10. Marulli GC, *et al.* Type I lamellar ichthyosis improved by tazarotene 0.1% gel. *Clin Exp Dermatol* 2003; **28:** 391–3.
11. Kundu RV, *et al.* Lamellar ichthyosis treated with tazarotene 0.1% gel. *J Am Acad Dermatol* 2006; **55** (suppl 5): S94–S95.
12. Phillips TJ, *et al.* Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. *Arch Dermatol* 2002; **138:** 1486–93.
13. Machtinger LA, *et al.* Histological effects of tazarotene 0.1% cream vs. vehicle on photodamaged skin: a 6-month, multicentre, double-blind, randomized, vehicle-controlled study in patients with photodamaged facial skin. *Br J Dermatol* 2004; **151:** 1245–52.
14. Kang S, *et al.* A multicenter, randomized, double-blind trial of tazarotene 0.1% cream in the treatment of photodamage. *J Am Acad Dermatol* 2005; **52:** 268–74.

Adverse Effects and Precautions

As for Tretinoin, p. 1726.1 and p. 1726.3.

Systemic absorption from tazarotene applied topically is low, and the most frequent adverse effects are on the skin; the incidence of adverse events appears to be concentration related.

Animal studies have indicated that tazarotene is fetotoxic and teratogenic. Licensed product information recommends that tazarotene should not be used during pregnancy or in women planning a pregnancy; it also advises starting therapy during normal menstruation, within 2 weeks of confirming a negative pregnancy test in women of child-bearing potential. Similarly, tazarotene should not be used, or used with caution, during breast feeding, as *animal* data indicate that it may be distributed into breast milk.

Effects on the skin. A 57-year-old man with diabetes and recalcitrant psoriasis on the trunk and limbs developed acute dermatitis[1] in the genital area 2 weeks after starting treatment with topical tazarotene 0.1%. The affected areas became ulcerated over the next few days. It was suspected that accidental contact with the tazarotene that had been applied to the truncal psoriasis was responsible. Pyogenic granuloma has been associated with topical tazarotene and other retinoids given orally or applied topically (see Effects on the Skin, Hair, and Nails, under Isotretinoin, p. 1709.1).

1. Wollina U. Genital ulcers in a psoriasis patient using topical tazarotene. *Br J Dermatol* 1998; **138:** 713–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zorac; ***Austria***: Zorac†; ***Belg.***: Zorac; ***Canad.***: Tazorac; ***Chile***: Aguder; ***China***: Le Wei (乐为); Que Wei (炔维); ***Cz.***: Tazorac†; ***Fr.***: Zorac; ***Gr.***: Zorac; ***India***: A-Ret TZ; La Tez; Tazret; ***Irl.***: Zorac†; ***Israel***: Zorac†; ***Ital.***: Zorac; ***Mex.***: Suretin; Tazmeral; ***Pol.***: Zorac; ***S.Afr.***: Zorak; ***Singapore***: Avage; ***Spain***: Zorac; ***Switz.***: Zorac†; ***UK***: Zorac; ***USA***: Avage; Fabior; Tazorac.

Thioglycollic Acid

Kwas tioglikolowy; Tioglicólico, ácido; Тиогликолевая Кислота.

Mercaptoacetic acid.

$C_2H_4O_2S$=92.11

CAS — 68-11-1.

UNII — 7857H94KHM.

Calcium Thioglycollate

Calcium Mercaptoacetate; Tioglicolato cálcico; Тиогликолят Кальция.

Calcium mercaptoacetate trihydrate.

$C_2H_2CaO_2S,3H_2O$=184.2

CAS — 814-71-1.

UNII — J96129652N (calcium thioglycollate); F376WF95N7 (calcium thioglycollate trihydrate).

Profile

Thioglycollic acid is used, usually as the calcium salt, in depilatory preparations. Thioglycollates are also used in hair waving or straightening products with potassium bromate

as the neutraliser. There have been reports of skin reactions associated with the use of thioglycollates.

Tioxolone *(BAN, rINN)*

OL-110; Thioxolone; Tioksolon; Tioksoloni; Tioxolon; Tioxolona; Tioxolonum; Тиоксолон.
6-Hydroxy-1,3-benzoxathiol-2-one.
$C_7H_4O_3S$=168.2
CAS — 4991-65-5.
ATC — D10AB03.
ATC Vet — QD10AB03.
UNII — S0FAJ1R9CD.

Pharmacopoeias. In *Pol.*

Profile

Tioxolone has astringent and keratolytic effects, and has been used topically in the treatment of various skin and scalp disorders.

Titanium Dioxide

CI Pigment White 6; Colour Index No. 77891; E171; Oxid titaničitý; Titaanidioksidi; Titandioxid; Titán-dioxid; Titane, dioxyde de; Titanii dioxidum; Titanio, dióxido de; Titanium Oxide; Titano dioksidas; Titanyum Dioksit; Tytanu(IV) tlenek; Диоксид Титана; Двуокись Титана.
TiO_2=79.86
CAS — 13463-67-7.
UNII — 15FIX9V2JP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Titanium Dioxide). A white or almost white powder. Practically insoluble in water; it does not dissolve in dilute mineral acids but dissolves slowly in hot concentrated sulfuric acid.

USP 36: (Titanium Dioxide). A white odourless powder. Insoluble in water, in hydrochloric acid, in nitric acid, and in 2N sulfuric acid; dissolves in hot sulfuric acid and in hydrofluoric acid; it is rendered soluble by fusion with potassium bisulfate or with alkali hydroxides or carbonates. A 10% suspension in water is neutral to litmus.

Profile

Titanium dioxide has an action on the skin similar to that of zinc oxide (p. 1729.1) and has similar uses. Titanium peroxide and titanium salicylate are used with titanium dioxide for nappy rash. Titanium dioxide reflects ultraviolet light and is used as a physical sunscreen (p. 1681.3). It is also an ingredient of some cosmetics. It is used to pigment and opacify hard gelatin capsules and tablet coatings and as a delustring agent for regenerated cellulose and other man-made fibres. Specially purified grades may be used in food colours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Sunsense Sensitive; ***Canad.***: Aquasmooth†; Creme de Soins†; Dermalogica Ultra Sensitive Face Block†; Luxiva Lasting†; Neutrogena Sensitive Skin†; Photogenic Concealer†; Revlon Complexion One Step†; Stila†; ***Chile***: Fotocrem P; Neutrogena Bloqueador Solar Piel Sensible†; Unitone 4; ***Ger.***: Haemo-Exhirud Bufexamac†; ***Hong Kong***: Sunsense Sun Sensitive; ***Malaysia***: Sunsense Sunsensitive; ***Mex.***: Blancaler; Uveil PS; ***NZ***: Active Duty Sunscreen; Hamilton Sunscreen†; ***Philipp.***: Innobloc; ***Port.***: Dermagor Ecran Solar†; ***Singapore***: Sunsense Sunsensitive; ***USA***: Hawaiian Tropic Protective Tanning; Neutrogena Chemical-Free; TI Baby Natural; TI Screen Natural; Vanicream; ***Venez.***: Uveil PS.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
BP 2014: Titanium Ointment.

Trafermin *(USAN, rINN)* ⊗

CAB-2001; Trafermina; Trafermine; Traferminum; Трафермин.
2-155-Basic fibroblast growth factor (human clone λKB7/λHFL1 precursor reduced).
CAS — 131094-16-1.

Profile

Trafermin is a human recombinant basic fibroblast growth factor (b-FGF) that promotes tissue granulation and the formation of new blood vessels. It is used as a topical liquid spray for the treatment of burns and intractable skin ulcers.

References.
1. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231:** 600–11.
2. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181:** 81–6.
3. Ichioka S, *et al.* The positive experience of using a growth factor product on deep wounds with exposed bone. *J Wound Care* 2005; **14:** 105–9.
4. Motomura H, *et al.* Aggressive conservative therapy for refractory ulcer with diabetes and/or arteriosclerosis. *J Dermatol* 2006; **33:** 353–9.
5. Hashimoto N, *et al.* Management of skull base defect with bFGF after extensive skull base surgery — two case reports. *Minim Invasive Neurosurg* 2008; **51:** 136–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Fiblast.

Tretinoin *(BAN, USAN, rINN)*

Ácido retinoico; NSC-122758; Retinoic Acid; Tretinoiini; Tretinoína; Tretinoinas; Trétinoïne; Tretinoinum; Tretynoina; Vitamin A Acid; Vitamina A ácida; Третиноин.
all-trans-Retinoic acid; 15-Apo-β-caroten-15-oic acid; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-*all-trans*-tetraenoic acid.
$C_{20}H_{28}O_2$=300.4
CAS — 302-79-4 (tretinoin); 40516-48-1 (tretinoin tocoferil).
ATC — D10AD01; L01XX14.
ATC Vet — QD10AD01; QL01XX14.
UNII — 5688UTC01R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Tretinoin). A yellow or light orange crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. It is sensitive to light, heat, and air, especially in solution. Store in airtight containers under an inert gas. Protect from light. The contents of an opened container should be used as soon as possible and any unused portion should be protected by an atmosphere of an inert gas.

USP 36: (Tretinoin). A yellow to light-orange crystalline powder. Insoluble in water; slightly soluble in alcohol and in chloroform. Store in airtight containers, preferably under an atmosphere of an inert gas. Protect from light.

Uses and Administration

Tretinoin is a retinoid and is the acid form of vitamin A (p. 2098.3).

Tretinoin is mainly used in the topical treatment of **acne vulgaris** when comedones, papules, and pustules predominate. It appears to stimulate mitosis and turnover of follicular epithelial cells and reduce their cohesiveness thereby facilitating the extrusion of existing comedones and preventing the formation of new ones. It also appears to have a thinning effect on the stratum corneum. Tretinoin is applied as a cream, gel, or alcoholic solution, usually containing 0.01 to 0.1%. The skin should be cleansed to remove excessive oiliness and dried before applying tretinoin lightly, once or twice daily according to response and irritation; some patients may require less frequent applications. Other topical preparations (including skin moisturisers) should not be applied at the same time as tretinoin is applied, and caution is required if other local irritants are used concurrently. There may be apparent exacerbations of the acne during early treatment and a therapeutic response may not be evident for 6 to 8 weeks. When the condition has resolved maintenance therapy should be less frequent.

Preparations containing 0.02 or 0.05% tretinoin have been used for the treatment of mottled hyperpigmentation, roughness, and fine wrinkling of **photodamaged skin**. It is applied once daily at night. Effects may not be seen until about 6 months after starting treatment.

Tretinoin is also used to induce remission in acute promyelocytic **leukaemia**. A daily dose of 45 mg/m² is given orally in 2 divided doses with food. Treatment is continued until complete remission has occurred or up to a maximum of 90 days. Dose reduction has been recommended in hepatic or renal impairment (see below).

For the use of tretinoin in children, see below.

A liposomal formulation of tretinoin for intravenous use has been investigated in T-cell non-Hodgkin's lymphoma, and acute and chronic leukaemia.

Tretinoin tocoferil (tocoretinate) has also been used.

Administration in children. Topical tretinoin is licensed in the UK for acne vulgaris but the product information does not give age limits or specify any particular patient population. It is not licensed for infantile acne although the *BNFC* suggests that it may be used under specialist supervision.

The use of oral tretinoin to induce remission in acute promyelocytic leukaemia (see Malignant Neoplasms, below) in children has been studied.[1-3] Although there is less experience than in adults, a similar dosage regimen of 45 mg/m² daily (see also above) has been used in children ranging in age from 1 to 16 years. Dose reduction should be considered if severe toxicity, particularly intractable headache, occurs. Although a lower dose of 25 mg/m² daily might reduce neurotoxicity[2,3] the two doses have not been directly compared.

1. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; **22:** 1404–12.
2. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; **106:** 447–53.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; **23:** 7632–40.

Administration in hepatic and renal impairment. Although dosage adjustment has not been studied in patients with hepatic or renal impairment, licensed UK product information suggests that oral doses of tretinoin for acute promyelocytic leukaemia should be reduced to 25 mg/m² daily.

There is a report[1] of 2 patients who required dialysis during tretinoin treatment for acute promyelocytic leukaemia and who achieved remission; one was given a dose of 20 mg/m² daily in 2 divided doses and the other received 35 mg/m² daily in 3 divided doses.

1. Takitani K, *et al.* Pharmacokinetics of all-trans retinoic acid in acute promyelocytic leukemia patients on dialysis. *Am J Hematol* 2003; **74:** 147–8.

Malignant neoplasms. Tretinoin differentiation therapy has become the established treatment for acute promyelocytic leukaemia (APL), a subtype of acute myeloid leukaemia (p. 693.1). Tretinoin is effective in APL because the characteristic chromosomal abnormalities result in an abnormal retinoic acid receptor. When given *orally*, it has produced complete remissions in more than 90% of patients.[1-4] However, the duration of remission is short unless consolidation, usually with an anthracycline- and cytarabine-based regimen, is given concurrently or subsequently. The combination of tretinoin and chemotherapy has been shown to result in improved survival compared with chemotherapy alone.[1,5,6] Prolonged maintenance therapy including intermittent tretinoin also appears to reduce the rate of relapse.[6] Although benefit has been reported with continuous tretinoin maintenance[7] this is generally considered to lead to resistance.[8] A life-threatening syndrome has developed in some patients who have received oral tretinoin for APL (see Retinoic Acid Syndrome, under Adverse Effects, p. 1726.2). Children seem particularly sensitive to the adverse effects of oral tretinoin on the CNS (see also Effects on the Eyes, p. 1726.1, and Administration in Children, above). A lipid-based *intravenous* formulation of tretinoin has been investigated for the treatment of APL.

Tretinoin has also been tried for *topical* chemoprevention in patients at increased risk of skin cancers, and in the management of oral leucoplakia (see Malignant Neoplasms under Isotretinoin, p. 1707.1).

1. Avvisati G, Tallman MS. All-trans retinoic acid in acute promyelocytic leukaemia. *Best Pract Res Clin Haematol* 2003; **16:** 419–32.
2. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; **22:** 1404–12.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; **23:** 7632–40.
4. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; **106:** 447–53.
5. Tallman MS, *et al.* Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002; **99:** 759–67.
6. Tallman MS, Nabhan C. Management of acute promyelocytic leukemia. *Curr Oncol Rep* 2002; **4:** 381–9.
7. Tallman MS, *et al.* All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood* 2002; **100:** 4298–4302.
8. Fenaux P, *et al.* A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999; **94:** 1192–1200.

Skin disorders. Topical treatment with tretinoin has been tried with varying success in many cutaneous conditions. Its use in acne (p. 1682.2) is well established. Some benefit has also been reported in rosacea[1] (p. 1688.3), in keratinisation disorders such as Darier's disease (p. 1683.2), and in pigmentation disorders (p. 1687.2) such as chloasma.[2] Healing of diabetic foot ulcers (see Diabetic Foot Disease, p. 464.2) was improved in a small placebo-controlled study of topical tretinoin.[3] The 0.05% solution was applied topically for 10 minutes of every day for 4 weeks.

Topical tretinoin is used to improve some of the signs of photoageing (p. 1686.2). Studies have found that tretinoin can improve fine facial wrinkling, with some reduction in coarse wrinkles, tactile roughness, sallowness, irregular pigmentation, and actinic lentigines.[4-6] Tretinoin appears to

prevent and repair collagen damage and reduce epidermal melanin content; there is also increased epidermal proliferation and thickening, compaction of the stratum corneum, and deposition of mucinous material.[5] The previous suggestion that skin irritation might be the mechanism behind tretinoin's effects on photodamaged skin has not been supported by clinical study.[4,5] It can take up to 4 months of treatment for a response to develop and the maximum response can be reached between 8 and 12 months. Continued use is necessary to maintain the effect of tretinoin, although it may be used less often.[5,6]

1. Ertl GA, *et al.* A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch Dermatol* 1994; **130:** 319–24.
2. Griffiths CEM, *et al.* Topical tretinoin (retinoic acid) improves melasma: a vehicle-controlled, clinical trial. *Br J Dermatol* 1993; **129:** 415–21.
3. Tom WL, *et al.* The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes. *Arch Dermatol* 2005; **141:** 1373–7.
4. Griffiths CEM. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clin Exp Dermatol* 2001; **26:** 613–18.
5. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; **65:** 1061–72.
6. Singh M, Griffiths CEM. The use of retinoids in the treatment of photoaging. *Dermatol Ther* 2006; **19:** 297–305.

Adverse Effects

Tretinoin is a skin irritant. Topical application may cause transitory stinging and a feeling of warmth, and in normal use it produces some erythema, dryness, pruritus, and peeling similar to that of mild sunburn. Sensitive individuals may have oedema, blistering, and crusting of the skin. Excessive application can cause severe erythema, peeling, and discomfort with no increase in efficacy. Photosensitivity may occur. Temporary hypopigmentation and hyperpigmentation have been reported.

Oral doses of tretinoin may produce similar adverse effects to those of isotretinoin (see p. 1707.2). Adverse cardiovascular effects have also been reported; the most common were arrhythmias, flushing, hypotension, hypertension, and heart failure. Less common events were cardiac arrest, myocardial infarction, cardiomegaly, heart murmur, ischaemia, stroke, myocarditis, pericarditis, pulmonary hypertension, and secondary cardiomyopathy. A potentially life-threatening 'retinoic acid syndrome' (see below) has been described after oral use.

References.

1. Geng A, *et al.* Tolerability of high-dose topical tretinoin: the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Br J Dermatol* 2009; **161:** 918–24.

Carcinogenicity. Studies in *mice* suggested that tretinoin could enhance photocarcinogenesis.[1] However, other studies refuted this[2] and evidence indicates that topical tretinoin is not carcinogenic in humans.

1. Epstein JH. Chemicals and photocarcinogenesis. *Australas J Dermatol* 1977; **18:** 57–61.
2. Epstein JH. All-trans-retinoic acid and cutaneous cancers. *J Am Acad Dermatol* 1986; **15:** 772–8.

Effects on the blood. Transient and asymptomatic thrombocytosis has been reported with the use of oral tretinoin, see under Isotretinoin, p. 1707.3.

Effects on the cardiovascular system. Tretinoin given for induction remission rapidly improves the coagulopathy associated with acute promyelocytic leukaemia, but there are associated reports of arterial and venous thromboembolism. In some cases the combination of tretinoin with an antifibrinolytic drug such as tranexamic acid may have increased the risk of thrombosis.[1-3] In other cases,[2,4] thrombosis occurred in the absence of tranexamic acid and appeared to be related to the retinoic acid syndrome (below). An assessment of 124 patients, including 11 who developed thrombosis, found that the expression of particular phenotypic and genotypic features of leukaemic cells may indicate an increased risk of thrombotic events in patients given tretinoin.[5]

For reports associated with other retinoids, see under Isotretinoin, p. 1707.3.

1. Brown JE, *et al.* All-trans retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. *Br J Haematol* 2000; **110:** 1010–12.
2. Goldschmidt N, *et al.* Extensive splenic infarction, deep vein thrombosis and pulmonary emboli complicating induction therapy with all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 1433–7.
3. Levin M-D, *et al.* Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukemia. *Haematologica* 2003; **88:** ECR21. Available at: http://www.haematologica.org/cgi/reprint/88/6/ECR21.pdf (accessed 28/07/08)
4. Torromeo C, *et al.* Intraventricular thrombosis during all-trans retinoic acid treatment in acute promyelocytic leukemia. *Leukemia* 2001; **15:** 1311–13.
5. Breccia M, *et al.* Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. *Leukemia* 2007; **21:** 79–83.

Effects on the eyes. Papilloedema, retinal haemorrhage and visual changes as a result of benign intracranial hypertension have been associated with oral tretinoin;[1] children appear to be particularly sensitive. For further information about oral retinoids, including tretinoin, causing benign intracranial hypertension, see Effects on the Eyes under Isotretinoin, p. 1707.3.

1. Mahmoud HH, *et al.* Tretinoin toxicity in children with acute promyelocytic leukaemia. *Lancet* 1993; **342:** 1394–5.

Effects on the musculoskeletal system. For reports of myositis occurring in patients receiving oral tretinoin, see under Isotretinoin, p. 1708.2.

Effects on the nervous system. Neurotoxicity (ataxia, dysarthria, and headache) has been reported in a woman with liver impairment using topical tretinoin 0.025% for acne.[1]

1. Bernstein AL, Leventhal-Rochon JL. Neurotoxicity related to the use of topical tretinoin (Retin-A). *Ann Intern Med* 1996; **124:** 227–8.

Effects on the skin. Painful scrotal ulcers, often accompanied by fever, have occurred in men receiving oral tretinoin for acute promyelocytic leukaemia.[1-5] The appearance of the ulcers ranged from days 9 to 30 of the tretinoin course and improved after it was stopped (either at complete remission or because of the ulceration or other adverse effects). Management of the ulcers often included an intravenous or topical corticosteroid and in some cases an antibacterial ointment. Genital ulcers have also been reported in 2 women;[3] an 8-year-old girl developed ulcers 5 days after finishing a course of tretinoin.[6]

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported in at least 12 patients treated with oral tretinoin for acute promyelocytic leukaemia.[7] In some cases there was also systemic involvement affecting muscle, kidneys, and lungs, and in a few cases patients also had retinoic acid syndrome (below). Most patients responded to systemic corticosteroid treatment and in some cases the course of tretinoin therapy could be continued as a result. There has also been a report[8] of Sweet's syndrome with myalgia and arthralgia in a child treated with oral tretinoin for acute myeloid leukaemia.

Details of other skin reactions to oral and topical retinoids, including tretinoin, are described under Isotretinoin, p. 1709.1.

1. Mori A, *et al.* Scrotal ulcer occurring in patients with acute promyelocytic leukemia during treatment with all-trans retinoic acid. *Oncol Rep* 1999; **6:** 55–8.
2. Charles KS, *et al.* Scrotal ulceration during all-trans retinoic (ATRA) therapy for acute promyelocytic leukaemia. *Clin Lab Haematol* 2000; **22:** 171–4.
3. Fukuno K, *et al.* Genital ulcers during treatment with ALL-trans retinoic acid for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 2009–13.
4. Gettinger S, *et al.* Scrotal ulceration during all-trans-retinoic acid therapy for acute promyelocytic leukemia. *J Clin Oncol* 2004; **22:** 4648–9.
5. Shimizu D, *et al.* Scrotal ulcers arising during treatment with all-trans retinoic acid for acute promyelocytic leukemia. *Intern Med* 2005; **44:** 480–3.
6. Ünal S, *et al.* Genital ulcers after treatment with all-trans-retinoic acid in a child with acute promyelocytic leukemia. *Pediatr Hematol Oncol* 2005; **22:** 357–9.
7. Astudillo L, *et al.* Sweet's syndrome associated with retinoic acid syndrome in a patient with promyelocytic leukemia. *Ann Hematol* 2002; **81:** 111–14.
8. Al-Saad K, *et al.* Sweet syndrome developing during treatment with all-trans retinoic acid in a child with acute myelogenous leukemia. *J Pediatr Hematol Oncol* 2004; **26:** 197–9.

Retinoic acid syndrome. A syndrome consisting mainly of fever and respiratory distress developed in 9 of 35 patients between 2 and 21 days after starting induction therapy with oral tretinoin for suspected acute promyelocytic leukaemia.[1] Other symptoms included weight gain, oedema of the lower extremities, pleural or pericardial effusions, and episodic hypotension. Symptoms were life-threatening in 5 patients, 3 of whom subsequently died of multi-system failure. Leucocytosis was frequently, although not invariably, associated with development of the syndrome. Experience showed that early treatment with high-dose corticosteroids should be given to these patients irrespective of the leucocyte count. An analysis[2] of 739 patients has reported similar findings and suggested that, although controversial, prophylactic treatment with corticosteroids may reduce the incidence of the more severe form of the syndrome. Renal failure and pulmonary infiltrates occurred quite frequently in such patients and an association between severity of the syndrome and coagulopathy, and death caused by haemorrhage was noted. There have also been a few reports of thrombosis occurring with the retinoic acid syndrome (see Effects on the Cardiovascular System, above).

Reviews[3,4] and an analysis[2] of this syndrome, known as the 'retinoic acid syndrome' or 'differentiation syndrome', reported that it occurs in about 25% of patients with acute promyelocytic leukaemia treated with tretinoin and that the median time to onset is 10 to 12 days after the start of treatment; the severity of the syndrome varies greatly. A high leucocyte count at diagnosis or a rapidly-increasing count on initiation of therapy appears to increase the likelihood of the syndrome occurring. Close monitoring of leucocyte counts and clinical signs is recommended; high-dose intravenous corticosteroids, and possibly antineoplastic drugs, should be given if symptoms appear or the leucocyte count increases rapidly.

A similar syndrome has been reported in patients with acute promyelocytic leukaemia treated with arsenic trioxide (see p. 2448.3). A capillary leak syndrome, similar to retinoic acid syndrome, has also been described with acitretin (see p. 1691.2).

1. Frankel SR, *et al.* The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992; **117:** 292–6.
2. Montesinos P, *et al.* Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood* 2009; **113:** 775–83.
3. Fenaux P, De Botton S. Retinoic acid syndrome: recognition, prevention and management. *Drug Safety* 1998; **18:** 273–9.
4. Larson RS, Tallman MS. Retinoic acid syndrome: manifestations, pathogenesis, and treatment. *Best Pract Res Clin Haematol* 2003; **16:** 453–61.

Vasculitic syndromes. For a report of vasculitis associated with oral tretinoin, see under Isotretinoin, p. 1709.2.

Precautions

Contact of tretinoin with the eyes, mouth, or other mucous surfaces should be avoided. It should not be applied to eczematous, sunburnt, or abraded skin and the effects of other topical treatment, especially with keratolytics, should be allowed to subside before topical use of tretinoin. Exposure to UV light and excessive exposure to sunlight should be avoided.

Absorption does not seem to occur to any great extent with topical use. Nevertheless, because of teratogenicity in *animal* studies and isolated cases of congenital abnormalities (see below), licensed product information suggests that the use of topical tretinoin should be avoided during pregnancy. It is unknown whether tretinoin is distributed into breast milk, and it should therefore be used topically with caution in breast-feeding mothers.

When tretinoin is given orally the precautions described under isotretinoin (see p. 1709.2) should be adopted. Oral tretinoin is contra-indicated in pregnancy and in breast-feeding mothers.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tretinoin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Although there have been isolated reports[1-4] of congenital abnormalities in infants born to mothers who used tretinoin topically before and during pregnancy, studies involving a total of 415 women[5-7] showed no increased risk for major congenital disorders in infants who had been exposed in the first trimester.

As a characteristic pattern of fetal malformation has been described with the use of oral retinoids, particularly isotretinoin (see p. 1709.3), licensed product information warns that oral tretinoin is contra-indicated during pregnancy and that conception should be avoided for at least one month after the end of treatment. Nevertheless, the outcomes of up to 20 cases have been reviewed,[8,9] in which a course of tretinoin was generally given in the second or third trimester for promyelocytic leukaemia; some women were also given cytotoxic chemotherapy. There were reports of transient pulmonary and cardiac complications in some infants, but no congenital malformations were described. In one case[10] tretinoin was started in the first trimester and continued throughout the pregnancy to avoid the use of cytotoxic chemotherapy. The small-for-date infant was born by caesarean section at week 32 with jaundice and respiratory distress syndrome, which both resolved within 11 days. At 15 months of age the infant had normal growth and development.

1. Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet* 1992; **339:** 687.
2. Lipson AH, *et al.* Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993; **341:** 1352–3.
3. Navarre-Belhassen C, *et al.* Multiple congenital malformations associated with topical tretinoin. *Ann Pharmacother* 1998; **32:** 505–6.
4. Colley SMJ, *et al.* Topical tretinoin and fetal malformations. *Med J Aust* 1998; **168:** 467.
5. Jick SS, *et al.* First trimester topical tretinoin and congenital disorders. *Lancet* 1993; **341:** 1181–2.
6. Shapiro L, *et al.* Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet* 1997; **350:** 1143–4.
7. Loureiro KD, *et al.* Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. *Am J Med Genet* 2005; **136A:** 117–21.
8. Giagounidis AAN, *et al.* Acute promyelocytic leukemia and pregnancy. *Eur J Haematol* 2000; **64:** 267–71.
9. Consoli U, *et al.* Acute promyelocytic leukemia during pregnancy: report of 3 cases. *Int J Hematol* 2004; **79:** 31–6.
10. Simone MD, *et al.* All-trans retinoic acid (ATRA) administration during pregnancy in relapsed acute promyelocytic leukemia. *Leukemia* 1995; **9:** 1412–13.

Skin fragility. As with other retinoids (see under Isotretinoin, p. 1710.1) the use of depilatory products should be avoided in patients treated with tretinoin. Erosions of the skin occurred in 2 patients after the use of wax depilation on facial areas also being treated topically with tretinoin.[1]

1. Goldberg NS, Zalka AD. Retin-A and wax epilation. *Arch Dermatol* 1989; **125:** 1717.

Interactions

As for Isotretinoin, p. 1710.1.

Tretinoin is metabolised by the hepatic cytochrome P450 isoenzyme system, therefore there is a potential for interaction between oral tretinoin and inhibitors or inducers of these enzymes.

Antifibrinolytics. Thrombotic events have occurred in patients being treated with tretinoin and *tranexamic acid* (see Effects on the Cardiovascular System, p. 1726.1). Licensed product information for tretinoin used in the treatment of acute promyelocytic leukaemia advises caution when it is given with drugs such as *aminocaproic acid*, *aprotinin*, and tranexamic acid, particularly in the first month of treatment.

Minoxidil. For the effect of tretinoin on the percutaneous absorption of minoxidil, see p. 1439.3.

Pharmacokinetics

After oral doses tretinoin is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur after 1 to 2 hours. Oral bioavailability is about 50%. Systemic absorption is minimal after topical application. Tretinoin is highly bound to plasma proteins. It undergoes metabolism in the liver by the cytochrome P450 isoenzyme system. Metabolites include isotretinoin, 4-oxo-*trans*-retinoic acid, and 4-oxo-*cis*-retinoic acid. The terminal elimination half-life of tretinoin is 0.5 to 2 hours. Tretinoin is excreted in the bile and the urine. There is some evidence that tretinoin induces its own metabolism.

References.

1. Regazzi MB, *et al.* Clinical pharmacokinetics of tretinoin. *Clin Pharmacokinet* 1997; **32:** 382–402.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: A Acido; Dorpiel; Eurotretin; Locacid; Lotioblanc; Neotretin; Niterey; Retacnyl; Reticne; Retin-A; Tretinoderm; Vesanoid; ***Austral.***: Retin-A†; ReTrieve; Stieva-A; Vesanoid; ***Austria***: Eudyna; Retin-A; Vesanoid; ***Belg.***: Vesanoid; ***Braz.***: Retin-A; Retinova†; Vesanoid; Vitacid; Vitanol-A; ***Canad.***: Rejuva-A; Renova; Retin-A; Retisol-A; Stieva-A; Vesanoid; ***Chile***: Dermodan; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***China***: Ailike (艾力可); Di Wei (迪维); Li Ling (丽英); Wei Ai (唯爱); ***Cz.***: Airol†; Locacid; Retin-A; Vesanoid; ***Fin.***: Avitcid; Vesanoid; ***Fr.***: Effederm; Ketrel; Locacid; Retacnyl; Retin-A†; Vesanoid; ***Ger.***: Airol; Cordes VAS; Vesanoid; ***Gr.***: Airol; Alfamatic; Retin-A; Vesanoid; ***Hong Kong***: Acta; Quali-A; Retin-A; ReTrieve; Stieva-A; Vesanoid; Vitamin A Acid†; ***India***: A-Ret; Airol; Comedolytic; Eudyna; Ontin; ***Indon.***: Eudyna; Jeraklin†; Melavita†; Nuface; Reticor; Retin-A; ReviDerm; Skinovit†; Tracne; Trentin; Vitacid; ***Irl.***: Retin-A; Vesanoid; ***Israel***: Airol†; Locacid; Retavit; Retin-A†; Vesanoid; ***Ital.***: Airol; Retin-A; Vesanoid; ***Jpn***: Olcenon; Vesanoid; ***Malaysia***: Alten†; Retacnyl; Retin-A; Stieva-A; T3 Actin; Tretinon; Vesanoid; ***Mex.***: Acnil; Arretin; Biovitol-C; Epitrel; Queratal; Reacel-A; Ret-A-Pres; Retacnyl; Retin-A; Stieva-A; Tocoderm; Vesanoid; ***Neth.***: Acid A Vit; Vesanoid; ***Norw.***: Aberela; ***NZ***: Retin-A; Retinova; ReTrieve; Vesanoid; ***Philipp.***: Airol†; Derm A; Retacnyl; Retin-A; Stieva-A; T3 Actin; Vesanoid; ***Pol.***: Arretin†; Atrederm; Locacid; Retin-A; Vesanoid; ***Port.***: Ketrel; Locacid; Retin-A; Vesanoid; ***Rus.***: Locacid (Локацид); Retin-A (Ретин-А); Vesanoid (Весаноид); ***S.Afr.***: Airol; Derma-T; Ilotycin-A; Renova; Retacnyl; Retin-A; Vesanoid; ***Singapore***: Alten†; Retacnyl; Retin-A; Retinova; ReTrieve; Stieva-A; T3 Actin; Vesanoid; ***Spain***: Dermojuventus†; Neocare; Retirides; Vesanoid; Vitanol†; ***Swed.***: Aberela; ***Switz.***: Airol; Retin-A; Vesanoid; ***Thai.***: Renova; Retacnyl; Retin-A; Stieva-A; Tina-A; Vesanoid; ***Turk.***: Acnelyse; Retino; Tretin; Vesanoid; ***UK***: Retin-A†; Vesanoid; ***Ukr.***: Vesanoid (Весаноид); ***USA***: Atralin; Avita; Refissa; Renova; Retin-A; Tretin-X; Vesanoid†; ***Venez.***: Betarretin; Retacnyl; Tretinax; Vesanoid.

Multi-ingredient Preparations. ***Arg.***: Acneout; Hidrosam T; Melasmax; Neoblanc; Puraloe; Stievamycin; Tratacne; Tri-Luma; Trimegtante; Verrugard; ***Austria***: Keratosis forte; ***Braz.***: Hormoskin; Suavicid; Tri-Luma; Triderm; Vitacid Acne; Vitacid Plus; ***Canad.***: Biacna; Solage; Stievamycin; ***Chile***: Dermodan Plus; Erylik; Stievamycin; Taripel; Tri-Luma; ***China***: Fuqing (芙晴); Jin Niu Er (金纽尔); ***Cz.***: Aknemycin Plus; ***Fin.***: Wicaran; ***Fr.***: Erylik; ***Ger.***: Aknemycin Plus; Balisa VAS; Carbamid + VAS; Pigmanorm; Ureotop + VAS; ***Hong Kong***: Aknemycin Plus; Erylik; Tri-Luma; ***Hung.***: Verra-med; ***India***: A-Ret HC; Acsolve-C; Acsolve-H; Aknemycin Plus; Depig-TM; Eveglow; M-Lite; Melacare; Melacut; Melalite Plus; Melalite-XL; Melalong; Melanorm-HC; Multi-HTM; ***Indon.***: Erymed Plus; Medi-Klin TR; Refaquin; ***Israel***: Aknemycin Plus; ***Malaysia***: Aknemycin Plus; Efasol; Tri-Luma; ***Mex.***: Stievamycin; Tri-Luma; ***Philipp.***: Tri-Luma; ***Pol.***: Aknemycin Plus; ***Singapore***: Aknemycin Plus; Tri-Luma; ***Spain***: Loderm Retinoico†; ***Switz.***: Carbamide + VAS; Pigmanorm; Sebo-Psor; Verra-med; ***Thai.***: Tri-Luma; ***Turk.***: Eritretin; ***UK***: Aknemycin Plus; ***USA***: Solage†; Tri-Luma; Ziana; ***Venez.***: Tri-Luma.

Pharmacopoeial Preparations
BP 2014: Tretinoin Gel; Tretinoin Solution;
USP 36: Tretinoin Cream; Tretinoin Gel; Tretinoin Topical Solution.

Trichloroacetic Acid

Acide Trichloracétique; Acidum trichloraceticum; Acidum Trichloroaceticum; Kwas trichlorooctowy; Kyselina trichloroctová; Trichloracetic Acid; Trichloracto rūgštis; Trichloressigsäure; Tricloroacético, ácido; Trikloorietikkahappo; Triklorättiksyra; Triklórecetsav; Трихлоруксусная Кислота.

$C_2HCl_3O_2$=163.4
CAS — 76-03-9.
UNII — 5V2JDO056X.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Trichloroacetic Acid). A very deliquescent white or almost white crystalline mass or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

Uses and Administration

Trichloroacetic acid is caustic and astringent. When used as an escharotic for warts it is applied as a strong solution; a range of concentrations have been used including 50% and 80%. The surrounding areas of skin should be protected. Trichloroacetic acid has also been used for the removal of tattoos and in cosmetic surgery for chemical peeling of the skin.

Tattoo removal. References to the use of trichloroacetic acid in the removal of tattoos.

1. Hall-Smith P, Bennett J. Tattoos: a lasting regret. *BMJ* 1991; **303:** 397.

Warts. References to the use of trichloroacetic acid in the treatment of genital warts (p. 1689.3).

1. Godley MJ, *et al.* Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* 1987; **63:** 390–2.
2. Davis AJ, Emans SJ. Human papilloma virus infection in the pediatric and adolescent patient. *J Pediatr* 1989; **115:** 1–9.
3. Boothby RA, *et al.* Single application treatment of human papillomavirus infection of the cervix and vagina with trichloroacetic acid: a randomized trial. *Obstet Gynecol* 1990; **76:** 278–80.
4. Abdullah AN, *et al.* Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. *Sex Transm Dis* 1993; **20:** 344–5.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Wartner Stift; ***Ital.***: CL tre; Verrupor; ***USA***: Tri-Chlor.

Multi-ingredient Preparations. ***Turk.***: IL-33.

Trioxysalen *(rINN)*

NSC-71047; Trioksisaleeni; Trioxisalen; Trioxisaleno; Trioxsalen (USAN); Trioxysalène; Trioxysalenum; Триоксизален; 4,5′,8-Trimethylpsoralen.

2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one.
$C_{14}H_{12}O_3$=228.2
CAS — 3902-71-4.
ATC — D05AD01; D05BA01.
ATC Vet — QD05AD01; QD05BA01.
UNII — Y6UY8OV51T.

Pharmacopoeias. In *US.*

USP 36: (Trioxsalen). A white to off-white or greyish, odourless, crystalline solid. Practically insoluble in water; soluble 1 in 1150 of alcohol, 1 in 84 of chloroform, 1 in 43 of dichloromethane, and 1 in 100 of methyl isobutyl ketone. Protect from light.

Profile

Trioxysalen, a psoralen, is a photosensitiser used similarly to methoxsalen in photochemotherapy or PUVA therapy (p. 1712.1). Trioxysalen may be used topically in the PUVA treatment of psoriasis. It has also been used orally in idiopathic vitiligo to enhance pigmentation or increase the tolerance to sunlight in selected patients.

References.

1. Snellman E, Rantanen T. Concentration-dependent phototoxicity in trimethylpsoralen bath psoralen ultraviolet A. *Br J Dermatol* 2001; **144:** 490–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Tripsor†; ***Gr.***: Trisoralen; ***India***: Dermtone; Dsorolen.

Pharmacopoeial Preparations
USP 36: Trioxsalen Tablets.

Urea ⊗

Carbamida; Carbamide; E927b; Harnstoff; Karbamid; Karbamidi; Mocznik; Močovina; Üre; Urée; Ureia; Ureum; Urėja; Карбамид; Мочевина.

Carbonic acid diamide.
$NH_2.CO.NH_2$=60.06
CAS — 57-13-6.
ATC — B05BC02; D02AE01.
ATC Vet — QB05BC02; QD02AE01.
UNII — 8W8T17847W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US. US* also includes Urea C13.

Ph. Eur. 8: (Urea). Transparent, slightly hygroscopic, crystals or a white or almost white, crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 36: (Urea). Colourless or white, practically odourless, prismatic crystals, or white crystalline powder or pellets. May gradually develop a slight odour of ammonia on prolonged standing. Soluble 1 in 1.5 of water, 1 in 10 of alcohol, and 1 in 1 of boiling alcohol; practically insoluble in chloroform and in ether. Solutions are neutral to litmus. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Urea can cause haemolysis when mixed with blood and should never be added to whole blood for transfusion or given through the same set by which blood is being infused.

Uses and Administration

Urea promotes hydration and is mainly applied topically in the treatment of ichthyosis and hyperkeratotic skin disorders (p. 1685.1). Used intravenously it has osmotic diuretic properties similar to mannitol (p. 1427.3) and has been used in the treatment of acute increases in intracranial pressure (p. 1271.3), due to cerebral oedema, and to decrease intra-ocular pressure in acute glaucoma (p. 1999.1), but has been largely superseded by mannitol. Urea has also been given intra-amniotically for the termination of pregnancy (p. 2131.3).

When applied topically urea has hydrating and keratolytic properties. In the management of ichthyosis and other dry skin disorders it is applied in creams or lotions containing 5 to 25% urea; higher concentrations of 30% and 40% have also been used in severe cases. A preparation containing 40% may be used for nail destruction.

For the reduction of raised intracranial or intra-ocular pressure, urea is given intravenously, as an infusion of a 30% solution in glucose 5 or 10% or invert sugar 10%, at a rate not exceeding 4 mL/minute, in a dose of 0.5 to 1.5 g/kg to a maximum of 120 g daily. Doses used in children are based on the same regimen, but see also below. Rebound increases in intracranial and intra-ocular pressure may occur after about 12 hours.

Solutions of urea 40 to 50% have been given by intra-amniotic injection for the termination of pregnancy.

Urea labelled with carbon-13 (p. 2470.3) is used in the *in vivo* diagnosis of *Helicobacter pylori* infection (see Peptic Ulcer Disease, p. 1813.2). The test involves collecting a breath sample before and after oral ingestion of a single dose of ^{13}C-urea. *H. pylori* produces urease which hydrolyses the urea to carbon dioxide and ammonia; therefore, an excess of carbon-13-labelled carbon dioxide in the sample, compared with a baseline sample, indicates infection. Doses of ^{13}C-urea include 50 mg, 75 mg, or 100 mg depending on the kit being used. Urea labelled with the radionuclide carbon-14 (p. 2223.2) is also used in a urea breath test for *H. pylori* detection.

Administration in children. For the reduction of raised intracranial or intra-ocular pressure in children, urea is given intravenously in dosage regimens similar to those used in adults (see above). However, for children under 2 years of age, a dose of 100 mg/kg may be adequate.

Breath test kits containing ^{13}C-urea for the diagnosis of *Helicobacter pylori* infection are available for children. However, the *BNFC* states that the appropriateness of testing in children has not been established, and that endoscopy with biopsy is more accurate than *in vivo* breath testing, which is frequently unreliable in children.

Syndrome of inappropriate ADH secretion. For mention of the use of oral urea in the syndrome of inappropriate ADH secretion, see p. 2351.2.

Adverse Effects and Precautions

As for Mannitol, p. 1428.3. Urea should also be used with caution in liver impairment as blood-ammonia concentrations can rise, and should be avoided in liver failure.

Urea is reported to be more irritant than mannitol, and intravenous use may cause venous thrombosis or phlebitis at the site of injection; extravasation may cause sloughing or necrosis. Only large veins should be used for infusion, and urea should not be infused into veins of the lower limbs of elderly patients. Extreme care is essential to prevent accidental extravasation of urea infusions.

Rapid intravenous injection of solutions of urea can cause haemolysis; the risk is reduced by using glucose or invert sugar solutions as diluent. Urea should not be mixed with whole blood.

Topical applications may be irritant to sensitive skin.

Infants and neonates. High plasma-urea concentrations have been reported[1,2] in neonates after topical application of emollient creams containing urea. Since there was no evidence of dehydration[2,3] absorption of urea through the skin was the likely cause. Raised plasma-urea concentrations have been reported[4] in infants with erythematous skin conditions who had not been treated with urea cream and this was attributed to dehydration due to increased insensible water loss through the damaged skin.

1. Beverley DW, Wheeler D. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1986; **61:** 696–8.
2. Oudesluys-Murphy AM, van Leeuwen M. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1987; **62:** 212.
3. Beverley DW, Wheeler D. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; **61:** 1245–6.
4. Garty BZ. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; **61:** 1245.

Pregnancy. There have been reports of women suffering coagulopathy associated with urea treatment given for termination of pregnancy.[1,2]

1. Grundy MFB, Craven ER. Consumption coagulopathy after intra-amniotic urea. *BMJ* 1976; **2:** 677–8.
2. Burkman RT, *et al.* Coagulopathy with midtrimester induced abortion: association with hyperosmolar urea administration. *Am J Obstet Gynecol* 1977; **127:** 533–6.

Pharmacokinetics

Urea is fairly rapidly absorbed from the gastrointestinal tract but causes gastrointestinal irritation. Urea is distributed into extracellular and intracellular fluids including lymph, bile, CSF, and blood. It is reported to cross the placenta, and penetrate the eye. It is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hidroplus; Keratopic; Locilherp; Nutralcon; Ureadin; Urecrem Hidro; Uremol; Xerobase; ***Austral.***: Aquacare; Hamilton Skin Therapy; Nutraplus; Urecare†; Urederm; ***Braz.***: Emoderm; Hidrapel Plus; Nutraplus; Ureadin; Ureativ; Urepel; ***Canad.***: Dermaflex HC; Dermaflex†; Simply Botanical Sensations Healing Hands; Urederm†; Uree†; Uremol; Urisec; ***Chile***: Ayr con urea; Ayr-5; Eucerin; Hyderm; Iso-Urea; Uramol; Ureadin 10 and 20; ***Cz.***: Elacutan†; Excipial U; Linola Urea†; ***Fin.***: Canoderm; Fenuril; ***Fr.***: Anti-Dessechement†; Keratosane; Nutraplus†; Onypso; Sedagel†; ***Ger.***: Balisa; Basodexan; Elacutan; Hyanit N†; Linola Urea; Nubral; Onychomal; Onypso; Onyster; Ureotop; ***Hong Kong***: Carmol; Caruderma; Euderm; Urecare; Urederm†; Ureson†; ***Hung.***: Linola Urea; ***Indon.***: Calmuderm†; Carmed; Moisderm; Soft U Derm; Urederm†; ***Irl.***: Aquadrate; Nutraplus; ***Ital.***: Dermal Care; ***Jpn***: Keratinamin; ***Malaysia***: Balneum Intensiv; Euderm†; Nutraplus; UO; ***Mex.***: Derma-Keri; Dermoplast; Karmosan; Nutraplus; Uramol; ***Norw.***: Canoderm; ***NZ***: Aquacare†; Nutraplus; ***Philipp.***: Nutraplus; ***Port.***: Ureadin 5, 10, 20, 30, and 40; ***S.Afr.***: Eulactol; Nutraplus; ***Singapore***: Aqurea; Excipial U; Nutraplus; UO; Urecare†; ***Swed.***: Calmuril; Canoderm; Caress; Fenuril; Karbasal; Monilen†; ***Switz.***: Carbaderm; Carbamide Creme Nouvelle Formule; Carbamide Emulsion; Cremolan; Eucerin peau seche; Excipial U; Linola Uree; Nutraplus; Onypso; Onyster; ***Thai.***: DiabeDerm; Nutraplus; U10; U20; UO; ***Turk.***: Excipial; Nutraplus; Urederm; ***UK***: Aquadrate; Dermatonics Heel Balm; Hydromol Intensive; Nutraplus; ***Ukr.***: Carboderm (Карбодерм); Excipial U (Эксипиал М); ***USA***: Aluvea; Aquacare; BP; Carmol; Dermal Therapy; Flexitol Heel Balm; Gormel; Hydro; Kerafoam; Keralac†; Kerol†; Lanaphilic; Nutraplus; RE-U40†; Rinnovi†; TL; Ultra Mide; Umecta; Uramaxin; Ureacin; Urealac†; Ureaphil†; Utopic; Vanamide; ***Venez.***: Aquaphar; Dermisol; Uricrim.

Multi-ingredient Preparations. ***Arg.***: Acilac; Akerat; Aloebel; Cremsor N; Hairplus; Hidrolac; Lactiderm; Lactocrem; Lactoplus; Masivol Urea; Novofarma; Oxidermos; Sadeltan F; Turgent Colageno; Turgent Emulsion; Ureadin Facial; Urecrem; Vansame; ***Austral.***: Aussie Tan Skin Moisturiser†; Calmuril; Dermadrate; FootSmart; Hamilton Skin Active Urederm Cream; Psor-Asist; Psor-Asist; ***Austria***: Calmurid; Canesten Bifonazol comp; Keratosis forte; Keratosis; Mirfulan; Optiderm; ***Braz.***: Donnagel; Oticerim; Tricolpex; Tricomax; Vagi Biotic; Vagi-Sulfa; ***Canad.***: Dr Scholl's Cracked Heel Relief†; Flexitol Heel Balm†; Hydrophil; Kerasal; Uremol-HC; ***Chile***: Akerat; Ureadin 30; Ureadin Facial Antiarrugas; Ureadin Facial; Ureadin Forte; Ureadin Pediatrics; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; Urealeti; ***China***: Compound Indometacin (复方吲哚美辛); Gan Bi Mei (干彼美); Runbao (润葆); ***Cz.***: Betacorton U†; Kerasal; Mycospor Sada na Nehty; ***Fin.***: Calmuril; Wicaran; Wicarba; ***Fr.***: Akerat; Amycor Onychoset; Day Peel†; Night Peel†; PSO†; Topicrem†; Totephan†; ***Ger.***: Balisa VAS; Brand- u. Wundgel-Medice; Canesten Extra Nagelset; Carbamid + VAS; Fungidexan; Hydrodexan; MedEctoin; Mirfulan; Optiderm; Psoradexan; Remederm; Ureotop + VAS; ***Gr.***: Lyoderm; Urecortin; ***Hong Kong***: Dermadrate; ***Hung.***: Canespro; Reseptyl-Urea; Squa-med; ***India***: Basic; Clomic-S; Copriderm; Cotaryl; Cutivate-MF; Dew Derm; Diafoot; Dibi; Diprosis; Diprovate-MF; Epicort-MK; Foot Care; Gowet; Heelcare; Lobate-S; Moisturex; ***Indon.***: Foothy; ***Irl.***: Alphaderm; Calmurid HC; Calmurid; Cymex; Itch Relief; ***Israel***: Agispor Onychoset; Calmurid†; Derma-Care†; Keratospor; U-Lactin Foot Cream; U-Lactin; ***Ital.***: Eudermico; Ipso Urea; Keraflex; Optiderm; Perfluxi Cremagel; Synchrobase Duo; Verunec; Xerial; ***Malaysia***: Balneum Intensiv Plus; Ucort; ***Mex.***: Lowila; Mycospor Onicoset; Suavene; Urader Lactato; Ureaderm Lactato; ***Neth.***: Calmurid HC; Calmurid; ***NZ***: Dermadrate†; ***Philipp.***: Remederm†; ***Pol.***: Hasceral; Keratolit†; Mycospor Onychoset; Optiderm†; SolcoKerasal; Sterovag†; ***Port.***: Calmurid; Creme Laser Hidrante†; U Lactin†; Ureadin 10 Plus; Ureadin Facial; Ureadin Forte; Ureadin Manos; Ureadin; ***Rus.***: Kleore (Клеоре); Mycospor (Микоспор); ***S.Afr.***: Covancaine; Mycospor Onycho-set†; ***Singapore***: Balneum Intensiv Plus; Balneum Intensiv; Dermadrate; Topicrem; U-Lactin†; Ucort; ***Spain***: Cortisdin Urea†; Kanapomada†; Mycospor Onicoset; Nasopomada†; ***Swed.***: Fenuril-Hydrokortison; ***Switz.***: Acne Gel; Betacortone; Calmurid; Carbamide + VAS; Kerasal; Klyx Magnum†; Optiderm; Pruri-med Lipolotion; Sebo-Psor; Turexan Capilla†; Undex; ***Thai.***: Gynestin; ***Turk.***: Betacorton; Kerasal; Mycospor; Ureacort; ***UK***: Alphaderm; Antipeol; Balneum Plus; Balneum; Calmurid HC; Calmurid; Cymex; E45 Itch Relief; Flexitol Heel Balm; Hydromol HC Intensive; St James Balm; Vesagex Heelbalm; ***Ukr.***: Canespor Set (Канеспор Набор); Kerasal (Керасал); Mycospor Kit (Микоспор Набор)†; Prednicarb (Предникарб); ***USA***: Accuzyme†; AllanEnzyme†; AllanfillEnzyme†; Amino-Cerv; Carb-O-Lac HP; Duraflex Comfort; Gladase-C†; Gladase†; Gold Bond Foot Pain Relieving; Hydrocerin Plus; Kerasal Ultra; Keratol HC; Kovia†; Latrix XM; Panafil-White†; Panafil†; Rosula NS†; Rosula†; Salvax Duo; Toetal Fresh; Ultralytic 2; Ziox†; Zoderm; ***Venez.***: Akerat; Caduril; Hidribet 5/5; Hidribet; Mycospor Onicoset; Pantonic; Pelset Plus; Ureaderm Lactato.

Homoeopathic Preparations. ***Ger.***: Girheulit HM†.

Pharmacopoeial Preparations
BP 2014: Urea Cream;
USP 36: Urea for Injection.

Ustekinumab *(BAN, USAN, rINN)*

CNTO-1275; Ustékinumab; Ustekinumabum; Устекинумаб.
Immunoglobulin G1, anti-(human interleukin-12 subunit beta (IL-12B, CLMF p40, NKSF2))(human monoclonal CNTO 1275 γ1-chain), disulfide with human monoclonal CNTO 1275 κ-chain, dimer.
CAS — 815610-63-0.
ATC — L04AC05.
ATC Vet — QL04AC05.
UNII — FU77B4U5Z0.

Uses and Administration

Ustekinumab is a human monoclonal antibody that binds to interleukins 12 and 23, and is used for the treatment of moderate to severe plaque psoriasis (p. 1688.1). It is given to patients aged 18 years and over who have not responded to, or are unable to take, other systemic therapies. Ustekinumab is given by subcutaneous injection, but it should not be injected into areas that show psoriasis. An initial dose of 45 mg is repeated after 4 weeks, then every 12 weeks thereafter. A dose of 90 mg should be used for patients weighing more than 100 kg. Treatment should be stopped if there is no response after 28 weeks of therapy.

Ustekinumab is under investigation in the treatment of psoriatic arthritis, Crohn's disease, and multiple sclerosis.

References.

1. Krueger GG, *et al.* A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; **356:** 580–92.
2. Leonardi CL, *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371:** 1665–74. Correction. *ibid.*; 1838.
3. Papp KA, *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371:** 1675–84.
4. Gottlieb A, *et al.* Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009; **373:** 633–40. Correction. *ibid.* 2010; **376:** 1542.
5. Griffiths CE, *et al.* ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; **362:** 118–28.
6. Croxtall JD. Ustekinumab: a review of its use in the management of moderate to severe plaque psoriasis. *Drugs* 2011; **71:** 1733–53.

Adverse Effects and Precautions

Upper respiratory-tract infections and nasopharyngitis are very common adverse effects of ustekinumab treatment. Other effects that occur commonly include pharyngolaryngeal pain, nasal congestion, cellulitis, diarrhoea, back pain, myalgia, pruritus, dizziness, headache, fatigue, and depression. Injection site reactions can occur, and hypersensitivity reactions such as rash and urticaria have been reported. Reduced efficacy has been found in patients who have developed antibodies to ustekinumab.

As a result of immunosuppression, patients given ustekinumab are at increased risk of infection. It should not be given to patients with a serious infection and should be used with care in those with chronic infection or a history of recurring infection. Serious bacterial, viral, and fungal infections have occurred. Live or live-attenuated vaccines should not be given during ustekinumab treatment because of the risk of infection. It should be withheld from at least 15 weeks before until 2 weeks after vaccination. Immunosuppression caused by ustekinumab might also increase the risk of developing malignancies, so it should be used with care in patients with a history of malignancy and those who develop malignancy during ustekinumab therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ustekinumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

For a warning concerning the use of live vaccines in patients receiving ustekinumab, see Adverse Effects and Precautions, above.

Pharmacokinetics

Peak serum concentrations of ustekinumab occur about 8.5 days after a subcutaneous dose, and its bioavailability is about 57%. Its elimination half-life is about 3 weeks, ranging from 15 to 32 days. Ustekinumab is cleared more rapidly in heavier patients (e.g. more than 100 kg). Pharmacokinetic analysis also suggests higher clearance in patients who test positive for antibodies to ustekinumab.

References.

1. Zhu Y, *et al.* Population pharmacokinetic modeling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40, in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol* 2009; **49:** 162–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Stelara; ***Austral.***: Stelara; ***Austria***: Stelara; ***Belg.***: Stelara; ***Braz.***: Stelara; ***Canad.***: Stelara; ***Cz.***: Stelara; ***Denm.***: Stelara; ***Fr.***: Stelara; ***Ger.***: Stelara; ***Gr.***: Stelara; ***Hong Kong***: Stelara; ***Hung.***: Stelara; ***Irl.***: Stelara; ***Israel***: Stelara; ***Jpn***: Stelara; ***Neth.***: Stelara; ***Norw.***: Stelara; ***Pol.***: Stelara; ***Port.***: Stelara; ***Rus.***: Stelara (Стелара); ***Singapore***: Stelara; ***Spain***: Stelara; ***Swed.***: Stelara; ***Switz.***: Stelara; ***Thai.***: Stelara; ***UK***: Stelara; ***USA***: Stelara.

Zinc Carbonate *(USAN)*

Zinc, carbonato de; Карбонат Цинка; Углекислый Цинк.
$ZnCO_3$=125.4
CAS — 3486-35-9.
UNII — EQR32Y7H0M.

Basic Zinc Carbonate

Zinc, carbonato básico de; Основный Карбонат Цинка; Основный Углекислый Цинк.

NOTE. The names zinc carbonate, hydrated zinc carbonate, zinc subcarbonate, and zinc carbonate hydroxide have all been applied to basic zinc carbonate of varying composition occurring naturally or produced by the reaction of a soluble zinc salt with sodium carbonate.

Pharmacopoeias. In *US.*

USP 36: (Zinc Carbonate). It corresponds to $3Zn(OH)_2.2ZnCO_3$ containing the equivalent of not less than 70% ZnO. Store in airtight containers.

Profile

Zinc carbonate is mildly astringent and protective to the skin and is used topically, mainly in the form of calamine (p. 1697.2), in a variety of skin conditions. In the USA the

name calamine is used for zinc oxide (rather than zinc carbonate) with a small proportion of ferric oxide.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ukr.***: Bezornil (Безорнил).

Zinc Oxide

Flowers of Zinc; Blanc de Zinc; Blanco de zinc; Cinko oksidas; Çinko Oksit; Cink-oxid; Cynku tlenek; Flores de zinc; Oxid zinečnatý; Sinkkioksidi; Zinc, óxido de; Zinc, oxyde de; Zinci oxidum; Zinci Oxydum; Zincum Oxydatum; Zinkoxid; Окись Цинка; Цинк Оксид.

ZnO=81.38

CAS — 1314-13-2.

UNII — SOI2LOH54Z.

NOTE. 'Zinc White' is a commercial form of zinc oxide used as a pigment.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes a neutral zinc oxide.

Ph. Eur. 8: (Zinc Oxide). A white or faintly yellowish-white, soft, amorphous powder, free from gritty particles. Practically insoluble in water and in alcohol; it dissolves in dilute mineral acids.

USP 36: (Zinc Oxide). A white or yellowish-white, odourless, amorphous, very fine powder, free from grittiness. It gradually absorbs carbon dioxide from air. Insoluble in water and in alcohol; soluble in dilute acids.

USP 36: (Zinc Oxide, Neutral). It is for use in sunscreen preparations only.

Incompatibility. Black discoloration has been reported when zinc oxide and glycerol are in contact in the presence of light.

Profile

Zinc oxide is mildly astringent and is used topically as a soothing and protective application in eczema and slight excoriations, in wounds, and for haemorrhoids. It is also used with coal tar (p. 1723.3) or ichthammol (p. 1705.3) in the treatment of eczema. Zinc oxide reflects ultraviolet radiation and is used as a physical sunscreen (see p. 1681.3).

In the USA the name calamine is used for zinc oxide with a small proportion of ferric oxide.

Zinc oxide is used as the basis for the production of many dental cements. Mixed with phosphoric acid it forms a hard material composed largely of zinc phosphate; mixed with clove oil or eugenol, it is used as temporary dental filling.

For further details of zinc and its salts, see p. 2126.1.

Complications of dental use. Solitary aspergillosis of the maxillary sinus in 29 of 30 patients was associated with zinc oxide from overfilled teeth.[1] Treatment consisted of removal of the fungal ball containing the zinc oxide; no antifungal treatment was necessary. Zinc oxide has been shown to accelerate the growth of *Aspergillus fumigatus*. Further cases have been reported, and adjunctive systemic antifungal treatment has been used.[2]

1. Beck-Mannagetta J, *et al.* Solitary aspergillosis of maxillary sinus, a complication of dental treatment. *Lancet* 1983; **ii:** 1260.
2. Martins WD, Ribeiro Rosa EA. Aspergillosis of the maxillary sinus: review and case report. *Scand J Infect Dis* 2004; **36:** 758–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cutidermin Bebe Crema Protectora†; Dermic; Sinamida D; Zincoxid; ***Austral.***: Clear Zinke; Curash Anti-Rash; Gelocast; Prickly Heat Powder; Rectogesic; Steripaste; Sudocrem; UV Triplegard Natural; Viscopaste; Zincaband; Zinke; Zipzoc; ***Braz.***: Bebex Previne; Dermodex Prevent; ***Canad.***: Aveeno Diaper Rash†; Diaper Rash; Diaper-Care†; Johnson's Diaper Rash†; Sunblock†; Viscopaste PB7; Woodward's Diaper Rash; Zinaderm; Zincoderm†; Zincofax; Zipzoc; ***Chile***: Desitin Creamy; Nenegloss Z; Unitone 4; ***Denm.***: Zipzoc; ***Fin.***: Zipzoc; ***Fr.***: Babygella; Oxyplastine; Veinopress A3 and A4; ***Ger.***: Guta; Pantederm N†; Retterspitz Heilsalbe ST; Zinksalbe Lichtenstein; ***Hong Kong***: Zinoxid†; ***Irl.***: Steripaste; Viscopaste; Zipzoc; ***Israel***: Dyprotex; Lotio Zinci; Zinc Lotion; ***Ital.***: Ceroxmed Tex; Cincream; Delicate Skin Pasta; Gelocast; Gelostretch; Milsana; Oz; Scherilan Crema; Sicura3 Fisionorm; Tayderm; Tendigrip; Triderm Crema; Triderm Zeta; Varicex; Viscopaste PB7; Zinco Acqua; Zincoderm; Zincotape; ***Mex.***: Pasta de Lassar; Saniderm; ***Neth.***: Daro Zinkzalf; Zinkolie; Zinkzalf; Zipzoc†; ***Philipp.***: Curash; Desitin; Rashfree; Spectraban 19; ***Port.***: Lassadermil; Zincoderma; Zipzoc; ***Rus.***: Cindol (Циндол); Desitin (Деситин); ***S.Afr.***: Clocktower†; Johnson's Baby Nappy Cream; Vernleigh Baby Cream; Viscopaste PB7†; ***Singapore***: Desitin; Nu-Derm Physical UV Block; ***Spain***: Anticongestiva; ***Swed.***: Zipzoc Salvstrumpa; ***Switz.***: Oxyplastine; Zin-Cream; ***Thai.***: Cabana; Nappy-Hippo; Spectraban†; ***UAE***: Proskin; ***UK***: Steripaste; Viscopaste PB7; Zincaband; Zipzoc; ***Ukr.***: Desitin (Деситин); ***USA***: Balmex Diaper Rash; Bensons Bottom; Borofax; Delazinc; Diaparene Diaper Rash; Dr Smiths; Triple Paste; ***Venez.***: Cicalfate; Lanol-Zinc; Oxyphar.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Canad.***: Homeo-S-Asp; Sportenine; ***Fr.***: Sportenine; ***Neth.***: Sportenine†.

Pharmacopoeial Preparations

BP 2014: Aqueous Calamine Cream; Calamine and Coal Tar Ointment; Calamine Lotion; Coal Tar and Zinc Ointment; Coal Tar Paste; Compound Aluminium Paste; Compound Zinc Paste; Dithranol Paste; Hexachlorophene Dusting Powder; Zinc and Castor Oil Ointment; Zinc and Coal Tar Paste; Zinc and Ichthammol Cream; Zinc and Salicylic Acid Paste; Zinc Cream; Zinc Ointment;

USP 36: Calamine Topical Suspension; Coal Tar Ointment; Compound Resorcinol Ointment; Zinc Oxide and Salicylic Acid Paste; Zinc Oxide Ointment; Zinc Oxide Paste.

Zinc Phenolsulfonate

4-Hidroxibencenosulfonato de zinc; Phenozin; Zinc, fenosulfonato de; Zinc 4-Hydroxybenzenesulphonate; Zinc Phenolsulphonate; Сульфофенолят Цинка; Фенолсульфонат Цинка.

Zinc *p*-hydroxybenzenesulphonate.

$C_{12}H_{10}O_8S_2Zn$=411.7

CAS — 127-82-2.

UNII — 4O71YT5YB5.

Profile

Zinc phenolsulfonate has astringent properties and has been used in multi-ingredient preparations applied topically for the treatment of a variety of disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Gineseptina; ***Braz.***: Lerin; Neo Quimica Colirio†; Visazul; ***Canad.***: Sil Trax Plus†; ***Ital.***: Antisettico Astringente Sedativo; Oftalmil; ***USA***: BFI.

Disinfectants and Preservatives

Contact lens care, p. 1730
Disinfection in Creutzfeldt-Jakob disease, p. 1730
Disinfection in dental practice, p. 1731
Disinfection of endoscopes, p. 1731
Disinfection in hepatitis and HIV infection, p. 1731
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Injection site and catheter care, p. 1732
Pre-operative skin disinfection, p. 1732
Wound disinfectian, p. 1732

This chapter describes those antimicrobial agents that are used for chemical methods of disinfection, antisepsis, preservation, and sterilisation. The collective term biocides has been used to describe such agents. There is some overlap between these procedures and some agents may be used as both disinfectants and preservatives. Iodine (p. 2336.3), not in this chapter, is also used for its disinfectant properties.

Definition of terms. There is often confusion between the terms disinfectant and antiseptic.

- The term **disinfectant** is applied to a chemical agent that destroys or inhibits the growth of pathogenic micro-organisms in the non-sporing or vegetative state; disinfectants do not necessarily kill all micro-organisms, but reduce them to a level that is harmful neither to health nor the quality of perishable goods. The term is applicable to agents used to treat inanimate objects and materials and may also be applied to agents used to treat the skin and other body membranes and cavities
- An **antiseptic** is a disinfectant that is used on skin and other living tissues thereby limiting or preventing infection
- **Sterilisation** is the total removal or destruction of all living micro-organisms; a few disinfectants (such as ethylene oxide) are capable of producing sterility under suitable conditions but, in general, sterility is produced by heat or radiation methods, with filtration being used for some heat-labile materials. Sterilisation by heating with a bactericide is no longer a recommended practice
- A **preservative** is one of several chemical agents that are included in preparations to prevent deterioration from oxidation **(antoxidants)** or to kill or inhibit the growth of micro-organisms inadvertently introduced during manufacture or use **(antimicrobial preservatives)**.

Use of disinfectants. Disinfectants are used in hospitals, industrial establishments, public buildings, on farms, and in the home for control and prevention of infection.

The choice of disinfectant depends on the purpose for which it is used and the likely contaminating organisms. In addition to vegetative bacteria, many common disinfectants could be expected to kill some fungi and lipid-containing viruses. Gram-negative bacteria, mycobacteria, and bacterial spores are generally more resistant to disinfectants, and some disinfectants are less effective against non-lipid enveloped viruses, for example the enteroviruses including polio and coxsackie. Prions are generally resistant to many disinfectants (see Disinfection in Creutzfeldt-Jakob Disease, below). Other factors affecting the efficacy of disinfectants include the contact time, concentration of the disinfectant, the pH of the system, the number and accessibility of the contaminating micro-organisms, and the presence of interfering substances including lipids, organic matter, rubber, and plastics. Aqueous solutions of disinfectants, particularly quaternary ammonium compounds (such as benzalkonium chloride and cetrimide), chlorhexidine, and phenols, may be susceptible to contamination with micro-organisms. To reduce this risk many preparations are provided for clinical use in a sterile form for single use.

Use of preservatives. Antimicrobial preservatives are used in sterile preparations such as eye drops and multidose injections to maintain sterility during use. They may also be added to aqueous injections that cannot be sterilised in their final containers and have to be prepared using aseptic precautions, unless the volume to be injected as a single dose exceeds 15 mL. Antimicrobial preservatives are also used in cosmetics, foods, and non-sterile pharmaceutical products such as oral liquids and creams to prevent microbial spoilage. They should not be used indiscriminately. Preparations that should *not* contain preservatives include those for injection into the CSF, eye, or heart. Generally, the antimicrobial preservatives that may be added to foods, animal feeding stuffs, and cosmetics are controlled.

Preservatives used as antoxidants may be classified in 3 groups:

- ***true antoxidants***, or anti-oxygens, which probably inhibit oxidation by reacting with free radicals blocking the chain reaction. Examples are the alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, nordihydroguaiaretic acid, and the tocopherols (see Vitamin E Substances, p. 2119.1)
- ***reducing agents***, which are substances having a lower redox potential than the drug or adjuvants that they are intended to protect and are therefore more readily oxidised. Reducing agents may act also by reacting with free radicals. Examples are ascorbic acid (p. 2110.3) and the potassium and sodium salts of sulfurous acid (see Sulfites and Sulfur Dioxide)
- ***antoxidant synergists***, which usually have little antoxidant effect themselves but probably enhance the action of antoxidants in the first group by reacting with heavy-metal ions which catalyse oxidation. Examples of synergists are citric acid (p. 2480.3), edetic acid and its salts (p. 1550.3), lecithin (p. 2542.2), and tartaric acid (p. 2626.1)

General references and guidelines for the use of disinfectants.

1. DoH. Standard principles for preventing hospital-acquired infections. *J Hosp Infect* 2001; **47** (suppl): S21–S37. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005481?IdcService=GET_FILE&dID=140080&Rendition=Web (accessed 27/08/08)
2. Block SS, ed. *Disinfection, sterilization, and preservation.* 5th ed. Philadelphia: Lippincott Williams and Wilkins, 2001.
3. Ayliffe GAJ, English MP. *Hospital infection: from Miasmas to MRSA.* Cambridge: Cambridge University Press,2003.
4. Fraise AP, *et al.* , eds. *Russel, Hugo and Ayliffe's principles and practice of disinfection, preservation, and sterilization.* 4th ed. Oxford: Blackwell Science, 2005.
5. Rutala WA, Weber DJ. Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for disinfection and sterilization in healthcare facilities, 2008. Available at: http://www.cdc.gov/hicpac/pdf/guidelines/Disinfection_Nov_2008.pdf (accessed 01/03/10)

Contact lens care

Wearers of contact lenses are at increased risk of corneal infections. Factors that predispose the cornea to infection include surface abrasions that may occur during normal wear, extended wear of soft (hydrogel) lenses, accidental trauma during insertion of a lens, and anoxia. In addition, the lens may provide a medium for introducing pathogens into the eye, especially if handling, cleaning, and disinfecting procedures are not followed. The most common pathogens are bacteria, in particular *Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Staph. epidermidis,* and *Streptococcus pneumoniae*. Fungi rarely cause lens-related keratitis, although contamination of soft lenses has been reported. *Acanthamoeba* can cause rare but serious corneal infections (see Acanthamoeba Keratitis, p. 919.3) mainly associated with soft contact lens wear; these protozoa are resistant to some commonly used disinfection systems and can colonise lens storage cases.

Lens care systems for **rigid** (hard or gas-permeable) lenses typically entail cleansing and disinfection stages.

- Daily cleansing with solutions containing surfactants and sometimes mild abrasives can substantially reduce microbial contamination as well as removing organic material which can compromise the activity of the disinfection stage. Cleansing solutions frequently contain substances that are irritant to the eye and should be removed by rinsing and soaking the lens.
- Soaking solutions also maintain lens hydration, disinfect the lens, and prevent contamination during storage. Although not intended for use in the eye, soaking solutions should be non-irritant.
- Commonly used disinfectants include benzalkonium chloride and chlorhexidine. Thiomersal is also used but has been associated with a high incidence of hypersensitivity reactions.
- Wetting or rewetting solutions are used to improve the comfort of the lens and, since they are applied to the eye, must be non-irritant. They commonly contain hypromellose, hyetellose, polyvinyl alcohol, or povidone, although a simple sodium chloride 0.9% solution may be used.

Initially chemical disinfection for **soft** contact lenses required 4 steps; cleaning, rinsing, soaking in a disinfectant, and final rinsing. The introduction of multipurpose solutions containing small amounts of surfactant cleaner and disinfectant have reduced the number of steps required.

- Soft contact lenses contain a high proportion of water and are liable to absorb substances from solution. For this reason some disinfectants, notably benzalkonium chloride, are not suitable for inclusion in solutions for soft lenses. Soft lenses may be disinfected by heating in a suitable unit, usually in isotonic saline solution, but this can shorten the life of the lens by denaturing the polymer or causing deposits of denatured protein, minerals, or preservatives from the saline solution. Stabilised hydrogen peroxide is suitable for cold disinfection of soft lenses and is particularly useful for preventing *Acanthamoeba* infections. However, it is irritant to the cornea and must be neutralised before the lens is inserted into the eye. Other disinfectants for soft lenses may include chlorhexidine and polihexanide.
- Cleansers for soft lenses may contain surfactants or enzymes, such as papain or pancreatin, that remove protein deposits.
- Wetting solutions may be used similarly to rigid lenses.

Reviews.

1. Rakow PL. Current contact lens care systems. *Ophthalmol Clin North Am* 2003; **16:** 415–32.

Disinfection in Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. The agent causing Creutzfeldt-Jakob disease (CJD) is resistant to many disinfection procedures including dry heat, ultraviolet irradiation, alcohols, ethylene oxide, eusol, formaldehyde, glutaral, hydrogen peroxide, iodine or iodophores, peracetic acid, phenolics, and propiolactone. Furthermore, aldehyde-type disinfectants have fixative proprieties and could anchor prion and other proteins to equipment and make them more difficult to remove by other means.[1] No sterilisation procedure can be guaranteed to be completely effective under all circumstances[1] and for disposable instruments and materials the safest method is to destroy them by incineration.[2] Neurosurgical and ophthalmic instruments should also be destroyed by incineration if used in patients with confirmed or suspected CJD. WHO[2] has developed guidelines for control of transmissible spongiform encephalopathies which include measures for the decontamination and cleaning of instruments and materials designed for re-use. They recommend that contaminated instruments and material should be kept moist between the time of use and decontamination and that one of the following methods of decontamination be used for heat-resistant instruments (listed in increasing order of severity):

- immerse in 1N sodium hydroxide and heat in a gravity displacement autoclave at 121 degrees for 30 minutes then clean, rinse in water, and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide or sodium hypochlorite (providing 20 000 ppm available chlorine) for 1 hour then transfer the instruments to water, heat in a gravity displacement autoclave at 121 degrees for 1 hour, then clean and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide or sodium hypochlorite (providing 20 000 ppm available chlorine) for 1 hour then remove and rinse in water, transfer to an open pan and heat in a gravity displacement (121 degrees) or porous load (134 degrees) autoclave for 1 hour, then clean and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide and boil for 10 minutes at atmospheric pressure then clean, rinse in water, and continue with routine sterilisation processes
- immerse in sodium hypochlorite (providing 20 000 ppm available chlorine) (preferred) or 1N sodium hydroxide (alternative) at ambient temperature for 1 hour then clean, rinse in water, and continue with routine sterilisation processes
- autoclave at 134 degrees for 18 minutes

Heat sensitive instruments and surfaces should be decontaminated by flooding with 2N sodium hydroxide or undiluted sodium hypochlorite and left to stand for 1 hour, then mopped up and rinsed with water. If these agents cannot be tolerated then thorough cleaning with a diluted solution or other partially effective agent is advised.[2] In the UK, it is recommended[1] that if it is the intention to reuse an endoscope that has been employed in patients with suspected CJD or has been used for invasive procedures in those at risk of CJD (e.g. haemophiliacs), then the endoscope should be disinfected with a non-aldehyde single use disinfectant separately from other endoscopes and quarantined for use only in the same patient or in those with confirmed CJD. If the patient has confirmed CJD, then the quarantined endoscope can only be used in the same patient.

Recommendations for disinfection and sterilisation in CJD have also been published in the UK[3] and USA.[4,5]

1. British Society of Gastroenterology. BSG Working Party Report 2008. BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/decontamination_2008.pdf (accessed 01/03/10)
2. WHO. *WHO infection control guidelines for transmissible spongiform encephalopathies: report of a WHO consultation*. Geneva: WHO, 1999. Available at: http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.3.pdf (accessed 15/03/06)
3. Advisory Committee on Dangerous Pathogens, Spongiform Encephalopathy Advisory Committee. *Transmissible spongiform encephalopathy agents: safe working and the prevention of infection*. London: DoH, 2003. Also available at: http://www.dh.gov.uk/ab/ACDP/TSEguidance/index.htm (accessed 01/04/10)
4. Rutala WA, Weber DJ. Creutzfeldt-Jakob disease: recommendations for disinfection and sterilization. *Clin Infect Dis* 2001; **32:** 1348–56.
5. Rutala WA, Weber DJ. Society for Healthcare Epidemiology of America. Guideline for disinfection and sterilization of prion-contaminated medical instruments. *Infect Control Hosp Epidemiol* 2010; **31:** 107–17. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/650197 (accessed 22/06/10)

Disinfection in dental practice

Dental patients and healthcare staff can be exposed to viruses and bacteria that are present in blood or colonise or infect the oral cavity and respiratory tract, such as CMV, hepatitis B and C viruses, herpes simplex virus types 1 and 2, HIV, *Mycobacterium tuberculosis*, staphylococci, and streptococci. For information on endocarditis prophylaxis with antibacterials, see p. 179.2. These organisms can be transmitted in dental settings through direct or indirect contact with blood, oral fluids, or other body matter; by indirect contact with contaminated objects (e.g. instruments, equipment, or environmental surfaces), or inhalation of airborne micro-organisms (which can remain suspended in the air for long periods).

Guidelines have been developed in the USA for preventing and controlling infectious diseases and managing personnel health and safety concerns related to infection control in dental settings.[1] **Hand hygiene** (see p. 1732.1) substantially reduces potential pathogens on the hands and is considered a critical measure for reducing the risk of transmitting organisms to patients and healthcare workers. For routine dental examinations and nonsurgical procedures, handwashing and hand antisepsis is achieved by using a plain or antimicrobial soap and water. If the hands are not visibly soiled, an alcohol-based hand rub may be used. Before surgical procedures an antimicrobial soap or alcohol hand rub with persistent activity should be used. This extended antimicrobial activity is needed to prevent the introduction of organisms, which can colonise the hands underneath gloves and enter the wound if gloves become punctured or torn.

Patient-care items such as dental instruments, devices, and equipment should be **cleaned** to remove debris as well as organic and inorganic contamination, before proceeding with disinfection and sterilisation. If manual cleaning cannot be done immediately, the instruments should be placed in a puncture-resistant container and soaked in a detergent, a disinfectant/detergent, or an enzymatic cleaner. Use of a liquid chemical sterilant/high-level disinfectant (e.g. glutaral) as a holding solution is not recommended.

Heat-tolerant dental instruments usually are **sterilised** by autoclaving, dry heat, or unsaturated chemical vapour. Three levels of **disinfection** are used for patient-care devices that do not require sterility:

- high (e.g. glutaral, hydrogen peroxide, hydrogen peroxide with peracetic acid, *o*-phthaldialdehyde, peracetic acid, and phenol with glutaral)
- intermediate (e.g. chlorine-containing products, iodophores, phenolics, and quaternary ammonium compounds with alcohol)
- low (e.g. quaternary ammonium compounds, some phenolics, and some iodophores)

Patient-care items are categorised as critical, semicritical, or noncritical, depending on the potential risk for infection associated with their intended use. Heat sterilisation is used for critical items (used to penetrate soft tissue or bone) also for semicritical items that touch mucous membranes or non-intact skin. Semicritical items that are heat-sensitive should be processed with high-level disinfection. Noncritical patient-care items, contacting only intact skin, just require cleaning, or if visibly soiled, cleaning followed by disinfection. When the item is visibly contaminated with blood or other potentially infectious material a disinfectant thought to be effective against tubercle bacilli (intermediate-level disinfectant) should be used.

Clinical contact surfaces can become contaminated from patient materials either by direct spray or spatter generated during dental procedures or by contact with dental healthcare workers' gloved hands. Two levels of disinfection, intermediate and low, are used for environmental surfaces. If protective barriers are not used, surfaces should be cleaned and disinfected between patients by using disinfectants effective against HIV or hepatitis B virus (low-level disinfectant) or a tuberculocidal disinfectant (intermediate-level disinfectant) if the surface is visibly contaminated with blood or other potentially infectious material. General cleaning and disinfection are recommended for clinical contact surfaces, dental unit surfaces, and countertops at the end of daily work activities and are required if surfaces have become contaminated since their last cleaning. Spills of blood and other body fluids should be removed with absorbent material (e.g. disposable paper towels). Nonporous surfaces should be cleaned and then decontaminated with disinfectant effective against hepatitis B virus and HIV (low-level disinfectant) or a tuberculocidal disinfectant (intermediate-level disinfectant).

1. Kohn WG, *et al*. CDC guidelines for infection control in dental healthcare settings—2003. *MMWR* 2003; **52** (RR-17): 1–61. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5217.pdf (accessed 17/03/06)

Disinfection of endoscopes

Whenever possible, medical equipment that comes into intimate contact with the body should be heat sterilised, but some equipment, notably endoscopes, will not withstand high temperatures. Low-temperature steam and formaldehyde or ethylene oxide will achieve sterilisation, but may not be practical in a clinical setting. Satisfactory chemical disinfection of endoscopes and other heat-sensitive instruments relies on initial thorough cleansing of the instrument and choice of an appropriate high-level disinfectant which should be rapidly active against a wide range of pathogens including vegetative bacteria, bacterial spores, mycobacteria, and viruses. The disinfectant should not damage the instrument or discolour the optical components, and it should not leave a toxic residue. Instruments should be rinsed after disinfection with water and dried with forced air.[1-4]

Glutaral 2% is commonly used.[1,4] To achieve sterilisation, immersion in glutaral 2% for 3 hours is necessary, but high-level disinfection, achieved by immersion for 20 minutes, is usually considered adequate for most endoscopes.[1,3,5,6] Immersion for a minimum of 20 minutes is required for elimination of tubercle bacilli, but immersion for 4 minutes may be adequate for gastroscopes, except those for use on immunocompromised patients. For specific information relating to hepatitis and HIV viruses, see below.

A disadvantage of glutaral is that it is irritant and may cause sensitisation. In addition, longer contact times are needed to eliminate atypical mycobacteria and glutaral-resistant strains of *M. chelonae* have been isolated from endoscope disinfecting equipment.[4,7] In fact, mycobacteria in general are known to be extremely resistant to glutaral.[3] It should also be noted that in the UK it is recommended that units should move away from the use of aldehyde-based disinfectants because of their fixative properties, which in theory could anchor prion and other protein within endoscopes.[3] The use of aldehydes as the primary disinfectant should also be avoided in units serving groups at risk of CJD, such as haemophilia centres (see also Disinfection in Creutzfeldt-Jakob Disease, p. 1730.3). Alternative disinfectants include peracetic acid, chlorine dioxide, *o*-phthaldialdehyde, and superoxidised water (hypochlorous acid).[3,4,6] Other alternatives include peroxygen compounds, quaternary ammonium compounds, glucoprotamine, electrolysed acid water, succinic dialdehyde, and alcohol 70%.[1,4,6] However, peracetic acid and chlorine dioxide produce irritant fumes, peroxygen-containing compounds and quaternary ammonium compounds have questionable activity against mycobacteria and viruses, and alcohol has several practical limitations.[4,6]

1. Ayliffe GAJ, *et al*. *Chemical disinfection in hospitals*. 2nd ed. London: PHLS, 1993.
2. Rutala WA, Weber DJ. Disinfection and sterilization in health care facilities: what clinicians need to know. *Clin Infect Dis* 2004; **39:** 702–9.
3. British Society of Gastroenterology. BSG Working Party Report 2008. BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/decontamination_2008.pdf (accessed 26/02/10)
4. Beilenhoff U, *et al*. ESGE Guidelines Committee. European Society of Gastrointestinal Endoscopy. European Society of Gastroenterology and Endoscopy Nurses and Associates. ESGE-ESGENA guideline: cleaning and disinfection in gastrointestinal endoscopy. *Endoscopy* 2008; **40:** 939–57. Also available at: http://www.esge.com/assets/downloads/pdfs/guidelines/2008_cleaning_and_disifnection.pdf (accessed 07/07/10)
5. American Society for Gastrointestinal Endoscopy. Multi-society guideline for reprocessing flexible gastrointestinal endoscopes. *Gastrointest Endosc* 2003; **58:** 1–8. Also available at: http://www.asge.org/WorkArea/showcontent.aspx?id=3376 (accessed 27/08/08) Also published in: Nelson DB *et al*. Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 2003; **24:** 532–7.
6. Alvarado CJ, *et al*. Association for Professionals in Infection Control. APIC guideline for infection prevention and control in flexible endoscopy. *Am J Infect Control* 2000; **28:** 138–55.
7. Griffiths PA, *et al*. Glutaraldehyde-resistant Mycobacterium chelonae from endoscope washer disinfectors. *J Appl Microbiol* 1997; **82:** 519–26.

Disinfection in hepatitis and HIV infection

Hepatitis viruses and HIV are susceptible to heat and the methods recommended for sterilisation of equipment in the UK[1] are conventional procedures using moist or dry heat. Heat-labile articles and surfaces may undergo chemical disinfection but only in the absence of a satisfactory alternative. Although various publications have claimed efficacy against HIV for a wide range of disinfectants and detergents, the evidence for some claims is equivocal.

Fresh aqueous solutions of sodium hypochlorite or troclosene sodium are recommended for general surface disinfection. If contaminated by blood, the concentration must be equivalent to 10 000 ppm of available chlorine. For non-corrosive disinfection of delicate items such as fibreoptic endoscopes, freshly activated alkaline glutaral 2% may be used following thorough washing (but see also Disinfection of Endoscopes, above). If a sterile body cavity will be entered the endoscope must be immersed for a minimum of 3 hours; otherwise a minimum of 30 minutes is sufficient, or 1 hour if the presence of *Mycobacterium tuberculosis* is suspected.

1. DoH. *UK Health Departments guidance for clinical health care workers: protection against infection with blood-borne viruses: recommendations of the expert advisory group on AIDS and the advisory group on hepatitis* (April 1998). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4014474.pdf (accessed 27/08/08)

Disinfection of water

Travellers to regions of the world where water is not disinfected at source should be advised to boil or chemically sterilise water for drinking, cleaning teeth, and washing fruit and vegetables.[1] Chlorine and chlorine-releasing disinfectants including tosylchloramide sodium, halazone, sodium hypochlorite, and troclosene sodium are commonly used to sterilise **drinking water**. Iodine-releasing disinfectants such as tetraglycine hydroperiodide, or iodine itself may be useful for short-term or emergency disinfection of small volumes of water.[2] Organic material suspended in the water may reduce the available halogen concentration, and cloudy water should be filtered or allowed to settle and decanted before treatment. Emergency treatment of drinking water with lemon juice has been suggested during epidemics of waterborne gastro-enteritis.[3]

Chlorine and chlorine-releasing disinfectants are also used for recreational and therapeutic **bathing** pools, often with ozone.[4,5] Bromine-based disinfectants and ultraviolet radiation may also be used.

Legionnaires' disease (p. 188.2) is commonly transmitted via cooling water in **air conditioning** systems or **hot water** supplies. Hyperchlorination has been attempted to eradicate the organism from contaminated water sources but has been largely ineffective[6,7] and is no longer recommended. Other disadvantages of using chlorine-based systems at these temperatures and concentrations are corrosion of the plumbing system[7] and the production of potentially carcinogenic byproducts.[8] Effective disinfection can be achieved by raising and maintaining the water temperature above 50 degrees, ultraviolet light, and copper-silver ionisation.

Haemodialysis patients are exposed to large quantities of municipal drinking water as it is used for the production of **dialysis** fluids and may also be used for dialyser rinsing and reuse. Many of the chemical substances in the water, such as calcium, sodium, aluminium, chloramines, fluoride, copper, zinc, sulfates, and nitrates are potentially dangerous for dialysis patients, and can lead to acute or chronic poisoning. There is also a microbiological risk associated with the control of bacterial growth in the water treatment and distribution system. Contaminants are therefore removed by water purification systems. Water is pre-treated with activated carbon filters to remove chlorine and its derivatives and other suspended particles, and the hardness of the water is decreased with sodium exchange cationic resins, which remove calcium and magnesium. The final purification process then involves the removal of dissolved salts, bacteria, and endotoxins by reverse osmosis. Reverse osmosis membranes need to be regularly disinfected with chemical agents (such as hypochlorite and peracetic acid), heat, or ozone.[9]

1. Backer H. Water disinfections for international and wilderness travelers. *Clin Infect Dis* 2002; **34:** 355–64.
2. WHO. Guidelines for drinking-water quality, third edition, incorporating first addendum: volume 1— recommendations. Geneva: WHO, 2006. Available at: http://www.who.int/water_sanitation_health/dwq/gdwq3/en/print.html (accessed 27/08/08)
3. D'Aquino M, Teves SA. Lemon juice as a natural biocide for disinfecting drinking water. *Bull Pan Am Health Organ* 1994; **28:** 324–30.
4. Dadswell JV. Managing swimming, spa, and other pools to prevent infection. *Commun Dis Rep* 1996; **6** (review 2): R37–R40.
5. WHO. Guidelines for safe recreational water environments: volume 2—swimming pools and similar recreational environments. Geneva: WHO, 2006.
6. Kurtz JB, *et al*. Legionella pneumophila in cooling water systems: report of a survey of cooling towers in London and a pilot trial of selected biocides. *J Hyg (Camb)* 1982; **88:** 369–81.
7. Helms CM, *et al*. Legionnaires' disease associated with a hospital water system: a five-year progress report on continuous hyperchlorination. *JAMA* 1988; **259:** 2423–7.
8. Morris RD, *et al*. Chlorination, chlorination by-products, and cancer: a meta-analysis. *Am J Public Health* 1992; **82:** 955–63.
9. Pontoriero G, *et al*. The quality of dialysis water. *Nephrol Dial Transplant* 2003;**18** (suppl 7): vii21–vii5.

Hand hygiene

Hospital-acquired infections, including those due to multidrug-resistant pathogens, such as meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staph. aureus*, and vancomycin-resistant enterococci, are a major problem in healthcare facilities.[1] Hand hygiene is one of the most important factors in preventing such infections, as it prevents transmission of pathogens by contact and the faecal-oral route. However, healthcare workers frequently do not wash their hands, and compliance rarely exceeds 40%.[2] A randomised study[3] to compare the efficacy of an alcohol-based solution for hand rubbing with hand washing with a medicated soap in reducing bacterial hand contamination during routine patient care found that the alcohol-based solution was significantly more effective (83% reduction versus 58%). The authors considered that the difference in efficacy might have been due to the duration of hand washing. Participants rubbed or washed their hands for about 30 seconds, but the recommended duration for hand washing is 30 seconds to 1 minute, a time that was adhered to in less than 35% of instances.

Some recommend[1,2] that alcohol-based hand rubs should replace hand washing as the standard for hand hygiene in all situations in which the hands are not visibly soiled. The basis for this is that hand rubbing requires less time, is microbiologically more effective, and is less irritating to skin than traditional hand washing with soap and water. Guidelines in the UK[4] and USA[5] do suggest alcohol as an alternative to soap and water in such situations but note that soap and water must be used if hands are visibly soiled. In addition, US guidelines advise[5] hand washing with a non-antimicrobial or antimicrobial soap and water when hands are contaminated with proteinaceous material, blood, or other body fluids and if exposure to *Bacillus anthracis* is suspected or proven. Alcohols, chlorhexidine, iodophores, and other antiseptic agents are not recommended for *B. anthracis* contamination as they have poor activity against the spores. Decontamination of the hands with an antiseptic hand rub or hand wash should occur before direct contact with patients, and before putting on sterile gloves when inserting catheters or other invasive devices that do not require a surgical procedure. Decontamination of the hands should also occur after contact with a patient's intact or non-intact skin, body fluids, mucous membranes, and wound dressings if hands are not visibly soiled. Hands should be decontaminated if moving from a contaminated body site to a clean body site during patient care, after contact with inanimate objects (including medical equipment) in the immediate vicinity of the patient, and after removing gloves. When performing surgical procedures hand hygiene with either an antimicrobial soap or an alcohol-based hand rub with persistent activity is recommended before putting on sterile gloves.

US guidelines[5] considers that the best antimicrobial efficacy can be achieved with alcohol (ethanol), isopropyl alcohol, and propyl alcohol, as their activity is broad and they are fast acting. Ethanol at high concentrations is the most effective treatment against non-enveloped viruses, whereas propyl alcohol seems to be more effective against the resident bacterial flora. Combinations of alcohols may have a synergistic effect. The antimicrobial efficacy of chlorhexidine (2 to 4%) and triclosan (1 to 2%) is both lower and slower. Bacterial resistance may occur, although the risk is higher for chlorhexidine than triclosan. Even if used with hand washing, they are still less effective than the alcohols. Plain soap and water has the lowest efficacy of all.

1. Trampuz A, Widmer AF. Hand hygiene: a frequently missed lifesaving opportunity during patient care. *Mayo Clin Proc* 2004; **79:** 109–16.
2. Widmer AF. Replace hand washing with use of a waterless alcohol hand rub? *Clin Infect Dis* 2000; **31:** 136–43.
3. Girou E, *et al*. Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial. *BMJ* 2002; **325:** 362–6.
4. Coia JE, *et al*. Joint Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *J Hosp Infect* 2006; **63** (suppl 1): S1–S44. Available at: http://www.his.org.uk/_db/_documents/MRSA_Guidelines_PDF.pdf (accessed 14/05/10)
5. CDC. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR* 2002; **51** (RR-16): 1–45. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf (accessed 15/03/06)

Injection site and catheter care

The need to disinfect the skin before injection is controversial.[1] Routine skin preparation of the injection site by swabbing with antiseptic has been reported to be both ineffective and unnecessary.[2,3] Central venous and arterial catheters, however, require the application of strict aseptic technique and injection site antisepsis to reduce the chance of infection.[4] Disinfection of catheter insertion sites with aqueous chlorhexidine 2% has been reported to be associated with fewer local and systemic infections than site preparation with either 10% povidone-iodine solution or 70% isopropyl alcohol,[5] although this has been challenged.[6] A subsequent study reported lower rates of catheter colonisation and catheter-related infection with an alcoholic solution of chlorhexidine 0.25% and benzalkonium chloride 0.025% than with povidone-iodine 10%.[7] In a study in preterm infants, technique had greater influence on bacterial counts at injection sites than the antiseptic used; chlorhexidine 0.5% in isopropyl alcohol and aqueous povidone-iodine 10% were equally effective, but cleansing with alcoholic chlorhexidine for 30 seconds or for two 10-second periods was more effective than cleansing for 5 or 10 seconds.[8]

The use of catheters impregnated with antiseptics or antibacterials has also been studied. Catheters impregnated with chlorhexidine and sulfadiazine silver on the external luminal surface, appear to be effective in reducing both catheter colonisation and related bloodstream infection in high-risk patients when used within 14 days.[9] Central venous catheters impregnated with minocycline and rifampicin have been reported to be associated with a lower infection rate than standard silicone catheters[10] and those impregnated with chlorhexidine and sulfadiazine silver.[11]

Guidelines have been produced for the prevention of infection associated with both peripheral intravascular and central venous catheterisation.[12-14]

1. Ayliffe GAJ, *et al*. *Chemical disinfection in hospitals*. 2nd ed. London: PHLS, 1993.
2. Dann TC. Routine skin preparation before injection: an unnecessary procedure. *Lancet* 1969; **ii:** 96–8.
3. Liauw J, Archer GJ. Swabaholics? *Lancet* 1995; **345:** 1648.
4. Shepherd A, Williams N. Care of long-term central venous catheters. *Br J Hosp Med* 1994; **51:** 598–602.
5. Maki DG, *et al*. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991; **338:** 339–43.
6. Segura M, Sitges-Serra A. Intravenous catheter sites and sepsis. *Lancet* 1991; **338:** 1218.
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8. Malathi I, *et al*.. Skin disinfection in preterm infants. *Arch Dis Child* 1993; **69:** 312–16.
9. Veenstra DL, *et al*. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999; **281:** 261–7.
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11. Darouiche RO, *et al*. A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 1999; **340:** 1–8.
12. DoH. Guidelines for preventing infections associated with the insertion and maintenance of central venous catheters. *J Hosp Infect* 2001; **47** (suppl): S47–S67. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005481?IdcService=GET_FILE&dID=14080&Rendition=Web (accessed 27/08/08)
13. O'Grady NP, *et al*. Guidelines for the prevention of intravascular catheter-related infections. *MMWR* 2002; **51** (RR-10): 1–29. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5110.pdf (accessed 15/03/06)
14. NICE. Infection control: prevention of healthcare-associated infections in primary and community care (June 2003). Section 5: central venous catheterisation. Available at: http://www.nice.org.uk/nicemedia/pdf/Infection_control_fullguideline.pdf (accessed 27/08/08)

Pre-operative skin disinfection

Skin preparation with antiseptics before surgery is generally carried out in an attempt to reduce the risks of surgical infection (see p. 209.1), but the evidence base for the practice is conflicting. The CDC recommends[1] pre-operative cleaning of skin at the incision site with either iodophores (e.g. povidone-iodine), alcohol-containing products, or chlorhexidine gluconate. While alcohol is considered to be the most effective and rapidly acting skin antiseptic, there are no appropriate studies to assess comparative efficacy. Furthermore, an analysis[2] of randomised studies comparing the use of pre-operative skin antiseptics with no antiseptics and studies comparing different skin antiseptics, found that there was insufficient evidence to conclude whether pre-operative skin antiseptics were effective in preventing postoperative surgical wound infection.

1. Mangram AJ, *et al*. CDC Hospital Infection Control Practices Advisory Committee. Guideline for prevention of surgical site infection, 1999. *Am J Infect Control* 1999; **27:** 97–132. Also available at: http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf (accessed 15/03/06)
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Wound disinfection

Antiseptic preparations are widely used to treat or prevent superficial infections and wounds, but their usefulness on broken skin and wounds has been questioned.[1] For further information on wound care, see p. 1690.1. Chlorine-releasing antiseptic solutions are generally regarded as irritant and although there is little direct evidence in patients there is concern that they may delay wound healing. Cetrimide,[2] tosylchloramide sodium,[3] hydrogen peroxide 3%,[4] iodophores,[4] and sodium hypochlorite solutions[2] are all reported to be cytotoxic *in vitro* or in *animal* models. Long-term or repeated use of these antiseptics for wound cleaning should probably be avoided. Chlorhexidine is relatively non-toxic.[2,3]

1. Brown CD, Zitelli JA. A review of topical agents for wounds and methods of wounding: guidelines for wound management. *J Dermatol Surg Oncol* 1993; **19:** 732–7.
2. Thomas S, Hay NP. Wound cleansing. *Pharm J* 1985; **2:** 206.
3. Brennan SS, *et al*. Antiseptic toxicity in wounds healing by secondary intention. *J Hosp Infect* 1986; **8:** 263–7.
4. Lineweaver W, *et al*. Topical antimicrobial toxicity. *Arch Surg* 1985; **120:** 267–70.

Acridine Derivatives

Acridina, derivados.

Description. Acridine derivatives are a group of quinoline antimicrobial dyes structurally related to acridine.

Acriflavinium Chloride *(rINN)*

Acriflavine; Acriflavine Hydrochloride; Acriflavinii Chloridum; Acriflavinii Dichloridum; Acriflavinio, cloruro de; Acriflavinium, Chlorure d'; Akriflavinium-chlorid; Cloruro de acriflavinio; Акрифлавиния Хлорид.

A mixture of 3,6-diamino-10-methylacridinium chloride hydrochloride and 3,6-diaminoacridine dihydrochloride.

CAS — 8063-24-9; 65589-70-0.
ATC — R02AA13.
ATC Vet — QG01AC90; QR02AA13.
UNII — 1S73VW819C.

NOTE. The nomenclature is confusing. Acriflavinium Chloride is *rINN* but was also the *BP* name for Acriflavinium Monochloride (see below).

Acriflavinium Monochloride

Acriflavinii Monochloridum; Acriflavinio, monocloruro de; Acriflavinium, monochlorure d'; Akriflavinio monochloridas; Akriflaviniummonoklorid; Akriflaviniummonokloridi; Euflaviini; Euflavin; Euflavine; Euflavinum; Neutral Acriflavine; Neutroflavin.

A mixture of 3,6-diamino-10-methylacridinium chloride and 3,6-diaminoacridine monohydrochloride. The latter is usually present to the extent of between 30 and 40%.

CAS — 68518-47-8.
ATC — D08AA03.
ATC Vet — QD08AA03.

NOTE. The nomenclature is confusing. Although the *BP* name was Acriflavinium Chloride this is also *rINN* for a related compound (see above).

Aminoacridine Hydrochloride *(BANM, rINNM)*

Aminacrine Hydrochloride (USAN); Aminacrine Hydrochloride; Aminoacridina, hidrocloruro de; Aminoacridine, Chlorhydrate d'; Aminoacridini Hydrochloridum; Hidrocloruro de aminoacridina; NSC-7571; Аминоакридина Гидрохлорид.

9-Aminoacridine hydrochloride monohydrate.

$C_{13}H_{10}N_2,HCl,H_2O$=248.7

CAS — 90-45-9 (aminoacridine); 134-50-9 (anhydrous aminoacridine hydrochloride).
ATC — D08AA02.
ATC Vet — QD08AA02.
UNII — OR5RM3Q5QL.

Ethacridine Lactate *(BANM, rINNM)*

Acrinol; Aethacridinium Lacticum; Etacridina, lactato de; Etakridiinilaktaatti; Etakridinlaktat; Etakridin-laktát; Etakridino laktatas; Etakrydyny mleczan; Éthacridine, lactate d'; Ethacridini Lactas; Ethakridin-laktát; Lactato de etacridina; Lactoacridine; Этакридина Лактат.

6,9-Diamino-2-ethoxyacridine lactate.

$C_{15}H_{15}N_3O,C_3H_6O_3$=343.4

CAS — 442-16-0 (ethacridine); 1837-57-6 (ethacridine lactate); 6402-23-9 (ethacridine lactate monohydrate).
ATC — B05CA08; D08AA01.
ATC Vet — QB05CA08; QD08AA01.
UNII — V5IL571C1T.

Pharmacopoeias. *Chin., Eur.* (see p. vii), and *Jpn* describe the monohydrate.

Ph. Eur. 8: (Ethacridine Lactate Monohydrate). A yellow crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 5.5 to 7.0. Protect from light.

Proflavine Hemisulfate

Hemisulfato de proflavina; Neutral Proflavine Sulphate; Proflavina, hemisulfato de; Proflavine, Hémisulfate de; Proflavine Hemisulphate (pINNM); Proflavine Hemisulphate; Proflavini Hemisulfas; Профлавина Гемисульфат.

3,6-Diaminoacridine sulphate dihydrate.

$(C_{13}H_{11}N_3)_2,H_2SO_4,2H_2O$=552.6

CAS — 92-62-6 (proflavine).

UNII — 27V8M747VB (proflavine hemisulfate); 2961Y60ATP (proflavine sulfate).

Profile

The acridine derivatives are slow-acting antiseptics. They are bacteriostatic against many Gram-positive bacteria but less effective against Gram-negative bacteria. They are ineffective against spores. Their activity is increased in alkaline solutions and is not reduced by tissue fluids.

The acridine derivatives have been used for the treatment of infected wounds or burns and for skin disinfection, although they have been largely superseded by other antiseptics or suitable antibacterials. Prolonged treatment may delay healing. They have also been used for the local treatment of ear, oropharyngeal, and genitourinary infections.

Aminoacridine is reported to be non-staining and is used as the hydrochloride as eye drops in the treatment and prophylaxis of superficial eye infections.

Ethacridine lactate is included in some preparations for the treatment of diarrhoea. It has also been given by extra-amniotic injection for the termination of pregnancy (p. 2131.3) but other methods are usually preferred.

Other acridine derivatives covered elsewhere in *Martindale* include mepacrine (p. 935.2), which is used in the treatment of giardiasis, and pyronaridine (p. 664.3), which is used to treat malaria. Amsacrine (p. 741.3) is a 9-anilinoacridine drug that is used in the treatment of adult leukaemias. Other acridine derivatives have also been investigated as anticancer drugs because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase enzymes.

Hypersensitivity to acridine derivatives has been reported.

References.
1. Wainwright M. Acridine—a neglected antibacterial chromophore. *J Antimicrob Chemother*. 2001; **47:** 1–13.
2. Denny WA. Acridine derivatives as chemotherapeutic agents. *Curr Med Chem* 2002; **9:** 1655–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aminopt†; ***China***: Bi Fen (彼芬); ***Ger.***: Metifex; Neochinosol; Rivanol; ***India***: Aborcin; Abortil; Emcredil†; Vecredil; ***Pol.***: Rivanol; Rivanolum; Rivel; Rywanol†; ***Turk.***: Rivanol.

Multi-ingredient Preparations. ***Arg.***: Carnot Topico; Nene Dent; Otocuril; ***Austral.***: Medijel; ***Austria***: Dermowund†; ***Braz.***: Acridin; Cystex; ***Chile***: Molca; ***Fr.***: Chromargon; Pyorex; ***Ger.***: Tannacomp; ***Hong Kong***: Medijel; ***Hung.***: Glycosept; ***India***: Emscab†; ***Irl.***: Aidex†; Medijel; ***Israel***: Medijel†; ***Malaysia***: Burnol Plus; Medijel; ***NZ***: Medijel; ***Pol.***: Septalan†; ***S.Afr.***: Achromide; Daromide†; Vagarsol; ***Singapore***: Burnol Plus; Medijel; ***Spain***: Antigrietun; Hepro; ***Switz.***: Haemolan†; Tyrothricin†; ***Thai.***: Burnol Plus; Flavinol; ***Turk.***: Derivit; Dervanol; ***UK***: Iglu; Medijel; ***USA***: Alasulf; Deltavac; DIT1-2.

Pharmacopoeial Preparations

BPC 1973: Proflavine Cream.

Alcohol ⊗

Aethanolum; Alcohol etílico; Alcool; Alkol; Etanol; Etanol (96%); Etanol bezwodny; Etanoli; Etanolis; Ethanol; Éthanol; Ethanolum; Ethyl Alcohol; Этанол; Алкоголь.

C_2H_5OH=46.07

CAS — 64-17-5.

ATC — D08AX08; V03AB16; V03AZ01.

ATC Vet — QD08AX08; QV03AB16; QV03AZ01.

UNII — 3K9958V90M.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of alcohol:

Booze; Drinks; Grog; Juice; Jungle juice; Liq; Liquor; Lunch head; Moonshine; Piss; Sauce; Schwillins.

Pharmacopoeias. Various strengths are included in *Br., Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.* Also in *USNF.*

In *Martindale* the term alcohol is used for alcohol 95 or 96% v/v.

Ph. Eur. 8: (Ethanol, Anhydrous; Ethanolum Anhydricum; Ethanol BP 2014). It contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH at 20 degrees. A colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame. B.p. about 78 degrees. Miscible with water and with dichloromethane. Protect from light.

The BP 2014 gives Absolute Alcohol and Dehydrated Alcohol as approved synonyms.

Ph. Eur. 8: (Ethanol (96 per cent)). It contains not less than 95.1% v/v or 92.6% w/w and not more than 96.9% v/v or 95.2% w/w of C_2H_5OH at 20 degrees, and water. A colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame. B.p. about 78 degrees. Miscible with water and with dichloromethane. Protect from light.

The BP 2014 gives Alcohol (96 per cent) as an approved synonym.

BP 2014: (Dilute Ethanols). The monograph describes several dilute alcohols containing between 20 and 90% v/v of C_2H_5OH, and one of these, ethanol (90%), is also known as rectified spirit.

USP 36: (Alcohol). It contains not less than 92.3% w/w or 94.9% w/v and not more than 93.8% w/w or 96.0% w/v of C_2H_5OH at 15.56 degrees. A clear, colourless, mobile, volatile liquid with a characteristic odour and burning taste; it is flammable. B.p. about 78 degrees. Miscible with water and with almost all other organic solvents. Store in airtight containers. Protect from light.

USP 36: (Dehydrated Alcohol). It contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH (sp. gr. not more than 0.7962 at 15.56 degrees). Store in airtight containers. Protect from light.

USNF 31: (Diluted Alcohol). It contains 48.4 to 49.5% v/v or 41 to 42% w/w of C_2H_5OH. Store away from fire in airtight containers.

Alcoholic strength. This is expressed as a percentage by volume of alcohol. It was previously often expressed in terms of *proof spirit*. Proof spirit contained about 57.1% v/v or 49.2% w/w of C_2H_5OH, and was defined as 'that which at the temperature of 51 degreesF weighs exactly twelve-thirteenths of an equal measure of distilled water'. Spirit of such a strength that 100 volumes contained as much ethyl alcohol as 160 volumes of proof spirit was described as '60 OP' (over proof). Spirit of which 100 volumes contained as much alcohol as 40 volumes of proof spirit was described as '60 UP' (under proof).

An alternative method of indicating spirit strength was used on the labels of alcoholic beverages in the UK when the strength was given as a number of degrees, proof spirit being taken as 100 degrees. In the USA alcoholic strength is expressed in degrees, the value of which is equal to twice the percentage by volume. Thus 70 degrees proof (old UK system) is equivalent to 40% v/v, and therefore to 80 degrees proof (USA system).

Uses and Administration

Alcohol has been used and abused for many thousands of years, in the form of alcoholic beverages, for its effects on the CNS. However, it also has pharmaceutical applications.

Alcohol is bacteriostatic at low concentrations but has bactericidal activity at higher concentrations; it does not, however, destroy bacterial spores. The mechanism of action appears to be denaturation of proteins. In the total absence of water, proteins are not denatured as rapidly as when water is present. Its bactericidal activity drops sharply when diluted below a 50% concentration and the optimal bactericidal concentration is 60 to 90% by volume. Alcohol also has some fungicidal and virucidal activity. It is used to disinfect skin before injection, venepuncture, or surgical procedures. It is also used to disinfect hands and clean surfaces. A concentration of 70%, often as methylated spirits (p. 1760.3), is commonly used for disinfection. Alcohol should not be used for disinfection of surgical or dental instruments because of its low efficacy against bacterial spores and inability to penetrate protein-rich materials.

Alcohol also has anhidrotic, rubefacient, and astringent and haemostatic properties. It is sometimes used for its skin-cooling properties and to harden the skin. It is an ingredient of several topical preparations used for skin disorders.

Alcohol is widely used as a solvent and preservative in pharmaceutical preparations.

Alcohol may be used as a neurolytic in the management of severe and chronic pain.

Alcohol is given intravenously in the treatment of acute poisoning from ethylene glycol (p. 2500.3) and methyl alcohol (p. 2196.3).

Alcohol is also used in sclerotherapy.

Pain. The use of alcohol as a neurolytic to produce destructive nerve block (see under Pain, p. 1977.1) has produced variable results, and some consider the risk of complications outweighs the benefits. However, alcohol has been injected into the pituitary gland for relief of severe pain of the head and neck;[1,2] doses of 1 mL of absolute alcohol have been used.[1] It may be useful in coeliac plexus block, and has been injected into the muscle sheath to relieve painful muscle spasms in patients with multiple sclerosis.[1] Alcohol 50 to 100% may be used for peripheral or central nerve block in terminally ill patients with pain that does not respond to drug therapy;[3,4] the block produced by alcohol may occasionally last up to 2 years, even longer than that produced by phenol. However, larger volumes of alcohol than phenol are required, which means that blockade may be less precise due to leakage to proximal sites;[4] in addition, alcohol may exacerbate local pain on injection, because of its irritant effect on the tissues, and injection of a local anaesthetic beforehand, or giving the alcohol combined with a local anaesthetic, may be necessary.[4,5]

Intrathecal injection of alcohol has also been used for the intractable pain of spasticity (p. 2014.2); early use, as soon as spasticity becomes painful and disabling, has been advocated.[6]

1. Lloyd JW. Use of anaesthesia: the anaesthetist and the pain clinic. *BMJ* 1980; **281:** 432–4.
2. Lipton S. Pain relief in active patients with cancer: the early use of nerve blocks improves the quality of life. *BMJ* 1989; **298:** 37–8.
3. Hardy, PAJ. The role of the pain clinic in the management of the terminally ill. *Br J Hosp Med* 1990; **43:** 142–6.
4. Gordin V, *et al.* Acute and chronic pain management in palliative care. *Best Pract Res Clin Obstet Gynaecol* 2001; **15:** 203–34.
5. Kongsgaard UE, *et al.* Nevrolytisk blokade hos kreftpasienter–fortsatt en nyttig behandling. *Tidsskr Nor Laegeforen* 2004; **124:** 481–3.
6. Viel E, *et al.* Spasticité: intérêt du testing par anesthésie locorégionale et blocs thérapeutiques. *Ann Fr Anesth Reanim* 2005; **24:** 667–72.

Sclerotherapy. Alcohol has been used successfully as a sclerosant in a variety of conditions including aldosterone-producing adenoma,[1] parathyroid adenomas,[2] thyroid nodules,[3,4] advanced rectal cancer,[5] hepatocellular carcinoma,[6,7] dysphagia associated with oesophogastric cancer,[8,9] hepatic[10] or renal[11] cysts, and gallbladder obstruction.[12] It has also been used in the sclerotherapy of oesophageal varices,[13,14] although the safety of this procedure has been questioned after a report of complications developing in 13 of 17 patients, 2 of whom died.[15] Other conditions in which alcohol has been used as a sclerosant include bleeding from ruptured hepatomas[16] and in peptic ulcer disease,[17] vascular malformations,[18] and obstructive cardiomyopathies[19] resistant to usual treatment.

Other sclerosants used in oesophageal varices are discussed on p. 2563.1.

1. Hokotate H, *et al.* Aldosteronomas: experience with superselective adrenal arterial embolization in 33 cases. *Radiology* 2003; **227:** 401–6.
2. Vergès B, *et al.* Traitement des adénomes parathyroïdiens par alcoolisation sous contrôle échographique. *Ann Chir* 2000; **125:** 457–60.
3. Monzani F, *et al.* Autonomous thyroid nodule and percutaneous ethanol injection. *Lancet* 1991; **337:** 743.
4. Bennedbaek FN, Hegedüs L. Alcohol sclerotherapy for benign solitary solid cold thyroid nodules. *Lancet* 1995; **346:** 1227.
5. Payne-James J, *et al.* Advanced rectal cancer. *BMJ* 1990; **300:** 746.
6. Lencioni R, *et al.* Alcoolizzazione percutanea dell'epatocarcinoma: risultati a lungo termine. *Radiol Med (Torino)* 1997; **94:** 8–13.
7. Ebara M, *et al.* Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol* 2005; **43:** 458–64.
8. Payne-James JJ, *et al.* Use of ethanol-induced tumor necrosis to palliate dysphagia in patients with esophagogastric cancer. *Gastrointest Endosc* 1990; **36:** 43–6.
9. Stanners AJ, *et al.* Alcohol injection for palliation of malignant oesophageal disease. *Lancet* 1993; **341:** 767.
10. Larsen TB, *et al.* Single-session alcohol sclerotherapy in symptomatic benign hepatic cysts: long-term results. *Acta Radiol* 1999; **40:** 636–8.
11. Mohsen T, Gomha MA. Treatment of symptomatic simple renal cysts by percutaneous aspiration and ethanol sclerotherapy. *BJU Int* 2005; **96:** 1369–72.
12. Asfar S, *et al.* Percutaneous sclerosis of gallbladder. *Lancet* 1989; **ii:** 387.
13. Meirelles-Santos JO, *et al.* Absolute ethanol and 5% ethanolamine oleate are comparable for sclerotherapy of esophageal varices. *Gastrointest Endosc* 2000; **51:** 573 6.
14. Ferrari AP, *et al.* Efficacy of absolute alcohol injection compared with band ligation in the eradication of esophageal varices. *Arq Gastroenterol* 2005; **42:** 72–6.
15. Bhargava DK, *et al.* Endoscopic sclerotherapy using absolute alcohol. *Gut* 1986; **27:** 1518.
16. Chung SCS, *et al.* Injection of alcohol to control bleeding from ruptured hepatomas. *BMJ* 1990; **301:** 421.
17. Lin HJ, *et al.* Heat probe thermocoagulation and pure alcohol injection in massive peptic ulcer haemorrhage: a prospective, randomised controlled trial. *Gut* 1990; **31:** 753–7.
18. Deveikis JP. Percutaneous ethanol sclerotherapy for vascular malformations in the head and neck. *Arch Facial Plast Surg* 2005; **7:** 322–5.
19. Knight CJ. Alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Heart* 2006; **92:** 1339–44.

Adverse Effects

Adverse effects of alcohol arise chiefly from the intake of alcoholic beverages. The concentration of alcohol in the blood producing a state of intoxication varies between individuals.

- Low concentrations (up to 180 mg per 100 mL) of alcohol may result in impaired vision, reaction time, and coordination and emotional lability.
- At low to moderate concentrations (180 to 350 mg per 100 mL), alcohol acts as an apparent stimulant; depression of cortical function causes loss of judgement, slurred speech, diplopia, blurred vision, ataxia, lack of

coordination, blackouts, sweating, tachycardia, nausea, vomiting, and incontinence. Alcohol inhibits the release of antidiuretic hormone resulting in enhanced diuresis. Acidosis (especially in children), hypoglycaemia, and hypokalaemia may occur.

- High concentrations (350 to 450 mg per 100 mL) of alcohol result in cold clammy skin, hypothermia, hypotension, stupor, coma, dilated pupils, and depressed or absent tendon reflexes. Severe hypoglycaemia, convulsions, respiratory depression, and metabolic acidosis may occur. Cardiac arrhythmias such as atrial fibrillation and AV block have been recorded.

The median lethal blood-alcohol concentration is generally estimated to be about 400 to 500 mg per 100 mL. Death may occur at lower blood-alcohol concentrations due to inhalation of vomit during unconsciousness.

Chronic excessive consumption of alcohol may cause damage to many organs, particularly the brain and the liver. Possible direct toxic effects of alcohol on the brain, as well as thiamine deficiency, may lead to Wernicke-Korsakoff syndrome. Fat deposits may occur in the liver and there may be a reduction in various blood cell counts. Nutritional diseases may occur due to inadequate diet. High alcohol consumption has been associated with pancreatitis, and an increased risk of cardiovascular disease, although some consider that moderate consumption might have a protective effect against ischaemic heart disease.

Alcohol consumption has also been associated with an increased risk of some types of cancer.

The term '**alcoholism**' may be used to denote dependence on alcohol, which is of the barbiturate-alcohol type (see Amobarbital, p. 1038.1) and usually involves tolerance to other sedatives and anaesthetics. After prolonged periods of excessive alcohol consumption, a drop in blood-alcohol concentration may precipitate a withdrawal syndrome characterised by tremor, agitation, feelings of dread, nausea, vomiting, and sweating; hallucinations, seizures, and delirium tremens may also develop.

A **fetal alcohol syndrome** may be noted in infants born to alcoholic mothers; such infants have a distinctive set of facial anomalies, growth retardation, and significant learning and/or behavioural problems. There have been some reports of the syndrome and other adverse effects on the fetus being associated with moderate alcohol intake in pregnancy. It is therefore generally suggested that alcohol is avoided, or at least intake limited, during pregnancy (see Pregnancy, p. 1735.1).

Frequent application of alcohol to the skin produces irritation and dry skin.

Effects on the skin. A 70% solution of alcohol, containing povidone-iodine, caused partial thickness chemical burns beneath tourniquets in 3 young children.[1] Other adverse effects on the skin reported with the topical application of alcohols have included necrosis after skin cleansing of preterm neonates with methylated spirits[2,3] and haemorrhagic skin necrosis due to the alcohol content of chlorhexidine in spirit used as a disinfectant in umbilical artery catheterisation in preterm infants.[4]

See also Children, under Adverse Effects of Isopropyl Alcohol, p. 1759.1.

1. Dickinson JC, Bailey BN. Chemical burns beneath tourniquets. *BMJ* 1988; **297:** 1513.
2. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982; **57:** 477–9.
3. Murch S, Costelloe K. Hyperosmolality related to propylene glycol in an infant. *BMJ* 1990; **301:** 389.
4. Al-Jawad ST. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1983; **58:** 395–6.

Treatment of Adverse Effects

Treatment of acute poisoning with alcohol should include hydration with intravenous fluids, control of nausea and vomiting, and correction of electrolyte imbalances, such as hypomagnesaemia. Protection of the airway is crucial and ventilation may be required in cases of respiratory depression. Glucose is indicated for patients with hypoglycaemia, while thiamine supplementation should be considered for chronic alcoholics. Hypothermia and hypotension should be corrected. Convulsions may be controlled with intravenous benzodiazepines or phenytoin. Haemodialysis is of value in severe alcohol poisoning. Gut decontamination and activated charcoal are unlikely to be of benefit due to the rapid absorption of alcohol through intestinal mucosa. The use of intravenous infusions of fructose to treat severe alcohol poisoning is not recommended.

The management of the alcohol withdrawal syndrome and long-term abstinence following withdrawal are discussed below.

Alcohol withdrawal and abstinence. The alcohol withdrawal syndrome presents in the early stages as a classical hyperadrenergic state with tremor, tachycardia, sweating, and hypertension. Sometimes this is accompanied by mild disorientation, anxiety, impaired concentration, depression, agitation, and gastrointestinal symptoms. Insomnia, nightmares, and transient hallucinations can also be present. The condition may be self-limiting without the need for therapeutic intervention or it may progress to the severe and potentially fatal condition of delirium tremens (DTs), often characterised by delirium, disorientation, and hallucinations. In some cases generalised tonic-clonic seizures occur within 24 hours of alcohol withdrawal and are followed by delirium tremens.

The general management of the alcohol **withdrawal** syndrome and maintenance of abstinence have been the subject of many reviews and discussions.[1-17] In most cases symptoms do not require treatment and disappear within a few days, but more severe cases may require managed withdrawal from alcohol to avoid complications.

Benzodiazepines are usually the drugs of first choice because of their sedative, anxiolytic and anticonvulsant properties. If given promptly, benzodiazepines can prevent progression to seizures and delirium tremens. Longer-acting drugs such as chlordiazepoxide or diazepam may be more effective against withdrawal seizures and provide smoother withdrawal, while shorter-acting ones such as lorazepam or oxazepam have a smaller risk of producing oversedation and may be more suitable for use in the elderly and, since they do not rely on hepatic enzymes for their metabolism, for patients with liver disease. Because of the risk of dependence benzodiazepines should only be given in short courses. Some advocate that benzodiazepine dosage should be adjusted according to the severity of symptoms with special care being paid to patients with a history of withdrawal seizures, comorbid conditions, or those using sedative or hypnotic medication. This reduces the amount of drug required and the duration of treatment but entails regular monitoring by trained nursing staff. For mild to moderate symptoms, standard anxiolytic or muscle-relaxing oral doses of benzodiazepines may be sufficient. For severe symptoms, or for the treatment of delirium tremens, higher doses and use of the intravenous route may be required. *Clomethiazole* appears to be an effective alternative to the benzodiazepines (but see under Interactions of Clomethiazole, p. 1055.1); although widely used in Europe, it is not available in the USA. Some centres use phenobarbital but *barbiturates* are generally not recommended for the treatment of alcohol withdrawal syndrome.

Antipsychotics are not usually recommended for use in the control of symptoms of alcohol withdrawal since they do not reduce delirium tremens and some may reduce the seizure threshold. However, they might be considered for use as adjuncts in patients requiring treatment of marked agitation or hallucinations.

The generalised tonic-clonic seizures associated with alcohol withdrawal are usually self-limiting and patients who have only one or two seizures do not usually require any specific treatment beyond continuing therapy with benzodiazepines or clomethiazole. For recurrent seizures or status epilepticus (p. 510.2) a benzodiazepine may be given intravenously. Other types of seizure may be associated with head trauma or pre-existing seizure disorders (p. 506.1) and should be treated accordingly. Other *antiepileptics* such as carbamazepine have been tried in the treatment of alcohol withdrawal seizures and may be of use as adjuncts in controlling other symptoms of alcohol withdrawal syndrome. As benzodiazepines are effective in preventing withdrawal seizures, other prophylactic drugs are not usually indicated.

Beta blockers can reduce symptoms of autonomic overactivity such as tachycardia, hypertension, tremor, and agitation but because they can mask these symptoms of withdrawal and do not prevent the development of more serious complications they should not be used alone. Some beta blockers such as propranolol that penetrate the CNS may produce CNS effects that complicate therapy. The alpha$_2$-adrenoceptor agonist *clonidine* may be of similar benefit as an adjunct.

Other drugs that have been reported to be of benefit in alcohol withdrawal syndrome include baclofen, nitrous oxide, and gamma-hydroxybutyrate.

It is essential that in all cases of alcohol withdrawal syndrome hypoglycaemia, dehydration, electrolyte disturbances (in particular magnesium), and vitamin deficiencies be corrected. However, hydration should be undertaken with care as alcoholics may be more prone to develop cerebral oedema, the management of which is discussed under Raised Intracranial Pressure on p. 1271.3. It is usually recommended that all patients should be given thiamine because of their increased risk of developing Wernicke-Korsakoff syndrome (p. 2103.3). It should be noted that giving intravenous glucose before thiamine may precipitate Wernicke's encephalopathy in thiamine-deficient patients.

Abstinence. Once the initial acute withdrawal of alcohol is achieved treatment may be required to maintain long-term abstinence. Pharmacotherapy should only be used as an adjunct to psychotherapy and supportive care. Drugs used to modify alcohol seeking behaviour either sensitise the patient to alcohol (aversive drugs) or reduce or alleviate the craving for alcohol. The main ones used for aversive therapy have historically been *disulfiram* and *calcium carbimide*. A patient who ingests alcohol after taking an adequate dose of one of these drugs will have a severe and unpleasant reaction (see Adverse Effects of Disulfiram, p. 2496.1). However, the deterrent value of aversive drugs, and their potential toxicity, has long been a matter of debate. Such treatment is likely to be of little use unless it is undertaken with the willing cooperation of the patient and is used with psychotherapy, and even then there is no evidence that it has any effect on the long-term course of alcoholism.

Of those drugs that have been reported to reduce alcohol craving *acamprosate* and *naltrexone* have been the most promising as adjuncts for management of alcohol dependence and have been shown to improve abstinence and reduce relapse rates. Whether benefit is maintained long-term after treatment is stopped is unclear. *Nalmefene* is also used to help reduce the level of alcohol consumption in patients who have a high drinking risk. *Other drugs* tried with varying benefit include aripiprazole, tiapride, baclofen, gamma-hydroxybutyrate, bromocriptine, and topiramate. Experimental evidence suggests that serotonin plays a role in the impulsivity and craving and is partly responsible for alcohol dependence. However, studies with SSRIs in alcohol dependence have been disappointing and it would appear that the benefit is in treating underlying depression rather than influencing drinking behaviour. Similar results have been noted with other drugs acting at serotonin receptors such as buspirone, ritanserin, and nefazodone. However, studies with ondansetron have shown some efficacy on drinking frequency and intake.

1. Mayo-Smith MF. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; **278:** 144–51.
2. O'Connor PG, Schottenfeld R S. Patients with alcohol problems. *N Engl J Med* 1998; **338:** 592–602.
3. Tinsley JA, *et al*. Developments in the treatment of alcoholism. *Mayo Clin Proc* 1998; **73:** 857–63.
4. Schaffer A, Naraiyo CA. Recommended drug treatment strategies for the alcoholic patient. *Drugs* 1998; **56:** 571–85.
5. Naik PC, Brownell LW. Treatment of psychiatric aspects of alcohol misuse. *Hosp Med* 1999; **60:** 173–7.
6. Garbutt JC, *et al*. Pharmacological treatment of alcohol dependence: a review of the evidence. *JAMA* 1999; **281:** 1318–25.
7. Swift RM. Drug therapy for alcohol dependence. *N Engl J Med* 1999; **340:** 1482–90.
8. Kraemer KL, *et al*. Managing alcohol withdrawal in the elderly. *Drugs Aging* 1999; **14:** 409–25.
9. Myrick H, *et al*. New developments in the pharmacotherapy of alcohol dependence. *Am J Addict* 2001; **10** (suppl): 3–15.
10. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med* 2003; **348:** 1786–95.
11. Mayo-Smith MF, *et al*. Management of alcohol withdrawal delirium: an evidence-based practice guideline. *Arch Intern Med* 2004; **164:** 1405–12.
12. Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs* 2004; **18:** 485–504.
13. Kenna GA, *et al*. Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 1. *Am J Health-Syst Pharm* 2004; **61:** 2272–9.
14. Kenna GA, *et al*. Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 2. *Am J Health-Syst Pharm* 2004; **61:** 2380–8.
15. Kiefer F, Mann K. New achievements and pharmacotherapeutic approaches in the treatment of alcohol dependence. *Eur J Pharmacol* 2005; **526:** 163–71.
16. Ait-Daoud N, *et al*. An overview of medications for the treatment of alcohol withdrawal and alcohol dependence with an emphasis on the use of older and newer anticonvulsants. *Addict Behav* 2006; **31:** 1628–49.
17. Leggio L, *et al*. New developments for the pharmacological treatment of alcohol withdrawal syndrome: a focus on non-benzodiazepine GABAergic medications. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 1106–17.

Precautions

Excessive alcohol intake should be avoided. In the UK, the DoH advises that men should not drink more than 3 to 4 units of alcohol daily, and women not more than 2 to 3 units of alcohol daily, regardless of whether one drinks every day, once or twice a week, or occasionally. A unit of alcohol is defined as 10 mL of pure alcohol. A normal measure of spirits in a public house contains about 1 unit of alcohol. A pint of ordinary strength lager or cider, a pint of bitter, or 175 mL glass of wine contain about 2 units of alcohol, while a pint of strong lager contains about 3 units of alcohol. Women and the elderly may be more susceptible to the adverse effects of alcohol ingestion.

Alcohol may aggravate peptic ulcer disease or hepatic impairment and impair control of diabetes mellitus or epilepsy. Ingestion of alcohol during pregnancy or breast feeding is not advisable. In chronic alcoholics there may be tolerance to the effects of other CNS depressants including general anaesthetics.

All processes requiring judgement and coordination are affected by alcohol and these include the driving of any form of transport and the operating of machinery. It is an offence in many countries for motorists to drive when the blood-alcohol concentration is above a stated value while in some countries any detectable concentration is an offence.

The alcohol concentration in urine and expired air can be used to estimate the blood-alcohol concentration.

It should be remembered that alcohol may be present in pharmaceutical preparations such as elixirs and mouthwashes, and that children may be particularly susceptible to its hypoglycaemic effects.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, ingestion of large amounts of alcohol by a breast-feeding mother may cause drowsiness, diaphoresis, deep sleep, weakness, decrease in linear growth, and abnormal weight gain in the infant; maternal ingestion of 1 g/kg or more daily decreases the milk ejection reflex.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Driving. In addition to the legal maximum blood-alcohol concentration permitted for motorists, in the UK there are restrictions on holding a driving licence for those who persistently misuse alcohol, have alcohol dependency, have had an alcohol-related seizure, or have an alcohol-related disorder.[1]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

Porphyria. Alcohol has been associated with acute attacks of porphyria and alcohol consumption should be avoided in porphyric patients.

Reviews.
1. Doss MO, *et al.* Alcohol and porphyrin metabolism. *Alcohol Alcohol* 2000; **35:** 109–25.

Pregnancy. Alcohol crosses the placenta and is both teratogenic and fetotoxic in humans.[1,2] Binge drinking or excessive alcohol intake is associated with low birthweight, behavioural and intellectual difficulties later in life, and fetal alcohol syndrome (see Adverse Effects, p. 1733.3). Alcohol consumption is also associated with an increased risk of miscarriage.[1] It is therefore generally agreed that pregnant women should avoid or limit their intake of alcohol although guidance from professional bodies has been slightly inconsistent.[3] In the UK, guidance from NICE[2] and the Royal College of Obstetricians and Gynaecologists[1] state that while the safest approach is to avoid any alcohol intake during pregnancy particularly the first trimester, there is no evidence of harm from infrequent or low levels of alcohol intake (no more than one or two units once or twice a week). However, in the USA, the Surgeon General's Office[4] and the American Academy of Pediatrics[5] advise women who are pregnant or women who are planning a pregnancy to avoid alcohol use completely.

1. Royal College of Obstetricians and Gynaecologists. RCOG Statement no. 5: alcohol consumption and the outcomes of pregnancy (issued March 2006). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/RCOGStatement5AlcoholPregnancy2006.pdf (accessed 19/09/06)
2. National Collaborating Centre for Women's and Children's Health/NICE. Antenatal care: routine care for the healthy pregnant woman (issued March 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG62FullGuidelineCorrectedJune2008July2009.pdf (accessed 19/03/10)
3. O'Leary CM, *et al.* A review of policies on alcohol use during pregnancy in Australia and other English-speaking countries, 2006. *Med J Aust* 2007; **186:** 466–71.
4. United States Department of Health and Human Services. News release: U.S. Surgeon General releases advisory on alcohol use in pregnancy (issued 21st February 2005). Available at: http://surgeongeneral.gov/pressreleases/sg02222005.html (accessed 19/09/06)
5. American Academy of Pediatrics: Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics* 2000; **106:** 358–61. Also available at: http://www.pediatrics.org/cgi/content/full/106/2/358 (accessed 19/09/06)

Interactions

Reports of interactions between alcohol and other drugs are not consistent, possibly because acute alcohol intake may inhibit drug metabolism while chronic alcohol intake can enhance the induction of drug-metabolising enzymes in the liver.

Alcohol can enhance the acute effects of CNS depressants, such as hypnotics, antihistamines, opioid analgesics, antiepileptics, antidepressants, antipsychotics, and sedatives. In addition 'dose dumping', rapid and potentially fatal release of high doses from modified-release formulations, has occurred when some opioid preparations were taken with alcohol.

Unpleasant reactions, similar to those occurring with disulfiram (p. 2496.1), may occur when alcohol is taken with chlorpropamide, griseofulvin, mepacrine, metronidazole and other nitroimidazoles, the nitrofuran derivatives furazolidone and nifuratel, procarbazine, or some cephalosporins. Alcoholic beverages containing tyramine may cause reactions when taken by patients receiving MAOIs.

Alcohol can cause hypoglycaemic reactions in patients receiving sulfonylurea antidiabetics or insulin, and orthostatic hypotension in patients taking drugs with a vasodilator action. It may enhance the hypotensive effects of antihypertensives and has also increased the sedative effect of indoramin. Alcohol may increase gastric bleeding caused by analgesics and can have a variable effect on oral anticoagulants. It may decrease the antidiuretic effect of vasopressin.

Reviews.
1. McInnes GT. Interactions that matter: alcohol. *Prescribers' J* 1985; **25:** 87–90.
2. Lieber CS. Interaction of alcohol with other drugs and nutrients: implications for the therapy of alcoholic liver disease. *Drugs* 1990; **40** (suppl 3): 23–44.
3. Fraser AG. Pharmacokinetic interactions between alcohol and other drugs. *Clin Pharmacokinet* 1997; **33:** 79–90.
4. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health* 1999; **23:** 40–54.

Cycloserine. Increased blood-alcohol concentrations have been reported in patients receiving cycloserine.[1]

1. Glass F, *et al.* Beobachtungen und untersuchungen über die gemeinsame wirkung von alkohol und D-cycloserin. *Arzneimittelforschung* 1965; **15:** 684–8.

Fomepizole. For the interaction between alcohol and fomepizole, see Interactions under Fomepizole, p. 1553.2.

H_2-antagonists. The existence of an interaction between H_2-antagonists and alcohol is controversial and has not been established. While some studies suggest that *cimetidine*[1-3] and *nizatidine*[3] can increase peak blood-alcohol concentrations the effects of *ranitidine*[2,4] have been variable; *famotidine* appears to have no significant effect.[2] Later studies report that any interaction between H_2-antagonists and alcohol is minor and unlikely to be of clinical importance.[5-8]

1. Caballeria J, *et al.* Effects of cimetidine on gastric alcohol dehydrogenase activity and blood ethanol levels. *Gastroenterology* 1989; **96:** 388–92.
2. DiPadova C, *et al.* Effects of ranitidine on blood alcohol levels after ethanol ingestion: comparison with other H_2-receptor antagonists. *JAMA* 1992; **267:** 83–6.
3. Holt S, *et al.* Evidence for an interaction between alcohol and certain H_2 receptor antagonists. *Gut* 1991; **32:** A1220.
4. Toon S, *et al.* Lack of effect of high dose ranitidine on the post-prandial pharmacokinetics of alcohol. *Gut* 1992; **33** (suppl): S10.
5. Raufman J-P, *et al.* Histamine-2 receptor antagonists do not alter serum ethanol levels in fed, nonalcoholic men. *Ann Intern Med* 1993; **118:** 488–94.
6. Levitt MD. Do histamine-2 receptor antagonists influence the metabolism of ethanol? *Ann Intern Med* 1993; **118:** 564–5.
7. Kleine M-W, Ertl D. Comparative trial in volunteers to investigate possible ethanol-ranitidine interaction. *Ann Pharmacother* 1993; **27:** 841–5.
8. Gugler R. H_2-antagonists and alcohol: do they interact? *Drug Safety* 1994; **10:** 271–80.

Paracetamol. The effects of paracetamol poisoning may be exacerbated by chronic alcohol consumption (see p. 116.2).

Verapamil. When verapamil has been taken with alcohol there has been a reported increase in peak blood-alcohol concentrations of about 17%.[1] Such an interaction may extend the toxic effects of alcohol and raise its blood concentration above the legal limit for driving.[2]

1. Schumock G, *et al.* Verapamil inhibits ethanol elimination. *Pharmacotherapy* 1989; **9:** 184–5.
2. Anonymous. Does verapamil increase the effects of alcohol? *Pharm J* 1990; **244:** 14.

Pharmacokinetics

Alcohol is rapidly absorbed from the gastrointestinal tract and is distributed throughout the body fluids. It readily crosses the placenta. Alcohol vapour can be absorbed through the lungs. Absorption through intact skin is said to be negligible.

The rate of absorption of alcohol from the gastrointestinal tract may be modified by such factors as the presence of food, the concentration of alcohol, carbonation of the alcoholic beverage, and the period of time during which it is ingested.

Alcohol is mainly metabolised in the liver; it is converted by alcohol dehydrogenase to acetaldehyde and is then further oxidised to acetate. A hepatic microsomal oxidising system is also involved. About 90 to 98% of alcohol is oxidised and the remainder is excreted unchanged by the kidneys and the lungs. It also appears in breast milk, sweat, and other secretions.

The rate of metabolism may be accelerated after repeated excessive intake and by certain substances including insulin.

Reviews.
1. Holford NHG. Clinical pharmacokinetics of ethanol. *Clin Pharmacokinet* 1987; **13:** 273–92.
2. Lotsof J. A revised pharmacokinetic model for alcohol. *Clin Pharmacokinet* 2003; **42:** 585–7.
3. Paton A. Alcohol in the body. *BMJ* 2005; **330:** 85–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Germikill; Higiemax; Sanitizante; ***Austral.***: Aqium; Microshield Antimicrobial Hand Gel†; ***Canad.***: Alcare†; Alcoscrub†; Bactisan†; Biobase; Digisan; Duonalc-E Mild†; Hand Sanitizer; Kimcare Instant Hand Sanitizer; Lever San†; One Step Hand Sanitizer; President's Choice Hand Sanitizer; Purell; Septe FX Skin Formula†; Soft Care Instant Hand Sanitizer; Stoko Hand Sanitizer; Surgicept†; ***Chile***: Gelicol; ***Fr.***: Curethyl; Pharmadose alcool; ***Ger.***: AHD 2000; Cutasept med; Fugaten; Manusept basic; Sterilium med; Sterillium Virugard; ***Indon.***: Handy Clean; ***Israel***: Alcotint; Dr-Fischer Pharma-Gel; ***Ital.***: Sicura3 Gel; ***Malaysia***: QuicKlean; ***Philipp.***: AHD 2000†; ***Thai.***: Cohol UD; ***USA***: Alcare; Bodi Line Action; Gel-Stat.

Multi-ingredient Preparations. ***Arg.***: Cutidermin Crema Antibacterial†; Higienizador Manos; Omicohol A; Pervicol Toallas; Pervicol; ***Austral.***: Clean & Clear Oil Controlling Toner; Dermatech Liquid†; Microshield Handrub; Microshield Tincture; Septivon; SM-33 Adult Formula; SM-33; ***Austria***: Dodesept Gefarbt; Dodesept N†; Dodesept; Skinsept mucosa†; Skinsept; ***Belg.***: Sabenyl†; Softa Man; ***Canad.***: Anti-Bacterial Deep Cleansing; Anti-Bacterial Waterless†; Avagard CHG; Biobase-G; Biomers; Biosurf; Biotext; Duonalc-E†; Green Antiseptic Mouthwash & Gargle†; Manorapid Synergy; Purmist; Sani-Dex†; Sterigel; ***Chile***: Acnoxyl Locion Tonica; Alcolex†; Listerine; Listermint Con Fluor†; Oralfresh Citrus†; Oralfresh Clasico†; Oralfresh; Pectokast; ***Cz.***: Promanum N; Softa-Man; ***Fin.***: Otiborin; ***Fr.***: Alco-Aloe†; Aniospray 29†; Clinogel Derma+; ***Ger.***: Aerodesin; Autoderm Extra; Bacillol AF; Bacillol Foam; Bacillol Tissues; Bacillol Wipes; Bacillol†; Betaseptic; Freka-Derm†; Freka-Nol†; Freka-Sept 80†; Hoffmannstropfen; Hospidermin; Hospisept; Incidin; Klosterfrau Franzbranntwein Latschenkiefer†; Klosterfrau Franzbranntwein Mentholt; Klosterfrau Franzbranntwein†; Klosterfrau Melissengeist; Manusept viruzid†; Mucasept-A; Promanum N; Skinsept G; Skinsept mucosa; Softa Man; Softasept N; Spirol; Spitacid; Virusept†; ***Gr.***: Faragel-Forte; Revigel; ***Hong Kong***: Duraprep†; Listerine Tartar Control; Listerine; ***India***: AM-PM Plus; AM-PM Special; Bayers Tonic; Cool Mint Listerine; Daslin; Dettol; Dettolin; Hexiprep-T; KMR; Listerine; Microgard; Neo-Cordial; Neogadine SG; Neogadine; Neurophosphates-Iron; ***Indon.***: Allerin; Benadryl CM†; Berlifed; Chlorphemin; Coricidin; Dactylen; Domeryl; Eksedryl Expectorant; Inadryl Plus; Inadryl; Koffex; Listerine Coolmint†; Listerine†; Neo Novapon; Nichodryl; Paradryl; ***Israel***: Alcosept; Alcoxidine; Salisol†; Septadine; Spirit Salicyl; V-Tabur; ***Ital.***: Bemonalcool; Citroclorex; Citromed 85; Citromed Chirurgico; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosteril Strumenti; Clorexan Ferri†; Eso Ferri Alcolico; Esoalcolico Incolore; Esoform Alcolico; Forbrand; Formedico; Incidin Spezial†; Incidur Spray†; Jodieci; Melsept Spray; Neomedil; Panseptil†; Sekumatic†; Simpottantacinque; Softa Man; ***Mex.***: Varicyl; ***Neth.***: Softa-Man; ***Philipp.***: BSI Medicated Spray; Dermablend Clarifying; Listerine Coolmint; Listerine Original; Zilactin; Ziladent; ***Port.***: Promanum†; Softasept; ***S. Afr.***: Clearasil Medicated Facial Cleanser†; Dry & Clear Medicated Skin Cleanser†; Listerine Antiseptic; Oxipor VHC†; Specific Nerve Pain Remedy†; ***Singapore***: Alcohol Hand Rub; Desderman; Hexodane Handrub; Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; ***Spain***: Alcohocel†; Alcohol Benzalconio; Alcohol CL Benz†; Alcohol Potenciado; Alcohol Potenciado; Beta Alcanforado†; Beta Romero; Embrocacion Gras†; Farmalcohol†; Linimento Naion; Menalcol; ***Swed.***: Vitatonin†; ***Switz.***: Betaseptic; Jodoplex Teinture†; Promanum N†; Silence†; Skinsept; Softasept N; ***Thai.***: Hand Joy; ***UK***: Brushtox; Clearasil Pore Cleansing Lotion; Medi-Wipe; Oxy Cleanser; Oxy Cleanser; Oxy Duo Pads; Oxy Duo Pads; Spectrum; ***Ukr.***: Softa-Man (Софта)†; ***USA***: Banadyne-3; Clearasil Double Clear; Clearasil Double Textured Pads; Lipmagik; Maximum Strength Anbesol; Orasol; Stri-Dex Pads; Tonsiline; ***Venez.***: Frixonil.

Pharmacopoeial Preparations
USP 36: Alcohol in Dextrose Injection; Cascara Sagrada Fluidextract; Dehydrated Alcohol Injection; Rubbing Alcohol.

Alexidine *(USAN, rINN)*

Alexidina; Alexidinum; Bisguadine; Compound 904; Win-21904; Алексидин.

1,1′-Hexamethylenebis[5-(2-ethylhexyl)biguanide].

$C_{26}H_{56}N_{10}$=508.8

CAS — 22573-93-9.

UNII — GVN71CAL3G.

Profile

Alexidine is a bisbiguanide antiseptic with properties similar to those of chlorhexidine (p. 1743.2). It is used in oral hygiene products for the treatment of inflammatory and infectious conditions including gingivitis, periodontitis, and stomatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Singapore***: Esemdent.

Alkyl Gallates

Galatos de alquilo; Алкилгаллаты.

Dodecyl Gallate

Dodecilo galatas; Dodécyle, gallate de; Dodecylgallat; Dodecyl-gallát; Dodecylis Gallas; Dodekyyligallaatti; E312; Galato de dodecilo; Lauryl Gallate; Laurylum Gallicum; Додецилгаллат.
Dodecyl 3,4,5-trihydroxybenzoate.
$C_{19}H_{30}O_5$=338.4
CAS — 1166-52-5.
UNII — 45612DY463.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dodecyl Gallate). A white or almost white crystalline powder. M.p. about 96 degrees. Very slightly soluble or practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in nonmetallic containers. Protect from light.

Ethyl Gallate

Galato de etilo; Этилгаллат.
Ethyl 3,4,5-trihydroxybenzoate.
$C_9H_{10}O_5$=198.2
CAS — 831-61-8.
UNII — 235I6UDD3L.

Pharmacopoeias. In *Br.*

BP 2014: (Ethyl Gallate). A white to creamy-white, odourless or almost odourless, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in ether; practically insoluble in arachis oil. Protect from light. Avoid contact with metals.

Octil Gallate

E311; Galato de octilo; Octyl Gallate; Octyle, gallate d'; Octylgallat; Octylis gallas; Oktilo galatas; Oktylgallat; Oktyl-gallát; Oktyyligallaatti; Октилгаллат.
Octyl 3,4,5-trihydroxybenzoate.
$C_{15}H_{22}O_5$=282.3
CAS — 1034-01-1.
UNII — 079IIA2811.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Octyl Gallate). A white or almost white crystalline powder. Practically insoluble in water and in dichloromethane; freely soluble in alcohol. Store in nonmetallic containers. Protect from light.

Propyl Gallate

E310; Galato de propilo; Propil-gallát; Propilo galatas; Propyle, gallate de; Propylgallat; Propyl-gallát; Propylis gallas; Propylu galusan; Propylum Gallicum; Propyyligallaatti; Пропилгаллат.
Propyl 3,4,5-trihydroxybenzoate.
$C_{10}H_{12}O_5$=212.2
CAS — 121-79-9.
UNII — 8D4SNN7V92.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Propyl Gallate). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Propyl Gallate). A white crystalline powder with a slight characteristic odour. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers. Avoid contact with metals. Protect from light.

Uses

The alkyl esters of gallic acid (3,4,5-trihydroxybenzoic acid) have antoxidant properties and are used as preservatives in pharmaceuticals and cosmetics. Alkyl gallates are also used as antoxidants in foods and are useful in preventing deterioration and rancidity of fats and oils. They are used in concentrations of 0.001 to 0.1%.

To improve acceptability and efficacy, the alkyl gallates are frequently used with other antoxidants such as butylated hydroxyanisole or butylated hydroxytoluene and with sequestrants and synergists such as citric acid and zinc salts.

The alkyl gallates have also been reported to have limited antibacterial and antifungal activity.

Adverse Effects and Precautions

The alkyl gallates may cause contact sensitivity and skin reactions.

Effects on the blood. Methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula has been reported.[1] Propyl gallate was suspected of being the most likely cause because its chemical structure is similar to pyrogallol (p. 1718.2), a methaemoglobinaemia inducer.

1. Nitzan M, *et al.* Infantile methemoglobinemia caused by food additives. *Clin Toxicol* 1979; **15:** 273–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: He Yue (和悦); Tian Fu Chu (天复初).

Alkyldimethylethylbenzyl Ammonium Chloride

CAS — 68956-79-6 (C12-C18 alkyldimethylethylbenzyl ammonium chloride); 85409-23-0 (C12-C14 alkyldimethylethylbenzyl ammonium chloride).

Profile

Alkyldimethylethylbenzyl ammonium chloride is a quaternary ammonium compound with similar properties to benzalkonium chloride (alkyldimethylbenzyl ammonium chloride; p. 1737.1). Mixtures of alkyldimethylethylbenzyl ammonium chlorides of different alkyl chain lengths are used as disinfectants, often with benzalkonium chloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Advance Quat; Brillex; Cadisan; Cetainty†; Kemsol; Prevent X†.

Ambazone *(BAN, rINN)*

Ambatsoni; Ambazon; Ambazona; Ambazonum; Амбазон.
4-Amidinohydrazonocyclohexa-1,4-dien-3-one thiosemicarbazone monohydrate.
$C_8H_{11}N_7S,H_2O$=255.3
CAS — 539-21-9 (anhydrous ambazone); 6011-12-7 (ambazone monohydrate).
ATC — R02AA01.
ATC Vet — QR02AA01.
UNII — BYK4592A3Q.

Profile

Ambazone is an antiseptic that is used in the form of lozenges for minor infections of the mouth and pharynx.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Faringosept; ***Rus.***: Faringosept (Фарингосепт); ***Ukr.***: Faringosept (Фарингосепт).

Aminoquinuride Hydrochloride *(rINNM)*

Aminoquinuride, Chlorhydrate d'; Aminoquinuridi Hydrochloridum; Hidrocloruro de aminoquinurida; Аминохинурида Гидрохлорид.
1,3-Bis(4-amino-2-methyl-6-quinolyl)urea dihydrochloride.
$C_{21}H_{20}N_6O,2HCl$=445.3
CAS — 3811-56-1 (aminoquinuride); 5424-37-3 (aminoquinuride hydrochloride).
UNII — P2YT71SUIU.

Profile

Aminoquinuride hydrochloride is an antiseptic that has been used in topical preparations for the treatment of mouth and skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Herviros.

Amylmetacresol *(BAN, rINN)*

Amilmetacresol; Amilmetakrezol; Amylmétacrésol; Amylmetacresolum; Amylmetakresol; Amyylimetakresoli; Амилметакрезол.
6-Pentyl-*m*-cresol; 5-Methyl-2-pentylphenol.
$C_{12}H_{18}O$=178.3
CAS — 1300-94-3.
UNII — 05W904P57F.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Amylmetacresol). A clear or almost clear liquid or a solid crystalline mass, colourless or slightly yellow when freshly prepared; it darkens or discolours to dark yellow, brownish-yellow, or pink on keeping. F.p. about 22 degrees. Practically insoluble in water; very soluble in alcohol and in acetone. Store in non-metallic airtight containers. Protect from light.

Profile

Amylmetacresol is a phenolic antiseptic used chiefly as an ingredient of lozenges in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Antiseptic Throat Drops†; Antiseptic Throat Lozenges; ***UK***: Antiseptic Throat Lozenges; Throaties Anti-Bacterial Pastilles.

Multi-ingredient Preparations. ***Arg.***: Strepsils Plus; Strepsils; ***Austral.***: Strepsils Numbing; Strepsils Plus†; Strepsils; ***Austria***: Coldangin; Neo-Angin; ***Belg.***: Strepsils + Lidocaine; Strepsils Cool Mint; Strepsils Menthol†; Strepsils Vit C; Strepsils; ***Canad.***: Cepacol Sensations Cooling; Cepacol Sensations Sore Throat & Blocked Nose; Cepacol Sensations Sore Throat & Cough; Cepacol Sensations Warming; Cepacol Sensations; Strepsils Cherry†; Strepsils Cool; Strepsils Sore Throat Blocked Nose; Strepsils; ***Cz.***: Neo-Angin; Strepsils Cooling Mint; Strepsils Menthol a Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; ***Denm.***: Strepsils; ***Fin.***: Med-Angin; Strepsils Menthol; Strepsils; ***Fr.***: Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsils; Strepsilspray; ***Ger.***: Dobendan Cool†; Dobendan Junior; Dobendan Synergie; Dobendan Warm; Neo-Angin; ***Gr.***: Strepsils Plus; Strepsils; ***Hong Kong***: Strepsils Dual Action; Strepsils; ***Hung.***: Neo-Angin; Strepsils Menthol and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; ***India***: Cof Q; Cofsils; ***Irl.***: Strepsils +Plus Anaesthetic; Strepsils Cool; Strepsils Dual Action†; Strepsils Sore Throat and Blocked Nose; Strepsils Throat; Strepsils Vitamin C; Strepsils; ***Israel***: Strepsils Plus; Strepsils with Menthol and Eucalyptus; Strepsils with Vitamin C; Strepsils; ***Ital.***: Benagol Mentolo-Eucaliptolo; Benagol Vitamina C; Benagol; ***Malaysia***: Chericof; Strepsils Dual Action; Strepsils; ***Neth.***: Strepsils Menthol & Eucalyptus†; Strepsils Sinaasappel & Vitamine C; Strepsils; ***NZ***: Strepsils Plus Anaesthetic; Strepsils with Vitamin C; Strepsils; ***Philipp.***: Strepsils; Strepsils; Therasil; ***Pol.***: Neo-Angin; Strepsils; ***Port.***: Benagol†; Strepsils; ***Rus.***: Astrasept (Астрасепт); Coldact Lorpils (Колдакт Лорпилс); Gorpils (ГОРПИЛС); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Strepsils with Vitamin C (Стрепсилс с Витамином С); Suprima-Lor (Суприма-Лор); Therasil (Терасил); ***S. Afr.***: Strepsils Eucalyptus Menthol†; Strepsils Orange-C†; Strepsils Plus; Strepsils Soothing Honey & Lemon†; Strepsils; ***Singapore***: Cofsils; Robitussin Medicated Lozenges; Strepsils Max Plus; Strepsils; ***Spain***: Strepsils con Vitamina C; Strepsils Lidocaina; Strepsils; ***Swed.***: Strepsils; ***Switz.***: Strepsils with Vitamin C; Strepsils; ***Thai.***: Strepsils Butter Menthol Capsicum†; Strepsils Maxipluzz; Strepsils Plus Vit C; Strepsils Sugar Free†; Throatsil Plus; Throatsil; ***Turk.***: Med-Angin; Strepsils C; Strepsils Mentol; Strepsils; ***UK***: Strepsils with Vitamin C; Strepsils; ***Ukr.***: Coldact Lor Pils (Колдакт Лор Пилс); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс).

Amylphenol

p-tert-Pentylphenol; 4-t-Amylphenol.
4-(1,1-Dimethylpropyl)phenol.
$C_{11}H_{16}O$=164.2
CAS — 80-46-6.
UNII — 6NP9LYK846.

Profile

Amylphenol has been used as a phenolic disinfectant and antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: BTK-Plus†.

Ascorbyl Palmitate

Ascorbilo, palmitato de; Ascorbyle, palmitate d'; Ascorbylis palmitas; Askorbilo palmitatas; Askorbylpalmitat; Askorbylpalmitát; Askorbylu palmitynian; Askorbyylipalmitaatti; Aszkorbil-palmitát; Palmitoylascorbinsäure; Vitamin C Palmitate; Аскорбилпальмитат.

L-Ascorbic acid 6-hexadecanoate; L-Ascorbic acid 6-palmitate; 3-Oxo-L-gulofuranolactone 6-palmitate.

$C_{22}H_{38}O_7$=414.5

CAS — 137-66-6.

UNII — QN83US2B0N.

NOTE. The code E304 is used for fatty acid esters of ascorbic acid, which include ascorbyl palmitate.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Ascorbyl Palmitate). A white or yellowish-white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol; practically insoluble in dichloromethane and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Ascorbyl Palmitate). A white to yellowish-white powder with a characteristic odour. Very slightly soluble in water, in chloroform, in ether, and in vegetable oils; soluble 1 in 125 of alcohol. Store at 8 degrees to 15 degrees in airtight containers.

Profile

Ascorbyl palmitate is an antoxidant used as a preservative in pharmaceutical products and foods. It is often used with alpha tocopherol (p. 2119.1), and this combination shows marked synergy. As it is a fat-soluble derivative of vitamin C (ascorbic acid, p. 2110.3), ascorbyl palmitate is sometimes used as a source of vitamin C in nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Neolucid-C†.

Multi-ingredient Preparations. ***Arg.***: Aminoterapia Capilar; ***Hong Kong***: Proflavanol†; ***Malaysia***: Proflavanol†; ***Singapore***: Proflavanol†; Scar Esthetique.

Benzalkonium Chloride *(BAN, rINN)*

Bensalkoniumklorid; Bentsalkoniumkloridi; Benzalconio Cloruro; Benzalconio, cloruro de; Benzalkonii Chloridum; Benzalkonio chloridas; Benzalkoniowy chlorek; Benzalkonium Chloratum; Benzalkonium, chlorure de; Benzalkoniumchlorid; Benzalkoniumchlorid; Benzalkónium-klorid; Benzalkonyum Klorür; Cloreto de Benzalconio; Cloruro de benzalconio; Бензалкония Хлорид.

CAS — 8001-54-5.

ATC — D08AJ01; D09AA11; R02AA16.

ATC Vet — QD08AJ01; QD09AA11; QR02AA16.

UNII — F5UM2KM3W7.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.* Some pharmacopoeias also have a monograph for a solution.

Chin. also includes benzalkonium bromide.

Ph. Eur. 8: (Benzalkonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups mainly having chain lengths of C_{12}, C_{14}, and C_{16}. It contains not less than 95% and not more than 104% of alkylbenzyldimethylammonium chlorides, calculated as $C_{22}H_{40}ClN$ with reference to the anhydrous substance.

A white or yellowish-white powder, or gelatinous, yellowish-white hygroscopic fragments. It forms a clear molten mass on heating. It contains not more than 10% of water. Very soluble in water and in alcohol. An aqueous solution froths copiously when shaken.

USNF 31: (Benzalkonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5.CH_2.N(CH_3)_2.R]Cl$, in which R represents a mixture of the alkyls having chain lengths from C_8 to C_{16}. It contains not less than 40% of the $C_{12}H_{25}$ compound, calculated on the anhydrous substance, not less than 20% of the $C_{14}H_{29}$ compound, and not less than 70% of the 2 compounds together.

A white or yellowish-white, thick gel, or gelatinous pieces with a mild aromatic odour. It contains not more than 15% of water. Very soluble in water and in alcohol; the anhydrous form is soluble 1 in 100 of ether and 1 in 6 of benzene. A solution in water is usually slightly alkaline and foams strongly when shaken. Store in airtight containers.

Incompatibility. Benzalkonium chloride is incompatible with soaps and other anionic surfactants, citrates, iodides, nitrates, permanganates, salicylates, silver salts, tartrates, and zinc oxide and sulfate. Incompatibilities have been noted with ingredients of some commercial rubber mixes or plastics. Incompatibilities have also been reported with other substances including aluminium, cotton dressings, fluorescein sodium, hydrogen peroxide, hypromellose, kaolin, hydrous wool fat, and some sulfonamides.

Uses and Administration

Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of the other cationic surfactants (see Cetrimide, p. 1742.1). It is also used as an antimicrobial preservative for pharmaceutical products. Benzalkonium bromide and benzalkonium saccharinate have also been used.

Solutions of benzalkonium chloride 0.01 to 0.1% are used for cleansing skin, mucous membranes, and wounds. More dilute solutions of 0.005% are suitable for irrigation of deep wounds. A 0.02 to 0.05% solution has been used as a vaginal douche. An aqueous solution containing 0.005 to 0.02% has been used for irrigation of the bladder and urethra and a 0.0025 to 0.005% solution for retention lavage of the bladder.

Creams containing benzalkonium chloride are used in the treatment of napkin rash and other dermatoses.

A 0.2 to 0.5% solution has been used as a shampoo in seborrhoeic dermatitis.

Lozenges containing benzalkonium chloride are used for the treatment of superficial infections of the mouth and throat.

Benzalkonium chloride is used as a preservative in ophthalmic solutions at a concentration of 0.01 to 0.02%, and in nasal and otic solutions at a concentration of 0.002 to 0.02%. Benzalkonium chloride is used for disinfecting rigid contact lenses (p. 1730.2) but is unsuitable as a preservative in solutions for washing and storing hydrophilic soft contact lenses (see also Effects on the Eyes, below).

Benzalkonium chloride is also used as a spermicide.

Solutions of 0.13% have been used for disinfection and storage of surgical instruments, sometimes with the addition of sodium nitrite to inhibit rust.

Action. The antibacterial effect of benzalkonium chloride 0.003% was enhanced by 0.175% of benzyl alcohol, phenylpropanol, or phenethyl alcohol.[1] For the use of phenethyl alcohol with benzalkonium chloride as a preservative for ophthalmic solutions, see Antimicrobial Action, under Phenethyl Alcohol, p. 1763.2.

1. Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against Pseudomonas aeruginosa by aromatic alcohols. *J Pharm Sci* 1973; **62:** 2035–7.

Catheter-related sepsis. Benzalkonium chloride has been investigated[1,2] for incorporation into catheters to reduce catheter-related sepsis (p. 1732.1).

1. Tebbs SE, Elliott TSJ. A novel, antimicrobial central venous catheter impregnated with benzalkonium chloride. *J Antimicrob Chemother* 1993; **31:** 261–71.
2. Moss HA, *et al.* A central venous catheter coated with benzalkonium chloride for the prevention of catheter-related microbial colonization. *Eur J Anaesthesiol* 2000; **17:** 680–7.

Adverse Effects, Treatment, and Precautions

As for Cetrimide, p. 1742.2. Because some rubbers are incompatible with benzalkonium chloride silicone rubber teats should be used on eye drop containers unless the suitability has been established.

Catheters and cannulas. For reference to benzalkonium chloride used in the manufacturing process of heparin-bonded catheters interfering with determination of serum concentrations of sodium and potassium, see under Precautions for Heparin, p. 1400.1.

Effects on the eyes. Benzalkonium chloride is one of the most disruptive ophthalmic additives to the stability of the lipid film and to corneal epithelial membranes.[1] Toxicity studies have tended to be carried out using relatively high concentrations of benzalkonium chloride.[2] However, damage to the tear film and corneoconjunctival surface and various forms of conjunctivitis have been reported in patients receiving regular long-term treatment for glaucoma with eye drops preserved with benzalkonium chloride in usual concentrations.[3-6]

Corneal toxicity[7] (with long-term recovery[8]) has also been reported in patients inadvertently exposed to benzalkonium chloride as a preservative in viscoelastic material during cataract surgery. The use of preservatives in eye drops should generally be avoided and the formulation of such preparations in single-dose containers is desirable.[1,2] Benzalkonium chloride is not suitable for use in solutions for storing and washing hydrophilic soft contact lenses, as it can bind to the lenses and may later produce ocular toxicity when the lenses are worn.[9] Similarly, benzalkonium chloride use in anaesthetic eye drops is discouraged, as the anaesthetic component reduces the blink reflex and increases the contact time with the eye drops which may consequently result in increased toxicity due to the preservative. Patients with dry eye syndrome are also at increased risk of toxicity as the corneal epithelium is exposed to the full strength of the eye drops, in addition to which these patients do not produce enough tears to dilute the preservative in the eye drops.

1. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Trans Ophthalmol Soc UK* 1985; **104:** 402–9.
2. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol* 1980; **25:** 15–30.
3. Herreras JM, *et al.* Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology* 1992; **99:** 1082–8.
4. Kuppens EVMJ, *et al.* Effect of timolol with and without preservative on the basal tear turnover in glaucoma. *Br J Ophthalmol* 1995; **79:** 339–42.
5. Gibran SK. Unilateral drug-induced ocular pseudopemphigoid. *Eye* 2004; **18:** 1270.
6. Kahana A, *et al.* Drug-induced cicatrising granulomatous conjunctivitis. *Br J Ophthalmol* 2007; **91:** 691–2.
7. Eleftheriadis H, *et al.* Corneal toxicity secondary to inadvertent use of benzalkonium chloride preserved viscoelastic material in cataract surgery. *Br J Ophthalmol* 2002; **86:** 299–305.
8. Hughes EH, *et al.* Long-term recovery of the human corneal endothelium after toxic injury by benzalkonium chloride. *Br J Ophthalmol* 2007; **91:** 1460–3.
9. Gasset AR. Benzalkonium chloride toxicity to the human cornea. *Am J Ophthalmol* 1977; **84:** 169–71.

Effects on the respiratory tract. Hypersensitivity to benzalkonium chloride, used as a preservative in nasal drops, was confirmed in a patient by a challenge that produced nasal congestion and irritation of the eyes and throat lasting 48 hours.[1] A review[2] of 18 studies (14 *in vivo*, 4 *in vitro*) where benzalkonium chloride was used as the preservative in multidose nasal products found that 8 studies (all *in vivo*) found no toxic effects, while 10 reported degenerative changes to the nasal epithelia or exacerbation of rhinitis medicamentosa. However, in only 2 of these 10 studies were the differences between benzalkonium chloride and control groups found to be significant, and both of these included the use of oxymetazoline, which is known to cause rhinitis medicamentosa.

Benzalkonium chloride used as a preservative in nebulised solutions of anti-asthma drugs has been reported to cause dose-related bronchoconstriction especially in asthmatic patients,[3] and has been associated with the precipitation of respiratory arrest.[4]

1. Hillerdal G. Adverse reaction to locally applied preservatives in nose drops. *ORL J Otorhinolaryngol Relat Spec* 1985; **47:** 278–9.
2. Marple B, *et al.* Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. *Otolaryngol Head Neck Surg* 2004; **130:** 131–41.
3. Committee on Drugs, American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; **99:** 268–78.
4. Boucher M, *et al.* Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; **26:** 772–4.

Interactions

Benzalkonium chloride is not suitable for use in eye drops containing local anaesthetics (see Effects on the Eyes, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hidratant; Pharmatex; ***Austral.***: Dettol Fresh; ***Belg.***: Cedium; Dettol†; ***Braz.***: Fluimucil Solucao Nasal; ***Canad.***: Anti-Microbe; Antiseptic Swabs; Ato Quat; Bac Liq; Bac-Killer; Bactocide; Bactol; Dermaguard†; Digisan E; Eco-Clean Elite†; Ecocare 360; Germiphene; Handclens; Hands Fresh; Hands On Antiseptic; Hands2Go; Hydra Bain/Bath†; Kid's Hand Gel; Loris BZK; Micro Clear; One Step Foaming Antiseptic Wash; One Step Foaming Hand Sanitizer; Ready Bath; Rinse-Free; Sani Hands AF; Soapopular; Soft T Cleanse†; Sting Stop; Swabplus Antiseptic†; Thuroclens; ***Chile***: Germosept; ***China***: Bang-Aid (邦迪); ***Cz.***: Dettol; Pharmatex; ***Fr.***: Dettolpro; Humex Fournier; Pharmatex; ***Ger.***: Killavon; Laudamonium; Mikrobac basic; ***Hong Kong***: Pharmatex; ***Hung.***: Pharmatex; ***India***: Iteol-H; ***Irl.***: Dettol Fresh†; Pharmatex; Preventex; ***Ital.***: Alfa C; Benalcon; Bergagyn; Bluesteril†; Citrosil; Citrosteril Ambiente; Citrosteril Deterferri; Detergil; DiMill; Diseptil†; Disigien; Disintyl; Display; Distasil†; Disteril; Eso Deterferri; Eso Ferri; Esosan Casa; Esosan Soap; Germicidin†; Germozero; Helis†; Hygienist Pavimenti e Piastrelle; Iridina Light; Lacribase; Lozione Vittoria; Maxisteril†; Neo-Desogen; Polisan†; Sanaform; SaniSteril Deterferri; Saquat†; Sguardi; Steramina G; Stilla Delicato; Ten-Quat; Video-Light; ***Mex.***: Derman Talco; ***Neth.***: Dettol med benzalkoniumchloride; ***NZ***: Dettol Fresh†; Dettol†; Virasolve; ***Port.***: Pharmatex†; ***Rus.***: Benatex (Бенатекс); Farmaginax (Фармагинэкс); Gynecotex (Гинекотекс); Kontratex (Контратекс); Pharmatex (Фарматекс); Spermatex (Сперматекс); ***Spain***: Crema Contraceptiva Lanzas; Dettolmed; Mini Ovulo Lanzas†; ***Swed.***: Dettolmed; ***Thai.***: Pose-Bac†; ***Turk.***: Zefan; Zefiran; Zefirolum; Zefol; Zefort†; Zefsolin; Zenfektol†; Zentan†; ***UK***: Bradosol; Dermax Therapeutic Shampoo; Dettol Antiseptic Wash; Dettol Fresh; ***Ukr.***: Erotex (Эротекс); Pharmatex (Фарматекс); Virotek Intim (Виротек Интим); ***USA***: Bacti-Cleanse; Benza; Remedy; Zephiran; ***Venez.***: Decomed.

Multi-ingredient Preparations. *Arg.*: Antiseptic Plus†; Collubiazol N; Crema de Ordene; Eurocoal; Gripace; Hexil Antiseptico; Merthiolate Anestesico; Merthiolate Nueva Formula; Muelita; Neo Coltirot; Polviderm NF; Soquette†; ***Austral.***: Animine†; Animine; Clean Skin Face Wash†; Mycil Healthy Feet; Oilatum Plus; Paxyl; QV Flare Up; Virasolve; ***Austria***: Dequonal; Dorithricin; Limexx†; Tyrothricin comp; ***Belg.***: Akinspray†; ***Braz.***: Belagin†; Colpist; Colpistar; Colpistatin; Dinill; Donnagel; Drapolene; Ginestatin†; Higicler; Kolpitrat; Kuramed; Limpele Ginecologico; Nasolin; Oxizinco†; Pomada Minancora; Soronal; Tricomax; Vagi Biotic; Visolon; ***Canad.***: Advance Quat; Anti-Bacterial Waterless†; Aseptone Quat; Avon Footworks Cracked Heel†; Bactine; Bio Klean; Brillex; Cadisan; Cetainty†; Dr Scholl's Cracked Heel Relief†; Family Medic First Aid Treatment; Kemsol; Medi-Dan; Prevent X†; Tanac; ***Chile***: Dermobarrina; Dexagin; ***China***: Drapolene (保英); ***Cz.***: Coldrex Proti Bolesti v Krku; Oilatum Plus; Septolete; ***Fr.***: Biseptine; Dermaspraid Antiseptique†; Dermobacter; Euvanol; Humex Mal de Gorge; Kenalcol†; Mercryl; Mercrylsoins; Mercrylspray; Rhinofluimucil; ***Ger.***: Cutasept; Dequonal; Dorithricin; Dynexan Mundgel; Freka-Derm†; Freka-Sept 80†; Gingicain D; Hexaquart S; Incidin extra N; Incidin perfekt; Incidin; Kohrsolin FF; Korsolex Extra; Korsolex FF; Mikrobac Tissues; Mikrobac; Sekusept Extra N; Skinman Soft; Ultrasol-F; ***Gr.***: Beta Opthiole; Cutasept; Derma; Olamyc; ***Hong Kong***: Dequasin; Dermobacter; Dermojela; Mycil†; Oilatum Plus; Oris-gel†; Protectaid; ***Hung.***: Dorithricin; Septolete; ***India***: Bonzela; Dentogel; Dologel-CT; Fairgenol-H; Happynap; Nitra-Dent; Oilatum Plus; Orex; Rash-free; ***Indon.***: Mexochrome†; Oilatum Plus†; ***Irl.***: Drapolene; Emulsiderm; Mycil; Oilatum Junior Flare-Up; Oilatum Plus; Torbetol†; ***Israel***: Aphtagone†; Aptha-X†; Claritone; Emulsiderm; Protectaid; ***Ital.***: AZ 15; Barrycidal; Bemonalcool; Cerosteril; Citrocil Alcolico†; Citromed 85; Citromed Chirurgico; Citromedics Pronto†; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosil Nubesan; Citrosteril Impronte; Citrosteril Pronto; Citrosteril Strumenti; Eso Ferri Alcolico; Eso S 80; Esoalcolico Incolore; Esoform 92; Esoform Alcolico; Esosan Pronto; Germozero Dermo; Incidin Spezial†; Incidur Spray†; Indulfan†; Linea F; Neo Emocicatrol; Neomedil; Norica Plus; Odongi; Pupilla Light; Rexichlor; Sangen Casa; Sangen Casa; Sicura3 Medical; Simp; Simpottantacinque; Sterosan; Tirs; Zincometil; ***Malaysia***: Drapolene; Oilatum Plus Antibacterial; QV Flare Up†; ***Mex.***: Dermacid; Glossderm; Novageon; ***NZ***: Oilatum Plus; ***Philipp.***: Drapolene; Oilatum Plus; ***Pol.***: Cholisept Intensive; Coldrex†; Oilatum Plus; Septolete; ***Rus.***: Bactoderm (Бактодерм); Dologel (Дологель); Drapolene (Драполен); Septogal (Септогал); Septolete (Септолете); ***S.Afr.***: Oilatum Plus; ***Singapore***: Dorithricin; Drapolene; Napitol; Oilatum Plus; QV Flare Up; ***Spain***: Aftajuventus; Alcohol Benzalconio; Alcohol CL Benz†; Alcohol Potenciado; Avril; Dermo H Infantil†; Desinvag†; Ginejuvent; Lindemil; Odamida; Otogen Calmante; Phonal; Resorborina; Sebumselen; Tulgrasum Cicatrizante; Vaselatum; ***Switz.***: Cutasept; Dequonal; Dettol; No Pic; Parapic†; ***Thai.***: Drapolene; Gynecon-T; Gynecon; Gynoco†; Gynova†; Gyonep; Gyracon; Napilene; Nystin; Oilatum Plus†; VG Med; ***Turk.***: Drapolene†; Kortos; ***UK***: Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus; Boots Mouth Ulcer Pastilles; Cetanorm; Conotrane; Dermol; Dettol; Drapolene; Emulsiderm; Iglu; Mycil; Neo Baby Cream; Oilatum Plus; Protectaid; ***Ukr.***: Drapolen (Драполен); Inflarax (Инфларакс); Septolete (Септолете); ***USA***: Bactine Antiseptic; Bactine Pain Relieving Cleansing; Cetylcide II; Cortic ND; Medi-First with Lidocaine; Medi-Quik; Mediotic-HC; Orajel Mouth Aid; Oxyzal; Pedi-Pro; Tanac Dual Core; Tanac; Tanac; Vagi-Gard Medicated Cream; Vi Rid-Ready; Zonite; ***Venez.***: Pedi-Lotion; Pedi-Lotion.

Pharmacopoeial Preparations
USNF 31: Benzalkonium Chloride Solution.

Benzethonium Chloride *(BAN, rINN)*

Bencetonio, cloruro de; Bensetoniumklorid; Bentsetoniumkloridi; Benzethonii Chloridum; Benzéthonium, chlorure de; Benzethoniumchlorid; Benzethonium-chlorid; Benzetonio chloridas; Benzetoniowy chlorek; Benzetónium-klorid; Cloruro de bencetonio; Diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride; Бензетония Хлорид.
Benzyldimethyl{2-[2-(4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl}ammonium chloride.
$C_{27}H_{42}ClNO_2$=448.1
CAS — 121-54-0.
ATC — D08AJ08; R02AA09.
ATC Vet — QD08AJ08; QR02AA09.
UNII — PH41D05744.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Benzethonium Chloride). A white or yellowish-white powder. Very soluble in water and in alcohol; freely soluble in dichloromethane. An aqueous solution froths copiously when shaken. Protect from light.

USP 36: (Benzethonium Chloride). White crystals with a mild odour. Soluble 1 in less than 1 of water, of alcohol, and of chloroform, and 1 in 6000 of ether. A 1% solution in water is slightly alkaline to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzethonium chloride is incompatible with soaps and other anionic surfactants.

Profile

Benzethonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used as a preservative in pharmaceutical and cosmetic products. It has also been used as a vaginal spermicide.

Benzethonium chloride, which produced mild skin irritation at a concentration of 5% but not lower, was not considered to be a sensitiser, and was considered to be safe at a concentration of 0.5% in cosmetics applied to the skin and at a maximum concentration of 0.02% in cosmetics used in the eye area.[1]

1. The Expert Panel of the American College of Toxicology. Final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride. *J Am Coll Toxicol* 1985; **4:** 65–106.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Avon Clearskin Invigorating Cleansing†; Clearskin Antibacterial†; Foamy Sanz; Gentle Fresh Sanitizer; Hand Sanitizer; Instant Hand Sanitizer; Kleen-San; Peri-Wash II; Sproam; Winning Hands Hand Sanitizer; Zep Foam San; ***Gr.***: Pan-Vasin†; ***Hong Kong***: Peri-Wash II†; ***S.Afr.***: Johnson's Antiseptic Powder†; ***USA***: Antiseptic Wound & Skin Cleanser.

Multi-ingredient Preparations. *Arg.*: Butimerin; Fil Olor; Gargadrin-R; Solumerin; Vagicural; ***Belg.***: Neo-Golaseptine; ***Braz.***: Andolba; Antimais Septico; Antiseptico Hertz†; Hipodex; Salvelox; Spray Anti-Septico; ***Canad.***: Lanacane Anti-Bacterial First Aid; Lipsorex Plus; Lipsorex; Marcorodex; ***Chile***: Aucusik; Lerfimin; Molca; ***Ger.***: Brand- u. Wundgel-Medice; ***Ital.***: Barrycidal; Sangen Casa; ***NZ***: VoSoL; ***S.Afr.***: Dry & Clear Medicated Skin Cleanser†; ***Spain***: Alcohol Potenciado; Eupnol; Halibut; ***Switz.***: Angidine†; Cemaquin†; Rhinocure simplex; Rhinocure; Tyrothricine + Gramicidine†; Undex†; ***Thai.***: Iwazin; Jawkepta; Sigatricin†; Tonsilon; ***USA***: Acetasol HC; Acetasol; Calagel; Dermoplast Antibacterial; Gold Bond Antiseptic First Aid Quick Spray; Skin Shield; StaphAseptic; Tecnu First Aid; Vagisil; VoSoL HC.

Pharmacopoeial Preparations
USP 36: Benzethonium Chloride Concentrate; Benzethonium Chloride Tincture; Benzethonium Chloride Topical Solution.

Benzoates

Benzoatos; Бензоаты.

Benzoic Acid

Acide benzoïque; Acidum benzoicum; Bensoesyra; Bentsoehappo; Benzoesäure; Benzoesav; Benzoico, ácido; Benzoinė rūgštis; Dracylic Acid; E210; Kwas benzoesowy; Kyselina benzoová; Бензойная Кислота.
$C_6H_5.CO_2H$=122.1
CAS — 65-85-0.
UNII — 8SKN0B0MIM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Benzoic Acid). A white or almost white, crystalline powder or colourless crystals, odourless or with a very slight characteristic odour. Slightly soluble in water; soluble in boiling water; freely soluble in alcohol and in fatty oils. M.p. 121 degrees to 124 degrees.

USP 36: (Benzoic Acid). White crystals, scales, or needles, with a slight characteristic odour. Soluble 1 in 300 of water, 1 in 3 of alcohol, 1 in 5 of chloroform, and 1 in 3 of ether; freely volatile in steam. Congealing range 121 degrees to 123 degrees.

Incompatibility. The incompatibilities of benzoic acid are described under Sodium Benzoate, below.

Sodium Benzoate

Benzoan sodný; Benzoato sódico; E211; Natrii Benzoas; Natrio benzoatas; Natrium Benzoicum; Natriumbensoat; Natriumbentsoaatti; Natriumbenzoat; Nátrium-benzoát; Sodii Benzoas; Sodium, benzoate de; Sodu benzoesan; Sodyum Benzoat; Бензоат Натрия.
$C_6H_5.CO_2Na$=144.1
CAS — 532-32-1.
UNII — OJ245FE5EU.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF*.

Ph. Eur. 8: (Sodium Benzoate). A white or almost white, slightly hygroscopic, crystalline or granular powder or flakes. Freely soluble in water; sparingly soluble in alcohol (90% v/v).

USNF 31: (Sodium Benzoate). A white, odourless or practically odourless, granular or crystalline powder. Soluble 1 in 2 of water, 1 in 75 of alcohol, and 1 in 50 of alcohol 90%.

Incompatibility. Benzoic acid and its salts are incompatible with quaternary compounds, calcium salts, ferric salts, and salts of heavy metals. Their activity is also diminished by nonionic surfactants or due to absorption by kaolin. They are relatively inactive above a pH of about 5.

Uses and Administration

Benzoates have antibacterial and antifungal properties. Their antimicrobial activity is due to the undissociated benzoic acid and is therefore pH-dependent. They are relatively inactive above a pH of about 5.

Benzoates are used as preservatives in pharmaceutical formulations including oral preparations; benzoic acid and sodium benzoate are typically used in concentrations of up to 0.2% and 0.5%, respectively. They are used as preservatives in foods, (and are also present naturally in some foods), and at similar concentrations in cosmetics.

Benzoic acid 6% with salicylic acid 3%, as Compound Benzoic Acid Ointment (BP 2014) (Whitfield's Ointment) has a long history of use as an antifungal (see Skin Infections, p. 568.1). Benzoic acid has also been used in desloughing preparations and has been given as a urinary antiseptic.

An injection of caffeine and sodium benzoate has been used as a CNS stimulant, but see Neonates, under Adverse Effects and Precautions, p. 1739.1 for a caution against its use in neonates.

Sodium benzoate is used as part of the treatment of hyperammonaemia that occurs in inborn errors of the urea cycle. It has also been reported to be effective in reducing plasma-glycine concentrations in nonketotic hyperglycinaemia (p. 2623.2), although it may not be effective in preventing mental retardation.

Sodium benzoate is a common ingredient of cough preparations.

Hyperammonaemia. Sodium benzoate is used for treatment of hyperammonaemia (p. 2049.3).[1-4] It is given with sodium phenylacetate (see p. 2619.2 for doses) and a combined preparation is available in some countries.

1. Maestri NE, *et al.* Long-term survival of patients with argininosuccinate synthetase deficiency. *J Pediatr* 1995; **127:** 929–35.
2. Maestri NE, *et al.* Long-term treatment of girls with ornithine transcarbamylase deficiency. *N Engl J Med* 1996; **335:** 855–9.
3. Zammarchi E, *et al.* Neonatal onset of hyperornithinemia-hyperammonemia-homocitrullinuria syndrome with favorable outcome. *J Pediatr* 1997; **131:** 440–3.
4. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356:** 2282–92.

Adverse Effects and Precautions

The benzoates can cause hypersensitivity reactions, but there have also been reports of non-immunological contact urticaria. The acid can be irritant to skin, eyes, and mucous membranes.

Infants given large doses of sodium benzoate have suffered vomiting. Symptoms of overdosage reported in this group have included vomiting, irritability and, in more severe cases, renal tubular dysfunction, hypokalaemia, hypocalcaemia, and metabolic acidosis.

Premature infants have been reported to be at risk of metabolic acidosis and kernicterus.

Hypersensitivity. Respiratory reactions to benzoates may occur, especially in patients susceptible to aspirin-induced asthma.[1,2] Urticarial reactions have also been associated with these compounds,[3,4] though at a lower incidence[5] and they can be non-immunological.[6] However, these reports have to be balanced against a controlled study[7] that showed no difference in the incidence of urticaria or atopic symptoms between patients given benzoic acid and those given lactose placebo. A retrospective study[8] of 47 patients who had previously shown a hypersensitivity reaction after ingesting food or products containing benzoate sodium found that the incidence of a repeat episode of acute urticaria or angioedema on re-challenge was very low (2%).

Anaphylactoid reactions have been reported in 2 patients.[9,10]

Erythema multiforme has occurred in several patients.[11]

1. Rosenhall L. Evaluation of intolerance to analgesics, preservatives and food colorants with challenge tests. *Eur J Respir Dis* 1982; **63:** 410–19.
2. Settipane GA. Aspirin and allergic diseases: a review. *Am J Med* 1983; **74** (suppl): 102–9.
3. Michaëlsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol* 1973; **88:** 525–32.
4. Warin RP, Smith RJ. Challenge test battery in chronic urticaria. *Br J Dermatol* 1976; **94:** 401–6.
5. Wüthrich B, Fabro L. Acetysalicylsäure-und lebensmitteladditiva-intoleranz bei urtikaria, asthma bronchiale und chronischer rhinopathie. *Schweiz Med Wochenschr* 1981; **III:** 1445–50.
6. Nethercott JR, *et al.* Airborne contact urticaria due to sodium benzoate in a pharmaceutical manufacturing plant. *J Occup Med* 1984; **26:** 734–6.

7. Lahti A, Hannuksela M. Is Benzoic acid really harmful in cases of atopy and urticaria? *Lancet* 1981; **ii:** 1055.
8. Nettis E, *et al*. Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. *Br J Dermatol* 2004; **151:** 898–902.
9. Moneret-Vautrin DA, *et al*. Anaphylactoid reaction to general anaesthesia: a case of intolerance to sodium benzoate. *Anaesth Intensive Care* 1982; **10:** 156–7.
10. Michils A, *et al*. Anaphylaxis with sodium benzoate. *Lancet* 1991; **337**: 1424–5.
11. Lewis MAO, *et al*. Recurrent erythema multiforme: a possible role of foodstuffs. *Br Dent J* 1989; **166:** 371–3.

Neonates. Serious metabolic disturbances in premature neonates given intravenous fluids with benzyl alcohol as a preservative have been attributed to the accumulation of benzoic acid, a metabolite of benzyl alcohol (see p. 1740.1). This risk led to the recommendation that Caffeine and Sodium Benzoate Injection (USP), which has been given as a respiratory stimulant, should not be used in neonates.[1]

Sodium benzoate has been tried in the treatment of some neonatal metabolic disorders (see Uses and Administration, p. 1738.3). However, benzoates can also displace bound bilirubin from albumin putting neonates at risk of kernicterus.[2] Three cases of toxicity have been reported after accidental high doses of intravenous sodium benzoate and sodium phenylacetate were given to children with hyperammonaemia.[3] All the children initially became agitated and confused, had Kussmaul respiration (rapid, deep breathing) and developed a partial metabolic acidosis with an increased anion gap. Two patients subsequently developed cerebral oedema and hypotension and died while the third survived after haemodialysis.

1. Edwards RC, Voegeli CJ. Inadvisability of using caffeine and sodium benzoate in neonates. *Am J Hosp Pharm* 1984; **41:** 658.
2. Schiff D, *et al*. Fixed drug combinations and the displacement of bilirubin from albumin. *Pediatrics* 1971: **48:** 139–41.
3. Praphanphoj V, *et al*. Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia. *J Inherit Metab Dis* 2000; **23:** 129–36.

Pharmacokinetics

The benzoates are absorbed from the gastrointestinal tract and conjugated with glycine in the liver to form hippuric acid, which is rapidly excreted in the urine.

Neonates. References.

1. Green TP, *et al*. Disposition of sodium benzoate in newborn infants with hyperammonemia. *J Pediatr* 1983; **102:** 785–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fu Tai (芙泰); ***Gr.***: Amzoate; ***Indon.***: Topix†; Yodsaben†; ***Spain***: Pastillas Dr Andreu.

Multi-ingredient Preparations. ***Arg.***: Expectosan Hierbas y Miel; Fungicida; Ixana; Ixana; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Pectobron; Refenax Jarabe; ***Austral.***: Whitfields (Benzoic Acid Compound) Ointment; ***Austria***: Acerbine; Mycopol; ***Belg.***: Pholco-Mereprine; Toplexil; ***Braz.***: Bronquidex; Bronquiogen†; Dermicon; Eaca Balsamico; Expec; Frenotosse; Fungolab†; Iodesin; KI-Expectorante; Micotiazol; Penetro; Po Antisseptico†; Toplexil; ***Canad.***: Bronco Asmol†; Larynsol†; Plax†; ***Chile***: Broncodeina; Caristop; Diencil; Fluorencil; Gruben; Listerine; Pectoral Pasteur; Pulmagol; ***China***: Bi Zhi Ke (比之可); ***Denm.***: Pectyl; ***Fr.***: Broncalene Nourisson†; Broncalene; Dinacode avec codeine; Ephydion†; Neo-Codion; Neo-Codion; Ozothine†; Paregorique†; Passedyl; Pastiserol†; Pate Suisse†; Pneumaseptic†; Pulmofluide Simple; Pulmosodyl; Rhinamide; ***Ger.***: Gero H3 Aslan†; ***Hong Kong***: Gly Thymol; Listerine Tartar Control; Listerine Teeth and Gum Defence; Listerine; ***Hung.***: Aknesol; Glycosept; Shilajit; ***India***: AM-PM Junior; AM-PM Plus; AM-PM Special; Colowash; Cool Mint Listerine; Elixir Efelin; Exomega; Exsora; Keralin; Listerine; Mycoderm; Pragmatar; Zoderm; ***Indon.***: Kalpanax; Kopamex†; Listerine Coolmint†; Mikorex†; Sapona†; ***Irl.***: Hemocane; Whitfield's Antifungal; ***Israel***: Oxacatin; Pertussol; Phytoderm Compositum; Pitrisan†; Pitrisol; Spirit Whitfield; To-Care; Tucare; Tussophedrine NF; ***Ital.***: Dentinale; Neo Borocillina Ant Oro; Neo Borocillina; Paracodina; Sedocalcio; Tiocosol†; ***Malaysia***: Nixoderm; ***Mex.***: Pulmovital; ***Mon.***: Glyco-Thymoline; ***NZ***: Listerine Citrus Fresh; Listerine Tartar Control†; Listerine Teeth Defence; Listerine; ***Philipp.***: Dermalin†; Listerine Coolmint; Listerine Freshburst; Listerine Original; Listerine Teeth & Gum Defense; United Home Whitfield's Ointment; ***Pol.***: Gargarin; ***Port.***: Broncodiazina†; Codol; Drenoflux; Micaveen†; ***Rus.***: Amtersol (Амтерсол); Mixture Conta Tussis for Adults (Микстура От Кашля Для Взрослых); Mosoile (Мозойл); Neo-Codion Babies (Нео-Кодион Для Младенцев)†; ***S.Afr.***: Aserbine; Dry & Clear Medicated Skin Cleanser†; ***Singapore***: Centa Skin; ETD; Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; Nixoderm; Poly-N; Robinson Ringworm & Whitespot; Veelanz's Ointment; ***Spain***: Acerbiol†; Broncoformo Muco Dexa†; Bronquidiazina CR; Etermol Antitusivo†; Pastillas Pectorales Kely†; Pazbronquial; Pulmofasa; Tos Mai; ***Switz.***: Nican†; Onguent aux herbes Keller; Pastilles pectorales du Dr. Welti; Phol-Tux; ***Thai.***: Benzo; Skin Soln; ***Turk.***: Artu; Fenasthma; Fenastma; Gayabeksin; Latusin†; Nesgarin; ***UK***: Eczema Ointment; Hemocane; Potters Gees Linctus; Sanderson's Throat Specific; Toepedo; ***Ukr.***: Acerbin (Ацербин); Extratherm (Экстратерм); Tos-Mai (Тос-Май); ***USA***: Ammonul; Atrosept; Bensal HP; Cystex; Hyophen; MHP-A; Prosed/DS; UAA; Ucephan†; Uriseptic; Uritact; ***Venez.***: Acetoben; Amodion; Dromil Sauco; Niosilin; Photoderm AKN; Pi-Fedrin; Tabonuco; Yerba Santa.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; ***Austria***: Globuli gegen Gelenkschmerzen; ***Canad.***: Arnica-Heel Comp†; Arthritic Pain; Backache with Arnica†; Bladder Irritation; Comp-Drops 8 Uri-Tract†; Homeo-Form AR†; Hyalgesic LBP†; Male +; Renelix; ***Chile***: Arnica Compuesta; Artroplex; ***Fr.***: Arthro-Drainol; Boripharm No 23; Hepatocynesine†; L 8; Ledum Complexe No 81; Natrum Carbonicum Complexe No 10†; Rhus Toxicodendron Compose; Rubia Complexe No 3; Urtica Complexe No 82†; ***Ger.***: Arthrorell N; Girheulit HM†; Girheulit HOM; Hevertnier Complex N†; Hewerheum N†; Levisticum S; Rheucostan R; ***Neth.***: Akutur spag; ***Switz.***: Akutur; Regenaplex Nr. 21e; Regenaplex Nr. 31b.

Pharmacopoeial Preparations
BP 2014: Benzoic Acid Solution; Compound Benzoic Acid Ointment; Tolu-flavour Solution;
USP 36: Benzoic and Salicylic Acids Ointment; Caffeine and Sodium Benzoate Injection.

Benzododecinium Bromide

Benzododecinio, bromuro de; Бензододециния Бромид.
Benzyldodecyldimethylammonium bromide.
$C_{21}H_{38}BrN$=384.4
CAS — 10328-35-5 (benzododecinium); 7281-04-1 (benzododecinium bromide).
ATC — D09AA05.
ATC Vet — QD09AA05.
UNII — IRY12B2TQ6.

Pharmacopoeias. In *Fr.*

Benzododecinium Chloride *(rINN)*

Benzododecinii Chloridum; Benzododecinio, cloruro de; Benzododécinium, Chlorure de; Cloruro de benzododecinio; Lauralkonium Chloride; Бензододециния Хлорид.
Benzyldodecyldimethylammonium chloride.
$C_{21}H_{38}ClN$=340.0
CAS — 139-07-1.
ATC — D09AA05.
ATC Vet — QD09AA05.
UNII — Y5A751G47H.

NOTE. The name Lauralkonium Chloride is also a *rINN* for another quaternary ammonium compound ($C_{29}H_{44}ClNO_2$; CAS – 19486-61-4).

Profile

Benzododecinium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in mouthwashes, eye preparations, and nasal sprays and solutions for the treatment of minor infections. It has also been used as a spermicide. Benzododecinium chloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Ajatin; ***Fr.***: Rhinedrine.

Multi-ingredient Preparations. ***Cz.***: Ophtal; ***Fr.***: Prorhinel; Sedacollyre†; ***Switz.***: Kemerhinose†; Prorhinel.

Benzoxonium Chloride *(rINN)*

Benzoxonii Chloridum; Benzoxonio, cloruro de; Benzoxonium, Chlorure de; Cloruro de benzoxonio; Бензоксония Хлорид.
Benzyldodecylbis(2-hydroxyethyl)ammonium chloride.
$C_{23}H_{42}ClNO_2$=400.0
CAS — 19379-90-9.
ATC — A01AB14; D08AJ05.
ATC Vet — QA01AB14; QD08AJ05.
UNII — 12IMO9R11X.

Profile

Benzoxonium chloride is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also used for instrument disinfection. Allergic contact dermatitis from benzoxonium chloride has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Orofar; ***Chile***: Bialcol; ***Gr.***: Orocil; ***Ital.***: Bactofen; Bialcol.

Multi-ingredient Preparations. ***Belg.***: Orofar Lidocaine; ***Braz.***: Halog Capilar; ***Chile***: Alcolex†; ***Cz.***: Orofar; ***Gr.***: Orocil Lido; ***Hung.***: Mebucain; Pedimed; ***Israel***: Merfen; Vita-Merfen NF; ***Philipp.***: Orofar-L; ***Pol.***: Orofar; ***Rus.***: Theraflu Lar (Терафлю Лар); ***Switz.***: Mebuca-Orange; Mebucalets f; Mebucaliquid; Mebucaspray; Merfen; Orofar; Vita-Merfen; ***Turk.***: Merfen; Vita-Merfen; ***Ukr.***: Theraflu LAR (Терафлю ЛАР)†.

Benzyl Alcohol *(rINN)*

Alcohol bencílico; Alcohol Benzylicus; Alcoholum Benzylicum; Alcool Benzylique; Alkohol benzylowy; Bensylalkohol; Bentsyylialkoholi; Benzenemethanol; Benzil-alkohol; Benzilo alkoholis; Benzylalkohol; Benzylique, alcool; Fenilmetanol; Phenylcarbinol; Phenylmethanol; Бензиловый Спирт.
$C_6H_5.CH_2OH$=108.1
CAS — 100-51-6.
UNII — LKG8494WBH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Benzyl Alcohol). A clear colourless, oily liquid. Soluble in water; miscible with alcohol, and with fatty and essential oils. Store under nitrogen in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USNF 31: (Benzyl Alcohol). A clear, colourless, oily liquid. Sparingly soluble in water; freely soluble in alcohol (50%); miscible with alcohol, with chloroform, and with ether. It is neutral to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzyl alcohol is incompatible with oxidising agents and strong acids. The antimicrobial activity may be reduced by nonionic surfactants and benzyl alcohol may be lost from solutions stored in polyethylene containers.

Stability. Benzyl alcohol oxidises to produce benzaldehyde and benzoic acid and oxidation may take place slowly on exposure to air. Benzaldehyde may also be produced on autoclaving.

Uses

Benzyl alcohol is used as an antimicrobial preservative. It is bacteriostatic mainly against Gram-positive organisms and some fungi. It is used in a range of pharmaceutical preparations in concentrations up to 2%. Concentrations of 5% or more are employed when it is used as a solubiliser. Benzyl alcohol is used as a preservative in foods and cosmetics. It is also used as a disinfectant at a concentration of 10%.

In addition to its antiseptic properties, concentrations of benzyl alcohol of up to 10% possess weak local anaesthetic and antipruritic activity.

A preparation containing 5% benzyl alcohol is used for the topical treatment of head pediculosis (p. 2147.3) in adults and children 6 months of age and older. It is inactive against the ova and a second application is needed after 7 days.

Adverse Effects and Precautions

Benzyl alcohol may produce hypersensitivity reactions, including local irritation and skin reactions.

The pure alcohol is irritant and requires handling with care; ingestion or inhalation can cause nausea, vomiting, diarrhoea, headache, and vertigo. Overexposure results in respiratory failure and CNS depression. However, concentrations of benzyl alcohol normally used are not associated with such effects.

There have been some instances of neurotoxic effects in patients given intrathecal injections that contained benzyl alcohol.

A fatal toxic syndrome in premature infants was attributed to benzyl alcohol present as a preservative in solutions used to flush intravenous catheters. This has led to restriction on the use of benzyl alcohol in neonates and young children, (see p. 1740.1).

Effects on the lungs. Severe bronchitis and haemoptysis was reported in a patient with obstructive pulmonary disease who, over a period of 2 years, had inhaled salbutamol nebuliser solution diluted with a bacteriostatic sodium chloride solution containing benzyl alcohol.[1]

1. Reynolds RD. Nebulizer bronchitis induced by bacteriostatic saline. *JAMA* 1990; **264**: 35.

Effects on the nervous system. Rapid development of flaccid areflexic paraplegia, total anaesthesia below the groin, and radicular abdominal pain occurred in a 64-year-old man after a lumbar intrathecal injection of cytarabine that contained 1.5% benzyl alcohol.[1] The patient recovered fully after 100 mL of CSF was replaced with sodium chloride 0.9% and 40 mg of methylprednisolone. Intrathecal

injections of cytarabine dissolved in sterile distilled water before and after the episode of paraplegia caused no neurologic symptoms. On reviewing 20 other cases of paraparesis associated with methotrexate or cytarabine intrathecal injections, benzyl alcohol had been used as a preservative in 7. Of these, 4 developed neurotoxicity immediately; in the other 3 it did not develop for between 6 and 48 hours. The duration varied. One patient did not improve, one made a partial recovery, a third took 6 weeks to recover, another took 5 days; yet 2 patients recovered within 1½ to 2½ hours while the final patient had only transient effects.

1. Hahn AF, *et al.* Paraparesis following intrathecal chemotherapy. *Neurology* 1983; **33:** 1032–8.

Hypersensitivity. Hypersensitivity reactions to benzyl alcohol have been reported.[1-3]

1. Grant JA, *et al.* Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med* 1982; **306:** 108.
2. Shmunes E. Allergic dermatitis to benzyl alcohol in an injectable solution. *Arch Dermatol* 1984; **120:** 1200–1.
3. Wilson JP, *et al.* Parenteral benzyl alcohol-induced hypersensitivity reaction. *Drug Intell Clin Pharm* 1986; **20:** 689–91.

Neonates. During 1981 and 1982 reports were published from 2 centres in the USA[1-3] of 20 deaths in low-birth-weight neonates attributed to the use of benzyl alcohol as a preservative in solutions used to flush their umbilical catheters and in some cases also to dilute their medication. The neonates suffered a toxic syndrome whose features included metabolic acidosis, symptoms of progressive encephalopathy, intracranial haemorrhage, and respiratory depression with gasping.

These deaths prompted the FDA[4] to recommend that benzyl alcohol should not be used in such flushing solutions; sodium chloride injection 0.9% without preservative should be used instead. The FDA had also advised against the use of benzyl alcohol or any preservative in fluids being used for the dilution or reconstitution of medicines for the newborn.

Those reporting the deaths[2,3] considered that the toxic syndrome could have been caused by the accumulation of the benzoic acid metabolite of benzyl alcohol, which could not be handled effectively by the immature liver; given the very low weight of the neonates they would have been receiving a comparatively high dose of benzyl alcohol. In commenting on the problem, the American Academy of Pediatrics[5] agreed that the FDA's warning was warranted, but pointed out that there was no evidence from controlled studies to confirm that benzyl alcohol was responsible.

1. Gershanik JJ, *et al.* The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; **29:** 895A.
2. Brown WJ, *et al.* Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1982; **i:** 1250.
3. Gershanik J, *et al.* The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982; **307:** 1384–8.
4. Anonymous. Benzyl alcohol may be toxic to newborns. *FDA Drug Bull* 1982; **12:** 10–11.
5. American Academy of Pediatrics. Benzyl alcohol: toxic agent in neonatal use. *Pediatrics* 1983; **72:** 356–7.

Pharmacokinetics

Benzyl alcohol is metabolised to benzoic acid. This is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. Benzaldehyde and benzoic acid are degradation products *in vitro*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: NeutraLice Advance; ***S. Afr.***: Cepacol; ***USA***: Ulesfia; Zilactin-L; Zilactin.

Multi-ingredient Preparations. ***Arg.***: Pastillas Pagliano; Standard XXI; ***Austral.***: Coso†; Soothe'n Heal†; ***Belg.***: Purigel Crisp†; Purigel NF; ***Chile***: Aucusik; Lerfimin; ***Denm.***: Doloproct; ***Fr.***: Biseptine; Dermaspraid Antiseptique†; Pastilles Medicinales Vicks; Sarnol; ***Ger.***: Autoderm Extra; Spitacid; ***India***: Accept; Acent; Alto; Arflur; Binpain; Dacpar; Delaxin-M; Dicloran-MS; Dicnap; Dion; Diplofen; Diptase; Dofec Plus; Duoflam Spy; Felini; Genoplex Forte; Imidil B; Imidil Plus; Intragesic; Jusgo; Kloser-D; L-Divon; Lenex; Linif; Nacmol Plus; Niclofen; Onspot; Opinac; Oronac; Orthodac; ***Irl.***: Sudocrem; ***Israel***: Otomycin; ***Ital.***: Foille Scottature; Foille Sole; Neo Borocillina Ant Oro; Pitiren; Prurex; Skab 2†; ***S.Afr.***: Medi-Keel A; ***Spain***: Acerbiol†; ***Switz.***: Skinsept; ***UK***: Sudocrem; ***Ukr.***: Sudocrem (Судокрем); ***USA***: MouthKote O/R; MuGard; Oragesic; Super Ivy Dry; Topic; Tucks.

Biclotymol *(rINN)*

Biclotimol; Biclotymolum; Биклотимол.
2,2′-Methylenebis(6-chlorothymole).
$C_{21}H_{26}Cl_2O_2$=381.3
CAS — 15686-33-6.
UNII — W4K0AE8XW9.

Profile

Biclotymol is a phenolic antiseptic that is used in lozenges and sprays for mouth and throat infections. It is also an ingredient of cough preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hexaspray; Humex Mal de Gorge; Sagaspray†; Solutricine Maux de Gorge; ***Hong Kong***: Hexaspray; ***Port.***: Hexaspray; ***Rus.***: Hexaspray (Гексаспрей); ***Ukr.***: Hexaspray (Гексаспрей).

Multi-ingredient Preparations. ***Fr.***: Hexalyse; Hexapneumine†; Hexapneumine; Hexarhume; ***Hong Kong***: Hexalyse; Hexapneumine†; Hexapneumine; ***Rus.***: Hexalyse (Гексализ); ***Ukr.***: Hexalyse (Гексализ); Hexapneumine for Children (Гексапневмин Для Детей)†.

Brilliant Green

CI Basic Green 1; Colour Index No. 42040; Diamond Green G; Emerald Green; Ethyl Green; Malachite Green G; Solid Green; Verde brillante; Viride Nitens; Бриллиантовый Зелёный.
4-(4-Diethylaminobenzhydrylidene)cycloheχa-2,5-dien-1-ylidenediethylammonium hydrogen sulphate.
$C_{27}H_{34}N_2O_4S$=482.6
CAS — 633-03-4.
UNII — G0L543D370.

NOTE. The name Emerald Green has also been used for copper acetoarsenite.

Profile

Brilliant green is a triphenylmethane antiseptic dye with actions similar to those of methylrosanilinium chloride (p. 1761.1). Its activity is greatly reduced in the presence of serum.

A gel containing brilliant green 0.5% with lactic acid was formerly used in the treatment of skin ulcers.

An alcoholic solution of brilliant green 0.5% and methylrosanilinium chloride 0.5% (Bonney's Blue) was formerly used for disinfecting the skin, but concern over evidence of *animal* carcinogenicity with methylrosanilinium chloride has led to a decline in its use. A solution of the two disinfectants has been used for marking incisions before surgery.

There have been occasional reports of sensitivity to brilliant green.

Adverse effects. For a report of necrotic skin reactions after application of a 1% solution of brilliant green to stripped skin, see under the Adverse Effects of Methylrosanilinium Chloride, p. 1761.2.

Bromchlorophen

Bromchlorophene; Bromochlorophane; Bromoclorofeno.
2,2′-Methylenebis[6-bromo-4-chlorophenol].
$C_{13}H_8Br_2Cl_2O_2$=426.9
CAS — 15435-29-7.
UNII — 2JZV1D2GW7.

Profile

Bromchlorophen is a halogenated bisphenol antiseptic more active against Gram-positive than Gram-negative bacteria. It is used for disinfection of the hands and skin. It has also been used in deodorants and toothpastes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Dibromol†.

Bromsalans

Bromosalicilanilidas.
CAS — 55830-61-0.

Description. Bromsalans are a series of brominated salicylanilides that possess antimicrobial activity.

Dibromsalan *(USAN, pINN)*

Dibromsalán; Dibromsalanum; NSC-20527; Дибромсалан.
4′,5-Dibromosalicylanilide; 5-Bromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.
$C_{13}H_9Br_2NO_2$=371.0
CAS — 87-12-7.
UNII — N9900K2RBT.

Metabromsalan *(USAN, pINN)*

Metabromsalán; Métabromsalan; Metabromsalanum; NSC-526280; Метабромсалан.
3,5-Dibromosalicylanilide; 3,5-Dibromo-2-hydroxy-*N*-phenylbenzamide.
$C_{13}H_9Br_2NO_2$=371.0
CAS — 2577-72-2.
UNII — 8Q21Y09R21.

Tribromsalan *(BAN, USAN, rINN)*

ET-394; NSC-20526; TBS; Tribromsalán; Tribromsalanum; Трибромсалан.
3,4′,5-Tribromosalicylanilide; 3,5-Dibromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.
$C_{13}H_8Br_3NO_2$=449.9
CAS — 87-10-5.
UNII — 6MCE3VTF0O.

Profile

Bromsalans have antibacterial and antifungal activity and have been used in medicated soaps, but there have been many reports of photosensitivity arising from this use.

Bronopol *(BAN, rINN)*

Bronopolum; Бронопол.
2-Bromo-2-nitropropane-1,3-diol.
$C_3H_6BrNO_4$=200.0
CAS — 52-51-7.
ATC Vet — QD01AE91.
UNII — 6PU1E16C9W.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Bronopol). White or almost white crystals or crystalline powder, odourless or almost odourless. Freely soluble in water and in alcohol; slightly soluble in glycerol and in liquid paraffin. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

Incompatibility. The activity of bronopol can be reduced by sodium metabisulfite, sodium thiosulfate, cysteine hydrochloride, and compounds with a thiol group. Incompatibility with unprotected aluminium affects packaging.

Stability. The stability of bronopol is affected by increases in temperature and by increases in pH above 8.

Creams and shampoos containing bronopol 0.01% as a preservative were found to contain free nitrite and, as a result of amines present in the preparations, nitrosamines.[1] It was recommended that nitrosamine formation could be reduced in preparations containing amines and bronopol by limiting the bronopol concentration to 0.01% and inclusion of alpha tocopherol 0.2% or butylated hydroxytoluene 0.05%.

1. Dunnett PC, Telling GM. Study of the fate of bronopol and the effects of antioxidants on N-nitrosamine formation in shampoos and skin creams. *Int J Cosmet Sci* 1984; **6:** 241–7.

Uses

Bronopol is active against a wide range of bacteria, including *Pseudomonas aeruginosa*, but is less active against moulds and yeasts. Bronopol is used as a preservative in shampoos, cosmetics, and both topical and oral pharmaceutical preparations; concentrations in pharmaceutical preparations range from 0.01 to 0.1%, with the usual concentration being 0.02%. It is also used for its antimicrobial properties in various industrial applications, including in air conditioning systems.

Adverse Effects

Bronopol may be irritant when applied topically and cases of contact dermatitis have been reported.

Pharmacokinetics

Bronopol is absorbed following topical use.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Antiseptic Hand Soap.

Butylated Hydroxyanisole *(BAN)*

BHA; Butilhidroksianizolas; Butilhidroxianisol; Butil-hidroxianizol; Butilidrossianisolo; Butylhydroxianisol; Butylhydroxyanisol; Butylhydroxyanisole; Butylhydroxyanisolum; Butylohydroksyanizol; Butyylihydroksianisoli; E320; Бутилгидроксианизол.

2-*tert*-Butyl-4-methoxyphenol; 2-(1,1-dimethylethyl)-4-methoxyphenol.
$C_{11}H_{16}O_2$=180.2
CAS — 25013-16-5.
UNII — REK4960K2U.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Butylhydroxyanisole; Butylated Hydroxyanisole BP 2014). A white, yellowish, or slightly pinkish, crystalline powder. It contains not more than 10% of 3-(1,1-dimethylethyl)-4-methoxyphenol. Practically insoluble in water; freely soluble in alcohol and in fatty oils; very soluble in dichloromethane; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Butylated Hydroxyanisole). A white, or slightly yellow, waxy solid with a faint characteristic odour. Insoluble in water; soluble 1 in 4 of alcohol, 1 in 2 of chloroform, and 1 in 1.2 of ether; freely soluble in propylene glycol.

Incompatibility. Butylated hydroxyanisole is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Uses

Butylated hydroxyanisole is an antioxidant with some antimicrobial activity. It is used as a preservative in cosmetics and foods as well as pharmaceutical preparations, particularly to delay or prevent oxidative rancidity of fats and oils in concentrations of up to 0.02%; higher concentrations have been used for essential oils. It is also used to prevent the loss of activity of oil-soluble vitamins. To improve efficacy, butylated hydroxyanisole is frequently used with other antoxidants such as butylated hydroxytoluene or an alkyl gallate and with sequestrants or synergists such as citric acid.

Commercial supplies of butylated hydroxyanisole used in food technology consist of mixtures of the 2-*tert* and 3-*tert* isomers.

Use in food. In the UK the Food Advisory Committee has recommended that the use of butylated hydroxyanisole and butylated hydroxytoluene should no longer be permitted as additives for infant formulas as they are no longer required for the economic manufacture of vitamin A and vitamin A esters.[1]

1. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. *FdAC/REP/12.* London: HMSO, 1992.

Adverse Effects

Butylated hydroxyanisole can be irritant to the eyes, skin, and mucous membranes and can cause depigmentation. There are also reports of contact urticaria.

Carcinogenicity. There has been concern as to whether butylated hydroxyanisole may be a carcinogen.[1,2] These concerns stem from a study in which *rodents* given food containing 1 to 2% butylated hydroxyanisole developed squamous cell carcinoma of the forestomach. No similar malignancies were found in studies with *animals* that do not have a forestomach. The IARC has concluded[2] that there is sufficient evidence for the carcinogenicity of butylated hydroxyanisole in *animals* but that there is no data on its carcinogenicity in humans.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_776.pdf (accessed 27/08/08)
2. IARC/WHO. Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 40* 1986. Available at: http://monographs.iarc.fr/ENG/Monographs/vol40/volume40.pdf (accessed 23/05/06)

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed, see under Adverse Effects in Alkyl Gallates (p. 1736.2).

Pharmacokinetics

Butylated hydroxyanisole is absorbed from the gastrointestinal tract, then metabolised and conjugated, and excreted in the urine; less than 1% is excreted in the urine as unchanged drug within 24 hours of ingestion.

Butylated Hydroxytoluene *(BAN)*

BHT; Butilhidroksitoluenas; Butilhidroxitolueno; Butil-hidroxitoluol; Butylhydroxitoluen; Butylhydroxitoluenum; Butylhydroxytoluen; Butylhydroxytoluene; Butylhydroxytoluène; Butylhydroxytoluenum; Butylhydroxytoluol; Butylohydroksytoluen; Butyylihydroksitolueeni; E321; Бутилгидрокситолуол; Бутилированный Гидрокситолуол.
2,6-Di-*tert*-butyl-*p*-cresol.
$C_{15}H_{24}O$=220.4
CAS — 128-37-0.
UNII — 1P9D0Z171K.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Butylhydroxytoluene; Butylated Hydroxytoluene BP 2014). A white or yellowish-white, crystalline powder. F.p. 69 degrees to 70 degrees. Practically insoluble in water; freely soluble in alcohol and in vegetable oils; very soluble in acetone.

USNF 31: (Butylated Hydroxytoluene). A white crystalline solid with a faint characteristic odour. Insoluble in water and in propylene glycol; soluble 1 in 4 of alcohol and 1 in 1.1 of chloroform and of ether.

Incompatibility. Butylated hydroxytoluene is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Uses

Butylated hydroxytoluene is an antoxidant with uses similar to those of Butylated Hydroxyanisole, above.

Adverse Effects

As for Butylated Hydroxyanisole, above.

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula, see under Adverse Effects in Alkyl Gallates, p. 1736.2.

Poisoning. A 22-year-old woman had severe epigastric cramping, nausea and vomiting, and generalised weakness, followed by dizziness, confusion, and a brief loss of consciousness after ingesting 4 g of butylated hydroxytoluene. She recovered after conservative treatment, which was given 2 days later. The antoxidant had been taken as an unauthorised remedy for genital herpes simplex.[1]

1. Shlian DM, Goldstone J. Toxicity of butylated hydroxytoluene. *N Engl J Med* 1986; **314:** 648–9.

Pharmacokinetics

Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract. It is excreted in the urine mainly as glucuronide conjugates of oxidation products.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Proseptine-Plus†.

Cadexomer-Iodine *(BAN)*

Cadexomer Iodine (USAN); Cadexomer Iodine; Cadexomerjod; Cadexómero yodado; Cadexomerum Iodum; Kadeksomeerijodi; Кадексомера-йодин.
2-Hydroxymethylene cross-linked (1→4)-α-D-glucan carboxymethyl ether containing iodine.
CAS — 94820-09-4.
ATC — D03AX01.
ATC Vet — QD03AX01.

Uses and Administration

Cadexomer-iodine, like povidone-iodine (p. 1767.1), is an iodophore that releases iodine. It is used for its absorbent and antiseptic properties in the management of venous leg ulcers and pressure sores. It is applied as a powder, ointment, or paste containing iodine 0.9%; sufficient powder or ointment should be applied to form a layer about 3 mm thick. Treatment should not usually be continued for more than 3 months.

Adverse Effects and Precautions

As for Povidone-Iodine, p. 1767.2. Some patients have stinging and erythema on application of cadexomer-iodine to their ulcers. Free iodine is released during exposure of cadexomer-iodine preparations to wound exudate and absorption of iodine may occur. Prolonged treatment with cadexomer-iodine should be given with caution in patients with thyroid disorders.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cadexomer-iodine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Iodosorb; ***Canad.***: Iodosorb; ***Ger.***: Iodosorb; ***Gr.***: Iodosorb; ***Irl.***: Iodoflex; ***Ital.***: Iodosorb; ***Malaysia***: Iodosorb; ***Neth.***: Iodosorb†; ***S.Afr.***: Iodosorb†; ***UK***: Iodoflex; Iodosorb; ***USA***: Iodosorb.

Calcium Peroxide

Calcium Dioxide; E930; Пероксид Кальция.
CaO_2=72.08
CAS — 1305-79-9.
UNII — 7FRO2ENO91.

Profile

The action of calcium peroxide is similar to that of hydrogen peroxide (p. 1755.2). Calcium peroxide is used in dental products for tooth whitening. It is also used as a flour bleaching and improving agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Hexiben.

Carbaethopendecinium Bromide

Carbethopendecinii Bromidum; Carbethoxypentadecyltrimethylammonium Bromide; Karbethopendecinium bromid.
1-Ethoxy-*N*,*N*,*N*-trimethyl-1-oxo-2-hexadecanaminium bromide.
$C_{21}H_{44}NO_2Br$=422.5
CAS — 10567-02-9.

Profile

Carbaethopendecinium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in topical preparations for disinfection of skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Mukoseptonex; Ophthalmo-Septonex; Septonex.

Multi-ingredient Preparations. ***Cz.***: Mesocain; Mukoseptonex E; Ophthalmo-Septonex; Septonex Plus; Septonex; Triamcinolon.

Cetalkonium Chloride *(BAN, USAN, rINN)*

Cetalconio, cloruro de; Cetalkonii Chloridum; Cétalkonium, Chlorure de; Cloruro de cetalconio; NSC-32942; Цеталкония Хлорид.
Benzylhexadecyldimethylammonium chloride.
$C_{25}H_{46}ClN$=396.1
CAS — 122-18-9.
UNII — 85474O1N9D.

Profile

Cetalkonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in a variety of topical preparations in the treatment of minor infections of the mouth and throat. It has also been used in the treatment of eye infections. Cetalkonium bromide has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pansoral; ***Austral.***: Bonjela; Sedagel; ***Belg.***: Teejel; ***Braz.***: Pondicilina; ***Canad.***: Bionet; ***Fr.***: Pansoral; ***Gr.***: Mundisal; ***Hong Kong***: Bonjela; ***Hung.***: Mundisal; ***Irl.***: Bonjela; Teejel†; ***Israel***: Baby Gum; Bonjela†; Teejel; ***Malaysia***: Bonjela; Cationorm; ***NZ***: Bonjela; ***Pol.***: Sachol zel Stomatologiczny; ***Rus.***: Cholisal (Холисал); Pansoral (Пансорал); ***S.Afr.***: Bonjela; ***Singapore***: Bonjela; ***Switz.***: Pansoral†; Tenderdol; ***Thai.***: Bonjela; ***UK***: Bonjela Cool Mint; Bonjela Teething Gel; Bonjela; ***Ukr.***: Cholisal (Холисал); ***USA***: Babee.

Cethexonium Bromide (rINNM)

Bromuro de cetexonio; Cetexonio, bromuro de; Cethexonii Bromidum; Céthexonium, Bromure de; Цетексония Бромид.
Hexadecyl(2-hydroxycyclohexyl)dimethylammonium bromide.
$C_{24}H_{50}BrNO$=448.6
CAS — 6810-42-0 (cethexonium); 1794-74-7 (cethexonium bromide).
UNII — F3T95WRD7W.

Profile

Cethexonium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, below). It is used in preparations for the local treatment of minor infections of the eye, nose, and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Biocidan; Monosept; Sedacollyre.

Multi-ingredient Preparations. ***Fr.***: Biocidan.

Cetrimide (BAN, rINN)

Cetrimid; Cetrimida; Cetrimidas; Cétrimide; Cetrimidum; Cetrymid; Setrimid; Setrimidi; Цетримид.
CAS — 1119-97-7 (trimethyltetradecylammonium bromide); 1119-94-4 (dodecyltrimethylammonium bromide); 8044-71-1 (cetrimide).
ATC — D08AJ04; D11AC01.
ATC Vet — QD08AJ04; QD11AC01.
UNII — 24QSH2NL8N.

NOTE. The name cetrimonium bromide was often formerly used for cetrimide. Cetrimonium bromide (see below) is hexadecyltrimethylammonium bromide.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Br. also includes strong cetrimide solution.

Ph. Eur. 8: (Cetrimide). It consists of trimethyltetradecylammonium bromide (=tetradonium bromide (*rINN*)) and may contain smaller amounts of dodecyltrimethylammonium bromide and hexadecyltrimethylammonium bromide (=cetrimonium bromide, below). A white or almost white, voluminous, free-flowing powder. Freely soluble in water and in alcohol. A 2.0% solution in water froths copiously when shaken.

BP 2014: (Strong Cetrimide Solution). It is an aqueous solution of cetrimide. It contains 20 to 40% w/v of cetrimide, calculated as $C_{17}H_{38}BrN$ and up to 10% alcohol or isopropyl alcohol, or both; alcohol may be replaced by industrial methylated spirit. It may be perfumed and may contain colouring matter. Store at a temperature above 15 degrees.

Incompatibility. Cetrimide is incompatible with soaps and other anionic surfactants, bentonite, iodine, phenylmercuric nitrate, and alkali hydroxides. Aqueous solutions react with metals.

Uses and Administration

Cetrimide is a quaternary ammonium antiseptic with actions and uses typical of cationic surfactants. These surfactants dissociate in aqueous solution into a relatively large and complex cation that is responsible for the surface activity and a smaller inactive anion. In addition to emulsifying and detergent properties, quaternary ammonium compounds have bactericidal activity against Gram-positive and, at a higher concentration, against some Gram-negative bacteria. Some *Pseudomonas* spp. are particularly resistant as are strains of *Mycobacterium tuberculosis*. They are ineffective against bacterial spores, have variable antifungal activity, and are effective against some viruses.

Quaternary ammonium compounds are most effective in neutral or slightly alkaline solution and their bactericidal activity is appreciably reduced in acid media; their activity is enhanced by alcohols.

Like other quaternary ammonium compounds, notably benzalkonium chloride (p. 1737.1), cetrimide has been employed for cleansing skin, wounds (but see under Wound Disinfection, p. 1732.2), and burns. For these purposes it has been used as a 0.1 to 1.0% aqueous solution, generally prepared by dilution of a more concentrated solution, or as a cream or spray containing 0.5%. However, a mixture of cetrimide with chlorhexidine (p. 1743.2) has often been preferred to cetrimide alone. This combination is also used in a lotion for acne (p. 1682.2).

Solutions containing up to 10% of cetrimide have been used as shampoos to remove the scales in seborrhoeic dermatitis (p. 1689.1).

Cetrimide solution 0.5 or 1% has been used as a scolicide to irrigate hydatid cysts during surgery (see Echinococcosis, p. 145.2) but systemic adverse effects have been reported (see below).

Cetrimide and benzalkonium chloride are also used as preservatives in cosmetics and pharmaceutical formulations including eye drops and in disinfecting solutions for hard contact lenses; neither compound should be used for disinfection of soft contact lenses.

Cetrimide is also present in some emulsifying preparations such as Cetrimide Emulsifying Ointment (BP 2014).

Adverse Effects and Treatment

At the concentrations used on the skin, solutions of cetrimide and other quaternary compounds do not generally cause irritation, but some patients become hypersensitive to cetrimide after repeated applications. Cetrimide powder is reported to be irritant. There have been rare reports of burns with concentrated solutions of cetrimide.

If ingested, cetrimide and other quaternary ammonium compounds cause nausea and vomiting; strong solutions may cause oesophageal damage and necrosis. They have depolarising muscle relaxant properties and toxic symptoms include dyspnoea and cyanosis due to paralysis of the respiratory muscles, possibly leading to asphyxia. CNS depression (sometimes preceded by excitement and convulsions), hypotension, coma, and death may also occur. Accidental intra-uterine or intravenous administration may cause haemolysis and pulmonary embolism.

Treatment of poisoning is symptomatic; demulcents and diluents may be given if necessary but emesis and lavage should be avoided, particularly if concentrated solutions have been ingested. Activated charcoal may be considered if the patient presents within an hour of ingestion. CNS stimulants and cholinesterase inhibitors are reported not to reverse paralysis due to cetrimide intoxication although sympathomimetics have been tried. Corticosteroids may reduce oropharyngeal oedema.

Effects after cyst irrigation. Adverse effects after irrigation with cetrimide solutions in the treatment of hydatid cysts have included chemical peritonitis,[1] methaemoglobinaemia with cyanosis,[2] and metabolic acidosis.[3]

1. Gilchrist DS. Chemical peritonitis after cetrimide washout in hydatid-cyst surgery. *Lancet* 1979; **ii:** 1374.
2. Baraka A, *et al.* Cetrimide-induced methaemoglobinaemia after surgical excision of hydatid cyst. *Lancet* 1980; **ii:** 88–9.
3. Momblano P, *et al.* Metabolic acidosis induced by cetrimonium bromide. *Lancet* 1984; **ii:** 1045.

Poisoning. The fatal dose of quaternary ammonium compounds was estimated to be 1 to 3 g.[1]

1. Arena JM. Poisonings and other health hazards associated with use of detergents. *JAMA* 1964; **190:** 56–8.

Precautions

Prolonged and repeated applications of cetrimide to the skin are inadvisable as hypersensitivity may occur. Contact with the eyes, brain, meninges, and middle ear should be avoided. Cetrimide is for external use only and should not be used in body cavities or as an enema.

Quaternary ammonium compounds are not reliable for sterilising surgical instruments and heat-labile articles. The antimicrobial activity of quaternary ammonium compounds may be reduced through absorption, or through combination with organic matter, or by reducing pH.

Solutions of quaternary ammonium compounds should not be used for disinfection of soft contact lenses.

Aqueous solutions of cetrimide or other quaternary ammonium disinfectants may be susceptible to contamination with micro-organisms. To reduce this risk, a sterilised preparation should be used or, where necessary, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Handling. Cetrimide powder is irritant; it has been recommended that the nose and mouth should be protected by a mask when working with the powder[1] and eyes should be protected by goggles.

1. Jacobs JY. Work hazards from drug handling. *Pharm J* 1984; **233:** 195–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Boucren; Sorbicet; ***Austral.***: Skin-Prep with Cetramide; ***Belg.***: Aseptiderm; ***Fr.***: Cetavlon; Sterilene; ***Gr.***: Cetavlon; ***Hong Kong***: Cetrol†; ***India***: Aceptik; Cetavlon; Cetrilak; Cetrim; Gemide; ***Irl.***: Vesagex; ***Malaysia***: Dermoplex Antiseptic; ***Port.***: Cetavlex; ***Turk.***: Cetyl; ***UK***: Cetavlex; Medi-Prep; Medicaid; Richmond Antiseptic Cream; Vesagex.

Multi-ingredient Preparations. ***Arg.***: Cerosporin; Jabonacid; Otidrops; Otocalmia Biotic; Sincerum; ***Austral.***: Acnederm Foaming Wash†; Dimethicream; Hamilton Pine Tar with Menthol; Medi Creme; Microshield Antiseptic†; Savlon Antiseptic; Soov Bite; Soov Burn; Soov Cream; ***Austria***: Lemocin; Xylonor; ***Belg.***: Lemocin; ***Canad.***: Savlodil†; Xylonor; ***Fin.***: Lakrimont; ***Fr.***: Biodicaine†; Dicagel†; Lysocalmspray†; Rectoquotane; Xogel; Xylonor; Ziacaine; Ziagel; ***Gr.***: Hibicet; ***Hong Kong***: Acnederm Wash; Borraginol-N†; DPH with Calamine†; Hamilton Skin Repair†; Medicreme†; Phytocine†; Soov Bite; Soov Cream; Tri-Gel†; Zinsomine; ***India***: Aceptik-HC; Aceptik-LA; Agloscab; Antiscab; Clenora; Clenorush; Coral; Dentakind; Dermogard; Endruff; Escab Plus; Freescab; Gamaley; Gamazex; GBTop; Gynocream; Intalon; Iteol-3; Klinit; Microgard; Microshield Antiseptic; New Iteol-3; Novascab; NT-Scab; O2-Fresh-GP; Ora-G; Scabine; Scarab; Siloderm; ***Indon.***: Benzomid; Bioacne; Borraginol-N; Borraginol-S; Neo Resiguard; Pravlon†; ***Irl.***: Cymex; Drapolene; Hibicet; Lypsyl Cold Sore Gel†; RBC†; Savlon; Sterets Tisept; Torbetol†; Xylonor; ***Israel***: Cetrin; Savior; Tisept; Travasept; Xylonor; ***Ital.***: Baxidin; Cetrexidin; Cetrifarm; Cetrisan†; Cuprosodio; Farvicett; Hibizene; Lidocaina Spray; Panseptil†; ***Malaysia***: Acnederm Foaming Wash; Burnol Plus; Drapolene; Norash; Soov Bite; ***Neth.***: Hibicet concentraat; Hibicet verdunning; ***NZ***: Acnederm Foaming Wash†; Medicreme†; Savlon; Soov Bite; Soov Burn; Soov Cream; Soov Gel; ***Philipp.***: Drapolene; ***Rus.***: Drapolene (Драполен); ***S.Afr.***: Germolene†; Orocaine; Savlon; Siopel; Trochain; ***Singapore***: Acnederm Foaming Wash; Burnol Plus; Drapolene; Napitol; Norash; Soov Bite; Soov Cream; Tisept; ***Switz.***: Xylonor; ***Thai.***: Bacard†; Bactricide; Burnol Plus; Chlorhex-C†; Clocimide; Dekka; Dekkalon; Drapolene; Frebac; Hibicet†; Inhibac; Killa; Napilene; Septol-C; Septrex; ***Turk.***: Deriseptol; Drapolene†; Savlex; Savlosol; Savonol; Savrolin; Setilin; ***UK***: Ceanel; Cetanorm; Cymex; Dermidex; Drapolene; Lypsyl Cold Sore Gel; Neo Baby Cream; Quinoderm Antibacterial Face Wash; Savlon Antiseptic Cream; Savlon Antiseptic Liquid; Siopel; Tisept; Torbetol; Travasept†; ***Ukr.***: Drapolen (Драполен); ***USA***: Scadan.

Pharmacopoeial Preparations
BP 2014: Cetrimide Cream; Cetrimide Emulsifying Ointment; Cetrimide Solution.

Cetrimonium Bromide (BAN, rINN)

Bromuro de cetrimonio; Cetrimonii Bromidum; Cetrimonio, bromuro de; Cétrimonium, Bromure de; Cetylotrimetyloamoniowy bromek; Cetyltrimethylammonium Bromide; CTAB; Цетримония Бромид.
Hexadecyltrimethylammonium bromide.
$C_{19}H_{42}BrN$=364.5
CAS — 6899-10-1 (cetrimonium); 57-09-0 (cetrimonium bromide).
ATC — D08AJ02; R02AA17.
ATC Vet — QD08AJ02; QR02AA17.
UNII — L64N7M9BWR.

NOTE. The name cetrimonium bromide was formerly applied to cetrimide (see above).

Pharmacopoeias. In *USNF.*

USNF 31: (Cetrimonium Bromide). A white to creamy white, voluminous, free-flowing powder, with a characteristic faint odour. Freely soluble in water and in alcohol; practically insoluble in ether.

Cetrimonium Chloride (BAN, rINNM)

Cetrimonii Chloridum; Cetrimonio, cloruro de; Cétrimonium, Chlorure de; Cloruro de cetrimonio; Цетримония Хлорид.
Hexadecyltrimethylammonium chloride.
$C_{19}H_{42}ClN$=320.0
CAS — 112-02-7.
ATC — D08AJ02; R02AA17.
ATC Vet — QD08AJ02; QR02AA17.
UNII — UC9PE95IBP.

Profile

Cetrimonium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, above). Cetrimonium chloride and cetrimonium tosilate are also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Neo-Intol; Senol; Sterilene; ***Switz.***: Aknex Cleaning†; Turisan†.

Multi-ingredient Preparations. ***Arg.***: Bagoderm; Eryteal; Klorane Bebe Eryteal; ***Belg.***: Cetavlex; HAC; Hacdil-S; ***Braz.***: Amigdalol; Cetrilan; Drapolene; ***Canad.***: Largal Ultra; Salvesept†; Xylonor; ***China***: Drapolene (保英); ***Fr.***: Nostril†; ***Ger.***: Lemocin†; ***Gr.***: Buccasept†; ***Indon.***: Lemocin; ***Israel***: Clearocin; Lemocin; ***Ital.***: Golamixin; Xylonor; ***Mex.***: Dermatolona; ***Pol.***: Cetriscabin†;

Spain: Diformiltricina†; Hongosan†; Xylonor; ***Switz.***: Lemocin; Mebu; Septivon; Turexan Capilla†; ***Venez.***: Kertyol.

Cetylpyridinium Chloride *(BAN, rINN)*

Cetilpiridinio cloridas; Cetilpiridinio, cloruro de; Cetilpiridinium-klorid; Cetylpyridinii Chloridum; Cetylpyridinii Chloridum Monohydricum; Cétylpyridinium, Chlorure de; Cetylpyridiniumchlorid; Cetylpyridinium-chlorid monohydrát; Cetylpyridiniumklorid; Cloruro de cetilpiridinio; Setilpiridinyum Klorür; Setyylipyridiniumkloridi; Цетилпиридиния Хлорид.

1-Hexadecylpyridinium chloride monohydrate.

$C_{21}H_{38}ClN,H_2O$=358.0

CAS — 7773-52-6 (cetylpyridinium); 123-03-5 (anhydrous cetylpyridinium chloride); 6004-24-6 (cetylpyridinium chloride, monohydrate).

ATC — B05CA01; D08AJ03; D09AA07; R02AA06.

ATC Vet — QB05CA01; QD08AJ03; QD09AA07; QR02AA06.

UNII — D9OM4SK49P (cetylpyridinium chloride) 6BR7T22E2S (anhydrous cetylpyridinium chloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cetylpyridinium Chloride). A white or almost white powder, slightly soapy to the touch. Soluble in water, frothing copiously when shaken; soluble in alcohol.

USP 36: (Cetylpyridinium Chloride). A white powder with a slight characteristic odour. Soluble 1 in 4.5 of water and of chloroform, and 1 in 2.5 of alcohol; slightly soluble in ether and in benzene.

Incompatibility. Cetylpyridinium chloride is incompatible with soaps and other anionic surfactants.

Profile

Cetylpyridinium chloride is a quaternary pyridinium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used chiefly as lozenges or solutions for the treatment of minor infections of the mouth and throat. It is also used topically for the treatment of skin and eye infections.

Cetylpyridinium bromide is used similarly for minor mouth and throat disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Higiemax; ***Austral.***: Cepacol; Dentyl; Lemsip Lozenges†; ***Austria***: Dobendan; Halset; ***Braz.***: Cepacol; Gargocetil; Gargomax; Laringex; ***Canad.***: Antiseptic Oral Rinse; Cepacol†; Crest Pro-Health; Rince Bouche Antiseptique; Throat Lozenges; ***Chile***: Freesept; ***China***: Ai Nuo Tian Jian (爱诺天健); Ben Li (本力); Kaikeli (开刻立); Liangqi (亮奇); Ya Liang (雅量); Yi Xin (忆信); ***Cz.***: Halset; Neoseptolete; ***Fr.***: Novoptine; Sedacollyre; ***Ger.***: Dobendan; Halstabletten akute†; ***Hong Kong***: Cepacol; Cetocomp; ***Hung.***: Halset; ***India***: Kolq; ***Irl.***: Merocets; ***Ital.***: Bat; Batzeta; Borocaina Gola; Cetilsan; Citromed Soap; Exil; Farin Gola; Golacetin; Golafair; Neo Cepacol Pastiglie; Neo Formitrol; Periogard Plus; Physioatтivo; Ragaden; Stomygen; ***Mex.***: Trociletas; ***Norw.***: Pyrisept; ***NZ***: Cepacol; Lemsip Throat Lozenges; ***Pol.***: Halset; Menthosept; Septolete Apple; Septolete Cherry; Septolete Lemon; ***Port.***: Septus; ***Rus.***: Septolete Neo (Септолете Нео); ***S.Afr.***: Cepacol; Goldex Throat Lollies; Universal Throat Lollies†; ***Singapore***: Cepacol; ***Switz.***: Halset; ***Thai.***: Cepacol; Hops†; Orasept; ***Turk.***: Aseptol†; Penipastil; ***UK***: Listermint; Merocets; ***Ukr.***: Septolete with lemon/cherry/apple (Септолете); ***USA***: Cepacol Mouthwash; Cepacol Throat; Choice DM Gentle Care; Scope; ***Venez.***: Cepacol.

Multi-ingredient Preparations. ***Arg.***: Ernex Duo; Periodil; Solumerin; ***Austral.***: Cepacaine; Cepacol Cough; Cepacol Plus; Difflam Anti-inflammatory Lozenges with Cough Suppressant; Difflam Lozenges; Difflam Mouth Gel; Duro-Tuss Dry Cough; Gentlees; Sedagel; ***Austria***: Coldistan; Dentinox†; Gurfix†; ***Braz.***: Cepacaina; Cepacol Menta; Lima C; Malvona; Neopiridin; Noplak Max; Pondicilina; Psiu; Sanilin; Silencium; Silencium; ***Canad.***: Cepacol Extra Strength†; Cepacol with Fluoride†; Green Antiseptic Mouthwash & Gargle†; Kank-A; Oral-B Anti-Bacterial with Fluoride; Throat Lozenges; ***Chile***: Adolex; Aftagel Bucal; Halita; Kank-Eze; Oralfresh; Pancrit; Perio-Aid c Cloruro de Cetilpiridinio; Vitis Encias Colutorio; Vitis Encias Pasta; Vitis Orthodontic Colutorio; ***Cz.***: Calgel; Neoseptolete Duo; Panlid†; ***Fin.***: Bafucin; ***Fr.***: Alodont; Codotussyl Maux de Gorge; Gum HaliControl; Gum HaliControl; Lysopaine; Parogencyl prevention gencives†; ***Ger.***: Dobendan Dolo; Frubienzym†; Tyrosur; Wick Sulagil; ***Gr.***: Bisoral; Rikospray Silicone; ***Hong Kong***: Dentinox Teething Gel; Dettol†; Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Mouth Gel; Pharynx; ***Hung.***: Mebucain; Tyrosur; ***India***: Garlin; Kofarest; ***Indon.***: Sentril†; ***Irl.***: Anbesol; Merocaine; Merocets Plus; Rinstead; Vicks Original Cough Syrup Chesty; ***Israel***: Cepadont†; Kank-A; ***Ital.***: Delta 80 Plus; Delta 80; Ginvapast; Gola Action; Neo-Stomygen; Neo-Stomygen; Oral-B Collutorio Denti Gengive; Ridiodent; Rikospray; Stomygen; Tantum Orosan; ***Jpn***: Colgen Gargle†; ***Malaysia***: Cetylpyridinium B; Dentinox Teething Gel; Difflam Anti-inflammatory Lozenges (with Antibacterial); Difflam Anti-Inflammatory Lozenges (with cough suppressant); Difflam Mouth Gel; Orregel; Pharynx; ***Mex.***: Cepacaina; Mentalgina; Trociletas B; ***Neth.***: Agre-Gola†; ***Norw.***: Aselli†; ***NZ***: Cepacaine; Cepacol Anaesthetic†; Cepacol Cough Discs; Cepacol Sore Throat; Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Cough; Difflam Mouth Gel; Duro-Tuss Lozenges; ***Philipp.***: Difflam Orange; Kene; Xylorinse; ***Pol.***: Calgel; Lidodent; Orofar Max; Septolete Plus; Tetesept†; Undofen; ***Port.***: Dropcina; Mebocaina; ***Rus.***: Calgel (Калгель); Grammidin Neo (Граммидин Нео); Grammidin with Anesthetic Neo (Граммидин с АнестетикОм Нео); Novosept (Новосепт Форте); Septolete Plus (Септолете Плюс); ***S.Afr.***: Anbesol†; Andolex-C; Cepacaine; Cepacol Cough Discs; Cepacol Cough; Cetoxol†; Colphen†; Endcol Lozenges; Medi-Kain; Medi-Keel A; Medi-Keel A; Prodol†; Vagarsol; Vicks Acta Plus†; Vicks Cough Syrup†; ***Singapore***: Dentinox Teething Gel; Difflam Anti-inflammatory Anti-Bacterial Lozenges; Difflam Cough Lozenges; Difflam Mouth Gel; Duro-Tuss Cough Lozenges; Pharynx; Soragel; ***Spain***: Alcohocel†; Babysiton†; Farmalcohol†; ***Swed.***: Bafucin; ***Switz.***: Angiben; Angina MCC; Anginazol; Angisan; Citropain nouvelle formule; Gem nouvelle formule contre le mal de gorge; Hextriletten†; Hextrimint†; Impuls†; Lidazon Actilong; Lidazon; Lysopaine N; Mebucaine; Neo-Angin; Otothricinol; Pastilles contre le mal de gorge†; Rotpunkt Apotheke nouvelle formule pastilles contre le mal de gorge†; Swidro nouvelle formule pastilles contre le mal de gorge†; Zurcher Bahnhof Apotheke pastilles contre le mal de gorge nouvelle formule†; ***Thai.***: Sentril†; Sore Mouth Gel†; ***Turk.***: Calgel; Garol; Nesgarin; Sorbeks; ***UAE***: B-Cool; New BCool; ***UK***: Adult Meltus for Chesty Coughs & Catarrh; Allens Dry Tickly Cough; Anbesol; Bonjela Junior; Calgel; Dentinox Teething Gel; Kilkof; Listermint with Fluoride; Macleans Mouthguard; Meltus Expectorant; Meltus Junior Expectorant; Merocaine; Merocets Plus; Rinstead; Woodwards Teething Gel; ***Ukr.***: Grammidin Neo (Граммидин Нео); Grammidin with Anaesthetic Neo (Граммидин С Анестетиком Нео); Septolete Plus (Септолете Плюс); ***USA***: Cepacol Maximum Strength Sore Throat†; Cylex; MouthKote O/R; Orajel Mouth Aid; Orasep; ***Venez.***: Borogin; Cepacol BE; Isospray; Lafarcaina; Solunovar Compuesto.

Pharmacopoeial Preparations

USP 36: Cetylpyridinium Chloride Lozenges; Cetylpyridinium Chloride Topical Solution.

Chlorhexidine *(BAN, rINN)*

Chlorhexidinum; Clorhexidina; Klooriheksidiini; Klorheksidin; Klorhexidin; Хлорексидин.

CAS — 55-56-1.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — R4KO0DY52L.

Chlorhexidine Acetate *(BANM, rINNM)*

Acetato de clorhexidina; Chlorheksidino diacetatas; Chlorhexidindiacetat; Chlorhexidin-diacetát; Chlorhexidine, Acétate de; Chlorhexidine Diacetate; Chlorhexidine, diacétate de; Chlorhexidini Acetas; Chlorhexidini Diacetas; Chloroheksydyny octan; Clorhexidina, acetato de; Klooriheksidiinidiasetaatti; Klorhexidindiacetat; Klórhexidin-diacetát; Хлоргексидина Ацетат.

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] diacetate.

$C_{22}H_{30}Cl_2N_{10},2C_2H_4O_2$=625.6

CAS — 56-95-1.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — 5908ZUF22Y.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Chlorhexidine Diacetate). A white or almost white, microcrystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycol.

USP 36: (Chlorhexidine Acetate). A white or almost white, microcrystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycerol. Protect from light.

Incompatibility. The incompatibilities of chlorhexidine salts are discussed under Chlorhexidine Hydrochloride, below.

Stability. The stability of chlorhexidine salts is discussed under Chlorhexidine Hydrochloride, p. 1744.1.

Chlorhexidine Gluconate *(BANM, USAN, rINNM)*

Chlorheksidino digliukonato tirpalas; Chlorhexidin-digluконát; Chlorhexidine Digluconate; Chlorhexidine, digluconate de; Chlorhexidine, Gluconate de; Chlorhexidini digluconas; Chlorhexidini Digluconatis Solutio; Chlorhexidini Gluconas; Chloroheksydyny diglukonianu roztwór; Clorhexidina, gluconato de; Gluconato de clorhexidina; Klooriheksidiinidiglukonaattiliuos; Klorheksidin Glukonat; Klorhexidindiglukonatlösning; Klórhexidin-diglükonát-oldat; Хлоргексидина Глюконат.

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] digluconate.

$C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$=897.8

CAS — 18472-51-0.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — MOR84MUD8E.

Pharmacopoeias. *Chin., Eur.* (see p. vii), *Jpn*, and *US* include a solution which contains 19 to 21% of chlorhexidine gluconate.

Ph. Eur. 8: (Chlorhexidine Digluconate Solution; Chlorhexidini Digluconatis Solutio; Chlorhexidine Gluconate Solution BP 2014). An aqueous solution which contains not less than 190g/litre and not more than 210g/litre of chlorhexidine gluconate. An almost colourless or pale-yellowish liquid. Miscible with water, with not more than 5 parts of alcohol, and with not more than 3 parts of acetone. A 5% v/v dilution in water has a pH of 5.5 to 7.0. Protect from light.

USP 36: (Chlorhexidine Gluconate Solution). An aqueous solution which contains not less than 19% and not more than 21% of chlorhexidine gluconate. An almost colourless or pale yellow, clear liquid. Miscible with water and with glacial acetic acid; miscible with five times its volume of dehydrated alcohol and with three times its volume of acetone; further addition of dehydrated alcohol or of acetone yields a white turbidity. A 5% v/v dilution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. The incompatibilities of chlorhexidine salts are discussed under Chlorhexidine Hydrochloride, below.

Stability. The stability of chlorhexidine salts is discussed under Chlorhexidine Hydrochloride, p. 1744.1.

Sterilisation. Dilutions of commercial concentrated solutions may be sterilised by autoclaving.

Chlorhexidine Hydrochloride

(BANM, USAN, rINNM)

AY-5312; Chlorheksidino dihidrochloridas; Chlorhexidindihydrochlorid; Chlorhexidindihydrochlorid; Chlorhexidine, Chlorhydrate de; Chlorhexidine, dichlorhydrate de; Chlorhexidine Dihydrochloride; Chlorhexidini Dihydrochloridum; Chlorhexidini Hydrochloridum; Clorhexidina, hidrocloruro de; Hidrocloruro de clorhexidina; Klooriheksidiinidihydrokloridi; Klorheksidin Hidroklorür; Klórhexidin-dihidroklorid; Klorhexidindihydroklorid; Хлоргексидина Гидрохлорид.

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] dihydrochloride.

$C_{22}H_{30}Cl_2N_{10},2HCl$=578.4

CAS — 3697-42-5.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — E64XL9U38K.

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn*, and *US.*

Ph. Eur. 8: (Chlorhexidine Dihydrochloride; Chlorhexidine Hydrochloride BP 2014). A white or almost white, crystalline powder. Sparingly soluble in water and in propylene glycol; very slightly soluble in alcohol.

USP 36: (Chlorhexidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in propylene glycol; very slightly soluble in alcohol. Protect from light.

Incompatibility. Chlorhexidine salts are incompatible with soaps and other anionic materials. Activity may be reduced in the presence of suspending agents such as alginates and tragacanth, insoluble powders such as kaolin, and insoluble compounds of calcium, magnesium, and zinc. Chlorhexidine acetate is incompatible with potassium iodide. At a concentration of 0.05%, chlorhexidine salts are incompatible with borates, bicarbonates, carbonates,

chlorides, citrates, nitrates, phosphates, and sulfates, forming salts of low solubility which may precipitate out of solution. At dilutions of 0.01% or more, these salts are generally soluble. Insoluble salts may form in hard water. Chlorhexidine salts are inactivated by cork.

References to incompatibilities of chlorhexidine with suspending agents and insoluble solids.[1-3]

1. McCarthy TJ. The influence of insoluble powders on preservatives in solution. *J Mond Pharm* 1969; **12:** 321–8.
2. Yousef RT, *et al*. Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
3. McCarthy TJ, Myburgh JA. The effect of tragacanth gel on preservative activity. *Pharm Weekbl* 1974; **109:** 265–8.

Stability. Chlorhexidine and its salts are stable at normal storage temperatures but when heated may decompose with the production of trace amounts of 4-chloroaniline. Chlorhexidine hydrochloride is less readily decomposed than chlorhexidine acetate and may be heated at 150 degrees for 1 hour without appreciable production of 4-chloroaniline. Aqueous solutions of chlorhexidine salts decompose with the formation of trace amounts of 4-chloroaniline. This decomposition is increased by heating and alkaline pH.

Uses and Administration

Chlorhexidine is a bisbiguanide antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of Gram-positive and Gram-negative bacteria. It is more effective against Gram-positive than Gram-negative bacteria, and some species of *Pseudomonas* and *Proteus* have low susceptibility. It is relatively ineffective against mycobacteria. Chlorhexidine inhibits some viruses and is active against some fungi. It is inactive against bacterial spores at room temperature. Chlorhexidine is most active at a neutral or slightly acid pH. Combinations of chlorhexidine with cetrimide (p. 1742.1) or in alcoholic solution are used to enhance efficacy.

Chlorhexidine is formulated as lotions, washes, and creams for disinfection and cleansing of skin and wounds (p. 1690.1), and as oral gels, sprays, and mouthwashes for mouth infections including candidiasis and to reduce dental plaque accumulation. It has also been used with neomycin to eliminate nasal carriage of staphylococci (p. 208.2) and for disinfection of some contact lenses (but see Precautions, p. 1745.3). It has been suggested for use with propamidine isetionate for the treatment of Acanthamoeba keratitis and in spermicides to prevent transmission of HIV infection (see HIV Infection Prophylaxis, p. 959.1).

For pre-operative skin disinfection and hand-washing, chlorhexidine is used as a 0.5% solution of the acetate or gluconate in alcohol (70%) or as a 2 or 4% detergent solution of the gluconate. For disinfection of wounds, burns, or other skin damage or disorders chlorhexidine is used as a 0.05% aqueous solution of the acetate or gluconate, as a tulle dressing impregnated with chlorhexidine acetate 0.5%, or as a cream or powder containing chlorhexidine acetate or gluconate 1%. Preparations containing chlorhexidine acetate or gluconate 0.015% and cetrimide 0.15% are also used for cleansing and disinfection of skin and wounds. In obstetrics, chlorhexidine gluconate is used as a 0.05% aqueous solution or a 1% cream. The cream is also used as a barrier against bacterial hand infection.

Chlorhexidine gluconate is used in a 1% dental gel, 0.2% oral spray, and 0.1 to 0.2% mouthwash for the prevention of plaque and the prevention and treatment of gingivitis and in the treatment of oral candidiasis. A slow-release formulation containing 2.5 mg of chlorhexidine gluconate for insertion into periodontal pockets is also available.

A 0.02% solution may be used as a bladder irrigation in some urinary-tract infections. A gel containing 0.25% chlorhexidine gluconate solution and lidocaine hydrochloride has been used in catheterisation and cystoscopy.

For the emergency disinfection of clean instruments, a 2-minute immersion in chlorhexidine acetate or gluconate 0.5% in alcohol (70%) is used; for the storage and disinfection of clean instruments a 30-minute immersion in a 0.05% aqueous solution containing 0.1% sodium nitrite to inhibit metal corrosion is used.

As an antimicrobial preservative, chlorhexidine is used at a concentration of 0.01% of the acetate or gluconate in eye drops. Solutions containing 0.002 to 0.006% of chlorhexidine gluconate have also been used for disinfection of hydrophilic contact lenses.

Acanthamoeba infections. As discussed on p. 919.3, the optimal antiamoebic therapy for *Acanthamoeba* keratitis has yet to be determined. Propamidine isetionate is commonly used, usually in combinations including a biguanide. A multicentre study[1] evaluated the efficacy of a combination of topical chlorhexidine 0.02% and propamidine 0.1% in 12 contact lens-wearing patients with confirmed *Acanthamoeba* keratitis. Patients were treated for between 2 to 6 months and resolution of signs occurred gradually over 5 to 28 weeks (mean 11 weeks). Resolution of symptoms occurred within 1 to 7 weeks (mean 3 weeks); patients noted a reduction of pain, photophobia and lid oedema after 3 weeks of treatment. No drug toxicity was noted in any of the patients. However, concern has been expressed over the possible toxicity of chlorhexidine at this concentration on the cornea (see Adverse Effects and Treatment, p. 1745.1).

Chlorhexidine is also an effective disinfectant against *Acanthamoeba* cysts and most bacteria found in contact lens storage cases.[2]

Chlorhexidine has also been used to treat skin lesions associated with disseminated *Acanthamoeba* infection[3] as an adjunct to systemic therapy (see p. 920.1).

1. Seal D, *et al*. Successful medical therapy of Acanthamoeba keratitis with topical chlorhexidine and propamidine. *Eye* 1996; **10:** 413–21.
2. Seal DV. Acanthamoeba keratitis. *BMJ* 1994; **308:** 1116–17.
3. Slater CA, *et al*. Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; **331:** 85–7.

Contraception. Bisbiguanides of the chlorhexidine type are reported to have the ability to diffuse into cervical mucus and render it impenetrable to sperm at concentrations as low as 1 mg/mL.[1] Higher concentrations of chlorhexidine structurally modify the mucus, producing a barrier to both the entry of sperm and chlorhexidine. The potency[1] of chlorhexidine in inhibiting sperm motility *in vitro* is identical to that of nonoxinol 9, but unlike spermicides containing nonoxinol 9, which tend to trickle out, the clearance of chlorhexidine from the vagina is delayed.[2] Chlorhexidine also has potential for reducing transmission of HIV infection as it does not disrupt the vaginal epithelium and has activity *in vitro* against the HIV virus in low concentrations.[2]

For a review of contraception, including the view that spermicides are not a particularly effective method unless used with other means of contraception, see p. 2232.3.

1. Pearson RM. Update on vaginal spermicides. *Pharm J* 1985; **234:** 686–7.
2. Anonymous. Multipurpose spermicides. *Lancet* 1992; **340:** 211–13.

Disinfection. Viable bacterial counts on the hands were reduced by a mean of 97.9% by the application of chlorhexidine gluconate 0.5% in alcohol 95%.[1] The reduction was not so substantial with a 0.5% chlorhexidine aqueous solution (65.1% reduction in bacterial count) or a 4% detergent solution (86.7%). Hand disinfection with chlorhexidine gluconate 4% appeared to be more effective than the use of isopropyl alcohol 60% and soap in preventing nosocomial infections in a study conducted in intensive care units but this may have been partly due to better compliance with hand-washing instructions when using chlorhexidine.[2] In another study,[3] pre-operative total body bathing with a 4% detergent did not decrease the risk of wound infection in patients compared with bathing in detergent alone.

Chlorhexidine 1% nasal cream failed to control an epidemic of meticillin-resistant *Staphylococcus aureus* in a neurosurgical ward[4] and handwashing with chlorhexidine soap failed to control an outbreak of infection with *Staph. aureus* resistant to meticillin and gentamicin in a neonatal intensive care unit.[5] The organisms were subsequently eradicated by the use of nasal mupirocin and hexachlorophene handwashing, respectively.

1. Lowbury EJL, *et al*. Preoperative disinfection of surgeons' hands: use of alcoholic solutions and effects of gloves on skin flora. *BMJ* 1974; **4:** 369–72.
2. Doebbeling BN, *et al*. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *N Engl J Med* 1992; **327:** 88–93.
3. The European Working Party on Control of Hospital Infections. A comparison of the effects of preoperative whole-body bathing with detergent alone and with detergent containing chlorhexidine gluconate on the frequency of wound infections after clean surgery. *J Hosp Infect* 1988; **11:** 310–20.
4. Duckworth G. New method for typing Staphylococcus aureus resistant to methicillin. *BMJ* 1986; **293:** 885.
5. Reboli AC, *et al*. Epidemic methicillin-gentamicin-resistant Staphylococcus aureus in a neonatal intensive care unit. *Am J Dis Child* 1989; **143:** 34–9.

INJECTION SITE AND CATHETER CARE. See p. 1732.1.

Endocarditis. Some guidelines[1] have recommended chlorhexidine mouthwash 0.2%, held in the mouth for 1 minute, as an adjunct to antimicrobials for the prophylaxis of endocarditis in at-risk patients undergoing dental procedures; however, subsequent guidelines[2,3] consider topical antiseptic rinses to be ineffective for such use and recommend that they should not be used. The protective cover required for such patients is discussed on p. 179.2.

1. Gould FK, *et al*. Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2006; **57:** 1035–42. Also available at: http://jac.oxfordjournals.org/cgi/reprint/dkl121v1.pdf (accessed 23/06/10)
2. Wilson W, *et al*. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116:** 1736–54. Also available at: http://circ.ahajournals.org/cgi/reprint/116/15/1736.pdf (accessed 23/06/10)
3. NICE. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (issued March 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG64NICEguidance.pdf (accessed 23/06/10)

Mouth disorders. Chlorhexidine mouthwashes, sprays, and gels are used to prevent accumulation of dental plaque (see Mouth Infections, p. 192.3). Early studies[1-4] generally showed chlorhexidine mouthwash 0.1 to 0.2% used 2 or 3 times daily to be effective in reducing plaque accumulation and gingivitis and provided limited evidence of efficacy in preventing caries in permanent teeth of children and adolescents. A retrospective review[5] of 22 controlled studies of chlorhexidine for caries prevention, found the evidence inconclusive in schoolchildren and adolescents with active caries and regular fluoride exposure; there was also no good evidence that it arrested root caries in patients with dry mouth and in frail elderly subjects. However, chlorhexidine varnishes showed a preventative effect for fissure caries compared with no treatment in children with low fluoride exposure. Other studies have shown that chlorhexidine reduces gingivitis by 60 to 90% but its use is limited by its unpleasant taste and staining properties; special circumstances in which chlorhexidine is helpful include management of acute gingivitis, control of periodontal involvement in immunocompromised patients, and promotion of healing after periodontal treatment.[6]

Chlorhexidine gluconate may be useful in controlling secondary bacterial infections of aphthous ulcers (see Mouth Ulceration, p. 1811.2). Local application of chlorhexidine has been reported to reduce the incidence[7] and duration and severity[8] of recurrent ulcers, although one study showed no benefit compared with placebo.[9] However, a retrospective review[10] of 7 studies comparing chlorhexidine with placebo or no treatment found no evidence that chlorhexidine prevents oral mucositis in patients receiving cancer treatment.

Chlorhexidine may be a useful adjunct to antifungal treatment of oral candidiasis[11] (p. 564.1).

For the need for a delay when using chlorhexidine with other oral hygiene preparations, see under Precautions, p. 1745.3.

1. Flötra L, *et al*. A 4-month study on the effect of chlorhexidine mouth washes on 50 soldiers. *Scand J Dent Res* 1972; **80:** 10–17.
2. O'Neil TCA, Figures KH. The effects of chlorhexidine and mechanical methods of plaque control on the recurrence of gingival hyperplasia in young patients taking phenytoin. *Br Dent J* 1982; **152:** 130–3.
3. de la Rosa M, *et al*. The use of chlorhexidine in the management of gingivitis in children. *J Periodontol* 1988; **59:** 387–9.
4. O'Neil TCA. The use of chlorhexidine mouthwash in the control of gingival inflammation. *Br Dent J* 1976; **141:** 276–80.
5. Twetman S. Antimicrobials in future caries control: a review with special reference to chlorhexidine treatment. *Caries Res* 2004; **38:** 223–9.
6. Greene JC, *et al*. Preventive dentistry II: periodontal diseases, malocclusion, trauma, and oral cancer. *JAMA* 1990; **263:** 421–5.
7. Hunter L, Addy M. Chlorhexidine gluconate mouthwash in the management of minor aphthous ulceration. *Br Dent J* 1987; **162:** 106–10.
8. Addy M, *et al*. Management of recurrent aphthous ulceration: a trial of chlorhexidine gluconate gel. *Br Dent J* 1976; **141:** 118–20.
9. Matthews RW, *et al*. Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; **63:** 189–91.
10. Worthington HV, *et al*. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/08/08).
11. WHO. *WHO model prescribing information: drugs used in skin diseases.* Geneva: WHO, 1997.

Obstetric use. Disinfection of the birth canal with chlorhexidine gluconate 0.05 to 0.4% during labour has been investigated as a method for reducing mother-to-child transmission of infections, including early-onset group B streptococcal infection and HIV.[1-6] Studies have shown that it has not reduced perinatal transmission of HIV except when membranes were ruptured for more than 4 hours before delivery[1] or if used before the membranes rupture and at higher concentrations.[4] A systematic review of 5 studies[5] to determine the efficacy of chlorhexidine vaginal disinfection for preventing early-onset group B streptococcal infection concluded that, although there was a statistically significant reduction in colonisation there was no significant reduction in early-onset infection, morbidity or mortality. Comparable results have been reported with the use of chlorhexidine gluconate 1% obstetric cream at each examination during labour.[3] Similarly, a large randomised controlled study assessing intrapartum and neonatal use of chlorhexidine 0.5%, concluded there was no effect on neonatal sepsis,[7] although it has been argued that this simple intervention should not be abandoned.[8]

A systematic review of 3 studies[6] to determine the efficacy of chlorhexidine vaginal disinfection for preventing perinatal transmission of infections other than group B streptococcal infection and HIV found no evidence to support its use. However, a study[2] conducted in Malawi

reported a reduction in neonatal morbidity and mortality from other neonatal infections.

1. Biggar RJ, *et al.* Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. *Lancet* 1996; **347:** 1647–50.
2. Taha TE, *et al.* Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. *BMJ* 1997; **315:** 216–20.
3. Lindemann R, *et al.* Vaginal chlorhexidine disinfection during labour. *Lancet* 1992; **340:** 792.
4. Gaillard P, *et al.* Vaginal lavage with chlorhexidine during labour to reduce mother-to-child HIV transmission: clinical trial in Mombasa, Kenya. *AIDS* 2001; **15:** 389–96.
5. Stade B, *et al.* Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 06/04/10).
6. Lumbiganon P, *et al.* Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding group B streptococcal and HIV). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 06/04/10).
7. Cutland CL, *et al.* PoPS Trial Team. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial. *Lancet* 2009; **374:** 1909–16.
8. Mullany LC, Biggar RJ. Vaginal and neonatal skin cleansing with chlorhexidine. *Lancet* 2009; **374:** 1873–5.

Urinary catheter-related infection. Chlorhexidine solutions have been used in the management of catheter-related bladder infections and for urinary catheter maintenance. Twice-daily bladder irrigation with chlorhexidine acetate 0.02% did not produce a reduction in urinary bacterial counts in geriatric patients with indwelling catheters, and there was a tendency for overgrowth of *Proteus* spp. in patients given chlorhexidine.[1] In patients undergoing prostatectomy, intermittent pre-operative bladder irrigation with chlorhexidine gluconate 0.05% reduced the incidence of bacteraemia and severe wound infection, although urinary infections were eradicated in only 3 of the 13 patients treated.[2]

Addition of chlorhexidine to catheter drainage bags was not shown to reduce the frequency of urinary infections,[3] but infection rates were reduced by combining this technique with the use of a catheter lubricant containing chlorhexidine, disinfection of the urethral meatus, and aseptic nursing procedures.[4] The use of lubricating gel containing chlorhexidine did not reduce the risk of urinary-tract infections associated with short-term catheterisation,[5] and in general external disinfection of the periurethral area alone does not seem to be of benefit in reducing the rate of catheter-related bacteriuria.[6,7]

The treatment of urinary-tract infections is discussed on p. 213.1.

1. Davies AJ, *et al.* Does instillation of chlorhexidine into the bladder of catheterized geriatric patients help reduce bacteriuria? *J Hosp Infect* 1987; **9:** 72–5.
2. Adesanya AA, *et al.* The use of intermittent chlorhexidine bladder irrigation in the prevention of post-prostatectomy infective complications. *Int Urol Nephrol* 1993; **25:** 359–67.
3. Gillespie WA, *et al.* Does the addition of disinfectant to urine drainage bags prevent infection in catheterised patients? *Lancet* 1983; **i:** 1037–9.
4. Southampton Infection Control Team. Evaluation of aseptic techniques and chlorhexidine on the rate of catheter-associated urinary-tract infection. *Lancet* 1982; **i:** 89–91.
5. Schiøtz HA. Antiseptic catheter gel and urinary tract infection after short-term postoperative catheterization in women. *Arch Gynecol Obstet* 1996; **258:** 97–100.
6. Webster J, *et al.* Water or antiseptic for periurethral cleaning before urinary catheterization: a randomized controlled trial. *Am J Infect Control* 2001; **29:** 389–94.
7. Koskeroglu N, *et al.* The role of meatal disinfection in preventing catheter-related bacteriuria in an intensive care unit: a pilot study in Turkey. *J Hosp Infect* 2004; **56:** 236–8.

Adverse Effects and Treatment

Skin sensitivity to chlorhexidine has occasionally been reported. Severe hypersensitivity reactions, including anaphylactic shock, have been reported rarely after topical use of chlorhexidine. Strong solutions may cause irritation of the conjunctiva and mucous membranes. The use of chlorhexidine dental gel and mouthwash has been associated with reversible discoloration of the tongue, teeth, and silicate or composite dental restorations. Transient taste disturbances and a burning sensation of the tongue may occur on initial use. Oral desquamation and occasional parotid gland swelling have been reported with the mouthwash. If desquamation occurs, 50% dilution of the mouthwash with water and less vigorous rinsing may allow continued use.

The main consequence of ingestion is mucosal irritation and systemic toxicity is rare due to minimal absorption from the gastrointestinal tract (see Poisoning, below). Haemolysis has been reported after accidental intravenous administration. Gastric lavage with demulcents has been suggested in some licensed product information for treatment of acute ingestion; however, other authorities recommend that the stomach should not be emptied as this may increase the risk of mucosal irritation. Small volumes of milk or water to drink may be warranted.

Effects on the eyes. Corneal damage was reported in 4 patients after use of chlorhexidine gluconate for pre-operative preparation of facial skin.[1] Severe corneal endothelium damage occurred in a further 3 patients[2] when chlorhexidine was inadvertently used as an intraocular irrigating solution and 2 of the patients subsequently required penetrating keratoplasty. Other adverse effects included pronounced iris atrophy, anterior chamber flattening, and a retrocorneal membrane; one patient developed raised intra-ocular pressure. In another case progressive ulcerative keratitis and almost total loss of the corneal epithelium was reported[3] after use of chlorhexidine gluconate 0.02% and propamidine 0.1% eye drops for 8 weeks for *Acanthamoeba* keratitis. In 2 patients[4] treated similarly for 4 to 6 months, deep marginal ulceration of the cornea developed, in each case requiring a penetrating graft; a mature cataract and an atrophic iris were seen in each patient after removal of the cornea. Due to the similarity of both cases, it was suggested that these complications were caused by the drugs rather than by amoeba-induced inflammation.

1. Tabor E, *et al.* Corneal damage due to eye contact with chlorhexidine gluconate. *JAMA* 1989; **261:** 557–8.
2. Anders N, Wollensak J. Inadvertent use of chlorhexidine instead of balanced salt solution for intraocular irrigation. *J Cataract Refract Surg* 1997; **23:** 959–62.
3. Murthy S, *et al.* Progressive ulcerative keratitis related to the use of topical chlorhexidine gluconate (0.02%). *Cornea* 2002; **21:** 237–9.
4. Ehlers N, Hjortdal J. Are cataract and iris atrophy toxic complications of medical treatment of acanthamoeba keratitis? *Acta Ophthalmol Scand* 2004; **82:** 228–31.

Effects on the nose. Temporary hyposmia (reduced sense of smell) in some patients after transsphenoidal pituitary adenoma operation was assumed to be caused by pre-operative disinfection of the nasal cavity with chlorhexidine gluconate solution.[1]

1. Yamagishi M, *et al.* Impairment of olfactory epithelium treated with chlorhexidine digluconate (Hibitane). *Pract Otol* 1985; **78:** 399–409.

Hypersensitivity. Both immediate and delayed hypersensitivity reactions have been reported after topical use of chlorhexidine[1] and from the use of chlorhexidine-containing urethral lubricants.[2] However, the incidence is low given the frequent use of chlorhexidine. Delayed hypersensitivity reactions such as contact dermatitis, fixed drug eruptions, and photosensitivity reactions are more common than immediate hypersensitivity reactions (acute urticaria, angioedema, and bronchospasm which may progress to anaphylactic shock).[1,3]

Immediate hypersensitivity reactions have also occurred with surgical disinfection. Signs appear 15 to 45 minutes after the start of surgery and include hypotension, urticaria, tachycardia, bronchospasm, and sometimes anaphylactic shock, cardiovascular collapse, or cardiac arrest.[3,4] In 1998 the FDA issued a public notice[5] warning of potential hypersensitivity reactions to chlorhexidine-impregnated intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh, based on reports of adverse events that had occurred in the USA and other countries.

Occupational asthma has been attributed to an alcoholic chlorhexidine spray.[6]

1. Krautheim AB, *et al.* Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis* 2004; **50:** 113–16.
2. Jayathillake A, *et al.* Allergy to chlorhexidine gluconate in urethral gel: report of four cases and review of the literature. *Urology* 2003; **61:** 837iv–837vi.
3. Beaudouin E, *et al.* Immediate hypersensitivity to chlorhexidine: literature review. *Allerg Immunol (Paris)* 2004; **36:** 123–6.
4. Chisholm DG, *et al.* Intranasal chlorhexidine resulting in an anaphylactic circulatory arrest. *BMJ* 1997; **315:** 785.
5. FDA. FDA Public Health notice potential hypersensitivity reactions to chlorhexidine-impregnated medical devices (issued 11th March, 1998). Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062306 (accessed 11/05/10)
6. Waclawski ER, *et al.* Occupational asthma in nurses caused by chlorhexidine and alcohol aerosols. *BMJ* 1989; **298:** 929–30.

Poisoning. Reports of adverse effects after ***ingestion*** of chlorhexidine salts include a neonate who developed multiple episodes of cyanosis and bradycardia;[1] the infant's mother had sprayed chlorhexidine onto her breasts to prevent mastitis. In contrast an 89-year-old woman only had mild giddiness, unusual laughter, and an increased appetite after mistakenly drinking 30 mL of a solution containing chlorhexidine gluconate 4% and isopropyl alcohol 4%.[2] A review[3] of 7 adult cases of deliberate ingestion of a commercially available mixture of cetrimide 3% and chlorhexidine gluconate 0.3%, concluded that symptoms were generally mild and included nausea, vomiting, sore throat, and abdominal pain. There has also been a report of a patient who developed gastritis after ingesting a pre-operative skin preparation containing chlorhexidine gluconate 4% when using it as a mouthwash.[4]

Another person had much more serious effects after drinking about 150 mL of chlorhexidine gluconate solution, corresponding to about 30 g of the pure substance.[5] Besides pharyngeal oedema and necrotic oesophageal lesions, the patient had aminotransferase concentrations that rose to 30 times normal 5 days after ingestion and were still 8 times normal one week later. After one month the serum aspartate aminotransferase was returning to normal while the serum alanine aminotransferase was still 3 times normal. Six months after ingestion the aminotransferase levels were normal. A liver biopsy performed soon after the peak in aminotransferase levels showed diffuse fatty degeneration and lobular hepatitis suggesting that chlorhexidine was absorbed from the gastrointestinal tract in a concentration high enough to produce liver necrosis. An 80-year-old woman had spontaneous vomiting and aspiration followed by acute respiratory distress syndrome within 5 hours of accidental ingestion of 200 mL of a chlorhexidine gluconate 5% solution.[6] Despite supportive treatment, the patient's condition continued to deteriorate and she developed shock and metabolic acidosis and died from cardiac arrest 12 hours after ingestion.

Accidental ***intravenous*** administration of 4 mL of a 20% chlorhexidine gluconate solution in a 67-year-old man undergoing a colectomy resulted in the sudden development of acute respiratory distress syndrome.[7] Respiratory failure progressed despite plasma exchange therapy over 3 consecutive days. Veno-arterial extracorporeal membrane oxygenation was started on the third day and after 72 hours improvement was noted and the patient subsequently recovered completely.

1. Quinn MW, Bini RM. Bradycardia associated with chlorhexidine spray. *Arch Dis Child* 1989; **64:** 892–3.
2. Emerson D, Pierce C. A case of a single ingestion of 4% Hibiclens. *Vet Hum Toxicol* 1988; **30:** 583.
3. Chan TYK. Poisoning due to Savlon (cetrimide) liquid. *Hum Exp Toxicol* 1994; **13:** 681–2.
4. Roche S, *et al.* Chlorhexidine-induced gastritis. *Postgrad Med J* 1991; **67:** 210–11.
5. Massano G, *et al.* Striking aminotransferase rise after chlorhexidine self-poisoning. *Lancet* 1982; **i:** 289.
6. Hirata K, Kurokawa A. Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome. *Vet Hum Toxicol* 2002; **44:** 89–91.
7. Ishigami S, *et al.* Intravenous chlorhexidine gluconate causing acute respiratory distress syndrome. *J Toxicol Clin Toxicol* 2001; **39:** 77–80.

Precautions

Since chlorhexidine is irritant it is recommended that it should not be used on the brain, meninges, middle ear, or other sensitive tissues. Contact with the eye should be avoided except for dilute solutions expressly for use in the eyes. Chlorhexidine may be adsorbed by some soft contact lenses and cause eye irritation, although it may be suitable for use with others (see Contact Lens Care, p. 1730.2). Syringes and needles that have been immersed in chlorhexidine solutions should be thoroughly rinsed with sterile water or saline before use.

Aqueous solutions of chlorhexidine salts may be susceptible to contamination with micro-organisms. To reduce this risk, a sterilised preparation should be used or, where necessary, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Aqueous solutions of chlorhexidine used for instrument storage should contain sodium nitrite 0.1% to inhibit metal corrosion, and should be changed every 7 days. Commercial 5% concentrate contains a nonionic surfactant to prevent precipitation on dilution with hard water and is not suitable for use in body cavities or for disinfection of instruments containing cemented glass components; dilutions of the 20% concentrate should be used for this purpose.

Contamination. *Ralstonia pickettii* (*Burkholderia pickettii*; *Pseudomonas pickettii*) septicaemia developed in 6 patients after the use of aqueous chlorhexidine 0.05%, prepared with contaminated twice-distilled water, for skin disinfection before venepuncture and it was considered that unsterilised 0.05% solutions should not be used for such skin preparation.[1] Positive blood cultures of *Burkholderia cepacia* (*Pseudomonas cepacia*) were found in 2 patients after inappropriate use of a chlorhexidine handwash for the same purpose.[2] Further studies showed that the handwash supported pseudomonal growth only when diluted.[3]

1. Kahan A, *et al.* Is chlorhexidine an essential drug? *Lancet* 1984; **ii:** 759–60.
2. Gosden PE, Norman P. Pseudobacteraemia associated with contaminated skin cleansing agent. *Lancet* 1985; **ii** 671–2.
3. Norman P, *et al.* Pseudobacteraemia associated with contaminated skin cleansing agent. *Lancet* 1986; **i:** 209.

Neonates. Haemorrhagic skin necrosis associated with umbilical artery catheterisation in a premature infant was attributed to damage by the alcohol from the use of chlorhexidine 0.5% in spirit 70% as a disinfectant.[1]

For reference to the percutaneous absorption of chlorhexidine after topical use in neonates and infants, see under Pharmacokinetics, p. 1746.1.

1. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982; **57:** 477–9.

Oral hygiene. Toothpastes may contain anionic surfactants such as sodium laurilsulfate, which are incompatible with chlorhexidine. In order that the antiplaque effect of

chlorhexidine is not reduced, it has been recommended that at least 30 minutes should be allowed to elapse between teeth brushing and rinsing with oral chlorhexidine preparations.[1]

1. Barkvoll P, *et al.* Interaction between chlorhexidine digluconate and sodium lauryl sulfate in vivo. *J Clin Periodontol* 1989; **16:** 593–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorhexidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Washing precautions. Fabrics that have been in contact with chlorhexidine solution may develop a brown stain if bleached with a hypochlorite. A peroxide bleach may be used instead.

Pharmacokinetics

Chlorhexidine is poorly absorbed from the gastrointestinal tract and skin.

Neonates. Occasional reports of the percutaneous absorption of chlorhexidine in neonates and infants include a study in which chlorhexidine was detected in low concentrations in the venous blood of 5 of 24 infants after washing them with a preparation containing chlorhexidine gluconate 4% (*Hibiscrub*); no adverse effects were noted.[1] Low concentrations have been found[2] in the venous blood of neonates after the topical use of a powder containing chlorhexidine 1%. Percutaneous absorption of chlorhexidine was reported in preterm neonates (but not full-term infants) treated with chlorhexidine 1% in alcohol for neonatal cord care; no such absorption occurred when a dusting powder containing chlorhexidine 1% and zinc oxide 3% was used.[3]

1. Cowen J, *et al.* Absorption of chlorhexidine from the intact skin of newborn infants. *Arch Dis Child* 1979; **54:** 379–83.
2. Alder VG, *et al.* Comparison of hexachlorophane and chlorhexidine powders in prevention of neonatal infection. *Arch Dis Child* 1980; **55:** 277–80.
3. Aggett PJ, *et al.* Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Child* 1981; **56:** 878–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acipoun; Antiminth; Biguanex; Bucogel; Elugel; Finaplac†; Hexidin†; Hexil-P; Hexil†; Hibiscott; Hibiscrub; Laclorhex; Periodil; Pervinox Clorhexidina; Pervinox Incoloro; Plac Out; ***Austral.***: Bactigras; Catheter Preparation†; Microshield; Periogard Chlorohex†; Plaqacide; Savacol Mouth and Throat Rinse; ***Austria***: Chlorhexamed; ***Belg.***: Astrexine; Baxil; Cedium Chlorhexidine; Cedixidin; Corsodyl; Golaseptine; Hansamedic†; Hibidil; Hibiguard†; Hibiscrub; Hibitane; Hibitane; Medisepta; Medixidin; Mefren; Mefren; Pixidin; Sterilon†; Uro-Tainer; ***Braz.***: Asseptcare; Asseptic; Hibitane; Marclorhex; Merthioclean; Noplak†; ***Canad.***: Antiseptic Cleanser; Antiseptic First Aid; Antiseptic Skin Cleanser; Bactigras†; Baxedin; Bioson; Biovac; Chlorhexseptic; Clean Derm; Endure Cida; Endure Scrub; First Aid Antiseptic Skin Cleanser; Germi Stat; Hibidil†; Hibitane; Oro-Clense; Oronine H†; Perichlor; Peridex; Periogard; Prevora 1; Provon Antiseptic; Soft Care CHG Antimicrobial; Solu-IV CHG; Solunet C; Solunet Mousse; Soluprep; Spectro Gram†; Stanhexidine; Sterixin; Tegaderm CHG; Vap; ***Chile***: AB; Bucoseptil; Dentilim; Elugel; Freshmel; Garonsept†; Graneodin; Oralgene; Ortoxine; Perio-Aid; Periokin†; ***China***: Jiu Tai (九泰); Kou Tai (口泰); Ya Nuo (雅诺); ***Cz.***: Corsodyl; Septofort; ***Denm.***: Hibitane; Periochip; ***Fin.***: Corsodyl; Klorhexol; Meridol Perio CHX; Periochip; Travahex; ***Fr.***: Baseal; Biorgasept; Cetavlex; Collunovar; Corsodyl; Dermachrome†; Diaseptyl; Dosiseptine; Elgydium; Elugel; Euraxsepti; Exoseptoplix; Hibidil; Hibiscrub; Hibisprint†; Hibitane; Paroex; Plurexid†; Prexidine; Septeal; Septidose; Septivon; Septivoncare; ***Ger.***: Bactigras; Cathejell S†; Chlorhexamed; Cidegol C; Dynexan Proaktiv; Endosgel; Lemocin CX†; Meridol med CHX; ***Gr.***: Hibitane; Lifo-Scrub; Periochip; Periogard; Plak Out; Spitaderm; ***Hong Kong***: Bacidin†; Corsodyl; Hexidine†; Hexisol†; Hydrex; Qualikin; Scanlin; Vick-Hexidine†; ***Hung.***: Septofort; ***India***: A'Fresh; Afresho; Arofil; C-Nate; Clohex; CMW; Coglu; Dencure; Dentrosym; Evergaurd; Freshex; Glihex; Hexabir; Hexatrin; Hexide; Hexidine; Hexigel; Hexiprep; Hygeen; Indent; Inhex; M-Rinse; Maghex-M; Microshield; Mouden; Nitra-Hex; Nusept; O2-Fresh; Orahex; Orbiz; Orinse; Orofact; Osihex; ***Indon.***: Mediscrub†; ***Irl.***: Cepton Medicated; Corsodyl; Hibiscrub; Hibitane; Hydrex; Periochip; Prevora Stage 1; Savlon Antiseptic Wound Wash; Sterets Unisept; ***Israel***: Bactoscrub†; Bactosept†; Cleardent; Corsodyl; GynaHex; Hexatate†; KxG; Medident; Periochip; Pharma-Dentix†; Septadine Scrub; Septal; Septalone; Septol; Tarodent; Xylodent†; ***Ital.***: Benodent CLX; Broxodin; Clarifex; Clomirex†; Clorexifarm; Clorosan; Corsodyl; Dempol; Dentosan Parodontale; Eburos; Ekuba; Esoform Mani-Cute; Esosan Gel Mani; Golasan; Iodosan Clorexidina; Lenil; Master-Aid; Neo-Destomygen; Neomercurocromo; Neoxene; Neoxinal; Parodontax; Periochip; Periogard Chlorohex; Plak Out; Plak; Sicura3; Triseptil†; ***Malaysia***: Baby Shield Plus; Bactigras; GynePro; Oradex; ***Mex.***: Perioxidin†; ***Neth.***: Corsodyl; Dettol Sterilon; Hibiscrub; Hibitane†; Hydrex†; Irrisol; Lifo-Scrub; Periochip; Urogliss-S; ***Norw.***: Corsodyl; Hibiscrub; Hibitane; Periochip; ***NZ***: DP Hand Rub†; Hibitane†; Riotane†; ***Philipp.***: Bactigras; GynePro; Orahex; Para-Tulle; ***Pol.***: Corsodyl; Septofervex†; ***Port.***: Alospray; Bexident; Cloraldin†; Corsodyl; Dialens†; Handscrub; Hibitane; Lifo-Scrub†; Periochip; ***Rus.***: Amident (Амидент); Elgydium (Эльгидиум); Elugel (Элюгель); Hexicon (Гексикон); ***S.Afr.***: Bactigras; Corsodyl; D-Germ†; Hexidin†; Hibiscrub†; Hibitane; Orosept†; ***Singapore***: Baby Shield Plus; Chlorohex; Elgydium; EluDental†; Elugel; Hexoscrub; Obstetric Care; Periochip†; Pfizer Obstetric Lotion†; Trihexid; ***Spain***: Clorxil; Cristalcrom; Cristalmina; Curafil†; Cuvefilm; Deratin; Hibimax†; Hibiscrub; Menalmina; Normosept; Septisan†; ***Swed.***: Corsodyl; Descutan; Hexident; Hibiscrub; Hibitane; Periochip; ***Switz.***: Atoseptal; Chlorhexamed; Corsodyl; Dentohexin; DermaPlast Desinfect; Dosiseptine†; Elgydium; Hexamedal; Hibidil; Hibiscrub; Hibitane†; Lifo-Scrub; Meridol Perio; Periochip; Plak Out; ***Thai.***: B-Mouthwash; Bacard Antiseptic; Bactigras; C-20; Chlorhex; Hexene; Hexide; Hexidine; Hibiscrub†; Hibitane†; Hydrex; Obitane; OR; Q-Bac†; ***Turk.***: Cloder; Disinfecting†; Gargarex; Hibitanol; Klorheksol; Klorhex; Mediscrub; Oroheks; Superheks; ***UAE***: Zordyl; ***UK***: Acriflex; Bactigras; Cepton; Chlorohex; Corsodyl; Curasept; CX Powder; Eczmol; Elgydium; Hibiscrub; Hibitane; Hydrex; Periogard†; Savlon Antiseptic Wound Wash; Serotulle; Spotoway; Steripod Chlorhexidine Gluconate; Unisept; Uriflex C; ***Ukr.***: Hexicon (Гексикон); ***USA***: Betasept; Biopatch; Dyna-Hex; Exidine; Hibiclens†; Hibistat; Peridex; Periochip; Periogard; Surgilube; ***Venez.***: Peridont.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Chlorhexidine Gluconate Eye Drops; Chlorhexidine Gluconate Gel; Chlorhexidine Irrigation Solution; Chlorhexidine Mouthwash; Lidocaine and Chlorhexidine Gel;

USP 36: Chlorhexidine Gluconate Oral Rinse; Chlorhexidine Gluconate Topical Solution.

Chlorinated Lime

Desmanche; Bleaching Powder; Cal clorada; Calcaria Chlorata; Calcii Hypochloris; Calcium Hypochlorite; Calcium Hypochlorosum; Calx Chlorata; Calx Chlorinata; Chloride of Lime; Chlorkalk; Chlorure de Chaux; Cloruro de Cal; Хлорная Известь.

CAS — 7778-54-3.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2014: (Chlorinated Lime). A dull white powder with a characteristic odour, containing not less than 30.0% w/w of 'available chlorine'. It becomes moist and gradually decomposes on exposure to air, carbon dioxide being absorbed and chlorine evolved. Partly soluble in water and in alcohol.

Uses and Administration

Chlorinated lime is a disinfectant and antiseptic with the general properties of chlorine (below).

Its action is rapid but brief, the 'available chlorine' soon being exhausted by combination with organic material. It is used to disinfect faeces, urine, and other organic material, and as a cleansing agent for lavatories, drains, and effluents.

Chlorinated lime is used in the preparation of Surgical Chlorinated Soda Solution (BPC 1973) (Dakin's Solution) which has been employed as a wound disinfectant, and Chlorinated Lime and Boric Acid Solution (BP 1993), (Eusol), which has been used as a disinfectant lotion and wet dressing, sometimes with equal parts of liquid paraffin. However, such solutions are irritant when applied undiluted, and are no longer recommended for use in this way. In addition, there is some evidence that such chlorine-releasing solutions may delay wound healing (see Disinfection, Wounds under Uses and Administration of Sodium Hypochlorite, p. 1769.1).

Homoeopathy

Chlorinated lime has been used in homoeopathic medicines under the following names: Calcarea hypochlorata; Calc hypochlor.

Adverse Effects, Treatment, and Precautions

As for Sodium Hypochlorite, p. 1769.2.

Preparations

Pharmacopoeial Preparations

BPC 1973: Surgical Chlorinated Soda Solution.

Chlorine

925; Chlor; Chlore; Chlorium; Cloro; Klor; Хлор.

Cl_2=70.90

CAS — 7782-50-5.

UNII — 4R7X1O2820 (chlorine); Q32ZN48698 (chloride ion).

Description. Chlorine is a greenish-yellow gas with a suffocating odour; commonly available as a pressurised liquid.

Uses and Administration

Chlorine is a disinfectant with a rapid potent brief bactericidal action. It is capable of killing most bacteria, and some fungi, yeasts, algae, viruses, and protozoa. It is slowly active against spores.

It is used for the treatment of water (p. 1731.3), but for most other purposes it is used in the form of hypochlorites, organic and inorganic chloramines, chlorinated hydantoins, chlorinated isocyanurates, and similar oxidising compounds capable of releasing chlorine. In the presence of water these compounds produce hypochlorous acid (HOCl) and hypochlorite ion (OCl^-) and it is generally considered that the lethal action on micro-organisms is due to chlorination of cell protein or enzyme systems by nonionised hypochlorous acid, although the hypochlorite ion may also contribute.

The activity of most of the compounds decreases with increase of pH, the activity of solutions of pH 4 to 7 being greater than those of higher pH values. However, stability is usually greater at an alkaline pH.

The potency of chlorine disinfectants is expressed in terms of **available chlorine**. This is based on the concept of chlorine gas (Cl_2) as the reference substance. Two atoms of chlorine (2 X Cl) yield in water only one molecule of hypochlorous acid (on which activity is based), while hypochlorites and chloramines yield one molecule of hypochlorous acid for each atom of chlorine as shown in the following equations:

$$Cl_2 + H_2O \leftrightarrow HOCl + H^+ + Cl^-$$
$$NaOCl + H_2O \leftrightarrow HOCl + NaOH$$

Thus the assayed chlorine in such compounds has to be multiplied by 2 to produce 'available chlorine'. The term 'active chlorine' has been used confusingly for either 'available chlorine' (Cl_2) or 'combined chlorine' (Cl).

Because they have relatively low residual toxicity, chlorine compounds are useful for the disinfection of relatively clean impervious surfaces, such as babies' feeding bottles, baths, and food and dairy equipment. A concentration of 100 to 300 ppm of 'available chlorine' is used; a detergent may be added to ensure wetting of the surface. Solutions containing 1000 ppm 'available chlorine' are recommended for minor surface contamination and as part of general good hygiene practice. Solutions containing 10 000 ppm 'available chlorine' are used to disinfect surfaces contaminated with spilled blood or body fluids; this strength is effective against viruses including human immunodeficiency virus (HIV) and hepatitis B virus (p. 1731.2). A concentration providing 20 000 ppm 'available chlorine' is used for material from patients with Creutzfeldt-Jakob disease (p. 1730.3).

On a large scale, chlorine gas is used to disinfect public water supplies. On a smaller scale, the use of chlorine compounds is more convenient and sodium hypochlorite, tosylchloramide sodium, chlorinated lime, chlorine dioxide, or halazone are used. After satisfying the chlorine demand (the amount of chlorine needed to react with organic matter and other substances), a free-residual content of 0.2 to 0.4 ppm 'available chlorine' should be maintained, though more is required for alkaline waters with a pH of 9 or more. For the disinfection of potentially contaminated water a concentration of 1 ppm is recommended. Excessive residual chlorine may be removed by adding a little citric acid or sodium thiosulfate.

For use in small swimming pools, sodium or calcium hypochlorite may be added daily to maintain a free-residual 'available chlorine' concentration of 1 to 3 ppm. Tosylchloramide sodium, chlorinated lime, and the isocyanurates (see Troclosene, p. 1774.1) may also be used. To minimise irritation of the eyes, maintain disinfectant activity, prevent precipitation of salts, and prevent metal corrosion, a pH of 7.2 to 7.8 should be maintained.

Solutions of chlorine-releasing compounds are also used in wound desloughing and disinfection (but see Disinfection: Wounds, under Sodium Hypochlorite, p. 1769.1).

Adverse Effects and Treatment

Chlorine gas is irritant and corrosive producing inflammation, burns, and necrosis. Inhalation may result in coughing, choking, headache, dyspnoea, dizziness, expectoration of frothy white sputum (which may be blood stained), a burning chest pain, and nausea. Bronchospasm, laryngeal oedema, acute pulmonary oedema with cyanosis, and hypoxia may occur. There may be vomiting and development of acidosis. Death may result from hypoxia.

Some of the toxicity of chlorine may be due to its dissolution in tissue water to produce hydrochloric acid and hypochlorite. After exposure to chlorine, conjunctivitis may

require a topical anaesthetic and frequent irrigations of water or saline. Respiratory distress should be treated with inhalations of humidified oxygen and bronchodilators; mechanical ventilation may be required. Corticosteroids have been given in an attempt to minimise pulmonary damage but their benefit is unproven. Acidosis may require the intravenous use of sodium bicarbonate or other suitable alkalising agent.

Effects on the eyes. Eye examinations of 50 subjects immediately before and after swimming in a chlorinated pool (chlorine range 1.0 to 1.5 ppm) showed that 68% had symptoms of corneal oedema and 94% had corneal epithelial erosions. No subject had a measurable decrease in visual acuity.[1]

1. Haag JR, Gieser RG. Effects of swimming pool water on the cornea. *JAMA* 1983; **249:** 2507–8.

Effects on the respiratory tract. An assessment of 847 adolescents who attended indoor or outdoor chlorinated swimming pools, has suggested such exposure may contribute to the development of asthma, hay fever, and allergic rhinitis.[1]

1. Bernard A, *et al.* Impact of chlorinated swimming pool attendance on the respiratory health of adolescents. *Pediatrics* 2009; **124:** 1110–18.

Poisoning. Experience gained from 186 cases of acute chlorine exposure indicated that medical support was required for only a short time even when exposure was repeated;[1] late sequelae were not seen, even in patients with abnormal respiratory function tests or blood gases on admission. Thirteen children who were accidentally exposed to chlorine products and gas at a community swimming pool complained of eye and throat irritation, chest pain and tightness, shortness of breath, wheezing, and anxiety and 5 children with hypoxia required hospital admission. These children received humidified oxygen, salbutamol, and, in 4 patients, methylprednisolone, and all were discharged 1 to 2 days later.[2] Another report on 76 children with chlorine poisoning revealed that the longest period of hospitalisation was 12 hours after treatment with oxygen and corticosteroids.[3] A 14-year-old boy with a history of asthma exposed to chlorine gas developed acute respiratory distress syndrome and required intubation, ventilatory support, salbutamol, and corticosteroids. He was extubated after 19 days and recovered well.[4] There have been reports of deliberate inhalation of chlorine,[5,6] in one instance for pleasure,[5] leading to severe adverse effects. Some individuals may be unduly insensitive to chlorine-induced irritation and workers should be warned that concentrations of chlorine which can be tolerated for short periods without undue discomfort can still cause serious injury which may not be immediately apparent.[6]

Guidelines[7,8] have been issued for the management of chlorine exposure.

1. Barret L, Faure J. Chlorine poisoning. *Lancet* 1984; **i:** 561–2.
2. Sexton JD, Pronchik DJ. Chlorine inhalation: the big picture. *Clin Toxicol* 1998; **36:** 87–93.
3. Fleta J, *et al.* Intoxication of 76 children by chlorine gas. *Hum Toxicol* 1986; **5:** 99–100.
4. Traub SJ, *et al.* Case report and literature review of chlorine gas toxicity. *Vet Hum Toxicol* 2002; **44:** 235–9.
5. Rafferty P. Voluntary chlorine inhalation: a new form of self-abuse? *BMJ* 1980; **281:** 1178–9.
6. Dewhurst F. Voluntary chlorine inhalation. *BMJ* 1981; **282:** 565–6.
7. DoH. Chlorine: guidelines for action in the event of a deliberate release (issued February 2004). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947362398 (accessed 27/08/08)
8. Agency for Toxic Substances and Disease Registry. Medical management guidelines (MMGs) for chlorine (Cl_2). Available at: http://www.atsdr.cdc.gov/MHMI/mmg172.html (accessed 15/03/06)

Precautions

The antimicrobial activity of chlorine disinfectants is reduced by the presence of organic material and by increasing pH. Hypochlorite solutions may delay wound healing (see Disinfection: Wounds under Uses and Administration of Sodium Hypochlorite, p. 1769.1).

Chlorine Dioxide

926; Cloro, dióxido de; Диоксид Хлора.

ClO_2=67.45

CAS — 10049-04-4.

UNII — 8061YMS4RM.

Profile

Chlorine dioxide is a strong oxidising agent with the general properties of chlorine (p. 1746.2). It is rapidly active against vegetative bacteria, including mycobacteria, and viruses and is also sporicidal. It is used for disinfection of medical equipment either in gaseous form or in a solution that requires activation before use and yields 700 to 1100 ppm 'available chlorine' (see p. 1746.3). Chlorine dioxide is irritant to the skin, eyes, and respiratory tract and should be stored in sealed containers. It is potentially corrosive to many materials and solutions may contain corrosion inhibitors.

Chlorine dioxide is also used for treatment and disinfection of water supplies.

General references.

1. WHO. Chlorine dioxide (gas). *Concise International Chemical Assessment Document 37* Geneva: WHO, 2002. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad37.pdf (accessed 14/03/06)

Disinfection of endoscopes. Chlorine dioxide solutions are used as an alternative to glutaral for the disinfection of endoscopes (p. 1731.2).

Halitosis. Chlorine dioxide has been used in mouthwashes for the control of halitosis.[1]

1. Frascella J, *et al.* Odor reduction potential of a chlorine dioxide mouthrinse. *J Clin Dent* 1998; **9:** 39–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Retardex; ***Philipp.***: Oracare; ***UK***: Retardex.

Chloroacetamide

Chloracetamide; Cloroacetamida; Хлорацетамид.

2-Chloroacetamide.

C_2H_4ClNO=93.51

CAS — 79-07-2.

UNII — 2R97846T1L.

Profile

Chloroacetamide is a preservative that has been used in topical pharmaceutical preparations and cosmetics.

N-(3-Chloroallyl)hexaminium Chloride

N-(3-Cloroalil)hexaminio, cloruro de; Quaternium-15; Кватерниум-15.

1-(3-Chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride.

$C_9H_{16}Cl_2N_4$=251.2

CAS — 4080-31-3.

UNII — E40U03LEM0; 2W5B4VJ152 (trans-form).

Profile

N-(3-Chloroallyl)hexaminium chloride is an antimicrobial preservative used in pharmaceutical preparations and cosmetics. Skin reactions have been reported.

Chlorobutanol *(BAN, rINN)*

Acetone-Chloroforme; Alcohol Trichlorisobutylicus; Chlorbutanol; Chlorbutanolum; Chlorbutol; Chloretone; Chlorobutanolis; Chlorobutanolum; Clorobutanol; Klooributanoli; Klorbutanol; Klorobutanol; Trichlorbutanolum; Хлоробутанол.

1,1,1-Trichloro-2-methylpropan-2-ol.

$C_4H_7Cl_3O$=177.4

CAS — 57-15-8 (anhydrous chlorobutanol); 6001-64-5 (chlorobutanol hemihydrate).

ATC — A04AD04.

ATC Vet — QA04AD04.

UNII — HM4YQM8WRC (chlorobutanol); 3X4P6271OX (chlorobutanol hemihydrate).

Pharmacopoeias. *Eur.* (see p. vii), *Int.*, and *USNF* allow either the anhydrous form or the hemihydrate; *Eur.* includes them as separate monographs. *Chin.* specifies the hemihydrate. *Jpn* permits up to 6% of water.

Ph. Eur. 8: (Chlorobutanol Hemihydrate; Chlorobutanol BP 2014). A white or almost white, crystalline powder or colourless crystals. It sublimes readily. M.p. about 78 degrees. Slightly soluble in water; very soluble in alcohol; soluble in glycerol (85%). Store in airtight containers.

Ph. Eur. 8: (Chlorobutanol, Anhydrous). A white or almost white, crystalline powder or colourless crystals. It sublimes readily. M.p. about 95 degrees. Slightly soluble in water; very soluble in alcohol; soluble in glycerol (85%). Store in airtight containers.

USNF 31: (Chlorobutanol). It is anhydrous or contains not more than one-half molecule of water of hydration. Colourless or white crystals with a characteristic, somewhat camphoraceous odour. M.p. about 76 degrees for the hemihydrate and about 95 degrees for the anhydrous form. Soluble 1 in 125 of water, 1 in 1 of alcohol, and 1 in 10 of glycerol; freely soluble in chloroform, in ether, and in volatile oils. Store in airtight containers.

Incompatibility and stability. The activity of chlorobutanol can be adversely affected by the presence of other compounds as well as by the packaging material. There may be sorption onto substances like magnesium trisilicate, bentonite, carmellose,[1] polyethylene,[2,3] or polyhydroxyethylmethacrylate that has been used in soft contact lenses.[4] Increasing heat[2,3] or pH[5,6] can reduce stability and activity.

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
2. Friesen WT, Plein EM. The antibacterial stability of chlorobutanol stored in polyethylene bottles. *Am J Hosp Pharm* 1971; **28:** 507–12.
3. Holdsworth DG, *et al.* Fate of chlorbutol during storage in polyethylene dropper containers and simulated patient use. *J Clin Hosp Pharm* 1984; **9:** 29–39.
4. Richardson NE, *et al.* The interaction of preservatives with polyhydroxyethylmethacrylate (polyHEMA). *J Pharm Pharmacol* 1978; **30:** 469–75.
5. Nair AD, Lach JL. The kinetics of degradation of chlorobutanol. *J Am Pharm Assoc (Sci)* 1959; **48:** 390–5.
6. Patwa NV, Huyck CL. Stability of chlorobutanol. *J Am Pharm Assoc* 1966; **NS6:** 372–3.

Uses and Administration

Chlorobutanol has antibacterial and antifungal properties and it is used at a concentration of 0.5% as a preservative in injections and in eye drops as well as cosmetics.

Chlorobutanol has been used as a mild sedative and local analgesic but other compounds are preferred. It has been used in preparations for inflammatory and painful conditions of the ear and oropharynx.

Adverse Effects

Acute poisoning with chlorobutanol may produce CNS depression with weakness, loss of consciousness, and depressed respiration. Delayed (type IV) hypersensitivity reactions have been reported rarely.

References.

1. Nordt SP. Chlorobutanol toxicity. *Ann Pharmacother* 1996; **30:** 1179–80.

Effects on the cardiovascular system. Rapid falls in arterial blood pressure were noted after injections of heparin containing chlorobutanol in patients undergoing coronary bypass.[1] No fall in blood pressure was seen in patients who received preservative-free heparin injection.

1. Bowler GMR, *et al.* Sharp fall in blood pressure after injection of heparin containing chlorbutol. *Lancet* 1986; **i:** 848–9.

Effects on mental function. The sedative effects of chlorobutanol have been reported to be a problem in a patient dependent on large doses (0.9 to 1.5 g daily with salicylamide 1.8 to 3.0 g daily)[1] and in another patient given high doses of morphine in an infusion preserved with chlorobutanol.[2]

1. Borody T, *et al.* Chlorbutol toxicity and dependence. *Med J Aust* 1979; **i:** 288.
2. DeChristoforo R, *et al.* High-dose morphine infusion complicated by chlorobutanol-induced somnolence. *Ann Intern Med* 1983; **98:** 335–6.

Hypersensitivity. A delayed, cellular type of hypersensitivity reaction to chlorobutanol used to preserve heparin injection after subcutaneous injection has been reported.[1] Pruritus from intranasal desmopressin has been attributed to the chlorobutanol preservative.[2]

1. Dux S, *et al.* Hypersensitivity reaction to chlorbutanol-preserved heparin. *Lancet* 1981; **i:** 149.
2. Itabashi A, *et al.* Hypersensitivity to chlorobutanol in DDAVP solution. *Lancet* 1982; **i:** 108.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cerax; Eludril; Otocalmia; ***Austral.***: Cerumol; ***Belg.***: Eludril; Givalex; Prurisedine†; ***Braz.***: Auritricin; ***Canad.***: Cerumol; DSO Dressing; Larynsol†; Neutralite; ***Chile***: Eludril; ***Fr.***: Alodont; Angispray; Balsamorhinol; Buccosoin; Eludril; Eludrilpro; Givalex; ***Gr.***: Evex; Heludril; ***India***: Andre; Borozin; Ceruklin; Clearwax; Desol; Despol; Dewax; Fastwax; I-Top; Moss Eye; Nayawax; Nill-O-Wax; Otoclean; Otorex; Parabec; Waxolve†; ***Irl.***: Cerumol; Eludril†; Karvol; ***Israel***: Cepadont†; Cerumol; Dentin; Karvol; Pitrisan†; ***Ital.***: Fialetta Odontalgica Dr Knapp; Gocce Odontalgiche; ***Malaysia***: Cerumol; ***NZ***: Frador†; ***Port.***: Eludril; Otoceril; ***Rus.***: Cameton (Каметон); Eludril (Элюдрил); ***S.Afr.***: Aurone Forte†; Cerumol; Chamberlains Traditional Colic Remedy†; Karvol†; ***Singapore***: Cerumol; Eludril; Karvol; ***Spain***: Eludril†; Otocerum; ***Switz.***: Baume Dalet; Cerumenol; Eludril; ***Thai.***: Opplin; Optal; Optic; ***Turk.***: Disinol; ***UK***: Cerumol; Cetanorm; DDD; DDD; Dermidex; Eludril; Frador; Karvol; ***Ukr.***: Angilex (Ангилекс); Givalex (Гивалекс); Heppylor (Хепилор); ***USA***: Outgro.

Chlorocarvacrol

5-Chlorocarvacrol; Clorcarvacrol; Clorcarvacrolum; Kloorikarvakroli; Klorkarvakrol; Monochloroisothymol.

4-Chloro-5-isopropyl-2-methylphenol.

$C_{10}H_{13}ClO$=184.7
CAS — 5665-94-1.

Profile

Chlorocarvacrol is a phenolic antiseptic that is used as an ingredient of preparations for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Delta-Hadensa; Hadensa; Hadensa; Haemanal; ***Chile***: Vatanal; ***Fin.***: Hadensa†; Hadensa; ***Neth.***: Epianal; ***Norw.***: Alcos-Anal; ***Spain***: Hadensa; ***Turk.***: Hedensa.

Chlorocresol *(USAN, rINN)*

Chlorkresol; Chlorkresolum; Chlorocrésol; Chlorocresolum; Chlorokrezolis; Clorocresol; Kloorikresoli; Klorkresol; Klorokrezol; Parachlorometacresol; PCMC; Хлорокрезол.
p-Chloro-*m*-cresol; 4-Chloro-3-methylphenol.
C_7H_7ClO=142.6
CAS — 59-50-7.
UNII — 36W53O7109.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Chlorocresol). A white or almost white, crystalline powder or compacted crystalline masses supplied as pellets or colourless or white crystals. M.p. 64 degrees to 67 degrees. Slightly soluble in water; very soluble in alcohol; freely soluble in fatty oils. It dissolves in solutions of alkali hydroxides. Protect from light.

USNF 31: (Chlorocresol). Colourless or practically colourless crystals or crystalline powder with a characteristic nontarry odour; it is volatile in steam. M.p. 63 degrees to 66 degrees. Soluble 1 in 260 of water; more soluble in hot water; soluble 1 in 0.4 of alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Incompatibility. Chlorocresol has long been recognised to be incompatible with a range of compounds including: calcium chloride, codeine phosphate, diamorphine hydrochloride, papaveretum, quinine hydrochloride,[1] methylcellulose,[2] and nonionic surfactants[3,4] such as cetomacrogol 1000 and polysorbate 80.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; **158:** 260–2.
2. Harris WA. The inactivation of cationic antiseptics by bentonite suspensions. *Australas J Pharm* 1961; **42:** 583–8.
3. *PSGB Lab Report P/70/15* 1970.
4. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.

Uses and Administration

Chlorocresol is a potent chlorinated phenolic disinfectant and antiseptic. It has bactericidal activity against Gram-positive and Gram-negative bacteria and is effective against fungi but has little activity against bacterial spores except at high temperatures. It is more active in acid than in alkaline solution.

Chlorocresol is used in preparations for disinfection of the skin and wounds. It is also used as a preservative in cosmetics and in creams and other preparations for external use that contain water.

Chlorocresol is used as a preservative in aqueous injections issued in multidose containers. It may also be added to aqueous preparations that cannot be sterilised in their final containers and have to be prepared using aseptic precautions. Concentrations of 0.1% have generally been used. Injections prepared with chlorocresol should not be injected into the CSF, the eye, or the heart. Also such injections should generally not be given in volumes greater than 15 mL. Sterilisation by heating with a bactericide such as chlorocresol is no longer a recommended practice.

Adverse Effects, Treatment, and Precautions

As for Phenol, p. 1764.2. The antimicrobial activity of chlorocresol may be reduced by incompatibility (see above), adsorption, increasing pH, or through combination with organic matter (including oils and fats) or nonionic surfactants.

Chlorocresol is less toxic than phenol. Sensitisation reactions may follow application to the skin and hypersensitivity has occurred after systemic use of injections containing chlorocresol as a preservative.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Perfungol†; Perfungol; ***Cz.***: Cyteal; ***Fr.***: Cicatryl; Cyteal; ***Ger.***: Bomix†; Helipur; ***Gr.***: Lyoderm; Octrene; ***Hong Kong***: Acnesol†; ***India***: Balderm; Beclex-GM; ***Irl.***: Anbesol; Cymex; ***Ital.***: Helipur; Hygienist; ***Philipp.***: Cyteal; ***Port.***: Cyteal; ***Rus.***: Cyteal (Цитеал); ***S.Afr.***: Anbesol†; ***Singapore***: Cyteal; ***UK***: Anbesol; Cymex; Cyteal; Valderma; ***Ukr.***: Cyteal (Цитеал).

Pharmacopoeial Preparations
BPC 1973: Proflavine Cream.

Chlorothymol

Clorotimol; Monochlorothymol; Хлоротимол.
6-Chlorothymol; 4-Chloro-2-isopropyl-5-methylphenol.
$C_{10}H_{13}ClO$=184.7
CAS — 89-68-9.
UNII — LJ25TI0CVT.

Profile

Chlorothymol is a chlorinated phenolic antiseptic used as an ingredient of preparations for hand and skin disinfection and topical treatment of fungal infections. It has also been used in preparations for anorectal disorders, cold symptoms, and mouth disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Pioral Pasta.

Multi-ingredient Preparations. ***India***: Aerway; Coriminic-Vaporise; Easi Breathe; Genvol Plus; Karvol Plus; Kolq Inhalant; Sinarest Vapocaps; ***Ital.***: Labocaina; Vagisil; ***Philipp.***: Calmoseptine.

Chloroxylenol *(BAN, USAN, rINN)*

Chloroxylénol; Chloroxylenolum; Cloroxilenol; Parachlorometaxylenol; PCMX; Хлороксиленол.
4-Chloro-3,5-xylenol; 4-Chloro-3,5-dimethylphenol.
C_8H_9ClO=156.6
CAS — 88-04-0.
ATC — D08AE05.
ATC Vet — QD08AE05.
UNII — 0F32U78V2Q.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Chloroxylenol). White or cream crystals or crystalline powder with a characteristic odour; volatile in steam. Very slightly soluble in water; freely soluble in alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.

USP 36: (Chloroxylenol). White crystals or crystalline powder with a characteristic odour; volatile in steam. Very slightly soluble in water; freely soluble in alcohol, in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.

Incompatibility. Chloroxylenol has been reported to be incompatible with nonionic surfactants and methylcellulose.

Uses and Administration

Chloroxylenol is a chlorinated phenolic antiseptic that is bactericidal against most Gram-positive bacteria but less active against staphylococci and Gram-negative bacteria, and is often inactive against *Pseudomonas* spp. Its activity against *Ps. aeruginosa* appears to be increased by the addition of edetic acid. It is inactive against bacterial spores.

Chloroxylenol Solution (BP 2014) is used for skin and wound disinfection, and chloroxylenol is used as a preservative in a variety of other topical formulations.

Adverse Effects and Precautions

Chloroxylenol in the recommended dilutions is generally non-irritant but skin sensitivity has occurred. There have been isolated reports of poisoning. Symptoms reported include corrosion of the oral mucosa, larynx, and the gastrointestinal tract, bradycardia, hypotension, and renal failure. Large amounts may cause CNS depression. Pulmonary aspiration of chloroxylenol-based disinfectants may result in pneumonia, acute respiratory distress syndrome, and cardiorespiratory arrest.

The antimicrobial activity of chloroxylenol may be diminished through combination with organic matter. Aqueous solutions of chloroxylenol may be susceptible to contamination with micro-organisms. To reduce this risk, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Poisoning. Reports of fatal or severe self-poisoning with chloroxylenol solution.[1-5]

1. Meek D, *et al.* Fatal self-poisoning with Dettol. *Postgrad Med J* 1977; **53:** 229–31.
2. Joubert P, *et al.* Severe Dettol (chloroxylenol and terpineol) poisoning. *BMJ* 1978; **1:** 890.
3. Chan TYK, *et al.* Chemical gastro-oesophagitis, upper gastrointestinal haemorrhage and gastroscopic findings following Dettol poisoning. *Hum Exp Toxicol* 1995; **14:** 18–19.
4. Chan TY, Critchley JA. Pulmonary aspiration following Dettol poisoning: the scope for prevention. *Hum Exp Toxicol* 1996; **15:** 843–6.
5. Joynt GM, *et al.* Delayed upper airway obstruction: a life-threatening complication of Dettol poisoning. *Anaesthesia* 1997; **52:** 261–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Espadol; Talowin; ***Austral.***: Dettol; ***Belg.***: Dettol; ***Canad.***: Antibacterial; Colourless Antiseptic; Contact; Dermex I; Dettol; Digiclean E Foam Hand Soap; Epi Wash†; Epicare; Germicidal Hand Soap; Grasp; Health Care Antiseptic Soap; Health Care E-2 Antis Lot Soap; Kimcare Antibacterial†; Medi-Scrub; Micrell; Phenrex; Prime Source with Chloroxylenol; Provon Antimicrobial; Provon Medicated with Chloroxylenol; Septiline; Soft Care Antiseptic; Soft Care Sanitizing; Softcide Handwash; Surgical Scrub and Handwash; Virobex-P; ***Cz.***: Dettolmed; ***Gr.***: Dettol; Dettolsept; ***Hong Kong***: Dettol†; New Dettol†; ***Irl.***: Dettol; ***Ital.***: Neomercurocromo; ***Malaysia***: Dettol; ***Neth.***: Dettol; ***NZ***: Dettol; ***S.Afr.***: Dettol; ***Singapore***: Dettol; ***Thai.***: Dettol; ***UK***: Dettol.

Multi-ingredient Preparations. ***Arg.***: Jabonacid; Kytinon ATM; Previnfec; ZeaSorb; ***Austral.***: Dettol Cream; ZeaSorb†; ***Canad.***: Antiseptic Lotion†; Ensuite; Inhibit; Sani-Dex†; Soothing Foot Spray; Uphold Plus; ZeaSorb; ***Chile***: Dermac Crema; ***Hong Kong***: Acne-Aid†; Dettol†; ***India***: Dettol Obstetric; Dettol; Dettolin; ***Indon.***: ZeaSorb; ***Irl.***: Dettol†; Rinstead; TCP; ZeaSorb; ***Israel***: Gargol; Hemo; Rexitol†; ***Ital.***: Foille Scottature; Foille Sole; ***Malaysia***: Acne-Aid†; Dettol; ***NZ***: Dettol; ***Philipp.***: Strepsils; ZeaSorb; ***Pol.***: Sterovag†; ***S.Afr.***: Respisniffers†; Woodwards Inhalant; ZeaSorb†; ***Singapore***: Acne-Aid†; Dettol; ZeaSorb; ***Thai.***: Dettol; ZeaSorb†; ***UK***: Dettol; Eradicil; Rinstead; Skintex; TCP; ZeaSorb; ***USA***: Calamycin; Cortamox†; Cortane-B; Cortic ND; Cyotic; Dermacoat; Foille; Fungi-Nail; Geri-Lav Free; Gordochom; Lobana Peri-Garde; Mediotic-HC; Oticin HC; Oticin; Oto-End; Otomar-HC; PramOtic; TriOxin; Unguentine Plus; Zinotic†; Zoto-HC.

Pharmacopoeial Preparations
BP 2014: Chloroxylenol Solution.

Cicliomenol *(rINN)*

Cicloménol; Cicliomenolum; Циклиоменол.
2-Cyclohexyl-4-iodo-3,5-xylenol.
$C_{14}H_{19}IO$=330.2
CAS — 10572-34-6.
UNII — GYU56H6EBV.

Profile

Cicliomenol is an antiseptic included in preparations intended for the topical treatment of mouth and throat infections.

Cinnamic Acid

Cinámico, ácido; Cinnamylic Acid; Коричная Кислота.
trans-3-Phenylpropenoic acid.
$C_6H_5.CH{:}CH.CO_2H$=148.2
CAS — 621-82-9.
UNII — U14A832J8D.

Pharmacopoeias. In *Br.*

BP 2014: (Cinnamic Acid). Colourless crystals with a faint balsamic odour. Very slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether.

Profile

Cinnamic acid has preservative properties. It is used with benzoic acid and other substances to simulate the flavour of tolu.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Novobroncol; ***Irl.***: Hemocane; ***UK***: Hemocane; Potters Gees Linctus; Sanderson's Throat Specific.

Pharmacopoeial Preparations
BP 2014: Tolu-flavour Solution.

Clorophene *(USAN)*

Clorfene; Clorofene (pINN); Clorofène; Clorofeno; Clorofenum; NSC-59989; Septiphene; Клорофен.
2-Benzyl-4-chlorophenol.
$C_{13}H_{11}ClO$=218.7
CAS — 120-32-1.
UNII — 7560BB0BO3.

Profile

Clorophene is a chlorinated phenolic antiseptic stated to be active against a wide range of bacteria, fungi, protozoa, and viruses. It is used as a skin disinfectant and for surface and instrument disinfection. Clorophene sodium has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Neo-Sabenyl; ***Canad.***: Aseptone 1; Aseptone 2; Aseptone 5; ***Ger.***: Bomix†; Freka-Derm†; Freka-Sept 80†; Helipur; ***Ital.***: Helipur; Hygienist; ***UAE***: Radol; ***USA***: BTK-Plus†.

Cresol

Crésol brut (cresol, crude); Cresolum; Cresolum crudum (cresol, crude); Cresylic Acid; Kresol; Kresol, rå (cresol, crude); Kresoli, raaka (cresol, crude); Kresolum Venale; Krezol; Krezolis, negrynintas (cresol, crude); Metacresol (BAN); Metilfenol; Tricresol; Trikresolum; Крезол.
Methylphenol.
C_7H_8O=108.1
CAS — 1319-77-3; 95-48-7 (o-cresol); 108-39-4 (m-cresol); 106-44-5 (p-cresol).
UNII — GF3CGH8D7Z (cresol); GGO4Y809LO (m-cresol); YW84DH5I7U (o-cresol); 1MXY2UM8NV (p-cresol).

NOTE. Some grades of mixed cresols may be equivalent to Tar Acids (p. 1771.2).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Eur. also includes metacresol.

Ph. Eur. 8: (Cresol, Crude; Cresolum Crudum). A mixture of *o-*, *m-*, and *p*-methylphenol. A colourless or pale brown liquid. Relative density 1.029 to 1.044. Sparingly soluble in water; miscible with alcohol and with dichloromethane. Protect from light.

Ph. Eur. 8: (Metacresol; Metacresolum). A colourless or yellowish liquid. Relative density about 1.03. M.p. about 11 degrees. Sparingly soluble in water; miscible with alcohol and with dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Cresol). A mixture of cresol isomers obtained from coal tar or petroleum. A colourless, yellowish to brownish-yellow, or pinkish, highly refractive liquid, becoming darker with age or on exposure to light, with a phenol-like, sometimes empyreumatic odour. Specific gravity 1.030 to 1.038. Sparingly soluble in water, usually forming a cloudy solution; miscible with alcohol, with ether, and with glycerol; dissolves in solutions of fixed alkali hydroxides. A saturated solution in water is neutral or slightly acid to litmus. Store in airtight containers. Protect from light.

Profile

Cresol is a disinfectant with a similar action to phenol (p. 1763.3); suitable precautions should be taken to prevent absorption through the skin.

It has been used as Cresol and Soap Solution (BP 1968) (Lysol) as a general disinfectant but it has been largely superseded by other, less irritant, phenolic disinfectants. Cresol has been used in dentistry, alone or with formaldehyde, but is caustic to the skin and unsuitable for skin and wound disinfection. The cresols have been widely used in disinfectants for domestic and hospital use. Cresol is also used as an antimicrobial preservative in parenteral pharmaceutical preparations and in some topical formulations.

Poisoning. References to poisoning with cresol solutions.[1-7]

1. Côté M-A, *et al*. Acute Heinz-body anaemia due to severe cresol poisoning: successful treatment with erythrocytapheresis. *Can Med Assoc J* 1984; **130:** 1319–22.
2. Wu ML, *et al*. Concentrated cresol intoxication. *Vet Hum Toxicol* 1998; **40:** 341–3.
3. Hashimoto T, *et al*. Marked increases of aminotransferase levels after cresol ingestion. *Am J Emerg Med* 1998; **16:** 667–8.
4. Sakai Y, *et al*. Chemical burn with systemic cresol intoxication. *Pediatr Int* 1999; **41:** 174–6.
5. Monma-Ohtaki J, *et al*. An autopsy case of poisoning by massive absorption of cresol a short time before death. *Forensic Sci Int* 2002; **126:** 77–81.
6. Hayakawa M. Severe hepatic dysfunction following cresol poisoning. *Intensive Care Med* 2002; **28:** 1190–1.
7. Kamijo Y, *et al*. Hepatocellular injury with hyperaminotransferasemia after cresol ingestion. *Arch Pathol Lab Med* 2003; **127:** 364–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Creolina.

Multi-ingredient Preparations. ***Arg.***: Algiodent; Sulfanoral T; ***Austral.***: Formo-Cresol Mitis†; ***Fr.***: Cidapex†; Endotine; Mepacyl; ***Switz.***: Eau Precieuse; ***USA***: Cresylate.

Dapabutan *(rINN)*

Dapabutano; Dapabutanum; Dodecylaminopropyl-β-aminobutyric acid; Дапабутан.
(±)-3-{[3-(Dodecylamino)propyl]amino}butyric acid.
$C_{19}H_{40}N_2O_2$=328.5
CAS — 6582-31-6.
UNII — 1R0Y7O07NF.

Profile

Dapabutan is a beta aminobutyric acid derivative used as an antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Sterlane.

Decamethoxine

Dekametoksin; Декаметоксин.
N,N,N′,N′-Tetramethyl-*N,N′*-bis(2-{[5-methyl-2-(1-methylethyl)-cyclohexyl]oxy}-2-oxoethyl)-1,10-decanediaminium dichloride.
$C_{38}H_{74}Cl_2N_2O_4$=693.9
CAS — 38146-42-8.

Profile

Decamethoxine is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used topically for disinfection of the skin and mucous membranes and for disinfection of equipment. Decamethoxine is also used as a gargle for infections of the oral cavity and has been used topically or as an irrigation for infections of the skin and various body cavities.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Oftadek (Офтадек); ***Ukr.***: Decasan (Декасан); Horosten (Горостен).

Dehydroacetic Acid

Deshidroacético, ácido; Methylacetopyronone; Дегидроацетовая Кислота.
3-Acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione (keto form); 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (enol form).
$C_8H_8O_4$=168.1
CAS — 520-45-6 (keto form); 771-03-9 (enol form).
UNII — 2KAG279R6R.

Pharmacopoeias. In *USNF*.

USNF 31: (Dehydroacetic Acid). A white or nearly white, crystalline powder. Very slightly soluble in water; soluble in aqueous solutions of alkalis. One g dissolves in about 35 mL of alcohol and in 5 mL of acetone.

Sodium Dehydroacetate

Dehydracetic Sodium; Deshidroacetato sódico; Дегидроацетат Натрия.
The sodium salt of 3-acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione.
$C_8H_7NaO_4$=190.1
CAS — 4418-26-2.
UNII — 8W46YN971G.

Pharmacopoeias. In *USNF*.

USNF 31: (Sodium Dehydroacetate). A white or practically white, odourless powder. Freely soluble in water, in glycerol, and in propylene glycol.

Incompatibility. The activity of sodium dehydroacetate may be reduced by alkaline pH or interaction with nonionic surfactants.

Profile

Dehydroacetic acid and sodium dehydroacetate have some antifungal activity and have been used in the preservation of cosmetics and oral preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Venez.***: Photoderm AKN.

Dequalinium Chloride *(BAN, rINN)*

BAQD-10; Cloruro de decualinio; Cloruro de dequalinio; Decalinium Chloride; Decaminum; Decualinio, cloruro de; Dekalinyum Klorür; Dekvalinio chloridas; Dekvalinium dichlorid; Dekvaliniumklorid; Dekvalinium-klorid; Dekvaliniumkloridi; Dequalinii chloridum; Dequalinii Dichloridum; Déqualinium, Chlorure de; Dequaliniumchlorid; Дekвалиния Хлорид.
N,N-Decamethylenebis(4-amino-2-methylquinolinium chloride).
$C_{30}H_{40}Cl_2N_4$=527.6
CAS — 6707-58-0 (dequalinium); 522-51-0 (dequalinium chloride); 4028-98-2 (dequalinium acetate); 16022-70-1 (dequalinium salicylate).
ATC — D08AH01; G01AC05; R02AA02.
ATC Vet — QD08AH01; QG01AC05; QR02AA02.
UNII — XYS8INN1I6.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dequalinium Chloride). A white or yellowish-white, hygroscopic powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Incompatibility. Dequalinium chloride is incompatible with soaps and other anionic surfactants, with phenol, and with chlorocresol.

Profile

Dequalinium chloride is a bisquaternary quinolinium antiseptic, bactericidal against many Gram-positive and Gram-negative bacteria, and effective against fungi. It is mainly used in the form of lozenges in the treatment of minor infections of the mouth and throat. It has been applied topically in the treatment of skin and vaginal infections.

Dequalinium salicylate and undecenoate have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Evazol; Tonsillol; ***Belg.***: Anginol; Laryngarsol†; ***Canad.***: Dequadin; ***China***: Delin (利林); Qingli (清利); ***Cz.***: Naxyl; ***Ger.***: Evazol†; Fluomizin; Fluomycin N†; Gurgellosung-ratiopharm; Sorot†; ***Gr.***: Decosan; ***Hong Kong***: Christon†; Decol†; Delin; Dequadin; Dexxon; Fluomizin; Nofrozic†; Roxine†; ***India***: Dequadin; ***Indon.***: Decamedin; Degirol; SP Troches; ***Irl.***: Dequadin; ***Ital.***: Dequadin; Dequosangola; Faringina; Goladin; Osangin; Pumilsan; ***Malaysia***: Delin; Dequadin; DQM; Roxine; SP Troches; ***Neth.***: Natterman Streptofree; ***Philipp.***: Dequadin; ***Rus.***: Fluomisin (Флуомизин); ***Singapore***: Beacons DQ; Dequa-loz; Dequadin; SP Troches; ***Switz.***: Decatylene†; Fluomizin; ***Thai.***: Baron; Decho†; Deo†; Dequadin†; Fluomizin; V Day Lozenges; ***Turk.***: Dequadin; Donaxyl; ***UK***: Dequadin; Labosept; ***Ukr.***: Fluomizin (Флуомизин); ***Venez.***: Dequadin; Laimolin.

Multi-ingredient Preparations. ***Austria***: Dequalinetten; Dequonal; Eucillin; Fluorex Plus; ***Belg.***: Angin-San; Anginol-Lidocaine; Dequalid; Ororhinathiol; ***Braz.***: Dequadin; ***China***: Deq (得益); ***Ger.***: Dequonal; Ephepect-Blocker-Pastillen N; Jasimenth CN; Wick Sulagil; ***Hong Kong***: Decatylen; Deq; Ephepect Blocker; Liqualon†; Quadezyme; Scassh Trouch Lozenge; ***Indon.***: Sentril†; ***Irl.***: Dequacaine; ***Ital.***: Lisomucil Gola; Transpulmina Gola; ***Malaysia***: Decatylen; Deq; Upha Lozenges; ***Mex.***: Angenovag; ***Norw.***: Apolar med dekvalin; ***Pol.***: Tetesept†; ***Port.***: Anginova; Decatyleno; Dek; Medifon†; ***S.Afr.***: Dequadin Mouth Paint; ***Singapore***: Decatylen; Deq; ***Spain***: Anginovag; Roberfarin; ***Switz.***: Anginova; Arbid-top; Decasept N†; Decatylene Neo; Dequonal; Tyroqualine; ***Thai.***: Deq; Sentril†; ***UK***: Dequacaine; ***Ukr.***: Anginovag (Ангиновaг); Decatylen (Декатилен); Efisol (Эфизол); Lisak (Лизак); Lizak (Лизак); ***Venez.***: Alantamida; Benzodiazol; Laimoqualin.

Diacetylaminoazotoluene

Diacetazotol; Diacetilaminoazotoluene; Pellidol; Диацетиламиноазотолуол.
4-Diacetylamino-2′,3-dimethylazobenzene.
$C_{18}H_{19}N_3O_2$=309.4
CAS — 83-63-6.

Profile

Diacetylaminoazotoluene is an antiseptic that has been used topically to promote wound healing.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Dermowund†.

Diazolidinyl Urea

Diazolidinylurea.
N-[1,3-Bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-*N,N'*-bis(hydroxymethyl)urea.
$C_8H_{14}N_4O_7$=278.2
CAS — 78491-02-8.
UNII — H5RIZ3MPW4.

Profile

Diazolidinyl urea is an imidazolidinyl preservative with similar properties and uses to imidurea (p. 1758.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Eucerin Piel Grasa†; ***India***: Emolene.

Dibrompropamidine Isetionate *(BANM, rINNM)*

Dibromipropamidiinidi-isetionaatti; Dibromopropamidine Isethionate; Dibromopropamidyny diizetionian; Dibrompropamidina, isetionato de; Dibrompropamidindiisetionat; Dibrompropamidin-diisetionát; Dibrompropamidine Diisetionate; Dibrompropamidine, diisétionate de; Dibrompropamidine, Isétionate de; Dibrompropamidini Diisetionas; Dibrompropamidini Isetionas; Isetionato de dibrompropamidina; Дибромпропамидина Изетионат.
3,3′-Dibromo-4,4′-trimethylenedioxydibenzamidine bis(2-hydroxyethanesulphonate).
$C_{17}H_{18}Br_2N_4O_2,2C_2H_6O_4S$=722.4
CAS — 496-00-4 (dibrompropamidine); 614-87-9 (dibrompropamidine isetionate).
ATC — D08AC01; S01AX14.
ATC Vet — QD08AC01; QS01AX14.
UNII — 12Y597MO62.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dibrompropamidine Diisetionate). A white or almost white, crystalline powder. Freely soluble or soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 5.0 to 6.0.

Profile

Dibrompropamidine isetionate is an aromatic diamidine antiseptic similar to propamidine (p. 1767.3). It is bactericidal against Gram-positive bacteria but is less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties. It is available as topical preparations for the local treatment of minor eye and skin infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Brulidine†; ***Irl.***: Brolene; Golden Eye; ***Norw.***: Brulidine; ***NZ***: Brolene; ***S.Afr.***: Brolene; ***UK***: Brolene; Brulidine; Golden Eye Ointment; Pickles Antiseptic Cream.

Multi-ingredient Preparations. ***UK***: Healthy Feet; No-Sor Nose Balm; RBC; Swarm.

Dichlordimethylhydantoin

Diclorodimetilhidantoína.
1,3-Dichloro-5,5-dimethylhydantoin; 1,3-Dichloro-5,5-dimethylimidazolidine-2,4-dione.
$C_5H_6Cl_2N_2O_2$=197.0
CAS — 118-52-5.

Profile

Dichlordimethylhydantoin is a disinfectant used as a source of chlorine, for sterilising food and dairy equipment and as a bleach. It contains about 72% w/w of 'available chlorine' (see p. 1746.3).

Bromochlorodimethylhydantoin ($C_5H_6N_2O_2BrCl$ = 241.5) is a closely related bromine-releasing compound used for the disinfection of swimming-pool water.

Dichlorobenzyl Alcohol

Alcohol diclorobencílico; 2,4-Dichlorbenzyl-alcoholum; Dichlorophenylcarbinol; 2,4-Diklooribentsyyli-alkoholi; 2,4-Diklorbensyylalkohol; Diklorobenzil Alkol; Дихлорбензиловый Спирт.
2,4-Dichlorobenzyl alcohol.
$C_7H_6Cl_2O$=177.0
CAS — 1777-82-8.
ATC — R02AA03.
ATC Vet — QR02AA03.
UNII — 1NKX3648J9.

Profile

Dichlorobenzyl alcohol is an antiseptic used chiefly as an ingredient of lozenges in the treatment of minor infections of the mouth and throat.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dichlorobenzyl alcohol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Neo Borocillina Collutorio; Neo Borocillina Spray.

Multi-ingredient Preparations. ***Arg.***: Strepsils Plus; Strepsils; ***Austral.***: Ayrtons Antiseptic; Logicin Rapid Relief; Strepsils Numbing; Strepsils Plus†; Strepsils; ***Austria***: Coldangin; Neo-Angin; Sulgan 99; ***Belg.***: Strepsils + Lidocaine; Strepsils Cool Mint; Strepsils Menthol†; Strepsils Vit C; Strepsils; ***Canad.***: Cepacol Sensations Cooling; Cepacol Sensations Sore Throat & Blocked Nose; Cepacol Sensations Sore Throat & Cough; Cepacol Sensations Warming; Cepacol Sensations; Strepsils Cherry†; Strepsils Cool; Strepsils Sore Throat Blocked Nose; Strepsils; ***Chile***: Hansaplast Antimicotico†; ***Cz.***: Neo-Angin; Strepsils Cooling Mint; Strepsils Menthol a Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; ***Denm.***: Strepsils; ***Fin.***: Bafucin; Med-Angin; Strepsils Menthol; Strepsils; ***Fr.***: Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsils; Strepsilspray; ***Ger.***: Dobendan Cool†; Dobendan Junior; Dobendan Synergie; Dobendan Warm; Neo-Angin; ***Gr.***: Strepsils Plus; Strepsils; ***Hong Kong***: Logicin Rapid Relief; Strepsils Dual Action; Strepsils; ***Hung.***: Neo-Angin; Strepsils Menthol and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; ***India***: Cofsils; ***Irl.***: Strepsils +Plus Anaesthetic; Strepsils Cool; Strepsils Dual Action†; Strepsils Sore Throat and Blocked Nose; Strepsils Throat; Strepsils Vitamin C; Strepsils; ***Israel***: Strepsils Plus; Strepsils with Menthol and Eucalyptus; Strepsils with Vitamin C; Strepsils; ***Ital.***: Arscolloid; Benagol Mentolo-Eucaliptolo; Benagol Vitamina C; Benagol; Bioarscolloid; Corti-Arscolloid; Neo Borocillina Balsamica; Neo Borocillina C; Neo Borocillina Tosse Compresse; Neo Borocillina; ***Malaysia***: Chericof; Strepsils Dual Action; Strepsils; ***Neth.***: Strepsils Menthol & Eucalyptus†; Strepsils Sinaasappel & Vitamine C; Strepsils; ***NZ***: Strepsils Plus Anaesthetic; Strepsils with Vitamin C; Strepsils; ***Philipp.***: Strepsils; Strepsils; Therasil; ***Pol.***: Neo-Angin; Strepsils; ***Port.***: Benagol†; Benoral; Dropcina; Strepsils; ***Rus.***: Astrasept (Астрасепт); Coldact Lorpils (Колдакт Лорпилс); Gorpils (ГОРПИЛС); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Strepsils with Vitamin C (Стрепсилс с Витамином С); Suprima-Lor (Суприма-Лор); Therasil (Терасил); ***S.Afr.***: Strepsils Eucalyptus Menthol†; Strepsils Orange-C†; Strepsils Plus; Strepsils Soothing Honey & Lemon†; Strepsils; ***Singapore***: Cofsils; Logicin Rapid Relief; Robitussin Medicated Lozenges; Strepsils Max Plus; Strepsils; ***Spain***: Strepsils con Vitamina C; Strepsils Lidocaina; Strepsils; ***Swed.***: Bafucin; Strepsils; ***Switz.***: Anginazol; Angisan; Hextriletten†; Lidazon; Strepsils with Vitamin C; Strepsils; Sulgan N; Sulgan N; ***Thai.***: Strepsils Butter Menthol Capsicum†; Strepsils Maxipluzz; Strepsils Plus Vit C; Strepsils Sugar Free†; Throatsil Plus; Throatsil; ***Turk.***: Med-Angin; Strepsils C; Strepsils Mentol; Strepsils; ***UK***: Strepsils with Vitamin C; Strepsils; ***Ukr.***: Angi Sept Dr Theiss (Анги Септ Др Тайсс); Coldact Lor Pils (Колдакт Лор Пилс); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс).

Dichloroxylenol *(BAN, rINN)*

DCMX; Dichlorometaxylenol; Dichloroxylénol; Dichloroxylenolum; Dicloroxilenol; Дихлороксиленол.
2,4-Dichloro-3,5-xylenol; 2,4-Dichloro-3,5-dimethylphenol.
$C_8H_8Cl_2O$=191.1
CAS — 133-53-9.
UNII — 51AC49OLT7.

Profile

Dichloroxylenol is a chlorinated phenolic antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Haffkinol.

Multi-ingredient Preparations. ***India***: Fairgenol; ***UAE***: Radol.

Didecyldimethylammonium Chloride

Didecildimetilamonio, cloruro de; Didecyldimonium Chloride; Дидецилдиметиламмония Хлорид.
N-Decyl-*N*,*N*-demethyl-1-decanaminium chloride.
$C_{22}H_{48}ClN$=362.1
CAS — 7173-51-5.
ATC — D08AJ06.
ATC Vet — QD08AJ06.
UNII — JXN4OO9Y9B.

Profile

Didecyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of the skin and mucous membranes. It is also used to disinfect instruments and surfaces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Basix Neutral; Bio-San; ***Ger.***: Amosept; Fungisept; ***Ital.***: Alfa Bergamon; Bergamon In; Farmasept; Septidil.

Multi-ingredient Preparations. ***Canad.***: Bio Klean; ***Fr.***: Aniospray 29†; Aniosyme†; Hexanios G+R†; Surfanios†; ***Ger.***: Almyrol; Freka-Nol†; Hexaquart plus; Hexaquart S; Kohrsolin extra; Kohrsolin FF; Korsolex Extra; Korsolex FF; Korsolex Plus; Lysoformin 3000; Lysoformin spezial; Meliseptol Rapid; Melsept SF; Melsitt; Mikrobac Tissues; Teta Extra†; ***Ital.***: Melsept SF; ***Switz.***: Desamon; ***USA***: Vi Rid-Ready.

1,6-Dihydroxy-2,5-dioxahexane

Ethylene Glycol Bis(semiformal); (Ethylenedioxy)dimethanol.
[1,2-Ethanediylbis(oxy)]bismethanol.
$C_4H_{10}O_4$=122.1
CAS — 3586-55-8.

Profile

1,6-Dihydroxy-2,5,-dioxahexane is an aldehyde that slowly releases formaldehyde. It is used for the disinfection of surfaces and of medical and surgical instruments.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Bacillol†; Kohrsolin extra; Kohrsolin†; Korsolex basic; Korsolex Extra.

Dioctyldimethylammonium Chloride

Dimethyldioctylammonium Chloride; Dioctyl Dimethyl Ammonium Chloride; Диоктилдиметиламмония Хлорид.
N,*N*-Dimethyl-*N*-octyl-1-octanaminium chloride.
$C_{18}H_{40}ClN$=306.0
CAS — 5538-94-3.

Profile

Dioctyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of surfaces.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Vi Rid-Ready.

Dodeclonium Bromide *(rINN)*

Bromuro de dodeclonio; Dodeclonii Bromidum; Dodeclonio, bromuro de; Dodéclonium, Bromure de; GR-412; Додекло-ния Бромид.
[2-(*p*-Chlorophenoxy)ethyl]dodecyldimethylammonium bromide.
$C_{22}H_{39}BrClNO$=448.9
CAS — 15687-13-5.
UNII — XD8BU85ZLK.

Profile

Dodeclonium bromide is an antiseptic that has been included in multi-ingredient preparations intended for the treatment of skin and anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Biogaze; ***Fr.***: Dermeol; Phlebocreme; Phlebosup; Sedaplaie†; Sedorrhoide.

Domiphen Bromide *(BAN, USAN, rINN)*

Bromuro de domifeno; Domifeenibromidi; Domifenbromid; Domifeno, bromuro de; Domiphène, Bromure de; Domipheni Bromidum; NSC-39415; PDDB; Phenododecinium Bromide; Домифена Бромид.

Dodecyldimethyl-2-phenoxyethylammonium bromide.

$C_{22}H_{40}BrNO$=414.5

CAS — 13900-14-6 (domiphen); 538-71-6 (domiphen bromide).

ATC — A01AB06.

ATC Vet — QA01AB06.

UNII — R4CY19YS7C.

Pharmacopoeias. In *Br. Chin.* includes the monohydrate.

BP 2014: (Domiphen Bromide). Colourless or faintly yellow, crystalline flakes. Freely soluble in water and in alcohol; soluble in acetone.

Incompatibility. Domiphen bromide is incompatible with soaps and other anionic surfactants.

Profile

Domiphen bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). Preparations containing domiphen bromide are used in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Antiseptique Pastilles†; Bronchodex Pastilles†; ***Gr.***: Desept; ***Ital.***: Bradoral; ***Malaysia***: Domidin; ***Port.***: Neobradoral.

Multi-ingredient Preparations. ***Austria***: Bepanthen†; Bradosol; ***Canad.***: Nupercainal; ***Chile***: Oralfresh; ***Fr.***: Fluoselgine; ***India***: Bradex-Vioform; ***Ital.***: Inalar; ***Pol.***: Viosept†; ***Ukr.***: Viosept (Виосепт)†.

Erythorbic Acid

D-Araboascorbic Acid; E315; Erycorbin; Glucosaccharonic Acid; Isoascorbic Acid; Isovitamin C; Saccharosonic Acid; Эриторбовая Кислота.

D-*erythro*-Hex-2-enoic acid γ-lactone; D-*erythro*-Hex-2-enonic acid γ-lactone.

$C_6H_8O_6$=176.1

CAS — 89-65-6.

UNII — 311332OII1.

Pharmacopoeias. In *USNF*.

USNF 31: (Erythorbic Acid). White or slightly yellow crystals or powder. It gradually darkens when exposed to light. In the dry state, it is reasonably stable in air, but in solution, it rapidly deteriorates in the presence of air. One g is soluble in about 2.5 mL of water and in about 20 mL of alcohol. Slightly soluble in glycerol. Store in airtight containers. Protect from light.

Sodium Erythorbate

E316; Sodium Isoascorbate; Sodium Isovitamin C; Эриторбат Натрия.

$C_6H_7NaO_6$=198.1

CAS — 6381-77-7 (anhydrous monosodium erythorbate); 7378-23-6 (anhydrous sodium erythorbate, xNa); 63524-04-9 (monosodium erythorbate monohydrate).

UNII — BZ468R6XRD.

Profile

Erythorbic acid is the stereoisomer of L-ascorbic acid (p. 2110.3), but has little vitamin-C potency. Erythorbic acid and its sodium salt are used as antoxidants in foods and oral pharmaceutical preparations.

Ethoxyquin

Etoxiquina; Этоксихин.

6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline.

$C_{14}H_{19}NO$=217.3

CAS — 91-53-2.

UNII — 9T1410R4OR.

Profile

Ethoxyquin has been used as an antoxidant for the prevention of common scald of apples and pears during storage and as an additive to animal feeds. Concern has been expressed over the toxicity of ethoxyquin and its residues on foodstuffs and its use is limited or restricted in some countries.

Ethylene Oxide

Dimethylene oxide; Epoxietano; 1,2-Epoxyethane; Etylenu tlenek; Óxido de etileno; Oxirane; Oxirano; Окись Этилена; Этиленоксид.

C_2H_4O=44.05

CAS — 75-21-8.

UNII — JJH7GNN18P.

Description. Ethylene oxide is a colourless flammable gas at room temperature and atmospheric pressure.

Stability. Mixtures of ethylene oxide with oxygen or air are explosive but the risk can be reduced by the addition of carbon dioxide or fluorocarbons.

Uses

Ethylene oxide is a bactericidal and fungicidal gaseous disinfectant that is effective against most micro-organisms, including viruses. It is also sporicidal. It is used for the gaseous sterilisation of heat-labile pharmaceutical and surgical materials that cannot be sterilised by other means.

Ethylene oxide forms explosive mixtures with air; this may be overcome by using mixtures containing 10% ethylene oxide in carbon dioxide, or by removing at least 95% of the air from the apparatus before admitting either ethylene oxide or a mixture of 90% ethylene oxide in carbon dioxide. Alternatively, non-flammable mixtures of dichlorodifluoromethane and trichlorofluoromethane with 9 to 12% w/w of ethylene oxide have been employed, but restrictions on the release of fluorocarbons or CFCs limit their use.

Effective sterilisation by ethylene oxide depends on exposure time, temperature, humidity, the amount and type of microbial contamination, and the partial pressure of the ethylene oxide in the exposure chamber. Concentrations of 400 to 1000 mg/litre are usually used for sterilisation and the process time may vary from 30 minutes to 10 hours. The material being sterilised must be permeable to ethylene oxide if occluded micro-organisms are present. The bactericidal action is accelerated by increase of temperature; the average temperature used is between 40 degrees and 50 degrees.

Moisture is essential for sterilisation by ethylene oxide. In practice, dry micro-organisms need to be rehydrated before ethylene oxide can be effective; humidification is normally carried out under vacuum before the introduction of ethylene oxide. Relative humidities of 40 to 60% are used.

Control of physical factors does not assure sterility, and the process should be monitored usually by using standardised suspensions of aerobic spores such as those of *Bacillus subtilis* var. *niger*.

Adverse Effects and Precautions

Ethylene oxide irritates the eyes and respiratory tract and may also cause nausea and vomiting, diarrhoea, headache, vertigo, CNS depression, dyspnoea, and pulmonary oedema. Liver and kidney damage and haemolysis may occur. Fatalities have occurred. Excessive exposure of the skin to liquid or solution causes burns, blistering, irritation, and dermatitis; percutaneous absorption may lead to systemic effects.

Many materials including plastics and rubber adsorb ethylene oxide. If such materials are being sterilised with ethylene oxide all traces of the gas must be removed before the materials can be used; removal may be by ventilation or more active means. Hypersensitivity reactions, including anaphylaxis, have been associated with ethylene oxide-contaminated materials. Ethylene oxide may also react with materials being sterilised to produce substances such as ethylene chlorohydrin (with chloride) or ethylene glycol (with water); these may contribute to any toxicity.

Pharmaceutical manufacturers within the EU have been advised to use ethylene oxide only when there is no alternative. Ethylene oxide has been shown to have carcinogenic and mutagenic properties and there is evidence of increased risk of neoplasms following occupational exposure.

Reviews.

1. WHO. Ethylene oxide. *Environmental Health Criteria 55*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc55.htm (accessed 15/03/06)
2. WHO. Ethylene oxide health and safety guide. *IPCS Health and Safety Guide 16*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg016.htm (accessed 15/03/06)
3. WHO. Ethylene oxide. *Concise International Chemical Assessment Document 54* Geneva: WHO, 2003. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad54.pdf (accessed 15/03/06)

Carcinogenicity. Exposure of workers to ethylene oxide has been associated with the development of lymphatic and haematopoietic cancer and there is concern that it may be linked to breast cancer. In order to evaluate the carcinogenicity of ethylene oxide the National Institute for Occupational Safety and Health (NIOSH), in the mid 1980s, assembled a cohort of about 18 000 workers exposed to ethylene oxide.[1-3] Results of the initial cohort followed up to 1987 showed no overall excess of haematopoietic cancer, but did find a significant excess of non-Hodgkin's lymphoma among men.[1] Based on limited clinical evidence from humans and from significant evidence in *animal* studies, the IARC concluded in 1994 that there was sufficient evidence to classify ethylene oxide as a definite human carcinogen.[4] A later evaluation[3] of the NIOSH cohort from 1987 to 1998 indicated that, despite 2852 deaths as opposed to 1177 deaths in the earlier study, there was little evidence of cancer excesses for ethylene oxide exposed workers versus the general population, with the exception of bone cancer (6 deaths), and no conclusion could be drawn from this small number. However, exposure-response analyses found statistically significant evidence of an association between increased exposure and some types of haematopoietic cancer (non-Hodgkin's lymphoma and lymphocytic leukaemia), particularly for males.[2,3] There was also some evidence for a positive exposure-response for breast cancer. Follow-up of a cohort of 2876 workers exposed to ethylene oxide in the UK[5] found no statistically significant increase in mortality from cancer overall, or from any specific category of tumour. A study[6] of a cohort of 7576 female workers exposed to ethylene oxide suggested that ethylene oxide was associated with breast cancer. However, the authors indicated weaknesses in the study that could have influenced the findings.

1. Steenland K, *et al*. Mortality among workers exposed to ethylene oxide. *N Engl J Med* 1991; **324:** 1402–7.
2. Stayner L, *et al*. Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol* 1993; **138:** 787–98.
3. Steenland K, *et al*. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occup Environ Med* 2004; **61:** 2–7.
4. IARC/WHO. Some industrial chemicals. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 60* 1994. Available at: http://monographs.iarc.fr/ENG/Monographs/vol60/volume60.pdf (accessed 23/05/06)
5. Coggon D, *et al*. Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. *Occup Environ Med* 2004; **61:** 358–62.
6. Steenland K, *et al*. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control* 2003; **14:** 531–9.

Effects on the nervous system. Four men exposed to ethylene oxide at a concentration of greater than 700 ppm developed neurological disorders. One experienced headaches, nausea, vomiting, and lethargy followed by major motor seizures. The others had headaches, limb numbness and weakness, increased fatigue, trouble with memory and thought processes, and slurred speech. Three also developed cataracts, and one required bilateral cataract extractions.[1] Rash, followed a few months later by hand numbness and weakness, headaches, and cognitive impairment, has been reported[2] in a cluster of 12 surgical nurses and technicians after exposure for 5 months to ethylene oxide-contaminated surgical gowns. Several patients showed signs of peripheral and CNS dysfunction and one patient had signs of axonal injury.

1. Jay WM, *et al*. Possible relationship of ethylene oxide exposure to cataract formation. *Am J Ophthalmol* 1982; **93:** 727–32.
2. Brashear A, *et al*. Ethylene oxide neurotoxicity: a cluster of 12 nurses with peripheral and central nervous system toxicity. *Neurology* 1996; **46:** 992–8.

Hypersensitivity. Anaphylactoid reactions in dialysis patients have resulted from the use of dialysis equipment sterilised with ethylene oxide.[1-3] There have also been reports of hypersensitivity[4] and anaphylactoid[5] reactions in plateletpheresis donors caused by residues of ethylene oxide in components of apheresis kits. The most common adverse reactions reported have been dyspnoea, wheezing, urticaria, flushing, headache, and hypotension, but acute severe bronchospasm, circulatory collapse, cardiac arrest, and death have also occurred. It was noted[6] that where severe, sometimes fatal, anaphylactoid reactions have occurred at the beginning of dialysis, ethylene oxide has almost universally been implicated, although exposure to cuprammonium cellulose (cuprophane) dialysis membranes may also have been involved.

It has been reported that there may be an increased risk of ethylene oxide-induced anaphylactic shock in children undergoing surgery for spina bifida.[7] Such children might be at increased risk of sensitisation and anaphylaxis, and came into frequent contact with ethylene oxide through multiple operations and catheterisations.

Occupational asthma and contact dermatitis have been attributed to residual ethylene oxide in surgical gloves.[8]

1. Bommer J, *et al.* Anaphylactoid reactions in dialysis patients: role of ethylene-oxide. *Lancet* 1985; **ii:** 1382–5.
2. Rumpf KW, *et al.* Association of ethylene-oxide-induced IgE antibodies with symptoms in dialysis patients. *Lancet* 1985; **ii:** 1385–7.
3. Röckel A, *et al.* Ethylene oxide hypersensitivity in dialysis patients. *Lancet* 1986; **i:** 382–3.
4. Leitman SF, *et al.* Allergic reactions in healthy plateletpheresis donors caused by sensitization to ethylene oxide gas. *N Engl J Med* 1986; **315:** 1192–6.
5. Muylle L, *et al.* Anaphylactoid reaction in platelet-pheresis donor with IgE antibodies to ethylene oxide. *Lancet* 1986; **ii:** 1225.
6. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. *BMJ* 1986; **292:** 1221–2.
7. Moneret-Vautrin DA, *et al.* High risk of anaphylactic shock during surgery for spina bifida. *Lancet* 1990; **335:** 865–6.
8. Verraes S, Michel O. Occupational asthma induced by ethylene oxide. *Lancet* 1995; **346:** 1434–5.

Pregnancy. A study[1] of female staff responsible for sterilising instruments was carried out in all general hospitals in Finland. The incidence of spontaneous abortion (analysed according to employment at the time of conception and corrected for maternal age, parity, decade of pregnancy, smoking, and consumption of alcohol and coffee) was significantly increased in those exposed to ethylene oxide during pregnancy compared with those not so exposed. This study provoked criticism,[2,3] and the authors conceded that the study was not large enough to compare abortion rates and known ethylene oxide concentrations.[4] A retrospective analysis[5] of 32 dental assistants who had been exposed to ethylene oxide during pregnancy suggested that, after adjusting for age, the risk of spontaneous abortions and preterm or post-term births may have been more than doubled.

1. Hemminki K, *et al.* Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. *BMJ* 1982; **285:** 1461–3.
2. Gordon JE, Meinhardt TJ. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976.
3. Austin SG. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976.
4. Hemminki K, *et al.* Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976–7.
5. Rowland AS, *et al.* Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth, and postterm birth. *Epidemiology* 1996; **7:** 363–8.

Pharmacokinetics

Ethylene oxide gas is rapidly absorbed through the lungs and distributed throughout the body. Percutaneous absorption can occur from aqueous solutions. It is rapidly metabolised by hydrolysis or conjugation with glutathione.

Ethylhexanal

2-Ethylcaproaldehyde; 2-Ethylhexylaldehyde; Octylaldehyde; Этилгексанол.

2-Ethylhexanal.

$C_8H_{16}O$=128.2

CAS — 123-05-7.

Profile

Ethylhexanal is an aldehyde disinfectant used for instrument disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Buraton 10 F†; Helipur H plus N.

Ethylhexylglycerin

Octoxyglycerin; Этилгексилглицерин.

3-[(2-Ethylhexyl)oxy]-1,2-propanediol.

$C_{11}H_{24}O_3$=204.3

CAS — 70445-33-9.

UNII — 147D247K3P.

Profile

Ethylhexylglycerin is a disinfectant used in a concentration of 0.3% in topical deodorant preparations. It is also used in products for disinfection of the hands.

References.

1. Stausbøl-Grøn B, Andersen KE. Allergic contact dermatitis to ethylhexylglycerin in a cream. *Contact Dermatitis* 2007; **57:** 193–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Uriage Desodorante Tri-Actif.

Formaldehyde

Formaldehid; Formaldehído; Formaldehyd; Формальдегид.

CH_2O=30.03

CAS — 50-00-0.

ATC Vet — QP53AX19.

UNII — 1HG84L3525.

Formaldehyde Solution

Formaldehído, solución de; Formaldehido tirpalas; Formaldehid-oldat; Formaldehyd roztok; Formaldéhyde, solution de; Formaldehydi solutio; Formaldehydiliuos; Formaldehydlösning; Formaldehydu roztwór.

NOTE. The names formalin and formol have been used for formaldehyde solution but in some countries they are trade marks.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Formaldehyde Solution (35 per cent); Formaldehyde Solution BP 2014). It contains 34.5 to 38.0% w/w of formaldehyde with methyl alcohol as a stabiliser. It is a clear, colourless, liquid. Miscible with water and with alcohol. It may be cloudy after storage. Store at a temperature between 15 degrees and 25 degrees. Protect from light.

USP 36: (Formaldehyde Solution). It contains not less than 34.5% w/w of formaldehyde with 9 to 15% methyl alcohol added to prevent polymerisation. It is a clear, colourless, or practically colourless liquid with a pungent, irritating odour. Miscible with water and with alcohol. Store at a temperature above 15 degrees in airtight containers. It may become cloudy on standing due to the separation of paraformaldehyde, especially if the solution is kept in a cold place; the cloudiness disappears on warming.

Strength of solutions. Formaldehyde solution is sometimes known simply as formaldehyde and this has led to confusion in interpreting the strength and the form in which formaldehyde is being used. In practice formaldehyde is available as formaldehyde solution which is diluted before use, the percentage strength being expressed in terms of formaldehyde solution rather than formaldehyde. For example, in the UK, formaldehyde solution 3% consists of 3 volumes of Formaldehyde Solution (35 Per Cent) (Ph. Eur. 8) diluted to 100 volumes with water and thus contains 1.04 to 1.14% w/w of formaldehyde; it is ***not*** prepared by diluting Formaldehyde Solution (35 Per Cent) (Ph. Eur. 8) to arrive at a solution containing 3% w/w of formaldehyde.

Incompatibility. Formaldehyde reacts with protein and this may diminish its antimicrobial activity.

Uses and Administration

Formaldehyde solution is a bactericidal disinfectant also effective against fungi and many viruses. It is slowly effective against bacterial spores but its sporicidal effect is greatly increased by increase in temperature.

Formaldehyde solution is usually used diluted and it is important to note that the strength of preparations is given in terms of the content of formaldehyde solution and not in terms of the final concentration of formaldehyde (see under Strength of Solutions, above).

Formaldehyde solution is used in the disinfection of blankets and bedding and in the disinfection of the membranes in dialysis equipment. It is important to ensure that there are no traces of formaldehyde on any equipment before it is used. Formaldehyde solution is also used with succinic dialdehyde for instrument disinfection.

When applied to the unbroken skin, formaldehyde solution hardens the epidermis, renders it tough and whitish, and produces a local anaesthetic effect. Diluted formaldehyde solutions, as well as a water-miscible gel containing formaldehyde 0.75% w/w, have been used for the treatment of warts on the palms of the hands and soles of the feet. Sweating of the feet may be treated by the application of formaldehyde solution in glycerol or alcohol but such applications are liable to produce sensitisation reactions and other treatments are regarded as more effective (see Hyperhidrosis, p. 1685.1).

After surgical removal of hydatid cysts, diluted formaldehyde solution has been used for irrigating the cavities to destroy scolices but other larvicides are preferred (see Echinococcosis, p. 145.2). It is generally too irritant for use on mucous membranes but it has been used in mouthwashes and pastes as an antiseptic and hardening agent for the gums. In dentistry it has been used in endodontic treatment.

Formaldehyde solution in concentrations of up to 10% v/v in saline is used as a preservative for pathological specimens. It is not suitable for preserving urine for subsequent examination. Formaldehyde solution is used for the inactivation of viruses in vaccine production.

Formaldehyde gas has little penetrating power and readily polymerises and condenses on surfaces and its efficacy depends on it dissolving in a film of moisture before acting on micro-organisms; in practice a relative humidity of 80 to 90% is necessary. Formaldehyde gas is used for the disinfection of rooms and cabinets. The gas may be produced from 500 mL of undiluted formaldehyde solution by boiling with 1 litre of water or by addition of potassium permanganate or by heating a formaldehyde-containing solid such as paraformaldehyde (p. 1763.1). Formaldehyde gas is used with low-temperature steam for the sterilisation of heat-sensitive items.

Other compounds which are thought to act by releasing formaldehyde include noxytiolin (p. 1762.1) and methenamine (p. 322.3).

Haemorrhagic cystitis. Formaldehyde has been used for local therapy of haemorrhagic cystitis (p. 2347.3), although there has been debate about the most appropriate regimen. The Fair regimen[1] for the intravesical use of formaldehyde solution in haemorrhagic cystitis involves passive irrigation of the bladder with 500 to 1000 mL of formaldehyde solution 1% v/v for a total of 10 minutes, the bladder subsequently being emptied and washed out with 1 litre of distilled water. Stronger concentrations of formaldehyde solution and other methods can be used if bleeding does not stop.[2] In a review of 118 patients treated with solutions of formaldehyde for intractable haematuria, the authors felt that this was probably the most effective treatment, but also probably the most dangerous.[3] More concentrated instillations, containing formaldehyde solution 5 to 10% seem to be generally viewed as unnecessary, and associated with an increased risk of complications which precludes their use.[4-7]

1. Fair WR. Formalin in the treatment of massive bladder hemorrhage: techniques, results, and complications. *Urology* 1974; **3:** 573–6.
2. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; **i:** 304–6.
3. Godec CJ, Gleich P. Intractable hematuria and formalin. *J Urol (Baltimore)* 1983; **130:** 688–91.
4. Bullock N, Whitaker RH. Massive bladder haemorrhage. *BMJ* 1985; **291:** 1522–3.
5. Donahue LA, Frank IN. Intravesical formalin for haemorrhagic cystitis: analysis of therapy. *J Urol (Baltimore)* 1989; **141:** 809–12.
6. Murray JA, *et al.* Massive bladder haemorrhage. *BMJ* 1986; **292:** 57.
7. Smith PJB, *et al.* Massive bladder haemorrhage. *BMJ* 1986; **292:** 412.

Adverse Effects and Precautions

Concentrated formaldehyde solutions applied to the skin cause whitening and hardening. Contact dermatitis and sensitivity reactions have occurred after the use of conventional concentrations and after contact with residual formaldehyde in resins.

Ingestion of formaldehyde solution causes intense burning pain in the mouth, throat, chest, and stomach, with inflammation, ulceration, and necrosis of mucous membranes. There may be nausea, vomiting, haematemesis, blood-stained diarrhoea, haematuria, and anuria; metabolic acidosis, vertigo, convulsions, loss of consciousness, and circulatory and respiratory failure may occur. Death has occurred after the ingestion of the equivalent of about 30 mL of formaldehyde solution. If the patient survives 48 hours, recovery is probable. Formaldehyde vapour is irritant to the eyes, nose, and upper respiratory tract, and may cause coughing, dysphagia, spasm and oedema of the larynx, bronchitis, pneumonia, and rarely, pulmonary oedema. Asthma-like symptoms have been reported after repeated exposure.

General references.

1. Health and Safety Executive. Formaldehyde. *Toxicity Review 2*. London: HMSO, 1981.
2. WHO. Formaldehyde. *Environmental Health Criteria 89*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc89.htm (accessed 15/03/06)
3. WHO. Formaldehyde health and safety guide. *IPCS Health and Safety Guide 57*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg057.htm (accessed 15/03/06)
4. WHO. Formaldehyde. *Concise International Chemical Assessment Document 40* Geneva: WHO, 2002. Available at: http://whqlibdoc.who.int/hq/2002/a73769.pdf (accessed 15/03/06)

Abuse. References to the abuse of embalming fluid (the primary ingredient of which is formaldehyde), usually in the form of marijuana treated with embalming fluid (street names include: dank; dip; fry; hydro; illy; sherm; wet); in some cases the embalming fluid contains phencyclidine.[1-6]

1. Holland JA, *et al.* Embalming fluid-soaked marijuana: new high or new guise for PCP? *J Psychoactive Drugs* 1998; **30:** 215–9.
2. Peters RJ, *et al.* Beliefs and social norms about cigarettes or marijuana sticks laced with embalming fluid and phencyclidine (PCP): why youth use "fry". *Subst Use Misuse* 2005; **40:** 563–71.

3. Singer M, *et al.* Dust in the wind: the growing use of embalming fluid among youth in Hartford, CT. *Subst Use Misuse* 2005; **40:** 1035–50.
4. Singer M, *et al.* When the drug of choice is a drug of confusion: embalming fluid use in inner city Hartford, CT. *J Ethn Subst Abuse* 2005; **4:** 73–96.
5. D'Onofrio G, *et al.* Illy: clinical and public health implications of a street drug. *Subst Abus* 2006; **27:** 45–51.
6. Marceaux JC, *et al.* Neuropsychological effects of formaldehyde use. *J Psychoactive Drugs* 2008; **40:** 207–10.

Carcinogenicity. There is controversy as to the risk formaldehyde presents as a carcinogen. Studies on the occupational exposure of medical personnel and industrial workers[1-3] to formaldehyde have generally concluded that although the risk is small or non-existent, the possibility that formaldehyde is a human carcinogen cannot be excluded. Reanalyses of some studies have led to different interpretations of the results, with some workers concluding that the risk of cancer from formaldehyde is greater than originally thought.[4] Analysis of mortality data[5] for a cohort of 25619 workers exposed to formaldehyde in the USA found some evidence of an association with nasopharyngeal cancer and possibly cancers at other upper respiratory-tract sites. Based on the results of this large cohort study and supported by evidence from other epidemiological and *animal* studies, the IARC concluded,[6] in 2004, that occupational exposure to formaldehyde does cause nasopharyngeal cancer. Furthermore, they found strong, but not sufficient, evidence to establish a causal link with leukaemia and limited evidence to suggest it causes sinonasal cancer. IARC has concluded that formaldehyde is a definite human carcinogen.[6]

1. Gérin M, *et al.* Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montreal. *Int J Cancer* 1989; **44:** 53–8.
2. Blair A, *et al.* Mortality from lung cancer among workers employed in formaldehyde industries. *Am J Ind Med* 1990; **17:** 683–99.
3. Coggon D, *et al.* Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst* 2003; **95:** 1608–15.
4. Sterling TD, Weinkam JJ. Mortality from respiratory cancers (including lung cancer) among workers employed in formaldehyde industries. *Am J Ind Med* 1994; **25:** 593–602.
5. Hauptmann M, *et al.* Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol* 2004; **159:** 1117–30.
6. IARC/WHO. Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxy-2-propanol. *IARC monographs on the evaluation of carcinogenic risks to humans volume 88* 2004. Available at: http://monographs.iarc.fr/ENG/Monographs/vol88/volume88.pdf (accessed 23/05/06)

Effects on the blood. Haemolysis during chronic haemodialysis was due to formaldehyde eluted from filters.[1]

1. Orringer EP, Mattern WD. Formaldehyde-induced hemolysis during chronic hemodialysis. *N Engl J Med* 1976; **294:** 1416–20.

Effects on the urinary tract. Adverse effects have resulted from intravesical instillation of formaldehyde solutions, ranging in strength from 1 to 10%, in the treatment of haemorrhagic cystitis. They include dysuria, suprapubic pain, ureteric and bladder fibrosis, hydronephrosis, vesicoureteral reflux, bilateral ureteral obstruction, papillary necrosis, bladder rupture, and acute tubular necrosis. Intraperitoneal spillage through a fistula, leading to adverse systemic effects, has also occurred.[1] Fatalities have resulted from cardiac arrest and acute renal failure.[1-3] See also Haemorrhagic Cystitis under Uses, p. 1752.3.

There has also been a report[4] of 4 patients exposed to high levels of atmospheric formaldehyde who developed membranous nephropathy, suggesting that there may be genetic susceptibility for this effect.

1. Capen CV, *et al.* Intraperitoneal spillage of formalin after intravesical instillation. *Urology* 1982; **19:** 599–601.
2. Melekos M, Lalos J. Intravesical instillation of formalin and its complications. *Urology* 1983; **21:** 331–2.
3. Sarnak MJ, *et al.* Intravesicular formaldehyde instillation and renal complications. *Clin Nephrol* 1999; **51:** 122–5.
4. Breysse P, *et al.* Membranous nephropathy and formaldehyde exposure. *Ann Intern Med* 1994; **120:** 396–7.

Hypersensitivity. Hypersensitivity to formaldehyde has had several manifestations. Effects on the skin have included acute exacerbation of eczema after injection of hepatitis B vaccine containing formaldehyde up to 20 micrograms/mL.[1] In another case, formaldehyde sensitivity was characterised by pruritus, burning, and redness within minutes of exposure to sunlight.[2] Painful, enlarged, and haemorrhagic gingival margins have occurred after the use of a toothpaste containing a solution of formaldehyde.[3] There is conflicting evidence of the respiratory effects of formaldehyde: although a low concentration has been reported not to trigger an asthma attack in patients with severe bronchial hyperresponsiveness,[4] occupational asthma has been documented.[5] More severe manifestations of hypersensitivity include 7 cases of shock of possible toxic or anaphylactic aetiology that occurred after the use of formaldehyde solutions during surgical removal of hydatid cysts.[6]

For mention of an allergic response to root canal paste containing paraformaldehyde, see p. 1763.1.

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patients. *Lancet* 1986; **ii:** 522–3.
2. Shelley WB. Immediate sunburn-like reaction in a patient with formaldehyde photosensitivity. *Arch Dermatol* 1982; **118:** 117–18.
3. Laws IM. Toothpaste formulations. *Br Dent J* 1984; **156:** 240.
4. Harving H, *et al.* Low concentrations of formaldehyde in bronchial asthma: a study of exposure under controlled conditions. *BMJ* 1986; **293:** 310.
5. Heard BE. Low concentrations of formaldehyde in bronchial asthma. *BMJ* 1986; **293:** 821.
6. Galland MC, *et al.* Risques thérapeutiques de l'utilisation des solutions de formol dans le traitement chirurgical des kystes hydatiques du foie. *Therapie* 1980; **35:** 443–6.

Treatment of Adverse Effects

Contaminated skin should be washed with soap and water. After ingestion water, milk, charcoal, and/or demulcents should be given; emesis should be avoided. Assisted ventilation may be required and shock should be alleviated appropriately. Convulsions should be controlled with diazepam and pain with morphine. Acidosis, resulting from metabolism of formaldehyde to formic acid, may require intravenous sodium bicarbonate or sodium lactate. The use of haemodialysis has been suggested.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Formol†; ***Ger.***: Lysoform; ***Rus.***: Formagel (Формагель); Formidron (Формидрон); ***UK***: Veracur; ***USA***: Formadon; Formalaz; Formalyde; Lazerformaldehyde.

Multi-ingredient Preparations. ***Arg.***: Cistimax Ungueal; Parodium; ***Austral.***: Formo-Cresol Mitis†; ***Canad.***: Duoplant†; ***Chile***: Parodium; ***Fr.***: Osomol; Parodium; ***Ger.***: Buraton 10 F†; Incidin perfekt; Lysoformin; Melsitt; Sekusept forte S; Sporcid; Ultrasol-F; ***Indon.***: Skintex†; ***Ital.***: Melsept; ***Rus.***: Parodium (Пародиум); Teimurov (Теймурова); ***Spain***: Viberol Tirotricina.

Glucoprotamine

Glucoprotamina; Глюкопротамин.

Reaction product of L-glutamic acid and cocopropylene-1,3-diamine.

Profile

Glucoprotamine is used as a disinfectant for surfaces and medical equipment.

References.
1. Disch K. Glucoprotamine—a new antimicrobial substance. *Zentralbl Hyg Umweltmed* 1994; **195:** 357–65.
2. Meyer B, Kluin C. Efficacy of glucoprotamin containing disinfectants against different species of atypical mycobacteria. *J Hosp Infect* 1999; **42:** 151–4.
3. Widmer AE, Frei R. Antimicrobial activity of glucoprotamin: a clinical study of a new disinfectant for instruments. *Infect Control Hosp Epidemiol* 2003; **24:** 762–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Incidin Plus; Sekusept Plus.

Multi-ingredient Preparations. ***Ger.***: Incidin extra N; Incidin.

Glutaral *(USAN, rINN)*

Adehyd glutarowy; Glutaraldehid; Glutaraldehído; Glutaraldehyde; Glutaralum; Glutaric Dialdehyde; Pentanedial; Глутарал.

Pentane-1,5-dial.

$C_5H_8O_2$=100.1

CAS — 111-30-8.

ATC — D08AX09.

UNII — T3C89M417N.

Pharmacopoeias. Solutions of glutaral are included in *Br.*, *Chin.*, and *US*. A solution is also in *USNF*.

BP 2014:: (Strong Glutaraldehyde Solution). It contains 47 to 53% w/w of glutaral. Store at a temperature not exceeding 15 degrees.

USP 36: (Glutaral Concentrate). It contains 50 to 52% w/w of glutaral and has a pH between 3.7 and 4.5. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

USNF 31: (Glutaral Disinfectant Solution). It has a pH between 2.7 and 3.7. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Uses and Administration

Glutaral is a bactericidal disinfectant that is rapidly effective against Gram-positive and Gram-negative bacteria. It is also effective against *Mycobacterium tuberculosis*, some fungi, and viruses, including hepatitis B virus and HIV, and is slowly effective against bacterial spores. Aqueous solutions show optimum activity between pH 7.5 and 8.5; such solutions are chemically stable for about 14 days. Solutions at lower pH values are more stable.

A 2% aqueous solution buffered to a pH of about 8 (activated glutaral; alkaline glutaral) may be used for the sterilisation of endoscopic and dental instruments, rubber or plastic equipment, and for other equipment which cannot be sterilised by heat. Glutaral is non-corrosive towards most materials. Complete immersion in the solution for 10 to 20 minutes is sufficient for rapid disinfection of thoroughly cleansed instruments but exposure for up to 10 hours may be necessary for sterilisation. For further details, see Disinfection of Endoscopes, p. 1731.2, and Disinfection in Hepatitis and HIV Infection, p. 1731.2.

A 10% solution is applied twice daily for the treatment of warts (p. 1689.3); a 5% solution and a 10% gel have also been used. Glutaral should not be used for facial or anogenital warts. Glutaral has also been used topically for treating hyperhidrosis of the palms and soles, although other agents are generally preferred (see p. 1685.1).

Adverse Effects

As for Formaldehyde Solution, p. 1752.3.

Effects on the gastrointestinal tract. Insufficient rinsing of a glutaral 2% solution from flexible endoscopes after disinfection appears to be responsible for outbreaks of glutaral-induced colitis in patients undergoing colonoscopy and sigmoidoscopy.[1-4] Symptoms may occur within minutes or up to 48 hours after endoscopy and are usually abdominal pain, mucous diarrhoea, and rectal bleeding. Fever, nausea, vomiting and leucocytosis have also been reported. A case of glutaral-induced colitis has also been attributed to inadequate flushing and drying of the endoscope channels.[2]

1. Durante L, *et al.* Investigation of an outbreak of bloody diarrhea: association with endoscopic cleaning solution and demonstration of lesions in an animal model. *Am J Med* 1992; **92:** 476–80.
2. West AB, *et al.* Glutaraldehyde colitis following endoscopy: clinical and pathological features and investigation of an outbreak. *Gastroenterology* 1995; **108:** 1250–5.
3. Fukunaga K, Khatibi A. Glutaraldehyde colitis: a complication of screening flexible sigmoidoscopy in the primary care setting. *Ann Intern Med* 2000; **133:** 315.
4. Stein BL, *et al.* Glutaraldehyde-induced colitis. *Can J Surg* 2001; **44:** 113–16.

Occupational exposure. Reviews[1,2] of the occupational hazards of glutaral have noted that several studies showed adverse effects, including nausea, headache, airway obstruction, asthma, rhinitis, eye irritation, and dermatitis, occurring among medical personnel exposed to glutaral, generally at concentrations below the recommended limits. Skin reactions were due to hypersensitivity or a direct irritant effect. It was concluded that, when using glutaral, workers should take suitable precautions to protect the skin and eyes and should avoid inhaling the vapour. Appropriate procedures should also be followed for disposal and clean-up of spills.

The risk of occupational exposure to glutaral vapour may be higher in warm climates.[3]

There has also been a report of accidental ocular contact with glutaral due to leakage of glutaral solution retained in an anaesthesia mask; moderate chemical conjunctivitis ensued.[4]

1. Burge PS. Occupational risks of glutaraldehyde. *BMJ* 1989; **299:** 342.
2. Ballantyne B, Jordan SL. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures. *J Appl Toxicol* 2001; **21:** 131–51.
3. Mwaniki DL, Guthua SW. Occupational exposure to glutaraldehyde in tropical climates. *Lancet* 1992; **340:** 1476–7.
4. Murray WJ, Ruddy MP. Toxic eye injury during induction of anaesthesia. *South Med J* 1985; **78:** 1012–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asepto-Glutaral; ***Austral.***: Diswart; ***Fr.***: Steranios†; ***Ger.***: Korsolex-Endo-Disinfectant; ***India***: Cadicide; Cidex; Glutihyde; ***Irl.***: Glutarol; ***Ital.***: Citrosteril Sterilferri; Diba; Eso H1; Ferriseptil†; SaniSteril Sterilferri; Sporex†; ***S.Afr.***: Virogerm†; ***Thai.***: Glutahyde; GTR; ***UK***: ASEP; Glutarol; ***USA***: Cetylcide-G; Cidex.

Multi-ingredient Preparations. ***Ger.***: Aerodesin; Bacillol plus; Buraton 10 F†; Helipur H plus N; Incidin perfekt; Incidur; Kohrsolin extra; Kohrsolin FF; Kohrsolin†; Korsolex basic; Korsolex Extra; Korsolex FF; Lysoformin 3000; Lysoformin; Melsept SF; Melsitt; Sekusept Extra N; Sekusept forte S; Sporcid; Ultrasol-F; ***Ital.***: Citrosteril Impronte; Esoform 92; Incidin Spezial†; Melsept SF; Melsept; Sekucid†; Sekumatic†; ***Rus.***: Combutec-2 (Комбутек-2); ***Thai.***: Posequat with GA†.

Pharmacopoeial Preparations

BP 2014: Glutaraldehyde Solution; Strong Glutaraldehyde Solution;
USNF 31: Glutaral Disinfectant Solution;
USP 36: Glutaral Concentrate.

Glyoxal

Biformilo; Etanodial; Ethanedial; Glioxal; Oxalaldehyde; Глиоксаль.

1,2-Ethanedione.

$C_2H_2O_2$=58.04

CAS — 107-22-2.

UNII — 50NP6JJ975.

Profile

Glyoxal is an aldehyde used for the disinfection of surfaces and of medical and surgical instruments.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Buraton 10 F†; Freka-Nol†; Incidin perfekt; Incidur; Lysoformin 3000; Meliseptol; Melsept SF; Ultrasol-F; ***Ital.***: Incidin Speział†; Indulfan†; Melsept SF; Melsept Spray; Melsept.

Halazone *(rINN)*

Halazona; Halazonum; Pantocide; Галазон.

4-(Dichlorosulphamoyl)benzoic acid.

$C_7H_5Cl_2NO_4S$=270.1

CAS — 80-13-7.

UNII — G359OL82VB.

Pharmacopoeias. In *US*.

USP 36: (Halazone). A white crystalline powder with a characteristic odour of chlorine. Soluble 1 in more than 1000 of water and of chloroform, 1 in 140 of alcohol, and 1 in more than 2000 of ether; soluble in glacial acetic acid. It dissolves in solutions of alkali hydroxides and carbonates with the formation of a salt. Store in airtight containers. Protect from light.

Profile

Halazone is a disinfectant with the general properties of chlorine (p. 1746.2) in aqueous solution and is used for the disinfection of drinking water (p. 1731.3). It contains about 52% of 'available chlorine' (see p. 1746.3). One tablet containing 4 mg of halazone, stabilised with sodium carbonate and sodium chloride, may be sufficient to treat about 1 litre of water in about 30 minutes to 1 hour. The taste of residual chlorine may be removed by adding sodium thiosulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Helporide; ***Turk.***: Haloseptil.

Pharmacopoeial Preparations

USP 36: Halazone Tablets for Solution.

Hexachlorophene *(BAN, rINN)*

G-11; Heksaklorofeeni; Hexachlorofen; Hexachlorophane; Hexachlorophène; Hexachlorophenum; Hexaclorofeno; Hexaklorofen; Гексахлорофен.

2,2′-Methylenebis(3,4,6-trichlorophenol).

$C_{13}H_6Cl_6O_2$=406.9

CAS — 70-30-4.

ATC — D08AE01.

ATC Vet — QD08AE01; QP52AG02.

UNII — IWW5FV6NK2.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Hexachlorophene). A white or pale buff, odourless or almost odourless, crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in acetone and in ether. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Hexachlorophene). A white or light tan, crystalline powder which is odourless or has a slight phenolic odour. Insoluble in water; freely soluble in alcohol, in acetone, and in ether; soluble in chloroform and in dilute solutions of fixed alkali hydroxides. Store in airtight containers. Protect from light.

Incompatibility. The activity of hexachlorophene may be reduced in the presence of blood or other organic material. It retains some activity in the presence of soap.

The activity has been reported[1] to be reduced by alkaline media and by nonionic surfactants such as polysorbate 80. It is extremely sensitive to iron, and to avoid discoloration due to traces of this metal in hexachlorophene detergent solutions, it is advisable to incorporate a sequestrant such as disodium edetate.[2]

1. Walter G, Gump W. Effect of pH on hexachlorophene. *Soap Chem Spec* 1963; **39:** 55–6.
2. Bell M. Hexachlorophene-based skin cleansers. *Specialities* 1965; **1:** 16–18.

Uses and Administration

Hexachlorophene is a chlorinated bisphenol antiseptic with a bacteriostatic action against Gram-positive organisms, but much less effective against Gram-negative organisms. It is most active at pH 5 to 6.

Hexachlorophene is mainly used in soaps and creams in a concentration of 0.23 to 3% and is an ingredient of various preparations used for skin disorders. After repeated use of these preparations for several days there is a marked diminution of the bacterial flora due to accumulation of hexachlorophene in the skin. This residual effect is rapidly lost after washing with unmedicated soap or alcohol.

A preparation containing 3% is used for the disinfection of the hands of surgeons and other healthcare personnel. Thorough rinsing is recommended before drying. Hexachlorophene has been applied as a 0.33% dusting powder to the umbilical cord stump for the control of staphylococcal infection in the newborn. However, care is necessary when using hexachlorophene in neonates (see below).

Hexachlorophene sodium has also been used.

Disinfection. Eradication of an outbreak of infection with meticillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit was achieved by use of hexachlorophene soap for hand washing. Previous infection-control measures including the use of chlorhexidine had failed.[1] For a discussion of staphylococcal infections and their treatment, see p. 208.2.

1. Reboli AC, *et al*. Epidemic methicillin-gentamicin-resistant Staphylococcus aureus in a neonatal intensive care unit. *Am J Dis Child* 1989; **143:** 34–9.

Adverse Effects and Treatment

After ingestion of hexachlorophene, anorexia, nausea, vomiting, diarrhoea, abdominal cramps, dehydration, shock, and confusion may occur. Convulsions and death may follow. CNS stimulation, convulsions, and death have also occurred after absorption of hexachlorophene from burns and damaged skin. There have been reports showing that hexachlorophene can be absorbed through the skin of infants in amounts sufficient to produce spongy lesions of the brain, sometimes fatal.

Photosensitivity and skin sensitisation have occasionally occurred after repeated use of hexachlorophene.

Treatment of adverse effects is as for Phenol, p. 1764.3.

Effects on the respiratory system. Asthma developed in a 43-year-old nurse after long-term exposure to hexachlorophene powder.[1]

1. Nagy L, Orosz M. Occupational asthma due to hexachlorophene. *Thorax* 1984; **39:** 630–1.

Precautions

Hexachlorophene should not be applied to mucous membranes, large areas of skin, or to burnt, damaged, or denuded skin and should not be used vaginally, applied under occlusive dressings, or applied to areas affected by dermatoses. It should be used with caution on infants, especially premature and low birth-weight neonates. Its use is not advised in pregnancy.

Preparations of hexachlorophene are liable to contamination, especially with Gram-negative bacteria.

Breast feeding. The American Academy of Pediatrics[1] considers that, while no effects on the infant have been reported, there is a possibility of contamination of breast milk with hexachlorophene used by breast-feeding mothers for nipple washing.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Neonates. Spongiform encephalopathy has occurred in neonates who were treated topically with hexachlorophene.[1] Neonates with a birth-weight of 1.4 kg or less appeared to be most susceptible, whereas those weighing over 2 kg were not considered to be at risk.[1,2] Also most of the reports involved hexachlorophene applied in a concentration of 3%.

1. Anonymous. Hexachlorophene today. *Lancet* 1982; **i:** 87–8.
2. Plueckhahn VD, Collins RB. Hexachlorophene emulsions and antiseptic skin care of newborn infants. *Med J Aust* 1976; **1:** 815–19.

Pregnancy. Hexachlorophene is absorbed from the skin and crosses the placenta, but whether it has produced teratogenic effects is subject to debate.[1,2] However, it is considered best to avoid its use during pregnancy.

1. Halling H. Suspected link between exposure to hexachlorophene and malformed infants. *Ann N Y Acad Sci* 1979; **320:** 426–35.
2. Baltzar B, *et al*. Pregnancy outcome among women working in Swedish hospitals. *N Engl J Med* 1979; **300:** 627–8.

Pharmacokinetics

Hexachlorophene is absorbed from the gastrointestinal tract after accidental ingestion, and through intact and denuded skin. Percutaneous absorption may be significant in premature infants and through damaged skin. Hexachlorophene crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Acnemask†; Incoliquid; ***Indon.***: Dermisan; ***Thai.***: Hexa Clean; ***Venez.***: Solu-Hex.

Multi-ingredient Preparations. ***Canad.***: pHisoHex; ***Cz.***: Septonex; ***Gr.***: Creme Phyllis de Jeunesse; Hemorrocort; Hemorroidal-H; Rysolone; ***Hung.***: Phlogosol; ***Indon.***: Topicide†; ***Irl.***: Torbetol†; ***Port.***: Anacal; ***Spain***: Cresophene; ***Thai.***: Cibis†; ***USA***: pHisoHex; ***Venez.***: Permucal.

Pharmacopoeial Preparations

BP 2014: Hexachlorophene Dusting Powder;

USP 36: Hexachlorophene Cleansing Emulsion; Hexachlorophene Liquid Soap.

Hexamidine Isetionate *(BANM, rINNM)*

Heksamidino diizetionatas; Hexamidina, isetionato de; Hexamidindiisetionat; Hexamidin-diisetionát; Hexamidindiizetionát; Hexamidine Diisetionate; Hexamidine, diisétionate d'; Hexamidine Isethionate; Hexamidine, Isétionate d'; Hexamidini Diisetionas; Hexamidini Isetionas; Isetionato de hexamidina; Гексамидина Изетионат.

4,4′-(Hexamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).

$C_{20}H_{26}N_4O_2,2C_2H_6O_4S$=606.7

CAS — 3811-75-4 (hexamidine); 659-40-5 (hexamidine isetionate).

ATC — D08AC04; R01AX07; R02AA18; S01AX08; S03AA05.

ATC Vet — QD08AC04; QR01AX07; QR02AA18; QS01AX08; QS03AA05.

UNII — 023XA5Z50L.

NOTE. The name Hexamidinum has been used for primidone (p. 547.1).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hexamidine Diisetionate; Hexamidine Isetionate BP 2014). A white or slightly yellow hygroscopic powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

Profile

Hexamidine isetionate has antibacterial and antifungal properties and is available in preparations for the local treatment of minor infections.

Acanthamoeba keratitis. Hexamidine was suggested[1] as a possible alternative to propamidine for the treatment of *Acanthamoeba* keratitis (p. 919.3) due to the poor cysticidal activity, chronic conjunctival infection, and resistance of some *Acanthamoeba* strains seen with propamidine.[1,2] Cures have been reported with 0.1% hexamidine used either as monotherapy[2,3] or with polihexanide.[2]

1. Perrine D, *et al*. Amoebicidal efficiencies of various diamidines against two strains of Acanthamoeba polyphaga. *Antimicrob Agents Chemother* 1995; **39:** 339–42.
2. Murdoch D, *et al*. Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; **26:** 231–6.
3. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; **17:** 893–905.

Adverse effects. A systemic allergic reaction in a patient after use of a topical antiseptic cream was confirmed, by skin prick tests, to be caused by hexamidine.[1]

1. Mullins RJ. Systemic allergy to topical hexamidine. *Med J Aust* 2006; **185:** 177.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Desomedine; Hexomedine; Ophtamedine; ***Fr.***: Desomedine; Hexaseptine; Hexomedine; ***Ger.***: Laryngomedin N†; ***Gr.***: Ophtamedine; ***Singapore***: Desomedine; ***Switz.***: Desomedine; ***Venez.***: Hexomedine.

Multi-ingredient Preparations. ***Austral.***: Medi Creme; Medi Pulv; ***Austria***: Imazol Duo; ***Belg.***: Colludol; Hexomedine†; ***Braz.***: Hexomedine; ***Cz.***: Cyteal; Imacort; Imazol Plus; ***Fr.***: Aurigoutte; Colludol; Cyteal; Doli Mal de Gorge; Ergix mal de gorge; Oto-

mide†; Solutricine Maux de Gorge†; ***Ger.***: Imazol comp; Imazol Plus; ***Gr.***: Octrene; Pulvo-Hexa; ***Hong Kong***: Medicreme†; ***Neth.***: Imazol Duo; ***NZ***: Medicreme†; Medipulv; ***Philipp.***: Cyteal; ***Pol.***: Imazol Plus; ***Port.***: Cyteal; ***Rus.***: Cyteal (Цитеал); ***Singapore***: Cyteal; ***Spain***: Tantum†; ***Switz.***: Imacort; Imazol; ***Thai.***: Pulvo 47†; ***Turk.***: Imazol; Pulvo 47; ***UK***: Cyteal; ***Ukr.***: Cyteal (Цитеал); Imacort (Имакорт).

Hexetidine *(BAN, rINN)*

Heksetidiini; Heksetidin; Heksetidinas; Hexetidin; Hexetidina; Hexétidine; Hexetidinum; Гексэтидин.

5-Amino-1,3-bis(2-ethylhexyl)hexahydro-5-methylpyrimidine.

$C_{21}H_{45}N_3$=339.6

CAS — 141-94-6.

ATC — A01AB12.

ATC Vet — QA01AB12.

UNII — 852A84Y8LS.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hexetidine). An oily, colourless or slightly yellow liquid. Very slightly soluble in water; very soluble in alcohol, in acetone, and in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Uses and Administration

Hexetidine is a bactericidal and fungicidal antiseptic. It is used for minor infections of mucous membranes, and in particular as a 0.1% mouthwash for local infections and oral hygiene.

Oral hygiene. A mouthwash containing 0.1% hexetidine was no more effective than placebo in the management of patients with aphthous ulceration (see Mouth Ulceration, p. 1811.2) and provided no additional benefits to oral hygiene or gingival health.[1] However, such a mouthwash does appear to be of benefit in reducing supragingival plaque and gingival inflammation.[2]

1. Chadwick B, *et al.* Hexetidine mouthrinse in the management of minor aphthous ulceration and as an adjunct to oral hygiene. *Br Dent J* 1991; **171:** 83–7.
2. Sharma NC, *et al.* Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash. *J Clin Periodontol* 2003; **30:** 590–4.

Adverse Effects

Allergic contact dermatitis, alterations in taste, and transient anaesthesia have occasionally been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duranil; ***Austria***: Hexoral; ***Belg.***: Hextril; ***Canad.***: Steri/Sol; ***Chile***: Duranil; ***Fr.***: Collu-Hextril; Hextril; ***Ger.***: Hexoral; Vagi-Hex; ***Gr.***: Hexalen; Hexalyse; Irin; ***Hong Kong***: Bactidol; ***Indon.***: Bactidol†; Hexadol; ***Irl.***: Oraldene; ***Ital.***: Actiseptic; ***Malaysia***: Hexadol; ***Neth.***: Hextril; ***Philipp.***: Bactidol; Vagi-Hex; ***Port.***: Collu-Hextril; Hextril; ***Rus.***: Hexoral (Гексорал); Stomatidine (Стоматидин); ***S.Afr.***: Oraldine; ***Singapore***: Bactidol; ***Switz.***: Drossadin; Hextril; Vagi-Hex; ***Turk.***: Heksoral; Hekzoton; Vagi-Hex; ***UK***: Oraldene; ***Ukr.***: Hexoral (Гексорал); Stomatidin (Стоматидин).

Multi-ingredient Preparations. ***Arg.***: Buchex; Mantus; ***Austria***: Gurfix†; Isozid-H; ***Belg.***: Givalex; ***Cz.***: Stopangin; Stopangin; ***Fr.***: Angispray; Givalex; ***Hong Kong***: Anso; ***Ital.***: Neo Emoform; ***Rus.***: Stopangin (Стопангин); ***Spain***: Abrasone Rectal; Mentamida†; ***Ukr.***: Angilex (Ангилекс); Givalex (Гивалекс); Heppylor (Хепилор); Stopangin (Стопангин); Stopangin (Стопангин).

Hexylresorcinol *(BAN)*

Esilresorcina; Heksilrezorcinolis; Heksyyliresorsinoli; Hexilresorcinol; Hexilrezorcin; Hexylresocinolum; Hexylresorc; Hexylresorcin; Hexylrésorcinol; Hexylresorcinolum; Гексилрезорцин.

4-Hexylbenzene-1,3-diol.

$C_{12}H_{18}O_2$=194.3

CAS — 136-77-6.

ATC — R02AA12.

ATC Vet — QR02AA12.

UNII — R9QTB5E82N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Hexylresorcinol). A colourless, yellowish or reddish crystalline powder or needles, turning brownish-pink on exposure to light or air. It exhibits polymorphism. M.p. 66 degrees to 68 degrees; melting may occur at about 60 degrees followed by solidification and a second melting at 66 degrees to 68 degrees. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Hexylresorcinol). M.p. 62 degrees to 67 degrees. Store in airtight containers. Protect from light.

Incompatibility. Hexylresorcinol is incompatible with alkalis and oxidising agents.

Profile

Hexylresorcinol is a phenolic antiseptic that is used topically for the treatment of minor infections of the skin and mucous membranes, and in the form of lozenges for the treatment of sore throat. It has also been used in vaginal spermicidal preparations.

High concentrations of hexylresorcinol are irritant and corrosive to skin and mucous membranes. Alcoholic solutions are vesicant.

It was formerly used as an anthelmintic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Strepsils Extra†; ***Canad.***: Antiseptic Throat Lozenges; Bradosol; Bronchodex Pastilles Antiseptiques†; Soothe Aid; Strepsils Anesthetic Formula; Sucrets Extra Strength; ***Cz.***: Strepsinol†; ***Hong Kong***: Strepsils Pain Relief; ***Irl.***: Strepsils Extra; ***Malaysia***: Strepsils Max; Strepsils Pain Relief†; ***Singapore***: Strepsils Max; ***UK***: Halls Soothers Triple Action; Lemsip Sore Throat; Soothers Triple Action; Strepsils Extra; TCP; ***USA***: ST 37; Sucrets Original Formula Sore Throat Original Mint.

Multi-ingredient Preparations. ***Arg.***: Algiodent; Balsamina; Caramelos Antibioticos Lefmar; Caramelos Antibioticos; Caramelos Oriental; Collubiazol; Dotrin; Fanaletas; Fungicida; Gargadrin-R; Ixana; No-Tos Adultos; No-Tos Pocket; Pastillas Medex; Refenax Caramelos Expectorantes; Suavisan N; ***Braz.***: Andriodermol; Andriodermol; ***Canad.***: Strepsils Extra; ***Chile***: Fittig Antimicotico; ***Cz.***: Coldrex Proti Bolesti v Krku; ***Hong Kong***: Dequasin; ***India***: Tytin; ***Pol.***: Cholisept Intensive; Coldrex†; ***UK***: Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus.

Pharmacopoeial Preparations

USP 36: Hexylresorcinol Lozenges.

Hydrargaphen *(BAN, rINN)*

Hidrargafeno; Hydraphen; Hydrargaphène; Hydrargaphenum; Hygraphen; Phenylmercuric Dinaphthylmethanedisulfonate; Гидраргафен.

μ-(2,2′-Binaphthalene-3-sulphonyloxy)bis(phenylmercury).

$C_{33}H_{24}Hg_2O_6S_2$=981.9

CAS — 14235-86-0.

UNII — DL2D409P9O.

Profile

Hydrargaphen is a mercurial antiseptic with antibacterial and antifungal properties. It has been used as a pesticide.

Hydrogen Peroxide

Hidrojen Peroksit; Hydrogène, peroxyde d'; Hydrogenii Peroxidum; Peróxido de hidrógeno; Перекись Водорода.

H_2O_2=34.01

CAS — 7722-84-1.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

UNII — BBX060AN9V.

NOTE. The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Incompatibility. Hydrogen peroxide solutions are incompatible with reducing agents, including organic matter and oxidisable substances, and with some metals, metallic salts, alkalis, iodides, permanganates, and other stronger oxidising agents.

Stability. Aqueous solutions of hydrogen peroxide gradually decompose on standing and if allowed to become alkaline. Decomposition is increased by light, agitation, and heat. Incompatibility may also produce decomposition. Solutions are comparatively stable in the presence of a slight excess of acid. Strong solutions are considered to be more stable than weak solutions.

Storage. Solutions of hydrogen peroxide should be stored in airtight containers at 15 degrees to 30 degrees (but see Hydrogen Peroxide Solution (30 per cent), below). Solutions should not be stored for long periods. Those not containing a stabiliser should be stored at a temperature not exceeding 15 degrees. Protect from light.

Hydrogen Peroxide Solution (3 per cent)

3%-os hidrogén-peroxid-oldat; Agua oxigenada (10 volúmenes); Dilute Hydrogen Peroxide Solution; Hydrogen Peroxide Solution (10-volume); Hydrogen Peroxide Topical Solution; Hydrogenii Peroxidum 3%; Hydrogenii Peroxidum 3 Per Centum; Oxydol; Peroxid vodíku 3%; Peróxido de hidrógeno, solución al 3%; Vandenilio peroksido 3% tirpalas; Väteperoxid 3%; Vetyperoksidi 3%; Wasserstoffperoxid-Lösung 3 %; Wodoru nadtlenek 3%.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Hydrogen Peroxide Solution (3 per cent)). A clear colourless liquid containing 2.5 to 3.5% w/w of H_2O_2 corresponding to about 10 times its volume of oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. Solutions not containing a stabilising agent should be stored at a temperature below 15 degrees. Protect from light.

The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

USP 36: (Hydrogen Peroxide Topical Solution). It contains 2.5 to 3.5% w/v of H_2O_2. It may contain up to 0.05% of a suitable preservative or preservatives. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Hydrogen Peroxide Solution (6 per cent)

Hydrog. Perox. Soln; Hydrogen Dioxide Solution; Hydrogen Peroxide Solution; Hydrogen Peroxide Solution (20-volume); Liq. Hydrog. Perox.; Liquor Hydrogenii Peroxidi; Peróxido de hidrógeno, solución al 6%; Solución de Bióxido de Hidrogeno; Soluté Officinal d'Eau Oxygénée; Wasserstoffsuperoxydlösung.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Br.*

BP 2014: (Hydrogen Peroxide Solution (6 per cent)). A clear colourless aqueous liquid containing 5.0 to 7.0% w/v of H_2O_2 corresponding to about 20 times its volume of available oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. It should not be stored for long periods. Solutions not containing a stabilising agent should be stored at a temperature below 15 degrees. Protect from light.

The BP directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Hydrogen Peroxide Solution (27 per cent)

Hydrogenii Peroxidum; Perossido d'Idrogeno Soluzione; Peróxido de hidrógeno, solución al 27%; Solutio Hydrogenii Peroxydati; Strong Hydrog. Perox. Soln; Strong Hydrogen Peroxide Solution.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Description. Hydrogen peroxide solution (27 per cent) is a clear, colourless aqueous solution containing 26 to 28% w/w of H_2O_2, corresponding to about 100 times its volume of available oxygen. It may contain a suitable stabilising agent.

The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Hydrogen Peroxide Solution (30 per cent)

30%-os hidrogén-peroxid-oldat; Hydrogen Peroxide Concentrate; Hydrogen Peroxide Solution (100-volume); Hydrogenii Peroxidum 30%; Hydrogenii Peroxidum 30 Per Centum; Peroxid vodíku 30%; Peróxido de hidrógeno, solución al 30%; Vandenilio peroksido 30% tirpalas; Väteperoxid 30%; Vetyperoksidi 30%; Wasserstoffperoxid-Lösung 30 %; Wodoru nadtlenek 30%.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Eur.* (see p. vii).

Chin. specifies 26 to 28%.

US and *Viet.* specify 29 to 32%.

Ph. Eur. 8: (Hydrogen Peroxide Solution (30 per cent)). A clear colourless liquid containing 29.0 to 31.0% w/w of H_2O_2 corresponding to about 110 times its volume of available oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. Solutions not containing a stabilising agent should be stored at a temperature below 15 degrees. Protect from light.

The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

USP 36: (Hydrogen Peroxide Concentrate). A clear, colourless liquid containing 29 to 32% w/w of H_2O_2. It may contain up to 0.05% of a suitable preservative or preservatives. It is acid to litmus. It slowly decomposes and is affected by light. Store in partially-filled containers having a small vent in the closure, at a temperature of 8 degrees to 15 degrees.

Uses and Administration

Hydrogen peroxide is an oxidising agent used as an antiseptic, disinfectant, and deodorant. It has weak antibacterial activity and is also effective against viruses, including HIV. It also has a mild haemostatic action. It owes its antiseptic action to its ready release of oxygen when applied to tissues, but the effect lasts only as long as the oxygen is being released and is of short duration; in addition the antimicrobial effect of the liberated oxygen is reduced in the presence of organic matter. The mechanical effect of effervescence is probably more useful for wound cleansing (p. 1732.2) than the antimicrobial action.

Hydrogen peroxide solutions are used to cleanse wounds and ulcers in concentrations of up to 6%; creams containing 1 or 1.5% stabilised hydrogen peroxide are also used. Although hydrogen peroxide alone is not considered effective on intact skin, it is used with other antiseptics for the disinfection of hands, skin, and mucous membranes. Injection into closed body cavities is dangerous (see below). Adhering and blood-soaked dressings may be released by the application of a solution of hydrogen peroxide.

A 1.5% solution of hydrogen peroxide has been used as a mouthwash in the treatment of acute stomatitis and as a deodorant gargle. A suitable solution can be prepared by diluting 15 mL of hydrogen peroxide 6% in half a tumblerful of warm water. An oral gel has also been used.

Hydrogen peroxide ear drops have been used for the removal of wax. Such ear drops were prepared by diluting a 6% solution of hydrogen peroxide with 3 parts of water preferably just before use.

Hydrogen peroxide 3% is used for disinfecting soft contact lenses.

Immersion for 30 minutes in hydrogen peroxide 6% has been suggested for disinfecting cleaned equipment.

For bleaching hair and delicate fabrics hydrogen peroxide 6% should be diluted with an equal volume of water.

Strong solutions (27 per cent and 30 per cent) of hydrogen peroxide are used for the preparation of weaker solutions and should not be applied to tissues undiluted.

Hydrogen peroxide and other peroxides have many industrial uses as bleaching and oxidising agents.

Disinfection. *CONTACT LENSES.* Hydrogen peroxide 3% is particularly useful for disinfecting soft contact lenses (p. 1730.2) and lens storage cases since it is effective against *Acanthamoeba* spp. However, it is irritant to the cornea and requires inactivating with sodium pyruvate, catalase, or sodium thiosulfate, or with a platinum catalyst, before the lenses are used.

DIALYSIS EQUIPMENT. A disinfectant containing hydrogen peroxide and peracetic acid (*Renalin*) was not completely effective in killing *Mycobacterium chelonae* in high-flux dialysers. This possibly led to infection of 5 dialysis patients.[1] For a report of haemolysis and methaemoglobinaemia after inadvertent contamination of dialysis fluid with hydrogen peroxide, see Intravascular Administration under Adverse Effects and Precautions, below.

1. Lowry PW, *et al.* Mycobacterium chelonae infection among patients receiving high-flux dialysis in a hemodialysis clinic in California. *J Infect Dis* 1990; **161:** 85–90.

ENDOSCOPES. Peroxygen compounds have been suggested for disinfection of endoscopes as an alternative to glutaral (p. 1731.2). In the USA, a product containing 7.5% hydrogen peroxide is available as a high level disinfectant for processing of reusable medical devices.[1] Products containing varying concentrations of hydrogen peroxide with peracetic acid have also been approved by the FDA.

Hydrogen peroxide damages external surfaces, particularly rubbers and plastics of the insertion tubes and can corrode aluminium, nickel-silver alloy, and chrome. It is not considered suitable for flexible endoscopes.[2] Other peroxygen-containing compounds have been assessed for disinfecting endoscopes, but they appear to be less active against enteroviruses[3] and mycobacteria.[4] The Working Party of the British Society of Gastroenterology does not recommend peroxygen disinfectants for gastrointestinal endoscopes, unless a hydrogen peroxide gas plasma system is used during the sterilisation of invasive flexible endoscopes.[5]

Residual hydrogen peroxide solution can cause mucosal damage (see Closed Body Cavities, under Adverse Effects and Precautions, below) and endoscopes should be thoroughly rinsed before use.

1. FDA. FDA-cleared sterilants and high level disinfectants with general claims for processing reusable medical and dental devices (issued May 13, 2005). Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ReprocessingofSingle-UseDevices/ucm133514 (accessed 06/04/10)
2. Society of Gastroenterology Nurses and Associates, Inc. Guideline for use of high level disinfectants and sterilants for reprocessing flexible gastrointestinal endoscopes (issued 2006). Available at: http://www.sgna.org/Resources/hldguidelinefinal2007v3.pdf (accessed 13/05/10)
3. Tyler R, *et al.* Virucidal activity of disinfectants: studies with the poliovirus. *J Hosp Infect* 1990; **15:** 339–45.
4. Broadley SJ, *et al.* Antimycobacterial activity of 'Virkon'. *J Hosp Infect* 1993; **23:** 189–97.
5. British Society of Gastroenterology. BSG Working Party Report 2008. BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/decontamination_2008.pdf (accessed 26/02/10)

Mouth ulceration and infection. The use of antiseptic mouthwashes may be helpful in the management of mouth ulcers (p. 1811.2), although the use of high concentrations of hydrogen peroxide is not advisable (see Effects on the Mouth, below). Application of a 1.5% solution to individual ulcers with a topical corticosteroid may be useful. A randomised placebo-controlled study[1] to test the efficacy of a 1.5% hydrogen peroxide and 0.05% sodium fluoride-based mouthwash on gingivitis and tooth whitening, over a 6-month period found that it effectively whitened teeth and significantly reduced gingival redness. However, a review of the literature with practice guidelines pertaining to oral care of the critically ill[2] concluded that hydrogen peroxide could not be recommended as a mouthwash in this group, due to lack of evidence regarding its safety and efficacy in critically ill patients. A hydrogen peroxide denture cleaner was not effective in either preventing re-infection or in reducing mucosal inflammation in a study of 49 patients.[3] For oral candidal infections, specific antifungals are recommended (see p. 564.1).

1. Hasturk H, *et al.* Efficacy of a fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis: a randomized clinical trial. *J Periodontol* 2004; **75:** 57–65.
2. O'Reilly M. Oral care of the critically ill: a review of the literature and guidelines for practice. *Aust Crit Care* 2003; **16:** 101–10.
3. Walker DM, *et al.* The treatment of denture-induced stomatitis: evaluation of two agents. *Br Dent J* 1981; **151:** 416–19.

Adverse Effects and Precautions

Strong solutions of hydrogen peroxide produce irritating 'burns' on the skin and mucous membranes with a white eschar, but the pain disappears in about an hour. Continued use of hydrogen peroxide as a mouthwash may cause reversible hypertrophy of the papillae of the tongue.

It is dangerous to inject or instil hydrogen peroxide into closed body cavities from which the released oxygen has no free exit. Colonic lavage with solutions of hydrogen peroxide has been followed by gas embolism, rupture of the colon, proctitis, ulcerative colitis, and gangrene of the intestine.

Closed body cavities. Liberation of oxygen during the use of hydrogen peroxide in surgical procedures has resulted in oxygen embolism and local emphysema.[1-3] Gas embolism has also been reported after accidental ingestion of hydrogen peroxide solution.[4] Local damage to the colonic and rectal mucosa has followed the use of hydrogen peroxide 3% as an enema[5,6] and from residual hydrogen peroxide after disinfection of endoscopes.[7]

1. Sleigh JW, Linter SPK. Hazards of hydrogen peroxide. *BMJ* 1985; **291:** 1706.
2. Saïssy JM, *et al.* Risques de l'irrigation au peroxyde d'hydrogène en chirurgie de guerre. *Ann Fr Anesth Reanim* 1994; **13:** 749–53.
3. Konrad C, *et al.* Pulmonary embolism and hydrogen peroxide. *Can J Anaesth* 1997; **44:** 338–9.
4. Rackoff WR, Merton DF. Gas embolism after ingestion of hydrogen peroxide. *Pediatrics* 1990; **85:** 593–4.
5. Auroux J, *et al.* Rectocolite aiguë iatrogène après lavement à l'eau oxygénée. *Rev Geriatr* 1997; **22:** 21–4.
6. Gan SI, Price LM. Waiting-list induced proctitis: the hydrogen peroxide enema. *Can J Gastroenterol* 2003; **17:** 727–9.
7. Ryan CK, Potter GD. Disinfectant colitis: rinse as well as you wash. *J Clin Gastroenterol* 1995; **21:** 6–9.

Effects on the mouth. Use of hydrogen peroxide 3% as a mouthwash has been reported to cause mouth ulceration. A review[1] on the safety of hydrogen peroxide in dentistry concluded that low concentrations of hydrogen peroxide (1.5 to 3%) used long-term in mouthwashes and dentifrices, resulted in no adverse changes to the hard or soft tissues in the mouth. However, irritation may occur with low concentrations in patients with a thin or ulcerated oral mucosa. Short-term exposure to higher concentrations (30 to 35%), such as those used in teeth bleaching products and procedures, have resulted in mucosal erythema and sloughing, while long-term exposure may cause inflammation or hyperplasia.

1. Walsh LJ. Safety issues relating to the use of hydrogen peroxide in dentistry. *Aust Dent J* 2000; **45:** 257–69.

Intravascular administration. Intravenous injection of hydrogen peroxide solutions as unconventional therapy for AIDS or cancer has resulted in severe acute haemolysis.[1,2] Haemolysis and methaemoglobinaemia have been reported due to contamination of haemodialysis fluid with hydrogen peroxide.[3,4]

1. Jordan KS, *et al.* A 39-year-old man with acute hemolytic crisis secondary to intravenous injection of hydrogen peroxide. *J Emerg Nurs* 1991; **17:** 8–10.
2. Hirschtick RE, *et al.* Death from an unconventional therapy for AIDS. *Ann Intern Med* 1994; **120:** 694.
3. Gordon SM, *et al.* Hemolysis associated with hydrogen peroxide at a pediatric dialysis center. *Am J Nephrol* 1990; **10:** 123–7.
4. Davidovits M, *et al.* Methaemoglobinaemia and haemolysis associated with hydrogen peroxide in a paediatric haemodialysis centre: a warning note. *Nephrol Dial Transplant* 2003; **18:** 2354–8.

Poisoning. Ingestion of small quantities of hydrogen peroxide 3% generally results in only mild gastrointestinal effects. Ingestion of solutions of 10% or greater or large quantities of 3% solutions have been associated with severe morbidity and mortality. Irritation of the gastrointestinal tract with nausea, vomiting, foaming at the mouth, and haematemesis may occur. Blistering of the mucosa or oropharyngeal burns are common with solutions of 30% or greater. Large volumes of oxygen gas are produced in the stomach and this may result in painful gastric distension and belching. Apnoea, coma, convulsions, confusion, cyanosis, lethargy, stridor, and cardiorespiratory arrest have also been reported. Oxygen gas embolism is particularly dangerous. Immediate and permanent neurological damage has been reported after ingestion of hydrogen peroxide 35% and deaths have been reported in children and adults. Inhalation of high concentrations of hydrogen peroxide may cause irritation of the mucous membranes causing coughing and dyspnoea. Shock, convulsions, pulmonary oedema, and coma may follow. Exposure of the skin to concentrated solutions of hydrogen peroxide has resulted in blistering, erythema, focal epidermal necrosis, and purpura. Concentrations above 10% may result in ulceration or perforation of the cornea if they enter the eyes.[1]

1. Watt BE, *et al.* Hydrogen peroxide poisoning. *Toxicol Rev* 2004; **23:** 51–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydrogen peroxide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aosept Plus; Oxysept Comfort; ***Austral.***: Aosept; Focus Care One Step†; Oxysept 1 Step; Peroxyl; ***Belg.***: Confosept Zuurstofwater; ***Braz.***: Oxysept†; ***Canad.***: Aosept; Butcher's Per Diem; Orajel Perioseptic†; Oxysept; Pero Vap; Perox-A-Mint†; Peroxyl; ***Denm.***: Microcid; ***Fr.***: Dentex; Dosoxygenee; ***Ger.***: Crystacide; ***Gr.***: Biosept†; Crystacide; Peroxyl; ***Irl.***: Hioxyl†; ***Ital.***: Crystacide; Oragard†; ***Norw.***: Microcid; ***NZ***: Aosept; Crystacide; ***Pol.***: Peroxy-Dental; Peroxygel; ***Port.***: Crystacide; ***Rus.***: Parkon (Паркон); ***Singapore***: Pineapple Brand Ear Drop; ***Swed.***: Microcid; ***Turk.***: Oksijenli; Perohid; ***UK***: Crystacide; Peroxyl; ***USA***: Aosept; MiraSept†; Oxysept†; Peroxyl.

Multi-ingredient Preparations. ***Arg.***: Arion Cronos; ***Austria***: Kodan; Skinsept mucosa†; ***Braz.***: Malvatricin Branqueador†; ***Canad.***: Actril; UltraCare†; ***Fr.***: Anioxyde†; ***Ger.***: AdaptaCide PAA-C; Skinsept F; Skinsept mucosa; ***Indon.***: Spitaderm†; ***Ital.***: Eso 70; Peresal†; Spitaderm†; ***Neth.***: Spitaderm†; ***NZ***: Oxysept 1 Step; ***Singapore***: Clearasil Ultra Spot Clearing Cream; ***Spain***: Oximen; ***USA***: Soft Mate Consept; UltraCare.

Pharmacopoeial Preparations
BP 2014: Hydrogen Peroxide Mouthwash;
USP 36: Hydrogen Peroxide Topical Solution.

Hydroxybenzoates

p-Hidroxibenzoatos; Parabenos; Parabens; Parahidroxibenzoatos; Гидроксибензоаты.

Benzyl Hydroxybenzoate

Benzyl Parahydroxybenzoate; Benzylparaben; Parahidroxibenzoato de bencilo; Бензил Гидроксибензоат.

Benzyl 4-hydroxybenzoate.

$C_{14}H_{12}O_3$=228.2

CAS — 94-18-8.

UNII — 8Y41DYV4VG.

Pharmacopoeias. In *Br.* and *Int.*

BP 2014: (Benzyl Hydroxybenzoate). A white to creamy-white, odourless or almost odourless, crystalline powder. Practically insoluble in water; freely soluble in alcohol and

in ether. It dissolves in solutions of alkali hydroxides. M.p. about 112 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Butyl Hydroxybenzoate

Butilo parahidroksibenzoatas; Butilparabeno; Butil-parahidroxi-benzoát; Butyl Parahydroxybenzoate; Butyle, parahydroxybenzoate de; Butyl-4-hydroxybenzoat; Butylis Parahydroxybenzoas; Butylis Paraoxybenzoas; Butylparaben; Butylparabenum; Butylparahydroxibensoat; Butylu parahydroksybenzoesan; Butyyliparahydroksibentsoaatti; Parahidroxibenzoato de butilo; Бутил Гидроксибензоат.

Butyl 4-hydroxybenzoate.

$C_{11}H_{14}O_3$=194.2

CAS — 94-26-8.

UNII — 3QPI1U3FV8.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Butyl Parahydroxybenzoate; Butyl Hydroxybenzoate BP 2014). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 68 degrees to 71 degrees.

USNF 31: (Butylparaben). Small colourless crystals or a white powder. Very slightly soluble in water and in glycerol; freely soluble in alcohol, in acetone, in ether, and in propylene glycol. M.p. 68 degrees to 71 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Ethyl Hydroxybenzoate

Aethylum Hydroxybenzoicum; E214; Ethyl Parahydroxybenzoate; Éthyle, parahydroxybenzoate d'; Ethyl-4-hydroxybenzoat; Ethylis parahydroxybenzoas; Ethylis Paraoxybenzoas; Ethylparaben; Ethylparabenum; Etilo parahidroksibenzoatas; Etilparabeno; Etil-parahidroxibenzoát; Etylparahydroxibensoat; Etylu parahydroksybenzoesan; Etyyliparahydroksibentsoaatti; Parahidroxibenzoato de etilo; Этил Гидроксибензоат.

Ethyl 4-hydroxybenzoate.

$C_9H_{10}O_3$=166.2

CAS — 120-47-8.

ATC — D01AE10.

ATC Vet — QD01AE10.

UNII — 14255EXE39.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Ethyl Parahydroxybenzoate; Ethyl Hydroxybenzoate BP 2014). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol.

USNF 31: (Ethylparaben). Small colourless crystals or a white powder. Slightly soluble in water and in glycerol; freely soluble in alcohol, in acetone, in ether, and in propylene glycol.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Methyl Hydroxybenzoate

E218; Metagin; Methyl Parahydroxybenzoate; Méthyle, parahydroxybenzoate de; Methyl-4-hydroxybenzoat; Methylis Oxybenzoas; Methylis parahydroxybenzoas; Methylis Paraoxibenzoas; Methylparaben (USAN); Methylparabenum; Metilo parahidroksibenzoatas; Metilparabeno; Metil-parahidroxibenzoát; Metylparahydroxibensoat; Metylu parahydroksybenzoesan; Metyyliparahydroksibentsoaatti; Parahidroxibenzoato de metilo; Метил Гидроксибензоат.

Methyl 4-hydroxybenzoate.

$C_8H_8O_3$=152.1

CAS — 99-76-3.

UNII — A2I8C7HI9T.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Methyl Parahydroxybenzoate; Methyl Hydroxybenzoate BP 2014). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 125 degrees to 128 degrees.

USNF 31: (Methylparaben). Colourless crystals or a white crystalline powder. Soluble 1 in 400 of water, 1 in 50 of water at 80 degrees, 1 in 3 of alcohol, and 1 in 10 of ether; freely soluble in methyl alcohol. M.p. 125 degrees to 128 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Propyl Hydroxybenzoate

E216; Parahidroxibenzoato de propilo; Propagin; Propilo parahidroksibenzoatas; Propilparabeno; Propil-parahidroxibenzoát; Propyl Parahydroxybenzoate; Propyle, parahydroxybenzoate de; Propyl-4-hydroxybenzoat; Propylis Oxybenzoas; Propylis Parahydroxybenzoas; Propylis Paraoxibenzoas; Propylparaben (USAN); Propylparabenum; Propylparahydroxibensoat; Propylu parahydrobenzoesan; Propylu parahydroksybenzoesan; Propyyliparahydroksibentsoaatti; Пропил Гидроксибензоат.

Propyl 4-hydroxybenzoate.

$C_{10}H_{12}O_3$=180.2

CAS — 94-13-3.

UNII — Z8IX2SC1OH.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Propyl Parahydroxybenzoate; Propyl Hydroxybenzoate BP 2014). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 96 degrees to 99 degrees.

USNF 31: (Propylparaben). Small colourless crystals or a white powder. Soluble 1 in 2500 of water, 1 in 400 of boiling water, 1 in 1.5 of alcohol, and 1 in 3 of ether. M.p. 96 degrees to 99 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Butyl Hydroxybenzoate

Butilparabeno sódico; *p*-Hidroxibenzoato sódico de butilo; Parahidroxibenzoato sódico de butilo; Sodium Butyl Parahydroxybenzoate; Sodium Butylparaben; Натрия Бутил Гидроксибензоат.

$C_{11}H_{13}NaO_3$=216.2

CAS — 36457-20-2.

UNII — MAR76J7VS.

Pharmacopoeias. In *Br.*

BP 2014: (Sodium Butyl Hydroxybenzoate). A white, odourless or almost odourless, hygroscopic powder. Freely soluble in water and in alcohol. A 0.1% solution in water has a pH of 9.5 to 10.5.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Ethyl Hydroxybenzoate

E215; Ethyl parahydroxybenzoate sodium; Éthyle (parahydroxybenzoate d') sodique; Ethylis Parahydroxybenzoas Natricum; Ethylis parahydroxybenzoas natricus; Ethylparaben sodná sůl; Etilo parahidroksibenzoato natrio druska; Etilparabeno sódico; Etylparahydroxibensoatnatrium; Etyyliparahydroksibentsoaattinatrium; Natriumethyl-4-hydroxybenzoat; Натрия Этил Гидроксибензоат.

$C_9H_9NaO_3$=188.2

CAS — 35285-68-8.

UNII — Z0D00IVA10.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Ethyl Parahydroxybenzoate; Ethyl Hydroxybenzoate Sodium BP 2014). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

The BP 2014 gives Ethylparaben Sodium as an approved synonym.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Methyl Hydroxybenzoate

E219; *p*-Hidroxibenzoato sódico de metilo; Méthyle (parahydroxybenzoate de) sodique; Methylis Parahydroxybenzoas Natricum; Methylis parahydroxybenzoas natricus; Methylparaben Sodium (USAN); Methylparaben sodná sůl; Methylparabenum Natricum; Metilo parahidroksibenzoato natrio druska; Metilparabeno sódico; Metil-parahidroxibenzoátnátrium; Natriummethyl-4-hydroxybenzoat; Natriummetylparahydroxibensoat; Natriummetyyliparahydroksibentsoaatti; Parahidroxibenzoato sódico de metilo; Sodium Methyl Parahydroxybenzoate; Sodium Methylparaben; Soluble Methyl Hydroxybenzoate; Натрия Метил Гидроксибензоат.

$C_8H_7NaO_3$=174.1

CAS — 5026-62-0.

UNII — CR6K9C2NHK.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Methyl Parahydroxybenzoate; Sodium Methyl Hydroxybenzoate BP 2014). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

USNF 31: (Methylparaben Sodium). A white, hygroscopic, powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Propyl Hydroxybenzoate

E217; *p*-Hidroxibenzoato sódico de propilo; Natriumpropyl-4-hydroxybenzoat; Natriumpropylparahydroxibensoat; Natriumpropyyliparahydroksibentsoaatti; Parahidroxibenzoato sódico de propilo; Propilo parahidroksibenzoato natrio druska; Propilparabeno sódico; Propil-parahidroxibenzoátnátrium; Propyle (parahydroxybenzoate de) sodique; Propylis Parahydroxybenzoas Natricum; Propylis parahydroxybenzoas natricus; Propylparaben Sodium (USAN); Propylparaben sodná sůl; Propylparabenum Natricum; Sodium Propyl Parahydroxybenzoate; Sodium Propylparaben; Soluble Propyl Hydroxybenzoate; Натрия Пропил Гидроксибензоат.

$C_{10}H_{11}NaO_3$=202.2

CAS — 35285-69-9.

UNII — 625NNB0G9N.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Propyl Parahydroxybenzoate; Sodium Propyl Hydroxybenzoate BP 2014). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

USNF 31: (Propylparaben Sodium). A white, hygroscopic, odourless powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

Incompatibility and stability. The activity of hydroxybenzoates can be adversely affected by the presence of other excipients or active ingredients. There may be adsorption onto substances like magnesium trisilicate, aluminium magnesium silicate, talc, polysorbate 80,[1,2] carmellose sodium,[3] or plastics.[4] Nonionic surfactants can reduce hydroxybenzoate activity,[5] as may essential oils.[6] Other incompatibilities that have been reported include atropine,[7] iron,[4] sorbitol,[8] weak alkalis,[4] and strong acids.[4] Syrup preserved with hydroxybenzoates is incompatible with a range of compounds.[9,10] Methyl hydroxybenzoate 0.1% was reported[11] to be a poor preservative in insulin preparations, especially soluble insulin preparations. Increasing heat or pH can reduce stability and activity;[12] freeze-drying may also lead to a loss of activity.[13]

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
2. Allwood MC. The adsorption of esters of p-hydroxybenzoic acid by magnesium trisilicate. *Int J Pharmaceutics* 1982; **11:** 101–7.
3. Fawcett JP, *et al.* Binding of parabens to sodium carboxymethylcellulose in oral liquid formulations. *Aust J Hosp Pharm* 1996; **26:** 552–4.
4. Haley S. Methylparaben. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association,2009: 441–5.
5. Yamaguchi M, *et al.* Antimicrobial activity of butylparaben in relation to its solubilization behavior by nonionic surfactants. *J Soc Cosmet Chem* 1982; **33:** 297–307.
6. Chemburkar PB, Joslin RS. Effect of flavoring oils on preservative concentrations in oral liquid dosage forms. *J Pharm Sci* 1975; **64:** 414–17.
7. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; **230:** 481.
8. Runesson B, Gustavii K. Stability of parabens in the presence of polyols. *Acta Pharm Suec* 1986; **23:** 151–62.
9. *PSGB Lab Report P/79/2* 1979.
10. *PSGB Lab Report P/80/1* 1980.
11. Allwood MC. The effectiveness of preservatives in insulin injections. *Pharm J* 1982; **229:** 340.
12. Sunderland VB, Watts DW. Kinetics of the degradation of methyl, ethyl and n-propyl 4-hydroxybenzoate esters in aqueous solution. *Int J Pharmaceutics* 1984; **19:** 1–15.
13. Flora KP, *et al.* The loss of paraben preservatives during freeze drying. *J Pharm Pharmacol* 1980; **32:** 577–80.

Uses

The hydroxybenzoate preservatives are alkyl esters of *p*-hydroxybenzoic acid with antibacterial and antifungal properties. They are more active against Gram-positive than against Gram-negative bacteria. They are active over a broad pH range (4 to 8), though are generally more active in acidic solutions. Activity increases with increasing alkyl chain length but aqueous solubility decreases, although this may be overcome by employing the more soluble sodium salts as long as the pH of the preparation is not increased. Activity may also be increased by combining two hydroxybenzoates with short alkyl chains. Another way of increasing activity is to use a hydroxybenzoate with propylene glycol.

Hydroxybenzoates are used as preservatives in pharmaceutical preparations in usual concentrations of up to 0.25%. Methyl hydroxybenzoate and propyl hydroxybenzoate are used together in some preparations. There have been reports of the hydroxybenzoates not being satisfactory preservatives for ophthalmic preparations because of their relative lack of efficacy against some Gram-negative bacteria, particularly *Pseudomonas aeruginosa*. The hydroxybenzoate preservatives are widely used in cosmetics and are also used for food preservation.

Hydroxybenzoates have been used in preparations promoted for the management of skin infections or pruritus.

Adverse Effects and Precautions

Hypersensitivity reactions occur with the hydroxybenzoates. Generally these are of the delayed type, appearing as contact dermatitis. Immediate reactions with urticaria and bronchospasm have occurred rarely.

Breast cancer. Some researchers[1] have questioned whether *p*-hydroxybenzoic acid esters, the most common preservatives found in body care cosmetic products, could increase the incidence of breast cancer in women. The esters have been shown to be oestrogenic *in vitro* and *in vivo* and have been detected in human breast tumour tissue, although a causal association cannot be confirmed.

1. Harvey PW, Darbre P. Endocrine disrupters and human health: could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? *J Appl Toxicol* 2004; **24:** 167–76.

Hypersensitivity. Immediate hypersensitivity reactions such as urticaria and bronchospasm with generalised pruritus, have been reported rarely on injection of preparations containing hydroxybenzoates.[1,2] Delayed contact dermatitis occurs more frequently, usually after use of topical medications, but has also occurred after use of an ester or of *p*-hydroxybenzoic acid in oral preparations.[3] Hypersensitivity reactions have also been reported in patients given local anaesthetics containing hydroxybenzoates[1,4] and cross-reactions with other para-amino compounds including benzocaine, paraphenylenediamine, and sulfonamides have occurred rarely.[5]

The incidence of sensitisation to hydroxybenzoates ranges from 0 to 3.5% but has tended to stay relatively constant over time.[5] A report from the North American Contact Dermatitis Group[6] in 1972 provided an incidence of 3%, while another later review[7] of a large number of patients gave an incidence of 2.2%. The Swiss Contact Dermatitis Research Group reported[8] a sensitisation rate of 1.7% based on a one-year study from 1989 to 1990 in 2295 patients.

Subjects with healthy skin exposed to hydroxybenzoates, for example in cosmetics, are considered to have a much lower incidence of reactions than patients with eczema or skin trauma. Unusually, patients who have reacted to a hydroxybenzoate with a contact dermatitis appear to be able to apply that preservative to another unaffected site and yet not suffer a reaction; this has been termed the 'paraben paradox'.[9]

1. Aldrete JA, Johnson DA. Allergy to local anaesthetics. *JAMA* 1969; **207:** 356–7.
2. Nagel JE, *et al*. Paraben allergy. *JAMA* 1977; **237:** 1594–5.
3. Kaminer Y, *et al*. Delayed hypersensitivity reaction to orally administered methylparaben. *Clin Pharm* 1982; **1:** 469–70.
4. Lederman DA, *et al*. An unusual skin reaction following local anesthetic injection: review of the literature and report of four cases. *Oral Surg* 1980; **49:** 28–33.
5. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther* 2004; **17:** 251–63.
6. North American Contact Dermatitis Group. Epidemiology of contact dermatitis in North America 1972. *Arch Dermatol* 1973; **108:** 537–40.
7. Moore J. Final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. *J Am Coll Toxicol* 1984; **3:** 147–209.
8. Perrenoud D, *et al*. Frequency of sensitization to 13 common preservatives in Switzerland. *Contact Dermatitis* 1994; **30:** 276–9.
9. Fisher AA. Cortaid cream dermatitis and the "paraben paradox". *J Am Acad Dermatol* 1982; **6:** 116–7.

Neonates. An *in-vitro* study on serum from neonates with hyperbilirubinaemia indicated that methyl hydroxybenzoate at a concentration of 200 micrograms/mL of serum increased the concentration of free unconjugated bilirubin and interfered with the binding of bilirubin to serum proteins. Methyl hydroxybenzoate was present in an injection of gentamicin sulfate at a concentration of 1.3 to 1.8 mg/mL. Neither gentamicin nor propyl hydroxybenzoate had a significant effect on bilirubin.[1]

1. Loria CJ, *et al*. Effect of antibiotic formulations in serum protein: bilirubin interaction of newborn infants. *J Pediatr* 1976; **89:** 479–82.

Pharmacokinetics

Neonates. After intramuscular injection, methyl hydroxybenzoate present in a gentamicin preparation was excreted in the urine of preterm infants to a variable extent and mainly in the conjugated form.[1] *p*-Hydroxybenzoic acid was detected as a metabolite. The injection contained methyl hydroxybenzoate 3.6 mg, propyl hydroxybenzoate 400 micrograms, and gentamicin 80 mg. Propyl hydroxybenzoate was also detected in the urine samples.

1. Hindmarsh KW, *et al*. Urinary excretion of methylparaben and its metabolites in preterm infants. *J Pharm Sci* 1983; **72:** 1039–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Nisapulvol†; Nisaseptol†; Nisasol†; ***Malaysia***: Nisapulvol.

Multi-ingredient Preparations. ***Austral.***: Mycoderm; ***Hong Kong***: Nisapulvol†; ***Malaysia***: Mycoderm†; ***Neth.***: Trachitol; ***UK***: Brushtox; ***USA***: Neosalus; ***Venez.***: Glizigen.

Imidurea

Imidazolidinyl Urea; Имидомочевина.

N,N''-Methylenebis{*N'*-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]urea}.

$C_{11}H_{16}N_8O_8$=388.3

CAS — 39236-46-9.

UNII — M629807ATL.

Pharmacopoeias. In *USNF*.

USNF 31: (Imidurea). A white odourless powder. Soluble in water and in glycerol; sparingly soluble in propylene glycol; insoluble in most organic solvents. A 1% solution in water has a pH of 6.0 to 7.5. Store in airtight containers.

Profile

Imidurea is used as an antimicrobial preservative in topical pharmaceutical and cosmetic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Venez.***: Exfoliderm.

Iodoform

Iodoformo; Triyodometano; Yodoformo; Иодоформ.

Tri-iodomethane.

CHI_3=393.7

CAS — 75-47-8.

ATC — D09AA13.

ATC Vet — QD09AA13.

UNII — KX12J76489.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Iodoform). A lustrous greenish-yellow powder or lustrous crystals. It is slightly volatile at ordinary temperatures and distils slowly with steam. It decomposes at high temperatures emitting vapours of iodine. Practically insoluble in water; sparingly soluble in alcohol, in glycerol, and in olive oil; soluble in boiling alcohol; freely soluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Iodoform slowly releases iodine (p. 2336.3) when applied to the tissues and is used for its mild antiseptic action. Bismuth Subnitrate and Iodoform Paste (BPC 1954) (BIPP) has been applied to wounds and abscesses. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.

Adverse effects on the nervous system. Encephalopathy has been associated with the use of bismuth subnitrate and iodoform paste (BIPP) for the packing of wound cavities after ear, nose, and throat, oral, and maxillofacial surgery,[1,2] although there is some debate as to whether the bismuth or the iodoform component is responsible.[1-3] However, encephalopathy has been reported after application of iodoform gauze without bismuth.[4,5] CNS toxicity due to both iodine and bismuth has been reported[6] in an 86-year-old woman from an intra-oral plug of BIPP following partial maxillectomy. Five days after surgery the patient started to experience loss of appetite and lightheadedness, and by day 11 was suffering from fainting episodes, confusion, and paranoid ideation and was becoming increasingly aggressive. On day 14 the BIPP pack was removed; 7 days later the patient's condition improved and when discharged 5 days later she was alert and cooperative.

1. Wilson APR. The dangers of BIPP. *Lancet* 1994; **344:** 1313–14.
2. Youngman L, Harris S. BIPP madness; an iatrogenic cause of acute confusion. *Age Ageing* 2004; **33:** 406–7.
3. Farrell RWR. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; **344:** 1637–8.
4. Roy P-M, *et al*. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; **344:** 1708.
5. Yamasaki K, *et al*. Delirium and a subclavian abscess. *Lancet* 1997; **350:** 1294.
6. Harris RA, Poole A. Beware of bismuth: post maxillectomy delirium. *Aust N Z J Surg* 2002; **72:** 846–7.

Hypersensitivity. A retrospective analysis of 185 patients[1] who were treated with a bismuth-iodoform-paraffin paste (BIPP) impregnated ribbon gauze pack after ear surgery found the incidence of allergic reactions to be 5.9%. A fivefold increase risk of developing allergic reactions was also found in those with previous exposure to BIPP. Three cases of allergic contact otitis externa have been reported after the use of bismuth subnitrate and iodoform paste to pack the ear after surgery.[2]

1. Lim PVH, *et al*. Hypersensitive allergic reactions to bismuth-iodoform-paraffin paste following ear surgery. *J Laryngol Otol* 1998; **112:** 335–7.
2. Roest MAB, *et al*. Allergic contact otitis externa due to iodoform in BIPP cavity dressings. *Contact Dermatitis* 2002; **46:** 360.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aseptobron; ***Austral.***: BIP; ***Ital.***: Pasta Iodoformica Radiopaca; ***Spain***: Alvogil†; ***Switz.***: Alvogyl; ***UK***: OxBipp.

Pharmacopoeial Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste; Compound Iodoform Paint.

Isopropyl Alcohol

Alkohol izopropylowy; Alcohol isopropílico; Alcohol Isopropylicus; Dimethyl Carbinol; Dimetilcarbinol; Isopropanol; Isopropylalkohol; Isopropylique, alcool; Isopropyylialkoholi; Izopropil Alkol; Izopropil-alkohol; Izopropiło alkoholis; 2-Propanol; Secondary Propyl Alcohol; Изопропиловый Спирт.

Propan-2-ol.

$(CH_3)_2CHOH$=60.10

CAS — 67-63-0.

ATC — D08AX05.

ATC Vet — QD08AX05.

UNII — ND2M416302.

Pharmacopoeias. In *Eur*. (see p. vii), *Int*., *Jpn*, and *US*.

Ph. Eur. 8: (Isopropyl Alcohol). A clear colourless liquid. Miscible with water and with alcohol. Protect from light.

USP 36: (Isopropyl Alcohol). A transparent, colourless, mobile, volatile, flammable liquid with a characteristic odour. Miscible with water, with alcohol, with chloroform, and with ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Isopropyl alcohol is an antiseptic with bactericidal properties similar to those of alcohol (p. 1733.2). It is used for preoperative skin cleansing in concentrations of about 60 to 70%, and is an ingredient of preparations used for disinfection of hands and surfaces. Its marked degreasing properties may limit its usefulness in preparations used repeatedly. It is also used as a solvent, especially in cosmetics, perfumes and pharmaceutical preparations, and as a vehicle for other disinfectant compounds.

Propyl alcohol (p. 1768.1) is also used as an antiseptic.

Adverse Effects, Treatment, and Precautions

Isopropyl alcohol is considered to be more toxic than ethyl alcohol (p. 1733.3), and the symptoms of intoxication appear to be similar, except that isopropyl alcohol has no initial euphoric action and gastritis, haemorrhage, pain, nausea, and vomiting are more prominent. The lethal oral dose is reported to be about 240 mL in adults; however, individuals can vary widely in their susceptibilities and toxic symptoms may be produced by as little as 20 mL. Ketoacidosis and ketonuria commonly occur due to the presence of the major metabolite, acetone, in the

circulation. Inhalation of isopropyl alcohol vapour has been reported to produce coma.

Application of isopropyl alcohol to the skin may cause dryness and irritation; suitable precautions should be taken to prevent absorption through the skin, particularly in infants.

Treatment of adverse effects is as for Alcohol, p. 1734.1.

General references.

1. WHO. 2-Propanol. *Environmental Health Criteria 103*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc103.htm (accessed 15/03/06)

Children. Reports of chemical skin burns caused by the topical application of isopropyl alcohol in premature infants.[1,2]

Haemorrhagic gastritis in a 2-year-old febrile child was attributed to topical absorption of isopropyl alcohol that had been used for sponge bathing and followed by wrapping the child tightly in a blanket.[3]

1. Schick JB, Milstein JM. Burn hazard of isopropyl alcohol in the neonate. *Pediatrics* 1981; **68:** 587–8.
2. Weintraub Z, Iancu TC. Isopropyl alcohol burns. *Pediatrics* 1982; **69:** 506.
3. Dyer S, *et al*. Hemorrhagic gastritis from topical isopropanol exposure. *Ann Pharmacother* 2002; **36:** 1733–5.

Rectal absorption. Intoxication and raised serum-creatinine concentrations due to absorption of isopropyl alcohol followed its use as a rectal douche.[1] An 85-year-old woman who accidentally received an isopropyl alcohol enema developed rapid CNS depression, renal failure, and metabolic acidosis. She became comatose within 15 minutes and died 12 hours later after a cardiac arrest. Post-mortem examination showed necrosis of the colon.[2]

1. Barnett JM, *et al*. Intoxication after an isopropyl alcohol enema. *Ann Intern Med* 1990; **113:** 638–9.
2. Haviv YS, *et al*. Accidental isopropyl alcohol enema leading to coma and death. *Am J Gastroenterol* 1998; **93:** 850–1.

Pharmacokinetics

Isopropyl alcohol is readily absorbed from the gastrointestinal tract but there appears to be little absorption through intact skin. The vapour may be absorbed through the lungs. Isopropyl alcohol is metabolised more slowly than ethyl alcohol and about 15% of an ingested dose is metabolised to acetone.

For reports of rectal absorption of isopropyl alcohol, see above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Medi-Swab; ***Canad.***: Alpet E3; Auro-Dri; Dermorapid†; Duonalc†; Isogel†; Viraguard Antiseptic Hand Spray; Viraguard Antiseptic Hand Wipes; Webcol; Zep E-3†; Zep Instant Hand Sanitizer; ***Ger.***: Aktivin; C 20; Dolobene Cool; Septoderm Hande; ***Ital.***: Esoform Mani-Cute; ***S. Afr.***: Medi-Swab†; ***Thai.***: Alcohol Sahakarn; Cohol Sahakarn; ***Turk.***: Opak†; ***UK***: Alcowipe; Medi-Swab; Sterets; Steriwipe; ***USA***: Auro-Dri.

Multi-ingredient Preparations. ***Arg.***: Pervinox Jabon; Sincerum Dry; ***Austral.***: Aqua Ear; Ear Clear for Swimmers Ear; Septivon; Uni-Solve; ***Austria***: Dodesept Gefarbt; Dodesept N†; Dodesept; Isozid-H; Kodan; Marcocid; Mycopol; Octeniderm; Skinsept; Sterillium; ***Belg.***: Braunoderm; ***Canad.***: Baxedin 2% - 70%; Dexidin; Duonalc-E†; Faces Antiseptic†; Germi Stat Prep; Hibistat†; Loris IV; Solu-IV CHD Alcool; Solu-IV CHG Alcohol†; Soluprep CHD-Alcohol; ***Chile***: NP-27; Solarcaine Spray Aerosol; ***Cz.***: Promanum N; Softa-Man; ***Fin.***: ChloraPrep; Sterillium; ***Fr.***: Chloraprep; Clinogel Derma+; Clinogel†; Sterillium; ***Ger.***: Autoderm Extra; Bacillol AF; Bacillol Foam; Bacillol plus; Bacillol Tissues; Bacillol Wipes; Bacillol†; Betaseptic; Braunoderm; Cutasept; Dibromol†; Freka-Steril†; HD 410; Helipur H plus N; Incidin; Kodan Tinktur Forte; Mucasept-A; Olbas; Poly-Alkohol†; Promanum N; Rutisept extra; Skinman Soft; Skinsept F; Skinsept G; Softasept N; Spitacid; Sterillium; ***Gr.***: Chiro Des; Cutasept; Octeniderm; Sterillium; ***Hong Kong***: Baxedin; ***Indon.***: Mexochrome†; Spitaderm†; ***Irl.***: Biofreeze†; Braunoderm†; ChloraPrep; Hibisol†; Manusept; Sterillium; ***Israel***: DryEars; Monorapid†; Skin Des†; Sterets H; ***Ital.***: Braunoderm; Citrocil Alcolico†; Citromed; Clorexan; Eso Ferri Plus; Panseptil†; Sekucid†; Spitaderm†; ***Neth.***: ChloraPrep; Hibisol; Spitaderm†; Sterillium; ***Port.***: Braunoderm†; Promanum†; Softasept; Sterillium; ***Singapore***: Desderman; Hibisol; Primasept Med; ***Swed.***: Chloraprep; Sterillium; ***Switz.***: Betaseptic; Braunoderm; Cutasept; Desamon; Hibital†; Hibitane Teinture†; Jodoplex Teinture†; Kodan forte; Octeniderm; Parapic; Promanum N†; Skinsept; Softa-Man†; Softasept N; ***Thai.***: Chlorsep; ***UK***: ChloraPrep; Hibi; Hibisol†; Manusept; Medi-Swab H; Sterets H; Swim-Ear; ***USA***: BactoShield; Blue Ice Gel; Chlorascrub; Clindacin ETZ; Clindacin P; Cresylate; Dri/Ear; Ear-Dry; Fungi-Nail; Klout; Lycelle; PledgaClin; Tinver.

Homoeopathic Preparations. ***Canad.***: ClearAc Cleanser†.

Pharmacopoeial Preparations

USP 36: Azeotropic Isopropyl Alcohol; Isopropyl Rubbing Alcohol.

Isothiazolinones

Isotiazolinonas; Изотиазолины.

Methylchloroisothiazolinone

Metilcloroisotiazolinona; Метилхлороизотиазолин.

5-Chloro-2-methyl-3(2*H*)-isothiazolone; 5-Chloro-2-methyl-4-isothiazolin-3-one.

CAS — 26172-55-4.

UNII — DEL7T5QRPN.

Methylisothiazolinone

Metilisotiazolinona; Метилизотиазолин.

2-Methyl-3(2*H*)-isothiazolone; 2-Methyl-4-isothiazolin-3-one.

CAS — 2682-20-4.

UNII — 229D0E1QFA.

Profile

A mixture of isothiazolinones consisting of methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) in a ratio of about 3:1 is used as a preservative in industry and in cosmetic and household products. It is effective at very low concentrations against a wide spectrum of Gram-positive and -negative bacteria, yeasts, and fungi. The mixture is often referred to as Kathon CG, one of its proprietary names.

Isothiazolinones may cause contact dermatitis and local irritation.

Hypersensitivity. There have been reports of sensitisation and allergic contact dermatitis arising from the use of isothiazolinones in cosmetics, paints and from industrial exposure.[1-11] The incidence of allergy to methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) is reported be dose-related and ranges from less than 1 to 8.4%.[4,8] A study[6] conducted in 4713 patients at 22 European contact dermatitis clinics over a 12 month period from 1988 to 1989 reported the frequency of positive reactions to 100 ppm MCI/MI to be 3%.

Most hypersensitivity reports are related to use in cosmetics, especially 'leave-on' products such as moisturising creams, while the risk attributed to their use in 'rinse-off' products such as shampoos is considered to be minimal.[4,7] A review[7] of such rinse-off products found that they were even well tolerated in MCI/MI sensitised people. Airborne contact dermatitis has been reported in people exposed to MCI/MI in paints.[9,10] Occupational contact allergy and dermatitis due to MCI/MI have also been reported,[11] and there has been a case report of occupational asthma developing in a worker 5 months after starting work in an isothiazolinone manufacturing plant.[5]

1. Björkner B, *et al*. Contact allergy to the preservative Kathon CG. *Contact Dermatitis* 1986; **14:** 85–90.
2. De Groot AC, Bos JD. Preservatives in the European standard series for epicutaneous testing. *Br J Dermatol* 1987; **116:** 289–92.
3. Fransway AF. Sensitivity to Kathon CG: findings in 365 consecutive patients. *Contact Dermatitis* 1988; **19:** 342–7.
4. De Groot AC, Herxheimer A. Isothiazolinone preservative: cause of a continuing epidemic of cosmetic dermatitis. *Lancet* 1989; **I:** 314–16.
5. Bourke SJ, *et al*. Occupational asthma in an isothiazolinone manufacturing plant. *Thorax* 1997; **52:** 746–8.
6. Menné T, *et al*. Contact sensitization to 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (MCI/MI): a European multicentre study. *Contact Dermatitis* 1991; **24:** 334–41.
7. Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999; **41:** 1–13.
8. Mowad CM. Methylchloro-isothiazolinone revisited. *Am J Contact Dermat* 2000; **11:** 115–18.
9. Bohn S, *et al*. Airborne contact dermatitis from methylchloroisothiazolinone in wall paint: abolition of symptoms by chemical allergen inactivation. *Contact Dermatitis* 2000; **42:** 196–201.
10. Reinhard E, *et al*. Preservation of products with MCI/MI in Switzerland. *Contact Dermatitis* 2001; **45:** 257–64.
11. Isaksson M, *et al*. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004; **15:** 201–5.

Laurylamine Dipropylenediamine

N-(3-Aminopropyl)-*N*-dodecyl-1,3-propanediamine; *N*-(3-Aminopropyl)-*N*dodecylpropane-1,3-diamine; Dodecylbispropylenetriamine; Dodecyldipropylenetriamine; Lauryldipropylenetriamine; *N,N*-Bis(3-aminopropyl)dodecylamine; *N, N*-Bis(3-aminopropyl)laurylamine.

$C_{18}H_{41}N_3$=299.5

CAS — 2372-82-9.

UNII — PCJ6308JUE.

Profile

Laurylamine dipropylenediamine is a polyamine disinfectant used for surface disinfection. Related polyamines such as lauryl 1,3-propyldiamine (*N*-dodecylpropane-1,3,-diamine) have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Almyrol; Hexaquart plus; Korsolex AF; Korsolex Plus; Mikrobac.

Lopobutan *(rINN)*

Lauryloxypropyl-β-aminobutyric Acid; Lopobutano; Lopobutanum; Лопобутан.

(±)-3-{[3-(Dodecyloxy)propyl]amino}butyric acid.

$C_{19}H_{39}NO_3$=329.5

CAS — 6582-30-5.

UNII — L6IE0KAZ8O.

Profile

Lopobutan is a beta aminobutyric acid derivative used as an antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Sterlane.

Magenta

Aniline Red; Basic Fuchsin; Basic Magenta; CI Basic Violet 14; Colour Index No. 42510; Fuchsine; Fucsina; Fucsina básica; Фуксин.

CAS — 569-61-9 (pararosaniline hydrochloride); 632-99-5 (rosaniline hydrochloride).

UNII — 5P5C03819W.

Description. Magenta is a mixture of the hydrochlorides of pararosaniline {4-[(4-aminophenyl)(4-iminocyclohexa-2,5-dien-1-ylidene)-methyl]aniline} and rosaniline {4-[(4-aminophenyl)(4-iminocyclohexa-2,5-dien-1-ylidene) methyl]-2-methylaniline}.

Pharmacopoeias. In *US.*

USP 36: (Basic Fuchsin). A mixture of rosaniline and pararosaniline hydrochlorides. It contains the equivalent of not less than 88% of rosaniline hydrochloride ($C_{20}H_{20}ClN_3$ = 337.9), calculated on the dried basis. A dark green powder or greenish glistening crystalline fragments with a bronze-like lustre and not more than a faint odour. Soluble in water, in alcohol, and in amyl alcohol; insoluble in ether.

Profile

Magenta is a triphenylmethane antiseptic dye effective against Gram-positive bacteria and some fungi. Magenta Paint (BPC 1973) (Castellani's Paint) was formerly used in the treatment of superficial dermatophytoses.

Decolorised magenta solution (Schiff reagent) is used as a test for the presence of aldehydes.

Concerns about possible carcinogenicity have restricted the use of magenta.

Carcinogenicity. The handling of magenta was not thought to induce carcinogenesis but its actual manufacture may produce tumours. The IARC has concluded that the manufacturing process of magenta involves exposure to substances that are considered to be definite human carcinogens. Pararosaniline hydrochloride (Basic Red 9), and magenta containing it, are considered possibly carcinogenic to humans.[1] Magenta was also considered to be unsafe for use in food.[2]

1. IARC/WHO. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC monographs on the evaluation of carcinogenic risks to humans volume 57* 1993. Available at: http://monographs.iarc.fr/ENG/Monographs/vol57/volume57.pdf (accessed 23/05/06)
2. FAO/WHO. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antoxidants: eighth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 309* 1965. Also available at: http://libdoc.who.int/trs/WHO_TRS_309.pdf (accessed 28/08/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Fucsina Fenica.

Pharmacopoeial Preparations

BPC 1973: Magenta Paint;

USP 36: Carbol-Fuchsin Topical Solution.

Magnesium Peroxide

Magnesii Peroxidum; Magnesium Perhydrolum; Magnésium, peroxyde de; Magnesiumperoksidi; Magnesiumperoxid; Magnézium-peroxid; Magnio peroksidas; Peroxid hořečnatý; Peróxido de magnesio; Перекись Магния.

CAS — 1335-26-8; 14452-57-4.
ATC — A02AA03; A06AD03.
ATC Vet — QA02AA03; QA06AD03.
UNII — X8YVJ0TN96.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Peroxide). A mixture of magnesium peroxide and magnesium oxide. It contains not less than 22% and not more than 28% of MgO_2. A white or slightly yellow, amorphous, light powder. Practically insoluble in water and in alcohol; dissolves in mineral acids. Protect from light.

Profile

Magnesium peroxide is used as an antiseptic. It is also an ingredient of preparations for gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Ozovit.

Multi-ingredient Preparations. ***Ital.***: Carbonesia; Ektogan.

Homoeopathic Preparations. ***Chile***: Ikoplex No 10; Ikoplex No 11.

Malachite Green

Aniline Green; China Green; CI Basic Green 4; Colour Index No. 42000; Diamond Green B; Verde de malaquita; Viride Malachitum; Zieleń malachitowa; Малахитовая Зелень.
[4-(4-Dimethylaminobenzhydrylidene)cyclohexa-2,5-dienylidene]dimethylammonium chloride.
CAS — 569-64-2.
ATC Vet — QP53AX16.
UNII — 12058M7ORO.

Profile

Malachite green is a triphenylmethane antiseptic dye with actions similar to those of brilliant green (p. 1740.2). It has been used for skin disinfection.

Mecetronium Etilsulfate *(BAN, rINN)*

Etilsulfato de mecetronio; Mecetronii Etilsulfas; Mecetronio, etilsulfato de; Mecetronium Ethylsulfate (USAN); Mecetronium Ethylsulphate; Mécétronium, Étilsulfate de; Мецетрония Этилсульфат.
Ethylhexadecyldimethylammonium ethyl sulphate.
$C_{22}H_{49}NO_4S$=423.7
CAS — 3006-10-8.
UNII — QM95LPV3CA.

Profile

Mecetronium etilsulfate is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is active against bacteria, including mycobacteria, fungi, and viruses, including hepatitis B virus. It is used in alcoholic solution for disinfection of the skin and hard surfaces.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Sterillium; ***Fin.***: Sterillium; ***Fr.***: Sterillium; ***Ger.***: Bacillol†; Sterillium; ***Gr.***: Sterillium; ***Irl.***: Sterillium; ***Neth.***: Sterillium; ***Port.***: Sterillium; ***Swed.***: Sterillium.

Merbromin *(rINN)*

Disodium 2,7-dibromo-4-hydroxymercurifluorescein; Merbromina; Merbromine; Merbrominum; Mercurescéine Sodique; Mercurochrome; Mercurodibromofluorescein; Merkürokrom; Мербромин.
The disodium salt of [2,7-dibromo-9-(2-carboxyphenyl)-6-hydroxy-3-oxo-3*H*-xanthen-5-yl]hydroxymercury.
$C_{20}H_8Br_2HgNa_2O_6$=750.7
CAS — 129-16-8.
ATC — D08AK04.
ATC Vet — QD08AK04.
UNII — M0T18YH28D.

NOTE. The use of the name Merbromin is limited; in some countries it is a trade-mark.

Pharmacopoeias. In *Fr., It., Jpn,* and *Viet.*

Incompatibility. Merbromin is incompatible with acids, most alkaloidal salts, many local anaesthetics, metals, and sulfides. Activity may be reduced in the presence of organic material.

Uses and Administration

Merbromin is a mercurial antiseptic that has been used for disinfection of skin and wounds.

Adverse Effects and Treatment

As for Mercury, p. 2556.1.

General references.

1. Risher JF, *et al.* Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; **18:** 109–60.

Toxicity. Reports of merbromin toxicity have included contact dermatitis[1] and epidermal cell toxicity.[2] A fatality has occurred after transcutaneous absorption of merbromin during treatment of infected omphalocele (umbilical hernia)[3,4] and death due to shock, with aplastic anaemia, has followed application to surgical wounds and decubitus areas.[5] Anaphylaxis has also occurred.[6] Extensive absorption after ingestion has also been reported.[7] There has also been a case report[8] of severe encephalopathy and meningitis within 24 hours of an accidental intrathecal application into a CSF fistula.

1. Camarasa G. Contact dermatitis from mercurochrome. *Contact Dermatitis* 1976; **2:** 120.
2. Anonymous. Topical antiseptics and antibiotics. *Med Lett Drugs Ther* 1977; **19:** 83–4.
3. Yeh T-F, *et al.* Mercury poisoning from mercurochrome therapy of infected omphalocele. *Lancet* 1978; **i:** 210.
4. Yeh TF, *et al.* Mercury poisoning from mercurochrome therapy of an infected omphalocele. *Clin Toxicol* 1978; **13:** 463–7.
5. Slee PHTJ, *et al.* A case of Merbromin (mercurochrome) intoxication possibly resulting in aplastic anemia. *Acta Med Scand* 1979; **205:** 463–6.
6. Galindo PA, *et al.* Mercurochrome allergy: immediate and delayed hypersensitivity. *Allergy* 1997; **52:** 1138–41.
7. Magarey JA. Absorption of mercurochrome. *Lancet* 1993; **342:** 1424.
8. Stark AM, *et al.* Accidental intrathecal mercury application. *Eur Spine J* 2004; **13:** 241–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Medichrom; ***Fr.***: Solucrom†; ***Gr.***: Merbromin; Mercurochrome; ***S.Afr.***: Red Seal†; ***Spain***: Cinfacromin†; Mercromina; Mercurin†; Mercurobromo†; Mercutina Brota†; ***Turk.***: Mersisol; Mersol.

Multi-ingredient Preparations. ***S.Afr.***: Achromide; Daromide†; Ung Vernleigh.

Mercurobutol *(rINN)*

L-542; Mercurobutolum; Меркуробутол.
4-*tert*-Butyl-2-chloro-mercuriphenol.
$C_{10}H_{13}ClHgO$=385.3
CAS — 498-73-7.
UNII — 8HJ49MW6V4.

Pharmacopoeias. In *Fr.*

Profile

Mercurobutol is an organic mercurial antiseptic with antifungal properties. It has been used in the treatment of infections of the skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Gr.***: Sabenyl.

Metalkonium Chloride *(rINN)*

Cloruro de metalconio; Dodecarbonium Chloride; Metalconio, cloruro de; Metalkonii Chloridum; Métalkonium, Chlorure de; Металкония Хлорид.
Benzyl(dodecylcarbamoylmethyl)dimethylammonium chloride.
$C_{23}H_{41}ClN_2O$=397.0
CAS — 100-95-8.
UNII — IM6BZ8F57J.

Profile

Metalkonium chloride is an antiseptic used for skin disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Theotex.

Methylated Spirits

Alcoholes desnaturalizados; Денатурированный Спирт(denatured alcohol).
CAS — 8013-52-3 (ethyl alcohol-methyl alcohol mixture, industrial methylated spirit).

Description. Three classes of methylated spirits are listed under the Methylated Spirits Regulations, 1987 (SI 1987: No. 2009): industrial methylated spirits, mineralised methylated spirits, and denatured ethanol (denatured alcohol).

Industrial Methylated Spirits is defined as 95 parts by volume of spirits mixed with wood naphtha (mostly methyl alcohol—p. 2196.2) 5 parts by volume. **Mineralised methylated spirits** is spirits mixed with wood naphtha 9.5 parts by volume and crude pyridine 0.5 parts by volume, and to every 2000 litres of this mixture is added 7.5 litres of mineral naphtha (petroleum oil) and 3 g of synthetic organic dyestuff (methyl violet). This is the only variety that may be sold in Great Britain for general use. **Denatured ethanol** is 999 parts by volume of spirits (of a strength not less than 85%) mixed with 1 part by volume of tertiary butyl alcohol, and to this mixture is added Bitrex (denatonium benzoate) 10 mg/litre.

As Industrial Methylated Spirit may contain small amounts of acetone it should not be used for the preparation of iodine solutions, since an irritating compound is formed by reaction between iodine and acetone; for such preparations Industrial Methylated Spirit (Ketone-free) should be used.

Pharmacopoeias. *Br.* includes Industrial Methylated Spirit and Industrial Methylated Spirit (Ketone-free).

BP 2014: (Industrial Methylated Spirit). A mixture of 19 volumes of ethyl alcohol of an appropriate strength with 1 volume of approved wood naphtha. Two strengths are available containing 99% and 95% v/v alcohol (also known as 74 OP and 66 OP respectively). It is a colourless, clear, mobile, volatile liquid with an odour which is spirituous and of wood naphtha. B.p. is about 78 degrees.

The BP 2014 gives Industrial Methylated Spirits and IMS as approved synonyms.

BP 2014: (Industrial Methylated Spirit (Ketone-free)). A mixture of the same strength as Industrial Methylated Spirit, but it is substantially free from ketones, containing not more than the equivalent of 500 ppm of acetone.

Uses and Administration

Industrial methylated spirit, in a concentration of about 70%, is the usual form in which alcohol (p. 1733.1) is used for disinfection. It is applied externally for its astringent action, but mucous membranes and excoriated skin surfaces must be protected. It may be used for skin preparation before injection.

Methylated spirits may be used in the form of Surgical Spirit (BP 2014), a mixture of methyl salicylate (0.5% v/v), diethyl phthalate (2% v/v), and castor oil (2.5% v/v) in industrial methylated spirit.

Adverse Effects

As for Alcohol, p. 1733.3, and Methyl Alcohol, p. 2196.2. Adverse effects are due chiefly to consumption of methylated spirits rather than its topical use as a disinfectant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Skinman; ***Ital.***: Esosan Gel.

Pharmacopoeial Preparations
BP 2014: Surgical Spirit.

Methylbenzethonium Chloride *(BAN, rINN)*

Cloruro de metilbencetonio; Methylbenzethonii Chloridum; Méthylbenzéthonium, Chlorure de; Metilbencetonio, cloruro de; Метилбензетония Хлорид.
Benzyldimethyl-2-{2-[4-(1,1,3,3-tetramethylbutyl)-*o*-tolyloxy]ethoxy}ethylammonium chloride monohydrate.
$C_{28}H_{44}ClNO_2.H_2O$=480.1
CAS — 25155-18-4 (anhydrous methylbenzethonium chloride); 1320-44-1 (methylbenzethonium chloride monohydrate).
UNII — 4XKK0M5H9M (anhydrous methylbenzethonium chloride); WOA57K8S5V (methylbenzethonium chloride monohydrate).

Pharmacopoeias. In *US.*

USP 36: (Methylbenzethonium Chloride). White hygroscopic crystals with a mild odour. Soluble 1 in 0.8 of water, 1 in 0.9 of alcohol, 1 in more than 10 000 of chloroform, and 1

in 0.7 of ether. Solutions are neutral or slightly alkaline to litmus. Store in airtight containers.

Profile

Methylbenzethonium chloride is a quaternary ammonium disinfectant and antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used topically for minor infections or irritation of the skin.

Leishmaniasis. Topical treatment of cutaneous leishmaniasis (p. 922.1) with methylbenzethonium chloride 12% and paromomycin sulfate has proved beneficial.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Israel***: Leshcutan; ***USA***: Acnotex; Dermasept Antifungal; Drytex; Finac; Orasept†.

Pharmacopoeial Preparations
USP 36: Methylbenzethonium Chloride Lotion; Methylbenzethonium Chloride Ointment; Methylbenzethonium Chloride Topical Powder.

Methylrosanilinium Chloride *(BAN, rINN)*

CI Basic Violet 3; Cloruro de metilrosanilina; Colour Index No. 42555; Crystal Violet; Fiolet krystaliczny; Gentian Violet; Hexamethylpararosaniline Chloride; Jansiyen Moru; Kristal Viyole; Kristallviolett; Methylrosaniline Chloride; Methylrosanilinii Chloridum; Méthylrosanilinium, Chlorure de; Methylrosanilinium-chlorid; Methylrosaniliniumchlorid; Metilrosanilina, cloruro de; Metilrozanilinio chloridas; Metilrozanilinyum Klorür; Metylrosaniliniumklorid; Metyylirosaniliniumkloridi; Pyoctaninum Caeruleum; Viola Crystallina; Метилрозанилиния Хлорид.

4-[4,4′Bis(dimethylamino)benzhydrylidene]cyclohexa-2,5-dien-1-ylidenedimethylammonium chloride.

$C_{25}H_{30}ClN_3$=408.0

CAS — 548-62-9.

ATC — D01AE02; G01AX09.

ATC Vet — QD01AE02; QG01AX09.

UNII — J4Z741D6O5.

NOTE. The name methyl violet—CI Basic Violet 1; Colour Index No. 42535—has been used as a synonym for methylrosanilinium chloride, but is applied to a mixture of the hydrochlorides of the higher methylated pararosanilines consisting mainly of the tetramethyl-, pentamethyl-, and hexamethyl-compounds.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Jpn includes a mixture of hexamethylpararosaniline hydrochloride with the tetramethyl- and pentamethyl-compounds.

Ph. Eur. 8: (Methylrosanilinium Chloride). A dark green, hygroscopic, shiny powder. It contains not more than 10% of pentamethyl-*p*-rosanilinium chloride. It is also known as crystal violet and gentian violet. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Gentian Violet). A dark green powder or greenish, glistening pieces with a metallic lustre, and with not more than a faint odour. Sparingly soluble in water; soluble 1 in 10 of alcohol and 1 in 15 of glycerol; soluble in chloroform; insoluble in ether.

Incompatibility. The antimicrobial activity of methylrosanilinium chloride may be reduced through incompatibilities, decreasing pH, or through combination with organic matter.

The antibacterial activity of methylrosanilinium chloride was inhibited in suspensions of bentonite with which it formed a stable complex.[1]

1. Harris WA. The inactivation of cationic antiseptics by bentonite suspensions. *Australas J Pharm* 1961; **42:** 583–8.

Uses and Administration

Methylrosanilinium chloride is a triphenylmethane antiseptic dye effective against some Gram-positive bacteria, particularly *Staphylococcus* spp., and some pathogenic fungi such as *Candida* spp. It is much less active against Gram-negative bacteria and ineffective against acid-fast bacteria and bacterial spores. Its activity increases as pH increases.

Methylrosanilinium chloride has been applied topically as a 0.25 to 2.0% aqueous solution or as a cream for the treatment of bacterial and fungal infections, but in the UK its use is now restricted to application to unbroken skin because of concern over *animal* carcinogenicity. It has also been used as a 0.5% solution with brilliant green 0.5% (Bonney's blue) for skin marking before surgery.

Adverse Effects and Precautions

Topical application of methylrosanilinium chloride can produce irritation and ulceration of mucous membranes. Ingestion of methylrosanilinium chloride during prolonged or frequent treatment for oral candidiasis has resulted in oesophagitis, laryngitis, and tracheitis; ingestion may also cause nausea, vomiting, diarrhoea, and abdominal pain. In the UK it is recommended that methylrosanilinium chloride should not be applied to mucous membranes or open wounds. Contact with the eyes or broken skin should be avoided. Methylrosanilinium chloride may stain skin and clothing.

Animal carcinogenicity has restricted its use.

Carcinogenicity. Methylrosanilinium chloride has been shown *in vitro* to be capable of interacting with DNA of living cells,[1] and has demonstrable carcinogenicity in *mice*.[2]

1. Rosenkranz HS, Carr HS. Possible hazard in use of gentian violet. *BMJ* 1971; **3:** 702–3.
2. MAFF Food Advisory Committee. Final report on the review of the Colouring Matter in Food Regulations 1973: FdAC/REP/4. London: HMSO, 1987.

Effects on the skin and mucous membranes. Necrotic skin reactions have been reported after the use of topical 1% aqueous solutions of methylrosanilinium chloride;[1] areas affected include the submammary folds, gluteal fold, genitalia, and toe-webs. Similar reactions were seen in 2 patients after use of 1% methylrosanilinium chloride or brilliant green on stripped skin.[1] Oral ulceration developed in all of 6 neonates treated with aqueous methylrosanilinium chloride 0.5 or 1% for oral candidiasis.[2]

In the UK it is recommended that methylrosanilinium chloride should not be applied to mucous membranes or open wounds.

1. Björnberg A, Mobacken H. Necrotic skin reactions caused by 1% gentian violet and brilliant green. *Acta Derm Venereol (Stockh)* 1972; **52:** 55–60.
2. Horsfield P, *et al.* Oral irritation with gentian violet. *BMJ* 1976; **2:** 529.

Effects on the urinary tract. Severe haemorrhagic cystitis rapidly occurred in a 32-year-old woman after accidental injection through the urethra of a solution of methylrosanilinium chloride 1% and alcohol 2%.[1] Two cases of severe cystitis were also reported after instillation into the bladder of an undiluted solution containing methylrosanilinium chloride and brilliant green 1:1 (Bonney's blue).[2] Haemorrhagic cystitis has also been reported in a 16-month-old boy after a diluted solution of methylrosanilinium chloride 1% was instilled into his bladder during an inguinal herniorrhaphy.[3]

1. Walsh C, Walsh A. Haemorrhagic cystitis due to gentian violet. *BMJ* 1986; **293:** 732.
2. Christmas TJ, *et al.* Bonney's blue. *Lancet* 1988; **ii:** 459–60.
3. Kim SJ, *et al.* Hemorrhagic cystitis due to intravesical instillation of gentian violet completely recovered with conservative therapy. *Yonsei Med J* 2003; **44:** 163–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Pioktanina; ***Spain***: Vigencial; ***Thai.***: Pyrad-Violet; ***Turk.***: Viojen.

Multi-ingredient Preparations. ***Chile***: Faxet.

Pharmacopoeial Preparations
USP 36: Gentian Violet Cream; Gentian Violet Topical Solution.

Miramistin

Myramistin; Мирамистин.

Alkylamidopropylmethylbenzylammonium chloride.

$C_{26}H_{47}N_2OCl$=439.1

CAS — 126338-77-0; 15809-19-5.

Profile

Miramistin is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also included in topical preparations for skin disorders when prone to infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Okomistin (Окомистин); ***Ukr.***: Myramydez (Мирамидез); Oftamirin (Офтамирин).

Multi-ingredient Preparations. ***Ukr.***: Panthestin (Пантестин); Trimistin (Тримистин).

Miripirium Chloride *(rINN)*

Cloruro de miripirio; Miripirii Chloridum; Miripirio, cloruro de; Miripirium, Chlorure de; Myristyl-gamma-picolinium Chloride; Мирипирия Хлорид.

4-Methyl-1-tetradecylpyridinium chloride.

$C_{20}H_{36}ClN$=326.0

CAS — 7631-49-4 (miripirium); 2748-88-1 (miripirium chloride).

UNII — 3D6CWI0P23.

Profile

Miripirium chloride is used as an antimicrobial preservative in some pharmaceutical products.

Hypersensitivity. Two patients who had a delayed hypersensitivity reaction to retrobulbar injection of methylprednisolone acetate suspension (*Depo-Medrol*)[1] were found on intradermal testing to be sensitive to methylprednisolone and to the preservative miripirium chloride included in the formulation. A similar case of contact allergy has been reported[2] in a 56-year-old woman who received an intra-articular injection of methylprednisolone acetate. Patch testing showed allergy to the preservative miripirium chloride.

1. Mathias CGT, Robertson DB. Delayed hypersensitivity to a corticosteroid suspension containing methylprednisolone. *Arch Dermatol* 1985; **121:** 258–61.
2. Färm G, Erikssohn I. Contact allergy to miripirium chloride in Depo-Medrol. *Contact Dermatitis* 2001; **44:** 127.

Miristalkonium Chloride *(BAN, rINN)*

Cloruro de miristalconio; Miristalconio, cloruro de; Miristalkonii Chloridum; Miristalkonium, Chlorure de; Myristylbenzalkonium Chloride; Tetradecylbenzyldimethylammonium Chloride; Миристалкония Хлорид.

Benzyldimethyltetradecylammonium chloride.

$C_{23}H_{42}ClN$=368.0

CAS — 139-08-2.

ATC — R02AA10.

ATC Vet — QR02AA10.

UNII — 0W255OL75T.

Profile

Miristalkonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It has been used in creams and lotions for disinfection of the skin and has been an ingredient of sprays used for the treatment of minor infections of the mouth and throat. It is also used as a vaginal spermicide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Alpagelle.

Multi-ingredient Preparations. ***Fr.***: Sterlane; ***Ital.***: Eburdent F.

Monothioglycerol

α-Monothioglycerol; Monotioglicerol; Thioglycerol; Тиоглицерин.

3-Mercaptopropane-1,2-diol.

$C_3H_8O_2S$=108.2

CAS — 96-27-5.

UNII — AAO1P0WSXJ.

Pharmacopoeias. In *USNF.*

USNF 31: (Monothioglycerol). A colourless or pale yellow, viscous, hygroscopic liquid with a slight odour of sulfide. Freely soluble in water; miscible with alcohol; insoluble in ether. A 10% solution in water has a pH of 3.5 to 7.0. Store in airtight containers.

Profile

Monothioglycerol is used as an antoxidant preservative in pharmaceutical preparations. It has some antimicrobial activity.

Nitromersol

Нитромерсол.

5-Methyl-2-nitro-7-oxa-8-mercurabicyclo[4.2.0]octa-1,3,5-triene.

$C_7H_5HgNO_3$=351.7

CAS — 133-58-4.

UNII — RU6242GP15.

Pharmacopoeias. In *US.*

USP 36: (Nitromersol). A brownish-yellow to yellow odourless powder or granules. Very slightly soluble in water, in alcohol, in acetone, and in ether; soluble in solutions of alkalis and of ammonia with the formation of salts. Store in airtight containers. Protect from light.

Incompatibility. Nitromersol is incompatible with metals and sulfides. Its antimicrobial activity may be diminished in the presence of organic material.

Uses and Administration

Nitromersol is a mercurial antiseptic effective against some bacteria. It is not effective against spores or acid-fast bacteria. It has been used for superficial skin infections and for disinfection of the skin before surgical treatment.

Adverse Effects and Treatment

As for Mercury, p. 2556.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Butesin†.

Pharmacopoeial Preparations
USP 36: Nitromersol Topical Solution.

Nordihydroguaiaretic Acid

Acidum Nordihydroguaiareticum; NDGA; Nordihidroguayarético, ácido; Nordihydroguajareettiha ppo; Nordihydroguajaretsyra; Нордигидроваяретовая Кислота.
4,4′-(2,3-Dimethyltetramethylene)bis(benzene-1,2-diol).
$C_{18}H_{22}O_4$=302.4
CAS — 500-38-9.

Profile

Nordihydroguaiaretic acid has been used as an antoxidant preservative. Allergic contact dermatitis has been reported.

Noxytiolin *(BAN, rINN)*

Noxitiolina; Noxythiolin; Noxytioline; Noxytiolinum; Нокситиолин.
1-Hydroxymethyl-3-methyl-2-thiourea.
$C_3H_8N_2OS$=120.2
CAS — 15599-39-0.
ATC — S01AX07.
ATC Vet — QS01AX07.
UNII — 4DN3AF1FU6.

Uses and Administration

Noxytiolin is an antiseptic with wide antibacterial and antifungal actions. It may act by slowly releasing formaldehyde in solution.

For instillation into, or irrigation of, the peritoneal cavity or other body cavities, a 1 or 2.5% solution is used. Solutions of noxytiolin should be warmed to 37 degrees before instillation or irrigation. Treatment is usually for 3 to 7 days. The normal total daily amount used in adults should not exceed 5 g for instillation or 10 g for continuous irrigation.

Action. Although noxytiolin has generally been thought to act, at least in part, by slowly releasing formaldehyde into solution, it has been reported[1] that much smaller amounts are released than have previously been thought and that the antimicrobial effects of noxytiolin solutions cannot be attributed solely to the presence of formaldehyde. There is evidence *in vitro* that noxytiolin might reduce the adherence of micro-organisms to epithelial surfaces.[2]

1. Gorman SP, *et al.* Formaldehyde release from noxythiolin solutions. *Pharm J* 1984; **234:** 62–3.
2. Anderson L, *et al.* Clinical implications of the microbial anti-adherence properties of noxythiolin. *J Pharm Pharmacol* 1985; **37** (suppl): 64P.

Infections of the pleural cavity. Three patients with pleural empyema or pneumonectomy space infection were treated by irrigation of the cavity with noxytiolin 1% in normal saline for 3 hours, followed by drainage for 1 hour, the cycle being repeated 4-hourly. Infection was eradicated within 21 days in all 3 patients.[1]

1. Rosenfeldt FL, *et al.* Comparison between irrigation and conventional treatment for empyema and pneumonectomy space infection. *Thorax* 1981; **36:** 272–7.

Adverse Effects and Treatment

When noxytiolin is given initially by irrigation for the treatment of the purulent infected bladder there may be an intense reaction with a burning sensation and the passage of large fibrin clumps. Giving it with a local anaesthetic such as tetracaine hydrochloride may control the pain.

Breath odour. A pervasive sweet breath odour characteristic of decaying vegetables has been noted in patients treated with peritoneal dialysis fluid containing noxytiolin.[1] The odour was attributed to unidentified sulfur metabolites.

1. Stewart WK, Fleming LW. Use your nose. *Lancet* 1983; **i:** 426.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Noxyflex†; ***Irl.***: Noxyflex S†; ***UK***: Noxyflex S.

Octafonium Chloride *(BAN, rINN)*

Cloruro de octafonio; Octafonii Chloridum; Octafonio, cloruro de; Octafonium, Chlorure d'; Octaphonium Chloride; Phenoctide; Октафония Хлорид.
Benzyldiethyl-2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethylammonium chloride monohydrate.
$C_{27}H_{42}ClNO,H_2O$=450.1
CAS — 15687-40-8 (anhydrous octafonium chloride); 78-05-7 (anhydrous octafonium chloride).
UNII — 5SEY06I0DA.

Profile

Octafonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in topical preparations for skin disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Irl.***: Germolene; ***S.Afr.***: Germolene†; ***UK***: Germolene.

Octenidine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de octenidina; Octenidina, hidrocloruro de; Octénidine, Chlorhydrate d'; Octenidini Hydrochloridum; Win-41464-2 (octenidine hydrochloride); Win-41464-6 (octenidine saccharin); Win-41464 (octenidine); Октенидина Гидрохлорид.
1,1′,4,4′-Tetrahydro-*N*,*N*′-dioctyl-1,1′-decamethylenedi-(4-pyridylideneamine) dihydrochloride.
$C_{36}H_{62}N_4,2HCl$=623.8
CAS — 71251-02-0 (octenidine); 70775-75-6 (octenidine hydrochloride).
UNII — U84956NU4B.

Profile

Octenidine is a bispyridine bactericidal antiseptic with some antiviral and antifungal activity. It has been used as the hydrochloride for skin and mucous membrane disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Stellisan.

Multi-ingredient Preparations. ***Austria***: Octeniderm; Octenisept; ***Cz.***: Octenisept; ***Ger.***: Linola Wundgel; Octenisept; ***Gr.***: Octeniderm; Octenisept; ***Pol.***: Octenisept; ***Rus.***: Octenisept (Октенисепт); ***Singapore***: Octenisan; Octenisept Wound Gel; Octenisept; ***Switz.***: Octeniderm; Octenisept; ***Ukr.***: Octenisept (Октенисепт); Oktenisept (Октенисепт).

Octyldecyldimethylammonium Chloride

Decyldimethyloctylammonium Chloride; Decyloctyldimethylammonium Chloride; Octyl Decyl Dimethyl Ammonium Chloride; Quaternium-24; Октилдецилдиметиламмоний Хлорид.
N,*N*-Dimethyl-*N*-octyl-1-decanaminium chloride.
$C_{20}H_{44}ClN$=334.0
CAS — 32426-11-2.
UNII — 0T2NG1539G.

Profile

Octyldecyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of hard surfaces and the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Vi Rid-Ready.

Orthophenylphenol

2-Biphenylol; E231; E232 (sodium-*o*-phenylphenol); 2-Hydroxybiphenyl; *o*-Hydroxydiphenyl; Ortofenilfenol; Ортофенилфенол.
(1,1′-Biphenyl)-2-ol.
$C_{12}H_{10}O$=170.2
CAS — 90-43-7.
ATC — D08AE06.
ATC Vet — QD08AE06.
UNII — D343Z75HT8.

Profile

Orthophenylphenol is a phenolic disinfectant with antimicrobial properties similar to those of chloroxylenol (p. 1748.2). It is used for disinfection of skin, hands, instruments, and hard surfaces. It also has many industrial and agricultural uses as a preservative for a wide range of materials, particularly against moulds and rots. Sodium-*o*-phenylphenol has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Amocid; ***Ital.***: Citromedics Disinfettante; Citrosteril Aspiratori; Crescom; Esofenol 60; Germozero; Helix I; Higesan; Neo Esoformolo.

Multi-ingredient Preparations. ***Austria***: Dodesept Gefarbt; Dodesept; Kodan; ***Canad.***: Aseptone 1; Aseptone 2; Aseptone 5; ***Ger.***: Bomix†; Freka-Derm†; Freka-Sept 80†; Helipur; Kodan Tinktur Forte; ***Ital.***: Esofenol Ferri; Germozero Dermo; Helipur; Hygienist; Norica Plus; Sangen Casa; Sterosan; ***Singapore***: Desderman; Primasept Med; ***Switz.***: Kodan forte; ***UK***: Eradicil; ***USA***: BTK-Plus†.

Oxychlorosene *(USAN)*

Monoxychlorosene; Oxicloroseno; Оксихлорозен.
$C_{20}H_{34}O_3S,HOCl$=407.0
CAS — 8031-14-9.
UNII — 3214M86B2N.

Oxychlorosene Sodium *(USAN)*

Oxicloroseno sódico; Sodium Oxychlorosene; Оксихлорозен Натрий.
CAS — 52906-84-0.
UNII — N693Q6RADF.

Profile

Oxychlorosene is the hypochlorous acid complex of a mixture of the phenyl sulfonate derivatives of aliphatic hydrocarbons. It is a chlorine-releasing antiseptic with the general properties of chlorine, p. 1746.2.

A 0.4% solution of oxychlorosene sodium has been used for cleansing wounds (although chlorine-releasing antiseptics are generally regarded as too irritant for this purpose—see Disinfection, Wounds, under Uses and Administration of Sodium Hypochlorite, p. 1769.1) and for pre-operative skin preparation; a 0.1 or 0.2% solution has been used in urological and ophthalmological disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Clorpactin WCS-90.

Oxymethurea

Carbamol; Dihydroxymethyl Carbamide; Dimethylolurea; Oximeturea; Диметилолмочевина; *N*,*N*′-di(hydroksimetyyli) karbamidi; *N*,*N*′-di(hydroximetyl)-karbamid; *N*,*N*′-di(hydroxymethyl)carbamidum.
N,*N*′-Bis(hydroxymethyl)urea.
$C_3H_8N_2O_3$=120.1
CAS — 140-95-4.
UNII — N68H97CAWG.

Profile

Oxymethurea is an antiseptic included in multi-ingredient preparations intended for the topical treatment of ear infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Otogesic.

Parachlorophenol

Paraclorofenol; Парахлорофенол.
4-Chlorophenol.
C_6H_5ClO=128.6
CAS — 106-48-9.
UNII — 3DLC36A01X.

Pharmacopoeias. In *US.*

US also includes camphorated parachlorophenol.

USP 36: (Parachlorophenol). It consists of white or pink crystals with a characteristic phenolic odour. M.p. about 42 degrees; congealing temperature between 42 degrees and 44 degrees. Sparingly soluble in water and in liquid paraffin; very soluble in alcohol, in chloroform, in ether, in glycerol, and in fixed and volatile oils; soluble in soft paraffin. A 1% solution in water is acid to litmus. Store in airtight containers. Protect from light.

USP 36: (Camphorated Parachlorophenol). It contains not less than 33% and not more than 37% of parachlorophenol and not less than 63% and not more than 67% of camphor, with the sum of the percentages of parachlorophenol and camphor not less than 97% and not more than 103%. Store in airtight containers. Protect from light.

Profile

Parachlorophenol is a chlorinated phenolic disinfectant and antiseptic with similar properties to phenol (below). Camphorated parachlorophenol has been used in dentistry in the treatment of infected root canals.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Cresophene; ***Fr.***: Cidapex†; Endotine; Mepacyl; ***Ital.***: Esofenol Ferri; Pasta Iodoformica Radiopaca; ***Spain***: Cresophene.

Paraformaldehyde

Paraform; Paraformaldehído; Paraformic Aldehyde; Paraformol; Polymerised Formaldehyde; Polyoxymethylene; Параформальдегид.
$(CH_2O)_n$
CAS — 30525-89-4.
UNII — Y19UC83H8E.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Paraformaldehyde is a disinfectant and antiseptic with the properties and uses of formaldehyde (p. 1752.2) and is used as a source of formaldehyde. To disinfect rooms it has been vapourised by heating. Tablets prepared for this purpose should be coloured by the addition of a suitable blue dye.

Paraformaldehyde has been used in lozenges for the treatment of minor throat infections. In dentistry, it has been used as an obtundent for sensitive dentine and as an antiseptic in mummifying pastes and for root canals. Paraformaldehyde may also be used for the decontamination of equipment thought to be contaminated with the spores of *Bacillus anthracis.*

Adverse Effects, Treatment, and Precautions

As for Formaldehyde Solution, p. 1752.3. There have been reports of allergic reactions and nerve damage associated with the dental use of paraformaldehyde as a root canal sealant; it should not extrude beyond the apex.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Formalin; ***Ital.***: Esoform 7 mc; Esoform 70 mc.

Multi-ingredient Preparations. ***Canad.***: Endomethasone; ***Fr.***: Caustinerf sans Arsenic; Yranicid sans Arsenic; ***Gr.***: Endomethasone†; ***Ital.***: Eso 70; Pasta Devitalizzante.

Peracetic Acid

Acetyl Hydroperoxide; Ácido peroxiacético; Acidum Peraceticum; Kyselina peroctová; Peracético, ácido; Peroxyacetic Acid; Надуксусная Кислота; Перуксусная Кислота.
$C_2H_4O_3$=76.05
CAS — 79-21-0.
UNII — 16KPI2E1HD.

Uses

Peracetic acid is a strong oxidising disinfectant. It is active against many micro-organisms including bacteria, spores, fungi, and viruses. It is used for disinfecting medical equipment including dialysers and endoscopes. It is used in the food industry and for disinfecting sewage sludge, and has been used as a spray for sterilisation of laboratories.

Reviews.
1. Kitis M. Disinfection of wastewater with peracetic acid: a review. *Environ Int* 2004; **30:** 47–55.

Disinfection of dialysis equipment. For use of peracetic acid with hydrogen peroxide in the disinfection of dialysis equipment, see under Hydrogen Peroxide, p. 1756.1.

Disinfection of endoscopes. Peracetic acid has been used to disinfect endoscopes;[1,2] it is a possible alternative to glutaral (see p. 1731.2).

1. Bradley CR, *et al.* Evaluation of the Steris system 1 peracetic acid endoscope processor. *J Hosp Infect* 1995; **29:** 143–51.
2. Middleton AM, *et al.* Disinfection of bronchoscopes, contaminated in vitro with Mycobacterium tuberculosis, Mycobacterium avium-intracellulare and Mycobacterium chelonae in sputum, using stabilized, buffered peracetic acid solution ('Nu-Cidex'). *J Hosp Infect* 1997; **37:** 137–43.

Adverse Effects and Precautions

Concentrated peracetic acid is corrosive to the skin. Inhalation may produce respiratory symptoms, including pulmonary oedema, although commercial solutions are claimed to have low vapour activity.

Occupational exposure. Although corrosive and highly irritating to skin, eyes, mucous membranes and respiratory tract, solutions of peracetic acid (with hydrogen peroxide) were thought unlikely to cause sensitisation leading to hypersensitivity reactions in healthcare workers who were occupationally exposed. In contrast, *o*-phthaldialdehyde, although its sensitising potential was much lower than that of glutaral, might cause respiratory and dermal sensitisation.[1]

1. Rideout K, *et al.* Considering risks to healthcare workers from glutaraldehyde alternatives in high-level disinfection. *J Hosp Infect* 2005; **59:** 4–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Sekusept; ***Ital.***: Esocetic; Esodrox; Ferrister†; Renaxid†; SaniDrox; Sekusept; Sporidox Plus†; ***Singapore***: PeraSafe.

Multi-ingredient Preparations. ***Canad.***: Actril; ***Fr.***: Anioxyde†; ***Ger.***: AdaptaCide PAA-C; ***Ital.***: Adaspor†; Peresal†; ***Singapore***: Virkon.

Phenethyl Alcohol *(BAN)*

Alcohol feniletílico; Alcohol Phenylethylicus; Alkohol fenyloetylowy; Benzyl Carbinol; Phenethanolum; Phenylethyl alcohol; Фенетиловый Спирт.
2-Phenylethanol.
$C_6H_5.CH_2.CH_2OH$=122.2
CAS — 60-12-8.
UNII — ML9LGA7468.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Phenylethyl Alcohol). A colourless liquid with a rose-like odour. Soluble 1 in 60 of water, 1 in less than 1 of alcohol, of chloroform, of ether, of benzyl benzoate, and of diethyl phthalate, and 1 in 2 of alcohol 50%; very soluble in glycerol, in propylene glycol, and in fixed oils; slightly soluble in liquid paraffin. Store in airtight containers in a cool, dry place. Protect from light.

Incompatibility. Phenethyl alcohol is incompatible with oxidising agents and proteins. Activity may be reduced by nonionic surfactants or by adsorption onto low density polyethylene containers.

Profile

Phenethyl alcohol is more active against Gram-negative than Gram-positive bacteria. It is used as a preservative in ophthalmic, nasal, and otic solutions at a concentration of 0.25 to 0.5%, usually with another bactericide, and up to 1% on its own in topical preparations. It is also used as an antiseptic in topical products in concentrations of up to 7.5%. It is also used as a component of flavouring essences and perfumes.

Phenethyl alcohol may cause eye irritation.

Antimicrobial action. Antimicrobial activity may be enhanced by the addition of phenethyl alcohol to solutions preserved with benzalkonium chloride, chlorhexidine acetate, phenylmercuric nitrate, chlorocresol, or chlorobutanol.[1]

1. Richards RME, McBride RJ. The preservation of ophthalmic solutions with antibacterial combinations. *J Pharm Pharmacol* 1972; **24:** 145–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Sebirinse; ***Canad.***: Sclerodex; ***Ger.***: Imazol; ***India***: Borozin; ***NZ***: Sebirinse; ***UK***: Ceanel.

Phenol

Ácido carbólico; Ácido fénico; Carbolic Acid; Fenol; Fenoli; Fenolis; Hidroxibenceno; Phenic Acid; Phénol; Phenolum; Phenyl Hydrate; Phenylic Acid; Оксибензол; Фенол.
Hydroxybenzene.
$C_6H_5.OH$=94.11
CAS — 108-95-2.
ATC — C05BB05; D08AE03; N01BX03; R02AA19.
ATC Vet — QC05BB05; QD08AE03; QN01BX03; QR02AA19.
UNII — 339NCG44TV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* *Br.*, *Swiss*, and *US* also include a monograph for Liquefied Phenol.

Ph. Eur. 8: (Phenol). Colourless or faintly pink or faintly yellow deliquescent crystals or crystalline masses. F.p. not less than 39.5 degrees. Soluble in water; very soluble in alcohol, in dichloromethane, and in glycerol. Store in airtight containers. Protect from light.

BP 2014: (Liquefied Phenol). An aqueous mixture containing phenol 77.0 to 81.5% w/w in purified water. A colourless to faintly coloured, caustic liquid with a characteristic and not tarry odour. Soluble in water; miscible with alcohol, with ether, and with glycerol. Protect from light. It may congeal or deposit crystals if stored at a temperature below 4 degrees. It should be completely melted before use.

When phenol is to be mixed with collodion, fixed oils, or paraffins, melted phenol should be used, and not Liquefied Phenol.

USP 36: (Phenol). Colourless to light pink, interlaced or separate, needle-shaped crystals, or a white to light pink crystalline mass, with a characteristic odour. It gradually darkens on exposure to light and air. Soluble 1 in 15 of water; very soluble in alcohol, in chloroform, in ether, in glycerol, and in fixed and volatile oils; soluble 1 in 70 of liquid paraffin. A solution of 1 g in 15 mL water is clear and is neutral or acid to litmus. Store in airtight containers. Protect from light.

USP 36: (Liquefied Phenol). Phenol maintained in a liquid condition by the presence of about 10% of water; it contains not less than 89% by weight of phenol. It may contain a suitable stabiliser. A colourless to pink liquid which may develop a red tint upon exposure to air or light, and with a characteristic, somewhat aromatic odour. Miscible with alcohol, with ether, and with glycerol. Store in airtight glass containers. Protect from light.

When phenol is to be mixed with a fixed oil, liquid paraffin, or white soft paraffin, crystalline Phenol and not Liquefied Phenol should be used.

Incompatibility. Phenol is incompatible with alkaline salts and nonionic surfactants. The antimicrobial activity of phenol may be diminished through increasing pH or through combination with blood and other organic matter.

Use for preservation. NOTE. Phenol should not be used to preserve preparations that are to be freeze-dried.

Uses and Administration

Phenol is an antiseptic and disinfectant effective against vegetative Gram-positive and Gram-negative bacteria, mycobacteria, and some fungi, but only very slowly effective against spores. It is also active against certain viruses. Phenol is more active in acid solution.

Aqueous solutions up to 1% are bacteriostatic while stronger solutions are bactericidal.

Phenol is a commonly used antimicrobial preservative in parenteral preparations; concentrations of up to 0.5% are usually used.

A 0.5 to 1% solution has been used for its local anaesthetic effect to relieve itching.

A 1.4% solution is used for pain or irritation of the mouth and throat. Weak concentrations (up to 2%) have also been used topically for disinfection. A 5% solution has been used as a disinfectant for excreta.

Oily Phenol Injection (BP 2014), up to 10 mL, has been injected into the tissues around internal haemorrhoids as an analgesic sclerosing agent, but alternative procedures may be preferred. Aqueous phenol has also been used as a sclerosant in the treatment of hydroceles.

Solutions of phenol in glycerol have been given intrathecally for the alleviation of spasticity (p. 2014.2) or

injected intrathecally or into soft-tissue structures for the treatment of chronic low back pain. Other types of severe intractable pain may be relieved by injecting aqueous phenol close to motor nerves. Aqueous phenol has been used for chemical sympathectomy in peripheral vascular disorders and for the treatment of urinary incontinence.

Liquefied phenol has been used in the treatment of ingrowing toenails.

Dystonias. Phenol appears to produce a decrease in muscle tone without profound weakness and is considered to be an effective agent in treating focal dystonias.[1] Intramuscular phenol was reported[2] to have produced improvement in 2 adult patients with moderately severe spasmodic torticollis (p. 2019.2) who had not responded adequately to intramuscular injections of botulinum A toxin. Response was maintained by re-injection every 6 months. Following this case report, an open study[3] was conducted on 3 patients with spasmodic torticollis who had not responded to botulinum toxin A and other drug treatments. After 10 intramuscular injections of phenol, given weekly and then monthly, 2 of the patients showed improvement; one reached partial remission while the other had improvement that lasted for 3 months. The third patient did not respond to treatment with phenol. A study[4] to determine the efficacy and adverse effects of a 2% phenol block in patients with spasmodic torticollis was conducted in 16 patients, all of whom were refractory to oral drug and rehabilitation therapies. Results showed significant improvement in neck movement and position. However, 4 patients developed reversible sensory disturbance of the transverse cutaneous nerve of the neck area. A patient who developed a focal dystonic contraction of the foot responded to single intramuscular injection of 5% aqueous phenol, after initial treatment with botulinum toxin A had shown no benefit.[5]

1. Zafonte RD, Munin MC. Phenol and alcohol blocks for the treatment of spasticity. *Phys Med Rehabil Clin N Am* 2001; **12:** 817–32.
2. Massey JM. Treatment of spasmodic torticollis with intramuscular phenol injection. *J Neurol Neurosurg Psychiatry* 1995; **58:** 258–9.
3. García Ruiz PJ, Sanchez Bernardos V. Intramuscular phenol injection for severe cervical dystonia. *J Neurol* 2000; **247:** 146–7.
4. Takeuchi N, *et al*. Phenol block for cervical dystonia: effects and side effects. *Arch Phys Med Rehabil* 2004; **85:** 1117–20.
5. Kim J-S, *et al*. Idiopathic foot dystonia treated with intramuscular phenol injection. *Parkinsonism Relat Disord* 2003; **9:** 355–9.

Haemorrhoids. Sclerotherapy with oily phenol injection has been used[1] to treat haemorrhoids (p. 1808.1). The technique for preventing mucosal prolapse is to inject small volumes (about 2 or 3 mL) of a 5% solution of phenol in arachis oil into the submucous space above each of the 3 principal haemorrhoids. Rather than causing the haemorrhoidal veins to thrombose, the injection works by producing submucosal fibrosis, fixing the mucosa to the underlying muscle. However, other techniques for mucosal fixation such as rubber band ligation or perhaps infrared coagulation are more effective and associated with fewer complications.[2-5]

1. Alexander-Williams J. The management of piles. *BMJ* 1982; **285:** 1137–9.
2. Gartell PC, *et al*. A randomised clinical trial to compare rubber band ligation with phenol injection in the treatment of haemorrhoids. *Gut* 1984; **25:** A563.
3. Ambrose NS, *et al*. Prospective randomised trial of injection therapy against photocoagulation therapy in first and second degree haemorrhoids. *Gut* 1984; **25:** A563–4.
4. Johanson JF, Rimm A. Optimal nonsurgical treatment of hemorrhoids: a comparative analysis of infrared coagulation, rubber band ligation, and injection sclerotherapy. *Am J Gastroenterol* 1992; **87:** 1601–6.
5. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities: a meta-analysis. *Dis Colon Rectum* 1995; **38:** 687–94.

Ingrowing toenails. Liquefied phenol (88%) ablation has been performed as an alternative to surgical avulsion in the treatment of ingrowing toenails.[1,2] A systematic review[3] concluded that simple nail avulsion combined with treating the nail-bed with phenol was more effective at preventing symptomatic recurrence of ingrowing toenails than cutting out the nail-bed. However, there was a significant increase in postoperative infections when phenol was used.

1. Bostanci S, *et al*. Chemical matricectomy with phenol for the treatment of ingrowing toenail: a review of the literature and follow-up of 172 treated patients. *Acta Derm Venereol* 2001; **81:** 181–3.
2. Andreassi A, *et al*. Segmental phenolization for the treatment of ingrowing toenails: a review of 6 years experience. *J Dermatol Treat* 2004; **15:** 179–81.
3. Rounding C, Bloomfield S. Surgical treatments for ingrowing toenails. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/03/06).

Pain. The neurolytic use of phenol to produce destructive nerve block (see under Pain, p. 1977.1) has produced variable results, and some consider the risk of complications outweighs the benefits. However, it may have the advantage over alcohol that it is painless on injection, and smaller volumes can be used, potentially allowing greater precision (see p. 1733.2).

Urinary incontinence. Although injection of phenol into the pelvic plexus to produce partial denervation has been used in the management of severe intractable urge incontinence, its use has been largely abandoned. Some patients, especially those with detrusor hyperreflexia, have derived benefit[1,2] but overall efficacy can be poor and benefits short-lived.[3]

1. Ewing R, *et al*. Subtrigonal phenol injection therapy for incontinence in female patients with multiple sclerosis. *Lancet* 1983; **i:** 1304–5.
2. Blackford HN, *et al*. Results of transvesical infiltration of the pelvic plexuses with phenol in 116 patients. *Br J Urol* 1984; **56:** 647–9.
3. Rosenbaum TP, *et al*. Trans-trigonal phenol failed the test of time. *Br J Urol* 1990; **66:** 164–9.

Adverse Effects

When ingested, phenol causes extensive local corrosion, with pain, nausea, vomiting, sweating, and diarrhoea. Excitation may occur initially but it is quickly followed by unconsciousness. There is depression of the CNS, with cardiac arrhythmias, and circulatory and respiratory failure, which may lead to death. Acidosis may develop and occasionally there is haemolysis and methaemoglobinaemia with cyanosis. The urine may become dark brown or green. Pulmonary oedema and myocardial damage may develop, and damage to the liver and kidneys may lead to organ failure.

Severe or fatal poisoning may occur from the absorption of phenol from unbroken skin or wounds and suitable precautions should be taken to prevent absorption. Applied to skin, phenol causes blanching and corrosion, sometimes with little pain. Aqueous solutions as dilute as 10% may be corrosive.

Toxic symptoms may also arise through absorption of phenol vapour by the skin or lungs. Phenol throat spray may cause local oedema.

Cresols and other phenolic substances have similar effects.

Effects on the heart. A 10-year-old boy developed life-threatening premature ventricular complexes during the application of a solution of phenol 40% and croton oil 0.8% in hexachlorophene soap and water for chemical peeling of a giant hairy naevus.[1] Cardiac arrhythmias have been reported after the use of phenol for chemical face peeling.[2] They were also seen in 3 of 16 children who received phenol 5% as a neurolytic.[3]

1. Warner MA, Harper JV. Cardiac dysrhythmias associated with chemical peeling with phenol. *Anesthesiology* 1985; **62:** 366–7.
2. Botta SA, *et al*. Cardiac arrhythmias in phenol face peeling: a suggested protocol for prevention. *Aesthetic Plast Surg* 1988; **12:** 115–17.
3. Morrison JE, *et al*. Phenol motor point blocks in children: plasma concentrations and cardiac dysrhythmias. *Anesthesiology* 1991; **75:** 359–62.

Effects on the kidneys. A 41-year-old man developed acute renal failure due to cutaneous absorption of phenol after falling into a shallow vat of industrial solvent containing 40% phenol in dichloromethane. No ingestion occurred. Other symptoms included 50% body-surface burns, cold extremities, nausea, vomiting, and respiratory distress. The patient required haemodialysis for 3 weeks; some abnormalities of renal function remained one year later.[1]

1. Foxall PJD, *et al*. Acute renal failure following accidental cutaneous absorption of phenol: application of NMR urinalysis to monitor the disease process. *Hum Toxicol* 1989; **9:** 491–6.

Effects on the liver. Phenol-induced hepatotoxicity has been reported[1] in a 43-year-old man after injection sclerotherapy for haemorrhoids with 5% phenol in arachis oil. During treatment the patient had pain radiating to the penis, then later developed backache and haematuria, and 6 days later was admitted to hospital with jaundice. He recovered well and his liver enzymes returned to normal levels after 6 months.

1. Suppiah A, Perry EP. Jaundice as a presentation of phenol induced hepatotoxocity [sic] following injection sclerotherapy for haemorrhoids. *Surgeon* 2005; **3:** 43–4.

Effects on sexual function. Three patients developed urinary symptoms and impotence which lasted up to one year after each receiving phenol 5% in arachis oil sclerotherapy for haemorrhoids.[1]

1. Bullock N. Impotence after sclerotherapy of haemorrhoids: case reports. *BMJ* 1997; **314:** 419.

Effects on the throat. Acute life-threatening epiglottitis occurred in a 49-year-old woman after the use of a throat spray containing the equivalent of 1.4% phenol. The reaction may have been anaphylactic or due to a direct toxic effect of the spray.[1] The UK CSM[2] reported in 1990 that it had received 4 reports of oedema of the epiglottis and/or larynx leading to respiratory difficulties. While the condition was rare, the effects were severe; 1 patient died and 2 survived only after emergency hospital treatment.

1. Ho S-L, Hollinrake K. Acute epiglottitis and Chloraseptic. *BMJ* 1989; **298:** 1584.
2. CSM. Chloraseptic throat spray and oedema of the epiglottis and larynx. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 17/06/10)

Treatment of Adverse Effects

If phenol has been swallowed, activated charcoal may be useful. Some sources suggest the cautious use of gastric lavage although this is generally inappropriate after ingestion of corrosive substances.

If phenol has been spilled on the skin removal of contaminated clothing and excess phenol should be followed by washing of the skin with glycerol or, alternatively, with copious amounts of water. Macrogol 300 and vegetable oils have also been used.

Contamination of the eyes should be treated by flooding with water or sodium chloride 0.9% only for at least 10 to 15 minutes.

The patient should be kept warm and given supportive treatment. Intravenous sodium bicarbonate should be given where there is metabolic acidosis.

Precautions

Solutions containing phenol should not be applied to large areas of skin or large wounds since sufficient phenol may be absorbed to give rise to toxic symptoms. Phenol should not be used as a throat spray in patients with epiglottitis, or in children aged under 6 years.

Pharmacokinetics

Phenol is absorbed from the gastrointestinal tract and through skin and mucous membranes. It is metabolised to phenylglucuronide and phenyl sulfate, and small amounts are oxidised to catechol and quinol which are mainly conjugated. The metabolites are excreted in the urine; on oxidation to quinones they may tint the urine dark brown or green.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Haemorol; ***Canad.***: Antiseptic Salve†; P & S; ***Chile***: Metapio; ***NZ***: Haemorol; ***S.Afr.***: Medi-Keel A; SB Aurico Ear Drops†; Septosol; ***Thai.***: Pose-Cresol†; ***UK***: Ultra Chloraseptic; ***Ukr.***: Orasept (Орасепт); ***USA***: Cheracol Sore Throat; Chloraseptic Kids Sore Throat Spray; Chloraseptic Sore Throat; Green Throat Spray; P & S; Phenaseptic; Red Throat Spray; Triaminic Sore Throat Spray; Ulcerease.

Multi-ingredient Preparations. ***Arg.***: Aceite Esmeralda Moone; Callicida; Manzan; Piracalamina; Prurisedan Rosa; Prurisedan; ***Austral.***: Ayrton's Chilblain†; EgoPsoryl TA; Nyal Toothache Drops; Sarna†; ***Austria***: Herposicc; ***Belg.***: Eucalyptine Pholcodine; Sedemol; Sulfa-Sedemol; ***Braz.***: Cloraseptic; Dentisan†; Otoloide; ***Canad.***: Ak Lip Balm†; Blistex DCT Lip Balm†; Blistex Lip Medex†; Blistex Medicated Lip Ointment†; Carmex Lip Balm; Carmex Lip Ointment; Lip Conditioner Lip Balm; Lip Medex†; Medicated Blistex DCT Lip Balm; Ozonol; ***Chile***: Blistex; Chapstick Medicated; ***China***: Posterisan (玻特利); ***Fr.***: Aldyzine; Brulex; Otylol; Pulperyl; Rockles; Sedapulpe†; Solute Physiologique Phenole Lavoisier; Yranol Eugenole; ***Hong Kong***: Cepastat; Egopsoryl TA; ***Hung.***: Reparon; ***Irl.***: Blistex Relief; Germolene First Aid; Germolene; TCP; TCP; ***Ital.***: Creososto Composto; Fucsina Fenica; Lavanda Sofar; Pinselina Knapp; ***Malaysia***: Egopsoryl TA; Sarna; ***Mex.***: Forcremol; ***Neth.***: Agre-Gola†; ***NZ***: Egopsoryl TA; ***Philipp.***: Calmoseptine; Sarna; ***Rus.***: Fucaseptol (Фукасептол); ***S.Afr.***: Adco-Biohist; Alpha Toothache Essence†; Blistex; Calasthetic; Germolene†; Prep†; SB Universal Ointment†; TCP†; ***Singapore***: Calamine and Menthol; Castellani's Paint; Cepastat; Egopsoryl TA; Sarna; ***Spain***: Dermomycose Liquido; Otocerum; Otogen Calmante; ***Thai.***: Con Con; Lanol; Sarna; Zema; ***Turk.***: Disinol; ***UK***: Blistex Relief; Chymol; Colsor; Dermacreme; Germolene; Germolene; Germolene; Lacto Calamine; TCP; TCP; TCP; ***USA***: Anbesol; Anbesol; Blistex Lip Balm; Blistex; Boil Ease; Campho-Phenique; Castaderm; Cepastat Cherry; Cepastat; Chapstick Medicated Lip Balm; Columbia Antiseptic Powder; Debacterol; Heal Aid Plus; Lip Medex; Lipmagik; Massengill; Mycinette; Nasal Jelly; Orabase Lip; Orasol; Phylorinol; Phylorinol; Skeeter Stik; Sting-Eze; Unguentine Plus; Unguentine.

Homoeopathic Preparations. ***Canad.***: Hylands Vaginitis†.

Pharmacopoeial Preparations
BP 2014: Aqueous Phenol Injection; Liquefied Phenol; Oily Phenol Injection; Phenol and Glycerol Injection;
BPC 1973: Magenta Paint;
USP 36: Camphorated Phenol Topical Gel; Carbol-Fuchsin Topical Solution; Liquefied Phenol; Phenolated Calamine Topical Suspension.

Phenoxyethanol

Ethylene Glycol 2-Monophenyl Ether; Ethyleneglycol Monophenylether; Fenoksietanoli; Fenoksietanolis; Fenoksyetanol; Fenoxietanol; Fenoxyethanol; Phenoxyaethanol;

Phénoxyéthanol; Phenoxyethanolum; 2-Phenoxyethyl Alcohol; β-Phenoxyethyl Alcohol; Феноксиэтанол.
2-Phenoxyethanol.
$C_8H_{10}O_2$=138.2
CAS — 122-99-6.
UNII — HIE492ZZ3T.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Phenoxyethanol). A colourless slightly viscous liquid. Slightly soluble in water, in arachis oil and in olive oil; miscible with alcohol, with acetone, and with glycerol.

USNF 31: (Phenoxyethanol). A colourless, slightly viscous liquid. Specific gravity 1.105 to 1.110 at 20 degrees. Slightly soluble in water; miscible with alcohol, with acetone, and with glycerol; slightly soluble in arachis oil and in olive oil. Store in a dry place, in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Incompatibility. The activity of phenoxyethanol may be reduced by interaction with nonionic surfactants and possibly by adsorption onto PVC.

Profile

Phenoxyethanol is effective against strains of *Pseudomonas aeruginosa* but less so against other Gram-negative and Gram-positive bacteria. It has been used as a preservative in cosmetics and topical pharmaceuticals at a concentration of 0.5 to 1%. It is often used with other preservatives, commonly hydroxybenzoates, to obtain a wider spectrum of antimicrobial activity.

Phenoxyethanol is used in concentrations of about 2% as an antiseptic for minor infections of skin, wounds, and mucous membranes. Aqueous solutions may be prepared by shaking the phenoxyethanol with hot water until dissolved, then adjusting to final volume when cool. Preparation of the solution can be aided by propylene glycol.

Phenoxypropanol and chlorophenoxyethanol are related compounds used in topical preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Biactol Liquid.

Multi-ingredient Preparations. ***Arg.***: Cicatul; Polviderm NF; ***Austral.***: QV Flare Up; ***Austria***: Octenisept; ***Canad.***: Marcorodex; ***Chile***: Eucerin Piel Grasa†; ***Cz.***: Octenisept; ***Fr.***: Alco-Aloe†; ***Ger.***: Linola Wundgel; Octenisept; ***Gr.***: Octenisept; ***India***: Exomega; ***Irl.***: Aidex†; ***Ital.***: Decon Ovuli; Fitostimoline; ***Mex.***: Fitoestimulina; Italdermol; ***NZ***: Acnederm; ***Pol.***: Octenisept; ***Port.***: Fitocreme; ***Rus.***: Octenisept (Октенисепт); ***Singapore***: Esemdent; Octenisept; ***Switz.***: Octenisept; ***Ukr.***: Denebol Gel (Денебол Гель); Octenisept (Октенисепт); Oktenisept (Октенисепт); ***USA***: Bodi Kleen; ***Venez.***: Glizigen; Photoderm AKN.

Phenoxyisopropanol

Fenoxiisopropanol; Phenoxyisopropyl Alcohol.
1-phenoxypropan-2-ol.
$C_9H_{12}O_2$=152.2
CAS — 770-35-4.
UNII — 87CZY0NY1A.

Profile

Phenoxyisopropanol is used as a preservative and as an antiseptic in preparations for the treatment of acne, insect bites, and minor abrasions to the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Clearasil Daily Face Wash†.

Multi-ingredient Preparations. ***Canad.***: Antiseptic Lotion†.

Phenylmercuric Salts

Fenilmercurio, sales.

Phenylmercuric Acetate

Fenilgyvsidabrio acetatas; Fenil-higany-acetát; Fenilmercurio, acetato de; Fenylhydrargyriumacetát; Fenylkvicksilveracetat; Fenylortęciowy octan; Fenyylimerkuriasetaatti; Phenylhydrargyni acetas; Phenylhydrargyri Acetas; Phénylmercure, acétate de; Phenylquecksilber(II)-acetat; PMA; Фенилмеркурацетат; Фенилртутьацетат.
(Acetato)phenylmercury.
$C_8H_8HgO_2$=336.7
CAS — 62-38-4.
UNII — OSX88361UX.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Phenylmercuric Acetate). A white or yellowish crystalline powder or small, colourless crystals. Slightly soluble in water; soluble in alcohol and in acetone. Protect from light.

USNF 31: (Phenylmercuric Acetate). A white to creamy-white, odourless, crystalline powder or small white prisms or leaflets. Soluble 1 in 180 of water, 1 in 225 of alcohol, 1 in 6.8 of chloroform, and 1 in 200 of ether; soluble in acetone. Store in airtight containers. Protect from light.

Incompatibility. The incompatibilities of phenylmercuric salts are described under Phenylmercuric Nitrate, below.

Phenylmercuric Borate *(rINN)*

Borato de fenilmercurio; Fenilgyvsidabrio boratas; Fenil-higany-borát; Fenilmercurio, borato de; Fenylhydrargyriumborát; Fenylkvicksilverborat; Fenylortęciowy boran; Fenyylimerkuriboraatti; Hydrargyrum Phenyloboricum; Phenomerborum; Phenylhydrargyri Boras; Phénylmercure, Borate de; Phenylmercuriborat; Фенилмеркурборат.
$C_6H_5HgOH,C_6H_5HgOB(OH)_2$ = 633.2 or C_6H_5HgOH, $C_6H_5HgBO_2$ = 615.2
CAS — 8017-88-7 ($C_{12}H_{13}BHg_2O_4$); 6273-99-0 ($C_{12}H_{11}BHg_2O_3$); 102-98-7 ($C_6H_7BHgO_3$).
ATC — D08AK02.
ATC Vet — QD08AK02.
UNII — ZT1TTY3NGJ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Phenylmercuric Borate). A compound consisting of equimolecular proportions of phenylmercuric orthoborate and phenylmercuric hydroxide ($C_{12}H_{13}BHg_2O_4$) or of the dehydrated form (metaborate, $C_{12}H_{11}BHg_2O_3$) or a mixture of the two compounds. Colourless shiny crystals or a white or slightly yellowish crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

Incompatibility. The incompatibilities of phenylmercuric salts are described under Phenylmercuric Nitrate, below.

Phenylmercuric Nitrate

Basic Phenylmercury Nitrate; Fenilgyvsidabrio nitratas; Fenil-higany-nitrát; Fenilmercurio, nitrato de; Fenylhydrargyriumnitrát; Fenylkvicksilvernitrat; Fenylortęci(II) azotan; Fenyylimerkurinitraatti; Phenylhydrargyri nitras; Phénylmercure, nitrate de; Phenylmercurinitrat; PMN; Фенилмеркурнитрат.
Nitratophenylmercury.
$C_6H_5HgOH,C_6H_5HgNO_3$=634.4
CAS — 8003-05-2 ($C_6H_5HgOH,C_6H_5HgNO_3$); 55-68-5 ($C_6H_5HgNO_3$).
ATC — D09AA04.
ATC Vet — QD09AA04.
UNII — CG8692ZN14.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Phenylmercuric Nitrate). A mixture of phenylmercuric nitrate and phenylmercuric hydroxide. A white or pale yellow powder. Very slightly soluble in water and in alcohol; slightly soluble in hot water; dissolves in glycerol and in fatty oils. Protect from light.

USNF 31: (Phenylmercuric Nitrate). A mixture of phenylmercuric nitrate and phenylmercuric hydroxide. A white crystalline powder. Soluble 1 in 600 of water; slightly soluble in alcohol and in glycerol; more soluble in the presence of nitric acid or alkali hydroxides. A saturated solution in water is acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. The activity of phenylmercuric salts may be reduced by interaction with compounds such as kaolin, magnesium trisilicate, starch, and talc.[1,2] Disodium edetate and sodium thiosulfate can also produce inactivation.[3] Sodium metabisulfite can lead to precipitation,[3] or chemical destruction,[4] but it can also produce increased activity.[3] Other incompatibilities include bromides, iodides (chlorides to a lesser extent), metals, and ammonia and its salts.[5] There can be adsorption onto rubber and some plastics[5,6] although sorption by low density polyethylene can be inhibited by phosphate ions.[7] Some filters, though not membrane filters, used for sterilisation removed considerable amounts of phenylmercuric nitrate from solution.[8] The pH may also affect activity.[9]

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
2. Horn NR, *et al.* Interactions between powder suspensions and selected quaternary ammonium and organomercurial preservatives. *Cosmet Toilet* 1980; **95:** 69–73.
3. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
4. Collins AJ, *et al.* Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; **37** (suppl): 123P.
5. Matthews BR. Phenylmercuric nitrate. In: Rowe RC, *et al.*, eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association, 2009: 496–9.
6. Aspinall JA, *et al.* The effect of low density polyethylene containers on some hospital-manufactured eyedrop formulations. *J Clin Hosp Pharm* 1980; **5:** 21–9.
7. Aspinall JE, *et al.* The effect of low density polyethylene containers on some hospital-manufactured eyedrop formulations II. Inhibition of the sorption of phenylmercuric acetate. *J Clin Hosp Pharm* 1983; **8:** 233–40.
8. Naido NT, *et al.* Preservative loss from ophthalmic solutions during filtration sterilisation. *Aust J Pharm Sci* 1972; **NS1:** 16–18.
9. Wessels JMC, Adema DMM. Some data on the relationship between fungicidal protection and pH. In: Walters AH, Elphick JJ, eds. *Biodeterioration of materials.* Amsterdam: Elsevier, 1968: 517–23.

Uses

Phenylmercuric salts have antibacterial and antifungal properties. They are mainly bacteriostatic compounds although they also have a slow bactericidal action. Their activity has been reported to be pH dependent.

Phenylmercuric compounds are used as preservatives in cosmetic, ophthalmic, or pharmaceutical preparations and as antiseptics. They have also been used as spermicides.

As a preservative in eye drops, a concentration of 0.002% is usually used; in injection solutions, the concentration is usually 0.001%.

Adverse Effects and Precautions

While the adverse effects of inorganic mercury (p. 2556.1) should be taken into account when considering the adverse effects of phenylmercuric compounds, there is little evidence of systemic toxicity arising from their use. They are irritant to the skin and may give rise to erythema and blistering. Hypersensitivity reactions have been reported. Topical application to eyes has been associated with mercurialentis and atypical band keratopathy; prolonged use of eye drops containing phenylmercuric preservatives is not recommended.

Effects on the eyes. References to primary atypical band keratopathy and pigmentation of the anterior capsule of the lens (mercurialentis) associated with the prolonged use of eye drops containing phenylmercuric preservative.

1. Kennedy RE, *et al.* Further observations on atypical band keratopathy in glaucoma patients. *Trans Am Ophthalmol Soc* 1974; **72:** 107–22.
2. Garron LK, *et al.* A clinical pathologic study of mercurialentis medicamentosus. *Trans Am Ophthalmol Soc* 1976; **74:** 295–320.
3. Brazier DJ, Hitchings RA. Atypical band keratopathy following long-term pilocarpine treatment. *Br J Ophthalmol* 1989; **73:** 294–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Kored; ***USA***: Hem-Prep.

o-Phthaldialdehyde

o-Ftaldialdehído; *o*-Phthalaldehyde; Phtharal; o-Фталевый Альдегид.
1,2-Benzenedicarboxaldehyde.
$C_8H_6O_2$=134.1
CAS — 643-79-8.
UNII — 4P8QP9768A.

Uses and Administration

o-Phthaldialdehyde is a bactericidal disinfectant with similar actions to those of glutaral (p. 1753.2) but it is reported to be more active against mycobacteria and to be stable at a wider pH range of 3 to 9. Unlike glutaral it requires no activation before use.

A 0.55% aqueous solution of *o*-phthaldialdehyde is used for high-level disinfection of medical equipment that cannot be sterilised by heat. It is non-corrosive towards most materials. Complete immersion in the solution for a minimum of 12 minutes at 20 degrees or 5 minutes at 25 degrees or higher is recommended. For further details, see Disinfection of Endoscopes, p. 1731.2.

References.

1. Cooke RPD, *et al.* An evaluation of Cidex OPA (0.55% ortho-phthalaldehyde) as an alternative to 2% glutaraldehyde for high-level disinfection of endoscopes. *J Hosp Infect* 2003; **54:** 226–31.

Adverse Effects and Precautions

As for Formaldehyde Solution, p. 1752.3.

Licensed product information states that *o*-phthaldialdehyde should not be used to process equipment used to treat patients with a history of bladder cancer as there have been associated rare reports of anaphylactoid reactions in such patients.

Occupational exposure. For mention of the potential of *o*-phthaldialdehyde to cause sensitisation in those occupationally exposed, see under Peracetic Acid, p. 1763.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Cidex OPA; ***USA***: Cidex OPA.

Picloxydine Dihydrochloride *(BANM, rINNM)*

Dihidrocloruro de picloxidina; Picloxydine, Dichlorhydrate de; Picloxydini Dihydrochloridum; Пиклоксидина Дигидрохлорид.

1,1′-[Piperazine-1,4-diylbis(formimidoyl)]bis[3-(4-chlorophenyl)guanidine] dihydrochloride.

$C_{20}H_{24}Cl_2N_{10}$,2HCl=548.3

CAS — 5636-92-0 (picloxydine); 19803-62-4 (picloxydine dihydrochloride).

ATC — S01AX16.

ATC Vet — QS01AX16.

Profile

Picloxydine is a biguanide disinfectant with properties similar to those of chlorhexidine (p. 1743.2). It is used in eye drops containing 0.05% of the dihydrochloride for the treatment of superficial infections of the eye. It has also been used as a surface disinfectant with quaternary ammonium compounds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vitabact; ***Rus.***: Vitabact (Витабакт).

Polihexanide *(BAN, rINN)*

ICI-9073; Polihexanida; Polihexanidum; Polyaminopropyl Biguanide; Polyhexamethylene Biguanide Hydrochloride; Polyhexanide; Полигексанид.

Poly(1-hexamethylenebiguanide hydrochloride).

$(C_8H_{17}N_5,HCl)_n$

CAS — 32289-58-0.

ATC — D08AC05.

ATC Vet — QD08AC05.

UNII — 322U039GMF.

Profile

Polihexanide has antibacterial and antiamoebic activity. It is used as a surface disinfectant and for disinfecting soft contact lenses (p. 1730.2). It is also used in the treatment of *Acanthamoeba* keratitis (p. 919.3) and has also been tried as a mouthwash in dental care.

Bacterial vaginosis. A study[1] of the efficacy of a 2% polihexanide vaginal gel in the treatment of bacterial vaginosis found that a single application was comparable to that of a 2% clindamycin gel applied once daily for 7 consecutive days.

1. Gerli S, *et al.* A new approach for the treatment of bacterial vaginosis: use of polyhexamethylene biguanide: a prospective, randomized study. *Eur Rev Med Pharmacol Sci* 2003; **7:** 127–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Equate All-in-One; ***Ger.***: Serasept; ***Rus.***: Lavasept (Лавасепт); ***Switz.***: Lavasept; ***UK***: Prontosan.

Multi-ingredient Preparations. ***Chile***: Biopiel; ***Fr.***: Aniospray 29†; Hexanios G+R†; ***Ger.***: Almyrol; Lavanid; Teta Extra†; Teta-S†; Urgosan.

Polynoxylin *(BAN, rINN)*

Polinoxilina; Polynoksyliini; Polynoxyline; Polynoxylinum; Полиноксилин.

Poly{[bis(hydroxymethyl)ureylene]methylene}.

$(C_4H_8N_2O_3)_n$

CAS — 9011-05-6.

ATC — A01AB05; D01AE05.

ATC Vet — QA01AB05; QD01AE05.

Profile

Polynoxylin is a condensation product of formaldehyde and urea. It is an antiseptic with antibacterial and antifungal actions and, like noxytiolin (p. 1762.1), may act by the release of formaldehyde. It is used topically for the local treatment of minor infections, usually at a concentration of 10%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Anaflex; ***Singapore***: Anaflex; ***UK***: Anaflex.

Potassium Nitrate ⊗

Dusičnan draselný; E252; Kalii Nitras; Kalio nitratas; Kalium Nitricum; Kaliumnitraatti; Kaliumnitrat; Kálium-nitrát; Nitrato potásico; Nitre; Potassium, nitrate de; Potasu azotan; Saltpetre; Нитрат Калия.

KNO_3=101.1

CAS — 7757-79-1.

UNII — RU45X2JN0Z.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Potassium Nitrate). Colourless crystals or a white or almost white, crystalline powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol.

USP 36: (Potassium Nitrate). Colourless crystals or a white crystalline powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. Store in airtight containers.

Nomenclature. The name saltpetre has been used as a generic term for a number of potassium- and sodium-based preservatives used in food manufacture. For a report of poisoning when a mixture of sodium nitrate and sodium nitrite was supplied for saltpetre, see p. 1769.3.

Uses and Administration

Potassium nitrate is used as a preservative in foods. It is also included in dentrifices to reduce the pain of hypersensitive teeth. When taken orally in dilute solution, it acts as a diuretic and was formerly used for this purpose.

Adverse Effects and Precautions

After ingestion potassium nitrate may be reduced to nitrite in the gastrointestinal tract by the action of bacteria and ingestion of large amounts can therefore cause methaemoglobinaemia. Gastrointestinal disturbances, vertigo, headache, flushing of the skin, hypotension, irregular pulse, cyanosis, convulsions, and collapse may occur. The toxic dose varies greatly; 15 g may prove fatal but much larger doses have been taken without serious effects. Poisoning has frequently been reported in infants given water from wells contaminated with nitrates.

Nitrites are precursors of nitrosamines, which are *animal* carcinogens, but a relationship with human cancer has not been established.

Concern has been expressed regarding the concentrations of nitrates and nitrites in the public drinking water supply. National limits are often set for permissible concentrations in drinking water.

Handling. Potassium nitrate has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Sensodyne ProNamel; ***Chile***: Crowne†; ***India***: Accent; Aquadent-K; Arident; Dencare; Denex-P; Denex-PF; Denopot; Denoseal; Densafe; Dentra; Desflor; Emoform; K-Dent; Knit; Ledent; Magdent-K; Nitrodent-K; O2-Fresh; Orofact; ***USA***: Denquel; Original Sensodyne.

Multi-ingredient Preparations. ***Arg.***: Aquafresh Sensitive; Bucal Hyper Sensitive; Esmedent Dientes Sens Blanq + Ctrol Sarro; Esmedent Dientes Sensibles; Fluorogel 2001 para Dientes Sensibles; Kdesin; Sebulex; Sensident; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Blanqueador; Sensodyne Cool; Sensodyne Proteccion Total; Sensodyne-F; Teys's; ***Braz.***: Malvatricin Dentes Sensiveis†; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool†; Sensodyne Fresh Mint; Sensodyne Protecao Total; Sensodyne-F†; ***Canad.***: Sensodyne-F; Sensodyne; ***Chile***: Caristop Sensitive; Sensaid; ***Fr.***: Emoform Dents Sensibles; Emoform Gencives; Fluocaril dents sensibles†; Sensigel; ***India***: Denoseal-F; Denpot-KF; Dordent-K; Hydent K; Icee Mth Wsh; K-Dent-F; Klinit; Listn; Magdent-KF; Nitra-OR; Nitra; Nitrodent-KF; ***Indon.***: Sensodyne Cool Gel; ***Ital.***: Actisens; Dentosan Sensibile; Emoform Actisens; Fluocaril; Oral-B Denti Sensibili; ***Mex.***: Cholal Modificado; Dentsiblen†; ***Rus.***: Sensigel (Сенсигель); ***Singapore***: 2Sensitive; Sensigel; ***Turk.***: Sensodyne Gel; Sensoral; ***UK***: Avoca; ***USA***: Fluoridex Daily Defense Sensitivity Relief; Grafco; Sensitivity Protection Crest; Sensodyne iso-active; Sensodyne-F; ***Venez.***: Sensodyne.

Homoeopathic Preparations. ***Fr.***: Abbe Chaupitre no 1†; Urtica Complexe No 82†; ***Ger.***: Pflugerplex Lemna; Phonix Silybum spag; Phonix Urtica-Arsenicum spag.

Pharmacopoeial Preparations

USP 36: Potassium Nitrate Solution.

Potassium Permanganate

Kalii Permanganas; Kalio permanganatas; Kalium Hypermanganicum; Kalium Permanganicum; Kaliumpermanganaatti; Kaliumpermanganat; Kálium-permanganát; Manganistan draselný; Permanganato potásico; Pot. Permang.; Potassium, permanganate de; Potasu nadmanganian; Potasyum Permanganat; Калия Перманганат.

$KMnO_4$=158.0

CAS — 7722-64-7.

ATC — D08AX06; V03AB18.

ATC Vet — QD08AX06; QV03AB18.

UNII — 00OT1QX5U4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Potassium Permanganate). Dark purple or almost black crystals or a dark purple or brownish-black granular powder, usually with a metallic lustre. It decomposes in contact with certain organic substances. Soluble in cold water and freely soluble in boiling water.

USP 36: (Potassium Permanganate). Dark purple crystals, almost opaque by transmitted light and with a blue metallic lustre by reflected light; its colour is sometimes modified by a dark bronze-like appearance. Soluble 1 in 15 of water and 1 in 3.5 of boiling water.

Incompatibility. Potassium permanganate is incompatible with iodides, reducing agents, and most organic substances.

Uses and Administration

Potassium permanganate possesses oxidising properties which in turn confer disinfectant and deodorising properties. It is also astringent. Though bactericidal *in vitro* its clinical value as a bactericide is minimised by its rapid reduction in the presence of body fluids.

Solutions are used as cleansing applications to wounds, ulcers, or abscesses and as wet dressings and in baths in eczematous conditions and acute dermatoses especially where there is secondary infection. It is often prepared as a concentrated 0.1% solution in water to be diluted 1 in 10 before use to provide a 0.01% (1 in 10000) solution. Solutions have also been used in bromhidrosis, in mycotic infections such as athlete's foot, and in poison ivy dermatitis.

Potassium permanganate is added to formaldehyde solution to produce formaldehyde vapour for the disinfection of rooms and cabinets (see p. 1752.2).

Adverse Effects, Treatment, and Precautions

The dry crystals or concentrated solutions of potassium permanganate are highly corrosive to tissue, while dilute solutions are mildly irritant. Contact with the skin causes irritation, redness, pain and burns, and even dilute solutions cause hardening of the outer layer of the skin and leave a brown stain on the skin. Exposure of the eye to dry crystals (including crystal dust) or concentrated solutions causes irritation, blurred vision, redness, brown staining of the conjunctiva, swelling of the eyelids, and corneal and conjunctival burns. For the effects of ingestion, see below.

The insertion into the vagina of potassium permanganate for its supposed abortifacient action causes corrosive burns, severe vaginal haemorrhage, and perforation of the vaginal wall, leading to peritonitis. Vascular collapse may occur.

Handling and storage. Potassium permanganate may be explosive if it is brought into contact with organic or other readily oxidisable substances. It has been used for the illicit preparation of fireworks; care is required with its supply.

Poisoning. Ingestion of dilute solutions of potassium permanganate may result in the mouth and throat being stained brown, sore throat, dysphagia, abdominal pain, diarrhoea, and vomiting. Ingestion of dry crystals and concentrated solutions causes oedema and necrosis of the mouth, larynx, gastrointestinal tract, and upper respiratory tract. In severe cases, acute respiratory distress syndrome, coagulopathy, hypotension, methaemoglobinaemia, hepatic necrosis, pancreatitis, and acute renal failure may develop. Oesophageal strictures and pyloric stenosis are possible long-term consequences. The fatal dose is probably about 10 g and death is usually as a result of pharyngeal oedema and cardiovascular collapse, although multiple organ failure may occur. Inhalation of potassium permanganate causes sore throat, coughing, and shortness

of breath. Chronic ingestion or inhalation of potassium permanganate has resulted in CNS symptoms such as sluggishness, sleepiness, weakness of the legs, tremor, spastic gait, and falling.

Symptoms of poisoning after ingestion of potassium permanganate should be treated symptomatically. Gut neutralisation and emesis are contra-indicated. Dilution with large quantities of water or milk is cautiously recommended, while the role of activated charcoal is unclear as it is unknown whether it binds potassium permanganate. Similarly, the role of corticosteroids is controversial and the efficacy of *N*-acetylcysteine for potassium permanganate hepatotoxicity is unproven. Eyes and skin contaminated with potassium permanganate should be thoroughly washed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Permasol; ***UK***: Permitabs.

Povidone-Iodine *(BAN)*

Iodinated Povidone; Jodowany powidon; Polivinilpirrolidona yodada; Polivodona yodada; Polyvidone-Iodine; Polyvinylpyrrolidone-Iodine Complex; Povidon-Iyot; Povidon, joderad; Povidon jodovaný; Povidona yodada; Povidonas, joduotas; Povidone iodée; Povidoni, jodattu; Povidon-jód; Povidonum iodinatum; Propyléneglycol, monostéarate de; PVP-Iodine; Повидон-йод.

CAS — 25655-41-8.

ATC — D08AG02; D09AA09; D11AC06; G01AX11; R02AA15; S01AX18.

ATC Vet — QD08AG02; QD09AA09; QD11AC06; QG01AX11; QG51AD01; QR02AA15; QS01AX18.

UNII — 85H0HZU99M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Povidone, Iodinated). A complex of iodine with povidone containing 9 to 12% of available iodine calculated with reference to the dried substance. Yellowish-brown or reddish-brown amorphous powder. It loses not more than 8% of its weight on drying. Soluble in water and in alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 1.5 to 5.0. Protect from light.

USP 36: (Povidone-Iodine). A complex of iodine with povidone containing 9 to 12% of available iodine calculated on the dried basis. A yellowish-brown to reddish-brown amorphous powder with a slight characteristic odour. It loses not more than 8% of its weight on drying. Soluble in water and in alcohol; practically insoluble in acetone, in carbon tetrachloride, in chloroform, in ether, and in petroleum spirit. Its solutions are acid to litmus. Store in airtight containers.

Incompatibility. Antimicrobial activity may be reduced at high pH.

Dermatological reactions, described as second- and third-degree burns, were seen in 4 patients in whom wounds were covered with a povidone-iodine soaked bandage secured to the skin by compound benzoin tincture. It was suggested that an interaction had occurred resulting in a more acidic pH.[1]

A mixture of povidone-iodine solution and hydrogen peroxide [brown bubbly] has caused explosions.[2]

1. Schillaci LJ, *et al.* Reduced pH associated with mixture of povidone-iodine and compound tincture of benzoin. *Am J Hosp Pharm* 1983; **40:** 1694–5.
2. Dannenberg E, Peebles J. Betadine-hydrogen peroxide irrigation solution incompatibility. *Am J Hosp Pharm* 1978; **35:** 525.

Uses and Administration

Povidone-iodine is an iodophore that is used as a disinfectant and antiseptic mainly for the treatment of contaminated wounds and pre-operative preparation of the skin and mucous membranes as well as for the disinfection of equipment.

Iodophores are loose complexes of iodine and carrier polymers. Solutions of povidone-iodine gradually release iodine to exert an effect against bacteria, fungi, viruses, protozoa, cysts, and spores; povidone-iodine is thus less potent than preparations containing free iodine but it is less toxic.

Many topical formulations are available, the majority containing about 4 to 10% of povidone-iodine; a 1% mouthwash has been used for oral infections including candidiasis and topical powders containing up to 2.5% povidone-iodine have been tried in the treatment and prevention of wound infection. For vaginal application povidone-iodine has also been used as pessaries containing 200 mg or as a 10% gel or solution.

Adverse Effects and Precautions

Povidone-iodine can cause hypersensitivity reactions and irritation of the skin and mucous membranes, although severe reactions are rare and povidone-iodine is considered to be less irritant than iodine.

The application of povidone-iodine to severe burns or to large areas otherwise denuded of skin may produce the systemic adverse effects associated with iodine (p. 2338.2) and metabolic acidosis, hypernatraemia, and renal impairment. Hyperthyroidism or hypothyroidism may occur after ingestion or absorption of large quantities. Hypothyroidism has occurred in neonates both as a result of absorption of iodine from povidone-iodine applied to the neonate and also to the mother during pregnancy or breast feeding. Povidone-iodine application is contra-indicated in premature neonates or those weighing less than 1.5 kg.

Regular or prolonged use should be avoided in patients with thyroid disorders or those receiving lithium therapy.

Acidosis. There have been reports of acidosis in patients whose burns were treated topically with povidone-iodine.[1,2] Fatal metabolic acidosis[3] and seizures[4] have been reported after mediastinal irrigation with povidone-iodine.

1. Pietsch J, Meakins JL. Complications of povidone-iodine absorption in topically treated burn patients. *Lancet* 1976; **i:** 280–2.
2. Scoggin C, *et al.* Hypernatraemia and acidosis in association with topical treatment of burns. *Lancet* 1977; **i:** 959.
3. Glick PL, *et al.* Iodine toxicity in a patient treated by continuous povidone-iodine mediastinal irrigation. *Ann Thorac Surg* 1985; **39:** 478–80.
4. Zec N, *et al.* Seizures in a patient treated with continuous povidone-iodine mediastinal irrigation. *N Engl J Med* 1992; **326:** 1784.

Breast feeding. Use of povidone-iodine in a vaginal gel by a breast-feeding woman resulted in elevated iodine concentrations in the breast milk and an odour of iodine on the infant's skin.[1] The American Academy of Pediatrics considers however that the use of povidone-iodine is usually compatible with breast feeding.[2]

For more on precautions in breast feeding when treated with iodine compounds see p. 2338.3.

1. Pastellon DC, Aranow R. Iodine in mother's milk. *JAMA* 1982; **247:** 463.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Hypersensitivity. Immediate type I hypersensitivity reactions have been reported after topical disinfection with povidone-iodine; anaphylaxis has been reported after vaginal application[1,2] and after wound disinfection during surgery.[3] In some cases[2,3] skin tests showed that the reactions were caused by the povidone component.

Contact dermatitis has been reported[4] in a 36-year-old man who received a compress with 10% povidone-iodine aqueous solution under an occlusive bandage. The patient had mild itching, erythema, exudation, and a bullous reaction, limited to the area of the compress, 48 hours after application. He responded to topical corticosteroids within 5 to 6 days, but an area of sharply demarcated brown hyperpigmentation persisted for a month. While this was considered to be suggestive of an irritant effect, a positive patch test supported an allergic mechanism. A study to evaluate the incidence of contact dermatitis associated with povidone-iodine[5] found that 14 of 500 patients (2.8%) had a positive patch test with 10% povidone-iodine aqueous solution. On retesting with the same solution using a repeated open application test only 2 of the 14 (0.4%) were found to have true contact dermatitis to povidone-iodine.

1. Waran KD, Munsick RA. Anaphylaxis from povidone-iodine. *Lancet* 1995; **345:** 1506.
2. Adachi A, *et al.* Anaphylaxis to polyvinylpyrrolidone after vaginal application of povidone-iodine. *Contact Dermatitis* 2003; **48:** 133–6.
3. Le Pabic F, *et al.* First case of anaphylaxis to iodinated povidone. *Allergy* 2003; **58:** 826–7.
4. Borja JM, *et al.* Contact dermatitis due to povidone-iodine: allergic or irritant? *J Investig Allergol Clin Immunol* 2003; **13:** 131–2.
5. Lachapelle JM. Allergic contact dermatitis from povidone-iodine: a re-evaluation study. *Contact Dermatitis* 2005; **52:** 9–10.

Neonates. Hypothyroidism has been reported in premature and very low birth-weight infants after the use of povidone-iodine for routine antisepsis,[1,2] and hyperthyroidism in a full-term infant following mediastinal lavage.[3]

Perinatal vaginal use of povidone-iodine may also cause neonatal thyroid dysfunction.[4]

1. Parravicini E, *et al.* Iodine, thyroid function, and very low birth weight infants. *Pediatrics* 1996; **98:** 730–4.
2. Linder N, *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; **131:** 434–9.
3. Bryant WP, Zimmerman D. Iodine-induced hyperthyroidism in a newborn. *Pediatrics* 1995; **95:** 434–6. Correction. *ibid.*; **96:** 779.
4. l'Allemand D, *et al.* Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine. *J Pediatr* 1983; **102:** 935–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antiseptico; Excelentia Solucion Antiseptica; Extraleci; Iodep; Iodomax; Iopox; Nu-Gel Hidrogel en Placa†; Pervinox D; Pervinox; Povi Complex; Povibac; Povicler; Povitiol; Tycoytycoy; ***Austral.***: Betadine; Microshield PVP-S†; Microshield PVP; Nyal Medithroat Gargle; Savlon Antiseptic†; ***Austria***: Betadona; Betaisodona; Betaseptic; Braunol; Braunovidon; Wundesin; ***Belg.***: Braunodine†; Braunol; Iodex; Iso-Betadine; ***Braz.***: Curativ; Laboriodine†; Marcodine; ***Canad.***: Betadine; Proviodine; Solunet 1†; Soluprep Povidone Iodee†; Spray I Dene†; ***Chile***: Difexon; ***China***: Ai Di Er (艾迪尔); Ai Ni Ya (艾妮亚); AiLiKe (艾利克); Dai Wei (黛卫); Li Le (丽乐); Li Ze (丽泽); Ri Jie Ning (日洁宁); Yi Su Xin (怡速欣); ***Cz.***: Betadine; Braunol; Braunovidon; Jodisol; ***Fin.***: Betadine; ***Fr.***: Betadine; Betaseptic†; Poliodine†; ***Ger.***: Betaisodona; Braunol; Braunovidon; Mercuchrom-Jod; Polydona; Polysept; PVP-Jod; Sepso J; Traumasept; ***Gr.***: Betadine; Betarem; Drapix; Eva Povi; Evinolut; Igiol; Iodovine; Jodocourir; Libidon; Lombocid; Oxisept; Poviodine; Tinsole; ***Hong Kong***: Betadine; Freka-cid†; Proviodine†; Videne; ***Hung.***: Betadine; Braunovidon; Colpo-Cleaner; ***India***: Aglodine; Alphadine; Balvidine; Bestodin; Betadine-AD; Betadine; Betakind; Betasym; Cadine; Cipladine; Curedine; Dovidone; Enodine-S; Eyedin; Intadine; Intodine; Iocandin; Iodolan; Lakdine; Medidine; Metpo; Microdine; Microshield PVP-S; Microshield PVP; Ovidine; Povidine; Wokadine; ***Indon.***: Abodine†; Asepta†; Betadine; Corsasep; Duvodine†; Erphaseptan; Forinfec; Isodine; Molexdine; Mugisept; Neo Iodine; Orodin; Scansepta; Septadine; Vidisep; ***Irl.***: Betadine; Braunol†; Braunosan†; Braunovidon†; Inadine; Savlon Dry; Videne; ***Israel***: Idovit†; Iodicare; Iodiflor; Iodispray; Iodo-Vit; Polydine; Polysept; Polyskin; PovEyeOdine; ***Ital.***: Asepsan; Betadine; Betaseptic; Braunol; Citro Jod; Destrobac; Eso-Jod; Esoform Jod 75; Farmaiod; Gammadin†; Golasept; Inadine; Iodosteril†; Iodoten; Jodocur; Jodogard†; Oftasteril; Poviderm; ***Jpn***: Finish†; Isodine; ***Malaysia***: Betadine; Freka-cid†; Poviderm; Septi-Aid†; Summer's Eve Medicated; ***Mex.***: Isodine; Losine; Yodacua†; Yodine; ***Neth.***: Betadine; Braunol; ***NZ***: Betadine; Biocil†; Riodine; ***Philipp.***: Bacticide; Betadine; Doseptidone; Povidine; Zigmadone; ***Pol.***: Betadine; Braunovidon; Jodi; Polodina-R; Polseptol†; PV Jod; ***Port.***: Betadine; Braunol; Ectodine; Ginoseptil†; Iodolab; Isodine†; Septil; ***Rus.***: Aquazan (Аквазан); Betadine (Бетадин); Iodovidon (Йодовидон); Iodoxyd (Йодоксид); Jodosept (Йодосепт); Wokadine (Вокадин)†; ***S.Afr.***: Betadine; Dermadine; Drygel†; Podine; Septadine; Septisooth; Steridine; Zedchem PVP-I; ***Singapore***: Betadine; ***Spain***: Acydona; Betadine; Betatul; Curadona; Heridine†; Iodina; Normovidona; Orto Dermo P†; Sanoyodo; Topionic; ***Switz.***: Betadine; Braunol; Braunosan H Plus†; Braunosan†; Braunovidon; Destrobac; Jodoplex; ***Thai.***: Annadine†; Bactedene; Betadine; Betamed; Eprodine; Freka-cid†; Ipodine; Isodine; Movidone†; P-Vidine; Pactadine; Pharmadine; Povadine; Povi-odine; Povidine; Pyrad-Povidone; Sepfadine; Septidine; Septyl; Upodine; Videne; X-Tardine; ***Turk.***: Batiodin; Batticon; Betakon; Biokadin; Isosol; Polyod; Poviiodex; Poviod; Poviseptin; Soliyod; Summer's Eve Medicated; ***UK***: Betadine; Inadine; Savlon Dry; Videne; ***Ukr.***: Betadine (Бетадин); Iodoxide (Йодоксид); Povisep (Повисеп); Ranostop (Раностоп); Wokadine (Вокадин); ***USA***: ACU-dyne; Betadine; Biodine; Efodine; GRX Dyne; Iodex; Massengill Medicated; Minidyne; Operand; Polydine; Summer's Eve Medicated; Yeast-Gard Medicated; ***Venez.***: Betadine; Intradine; Intradyn; Norlidine.

Multi-ingredient Preparations. ***Arg.***: Merthiolate Iodopovidona; ***Belg.***: Braunoderm; ***Cz.***: Jox; ***Ger.***: Betaseptic; Braunoderm; Repithel; ***India***: Atodine-M; Balvidine-M; Bestodin-M; Cezel-PT; Dinemet-M; Drez; E-Dine-M; Ecoseptic; Eczo-Wokadine; Fastaid; Flotears; Healin; Iocandin Sol; Iocandin-M; Lacrisol; Metro Plus; Metro-P; Metrogyl-P; Metrokind-P; Mezodin; Misodine-M; Ovidine-M; ***Indon.***: Kalpanax; Kopamex†; ***Irl.***: Braunoderm†; ***Ital.***: Braunoderm; Jodieci; ***Jpn***: U-Pasta; ***Mex.***: Bano Coloide; Riban; ***Port.***: Braunoderm†; ***Rus.***: Jox (Йокс); ***Switz.***: Betaseptic; Braunoderm; Jodoplex Teinture†; ***Ukr.***: Jox (Йокс); ***USA***: Anbesol; Orasol; ProTech.

Pharmacopoeial Preparations

BP 2014: Povidone-Iodine Eye Drops; Povidone-Iodine Mouthwash; Povidone-Iodine Solution;

USP 36: Povidone-Iodine Cleansing Solution; Povidone-Iodine Ointment; Povidone-Iodine Topical Aerosol; Povidone-Iodine Topical Solution.

Propamidine Isetionate *(BANM, rINNM)*

Isetionato de propamidina; M&B-782; Propamidina, isetionato de; Propamidine Isethionate; Propamidine, Isétionate de; Propamidini Isetionas; Пропамидина Изетионат.

4,4′-Trimethylenedioxydibenzamidine bis(2-hydroxyethanesulphonate).

$C_{17}H_{20}N_4O_2.2C_2H_6O_4S$=564.6

CAS — 104-32-5 (propamidine); 140-63-6 (propamidine isetionate).

ATC — D08AC03; S01AX15.

ATC Vet — QD08AC03; QS01AX15.

UNII — 7T9IJ84C42.

Profile

Propamidine isetionate is an aromatic diamidine antiseptic that is active against Gram-positive bacteria, but less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties and is active against *Acanthamoeba*. Ophthalmic solutions containing 0.1% of propamidine isetionate are used for the treatment of conjunctivitis and blepharitis.

Acanthamoeba keratitis. The optimal regimen for the treatment of *Acanthamoeba* keratitis (p. 919.3) has yet to be determined. Propamidine isetionate applied topically was the first drug used with some success.[1,2] It was used with an aminoglycoside such as neomycin or a neomycin-polymyxin-gramicidin preparation and a cure was achieved in about 50% of cases. However, most cysts are resistant to neomycin and due to surface toxicity and poor *in-vitro* sensitivity, neomycin is no longer recommended.[2] Propamidine was later used with chlorhexidine or polihexanide. However, poor cysticidal activity, chronic conjunctival infection, and resistance of some strains of *Acanthamoeba* to propamidine has prompted the suggestion that it should be replaced by another diamidine such as hexamidine.[3]

1. Murdoch D, *et al*. Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; **26:** 231–6.
2. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; **17:** 893–905.
3. Perrine D, *et al*. Amoebicidal efficiencies of various diamidines against two strains of Acanthamoeba polyphaga. *Antimicrob Agents Chemother* 1995; **39:** 339–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Brolene; ***Gr.***: Brolene; ***Irl.***: Brolene; Golden Eye; ***NZ***: Brolene; ***S.Afr.***: Brolene; ***UK***: Brolene; Golden Eye Drops.

Propiolactone *(BAN, USAN, rINN)*

BPL; NSC-21626; 2-Oxetanone; Propanolide; Propiolactona; β-Propiolactone; Propiolactonum; Пропиолактон.
Propiono-3-lactone.
$C_3H_4O_2$=72.06
CAS — 57-57-8.
UNII — 6RC3ZT4HB0.

Profile

Propiolactone vapour is an irritant, mutagenic, possibly carcinogenic, disinfectant which is very active against most micro-organisms including viruses. It is rather less effective against bacterial spores.

Propiolactone vapour has been used for the gaseous sterilisation of pharmaceutical and surgical materials and for disinfecting large enclosed areas. It has low penetrating power. Propiolactone liquid has also been used.

Propyl Alcohol

Alcohol propílico; Normal Propyl Alcohol; Primary Propyl Alcohol; 1-Propanol; Propanol; Propanoli; Propanolis; Propanolum; Пропиловый Спирт.
Propan-1-ol.
$CH_3.CH_2.CH_2OH$=60.10
CAS — 71-23-8.
ATC — D08AX03.
ATC Vet — QD08AX03.
UNII — 96F264O9SV.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Propanol). A clear colourless liquid. Miscible with water and with dehydrated alcohol. Protect from light.

Uses and Administration

Propyl alcohol, an antiseptic with properties similar to those of alcohol (p. 1733.2), is used in preparations for disinfection of the hands, skin, surfaces, and instruments.

Isopropyl alcohol (p. 1758.3) is also used as an antiseptic.

Adverse Effects and Treatment

As for Alcohol, p. 1733.3; propyl alcohol is considered more toxic.

References.
1. WHO. 1-Propanol. *Environmental Health Criteria 102*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc102.htm (accessed 15/03/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Skinman Asept†; Skinman clear.

Multi-ingredient Preparations. ***Austria***: Dodesept; Isozid-H; Kodan; Marcocid; Octeniderm; Sterillium; ***Belg.***: Softa Man; ***Canad.***: Manorapid Synergy; ***Fin.***: Sterillium; ***Fr.***: Anios DD†; Sterillium; ***Ger.***: Aerodesin; Bacillol AF; Bacillol Foam; Bacillol plus; Bacillol Tissues; Bacillol Wipes; Bacillol†; Freka-Steril†; HD 410; Hospisept; Incidin; Incidin; Kodan Tinktur Forte; Manusept viruzid†; Meliseptol Rapid; Meliseptol; Softa Man; Sterillium; Virusept†; ***Gr.***: Chiro Des; Octeniderm; Sterillium; ***Irl.***: Sterillium; ***Ital.***: Softa Man; ***Neth.***: Softa-Man; Sterillium; ***Port.***: Sterillium; ***Singapore***: Listerine Bright & Clean; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Primasept Med; ***Swed.***: Sterillium; ***Switz.***: Kodan forte; Octeniderm; Softa-Man†; ***Ukr.***: Softa-Man (Софта)†.

Ritiometan *(rINN)*

Ritiometán; Ritiométan; Ritiometanum; Ритиометан.
(Methylidynetrithio)triacetic acid.
$C_7H_{10}O_6S_3$=286.3
CAS — 34914-39-1.
ATC — R01AX05.
ATC Vet — QR01AX05.
UNII — J89LM8QVEE.

Profile

Ritiometan is used as the magnesium salt in an aerosol preparation for the treatment of infections of the nose and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Necyrane.

Scarlet Red

Biebrich Scarlet R Medicinal; CI Solvent Red 24; Colour Index No. 26105; Fat Ponceau R; Rojo escarlata; Rojo Sudán IV; Rubrum Scarlatinum; Scharlachrot; Sudan IV; Судан IV.
1-[4-(*o*-Tolylazo)-*o*-tolylazo]naphth-2-ol.
$C_{24}H_{20}N_4O$=380.5
CAS — 85-83-6.

Profile

Scarlet red is an antiseptic dye that has been used topically. It can be irritant. Scarlet red is not permitted as a food colour in the EU, as it is thought to be a genotoxic carcinogen.

Sodium Azide

Azida sódica; Sodu azydek; Азид Натрия.
N_3Na=65.01
CAS — 26628-22-8.

Uses

Sodium azide has been used as an antimicrobial preservative in laboratory reagents, serum samples, and dialysis equipment. It is also used in car airbags; sudden impact triggers an electrical charge causing the sodium azide to explode and nitrogen gas is released.

Adverse Effects and Precautions

Sodium azide is a potent vasodilator and the most common adverse effect, regardless of the route of exposure, is hypotension. Hypotension developing more than an hour after exposure is associated with more severe toxicity and fatality. Other severe symptoms include seizure, coma, arrhythmia, tachypnoea, pulmonary oedema, metabolic acidosis, and cardiorespiratory arrest. Milder symptoms include nausea, vomiting, diarrhoea, headache, dizziness, temporary loss of vision, palpitations, dyspnoea, temporary loss of consciousness, or decreased mental status. There is no specific antidote for sodium azide intoxication.

Solutions containing sodium azide must not be disposed of into drain pipelines containing copper, lead, or brass since highly explosive heavy metal azides may be produced.

References to acute poisoning with sodium azide.

1. Edmonds OP, Bourne MS. Sodium azide poisoning in five laboratory technicians. *Br J Ind Med* 1982; **39:** 308–9.
2. Klein-Schwartz W, *et al*. Three fatal sodium azide poisonings. *Med Toxicol Adverse Drug Exp* 1989; **4:** 219–27.
3. Anonymous. Sodium azide contamination of hemodialysis water supplies. *JAMA* 1989; **261:** 2603.
4. Chang S, Lamm SH. Human health effects of sodium azide exposure: a literature review and analysis. *Int J Toxicol* 2003; **22:** 175–86.

Airbag deployment. Chemical and thermal burns have occurred after accidental perforation of airbags in motor vehicles and the release of sodium azide and other byproducts. Irritant contact dermatitis usually affecting the upper chest, arms, and face, and blunt trauma have also been reported.[1,2]

1. Corazza M, *et al*. Effects of airbag deployment: lesions, epidemiology, and management. *Am J Clin Dermatol* 2004; **5:** 295–300.
2. Suhr M, Kreusch T. Burn injuries resulting from (accidental) airbag inflation. *J Craniomaxillofac Surg* 2004; **32:** 35–7.

Effects on the nervous system. A study[1] to evaluate occupational neurotoxicity to sodium azide over a period of 3 years found that the only significant chronic symptom was trembling of the hands, occurring in 15 of 41 exposed workers compared with none of 42 controls. There was no difference between the 2 groups for other psychological or neuropsychological tests. Acute adverse effects most commonly reported by the exposed workers were heart palpitations, fatigue, nausea, vertigo, and irritated or red eyes.

1. Miljours S, Braun CMJ. A neuropsychotoxicological assessment of workers in a sodium azide production plant. *Int Arch Occup Environ Health* 2003; **76:** 225–32.

Haemodialysis. Of 10 investigations by the CDC[1] into outbreaks of disease caused by chemicals in haemodialysis facilities between 1979 and 1999, one was due to sodium azide. Inadequate rinsing of water filters resulted in the exposure of 9 patients to sodium azide in a dialysis centre. Patients experienced sudden hypotension, blurred vision, headache, nausea, vomiting, syncope, and 1 patient had cramps.

1. Arduino MJ. CDC investigations of noninfectious outbreaks of adverse events in hemodialysis facilities, 1979-1999. *Semin Dial* 2000; **13:** 86–91.

Sodium Diacetate

Diacetato de sodio; E262; Диацетат Натрия.
Sodium hydrogen diacetate.
$CH_3COONa,CH_3COOH(+xH_2O)$
CAS — 126-96-5 (anhydrous sodium diacetate).
UNII — 26WJH3CS0B.

Profile

Sodium diacetate is used as a preservative in foods, particularly as an inhibitor of moulds and rope-forming micro-organisms in bread.

Sodium Formaldehyde Sulfoxylate

Formaldehído sulfoxilato sódico; Natrii Formaldehydosulfoxylas; Sodium Formaldehyde Sulphoxylate; Sodu formaldehydosulfoksylan; Натрия Формальдегидсульфоксилат.
Sodium hydroxymethanesulphinate dihydrate.
$CH_3NaO_3S,2H_2O$=154.1
CAS — 149-44-0 (anhydrous sodium formaldehyde sulfoxylate); 6035-47-8 (sodium formaldehyde sulfoxylate, dihydrate).
UNII — X4ZGP7K714.

Pharmacopoeias. In *Pol.* Also in *USNF*.

USNF 31: (Sodium Formaldehyde Sulfoxylate). White crystals or hard white masses with the characteristic odour of garlic. Soluble 1 in 3.4 of water, 1 in 510 of alcohol, 1 in 175 of chloroform, and 1 in 180 of ether; slightly soluble in benzene. A 2% solution in water has a pH of 9.5 to 10.5. Store at 15 degrees to 30 degrees. Protect from light.

Profile

Sodium formaldehyde sulfoxylate is an antoxidant used as a preservative in pharmaceuticals. It has been used in the treatment of acute mercury poisoning (p. 2556.3).

Sodium Hypochlorite

Hipoclorito sódico; Lejía; Гипохлорит Натрия.
NaOCl,$5H_2O$=164.5
CAS — 7681-52-9.
ATC — D08AX07.
ATC Vet — QD08AX07.
UNII — DY38VHM5OD.

NOTE. The term 'liquid chlorine' (Cloro líquido) has been used for solutions of sodium hypochlorite. These should not be confused with the pressurised form of chlorine gas (p. 1746.2) which is also liquid and has been referred to similarly.

Pharmacopoeias. *Br.*, *Fr.*, and *US* include sodium hypochlorite solutions.

BP 2014: (Dilute Sodium Hypochlorite Solution). It contains 1% of available chlorine. Store away from acids at a temperature not exceeding 20 degrees. Protect from light.

BP 2014: (Strong Sodium Hypochlorite Solution). It contains not less than 8% of available chlorine. It should be diluted before use. Store away from acids at a temperature not exceeding 20 degrees. Protect from light.

USP 36: (Sodium Hypochlorite Solution). It contains not less than 4% and not more than 6% w/w of anhydrous sodium hypochlorite. It is not suitable for application to wounds. Store in airtight containers. Protect from light.

USP 36: (Sodium Hypochlorite Topical Solution). It contains 0.025% sodium hypochlorite. Store in airtight containers. Protect from light.

Incompatibility. The antimicrobial activity of hypochlorites is rapidly reduced in the presence of organic material; it is also pH dependent being greater in acid pH although hypochlorites are more stable at alkaline pH.

Sodium hypochlorite solutions should not be mixed with solutions of strong acids or ammonia; the subsequent reactions release chlorine gas and tosylchloramide sodium gas, respectively.

Stability. The stability of sodium hypochlorite solutions increases with pH, solutions of pH 10 or more being most stable.[1] Stability studies have shown that solutions providing 0.04 to 0.12% 'available chlorine' stored in amber glass bottles at room temperature could carry a 23-month expiry date.[2]

1. Bloomfield SF, Sizer TJ. Eusol BPC and other hypochlorite formulations used in hospitals. *Pharm J* 1985; **235:** 153–5 and 157.
2. Fabian TM, Walker SE. Stability of sodium hypochlorite solutions. *Am J Hosp Pharm* 1982; **39:** 1016–17.

Uses and Administration

Sodium hypochlorite is a disinfectant and antiseptic with the brief and rapid actions of chlorine (see p. 1746.3). Sodium hypochlorite pentahydrate contains about 43% of 'available chlorine' (see p. 1746.3); anhydrous sodium hypochlorite contains about 95%. Powders and solutions are commonly used for the rapid disinfection of hard surfaces (see Disinfection in Creutzfeldt-Jakob Disease, p. 1730.3 and in Hepatitis and HIV Infection, p. 1731.2), food and dairy equipment, babies' feeding bottles, excreta, and water (p. 1731.3). Solutions for use as domestic bleaches contain up to 5.25% of hypochlorite. Only diluted solutions containing up to 0.5% of 'available chlorine' are suitable for use on the skin and in wounds (but see Wound Disinfection, p. 1732.2). Sodium hypochlorite solutions ranging from 0.5 to 5.25% are used in dentistry for root canal irrigation.

Solutions of hypochlorites used as disinfectants have included Labarraque's Solution containing sodium hypochlorite with an alkali, and Eau de Javel, containing sodium or potassium hypochlorite.

Disinfection. *INSTRUMENTS.* Needles and syringes should not usually be sterilised chemically. However, cleaning of injection equipment with hypochlorite has been suggested as a last resort in the absence of sterile equipment, to reduce the risk of HIV transmission associated with the enforced re-use of injection equipment by injection drug users.[1] Use of full-strength domestic bleach (about 5% sodium hypochlorite, about 2% of 'available chlorine') was reported to be effective for the cleaning of intravenous drug users' equipment; a 30-second contact time was required.[1,2] A 1 in 10 dilution of bleach was not effective after exposure for 5 minutes.[2] Despite rinsing with water, a low residual concentration of hypochlorite and microaggregates of blood are likely to remain on the cleaned instruments. Free chlorine is a potent oxidant and low concentrations of oxidants have been shown to enhance tissue inflammation *in vivo* as well as HIV-1 replication *in vitro*. This has led some researchers to suggest that there may be an increased possibility of an injection drug user contracting HIV-1 through the sharing of a bleach-cleaned blood-contaminated syringe as a consequence of the concomitant transmission of residual bleach; however, there is no epidemiological evidence to confirm this.[3]

1. Donoghoe MC, Power R. Household bleach as disinfectant for use by injecting drug users. *Lancet* 1993; **341:** 1658.
2. Watters JK, *et al*. Household bleach as disinfectant for use by injecting drug users. *Lancet* 1993; **342:** 742–3.
3. Contoreggi C, *et al*. Effects of varying concentrations of bleach on in vitro HIV-1 replication and the relevance to injection drug use. *Intervirology* 2000; **43:** 1–5.

WORMS. Sodium hypochlorite in aqueous solution at a concentration of 3.75% (or greater) is an effective ovicide for *Echinococcus* and may be used on hard surfaces, glassware, and sinks.[1]

1. Craig PS, Macpherson CNL. Sodium hypochlorite as an ovicide for Echinococcus. *Ann Trop Med Parasitol* 1988; **82:** 211–13.

WOUNDS. Hypochlorite solutions are now generally considered to be too irritant for use in the management of wounds (p. 1690.1). Studies suggest that they may delay wound healing if repeatedly applied to open wounds.[1,2] It has been suggested that they may be of use in debriding burns (p. 1683.1) or necrotic chronic wounds,[3] but also that any benefit that might be seen from the desloughing of necrotic tissue might be produced by damage of the superficial cell layer leading to separation[4] or from tissue hydration produced by wet dressing packs.[5] However, some burns units have found that hypochlorite as Dakin's solution (see Chlorinated Lime, p. 1746.2) produces better healing than other antibacterials.[6]

See also p. 1732.2.

1. Thomas S, Hay NP. Wound healing. *Pharm J* 1985; **235:** 206.
2. Lineweaver W, *et al*. Topical antimicrobial toxicity. *Arch Surg* 1985; **120:** 267–70.
3. Leaper DJ. Eusol. *BMJ* 1992; **304:** 930–1.
4. Anonymous. Local applications to wounds—I: cleansers, antibacterials, debriders. *Drug Ther Bull* 1991; **29:** 93–5.
5. Thomas S. Milton and the treatment of burns. *Pharm J* 1986; **236:** 128–9.
6. Murphy KD, *et al*. Current pharmacotherapy for the treatment of severe burns. *Expert Opin Pharmacother* 2003; **4:** 369–84.

Adverse Effects

Hypochlorite solutions release hypochlorous acid upon contact with gastric juice and acids. Most patients ingesting hypochlorites will develop only mild gastrointestinal irritation. However, ingestion of small amounts of 3 to 5% hypochlorite solutions may result in irritation of the oropharynx, a burning sensation in the mouth and throat, and thirst. Nausea, vomiting, and haematemesis may occur. Ingestion of large amounts or more concentrated solutions causes irritation and corrosion of mucous membranes with chest and abdominal pain and tenderness, vomiting, haematemesis, watery diarrhoea and sometimes melaena. Ingestion of extremely large volumes may rarely cause hypernatraemia, hyperchloraemia, hypotension, and changes in mental status. In very severe cases ulceration or perforation of the oesophagus or stomach may occur leading to haemorrhage and shock.

Inhalation of the fumes is irritant to the eyes, nose, and respiratory tract. Sore throat, cough, bronchoconstriction, headache, ataxia, and confusion may develop. In severe cases dyspnoea and stridor due to laryngeal oedema may develop with breathlessness, wheeze, hypoxia, cyanosis, pneumonitis, and pulmonary oedema.

Hypochlorite solutions may be irritating to the skin and allergic contact dermatitis has been reported. Hypochlorite solutions may cause an alkali-type burn when splashed into the eye.

General references.

1. Racioppi F, *et al*. Household bleaches based on sodium hypochlorite: review of acute toxicology and Poison Control Center experience. *Food Chem Toxicol* 1994; **32:** 845–61.

Effects on the blood. A child with G6PD deficiency had an acute haemolytic crisis after swimming for about 4 hours in an indoor pool containing very high concentrations of sodium hypochlorite.[1]

1. Ong SJ, Kearney B. Local swimming pool and G-6-PD deficiency. *Med J Aust* 1994; **161:** 226–7.

Effects on wound healing. For comment on the adverse effects of hypochlorite solutions on wound healing, see Disinfection: Wounds under Uses and Administration above.

Toxicity from mixing cleaning agents. Mixing the household cleaning agents bleach (5.25% sodium hypochlorite solution) and 4% phosphoric acid (p. 2589.1) causes chlorine gas and water to be released. The chlorine in turn reacts with the water to form hydrochloric and hypochlorous acids. There have been case reports[1] of patients and hospital staff who have been accidentally exposed to chlorine gas as a result of mixing of these two cleaning agents. They had temporary illness and symptoms typical of chlorine toxicity; irritation of the eyes, nose and throat, headache, dizziness, nausea, cough, and chest pain or tightness. One patient had an acute exacerbation of asthma.

Tosylchloramide sodium gas is produced when common household cleaning agents containing sodium hypochlorite and ammonia (p. 2441.2) are mixed together. On inhalation the water in the respiratory tract reacts with the tosylchloramide sodium gas to release ammonia, hydrochloric acid and oxygen free radicals. Many case reports have described the symptoms resulting from inhalation of these gases. A 12-month review[2] of 216 patients who reported to a regional poison information centre after exposure to tosylchloramide sodium gas as a result of mixing cleaning products found that only 1 patient, with a pre-existing respiratory-tract infection, required hospital admission for ongoing respiratory distress. The most frequent symptoms were cough and shortness of breath and other symptoms experienced were those commonly associated with exposure to chlorine gas (p. 1746.3). Most (200) of the patients' symptoms resolved within 6 hours and 145 patients were treated at home, while 71 were referred for further medical care. Oxygen was given to 62 patients, bronchodilators to 9 patients and 3 patients received corticosteroids. Similar symptoms and findings were reported[3] when 2 groups of 36 soldiers were exposed to tosylchloramide sodium gas as a result of mixing sodium hypochlorite and ammonia containing cleaning agents. Only 2 soldiers required hospital admission for persistent respiratory symptoms, with one of them requiring a few days of treatment in intensive care. Another case report[4] described a previously healthy 53-year-old woman who had shortness of breath progressing to pneumonitis and required emergency tracheostomy after a similar exposure to tosylchloramide sodium gas.

1. CDC. Epidemiologic notes and reports: chlorine gas toxicity from mixture of bleach with other cleaning products—California. *MMWR* 1991; **40:** 619–21, 627–9. Corrections. *ibid.*; 646, 819.
2. Mrvos R, *et al*. Home exposures to chlorine/chloramine gas: review of 216 cases. *South Med J* 1993; **86:** 654–7.
3. Pascuzzi TA, Storrow AB. Mass casualties from acute inhalation of chloramine gas. *Mil Med* 1998; **163:** 102–4.
4. Tanen DA, *et al*. Severe lung injury after exposure to chloramine gas from household cleaners. *N Engl J Med* 1999; **341:** 848–9.

Toxicity during root canal irrigation. A review of case reports[1] where sodium hypochlorite had been inadvertently injected into the periapical tissues during root canal irrigation reported that most patients had immediate severe pain and swelling of the neighbouring soft tissue, which could possibly spread over the injured side of the face, upper lip and infra-orbital region. Other symptoms included bleeding from the root canal, interstitial bleeding with haemorrhage of the skin and mucosa, a chlorine taste, irritation of the throat, and reversible anaesthesia or paraesthesia.

1. Hülsmann M, Hahn W. Complications during root canal irrigation—literature review and case reports. *Int Endod J* 2000; **33:** 186–93.

Treatment of Adverse Effects

If sodium hypochlorite solution is ingested symptomatic care, including dilution with water, milk, or other demulcents should be given; opinion over the use of antacids is divided. If spilled on skin or eyes, washing with copious amounts of water is recommended.

Poisoning. A patient who accidentally received an intravenous infusion of 150 mL of a 1% solution of sodium hypochlorite had a slow heart rate, mild hypotension, and increased respiratory rate. The slow heart rate persisted for 3 days but other parameters returned to normal after symptomatic treatment.[1]

1. Marroni M, Menichetti F. Accidental intravenous infusion of sodium hypochlorite. *DICP Ann Pharmacother* 1991; **25:** 1008–9.

Precautions

Topically applied hypochlorites may dissolve blood clots and cause bleeding.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Milton; ***Belg.***: Dakincooper; ***Canad.***: Advance 12A; Ali-Flex; Basic 12†; Chemspec; Dakin's Solution; Exsept; Hygeol†; ***Fr.***: Dakin; ***Israel***: Chlorasol; ***Ital.***: Amukine Med; Milton; ***UK***: Milton; ***USA***: Hysept.

Multi-ingredient Preparations. ***Fr.***: Amukine; ***Gr.***: Amuchina; ***Switz.***: Amukina.

Pharmacopoeial Preparations

BP 2014: Dilute Sodium Hypochlorite Solution; Strong Sodium Hypochlorite Solution;

USP 36: Sodium Hypochlorite Solution; Sodium Hypochlorite Topical Solution.

Sodium Nitrate

E251; Natrii Nitras; Natrium Nitricum; Nitrato sódico; Sodu azotan; Нитрат Натрия.

$NaNO_3$=84.99

CAS — 7631-99-4.

UNII — 8M4L3H2ZVZ.

NOTE. Crude sodium nitrate is known as Chile Saltpetre (Nitrato de Chile; Nitro de Chile; Salitre Chileno).

Profile

Sodium nitrate has similar actions to potassium nitrate (p. 1766.2) and is used as a preservative in foods, particularly in meat products.

Crude sodium nitrate is used as a fertiliser.

Handling. Sodium nitrate has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Poisoning. Cyanosis and methaemoglobinaemia has been reported[1] in 3 patients after eating sausages that had been preserved mistakenly with a mixture of sodium nitrate

and sodium nitrite rather than with potassium nitrate (saltpetre). The name saltpetre is used as a generic term for a number of potassium- or sodium-based preservatives used in food manufacture.

1. Kennedy N, *et al.* Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; **76:** 367–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Fr.***: Aesculus Complexe No 103; Mercurius Solubilis Complexe No 39; ***Ger.***: Rheuma-Pasc.

Sodium Perborate Monohydrate *(USAN)*

Натрия Перборат Моногидрат.
$NaBO_3,H_2O$=99.81
CAS — 7632-04-4 (anhydrous sodium perborate); 10332-33-9 (sodium perborate monohydrate).
ATC — A01AB19.
ATC Vet — QA01AB19.
UNII — Y9UKD0XE6F.

Sodium Perborate

Natrii Perboras; Natrio perboratas; Natriumperboraatti; Natriumperborat; Nátrium-perborát; Perborato sódico; Perboritan sodný; Sod. Perbor.; Sodium, perborate de; Sodium Perborate Tetrahydrate; Натрия Перборат.
$NaBO_3,4H_2O$=153.9
CAS — 10042-94-1.
ATC — A01AB19.
ATC Vet — QA01AB19.
UNII — Y52BK1W96C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Perborate, Hydrated; Sodium Perborate BP 2014). Colourless prismatic crystals or a white or almost white powder, stable in crystalline form. Sparingly soluble in water, with slow decomposition. It dissolves in dilute mineral acids. Store in airtight containers.

Uses and Administration

Sodium perborate is a mild disinfectant and deodorant. It readily releases oxygen in contact with oxidisable matter and has been used in aqueous solutions for purposes similar to weak solutions of hydrogen peroxide.

Sodium perborate is used for tooth whitening and has also been used, with calcium carbonate, as a toothpowder. A freshly prepared solution is used as a mouthwash.

The monohydrate is used similarly.

Adverse Effects

Frequent use of toothpowders containing sodium perborate may cause blistering and oedema. Hypertrophy of the papillae of the tongue has also been reported. The effects of swallowed sodium perborate are similar to those of boric acid (p. 2460.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hifamonil; ***Canad.***: Amosan; ***Fr.***: Nettoyant Essilor†; ***India***: Fittydent; Steradent; ***Irl.***: Bocasan†; ***Neth.***: Bocasan†; ***USA***: Amosan.

Multi-ingredient Preparations. ***Austral.***: Amosan†; ***Braz.***: Anginotricin; Malvatricin Branqueador†; Oticerim; ***Fr.***: Bactident†; Hydralin Classic; ***Hong Kong***: Hydralin; ***Spain***: Lema C; ***USA***: Trichotine; ***Venez.***: Novafix.

Sodium Percarbonate

Percarbonato sódico; Sodium Carbonate Peroxide; Надуглекислый Натрий; Перкарбонат Натрия.
$Na_2CO_3,1½H_2O_2$=157.0
CAS — 15630-89-4.
UNII — Z7G82NV92P.

Profile

Sodium percarbonate has similar uses to sodium perborate (above).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Ascoxal†; ***Mex.***: Ascoxal†.

Sorbates

Sorbatos; Сорбаты.

Sorbic Acid

Acide sorbique; Acidum sorbicum; E200; Kwas sorbowy; Kyselina sorbová; Sórbico, ácido; Sorbiinihappo; Sorbinsäure; Sorbinsyra; Sorbo rūgštis; Szorbinsav; Сорбиновая Кислота.
(*E,E*)-Hexa-2,4-dienoic acid.
$C_6H_8O_2$=112.1
CAS — 22500-92-1.
UNII — X045WJ989B.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbic Acid). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in alcohol. Protect from light.

USNF 31: (Sorbic Acid). A free-flowing white crystalline powder with a characteristic odour. Soluble 1 in 1000 of water, 1 in 10 of alcohol, 1 in 8 of dehydrated alcohol, 1 in 15 of chloroform, 1 in 30 of ether, 1 in 8 of methyl alcohol, and 1 in 19 of propylene glycol. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Incompatibility. The incompatibility of sorbates is discussed under Potassium Sorbate, below.

Potassium Sorbate

E202; Kalii Sorbas; Kalio sorbatas; Kaliumsorbaatti; Kaliumsorbat; Kalium-sorbát; Kálium-szorbát; Potassium, sorbate de; Sorbato potásico; Сорбат Калия.
Potassium (*E,E*)-hexa-2,4-dienoate.
$C_6H_7KO_2$=150.2
CAS — 590-00-1; 24634-61-5.
UNII — 1VPU26JZZ4.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Potassium Sorbate). White or almost white granules or powder. Very soluble in water; slightly soluble in alcohol. Protect from light.

USNF 31: (Potassium Sorbate). White crystals or powder with a characteristic odour. Soluble 1 in 4.5 of water, 1 in 35 of alcohol, and 1 in more than 1000 of chloroform and of ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Incompatibility. Sorbic acid can be inactivated by oxidation and to some extent by nonionic surfactants and plastics. Activity of the sorbates may be reduced by increases in pH.[1]

1. Cook W, *et al.* Sorbic acid. In: Rowe RC, *et al.*, eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association,2009: 672–5.

Uses

Potassium sorbate and sorbic acid possess antifungal, and to a lesser extent antibacterial, activity. They are relatively ineffective above a pH of about 6. They are used as preservatives in pharmaceutical preparations in concentrations of up to 0.2%, in enteral formulas, foods, and in cosmetic preparations.

Adverse Effects and Precautions

The sorbates can be irritant and have caused contact dermatitis.

Hypersensitivity. References to allergic-type skin reactions[1] and non-allergic irritant-type reactions[2,3] with potassium sorbate or sorbic acid.

1. Saihan EM, Harman RRM. Contact sensitivity to sorbic acid in 'Unguentum Merck'. *Br J Dermatol* 1978; **99:** 583–4.
2. Soschin D, Leyden JJ. Sorbic acid-induced erythema and edema. *J Am Acad Dermatol* 1986; **14:** 234–41.
3. Fisher AA. Erythema limited to the face due to sorbic acid. *Cutis* 1987; **40:** 395–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Caprilate†; ***Ger.***: Saseem; ***Ital.***: Evasen Dischetti; Evasen Liquido; ***Mex.***: Adapettes; ***UK***: Feminesse; Relaxit; ***USA***: Clear Eyes Contact Lens Relief; ***Venez.***: Saxacid.

Sulfites and Sulfur Dioxide

Sulfitos y dióxido de azufre.

Potassium Bisulfite

Bisulfito potásico; E228; Potassium Bisulphite; Potassium Hydrogen Sulphite; Бисульфит Калия; Гидросульфит Калия.
$KHSO_3$=120.2
CAS — 7773-03-7.
UNII — QJK5LO891P.

Potassium Metabisulfite

Dipotassium Pyrosulphite; Disiřičitan draselný; E224; Kalii Disulfis; Kalii metabisulfis; Kalio metabisulfitas; Kaliummetabisulfiitti; Kaliummetabisulfit; Metabisulfito potásico; Potassium, métabisulfite de; Potassium Metabisulphite; Potassium Pyrosulphite; Potasu pirosiarczyn; Пиросульфит Калия.
$K_2S_2O_5$=222.3
CAS — 16731-55-8.
UNII — 65OE787Q7W.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Potassium Metabisulfite). A white or almost white powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.5. Store in airtight containers. Protect from light.

USNF 31: (Potassium Metabisulfite). White or colourless, free-flowing crystals, crystalline powder, or granules, usually with an odour of sulfur dioxide. Gradually oxidises in air to the sulfate. Soluble in water; insoluble in alcohol. Its solutions are acid to litmus. Store in well-filled airtight containers at a temperature not exceeding 40 degrees.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, p. 1771.1.

Sodium Bisulfite

Bisulfito sódico; E222; Sodium Bisulphite; Sodium Hydrogen Sulphite; Гидросульфит Натрия.
$NaHSO_3$=104.1
CAS — 7631-90-5.
UNII — TZX5469Z6I.

Pharmacopoeias. In *Chin.* and *Jpn,* described in both as consisting of a mixture of sodium bisulfite and sodium metabisulfite.

Sodium Metabisulfite

Disiřičitan sodný; Disodium Pyrosulphite; E223; Metabisulfito sódico; Natrii Disulfis; Natrii Metabisulfis; Natrii Pyrosulfis; Natrio metabisulfitas; Nátrium-diszulfit; Natriummetabisulfiitti; Natriummetabisulfit; Sodium Disulphite; Sodium, métabisulfite de; Sodium Metabisulphite; Sodium Pyrosulphite; Sodu pirosiarczyn; Пиросульфит Натрия.
$Na_2S_2O_5$=190.1
CAS — 7681-57-4.
UNII — 4VON5FNS3C.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Sodium Metabisulfite). Colourless crystals or a white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 5.0. Protect from light.

USNF 31: (Sodium Metabisulfite). White crystals or a white to yellowish crystalline powder with an odour of sulfur dioxide. Freely soluble in water and in glycerol; slightly soluble in alcohol. Store in well-filled airtight containers at a temperature not exceeding 40 degrees.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, p. 1771.1.

Sodium Sulfite

Anhydrous Sodium Sulphite; E221; Exsiccated Sodium Sulphite; Natrii Sulfis; Natrii sulfis anhydricus; Natrii Sulfis Siccatus; Natrii Sulphis; Natrio sulfitas, bevandenis; Natriumsulfiitti, vedetön; Natriumsulfit, vattenfritt; Siřičitan sodný; Sodium (sulfite de) anhydre; Sodium Sulphite; Sodu siarczyn; Sulfito sódico; Vízmentes nátrium-szulfit; Сульфит Натрия.
Na_2SO_3=126.0
CAS — 7757-83-7.
UNII — VTK01UQK3G.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Eur. also includes the heptahydrate.

Ph. Eur. 8: (Sodium Sulfite, Anhydrous; Natri Sulfis Anhydricus). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Ph. Eur. 8: (Sodium Sulphite Heptahydrate; Natrii Sulfis Heptahydricus). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol.

USNF 31: (Sodium Sulfite). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

Sulfur Dioxide

Anhídrido sulfuroso; Dióxido de azufre; E220; Kükürt Dioksit; Siarki dwutlenek; Sulphur Dioxide; Диоксид Серы.

SO_2=64.06

CAS — 7446-09-5.

UNII — 0UZA3422Q4.

Pharmacopoeias. In *USNF*.

USNF 31: (Sulfur Dioxide). A colourless non-flammable gas with a strong suffocating odour characteristic of burning sulfur. It condenses readily under pressure to a colourless liquid that boils at -10 degrees and has a wt per mL of about 1.5 g. Soluble 36 in 1 of water and 114 in 1 of alcohol by vol. at 20 degrees and standard pressure. Soluble in chloroform and in ether. Store in cylinders. It is usually packaged under pressure in liquid form.

Incompatibility and stability. Sulfite antoxidants can react with and inactivate sympathomimetics such as adrenaline.[1] Measures need to be taken to prevent such a reaction if sulfites have to be used. Cisplatin is another compound that can be inactivated.[2] Phenylmercuric nitrate may be inactivated or its activity enhanced.[3,4] Sulfites are reported to react with chloramphenicol.[1] Hydrogen peroxide generation has been reported on exposure to light of amino acid solutions containing sulfites.[5] When used in foods there can be a noticeable taste and a reduction in thiamine content.[6] Stability is affected by air and moisture, and there is decomposition at very low pH.[7] There can be adsorption on to rubber closures.[8]

1. Higuchi T, Schroeter LC. Reactivity of bisulfite with a number of pharmaceuticals. *J Am Pharm Assoc (Sci)* 1959; **48:** 535–40.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24:** 91–9.
3. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
4. Collins AJ, *et al.* Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; **37** (suppl): 123P.
5. Brawley V, *et al.* Effect of sodium metabisulfite on hydrogen peroxide production in light-exposed pediatric parenteral amino acid solutions. *Am J Health-Syst Pharm* 1998; **55:** 1288–92.
6. FAO/WHO. Evaluation of the toxicity of a number of antimicrobials and antioxidants: sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 228* 1962. Also available at: http://libdoc.who.int/trs/WHO_TRS_228.pdf (accessed 25/06/10)
7. Kabir MA, Reo JP. Sodium metabisulfite. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press, and the American Pharmaceutical Association 2009: 654–6.
8. Schroeter LC. Sulfurous acid salts as pharmaceutical antioxidants. *J Pharm Sci* 1961; **50:** 891–901.

Uses

Sulfur dioxide and the sulfites that produce sulfur dioxide and sulfurous acid are strong reducing agents and are used as antoxidants. Concentrations of the sulfites in pharmaceutical preparations have ranged from 0.01 to 1.0%. At higher concentrations and preferably at an acid pH sulfur dioxide and the sulfites have antimicrobial activity.

Sulfur dioxide and the sulfites are used in the food industry as antoxidants, antimicrobial preservatives, and anti-browning agents. They are used in wine making where tabletted sodium metabisulfite is commonly known as Campden Tablets. Concentrations of sulfites above 500 ppm impart a noticeable unpleasant taste to preparations. There is concern over the risk of severe allergic reactions arising from the use of sulfites in foods (see Hypersensitivity, below).

Adverse Effects and Precautions

Gastric irritation due to liberation of sulfurous acid can follow ingestion of sodium metabisulfite and other sulfites. Large doses of sulfites may cause gastrointestinal upsets, respiratory or circulatory failure, and CNS disturbances.

Concentrated solutions of salts of sulfurous acid are irritant to skin and mucous membranes.

Sulfur dioxide is highly irritant to the eyes, skin, and mucous membranes. Inhalation results in irritation of the respiratory tract which may lead to bronchoconstriction and pulmonary oedema; very high concentrations may cause respiratory arrest and asphyxia. Contact with liquid sulfur dioxide results in acid burns.

Allergic reactions including anaphylaxis and deaths have been reported.

Hypersensitivity. Hypersensitivity reactions including bronchospasm, anaphylaxis, and some deaths have occurred in subjects, especially those with a history of asthma or atopic allergy, exposed to sulfites used as preservatives in foods.[1] These reactions have led to restrictions by the FDA on such use.[2] There have been case reports of reactions to sulfites in medicines;[3-9] such reports are considered to be few in number and the FDA has not extended the restriction on sulfites in foods to apply to their use in drugs since it was felt that in certain cases there was no suitable alternative to a sulfite.[2] It was even accepted that adrenaline recommended for use in treating allergic reactions could itself contain sulfite and that its presence should not preclude use of the adrenaline preparation even in sulfite-sensitive patients.[2]

1. Anonymous. Sulfites in drugs and food. *Med Lett Drugs Ther* 1986; **28:** 74–5.
2. Anonymous. Warning for prescription drugs containing sulfites. *FDA Drug Bull* 1987; **17:** 2–3.
3. Baker GJ, *et al.* Bronchospasm induced by metabisulphite-containing foods and drugs. *Med J Aust* 1981; **ii:** 614–17.
4. Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). *JAMA* 1982; **248:** 2030–1.
5. Koepke JW, *et al.* Dose-dependent bronchospasm from sulfites in isoetharine. *JAMA* 1984; **251:** 2982–3.
6. Mikolich DJ, McCloskey WW. Suspected gentamicin allergy could be sulfite sensitivity. *Clin Pharm* 1988; **7:** 269.
7. Deziel-Evans LM, Hussey WC. Possible sulfite sensitivity with gentamicin infusion. *DICP Ann Pharmacother* 1989; **23:** 1032–3.
8. Campbell JR, *et al.* Allergic response to metabisulfite in lidocaine anesthetic solution. *Anesth Prog* 2001; **48:** 21–6.
9. Riemersma WA, *et al.* Type IV hypersensitivity to sodium metabisulfite in local anaesthetic. *Contact Dermatitis* 2004; **51:** 148.

Pharmacokinetics

Sulfites and metabisulfites are oxidised in the body to sulfate and excreted in the urine. Any sulfurous acid or sulfur dioxide is also converted to sulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Thai.***: Peritoneal Lactate†.

Tar Acids

Alquitrán, ácidos de.

Description. Tar acids are phenolic substances derived from the distillation of coal tar or petroleum fractions. The lowest boiling fraction of coal tar, distilling at 188 degrees to 205 degrees, consists of mixed cresol isomers. The middle fraction, known as 'cresylic acids', distils at 205 degrees to 230 degrees and consists of cresols and xylenols. The 'high-boiling tar acids', distilling at 230 degrees to 290 degrees, consist mainly of alkyl homologues of phenol, with naphthalenes and other hydrocarbons. Cresol is described on p. 1749.1.

- **Black Fluids** are homogeneous solutions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons and with a suitable emulsifying agent.
- **White Fluids** are finely dispersed emulsions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons.
- **Modified Black Fluids** and **Modified White Fluids** may contain, as an addition, any other active ingredients, but if these are used, the type and amount must be disclosed, if required.

Uses

Tar acids are the phenolic components of coal tar and are used in the preparation of a range of fluids of varied activity used for household and general disinfection purposes.

Hydrocarbons are often used to enhance the activity of the tar acids in disinfectant fluids; they also help to reduce crystallisation of phenols.

Adverse Effects and Treatment

As for Phenol, p. 1764.2.

Tar acids are generally very irritant and corrosive to the skin, even when diluted to concentrations used for disinfection.

Poisoning. A report of fatal self-poisoning in a 59-year-old man after the ingestion of about 250 mL of a xylenol-containing disinfectant (*Stericol Hospital Disinfectant*).[1]

1. Watson ID, *et al.* Fatal xylenol self-poisoning. *Postgrad Med J* 1986; **62:** 411–12.

Tertiary Butylhydroquinone

Butilhidroquinona terciaria; TBHQ; Третичного Бутилгидрохинона.

2-*tert*-butylhydroquinone.

$C_{10}H_{14}O_2$=166.2

CAS — 1948-33-0.

UNII — C126749428.

Profile

Tertiary butylhydroquinone is an antoxidant preservative used in foods. It has some antimicrobial activity.

Tetrabromocresol

3,4,5,6-Тетрабром-о-крезол.

3,4,5,6-Tetrabromo-o-cresol.

$C_7H_4Br_4O$=423.7

CAS — 576-55-6.

Profile

Tetrabromocresol is a brominated phenolic antiseptic. It has been used for hand disinfection and is applied topically in preparations for the treatment of fungal infections of the skin and bromhidrosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Pedoz.

Tetraglycine Hydroperiodide

Tetraglicina, hidroperioduro de; Гидропериодид Тетраглицина.

$C_{16}H_{42}I_7N_8O_{16}$=1490.9

CAS — 7097-60-1.

Profile

Tetraglycine hydroperiodide is an iodine-based disinfectant that is used in the emergency treatment of drinking water (p. 1731.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Potable Aqua; ***USA***: Potable Aqua.

Thiomersal *(BAN, rINN)*

Mercurothiolate; Mercurothiolate Sodique; Sodium Ethyl Mercurithiosalicylate; Thimerosal; Thiomersalate; Thiomersalum; Tiomersaali; Tiomersal; Tiomersalis; Tiomerzál; Тиомерсал.

Sodium (2-carboxyphenylthio)ethylmercury.

$C_9H_9HgNaO_2S$=404.8

CAS — 54-64-8.

ATC — D08AK06.

ATC Vet — QD08AK06.

UNII — 2225PI3MOV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Thiomersal). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble or soluble in alcohol; practically insoluble in dichloromethane. A 0.8% solution in water has a pH of 6.0 to 8.0. Protect from light.

USP 36: (Thimerosal). A light cream-coloured crystalline powder with a slight characteristic odour. Soluble 1 in 1 of water and 1 in 12 of alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 6.7. Store in airtight containers. Protect from light.

Incompatibility. Thiomersal is incompatible with acids, metal ions, and iodine. It forms precipitates with many alkaloids. The rate of oxidation of thiomersal in solution is greatly increased by traces of copper ions. In slightly acid solution thiomersal may be precipitated as the corresponding acid which undergoes slow decomposition with the formation of insoluble products. The activity of thiomersal may also be reduced by boric acid, edetic acid, or sodium thiosulfate or by the presence of blood or organic matter. Thiomersal may be adsorbed by plastic or rubber packaging materials.

References.

1. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
2. Reader MJ. Influence of isotonic agents on the stability of thimerosal in ophthalmic formulations. *J Pharm Sci* 1984; **73:** 840–1.
3. Morton DJ. EDTA reduces antimicrobial efficacy of thiomersal. *Int J Pharmaceutics* 1985; **23:** 357–8.

Uses and Administration

Thiomersal is a bacteriostatic and fungistatic mercurial antiseptic that has been applied topically usually in a concentration of 0.1%. Its antibacterial action results from the release of ethylmercury after breakdown to thiosalicylate and ethylmercury.

Thiomersal, 0.001 to 0.01%, is used as a preservative in biological and pharmaceutical products. It has also been used to preserve solutions used in the care of contact lenses (p. 1730.2).

Adverse Effects, Treatment, and Precautions

As for Mercury, p. 2556.1.

Hypersensitivity reactions occasionally occur. Allergic conjunctivitis has been reported.

General references.

1. Risher JF, *et al.* Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; **18:** 109–60.

Hypersensitivity. Both delayed (allergic contact) and immediate (including anaphylaxis and immune complex mediated disorders) hypersensitivity reactions have been associated with thiomersal.[1] The frequency of positive patch tests varies, with the National Advisory Committee on Immunization in Canada reporting[1] an average incidence of 16 to 18% and a centre in the USA an incidence of 8.7%.[2] Most reactions are local and mild,[1,3] involving application sites or blepharoconjunctivitis from ocular preparations,[3] although some people may get a delayed generalised dermatitis that can be long lasting, or have exacerbation of an existing skin condition.[1] There has also been a report of acute laryngeal obstruction in a patient previously sensitised to the substance who used a throat spray preserved with thiomersal.[4] A case of occupational allergic contact dermatitis has been reported in a nurse as a result of contact with thiomersal as a preservative in childhood vaccines.[5] A generalised maculopapular eruption from an influenza vaccine containing thiomersal has also been reported.[6] The main source of sensitisation is thought to be thiomersal-preserved vaccines. Most people with patch tests positive to thiomersal are able to tolerate thiomersal-containing vaccines, although some individuals may have long-lasting cutaneous reactions.[1] If there is a definite history of anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis to thiomersal in any product, vaccines containing thiomersal should not be given. However, while such reactions have not been shown to occur as a result of thiomersal in vaccines, they remain a theoretical risk.[1]

1. National Advisory Committee on Immunization (NACI). Thimerosal: updated statement. *Can Commun Dis Rep* 2007; **33** (ACS-6): 1–13. Also available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-06.pdf (accessed 29/03/10)
2. Suneja T, Belsito DV. Thimerosal in the detection of clinically relevant allergic contact reactions. *J Am Acad Dermatol* 2001; **45:** 23–7.
3. Wilson LA, *et al.* Delayed hypersensitivity to thiomersal in soft contact lens wearers. *Ophthalmology* 1981; **88:** 804–9.
4. Maibach H. Acute laryngeal obstruction presumed secondary to thiomersal (merthiolate) delayed hypersensitivity. *Contact Dermatitis* 1975; **1:** 221–2.
5. Kiec-Swierczynska M, *et al.* Occupational allergic contact dermatitis due to thimerosal. *Contact Dermatitis* 2003; **48:** 337–8.
6. Lee-Wong M, *et al.* A generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol* 2005; **94:** 90–4.

Poisoning. Serious adverse effects have followed parenteral and topical use of thiomersal.

Six poisonings (5 fatal) resulted from the use of 1000 times the normal concentration of thiomersal in a preparation of chloramphenicol for intramuscular injection.[1] There has also been a case report[2] of mercury poisoning associated with the intravenous use of high-dose hepatitis B immunoglobulin, preserved with thiomersal, after liver transplantation. Initial symptoms were paranoia, which rapidly progressed to severe dysarthria, static tremor, chorea, and decreased motor strength, as well as haemorrhagic gastritis. The patient responded well to chelation therapy.

Thiomersal used in topical antiseptic preparations was found to be toxic to epidermal cells.[3] After the death of 10 of 13 children as a result of treatment of omphaloceles (umbilical hernia) with a tincture of thiomersal, it was recommended that organic mercurial disinfectants be heavily restricted or withdrawn from hospital use as absorption occurred readily through intact membranes.[4]

A 44 year-old man who drank 83 mg/kg of a thiomersal-containing solution in an attempted suicide, spontaneously vomited after 15 minutes.[5] On admission to hospital a gastric lavage was performed and chelating drugs given. Despite this he developed gastritis, renal failure, dermatitis, gingivitis, delirium, polyneuropathy, respiratory failure, and coma. The patient was treated symptomatically, and 148 days after ingestion had recovered fully, except for sensory defects in two toes.

1. Axton JHM. Six cases of poisoning after a parenteral organic mercurial compound (Merthiolate). *Postgrad Med J* 1972; **48:** 417–21.
2. Lowell JA, *et al.* Mercury poisoning associated with high-dose hepatitis-B immune globulin administration after liver transplantation for chronic hepatitis B. *Liver Transpl Surg* 1996; **2:** 475–8.
3. Anonymous. Topical antiseptics and antibiotics: organic mercurials. *Med Lett Drugs Ther* 1977; **19:** 83.
4. Fagan DG, *et al.* Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Arch Dis Child* 1977; **52:** 962–4.
5. Pfab R, *et al.* Clinical course of severe poisoning with thiomersal. *J Toxicol Clin Toxicol* 1996; **34:** 453–60.

Vaccines. The use of thiomersal as a preservative in vaccines and its role as a possible cause of autism and neurodevelopmental disorders has been a controversial topic since 1999[1] when the regulatory authorities in both Europe[2] and the USA[3] issued statements recommending that the use of thiomersal in vaccines be phased out. This was based on the fact that the cumulative amount of mercury in the infant immunisation schedule potentially exceeds the recommended maximum level set by the US government for methyl mercury. More recently, however, studies[4] have indicated a lack of association between thiomersal-containing vaccines and neurodevelopmental disorders such as autism and speech disorders. These findings were supported by the fact that thiomersal is metabolised to ethylmercury, which has substantially different pharmacokinetics to methylmercury. Ethylmercury is more rapidly excreted and does not accumulate in the body. The EMEA has issued a further statement[5] in which it confirmed that thiomersal could be used as a preservative when no alternative was available, subject to certain labelling requirements regarding hypersensitivity. The UK CSM,[6] the US FDA,[7] and Canada's Advisory Committee on Immunization[8] have similarly concluded that there is no evidence of neurological adverse effects caused by the small amounts of thiomersal present in some vaccines; despite this, all endorse the view that the use of vaccines without thiomersal would be a prudent precautionary measure. WHO states[9,10] that there is no compelling scientific evidence of safety problems and advises that thiomersal-containing vaccines may continue to be used for global immunisation programmes because the benefit outweighs any theoretical risk of toxicity.

1. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; **28:** 89–101.
2. European Agency for the Evaluation of Medicinal Products (EMEA). EMEA public statement on thiomersal containing medicinal products (July 1999). EMEA publication no. 20962/99. Full version: http://www.emea.europa.eu/pdfs/human/press/pus/2096299EN.pdf (accessed 01/03/10)
3. American Academy of Pediatrics, United States Public Health Service. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* 1999; **48:** 563–5.
4. Parker SK, *et al.* Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics* 2004; **114:** 793–804.
5. European Agency for the Evaluation of Medicinal Products (EMEA). EMEA public statement on thiomersal in vaccines for human use—recent evidence supports safety of thiomersal-containing vaccines (March 2004). EMEA publication no. 1194/04. Full version: http://www.emea.europa.eu/pdfs/human/press/pus/119404en.pdf (accessed 01/03/10)
6. CSM/MHRA. Safety of thiomersal-containing vaccines. *Current Problems* 2003; **29:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 01/03/10)
7. FDA. Thimerosal in vaccines (updated February 2009). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228 (accessed 01/03/10)
8. National Advisory Committee on Immunization (NACI). Thimerosal: updated statement. *Can Commun Dis Rep* 2007; **33** (ACS-6): 1–13. Also available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-06.pdf (accessed 29/03/10)
9. WHO. Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. *WHO Tech Rep Ser 926* 2004. Available at: http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%204%20(95-102)TRS926thiomersal.pdf (accessed 01/03/10)
10. WHO. Statement on thiomersal (issued July 2006). Available at: http://www.who.int/vaccine_safety/topics/thiomersal/statement_jul2006/en/index.htm (accessed 01/03/10)

Interactions

Tetracyclines. Nine patients using a contact lens solution containing 0.004% thiomersal developed varying degrees of ocular irritation after taking oral *tetracyclines* concurrently. Exposure to either the tetracyclines or thiomersal alone did not cause the response.[1]

1. Crook TG, Freeman JJ. Reactions induced by the concurrent use of thimerosal and tetracycline. *Am J Optom Physiol Opt* 1983; **60:** 759–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lithiorsan†; Merthiolate; ***Chile***: Intrasept; ***Mon.***: Vitaseptol†; ***S.Afr.***: Merthiolate; Thiomersalate†; ***Thai.***: Merthiolate; Pyrad Thimero Sahakarn; ***USA***: Aeroaid†; Mersol†; ***Venez.***: Merthiolate.

Multi-ingredient Preparations. ***Spain***: Proskin.

Pharmacopoeial Preparations

USP 36: Thimerosal Tincture; Thimerosal Topical Aerosol; Thimerosal Topical Solution.

Thymol

Acido Timico; Ácido tímico; Isopropylmetacresol; Thymolum; Timol; Timolis; Tymol; Tymoli; Тимол.

2-Isopropyl-5-methylphenol.

$C_{10}H_{14}O$=150.2

CAS — 89-83-8.

ATC Vet — QP53AX22.

UNII — 3J50XA376E.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8 (Thymol). Colourless crystals. The melting range is 48 degrees to 52 degrees. Very slightly soluble in water; very soluble in alcohol; freely soluble in volatile and in fixed oils; sparingly soluble in glycerol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Thymol). Colourless, often large, crystals or a white crystalline powder with an aromatic thyme-like odour. The melting range is 48 degrees to 51 degrees; when melted it remains liquid at a considerably lower temperature. Soluble 1 in 1000 of water, 1 in 1 of alcohol and of chloroform, 1 in 1.5 of ether, and 1 in 2 of olive oil; soluble in glacial acetic acid and in fixed and volatile oils. Store in airtight containers. Protect from light.

Incompatibility. The antimicrobial activity of thymol is reduced by combination with protein.

Uses and Administration

Thymol is a phenolic antiseptic with antibacterial and antifungal activity. It is more powerful than phenol but its use is limited by its low solubility in water, irritancy, and susceptibility to protein.

Thymol is used chiefly as a deodorant in mouthwashes and gargles such as Compound Thymol Glycerin (BP 1988), an aqueous mixture of thymol 0.05% and glycerol 10% with colouring and flavouring, which may be used diluted with about 3 times its volume of warm water before use. Thymol has been used topically in the treatment of skin disorders and is also inhaled, with other volatile substances, for colds, coughs, and associated respiratory disorders.

Thymol 0.01% is added as an antoxidant to halothane, trichloroethylene, and tetrachloroethylene.

Thymol iodide is used in preparations for dental hygiene.

Adverse Effects, Treatment, and Precautions

As for Phenol, p. 1764.2.

When ingested, thymol is less toxic than phenol. It is irritant to the gastric mucosa. Fats and alcohol increase absorption and aggravate the toxic symptoms.

Hypersensitivity. Contact allergy to a heparinoid cream was due to an allergen formed by the reaction between thymol and the degradation products of a triazine derivative, both present as preservatives.[1]

1. Smeenk G, *et al.* Contact allergy to a reaction product in Hirudoid cream: an example of compound allergy. *Br J Dermatol* 1987; **116:** 223–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Benefect†; ***S.Afr.***: Listerine Cool Mint; Listerine Freshburst.

Multi-ingredient Preparations. ***Arg.***: Fungicida; Inhalador Medex; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; Manzan; Pastillas Pagliano; Periobacter Prof Avio; Pervinox Extra Mint; Pervinox Fresh Mint; Pervinox Fruit; Vagicural; ***Austral.***: SM-33; Vicks Vaporub; ***Austria***: DDD†; Kinder Luuf; Luuf Balsam; Pe-Ce†; Spasmo Claim†; Thrombocid; Wick Vaporub; ***Belg.***: Borostyrol; Dentophar†; Perubore†; Vicks Vaporub; ***Braz.***: Angino-Rub; Cloraseptic; Cutisanol; Fluomint†; Salonpas; Vick Vaporub; ***Canad.***: Antiseptic Mouthwash; Carboseptol†; Cresophene; Endomethasone; Faces Antiseptic†; Lipsorex Plus; Lipsorex; Listerine Antiseptic Tartar Control; Listerine Antiseptic with Fluoride; Listerine; Original Antiseptic Mouthwash†; Thermo-Gel; Vaporizing Ointment†; ***Chile***: Hansaplast Descongestionante†; Listerine; Listermint Con Fluor†; Oralfresh Citrus†; Oralfresh Clasico†; Salonpas; ***China***: Kamistad (甘美达); ***Cz.***: Pinosol†; Pinosol; Septolete; ***Fin.***: Vicks Vaporub; ***Fr.***: Activox; Borostyrol; Cresophene; Eucaryl; Listerine protection dents et gencives; Listerine Stay White; Nisacalm†; Pastilles Medicinales Vicks; Perubore; Valda†; Vicks Vaporub; ***Ger.***: Pulmotin; Retterspitz Ausserlich; Retterspitz Quick Bronchial; Retterspitz Quick Muskel; Salviathymol N; Thrombocid; ***Gr.***: EKS; Endomethasone†; Export Salonpas; Oulogram; Revigel; Santoux; Vicks Vaporub; ***Hong Kong***: Gly Thymol; Glycerine Thymol Co†; Kamistad; Listerine Cool Mint; Listerine Tartar Control; Listerine Teeth and Gum Defence; Listerine; Salomethyl†; Salonpas Medicated Plaster†; ***Hung.***: Diapulmon; Kinder Luuf Balsam; Pinosol; Pinosol; Pulminetta; Salonpas Liniment; Septolete; ***India***: AM-PM Special; Arofil; Artrex; Cool Mint Listerine; Cureg; Dordent; Icee; Listerine; Me-Fresh Gum Paint; ***Indon.***: Dactylen; Listerine Coolmint†; Listerine†; Skintex†; Vital Ear Oil; ***Irl.***: Karvol; ***Israel***: Cresophene†; Gargol; Karvol; Pronestin; Rectozorin; Rectozorin; ***Ital.***: Eugenol-Guaiacolo Composto; Listerine Fresh Citrus; Listerine Tartar Control; Pinselina Knapp; Rinostil; ***Malaysia***: Salonpas; ***Mex.***: Dermacid; Listerine; ***Mon.***: Glyco-Thymoline; ***Neth.***: Vicks Vaporub; ***NZ***: Listerine Citrus Fresh; Listerine Tartar Control†; Listerine Teeth Defence; Listerine; Vicks Vaporub; ***Philipp.***: Calmoseptine; Listerine Coolmint; Listerine Fresh Citrus; Listerine Freshburst; Listerine Original; Listerine Tartar

Control; Listerine Teeth & Gum Defense; Mentopas; ***Pol.***: Afronis; Bronchosol; Derhotill; Icy Rub; Pinosol†; Pulmonil; Rub-Arom; Septolete; Sonol; Wick Vaporub; ***Port.***: Thrombocid; ***Rus.***: Bioprost (Биопрост); Doktor Mom (Доктор Мом); Efcamon (Эфкамон); Eucasept (Эвкасепт); Inhalipt (Ингалипт); Novoinhalipt (Новоингалипт); Parodontocide (Пародонтоцид); Pinosol (Пиносол); Pinosol (Пиносол); Pinosol (Пиносол); Pinovitum (Пиновитум); Septogal (Септогал); Septolete (Септолете); Suprima-Plus (Суприма-Плюс); ***S.Afr.***: Karvol†; Listerine Antiseptic; Prep†; Tartar Control Listerine†; Vicks Vaporub†; ***Singapore***: Kamistad†; Karvol; Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; ***Spain***: Arkoresp†; Co Bucal; Mentobox; Piorlis†; Vicks Vaporub; ***Swed.***: Vicks Vaporub; ***Switz.***: Butaparin†; Denosol; Eau-de-vie de France Klosterfrau au menthol; Ederphyt†; Furodermal†; Heparinol†; Penta†; Rapura; Vicks Vaporub N; ***Thai.***: Analgen; Burnol Plus; Flavinol; Kamistad†; Methyl Salicylate Cream, Compound; Patarver; Stopain; ***Turk.***: Garol; Kataljin; Mentimol; Mentolin; Oka Mentol; Otaci Meyanbali; Otaci Oka Mentol; Otaci Salvia; Vicks Vaporub; ***UK***: Antiseptic Mouthwash; DDD; DDD; Dragon Balm; Karvol; Listerine Antiseptic Mouthwash; No-Sor Vapour Rub; Potter's Catarrh Pastilles; ***Ukr.***: Doktor Mom (Доктор Мом); Helpex Effect (Хелпекс Эффект); Kamident (Камідент); Pinosol (Пиносол)†; Pinosol (Пиносол); Pinosol (Пиносол); Pinovit (Піновіт); Rostiran (Розтиран); Septolete (Септолете); ***USA***: BFI; Boil Ease; Listerine; Massengill; Vicks Menthol Cough Drops; Zonite; ***Venez.***: Amicets; Lafarcaina.

Tosylchloramide Sodium *(BAN, rINN)*

Chloramidum; Chloramina; Chloramine; Chloramine T; Chloraminum; Cloramina; Klóramin; Mianin; Natrium Sulfaminochloratum; Tosilchloramido natrio druska; Tosilcloramida sódica; Tosylchloramid-Natrium; Tosylchloramid sodná sůl trihydrát; Tosylchloramide Sodique; Tosylchloramidum Natricum; Tosylchloramidum Natricum Trihydricum; Tosylkloramidnatrium; Tosyylikloramidinatrium; Тозилхлорамид Натрий.

Sodium *N*-chlorotoluene-*p*-sulphonimidate trihydrate.

$C_7H_7ClNNaO_2S,3H_2O$=281.7

CAS — 144-86-5 (tosylchloramide); 127-65-1 (tosylchloramide sodium).

ATC — D08AX04.

ATC Vet — QD08AX04.

UNII — 4IU6VSV0EI (tosylchloramide sodium); 328AS34YM6 (anhydrous tosylchloramide sodium).

NOTE. The name Chloramin has also been used for a preparation of chlorphenamine maleate (p. 620.3).

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Tosylchloramide Sodium). A white or slightly yellow, crystalline powder. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 8.0 to 10.0. Store in airtight containers. Protect from light.

Uses and Administration

Tosylchloramide sodium is an organic chlorine-releasing compound. It has general properties similar to those of chlorine (p. 1746.2) but is more stable. It contains about 25% w/w of 'available chlorine' (see p. 1746.3). It is stable at an alkaline pH although it is much more active in acid media. It is more slowly active than hypochlorite solutions.

Tosylchloramide sodium is used for the treatment of minor wound infections and as a skin and hard surface disinfectant. It is also used for the treatment of drinking water (p. 1731.3). It was formerly used as a spermicide.

Tosylchloramide sodium B (chlorogenium; sodium *N*-chlorobenzenesulphonimidate sesquihydrate) has been used similarly to tosylchloramide sodium.

Adverse Effects and Treatment

Vomiting, cyanosis, circulatory collapse, frothing at the mouth, and respiratory failure can occur within a few minutes of tosylchloramide sodium ingestion. Fatalities have occurred. Tosylchloramide sodium in tap water has caused methaemoglobinaemia and haemolysis in patients undergoing dialysis. Bronchospasm has occurred after inhalation.

Treatment of adverse effects is similar to that for Sodium Hypochlorite, p. 1769.3.

Effects on the lungs. A study in Finland in dental staff who had reported occupational respiratory hypersensitivity between 1990 and 1998 found that 1 of 28 cases of rhinitis and 3 of 28 cases of asthma could be attributed to tosylchloramide sodium.[1] For further reference to respiratory effects associated with tosylchloramide sodium gas, see under Sodium Hypochlorite: Toxicity from mixing cleaning agents, p. 1769.2.

1. Piirilä P, *et al.* Occupational respiratory hypersensitivity in dental personnel. *Int Arch Occup Environ Health* 2002; **75:** 209–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Chloraseptine; Chlorazol; Chloronguent; Clonazone; ***Fr.***: Clonazone†; Hydroclonazone; ***Ger.***: Chloramin T; Clorina; Trichlorol; ***Hung.***: Neomagnol; ***Ital.***: Citromed Chlor; Dermedal; Euclorina; Minachlor; Steridrolo.

Triclocarban *(USAN, rINN)*

NSC-72005; TCC; Triclocarbán; Triclocarbanum; Триклокарбан; 3,4,4′-Trichlorocarbanilide.

1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea.

$C_{13}H_9Cl_3N_2O$=315.6

CAS — 101-20-2.

UNII — BGG1Y1ED0Y.

Uses and Administration

Triclocarban is an anilide antiseptic. It is bacteriostatic against Gram-positive organisms but is not effective against Gram-negative organisms. It inhibits growth of some fungi. It is used in antiperspirants and soaps for disinfection of skin and mucous membranes.

Adverse Effects and Precautions

When subjected to prolonged high temperatures triclocarban can decompose to form toxic chloroanilines, which can be absorbed through the skin and cause methaemoglobinaemia. Mild photosensitivity has been seen in patch testing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sodorant; Ungel; ***Fr.***: Cutisan; Nobacter; Solubacter; ***Gr.***: Antibacter Forte; ***Hong Kong***: Solubacter†; ***India***: Neko; ***Ital.***: Sangen Sapone Disinfettante; ***UK***: Valderma.

Multi-ingredient Preparations. ***Arg.***: Sodorant; ***Braz.***: Soapex; ***Fr.***: Septosan†; Spray du Marcheur†; ***Mex.***: Septosan; ***Switz.***: Septivon.

Triclosan *(BAN, USAN, rINN)*

CH-3565; Cloxifenol; Triclosán; Triclosanum; Триклозан.

5-Chloro-2-(2,4-dichlorophenoxy)phenol; 2,4,4′-Trichloro-2′-hydroxydiphenyl ether.

$C_{12}H_7Cl_3O_2$=289.5

CAS — 3380-34-5.

ATC — D08AE04; D09AA06.

ATC Vet — QD08AE04; QD09AA06.

UNII — 4NM5039Y5X.

Pharmacopoeias. In *US.*

USP 36: (Triclosan). A fine whitish crystalline powder. M.p. about 57 degrees. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; slightly soluble in petroleum spirit. Store in airtight containers. Protect from light.

Profile

Triclosan is a chlorinated bisphenol antiseptic, effective against Gram-positive and most Gram-negative bacteria but with variable or poor activity against *Pseudomonas* spp. It is also active against fungi. It is used in soaps, creams, and solutions in concentrations of up to 2% for disinfection of the hands and wounds and for disinfection of the skin before surgery, injections, or venepuncture. It is also used in oral hygiene products and in preparations for acne. There have been isolated reports of contact dermatitis.

Consumer products. Triclosan in relatively low concentrations (typically 0.1 to 0.45%) is commonly found in soaps used in community settings, although a review[1] has concluded that such use is usually no more effective than plain soap. Furthermore, there may be a risk of developing triclosan-adapted antibacterial cross-resistance. The FDA intends to review the benefit and safety of triclosan in consumer products and will consider such data as well as reports from *animal* studies which have suggested it may also alter levels of various hormones.[2]

1. Aiello AE, *et al.* Consumer antibacterial soaps: effective or just risky? *Clin Infect Dis* 2007; **45** (suppl 2): S137–S147.
2. FDA. Triclosan Facts (issued March 2010). Available at: http://www.epa.gov/oppsrrd1/REDs/factsheets/triclosan_fs.htm (accessed 03/08/10)

MRSA control. Control of meticillin-resistant *Staphylococcus aureus* (MRSA) infection in surgical units has been achieved by procedures including handwashing and bathing with triclosan.[1-3] In the UK, guidelines on the control of MRSA recommend it as one of several alternatives for such purposes,[4] although alcohol hand rubs (also mentioned in the guidelines) are currently preferred for general hand hygiene (see p. 1732.1). However, triclosan resistance has been reported.[5-7]

1. Bartzokas CA, *et al.* Control and eradication of methicillin-resistant Staphylococcus aureus on a surgical unit. *N Engl J Med* 1984; **311:** 1422–5.
2. Bartzokas CA. Eradication of resistant Staphylococcus aureus on a surgical unit. *N Engl J Med* 1985; **312:** 858–9.
3. Brady LM, *et al.* Successful control of endemic MRSA in a cardiothoracic surgical unit. *Med J Aust* 1990; **152:** 240–5.
4. Coia JE, *et al.* Joint Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *J Hosp Infect* 2006; **63** (suppl 1): S1–S44. Also available at: http://www.his.org.uk/_db/_documents/MRSA_Guidelines_PDF.pdf (accessed 14/05/10)
5. Cookson BD, *et al.* Transferable resistance to triclosan in MRSA. *Lancet* 1991; **337:** 1548–9.
6. Sasatsu M, *et al.* Triclosan-resistant Staphylococcus aureus. *Lancet* 1993; **341:** 756. Correction. *ibid.*; **342:** 248.
7. Suller MT, Russell AD. Triclosan and antibiotic resistance in Staphylococcus aureus. *J Antimicrob Chemother* 2000; **46:** 11–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daewo; Hekabetol; Xicanil Control Dermo; ***Austral.***: Clean & Clear Foaming Facial Wash; Dettol Liquid Wash; Gamophen; Microshield T; Neutrogena Acne Skin Cleanser; Oxy Medicated Skin Wash†; pHisoHex Face Wash; Sapoderm; ***Braz.***: Clean & Clear Sabonete Liquido Facial; Hygine; Johnson's Sabonete Liquido Anti-Septico; Soapelle; Soapex; Theracne; ***Canad.***: Acnopur†; Adasept; After Sport; Anti-Bac; Anti-Bacterial Moisturizing; Anti-Microbial; Antiseptic Hand Soap; Applaud; Asept; Aspen Hand Soap; Bacti-Foam; Bacti-Stat; Bio-Safe; Bioclenz†; Cherry Creme Hand Soap; Chlorosept†; Clean & Clear Foaming Facial Cleanser; Clearskin Dual Action†; Clinishield; Crown Antiseptic Hand Soap; Dermacne; Dermasept Plus†; Dial Complete; Digiclean Antibacterial; Digiclean E Hand Soap†; Digiclean Slim-Line; Eco-Clean†; Ecocare 250; Endure; Episoft; Florafree; Fresh Power Gold; Gentle Fresh Defense; Gentle Rain; Hands On Defense; HFS; Kimcare Antibacterial†; Lever; Lotion Kleen Green; Moisturizing Antibacterial Hand Cleanser; Naturals Antibacterial Liquid Soap; Noxzema Triple Clean; Perle + Antiseptic; Prime Source; Provon Medicated; Reliable Mousse Foaming Antiseptic; Signatry; Simply Botanical Sensations Soothing Skin; Skin Shield; Skinvisible; Soapy Sudz; Soft Care Antibacterial; Soft Care Cross-Contamination Control; Soft Care Foam Select; Soft Care Nutra-Germ; Softcide EC; Sport Gel†; Stoko; Summer Rain; Surgi Bac†; Sysco Antimicrobial†; Tersaseptic; Valour; West Antiseptic Soap; Winning Hands Hand Cleanser; Zep; ***Chile***: Antiseptin; Lavasept; Sanigermin; ***China***: Sicorten Plus (新适确得); ***Fr.***: Nobacter; ***Gr.***: Ampitasol; ***Hong Kong***: Dettol†; Oxy Daily Wash†; ***India***: Medsop; Microshield T; ***Indon.***: pHisoHex Reformulated; ***Israel***: Dermax; ***Ital.***: Cetriderm con Triclosan†; Derman Plus†; Geroderm; Ippi Verde†; Irgaman; Lactacyd Antibatterico†; Till; ***Malaysia***: A-Septic AS; ***Mex.***: Axel; ***NZ***: Dalacin T Prewash; Liquid Soap Pre-Op; ***Philipp.***: Lipo Sol†; ***S.Afr.***: Acneclear†; ***Singapore***: T3 Continuous Control Wash; ***Switz.***: Clinideram; Cremolan; Lipo Sol; Procoutol; ***Thai.***: Virulex†; ***UK***: Aquasept†; Gamophen; Oxy Facial Wash; Ster-Zac†; ***USA***: AmeriWash; ASC; Ca-Rezz; Clean & Clear Foaming Facial Cleanser; Clearasil Daily Face Wash; Oxy Medicated Soap; Sarna Sensitive; Stri-Dex Antibacterial Cleansing; Stri-Dex Face Wash.

Multi-ingredient Preparations. ***Arg.***: Bentophyto; Dettonjab; Emoform Total; Esmedent con Fluor; Esmedent Dientes Sensibles; Heduline; Hekabetol; Neoceuticals Gel de Limpieza Facial; Prurigel; Sebosoap; Sebulex; Xicanil Control NF Crema; Xicanil Control NF Locion; Xicanil Control NF; Xicanil Control†; ***Austral.***: Clearasil Pimple Treatment Cream†; Dettol Cream; Oilatum Plus; QV Flare Up; ***Braz.***: Fisohex II; Malvatricin Antiplaca†; Malvatricin Branqueador†; Malvatricin Dentes Sensiveis†; Malvatricin Plus†; Salisoap; Soapex; Suavederin; ***Canad.***: Adasept; Anti-Bacterial Deep Cleansing; Antiseptic Hand Soap; Ensuite; Inhibit; PanOxyl Clear Acne†; Solarcaine; Soothing Foot Spray; Uphold Plus; ***Chile***: Ac-Sal†; Acniben Toallitas; Cariamyl; Cariamyl; Dermaliv; Fittig Desodorante; Hansaplast Antimicotico†; Hansaplast Footcare†; Normaderm Stick Secante Camufu Imperfecciones; Softcain; Solarcaine Spray Aerosol; ***Cz.***: Oilatum Plus; ***Fin.***: Wicnelact; ***Fr.***: Clinogel†; Dermalibour; Ephydrol; Poudre du Marcheur†; Septosan†; Spray du Marcheur†; ***Ger.***: DuoGalen; InfectoCortiSept; Rutisept extra; Sicorten Plus†; ***Hong Kong***: Dettol†; Oilatum Plus; Sensodyne Gentle†; ***Hung.***: Aurobin; ***India***: Acnelak; AM-PM Junior; AM-PM Plus; AM-PM Special; Clin-3; Deosan; Kidodent; Klinit; Oilatum Plus; ***Indon.***: Betiga†; Oilatum Plus†; Verile; ***Irl.***: Colgate Total; Dettol†; Manusept; Oilatum Junior Flare-Up; Oilatum Plus; TCP; ***Israel***: Pedisol†; ***Ital.***: Akricare Cleanser; Angstrom Viso; AZ Protezione Gengive; Colgate Total; Dopo Pik; Geroderm Zolfo; Plax; Sensigel; Sensiquell; Steril Zeta; Steril Zeta; ***Malaysia***: AcneCare; Clearasil Pimple Treatment; Dettol; Oilatum Plus Antibacterial; QV Flare Up†; T3 Acne; T3 Concealer; ***Mex.***: Axel; Cetaphil Antibacterial; Dermobras; Periodentyl; Periodentyl; Prespir; Sebryl Plus; Septosan; ***NZ***: Clearasil; Dettol; Oilatum Plus; Solarcaine†; ***Philipp.***: Oilatum Plus; Sebo Fluid†; ***Pol.***: Oilatum Plus; ***Port.***: Aknicare; Alkagin; Bexident; Lambda; ***Rus.***: Aurobin (Ауробин); ***S.Afr.***: Clearasil T†; Oilatum Plus; ***Singapore***: Burnaid; Clearasil Pimple Treatment; Dettol; Oilatum Plus; QV Flare Up; T3; ***Spain***: Doctodermis; Sicorten Plus†; Vaselatum; ***Switz.***: Acne Creme; Acne Gel; Acne Lotion;

Antebor N†; Pixor Stick Anti-acne N; Sicorten Plus; Sulgan N; Undex†; ***Thai.***: Dettol; Hand Joy; Oilatum Plus†; ***Turk.***: Alkagin; ***UK***: Clearasil Active Treatment Cream; Dentyl pH; Dettol; Manusept; Oilatum Plus; Oxy Clean Facial Scrub; Oxy Cleanser; Oxy Dots; Oxy Duo Pads; Sensodyne-F; Solarcaine; TCP; ***Ukr.***: Aurobin (Аурoбин); ***USA***: Clearasil Antibacterial; Solarcaine; ***Venez.***: Exfoliderm.

Troclosene *(rINNM)*

Dichloroisocyanuric Acid; Troclosène; Trocloseno; Troclosenum; Троклозен.
1,3-Dichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.
$C_3HCl_2N_3O_3$=198.0
CAS — 2782-57-2.
UNII — PHR838Y52L.

Troclosene Potassium *(USAN, rINN)*

Potassium Dichloroisocyanurate; Potassium Troclosene; Troclosène Potassique; Trocloseno de potasio; Troclosenum Kalicum; Троклозен Калий.
$C_3Cl_2KN_3O_3$=236.0
CAS — 2244-21-5.
UNII — 8A85D111P0.

Troclosene Sodium *(rINNM)*

Dicloroisocianurato sódico; Sodium Dichloroisocyanurate; Sodium Dichloro-*s*-triazinetrione; Sodium Troclosene; Troclosène Sodique; Trocloseno sódico; Troclosenum Natricum; Троклозен Натрий.
$C_3Cl_2N_3NaO_3$=219.9
CAS — 2893-78-9.
UNII — 07M9U9U0LK.

Profile

Troclosene sodium is a disinfectant with the general properties of chlorine (p. 1746.2) and sodium hypochlorite (p. 1768.3) but it remains active as pH increases from 6 to 10 and is reported to be less susceptible to inactivation by organic material. It contains about 56 to 65% of 'available chlorine' (see p. 1746.3).

Troclosene sodium is used for disinfecting hard surfaces (see Disinfection in Hepatitis and HIV Infection, p. 1731.2), babies' feeding bottles, and food and dairy equipment, for treating water (p. 1731.3), for rapid disinfection of swimming pools, for soft contact lens care (p. 1730.2), and in various commercial bleach detergents and scouring powders as a relatively stable source of chlorine.

Troclosene, troclosene potassium, and symclosene (trichloroisocyanuric acid $C_3Cl_3N_3O_3$ = 232.4) are similarly used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aquatabs; Milton; ***Fr.***: Aquatabs; Steritabs; ***Hong Kong***: Actichlor; ***Israel***: K-sept; K-sorb; Klor-De; Oral-Blue†; Taharmayim; Taharsept; Tahartaf; ***Ital.***: Dicloraster; ***NZ***: Puritabs; ***S.Afr.***: Softab†; ***Singapore***: Biospot; ***UK***: Milton; Presept.

Multi-ingredient Preparations. ***Fr.***: Micropur Forte DCCNa.

Undebenzophene

Parahydroxybenzoate Phenoxyethanol; Undebenzofeno.
2-Phenoxyethyl *p*-hydroxybenzoate.
$C_{15}H_{14}O_4$=258.3
CAS — 55468-88-7.

Profile

Undebenzophene is an antiseptic that has been included in preparations intended for wound and burn disinfection.

Urea Hydrogen Peroxide

Carbamide Peroxide; Hydroperite; Peróxido de carbamida; Peróxido de hidrógeno y urea; Urea Peroxide; Гидроперит.
$NH_2.CO.NH_2.H_2O_2$=94.07
CAS — 124-43-6.
UNII — 31PZ2VAU81.

Pharmacopoeias. In *US.*

USP 36: (Carbamide Peroxide). Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Urea hydrogen peroxide consists of hydrogen peroxide and urea in equimolecular proportions. It is used for the extemporaneous preparation of hydrogen peroxide. It is used for tooth whitening, and has been used for infections of the ear, mouth, skin, and mucous membranes and for softening ear wax.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Blanc Dient; Yadid; ***Austral.***: Ear Clear; ***Braz.***: Aceratum; ***Ger.***: Elawox†; ***Gr.***: Unisept; ***Hong Kong***: Ear Clear; ***Hung.***: Hyperol; ***Irl.***: Exterol; ***Israel***: Exterol; ***Ital.***: Debrox; Dermoxyl; Ginoxil; ***NZ***: Earclear; ***Pol.***: Pertlenon; ***UK***: Exterol; Otex; ***USA***: Auraphene-B; Auro; Debrox; ERO; Gly-Oxide; Mollifene; Murine; Orajel Perioseptic.

Pharmacopoeial Preparations
USP 36: Carbamide Peroxide Topical Solution.

Zinc Peroxide

Peróxido de zinc; Zinc Dioxide; Zinc Superoxide; ZPO; Перекись Цинка; Цинк Пероксид.
ZnO_2=97.38
CAS — 1314-22-3.
UNII — 01969DVM77.

Profile

The action of zinc peroxide is similar to that of hydrogen peroxide (p. 1755.2). Applied locally it has been used for disinfecting and deodorising burns, wounds, and various ulcers and lesions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Anaseptil; ***Fr.***: Bioxyol; ***Ital.***: Ektogan.

Electrolytes

Acid–base Balance, p. 1775
Metabolic acidosis, p. 1775
Metabolic alkalosis, p. 1775
Calcium Homoeostasis, p. 1775
Hypercalcaemia, p. 1776
Hypercalcaemia of malignancy, p. 1776
Hyperparathyroidism, p. 1776
Vitamin D-mediated hypercalcaemia, p. 1776
Hypocalcaemia, p. 1776
Magnesium Homoeostasis, p. 1776
Hypermagnesaemia, p. 1776
Hypomagnesaemia, p. 1776
Phosphate Homoeostasis, p. 1776
Hyperphosphataemia, p. 1776
Hypophosphataemia, p. 1777
Potassium Homoeostasis, p. 1777
Hyperkalaemia, p. 1777
Hyperkalaemic periodic paralysis, p. 1777
Hypokalaemia, p. 1777
Bartter's syndrome, p. 1777
Diuretic-induced hypokalaemia, p. 1777
Hypokalaemic periodic paralysis, p. 1777
Sodium Homoeostasis, p. 1777
Hypernatraemio, p. 1778
Hyponatraemia, p. 1778

Electrolytes are used to correct disturbances in fluid and electrolyte homoeostasis or acid–base balance and to re-establish osmotic equilibrium of specific ions. The osmotic effects of solutions may be expressed in terms of

- osmolality, which is defined as the 'molal' concentration in moles (or osmoles) per kg of solvent

or

- osmolarity, which is the 'molar' concentration in moles (or osmoles) per litre of solution

In clinical practice, solute concentrations are measured per litre of solution and are expressed as millimoles (mmol) per litre or sometimes as milliequivalents (mEq) per litre. Milliequivalents are converted to millimoles by dividing by the valency of the ion.

Positively charged ions are known as *cations* and include calcium, magnesium, potassium, and sodium ions. Negatively charged ions are known as *anions* and include bicarbonate, chloride, and phosphate ions. The ions principally involved in fluid and electrolyte homoeostasis and acid–base balance are sodium, chloride, bicarbonate, and potassium. Calcium, phosphate, and magnesium have a central role in the formation of bone mineral.

Acid–base Balance

Within the body, acid is mostly produced during cellular respiration in the form of carbon dioxide. Small amounts of various non-volatile acids are generated via metabolism, including lactic acid, uric acid, keto acids, and some inorganic acids such as sulfuric and phosphoric acids. For normal tissue function, the pH of the body needs to be held within a narrow range. The pH of arterial blood is normally maintained between about 7.38 and 7.42 by means of compensatory respiratory, renal, and buffering mechanisms.

The most important buffer system in the extracellular fluid is the bicarbonate-carbonic acid system. Bicarbonate and hydrogen ions are in equilibrium with carbonic acid which is in turn in equilibrium with carbon dioxide in the body fluid, as expressed by:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

A normal plasma-bicarbonate concentration in adults is in the range of 20 to 30 mmol/litre and arterial partial pressure of carbon dioxide (P_aCO_2) is normally 4.7 to 5.7 kPa (35 to 43 mmHg).

Ultimately, excess acid must be removed from the body and base regenerated. P_aCO_2 is under respiratory control with carbon dioxide being excreted by the lungs. Plasma-bicarbonate concentrations are regulated by the kidneys, where bicarbonate is actively regenerated or reabsorbed. Organic acids such as lactic acid may be eliminated by metabolism; and other non-volatile acids, such as the inorganic acids of phosphate and sulfate, are excreted via the kidneys with simultaneous regeneration of bicarbonate.

The relationship between plasma pH, P_aCO_2, and bicarbonate is defined by the Henderson-Hasselbalch equation which is used to assess acid–base balance.

For clinical purposes, this equation becomes

$$pH = pK_{CO2} + \log (C_{HCO3}/\alpha \times P_aCO_2)$$

where pH is the plasma pH, pK_{CO2} is the carbonic acid dissociation constant (6.1), C_{HCO3} is the plasma-bicarbonate concentration, α is a value representing carbon dioxide solubility, and P_aCO_2 is the arterial partial pressure of carbon dioxide. Disorders of acid–base balance may be due to a change in plasma-bicarbonate concentrations (metabolic) or to a change in P_aCO_2 (respiratory), although mixed disorders do occur.

The 4 major acid–base disturbances are:

- metabolic acidosis—a decrease in the plasma-bicarbonate concentration
- metabolic alkalosis—an increase in the plasma-bicarbonate concentration
- respiratory acidosis—hypoventilation and a raised P_aCO_2
- respiratory alkalosis—hyperventilation and a reduced P_aCO_2

A further measure that may provide useful information in the assessment of metabolic acidosis is the plasma anion gap. This is the difference in ionic charge between the principal plasma cation (sodium) and anions (chloride and bicarbonate), and provides an estimation of unmeasured serum anions, which include inorganic and organic acids.

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Metabolic acidosis. Metabolic acidosis, characterised by a low plasma-bicarbonate concentration and a tendency towards a fall in arterial pH, is the most frequent acid–base abnormality.

Metabolic acidosis with a *normal anion gap* is usually caused by excessive losses of bicarbonate from the gastrointestinal tract (as in severe diarrhoeas) or failure of the kidneys to reabsorb or regenerate adequate bicarbonate (as in the renal tubular acidoses). Ingestion of acidifying salts such as ammonium chloride, which generate hydrochloric acid, can also result in this type of acidosis. Metabolic acidosis characterised by an *increased anion gap* is often due to a reduction in the renal excretion of inorganic acids such as phosphates and sulfates as in renal failure (uraemic acidosis), or to the net accumulation of organic acids as, for example, in lactic acidosis or diabetic ketoacidosis.

Metabolic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH, and P_aCO_2. There is often hyperventilation with reduced cardiac function, constriction of peripheral veins, inhibition of the hepatic metabolism of lactate, and impairment of consciousness.

The main aim of **treatment** is to manage any underlying disorder,[1,2] and in some cases this will be sufficient to enable the body's homoeostatic mechanisms to correct the acid–base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including over-alkalinisation, and in consequence such therapy tends to be reserved for more persistent or severe cases.

The usual alkalinising agent is sodium bicarbonate. It may be given orally to replace bicarbonate losses in various chronic metabolic acidoses such as uraemic acidosis or renal tubular acidosis. Potassium bicarbonate may be preferred if the acidosis is associated with potassium deficiency. Potassium citrate and sodium citrate have also been used. More severe and acute cases (particularly where arterial pH is below 7.1) may require intravenous sodium bicarbonate therapy. Intravenous sodium bicarbonate has a role in acute metabolic acidoses attributable to severe renal failure, severe secretory diarrhoeas, and renal tubular acidosis. Although hypertonic solutions have been used, for example, in patients with circulatory overload, roughly isotonic bicarbonate solutions are otherwise preferred; arterial pH and plasma bicarbonate should be raised a little at a time and the patient's response monitored.

Although the role of bicarbonate is accepted in the forms of metabolic acidosis mentioned, its use in the treatment of metabolic acidosis with concomitant tissue hypoxia, particularly lactic acidosis, is controversial.[1-4] The administration of bicarbonate generates carbon dioxide which, if not appropriately eliminated, due to poor tissue perfusion or impaired ventilation or both, diffuses rapidly into the cells exacerbating intracellular acidosis. In addition, in metabolic acidosis associated with organic acids such as lactic acid, there is a risk of over-alkalinisation due to the metabolism of the acid after correction of the arterial pH.

For similar reasons, the use of sodium bicarbonate in advanced cardiac life support (see Cardiac Arrest, p. 1268.3) is no longer routine, although current guidelines permit consideration of its use when cardiac arrest is associated with hyperkalaemia or tricyclic antidepressant overdose.

The role of bicarbonate in the management of diabetic ketoacidosis is also limited, although it may be appropriate in certain situations—see Diabetic Emergencies, p. 465.3.

Because of concerns about the effects of bicarbonate, other agents have been investigated for the treatment of metabolic acidosis, including trometamol (THAM) and sodium dichloroacetate.[1-4] Alkalinising agents that have to be metabolised to bicarbonate before they have an effect, such as sodium lactate, are not generally used as many patients with acute acidosis have impaired metabolic activity, particularly of lactate.

Peritoneal dialysis, haemodialysis, or haemofiltration is required for refractory metabolic acidosis associated with acute renal failure (p. 1779.1).

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4. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998; **338:** 26–34. Correction. *ibid*. 1999; **340:** 247.

Metabolic alkalosis. Metabolic alkalosis with an increased plasma-bicarbonate concentration and a sustained elevation in arterial pH results from excessive renal reabsorption and/or regeneration of bicarbonate. It is commonly seen with volume contraction (chloride depletion), potassium depletion, or mineralocorticoid excess, and may occur with excessive alkali intake as in the milk-alkali syndrome. If the metabolic alkalosis is severe, cardiac arrhythmias and hypoventilation may develop and there can be symptoms of concomitant hypokalaemia such as muscle weakness.

Treatment is generally aimed at the underlying disturbances.[1-3] Correcting volume depletion by giving a chloride salt often obviates the need for other treatment; sodium chloride is normally used. However, potassium chloride may also be required if there is potassium depletion, particularly if this is severe. Rarely, direct acidification with ammonium chloride, dilute hydrochloric acid, or acidifying salts such as lysine hydrochloride or arginine hydrochloride may be required if the alkalosis is severe.

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Calcium Homoeostasis

The adult body contains about 1.2 kg of calcium, of which about 99% is incorporated into the skeleton where its primary role is structural. The remaining 1% is found in body tissues and fluids and is essential for normal nerve conduction, muscle activity, and blood coagulation.

The concentration of calcium in plasma is normally kept within a narrow range (total calcium about 2.15 to 2.60 mmol/litre) by homoeostatic mechanisms involving parathyroid hormone, calcitonin, and vitamin D. Normally about 50% of calcium in plasma is in the ionised physiologically active form (giving a usual range of about 1.1 to 1.3 mmol/litre), about 10% is complexed with anions such as phosphate or citrate, and the remainder is bound to proteins, principally albumin. If the plasma-albumin concentration is raised (as in dehydration) or reduced (as is common in malignancy) it will affect the proportion of ionised calcium. Thus, the total plasma-calcium concentration is commonly adjusted for plasma albumin.

Hypercalcaemia. Hypercalcaemia, an increase in plasma-calcium concentration above the normal range, is most commonly due to primary hyperparathyroidism (p. 1170.3) or malignant disease.[1-4] Less common causes of hypercalcaemia include vitamin D intoxication, granulomatous diseases such as sarcoidosis, familial benign hypercalcaemia, renal failure, thyrotoxicosis, and excess calcium carbonate ingestion (milk-alkali or calcium-alkali syndrome).[1-4]

Mild asymptomatic hypercalcaemia is often associated with a plasma-concentration elevated above the normal but below 3.00 mmol/litre. Severe symptomatic hypercalcaemia is broadly correlated with a plasma-calcium concentration of more than 3.50 mmol/litre.

Symptoms of hypercalcaemia include thirst, polyuria, anorexia, constipation, muscle weakness, fatigue, and confusion. In severe cases, there may be nausea and vomiting; cardiac arrhythmias may develop but are rare. Extreme hypercalcaemia may result in coma and death. Chronic hypercalcaemia can lead to interstitial nephritis and calcium renal calculi.[3]

Mild asymptomatic hypercalcaemia is best corrected by increasing oral fluid intake and treating any identified underlying disease. Patients with more severe hypercalcaemia, and/or significant symptoms, need prompt **treatment** to reduce plasma-calcium concentrations independent of the cause.[2,3]

The first step is rehydration with intravenous sodium chloride 0.9% to restore the intravascular volume and to promote renal excretion of calcium. Loop diuretics will enhance calcium excretion, but are usually only given to prevent fluid overload or heart failure.[1-4] Thiazide diuretics should be avoided[2] as they increase the renal tubular reabsorption of calcium. Peritoneal dialysis or haemodialysis with calcium-free dialysate should be considered[2,4,5] in patients with renal failure for whom urinary excretion of calcium is inadequate.

In life-threatening hypercalcaemia, more specific immediate therapy is generally required in addition to saline.[2,3] Most experience has been gained in the treatment of hypercalcaemia of malignancy (p. 1167.2) using drugs that inhibit bone resorption, notably bisphosphonates.[1-5] Calcitonins have a rapid onset of action, but their effect is moderate and generally short-lived. Thus, they are seldom used alone, or as first-line agents; they may be given with bisphosphonates to rapidly lower serum calcium.[2,4] Plicamycin lowers serum calcium quickly but toxicity has limited its use.[2,3] Gallium nitrate is also effective when given continuously over several days; adverse effects such as nephrotoxicity are frequent and severe.[2,4] Corticosteroids are particularly effective for hypercalcaemia secondary to haematological malignancy, or associated with vitamin D toxicity, such as sarcoidosis.[1-5] They have been used to prolong the efficacy of calcitonin. Intravenous phosphates rapidly lower plasma-calcium concentrations but can cause soft tissue calcification (resulting in serious adverse effects such as irreversible renal damage and hypotension), and are best avoided.[2,3] Where intestinal calcium absorption is increased, dietary calcium and vitamin D intake should be restricted,[4,5] although some consider this unnecessary and ineffective.[1]

Choice of subsequent therapy is likely to depend on the specific cause.

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HYPERCALCAEMIA OF MALIGNANCY. About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive. Bisphosphonates are the preferred drugs for treating hypercalcaemia once the patient has been adequately rehydrated (see Hypercalcaemia of Malignancy, p. 1167.2).

HYPERPARATHYROIDISM. Excess secretion of parathyroid hormone in primary hyperparathyroidism (p. 1170.3) is characterised by hypercalcaemia, which is most frequently asymptomatic, and by hypophosphataemia. Oral phosphates and bisphosphonates have been used to control hypercalcaemia. However, in the long term, hypercalcaemia associated with primary hyperparathyroidism appears to be best managed by parathyroidectomy. Symptomatic hypocalcaemia may occur after surgery, requiring short-term treatment with calcium supplements and vitamin D.

VITAMIN D-MEDIATED HYPERCALCAEMIA. Hypercalcaemia can occur because of increased gastrointestinal absorption of calcium mediated by the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol). This may be a feature of diseases associated with increased vitamin D sensitivity or increased vitamin D production, or may occur due to overdose of vitamin D. For example, granulomatous diseases such as sarcoidosis (p. 1612.2) are associated with unregulated production of 1,25-dihydroxycholecalciferol. Hypercalcaemia due to vitamin D is most commonly seen in patients with renal failure receiving vitamin D analogues such as ergocalciferol.

Treatment of severe hypercalcaemia requires prompt rehydration regardless of the cause (see Hypercalcaemia, above). Where hypercalcaemia is due to excessive doses of a vitamin D analogue, it should be discontinued until normocalcaemia is achieved. Corticosteroids effectively reduce gastrointestinal absorption of calcium, and these may be used intravenously as adjuncts to rehydration in severe hypercalcaemia, and orally for milder hypercalcaemia or longer term therapy. Oral sodium cellulose phosphate, which binds calcium in the gastrointestinal tract, and a low-calcium diet may also be considered. Oral chloroquine or hydroxychloroquine have been used in hypercalcaemia associated with sarcoidosis. Ketoconazole may be useful as an alternative to corticosteroids.

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Hypocalcaemia. Hypocalcaemia, a decrease in plasma-calcium concentration below the normal range, may be due to impaired or reduced absorption of calcium from the gastrointestinal tract, as with vitamin D deficiency disorders (see Osteomalacia and Rickets, p. 1168.1) and chronic renal failure (see Renal Osteodystrophy, p. 1170.1). Alternatively, it may be due to deficient parathyroid hormone secretion and/or action as in hypoparathyroidism (p. 1171.2) and hypomagnesaemia (see below). Excessive phosphate administration is also a cause of hypocalcaemia (see Hyperphosphataemia, below). Rarely, hypocalcaemia may follow repeated infusions of citrate ions, for example, during transfusions utilising citrated blood, as the citrate complexes with the calcium ion. Respiratory alkalosis due to hyperventilation can also lead to depression of ionised plasma-calcium concentrations.

Where symptoms of hypocalcaemia occur, they are typically associated with increased neuromuscular excitability; paraesthesias can occur and in more severe cases, carpopedal spasm, muscle cramps, tetany, and convulsions may develop.[1-4] Other symptoms include ECG changes and mental disturbances such as irritability and depression. Prolonged hypocalcaemia can lead to dental defects, cataract formation, and in children can result in mental retardation.

In patients with hypocalcaemia due to an underlying disease, long-term management should be aimed at **treating** this disease. Vitamin D supplements are widely used to enhance calcium absorption and correct vitamin D deficiency disorders and hypoparathyroidism. Oral supplements of calcium salts are often also given. Acute hypocalcaemia or hypocalcaemic tetany require emergency treatment with intravenous calcium salts.[2-4]

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Magnesium Homoeostasis

Magnesium is an essential body cation that is involved in numerous enzymatic reactions and physiological processes including energy transfer and storage, skeletal development, nerve conduction, and muscle contraction. Over half of the magnesium in the body is found in bone, about 40% is present in muscle and soft tissue, and only about 1% is present in the extracellular fluid. A normal concentration for magnesium in plasma is from about 0.7 to 1.0 mmol/litre.

Magnesium homoeostasis appears to be primarily regulated by the kidney where magnesium is extensively reabsorbed. Bone may act as a magnesium reservoir to reduce plasma-magnesium fluctuations. Magnesium is actively absorbed from the gastrointestinal tract and this is enhanced to some extent by 1,25-dihydroxycholecalciferol (calcitriol).

Hypermagnesaemia. Hypermagnesaemia is an increase in the plasma concentration of magnesium above the normal range, as may follow excessive parenteral doses of salts such as magnesium sulfate. Hypermagnesaemia due to oral intake is uncommon as the kidneys are able to excrete a relatively large magnesium load. However, it may occur in patients with impaired renal function taking large amounts of magnesium, for example, in antacids or laxatives.

Symptoms of hypermagnesaemia include nausea, vomiting, CNS and respiratory depression, hyporeflexia, muscle weakness, and cardiovascular effects including peripheral vasodilatation, hypotension, bradycardia, and cardiac arrest.

Treatment of mild hypermagnesaemia is usually limited to restricting magnesium intake. In severe hypermagnesaemia, ventilatory and circulatory support may be required. Slow intravenous injection of calcium gluconate is recommended to reverse the effects on cardiovascular and respiratory systems. If renal function is normal, adequate fluids should be given to promote renal magnesium clearance. This may be increased by the use of furosemide. Haemodialysis using a magnesium-free dialysis solution effectively removes magnesium, and this may be necessary in patients with renal impairment, or for whom other methods prove ineffective.

Hypomagnesaemia. Hypomagnesaemia, a plasma-magnesium concentration below the normal range, may result from a reduced magnesium intake as in dietary deficiency or malabsorption syndromes. Alternatively, it may be due to excessive magnesium loss, either via the kidney because of inadequate reabsorption, or more often from the gut, for example during chronic diarrhoea. Drugs that may cause renal magnesium wasting include aminoglycosides, amphotericin B, ciclosporin, cisplatin (see Effects on Electrolytes, p. 767.2), and diuretics.[1]

Hypomagnesaemia is closely associated with other electrolyte disturbances, especially hypocalcaemia (see above) and hypokalaemia (see p. 1777.2), and rarely occurs alone. Specific symptoms are therefore difficult to determine but may include anorexia, nausea, weakness, neuromuscular dysfunction such as tetany, tremor, and muscle fasciculations, and rarely seizures. Cardiac arrhythmias may occur, but the relative contribution of hypomagnesaemia and hypokalaemia to these is uncertain.

Magnesium salts can be given orally for the **treatment** of chronic or asymptomatic magnesium deficiency.[2,3] Parenteral therapy may be preferred in patients with poor gastrointestinal absorption of magnesium or who are unable to tolerate oral supplements (usually because they cause diarrhoea); magnesium sulfate can be given by intravenous or intramuscular injection. In acute symptomatic hypomagnesaemia, rapid replacement therapy with intravenous magnesium salts may be necessary. Renal function and plasma-magnesium concentrations should be monitored.

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Phosphate Homoeostasis

Phosphate is an essential bone mineral; about 80% of phosphorus in an adult body is incorporated into the skeleton as a calcium salt where it is required to give rigidity. The remainder is present in the soft tissues and is involved in several metabolic and enzymatic reactions including energy storage and transfer.

Phosphate exists in body fluids mainly as the divalent HPO_4^{2-} ion (about 80%) or monovalent $H_2PO_4^-$ ion (about 20%). Phosphate measurements are usually expressed as inorganic phosphorus to avoid confusion with the anion content. A normal range for phosphorus in plasma in adults is about 0.85 to 1.45 mmol/litre, but as only a small proportion of body phosphate is found in the extracellular fluid, plasma-phosphorus levels may not always reflect total body stores or predict replacement needs.

Phosphate concentrations in plasma are primarily regulated by renal excretion; parathyroid hormone reduces the renal tubular reabsorption of phosphate. Intestinal absorption of phosphate is enhanced by the vitamin D metabolite, 1,25-dihydroxycholecalciferol.

Hyperphosphataemia. Hyperphosphataemia, an abnormally raised plasma-phosphorus concentration, is usually associated with renal failure and may lead to renal osteodystrophy (p. 1170.1). Hyperphosphataemia may also be a consequence of release of phosphate from cells; this can occur in conditions of cell breakdown such as haemolysis or rhabdomyolysis, during chemotherapy (when it may be part of the tumour lysis syndrome), or as a result of acidoses. Hypoparathyroidism may also lead to hyperphosphataemia due to decreased levels of parathyroid hormone (see Hypoparathyroidism, p. 1171.2). Other causes include excessive phosphate doses during treatment of hypophosphataemia, overuse of phosphate enemas or oral phosphate bowel preparations, and excessive vitamin D intake.

Hyperphosphataemic symptoms include those of associated hypocalcaemia (see above). Complexation with calcium may lead to metastatic calcification.

The **treatment** of hyperphosphataemia[1,2] usually involves control of the relevant underlying condition, and the use of low-phosphate diets, and if necessary oral phosphate-binding agents, such as calcium acetate or carbonate or aluminium hydroxide. Sevelamer, a polymer

capable of binding phosphate, may also be given.[2,3] Lanthanum carbonate has also been used.[2-4] Haemodialysis has been used to correct hyperphosphataemia in renal failure.[4]

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Hypophosphataemia. Hypophosphataemia, a reduction in plasma-phosphorus concentrations below the normal range, may be due to insufficient absorption of phosphate or increased renal clearance as in primary hyperparathyroidism, vitamin D deficiency, or X-linked familial hypophosphataemia. An increased cell uptake of phosphate can also result in hypophosphataemia, for example in chronic respiratory alkalosis and related disorders including alcoholism, hepatic failure, and septicaemia. As phosphate is widely available in foods, dietary deficiency is rare though it may occur in infants of low birth-weight fed exclusively on human breast milk (see Rickets of Prematurity, p. 1792.1). The absorption of phosphate from the gastrointestinal tract can be reduced if phosphate-binding antacids are taken in large amounts.

Hypophosphataemia is usually asymptomatic but clinical symptoms become apparent when plasma-phosphorus concentrations fall below 0.3 mmol/litre.[1-4] Symptoms include neuromuscular dysfunction such as muscle weakness and paraesthesias, convulsions, cardiomyopathy, respiratory failure, and haematological abnormalities. Prolonged hypophosphataemia can result in rickets or osteomalacia (p. 1168.1).

Treatment of hypophosphataemia primarily involves correction of any underlying disease.[4] Milk or oral phosphate supplements may be appropriate if a phosphate deficiency is identified or in certain disorders such as X-linked hypophosphataemic rickets. Intravenous phosphate may be required for severe hypophosphataemia (see p. 1791.3), but this should be used cautiously to avoid hypocalcaemia and metastatic calcification.[2,3] Consideration should be given to correcting concomitant electrolyte disturbances such as hypomagnesaemia.

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Potassium Homoeostasis

Potassium is mainly an intracellular cation, primarily found in muscle; only about 2% is present in the extracellular fluid. It is essential for numerous metabolic and physiological processes including nerve conduction, muscle contraction, and acid–base regulation. A normal concentration of potassium in plasma is about 3.5 to 5.0 mmol/litre, but factors influencing transfer between intracellular and extracellular fluids such as acid–base disturbances can distort the relationship between plasma concentrations and total body stores. The body content of potassium is primarily regulated by renal glomerular filtration and tubular secretion. Aldosterone enhances the renal secretion of potassium and other factors such as sodium excretion, dietary potassium intake, and plasma pH can modulate the excretion of potassium by the kidney. Insulin, beta$_2$ agonists, and aldosterone, and increases in plasma pH, can promote the cellular uptake of potassium. The passage of potassium into the cells and retention against the concentration gradient requires active transport via the Na^+/K^+ ATPase enzyme.

Hyperkalaemia. Hyperkalaemia, an abnormally raised plasma-potassium concentration, can occur if the potassium intake is increased, if the renal excretion decreases (as in renal failure or adrenocortical insufficiency), or if there is a sudden efflux of potassium from intracellular stores, (as in acidosis, or cell destruction due to tissue trauma, burns, haemolysis, or rhabdomyolysis). Renal failure is the commonest cause of severe hyperkalaemia.[1] Hyperkalaemia may also be induced by drugs such as the potassium-sparing diuretics, ciclosporin, tacrolimus, NSAIDs, or ACE inhibitors.[2,3] Usually the renal mechanisms for potassium excretion adapt readily to an increased potassium load, and hyperkalaemia due to increased dietary intake is rare unless renal function is also impaired.

Hyperkalaemia mainly affects the heart, but skeletal muscle function may also be affected. Symptoms include ECG abnormalities, ventricular arrhythmias, cardiac arrest, and also neuromuscular dysfunction such as muscle weakness and paralysis.[3,4]

Treatment involves giving calcium to counteract the negative effects of hyperkalaemia on cardiac excitability, drugs such as insulin or sodium bicarbonate to promote the transfer of potassium from the extracellular to the intracellar fluid compartment, and enhancing potassium excretion with exchange resins or dialysis.[3,4] The methods used depend largely on the severity of the hyperkalaemia and critically, any associated ECG changes. Hyperkalaemia associated with a plasma concentration of potassium above 6.0 to 7.0 mmol/litre or with ECG changes is usually considered a medical emergency.

If effects on the heart are present, then first-line therapy should be with a calcium salt given intravenously; typically, calcium gluconate is given by slow intravenous injection, the dosage being titrated and adjusted based on ECG improvement.

Calcium will not, however, reduce the plasma-potassium concentration. In moderate to severe hyperkalaemia, insulin, together with glucose to prevent hypoglycaemia, is given intravenously to reduce the potassium concentration by stimulating the uptake of potassium by cells.[1,5] Insulin is given as a rapid-acting soluble insulin and typical doses are 5 to 10 units with 50 mL of glucose 50% given slowly over 5 to 15 minutes. Doses may need to be repeated as necessary. Alternatively or additionally, intravenous sodium bicarbonate may be used to correct acidosis and promote cellular uptake of potassium (but see Metabolic Acidosis p. 1775.2). Opinions vary on its value[5] and on the appropriate dose and concentration, but it may be indicated where there is severe associated acidosis (pH less than 7.2).[1]

The beta$_2$ agonist, salbutamol, given intravenously or by a nebuliser, has also been found to enhance the cellular uptake of potassium and reduce plasma-potassium concentrations.[3-6] However, its effect may be inconsistent,[6] and some clinicians prefer to avoid beta$_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7] Some consider that it should only ever be used with insulin, as up to 40% of patients may not respond.[1]

After the plasma-potassium concentration has been reduced in the immediate term by enhancing cellular potassium uptake, treatments are often required that will remove excess potassium from the body over the longer term. Cation exchange resins such as calcium or sodium polystyrene sulfonate can be given orally or rectally and, after about 1 to 2 hours, will begin to remove potassium from the body, although the evidence to support their use is lacking.[5] Haemodialysis removes potassium from the body very effectively[5] and is particularly useful in patients with acute renal failure, hypervolaemia, hypernatraemia, or severe hyperkalaemia. Peritoneal dialysis is effective in some patients.

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HYPERKALAEMIC PERIODIC PARALYSIS. Hyperkalaemic periodic paralysis is an inherited disorder in which sudden increases in plasma-potassium concentrations cause muscle paralysis, sometimes followed by myotonia. An acute attack may require intravenous calcium gluconate and insulin with glucose (see Hyperkalaemia, above). Inhalation of a beta$_2$ agonist such as salbutamol has been used to treat or abort attacks.[1,2] Diuretics such as acetazolamide, diclofenamide, or the thiazides are used prophylactically to reduce the frequency of attacks.[2-4]

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Hypokalaemia. Chronic hypokalaemia, a prolonged reduction of the plasma concentration of potassium, usually indicates a reduction in total body potassium. It may result from an inadequate intake, or gastrointestinal losses, for example in patients with secretory diarrhoeas, or from excessive renal losses as in hyperaldosteronism, Cushing's syndrome, or chronic metabolic alkalosis. Thiazides or loop diuretics increase urinary-potassium losses. Other drugs, notably corticosteroids and some antibacterials such as gentamicin, also have this effect. Hypokalaemia can also be caused by an increased cellular uptake of potassium rather than excess body losses. This may occur with drugs such as beta$_2$ agonists or xanthines, during insulin therapy, acute alkalosis, or possibly be induced by catecholamines after myocardial infarction. Hypokalaemia secondary to hypomagnesaemia (see p. 1776.3) can occur.

Hypokalaemia results in neuromuscular disturbances ranging from muscle weakness to paralysis and respiratory insufficiency and can also cause rhabdomyolysis, ECG abnormalities, and ileus. Chronic hypokalaemia may lead to renal tubular damage (hypokalaemic nephropathy). Hypokalaemia increases the risk of digoxin toxicity.

Treatment involves correcting any underlying disorder and replacement therapy with potassium salts. Oral potassium supplements are generally preferred but in severe hypokalaemia associated with cardiac arrhythmias, paralysis or diabetic ketoacidosis, parenteral therapy may be necessary. Potassium salts, usually potassium chloride, may be given by intravenous infusion but must be administered slowly to avoid causing hyperkalaemia and associated cardiactoxicity; plasma-potassium concentrations should be closely monitored and ECG monitoring may be required. The choice of salt for oral potassium replacement depends on co-existing acid–base and electrolyte disturbances. Potassium chloride is generally the drug of choice for the treatment of hypokalaemia in patients with metabolic alkalosis with hypochloraemia, whereas a salt such as the bicarbonate may be preferred in patients with hyperchloraemic acidosis as in some renal tubular acidoses. Hypokalaemia secondary to hypomagnesaemia requires magnesium replacement therapy.

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BARTTER'S SYNDROME. Bartter's syndrome is a set of closely related disorders thought to result from inherited defects in ion transport in various sections of the renal tubule.[1,2] Patients exhibit hyperplasia of the juxtaglomerular cells, hypokalaemia and metabolic alkalosis, and excess aldosterone, prostaglandin, and renin production. Symptoms are primarily those of the hypokalaemia, including muscle weakness; polyuria and enuresis, and growth retardation in children, can occur. In contrast to other hyperreninaemic states, patients do not have hypertension or oedema.

Treatment rarely completely corrects hypokalaemia. Potassium supplementation may be given, while a cyclooxygenase inhibitor such as indometacin, or an ACE inhibitor such as captopril, can produce benefit.[2] Spironolactone and propranolol have also been tried and magnesium salts may be given if there is hypomagnesaemia.[2]

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DIURETIC-INDUCED HYPOKALAEMIA. Reduced potassium concentrations may result from the use of potassium-losing diuretics, particularly thiazides and loop diuretics. Clinically significant hypokalaemia is unlikely at the doses used in hypertension and the routine use of potassium supplements is no longer recommended. However, the concomitant use of a potassium-sparing diuretic such as amiloride or, less usually, a potassium supplement, may be necessary in patients at risk of hypokalaemia (see also Hydrochlorothiazide, Effects on Electrolyte Balance, p. 1404.2).

HYPOKALAEMIC PERIODIC PARALYSIS. Hypokalaemic periodic paralysis is an inherited disorder in which episodes of hypokalaemia with muscle weakness or paralysis appear to be associated with a shift in potassium from the extracellular to the intracellular fluid. Acute attacks are treated with potassium, given orally or intravenously. Prophylaxis with acetazolamide[1,2] or diclofenamide[3] has been found to reduce the frequency and severity of attacks.

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Sodium Homoeostasis

Sodium is the principal cation in the extracellular fluid and is responsible for the maintenance of the extracellular fluid volume and osmolality. In addition, sodium is also involved in nerve conduction, muscle contraction, acid–base balance, and cell nutrient uptake. A usual plasma concentration of sodium would be expected to be within 135 to 145 mmol/litre.

Sodium homoeostasis is complex and closely associated with fluid balance. The osmolality and volume of the extracellular fluid are tightly regulated. Small changes in osmolality (plasma-sodium concentrations) are corrected by alteration of extracellular volume. This balance of plasma osmolality is achieved by the secretion or suppression of antidiuretic hormone (ADH; vasopressin), which primarily controls water excretion by the kidney. A tendency towards

hyponatraemia suppresses ADH secretion and promotes renal loss of water; an increase in ADH secretion increases water reabsorption by the renal distal tubules. Changes in extracellular volume will also affect ADH release independently of osmolality. In addition, changes in extracellular volume result in modulation of the renal excretion of sodium.

Total body sodium content is regulated by renal sodium excretion, which can vary widely depending on dietary intake. Various mechanisms are involved in controlling renal sodium excretion including the renin-angiotensin system, glomerular filtration rate, and natriuretic factors. A reduction in extracellular fluid volume leads to the production of angiotensin II which stimulates the secretion of aldosterone. Aldosterone promotes the reabsorption of sodium ions by the distal tubules. There may be significant effects on sodium homoeostasis if adrenal insufficiency or mineralocorticoid excess disturb this mechanism.

Hypernatraemia. Hypernatraemia is an abnormal rise in the plasma-sodium concentration with a simultaneous rise in plasma osmolality. It is generally associated with volume depletion when water intake is less than water losses through renal or extrarenal routes. The causes include impaired thirst, as in coma or essential hypernatraemia, osmotic diuresis (solute diuresis), as in diabetic ketoacidosis (see Diabetic Emergencies, p. 465.3) or after drugs such as mannitol, and excessive water losses, either from the kidney, as in diabetes insipidus (p. 2348.2), or extrarenally, for example because of excessive sweating or diarrhoea.

Hypernatraemia can also occur after excessive oral sodium intake (but this is uncommon) and after inappropriate use of intravenous sodium chloride.

The clinical manifestations of hypernatraemia are caused by the effect of increased plasma osmolality on the brain and include somnolence, confusion, respiratory paralysis, and coma. CNS symptoms are more severe when hypernatraemia develops rapidly. If there is volume depletion, other symptoms such as hypotension, tachycardia, and symptoms of circulatory insufficiency may occur as well. A high volume of dilute urine is seen in patients with abnormal renal water conservation, whereas a low volume of concentrated urine is expected in patients with impaired thirst or excessive extrarenal water loss.

Treatment of hypernatraemia usually requires water replacement, and drinking water may be sufficient for some patients. In more severe conditions, glucose 5% may be given by slow intravenous infusion. Alternatively, some recommend the use of sodium chloride 0.9% if volume depletion is severe. Care is required, as too rapid correction can induce cerebral oedema, particularly in chronic conditions.

If the total body sodium is too high, loop diuretics may be used to increase sodium excretion, with fluid losses being replaced by an infusion of glucose 5% and potassium chloride. It has also been suggested that dialysis may be necessary if there is significant renal impairment, if the patient is moribund, or if the serum-sodium concentration is greater than 200 mmol/litre.

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Hyponatraemia. Hyponatraemia, an abnormal fall in the plasma-sodium concentration, usually with a simultaneous fall in the plasma osmolality, is not uncommon, and may occur in diseases as diverse as heart failure, cirrhosis, adrenocortical insufficiency, hyperglycaemia, and AIDS.

The kidney is able to conserve sodium, and sodium depletion due to low salt intake is rare. Sodium depletion may occur if there are abnormal losses, either from the gut as a consequence of repeated diarrhoea and/or vomiting or from the kidney, for example, due to various renal disorders or the overuse of diuretics (see under Hydrochlorothiazide, Effects on Electrolyte Balance, p. 1404.3).

The most common cause of hyponatraemia is dilution. This may result from excessive fluid intake, for example the ingestion of large volumes of water in patients with primary polydipsia (psychogenic polydipsia). More often, however, it is a result of reduced water excretion, as in renal impairment or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH—p. 2351.2). Postoperative hyponatraemia is a frequent complication which can be exacerbated by the inappropriate intravenous use of hypotonic,[1] or even isotonic,[2] fluids.

Hyponatraemia due to sodium depletion in the presence of volume contraction may cause orthostatic hypotension and circulatory insufficiency. Dilutional hyponatraemia can be asymptomatic but headache, confusion, nausea, vomiting, somnolence, and weakness may occur. If severe, cerebral oedema may lead to respiratory arrest, convulsions, and coma. CNS symptoms are more common when the condition is acute.

Therapy is guided by the rate of development and degree of hyponatraemia, accompanying symptoms, and the state of water balance, and should also take into account the underlying cause. Mild asymptomatic hyponatraemia does not usually require specific therapy. Chronic mild to moderate sodium depletion, such as occurs in salt-losing bowel or renal disease, may be treated with oral sodium chloride supplements while ensuring adequate fluid intake.

When there is substantial volume depletion, volume replacement is necessary and intravenous sodium chloride 0.9% is often used.[3-5]

Chronic dilutional hyponatraemia, which is often asymptomatic, can generally be managed by correcting the underlying disease; water restriction may also be necessary and drugs that interfere with the action of ADH such as demeclocycline or lithium carbonate may be useful in SIADH.[3-6] Furosemide plus oral sodium chloride supplements have also been used.[7]

Acute symptomatic hyponatraemia (water intoxication) is generally associated with plasma-sodium concentrations below 120 mmol/litre and requires more aggressive therapy. This involves giving hypertonic or isotonic sodium chloride intravenously, often with a loop diuretic such as furosemide, especially if fluid overload is likely to be a problem.[4,6,7] The aim is to render the patient asymptomatic, with a plasma-sodium concentration of 120 to 130 mmol/litre; the plasma-sodium concentration should not be corrected to normal values nor should hypernatraemia be allowed to develop.[1,6,7] Plasma-sodium concentrations and the total body-water volume should be monitored throughout.

A rare neurological syndrome known as central pontine myelinolysis (osmotic demyelination) has been associated with the over-rapid correction of symptomatic hyponatraemia, particularly if the condition is well established. However, there is no consensus about the optimal administration of intravenous sodium chloride, and a number of regimens have been suggested. Generally, it has been recommended that the rate of correction of plasma-sodium should be 0.5 to 1 mmol/litre per hour, and not exceeding 2 mmol/litre per hour; maximum corrections have included 8 mmol/litre per 24 hours,[7] 12 mmol/litre per 24 hours or 18 mmol/litre over the first 48 hours,[6] and 20 mmol/litre in the first 48 hours.[1] Some[1,5] have given more specific recommendations depending on the severity of symptoms, suggesting that patients with severe symptoms, such as seizures, respiratory arrest, or neurogenic pulmonary oedema, require rapid correction in the first few hours, aiming for an initial increase in plasma-sodium of 2 to 4 mmol/litre, followed by a continuous infusion.

More recently, the vasopressin receptor antagonists conivaptan[5,6] and tolvaptan have become available for the management of euvolaemic and hypervolaemic hyponatraemia. Conivaptan is given intravenously whereas tolvaptan is given orally.

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Dialysis Solutions

Soluciones para diálisis; Растворы Для Диализа.

Pharmacopoeias. In *Eur.* (see p. vii), which includes separate monographs for solutions for haemodialysis, haemofiltration and haemodiafiltration, and peritoneal dialysis.

Dialysis and Haemofiltration

Dialysis and filtration solutions are solutions of electrolytes formulated in concentrations similar to those of extracellular fluid or plasma. They always contain sodium and chloride and bicarbonate or a bicarbonate precursor. In addition, they often contain calcium and magnesium, and rarely potassium. Glucose may be added as an osmotic agent. These solutions allow the removal of water and metabolites and the replacement of electrolytes.

In *haemodialysis*, the exchange of ions between the solution and the patient's blood is made across a semipermeable membrane, primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by a pressure gradient. Membranes are either derived from cellulose (e.g. cuprophane) or are synthetic. Bicarbonate rather than a bicarbonate precursor is increasingly preferred as the bicarbonate source in haemodialysis since the problems of precipitation of calcium and magnesium have been overcome by changes in dialysis technique. Acetate is still used in some dialysers, but is thought to have vasodilator and cardiodepressant actions, and may not be converted to bicarbonate fast enough for high-flux haemodialysis or in patients with liver disease. Haemodialysis solutions are provided in a sterile concentrated form for dilution with water before use; this water need not be sterile.

In *peritoneal dialysis*, the exchange is made across the membranes of the peritoneal cavity primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by the use of osmotic agents such as glucose. The problems of calcium bicarbonate precipitation have not yet been overcome, and lactate is generally used as the bicarbonate precursor. Peritoneal dialysis solutions must be sterile and apyrogenic.

In *haemofiltration*, blood is filtered rather than dialysed. Metabolites are removed by convective transport, and excess water by hydrostatic ultrafiltration. Fluid and electrolytes are replaced by direct intravenous infusion. Most haemofiltration solutions use acetate or lactate as the bicarbonate source. Haemofiltration solutions must be sterile and apyrogenic.

Uses and Administration

Dialysis and filtration procedures are used in renal failure to correct electrolyte imbalance, correct fluid overload, and remove metabolites. They also have a limited role in the treatment of overdosage and poisoning. The two main techniques are haemodialysis and peritoneal dialysis; haemofiltration is used less frequently. The choice of technique will depend on the condition to be treated, the clinical state of the patient, patient preference, and availability.

Haemodialysis is more efficient than peritoneal dialysis at clearing small molecules such as urea, whereas peritoneal dialysis may be better at clearing larger molecules. Haemodialysis is considered to be less physiological as it alternates periods of high clearance with periods of no clearance.

Haemodialysis is usually performed intermittently (often 3 times a week); a typical session takes 3 to 5 hours. More recently high-flux dialysers have been developed which have reduced the time required for dialysis sessions.

Peritoneal dialysis may be performed continuously or intermittently. Continuous ambulatory peritoneal dialysis (CAPD) is the most commonly used technique. Patients remain mobile, except during exchanges, and can carry out the procedure themselves. There is always dialysis solution in the peritoneal cavity, and this is drained and replaced 3 to 5 times daily. Continuous cycle peritoneal dialysis (CCPD) is similar, except that exchanges are carried out automatically overnight, and patients do not have to carry out any exchanges during the day. Intermittent peritoneal dialysis (IPD) requires the patient to be connected to a dialysis machine for 12 to 24 hours 2 to 4 times a week. During this time, dialysis solution is pumped into and out of the peritoneal cavity, with a dwell time of about 10 to 20 minutes.

Haemofiltration is usually performed as a continuous technique and, as it is not portable, its principal use is in intensive care units. It may also be used intermittently as an adjunct to haemodialysis in patients with excess fluid weight gain. Continuous arteriovenous or venovenous haemodiafiltration (CAVHD or CVVHD) combines dialysis and filtration.

Assessing serum concentrations of urea or creatinine before the next dialysis session is not a good measure of the adequacy of the dialysis, so various other measures have been developed including the urea reduction ratio and urea kinetic modelling. The use of such measures is more established for haemodialysis than for peritoneal dialysis.

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Acute renal failure. Acute renal failure (acute renal injury) is characterised by a rapid decline in kidney function, and has a variety of causes.[1-8] It is often classified by origin as *prerenal* (e.g. due to hypovolaemia such as that associated with shock, burns, or dehydration; congestive heart failure; or renal artery obstruction), *renal* (such as acute tubular necrosis or interstitial nephritis of various causes, including nephrotoxic drugs and infections), or *postrenal* (acute urinary tract obstruction). The prognosis depends on the underlying disease, which should be identified and treated if possible, but the mortality may still be as high as 60%, particularly after surgery or trauma and in patients who become oliguric. Management is essentially supportive in the hope that renal function will recover. Complications of acute renal failure include extracellular volume overload and hyponatraemia, hyperkalaemia, metabolic acidosis, hyperphosphataemia and hypocalcaemia. Those complications requiring urgent treatment, often including the use of dialysis, are severe hyperkalaemia (p. 1777.1), pulmonary oedema, pericarditis, and severe metabolic acidosis (p. 1775.2). The use of dialysis before clinical signs of uraemia is a matter of debate since it does not appear to hasten recovery *per se*,[1] but all save the shortest episodes of acute renal failure will require some form of renal replacement therapy with dialysis or filtration. Intermittent haemodialysis and peritoneal dialysis are both used, but the newer haemofiltration techniques have theoretical advantages in terms of volume control and cardiovascular stability, and are increasingly preferred.[2,9,10]

Numerous drugs have been tried in attempts to attenuate renal injury or hasten recovery in patients with acute tubular necrosis due to ischaemia or nephrotoxins.[1,5,11,12] These include drugs to increase renal blood flow (e.g. low-dose dopamine, atrial natriuretic peptide, or prostaglandins), drugs to increase urine flow and protect the epithelial cells (mannitol and loop diuretics, calcium-channel blockers), or the use of chelating agents or antidotes against specific nephrotoxins. Consistent clinical benefit has not, however, been shown and some would argue against the routine use of such drugs.[4]

Acute renal failure is reversible in about 95% of patients who survive the complications. A few patients who survive acute renal failure will require long-term dialysis or kidney transplantation (p. 1935.2).

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Chronic renal failure. Chronic renal failure is the irreversible, usually progressive, loss of renal function that eventually results in end-stage renal disease (ESRD) and the need for renal replacement therapy (dialysis or renal transplantation). The rate of decline in renal function is generally constant for each patient and is usually monitored by measuring serum-creatinine concentrations as an indirect index of the glomerular filtration rate (GFR). In its early stages when the patient is asymptomatic, progressive loss of renal function is described as diminished renal reserve or chronic renal insufficiency. When the limits of renal reserve have been exceeded and symptoms become apparent, it is termed chronic renal failure or overt renal failure. When renal function is diminished to such an extent that life is no longer sustainable (GFR less than 5 mL/minute), the condition is termed ESRD or uraemia. Many diseases can lead to ESRD, the most common being diabetic nephropathy (p. 465.1), glomerulonephritis (p. 1604.3), and hypertension (p. 1251.1).

The management of patients with chronic renal failure prior to ESRD involves measures to conserve renal function and compensate for renal insufficiency. Methods to slow the progression of renal failure include the treatment of hypertension (p. 1251.1), reduction of proteinuria, and the reduction of hyperlipidaemia (p. 1248.1). ACE inhibitors (p. 1284.1) or angiotensin II receptor antagonists (see Losartan, p. 1423.3) are used for the reduction of proteinuria and the control of hypertension. Dietary protein restriction (see Renal Failure, p. 2043.3) has also been used for control of proteinuria, but conclusive evidence for a renal protective effect is lacking. Anaemia (p. 1142.3), hyperphosphataemia (p. 1776.3), secondary hyperparathyroidism (p. 1170.3), and renal osteodystrophy (p. 1170.1) often require active treatment. Nephrotoxic drugs, including NSAIDs, should be avoided.

The choice between haemodialysis, peritoneal dialysis, and organ transplantation is considered, and the patient prepared, before it is actually required. In patients for whom transplantation is the preferred option, dialysis may still be required while waiting for a kidney. Kidney transplantation is discussed on p. 1935.2. There are differences between countries in the choice of dialysis technique for patients with ESRD. For example, in-centre haemodialysis is used in about 80% of patients in the USA, whereas CAPD is used in over 50% of patients in the UK. Overall survival appears to be similar between the 2 techniques, but more patients on CAPD will eventually require a change to another dialysis method because of treatment failure.

Unlike renal transplant patients, dialysis patients still require replacement therapy with hormones that are usually produced by the kidney. Thus, recombinant erythropoietin and hydroxylated vitamin D analogues are commonly given.

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Electrolyte disturbances. Haemodialysis with magnesium-free dialysis solution has been used to remove magnesium from the body in severe hypermagnesaemia (p. 1776.2). Similarly, haemodialysis, and sometimes peritoneal dialysis, has been used in treating hypercalcaemia (p. 1776.1), hyperkalaemia (p. 1777.1), hypernatraemia (p. 1778.1), and hyperphosphataemia (p. 1776.3).

Overdosage and poisoning. Haemodialysis, or less often peritoneal dialysis, can be used to remove some substances from the body after overdosage or poisoning. Substances most readily removed have a low molecular weight, low volume of distribution, low protein binding, high water solubility, and high renal clearance. Examples of agents for which haemodialysis may have a role in the treatment of severe overdosage include alcohol (p. 1734.1), ethylene glycol (p. 2500.3), methyl alcohol (p. 2196.3), lithium (p. 430.2), and salicylates such as aspirin (p. 24.2). Dialysis may be particularly important when poisoning with these agents is complicated by renal failure.

Adverse Effects

Adverse effects occurring during *haemodialysis* include nausea, vomiting, hypotension, muscle cramps, and air embolus. Effects related to vascular access include infection, thrombosis, and haemorrhage. Adverse effects occurring during *haemofiltration* are similar to those for haemodialysis.

The most common adverse effects associated with *peritoneal dialysis* include peritonitis, hernias, hyperglycaemia, protein malnutrition, and catheter complications.

Long-term complications in dialysed patients, some of which may relate to renal failure itself, include haemodialysis-related amyloidosis, acquired cystic kidney disease, and accelerated atherosclerosis. Dialysis dementia is a special hazard of aluminium overload. Long-term peritoneal dialysis results in progressive structural changes to the peritoneal membrane ultimately resulting in dialysis failure.

References.
1. Himmelfarb J. Hemodialysis complications. *Am J Kidney Dis* 2005; **45:** 1122–31.

Aluminium overload. Accumulation of aluminium in patients on dialysis may result in dialysis dementia, anaemia, and aluminium-related bone disease (see also p. 2439.2). Sources of aluminium include the water used for preparation of dialysis fluids and aluminium-containing phosphate binders used in treating renal osteodystrophy (p. 1170.1). It is therefore important that water used for the preparation of dialysis fluids has a low aluminium concentration; Ph. Eur. 8 specifies a limit for aluminium of 10 micrograms/litre. Non-aluminium-containing phosphate binders such as calcium acetate or calcium carbonate may be preferred for long-term therapy. Aluminium overload in patients on dialysis has been treated with desferrioxamine (p. 1544.3).

Copper toxicity. Liver and haematological toxicity has occurred as a result of absorption of copper from dialysis fluids (see Adverse Effects of Copper, p. 2058.1).

Haemodialysis-induced cramp. Muscle cramps (see Muscle Spasms, p. 2014.1) commonly occur during haemodialysis procedures and between sessions. Cramping usually affects the lower extremities, causing severe pain, and is a common reason for avoiding or stopping haemodialysis. The aetiology is not clear but possibly related to hypovolaemia, hypotension, changes in plasma osmolality, and hyponatraemia.[1]

Non-pharmacological measures to treat cramp during haemodialysis include the local application of moist heat and massage, and stretching the affected muscle. If present, hypotension should be corrected, by slowing or stopping ultrafiltration, and possibly giving isotonic or hypertonic sodium chloride infusion.[1] Midodrine has also been used for the management of hypotension.[2] Hypertonic solutions of sodium chloride or glucose may be used to raise plasma osmolality; mannitol has also been used but may accumulate in the extracellular space.[1]

Quinine has been widely used for the prevention of haemodialysis-induced cramp, but it can cause serious adverse effects and such use has been discouraged.[1] Other treatments that have been tried as prophylaxis include carnitine, creatine, and vitamins C and E. However, information on these is limited and data on long-term efficacy and safety are lacking.[1] There is also limited evidence that a traditional herbal medicine, shao-yao-gan-cao-tang (shakuyaku-kanzo-to), comprising extracts of peony and liquorice roots, may be of benefit for both prevention and treatment of haemodialysis-induced cramp.[1]

1. Kobrin SM, Berns JS. Quinine—a tonic too bitter for hemodialysis-associated muscle cramps? *Semin Dial* 2007; **20:** 396–401.
2. Prakash S, *et al.* Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; **19:** 2553–8.

Hypersensitivity. For anaphylactic reactions associated with the use of ethylene oxide for the disinfection of dialysis equipment, see p. 1751.3.

Infections. Patients undergoing haemodialysis are at risk of infections from microbial contamination of dialysis fluid, and from inadequate care of vascular access sites. Maximum microbial counts and limits for endotoxins have been specified for water used in dialysis fluids. Bicarbonate-based dialysis solutions are more susceptible to microbial growth than acetate-based solutions.

Peritonitis is common in patients receiving peritoneal dialysis. The risk of infection may be minimised by using disconnect systems, good aseptic technique, and by good care of catheters. Treatment of bacterial peritonitis requires intraperitoneal antibacterials, which are usually added to the dialysis fluid (see PD Peritonitis, under Peritonitis, p. 197.2).

Dialysis equipment should be regularly disinfected with agents such as formaldehyde (p. 1752.2) or ethylene oxide (p. 1751.2), but for mention of ethylene oxide anaphylactoid reactions, see p. 1751.3.

Metabolic complications. The high concentrations of glucose in peritoneal dialysis solutions required to form an osmotic gradient can lead to weight gain, hyperglycaemia, hyperlipidaemia, and increased protein loss. Alternative osmotic agents such as icodextrin (p. 2059.2) can be used, and amino acid-based solutions are also available.

References.
1. Burkart J. Metabolic consequences of peritoneal dialysis. *Semin Dial* 2004; **17:** 498–504.

Precautions

Peritoneal dialysis is not appropriate for patients with abdominal sepsis, previous abdominal surgery, or severe inflammatory bowel disease.

Haemodialysis should be used with caution in patients with unstable cardiovascular disease or active bleeding. During haemodialysis and haemofiltration, heparin (see Extracorporeal Circulation, p. 1398.2) or epoprostenol (Uses, p. 1375.1) are required to prevent clotting of the blood in the extracorporeal circuit.

Dialysis solutions should be warmed to body temperature with dry heat because wet heat carries a risk of microbial contamination.

Interactions

The effects of dialysis and filtration procedures on drug concentrations in the body can be complex. More drug may be removed by one dialysis technique than another. In general, drugs of low molecular weight, high water solubility, low volume of distribution, low protein binding, and high renal clearance are most extensively removed by dialysis. For example, aminoglycosides are extensively removed by dialysis procedures, and extra doses may be needed to replace losses. Specific drug dosage adjustments for dialysis procedures may be used where these are known. For drugs where the effect of dialysis is unknown, it is usual to give maintenance doses after dialysis. Dialysis has been used to remove some drugs in the treatment of overdosage and poisoning (see p. 1779.2).

Dialysis-induced changes in fluids and electrolytes have the potential to alter the effects of some drugs. For example, hypokalaemia predisposes to digoxin toxicity.

In patients undergoing peritoneal dialysis, drugs such as insulin and antibacterials may be added to the dialysis fluid. Consideration should be given to the possibility of adsorption of drugs onto the PVC bags.

References.
1. Aronson JK. The principles of prescribing in renal failure. *Prescribers' J* 1992; **32:** 220–31.
2. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. *J Antimicrob Chemother* 1995; **36:** 773–80.
3. Aronoff GR, *et al. Drug prescribing in renal failure: dosing guidelines for adults.*4th ed. Philadelphia: American College of Physicians, 1999.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Solutions for Haemodialysis; Solutions for Haemofiltration and for Haemodiafiltration; Solutions for Peritoneal Dialysis.

Oral Rehydration Solutions

Soluciones de rehidratación oral; Растворы Для Пероральной Регидратации.

Oral rehydration solutions have 4 main constituents:
- electrolytes—typically sodium chloride and potassium chloride
- a bicarbonate source to correct or prevent metabolic acidosis, such as sodium bicarbonate or sodium citrate
- water to replace fluid losses
- a carbohydrate source to maximise absorption of fluid and electrolytes—typically glucose, although cereal-based formulations may also be used.

They are most commonly available as oral powders (oral rehydration salts) that are reconstituted with water before use, but effervescent tablets and ready-to-use oral solutions are also available.

Uses and Administration

Oral rehydration solutions are used for oral replacement of electrolytes and fluids in patients with dehydration, particularly that associated with acute diarrhoea of various aetiologies (p. 1805.2).

The dosage of oral rehydration solutions should be tailored to the individual based on body-weight and the stage and severity of the condition. The initial aim of treatment is to rehydrate the patient, and, subsequently, to maintain hydration by replacing any further losses due to continuing diarrhoea and vomiting and normal losses from respiration, sweating, and urination. Initial rehydration should be rapid, over 3 to 4 hours, unless the patient is hypernatraemic, in which case rehydration over 12 hours is appropriate.

For adults, a usual dose of 200 to 400 mL of oral rehydration solution for every loose motion has been suggested.

For dosage in children, see below.

Administration in children. Fluid and electrolytes may be replaced orally in children who are dehydrated, for example due to diarrhoea, using a dose of 200 mL of oral rehydration solution for every loose motion. In infants, the dose is 1 to 1.5 times their usual feed volume. Normal feeding can continue after the initial fluid deficit has been corrected. Breast feeding should continue between administrations of oral rehydration solution.

Sodium content and osmolarity. The original standard WHO oral rehydration solution contained 90 mmol/litre of sodium and 111 mmol/litre of glucose.[1-3] While it has been used safely and effectively,[4] it does not reduce the volume or duration of diarrhoea,[3] and solutions with reduced sodium content and osmolarity have been suggested to be more effective.[1,2] WHO and UNICEF now recommend a solution containing 75 mmol/litre of sodium and 75 mmol/litre of glucose, with a reduced osmolarity.[4] However, there have been concerns that the reduced sodium content of this formulation may increase the risk of hyponatraemia in patients with cholera,[3,5,6] and especially in adults.[4] WHO and UNICEF have stated that hyponatraemia may also occur with the standard WHO formulation, and that there is no evidence to suggest that this transient hyponatraemia has had significant adverse clinical consequences for cholera patients.[4] Solutions containing less sodium have been recommended in more developed countries: 60 mmol/litre in Europe,[7] and 45 to 90 mmol/litre in the USA.[8]

For discussion of modified formulations of oral rehydration solutions in the treatment of diarrhoea, including the use of cereal-based and low osmolarity preparations, see oral rehydration therapy under Diarrhoea, p. 1805.2.

1. Hahn S, *et al.* Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/06/05).
2. CHOICE Study Group. Multicenter, randomized, double-blind clinical trial to evaluate the efficacy and safety of a reduced osmolarity oral rehydration salts solution in children with acute watery diarrhea. *Pediatrics* 2001; **107:** 613–18.
3. Fuchs GJ. A better oral rehydration solution? An important step, but not a leap forward. *BMJ* 2001; **323:** 59–60.
4. Anonymous. New oral rehydration solution adopted by WHO and UNICEF. *WHO Drug Inf* 2004; **18:** 138–40.
5. Hirschhorn N, *et al.* Formulation of oral rehydration solution. *Lancet* 2002; **360:** 340–1.
6. Cash R, *et al.* Oral rehydration and hyponatraemia. *Lancet* 1999; **354:** 1733–4.
7. Booth I, *et al.* Recommendations for composition of oral rehydration solutions for the children of Europe: report of an ESPGAN working group. *J Pediatr Gastroenterol Nutr* 1992; **14:** 113–15.
8. King CK, *et al.* Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR* 2003; **52** (RR-16): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5216.pdf (accessed 20/08/10)

Oral versus intravenous rehydration. Although intravenous rehydration is advised for patients with the most severe dehydration (see Diarrhoea, p. 1805.2) it is also widely used in some countries in the management of less severe degrees of fluid loss.[1,2] However, a meta-analysis of 16 randomised controlled studies in children with gastroenteritis (5 of which included children with severe dehydration) found that oral or nasogastric rehydration with an appropriate rehydration solution was at least as effective as intravenous rehydration in terms of weight gain and intestinal losses, and was associated with a lower incidence of adverse effects and a reduced length of hospital stay.[3] The authors concluded that there was no evidence to support the ongoing use of intravenous rehydration in most cases of childhood gastroenteritis.

1. Elliott EJ, *et al.* Pre-admission management of acute gastroenteritis. *J Paediatr Child Health* 1996; **32:** 18–21.
2. Ford-Jones EL, *et al.* Hospitalization for community-acquired, rotavirus-associated diarrhea: a prospective, longitudinal, population-based study during the seasonal outbreak. *Arch Pediatr Adolesc Med* 2000; **154:** 578–85.
3. Fonseca BK, *et al.* Enteral vs intravenous rehydration therapy for children with gastroenteritis: a meta-analysis of randomized controlled trials. *Arch Pediatr Adolesc Med* 2004; **158:** 483–90.

Adverse Effects

Vomiting can occur after taking oral rehydration solution, and may be an indication that it was given too quickly. If vomiting occurs, administration should be halted for 10 minutes then resumed in smaller, more frequent, amounts.

The risk of hypernatraemia or overhydration with oral rehydration solutions is low in patients with normal renal function. Overdosage of oral rehydration solutions in patients with renal impairment may lead to hypernatraemia and hyperkalaemia.

Precautions

Oral rehydration salts or effervescent tablets should be reconstituted only with water and at the volume stated. Fresh drinking water is generally appropriate, but freshly boiled and cooled water is preferred when the solution is for infants or when drinking water is not available. The solution should not be boiled after it is prepared. Other ingredients such as sugar should not be added. Unused solution should be stored in a refrigerator and discarded within 24 hours of preparation.

Oral rehydration solutions are not appropriate for patients with gastrointestinal obstruction, oliguric or anuric renal failure, or when parenteral rehydration therapy is indicated as in severe dehydration or intractable vomiting.

Preparations

Pharmacopoeial Preparations
BP 2014: Oral Rehydration Salts;
USP 36: Oral Rehydration Salts;
WHO/UNICEF: Oral Rehydration Salts.

Bicarbonate

Bicarbonato; Бикарбонат.
UNII — HN1ZRA3Q20.

Description. Bicarbonate is an alkalinising agent given as bicarbonate-containing salts (sodium or potassium bicarbonate) or bicarbonate-producing salts (acetate, citrate, or lactate salts). Allowance should be made for the effect of the cation.

Incompatibility. Bicarbonate-producing or bicarbonate-containing solutions have been reported to be incompatible with a wide range of drugs. In many cases this incompatibility is a function of the alkaline nature of the bicarbonate solution. Precipitation of insoluble carbonates may occur, as may production of gaseous carbon dioxide when the bicarbonate ion is reduced by acidic solutions.

Potassium Bicarbonate

Bicarbonato potásico; E501; Hidrogenocarbonato de potasio; Hydrogenuhličitan draselný; Kalii Hydrocarbonas; Kalii Hydrogenocarbobnas; Kalii hydrogenocarbonas; Kaliovandenilio karbonatas; Kálium-hidrogén-karbonát; Kaliumhydrogencarbonat; Kaliumvätekarbonat; Kaliumvetykarbonaatti; Monopotassium Carbonate; Potasio, bicarbonato de; Potassium, bicarbonate de; Potassium Hydrogen Carbonate; Potasu wodorowęglan; Potasyum Bikarbonat; Калий Бикарбонат; Бикарбонат Калия; Гидрокарбонат Калия; Двууглекислый Калий.
$KHCO_3$=100.1
CAS — 298-14-6.
ATC — A12BA04.
ATC Vet — QA12BA04.
UNII — HM5Z15LEBN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Potassium Hydrogen Carbonate; Potassium Bicarbonate BP 2014). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. When heated in the dry state or in solution, it is gradually converted to potassium carbonate. A freshly prepared 5% solution in water has a pH of not more than 8.6.

USP 36: (Potassium Bicarbonate). Colourless, odourless, transparent monoclinic prisms or white granular powder. Freely soluble in water; practically insoluble in alcohol. Its solutions are neutral or alkaline to phenolphthalein.

Equivalence. Each g of potassium bicarbonate represents about 10 mmol of potassium and of bicarbonate. Potassium bicarbonate 2.56 g is equivalent to about 1 g of potassium.

Potassium Citrate

Citrato tripotásico; Citronan draselný monohydrát; E332; Kalii citras; Kalii Citras Monohydricus; Kalio citratas; Kaliumcitrat; Kaliumsitraatti; Potasio, citrato de; Potassium, citrate de; Potasu cytrynian; Potasyum Sitrat; Trikálium-citrát; Tripotassium Citrate; Калий Цитрат; Лимоннокислый Калий.
Tripotassium 2-hydroxypropane-1,2,3-tricarboxylate monohydrate.
$C_6H_5K_3O_7,H_2O$=324.4
CAS — 866-84-2 (anhydrous potassium citrate); 6100-05-6 (potassium citrate monohydrate).
ATC — A12BA02.
ATC Vet — QA12BA02.
UNII — EE90ONI6FF (potassium citrate monohydrate); 86R1NVR0HW (anhydrous potassium citrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Potassium Citrate). Transparent, hygroscopic crystals or a white or almost white granular powder. Very soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Potassium Citrate). Transparent crystals or a white granular powder. It is odourless and is deliquescent in moist air. Soluble 1 in 1 of water and 1 in 2.5 of glycerol; almost insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of potassium citrate (anhydrous) represents about 9.8 mmol of potassium and 3.26 mmol of citrate. Each g of potassium citrate (monohydrate) represents about 9.3 mmol of potassium and 3.08 mmol of citrate. Potassium citrate (monohydrate) 2.77 g is equivalent to about 1 g of potassium.

Sodium Acetate

Acetato sódico; E262; Natrii Acetas; Natrii acetas trihydricus; Natrio acetatas trihidratas; Natrium Aceticum; Nátrium-acetát; Natriumacetat trihydrat; Natriumasetaattitrihydraatti; Octan sodný trihydrát; Sodio, acetato de; Sodium (acétate de) trihydraté; Sodu octan; Ацетат Натрия; Уксуснокислый Натрий.

$CH_3.CO_2Na,3H_2O$=136.1

CAS — 127-09-3 (anhydrous sodium acetate); 6131-90-4 (sodium acetate trihydrate).

ATC — B05XA08.

ATC Vet — QB05XA08.

UNII — NVG71ZZ7P0 (anhydrous sodium acetate); 4550K0SC9B (sodium acetate trihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

US also allows the anhydrous form.

Ph. Eur. 8: (Sodium Acetate Trihydrate). Colourless crystals. Very soluble in water; soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Store in airtight containers.

USP 36: (Sodium Acetate). It contains three molecules of water of hydration or is anhydrous. Colourless, transparent crystals, or a white, granular crystalline powder, or white flakes. It is odourless or has a faint acetous odour. It is efflorescent in warm dry air. Soluble 1 in 0.8 of water, 1 in 0.6 of boiling water, and 1 in 19 of alcohol. pH of a solution in water containing the equivalent of 3% of anhydrous sodium acetate is between 7.5 and 9.2. Store in airtight containers.

Equivalence. Each g of sodium acetate (anhydrous) represents about 12.2 mmol of sodium and of acetate. Each g of sodium acetate (trihydrate) represents about 7.3 mmol of sodium and of acetate. Sodium acetate (anhydrous) 3.57 g is equivalent to about 1 g of sodium. Sodium acetate (trihydrate) 5.92 g is equivalent to about 1 g of sodium.

Sodium Acid Citrate

Disodium Hydrogen Citrate; Disodu wodorocytrynian; E331; Hidrogenocitrato de disodio; Natrium Citricum Acidum; Sodio, citrato ácido de; Цитрат Натрия Двузамещенный.

$C_6H_6Na_2O_7,1½H_2O$=263.1

CAS — 144-33-2.

UNII — 6FO62KCQ7A.

Pharmacopoeias. In *Br.*

BP 2014: (Sodium Acid Citrate). A white, odourless or almost odourless, powder. Freely soluble in water; practically insoluble in alcohol. A 3% solution in water has a pH of 4.9 to 5.2.

The BP gives Disodium Hydrogen Citrate as an approved synonym.

Equivalence. Each g of sodium acid citrate (sesquihydrate) represents about 7.6 mmol of sodium and 3.8 mmol of citrate. Sodium acid citrate (sesquihydrate) 5.72 g is equivalent to about 1 g of sodium.

Sodium Bicarbonate

Sodio, hidrogenocarbonato de; Baking Soda; Bicarbonato sódico; E500; Hidrogenocarbonato de sodio; Hydrogenuhličitan sodný; Monosodium Carbonate; Natrii Bicarbonas; Natrii Hydrogenocarbonas; Natrio-vandenilio karbonatas; Nátrium-hidrogén-karbonát; Natriumhydrogencarbonat; Natriumvätekarbonat; Natriumvetykarbonaatti; Sal de Vichy; Sodium Acid Carbonate; Sodium, bicarbonate de; Sodium Hydrogen Carbonate; Sodu wodoroweglan; Sodyum Bikarbonat; Питьевая Сода; Бикарбонат Натрия; Гидрокарбонат Натрия; Двууглекислый Натрий.

$NaHCO_3$=84.01

CAS — 144-55-8.

ATC — B05CB04; B05XA02.

ATC Vet — QB05CB04; QB05XA02; QG04BQ01.

UNII — BMDF5V39QO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Hydrogen Carbonate; Sodium Bicarbonate BP 2014). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. The pH of a freshly prepared 5% solution in water is not more than 8.6. When heated in the dry state or in solution, it gradually changes into sodium carbonate.

USP 36: (Sodium Bicarbonate). A white crystalline powder that slowly decomposes in moist air. Soluble 1 in 12 of water; insoluble in alcohol. Its solutions, when freshly prepared with cold water, without shaking, are alkaline to litmus; alkalinity increases on standing, agitation, or heating.

Equivalence. Each g of sodium bicarbonate (anhydrous) represents about 11.9 mmol of sodium and of bicarbonate. Sodium bicarbonate 3.65 g is equivalent to about 1 g of sodium.

Sodium Citrate

Citrato trisódico; Citronan sodný dihydrát; E331; Natrii Citras; Natrii Citras Dihydricus; Natrio citratas; Natriumcitrat; Natriumsitraatti; Sodio, citrato de; Sodium, citrate de; Sodu cytrynian; Sodyum Sitrat; Trinátrium-citrát; Trisodium Citrate; Цитрат Натрия Трёхзамещенный.

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate.

$C_6H_5Na_3O_7,2H_2O$=294.1

CAS — 68-04-2 (anhydrous sodium citrate); 6132-04-3 (sodium citrate dihydrate).

ATC — B05CB02.

ATC Vet — QB05CB02.

UNII — RS7A450LGA (anhydrous sodium citrate); 1Q73Q2JULR (sodium citrate); B22547B95K (sodium citrate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.*

Int. and *US* specify anhydrous or dihydrate.

Ph. Eur. 8: (Sodium Citrate). A white or almost white, crystalline powder or white or almost white, granular crystals; slightly deliquescent in moist air. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Sodium Citrate). It is anhydrous or contains two molecules of water of hydration. Colourless crystals, or a white crystalline powder. The hydrous form is soluble 1 in 1.5 of water and 1 in 0.6 of boiling water; insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of sodium citrate (anhydrous) represents about 11.6 mmol of sodium and 3.9 mmol of citrate. Each g of sodium citrate (dihydrate) represents about 10.2 mmol of sodium and 3.4 mmol of citrate. Sodium citrate (anhydrous) 3.74 g is equivalent to about 1 g of sodium. Sodium citrate (dihydrate) 4.26 g is equivalent to about 1 g of sodium.

Storage. Sterilised solutions when stored may cause separation of particles from glass containers and solutions containing such particles must not be used.

Sodium Lactate

E325; Lactato de sodio; Lactato sódico; Natrii Lactatis; Natriumlaktaatti; Natriumlaktat; Sodium, lactate de; Лактат Натрия; Молочнокислый Натрий.

Sodium 2-hydroxypropionate.

$C_3H_5NaO_3$=112.1

CAS — 72-17-3.

UNII — TU7HW0W0QT (sodium lactate); P2Y1C6M9PS (L-sodium lactate); FM1Z1J8373 (D-sodium lactate).

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), and *US* include preparations of sodium lactate.

Ph. Eur. 8: (Sodium Lactate Solution). It contains a minimum declared content of 50% w/w of sodium lactate and is a mixture of the two enantiomers in about equal proportions. Sodium (*S*)-Lactate Solution contains a minimum of 50% w/w of sodium lactate, not less than 95% of which is the (*S*)-enantiomer. The solutions are clear, colourless, slightly syrupy liquids. Miscible with water and with alcohol. pH 6.5 to 9.0.

USP 36: (Sodium Lactate Solution). It is an aqueous solution containing at least 50% sodium lactate. A clear, colourless or practically colourless, slightly viscous liquid, odourless or having a slight, not unpleasant, odour. Miscible with water. pH between 5.0 and 9.0. Store in airtight containers.

Equivalence. Each g of sodium lactate (anhydrous) represents about 8.9 mmol of sodium and of lactate. Sodium lactate (anhydrous) 4.88 g is equivalent to about 1 g of sodium.

Uses and Administration

Bicarbonate-providing salts are alkalinising agents used for a variety of purposes including the correction of metabolic acidosis, alkalinisation of the urine, and as antacids.

When an alkalinising agent is indicated for treating acute or chronic **metabolic acidosis** (p. 1775.2), sodium bicarbonate is usually used. In conditions when acute metabolic acidosis is associated with tissue hypoxia, such as *cardiac arrest* and *lactic acidosis*, the role of such alkalinising agents is controversial (see p. 1775.2, and for guidelines on advanced cardiac life support, see Cardiac Arrest, p. 1268.3). Sodium lactate has been given as an alternative to sodium bicarbonate in acute metabolic acidosis, but is no longer recommended because of the risk of precipitating lactic acidosis. In *chronic hyperchloraemic acidosis* associated with potassium deficiency, potassium bicarbonate may be preferred to sodium bicarbonate. The citrate salts of potassium or sodium have also been used as alternatives to sodium bicarbonate in treating chronic metabolic acidosis resulting from *renal disorders*. Sodium bicarbonate, lactate and acetate, and potassium acetate are used as bicarbonate sources in *dialysis fluids* (p. 1778.2).

The dose of bicarbonate required for the treatment of acidotic states must be calculated on an individual basis, and is dependent on the acid–base balance and electrolyte status of the patient. In the treatment of chronic acidosis, bicarbonate has been given orally and doses providing 57 mmol (4.8 g sodium bicarbonate) or more daily may be required. In severe acidosis, sodium bicarbonate has been given intravenously by continuous infusion usually as a 1.26% (150 mmol/litre) solution or by slow intravenous injection of a stronger (hypertonic) solution of up to 8.4% (1000 mmol/litre) sodium bicarbonate (but see the discussion on metabolic acidosis, p. 1775.2). For the correction of acidosis during advanced cardiac life support procedures, doses of 50 mmol of sodium bicarbonate (50 mL of an 8.4% solution) may be given intravenously to adults. Frequent monitoring of serum-electrolyte concentrations and acid–base status is essential during treatment of acidosis.

Sodium bicarbonate may be used in the management of **hyperkalaemia** (p. 1777.1) to promote the intracellular uptake of potassium and correct associated acidosis, although there is some debate as to its value. Some sources suggest that 50 to 100 mL of an 8.4% solution may be given in severe hyperkalaemia accompanied by acidosis, although more dilute solutions have been used, and care is required, particularly if there is accompanying renal impairment.

Sodium bicarbonate, sodium citrate, and potassium citrate cause **alkalinisation of the urine**. They may therefore be given to relieve discomfort in mild *urinary-tract infections* (p. 213.1) and to prevent the development of uric-acid renal calculi in the initial stages of *uricosuric* therapy for hyperuricaemia in chronic gout (for example, see Precautions for Probenecid, p. 608.1). In both cases, they are given with a liberal fluid intake, usually orally, in divided doses of up to about 10 g daily. Sodium bicarbonate may also be used to alkalinise the urine in *acute poisoning* with weakly acidic drugs such as salicylates and phenoxyacetate pesticides; use with a diuretic for 'forced alkaline diuresis' is no longer recommended.

When given orally, sodium bicarbonate and potassium bicarbonate neutralise acid secretions in the gastrointestinal tract and sodium bicarbonate in particular is therefore frequently included in **antacid** preparations (p. 1803.1). To relieve *dyspepsia* doses of about 1 to 5 g of sodium bicarbonate in water have been taken when required. Sodium citrate has been widely used as a 'clear' (non-particulate) antacid, usually with an H_2-antagonist, for the *prophylaxis of acid aspiration* associated with anaesthesia (p. 1804.2). Sodium bicarbonate is also used in various preparations for *double-contrast radiography* where production of gas (carbon dioxide) in the gastrointestinal tract is necessary. Similarly, solutions containing sodium bicarbonate or citrate have been used to treat acute *oesophageal impaction*.

Sodium bicarbonate and sodium or potassium citrate are used as buffering or alkalinising agents in *pharmaceutical formulation*. Sodium or potassium bicarbonate and anhydrous sodium citrate are used in effervescent tablet formulations.

Individual salts also have **other specific uses**. A 5% solution of sodium bicarbonate can be administered as ear drops to soften and remove *ear wax* (see under Docusates, p. 1836.3). Sodium bicarbonate injection has been used to treat *extravasation of anthracycline antineoplastics* (p. 731.3) although as mentioned in Adverse Effects, p. 1782.2, hypertonic solutions may themselves cause necrosis.

Sodium citrate has anti-clotting properties and is used, as sodium acid citrate, with other agents in solutions for the anticoagulation and preservation of blood for *transfusion* purposes. Similarly, sodium citrate 3% irrigation may be useful for the dissolution of *blood clots in the bladder* as an alternative to sodium chloride 0.9%. Enemas containing sodium citrate are given rectally as *osmotic laxatives*. Sodium citrate is also a common ingredient in *cough* mixtures. Eye drops containing sodium citrate 10% have been used in the treatment of chemical *eye burns* (p. 1782.1); they may be used with potassium ascorbate eye drops (see Uses of Vitamin C Substances, p. 2111.1).

Eye disorders. Sodium bicarbonate is used in the management of blepharitis, an inflammation of the margin of the eyelids with various causes. It may be allergic in nature or associated with seborrhoea of the scalp. Infection of the eyelids can produce ulcerative blepharitis, a condition characterised by the formation of yellow crusts which may glue the eyelashes together. Parasites occasionally cause blepharitis. The condition is first treated by cleaning the eyes and eyelids with sodium bicarbonate solution or a suitable bland eye lotion; simple eye ointment or diluted baby shampoo can also be used to soften crusts to aid removal. If an infection is present, antibacterials may be required (p. 182.1). Long-term management consists of daily cleansing of the lid margins with a bland eye lotion.

EYE BURNS. Both heat and chemicals can burn the eye, causing damage to the conjunctiva, cornea, and underlying structures. Burn severity may be influenced by the amount of burning substance that enters the eye and the duration of contact, its temperature and impact force, whether it is a liquid or solid, its pH, and osmolarity.[1,2] Hydrofluoric acid, sulfurous acid, and alkalis readily penetrate the corneal stroma.[2] Immediate irrigation is essential, and a duration of at least 15 to 30 minutes is recommended; it may need to be repeated periodically. Water or sodium chloride 0.9% solution may be used initially, but because they are hypotonic to the eye there can be an increased uptake of the fluid and diffusion of the burning substance into the deeper layers of the cornea, resulting in oedema. To reduce this risk solutions with higher osmolarities have been suggested, if available, and include balanced salt solution, buffered solutions such as lactated Ringer's solution, and commercial decontamination preparations with amphoteric and chelating properties.[1,2]

For acid and alkali burns ascorbate and citrate eye drops have been tried, and ascorbate given orally, based on suggestions that ascorbate may scavenge free radicals and citrate may reduce the release of free radicals and proteolytic enzymes in burn tissue.[1] However, a retrospective analysis of 121 patients with alkali burns to the eye suggested those with less severe burns (grades 1 and 2) did not benefit from an intensive topical therapy regimen including 10% ascorbate drops and 10% citrate drops;[3] a trend to more rapid healing and better visual outcome were seen in patients with grade 3 burns but in those with the most severe damage (grade 4) the regimen made no difference. In the management of hydrofluoric acid burns of the eye, Hexafluorine has been used for irrigation (but see p. 2529.2). Other general treatments that may be required include topical application of anaesthesia, corticosteroids, and antibacterials, treatment for glaucoma, and surgery.[1,2]

1. Schrage NF, *et al.* Eye burns: an emergency and continuing problem. *Burns* 2000; **26:** 689–99.
2. Kuckelkorn R, *et al.* Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand* 2002; **80:** 4–10.
3. Brodovsky SC, *et al.* Management of alkali burns: an 11-year retrospective review. *Ophthalmology* 2000; **107:** 1829–35.

Osteoporosis. Potassium bicarbonate in an oral dose of 1 to 2 mmol/kg daily improved mineral balance and bone metabolism in a short-term study.[1] However, the authors cautioned against the use of bicarbonate to treat or prevent osteoporosis (p. 1168.1) without further study.[2]

1. Sebastian A, *et al.* Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994, **330:** 1776–81.
2. Sebastian A, Morris RC. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; **331:** 279.

Renal calculi. Citrate forms soluble complexes with calcium, thereby reducing urinary saturation of stone-forming calcium salts. Potassium citrate has a hypocalciuric effect when given orally, probably due to enhanced renal calcium absorption. Urinary calcium excretion is unaffected by sodium citrate, since the alkali-mediated hypocalciuric effect is offset by a sodium-linked calciuresis.[1] Potassium citrate may be beneficial in reducing the rate of stone formation in patients with hypocitraturia[2,3] or hypercalciuria.[4] As mentioned in Uses on p. 1781.2, sodium bicarbonate or sodium or potassium citrate may also be used for their alkalinising action, as an adjunct to a liberal fluid intake, to prevent development of uric-acid renal calculi during uricosuric therapy.

Other causes of renal calculi and their treatment are discussed on p. 2350.3.

Urinary alkalinisation with potassium bicarbonate or potassium citrate may be useful in the management of cystine stone formation in patients with cystinuria (see under Penicillamine, p. 1567.2).

1. Anonymous. Citrate for calcium nephrolithiasis. *Lancet* 1986; **i:** 955.
2. Pak CYC, Fuller C. Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med* 1986; **104:** 33–7.
3. Tekin A, *et al.* Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol (Baltimore)* 2002; **168:** 2572–4.
4. Pak CYC, *et al.* Prevention of stone formation and bone loss in absorptive hypercalciuria by combined dietary and pharmacological interventions. *J Urol (Baltimore)* 2003; **169:** 465–9.

Adverse Effects and Treatment

Excessive use of bicarbonate or bicarbonate-forming compounds may lead to hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Symptoms include mood changes, tiredness, slow breathing, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop, especially in hypocalcaemic patients. Treatment of metabolic alkalosis associated with bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium ions may be of particular importance.

Excessive doses of *sodium salts* may also lead to sodium overloading and hyperosmolality (see Adverse Effects of Sodium, p. 1795.2). Sodium bicarbonate given orally can cause stomach cramps, belching, and flatulence. Extravasation of irritant hypertonic sodium bicarbonate solutions resulting in local tissue necrosis has been reported after intravenous dosage.

Excessive doses of *potassium salts* may lead to hyperkalaemia (see Adverse Effects of Potassium, p. 1794.1). Ingestion of potassium salts can cause gastrointestinal adverse effects, and tablet formulations may cause contact irritation due to high local concentrations of potassium.

Excessive oral doses of *citrate salts* may have a laxative effect.

Effects on the gastrointestinal tract. In addition to minor gastrointestinal effects (see above), spontaneous rupture of the stomach, although an exceedingly rare event, has been reported on several occasions after ingestion of sodium bicarbonate. The bicarbonate was believed to have resulted in the rapid production of enough carbon dioxide to rupture a stomach already distended with food, liquid, or air.[1,2]

1. Mastrangelo MR, Moore EW. Spontaneous rupture of the stomach in a healthy adult man after sodium bicarbonate ingestion. *Ann Intern Med* 1984; **101:** 649.
2. Lazebnik N, *et al.* Spontaneous rupture of the normal stomach after sodium bicarbonate ingestion. *J Clin Gastroenterol* 1986; **8:** 454–6.

Effects on mental state. Sodium lactate infusions have been reported to induce panic attacks, especially in patients with anxiety states, and have been used as a pharmacological model in the evaluation of mechanisms involved in panic disorder.[1] However, the mechanism that underlies panic attacks induced by lactate remains unknown,[1] and it has been suggested[2] that rapid administration of the large sodium load may be involved. There has also been a report[3] of a patient receiving oral lactate (as calcium lactate) who was suffering from panic disorder associated with agoraphobia; when lactate was discontinued, the patient reported a reduction in panic intensity without a decrease in the frequency of attacks.

1. Bourin M, *et al.* Provocative agents in panic disorder. *Therapie* 1995; **50:** 301–6.
2. Peskind ER, *et al.* Sodium lactate and hypertonic sodium chloride induce equivalent panic incidence, panic symptoms, and hypernatremia in panic disorder. *Biol Psychiatry* 1998; **44:** 1007–16.
3. Robinson D, *et al.* Possible oral lactate exacerbation of panic disorder. *Ann Pharmacother* 1995; **29:** 539–40.

Epileptogenic effect. Alkalosis may precipitate seizures; however, absence seizures have also been reported to be associated with sodium bicarbonate administration in a child in whom the serum pH was normal.[1]

1. Reif S, *et al.* Absence seizures associated with bicarbonate therapy and normal serum pH. *JAMA* 1989; **262:** 1328–9.

Precautions

Bicarbonate or bicarbonate-forming compounds should not generally be given to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria. During treatment of acidosis, frequent monitoring of serum-electrolyte concentrations and acid–base status is essential.

Sodium-containing salts should be given extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, eclampsia, or aldosteronism (see Precautions for Sodium, p. 1795.3).

Potassium-containing salts should be given with considerable care to patients with renal or adrenocortical insufficiency, cardiac disease, or other conditions that may predispose to hyperkalaemia (see Precautions for Potassium, p. 1794.2).

Abuse. High doses of bicarbonate have been taken by athletes to enhance performance in endurance sports by buffering hydrogen ions produced in conjunction with lactic acid.[1] Bicarbonates have also been used to alkalinise the urine and prolong the half-life of basic drugs, notably sympathomimetics and stimulants, thereby avoiding detection; however, such a practice may enhance toxicity.

1. Kennedy M. Drugs and athletes—an update. *Adverse Drug React Bull* 1994; (Dec): 639–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium citrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

The effect of oral bicarbonate or bicarbonate-forming compounds in raising intra-gastric pH may reduce or increase the rate and/or extent of absorption of a number of drugs (see also Antacids, p. 1803.1). Alkalinisation of the urine leads to increased renal clearance of acidic drugs such as salicylates, tetracyclines, and barbiturates. Conversely, it prolongs the half-life of basic drugs and may result in toxicity (see also under Abuse, above).

Sodium bicarbonate enhances lithium excretion. The use of *potassium-containing salts* with drugs that increase serum-potassium concentrations such as ACE inhibitors and potassium-sparing diuretics should generally be avoided (p. 1794.2). *Citrate salts* taken orally can enhance the absorption of aluminium from the gastrointestinal tract (see Toxicity, p. 1817.3 under Adverse Effects of Aluminium Hydroxide). Patients with impaired renal function are particularly susceptible to aluminium accumulation and citrate-containing oral preparations, including many effervescent or dispersible tablets, are best avoided by patients with renal failure taking aluminium-containing compounds.

Pharmacokinetics

Oral bicarbonate, such as sodium bicarbonate, neutralises gastric acid with the production of carbon dioxide. Bicarbonate not involved in that reaction is absorbed and in the absence of a deficit of bicarbonate in the plasma, bicarbonate ions are excreted in the urine, which is rendered alkaline, and there is an accompanying diuresis.

Acetates such as potassium acetate and sodium acetate, citrates such as potassium citrate, sodium acid citrate, and sodium citrate, and lactates such as sodium lactate are metabolised, after absorption, to bicarbonate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: LTK250; Urokit; ***Austral.***: Chlorvescent; Sodibic; Urocit-K; ***Austria***: Uralyt-U; ***Belg.***: Natribic; Uralyt-U; ***Braz.***: Litocit; ***Canad.***: Bicart; Bromo Seltzer†; Cystoplus; Eno; Formula No 2K†; Hema BP-38; K-Citra; K-Lyte; Polycitra-K†; Urocit-K; ***Chile***: Acalka†; Eucerin; ***China***: Keweijia (可维加); Uralyt-U (友来特); ***Cz.***: Uralyt-U; ***Fin.***: Selutrio; ***Fr.***: Bibag†; Hospasol; Soludial†; ***Ger.***: Alkala T; Apocit; bicaNorm; Blanel; Kalitrans; Kalium; Kohlensauerbad Bastian; Nephrotrans; Uralyt-U; ***Gr.***: Citrolithin; ***Hong Kong***: Antacimin†; Citral†; Urocit-K; ***Hung.***: Alkaligen; ***India***: Adkalizer; Alkacool; Alkaline Citrate; Alkanil; Alkanorm; Alkaryl; Alkasol; Alkos; Allcitra; Ample; Cital; Citra; Citraglow; Citrakul; Citralka; Fulflo; Intalka; Jucitron; Metalka; Oricitral; ***Irl.***: Cystopurin; Diarrest RF†; ***Israel***: Al-Karish†; Babic†; Uralyt-U; ***Ital.***: Citrosodina; Uralyt-U; ***Jpn***: Meylon; ***Malaysia***: Urocit-K; ***Mex.***: Betsol Z; Bicarnat†; Debonal; ***Neth.***: Citra-Lock; Hospasol; ***Norw.***: Kajos; ***NZ***: Citravescent†; ***Philipp.***: Acalka; K-Cit; Zegacid; ***Pol.***: Citrolyt; Litocid; ***Port.***: Acalka; Alka-Seltzer; Extraneal; Hospasol; Uralyt-U; ***Rus.***: Uralit-U (Уралит-У); ***S.Afr.***: Crystacit; SB Gripe Water†; Uralyt-U; ***Singapore***: Carrington's Gripe Water; Citral; Urocit-K; ***Spain***: Acalka; Alka-Seltzer New Formula; Hospasol; Venofusin Bicarbonato; ***Swed.***: Kajos; ***Switz.***: Nephrotrans; Urocit; ***Thai.***: Acalka; Arc-Soda; Carminative Medicine; Darbie; Sodamint Frx; Uralyt-U; ***Turk.***: Anti-Asidoz; Parodontax; Urocit-K; ***UK***: Boots Gripe Mixture 1 Month Plus; Canesten Oasis; Cymalon Cranberry; Cystitis Relief; Cystocalm; Cystopurin; SodiBic; ***Ukr.***: Soda-Bufer (Сода-Буфер); Uralyt-U (Уралит-У); ***USA***: Citra pH; K-Bicarb; K-Lyte; Neut; Urocit-K; ***Venez.***: Policitra.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Ger.***: HanoOxygen E.

Pharmacopoeial Preparations

BP 2014: Alginate Raft-forming Oral Suspension; Alkaline Gentian Mixture; Aromatic Magnesium Carbonate Mixture; Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution; Compound Magnesium Trisilicate Oral Powder; Compound Sodium Bicarbonate Tablets; Compound Sodium Chloride Mouthwash; Compound Sodium Lactate Infusion; Kaolin and Morphine Mixture; Kaolin Mixture; Magnesium Trisilicate Mixture; Potassium Citrate Mixture; Sodium Bicarbonate Ear Drops; Sodium Bicarbonate Eye Lotion; Sodium Bicarbonate Infusion; Sodium Bicarbonate Oral Solution; Sodium Citrate Eye Drops; Sodium Citrate Irrigation Solution;

All cross-references refer to entries in Volume A

Sodium Lactate Infusion;
BPC 1968: Effervescent Potassium Tablets;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 36: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Anticoagulant Sodium Citrate Solution; Half-strength Lactated Ringer's and Dextrose Injection; Imipenem and Cilastatin for Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; PEG 3350 and Electrolytes for Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Bicarbonate Effervescent Tablets for Oral Solution; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Potassium Citrate Extended-release Tablets; Potassium Citrate Tablets; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Sodium Acetate Injection; Sodium Acetate Solution; Sodium Bicarbonate Injection; Sodium Bicarbonate Oral Powder; Sodium Bicarbonate Tablets; Sodium Citrate and Citric Acid Oral Solution; Sodium Lactate Injection; Sodium Lactate Solution; Tricitrates Oral Solution; Trikates Oral Solution.

Calcium

Calcio; Kalsiyum; Kalzium; Кальций.
Ca=40.078
UNII — SY7Q814VUP (calcium); 2M83C4R6ZB (calcium ion).

Description. Calcium is a cation given as various calcium-containing salts.

Incompatibility. Calcium salts have been reported to be incompatible with a wide range of drugs and parenteral mixtures containing, for example, phosphate. Complexes may form resulting in the formation of a precipitate.

References.
1. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. *Am J Health-Syst Pharm* 2008; **65:** 73–80.

Calcium Acetate

Acetate of Lime; Calcii Acetas; Calcio, acetato de; Calcium, acétate de; Calciumacetat; E263; Kalcio acetatas; Kalciumacetat; Kalcium-acetát; Kalsiumasetaatti; Kalsiyum Asetat; Lime Acetate; Ацетат Кальция; Уксуснокислый Кальций.
$C_4H_6CaO_4$=158.2
CAS — 62-54-4.
ATC — A12AA12.
ATC Vet — QA12AA12.
UNII — Y882YXF34X.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Calcium Acetate, Anhydrous). A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 7.2 to 8.2. Store in airtight containers.

USP 36: (Calcium Acetate). A white, odourless or almost odourless, hygroscopic, crystalline powder. It decomposes to calcium carbonate and acetone when heated to above 160 degrees. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in dehydrated alcohol, in acetone, and in benzene. A 5% solution in water has a pH of 6.3 to 9.6. Store in airtight containers.

Equivalence. Each g of calcium acetate (anhydrous) represents about 6.3 mmol of calcium. Calcium acetate (anhydrous) 3.95 g is equivalent to about 1 g of calcium.

Calcium Chloride

Calcii Chloridum; Calcii chloridum dihydricum; Calcio, cloruro de; Calcium Chloratum; Calcium, chlorure de; Chlorid vápenatý; Cloreto de Cálcio; Cloruro cálcico; Cloruro de calcio; E509; Kalcio chloridas; Kalcium-klorid; Kalciumklorid; Kalsiumkloridi; Kalsiyum Klorür; Wapnia chlorek; Кальций Хлорид; Кальций Хлористый.
$CaCl_2.xH_2O$=110.0 (anhydrous); 147.0 (dihydrate)
CAS — 10043-52-4 (anhydrous calcium chloride); 7774-34-7 (calcium chloride hexahydrate); 10035-04-8 (calcium chloride dihydrate).
ATC — A12AA07; B05XA07; G04BA03.
ATC Vet — QA12AA07; QB05XA07; QG04BA03.
UNII — OFM21057LP (anhydrous calcium chloride); M4I0D6VV5M (calcium chloride dihydrate).

Pharmacopoeias. *Chin., Eur.* (see p. vii), *Jpn, US,* and *Viet.* include the dihydrate.

Eur. also specifies the hexahydrate.

Ph. Eur. 8: (Calcium Chloride Dihydrate; Calcii Chloridum Dihydricum). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol. Store in airtight containers.

Ph. Eur. 8: (Calcium Chloride Hexahydrate; Calcii Chloridum Hexahydricum). A white or almost white, crystalline mass or colourless crystals. Very soluble in water; freely soluble in alcohol. F.p. about 29 degrees.

USP 36: (Calcium Chloride). White, hard, odourless fragments or granules. Is deliquescent. Soluble 1 in 0.7 of water, 1 in 0.2 of boiling water, 1 in 4 of alcohol, and 1 in 2 of boiling alcohol. pH of a 5% solution in water is between 4.5 and 9.2. Store in airtight containers.

Equivalence. Each g of calcium chloride (dihydrate) represents about 6.8 mmol of calcium and 13.6 mmol of chloride. Calcium chloride (dihydrate) 3.67 g is equivalent to about 1 g of calcium.

Each g of calcium chloride (hexahydrate) represents about 4.56 mmol of calcium and 9.13 mmol of chloride. Calcium chloride (hexahydrate) 5.47 g is equivalent to about 1 g of calcium.

Calcium Citrate

Calcio, citrato de; Citrato tricálcico; Tricalcium Citrate; Лимоннокислый Кальций; Цитрат Кальция.
Tricalcium 2-hydroxypropane-1,2,3-tricarboxylate tetrahydrate.
$C_{12}H_{10}Ca_3O_{14}.4H_2O$=570.5
CAS — 5785-44-4.
UNII — MLM29U2X85.

Pharmacopoeias. In *US.*

USP 36: (Calcium Citrate). A white, odourless, crystalline powder. Slightly soluble in water; insoluble in alcohol; freely soluble in diluted 3N hydrochloric acid and in diluted 2N nitric acid.

Equivalence. Each g of calcium citrate (tetrahydrate) represents about 5.3 mmol of calcium and 3.5 mmol of citrate. Calcium citrate (tetrahydrate) 4.74 g is equivalent to about 1 g of calcium.

Calcium Glubionate *(USAN, rINN)*

Calcii Glubionas; Calcio, glubionato de; Calcium Gluconate Lactobionate Monohydrate; Calcium Gluconogalactogluconate Monohydrate; Calcium Gluconolactobionate; Glubionate de Calcium; Glubionato de calcio; Кальция Глубионат.
Calcium D-gluconate lactobionate monohydrate.
$(C_{12}H_{21}O_{12}.C_6H_{11}O_7)Ca.H_2O$=610.5
CAS — 31959-85-0 (anhydrous calcium glubionate); 12569-38-9 (calcium glubionate monohydrate).
ATC — A12AA02.
ATC Vet — QA12AA02.
UNII — 3CF7K0SD0Q.

Pharmacopoeias. *US* includes Calcium Glubionate Syrup.

Equivalence. Each g of calcium glubionate (monohydrate) represents about 1.6 mmol of calcium. Calcium glubionate (monohydrate) 15.2 g is equivalent to about 1 g of calcium.

Calcium Gluceptate

Calcii Glucoheptonas; Calcio, glucoheptonato de; Calcium Glucoheptonate (pINN); Calcium, glucoheptonate de; Calcium Glucosemonocarbonate; Calciumglucoheptonat; Gluceptato de calcio; Glucoheptonate de Calcium; Glucoheptonato de calcio; Kalcio gliukoheptonatas; Kalcium-glükoheptonát; Kalciumglukoheptonat; Kalcium-glukoheptonát; Kalsiumglukoheptonaatti; Кальция Глюкогептонат.
$C_{14}H_{26}CaO_{16}$=490.4
CAS — 17140-60-2 (anhydrous calcium gluceptate); 29039-00-7 (anhydrous calcium gluceptate).
ATC — A12AA10.
ATC Vet — QA12AA10.
UNII — L11651398J.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows anhydrous or with varying amounts of water of hydration.

Ph. Eur. 8: (Calcium Glucoheptonate). A mixture in variable proportions of calcium di(D-*glycero*-D-*gulo*-heptonate) and calcium di(D-*glycero*-D-*ido*-heptonate). A white or very slightly yellow, hygroscopic, amorphous powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 10% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

USP 36: (Calcium Gluceptate). It is anhydrous or contains varying amounts of water of hydration. It consists of the calcium salt of the alpha-epimer of glucoheptonic acid or of a mixture of the alpha and beta epimers of glucoheptonic acid. A white to faintly yellow amorphous powder. It is stable in air, but the hydrous forms may lose part of their water of hydration on standing. Freely soluble in water; insoluble in alcohol and in many other organic solvents. pH of a 10% solution in water is between 6.0 and 8.0.

Equivalence. Each g of calcium gluceptate (anhydrous) represents about 2 mmol of calcium. Calcium gluceptate (anhydrous) 12.2 g is equivalent to about 1 g of calcium.

Calcium Gluconate

Calcii gluconas; Calcii Gluconas Monohydricus; Calcio, gluconato de; Calcium, gluconate de; Calcium Glyconate; Calciumgluconat; E578; Gluconato cálcico; Glukonan vápenatý monohydrát; Kalcio gliukonatas; Kalcium-glükonát; Kalciumglukonat; Kalsiumglukonaatti; Wapnia glukonian; Кальций Глюконат.
Calcium D-gluconate monohydrate.
$C_{12}H_{22}CaO_{14}.H_2O$=448.4
CAS — 299-28-5 (anhydrous calcium gluconate); 18016-24-5 (calcium gluconate monohydrate).
ATC — A12AA03; D11AX03.
ATC Vet — QA12AA03; QD11AX03.
UNII — SQE6VB453K (calcium gluconate); CZN0MI5R31 (calcium gluconate monohydrate).

Pharmacopoeias. In *Chin., Int., Jpn,* and *Viet.* Also in *Eur.* (see p. vii) and *US* as the anhydrous or the monohydrate form.

Calcium borogluconate is included as an injection in *BP (Vet).*

Ph. Eur. 8: (Calcium Gluconate). A white or almost white, crystalline or granular, powder. Sparingly soluble in water; freely soluble in boiling water.

Ph. Eur. 8: (Calcium Gluconate, Anhydrous). A white or almost white, crystalline, or granular powder. Sparingly soluble in water; freely soluble in boiling water.

USP 36: (Calcium Gluconate). It is anhydrous or contains one molecule of water of hydration. White, odourless, crystalline granules or powder. Slowly soluble 1 in 30 of water; soluble 1 in 5 of boiling water; insoluble in alcohol. Its solutions are neutral to litmus.

Equivalence. Each g of calcium gluconate (monohydrate) represents about 2.2 mmol of calcium. Calcium gluconate (monohydrate) 11.2 g is equivalent to about 1 g of calcium.

Calcium Glycerophosphate

Calcii Glycerophosphas; Calcio, glicerofosfato de; Calcium Glycerinophosphate; Calcium, glycérophosphate de; Calcium Glycerylphosphate; Calciumglycerophosphat; Glicerofosfato cálcico; Glycerofosforečnan vápenatý; Kalcio glicerofosfatas; Kalcium-glicerofoszfát; Kalciumglycerofosfat; Kalsiumglyserofosfaatti; Кальций Глицерофосфат.
$C_3H_7CaO_6P.xH_2O$=210.1 (anhydrous)
CAS — 27214-00-2 (anhydrous calcium glycerophosphate).
ATC — A12AA08.
ATC Vet — QA12AA08.
UNII — XWV9Z12C1C.

Pharmacopoeias. In *Eur.* (see p. vii), *US.*, and *Viet.*

Ph. Eur. 8: (Calcium Glycerophosphate). A mixture in variable proportions of calcium (*RS*)-2,3-dihydroxypropyl phosphate and of calcium 2-hydroxy-1-(hydroxymethyl) ethyl phosphate, which may be hydrated. It contains not less than 18.6% and not more than 19.4% of calcium, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. It loses not more than 12% of its weight on drying.

USP 36: (Calcium Glycerophosphate). A mixture, in variable proportions, of calcium *(RS)*-2,3-dihydroxypropyl phosphate and calcium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated. It contains not less than 18.6% and not more than 19.4% of calcium, calculated with reference to the dried substance. Store at a temperature between 20 degrees and 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Equivalence. Each g of calcium glycerophosphate (anhydrous) represents about 4.8 mmol of calcium. Calcium glycerophosphate (anhydrous) 5.24 g is equivalent to about 1 g of calcium.

Calcium Hydrogen Phosphate

Calcii et Hydrogenii Phosphas; Calcii Hydrogenophosphas; Calcio, hidrogenofosfato de; Calcium, hydrogénophosphate

de; Calcium Hydrophosphoricum; Calcium Monohydrogen Phosphate; Dibasic Calcium Phosphate; Dicalcium Orthophosphate; Dicalcium Phosphate; E341; Fosfato dibásico de calcio; Hydrogenfosforečnan vápenatý; Kalcio-vandenilio fosfatas; Kalcium-hidrogén-foszfát; Kalciumvätefosfat; Kalsiumvetyfosfaatti; Wapnia wodorofosforan; Ортофосфат Кальция Двузамещенный; Дикальций-фосфат.

Calcium hydrogen orthophosphate.

$CaHPO_4$=136.1 (anhydrous); 172.1 (dihydrate)

CAS — 7757-93-9 (anhydrous calcium hydrogen phosphate); 7789-77-7 (calcium hydrogen phosphate dihydrate).

UNII — L11K75P92J (anhydrous calcium hydrogen phosphate); O7TSZ97GEP (calcium hydrogen phosphate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*, which includes monographs for the anhydrous substance and the dihydrate form.

Ph. Eur. 8: (Calcium Hydrogen Phosphate, Anhydrous; Calcii Hydrogenophosphas Anhydricus). A white or almost white, crystalline powder. Practically insoluble in water and in alcohol; dissolves in dilute hydrochloric acid and in dilute nitric acid.

Ph. Eur. 8: (Calcium Hydrogen Phosphate Dihydrate; Calcii Hydrogenophosphas Dihydricus; Calcium Hydrogen Phosphate BP 2014). A white or almost white, crystalline powder. Practically insoluble in cold water and in alcohol; dissolves in dilute hydrochloric acid and in dilute nitric acid.

The BP 2014 gives Dibasic Calcium Phosphate as an approved synonym.

USP 36: (Anhydrous Dibasic Calcium Phosphate).

USP 36: (Dibasic Calcium Phosphate Dihydrate).

Equivalence. Each g of calcium hydrogen phosphate (dihydrate) represents about 5.8 mmol of calcium and of phosphate. Calcium hydrogen phosphate (dihydrate) 4.29 g is equivalent to about 1 g of calcium.

Calcium Lactate

Calcii Lactas; Calcio, lactato de; Calcium, lactate de; E327; Kalcio laktatas; Kalciumlaktat; Kalcium-laktát; Kalsiumlaktaatti; Kalsiyum Laktat; Lactato cálcico; Mléčnan vápenatý; Wapnia mleczan; Лактат Кальция; Молочнокислый Кальций.

Calcium 2-hydroxypropionate.

$C_6H_{10}CaO_6.xH_2O$=218.2 (anhydrous); 308.3 (pentahydrate); 272.3(trihydrate)

CAS — 814-80-2 (anhydrous calcium lactate); 41372-22-9 (hydrated calcium lactate); 5743-47-5 (calcium lactate pentahydrate); 63690-56-2 (calcium lactate pentahydrate).

ATC — A12AA05.

ATC Vet — QA12AA05.

UNII — 2URQ2N32W3 (anhydrous calcium lactate); 4FM1N296CM (calcium lactate pentahydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Eur. has separate monographs for the anhydrous substance, the monohydrate, the pentahydrate, and the trihydrate. *US* allows anhydrous or hydrous forms. *Viet.* has monographs for the pentahydrate and the trihydrate.

Ph. Eur. 8: (Calcium Lactate, Anhydrous; Calcii Lactas Anhydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

Ph. Eur. 8: (Calcium Lactate Monohydrate; Calcii Lactas Monohydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

Ph. Eur. 8: (Calcium Lactate Pentahydrate; Calcii Lactas Pentahydricus). A white or almost white, slightly efflorescent, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

The BP 2014 gives Calcium Lactate as an approved synonym.

Ph. Eur. 8: (Calcium Lactate Trihydrate; Calcii Lactas Trihydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

USP 36: (Calcium Lactate). White, practically odourless, granules or powder. The pentahydrate is somewhat efflorescent and at 120 degrees becomes anhydrous. The pentahydrate is soluble 1 in 20 of water and practically insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of calcium lactate (trihydrate) represents about 3.7 mmol of calcium. Each g of calcium lactate (pentahydrate) represents about 3.2 mmol of calcium. Calcium lactate (pentahydrate) 7.7 g and calcium lactate (trihydrate) 6.8 g are each equivalent to about 1 g of calcium.

Calcium Lactate Gluconate

Calcio, gluconato lactato de; Calcium Gluconolactate.

$Ca_5(C_3H_5O_3)_6.(C_6H_{11}O_7)_4.2H_2O$=1551.4

CAS — 11116-97-5.

ATC — A12AA06.

ATC Vet — QA12AA06.

UNII — 472LWJ3Y9N.

Equivalence. Each g of calcium lactate gluconate (dihydrate) represents about 3.2 mmol of calcium. Calcium lactate gluconate (dihydrate) 7.74 g is equivalent to about 1 g of calcium.

Calcium Lactobionate

Calcii Lactobionas; Calcio, lactobionato de; Calcium Lactobionate Dihydrate; Kalciumlaktobionat; Kalsiumlaktobionaatti; Lactobionato cálcico dihidrato; Кальция Лактобионат.

Calcium 4-*O*-β-D-galactopyranosyl-D-gluconate dihydrate.

$C_{24}H_{42}CaO_{24}.2H_2O$=790.7

CAS — 110638-68-1.

UNII — 7D8YVA497F.

Pharmacopoeias. In *US*.

USP 36: (Calcium Lactobionate). pH of a 5% solution in water is between 5.4 and 7.4.

Equivalence. Each g of calcium lactobionate (dihydrate) represents about 1.3 mmol of calcium. Calcium lactobionate (dihydrate) 19.7 g is equivalent to about 1 g of calcium.

Calcium Levulinate *(BAN)*

Calcii Laevulas; Calcii Laevulinas; Calcii Laevulinas Dihydricus; Calcii Levulinas Dihydricum; Calcio, levulinato de; Calcium Laevulate; Calcium Laevulinate; Calcium, lévulinate de; Kalcio levulinatas; Kalciumlevulat; Kalcium-levulát dihydrát; Kalciumlevulinat; Kalcium-levulinát; Kalsiumlevulaatti; Kalsiumlevulinaatti; Lévulinate Calcique; Levulinato cálcico dihidrato; Кальция Левулат.

Calcium 4-oxovalerate dihydrate.

$C_{10}H_{14}CaO_6.2H_2O$=306.3

CAS — 591-64-0 (anhydrous calcium levulinate); 5743-49-7 (calcium levulinate dihydrate).

ATC — A12AA30.

ATC Vet — QA12AA30.

UNII — T6133SO781.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Calcium Levulinate Dihydrate). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 6.8 to 7.8. Protect from light.

USP 36: (Calcium Levulinate). A white crystalline or amorphous powder, having a faint odour suggestive of burnt sugar. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.5.

Equivalence. Each g of calcium levulinate (dihydrate) represents about 3.3 mmol of calcium. Calcium levulinate (dihydrate) 7.64 g is equivalent to about 1 g of calcium.

Calcium Phosphate

Calcii Phosphas; Calcio, fosfato de; Calcium Orthophosphate; E341; Fosfato Tricalcico; Fosfato Tricálcico; Fosforečnan vápenatý; Kalcio fosfatas; Kalcium-foszfát; Phosphate Tertiaire de Calcium; Phosphate tricalcique; Precipitated Calcium Phosphate; Tricalcii Phosphas; Tricalcium Phosphate; Tricalciumphosphat; Trikalciumfosfat; Trikalsiumfosfaatti; Wapnia fosforan; Ортофосфат Кальция Трёхзамещенный.

CAS — 7758-87-4 (tricalcium diorthophosphate); 12167-74-7 (calcium hydroxide phosphate).

ATC — A12AA01.

ATC Vet — QA12AA01.

UNII — 97Z1WI3NDX (calcium phosphate); K4C08XP666 (tricalcium diorthophosphate).

Description. Calcium phosphate is not a clearly defined chemical entity but is a mixture of calcium phosphates that has been most frequently described as either tricalcium diorthophosphate, $Ca_3(PO_4)_2$ = 310.2, or calcium hydroxide phosphate, $Ca_5OH(PO_4)_3$ = 502.3.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Viet.* Also in *USNF*.

Br. also includes a form for homoeopathic preparations.

Ph. Eur. 8: (Calcium Phosphate). It consists of a mixture of calcium phosphates and contains 35 to 40% of Ca. A white or almost white powder. Practically insoluble in water; dissolves in dilute hydrochloric acid and in dilute nitric acid.

The BP 2014 gives Tribasic Calcium Phosphate as an approved synonym.

USNF 31: (Tribasic Calcium Phosphate). It consists of a variable mixture of calcium phosphates having the approximate composition $10CaO.3P_2O_5.H_2O$. It contains not less than 34% and not more than 40% of calcium. A white, odourless, powder. Practically insoluble in water; insoluble in alcohol; readily soluble in 3N hydrochloric acid and in 2N nitric acid.

BP 2014: (Calcium Phosphate for Homoeopathic Preparations; Calcium Phosphoricum for Homoeopathic Preparations).

Calcium Pidolate *(pINNM)*

Calcii Pidolas; Calcio, pidolato de; Calcium Pyroglutamate; Pidolate de Calcium; Pidolato cálcico; Pidolato de calcio; Кальций Пидолат.

Calcium 5-oxopyrrolidine-2-carboxylate.

$Ca(C_5H_6NO_3)_2$=296.3

CAS — 31377-05-6.

UNII — 7Y2LVU5EKK.

Equivalence. Each g of calcium pidolate (anhydrous) represents about 3.4 mmol of calcium. Calcium pidolate (anhydrous) 7.39 g is equivalent to about 1 g of calcium.

Calcium Silicate

Calcio, silicato de; E552; Silicato cálcico; Кремнекислый Кальций; Силикат Кальция.

CAS — 1344-95-2; 10101-39-0 (calcium metasilicate); 10034-77-2 (calcium diorthosilicate); 12168-85-3 (calcium trisilicate).

ATC — A02AC02.

ATC Vet — QA02AC02.

UNII — S4255P4G5M.

Description. A naturally occurring mineral, the most common forms being calciummetasilicate ($CaSiO_3$ = 116.2), calcium diorthosilicate (Ca_2SiO_4 = 172.2), and calcium trisilicate (Ca_3SiO_5 = 228.3). It is usually found in hydrated forms containing various amounts of water of crystallisation. Commercial calcium silicate is prepared synthetically.

Pharmacopoeias. In *USNF*.

USNF 31: (Calcium Silicate). Crystalline or amorphous calcium silicate is a compound of calcium oxide and silicon dioxide containing not less than 4% of CaO and not less than 35% of SiO_2. A white to off-white free-flowing powder. Insoluble in water; with mineral acids it forms a gel. A 5% aqueous suspension has a pH of 8.4 to 11.2.

Calcium Sodium Lactate

Calcio, lactato sódico de.

$2C_3H_5NaO_3.(C_3H_5O_3)_2Ca.4H_2O$=514.4

Equivalence. Each g of calcium sodium lactate (tetrahydrate) represents about 1.9 mmol of calcium and 3.9 mmol of sodium and of lactate. Calcium sodium lactate (tetrahydrate) 12.8 g is equivalent to about 1 g of calcium.

Uses and Administration

Calcium salts are used in the management of **hypocalcaemia** (p. 1776.2) and **calcium deficiency states** resulting from dietary deficiency or ageing (see also Osteoporosis, p. 1168.1). Doses may be expressed in terms of mmol or mEq of calcium, mass (mg) of calcium, or mass of calcium salt (for comparative purposes, see Table 1, p. 1785).

In simple deficiency states calcium salts may be given orally, usually in doses of 10 to 50 mmol (400 mg to 2 g) of calcium daily adjusted to the individual patient's requirements.

In severe acute hypocalcaemia or hypocalcaemic tetany parenteral dosage is necessary, generally by slow intravenous injection or continuous infusion of calcium chloride or calcium gluconate (see also Administration, p. 1785.2). A typical dose is 2.25 to 4.5 mmol of calcium by slow intravenous injection. This may be repeated as required, or followed by continuous intravenous infusion. One suggested regimen for infusion is 22.5 mmol of calcium as calcium gluconate in 1 litre of infusion solution, given at an initial rate of 50 mL/hour. Plasma-calcium may be monitored every 4 to 6 hours and the dose adjusted accordingly. About 2.25 mmol of calcium is provided by 10 mL of calcium gluconate 10%. Calcium gluceptate and calcium glycerophosphate with calcium lactate have been given by the intramuscular route; the chloride and

Table 1. Some calcium salts and their calcium content.

Calcium salt	Calcium content per g		
	mg	mmol	mEq
Calcium acetate (anhydrous)	253	6.3	12.6
Calcium carbonate	400	10.0	20.0
Calcium chloride (dihydrate)	273	6.8	13.6
Calcium chloride (hexahydrate)	183	4.6	9.1
Calcium citrate (tetrahydrate)	211	5.3	10.5
Calcium glubionate (monohydrate)	66	1.6	3.3
Calcium gluceptate (anhydrous)	82	2.0	4.1
Calcium gluconate (monohydrate)	89	2.2	4.5
Calcium glycerophosphate (anhydrous)	191	4.8	9.5
Calcium hydrogen phosphate (dihydrate)	233	5.8	11.6
Calcium lactate (anhydrous)	184	4.6	9.2
Calcium lactate (trihydrate)	147	3.7	7.3
Calcium lactate (pentahydrate)	130	3.2	6.5
Calcium lactate gluconate (dihydrate)	129	3.2	6.4
Calcium lactobionate (dihydrate)	51	1.3	2.5
Calcium levulinate (dihydrate)	131	3.3	6.5
Calcium phosphate [$10CaO.3P_2O_5.H_2O$]	399	10.0	19.9
Calcium pidolate (anhydrous)	135	3.4	6.7
Calcium silicate [$CaSiO_3$]	345	8.6	17.2
Calcium sodium lactate (tetrahydrate)	78	1.9	3.9

gluconate are unsuitable for this route because of their irritancy.

Intravenous calcium salts are also used to reverse the toxic cardiac effects of potassium in the emergency treatment of severe **hyperkalaemia** (p. 1777.1), and as an antidote to magnesium in severe **hypermagnesaemia** (p. 1776.2). For these indications, 2.25 to 4.5 mmol of calcium (10 to 20 mL of calcium gluconate 10%) is commonly used.

Individual calcium salts have specific uses. Calcium carbonate (p. 1824.3) or acetate are effective phosphate binders and are given orally to reduce phosphate absorption from the gut in patients with **hyperphosphataemia**; this is particularly relevant to patients with chronic renal failure in order to prevent the development of renal osteodystrophy (p. 1170.1). Doses are adjusted according to serum phosphate concentrations. Typical oral doses of calcium carbonate range from about 3 to 7 g (1.2 to 2.8 g calcium) daily in divided doses. Usual oral doses of calcium acetate are about 4 to 8 g (1 to 2 g calcium) daily in divided doses; a daily maximum of calcium acetate 12 g (3 g calcium) has been recommended. However, the US National Kidney Foundation suggests that the total dose of elemental calcium provided by the calcium-based phosphate binder should not exceed 1.5 g daily in those with kidney failure.

Calcium carbonate and calcium silicate, given orally, are used for their **antacid** properties (p. 1803.1). A supersaturated calcium phosphate solution is used topically as a mouthwash to manage conditions such as **dry mouth** (p. 2175.3) and **mucositis** associated with chemotherapy or radiotherapy (p. 732.1).

Some of the calcium salts discussed here also have *pharmaceutical uses* as diluents in capsules and tablets, buffers and dissolution aids in dispersible tablets, disintegrant and anticaking agents, and as a basis or abrasive in dental preparations. Calcium phosphate is also used as a bone graft substitute.

Homoeopathy

Various calcium salts have been used in homoeopathic medicines under the following names:

- Calcium acetate: Calcarea acetica; Calc acet; Calc. ace.
- Calcium arsenite: Calcium arsenicosum; Calcarea arsenicosa; Cal. ars.
- Calcium chloride: Calcarea muriatica; Cal. mur.; Calc mur
- Calcium hydrogen phosphate: Calcium phosphoricum
- Calcium lactate: Calcarea lactica; Calc lac
- Calcium oxalate: Calcarea oxalica; Cal. oxal.; Calc oxal
- Calcium phosphate: Calcarea phosphorica; Calc. phos.; Cal. phos.
- Calcium silicate: Calcarea silicata; Calc. sil.

Other calcium salts used in homoeopathy and described elsewhere include: calcium bromide (p. 2461.1), calcium carbonate (p. 1824.3), calcium fluoride (p. 2053.1), calcium hydroxide (p. 2465.1), calcium hypophosphite (p. 2530.3), calcium iodide (p. 1658.1), and calcium sulfate (p. 2173.1).

Administration. Some prefer calcium chloride to calcium gluconate for parenteral preparations,[1,2] because retention of the chloride is greater and more predictable than of the gluconate, and results in a more predictable increase in extracellular ionised calcium concentration. However, calcium chloride is considered to be the most irritant of the calcium salts in general use (see Adverse Effects, p. 1786.1).

Calcium gluconate has been given by the intraperitoneal route[3] for the treatment of chronic hypocalcaemia after parathyroidectomy in a patient undergoing continuous ambulatory peritoneal dialysis, resulting in improved systemic bioavailability compared with oral and intravenous use.

1. WorthleyLIG, Phillips PJ. Intravenous calcium salts. *Lancet* 1980; **ii:** 149.
2. Broner CW, *et al.* A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr* 1990; **117:** 986–9.
3. Stamatakis MK, Seth SK. Treatment of chronic hypocalcemia with intraperitoneal calcium. *Am J Health-Syst Pharm* 1995; **52:** 201–3.

Bites and stings. Calcium gluconate 10% solution has been given intravenously as an alternative to the use of conventional muscle relaxants for the management of pain and muscle spasm associated with neurotoxic spider envenomation (p. 2420.1) by species such as *Latrodectus mactans* (black widow spider).[1,2] Although the precise mechanism of action of calcium in the alleviation of neuromuscular symptoms is unknown it is believed to be due to the replenishment of calcium stores in the sarcoplasmic reticulum of muscle depleted by stimulation.

1. Binder LS. Acute arthropod envenomation: incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 163–73.
2. Woestman R, *et al.* The black widow: is she deadly to children? *Pediatr Emerg Care* 1996; **12:** 360–4.

Bone disease. Calcium is essential for the development and maintenance of normal bone, and calcium salts may be indicated in the treatment of some bone disorders associated with calcium deficiency, such as certain types of osteomalacia and rickets (p. 1168.1). Oral doses of 1 to 3 g of calcium daily are used in osteomalacia.

Oral calcium supplements can also be used as an adjunct in the management of osteoporosis (p. 1168.1) and corticosteroid-induced osteoporosis (see Effects on Bones and Joints, under Corticosteroids, p. 1616.2).

Cramps. Calcium salts are one of a number of interventions that have been tried in the management of cramps (see Muscle Spasm, p. 2014.1). However, evidence for these interventions is mostly lacking and a small systematic review concluded that oral calcium was not of benefit for leg cramps during pregnancy.[1]

1. Young G, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/06/05).

Diagnosis of insulinoma. Calcium stimulates the release of insulin from insulinomas (see Neuroendocrine Tumours, p. 716.3). Intra-arterial calcium gluconate, followed by hepatic venous sampling, has been found to be accurate and sensitive in the diagnosis and localisation of insulinomas,[1-4] even when other investigations have been negative.[5,6]

1. Doppman JL, *et al.* Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann Intern Med* 1995; **123:** 269–73.
2. Lo CY, *et al.* Value of intra-arterial calcium stimulated venous sampling for regionalization of pancreatic insulinomas. *Surgery* 2000; **128:** 903–9.
3. Brändle M, *et al.* Assessment of selective arterial calcium stimulation and hepatic venous sampling to localize insulin-secreting tumours. *Clin Endocrinol (Oxf)* 2001; **55:** 357–62.
4. Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol* 2005; **19:** 783–98.
5. O'Shea D, *et al.* Localization of insulinomas by selective intraarterial calcium injection. *J Clin Endocrinol Metab* 1996; **81:** 1623–7.
6. Pereira PL, *et al.* Insulinoma and islet cell hyperplasia: value of the calcium intraarterial stimulation test when findings of other preoperative studies are negative. *Radiology* 1998; **206:** 703–9.

Fluoride toxicity. Inorganic fluoride is corrosive to skin and mucous membranes and acute intoxication disrupts many physiological systems; severe burns and profound hypocalcaemia may ensue. Absorption of the fluoride can be prevented by conversion to an insoluble form such as calcium fluoride and thus irrigation of skin (or gastric lavage as appropriate) with lime water, milk, or a 1% solution of calcium gluconate is recommended. Immediate treatment should also consist of 10 mL of calcium gluconate 10% intravenously, repeated after one hour; 30 mL should be given if tetany is present. In the short term affected skin and tissue should be injected with a 10% solution of calcium gluconate at a dose of 0.5 mL/cm^2 and burnt skin treated with a calcium gluconate 2.5% gel.[1]

See also under Hydrofluoric Acid, p. 2529.2.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.

Hypertension. Meta-analysis suggests that calcium supplementation results in a small reduction in both systolic and diastolic blood pressure,[1] or in systolic blood pressure alone.[2] However, the effect was too small to support the use of calcium supplementation for preventing or treating hypertension (p. 1251.1). The poor quality of the studies and the heterogeneity between them was also commented on.[2] In a controlled study, calcium with vitamin D supplementation reduced systolic blood pressure more effectively than calcium alone.[3]

1. Griffith LE, *et al.* The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 1999; **12:** 84–92.
2. Dickinson HO, *et al.* Calcium supplementation for the management of primary hypertension in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 06/03/09).
3. Pfeifer M, *et al.* Effects of a short-term vitamin D_3 and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001; **86:** 1633–7.

PREGNANCY. Despite an earlier meta-analysis[1] which concluded that calcium supplementation during pregnancy reduced systolic and diastolic blood pressure and the incidence of pre-eclampsia and hypertension, results from a double-blind, placebo-controlled study in a total of 4589 women indicated that calcium supplementation during normal pregnancy did not prevent pre-eclampsia, pregnancy-associated hypertension without pre-eclampsia, or a number of other related disorders.[2] A subsequent review[3] found that calcium supplementation was beneficial, but it was noted that there was a wide variation in results between different studies; most of the effect was in studies including women identified as being at high risk for pre-eclampsia, and results from studies including lower-risk women found that calcium had no effect. The high-risk studies were carried out in areas with a low dietary calcium intake, suggesting that benefit might be greatest in such populations. However, a further study[4] in 8325 women living in areas with a low calcium intake but not specifically at high risk found that calcium supplementation had no significant effect on the incidence of pre-eclampsia, although it did reduce the risk of severe pre-eclamptic complications. An updated meta-analysis,[5] which included this study, concluded that calcium supplementation during pregnancy was safe and that it did reduce the incidence of pre-eclampsia and serious complications, particularly in high-risk women.

For discussions of hypertension in pregnancy and eclampsia and pre-eclampsia, see p. 1251.1 and p. 511.1, respectively.

1. Bucher HC, *et al.* Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275:** 1113–17. Correction. *ibid.*; **276:** 1388.
2. Levine RJ, *et al.* Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997; **337:** 69–76.
3. DerSimonian R, Levine RJ. Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. *JAMA* 1999; **282:** 664–70.
4. Villar J, *et al.* World Health Organization Calcium Supplementation for the Prevention of Preeclampsia Trial Group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. *Am J Obstet Gynecol* 2006; **194:** 639–49.
5. Hofmeyr GJ, *et al.* Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 20/08/10).

Malignant neoplasms. There is some evidence that calcium supplementation may modestly reduce the risk[1-3] of colorectal cancer and its recurrence (p. 707.2).[4-6] This protective effect appears to be more pronounced for advanced colorectal lesions,[7] and when serum concentrations of vitamin D are in the higher range.[8]

1. Wu K, *et al.* Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* 2002; **94:** 437–46.
2. McCullough ML, *et al.* Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* 2003; **14:** 1–12.
3. Cho E, *et al.* Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst* 2004; **96:** 1015–22. Correction. *ibid.*; 1724.
4. Baron JA, *et al.* Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999; **340:** 101–7.
5. Bonithon-Kopp C, *et al.* Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 2000; **356:** 1300–6.
6. Martínez ME, *et al.* Calcium, vitamin D, and risk of adenoma recurrence (United States). *Cancer Causes Control* 2002; **13:** 213–20.
7. Wallace K, *et al.* Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; **96:** 921–5.
8. Grau MV, *et al.* Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1765–71.

Premenstrual syndrome. Calcium supplementation was effective in relieving the luteal phase symptoms of premenstrual syndrome (p. 2272.3) in 1 study.[1] A review of this and other studies suggested that calcium supplementation at a dose of 1.2 to 1.6 g daily should be considered in patients with premenstrual syndrome.[2]

1. Thys-Jacobs S, *et al.* Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998; **179:** 444–52.
2. Ward MW, Holimon TD. Calcium treatment for premenstrual syndrome. *Ann Pharmacother* 1999; **33:** 1356–8.

Adverse Effects and Treatment

Oral calcium salts can cause gastrointestinal irritation; calcium chloride is generally considered to be the most irritant of the commonly used calcium salts.

Injection of calcium salts can also produce irritation, and intramuscular or subcutaneous injection in particular can cause local reactions including sloughing or necrosis of the skin; solutions of calcium chloride are extremely irritant and should not be injected intramuscularly or subcutaneously. Soft-tissue calcification has followed the use of calcium salts parenterally.

Excessive amounts of calcium salts may lead to hypercalcaemia. This complication is usually associated with parenteral use, but can occur after oral dosage, usually in patients with renal failure or who are also taking vitamin D. Symptoms of hypercalcaemia include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, nephrocalcinosis, renal calculi, and, in severe cases, cardiac arrhythmias and coma. Too rapid intravenous injection of calcium salts may also lead to symptoms of hypercalcaemia, as well as a chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalcaemia will usually resolve if calcium and other contributory drugs such as vitamin D are stopped (see also Vitamin D-mediated Hypercalcaemia, p. 1776.1). If hypercalcaemia is severe, urgent treatment is required as outlined on p. 1776.1.

Effects on the cardiovascular system. The results of a meta-analysis suggested that the use of oral calcium supplements alone (without vitamin D) might be associated with an increased risk of myocardial infarction.[1] However, none of the 15 included studies had cardiovascular outcomes as primary end-points, and collection of the data on cardiovascular events was not standardised. Also, the results of this analysis may not apply to the use of calcium supplements with vitamin D, which is generally recommended in the treatment and prevention of osteoporosis (p. 1168.1).

1. Bolland MJ, *et al*. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; **341**: 289. Full version: http://www.bmj.com/cgi/reprint/341/jul29_1/c3691 (accessed 18/08/10)

Precautions

Solutions of calcium salts, particularly calcium chloride, are irritant, and care should be taken to prevent extravasation during intravenous injection. Calcium salts should be given cautiously to patients with renal impairment, or diseases associated with hypercalcaemia such as sarcoidosis and some malignancies. In addition, they should generally be avoided in patients with calcium renal calculi, or a history of renal calculi. Calcium chloride, because of its acidifying nature, is unsuitable for the treatment of hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure.

Plasma-calcium concentrations should be monitored closely in patients with renal impairment and during parenteral dosage and if large doses of vitamin D are used concurrently.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcium glubionate and calcium lactate gluconate as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Hypercalcaemia has occurred when calcium salts are given with thiazide diuretics or vitamin D. Vitamin D increases the gastrointestinal absorption of calcium and thiazide diuretics decrease its urinary excretion. Plasma-calcium concentrations should be monitored in patients receiving the drugs together.

Bran decreases the gastrointestinal absorption of calcium, and may therefore decrease the efficacy of calcium supplements. Corticosteroids also reduce calcium absorption.

Calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication; parenteral calcium therapy is best avoided in patients receiving cardiac glycosides. Citrate salts increase the absorption of aluminium from the gastrointestinal tract (see Toxicity, under Adverse Effects of Aluminium Hydroxide, p. 1817.3), therefore patients with renal failure taking aluminium compounds should avoid taking calcium citrate. Calcium salts reduce the absorption of a number of other drugs such as bisphosphonates, fluoride, some fluoroquinolones, and tetracyclines; doses should be separated by at least 3 hours.

Pharmacokinetics

Calcium is absorbed mainly from the small intestine by active transport and passive diffusion. About one-third of ingested calcium is absorbed although this can vary depending upon dietary factors and the state of the small intestine; also absorption is increased in calcium deficiency and during periods of high physiological requirement such as during childhood or pregnancy and lactation. 1,25-Dihydroxycholecalciferol (calcitriol), a metabolite of vitamin D, enhances the active phase of absorption.

Excess calcium is mainly excreted renally. Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice. Minor amounts are lost in the sweat, skin, hair, and nails. Calcium crosses the placenta and is distributed into breast milk.

Human Requirements

Calcium is the most abundant mineral in the body and is an essential body electrolyte. However, defining individual calcium requirements has proved difficult and guidelines vary widely by country and culture. Some authorities have adopted a factorial approach. For example, in the UK the dietary reference value (DRV) represents the apparent calcium requirements of healthy people under the prevailing dietary circumstances. The amount of calcium absorbed varies according to several factors including the requirements of the body, but is normally only about 30 to 40% of the dietary intake.

The richest dietary sources of calcium are milk and milk products. Significant amounts can also be consumed in green leafy vegetables, fortified flour, the soft bones of fish, and hard water.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1) have been published for calcium.[1] In the USA recommended dietary allowances (RDA) had been set,[2] but have been replaced by dietary reference intakes (see p. 2046.1).[3] In the UK the estimated average requirement (EAR) for adults is 525 mg (13.1 mmol) daily and the reference nutrient intake (RNI) for adults is 700 mg (17.5 mmol) daily; these figures are based on a mean absorption of calcium of 30% from mixed diets. In the USA the traditional RDA was 800 mg daily for adults aged over 25 years; this figure was based on an absorption rate of 40%. Under the new dietary reference intakes, adequate intakes (AI) for calcium have been set, which are higher in some age groups than the previous RDAs.[3] For adults aged up to 50 years the AI is 1 g daily, and for those 51 years or older, it is 1.2 g daily.[3] The tolerable upper intake is considered to be 2.5 g daily.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Calcimax; Calcio Cit Simple†; Calcional Citrato; Calcium-Sandoz; Citramar†; Findeclin Combi; Ostram; Procalcio†; Raffo-Ca; Regucal; Renacalcio; Royen; Sigmacal; ***Austral.***: Celloids CP 57†; Citracal; Sandocal†; ***Austria***: Calcium Fresenius; Calcium-Sandoz†; Calcium-Sandoz; OsvaRen; Phos-Ex; ***Belg.***: Calciclo; PhosLo; Sandoz Calcium; Sandoz Calcium; ***Braz.***: Calcium-Sandoz F; Calcium-Sandoz; Miocalven; ***Canad.***: Calciforte†; Calciject; Calcium-Sandoz; Citracal + D; Dicalcine†; Formula Cal-Phos†; Osteocit; PhosLo; Solucal; ***Chile***: Calcimax; Calcimin†; Calcium-Sandoz†; Kaplus; Ostram†; PhosLo; ***China***: A Si Ka (阿斯卡); Gai Tian Li (盖天力); Hong Tai (弘泰); Huoligai (活力钙); Jia Jia Gai (佳加盖); Kai Ti (凯替); Si Lin Tuo (斯林妥); Si Te Li (司特立); Wei Li Tian (维立添); You Ni Le (尤尼乐); ***Cz.***: Calcium Biotika; Phosphosorb; ***Denm.***: Calcium-Sandoz; Calcium-Sandoz; Phos-Ex; ***Fin.***: Calcium-Sandoz†; Calcium-Sandoz; Phos-Ex; Selutrio; ***Fr.***: CAL'Ocean†; Calcium-Sandoz; Glucalcium†; Ostram; Phosphosorb; ***Ger.***: Calcet; Calciretard; Calcitrat; Calcium-Sandoz†; Cerasorb; OsvaRen; Phos-Ex†; Phosphosorb; ***Gr.***: Calciforte; Decalcit; Neocalcit; Ormitac; Osteorel; Osteus; Ostram; Phosphosorb; ***Hong Kong***: Calcium Unison; Calcium-Sandoz; Calforte†; Citracal†; Citracium; Kalac†; Mega-Cal; ***Hung.***: Bano; Calcimusc; Calcium-Sandoz; Citrokalcium; ***India***: Calbin; Calzorb; CCM; Ezorb; Hypophos; Milkal-G; Miltab; Phosforid; ***Indon.***: Calnic; Dumocalcin; Lakalsik; Licokalk; Pro Kalk; ***Irl.***: Calcium-Sandoz; Everose†; Phosex; Sandocal; ***Israel***: Calcium-Sandoz†; Calcium-Sandoz; Ferrocal; ***Ital.***: Calcetat; Calcium-Sandoz; ***Malaysia***: Calcium Upha†; ***Mex.***: Bionokaltran; Calcidef; Calcifox†; Calcigenol Doble; Calciofem; Calcium-Sandoz; Calcival; ***Neth.***: Calcium-Sandoz; Calcium-Sandoz; Phos-Ex†; PhosLo; Phosphosorb; ***Norw.***: Calcium-Sandoz; Phos-Ex; ***NZ***: Calcium-Sandoz†; ***Philipp.***: Calcebone; Calcinate; United Home Calactate; ***Pol.***: Calcium Calfit†; Calcium Syrop; Calcium-Sandoz Forte; Ostical†; Ostram; Sanosvit Calcium; Satural; ***Port.***: Calcium-Sandoz; Extraneal; Phosphosorb; Sandocal†; ***Rus.***: Calcium-Sandoz Forte (Кальций-Сандоз Форте); Vita-Iodurol (Вита-иодурол); ***S.Afr.***: Calcium-Sandoz; Glucal†; ***Singapore***: Calcium-Sandoz Forte; Citracal†; Dorama-neo; Hydrofluoric Acid Antidote; Os-Cal; Vitacal; ***Spain***: Calcio 20 Emulsion; Calcium-Sandoz Forte†; Ibercal; Ostram; PhosLo; Royen; Suplecal; Tepox Cal; ***Swed.***: Calcium-Sandoz; Calcium-Sandoz; Phos-Ex; ***Switz.***: AcetaPhos; Calcium-Sandoz; Calcium-Sandoz; Renacet; ***Thai.***: BO Cal; Cal-Cit; Cal-med; Calcetate; Calcion; Calcipac; Calcium Unison†; Calcium Utopian; Calcium-Sandoz; Calsorp; Caltab Forte†; Calvin; Cebrin-Fe; Kal-Forte; Lo-P-Caps; ***Turk.***: Anti-Fosfat Ca; Calcium-Sandoz; Calcium-Sandoz; Phos-Bind; Phos-Ex; Phos-Out; ***UK***: BioCalth; Calcium-Sandoz; Caphosol; Ostram; Phos-Ex; PhosLo; Sandocal; ***USA***: Cal-C; Cal-Citrate; Cal-G; Cal-Lac; Calphron; Caphosol; Citracal; Eliphos; Oyster Calcium; PhosLo; Posture; Prelief; ***Venez.***: Calcibon; Calcitrex; Calcium-Sandoz; Calcium-Sandoz; Citracal; Maxical; Oscale.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Hung.***: Kalmopyrin; ***Pol.***: Polopiryna C Plus; ***Swed.***: Deltison.

Homoeopathic Preparations. ***Austria***: China Med Complex; Colchicum Med Complex; Globuli gegen Gelenkschmerzen; Lymphomyosot; Osanit Zahnungskugelchen; Osteoplex; Steiroplex; Zahnkugelchen; ***Canad.***: Biochemic Phosphates; Calms Forte 4 Kids; Calms Forte; Combinaison†; Diamite; Fibromyalgie; Fucus L111†; Hylands Bioplasma; Hylands Formula CF; Hylands Formula NT; Hylands Kinder-T†; Ikoplex 5†; Melange†; Minerals+; Nerve Tonic; Nuage Bioplasma†; Osteel†; Phyto-Cal; Rexorubia†; Sorinoheel; Teething; Ton 1 Complex†; Ursical Formula†; Urticalcin; ***Chile***: Bioactiv D; Ikoplex No 15; Ikoplex No 1; Ikoplex No 20; Ikoplex No 22; Ikoplex No 2; Ikoplex No 4; Ikoplex No 6; Ikoplex No 9; ***Cz.***: Lymphomyosot; ***Fr.***: Abbe Chaupitre no 1†; Abbe Chaupitre no 6; Abbe Chaupitre no 91†; Calcarea Compose; Dolisedal†; Fucus Complexe No 111; Hypophysis Complexe No 31†; L 28; Osteocynesine; Rexorubia; Triphosphates; ***Ger.***: Alho-Arthrosan N; Araniforce rheuma†; Disci Bamb; Disco-cyl Ho-Len-Complex; Drufusan N†; Drufusan; Girheulit HM†; Infi-Symphytum; Lumbago-Gastreu S R11; Lymphomyosot N; Lymphomyosot; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Osanit; Osteoplex; Pascoe-Agil HOM; Ranocalcin HM; Refesan T; Roth's RKT Tropfen; Steirocall; Steiroplex†; ***Hung.***: Lymphomyosot; Osteoheel; ***Neth.***: Dulcarhus-Gastreu R11; Emvita 2; Kind 0-6 Caltrivat; Lymfelite; Osteocynesine†; ***Port.***: Osteocynesine; ***S.Afr.***: Lymphomyosot; ***Switz.***: Osteoheel; Regenaplex Nr 38b; Silacten; Urticalcin; ***UK***: New Era Elasto; New Era Nervone; ***Ukr.***: Immunokind (Иммунокинд); Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations

BP 2014: Calcium and Ergocalciferol Tablets; Calcium Chloride Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Chewable Calcium and Ergocalciferol Tablets; Chewable Calcium Gluconate Tablets; Compound Sodium Lactate Infusion; Effervescent Calcium Gluconate Tablets;

BPC 1973: Calcium with Vitamin D Tablets;

USP 36: Aluminum Sulfate and Calcium Acetate for Topical Solution; Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution; Calcium Acetate Tablets; Calcium and Vitamin D with Minerals Tablets; Calcium Chloride Injection; Calcium Citrate Tablets; Calcium Glubionate Syrup; Calcium Gluceptate Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Calcium Levulinate Injection; Calcium with Vitamin D Tablets; Dibasic Calcium Phosphate Tablets; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Minerals Capsules; Minerals Tablets; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 4; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes Injection Type 2; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Ringer's and Dextrose Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Magnesium

Magnesio; Magnésium; Magnez; Магний.

Mg=24.305

UNII — I38ZP9992A (magnesium); T6V3LHY838 (magnesium ion).

Description. Magnesium is a cation given as various magnesium-containing salts.

Incompatibility. Magnesium salts have been reported to be incompatible with a wide range of drugs.

Magnesium Acetate

Acetato magnésico; Magnesii Acetas Tetrahydricus; Magnesio, acetato de; Magnésium (acétate de) tétrahydraté; Magnesiumacetattetrahydrat; Magnesiumasetaattitetrahydraatti; Magnézium acetáttetrahidrát; Magnezu octan; Magnio acetatas tetrahidratas; Octan hořečnatý tetrahydrát; Ацетат Магния; Уксуснокислый Магний.

$C_4H_6MgO_4.4H_2O$=214.5

CAS — 142-72-3 (anhydrous magnesium acetate); 16674-78-5 (magnesium acetate tetrahydrate).

UNII — 0E95JZY48K (magnesium acetate); I01G0EJC3B (magnesium acetate tetrahydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Acetate Tetrahydrate). Colourless crystals or a white or almost white, crystalline powder. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 7.5 to 8.5.

Equivalence. Each g of magnesium acetate (tetrahydrate) represents about 4.7 mmol of magnesium and the equivalent of bicarbonate. Magnesium acetate (tetrahydrate) 8.83 g is equivalent to about 1 g of magnesium.

Magnesium Ascorbate

Ascorbato magnésico; Magnesio, ascorbato de; Магния Аскорбат.

$(C_6H_7O_6)_2Mg$=374.5

CAS — 15431-40-0.

UNII — 0N1G678593.

Equivalence. Each g of magnesium ascorbate (anhydrous) represents about 2.7 mmol of magnesium. Magnesium ascorbate (anhydrous) 15.4 g is equivalent to about 1 g of magnesium.

Magnesium Aspartate

Aspartato magnésico; Bázisos magnézium-aszpartát-dihidrát; Magnesii aspartas dihydricus; Magnesii Hydrogenoaspartas Dihydricus; Magnesio, aspartato de; Magnésium (aspartate de) dihydraté; Magnesium Aspartate Dihydrate; Magnesiumaspartaattidihydraatti; Magnesiumaspartat-Dihydrat; Magnesiumaspartatdihydrat; Magnesium-hydrogenaspartát dihydrát; Magnio aspartatas dihidratas; Магния Аспарагинат.

Magnesium aminosuccinate dihydrate; Magnesium di[(*S*)-2-aminohydrogenobutane-1,4-dioate].

$C_8H_{12}MgN_2O_8.2H_2O$=324.5

CAS — 18962-61-3 (anhydrous magnesium aspartate); 2068-80-6 (anhydrous magnesium aspartate or magnesium aspartate dihydrate); 7018-07-7 (magnesium aspartate tetrahydrate).

ATC — A12CC05.

ATC Vet — QA12CC05.

UNII — R17X820ROL.

Pharmacopoeias. *Eur.* (see p. vii) includes the dihydrate form of the (*S*)-aspartate. *Ger.* includes the tetrahydrate form of the racemic aspartate.

Ph. Eur. 8: (Magnesium Aspartate Dihydrate; Magnesium Aspartate BP 2014). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water. A 2.5% solution in water has a pH of 6.0 to 8.0.

Equivalence. Each g of magnesium aspartate (dihydrate) represents about 3.1 mmol of magnesium. Magnesium aspartate (dihydrate) 13.4 g is equivalent to about 1 g of magnesium.

Each g of magnesium aspartate (tetrahydrate) represents about 2.8 mmol of magnesium. Magnesium aspartate (tetrahydrate) 14.8 g is equivalent to about 1 g of magnesium.

Magnesium Chloride

Magnesiumklorid; Chlorid hořečnatý; Chlorure de Magnésium Cristallisé; Cloreto de Magnésio; Cloruro magnésico; E511; Magnesii chloridum; Magnesio, cloruro de; Magnesium Chloratum; Magnésium, chlorure de; Magnesiumkloridi; Magnézium-klorid; Magnezu chlorek; Magnio chloridas; Магния Хлорид.

$MgCl_2.xH_2O$=95.20 (anhydrous); 203.3 (hexahydrate)

CAS — 7786-30-3 (anhydrous magnesium chloride); 7791-18-6 (magnesium chloride hexahydrate).

ATC — A12CC01; B05XA11.

ATC Vet — QA12CC01; QB05XA11.

UNII — 02F3473H9O (magnesium chloride); 59XN63C8VM (anhydrous magnesium chloride).

Pharmacopoeias. *Eur.* (see p. vii), *US*, and *Viet.* include the hexahydrate.

Eur. also includes magnesium chloride 4.5-hydrate.

Ph. Eur. 8: (Magnesium Chloride Hexahydrate; Magnesii Chloridum Hexahydricum). Colourless, hygroscopic crystals. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

Ph. Eur. 8: (Magnesium Chloride 4.5-Hydrate; Magnesii Chloridum 4.5-Hydricum; Partially Hydrated Magnesium Chloride BP 2014). A white or almost white, hygroscopic, granular powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 36: (Magnesium Chloride). Colourless, odourless, deliquescent flakes or crystals, which lose water when heated to 100 degrees and lose hydrochloric acid when heated to 110 degrees. Very soluble in water; freely soluble in alcohol. pH of a 5% solution in water is between 4.5 and 7.0. Store in airtight containers.

Equivalence. Each g of magnesium chloride (hexahydrate) represents about 4.9 mmol of magnesium and 9.8 mmol of chloride. Magnesium chloride (hexahydrate) 8.36 g is equivalent to about 1 g of magnesium.

Magnesium Gluceptate

Gluceptato magnésico; Magnesio, glucoheptonato de; Magnesium Glucoheptonate; Магния Глюцептат.

$C_{14}H_{26}MgO_{16}$=474.7

UNII — NR47LC4280.

Equivalence. Each g of magnesium gluceptate (anhydrous) represents about 2.1 mmol of magnesium. Magnesium gluceptate (anhydrous) 19.5 g is equivalent to about 1 g of magnesium.

Magnesium Gluconate

Gluconato magnésico; Magnesii gluconas; Magnesio, gluconato de; Magnésium, gluconate de; Magnesiumgluconat; Магния Глюконат.

Magnesium D-gluconate hydrate.

$C_{12}H_{22}MgO_{14}.xH_2O$=414.6 (anhydrous)

CAS — 3632-91-5 (anhydrous magnesium gluconate); 59625-89-7 (magnesium gluconate dihydrate).

ATC — A12CC03.

ATC Vet — QA12CC03.

UNII — T42NAD2KHC.

Pharmacopoeias. In *Eur.* (see p. vii), which allows either anhydrous or hydrated forms, and in *US*, which allows either anhydrous or the dihydrate.

Ph. Eur. 8: (Magnesium Gluconate). A white or almost white, amorphous, hygroscopic, crystalline or granular powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. Store in airtight containers.

USP 36: (Magnesium Gluconate). Colourless crystals or a white powder or granules. Is odourless. Freely soluble in water; very slightly soluble in alcohol; insoluble in ether. pH of a 5% solution in water is between 6.0 and 7.8.

Equivalence. Each g of magnesium gluconate (anhydrous) represents about 2.4 mmol of magnesium. Magnesium gluconate (anhydrous) 17.1 g is equivalent to about 1 g of magnesium.

Magnesium Glycerophosphate

Glicerofosfato magnésico; Glycerofosforečnan hořečnatý; Magnesii Glycerophosphas; Magnesio, glicerofosfato de; Magnesium Glycerinophosphate; Magnésium, glycérophosphate de; Magnesiumglycerofosfat; Magnesiumglycerophosphat; Magnesiumglyserofosfaatti; Magnézium-glicerofoszfát; Magnio glicerofosfatas; Магния Глицерофосфат.

$C_3H_7MgO_6P.xH_2O$=194.4 (anhydrous)

CAS — 927-20-8 (anhydrous magnesium glycerophosphate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Glycerophosphate). A mixture, in variable proportions, of magnesium (*R,S*)-2,3-dihydroxypropyl phosphate and magnesium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate. It may be hydrated. A white or almost white, hygroscopic powder. Practically insoluble in alcohol; dissolves in dilute solutions of acids. Store in airtight containers.

Equivalence. Each g of magnesium glycerophosphate (anhydrous) represents about 5.1 mmol of magnesium. Magnesium glycerophosphate (anhydrous) 8 g is equivalent to about 1 g of magnesium.

Magnesium Lactate

Lactato magnésico; Magnesii Lactas; Magnesio, lactato de; Magnésium, lactate de; Magnesiumlaktaatti; Magnesiumlaktat; Magnesium-laktát; Magnezu mleczan; Молочнокислый Магний; Магния Лактат.

Magnesium 2-hydroxypropionate.

$C_6H_{10}MgO_6$=202.4

CAS — 18917-93-6.

ATC — A12CC06.

ATC Vet — QA12CC06.

UNII — MT6QI8324A.

Pharmacopoeias. *Eur.* (see p. vii) includes the dihydrate.

Ph. Eur. 8: (Magnesium Lactate Dihydrate; Magnesii Lactas Dihydricus). A white or almost white, crystalline or granular powder. Slightly soluble in water; soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 6.5 to 8.5.

Equivalence. Each g of magnesium lactate (anhydrous) represents about 4.9 mmol of magnesium. Magnesium lactate (anhydrous) 8.33 g is equivalent to about 1 g of magnesium.

Magnesium Phosphate

Fosfato magnésico trifásico; Magnesio, fosfato de; Tribasic Magnesium Phosphate; Trimagnesium Phosphate; Ортофосфат Магния Трёхзамещенный.

$Mg_3(PO_4)_2.5H_2O$=352.9

CAS — 7757-87-1 (anhydrous magnesium phosphate); 10233-87-1 (magnesium phosphate pentahydrate).

ATC — B05XA10.

ATC Vet — QB05XA10.

UNII — 453COF7817 (magnesium phosphate pentahydrate); XMK14ETW2D (anhydrous magnesium phosphate).

Pharmacopoeias. In *US.*

Ger. includes Magnesium Hydrogen Phosphate Trihydrate ($MgHPO_4.3H_2O$ = 174.3).

USP 36: (Magnesium Phosphate). A white, odourless, powder. Almost insoluble in water; readily soluble in dilute mineral acids.

Equivalence. Each g of magnesium phosphate (pentahydrate) represents about 8.5 mmol of magnesium and 5.7 mmol of phosphate. Magnesium phosphate (pentahydrate) 4.84 g is equivalent to about 1 g of magnesium.

Magnesium Pidolate *(pINNM)*

Magnesii Pidolas; Magnesio, pidolato de; Magnésium, pidolate de; Magnesium Pyroglutamate; Magnesiumpidolaatti; Magnesiumpidolat; Magnesium-pidolát; Magnéziumpidolát; Magnio pidolatas; Pidolate de Magnesium; Pidolato de magnesio; Pidolato magnésico; Магния Пидолат.

Magnesium 5-oxopyrrolidine-2-carboxylate.

$(C_5H_6NO_3)_2Mg$=280.5

CAS — 62003-27-4.

ATC — A12CC08.

ATC Vet — QA12CC08.

UNII — V5PC588N7G.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Pidolate). An amorphous, white or almost white, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 10% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Equivalence. Each g of magnesium pidolate (anhydrous) represents about 3.6 mmol of magnesium. Magnesium pidolate (anhydrous) 11.5 g is equivalent to about 1 g of magnesium.

Magnesium Sulfate

518; Epsom Salts; Magnesii Sulfas; Magnesio, sulfato de; Magnésium, sulfate de; Magnesium Sulphate; Magnesiumsulfaatti; Magnesiumsulfat; Magnézium-szulfát; Magnezu siarczan; Magnio sulfatas; Sal Amarum; Sel Anglais; Sel de Sedlitz; Síran hořečnatý; Sulfato magnésico; Сульфат Магния.

$MgSO_4.xH_2O$=120.4 (anhydrous); 246.5 (heptahydrate)

CAS — 7487-88-9 (anhydrous magnesium sulfate); 10034-99-8 (magnesium sulfate heptahydrate).

ATC — A06AD04; A12CC02; B05XA05; D11AX05; V04CC02.

ATC Vet — QA06AD04; QA12CC02; QB05XA05; QD11AX05; QV04CC02.

UNII — ML30MJ2U7I (anhydrous magnesium sulfate); DE08037SAB (magnesium sulfate); E2L2TK027P (magnesium sulfate monohydrate); SK47B8698T (magnesium sulfate heptahydrate).

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.* include the heptahydrate.

US allows the dried form, the monohydrate, or the heptahydrate form.

The dried form is included in *Br.*

Ph. Eur. 8: (Magnesium Sulfate Heptahydrate; Magnesii Sulfas Heptahydricus). A white or almost white, crystalline powder or brilliant, colourless crystals. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol.

The BP 2014 gives Epsom Salts as an approved synonym.

BP 2014: (Dried Magnesium Sulfate). A white odourless or almost odourless powder, prepared by drying magnesium sulfate (heptahydrate) at 100 degrees until it has lost about 25% of its weight; it contains 62 to 70% of $MgSO_4$. Freely soluble in water; more rapidly soluble in hot water.

The BP gives Dried Epsom Salts as an approved synonym.

USP 36: (Magnesium Sulfate). It is the dried form, monohydrate, or the heptahydrate. Small, colourless crystals, usually needle-like. It effloresces in warm dry air. Soluble 1 in 0.8 of water and 1 in 0.5 of boiling water; freely but slowly soluble 1 in 1 of glycerol; sparingly soluble in alcohol. pH of a 5% solution in water is between 5.0 and 9.2.

Equivalence. Each g of magnesium sulfate (heptahydrate) represents about 4.1 mmol of magnesium. Magnesium sulfate (heptahydrate) 10.1 g is equivalent to about 1 g of magnesium.

Uses and Administration

Some magnesium salts are given as a source of magnesium ions in the treatment of **magnesium deficiency and hypomagnesaemia** (p. 1776.3). Doses may be expressed in terms of mmol or mEq of magnesium, mass (mg) of magnesium, or mass of magnesium salt (for comparative purposes, see Table 2, below). In acute or severe hypomagnesaemia, magnesium may be given parenterally, usually as the chloride or sulfate. One suggested regimen is 20 mmol of magnesium in 1 litre of infusion solution (glucose 5% or sodium chloride 0.9%) given *intravenously* over 3 hours. Alternatively, 35 to 50 mmol of magnesium in 1 litre of infusion solution may be given over a period of 12 to 24 hours. Up to a total of 160 mmol may be required over 5 days. In those receiving parenteral nutrition, doses of about 12 mmol magnesium daily may be given to prevent recurrence of the deficit. Magnesium sulfate can also be given *intramuscularly* for severe magnesium deficiency. A recommended dose is 1 mmol/kg of magnesium, given over a period of 4 hours; this route is stated to be painful. Careful monitoring of plasma-magnesium and other electrolyte concentrations is essential. Doses should be reduced in renal impairment. Other salts which are, or have been, used parenterally include magnesium ascorbate, magnesium aspartate hydrochloride, and magnesium pidolate.

In simple deficiency states magnesium salts may be given *orally* in doses adjusted according to individual requirements. For preventing recurrence of hypomagnesaemia, doses of 24 mmol daily in divided doses have been recommended. Salts that are, or have been, used orally include magnesium aspartate, magnesium chloride, magnesium citrate, magnesium fluoride, magnesium gluceptate, magnesium gluconate, magnesium glycerophosphate, magnesium lactate, magnesium levulinate, magnesium orotate, and magnesium pidolate.

Magnesium salts such as the carbonate, hydroxide, oxide, and trisilicate are widely used for their **antacid** properties (p. 1803.1). Magnesium salts also act as **osmotic laxatives** (p. 1804.1); the salts generally used for this purpose are magnesium sulfate (an oral dose of 5 to 10 g in 250 mL of water being given for rapid bowel evacuation) and magnesium hydroxide (p. 1857.2).

Table 2. Some magnesium salts and their magnesium content.

	Magnesium content per g		
Magnesium salt	mg	mmol	mEq
Magnesium acetate (tetrahydrate)	113	4.7	9.3
Magnesium ascorbate (anhydrous)	65	2.7	5.3
Magnesium aspartate (dihydrate)	75	3.1	6.2
Magnesium aspartate (tetrahydrate)	67	2.8	5.5
Magnesium chloride (hexahydrate)	120	4.9	9.8
Magnesium gluceptate (anhydrous)	51	2.1	4.2
Magnesium gluconate (anhydrous)	59	2.4	4.8
Magnesium glycerophosphate (anhydrous)	125	5.1	10.3
Magnesium lactate (anhydrous)	120	4.9	9.9
Magnesium phosphate (pentahydrate)	207	8.5	17.0
Magnesium pidolate (anhydrous)	87	3.6	7.1
Magnesium sulfate (heptahydrate)	99	4.1	8.1

Parenteral magnesium sulfate has some specific uses. It is used for the emergency treatment of some **arrhythmias** such as torsade de pointes (see below) and those associated with hypokalaemia (p. 1777.2). The usual dose is 2 g of magnesium sulfate (8 mmol of magnesium) given intravenously over 10 to 15 minutes and repeated once if necessary.

Parenteral magnesium sulfate is also used for the treatment and prevention of seizures in pregnant women with **eclampsia and pre-eclampsia** (see below). Debate continues as to which dosage regimen is most appropriate. Typically an intravenous loading dose of 4 g of magnesium sulfate (16 mmol of magnesium) is given over 5 to 15 minutes. This is then followed by either an infusion of 1 g (4 mmol magnesium) per hour (for at least 24 hours after the last seizure) or by deep intramuscular injection of 5 g (20 mmol magnesium) into each buttock then 5 g intramuscularly every 4 hours (for at least 24 hours after the last seizure). Should seizures recur under either regimen, then an additional intravenous dose of 2 to 4 g can be given. It is essential to monitor for signs of hypermagnesaemia, and to stop magnesium dosage should this occur. Doses should be reduced in renal impairment.

The use of magnesium sulfate in **acute myocardial infarction** and **premature labour** is discussed below (see below and p. 1789.1, respectively).

Dried magnesium sulfate has been used in the form of Magnesium Sulphate Paste (BP 2014) as an application to inflammatory skin conditions such as boils and carbuncles, but prolonged or repeated use may damage the surrounding skin.

General references.

1. McLean RM. Magnesium and its therapeutic uses: a review. *Am J Med* 1994; **96:** 63–76.
2. Fawcett WJ, *et al.* Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; **83:** 302–20.
3. Fox C, *et al.* Magnesium: its proven and potential clinical significance. *South Med J* 2001; **94:** 1195–1201.
4. Gums JG. Magnesium in cardiovascular and other disorders. *Am J Health-Syst Pharm* 2004; **61:** 1569–76.

Anaesthesia. Magnesium sulfate has been used to prevent the undesirable haemodynamic response sometimes associated with intubation (p. 2028.1). It has also been tried in the treatment of postoperative shivering (p. 1897.2).

Arrhythmias. Cardiac function is strongly influenced by electrolyte concentrations and some cardiac arrhythmias (p. 1266.1) may be associated with magnesium deficiency. Parenteral magnesium has a role in the management of torsade de pointes and some other arrhythmias, and has also been used to prevent postoperative atrial fibrillation. However, for a review of the debate over magnesium's possible antiarrhythmic effect in patients with myocardial infarction, see Myocardial Infarction, below.

Further references.

1. Frick M, *et al.* The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. *Eur Heart J* 2000; **21:** 1177–85.
2. Stuhlinger HG, *et al.* Der Stellenwert von Magnesium bei Herzrhythmusstorungen. *Wien Med Wochenschr* 2000; **150:** 330–4.
3. Piotrowski AA, Kalus JS. Magnesium for the treatment and prevention of atrial tachyarrhythmias. *Pharmacotherapy* 2004; **24:** 879–95.
4. Shiga T, *et al.* Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. *Am J Med* 2004; **117:** 325–33.
5. Alghamdi AA, *et al.* Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. *J Card Surg* 2005; **20:** 293–9.
6. Miller S, *et al.* Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart* 2005; **91:** 618–23.
7. Ho KM, *et al.* Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. *Heart* 2007; **93:** 1433–40.
8. Onalan O, *et al.* Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. *Am J Cardiol* 2007; **99:** 1726–32.

Eclampsia and pre-eclampsia. Parenteral magnesium sulfate has become the preferred treatment for seizures associated with **eclampsia** (p. 511.1). Studies and systematic reviews have shown it to be more effective than phenytoin,[1,2] diazepam,[1,3] or lytic cocktail,[4] as well as causing fewer adverse effects. Its advantages included a rapid effect and lack of sedation in the mother or the infant.[5] It was also considered to have a wide safety margin with the added security of calcium gluconate being an easily available antidote should overdose occur. Subsequent meta-analysis[6] and systematic review[2-4] reinforced this favourable view.

Magnesium sulfate may also be used to prevent eclampsia in **pre-eclamptic** patients; studies have shown it to be more effective than phenytoin,[7] or nimodipine.[8] A randomised placebo-controlled study[9] involving over 10 000 women in 33 countries found that treatment with magnesium sulfate approximately halved the risk of developing eclampsia; the number of maternal deaths was also less in the treatment group although the differences in risk between this group and the placebo group were not significant.

Despite some concerns about the effects on the fetus of magnesium sulfate use in premature labour, (see p. 1789.1), many,[10,11] including WHO, consider magnesium sulfate the drug of choice for both treatment and prevention of eclampsia. Moreover, follow-up studies of the international study mentioned above found that it was not associated with an increased risk of death or disability in the children at 18 months[12] and in the mothers at 2 years.[13]

1. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345:** 1455–63. Correction. *ibid.*; **346:** 258.
2. Duley L, Henderson-Smart DJ. Magnesium sulphate versus phenytoin for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 09/03/09).
3. Duley L, Henderson-Smart DJ. Magnesium sulphate versus diazepam for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 09/03/09).
4. Duley L, Gulmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 09/03/09).
5. Saunders N, Hammersley B. Magnesium for eclampsia. *Lancet* 1995; **346:** 788–9.
6. Chien PFW, *et al.* Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials. *Br J Obstet Gynaecol* 1996; **103:** 1085–91.
7. Lucas MJ, *et al.* A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995; **333:** 201–5.
8. Belfort MA, *et al.* A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med* 2003; **348:** 304–11.
9. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; **359:** 1877–90.
10. Roberts JM, *et al.* Preventing and treating eclamptic seizures. *BMJ* 2002; **325:** 609–10.
11. WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors.* GENEVA: WHO, 2000. Available at: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf (accessed 20/08/10)
12. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for children at 18 months. *BJOG* 2007; **114:** 289–99.
13. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for women at 2 years. *BJOG* 2007; **114:** 300–9.

Hypokalaemia. Potassium and magnesium homoeostasis are linked, and hypokalaemia with increased urine potassium excretion may occur in patients with hypomagnesaemia. In this situation, correction of potassium deficit usually requires magnesium to be given as well. Magnesium sulfate at doses greater than those required to correct hypomagnesaemia has been associated with greater improvements in potassium balance than doses just sufficient to correct hypomagnesaemia.[1]

1. Hamill-Ruth RJ, McGory R. Magnesium repletion and its effect on potassium homeostasis in critically ill adults: results of a double-blind, randomized, controlled trial. *Crit Care Med* 1996; **24:** 38–45.

Migraine. Low magnesium concentrations are thought to be important in the pathogenesis of migraine (p. 670.3), but the precise role of magnesium supplementation in the disorder remains to be determined.[1] In a double-blind study,[2] 24 mmol magnesium daily (in the form of oral magnesium citrate) reduced the incidence of migraine headache by 42% compared with a reduction of 16% with placebo. However, in another similar study,[3] 20 mmol magnesium daily (in the form of oral magnesium aspartate hydrochloride) was no more effective than placebo in producing a 50% reduction in migraine frequency or intensity. Intravenous magnesium sulfate has shown benefit in the treatment of migraine attacks,[4] especially in those with aura,[5,6] or in patients with low serum-magnesium levels.[7]

1. Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. *Clin Neurosci* 1998; **5:** 24–7.
2. Peikert A, *et al.* Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996; **16:** 257–63.
3. Pfaffenrath V, *et al.* Magnesium in the prophylaxis of migraine: a double-blind placebo-controlled study. *Cephalalgia* 1996; **16:** 436–40.
4. Demirkaya Ş, *et al.* Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache* 2001; **41:** 171–7.
5. Bigal ME, *et al.* Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2002; **22:** 345–53.
6. Bigal ME, *et al.* Eficácia de três drogas sobre a aura migranosa: um estudo randomizado placebo controlado. *Arq Neuropsiquiatr* 2002; **60:** 406–9.
7. Mauskop A, *et al.* Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels: a pilot study. *Clin Sci* 1995; **89:** 633–6.

Myocardial infarction. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium. Magnesium might have an antiarrhythmic effect (see also Arrhythmias, above) and protect the myocardium against reperfusion injury including myocardial stunning (delayed recovery of myocardial contractility function). Intravenous magnesium salts have been used for cardiac arrhythmias and in an overview of studies in patients with suspected myocardial infarction their use, generally within 12 hours of the onset of chest pain, reduced mortality.[1] The beneficial effect on mortality appeared to be confirmed by the LIMIT-2 study[2] in which 8 mmol of magnesium was given by intravenous injection before thrombolysis and followed

by a maintenance infusion of 65 mmol over the next 24 hours. Benefit was confirmed at follow-up an average of 2.7 years later;[3] however, there was no evidence of an antiarrhythmic effect. These beneficial effects were not borne out by the larger ISIS-4 study,[4] although there were slight differences in the magnesium regimen and its timing which might have played a part in these contradictory results. In an attempt to resolve the controversy, the MAGIC trial[5] was designed to test the hypothesis that early use of magnesium in a similar dose to that used in the LIMIT-2 study would reduce short-term mortality in patients with ST elevation myocardial infarction. No benefit or harm of magnesium was observed. A later systematic review of intravenous magnesium for acute myocardial infarction[6] concluded that although it may have some beneficial effects, such as reducing certain arrhythmias, magnesium is unlikely to reduce mortality and may increase certain adverse effects. At present the routine use of magnesium in myocardial infarction (p. 1257.1) cannot be recommended.

Patients with acute myocardial infarction may have magnesium deficiency and long-term treatment with oral magnesium has been tried, but in one study was associated with an increased risk of adverse cardiac events and could not be recommended for secondary prevention.[7]

1. Teo KK, *et al*. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* 1991; **303:** 1499–1503.
2. Woods KL, *et al*. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992; **339:** 1553–8.
3. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1994; **343:** 816–19.
4. Fourth International Study of Infarct Survival Collaborative Group. ISIS–4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.
5. The Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) trial: a randomised controlled trial. *Lancet* 2002; **360:** 1189–96.
6. Li J, *et al*. Intravenous magnesium for acute myocardial infarction. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/03/09).
7. Galløe AM, *et al*. Influence of oral magnesium supplementation on cardiac events among survivors of an acute myocardial infarction. *BMJ* 1993; **307:** 585–7.

Porphyria. Magnesium sulfate is one of the drugs that has been used for seizure prophylaxis in patients with porphyria who continue to experience convulsions while in remission.

Premature labour. Magnesium sulfate has been given intravenously to suppress initial uterine contractions in the management of premature labour[1-3] (p. 2131.1). Although it has been found to possess similar efficacy to beta$_2$ agonists,[4,5] and is widely used, in particular in the USA, a systematic review[6] concluded it was ineffective at delaying birth or preventing preterm birth. Other magnesium salts have also sometimes been given orally.[7,8]

Retrospective observational studies found a lower incidence of cerebral palsy in children with birth-weights of less than 1500 g when mothers were treated with magnesium sulfate for pre-eclampsia, eclampsia or premature labour.[9,10] However, increased total paediatric mortality was noted in an interim analysis of a study of antenatal magnesium sulfate in preterm labour,[11] and the study was subsequently stopped. Although they considered the safety of magnesium sulfate well established in gestation at term, the authors cautioned against the use of magnesium sulfate in very preterm labour. Subsequent studies found that magnesium sulfate was associated with increased perinatal mortality in low birth-weight offspring, particularly when doses of more than 48 g were used,[12] and that neonates with intraventricular haemorrhage (p. 1128.3) had mothers with higher serum-magnesium concentrations at delivery.[13] Some have commented[14,15] on other results, including studies of magnesium for treatment and prevention of eclampsia (see p. 1788.2), and concluded, along with a systematic review,[6] that its use as a tocolytic increased the risk of infant mortality. Nevertheless, further study has been undertaken on the use of magnesium sulfate solely for neuroprotection in preterm infants. More than 2000 women at high risk for premature delivery (gestation of 24 to 31 weeks and birth planned or expected within 2 to 24 hours), were included in a randomised, placebo-controlled study.[16] There was a significant decrease in the risk of moderate or severe cerebral palsy in the infants of women given magnesium sulfate, and the risk of paediatric death was slightly, but not significantly, increased. A similar study[17] in more than 1000 women also found significantly fewer cases of substantial motor dysfunction (including cerebral palsy) in infants who had been exposed to prenatal magnesium sulfate. In this study, however, the risk of death was slightly decreased. A systematic review[18] of 5 studies, including these two, concluded that magnesium sulfate used for neuroprotection reduced the risk of cerebral palsy, and did not increase the risk of paediatric death. However, it was still unclear which patients might benefit most, and questions remained about the most appropriate dose and timing of administration, whether maintenance therapy is needed, and whether treatment should be repeated.

Although magnesium sulfate is widely used, the American College of Obstetricians and Gynecologists does not promote it (or any drug) for first-line tocolysis.[19] It is not recommended in Europe,[20] and some in the USA have called for such use to be stopped.[21,22]

1. Amon E, *et al*. Tocolysis with advanced cervical dilatation. *Obstet Gynecol* 2000; **95:** 358–62.
2. Terrone DA, *et al*. A prospective, randomized, controlled trial of high and low maintenance doses of magnesium sulfate for acute tocolysis. *Am J Obstet Gynecol* 2000; **182:** 1477–82.
3. Katz VL, Farmer RM. Controversies in tocolytic therapy. *Clin Obstet Gynecol* 1999; **42:** 802–19.
4. Wilkins IA, *et al*. Efficacy and side effects of magnesium sulfate and ritodrine as tocolytic agents. *Am J Obstet Gynecol* 1988; **159:** 685–9.
5. Chau AC, *et al*. A prospective comparison of terbutaline and magnesium for tocolysis. *Obstet Gynecol* 1992; **80:** 847–51.
6. Crowther CA, *et al*. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 21/06/05).
7. Martin RW, *et al*. Comparison of oral ritodrine and magnesium gluconate for ambulatory tocolysis. *Am J Obstet Gynecol* 1988; **158:** 1440–3.
8. Ridgway LE, *et al*. A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. *Am J Obstet Gynecol* 1990; **163:** 879–82.
9. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995; **95:** 263–9.
10. Schendel DE, *et al*. Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. *JAMA* 1996; **276:** 1805–10.
11. Mittendorf R, *et al*. Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 1997; **350:** 1517–18.
12. Scudiero R, *et al*. Perinatal death and tocolytic magnesium sulfate. *Obstet Gynecol* 2000; **96:** 178–82.
13. Mittendorf R, *et al*. Association between maternal serum ionized magnesium levels at delivery and neonatal intraventricular hemorrhage. *J Pediatr* 2002; **140:** 540–6.
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15. Mittendorf R, *et al*. The Magpie trial. *Lancet* 2002; **360:** 1330–1.
16. Rouse DJ, *et al*. Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359:** 895–905.
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18. Doyle LW, *et al*. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 12/03/09).
19. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Management of preterm labor (ACOG Practice Bulletin number 43, May 2003). *Obstet Gynecol* 2003; **101:** 1039–47.
20. Di Renzo GC, Roura LC. European Association of Perinatal Medicine-Study Group on Preterm Birth. Guidelines for the management of spontaneous preterm labor. *J Perinat Med* 2006; **34:** 359–66. Also available at: http://www.reference-global.com/doi/pdfplus/10.1515/JPM.2006.073 (accessed 02/07/08)
21. Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. *Obstet Gynecol* 2006; **108:** 986–9.
22. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007; **357:** 477–87.

Pulmonary hypertension of the newborn. Intravenous magnesium sulfate has been studied in persistent pulmonary hypertension of the newborn (p. 1278.2) but does not yet have an established role.

Respiratory disorders. Magnesium sulfate, given intravenously over 20 minutes in doses of 1.2 g to patients with acute exacerbations of chronic obstructive pulmonary disease (p. 1199.1) who had received inhaled salbutamol, appeared to have moderate efficacy.[1]

Infusion of magnesium has been reported to be of benefit in some patients with acute asthma (p. 1195.2), but results have been conflicting;[2-5] meta-analyses of these and other studies concluded that its routine use was not justified, but that it may benefit some patients with severe exacerbations.[6,7] A meta-analysis of 5 studies in children concluded that intravenous magnesium sulfate is likely to be an effective adjunct to standard therapy in the symptomatic treatment of moderate to severe acute childhood asthma.[8] Inhalation of magnesium has also been investigated, either alone or with salbutamol, and meta-analyses[9,10] have shown that it improves pulmonary function, particularly when given with a beta$_2$ agonist, with the best results seen in more severe cases. However, evidence of positive effects on clinically more important outcomes is lacking.

1. Skorodin MS, *et al*. Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 1995; **155:** 496–500.
2. Skobeloff EM, *et al*. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA* 1989; **262:** 1210–13.
3. Green SM, Rothrack SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med* 1992; **21:** 260–5.
4. Ciarallo L, *et al*. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr* 1996; **129:** 809–14.
5. Silverman RA, *et al*. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002; **122:** 489–97.
6. Rowe BH, *et al*. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 21/06/05).
7. Alter HJ, *et al*. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. *Ann Emerg Med* 2000; **36:** 191–7.
8. Cheuk DKL, *et al*. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005; **90:** 74–7.
9. Blitz M, *et al*. Inhaled magnesium sulfate in the treatment of acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/12/07).
10. Villeneuve EJ, Zed PJ. Nebulized magnesium sulfate in the management of acute exacerbations of asthma. *Ann Pharmacother* 2006; **40:** 1118–24.

Stroke. Intravenous magnesium sulfate may have a neuroprotective effect in patients with stroke (p. 1269.2). A systematic review[1] found that, when given with nimodipine, daily magnesium treatment for up to 3 weeks reduced the risk of poor outcome in patients with subarachnoid haemorrhage. However, the results of an earlier randomised controlled study[2] in patients with ischaemic and non-ischaemic stroke showed no significant reduction in the risk of death or disability with a single, 24-hour infusion magnesium starting within 12 hours of an acute event.

1. Dorhout Mees S, *et al*. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/03/09).
2. Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004; **363:** 439–45.

Tetanus. Magnesium sulfate has been found to minimise autonomic disturbance in ventilated patients and control spasms in non-ventilated patients when used in the treatment of tetanus (p. 2029.2).

References.

1. Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia* 2002; **57:** 811–17.
2. William S. Use of magnesium to treat tetanus. *Br J Anaesth* 2002; **88:** 152–3.

Adverse Effects

Excessive parenteral doses of magnesium salts lead to the development of hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade. Other symptoms of hypermagnesaemia may include nausea, vomiting, flushing of the skin, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision, muscle weakness, bradycardia, coma, and cardiac arrest.

Hypermagnesaemia is uncommon after oral magnesium salts except in the presence of renal impairment. Ingestion of magnesium salts may cause gastrointestinal irritation and watery diarrhoea.

Effects on the gastrointestinal tract. There are isolated reports of paralytic ileus in patients receiving magnesium salts.[1,2] Delayed intestinal transit has also been reported in a neonate who received an intramuscular overdose of magnesium.[3] See also Pregnancy, under Precautions, p. 1790.1.

1. Hill WC, *et al*. Maternal paralytic ileus as a complication of magnesium sulfate tocolysis. *Am J Perinatol* 1985; **2:** 47–8.
2. Golzarian J, *et al*. Hypermagnesemia-induced paralytic ileus. *Dig Dis Sci* 1994; **39:** 1138–42.
3. Narchi H. Neonatal hypermagnesemia: more causes and more symptoms. *Arch Pediatr AdolescMed* 2001; **155:** 1074.

Hypersensitivity. Hypersensitivity reactions characterised by urticaria were described in 2 women after receiving magnesium sulfate intravenously.[1]

1. Thorp JM, *et al*. Hypersensitivity to magnesium sulfate. *Am J Obstet Gynecol* 1989; **161:** 889–90.

Treatment of Adverse Effects

The management of hypermagnesaemia is reviewed on p. 1776.2.

Hypermagnesaemia. A patient with hypermagnesaemia of a degree that is normally fatal was successfully treated using assisted ventilation, intravenous calcium chloride, and forced diuresis with mannitol infusions.[1] In another report, a 7-year-old boy given an Epsom salt (magnesium sulfate) enema for abdominal cramping, developed asystole and died, despite aggressive attempts at resuscitation. Such enemas should be avoided because of the risk of significant, unpredictable rectal absorption, leading to toxic hypermagnesaemia.[2]

1. Bohman VR, Cotton DB. Supralethal magnesemia with patient survival. *Obstet Gynecol* 1990; **76:** 984–6.
2. Tofil NM, *et al*. Fatal hypermagnesaemia caused by an Epsom salt enema: a case illustration. *South Med J* 2005; **98:** 253–6.

Precautions

Parenteral magnesium salts should generally be avoided in patients with heart block or severe renal impairment. They should be used with caution in less severe degrees of renal impairment and in patients with myasthenia gravis. Patients should be monitored for clinical signs of excess magnesium (see Adverse Effects, p. 1789.3), particularly when being treated for conditions not associated with hypomagnesaemia such as eclampsia. An intravenous preparation of a calcium salt should be available in case of toxicity. When used for hypomagnesaemia, serum-magnesium concentrations should be monitored.

Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored and use within 2 hours of delivery should be avoided (see also Pregnancy, below).

Oral magnesium salts should be used cautiously in patients with renal impairment. Taking with food may decrease the incidence of diarrhoea. Chronic diarrhoea from long-term use may result in electrolyte imbalance.

Breast feeding. In breast milk samples from 10 pre-eclamptic women given magnesium sulfate, mean magnesium concentrations 24 hours after delivery were about 6.4 mg per 100 mL, and significantly higher than those in control subjects. However, by 48 and 72 hours after delivery, values were not significantly different. In both treated and control subjects, milk-magnesium concentrations were about twice those of maternal plasma concentrations. Although total doses of magnesium given to mothers may differ, the authors considered any increased magnesium load to a breast-fed infant to be quite small, about 1.5 mg of additional magnesium daily, and unlikely to significantly alter magnesium clearance from the neonate.[1] Based on this, the American Academy of Pediatrics considers that use of magnesium sulfate is therefore usually compatible with breast feeding.[2]

1. Cruikshank DP, *et al.* Breast milk magnesium and calcium concentrations following magnesium sulfate treatment. *Am J Obstet Gynecol* 1982; **143:** 685–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/04)

Hepatic disorders. Severe hypermagnesaemia and hypercalcaemia developed in 2 patients with hepatic encephalopathy given magnesium sulfate enemas; both patients died, one during and one after asystole. It was recommended that patients with liver disease who might develop renal impairment, or in whom renal failure is established, should not be prescribed enemas containing magnesium for treatment of hepatic encephalopathy as serious magnesium toxicity can occur, which may contribute to death.[1]

1. Collinson PO, Burroughs AK. Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma. *BMJ* 1986; **293:** 1013–14. Correction. *ibid.;* 1222.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies magnesium sulfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. The meconium-plug syndrome (abdominal distention and failure to pass meconium) has been described in 2 neonates who were hypermagnesaemic after their mothers had received magnesium sulfate for eclampsia.[1] It was believed that the hypermagnesaemia may have depressed the function of intestinal smooth muscle. See also Effects on the Gastrointestinal Tract, p. 1789.3. In 36 hypermagnesaemic infants born to pre-eclamptic mothers treated with magnesium sulfate, significant neurobehavioural impairment persisted for over 24 hours after birth. Impairment was manifest by prolonged weakness in activities such as head lag, ventral suspension, suck reflex, and cry response; improvement corresponded to the decrease in plasma-magnesium concentrations.[2]

In studies in women with[3] and without[4] pre-eclampsia there were decreases in short-term fetal heart rate variability when women were given intravenous magnesium sulfate; however, although variability is considered a sign of fetal well-being the decrease was considered clinically insignificant.

1. Sokal MM, *et al.* Neonatal hypermagnesemia and the meconium-plug syndrome. *N Engl J Med* 1972; **286:** 823–5.
2. Rasch DK, *et al.* Neurobehavioral effects of neonatal hypermagnesemia. *J Pediatr* 1982; **100:** 272–6.
3. Atkinson MW, *et al.* The relation between magnesium sulfate therapy and fetal heart rate variability. *Obstet Gynecol* 1994; **83:** 967–70.
4. Hallak M, *et al.* The effect of magnesium sulfate on fetal heart rate parameters: a randomized, placebo-controlled trial. *Am J Obstet Gynecol* 1999; **181:** 1122–7.

Interactions

Parenteral magnesium sulfate potentiates the effects of competitive and depolarising neuromuscular blockers (p. 2033.2). The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive. Similarly, parenteral magnesium sulfate and nifedipine have been reported to have additive effects (p. 1454.2).

Oral magnesium salts decrease the absorption of tetracyclines and bisphosphonates, and doses should be separated by a number of hours.

Pharmacokinetics

About one-third of magnesium is absorbed from the small intestine after oral doses and even soluble magnesium salts are generally very slowly absorbed. The fraction of magnesium absorbed increases if magnesium intake decreases. In plasma, about 25 to 30% of magnesium is protein bound. Parenteral magnesium salts are excreted mainly in the urine, and oral doses are eliminated in the urine (absorbed fraction) and the faeces (unabsorbed fraction). Small amounts are distributed into breast milk. Magnesium crosses the placenta.

Human Requirements

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte which is a cofactor in numerous enzyme systems.

The body is very efficient at maintaining magnesium concentrations by regulating absorption and renal excretion, and symptoms of deficiency are rare. It is therefore difficult to establish a daily requirement.

Foods rich in magnesium include nuts, unmilled grains, and green vegetables.

UK and US recommended dietary intake. In the United Kingdom dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] and in the United States recommended daily allowances (RDA)[2] have been published for magnesium. In the UK the estimated average requirement (EAR) is 200 mg (or 8.2 mmol) daily for adult females and 250 mg (or 10.3 mmol) daily for adult males; the reference nutrient intake (RNI) is 270 mg (or 10.9 mmol) daily for adult females and 300 mg (or 12.3 mmol) daily for adult males; no increment is recommended during pregnancy but an increment of 50 mg (or 2.1 mmol) daily in the RNI is advised during lactation. In the USA under the new dietary reference intakes an EAR of 330 to 350 mg daily has been set in adult males and 255 to 265 mg daily in adult females; the corresponding RDAs are 400 to 420 mg and 310 to 320 mg daily.[2] An increase in RDA to 350 to 360 mg is recommended during pregnancy but the standard RDA is considered adequate during lactation. A tolerable upper intake level of 350 mg daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biomag; Magnebe; Magnesio Vital; Total Magnesiano; ***Austral.***: Celloids MP 65†; Magmin†; ***Austria***: Cormagnesin; Emgecard; FX Passage; Magnesiocard; Magnesium Verla; Magnesium Verla; Magvital†; ***Belg.***: Magnespasmyl; Ultra-Mg; ***Braz.***: Magnoston; Pidomag; Sal Amargo Purificado†; ***Canad.***: Epsom; Maglucate; Magnogene†; Magnonat†; Pansement Mag†; Proflavanol C†; Spasmag†; ***Chile***: Mag-Tab; ***China***: Bao Le (包乐); Panangin (潘南金); Tian Jia Yuan (天甲元); ***Cz.***: Magnerot; ***Fin.***: Selutrio; ***Fr.***: Efimag†; Mag 2; Maginjectable; Magnespasmyl; Magnogene; Megamag; Spasmag; Top-Mag†; ***Ger.***: Basti-Mag; Cormagnesin; FX Passage; Magium†; Magnaspart; Magnerot A; magnerot Classic; Magnerot; Magnesiocard; Magnesium Diasporal; Magnesium Verla N; Magnesium Verla N; Magnesium Verla; Magnesium Verla; Magnesium Verla; Magnesium-Sandoz forte†; Magnesium-Sandoz†; Magnesorot; Mg 5-Longoral; Mg 5-Sulfat; Mgnor; Power Orot†; Retterspitz Darmreinigungspulver ST; ***Gr.***: Mag 2; Solumag; Trofocard; Ultra-Mg; ***Hong Kong***: Faulding Remedies Epsom Salts†; ***Hung.***: Cormagnesin; Magnerot; Magnesiocard†; ***India***: Mag; Magneon; ***Irl.***: Magnesium Verla; ***Ital.***: Mag 2; MG 50; Solumag; ***Mex.***: Ifupeptol Magnesiado; ***Mon.***: Oromag; ***Norw.***: Nycoplus Magnesium; ***Pol.***: Asmag; Biomag†; Laktomag B_6; Laktomag; Magnefar; Slow-Mag; ***Port.***: Extraneal; Magnesiocard; Magnesona; Magnespasmil; Magnoral; Metabol-Mg; ***Rus.***: Cormagnesin (Кормагнезин); Magnerot (Магнерот); Vita-Iodurol (Вита-иодурол); ***S.Afr.***: Be-Lax; Mag SR; Magnesit; SB Laxative Mixture†; Slow-Mag; ***Spain***: Actimag; Magnesioboi; ***Switz.***: Actimagon†; Mag 2; Mag-Min†; Magnegon; Magnesiocard; Magnesium Biomed; Magnesium Biomed; Magnesium Vital; Magnesium-Sandoz; Mg 5-Granoral; Mg 5-Longoral; Mg 5-Oraleff; Solmag†; ***Thai.***: Magfifty; Maglax; ***Turk.***: Magnesiocard; ***UK***: Kest; Magnaphate; Magnaspartate; ***Ukr.***: Cormagnesin (Кормагнезин); Magnerot (Магнерот); ***USA***: Chloromag; Mag-G; Mag-SR; Mag-Tab; Maginex; Magtrate; Slow-Mag.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Colic Relief; Nervatona Focus; ***Austria***: Osanit Zahnungskugelchen; ***Canad.***: Biochemic Phosphates; Biomag†; Calms Forte; Col 138†; Combinaison†; Diamite; Ervopax†; Fibromyalgie; Formula C Doroon†; Formula FA 224†; Formula PC 223†; Homeo-Form T†; Hylands Bioplasma; Hylands Formula CF; Hylands Formula MC; Hylands Formula NT; Hylands LCQ; Hylands Leg Cramps; Hylands Menstrual Cramps†; Ikoplex 14†; Ikoplex 5†; Kid's Colic; Leg Cramps with Quinine; Melange†; Minerals+; Nerve Tonic; Nuage Bioplasma†; Passiflora Complex†; Rexorubia†; Spa Complex†; Spascupreel; Ton 1 Complex†; ***Chile***: Ikoplex No 10; Ikoplex No 14; Ikoplex No 1; Ikoplex No 20; Ikoplex No 23; Ikoplex No 3; Ikoplex No 4; Ikoplex No 5; Ikoplex No 6; Ikoplex No 9; Lumboplex; ***Cz.***: Spascupreel S†; ***Fr.***: Aloe Compose; Bilinum Complexe No 113; Biomag; Boripharm No 11†; Boripharm No 12†; Chelidonium Compose; Hepatocynesine†; L 25; Nervopax; Passiflora Compose; Rexorubia; Silicea Complexe No 11; Sulfur Complexe No 12; ***Ger.***: Carminativum Hevert; Disci Bamb; Disco-cyl Ho-Len-Complex; Dolo-Injektopas; Drufusan N†; Drufusan; Dysmenorrhoe-Gastreu S R75; Femin-Do; Gastro Magentabletten; Girheulit HM†; Homviohepan; Infi-China; Lithias-cyl L Ho-Len-Complex; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Osanit; Pectapas SL; Refesan T; Rufebran neuro†; Spascupreel; Spasmoject F; Spasmosyx F; Zitronensaurezyklus-Heel; ***Hung.***: Spascupreel; ***Neth.***: Co-Hypert; Kind 0-3 Cinababy; Spascupreel H; ***Rus.***: Menalgin (Менальгин); ***UK***: Medicinal Gargle; New Era Elasto; New Era Nervone; ***Ukr.***: Enterocind (Энтерокинд).

Pharmacopoeial Preparations

BP 2014: Chewable Magnesium Glycerophosphate Tablets; Magnesium Chloride Injection; Magnesium Glycerophosphate Oral Solution; Magnesium Sulphate Injection; Magnesium Sulphate Mixture; Magnesium Sulphate Paste;

USP 36: Calcium and Vitamin D with Minerals Tablets; Magnesium Gluconate Tablets; Magnesium Sulfate in Dextrose Injection; Magnesium Sulfate Injection; Minerals Capsules; Minerals Tablets; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 4; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes Injection Type 1; Multiple Electrolytes Injection Type 2; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Phosphate

Fosfato; Фосфат.

UNII — NK08V8K8HR.

Description. Phosphate is an anion given as various potassium or sodium salts.

Incompatibility. Phosphates are incompatible with calcium salts; the mixing of calcium and phosphate salts can lead to the formation of insoluble calcium-phosphate precipitates. Incompatibility has also been reported with magnesium salts.

Monobasic Potassium Phosphate

Dihydrogenfosforečnan draselný; E340; Fosfato monobásico de potasio; Kalii Dihydrogenophosphas; Kalio-divandenilio fosfatas; Kálium-dihidrogén-foszfát; Kaliumdihydrogenphosphat; Kaliumdivätefosfat; Kaliumdivetyfosfaatti; Monopotassium Phosphate; Phosphate monopotassique; Potasio, dihidrogenofosfato de; Potassium Acid Phosphate; Potassium Biphosphate; Potassium Dihydrogen Phosphate; Potasu diwodorofosforan; Ортофосфат Калия Однозамещенный.

Potassium dihydrogen orthophosphate.

KH_2PO_4=136.1

CAS — 7778-77-0.

UNII — 4J9FJ0HL51.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Potassium Dihydrogen Phosphate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

USNF 31: (Monobasic Potassium Phosphate). Colourless crystals or a white granular or crystalline powder. Is odourless. Freely soluble in water; practically insoluble in

alcohol. pH of a 1% solution in water is about 4.5. Store in airtight containers.

Equivalence. Each g of monobasic potassium phosphate represents about 7.3 mmol of potassium and of phosphate.

Dibasic Potassium Phosphate

Dikalii Phosphas; Dikalio fosfatas; Dikaliumfosfaatti; Dikaliumfosfat; Dikálium-hidrogén-foszfát; Dipotasio, hidrogenofosfato de; Dipotassium Hydrogen Phosphate; Dipotassium Phosphate; Dipotasu wodorofosforan; E340; Fosfato dibásico de potasio; Hydrogenfosforečnan draselný; Kalii Hydrogenophosphas; Kaliummonohydrogenphosphat; Phosphate dipotassique; Potassium Phosphate; Ортофосфат Калия Двузамещенный.

Dipotassium hydrogen orthophosphate.

K_2HPO_4=174.2

CAS — 7758-11-4.

UNII — B7862WZ632 (potassium phosphate); CI71S98N1Z (dibasic potassium phosphate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dipotassium Phosphate; Dipotassium Hydrogen Phosphate BP 2014). A very hygroscopic, white or almost white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. Store in airtight containers.

USP 36: (Dibasic Potassium Phosphate). Colourless or white, somewhat hygroscopic, granular powder. Freely soluble in water; very slightly soluble in alcohol. pH of a 5% solution in water is between 8.5 and 9.6.

Equivalence. Each g of dibasic potassium phosphate represents about 11.5 mmol of potassium and 5.7 mmol of phosphate.

Monobasic Sodium Phosphate

Dihydrogenfosforečnan sodný; E339; Fosfato monobásico de sodio; Monobazik Sodyum Fosfat; Natrii Dihydrogenophosphas; Natrio-divandenilio fosfatas; Natrium Phosphoricum Monobasicum; Nátrium-dihidrogén-foszfát; Natriumdivätefosfat; Natriumdivetyfosfaatti; Phosphate monosodique; Sodio, dihidrogenofosfato de; Sodium Acid Phosphate; Sodium Biphosphate; Sodium Dihydrogen Phosphate; Sodu diwodorofosforan; Sodyum Dihidrojen Fosfat; Ортофосфат Натрия Однозамещенный.

Sodium dihydrogen orthophosphate.

$NaH_2PO_4.xH_2O$

CAS — 7558-80-7 (anhydrous monobasic sodium phosphate); 10049-21-5 (monobasic sodium phosphate monohydrate); 13472-35-0 (monobasic sodium phosphate dihydrate).

ATC — A06AD17; A06AG01.

ATC Vet — QA06AD17; QA06AG01.

UNII — 3980JIH2SW (monobasic sodium phosphate); KH7I04HPUU (anhydrous monobasic sodium phosphate); 593YOG76RN (monobasic sodium phosphate monohydrate); 5QWK665956 (monobasic sodium phosphate dihydrate).

Pharmacopoeias. *Br., Chin., Eur.* (see p. vii), and *US* may specify one or more states of hydration; monographs and specifications can be found for the anhydrous form (NaH_2PO_4 =120.0), the monohydrate ($NaH_2PO_4.H_2O$ =138.0), and the dihydrate ($NaH_2PO_4.2H_2O$ =156.0), although not necessarily all will be found in any one pharmacopoeia.

Ph. Eur. 8: (Sodium Dihydrogen Phosphate Dihydrate; Natrii Dihydrogenophosphas Dihydricus). A white or almost white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

The BP 2014 gives Sodium Acid Phosphate as an approved synonym.

BP 2014: (Anhydrous Sodium Dihydrogen Phosphate). A white, slightly deliquescent, crystals or granules. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

BP 2014: (Sodium Dihydrogen Phosphate Monohydrate). A white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

USP 36: (Monobasic Sodium Phosphate). It contains one or two molecules of water of hydration, or is anhydrous. Colourless crystals or white crystalline powder. Is odourless and is slightly deliquescent. Freely soluble in water; practically insoluble in alcohol. Its solutions are acid to litmus and effervesce with sodium carbonate. pH of a 5% solution in water of the monohydrate form is between 4.1 and 4.5.

Equivalence. Each g of monobasic sodium phosphate (anhydrous) represents about 8.3 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (monohydrate) represents about 7.2 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (dihydrate) represents about 6.4 mmol of sodium and of phosphate.

Dibasic Sodium Phosphate

Dibazik Sodyum Hidrojen Fosfat; Dinatrii Phosphas; Dinatrio fosfatas; Dinatriumfosfaatti; Dinatriumfosfat; Dinátrium-hidrogén-foszfát; Disodio, hidrogenofosfato de; Disodium Hydrogen Phosphate; Disodium Phosphate; Disodu fosforan; Disodu wodorofosforan; Disodyum Hidrojen Fosfat; E339; Fosfato dibásico de sodio; Hydrogenfosforečnan sodný; Natrii Hydrogenophosphas; Natrii Phosphas; Natrii Phosphatis; Natriumfosfaatti; Natriumfosfat; Phosphate disodique; Sodium Phosphate; Ортофосфат Натрия Двузамещенный.

Disodium hydrogen orthophosphate.

$Na_2HPO_4.xH_2O$

CAS — 7558-79-4 (anhydrous dibasic sodium phosphate); 10028-24-7 (dibasic sodium phosphate dihydrate); 7782-85-6 (dibasic sodium phosphate heptahydrate); 10039-32-4 (dibasic sodium phosphate dodecahydrate).

ATC — A06AD17; A06AG01; B05XA09.

ATC Vet — QA06AD17; QA06AG01; QB05XA09.

UNII — SE337SVY37 (sodium phosphate); GR686LBA74 (dibasic sodium phosphate); 22ADO53M6F (anhydrous dibasic sodium phosphate); 94255I6E2T (dibasic sodium phosphate dihydrate); 70WT22SF4B (dibasic sodium phosphate heptahydrate); E1W4N241FO (dibasic sodium phosphate dodecahydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.* The pharmacopoeias may specify one or more states of hydration; monographs and specifications can be found for the anhydrous form (Na_2HPO_4 = 142.0), the dihydrate ($Na_2HPO_4.2H_2O$ = 178.0), the heptahydrate ($Na_2HPO_4.7H_2O$ = 268.1), and the dodecahydrate ($Na_2HPO_4.12H_2O$ = 358.1), although not necessarily all will be found in any one pharmacopoeia.

Ph. Eur. 8: (Disodium Phosphate, Anhydrous; Dinatrii Phosphas Anhydricus; Anhydrous Disodium Hydrogen Phosphate BP 2014). A white or almost white, hygroscopic powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water is slightly alkaline. Store in airtight containers.

Ph. Eur. 8: (Disodium Phosphate Dihydrate; Dinatrii Phosphas Dihydricus; Disodium Hydrogen Phosphate Dihydrate BP 2014). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 5% solution in water is slightly alkaline.

The BP 2014 gives Sodium Phosphate Dihydrate as an approved synonym.

Ph. Eur. 8: (Disodium Phosphate Dodecahydrate; Dinatrii Phosphas Dodecahydricus; Disodium Hydrogen Phosphate Dodecahydrate BP 2014). Colourless, transparent, very efflorescent crystals. Very soluble in water; practically insoluble in alcohol. A 10% solution in water is slightly alkaline.

USP 36: (Dibasic Sodium Phosphate). It is dried, or contains one, two, seven, or twelve molecules of water of hydration.

The dried substance is a white powder that readily absorbs moisture. It is soluble 1 in 8 of water; insoluble in alcohol.

The heptahydrate is a colourless or white, granular or caked salt that effloresces in warm, dry air. It is freely soluble in water; very slightly soluble in alcohol. Its solutions are alkaline to phenolphthalein, a 0.1M solution having a pH of about 9.

Store all forms in airtight containers.

Equivalence. Each g of dibasic sodium phosphate (anhydrous) represents about 14.1 mmol of sodium and 7.0 mmol of phosphate. Each g of dibasic sodium phosphate (dihydrate) represents about 11.2 mmol of sodium and 5.6 mmol of phosphate. Each g of dibasic sodium phosphate (heptahydrate) represents about 7.5 mmol of sodium and 3.7 mmol of phosphate. Each g of dibasic sodium phosphate (dodecahydrate) represents about 5.6 mmol of sodium and 2.8 mmol of phosphate.

Tribasic Sodium Phosphate

E339; Fosfato de trisodio; Ortofosfato de trisodio; Sodio, fosfato de; Trisodium Orthophosphate; Trisodium Phosphate; Ортофосфат Натрия Трехзамещенный.

Na_3PO_4=163.9

CAS — 7601-54-9.

ATC — A06AD17; A06AG01.

ATC Vet — QA06AD17; QA06AG01.

UNII — A752Q30A6X (tribasic sodium phosphate); SX01TZO3QZ (anhydrous tribasic sodium phosphate); J9O85FKF29 (tribasic sodium phosphate monohydrate); B70850QPHR (tribasic sodium phosphate dodecahydrate).

Pharmacopoeias. In *USNF.*

USNF 31: (Tribasic Sodium Phosphate). It is anhydrous or contains 1 to 12 molecules of water of hydration. White, odourless crystals or granules, or a crystalline powder. Freely soluble in water; insoluble in alcohol. pH of a 1% solution in water is between 11.5 and 12.0. Store in airtight containers.

Equivalence. Each g of tribasic sodium phosphate (anhydrous) represents about 18.3 mmol of sodium and 6.1 mmol of phosphate.

Uses and Administration

Phosphates are used in the management of **hypophosphataemia** caused by phosphate deficiency or hypophosphataemic states (p. 1777.1). Doses of up to 100 mmol of phosphate daily may be given orally. The intravenous route is seldom necessary, but a dose of up to 9 mmol of phosphate as monobasic potassium phosphate may be given over 12 hours and repeated every 12 hours as necessary for severe hypophosphataemia. Alternatively, 0.2 to 0.5 mmol/kg phosphate, up to a maximum of 50 mmol, may be given over 6 to 12 hours (see also Hypophosphataemia, below). Plasma-electrolyte concentrations, especially phosphate and calcium, and renal function should be carefully monitored. Reduced doses may be necessary in patients with renal impairment. Phosphate supplements are used in total parenteral nutrition regimens; typical daily requirements are 20 to 30 mmol of phosphate.

Phosphates act as mild osmotic **laxatives** (p. 1804.1) when given orally as dilute solutions or by the rectal route. Phosphate enemas or concentrated oral solutions are used for bowel cleansing before surgery or endoscopy procedures. Preparations typically combine monobasic and dibasic sodium phosphates but the composition and dosage do vary slightly. Phosphate enemas act within 2 to 5 minutes, whereas the oral solutions act within 30 minutes to 6 hours.

Phosphates also have **other uses**. They lower the pH of urine and have been given as adjuncts to urinary antibacterials that depend on an acid urine for their activity. Phosphates have also been used for the prophylaxis of calcium renal calculi; the phosphates reduce urinary excretion of calcium thus preventing calcium deposition. A suggested oral dose for both uses is 7.4 mmol of phosphate four times daily.

Butafosfan (1-butylamino-1-methylethylphosphinic acid) and the sodium salt of toldimfos (4-dimethylamino-*O*-tolylphosphinic acid) are used as phosphorus sources in veterinary medicine.

Administration in children. For doses of phosphate to be used in children to treat vitamin-D-resistant rickets and rickets of prematurity, see p. 1792.1.

Bowel evacuation. A review concluded that the efficacy and tolerability of oral sodium phosphate solution was generally similar to, or significantly better than, that of polyethylene glycol-based or other colorectal cleansers in patients preparing for colorectal-related procedures.[1]

1. Curran MP, Plosker GL. Oral sodium phosphate solution: a review of its use as a colorectal cleanser. *Drugs* 2004; **64:** 1697–1714.

Hypercalcaemia. Intravenous phosphates have been used to lower plasma-calcium concentrations in hypercalcaemic emergencies (p. 1776.1), but because of their potential to cause serious adverse effects other drugs are now preferred. Oral phosphates may be used to prevent gastrointestinal absorption of calcium in the treatment of hypercalcaemia. The dose in adults is up to 100 mmol phosphate daily adjusted according to response.

Hypophosphataemia. Phosphate salts are given in the management of hypophosphataemia when a phosphate deficiency is identified, as discussed in Uses and Administration, above. Intravenous phosphates are associated with serious adverse effects if hypophosphataemia is over-corrected, and the rise in serum-phosphorus concentration cannot be predicted from a given dose. Consequently, it has been recommended[1-4] that intravenous phosphate be used cautiously in the treatment of severe hypophosphataemia (for the standard rate and dose see Uses and Administration, above). However, some advocate a more aggressive fixed-dose regimen in critically ill patients.[5-7]

1. Vannatta JB, *et al.* Efficacy of intravenous phosphorus therapy in the severely hypophosphataemic patient. *Arch Intern Med* 1981; **141:** 885–7.
2. Anonymous. Treatment of severe hypophosphatemia. *Lancet* 1981; **ii:** 734.
3. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; **7:** 123–8.
4. Coyle S, *et al.* Treatment of hypophosphataemia. *Lancet* 1992; **340:** 977.
5. Perreault MM, *et al.* Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Ann Pharmacother* 1997; **31:** 683–8.

6. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics. *Am J Emerg Med* 2000; **18:** 457–61.
7. Charron T, *et al*. Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. *Intensive Care Med* 2003; **29:** 1273–8.

Osteomalacia. Vitamin D deficiency, or its abnormal metabolism, is the most usual cause of osteomalacia and rickets (p. 1168.1); however, phosphate depletion may also contribute, and phosphate supplementation may be given as appropriate.

A suggested oral dose for vitamin-D-resistant hypophosphataemic osteomalacia in adults is 65 to 100 mmol phosphate daily. The *BNFC* suggests the following oral phosphate doses:

- for neonates, 1 mmol/kg daily given as a single dose or in 2 divided doses; alternatively it may be given via fortified breast milk
- older children may be given 2 to 3 mmol/kg daily, in 2 to 4 divided doses; a maximum dose of 48 mmol daily is recommended in those up to 5 years of age, and a maximum of 97 mmol daily for those aged 5 years and over.

If parenteral administration is indicated, an intravenous infusion of 1 mmol/kg daily may be given to neonates, 0.7 mmol/kg daily to children aged 1 month to 2 years, and 0.4 mmol/kg daily to those aged 2 to 18 years. Doses should be adjusted as necessary.

RICKETS OF PREMATURITY. Dietary deficiency of phosphorus is unusual, but can occur in small premature infants fed exclusively on human breast milk. The phosphate intake in these infants appears to be inadequate to meet the needs of bone mineralisation, and hypophosphataemic rickets can develop. This condition, variably called metabolic bone disease of prematurity, or rickets of prematurity, can be prevented by ensuring an adequate phosphate intake by very low-birth-weight babies. Adequate intake of calcium and vitamin D is also essential. Phosphate supplementation, with calcium and vitamin D, may be given orally either in formula feeds or as fortification of human breast milk, or intravenously in parenteral nutrition solutions.[1,2]

Dosage recommendations for phosphate may vary, but the *BNFC* suggests a daily dose of 1 mmol/kg; if given orally, this may be as a single dose or in 2 divided doses.

1. Ryan S. Nutritional aspects of metabolic bone disease in the newborn. *Arch Dis Child Fetal Neonatal Ed* 1996; **74:** F145–8.
2. Harrison CM, *et al*. Osteopenia of prematurity: a national survey and review of practice. *Acta Paediatr* 2008; **97:** 407–13.

Adverse Effects and Treatment

Excessive doses of intravenous phosphate cause hyperphosphataemia, particularly in patients with renal failure. Hyperphosphataemia leads in turn to hypocalcaemia, which may be severe, and to ectopic calcification, particularly in patients with initial hypercalcaemia. Tissue calcification may cause hypotension and organ damage and result in acute renal failure. Hyperphosphataemia, hypocalcaemia, and tissue calcification are rare after oral or rectal doses (but see Effects on Electrolytes, and Effects on the Kidneys, below).

Adverse effects of oral phosphates may include nausea, vomiting, diarrhoea, and abdominal pain. When they are being used for indications other than their laxative effects, diarrhoea may necessitate a reduction in dosage. Sodium phosphates given rectally for bowel evacuation may cause local irritation.

Phosphates are given as the potassium or sodium salts or both, and may thus be associated with hyperkalaemia, and hypernatraemia and dehydration. Sodium phosphate may cause hypokalaemia.

Treatment of adverse effects involves withdrawal of phosphate, general supportive measures, and correction of serum-electrolyte concentrations, especially calcium. Measures to remove excess phosphate such as oral phosphate binders and haemodialysis may be required (see also Hyperphosphataemia, p. 1776.3).

Effects on electrolytes. Although less common than after intravenous therapy, hyperphosphataemia, accompanied by hypocalcaemia or other severe electrolyte disturbances and resulting in tetany[1,2] and even death,[2] has been reported after the use of phosphate enemas. Similar effects have also been reported with the use of oral phosphate laxatives,[3-7] and in the USA, the FDA has issued warnings of the risk of electrolyte disturbances after the use of high oral doses of sodium phosphate, particularly in vulnerable patients.[8] Infants or children,[2,9,10] the elderly,[4,11] and those with renal impairment,[1,4,11] or congestive heart failure[4] have often had these adverse effects. Licensed product information for one oral sodium phosphate bowel cleanser (*Visicol; Salix, USA*) states that there have been reports of generalised tonic-clonic seizures and/or loss of consciousness in patients with no history of seizures; these cases were associated with electrolyte abnormalities, and low serum osmolality.

Hyperphosphataemia may precipitate nephrocalcinosis, causing an acute phosphate nephropathy, see Effects on the Kidneys, below.

1. Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema. *Lancet* 1985; **ii:** 1433.
2. Martin RR, *et al*. Fatal poisoning from sodium phosphate enema: case report and experimental study. *JAMA* 1987; **257:** 2190–2.
3. Peixoto Filho AJ, Lassman MN. Severe hyperphosphatemia induced by a phosphate-containing oral laxative. *Ann Pharmacother* 1996; **30:** 141–3.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with oral phosphate bowel preparations. *Aust Adverse Drug React Bull* 1997; **16:** 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 04/08/08)
5. Ullah N, *et al*. Fatal hyperphosphatemia from a phosphosoda bowel preparation. *J Clin Gastroenterol* 2002; **34:** 457–8.
6. Woo YM, *et al*. A life threatening complication after ingestion of sodium phosphate bowel preparation. *BMJ* 2006; **333:** 589–90.
7. Domico MB, *et al*. Severe hyperphosphatemia and hypocalcemic tetany after oral laxative administration in a 3-month-old infant. *Pediatrics* 2006; **118:** e1580–e1583. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/e1580 (accessed 13/12/06)
8. FDA. Safety of Sodium Phosphates Oral Solution (issued 17th September, 2001). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm173897.htm (accessed 20/08/10)
9. McCabe M, *et al*. Phosphate enemas in childhood: cause for concern. *BMJ* 1991; **302:** 1074.
10. Harrington L, Schuh S. Complications of Fleet enema administration and suggested guidelines for use in the pediatric emergency department. *Pediatr Emerg Care* 1997; **13:** 225–6.
11. Boivin MA, Kahn SR. Symptomatic hypocalcemia from oral sodium phosphate: a report of two cases. *Am J Gastroenterol* 1998; **93:** 2577–9.

Effects on the kidneys. Acute renal failure and nephrocalcinosis have been reported after the use of oral phosphate-based cathartics for bowel cleansing.[1,2] Although relatively rare with oral preparations, this acute phosphate nephropathy is a serious adverse effect; most patients were left with chronic renal insufficiency, and some developed end-stage renal disease. Potential contributing factors include inadequate hydration, increased age, a history of hypertension and arteriosclerosis, and concurrent use of ACE inhibitors, angiotensin receptor antagonists, diuretics, or NSAIDs.[2] The FDA has issued warnings[3] about the use of oral sodium phosphate products, especially in patients with impaired renal function, hypovolaemia, decreased intravascular volume, or dehydration, or in those taking drugs likely to contribute to the risk of nephropathy. Patients with bowel obstruction or active colitis may also be at risk. Patient advice includes the need to take the correct dose of oral sodium phosphate, to drink sufficient liquid during bowel cleansing, and to avoid other phosphate-containing laxatives. Patients at increased risk should have their electrolytes and renal function monitored.

Nephrocalcinosis has also been reported in children with hypophosphataemic rickets treated with calcitriol and phosphate supplements; this was found to be associated with the phosphate dose.[4]

1. Desmeules S, *et al*. Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003; **349:** 1006–7.
2. Markowitz GS, *et al*. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005; **16:** 3389–96.
3. FDA. Oral sodium phosphate (OSP) products for bowel cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription) (issued 12th November, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103354.htm (accessed 20/08/10)
4. Verge CF, *et al*. Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med* 1991; **325:** 1843–8.

Local toxicity. Rectal gangrene has been associated with the use of phosphate enemas in elderly patients and was believed to be due to a direct necrotising effect of the phosphate on the rectum.[1]

1. Sweeney JT, *et al*. Rectal gangrene: a complication of phosphate enema. *Med J Aust* 1986; **144:** 374–5.

Precautions

Phosphates should not generally be given to patients with severe renal impairment. They should be avoided in patients who may have low serum-calcium concentrations, as these may decrease further, and in patients with infected phosphate renal calculi. Potassium phosphates should be avoided in patients with hyperkalaemia and sodium phosphates should generally be avoided in patients with congestive heart failure, hypertension, and oedema. Serum electrolytes and renal function should be monitored during therapy, particularly if phosphates are given parenterally.

Oral or rectal sodium phosphate preparations for bowel evacuation should not be used in patients with gastrointestinal obstruction, inflammatory bowel disease, and conditions where there is likely to be increased colonic absorption. They should be used cautiously in elderly and debilitated patients, and in those with pre-existing electrolyte disturbances (see Effects on Electrolytes, above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium and sodium phosphates as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Oral phosphate supplements should not be used with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce its absorption. Vitamin D increases the gastrointestinal absorption of phosphates and therefore increases the potential for hyperphosphataemia.

Hyperphosphataemia, hypocalcaemia, and hypernatraemia are more likely to occur with phosphate enemas or oral laxatives if these are given to patients receiving diuretics or other drugs that may affect serum electrolytes. The risk of ectopic calcification may be increased by concurrent use of calcium supplements or calcium-containing antacids.

The risk of hyperkalaemia is increased if potassium phosphates are given with drugs that can increase serum-potassium concentrations.

Pharmacokinetics

About two-thirds of ingested phosphate is absorbed from the gastrointestinal tract. Excess phosphate is mainly excreted in the urine, the remainder being excreted in the faeces.

References.

1. Larson JE, *et al*. Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; **5:** 45–9.

Human Requirements

Phosphorus requirements are usually regarded as equal to those of calcium.

Most foods contain adequate amounts of phosphate, particularly meat and dairy products, hence deficiency is virtually unknown except in certain disease states, in patients receiving total parenteral nutrition, or in those who have received phosphate-binding drugs for prolonged periods; for further details see under Hypophosphataemia, p. 1777.1.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] and in the USA dietary reference intakes including recommended dietary allowances (RDA)[2] have been published for phosphorus. In the UK the reference nutrient intake (RNI) for adults is about 550 mg (17.5 mmol) daily; no additional amount is recommended for pregnancy although an additional amount of about 440 mg (14.3 mmol) daily is advised during lactation. In the USA the RDA is 1250 mg daily for those aged 9 to 18 years and 700 mg daily in adults; no increase in RDA is recommended during pregnancy and lactation. A tolerable upper intake level of 4 g daily has been set in adults aged up to 70 years; in those older than 70 a maximum of 3 g daily is recommended.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Denverlax; Dicofan; Enemol; Fosfacol; Fosfafarma†; Fosfalax; Fosfo-Dom; Fosfoadital; Fosfobarigraf; Gadolax; Kritel Enema; Prontonema; Silaxa; Tekfema; ***Austral.***: Celloids PP 85†; Celloids SP 96†; Diacol; Fleet Phospho-Soda; Fleet Ready-to-Use; Phosphate-Sandoz; Phosphoprep†; ***Austria***: Fleet Phospho-Soda; Relaxyl†; ***Belg.***: Colexklysma; Fleet Enema; Fleet Phospho-Soda; Kaliphos; Sodiphos; ***Braz.***: Fleet Enema; Phosfoenema; ***Canad.***: Enema; Fleet Enema; Phoslax; Phosphates; Relieve†; ***Chile***: Fabulaxol; Fleet Enema; Fleet Fosfosoda; ***China***: Fleet Enema (辉力); Fleet Phospho-Soda (辉灵); Gu Ping (固平); Qing Ke Long (清可隆); ***Denm.***: Fleet; Phosphoral; ***Fin.***: Phosphoral; ***Fr.***: Colokit; Fleet Phospho-Soda; ***Ger.***: Fleet Phospho-Soda; Freka-Clyss†; Isogutt†; ***Gr.***: Bioklysm; Enema Cooper; Fleet Enema; Fleet Ready-to-Use; Fosfolax; Klysmol; ***Hong Kong***: Enemol†; Fleet Enema; Fleet Phospho-Soda; Unima; ***Hung.***: Fleet Phospho-Soda; Optacid; ***India***: Exelyte; Exit; ***Indon.***: Fleet Enema; Fleet Phosposoda; ***Irl.***: Fleet Phospho-Soda; Fleet; ***Israel***: Fleet Enema; ***Malaysia***: Fleet Enema; Fleet Phospho-Soda; ***Mex.***: Fleet Enema Fosf-Sodio; Fleet PS; ***Neth.***: Fleet Gebruiksklaar Klysma†; Phosphoral; ***Norw.***: Fleet Phospho-Soda; Phosphoral; ***NZ***: Fleet Phosphate Enema; Fleet Phospho-Soda; ***Philipp.***: Fleet Enema; Oksna†; Phospho-Soda; ***Pol.***: Enema; Fleet Phospho-Soda; Phospho-Laxative†; Rectanal; ***Port.***: Fleet Enema; Fleet Phospho-Soda; ***Rus.***: Fleet Phospho-Soda (Флит Фосфосода); ***Singapore***: Fleet Enema; Fleet Phospho-Soda; Phosphates; ***Spain***: Fosfoevac; Fosfosoda; Lainema; ***Swed.***: Phosphoral; ***Switz.***: Freka-Clyss; ***Thai.***: Patar 88 Enema; RISS;

Turk.: BT Enema; Fleet Enema; Fleet Fosfo Soda; ***UK***: Diafalk; Fleet Phospho-Soda; Fleet Ready-to-Use; OsmoPrep; ***Ukr.***: Fleet (Флит); ***USA***: Fleet Enema; Fleet Phospho-Soda†; K-Phos Original; OsmoPrep; Pedia-Lax; Visicol; ***Venez.***: Fleet Enema; Fleet Fosfosoda.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Hangover Relief; Nervatona Focus; ***Austria***: Lakrima; ***Canad.***: Alfalfa Tonic; Barijodeel†; Bioactiv E†; Bioactiv S†; Biochemic Phosphates; Biomag†; Calms Forte; Combinaison†; Comp-Drops 7 Sleepless†; Diamite; Eczema L87; Formula FA 224†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Hylands Formula CF; Hylands Formula NT; Hylands Insomnia; Ikoplex 11 Digestion Aid†; Ikoplex 21†; Ikoplex 5†; Melange†; Minerals+; Nerve Tonic; Nervita; Nuage Bioplasma†; Rexorubia†; Selenium Homaccord†; Sore Throat L39†; Ton 1 Complex†; Ursical Formula†; Urticalcin; ***Chile***: Anacardio con Fosforo; Bioactiv E; Bioactiv F; Bioactiv M; Ikoplex No 10; Ikoplex No 11; Ikoplex No 13; Ikoplex No 15; Ikoplex No 18; Ikoplex No 19; Ikoplex No 1; Ikoplex No 20; Ikoplex No 21; Ikoplex No 22; Ikoplex No 24; Ikoplex No 2; Ikoplex No 5; Ikoplex No 8; Ikoplex No 9; ***Fr.***: Acidum Phosphoricum Compose†; Billerol; Biomag; Boripharm No 12†; Boripharm No 15†; Boripharm No 31; Boripharm No 3; Cistus Canadensis Complexe No 86†; Diabene; Diacure; Kalium Phosphoricum Complexe No 100; Mercurius Solubilis Complexe No 39; Natrum Carbonicum Complexe No 10†; Rexorubia; Scabiosa Complexe No 87; Stressdoron; Triphosphates; Zenalia; ***Ger.***: Cefasept N; Cefasept†; Cefasept; Dormi-cyl L Ho-Len-Complex; Drufusan N†; Drufusan; Girheulit HM†; HanoOxygen E; Infi-China; Influvit; Neurodoron; Refesan T; Rufebran allergo†; Rufebran regeno†; Tondinel; Viscum album H†; Zappelin N; ***Neth.***: Apo-STOM; Cerebrum comp; Lymfelite; Nervival; ***S.Afr.***: Kalium Phos Comp†; ***Switz.***: Urticalcin; ***UK***: New Era Nervone; ***Ukr.***: Kindinorm (Киндинорм).

Pharmacopoeial Preparations

BP 2014: Dipotassium Hydrogen Phosphate Injection; Phosphate Oral Solution; Phosphates Enema; Potassium Dihydrogen Phosphate Oral Solution; Sterile Potassium Dihydrogen Phosphate Concentrate;

Ph. Eur.: Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);

USP 36: Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Multiple Electrolytes and Invert Sugar Injection Type 1; Potassium Phosphates Injection; Sodium Phosphates Injection; Sodium Phosphates Oral Solution; Sodium Phosphates Rectal Solution.

Potassium

Kalium; Potasio; Калий.

K=39.0983

UNII — RWP5GA015D (potassium); 295O53K152 (potassium ion).

Description. Potassium salts covered in this section are those principally given as a source of potassium ions, but consideration should also be given to the effect of the anion. Phosphate salts of potassium are covered under Phosphate, p. 1790.3, and the bicarbonate and citrate salts under Bicarbonate, p. 1780.3.

Potassium Acetate

Acetato potásico; E261; Kalii Acetas; Kalio acetatas; Kaliumacetat; Kálium-acetát; Kaliumasetaatti; Octan draselný; Potasio, acetato de; Potassium, acétate de; Potasu octan; Калия Ацетат; Уксуснокислый Калий.

CH_3CO_2K=98.14

CAS — 127-08-2.

ATC — B05XA17.

ATC Vet — QB05XA17.

UNII — M911911U02.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Potassium Acetate). Deliquescent white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Protect from moisture.

USP 36: (Potassium Acetate). Colourless, monoclinic crystals, or a white crystalline powder. It is odourless or has a faint acetous odour. Deliquesces on exposure to moist air. Soluble 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 3 of alcohol. pH of a 5% solution in water is between 7.5 and 8.5. Store in airtight containers.

Equivalence. Each g of potassium acetate (anhydrous) represents about 10.2 mmol of potassium. Potassium acetate (anhydrous) 2.51 g is equivalent to about 1 g of potassium.

Potassium Aspartate

Aspartate monopotassique hémihydraté; Kalii Hydrogenoaspartas Hemihydricus; Kalio-divandenilio aspartatas hemihidratas; Kaliumhydrogenaspartat-Hemihydrat; Kaliumhydrogen-aspartát hemihydrát; Kaliumväteaspartathemihydrat; Kaliumvetyaspartaattihemihydraatti; Potassium Hydrogen Aspartate Hemihydrate; Калия Аспартат.

Potassium aminosuccinate hemihydrate.

$C_4H_6KNO_4$,½H_2O=180.2

CAS — 7259-25-8 (hemihydrate).

UNII — OC4598NZEQ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Potassium Hydrogen Aspartate Hemihydrate). A white or almost white, powder or crystalline powder, or colourless crystals. Very soluble in water; practically insoluble in alcohol and in dichloromethane. pH of a 2.5% solution in water is between 6.0 and 7.5.

Equivalence. Each g of potassium aspartate represents about 5.5 mmol of potassium. Potassium aspartate 4.61 g is equivalent to about 1 g of potassium.

Potassium Chloride

Chlorid draselný; Cloreto de Potássio; Cloruro potásico; E508; Kalii chloridum; Kalio chloridas; Kalium Chloratum; Kaliumchlorid; Kaliumklorid; Kálium-klorid; Kaliumkloridi; Potasio, cloruro de; Potassium, chlorure de; Potasu chlorek; Хлорид Калия.

KCl=74.55

CAS — 7447-40-7.

ATC — A12BA01; B05XA01.

ATC Vet — QA12BA01; QB05XA01.

UNII — 660YQ98I10.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Potassium Chloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in dehydrated alcohol.

USP 36: (Potassium Chloride). Colourless, elongated, prismatic, or cubical crystals, or a white, granular powder. Is odourless. Soluble 1 in 2.8 of water, and 1 in 2 of boiling water; insoluble in alcohol. Its solutions are neutral to litmus.

Equivalence. Each g of potassium chloride represents about 13.4 mmol of potassium. Potassium chloride 1.91 g is equivalent to about 1 g of potassium.

Potassium Gluconate

E577; Gluconato potásico; Potasio, gluconato de; Калия Глюконат.

Potassium D-gluconate.

$CH_2OH.[CH(OH)]_4.CO_2K$=234.2

CAS — 299-27-4 (anhydrous potassium gluconate); 35398-15-3 (potassium gluconate monohydrate).

ATC — A12BA05.

ATC Vet — QA12BA05.

UNII — 12H3K5QKN9.

Pharmacopoeias. In *Fr.*

US permits anhydrous or the monohydrate.

USP 36: (Potassium Gluconate). It is anhydrous or contains one molecule of water of hydration. A white or yellowish-white, odourless, crystalline powder or granules. Soluble 1 in 3 of water; practically insoluble in dehydrated alcohol, in chloroform, in ether, and in benzene. Its solutions are slightly alkaline to litmus. Store in airtight containers.

Equivalence. Each g of potassium gluconate (anhydrous) represents about 4.3 mmol of potassium. Each g of potassium gluconate (monohydrate) represents about 4 mmol of potassium. Potassium gluconate (anhydrous) 5.99 g and potassium gluconate (monohydrate) 6.45 g are each equivalent to about 1 g of potassium.

Potassium Sulfate *(USAN)*

E515; Kalii Sulfas; Kalio sulfatas; Kalium Sulfuricum; Kaliumsulfaatti; Kaliumsulfat; Potasio, sulfato de; Potassii Sulphas; Potassium, sulfate de; Potassium Sulphate; Síran draselný; Sulfato potásico; Tartarus Vitriolatus; Калия Сульфат.

K_2SO_4=174.3

CAS — 7778-80-5.

UNII — 1K573LC5TV.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Potassium Sulfate). A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in dehydrated alcohol.

Equivalence. Each g of potassium sulfate represents about 11.5 mmol of potassium. Potassium sulfate 2.23 g is equivalent to about 1 g of potassium.

Potassium Tartrate

E336; Potasio, tartrato de; Potasu winian; Tartrato potásico; Тартрат Калия.

$C_4H_4K_2O_6$,½H_2O=235.3

CAS — 921-53-9 (anhydrous potassium tartrate).

UNII — O9WLL1ZL8S.

Equivalence. Each g of potassium tartrate (hemihydrate) represents about 8.5 mmol of potassium. Potassium tartrate (hemihydrate) 3.00 g is equivalent to about 1 g of potassium.

Uses and Administration

Potassium salts in this section are used for the prevention and treatment of potassium depletion and/or **hypokalaemia** (p. 1777.2) and have been used in the prevention of **diuretic-induced hypokalaemia** (see Hydrochlorothiazide, Effects on Electrolyte Balance, p. 1404.2). Doses may be expressed in terms of mmol or mEq of potassium, mass (mg) of potassium, or mass of potassium salt (for comparative purposes see Table 3, below). Treatment should be monitored by plasma-potassium estimations because of the risk of inducing hyperkalaemia, especially where there is renal impairment.

Potassium chloride is probably the most commonly used potassium salt; this is because hypochloraemic alkalosis, which is often associated with hypokalaemia, can be corrected by the chloride ions. An alkalinising salt such as potassium acetate, potassium bicarbonate, or potassium citrate may be preferable if a metabolic acidosis, such as occurs in renal tubular acidosis, accompanies the hypokalaemia (see p. 1775.2). Other salts that are or have been used in the management of potassium deficiency include potassium ascorbate, potassium aspartate, potassium benzoate, potassium gluceptate, potassium gluconate, potassium phosphate, and potassium tartrate. Typical doses for the prevention of hypokalaemia may be up to 50 mmol daily and similar doses may be adequate in mild potassium deficiency. However, higher doses may be needed in more severe deficiency. Patients with renal impairment should receive correspondingly lower doses. *Oral* treatment is used for prophylaxis and is also suitable for treating most cases of hypokalaemia. Oral potassium salts are more irritating than the corresponding sodium salts; they should be taken with or after meals with plenty of fluid; liquid preparations are preferable.

An *intravenous* potassium salt may be required in severe acute hypokalaemia. This normally entails infusing a solution containing 20 mmol of potassium in 500 mL over 2 to 3 hours under ECG control. A recommended maximum dose is 2 to 3 mmol/kg of potassium in 24 hours. Higher concentrations have been given when an infusion pump has been used (see Administration p. 1794.1). Adequate urine flow must be ensured and careful monitoring of plasma-potassium and other electrolyte concentrations is essential. Potassium chloride is the salt most commonly used and solutions intended for intravenous use that are in a concentrated form (such as 1.5 or 2 mmol/mL) *must* be diluted to the appropriate concentration before use. There should be careful and thorough mixing when adding concentrated potassium chloride solutions to infusion fluids. Potassium chloride is also available as premixed infusions with sodium chloride and/or glucose containing 10 to 40 mmol/litre of potassium (but see also Administration, p. 1794.1). Potassium acetate is also given intravenously.

Amongst **other uses**, the sulfate, and tartrate salts of potassium have been given orally as osmotic laxatives (p. 1804.1).

Some potassium salts are used as sodium-free condiments when sodium intake must be restricted.

Potassium chloride is sometimes used as an excipient in pharmaceutical formulations.

Table 3. Some potassium salts and their potassium content.

	Potassium content per g		
Potassium salt	mg	mmol	mEq
Potassium acetate (anhydrous)	398	10.2	10.2
Potassium aspartate	217	5.5	5.5
Potassium bicarbonate	391	10.0	10.0
Potassium chloride	524	13.4	13.4
Potassium citrate (anhydrous)	383	9.8	9.8
Potassium citrate (monohydrate)	361	9.3	9.3
Potassium gluconate (anhydrous)	167	4.3	4.3
Potassium gluconate (monohydrate)	155	4.0	4.0
Potassium sulfate (anhydrous)	449	11.5	11.5
Potassium tartrate (hemihydrate)	332	8.5	8.5

Administration. The standard concentration and rate of administration of potassium chloride for infusion is discussed in Uses and Administration, p. 1793.3. However, higher concentrations (200 or 300 mmol/litre) and faster infusion rates have been used, via an infusion pump, for cases of severe symptomatic hypokalaemia, especially with fluid overload.[1,2]

There has been controversy regarding the preferred route of administration of these higher concentrations of potassium chloride.[1] The central route avoids the problems of pain and phlebitis when potassium is given peripherally. However, it has been suggested that high concentrations of potassium given centrally may carry a greater risk of cardiac toxicity if the infusion is carried directly to the heart. Use of lidocaine has improved tolerability of peripheral administration of potassium chloride.[2]

Intravenous potassium is usually given in sodium chloride and/or glucose infusion. However, it has been pointed out that glucose can reduce serum-potassium concentrations, and that glucose-free solutions should be used for the initial intravenous administration of potassium in hypokalaemia.[3]

1. Kruse JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med* 1990; **150:** 613–17.
2. Pucino F, *et al.* Patient tolerance to intravenous potassium chloride with and without lidocaine. *Drug Intell Clin Pharm* 1988; **22:** 676–9.
3. Agarwal A, Wingo CS. Treatment of hypokalaemia. *N Engl J Med* 1999; **340:** 154–5.

Diabetic ketoacidosis. As discussed under Diabetic Emergencies on p. 465.3, potassium replacement is given in diabetic ketoacidosis to restore total body stores of potassium and thereby prevent the hypokalaemia induced by insulin.

Hypertension. A meta-analysis[1] has reported that potassium supplementation reduces both systolic and diastolic blood pressure. The size of the effect in hypertensive patients was great enough to suggest a possible role in the treatment of hypertension (p. 1251.1); effects in normotensive subjects were less marked but consistent with a similar role for preventing hypertension. Most studies have used potassium chloride, but an effect has also been found with the aspartate[2] and the citrate.[3]

1. Whelton PK, *et al.* Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277:** 1624–32.
2. Franzoni F, *et al.* Antihypertensive effect of oral potassium aspartate supplementation in mild to moderate arterial hypertension. *Biomed Pharmacother* 2005; **59:** 25–9.
3. He FJ, *et al.* Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. *Hypertension* 2005; **45:** 571–4.

Myocardial infarction. A glucose, insulin, and potassium infusion has been investigated in acute myocardial infarction (see p. 482.3).

Termination of pregnancy. Solutions of potassium chloride are used to reduce fetal numbers in multifetal pregnancies[1-3] or for severe fetal malformation by abolishing the fetal cardiac activity. The solution is injected into the thorax of the fetus without affecting the others, which are allowed to continue to term. Alternatively, potassium chloride may be injected into the umbilical vein when access to the fetal heart is difficult. A retrospective comparison[4] found both techniques to be effective. Significantly smaller doses were required for the umbilical route, possibly because a sustained dose is delivered directly to the fetal heart and myocardium, compared with intraventricular injection.

1. Wapner RJ, *et al.* Selective reduction of multifetal pregnancies. *Lancet* 1990; **335:** 90–3.
2. Berkowitz RL, *et al.* The current status of multifetal pregnancy reduction. *Am J Obstet Gynecol* 1996; **174:** 1265–72.
3. De Catte L, Foulon W. Obstetric outcome after fetal reduction to singleton pregnancies. *Prenat Diagn* 2002; **22:** 206–10.
4. Bhide A, *et al.* Comparison of feticide carried out by cordocentesis versus cardiac puncture. *Ultrasound Obstet Gynecol* 2002; **20:** 230–2.

Adverse Effects

Excessive doses of potassium may lead to the development of hyperkalaemia (p. 1777.1), especially in patients with renal impairment. Symptoms include paraesthesia of the extremities, muscle weakness, paralysis, cardiac arrhythmias, heart block, cardiac arrest, and confusion. Cardiac toxicity is of particular concern after intravenous dosage.

Pain or phlebitis may occur when given intravenously via peripheral veins, particularly at higher concentrations.

Nausea, vomiting, diarrhoea, and abdominal cramps may occur with oral potassium salts. There have been numerous reports of gastrointestinal ulceration, sometimes with haemorrhage and perforation or with the late formation of strictures, after the use of enteric-coated tablets of potassium chloride. Ulceration has also occurred after the use of sustained-release tablets.

Treatment of Adverse Effects

The treatment of hyperkalaemia discussed on p. 1777.1 also applies when hyperkalaemia occurs during potassium therapy. However, in mild hyperkalaemia that has developed on long-term treatment, stopping the potassium supplement and other drugs that may increase plasma-potassium concentrations, and avoidance of foods with a high potassium content may be sufficient to correct the hyperkalaemia.

In cases of acute oral overdosage of potassium supplements, the stomach should be emptied by gastric lavage in addition to the measures described on p. 1777.1.

Precautions

Potassium salts should be given with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Excessive use of potassium-containing salt substitutes or potassium supplements may lead to accumulation of potassium especially in patients with renal insufficiency. Regular monitoring of clinical status, serum electrolytes, and the ECG is advisable in patients receiving potassium therapy, particularly those with cardiac or renal impairment.

Liquid or effervescent preparations are preferred to solid dosage forms for oral use; use of the former, with or after food, may reduce gastric irritation. Solid oral dosage forms of potassium salts should not be given to patients with gastrointestinal ulceration or obstruction. They should be given with care to patients in whom passage through the gastrointestinal tract may be delayed, as in pregnant patients. Treatment should be stopped if severe nausea, vomiting, or abdominal distress develops.

Potassium chloride should not be used in patients with hyperchloraemia.

Direct injection of potassium chloride concentrates without appropriate dilution may cause instant death. For the view that glucose-containing solutions should not be used for the initial intravenous administration of potassium in hypokalaemia see Administration, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium chloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Potassium supplements should be used with caution, if at all, in patients receiving drugs that increase serum-potassium concentrations. These include potassium-sparing diuretics, ACE inhibitors, ciclosporin, and drugs that contain potassium such as the potassium salts of penicillin. Similarly, the concomitant use of potassium-containing salt substitutes for flavouring food should be avoided. Antimuscarinics delay gastric emptying and consequently may increase the risk of gastrointestinal adverse effects in patients receiving solid oral dosage forms of potassium.

Pharmacokinetics

Potassium salts other than the phosphate, sulfate, and tartrate are generally readily absorbed from the gastrointestinal tract. Potassium is excreted mainly by the kidneys; it is secreted in the distal tubules in exchange for sodium or hydrogen ions. Some potassium is excreted in the faeces and small amounts may also be excreted in sweat.

Human Requirements

Potassium is an essential body electrolyte. However, requirements are difficult to determine and have been estimated from the amount accumulated during growth and reported urinary and faecal excretion.

Over 90% of dietary potassium is absorbed from the gastrointestinal tract. Potassium is particularly abundant in vegetables, potatoes, and fruit.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] have been estimated for potassium. The reference nutrient intake (RNI) for adults is 3.5 g (90 mmol) daily. In the USA, no recommended dietary allowance (RDA) has been established for potassium. However a daily intake of 1.6 to 2 g (40 to 50 mmol) is considered adequate for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Co-Salt; Control K; Gluco-K; Kaon; Orakit; Potamkim; ***Austral.***: Celloids PC 73†; Celloids PS 29†; Chlorvescent; Duro-K; Slow-K; Span-K; ***Austria***: KCl-retard; Micro-Kalium; ***Belg.***: Chloropotassuril; Kali-Sterop; Steropotassium; Ultra-K; ***Braz.***: Clotassio; Decorfen; Slow-K; ***Canad.***: Apo-K; Essential Liquid Mineral; K-10; K-Dur; K-Lyte/Cl†; Micro-K; Odan K-20; Pro-600K; Proflavanol C†; Riva K; Slo-Pot; Slow-K; ***Chile***: Kaion Retard; Sal Dietetica; Slow-K; Yonka; ***China***: Budaxiu (补达秀); Di Jia (迪佳); Lai Ding Jia (莱丁甲); Lejia (乐甲); Li Bei Jia (立贝甲); Panangin (潘南金); Xian Jia (先甲); Xin Jian Ju (欣健聚); ***Cz.***: Kaldyum; Kalnormin; ***Denm.***: Kaleorid; ***Fin.***: Kaleorid; Kalinorm†; Kalisol; ***Fr.***: Diffu-K; Kaleorid; Nati-K; ***Ger.***: Kalinor-retard P; KCl-retard; Rekawan; ***Gr.***: Acronitol; Acroser; Sopa-K; ***Hong Kong***: Apo-K; KSR; Slow-K; Span-K; ***Hung.***: Kaldyum; Kalium Durules†; Kalium-R; ***India***: K-Card; Kay Ciel; Keylyte; Potklor; ***Indon.***: Aspar-K; Kalipar; KSR; ***Irl.***: Diarrest RF†; Kay-Cee-L; Slow-K; ***Israel***: Moviprep; Slow-K; ***Ital.***: K-Flebo; Kadalex; Lento-Kalium; ***Malaysia***: Apo-K; Beacon K; Slow-K; ***Mex.***: Ceposil†; Clor-K-Zaf; Corpotasin GK; Corpotasin LP; Efilat; K-Dur; Kaliolite; Kelefusin; Potasoral†; ***Neth.***: Slow-K; ***Norw.***: Kaleorid; ***NZ***: Chlorvescent; Slow-K†; Span-K; ***Philipp.***: Ion-O-Trate†; Kalium; ***Pol.***: Kaldyum; Kalimat†; Kalipoz; ***S.Afr.***: Flexivial; Micro-K†; Plenish-K; Sandoz K; Slow-K; ***Singapore***: Apo-K; Dorama-neo; Slow-K; ***Spain***: AP-Inyect; Boi-K Aspartico; Boi-K; Potasion Solucion; Potasion; ***Swed.***: Kaleorid; Kalium Retard†; ***Switz.***: Kaliglutol†; Plus Kalium retard; ***Thai.***: Addi-K; Enpott; Kaliject; Kaylyte; Potassride; Strong Pot Chloride; ***Turk.***: Kadaleks; ***UK***: Kay-Cee-L; Slow-K; ***Ukr.***: Caldium (Кальдиум)†; Gik (Гик); Kalium-Normin (Калий-Нормин); ***USA***: Adolphs Salt Substitute; Cena-K; Gen-K; K + 10; K-Dur; K-G Elixir; K-Lor; K-Lyte/Cl; K-Tab; Kaon-Cl; Kaon; Klor-Con; Klorvess; Klotrix; Micro-K; Potasalan; Ten-K.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austria***: Tonsillopas; ***Canad.***: Combinaison†; Diamite; Earache; Formula PC 223†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Ikoplex 21†; Melange†; Nuage Bioplasma†; Optalia†; Sinus Ease; Sinuspax†; ***Chile***: Ikoplex No 13; Ikoplex No 15; Ikoplex No 17; Ikoplex No 18; Ikoplex No 19; Ikoplex No 20; Ikoplex No 21; Ikoplex No 22; Ikoplex No 23; Ikoplex No 3; Ikoplex No 5; Ikoplex No 8; Ikoplex No 9; ***Fr.***: Boripharm No 10†; Boripharm No 22†; Kalium Muriaticum Complexe No 41†; Sinuspax; ***Ger.***: Drufusan N†; Drufusan; Hevertotox; Hevertotox; Jowidarmin; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Odonton-Echtroplex; Pyrogenium; Sinusyx; Tonsillopas; ***UK***: New Era Nervone.

Pharmacopoeial Preparations

BP 2014: Bumetanide and Prolonged-release Potassium Tablets; Compound Sodium Lactate Infusion; Effervescent Potassium Chloride Tablets; Oral Rehydration Salts; Potassium Ascorbate Eye Drops; Potassium Chloride and Glucose Infusion; Potassium Chloride and Sodium Chloride Infusion; Potassium Chloride Oral Solution; Potassium Chloride, Sodium Chloride and Glucose Infusion; Prolonged-release Potassium Chloride Tablets; Sterile Potassium Chloride Concentrate;

USP 36: Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Minerals Capsules; Minerals Tablets; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3; Multiple Electrolytes Injection Type 1; Multiple Electrolytes Injection Type 2; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Oral Rehydration Salts; PEG 3350 and Electrolytes for Oral Solution; Potassium Acetate Injection; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Chloride Extended-release Capsules; Potassium Chloride Extended-release Tablets; Potassium Chloride for Injection Concentrate; Potassium Chloride for Oral Solution; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Potassium Chloride Oral Solution; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Gluconate and Potassium Chloride for Oral Solution; Potassium Gluconate and Potassium Chloride Oral Solution; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate Elixir; Potassium Gluconate Tablets; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Ringer's and Dextrose Injection; Trikates Oral Solution; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Sodium

Natrium; Sód; Sodio; Натрий.
Na=22.98976928
UNII — 9NEZ333N27 (sodium); LYR4M0NH37 (sodium ion).

Description. Sodium chloride is the principal sodium salt used as a source of sodium ions. Sodium salts used chiefly as sources of bicarbonate ions, such as the acetate, bicarbonate, citrate, and lactate, are covered under Bicarbonate, p. 1780.3. Phosphate salts of sodium are covered under Phosphate, p. 1790.3.

Sodium Chloride

Chlorid sodný; Chlorure de Sodium; Cloreto de Sódio; Cloruro sódico; Natrii Chloridum; Natrio chloridas; Natrium-chlorid; Natriumklorid; Nátrium-klorid; Natriumkloridi; Salt; Sodio, cloruro de; Sodium, chlorure de; Sodu chlorek; Sodyum Klorür; Натрия Хлорид.
NaCl=58.44
CAS — 7647-14-5.
ATC — A12CA01; B05CB01; B05XA03.
ATC Vet — QA12CA01; QB05CB01; QB05XA03.
UNII — 451W47IQ8X.

NOTE. An aqueous solution of sodium chloride 0.9% is often known as physiological saline.

SALINE is a code approved by the BP 2014 for use on single unit doses of eye drops containing sodium chloride 0.9% where the individual container may be too small to bear all the appropriate labelling information. HECL is a similar code approved for hyetellose and sodium chloride eye drops.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Chloride). A white or almost white, crystalline powder or colourless crystals or white or almost white pearls. Freely soluble in water; practically insoluble in dehydrated alcohol.

USP 36: (Sodium Chloride). Colourless cubic crystals or white crystalline powder. Soluble 1 in 2.8 of water, 1 in 2.7 of boiling water, and 1 in 10 of glycerol; slightly soluble in alcohol.

Equivalence. Each g of sodium chloride represents about 17.1 mmol of sodium and of chloride. Sodium chloride 2.54 g is equivalent to about 1 g of sodium.

Storage. Solutions of some sodium salts, including sodium chloride, when stored, may cause separation of solid particles from glass containers and solutions containing such particles must not be used.

Uses and Administration

Sodium chloride is used in the management of deficiencies of sodium and chloride ions in salt-losing conditions (see Hyponatraemia, p. 1778.1). Sodium chloride solutions are used as a source of sodium chloride and water for hydration.

A 0.9% solution in water is iso-osmotic, and thus in most cases isotonic with serum and lachrymal secretions. Doses may be expressed in terms of mEq or mmol of sodium, mass (mg) of sodium, or mass of sodium salt (for comparative purposes, see Table 4, below).

A typical oral replacement dose of sodium chloride in **chronic salt-losing conditions** is about 2.4 to 4.8 g (about 40 to 80 mmol of sodium) daily as a modified-release preparation, accompanied by a suitable fluid intake; doses of up to 12 g daily may be necessary in severe cases. Oral supplements are also used for the prevention of muscle cramps during routine haemodialysis (p. 1779.3); a suggested dose is about 6 to 10 g of a modified-release preparation per dialysis session.

Glucose facilitates the absorption of sodium from the gastrointestinal tract, and solutions containing sodium chloride and glucose usually with additional electrolytes (see p. 1780.1) are used for oral rehydration in acute diarrhoea (p. 1805.2).

The concentration and dosage of sodium chloride solutions for intravenous use is determined by several factors including the age, weight, and clinical condition of the patient and in particular the patients' hydration state. Serum-electrolyte concentrations should be carefully monitored. In severe sodium depletion, 2 to 3 litres of sodium chloride 0.9% may be given over 2 to 3 hours and thereafter at a slower rate. If there is combined water and sodium depletion a 1 to 1 mixture of sodium chloride 0.9% and glucose 5% may be appropriate. Although hypertonic sodium chloride solutions may be used in certain patients with severe acute dilutional hyponatraemia, over-rapid correction may have severe neurological adverse effects (see Hyponatraemia, p. 1778.1). Solutions containing 1.8 to 5% are available.

In **hypernatraemia** with volume depletion (p. 1778.1), sodium chloride 0.9% may be used to maintain plasma-sodium concentrations with expanding fluid volume. Sodium chloride 0.9% (or rarely, in marked hypernatraemia, 0.45%) is used for fluid replacement in diabetic ketoacidosis (see Diabetic Emergencies, p. 465.3).

Among its **other uses**, sodium chloride solution 0.9%, being isotonic, is a useful fluid for sterile irrigations, for example, of the eye or bladder, and general skin or wound cleansing. The 0.9% concentration is also widely used as a vehicle or diluent for the parenteral administration of other drugs. Nasal drops of sodium chloride 0.9% are used to relieve nasal congestion. A mouthwash containing sodium chloride is also available for oral hygiene.

Sodium chloride in the form of sea water or sea salt (see p. 2612.1) has been also used for nasal irrigations.

Sodium chloride solutions should *not* be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Sodium chloride is sometimes used as an excipient in capsules and tablets.

Homoeopathy

Sodium chloride has been used in homoeopathic medicines under the following names: Natrium muriaticum; Nat. Mur.; Natrii chloridum; Natricum chloratum; Natrum muriaticum.

NOTE. Do not confuse Natricum chloratum with sodium chlorate (p. 2618.1).

Catheters and cannulas. For reference to sodium chloride 0.9% being used to maintain the patency of catheters and cannulas, and to its equivalent efficacy to heparin, see Catheters and Cannulas under Uses and Administration of Heparin, p. 1398.1.

Cystic fibrosis. Inhalation of 4 mL of a hypertonic solution of sodium chloride (7%) twice daily for 48 weeks in 82 patients with stable cystic fibrosis (p. 177.2) was associated with a moderate but sustained improvement in lung function and a marked reduction in the number of exacerbations and need for antibacterials, when compared with 80 placebo-treated patients.[1] There was, however, no difference in the rate of change of lung function. Each inhalation was preceded by a bronchodilator to minimise airway narrowing; adverse reactions to the active treatment were nonetheless reported in 14 patients and included cough, chest tightness or pharyngitis, sinusitis, haemoptysis, sneezing, and vomiting. As a result, 6 patients withdrew from the study, but the effects resolved in the remainder without the need for dose reduction or interruption. Hypertonic saline was considered to be an inexpensive and safe adjunctive therapy in patients with cystic fibrosis.

1. Elkins MR, *et al.* A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006; **354:** 229–40.

Termination of pregnancy. Trans-abdominal intra-amniotic instillation of sodium chloride 20% (maximum volume 200 to 250 mL) has been used for the termination of second-trimester pregnancy. However, serious adverse effects have occurred (see below), and other methods are generally preferred (p. 2131.3).

Adverse Effects

Adverse effects of sodium salts are attributable to electrolyte imbalances from excess sodium; there may also be effects due to the specific anion.

Retention of excess sodium in the body usually occurs when there is defective renal sodium excretion. This leads to the accumulation of extracellular fluid to maintain normal plasma osmolality, which may result in pulmonary and peripheral oedema and their consequent effects.

Hypernatraemia (a rise in plasma osmolality) is usually associated with inadequate water intake, or excessive water losses (see p. 1778.1). It rarely occurs after therapeutic doses of sodium chloride, but has occurred with the use of hypertonic saline for induction of emesis or for gastric lavage and after errors in the formulation of infant feeds. Hypernatraemia may also occur after inappropriate intravenous use of hypertonic saline.

The most serious effect of hypernatraemia is dehydration of the brain which causes somnolence and confusion progressing to convulsions, coma, respiratory failure, and death. Other symptoms include thirst, reduced salivation and lachrymation, fever, sweating, tachycardia, hypertension or hypotension, headache, dizziness, restlessness, irritability, weakness, and muscular twitching and rigidity.

Gastrointestinal effects associated with acute oral ingestion of hypertonic solutions or excessive amounts of sodium chloride include nausea, vomiting, diarrhoea, and abdominal cramps.

Excessive use of chloride salts may cause a loss of bicarbonate with an acidifying effect.

Intra-amniotic injection of hypertonic solutions of sodium chloride, which has been used for termination of pregnancy, has been associated with serious adverse effects including disseminated intravascular coagulation, renal necrosis, cervical and uterine lesions, haemorrhage, pulmonary embolism, pneumonia, and death.

General references.

1. Moder KG, Hurley DL. Fatal hypernatremia from exogenous salt intake: report of a case and review of the literature. *Mayo Clin Proc* 1990; **65:** 1587–94. Correction. *ibid.* 1991; **66:** 439.
2. Martos Sánchez I, *et al.* Hipernatremia grave por administración accidental de sal común. *An Esp Pediatr* 2000; **53:** 495–8.
3. Adeleye O, *et al.* Hypernatremia in the elderly. *J Natl Med Assoc* 2002; **94:** 701–5.
4. Coulthard MG, Haycock GB. Distinguishing between salt poisoning and hypernatraemic dehydration in children. *BMJ* 2003; **326:** 157–60. Correction. *ibid.;* 497.

Treatment of Adverse Effects

In patients with mild sodium excess, drinking water and restricting sodium intake is sufficient. However, in the event of recent acute oral overdose of sodium chloride, gastric lavage should be carried out along with general symptomatic and supportive treatment. Serum-sodium concentrations should be measured, and if severe hypernatraemia is present this should be treated (see p. 1778.1).

Precautions

Sodium salts should be used with caution in patients with hypertension, heart failure, peripheral or pulmonary oedema, renal impairment, pre-eclampsia, or other conditions associated with sodium retention.

When sodium supplements are given orally, adequate water intake should be maintained. Modified-release tablets should not be given to patients with gastrointestinal disorders associated with strictures or diverticula because of the risk of obstruction.

Sodium chloride solutions should *not* be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium chloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pharmacokinetics

Sodium chloride is well absorbed from the gastrointestinal tract. Excess sodium is mainly excreted by the kidney, and small amounts are lost in the faeces and sweat.

Human Requirements

The body contains about 4 mol (92 g) of sodium of which about one-third is found in the skeleton and about half is present in the extracellular fluid.

The body can adapt to a wide range of intakes by adjustment of renal excretion through physical and hormonal factors. Loss through the skin is significant only if excessive sweating occurs. Sodium requirements may be increased with exercise or exposure to high ambient temperatures in the short term, until the body adjusts.

Sodium is widely available in foods and is also added as salt during processing, cooking, and at the table. Dietary deficiency of sodium is therefore extremely rare and more concern has been expressed that current intakes are excessive. Restriction of sodium intake, by limiting the amount of culinary salt consumed, may be a useful aid in the management of some patients with hypertension (p. 1251.1).

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] have been published for sodium. The reference nutrient intake (RNI) for adults is 1.6 g of sodium (70 mmol) daily, which is about 4g of sodium chloride. In

Table 4. Some sodium salts and their sodium content.

	Sodium content per g		
Sodium salt	mg	mmol	mEq
Sodium acetate (anhydrous)	280	12.2	12.2
Sodium acetate (trihydrate)	169	7.3	7.3
Sodium acid citrate	175	7.6	7.6
Sodium bicarbonate	274	11.9	11.9
Sodium chloride	394	17.1	17.1
Sodium citrate (anhydrous)	267	11.6	11.6
Sodium citrate (dihydrate)	235	10.2	10.2
Sodium lactate	205	8.9	8.9

the USA, it has been recommended that daily intakes of sodium be limited to 2.4 g (6 g of sodium chloride) or less.[2] Dietary intake is often in excess of these recommendations, and may be a factor in essential hypertension,[3] and osteoporosis.[4] A possible association with cardiovascular disease has also been suggested by the long-term follow-up of two hypertension studies.[5] Results found that reducing sodium intake may also reduce the risk of cardiovascular events.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
3. Midgley JP, *et al*. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275:** 1590–7.
4. Devine A, *et al*. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* 1995; **62:** 740–5.
5. Cook NR, *et al*. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). Abridged version: *BMJ* 2007; **334:** 885–8. Full version: http://www.bmj.com/cgi/reprint/334/7599/885 (accessed 13/03/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aqua Lent Limpia Cristales; Cutidermin Bebe Gel Nasal†; Hypersol; Larmabak; Muro 128; Oftalook; Relente; Suaviler; Xylisol; Yusin Tears I; ***Austral.***: Dimetapp Infants Nasal Relief; Ear Clear Ear Cleanser; Fess; Hypergel; Lens Plus; Mesalt; Narium; Normlgel; Otrivin Saline Baby; Sensitive Eyes Saline; Slow-Sodium; ***Austria***: Kochsalz; SmartDose†; ***Belg.***: Natriclo; Physiologica; Physiorhine; ***Braz.***: Advnasal†; Afrin Natural; Alive; Conidrin Baby; Conidrin Salina; Deltasoro; Descodrin; Fisiorinus; Fluimare; Fluimucil Solucao Nasal; Maresis; Maxidrate; Multisoro; Naridrin Bebe; Naridrin H; Narisoro; Neorino; Neosoro H; Neosoro Infantil; Novo Rino-S; Pratsorin; Rinoben; Rinoflux†; Rinosoft S; Rinosoro; Salsep; Sinustrat Solucao Natural; Snif; Sonarin (INF); Sorine Pediatrico; Sorine; Sorofar; Soroliv; Soroneo; ***Canad.***: Hypergel; Mesalt; Muro 128; Nebusal; Normigel; Rhinaris Saline; Rhinaris Sinus; Salinex; Sea Clens†; Softwear†; Thalanex†; Thalaris†; ***Chile***: Fisiolimp; Larmabak†; Pediasea; Printan; Respirex†; Rinodan; Rinokid; Rinosteryl; Sinus; ***China***: Ai Na Duo (艾那多); ***Fin.***: Natrosteril†; Selutrio; ***Fr.***: Erjean; Hypergel; Jellywash; Larmabak; Larmes Artificielles; Multilarm†; Normlgel; Physiologica†; Polyrinse†; Selgine; ***Ger.***: Adsorbonac†; Freka-Drainjet†; Hylase; Isogutt akut; Isotone Kochsalz; Isotonische Kochsalzlosung; Olynth salin; Omni-Sorb; Tetrisal; Tussamag Nasenspray Pur†; Urgo sterile; ***Gr.***: Babynose; Clinofar; Larmabak; Otrisalin; Phy-O; Rhinodose; Selva N; ***Hong Kong***: Ayr Saline†; Earinse; Larmabak; Nasal Physiological Solution; Physiodose; Unison Enema; ***Hung.***: Rins-Sal; Salsol A†; ***India***: Hold; Hynasal; Hypersol; Hytosol; Izabel; Libna; Nam Cold-NS; Nasalt; Nasivion-S; Nasoclear; Nipit; Nos-Air Saline; Ocutone; Osmogel; Otrivin-S; ***Indon.***: Breathy; Infusan-NS; Otsu-NS; Wida NS; Wida NSI; ***Irl.***: Diarrest RF†; ***Israel***: Af-Kid; Af-Tiponet; Alrin Baby; Baby AF; Baby Saline†; Clean-AF; L'Batzeket; Moviprep; Normasol; Ocean Spray; Otrivini; Tinok AF; Tipotaf; ***Ital.***: Adsorbonac†; Hydrabak; Libenar; Narhinel; Otrivin Baby†; Physiodose; Respifree Baby; Rinowash; ***Mex.***: Corni Limp; Hiperton; Muro 128; Phylarm; ***Mon.***: Unilarm; ***NZ***: Narium; ***Philipp.***: Hypersalt; Hyperton-Opta; Larmabak†; Muconase; SalinaGel; Salinase; Snif; ***Pol.***: Oftarinol; Solnasin†; ***Port.***: Extraneal; ***Rus.***: Aquamaster (Аквамастер); Rizosin (Ризосин); Salin (Салин); ***S.Afr.***: Polyrinse†; Vicks Vapomist†; ***Singapore***: Adsorbonac†; Dorama-neo; Larmabak; Normasol; Oftalmolosa Cusi Antiedema†; Otrivin Saline Nasal Spray; Salacyn; ***Spain***: Antiedema; Apiroserum Clorurado; Fisiologica†; Fisiologico Bieffe Medital†; Fisiologico Braun; Fisiologico Mein; Fisiologico Serra Pamies†; Fisiologico Vitulia†; Fisiologico†; Flebobag Fisio; Fleboflex Salina Fisiologica†; Fleboplast Fisio; Freeflex Cloruro Sodico; Hidrathea; Meinvenil Fisiologico†; Plast Apyr Fisiologico; Solucion Fisiologica Respitol; Suero Fisiologico; Suero Fisiologico; ***Switz.***: Physiologic; Physiosoin†; Serophy; ***Thai.***: Patar Enema; Royal-C; U-Enema; Unison Enema; ***Turk.***: Berko-Fiz; Droser; Fizyolen; Fizyolik; Fizyosol; Larmabak; Otrisalin; Physiodese; Physiologica Gifrer; Ser Damla†; Serum Fizyolojik; ***UAE***: Normaline; ***UK***: Askina; Equaleze; Irriclens; Irripod; Miniversol; MucoClear; Nasosal; Nebusal; Normasol; Slow-Sodium; SodiClor; Stericlens; Steripod; Tubilux; Uriflex S; Uro-Tainer M; Versol; ***Ukr.***: No-Sol (Но-Соль); ***USA***: Adsorbonac†; Ak-NaCl; Ayr Saline; Breathe Free; Broncho Saline; Dristan Saline Spray; Entsol; HuMist Nasal Mist; Marlin Salt System†; Muro 128; Muroptic; Nasal Moist; NaSal; Normaline; Ocean; Pretz; Rhinaris; Salinex; SeaMist; Sochlor; Your Choice†; ***Venez.***: Larmabak; Nafavine.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Childrens Runny Nose Relief; Respatona Head Cold; Vitatona Energy†; ***Austria***: Globuli gegen Hautausschlage; ***Canad.***: Adrisin†; Calms Forte 4 Kids; Cold Sores & Fever Blisters; Combinaison†; Diamite; Eczema; Hives; Homeoknop Bioactiv O Weight Loss Aid†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Hylands Vaginitis†; Hylavir FB†; Ikoplex 11 Digestion Aid†; Ikoplex 14†; Melange†; Nuage Bioplasma†; Sore Throat L39†; Sorinoheel; ***Chile***: Anacardio con Fosforo; Bioactiv M; Bioactiv O; Bioactiv P; Ikoplex No 11; Ikoplex No 13; Ikoplex No 14; Ikoplex No 17; Ikoplex No 19; Ikoplex No 6; Ikoplex No 7; Ikoplex No 8; ***Fr.***: Billerol; Pulsatilla Complexe No 60†; Soludor; ***Ger.***: Derivatio H; Drufusan N†; Drufusan; Herpes-Gastreu R68; Hewelymphon N†; Muco-cyl L Ho-Len-Complex; Nuxal comp; Schleimhaut-Komplex L Ho-Fu-Complex; ***Neth.***: Ailgeno spag; Hemorrolite; Urtizon complex; ***Rus.***: Diet-Comfort (Диет-Комфорт); ***Switz.***: Regenaplex Nr 28b.

Pharmacopoeial Preparations

BP 2014: Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution; Compound Sodium Chloride Mouthwash; Compound Sodium Lactate Infusion; Oral Rehydration Salts; Potassium Chloride and Sodium Chloride Infusion; Potassium Chloride, Sodium Chloride and Glucose Infusion; Sodium Chloride and Glucose Infusion; Sodium Chloride Eye Drops; Sodium Chloride Eye Lotion; Sodium Chloride Eye Ointment; Sodium Chloride Infusion; Sodium Chloride Irrigation Solution; Sodium Chloride Nebuliser Solution; Sodium Chloride Oral Solution; Sodium Chloride Solution; Soluble Sodium Chloride Tablets;

USP 36: Bacteriostatic Sodium Chloride Injection; Cimetidine in Sodium Chloride Injection; Cisplatin for Injection; Dextran 40 in Sodium Chloride Injection; Dextran 70 in Sodium Chloride Injection; Dextrose and Sodium Chloride Injection; Fructose and Sodium Chloride Injection; Half-strength Lactated Ringer's and Dextrose Injection; Inulin in Sodium Chloride Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Mannitol in Sodium Chloride Injection; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Dextrose Injection Type 4; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3; Multiple Electrolytes Injection Type 1; Multiple Electrolytes Injection Type 2; Oral Rehydration Salts; PEG 3350 and Electrolytes for Oral Solution; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Ringer's and Dextrose Injection; Sodium Chloride and Dextrose Tablets; Sodium Chloride Inhalation Solution; Sodium Chloride Injection; Sodium Chloride Irrigation; Sodium Chloride Ophthalmic Ointment; Sodium Chloride Ophthalmic Solution; Sodium Chloride Tablets for Solution; Sodium Chloride Tablets.

Gases

This chapter includes monographs on gases with medical or pharmaceutical uses and applications (such as oxygen, carbon dioxide, helium, and nitrogen) and some whose main medical interest is management of their toxicity or adverse effects (such as carbon monoxide or hydrogen sulfide). Also included are some compressed and liquefied gases used as refrigerants and aerosol propellants. Nitric oxide gas is used in bronchopulmonary disorders and is discussed in Cardiovascular Drugs (p. 1457.1). Other gases with medical uses can be found in Disinfectants and Preservatives (p. 1730.1) and General Anaesthetics (p. 1896.1).

Refrigerants and Aerosol Propellants

Some gases have properties that make them suitable for use as refrigerants and as aerosol propellants; these include nitrogen, nitrous oxide, carbon dioxide, and hydrocarbons such as propane, and the butanes. Chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs) have been widely used but are generally being phased out due to their environmental effects, particularly depletion of the ozone layer. Nonchlorinated fluorocarbons (hydrofluorocarbons; HFCs) do not affect the ozone layer (although they may contribute to global warming) and are a possible alternative; however, their physical properties may be less suitable. Ammonia gas (see p. 2441.2) may be used as an industrial refrigerant.

The evaporation of propellants such as halogenated hydrocarbons and dimethyl ether produces an intense cold. Topical application has a numbing effect on tissues and has been used for analgesia (see Rubefacients and Topical Analgesia, p. 6.3), although cold injury, including frostbite, has been reported.

Refrigerants and aerosol propellants have been subject to deliberate abuse. They have similar effects to volatile solvents (see Abuse, under Adverse Effects of Toluene, p. 2216.3), and both acute and chronic toxicity may occur. Inhalation of high concentrations of halogenated hydrocarbons for their euphoriant effect may result in CNS depression, cardiac arrhythmias, respiratory depression, and death, while propane and butane can act as simple asphyxiants. Toxicity may also result from decomposition products, such as hydrogen chloride and phosgene from heating halogenated hydrocarbons.

Toxicity. The toxicity resulting from abuse by deliberate inhalation of propellants has been reviewed.[1-4] Further references relevant to the toxicity of individual agents are given in the monographs.

1. Kurtzman TL, *et al.* Inhalant abuse by adolescents. *J Adolesc Health* 2001; **28:** 170–80.
2. Brouette T, Anton R. Clinical review of inhalants. *Am J Addict* 2001; **10:** 79–94.
3. Anderson CE, Loomis GA. Recognition and prevention of inhalant abuse. *Am Fam Physician* 2003; **68:** 869–74.
4. Williams JF, Storck M. American Academy of Pediatrics Committee on Substance Abuse. Inhalant abuse. *Pediatrics* 2007; **119:** 1009–17.

Argon

Argón; Argonum; E938; Аргон.
CAS — 7440-37-1.
UNII — 67XQY1V3KH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Argon). A colourless gas. Soluble 1 in about 29 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas or liquid in appropriate containers.

Profile

Argon is an inert gas and is used to replace air in containers containing oxidisable substances.

Bromochlorodifluoromethane

Bromoclorodifluorometano; Halon 1211; R-12B1; Бромхлордифторметан.
$CBrClF_2$=165.4
CAS — 353-59-3.
UNII — 9115X8AJXS.

Profile

Bromochlorodifluoromethane is a halogenated hydrocarbon that has been used as a fire-extinguishing agent. Like chlorofluorocarbons it causes ozone depletion and other environmental effects and its use is generally being phased out.

Toxicity has been reported after the misuse or abuse of fire extinguishers containing bromochlorodifluoromethane,[1-3] and in persons exposed in other ways.[4,5]

1. Steadman C, *et al.* Abuse of fire-extinguishing agent and sudden death in adolescents. *Med J Aust* 1984; **141:** 115–17.
2. Lerman Y, *et al.* Fatal accidental inhalation of bromochlorodifluoromethane (Halon 1211). *Hum Exp Toxicol* 1991; **10:** 125–8.
3. Gerhardt RT. Acute Halon (bromochlorodifluoromethane) toxicity by accidental and recreational inhalation. *Am J Emerg Med* 1996; **14:** 675–7.
4. Matrat M, *et al.* Reactive airways dysfunction syndrome caused by bromochlorodifluoromethane from fire extinguishers. *Occup Environ Med* 2004; **61:** 712–14.
5. Lo SH, *et al.* Grand rounds: outbreak of hematologic abnormalities in a community of people exposed to leakage of fire extinguisher gas. *Environ Health Perspect* 2006; **114:** 1713–17.

Butane

n-Butane; Butano; E943a; Бутан.
C_4H_{10}=58.12
CAS — 106-97-8.
UNII — 6LV4FOR43R.

Pharmacopoeias. In *USNF.*

USNF 31: (Butane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Butane is used as an aerosol propellant (above). It is widely used as a fuel.

Abuse. Toxicity has been reported with the abuse of butane.[1-10]

1. Gunn J, *et al.* Butane sniffing causing ventricular fibrillation. *Lancet* 1989; **i:** 617.
2. Siegel E, Wason S. Sudden death caused by inhalation of butane and propane. *N Engl J Med* 1990; **323:** 1638.
3. Roberts MJD, *et al.* Asystole following butane gas inhalation. *Br J Hosp Med* 1990; **44:** 294.
4. Williams DR, Cole SJ. Ventricular fibrillation following butane gas inhalation. *Resuscitation* 1998; **37:** 43–5.
5. Rieder-Scharinger J, *et al.* Multiorganversagen nach Butangasinhalation: ein Fallbericht. *Wien Klin Wochenschr* 2000; **112:** 1049–52.
6. Wehner F, *et al.* Tödliche Inhalation von Butan-Propan-Gas. *Arch Kriminol* 2002; **209:** 164–8.
7. El-Menyar AA, *et al.* A teenager with angiographically normal epicardial coronary arteries and acute myocardial infarction after butane inhalation. *Eur J Emerg Med* 2005; **12:** 137–41.
8. Harris D, Mirza Z. Butane encephalopathy. *Emerg Med J* 2005; **22:** 676–7.
9. Doogue M, Barclay M. Death due to butane abuse—the clinical pharmacology of inhalants. *N Z Med J* 2005; **118:** U1732.
10. Girard F, *et al.* Fibrillation ventriculaire par inhalation de spray déodorant. *Ann Fr Anesth Reanim* 2008; **27:** 83–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Frionex.

Carbon Dioxide

Anglies dioksidas; Anhídrido carbónico; Carbone, dioxyde de; Carbonei Dioxidum; Carbonei Dioxydum; Carbonic Acid Gas; Carbonic Anhydride; Dióxido de carbono; E290; Gaz Carbonique; Hiilidioksidi; Kohlendioxid; Koldioxid; Oxid uhličitý; Szén-dioxid; Węgla dwutlenek; Диоксид Углерода; Двуокись Углерода; Углекислый Газ.
CO_2=44.01
CAS — 124-38-9.
ATC — V03AN02.
ATC Vet — QV03AN02.
UNII — 142M471B3J.

NOTE. Carbon dioxide is about 1½ times as heavy as air.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Carbon Dioxide). A colourless gas. Soluble 1 in about 1 of water by volume at 20 degrees and at a pressure of 101 kpA. Store liquefied under pressure in suitable containers.

The BP 2014 directs that carbon dioxide should be kept in approved metal cylinders which are painted grey and carry a label stating 'Carbon Dioxide'. In addition, 'Carbon Dioxide' or the symbol 'CO_2' should be stencilled in paint on the shoulder of the cylinder.

USP 36: (Carbon Dioxide). A colourless, odourless gas. Its solutions are acid to litmus. One volume dissolves in about 1 volume of water. Store in cylinders.

Uses and Administration

Carbon dioxide is a product of respiration and blood concentrations are normally kept within strict physiological limits. Manipulation of carbon dioxide concentrations has been used therapeutically (see below) but hypocapnia is not always desirable and carbon dioxide has been added to the oxygen in pump oxygenators to prevent hypocapnia developing.

Carbon dioxide acts as a respiratory stimulant, but is rarely used therapeutically for this purpose. However, inhalation of low concentrations has been tried in the management of neonatal apnoea (p. 1204.3).

Carbon dioxide may be used as the insufflating gas for laparoscopy, and to flood the surgical field to prevent formation of gas emboli during cardiac surgery. It may also be used as a contrast agent in radiography (p. 1580.1).

Solid carbon dioxide, or 'dry ice' has a temperature of -80 degrees and has been used to treat warts (p. 1689.3) and naevi by cryotherapy.

Pharmaceutically, carbon dioxide is used as an aerosol propellant and as a replacement for air to preserve oxidisable substances. Carbonated vehicles are useful for masking the unpleasant taste of some medicinal preparations.

Manipulation of carbon dioxide concentrations in the blood may be achieved by ventilatory techniques and has been used therapeutically. Examples include the use of hyperventilation in the management of raised intracranial pressure (p. 1271.3) and breath-holding or rebreathing for intractable hiccup (p. 1046.3).

Adverse Effects

Carbon dioxide has direct toxic effects and also acts as an asphyxiant. Above a concentration of about 6%, it causes headache, dizziness, confusion, palpitations, hypertension, dyspnoea, increased depth and rate of respiration, and CNS depression. Concentrations of about 20% and higher produce convulsions and loss of consciousness; inhalation of 50% carbon dioxide is reported to produce central effects similar to anaesthetics. The inhalation of high concentrations may produce respiratory acidosis.

Abrupt withdrawal of carbon dioxide after prolonged inhalation may produce malaise, pallor, headache, and nausea or vomiting.

Skin contact with solid carbon dioxide may cause frostbite.

References.

1. Halpern P, *et al.* Exposure to extremely high concentrations of carbon dioxide: a clinical description of a mass casualty incident. *Ann Emerg Med* 2004; **43:** 196–9.
2. Langford NJ. Carbon dioxide poisoning. *Toxicol Rev* 2005; **24:** 229–35.
3. Srisont S, *et al.* A carbon dioxide fatality from dry ice. *J Forensic Sci* 2009; **54:** 961–2.
4. Leikin JB, *et al.* Carbon dioxide-induced narcosis due to dry ice exposure in a patient with sleep apnea. *Ann Intern Med* 2009; **150:** 361–2.
5. Dunford JV, *et al.* Asphyxiation due to dry ice in a walk-in freezer. *J Emerg Med* 2009; **36:** 353–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Carbogen.

Carbon Monoxide *(USAN)*

Anglies monoksidas; Carbone, monoxyde de; Carbonei Monoxidum; Hiilimonoksidi; Karbon Monoksit; Kolmonoxid; Monóxido de carbono; Węgla tlenek; Монооксид Углерода; Окись Углерода; Угарный Газ.
CO=28.01
CAS — 630-08-0.
UNII — 7U1EE4V452.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Carbon Monoxide). A colourless, flammable gas obtained by steam reforming (catalytic oxidation) of hydrocarbons. Soluble 2.266 in 100 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas in appropriate containers.

Uses

Carbon monoxide has been used in low concentrations as a tracer gas in measurements of lung function. It is also reported to have anti-inflammatory properties and is under investigation for various medical uses, including the management of delayed graft function. It appears to have a physiological role as a signalling molecule. Carbon

monoxide labelled with carbon-11 may be used to assess the blood volume.

General references.

1. Foresti R, *et al*. Use of carbon monoxide as a therapeutic agent: promises and challenges. *Intensive Care Med* 2008; **34:** 649–58.
2. Bauer I, Pannen BH. Bench-to-bedside review: carbon monoxide—from mitochondrial poisoning to therapeutic use. *Crit Care* 2009; **13:** 220.
3. Ghosh S, *et al*. Carbon monoxide: endogenous mediator, potential diagnostic and therapeutic target. *Ann Med* 2010; **42:** 1–12.

Adverse Effects

Carbon monoxide is produced by incomplete combustion of organic materials and is highly toxic when inhaled; infants, small children, and elderly people are particularly susceptible. Although the number of cases of poisoning in countries such as the UK has fallen as the availability of coal gas has declined and as changes have been made to motor vehicles to improve their exhaust fumes, carbon monoxide is still a major cause of poisoning. Common sources of carbon monoxide include poorly maintained and ventilated heating systems and improperly burnt fuel in domestic fires.

When inhaled, carbon monoxide combines with haemoglobin in the blood to form carboxyhaemoglobin; this complex is unable to transport oxygen, and cellular hypoxia therefore results. Most of the symptoms of poisoning are due to anoxia, but carbon monoxide also has a direct toxic effect on cells, which may contribute. The skin and tissues may turn a classic cherry red in patients poisoned with carbon monoxide although this is seen most often after death.

The symptoms of carbon monoxide poisoning are varied and depend on the degree and duration of exposure, although there is wide variation between individuals. Unconsciousness may occur suddenly but is commonly preceded by headache, dizziness, weakness, nausea, and vomiting, which may be misdiagnosed as a viral illness or food poisoning. Other symptoms may include skin lesions, excessive sweating, pyrexia, increased respiration, mental dullness and confusion, visual disturbances, convulsions, hypotension, tachycardia or other cardiac arrhythmias, myocardial ischaemia, and possibly myocardial infarction. Death may result from respiratory failure, pulmonary oedema, cardiovascular failure, or cerebral damage. Carboxyhaemoglobin concentrations are a guide to the severity of poisoning, although they are not a reliable measure of toxicity; the lethal concentration of carboxyhaemoglobin in the blood is about 50% or more. Concentrations over 1000 ppm of carbon monoxide in inspired air may be fatal in 1 hour. Neurological and psychiatric sequelae may develop some weeks later in the survivors of severe poisoning and therefore a prolonged follow-up of such patients is advised; symptoms include memory impairment, apathy, mutism, irritability, personality change, gait disturbance, and urinary and faecal incontinence. Chronic carbon monoxide exposure may present as a non-specific illness with headache, nausea, and flu-like symptoms.

General references.

1. WHO. Carbon Monoxide. *Environmental Health Criteria 213*. Geneva: WHO, 1999. Available at: http://www.inchem.org/documents/ehc/ehc/ehc213.htm (accessed 05/07/04)
2. Satran D, *et al*. Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. *J Am Coll Cardiol* 2005; **45:** 1513–16.
3. Kao LW, Nañagas KA. Toxicity associated with carbon monoxide. *Clin Lab Med* 2006; **26:** 99–125.
4. Cevik AA, *et al*. Interrelation between the Poisoning Severity Score, carboxyhaemoglobin levels and in-hospital clinical course of carbon monoxide poisoning. *Int J Clin Pract* 2006; **60:** 1558–64.
5. Prockop LD, Chichkova RI. Carbon monoxide intoxication: an updated review. *J Neurol Sci* 2007; **262:** 122–30.
6. Grieb G, *et al*. The diversity of carbon monoxide intoxication: medical courses can differ extremely—a case report. *Inhal Toxicol* 2008; **20:** 911–5.
7. Weaver LK. Carbon monoxide poisoning. *N Engl J Med* 2009; **360:** 1217–25.

Treatment of Adverse Effects

The patient should be removed from the contaminated atmosphere and an effective airway established. Oxygen (100%) should be given until the blood carboxyhaemoglobin concentration has fallen below dangerous levels (usually 5%). Management is then usually symptomatic and supportive with attention being given to the possible need to treat or correct any cardiovascular disorders, metabolic acidosis, or cerebral oedema. Hyperbaric oxygen therapy may be considered in pregnant patients or in severe poisoning (if the patient is, or has been, unconscious, or if there are neurological symptoms or cardiac complications) but is of unproven benefit (see below) and its use is controversial.

Hyperbaric oxygen therapy. The use of hyperbaric oxygen therapy in the management of carbon monoxide poisoning is controversial.[1-5] The rationale for using hyperbaric oxygen is that it increases the rate at which carboxyhaemoglobin dissociates, shortening the half-life from about 2 hours with normobaric 100% oxygen to about 30 minutes with hyperbaric oxygen. Theoretically, this should be of benefit, and retrospective studies have shown improved symptoms in patients given hyperbaric oxygen, particularly in terms of neurological outcomes.[6] However, controlled studies have had conflicting results, and systematic reviews[1-4] have found insufficient evidence to determine the value of hyperbaric oxygen. Although hyperbaric oxygen has been widely recommended, particularly in severe poisoning, availability is limited and it remains unclear which patients should be considered for therapy. There is some evidence that older patients, and those with loss of consciousness, prolonged exposures, or high carboxyhaemoglobin concentrations gain most benefit,[7] but this is not established. It is also unclear whether use in pregnancy should be recommended, since few studies have included pregnant patients. Case reports suggest that hyperbaric oxygen is safe in pregnancy,[8] and there is a theoretical basis for therapy since fetal carboxyhaemoglobin concentrations are higher than maternal concentrations, but evidence is limited and successful outcomes without the use of hyperbaric oxygen have also been reported.[9]

1. Juurlink DN, *et al*. Hyperbaric oxygen for carbon monoxide poisoning. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 20/06/08).
2. Buckley NA, *et al*. Hyperbaric oxygen for carbon monoxide poisoning: a systematic review and critical analysis of the evidence. *Toxicol Rev* 2005; **24:** 75–92.
3. Domachevsky L, *et al*. Hyperbaric oxygen in the treatment of carbon monoxide poisoning. *Clin Toxicol* 2005; **43:** 181–8.
4. Silver S, *et al*. Should hyperbaric oxygen be used for carbon monoxide poisoning? *CJEM* 2006; **8:** 43–6.
5. Wolf SJ, *et al*. American College of Emergency Physicians. Clinical policy: critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. *Ann Emerg Med* 2008; **51:** 138–52.
6. Hawkins M, *et al*. Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. *Br J Anaesth* 2000; **84:** 584–6.
7. Weaver LK, *et al*. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Respir Crit Care Med* 2007; **176:** 491–7.
8. Van Hoesen KB, *et al*. Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning: a case report and literature review. *JAMA* 1989; **261:** 1039–43. Correction. *ibid*. 1990; **263:** 2750.
9. Bar R, *et al*. Pre-labor exposure to carbon monoxide: should the neonate be treated with hyperbaric oxygenation? *Clin Toxicol* 2007; **45:** 579–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Lung Diffusion Test Mix No Ne Co; Lung Diffusion Test Mixture Gas.

Chlorofluorocarbons

CFCs; Clorofluorocarbonos; Хлорофтороуглеводороды; Хлорфторуглероды.

Cryofluorane (rINN)

CFC-114; Criofluorano; Cryofluoranum; Dichlorotetrafluoroethane; Propellant 114; Refrigerant 114; Tetrafluorodichloroethane; Криофлуоран.

1,2-Dichloro-1,1,2,2-tetrafluoroethane.

$C_2Cl_2F_4$=170.9

CAS — 76-14-2.

UNII — 6B5VVT93AR.

Pharmacopoeias. In *USNF*.

USNF 31: (Dichlorotetrafluoroethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Dichlorodifluoromethane

CFC-12; Diclorodifluorometano; Difluorodichloromethane; Propellant 12; Refrigerant 12; Дифтордихлорметан; Дихлордифторметан.

CCl_2F_2=120.9

CAS — 75-71-8.

UNII — OFM06SG1KO.

Pharmacopoeias. In *USNF*.

USNF 31: (Dichlorodifluoromethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Trichlorofluoromethane

CFC-11; Fluorotrichloromethane; Fluorotriclorometano; Propellant 11; Refrigerant 11; Trichloromonofluoromethane; Triclorofluorometano; Tricloromonofluorometano; Фтортрихлорметан.

CCl_3F=137.4

CAS — 75-69-4.

UNII — 990TYB331R.

NOTE. Trichlorofluoromethane is a gas above 24 degrees.

Pharmacopoeias. In *USNF*.

USNF 31: (Trichloromonofluoromethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Chlorofluorocarbons are halogenated hydrocarbons that contain only chlorine, fluorine, and carbon. They have been widely used as refrigerants and as aerosol propellants (p. 1797.1), but have been phased out in most countries due to their effects on atmospheric ozone. Medicinally, they have been used in metered dose inhalers and in cold sprays for topical anaesthesia, but alternatives are now preferred.

References.

1. WHO. Fully halogenated chlorofluorocarbons. *Environmental Health Criteria 113*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc113.htm (accessed 08/06/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Algispray; ***Austral.***: Derm-Freeze†; ***USA***: Aerofreeze†; Fluro-Ethyl†.

Dimethyl Ether

Dimethyl Oxide; Éter dimetílico; Methoxymethane; Oxybismethane; Простой Диметиловый Эфир; Диметилэфир.

C_2H_6O=46.07

CAS — 115-10-6.

UNII — AM13FS69BX.

Profile

Dimethyl ether is used as a refrigerant, aerosol propellant (p. 1797.1), and topical anaesthetic. It has also been used as a fuel.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: ActiFreeze.

Multi-ingredient Preparations. ***Ger.***: Wartner; ***Irl.***: Wartner; ***Israel***: Wartner†; ***NZ***: Wartner; ***Singapore***: Wartner; ***Switz.***: Wartner; ***UK***: Histofreezer; PR Freeze Spray; Ralgex Freeze Spray†; Wartner; ***USA***: Compound W Freeze Off.

Helium

E939; Helio; Hélium; Гелий.

He=4.002602

CAS — 7440-59-7.

ATC — V03AN03.

ATC Vet — QV03AN03.

UNII — 206GF3GB41.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Helium). A colourless, inert gas. Store as a compressed gas or liquid at cryogenic temperatures, in appropriate containers.

USP 36: (Helium). A colourless, odourless, tasteless gas which is not combustible and does not support combustion. Very slightly soluble in water. Store in cylinders.

Profile

As helium is less dense than nitrogen, breathing a mixture of 80% helium and 20% oxygen requires less effort than breathing air. Thus mixtures containing various concentrations of oxygen ('Heliox') have been used in patients with respiratory disorders. Mixtures of helium and oxygen have also been used as an alternative to compressed air by divers or others working under high pressure, to prevent the development of nitrogen narcosis. Helium has been used in pulmonary function testing.

Breathing helium increases vocal pitch and causes voice distortion. Cerebral artery gas embolism has been reported after inhalation of helium from a pressurised container.

Although individual studies may have shown benefit, systematic reviews of the use of helium and oxygen mixtures (heliox) in various respiratory disorders have generally failed to find convincing evidence of value.

References to the use of helium or heliox.

1. Rodrigo GJ, *et al*. Heliox for treatment of exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 22/02/10).
2. Rodrigo GJ, *et al*. Heliox for nonintubated acute asthma patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 22/02/10).
3. Colebourn CL, *et al*. Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia* 2007; **62:** 34–42.
4. Harris PD, Barnes R. The uses of helium and xenon in current clinical practice. *Anaesthesia* 2008; **63:** 284–93.
5. McGarvey JM, Pollack CV. Heliox in airway management. *Emerg Med Clin North Am* 2008; **26:** 905–20.

6. Migliori C, *et al*. The effects of helium/oxygen mixture (heliox) before and after extubation in long-term mechanically ventilated very low birth weight infants. *Pediatrics* 2009; **123:** 1524–8.
7. Vorwerk C, Coats T. Heliox for croup in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 22/02/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Heliox; Lung Diffusion Test Mixture Gas.

Hydrochlorofluorocarbons

HCFCs; Hidroclorofluorocarbonos; Гидрохлорфторуглероды.

Chlorodifluoroethane

Clorodifluoroetano; Propellant 142b; Refrigerant 142b; Дифтормонохлорэтан.
1-Chloro-1,1-difluoroethane.
$C_2H_3ClF_2$=100.5
CAS — 75-68-3.

Chlorodifluoromethane

Clorodifluorometano; Propellant 22; Refrigerant 22; Дифтормонохлорметан; Хлордифторметан.
$CHClF_2$=86.47
CAS — 75-45-6.

Profile

Hydrochlorofluorocarbons are hydrogenated chlorofluorocarbons. They have been used similarly to chlorofluorocarbons as refrigerants and as aerosol propellants (p. 1797.1) but share the same environmental effects and have been or are being phased out in most countries.

References to toxicity.

1. Dekant W. Toxicology of chlorofluorocarbon replacements. *Environ Health Perspect* 1996; **104** (suppl 1): 75–83.
2. Kubota T, Miyata A. Acute inhalational exposure to chlorodifluoromethane (freon-22): a report of 43 cases. *Clin Toxicol* 2005; **43:** 305–8.
3. Koreeda A, *et al*. An accidental death due to Freon 22 (monochlorodifluoromethane) inhalation in a fishing vessel. *Forensic Sci Int* 2007; **168:** 208–11.
4. Lee J, *et al*. Uncontrolled occupational exposure to 1,1-dichloro-1-fluoroethane (HCFC-141b) is associated with acute pulmonary toxicity. *Chest* 2009; **135:** 149–55.

Hydrofluorocarbons

HFAs; HFCs; Hidrofluoroalcanos; Hidrofluorocarbonos; Hydrofluroalkanes; Гидрофторуглероды.

Apaflurane *(BAN, rINN)*

Apaflurano; Apafluranum; Heptafluoropropane; HFA-227; HFC-227; Апафлуран.
1,1,1,2,3,3,3-Heptafluoropropane.
C_3HF_7=170.0
CAS — 431-89-0.
UNII — R40P36GDK6.

Difluoroethane

Difluoroetano; Ethylene Fluoride; Fluoruro de etileno; HFC-152a; Propelente 152a; Propellant 152a; Refrigerant 152a; Refrigerante 152a; Дифторэтан.
1,1-Difluoroethane.
$C_2H_4F_2$=66.05
CAS — 75-37-6.
UNII — 0B1U8K2ME0.

Norflurane *(BAN, USAN, rINN)*

Fluorocarbon 134a; Fluorocarbono 134a; GR-106642X; HFA-134a; HFC-134a; Norflurano; Norfluranum; Propellant 134a; Refrigerant 134a; Норфлуран.
1,1,1,2-Tetrafluoroethane.
$C_2H_2F_4$=102.0
CAS — 811-97-2.
UNII — DH9E53K1Y8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Norflurane). A clear, colourless gas, liquid under pressure. At 20 degrees and at a pressure of 101 kPa, slightly soluble in water; freely soluble in alcohol. Relative density about 1.23, for the gas in the liquid phase. B.p. about -26 degrees. It is a hygroscopic, non-flammable gas.

Pentafluoropropane

HFC-245fa; R-245fa; Пентафторпропан.
1,1,1,3,3-Pentafluoropropane.
$C_3H_3F_5$=134.0
CAS — 460-73-1.
UNII — TA9UOF49CY.

Profile

Hydrofluorocarbons are halogenated hydrocarbons that contain only hydrogen, fluorine, and carbon. They do not affect atmospheric ozone and have been used as replacements for chlorofluorocarbons and hydrochlorofluorocarbons as refrigerants and as aerosol propellants (p. 1797.1). Apaflurane and norflurane are also used in metered dose inhalers. Norflurane and pentafluoropropane have been used as topical anaesthetics.

References to abuse and toxicity.

1. Dekant W. Toxicology of chlorofluorocarbon replacements. *Environ Health Perspect* 1996; **104** (suppl 1): 75–83.
2. Kuspis DA, Krenzelok EP. Oral frostbite injury from intentional abuse of a fluorinated hydrocarbon. *J Toxicol Clin Toxicol* 1999; **37:** 873–5.
3. Sasaki C, *et al*. A fatality due to inhalation of 1,1-difluoroethane (HFC-152a) with a peculiar device. *Forensic Toxicol* 2009; **27:** 45–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Wartner Kids†.

Multi-ingredient Preparations. *USA*: Gebauers Spray & Stretch.

Hydrogen Sulfide

Ácido sulfhídrico; Hydrogen Sulphide; Siarkowodór; Sulfuro de hidrógeno; Sulphuretted Hydrogen; Сульфид Водорода; Сероводород.
H_2S=34.08
CAS — 7783-06-4.
UNII — YY9FVM7NSN.

Description. Hydrogen sulfide is a colourless flammable gas with a characteristic odour.

Uses

Hydrogen sulfide is used in industrial processes as a source of sulfur and in the manufacture of other chemicals, although it is mainly encountered as a byproduct. It appears to have a physiological role as a signalling molecule and has been investigated for therapeutic use.

Adverse Effects

Hydrogen sulfide is a common industrial hazard and is encountered in such places as chemical works, mines, sewage works, and stores of decomposing protein. Concentrations of 0.1 to 0.2% in the atmosphere may be fatal in a few minutes. At concentrations of about 0.005% and above hydrogen sulfide causes anosmia and its unpleasant odour is no longer detectable. Pulmonary irritation, oedema, and respiratory failure usually occur after acute poisoning; prolonged exposure to low concentrations may cause severe conjunctivitis with photophobia and corneal opacity, irritation of the respiratory tract, cough, nausea, vomiting and diarrhoea, pharyngitis, headache, dizziness, and lassitude. There are some similarities to poisoning with cyanides.

General references.

1. WHO. Hydrogen Sulfide. *Environmental Health Criteria 19*. Geneva: WHO, 1981. Available at: http://www.inchem.org/documents/ehc/ehc/ehc019.htm (accessed 05/07/04)

Treatment of Adverse Effects

In poisoning with hydrogen sulfide the patient should be removed from the contaminated atmosphere and an effective airway established. Inhalation of amyl nitrite or parenteral therapy with sodium nitrite have been suggested for severe poisoning; this produces methaemoglobin, which may bind sulfide. Oxygen should be given; hyperbaric oxygen therapy has also been suggested. The conjunctival sacs should be carefully washed out if eye irritation is severe. Management is then usually symptomatic and supportive.

Isobutane

E943b; Isobutano; 2-Methylpropane; 2-Metilpropano; Изобутан.
C_4H_{10}=58.12
CAS — 75-28-5.
UNII — BXR49TP611.

Pharmacopoeias. In *USNF*.

USNF 31: (Isobutane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Isobutane is used as an aerosol propellant (p. 1797.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Histofreezer; *USA*: Compound W Freeze Off.

Nitrogen

Azot; Azotas; Azote; Dusík; E941; Kvävgas; Nitrogén; Nitrogenium; Nitrógeno; Nitrogenum; Stickstoff; Typpi; Азот.
N_2=28.014
CAS — 7727-37-9.
ATC — V03AN04.
ATC Vet — QV03AN04.
UNII — N762921K75.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Nitrogen). The monograph applies to nitrogen for medicinal use. A colourless, odourless gas. Soluble 1 in about 62 of water and 1 in about 10 of alcohol by volume at 20 degrees and at a pressure of 101 kpA. Store as a compressed gas or a liquid in appropriate containers.

The BP 2014 directs that nitrogen should be kept in approved metal cylinders, the shoulders of which are painted black and the remainder grey. The cylinder should carry a label stating 'Nitrogen'.

Ph. Eur. 8: (Nitrogen, Low-oxygen). The monograph applies to nitrogen used in the production of an inert atmosphere for finished medicinal products that are particularly sensitive to degradation by oxygen. A colourless, odourless gas. Soluble 1 in about 62 of water and 1 in about 10 of alcohol by volume at 20 degrees and at a pressure of 101 kpA. Store as a compressed gas or a liquid in appropriate containers.

USNF 31: (Nitrogen). A colourless, odourless, tasteless gas. It is non-flammable and does not support combustion. Soluble 1 in about 65 of water v/v and 1 in about 9 of alcohol v/v at 20 degrees and at a pressure of 760 mmHg. Store in cylinders.

USNF 31: (Nitrogen 97 Percent). It contains not less than 97% v/v of nitrogen. Store in cylinders or in a low-pressure collecting tank.

Uses and Administration

Nitrogen is used as a diluent for pure oxygen or other active gases and as an inert gas to replace air in containers holding oxidisable substances. It is also used as an aerosol propellant. Liquid nitrogen is used as a cryotherapeutic agent for the removal of warts (p. 1689.3) and for preservation of tissues and organisms.

Adverse Effects

Nitrogen narcosis has been reported after use of nitrogen mixtures (such as air) at high pressure, for example in deep-water diving. Under high pressure, nitrogen dissolves in blood and lipid. If decompression is too rapid, nitrogen effervesces from body stores producing gas emboli and leads to the syndrome of decompression sickness. High inhaled concentrations of nitrogen are asphyxiant. Skin contact with liquid nitrogen causes frostbite or burns.

References.

1. Roblin P, *et al*. Liquid nitrogen injury: a case report. *Burns* 1997; **23:** 638–40.
2. Kernbach-Wighton G, *et al*. Clinical and morphological aspects of death due to liquid nitrogen. *Int J Legal Med* 1998; **111:** 191–5.
3. Koplewitz BZ, *et al*. Gastric perforation attributable to liquid nitrogen ingestion. *Pediatrics* 2000; **105:** 121–3.
4. Kim DH, Lee HJ. Evaporated liquid nitrogen-induced asphyxia: a case report. *J Korean Med Sci* 2008; **23:** 163–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Airapy; *Neth.*: Airapy.

Multi-ingredient Preparations. *Canad.*: Lung Diffusion Test Mix No Ne Co; Lung Diffusion Test Mixture Gas; *Denm.*: Airapy; *Fin.*: Airapy.

Oxygen

Deguonis; E948; Happi; Kyslík; Ossigeno; Oxigén; Oxígeno; Oxygène; Oxygenium; Oxygenum; Sauerstoff; Tlen; Кислород.
O_2=31.998

CAS — 7782-44-7.
ATC — V03AN01.
ATC Vet — QV03AN01.
UNII — S88TT14065.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Oxygen). A colourless gas. Soluble 1 in about 32 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas or liquid in appropriate containers. Oils and grease are not to be used unless oxygen-compatible.

The BP 2014 directs that oxygen should be kept in approved metal cylinders, the shoulders of which are painted white and the remainder black. The cylinder should carry a label stating 'Oxygen'. In addition, 'Oxygen' or the symbol 'O_2' should be stencilled in paint on the shoulder of the cylinder.

Ph. Eur. 8: (Oxygen (93 per cent)). It contains 90.0% v/v to 96.0% v/v of O_2, the remainder mainly consisting of argon and nitrogen. A colourless gas. It is normally used on the site where it is produced. It is fed directly into a medicinal gas pipeline or administration system. Where authorised, it may be stored in suitable containers. Oils and grease are not to be used unless oxygen-compatible.

Ph. Eur. 8: (Air, Medicinal; Aer Medicinalis; Medical Air BP 2014). It is compressed ambient air containing not less than 20.4% and not more than 21.4% of oxygen. A colourless, odourless gas. Soluble 1 in about 50 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a gas in suitable containers.

Ph. Eur. 8: (Air, Synthetic Medicinal; Aer Medicinalis Artificiosus; Synthetic Air BP 2014). It is a mixture of nitrogen and oxygen containing between 21.0% and 22.5% of oxygen. A colourless, odourless gas. Soluble 1 in about 50 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas in suitable containers.

USP 36: (Oxygen). A colourless, odourless, tasteless gas that supports combustion more energetically than does air. Soluble 1 in about 32 of water v/v and 1 in about 7 of alcohol v/v at 20 degrees and at a pressure of 760 mmHg. Store in cylinders or in a pressurised storage tank.

USP 36: (Medical Air). A natural or synthetic mixture of gases consisting largely of nitrogen and oxygen. It contains not less than 19.5% and not more than 23.5% of oxygen. Store in cylinders or in a low pressure collecting tank.

USP 36: (Oxygen 93 Percent). It contains not less than 90% v/v and not more than 96% v/v of oxygen, the remainder consisting mostly of argon and nitrogen. Store in cylinders or in a low-pressure collecting tank.

Uses and Administration

Oxygen comprises about 21% of ambient air (at sea level) and is essential for human life. Supplementary inhaled oxygen may be necessary to prevent or correct hypoxaemia and increase oxygen delivery to the tissues in situations where the ambient air is unable to meet the body's demands. It is used in respiratory failure (p. 1801.1), as an adjunct to specific treatment of the underlying cause and general measures such as correction of anaemia or repositioning of the patient. It is also used in situations where the oxygen content of the air breathed is inadequate, for example in the management of high-altitude disorders (p. 1276.2).

Oxygen is of value in the treatment of poisoning with several substances, including carbon monoxide (p. 1798.1), cyanides (see under Hydrocyanic Acid, p. 2156.2), and dichloromethane (p. 2181.2). It is also used in inhalation injury and in poisoning with asphyxiant gases. Workers in pressurised spaces and divers may breathe oxygen rather than air to reduce the risk of nitrogen narcosis, although mixtures of oxygen with an inert gas such as helium may be preferred to reduce the risk of oxygen toxicity. Oxygen is also used as a diluent of volatile and gaseous anaesthetics.

Supplementary oxygen is usually provided at a concentration of 100% as a compressed gas in metal cylinders, but is also available as liquid oxygen, supplied at low temperatures in insulated containers. Oxygen concentrators, which extract oxygen from the air, can provide concentrations of 95 to 98% and are useful for domiciliary therapy, especially in patients using large quantities of oxygen. Oxygen is used in varying concentrations, and this is controlled by the flow rate and delivery system. In general, the exact concentration inhaled is not critical, and most delivery systems work by adjusting the flow rate to provide an approximate dose. Nasal cannulae deliver concentrations of 24 to 40% at flow rates of 1 to 4 litres/minute and are widely used, particularly for domiciliary therapy. Standard face masks deliver concentrations of 40 to 60% at flow rates of 5 to 10 litres/minute, while reservoir masks allow flow rates of 10 to 15 litres/minute and oxygen concentrations of 60 to 90%. Where more precise dosage is required Venturi masks may be used; these provide a set oxygen concentration independent of the flow rate and are available for a range of concentrations between 24 and 60%. If very high doses are required, endotracheal tubes or oxygen tents can be used to deliver concentrations of up to 100%.

The concentration of inspired oxygen used has generally been determined by the condition being treated, but for acute therapy it is now considered preferable to adjust the concentration in line with the patient's oxygen saturation. For most patients, the **target oxygen saturation**, measured by pulse oximetry, should be 94 to 98%. However, for patients with hypercapnia or at risk of hypercapnia, a lower target range of 88 to 92% is recommended (see Chronic Lung Disorders under Precautions, p. 1802.1). Suggested initial concentrations and delivery systems are as follows:

- critically ill patients, including those with carbon monoxide poisoning: **high** concentration oxygen (reservoir mask at flow rate of 15 litres/minute)
- patients with acute hypoxaemia due to conditions such as acute asthma, pneumonia, pulmonary embolism, and postoperatively: **moderate** concentration therapy
  - oxygen saturation below 85%: reservoir mask at flow rate of 10 to 15 litres/minute
  - oxygen saturation 85% or higher: nasal cannulae or simple face mask at flow rate of 2 to 10 litres/minute
- patients with chronic obstructive pulmonary disease or otherwise at risk of hypercapnia: **low** concentration (controlled) oxygen therapy
  - if oxygen saturation unknown: 28% at 4 litres/minute, or 24% at 2 to 4 litres/minute if there is a history of hypercapnia (via Venturi mask)
  - oxygen saturation below 88%: nasal cannulae at 2 to 6 litres/minute or simple face mask at 5 litres/minute

Hyperbaric oxygen therapy, in which oxygen is given at pressures greater than 1 atmosphere, has an established role in the management of decompression sickness and gas emboli. It may also be used in carbon monoxide poisoning, severe anaerobic infection, and several other conditions, although this is more controversial; for further discussion, see below.

General references.

1. Bateman NT, Leach RM. ABC of oxygen: acute oxygen therapy. *BMJ* 1998; **317:** 798–801.
2. Rees PJ, Dudley F. ABC of oxygen: oxygen therapy in chronic lung disease. *BMJ* 1998; **317:** 871–4.
3. Rees PJ, Dudley F. ABC of oxygen: provision of oxygen at home. *BMJ* 1998; **317:** 935–8.
4. Treacher DF, Leach RM. ABC of oxygen: oxygen transport: basic principles. *BMJ* 1998; **317:** 1302–6.
5. Leach RM, Treacher DF. ABC of oxygen: oxygen transport: tissue hypoxia. *BMJ* 1998; **317:** 1370–3.
6. Kallstrom TJ. American Association for Respiratory Care (AARC). AARC clinical practice guideline: oxygen therapy for adults in the acute care facility—2002 revision & update. *Respir Care* 2002; **47:** 717–20. Also available at: http://www.rcjournal.com/cpgs/pdf/06.02.717.pdf (accessed 26/02/10)
7. American Association for Respiratory Care (AARC). AARC clinical practice guideline: oxygen therapy in the home or alternate site health care facility—2007 revision & update. *Respir Care* 2007; **52:** 1063–8. Also available at: http://www.rcjournal.com/cpgs/pdf/08.07.1063.pdf (accessed 26/02/10)
8. O'Driscoll BR, *et al.* British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; **63** (suppl 6): vi1–vi68. Correction. *ibid.* 2009; **64:** 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)
9. Balfour-Lynn IM, *et al.* British Thoracic Society. BTS guidelines for home oxygen in children. *Thorax* 2009; **64** (suppl 2): ii1–ii26. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Home%20Oxygen/Home%20Oxygen%20Guideline/HomeOxygen-in-children-full-guideline.pdf (accessed 26/02/10)

Cluster headache. Randomised studies[1,2] and case series[3] have suggested that inhalation of 100% oxygen can provide rapid and effective treatment of cluster headache attacks (p. 670.1), although the evidence is limited.[4] Treatment with 100% oxygen should therefore be considered in all patients,[5] although practical issues may limit its use.

1. Fogan L. Treatment of cluster headache: a double-blind comparison of oxygen v air inhalation. *Arch Neurol* 1985; **42:** 362–3.
2. Cohen AS, *et al.* High-flow oxygen for treatment of cluster headache: a randomized trial. *JAMA* 2009; **302:** 2451–7.
3. Rozen TD. High oxygen flow rates for cluster headache. *Neurology* 2004; **63:** 593.
4. Bennett MH, *et al.* Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 21/08/08).
5. Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (issued November 2008). Available at: http://www.sign.ac.uk/pdf/sign107.pdf (accessed 26/01/09)

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy[1-3] involves the inhalation of 100% oxygen at a pressure of greater than 1 atmosphere and is given by enclosing the patient in a special high-pressure chamber. The optimum pressure and duration of treatment depend on the indication, but pressures of 2.5 to 3 atmospheres for periods from 45 minutes to 2 hours are commonly used. A single session may be adequate for some indications, but treatment is usually repeated once or twice daily and up to 40 sessions may be required. Hyperbaric oxygen therapy is generally safe, but adverse effects may occur (see p. 1801.3); intermittent replacement of oxygen with air as the inspired gas may reduce the risk of oxygen toxicity.[2]

Hyperbaric oxygen therapy appears to act by 2 main mechanisms. The increased pressure has a physical effect, reducing the size of gas bubbles within the circulation, which is of benefit in decompression sickness and gas embolism. In addition, the amount of oxygen dissolved in the blood increases under pressure, increasing tissue oxygen supply. This hyperoxia has various physiological and biochemical effects, including stimulation of wound healing and tissue repair and improved resistance to infection.

Therapy with hyperbaric oxygen has been tried in many disorders, but for most there have been few controlled studies and evidence of benefit is therefore limited. However, there are several accepted indications, and research continues in many other disorders.

The role of hyperbaric oxygen therapy as a safe and effective primary therapy for *decompression sickness* and *air or gas embolism* is well established. Reduction in bubble size is the main action, although the increase in oxygenation may also be beneficial. Pressures are generally similar to those used for other indications (initially about 2.8 atmospheres), although up to 6 atmospheres may be required. The pressure may then be gradually reduced at a safe rate.

Hyperbaric oxygen therapy has been widely recommended for *carbon monoxide poisoning* but its precise role remains unclear (see p. 1798.1); it may be considered in selected patients. Its mechanism of action is not fully understood; it increases the rate at which carboxyhaemoglobin concentrations decline, increases intracellular delivery of oxygen, and may also reduce lipid peroxidation and thus spare neuronal cell membranes.

In the management of *wounds and infections*, hyperbaric oxygen has various applications.[4] It is used as adjunctive therapy in *clostridial infections (gas gangrene)* (p. 182.2). Early treatment appears to reduce systemic toxic reactions (probably by inhibiting the production of alpha toxin by the anaerobic bacteria, *Clostridium*) thus enabling patients to tolerate surgery more readily; additionally there is a clearer demarcation of viable and nonviable tissue. *Necrotising fasciitis* (p. 193.1) is another infection in which hyperbaric oxygen therapy may be useful, although evidence is limited. Other infections in which hyperbaric oxygen therapy may be used include osteomyelitis, and intracranial abscesses.

There is some evidence that hyperbaric oxygen may be useful in non-infected wounds where hypoxia contributes to poor healing.[5,6] In *problem wounds*, including venous ulcers, therapy may increase the tissue oxygen tension and stimulate angioneogenesis but it is emphasised that it is adjunctive therapy and not a replacement for meticulous local care. Hyperbaric oxygen therapy might also reduce the risk of major amputation in patients with chronic *diabetic foot ulcer*.[7,8] Improved healing of leg ulcers has been reported[9] with use of hyperbaric oxygen therapy in patients with livedoid vasculopathy. Other wounds in which therapy may be beneficial include thermal burns and compromised skin grafts and flaps. The management of burns and wounds is described on p. 1683.1 and p. 1690.1, respectively. Hyperbaric oxygen may also be of benefit in patients with acute trauma and *crush injuries*;[10] it reduces oedema by causing vasoconstriction and may reverse ischaemia by increasing oxygen delivery.

In patients with malignancy, hyperbaric oxygen may have a role in the treatment of *radiation-induced tissue damage*;[11] radiation therapy can damage normal adjacent tissue resulting in tissue hypoxia and eventual cell death but hyperbaric oxygen therapy appears to aid in salvaging such tissue by stimulating angioneogenesis in marginally viable tissue. There is some evidence of benefit in osteoradionecrosis, soft-tissue damage, and radiation-induced haemorrhagic cystitis (p. 2347.3), although a randomised study[12] failed to confirm this in patients with jaw osteoradionecrosis. Hyperbaric oxygen has also been tried as an adjunct to standard treatment for malignant neoplasms but does not yet have an established role.[13]

Evidence to support the use of hyperbaric oxygen in *neurological disorders* is limited. Benefits have been reported in children with *cerebral palsy*, but this has not been established, and there is some evidence that it is no better than pressurised air.[14] Improvement has been reported in neonates with hypoxic-ischaemic encephalopathy,[15] but again further research is needed. A study of hyperbaric 24% oxygen in children with autism has also suggested benefits.[16]

Hyperbaric oxygen may also have a limited role in the management of severe anaemia (p. 1121.2) due to massive blood loss, since it enables sufficient oxygen to be dissolved in the blood to meet tissue demands, independent of haemoglobin. However, practical issues mean that other treatments are generally preferred.

1. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med* 1996; **334:** 1642–8.

2. Leach RM, *et al.* ABC of oxygen: hyperbaric oxygentherapy. *BMJ* 1998; **317:** 1140–3.
3. Gill AL, Bell CNA. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *Q J Med* 2004; **97:** 385–95.
4. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. *Emerg Med Clin North Am* 2008; **26:** 571–95.
5. Thackham JA, *et al.* The use of hyperbaric oxygen therapy to treat chronic wounds: a review. *Wound Repair Regen* 2008; **16:** 321–30.
6. Kulikovsky M, *et al.* Hyperbaric oxygen therapy for non-healing wounds. *Isr Med Assoc J* 2009; **11:** 480–5.
7. Wang C, *et al.* Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg* 2003; **138:** 272–9.
8. Roeckl-Wiedmann I, *et al.* Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg* 2005; **92:** 24–32.
9. Juan W-H, *et al.* Livedoid vasculopathy: long-term follow-up results following hyperbaric oxygen therapy. *Br J Dermatol* 2006; **154:** 251–5.
10. Garcia-Covarrubias L, *et al.* Adjuvant hyperbaric oxygen therapy in the management of crush injury and traumatic ischemia: an evidence-based approach. *Am Surg* 2005; **71:** 144–51.
11. Pasquier D, *et al.* Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. *Radiother Oncol* 2004; **72:** 1–13.
12. Annane D, *et al.* Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004; **22:** 4893–4900.
13. Daruwalla J, Christophi C. Hyperbaric oxygen therapy for malignancy: a review. *World J Surg* 2006; **30:** 2112–31.
14. McDonagh MS, *et al.* Systematic review of hyperbaric oxygen therapy for cerebral palsy: the state of the evidence. *Dev Med Child Neurol* 2007; **49:** 942–7.
15. Liu Z, *et al.* Clinical effectiveness of treatment with hyperbaric oxygen for neonatal hypoxic-ischaemic encephalopathy: systematic review of Chinese literature. *BMJ* 2006; **333:** 374–6.
16. Rossignol DA, *et al.* Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. *BMC Pediatr* 2009; **9:** 21.

Respiratory failure. Respiratory failure is a clinical condition in which the arterial plasma partial pressure of oxygen (P_aO_2) and of carbon dioxide (P_aCO_2) cannot be maintained within normal physiological limits. It may result from an abnormality in any part of the respiratory system, including airways, alveoli, CNS, respiratory muscles, and circulation, and may be associated with various underlying disorders; it may be acute or chronic. In type I respiratory failure P_aO_2 is low (hypoxaemia) but P_aCO_2 may be normal or low, whereas in type II respiratory failure $P_aO_2$is low but $P_aCO_2$is raised (hypercapnia). Type I respiratory failure is most common and can occur in most acute lung disorders; examples include pulmonary oedema, pneumonia, and pulmonary haemorrhage. Type II respiratory failure (also known as ventilatory failure) is associated with conditions such as drug overdosage, neuromuscular disorders, and chronic obstructive airways disease. Patients with asthma may develop either type of respiratory failure.

The signs and symptoms of respiratory failure are those of the underlying condition plus any associated hypoxaemia or hypercapnia. Dyspnoea (painful or difficult breathing) is common, and patients may also have tachypnoea, tachycardia and other arrhythmias, signs of cyanosis, and neurological symptoms such as confusion and somnolence.

Management of respiratory failure mainly involves giving oxygen to reverse hypoxaemia, and specific therapy for any underlying condition. Invasive or non-invasive ventilatory support may be required in severe cases. Respiratory stimulants have a limited role but may be considered in some situations.

In acute respiratory failure, oxygen is the mainstay of therapy.[1,2] The concentration given should be the minimum required to reverse hypoxaemia and, ideally, should be determined by blood gas measurements or pulse oximetry. Use of oxygen in patients who are not hypoxaemic is not generally recommended,[3] and there is no evidence that it is beneficial for dyspnoea associated with causes such as cancer or heart failure.[4]

In ***type I respiratory failure*** high initial oxygen concentrations are given using nasal cannulae or face masks and target oxygen saturations are 94 to 98%. Ventilatory support may be required if adequate saturations cannot be maintained using reservoir masks.

In ***type II respiratory failure*** initial oxygen concentrations depend on the risk of exacerbating hypercapnia and acidosis:

- In *acute severe asthma* (p. 1195.2), hypercapnia is not a barrier to oxygen therapy and oxygen should be given from a reservoir mask, at a flow rate of 10 to 15 litres/minute (if oxygen saturation is below 85%), or from nasal cannulae or a simple face mask at a flow rate of 2 to 10 litres/minute if oxygen saturation is 85% or higher.[3] (The *BNF* notes that if the P_aCO_2 remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.)
- In exacerbations of chronic respiratory disorders such as *chronic obstructive pulmonary disease* (COPD, p. 1199.1), cystic fibrosis (p. 177.2), or neuromuscular disorders, high concentrations of oxygen may exacerbate hypercapnia (see Precautions, p. 1802.1), particularly if given for a long period. Controlled delivery of low concentrations (24 to 28%) is therefore recommended for initial therapy,[3,5] although this is based on consensus opinion rather than controlled studies.

Ventilatory support is required in patients with respiratory failure when hypoxaemia persists or if hypercapnia and acidosis worsen. This generally involves endotracheal intubation and invasive ventilation, but the use of non-invasive methods is increasing and may be preferred in many situations, particularly in exacerbations of chronic conditions.[6] Use of gas mixtures that are less dense than air, such as mixtures of helium and oxygen, has been tried in acute respiratory failure to reduce the work of breathing, but is not of established benefit.[7] In extreme cases of respiratory failure, such as acute respiratory distress syndrome, extracorporeal membrane oxygenation (ECMO) may be tried,[8] although evidence for benefit is limited.

Respiratory stimulants such as doxapram have been used in respiratory failure but their role is limited. In patients with exacerbations of chronic ventilatory failure, the central drive to respiratory muscles is already increased and stimulants have little effect, although they may be tried in patients who are unsuitable for mechanical ventilation or where this is unavailable. Respiratory stimulants may also be considered in the management of *postanaesthetic hypoventilation*. Specific antagonists such as naloxone and flumazenil may have a role if respiratory depression is due to drugs such as opioids or benzodiazepines, respectively, although care is needed since therapeutic effects may be reduced.

Severe respiratory failure in *neonates* may result from various disorders. Use of surfactant or inhaled nitric oxide may be of benefit in some cases but ECMO may be required.[9]

In **chronic respiratory failure**, management involves treating the underlying cause and dealing with acute exacerbations, but oxygen therapy may have a role in some patients with stable disease. Long-term oxygen therapy, given by nasal cannulae, may improve survival in patients with severe chronic obstructive pulmonary disease and persistent hypoxaemia, and should be given for at least 15 hours each day.[5,10] Patients may also use intermittent, 'short-burst' oxygen to improve symptoms associated with exercise, although benefit is not established.[5,10] There is also limited evidence to support the use of nocturnal oxygen in patients with nocturnal hypoxaemia.[5]

1. Chakrabarti B, Calverley PM. Management of acute ventilatory failure. *Postgrad Med J* 2006; **82:** 438–45.
2. Goldring JJP, Wedzicha JA. Managing acute on chronic respiratory failure: a guide to non-invasive ventilation. *Br J Hosp Med* 2008; **69:** 444–9.
3. O'Driscoll BR, *et al.* British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; **63** (suppl 6): vi1–vi68. Correction. *ibid.* 2009; **64:** 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)
4. Cranston JM, *et al.* Oxygen therapy for dyspnoea in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 01/03/10).
5. Abramson M, *et al.* The COPDX plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease 2009. Available at: http://www.copdx.org.au/guidelines/documents/COPDX_V2_18.pdf (accessed 01/03/10)
6. Garpestad E, *et al.* Noninvasive ventilation for critical care. *Chest* 2007; **132:** 711–20.
7. Colebourn CL, *et al.* Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia* 2007; **62:** 34–42.
8. Schuerer DJ, *et al.* Extracorporeal membrane oxygenation: current clinical practice, coding, and reimbursement. *Chest* 2008; **134:** 179–84.
9. Barrington KJ, Finer NN. Care of near term infants with respiratory failure. *BMJ* 1997; **315:** 1215–18.
10. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; **59** (suppl 1): 1–232. Also available at: http://www.nice.org.uk/nicemedia/pdf/CG012_niceguideline.pdf (accessed 16/04/10)

Wounds. Hyperbaric oxygen therapy may have a role in the management of infected and problem wounds (see p. 1800.2). Supplemental normobaric oxygen has also been tried in the prevention of postoperative wound infections. Although the results of individual studies remain contradictory, a meta-analysis[1] concluded that oxygen, at 80%, provided a beneficial effect. However, a more recent multicentre study[2] found no reduced risk of infection after 80% rather than 30% oxygen, during, and for 2 hours after, surgery.

Oxygen has also been applied topically to wounds.[3]

1. Qadan M, *et al.* Perioperative supplemental oxygen therapy and surgical site infection: a meta-analysis of randomized controlled trials. *Arch Surg* 2009; **144:** 359–66.
2. Meyhoff CS, *et al.* Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009; **302:** 1543–50.
3. Gordillo GM, Sen CK. Evidence-based recommendations for the use of topical oxygen therapy in the treatment of lower extremity wounds. *Int J Low Extrem Wounds* 2009; **8:** 105–11.

Adverse Effects

Oxygen is essential for life but inhalation of high concentrations may have adverse effects, particularly with prolonged exposure at higher pressures. Both pulmonary and CNS effects may occur. Pulmonary toxicity usually results from prolonged or repeated exposure. Symptoms include cough, dyspnoea, and substernal discomfort, and there may also be a reduction in vital capacity; alveolar collapse (absorption atelectasis), pulmonary oedema, and pneumonitis have also been reported. CNS toxicity is usually only seen at pressures above 2 atmospheres absolute but generally precedes pulmonary toxicity; the risk is higher in wet conditions and with physical activity. Symptoms include nausea, mood changes, vertigo, twitching, convulsions, and loss of consciousness. Toxic effects on the eyes may also occur (see Hyperbaric Oxygen Therapy, and Retinopathy of Prematurity, below).

The mechanism of oxygen toxicity is not clear, but may involve an increase in oxygen free radicals. Hyperoxaemia may also have adverse physiological effects related to cerebral and coronary vasoconstriction. It is also increasingly recognised that high inhaled concentrations of oxygen may be detrimental in patients with chronic lung disorders due to the effects of oxygen on ventilation (see Precautions, p. 1802.1).

Hyperbaric oxygen therapy. CNS toxicity is an important and unpredictable adverse effect with inhalation of oxygen at pressures higher than atmospheric, both during hyperbaric oxygen therapy and when used by divers.[1] Hyperbaric oxygen is also associated with pulmonary toxicity, particularly after repeated treatments. Complications related to the increased pressure also occur.[2-5] Barotrauma affecting the middle ear and sinuses is relatively common, and tympanic membrane rupture may result. Pulmonary barotrauma and pneumothorax have been reported, and dental barotrauma may rarely cause pain under a dental filling. Visual changes including myopia may occur, but are reversible once treatment is stopped; cataracts have been reported but there is no evidence that hyperbaric oxygen is the cause. Psychological adverse effects such as claustrophobia may also occur.

1. Bitterman N. CNS oxygen toxicity. *Undersea Hyperb Med* 2004; **31:** 63–72.
2. Grim PS, *et al.* Hyperbaric oxygen therapy. *JAMA* 1990; **263:** 2216–20.
3. Plafki C, *et al.* Complications and side effects of hyperbaric oxygen therapy. *Aviat Space Environ Med* 2000; **71:** 119–24.
4. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *Q J Med* 2004; **97:** 385–95.
5. Huang K-C, *et al.* Hyperbaric oxygen therapy in orthopedic conditions: an evaluation of safety. *J Trauma* 2006; **61:** 913–17.

Retinopathy of prematurity. The role of oxygen in the development of retinopathy of prematurity has been controversial.[1,2] In the 1940s and 1950s an epidemic of retinopathy of prematurity, affecting perhaps 10 000 babies, was attributed to excessive use of oxygen in neonates. This resulted in the use of oxygen being reduced or curtailed and the incidence of the condition fell dramatically. However, other complications increased and use of oxygen was later liberalised, possibly contributing to a resurgence of cases in the 1970s, although other factors such as the improved survival of very preterm neonates were probably more important. It is now generally accepted that very low birth-weight and extreme prematurity are the major risk factors for retinopathy of prematurity, but that excessive oxygen use also has an important role.[3] Retinal development occurs late in gestation and depends to some extent on the relative hypoxia of the uterine environment. Supplementary oxygen inhibits production of vascular endothelial growth factor, thereby inhibiting retinal vascularisation. The lack of retinal blood vessels then leads to hypoxia, which stimulates excessive neovascularisation, leading to retinal fibrosis and detachment in severe cases. Generation of reactive oxygen species may also play a role.

The optimum approach to oxygen supplementation in infants and neonates remains unclear (see under Precautions, p. 1802.2). Studies[4,5] have suggested that policies in which oxygen use is adjusted for the individual neonate to maintain oxygen saturation (measured by pulse oximetry) within specific limits, avoiding both hyperoxia and hypoxia, can reduce the incidence of retinopathy, and one study[6] found that this had no deleterious effect on development at 18 months. The most appropriate oxygen saturation has not been determined, but may depend on the age of the infant; target saturations of 85 to 92% for gestational age less than 34 weeks and 92 to 97% for gestational age 34 weeks and above have been suggested.[7] For infants who develop signs of retinopathy, higher saturations may also be appropriate; a study[8] of supplemental oxygen for treating pre-threshold retinopathy suggested that therapy was safe, but a beneficial effect could not be confirmed.

1. Saugstad OD. Oxygen and retinopathy of prematurity. *J Perinatol* 2006; **26** (suppl 1): S46–S50.
2. Harrell SN, Brandon DH. Retinopathy of prematurity: the disease process, classifications, screening, treatment, and outcomes. *Neonatal Netw* 2007; **26:** 371–8.
3. Tin W, *et al.* Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F106–F110.

4. Chow LC, *et al*. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003; **111:** 339–45.
5. Wright KW, *et al*. A physiologic reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity. *Trans Am Ophthalmol Soc* 2006; **104:** 78–84.
6. Deulofeut R, *et al*. Avoiding hyperoxia in infants ≤1250 g is associated with improved short- and long-term outcomes. *J Perinatol* 2006; **26:** 700–705.
7. Sears JE, *et al*. A change in oxygen supplementation can decrease the incidence of retinopathy of prematurity. *Ophthalmology* 2009; **116:** 513–18.
8. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. *Pediatrics* 2000; **105:** 295–310.

Precautions

Any fire or spark is highly dangerous in the presence of increased oxygen concentrations especially when oxygen is used under pressure.

Metal cylinders containing oxygen should be fitted with a reducing valve by which the rate of flow can be controlled. It is important that the reducing valve should be free from all traces of oil or grease (unless it is oxygen-compatible) as otherwise a violent explosion may occur. Combustible material soaked in liquid oxygen is potentially explosive and the low temperature of liquid oxygen may cause unsuitable equipment to become brittle and crack. Liquid oxygen should not be allowed to come into contact with the skin as it produces severe 'cold burns'.

Oxygen intended for aviation or mountain rescue must have a sufficiently low moisture content to avoid blocking of valves by ice at low temperatures.

Excessive oxygen may be detrimental in some patients with chronic lung disorders and in neonates, and high initial concentrations should generally be avoided until oxygen saturations are known (see below). Prophylactic oxygen is given in many acute situations but there is some evidence that it may be detrimental in non-hypoxic patients and routine use may not be advisable (see Myocardial Infarction and Pregnancy, below).

Oxygen should be avoided in the initial management of paraquat poisoning since it may increase pulmonary damage. Pulmonary toxicity associated with bleomycin toxicity may also be exacerbated by oxygen use.

Chronic lung disease. Breathless patients are frequently treated with 100% oxygen but, paradoxically, this may be detrimental in those with chronic lung disorders.[1-3] In chronic obstructive pulmonary disease and in patients with chest wall deformities or musculoskeletal disorders, high concentrations of inhaled oxygen may lead to carbon dioxide retention (hypercapnia) and acidosis, which may in turn lead to organ dysfunction. The mechanism by which this occurs is complex but probably involves a reduction in hypoxic drive and an increased mismatching of blood flow and gas flow to the lungs. A lower target oxygen saturation of 88 to 92% is recommended in such patients[3] and initial oxygen concentrations of 24 to 28% should be used until oxygen saturation is known.

1. New A. Oxygen: kill or cure? Prehospital hyperoxia in the COPD patient. *Emerg Med J* 2006; **23:** 144–6.
2. Beasley R, *et al*. Is it time to change the approach to oxygen therapy in the breathless patient? *Thorax* 2007; **62:** 840–1.
3. O'Driscoll BR, *et al*. British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; **63** (suppl 6): vi1–vi68. Correction. *ibid*. 2009; **64:** 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)

Myocardial infarction. Oxygen is routinely recommended for patients with acute myocardial infarction (see p. 1257.1). However, a systematic review[1] found that studies were lacking, and the very limited evidence available indicated that the use of high-flow oxygen in myocardial infarction might increase infarct size and raise the risk of mortality, possibly due to a reduction in coronary blood flow. The authors concluded that there was insufficient evidence to support the practice, and that further study was urgently needed.

1. Wijesinghe M, *et al*. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009; **95:** 198–202.

Neonates and infants. The use of supplemental oxygen in neonates and infants is controversial.[1-3] For the *resuscitation* of asphyxiated term neonates, use of 100% oxygen has been standard, but there is some evidence that the use of room air (21% oxygen) is equally effective and possibly safer. However, a systematic review[4] concluded that there was insufficient evidence for recommendations to be made. Guidelines[5,6] for neonatal resuscitation recommend the use of either air or blended oxygen to achieve target oxygen saturations,[5,6] although increasing to 100% oxygen might be suitable for those who remain bradycardic after 90 seconds of resuscitation at lower concentrations.[6] Pulse oximetry should be used to guide treatment, with care taken to avoid both hypoxia and hyperoxia.[5,6] A study[7] in preterm neonates found that room air (21% oxygen) was insufficient to maintain adequate oxygen saturations and the authors suggested that an initial oxygen concentration of 30 to 40% might be more appropriate.

For *respiratory support* in preterm neonates and infants, oxygen use should be closely monitored. Excessive use of supplementary oxygen has been associated with retinopathy of prematurity and chronic lung disease,[8] and there is some evidence for a link between neonatal oxygen supplementation and childhood cancer,[9] although this remains to be confirmed. However, untreated hypoxia may result in permanent brain injury or death,[3] and it has been suggested that oxygen supplementation improves sleep and respiratory patterns in healthy preterm infants.[10] Unrestricted use of inhaled oxygen is therefore not advised, and the concentration given should be adjusted individually based on arterial-oxygen saturation measured by pulse oximetry. The optimum saturation range is not entirely clear,[11] but target saturations of between 85 and 93 to 94% have been suggested[2,3] for preterm neonates.

1. Higgins RD, *et al*. Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. *Pediatrics* 2007; **119:** 790–6.
2. Sola A, *et al*. Oxygen as a neonatal health hazard: call for détente in clinical practice. *Acta Paediatr* 2007; **96:** 801–12.
3. Walsh BK, *et al*. Oxygen therapy in the neonatal care environment. *Respir Care* 2009; **54:** 1193–202.
4. Tan A, *et al*. Air versus oxygen for resuscitation of infants at birth. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 07/06/06).
5. Resuscitation Council (UK). 2010 Resuscitation Guidelines: newborn life support. Available at: http://www.resus.org.uk/pages/nls.pdf (accessed 09/02/11)
6. The American Heart Association. Part 15: neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; **122** (suppl 3): S909–S919. Also available at: http://circ.ahajournals.org/cgi/reprint/122/18_suppl_3/S909.pdf (accessed 09/02/11)
7. Wang CL, *et al*. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics* 2008; **121:** 1083–9.
8. Askie LM, *et al*. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 25/02/10).
9. Spector LG, *et al*. Childhood cancer following neonatal oxygen supplementation. *J Pediatr* 2005; **147:** 27–31.
10. Simakajornboon N, *et al*. Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. *Pediatrics* 2002; **110:** 884–8.
11. Tin W, Gupta S. Optimum oxygen therapy in preterm babies. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F143–7.

Pregnancy. Oxygen has commonly been given to women during labour as a treatment for fetal distress; however, a systematic review[1] found little evidence to support its use. Furthermore, prophylactic oxygen given during labour may be harmful to the fetus,[2] and guidelines[3] therefore do not recommend this practice.

1. Fawole B, Hofmeyr GJ. Maternal oxygen administration for fetal distress. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 01/05/09).
2. Simpson KR. Intrauterine resuscitation during labor: should maternal oxygen administration be a first-line measure? *Semin Fetal Neonatal Med* 2008; **13:** 362–7.
3. O'Driscoll BR, *et al*. British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; **63** (suppl 6): vi1–vi68. Correction. *ibid*. 2009; **64:** 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Airapy; ***Cz.***: Conoxia; ***Denm.***: Conoxia; ***Fin.***: Conoxia; ***Ger.***: Conoxia; ***Ital.***: Aria; ***Neth.***: Airapy; Conoxia; Keol-C; Loxmed; Mediox; ***Norw.***: Conoxia; ***Spain***: Conoxia; Keol-S.

Multi-ingredient Preparations. ***Belg.***: Kalinox; ***Canad.***: Alnox; Carbogen; Entonox; Heliox; Liqui-Med; Lung Diffusion Test Mix No Ne Co; Lung Diffusion Test Mixture Gas; ***Cz.***: Entonox; ***Denm.***: Airapy; Kalinox; Livopan; Medimix; ***Fin.***: Airapy; Livopan; ***Fr.***: Antasol; Entonox; Kalinox; Oxynox; ***Ger.***: Livopan; ***Irl.***: Entonox; ***Neth.***: Donopa; Relivopan; ***Pol.***: Entonox; ***S.Afr.***: Entonox; ***Spain***: Entonox; Kalinox; ***Swed.***: Livopan; Medimix; ***Switz.***: Entonox; Kalinox; Medimix†; ***UK***: Entonox; Equanox.

Propane

Dimethylmethane; E944; Propano; Propyl Hydride; Пропан.

C_3H_8=44.10

CAS — 74-98-6.

UNII — T75W9911L6.

Pharmacopoeias. In *USNF*.

USNF 31: (Propane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Propane is used as a refrigerant and as an aerosol propellant (p. 1797.1). It is also widely used as a fuel.

Toxicity has been reported[1-8] with the abuse or misuse of propane.

1. James NK, Moss ALH. Cold injury from liquid propane. *BMJ* 1989; **299:** 950–1.
2. Siegel E, Wason S. Sudden death caused by inhalation of butane and propane. *N Engl J Med* 1990; **323:** 1638.
3. Tsoukali H, *et al*. Death during deliberate propane inhalation. *Forensic Sci Int* 1998; **93:** 1–4.
4. McLennan JJ, *et al*. Propane-associated autoerotic fatalities. *Am J Forensic Med Pathol* 1998; **19:** 381–6.
5. Grosse K, Grosse J. Propanmissbrauch: extreme Dosissteigerung durch Toleranzentwicklung. *Nervenarzt* 2000; **71:** 50–3.
6. Jackowski C, *et al*. Autoerotic accident by inhalation of propane-butane gas mixture. *Am J Forensic Med Pathol* 2005; **26:** 355–9.
7. Stemberga V, *et al*. Propane-associated autoerotic asphyxiation: accident or suicide? *Coll Antropol* 2007; **31:** 625–7.
8. Bonamonte D, *et al*. Cold burn from contact with a propane and butane gas blend inside a spray canister used as a hooter. *Contact Dermatitis* 2008; **59:** 61–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Olbas; Wartner; ***Irl.***: Wartner; ***Israel***: Wartner†; ***NZ***: Wartner; ***Singapore***: Wartner; ***Switz.***: Wartner; ***UK***: Histofreezer; Wartner; ***USA***: Compound W Freeze Off.

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This chapter describes the principal drugs used in the treatment of gastrointestinal disorders, and the choice of treatment for some of the main disorders.

Gastrointestinal Drug Groups

Antacids

Antacids are basic compounds that neutralise hydrochloric acid in the gastric secretions. They are used in the symptomatic management of gastrointestinal disorders associated with gastric hyperacidity such as dyspepsia (p. 1806.3), gastro-oesophageal reflux disease (p. 1807.2), and peptic ulcer disease (see p. 1813.2).

Antacids do not reduce the volume of hydrochloric acid secreted and elevation of the gastric pH may actually promote an increase in acid secretion. However, this is usually minor and short-lived except after large doses of calcium carbonate. Antacids are normally given between meals and at bedtime when symptoms of gastric hyperacidity usually occur; the presence of food in the stomach can prolong the neutralising activity. Some calculate doses as mEq or mmol of acid-neutralising capacity, but the relationship between neutralising capacity and beneficial effect is not straightforward. Other factors, including formulation (liquid preparations are more effective than solids) and duration of action (relatively insoluble antacids are longer acting) are also important.

Aluminium salts tend to produce constipation and to delay gastric emptying, while magnesium salts have the reverse effect; a combination of the two may reduce adverse gastrointestinal effects. Another advantage of combined antacid formulations is that a slow-acting antacid such as aluminium hydroxide may be combined with a more rapidly acting drug such as magnesium hydroxide to improve the onset and duration of effect. Alternatively, complexes containing both aluminium and magnesium may be used, such as almasilate, hydrotalcite, and magaldrate. Other drugs that may be combined with antacid formulations include simeticone, which acts as a defoaming agent to reduce excess gas in the stomach, and alginates, which form a gel or foam on the surface of the stomach contents thereby impeding reflux and protecting the oesophageal mucosa from acid attack.

Calcium carbonate and sodium bicarbonate are both rapidly acting but have disadvantages: calcium carbonate is usually reserved for short-term treatment because of the risks of rebound acid secretion and metabolic alkalosis, while sodium bicarbonate is absorbed and is contra-indicated in patients who must control sodium intake (e.g. in heart failure, hypertension, renal failure, cirrhosis, or pregnancy).

Antacids may interact with numerous other drugs, affecting the rate and extent of their absorption, and in some cases their renal elimination. Changes in gastric pH affect the dissolution of other drugs, and together with altered gastric emptying can markedly influence absorption. Aluminium compounds in particular are noted for their propensity to adsorb other drugs and to form insoluble complexes that are not absorbed. Antacids that alter urinary pH will affect renal clearance of drugs that are weak acids or bases. Several mechanisms may play a part in any particular interaction. Interactions can be minimised by giving antacids and other medication 2 to 3 hours apart.

Antacids in this chapter include aluminium salts, magnesium salts, and calcium carbonate. For sodium bicarbonate, see p. 1781.1.

Described in this chapter are

Aceglutamide Aluminium, p. 1814.3
Alexitol Sodium, p. 1815.1
Almagate, p. 1815.3
Almasilate, p. 1815.3
Aloglutamol, p. 1816.2
Aluminium Glycinate, p. 1817.2
Aluminium Hydroxide, p. 1817.2
Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel, p. 1818.2
Aluminium Phosphate, p. 1818.3
Aluminium Sodium Silicate, p. 1818.3
Basic Aluminium Carbonate, p. 1817.1
Bismuth Compounds, p. 1821.3
Calcium Carbonate, p. 1824.3
Dihydroxyaluminum Sodium Carbonate, p. 1835.2
Hydrotalcite, p. 1845.2
Magaldrate, p. 1856.1
Magnesium Carbonate, p. 1856.2
Magnesium Hydroxide, p. 1857.2
Magnesium Oxide, p. 1857.3
Magnesium Trisilicate, p. 1858.1

Antidiarrhoeals

Antidiarrhoeals are used as adjuncts in the symptomatic treatment of diarrhoea (see p. 1805.2), although the main aim in the management of *acute* diarrhoea is the correction of fluid and electrolyte depletion with rehydration therapy; this is especially important in infants and young children and antidiarrhoeals are not generally recommended for this age group. Their use is also limited in *chronic* diarrhoea since treatment aimed at the underlying disorder will often alleviate the diarrhoea.

Described in this chapter are drugs that reduce intestinal motility such as the opioid analogues diphenoxylate and loperamide, and adsorbents such as attapulgite and kaolin. Bulking agents (which include bran and ispaghula) have also been used for diarrhoea and for adjusting faecal consistency in patients with colostomies.

Described in this chapter are

Albumin Tannate, p. 1815.1
Attapulgite, p. 1820.1
Bismuth Compounds, p. 1821.3
Bran, p. 1823.3
Chalk, p. 1826.3
Crofelemer, p. 1833.3
Difenoxin, p. 1835.2
Diphenoxylate, p. 1835.3
Ispaghula, p. 1849.1
Kaolin, p. 1850.1
Lidamidine, p. 1853.1
Loperamide, p. 1854.2
Racecadotril, p. 1881.3
Smectites, p. 1887.1
Zaldaride, p. 1895.3

Antiemetics

Antiemetics are a diverse group of drugs used to treat or prevent nausea and vomiting, including that associated with cancer therapy, anaesthesia, and motion sickness (see p. 1811.3).

The choice of drug depends partly on the cause of nausea and vomiting. For example, hyoscine or an antihistamine are used in motion sickness whereas dopamine antagonists (such as metoclopramide and domperidone) and serotonin 5-HT_3-receptor antagonists (5-HT_3 antagonists), such as ondansetron, are ineffective. Conversely, nausea and vomiting associated with cancer chemotherapy is often hard to control and special regimens have been devised including the use of the 5-HT_3 antagonists, dexamethasone, and, more recently, the neurokinin-1 receptor antagonists aprepitant and casopitant.

Described in this chapter are

Alizapride, p. 1815.2
Aprepitant, p. 1819.2
Azasetron, p. 1820.2
Bromopride, p. 1824.2
Casopitant, p. 1826.2
Cerium Oxalate, p. 1826.2
Clebopride, p. 1833.1
Difenidol, p. 1835.1
Dolasetron, p. 1837.2
Domperidone, p. 1838.1
Dronabinol, p. 1840.1
Fosaprepitant, p. 1843.2
Ginger, p. 1844.1
Granisetron, p. 1844.3
Hyoscine, p. 1845.3
Indisetron, p. 1848.3
Itopride, p. 1850.1
Mecloxamine Citrate, p. 1859.1
Metoclopramide, p. 1862.2
Metopimazine, p. 1865.1
Nabilone, p. 1865.2
Ondansetron, p. 1872.1
Palonosetron, p. 1875.1
Ramosetron, p. 1881.3
Tropisetron, p. 1894.1

Antisecretory drugs

Antisecretory drugs are used in the treatment and prophylaxis of peptic ulcer disease (p. 1813.2); some are also employed in other disorders associated with gastric hyperacidity such as gastro-oesophageal reflux disease (p. 1807.2) and dyspepsia (p. 1806.3). They may generally be divided into:

- *Histamine H_2-receptor antagonists* (H_2-antagonists), which act by blocking histamine H_2-receptors on gastric parietal cells, thereby antagonising the normal stimulatory effect of endogenous histamine on gastric acid production. Those described in this chapter include cimetidine, famotidine, nizatidine, and ranitidine.
- *Proton pump inhibitors*, which act by blocking the enzyme system responsible for active transport of protons into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) of the gastric parietal cell, also known as the 'proton pump'. Those described in this chapter include lansoprazole, omeprazole, pantoprazole, and rabeprazole.
- *Selective antimuscarinics*, which block cholinergic stimulation of gastric acid production with fewer adverse effects than less selective antimuscarinics (see Action of Antimuscarinics, p. 1310.3), but have largely been superseded. Pirenzepine is an example.
- *Prostaglandin analogues*, which inhibit gastric acid secretion by a direct action on the parietal cell and may also inhibit gastrin release and possess cytoprotective properties. Misoprostol (p. 2140.3) is an example.

Described in this chapter are

Cimetidine, p. 1827.1
Dexlansoprazole, p. 1834.2
Eseridine Salicylate, p. 1840.3
Esomeprazole, p. 1841.1
Famotidine, p. 1842.1
Ilaprazole, p. 1848.2
Lafutidine, p. 1851.3
Lansoprazole, p. 1851.3
Nizatidine, p. 1866.1
Omeprazole, p. 1867.2
Pantoprazole, p. 1875.3
Pirenzepine, p. 1878.2
Proglumide, p. 1880.1
Rabeprazole, p. 1881.1
Ranitidine, p. 1882.1
Ranitidine Bismuth Citrate, p. 1883.3
Revaprazan, p. 1884.2
Roxatidine, p. 1884.3
Tenatoprazole, p. 1893.3
Urogastrone, p. 1894.3

Antispasmodics

Antispasmodics are drugs used for their relaxant action on smooth muscle, either direct or through an antimuscarinic action on the parasympathetic innervation. They play a role in the management of gastrointestinal spasm (p. 1807.1) and irritable bowel syndrome (p. 1810.3) as well as other disorders associated with smooth muscle spasm. Those described in this chapter are mainly antimuscarinics; drugs in other chapters that may be used for relaxation of smooth muscle include calcium-channel blockers (p. 1244.2) and nitrates (p. 1245.2), as well as drugs with less well defined mechanisms of action such as papaverine (p. 2362.2).

Described in this chapter are

Alverine Citrate, p. 1819.1
Butropium Bromide, p. 1824.3
Ciclonium Bromide, p. 1827.1
Cimetropium Bromide, p. 1831.3
Clidinium Bromide, p. 1833.2
Dicycloverine Hydrochloride, p. 1834.2
Difemerine Hydrochloride, p. 1835.1
Dihexyverine Hydrochloride, p. 1835.2
Diisopromine Hydrochloride, p. 1835.3
Drofenine Hydrochloride, p. 1839.3
Hyoscine, p. 1845.3
Hyoscine Butylbromide, p. 1845.3
Hyoscine Hydrobromide, p. 1845.3
Hyoscine Methobromide, p. 1846.1
Hyoscine Methonitrate, p. 1846.1
Hyoscyamine, p. 1848.1
Hyoscyamine Hydrobromide, p. 1848.1
Hyoscyamine Sulfate, p. 1848.1
Isopropamide Iodide, p. 1848.3
Mebeverine Hydrochloride, p. 1858.3
Mepenzolate Bromide, p. 1859.1
Methanthelinium Bromide, p. 1861.3
Methylbenactyzium Bromide, p. 1861.3
Octatropine Methylbromide, p. 1866.2
Oxapium Iodide, p. 1874.3
Oxyphencyclimine Hydrochloride, p. 1875.1
Oxyphenonium Bromide, p. 1875.1
Pargeverine Hydrochloride, p. 1877.1
Peppermint Leaf, p. 1877.1
Peppermint Oil, p. 1877.1
Pipenzolate Bromide, p. 1878.1

Piperidolate Hydrochloride, p. 1878.1
Pipethanate Ethobromide, p. 1878.2
Platyphylline Acid Tartrate, p. 1878.3
Poldine Metilsulfate, p. 1879.1
Prifinium Bromide, p. 1879.3
Propantheline Bromide, p. 1880.1
Tiemonium, p. 1893.3
Timepidium Bromide, p. 1894.1
Tiquizium Bromide, p. 1894.1
Valethamate Bromide, p. 1895.2

Laxatives

Laxatives (purgatives or cathartics) promote defaecation and are used in the treatment of constipation (see below) and for bowel evacuation before investigational procedures, such as endoscopy or radiological examination, or before surgery.

Laxatives are frequently used for self-medication. Abuse of laxatives is a well-known phenomenon that may occasionally lead to toxicity.

Laxatives may be classified according to their mode of action. There is, however, a degree of overlap between the various groups and in some cases the precise mechanisms of action are not fully understood. Many traditionally used laxatives have fallen from use owing to the violence of their action or their adverse effect profile.

- *Bulk laxatives* (bulk-forming laxatives or bulking agents) cause retention of fluid and an increase in faecal mass resulting in stimulation of peristalsis. Owing to their hydrophilic nature, bulk laxatives may also be used to control diarrhoea and to regulate the consistency of effluent in colostomy patients. Those described in this chapter include bran, ispaghula, and sterculia.
- *Stimulant laxatives* (contact laxatives) act by directly stimulating nerve endings in the colonic mucosa, thereby increasing intestinal motility. It is this group of laxatives which is most commonly associated with abuse. Those described in this chapter include bisacodyl, cascara, phenolphthalein, senna, and sodium picosulfate.
- *Osmotic laxatives* act by increasing intestinal osmotic pressure thereby promoting retention of fluid within the bowel. Those described in this chapter include saline laxatives such as magnesium citrate, magnesium hydroxide, and sodium sulfate (for magnesium sulfate and sodium phosphate see p. 1787.3 and p. 1791.1 respectively). Lactulose may also be classified as an osmotic laxative because its breakdown products exert a similar effect. Also included in this group are the hyperosmotic laxatives such as glycerol (p. 2517.2) and sorbitol (p. 2092.1), and the macrogols (p. 2547.3).
- *Faecal softeners* (emollient laxatives) are claimed to act by decreasing surface tension and increasing penetration of intestinal fluid into the faecal mass. Those described in this chapter include docusate (which is also believed to have a stimulant action).

For the lubricant laxative liquid paraffin see p. 2191.2.

Described in this chapter are

Aloes, p. 1816.1
Aloin, p. 1816.2
Bisacodyl, p. 1821.1
Bisoxatin, p. 1823.2
Bran, p. 1823.3
Buckthorn, p. 1824.2
Casanthranol, p. 1826.1
Cascara, p. 1826.1
Cassia Pulp, p. 1826.2
Colocynth, p. 1833.3
Dantron, p. 1833.3
Docusates, p. 1836.2
Euonymus, p. 1842.1
Fig, p. 1843.2
Frangula, p. 1843.3
Ispaghula, p. 1849.1
Jalap, p. 1850.1
Lactitol, p. 1850.3
Lactulose, p. 1850.3
Liquorice, p. 1853.2
Magnesium Citrate, p. 1857.1
Magnesium Hydroxide, p. 1857.2
Magnesium Oxide, p. 1857.3
Manna, p. 1858.2
Pentaerythritol, p. 1877.1
Phenolphthalein, p. 1877.3
Polycarbophil, p. 1879.1
Potassium Acid Tartrate, p. 1879.2
Potassium Sodium Tartrate, p. 1879.3
Prune, p. 1881.1
Psyllium Seed, p. 1849.1
Rhubarb, p. 1884.2
Senna, p. 1885.1
Sodium Picosulfate, p. 1887.2
Sodium Sulfate, p. 1888.1
Sodium Tartrate, p. 1888.2
Sterculia, p. 1888.3
Tamarind, p. 1892.2

Mucosal protectants

Cytoprotective drugs (mucosal protectants) play a role in the management of peptic ulcer disease (p. 1813.2). They may be divided into:

- *Chelates or complexes*, which coat the gastric mucosa preferentially at sites of ulceration by forming an adherent complex with proteins. Those described in this chapter include sucralfate and tripotassium dicitratobismuthate (which also has an antibacterial role in regimens aimed at eradicating *Helicobacter pylori*)
- *Miscellaneous drugs* include liquorice and its derivatives, such as carbenoxolone, which may act by stimulating the synthesis of protective mucus

Described in this chapter are

Benexate, p. 1821.1
Carbenoxolone, p. 1825.3
Cetraxate, p. 1826.3
Dosmalfate, p. 1839.3
Ecabet, p. 1840.2
Enoxolone Aluminium, p. 1840.3
Gefarnate, p. 1844.1
Irsogladine, p. 1848.3
Liquorice, p. 1853.2
Plaunotol, p. 1879.1
Polaprezinc, p. 1879.1
Rebamipide, p. 1884.1
Sofalcone, p. 1888.2
Sucralfate, p. 1889.1
Sulglicotide, p. 1892.2
Teprenone, p. 1893.3
Tripotassium Dicitratobismuthate, p. 1822.2
Troxipide, p. 1894.3

Prokinetic drugs

Prokinetic drugs stimulate the motility of the gastrointestinal tract. Gastrointestinal smooth muscle exhibits intrinsic motor activity which is modified by autonomic innervation, local reflexes, and gastrointestinal hormones. This activity produces peristaltic waves, which move the gut contents from stomach to anus, and segmentations, which encourage digestion. Prokinetic drugs may act at various points within this complex system to enhance gastrointestinal movement. Those described in this chapter include metoclopramide, cisapride, and domperidone. Other drugs with prokinetic properties include parasympathomimetics such as bethanechol (p. 2456.2) or neostigmine (p. 687.1), and the macrolide antibacterial erythromycin (p. 291.2).

Described in this chapter are

Aclatonium Napadisilate, p. 1815.1
Acotiamide Hydrochloride, p. 1815.1
Bromopride, p. 1824.2
Cinitapride, p. 1831.3
Cisapride, p. 1831.3
Clebopride, p. 1833.1
Domperidone, p. 1838.1
Itopride, p. 1850.1
Linaclotide, p. 1853.1
Lubiprostone, p. 1856.1
Metoclopramide, p. 1862.2
Mosapride, p. 1865.2
Prucalopride, p. 1880.2
Renzapride, p. 1884.1
Tegaserod, p. 1893.1

Management of Gastrointestinal Disorders

The management of some gastrointestinal disorders is discussed below.

Aspiration syndromes

Regurgitation and aspiration of gastric contents (Mendelson's syndrome) is a potential cause of morbidity and mortality associated with anaesthesia, especially in obstetrics and in emergency surgery. Chemical pneumonitis and respiratory distress result from the acid aspiration, the risk of which is increased by the drugs given as adjuncts to anaesthesia such as opioid analgesics and atropine.

Apart from good anaesthetic technique, including a prohibition on oral intake before elective procedures, efforts to **prevent** or reduce the problem have focussed mainly on increasing the pH of gastric contents to above 2.5, and in reducing gastric volume. However, there is little evidence to show that reduced gastric acidity or volume is associated with decreased morbidity or mortality in patients who have aspirated gastric contents,[1] and some do not recommend the routine pre-operative use of pharmacological prophylaxis in patients undergoing elective surgery with no apparent increased risk for pulmonary aspiration.[1] Similarly there is little evidence to support the routine use of prophylactic drugs in women undergoing normal labour (particularly with the increased use of regional anaesthetic techniques).[2]

The *H_2-antagonists* decrease gastric acid secretion and may decrease gastric fluid volume. However, they do not affect the pH of fluid already in the stomach; they must therefore be given some time before anaesthesia, which limits their value in emergency procedures. Cimetidine is considered effective in most patients, although where more prolonged reduction of acidity is required H_2-antagonists with a longer duration of action such as ranitidine or famotidine may be preferred. Nizatidine has the advantage of a relatively rapid onset of action.[3] The *proton pump inhibitors* (PPIs) have also been tried, but results have been variable. A meta-analysis[4] suggested that ranitidine was more effective than a PPI in reducing the volume of gastric secretions and increasing their pH. Combination of a PPI with a prokinetic drug may produce better results.[5]

Because of the lack of effect of antisecretory drugs on the pH of existing gastric fluid H_2-antagonists may be combined with *antacids* to neutralise gastric acidity. Although magnesium trisilicate has been extensively used[6] without apparent problems particulate antacids are potentially toxic to the lung, which is why soluble antacids such as sodium citrate have been widely favoured. An effervescent formulation of sodium citrate with cimetidine has been reported to raise gastric pH above 2.5 in more than 98% of patients undergoing caesarean section.[7]

A third component of prophylactic regimens for acid aspiration may be use of a *prokinetic drug* such as metoclopramide. These increase gastric emptying and thereby decrease the volume of stomach contents, and also increase pressure at the lower oesophageal sphincter. The ability of metoclopramide to reverse the effects of opioids on gastric emptying appears to depend on the route: 10 mg given intravenously after opioid analgesia is reported to be effective in promoting gastric emptying, whereas the same dose intramuscularly is not.[8]

If aspiration occurs, pulmonary damage may result within seconds; **treatment** has included removal of any particulate matter, and measures to maintain the airway and ensure adequate oxygenation. Corticosteroids have been used but are no longer considered helpful.[9]

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Constipation

The pattern of normal defaecation is extremely variable, which makes constipation hard to define, and to some extent subjective. However, expert consensus considers that it occurs if 2 or more of the following features are present for at least 12 weeks in the previous year: less than 3 defaecations in a week, or hard or lumpy stool, straining, feeling of incomplete evacuation or anorectal blockage, or need for manual assistance, on at least a quarter of occasions.[1,2] New onset constipation, especially in patients over 50 years of age, or accompanying symptoms such as anaemia, abdominal pain, weight loss, or overt or occult blood in the stool should provoke urgent investigation because of the risk of malignancy or other serious bowel disorder.[2-5] Constipation can be a symptom of a range of disorders or of drug toxicity[2,5,6] and appropriate management of any underlying cause is required. It tends to be more common in the elderly, in women, and in late pregnancy.[1,2]

Certain subtypes of constipation have been identified: patients may be subdivided according to whether intestinal transit time is slow or normal, or whether there is pelvic floor dysfunction (dyssynergia; outlet obstruction; anismus).[2,3,5,7]

There is relatively little evidence to guide management. In general, stepped or graded management is favoured, beginning with advice on lifestyle (including exercise and adequate hydration), and dietary modification if appropriate.[2,4-6,8] An increase in fibre intake, preferably through a high-fibre diet, is useful in patients with normal transit times although it is less beneficial in slow-transit constipation.[5,7] In patients with pelvic floor dysfunction, biofeedback training may be instituted.[3,5,7]

Where lifestyle changes and dietary modification are insufficient, a laxative may be considered. Because of the lack of clear evidence to guide the choice of laxative, practice varies considerably. Many favour the use of either a bulk laxative or an osmotic laxative as a first choice option,[2-4,7] with stimulant laxatives tending to be reserved as a second-line option, and diphenylmethane derivatives being preferred to anthraquinones.[3,6] For the treatment of opioid-induced constipation unresponsive to usual laxative therapy opioid antagonists such as *methylnaltrexone* have been tried.

- *Bulk laxatives* include bran, ispaghula, methylcellulose and related compounds, psyllium, or sterculia. Bulk laxatives are of particular value in those with small hard stools. However, they have a delayed onset of action (up to 72 hours) and they may exacerbate symptoms of flatulence, bloating, and cramping;[6] use should be avoided where these are severe. A gradual increase in dose may help reduce such effects.[7] They may not be the first choice for elderly patients who are frail or immobile since the resulting soft faeces may result in faecal incontinence,[9] and should only be given where fluid intake is adequate, because of the risk of obstruction.[7]
- *Osmotic laxatives* include saline laxatives such as magnesium hydroxide and magnesium sulfate, poorly absorbed sugars such as lactulose or sorbitol, and macrogols (often formulated with electrolytes). Some favour the use of macrogol 3350 or 4000, for which there is reasonable evidence of benefit in chronic constipation.[5,6,10] However, in practice lactulose is widely used,[6] although it is less effective in the elderly than a combination of bulking and stimulant laxatives (see below). In the USA, a saline laxative such as magnesium hydroxide has been

recommended,[3,4,7] although saline laxatives may not be acceptable to some patients because they can cause watery stool and urgency.

- *Stimulant laxatives* in current use include diphenylmethane derivatives such as bisacodyl or sodium picosulfate, and anthraquinone-containing drugs such as senna. They have a more rapid onset of action than bulk laxatives or lactulose, and are usually given at night to help produce a bowel motion the following morning. Many traditional stimulant laxatives have fallen from use because of adverse effects, and it has been widely thought that their prolonged use or abuse may irreversibly damage colonic nerves and muscles; however, the evidence for this is poor, and appropriate stimulant laxatives used at licensed doses are unlikely to cause significant harm.[11,12] Tolerance can occur but seems to be uncommon in the majority of users.[11,12] Combined preparations are also available, and a combination of senna and fibre has been found to be more effective than the osmotic laxative lactulose in elderly patients with chronic constipation.[13]
- *Other laxatives* include the docusates, surfactants that are used as stool softeners,[7] but their efficacy used alone for constipation is not well established;[4] perhaps for this reason, they are often formulated with a stimulant or osmotic laxative. Stool softeners would have potential value for patients with haemorrhoids or anal fissures, or those in whom straining is potentially hazardous (such as the elderly or those with existing cardiovascular disease). Liquid paraffin has also been used as a lubricant for the passage of stool,[7] but should be used with caution because of its adverse effects, which include anal seepage and the risks of granulomatous disease of the gastrointestinal tract or of lipoid pneumonia on aspiration. Although it has been recommended in some countries for constipation in children,[14,15] the UK CSM considers it should not be used in those under 3 years of age. Prokinetic drugs have theoretical advantages in patients with slow-transit constipation, but few suitable drugs are available,[5] although the selective 5-HT_4 agonist prucalopride may be tried in chronic constipation, and tegaserod has been used in constipation-predominant irritable bowel syndrome (p. 1810.3) and in chronic constipation. The chloride-channel activator lubiprostone and the guanylate cyclase-C agonist linaclotide are also used in chronic constipation and constipation-predominant irritable bowel syndrome.

Rectal administration of laxatives using enemas or suppositories is appropriate in patients requiring rapid relief from constipation. Phosphate enemas should be used with caution because of the risks of absorption of significant amounts of phosphate.[4] Glycerol and bisacodyl may be given as suppositories to promote faecal evacuation; they should not be used regularly, as changes in the rectal epithelium have been seen with bisacodyl, and the effect of glycerol on rectal mucosa is unclear.[4]

During *pregnancy* the preferred options for management are increased fluid intake, exercise, and dietary fibre;[2] bulking agents may be given as fibre supplements, and stimulant laxatives such as senna reserved for cases where these are ineffective.[2,16]

Faecal impaction is the inability to pass a hard collection of stool, and may result in overflow diarrhoea. Faecal impaction should be treated with a laxative enema and/or a lubricant and manual disimpaction.[4,5,9] Oral laxatives should not be used because of the risk of colonic perforation.[9] When all stool has been cleared, it is important to institute measures, often including regular laxatives, to prevent constipation and recurrent impaction.[5,7,9]

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Decreased gastrointestinal motility

Decreased gastrointestinal motility may occur in any part of the gastrointestinal tract, with symptoms depending on the site. It is of varying aetiology and often secondary to some other disorder, such as infection, metabolic or electrolyte disturbance (for example in gastroparesis due to diabetic neuropathy—see also p. 465.2), or insult to the gastrointestinal tract (for example, paralytic or adynamic ileus is frequently a consequence of abdominal surgery and is a serious adverse effect of some drugs).

Acute loss of gastrointestinal motility is often self-limiting once the underlying cause has been treated. Provided the ability of gastrointestinal smooth muscle to contract has not been lost, however, prokinetic drugs such as metoclopramide or domperidone, or erythromycin, or drugs capable of stimulating functional contraction including parasympathomimetics such as neostigmine or bethanechol, may be used. The opioid μ-receptor antagonist alvimopan has recently been introduced for the treatment of postoperative ileus. Injection of botulinum toxin into the pyloric sphincter may produce temporary symptomatic improvement in patients with refractory gastroparesis. Gastric electrical stimulation may also be an option.

Drugs are less successful in chronic conditions such as chronic intestinal pseudo-obstruction where neuromuscular function of the gastrointestinal tract has some intrinsic abnormality.

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Diarrhoea

Diarrhoea is characterised by liquid stools and increased stool weight and frequency of defaecation. Although diarrhoea is commonly associated with infection (see Gastro-enteritis, p. 182.2), it may also result from the accumulation of nonabsorbed osmotically active solutes in the gastrointestinal lumen, as in lactase deficiency, or from the gastrointestinal effects of secretory stimuli other than the enterotoxins from an infection. It may also occur when intestinal motility or morphology is altered.

Acute diarrhoea may lead to excessive water and electrolyte loss and dehydration, and is potentially life-threatening in infants; frail and elderly patients are also at risk. Severe dehydration associated with acute diarrhoea (greater than 10% loss of body-weight), requires *intravenous rehydration therapy* with Ringer's lactate solution or normal saline.[1-4] Intravenous therapy is also needed for patients who are unable to drink. Otherwise, *oral rehydration therapy* to correct fluid and electrolyte depletion should form the basis of treatment for acute diarrhoea[1-6] and an oral rehydration solution containing essential electrolytes (sodium, potassium, chloride, and bicarbonate or citrate) and glucose is indicated regardless of the age of the patient or the cause of the diarrhoea. A rehydration phase, which involves the replenishment of fluid and electrolytes lost through the diarrhoea, is followed by a maintenance phase to replace continuing losses. Oral rehydration therapy does not stop diarrhoea, which usually continues for a limited period, although it can reduce stool output and vomiting. Oral rehydration therapy may need to be modified if the diarrhoea is associated with malnutrition.[7] The rationale for the composition of oral rehydration solutions is that glucose absorption is coupled to the active transport of electrolytes,[8] the absorption of which theoretically increases in efficiency as the ratio of carbohydrate to sodium approaches 1:1.

WHO originally recommended a solution containing 90 mmol/litre of sodium and 111 mmol/litre of glucose; this type of preparation has been used effectively in developing countries where diarrhoeas are commonly bacterial in origin. There is now evidence from studies and meta-analyses to suggest that solutions of reduced sodium content and osmolarity are safe and effective and may be preferable to the original standard WHO solution, even in developing countries,[9-12] and WHO and UNICEF now recommend a solution containing 75 mmol/litre of sodium and 75 mmol/litre of glucose, with a reduced total osmolarity of 245 mmol/litre.[13] Despite concerns about the possible increased risk of hyponatraemia with the use of the reduced osmolarity solutions in patients with cholera,[14-16] WHO and UNICEF have stated that hyponatraemia may also occur with the standard WHO formulation, and that there is no evidence to suggest that this transient hyponatraemia has had significant adverse clinical consequences for cholera patients.[13]

In developed countries viral diarrhoeas, which are associated with less electrolyte loss, are more common, and reduced osmolarity solutions are favoured.[2] Commercial preparations available in the UK, for example, usually provide 50 to 60 mmol/litre of sodium and 90 to 111 mmol/litre of glucose; the total osmolarity is slightly hypotonic (about 250 mmol/litre) to prevent possible induction of osmotic diarrhoea.[17] Similar preparations are available in other developed countries.[18]

Areas of debate have included the necessity for inclusion of citrate or bicarbonate,[17] and whether cereal-based rather than glucose-based rehydration solutions would be preferable. There is considerable evidence that cereal-based solutions tend to produce more rapid resolution of diarrhoea, although one study has suggested that the reduction in stool output is temporary,[19] and another found that a glucose-based solution was equally effective when combined with early re-introduction of feeding.[20] In 1994, a review of clinical studies concluded that a rice-based rehydration solution should be recommended for patients with cholera, but that there was no reason to change from WHO's glucose-based formulation for children with non-cholera diarrhoea.[21] A study in 48 patients with cholera compared the use of standard glucose-based oral rehydration therapy, standard therapy plus rice flour, and standard therapy plus amylase-resistant starch.[22] The addition of amylase-resistant starch to standard oral rehydration solution was shown to reduce stool output and to reduce the duration of diarrhoea,[22] although the methodology of this study was questioned[23] and further investigation of such solutions is required.

Home remedies[1] that have been used to prevent dehydration include coconut water, rice water, soups, unsweetened fresh fruit juice, and unsweetened weak tea; these may be of value when more conventional oral rehydration solutions are unavailable. The use of cordials and soft drinks with low pH and high osmolality, however, may exacerbate diarrhoea and dehydration.[1,18]

Oral rehydration therapy should be combined with *dietary measures*, particularly in children, to avoid malnutrition owing to low food intake during the illness, and as mentioned above, may need to be modified if the diarrhoea is associated with malnutrition. Breast feeding should be continued throughout rehydration therapy,[2,4,6,17] as such feeding may decrease stool output and shorten the duration of diarrhoea.[2] Dilution of formula feeds does not seem to be of clinical benefit and may even prolong symptoms.[4,8] Generally food should not be withheld in adults or children with diarrhoea, but for those with some signs of dehydration, food is not normally given during the initial rehydration period.[1]

To reduce the duration and severity of diarrhoea, and to prevent recurrence, zinc supplements are recommended by WHO as adjunctive therapy to oral rehydration salts for acute diarrhoea, see p. 2127.2. Children with persistent diarrhoea, lasting at least 14 days, should receive zinc as part of a multivitamin and mineral supplement.[1] Vitamin A may be important in reducing mortality, see p. 2100.1.

There is considerable interest in the potential use of probiotic bacteria, or prebiotic foods intended to stimulate the growth of beneficial species in the gastrointestinal tract, in the management of diarrhoea. Although meta-analyses have suggested that treatment with lactic-acid producing organisms may reduce stool frequency and disease duration in children with acute infectious diarrhoea,[24] and may reduce the risk of antibacterial-associated diarrhoea in children,[25] the role of probiotics and prebiotics remains to be established,[4,8] particularly since many commercial products are poorly characterised.

Oral rehydration therapy prevents dehydration, but does not necessarily shorten the duration of the diarrhoea, and patients therefore frequently desire the symptomatic relief provided by *drug therapy*. Use of such therapy should be

balanced against the risk that it may distract from the need for oral rehydration therapy and may have undesirable adverse effects. WHO considers that antidiarrhoeal drug therapy is of limited value for acute infectious diarrhoea, does not reduce fluid and electrolyte loss, may delay the expulsion of causative micro-organisms, and should never be used in children.[26] However, it has been pointed out that extrapolating results in children to adult treatment is unwarranted; there is no good evidence that antidiarrhoeal drugs prolong illness or retard expulsion of pathogens, and no reason to withhold medication in otherwise healthy adults.[27] Short courses of antidiarrhoeals are often used in practice (frequently as self medication) if symptoms are causing discomfort.[3,27,28]

The main groups of antidiarrhoeal drugs are adsorbents such as attapulgite, kaolin, and pectin, and drugs that reduce intestinal motility such as diphenoxylate, loperamide, and codeine. Oral loperamide has been recommended as the treatment of choice, particularly for self-medication,[3,27] although bismuth salicylate, which has antisecretory properties, is probably equally effective,[3] and may be preferred in some countries such as the USA.[28] Other drugs with antisecretory properties are under investigation; they include the enkephalinase inhibitor racecadotril, which unlike other antidiarrhoeal drugs is of interest as a potential adjunct in children.[4] Bulk laxatives such as methylcellulose have also been used for symptomatic treatment because of their absorptive capacity.

Antibacterial and antiprotozoal drugs have been used for infective diarrhoeas, including the prophylaxis and treatment of travellers' diarrhoea (see Gastro-enteritis, p. 182.2 and p. 921.2), but their overuse encourages the development of resistance and prophylaxis is not recommended. Vaccines are being developed for the prevention of rotaviral diarrhoeas (p. 2416.1).

Chronic diarrhoea may be associated with underlying disease and therefore symptomatic relief is less appropriate than treatment of the disease itself. For example, colestyramine will reduce the diarrhoea associated with bile acid malabsorption. Where the disease process responsible for chronic diarrhoea cannot be satisfactorily suppressed, however, symptomatic relief may be appropriate,[29] for example in diabetic diarrhoea (see p. 464.1).

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Diverticular disease

Diverticula are small hernias or pouches of mucosa that develop through the muscular wall of the gut (especially the colon) or other hollow organs; they increase in prevalence with increasing age. Diverticular disease (the presence of colonic diverticula) is usually asymptomatic, but may be associated with symptoms of abdominal pain and altered bowel habit (diverticulosis). Occasionally there may be severe life-threatening complications such as inflammation and necrosis of diverticula (diverticulitis), perforation, fistula formation, obstruction, or haemorrhage. There is some evidence that the use of NSAIDs may be associated with an increase in diverticular complications such as perforation.

In uncomplicated diverticular disease, treatment is with a high-fibre diet, gradually supplemented if necessary with a bulk laxative such as bran or ispaghula, to ease constipation, although the evidence to support such management is limited. Supplements may not relieve the other symptoms of diverticular disease. The antibacterial rifaximin may be of benefit in improving symptoms; giving rifaximin and fibre supplementation has been shown to be more effective than fibre supplementation alone. Rifaximin has also been combined with 5-aminosalicylates, chiefly mesalazine; the latter may be of benefit in maintaining remission. Use of probiotics, in the form of lactic-acid-producing organisms, after a non-absorbed antibacterial such as rifaximin has also produced some evidence of additional benefit. Antispasmodics such as antimuscarinics or mebeverine may be useful in relieving pain due to muscle spasm.

Diverticulitis requires treatment with broad-spectrum antibacterials and fluid support; analgesia may be needed for severe pain. If peritonitis or abscess develops, surgical intervention may be necessary. Surgical resection is usually considered when fistula, perforation, or obstruction are present.

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Dumping syndrome

The word dumping in this context is used to describe the unnaturally rapid transport of gastric contents to the small intestine. The dumping syndrome is an important cause of morbidity after gastrointestinal surgery, and is thought to be due to the destruction of normal regulatory mechanisms in the upper gastrointestinal tract.[1-3] Early dumping begins within 10 to 30 minutes of the ingestion of a meal (typically, symptoms are triggered by hyperosmolar, carbohydrate-rich food) and has gastrointestinal symptoms (fullness, abdominal pain, nausea and vomiting, explosive diarrhoea) and vasomotor symptoms (sweating, weakness, dizziness, flushing, and palpitations). The effects are thought to be due to fluid shifts from the intravascular space to the bowel lumen. Some patients have late dumping, 1 to 4 hours after a meal, with only the vasomotor symptoms; it appears to be due to reactive hypoglycaemia caused by high carbohydrate concentrations in the small intestine.

The mainstays of therapy are dietary modifications, taking small frequent meals low in carbohydrate, followed by liquids 30 minutes later. Attempts to slow or reduce carbohydrate absorption have involved the use of dietary fibre (guar gum or pectin) or α-glucosidase inhibitors such as acarbose; acarbose and pectin have also been tried in combination.[4] However, such agents may themselves cause gastrointestinal disturbances and they do not seem to be helpful in most patients.[2] However, beneficial results with somatostatin have led to the use of its longer-acting analogue, octreotide.[2,5] Octreotide substantially reduces the symptoms of both early and late dumping, probably by slowing gastric emptying and by inhibiting the release of gastrointestinal mediators (peptide hormones such as neurotensin), and prevents hyperinsulinaemia and subsequent reactive hypoglycaemia. It may be given up to 2 hours before a meal, or as long-acting formulation.[3]

In the minority of patients who do not respond to medical therapy surgery may be required.[1-3]

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Dyspepsia

Dyspepsia, also commonly known as indigestion or heartburn, is a frequent but ill-defined disorder primarily associated with epigastric discomfort or pain. It may be a symptom of specific diseases such as peptic ulcer disease, gastro-oesophageal reflux disease, gastric carcinoma, chronic pancreatitis, or gallstones. However, in many patients there is no identifiable systemic disease, in which case it is known as non-ulcer dyspepsia or functional dyspepsia.

Many reviews and recommendations have addressed the subject of dyspepsia,[1-7] and, in the UK, various authoritative guidelines have been issued.[8,9] The initial management of non-ulcer dyspepsia usually includes advice to avoid alcohol, caffeine, smoking, and aggravating foods, and to eat small regular meals to aid digestion. Results of studies of drugs for non-ulcer dyspepsia have been variable and difficult to evaluate since the condition tends to be self-limiting, and there is often a large placebo response.[10]

Drugs that suppress gastric acid such as antacids or antisecretory drugs are often used. Antacids may give some symptomatic relief, and are widely used for self-medication.[9] However, long-term use is inappropriate. Similarly, H_2-antagonists are often tried, especially for symptoms of reflux, and a systematic review[10] has suggested benefit, at least in a proportion of patients. Proton pump inhibitors (PPIs) are also widely used; although a systematic review had considered their relative efficacy in non-ulcer dyspepsia versus H_2-antagonists to be unclear,[11] others[5-7,12] consider them superior to H_2-antagonists. They may be useful for on-demand therapy to manage symptoms long-term.[9]

It is not clear what role *Helicobacter pylori* plays in the pathology of non-ulcer dyspepsia. One meta-analysis found eradication to be of no benefit in non-ulcer dyspepsia,[13] but another, incorporating more patients, found that a small benefit existed,[14] although it noted that most patients positive for *H. pylori* will continue to have symptoms after eradication. As a result there has been much debate about the appropriateness of so-called 'test and treat' strategies, but UK[9] and US[4,5] guidelines consider them a valid alternative to a trial of a PPI in the initial management of uninvestigated dyspepsia.

Initial management of dyspepsia in patients under 55 years of age who do not have so-called 'alarm symptoms' (such as chronic gastrointestinal bleeding, unintentional weight loss, difficulty swallowing, persistent vomiting, iron deficiency anaemia, or epigastric mass) should therefore consist of either:[4,9]

- an empirical one-month course of a PPI, *or*
- testing for *Helicobacter pylori* and appropriate eradication therapy. Those who are *H. pylori*-negative should be prescribed an empirical trial of acid suppression with a PPI for 1 to 2 months

Patients over 55 years of age, or those with alarm symptoms, should be referred for endoscopy. After endoscopy, treatment should be targeted at the underlying diagnosis.[4]

Prokinetic drugs may be given, particularly if an underlying gastrointestinal motility disorder is suspected. Meta-analysis has suggested that prokinetic therapy may be more effective than an H_2-antagonist in non-ulcer dyspepsia,[10,15] but this may be due to publication bias.[10] In addition, cisapride is no longer available in many countries and evidence for domperidone or metoclopramide is limited. Results with motilin agonists (derivatives of erythromycin) and 5-HT_3 antagonists have been disappointing to date.[3] Other approaches to drug therapy include the use of an insoluble bismuth salt, and the use of antispasmodics. Antidepressants may have a limited role in some patients,[5,7] and various herbal medications have been tried, though the quality of any studies is generally poor.[7]

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Eosinophilic oesophagitis

Eosinophilic oesophagitis is a disease of the oesophagus characterised by a marked accumulation of eosinophils in the oesophageal mucosa. Severe squamous epithelial hyperplasia generally occurs, resulting in complications such as oesophageal strictures and a narrow oesophagus. Symptoms include heartburn, chest pain, dysphagia, pain on swallowing, vomiting, food impaction, and feeding intolerance in children.

Although data on treatments are sparse, corticosteroids are considered appropriate. Systemic and topical corticosteroids are effective at relieving acute symptoms, although symptoms usually recur when treatment is stopped. Gastro-oesophageal reflux disease may coexist with eosinophilic oesophagitis; however, the symptoms and pathological features of eosinophilic oesophagitis do not respond to acid suppression treatment. Allergy has been implicated in eosinophilic oesophagitis, with many patients being atopic. Dietary therapy based on eliminating exposure to food allergens is considered an effective treatment option for children, in whom most of the research has been carried out.[1]

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Gastrointestinal spasm

Pain or discomfort of the gastrointestinal tract may be due to spasm of the smooth muscle of the gut; such pain and spasm may be associated with the irritable bowel syndrome (see p. 1810.3), dyspepsia (see p. 1806.3), or diverticular disease (see p. 1806.2). Antispasmodic drugs have traditionally been used in patients thought to have gastrointestinal spasm, and have mainly been of two types: antimuscarinics such as dicycloverine, and direct smooth muscle relaxants such as mebeverine; use of antimuscarinics, in particular, has tended to be limited by concern about their adverse effects.

Colic is a general term used to describe spasmodic or griping pain, usually of the viscera, and when not otherwise qualified is often understood to refer to pain in the gastrointestinal tract. Infant colic is common in the first few months of childhood,[1,2] and tends to be managed by nonpharmacological measures and assessment of the feeding technique. Elimination of cow's milk protein appears to be of benefit, but use of a low-lactose formula is not.[1] Tilactase has been added to feeds to aid lactose digestion but the extent of any benefit is unclear. Traditional remedies such as gripe water, which contains essential oils of dill or fennel and is mildly carminative, are of dubious efficacy. Antimuscarinic antispasmodics, although effective[1,2] may be associated with adverse effects, and are no longer considered appropriate.[3] Simeticone suspension, given before feeds, is commonly used but has been found to be no better than placebo.[3,4] It has been reported that sucrose, given as a 12% solution, improves infant colic.[5] Glucose solution may also have some benefit.[2]

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Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease results from the reflux of gastric or duodenal contents into the oesophagus. Symptoms include heartburn, acid regurgitation, and dysphagia (difficulty in swallowing); oesophageal inflammation and ulceration (reflux oesophagitis), and stricture formation may occur. Extra-oesophageal symptoms may include cough, horseness, and asthma. Some patients develop Barrett's oesophagus (below), which is a risk factor for oesophageal cancer (p. 705.3).

Lifestyle advice on weight loss, raising the head of the bed, stopping smoking, and avoidance of alcohol and aggravating foods such as chocolate and coffee is often given as part of initial **management**,[1-6] although the evidence for most of these interventions other than weight loss and bed position is lacking.[3]

Patients often manage initial mild symptoms with over-the-counter therapies, including *antacids* and antisecretory drugs. Although the placebo response is often high, meta-analysis has shown some additional symptomatic benefit from antacids, *histamine H_2-antagonists*, and in particular for combinations of an antacid with an alginate;[7] such combinations are believed to form an alkaline 'raft' above the stomach contents that impedes reflux and protects the oesophageal mucosa.

The symptoms and management of gastro-oesophageal reflux disease may overlap with those of dyspepsia (see p. 1806.3), and initial symptomatic management is likely to be similar.[4] Patients who do not have alarm symptoms that would indicate a need for prompt endoscopy should be treated with an appropriate dose of a *proton pump inhibitor* (PPI) for 1 to 2 months.[4,5] Such treatment is more effective for empirical management than an H_2-antagonist,[8] and is appropriate therapy for endoscopy-negative disease[8] as well as for patients with reflux oesophagitis.[9] There is no evidence for the superiority of any particular PPI, nor for greater benefit from doubling doses in patients with reflux oesophagitis.[8]

A significant minority of patients do not, however, respond to PPIs; reasons may include poor compliance, nocturnal acid breakthrough, non-acid reflux, and hypersensitivity to acid.[4,5] Trying an alternative PPI, increasing the dose, or adding a H_2-antagonist to PPI treatment have been suggested for patients with persistent symptoms,[4,10] although evidence of improved efficacy is generally lacking.[6,9,11] Some benefit has been reported in extensive metabolisers of rabeprazole when famotidine was added to treatment compared with an increased rabeprazole dose.[12]

Alternatively, a *prokinetic drug* such as metoclopramide may improve gastro-oesophageal sphincter function and accelerate gastric emptying. These appear to be as effective as H_2-antagonists,[1] although they are probably less effective than PPIs.[8] An H_2-antagonist used with cisapride may be more effective than either drug alone.[1] However, concern over the risk of cardiotoxicity and potential for serious interactions with cisapride has led to severe restrictions on its use.

In patients with mild disease, a trial of withdrawal of drug therapy is appropriate after successful initial treatment.[1] Short courses of therapy as and when symptoms demand (intermittent treatment) may be effective in uncomplicated disease.[13] However, most patients with oesophagitis relapse when treatment is withdrawn, and long-term **maintenance** therapy is likely to be required.[1,4,5] As in acute management, PPIs appear to be the most effective maintenance treatment, although the 'step-down' approach of reduced maintenance doses, which is widely favoured,[4,5] may produce less benefit than continuing to give full dose PPIs.[14] H_2 antagonists were found to be of marginal benefit for maintenance, although they did give some symptomatic relief, and although prokinetic drugs (cisapride) and sucralfate were also reported to be more effective than placebo their value was considered dubious.[14] Another approach is to use a combination for maintenance, and in one study omeprazole with cisapride provided more effective maintenance than ranitidine or cisapride alone or together.[15] Again, however, cisapride is now unlikely to be used in practice because of the risks.

Helicobacter pylori **eradication** does not heal or prevent relapse of gastro-oesophageal reflux disease,[1] and some epidemiological evidence has appeared to suggest that *H. pylori* infection protects against gastro-oesophageal reflux disease.[16] However, there is no clinical evidence that eradication of *H. pylori* exacerbates gastro-oesophageal reflux disease or significantly increases the risk of its development.[17,18]

In patients who have a poor response to drug therapy, or in those with complications such as oesophageal stricture or ulceration, **surgery** to re-establish gastro-oesophageal competence may be considered.[1,4,5] Submucosal implants and various other endoscopic techniques have also been investigated.[4] Although surgery is as effective as drug treatment, it carries greater associated risks, and many patients continue to require antisecretory drugs.[4]

Investigational approaches to drug therapy include the development of drugs with GABAergic actions similar to those of baclofen (but without its CNS effects), cholecystokinin antagonists such as loxiglumide, and cannabinoid CB_1 agonists; motilin receptor agonists such as alemcinal and mitemcinal do not appear to be of much benefit.[19]

A minority of patients with gastro-oesophageal reflux disease develop **Barrett's oesophagus** (columnar lined oesophagus, CLO), in which the normal oesophageal squamous lining is replaced with a metaplastic columnar epithelium. This is most common in patients with long-standing disease but may represent part of a spectrum of possible responses to acid reflux rather than a progression from less severe to more severe disease.[4] The abnormal epithelium in Barrett's oesophagus shows dysplastic changes that may progress to oesophageal adenocarcinoma. However, not all patients go on to develop cancer, and many aspects of management are controversial.

Management of acid reflux, as for other forms of gastro-oesophageal reflux disease, is the mainstay of management.[20-23] Long-term treatment with PPIs appears to be effective;[22] the use of maximal doses, perhaps with an H_2-antagonist at night, is advocated by some[23] but evidence to support twice daily (double) dosing is lacking.[22] As the altered epithelium is relatively less sensitive to acid, symptom control does not necessarily equate to suppression of reflux.[23] There is a lack of good evidence that control of acid reflux produces anything other than limited regression of the abnormal epithelium, or alters the risk of progression to malignancy,[22,23] although there are some results that suggest benefit.[24,25] Some evidence suggests that additional chemoprevention with aspirin or another NSAID might offer benefits in reducing cancer risk,[22,26] but this remains investigational. The roles of screening, surveillance, and endoscopic ablation therapy or photodynamic therapy (5-aminolaevulinic acid or porfimer) remain matters of debate.[20,22,23]

In **infants**, gastro-oesophageal reflux is common but usually resolves spontaneously with increasing age and requires no treatment. Occasionally, it may be associated with complications such as failure to thrive, oesophagitis, and pulmonary symptoms of acid regurgitation, but can be managed by upright positioning and the use of thickened foods; drug therapy is controversial,[27] and the evidence base is poor.[28] It has been suggested that where drug therapy is needed, an alginate-antacid combination may be appropriate initially;[27] PPIs are probably safe but are not well studied in infants.[28] Cisapride has been given[27,28] but the risk of cardiotoxicity makes the use of cisapride in infants extremely problematic (see p. 1832.2). Metoclopramide may have some benefit but again this must be weighed against the risk of adverse effects.[29] Evidence of benefit with domperidone is poor,[30] and it too has the potential for serious adverse effects, but restrictions on cisapride have led to its over-use.[28] Erythromycin has been investigated in infants with food intolerance, though not in gastro-oesophageal reflux itself; there is a risk of promoting bacterial resistance from such use.[28]

Gastro-oesophageal reflux is commonly encountered during normal **pregnancy**, and is generally managed by lifestyle and dietary modifications.[31] If drug therapy is required, nonsystemically absorbed antacids or sucralfate should be tried first. If these are ineffective, ranitidine may be tried. Proton pump inhibitors are reserved for women with severe or complicated reflux disease,[31] due to concerns about their safety in pregnancy, although the relative risk associated with exposure seems to be quite low (see under Precautions of Omeprazole, p. 1870.3).

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Haemorrhoids

Haemorrhoids ('piles') are venous swellings of the tissues around the anus: those above the dentate line (the point where the modified skin of the outer anal canal becomes gut epithelium), which usually protrude into the anal canal, are termed internal haemorrhoids, while those below this point are called external haemorrhoids. Due to internal pressure, internal haemorrhoids tend to congest, bleed, and eventually prolapse; with external haemorrhoids painful thrombosis may develop.[1-3]

Initial treatment of internal haemorrhoids involves a high-fibre diet and avoidance of straining at stool,[2,4] so bulk laxatives and faecal softeners may be indicated.[2] The prime objective of drug therapy is to control the acute bleeding phase so that definitive therapy can be scheduled.[1] Small bleeding haemorrhoids may be injected with a sclerosing agent such as oily phenol injection, but rubber band ligation, or perhaps a technique such as infra-red coagulation, is more effective and associated with fewer complications.[3,5,6] More severe and prolonged prolapse generally requires surgery.[2-4,7] Surgical excision to remove the clot is used for thrombosed external haemorrhoids.[8]

An enormous range of mainly topical drug treatments is available for symptomatic relief, but in many cases their value is at best unproven.

Topical preparations are usually made up in a lubricating or emollient base. Local anaesthetics may be included to relieve pain, and corticosteroids may be used where infection is not present: preparations containing either group of drugs are intended only for short-term use. Inclusion of antibacterials is thought to be of little value and may encourage the development of resistant organisms. Some preparations include heparinoids. Other agents frequently included for their soothing properties include various bismuth salts, zinc oxide, hamamelis, resorcinol, and peru balsam.[2,3] Topical nitrates have also been used.[1]

Bioflavonoids and various derivatives of aesculus may also be included in topical preparations; they have also been given systemically in some countries as have some other compounds such as calcium dobesilate and tribenoside, presumably for their supposed action on venous capillary walls. Oral micronised bioflavonoid preparations may reduce symptoms as an adjunct to surgery.[1,7,9]

Other agents that have been used in the treatment of haemorrhoids include pilewort (ficaria) and combinations of yeast extract with shark-liver oil.

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Hepatic encephalopathy

Hepatic encephalopathy (portal systemic encephalopathy) is a metabolically related dysfunction of the brain associated with abnormalities of liver function. It may be acute, as in patients with fulminant hepatic failure, or chronic, with acute episodes precipitated by some triggering factor, as in patients with cirrhosis or other chronic liver disease.

Treatment is aimed at identifying and correcting any precipitating factor, decreasing the production and absorption of ammonia in the gut, and increasing metabolism of ammonia in the tissues. Precipitating factors include infection, increased protein load due to gastrointestinal haemorrhage or high protein intake, alcohol abuse, electrolyte imbalance, and certain drugs (notably anxiolytics, hypnotics, and diuretics).

Restriction of dietary protein intake is a mainstay of short-term treatment, but in the long-term, care must be taken to provide adequate protein to avoid malnutrition. A daily protein intake of 0.5 to 1.5 g/kg has been recommended.[1-3] There is some evidence that vegetable protein is better tolerated than animal protein.[4,5] Giving branched-chain amino acids (valine, isoleucine, and leucine) by infusion or as dietary supplements may facilitate adequate protein intake in some patients.[1,3-5] Supplementation with ornithine aspartate has been used to increase metabolic conversion of ammonia to urea and glutamine.[2,4,5] Sodium benzoate has also been tried.[4,5]

Active drug treatment may begin with bowel cleansing by means of a magnesium sulfate enema, especially if the patient is constipated. Lactulose is then the treatment of choice in many cases, particularly in the elderly, the constipated, and those with renal impairment. It is usually given orally although it may be used rectally[2,5] or by nasogastric tube[2] when oral use is not feasible.[5] It reduces colonic pH and absorption of ammonia and aromatic amino acids. The lactulose analogue lactitol is also used.[6] However, a recent meta-analysis[7] was unable to find sufficient evidence to support or refute the use of nonabsorbable disaccharides, such as lactulose and lactitol, for hepatic encephalopathy. The disaccharidase inhibitor voglibose has been tried to reduce intestinal uptake of disaccharides and promote fermentation, with effects similar to lactulose.[5]

Alternatively, locally active antibacterials have been given to reduce the urease-producing bacteria.[2] Neomycin is the traditional drug but adverse effects such as ototoxicity and nephrotoxicity may be a problem, particularly if used long-term. Metronidazole[4] and rifaximin[4,8,9] are also used. A combination of lactulose and neomycin[4] or metronidazole has been tried in patients who fail to respond to single-drug therapy.

In low grade chronic recurrent encephalopathy *Lactobacillus acidophilus* or *Enterococcus faecium* SF68 have been tried orally in an attempt to produce a more favourable bowel flora. Results have been inconsistent.[5,10] *Helicobacter pylori* is a urease-producing organism, but the relevance of *H. pylori* infection to hepatic encephalopathy is unclear.[11]

Investigational therapy has also attempted to affect cerebral function directly. Flumazenil, a benzodiazepine antagonist, has been tried, on the basis of the suspected role of endogenous benzodiazepine-like agonists.[2,12] A systematic review[13] concluded that flumazenil did produce short-term improvement of hepatic encephalopathy but had no effect on recovery or survival; it might be considered for patients with chronic liver disease and hepatic encephalopathy but routine clinical use was not recommended. Similarly, although dopaminergics such as levodopa or bromocriptine have been given, on the grounds that impaired dopaminergic neurotransmission may play a role in the syndrome,[2] evidence to support their use was not forthcoming from a systematic review.[14]

Liver transplantation (p. 1936.3) is the ultimate therapy for end-stage cirrhosis, acute liver failure, or patients with severe refractory hepatic encephalopathy.[4]

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Inflammatory bowel disease

Inflammatory bowel disease (IBD) covers chronic non-specific inflammatory conditions of the gastrointestinal tract, of which the two major forms are *Crohn's disease* and *ulcerative colitis*.

Crohn's disease is characterised by thickened areas of the gastrointestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas; affected areas may occur in any part of the gastrointestinal tract, interspersed with areas of relatively normal tissue; the terminal ileum is frequently involved. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss, and rectal bleeding. Extra-intestinal manifestations may include joint inflammation, skin lesions, mouth ulcers, and liver disorders.

In **ulcerative colitis**, disease is confined to the colon and rectum, inflammation is superficial but continuous over the affected area, and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis); in severe disease, ulceration is extensive and much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication. Symptoms include diarrhoea and rectal bleeding. The extra-intestinal manifestations are similar to those of Crohn's disease.

Drug treatments.

Although there are important differences between Crohn's disease and ulcerative colitis which affect their management, the broad principles of treatment, and the drugs used, are similar.[1-6] The aminosalicylate derivatives are generally the first choice in mild to moderate active disease, and are of particular value for maintenance treatment of ulcerative colitis; the role of maintenance treatment in Crohn's disease is less well established. Corticosteroids are also used in the initial treatment of active disease, dosage and route varying with disease site and severity. Immunosuppressant or biological therapy may be helpful in severe or chronic active disease. For Crohn's disease an elemental diet (see Inflammatory Bowel Disease, p. 2043.2) may have some value in active disease, but diet plays a lesser role in ulcerative colitis.

- Oral sulfasalazine, a **5-aminosalicylate** derivative (5-aminosalicylic acid linked to sulfapyridine), is of value in producing remission of mild ulcerative colitis;[7] results in Crohn's disease have been more equivocal.[4,8]

  The discovery that 5-aminosalicylate was the active component of sulfasalazine led to the development of numerous derivatives, including mesalazine (5-amino-

salicylic acid itself, either used rectally, or orally in slow-release or enteric-coated form), olsalazine (2 molecules of 5-aminosalicylic acid joined by an azo bond), and a variety of forms, such as balsalazide, in which the active moiety was joined to inert carriers. All the above have been shown to be effective in active ulcerative colitis, and may be better tolerated than sulfasalazine, since many of the latter's adverse effects are due to its sulfonamide portion. In patients who can tolerate sulfasalazine, the newer drugs have no clinical advantage for remission induction.[7] Nevertheless, the risk of adverse effects on starting sulfasalazine therapy has led to increasing use of the newer derivatives. The 5-aminosalicylates are also recommended for the maintenance of remission in ulcerative colitis;[3,6,9] in contrast, although they are often used in practice it is unclear that they are of value for maintenance in patients with Crohn's disease.[3-5,10]

- The other major group of drugs used in the treatment of IBD is the **corticosteroids**, particularly for more severe ulcerative colitis, and in Crohn's disease. Rectal use may be appropriate in some patients with distal ulcerative colitis or proctitis; oral prednisone or prednisolone is often used in more severe and extensive disease, and in the most severe cases intravenous corticosteroids (usually hydrocortisone or methylprednisolone) may be given. Unfortunately, treatment of IBD is often prolonged, and adverse effects remain a problem, hence the interest in poorly absorbed or rapidly metabolised corticosteroids such as beclometasone, budesonide, or tixocortol. Oral budesonide is more effective than mesalazine in inducing remission in Crohn's disease and although it may be slightly less effective than conventional corticosteroids, adverse effects are reduced.[11] Corticosteroids are not suitable for maintenance of remission in IBD,[3,12] and inability to withdraw corticosteroid treatment without precipitating relapse (corticosteroid dependence) is a therapeutic challenge.
- Other drugs used in active IBD include **immunosuppressants**. The majority of studies have been with azathioprine, or its metabolite mercaptopurine. Because they have a slow onset of action (months) their use in acute disease is limited, but they are of benefit in remission induction in patients with chronically active disease, particularly corticosteroid-resistant or corticosteroid-dependent disease; they may also be used for maintenance in both ulcerative colitis and Crohn's disease, often with other drugs.[3-6,13,14] Low-dose intramuscular methotrexate also appears to be useful for induction[15] and maintenance[16] of remission in Crohn's disease, although it is often given subcutaneously in practice. Evidence for the oral route is lacking,[15,16] and it does not appear to be of value in ulcerative colitis.[5,6] Conversely, ciclosporin has not generally proved useful in chronically active inflammatory bowel disease but may have some value in the short-term treatment of acute severe ulcerative colitis.[5,17] Tacrolimus also appears to be of benefit in severe ulcerative colitis,[5] and possibly in Crohn's disease;[18] mycophenolate mofetil has been tried, although the limited evidence is equivocal.[18]
- Of increasing importance in the management of severe or refractory forms of IBD are the so-called '**biological therapies**', comprising in particular anti-tumour-necrosis factor antibodies such as infliximab, adalimumab, and certolizumab pegol. These have been shown to be effective for induction therapy and maintenance in Crohn's disease;[5,19,20] infliximab[5,20] and adalimumab[21,22] are also used for induction and maintenance of remission in ulcerative colitis.[5,20] Golimumab is another drug in this group that may be used for ulcerative colitis. The anti-integrin antibody natalizumab is effective in inducing remission in Crohn's disease.[23] Thalidomide, a tumour necrosis factor inhibitor, has also been tried in Crohn's disease with some benefit,[18,24] but another such inhibitor, pentoxifylline, was ineffective.[25]
- **Metronidazole** is useful in fistulising perineal Crohn's disease and may be used in colonic Crohn's disease. It is usually given for 3 months. Ciprofloxacin is an alternative, and has also been given with metronidazole,[26,27] although the combination may not be very well tolerated. There has been interest in the possible causal role of *Mycobacterium paratuberculosis* in Crohn's disease,[28] but a study of 2 years of antituberculous therapy with clarithromycin, rifabutin, and clofazimine in patients with Crohn's disease found no evidence of sustained benefit, suggesting that the organism probably did not play a significant role.[29] In contrast, a meta-analysis[30] of several mostly small studies suggested that long-term treatment with a nitroimidazole such as metronidazole, or with clofazimine, might have benefits in patients with Crohn's disease. Antibacterials do not have a role in ulcerative colitis, except for infection prophylaxis in severe attacks.
- Many **other drugs** are being or have been tried in IBD, including immunoglobulins, some interleukins, interferons, short-chain fatty acids, heparin, factor XIII, rosiglitazone, and aminosalicylic acid (4-aminosalicylic acid as opposed to 5-aminosalicylic acid). There have been some short-term responses to the anti-integrin antibody, vedolizumab,[31] and to the anti-interleukin-12 antibody, briakinumab.[32] There is limited evidence of improvement in disease severity from the use of the granulocyte-macrophage colony-stimulating factor sargramostim,[33] which is thought able to stimulate intestinal innate immune defence processes that may be impaired in Crohn's disease. Other biological therapies which are being investigated include the ICAM-antisense oligonucleotide alicaforsen, the T-cell costimulation blocker abatacept, the anti-CD3 antibody visilizumab, and the CCR9 chemokine receptor inhibitor CCX-282.[34] Nicotine has been tried in ulcerative colitis, based on the observation that the disease is rare in smokers. Studies have suggested that nicotine, supplied via transdermal patch, may have benefit in active disease,[35] although it is ineffective for maintenance.[36] Rectal and oral formulations of nicotine are under investigation.

Nutritional and dietary therapies.

Correction of nutritional deficiencies may be necessary in severe IBD, but dietary modification may also have therapeutic effects. In Crohn's disease, enteral feeding, often with an elemental diet is effective in inducing remission (see Inflammatory Bowel Disease, p. 2043.2), although corticosteroids are more effective;[37] there is also some evidence of benefit in maintaining remission.[38] Elemental diets are useful in children and those unable to tolerate corticosteroids. The role of omega-3 fatty acids has been investigated, but systematic reviews have concluded that they are ineffective for maintenance of remission in Crohn's[39] and ulcerative colitis.[40]

There has been some interest in manipulation of the bowel flora through use of lactobacilli and other probiotic bacteria.[41] There have been some reports of benefit in ulcerative colitis,[42,43] and probiotics may be useful in the management of pouchitis,[3,6] but there is no good evidence to date of benefit in Crohn's disease.[44] The observation that inflammatory bowel disease is uncommon in developing countries where most people carry helminths has led to preliminary studies of bowel colonisation using *Trichuris suis* ova (porcine whipworm) in active Crohn's disease[45] and ulcerative colitis.[46]

Surgery.

In patients with ulcerative colitis surgical colectomy is curative, and may avoid the risks of long-term corticosteroid therapy and the increased risk of bowel cancer to which patients with inflammatory bowel disease are subject. Formation of an ileoanal pouch, which acts as a reservoir for the ileal contents, avoids the necessity for a standard ileostomy and maintains a degree of continence in suitable patients. Curative surgery is not possible in Crohn's disease, since recurrence elsewhere in the gut is almost inevitable, but resection of the affected area becomes necessary in many patients during the course of their illness.

CHOICE OF THERAPY

Ulcerative colitis.

- ACTIVE DISEASE:
  - ***mild to moderate***

    In mild to moderate *distal* disease topical mesalazine, preferably with an oral aminosalicylate (balsalazide, mesalazine, or olsalazine), is the treatment of choice.[3,6] Selected patients may benefit from oral sulfasalazine. Patients intolerant of topical mesalazine may be given a topical corticosteroid instead, though they are less effective.[47] Suppositories are suitable for *proctitis* but foam or liquid enemas are required for more proximal disease (*proctocolitis*).[3] Patients who fail to improve on a combination of oral aminosalicylate with topical mesalazine or corticosteroid may require an oral corticosteroid (e.g. prednisone or prednisolone 40 mg daily).[3,5,48] Infliximab is an alternative.[6]

    In *left-sided* or more *extensive* ulcerative colitis the preferred therapy is an oral aminosalicylate;[3,5,6] olsalazine is best avoided in patients with *pancolitis* as it may be more likely to produce diarrhoea than mesalazine or balsalazide.[3] There is some evidence that the benefits of aminosalicylates are dose related,[5,6] and some controversy exists as to the optimum induction dose: use of higher doses initially may produce better responses,[5,6] but there is an increased risk of toxicity. Some recommend the addition of topical aminosalicylates as the combination is considered more effective than oral treatment alone.[48]

    Patients who fail to respond to aminosalicylates should be given an oral corticosteroid (as above).[3,6,48] The corticosteroid should be reduced gradually (tapered) over several weeks once response is achieved.[3,6] Since long-term treatment with corticosteroids is undesirable, patients with *chronic active disease* who are at high risk of relapse when the corticosteroid is withdrawn (corticosteroid-dependent disease) should be treated with a thiopurine (azathioprine or mercaptopurine) as a corticosteroid-sparing drug.[3,6,48] Thiopurines may also be effective in inducing remission in some patients who do not respond to oral corticosteroids, although their slow onset of action is problematic.[6] In patients with more extensive, moderate to severe disease, infliximab may be an option.[5,6] Adalimumab and golimumab are also licensed for use in such patients.
  - ***severe***

    Patients who present with severe colitis or who fail to respond to maximal oral treatment should be admitted to hospital for treatment with intravenous corticosteroids.[3,5,6,48] Patients should be given appropriate supportive therapy (including nutritional support if the patient is malnourished, intravenous antibacterials for infection, and blood transfusion if markedly anaemic).[3,6] Intravenous ciclosporin may be a useful option in patients with severe disease who cannot tolerate corticosteroids.[48] Ciclosporin should also be considered as a second-line treatment for those who fail to respond to intravenous corticosteroids within a few days.[3,5,6,48] Infliximab or tacrolimus are also options.[5,6,48] Patients who respond to intravenous ciclosporin may be given oral continuation treatment for 3 to 6 months.[3] Drug therapy is ineffective in up to 40% of patients with severe colitis,[6] and colectomy is an alternative.[3,6]
- MAINTENANCE:

  Lifelong maintenance therapy is generally recommended for patients with ulcerative colitis once remission is achieved, particularly in those with left-sided or more extensive disease, or those with distal disease who relapse more than once a year.[3] The treatment of choice is an oral aminosalicylate,[3,5,6,48] most often mesalazine,[5] although in those that can tolerate it sulfasalazine is possibly more effective.[9] A combination of oral and topical aminosalicylates has been recommended as a second-line maintenance treatment.[48] Topical aminosalicylates alone have been used for maintenance in patients with proctitis, left-sided,[48] or distal disease;[3,5] a combination of oral and rectal aminosalicylates can be used second line.[48] Corticosteroids are ineffective in maintaining remission and associated with severe adverse effects on prolonged use. Azathioprine may be used for maintenance therapy, but is best reserved for patients who relapse frequently despite aminosalicylate maintenance, or who are unable to tolerate such therapy.[3,6,48] Patients with gastrointestinal intolerance of azathioprine may be tried cautiously with mercaptopurine; alternatively, surgery may be considered.[3] Infliximab is also effective for maintenance of remission,[6] especially in patients who remain corticosteroid dependent despite alternative therapies.[5] Golimumab is also used.
- POUCHITIS.

  Ileoanal pouch anastomosis allows for surgical removal of the colon without loss of continence or the need for an ostomy, but subsequent inflammation of the pouch (pouchitis) occurs in about half of all patients.[6] On the basis of limited evidence it is considered to be best treated by a short course of antibacterials (metronidazole or ciprofloxacin).[3,6] If these are ineffective, mesalazine or corticosteroids may be considered.[3] Use of a probiotic formulation, VSL 3, containing a mixture of bacteria, may also be of benefit.[3,6]

Crohn's disease.

- ACTIVE DISEASE:
  - ***mild to moderate***

    First-line therapy in mild to moderate Crohn's disease is a matter of some debate. Oral mesalazine is of limited benefit in *ileal* or *ileocaecal* disease,[4,5] and some consider that it should not be used at all,[5] although others recommend high doses as an appropriate initial therapy.[3] Aminosalicylates may be of more benefit in *colonic* disease, particularly sulfasalazine if it can be tolerated.[3-5] Others favour the use of oral budesonide as first-line therapy for mild to moderate ileocaecal disease;[4,5] although it is somewhat less effective than conventional oral corticosteroids, which are an option in more active disease,[3,4] it produces fewer adverse effects.[11] Opinion also varies on the use of topical mesalazine in colonic disease,[3,4] although it is widely used.[4] Nutritional support (enteral feeding or the use of elemental diets) may be considered as an alternative to drug therapy or surgery in selected patients.[3]
  - ***moderate to severe***

    In outpatients with moderate to severe disease, and those who fail to respond to initial therapy with budesonide or aminosalicylates, conventional oral corticosteroids, typically in a dose corresponding to

40 mg of prednisolone daily (or up to 1 mg/kg daily), are recommended.[3-5] Once response has been achieved, dosage should be gradually tapered off.[3,4]
In patients who have relapsed, azathioprine or mercaptopurine may be added,[4] but they are not best suited to induction of remission because of the delay in onset.[5] Methotrexate may be an alternative in selected patients.[4]
In patients with severe extensive or *fulminant* disease intravenous corticosteroids should be given.[3-5] Adding intravenous metronidazole may be advisable, because of the difficulty of distinguishing active disease from a septic complication.[3] Infliximab should be considered in patients with disease *refractory* to corticosteroids;[3-5] adalimumab or certolizumab pegol may be alternatives.[5]

- ***fistulising disease***
  Simple perianal fistulae can be treated with metronidazole or ciprofloxacin.[3,5] Azathioprine or mercaptopurine are also potentially effective,[3] while infliximab is recommended in patients who do not respond to other treatment.[3,5] An alternative to infliximab is adalimumab.[5] Surgery is appropriate for complex or persistent fistulae.[3,5]
- ***chronic active and corticosteroid dependent disease***
  Azathioprine or mercaptopurine are the drugs of choice in corticosteroid dependent disease.[3] If they are ineffective or not tolerated, intramuscular methotrexate may be considered;[4] it is also considered appropriate for the management of chronic active disease.[3] Infliximab is generally reserved for patients who fail first-line therapy, as an alternative to surgical resection.[3]

- MAINTENANCE:
  The most important intervention in maintaining remission in patients with Crohn's disease is probably to persuade those who smoke to stop smoking.[3] Mesalazine appears to be of limited benefit at best for the maintenance of remission,[3,4,10,49] although it is widely used,[5] and the other aminosalicylates are considered inappropriate.[3,4] Corticosteroids are also not effective for maintenance,[3,4,12] although budesonide may delay relapse for a limited period.[4,5] In patients who required corticosteroids to achieve remission, the usual drug treatment for maintenance is a thiopurine (azathioprine or mercaptopurine).[3-5]
  In patients who achieved remission with intramuscular methotrexate, it may be continued for maintenance;[3] it is also an option in patients intolerant of thiopurines.[4] Thiopurine maintenance may need to be continued for several years,[4] or even indefinitely.[5] Infliximab is also an option for maintenance, particularly in patients brought to remission with the same drug,[3,4] or those who cannot maintain remission or who remain corticosteroid dependent despite the use of maintenance immunosuppression.[5] Alternatives may be adalimumab or certolizumab pegol.[5] To prevent recurrence following surgery, short-term antibacterial therapy with nitroimidazoles has been recommended in those with risk factors for early recurrence, although adverse effects limit longer-term use. Mesalazine has also shown benefit in maintaining a surgically-induced remission, as have azathioprine and mercaptopurine, although the risk of adverse effects is higher with the immunosuppressants. Promising results have been reported from early studies using postoperative infliximab.[50]

Patients with inflammatory bowel disease have an increased risk of developing colorectal cancer and chemoprevention has been investigated. The aminosalicylates have shown a preventive effect in most studies, and there is strong evidence that ursodeoxycholic acid reduces colorectal cancer in patients with ulcerative colitis who also have primary sclerosing cholangitis.[51]

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Irritable bowel syndrome

Irritable bowel syndrome is a functional gastrointestinal disorder of abdominal pain and altered bowel habit; pain is characteristically relieved by defaecation and may be associated with increase or decrease in stool frequency. There may be abdominal bloating. Women are more often affected than men. Most patients have symptoms intermittently, with flares lasting several days followed by periods of remission.[1] Patients may be classified as having different subtypes of the syndrome, depending on the nature of the main symptoms.

Given the heterogeneity of the condition, only a minority of patients will respond to any given treatment, and this together with a high placebo response rate limits the evidence base for treatment.[1-3] The mainstay of treatment is explanation and reassurance, coupled with sensible advice about lifestyle.[1,4] Dietary modification should involve increasing the amount of vegetable fibre in the diet initially (but see below); some patients respond to exclusion of particular foods but this is probably best reserved for more refractory cases, and should not be allowed to compromise proper nutrition.[1]

Formal psychological therapies may be appropriate in some patients, especially if they have other psychological problems such as marked anxiety or depression, or are unwilling to consider symptomatic drug therapy.[1] Hypnotherapy may have a role in refractory patients,[1] but a systematic review, although noting promising results, was unable to confirm benefit.[5]

Many drug treatments have been tried in irritable bowel syndrome. Short-term drug therapy may be useful in managing symptoms,[1-4,6-8] and should be directed according to which predominate:

- in patients in whom *diarrhoea* is predominant, loperamide may be considered; it is preferred to other opioid antidiarrhoeal drugs because it does not pass the blood-brain barrier. Alternatively, colestyramine may be of benefit. The 5-HT_3 antagonist alosetron is also available in some countries for use in women with severe symptoms unresponsive to conventional therapy; it was previously withdrawn due to gastrointestinal toxicity
- in *constipation-predominant* forms of the syndrome fibre supplementation is often advocated. However, insoluble fibre, such as bran, may exacerbate pain and bloating in some patients, and if fibre supplements are to be given, soluble fibre, such as ispaghula, is preferable.[1] The benefits of bulking agents in general have been questioned.[9] An osmotic laxative or stool softener may be added in patients who fail to respond to fibre, but stimulant laxatives should be avoided or used only occasionally.[1] The synthetic peptide linaclotide acts locally to activate guanylate cyclase-C receptors and reduce constipation.[10] Tegaserod, a partial agonist at 5-HT_4 receptors, has also been effective in this group of patients, although it has been withdrawn from the market in many countries due to cardiovascular ischaemic events
- in patients with *abdominal pain*, 'as-needed' antispasmodics may be tried. These should be taken before meals if abdominal pain occurs principally after eating. Examples include alverine, dicycloverine, hyoscine, mebeverine, peppermint oil, and pinaverium. Systematic reviews considered the evidence of benefit to be greatest for hyoscine and its derivatives[11] cimetropium, dicycloverine, trimebutine, and pinaverium;[9] peppermint oil was also considered effective.[9,11] Low-dose tricyclics have been suggested for second-line use in patients unresponsive to antispasmodics.[1] Reviews[9,12] found antidepressants more beneficial than placebo for treating symptoms of irritable bowel syndrome. Tricyclic antidepressants and SSRIs were considered equally effective
- patients whose symptoms are associated with mild or masked *depression* may also obtain benefit from antidepressant therapy; a depressed patient with increased bowel frequency and abdominal pain may benefit from a tricyclic antidepressant, which slows intestinal transit. It has been suggested that patients with constipation may be better treated with an SSRI

Many other drugs have been tried in irritable bowel syndrome, but results have mostly been variable.[2,3] Interest in new pharmacological approaches has included investigation of cholecystokinin antagonists (loxiglumide and dexloxiglumide); 5-HT_4-agonists such as ATI-7505 as well as compounds with mixed actions such as renzapride; κ-opioid agonists such as asimadoline and possibly μ-opioid antagonists such as alvimopan; the 2,3-benzodiazepine receptor modulator dextofisopam; chloride channel activators such as lubiprostone; melatonin; non-absorbed antibacterials such as neomycin or rifaximin, or more promisingly the use of probiotic mixtures of lactic acid-producing organisms; and recombinant human nerve growth factors.[13-15] Many herbal medicines have also been tried: a systematic review found the studies mostly to be small and of poor quality, but suggested that there was evidence of benefit for some herbal combinations including Chinese traditional medicines such as tongxie yaofang.[16]

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Microscopic colitis

Microscopic colitis covers the diseases collagenous colitis and lymphocytic colitis, which are characterised by chronic, watery, non-bloody diarrhoea with intra-epithelial lymphocytic infiltration; in collagenous colitis this is accompanied by a thickened band of collagen immediately below the surface epithelium of the colonic mucosa.[1-4] Although originally considered to be rare, more recent studies have suggested an increased incidence;[2-4] differentiating from the diarrhoea-predominant form of irritable bowel syndrome (p. 1810.3) may be difficult. It has been suggested that the disease is more common in middle-aged women,[2] but others dispute this.[3]

The evidence base for management is limited, and is complicated by the fact that the disease may remit spontaneously.[2-4] Initial measures may include dietary modification, with avoidance of caffeine[2,3] or lactose-containing foods.[2] A possible association with NSAIDs has been suggested; such drugs should be withdrawn, or their use minimised, if possible.[2,3] Drug treatment has been largely empirical, and relapse is quite common once treatment stops. Antidiarrhoeal treatment with loperamide or fibre supplements has been proposed initially.[1-3,5] Systematic review[6] has suggested that budesonide (see also p. 1626.1), and probably bismuth salicylate, are of benefit in collagenous colitis, and they may be considered for second-line therapy.[3] Data from a small study suggested that bismuth salicylate might also be beneficial for lymphocytic colitis, although no firm conclusions could be drawn.[7] In unresponsive patients, sulfasalazine or another 5-aminosalicylate may be considered;[1-3] it has been suggested that mesalazine or olsalazine may be less effective (though better tolerated) than sulfasalazine.[1,2] Other drugs that may be tried in resistant cases include colestyramine, antibacterials such as metronidazole or erythromycin, oral prednisolone, or immunosuppressants such as azathioprine, mercaptopurine, or methotrexate.[1-3,5] Octreotide and verapamil have also been reported to relieve symptoms.[3]

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Mouth ulceration

Recurrent ulceration of the oral mucosa is usually idiopathic and self-limiting and is known as recurrent aphthous stomatitis or recurrent aphthous ulceration. However, oral ulcers (canker sores) may also be caused by mechanical trauma, nutritional deficiencies (particularly iron, folic acid, or vitamin B_{12}), drug reactions, or underlying disease such as Behçet's syndrome (p. 1601.1).

Management includes identifying any underlying disease or nutritional deficiency and treating these as appropriate. Usually no underlying cause can be found, and treatment is purely symptomatic; it may include topical anti-inflammatories, local anaesthetics, antiseptics, astringents, or antihistamines. The value of many of these drugs in reducing symptoms remains anecdotal, and no treatments have yet been proven to reduce the incidence of recurrences.

Where ulceration is due to minor trauma frequent use of a warm saline or compound thymol glycerin mouthwash may be all that is required to relieve discomfort and swelling. Alternatively, pain relief may be obtained with local anaesthetics or analgesics, but their efficacy in oral ulceration is limited by their relatively short duration of action when applied topically. Salicylates are widely used, mainly as choline salicylate gel, although they themselves have the potential for local irritation and ulceration. Benzydamine spray or mouthwash may also be helpful. Lidocaine, as a gel or lozenges, may be of value in pain that has not responded to other measures. Topical corticosteroids are probably the most effective symptomatic treatment for recurrent aphthous stomatitis. Pellets or lozenges of hydrocortisone are allowed to dissolve next to an ulcer, or triamcinolone in an oral paste formulation may be used, although the paste may sometimes be difficult to apply. Mouthwashes have been employed particularly when ulceration is widespread in the mouth and a dexamethasone mouthwash has been used effectively. The healing properties of carbenoxolone have also been employed as a gel or mouthwash, and the mast-cell stabilising agent amlexanox is also used as an oral paste.

Mechanical protection may be provided by a paste or powder of carmellose sodium, although application may be difficult.

Use of an antiseptic mouthwash such as chlorhexidine or povidone-iodine may be helpful, since secondary bacterial infection can delay healing. Chlorhexidine is also available as a gel. Tetracyclines, used as mouthwashes, reportedly reduce ulcer pain and duration, but their potential for adverse effects if swallowed must be borne in mind. Use of hydrogen peroxide 3% is inadvisable, as it can cause ulceration, but application of a 1.5% solution to individual ulcers, with a topical corticosteroid, may be helpful in producing resolution.

Many other drugs have been tried in aphthous ulceration. Sucralfate may be of benefit. Drugs such as levamisole and thalidomide, although possibly beneficial, are unlikely to be suitable in most cases because of their adverse effects, although thalidomide is used, for example, for aphthous stomatitis in patients with AIDS. Pentoxifylline, which, like thalidomide, inhibits tumour necrosis factor production, has been used in patients with minor recurrent aphthous ulceration. Systemic corticosteroids are generally reserved for cases with severe underlying disease.

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Nausea and vomiting

Vomiting follows stimulation of the vomiting centre in the medulla of the brain. This may be via the chemoreceptor trigger zone, which is sensitive to many drugs and to certain metabolic disturbances, or from actions on other areas such as the vestibular apparatus of the ear (in motion sickness), the cerebral cortex (in psychogenic vomiting), and multiple peripheral receptors. In adults vomiting is almost invariably preceded by a sensation of nausea.

In situations where it can be anticipated, such as motion sickness, surgery, and cancer therapy, antiemetic drugs are given prophylactically, but if this fails they may need to be given therapeutically. Vomiting of unknown origin should ideally not be treated until the underlying cause has been found. If vomiting is prolonged, dehydration, hypokalaemia, and alkalosis may occur and replacement of fluid and electrolytes may be necessary, especially in young children and the elderly.

Cancer chemotherapy. Nausea and vomiting are common adverse effects of cancer chemotherapy and for many patients represent a major drawback to treatment. Once experienced, anticipatory vomiting may occur at the sight of medical staff or a needle and this problem may be severe enough in some cases to hinder or prevent further treatment.

Antineoplastic or cytotoxic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone and a peripheral action on the gastrointestinal tract. The cerebral cortex is probably responsible for anticipatory vomiting. Mechanisms involving 5-HT_3-receptors are important in the pathogenesis of *acute cisplatin-associated vomiting*, whereas different mechanisms are probably involved in *delayed emesis*.

The emetic potential of antineoplastics varies in terms of severity and incidence. A risk classification system, based on the proportion of patients who have emesis in the absence of effective antiemetic prophylaxis, has been developed. Although there are slight variations in published lists,[1-3] examples of risk for some common drugs include:

- *high (more than 90% frequency of emesis)* and can be very severe with chlormethine, cisplatin, high-dose cyclophosphamide, dacarbazine, dactinomycin, oral procarbazine, and streptozocin
- *moderate (30 to 90% frequency of emesis)* with carboplatin, more modest doses of cyclophosphamide, daunorubicin, doxorubicin, epirubicin, oral etoposide, idarubicin, oral imatinib, irinotecan, high-dose methotrexate, oxaliplatin, oral temozolomide, and oral vinorelbine
- *low (10 to 30% frequency of emesis)* with oral capecitabine, etoposide, oral fludarabine, fluorouracil, gemcitabine, lower doses of methotrexate, mitomycin, mitoxantrone, pemetrexed, and taxanes
- *minimal (less than 10% frequency of emesis)* with bleomycin, busulfan, oral chlorambucil, cladribine, oral erlotinib, fludarabine, oral gefitinib, oral hydroxycarbamide, oral methotrexate, rituximab, oral tioguanine, and vinca alkaloids

Emetogenicity may depend to some extent on the dose, route, and schedule of chemotherapy. Some combination therapy has resulted in a higher incidence of vomiting than would be expected from the constituents.

The *onset and duration* of vomiting also varies from drug to drug. For cisplatin the onset may be between 4 and 8 hours after a dose, while the duration may be up to 48 hours or occasionally even longer; a persistent feeling of nausea, and sometimes vomiting, lasting for several days may also occur. After chlormethine, vomiting may begin within a half to 2 hours, whereas after cyclophosphamide there may be a latent interval of 9 to 18 hours, but in both cases vomiting is generally less prolonged than with cisplatin. *Acute emesis* (that occurring within 24 hours of chemotherapy) has generally been easier to control than *delayed emesis* (that occurring more than 24 hours after chemotherapy) or *anticipatory emesis*. In patients whose regimens are given over several days delayed emesis from the initial doses may overlap with acute emesis from later doses.

MANAGEMENT. Guidelines for the management of nausea and vomiting associated with chemotherapy have been produced.[1-3] It is important that effective antiemetic prophylaxis is given from the first course of chemotherapy, to avoid subsequent problems with anticipatory vomiting. With the antiemetic drugs now available it should be possible to control acute emesis; delayed emesis has proved more resistant but new treatments are becoming available. Drugs used in antiemetic regimens have included:

- dopamine antagonists such as metoclopramide, domperidone, and some phenothiazines such as prochlorperazine
- corticosteroids such as dexamethasone
- 5-HT_3 antagonists such as ondansetron

- neurokinin-1 (NK-1) receptor antagonists such as aprepitant
- cannabinoids such as nabilone
- benzodiazepines such as lorazepam
- antihistamines such as diphenhydramine

The choice depends on the emetogenicity of the cancer chemotherapy regimen, as well as factors such as the age of the patient.

- For prophylaxis of *acute emesis* associated with *highly emetogenic chemotherapy*, a 5-HT_3 antagonist with dexamethasone and aprepitant (or fosaprepitant) is recommended.[1-3] At equipotent doses, dolasetron, granisetron, ondansetron, and tropisetron are effective and equally safe.[1,2] Palonosetron, which has a prolonged action, may also be used.[2] High-dose metoclopramide was formerly used, but frequently caused extrapyramidal adverse effects, particularly in patients under 30 years of age; diphenhydramine was used to reduce these effects
- For prophylaxis of *acute emesis* associated with *moderately emetogenic chemotherapy*, dexamethasone with a 5-HT_3 antagonist is suggested.[1-3] Aprepitant (or fosaprepitant) may be added for patients given an anthracycline and cyclophosphamide or other chemotherapy drugs of moderate emetic risk
- Dexamethasone alone may be used for prophylaxis with chemotherapy of *low emetic risk*;[1-3] alternatives include prochlorperazine or metoclopramide.[2] No routine prophylactic antiemetic needs to be given for chemotherapy of *minimal emetic risk*;[1-3] however, as-needed or prophylactic use of dexamethasone, a phenothiazine, or metoclopramide is common, particularly for patients with poor emetic control during previous therapy[1]
- Lorazepam may be used for its amnestic, sedative, and anxiolytic effects as an adjunct to antiemetics when *anticipatory emesis* is a problem
- Good control of acute emesis is important in preventing *delayed emesis*. In addition, for prophylaxis of delayed emesis from highly emetogenic chemotherapy, a combination of dexamethasone with aprepitant may be used. After moderately emetogenic chemotherapy, prophylaxis with a single drug such as dexamethasone or a 5-HT_3 antagonist may be sufficient.[1,3] Aprepitant or dexamethasone alone has been suggested for patients given an anthracycline with cyclophosphamide[1,3]

Cannabinoids such as dronabinol and nabilone have been used for chemotherapy-induced nausea and vomiting, usually as second-line drugs. Although they have some advantages because of their effects on mood, their use is limited by adverse effects.[4]

If *breakthrough emesis* occurs, management is often difficult. The general principle of treatment is to add an additional antiemetic from a different class; multiple concurrent drugs, perhaps in alternating schedules or by alternating routes may need to be considered. Since oral dosage may not be feasible because of ongoing vomiting, treatment is often given by the rectal or intravenous routes.[2] More intensive prophylactic treatment should be considered in subsequent courses.

Motion sickness has been described as a normal reaction to stimuli that occur during passive transportation and to which the individual is not adapted. The term embraces all forms of travel sickness including sea sickness, car sickness, train sickness, and air sickness. It is a type of vertigo in which autonomic symptoms predominate, therefore signs and symptoms include pallor, sweating, increased salivation, yawning, malaise, and hyperventilation.

MANAGEMENT. The aim is to *prevent* motion sickness and antiemetics are more effective if given prophylactically before nausea and vomiting has developed. The principal drugs used are the antimuscarinic hyoscine and some of the centrally acting antihistamines.[5,6] In some countries dexamfetamine has been tried,[6] although its adverse effects and the risk of abuse make it an unlikely choice. Antiemetic drugs *not* effective against motion sickness include metoclopramide, domperidone, chlorpromazine, and 5-HT_3 antagonists. Ginger has been tried. Evidence for the value of wrist acupressure is equivocal.[6]

For short-term protection against motion sickness hyoscine hydrobromide has been shown to be effective.[7] It can be taken orally about 30 minutes before a journey followed by further doses every 6 hours if necessary. Transdermal hyoscine has a longer duration of action, but the patches need to be applied to the skin several hours before travelling.

There is little good evidence comparing the efficacy of antihistamines with hyoscine against motion sickness,[7] but they are often better tolerated. They are usually given orally and include cinnarizine, cyclizine, dimenhydrinate, meclozine, and promethazine; all have similar efficacy, but differ in onset and duration of action and in the extent of adverse effects such as drowsiness. Their antimuscarinic properties may contribute to their effects. Non-sedating antihistamines (e.g. astemizole and terfenadine) penetrate poorly into the CNS and do not appear to be effective against motion sickness.

Once motion sickness has developed, gastric motility is inhibited and oral antiemetics are unlikely to be effective. Where intramuscular injection is feasible, promethazine appears to be the most effective treatment. If exposure is likely to be prolonged, transdermal hyoscine may be useful, but will not provide benefit for some hours.[6]

Palliative care. Nausea and vomiting are common in terminal illness, and may be prolonged. Causes may include gastric irritation or stasis, bowel obstruction, renal failure, hypercalcaemia, raised intracranial pressure, infection, or the effects of drugs or radiation; anxiety, cough, and pain may exacerbate the condition.[8-11]

MANAGEMENT. Management will depend on the cause of the nausea and vomiting.[9,10] The evidence base for many antiemetics in terminal care is poor; it is perhaps best for metoclopramide, but evidence for many common and apparently effective interventions, such as haloperidol, cyclizine, and levomepromazine, is conflicting.[12] However, guidelines have been developed, either empirically or based on considerations of the likely causes. Recommendations include:[9]

- any correctable causes should be managed appropriately, and treatment for exacerbating conditions (such as anxiety) given
- an appropriate antiemetic should be given immediately, and repeated as often as necessary. If nausea is continuous or vomiting frequent, subcutaneous injection or continuous subcutaneous infusion may be preferred to the oral route. The usual initial choice for palliative care in the UK is between metoclopramide (preferred if the cause is gastric stasis, gastritis, or functional bowel obstruction), haloperidol (favoured in drug-induced vomiting, hypercalcaemia, and renal failure), and cyclizine (raised intracranial pressure, motion sickness, organic bowel obstruction)
- if treatment fails an alternative drug may be considered, or combination therapy may be necessary (prokinetics such as metoclopramide should not be combined with antimuscarinic drugs as their actions are antagonistic). Dexamethasone (usually added to the regimen), or levomepromazine or olanzapine (broad-spectrum antiemetics; these are usually substituted for the previous regimen) are useful where first-line drugs fail. Olanzapine is usually used if levomepromazine is too sedative. Other phenothiazines, notably prochlorperazine, and the phenothiazine antihistamine promethazine, are sometimes still used, but chlorpromazine is less effective than levomepromazine where a broad-spectrum drug is required. The role of 5-HT_3 antagonists is limited but they may be useful in nausea and vomiting secondary to chemotherapy (above) or radiotherapy (below), or sometimes in bowel obstruction or renal failure
- if there is colic or a need to reduce secretions, hyoscine butylbromide should be given, alone or with cyclizine. If this is inadequate in patients with obstruction, octreotide may be helpful

Non-drug measures may include appropriate diet and avoidance of unpleasant odours, adequate hydration, and regular mouth care.[8,10] Acupressure and acupuncture may provide some benefit.[10,13]

Postoperative nausea and vomiting (PONV) is a common and distressing adverse effect of anaesthesia and surgery;[14-18] it is seen in some 20 to 30% of patients undergoing surgery under general anaesthesia,[15,16,19] and is perceived by patients as a problem comparable to postoperative pain.[20]

Risk factors for PONV include a history of motion sickness or previous PONV, female sex, not smoking, use of opioids during or after surgery, use of volatile inhaled anaesthetics or nitrous oxide, and prolonged surgery.[15-19,21,22] It is widely considered that certain types of surgery carry an increased risk, but it is unclear whether the increase is due to the type of surgery or independent risk factors.[15,16] A study comparing various predictive models found that none was perfect, but that a simplified model based on history, sex, smoking status, and opioid use was as effective as more complex methods.[21]

MANAGEMENT. Prediction of risk is of value since much of the management of PONV focuses on prevention. It is generally agreed that prophylaxis should be reserved for patients at moderate to high risk. In these, various strategies may be adopted to *reduce risk* where possible, including the use of regional anaesthesia or total intravenous anaesthesia with propofol (but see also p. 1910.2), avoidance of nitrous oxide, minimal use of opioids, adequate hydration (especially with colloids), and possibly the use of intraoperative supplemental oxygen (although not all studies found this of benefit).[15,16] Avoidance of high-dose neostigmine (limiting the dose to a maximum of 2.5 mg in adults) has also been suggested.[16] There is evidence that some nonpharmacological interventions, such as acupuncture of the P6 point, may also be effective, especially for nausea.[23]

Many types of drugs have been tried as *prophylactic antiemetics*. These include the 5-HT_3 antagonists, phenothiazines such as prochlorperazine, butyrophenones such as droperidol, antihistamines such as promethazine, cyclizine, or dimenhydrinate, and some other drugs such as dexamethasone and hyoscine.[18,22] A large and well-designed multicentre study (IMPACT) has shown that ondansetron, droperidol, and dexamethasone are of similar efficacy;[24] it also confirmed that avoidance of volatile anaesthetics and nitrous oxide was of as much benefit in preventing PONV as use of a prophylactic antiemetic. The evidence suggests that other 5-HT_3 antagonists are of similar efficacy to ondansetron.[16] Evidence for some of the older drugs is less extensive, although benefit has often been shown in individual studies.[16] Systematic reviews have confirmed the benefit of prophylaxis with dimenhydrinate[25] and transdermal hyoscine[26] but have suggested that metoclopramide, which has been widely used, is in fact of little value in preventing PONV,[27,28] perhaps because the doses used are too low.[28] However, another systematic review[29] included metoclopramide in a list of drugs that reliably prevented PONV compared with placebo; other drugs listed were cyclizine, dexamethasone, dolasetron, droperidol, granisetron, ondansetron, and tropisetron. Ginger root has also been suggested, but again does not seem to be effective in this context,[30] although there is some evidence of benefit for intramuscular ephedrine.[31] Clonidine has also been reported to produce benefit,[32,33] possibly secondary to reduced sympathetic tone and lower use of inhalation anaesthetics and opioids. Neurokinin-1 antagonists such as aprepitant may also be effective.[22]

In patients at moderate risk of PONV, therefore, in addition to risk reduction, use of 1 or 2 prophylactic antiemetics may be considered,[15,16] such as a 5-HT_3 antagonist, droperidol (although concerns about effects on QT interval have restricted its availability), or dexamethasone; or perhaps transdermal hyoscine, dimenhydrinate, or another drug such as promethazine or a heterocyclic phenothiazine (prochlorperazine or perphenazine). In patients at higher risk, or in whom nausea and vomiting would be particularly problematic, a combination of antiemetics from different classes should be given,[15,16] since the IMPACT study has shown that the effects of such interventions are additive.[24]

If PONV develops, *treatment* will depend on whether prophylaxis was given. In patients who have received no prophylaxis, or only dexamethasone, a small dose of a 5-HT_3 antagonist has been recommended.[15,16] If PONV occurs within 6 hours of surgery despite antiemetic prophylaxis, additional doses of the same drug convey no further benefit, and treatment with drugs from another class is recommended.[15,16,18,22] Beyond this time any suitable drug may be used, but dexamethasone and transdermal hyoscine are not recommended for treatment because of their slow onset of action.[16]

Pregnancy. Nausea and vomiting or 'morning sickness' is common in the first trimester of pregnancy, but is generally mild and does not require drug therapy. Dietary modification such as eating small frequent carbohydrate meals is widely thought to be helpful.[34] A systematic review has suggested that pyridoxine, which has been shown to be of benefit, should be tried first if drug therapy is required.[34] Benefit has also been reported with ginger root,[34,35] but evidence of benefit from stimulation of the P6 acupuncture point is ambiguous.[34] Antihistamines such as buclizine, dimenhydrinate, hydroxyzine, meclozine, promethazine, and thiethylperazine have also been tried, and appear to be more effective than placebo,[34] but there are obvious concerns about potential effects on the fetus (see Pregnancy, under Precautions for Antihistamines, p. 614.2). Although no real evidence of a teratogenic effect exists,[36] therapy has tended to be reserved for severe cases, and short-term use. In some countries metoclopramide has been widely used; there is evidence for a lack of adverse effects on the fetus,[37] but younger mothers may be at increased risk of extrapyramidal effects.

Persistent vomiting and severe nausea may progress to *hyperemesis gravidarum* if adequate hydration cannot be maintained; the condition occurs in up to 1% of pregnancies.[38] Management of hyperemesis includes hospitalisation for intravenous fluid and electrolyte replacement, and this is usually sufficient. Routine thiamine supplementation, orally if tolerated, otherwise parenterally, has been recommended to reduce the risk of Wernicke's encephalopathy[38,39] (see Wernicke-Korsakoff Syndrome, p. 2103.3), although there is some dissent from this view.[40] If hyperemesis fails to respond to rehydration, antiemetics should be used; options include domperidone, phenothiazines, and antihistamines.[38] It has been suggested that hyperemesis unresponsive to conventional therapy may respond to oral prednisolone or intravenous hydrocortisone.[38] There have also been anecdotal reports of ondansetron being used successfully in life-threatening

hyperemesis gravidarum unresponsive to conventional treatment,[41] although a double-blind pilot study found it to be no more effective than promethazine.[42] A systematic review found no evidence of benefit for any intervention in hyperemesis gravidarum.[34]

After a review[43] of the data the American Gastroenterological Association Institute considered[44] that metoclopramide, prochlorperazine, promethazine, trimethobenzamide, and ondansetron were of low risk in pregnant women and could be used for nausea and vomiting and for hyperemesis gravidarum.

Radiotherapy. The risk of emesis with radiotherapy varies with the treatment given, particularly the area of the body irradiated. However, emetic risk, and recommendations for use of antiemetics, are less clearly defined than in the situation of chemotherapy-induced nausea and vomiting.[1] Use of a prophylactic 5-HT_3 antagonist with or without dexamethasone is usually recommended in patients receiving radiation to the upper abdomen or total body irradiation.[1,2] For radiotherapy of minimal emetogenic potential, treatment on an as-needed only basis has been suggested.[1]

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Oesophageal motility disorders

Oesophageal disorders, many due to disturbances in oesophageal motility, may produce non-cardiac chest pain, similar to that of angina pectoris, from which they must be differentiated.

Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. It is accompanied by dilatation and abnormal peristalsis in the oesophagus, which becomes a reservoir for the unassimilated matter; symptoms include dysphagia and sometimes pain. The treatment of choice is mechanical dilatation of the sphincter or surgery. Laparoscopic techniques have reduced the risks associated with surgery, and this may become the preferred treatment. Taking isosorbide dinitrate or nifedipine before eating results in some improvement in achalasia, but these drugs have a role only as a temporary measure, or when other options are not suitable. Sildenafil is under investigation. More recently, injection of botulinum toxin into the lower oesophageal sphincter has been found to be effective, but remission in the long-term is better with mechanical dilatation than botulinum toxin. Therefore, it has been recommended that botulinum toxin be reserved for patients thought to be at risk from mechanical dilatation or surgery.

Oesophageal spasm, although frequently asymptomatic, can produce dysphagia and pain. Drug treatment of diffuse oesophageal spasm, or its variant 'nutcracker oesophagus' which is characterised by high amplitude peristalsis in the oesophagus, is often ineffective. Antimuscarinic antispasmodics, nitrates, and calcium-channel blockers have been tried in an attempt to relax the smooth muscle, but results are often disappointing; experience with nifedipine in patients with nutcracker oesophagus suggests that decrease in oesophageal pressure may not correlate with reduction in pain. As with achalasia, minimally invasive surgery is effective for these conditions. Sildenafil is also under investigation.

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Peptic ulcer disease

Peptic ulceration is a common condition consisting of a distinct break in the gastrointestinal mucosa, usually of the stomach or duodenum. Duodenal ulcers are rarely malignant but gastric ulcers are more commonly associated with malignancy.

The aetiology of peptic ulcer disease is probably multifactorial but the bacterium *Helicobacter pylori* plays an important role. Abnormalities of normal mucosal defence mechanisms, and, in the case of gastric ulcer, reflux of duodenal contents into the stomach or delayed gastric emptying may also be involved. Other factors include emotional stress, smoking, alcohol, and drugs such as NSAIDs or corticosteroids.

Peptic ulcer disease usually presents as dyspeptic pain, sometimes associated with nausea, vomiting, anorexia, heartburn, or bloating. Patients may develop complications such as bleeding, obstruction, or perforation.

Certain simple measures such as bed rest, dietary modification, and cessation of smoking, may accelerate ulcer healing, but these play an adjuvant role, and the basis of treatment is pharmacological. Treatment is aimed at eradicating *H. pylori* with antibacterials and neutralising or inhibiting acid activity with antisecretory drugs. Surgical treatment is used in patients with acute complications such as perforation, haemorrhage, obstruction, or pyloric stenosis, or in patients with recurrent or intractable ulcer disease, or where there is suspicion of malignancy.

Anti-Helicobacter therapy. The presence of *H. pylori* should usually be confirmed before therapy to eradicate the infection is started. The urea breath test is the most widely used method to test for *H. pylori*, but may produce false-negatives if used during or too soon after treatment with proton pump inhibitors (see Helicobacter Infection under Precautions for Omeprazole, p. 1870.2) or antibacterials. There is good evidence that eradication therapy has benefits both in healing ulcers and preventing recurrence, especially for duodenal ulcer.[1] Many different regimens have been tried, using various combinations of oral antibacterials with antisecretory drugs. Expert consensus is that any treatment regimen should achieve at least 80% eradication of *H. pylori*,[2] and the most appropriate regimen may therefore depend to some extent on local patterns of resistance.

The following recommendations have been made by an international expert group:[2]

- ***where clarithromycin resistance is below 15 to 20%***
  - **triple therapy** with a proton pump inhibitor (PPI), clarithromycin, and metronidazole (provided the prevalence of metronidazole resistance is less than 40%), for 14 days
    or
    PPI, clarithromycin, and amoxicillin, for 14 days
    or
  - **quadruple therapy** with a bismuth compound, a PPI, and two antibacterials, for 14 days. Such a regimen as used in the UK (usually for rescue therapy, see below) comprises a proton pump inhibitor with tripotassium dicitratobismuthate, tetracycline, and metronidazole.
  - Treatment for 7 days rather than 14 may be acceptable where local studies show it to be effective (in the UK, the *BNF* considers that adverse effects and poor compliance are likely to offset any therapeutic gain from 14-day regimens)
- ***in areas of high clarithromycin resistance*** it may be appropriate to consider antibacterial susceptibility testing before beginning treatment; regimens that may be considered include:
  bismuth-containing quadruple therapy as above
  or
  PPI, amoxicillin, and metronidazole (provided metronidazole resistance is low)
  or
  PPI, tetracycline, and metronidazole
- testing to confirm eradication, at least 4 weeks after treatment, is recommended; a urea breath test is the preferred method
- rescue treatments in patients with refractory disease should be based on antibacterial susceptibility testing. In the UK, the *BNF* considers that the bismuth-based quadruple therapy regimen referred to above may be effective.
- other antibacterials that have been investigated in eradication regimens (mainly as rescue treatments) include rifabutin and levofloxacin, although there might be concerns about selecting for mycobacterial resistance if the former were to be used widely, and increasing fluoroquinolone resistance may limit the value of the other

There is some evidence that a **sequential regimen** of a PPI with amoxicillin for 5 days, followed by the PPI with a nitroimidazole antibacterial (tinidazole) and clarithromycin for a further 5 days, is more effective than a standard 7- or 10-day triple therapy regimen in treatment-naive patients.[3] The potential value of such regimens remains to be more widely proven.[2,4]

The use of **dual therapy** regimens comprising a PPI and an antibacterial is no longer recommended. Similarly, although acid suppressive therapy has sometimes been continued after completing eradication therapy, the *BNF* considers this unnecessary, unless the ulcer is large or complicated by bleeding or perforation.

Before the advent of *H. pylori* eradication therapy, drug treatment of gastric and duodenal ulcers relied mainly on antisecretory therapy. Four to 8 weeks of H_2-antagonist or proton pump inhibitor therapy was required for ulcer

healing. Because of the high incidence of relapse, these drugs were then often given as maintenance therapy. Numerous other drugs were formerly used in peptic ulcer disease before the development of H_2-antagonists and proton pump inhibitors, including antacids, antimuscarinics such as pirenzepine, and mucosal protectants such as sucralfate.

NSAID-induced ulceration. The ulcerogenic effects of NSAIDs have been attributed to inhibition of prostaglandin synthesis and mucosal cell proliferation, and the ulcers they cause may differ from non-iatrogenic ulcers in their pathology and prognosis.[5,6] As many as 25% of chronic NSAID users will develop ulcers, and 2 to 4% will bleed or perforate.[7] Although considered to be independent risk factors for peptic ulcer disease, *H. pylori* infection and NSAID use may act synergistically in peptic ulceration and ulcer bleeding.[8,9] If peptic ulceration develops during treatment with an NSAID the drug should be withdrawn if possible. If this can be done, the ulcer may be treated with an antisecretory drug such as an H_2-antagonist or PPI given for 4 to 8 weeks. If NSAIDS have to be continued, *treatment* is with antisecretory drugs or the prostaglandin analogue misoprostol.[5,6] Ulcers tend to heal more slowly with H_2-antagonists if NSAIDs are continued, whereas the rate of ulcer healing with PPIs appears not to be affected. There is also some evidence that omeprazole is more effective at healing NSAID-associated ulceration than misoprostol.[10] Patients at high risk of NSAID-associated gastrointestinal complications, including those with a history of these events, should receive *prophylactic therapy* if NSAID treatment is absolutely necessary.[5-7] A systematic review[11] concluded that misoprostol, PPIs, and double-dose H_2 antagonists are effective at preventing chronic NSAID-associated gastric and duodenal ulcers. Standard doses of H_2-antagonists prevent NSAID-associated duodenal ulceration, but appear to be less effective in preventing gastric ulceration. Another systematic review also found that misoprostol, and probably PPIs, were effective in reducing the risk of symptomatic NSAID-associated ulceration, as was the use of specific inhibitors of cyclo-oxygenase-2 such as celecoxib;[12] use of a cyclo-oxygenase-2 inhibitor with a PPI may be appropriate in very high risk patients.[13] After healing of NSAID-associated ulceration, prophylaxis with a proton pump inhibitor was more effective at preventing recurrence than an H_2 antagonist,[14,15] and omeprazole was more effective and better tolerated than misoprostol.[10] Whether *H. pylori* eradication is appropriate in patients receiving long-term NSAIDs remains debatable. There is some evidence that eradication reduces the risk of bleeding in patients who have not previously taken NSAIDs,[2,16] and testing and eradication in patients taking PPIs long-term for prevention of NSAID-induced ulceration has been advocated by an expert consensus, since there is evidence that combination of *H. pylori* infection and long-term acid suppression may accelerate the development of pre-malignant changes in the stomach.[2] However, PPI maintenance is more effective than *H. pylori* eradication in preventing ulcer recurrence or bleeding in patients taking NSAIDs,[2] and there is no convincing evidence that eradication speeds ulcer healing.[16]

Stress ulceration may occur in the stomach or the duodenum after major physical trauma such as burns or surgery, or after severe sepsis or illness. H_2-antagonists and sucralfate are widely used for the prevention of stress ulceration in high-risk patients in intensive care units,[17-19] and prophylactic therapy is increasingly used, though with little evidence, in less severely ill patients.[20] Pirenzepine is used in a few countries, and some[17] prefer it in neurosurgical patients and those with head trauma. H_2-antagonists may be given orally, by nasogastric tube, or by the intravenous route (intermittent or continuous). Meta-analysis has indicated that sucralfate may be as effective as an H_2-antagonist in reducing bleeding, and is associated with lower rates of mortality and pneumonia.[21] For discussion of the possible increased risk of infections with acid suppressing drugs, see Infection, under Omeprazole, p. 1870.1. The findings of a subsequent large randomised study[22] by the same authors were at odds with those of this meta-analysis, suggesting that intravenous ranitidine was more effective than sucralfate given orally or via nasogastric tube in reducing clinically significant gastrointestinal bleeding. Moreover, there was no difference in rate of ventilator-associated mortality between ranitidine and sucralfate recipients. A further meta-analysis[23] has in turn raised doubts about the efficacy of ranitidine; no significant benefit was found for ranitidine, compared with placebo, in the prevention of bleeding. One clinical guideline suggests that, given the conflicting evidence, the choice between antacids, H_2-antagonists, and sucralfate be made on an institutional basis.[18] PPIs are also used for stress ulcer prophylaxis, although evidence for such use is lacking.[19]

Bleeding ulcer. Peptic ulceration is responsible for about 50% of all cases of upper gastrointestinal bleeding: the condition is potentially life-threatening and in severe cases prompt resuscitation with intravenous fluids and blood may be required. About 80% of patients will stop bleeding spontaneously without recurrence, but the remaining 20% are at risk of severe morbidity or death,[24] and early stratification into low- and high-risk categories on the basis of clinical and endoscopic criteria is important for proper management.[24,25] No treatment may be needed for low-risk patients, but those with a clot in an ulcer bed should undergo irrigation and appropriate treatment of the underlying lesion, and high-risk patients should be given immediate endoscopic injection therapy for haemostasis.[24]

Many different solutions have been used for endoscopic injection, including adrenaline (alone or with sclerosants such as monoethanolamine or lauromacrogol), alcohol, fibrin glue, sodium tetradecyl sulfate, thrombin, or saline (normal or hypertonic). None has been clearly shown to be superior,[24] but sclerosants and alcohol increase the risk of complications such as perforation and necrosis compared with adrenaline.[25] Adrenaline injection 1 in 10 000 is commonly used; a large volume (over 13 mL) is considered more effective at achieving sustained haemostasis than smaller volumes.[25] Thermal, laser, or multipolar (coaptive) or plasma electrocoagulative endoscopic techniques are also of benefit, and again there is no clear evidence to prefer one over another.[24] The use of mechanical clips may also be effective.[24,25] A combination of endoscopic therapies may be of greater benefit than monotherapy.[24,25] If endoscopic treatments fail to stop bleeding, or rebleeding occurs, further endoscopic therapy may be considered, but otherwise patients require surgery,[24,25] or selective arterial embolisation.[25]

There is good evidence from systematic review[26] that treatment with PPIs reduces rebleeding and surgery in patients with acute bleeding peptic ulcers; one such review did not show reduced mortality,[26] although others consider it to have been proven.[24] An intravenous bolus of a PPI followed by continuous infusion for 72 hours is recommended in patients who have undergone successful endoscopic therapy.[24,25] There is no evidence that any PPI is superior to others.[24,27] Some suggest that high-dose PPI therapy (oral or intravenous, depending on the degree of risk) should also be considered in patients awaiting endoscopy.[24]

In contrast, there is no evidence that H_2-antagonists are of benefit in the treatment of acute non variceal bleeding, and somatostatin, octreotide, or tranexamic acid are not recommended.[24,25,28]

Eradication of *H. pylori* is recommended in those patients positive for the organism;[24,25] eradication therapy is superior to antisecretory drugs alone in preventing rebleeding.[29]

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Zollinger-Ellison syndrome

Zollinger-Ellison syndrome is a rare disorder characterised by the presence of a gastrin-producing tumour (gastrinoma), which leads to hypersecretion of gastric acid and consequent peptic ulcer disease (often with complications such as perforation or bleeding), diarrhoea, or malabsorption. Gastrinomas usually occur in the non-beta islet cells of the pancreas or in the duodenal wall. Up to two-thirds are malignant. About 20 to 25% of cases are seen in patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome.

Initial treatment is aimed at controlling the hypersecretion of gastric acid with an antisecretory drug. Giving enough medication just to control symptoms is not considered adequate, and it is important that acid secretion is reduced below 10 mmol/hour. Intravenous H_2-antagonists or proton pump inhibitors may be required initially. Once the symptoms have been controlled the tumour can be investigated for surgical removal. When complete removal is not possible then antisecretory therapy is continued indefinitely. A proton pump inhibitor is the drug of choice; it profoundly reduces acid secretion with once- or twice-daily use, although relatively high doses are required compared with those used in other conditions. An H_2-antagonist such as cimetidine or ranitidine may be used as an alternative to omeprazole, and, as with omeprazole, daily doses are higher than those used for other conditions; they are given in 3 or 4 divided doses. The somatostatin analogue octreotide can be used to reduce serum gastrin, but has to be given subcutaneously, and is not well tolerated.

Parietal cell vagotomy may be performed to reduce acid secretion if the tumour is not found, to allow lower doses of antisecretory drugs to be used.

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Aceglutamide Aluminium *(rINNM)*

Aceglutamida de aluminio; Aceglutamide Aluminum (USAN); Acéglutamide d'Aluminium; Aluminii Aceglutamidum; KW-110; Алюминий Ацеглутамид.

Pentakis (N^2-acetyl-L-glutaminato)tetrahydroxytrialuminium.

$C_{35}H_{59}Al_3N_{10}O_{24}$=1084.8

CAS — 12607-92-0.

UNII — R7QTG0PMPX.

Pharmacopoeias. In *Jpn.*

Profile

Aceglutamide aluminium, a complex of aceglutamide with aluminium hydroxide, is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2). It is given orally in a usual dose of 700 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Glumal.

Aclatonium Napadisilate *(BAN, rINN)*

Aclatonii Napadisilas; Aclatonium Napadisylate; Celatonium Napadisilate; Choline Naphthalene-1,5-Disulphonate (2:1) Dilactate Diacetate; Napadisilate d'Aclatonium; Napadisilato de aclatonio; SKF-100916-J; TM-723; Аклатония Нападизилат.

2-(2-Acetoxypropionyloxy)ethyltrimethylammonium naphthalene-1,5-disulphonate (2:1).

$2C_{10}H_{20}NO_4.C_{10}H_6O_6S_2$=722.8

CAS — 55077-30-0.

UNII — YX23434YHQ.

Profile

Aclatonium napadisilate is a cholinergic agonist given orally for its prokinetic properties in the management of decreased gastrointestinal motility (p. 1805.2) after gastrointestinal surgery, and to relieve symptoms of biliary dyskinesia and chronic gastritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Abovis.

Acotiamide Hydrochloride *(USAN, rINNM)*

Acotiamide, Chlorhydrate d'; Acotiamidi Hydrochloridum; Hidrocloruro de acotiamida; YM-443; Z-338; Акотиамида Гидрохлорид.

N-{2-[bis(1-Methylethyl)amino]ethyl}-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide monohydrochloride trihydrate.

$C_{23}H_{30}N_4O_5S.HCl.3H_2O$=541.1

CAS — 773092-05-0.

UNII — NMW7447A9A.

Profile

Acotiamide hydrochloride inhibits peripheral anticholinesterase activity which improves gastrointestinal motility and gastric emptying; it is used orally in the symptomatic relief of functional dyspepsia. Adverse effects have included constipation, diarrhoea, and nasopharyngitis; raised triglyceride, liver enzymes, and prolactin levels have also been reported.

References.

1. Nolan ML, Scott LJ. Acotiamide: first global approval. *Drugs* 2013; **73:** 1377–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Acofide.

Albumin Tannate

Albumiinitannaatti; Albúmina, tanato de; Albumini Tannas; Albumintannat; Albutannin; Tannin Albuminate; Альбумин Таннат.

CAS — 9006-52-4.

ATC — A07XA01.

ATC Vet — QA07XA01.

Pharmacopoeias. In *Jpn*.

Profile

Albumin tannate, a compound of tannin with albumin, is given orally for its astringent properties in the treatment of diarrhoea (p. 1805.2). It is stated to liberate tannic acid (p. 2625.2) in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Tannalbin; ***China***: Dan Na Er Bin (单那尔滨); ***Ger.***: Tannalbin; ***Neth.***: Entosorbine-N; ***Pol.***: Taninal.

Multi-ingredient Preparations. ***Austria***: Neoplex; ***Belg.***: Tanalone; ***Fin.***: Tannopon†; ***Ger.***: Tannacomp; ***Hung.***: Bolus Adstringens; ***Pol.***: Salotannal†; ***Spain***: Demusin†; Salitanol Estreptomicina†.

Alexitol Sodium *(BAN, rINN)*

Alexitol sódico; Alexitol Sodique; Alexitolum Natricum; Алекситол Натрий.

Sodium poly(hydroxyaluminium) carbonate-hexitol complex.

CAS — 66813-51-2.

Profile

Alexitol sodium is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2). It is given orally in doses of 360 to 720 mg when required, up to a maximum of sixteen 360-mg tablets in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Actal; ***Malaysia***: Actal†; ***Singapore***: Actal; ***Thai.***: Actal†; ***UK***: Actal.

Multi-ingredient Preparations. ***Malaysia***: Actal Plus†.

Alicaforsen *(rINN)*

Alicaforsén; Alicaforsenum; Аликафорсен.

2′-Deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxyadenosine.

$C_{192}H_{244}N_{75}O_{98}P_{19}S_{19}$=6368.1

CAS — 185229-68-9.

Alicaforsen Sodium *(USAN, rINNM)*

Alicaforsen Nonadecasodium; Alicaforsén sódico; Alicaforsen Sodique; Alicaforsenum Natricum; Isis-2302; Аликафорсен Натрий.

$C_{192}H_{225}N_{75}Na_{19}O_{98}P_{19}S_{19}$=6785.8

CAS — 331257-52-4.

UNII — 4TWN6SZB8W.

Profile

Alicaforsen is an antisense oligonucleotide that inhibits the production of the cellular adhesion molecule ICAM-1, which plays a role in the inflammatory response involved in inflammatory bowel disease. It has been tried in ulcerative colitis and pouchitis, and with less success in Crohn's disease.

References.

1. Barish CF. Alicaforsen therapy in inflammatory bowel disease. *Expert Opin Biol Ther* 2005; **5:** 1387–91.
2. Miner PB, *et al.* Safety and efficacy of two dose formulations of alicaforsen enema compared with mesalazine enema for treatment of mild to moderate left-sided ulcerative colitis: a randomized, double-blind, active-controlled trial. *Aliment Pharmacol Ther* 2006; **23:** 1403–13. Correction. *ibid.*; **24:** 1268.
3. van Deventer SJ, *et al.* A phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2006; **23:** 1415–25.
4. Miner PB, *et al.* Bioavailability and therapeutic activity of alicaforsen (ISIS 2302) administered as a rectal retention enema to subjects with active ulcerative colitis. *Aliment Pharmacol Ther* 2006; **23:** 1427–34.
5. Yacyshyn B, *et al.* A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease. *Clin Gastroenterol Hepatol* 2007; **5:** 215–20.

Alizapride Hydrochloride *(rINNM)*

Alizaprida, hidrocloruro de; Alizapride, Chlorhydrate d'; Alizapridi Hydrochloridum; Hidrocloruro de alizaprida; Ализаприда Гидрохлорид.

N-(1-Allyl-2-pyrrolidinylmethyl)-6-methoxy-1*H*-benzotriazole-5-carboxamide hydrochloride.

$C_{16}H_{21}N_5O_2.HCl$=351.8

CAS — 59338-93-1 (alizapride); 59338-87-3 (alizapride hydrochloride).

ATC — A03FA05.

ATC Vet — QA03FA05.

UNII — 41BT72BOQ7.

Uses and Administration

Alizapride is a substituted benzamide similar to metoclopramide (p. 1862.2), which is used to control nausea and vomiting (p. 1811.3) associated with a variety of disorders. It is given as the hydrochloride but doses are expressed in terms of the base. Alizapride 50 mg is equivalent to about 55.8 mg of alizapride hydrochloride.

Alizapride hydrochloride is given in usual oral doses equivalent to 75 to 300 mg of alizapride daily in divided doses. For children's doses, see below. It is also given by intravenous or intramuscular injection in doses equivalent to 50 to 200 mg of alizapride daily.

For patients receiving cancer chemotherapy usual daily doses equivalent to alizapride 2 to 5 mg/kg have been given intravenously or intramuscularly in 2 divided doses, one 30 minutes before and one 4 to 8 hours after the cytotoxic regimen. For highly emetic regimens requiring doses above 5 mg/kg it may be given by intravenous infusion over 15 minutes every 2 hours for 5 doses, starting 30 minutes before the cytotoxic. It has been recommended that the total dose given with a course of chemotherapy does not exceed 4.5 g.

Administration in children. Alizapride hydrochloride has been given to children for the symptomatic treatment of nausea and vomiting in oral doses equivalent to 5 mg/kg of alizapride daily.

Adverse Effects and Precautions

As for Metoclopramide, (see p. 1863.2).

Pharmacokinetics

Alizapride is well absorbed from the gastrointestinal tract. It is mainly excreted unchanged in the urine and has an elimination half-life of about 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gastriveran; ***Belg.***: Litican; ***Braz.***: Superan; ***Fr.***: Plitican; ***Ger.***: Vergentan; ***Gr.***: Lyostene; ***Ital.***: Limican; ***Neth.***: Litican.

Almagate *(BAN, USAN, rINN)*

Almagaatti; Almagat; Almagát; Almagatas; Almagato; Almagatum; LAS-3876; Альмагат.

Aluminium trimagnesium carbonate heptahydroxide dihydrate.

$AlMg_3(CO_3)(OH)_7.2H_2O$=315.0

CAS — 66827-12-1 (almagate); 72526-11-5 (anhydrous almagate).

ATC — A02AD03.

ATC Vet — QA02AD03.

UNII — 568Z59H7ZJ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Almagate). A white or almost white, fine crystalline powder. It contains 15.0 to 17.0% aluminium calculated as aluminium oxide, 36.0 to 40.0% magnesium calculated as magnesium oxide, and 12.5 to 14.5% carbonic acid calculated as carbon dioxide. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves with effervescence and heating in dilute mineral acids. The filtrate of a 4% suspension in water has a pH of 9.1 to 9.7. Store in airtight containers.

Profile

Almagate is a hydrated aluminium-magnesium hydroxycarbonate. It is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2) and magnesium carbonate (p. 1856.2). It has been given orally in doses of 1 to 1.5 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Almax; ***Spain***: Almax.

Almasilate *(BAN, rINN)*

Almasilato; Almasilatum; Aluminium Magnesium Silicate Hydrate; Magnesium Aluminosilicate Hydrate; Magnesium Aluminum Silicate Hydrate; Алмазилат.

$Al_2O_3.MgO.2SiO_2.xH_2O$=262.4 (anhydrous)

CAS — 71205-22-6; 50958-44-6.

ATC — A02AD05.

ATC Vet — QA02AD05.

UNII — 7TO1453RTL (anhydrous almasilate); OZQ8O62H53 (almasilate monohydrate).

Profile

Almasilate is an artificial form of aluminium magnesium silicate hydrate. It is an antacid (p. 1803.1) that is given orally in doses of up to about 1 g.

A hydrated native aluminium magnesium silicate (p. 2168.2) is used as a suspending, thickening, and stabilising agent in pharmaceutical preparations. Attapulgite (p. 1820.1) is another native form.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Gelusil; Megalac; Simagel; ***Rus.***: Simagel (Симагель); ***Spain***: Alubifar†.

Multi-ingredient Preparations. ***Ger.***: Gelusil-Lac; Neo-Pyodron N†; Ultilac N; ***India***: Entasid; Intacid-MPS; ***Jpn***: Eki Cabe U; ***Spain***: Dolcopin; ***Switz.***: Gelusil N†.

Aloes

Acíbar; Alavijų sultys, koncentruotos ir išdžiovintos (Cape aloes); Áloe, acíbar; Aloe barbadensis (Barbados aloes); Aloe, Barbados (Barbados aloes); Aloe barbadoská (Barbados aloes); Aloe capensis (Cape aloes); Aloe, Kap (Cape aloes); Aloe kapská (Cape aloes); Aloès des Barbades (Barbados aloes); Aloès du Cap (Cape aloes); Alona barbadoska (Barbados aloes); Alona przyłądkowa (Cape aloes); Barbadosi áloé (Barbados aloes); Barbadosin aloe (Barbados aloes); Kapáloé (Cape aloes); Kapin aloe (Cape aloes); Tikrųjų alavijų sultys, koncentruotos ir išdžiovintos (Barbados aloes); Алоэ барбадосское (Barbados aloes); Алоэ Капское (Cape aloes).

CAS — 8001-97-6; 67479-27-0 (aloe gum).

ATC Herb — HA06AB5001 (Aloe ferox: dry leaf juice).

UNII — 0D145J8EME (Aloe ferox leaf); V5VD430YW9 (socotrine aloe).

NOTE. Do not confuse with Aloe vera (p. 1693.2).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Aloes, Barbados; Aloe barbadensis). The concentrated and dried juice of the leaves of *Aloe barbadensis*. It contains not less than 28% of hydroxyanthracene derivatives expressed as barbaloin and calculated with reference to the dried drug. Dark brown masses, slightly shiny or opaque with a conchoidal fracture, or a brown powder. Partly soluble in boiling water; soluble in hot alcohol. Store in airtight containers. Protect from light.

The BP 2014 lists Curaçao Aloes as an approved synonym.

Ph. Eur. 8: (Aloes, Cape; Aloe capensis). The concentrated and dried juice of the leaves of various species of *Aloe*, mainly *Aloe ferox* and its hybrids. It contains not less than 18% of hydroxyanthracene derivatives expressed as barbaloin and calculated with reference to the dried drug. Dark brown masses tinged with green and having a shiny conchoidal fracture, or a greenish-brown powder. Partly soluble in boiling water; soluble in hot alcohol; practically insoluble in ether. Store in airtight containers. Protect from light.

USP 36: (Aloe). The dried latex of the leaves of *Aloe barbadensis* (*A. vera*) known in commerce as Curaçao Aloe, or of *A. ferox* and its hybrids, known in commerce as Cape Aloe (Liliaceae). It yields not less than 50% of water-soluble extractive. It has a characteristic, somewhat sour and disagreeable, odour. Curaçao Aloe is brownish-black, opaque masses with a fractured, uneven, waxy, and somewhat resinous surface. Cape Aloe is dusty to dark brown irregular masses, the surfaces of which are often covered with a yellowish powder. Its fracture is smooth and glassy.

Uses and Administration

Aloes is an anthraquinone stimulant laxative (p. 1804.1) but other less toxic drugs are generally preferred.

Homoeopathy

Aloes have been used in homoeopathic medicines under the following names: Aloe; Cape aloes; Aloe capensis; Aloe socotrina; Alo. soc.

Adverse Effects and Precautions

As for Senna, p. 1885.3, although aloes has a more drastic and irritant action.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Contre-Coups de l'Abbe Perdrigeon; Vulcase; ***Ger.***: HemoClin†; Krauterlax; ***Pol.***: Biostymina; ***Switz.***: HemoClin†.

Multi-ingredient Preparations. ***Arg.***: Genolaxante; ***Austral.***: Peritone; ***Austria***: Artin†; Waldheim Abfuhrdragees forte†; ***Braz.***: Camomila; Paratonico†; Vitonico; ***Canad.***: Friar's Balsam; Laxatil; Laxolax; Traditional Herbal Laxative†; Traditional Laxative; ***Chile***: Aloelax; Bulgarolax†; ***Cz.***: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; ***Fr.***: Alco-Aloe†; Dolores; Elusanes Algues brunes/aloes†; Ideolaxyl; Laxilo†; Opobyl†; Petites Pilules Carters†; Tisane D'Ars†; Tonilax; ***Ger.***: Chol-Kugeletten Neu†; Cholhepan N; ***Hung.***: Bano Svedkeseru; ***India***: Aloederm-B; Aloederm-G; Aloederm; Alorex; Calkem; Clarina; Climdan; Climdan; Clin-3; Cytozen; Danclear; Garlill; Koiz; Livomyn; Lunarex; Marc Free; Paedritone; ***Israel***: Laxative Compound; ***Ital.***: Emoform Alifresh; Grani di Vals†; Lassativi Vetegali†; ***Pol.***: Alax; Apinorm†; Bioaron C; Boldaloin; Boldovera; Tabulettae Laxantes; ***Rus.***: Alorom (Алором); Bioaron C (Биоарон С); Doktor Mom (Доктор Мом); ***S.Afr.***: Helmontskruie†; Lewensessens; Moultons Herbal Extract†; Turulington Tincture†; Wonderkroonessens; ***Singapore***: Nu-Derm Toner; Sankaijo; ***Spain***: Alofedina; Crislaxo; Cynaro Bilina†; Laxadinas†; Laxante Sanatorium†; Nico Hepatocyn; Opobyl; Pildoras Zeninas; ***Switz.***: Padma-Lax; Padmed Laxan; Schweden-Mixtur H; ***UK***: Cassilax; Dual-Lax Normal Strength; Laxative Tablets; Natural Herb Tablets; Out-of-Sorts; Senokot Dual Relief; Sure-Lax (Herbal); ***Ukr.***: Bioaron C (Биоарон С); Doktor Mom (Доктор Мом сироп); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***USA***: Diaparene Corn Starch; Vagisil.

Homoeopathic Preparations. ***Austria***: Haemex; ***Canad.***: Cynara Complex†; ***Fr.***: Aesculus Complexe No 103; Aloe Compose; Ferrum Complexe No 29; Grindelia Complexe No 58; Homeogene 22†; L 25; Poconeol no 82†; Sepia Compose; Yucca Complexe No 110; ***Switz.***: Hemolingual; Regenaplex Nr. 12; Regenaplex Nr. 25b; Regenaplex Nr. 31c; Regenaplex Nr. 3; Regenaplex Nr. 50b; Regenaplex Nr. 59b; Regenaplex Nr. 71b; Regenaplex Nr. 80aN.

Pharmacopoeial Preparations

BP 2014: Compound Benzoin Tincture;
Ph. Eur.: Aloes Dry Extract, Standardised;
USP 36: Compound Benzoin Tincture.

Aloglutamol

Trometamol Glucaldrate; Алоглутамол.

2-Amino-2-hydroxymethylpropane-1,3-diol gluconate dihydroxyaluminate.

$C_{10}H_{24}AlNO_{12}$=377.3

CAS — 13755-41-4.

ATC — A02AB06.

ATC Vet — QA02AB06.

Profile

Aloglutamol has been used as an antacid (p. 1803.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Sabro.

Aloin *(BAN)*

Alloin; Aloína; Алоин.

CAS — 5133-19-7; 8015-61-0; 1415-73-2 (barbaloin).

UNII — W41H6S09F4.

Profile

Aloin is a crystalline substance obtained from aloes (see above). It consists of *C*-glycosides such as barbaloin. Aloin is an anthraquinone stimulant laxative. Like aloes it is very irritant and other less toxic laxatives are generally preferred. Aloin is used as a flavouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Calsalettes.

Multi-ingredient Preparations. ***Austral.***: Ford Pills†; ***Braz.***: Pilulas Ross; ***Canad.***: Bicholate†; ***Israel***: Laxative Compound; ***Ital.***: Boldina He; Cuscutine†; Grani di Vals†; ***Mex.***: Redotex NF; Redotex; ***S.Afr.***: Brooklax Pills†; Doans Backache Pills†; SB 3 Triple Action Pills†; ***Spain***: Laxante Bescansa Aloico†; ***UK***: Dual-Lax Extra Strong; Modern Herbals Laxative.

Alosetron Hydrochloride

(BANM, USAN, rINNM)

Alosétron, Chlorhydrate d'; Alosetrón, hidrocloruro de; Alosetroni Hydrochloridum; GR-68755C; Hidrocloruro de alosetrón; Алосетрона Гидрохлорид.

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-imidazol-4-yl) methyl]-1*H*-pyrido[4,3-*b*]indol-1-one hydrochloride.

$C_{17}H_{18}N_4O$,HCl=330.8

CAS — 122852-42-0 (alosetron); 122852-69-1 (alosetron hydrochloride).

ATC — A03AE01.

ATC Vet — QA03AE01.

UNII — 2F5R1A46YW.

Uses and Administration

Alosetron is a 5-HT_3 antagonist used in the treatment of severe diarrhoea-predominant irritable bowel syndrome (p. 1810.3) in women who have not responded to conventional therapy; efficacy in men has not been established. It is given orally as the hydrochloride but doses are expressed in terms of the base; alosetron hydrochloride 1.12 mg is equivalent to about 1 mg of alosetron.

The initial dose is the equivalent of alosetron 500 micrograms twice daily. Patients who become constipated on this dose should stop alosetron until the constipation resolves; they may then be restarted on 500 micrograms once daily. If constipation recurs at the lower dose, alosetron treatment should be stopped. Patients who tolerate 500 micrograms once or twice daily may continue this dose for 4 weeks. If symptom control is still inadequate after this time, the dose may then be increased up to 1 mg twice daily. If symptoms are not adequately controlled after 4 weeks of treatment with the higher dose, alosetron should be stopped.

References.

1. Lembo A, *et al.* Alosetron in irritable bowel syndrome: strategies for its use in a common gastrointestinal disorder. *Drugs* 2003; **63:** 1895–1905.
2. Mayer EA, Bradesi S. Alosetron and irritable bowel syndrome. *Expert Opin Pharmacother* 2003; **4:** 2089–98.
3. Cremonini F, *et al.* Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2003; **15:** 79–86.
4. Andresen V, Hollerbach S. Reassessing the benefits and risks of alosetron: what is its place in the treatment of irritable bowel syndrome? *Drug Safety* 2004; **27:** 283–92.
5. Lembo AJ, *et al.* Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-predominant irritable bowel syndrome: analysis of two controlled trials. *Clin Gastroenterol Hepatol* 2004; **2:** 675–82.
6. Chey WD, *et al.* Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2004; **99:** 2195–2203.
7. Chang L, *et al.* A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *Am J Gastroenterol* 2005; **100:** 115–23.
8. Rahimi R, *et al.* Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: a meta-analysis of eight randomized, placebo-controlled, 12-week trials. *Clin Ther* 2008; **30:** 884–901.
9. Lewis JH. Alosetron for severe diarrhea-predominant irritable bowel syndrome: safety and efficacy in perspective. *Expert Rev Gastroenterol Hepatol* 2010; **4:** 13–29.

Adverse Effects

Serious gastrointestinal adverse effects have occurred with alosetron, and as a result, it was withdrawn from the market in the USA and subsequently reintroduced with more restricted indications. These adverse effects include severe constipation leading to obstruction, ileus, perforation, impaction, toxic megacolon, and secondary ischaemia, as well as ischaemic colitis. Fatalities have been reported.

Other gastrointestinal effects reported include abdominal distension and pain, nausea, reflux, and haemorrhoids. Adverse effects reported rarely include cardiac arrhythmias, cholecystitis, altered bilirubin levels, tremor, headache, myalgia, malaise, fatigue, and CNS effects such as confusion, anxiety, depression, and sedation. Urticaria, skin reactions, nail disorders, and alopecia can occur. Hyperglycaemia, hypoglycaemia, and disorders of calcium and phosphate metabolism have been reported.

Incidence of adverse effects. The incidence of serious gastrointestinal adverse effects with alosetron has been reviewed.[1,2] Pooled data from clinical studies suggested that the rate of ischaemic colitis in patients taking alosetron was about 0.15%, or 6.4 cases per 1000 patient-years. Results from postmarketing surveillance (before and after its temporary withdrawal from the US market) were estimated to represent a rate of 1 case per 1000 patient-years. Serious complications of constipation are less markedly increased in the population of alosetron users. A meta-analysis of 8 studies[3] reported that the incidence of serious complications of constipation was 0.08% in alosetron users; the incidence of ischaemic colitis was 0.16%. Overall, constipation and abdominal discomfort were the only adverse effects significantly associated with alosetron use, the relative risks being 4.35 and 1.96 respectively.

1. Chang L, *et al.* Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol* 2006; **101:** 1069–79.
2. Chang L, *et al.* Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. *Am J Gastroenterol* 2010; **105:** 866–75.
3. Rahimi R, *et al.* Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: a meta-analysis of eight randomized, placebo-controlled, 12-week trials. *Clin Ther* 2008; **30:** 884–901.

Precautions

Alosetron should be stopped immediately in patients who develop constipation or symptoms of ischaemic colitis such as new or worsening abdominal pain or blood in the stool. Treatment with alosetron should not be resumed in patients who develop ischaemic colitis.

Alosetron should not be used in patients with a history of severe or chronic constipation, intestinal obstruction or stricture, toxic megacolon, or gastrointestinal perforation or adhesions. It is also contra-indicated in patients with a history of ischaemic colitis, impaired intestinal circulation,

thrombophlebitis, or hypercoagulable state, and those with current or previous inflammatory bowel disease or diverticulitis.

Alosetron should not be used in those with severe hepatic impairment or a history thereof; it should be used with caution in patients with mild to moderate hepatic impairment. Elderly patients may be at increased risk of severe complications if constipation develops.

Interactions

Plasma concentrations of alosetron are markedly increased, and its half-life prolonged roughly threefold, when given with fluvoxamine; such a combination should be avoided. Licensed product information recommends that use with other more moderate inhibitors of cytochrome P450 isoenzyme CYP1A2 (such as quinolone antibacterials and cimetidine) should be avoided unless clinically necessary, because of the risk of similar interactions. Ketoconazole also increases plasma alosetron concentrations; care should be taken if alosetron is used with this or other potent inhibitors of the CYP3A4 isoenzyme (including clarithromycin, telithromycin, HIV-protease inhibitors, voriconazole, and itraconazole).

Pharmacokinetics

Alosetron is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations occur about 1 hour after an oral dose. Plasma concentrations are 30 to 50% lower in men than in women given the same oral dose; clearance is lower in women. Bioavailability is about 60%; the extent and rate of absorption are slightly reduced by food. Plasma protein binding is about 82%. Alosetron is extensively metabolised via cytochrome P450 isoenzymes, particularly CYP1A2, although CYP2C9 and CYP3A4 also play a role. Numerous metabolites are excreted in the urine and faeces; only 6% of a dose is recovered unchanged from the urine. The terminal elimination half-life of alosetron is reported to be about 1.5 hours.

References.
1. Koch KM, *et al.* Sex and age differences in the pharmacokinetics of alosetron. *Br J Clin Pharmacol* 2002; **53:** 238–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Lotronex.

Basic Aluminium Carbonate

Aluminium Hydroxycarbonate; Aluminum Carbonate, Basic (USAN); Basic Aluminum Carbonate; Carbonato básico de aluminio; Основный Углекислый Алюминий.

UNII — 1GA689N629.

Profile

Basic aluminium carbonate is a combination of aluminium hydroxide and aluminium carbonate. It is an antacid with general properties similar to those of aluminium hydroxide (below).

Basic aluminium carbonate has also been given orally as a phosphate binder in the treatment of hyperphosphataemia. For a discussion of the choice of phosphate binders, see Renal Osteodystrophy, p. 1170.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Lithiagel.

Multi-ingredient Preparations. ***Port.***: Gastropensan†.

Aluminium Formate

Aluminium Triformate; Aluminum Formate; Муравьинокислый Алюминий; Формиат Алюминия.

$Al(CHO_2)_3.3H_2O$=216.1

CAS — 7360-53-4 (anhydrous aluminium formate).

UNII — 0D34IG724V.

Profile

Aluminium formate has astringent properties and has been used in topical preparations for mouth disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Dynexan Zahnfleischtropfen.

Multi-ingredient Preparations. ***Austria***: Cional; Dynexan; ***S.Afr.***: Dynexan; ***Switz.***: Mucosan†.

Aluminium Glycinate

Aluminio, glicinato de; Aluminum Glycinate; Basic Aluminium Aminoacetate; Dihydroxyaluminum Aminoacetate; Алюминия Глицинат.

(Glycinato-*N*,*O*)dihydroxyaluminium hydrate.

$C_2H_6AlNO_4(+xH_2O)$=135.1 (anhydrous)

CAS — 13682-92-3 (anhydrous aluminium glycinate); 41354-48-7 (aluminium glycinate hydrate).

ATC — A02AB07.

ATC Vet — QA02AB07.

UNII — DO250MG0W6 (aluminium glycinate hydrate); 1K713C615K (anhydrous aluminium glycinate).

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Aluminium Glycinate). A white or almost white, odourless or almost odourless, powder. It contains 34.5 to 38.5% of Al_2O_3 calculated on the dried substance, and not more than 12% loss of weight on drying. Practically insoluble in water and in organic solvents; it dissolves in dilute mineral acids and in aqueous solutions of alkali hydroxides. A 4% suspension in water has a pH of 6.5 to 7.5.

USP 36: (Dihydroxyaluminum Aminoacetate). A white, odourless, powder. It may contain small amounts of aluminium oxide and aminoacetic acid. It loses not more than 14.5% of its weight on drying. Insoluble in water and in organic solvents; soluble in dilute mineral acids and in solutions of fixed alkalis. A 4% suspension in water has a pH of 6.5 to 7.5.

Profile

Aluminium glycinate is an antacid with general properties similar to those of aluminium hydroxide (below). It has been given in oral doses of up to 1.5 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Dafne; ***Austria***: Acidrine; ***Belg.***: Alucid; ***Chile***: Sinacid†; ***Denm.***: Alminox; ***Fr.***: Acidrine; ***Gr.***: Novalox; ***Indon.***: Acidrine; ***Ital.***: Acidrine; ***Pol.***: Proacid†; ***Spain***: Meteoril; Secrepat; ***Thai.***: New Gel; ***Turk.***: Acidrine; Alma; ***Ukr.***: Secrepat Forte (Секрепат Форте).

Used as an adjunct in:. ***Austria***: Indobene; ***Braz.***: Somalgin; ***Chile***: Butartrol; Flexono; ***Ital.***: Aspirina 03; ***Switz.***: Bonidon†; ***USA***: Buffex.

Pharmacopoeial Preparations

USP 36: Dihydroxyaluminum Aminoacetate Magma.

Aluminium Hydroxide

Aliuminio hidroksidas; Alumiinihydroksidi; Aluminii Hydroxidum; Aluminii oxidum hydricum; Aluminium Oxidum Hydricum; Aluminium (oxyde d') hydraté; Aluminiumhydroxid; Aluminum Hydroxide; Alüminyum Hidroksit; Glinu wodorotlenek; Hidróxido de aluminio; Hydroxid hlinitý; Wasserhaltiges Aluminiumoxid; Алюминий Гидроксид.

CAS — 21645-51-2 [$Al(OH)_3$].

ATC — A02AB01.

ATC Vet — QA02AB01.

UNII — 5QB0T2IUN0.

NOTE. Algeldrate (*USAN*, *pINN*) is defined as a hydrated aluminium hydroxide with the general formula $Al(OH)_3$, xH_2O.

Compounded preparations of aluminium hydroxide may be represented by the following names:

- Co-magaldrox *x*/*y* (*BAN*)—where *x* and *y* are the strengths in milligrams of magnesium hydroxide and aluminium hydroxide respectively.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Aluminium Oxide, Hydrated; Dried Aluminium Hydroxide BP 2014). It contains the equivalent of 47 to 60% Al_2O_3. It is a white or almost white, amorphous powder. Practically insoluble in water; it dissolves in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers at a temperature not exceeding 30 degrees.

Ph. Eur. 8: (Aluminium Hydroxide, Hydrated, for Adsorption; Aluminii Hydroxidum Hydricum ad Adsorptionem). A white or almost white, translucent, viscous, colloidal gel. A supernatant may be formed upon standing. A clear or almost clear solution is obtained with alkali hydroxide solutions and with mineral acids. pH 5.5 to 8.5. Store at a temperature not exceeding 30 degrees. Do not allow to freeze.

USP 36: (Aluminum Hydroxide Gel). A suspension of amorphous aluminium hydroxide in which there is a partial substitution of carbonate for hydroxide. It is a white viscous suspension from which small amounts of clear liquid may separate on standing. It has a pH of between 5.5 and 8.0. Store in airtight containers. Avoid freezing.

USP 36: (Dried Aluminum Hydroxide Gel). An amorphous form of aluminium hydroxide in which there is a partial substitution of carbonate for hydroxide. It contains the equivalent of not less than 76.5% of $Al(OH)_3$ and may contain varying quantities of basic aluminium carbonate and bicarbonate. The labelling requirements states that 1 g of dried aluminium hydroxide gel is equivalent to 765 mg of $Al(OH)_3$. It is a white, odourless, tasteless, amorphous powder. Insoluble in water and in alcohol; soluble in dilute mineral acids and in solutions of fixed alkali hydroxides. A 4% aqueous dispersion has a pH of not more than 10.0. Store in airtight containers.

Uses and Administration

Aluminium hydroxide is used as an antacid (p. 1803.1). It is given orally in doses of up to about 1 g, between meals and at bedtime. In order to reduce the constipating effects, aluminium hydroxide is often given with a magnesium-containing antacid, such as magnesium oxide or magnesium hydroxide.

Aluminium hydroxide binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It may thus be used to treat hyperphosphataemia in patients with chronic renal failure (although aluminium accumulation may be a problem—see Renal Osteodystrophy, p. 1170.1) or associated secondary hyperparathyroidism (p. 1170.3). With this use the dose must be adjusted to the individual patient's requirement but up to about 10 g daily may be given orally in divided doses with meals.

Aluminium hydroxide is also used as an adjuvant in adsorbed vaccines.

Polymyositis and dermatomyositis. Corticosteroids form the basis of the management of polymyositis (p. 1611.1) but the calcinosis that may occur in dermatomyositis does not always respond well. Aluminium hydroxide 1.68 to 2.24 g daily produced clinical improvement with complete clearing of most calcified nodules after 1 year in a patient with calcinosis cutis complicating juvenile dermatomyositis.[1] The calcified masses are made up of hydroxyapatite and amorphous calcium phosphate and reduction in phosphate absorption by aluminium hydroxide probably helped to reverse their formation. Subsequent cases[2,3] have also reported benefit from aluminium hydroxide treatment in the management of calcinosis.

1. Wang W-J, *et al.* Calcinosis cutis in juvenile dermatomyositis: remarkable response to aluminium hydroxide therapy. *Arch Dermatol* 1988; **124:** 1721–2.
2. Nakagawa T, Takaiwa T. Calcinosis cutis in juvenile dermatomyositis responsive to aluminium hydroxide treatment. *J Dermatol* 1993; **20:** 558–60.
3. Wananukul S, *et al.* Calcinosis cutis presenting years before other clinical manifestations of juvenile dermatomyositis: report of two cases. *Australas J Dermatol* 1997; **38:** 202–5.

Adverse Effects and Precautions

Aluminium hydroxide, like other aluminium compounds, is astringent and may cause constipation; large doses can cause intestinal obstruction.

Excessive doses, or even normal doses in patients with low-phosphate diets, may lead to phosphate depletion accompanied by increased bone resorption and hypercalciuria with the risk of osteomalacia.

Aluminium salts are not, in general, well absorbed from the gastrointestinal tract, and systemic effects are therefore rare in patients with normal renal function. However, care is necessary in patients with chronic renal impairment: osteomalacia or adynamic bone disease, encephalopathy, dementia, and microcytic hypochromic anaemia have been associated with aluminium accumulation in such patients given large doses of aluminium hydroxide as a phosphate-binding agent. Similar adverse effects have also been associated with the aluminium content of dialysis fluids.

Aluminium hydroxide used as an adjuvant in adsorbed vaccines has been associated with the formation of granulomas.

Children. For the suggestion that aluminium-containing antacids should not be used in infants, see Toxicity, below.

Porphyria. UK licensed product information states that aluminium hydroxide may be unsafe in patients with porphyria undergoing haemodialysis. However, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, has not classified aluminium hydroxide.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Toxicity. References to aluminium toxicity in dialysis patients and the possible association between aluminium

ingestion and Alzheimer's disease are included under Aluminium (see p. 2440.1).

Aluminium accumulation does not generally appear to be significant in patients with normal renal function taking therapeutic doses of aluminium-containing antacids, and there is little evidence that such antacids are a risk factor for Alzheimer's disease.[1] Elevated plasma-aluminium concentrations have been reported in infants with normal renal function given aluminium-containing antacids but there were no obvious signs of toxicity.[2] There have, however, been reports of phosphate depletion and rickets in a few infants caused by the use of antacids containing magnesium and aluminium hydroxides. In these cases the antacid had been started within a few months of birth and continued for up to 8 months. In reports that described a total of 3 infants,[3,4] the authors suggested that the use of soya-based infant feeding formulas, the phytates of which can interfere with mineral absorption, may have exacerbated the phosphate-binding effect of the antacid. In another case[5] a dosing error resulted in the infant receiving an excessive dose of antacid for 6 months. The *BNFC* advises against the use of any aluminium-containing antacid in neonates and infants.

Aluminium accumulation resulting in osteomalacia or encephalopathy with seizures and dementia has been reported in children with renal failure (but not on dialysis) treated with aluminium-containing phosphate binders.[6-10] In an adult male patient with severe chronic renal failure who was not on dialysis, self-medication with antacids for at least 3 years resulted in aluminium toxicity associated with encephalopathy, bone disease, and microcytic anaemia.[11] Aluminium-containing antacids should therefore be used with caution in patients with chronic renal failure, especially children.

Oral citrate salts increase the absorption of aluminium from the gastrointestinal tract[12] and patients with renal failure taking aluminium compounds should avoid citrate-containing preparations, which include many effervescent or dispersible tablets.[13,14] Ascorbic acid has also been reported to enhance aluminium absorption.[15]

1. Flaten TP, *et al.* Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; **45:** 203–6.
2. Tsou VM, *et al.* Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. *Pediatrics* 1991; **87:** 148–51.
3. Pivnick EK, *et al.* Rickets secondary to phosphate depletion: a sequela of antacid use in infancy. *Clin Pediatr (Phila)* 1995; **34:** 73–8.
4. Shetty AK, *et al.* Rickets and secondary craniosynostosis associated with long-term antacid use in an infant. *Arch Pediatr Adolesc Med* 1998; **152:** 1243–5.
5. Robinson RF, *et al.* Metabolic bone disease after chronic antacid administration in an infant. *Ann Pharmacother* 2004 **38:** 265–8.
6. Pedersen S, Nathan E. Water treatment and dialysis dementia. *Lancet* 1982; **ii:** 1107.
7. Griswold WR, *et al.* Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. *Pediatrics* 1983; **71:** 56–8.
8. Randall ME. Aluminium toxicity in an infant not on dialysis. *Lancet* 1983; **i:** 1327–8.
9. Sedman AB, *et al.* Encephalopathy in childhood secondary to aluminum toxicity. *J Pediatr* 1984; **105:** 836–8.
10. Andreoli SP, *et al.* Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. *N Engl J Med* 1984; **310:** 1079–84.
11. Zatta P, *et al.* A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis. *Nephrol Dial Transplant* 2004; **19:** 2929–31.
12. Walker JA, *et al.* The effect of oral bases on enteral aluminum absorption. *Arch Intern Med* 1990; **150:** 2037–9.
13. Mees EJD, Basçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; **59:** 322.
14. Main J, Ward MK. Potentiation of aluminium absorption by effervescent analgesic tablets in a haemodialysis patient. *BMJ* 1992; **304:** 1686.
15. Domingo JL, *et al.* Effect of ascorbic acid on gastrointestinal aluminium absorption. *Lancet* 1992; **338:** 1467.

Interactions

As outlined on p. 1803.1, aluminium compounds used as antacids interact with many other drugs, both by alterations in gastric pH and emptying, and by direct adsorption and formation of complexes that are not absorbed. Interactions can be minimised by giving the aluminium compound and any other medication 2 to 3 hours apart. The absorption of aluminium from the gastrointestinal tract may be enhanced if aluminium compounds are taken with citrates or ascorbic acid (see Toxicity, p. 1817.3).

Pharmacokinetics

Aluminium hydroxide, given orally, slowly reacts with the hydrochloric acid in the stomach to form soluble aluminium chloride, some of which is absorbed. The presence of food or other factors that decrease gastric emptying prolongs the availability of aluminium hydroxide to react and may increase the amount of aluminium chloride formed. About 100 to 500 micrograms of the cation is reported to be absorbed from standard daily doses of an aluminium-containing antacid, leading to about a doubling of usual aluminium concentrations in the plasma of patients with normal renal function.

Absorbed aluminium is eliminated in the urine, and patients with renal failure are therefore at particular risk of accumulation (especially in bone and the CNS), and aluminium toxicity (see p. 1817.3).

The aluminium compounds remaining in the gastrointestinal tract, which account for most of a dose, form insoluble, poorly absorbed aluminium salts in the intestines including hydroxides, carbonates, phosphates and fatty acid derivatives, which are excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pepsamar; ***Austral.***: Alu-Tab†; ***Austria***: Anti-Phosphat; ***Braz.***: Aludroxil; Aziram; Ductogel; Gastromax; Gastrox; Mylanta Plus; Pepgastrin†; Pepsamar; Peptgel; ***Canad.***: Amphojel; ***Ger.***: Aludrox†; Antiphosphat; ***Gr.***: Alu-Cap; Pepsamar; ***Hong Kong***: Alu-Tab; Gasteel; ***India***: Aludrox; Dizicum; Tricaine-MPS; ***Indon.***: Actal; ***Irl.***: Aludrox†; ***Malaysia***: Alu-Tab; ***Mex.***: Domigel†; ***NZ***: Alu-Tab; ***Philipp.***: Alu-Tab; ***Pol.***: Alusal; ***Port.***: Almigastrico; Pepsamar; ***S.Afr.***: Acidex†; Alukon†; Amphojel; ***Singapore***: Alu-Tab†; Alutacid; ***Spain***: Alugel†; Pepsamar†; ***Switz.***: Anti-phosphate†; ***Thai.***: Alumina-Magnesia; New Gel; ***UK***: Alu-Cap; ***USA***: ALternaGEL; Amphojel; Dialume†; Nephrox.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Arg.***: Dristan Compuesto; ***Braz.***: Engov; Enjoy; Posdrink†; Resprax†; ***Gr.***: Ascriptin; ***Indon.***: Naspro; ***Ital.***: Ascriptin; ***Mex.***: Ascriptin; Meprosona-F; ***Switz.***: Alcacyl; Contre-Douleurs plus; ***USA***: Arthritis Pain Formula; Ascriptin; Cama Arthritis Pain Reliever; Cope; Vanquish; ***Venez.***: Ascriptin.

Homoeopathic Preparations. ***Chile***: Ikoplex No 19; ***Cz.***: Lamioflur†.

Pharmacopoeial Preparations
BP 2014: Aluminium Hydroxide Oral Suspension; Chewable Aluminium Hydroxide Tablets; Chewable Compound Magnesium Trisilicate Tablets; Co-magaldrox Oral Suspension; Co-magaldrox Tablets;
USP 36: Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aluminum Hydroxide Gel; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Dried Aluminum Hydroxide Gel Capsules; Dried Aluminum Hydroxide Gel Tablets; Dried Aluminum Hydroxide Gel.

Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel

Aluminum Hydroxide-Magnesium Carbonate Co-dried Gel; F-MA 11; Hidróxido de aluminio y carbonato de magnesio desecado, gel de.

Profile

Aluminium hydroxide-magnesium carbonate co-dried gel is a co-precipitate of aluminium hydroxide and magnesium carbonate dried to contain a proportion of water for antacid activity. It is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2) and magnesium carbonate (p. 1856.2). It has been given in oral doses of about 450 to 900 mg, usually 3 times daily after meals and before bedtime.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combinations and complexes of aluminium, calcium, and magnesium compounds for acid related disorders as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Link; ***Fin.***: Link; ***Gr.***: Regla pH; ***Indon.***: Stomacain; Veragel†; ***Mex.***: Gelasim; ***Neth.***: Regla pH; Remegel; ***Norw.***: Link; ***Swed.***: Link†.

Multi-ingredient Preparations. ***Belg.***: Barexal; Regla pH Forte; Syngel; ***Braz.***: Andursil; ***Canad.***: Diovol Plus; Diovol; Gastrocalm; ***Chile***: Algicote†; Disfrutab†; Ditopax; Reflumox; ***Fr.***: Gastropulgite; ***Ger.***: Colina Spezial; Duoventrinetten N; ***Hong Kong***: Diovol Plus; Veragel; ***Indon.***: Aludonna; Di-Gel; Farmacrol; Gastran†; Oskamag†; Polycrol; Simeco†; ***Irl.***: Smecta; ***Mex.***: Ditopax-F†; Ditopax†; ***Neth.***: Algicon; Algicon; Rigoletten; ***Port.***: Di-Gel†; ***Singapore***: Meclosil; Veragel; ***Switz.***: Andursil; ***Thai.***: Defomil; Diovol†; Kremil-S; Kremil; Machto; Simeco†; Tocid; Veragel; ***UK***: Simeco; ***Ukr.***: Gastal (Гастал); ***Venez.***: Ditosil Plus; Ditosil.

Used as an adjunct in:. ***Indon.***: Rheumapill†.

Aluminium Phosphate

Aliuminio fosfatas; Alumiinifosfaatti; Aluminii phosphas; Aluminio, fosfato de; Aluminium, phosphate d'; Aluminiumfosfat; Alumínium-foszfát; Aluminum Phosphate; Fosfato de aluminio; Fosforečnan hlinitý; Glinu fosforan; Glinu fosforanu; Алюминия Фосфат.
CAS — 7784-30-7 ($AlPO_4$).
ATC — A02AB03.
ATC Vet — QA02AB03.
UNII — F92V35521O.

Pharmacopoeias. In *Viet.*

Eur. (see p. vii) includes hydrated aluminium phosphate and also a gel. *US* includes as a gel.

Ph. Eur. 8: (Aluminium Phosphate, Hydrated; Aluminii Phosphas Hydricus; Dried Aluminium Phosphate BP 2014). A white or almost white powder. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and mineral acids. A 4% suspension in water has a pH of 5.5 to 7.2. Store in airtight containers.

Ph. Eur. 8: (Aluminium Phosphate Gel; Aluminii Phosphatis Liquamen). It is aluminium phosphate in gel form containing 19 to 21% of $AlPO_4$. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in dilute solutions of mineral acids. pH 6.0 to 8.0. Store in airtight containers.

USP 36: (Aluminum Phosphate Gel). A 4 to 5% suspension of aluminium phosphate ($AlPO_4$) in water and has a pH of 6.0 to 7.2. It is a white viscous suspension from which small amounts of water separate on standing. Store in airtight containers.

Profile

Aluminium phosphate is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2), but it does not produce phosphate depletion.

Aluminium phosphate is also used as an adjuvant in adsorbed vaccines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Colphos (吉福士); Gui Ding Kang (贵鼎康); Phosgel (洁维乐); Yu Er (裕尔); ***Fr.***: Phosphalugel; ***Ger.***: Phosphalugel; ***Ital.***: Fosfalugel; ***Port.***: Phosphalugel; ***Rus.***: Phosphalugel (Фосфалюгель); ***Ukr.***: Phosphalugel (Фосфалюгель).

Multi-ingredient Preparations. ***Fr.***: Isudrine†; Moxydar; Seroxydar†.

Pharmacopoeial Preparations
USP 36: Aluminum Phosphate Gel.

Aluminium Sodium Silicate

Aluminium-Natrium-Silicat; Aluminum Sodium Silicate; E554; Natrii aluminii silicas; Silicato de sodio y de aluminio; Sodium Aluminium Silicate; Sodium Aluminosilicate; Sodium et aluminium, silicate de; Sodium Silicoaluminate; Алюмосиликат Натрия.
CAS — 1344-00-9.
UNII — 058TS43PSM.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Aluminium Sodium Silicate). It is a silicic acid aluminium sodium salt of synthetic origin. It contains 2.7 to 7.9% aluminium and 3.7 to 6.3% sodium, both calculated with reference to the dried substance. A white or almost white, fine, light, amorphous powder. Practically insoluble in water and in organic solvents. A 5% dispersion in water has a pH of 9.5 to 11.5.

Profile

Aluminium sodium silicate is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2). Aluminium silicate has been used similarly. They are also used as food additives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Sulfuryl†; ***Indon.***: Cerplast; ***Port.***: Acnoil Free†.

Multi-ingredient Preparations. ***Arg.***: Gastranil; ***Fr.***: Cerat Inalterable†; Sulfuryl; ***Ger.***: Enelbin-Paste N†; Enelbin-Paste†; ***Hong Kong***: Epilon; ***India***: Acnil; ***Thai.***: Ulgastrin.

Homoeopathic Preparations. ***Neth.***: Phonix Solidago comp.

Alverine Citrate *(BANM, USAN, rINNM)*

Alverina, citrato de; Alverincitrat; Alvérine, Citrate d'; Alverini Citras; Citrato de alverina; Dipropyline Citrate; Phenpropamine Citrate; Альверина Цитрат.

N-Ethyl-3,3′-diphenyldipropylamine citrate.

$C_{20}H_{27}N,C_6H_8O_7$=473.6

CAS — 150-59-4 (alverine); 5560-59-8 (alverine citrate).

ATC — A03AX08.

ATC Vet — QA03AX08.

UNII — 9JFB58YK1E.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Alverine Citrate). A white or almost white crystalline powder. Slightly soluble in water and in dichloromethane; sparingly soluble in alcohol. A 0.5% solution in water has a pH of 3.5 to 4.5. Protect from light.

Uses and Administration

Alverine is an antispasmodic that acts directly on intestinal and uterine smooth muscle. It is used for the relief of smooth muscle spasm in the treatment of gastrointestinal disorders such as irritable bowel syndrome (p. 1810.3). It is also used in the treatment of dysmenorrhoea (p. 8.2).

Alverine citrate is given in oral doses of 60 to 120 mg one to three times daily. Alverine has also been given by suppository as the base.

Administration in children. Alverine citrate may be given to adolescents from the age of 12 years in the same doses as adults, see above.

Irritable bowel syndrome. Alverine citrate is widely used as an antispasmodic in the management of irritable bowel syndrome. However, a 12-week study[1] in 107 patients found that alverine citrate was no better than placebo for the relief of symptoms and improvement in general well-being. A marked placebo effect occurred and symptomatic improvement was reported by at least half the placebo group.

1. Mitchell SA, *et al.* Alverine citrate fails to relieve the symptoms of irritable bowel syndrome: results of a double-blind, randomized, placebo-controlled trial. *Aliment Pharmacol Ther* 2002; **16:** 1187–95.

Adverse Effects and Precautions

Nausea, headache, pruritus, rash, and dizziness have been reported. Allergic reactions, including anaphylaxis, have also occurred. Alverine is contra-indicated in patients with intestinal obstruction or paralytic ileus.

Effects on the liver. Acute hepatitis was attributed to alverine citrate in 2 separate cases.[1,2] Evidence of an immune reaction, including antinuclear antibodies, was found in 1 case.[1]

1. Malka D, *et al.* Acute hepatitis caused by alverine associated with anti-lamin A and C autoantibodies. *J Hepatol* 1997; **27:** 399–403.
2. Arhan M, *et al.* Alverine citrate induced acute hepatitis. *World J Gastroenterol* 2004; **10:** 2303–4.

Pharmacokinetics

Alverine is absorbed from the gastrointestinal tract after oral doses and is rapidly metabolised to an active metabolite, peak plasma concentrations of which occur 1 to 1.5 hours after an oral dose. Further metabolism to inactive metabolites occurs; metabolites are excreted in the urine by active renal secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Spasmine; ***China***: Spasmonal (斯莫纳); ***Hong Kong***: Profenil; Spasmonal†; ***Irl.***: Spasmonal; ***Pol.***: Spasmolina; ***Singapore***: Spasmonal; ***Thai.***: Spasmonal†; ***UK***: Audmonal; Spasmonal.

Multi-ingredient Preparations. ***Arg.***: Meteospasmyl; ***China***: Meteospasmyl (乐健素); ***Cz.***: Meteospasmyl; ***Fr.***: Hepatoum; Meteospasmyl; Schoum; ***Hung.***: Meteospasmyl; ***Indon.***: Spasmium; ***Malaysia***: Meteospasmyl; ***Mex.***: Meteospasmyl; ***Pol.***: Meteospasmyl; ***Rus.***: Meteospasmyl (Метеоспазмил); ***Singapore***: Meteospasmyl; ***Thai.***: Avarin; Meteospasmyl†; ***Turk.***: Meteospasmyl; ***Ukr.***: Meteospasmyl (Метеоспазмил).

Pharmacopoeial Preparations
BP 2014: Alverine Capsules.

Alvimopan *(BAN, USAN, rINN)*

ADL-8-2698; Alvimopán; Alvimopanum; LY-246736; Альвимопан.

[((2*S*)-2-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-3-phenylpropanoyl)amino]acetic acid.

$C_{25}H_{32}N_2O_4$=424.5

CAS — 156053-89-3 (anhydrous alvimopan); 170098-38-1 (alvimopan dihydrate).

ATC — A06AH02.

ATC Vet — QA06AH02.

UNII — 677C126AET (alvimopan); Q153V49P3Z (anhydrous alvimopan).

Uses and Administration

Alvimopan is a peripherally acting selective antagonist of opioid μ-receptors that is used in the treatment of postoperative ileus after partial large or small bowel resection surgery with primary anastomosis. It is given in a 12-mg oral dose between 30 minutes and up to 5 hours before surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge. A maximum of 15 doses of alvimopan should be given.

References.

1. Herzog TJ, *et al.* A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. *Am J Obstet Gynecol* 2006; **195:** 445–53.
2. Tan EK, *et al.* Meta-analysis: Alvimopan vs. placebo in the treatment of post-operative ileus. *Aliment Pharmacol Ther* 2007; **25:** 47–57.
3. Curran MP, *et al.* Alvimopan. *Drugs* 2008; **68:** 2011–19. Correction. *ibid.*; 2324.
4. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet* 2009; **373:** 1198–1206.
5. Bream-Rouwenhorst HR, Cantrell MA. Alvimopan for postoperative ileus. *Am J Health-Syst Pharm* 2009; **66:** 1267–77.

Adverse Effects and Precautions

Gastrointestinal disorders such as constipation, dyspepsia, and flatulence have been reported after use of alvimopan. Anaemia, back pain, hypokalaemia, and urinary retention have also occurred.

Alvimopan should not be used in patients who have taken therapeutic doses of opioids for more than 7 consecutive days, as they are expected to be more sensitive to its effects. Use in patients with severe hepatic impairment or end-stage renal disease is not recommended due to a lack of data. Alvimopan is also not recommended in patients undergoing surgery for complete bowel obstruction.

Pharmacokinetics

Plasma-alvimopan concentrations peak about 2 hours after an oral dose. High-fat meals decrease the extent and rate of absorption. Alvimopan binds to albumin, with an average plasma protein binding of 80%. Biliary secretion is considered the primary pathway for elimination of alvimopan, but renal excretion also contributes. Unabsorbed alvimopan is metabolised by gut microflora to an amide hydrolysis compound which is also an antagonist of opioid μ-receptors. This metabolite is then excreted in the faeces and urine. The mean terminal half-life of alvimopan after multiple oral doses ranged from 10 to 17 hours.

References.

1. Foss JF, *et al.* Pharmacokinetics of alvimopan and its metabolite in healthy volunteers and patients in postoperative ileus trials. *Clin Pharmacol Ther* 2008; **83:** 770–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Entereg.

Aprepitant *(USAN, rINN)*

Aprépitant; Aprepitantum; L-754030; MK-0869; MK-869; Апрепитант.

3-[((2*R*,3*S*)-3-(*p*-Fluorophenyl)-2-{[(α*R*)-α-methyl-3,5-bis(trifluoromethyl)benzyl]oxy}morpholino)methyl]-Δ^2-1,2,4-triazolin-5-one.

$C_{23}H_{21}F_7N_4O_3$=534.4

CAS — 170729-80-3.

ATC — A04AD12.

ATC Vet — QA04AD12.

UNII — 1NF15YR6UY.

Uses and Administration

Aprepitant is a neurokinin-1 (NK_1) receptor antagonist used in the management of nausea and vomiting (p. 1811.3). It is given orally in doses up to 125 mg, with a corticosteroid and a 5-HT_3 antagonist, in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy (for details, see Administration, below).

For the prevention of postoperative nausea and vomiting a single oral dose of aprepitant 40 mg may be given within the 3 hours before induction of anaesthesia.

Where the intravenous route is preferred, it may be given as its prodrug, fosaprepitant (for details of regimens, see Uses and Administration, under Fosaprepitant, p. 1843.3).

References.

1. Diemunsch P, *et al.* Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. *Curr Med Res Opin* 2007; **23:** 2559–65.
2. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2004; **64:** 777–94.
3. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother* 2005; **39:** 77–85.
4. Warr D. The neurokininl receptor antagonist aprepitant as an antiemetic for moderately emetogenic chemotherapy. *Expert Opin Pharmacother* 2006; **7:** 1653–8.
5. Curran MP, Robinson DM. Aprepitant: a review of its use in the prevention of nausea and vomiting. *Drugs* 2009; **69:** 1853–78.

Administration. Licensed product information for aprepitant suggests the following 4-day regimen for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy:

- day 1: oral aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg and intravenous ondansetron 32 mg (both 30 minutes before chemotherapy)
- days 2 and 3: oral aprepitant 80 mg with oral dexamethasone 8 mg in the morning
- day 4: oral dexamethasone 8 mg in the morning.

In patients receiving moderately emetogenic chemotherapy, a 3-day regimen has been suggested as follows:

- day 1: oral aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg (30 minutes before chemotherapy); ondansetron is given in 2 oral doses of 8 mg, one taken 30 to 60 minutes before chemotherapy, and one taken 8 hours after the first dose
- days 2 and 3: oral aprepitant 80 mg in the morning.

Administration in renal impairment. A study in 8 patients with severe renal impairment (24-hour creatinine clearance less than 30 mL/minute per 1.73 m^2) and 8 patients with end-stage renal disease requiring haemodialysis found that pharmacokinetic parameters of aprepitant were not sufficiently different from those in 16 matched controls to warrant dosage adjustment in renal impairment.[1] Licensed product information concurs with this.

1. Bergman AJ, *et al.* Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. *Clin Pharmacokinet* 2005; **44:** 637–47.

Pruritus. An improvement in pruritus was reported after oral aprepitant 80 mg daily was started in 3 patients with the Sézary syndrome. Topical corticosteroid treatment had previously been unsuccessful, but improvements were noted within 2 days of starting aprepitant.[1] Beneficial results were also reported[2] in 16 of 20 patients with refractory chronic pruritus of various causes who were given 80 mg daily for 3 to 13 days; 4 patients had complete or nearly complete cessation of itch and 12 had lesser degrees of reduction. Patients with atopic dermatitis or prurigo appeared to respond better than those in whom pruritus was associated with chronic kidney disease. Aprepitant is an antagonist of the neurokinin-1 receptor, a receptor for substance P which is a mediator in the itch sensation.[1,2]

For reference to aprepitant's efficacy in managing erlotinib-induced pruritus, see Effects on the Skin, Hair, and Nails, under Erlotinib, p. 789.2.

1. Duval A, Dubertret L. Aprepitant as an antipruritic agent? *N Engl J Med* 2009; **361:** 1415–16.
2. Ständer S, *et al.* Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One* 2010; **5:** e10968.

Adverse Effects and Precautions

The most common adverse effects associated with aprepitant are headache, constipation, diarrhoea, dyspepsia, anorexia, fatigue, hiccups, eructation, and dizziness. Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations are common. Other reported effects have included abdominal pain, oedema, tinnitus, neutropenic colitis, chills, gait disturbances, and flushing. Epigastric discomfort, dysgeusia, dry mouth, and stomatitis have also occurred. Thirst, polyuria, dysuria, haematuria, urinary frequency, arthralgia, myalgia, muscular weakness, hyperglycaemia, disorientation, euphoria, anxiety, photosensitivity, and skin disorders such as rash and pruritus have been reported. Anaemia and febrile neutropenia have occurred with aprepitant, as have cardiovascular disorders including hypertension or hypotension, palpitations, and bradycardia. Other adverse effects reported include hyponatraemia, hypokalaemia, insomnia, drowsiness, miosis, reduced visual acuity, weight changes, sensory disturbances, throat irritation, sneezing, abnormal bowel sounds, acid reflux, perforating duodenal ulcer,

dyspnoea, cough, wheezing, and hyperhidrosis. Conjunctivitis, pharyngitis, respiratory-tract infections, urinary-tract infections, candidiasis, and herpes simplex can occur. Hypersensitivity reactions including anaphylaxis, Stevens-Johnson syndrome, and angioedema with urticaria have been reported.

Licensed product information recommends caution in patients with severe hepatic impairment as clinical data are lacking in this patient group.

Interactions

During its use for 3 or 4 days in the prevention of nausea and vomiting associated with cancer chemotherapy, aprepitant produces moderate inhibition of the cytochrome P450 isoenzyme CYP3A4. Exposure to oral CYP3A4 substrates may increase substantially; the effect of aprepitant on intravenous CYP3A4 substrates is expected to be less. However, on cessation of aprepitant a transient mild induction of CYP3A4 may become apparent with a maximum effect reached 3 to 5 days later; this effect is maintained for a few days then slowly declines and is clinically insignificant about 2 weeks after stopping aprepitant. Caution is therefore required when using it with drugs that are primarily metabolised by this isoenzyme. Aprepitant should not be given with astemizole, cisapride, pimozide, terfenadine, or tolvaptan as increased plasma concentrations of these drugs could cause serious life-threatening reactions. As aprepitant is also a substrate for CYP3A4, other drugs that inhibit or induce this isoenzyme may in turn increase or decrease plasma concentrations of aprepitant.

When aprepitant is used to prevent postoperative nausea and vomiting, in a single lower dose than that used with cancer chemotherapy, the effect of aprepitant on CYP3A4 is not expected to be clinically significant.

Aprepitant also causes a delayed induction of CYP2C9 and may lower plasma concentrations of drugs metabolised by this isoenzyme, such as warfarin, phenytoin, or tolbutamide.

Aprepitant may increase systemic exposure to corticosteroids; when given together it is recommended that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. It should be noted that the dose of dexamethasone in the regimens recommended for nausea and vomiting associated with cancer chemotherapy already accounts for this interaction (see Administration, p. 1819.3).

The efficacy of oral contraceptives might be reduced by aprepitant. Licensed product information suggests that alternative methods of contraception should be used during and for 1 to 2 months after stopping any dose of aprepitant.

Pharmacokinetics

Aprepitant is absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 4 hours. Bioavailability is about 60% at usual doses. It crosses the blood-brain barrier; plasma protein binding is reported to be more than 95%. Aprepitant undergoes extensive hepatic metabolism, mainly via oxidation by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP1A2 and CYP2C19 mediate minor metabolic pathways. The resultant metabolites have weak activity and are excreted in the urine and in the faeces. Aprepitant is not excreted unchanged in the urine. The terminal half-life is about 9 to 13 hours.

References.
1. Majumdar AK, *et al*. Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. *J Clin Pharmacol* 2006; **46:** 291–300.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Emend; ***Austral.***: Emend; ***Austria***: Emend; ***Belg.***: Emend; ***Braz.***: Emend; ***Canad.***: Emend; ***Chile***: Emend; ***Cz.***: Emend; ***Denm.***: Emend; ***Fin.***: Emend; ***Fr.***: Emend; ***Ger.***: Emend; ***Gr.***: Emend; ***Hong Kong***: Emend; ***Hung.***: Emend; ***India***: Aprecap; ***Irl.***: Emend; ***Israel***: Emend; ***Ital.***: Emend; ***Jpn***: Emend; ***Malaysia***: Emend; ***Neth.***: Emend; ***Norw.***: Emend; ***NZ***: Emend; ***Pol.***: Emend; ***Port.***: Emend; ***Rus.***: Emend (Эменд); ***S.Afr.***: Emend; ***Singapore***: Emend; ***Spain***: Emend; ***Swed.***: Emend; ***Switz.***: Emend; ***Thai.***: Emend; ***Turk.***: Emend; ***UK***: Emend; ***Ukr.***: Emend (Эменд); ***USA***: Emend; ***Venez.***: Emend.

Attapulgite

Atapulgit; Atapulgita; Аттапульгит.

CAS — 1337-76-4; 12174-11-7.
ATC — A07BC04.
ATC Vet — QA07BC04.
UNII — U6V729APAM.

Pharmacopoeias. In *Br.*

Activated attapulgite is included in *Br., It.*, and *US*. Colloidal activated attapulgite is included in *US*.

BP 2014: (Attapulgite). A purified native hydrated aluminium magnesium silicate essentially consisting of the clay mineral palygorskite. A light, cream or buff, very fine powder, free or almost free from gritty particles. A 5% suspension in water has a pH of 7.0 to 9.5.

BP 2014: (Activated Attapulgite). Attapulgite that has been carefully heated to increase its adsorptive capacity.

USP 36: (Activated Attapulgite). Processed native aluminium magnesium silicate which has been carefully heated. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water.

USP 36: (Colloidal Activated Attapulgite). A native aluminium magnesium silicate that has been purified. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water. A 10% suspension in water has a pH of 7.0 to 9.5.

NOTE. Another native aluminium magnesium silicate is described on p. 2168.2.

Profile

Attapulgite is highly adsorbent and is used in a wide range of products including fertilisers, pesticides, and pharmaceuticals. Activated attapulgite is an adsorbent antidiarrhoeal used as an adjunct in the management of diarrhoea (p. 1805.2) in a daily dose of up to 9 g orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Actapulgite; ***Canad.***: Kaopectate; ***Fr.***: Actapulgite; ***Hong Kong***: Gastrosorb†; ***Indon.***: Biodiar; Enterogit†; Kaotate†; New Diatabs; Teradi; ***Philipp.***: Polymagma†; ***Rus.***: Neointestopan (Неоинтестопан); ***Singapore***: Gastrosorb; ***Switz.***: Actapulgite†; ***Thai.***: Entox-P; ***Turk.***: Diasorb; Diyasorb†; ***UAE***: Kaptin II; ***USA***: Diasorb; Kaopectate Maximum Strength; ***Venez.***: Streptomagma.

Multi-ingredient Preparations. ***Arg.***: Enterobacticel; ***Austral.***: Diarezе†; ***Braz.***: Diazol; Dispeptrin†; ***Chile***: Diaren; Entero Micinovo; Enterol†; Liracol; Nifurat; ***Fr.***: Gastropulgite; Mucipulgite†; ***Hong Kong***: Enterocin Compound†; ***Indon.***: Andikap†; Arcapec; Diagit; Entrogard; Fitodiar; Licopec; Molagit; Neo Diastop; Neo Entrostop; Neo Koniform†; ***S.Afr.***: Kantrexil; ***Switz.***: Mucipulgite†; ***Turk.***: Streptomagma; ***UK***: Diocalm Dual Action; ***Venez.***: Micyn-2; Streptomagma.

Azasetron Hydrochloride *(rINNM)*

Azasétron, Chlorhydrate d'; Azasetrón, hidrocloruro de; Azasetroni Hydrochloridum; Hidrocloruro de azasetrón; Nazasetron Hydrochloride; Y-25130; Азасетрона Гидрохлорид.

(±)-6-Chloro-3,4-dihydro-4-methyl-3-oxo-*N*-3-quinuclidinyl-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride.

$C_{17}H_{20}ClN_3O_3$,HCl=386.3

CAS — 123040-69-7 (azasetron); 141922-90-9 (azasetron hydrochloride).
UNII — 2BSS7XL60S.

Profile

Azasetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p. 1872.1). It is used as an antiemetic in the management of nausea and vomiting induced by cytotoxic therapy. Azasetron hydrochloride is given in a usual dose of 10 mg once daily by mouth or intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Shi Tong (安世通); Ding Yue (丁悦); Gan Su (感苏); Ou Li Kang Ding (欧立康定); Ou Ting (欧亭); Ri An (日安); Rui Di Su (瑞帝苏); Tan Si Ke (坦斯克); Wan Wei (万唯); Yi Qiong (依琼); Yi Su Lin (怡苏林); ***Jpn***: Serotone.

Balsalazide Sodium *(BANM, rINNM)*

Balsalazida sódica; Balsalazide Disodium (USAN); Balsalazide Sodique; Balsalazine Disodium; BX-661A; Natrii Balsalazidum; Натрий Балсалазид.

5-[4-(2-Carboxyethylcarbamoyl)phenylazo]salicylic acid, disodium salt, dihydrate.

$C_{17}H_{13}N_3Na_2O_6.2H_2O$=437.3

CAS — 80573-04-2 (balsalazide); 150399-21-6 (balsalazide disodium dihydrate).
ATC — A07EC04.
ATC Vet — QA07EC04.
UNII — 1XL6BJI034 (balsalazide sodium dihydrate); 15ASW03C9S (anhydrous balsalazide sodium).

Pharmacopoeias. In *US*.

USP 36: (Balsalazide Disodium). An orange to yellow powder. Freely soluble in water and in isotonic saline; sparingly soluble in alcohol and in methyl alcohol; practically insoluble in all other organic solvents. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Balsalazide consists of mesalazine linked to 4-aminobenzoylalanine via an azo bond. This bond is broken by colonic bacteria, releasing the active mesalazine (p. 1859.2). Balsalazide sodium is given in the treatment of mild to moderate active ulcerative colitis (p. 1808.3), in an oral dose of 2.25 g three times daily until remission or for up to 12 weeks. For maintenance of remission of ulcerative colitis a dose of 1.5 g twice daily is recommended, adjusted as necessary up to 6 g daily. For doses in children, see below.

Reviews.
1. Muijsers RBR, Goa KL. Balsalazide: a review of its therapeutic use in mild-to-moderate ulcerative colitis. *Drugs* 2002; **62:** 1689–705.
2. Patil SA, Moss AC. Balsalazide disodium for the treatment of ulcerative colitis. *Expert Rev Gastroenterol Hepatol* 2008; **2:** 177–84.
3. Rahimi R, *et al*. Comparison of mesalazine and balsalazide in induction and maintenance of remission in patients with ulcerative colitis: a meta-analysis. *Dig Dis Sci* 2009; **54:** 712–21.

Administration in children. Balsalazide sodium is not licensed in the UK for use in children under 18 years of age. However, the *BNFC* recommends that, in those aged 12 years and over, 2.25 g may be given orally three times daily for an acute attack of mild to moderate ulcerative colitis, until remission occurs, or for up to 12 weeks. For maintenance, 1.5 g twice daily is recommended, adjusted according to response up to a maximum of 6 g daily.

In the USA, licensed doses in children aged 5 to 17 years are 750 mg three times daily by mouth, or 2.25 g three times daily; treatment may be continued for up to 8 weeks.

Adverse Effects and Precautions

As for Mesalazine, p. 1860.1. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. Balsalazide should not be used in patients with severe hepatic impairment or moderate or severe renal impairment; care is required in those with lesser degrees of hepatic or renal impairment, and in asthma, bleeding disorders, or active peptic ulcer disease.

Reviews.
1. Baker DE. Safety of balsalazide therapy in the treatment of inflammatory bowel disease. *Rev Gastroenterol Disord* 2005; **5:** 135–41.

Effects on the cardiovascular system. Myocarditis similar to that seen with mesalazine (see p. 1860.2) has been described in a patient some days after his treatment was altered from mesalazine to balsalazide; the condition resolved once balsalazide was withdrawn.[1]

See also Hypersensitivity, below.

1. Robertson E, *et al*. Balsalazide-induced myocarditis. *Int J Cardiol* 2008; **130:** e121–e122.

Hypersensitivity. A case of acute pericarditis, cholestasis, and vasculitis resulting from hypersensitivity to balsalazide has been reported.[1] The authors noted similarities to mesalazine-associated pericarditis and lupus-like syndrome (see Effects on the Cardiovascular System, p. 1860.2).

1. Adhiyaman V, *et al*. Hypersensitivity reaction to balsalazide. *BMJ* 2000; **320:** 613.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies balsalazide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Pharmacokinetics

Very little of an oral dose of balsalazide is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 5-aminosalicylic acid (mesalazine), which is active, and 4-aminobenzoylalanine, which is considered to be an inert carrier. About 25% of the released mesalazine is absorbed and acetylated, as described under mesalazine (p. 1861.2). A small proportion of 4-aminobenzoylalanine is absorbed and

acetylated by first-pass metabolism through the liver. The acetylated metabolites are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Benoquin; ***Austral.***: Colazide; ***China***: Ao Rui Xin (奥瑞欣); Bei Le Si (贝乐司); Sai Lai De (塞莱得); ***Denm.***: Premid; ***India***: Balacol; Colorex; Cozabal; Intazide; ***Ital.***: Balzide; ***Norw.***: Colazid; ***UK***: Colazide; ***USA***: Colazal.

Multi-ingredient Preparations. ***Swed.***: Colazid.

Pharmacopoeial Preparations
USP 36: Balsalazide Disodium Capsules.

Benexate Hydrochloride *(rINNM)*

Bénexate, Chlorhydrate de; Benexati Hydrochloridum; Hidrocloruro de benexato; Бенексата Гидрохлорид.
Benzyl salicylate *trans*-4-(guanidinomethyl)cyclohexanecarboxylate hydrochloride.
$C_{23}H_{27}N_3O_4$,HCl=445.9
CAS — 78718-52-2 (benexate); 78718-25-9 (benexate hydrochloride); 91574-91-3 (benexate hydrochloride betadex).
UNII — QVN4YYK2C6.

Profile

Benexate hydrochloride is a mucosal protectant that has been used in the management of peptic ulcer disease. The β-cyclodextrin clathrate, benexate hydrochloride betadex, has been given in an oral dose of 400 mg twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Ulgut.

Bisacodyl *(BAN, rINN)*

Bisacodilo; Bisacodylum; Bisakodil; Bisakodilis; Bisakodyl; Bisakodyyli; Biszakodil; Бисакодил.
4,4′-(2-Pyridylmethylene)di(phenyl acetate).
$C_{22}H_{19}NO_4$=361.4
CAS — 603-50-9.
ATC — A06AB02; A06AG02.
ATC Vet — QA06AB02; QA06AG02.
UNII — 10X0709Y6I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Bisacodyl). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute mineral acids. Protect from light.

USP 36: (Bisacodyl). A white to off-white crystalline powder. Practically insoluble in water; soluble in benzene; soluble 1 in 210 of alcohol, 1 in 2.5 of chloroform, and 1 in 275 of ether; sparingly soluble in methyl alcohol.

Bisacodyl Tannex *(BANM, USAN, rINNM)*

CAS — 1336-29-4.
ATC — A06AB02; A06AG02.
ATC Vet — QA06AB02; QA06AG02.

Uses and Administration

Bisacodyl is a diphenylmethane stimulant laxative (p. 1804.1) used for the treatment of constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. Its action is mainly in the large intestine and it is usually effective within 6 to 12 hours after oral doses, within 15 to 60 minutes after rectal use by suppository, and within 5 to 20 minutes when given as an enema. Bisacodyl tablets should be swallowed whole and should not be taken within 1 hour of milk or antacids.

For constipation, bisacodyl is given in usual doses of 5 to 10 mg daily as enteric-coated tablets given at night; up to 20 mg may be given if necessary. Alternatively a dose of 10 mg as a suppository or enema may be given in the morning. For complete bowel evacuation, an oral dose of 10 to 20 mg may be given the night before the procedure, followed by 10 mg as a suppository the next morning. Alternatively, an oral dose of 10 mg may be given on each of the 2 nights before the procedure. For doses in children, see below.

A complex of bisacodyl with tannic acid (bisacodyl tannex) has been given with a barium sulfate enema before radiographic examination of the colon.

Administration in children. For **constipation**, the following oral doses of bisacodyl are recommended for children, to be taken at night:
- 4 to 10 years: 5 mg
- over 10 years: 5 to 10 mg, increased if necessary to a maximum of 20 mg

Alternatively, the following rectal doses are recommended, to be inserted in the morning:
- up to 10 years: 5 mg
- over 10 years: 10 mg

The *BNFC* gives similar doses, but limits the use of suppositories in children to those aged over 2 years.

For **bowel clearance before surgery or radiological investigation**, the following doses are recommended:
- 4 to 10 years: 5 mg orally the night before, followed by 5 mg as a suppository the next morning
- over 10 years: 10 to 20 mg orally the night before, followed by 10 mg as a suppository the next morning

The *BNFC* gives similar doses but allows for the use of oral doses for 2 nights before the procedure, followed, if necessary, by the rectal dose 1 hour before the procedure.

Adverse Effects

Bisacodyl and other stimulant laxatives may cause abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Haematochezia (blood in the stool) may be seen but is usually mild and self-limiting; more severe bloody diarrhoea may be associated with colonic mucosal ischaemia. Hypersensitivity reactions, including angioedema and anaphylactoid reactions, have been reported rarely. When given rectally, bisacodyl sometimes causes irritation and may cause proctitis or sloughing of the epithelium. To avoid gastric irritation bisacodyl tablets are enteric-coated.

Precautions

As with other laxatives, prolonged use should be avoided. Bisacodyl should not be given to patients with intestinal obstruction or acute abdominal conditions such as appendicitis; care should also be taken in patients with inflammatory bowel disease. It should not be used in patients with severe dehydration. The suppositories should preferably be avoided in patients with anal fissures, proctitis, or ulcerated haemorrhoids.

Handling. Inhalation of bisacodyl powder and contact with eyes, skin, and mucous membranes should be avoided.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bisacodyl as probably not porphyrinogenic when given as tablets or suppositories, and not porphyrinogenic as an enema; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/11/11)

Pharmacokinetics

On oral or rectal use bisacodyl is converted to the active desacetyl metabolite bis(*p*-hydroxyphenyl)pyridyl-2-methane by intestinal and bacterial enzymes. Absorption from the gastrointestinal tract is minimal with enteric-coated tablets or suppositories; the small amount absorbed is excreted in the urine as the glucuronide. Bisacodyl is mainly excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dulcolax; Laxamin; Modaton; Tractoduo; ***Austral.***: Bisalax; Dulcolax; Lax-Tab; ***Austria***: Dulcolax; Laxbene; ***Belg.***: Bisolax; Carters; Dulcolax; Henafurine†; Mucinum; Purgo-Pil; ***Braz.***: Bisalax; Cronoplex†; Deltalax; Dulcolax; Fideine; Isilax; Plesonax; ***Canad.***: Alophen†; Bisacolax; Carters Little Pills; Codulax; Correctol; Dulcolax; Silver Bullet; Soflax EX; The Magic Bullet; Woman's Laxative; ***Chile***: Alsylax; ***China***: Dulcolax (乐可舒); Jie Tai (解泰); Longshutong (隆舒通); ***Cz.***: Dulcolax; Fenolax; Stadalax; ***Denm.***: Dulcolax; Perilax; Toilax; ***Fin.***: Metalax; Toilax; ***Fr.***: Contalax; Dulcolax; ***Ger.***: Bekunis Bisacodyl; Bisco-Zitron; Drix Bisacodyl; Dulcolax; Florisan N†; Laxagetten; Laxans-ratiopharm; Laxans; Laxysat Burger†; Mediolax; Pyrilax; Tempolax†; Tirgon; ***Gr.***: Dulcolax; Florisan N; ***Hong Kong***: Bicolax†; Bisedyl†; Dulax†; Dulcolax; Marcholax†; Monolax†; ***Hung.***: Dulcolax; Stadalax; ***India***: Bidlax; Bisariv; Bo-Lax; Conlax; Dulcolax; JuLax; Junifree; Laxodyl; ***Indon.***: Bicolax; Custodiol; Dulcolax; Laxacod†; Laxamex†; Laxana; Stolax; ***Irl.***: Dulcolax; Toilax; ***Israel***: Atzirut X; Contalax; Laxadin; ***Ital.***: Alaxa; Confetto CM; Dulcolax; Normalene; Sacodil; Stixenil; Verecolene CM; ***Malaysia***: Dulcolax; ***Mex.***: Dulcolan; Dulcolax; ***Neth.***: Dulcolax; Kruidvat Laxeertabletten; Laxeerdragees†; Laxeertabletten; Laxeerzetpillen†; Nourilax; Trekpleister Laxeertabletten; ***Norw.***: Dulcolax; Toilax; ***NZ***: Dulcolax; Fleet Laxative†; Lax-Tab; ***Philipp.***: Bisalax; Dulcolax; Vesilac; ***Port.***: Bekunis Laxante Bisacodil; Dulcolax; Moderlax; ***Rus.***: Dulcolax (Дульколакс); ***S.Afr.***: Dulcolax; Megalax; Perilax†; ***Singapore***: Bicolax; Biolax; Dilax; Dulcolax; Ebolin; Laxodyl; SL Laxative; Sunny Laxative; Unilax; ***Spain***: Dulcolaxo; Laxabixal; ***Swed.***: Dulcolax; Toilax; ***Switz.***: Bekunis Dragees; Demolaxin†; Dulcolax; Muxol; Prontolax; Softala-X; Tavolax; ***Thai.***: Bisacod; Bisacodylcoated; Conlax; Dulcolax; Emulax; Gencolax; Kadolax; KB Biscod; Laxadryl; Laxcodyl; Laxitab†; Monolax; Vacolax†; ***Turk.***: Bisakol; Laksotek; Sekolaks; ***UAE***: Laxocodyl; ***UK***: Biolax; Boots Constipation Relief; Dulcolax; Entrolax; ***USA***: Alophen; Bisa-Lax; Correctol; Doxidan†; Dulcolax; Evac-Q-Tabs; Ex-Lax Ultra; Feen-A-Mint; Fleet Bisacodyl; Fleet Laxative; Gentlax; Modane; ***Venez.***: Dulcolan.

Multi-ingredient Preparations. ***Arg.***: En-Ga-Lax; Fosfo-Dom Kit; Laxicona; Nigalax; Nigalax; ***Austral.***: Coloxyl; Go Kit Plus; Go Kit; ***Austria***: Laxbene; Prepacol; Purgazen†; ***Belg.***: Prepacol; Softene; ***Braz.***: Belpidex; ***Canad.***: Bekunis†; Bi-PegLyte; Bicholate†; Gentlax S†; Royvac Kit†; ***Chile***: Laxogeno; ***Cz.***: Prepacol; ***Fr.***: Prepacol; ***Ger.***: Prepacol; ***Gr.***: Florisan; ***Hung.***: Laxbene; ***NZ***: Coloxyl†; ***Port.***: Bekunis; ***Spain***: Bekunis Complex; ***Thai.***: Bisolax; Chinta-lax; T Man Lax; ***Turk.***: Bekunis; ***USA***: Dulcolax Bowel Prep Kit; Fleet Prep Kit No. 1†; Fleet Prep Kit No. 2†; Fleet Prep Kit No. 3; HalfLytely and Bisacodyl Bowel Prep Kit; X-Prep Bowel Evacuant Kit-1†.

Pharmacopoeial Preparations
BP 2014: Bisacodyl Suppositories; Gastro-resistant Bisacodyl Tablets;
USP 36: Bisacodyl Delayed-release Tablets; Bisacodyl Rectal Suspension; Bisacodyl Suppositories.

Bismuth Compounds

Bismuto, compuestos de; Висмут Соединения.

Profile

Bismuth compounds have been used for their astringent and antidiarrhoeal properties in a variety of gastrointestinal disorders, and have been applied topically in skin disorders and anorectal disorders such as haemorrhoids. Certain salts are active against *Helicobacter pylori* and are used in the treatment of peptic ulcer disease.

Bismuth Aluminate *(USAN)*

Aluminato de bismuto; Aluminum Bismuth Oxide; Алюминат Висмута.
$Bi_2(Al_2O_4)_3.10H_2O$=952.0
CAS — 12284-76-3 (anhydrous bismuth aluminate).
UNII — JB5Y63JDHJ.

Pharmacopoeias. In *Chin.* and *Fr.*

Bismuth Citrate

Citrato de bismuto; Цитрат Висмута.
$BiC_6H_5O_7$=398.1
CAS — 813-93-4.
UNII — N04867Y76N.

NOTE. Do not confuse with bismuth subcitrate potassium (p. 1822.1) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, p. 1822.2).

Pharmacopoeias. In *US*.

USP 36: (Bismuth Citrate). A white, amorphous or crystalline powder. Insoluble in water and in alcohol; soluble in dilute ammonia solution and in solutions of alkali citrates. Store in airtight containers. Protect from light. Prevent exposure to temperatures above 40 degrees.

Bismuth Oxide

Bismuth Trioxide; Óxido de bismuto; Оксид Висмута.
Bi_2O_3=466.0
CAS — 1304-76-3.
UNII — A6I4E79QF1.

Bismuth Salicylate

Basic Bismuth Salicylate; Bázisos bizmut-szalicilát; Bismuth Oxysalicylate; Bismuth, sous-salicylate de; Bismuth Subsalicylate (USAN); Bismuthi subsalicylas; Bismuto subsalicilatas; Bismutsalicylat, Basisches; Salicilato de bismuto; Salicylan bismutitý zásaditý; Vismutsubsalicylat; Vismuttisubsalisylaatti; Салицилат Висмута.
$C_7H_5BiO_4$=362.1
CAS — 14882-18-9.
UNII — 62TEY51RR1.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Bismuth Subsalicylate). A complex of bismuth and salicylic acid. It contains not less than 56% and not

more than 59.4% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition. Protect from light.

USP 36: (Bismuth Subsalicylate). A basic salt corresponding to $C_7H_5BiO_4$ and containing not less than 56.0% and not more than 59.4% of Bi and not less than 36.5% and not more than 39.3% of total salicylates. It is a fine, odourless, white to off-white microcrystalline powder. Practically insoluble in water, in alcohol, and in ether. It reacts with alkalis and mineral acids. Store in airtight containers. Protect from light.

Bismuth Subcarbonate *(USAN)*

Basic Bismuth Carbonate; Basisches Wismutkarbonat; Bázisos bizmutkarbonát; Bism. Carb.; Bismutcarbonat, Basisches; Bismuth Carbonate; Bismuth Oxycarbonate; Bismuth, sous-carbonate de; Bismuthi Subcarbonas; Bismuto subkarbonatas; Bismutylum Carbonicum; Carbonato de Bismutila; Subcarbonato de bismuto; Uhličitan bismutitý zásaditý; Vismutsubkarbonat; Vismuttisubkarbonaatti; Основный Углекислый Висмут.

CBi_2O_5=510.0

CAS — 5892-10-4 (anhydrous bismuth subcarbonate); 5798-45-8 (bismuth subcarbonate hemihydrate).

UNII — M41L2IN55T (bismuth subcarbonate); NJT50MK51G (bismuth subcarbonate hemihydrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in mineral acids with effervescence. Protect from light.

USP 36: (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water, in alcohol, and in ether; dissolves in dilute acids with effervescence. Protect from light.

Bismuth Subcitrate Potassium *(USAN)*

1001277; Biskalcitrate potassium; Bismuth Biscalcitrate; Bismuth biskalcitrate; Основный Калиевый Цитрат Висмута. Bismuth pentapotassium dihydroxide bis(2-hydroxypropane-1,2,3-tricarboxylate hydrate).

$C_{12}H_{14}BiK_5O_{17}$=834.7

CAS — 880149-29-1.

UNII — R3O80H60KX.

NOTE. Do not confuse with bismuth citrate (p. 1821.3) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, below).

Bismuth Subgallate *(USAN)*

Basic Bismuth Gallate; Basisches Wismutgallat; Bázisos bizmut-gallát; Bism. Subgall.; Bismutgallat, Basisches; Bismuth Oxygallate; Bismuth, sous-gallate de; Bismuthi Subgallas; Bismuto subgalatas; Bizmut Subgalat; Bizmutu galusan zasadowy; Gallan bismutitý zásaditý; Subgalato de bismuto; Vismutsubgallat; Vismuttisubgallaatti; Основный Галловокислый Висмут.

$C_7H_5BiO_6$=394.1

CAS — 99-26-3.

UNII — YIW503MI7V.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Bismuth Subgallate). A complex of bismuth and gallic acid. It contains not less than 48% and not more than 51% of Bi, calculated with reference to the dried substance. A yellow powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition and in alkali hydroxides, producing a reddish-brown liquid. Protect from light.

USP 36: (Bismuth Subgallate). A basic salt containing 52 to 57% of Bi_2O_3 when dried at 105 degrees for 3 hours. It is an odourless amorphous bright yellow powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; insoluble in very dilute mineral acids; dissolves readily with decomposition in warm, moderately dilute hydrochloric, nitric, or sulfuric acids; readily dissolves in solutions of alkali hydroxides to form a clear yellow liquid which rapidly becomes deep red. Store in airtight containers. Protect from light.

Bismuth Subnitrate

Subazotato de Bismuto; Basic Bismuth Nitrate; Basisches Wismutnitrat; Bázisos bizmut-nitrát; Bism. Subnit.; Bismuth Hydroxide Nitrate Oxide; Bismuth Nitrate, Heavy; Bismuth Oxynitrate; Bismuth (Sous-Nitrate de) Lourd; Bismuth, sous-nitrate de; Bismuthi Subnitras; Bismuthyl Nitrate; Bismuto subnitratas; Bismuto subnitratas sunkusis; Bizmut Subnitrat; Bizmutu azotan zasadowy; Bizmutu(III) azotan zasadowy; Magistery of Bismuth; Nitrato de Bismutilo; Subnitrato de bismuto; Vismutsubnitrat; Vismuttisubnitraatti; White Bismuth; Основный Азотнокислый Висмут.

$Bi_5O(OH)_9(NO_3)_4$=1462.0

CAS — 1304-85-4.

ATC — A02BX12.

ATC Vet — QA02BX12.

UNII — H19J064BA5.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Fr. also includes Bismuth (Sous-Nitrate de) Léger (Bismuthi Subnitras Levis) which is described as a variable mixture of bismuth hydroxide, carbonate, and subnitrate.

Ph. Eur. 8: (Bismuth Subnitrate, Heavy). It contains not less than 71% and not more than 74% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition.

USP 36: (Bismuth Subnitrate). A basic salt containing not less than 79% of Bi_2O_3 calculated on the dried basis. It is a white, slightly hygroscopic powder. Practically insoluble in water and in alcohol; readily dissolves in nitric and hydrochloric acids.

Tripotassium Dicitratobismuthate

Bizmut Subsitrat; Colloidal Bismuth Subcitrate; Dicitratobismutato tripotásico; Tripotasyum Disitratobizmutat; Висмут Трикалия Дицитрат.

CAS — 57644-54-9.

ATC — A02BX05.

ATC Vet — QA02BX05.

NOTE. Do not confuse with bismuth citrate (p. 1821.3) or bismuth subcitrate potassium (above).

Uses and Administration

Some insoluble salts of bismuth are given orally for their supposed antacid action and for their mildly astringent action in various gastrointestinal disorders, including diarrhoea (p. 1805.2) and dyspepsia (p. 1806.3). Such salts include the aluminate, salicylate, subcarbonate, and subnitrate. Bismuth salicylate, which is given as an antidiarrhoeal and weak antacid in doses up to about 4 g daily in divided doses, possesses in addition the properties of the salicylates.

Tripotassium dicitratobismuthate is active against *Helicobacter pylori* and has been used as triple therapy (with metronidazole and either tetracycline or amoxicillin) to eradicate this organism and thereby prevent relapse of duodenal ulcer. It is also used as a mucosal protectant for the treatment of peptic ulcer disease (p. 1813.2). Bismuth subcitrate potassium and bismuth salicylate are also active against *H. pylori* and have been used similarly in eradication regimens.

The usual oral dose of tripotassium dicitratobismuthate in benign gastric and duodenal ulceration is 240 mg twice daily, or 120 mg four times daily before food. Treatment is for a period of 4 weeks, extended to 8 weeks if necessary. Maintenance therapy with tripotassium dicitratobismuthate is not recommended although treatment may be repeated after a drug-free interval of one month. When used as part of triple therapy the usual dose of tripotassium dicitratobismuthate has been 120 mg four times daily for 2 weeks. The usual dose of bismuth salicylate as part of triple therapy is 525 mg four times daily for 2 weeks. Appropriate antisecretory treatment with a histamine H_2-antagonist or a proton pump inhibitor is usually added to these regimens.

A complex of bismuth citrate with ranitidine, ranitidine bismuth citrate (p. 1883.3), has also been used in the treatment of peptic ulcer disease. Colloidal bismuth pectin, a complex salt of bismuth, potassium, and *d*-polygalacturonic acid, has also been used.

Some insoluble salts of bismuth have been used topically in the treatment of skin disorders, wounds, and burns. Some have been used as ingredients of ointments or suppositories (sometimes containing more than one bismuth salt) in the treatment of haemorrhoids and other anorectal disorders (p. 1808.1). Bismuth compounds that have been used topically and/or rectally include the oxide, subgallate, and subnitrate; bismuth resorcinol compounds have also been used. For the use of bismuth subnitrate and iodoform paste as a wound dressing, see Iodoform, p. 1758.2.

Numerous other salts and compounds of bismuth have been promoted for various therapeutic purposes. Glycobiarsol was formerly given orally as an amoebicide.

Homoeopathy

Bismuth has been used in homoeopathic medicines under the following names: Bismuthum; Bismutum metallicum; Bismuthum metallicum; Bismuth met.

Bismuth oxide has been used in homoeopathic medicines under the following names: Bismuthum oxydatum; Bismuth oxyd; Bis. ox.

Bismuth subnitrate has been used in homoeopathic medicines under the following names: Heavy bismuth subnitrate; Bismuthi subnitras ponderosus; Bismuthum subnitricum; Bismuth sub; Bismutum subnitricum; Bism. sub.

Adverse Effects, Treatment, and Precautions

The bismuth compounds listed above are insoluble or very poorly soluble, and bismuth toxicity does not appear to be common if they are used for limited periods. However, excessive or prolonged dosage may produce symptoms of bismuth poisoning, and for this reason long-term systemic therapy is not recommended. Reversible encephalopathy (see below) was once a problem in some countries, notably France and Australia; bone and joint toxicity had also occurred, sometimes associated with the encephalopathy. This led to restrictions on the use of bismuth salts and a virtual disappearance of these toxic effects.

Nausea and vomiting have been reported. Darkening or blackening of the faeces and tongue may occur due to conversion to bismuth sulfide in the gastrointestinal tract.

The effects of *acute bismuth intoxication* include gastrointestinal disturbances, skin reactions, stomatitis, and discoloration of mucous membranes; a characteristic blue line may appear on the gums. There may be renal failure and liver damage.

Other adverse effects may not be related to the bismuth content. With bismuth subnitrate given orally there is a risk of the nitrate being reduced in the intestines to nitrite and the development of methaemoglobinaemia. Absorption of salicylate occurs from oral bismuth salicylate and therefore the adverse effects, treatment of adverse effects, and precautions of aspirin (p. 24.2) should be considered.

Gastric lavage should be considered in overdosage; oral activated charcoal and the use of a chelating agent such as dimercaprol, succimer, or unithiol have been recommended (see also Overdosage, below). Renal function should be monitored for 10 days after acute overdosage.

Bismuth compounds should not be given to patients with moderate to severe renal impairment.

Encephalopathy. Reviews[1,2] and reports[3-11] of reversible bismuth encephalopathy. Many of the original reports implicated bismuth subgallate or subnitrate, in most but not all cases at high doses or for prolonged periods; toxicity has also occurred with other salts.[6-9] Patients receiving the subcitrate (480 mg daily) or the subnitrate (1.8 g daily) for 8 weeks in the treatment of *Helicobacter pylori* infection, showed no evidence of neurological changes compared with a control group.[12]

1. Winship KA. Toxicity of bismuth salts. *Adverse Drug React Acute Poisoning Rev* 1983; **2:** 103–21.
2. Slikkerveer A, de Wolff FA. Pharmacokinetics and toxicity of bismuth compounds. *Med Toxicol Adverse Drug Exp* 1989; **4:** 303–23.
3. Morrow AW. Request for reports: adverse reactions with bismuth subgallate. *Med J Aust* 1973; **1:** 912.
4. Martin-Bouyer G. Intoxications par les sels de bismuth administrés par voie orale: enquête épidémiologique. *Therapie* 1976; **31:** 683–702.
5. Stahl JP, *et al.* Encéphalites au sel insoluble de bismuth: toujours d'actualité. *Nouv Presse Med* 1982; **11:** 3856.
6. Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; **2:** 167.
7. Weller MPI. Neuropsychiatric symptoms following bismuth intoxication. *Postgrad Med J* 1988; **64:** 308–10.
8. Mendelowitz PC, *et al.* Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; **112:** 140–1.
9. Playford RJ, *et al.* Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure. *Gut* 1990; **31:** 359–60.
10. Von Bose MJ, Zaudig M. Encephalopathy resembling Creutzfeldt-Jakob disease following oral, prescribed doses of bismuth nitrate. *Br J Psychiatry* 1991; **158:** 278–80.
11. Teepker M, *et al.* Myoclonic encephalopathy caused by chronic bismuth abuse. *Epileptic Disord* 2002; **4:** 229–33.
12. Noach LA, *et al.* Bismuth salts and neurotoxicity: a randomised, single-blind and controlled study. *Hum Exp Toxicol* 1995; **14:** 349–55.

TOPICAL APPLICATION. Encephalopathy has been associated with the use of bismuth iodoform paraffin paste (BIPP) for the packing of wound cavities after surgery to the head and neck, although there is some debate as to whether the bismuth or the iodoform component is responsible—see p. 1758.2.

Overdosage. Bismuth salicylate or tripotassium dicitratobismuthate in recommended doses are rarely associated with serious adverse effects but there are reports of renal failure,[1-7] encephalopathy,[8-10] and neurotoxicity[1] in acute[1-6,9] or chronic[8,10] overdose. Bismuth has been detected in the blood, urine, stools, and kidneys of these patients; a blood concentration of 1.6 micrograms/mL was found[2] 4 hours after an oral dose of 9.6 g.

The optimal treatment of bismuth overdosage is unknown. Gastric lavage, purgation, and hydration should be considered, even if the patient presents late, as bismuth may be absorbed from the colon.[1,2] Chelating agents may be effective; unithiol has been reported to increase the renal clearance of bismuth with a reduction in the blood concentration.[8] Haemodialysis may be necessary[1-3] but

whether this hastens tissue clearance is uncertain. Haemodialysis plus unithiol treatment has been reported to successfully eliminate bismuth.[6] Peritoneal dialysis has also been effectively used in a paediatric patient.[5]

Prolonged ingestion of bismuth salicylate in excessive doses by an elderly diabetic was associated with hearing disturbances, vertigo, acid–base abnormalities and mild clotting disturbances.[11] The toxicity was thought to be due to the salicylate component.

1. Hudson M, Mowat NAG. Reversible toxicity in poisoning with colloidal bismuth subcitrate. *BMJ* 1989; **299:** 159.
2. Taylor EG, Klenerman P. Acute renal failure after colloidal bismuth subcitrate overdose. *Lancet* 1990; **335:** 670–1.
3. Huwez F, *et al*. Acute renal failure after overdose of colloidal bismuth subcitrate. *Lancet* 1992; **340:** 1298.
4. Akpolat I, *et al*. Acute renal failure due to overdose of colloidal bismuth. *Nephrol Dial Transplant* 1996; **11:** 1890–8.
5. İ. şlek İ, *et al*. Reversible nephrotoxicity after overdose of colloidal bismuth subcitrate. *Pediatr Nephrol* 2001; **16:** 510–14.
6. Hruz P, *et al*. Fanconi's syndrome, acute renal failure, and tonsil ulcerations after colloidal bismuth subcitrate intoxication. *Am J Kidney Dis* 2002; **39:** E18.
7. Cengiz N, *et al*. Acute renal failure after overdose of colloidal bismuth subcitrate. *Pediatr Nephrol* 2005; **20:** 1355–8.
8. Playford RJ, *et al*. Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure. *Gut* 1990; **31:** 359–60.
9. Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; **2:** 167.
10. Mendelowitz PC, *et al*. Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; **112:** 140–1.
11. Vernace MA, *et al*. Chronic salicylate toxicity due to consumption of over-the-counter bismuth subsalicylate. *Am J Med* 1994; **97:** 308–9.

Toxicity from non-conventional use. The FDA has warned against use of an injectable product called bismacine or chromacine, which contains large amounts of bismuth. There are reports of death or serious adverse effects associated with its use. Although unlicensed for any use, bismacine has apparently been used in alternative medicine to treat Lyme disease.[1]

1. FDA. FDA warns consumers and health care providers not to use bismacine, also known as chromacine (issued 21st July 2006). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108696.htm (accessed 15/07/10)

Interactions

Bismuth salts given orally reduce the absorption of tetracyclines, possibly by chelation or by reducing tetracycline solubility as a result of increasing the gastric pH. This interaction can be minimised by separating doses of the two drugs by a couple of hours. The clinical significance of this interaction to the use of bismuth salts for peptic ulcer disease is unclear; tripotassium dicitratobismuthate or bismuth salicylate have been given at the same time as tetracycline as part of triple therapy for the eradication of *Helicobacter pylori*.

Antisecretory drugs. Pretreatment with *omeprazole* resulted in about a threefold increase in absorption of bismuth from tripotassium dicitratobismuthate in 6 healthy subjects.[1] The mean peak plasma concentration of bismuth after a single dose of 240 mg of tripotassium dicitratobismuthate was increased from 36.7 to 86.7 nanograms/mL after omeprazole suggesting an increased risk of toxicity from combined therapy. The mechanism was thought to be the increase in gastric pH produced by the antisecretory drug as similar results had been reported with *ranitidine*.[2] However, the clinical significance of these interactions to the use of antisecretory drugs with bismuth compounds for eradication of *Helicobacter pylori* is unclear; bismuth compounds have been combined with proton pump inhibitors or H_2 antagonists in short-term regimens as part of triple or quadruple therapy.

1. Treiber G, *et al*. Omeprazole-induced increase in the absorption of bismuth from tripotassium dicitrato bismuthate. *Clin Pharmacol Ther* 1994; **55:** 486–91.
2. Nwokolo CU, *et al*. The effect of histamine H_2-receptor blockade on bismuth absorption from three ulcer-healing compounds. *Gastroenterology* 1991; **101:** 889–94.

Pharmacokinetics

Poorly soluble bismuth compounds are largely converted to insoluble bismuth oxide, hydroxide, and oxychloride in the acidic environment of the stomach. Most of the bismuth compounds included in this monograph are thus only slightly absorbed. Increased gastric pH may increase bismuth absorption—see Antisecretory Drugs, above. Unabsorbed bismuth is excreted in the faeces. Absorbed bismuth is distributed throughout body tissues, including bone, and is slowly excreted in the urine and bile. It has a plasma half-life of about 5 days and continues to be excreted for about 12 weeks after stopping therapy.

References.

1. Nwokolo CU, *et al*. The absorption of bismuth from oral doses of tripotassium dicitrato bismuthate. *Aliment Pharmacol Ther* 1989; **3:** 29–39.
2. Froomes PRA, *et al*. Absorption and elimination of bismuth from oral doses of tripotassium dicitrato bismuthate. *Eur J Clin Pharmacol* 1989; **37:** 533–6.
3. Lacey LF, *et al*. Comparative pharmacokinetics of bismuth from ranitidine bismuth citrate (GR122311X), a novel anti-ulcerant and tripotassium dicitrato bismuthate (TDB). *Eur J Clin Pharmacol* 1994; **47:** 177–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Re-Dux; Sesamoil; ***Braz.***: Pepto-Bismol†; Peptozil; Peptulan; ***Canad.***: Devrom; Maalox Multi-action†; Neo-Laryngobis; Pepto-Bismol; Stomak-Care; Xeroform; ***China***: Ai Xi (艾悉); De Bi Tai (得必泰); De-Nol (德诺); Li Bi De (力比得); Wei Di Ya (唯迪亚); Xi Xin (悉欣); ***Ger.***: Haemo-Exhirud Bufexamac†; Stryphnasal N; ***Gr.***: De-Nol; ***Hong Kong***: De-Nol; Pepto-Bismol†; ***India***: Denol; Trymo; ***Indon.***: Scantoma; Stobiol; ***Israel***: BITNI X; Kalbeten; Peptolite; Pink Bismuth; ***Ital.***: De-Nol; ***Mex.***: Bismed; Bismofarma; Bisval†; Facidmol; Itamol; Pepto-Bismol; Siparox; Sucrato; ***Neth.***: De-Nol; ***NZ***: De-Nol; ***Rus.***: De-Nol (Де-Нол); ***S.Afr.***: De-Nol; ***Singapore***: De-Nol; ***Spain***: Gastrodenol; Rectamigdol†; ***Switz.***: Amygdorectol; ***Thai.***: Besmal; De-Nol; Gastro-Bismol; ***Turk.***: De-Nol; Dermatol; ***UK***: De-Noltab; Pepto-Bismol; ***Ukr.***: De-Nol (Де-Нол); Gastro-Norm (Гастро-Норм); Vis-nol (Вис-Нол); ***USA***: Bismatrol; Children's Kaopectate; Devrom; Kao-Tin; Kaopectate; Kapectolin†; Maalox Total Relief; Peptic Relief; Pepto-Bismol.

Multi-ingredient Preparations. ***Arg.***: Anusol Duo S; Anusol-HC; Anusol†; Benitol; Colistop; Crema De Bismuto; Gastop; Gastranil; Gastricur; Lemil; Mabis†; Macoderm; Neoastrin; ***Austral.***: BIP; ***Belg.***: Procto-Synalar; Rectovasol; ***Braz.***: Aftine; Anusol-HC; Bismu-Jet; Claudemor; Colutoide; Cutisanol; Cutisanol; Hemodase; Magnesia Bisurada; ***Canad.***: Bismutal; Bismuth + Antacid; Onrectal†; Pepto-Bismol; Watkins Settelz†; ***China***: Chanyanling (肠炎灵); Ge Lai Shi (格来士); Pepto-Bismol (佩普); Qiyu (奇钰); Yi Shuang Bi (易双必); Yilishu (宜立舒); ***Cz.***: Carbocit; Mastu S†; Spofax; Suspensio Visnevski cum Pice Liquida HBF; ***Fin.***: Tannopon†; ***Fr.***: Anusol†; Bi-Qui-Nol; Cutiphile†; Paps†; Pholcones Bismuth; ***Ger.***: Anaesthesin akut†; Angass†; Bismolan H Corti; Eulatin NH; Eulatin NH; Faktu akut†; Hamo-ratiopharm N†; Hamoagil plus†; Hexamon Bufexamac†; Mastu akut†; Mastu; Ventricon N†; ***Gr.***: Hemorroidal; ***Hong Kong***: Anusol; Anuzinc†; Haemoral†; Mastu S†; Rowatanal; ***Hung.***: Bolus Adstringens; Gastritec; Mastu S†; Nilacid; ***Indon.***: Anusol-HC†; Anusol†; ***Irl.***: Anugesic-HC; Anugesic-HC; Anusol-HC; Anusol; Anusol; Hemocane; Pylera; Rowatanal; ***Israel***: Hemo; Hemo; Rectozorin; Rectozorin; Rekiv†; ***Ital.***: Antiemorroidali†; ***Malaysia***: Rowatanal; ***Mex.***: Estomacurol†; Heliton; Pepti-Max; ***Neth.***: Anaesthetica†; Roteroblong Maagtabletten; Suppositoria contra haemorrhoides; Theranal; ***Pol.***: Gastro†; Hemorectal; ***Port.***: Synalar Rectal; ***Rus.***: Anaesthesol (Анестезол); Anusol (Анузол); Neo-Anusol (Неоанузол); Proctosan (Проктозан); Simetrid (Симетрид); Vicair (Викаир); Vicalin (Викалин); ***S.Afr.***: Adco-Biskapect†; Anugesic†; Anusol; Arola Rosebalm†; Chloropect; Enterodyne†; Kantrexil; Sentinel Ulcer Mixture†; ***Singapore***: Rowatanal†; ***Spain***: Grietalgen; Nasopomada†; Synalar Rectal; ***Switz.***: Bismorectal†; Cicafissan; Furodermal†; Haemocortin†; Haemolan†; La pommade du Dr Brand; Rectoseptal-Neo bismuthe; ***Thai.***: Antidiarrhoeals for children; Anusol†; Biodan; Bismocane; Mastu S†; Ulgastrin; ***Turk.***: Deriseptol; Derivit; Dermikolin; Dervanol; Hemoralgine; Kortos; Metamorfoz; ***UK***: Anugesic-HC†; Anugesic-HC; Anusol-HC, Plus HC; Anusol; Anusol; Bisma-Rex; Hemocane; Moorland; OxBipp; Stomach Mixture; ***Ukr.***: Proctosan (Проктозан); Vicair (Викаир); Vicalin (Викалин); ***USA***: Anumed HC; Anumed; BFI; Calmol; Helidac; Hem-Prep; Hemril; K-C; Kao-Paverin; Kaodene Non-Narcotic; Mammol; Pylera; Rectagene Medicated Rectal Balm; ***Venez.***: Klincosal; Polantac.

Homoeopathic Preparations. ***Austria***: Astomera; ***Fr.***: Argentum Complexe no 98; ***Ger.***: Gastritis Complex; Gastro Magentabletten; Nuxal comp.

Pharmacopoeial Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste;
USP 36: Bismuth Subsalicylate Magma; Bismuth Subsalicylate Oral Suspension; Bismuth Subsalicylate Tablets; Compound Resorcinol Ointment; Milk of Bismuth.

Bisoxatin Acetate *(BANM, USAN, rINNM)*

Acetato de bisoxatina; Bisoxatin Diacetate; Bisoxatina, acetato de; Bisoxatine, Acétate de; Bisoxatini Acetas; Wy-8138; Бизоксатина Ацетат.

2,2-Bis(4-hydroxyphenyl)-1,4-benzoxazin-3(2*H*,4*H*)-one diacetate.

$C_{24}H_{19}NO_6$=417.4

CAS — 17692-24-9 (bisoxatin); 14008-48-1 (bisoxatin acetate).
ATC — A06AB09.
ATC Vet — QA06AB09.
UNII — 79W5LFS83K.

Profile

Bisoxatin acetate is a stimulant laxative that has been used in a usual oral dose of 120 mg at night in the treatment of constipation (p. 1804.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Wylaxine; ***Venez.***: Regoxal.

Bran

Crusca; Farelo; Kleie; Salvado; Son; Отруби.

UNII — 1L922R9NG2 (bran fibre); KQX236OK4U (oat bran); R60QEP13IC (rice bran); 6L966A1IMR (wheat bran).

Description. Bran consists of the fibrous outer layers of cereal grains. It contains celluloses, polysaccharides or hemicelluloses, protein, fat, minerals, and moisture and may contain part of the germ or embryo. Bran provides water-insoluble fibre and, depending on the source, may also provide water-soluble fibre (see also Dietary Role, below). It comprises about 12% of the weight of the grain and is a byproduct of flour milling. It is available in various grades.

Pharmacopoeias. *US* includes wheat bran.

USP 36: (Wheat Bran). The outer fraction of the cereal grain (comprising the pericarp, seed coat (testa), nucellar tissue, and aleurone layer) derived from *Triticum aestivum, T. compactum, T. durum,* or other common einkorn and emmer wheat cultivars. It is obtained by milling and processing the whole wheat grain, and is available in a variety of particle sizes depending on the degree of milling. It contains not less than 36% of dietary fibre. It is a light tan powder having a characteristic aroma. Practically insoluble in cold water and in alcohol.

Uses and Administration

The main use of bran is as a bulk laxative and source of dietary fibre in the management of disorders of the gastrointestinal tract such as constipation (p. 1804.3), especially in diverticular disease (p. 1806.2); it is also widely used in irritable bowel syndrome, although its value has been questioned (see p. 1810.3). It should always be taken with plenty of fluid.

Bran is used as the basis for some breakfast cereals.

Dietary role. There is no precise definition for the complex mixture of substances known as dietary fibre. It has been defined as *plant* polysaccharides and lignin resistant to hydrolysis by the digestive enzymes of humans but this covers many substances other than cell-wall and related polysaccharides. Non-starch polysaccharides are the major component of the plant cell wall and are used as an index of dietary fibre. They comprise water-soluble fibres such as pectins, gums, and mucilages and water-insoluble fibres such as cellulose. Wheat, maize, and rice contain mainly insoluble non-starch polysaccharides whereas oats, barley, and rye have a significant proportion of soluble fibres.[1] Because the USA originally included nondigestible *animal* carbohydrates in the definition of fibre, the Food and Nutrition Board in the USA proposed a new definition of fibre, whereby dietary fibre consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants, and functional fibre consists of isolated, nondigestible plant or animal carbohydrates that have beneficial physiological effects in humans. Total fibre is the sum of dietary and functional fibre.[2]

In the UK, dietary reference values (DRV) have been published for non-starch polysaccharides.[1] It has been proposed[1] that adult diets should contain an average for the population of 18 g daily (individual range 12 to 24 g daily) non-starch polysaccharide from a variety of foods whose constituents contain it as a naturally integrated component. Children should receive proportionately less non-starch polysaccharide according to body size. No evidence exists for benefit of intakes of non-starch polysaccharide in excess of 32 g daily, and therefore there is no advantage in exceeding this amount.

In the USA, a total dietary fibre intake of 14 g of fibre per 1000 calories consumed has been suggested for adults and children aged from 1 year.[3]

1. DOH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids.* Washington DC: National Academy Press, 2002/2005. Also available at: http://www.nap.edu/openbook.php?record_id=10490 (accessed 04/04/08)
3. Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2008; **108:** 1716–31. Correction. *ibid.* 2009; **109:** 350. Also available at: http://www.eatright.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=8442 (accessed 15/07/10)

Disease prevention. Diseases such as colorectal cancer, ischaemic heart disease, diabetes mellitus, and obesity are common in affluent developed countries but occur rarely

in rural Africa. This difference in disease patterns has been linked to the low fibre intake in developed countries compared with rural Africans. However, there are many other differences in diet and lifestyle, such as a lower intake of fat, protein, and sugar in rural Africans and less exposure to toxins and pollutants, any of which could contribute to the difference. The excessive consumption of energy-rich foods may be more to blame for diseases of affluence than is deficiency of dietary fibre.[1]

Results from large prospective cohort studies have been conflicting as to whether there is any *reduction in risk* of **colorectal cancer** associated with a high intake of dietary fibre, and have mostly failed to show a reduction in the *recurrence rate* of colorectal adenomas (although most adenomas do not develop into cancer, and so the relevance of these results is unclear[2]). A pooled analysis of 13 prospective cohort studies found a significant inverse association between dietary fibre intake and colorectal cancer. However, after adjusting for other risk factors, this association was attenuated and no longer statistically significant. There was some suggestion that intake of dietary fibre from cereals and from whole-grain foods were both associated with a weak reduction in the risk of rectal cancer.[3] Some have commented[4] that fibre is a broad term encompassing a wide range of organic material, which may have a large number of actions on digestive physiology. Furthermore, there is some concern that the use of fibre supplements is not entirely without harmful effects: it has been pointed out that fermentable fibre substrates can stimulate cell proliferation in the colon.[5] However, the role of cell proliferation as a marker for the development of colonic cancer is questioned by some authors.[6]

A small randomised crossover study[7] in patients with type 2 **diabetes mellitus** suggested that an increased intake of dietary fibre was associated with improved glycaemic control, decreased hyperinsulinaemia, and lower plasma lipid concentrations. In prospective cohort studies, inverse associations were found between whole-grain intake and the risk of type 2 diabetes mellitus;[8-11] in some studies, this inverse association persisted for cereal fibre intake,[9-11] but in one the protective effect of whole grain could not entirely be explained by fibre content.[8]

Fibre may act as an obstacle to energy intake by displacing available calories and nutrients from the diet, by increasing satiety, and by decreasing the absorption efficiency of the small intestine. Epidemiological studies support the hypothesis that a higher dietary fibre intake prevents **obesity**; populations that report higher fibre consumption also demonstrate lower obesity rates.[12] Weight gain was inversely associated with increases in the intake of whole grains but positively associated with increases in the intake of refined grains, emphasising the importance of distinguishing whole-grain from refined-grain products.[13]

A large prospective cohort study in men found an inverse association between whole-grain intake and the incidence of **coronary heart disease**; the finding was even stronger for bran intake. These associations were attenuated, but not eliminated, by adjustment for other risk factors for coronary heart disease.[14] There is some suggestion that diets high in fibre may have a moderate effect on blood pressure reduction.[15]

1. Anonymous. The bran wagon. *Lancet* 1987; **i:** 782–3.
2. Byers T. Diet, colorectal adenomas, and colorectal cancer. *N Engl J Med* 2000; **342:** 1206–7.
3. Park Y, *et al*. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 2005; **294:** 2849–57.
4. Goodlad RA. Dietary fibre and the risk of colorectal cancer. *Gut* 2001; **48:** 587–9.
5. Wasan HS, Goodlad RA. Fibre-supplemented foods may damage your health. *Lancet* 1996; **348:** 319–20.
6. Hill MJ, Leeds AR. Fibre and colorectal cancer. *Lancet* 1996; **348:** 957.
7. Chandalia M, *et al*. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 1392–8.
8. Liu S, *et al*. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000; **90:** 1409–15.
9. Meyer KA, *et al*. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000; **71:** 921–30.
10. Fung TT, *et al*. Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr* 2002; **76:** 535–40.
11. Montonen J, *et al*. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* 2003; **77:** 622–9.
12. Slavin JL. Dietary fiber and body weight. *Nutrition* 2005; **21:** 411–18.
13. Liu S, *et al*. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. *Am J Clin Nutr* 2003; **78:** 920–7.
14. Jensen MK, *et al*. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* 2004; **80:** 1492–9.
15. He J, *et al*. Effect of dietary fiber intake on blood pressure: a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2004; **22:** 73–80.

Adverse Effects

Large quantities of bran may temporarily increase flatulence and abdominal distension, and intestinal obstruction may occur rarely.

Colonic atony. Colonic atony has been reported in patients who had increased their intake of dietary fibre to relieve constipation associated with systemic sclerosis.[1]

1. Gough A, *et al*. Dietary advice in systemic sclerosis: the dangers of a high fibre diet. *Ann Rheum Dis* 1998; **57:** 641–2.

Diarrhoea. A report of diarrhoea induced by a dramatic increase in fibre intake. Reduction of dietary fibre led to a return to normal bowel habit in 2 to 3 days.[1]

1. Saibil F. Diarrhea due to fiber overload. *N Engl J Med* 1989; **320:** 599.

Intestinal obstruction. Intestinal obstruction associated with excessive bran intake has been reported.[1-3]

1. Allen-Mersh T, De Jode LR. Is bran useful in diverticular disease? *BMJ* 1982; **284:** 740.
2. Cooper SG, Tracey EJ. Small-bowel obstruction caused by oat-bran bezoar. *N Engl J Med* 1989; **320:** 1148–9.
3. Miller DL, *et al*. Small-bowel obstruction from bran cereal. *JAMA* 1990; **263:** 813–14.

Precautions

Bran is contra-indicated in patients with intestinal obstruction or with undiagnosed abdominal symptoms. There is a particular risk of intestinal or oesophageal obstruction if bulk laxatives are swallowed dry; they should be taken with sufficient fluid and should not be taken immediately before going to bed. Wheat bran should be avoided in gluten enteropathies and coeliac disease.

Interactions

Bran may reduce the absorption of some drugs when given together orally. Interference with iron, zinc, and calcium absorption has been reported; calcium phosphate may be added to bran to neutralise fytic acid, which can contribute to such interference.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Trifibra Mix; ***China***: Fiberform (非比麸); ***Fr.***: Doses-O-Son; Infibran†; ***India***: Imbran; ***Neth.***: Fiberform; ***Port.***: Infibran†; ***Swed.***: Fiberform Mix†; Fiberform†.

Multi-ingredient Preparations. ***Arg.***: Adelgacin; Gelax; ***Chile***: Naticare; ***Mex.***: Psilumax†; ***Pol.***: Magnezytki†; Otrebuski†.

Bromopride *(rINN)*

Bromoprida; Bromopridum; CM-8252; VAL-13081; Бромоприд.

4-Amino-5-bromo-*N*-(2-diethylaminoethyl)-*o*-anisamide.

$C_{14}H_{22}BrN_3O_2$=344.3

CAS — 4093-35-0.

ATC — A03FA04.

ATC Vet — QA03FA04.

UNII — 75473V2YZK.

Profile

Bromopride is a substituted benzamide similar to metoclopramide (p. 1862.2), used in a variety of gastrointestinal disorders including nausea and vomiting (p. 1811.3) and motility disorders. It is given in a usual oral dose of 20 to 60 mg daily in divided doses, or 10 to 20 mg daily by intramuscular or intravenous injection. The hydrochloride is also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Bilenzima†; Bromogex; Bromopan; Digerex†; Digesan; Digesprid; Digestil; Digestina; Pangest; Plamet; Pridecil; ***Ital.***: Procirex; Valopride.

Multi-ingredient Preparations. ***Braz.***: Digecap-Zimatico; Lansoprid†; Primeral; ***Port.***: Modulanzime.

Buckthorn

Bacca Spinae Cervinae; Espino Cerval; Kreuzdorn; Nerprun; Крушина Слабительная; Жостер Слабительный.

UNII — B4R1EZ1R1D (buckthorn extract).

NOTE. Distinguish from Alder Buckthorn Bark (see Frangula Bark, p. 1843.3) and from Sea Buckthorn (p. 2611.3).

Pharmacopoeias. In *Ger*.

Profile

Buckthorn is the dried ripe fruit of *Rhamnus cathartica* (Rhamnaceae); the bark is also occasionally used. Buckthorn is an anthraquinone stimulant laxative.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Colon Care; Detox Program; Neo-Cleanse; ***Rus.***: Laxantis Species No 1 (Слабительный Сбор 1); Proctophytol (Проктофитол); Vicalin (Викалин); ***UK***: Cleansing Herbs; Lion Cleansing Herbs; ***USA***: Detox.

Butropium Bromide *(rINN)*

Bromuro de butropio; Butropii Bromidum; Butropio, bromuro de; Butropium, Bromure de; Бутропия Бромид.

(-)-(1*R*,3*r*,5*S*)-8-(4-Butoxybenzyl)-3-[(*S*)-tropoyloxy]tropanium bromide.

$C_{28}H_{38}BrNO_4$=532.5

CAS — 29025-14-7.

UNII — R3K4503MV7.

Pharmacopoeias. In *Jpn*.

Profile

Butropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used in the symptomatic treatment of visceral spasms in an oral dose of 30 mg daily in 3 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Coliopan†; ***Jpn***: Coliopan; ***Malaysia***: Coliopan.

Calcium Carbonate

Calcii carbonas; Calcii Carbonas Praecipitatus (precipitated calcium carbonate); Calcium, carbonate de; Calciumcarbonat; Carbonato de calcio; Creta Preparada; E170; Kalcio karbonatas; Kalciumkarbonat; Kalcium-karbonát; Kalsiumkarbonaatti; Kalsiyum Karbonat; Precipitated Calcium Carbonate; Precipitated Chalk; Uhličitan vápenatý; Wapnia węglan; Wapnia węglan strącony (precipitated calcium carbonate); Кальция Карбонат.

$CaCO_3$=100.1

CAS — 471-34-1.

ATC — A02AC01; A12AA04.

ATC Vet — QA02AC01; QA12AA04.

UNII — H0G9379FGK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US includes Ground Limestone.

Ph. Eur. 8: (Calcium Carbonate). A white or almost white powder. Practically insoluble in water.

USP 36: (Calcium Carbonate). A fine, white, odourless, microcrystalline powder. Practically insoluble in water; its solubility in water is increased by the presence of carbon dioxide or ammonium salts although the presence of any alkali hydroxide reduces its solubility; insoluble in alcohol; dissolves with effervescence in acetic acid, in hydrochloric acid, and in nitric acid.

USP 36: (Ground Limestone). A white to off-white, fine microcrystalline powder mostly consisting of calcium carbonate.

Uses and Administration

Calcium carbonate is used as an antacid (p. 1803.1), usually in oral doses of up to about 1.5 g. It is often given with other antacids, especially magnesium-containing antacids.

Calcium carbonate is also used as a calcium supplement in deficiency states and as an adjunct in the management of osteoporosis, as described under Calcium, p. 1784.3.

Calcium carbonate binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It is used to treat hyperphosphataemia in patients with chronic renal failure (see Renal Osteodystrophy, p. 1170.1) or associated secondary hyperparathyroidism (p. 1170.3). Doses are adjusted according to serum phosphate concentrations. Typical oral doses of calcium carbonate range from about 3 to 7 g (1.2 to 2.8 g calcium) daily in divided doses, although the US National Kidney Foundation suggests that the total dose of elemental calcium provided by the calcium-based phosphate binder should not exceed 1.5 g daily in those with kidney failure. For doses in children, see p. 1825.1.

Calcium carbonate is also used as a food additive.

Homoeopathy

Native forms of calcium carbonate have been used in homoeopathic medicines under the following names: Calcarea Carbonica; Calc. Carb.; Calcium carbonicum

Hahnemanni; Conchae; Calcium Carbonate of Hahnemann; Cal. carb.

Administration in children. Calcium carbonate can be used as a phosphate binder in children with renal failure and hyperphosphataemia. The *BNFC* suggests the following oral doses of calcium carbonate, given 3 or 4 times daily with or before meals, and adjusted as necessary:

- 1 month to 1 year of age: 120 mg
- 1 to 6 years: 300 mg
- 6 to 12 years: 600 mg
- 12 to 18 years: 1.25 g

Adverse Effects, Treatment, and Precautions

Calcium carbonate may occasionally cause constipation. Flatulence from released carbon dioxide may occur in some patients. High doses or prolonged use may lead to gastric hypersecretion and acid rebound. Like other calcium salts (see p. 1786.1), calcium carbonate can cause hypercalcaemia, particularly in patients with renal impairment or after high doses. Alkalosis (p. 1775.3) may also occur as a result of the carbonate anion. There have been rare reports of the milk-alkali syndrome, see below, and tissue calcification. The possibility of an increased risk of myocardial infarction associated with the use of calcium supplements has been raised (see Effects on the Cardiovascular System, p. 1786.1).

For precautions to be observed with the use of calcium carbonate, see Calcium, p. 1786.1.

Milk-alkali syndrome. The milk-alkali syndrome of hypercalcaemia, alkalosis and renal impairment was first identified in the 1920s and may still occur in patients who take large amounts of calcium and absorbable alkali.[1-3] With chronic ingestion, abnormal calcification can develop.[3]

Calcium carbonate is a common source of calcium and alkali, and milk-alkali syndrome can be seen in patients being treated for osteoporosis and after high intake of antacids.[3] Although an elemental calcium intake of up to 2 g daily is considered safe, milk-alkali syndrome has been reported with even lower daily doses.[1,3] Some patients may be more susceptible; predisposing factors include the chronic vomiting associated with bulimia or hyperemesis of pregnancy,[3] pre-existing renal failure, and concomitant use of other medicines which alter calcium homoeostasis.[1,3]

For reference to thiazide diuretics increasing the risk of the milk-alkali syndrome in patients taking moderately large doses of calcium carbonate, see p. 1406.2.

1. Picolos MK, *et al*. Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol (Oxf)* 2005; **63:** 566–76.
2. Felsenfeld AJ, Levine BS. Milk alkali syndrome and the dynamics of calcium homeostasis. *Clin J Am Soc Nephrol* 2006; **1:** 641–54.
3. Medarov BI. Milk-alkali syndrome. *Mayo Clin Proc* 2009; **84:** 261–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcium carbonate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for other calcium salts, p. 1786.1.

As outlined on p. 1803.1, antacids, including calcium salts, interact with many other drugs both by alterations in gastric pH and emptying, and by formation of complexes that are not absorbed. Interactions can be minimised by giving calcium carbonate and any other medication 2 to 3 hours apart.

Omeprazole. In a study[1] of 18 women over the age of 65, the use of omeprazole for a week significantly reduced the absorption of calcium from a calcium carbonate supplement given on an empty stomach. Fractional calcium absorption was reduced from 9.1% with placebo to 3.5% with omeprazole.

1. O'Connell MB, *et al*. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med* 2005; **118:** 778–81.

Pharmacokinetics

Calcium carbonate is converted to calcium chloride by gastric acid. Some of the calcium is absorbed from the intestines and the unabsorbed portion is excreted in the faeces, as described for other calcium salts, p. 1786.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acomplex P; Calcio Acido; Calcional; Calcium-Sandoz; Pluscal; Renacalcio; Ultracalcium; Uvasal Tums; ***Austral.***: Andrews Tums; Cal-Sup; Caltrate; Sandocal†; Titralac; ***Austria***: Calcium-Sandoz; Dreisacarb; ***Belg.***: Cacit; Calci-Chew; Sandoz Calcium; Steocar; ***Braz.***: Calcium-Sandoz F; Calsan; Fontical; Maxicalc; Os-Cal; Osseopor; Rhamical; ***Canad.***: Apo-Cal; Cal-500; Calciforte†; Calcium Oyster Shell†; Calcium-Sandoz; Calsan; Caltrate; Hi Potency Cal†; Neo Cal†; Nu-Cal; Os-Cal†; Trial Antacid†; Tums; ***Chile***: Calcefor; Calcio†; Calcium Factor†; Calcium-Sandoz†; Calcivorin; Caprimida; Elcal; Kaplus; Levucal; Natecal; Sanidecal; ***China***: Calcichew (凯思立); Gu Yuan (固元); Kaifang (凯方); Mylanta (兰达); Na Nuo Ka (纳诺卡); Xie Da Li (协达利); ***Cz.***: Maxi-Kalz; Vitacalcin; ***Denm.***: Calcium-Sandoz; ***Fin.***: Calcichew; Calcium-Sandoz†; Kalcidon†; Kalcipos; ***Fr.***: Cacit; Calcidia; Calcidose; Calciprat; Calcium-Sandoz; Calperos; Calprimum; Caltrate; Densical; Eucalcic†; Fixical; Osteocal†; Perical†; ***Ger.***: Calci-Gry†; Calcimagon; Calcimed; Calcium AL†; Calcium beta; Calcium Stada†; Calcium Verla; Calcium-CT†; Calcium-Sandoz†; CC-Nefro; Dreisacarb; Loscalcon†; Ospur Ca; ***Gr.***: Alcamex; Body-Calcin; Calciform; Calciforte; Calcioral; Frubiose-N; ***Hong Kong***: Apo-Cal; Calcium-Sandoz; Caltrate; Doctor's Choice Calcium†; Os-Cal; Scott's Hi-Calcium†; Titralac†; ***Hung.***: Beres Calcium; Calcicarb; Calcichew; Calcium-Sandoz; Remegel; ***India***: Bonycal; Calcicip; Calcium-Sandoz; Calibon-Z; Oscal; Sandocal; ***Indon.***: Calcium-Sandoz Junior Strength; Calnat; Calos; Calsan†; Osteocal; Stomacain; ***Irl.***: Cacit†; Calcichew; Remegel; Rennie Chewable Tablets; Rowarolan; Sandocal; ***Israel***: Calci-Rav; Calcimore; Calcium-Sandoz; Caltrate†; Fast; Kal Zarevet†; N-Zarevet; Tums; Tzarevet X; ***Ital.***: Adiecal; Biocalcium†; Cacit; Cal-Car; Calciodie; Calciopiu†; Calcium-Sandoz; Calma; Carbosint; Idracal; Lubical; Metocal; Recal; Savecal†; Top Calcium†; ***Malaysia***: Cal-Sup†; Caltrate; ***Mex.***: Bexacal; Calcidef; Calcifar; Calcium-Sandoz; Calsan; Caltrate; Ciocar†; Mubonet; Osteomin; Solibone†; Tums; ***Mon.***: Orocal; ***Neth.***: Cacit; Calci-Chew; Calcium-Sandoz; ***Norw.***: Calcium-Sandoz; Titralac; ***NZ***: Calcium-Sandoz†; Caltrate; Osteo; Titralac; ***Philipp.***: Calbone; Calci-Aid; Calcium-Sandoz†; Calmate†; Calsan; Tums; ***Pol.***: Additiva Calcium†; Calcium-Sandoz Forte; Calperos; FrutiCal†; Ostical†; Vicalvit†; ***Port.***: Calcior; Calcioral; Calcitab; Calcium-Sandoz; Natecal; Sandocal†; Tums; ***Rus.***: Calcium-Sandoz Forte (Кальций-Сандоз Форте); ***S.Afr.***: B-Cal; Calcichew; Calcium-Sandoz; Calsuba†; Caltrate; Fizzical; Titralac†; Tums†; ***Singapore***: Apo-Cal; Bonacal; Cal-Sup†; Calcium-Sandoz Forte; Calperos; Caltrate; Remegel; ***Spain***: Calcium-Sandoz Forte†; Caosina; Carbocal; Cimascal; Densical†; Mastical; Natecal; Osteocal†; ***Swed.***: Calcitugg; Calcium-Sandoz; Kalcidon; Kalcipos; Kalcitena†; ***Switz.***: Calcium-Sandoz; Calperos; Fixateur phospho-calcique; Natecal D; ***Thai.***: BayCal; Bo-Ne-Ca; Bonetec; Cal-Os; Cal-ups; Calbone†; Calcanate; Calcap; Calcar; Calcarbonate†; Calcium Central Poly; Calcium TO; Calcium-Sandoz Bonacal; Calcium-Sandoz; Calhof; Calmate; Calsum; Caltab Forte†; Caltab; Caltrate; Caltrex; Carbocal; Carbocalc†; Chalkcap; Chalktab; GPO Cal; Kal-Forte; OB Cal; Patar Kal; Pharcal; Prima-Cal; T-Bon; V-Calcium; Weifa-Calcium†; ***Turk.***: Anti-Fosfat Cc; Calcimed; Calcium-Sandoz; Ostram; ***UK***: Adcal; Cacit; Calcichew; Rap-eze; Remegel; Rennie Soft Chews; Sandocal; Sea-Cal; Setlers; Tums; ***USA***: Alka-Mints; Antacid; Calci-Chew; Calci-Mix; Calcium-600; Caltrate; Chooz; Maalox Antacid Barrier; Maalox Childrens; Mallamint; Mylanta†; Nephro-Calci; Os-Cal; Oysco; Oyst-Cal; Pepto Children's; Rolaids Extra Strength Softchews; Surpass; Titralac Extra Strength; Trial Antacid; Tums; ***Venez.***: Calcion; Calcium-Sandoz; Foscalvit; Frutacid; Sandocal; Titralac; Tums.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Arg.***: Aspirina; ***Braz.***: Bufferin; ***Canad.***: Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA†; ***Mex.***: Reumophan Alka; ***Pol.***: Calcipiryna†; Polopiryna S; ***USA***: Adprin-B; Ascriptin; Bufferin; Extra Strength Bayer Plus.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Elimitona Slim & Detox; ***Austria***: Osanit Zahnungskugelchen; Osteoplex; Steiroplex; Zahnkugelchen; ***Canad.***: Bioactiv E†; Bioactiv R†; Earache; Formula DE 226†; Hea Complex†; Hepar Compositum; Homeo-Form P†; Hylands Formula S; Hylands Sinus†; Minerals+; Phyto-Cal; Rexorubia†; Sinus Ease; Sinus; Sinuspax†; Sorinoheel; Tee Complex†; Ubicoenzyme; Ursical Formula†; Urticalcin; Viburcol; ***Chile***: Bioactiv D; Bioactiv E; Bioactiv R; ***Cz.***: Hormeel S; Viburcol; ***Fr.***: Abbe Chaupitre no 44†; Abbe Chaupitre no 48†; Calcarea Compose; Dolitravel†; Jenoverine†; Osteocynesine; Rexorubia; Sels Calcaires Nutritifs; Sepia Complexe No 20; Sinuspax; Slimum†; Veino-Drainol†; ***Ger.***: Agaricus comp Phosphorus; Araniforce rheuma†; Calciurell; Chirofossat; Feminon N; Hepar comp; Hewelymphon N†; Infi-Symphytum; Infifer N; Infihepan; Osanit; Osteoplex; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pflugerplex Lemna; Ranocalcin HM; Sepia comp; Steirocall; Steiroplex†; Viburcol N; ***Hung.***: Hormeel S; Viburcol; ***Neth.***: Auriculite; Dermafleur; Jenoverine†; Kind 0-6 Caltrivat; Lergilite; Myamolite; Osteocynesine†; Prurilite; Urtizon complex; Venafleur; Viburcol H; ***Port.***: Osteocynesine; ***Rus.***: Berberis-Plus (Берберис-Плюс); Hormeel SN (Гормель СН); Urtica-Plus (Уртика-Плюс); ***S.Afr.***: Aufbaukalk II†; Viburcol; ***Switz.***: Regenaplex Nr. 51c; Regenaplex Nr. 88b; Urticalcin; Viburcol N; ***UK***: Conchae comp.; Fragador; ***Ukr.***: Immunokind (Иммунокинд).

Pharmacopoeial Preparations

BP 2014: Alginate Raft-forming Oral Suspension; Calcium and Colecalciferol Tablets; Chewable Calcium and Colecalciferol Tablets; Chewable Calcium Carbonate and Heavy Magnesium Carbonate Tablets; Chewable Calcium Carbonate Tablets;

USP 36: Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Aluminum Subacetate Topical Solution; Calcium and Magnesium Carbonates Oral Suspension; Calcium and Magnesium Carbonates Tablets; Calcium Carbonate and Magnesia Tablets; Calcium Carbonate Lozenges; Calcium Carbonate Oral Suspension; Calcium Carbonate Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets.

Carbenoxolone Sodium *(BANM, USAN, rINNM)*

Carbenoxolona sódica; Carbénoxolone Sodique; Disodium Enoxolone Succinate; Karbenoksolon Sodyum; Natrii Carbenoxolonum; Натрий Карбеноксолон.

3β-(3-Carboxypropionyloxy)-11-oxo-olean-12-en-30-oic acid, Disodium Salt.

$C_{34}H_{48}Na_2O_7$=614.7

CAS — 5697-56-3 (carbenoxolone); 7421-40-1 (carbenoxolone disodium).

ATC — A02BX01.

ATC Vet — QA02BX01.

UNII — F1MP7242Z5.

Pharmacopoeias. In *Br.*

BP 2014: (Carbenoxolone Sodium). A white or pale cream-coloured, hygroscopic powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 10% solution in water has a pH of 8.0 to 9.2.

Profile

Carbenoxolone sodium is a synthetic derivative of glycyrrhizic acid (p. 2520.2) that is one of many topical treatments for the symptomatic management of mouth ulceration (p. 1811.2). It is usually used as a 2% gel; a 1% mouthwash has been used. It was formerly also used as a mucosal protectant in peptic ulcer disease and has been given with antacids and alginic acid in gastro-oesophageal reflux disease.

Adverse effects. Carbenoxolone has mineralocorticoid-like effects and ingestion has been associated with sodium and water retention and hypokalaemia. Muscle weakness,[1-5] muscle necrosis,[4] myopathy,[1] hypertension,[2] headache,[2] cardiac failure,[2] mental confusion,[4] areflexia,[3] renal tubular dysfunction,[5] and acute tubular necrosis[4] have all been associated with carbenoxolone-induced hypokalaemia. Carbenoxolone-induced hypertension may have precipitated the onset of fatal polyarteritis in a patient predisposed to this condition.[6]

1. Fyfe T, *et al*. Myopathy and hypokalaemia in carbenoxolone therapy. *BMJ* 1969; **3:** 476.
2. Davies GJ, *et al*. Complications of carbenoxolone therapy. *BMJ* 1974; **3:** 400–2.
3. Royston A, Prout BJ. Carbenoxolone-induced hypokalaemia simulating Guillain-Barré syndrome. *BMJ* 1976; **2:** 150–1.
4. Descamps C, *et al*. Rhabdomyolysis and acute tubular necrosis associated with carbenoxolone and diuretic treatment. *BMJ* 1977; **1:** 272.
5. Dickinson RJ, Swaminathan R. Total body potassium depletion and renal tubular dysfunction following carbenoxolone therapy. *Postgrad Med J* 1978; **54:** 836–7.
6. Sloan J, Weaver JA. A case of polyarteritis developing after carbenoxolone therapy. *Ir Med J* 1968; **1:** 505–7.

Handling. Carbenoxolone sodium powder is irritant to nasal membranes.

Mental function. High cortisol concentrations have been associated with poorer memory and neuronal loss in some patients. Carbenoxolone inhibits 11-β-hydroxysteroid dehydrogenase type 1, and thus may selectively lower intracellular cortisol. In a small crossover study[1] in 10 healthy elderly men, oral carbenoxolone 100 mg three times daily for 4 weeks significantly improved verbal fluency compared with placebo, but did not influence visual or verbal memory, nonverbal reasoning, or processing speed. Twelve patients with stable type 2 diabetes were given carbenoxolone at the same dose for 6 weeks. Verbal memory was significantly improved compared with placebo, but verbal fluency and other scores were unaltered. All subjects were given amiloride 10 mg daily to prevent mineralocorticoid adverse effects[1] (although this has been reported to reduce the efficacy of carbenoxolone).

1. Sandeep TC, *et al*. 11 β -Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc Natl Acad Sci U S A* 2004; **101:** 6734–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bioral†; ***Austria***: Rowadermat; ***Hong Kong***: Herpesan; ***Hung.***: Carbosan; ***Irl.***: Carbosan; ***Malaysia***: Herpesan; ***Philipp.***: Rowagel; ***Singapore***: Herpesan†; ***Spain***: Sanodin.

Multi-ingredient Preparations. ***Irl.***: Pyrogastrone†.

Casanthranol *(USAN)*

Casantranol; Казантранол.
CAS — 8024-48-4.
UNII — 3SJ3U7J6V2.

Pharmacopoeias. In *US.*

USP 36: (Casanthranol). It is obtained from cascara. It contains not less than 20% of total hydroxyanthracene derivatives calculated on the dried basis, of which not less than 80% consists of cascarosides, both calculated as cascaroside A ($C_{27}H_{32}O_{14}$ = 580.5).

It is a light tan to brown, amorphous, hygroscopic powder. Freely soluble in water with some residue; partially soluble in methyl alcohol and in hot isopropyl alcohol; practically insoluble in acetone. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Profile

Casanthranol is an anthraquinone stimulant laxative with general properties similar to those of senna (p. 1885.1). It is given in usual oral doses of 30 to 60 mg daily with a faecal softener. In severe cases a dose of 90 mg daily, or 60 mg twice daily, may be given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Cascalax†.

Multi-ingredient Preparations. ***Arg.***: Bil 13; En-Ga-Lax; ***Canad.***: Laxolax Phyto†; ***Spain***: Laxvital†; ***USA***: Black-Draught; Docusoft Plus; Laxative & Stool Softener.

Cascara

Amerikinių šaltekšnių žievė; Cáscara sagrada; Cascararinde; Chittem Bark; Kaszkarabokor kéreg; Kůra řešetláku Purshova; Rhamni Purshianae Cortex; Rhamni Purshiani Cortex; Sacred Bark; Sagradabark; Sagradankuori; Крушина Пурша; Жостер Пурша.
CAS — 8047-27-6; 8015-89-2 (cascara sagrada extract).
ATC — A06AB07.
ATC Vet — QA06AB07.
*ATC Herb — HA06AB5014 (*Rhamnus purshiana*: bark).*
UNII — 4VBP01X99F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cascara). The dried, whole or fragmented bark of *Rhamnus purshianus* (=*Frangula purshiana*). It contains not less than 8.0% of hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both expressed as cascaroside A ($C_{27}H_{32}O_{14}$ = 580.5). and calculated with reference to the dried drug. Protect from light.

USP 36: (Cascara Sagrada). The dried bark of *Rhamnus purshianus* (Rhamnaceae). It contains not less than 7% of total hydroxyanthracene derivatives calculated on the dried basis, of which not less than 60% consists of cascarosides, both calculated as cascaroside A. It has a distinct odour.

Profile

Cascara is an anthraquinone stimulant laxative with general properties similar to those of senna (p. 1885.1). It has been used in the treatment of constipation in oral doses equivalent to about 20 to 30 mg of total hydroxyanthracene derivatives daily.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cascara, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Natulax†; ***Belg.***: Laxafytol; ***Braz.***: Laxsotrin†; Verilax; ***Fr.***: Peristaltine†; ***Ger.***: Legapas.

Multi-ingredient Preparations. ***Arg.***: Bilidren; Cascara Sagrada Bouzen; Cascara Sagrada Oligoplex; Cascara Sagrada Puler; Natulax Plus; Veracolate†; ***Austral.***: Colax†; Colax; Peritone; ***Austria***: Silberne†; ***Belg.***: Vethoine; ***Braz.***: Chofranina†; Eparema; Solvobil; ***Canad.***: Bicholate†; Bilonat; Cas-Mag; Control†; Depuratif des Trappistes; Doulax; Eliminex; Formula B-1†; Formula T5 Tea†; Hepaticol; Herba Tone†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Herbal Tabs†; Herbanat†; Herbolax†; Laxanat; Melange de Plantes Formula L1 Laxatif†; Metab Herbs No 1†; Stomach Ease; Traditional Herbal Laxative†; Traditional Laxative; Ultra-Lax†; ***Chile***: Bulgarolax†; ***Fr.***: Dragees Fuca; Dragees Vegetales Rex; Imegul†; Mucinum a l'Extrait de Cascara; Spevin†; ***Hong Kong***: Mucinum†; ***India***: Hepachol; Livotone; ***Ital.***: Alosen†; Amaro Medicinale; Combilax; Confetti Lassativi CM; Dis-Cinil Complex; Draverex; Eparema-Levul; Eparema; Estilax; Eupatol; Fave di Fuca; Grani di Vals†; Hepatos B12; Hepatos; Solvobil†; ***Neth.***: Temoe Lawak; ***Norw.***: Cosylan; ***Port.***: Doce Alivio; Mucinum; ***S.Afr.***: Moultons Herbal Extract†; ***Spain***: Crislaxo; Fave de Fuca; Favilax; Fucapan; Laxodiex; Lipograsil†; Nico Hepatocyn; Pildoras Zeninas; ***Switz.***: Padma-Lax; Padmed Laxan; ***Thai.***: Corisul; Flataco; Flatulence†; Hemolax†; Patarcolate; Patarsul; Veracolate†; ***UK***: Cassilax; Dual-Lax Extra Strong; Dual-Lax Normal Strength; Jacksons Herbal Laxative; Laxative Tablets; Modern Herbals Laxative; Modern Herbals Pile; Napiers Oral Skin Soother Herbal Relief; Natural Herb Tablets; Out-of-Sorts; Pileabs; Piletabs; Rhuaka; Senokot Dual Relief; Skin Eruptions Mixture; ***USA***: Concentrated Milk of Magnesia-Cascara†; Detox; ***Venez.***: Gameral.

Homoeopathic Preparations. ***Canad.***: Cynara Complex†.

Pharmacopoeial Preparations
BP 2014: Cascara Tablets;
USP 36: Aromatic Cascara Fluidextract; Cascara Sagrada Extract; Cascara Sagrada Fluidextract; Cascara Tablets.

Casopitant *(rINN)*

Capsipitant; Casopitantum; GW-679769; Казопитант.
(2*R*,4*S*)-4-(4-Acetylpiperazin-1-yl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide.
$C_{30}H_{35}F_7N_4O_2$=616.6
CAS — 414910-27-3.
ATC — A04AD13.
ATC Vet — QA04AD13.
UNII — 3B03KPM27L.

Casopitant Mesilate *(rINNM)*

Casopitant, Mésilate de; Casopitant Mesylate (USAN); Casopitanti Mesilas; GW-679769B; Mesilato de casopitant; Казопитанта Мезилат.
(2*R*,4*S*)-4-(4-Acetylpiperazin-1-yl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide methanesulfonate.
$C_{30}H_{35}F_7N_4O_2.CH_3SO_3H$=712.7
CAS — 414910-30-8.
ATC — A04AD13.
ATC Vet — QA04AD13.
UNII — 7VSV9BL497.

Profile

Casopitant is a neurokinin-1 receptor antagonist like aprepitant (p. 1819.2) that has been investigated for the prevention of chemotherapy-induced nausea and vomiting.

References.
1. Ruhlmann C, Herrstedt J. Casopitant: a novel NK(1)-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting. *Ther Clin Risk Manag* 2009; **5:** 375–84.
2. Grunberg SM, *et al.* Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10:** 549–58.
3. Herrstedt J, *et al.* Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. *J Clin Oncol* 2009; **27:** 5363–9.

Cassia Pulp

Fístula, pulpa de caña; Мякоть Амалтас.
*ATC Herb — HA06AX5001 (*Cassia fistula*: fruit).*

Profile

Cassia pulp is the evaporated aqueous extract of crushed ripe cassia fruits (cassia pods), *Cassia fistula* (Leguminosae). It is a mild anthraquinone stimulant laxative with general properties similar to those of senna (p. 1885.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; ***Fr.***: Benetransit†; ***Gr.***: Tamarine; ***Ital.***: Tamarine; ***Mex.***: MD Lax; Naturetti; ***Rus.***: Pilex (Пайлекс); ***Spain***: Pruina; ***Ukr.***: Softovak (Софтовак).

Cerium Oxalate

Cerii Oxalas; Cerio, oxalato de; Ceriumoksalaatti; Ceriumoxalat; Церия Оксалат.
CAS — 139-42-4 (anhydrous cerous oxalate); 15053-73-3 (cerous oxalate decahydrate).
ATC — A04AD02.
ATC Vet — QA04AD02.
UNII — 96P72VE680 (cerium oxalate); 0UV74P3R0J (cerium oxalate nonahydrate).

NOTE. Cerium oxalate has been defined as consisting of about 50% of cerous oxalate ($(C_2O_4)_3Ce_2.10H_2O$) with the oxalates of numerous other rare earths, especially lanthanum, praseodymium, and neodymium. Oxalates of the form $(C_2O_4)_3Ce_2.xH_2O$ are also referred to as cerium or cerous oxalate.

Profile

Cerium oxalate has been used as an antiemetic.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Canad.***: Ubicoenzyme; ***Fr.***: Aurum Complexe No 38†; Badiaga Complexe No 47.

Cetraxate Hydrochloride *(USAN, rINNM)*

Cétraxate, Chlorhydrate de; Cetraxati Hydrochloridum; Cetraxato, hidrocloruro de; DV-1006; Hidrocloruro de cetraxato; Цетраксата Гидрохлорид.
4-(2-Carboxyethyl)phenyl tranexamate hydrochloride; 4-(2-Carboxyethyl)phenyl *trans*-4-aminomethylcyclohexanecarboxylate hydrochloride.
$C_{17}H_{23}NO_4$.HCl=341.8
CAS — 34675-84-8 (cetraxate); 27724-96-5 (cetraxate hydrochloride).
UNII — 08IT6P8VHY.

NOTE. The names Eluglilu, Lacmarze, LK, and Reslart have been used as trade marks for cetraxate hydrochloride.

Pharmacopoeias. In *Jpn.*

Profile

Cetraxate hydrochloride is stated to be a mucosal protectant with actions on gastric microcirculation as well as prostaglandin synthesis and kallikrein. It is used in the treatment of gastritis and peptic ulcer disease (p. 1813.2) in oral doses of 600 to 800 mg daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Neuer.

Chalk

Creta; Prepared Chalk; Мел.
$CaCO_3$=100.1
CAS — 13397-25-6.

Pharmacopoeias. In *Br.*

BP 2014: (Chalk). A native form of calcium carbonate freed from most of its impurities by elutriation and dried. It consists of the calcareous shells and detritus of various foraminifera and contains not less than 97.0% and not more than 100.5% of $CaCO_3$, calculated with reference to the dried substance.

White or greyish-white, odourless or almost odourless, amorphous, earthy, small friable masses, usually conical in form, or in powder. Practically insoluble in water; slightly soluble in water containing carbon dioxide; it absorbs water readily.

Profile

Chalk has been used as an adsorbent antidiarrhoeal. Calcium carbonate (precipitated chalk) is used as an antacid, calcium supplement, and phosphate binder, see p. 1824.3.

Calabash chalk, also known as Calabar stone, la craie or argile, nzu, mabele, ebumba, or ulo, is ingested by some pregnant women to alleviate morning sickness. It is traditionally used by Nigerian or West African women in the form of blocks, pellets, or powders. Calabash chalk either occurs naturally or is produced from clay and mud that may be mixed with other ingredients including sand, wood ash, and sometimes, salt. However, it contains high levels of lead, as well as arsenic (see Contamination, below).

Contamination. Concern with regard to the safety of calabash chalk has arisen, particularly with regard to its lead and arsenic content.[1-4] Analysis of calabash chalk samples available in the UK found that the major component of calabash chalk was an aluminium silicate hydroxide from the kaolin clay group. Lead concentrations in the samples were found to be about 40 mg/kg, almost 40 times the EU recommended guidelines. Potentially toxic chromium concentrations (dependent on the oxidation state) were also found. Arsenic, cadmium, and mercury were not detect-

able in any of the analysed samples. Persistent organic pollutants were also identified in one sample.[1] Calabash chalk is traditionally used by pregnant women, often those from Nigerian and West African communities, as a remedy for morning sickness. Health authorities in various countries have issued warnings, and advised people, especially pregnant and breast-feeding women, not to consume calabash chalk.[2-4]

1. Dean JR, *et al.* Characterisation and analysis of persistent organic pollutants and major, minor and trace elements in calabash chalk. *Chemosphere* 2004; **57:** 21–5.
2. Health Canada. Calabash chalk may pose health risk for pregnant and breastfeeding women (issued 2nd October 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_136_e.html (accessed 03/10/07)
3. Food Standards Agency. Lead contamination of calabash chalk (issued 15th October 2002). Available at: http://www.food.gov.uk/enforcement/alerts/2002/oct/94151 (accessed 03/10/07)
4. FDA. Nzu, traditional remedy for morning sickness (issued 31st December 2009). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196045.htm (accessed 01/03/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Behoedmiddel vir Kinders; ***Thai.***: Antidiarrhoeals for children.

Pharmacopoeial Preparations
BP 2014: Compound Magnesium Trisilicate Oral Powder.

Ciclonium Bromide *(rINN)*

Asta-3746; Bromuro de ciclonio; Ciclonii Bromidum; Ciclonio, bromuro de; Ciclonium, Bromure de; Циклония Бромид.
Diethylmethyl[2-[(α-methyl-α-5-norbornen-2-ylbenzyl)oxy]ethyl}ammonium bromide.
$C_{22}H_{34}BrNO$=408.4
CAS — 29546-59-6.
UNII — 72R7F44611.

NOTE. The name Cyclonium or Ciclonium Iodide has been used to describe an unrelated antispasmodic, Oxapium Iodide (p. 1874.3).

Profile

Ciclonium bromide is an antimuscarinic that has been used in the treatment of gastrointestinal and urinary-tract disorders associated with smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Turk.***: Doladamon.

Cimetidine *(BAN, USAN, rINN)*

Cimetidin; Cimetidina; Cimetidinas; Cimétidine; Cimetidinum; Cymetydyna; Simetidiini; Simetidin; SKF-92334; Циметидин.
2-Cyano-1-methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]guanidine.
$C_{10}H_{16}N_6S$=252.3
CAS — 51481-61-9.
ATC — A02BA01.
ATC Vet — QA02BA01.
UNII — 80061L1WGD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cimetidine). A white or almost white, polymorphic powder. Slightly soluble in water; soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

USP 36: (Cimetidine). A white to off-white crystalline powder, odourless or with a slight mercaptan odour. Slightly soluble in water and in chloroform; soluble in alcohol and in macrogol 400; practically insoluble in ether; sparingly soluble in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Cimetidine Hydrochloride *(BANM, USAN, rINNM)*

Cimetidina, hidrocloruro de; Cimétidine, chlorhydrate de; Cimetidin-hidroklorid; Cimetidinhydrochlorid; Cimetidinhydroklorid; Cimetidinhydrochlorid; Cimetidini Hydrochloridum; Cimetidino hidrochloridas; Hidrocloruro de cimetidina; Simetidiinihydrokloridi; Циметидина Гидрохлорид.
$C_{10}H_{16}N_6S$,HCl=288.8
CAS — 70059-30-2.
ATC — A02BA01.
ATC Vet — QA02BA01.
UNII — WF10491673.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cimetidine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in dehydrated alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Cimetidine Hydrochloride). Store in airtight containers. Protect from light.

Uses and Administration

Cimetidine is a histamine H_2-antagonist and inhibits actions of histamine mediated by H_2-receptors such as gastric acid secretion and pepsin output. It is used where inhibition of gastric acid secretion may be beneficial, as in peptic ulcer disease, including stress ulceration (p. 1813.2), gastro-oesophageal reflux disease (p. 1807.2), selected cases of persistent dyspepsia (p. 1806.3), scleroderma of the oesophagus, pathological hypersecretory states such as the Zollinger-Ellison syndrome (p. 1814.3), and in patients at risk of acid aspiration (p. 1804.2) during general anaesthesia or child birth. Cimetidine may also be used to reduce malabsorption and fluid loss in patients with the short bowel syndrome and to reduce the degradation of enzyme supplements given to patients with pancreatic insufficiency.

Cimetidine may be given orally or parenterally by the intravenous or intramuscular routes; the total daily dose by any route should not normally exceed 2.4 g. Although some formulations are prepared as the hydrochloride, strengths and doses are expressed in terms of the base. Cimetidine 100 mg is equivalent to about 114.5 mg of cimetidine hydrochloride. Doses should be reduced in renal impairment and may also need to be reduced in hepatic impairment (see below).

For doses in children, see Administration in Children, below.

In the management of benign **gastric** and **duodenal ulceration** a single daily oral dose of 800 mg at bedtime or 400 mg twice daily is recommended, which should be given for at least 4 weeks for duodenal ulcers (6 weeks for gastric ulcers, 8 weeks for NSAID-associated ulcers); when necessary the dose may be increased to 400 mg four times daily. Where appropriate a maintenance dose of 400 mg may then be given once daily at bedtime, or twice daily in the morning and at bedtime. Other regimens have also been used for treatment and maintenance.

In **gastro-oesophageal reflux disease** the recommended oral dose is 400 mg four times daily (with meals and at bedtime), or 800 mg twice daily, for 4 to 12 weeks. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, an oral dose of 300 or 400 mg four times daily is normally used, although sometimes higher doses may be necessary.

Doses of 200 to 400 mg orally every 4 to 6 hours are recommended for prophylaxis of haemorrhage from **stress ulceration**. In patients at risk of developing the **acid aspiration syndrome**, an oral dose of 400 mg may be given 90 to 120 minutes before the induction of anaesthesia, or at the start of labour (in obstetric practice), and doses of up to 400 mg may be repeated at intervals of 4 hours if required.

Doses of up to 800 mg daily in divided doses have been taken for non-ulcer **dyspepsia**; 100 mg at night has been used in the prophylaxis of nocturnal heartburn.

For **scleroderma of the oesophagus**, the usual dose is 1.2 g orally in divided doses.

For **short bowel syndrome**, an initial oral dose of cimetidine 400 mg twice daily is adjusted according to response.

To reduce the degradation of pancreatic enzyme supplements, patients with **pancreatic insufficiency**, as in cystic fibrosis (p. 177.2), may be given oral cimetidine 800 mg to 1.6 g daily in 4 divided doses, 60 to 90 minutes before meals.

PARENTERAL ADMINISTRATION.

Cimetidine may be diluted before intravenous use; commonly used intravenous solutions such as sodium chloride 0.9%, glucose 5 or 10%, and lactated Ringer's solution are compatible. Parenteral dosage recommendations are 300 mg every 6 to 8 hours by intramuscular injection or by slow intravenous injection, diluted to 20 mL, over at least 5 minutes; the same dosage may be given by intermittent intravenous infusion, diluted to at least 50 mL, over 15 to 20 minutes. If higher doses are required, intravenous injections or infusions may be given more frequently up to the maximum total daily dose of 2.4 g. For continuous intravenous infusion (diluted in up to 1 litre) the recommended rate is 37.5 mg/hour, which may be preceded by 150 mg as an intravenous loading dose. Higher rates may be required in some patients; a rate of 50 mg/hour is recommended for prevention of stress ulceration.

Administration in children. Cimetidine is used in children in the management of conditions where gastric acid reduction is beneficial including benign duodenal and gastric ulceration, reflux oesophagitis, and Zollinger-Ellison syndrome. Experience in children is more limited than that in adults and regulatory authorities in some countries do not recommend its use unless the benefits of cimetidine outweigh its potential risks; an oral or intravenous dose of 20 to 40 mg/kg daily in divided doses has been suggested for children under 16 years of age. Licensed oral doses for children over 1 year of age range from 20 to 30 mg/kg daily in divided doses. An oral dose of 20 mg/kg daily in divided doses has been suggested for infants under 1 year. A lower dose of 10 to 15 mg/kg daily in 4 to 6 divided doses is recommended for neonates.

For differences in pharmacokinetics in children which may affect dosing, see p. 1831.2.

Administration in hepatic impairment. The bioavailability of cimetidine may be increased in patients with cirrhosis[1,2] and a dosage reduction of up to 40% has been suggested in patients with portal systemic encephalopathy.[3] However, UK and US licensed product information does not include recommendations for dosage adjustment in hepatic impairment.

1. Gugler R, *et al.* Altered disposition and availability of cimetidine in liver cirrhotic patients. *Br J Clin Pharmacol* 1982; **14:** 421–30.
2. Cello JP, Øie S. Cimetidine disposition in patients with Laennec's cirrhosis during multiple dosing therapy. *Eur J Clin Pharmacol* 1983; **25:** 223–9.
3. Ziemniak JA, *et al.* Hepatic encephalopathy and altered cimetidine kinetics. *Clin Pharmacol Ther* 1983; **34:** 375–82.

Administration in renal impairment. The dosage of cimetidine should be reduced in patients with renal impairment. UK licensed product information suggests the following oral doses according to creatinine clearance (CC):

- CC over 50 mL/minute: normal dosage
- CC 30 to 50 mL/minute: 200 mg four times daily
- CC 15 to 30 mL/minute: 200 mg three times daily
- CC 0 to 15 mL/minute: 200 mg twice daily

US licensed product information suggests a dose of 300 mg every 12 hours orally or by intravenous injection in those with severe impairment, increasing the frequency with caution if required. Patients with a creatinine clearance of < 30 mL/minute who are being treated for prevention of stress ulceration should be given half the usual intravenous dose, see Uses and Administration, above.

Cimetidine is removed by haemodialysis, but not significantly removed by peritoneal dialysis.

Bladder disorders. Cimetidine effectively relieved symptoms in patients with painful bladder disease (encompassing conditions including cystitis, painful bladder syndrome, and urethral syndrome), especially suprapubic pain and nocturia, despite no apparent histological change in the bladder mucosa after treatment.[1]

1. Thilagarajah R, *et al.* Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001; **87:** 207–12.

Dapsone toxicity. Cimetidine might reduce methaemoglobinaemia associated with dapsone. For references supporting this suggestion, see Effects on the Blood, under Dapsone, p. 282.2.

Diagnostic use. Cimetidine blocks renal tubular secretion of creatinine and has been used experimentally to improve the accuracy of estimations of glomerular filtration rate from creatinine clearance.[1] Although the optimal dose has not been established, in renal transplant recipients an oral dose of 1 g given in 4 divided doses seemed to provide a useful measure of glomerular filtration rate when the plasma creatinine concentration was below 2.5 mg/litre. At higher creatinine concentrations, a higher dose was required to block tubular excretion effectively.

1. Kabat-Koperska J, *et al.* Creatinine clearance after cimetidine administration— is it useful in the monitoring of the function of transplanted kidney? *Ren Fail* 2007; **29:** 667–72.

Echinococcosis. Cimetidine has been given with albendazole to increase its effect (by inhibiting its metabolism) in the treatment of echinococcosis (p. 145.2).

Immunomodulation. Studies in *mice* and humans have shown that H_2-antagonists have an immunoregulatory effect.[1] T-lymphocyte suppressor cells have histamine H_2 receptors and cimetidine has been reported to reduce activity of these cells, thus enhancing immune response.[1,2] There is also some evidence that it enhances cellular immunity, notably natural killer cell activity.[3] This discovery has led to the investigation of cimetidine in disorders associated with alteration of the immune response including eosinophilic fasciitis, herpesvirus infections, mucocuta-

neous candidiasis,[4] hypogammaglobulinaemia,[5] and various malignancies.[1]

1. Kumar A. Cimetidine: an immunomodulator. *DICP Ann Pharmacother* 1990; **24:** 289–95.
2. Snyman JR, *et al*. Cimetidine as modulator of the cell-mediated immune response in vivo using the tuberculin skin test as parameter. *Br J Clin Pharmacol* 1990; **29:** 257–60.
3. Katoh J, *et al*. Cimetidine and immunoreactivity. *Lancet* 1996; **348:** 404–5.
4. Polizzi B, *et al*. Successful treatment with cimetidine and zinc sulphate in chronic mucocutaneous candidiasis. *Am J Med Sci* 1996; **311:** 189–90.
5. White WB, Ballow M. Modulation of suppressor-cell activity by cimetidine in patients with common variable hypogammaglobulinemia. *N Engl J Med* 1985; **312:** 198–202.

EOSINOPHILIC FASCIITIS. Eosinophilic fasciitis is a scleroderma-like syndrome of inflammation of the muscle fascia and associated eosinophilia and hypergammaglobulinaemia. Although it responds well to corticosteroid therapy in most cases, cimetidine has also been tried. The effect of cimetidine on eosinophilic fasciitis is unpredictable with both remission[1-4] and lack of response[5,6] having been reported in a few patients. In one case series of 17 patients, 9 remitted with initial cimetidine treatment, while 5 showed a partial response.[7]

1. Solomon G, *et al*. Eosinophilic fasciitis responsive to cimetidine. *Ann Intern Med* 1982; **97:** 547–9.
2. Laso FJ, *et al*. Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; **98:** 1026.
3. Garcia-Morteo O, *et al*. Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1984; **100:** 318–19.
4. Farrell AM, *et al*. Eosinophilic fasciitis associated with autoimmune thyroid disease and myelodysplasia treated with pulsed methylprednisolone and antihistamines. *Br J Dermatol* 1999; **140:** 1185–7.
5. Loftin EB. Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; **98:** 111–12.
6. Herson S, *et al*. Cimetidine in eosinophilic fasciitis. *Ann Intern Med* 1990; **113:** 412–13.
7. Naschitz JE, *et al*. The fasciitis-panniculitis syndromes: clinical and pathologic features. *Medicine (Baltimore)* 1996; **75:** 6–16.

HERPESVIRUS AND PAPILLOMAVIRUS INFECTIONS. Although there have been numerous isolated and anecdotal reports of a beneficial response to cimetidine in patients with infections due to various *herpesviruses* (p. 954.1), including genital herpes simplex,[1] infectious mononucleosis,[2,3] and herpes zoster[4-7] some of these reports have been criticised[8,9] mainly on the grounds that the majority of cases of herpes zoster will resolve within 2 to 3 weeks whether any treatment is given or not. Also, a double-blind placebo-controlled study involving 63 patients with herpes zoster[10] found no evidence that cimetidine relieved the pain or accelerated the rate of healing of lesions.

There are reports[11] of benefit from the use of cimetidine in patients with *viral warts* (p. 1689.3) and an 8-year retrospective analysis of 216 patients with plantar warts reported a success rate of about 80%, although warts recurred in 12 patients.[12] However, controlled studies have failed to show significant benefit,[13,14] and a review concluded that use of H_2-antagonists for warts could not be recommended based on the available evidence.[15]

1. Wakefield D. Cimetidine in recurrent genital herpes simplex infection. *Ann Intern Med* 1984; **101:** 882.
2. Goldstein JA. Cimetidine and mononucleosis. *Ann Intern Med* 1983; **99:** 410–11.
3. Goldstein JA. Cimetidine, ranitidine, and Epstein-Barr virus infection. *Ann Intern Med* 1986; **105:** 139.
4. Hayne ST, Mercer JB. Herpes zoster: treatment with cimetidine. *Can Med Assoc J* 1983; **129:** 1284–5.
5. Shandera R. Treatment of herpes zoster with cimetidine. *Can Med Assoc J* 1984; **131:** 279.
6. Mavligit GM, Talpaz M. Cimetidine for herpes zoster. *N Engl J Med* 1984; **310:** 318–19.
7. Arnot RS. Herpes zoster and cimetidine. *Med J Aust* 1984; **141:** 903.
8. Tyrrell DL. Course of herpes zoster. *Can Med Assoc J* 1984; **130:** 1109.
9. Giles KE. Herpes zoster and cimetidine. *Med J Aust* 1985; **142:** 283.
10. Levy DW, *et al*. Cimetidine in the treatment of herpes zoster. *J R Coll Physicians Lond* 1985; **19:** 96–8.
11. Glass AT, *et al*. Cimetidine therapy for recalcitrant warts in adults. *Arch Dermatol* 1996; **132:** 680–2.
12. Mullen BR, *et al*. Cimetidine as a first-line therapy for pedal verruca: eight-year retrospective analysis. *J Am Podiatr Med Assoc* 2005; **95:** 229–34.
13. Karabulut AA, *et al*. Is cimetidine effective for nongenital warts: a double-blind, placebo-controlled study. *Arch Dermatol* 1997; **133:** 533–4.
14. Rogers CJ, *et al*. Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? *J Am Acad Dermatol* 1999; **41:** 123–7.
15. Fit KE, Williams PC. Use of histamine$_2$-antagonists for the treatment of verruca vulgaris. *Ann Pharmacother* 2007; **41:** 1222–6.

MALIGNANT NEOPLASMS. Because of its immunomodulatory effects cimetidine has been tried as an adjuvant in the management of a variety of malignant neoplasms such as those of the gastrointestinal tract (see p. 705.2). Cimetidine may also have inhibitory effects on tumour growth and inhibit cancer cell migration and adhesion to epithelial cells.[1] Positive effects on survival have been reported in some studies in gastrointestinal cancer,[2-4] although a large, randomised, placebo-controlled study with cimetidine,[5] and a similar study with ranitidine,[6] failed to show any benefit. A study in colorectal cancer found improved survival and a reduced frequency of metastasis with cimetidine in patients whose tumour cells expressed high levels of the sialyl Lewis-X and sialyl Lewis-A antigens. The presence of these antigens mediates the adhesion of cancer cells to endothelium and is considered to lead to metastasis.[7]

Famotidine has also been investigated as an adjunct in patients with malignant neoplasms, usually given with interleukin-2; some success has been reported in small numbers of patients.[8,9]

1. Lefranc F, *et al*. Cimetidine, an unexpected anti-tumor agent, and its potential for the treatment of glioblastoma (review). *Int J Oncol* 2006; **28:** 1021–30.
2. Tønnesen H, *et al*. Effect of cimetidine on survival after gastric cancer. *Lancet* 1988; **ii:** 990–2.
3. Adams WJ, Morris DL. Short-course cimetidine and survival with colorectal cancer. *Lancet* 1994; **344:** 1768–9.
4. Matsumoto S. Cimetidine and survival with colorectal cancer. *Lancet* 1995; **346:** 115.
5. Langman MJS, *et al*. Prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. *Br J Cancer* 1999; **81:** 1356–62.
6. Primrose JN, *et al*. A prospective randomised controlled study of the use of ranitidine in patients with gastric cancer. *Gut* 1998; **42:** 17–19.
7. Matsumoto S, *et al*. Cimetidine increases survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells. *Br J Cancer* 2002; **86:** 161–7.
8. Parshad R, *et al*. Effect of preoperative short-course famotidine on TILs and survival in breast cancer. *Indian J Cancer* 2005; **42:** 185–90.
9. Quan WD, Quan FM. Activity of continuous infusion + pulse interleukin-2 with famotidine in metastatic melanoma. *Cancer Biother Radiopharm* 2009; **24:** 1–6.

Mastocytosis. Cimetidine, alone or with an antihistamine (histamine H_1-antagonist), has been reported to relieve gastrointestinal symptoms,[1,2] pruritus, and urticaria[3,4] in patients with mastocytosis (p. 1226.3).

1. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. *Ann Intern Med* 1979; **90:** 769–71.
2. Linde R, *et al*. Combination H1 and H2 receptor antagonist therapy in mastocytosis. *Ann Intern Med* 1980; **92:** 716.
3. Simon RA. Treatment of systemic mastocytosis. *N Engl J Med* 1980; **302:** 231.
4. Frieri M, *et al*. Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis: results of a double-blind clinical trial. *Am J Med* 1985; **78:** 9–14.

Paracetamol toxicity. It has been suggested that cimetidine might be of use in the treatment of paracetamol poisoning (see p. 116.2) because of its inhibition of the cytochrome P450 system. However, there appears to be no strong evidence to support its use.[1,2]

1. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; **55:** 1516–19.
2. Brok J, *et al*. Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/09).

Porphyria. There are reports[1-3] of patients with acute intermittent porphyria (p. 1556.1) showing clinical and biochemical improvement during treatment with cimetidine.

1. Baccino E, *et al*. Cimetidine in the treatment of acute intermittent porphyria. *JAMA* 1989; **262:** 3000.
2. Horie Y, *et al*. Clinical usefulness of cimetidine treatment for acute relapse in intermittent porphyria. *Clin Chim Acta* 1995; **234:** 171–5.
3. Cherem JH, *et al*. Cimetidine and acute intermittent porphyria. *Ann Intern Med* 2005; **143:** 694–5.

Skin disorders. Cimetidine has been used alone[1-8] or with an antihistamine (H_1-antagonist)[5,8,9] in various skin disorders. H_2-antagonists such as cimetidine and ranitidine have produced improvement in certain types of *urticaria* (p. 1689.2), especially those associated with cold or angioedema. Although they may act by antagonism of H_2-receptors on cutaneous blood vessels, other mechanisms of action may be involved.[8] A pharmacokinetic interaction between cimetidine and hydroxyzine resulting in increased serum concentrations of hydroxyzine has been reported when such a combination was given, see p. 631.2. Routine use of H_2-antagonists in urticaria is controversial, but in practice they may be added to conventional treatment in resistant cases.[10-12] Little additional benefit has been found with combination therapy in dermographic urticaria.[13]

Patients with *pruritus* (p. 1687.3) of various causes may also respond to H_2-antagonists,[1,2,6,7,9] but studies in larger groups of patients have found no benefit.[3-5,14]

1. Easton P, Galbraith PR. Cimetidine treatment of pruritus in polycythemia vera. *N Engl J Med* 1978; **299:** 1134.
2. Hess CE. Cimetidine for the treatment of pruritus. *N Engl J Med* 1979; **300:** 370.
3. Harrison AR, *et al*. Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; **300:** 433–4.
4. Scott GL, Horton RJ. Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; **300:** 434. Correction. *ibid.*; 936.
5. Zappacosta AR, Hauss D. Cimetidine doesn't help pruritus of uremia. *N Engl J Med* 1979; **300:** 1280.
6. Schapira DV, Bennett JM. Cimetidine for pruritus. *Lancet* 1979; **i:** 726–7.
7. Aymard JP, *et al*. Cimetidine for pruritus in Hodgkin's disease. *BMJ* 1980; **280:** 151–2.
8. Theoharides TC. Histamine$_2$ (H_2)-receptor antagonists in the treatment of urticaria. *Drugs* 1989; **37:** 345–55.
9. Deutsch PH. Dermatographism treated with hydroxyzine and cimetidine and ranitidine. *Ann Intern Med* 1984; **101:** 569.
10. Advenier C, Queille-Roussel C. Rational use of antihistamines in allergic dermatological conditions. *Drugs* 1989; **38:** 634–44.
11. Ormerod AD. Urticaria: recognition, causes, and treatment. *Drugs* 1994; **48:** 717–30.
12. Greaves MW. Chronic urticaria. *N Engl J Med* 1995; **332:** 1767–72.
13. Sharpe GR, Shuster S. In dermographic urticaria H_2 receptor antagonists have a small but therapeutically irrelevant additional effect compared with H_1 antagonists alone. *Br J Dermatol* 1993; **129:** 575–9.
14. Raisch DW, *et al*. Evaluation of a non-food and drug administration-approved use of cimetidine: treatment of pruritus resulting from epidural morphine analgesia. *DICP Ann Pharmacother* 1991; **25:** 716–8.

Adverse Effects

Adverse reactions to cimetidine and other histamine H_2-antagonists are generally infrequent. The commonest adverse effects reported have been diarrhoea and other gastrointestinal disturbances, dizziness, tiredness, headache, and rashes. Myalgia and arthralgia can occur.

Altered liver function tests have occurred and there have been rare reports of hepatotoxicity. Reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure, have occasionally occurred. Other adverse effects that have been reported rarely are hypersensitivity reactions and fever, reversible alopecia, blood disorders including agranulocytosis, leucopenia, and thrombocytopenia, acute pancreatitis, interstitial nephritis, hallucinations and depression, and cardiovascular disorders including bradycardia, tachycardia, and heart block. Rapid intravenous injection should be avoided as there have been rare associations with cardiac arrest and arrhythmias; transient hypotension has also been seen.

In patients such as the elderly, those with chronic lung disease, diabetes mellitus, or the immunocompromised, treatment with H_2-antagonists may be associated with an increased risk of developing community-acquired pneumonia.

Cimetidine has a weak anti-androgenic effect and gynaecomastia and impotence have also occasionally occurred in men; these are usually reversible.

Incidence of adverse effects. In a meta-analysis of 24 double-blind placebo-controlled studies,[1] the incidence of adverse effects with cimetidine was not significantly different from placebo. The most common adverse effects reported by patients taking cimetidine who were followed up for at least one year[2,3] were diarrhoea, headache, fatigue, skin rash or pruritus, and gynaecomastia. The incidence of adverse effects was dose-related and decreased with length of treatment.[3] No fatal adverse effect of cimetidine could be found in a mortality survey involving 9928 patients taking cimetidine and 9351 controls;[4] although the mortality rate was higher in the cimetidine patients, this was explained by the presence of underlying disease (known or unknown) before starting cimetidine treatment and the use of cimetidine to counter adverse gastric effects of other drugs. Follow-up of 9377 of these cimetidine-treated patients for a further 3 years[5] still revealed no fatal disorder attributable to cimetidine treatment and a steady fall in the excess death rate in cimetidine users was seen with increasing length of follow-up; by the fourth year there was little difference between the observed and expected death rate. Cimetidine still appeared to be safe after 10 years of follow-up.[6]

1. Richter JM, *et al*. Cimetidine and adverse reactions: a meta-analysis of randomized clinical trials of short-term therapy. *Am J Med* 1989; **87:** 278–84.
2. Colin Jones DG, *et al*. Post-marketing surveillance of the safety of cimetidine: twelve-month morbidity report. *Q J Med* 1985; **54:** 253–68.
3. Bardhan KD, *et al*. Safety of longterm cimetidine (CIM) treatment: the view from one centre. *Gut* 1990; **31:** A599.
4. Colin-Jones DG, *et al*. Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; **286:** 1713–16.
5. Colin-Jones DG, *et al*. Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; **291:** 1084–8.
6. Colin-Jones DG, *et al*. Postmarketing surveillance of the safety of cimetidine: 10 year mortality report. *Gut* 1992; **33:** 1280–4.

Carcinogenicity. An association between H_2-antagonists and gastric cancer was proposed after individual case reports, the finding of tumours in long-term high-dose *animal* studies, and the possibility that nitrites and nitroso compounds may be produced, but seemed of little clinical relevance.[1,2] Although a small increase in the risk of gastric cancer has been reported with the use of H_2-antagonists,[3] the excess risk in patients taking cimetidine[4-7] or ranitidine[7] decreases with time and there is no evidence for any long-term persistence of the effect.[7] The increased risk may be explained by misdiagnosis and inappropriate cimetidine treatment of existing malignancy,[4-6] or by confounding by indication,[3] since the excessive gastric-acid production for which the drugs are given may itself be associated with an increased risk of gastric cancer. An apparently protective effect has been seen for H_2-antagonist use starting 10 or more years before diagnosis of gastric cancer.[7]

The observed excess risk for cancers of the respiratory system is probably related to smoking, since this is causally related to both peptic ulcer and lung cancer and the excess risk does not decline with time.[4-6]

The hormonal effects of cimetidine have also led to study into its association with cancers of the breast or prostate. In general, use of cimetidine or other H_2-antagonists has not

affected the risk of breast cancer,[8-10] although current use of ranitidine was associated with an increased risk for hormone receptor-positive ductal carcinoma in one study.[9] In prostate cancer, a large cohort study found an increased risk only in men who took cimetidine daily over 10 years compared with men who did not use H_2-antagonists.[11] Prostate cancer risk was not affected by less frequent cimetidine use or by any use of other H_2-antagonists. Another study[10] found a modest increase in the risk of prostate cancer only in men who had received more than 20 prescriptions for cimetidine, compared with patients who had taken other H_2-antagonists.

1. Penston J, Wormsley KG. H_2-receptor antagonists and gastric cancer. *Med Toxicol* 1986; **1:** 163–8.
2. Møller H, *et al*. Use of cimetidine and other peptic ulcer drugs in Denmark 1977–1990 with analysis of the risk of gastric cancer among cimetidine users. *Gut* 1992; **33:** 1166–9.
3. Tamim H, *et al*. Association between use of acid-suppressive drugs and risk of gastric cancer: a nested case-control study. *Drug Safety* 2008; **31:** 675–84.
4. Colin-Jones DG, *et al*. Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; **286:** 1713–16.
5. Colin-Jones DG, *et al*. Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; **291:** 1084–8.
6. Møller H, *et al*. Cancer occurrence in a cohort of patients treated with cimetidine. *Gut* 1989; **30:** 1558–62.
7. La Vecchia C, *et al*. Histamine-2-receptor antagonists and gastric cancer risk. *Lancet* 1990; **336:** 355–7.
8. Coogan PF, *et al*. Cimetidine and other histamine$_2$-receptor antagonist use in relation to risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005; **14:** 1012–15.
9. Mathes RW, *et al*. Relationship between histamine$_2$-receptor antagonist medications and risk of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008; **17:** 67–72.
10. Rossing MA, *et al*. Cimetidine use and risk of prostate and breast cancer. *Cancer Epidemiol Biomarkers Prev* 2000; **9:** 319–23.
11. Velicer CM, *et al*. Cimetidine use and the risk for prostate cancer: results from the VITAL cohort study. *Ann Epidemiol* 2006; **16:** 895–900.

Effects on the blood. A review[1] in 1988 noted that leucopenia, thrombocytopenia, and pancytopenia have all been reported with cimetidine and ranitidine, with neutropenia and agranulocytosis occurring most often. There were also isolated reports of haemolytic anaemia and leucocytosis associated with cimetidine therapy. The overall incidence of cimetidine-associated blood cytopenia was estimated as 2.3 per 100 000 treated patients; the incidence for ranitidine was less and although there were reports with famotidine the incidence had not been determined. A subsequent case-control study,[2] concluded that the risk of hospitalisation due to neutropenia in patients receiving a 6-week course of cimetidine was no more than 1 in 116 000, while agranulocytosis did not occur in more than 1 in 573 000 patients.

A review[3] of the safety profile of famotidine noted that as of May 1992 there had been 60 reports of serious blood dyscrasias in patients receiving famotidine, of which 22 were considered possibly related to drug therapy (6 cases of pancytopenia or bone marrow depression, 5 of thrombocytopenia, 4 of leucopenia, 3 of combined leucopenia and thrombocytopenia, and 3 of agranulocytosis).

1. Aymard J-P, *et al*. Haematological adverse effects of histamine H_2-receptor antagonists. *Med Toxicol* 1988; **3:** 430–48.
2. Strom BL, *et al*. Is cimetidine associated with neutropenia? *Am J Med* 1995; **99:** 282–90.
3. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; **18:** 36–54.

Effects on bone. An observational study[1] of the role of histamine in bone turnover, found that bone mineral density (BMD) at the femoral neck was reduced in patients taking H_2-antagonists, especially when calcium or vitamin D intake was reduced. The authors concluded that although the risk estimates of the BMD changes did not seem to be large, the clinical sequelae were uncertain.

1. Kinjo M, *et al*. Antihistamine therapy and bone mineral density: analysis in a population-based US sample. *Am J Med* 2008; **121:** 1085–91.

Effects on the cardiovascular system. Reports of cardiovascular effects associated with H_2-antagonists have mostly involved dysrhythmias;[1] bradycardia, AV block, sinus or cardiac arrest, atrial fibrillation, ventricular extrasystoles, tachycardia, and ventricular fibrillation have all been reported with cimetidine, the oldest H_2-antagonist. Similar adverse effects have been reported with ranitidine; with famotidine, QT prolongation has also been described.[2,3] Although cardiovascular adverse effects are considered infrequent, they have occurred after intravenous and oral dosage, as well as after single-dose or long-term treatment.[1]

Studies into the haemodynamic effects of H_2-antagonists have reported disparate results. Apparent differences in effect have been seen for different H_2-antagonists at equipotent doses.[1] Some studies in healthy subjects,[4-6] and critically ill[7,8] and other[9] patients being treated with H_2-antagonists found no adverse haemodynamic effects with cimetidine, famotidine, or ranitidine. However, other studies in healthy subjects have noted negative inotropic effects with both famotidine and nizatidine. Falls in heart rate and cardiac output with nizatidine were not reproduced after pre-treatment with ranitidine[10] or pirenzepine,[11] and falls in cardiac output and stroke volume with famotidine[12] were delayed by pre-treatment with ranitidine.[10] It has been suggested that there is a small proportion of patients more susceptible to the cardiovascular effects of H_2-antagonists.[5] Caution is recommended if H_2-antagonists are given intravenously to patients with cardiovascular disease (see Precautions, p. 1830.2).

See also under Overdosage, p. 1830.1.

1. Hinrichsen H, *et al*. Clinical aspects of cardiovascular effects of H_2-receptor antagonists. *J Clin Pharmacol* 1995; **35:** 107–16.
2. Endo T, *et al*. Famotidine and acquired long QT syndrome. *Am J Med* 2000; **108:** 438–9.
3. Lee KW, *et al*. Famotidine and long QT syndrome. *Am J Cardiol* 2004; **93:** 1325–7.
4. Hilleman DE, *et al*. Impact of chronic oral H_2-antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.
5. Hughes DG, *et al*. Cardiovascular effects of H_2-receptor antagonists. *J Clin Pharmacol* 1989; **29:** 472–7.
6. Rocha GR, *et al*. Effects of cimetidine on chronotropic response to cardiopulmonary exercise testing. *Arq Bras Cardiol* 2006; **86:** 206–10.
7. Vohra SB, *et al*. The haemodynamic effects of ranitidine injected centrally in optimally resuscitated patients. *Br J Hosp Med* 1989; **42:** 149.
8. Heiselman DE, *et al*. Hemodynamic status during famotidine infusion. *DICP Ann Pharmacother* 1990; **24:** 1163–5.
9. Jackson G, Upward JW. Cimetidine, ranitidine, and heart rate. *Lancet* 1982; **2:** 265.
10. Mescheder A, *et al*. Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
11. Hinrichsen H, *et al*. Dose-dependent heart rate reducing effect of nizatidine, a histamine H_2-receptor antagonist. *Br J Clin Pharmacol* 1993; **35:** 461–6.
12. Hinrichsen H, *et al*. Hemodynamic effects of different H_2-receptor antagonists. *Clin Pharmacol Ther* 1990; **48:** 302–8.

Effects on the endocrine system. Cimetidine has dose-related mild anti-androgenic properties and reduced sperm counts and raised serum-prolactin concentrations have been reported in men during cimetidine treatment[1] as have gynaecomastia, breast tenderness, and impotence.[2] Those symptoms resolved after withdrawal of cimetidine,[1,2] reduction of the dose,[2] or transfer to ranitidine.[2]

A study by the Boston Collaborative Drug Surveillance Program, using data from 81 535 men in the UK, found that cimetidine was associated with an incidence of 3.29 cases of gynaecomastia per 1000 person years, representing a relative risk 7.2 times greater than that of non-users.[3] The period at highest risk seemed to be between the seventh and twelfth month after starting treatment, and the occurrence was related to dose, with most of the risk associated with doses over 1 g daily. This large study found no significant risk of gynaecomastia with ranitidine or omeprazole.

Unlike cimetidine, famotidine, nizatidine, and ranitidine are considered to have little, if any, anti-androgenic effect. Studies in men taking ranitidine for the management of duodenal ulcer[4,5] reported no significant changes in the plasma concentrations of testosterone, luteinising hormone, follicle-stimulating hormone, or prolactin after up to 2 years of treatment; no significant changes in sperm concentration, motility, or morphology were noted.[4] However, there have been isolated reports of galactorrhoea with famotidine,[6] gynaecomastia with ranitidine,[7,8] hyperprolactinaemia with famotidine[6,9] and ranitidine,[8] and impotence with famotidine,[10] nizatidine,[10] and ranitidine.[8,10]

1. Wang C, *et al*. Effect of cimetidine on gonadal function in man. *Br J Clin Pharmacol* 1982; **13:** 791–4.
2. Jensen RT, *et al*. Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308:** 883–7.
3. García Rodríguez LA, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994; **308:** 503–6. Correction. *ibid.;* 819.
4. Wang C, *et al*. Ranitidine does not affect gonadal function in man. *Br J Clin Pharmacol* 1983; **16:** 430–2.
5. Knigge U, *et al*. Plasma concentrations of pituitary and peripheral hormones during ranitidine treatment for two years in men with duodenal ulcer. *Eur J Clin Pharmacol* 1989; **37:** 305–7.
6. Güven K, Kelestimur F. Hyperprolactinemia and galactorrhea with standard-dose famotidine therapy. *Ann Pharmacother* 1995; **29:** 788.
7. Tosi S, Cagnoli M. Painful gynaecomastia with ranitidine. *Lancet* 1982; **2:** 160.
8. Bera F, *et al*. Impuissance et gynécomastie secondaires à une hyperprolactinémie induite par la ranitidine. *Therapie* 1994; **49:** 361–2.
9. Delpre G, *et al*. Hyperprolactinaemia during famotidine therapy. *Lancet* 1993; **342:** 868.
10. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **1:** 963.

Effects on the eyes. Ocular pain, blurred vision, and a rise in intra-ocular pressure occurred in a patient with chronic glaucoma during treatment with cimetidine; ocular symptoms associated with raised intra-ocular pressure subsequently developed during ranitidine treatment.[1] However, a study suggested that cimetidine had no effect on intra-ocular pressure.[2] A cohort study involving 140 128 patients receiving anti-ulcer therapy, 68 504 of whom received cimetidine, found no evidence that any of the drugs were associated with a major increased risk of vascular or inflammatory disorders of the eye.[3]

1. Dobrilla G, *et al*. Exacerbation of glaucoma associated with both cimetidine and ranitidine. *Lancet* 1982; **1:** 1078.
2. Feldman F, Cohen MM. Intraocular pressure and H_2 receptor antagonists. *Lancet* 1982; **1:** 1359.
3. García Rodríguez LA, *et al*. A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.

Effects on the kidneys. A review[1] of the nephrotoxicity and hepatotoxicity of H_2-antagonists noted that mild elevation of serum-creatinine was relatively common after use of cimetidine but appeared to have no clinical significance. However, the authors found 25 published reports of acute interstitial nephritis associated with this class of drug (20 with cimetidine, 4 with ranitidine, and 1 with famotidine) and 16 cases reported to the Australian Drug Reaction Advisory Committee (ADRAC) between 1972 and 1999 (11 with cimetidine, 4 with ranitidine, and 1 with famotidine). Symptoms were mostly non-specific, and did not seem to be associated with the rash, arthralgia, and flank pain that may be seen in nephritis induced by other drugs. Nephritis was rare (an earlier analysis estimated an incidence of around 1 in 100 000 treated patients[2]) and invariably resolved when the drug was withdrawn. In 6 cases, rechallenge resulted in prompt return of clinical features, although there was some evidence that patients who developed nephrotoxicity with one H_2-antagonist might be able to tolerate substitution with another.

1. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H_2 receptor antagonists. *Drug Safety* 2001; **24:** 39–57.
2. Rowley-Jones D, Flind AC. Cimetidine-induced renal failure. *BMJ* 1982; **285:** 1422–3.

Effects on the liver. Hepatotoxicity has been reported with cimetidine,[1,2] ranitidine,[3-5] and famotidine.[2,6] A cohort study[7] involving 108 891 patients given cimetidine, ranitidine, famotidine, or omeprazole between 1990 and 1993, found 33 cases meeting the authors' definition of clinically serious liver injury (cholestatic in 8 cases, hepatocellular in 15 and mixed in 10), most of whom presented with jaundice. Of these cases of liver injury, 12 were among current users of cimetidine, compared with 5 among users of ranitidine and 1 omeprazole user. It was estimated that the incidence of hepatotoxicity among patients using cimetidine was 2.3 cases per 10 000 users, and the adjusted relative risk was 5.5 times that of non-users. The relative risk for use of ranitidine or omeprazole was calculated at 1.7 and 2.1 respectively. The risk with cimetidine was greatest at high doses (800 mg daily or above) and at the beginning of therapy. A review concluded that although hepatotoxicity is very rare, it can occur with all H_2-antagonists and can include both hepatocellular and cholestatic features.[8]

1. Boyd PT, *et al*. Chronic active hepatitis associated with cimetidine. *BMJ* 1989; **298:** 324–5.
2. Hashimoto F, *et al*. Hepatitis following treatments with famotidine and then cimetidine. *Ann Pharmacother* 1994; **28:** 37–9.
3. Souza Lima MA. Ranitidine and hepatic injury. *Ann Intern Med* 1986; **105:** 140.
4. Ramrakhiani S, *et al*. Possible cholestatic injury from ranitidine with a review of the literature. *Am J Gastroenterol* 1998; **93:** 822–6.
5. Liberopoulos EN, *et al*. Possible ranitidine-induced cholestatic jaundice. *Ann Pharmacother* 2002; **36:** 172.
6. Ament PW, *et al*. Famotidine-induced mixed hepatocellular jaundice. *Ann Pharmacother* 1994; **28:** 40–2.
7. García Rodríguez LA, *et al*. The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. *Br J Clin Pharmacol* 1997; **43:** 183–8.
8. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H_2-receptor antagonists. *Drug Safety* 2001; **24:** 39–57.

Effects on the nervous system. CNS reactions have been reported with all H_2-antagonists.[1] These reactions occurred within 2 weeks of starting therapy in most cases, and resolved within 3 to 7 days of stopping treatment. After a reaction, it has been reported that most patients tolerate a different H_2-antagonist, but some will react to more than one. Confusion, disorientation, agitation, hostility, delirium, and hallucinations were most commonly described; obtundation, drowsiness, psychosis, and paranoia have also been reported. Proposed risk factors for CNS reactions associated with H_2-antagonist use include increasing age, critical illness, concomitant use of psychotropic medicines, pre-existing psychiatric disease, and liver or kidney disease. However, the evidence is sparse and the risk factors and the relative incidence of reactions with different H_2-antagonists remain to be established.

The effect of H_2-antagonists on cognitive function has also been studied. Despite early data suggesting their use was associated with a reduced risk of Alzheimer's disease, further analysis did not confirm the link.[2] Furthermore, a 5-year prospective study[3] suggested that continuous use of H_2-antagonists was associated with an increased risk of cognitive impairment in elderly African Americans.

1. Cantú TG, Korek JS. Central nervous system reactions to histamine-2 receptor blockers. *Ann Intern Med* 1991; **114:** 1027–34.
2. Zandi PP, *et al*. Cache County Study Investigators. Reduced incidence of AD with NSAID but not H_2 receptor antagonists: the Cache County Study. *Neurology* 2002; **59:** 880–6.
3. Boustani M, *et al*. The association between cognition and histamine-2 receptor antagonists in African Americans. *J Am Geriatr Soc* 2007; **55:** 1248–53.

Effects on the skin. Widespread erythrosis-like lesions in a 36-year-old man were probably induced by cimetidine.[1]

There has been a report[2] of a skin eruption clinically consistent with erythema annulare centrifugum developing in a patient after 6 months of treatment with cimetidine; the eruption resolved after withdrawal of cimetidine and reappeared on rechallenge. The condition had not recurred during therapy with ranitidine. A mainly symmetrical, intertriginous pattern of erythema has also been reported with cimetidine use.[3] Erythema multiforme eruptions occurred after both cimetidine and famotidine in one patient.[4] There have been reports of the Stevens-Johnson syndrome during cimetidine treatment in patients with a history of hypersensitivity to penicillin[5] or sulfonamides,[6] and toxic epidermal necrolysis has been reported with cimetidine[7] and famotidine.[8] Vasculitic rashes have been reported with cimetidine,[9] nizatidine,[10] and ranitidine.[11] Alopecia[12] has been associated with cimetidine treatment.

1. Angelini G, *et al.* Cimetidine and erythrosis-like lesions. *BMJ* 1979; **i:** 1147–8.
2. Merrett AC, *et al.* Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine. *BMJ* 1981; **283:** 698.
3. Helmbold P, *et al.* Symmetric ptychotropic and nonpigmenting fixed drug eruption due to cimetidine (so-called baboon syndrome). *Dermatology* 1998; **197:** 402–3.
4. Horiuchi Y, Ikezawa K. Famotidine-induced erythema multiforme: cross-sensitivity with cimetidine. *Ann Intern Med* 1999; **131:** 795.
5. Ahmed AH, *et al.* Stevens-Johnson syndrome during treatment with cimetidine. *Lancet* 1978; **ii:** 433.
6. Guan R, Yeo PPB. Stevens-Johnson syndrome: was it cimetidine? *Aust N Z J Med* 1983; **13:** 182.
7. Tidwell BH, *et al.* Cimetidine-induced toxic epidermal necrolysis. *Am J Health-Syst Pharm* 1998; **55:** 163–4.
8. Brunner M, *et al.* Toxic epidermal necrolysis (Lyell syndrome) following famotidine administration. *Br J Dermatol* 1995; **133:** 814–15.
9. Mitchell GG, *et al.* Cimetidine-induced cutaneous vasculitis. *Am J Med* 1983; **75:** 875–6.
10. Suh J-G, *et al.* Leukocytoclastic vasculitis associated with nizatidine therapy. *Am J Med* 1997; **102:** 216–17.
11. Haboubi N, Asquith P. Rash mediated by immune complexes associated with ranitidine treatment. *BMJ* 1988; **296:** 897.
12. Khalsa JH, *et al.* Cimetidine-associated alopecia. *Int J Dermatol* 1983; **22:** 202--4.

Fever. There are reports of febrile reactions associated with cimetidine,[1-4] famotidine,[5] and ranitidine.[1,6]

1. Potter HP, *et al.* Fever after cimetidine and ranitidine. *J Clin Gastroenterol* 1986; **8:** 275–6.
2. Parenti CM, Hoffman JE. Hyperpyrexia associated with intravenous cimetidine therapy: report of a case. *Arch Intern Med* 1986; **146:** 1821–2.
3. Hiraide A, *et al.* IgE-mediated drug fever due to histamine H2-receptor blockers. *Drug Safety* 1990; **5:** 455–7.
4. Chia JK, *et al.* Recurrent fever, leukocytosis, and abdominal pain due to treatment with cimetidine. *Clin Infect Dis* 1994; **18:** 468–9.
5. Norwood J, *et al.* Famotidine and hyperpyrexia. *Ann Intern Med* 1990; **112:** 632.
6. Kavanagh GM, *et al.* Ranitidine fever. *Lancet* 1993; **341:** 1422.

Hypersensitivity. Facial oedema,[1] laryngospasm,[1] pruritus,[2,3] rash,[2,3] angioedema[3] and anaphylaxis[4] have been reported in patients receiving cimetidine orally or intravenously. Respiratory stridor and a diffuse urticarial rash occurred in a patient shortly after taking the first oral dose of ranitidine;[5] the symptoms responded to subcutaneous adrenaline. Anaphylaxis has also been reported after famotidine.[6] See also Effects on the Skin, p. 1829.3.

It has also been suggested that cimetidine might potentiate hypersensitivity reactions to other antigens through its actions on histamine and H_2-receptors.[7]

1. Delaunois L. Hypersensitivity to cimetidine. *N Engl J Med* 1979; **300:** 1216.
2. Hadfield WA. Cimetidine and giant urticaria. *Ann Intern Med* 1979; **91:** 128–9.
3. Sandhu BS, Requena R. Hypersensitivity to cimetidine. *Ann Intern Med* 1982; **97:** 138.
4. Knapp AB, *et al.* Cimetidine-induced anaphylaxis. *Ann Intern Med* 1982; **97:** 374–5.
5. Brayko CM. Ranitidine. *N Engl J Med* 1984; **310:** 1601–2.
6. Kim YI, *et al.* A case of famotidine-induced anaphylaxis. *J Investig Allergol Clin Immunol* 2010; **20:** 166–9.
7. Evans RDL, *et al.* Cimetidine and a delayed hypersensitivity reaction. *Clin Podiatr Med Surg* 2000; **17:** 371–5.

Infection. For discussion of the possible increased risk of infections with acid suppressing drugs, see Omeprazole, p. 1870.1.

Malabsorption. A case-control study[1] in elderly patients found that chronic use (12 months or more) of acid-suppressive therapy, including H_2-antagonists, increased the risk of vitamin B_{12} deficiency. It has been suggested that deficiency might result from impaired release of vitamin B_{12} from food protein, which requires gastric acid and pepsin.[2]

1. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B_{12} deficiency in older adults. *J Clin Epidemiol* 2004; **57:** 422–8.
2. Ruscin JM, *et al.* Vitamin B_{12} deficiency associated with histamine$_2$-receptor antagonists and a proton-pump inhibitor. *Ann Pharmacother* 2002; **36:** 812–16.

Overdosage. No serious toxic effects were noted in reports[1-3] of overdosage in patients who took cimetidine 5.2 to 20 g (including one patient who took about 12 g daily for 5 days[1]). Resultant plasma concentrations had been up to 57 micrograms/mL compared with a usual peak plasma concentration of 1 microgram/mL after a 200-mg dose. However, an overdose of about 12 g produced high pulse rate, dilated pupils, speech disturbances, agitation and disorientation in one patient[4] and respiratory depression in another patient who had chronic schizophrenia and was also taking trifluoperazine and hydroxyzine.[5] Also, fatal bradycardia has been reported after overdosage with an unknown amount of cimetidine and diazepam.[6] In a review of 881 cases of cimetidine overdose, excluding cases where several drugs were taken, it was concluded that the toxicity of cimetidine after acute overdose was very low.[7] No symptoms were seen in 79% of cases, which included ingestions of up to 15 g of cimetidine, and only 3 patients had moderate clinical manifestations (dizziness and bradycardia; CNS depression; vomiting). No patients had major medical outcomes and there were no fatalities. Gastric emptying was performed in 34% of cases but supportive measures and symptomatic treatment alone may be adequate. Forced diuresis does not appear to enhance the excretion of cimetidine from the body, and is not recommended.[3]

1. Gill GV. Cimetidine overdose. *Lancet* 1978; **i:** 99.
2. Illingworth RN, Jarvie DR. Absence of toxicity in cimetidine overdosage. *BMJ* 1979; **i:** 453–4.
3. Meredith TJ, Volans GN. Management of cimetidine overdose. *Lancet* 1979; **ii:** 1367.
4. Nelson PG. Cimetidine and mental confusion. *Lancet* 1977; **ii:** 928.
5. Wilson JB. Cimetidine overdosage. *BMJ* 1979; **i:** 955.
6. Hiss J, *et al.* Fatal bradycardia after intentional overdose of cimetidine and diazepam. *Lancet* 1982; **ii:** 982.
7. Krenzelok EP, *et al.* Cimetidine toxicity: an assessment of 881 cases. *Ann Emerg Med* 1987; **1:** 1217–21.

Precautions

Before giving cimetidine or other histamine H_2-antagonists to patients with gastric ulcers the possibility of malignancy should be considered since these drugs may mask symptoms and delay diagnosis. They should be given in reduced dosage to patients with renal impairment.

Intravenous injections of cimetidine should be given slowly and intravenous infusion is preferred, particularly for high doses and in patients with cardiovascular impairment.

Allergy testing. A small study in 21 patients found that ranitidine suppressed the cutaneous response to allergens in skin-prick tests.[1] The authors highlighted the importance of considering the possible influence of H_2-antagonists on allergy diagnosis and treatment.

1. Kupczyk M, *et al.* Ranitidine (150 mg daily) inhibits wheal, flare, and itching reactions in skin-prick tests. *Allergy Asthma Proc* 2007; **28:** 711–15.

Breast feeding. In the UK, licensed product information advises that mothers receiving cimetidine avoid breast feeding. Cimetidine is reported to be actively transported into breast milk, resulting in a milk:serum ratio 5.5 times higher than that expected with passive diffusion.[1] In one case, where cimetidine was detected in the milk of a nursing mother in concentrations higher than in her plasma, it was calculated[2] that the maximum amount of cimetidine that an infant could ingest assuming an intake of about 1 litre of milk daily and fed at the time of peak concentrations would be about 6 mg. However, the Committee on Drugs of the American Academy of Pediatrics has pointed out that there was no evidence of signs or symptoms attributable to the drug in the infant in this case,[3] despite 6 months of breast feeding, and cimetidine has been classified by that body as usually compatible with breast feeding.[4]

1. Oo CY, *et al.* Active transport of cimetidine into human milk. *Clin Pharmacol Ther* 1995; **58:** 548–55.
2. Somogyi A, Gugler R. Cimetidine excretion into breast milk. *Br J Clin Pharmacol* 1979; **7:** 627–9.
3. Berlin CM. Cimetidine and breast-feeding. *Pediatrics* 1991; **88:** 1294.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)

Burns. The clearance of cimetidine has been reported to be increased in burn patients, with the increase correlating to the size of the burn.[1] Despite another study that reported a decreased renal clearance (but an increased non-renal clearance) early in the evolution of burn injury,[2] it has been recommended that the dosage of cimetidine be increased in patients with burns, depending on the extent of injury. A requirement for increased dosage has also been noted in paediatric burns patients.[3]

1. Martyn JAJ, *et al.* Increased cimetidine clearance in burn patients. *JAMA* 1985; **253:** 1288–91.
2. Ziemniak JA, *et al.* Cimetidine kinetics during resuscitation from burn shock. *Clin Pharmacol Ther* 1984; **36:** 228–33.
3. Martyn JAJ, *et al.* Alteration by burn injury of the pharmacokinetics and pharmacodynamics of cimetidine in children. *Eur J Clin Pharmacol* 1989; **36:** 361–7.

Helicobacter pylori testing. A study in 118 patients with *Helicobacter pylori* infection showed that 14 days of treatment with ranitidine could produce false negative results with urea breath testing, regardless of the dose used.[1] All breath tests became positive within 14 days of stopping treatment. The manufacturers of the breath test recommend it should not be performed for at least 2 weeks after stopping antisecretory drug therapy.

1. Savarino V, *et al.* Negative effect of ranitidine on the results of urea breath test for the diagnosis of Helicobacter pylori. *Am J Gastroenterol* 2001; **96:** 348–52.

Hepatic impairment. An increased resistance to H_2-receptor antagonists has been reported in patients with cirrhosis.[1] Plasma concentrations were higher in responders than nonresponders; however, the authors considered concentrations in both groups to be sufficient for an effect and could not account for the results.

For a suggestion that dosage reduction of cimetidine may be required in patients with portal systemic encephalopathy, see Administration in Hepatic Impairment, p. 1827.3.

1. Walker S, *et al.* Frequent non-response to histamine H_2-receptor antagonists in cirrhotics. *Gut* 1989; **30:** 1105–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cimetidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

For reference to clinical and biochemical improvement in porphyric patients receiving cimetidine, see p. 1828.2.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Data from prospective[1,2] and retrospective[3] cohort studies in pregnant women who had taken H_2-antagonists mainly during the first trimester, have not indicated an increased risk of major malformations. H_2-antagonists were also not associated with perinatal mortality, low birth-weight, or low Apgar scores;[1-3] although one study noted a higher rate of preterm births in the group exposed to H_2-antagonists,[2] this was not supported by other studies.[1,3] Additionally, UK licensed product information states that ranitidine has been given to women in labour or undergoing caesarean section without any adverse effects on labour, delivery, or the child. However, product information for cimetidine and ranitidine advises they should be avoided during pregnancy unless essential, as both cross the placenta.

1. Ruigómez A, *et al.* Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999; **150:** 476–81.
2. Garbis H, *et al.* Pregnancy outcome after exposure to ranitidine and other H2-blockers: a collaborative study of the European Network of Teratology Information Services. *Reprod Toxicol* 2005; **19:** 453–8.
3. Matok I, *et al.* The safety of H_2-blockers use during pregnancy. *J Clin Pharmacol* 2010; **50:** 81–7.

Interactions

Cimetidine and other H_2-antagonists can reduce the absorption of drugs such as dasatinib, ketoconazole, itraconazole, and possibly posaconazole, whose absorption is dependent on an acid gastric pH. For the effect of itraconazole on cimetidine see Antifungals, p. 1831.1.

Cimetidine may inhibit the hepatic metabolism of many drugs by binding to cytochrome P450 isoenzymes, including CYP1A2, CYP2C9, CYP2D6, CYP3A3, CYP3A4, and CYP2C18. Although many such interactions may occur, only a few are considered clinically significant, notably those with phenytoin, theophylline, lidocaine, and oral anticoagulants. Avoidance of the combination, or a reduction in the dosage of these drugs may be required.

Cimetidine can affect many drugs[1-4] but these interactions are of clinical significance for only a few, particularly those that have a narrow therapeutic index where the risk of toxicity may necessitate adjustment of dosage. The majority of interactions are due to binding of cimetidine to cytochrome P450 isoenzymes in the liver with subsequent inhibition of microsomal oxidative metabolism and increased bioavailability or plasma concentrations of drugs metabolised by these enzymes. A few interactions are due to competition for renal tubular secretion. Other mechanisms of interaction such as changes in hepatic blood flow play only a minor role.

Significant interactions have occurred with:

- antiarrhythmics such as dofetilide (p. 1367.2), lidocaine (p. 1991.2), and procainamide (p. 1477.2)
- antiepileptics such as phenytoin (p. 544.3) and carbamazepine (p. 517.3)
- biguanide antidiabetics (p. 469.1)
- moclobemide (p. 438.1)
- nifedipine (p. 1454.1)
- opioid analgesics (p. 111.3)
- nitrosoureas such as carmustine (p. 762.1)
- sildenafil (p. 2366.3)
- theophylline (p. 1236.1)
- tricyclic antidepressants such as amitriptyline (p. 407.1)
- warfarin and other oral anticoagulants (p. 1534.1)
- zalcitabine (p. 1023.3)
- zolmitriptan (p. 682.3)

Combinations of these drugs and cimetidine should be avoided or used with caution, with monitoring of effects or

plasma-drug concentrations and reductions in dosage as appropriate.

Famotidine, nizatidine, and ranitidine do not inhibit cytochrome P450, and the potential for drug interactions is therefore reduced.

1. Penston J, Wormsley KG. Adverse reactions and interactions with H_2-receptor antagonists. *Med Toxicol* 1986; **1:** 192–216.
2. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine 1987. *Clin Pharmacokinet* 1987; **12:** 321–66.
3. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.
4. Shinn AF. Clinical relevance of cimetidine drug interactions. *Drug Safety* 1992; **7:** 245–67.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p. 1735.2).

Antacids. Single-dose studies of the interaction between cimetidine famotidine, or ranitidine and antacids[1] have generally shown a reduced bioavailability of H_2-antagonist. The neutralising capacity of the antacid appears to be a factor in determining whether an interaction occurs and a dose with less than 50 mmol neutralising capacity will have little, if any, effect on H_2-antagonist absorption. Smaller doses of antacid taken separately from the H_2-antagonist should reduce the impact of this interaction, and there are some data to suggest that absorption is not as greatly affected with concomitant longer-term use.

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.

Antifungals. *Itraconazole* increased the area under the concentration-time curve of cimetidine, and reduced the total plasma clearance and renal tubular secretory clearance of cimetidine in a pharmacokinetic study in 8 healthy subjects.[1] The authors proposed that this was due to inhibition of P-glycoprotein-mediated renal tubular secretion.

1. Karyekar CS, *et al.* Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol* 2004; **44:** 919–27.

Antihistamines. Cimetidine may increase the serum concentration of hydroxyzine, see p. 631.2.

Antimuscarinics. The antimuscarinic *propantheline* delays gastric emptying and reduces intestinal motility and has been reported to reduce the bioavailability of cimetidine.[1]

1. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11:** 629–31.

Histamine. For the effect of cimetidine on histamine given exogenously, see p. 2525.3.

Melatonin. For the effect of cimetidine on melatonin, see p. 2552.2.

Probenecid. Probenecid reduced the clearance of both cimetidine[1] and famotidine[2] in small studies in healthy subjects. It was suggested that probenecid inhibited renal tubular secretion, although it was felt that the interaction was unlikely to be clinically significant.[1]

1. Gisclon LG, *et al.* The effect of probenecid on the renal elimination of cimetidine. *Clin Pharmacol Ther* 1989; **45:** 444–52.
2. Inotsume N, *et al.* The inhibitory effect of probenecid on renal excretion of famotidine in young, healthy volunteers. *J Clin Pharmacol* 1990; **30:** 50–6.

Prokinetic drugs. *Metoclopramide* may reduce the bioavailability of cimetidine possibly due to reduction of gastrointestinal transit time.[1-3] A similar interaction has been reported between the prokinetic drug *cisapride* and both cimetidine[4] and ranitidine.[5] The clinical significance of this interaction is questionable since such combinations may be clinically effective, although the use of cisapride is now restricted in many countries. For the effect of cimetidine on cisapride, see p. 1833.1.

1. Gugler R, *et al.* Impaired cimetidine absorption due to antacids and metoclopramide. *Eur J Clin Pharmacol* 1981; **20:** 225–8.
2. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11:** 629–31.
3. Barzaghi N, *et al.* Effects on cimetidine bioavailability of metoclopramide and antacids given two hours apart. *Eur J Clin Pharmacol* 1989; **37:** 409–10.
4. Kirch W, *et al.* Cisapride-cimetidine interactions; enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11:** 411–14.
5. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–5.

Sucralfate. Licensed product information for the mucosal protectant sucralfate states that it has been shown to reduce the bioavailability of cimetidine and other H_2-antagonists, presumably due to binding in the gastrointestinal tract. The effect can be avoided by separating doses of the two drugs by 2 hours, but it is not clear whether the interaction has a clinical significance.

Pharmacokinetics

Cimetidine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after about an hour when given on an empty stomach; a second peak may be seen after about 3 hours. Food delays the rate and may slightly decrease the extent of absorption, with the peak plasma concentration occurring after about 2 hours.

The bioavailability of cimetidine after oral doses is about 60 to 70%, due to hepatic first-pass metabolism. Cimetidine is widely distributed and has a volume of distribution of about 1 litre/kg and is weakly bound, about 20%, to plasma proteins. The elimination half-life from plasma is about 2 hours and is increased in renal and hepatic impairment. Cimetidine is partially metabolised in the liver to the sulfoxide and to hydroxymethylcimetidine. About 50% of an oral dose, and 75% of an intravenous dose, is excreted unchanged in the urine in 24 hours. After an oral or parenteral dose of 300 mg, blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours. Cimetidine crosses the placental barrier and is distributed into breast milk.

Reviews.

1. Somogyi A, Gugler R. Clinical pharmacokinetics of cimetidine. *Clin Pharmacokinet* 1983; **8:** 463–95.
2. Lin JH. Pharmacokinetic and pharmacodynamic properties of histamine H_2-receptor antagonists: relationship between intrinsic potency and effective plasma concentrations. *Clin Pharmacokinet* 1991; **20:** 218–36.
3. Gladziwa U, Klotz U. Pharmacokinetics and pharmacodynamics of H_2-receptor antagonists in patients with renal insufficiency. *Clin Pharmacokinet* 1993; **24:** 319–32.

Children. Renal function is limited in the first few months of life and half-lives of 1.1 to 3.7 hours have been reported for cimetidine in neonates;[1-3] less frequent dosing may therefore be required for preterm neonates and those with renal impairment.[1]

In older infants and children maturation of renal function is complete and the clearance of cimetidine is increased compared with that in adults; younger children show higher clearance values than older children.[4]

For details of doses used in children, see Administration in Children, p. 1827.3.

1. Ziemniak JA, *et al.* The pharmacokinetics and metabolism of cimetidine in neonates. *Dev Pharmacol Ther* 1984; **7:** 30–8.
2. Lloyd CW, *et al.* The pharmacokinetics of cimetidine and metabolites in a neonate. *Drug Intell Clin Pharm* 1985; **19:** 203–5.
3. Stile IL, *et al.* Pharmacokinetic evaluation of cimetidine in newborn infants. *Clin Ther* 1985; **7:** 361–4.
4. Somogyi A, *et al.* Cimetidine pharmacokinetics and dosage requirements in children. *Eur J Pediatr* 1985; **144:** 72–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ulcerfen; ***Austral.***: Cimehexal†; Magicul; Tagamet; ***Austria***: Cimetag†; Neutromed; Neutronorm; Sodexx Cimetidine†; Ulcometin†; Ulcostad; ***Belg.***: Doccimeti†; Nuardin; ***Braz.***: Cigamete†; Cimedax; Cimetidan; Cimetilab; Cimetinax; Cimetival; Cintag; Cintidina; Etidine; Pristonal; Prometidine; Tagaliv; Tagamet; Ulcedine; Ulcenon; Ulcerac†; Ulcimet; Ulcinax; Ulcitrat; ***Canad.***: Novo-Cimetine; Nu-Cimet; ***China***: A Li Wei (阿立维); Changfu YouShu (长富优舒); Hai Fu Xin (海扶鑫); Nuo Mei Shu (诺美舒); Tagamet (泰胃美); Tang Feng (唐丰); Xiweining (希卫宁); Ying Qu (英曲); You Ni Ding (尤尼丁); ***Cz.***: Primamet†; ***Fr.***: Stomedine; Tagamet†; ***Ger.***: Cimebeta†; Cimehexal†; CimLich†; H 2 Blocker; ***Gr.***: Alkastom; Besidin; Campanex; Cimeton; Gastrolene; Grinolon; Haldin; Ipirovet; Medelan; Metracine; Oskoval; Pallosixanet; Piovalen; Sasapir; Tagamet; Tamper; Tanapas; Therapelcin; Tinder; Trisolvenol; Ulcogranil; ***Hong Kong***: Cementin; Cimedine†; Cimeta; Citidine; Gastab†; Gastidine†; Magicul†; Maritidine†; Simaglen; Syncomet†; Tagamet; Timet†; Ulcerin; Ulcomet; ***India***: Cimetin; Lock-2; ***Indon.***: Cimexol; Corsamet; Licomet; Nulcer; Sanmetidin; Tagamet†; Ulcedine†; Ulcumet; Ulcusan†; Ulsikur; Xepamet; ***Irl.***: Cedine†; Cimagen†; Cimeldine; Dyspamet†; Galenamet†; Geramet†; Pinamet†; Rimatidine†; Tagamet†; ***Israel***: Cemidin; Cimetag†; Tagamet†; ***Ital.***: Biomag; Brumetidina†; Etideme; Tagamet; Temic; Ulcedin; Ulis; ***Malaysia***: Cimulcer; Shintamet; Tagamet; ***Mex.***: Cimebec†; Cimedul; Cimeffer; Cimetase; Colimet†; Gastrodina; Procimeti†; Sercim; Sinegastrin†; Tagamet; Ulmarin; Ulserral; ***Neth.***: Tagamet†; ***NZ***: Cytine; ***Philipp.***: Antag†; Ciclem; Cimecid†; Cimulcer†; Duogastril; Montidin†; Shintamet; Tagamet; Temaril; Ulcenon†; ***Pol.***: Altramet†; Cimegast†; ***Port.***: Cim; Tagamet; ***Rus.***: Histodil (Гистодил)†; ***S.Afr.***: Aci-Med†; Acidown; Cimlok; Cinadinet†; Cymi†; Hexamet; Lenamet; Lesacid; Secadine; Tagamet; Ulcim†; ***Singapore***: Cementin; Cimulcer; Citidine; Erlmetin; Himetin; Shintamet; Tagamet; Xepamet; ***Spain***: Ali Veg†; Fremet†; Tagamet†; ***Thai.***: Alserine; Cencamat; Chintamet; Cidine; Cigamet; Cimag; Cimet-P; Cimet; Cimetin†; Cimetine†; Ciminpac; Citidine; Clinimet; Duotric; Gastasil; GI; Iwamet†; KB Cymedin; Lakamed; Manomet; Milamet; Peptica†; Peptidine; Pondarmett†; Promet†; Rinadine†; Sertidine; Setard†; Shintamet†; Siamidine; Simaglen†; Simex†; Sincimet; Startidine; Stomedine; Tacamac; Tagapro; Ulcacin; Ulcedine†; Ulcemet; Ulcimet; Ulcine†; Ulsamet; Umamett†; ***UAE***: Cimetag; ***UK***: Dyspamet; Galenamet; Tagamet; Zita; ***USA***: Tagamet; ***Venez.***: Gadol.

Pharmacopoeial Preparations

BP 2014: Cimetidine Injection; Cimetidine Oral Solution; Cimetidine Oral Suspension; Cimetidine Tablets;

USP 36: Cimetidine in Sodium Chloride Injection; Cimetidine Injection; Cimetidine Tablets.

Cimetropium Bromide *(rINN)*

Bromuro de cimetropio; Cimetropii Bromidum; Cimetropio, bromuro de; Cimétropium, Bromure de; DA-3177; Hyoscine-*N*-(cyclopropylmethyl) Bromide; Циметропия Бромид.

8-(Cyclopropylmethyl)-6β,7β-epoxy-3α-hydroxy-1αH,5αH-tropanium bromide, (-)-(*S*)-tropate.

$C_{21}H_{28}BrNO_4$=438.4

CAS — 51598-60-8.

ATC — A03BB05.

ATC Vet — QA03BB05.

UNII — 0C7M5WE60Q.

Profile

Cimetropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an antispasmodic in the treatment of gastrointestinal disorders, in usual doses of 50 mg two or three times daily orally or by rectal suppository. It has also been given intramuscularly or intravenously in usual doses of 5 mg.

References.

1. Dobrilla G, *et al.* Longterm treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. *Gut* 1990; **31:** 355–8.
2. Marzio L, *et al.* Effect of cimetropium bromide on esophageal motility and transit in patients affected by primary achalasia. *Dig Dis Sci* 1994; **39:** 1389–94.
3. Savino F, *et al.* Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr Gastroenterol Nutr* 2002; **34:** 417–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Alginor.

Cinitapride *(rINN)*

Cinitaprida; Cinitapridum; Цинитаприд.

4-Amino-*N*-[1-(3-cyclohexen-1-ylmethyl)-4-piperidyl]-2-ethoxy-5-nitrobenzamide.

$C_{21}H_{30}N_4O_4$=402.5

CAS — 66564-14-5.

UNII — R8I9712L24.

Profile

Cinitapride is a substituted benzamide used for its prokinetic properties. It is given as the acid tartrate in oral doses of 1 mg three times daily before meals in the management of gastroparesis and gastro-oesophageal reflux disease (p. 1807.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cinigest; Paxapride; Rogastril; ***Mex.***: Binitab; Pemix; ***Spain***: Blaston; Cidine.

Multi-ingredient Preparations. ***Mex.***: Pridamiral Pack.

Cisapride *(BAN, USAN, rINN)*

Cisaprid; Cisaprida; Cisapridas; Cisapride monohydraté; Cisapridum; Cisapridum monohydricum; Ciszaprid; Cyzapryd jednowodny; R-51619; Sisapridi; Цизаприд.

cis-4-Amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidyl]-2-methoxybenzamide monohydrate.

$C_{23}H_{29}ClFN_3O_4.H_2O$=484.0

CAS — 81098-60-4 (anhydrous cisapride).

ATC — A03FA02.

ATC Vet — QA03FA02.

UNII — UVL329170W (cisparide); VZV0A4I38W (cisapride monohydrate).

Pharmacopoeias. *US.*

USP 36: (Cisapride). A white or almost white powder. Practically insoluble in water; sparingly soluble in methyl alcohol; soluble in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Cisapride Tartrate *(BANM, rINNM)*

Cisaprida, tartrato de; Cisapride, Tartrate de; Cisapridi Tartras; Cisaprido tartratas; Cisaprid-tartarát; Cisapridtartrat; Cisza-

The symbol † denotes a preparation no longer actively marketed

prid-tartarát; Sisapriditartraatti; Tartrato de cisaprida; Цизаприда Тартрат.
$C_{27}H_{35}ClFN_3O_{10}$=616.0

Uses and Administration

Cisapride is a substituted benzamide used for its prokinetic properties. It stimulates gastrointestinal motility, probably by increasing the release of acetylcholine in the gut wall at the level of the myenteric plexus, increases the resting tone of the lower oesophageal sphincter, and increases the amplitude of lower oesophageal contractions. Gastric emptying is accelerated and the mouth-to-caecum transit time is reduced. Colonic peristalsis is also increased which decreases colonic transit time. Cisapride apparently lacks antidopaminergic effects (unlike metoclopramide, p. 1862.2, to which it is chemically related) or direct parasympathomimetic activity and it does not affect prolactin release or gastric secretion. It is reported to be an agonist at serotonin-4 (5-HT_4) receptors.

Cisapride has been used mainly in the treatment of gastro-oesophageal reflux disease (p. 1807.2), in disorders associated with decreased gastric motility (p. 1805.2), and in non-ulcer dyspepsia. However, as mentioned under Effects on the Heart, below, its use is severely restricted by its propensity to cause cardiac arrhythmias, and it has been withdrawn completely in many countries, including the UK.

Cisapride is given as the monohydrate, but doses are calculated in terms of the anhydrous substance. Cisapride monohydrate 10.39 mg is equivalent to about 10 mg of anhydrous cisapride. It is taken orally 15 to 30 minutes before a meal and at bedtime, if necessary. Where still licensed, a usual oral dose is 5 to 10 mg three to four times daily up to a maximum daily dose of 40 mg. For discussion of dosage and use in children, see below.

Doses of cisapride should be reduced in patients with hepatic or renal impairment (see below).

Administration in children. Where still licensed, neonates, infants, and children have been given cisapride 200 micrograms/kg orally three or four times daily up to a maximum daily dose of 800 micrograms/kg. However, there are particular safety concerns over the use of cisapride in children because of the risk of cardiac arrhythmias (see Effects on the Heart, below). Special care is needed in neonates and cisapride is contra-indicated in premature neonates for 3 months after birth due to the increased risk of QT interval prolongation in this patient group.

Its efficacy has also been questioned and a systematic review[1] of the use of cisapride in children found no clear evidence that cisapride had a statistically significant effect in reducing symptoms of gastro-oesophageal reflux disease compared with placebo.

1. MacLennan S, *et al.* Cisapride treatment for gastro-oesophageal reflux in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 15/07/10).

Administration in hepatic or renal impairment. In patients with hepatic impairment the dose of cisapride should be half the usual dose, followed by adjustment depending on clinical response. In cases where renal impairment is not considered to contra-indicate the use of cisapride, a similar reduction in dose has been recommended.

Adverse Effects

The most commonly reported adverse effects with cisapride are gastrointestinal disturbances including abdominal cramps, borborygmi, and diarrhoea. Headache and lightheadedness may also occur. Hypersensitivity (including rash, pruritus, and bronchospasm), convulsions, extrapyramidal effects, and increased urinary frequency, have occasionally been reported. Cases of arrhythmia, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT interval prolongation have occurred rarely; fatalities have resulted, and have led to severe restrictions on its use (see Effects on the Heart, below). There have been a few cases of disturbances in liver function among patients receiving cisapride.

Incidence of adverse effects. A comparison of data from prescription-event monitoring in over 13 000 recipients of cisapride and from a further 9726 recipients involved in a controlled study showed that diarrhoea, in about 2 to 4% of patients, was the commonest adverse effect reported.[1] Other relatively common adverse effects were headache, abdominal pain, nausea and vomiting, and constipation, all in around 1 to 1.5% of patients. There were 46 reports in the prescription-event monitoring data of increased urinary frequency (plus a further 20 among the controlled study patients), and 5 reports of arrhythmias.

1. Wager E, *et al.* A comparison of two cohort studies evaluating the safety of cisapride: prescription-event monitoring and a large phase IV study. *Eur J Clin Pharmacol* 1997; **52:** 87–94.

Effects on the heart. Seven reports[1] of cardiac effects associated with cisapride were submitted to the WHO Programme for International Drug Monitoring between 1989 and 1991. They included palpitations in 4, tachycardia and hypertension in 1, and extrasystole in 2. Subsequent reports implicated cisapride in the development of prolonged QT interval and torsade de pointes or ventricular fibrillation or both.[2,3] By December 1999 the FDA had received 341 reports of heart rhythm abnormalities associated with cisapride use, including 80 reports of deaths. Most patients were either receiving other drugs known to impair cisapride metabolism (see Interactions, below) or had other factors predisposing to arrhythmias. In the light of earlier reports of cardiac effects and of evidence for a direct effect of cisapride on the heart at therapeutic concentrations, in 1998 the UK CSM **contra-indicated**[2] the use of cisapride in patients receiving drugs that could inhibit cisapride metabolism or that prolong the QT interval, as well as in patients with a history of QT interval prolongation, ventricular arrhythmia, or torsade de pointes, or other risk factors for arrhythmia (see Precautions, below). Neonates[4] (especially of low gestational age[5]) are vulnerable to cisapride-induced QT interval prolongation, and the CSM also specifically contra-indicated use in premature neonates[2] and noted that there were insufficient data to support use in children up to the age of 12. Other studies have also noted a prolongation of QT interval in children.[6,7] However, some commentators have questioned the general contra-indication in prematurity,[8] and one retrospective analysis estimated the rate of serious adverse events such as arrhythmia in premature newborns to be less than 1 in 11 000, excluding those cases related to concurrent treatment with a contra-indicated drug or to overdose.[9] Conversely, others emphasise the lack of objective evidence of benefit for cisapride in most paediatric indications.[10] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition has published recommendations on the use of cisapride in paediatric gastro-oesophageal reflux disease,[11] including that the total daily dose of cisapride should rarely exceed 800 micrograms/kg, and that ECG monitoring should be performed before and after 3 days of treatment in certain groups such as premature infants.

The use of cisapride has also been the subject of warnings and restrictions in other countries. In the USA, prescribing information was amended in January 2000 to recommend that all patients should receive an ECG before beginning cisapride therapy and extending the contra-indications to use; the drug was subsequently **withdrawn** from general supply, remaining available only in severely restricted cases. In July 2000 cisapride was also withdrawn completely from the UK market.[12] In Europe, the European Commission decided that cisapride-containing products could be maintained with restricted indications; all patients given cisapride should be enrolled in either a study or registry of clinical safety, or a study of clinical efficacy.[13] Despite a withdrawal of cisapride from general supply, a retrospective cohort study in South Korea found that it was still in use there up to 2 years later; in many instances cisapride had been given with contra-indicated drugs, which was associated with an increase in the risk of all-cause mortality.[14]

1. Olsson S, Edwards IR. Tachycardia during cisapride treatment. *BMJ* 1992; **305:** 748–9.
2. CSM/MCA. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; **24:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
3. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* 1996; **335:** 290–1.
4. Bernardini S, *et al.* Effect of cisapride on QTc interval in neonates. *Arch Dis Child Fetal Neonatal Ed* 1997; **77:** F241–3.
5. Dubin A, *et al.* Cisapride associated with QTc prolongation in very low birth weight preterm infants. *Pediatrics* 2001; **107:** 1313–16.
6. Hill SL, *et al.* Proarrhythmia associated with cisapride in children. *Pediatrics* 1998; **101:** 1053–6.
7. Khongphatthanayothin A, *et al.* Effects of cisapride on QT interval in children. *J Pediatr* 1998; **133:** 51–6.
8. Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants, and children. *Arch Dis Child* 1998; **79:** 469–71.
9. Ward RM, *et al.* Cisapride: a survey of the frequency of use and adverse events in premature newborns. *Pediatrics* 1999; **103:** 469–72.
10. Cairns P. The risks and benefits of cisapride. *Arch Dis Child* 1999; **80:** 493.
11. Vandenplas Y, *et al.* The role of cisapride in the treatment of pediatric gastroesophageal reflux: the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999; **28:** 518–28.
12. CSM/MCA. Cisapride (Prepulsid) withdrawn. *Current Problems* 2000; **26:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074608&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
13. CSM/MHRA. Cisapride: licences cancelled. *Current Problems* 2004; **30:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
14. Choi N-K, *et al.* Increase in mortality rate following coprescription of cisapride and contraindicated drugs. *Ann Pharmacother* 2007; **41:** 667–73.

Effects on the respiratory system. Chest tightness, wheezing, and a fall in peak flow rate occurred in a patient with severe brittle asthma after taking cisapride 10 mg.[1] Four other cases of bronchospasm associated with cisapride were discussed in a subsequent report;[2] in 2 of these cases symptoms resolved on withdrawal and recurred on rechallenge.

1. Nolan P, *et al.* Cisapride and brittle asthma. *Lancet* 1990; **336:** 1443.
2. Pillans P. Bronchospasm associated with cisapride. *BMJ* 1995; **311:** 1472.

Effects on the urinary tract. There had been 12 cases of urinary disturbances associated with use of cisapride[1] reported to the Australian Adverse Drug Reactions Advisory Committee between March 1991 and July 1993. Five reports were of urinary incontinence, 8 involved frequency, and individual reports involved cystitis, hesitancy, and urinary retention. The majority of the cases involved women, and most patients were elderly.

1. Boyd IW, Rohan AP. Urinary disorders associated with cisapride. *Med J Aust* 1994; **160:** 579–80.

Precautions

Cisapride should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions as in gastrointestinal haemorrhage, obstruction, perforation, or immediately after surgery.

Cisapride is **contra-indicated** in the following patients:

- those receiving potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as macrolide antibacterials, azole antifungals, HIV-protease inhibitors, or nefazodone (see also Interactions, below)
- those taking other drugs that predispose to electrolyte disturbances or that prolong the QT interval
- those with a personal or family history of QT interval prolongation
- those with a history of ventricular arrhythmia or torsade de pointes

Furthermore, it should not be given to those with other risk factors for arrhythmia including:

- clinically significant heart disease
- uncorrected electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia)
- renal failure
- respiratory failure

Use is also contra-indicated in premature infants for up to 3 months after birth.

Cisapride should be used with caution and in reduced doses in patients with hepatic or renal impairment. All patients should have their ECG, serum electrolytes, and renal function monitored before and during treatment.

Care should be taken not to exceed the recommended dose.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cisapride, and the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cisapride as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Cisapride is metabolised by the cytochrome P450 isoenzyme CYP3A4. Use with drugs that significantly inhibit this enzyme is contra-indicated as it may result in increased plasma concentrations of cisapride and hence a greater risk of QT interval prolongation and ventricular arrhythmias. Examples of such drugs include the azole antifungals ketoconazole, fluconazole, itraconazole, and miconazole; the macrolide antibacterials troleandomycin, azithromycin, erythromycin, and clarithromycin; the NNRTIs delavirdine and efavirenz; and the HIV-protease inhibitors. Nefazodone may interact similarly.

Cisapride should not be used in patients receiving other medication known to prolong the QT interval, including quinine or halofantrine, terfenadine, astemizole, certain antiarrhythmics such as amiodarone or quinidine, some antidepressants such as amitriptyline, phenothiazine antipsychotics, and sertindole. Cimetidine may enhance cisapride bioavailability. Grapefruit juice also increases the bioavailability of cisapride and they should not be taken together. In addition, drugs such as potassium-sparing diuretics, or insulin in acute settings, can result in altered electrolyte balance, and use with cisapride may also increase the risk of arrhythmias.

Antimuscarinics and possibly opioid analgesics may antagonise the gastrointestinal effects of cisapride. Because

cisapride increases intestinal motility it may affect the absorption of other drugs, either diminishing absorption from the stomach or enhancing absorption from the small intestine. Prothrombin times may be increased in some patients receiving oral anticoagulants, and the effects of alcohol and some other CNS depressants may be enhanced.

Reviews.
1. Bedford TA, Rowbotham DJ. Cisapride: drug interactions of clinical significance. *Drug Safety* 1996; **15:** 167–75.
2. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet* 2000; **39:** 49–75.

Cardiovascular drugs. Near syncope and a prolonged QT interval occurred in a patient taking cisapride and *diltiazem*.[1] Diltiazem may have inhibited the metabolism of cisapride. For mention of cisapride possibly reducing the absorption of *digoxin*, see p. 1357.3.

1. Thomas AR, *et al*. Prolongation of the QT interval related to cisapride-diltiazem interaction. *Pharmacotherapy* 1998; **18:** 381–5.

H_2-antagonists. *Cimetidine*[1] but not *ranitidine*[2] has been reported to enhance the bioavailability of oral cisapride, possibly by inhibition of cisapride metabolism (cimetidine is an inhibitor of the cytochrome P450 isoenzyme CYP3A4). Cisapride conversely increases the rate of absorption and decreases the oral bioavailability of both cimetidine[1] and ranitidine (see Prokinetic Drugs, p. 1831.1).

1. Kirch W, *et al*. Cisapride-cimetidine interaction: enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11:** 411–14.
2. Rowbotham DJ, *et al*. Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–305.

Pharmacokinetics

Cisapride is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 2 hours after an oral dose. It undergoes extensive first-pass metabolism in the liver and gut wall, resulting in an absolute bioavailability of 35 to 40%. The main metabolic pathways are oxidative *N*-dealkylation by the cytochrome P450 isoenzyme CYP3A4, producing the major metabolite norcisapride, and aromatic hydroxylation. More than 90% of a dose is excreted as metabolites in the urine and faeces in about equal amounts. A small amount is distributed into breast milk. The elimination half-life is about 10 hours. Cisapride is about 98% bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cispride; Fabrapride†; Pulsar; ***Belg.***: Prepulsid†; ***Braz.***: Prepulsid; ***Chile***: Gastromet; Ondax; ***China***: Bi Na Wei (必纳维); Chang Wei Xi (畅维禧); Ge Rui Xi (格瑞西); Prepulsid (普瑞博思); Wei Fu Lai (谓富莱); Yirui (怡瑞); ***Fr.***: Prepulsid†; ***Gr.***: Alimix; Bozaktral; Cefanyl; Cevilor; Circocric; Cisarid; Desonil; Dolyzinax; Elpegon; Epasan; Evifix; Gastridol; Kinussen; Lamafer; Lasapride; Lirebin; Lycalin; Minsk; Nastilox; Oferin; Ruvetine; Saprimix; Spabucol; Systilan; Zenopar; ***India***: Alipride; Cenz; Cisalone; Cisanorm; Cisapid; Cisapro; Cisariv; Cisaten DT; Cisawal; Cispel; Ciszy; Ciza; Cizafast; Cizap; Esorid; Gastro; Gastron; Gastropen; Kemopride; Lakpride; ***Indon.***: Acpulsif; Disflux; Ethiprid; Guarposid; Pridesia; Stimulit; ***Israel***: Prepulsid†; ***Mex.***: Aposada; Cepriser; Enteropride; Eriken; Expril†; Kinestase; Maprilex; Mavisid; Nodrix; Presistin; Prixin; Profercol; Sapriken; Unamol; ***Neth.***: Prepulsid†; ***Pol.***: Gasprid; Gastronax†; ***Port.***: Prepulsid†; ***S.Afr.***: Prepulsid†; ***Singapore***: Prepulsid; ***Thai.***: Cipasid; Cisapac; Cisapid; Cisaride; Palcid; Pri-De-Sid; ***Venez.***: Cisamod.

Multi-ingredient Preparations. ***India***: Alipride MPS; Cisacone; Cisapid-MPS; Ciza-MPS; Cizap-MPS; Esorid MPS; Eza MPS; Gastro MPS; Gastropen-MPS; Kemopride MPS; Manotac Plus; ***Mex.***: Ergex.

Clebopride *(BAN, USAN, rINN)*

Cleboprida; Clébopride; Clebopridum; LAS-9273; Клебоприд.

4-Amino-*N*-(1-benzyl-4-piperidyl)-5-chloro-*o*-anisamide.

$C_{20}H_{24}ClN_3O_2$=373.9

CAS — 55905-53-8.

ATC — A03FA06.

ATC Vet — QA03FA06.

UNII — I0A84520Y9.

Clebopride Malate *(BANM, rINNM)*

Cleboprida, malato de; Clébopride, Malate de; Clebopridi Malas; Clebopridmalat; Kleboprid malát; Klebopridimalaatti; Klebopridmalat; Kleboprid-malát; Kleboprido malatas; Malato de cleboprida; Клебоприда Малат.

$C_{20}H_{24}ClN_3O_2.C_4H_6O_5$=508.0

CAS — 57645-91-7.

ATC — A03FA06.

ATC Vet — QA03FA06.

UNII — H9490V5216.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clebopride Malate). A white or almost white, crystalline powder. Sparingly soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane. The pH of a 1% solution in water is 3.8 to 4.2. Protect from light.

Profile

Clebopride is a substituted benzamide similar to metoclopramide (p. 1862.2), that is used for its antiemetic and prokinetic actions in nausea and vomiting (p. 1811.3) and various other gastrointestinal disorders. It is given as the malate but doses are expressed in terms of the base. Clebopride malate 679 micrograms is equivalent to about 500 micrograms of clebopride.

Clebopride malate is given in a usual oral dose equivalent to clebopride 500 micrograms three times daily before meals or 0.5 to 1 mg by intramuscular or intravenous injection for acute symptoms. For dosage in children see below.

Administration in children. Adolescents aged 12 to 20 years may be given clebopride malate orally in a dose equivalent to clebopride 250 micrograms three times daily. An oral dose of 15 to 20 micrograms/kg daily in 3 divided doses may be used for children under 12; the following doses have been recommended:
- 1 to 4 years: 50 micrograms 3 times daily
- 4 to 8 years: 100 micrograms 3 times daily
- 8 to 10 years: 150 micrograms 3 times daily
- 10 to 12 years: 200 micrograms 3 times daily

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gastridin; ***China***: Si Wei Si (思谓斯); Wei Heng (维恒); ***Indon.***: Clast; ***Ital.***: Cleboril; Motilex; ***Mex.***: Eborix; ***Port.***: Clebofex; Clebutec; ***Spain***: Cleboril.

Multi-ingredient Preparations. ***Arg.***: Eudon; Gastridin-E; Somasedan; ***Spain***: Clanzoflat†; Flatoril.

Clidinium Bromide *(BAN, USAN, rINN)*

Bromuro de clidinio; Clidinii Bromidum; Clidinio, bromuro de; Clidinium, Bromure de; Klidiniumbromid; Klidiniumbromidi; Klidinyum Bromür; Ro-2-3773; Клидиния Бромид.

3-Benziloyloxy-1-methylquinuclidinium bromide.

$C_{22}H_{26}BrNO_3$=432.4

CAS — 7020-55-5 (clidinium); 3485-62-9 (clidinium bromide).

UNII — 91ZQW5JF1Z.

Pharmacopoeias. In *US.*

USP 36: (Clidinium Bromide). A white or nearly white, practically odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clidinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used alone or more often with chlordiazepoxide in the symptomatic treatment of peptic ulcer disease and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Chlordibrax.

Multi-ingredient Preparations. ***Arg.***: Libraxin; ***Canad.***: Apo-Chlorax; Librax; Pro Chlorax†; ***Chile***: Gastrolen; Lerogin; Libraxin; Tensoliv; ***Fin.***: Librax; ***Fr.***: Librax; ***Gr.***: Distedon; Librax; ***Hong Kong***: Librax; ***India***: Acirex; Alspas Forte; Cebrex Forte; Cebrex; Cibis; Clidox; Colinorm; Cypa; Dorpep; Equirex; IBS; Librax; Librospas; Neurospas-CD; Normaxin-RT; Normaxin; Orlidox-D; Orlidox; Spasrax; ***Indon.***: Braxidin; Cliad; Klidibrax; Librax; Melidox; Renagas; ***Israel***: Nirvaxal†; ***Ital.***: Librax; ***Malaysia***: Liblan; ***Port.***: Librax; ***S.Afr.***: Libraxt†; ***Singapore***: Apo-Chlorax; Chlobax; Libraxt†; Medocalum†; Syntabrax; ***Switz.***: Librax; Librocol; ***Thai.***: Cebaraxt†; Dirax; Kenspa; Librax; Licon; Modurax; Pobrax; Radibrax; Tumax; Utorax; ***Turk.***: Klipaks; Librax; ***USA***: Clindex; Librax; ***Venez.***: Librax.

Pharmacopoeial Preparations

USP 36: Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules.

Colocynth

Bitter Apple; Bitter Cucumber; Colocinto; Colocynth Pulp; Colocynthis; Coloquinte; Coloquintidas; Koloquinthen; Колоцинт.

UNII — Z70W98921V (Citrullus colocynthis); 0E49E3V9U6 (Citrullus colocynthis fruit); 23H32AOH17 (Citrullus colocynthis fruit pulp).

NOTE. The synonym Bitter Apple has also been applied to the fruits of *Solanum incanum*.

Pharmacopoeias. *Br.* includes Citrullus Colocynthis Fruit for Homoeopathic Preparations.

BP 2014: (Citrullus Colocynthis Fruit for Homoeopathic Preparations). The dried, peeled fruits of *Citrullus colocynthis* with the seeds removed.

Profile

Colocynth is the dried pulp of the fruit of *Citrullus colocynthis* (Cucurbitaceae). It has a drastic purgative and irritant action and has been superseded by less toxic laxatives.

Homoeopathy

Colocynth has been used in homoeopathic medicines under the following names: Colocynthis; Coloc.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Neth.***: Diarrheel S.

Homoeopathic Preparations. ***Austral.***: Colic Relief; IBS Eze; Teething Relief; ***Austria***: Diluplex; ***Canad.***: Berberis-Homaccord†; Carduus Plex†; Cocyntal; Col 138†; Colic; Comp-Drops 8 Uri-Tract†; Diarrhea; Formula ES 211; Formula FV 213; Hylands Formula MC; Hylands Kinder-CL†; Hylands Menstrual Cramps†; Kid's Colic; Spascupreel; ***Chile***: Lumboplex; ***Cz.***: Hepeel; ***Fr.***: Aloe Compose; Berberis Complexe No 83; Formica Rufa Compose; Gelsemium Complexe No 70; L 107; Ranunculus Complexe No 79; ***Ger.***: Araniforce arthro; Carminativum Hevert; Chole-cyl L Ho-Len-Complex; Colintest-Gastreu; Cranio-cyl Ho-Len-Complex; Diluplex; Dolo-Injektopas; Entero-Gastreu S R4; gastri-loges N; Gastriselect N; Gelsemium Comp; Gelsemium Comp; HanoHepan; Intercostal-Gastreu; Lithias-cyl L Ho-Len-Complex; Lowe-Komplex Nr 6; Magen-Darm-Entoxin N; Neuralgie-Gastreu R70; Neuri-cyl N Ho-Len-Complex; Nuxal H; Pancreas-Gastreu N; Pascofemin spasmo; Pascosabal; Spascupreel; Spasmo-Bomaleb†; Spasmoject F; ***Hung.***: Hepeel; Spascupreel; ***Neth.***: Apo-STOM; Colocynthis-Homaccord; Entero-Gastreu R4; Gastrifleur; Homeocare Digesto; Kind 0-3 Cinababy; Nux Vomica-Homaccord; Spascupreel H; Spiroflor; ***Rus.***: Menalgin (Менальгин); ***Switz.***: Diarrheel S; Gastronol; Hepeel; ***Ukr.***: Enterocind (Энтерокинд).

Crofelemer *(USAN)*

SP-303.

CAS — 148465-45-6.

Profile

Crofelemer is a proanthocyanidin from the bark latex of the tree *Croton lechleri* that acts locally on the intestinal lumen to normalise flow of chloride ions and water into the gastrointestinal tract. It is used in the management of non-infectious diarrhoea in patients with HIV and AIDS on antiretroviral therapy (see HIV-associated Wasting, p. 959.1). A dose of 125 mg is given orally twice daily.

Crofelemer is also under investigation in the treatment of other forms of secretory diarrhoea and diarrhoea-predominant irritable bowel syndrome.

References.
1. Mangel AW, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. *Digestion* 2008; **78:** 180–6.
2. Crutchley RD, *et al*. Crofelemer, a novel agent for treatment of secretory diarrhea. *Ann Pharmacother* 2010; **44:** 878–84.
3. Cottreau J, *et al*. Crofelemer for the treatment of secretory diarrhea. *Expert Rev Gastroenterol Hepatol* 2012; **6:** 17–23.
4. Frampton JE. Crofelemer: a review of its use in the management of non-infectious diarrhoea in adult patients with HIV/AIDS on antiretroviral therapy. *Drugs* 2013; **73:** 1121–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Fulyzaq.

Dantron *(BAN, rINN)*

Antrapurol; Chrysazin; Danthron; Dantrón; Dantrone; Dantroni; Dantronum; Dianthon; Dioxyanthrachinonum; Дантрон.

1,8-Dihydroxyanthraquinone.

$C_{14}H_8O_4$=240.2

CAS — 117-10-2.

ATC — A06AB03.

ATC Vet — QA06AB03.
UNII — Z4XE6IBF3V.

NOTE. Compounded preparations of dantron may be represented by the following names:
- Co-danthramer *x*/*y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively
- Co-danthrusate (*BAN*)—dantron 5 parts and docusate sodium 6 parts (w/w).

Pharmacopoeias. In *Br.*

BP 2014: (Dantron). An orange, odourless or almost odourless, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether; dissolves in solutions of alkali hydroxides.

Uses and Administration

Dantron is an anthraquinone stimulant laxative but, unlike senna (p. 1885.1), it is not a glycoside. It is given orally to treat constipation (p. 1804.3) and is effective within 6 to 12 hours. However, because of concern over *rodent* carcinogenicity it has been withdrawn in some countries, and its use restricted in others. In the UK, it may be used only in terminally ill patients.

Dantron is given in doses of 25 to 75 mg when given with poloxamer 188 (p. 2202.1) as co-danthramer, and in doses of 50 to 150 mg when given with docusate sodium (p. 1836.2) as co-danthrusate. Doses are usually given at bedtime. For doses in children, see below.

Administration in children. In the UK, the use of dantron is restricted to the treatment of constipation in terminally ill patients; children under 12 years have been given dantron 12.5 to 25 mg orally as co-danthramer or 50 mg as co-danthrusate. Doses are usually given at bedtime. Children aged 12 years and over may be treated with the adult dose (see Uses and Administration, above).

The *BNFC* recommends similar doses to these, but restricts the use of co-danthramer to children aged 2 years and over, and the use of co-danthrusate to those aged 6 years and over.

Dantron should not be used in infants wearing nappies (diapers) as it may cause discoloration and superficial sloughing of the skin.

Adverse Effects and Precautions

As for Senna, p. 1885.3. Dantron may colour the urine pink or red. Discoloration and superficial sloughing of perianal skin can occur after prolonged contact, therefore dantron should not be used in infants wearing nappies (diapers) and should be used with caution in incontinent patients. The mucosa of the large intestine may be discoloured with prolonged use or high dosage.

In *rodents*, dantron has been associated with the development of intestinal and liver tumours. Consequently, its use has been restricted, see Uses and Administration, above.

References to adverse effects occurring with dantron-containing laxatives include individual cases of leucopenia with liver damage,[1] greyish-blue skin discoloration,[2] and orange vaginal discharge.[3] There has also been a report of intestinal sarcoma in an 18-year-old girl with a history of prolonged use of a dantron-containing laxative.[4] In May 2000 the UK CSM restricted the use of dantron to terminally ill patients on the grounds that pre-clinical evidence had increased and dantron was now established as a potential human carcinogen.[5]

1. Tolman KG, *et al.* Possible hepatotoxicity of Doxidan. *Ann Intern Med* 1976; **84:** 290–2.
2. Darke CS, Cooper RG. Unusual case of skin discoloration. *BMJ* 1978; **1:** 1188–9.
3. Greer IA. Orange periods. *BMJ* 1984; **289:** 323.
4. Patel PM, *et al.* Anthraquinone laxatives and human cancer: an association in one case. *Postgrad Med J* 1989; **65:** 216–17.
5. CSM/MCA. Danthron restricted to constipation in the terminally ill. *Current Problems* 2000; **26:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 08/11/06)

Breast feeding. The American Academy of Pediatrics[1] state that, although usually compatible with breast feeding, use of dantron by breast-feeding mothers has been reported to cause increased bowel activity in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/06)

Pharmacokinetics

Dantron is metabolised by bacteria in the colon. Dantron or its metabolites are absorbed from the gastrointestinal tract, as indicated by discoloration of urine in some patients. Dantron or its metabolites are excreted in the faeces and the urine, and also in other secretions including breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Modane; ***Irl.***: Ailax†; Codalax; Cotron; ***Mex.***: Modaton; ***NZ***: Pinorax; ***UK***: Capsuvac; Codalax; Danlax; Normax.

Pharmacopoeial Preparations
BP 2014: Co-danthrusate Capsules.

Dexlansoprazole *(USAN, rINN)*

Dexlansoprazol; Dexlansoprazolum; *R*-lansoprazole; T-168390; TAK-390; Декслансопразол.
(+)-2-({*R*)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl)-1*H*-benzamidazole.
$C_{16}H_{14}F_3N_3O_2S$=369.4
CAS — 138530-94-6.
UNII — UYE4T5I70X (dexlansoprazole); HS2S9VK3NH (dexlansoprazole sesquihydrate).

Uses and Administration

Dexlansoprazole, the *R*-isomer of the proton pump inhibitor lansoprazole (p. 1851.3), is given for the management of severe or symptomatic gastro-oesophageal reflux disease.

An oral dose of dexlansoprazole 60 mg is given once daily for up to 8 weeks to heal erosive oesophagitis. Once erosions have healed, 30 mg once daily is given for maintenance. For symptomatic non-erosive gastro-oesophageal reflux disease, 30 mg is given once daily for 4 weeks.

For doses in hepatic impairment, see below.

References.
1. Fass R, *et al.* Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2009; **29:** 1261–72.
2. Metz DC, *et al.* Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2009; **29:** 928–37.
3. Anonymous. Dexlansoprazole (Kapidex) for GERD and erosive esophagitis. *Med Lett Drugs Ther* 2009; **51:** 21–2.
4. Abel C, *et al.* Dexlansoprazole in the treatment of esophagitis and gastroesophageal reflux disease. *Ann Pharmacother* 2010; **44:** 871–7.
5. Croxtall JD, Scott LJ. Dexlansoprazole modified release: in erosive oesophagitis and non-erosive reflux disease. *Drugs* 2010; **70:** 1593–1601.

Administration. Dexlansoprazole is given orally as capsules containing enteric-coated granules, which should be swallowed whole. Alternatively, capsules can be opened and the granules sprinkled on apple sauce before swallowing without chewing.

Administration in hepatic impairment. No dosage adjustment of dexlansoprazole is considered necessary for patients with mild hepatic impairment (Child-Pugh class A). For patients with moderate hepatic impairment (Child-Pugh class B), a daily oral dose of 30 mg should not be exceeded. There are limited data on the use of dexlansoprazole in patients with severe hepatic impairment (Child-Pugh class C).

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

Interactions

As for Omeprazole, p. 1870.3.

Pharmacokinetics

After an oral dose of a delayed-release formulation of dexlansoprazole, peak plasma concentrations occur 1 to 2 hours after dosing, followed by a second peak within 4 to 5 hours. Plasma protein binding varies from about 96 to 99%. Dexlansoprazole is extensively metabolised in the liver to inactive metabolites. Oxidative metabolites are formed by cytochrome P450 isoenzymes CYP2C19 and CYP3A4. Dexlansoprazole has a half-life of about 1 to 2 hours. Metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Dexilant; ***Jpn***: Kapidex†; ***USA***: Dexilant.

Dicycloverine Hydrochloride

(BANM, rINNM)

Cloridrato de Diciclоverina; Diciclоverina, hidrocloruro de; Dicikloverin-hidroklorid; Dicikloverino hidrochloridas; Dicyclomine Hydrochloride; Dicyclovérine, Chlorhydrate de; Dicycloverinhydrochlorid; Dicycloverini Hydrochloridum; Dicykloverin-hydrochlorid; Dicykloverinhydroklorid; Disyklоveriinihydrokloridi; Hidrocloruro de diciclоverina; Дицикловерина Гидрохлорид.
2-Diethylaminoethyl bicyclohexyl-1-carboxylate hydrochloride.
$C_{19}H_{35}NO_2$,HCl=346.0
CAS — 77-19-0 (dicycloverine); 67-92-5 (dicycloverine hydrochloride).
ATC — A03AA07.
ATC Vet — QA03AA07.
UNII — CQ903KQA31.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dicycloverine Hydrochloride). A white or almost white, crystalline powder. It shows polymorphism. Soluble in water; freely soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.0 to 5.5.

USP 36: (Dicyclomine Hydrochloride). A fine white, practically odourless, crystalline powder. Soluble 1 in 13 of water, 1 in 5 of alcohol, 1 in 2 of chloroform and of glacial acetic acid, and 1 in 770 of ether. pH of a 1% solution in water is between 5.0 and 5.5.

Uses and Administration

Dicycloverine hydrochloride is a tertiary amine antimuscarinic with effects similar to but weaker than those of atropine (p. 1312.1); it also has a direct antispasmodic action.

Dicycloverine is used in gastrointestinal spasm, particularly that associated with irritable bowel syndrome. An oral dose of 10 to 20 mg of dicycloverine hydrochloride is given 3 times daily; in the USA, up to 40 mg four times daily may be given where adverse effects permit.

Dicycloverine hydrochloride may be given intramuscularly in doses of 10 to 20 mg 4 times daily to patients in whom oral therapy is temporarily impractical, but should not be used for longer than 1 to 2 days.

For doses in children, see below.

Administration in children. Dicycloverine hydrochloride is used in children for symptomatic relief of gastrointestinal smooth muscle spasm. The following oral doses are given according to age:
- 6 months to 2 years: 5 to 10 mg three or four times daily, 15 minutes before meals; maximum daily dose of 40 mg
- 2 to 12 years: 10 mg three times daily
- over 12 years: adult doses may be given, see above

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Dicycloverine hydrochloride should not be given to infants younger than 6 months of age.

Dicycloverine has been reported to suppress lactation. Inadvertent intravenous administration has resulted in thrombosis, thrombophlebitis, and injection site reactions including pain, oedema, skin colour changes, and reflex sympathetic dystrophy syndrome.

Dicycloverine should be used with caution in patients with hepatic or renal impairment; licensed product information states that there is a lack of data in such patients.

Apnoea. Reports[1-3] of severe apnoea in infants aged 5 to 10 weeks associated with the use of dicycloverine.

1. Williams J, Watkin-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. *BMJ* 1984; **288:** 901.
2. Edwards PDL. Dicyclomine in babies. *BMJ* 1984; **288:** 1230.
3. Spoudeas H, Shribman S. Dicyclomine in babies. *BMJ* 1984; **288:** 1230.

Pregnancy. For a review of the risks to the fetus of antiemetic therapy during pregnancy, with particular reference to *Debendox* (*Bendectin*: dicycloverine with doxylamine and pyridoxine), see under Antihistamines on p. 614.2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Dicycloverine is rapidly absorbed after oral dosing with peak plasma concentrations occurring within 1 to 1.5 hours. The bioavailability after intramuscular injection is greater than that after oral dosing. Dicycloverine is excreted mainly in the urine (nearly 80% of a dose), with a small amount in the faeces (about 8%). The mean elimination half-life for the first 9 hours after a single dose is about 1.8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Babypasmil; ***Braz.***: Bentyl; ***Canad.***: Bentylol; Formulex; Lomine†; Protylol; ***Hong Kong***: Cyclomine†; Dicymine; Uni-Cycolac†; ***India***: Centwin; Coligon;

Colinet; Coliza; Cyclominol†; Cyclopam; Decolic; Diospas; Dysmen; Lupispas; Meftal-Spas; NT-Spas; Spasmo-Proxyvon; Spasmonil; ***Israel***: Notensyl; ***Mex.***: Bentyl; Clominal; Dicigon; Diclomin†; Sediclon; ***Philipp.***: Bentyl; Dilomin; Relestal; Spasdon; ***Rus.***: Trigan (Триган); ***S.Afr.***: Merbentyl†; ***Thai.***: Dicomin†; Dicymine; Spasminar; ***UK***: Merbentyl†; ***USA***: Antispas; Bentyl; Byclomine†; Dibent†; Or-Tyl†; ***Venez.***: Mabex.

Multi-ingredient Preparations. ***Arg.***: Colchimax; Dafne; ***Canad.***: Diclophen†; ***Chile***: Profisin; ***Gr.***: Dispalgine; ***Hong Kong***: Berber CO†; Colimix; Cycolsim†; Dicymine Co; Epilon; Uni-Cycolac-SM†; Veragel; ***India***: Actispas Plus; Actispas-R; Aglopam; Amicline Plus; Arsulide-D; Asimol-DC; Avid Plus; Avispas; Betaspasm Forte; Bral; Cataspa; Cebrex Forte; Centwin; Centwin; Cibis; Cloact; Colicspam; Colicspam; Colidex; Coligon Plus; Coligon-O; Colimef; Colimex; Colimex; Colinorm; Colirid; Colispas-P; Colispas; Colispas; Colixin MPS; Combispas; Comspa; Cyclo-P; Cyclocos; Cyclomeff; Cyclopam Plus; Cyclopam; Cyclopam; Cyclosym; Cyclowin; Cyclowin; Cyclozed-N; Cyclozed; Cyclozobid; Cypa; Dam-Spas DPS P; Dam-Spas; Decolic-V; Decolic; Deepas; Depas; Diclogesic Spas; Diclonij Spas; Diclospa; Dicomin; Dicyclome-P; Dolospan; Domspas; DP-Spas; Duospan; Dymef; Dynamet; Dysmen; Dysmeryl; Dyspas; Efespas; Eginor; Endospas; Fri-Spas; Frispas-P; Gastrogyl Plus; Gefspass; Griprid; Haspas; Hyvon-Spas; Jagril-Spas; Kolispas; Litspas; Lowdol; Mafia; Medilop; Mefac Spas; Mefamic-D; Mefar-PD; Mefatin-Spas; Mefcil Spas; Mefdic; Mefdol Spas; Meflaxin; Mefmin Spas; Mefnic Spas; Mefsaid; Mefsym-Plus; Mefsym-Spas; Meftagesic; Meftal-Spas; Meftal-Spas; Mefze Spas; Mespas; Neurospas-CD; Neurospas-MF; Neurospas; Neurospas; Nicispas; Nidic; Nimkul DCM; Nimspa; Nimspas; Nimuspas; Niza-Spas; Normaxin-RT; Normaxin; Normospas; NT-Spas; NTSpass; Orlidox-D; Pamol DCM; Paraclo; Paraspas; Parvon Spas; Spasmo-Flexon; Spasmo-Proxyvon Forte; Spasmo-Proxyvon; Spasmocip Plus; Spasmonil Plus; Spasmonil; Spasmonil; Trigan-D; Ze-Spas; ***Ital.***: Merankol Pastiglie; ***Malaysia***: Colimix; ***Mex.***: Alphalox-D; Exhidrol; Farcolan; ***Port.***: Nausefe; ***Rus.***: Trigan-D (Триган-Д); ***S.Afr.***: Acugel†; Adco-Medigel; Adco-Neutragel D; Alkalite D†; Alumag D; Alumite D†; Aluspastyl†; Asic; Betaclomin; Co-Gel; Gelumen; Kolantyl†; Microgel†; Neuragel-D†; Propan Gel-S; Remotrox†; Spasmogel; ***Singapore***: Acolic; Colimix; Meclosil; Veragel; ***Spain***: Colchimax; Neocolan†; ***Thai.***: Anpuzz; Berclomine; Biodan; Cymine; Difemic; Kremil-S; Mainnox; Simcomine; Spasticone†; Tocid; Veragel; ***UK***: Kolanticon; ***Ukr.***: Diaremix (Диаремикс); Movespasm (Мовеспаем); No-Spasma (Но-Спазма)†; ***Venez.***: Dicigel.

Pharmacopoeial Preparations
BP 2014: Dicycloverine Oral Solution; Dicycloverine Tablets;
USP 36: Dicyclomine Hydrochloride Capsules; Dicyclomine Hydrochloride Injection; Dicyclomine Hydrochloride Syrup; Dicyclomine Hydrochloride Tablets.

Difemerine Hydrochloride *(rINNM)*

Difemerina, hidrocloruro de; Difémérine, Chlorhydrate de; Difemerini Hydrochloridum; Hidrocloruro de difemerina; UP-57; Дифемерина Гидрохлорид.
2-Dimethylamino-1,1-dimethylethyl benzilate hydrochloride.
$C_{20}H_{25}NO_3$,HCl=363.9
CAS — 80387-96-8 (difemerine); 70280-88-5 (difemerine hydrochloride).
ATC — A03AA09.
ATC Vet — QA03AA09.
UNII — 00JM91Q28F.

Profile

Difemerine hydrochloride is an antimuscarinic with effects similar to those of atropine (p. 1312.1) and was used in the symptomatic treatment of visceral spasms.

Difenidol Hydrochloride *(BANM, rINNM)*

Difénidol, Chlorhydrate de; Difenidol, hidrocloruro de; Difenidoli Hydrochloridum; Diphenidol Hydrochloride (USAN); Hidrocloruro de difenidol; SKF-478 (difenidol); SKF-478-A; SKF-478-J (difenidol embonate); Дифенидола Гидрохлорид.
1,1-Diphenyl-4-piperidinobutan-1-ol hydrochloride.
$C_{21}H_{27}NO$,HCl=345.9
CAS — 972-02-1 (difenidol); 3254-89-5 (difenidol hydrochloride); 26363-46-2 (difenidol embonate).
UNII — DG355XWQ4T.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Difenidol hydrochloride is an antiemetic that probably acts through the chemoreceptor trigger zone. It is claimed to control vertigo by means of a specific effect on the vestibular apparatus. Difenidol also has a weak peripheral antimuscarinic action.

It has been used in the treatment of some forms of nausea and vomiting (p. 1811.3) such as those associated with surgery, radiotherapy, and cancer chemotherapy. It has also been used for the symptomatic treatment of vertigo (p. 612.3), nausea and vomiting due to Ménière's disease (p. 611.2), and other labyrinthine disturbances.

It has been given in oral doses equivalent to 25 to 50 mg of difenidol every 4 hours as required. Difenidol hydrochloride has also been given parenterally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Vontrol; ***Jpn***: Cephadol; ***Malaysia***: Cephadol†; ***Mex.***: Biomitin; Diphafen; Docita; Hemetiken; Lansenol; Nautrol; Normavom; Serratol; Sons; Vontrol; Voxamine; ***Philipp.***: Cephadol†; ***Singapore***: Cephadol; ***Thai.***: Cephadol†.

Difenoxin *(BAN, USAN, rINN)*

Difenoxilic Acid; Difenoxina; Difénoxine; Difenoxinum; Diphenoxylic Acid; McN-JR-15403-11; Дифеноксин.
1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid.
$C_{28}H_{28}N_2O_2$=424.5
CAS — 28782-42-5.
ATC — A07DA04.
ATC Vet — QA07DA04.
UNII — 3ZZ5BJ9F2Q.

Difenoxin Hydrochloride *(BANM, rINNM)*

Difenoxina, hidrocloruro de; Difénoxine, Chlorhydrate de; Difenoxini Hydrochloridum; Difenoxylic Acid Hydrochloride; Diphenoxylic Acid Hydrochloride; Hidrocloruro de difenoxina; R-15403; Дифеноксина Гидрохлорид.
$C_{28}H_{28}N_2O_2$,HCl=461.0
CAS — 35607-36-4.
ATC — A07DA04.
ATC Vet — QA07DA04.
UNII — VQZ63K01IW.

Profile

Difenoxin is the principal active metabolite of diphenoxylate (below) and has similar actions and uses. It is given orally as the hydrochloride, but doses are in terms of the base; difenoxin hydrochloride 1.1 mg is equivalent to about 1 mg of difenoxin.

In the treatment of diarrhoea (p. 1805.2), the usual dose in adults is the equivalent of difenoxin 2 mg initially, followed by 1 mg after each loose stool or every 3 to 4 hours as required, up to a maximum of 8 mg daily.

Preparations of difenoxin usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Motofen.

Dihexyverine Hydrochloride *(USAN, rINNM)*

Dihexiverina, hidrocloruro de; Dihexiverine Hydrochloride; Dihexyvérine, Chlorhydrate de; Dihexyverini Hydrochloridum; Hidrocloruro de dihexiverina; JL-1078; Дигексиверина Гидрохлорид.
2-Piperidinoethyl bicyclohexyl-1-carboxylate hydrochloride.
$C_{20}H_{35}NO_2$,HCl=358.0
CAS — 561-77-3 (dihexyverine); 5588-25-0 (dihexyverine hydrochloride).
ATC — A03AA08.
ATC Vet — QA03AA08.
UNII — 336704VYVB.

Profile

Dihexyverine hydrochloride is an antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been given in the symptomatic treatment of gastrointestinal spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Spasmodex.

Dihydroxyaluminum Sodium Carbonate

Aluminium Sodium Carbonate Hydroxide; Carbonato sódico de dihidroxialuminio; Dihidroksialüminyum Sodyum Karbonat; Dihydroksialuminiumnatriumkarbonaatti; Dihydroxialuminiinatrii Carbonas; Dihydroxialuminiumnatriumkarbonat; Dihydroxyaluminium Sodium Carbonate; Дигидрооксиалюминия Натрия Карбонат.
Sodium (carbonato)dihydroxyaluminate(1-).
CH_2AlNaO_5=144.0
CAS — 41342-54-5 (carbaldrate); 12011-77-7 (dihydroxyaluminium sodium carbonate); 16482-55-6 (dihydroxyaluminium sodium carbonate).
ATC — A02AB04.
ATC Vet — QA02AB04.
UNII — 84H8Z9550J.

NOTE. The name Carbaldrate (*rINN*) has been applied to (CH_2AlNaO_5,nH_2O), a form of sodium (carbonato)dihydroxyaluminate(1-) hydrate.

Pharmacopoeias. In *US*.

USP 36: (Dihydroxyaluminum Sodium Carbonate). A fine white odourless powder. It loses not more than 14.5% of its weight on drying. Practically insoluble in water and in organic solvents; soluble in dilute mineral acids with the evolution of carbon dioxide. A 4% suspension in water has a pH of 9.9 to 10.2. Store in airtight containers.

Profile

Dihydroxyaluminum sodium carbonate is an antacid with general properties similar to aluminium hydroxide (p. 1817.2) that is given in oral doses of about 300 to 600 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Antacidum†; ***Denm.***: Noacid; ***Ger.***: Kompensan; ***Pol.***: Alugastrin; Gastrinal†; ***Port.***: Kompensan; ***Switz.***: Kompensan†; ***Turk.***: Dank; Kompensan; Seskasid.

Multi-ingredient Preparations. ***Port.***: Kompensan-S.

Pharmacopoeial Preparations
USP 36: Dihydroxyaluminum Sodium Carbonate Tablets.

Diisopromine Hydrochloride *(rINNM)*

Diisopromina, hidrocloruro de; Diisopromine, Chlorhydrate de; Di-isopromine Hydrochloride; Diisopromini Hydrochloridum; Hidrocloruro de diisopromina; Диизопромина Гидрохлорид.
NN-Di-isopropyl-3,3-diphenylpropylamine hydrochloride.
$C_{21}H_{29}N$,HCl=331.9
CAS — 5966-41-6 (diisopromine); 24358-65-4 (diisopromine hydrochloride).
ATC — A03AX02.
ATC Vet — QA03AX02.
UNII — 9E8EN393AL.

Profile

Diisopromine hydrochloride is an antispasmodic used with sorbitol in various gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Agofell†.

Diphenoxylate Hydrochloride

(BANM, rINNM)

Difenoksilaattihydrokloridi; Difenoksilat Hidroklorür; Difenoksilato hidroclorídas; Difenoxilát-hidroklorid; Difenoxilathydroklorid; Difenoxilato, hidrocloruro de; Difenoxylát-hydrochlorid; Diphénoxylate, Chlorhydrate de; Diphenoxylathydrochlorid; Diphenoxylati Hydrochloridum; Hidrocloruro de difenoxilato; R-1132; Дифеноксилата Гидрохлорид.
Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride.
$C_{30}H_{32}N_2O_2$,HCl=489.1
CAS — 915-30-0 (diphenoxylate); 3810-80-8 (diphenoxylate hydrochloride).
ATC — A07DA01.
ATC Vet — QA07DA01.
UNII — W24OD7YW48.

NOTE. Compounded preparations of diphenoxylate hydrochloride may be represented by the following names:
- Co-phenotrope (*BAN*)—diphenoxylate hydrochloride 100 parts and atropine sulfate 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Diphenoxylate Hydrochloride). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Diphenoxylate Hydrochloride). A white odourless crystalline powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol and in acetone; freely soluble in chloroform; practically insoluble in ether and in petroleum spirit; soluble in methyl alcohol. A saturated solution in water has a pH of about 3.3.

Uses and Administration

Diphenoxylate hydrochloride is a synthetic derivative of pethidine (p. 121.3) with little or no analgesic activity; it reduces intestinal motility and is used in the symptomatic treatment of acute and chronic diarrhoea (p. 1805.2). It may also be used to reduce the frequency and fluidity of the stools in patients with colostomies or ileostomies.

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse; UK preparations are all in the form of co-phenotrope (see NOTE, p. 1835.3).

In **acute diarrhoea** the usual initial dose is 10 mg orally, followed by 5 mg every six hours, later reduced as the diarrhoea is controlled. For doses in children, see below.

Similar initial doses are used for **chronic diarrhoea**, and subsequently reduced as necessary. If clinical improvement is not seen after 10 days of treatment with the maximum daily dose of 20 mg (in adults) further use is unlikely to result in any benefit.

Administration in children. Diphenoxylate hydrochloride can be used in children as an adjunct in the symptomatic treatment of acute diarrhoea, and to reduce the frequency and fluidity of the stools in patients with colostomies or ileostomies. In the UK, it is licensed for children from 4 years of age; recommended oral doses of diphenoxylate hydrochloride (given as co-phenotrope) are:

- 4 to 9 years: 2.5 mg three times daily
- 9 to 12 years: 2.5 mg four times daily
- 12 to 16 years: 5 mg three times daily

While emphasising that antimotility drugs are not recommended for acute diarrhoea in children under 12 years of age, the *BNFC* allows for a dose of 1.25 mg three times daily for children aged 2 to 4 years.

In the USA, diphenoxylate is licensed for children from the age of 2 years and an initial dose of 300 to 400 micrograms/kg (up to an effective maximum of 10 mg) daily in 4 divided doses is suggested for children aged 2 to 12 years.

For the view that antidiarrhoeal drugs should not be used at all in children with acute diarrhoea, see p. 1805.2.

Diarrhoea. Co-phenotrope (see NOTE, p. 1835.3) may be considered as an alternative to loperamide in the management of faecal incontinence in adults, see Diarrhoea, under Loperamide, p. 1854.3.

Substance dependence. Diphenoxylate may be useful[1] in the symptomatic management of diarrhoea associated with opioid withdrawal syndromes (p. 109.2).

1. DOH. *Drug misuse and dependence: guidelines on clinical management.* London: HMSO, 1999. Also available at: http://www.dh.gov.uk/assetRoot/04/07/81/98/04078198.pdf (accessed 18/01/06)

Dependence and Withdrawal

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse. Short-term use of diphenoxylate with atropine in the recommended dosage carries a negligible risk of dependence, although prolonged use or use of high doses may produce dependence of the opioid type (see p. 109.1).

Adverse Effects and Treatment

Diphenoxylate is related to the opioid analgesics and its adverse effects and their treatment are similar (p. 110.1), particularly in overdosage. Reported adverse effects include: gastrointestinal effects such as anorexia, nausea and vomiting, abdominal distension or discomfort, paralytic ileus, toxic megacolon, and pancreatitis; nervous system effects such as headache, drowsiness, dizziness, restlessness, euphoria, depression, numbness of the extremities; and hypersensitivity reactions including angioedema, urticaria, pruritus, and swelling of the gums. Signs of overdosage may be delayed and patients should be observed for at least 48 hours. Young children are particularly susceptible to the effects of overdosage.

The presence of subclinical doses of atropine sulfate in preparations containing diphenoxylate may give rise to the adverse effects of atropine in susceptible individuals or in overdosage—see Atropine Sulfate, p. 1312.1.

Precautions

Diphenoxylate hydrochloride should be avoided in patients with jaundice, intestinal obstruction, antibiotic-associated colitis, or diarrhoea associated with enterotoxin-producing bacteria, and should be used with caution in patients with hepatic impairment. It should also be used with caution in young children, in whom response is more variable, and is not generally recommended for use in infants. Patients with inflammatory bowel disease receiving diphenoxylate should be carefully observed for signs of toxic megacolon and diphenoxylate stopped promptly should abdominal distension occur.

Interactions

Because of the structural relationship of diphenoxylate to pethidine (p. 121.3) there is a theoretical risk of hypertensive crisis if diphenoxylate is used with MAOIs. Diphenoxylate may potentiate the effects of other CNS depressants such as alcohol, barbiturates, and some anxiolytics.

Pharmacokinetics

Diphenoxylate hydrochloride is well absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver, mainly to diphenoxylic acid (difenoxin, p. 1835.2), which has antidiarrhoeal activity; other metabolites include hydroxydiphenoxylic acid. It is excreted mainly as metabolites and their conjugates in the faeces; lesser amounts are excreted in urine. It may be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Lofenoxal; Lomotil; ***Braz.***: Lomotil; ***Canad.***: Lomotil; ***Cz.***: Reasec; ***Gr.***: Reasec; ***Hong Kong***: Dhamotil; Diamotil†; Diarest†; Diatrol†; Dimotil; Lomotil; Syncomil†; ***Hung.***: Reasec; ***India***: Lomotil; ***Irl.***: Lomotil; ***Malaysia***: Beamotil; Dhamotil; Diphenoxylate A; ***NZ***: Diastop; ***Pol.***: Reasec; ***S.Afr.***: Lomotil; ***Singapore***: Beamotil; Dhamotil; SP-Arnox; ***Thai.***: Ditropine; Lomotil; Spasil; ***Turk.***: Lomotil; ***UAE***: Intard; ***UK***: Dymotil; Lomotil; ***USA***: Logen; Lomotil; Lonox.

Multi-ingredient Preparations. ***Braz.***: Colestase; ***India***: Lomofen; ***Singapore***: Sun-Dianox.

Pharmacopoeial Preparations

USP 36: Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Docusates

Docusatos.

UNII — M7P27195AG.

Docusate Calcium *(USAN)*

Dioctyl Calcium Sulfosuccinate; Dioctyl Calcium Sulphosuccinate; Docusato cálcico; Докузат Кальция.

Calcium 1,4-bis(2-ethylhexyl) sulphosuccinate.

$C_{40}H_{74}CaO_{14}S_2$=883.2

CAS — 128-49-4.

UNII — 6K7YS503HC.

Pharmacopoeias. In *US.*

USP 36: (Docusate Calcium). A white amorphous solid with the characteristic odour of octil alcohol. Soluble 1 in 3300 of water; very soluble in alcohol, in macrogol 400, and in maize oil.

Docusate Potassium *(USAN)*

Dioctyl Potassium Sulfosuccinate; Dioctyl Potassium Sulphosuccinate; Docusato potásico; Докузат Калия.

Potassium 1,4-bis(2-ethylhexyl) sulphosuccinate.

$C_{20}H_{37}KO_7S$=460.7

CAS — 7491-09-0.

UNII — CIK9F54ZHR.

Pharmacopoeias. In *US.*

USP 36: (Docusate Potassium). A white amorphous solid with a characteristic odour suggestive of octil alcohol. Sparingly soluble in water; soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Docusate Sodium *(BAN, USAN, rINN)*

Dioctyl Sodium Sulfosuccinate; Dioctyl Sodium Sulphosuccinate; Docusat-Natrium; Docusate Sodique; Docusato de sodio; Docusato sódico; Docusatum Natricum; Dokusaattinatrium; Dokusát sodná sůl; Dokusatnatrium; Dokuzát-nátrium; Dokuzato natrio druska; DSS; Natrii docusas; Sodium Dioctyl Sulphosuccinate; Sodu dokuzynian; Докузат Натрий.

Sodium 1,4-bis(2-ethylhexyl) sulphosuccinate.

$C_{20}H_{37}NaO_7S$=444.6

CAS — 577-11-7.

ATC — A06AA02.

ATC Vet — QA06AA02.

UNII — F05Q2T2JA0.

NOTE. Compounded preparations of docusate sodium may be represented by the following names:

- Co-danthrusate (*BAN*)—docusate sodium 6 parts and dantron 5 parts.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Docusate Sodium). White or almost white, hygroscopic, waxy masses or flakes. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Docusate Sodium). A white wax-like plastic solid with a characteristic odour suggestive of octil alcohol. Slowly soluble 1 in 70 of water; freely soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Uses and Administration

Docusates are given as the calcium or sodium salt and are used as laxatives in the management of constipation (p. 1804.3) or to reduce straining in patients with haemorrhoids (p. 1808.1) or anal fissure. They are also used as adjuncts for bowel evacuation before abdominal radiological procedures. Docusate potassium has also been used.

Docusates are anionic surfactants which have been considered to act primarily by increasing the penetration of fluid into the faeces, but may also have other effects on intestinal fluid secretion, and probably act both as stimulants and as faecal softening agents.

The usual daily oral dose of docusate calcium is 240 mg. Docusate sodium is given in usual oral doses of 50 to 300 mg daily in divided doses, although doses of up to 500 mg daily may be used. (For doses in children, see below.) The effect is usually seen within 12 to 72 hours. When used as an adjunct to abdominal radiological procedures, an oral dose of 400 mg is given with the barium meal. It is also given rectally as an enema in doses of 120 mg; the effect is usually seen in 5 to 20 minutes. Docusate sodium is also used with anthraquinone stimulant laxatives such as casanthranol (p. 1826.1), dantron (p. 1833.3), and senna (p. 1885.1).

Docusate sodium is used for softening wax in the ear as ear drops containing 0.5 or 5%.

Docusate sodium and other docusate salts are widely used as anionic surfactants in pharmaceutical formulations.

Administration in children. Oral docusate sodium is licensed in the UK for the treatment of **chronic constipation** in children aged 6 months and over. More specific dose details are also provided in the *BNFC* as follows:

- 6 months to 2 years: 12.5 mg three times daily
- 2 to 12 years: 12.5 to 25 mg three times daily

Children aged 12 years and over may be given the adult doses for constipation, either orally or rectally (see Uses and Administration, above). Adult formulations are not licensed for use in children under 12 years.

In the USA, children aged 2 to 12 years may be given docusate sodium in doses of 50 to 150 mg daily, either as a single daily dose or in divided doses. Docusate *calcium* is generally only used in the USA for children aged 12 years and over.

Docusate sodium is also used as an **adjunct in abdominal radiological procedures**. UK licensed product information suggests that children may be given an oral dose of 75 mg (30 mL of docusate sodium paediatric solution 12.5 mg per 5 mL) with the barium meal. The *BNFC* recommends that those aged 12 years and over are given the usual adult dose (see above).

Ear wax removal. Cerumen or ear wax is a normal secretion of the ceruminous glands present in the lining of the external auditory canal. Excessive accumulation or impaction of ear wax may decrease hearing acuity, and may also produce dizziness, vertigo, reflex coughing, tinnitus, and otalgia.

Syringing of the external auditory canal with warm water may be used to remove wax from the ear. However, complications include pain, perforation of the ear drum, deafness, dizziness, vertigo, tinnitus, and infection.[1-6] Contra-indications to ear syringing include past perforation, ear infection, previous ear surgery; syringing may be difficult in children.[1,6]

A ceruminolytic agent may be given as ear drops to soften, loosen, or dissolve cerumen instead. They may also be used immediately before syringing, or for several days beforehand.[1-3,5,6] Traditionally, fixed oils such as arachis oil, olive oil, or almond oil have been used.[1] Some still advocate the use of olive oil to reduce the recurrence of impacted cerumen,[3] while others consider it to be ineffective.[5] Other ceruminolytics that have been reported as effective include docusates,[4,7,8] peroxides such as hydrogen peroxide or urea hydrogen peroxide,[4,9] and trolamine polypeptide oleate-condensate,[4,8] although some studies have found these to be

no more effective in removing wax than a saline control.[10,11] Other agents that have been used include acetic acid,[4] choline salicylate,[12] methyltrypsin solution,[5] and an oily solution of paradichlorobenzene and chlorobutanol.[4,12] Glycerol and sodium bicarbonate solution have also been used. However, a comparative study *in vitro* of the efficacy of various wax dispersing agents found the most effective to be water, which had originally been included as a control,[13] and a systematic review[14] concluded that saline or water ear drops seemed to be as good as proprietary agents for the removal of ear wax, although there was a lack of good quality studies on which to base recommendations.

Ear candling is a traditional folk remedy that has been used to remove cerumen, but studies indicate it is ineffective, and may deposit wax in the ear canal or cause burn injuries.[3,4]

1. Sharp JF, *et al.* Ear wax removal: a survey of current practice. *BMJ* 1990; **301:** 1251–3.
2. Grossan M. Cerumen removal—current challenges. *Ear Nose Throat J* 1998; **77:** 541–6, 548.
3. Grossan M. Safe, effective techniques for cerumen removal. *Geriatrics* 2000; **55:** 80, 83–6.
4. Dimmitt P. Cerumen removal products. *J Pediatr Health Care* 2005; **19:** 332–6.
5. Midani A, *et al.* Safety and efficacy of Sofenz ceruminolytic solution. *Ear Nose Throat J* 2006; **85:** 87–8, 90–2.
6. Aung T, Mulley GP. Removal of ear wax. *BMJ* 2002; **325:** 27.
7. Chen DA, Caparosa RJ. A nonprescription cerumenolytic. *Am J Otol* 1991; **12:** 475–6.
8. Singer AJ, *et al.* Ceruminolytic effects of docusate sodium: a randomized, controlled trial. *Ann Emerg Med* 2000; **36:** 228–32.
9. Fahmey S, Whitefield M. Multicentre clinical trial of Exterol as a cerumenolytic. *Br J Clin Pract* 1982; **36:** 197–204.
10. Whatley VN, *et al.* Randomized clinical trial of docusate, triethanolamine polypeptide, and irrigation in cerumen removal in children. *Arch Pediatr Adolesc Med* 2003; **157:** 1177–80.
11. Roland PS, *et al.* Randomized, placebo-controlled evaluation of Cerumenex and Murine earwax removal products. *Arch Otolaryngol Head Neck Surg* 2004; **130:** 1175–7.
12. Dummer DS, *et al.* A single-blind, randomized study to compare the efficacy of two ear drop preparations ('Audax' and 'Cerumol') in the softening of ear wax. *Curr Med Res Opin* 1992; **13:** 26–30.
13. Andaz C, Whittet HB. An in vitro study to determine efficacy of different wax-dispersing agents. *ORL J Otorhinolaryngol Relat Spec* 1993; **55:** 97–9.
14. Burton MJ, Doree CJ. Ear drops for the removal of ear wax. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 06/07/09).

Adverse Effects and Precautions

Adverse effects occur rarely with docusates; diarrhoea, nausea, abdominal cramps, and skin rash have been reported. Anorectal pain or bleeding have occasionally occurred after rectal doses.

Like all laxatives, docusates should not be used when intestinal obstruction or undiagnosed abdominal symptoms are present; prolonged use should be avoided. Docusate sodium should not be given rectally to patients with haemorrhoids or anal fissures.

Docusate sodium should not be used to soften ear wax when the ear is inflamed or the ear drum perforated.

Hypersensitivity. Docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Allergic contact dermatitis has been reported from one such preparation; patch testing confirmed the reaction to docusate sodium.[1]

1. Lee A-Y, Lee K-H. Allergic contact dermatitis from dioctyl sodium sulfosuccinate in a topical corticosteroid. *Contact Dermatitis* 1998; **38:** 355–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies docusate sodium as not porphyrinogenic when used as an enema; it may be used as a drug of first choice and no precautions are needed.[1] NAPOS has not classified other formulations.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Hypomagnesaemia in a neonate, manifested by jitteriness, was considered to be secondary to maternal hypomagnesaemia caused by maternal use of docusate sodium during pregnancy.[1]

1. Schindler AM. Isolated neonatal hypomagnesaemia associated with maternal overuse of stool softener. *Lancet* 1984; **ii:** 822.

Interactions

Docusates may enhance the gastrointestinal uptake of other drugs, such as liquid paraffin (and the two should not be given together). Dosage of anthraquinone laxatives may need to be reduced if used with docusates. It has also been suggested that giving docusates with aspirin increases the incidence of adverse effects on the gastrointestinal mucosa.

Pharmacokinetics

Docusate salts are absorbed from the gastrointestinal tract and excreted in bile. Docusate sodium is also distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cerumex; Phillips; ***Austral.***: Coloxyl; Rectalad†; Waxsol; ***Belg.***: Norgalax; ***Canad.***: Calax; Colace; Correctol Stool Softener; Selax; Silace; Soflax C; Soflax; Stool Softener; ***China***: Yi Ke Long (泄可隆); ***Fr.***: Doculyse; Jamylene; Norgalax; ***Ger.***: Otitex; Otowaxol†; ***Hong Kong***: Pedia-Lax; Waxsol†; ***India***: Cellubril; Doslax; Laxicon; Otosoft; ***Indon.***: Forumen; Waxsol†; ***Irl.***: Waxsol; ***Malaysia***: Soluwax; ***Neth.***: Norgalax; ***NZ***: Coloxyl; Waxsol; ***Philipp.***: Irwax; Otosol; Otowax; ***Pol.***: Doculax; Laxol; Laxopol†; ***Port.***: Norgalax; ***S. Afr.***: Waxsol; ***Singapore***: Solfen; Soluwax; Waxsol; ***Switz.***: Norgalax; ***Thai.***: Cusate; Dewax; Waxsol; ***UK***: Clear Ear; Dioctyl; Docusol; DulcoEase; Molcer; Norgalax; Waxsol; ***Ukr.***: Norgalax (Норгалакс); ***USA***: Colace; D-S-S; DC Softgels; Diocsate; DocQlace; Docusoft-S; Docusoft; Docusol; DOK; DOS Softgel; Dulcolax Stool Softener; Enemeez; Ex-Lax Stool Softener; Pedia-Lax; Silace; Sof-lax; Sulfolax; Surfak.

Multi-ingredient Preparations. ***Arg.***: Candilax†; Nigalax; Nigalax; ***Austral.***: Chemists Own Natural Laxative with Softener; Coloxyl with Senna; Coloxyl; Combilax†; Sennesoft; Soflax; ***Austria***: Yal; ***Belg.***: Laxavit; Softene; ***Braz.***: Belpidex; ***Canad.***: Gentlax S†; Senna-S; Senokot-S; ***Cz.***: Yal; ***Denm.***: Glyoktyl; Klyx; ***Fin.***: Klyx; ***Ger.***: Norgalax Miniklistier†; Norgalax Rektalgel; Yal; ***Gr.***: Florisan; Heludril; ***India***: Endos; Fejet-OD; ***Israel***: Migraleve; ***Ital.***: Macrolax; Sorbiclis; ***Mex.***: Clyss-Go; ***Neth.***: Klyx; ***Norw.***: Klyx; ***NZ***: Coloxyl with Senna; Coloxyl†; Laxsol; ***Port.***: Clyss-Go; ***Singapore***: Togilin; ***Spain***: Docuxen†; Laxvital†; Migraleve; ***Swed.***: Klyx; ***Switz.***: Klyx Magnum†; Yal; ***Thai.***: Bisolax; Chinta-lax; Hemorhin†; T Man Lax; ***Turk.***: Yal; ***UK***: Capsuvac; Normax; ***USA***: Docusoft Plus; Dok Plus; Dulcolax Bowel Prep Kit; Enemeez Plus; Ex-Lax Gentle Strength†; Laxacin; Laxative & Stool Softener; Nu-Natal Advanced; Peri-Colace; PreNexa; Senna Plus; Senna-S; Senokot-S; Therevac Plus; Therevac SB; X-Prep Bowel Evacuant Kit-1†; ***Venez.***: Senokot con Docusato.

Used as an adjunct in:. ***India***: Anofer; Blush; Hepasules†; Softeron-Z; Softeron; ***Indon.***: Fercee; Viliron; ***Philipp.***: TriHEMIC; ***USA***: Citracal Prenatal + DHA; Citracal Prenatal; CitraNatal Harmony; Embrex; Extra-Virt Plus DHA; FeRiva; Ferralet 90; Ferro-Dok; Hem Fe; Infanate Balance; Macnatal CN DHA; Natalvirt CA; Natalvirt DHA; Nephron FA; Nexa Plus; Nexa Select; Obstetrix; Optinate Omega-3; PNV OB+DHA; Prena-Care; Prenaissance DHA; Prenaissance Promise; Prenaissance; Prenatal; PreQue 10; TriHEMIC; Triveen-PRx RNF; Vinate GT; Virt-Select; VP-CH-PNV.

Pharmacopoeial Preparations

BP 2014: Co-danthrusate Capsules; Compound Docusate Enema; Docusate Capsules; Docusate Oral Solution; Paediatric Docusate Oral Solution;

USP 36: Docusate Calcium Capsules; Docusate Potassium Capsules; Docusate Sodium Capsules; Docusate Sodium Solution; Docusate Sodium Syrup; Docusate Sodium Tablets; Ferrous Fumarate and Docusate Sodium Extended-release Tablets.

Dolasetron Mesilate *(BANM, rINNM)*

Dolasétron, Mésilate de; Dolasetrón, mesilato de; Dolasetron Mesylate (USAN); Dolasetroni Mesilas; MDL-73147EF (dolasetron or dolasetron mesilate); Mesilato de dolasetrón; Доласетрона Мезилат.

(6*R*,8*r*,9a*S*)-3-Oxoperhydro-2*H*-2,6-methanoquinolizin-8-yl indole-3-carboxylate methanesulphonate.

$C_{19}H_{20}N_2O_3,CH_4O_3S$=420.5

CAS — 115956-12-2 (dolasetron); 115956-13-3 (dolasetron mesilate).

ATC — A04AA04.

ATC Vet — QA04AA04.

UNII — U3C8E5BWKR.

Pharmacopoeias. In *US.*

USP 36: (Dolasetron Mesylate). A white to off-white powder. Freely soluble in water and in propylene glycol; slightly soluble in alcohol and in sodium chloride 0.9%. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dolasetron mesilate 10 mg/mL prepared from commercially available tablets found them to be stable for at least 90 days when stored at 3 to 5 degrees and at 23 to 25 degrees.

1. Johnson CE, *et al.* Stability of dolasetron in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; **60:** 2242–4.

Uses and Administration

Dolasetron is a 5-HT_3 antagonist with antiemetic actions similar to those of ondansetron (see p. 1872.2). It is used as the mesilate in the prevention of nausea and vomiting (p. 1811.3) associated with chemotherapy, and in the prevention and treatment of postoperative nausea and vomiting, although licensed indications and doses may vary from country to country. Dolasetron mesilate can be given orally or intravenously, either by bolus injection at a rate of up to 100 mg over 30 seconds or diluted to 50 mL with a suitable infusion solution such as sodium chloride 0.9% or glucose 5% and infused over up to 15 minutes.

For *prevention* of acute **nausea and vomiting** associated with **chemotherapy** dolasetron mesilate may be given orally in a dose of 100 mg or 200 mg within 1 hour before treatment. Alternatively, it may be given in an intravenous dose of 1.8 mg/kg, or 100 mg, about 30 minutes before chemotherapy. To protect against delayed emesis after the end of a chemotherapy cycle, some countries allow for further oral doses of 200 mg once daily. Dolasetron may be given for 4 to 7 consecutive days per chemotherapy cycle.

For the *prevention* of **postoperative** nausea and vomiting dolasetron mesilate may be given orally in a dose of 50 mg at the induction of anaesthesia, or 100 mg within 2 hours before surgery. Alternatively, a single intravenous dose of 12.5 mg may be given about 15 minutes before the end of anaesthesia, or at the end of anaesthesia. The same intravenous dose may be given for the *treatment* of postoperative nausea and vomiting.

For doses in children, see below.

Reviews.

1. Balfour JA, Goa KL. Dolasetron: a review of its pharmacology and therapeutic potential in the management of nausea and vomiting induced by chemotherapy, radiotherapy or surgery. *Drugs* 1997; **54:** 273–98.
2. Anonymous. Dolasetron for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drug Ther* 1998; **40:** 53–4.

Administration in children. The use of dolasetron mesilate in children is licensed in some countries, including the USA. However, others have not licensed such use and in Australia and Canada it is contra-indicated in children and adolescents under 18 years of age because they may be at increased risk of acute changes in the QT interval, and there have been reports of cardiac conduction disorders, cardiac arrest, and myocardial infarction in children treated with dolasetron.

In the USA, children from 2 years of age may be given dolasetron mesilate 1.8 mg/kg orally (within 1 hour before chemotherapy) up to a maximum dose of 100 mg, to prevent acute *chemotherapy-induced* nausea and vomiting. For prevention of *postoperative* nausea and vomiting, an oral dose of 1.2 mg/kg, up to a maximum of 100 mg, may be given within 2 hours before surgery; or an intravenous dose of 350 micrograms/kg, up to a maximum of 12.5 mg, may be given 15 minutes before the end of anaesthesia. The same intravenous dose may be given to treat established postoperative nausea and vomiting.

Pruritus. Dolasetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p. 1873.1).

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2. Diarrhoea, anorexia, and abdominal pain may also occur.

Various ECG changes have been noted with dolasetron. Dolasetron should be used with caution in patients who have, or may develop, prolongation of the QT interval or other alterations in cardiac conduction intervals, and in those with electrolyte imbalances. In some countries use is considered contra-indicated in children because they are thought to be at increased risk (see Administration in Children, above).

Other adverse effects include dyspepsia, flatulence, taste disturbances, fever, chills or shivering, sleep disorders, fatigue, and drowsiness. There have been rare reports of intestinal obstruction, pancreatitis, jaundice, seizures, bronchospasm, cardiac arrhythmias, and oedema. Local reactions may occur on intravenous use. No dosage reduction is considered necessary in renal or hepatic impairment, despite possible reductions in clearance.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Phlebitis. Venous irritation has been reported after intravenous use of dolasetron; diluting subsequent doses with sodium chloride 0.9% and infusing it more slowly markedly reduced the frequency of phlebitis.[1]

1. Oshiro MM. Dolasetron-associated venous irritation. *Am J Health-Syst Pharm* 2000; **57:** 1533–4.

Interactions

Plasma concentrations of hydrodolasetron, the active metabolite of dolasetron, are increased by cimetidine and atenolol and decreased by rifampicin. Dolasetron should be used with caution in patients taking drugs that prolong the QT interval, including those likely to cause electrolyte disturbances (see also p. 1874.2).

Pharmacokinetics

Dolasetron given orally or intravenously is rapidly converted to the active metabolite hydrodolasetron by carbonyl reductase, a ubiquitous enzyme. Peak plasma concentrations of hydrodolasetron occur 1 hour after oral, and 0.6 hours after intravenous, doses of dolasetron. The apparent oral bioavailability of dolasetron determined as hydrodolasetron is about 75%. It has a mean elimination half-life of about 7 to 8 hours.

Hydrodolasetron is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A and about 50 to 60% is eliminated unchanged in the urine. Two thirds of a dose of dolasetron is recovered in the urine and one third in the faeces.

Clearance of hydrodolasetron is increased in children, but is not altered in the elderly. Clearance is reduced in severe hepatic impairment (Child-Pugh category B or C) and in severe renal impairment (creatinine clearance less than 10 mL/min) after oral use. After intravenous use, clearance is reduced in severe renal impairment but apparently unchanged in severe hepatic impairment.

References.
1. Lerman J, *et al*. Pharmacokinetics of the active metabolite (MDL 74,156) of dolasetron mesylate after oral or intravenous administration to anesthetized children. *Clin Pharmacol Ther* 1996; **60:** 485–92.
2. Dempsey E, *et al*. Pharmacokinetics of single intravenous and oral doses of dolasetron mesylate in healthy elderly volunteers. *J Clin Pharmacol* 1996; **36:** 903–10.
3. Stubbs K, *et al*. Pharmacokinetics of dolasetron after oral and intravenous administration of dolasetron mesylate in healthy volunteers and patients with hepatic dysfunction. *J Clin Pharmacol* 1997; **37:** 926–36.
4. Dimmitt DC, *et al*. Pharmacokinetics of oral and intravenous dolasetron mesylate in patients with renal impairment. *J Clin Pharmacol* 1998; **38:** 798–806.
5. Dimmitt DC, *et al*. Effect of infusion rate on the pharmacokinetics and tolerance of intravenous dolasetron mesylate. *Ann Pharmacother* 1998; **32:** 39–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Anzemet; ***Braz.***: Anzemet; ***Canad.***: Anzemet; ***China***: Li Bi Fu (立必复); ***Fr.***: Anzemet†; ***Ger.***: Anemet†; ***Gr.***: Anzemet; ***Ital.***: Anzemet; ***Mex.***: Anzemet; ***S.Afr.***: Zamanon; ***Switz.***: Anzemet†; ***UK***: Anzemet†; ***USA***: Anzemet; ***Venez.***: Anzemet.

Pharmacopoeial Preparations
USP 36: Dolasetron Mesylate Injection; Dolasetron Mesylate Oral Solution; Dolasetron Mesylate Oral Suspension; Dolasetron Mesylate Tablets.

Domperidone *(BAN, USAN, rINN)*

Domperidon; Domperidona; Domperidonas; Dompéridone; Domperidoni; Domperidonum; R-33812; Домперидон.

5-Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl}benzimidazolin-2-one.

$C_{22}H_{24}ClN_5O_2$=425.9

CAS — 57808-66-9.

ATC — A03FA03.

ATC Vet — QA03FA03.

UNII — 5587267Z69.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Domperidone). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in dimethylformamide. Protect from light.

Domperidone Maleate *(BANM, rINNM)*

Domperidona, maleato de; Dompéridone, maléate de; Domperidoni maleas; Domperidonimaleaatti; Domperidon-maleat; Domperidon-maleát; Domperidon-maleinát; Domperidono maleatas; Maleato de domperidona; Домперидона Малеат.

$C_{22}H_{24}ClN_5O_2.C_4H_4O_4$=542.0

CAS — 99497-03-7.

ATC — A03FA03.

ATC Vet — QA03FA03.

UNII — 899U5WF46A.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Domperidone Maleate). A white or almost white powder; it exhibits polymorphism. Very slightly soluble in water and in alcohol; sparingly soluble in dimethylformamide; slightly soluble in methyl alcohol. Protect from light.

Uses and Administration

Domperidone is a dopamine antagonist with actions and uses similar to those of metoclopramide (p. 1862.2). It is used as an antiemetic for the short-term treatment of nausea and vomiting of various aetiologies (p. 1811.3). It is not considered suitable for chronic nausea and vomiting, nor for the routine prophylaxis of postoperative vomiting. Domperidone is also used for its prokinetic actions in dyspepsia (p. 1806.3) and has been tried in diabetic gastroparesis (see Diabetic Neuropathy, p. 465.2). It has been given with paracetamol in the symptomatic treatment of migraine (p. 670.3).

Domperidone is used as the maleate in tablet preparations and as the base in suppositories and the oral suspension; doses are expressed in terms of the base. Domperidone maleate 12.73 mg is equivalent to about 10 mg of domperidone. Domperidone has been given parenterally, but this route has been associated with severe adverse effects (see below).

For the treatment of **nausea and vomiting** and for the symptomatic management of non-ulcer **dyspepsia**, domperidone may be given in oral doses of 10 to 20 mg three or four times daily up to a maximum daily dose of 80 mg or it may be given rectally in a dose of 60 mg twice daily. The initial course of treatment is up to 4 weeks. For doses in children see below.

The hydrochloride salt and domperidone betadex (domperidone betacyclodextrin) have also been used.

Reviews.
1. Prakash A, Wagstaff AJ. Domperidone: a review of its use in diabetic gastropathy. *Drugs* 1998; **56:** 429–45.
2. Barone JA. Domperidone: a peripherally acting dopamine$_2$-receptor antagonist. *Ann Pharmacother* 1999; **33:** 429–40.
3. Ahmad N, *et al*. Making a case for domperidone in the treatment of gastrointestinal motility disorders. *Curr Opin Pharmacol* 2006; **6:** 571–6.
4. Reddymasu SC, *et al*. Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol* 2007; **102:** 2036–45.

Administration in children. Domperidone is used in children as an antiemetic for nausea and vomiting and as a motility stimulant for gastrointestinal stasis. For nausea and vomiting, UK licensed product information states that children may be given domperidone in oral doses equivalent to 250 to 500 micrograms/kg three or four times daily; a total daily dose of 2.4 mg/kg or 80 mg, whichever is less, should not be exceeded. Alternatively, children weighing more than 15 kg may be given a rectal dose of 30 mg twice daily. Children over 12 years and weighing 35 kg or more may be given adult doses either orally or rectally, see above.

Although unlicensed for gastrointestinal stasis in the UK, the *BNFC* suggests oral doses given before food, according to age:

- neonates: 100 to 300 micrograms/kg four to six times daily
- 1 month to 12 years: 200 to 400 micrograms/kg (to a maximum of 20 mg) three or four times daily
- 12 years and over: doses similar to those used in adults for nausea and vomiting may be given

Similar doses may be used in infants and young children with gastro-oesophageal reflux disease, but see below.

Gastro-oesophageal reflux disease. A systematic review of the use of domperidone in infants and young children with gastro-oesophageal reflux (GORD; p. 1807.2), which identified 4 randomised controlled studies of such use, considered that there was very little evidence of its efficacy in reducing symptoms.[1] Some suggest that it has been overused because of the lack of a suitable alternative after withdrawal of cisapride in many countries.[2] The *BNFC* reinforces the idea that evidence for the long-term efficacy of motility stimulants (including domperidone) in the management of GORD is unconvincing. If domperidone is to be used, the *BNFC* suggests doses similar to those used for gastrointestinal stasis in children, see above.

1. Pritchard DS, *et al*. Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. *Br J Clin Pharmacol* 2005; **59:** 725–9.
2. Vandenplas Y, *et al*. The diagnosis and management of gastro-oesophageal reflux in infants. *Early Hum Dev* 2005; **81:** 1011–24.

Parkinsonism. Domperidone is used to control gastrointestinal effects of dopaminergic drugs given in the management of parkinsonism (p. 889.1). It may be of use in those patients who have peripheral effects with levodopa despite the use of peripheral dopa-decarboxylase inhibitors and for patients using dopamine agonists such as bromocriptine or apomorphine since peripheral dopa-decarboxylase inhibitors are ineffective for preventing the peripheral effects of these drugs. Although domperidone does not readily cross the blood-brain barrier there have been isolated reports of extrapyramidal effects associated with its use (see p. 1839.1). Consequently there has been concern over its potential to produce central effects and some consider that domperidone should only be used in patients with parkinsonism when safer antiemetic measures have failed.[1,2] However, this view has been contested both by the manufacturers and other authors.[3,4] In a subsequent review of the use of domperidone in Parkinson's disease it was considered[5] that domperidone might produce central blockade of the therapeutic effects of levodopa if given at a high oral dosage such as 120 mg daily for prolonged periods but also noted that such high doses were rarely required to control levodopa-induced vomiting.

Domperidone was found to significantly improve anorexia, nausea, vomiting, abdominal bloating, and regurgitation in patients taking levodopa.[6] Dysphagia and constipation were unaffected; these are thought to be more likely a reflection of the disease process. Doses ranged from 50 to 120 mg daily, with most patients responding to 80 mg daily. No central effects were noted.

1. Leeser J, Bateman DN. Domperidone. *BMJ* 1985; **290:** 241.
2. Bateman DN. Domperidone. *BMJ* 1985; **290:** 1079.
3. Lake-Bakaar G, Cameron HA. Domperidone. *BMJ* 1985; **290:** 241–2.
4. Critchley P, *et al*. Domperidone. *BMJ* 1985; **290:** 788.
5. Parkes JD. Domperidone and Parkinson's disease. *Clin Neuropharmacol* 1986; **9:** 517–32.
6. Soykan I, *et al*. Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. *Mov Disord* 1997; **12:** 952–7.

Adverse Effects

Dry mouth occurs commonly with domperidone; other adverse effects occur more rarely. Plasma-prolactin concentrations may increase with use of domperidone, which may lead to galactorrhoea, gynaecomastia, or amenorrhoea. Breast pain and tenderness may also occur. Domperidone does not readily cross the blood-brain barrier and the incidence of central effects such as extrapyramidal reactions or drowsiness may be lower than with metoclopramide (p. 1863.2); however, there have been reports of dystonic reactions and convulsions.

Domperidone has been associated with QT prolongation, serious ventricular arrhythmias, and sudden cardiac death. Fatalities have restricted intravenous use.

Hypersensitivity reactions include anaphylaxis and angioedema. Skin reactions such as rash, pruritus, and urticaria have occurred. Diarrhoea and transient intestinal cramps can also occur. There have been reports of anxiety or nervousness, agitation, loss of libido, asthenia, and headache. Urinary retention, abnormal liver function tests, and oculogyric crisis have also been reported.

Effects on the cardiovascular system. Between 1985 and 2006 Health Canada received 9 reports of heart rate and rhythm disorders suspected of being associated with domperidone use.[1] An increased QT interval was described in 2 cases, torsade de pointes in 4 cases, and the remaining 3 cases described arrhythmia, atrial fibrillation, ventricular tachycardia, bradycardia, and palpitation. Causality was hard to establish as most cases were complex, with multiple medicines prescribed. Prolongation of the QT interval has been reported in an infant given *oral* domperidone, with normalisation after the drug was stopped.[2] A prolonged QT interval was also reported in a small study in neonates given oral domperidone for gastro-oesophageal reflux disease; no cardiac arrhythmias developed.[3] A serum potassium concentration at the upper limit of normal or a gestational age of 32 weeks or more were risk factors for QT prolongation.

Sudden death has occurred in cancer patients given domperidone *intravenously* in high doses.[4-6] Four cancer patients had cardiac arrest after high intravenous doses[7] and 2 of 4 similar patients had ventricular arrhythmias.[8] After such reports the injection has been withdrawn from general use in many countries, including the UK.

A case-control study to investigate the association between the use of domperidone and the occurrence of serious ventricular arrhythmias found that current use of domperidone in high doses (defined as more than 30 mg daily; route not specified) was associated with a substantially increased risk of sudden cardiac death; non-fatal ventricular arrhythmias could not be assessed due to the lack of confirmed cases.[9]

1. Health Canada. Domperidone: heart rate and rhythm disorders. *Can Adverse React News* 2007; **17:** 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n1-eng.pdf (accessed 12/06/09)
2. Rocha CMG, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in an infant. *Pediatr Cardiol* 2005; **26:** 720–3.
3. Djeddi D, *et al*. Effect of domperidone on QT interval in neonates. *J Pediatr* 2008; **153:** 663–6.
4. Joss RA, *et al*. Sudden death in cancer patient on high-dose domperidone. *Lancet* 1982; **i:** 1019.
5. Giaccone G, *et al*. Two sudden deaths during prophylactic antiemetic treatment with high doses of domperidone and methylprednisolone. *Lancet* 1984; **ii:** 1336–7.
6. Weaving A, *et al*. Seizures after antiemetic treatment with high dose domperidone: report of four cases. *BMJ* 1984; **288:** 1728.
7. Roussak JB, *et al*. Cardiac arrest after treatment with intravenous domperidone. *BMJ* 1984; **289:** 1579.
8. Osborne RJ, *et al*. Cardiotoxicity of intravenous domperidone. *Lancet* 1985; **ii:** 385.
9. van Noord C, *et al*. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Safety* 2010; **33:** 1003–14.

Effects on the endocrine system. There have been reports of galactorrhoea with gynaecomastia[1] or mastalgia[2,3] generally associated with raised serum-prolactin concentra-

tions. Gynaecomastia without galactorrhoea has also been reported.[4]

1. Van der Steen M, *et al*. Gynaecomastia in a male infant given domperidone. *Lancet* 1982; **ii:** 884–5.
2. Cann PA, *et al*. Galactorrhoea as side effect of domperidone. *BMJ* 1983; **286:** 1395–6.
3. Cann PA, *et al*. Oral domperidone: double blind comparison with placebo in irritable bowel syndrome. *Gut* 1983; **24:** 1135–40.
4. Keating JP, Rees M. Gynaecomastia after long-term administration of domperidone. *Postgrad Med J* 1991; **67:** 401–2.

Extrapyramidal effects. There are reports of extrapyramidal symptoms,[1,2] including acute dystonic reactions[3] and neuroleptic malignant syndrome[4] in individual patients given domperidone.

1. Sol P, *et al*. Extrapyramidal reactions due to domperidone. *Lancet* 1980; **ii:** 802.
2. Debontridder O. Extrapyramidal reactions due to domperidone. *Lancet* 1980; **ii:** 802. Correction, *ibid.*; 1259.
3. Casteels-Van Daele M, *et al*. Refusal of further cancer chemotherapy due to antiemetic drug. *Lancet* 1984; **i:** 57.
4. Spirt MJ, *et al*. Neuroleptic malignant syndrome induced by domperidone. *Dig Dis Sci* 1992; **37:** 946–8.

Precautions

Domperidone is not recommended for chronic use or for the routine prophylaxis of postoperative nausea and vomiting. Domperidone should be used with great caution if given intravenously, because of the risk of arrhythmias, especially in patients predisposed to cardiac arrhythmias or hypokalaemia.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given domperidone, and the last available guidance from the American Academy of Pediatrics considered[1] domperidone to be usually compatible with breast feeding. However, the FDA in the USA has issued a warning against the use of domperidone to increase milk production because of the possibility of serious adverse effects.[2] Others have commented that these warnings were based on data from patients with malignant disease receiving high doses of intravenous domperidone, and that if the mother were taking smaller oral doses, the total amount of drug ingested by an infant would be extremely small. They recommend that low-dose domperidone should still be considered for lactating women with decreased milk supply who are unresponsive to non-pharmacological measures to enhance lactation. However, patients should be warned of the risk of arrhythmias at high doses, and women with known cardiac disease should not take domperidone.[3]

In a small controlled study to determine the effect of domperidone on the nutrient composition of breast milk, breast milk volume was increased with domperidone use, nutrient composition was not substantially altered, and no significant adverse effects were seen in mothers or infants.[4]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)
2. FDA. FDA warns against women using unapproved drug, domperidone, to increase milk production (June 7, 2004). Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm (accessed 17/12/10)
3. da Silva OP, Knoppert DC. Domperidone for lactating women. *Can Med Assoc J* 2004; **171:** 725–6.
4. Campbell-Yeo ML, *et al*. Effect of domperidone on the composition of preterm human breast milk. *Pediatrics* 2010; **125:** e107–e114. Available at: http://pediatrics.aappublications.org/cgi/reprint/125/1/e107 (accessed 17/12/10)

Interactions

As with other dopamine antagonists (see Metoclopramide, p. 1864.3), there is a theoretical potential that domperidone may antagonise the hypoprolactinaemic effect of drugs such as bromocriptine. In addition, the prokinetic effects of domperidone may alter the absorption of some drugs. Opioid analgesics and antimuscarinics may antagonise the prokinetic effects of domperidone.

Domperidone is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with ketoconazole has been reported to produce a threefold increase in plasma concentrations of domperidone, and an associated slight prolongation in QT interval. Similar increases in domperidone concentrations might theoretically be seen with other potent inhibitors of CYP3A4 such as erythromycin or ritonavir, and such combinations may be best avoided.

Pharmacokinetics

Although absorption is rapid, the systemic bioavailability of domperidone is only about 15% in fasting subjects given an oral dose; this is increased when domperidone is given after food. The low bioavailability is thought to be due to first-pass hepatic and intestinal metabolism. The bioavailability of rectal domperidone is similar to that after oral doses, although peak plasma concentrations are only about one-third that of an oral dose and occur after about an hour, compared with 30 minutes after an oral dose.

Domperidone is more than 90% bound to plasma proteins, and has a terminal elimination half-life of about 7.5 hours. It undergoes rapid and extensive hepatic metabolism. The main metabolic pathways are *N*-dealkylation by cytochrome P450 isoenzyme CYP3A4, and aromatic hydroxylation by CYP3A4, CYP1A2, and CYP2E1. About 30% of an oral dose is excreted in urine within 24 hours, almost entirely as metabolites; the remainder of a dose is excreted in faeces over several days, about 10% as unchanged drug. It does not readily cross the blood-brain barrier.

Small amounts of domperidone are distributed into breast milk; concentrations are 10 to 50% of those in maternal serum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ecuamon; Euciton; Moperidona; Motilium; Peridon; ***Austral.***: Motilium; ***Austria***: Motilium; ***Belg.***: Docdomperi†; Domperitop; Motilium; Oroperidys; Zilium; ***Braz.***: Dompgran; Dompliv; Motilium; Peridal; Peridona; ***Chile***: Docivin; Domevol; Dompesin; Donegal; Dosin; Gasdol; Idon; Restol; Siligaz; ***China***: Bang Neng (邦能); Domperid (益动); Duo Pai Tong (多派通); Heng Bang (恒邦); Motilium (吗丁啉); You Ma Lin (优玛琳); ***Cz.***: Motilium; Oroperidys; ***Denm.***: Motilium; ***Fr.***: Biperidys; Motilium; Oroperidys; Peridys; ***Ger.***: Domidon†; Motilium; ***Gr.***: Cilroton; Oroperidys; ***Hong Kong***: Apuldon; Costi; Dompeon†; Domper; Doridone; Floralin†; Motilium; Qualidom; Rabugen; Vicktilin†; Vicktilium†; ***Hung.***: Motilium; ***India***: Aglodom; Aldom; Aziorm; Casdom; Cosdome; Cudom; DMP; Dom-DT; Dom; Domacare; Domact; Dombus; Domcolic; Domday; Domden; Domdon; Domel-MT; Domerit; Domi; Domitil; Domkair; Domlyx; Domne; Domped; Domperi; Domperistal; Domperon; Dompet; Dompon; Dompro; Domsi; Domsin; Domstal; Domtop; Doven; Emestal; Emidon; Emitin; Endopace; Gastractiv; Gastrium; Judom; Junidom; Motilium-M; Motinorm; Motiwin; Naushi; Nausidome; Nautigo†; Normetic; Otron-D; Ozo-D; Pantin-RD; Stopvom; Vomistop; ***Indon.***: Costil; DOM; Dombaz; Domedon; Domet†; Dometa; Dometic; Dominal; Galflux; Gerdilium; Monell; Motilium; Novotil; Regit; Tilidon; Vesperum; Vomecho; Vomerin; Vometa; Vomidone; Vomina; Vomistop; Vomitas; Vosedon; Yaridon; ***Irl.***: Domerid; Motilium; ***Israel***: Motilium; ***Ital.***: Alvavitaros; Cattalorex; Dalia; Diedafont; Digestivo Giuliani; Gastronorm†; Gerdi; Lauter; Motilium; Peridon; Permotil; Riges; Stalcare; ***Jpn***: Nauzelin; ***Malaysia***: Domper; Motidone; Motilium; Rabugen; ***Mex.***: Biolix; Emiken; Motidom; Motilium; Seronex; ***Neth.***: Actadomp; Motilium; ***NZ***: Motilium; ***Philipp.***: Andiogan; Domelong; Dompenyl; Domper; Domperone; Gasidone; Gastrodin; Gilax; Motilium; Pepridon; Perilax; Toridon; Vometa; ***Port.***: Cinet; Mogasinte†; Motilium; Nausidone; Oroperidys; Perinauz†; Remotil; ***Rus.***: Damelium (Дамелиум); Domet (Домет); Domstal (Домстал); Motilak (Мотилак); Motilium (Мотилиум); Motinorm (Мотинорм); Motonium (Мотониум); Passagix (Пассажикс); ***S.Afr.***: Motilium; Vomidon; ***Singapore***: Dompel; Domper; Doridone; Gastrium; Mirax; Motilium; Peptomet; ***Spain***: Motilium; ***Switz.***: Motilium; ***Thai.***: Auto; Avomit-M; Dany; Dolium; Domerdon; Domidone†; Domp-M; Domp; Domper-M; Domperdone; Donox†; Donum†; Doper†; Emex; Falium†; Meridone; Mirax; Mocydone; Modomed; Molax; Moticon; Motidom; Motilar; Motilin; Motilium; Movelium; Ninlium; Peridom-M; Pondperdone; Rabugen-M; Vesperidone; ***Turk.***: Motilium; Motis; ***UAE***: Mododom; ***UK***: Motilium; Vivadone; ***Ukr.***: Brulium (Брюлиум); Domidon (Домидон); Motilium (Мотилиум); Motorix (Моторикс); Peridonium (Перидониум)†; ***Venez.***: Agilam; Tilium; Tonum†.

Multi-ingredient Preparations. ***Arg.***: Alplax Net; Ansielix Digest; Bigetric; Bilagol Antigas; Dom Simecon; Dom-Polienzim; Euciton Complex; Euciton Reflux; Euciton Stress; Faradil Novo; Gastrosedol Plus; Megalex; Moperidona AF; Moperidona Enzimatica†; Praxis; Sidomal; Tensium Gastric; Tetralgin Novo; Vegestabil Digest; ***Belg.***: Touristil; ***Braz.***: Lansodom†; ***Chile***: Faronkal; ***India***: Abcid-D; Abcool-D; Abra-D; Acera; Achpilori-D; Aciban-DSR; Acidom; Acidopent-DSR; Acigone-D; Aciloc RD; Acio; Acistal-D; Acitec-D; Actidol-DP; Actiran-D; Adprazole-D; Adzole-DM; Affirab-D; Aldepraz-D; Alice-D; Alizole-DSR; Anatyl-D; Antuc DSR; Anzop-D; Apentral-D; Aptase-DSR HG; Aribzol-D; Aridom-C; Aripan-D; Arloc-D; Armcid D; Asalt-D; Asipan-D; Asirab-D; Atozol-D; Avizol-D; Avopan-D; Azinorm C; Azinorm O; Aztec-D; B-Joy Plus; Bemez-D; Biomac-D; Biopar; Bizo-D; Brazo-D; Brozol-D; Brozole-D; Bus-D; C-Praz-D; Canozol-D; Capcid-D; Capocid-DM; Casdom-P; Cazole-D; Cidrid; Cimdom; Cinact-D; Cinadil-D; Cingeron-D; Cinnasia-D; Cintac-D; Comvine; Concid-DM; Concid-DSR; Cool Zone D; Coszol-D; Coz-D; Cucid-DM; Cudom-P; Cupan-DSR; Curab-D; Cuzole-D; Cyclochek; Cypan-D; Cyra-D; D-Rabibit-D; Dazole-D; Decotram-PD; Deepen-D; Degurge-D; Demo D; Depam; Dexrobel-D; DGR-Plus; Didol-D; Digerab-D; Diike; Diocid-D; Dirab-D; DMP Plus; Dols Plus; Dom-MPS; Dom-P; Domac; Domact-P; Domcet; Domci; Domden-P; Domepraz; Domeway; Domezol; Domizol-DS; Domkair-P; Domocid-PX; Domocid; Dompan; Dompar; Domped-OZ; Domperon Plus; Domperon-O; Dompon CZ; Dompon F; Dompon P; Dompra; Dompro-C; Domrab; Domsettler; Domsin-LA; Domsin-O; Domspas; Domstal MPS; Domstal-CZ; Domstal-O; Domstal-P; Domstal-RD; Domtac; Domtec-P; Domz; Domzole-R; Donriz; Dorafem; Dorcan-D; Doset Plus; Drag-D; Duogel; Dupent-D; Dyoflux; E-Pento-D; E-Zole-D; Egrin; Eldom-P; Elpra-D; Elrab-D; Emidon-OM; Emopaz-D; Eracid-D; Esofag-D; Esoga-RD; Esoz-D; Eupanta D; FB; Forzole-D; Fozole-D; FS-D; Fulpan-D; Furab-D; Gasorab-D; Gaspaz; Gastrazole-D; Genpen-D; Genrab-D; Gerdom; Gi-Fri; Glopan-D; GR8-OD; GR8; Gredol; Grenil; Happi-D; Helirab-D; Helkoss-D; Hurtiz-DSR; Hypa-D; Hyzole-DP; Icer-D; Ignis; Ingesic Forte; Inpan-D; Intapan-D; IPD; Izra-D; Jeprab-D; Jotac-D; Kandor CZ; Kapyl-D; Kenta-D; Kevtram-DP; Klenz-D; Konzol-D; Kurab-D; Kurepane-D; L-Dom; Lance-D; Lancidom; Lanip-D; Lans-DX; Lanspro-D; Lanzee-DM; Lapra-D; Lasole-D; Latop-D; Leedom; Leetop-D; Lesozap-D; Lexcid-DM; Litom-D; Liza-D; Locid-D; Lomecid-D; Lopra-D; Lupome-D; Mac-RD; Medipent-D; Meditin Plus; Mepraz-D; Meridol-D; Miliom-D; Minisec-AR; Mosic; Motinorm-P; Multipan-D; Mygran; Naprodom; Naxdom; Netom-D; Neutraflux; Neutral-O; Nexpro-RD; Nitpep-D; Nitzole-D; Nogacid D; Normocid; Nosirid-P; Novacid-D; Novagel-D; Novorab-D; Nucid-D; Nuloc-D; Nupan-D; Nura-D; Nutec MPS; O & D; O-Bit-DM; Ocid-D; Ocinil-D; Od; Odipan-D; Odipep; Odoman; Ogestrel-D; Okacid D; Okalan D; Olicap-D; Olla-D; Ombel-D; Ombest-D; Omcare-D; Omcure-D; Omdom; Omecer-D; Omecid-D; Omecid-RD; Omecip-D; Omecos-D; Omeezol-D; Omejel-DM; Omelax-D; Omen-D; Omentum-D; Omeraze-D; Omeris-D; Omesun-D; Omesym-D; Omevar-D; Omez-D; Omfact-D; Omibase-D; Omic-D; Omicas-D; Omicool-D; Omidec-ES; Omidec; Omidip; Omidom; Omiflux; Omig-DM; Omilee-D; Omitive-D; Omitop-DM; Omitop; Omizol-D; Omkair-D; Omlink-D; Omlo-D; Ommac Plus; Omore-D; Ompli-D; Ompraz-D; Omprest-D; Omracap-DM; Omriz-D; Omven-D; Omzee-D; Onazole-DP; Onazole-RD; Once-D; Oned; Onto-D; Op-Zole D; Opaz-DM; Opel-D; Opera-D; Opiate-PD; Orapan-D; Oraz-D; Oritop-D; Orole-D; Oshzol-D; Ospicid-D; Ossum-D; OTG-D; Otto-D; Oxokool Plus; Oxypan-D; Ozed-D; Ozodom; Ozol-D; Pacidom-C; Pacidom-O; Pacidom-P; Pacinac-NP; Palgic-D; Palin-D; Palio-D; Palzic-D; Pan-D; Pancas-D; Pandat-D; Pandiff; Pandom; Pandostal; Pandosun-D; Pandry D; Panfast-D; Pangy-DM; Pankai-D; Panlee-D; Panmint-D; Pano-D; Panopaz-D; Panor-D; Panpac-D; Panpari-D; Panpra-D; Panpro-D; Panrole-D; Pansa-D; Pansafe-D; Pansaul-D; Pansi-SD; Pansoft-D; Panstrike-D; Pantabit-D; Pantabol-D; Pantact-D; Pantadal-D; Pantadom; Pantagon-DM; Pantamep-D; Pantanib-D; Pantapil-D; Pantec-D; Pantest-D; Pantin-D; Pantium-D; Panto-D; Pantocar-D; Pantocid-D; Pantocos-D; Pantodac-D; Pantoday-D; Pantofer-D; Pantoflux; Pantol-D; Pantolex-D; Pantom-D; Pantomas-D; Pantomed-D; Pantomore-D; Pantonid-D; Pantop-D; Pantopik-D; Pantosec D; Pantosh D; Pantosig-D; Pantosym-D; Pantotive-D; Pantovar-D; Pantovom; Pantox-D; Pantoz-D; Pantozol-D; Pantra-D; Pantry-D; Pantz-D; Pantz-DM; Panum-D; Panz-D; Panz-SR; Panzac-D; Panzo-D; Praize-D; Vertigil; ***Philipp.***: Stugil; ***Rus.***: Domstal-O (Домстал-О); Omez D (Омез Д); ***Thai.***: Dominox; ***Ukr.***: Limzer (Лімзер); Omez-D (Омез-Д); Rabiril (Рабирил).

Pharmacopoeial Preparations
BP 2014: Domperidone Tablets.

Dosmalfate *(rINN)*

Dosmalfato; Dosmalfatum; F-3616; Дозмальфат.

{μ_7-[(Diosmin heptasulfato)(7-)]}tetracontahydroxytetradecaaluminium.

$C_{28}H_{60}Al_{14}O_{71}S_7$=2134.9

CAS — 122312-55-4.

UNII — P764IU074T.

Profile

Dosmalfate is a cytoprotective drug derived from diosmin (p. 2505.2), that has been used for the treatment of peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Diotul†.

Drofenine Hydrochloride *(pINNM)*

Drofenina, hidrocloruro de; Droféníne, Chlorhydrate de; Drofenini Hydrochloridum; Hexahydroadiphenine Hydrochloride; Hidrocloruro de drofenina; Дрофенина Гидрохлорид.

2-(Diethylamino)ethyl α-phenylcyclohexaneacetate hydrochloride.

$C_{20}H_{31}NO_2$,HCl=353.9

CAS — 1679-76-1 (drofenine); 548-66-3 (drofenine hydrochloride).

UNII — MVB31OPW05.

Pharmacopoeias. In *Swiss*.

Profile

Drofenine hydrochloride is an antimuscarinic available in preparations for the treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Espasmo Cibalena; ***Austria***: Spasmoplus; ***Chile***: Espasmo Cibalgina Compuesta†; Espasmo Cibalgina; ***Mex.***: Espasmo Cibalgina; ***Switz.***: Lunadon†.

Dronabinol *(USAN, rINN)* ⊗

Dronabinolum; NSC-134454; Дронабинол.

(6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol.

$C_{21}H_{30}O_2$=314.5

CAS — 1972-08-3.

ATC — A04AD10 (dronabinol); N02BG10 (nabiximols).

ATC Vet — QA04AD10.

UNII — 7J8897W37S.

Pharmacopoeias. In *US*.

USP 36: (Dronabinol). Store at a temperature between 8 degrees and 15 degrees in airtight glass containers in an inert atmosphere. Protect from light.

Uses and Administration

Dronabinol, the major psychoactive constituent of cannabis (p. 2467.1), has antiemetic properties and is used for the control of **nausea and vomiting** associated with cancer chemotherapy (p. 1811.3) in patients who have failed to respond adequately to conventional antiemetics.

The usual initial oral dose of dronabinol is 5 mg/m² given 1 to 3 hours before the first dose of the antineoplastic drug with subsequent doses being given every 2 to 4 hours after chemotherapy to a maximum of 4 to 6 doses daily. If necessary, the dose may be increased by increments of 2.5 mg/m² to a maximum dose of 15 mg/m², if adverse effects permit.

Dronabinol also has appetite-stimulant effects and is used in the treatment of **anorexia** associated with weight loss in patients with AIDS. For this purpose 2.5 mg may be taken twice daily, before lunch and supper, reduced to a single 2.5-mg dose in the evening in patients who tolerate the drug poorly. If necessary, and if adverse effects permit, doses may also be increased up to 20 mg daily in divided doses.

A buccal spray preparation containing cannabis extracts, whose main active ingredients are dronabinol and cannabidiol, is used as adjunctive treatment for the symptomatic relief of **spasticity** and **neuropathic pain** in multiple sclerosis in adults; this combination is also used as adjunctive analgesic treatment in adult patients with advanced cancer (see Nabiximols, p. 2566.3) and is under investigation for several other conditions.

General references.

1. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Ann Intern Med* 1997; **126:** 791–8.
2. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs* 2000; **60:** 1303–14.
3. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; **323:** 16–21.
4. Berman JS, *et al.* Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; **112:** 299–306.
5. Costa B. On the pharmacological properties of Delta9-tetrahydrocannabinol (THC). *Chem Biodivers* 2007; **4:** 1664–77.
6. Beaulieu P, Ware M. Reassessment of the role of cannabinoids in the management of pain. *Curr Opin Anaesthesiol* 2007; **20:** 473–7.

Alzheimer's disease. There are limited data to suggest that dronabinol may decrease agitation in patients with Alzheimer's disease[1] or dementia.[2]

1. Volicer L, *et al.* Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; **12:** 913–19.
2. Walther S, *et al.* Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl)* 2006; **185:** 524–8.

Anorexia. Dronabinol is used for the management of anorexia in patients with HIV-associated wasting (p. 959.1). However, although dronabinol may stimulate appetite and prevent weight loss,[1] it does not appear to produce significant weight gain, and may produce less benefit than megestrol acetate.[2] Benefits were also less than those of megestrol in patients with anorexia associated with malignant disease.[3]

1. Beal JE, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995; **10:** 89–97.
2. Timpone JG, *et al.* The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997; **13:** 305–15.
3. Jatoi A, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; **20:** 567–73.

Multiple sclerosis. Anecdotal evidence has suggested that cannabinoids might improve symptoms in patients with multiple sclerosis (p. 996.3); a review[1] considered evidence of efficacy to be lacking. In a large placebo-controlled study, treatment with dronabinol or oral cannabis extract had no benefit on objective assessment of spasticity;[2] however, there were improvements in walking time, and subjective improvements in both spasticity and pain. A subsequent small controlled study found dronabinol to have a modest but clinically relevant effect on central neuropathic pain in patients with multiple sclerosis.[3]

A buccal spray preparation containing cannabis extracts, whose main active ingredients are dronabinol and cannabidiol, is used for the symptomatic relief of spasticity and neuropathic pain in multiple sclerosis in adults.

1. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.
2. Zajicek J, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362:** 1517–26.
3. Svendsen KB, *et al.* Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; **329:** 253–7.

Tourette's syndrome. Preliminary studies[1,2] indicate that dronabinol may reduce tic severity in Tourette's syndrome (see Tics, p. 1030.1).

1. Müller-Vahl KR, *et al.* Treatment of Tourette's syndrome with Δ⁹-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; **35:** 57–61.
2. Müller-Vahl KR, *et al.* Δ⁹-Tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003; **64:** 459–65.

Adverse Effects and Precautions

As for Nabilone, p. 1865.3. The most frequent adverse effects of dronabinol include abdominal pain, nausea and vomiting, dizziness, euphoria, paranoid reactions, and somnolence. Seizures and seizure-like activity have been reported; dronabinol should be used with caution in those with a history of seizure disorders, and therapy should be stopped if seizures occur.

Abuse. The abuse liability of dronabinol was rated as being substantially lower than that of cannabis.[1]

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 03/07/08)

Breast feeding. US licensed product information states that dronabinol is concentrated in breast milk and recommends that it should not be used in breast-feeding mothers.

Pharmacokinetics

After oral doses dronabinol is slowly and erratically absorbed from the gastrointestinal tract; the bioavailability of an oral dose is about 10 to 20%, due to extensive first-pass metabolism. Peak plasma concentrations of dronabinol and its 11-hydroxy metabolite occur about 2 to 4 hours after an oral dose. It is widely distributed and is extensively protein bound, with a volume of distribution of about 10 litres/kg. Elimination is biphasic, with an initial half-life of about 4 hours, and a terminal half-life of about 25 to 36 hours.

Dronabinol is extensively metabolised, mainly in the liver by cytochrome P450 isoenzymes; the primary metabolite, 11-hydroxydronabinol is also active. The 11-hydroxy metabolite is converted to other, more polar and acidic compounds which are excreted in faeces via the bile, and in the urine. About 50% of an oral dose is recovered in faeces within 72 hours and 10 to 15% in urine. Many of the metabolites have relatively prolonged half-lives, and accumulation may occur with repeated dosage.

Dronabinol is distributed into breast milk and crosses the placenta.

References.

1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42:** 327–60.
2. McGilveray IJ. Pharmacokinetics of cannabinoids. *Pain Res Manag* 2005; **10:** 15A–22A.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Marinol†; ***USA***: Marinol.

Pharmacopoeial Preparations

USP 36: Dronabinol Capsules.

Ecabet Sodium *(rINNM)*

Ecabet sódico; Écabet Sodique; Natrii Ecabetum; 12-Sulphodehydroabietic Acid, Monosodium Salt; TA-2711; Экабет Натрий.

13-Isopropyl-12-sulphopodocarpa-8,11,13-trien-15-oic acid pentahydrate, sodium salt.

$C_{20}H_{27}NaO_5S,5H_2O$=492.6

CAS — 33159-27-2 (ecabet); 86408-72-2 (ecabet sodium).

UNII — 51MO2B2OSB.

Profile

Ecabet sodium is a cytoprotective drug used in the treatment of peptic ulcer disease (p. 1813.2). The suggested oral dose is 1 g of ecabet sodium twice daily.

It is also under investigation as eye drops in the management of dry eye.

References.

1. Murata H, *et al.* Combination therapy of ecabet sodium and cimetidine compared with cimetidine alone for gastric ulcer: prospective randomized multicenter study. *J Gastroenterol Hepatol* 2003; **18:** 1029–33.
2. Lee JH, *et al.* Efficacy and safety of ecabet sodium on functional dyspepsia: a prospective, double-blinded, randomized, multi-center controlled trial. *World J Gastroenterol* 2006; **12:** 2756–61.

Administration. The use of ecabet sodium as a rectal enema has been investigated in patients with ulcerative colitis.[1,2]

1. Kono T, *et al.* Effect of ecabet sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. *Am J Gastroenterol* 2001; **96:** 793–7.
2. Iizuka M, *et al.* Efficacy of ecabet sodium enema on steroid resistant or steroid dependent ulcerative colitis. *Gut* 2006; **55:** 1523.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Gastrom (盖爽); ***Jpn***: Gastrom.

Egualen Sodium *(rINN)*

Azuletil Sodium; Egualen Sodium Hydrate; Égualène Sodique; Egualeno sódico; KT-1-32; Natrii Egualenum; Натрий Эгуален.

Sodium 3-ethyl-7-isopropyl-1-azulenesulfonate.

$C_{15}H_{17}O_3SNa$=300.3

CAS — 97683-31-3.

Profile

Egualen sodium is a mucosal protectant used with H_2-receptor antagonists for the treatment of gastric ulceration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Azuloxa.

Enoxolone Aluminium *(BANM, rINNM)*

Aluminii Enoxolonum; Aluminium Glycyrrhetate; Aluminium Glycyrrhetinate; Enoxolona de aluminio; Enoxolone Aluminum; Énoxolone d'Aluminium; Алюминий Эноксолон.

3β-Hydroxy-11-oxo-olean-12-en-30-oic acid, aluminium salt.

$(C_{30}H_{46}O_4)_3$.Al=1439.1

CAS — 4598-66-7.

ATC — D03AX10.

ATC Vet — QD03AX10.

Profile

Enoxolone aluminium is an analogue of carbenoxolone (p. 1825.3) that has been used in preparations for the treatment of peptic ulcer disease and other gastrointestinal disorders. It has also been used in preparations for skin disorders and mouth and throat disorders.

Pulmonary hypertension. *In-utero* exposure to enoxolone was implicated in a fatal case of neonatal pulmonary arterial hypertension; the mother had used a lotion for prurigo that contained enoxolone and the authors supposed it had contributed at least in part to the pulmonary hypertension.[1]

1. Navarre-Belhassen C, *et al.* An unexpected case of primary pulmonary hypertension of the neonate (PPHN): potential role of topical administration of enoxolone. *J Perinat Med* 2002; **30:** 437–9.

Eseridine Salicylate *(rINNM)*

Eseridina, salicilato de; Ésséridine, Salicylate d'; Eseridini Salicylas; Eserine Aminoxide Salicylate; Eserine Oxide Salicylate; Physostigmine Aminoxide Salicylate; Physostigmine *N*-Oxide Salicylate; Salicilato de eseridina; Эзеридина Салисилат.

(4a*S*,9a*S*)-2,3,4,4a,9,9a-Hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-*b*]indol-6-ylmethylcarbamate salicylate.

$C_{15}H_{21}N_3O_3,C_7H_6O_3$=429.5

CAS — 25573-43-7 (eseridine); 5995-96-0 (eseridine salicylate).

Profile

Eseridine salicylate, a derivative of physostigmine (p. 2009.3), is an inhibitor of cholinesterase activity that has been given orally for dyspepsia in doses of up to 4.5 mg 3 times daily, taken 30 minutes before meals.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Geneserine.

Esomeprazole *(BAN, rINN)*

Esomepratsoli; Esomeprazol; Ésoméprazole; Esomeprazolum; H-199/18; Perprazole; Эзомепразол.

5-Methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]benzimidazole.

$C_{17}H_{19}N_3O_3S$=345.4

CAS — 119141-88-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — N3PA6559FT.

Esomeprazole Magnesium

(BANM, USAN, rINNM)

Esomeprazol magnésico; Ésoméprazole Magnesique; Ésoméprazole magnésique; Esomeprazolum magnesicum; Magnesii Esomeprazolum; Магния Эзомепразол.

$C_{34}H_{36}MgN_6O_6S_2,3H_2O$=767.2

CAS — 217087-09-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — R6DXU4WAY9.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Esomeprazole Magnesium Trihydrate). A white or slightly coloured, slightly hygroscopic powder. Slightly soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 36: (Esomeprazole Magnesium). A white to slightly coloured powder. Slightly soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

Esomeprazole Potassium *(BANM, USAN, rINNM)*

Esomeprazol potásico; Ésoméprazole Potassique; Kalii Esomeprazolum; Калия Эзомепразол.

$C_{17}H_{18}KN_3O_3S$=383.5

CAS — 161796-84-5.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — F37S7G37O2.

Esomeprazole Sodium *(BANM, USAN, rINNM)*

Esomeprazol sódico; Ésoméprazole Sodique; Natrii Esomeprazolum; Натрия Эзомепразол.

$C_{17}H_{19}N_3NaO_3S$=368.4

CAS — 161796-78-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — L2C9GWQ43H.

Esomeprazole Strontium *(USAN, rINNM)*

Esomeprazol estroncio; Ésoméprazole Strontium; FM-0F67; Эзомепразол Стронция.

$(C_{17}H_{18}N_3O_3S)_2Sr,4H_2O$=848.5

CAS — 934714-36-0.

UNII — C5N25H3803.

Uses and Administration

Esomeprazole is the *S*-isomer of the proton pump inhibitor omeprazole (p. 1867.2) and is used similarly in the treatment of peptic ulcer disease and NSAID-associated ulceration (p. 1813.2), in gastro-oesophageal reflux disease (p. 1807.2), and the Zollinger-Ellison syndrome (p. 1814.3). It is given as the magnesium, sodium, or strontium salts but doses are calculated in terms of esomeprazole. Esomeprazole magnesium 22.2 mg, esomeprazole sodium 21.3 mg, and esomeprazole strontium 24.7 mg are each equivalent to about 20 mg of esomeprazole.

Usual oral doses in **peptic ulcer disease**, for *Helicobacter pylori* eradication as a component of a triple therapy regimen with amoxicillin and clarithromycin, are the equivalent of 20 mg esomeprazole twice daily for 7 days, or 40 mg once daily for 10 days.

Oral doses of 20 mg daily, for 4 to 8 weeks, are used in the treatment of **NSAID-associated ulceration**; a dose of 20 or 40 mg daily may also be used for prophylaxis in patients at risk of such lesions who require continued NSAID treatment.

In the UK, the dose for treatment of severe (erosive) **gastro-oesophageal reflux disease** is 40 mg once daily for 4 weeks, extended for a further 4 weeks if necessary; in the USA, where doses of 20 or 40 mg daily are permitted for initial treatment, a further 4 to 8 weeks of treatment may be considered for patients who do not heal after 4 to 8 weeks. For maintenance, or for symptomatic disease without erosive oesophagitis, doses equivalent to 20 mg of esomeprazole daily may be used in both countries.

For the treatment of **Zollinger-Ellison syndrome**, the recommended initial oral dose of esomeprazole is 40 mg twice daily, which is then adjusted as needed. The majority of patients can be controlled on doses between 80 and 160 mg daily, although daily doses of 240 mg have been given. Doses above 80 mg daily should be given in 2 divided doses. For doses in children, see below.

PARENTERAL DOSAGE.

Similar doses to the above may be given intravenously for gastro-oesophageal reflux disease and NSAID-associated ulceration. Esomeprazole is given as the sodium salt by slow intravenous injection over at least 3 minutes or by intravenous infusion over 10 to 30 minutes.

For the **prevention of rebleeding** of gastric and duodenal ulcers after therapeutic endoscopy, 80 mg esomeprazole can be given as an intravenous infusion over 30 minutes, followed by a continuous intravenous infusion of 8 mg/hour over 72 hours. This parenteral treatment period is then followed by oral therapy; 40 mg is given once daily for 4 weeks.

Doses of esomeprazole may need to be reduced in patients with hepatic impairment (see below).

References.

1. Maton PN, *et al.* Safety and efficacy of long term esomeprazole therapy in patients with healed erosive oesophagitis. *Drug Safety* 2001; **24:** 625–35.
2. Keating GM, Figgitt DP. Intravenous esomeprazole. *Drugs* 2004; **64:** 875–82.
3. Metz DC, *et al.* Comparison of the effects of intravenously and orally administered esomeprazole on acid output in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; **22:** 813–21.
4. Edwards SJ, *et al.* Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther* 2006; **24:** 743–50.
5. Morgner A, *et al.* Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. *Expert Opin Pharmacother* 2007; **8:** 975–88.
6. Blandizzi C, *et al.* Clinical efficacy of esomeprazole in the prevention and healing of gastrointestinal toxicity associated with NSAIDs in elderly patients. *Drugs Aging* 2008; **25:** 197–208.
7. McKeage K, *et al.* Esomeprazole: a review of its use in the management of gastric acid-related diseases in adults. *Drugs* 2008; **68:** 1571–1607.
8. Sung JJY, *et al.* Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2009; **150:** 455–64.

Administration. *In-vitro* studies found that almost the entire contents of an esomeprazole capsule is deliverable through small calibre and standard sizes of nasogastric and gastrostomy tubes.[1,2]

1. White CM, *et al.* Delivery of esomeprazole magnesium enteric-coated pellets through small caliber and standard nasogastric tubes and gastrostomy tubes in vitro. *Am J Health-Syst Pharm* 2002; **59:** 2085–8.
2. Shah SA, *et al.* Delivery of esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. *Am J Health-Syst Pharm* 2006; **63:** 1882–7.

Administration in children. Esomeprazole is given orally to children for the treatment of gastro-oesophageal reflux disease and erosive oesophagitis,[1,2] and for duodenal ulcers caused by *Helicobacter pylori*.

For gastro-oesophageal reflux disease, children aged from 1 to 11 years and weighing 10 kg and over are given 10 mg once daily for up to 8 weeks.

In erosive oesophagitis, doses are based on body-weight and given once daily for 8 weeks:

- 10 kg up to 20 kg: 10 mg
- ⩾ 20 kg: 10 or 20 mg

For the eradication of *H. pylori* in duodenal ulceration in children over 4 years of age, oral esomeprazole is given with amoxicillin and clarithromycin for 1 week; doses are according to weight:

- < 30 kg: 10 mg twice daily
- ⩾ 30 kg: 20 mg twice daily

Regardless of indication, children from 12 years of age may be given adult doses, see above.

For doses in children with hepatic impairment, see below.

Esomeprazole is unlicensed in children under 1 year of age; however, a pharmacokinetic study in preterm and term neonates with gastro-oesophageal reflux disease found oral esomeprazole 500 micrograms/kg once daily for 7 days reduced oesophageal acid exposure and gastric acidity but had no effect on bolus reflex characteristics, findings that were consistent with those reported in adults. Systemic exposure to esomeprazole was proportionally higher in neonates compared with older infants.[3]

For findings from a review regarding the efficacy and safety of proton pump inhibitors in infants, children, and adolescents, see Administration in Children, under Omeprazole, p. 1867.3.

1. Croxtall JD, *et al.* Esomeprazole: in gastroesophageal reflux disease in children and adolescents. *Paediatr Drugs* 2008; **10:** 199–205.
2. Guimarães EV, *et al.* Management of gastroesophageal reflux disease and erosive esophagitis in pediatric patients: focus on delayed-release esomeprazole. *Ther Clin Risk Manag* 2010; **6:** 531–7.
3. Omari T, *et al.* Pharmacodynamics and systemic exposure of esomeprazole in preterm infants and term neonates with gastro-esophageal reflux disease. *J Pediatr* 2009; **155:** 222–8.

Administration in hepatic impairment. No dosage adjustment of esomeprazole is considered necessary for patients with mild to moderate hepatic impairment (Child-Pugh Classes A and B, respectively). In severe hepatic impairment (Child-Pugh Class C), US licensed product information recommends that a daily dose of 20 mg, orally or intravenously, should not be exceeded. In the UK, licensed product information specifies a maximum daily intravenous dose of esomeprazole 20 mg in those aged 18 years and over, although when given for prevention of rebleeding of gastric and duodenal ulcers after endoscopy in those with severe hepatic impairment, an initial intravenous infusion of 80 mg over 30 minutes, may be followed by a continuous intravenous infusion of 4 mg/hour over about 72 hours. A maximum daily oral dose of esomeprazole 20 mg is recommended in patients from 12 years of age, and 10 mg in those aged 1 to 11 years.

Administration in renal impairment. Although no dosage adjustment is considered necessary in patients with renal impairment, UK licensed product information advises caution in those with severe renal impairment, as experience in these patients is limited.

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

General references.

1. Davies M, *et al.* Safety profile of esomeprazole: results of a prescription-event monitoring study of 11 595 patients in England. *Drug Safety* 2008; **31:** 313–23.

Effects on the cardiovascular system. For discussion of cardiac effects ostensibly seen with esomeprazole, see under Omeprazole, p. 1868.2.

Effects on the kidneys. For reports of interstitial nephritis associated with esomeprazole see p. 1869.1.

Effects on the skin. For mention of exacerbation of vitiligo with esomeprazole, see p. 1869.2.

Fever. For a report of hyperpyrexia associated with esomeprazole, see p. 1869.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies esomeprazole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Interactions

As for Omeprazole, p. 1870.3.

References.

1. Andersson T, *et al.* Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40:** 523–37.

Pharmacokinetics

Esomeprazole is rapidly absorbed after oral doses and peak plasma levels occur after about 1 to 2 hours. It is acid labile and an enteric-coated formulation has been developed. Bioavailability of esomeprazole increases on repeated dosage to about 68 and 89% for doses of 20 and 40 mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on intragastric acidity. Esomeprazole is about 97% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. The remainder is metabolised by the cytochrome P450 isoenzyme CYP3A4 to esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme. However, there is no accumulation during once daily use. The plasma elimination half-life is about 1.3 hours. Almost 80% of an oral dose is eliminated as metabolites in the urine, the remainder in the faeces.

References.

1. Andersson T, *et al.* Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40:** 411–26.

2. Sostek MB, *et al.* Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole. *Br J Clin Pharmacol* 2007; **64:** 386–90.

Metabolism. As for omeprazole (p. 1871.2), the cytochrome P450 isoenzyme CYP2C19 is involved in the metabolism of esomeprazole, and individuals who are deficient in this enzyme are poor metabolisers of esomeprazole. However, there is some suggestion that the metabolism of esomeprazole is less dependent on this genotype, as there may be a metabolic shift towards the CYP3A4-mediated pathway.[1]

1. Schwab M, *et al.* Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. *Clin Pharmacol Ther* 2005; **78:** 627–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Esomax; Esoprazol; Nexium; Ultrex; ***Austral.***: Nexium; ***Austria***: Nexium; ***Belg.***: Nexiam; ***Braz.***: Nexium; ***Canad.***: Nexium; ***Chile***: Cor; Cronopep; Emezol; Exicross; Neoren; Nexium; Ulcratex; ***China***: Nexium (耐信); ***Cz.***: Emanera; Emozul; Esomylan; Helides; Moproc; Nexium†; Prazectol; ***Denm.***: Emanera; Emprozal†; Eprasol†; Escadra; Esodec; Esomel; Esompro†; Esopral; Esotar; Essec†; Eudresc†; Ezoret; Hydresc†; Inexium; Nexium; Slodra†; ***Fin.***: Nexium; ***Fr.***: Inexium; ***Ger.***: Nexium; ***Gr.***: Nexium; ***Hong Kong***: Nexium; ***Hung.***: Emozul; Nexium; Raciper; ***India***: Ceso; Cucid-ES; Es-Care; Es-OD; Esocool; Esofag; Esoflo; Esomac; Esorest; Esoriv; Esotrax; Esoz; Espra; Estab; Izra; Neksium; Nexpro; Nuloc; Omipure; Sompraz; ***Indon.***: Nexium; ***Irl.***: Emazole; Nepramel; Nexium; ***Israel***: Nexium; ***Ital.***: Axagon; Esopral; Espeyen; Ezoran; Lucen; Nexium; ***Jpn***: Nexium; ***Malaysia***: Nexium; ***Mex.***: Nexium; ***Neth.***: Esobax; Esopral; Nexium; Zolex; ***Norw.***: Esopral; Inexium; Nexium; ***Philipp.***: Esomep; Nexium; ***Pol.***: Emanera; Nexium; ***Port.***: Nexium; ***Rus.***: Nexium (Нексиум); ***S.Afr.***: Nexiam; ***Singapore***: Nexium; ***Spain***: Axiago; Nexium; ***Swed.***: Nexium; ***Switz.***: Esomep; Nexium; ***Thai.***: Nexium; ***Turk.***: Nexium; ***UK***: Emozul; Nexium; ***Ukr.***: Esonexa (Эзонекса); Esoxium (Эзоксиум); Ezolong (Езолонг); Nexium (Нексиум); ***USA***: Nexium; ***Venez.***: Esoz; Nexium.

Multi-ingredient Preparations. ***Austral.***: Nexium Hp; ***Canad.***: Nexium 1-2-3 A; ***India***: Esofag-D; Esoz-D; Ignis; Izra-D; Neutraflux; Nexpro-RD; Omidec-ES; ***Swed.***: Nexium Hp; ***Ukr.***: Esoxium Combi (Эзоксиум Комби).

Used as an adjunct in:. ***Austral.***: Vimovo; ***Belg.***: Aspaxa; Vimovo; ***Canad.***: Vimovo; ***Cz.***: Axanum; Vimovo; ***Denm.***: Vimovo; ***Fin.***: Vimovo; ***Ger.***: Axanum; ***Irl.***: Vimovo; ***Israel***: Vimovo; ***Ital.***: Vimovo; ***Neth.***: Axanum; Vimovo; ***Norw.***: Axanum; Vimovo; ***NZ***: Vimovo; ***Singapore***: Vimovo; ***Spain***: Vimovo; ***Swed.***: Vimovo; ***Switz.***: Axanum; Vimovo; ***UK***: Vimovo; ***USA***: Vimovo.

Pharmacopoeial Preparations
USP 36: Esomeprazole Magnesium Delayed-Release Capsules.

Euonymus

Bonetero; Bonetillo; Evónimo; Fusain Noir Pourpré; Spindle Tree Bark; Wahoo Bark; Бересклетова Кора.

*ATC Herb — HC01EB5015 (*Euonymus atropurpureus*: bark); HA06AX5003 (*Euonymus atropurpureus*: bark); HA05WA5008 (*Euonymus atropurpureus*: bark).*

*UNII — 1H5XDT80QO (euonymus); WJK59V19EW (*Euonymus atropurpureus *bark).*

Profile

Euonymus is the dried root-bark of *Euonymus atropurpureus* (=*Evonymus atropurpurea*) (Celastraceae). It is reported to have laxative, choleretic, and diuretic activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Jecopeptol†; ***UK***: Acidosis; GB Tablets; Indigestion Mixture.

Famotidine *(BAN, USAN, rINN)*

Famotidiini; Famotidin; Famotidina; Famotidinas; Famotidinum; L-643341; MK-208; YM-11170; Фамотидин.

3-[2-(Diaminomethyleneamino)thiazol-4-ylmethylthio]-*N*-sulphamoylpropionamidine.

$C_8H_{15}N_7O_2S_3$=337.4

CAS — 76824-35-6.

ATC — A02BA03.

ATC Vet — QA02BA03.

UNII — 5QZO15J2Z8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8 (Famotidine). A white or yellowish-white, crystalline powder or crystals. It exhibits polymorphism. Very slightly soluble in water and in dehydrated alcohol; freely soluble in glacial acetic acid; practically insoluble in ethyl acetate. It dissolves in dilute mineral acids. Protect from light.

USP 36: (Famotidine). A white to pale yellowish-white crystalline powder. Very slightly soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethylformamide and in glacial acetic acid; slightly soluble in methyl alcohol. Protect from light.

Stability. References.

1. Quercia RA, *et al.* Stability of famotidine in an extemporaneously prepared oral liquid. *Am J Hosp Pharm* 1993; **50:** 691–3.
2. Dentinger PJ, *et al.* Stability of famotidine in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2000; 1340–2.

Uses and Administration

Famotidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p. 1827.2).

Famotidine may be given orally or intravenously.

In the management of benign **gastric** and **duodenal ulceration** (see Peptic Ulcer Disease, p. 1813.2) the dose is 40 mg daily orally at bedtime, for 4 to 8 weeks. A dose of 20 mg twice daily has also been given. A maintenance dose of 20 mg at bedtime may be given to prevent recurrence of duodenal ulceration. In **gastro-oesophageal reflux disease** (p. 1807.2) the recommended oral dose is 20 mg twice daily for 6 to 12 weeks, or up to 40 mg twice daily if there is oesophageal erosion or ulceration. A maintenance dose of 20 mg twice daily may be given to prevent recurrence. For the short-term symptomatic relief of heartburn or non-ulcer **dyspepsia** (p. 1806.3) a dose of 10 mg up to twice daily is suggested. In the **Zollinger-Ellison syndrome** (p. 1814.3) the initial oral dose is 20 mg every 6 hours, increased as necessary; doses up to 800 mg daily have been used.

The usual dose of famotidine by the intravenous route is 20 mg and may be given by injection over at least 2 minutes or as an infusion over 15 to 30 minutes; the dose may be repeated every 12 hours.

Doses of famotidine should be reduced in patients with renal impairment (see below). For doses in children, see below.

Administration. Although famotidine is usually given as a film-coated tablet, an alternative wafer formulation, designed to dissolve on the tongue without the need for water, has also been developed.[1]

Parenteral formulations of famotidine are also available in some countries. Licensed product information recommends intravenous injection over at least 2 minutes or intravenous infusion over 15 to 30 minutes; however, a study that compared rapid intravenous injection (over up to 1 minute) with slow intravenous infusion found rapid injection to be comparable with infusion in terms of safety.[2] Continuous infusion has however been reported by others[3] to be more effective in the prevention of stress ulceration than bolus injection.

1. Schwartz JI, *et al.* Novel oral medication delivery system for famotidine. *J Clin Pharmacol* 1995; **35:** 362–7.
2. Fish DN. Safety and cost of rapid iv injection of famotidine in critically ill patients. *Am J Health-Syst Pharm* 1995; **52:** 1889–94.
3. Baghaie AA, *et al.* Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: results of a prospective, randomized, crossover study. *Crit Care Med* 1995; **23:** 687–91.

Administration in children. Famotidine is licensed for use in children in some countries, including the USA. It is used to inhibit gastric acid secretion and may be given orally or intravenously.

In the management of **gastro-oesophageal reflux disease**, the following initial oral doses of famotidine are suggested, according to age:

- under 3 months: 500 micrograms/kg once daily
- 3 months up to 1 year: 500 micrograms/kg twice daily
- 1 to 16 years: 500 micrograms/kg twice daily; up to 40 mg twice daily may be given

Famotidine may also be given intravenously to children from 1 to 16 years. An initial dose of 250 micrograms/kg is suggested for gastro-oesophageal reflux disease, given by injection over at least 2 minutes or as an infusion over 15 minutes, and repeated every 12 hours. Up to 40 mg daily may be given.

In the management of **peptic ulcers**, famotidine may be given to children from 1 to 16 years in an initial oral dose of 500 micrograms/kg daily, either in a single dose at night or in 2 divided doses; up to 40 mg daily may be given.

Administration in renal impairment. In patients with renal impairment, famotidine clearance is reduced and the elimination half-life increased, resulting in increased serum-drug concentrations. The half-life of famotidine in healthy subjects is about 3 hours, but in patients with a creatinine clearance (CC) less than 38 mL/min[1] or those with end-stage renal disease[2] it has been reported to be 19.3 hours and 27.2 hours, respectively. A reduced dose has therefore been recommended in patients with renal impairment, although it may not be sufficient to adjust the dose only on the basis of creatinine clearance since famotidine is partly eliminated by tubular secretion, which may also be diminished.[1] Licensed product information recommends reducing the dose by half or increasing the dosage interval to 36 to 48 hours for patients with moderate or severe renal impairment (CC less than 50 mL/min). A chart review[3] in patients with end-stage renal disease suggested that most patients would tolerate a dose of 20 mg daily, although a few might need further adjustment to prevent mental status changes.

Haemodialysis does not effectively remove famotidine from the systemic circulation. The proportion removed depends on the type of membrane used; with a high flux polysulfone membrane about 16% is reported to be removed, but only 6% with a cuprophan membrane.[2] Continuous ambulatory peritoneal dialysis removes about 5% of a dose.[2] Continuous haemofiltration may remove about 16% of a dose[2] and intermittent haemofiltration is reported to remove about 4%[4] or 8%.[2] Dosage supplements of famotidine are not required during or after dialysis or filtration procedures.

1. Inotsume N, *et al.* Pharmacokinetics of famotidine in elderly patients with and without renal insufficiency and in healthy young volunteers. *Eur J Clin Pharmacol* 1989; **36:** 517–20.
2. Gladziwa U, *et al.* Pharmacokinetics and dynamics of famotidine in patients with renal failure. *Br J Clin Pharmacol* 1988; **26:** 315–21.
3. Redmond AM, *et al.* Use of famotidine in adult patients with end-stage renal disease: assessment of dosing and mental status changes. *Am J Med Sci* 2005; **330:** 8–10.
4. Saima S, *et al.* Hemofiltrability of H_2-receptor antagonist, famotidine, in renal failure patients. *J Clin Pharmacol* 1990; **30:** 159–62.

Immunomodulation. For reference to the use of H_2-antagonists as immunomodulators, see Cimetidine, p. 1827.3.

Schizophrenia. There are reports of improvement in schizophrenic symptoms (p. 1031.3) in patients given famotidine.[1-4]

1. Kaminsky R, *et al.* Effect of famotidine on deficit symptoms of schizophrenia. *Lancet* 1990; **335:** 1351–2.
2. Rosse RB, *et al.* Famotidine adjunctive pharmacotherapy of schizophrenia: a case report. *Clin Neuropharmacol* 1995; **18:** 369–74.
3. Rosse RB, *et al.* An open-label study of the therapeutic efficacy of high-dose famotidine adjuvant pharmacotherapy in schizophrenia: preliminary evidence for treatment efficacy. *Clin Neuropharmacol* 1996; **19:** 341–8.
4. Martinez MC. Famotidine in the management of schizophrenia. *Ann Pharmacother* 1999; **33:** 742–7.

Adverse Effects

As for Cimetidine, p. 1828.3. Unlike cimetidine, famotidine is reported to have little or no anti-androgenic effect, although there are isolated reports of gynaecomastia and impotence.

General references.

1. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; **18:** 36–54.

Precautions

As for Cimetidine, p. 1830.2.

Hepatic impairment. For a report of increased resistance to H_2-antagonists in patients with liver cirrhosis, see Cimetidine, p. 1830.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies famotidine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For information on the use of H_2-antagonists during pregnancy, see Cimetidine, p. 1830.3.

Interactions

Unlike cimetidine (see p. 1830.3) famotidine does not inhibit cytochrome P450 isoenzymes, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of drugs whose absorption is dependent on an acid gastric pH.

Antacids. For discussion of the effect of antacids on the bioavailability of H_2-antagonists including famotidine, see Cimetidine, p. 1831.1.

Probenecid. For mention of the reduced clearance of famotidine when given with probenecid, see Cimetidine, p. 1831.1.

Sucralfate. For information on the effect of sucralfate on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Theophylline. Although famotidine is considered not to interfere with the metabolism of other drugs there is a report of a clinically significant interaction with theophylline—see p. 1236.1.

Pharmacokinetics

Famotidine is readily but incompletely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring 1 to 3 hours after oral doses. The bioavailability of oral famotidine is about 40 to 45% and is not significantly affected by the presence of food.

The elimination half-life from plasma is reported to be about 3 hours and is prolonged in renal impairment (see also Administration in Renal Impairment, p. 1842.2). Famotidine is weakly bound, about 15 to 20%, to plasma proteins. A small proportion of famotidine is metabolised in the liver to famotidine *S*-oxide. About 25 to 30% of an oral dose, and 65 to 70% of an intravenous dose, is excreted unchanged in the urine, primarily by active tubular secretion. Famotidine is also found in breast milk.

Reviews.

1. Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. *Clin Pharmacokinet* 1991; **21:** 178–94.

Children. Famotidine 300 micrograms/kg intravenously was given to 10 children aged 2 to 7 years, after cardiac surgery and before extubation, to prevent aspiration.[1] This dose (equivalent to about 20 mg in adults) induced a rise in the intragastric pH within 1 hour of being given and the pH remained above 3.5 for about 9 hours. The mean elimination half-life was 3.3 hours, similar to the value in healthy adults and it was considered that doses in children need therefore only be adjusted according to body-weight and renal function. This conclusion was supported by a review of 8 studies in children over 1 year of age.[2] Conversely, in infants aged 5 to 19 days, the mean elimination half-life was prolonged (10.5 hours) secondary to reduced renal clearance.[3] This was confirmed by another study,[4] which indicated that reduced clearance was found in infants under 3 months of age, but that pharmacokinetics in older infants were similar to those previously reported for children and adults.

1. Kraus G, *et al*. Famotidine: pharmacokinetic properties and suppression of acid secretion in paediatric patients following cardiac surgery. *Clin Pharmacokinet* 1990; **18:** 77–81.
2. James LP, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in paediatric patients. *Clin Pharmacokinet* 1996; **31:** 103–10.
3. James LP, *et al*. Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 1998; **38:** 1089–95. Correction. *ibid*. 2000; **40:** 1298.
4. Wenning LA, *et al*. Pharmacokinetics of famotidine in infants. *Clin Pharmacokinet* 2005; **44:** 395–406.

Distribution into breast milk. The peak concentration of famotidine in breast milk, which occurred in 8 women 6 hours after a 40 mg oral dose, was similar to the peak plasma concentration, which occurred 2 hours after the dose.[1]

1. Courtney TP, *et al*. Excretion of famotidine in breast milk. *Br J Clin Pharmacol* 1988; **26:** 639P.

Enterohepatic recirculation. Some individuals have a second peak in the plasma concentration of famotidine, which could be due to enterohepatic recirculation. However, a maximum of 0.43% of a dose of famotidine was excreted in the bile of 2 patients after single doses of 20 mg intravenously or 40 mg orally indicating that significant recirculation had not occurred.[1]

1. Klotz U, Walker S. Biliary excretion of H_2-receptor antagonists. *Eur J Clin Pharmacol* 1990; **39:** 91–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ulcelac; ***Austral.***: Arfam; Ausfam; Famohexal†; Pamacid; Pepcidine; Pepzan; ***Austria***: Famohexal; Famosin; Sodexx Famotidine; Ulcusan; ***Braz.***: Famoset; Famotid; Famox; ***Canad.***: Acid Control; Maalox H_2 Acid Controller†; Pepcid; Peptic Guard; Ulcidine; ***Chile***: Anulcer; Gastrium; ***China***: An Wei Te (安威特); Bei Lan De (贝兰德); Bin Xin (滨欣); Bo La Kang Wei (博拉康唯); Ding Huan (丁缓); Duo An (道安); Duo Yi (朵颐); Gai Shi Te (盖世特); Gaster (高舒达); Jie Ke Da (捷可达); Kai Su Te (凯速特); Li Luo Lan (利洛兰); Lifuding (立复丁); Wei Tian (唯天); Wei Xin (维欣); Xinfading (信法丁); ***Cz.***: Famosan; Quamatel; Ulfamid; ***Fin.***: Pepcid; Pepcidin†; ***Fr.***: Pepcidac; Pepdine†; ***Ger.***: Fadul†; Famobeta; Famonerton†; Pepdul; ***Gr.***: Ansilan; Banatin; Cepal; Citilat; Esseldon; Gasterogen; Imposergon; Mostrelan; Panalba; Peptan; Rosagenus; Sedanium-R; Vexurat; ***Hong Kong***: Aulzadin†; Ausfam; Beilande; Facidin†; Fadine†; Famine†; Famocid†; Famodine†; Famolta; Famonox†; Famopsin†; Famotab†; Famotin; Famox; Gastrodomina†; Interfam; LAfamo†; Marmodine†; Motidine; Pepcidine; Phyzidin e; Quamatel†; Unicidine†; Vickmodine†; Vida Famodine†; ***Hung.***: Motidin; Quamatel; ***India***: Acilo; Acipep; Acredin; Autidine; Blocacid; Facid; Fadine; Faltidin; Famocid; Famodin; Famonext; Famonite; Famopril; Famotin; Famowal; Famtac; Famtin; Febcid; Femidin; Fontain; Fudone; Noctin; Ulcimax; ***Indon.***: Antidine; Corocyd; Denufam; Faberdin†; Facid; Famocid; Fluktan†; Gasfamin; Gaster; Gestofam; Ifamul†; Interfam; Lexmodine; Nulcefam; Pompaton; Pratifar; Promocid; Purifam†; Regastin; Renapepsa; Tismafam; Ulcerid; Ulfam†; Ulmo; ***Irl.***: Famulco†; Pepcid; ***Israel***: Famo; Gastro; Rogasti; ***Ital.***: Famodil; Gastridin; Motiax; ***Jpn***: Gaster; ***Malaysia***: Famodine; Famopsin; Pepcidine†; Pepzan; Ulceran; Voker; ***Mex.***: Adiatin; Androtin†; Durater; Fabutin†; Famoxal; Ludex†; Pepcidine; Sertidine; Ultidin; ***Neth.***: Pepcid†; Pepcidin†; ***Norw.***: Pepcid; Pepcidin†; ***NZ***: Famox; Pepzan; ***Philipp.***: Acrilo; Famorila; Famtine; H2 Bloc; Hista-Bloc; Modin; Motid; Pepcidine†; Peptodin; Ulcefam; ***Pol.***: Famidyna; Famogast; Quamatel; Ulfamid; ***Port.***: Fatidin†; Lasa; Pepcidina; ***Rus.***: Famocid (Фамоцид)†; Famonit (Фамонит)†; Famosan (Фамосан); Gastrosidin (Гастросидин); Quamatel (Квамател); Ulceran (Ульцеран)†; Ulfamid (Ульфамид); ***Singapore***: Famoc; Famodine; Famonit; Famopsin; Famotin; Famox†; Febcid; Motidine; Pepcidine; Pepzan; Sunpepcin; Ulceran; ***Spain***: Confobos†; Cronol; Digervin†; Eviantrina†; Fagastril†; Famulcer†; Gastrodomina†; Ingastri†; Nos†; Nulcerin; Nulcex; Pepcid; Tairal†; Tamin†; Tipodex†; Ulcetrax; Vagostal†; ***Swed.***: Pepcid; ***Thai.***: Agufam†; Fad; Famoc†; Famocid; Famonox; Famopac; Famopsin; Famosia; Famotab; Fasidine; Motidine†; Pepcidine†; Pepcine†; Pepdenal; Pepfamin; Peptoci; Pharmotidine; Ulceran; Ulfamet; Vesmotidine; ***Turk.***: Duovel; Fagastril; Famec; Famo; Famodin; Famogast; Famoser; Famotep; Famotsan; Gasterol; Gastifam; Gastrofam; Gastrosidin; Neotab; Nevofam; Notidin; Pepdif; Seskatidin; Ulcusar; ***UAE***: Famotec; ***UK***: Pepcid†; Ultra Heartburn Relief; ***Ukr.***: Famodinhexal (Фамодингексал)†; Quamatel (Квамател); ***USA***: Pepcid; ***Venez.***: Dinamot; Famogel; Famulcer; Isomina; Klinotal; Medalin; Neutracid; Ulcenol.

Multi-ingredient Preparations. ***Arg.***: Actual; Lyncis; Megalex Antiacido; Mylanta Extra; ***Canad.***: Pepcid Complete; ***China***: Jin Nuo (津诺); Shi Wei (仕卫); Wei Nuo Ping (唯诺平); WeiPing (谓屏); ***Fin.***: Pepcid Duo; ***Fr.***: Pepcidduo; ***Ger.***: Pepcidual†; ***India***: Diclosef; Dipal-F; Dompon F; Mefatin-Spas; Neutracaine; ***Indon.***: Antasida Plus Famotidine; Magard FA; Neosanmag; Polysilane Max; Promag Double Action; ***Irl.***: Pepcidtwo; ***Ital.***: Pepciddual; ***Mex.***: Facidex Total; Gex; ***Norw.***: Pepcidduo; ***Spain***: Pepdual†; ***Swed.***: Pepcid Duo; ***UK***: Pepcidtwo; ***Ukr.***: Gastromax (Гастромакс); ***USA***: Dual Action Complete; Pepcid Complete; Tums Dual Action.

Used as an adjunct in:. ***USA***: Duexis.

Pharmacopoeial Preparations

BP 2014: Famotidine Tablets;
USP 36: Famotidine for Oral Suspension; Famotidine Injection; Famotidine Tablets.

Fig

Carica; Ficus; Higo; Инжир; Фикус.
ATC Herb — HA06AX5004 (Ficus carica: fruit).
UNII — TGD87RII2U.

Pharmacopoeias. In *Br.* and *Swiss.*

BP 2014: (Fig). The sun-dried succulent fruit of *Ficus carica* containing not less than 60.0% of water-soluble extractive. Store in a dry place.

Profile

Fig is a mild laxative and demulcent usually used with other laxatives.

Effects on the skin. Skin reactions and photodermatitis have followed application of home-made decoctions of fig leaves to the skin.[1,2]

1. Ozdamar E, *et al*. An unusual cause of burn injury: fig leaf decoction used as a remedy for a dermatitis of unknown etiology. *J Burn Care Rehabil* 2003; **24:** 229–33.
2. Bassioukas K, *et al*. Erythrodermic phytophotodermatitis after application of aqueous fig-leaf extract as an artificial suntan promoter and sunbathing. *Contact Dermatitis* 2004; **51:** 94–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Carilax; Frugelletten; Neda Fruchtewurfel; ***Fr.***: Preservation; Resource Prunogil†; ***Ger.***: florabio Manna-Feigen†; ***Switz.***: Agarol Soft†; Dragees aux figues avec du sene; Fruttasan†; Pursana; Valverde Constipation dragees; Valverde Constipation sirop; ***UK***: Califig; Califig.

Homoeopathic Preparations. ***Fr.***: Poconeol no 79.

Fosaprepitant *(BAN, rINN)*

Fosaprépitant; Fosaprepitantum; Фозапрепитант.
{3-[((2*R*,3*S*)-2-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)morpholin-4-yl)methyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}phosphonic acid.
$C_{23}H_{22}F_7N_4O_6P$=614.4
CAS — 172673-20-0.
UNII — 6L8OF9XRDC.

Fosaprepitant Meglumine *(rINNM)*

Fosaprepitant Dimeglumide (BANM); Fosaprepitant Dimeglumine; Fosaprepitant meglumina; Fosaprépitant Méglumine; Meglumini Fosaprepitantum; MK-0517; Меглумина Фозапрепитант.
1-Deoxy-1-(methylamino)-D-glucitol {3-[((2*R*,3*S*)-2-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-4-morpholinyl)methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl} phosphonate.
$C_{23}H_{22}F_7N_4O_6P$, $2C_7H_{17}NO_5$=1004.8
CAS — 265121-04-8.
UNII — D35FM8T64X.

Stability. US licensed product information states that, once reconstituted and diluted as directed in sodium chloride 0.9%, a solution of fosaprepitant meglumine is stable for 24 hours at room temperature (at or below 25 degrees).

Uses and Administration

Fosaprepitant is a prodrug of the antiemetic aprepitant (p. 1819.2), which is a neurokinin-1 receptor antagonist. Fosaprepitant meglumine is used for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy. Doses are expressed in terms of the base; 188 mg of fosaprepitant meglumine is equivalent to about 115 mg of fosaprepitant. It is given intravenously 30 minutes before the start of chemotherapy, with a corticosteroid such as oral dexamethasone and a 5-HT_3 antagonist:

- *either* as a single intravenous dose equivalent to fosaprepitant 150 mg infused over 20 to 30 minutes on day 1 of the chemotherapy regimen
- *or* as an intravenous dose equivalent to fosaprepitant 115 mg infused over 15 minutes on day 1, followed by an oral dose of aprepitant 80 mg on days 2 and 3

The reconstituted dose of fosaprepitant is diluted in sodium chloride 0.9% to a final concentration of 1 mg/mL.

References.

1. Navari RM. Fosaprepitant (MK-0517): a neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Expert Opin Invest Drugs* 2007; **16:** 1977–85.
2. Van Belle SJP, Cocquyt V. Fosaprepitant dimeglumine (MK-0517 or L-785,298), an intravenous neurokinin-1 antagonist for the prevention of chemotherapy induced nausea and vomiting. *Expert Opin Pharmacother* 2008; **9:** 3261–70.

Adverse Effects and Precautions

As for Aprepitant, p. 1819.3.

Interactions

As for Aprepitant, p. 1820.1.

Pharmacokinetics

Fosaprepitant is rapidly converted to aprepitant; for the pharmacokinetics of aprepitant, see p. 1820.1.

Bioavailability. A pharmacokinetic study found fosaprepitant 115 mg by intravenous infusion to be bioequivalent to an oral dose of aprepitant 125 mg, suggesting that these doses could be used interchangeably (see Uses and Administration, above).[1]

1. Lasseter KC, *et al*. Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. *J Clin Pharmacol* 2007; **47:** 834–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Emend; ***Austria***: Ivemend; ***Canad.***: Emend; ***Cz.***: Ivemend; ***Denm.***: Ivemend†; ***Fr.***: Ivemend†; ***Ger.***: Ivemend; ***Gr.***: Ivemend; ***Irl.***: Ivemend; ***Israel***: Emend; ***Jpn***: Proemend; ***Neth.***: Ivemend; ***Norw.***: Ivemend; ***NZ***: Emend; ***Pol.***: Ivemend; ***Port.***: Ivemend; ***Singapore***: Emend; ***Spain***: Ivemend; ***Swed.***: Ivemend; ***Switz.***: Ivemend; ***UK***: Ivemend; ***USA***: Emend.

Frangula Bark

Alder Buckthorn Bark; Amieiro Negro; Bourdaine; Faulbaumrinde; Frángula, corteza de; Frangulabark; Frangulae cortex; Kora kruszyny; Krušinová kůra; Kutyabengekéreg; Paatsamankuori; Rhamni Frangulae Cortex; Šaltekšnių žievė; Kopa Крушины.
CAS — 8057-57-6 (frangula extract).
ATC Herb — HA06AB5013 (Rhamnus frangula: bark).
UNII — S2D77IH61R.

NOTE. The name Buckthorn Bark has also been used; distinguish Frangula Bark from Buckthorn (p. 1824.2) and from Sea Buckthorn (p. 2611.3).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Frangula Bark). The dried, whole or fragmented bark of the stems and branches of *Rhamnus frangula* (=*Frangula alnus*). It contains not less than 7.0% of glucofrangulins, expressed as glucofrangulin A ($C_{27}H_{30}O_{14}$ = 578.5) and calculated with reference to the dried drug. Protect from light.

Profile

Frangula bark is an anthraquinone stimulant laxative with actions and uses similar to those of senna (p. 1885.1).

Homoeopathy

Frangula bark has been used in homoeopathic medicines under the following names: Frangula; Rhamnus frangula; Rhamnus frang; Rham. fr.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Altra; Figura 2; Normolax; ***Switz.***: Arkocaps Bourdaine; Elixir frangulae compositum.

Multi-ingredient Preparations. ***Arg.***: Gastricur; ***Austral.***: Normacol Plus; ***Austria***: Artin†; Laxalpin†; Mag Kottas Krauterexpress Abfuhrtee; Planta Lax; ***Canad.***: Bilonat; Formula T5 Tea†; Herbal Laxative†; Kalenite†; Laxatil; Laxolax; Linoforce; ***Cz.***: Cholagol; Reduktan; The Salvat; ***Denm.***: Ferroplex-frangula; ***Fr.***: Boldoflorine; Boribel Tisane No 13†; Dragees Fuca; Dragees Vegetales Rex; Tonilax; Yerbalaxa; ***Gr.***: Normacol Plus; ***Hong Kong***: Hepatofalk†; Normacol Plus†; ***Hung.***: Cholagol; ***India***: Kanormal†; ***Irl.***: Normacol Plus; ***Israel***: Rekiv†; ***Ital.***: Alosen†; Draverex; Estilax; Fave di Fuca; Ginolax; Lactolas; ***Neth.***: Roteroblong Maagtabletten; ***NZ***: Granocol†; Normacol Plus; ***Pol.***: Alax; Cholavisol; Cholesol; Gastro†; Laxantol†; Normosan†; Rhelax; Senalax K; Tabletki Przeciw Niestrawnosci; Tabulettae Laxantes; ***Port.***: Normacol Plus; ***Rus.***: Vicair (Викаир); ***S.Afr.***: Normacol Plus; ***Singapore***: Normacol Plus; ***Spain***: Fave de Fuca; Favilax; Fucapan; Laxodiex; LinoMed; ***Switz.***: Colosan plus; Lapidar 10; Linoforce; LinoMed; Padma-Lax; Padmed Laxan; Phyto-Laxia†; ***UK***: Herbulax; Linoforce; Lustys Herbalene; Natravene; Normacol Plus; ***Ukr.***: Vicair (Викаир); Vicalin (Викалин).

Homoeopathic Preparations. ***Canad.***: Homeo-Form S†; Vegetal Tonic; Weight Control; ***Fr.***: Digeoslor; Tonique Vegetal.

Pharmacopoeial Preparations

Ph. Eur.: Frangula Bark Dry Extract, Standardised.

Gefarnate *(BAN, rINN)*

DA-688; DE-099; Géfarnate; Gefarnato; Gefarnatum; Geranyl Farnesylacetate; Гефарнат.

A mixture of stereoisomers of 3,7-dimethylocta-2,6-dienyl 5,9,13-trimethyltetradeca-4,8,12-trienoate.

$C_{27}H_{44}O_2$=400.6

CAS — 51-77-4.

ATC — A02BX07.

ATC Vet — QA02BX07.

UNII — 1ISE2Y6ULA.

Profile

Gefarnate is a cytoprotective that has been used in the treatment of peptic ulcer disease and gastritis. An ophthalmic preparation is under investigation for the treatment of corneal and conjunctival epithelial disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Wycakon-G (惠加强-G); ***Jpn***: Gefanil.

Ginger

Gengibre; Gingembre; Gyömbér gyökértörzs; Imbierų šakniastiebiai; Ingefära; Ingwer; Ingwerwurzelstock; Inkivääri; Jengibre; Zázvorový oddenek; Zingib.; Zingiber; Zingiberis rhizoma; Имбирь.

ATC Herb — HM01AW5029 (Zingiber officinale: rhizome); HC01EB5024 (Zingiber officinale: rhizome); HA04WX5004 (Zingiber officinale: rhizome); HA03AW5067 (Zingiber officinale: rhizome); HA09WX5003 (Zingiber officinale: rhizome).

UNII — C5529G5JPQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *US* also includes the powdered form.

Ph. Eur. 8: (Ginger). The dried, whole or cut rhizome of *Zingiber officinale*, with the cork removed, either completely or from the wide flat surfaces only. Whole or cut, it contains not less than 1.5% of essential oil, calculated with reference to the anhydrous drug. It has a characteristic aromatic odour. Protect from light.

The BP 2014 states that ginger may be known in commerce as unbleached ginger.

USP 36: (Ginger). The scraped, partially scraped, or unscraped rhizome of *Zingiber officinale* (Zingiberaceae), known in commerce as unbleached ginger. It contains not less than 4.5% of alcohol-soluble extractive and not less than 10% of water-soluble extractive. Store at 8 degrees to 15 degrees. Protect from light and moisture.

Profile

Ginger has carminative properties. It is used as a flavouring agent and has been tried for the prophylaxis of motion sickness and nausea and vomiting in pregnancy, although it does not seem to be effective for postoperative nausea and vomiting (p. 1811.3).

Ginger oil is used in aromatherapy.

Homoeopathy

Ginger has been used in homoeopathic medicines under the following names: Zingiber; Zingiber officinale; Zing.

General reviews.

1. Afzal M, *et al*. Ginger: an ethnomedical, chemical and pharmacological review. *Drug Metabol Drug Interact* 2001; **18:** 159–90.
2. Chrubasik S, *et al*. Zingiberis rhizoma: a comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* 2005; **12:** 684–701.
3. Shukla Y, Singh M. Cancer preventive properties of ginger: a brief review. *Food Chem Toxicol* 2007; **45:** 683–90.
4. Ali BH, *et al*. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research. *Food Chem Toxicol* 2008; **46:** 409–20.
5. Nicoll R, Henein MY. Ginger (Zingiber officinale Roscoe): a hot remedy for cardiovascular disease? *Int J Cardiol* 2009; **131:** 408–9.

Nausea and vomiting. Ginger has been widely used as an antiemetic, although good evidence of efficacy has sometimes been rather scanty.

Systematic reviews and meta-analyses.

1. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth* 2000; **84:** 367–71.
2. Betz O, *et al*. Ist Ingwer ein klinisch relevantes Antiemetikum? Eine systematische übersicht randomisierter kontrollierter Studien. *Forsch Komplementarmed Klass Naturheilkd* 2005; **12:** 14–23.
3. Chaiyakunapruk N, *et al*. The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. *Am J Obstet Gynecol* 2006; **194:** 95–9.

Osteoarthritis. A report that included information from 3 randomised studies found oral ginger to have moderately beneficial effects in reducing pain and disability in osteoarthritis patients.[1]

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 15/06/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: EziTravel†; Travacalm Natural; ***Austria***: Zintona; ***Canad.***: Gravol Natural Source; ***Ger.***: Zintona; ***Ital.***: Novomit; ***Pol.***: Zingibir; ***Rus.***: Avioplant (Авиоплант); ***UK***: Puncto Digest; Puncto Travel; Tradimed; Travel Sickness; Zinaxin; ***Ukr.***: Avioplant (Авиоплант)†.

Multi-ingredient Preparations. ***Austral.***: AB Carsa Giox; AB Oriostin; Airborne Immunity; Arthro-Eze; Asa Right Powder†; Bioflex†; Boswellia Complex; Boswellia Compound; Broncafect; Cal Alkyline†; Cramplex; Curcuminoid; DiaCo; Digest Aid; DiGest; Digestive Aid; Dyzco†; Extralife Arthri-Care†; Fe-Max; Feminine Herbal Complex; Ginger-Vite Forte†; Mindac; Morning Sickness Formula; Natal Plus; Peritone; PM Meno-Care; Psylli-Mucil Plus†; ResCo; Vegie Digestaid; ***Austria***: Klosterfrau Melissengeist; Mariazeller; Pervivo; ***Braz.***: Broncol†; ***Canad.***: Laxolax Phyto†; ***Cz.***: Klosterfrau Melisana; ***Fr.***: Aromadigest†; Aromavital†; Cuivramine; Doluperine; Evacrine; Fibromyalgine; Phytemag; Trikatu; ***Ger.***: Gallexier; Gastrysat†; Klosterfrau Melissengeist; ***Hong Kong***: Magesto; ***Hung.***: Antifront; Antifront; Bittner; Herbadict; Klosterfrau Melisana; Munipyrin; Travelon; ***India***: Abana; Aglotus; Aptizooom; Arthopack; Artrex; Carmicide; Cephagraine; Cephagraine; EC-Morning; Evepearl-PMS; Happy'tizer†; Nicy Days; Papytazyme; Tummy Ease†; ***Indon.***: Afomix; Avogin; Pectum; Pregnasea; Prenatal EM; Vitamam I; Vomil; ***Irl.***: Seven Seas Active Sport†; ***Israel***: Emetics; ***Ital.***: Donalg; Lik-Gel†; Lozione Same Urto; No Gas Enzimi; Pik Gel; ***Jpn***: Bofutsushosan; Boiogito; Bukuryoin; Bukuryoingohangekobokuto; Chikujountanto; Chotosan; Daibofuto; Daikenchuto; Daisaikoto; Eppikajutsuto; Goshakusan; Goshuyuto; Hainosankyuto; Hangebyakujutsutemmato; Hangekobokuto; Hangeshashinto; Heiisan; Hochuekkito; Ireito; Jinsoin; Jumihaidokuto; Kakkonto; Kakkontokasenkyushin'i; Kamikihito; Kamishoyosan; Keishikajutsubuto; Keishikaryukotsuboreito; Keishikashakuyakudaioto; Keishikashakuyakuto; Keishininjinto; Keishito; Kihito; Kososan; Nichinto; Nijutsuto; Ninjinto; Ogikenchuto; Orento; Rikkunshito; Ryokankyomishingeninto; Ryokyojutsukanto; Saibokuto; Saikanto; Saikokaryukotsuboreito; Saikokeishikankyoto; Saikokeishito; Saireito; Seihaito; Shakanzoto; Shikunshito; Shimbuto; Shohangekabukuryoto; Shokenchuto; Shomakakkonto; Shosaikoto; Shosaikotokakikyosekko; Shoseiryuto; Sokeikakketsuto; Tokikenchuto; Tokishigyakukagoshuyushokyoto; Tokito; Unkeito; ***Malaysia***: Strepsils Cough Lozenge†; Strepsils Cough Syrup†; ***Philipp.***: Bo-D-Fense†; Ruflex; ***Pol.***: Melisana Klosterfrau; Pervivo; ***Rus.***: Dipana (Дипана); Doktor Mom (Доктор Мом); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Sodecor (Содекор); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); Zinaxin (Зинаксин); ***S.Afr.***: Helmontskruie†; Lewensessens; Wonderkroonessens; ***Singapore***: Artrex; Ruflex; Strepsils Cough Lozenge (with natural herbs); Strepsils Cough Syrup†; ***Switz.***: Padma-Lax; Padmed Laxan; Tisane pour les problemes de prostate; Wala Elixir amer; ***Thai.***: Carminative Patar; Carminative Sahakarn; Caryopin; Corisul; Flataco; Flatulence†; Magesto; Mesto-Of; Mist Carminative; Patarsul; Zinaxin Plus†; ***UK***: Arheumacare; Digestive; HRI Golden Seal Digestive; Indian Brandee; Indigestion Relief; Jointace; Neo Baby Gripe Mixture; Neo Gripe Mixture; Wind & Dyspepsia Relief; Zinopin; ***Ukr.***: Antifront (Антифронт); Antifront (Антифронт); Apitol (АПИТОЛ); Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Bronchomed (Бронхомед); Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Ektis (Эктис); Lipomin (Липомин); Liponorm (Липонорм); Maraslavin (Мараславин); Memory Booster (Мемори Бустер); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Travisil (Трависил); Trypsidan (Трипсидан)†; Vitrum Beauty Elite (Витрум Бьюти Элит); Zinaxin (Зинаксин); ***USA***: B-Nexa; Prenate AM with Quatrefolic; VP-GGR-B6; ***Venez.***: Ervossil; Jengimiel Sabila; Jengimiel; Jengimiel.

Pharmacopoeial Preparations

BP 2014: Aromatic Cardamom Tincture; Strong Ginger Tincture; Weak Ginger Tincture;

USP 36: Ginger Capsules; Ginger Tincture.

Granisetron Hydrochloride

(BANM, USAN, rINNM)

BRL-43694A; Granisétron, chlorhydrate de; Granisetrón, hidrocloruro de; Granisetron-hydrochlorid; Granisetronhydrochlorid; Granisetronhydroklorid; Granisetroni Hydrochloridum; Granisetronihydrokloridi; Granisetrono hidrocloridas; Hidrocloruro de granisetrón; Гранисетрона Гидрохлорид.

1-Methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide hydrochloride.

$C_{18}H_{24}N_4O$, HCl=348.9

CAS — 109889-09-0 (granisetron); 107007-99-8 (granisetron hydrochloride).

ATC — A04AA02.

ATC Vet — QA04AA02.

UNII — 318F6L70J8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Granisetron Hydrochloride). A white or almost white powder. Freely soluble in water; sparingly soluble in dichloromethane; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 6.5.

USP 36: (Granisetron Hydrochloride). A white or almost white powder. Freely soluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 6.5. Protect from light.

Uses and Administration

Granisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p. 1872.2). It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of postoperative nausea and vomiting (p. 1811.3). Granisetron is given as the hydrochloride, but doses are expressed in terms of the base. Granisetron hydrochloride 1.1 mg is equivalent to about 1 mg of granisetron base. The efficacy of granisetron may be enhanced by the use of corticosteroids such as dexamethasone or methylprednisolone.

For acute **nausea and vomiting** associated with **chemotherapy** granisetron is used in *prevention* and *treatment* in similar doses.

In the UK, a dose equivalent to 1 or 3 mg of granisetron as a 1 mg/mL solution is given intravenously within 30 minutes before the start of chemotherapy, either diluted in 20 to 50 mL of a suitable infusion solution and given over 5 minutes, or added to 4 times its own volume of infusion solution and given as a bolus over at least 30 seconds. Any further doses should be given at least 10 minutes apart. The recommended oral dose is 1 to 2 mg within one hour before therapy begins, then 2 mg daily as a single dose or in 2 divided doses for up to 1 week after chemotherapy. The total maximum dose by any route in 24 hours is granisetron 9 mg.

In the USA, lower intravenous doses of the equivalent of granisetron 10 micrograms/kg are recommended, beginning within 30 minutes before chemotherapy. Oral doses are similar to those described for the UK above: a single dose of

2 mg may be given up to 1 hour before chemotherapy, or, alternatively, 1 mg can be taken up to 1 hour before chemotherapy with another dose of 1 mg 12 hours later. Granisetron is given only on the days that chemotherapy is administered.

Granisetron can also be delivered transdermally to prevent nausea and vomiting caused by moderately or highly emetogenic chemotherapy. One patch supplying 3.1 mg granisetron per 24 hours is applied to the upper arm 24 to 48 hours before chemotherapy and removed at least 24 hours after chemotherapy ends. The patch can be worn for up to 7 days.

For the *prevention* of nausea and vomiting associated with **radiotherapy** the recommended oral dosage is 2 mg daily taken within 1 hour of irradiation. The drug is also given intravenously for the *treatment and prevention* of nausea and vomiting associated with radiotherapy, in the same doses as those recommended above for emetogenic chemotherapy in the UK.

For doses in children, see below.

For the *prevention* of **postoperative** nausea and vomiting 1 mg is diluted to 5 mL and given before the induction of anaesthesia by slow intravenous injection. For *treatment*, the same dose may be repeated up to a maximum of 3 mg in 24 hours.

Intranasal formulations of granisetron are under investigation.

References.

1. Adams VR, Valley AW. Granisetron: the second serotonin-receptor antagonist. *Ann Pharmacother* 1995; **29:** 1240–51. Correction. *ibid.* 1996; **30:** 1043.
2. Blower PR. Granisetron: relating pharmacology to clinical efficacy. *Support Care Cancer* 2003; **11:** 93–100.
3. Minami M. Granisetron: is there a dose-response effect on nausea and vomiting? *Cancer Chemother Pharmacol* 2003; **52:** 89–98.
4. Prentice HG. Granisetron in the control of nausea and vomiting associated with bone marrow transplantation: a review of its efficacy and tolerability. *Support Care Cancer* 2003; **11:** 501–8.
5. Corman SL, *et al.* Low-dose granisetron for postoperative nausea and vomiting prophylaxis. *Ann Pharmacother* 2004; **38:** 710–13.
6. Goldsmith B. First choice for radiation-induced nausea and vomiting—the efficacy and safety of granisetron. *Acta Oncol* 2004; **43** (suppl 15): 19–22.
7. Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. *Oncologist* 2004; **9:** 673–86.
8. Duggan ST, Curran MP. Transdermal granisetron. *Drugs* 2009; **69:** 2597–2605.

Administration in children. In the UK and USA, granisetron hydrochloride is licensed for use in children from 2 years of age for the management of acute nausea and vomiting associated with chemotherapy. Similar doses are used for both prevention and treatment.

- An intravenous infusion equivalent to granisetron 10 to 40 micrograms/kg, up to a maximum of 3 mg is given before the start of chemotherapy; doses should be diluted in 10 to 30 mL of infusion fluid, and given over 5 minutes. One additional dose may be given within 24 hours, but at least 10 minutes after the original infusion.
- The *BNFC* suggests that granisetron can also be given to children aged from 1 month; doses are as for those used in older children.

Oral granisetron may be given to children from 12 years of age; the adult dose can be used, see p. 1844.3.

Although not licensed in the UK, the *BNFC* recommends that similar intravenous doses to those given above can be used for both the treatment and prevention of radiotherapy-induced nausea and vomiting in children from 1 month and over.

Pain. For reference to the use of granisetron in various painful syndromes see under Uses and Administration of Ondansetron, p. 1873.1

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2, although no dosage reduction is considered necessary in renal or hepatic impairment.

Carcinogenicity. The manufacturer (*Roche*) has reported an increased incidence of hepatic neoplasms in *rodents* given very high doses of granisetron for prolonged periods, but the clinical relevance of these results is unknown. Although mutagenicity and genotoxicity have not been seen in some tests, others have reported an increased incidence of polyploidy or unscheduled DNA synthesis in exposed cells.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies granisetron as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

The metabolism of granisetron is induced by phenobarbital.

Pharmacokinetics

Granisetron is rapidly absorbed after oral doses and peak plasma concentrations occur after about 2 hours. Oral bioavailability is about 60% as a result of first-pass hepatic metabolism. Granisetron has a large volume of distribution of around 3 litres/kg; plasma protein binding is about 65%. The pharmacokinetics exhibit considerable interindividual variation, and the elimination half-life after an intravenous dose is reported to be around 4 to 5 hours in healthy subjects but about 9 to 12 hours in cancer patients. It is metabolised in the liver, primarily by *N*-demethylation, with less than 20% of a dose recovered unchanged in urine, the remainder being excreted in faeces and urine as metabolites. Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aludal; Granitron; ***Austral.***: Kytril; ***Austria***: Granitron; Kytril; ***Belg.***: Kytril; ***Braz.***: Kidazom; Kytril; ***Canad.***: Kytril; ***Chile***: Kytril; ***China***: An Si Ping (安斯平); Ba Tai (巴泰); Bai Hong (百宏); BiLi (比立); Da Fen Ke Quan (达芬可泉); Da Sheng Xin Er (大生欣尔); Ge Nai Ya (格奈雅); Ge Ou Shu (格欧舒); Ge Rui Tong (格瑞同); Gudi (古迪); Jie Dan (洁丹); Jun Kai (君凯); KangXin (康欣); Ke Rui Qi (珂瑞琦); Kytril (凯特瑞); Lai Qi (莱琪); Lei Sai Long (雷赛隆); Ling Ding (凌顶); Mei Fu Qiong (美芙琼); Ou Ke Ning (欧可宁); Ou Pu Ding (欧普定); Ou Zhi Ning (欧智宁); Pa Rui Da (帕瑞达); Qi Ke Ou (奇克欧); Qiong Sha Ao (琼沙奥); Run Dan (润丹); Sheng Jin Nuo (盛金诺); Shu Er Zhi (舒尔止); Si Nuo Kang Xin (斯诺康欣); Sulingqiong (苏令琼); Tu Ting (图婷); Wei Kun (唯坤); Xin Ge (新革); Yi Ge (伊格); YiXin (怡新); Zuo Tan (佐坦); Zuxin (枢星); ***Cz.***: Emegar; Granegis; Grateva; Kytril; ***Denm.***: Kytril†; ***Fin.***: Kytril; ***Fr.***: Kytril; ***Ger.***: Axigran; Kevatril; Ribosetron; ***Gr.***: Dialgyl; Granitron; Granitryl; Kytril; Toribix; ***Hong Kong***: Kytril; ***Hung.***: Granegis; Granigen; Kytril; ***India***: Cadigran; Emegran; Grandem; Granicip; Graniforce; Graniset; Granisol; Granitero; Nisley; ***Indon.***: Granon; Kytril; ***Irl.***: Kytril; ***Israel***: Kytril; Setron; ***Ital.***: Kytril; ***Jpn***: Kytril; ***Malaysia***: Kytril; ***Mex.***: Kogra; Kytril; Vogracen; ***Neth.***: Kytril; ***NZ***: Kytril†; ***Philipp.***: Kytril; Sancuso; ***Port.***: Kytril; ***Rus.***: Kytril (Китрил); Notirol (Нотирол); ***S.Afr.***: Granicip; Granitril; Kytril; ***Singapore***: Kytril; ***Spain***: Kytril; ***Swed.***: Kytril; ***Switz.***: Kytril; ***Thai.***: Kytril; ***Turk.***: Emetril; Granexa; Kytril; Neoset; Setron; Sinarex; ***UK***: Kytril; Sancuso; ***Ukr.***: Granitron (Гранитрон); Vomitran (Вомитран); ***USA***: Granisol; Kytril†; Sancuso; ***Venez.***: Granicip; Kytril; Rubrum.

Pharmacopoeial Preparations
USP 36: Granisetron Hydrochloride Injection; Granisetron Hydrochloride Oral Suspension; Granisetron Hydrochloride Tablets.

Hydrotalcite *(BAN, rINN)*

Hidrotalcita; Hidrotalsit; Hydrotalcit; Hydrotalcitum; Hydrotalsiitti; Гидроталцит.

Aluminium magnesium carbonate hydroxide hydrate.

$Mg_6Al_2(OH)_{16}CO_3,4H_2O$=604.0

CAS — 12304-65-3.

ATC — A02AD04.

ATC Vet — QA02AD04.

UNII — 17432CG1KU.

NOTE. Compounded preparations of hydrotalcite may be represented by the following names:

- Co-simalcite *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

Pharmacopoeias. In *Br.*

BP 2014: (Hydrotalcite). A hydrated form of an aluminium magnesium basic carbonate corresponding to the formula $Al_2Mg_6(OH)_{16}CO_3,4H_2O$. It contains not less than 15.3% and not more than 18.7% of Al_2O_3 and not less than 36.0% and not more than 44.0% of MgO. The ratio of Al_2O_3 to MgO is not less than 0.40 and not more than 0.45. A white or almost white, free-flowing, granular powder. Practically insoluble in water; it dissolves in dilute mineral acids with slight effervescence. A 4% suspension in water has a pH of 8.0 to 10.0.

Profile

Hydrotalcite is an antacid (see p. 1803.1) that is given in oral doses of up to about 1 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Talcid; Talidat; ***China***: An Da (安达); Hai Di Te (海地特); Tai Er Sai Ke (泰尔赛克); Talcid (达喜); Wei Di Mei (威地美); Wei Tai (唯泰); ***Cz.***: Rutacid; Talcid; Talidat; ***Fr.***: Rennieliquo; ***Ger.***: Ancid†; Megalac; Talcid; Talidat; ***Gr.***: Talcid; ***Hung.***: Talcid; Tisacid; ***Malaysia***: Swecon; ***Mex.***: Talcid; ***Neth.***: Ultacit; ***Philipp.***: Gaspen; ***Pol.***: Malgacid; Rutacid†; Talcid; Ulcetal; ***Port.***: Talcid†; ***Rus.***: Rutacid (Рутацид); Talcid (Тальцид); Tisacid (Тисацид); ***S.Afr.***: Altacite†; ***Spain***: Talcid†; ***Switz.***: Rennie Gel; ***Turk.***: Hidrasit; Medalcite; Talcid.

Multi-ingredient Preparations. ***Indon.***: Promag; ***Jpn***: Cabe 2 New; Eki Cabe S; Eki Cabe U; ***Philipp.***: Simeco; ***Rus.***: Gastal (Гастал); ***UK***: Altacite Plus.

Pharmacopoeial Preparations
BP 2014: Hydrotalcite Tablets.

Hyoscine *(BAN)*

Escopolamina; Hioscina; Hioscyna; Hyoscin; Hyoscinum; Hyoskiini; Scopolamin; Scopolamine; Scopolaminum; Skopolamiini; Skopolamin; Skopolamina; Tropato de epoxitropina; Гиосцин.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*s*)-6,7-Epoxy-3[(*S*)-tropoyloxy] tropane.

$C_{17}H_{21}NO_4$=303.4

CAS — 51-34-3.

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.

UNII — DL48G20X8X.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of hyoscine:

Burundanga.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hyoscine). A white or almost white, crystalline powder or colourless crystals. M.p. 66 degrees to 70 degrees. Soluble in water; freely soluble in alcohol.

Hyoscine Butylbromide *(BANM)*

Butilbromuro de hioscina; Butylscopolamine Bromide; Butylscopolaminii Bromidum; Butylscopolaminiumbromid; *N*-Butylscopolammonium Bromide; Butylscopolamonii Bromidum; Butylskopolaminium-bromid; Escopolamina, butilbromuro de; Hioscino butilbromidas; Hioszcin-butilbromid; Hiyosin Bütilbromür; Hyoscinbutylbromid; Hyoscine-*N*-butyl Bromide; Hyoscini Butylbromidum; Hyoskiinibutyylibromidi; Scopolamine *N*-Butyl Bromide; Scopolamine Butylbromide; Scopolamine, butylbromure de; Scopolamini Butylbromidum; Scopolomini Butylbromidum; Skopolamino butilbromidas; Szkopolamin-butilbromid; Гиосцина Бутилбромид.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*r*)-6,7-Epoxy-8-butyl-3-[(*S*)-tropoyloxy]tropanium bromide.

$C_{21}H_{30}BrNO_4$=440.4

CAS — 149-64-4.

ATC — A03BB01.

ATC Vet — QA03BB01.

UNII — 0GH9JX37C8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Hyoscine Butylbromide). A white or almost white, crystalline powder. Freely soluble in water and in dichloromethane; sparingly soluble in dehydrated alcohol. A 5% solution in water has a pH of 5.5 to 6.5.

Hyoscine Hydrobromide *(BANM)*

Bromhidrato de Escopolamina; Escopolamina, hidrobromuro de; Hidrobromuro de hioscina; Hioscino hidrobromidas; Hioscyny bromowodorek; Hioszcin-hidrobromid; Hiyosin Hidrobromür; Hyoscinhydrobromid; Hyoscini Hydrobromidum; Hyoskiinihydrobromidi; Ioscina Bromidrato; Scopolamine Bromhydrate; Scopolamine, bromhydrate de; Scopolamine Hydrobromide; Scopolaminhydrobromid; Scopolamini Hydrobromidum; Scopolamini Hydrobromidum Trihydricum; Skopolamiinihydrobromidi; Skopolaminbromid trihydrát; Skopolaminhydrobromid; Skopolamino hidrobromidas; Szkopolamin-butilbromid; Гиосцина Гидробромид.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxytropan-3-yl (*S*)-tropate hydrobromide trihydrate.

$C_{17}H_{21}NO_4$,HBr,3H_2O=438.3

CAS — 114-49-8 (anhydrous hyoscine hydrobromide); 6533-68-2 (hyoscine hydrobromide trihydrate).

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.

UNII — 451IFR0GXB.

NOTE. HYO is a code approved by the BP 2014 for use on single unit doses of eye drops containing hyoscine hydrobromide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Hyoscine Hydrobromide). A white or almost white, efflorescent, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Store in well-filled airtight containers of small capacity. Protect from light.

USP 36: (Scopolamine Hydrobromide). Colourless or white crystals, or white granular powder. Is odourless and slightly efflorescent in dry air. Soluble 1 in 1.5 of water and 1 in 20 of alcohol; slightly soluble in chloroform; insoluble in ether. pH of a 5% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Hyoscine Methobromide *(BAN)*

Epoxymethamine Bromide; Escopolamina, metilbromuro de; Hyoscine Methylbromide; Methscopolamine Bromide; Metilbromuro de hioscina; Metobromuro de escopolamina; Metobromuro de hioscina; Scopolamine Methobromide; Scopolamine Methylbromide; Гиосцина Метобромид.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxy-8-methyl-3-[(*S*)-tropoyloxy]tropanium bromide.

$C_{18}H_{24}BrNO_4$=398.3

CAS — *155-41-9.*

ATC — *A03BB03; S01FA03.*

ATC Vet — *QA03BB03; QS01FA03.*

UNII — *RTN51LK7WL.*

Pharmacopoeias. In *US*.

USP 36: (Methscopolamine Bromide). Store in airtight containers. Protect from light.

Hyoscine Methonitrate *(BANM)*

Escopolamina, metilnitrato de; Hyoscine Methylnitrate; Methscopolamine Nitrate; Methylhyoscini Nitras; Methylscopolamine Nitrate; Methylscopolamini Nitras; Metilnitrato de hioscina; Metonitrato de escopolamina; Metonitrato de hioscina; Metylskopolaminnitrat; Metyyliskopolamiininitraatti; Scopolamine Methonitrate; Scopolamine Methylnitrate; Гиосцина Метонитрат.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxy-8-methyl-3-[(*S*)-tropoyloxy]tropanium nitrate.

$C_{18}H_{24}N_2O_7$=380.4

CAS — *6106-46-3.*

ATC — *A03BB03; S01FA03.*

ATC Vet — *QA03BB03; QS01FA03.*

UNII — *K0813KQM3V.*

Uses and Administration

Hyoscine is a tertiary amine antimuscarinic with central and peripheral actions (see Action of Antimuscarinics, p. 1310.3). It is a more powerful suppressant of salivation than atropine, and usually slows rather than increases heart rate, especially in low doses. Its central action differs from that of atropine in that it depresses the cerebral cortex and produces drowsiness and amnesia. Hyoscine hydrobromide is also a tertiary amine, whereas hyoscine butylbromide, hyoscine methobromide, and hyoscine methonitrate are quaternary ammonium derivatives.

Hyoscine and hyoscine hydrobromide are used in the management of motion sickness and other forms of nausea and vomiting (below); hyoscine hydrobromide is also given as a premedicant in anaesthesia (below), and to produce mydriasis and cycloplegia (below). Hyoscine butylbromide and other quaternary ammonium derivatives are used in conditions associated with visceral spasms. Hyoscine methobromide has also been employed as an adjunct in the treatment of peptic ulcer disease (below).

Other hyoscine salts or derivatives that have been used include hyoscine borate, hyoscine hydrochloride, and hyoscine oxide hydrobromide.

Anaesthesia. The role of antimuscarinics, including hyoscine, in anaesthesia is discussed under Atropine on p. 1311.1. For the use of hyoscine in the prevention of postoperative nausea and vomiting, see below.

For premedication hyoscine hydrobromide is injected subcutaneously or intramuscularly in doses of 200 to 600 micrograms, usually with papaveretum about half to one hour before induction of general anaesthesia. In the UK, a dose of 15 micrograms/kg is licensed in children (the *BNFC* suggests that this dose is appropriate from 1 to 12 years of age; older children may be given the adult dose). If necessary for acute use, the same doses may be given by intravenous injection.

Anoxic seizures. For mention of the use of transdermal hyoscine as an alternative to atropine in the management of reflex anoxic seizures in children, see p. 1311.3.

Biliary and renal colic. Hyoscine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p. 6.3) although the evidence for such use is weak. Hyoscine butylbromide 20 mg is given by intramuscular or slow intravenous injection; this may be repeated after 30 minutes if necessary to a maximum daily dose of 100 mg. See also Palliative Care, below.

References.

1. Holdgate A, Oh CM. Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol (Baltimore)* 2005; **174:** 572–5.

Cardiac disorders. Although hyoscine is not one of the conventional therapies for heart failure (p. 1262.3) or myocardial infarction (p. 1257.1), low-dose transdermal hyoscine can increase cardiac vagal activity and thereby reduce the autonomic imbalance seen in patients with these conditions.[1-3] Improved exercise tolerance has been reported after 1 week of treatment with transdermal hyoscine in a small open study in 14 patients with mild to moderate heart failure.[4]

1. Casadei B, *et al.* Low doses of scopolamine increase cardiac vagal tone in the acute phase of myocardial infarction. *Circulation* 1993; **88:** 353–7.
2. La Rovere MT, *et al.* Scopolamine improves autonomic balance in advanced congestive heart failure. *Circulation* 1994; **90:** 838–43.
3. Venkatesh G, *et al.* Double blind placebo controlled trial of short term transdermal scopolamine on heart rate variability in patients with chronic heart failure. *Heart* 1996; **76:** 137–43.
4. De Vecchis R, *et al.* Different impact of carvedilol and transdermal scopolamine on cardiovascular performance of mild-moderate chronic heart failure patients: evidence of useful effects of scopolamine on tolerance to work load. *Minerva Cardioangiol* 2000; **48:** 393–401.

Depression. Rapid reductions in severity of depression were seen after intravenous hyoscine hydrobromide 4 micrograms/kg was given to patients with major depressive disorders or bipolar disorders (see Depression, p. 398.1). Repeat doses showed more benefit than single doses. Clinical effects persisted beyond the treatment period, which led the authors to conclude the effects were not due to anticholinergic euphoria. While noting that the optimal schedule and potential long-term use of hyoscine as an antidepressant needed further study, they also concluded that hyoscine could be a relatively safe and well-tolerated intervention for achieving a rapid initial antidepressant response.[1]

1. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 2006; **63:** 1121–9.

Dysmenorrhoea. Hyoscine as the butylbromide or hydrobromide has been used for its antispasmodic action in the treatment of dysmenorrhoea. (p. 8.2), but the *BNF* considers that antispasmodics do not generally provide significant relief.

Eye disorders. Hyoscine hydrobromide is used in the eye for its mydriatic and cycloplegic actions (p. 2000.2) usually in a concentration of 0.25%. It has a faster onset and shorter duration of action than atropine although the effects may still persist for up to 3 to 7 days. It may be useful for patients who are hypersensitive to atropine.

Hyperhidrosis. Adverse effects of antimuscarinics given orally generally preclude their use by this route for the management of hyperhidrosis (p. 1685.1), but some, such as hyoscine, have been applied topically as alternatives to aluminium salts. Hyoscine hydrobromide applied as a 3% cream was successful in reducing gustatory sweating, consisting of flushing and sweating over the right mandible during eating, in a patient who had previously undergone surgical excision of the right submandibular salivary gland.[1] The use of transdermal or injectable hyoscine was reported[2] to be effective for the control of opioid-associated sweating in 2 patients receiving palliative care (see also below for other uses of hyoscine in palliative care).

1. Bailey BMW, Pearce DE. Gustatory sweating following submandibular salivary gland removal. *Br Dent J* 1985; **158:** 17–18.
2. Mercadante S. Hyoscine in opioid-induced sweating. *J Pain Symptom Manage* 1998; **15:** 214–15.

Nausea and vomiting. Hyoscine is effective in the prevention of **motion sickness** and is one of the principal drugs used. It may be given orally for short-term protection or by transdermal patch for a prolonged duration of action.

In the UK, a dose of hyoscine hydrobromide is taken 20 to 30 minutes before a journey, followed by the same dose every 6 hours if required up to a maximum of 3 doses in 24 hours. The usual dose in adults is 300 micrograms. Children aged 4 to 10 years may be given 75 to 150 micrograms and those over 10 years, 150 to 300 micrograms. Children aged 3 to 4 years may be given 75 micrograms, repeated once if necessary to a maximum total dose of 150 micrograms in 24 hours. Hyoscine is also given via a transdermal patch which is placed behind the ear and supplies 1 mg over 3 days. The patch is licensed in the UK for adults and children aged 10 years and over and should be applied 5 to 6 hours before travelling or on the preceding evening and removed at the end of the journey.

An intranasal formulation of hyoscine hydrobromide has been investigated for the treatment and prevention of motion sickness.

Transdermal hyoscine has been used in adults and children for the prevention of **postoperative nausea and vomiting**.

Hyoscine hydrobromide has also been given by intravenous, subcutaneous, or intramuscular injection for its antiemetic effect in doses ranging from 200 micrograms to 1 mg in adults.

The other drugs used in the management of motion sickness and postoperative nausea and vomiting are discussed on p. 1811.3.

References.

1. Kranke P, *et al.* The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2002; **95:** 133–43.
2. Nachum Z, *et al.* Transdermal scopolamine for prevention of motion sickness: clinical pharmacokinetics and therapeutic applications. *Clin Pharmacokinet* 2006; **45:** 543–66.
3. Spinks AB, *et al.* Scopolamine (hyoscine) for preventing and treating motion sickness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 03/04/08).

Palliative care. The *BNF* includes doses for hyoscine in palliative care. *Hyoscine hydrobromide* is used in palliative care for the treatment of bowel colic and to reduce excessive respiratory secretions, although care should be taken to avoid the discomfort of a dry mouth. The following parenteral doses have been suggested for adults:

- 400 micrograms by subcutaneous injection, usually given every 4 hours when required, although hourly use is sometimes necessary
  or
- 1.2 to 2 mg by continuous subcutaneous infusion over 24 hours

To reduce excessive respiratory secretions in children, the *BNFC* suggests parenteral doses of:

- 10 micrograms/kg (maximum 600 micrograms) by subcutaneous or intravenous injection every 4 to 8 hours
  or
- 40 to 60 micrograms/kg by continuous subcutaneous or intravenous infusion over 24 hours

Oral and sublingual doses have also been suggested for children, according to age:

- 2 to 12 years: 10 micrograms/kg (maximum 300 micrograms) four times daily
- 12 to 18 years: 300 micrograms four times daily

Alternatively, hyoscine hydrobromide may be given as a transdermal patch in the following doses:

- 1 month to 3 years: 250 micrograms (quarter of a patch) every 72 hours
- 3 to 10 years: 500 micrograms (half a patch) every 72 hours
- 10 to 18 years: 1 mg (one patch) every 72 hours

Hyoscine has also been used transdermally in adults for reducing respiratory secretions; one regimen uses 2 to 4 mg (two to four patches) every 72 hours with additional parenteral doses of glycopyrronium bromide (see p. 2520.1).[1]

Hyoscine butylbromide is also used in palliative care; the *BNF* suggests the following doses for adults:

- bowel colic: 60 to 300 mg by continuous subcutaneous infusion over 24 hours
- excessive respiratory secretions: 20 to 120 mg by continuous subcutaneous infusion over 24 hours
  or
- bowel colic and excessive respiratory secretions: 20 mg by subcutaneous injection, usually given every 4 hours when required, although hourly use is sometimes necessary

The use of hyoscine in palliative care has been reviewed.[2,3] Hyoscine hydrobromide may be more effective than glycopyrronium bromide in drying secretions, and has a rapid onset of action, but it can produce both sedation and agitation;[4] there is no clear evidence favouring one antimuscarinic over another.[4,5]

1. Kintzel PE, *et al.* Anticholinergic medications for managing noisy respirations in adult hospice patients. *Am J Health-Syst Pharm* 2009; **66:** 458–64.
2. Muir JC, von Gunten CF. Antisecretory agents in gastrointestinal obstruction. *Clin Geriatr Med* 2000; **16:** 327–34.
3. Spiller JA, Fallon M. The use of Scopoderm in palliative care. *Hosp Med* 2000; **61:** 782–4.
4. Bennett M, *et al.* Association for Palliative Medicine. Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care. *Palliat Med* 2002; **16:** 369–74.
5. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 04/06/09).

Smooth muscle spasm. Hyoscine has been used as an antispasmodic (p. 1803.3) to relieve the pain of smooth muscle spasm associated with the gastrointestinal tract and genito-urinary tract. In adults, *hyoscine butylbromide* 20 mg

may be given orally four times daily; children aged 6 to 12 years may be given 10 mg three times daily. It is also used in adults with irritable bowel syndrome (p. 1810.3); the recommended oral starting dose is 10 mg three times daily which may be increased to 20 mg four times daily, if necessary. Hyoscine butylbromide may also be given by intramuscular or slow intravenous injection for acute spasm and as an antispasmodic in diagnostic procedures. Adults may be given a dose of 20 mg, repeated after 30 minutes if necessary, up to a maximum of 100 mg daily. Although hyoscine butylbromide injection is unlicensed in the UK for use in children, the *BNFC* suggests the following doses repeated after 30 minutes if necessary (but more frequently in endoscopy):

- 2 to 6 years: 5 mg (maximum 15 mg daily)
- 6 to 12 years: 5 to 10 mg (maximum 30 mg daily)
- 12 to 18 years: 20 mg (maximum 80 mg daily)

As an adjunct in the treatment of peptic ulcer disease; *hyoscine methobromide* has been licensed in the USA in a dose of 2.5 mg half an hour before meals and 2.5 to 5 mg at bedtime.

References.
1. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs* 2007; **67:** 1343–57.

Urinary incontinence. Antimuscarinics have been used in the management of urge incontinence (p. 2349.2) but the incidence of adverse effects can be high. Results of a small study[1] suggested that transdermal hyoscine might be of benefit in females with detrusor instability.

1. Muskat Y, *et al.* The use of scopolamine in the treatment of detrusor instability. *J Urol (Baltimore)* 1996; **156:** 1989–90.

Vertigo. Hyoscine has a long history of use in the management of vertigo, although other drugs are now preferred (p. 612.3).

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. In contrast to atropine, hyoscine produces central depression at therapeutic doses and symptoms include drowsiness and fatigue. Toxic doses of hyoscine produce stimulation of the CNS in a similar manner to atropine. However, hyoscine does not stimulate the medullary centres and therefore does not produce the increases in respiration rate or blood pressure seen with atropine. Hyoscine may produce CNS stimulation rather than depression at therapeutic doses if used in the presence of pain without opioid analgesics; symptoms include excitement, restlessness, hallucinations, or delirium.

Patients who experience drowsiness should not drive or operate machinery. Caution has been advised in elderly patients and in patients with impaired liver, or kidney function, as adverse CNS effects have been stated to be more likely in these patients. There have been rare reports of an increase in frequency of seizures in epileptic patients.

The quaternary derivatives, such as the butylbromide, methobromide, or methonitrate, do not readily cross the blood-brain barrier, so central effects are rare.

Abuse. Hyoscine has been used by criminals to incapacitate and produce anterograde amnesia in their victims in crimes such as drug-facilitated rape ('date rape'), robbery, and kidnapping. In some countries in South America there has been a particular problem with the use of powders or extracts of plants containing hyoscine for such crimes. A powder, known locally as burundanga, prepared from the borrachero or borracchio tree (also referred to as cacao sabanero) has been blown into the victim's face or given in drinks, chocolate, or chewing gum.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of hyoscine by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/01/06)

Effects on body temperature. Central anticholinergic syndrome was thought to be responsible for hyperthermia and consequent multi-organ failure in an adolescent with cerebral palsy who was receiving symptomatic treatment with transdermal hyoscine.[1] Although the condition was rare in children it should be considered in those being given antimuscarinics if fever developed, particularly in the absence of sweating.

1. Frampton A, Spinks J. Hyperthermia associated with central anticholinergic syndrome caused by a transdermal hyoscine patch in a child with cerebral palsy. *Emerg Med J* 2005; **22:** 678–9.

Effects on the eyes. *ANISOCORIA.* Although bilateral mydriasis has occurred with the use of transdermal hyoscine, development of a unilateral fixed dilated pupil (anisocoria) may be due to contamination of a finger with hyoscine in handling the device, and then rubbing the eye.[1-6] Similarly, anisocoria has been attributed[7] to ocular contamination after handling broken hyoscine methobromide tablets.

1. Chiaramonte JS. Cycloplegia from transdermal scopolamine. *N Engl J Med* 1982; **306:** 174.
2. Lepore FE. More on cycloplegia from transdermal scopolamine. *N Engl J Med* 1982; **307:** 824.
3. McCrary JA, Webb NR. Anisocoria from scopolamine patches. *JAMA* 1982; **248:** 353–4.
4. Bienia RA, *et al.* Scopolamine skin-disks and anisocoria. *Ann Intern Med* 1983; **99:** 572–3.
5. Riddick FA, Jordan JD. Cruise ship anisocoria. *Ann InternMed* 1992; **117:** 95.
6. Lin Y-C. Anisocoria from transdermal scopolamine. *Paediatr Anaesth* 2001; **11:** 626–7.
7. Nussdorf JD, Berman EL. Anisocoria associated with the medical treatment of irritable bowel syndrome. *J Neuroophthalmol* 2000; **20:** 100–101.

GLAUCOMA. A few cases of angle-closure glaucoma, both unilateral[1] and bilateral,[2] have been associated with transdermal hyoscine devices.

1. Hamill MB. *et al.* Transdermal scopolamine delivery system (TRANSDERM-V) and acute angle-closure glaucoma. *Ann Ophthalmol* 1983; **15:** 1011–12.
2. Fraunfelder FT. Transdermal scopolamine precipitating narrow-angle glaucoma. *N Engl J Med* 1982; **307:** 1079.

STRABISMUS. Strabismus developed in a 4-year-old boy during treatment with transdermal hyoscine patches for drooling.[1] The strabismus resolved shortly after stopping hyoscine.

1. Good WV, Crain LS. Esotropia in a child treated with a scopolamine patch for drooling. *Pediatrics* 1996; **97:** 126–7.

Effects on mental function. There have been reports of psychotic reactions associated with the transdermal use of hyoscine.[1-6] Psychotic reactions have also occurred after instillation of hyoscine eye drops.[7]

1. Osterholm RK, Camoriano JK. Transdermal scopolamine psychosis. *JAMA* 1982; **247:** 3081.
2. Rodysill KJ, Warren JB. Transdermal scopolamine and toxic psychosis. *Ann Intern Med* 1983; **98:** 561.
3. MacEwan GW, *et al.* Psychosis due to transdermally administered scopolamine. *Can Med Assoc J* 1985; **133:** 431–2.
4. Ziskind AA. Transdermal scopolamine-induced psychosis. *Postgrad Med* 1988; **84:** 73–6.
5. Rubner O, *et al.* Ungewöhnlicher Fall einer Psychose infolge einer Langzeiteinwirkung mit einem Skopolaminmembranpflaster: Paranoid-halluzinatorische und delirante Symptomatik. *Nervenarzt* 1997; **68:** 77–9.
6. Minagar A, *et al.* Transderm-induced psychosis in Parkinson's disease. *Neurology* 1999; **53:** 433–4.
7. Barker DB, Solomon DA. The potential for mental status changes associated with systemic absorption of anticholinergic ophthalmic medications: concerns for the elderly. *DICP Ann Pharmacother* 1990; **24:** 847–50.

Effects on the oesophagus. A patient developed pain on swallowing after 4 days of treatment with hyoscine. Endoscopy showed oesophageal ulceration, which healed completely after 8 weeks of esomeprazole treatment.[1]

1. Philcox S, Keegan A. A case of hyoscine-related oesophagitis. *Med J Aust* 2007; **186:** 650–1.

Effects on the skin. Contact dermatitis occurred in 16 men being treated for seasickness with transdermal hyoscine for 6 weeks to 15 months.[1]

1. Gordon CR, *et al.* Allergic contact dermatitis caused by transdermal hyoscine. *BMJ* 1989; **298:** 1220–1.

Migraine. A small case-control study[1] suggested that hyoscine could trigger or exacerbate migraine in patients with a history of the condition.

1. Ikeda K, *et al.* Scopolamine-induced migraine like headache. *Intern Med* 2009; **48:** 681–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hyoscine butylbromide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. A report[1] of hyoscine toxicity in a neonate born to a mother who had received a total of 1.8 mg of hyoscine in divided doses with pethidine and levorphanol before delivery. The neonate was lethargic, barrel chested, and had a heart rate of 200 beats/minute. Symptoms subsided when physostigmine 100 micrograms was given intramuscularly.

1. Evens RP, Leopold JC. Scopolamine toxicity in a newborn. *Pediatrics* 1980; **66:** 329–30.

Withdrawal. A withdrawal syndrome of dizziness and nausea[1,2] can occur in patients who have used transdermal hyoscine patches for several days; hypersalivation and diarrhoea has also been described.[3] In reported cases, transdermal hyoscine had been used continuously for 7 or 10 days to prevent motion sickness. Symptoms usually begin 2 or 3 days after the last patch has been removed, and may last for a few days.

1. Meyboom RHB. More on Transderm Scop patches. *N Engl J Med* 1984; **311:** 1377.
2. Saxena K, Saxena S. Scopolamine withdrawal syndrome. *Postgrad Med* 1990; **87:** 63–6.
3. Feder RE. Transdermal scopolamine withdrawal syndrome. *Clin Neuropharmacol* 1999; **22:** 120.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

The sedative effect of hyoscine may be enhanced by alcohol or other CNS depressants.

Pharmacokinetics

Hyoscine is readily absorbed from the gastrointestinal tract after oral doses of the hydrobromide. It is almost entirely metabolised, probably in the liver; only a small proportion of an oral dose is excreted unchanged in the urine. It crosses the blood-brain barrier and has been stated to cross the placenta. Hyoscine is also well absorbed after application to the skin.

The quaternary derivatives, such as the butylbromide or methobromide, are poorly absorbed from the gastrointestinal tract and do not readily pass the blood-brain barrier.

References.
1. Ebert U, *et al.* Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. *J Clin Pharmacol* 1998; **38:** 720–6.
2. Nachum Z, *et al.* Scopolamine bioavailability in combined oral and transdermal delivery. *J Pharmacol Exp Ther* 2001; **296:** 121–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Buscapina; Cifespasmo; Colobolina; Excelentia Antiespasmodico; Luar-G; Pasmodina; Rupe-N; ***Austral.***: Buscopan; Kwells; Setacol; Stomex; Travacalm HO; ***Austria***: Buscapina; Buscopan; ***Belg.***: Buscopan; ***Braz.***: Belscopan; Buscopan; Hiospan; Uni Hioscin; ***Canad.***: Buscopan; Transderm-V; ***Chile***: Buscapina; ***China***: Buscopan; Gan Mei Duo Lan (甘美多兰); Kimite (可弥特); ***Cz.***: Buscopan; ***Denm.***: Buscopan; Scopoderm; ***Fin.***: Buscopan; Scopoderm; ***Fr.***: Scoburen; Scopoderm TTS; ***Ger.***: Boro-Scopol; BS Carino; BS-ratiopharm; Buscopan; Scopoderm TTS†; Spasman scop†; ***Gr.***: Avotrin; Buscopan; Naftex; Scopoderm TTS; ***Hong Kong***: Ariel; BF-Horloten†; Buscopan; Busopin; Colospan†; Copan†; Dhacopan; Holomine†; Hyomide; Hysopan†; Spasmoliv†; Vidaspan†; ***Hung.***: Buscopan; ***India***: Belloid; Buscopan; Hyospan; Hyospas; Hyoswift; ***Indon.***: Buscopan; Dormi; Gitas; Hyscopan; Scobutrin; Scopamin; Scopma; Spashi; Spasmolit; Stomica; ***Irl.***: Buscopan; Kwells; ***Ital.***: Addofix; Buscopan; Transcop; ***Jpn***: Buscopan; ***Malaysia***: Buscopan; Buston; Copan; Dhacopan; Encodex; Fucon; Hyomide; Spasmoliv†; Vacopan; ***Mex.***: Alpin; Biomesina; Bipasmin; Brolamina†; Buscapina; Busina†; Busprina-S; Butiral; Cryopina; Espacil; Espafarm; Excosine-S; Grafin; Hiosultrina; Lemophar; Selpiran-S; Serralpina; ***Neth.***: Buscopan; Scopoderm TTS; ***Norw.***: Buscopan; Scopoderm; ***NZ***: Buscopan; Gastro-Soothe; Scopoderm TTS; ***Philipp.***: Amucin; Ascopen; Buscin; Buscomed; Buscopan; Busopin; Buston; Fucon; Gascopan; Gastride; Losil; Rotomide; Scolmin; Spasmosan; Xspas; ***Pol.***: Buscolysin; Buscopan; Scopolan; ***Port.***: Buscopan; ***Rus.***: Buscopan (Бускопан); ***S.Afr.***: Buscopan; Hyospasmol; Scopaject; Scopex; ***Singapore***: Buscopalamin; Buscopan; Colospan; Copan; Cospan; Dhacopan; Dividol; Fucon; Hyomide; Hyosun; Scopoderm TTS; SP-Anspaz; Spasmoliv; Vacopan; ***Spain***: Buscapina; ***Swed.***: Buscopan; Scopoderm; ***Switz.***: Buscopan; ***Thai.***: Amcopan; Antispa Plus; Antispa; Bacotan; Buscono; Buscopan; Butyl; Cencopan; Eralgavvv†; Fucon†; Higan†; Hy-Spa; Hybutyl; Hyosman; Hyosmed; Hyospan; Hyostan; Hyozin; Kanin; Myspa; Scopas; Spalox†; Spascopan; Spasgone-H; Spasmo; U-Oscine; Uospan; Uricine†; Vacopan; Vescopolamine; ***Turk.***: Buscopan; Butopan; Molit; Spazmol; Spazmotek; ***UAE***: Scopinal; ***UK***: Buscopan; Joy-Rides; Kwells; Scopoderm TTS; ***Ukr.***: Spasmobru (Спазмобрю); ***USA***: Pamine; Scopace†; Transderm Scop; ***Venez.***: Buscapina; Hiocin.

Multi-ingredient Preparations. ***Arg.***: 6-Copin†; 6-Copin; Buscapina Compositum N; Buscapina Compositum; Buscapina Fem; Cifespasmo Compuesto; Colobolina D; Espasmo Biotenk; Espasmol; Feminity; Gastrolina Compuesta; Hioscina Compuesta; Ibu-Buscapina; Ibuxim Fem; Labsyna Fem; Lisalgil Compuesto; Luar-G Compositum; Novopasmil Compuesto; Pasmodina Compuesta; Rupe-N Compuesto; Tafirol Mujer; ***Austral.***: Donnagel; Donnalix; Donnatab; Travacalm; ***Austria***: Buscopan Compositum; ***Belg.***: Buscopan Compositum; ***Braz.***: Algexin; Atroveran Plus; Belspan; Binospan; Buscoduo; Buscopan Composto; Buscopan Plus; Buscoveran Composto; Butilamin†; Disbuspan†; Dorspan Composto; Espasmodid Composto; Hioariston; Hiospan Composto; Kindpasm†; Neocopan; Tropinal; Veratropan Composto†; ***Chile***: Algion†; Buscapina Compositum; Crotalgina; Dolcopin; Novalona; ***Ger.***: Buscopan Plus; ***Gr.***: Buscopan Plus; Colik; Spasmo-Apotel; ***Hong Kong***: Epilon; Unigan; Virulex Forte; ***Indon.***: Aludonna; Aludonna; Buscopan Plus; Dormi Comp; Gitas Plus; Procolic; Scopamin Plus; Scopma Plus; Spashi Plus; Spaslic; Spasmacine; Unthecol†; ***Irl.***: Feminax; ***Ital.***: Buscopan Compositum; Spasmeridan†; ***Mex.***: Algosfar; Anadil; Benfol†; Biomesina Compuesta; Bipasmin Compuesto; Buscapina Compositum N; Buscapina Composi-

tum; Buscapina Fem; Busconet; Busepan; Busprina; Colepren; Doltrix; Donodol Compuesto; Escapin-N; Espacil Compuesto; Espasmogress; Hiosultrina-F; Infafren Compuesto†; Mebuxina; Neo-Pasmonal; Pasmodil†; Pirobutil; Precicol; Prestodol Compuesto; Retodol Compositum; Selpiran Compuesto; Selpiran; Serralpina Compuesta; Viladol Plus; Viladol-Met†; ***Philipp.***: Buscopan Plus; Unigan; ***Pol.***: Scopolan Compositum; Vegantalgin H; ***Port.***: Buscopan Compositum N; ***S.Afr.***: Buscopan Compositum; Donnatal†; Millerspas†; Respinol Compound†; Scopex Co; ***Spain***: Buscapina Compositum; Midriatico†; Oragalin Espasmolitico; Psico Blocan†; ***Swed.***: Spasmofen; ***Thai.***: Amcopan Plus; Buscopan Plus†; Hyosman Plus; Pacopan; Spascopan-510; Spasgone; Unigan; ***Turk.***: Buscopan Compositum†; Buscopan Plus; Molit Plus; Skopolin†; Spazmol Plus; Spazmotek Plus; Tanko-Buskas†; Tranko-Buskas; ***UK***: Feminax; ***USA***: AeroHist Plus; AeroKid; AH-chew; Alkabel; AllePak; AlleRx DF; AlleRx†; Antispasmodic Elixir; Bellahist-D; Bellatal; Chlor-Mes D†; Chlor-Mes; CPM PSE MSC; CPM/PE/MSC; DA Chewable; DA II; Dallergy PE†; Dehistine; Dexphen M; Donnatal; DriHist; DryMax; Dura-Vent/DA; Durahist D†; Durahist†; Ex-Histine; Extendryl DM; Extendryl PEM; Extendryl; Histatab D; Histor-D Timecelles; Hyosophen; Murocoll-2†; Nacon; NoHist Plus; Omnihist LA; Pamine FQ Kit; Pannaz; PB-Hyos; PCM; PE-CPM-MSN; PE-HCL-CPM-MSN; Prehist D; PSE MSC; Quadrapax; Ralix; Redur-PCM†; RelCof CPM; RelCof DN PE; RelCof DN PSE; RelCof PSE; Ryneze; Se-Donna PB HYOS; Servira; Stahist; Susano; SymPak II; SymPak PDX; SymPak†; ***Venez.***: Brugesina; Buscapina Compositum; Buscapina Plus; Butilamina Compuesta; Vuscobras.

Used as an adjunct in:. ***Singapore***: SP-Arnox.

Pharmacopoeial Preparations
BP 2014: Hyoscine Butylbromide Injection; Hyoscine Butylbromide Tablets; Hyoscine Eye Drops; Hyoscine Injection; Hyoscine Tablets;
USP 36: Methscopolamine Bromide Tablets; Scopolamine Hydrobromide Injection; Scopolamine Hydrobromide Ophthalmic Ointment; Scopolamine Hydrobromide Ophthalmic Solution; Scopolamine Hydrobromide Tablets.

Hyoscyamine *(BAN)*

Hiosciamina; Hyoscyamin; (-)-Hyoscyamine; *l*-Hyoscyamine; Hyoscyaminum; Hyoskyamiini; Гиосциамин.
(-)-(1*R*,3*r*,5*S*)-Tropan-3-yl (*S*)-tropate.
$C_{17}H_{23}NO_3$=289.4
CAS — 101-31-5.
ATC — A03BA03.
ATC Vet — QA03BA03.
UNII — PX44XO846X.

Description. Hyoscyamine is an alkaloid obtained from various solanaceous plants. It is the laevo-isomer of atropine into which it can be converted by heating or by the action of alkali.

Pharmacopoeias. In *US*.

USP 36: (Hyoscyamine). A white crystalline powder. M.p. 106 degrees to 109 degrees. Slightly soluble in water and in benzene; freely soluble in alcohol, in chloroform, and in dilute acids; sparingly soluble in ether. Its solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Hyoscyamine Hydrobromide *(BANM)*

Bromidrato de Hiosciamina; Hiosciamina, hidrobromuro de; Hyoscyamine Bromhydrate; Гиосциамина Гидробромид.
$C_{17}H_{23}NO_3$,HBr=370.3
CAS — 306-03-6.
ATC — A03BA03.
ATC Vet — QA03BA03.
UNII — IWT50P9S79.

Pharmacopoeias. In *US*.

USP 36: (Hyoscyamine Hydrobromide). White, odourless, crystals or crystalline powder. M.p. not less than 149 degrees. Freely soluble in water; soluble 1 in 2.5 of alcohol, 1 in 1.7 of chloroform, and 1 in 2300 of ether. pH of a 5% solution in water is about 5.4. Store in airtight containers. Protect from light.

Hyoscyamine Sulfate *(BANM)*

Hiosciamina, sulfato de; Hiosciamino sulfatas; Hioscyjaminy siarczan; Hioszciamin-szulfát; Hyoscyamin sulfát dihydrát; Hyoscyamine, sulfate d'; Hyoscyamine Sulphate; Hyoscyamini sulfas; Hyoscyamini Sulfas Dihydricus; Hyoscyaminsulfat; Hyoscyaminum Sulfuricum; Hyoskyamiinisulfaatti; Iosciamina Solfato; Гиосциамина Сульфат.
$(C_{17}H_{23}NO_3)_2H_2SO_4.2H_2O$=712.9
CAS — 620-61-1 (anhydrous hyoscyamine sulfate); 6835-16-1 (hyoscyamine sulfate dihydrate).
ATC — A03BA03.

All cross-references refer to entries in Volume A

ATC Vet — QA03BA03.
UNII — F2R8V82B84.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Hyoscyamine Sulfate). A white or almost white, crystalline powder or colourless needles. Very soluble in water; sparingly soluble or soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Store in airtight containers. Protect from light.

USP 36: (Hyoscyamine Sulfate). A white or almost white, crystalline powder or colourless needles. It is deliquescent and affected by light. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; practically insoluble in ether. pH of a 1% solution in water is about 5.3.

Uses and Administration

Hyoscyamine is a tertiary amine antimuscarinic with the actions of atropine (which is racemic hyoscyamine, see p. 1312.1); hyoscyamine, the laevo-isomer, has about twice the potency of atropine since the dextro-isomer has only very weak antimuscarinic activity. Hyoscyamine is used mainly in the relief of conditions associated with visceral spasm. It has also been given for rhinitis and was formerly used in the treatment of parkinsonism.

Hyoscyamine is given in usual oral doses of 150 to 300 micrograms up to four times daily, but it is more usually employed as the sulfate; the hydrobromide is also used. Suggested doses of hyoscyamine sulfate are 125 to 250 micrograms orally or sublingually every four hours as needed, up to a maximum of 1.5 mg in 24 hours. Modified-release oral preparations of hyoscyamine sulfate are available in some countries; dosage is specific to a particular formulation. Hyoscyamine sulfate has also been given by injection.

Homoeopathy

Hyoscyamine hydrobromide has been used in homoeopathic medicines under the following names: Hyoscyaminum hydrobromatum.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Egazil; ***Hong Kong***: Levsin; ***Norw.***: Egazil; ***Swed.***: Egazil; ***USA***: Anaspaz†; Cystospaz†; Donnamar; ED-SPAZ; Gastrosed; HyoMax; IB-Stat†; Levbid; Levsin; Levsinex†; Mar-Spas; Neosol†; NuLev; Oscimin; Symax.

Multi-ingredient Preparations. ***Austral.***: Donnagel; Donnalix; Donnatab; ***Braz.***: Neogrein; Ormigrein; Tropinal; ***Indon.***: Aludonna; Feminax†; ***S.Afr.***: Donnatal†; Millerspas†; ***USA***: Alkabel; Antispasmodic Elixir; Atrosept; Bellacane; Bellahist-D; Bellatal; Darpaz†; Digex NF; Digex†; Donnatal; Hyophen; Hyosophen; MHP-A; MSP-Blu; PB-Hyos; PhenazoForte Plus; Phenazopyridine Plus; Phosphasal; Prosed/DS; Pyrelle HB†; Pyridium Plus; Quadrapax; Se-Donna PB HYOS; Servira; Stahist; Susano; Trellium Plus†; UAA; Urelief Plus; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Urogesic Blue; Uryl; Ustell; Uticap; Utira; Utrona-C.

Pharmacopoeial Preparations
USP 36: Hyoscyamine Sulfate Elixir; Hyoscyamine Sulfate Injection; Hyoscyamine Sulfate Oral Solution; Hyoscyamine Sulfate Tablets; Hyoscyamine Tablets.

Ilaprazole *(rINN)*

Gilaprazole; Ilaprazol; Ilaprazolum; IY-81149; Илапразол.
2-{(*RS*)-[(4-Methoxy-3-methylpyridin-2-yl)methyl]sulfinyl}-5-(1*H*-pyrrol-1-yl)-1*H*-benzimidazole.
$C_{19}H_{18}N_4O_2S$=366.4
CAS — 172152-36-2.
UNII — 776Q6XX45J.

Profile

Ilaprazole is a proton pump inhibitor that is under investigation for the treatment of peptic ulcer disease and gastro-oesophageal reflux disease.

References.

1. Li Y, *et al.* Pharmacokinetics of the new proton pump inhibitor ilaprazole in Chinese healthy subjects in relation to CYP3A5 and CYP2C19 genotypes. *Clin Chim Acta* 2008; **391:** 60–7.
2. Ho KY, *et al.* Randomized, parallel, double-blind comparison of the ulcer-healing effects of ilaprazole and omeprazole in the treatment of gastric and duodenal ulcers. *J Gastroenterol* 2009; **44:** 697–707.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: YiLi An (壹丽安).

Indisetron Hydrochloride *(rINNM)*

Hidrocloruro de indisetrón; Indisétron, Chlorhydrate d'; Indisetron Dihydrochloride; Indisetroni Hydrochloridum; N-3389; Индистрона Гидрохлорид.
N-(3,9-Dimethyl-*endo*-3,9-diazabicyclo[3.3.1]non-7-yl)-1*H*-indazole-3-carboxamide dihydrochloride.
$C_{17}H_{23}N_5O$,2HCl=386.3
CAS — 141549-75-9 (indisetron); 160472-97-9 (indisetron dihydrochloride).
UNII — NBN3HB12DW.

Profile

Indisetron is a 5-HT_3-receptor antagonist with general properties similar to those of ondansetron (p. 1872.1); it is also stated to be an antagonist at 5-HT_4 receptors. Indisetron hydrochloride is used as an antiemetic in the management of nausea and vomiting associated with chemotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Sinseron.

Irsogladine Maleate *(rINNM)*

Irsogladina, maleato de; Irsogladine, Maléate d'; Irsogladini Maleas; Maleato de irsogladina; MN-1695; Ирсогладина Малеат.
2,4-Diamino-6-(2,5-dichlorophenyl)-*S*-triazine maleate.
$C_9H_7Cl_2N_5.C_4H_4O_4$=372.2
CAS — 57381-26-7 (irsogladine); 84504-69-8 (irsogladine maleate).

Profile

Irsogladine maleate is a cytoprotective drug that is used in the treatment of peptic ulcer disease (p. 1813.2) in a usual oral dose of 4 mg daily. It has also been investigated for mucositis and mouth ulceration.

References.

1. Hiraishi H, *et al.* Clinical trial: irsogladine maleate, a mucosal protective drug, accelerates gastric ulcer healing after treatment for eradication of *Helicobacter pylori* infection—the results of a multicentre, double-blind, randomized clinical trial (IMPACT study). *Aliment Pharmacol Ther* 2010; **31:** 824–33.

Mucositis. Oral irsogladine maleate 2 mg twice daily has been reported[1] to reduce the incidence of aphthous stomatitis in a small study in patients being treated with methotrexate for rheumatoid arthritis.

1. Yoshida T, Hirakata M. Therapeutic benefits of irsogladine maleate on aphthous stomatitis induced by methotrexate in rheumatoid arthritis. *J Rheumatol* 2003; **30:** 2082–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Gaslon N (盖世龙); Hengzhi (恒至); Ke Ma Nuo (科玛诺); Yi Ge Ding (一格定); ***Jpn***: Gaslon N.

Isopropamide Iodide *(BAN, rINN)*

Ioduro de isopropamida; Isopropamida, ioduro de; Isopropamide, Iodure d'; Isopropamidi Iodidum; Изопропамида Йодид.
(3-Carbamoyl-3,3-diphenylpropyl)di-isopropylmethylammonium iodide.
$C_{23}H_{33}IN_2O$=480.4
CAS — 7492-32-2 (isopropamide); 71-81-8 (isopropamide iodide).
ATC — A03AB09.
ATC Vet — QA03AB09.
UNII — E0KNA372SZ.

Pharmacopoeias. In *US*.

USP 36: (Isopropamide Iodide). A white to pale yellow crystalline powder. Soluble 1 in 50 of water, 1 in 10 of alcohol, and 1 in 5 of chloroform; very slightly soluble in ether and in benzene. Protect from light.

Profile

Isopropamide iodide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease, in the relief of gastrointestinal and

urinary-tract disorders associated with smooth muscle spasm, in rhinitis, and for the relief of symptoms of colds.

Isopropamide bromide has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Raspon.

Multi-ingredient Preparations. ***India***: Gastabid; ***Ital.***: Influmed C; Influmed; Raffreddoremed; Valtrax; ***Mex.***: Stelabid.

Pharmacopoeial Preparations
USP 36: Isopropamide Iodide Tablets.

Ispaghula

Egyiptomi útifűmag (ispaghula seed); Egyiptomi útifűmaghéj (ispaghula husk); Ispaghul, graine d' (ispaghula seed); Ispaghul (graine d'), tégument de la (ispaghula husk); Ispagula; Ispagula Kabuğu; Ispagulafrö (ispaghula seed); Ispagulafröskal (ispaghula husk); Ispagulansiemen (ispaghula seed); Ispagulansiemenkuori (ispaghula husk); Kepek; Kiaušininių gysločių sėklų luobelės (ispaghula husk); Kiaušininių gysločių sėklos (ispaghula seed); Łupina nasienna babki jajowatej (ispaghula husk); Nasienie babki jajowatej (ispaghula seed); Osemení jitrocele vejčitého (ispaghula husk); Plantaginis ovatae semen (ispaghula seed); Plantaginis ovatae seminis tegumentum (ispaghula husk); Psilio; Semeno jitrocele vejčitého (ispaghula seed); Zaragatona; Шелуха Исфагулы (ispaghula husk).

*ATC Herb — HA06AC5010 (*Plantago ovata*: seed husk).*

*UNII — UD50RBY30F (*Plantago ovata *seed); 0SHO53407G (psyllium husk); NU5XN4136K (*Plantago ovata *seed coat).*

Pharmacopoeias. Monographs for the husk and seed are included in *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ispaghula Husk; Plantaginis Ovatae Seminis Tegumentum). The episperm and collapsed adjacent layers removed from the seeds of *Plantago ovata* (*P. ispaghula*). The powdered drug loses not more than 12.0% of its weight on drying. Protect from light.

Ph. Eur. 8: (Ispaghula Seed; Plantaginis Ovatae Semen). The dried ripe seeds of *Plantago ovata* (*P. ispaghula*). The powdered drug loses not more than 10.0% of its weight on drying. Protect from light.

USP 36: (Psyllium Husk). The cleaned, dried seed coat (epidermis), in whole or in powdered form, separated by winnowing and threshing from the seeds of *Plantago ovata* (known in commerce as Blond Psyllium, Indian Psyllium, or Ispaghula), or from *Plantago arenaria* (*Plantago psyllium*), known in commerce as Spanish or French Psyllium.

USP 36: (Plantago Seed). The cleaned, dried, ripe seed of *Plantago ovata*, or of *Plantago psyllium*, or of *Plantago indica* (*P. arenaria*).

Psyllium Hemicellulose *(USAN)*

CAS — 9034-32-6.

UNII — Y2HNG56689.

Pharmacopoeias. In *US*.

USP 36: (Psyllium Hemicellulose). The alkali soluble fraction of the husk from *Plantago ovata* consisting of highly substituted arabinoxylan polysaccharides. These polysaccharides are linear chains of xylose units to which are attached single units of arabinose and additional xylose. Rhamnose, galactose, glucose, and rhamnosyluronic acid residues are also present as minor constituents. It contains not less than 75.0% of dietary soluble fibre, calculated on the dried basis. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Psyllium Seed

Blešníkové semeno; Bolhafűmag; Flea Seed; Flohsamen; Loppfrö; Nasienie płesznika; Psilio, semilla de; Psyllii semen; Psyllium, graine de; Psylliuminsiemen; Smiltyninių gysločių sėklos.

ATC — A06AC01.

ATC Vet — QA06AC01.

*ATC Herb — HA06AC5008 (*Plantago afra*: seed); HA07BW5004 (*Plantago ovata*: seed); HA06AC5009 (*Plantago ovata*: seed); HA07BW5003 (*Plantago afra*: seed).*

UNII — 9C60Y73166.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *US* under the title of Plantago Seed.

Ph. Eur. 8: (Psyllium Seed). The ripe, whole, dry seeds of *Plantago afra* (*P. psyllium*) or *Plantago indica* (*P. arenaria*). It loses not more than 14.0% of its weight on drying. Protect from light and moisture.

USP 36: (Plantago Seed). The cleaned, dried, ripe seed of *Plantago ovata*, or of *Plantago psyllium*, or of *Plantago indica* (*P. arenaria*) (see also Ispaghula, above).

Uses and Administration

Ispaghula seed, ispaghula husk, and psyllium seed are bulk laxatives (p. 1804.1). They absorb water in the gastrointestinal tract to form a mucilaginous mass which increases the volume of faeces and hence promotes peristalsis. They are used in the treatment of constipation (p. 1804.3), especially in diverticular disease (p. 1806.2) and irritable bowel syndrome (p. 1810.3), and when excessive straining at stool must be avoided, for example after anorectal surgery or in the management of haemorrhoids. The ability to absorb water and increase faecal mass means that they may also be used in the management of diarrhoea (p. 1805.2) and for adjusting faecal consistency in patients with colostomies.

The usual oral dose is about 3.5 g one to three times daily, although higher doses have been given. It should be taken immediately after mixing in at least 150 mL water or fruit juice. The full effect may not be achieved for up to 3 days. For doses in children, see below.

Ispaghula is also given for mild to moderate hypercholesterolaemia as an adjunct to a lipid-lowering diet. The recommended dose is about 7.5 to 10 g daily.

Administration in children. Ispaghula husk can be given orally to treat constipation in children; doses vary slightly according to the preparation used. A typical preparation (*Fybogel; Reckitt Benckiser, UK*), which contains ispaghula husk 1.75 g per level 5-mL spoonful, recommends children aged 12 years and under be given ½ to 1 level 5-mL spoonful dissolved in water twice daily. The *BNFC* recommends the same dose, but restricts the use of ispaghula husk to children aged 6 years and over. Children aged 12 years and over are usually given adult doses, see above.

Hyperlipidaemias. Preparations of ispaghula have been reported[1-4] to lower serum-cholesterol concentrations in patients with mild to moderate hypercholesterolaemia. They have also been given with reduced doses of a bile-acid binding resin in the treatment of hyperlipidaemia,[5] which is reported to be effective and better tolerated than full doses of the resin alone. Similarly, psyllium supplementation with 10 mg of simvastatin was found to be as effective in lowering cholesterol as 20 mg of simvastatin alone.[6] However, ispaghula or psyllium should be regarded as adjuncts to dietary modification rather than substitutes for it. For a discussion of the hyperlipidaemias and their management, see p. 1248.1.

1. Anderson JW, *et al.* Cholesterol-lowering effect of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med* 1988; **148:** 292–6.
2. Bell LP, *et al.* Cholesterol-lowering effects of psyllium hydrophilic mucilloid: adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. *JAMA* 1989; **261:** 3419–23.
3. Anderson JW, *et al.* Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr* 2000; **71:** 472–9.
4. Anderson JW, *et al.* Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr* 2000; **71:** 1433–8.
5. Spence JD, *et al.* Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. *Ann Intern Med* 1995; **123:** 493–9.
6. Moreyra AE, *et al.* Effect of combining psyllium fiber with simvastatin in lowering cholesterol. *Arch Intern Med* 2005; **165:** 1161–6.

Adverse Effects and Precautions

Large quantities of ispaghula and other bulk laxatives may temporarily increase flatulence and abdominal distension; hypersensitivity reactions have been reported. There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such compounds are taken with insufficient fluid. Therefore, they should always be taken with at least 150 mL of water or other liquid. Ispaghula and bulk laxatives should not be taken immediately before going to bed because reduced gastric motility may impair intestinal passage and cause obstruction. They should be avoided by patients who have difficulty swallowing.

Bulk laxatives should not be given to patients with pre-existing faecal impaction, intestinal obstruction, or colonic atony.

Hypersensitivity. Hypersensitivity reactions associated with the ingestion or inhalation of ispaghula or psyllium have been reported.[1-9] Symptoms have included rash, rhinitis, urticaria, bronchospasm, and anaphylactic shock; in one case, anaphylaxis was fatal.[9] In most patients, sensitisation was thought to have occurred during occupational exposure.

1. Busse WW, Schoenwetter WF. Asthma from psyllium in laxative manufacture. *Ann Intern Med* 1975; **83:** 361–2.
2. Gross R. Acute bronchospasm associated with inhalation of psyllium hydrophilic mucilloid. *JAMA* 1979; **241:** 1573–4.
3. Suhonen R, *et al.* Anaphylactic shock due to ingestion of psyllium laxative. *Allergy* 1983; **38:** 363–5.
4. Zaloga GP, *et al.* Anaphylaxis following psyllium ingestion. *J Allergy Clin Immunol* 1984; **74:** 79–80.
5. Kaplan MJ. Anaphylactic reaction to "Heartwise". *N Engl J Med* 1990; **323:** 1072–3.
6. Lantner RR, *et al.* Anaphylaxis following ingestion of a psyllium-containing cereal. *JAMA* 1990; **264:** 2534–6.
7. Freeman GL. Psyllium hypersensitivity. *Ann Allergy* 1994; **73:** 490–2.
8. Vaswani SK, *et al.* Psyllium laxative-induced anaphylaxis, asthma, and rhinitis. *Allergy* 1996; **51:** 266–8.
9. Khalili B, *et al.* Psyllium-associated anaphylaxis and death: a case report and review of the literature. *Ann Allergy Asthma Immunol* 2003; **91:** 579–84.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ispaghula as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/10/11)

Interactions

Ispaghula and other bulk-forming laxatives may delay or reduce the gastrointestinal absorption of other drugs such as cardiac glycosides, coumarin derivatives, lithium, or vitamins (such as vitamin B_{12}) and minerals (such as calcium, iron, or zinc). Intervals of 30 minutes to 1 hour are recommended between ispaghula and other drugs or food, although some recommend as much as 3 hours between bulk-forming laxatives and other drugs. The dose of insulin may need to be reduced in diabetic patients taking ispaghula.

Lithium. For reference to ispaghula possibly reducing the absorption of lithium, see Gastrointestinal Drugs, p. 432.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agiofibras; CTabs-Correctol; Fibras Ewe; Konsyl; Lostamucil; Metamucil; Motional; Mucofalk†; Plantaben; Salutaris; ***Austral.***: Agiofibe; Ford Fibre†; Fybogel; Metamucil; ***Austria***: Agiocur; Plantaben; ***Belg.***: Colofiber; Spagulax M; Spagulax; ***Braz.***: Agiofibra; Fibracare†; Metamucil; Plantaben; ***Canad.***: Easy Lax†; Fiber 5; Laxucil†; Metamucil; Mucillium; Musilax; Naturfibr†; Novo-Mucilax†; Super CC†; ***Chile***: Euromucil; Fibrasol; Plantaben; ***China***: Konsyl (恺司尔); ***Denm.***: Vi-Siblin; ***Fin.***: Agiocur; Laxamucil; Vi-Siblin; ***Fr.***: Mucivital; Phytofibre†; Spagulax Mucilage; Spagulax; Transilane; ***Ger.***: Agiocur; Flosine; Kneipp Cholesterin Control†; Metamucil; Mucofalk; Pascomucil; ***Hong Kong***: Agiocur; Fibermate†; Metamucil; Mucofalk; Naturlax; Plantaben; Transilane†; ***Hung.***: Colon Cleanse; Husk; Mucofalk; Nature Care; ***India***: Cremadiet; Eva-Q; Fibradiet; Fibril; Fybogel; Husky; Igol; Inulax; Isbis; Isogel; Itworks; Laxataur; Naturolax; ***Indon.***: Mucofalk†; Mulax; ***Irl.***: Fybogel; Regulan; ***Israel***: Agiocur; Kalsiv; Konsyl; Sivay Psyllium; ***Ital.***: Agiofibre; Fibrolax; Plantalax; Planten; Psyllogel; ***Malaysia***: Fybogel; Mucofalk†; ***Mex.***: Agiofibra; Fibromucil; Finalax; Fybogel†; Hormolax†; Metamucil; Mucilag†; Mugasin; Naxar-P; Novagon; Plantaben; ***Mon.***: Psylia; ***Neth.***: Metamucil; Regucol†; Volcolon; ***Norw.***: Lunelax; Vi-Siblin; ***NZ***: Isogel†; Metamucil; Mucilax; ***Philipp.***: Fibermate; Mucofalk; ***Pol.***: Mucofalk; ***Port.***: Agiocur; Agiofibra; Laxat†; Mucofalk; Pepsa-lax; Prontolax; Vetilax†; ***Rus.***: Fiberlax (Файберлекс); Mucofalk (Мукофальк); Naturolax (Натуролакс); ***S.Afr.***: Agiobulk; Fybogel; Ispagel; ***Singapore***: Fybogel; Mucilin; Mucofalk†; ***Spain***: Biolid; Cenat; Filaxan; Laxabene; Metamucil; Plantaben; Plantasor; Plantax; ***Swed.***: Lunelax; Vi-Siblin; ***Switz.***: Agiolax mite; Laxiplant Soft; Metamucil; Mucilar; ***Thai.***: Agiocur; Detolax; Fybogel; Igol; Metamucil; Mucilin; Plantaben; ***Turk.***: Otaci Musillium†; ***UK***: Fibrelief†; Fybogel; Isogel; Ispagel; Regulan; ***Ukr.***: Defenorm (Дефенорм); Mucofalk Orange (Мукофальк Апельсин); Transilan (Транзилан); ***USA***: Fiber Therapy Original Texture; Fiberall; Geri-Mucil; Hydrocil Instant; Konsyl-D; Konsyl; Metamucil; Perdiem Fiber; Reguloid; Serutan; Syllact; ***Venez.***: Agiofibe; Siliumbran.

Multi-ingredient Preparations. ***Arg.***: Adelgazar; Agiolax; Gelax; Isalax Fibras; Medilaxan; Mermelax; Rapilax Fibras; ***Austral.***: Agiolax; Colon Care; Detox Program; Nucolox†; Psylli-Mucil Plus†; ***Austria***: Agiolax; ***Belg.***: Agiolax; Spagulax K†; Spagulax Sorbitol†; ***Braz.***: Agiolax; Parapsyl; ***Canad.***: Fiber Plus; Floradix Kindervital†; Intestinal Bulking Agent II†; Laxolax; Metamucil plus Calcium; Special Formula Bulking Agent†; ***Chile***: Bilaxil; ***China***: Agiolax (艾者思); ***Cz.***: Agiolax†; ***Fin.***: Agiolax; ***Fr.***: Agiolax; Imegul†; Parapsyllium; Spagulax au Citrate de Potassium†; Spagulax au Sorbitol†; ***Ger.***: Agiolax; ***Gr.***: Agiolax; ***Hong Kong***: Agiolax; Lepicol; ***Hung.***: Agiolax; Lipolest; Super Colon Cleanse; ***India***: Bolax; Chitosyl; Consticare; Fibropil; Lactifiber; Laxive; Morease-I; ***Irl.***: Agiolax; Fybogel Mebeverine; ***Israel***: Agiolax; Biolax Protect; Biolax†; ***Ital.***: Agiolax; Agioslim; Duofibra; Duolaxan; Fibranorm; Fibrolax Complex; Ginolax; Promolax; Psyllogel Fermenti; ***Jpn***: Ryutanshakanto; Seishinrenshiin; ***Malaysia***: Agiolax; ***Mex.***: Agiolax; Psilumax†; ***Neth.***: Agiolax; ***Norw.***: Agiolax†; ***Pol.***: Agiolax; Laxamix†; Otrebuski†; ***Port.***: Agiolax; ***S.Afr.***: Agiolax; ***Spain***: Agiolax; ***Swed.***: Agiolax†; ***Switz.***: Agiolax; Mucilar Avena; ***Thai.***: Agiolax; ***Turk.***: Otaci Diyet Life Psyllium Plus†; ***UK***: Cleansing Herbs; Fibre Dophilus; Fibre Plus; Fybogel Mebeverine; Lion Cleansing Herbs;

Manevac; ***Ukr.***: Softovak (Софтовак); ***USA***: Perdiem†; Senna Prompt; ***Venez.***: Agiolax; Avensyl; Fiberfull.

Pharmacopoeial Preparations
BP 2014: Ispaghula Husk Effervescent Granules; Ispaghula Husk Granules; Ispaghula Husk Oral Powder;
USP 36: Psyllium Hydrophilic Mucilloid for Oral Suspension.

Itopride Hydrochloride *(rINNM)*

HC-803; Hidrocloruro de itoprida; HSR-803; Itoprida, hidrocloruro de; Itopride, Chlorhydrate d'; Itopridi Hydrochloridum; Итоприда Гидрохлорид.
N-[p-[2-(Dimethylamino)ethoxy]benzyl]veratramide hydrochloride.
$C_{20}H_{26}N_2O_4$,HCl=394.9
CAS — 122898-67-3 (itopride).
UNII — 2H9NV66W0I.

Profile

Itopride hydrochloride is a substituted benzamide with general properties similar to those of metoclopramide (p. 1862.2) that has been used for its prokinetic and antiemetic actions in oral doses of 50 mg three times daily before meals.

References.

1. Holtmann G, *et al*. A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006; **354:** 832–40.
2. Talley NJ, *et al*. Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. *Gut* 2008; **57:** 740–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Wei Xian (奥为仙); Bi Jia Si (比佳斯); Dai Lin (代林); Elthon (为力苏); Kai Ting (凯亭); Ruifulin (瑞复啉); WeiTai (威太); Yi Tian (伊天); ***Cz.***: Ganaton; ***India***: Ampty; Ganaton; Gepride; Gi-Tune; Itcan; Itokine; Itonorm; Itoprid; Itotor-OD; Itoz; Motiza; ***Jpn***: Ganaton; ***Malaysia***: Ganaton; ***Philipp.***: Ganaton; ***Rus.***: Ganaton (Ганатон); ***Thai.***: Ganaton; ***Ukr.***: Itomed (Итомед).

Multi-ingredient Preparations. ***Cz.***: Kinito; ***India***: Bizo-IT; Cool Rab-It; Ganaton Total; Gi-Tune MPS; Itorab; Itorbe; Mac-IT; Motiza-MPS; Nura-IT; Pantocid-IT.

Jalap

Jalap Root; Jalap Tuber; Jalapa; Jalapenwurzel; Vera Cruz Jalap; Ялапа.
ATC Herb — HA06AB5009 (Ipomoea purga: tuber); HA06AB5008 (Ipomoea purga: resin).
UNII — 4UDO46YBK2.

Jalap Resin

Jalapa, resina de; Jalapenharz.
CAS — 9000-35-5.
UNII — E1C012DG4R.

Profile

Jalap is the dried tubercles of *Ipomoea purga* (=*Exogonium purga*) (Convolvulaceae). Jalap resin is a mixture of glycosidal resins obtained by extraction of jalap with alcohol and it has a drastic purgative and irritant action. It has been superseded by less toxic laxatives.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Herbal Laxative†; ***S.Afr.***: SB 3 Triple Action Pills†.

Homoeopathic Preparations. ***Fr.***: Dolisedal†; Noctium; ***Switz.***: Sleepium.

Kaolin

Bolus Alba; Caolín; E559; Kaoliini; Kaolinas; Kaolinum; Weisser Ton; Каолин.
CAS — 1332-58-7.
ATC — A07BC02.
ATC Vet — QA07BC02.
UNII — 24H4NWX5CO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet*. Some pharmacopoeias do not differentiate between the heavy and light varieties.

Ph. Eur. 8: (Kaolin, Heavy). A purified, natural, hydrated aluminium silicate of variable composition. It is a fine, white or greyish-white, unctuous powder. Practically insoluble in water and in organic solvents.

BP 2014: (Light Kaolin). A native hydrated aluminium silicate, freed from most of its impurities by elutriation, and dried. It contains a suitable dispersing agent. It is a light, white, odourless or almost odourless, unctuous powder free from gritty particles. Practically insoluble in water and in mineral acids.

The BP 2014 directs that when Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

BP 2014: (Light Kaolin (Natural)). It is Light Kaolin which does not contain a dispersing agent. It is a light, white, odourless or almost odourless, unctuous powder free from gritty particles. Practically insoluble in water and in mineral acids.

The BP 2014 directs that when Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

USP 36: (Kaolin). A native hydrated aluminium silicate, powdered and freed from gritty particles by elutriation. It is a soft, white or yellowish-white powder or lumps with an earthy or clay-like taste and when moistened with water assumes a darker colour and develops a marked clay-like odour. Insoluble in water, in cold dilute acids, and in solutions of alkali hydroxides.

Profile

Light kaolin and light kaolin (natural) are adsorbent antidiarrhoeal agents that have been used as adjuncts to rehydration therapy in the management of diarrhoea (p. 1805.2). Up to about 24 g daily may be taken orally in divided doses. Kaolin is often combined with other antidiarrhoeals, especially pectin.

Kaolin can form insoluble complexes with some drugs in the gastrointestinal tract and reduce their absorption; oral doses should not be taken at the same time.

Externally, light kaolin is used as a dusting powder. Kaolin is liable to be heavily contaminated with bacteria, and when used in dusting powders, it should be sterilised.

Heavy kaolin is used in the preparation of kaolin poultice, which is applied topically with the intention of reducing inflammation and alleviating pain (see Rubefacients and Topical Analgesia, p. 6.3).

Light kaolin is also used as a food additive.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Elusanes Calmodiger†; ***UK***: Childrens Diarrhoea Mixture; Entrocalm.

Multi-ingredient Preparations. ***Arg.***: Anusol-A; Argeal; Cleanance; Opocarbon; ***Austral.***: Diarcalm†; Donnagel; ***Belg.***: Alopate; Neutroses; Restofit; ***Braz.***: Gastrobene; Kaomagma; ***Chile***: Argeal; Furazolidona; Normaderm Concentrado Activo; ***Fr.***: Argeal; Gastropax; Kaobrol; Kaologeais†; Kaomuth; Karayal; Keracnyl; Neutroses; Supro; ***Gr.***: Enteromyk; Fissan-Pate; Kaopectate; Polypictine; ***Hong Kong***: Diapectin†; Kaopectin; Pectolin†; Uni-Kaotin; ***Hung.***: Bolus Adstringens; Bolus Laxans; Pasta Cool; ***Indon.***: Diaend; Envios; Kaopectate†; Neo Diaform; Neo Kaocitin; Neo Kaolana; Neo Kaominal; Opidiar; ***Israel***: Kaopectin; Zincod; ***Ital.***: Katoxyn; Keromicil; Neutrose S Pellegrino; Streptomagma; ***Mex.***: Ameban; Caopecfar†; Colfur†; Colistin Magma†; Coralzul; Depofin; Dia-Par Compuesto; Dibapec Compuesto†; Estibal; Exofur; Facetin-D; Farpectol; Furoxona CP; Isocar; K-Omistron; Kaomycin†; Kaopectate†; Kapecfuran; Kediar; Lactopectin†; Neokap; Neoxil; Nineka; Olam†; Optazol; Quimefuran; Suyodil; Treda; Yodozona; ***S.Afr.***: Adco-Biskapect†; Betapect; Bipectinol†; Bolus Eucalypti Comp†; Chloropect; Collodene†; Enterolyte; Gastropect; Kaostatex; Pectin-K†; Pectrolyte; SB Diarrhoea Mixture†; ***Singapore***: Axcel Kaopec; Beakopectin; Bio-Taches Masque†; Diapectin; Kaomix; Pectolin; ***Switz.***: Cicafissan; Creme vulneraire; Neo-Decongestine; Neutroses; Padma-Lax; Padmed Laxan; Phlogantin†; ***Thai.***: Alkamine†; Alumag; Alupep; Cenopect†; Coccila; Coccila; Conmag; Diaropect; Difuran; Diocin; Disento PF; Disento; Droximag-P; Furamed; Furasian; Furopectal; Furopectin; Kaolin Mixture w/ Pectin; Kaolin Mixture; Kaopectal; Kaptate; Patarlin; Profura; Siemag; Suratin; ***UAE***: Kaptin; ***UK***: Collis Browne's; De Witt's Antacid; Junior Kao-C; KLN; Moorland; Opazimes; ***USA***: K-C; Kao-Paverin; Kao-Spen; Kaodene Non-Narcotic; Mexsana; ***Venez.***: Argeal; Klincosal; Niosilin.

Homoeopathic Preparations. ***Ger.***: Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; ***Neth.***: Phonix Hydrargyrum; ***UK***: Bolus Eucalypti Comp.

Pharmacopoeial Preparations
BP 2014: Kaolin and Morphine Mixture; Kaolin Mixture; Kaolin Poultice.

Lactitol *(BAN, rINN)*

E966; β-Galactosido-sorbitol; Lactit; Lactitolum; Lactobiosit; Lactositol; Laktitol; Laktitoli; Laktitolis; Лактитол.
4-*O*-(β-D-Galactopyranosyl)-D-glucitol.
$C_{12}H_{24}O_{11}$=344.3
CAS — 585-86-4.
ATC — A06AD12.
ATC Vet — QA06AD12.
UNII — L2B0WJF7ZY (lactitol); UH2K6W1Y64 (lactitol monohydrate).

Pharmacopoeias. In *USNF*. *Eur.* (see p. vii) includes the monohydrate.

Ph. Eur. 8: (Lactitol Monohydrate). A white or almost white crystalline powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

USNF 31: (Lactitol). It may be the anhydrous form, the monohydrate, or the dihydrate. White or light brown, odourless, crystals. It has a mild, sweet taste, and no aftertaste.

Profile

Lactitol is a disaccharide analogue of lactulose (below) and has similar actions and uses.

Lactitol monohydrate is used as an oral powder or solution in the management of hepatic encephalopathy (p. 1808.2) and in constipation (p. 1804.3). Lactitol monohydrate 1.05 g is equivalent to about 1 g of anhydrous lactitol.

In the treatment of **hepatic encephalopathy**, lactitol monohydrate is given in usual oral doses of 500 to 700 mg/kg daily in 3 divided doses at meal times. The dose is subsequently adjusted to produce 2 soft stools daily.

In the treatment of **constipation**, lactitol monohydrate is given in an initial dose of 20 g daily as a single dose with the morning or evening meal, subsequently adjusted to produce one stool daily. A dose of 10 g daily may be sufficient for many patients.

Doses should be mixed with food or liquid, and 1 to 2 glasses of liquid should be drunk with the meal.

Lactitol is a permitted sweetener in foods.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lactitol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Imporal; ***Belg.***: Imporal; Normolaxil†; Portolac†; ***Braz.***: Sigmalac; ***China***: Kang Xin (康欣); ***Fin.***: Imporal Ex-Lax†; Lalax†; ***Fr.***: Imporal; ***Ger.***: Imporal†; ***Gr.***: Imporal; ***India***: Encelax; Eva-Q; Lactihep; ***Israel***: Novolax; ***Ital.***: Portolac; ***Jpn***: Portolac; ***Neth.***: Imporal; ***NZ***: Imporal; ***Port.***: Imporal; ***Rus.***: Exportale (Экспортал); ***Spain***: Emporal; Oponaf; ***Swed.***: Imporal; ***Switz.***: Imporal; ***Thai.***: Imporal†; ***Turk.***: Imporal.

Multi-ingredient Preparations. ***India***: Lactifiber; ***Ital.***: Levoplus.

Lactulose *(BAN, USAN, rINN)*

Lactulosa; Lactulosum; Laktuliozė; Laktuloosi; Laktulos; Laktulosa; Laktüloz; Laktulóz; Лактулоза.
4-*O*-β-D-Galactopyranosyl-D-fructose.
$C_{12}H_{22}O_{11}$=342.3
CAS — 4618-18-2.
ATC — A06AD11.
ATC Vet — QA06AD11.
UNII — 9U7D5QH5AE.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. *Chin.* only contains specifications for a solution. *US* only contains specifications for a solution and a concentrated liquid.

Ph. Eur. 8: (Lactulose). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in toluene.

Ph. Eur. 8: (Lactulose, Liquid; Lactulose Solution BP 2014). An aqueous solution of lactulose. It contains not less than 62.0% w/v of lactulose; it may contain other sugars including lactose, epilactose, galactose, tagatose, and fructose. It may contain a suitable antimicrobial preservative. It is a clear, colourless or pale brownish-yellow, viscous liquid. Miscible with water. It may be a supersaturated solution or may contain crystals that disappear on heating. A 10.0% solution in water has a pH of 3.0 to 7.0.

USP 36: (Lactulose Concentrate). A colourless to amber syrupy liquid that may exhibit some precipitation and

darkening on standing. Miscible with water. Store in airtight containers preferably at a temperature between 2 degrees and 30 degrees.

Uses and Administration

Lactulose is a synthetic disaccharide osmotic laxative (p. 1804.1) used in the treatment of constipation (p. 1804.3) and in hepatic encephalopathy (p. 1808.2). Lactulose is broken down by colonic bacteria mainly into lactic acid. This exerts a local osmotic effect in the colon resulting in increased faecal bulk and stimulation of peristalsis. It may take up to 48 hours before an effect is obtained. When larger doses are given for hepatic encephalopathy the pH in the colon is reduced significantly and the absorption of ammonium ions and other toxic nitrogenous compounds is decreased, leading to a fall in blood-ammonia concentration and an improvement in mental function.

Lactulose is usually given orally as a solution containing about 3.35 g of lactulose per 5 mL, with other sugars such as galactose and lactose; an oral powder formulation is also available in some countries. In the treatment of **constipation**, the usual initial dose is 10 to 20 g (15 to 30 mL) given daily in a single dose or in 2 divided doses; doses up to 45 mL daily of the solution (or up to 40 g of the reconstituted oral powder formulation) have been given. The dose is gradually adjusted according to the patient's needs. For doses in children, see below.

In **hepatic encephalopathy**, an oral dose of 60 to 100 g (90 to 150 mL) is given daily in 3 divided doses. The dose is subsequently adjusted to produce 2 or 3 soft stools each day. Lactulose solution 200 g (300 mL) mixed with 700 mL of water or sodium chloride 0.9% has been used as a retention enema; the enema is retained for 30 to 60 minutes, repeated every 4 to 6 hours until the patient is able to take oral medication.

References.
1. Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora: clinical consequences. *Drugs* 1997; **53:** 930–42.
2. Schumann C. Medical, nutritional and technological properties of lactulose: an update. *Eur J Nutr* 2002; **41** (suppl): I17–I25.

Administration in children. In the UK, children may be given the following oral doses of lactulose 3.35 g per 5 mL solution for constipation; doses may be adjusted according to response:

- 1 month to 1 year: 2.5 mL twice daily
- 1 to 5 years: 5 mL twice daily
- 5 to 10 years: 10 mL twice daily
- 10 to 18 years: 15 mL twice daily

Diagnosis and testing. *THE SUGAR ABSORPTION TEST.* In healthy individuals lactulose is largely unabsorbed from the gastrointestinal tract, but in, for example, coeliac disease there is increased permeability to disaccharides such as lactulose and a paradoxical decrease in the absorption of monosaccharides. This led to the development of the differential sugar absorption test in which 2 sugars are given simultaneously by mouth and the urinary recovery of each is determined; mannitol is commonly used as the monosaccharide component and lactulose as the disaccharide. Alternatives include mannitol plus cellobiose and rhamnose plus lactulose. This absorption test is useful in the investigation of intestinal disease.[1]

The lack of a standardised test solution has hampered comparison of test results. Although hyperosmolar solutions are better at determining intestinal damage,[2] some have preferred to use low osmolar solutions because of the risk of inducing osmotic diarrhoea, especially in children.

A study found the sugar absorption test to be strongly predictive of an organic cause of chronic diarrhoea; it may be useful in improving the selection of patients who need further evaluation.[3]

THE LACTULOSE BREATH TEST(hydrogen breath test). Lactulose is converted by bacteria in the large bowel to short chain fatty acids with the production of small quantities of hydrogen gas. The hydrogen is rapidly absorbed and is exhaled in the breath and measurement of its production is used to measure orocaecal transit time and carbohydrate malabsorption. However, even small doses of lactulose shortens transit time, which may limit the value of this test.[4]

The test is also diagnostic for bacterial overgrowth in the small intestine, which is increased in irritable bowel syndrome. Although hydrogen is produced in most subjects, methane is also produced in up to 50% of healthy subjects, and data suggest there may be clinical implications to different gas profiles. A study found that the presence of methane was associated with constipation, and with constipation-predominant irritable bowel syndrome. Methane production was infrequent in diarrhoea-predominant irritable bowel syndrome and virtually absent in inflammatory bowel disease. Diarrhoea and inflammatory bowel disease were associated with hydrogen production. Whether the type of bacterial flora causally determines symptoms is as yet unknown.[5] The diagnostic value of the test in irritable bowel syndrome has, however, been questioned.[6]

1. Uil JJ, *et al.* Clinical implications of the sugar absorption test: intestinal permeability test to assess mucosal barrier function. *Scand J Gastroenterol* 1997; **223** (suppl): 70–8.
2. Uil JJ, *et al.* Sensitivity of a hyperosmolar or "low" -osmolar test solution for sugar absorption in recognizing small intestinal mucosal damage in coeliac disease. *Dig Liver Dis* 2000; **32:** 195–200.
3. Di Leo V, *et al.* Lactulose/mannitol test has high efficacy for excluding organic causes of chronic diarrhea. *Am J Gastroenterol* 2003; **98:** 2245–52.
4. Miller MA, *et al.* Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. *Dig Dis Sci* 1997; **42:** 10–18.
5. Pimentel M, *et al.* Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci* 2003; **48:** 86–92.
6. Bratten JR, *et al.* Lactulose breath testing does not discriminate patients with irritable bowel syndrome from healthy controls. *Am J Gastroenterol* 2008; **103:** 958–63.

Adverse Effects

Lactulose may cause abdominal discomfort associated with flatulence or cramps. Nausea and vomiting have occasionally been reported after high doses. Some consider the taste to be unpleasant; this can be minimised by dilution in water, fruit juice, or milk, or by mixing the dose with food. Prolonged use or excessive dosage may result in diarrhoea with excessive loss of water and electrolytes, particularly potassium. Hypernatraemia has been reported.

Lactic acidosis. Severe lactic acidosis developed in a patient with adynamic ileus who was being given lactulose for hepatic encephalopathy.[1]

1. Mann NS, *et al.* Lactulose and severe lactic acidosis. *Ann Intern Med* 1985; **103:** 637.

Precautions

Lactulose should not be given to patients with galactosaemia or intestinal obstruction. It should not be used in patients on a low galactose diet and care should be taken in patients with lactose intolerance or in diabetic patients because of the presence of some free galactose and lactose.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lactulose as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Taken orally, lactulose passes essentially unchanged into the large intestine where it is metabolised by saccharolytic bacteria with the formation of simple organic acids, mainly lactic acid and small amounts of acetic and formic acids. The small amount of absorbed lactulose is subsequently excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Genocolan; Lactulon; Lafelax; Medixin; Tenualax; ***Austral.***: Actilax; Duphalac; Genlac†; Lac-Dol; Lactocur; ***Austria***: Bifiteral†; Duphalac; Laevolac; ***Belg.***: Bifiteral; Duphalac; ***Braz.***: Colonac; Duphalac; Farlac; Lactuliv; Lactulona; Normolax; Pentalac; ***Canad.***: Euro-Lac; Gen-Lac†; ***Chile***: Axant; Dicelax; Dismam; Duphalac; ***China***: Danilax (丹尼莱克); Duphalac (杜密克); Laevolac (拉韦); Lidong (利动); ***Cz.***: Duphalac; Lactecon†; Lactorin; ***Denm.***: Favolax†; Medilax; ***Fin.***: Duphalac; Lactecon†; Laxorin; Levolac; ***Fr.***: Duphalac; Laxaron; ***Ger.***: Bifinorma†; Bifiteral; Eugalac†; Lactuflor; LactuGel; Lactulade; Lactuverlan†; Tulotract†; ***Gr.***: Duphalac; Neosoldan; Purgolac; Purselect; ***Hong Kong***: Danilax; Dhactulose; Duphalac; Laevolac; Martulose†; ***Hung.***: Duphalac; Laevolac; ***India***: Bowelac; Bowlease; Canphalac-Sol; Daffolac; Duphalac; Evacuate; Evict; Eziluk; Fresky; Gush; Lace; Laclouse; Lacrest; Lactucos; Lactulax; Lactulin; Lactusan; Laxan; Laxatin; Laxicare Soft; Laxil; Laxitose; Laxobus; Laxolin; Laxose; Livintact-EV; Livoluk; Looz; Loozit; Loozylax; MTLac; Normalac; Nostipan; Novalak; ***Indon.***: Constipen; Dulcolactol; Duphalac; Lacons; Lactulax; Lantulos; Laxadilac†; Opilax; Pralax; Solac; ***Irl.***: Duphalac; Gerelax†; Lactugal†; Laevolac; Laxose; ***Israel***: Avilac; Gerelax; Laevolac; Normase; ***Ital.***: Dia-Colon; Duphalac; Epalat EPS†; Epalfen; Laevolac; Lattulac; Normase; Osmolac; Verelait; ***Jpn***: Monilac; ***Malaysia***: Dhactulose; Duphalac; Lactul; ***Mex.***: Duphalac; Lactulax; Quimtulac; Regulact; ***Neth.***: Duphalac; Epalfen†; Kruidvat Laxeerdrank; Laevolac; Laxeerdrank; Laxeersiroop; Legendal; ***Norw.***: Duphalac; Levolac; ***NZ***: Duphalac; Laevolac†; ***Philipp.***: Duphalac; Lactul; Lilac; Rilax; ***Pol.***: Duphalac; Lactulol; Normalac; Normase†; ***Port.***: Colsanac; Duphalac; Laevolac; Obstipar†; ***Rus.***: Duphalac (Дюфалак); Gudlac (Гудлак); Livoluk-PB (Ливолюк-ПБ); Normase (Нормазе); Portalac (Порталак); Romfalak (Ромфалак); ***S.Afr.***: Aculax; Adco-Liquilax; Duphalac; Lacson; Laxette; ***Singapore***: Dhactulose; Duphalac; Lactus; ***Spain***: Belmalax†; Duphalac; ***Swed.***: Duphalac; Laktipex; ***Switz.***: Duphalac; Gatinar; Legendal; Rudolac; ***Thai.***: Duphalac; Hepalac; Laevolac; Losalac; Safex; ***Turk.***: Duphalac; Lactulac; Laevolac; Laktol†; Osmolak; ***UAE***: Soflax; ***UK***: Duphalac; Lactugal; Lemlax; Regulose; ***Ukr.***: Bioflorax (Биофлоракс)†; Duphalac (Дуфалак); Lactuvit (Лактувит); Laxarin (Лаксарин); Medulac (Медулак); Normase (Нормазе); Normolact (Нормолакт); ***USA***: Cephulac; Chronulac†; Constilac†; Constulose; Duphalac†; Enulose; Generlac; Kristalose; ***Venez.***: Lactulona; Moderan.

Multi-ingredient Preparations. ***Arg.***: Bifidosa; ***Belg.***: Transitol; ***Fr.***: Melaxose; Transulose; ***Ger.***: Eugalan Topfer†; ***India***: Osmowin; ***Indon.***: Laktobion; ***Ital.***: Combilax; Lactolas; Lactomannan; Levoplus; Naturalass; Plurilac; Transitol; Transulose; ***Mex.***: Transilax; ***Neth.***: Transulose; ***Port.***: Melaxose; ***Rus.***: Lactofiltrum (Лактофильтрум); ***Ukr.***: Lactofiltrum-ECO (Лактофильтрум-Эко); Transuloza (Трансулоза).

Pharmacopoeial Preparations
BP 2014: Lactulose Oral Powder;
Ph. Eur.: Liquid Lactulose;
USP 36: Lactulose Solution.

Lafutidine *(rINN)*

FRG-8813; Lafutidina; Lafutidinum; Лафутидин.
(±)-2-(Furfurylsulfinyl)-*N*-[(*Z*)-4-{[4-(piperidinomethyl)-2-pyridyl]oxy}-2-butenyl]acetamide.
$C_{22}H_{29}N_3O_4S$=431.6
CAS — 118288-08-7.
ATC — A02BA08.
ATC Vet — QA02BA08.
UNII — 495407ADLC.

Profile

Lafutidine, like cimetidine (p. 1827.1), is a histamine H_2-antagonist. It is used in the management of peptic ulcer disease and gastritis. Lafutidine is given orally; a usual dose for peptic ulcers is 10 mg twice daily, and for gastritis, 10 mg daily in the evening. Care is required in patients with renal or hepatic impairment.

References.
1. Uesugi T, *et al.* The efficacy of lafutidine in improving preoperative gastric fluid property: a comparison with ranitidine and rabeprazole. *Anesth Analg* 2002; **95:** 144–7.
2. Mikawa K, *et al.* Lafutidine vs cimetidine to decrease gastric fluid acidity and volume in children. *Can J Anaesth* 2003; **50:** 425–6.
3. Inamori M, *et al.* Early effects of lafutidine or rabeprazole on intragastric acidity: which drug is more suitable for on-demand use? *J Gastroenterol* 2005; **40:** 453–8.
4. Higuchi K, *et al.* Lafutidine can improve the quality of gastric ulcer healing in humans: a randomized, controlled, multicenter trial. *Inflammopharmacology* 2006; **14:** 226–30.
5. Yamagishi H, *et al.* Stronger inhibition of gastric acid secretion by lafutidine, a novel H(2) receptor antagonist, than by the proton pump inhibitor lansoprazole. *World J Gastroenterol* 2008; **14:** 2406–10.
6. Kim N, *et al.* Lafutidine versus lansoprazole in combination with clarithromycin and amoxicillin for one versus two weeks for Helicobacter pylori eradication in Korea. *Helicobacter* 2008; **13:** 542–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: He Ke Di Si (赫克迪思); Lemeiting (乐美汀); Ning Wei Shu (宁维舒); Nuo Fei (诺非); Shun Ru (顺儒); Weisida (卫斯大); ***Jpn***: Protecadin; Stogar†.

Lansoprazole *(BAN, USAN, rINN)*

A-65006; AG-1749; CG-4801; Lansopratsoli; Lansoprazol; Lansoprazolum; Лансопразол.
2-({3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl}methyl} sulphinylbenzimidazole.
$C_{16}H_{14}F_3N_3O_2S$=369.4
CAS — 103577-45-3.
ATC — A02BC03.
ATC Vet — QA02BC03.
UNII — 0K5C5T2QPG.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lansoprazole). A white or brownish powder. Practically insoluble in water; soluble in anhydrous alcohol; very slightly soluble in acetonitrile. It exhibits polymorphism. Store in airtight containers. Protect from light.

USP 36: (Lansoprazole). A white to brownish-white powder. Practically insoluble in water; freely soluble in dimethylformamide. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Lansoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p. 1867.2). It is used in the treatment of peptic ulcer disease and in other conditions where inhibition of gastric acid secretion may be beneficial.

Lansoprazole is given orally as capsules, dispersible tablets, or suspension containing enteric-coated granules. Once daily regimens are taken before food in the morning. Lansoprazole has also been given intravenously.

For the relief of acid-related **dyspepsia** (p. 1806.3) intermittent courses of lansoprazole may be given in oral doses of 15 or 30 mg once daily, for 2 to 4 weeks.

In the treatment of **gastro-oesophageal reflux disease** (p. 1807.2) the usual oral dose is 15 to 30 mg once daily for 4 to 8 weeks; thereafter maintenance therapy can be continued with 15 or 30 mg once daily according to response.

Lansoprazole is given orally for the treatment of **peptic ulcer disease** (p. 1813.2); in the UK usual doses are 30 mg once daily. Treatment is continued for 2 to 4 weeks for duodenal and 4 to 8 weeks for gastric ulcer. In the USA, a dose of 15 mg daily for 4 weeks is recommended for duodenal ulcer, and 30 mg once daily is given for up to 8 weeks for gastric ulceration. When appropriate, 15 mg daily may be used as maintenance therapy for the prevention of relapse of duodenal ulcer. Lansoprazole may be combined with antibacterials in 7- to 14-day **triple therapy** regimens for the eradication of *Helicobacter pylori*. Effective regimens include lansoprazole 30 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily; lansoprazole with amoxicillin and metronidazole has also been used. **Dual therapy** with lansoprazole 30 mg three times daily and amoxicillin for 14 days is also used, but may be less effective. In patients with **NSAID-associated ulceration** a dose of 30 mg daily for 4 to 8 weeks is recommended; 15 to 30 mg daily may be used as prophylaxis for patients who require continued NSAID treatment.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p. 1814.3) the initial oral dose is 60 mg once daily, adjusted as required. Doses of up to 90 mg twice daily have been used. Daily doses greater than 120 mg should be given in divided doses.

For doses in children and in hepatic impairment, see below.

General references. For general reviews of proton pump inhibitors, see Omeprazole, p. 1867.3.

1. Langtry HD, Wilde MI. Lansoprazole: an update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997; **54:** 473–500.
2. Matheson AJ, Jarvis B. Lansoprazole: an update of its place in the management of acid-related disorders. *Drugs* 2001; **61:** 1801–33.
3. Freston JW, *et al*. Lansoprazole for maintenance of remission of erosive oesophagitis. *Drugs* 2002; **62:** 1173–84.
4. Dando TM, Plosker GL. Intravenous lansoprazole: in erosive oesophagitis. *Drugs* 2004; **64:** 2085–9.
5. Croom KF, Scott LJ. Lansoprazole: in the treatment of gastro-oesophageal reflux disease in children and adolescents. *Drugs* 2005; **65:** 2129–35.

Administration. Lansoprazole *capsules* should be swallowed whole and not crushed or chewed. Lansoprazole *dispersible tablets* should be placed on the tongue and allowed to disintegrate and the resultant granules swallowed; alternatively, the tablets may be swallowed whole with a glass of water. The tablets should not be crushed or chewed. The tablets may also be dispersed in a small amount of water and given via an oral syringe, or via a nasogastric tube. Lansoprazole *granules for oral suspension* should be reconstituted in a little water and swallowed immediately. Where the suspension formulation is not available, the contents of the capsules (enteric-coated granules) can be sprinkled on a small amount of soft food (such as yogurt or apple sauce) or mixed with a little fruit juice and swallowed. For dosage via a nasogastric tube, the contents of a capsule may be mixed with 40 mL of apple juice; additional apple juice may be used to flush the tube.

Administration in children. In the USA, children may be given lansoprazole for the short-term treatment of erosive oesophagitis and symptomatic gastro-oesophageal reflux disease. In children aged 1 to 11 years, the following oral doses may be given once daily for up to 12 weeks, according to body-weight:

- 30 kg or less: 15 mg
- over 30 kg: 30 mg

Doses of up to 30 mg twice daily have been used in children who remain symptomatic after 2 or more weeks of treatment.

In children aged from 12 to 17 years, oral lansoprazole 30 mg once daily for up to 8 weeks may be given for erosive oesophagitis, and 15 mg once daily for up to 8 weeks may be given for symptomatic non-erosive gastro-oesophageal reflux disease.

Although not licensed for children in the UK, the *BNFC* recommends lansoprazole in the treatment of gastro-oesophageal reflux disease, acid-related dyspepsia, duodenal and benign gastric ulcer including those complicating NSAID therapy, and fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis; comparable oral doses may be given once daily in the morning:

- up to 30 kg: 0.5 to 1 mg/kg (maximum 15 mg)
- over 30 kg: 15 to 30 mg

Studies of oral lansoprazole in infants with gastro-oesophageal reflux disease have produced conflicting results. Lansoprazole reduced symptoms in one study compared with treatment with a hydrolysed formula feed,[1] whereas another study found lansoprazole to be no more effective than placebo; a higher incidence of adverse effects was also reported with lansoprazole therapy.[2] For findings from a review (including these references) regarding the efficacy and safety of proton pump inhibitors in infants, children, and adolescents, see Administration in Children, under Omeprazole, p. 1867.3.

1. Khoshoo V, Dhume P. Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2008; **46:** 352–4.
2. Orenstein SR, *et al*. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr* 2009; **154:** 514–20.

Administration in hepatic impairment. Exposure to lansoprazole is increased in patients with hepatic impairment. UK licensed product information suggests that patients with moderate to severe liver disease should be kept under supervision, and the oral daily dose reduced by 50%.

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

Reviews.

1. Freston JW, *et al*. Safety profile of lansoprazole: the US clinical trial experience. *Drug Safety* 1999; **20:** 195–205.
2. Claessens AA, *et al*. Safety review in 10,008 users of lansoprazole in daily practice. *Pharmacoepidemiol Drug Safety* 2000; **9:** 383–91.

Effects on the blood. For a report of thrombocytopenia with lansoprazole, see under Omeprazole, p. 1868.2.

Effects on electrolytes. For mention of a fall in electrolytes during treatment with proton pump inhibitors including lansoprazole, see Omeprazole, p. 1868.3.

Effects on the endocrine system. For cases of gynaecomastia associated with lansoprazole, see p. 1868.3.

Effects on the gastrointestinal tract. Glossitis (associated in some cases with black tongue or stomatitis) has been reported in a few patients taking lansoprazole as part of a triple therapy regimen for *Helicobacter pylori* elimination in peptic ulcer disease.[1] Discoloured tongue has been reported in a patient taking lansoprazole alone.[2]

An increase in gastritis occurred in patients infected with *Helicobacter pylori* when given long-term lansoprazole therapy.[3] For further discussion of the link between *H. pylori*, gastritis, and proton pump inhibitor use, see Gastrointestinal Tumours, p. 1869.3.

For a suggestion that the incidence of diarrhoea may be greater with lansoprazole than omeprazole see Incidence of Adverse Effects, p. 1868.2. Cases of microscopic colitis have been reported with use of lansoprazole.[4] UK licensed product information states that stopping therapy should be considered in the case of severe and/or persistent diarrhoea.

1. Greco S, *et al*. Glossitis, stomatitis, and black tongue with lansoprazole plus clarithromycin and other antibiotics. *Ann Pharmacother* 1997; **31:** 1548.
2. Scully C. Discoloured tongue: a new cause? *Br J Dermatol* 2001; **144:** 1293–4.
3. Berstad AE, *et al*. Helicobacter pylori gastritis and epithelial cell proliferation in patients with reflux oesophagitis after treatment with lansoprazole. *Gut* 1997; **41:** 740–7.
4. Hilmer SN, *et al*. Microscopic colitis associated with exposure to lansoprazole. *Med J Aust* 2006; **184:** 185–6.

Effects on the musculoskeletal system. For reference to a case of eosinophilia and myalgia related to lansoprazole therapy, see p. 1869.1.

Effects on the skin. For mention of skin reactions to lansoprazole, see p. 1869.2.

Hypersensitivity. For a suggestion that lansoprazole may be tolerated in patients sensitive to omeprazole and pantoprazole see p. 1870.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lansoprazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Interactions

As for Omeprazole, p. 1870.3. Antacids and sucralfate may reduce the bioavailability of lansoprazole, and should not be taken within 1 hour of a dose of lansoprazole.

For reference to a lack of effect of lansoprazole on diazepam, see Gastrointestinal Drugs, p. 1069.3, and for a clinically insignificant effect on theophylline clearance, see p. 1236.1. For reference to glossitis occurring when lansoprazole was used with some antibacterials, see Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

Lansoprazole is rapidly absorbed after oral doses and peak plasma concentrations occur after about 1.5 to 2 hours. Bioavailability is reported to be 80% or more even with the first dose, although the drug must be given in an enteric-coated form since lansoprazole is unstable at acid pH. Food slows the absorption of lansoprazole and reduces the bioavailability by about 50%. Lansoprazole is about 97% bound to plasma protein. It is extensively metabolised in the liver, primarily by cytochrome P450 isoenzyme CYP2C19 to form 5-hydroxyl-lansoprazole and by CYP3A4 to form lansoprazole sulfone. Metabolites are excreted mainly in faeces via the bile; only about 15 to 30% of a dose is excreted in urine. The plasma elimination half-life is around 1 to 2 hours but the duration of action is much longer. Clearance is decreased in elderly patients, and in hepatic impairment.

References.

1. Hussein Z, *et al*. Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. *Br J Clin Pharmacol* 1993; **36:** 391–8.
2. Flouvat B, *et al*. Single and multiple dose pharmacokinetics of lansoprazole in elderly subjects. *Br J Clin Pharmacol* 1993; **36:** 467–9.
3. Delhotal-Landes B, *et al*. Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. *Eur J Clin Pharmacol* 1993; **45:** 367–71.
4. Delhotal Landes B, *et al*. Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet* 1995; **28:** 458–70.
5. Karol MD, *et al*. Lansoprazole pharmacokinetics in subjects with various degrees of kidney function. *Clin Pharmacol Ther* 1997; **61:** 450–8.
6. Tran A, *et al*. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther* 2002; **71:** 359–67.
7. Zhang W, *et al*. Age-dependent pharmacokinetics of lansoprazole in neonates and infants. *Paediatr Drugs* 2008; **10:** 265–74.

Metabolism. As for omeprazole (p. 1871.2), the cytochrome P450 isoenzyme CYP2C19 (*S*-mephenytoin hydroxylase) is involved in the hydroxylation of lansoprazole, and individuals who are deficient in this enzyme are poor metabolisers of lansoprazole.[1,2] There is some suggestion that the effect of this genetic polymorphism on lansoprazole may be less than the effect on omeprazole.[3]

1. Pearce RE, *et al*. Identification of the human P450 enzymes involved in lansoprazole metabolism. *J Pharmacol Exp Ther* 1996; **277:** 805–16.
2. Sohn DR, *et al*. Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4′-hydroxylation phenotype status. *Clin Pharmacol Ther* 1997; **61:** 574–82.
3. Kim K-A, *et al*. Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther* 2002; **72:** 90–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lanzoacid; Lanzopral; Mesactol; ***Austral.***: Lanzopran; Zopral; Zoton; ***Austria***: Agopton; Lansobene; Lansohexal; ***Belg.***: Dakar; ***Braz.***: Alkazol†; Lanogastro; Lanz; Lanzol; Lanzopept; Lanzopran; Lispelin; Neozol; Ogastro; Prazol; Ulcestop; ***Canad.***: Prevacid; ***Chile***: Fudermex; Gastride; Langastrol; Lanzopral; Unimet; Unival; ***China***: Lan Xi Duo (兰悉多); Prevacid (普托平); Richwe (拉索脱); Takepron (达克普隆); ***Cz.***: Lansoprol; Lansoram; Lanzul; ***Fin.***: Gasterix; Lanrec; Lantil; Lanvone; Zolt; ***Fr.***: Lanzor; Ogast; Ogastoro; ***Ger.***: Agopton; Lanso Tad†; Lanso-Q†; Lansogamma†; Lanzor†; ***Gr.***: Apradil; Elcodil; Lanciprol; Lanso; Lanzol; Laprazol; Prevacid; Zoletad; ***Hong Kong***: Emlansa; Lanzol; Lasoprol; Takepron; ***Hung.***: Emillan; Landia; Lansacid; Lansogen; Lansone; Lansoptol; Levant†; Protonexa; Refluxon; ***India***: Aclanz; Arlan; Bal-Lanz; Cap Loc; Chexid; Culans; Juniorlanzol; L-30; Lampo; Lan; Lance; Lancer; Lanchek; Lancibay; Lancid; Lancus; Lands; Lanip; Lanogard; Lanoz; Lanpro; Lans-OD; Lansec; Lanset; Lanso; Lansofast; Lansol; Lansomac; Lansoriv; Lansoz; Lanspep; Lanspro; Lanzap; Lanzee; Lanzip; Lanzo; Lanzol; Lanzopen; Lasole; Laz; Lepez; Levant; Lezo; Liza; Locid; LP; Lupizole; Okalan; Olez; ***Indon.***: Betalans; Caprazol; Compraz; Digest; Erphalanz; Gastrolan; Inhipraz; Lagas; Lancid; Lanpracid; Lapraz; Laproton; Lasgan; Laz; Lazol; Lexid; Loprezol; Nufaprazol; Prazotec; Prolanz†; Prosogan; Protica; Pysolan; Solans; Sopralan; Ulceran; ***Irl.***: ByLans; Lanziop†; Lanzol; Razolager; Zomel; Zoton; Zotrole; ***Israel***: Lanso; Lanton; Zoton; ***Ital.***: Ermes; Frilans; Krovaneg; Lansox; Levogenix; Limpidex; Lomevel; Peptirex; Pergastid; Zoton; ***Jpn***: Prevacid†; Takepron; ***Malaysia***: Gastrovex; Julphasole; Lanpro; Lans-OD; Lanso; Levant; Prevacid; ***Mex.***: Amdory; Arular†; Bonzol; Gavonad; Ilsatec; Imidex; Keval†; Lafin; Lanodizol; Mavilan; Mediprim; Ogastro; Olan; Palatrin; Pranix; Safemar; Serax; Uldapril; Ulpax; ***Neth.***: Lanzatol; Prezal; ***Norw.***: Lanzo; ***NZ***: Lanzol; Solox; ***Philipp.***: Lansodin; Lanspro; Lanzep; Lanzohex†; Lanzole; Prevacid; Propilan; Pylison; Pysolan; Taquidine; ***Pol.***: Lanbax; LansoLek†; Lantrea; Lanzogen; Lanzostad; Lanzul; Rapilazole; Renazol; Zalanzo; ***Port.***: Alexin; Alprotec; Belmural; Dispepci; Doxatec; Gastrex; Gastribien; Gastrolanzo†; Gastroliber; Hepizol†; Lansox; Lanzogastro; Lapol; Ogasto; Pampe; Ulcertec; ***Rus.***: Acrilans (Акриланз)†; Epicur (Эпикур); Helicol (Геликол); Lancid (Ланцид); Lansofed (Лансофед); Lansoptol (Лансоптол); Lanzabel (Ланзабел); Lanzap (Ланзап); Loenzar (Лоэнзар); ***S.Afr.***: Adco-Roznal; Gastrid; Lancap; Lansoloc; Lanzor; ***Singapore***: Lasoprol; Prevacid; ***Spain***: Bamalite†; Estomil; Eudiges†; Lanzol; Monolitum; Opiren; Pasgram†; Pro Ulco; Protoner; ***Swed.***: Lanzo; Nixacid; ***Switz.***: Agopton; Lansoprax;

Thai.: Prevacid; ***Turk.***: Aprazol; Degastrol; Helicol; Lansazol; Lansoprol; Lansor; Lanzedin; Lukazrol; Ogastro; Opagis; Progis; Vogast; Zoprol; ***UAE***: Lanfast; ***UK***: Zoton; ***Ukr.***: Lancerol (Ланцерол); Lansoprol (Лансопрол); Lanzap (Ланзап); ***USA***: Prevacid; ***Venez.***: Biolanz; Gastrazol; Lansovax; Lanzol; Lanzopral; Ogastro.

Multi-ingredient Preparations. ***Braz.***: H Bacter; Helicopac; Heliklar; Lansodom†; Lansoprid†; Pylorikit; Pyloripac Retrat; Pyloripac; Pyloriset; Pyloritrat; ***Canad.***: Hp-Pac; ***Chile***: Lanzopral Heli-Pack; Pylopac; ***Fin.***: Helipak A; Helipak K; Helipak T; ***India***: Domsin-LA; Heligo; L-Dom; Lance-D; Lancidom; Lanip-D; Lans-DX; Lansi Kit; Lanspro-D; Lanzee-DM; Lapra-D; Lasole-D; Leedom; Lesozap-D; Liza-D; Locid-D; LTC-Kit; Okalan D; Pylokit; ***Mex.***: Pylopac; ***Turk.***: Helipak; Trio; ***USA***: Prevpac.

Used as an adjunct in:. ***Turk.***: Napro-Pac; ***USA***: Prevacid NapraPAC†.

Pharmacopoeial Preparations
BP 2014: Gastro-resistant Lansoprazole Capsules; Gastro-resistant Lansoprazole Tablets;
USP 36: Lansoprazole Delayed-Release Capsules.

Lidamidine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lidamidina; Lidamidina, hidrocloruro de; Lidamidine, Chlorhydrate de; Lidamidini Hydrochloridum; WHR-1142A; Лидамидина Гидрохлорид.

N-(2,6-Dimethylphenyl)-*N'*-[imino(methylamino)methyl]urea hydrochloride.

$C_{11}H_{16}N_4O,HCl$=256.7

CAS — 66871-56-5 (lidamidine); 65009-35-0 (lidamidine hydrochloride).

UNII — 3Q1Q4QJV3V.

Profile

Lidamidine is an alpha$_2$-adrenergic receptor stimulant used as the hydrochloride for the management of diarrhoea and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Supra.

Linaclotide *(USAN, rINN)*

Linaclotida; Linaclotidum; Линакльотид.

[9-L-Tyrosine]heat-stable enterotoxin (Escherichia coli)-(6-19)-peptide.

$C_{59}H_{79}N_{15}O_{21}S_6$=1526.7

CAS — 851199-59-2.

ATC — A06AX04.

ATC Vet — QA06AX04.

UNII — N0TXR0XR5X.

Linaclotide Acetate *(USAN, rINNM)*

Acetato de linaclotida; Linaclotide, Acétate de; Linaclotidi Acetas; MD-1100; MM-416775; Линакльотида Ацетат.

$C_{59}H_{79}N_{15}O_{21}S_6,C_2H_4O_2$=1586.8

CAS — 851199-60-5.

ATC — A06AX04.

ATC Vet — QA06AX04.

UNII — NSF067KU1M.

Uses and Administration

Linaclotide is a 14-amino acid synthetic peptide structurally related to the endogenous guanylin peptide family. Both linaclotide and its active metabolite bind as agonists to the guanylate cyclase-C receptor on the luminal surface of the intestinal epithelium. It is used in the treatment of constipation-predominant irritable bowel syndrome (p. 1810.3) and chronic idiopathic constipation (p. 1804.3). Oral doses are taken on an empty stomach, at least 30 minutes before the first meal of the day.

For constipation-predominant irritable bowel syndrome linaclotide 290 micrograms is taken orally once daily. If there is no improvement in symptoms after 4 weeks, continued treatment should be reconsidered.

For chronic idiopathic constipation linaclotide 145 micrograms is taken orally once daily.

References.

1. Wensel TM, Luthin DR. Linaclotide: a novel approach to the treatment of irritable bowel syndrome. *Ann Pharmacother* 2011; **45:** 1535–43.
2. Lembo AJ, *et al.* Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 2011; **365:** 527–36.
3. Rao S, *et al.* A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012; **107:** 1714–24.
4. Chey WD, *et al.* Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012; **107:** 1702–12.
5. Lee N, Wald A. Linaclotide: evidence for its potential use in irritable bowel syndrome and chronic constipation. *Core Evid* 2012; **7:** 39–47.

Adverse Effects and Precautions

The most commonly reported adverse effect of linaclotide is diarrhoea, and treatment may need to be withheld for severe diarrhoea or prolonged episodes lasting longer than 1 week. Other gastrointestinal effects include abdominal pain or distention, flatulence, vomiting, and dyspepsia. Headache, fatigue, viral gastroenteritis, upper respiratory-tract infections, and sinusitis have also been reported.

Linaclotide is not recommended for children or adolescents as it has not been studied in this population. Guanylate cyclase-C receptors are known to be overexpressed in infancy and children younger than 2 years may be particularly sensitive to linaclotide effects. Linaclotide is also not recommended in those with inflammatory bowel disease due to a lack of data. It should not be used in patients with known or suspected gastrointestinal obstruction.

Pharmacokinetics

Linaclotide has low bioavailability after oral dosing and is virtually undetectable in the plasma. It is broken down within the gastrointestinal tract by proteolysis to its main des-tyrosine active metabolite MM-419447, and then further degraded or reduced to smaller peptides and amino acids. About 4% of a dose is excreted in the faeces as the active metabolite.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Constella; ***UK***: Constella; ***USA***: Linzess.

Liquorice

Alcaçuz; Édesgyökér; Gancao; Glycyrrhiza; Korzeń łukrecji; Lakritsijuuri; Lakritsrot; Lékořicový kořen; Licorice; Liquiritiae Radix; Liquorice Root; Orozuz; Raiz de Regaliz; Raíz de regaliz; Regaliz; Réglisse, racine de; Saldymedžių šaknys; Süssholzwurzel; Лакрица.

*ATC Herb — HR05WA5014 (*Glycyrrhiza glabra*: root); HA02WA5001 (*Glycyrrhiza glabra*: root).*

*UNII — 61ZBX54883 (liquorice); 2788Z9758H (*Glycyrrhiza glabra *root).*

Description. The dried rhizome and roots of *Glycyrrhiza glabra* var. *typica* are known in commerce as Spanish Liquorice, those of *G. glabra* var. *glandulifera* as Russian Liquorice, and those of *G. glabra* var. β-*violacea* as Persian Liquorice.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *Eur.* (see p. vii) also includes Liquorice Dry Extract for Flavouring Purposes. *US* also includes Powdered Licorice and Powdered Licorice Extract. *Br.* also includes Liquorice Root for use in Traditional Chinese Medicine and Processed Liquorice Root for use in Traditional Chinese Medicine.

Ph. Eur. 8: (Liquorice Root; Liquorice BP 2014). The dried unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* and/or *G. inflata* and/or *G. uralensis*. It contains not less than 4% of 18β-glycyrrhizic acid. Protect from light.

USP 36: (Licorice). The roots, rhizomes, and stolons of *Glycyrrhiza glabra* or *G. uralensis*. It contains not less than 2.5% of glycyrrhizic acid, calculated on the dried basis. Store in a cool, dry place.

BP 2014: (Liquorice Root for use in TCM). It is the dried unpeeled root and rhizome of *Glycyrrhiza uralensis*, *G. inflata*, or *G. glabra*, or a mixture of these. For use in traditional Chinese medicines. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

BP 2014: (Processed Liquorice Root for use in TCM). Liquorice Root for use in TCM which has been cleaned, softened, sliced transversely or longitudinally to form uniform pieces, and dried. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

Uses and Administration

Liquorice is used as a flavouring and sweetening agent. It has demulcent and expectorant properties and has been used in cough preparations. It has ulcer-healing properties that may result from stimulation of mucus synthesis. It contains constituents that produce mineralocorticoid effects (see below). Liquorice may also possess some antispasmodic and laxative properties.

Deglycyrrhizinised liquorice has a reduced mineralocorticoid activity and has been used, usually with antacids, for the treatment of peptic ulcer disease (p. 1813.2).

Reviews.

1. Fiore C, *et al.* A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol* 2005; **99:** 317–24.

Adverse Effects and Precautions

Liquorice has mineralocorticoid-like actions manifesting as sodium and water retention and hypokalaemia (see below).

Deglycyrrhizinised liquorice is not usually associated with such adverse effects.

Mineralocorticoid effects. Mineralocorticoid effects have been reported after excessive or prolonged ingestion of liquorice. The liquorice may be ingested in confectionery (including liquorice-flavoured chewing gum), tea, soft drinks, herbal medicines, cough mixtures, or by chewing tobacco. The enzyme 11-β-hydroxysteroid dehydrogenase (cortisol oxidase) converts cortisol to cortisone, preventing cortisol gaining access to non-specific mineralocorticoid receptors. This enzyme is inhibited by glycyrrhetinic acid (produced by the hydrolysis of glycyrrhizic acid, a natural constituent of liquorice), resulting in increased concentrations of cortisol in the body, enhancing its physiological effects.[1-3]

Clinical manifestations include consequences of sodium retention such as hypertension,[4-10] and hypokalaemia, which can result in neuromuscular disturbances ranging from muscle weakness,[11] myoclonus,[12] and myopathy[10] to paralysis[13-15] and rhabdomyolysis.[15-18] Arrhythmias[16,19] and fatal cardiac arrest[20] have also been reported.

Increased amounts of cortisol in vascular smooth muscle may cause vasoconstriction. Vasospasm of vessels supplying the optic nerve may have caused transient visual disturbances reported after liquorice ingestion.[2] Liquorice has also been reported to cause symptoms including recurrent thunderclap headaches with intermittent loss of vision, severe transient hypertension, and seizures; reversible angiographic abnormalities and bilateral lobar haemorrhages suggested reversible cerebral vasoconstriction, whereas brain oedema was consistent with posterior reversible encephalopathy.[21]

Other reported effects of liquorice include growth retardation in a boy with Addison's disease;[22] liquorice was thought to have potentiated the effect of hydrocortisone.

Endocrine effects of liquorice have been reviewed.[23] Conflicting effects on testosterone and prolactin have been reported. Components of liquorice root (which has been tried for menopausal symptoms) have both oestrogenic and anti-oestrogenic activity, and it has reportedly caused gynaecomastia.

Individuals vary markedly in their susceptibility to liquorice-induced adverse effects.[1] Those consuming 400 mg glycyrrhetinic acid daily generally have adverse effects, but a regular daily intake of no more than 100 mg of glycyrrhetinic acid (about 50 g of liquorice sweets) has produced adverse effects in some who appear more sensitive to its effects. Some consider a daily intake of 10 mg glycyrrhetinic acid to be a safe daily dose for adults; the amount of salt consumed needs to be considered as even a low dose of liquorice may induce sodium overload in those consuming high amounts of sodium chloride.[3]

1. Walker BR, Edwards CR. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am* 1994; **23:** 359–77.
2. Dobbins KRB, Saul RF. Transient visual loss after licorice ingestion. *J Neuroophthalmol* 2000; **20:** 38–41.
3. Frey FJ, Ferrari P. Pastis and hypertension—what is the molecular basis? *Nephrol Dial Transplant* 2000; **15:** 1512–14.
4. van Uum SH. Liquorice and hypertension. *Neth J Med* 2005; **63:** 119–20.
5. Dellow EL, *et al.* Pontefract cakes can be bad for you: refractory hypertension and liquorice excess. *Nephrol Dial Transplant* 1999; **14:** 218–20.
6. Woywodt A, *et al.* Turkish pepper (extra hot). *Postgrad Med J* 2000; **76:** 426–8.
7. Janse A, *et al.* The old lady who liked liquorice: hypertension due to chronic intoxication in a memory-impaired patient. *Neth J Med* 2005; **63:** 149–50.
8. Russo S, *et al.* Low doses of liquorice can induce hypertension encephalopathy. *Am J Nephrol* 2000; **20:** 145–8.
9. Hall RC, Clemett RS. Central retinal vein occlusion associated with liquorice ingestion. *Clin Experiment Ophthalmol* 2004; **32:** 341.
10. Hussain RM. The sweet cake that reaches parts other cakes can't! *Postgrad Med J* 2003; **79:** 115–16.
11. Yoshida S, Takayama Y. Licorice-induced hypokalemia as a treatable cause of dropped head syndrome. *Clin Neurol Neurosurg* 2003; **105:** 286–7.
12. Ishiguchi T, *et al.* Myoclonus and metabolic alkalosis from licorice in antacid. *Intern Med* 2004; **43:** 59–62.
13. Elinav E, Chajek-Shaul T. Licorice consumption causing severe hypokalemic paralysis. *Mayo Clin Proc* 2003; **78:** 767–8.
14. Lin S-H, *et al.* An unusual cause of hypokalemic paralysis: chronic licorice ingestion. *Am J Med Sci* 2003; **325:** 153–6.
15. van den Bosch AE, *et al.* Severe hypokalaemic paralysis and rhabdomyolysis due to ingestion of liquorice. *Neth J Med* 2005; **63:** 146–8.
16. Bauchart J-J, *et al.* Alcohol-free pastis and hypokalaemia. *Lancet* 1995; **346:** 1701.
17. Firenzuoli F, Gori L. Rabdomiolisi da liquirizia. *Recenti Prog Med* 2002; **93:** 482–3.

18. Lapi F, *et al.* Myopathies associated with red yeast rice and liquorice: spontaneous reports from the Italian Surveillance System of Natural Health Products. *Br J Clin Pharmacol* 2008; **66:** 572–4.
19. Eriksson JW, *et al.* Life-threatening ventricular tachycardia due to liquorice-induced hypokalaemia. *J Intern Med* 1999; **245:** 307–10.
20. Haberer JP, *et al.* Severe hypokalaemia secondary to overindulgence in alcohol-free "pastis". *Lancet* 1984; **i:** 575–6.
21. Chatterjee N, *et al.* Licorice-associated reversible cerebral vasoconstriction with PRES. *Neurology* 2010; **75:** 1939–41.
22. Docker BM, Andler W. Liquorice, growth retardation and Addison's disease. *Horm Res* 1999; **52:** 253–5.
23. Armanini D, *et al.* History of the endocrine effects of licorice. *Exp Clin Endocrinol Diabetes* 2002; **110:** 257–61.

Pregnancy. Studies in Finnish women indicated that heavy consumption of liquorice (equivalent to ≥ 500 mg/week of glycyrrhizic acid) during pregnancy was associated with an increased risk of preterm delivery.[1,2] Consumption of large amounts of liquorice was a social habit noted to occur in some northern European countries.

1. Strandberg TE, *et al.* Birth outcome in relation to licorice consumption during pregnancy. *Am J Epidemiol* 2001; **153:** 1085–8.
2. Strandberg TE, *et al.* Preterm birth and licorice consumption during pregnancy. *Am J Epidemiol* 2002; **156:** 803–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Alcalergin†; ***China***: Toynox (泰诺); ***Denm.***: Futura Hostlet; ***Fr.***: Depiderm; Trio D; ***India***: Anaproct; Bacup; Liv-Shreyas; Ned; Neo.

Multi-ingredient Preparations. ***Arg.***: Drenocol; No-Tos Adultos; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Noacid Diates†; Urinefrol; ***Austral.***: Adrenal Complex; Asa Tones†; Betaine Digestive Aid; Broncafect; Colon Care; Detox Program; DiaCo; Fe-Max; Feminine Herbal Complex; HiPep; HRF; Neo-Cleanse; Nyal Cough, Cold & Flu Day + Night; Nyal Night-Time Cough; Olf†; ResCo; Senega and Ammonia; Withania Complex; ***Austria***: Heumann's Bronchialtee; Iberogast; Laxalpin†; Midro Tee; Neoplex; Pervivo; Sigman-Haustropfen; ***Braz.***: Camomilina C; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; ***Canad.***: Floradix Kindervital†; Formula T13 Tea†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Herbolax†; Laxanat; Magen- und Darmtee N†; Melange de Plantes Formula Ll Laxatif†; Milk Thistle Extract Formula; Phytoestrin; Stomach Ease; Traditional Herbal Laxative†; Ultra-Lax†; ***Chile***: Eucerin; Instalax; Naturlax†; NeoStrata; Pectokast; Pectoral Pasteur; ***China***: Gan Han (甘含); Wei Tai Kang (谓泰康); ***Cz.***: Biotussil; Cajova Smes pri Nachlazeni; Detska Cajova Smes; Detsky Caj s Hermankem; Diabetan; Iberogast; Projimava; Pruduskova; Pulmoran; Reduktan; Species Pectorales Planta; Tormentan; Zaludecni Cajova Smes; ***Fr.***: Calmiflorine†; Mediflor Contre la Constipation Passagere No 7; Mediflor Hepatique No 5; Peptyl; Topialyse Sensitive; ***Ger.***: Broncholitan; Gastritol; Heumann Bronchialtee Solubifix T; Heumann Magentee Solu-Vetan; Iberogast; Liquirit; Rabro N; Renob Blasen- und Nierentee†; ***Hong Kong***: Brown Mixture†; Mist Expect Stim†; Phytoestrin†; ***Hung.***: Antifront; Antifront; Bittner; Iberogast; Lactonic; Majvedo es Detoxikalo; Munipyrin; Tamarinlax; ***India***: Abana; Almacarb; Alsarex; Alupectin DGL; Ampucare; Arowash†; Attentio; Britesite; Cephagraine; Cofeze; Dermec; Diabecon; Diakof; Diovol Forte DGL; Disocain; Disogel; Extrammune; FN-T-Tus†; Geriforte; Geriforte; Haleezy; Herbolax; Kofarest-H; Koflet; Lactacrat; Lactare; Lactare; Lactonic; Livosil-H; Manoll; Memtone; Menosan; Mentofer; Mustong; Neo-Cordial; Niltan; Ojus; Oxitard; Paedritone; ***Indon.***: Bio-Curliv; Bionam; Curliv Plus; Curliv Plus; Curliv; Enkasari; Fortusin; Ika Sariawan; Kafsir; OBH; OBHdryl; Pectum; Proliva; Transpulmin; ***Israel***: Lido Tea†; Midro-Tea; ***Ital.***: Allerlux; Cadifen; Cadimint; Dicalmir; Flodolor; Influ-Zinc Gola; Midro; Proctopure; Sciroppo Berta; Tamarine; Tussol; ***Jpn***: Anchusan; Bakumondoto; Bofutsushosan; Boiogito; Byakkokaninjinto; Chikujountanto; Choijokito; Chotosan; Colgen Maoto; Daibofuto; Daiokanzoto; Eppikajutsuto; Gokoto; Gorinsan; Goshakusan; Hainosankyuto; Hangeshashinto; Heiisan; Hochuekkito; Ireito; Jidabokuippo; Jiinkokato; Jiinshihoto; Jinsoin; Jizusoippo; Jumihaidokuto; Junchoto; Juzentaihoto; Kakkonto; Kakkontokasenkyushin'i; Kambakutaisoto; Kamikihito; Kamishoyosan; Keigairengyoto; Keihito; Keishikajutsubuto; Keishikaryukotsuboreito; Keishikashakuyakudaioto; Keishikashakuyakuto; Keishininjinto; Keishito; Kihito; Kikyoto; Kososan; Kyukikyogaito; Makyokansekito; Makyoyokukanto; Maoto; Nichinto; Nijutsuto; Ninjin'yoeito; Ninjinto; Nyoshinsan; Ogikenchuto; Orento; Otsujito; Rikkosan; Rikkunshito; Ryokankyomishingeninto; Ryokeijutsukanto; Ryokyojutsukanto; Ryutanshakanto; Saibokuto; Saikanto; Saikokeishikankyoto; Saikokeishito; Saikoseikanto; Saireito; Sansoninto; Seihaito; Seijobofuto; Seishinrenshiin; Seishoekkito; Senkyuchachosan; Shakanzoto; Shakuyakukanzoto; Shigyakusan; Shikunshito; Shimpito; Shofusan; Shokenchuto; Shomakakkonto; Shosaikoto; Shosaikotokakikyosekko; Shoseiryuto; Sokeikakketsuto; Tokakujokito; Tokiinshi; Tokikenchuto; Tokishigyakukagoshuyushokyoto; Tokito; Tsudosan; Unkeito; Yokuininto; Yokukansan; Yokukansankachimpihange; ***Malaysia***: Elgucare; Rumalaya; Strepsils Cough Lozenge†; Strepsils Cough Syrup†; Taisho Kampo; ***Mex.***: MD Lax; Naturetti; ***Mon.***: Blackoids du Docteur Meur; ***Neth.***: Iberogast; Verzachtende Hoestsiroop met tijm; ***Norw.***: Bronchosan†; Solvipect comp; Solvipect; ***NZ***: Bonningtons Irish Moss; ***Philipp.***: Boie Carminative (Carminasen); BSI Medicated Spray; Hemofer; ***Pol.***: Alax; ApiHelix†; Gastro†; Hedelicum; Herbogastrin; Iberogast; Padma 28; Pastylki Wykrztusne; Pectobonisol; Pervivo; PiniHelix; Reumpapai; Tussipect; ***Rus.***: Amtersol (Амтерсол); Bonjigar (Бонджигар); Codelac (Коделак); Codelac Phyto (Коделак Фито); Diureticae Species No2 (Мочегонный Сбор 2); Doktor Mom (Доктор Мом); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Elecasol (Элекасол); Evalar (Эвалар); Insti (Инсти); Kliophyt (Клиофит); Linkus (Линкас); Linkus Lor (Линкас Лор); Mixture Conta Tussis for Adults (Микстура От Кашля Для Взрослых); Mixture Conta Tussis for Children (Микстура От Кашля Для Детей); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Pectorales Elixir (Грудной Эликсир); Pectorales Species No 2 (Грудной Сбор 2); Pectorales Species No 3 (Грудной Сбор 3); Pectorales Species No 4 (Грудной Сбор 4); Phytogastrol (Фитогастрол); Proctophytol (Проктофитол); Prostanorm (Простанорм); Relcer (Релцер); Sedativae Species No 2 (Седативный Сбор 2); Sodecor (Содекор); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); ***S.Afr.***: Borsdruppels; Chamberlains Cough Remedy Regular†; Puma Cough Balsam†; ***Singapore***: Claricof; Disco; Imunomet; New Tonin Troche; Phytoestrin†; Pico's Cough; Robi's Cough; Septilin; Septilin; Strepsils Cough Lozenge (with natural herbs); Strepsils Cough Syrup†; Vi-Ron; Vyling Gastric; ***Spain***: Iberogast; Pastillas Pectorales Kely†; ***Swed.***: Iberogast; ***Switz.***: Arteria-vita; Bronchosan; DAM Antacidum†; DemoPectol; DemoTussil; Iberogast; Impuls pastilles pour les bronches; Kernosan 24; Kernosan 26; Kernosan Eau Dentifrice†; Kernosan Elixir; Lapidar 10; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Padma 28; Pastilles bronchiques S; Pastilles pectorales du Dr. Welti; Rotpunkt Apotheke pastilles pour les bronches avec codeine; Sirop pectoral contre la toux S; Strath Gouttes pour l'estomac; Tisane laxative; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; ***Thai.***: Brown Mixture; Caryopin; Iyara Ma-Weang; Meloids; Mist Tussis; Mixture Tussis; Ulgastrin; Venium; ***Turk.***: Piyraleks; Sena-Oil; ***UK***: Allens Pine & Honey; Asthma & Catarrh Relief; Bronchoforce Chesty Cough Ivy Complex; Chesty Cough Relief; Covonia Herbal Mucus Cough Syrup; Covonia Mentholated; Honey & Molasses; Jamaican Sarsaparilla; Lightning Cough Remedy; Nigroids; Padma 28; Padma Circosan; Potters Sugar Free Cough Pastilles; Red Sage Catarrh Remedy; Revitonil; Tickly Cough & Sore Throat Relief; Vegetable Cough Remover; Vocalzone; ***Ukr.***: Antifront (Антифронт); Antifront (Антифронт); Bon-Apetit (Бон-Аппетит); Bonjigar (Бонджигар); Bronchomed (Бронхомед); Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Elecasol (Элткасол); Florised (Флорисед); Gastritol (Гастритол); Gynopower (Гинопауэр); Iberogast (Иберогаст); Insti (Інсті); Kofanol (Кофанол)†; Linkus (Линкас); Relcer (Релцер)†; Septilin (Септилин); Softovak (Софтовак); Travisil (Трависил); Vitokan (Витокан); ***USA***: Detox; Mucotrol.

Homoeopathic Preparations. ***Austria***: Astomera.

Pharmacopoeial Preparations

Ph. Eur.: Liquorice Ethanolic Liquid Extract, Standardised; **USP 36:** Licorice Fluidextract.

Loperamide Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de loperamida; Loperamid Hidroklorür; Loperamid hydrochlorid; Loperamida, hidrocloruro de; Lopéramide, chlorhydrate de; Loperamid-hidroklorid; Loperamidhydrochlorid; Loperamidhydroklorid; Loperamidi Hydrochloridum; Loperamidihydrokloridi; Loperamido hidrochloridas; R-18553; Лоперамида Гидрохлорид.

4-(4-*p*-Chlorophenyl-4-hydroxypiperidino)-*NN*-dimethyl-2,2-diphenylbutyramide hydrochloride.

$C_{29}H_{33}ClN_2O_2,HCl$=513.5

CAS — 53179-11-6 (loperamide); 34552-83-5 (loperamide hydrochloride).

ATC — A07DA03.

ATC Vet — QA07DA03.

UNII — 77TI35393C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Loperamide Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Loperamide Hydrochloride). A white to slightly yellow powder. Slightly soluble in water and in dilute acids; freely soluble in chloroform and in methyl alcohol; very slightly soluble in isopropyl alcohol.

Loperamide Oxide *(BAN, rINN)*

Loperamid oxid; Loperamida, óxido de; Lopéramide Oxyde; Lopéramide, oxyde de; Loperamidi Oxidum; Loperamidioksidi; Loperamido oksidas; Loperamidoxid; Loperamidum Oxidum; Óxido de loperamida; R-58425; Лоперамида Оксид.

$C_{29}H_{33}ClN_2O_3$=493.0

CAS — 106900-12-3.

ATC — A07DA05.

ATC Vet — QA07DA05.

UNII — H3VOT77DE1.

Pharmacopoeias. *Eur.* (see p. vii) includes the monohydrate.

Ph. Eur. 8 (Loperamide Oxide Monohydrate; Loperamidi Oxidum Monohydricum). A white or almost white, slightly hygroscopic, powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies or ileostomies to reduce the volume of discharge.

In **acute diarrhoea** the usual initial dose is loperamide hydrochloride 4 mg followed by 2 mg after each loose stool to a maximum of 16 mg daily; the usual daily dose is 6 to 8 mg.

In **chronic diarrhoea** the usual initial dose is 4 to 8 mg daily in divided doses subsequently adjusted as necessary; doses of 16 mg daily should not be exceeded. If no improvement has been seen after treatment with 16 mg daily for at least 10 days, further use is unlikely to be of benefit.

For doses in children, see below

Loperamide is also given as the prodrug, **loperamide oxide**, which is converted to loperamide in the gastrointestinal tract. It has been given for acute diarrhoea in doses of 2 to 4 mg initially followed by 1 mg after each loose stool, to a maximum of 8 mg daily.

Administration in children. Loperamide can be used in children as an adjunct in the symptomatic treatment of acute and chronic diarrhoeas, and in the management of colostomies or ileostomies to reduce the volume of discharge.

In **acute diarrhoea** dose regimens vary according to country. In the UK, it is licensed for children from 4 years of age; recommended oral doses of loperamide hydrochloride are:

- 4 to 8 years: 1 mg three or four times daily for up to 3 days
- over 8 years: 2 mg four times daily for up to 5 days

The *BNFC* suggests using adult doses (see above) in children from 12 years of age.

In the USA, loperamide is licensed for children from 2 years of age. The recommended initial oral dose for children aged 2 to 5 years is 1 mg three times daily.

For restrictions on the use of loperamide in children and the view that antidiarrhoeal drugs should not be used at all in children with acute diarrhoea, see Diarrhoea, below.

Although not licensed for use in children for **chronic diarrhoea**, in the UK the *BNFC* allows for the following oral doses:

- 1 month to 1 year: 100 to 200 micrograms/kg twice daily, given 30 minutes before feeds; up to a maximum of 2 mg/kg daily in divided doses may be required
- 1 to 12 years: 100 to 200 micrograms/kg (maximum dose 2 mg) three to four times daily; up to 1.25 mg/kg daily in divided doses may be required, to a maximum of 16 mg daily
- 12 to 18 years: adult doses can be given

Diarrhoea. The mainstay of treatment for acute diarrhoea (p. 1805.2) is rehydration therapy. Antidiarrhoeals may have a role for symptomatic relief in adults with acute diarrhoea, and loperamide is often chosen in such circumstances,[1] but WHO does not recommend the use of *any* antidiarrhoeal drug in children with diarrhoea. Similarly, in the UK the *BNFC* states that antimotility drugs are not recommended for acute diarrhoea in children under 12 years of age. There have been problems regarding the use of antidiarrhoeals such as loperamide in young children in developing countries. Manufacturers have considered that a lower age limit is acceptable in those countries than is recommended in the UK or USA; even that lower limit is not always observed in practice and there have been reports of serious toxicity in very young children.[2] In response to such reports the manufacturers withdrew concentrated drops of loperamide worldwide and the syrup from countries where the WHO had a programme for control of diarrhoeal diseases,[3] but tablets and capsules remain available. In some countries the use of antidiarrhoeals is now restricted by law.

In the UK, NICE states that loperamide is the antidiarrhoeal of first choice in adults with faecal incontinence;[4] it can be used long-term in doses from 500 micrograms to 16 mg daily as needed. Loperamide should be started at a very low dose which can be increased as needed, and then adjusted in response to stool consistency. It should not be given to those with hard or

infrequent stools, those with acute diarrhoea of unknown cause, or with acute ulcerative colitis. Patients who are unable to tolerate loperamide may be offered codeine phosphate (p. 40.2) or co-phenotrope (see Diphenoxylate Hydrochloride, p. 1835.3).

For mention of the use of loperamide in the management of diarrhoea caused by chemotherapy, see p. 731.3.

1. Wingate D, *et al.* Guidelines for adults on self-medication for the treatment of acute diarrhoea. *Aliment Pharmacol Ther* 2001; **15:** 773–82.
2. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; **335:** 363.
3. Gussin RZ. Withdrawal of loperamide drops. *Lancet* 1990; **335:** 1603–4.
4. NICE. Faecal incontinence: the management of faecal incontinence in adults (issued June 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG49NICEGuidance.pdf (accessed 31/03/08)

PRODRUG THERAPY. References to the use of *loperamide oxide* in diarrhoea.

1. Van Den Eynden B, *et al.* New approaches to the treatment of patients with acute, nonspecific diarrhea: a comparison of the effects of loperamide and loperamide oxide. *Curr Ther Res* 1995; **56:** 1132–41.
2. Hughes IW, *et al.* First-line treatment in acute non-dysenteric diarrhoea: clinical comparison of loperamide oxide, loperamide and placebo. *Br J Clin Pract* 1995; **49:** 181–5.
3. van Outryve M, Toussaint J. Loperamide oxide for the treatment of chronic diarrhoea in Crohn's disease. *J Int Med Res* 1995; **23:** 335–41.
4. Sun WM, *et al.* Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scand J Gastroenterol* 1997; **32:** 34–8.

Adverse Effects and Treatment

Abdominal pain or bloating, nausea, constipation, dry mouth, dizziness, fatigue, and hypersensitivity reactions including skin rashes have been reported. Loperamide has been associated with paralytic ileus, particularly in infants and young children, and deaths have been reported. Depression of the CNS, to which children or those with hepatic impairment may be more sensitive, may be seen in overdosage; constipation and urinary retention also occur. Naloxone hydrochloride (see p. 1563.3) has been recommended for treatment of severe overdosage.

Toxicity. Toxic megacolon has been reported[1,2] after use of loperamide. Severe effects reported in young children have included loss of consciousness[3,4] and delirium.[5] Several cases of paralytic ileus have also occurred in children,[6,7] some of which were fatal.[6]

1. Brown JW. Toxic megacolon associated with loperamide therapy. *JAMA* 1979; **241:** 501–2.
2. Walley T, Milson D. Loperamide related toxic megacolon in Clostridium difficile colitis. *Postgrad Med J* 1990; **66:** 582.
3. Minton NA, Smith PGD. Loperamide toxicity in a child after a single dose. *BMJ* 1987; **294:** 1383.
4. Chanzy S, *et al.* Perte de connaissance chez une jeune enfant secondaire à la prise de lopéramide. *Arch Pediatr* 2004; **11:** 826–7.
5. Schwartz RH, Rodriguez WJ. Toxic delirium possibly caused by loperamide. *J Pediatr* 1991; **118:** 656–7.
6. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; **335:** 363.
7. Dudink J, *et al.* Ileus na gebruik van loperamide bij een kind met acute diarree. *Ned Tijdschr Geneeskd* 2003; **147:** 670–2.

Precautions

Loperamide should not be used when inhibition of peristalsis is to be avoided, in particular where ileus or constipation occur, and should be avoided in patients with abdominal distension, acute inflammatory bowel disease, or antibiotic-associated colitis. Loperamide should not be used alone in patients with dysentery.

Loperamide should be used with caution in patients with hepatic impairment because of its considerable first-pass metabolism in the liver. It should also be used with caution in young children because of a greater variability of response in this age group; it is not recommended for use in infants (but see Administration in Children, p. 1854.3).

Breast feeding. Loperamide is distributed into breast milk in small amounts.[1] The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of loperamide by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Nikodem VC, Hofmeyr GJ. Secretion of the antidiarrhoeal agent loperamide oxide in breast milk. *Eur J Clin Pharmacol* 1992; **42:** 695–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/01/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies loperamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. A study[1] in 105 women who had used loperamide during pregnancy (89 in the first trimester) found no increase in major congenital defects compared with controls. However, another study[2] of loperamide use in early pregnancy in 638 women reported an increased risk of congenital malformations; the adjusted odds ratio was 1.41 (with a 95% confidence interval of 1.03-1.93) based on 43 affected children. The authors warned that the results could have arisen by chance and further studies were needed to verify the effect.

1. Einarson A, *et al.* Prospective, controlled, multicentre study of loperamide in pregnancy. *Can J Gastroenterol* 2000; **14:** 185–7.
2. Källén B, *et al.* Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatr* 2008; **97:** 541–5.

Interactions

Loperamide may increase the gastrointestinal absorption of desmopressin (p. 2357.1).

Antifungals. A pharmacokinetic study in 12 healthy subjects found that *itraconazole* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Itraconazole also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of itraconazole with gemfibrozil (see Cardiovascular Drugs, below) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; **62:** 463–72.

Antivirals. In a single-dose study,[1] oral *ritonavir* significantly increased the bioavailability of loperamide, possibly through inhibition of the cytochrome P450 isoenzyme CYP3A4, and not necessarily as originally supposed through P-glycoprotein inhibition. No serious adverse effects occurred. Licensed information for one UK preparation of loperamide (*Imodium; Janssen-Cilag, UK*) states that the clinical relevance of the pharmacokinetic interaction with P-glycoprotein inhibitors such as ritonavir is unknown.

For the effect of loperamide on *saquinavir*, and the corresponding effect of the antiviral on loperamide concentrations, see Gastrointestinal Drugs, under Interactions of Indinavir, p. 988.1.

1. Tayrouz Y, *et al.* Ritonavir increases loperamide plasma concentrations without evidence for P-glycoprotein involvement. *Clin Pharmacol Ther* 2001; **70:** 405–14.

Cardiovascular drugs. A pharmacokinetic study in 12 healthy subjects found that *gemfibrozil* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Gemfibrozil also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of gemfibrozil with itraconazole (see Antifungals, above) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; **62:** 463–72.

Co-trimoxazole. Use with co-trimoxazole increases the bioavailability of loperamide,[1] apparently by inhibiting its first-pass metabolism.

1. Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* 1996; **41:** 125–8.

Quinidine. A small study[1] found that giving quinidine with loperamide caused respiratory depression in 8 healthy subjects; when given with placebo, loperamide produced no respiratory depression. The authors supposed that inhibition of P-glycoprotein by quinidine had increased entry of loperamide into the CNS.

1. Sadeque AJM, *et al.* Increased drug delivery to the brain by P-glycoprotein inhibition. *Clin Pharmacol Ther* 2000; **68:** 231–7.

Pharmacokinetics

About 40% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract to undergo first-pass metabolism in the liver and excretion in the faeces via the bile as inactive conjugate; there is slight urinary excretion. Little intact drug reaches the systemic circulation. The elimination half-life is reported to be about 10 hours.

Metabolism. Loperamide is metabolised to desmethylloperamide through *N*-demethylation. An *in-vitro* study established that this occurs mainly via cytochrome P450 isoenzymes CYP2C8 and CYP3A4; CYP2B6 and CYP2D6 also play a role. Loperamide is also a substrate of P-glycoprotein.[1]

1. Kim K-A, *et al.* Identification of cytochrome P450 isoforms involved in the metabolism of loperamide in human liver microsomes. *Eur J Clin Pharmacol* 2004; **60:** 575–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Colifilm; Contem; Custey; Dotalsec; Elcoman; Excelentia Antidiarreico; Ionet; Lansek A; Lefa Enteril L; Minicam; Nodiar; Normasec; Plexol; Plorinoc; Regulane; Suprasec; Viltar; ***Austral.***: Chemists Own Diarrhoea Relief; Diareze; Gastro-Stop; Harmonise; Imodium; Lopedium; ***Austria***: Enterobene; Imodium; Normakut; ***Belg.***: Imodium; Transityl; ***Braz.***: Diafuran; Diasec; Imosec; Loperin; Magnostase; ***Canad.***: Diarr-Eze; Diarrhea Relief; Imodium; Loperacap; ***Chile***: Capent; Coliper; Lopediar†; Salvacoll; ***China***: Fu Xie Ding (腹泻啶); Imodium (易蒙停); Luobaomai (罗宝迈); Ya Bang (雅邦); ***Cz.***: Dissenten†; Imodium; Loperon; ***Denm.***: Imodium; Imolope; Propiden; ***Fin.***: Imocur; Imodium Pro†; Imodium; Lopacut; Lopex; ***Fr.***: Altocel; Arestal; Diaretyl; Diastrolib; Dyspagon; Ercestop; Imodium; Imodiumcaps; Imodiumlingual; Indiaral; Peracel; ***Ger.***: Imodium; Lop-Dia†; Lopedium†; Loperhoe; ***Gr.***: Imodium; Neo-Enteroseptol; Neo-Septol; ***Hong Kong***: Diacure†; Diatabs Reformulated; Imodium; Imodonl; Lopa; Loper; Loperamil; Loperax; Loperium†; Lopil†; Mar-Loper†; NT-Diorea†; Reximide†; Synodium†; Uni-Motil†; Vidaperamide†; ***Hung.***: Enterobene; Imodium; Lopedium; ***India***: Andial; Diarlop Plus; Diarlop; Eldoper; Imodium; Lofact; Lomin; Lopamide; Loperam; Loperiv; Lopona; Roko; ***Indon.***: Alphamid†; Amerol; Antidia†; Colidium; Diadium; Diasec; Diaston; Imodan; Imodium; Imomed†; Imore†; Imosa; Inamid; Lexadium; Licodium; Lodia; Loremid; Motilex; Normotil; Normudal; Opox; Oramide†; Primodium; Renamid; Rhomuz; Xepare; Zeroform; ***Irl.***: Arret; Diareze†; Diarrest RF†; Imodium; ***Israel***: Imodium; Loperid; Lopi-Care; Loprex; Rekamide; Shilshul X; Stopit; ***Ital.***: Diarstene; Diarstop; Diarzero; Dissenten; Imodium; Lopemid; ***Malaysia***: Beamodium; Imodium; Loperax†; Loperium; Lopermide; Loramide; Reximide; Vacontil; ***Mex.***: Acanol; Acqta; Apo-Pera; Biolid; Cryoperacid; Deroser; Diaperol; Exclefin; Hurplex; Imodium; Lomidal; Lomotil; Lop; Nodiamex; Permidal; Pramidal; Rediarin; Top-Dal; Valfam; ***Neth.***: Arestal; Diacure; Diarem†; Diarreeremmer; Imodium; Kruidvat Diarreeremmer; Trekpleister Diarreeremmer; ***Norw.***: Imodium; ***NZ***: Diamide; Dicap†; Imodium; Nodia; ***Philipp.***: Bryper; Diamide; Diaperyl; Diastop; Diatabs (Reformulated); Gastromed; Imodium; LBX; Lomotil; Lormide; Permid†; Tymedon; ***Pol.***: Imodium; Laremid; Stoperan; ***Port.***: Dyspagon†; Fulcalrex†; Fulcralex†; Imodium; Lopitum; Loprex†; Loride; ***Rus.***: Diara (Диара); Imodium (Имодиум); Lopedium (Лопедиум); Superilop (Суперилоп); ***S.Afr.***: Betaperamide; Gastron; Imodium; Lenide-T†; Lopedium; Loperastat; Norimode; Prodium; ***Singapore***: Colodium; Diatrol; Eldoper; Imodium; Loperamil; Loperax; Lopermide; Loramide; Lorpa; Reximide; SP-Emoloc; Vacontil; ***Spain***: Diarfin; Elissan; Fortasec; Imodium; Loperan; Loperkey; Protector†; Salvacolina; Taguinol†; ***Swed.***: Dimor; Imodium; Lopacut; Primodium; Travello†; ***Switz.***: Binaldan; Imodium; Lopimed; Lopisol; ***Thai.***: Diara; Diarent; Diarine; Diarodil; Dicotil; Entermid; Imodium; Imonox; Impelium; KB Peramide; Leon; Lomide; Lomy; Lopela; Lopercin; Loperdium; Loperia†; Lopermide†; Lopil; Mantil; Miderlar; Operium; Patardium; Perasian; Ropa; Ropermide; SBOB; Setonox; Tedium; ***Turk.***: Diadef; Lopermid; ***UK***: Arret; Boots Diarrhoea Relief; Diah-Limit; Diaquitte; Diareze; Diocalm Ultra; Diocaps; Entrocalm; Imodium; Norimode; Normaloe; ***Ukr.***: Imodium (Имодиум); Lopedium (Лопедиум); Stoperan (Стоперан); ***USA***: Imodium; K-Pek II; Kao-Paverin; Neo-Diaral; Pepto Diarrhea Control; ***Venez.***: Glucitol; Imodium; Loperam.

Multi-ingredient Preparations. ***Arg.***: Neo Kef; Neomas L; Regulane AF; ***Austral.***: Imodium Advanced; ***Austria***: Imodium Plus; ***Belg.***: Imodium Duo; ***Canad.***: Imodium Advanced; ***Cz.***: Imodium Duo Action; Imodium Plus; ***Denm.***: Imodium Plus; ***Fin.***: Imodium Plus; ***Fr.***: Imodiumduo; ***Ger.***: Imodium akut N duo; Imodium complex†; Imodium Plus†; ***Gr.***: Imodium Plus; ***Hong Kong***: Imodium Plus; ***India***: Dylock-LB; Eldoper Plus; Medilop; ***Irl.***: Imodium Plus; ***Israel***: Imodium Plus; ***Mex.***: Imodium Plus; ***Neth.***: Imodium Combi†; Imodium Duo; ***Norw.***: Imodium Comp; ***NZ***: Imodium Advanced; ***Pol.***: Imodium Plus; ***Port.***: Imodium Plus; ***Rus.***: Imodium Plus (Имодиум Плюс); ***S. Afr.***: Imodium Plus; ***Spain***: Imodium Duo; ***Swed.***: Imodium Plus; ***Switz.***: Imodium Duo; ***Thai.***: Imodium Plus†; ***UK***: Imodium Plus; ***Ukr.***: Diaremix (Диаремикс); ***USA***: Imodium Advanced; Imodium Multi-Symptom Relief.

Pharmacopoeial Preparations

BP 2014: Loperamide Capsules;
USP 36: Loperamide Hydrochloride Capsules; Loperamide Hydrochloride Oral Solution; Loperamide Hydrochloride Tablets.

Loxiglumide *(rINN)*

CR-1505; CR-2017 (dexloxiglumide); Loxiglumida; Loxiglumidum; Локсиглумид.

(±)-4-(3,4-Dichlorobenzamido)-*N*-(3-methoxypropyl)-*N*-pentylglutaramic acid.

$C_{21}H_{30}Cl_2N_2O_5$=461.4

CAS — 107097-80-3 (loxiglumide); 119817-90-2 (dexloxiglumide).

UNII — 77MPX3N42I.

Profile

Loxiglumide is a specific cholecystokinin antagonist related to proglumide (see p. 1880.1), and has been investigated in

biliary and gastrointestinal dyskinesias, constipation and irritable bowel syndrome, and pancreatitis.

The *R*-isomer of loxiglumide, dexloxiglumide is also under investigation for constipation-predominant irritable bowel syndrome.

References.
1. Shiratori K, *et al.* Clinical evaluation of oral administration of a cholecystokinin-A receptor antagonist (loxiglumide) to patients with acute, painful attacks of chronic pancreatitis: a multicenter dose-response study in Japan. *Pancreas* 2002; **25:** e1–e5.
2. Cremonini F, *et al.* Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005; **100:** 652–63.
3. Persiani S, *et al.* Pharmacokinetic profile of dexloxiglumide. *Clin Pharmacokinet* 2006; **45:** 1177–88.

Lubiprostone *(USAN, rINN)*

Lubiprostona; Lubiprostonum; RU-0211; SPI-0211; Лубипростон.

(-)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-Difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid.

$C_{20}H_{32}F_2O_5$=390.5

CAS — 136790-76-6; 333963-40-9.

ATC — A06AX03.

ATC Vet — QA06AX03.

UNII — 7662KG2R6K.

Uses and Administration

Lubiprostone is a chloride-channel activator that acts locally in the gut to increase intestinal fluid secretion, which increases motility. It is used in the treatment of chronic idiopathic constipation (p. 1804.3) in a dose of 24 micrograms twice daily, taken orally with food. It is also used in women for the treatment of constipation-predominant irritable bowel syndrome (p. 1810.3) in a dose of 8 micrograms twice daily, taken orally with food.

References.
1. McKeage K, *et al.* Lubiprostone. *Drugs* 2006; **66:** 873–9.
2. Anonymous. Lubiprostone (Amitiza) for chronic constipation. *Med Lett Drugs Ther* 2006; **48:** 47–8.
3. Ambizas EM, Ginzburg R. Lubiprostone: a chloride channel activator for treatment of chronic constipation. *Ann Pharmacother* 2007; **41:** 957–64.
4. Ginzburg R, Ambizas EM. Clinical pharmacology of lubiprostone, a chloride channel activator in defecation disorders. *Expert Opin Drug Metab Toxicol* 2008; **4:** 1091–7.
5. Lacy BE, Chey WD. Lubiprostone: chronic constipation and irritable bowel syndrome with constipation. *Expert Opin Pharmacother* 2009; **10:** 143–52.
6. Carter NJ, Scott LJ. Lubiprostone: in constipation-predominant irritable bowel syndrome. *Drugs* 2009; **69:** 1229–37.
7. Barish CF, *et al.* Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci* 2010; **55:** 1090–7.
8. O'Brien CE, *et al.* Use of the chloride channel activator lubiprostone for constipation in adults with cystic fibrosis: a case series. *Ann Pharmacother* 2010; **44:** 577–81.

Adverse Effects and Precautions

The most common adverse effect of lubiprostone is nausea, which is dose-dependent and may be severe in some patients. Symptoms can be reduced by taking lubiprostone with food. Diarrhoea also occurs commonly, and other gastrointestinal effects include abdominal distension and pain, flatulence, and vomiting. Other reported adverse effects include headache, dizziness, fatigue, dyspnoea, chest discomfort, and peripheral oedema. Intestinal functional disorder, constipation, cough, dysgeusia, eructation, decreased appetite, gastro-oesophageal reflux disease, gastritis, increased weight, and rectal haemorrhage have been reported rarely, as have muscle cramps, joint swelling, myalgia, fibromyalgia, hyperhidrosis, pain (including pharyngolaryngeal pain), anxiety, influenza, syncope, tremor, dry mouth, increased liver enzyme values, erythema, palpitations, urinary-tract infection, and depression.

Lubiprostone is contra-indicated in patients with a history of mechanical gastrointestinal obstruction.

Pharmacokinetics

A negligible amount of lubiprostone is absorbed after an oral dose. It is rapidly and extensively metabolised by carbonyl reductase, probably in the stomach and jejunum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn:*** Amitiza; ***Switz.:*** Amitiza; ***UK:*** Amitiza; ***USA:*** Amitiza.

Magaldrate *(BAN, USAN, rINN)*

Aluminum Magnesium Hydroxide Sulfate; AY-5710; Hidroxidosulfato de aluminio y magnesio hidratado; Magaldraatti; Magaldrat; Magaldrát; Magaldratas; Magaldrato; Magaldratum; Магальдрат.

$Al_5Mg_{10}(OH)_{31}(SO_4)_2.xH_2O$=1097.3 (anhydrous)

CAS — 74978-16-8.

ATC — A02AD02.

ATC Vet — QA02AD02.

UNII — 0MFM55849I (anhydrous magaldrate); 6V88E24N5T (magaldrate hydrate).

NOTE. Magaldrate was formerly described as Aluminium Magnesium Hydroxide ($AlMg_2(OH)_7$ monohydrate, *CAS— 1317-26-6*).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Magaldrate). A combination of aluminium and magnesium hydroxides (see p. 1817.2 and p. 1857.2 respectively) and sulfates. It contains the equivalent of 90 to 105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated with reference to the dried substance. It contains a variable amount of water. A white or almost white crystalline powder. Practically insoluble in water and in alcohol; soluble in dilute mineral acids. It loses between 10 and 20% of its weight on drying at 200 degrees for 4 hours.

USP 36: (Magaldrate). A combination of aluminium and magnesium hydroxides and sulfates. It contains the equivalent of 90 to 105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated on the dried basis. A white odourless crystalline powder. Insoluble in water and in alcohol; soluble in dilute solutions of mineral acids. It loses between 10 and 20% of its weight on drying at 200 degrees for 4 hours.

Profile

Magaldrate is an antacid (see p. 1803.1) that is given in oral doses of up to about 2 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Minicidez; Riopan; ***Austria:*** Riopan; ***Belg.:*** Gastricalm; Riopan; ***Braz.:*** Riopan; ***Fr.:*** Riopan; ***Ger.:*** Bisco-Magaldrat†; Gastripan†; Glysan; Magastron†; Marax; Riopan; ***Gr.:*** Atractylon; Felfar; Riopan; ***Indon.:*** Gestabil Forte; Gestabil; ***Ital.:*** Gadral; Magaltop; Magralibi; Riopan; ***Pol.:*** Malugastrin†; ***Port.:*** Riopan; ***Rus.:*** Magalphil (Магалфил); ***S. Afr.:*** Riopone†; ***Spain:*** Bemolan; Gastromol†; Magion; Minoton; ***Switz.:*** Riopan; ***Ukr.:*** Almagel T (Алмагель Т); Riopan (Риопан); ***USA:*** Iosopan†; Riopan†; ***Venez.:*** Cremag.

Multi-ingredient Preparations. ***Arg.:*** Aci-Tip; ***Austral.:*** Mylanta Heartburn Relief; ***Braz.:*** Riopan Plus; ***Chile:*** Antiax; ***India:*** Acigone-D; Acihit; Acixx; Afocid; Afra-Z; Alcaine; Almag; Amalset; Anatyl-D; Anatyl; Avicid; Bestocid-O; Bestocid; Bipgel; Bluegel-O; Bluegel; Cadgil; Coligon-O; Depcid-O; Digiflux-A; Digirest; Domgel; Duogel; Elcid; Eldrate-S; Endcid; Fomacid; Forzole Gel; G-Gel; Gelone; Glocid; Graster; Hilcid; Icer-MS; Iceron; Kaicid-O; Kaicid; Madarat-S; Madrat-S; Magacone; Magel-MPS; Maglid; Magnadrox; Merigel-A; Merigel; Metadrate; Moska; NBCid; NCA; Netrocid; Neugel; Neutracaine; Nilcid-MPS; Normocid; Norper; Novagel-D; Nulasta; Numeg; Nutec MPS; Ocinil; pH4; Rolac Plus; Ulgel; ***Indon.:*** Asidrat†; Magalat; Nudramag; ***Mex.:*** Gex; Masedi; Riopan; ***Turk.:*** Asidopan Plus; Simelgat Plus; ***UK:*** Bisodol Extra; Bisodol Heartburn Relief; ***USA:*** Iosopan Plus†; Lowsium Plus; Riopan Plus; ***Venez.:*** Cremalon.

Pharmacopoeial Preparations

BP 2014: Magaldrate Oral Suspension;

USP 36: Magaldrate and Simethicone Oral Suspension; Magaldrate and Simethicone Tablets; Magaldrate Oral Suspension; Magaldrate Tablets.

Magnesium Carbonate

Bázisos magnézium-karbonát; E504; Magnesii Carbonas; Magnesii Subcarbonas; Magnesio, carbonato de; Magnésium, carbonate de; Magnesiumsubkarbonaatti; Magnesiumsubkarbonat; Magnezu węglan; Magnezyum Karbonate; Magnio subkarbonatas; Uhličitan hořečnatý zásaditý; Магния Карбонат.

CAS — 546-93-0 (anhydrous magnesium carbonate); 23389-33-5 (hydrated normal magnesium carbonate); 39409-82-0 (hydrated basic magnesium carbonate).

ATC — A02AA01; A06AD01.

ATC Vet — QA02AA01; QA06AD01.

UNII — 0E53J927NA.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn, US,* and *Viet.* Some pharmacopoeias include a single monograph that permits both the light and heavy varieties while some have 2 separate monographs for the 2 varieties.

Ph. Eur. 8: (Magnesium Carbonate, Heavy; Magnesii Subcarbonas Ponderosus). A hydrated basic magnesium carbonate containing the equivalent of 40 to 45% of MgO. A white or almost white powder. Practically insoluble in water; dissolves in dilute acids with strong effervescence.

Ph. Eur. 8: (Magnesium Carbonate, Light; Magnesii Subcarbonas Levis). A hydrated basic magnesium carbonate containing the equivalent of 40 to 45% of MgO. A white or almost white powder. Practically insoluble in water; dissolves in dilute acids with strong effervescence.

USP 36: (Magnesium Carbonate). A basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate containing the equivalent of 40.0 to 43.5% of MgO. It is an odourless, bulky white powder or light, white, friable masses. Practically insoluble in water; insoluble in alcohol; dissolves in dilute acids with effervescence.

Profile

Magnesium carbonate is an antacid with general properties similar to those of magnesium hydroxide (p. 1857.2) that is given in oral doses of up to about 500 mg. When given orally, it reacts with gastric acid to form soluble magnesium chloride and carbon dioxide in the stomach; the carbon dioxide may cause flatulence and eructation. Magnesium carbonate is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium carbonate may be used as a magnesium supplement. It is also used as a food additive, and as a binder and diluent in tablet-making.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Polvo Roge; Total Magnesiano; ***Austria:*** Magnofit; OsvaRen; ***Canad.:*** Magmix II; ***Fr.:*** Mag 2 Junior†; Mag 2; Sargemag; ***Ger.:*** Biolectra Magnesium 365; OsvaRen; Palmicol†; ***Gr.:*** Limonata Citromagnes; ***Hung.:*** Magnosolv; ***Ital.:*** Magnofit; ***Pol.:*** Additiva Magnesium†; Magnezin; ***S.Afr.:*** Be-Lax; ***Switz.:*** Magnesium Nutrimed; ***Turk.:*** Magnesium Nutrimed; ***USA:*** Mag-Carb.

Multi-ingredient Preparations. ***Arg.:*** Acinat; Antiacid; Benitol; Calmose; Gastranil; Gastricur; Holomagnesio Vital; Magnesio + C/Mag-CE; Mucaine; Polper Calcio-Magnesio; Rennie; Rennie; Total Magnesiano E; Total Magnesiano Energizante; Total Magnesiano Fem; Total Magnesiano Sport; Total Magnesiano; ***Austral.:*** Antacid Chewable Tablets†; Cal Alkyline†; Degas Extra†; Rennie; ***Austria:*** Magnosolv; Rennie Digestif; Rennie; ***Belg.:*** Magnesie Plus; Neutroses; Rennie†; Rennie; ***Braz.:*** Gaviz; Magnesia Bisurada; ***Canad.:*** Calmax†; Dol-Mite†; Gaviscon Heartburn & Acid Reflux Relief; Gaviscon Maxrelief; Maalox HRF†; Mega Dole†; ***Chile:*** Algicote†; Nogastra; Peptinal Forte†; Peptinal†; Reflumox; ***China:*** JieAn (捷安); Rennie (罗内); ***Cz.:*** Digestif Rennie†; Gastal†; Magnosolv; OsvaRen; Rennie Duo†; Rennie; Tums†; ***Denm.:*** BiOrto Al-C; Novaluzid; OsvaRen; ***Fin.:*** Novaluzid; OsvaRen; Rennie; ***Fr.:*** Actigess†; Bouillet; Citrocholine†; Dops†; Gastropax; Ginvit; Hepatoum Brulures d'Estomac†; Kaobrol; Magnesie Composee†; Neutroses; Nutri Yin-Nutri Yang†; Pelvimag; Peptyl; Rennie Deflatine; Rennie; Renniechew†; Topaal; Topalkan†; Vascocitrol†; ***Ger.:*** Liquirit; Losnesium; Rennie; ***Gr.:*** Alcamex-Mg; Andrews Antacid; Conquista; Dyspagone; Elkopas; KH3; OsvaRen; Rennie; Tums; ***Hong Kong:*** Antacaine; Mucaine†; ***Hung.:*** Digestif Rennie†; Rennie; ***India:*** Almacarb; Diovol; Ossofez; ***Indon.:*** Minos†; Yanthi Baby & Bath Powder†; ***Irl.:*** Andrews Antacid†; Bisodol Extra Strong Mint Tablets; Bisodol†; Bisodol; OsvaRen; Rennie Deflatine; Rennie Dual Action; Rennie Peppermint; Rennie Spearmint; Rennie Sugar Free; Topaal; ***Israel:*** Fresco; Rekiv†; Rennie; ***Ital.:*** Citrato Espresso Gabbiani; Citromagnesiaca; Magnesia Bisurata Aromatic; Magnosol; Neutrose S Pellegrino; Rennie; ***Jpn:*** Cabe 2†; The Guard Seichojo; ***Neth.:*** Algicon; Algicon; OsvaRen; Rennie Deflatine; Rennie Duo; Rennie; Roteroblong Maagtabletten; ***Norw.:*** Novaluzid; OsvaRen; ***NZ:*** KH3; ***Philipp.:*** Algycon; Novaluzid†; Vita SL; ***Pol.:*** Dolomit; Gastal; Gastro†; Gastrofan†; Osteogel; Proacid†; Redinact†; Rennie; Ulgamax†; ***Port.:*** Bisodol†; OsvaRen; Rennie Digestif; ***Rus.:*** Inalan (Иналан); Magnesium Plus (Магний Плюс); Rennie (Ренни); Vicair (Викаир); Vicalin (Викалин); ***S.Afr.:*** Adcomag Trisil†; Be-Tabs Antacid†; Behoedmiddel vir Kinders; Bisodol†; Carminex†; Digestif Rennie; Gentrisil†; ***Singapore:*** Aromag; Baby Brand Antacid; Bismag†; Inon; Kaomix; Magtasil; Rennie Deflatine; Rennie; ***Spain:*** Eupeptina; Gelodrox; Hectonona; Mabogastrol†; OsvaRen; Rennie; Sales Fruta Mag Viviart†; ***Swed.:*** Novaluzid; OsvaRen; Rennie; Samarin; ***Switz.:*** Neutroses; Rennie Deflatine; Rennie Ice; Rennie; ***Thai.:*** Algycon; Carbonpectate; KH3†; Mucaine†; ***Turk.:*** Bisman; Bismomagnesie†; Bismomagnesie; Calmy Plus; Calmy; Magcar; Rennie Duo; Rennie; ***UAE:*** JulMag; ***UK:*** Actonorm; Andrews Antacid; Birley's; Bisma-Rex; Bisodol Wind Relief; Bisodol; Bisodol; Calcium Clear; De Witt's Antacid; De Witt's Antacid; Moorland; Opas; OsvaRen; Rennie Deflatine; Rennie Duo†; Rennie; Topal; Uriflex R; Uro-Tainer Solution R; Valonorm; ***Ukr.:*** Remmax (Реммакс); Rennie (Ренни); Vicair (Викаир); Vicalin (Викалин); ***USA:*** Acid Gone; Alenic Alka; Extra Strength Genaton; Gaviscon Extra Strength Relief Formula; Gaviscon Extra Strength; Gaviscon; Genaton; MagneBind; Marblen; Mi-Acid Gelcaps; Mylagen; Renacidin; Tonsiline.

Used as an adjunct in:. ***Arg.:*** Dristan Compuesto; ***Braz.:*** Bufferin; Somalgin; ***Canad.:*** Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA†; ***USA:*** Adprin-B; Bufferin; Buffex; Extra Strength Bayer Plus.

Homoeopathic Preparations. ***Canad.:*** Homeo-Form CO†; Optalia†; Tyglan†; ***Fr.:*** Aftosium; Homeoptic; ***Ger.:*** Gastritis Complex; Prostata-Komplex L Ho-Fu-Complex; Prostata-Komplex N Ho-Fu-Complex†; ***Neth.:*** Homeoptic†; Kind 0-6 Kindival; ***Rus.:***

Tabacum-Plus (Табакум-Плюс); ***Switz.***: Regenaplex Nr. 88b; ***Ukr.***: Dormikind (Дормикинд).

Pharmacopoeial Preparations
BP 2014: Aromatic Magnesium Carbonate Mixture; Chewable Calcium Carbonate and Heavy Magnesium Carbonate Tablets; Compound Magnesium Trisilicate Oral Powder; Kaolin Mixture; Magnesium Sulphate Mixture; Magnesium Trisilicate Mixture;
USP 36: Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Calcium and Magnesium Carbonates Oral Suspension; Calcium and Magnesium Carbonates Tablets; Magnesium Carbonate and Citric Acid for Oral Solution; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Magnesium Citrate Oral Solution.

Magnesium Citrate

Magnesii citras; Magnesio, citrato de; Magnésium, citrate de; Магний Цитрат.

$C_{12}H_{10}Mg_3O_{14}$=451.1

CAS — 3344-18-1 (anhydrous magnesium citrate); 153531-96-5 (magnesium citrate nonahydrate); 144-23-0 (dibasic magnesium citrate).

ATC — A06AD19; A12CC04; B05CB03.

ATC Vet — QA06AD19; QA12CC04; QB05CB03.

UNII — RHO26O1T9V.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Magnesium Citrate, Anhydrous). A white or almost white, fine, slightly hygroscopic powder. Soluble in water; practically insoluble in alcohol. It dissolves in dilute hydrochloric acid. Store in non-metallic, airtight containers.

Ph. Eur. 8: (Magnesium Citrate Dodecahydrate). A white or almost white, fine powder. Sparingly soluble in water; practically insoluble in alcohol; dissolves in dilute hydrochloric acid. A 5% solution in water has a pH of 6.0 to 8.5.

Ph. Eur. 8: (Magnesium Citrate Nonahydrate). A white or almost white, fine powder. Sparingly soluble in water; practically insoluble in alcohol; dissolves in dilute hydrochloric acid. A 5% solution in water has a pH of 6.0 to 8.5.

USP 36: (Magnesium Citrate). A 5% suspension in water has a pH of 5.0 to 9.0. Store in airtight containers.

Profile

Magnesium citrate is an osmotic laxative (p. 1804.1) used as a bowel evacuant before investigational procedures or surgery of the colon. Dosages have ranged from about 11 to 25 g of magnesium citrate. In the UK, an aqueous solution containing magnesium citrate is prepared from a sachet (*Citramag; Sanochemia, UK*) containing about 11.6 g of magnesium carbonate and about 17.8 g of anhydrous citric acid by mixing with 200 mL of hot water. After the solution has cooled, one dose (the contents of one sachet) is taken orally at 8 a.m. the day before the procedure, and a second dose between 2 and 4 p.m. For doses in children, see below. A high fluid intake and low residue diet are needed with such bowel preparations. Magnesium citrate is also used with sodium picosulfate, see p. 1887.2.

Magnesium citrate is given as a magnesium supplement in oral doses of up to about 1.9 g daily.

Dibasic magnesium citrate (magnesium hydrogen citrate) has also been used.

For the general properties of magnesium salts, see p. 1786.3.

References.
1. Hoy SM, *et al.* Sodium picosulfate/magnesium citrate: a review of its use as a colorectal cleanser. *Drugs* 2009; **69:** 123–36.

Administration in children. The *BNFC* recommends the following oral doses of magnesium citrate (*Citramag; Sanochemia, UK*) for use as a bowel cleanser in children, to be taken on the day before the procedure:
- 5 to 10 years: of a sachet at 8 a.m. and of a sachet between 2 and 4 p.m.
- 10 to 18 years: ½ to 1 sachet at 8 a.m. and ½ to 1 sachet between 2 and 4 p.m.

For reconstitution directions, see above.

Migraine. For mention of the use of magnesium supplementation, including magnesium citrate, for the prophylaxis of migraine, see p. 1788.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Holomagnesio; Limonada Roge; Total Magnesiano; ***Austria***: Magnesium Diasporal; Magnesium Verla; Magnofit; ***Canad.***: Citro-Mag; Citrodan; Mag-Citrate; Magnesit; Royvac†; ***Ger.***: Magnesium Diasporal; Magnesium Verla N; Magnesium-Sandoz forte†; ***Israel***: Magnesium Diasporal; ***Mon.***: Oromag; ***Norw.***: Nycoplus Magnesium; ***Pol.***: Magnesol; ***Switz.***: Actimagon†; Magnegon; Magnesium Biomed; Magnesium Diasporal; Magnesium-Sandoz; ***Turk.***: Magnezyum Diasporal; ***UK***: Citramag; ***USA***: Evac-Q-Mag.

Multi-ingredient Preparations. ***Arg.***: Holomagnesio B6; Magnebe; Total Magnesiano B6; ***Austral.***: Go Kit Plus; Go Kit; Magnesium Powder; ***Belg.***: Carbobel; ***Braz.***: Emidrat; ***Canad.***: Bio-Gyn†; Cal-Mag Citrate with Zinc and Vitamin D; Femidause†; Royvac Kit†; ***Chile***: Laxogeno; ***Fr.***: Citrocholine†; Magnevie B6; ***Ger.***: Biomagnesin; Magnerot N; ***Gr.***: Magnesium Sandoz; ***Hong Kong***: Active Calcium†; ***Hung.***: Beres Magnezium + B_6; Magne-B_6 Extra; Pregmag†; ***India***: Alkamax-MB6; Noculi; ***Ital.***: Bionefrol; Litostop; Pomag; ***Philipp.***: Nutrafem; ***Pol.***: Aronomag†; ***Port.***: Detoxergon; ***Spain***: Salmagne; ***UK***: CitraFleet; Picolax; ***Ukr.***: Magne B6 Premium (Магне-В6 Премиум)†.

Pharmacopoeial Preparations
USP 36: Magnesium Citrate for Oral Solution.

Magnesium Hydroxide

E528; Hydroxid hořečnatý; Magnesii hydroxidum; Magnesio, hidróxido de; Magnesium Hydrate; Magnésium, hydroxyde de; Magnesiumhydroksidi; Magnesiumhydroxid; Magnézium-hidroxid; Magnezyum Hidroksit; Magnio hidroksidas; Магния Гидроксид.

$Mg(OH)_2$=58.32

CAS — 1309-42-8.

ATC — A02AA04; G04BX01.

ATC Vet — QA02AA04; QG04BX01.

UNII — NBZ3QY004S.

NOTE. Compounded preparations of magnesium hydroxide may be represented by the following names:
- Co-magaldrox *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of magnesium hydroxide and aluminium hydroxide respectively.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Magnesium Hydroxide). A fine white or almost white amorphous powder. Practically insoluble in water; dissolves in dilute acids. A solution in water is alkaline to phenolphthalein.

USP 36: (Magnesium Hydroxide). A bulky white powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; soluble in dilute acids. Store in airtight containers.

Uses and Administration

Magnesium hydroxide is an antacid (see p. 1803.1) that is given in oral doses of up to about 1 g. It is often given with aluminium-containing antacids such as aluminium hydroxide which counteract its laxative effect.

Magnesium hydroxide is also given as an osmotic laxative (p. 1804.1) in oral doses of about 2 to 5 g.

Magnesium hydroxide has also been used as a food additive and as a magnesium supplement in deficiency states.

Adverse Effects, Treatment, and Precautions

As for magnesium salts in general, see p. 1789.3. Magnesium hydroxide may cause diarrhoea, an effect that is dose-dependent. Hypermagnesaemia may occur, usually in patients with renal impairment.

Hypermagnesaemia. There have been reports of hypermagnesaemia in infants given magnesium-containing antacids,[1-3] and in an adult patient with normal renal function but bowel obstruction.[4]

1. Brand JM, Greer FR. Hypermagnesemia and intestinal perforation following antacid administration in a premature infant. *Pediatrics* 1990; **85:** 121–4.
2. Alison LH, Bulugahapitiya D. Laxative induced magnesium poisoning in a 6 week old infant. *BMJ* 1990; **300:** 125.
3. Sullivan JE, Berman BW. Hypermagnesemia with lethargy and hypotonia due to administration of magnesium hydroxide to a 4-week-old infant. *Arch Pediatr Adolesc Med* 2000; **154:** 1272–4.
4. Laughlin SA, McKinney PE. Antacid-induced hypermagnesemia in a patient with normal renal function and bowel obstruction. *Ann Pharmacother* 1998; **32:** 312–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies magnesium hydroxide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Interactions

As outlined on p. 1803.1, antacids, including magnesium salts, interact with many other drugs both by alterations in gastric pH and emptying, and by formation of complexes that are not absorbed. Interactions can be minimised by giving the antacid and any other medications 2 to 3 hours apart.

Pharmacokinetics

Magnesium hydroxide, given orally, reacts relatively rapidly with hydrochloric acid in the stomach to form magnesium chloride and water. About 30% of the magnesium ions are absorbed from the small intestine, as described for Magnesium Salts, p. 1790.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Leche de Magnesia Phillips; Magnesia San Pellegrino; ***Braz.***: Leite de Magnesia de Phillips; Mylanta Plus; ***Canad.***: Milk of Magnesia; Phillips' Magnesia Tablets; Phillips' Milk of Magnesia; ***Chile***: Leche de Magnesia Phillips; Magnesia Pasteur; Tabletas Antiacidas; ***Denm.***: Magnesia; ***Fin.***: Emgesan; Magnesiamaito; ***Fr.***: Magnesie San Pellegrino; ***Gr.***: Milk of Magnesia; ***Hong Kong***: Pedia-Lax; ***Hung.***: Antagel M; ***India***: Dey's Milk of Magnesia; Tricaine-MPS; ***Indon.***: Laxasium; ***Irl.***: Milk of Magnesia; ***Israel***: Magnesia S Pellegrino; Milk of Magnesia; ***Ital.***: Citrato Espresso S. Pellegrino; Magnesia S Pellegrino; ***Mex.***: Agrulex†; Leche de Magnesia Normex; ***Mon.***: Chlorumagene; ***Port.***: Leite Magnesia Phillips; Magnesia San Pellegrino†; ***S.Afr.***: Babys Own Tummy Tablets†; ***Spain***: Magnesia San Pellegrino; Magnesia; ***Swed.***: Emgesan; ***Switz.***: Magnesia S Pellegrino; ***Thai.***: Alumina-Magnesia; Emulax MOM; Mag-Mag; Magnesia; Milk of Magnesia; ***Turk.***: Magcine; Magnesie Calcinee; Magnesium Naneli Lafar†; Magnokal; ***UK***: Milk of Magnesia; ***USA***: Dulcolax; Milk of Magnesia; Pedia-Lax; Phillips' Chewable; Phillips' Milk of Magnesia; ***Venez.***: Magnesia San Pellegrino; Philips Leche de Magnesia.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Denm.***: Kodamid; Kodimagnyl; Magnyl; ***Gr.***: Ascriptin; ***Indon.***: Naspro; Rheumapill†; ***Ital.***: Ascriptin; Aspirina 03; ***Mex.***: Ascriptin; ***Rus.***: Cardiomagnyl (Кардиомагнил); ***Ukr.***: Cardiomagnyl (Кардиомагнил); Combi-ASA (Комби-АСК); Magnikor (Магникор); ***USA***: Arthritis Pain Formula; Ascriptin; Cope; Vanquish; ***Venez.***: Ascriptin.

Homoeopathic Preparations. ***Ger.***: Hepar-Magnesium.

Pharmacopoeial Preparations
BP 2014: Co-magaldrox Oral Suspension; Co-magaldrox Tablets; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion; Magnesium Hydroxide Mixture;
USP 36: Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Aspirin, Alumina, and Magnesia Tablets; Calcium Carbonate and Magnesia Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets; Magnesia Tablets; Magnesium Hydroxide Paste; Milk of Magnesia.

Magnesium Oxide

E530; Magnesii Oxidum; Magnesio, óxido de; Magnésium, oxyde de; Magnesiumoksidi; Magnesiumoxid; Magnezu tlenek; Magnezyum Oksit; Magnio oksidas; Nehéz magnézium; Oxid hořečnatý; Магния Оксид.

MgO=40.30

CAS — 1309-48-4.

ATC — A02AA02; A06AD02; A12CC10.

ATC Vet — QA02AA02; QA06AD02; QA12CC10.

UNII — 3A3U0GI71G.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include a single monograph that permits both the light and heavy varieties while some have 2 separate monographs for the 2 varieties.

Ph. Eur. 8: (Magnesium Oxide, Heavy; Magnesii Oxidum Ponderosum). A fine, white or almost white powder. 15 g has an apparent volume before settling of not more than 60 mL. Practically insoluble in water; dissolves in dilute acids with at most slight effervescence.

Ph. Eur. 8: (Magnesium Oxide, Light; Magnesii Oxidum Leve). A fine, white or almost white, amorphous powder. 15 g has an apparent volume before settling of at least 100 mL. Practically insoluble in water; dissolves in dilute acids with at most slight effervescence.

USP 36: (Magnesium Oxide). A very bulky, white powder, or a relatively dense, white powder, or a granulated powder. Practically insoluble in water; insoluble in alcohol; soluble in dilute acids. Store in airtight containers.

Profile

Magnesium oxide is an antacid with general properties similar to those of magnesium hydroxide (above). It is given in usual oral doses of about 400 mg. It is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium oxide has been used for its osmotic laxative properties in bowel preparation; oral doses of 3.5 g are given for this purpose, combined with bisacodyl or sodium picosulfate.

Magnesium oxide is also used as a magnesium supplement in deficiency states in oral doses of up to 800 mg (20 mmol) daily. It is also used as a food additive.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies magnesium oxide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Magnesio Vital; Polvo Roge; SG33; ***Austria***: Magnonorm; ***Canad.***: Urologic G; ***Denm.***: Salilax†; ***Fr.***: Easymagnevie; Mag 2 Junior†; MAG'Ocean†; Sargemag; Thalamag; ***Ger.***: Biolectra Magnesium 240; Biolectra Magnesium 365; Magium†; Magnesium Diasporal; Magnesium Tonil†; Magnetrans extra; Magnetrans forte; Magno Sanol; ***Hung.***: Magnosolv; ***S.Afr.***: Solumag; ***Swed.***: Salilax†; ***Switz.***: Andreamag; Solmag; ***Thai.***: Magoral; ***Turk.***: Biolectra Magnesium; Magnezi Kalsine; ***USA***: Mag-200; Mag-Ox; Maox; Uro-Mag.

Multi-ingredient Preparations. ***Arg.***: Benitol; Chiafibra; Complex B Calcio Y Magnesio; Dafne; LX-30†; Total Magnesiano NF; ***Austral.***: AB Extra Bone-Care +; Bio Magnesium; Bone Builder; Caltrate Plus; FAB Tri-Cal†; Machlor; Meno Support Plus; NA Neurocard; PicoPrep; ***Austria***: Magnosolv; ***Belg.***: Regla pH Forte; ***Canad.***: Artechol†; Articho-Nat; Cal-Mag with Vitamin D & Zinc; Cal-Mag†; Caltrate Plus; Formula C 29†; Hepartichaut†; Pico-Salax; Picodan; Purg-Odan; ***Chile***: Berocca Plus; Calcio 520; Fercovit; Oblax A-1-1; Polvos Alcalinos; ***China***: Piaojiamei (朴佳美); ***Cz.***: Caltrate Plus; Magnesium Pharmavit; Magnosolv; Picoprep; ***Denm.***: Alminox; CitraFleet; Picoprep; ***Fin.***: CitraFleet; Picoprep; ***Fr.***: Carbosymag; CitraFleet; Forcadion; Isudrine†; Kaologeais†; Karayal; Mutesa†; Picoprep; Sympathyl; Thalamag fer B_9; Verrulyse-Methionine; ***Ger.***: Citra-Fleet; Losnesium; Magnesium-Plus-Hevert†; Mapurit†; Picoprep; Rabro N; Ventricon N†; ***Gr.***: Aludrox; Novalox; Oxaine-M; ***Hong Kong***: Active Calcium†; Epilon; Picolax; ***Hung.***: Antagel; Beres Magnezium + B_6; Magnevital†; Nilacid; Picoprep; ***India***: Bescal; Bonforte; Cavit-PM; Elcal-Cit; Enhance; Levicit; Literate-CT; Menosoft; Moxafav; Neuratab B6; Neurocit; Ostebon-M; ***Indon.***: Aludonna; Day-Cal; Hical; Osfit; Vitacal-D; ***Irl.***: Asilone†; CitraFleet; Picolax; ***Israel***: Pico-Salax; ***Ital.***: Carbonesia; Citrato Espresso Gabbiani; Magnosol; Vitreosan; ***Malaysia***: Gerskin; Obical; Picoprep†; ***Mex.***: Alfem; ***Mon.***: Evestrel Jour Nuit†; ***Neth.***: Picoprep; ***Norw.***: CitraFleet; Picoprep; ***NZ***: Picoprep; ***Philipp.***: Lungcaire Plus; Sleepasil; ***Pol.***: MBE; Naturapia Calcium Complex†; Naturapia Menopauza; Nervomag; Suplemag B_6; ***Port.***: CitraFleet; ***Rus.***: Altacid (Алтацид); Calcemin Advance (Кальцемин Адванс); Sympathyl (Симпатил); ***S.Afr.***: Adco-Mayogel; Adco-Medigel; Adco-Neutragel D; Alkalite D†; Alumag D; Alumite D†; Aluspastyl†; Betaclomin; Co-Gel; Gelumen; Kolantyl†; Microgel†; Neuragel-D†; Pedimed†; Picoprep†; Propan Gel-S; Remotrox†; Spasmogel; ***Singapore***: Gerskin; Obical; ***Spain***: CitraFleet; Edigastrol†; Eupeptina; ***Swed.***: CitraFleet; Picoprep; ***Switz.***: Neurocalme; Picoprep; ***Turk.***: Magnezinc; Seldiyet; ***UK***: Asilone†; Kolanticon; Magnesium-OK; Uriflex G; Uro-Tainer Suby G; ***Ukr.***: Altacid (Алтацид)†; Calcemin Advance (Кальцемин Адванс); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Vitrum Osteomag (Витрум Остеомаг); ***USA***: Beelith; Prepopik; REQ49+; ***Venez.***: Calcibon D Magnesio; Calcibon D Soya; Dicigel; Hepasil; Polantac.

Used as an adjunct in:. ***Arg.***: Aspirina; ***Braz.***: Bufferin; ***Canad.***: Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA†; ***Pol.***: Aspimag; Cardiofil; ***USA***: Adprin-B; Bufferin; Cama Arthritis Pain Reliever; Extra Strength Bayer Plus.

Pharmacopoeial Preparations

USP 36: Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aromatic Cascara Fluidextract; Aspirin, Alumina, and Magnesium Oxide Tablets; Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation; Magnesium Oxide Capsules; Magnesium Oxide Tablets.

Magnesium Trisilicate

E553(a); Magnesii trisilicas; Magnesio, trisilicato de; Magnésium, trisilicate de; Magnesiumtrisilicat; Magnesiumtrisilikaatti; Magnesiumtrisilikat; Magnézium-triszilikát; Magnezyum Trisilikat; Magnio trisilikatas; Trikřemičitan hořečnatý; Магния Трисиликат.

CAS — 14987-04-3 (anhydrous magnesium trisilicate); 39365-87-2 (magnesium trisilicate hydrate).

UNII — C2E1CI501T.

Description. Magnesium trisilicate is a hydrated magnesium silicate. The code E553(a) has been applied to both magnesium silicate and to magnesium trisilicate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Magnesium Trisilicate). It has a variable composition corresponding approximately to the formula $Mg_2Si_3O_8.xH_2O$ containing not less than 29% of magnesium oxide and not less than the equivalent of 65% of silicon dioxide, both calculated with reference to the ignited substance. A white or almost white powder. Practically insoluble in water and in alcohol.

USP 36: (Magnesium Trisilicate). A compound of magnesium oxide and silicon dioxide with varying proportions of water. It contains not less than 20% of magnesium oxide and not less than 45% of silicon dioxide. A fine, white, odourless, powder, free from grittiness. Insoluble in water and in alcohol. It is readily decomposed by mineral acids.

Profile

Magnesium trisilicate is a hydrated magnesium silicate. It is an antacid with general properties similar to those of magnesium hydroxide (p. 1857.2). It may be given in typical oral doses of up to about 500 mg as required, although higher doses have been given. When given orally it reacts more slowly with hydrochloric acid in the stomach than magnesium hydroxide. Magnesium trisilicate is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium trisilicate is also used as a food additive and as a pharmaceutical excipient.

Effects on the kidneys. The formation of renal calculi containing silica is unusual, but has been reported in a small number of patients. In most of these cases, stone formation was attributed to the prolonged, and sometimes excessive, intake of antacids that contained magnesium trisilicate.[1,2]

1. Haddad FS, Kouyoumdjian A. Silica stones in humans. *UrolInt* 1986; **41:** 70–6.
2. Lee M-H, *et al.* Silica stone—development due to long time oral trisilicate intake. *Scand J Urol Nephrol* 1993; **27:** 267–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Singapore***: Magsil.

Multi-ingredient Preparations. ***Arg.***: Dosulfin Bronquial; Gastranil; Mylanta Reflux; ***Austral.***: Gastrogel; Gastrogel; Gaviscon; ***Austria***: Neoplex; ***Belg.***: Alucid; Gaviscon; Neutroses; Syngel; ***Braz.***: Gastrobene; Gastrobene; Gaviz; Kolantyl; ***Canad.***: Gasulsol†; ***Chile***: Gaviscon†; ***China***: Aoweishu (澳谓舒); Rudd-U (立愉); Wei Tai Kang (谓泰康); ***Fr.***: Gastropax; Magnesie Composee†; Neutroses; ***Ger.***: Duoventrinetten N; Progastrit†; ***Gr.***: Gaviscon; Neo-Elcosal; ***Hong Kong***: Aluvit-U†; Antacin-D; Fedra-Gel-S†; Gastrogel†; Gastrogel; Gaviscon; Gelucom†; Gelumag†; Gelusil; Oxema Improved; Silox-50; Triloxane†; Uni-Magel-SM†; Uni-Magel†; ***Hung.***: Nilacid; ***India***: Acigon; Alupectin DGL; Alupectin; Ancid; Bestec; Briflam; Buwin Plus; Catoxymag; Dacron-Plus; Delcid; Densera-D; Don-MR; Don; Fitflam; Gastracid; Gaviscon; Gelusil; Ibumax; Ibupar-M; Larigox; Magnine; Minidolo; Neurophen; Raftace; Raftace; Solacid; ***Indon.***: Biogastron†; Corsamag; Gastrinal; Gelusil†; Lexacrol; Methaphyllin†; Progastric; Sanmag; Sanmag; Stomagel; Tri Act†; ***Irl.***: Gaviscon†; Pyrogastrone†; ***Israel***: Fresco; ***Ital.***: Gaviscon†; Merankol Pastiglie; Neutrolac; Neutrose S Pellegrino; ***Malaysia***: Dhalumag; Gaviscon†; Gelusil; ***Neth.***: Alcasedine†; Gaviscon Forte†; ***NZ***: Gaviscon; ***Philipp.***: Contylan; ***Rus.***: Gestid (Гестид); ***S.Afr.***: Aciban; Adcomag Trisil†; Alusil†; Be-Tabs Antacid†; Gaviscon; Gelacid; Gelusil; Gentrisil†; Infant Gaviscon; Kolantyl†; ***Singapore***: Allumag M; Allumag MPS; Alumag Plus; Alumag; Cenvite; Dhalumag; Gastrogel; Gaviscon†; Gelumag; Guardian Antacid; Magtasil; Neutrazid; Polysilic; Semor Stomach; SP-Alusil; Suntacid; Vi-Ron; Vyling Gastric; Welusil; ***Spain***: Dolcopin; Gelodrox; Meteoril; Secrepat; ***Swed.***: Gastrosan; ***Switz.***: Comprimes a croquer Estomac†; Drofaron†; Neutroses; ***Thai.***: Admag-M; Airtab†; Alkamine†; Almag; Alumag; Alupep; Amacone; Amco; Amico; ANH Mat; Antacia; Conmag; Dissowel; Droximag-P; Gacida; Gelusil†; KB Alu; L-Dacin; Maalox; Machto; New Gel-D; RT Gen†; Siemag; Sinlumag; Stomac†; Ulcid†; ***Turk.***: Gaviscon; ***UK***: Actonorm; Birley's; Bisma-Rex; De Witt's Antacid; De Witt's Antacid; Gastrocote; Moorland; Opas; Pegina; Valonorm; ***Ukr.***: Secrepat Forte (Секрепат Форте); ***USA***: Alenic Alka; Gaviscon; Genaton; ***Venez.***: Polantac.

Used as an adjunct in:. ***Hong Kong***: Artrolin-F†; ***India***: IPM; Osyfen Plus; Oxyprem; ***Swed.***: Deltison.

Pharmacopoeial Preparations

BP 2014: Chewable Compound Magnesium Trisilicate Tablets; Compound Magnesium Trisilicate Oral Powder; Magnesium Trisilicate Mixture;

USP 36: Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Magnesium Trisilicate Tablets.

Manna

Maná; Manne en Larmes; Манна.

UNII — Q0MN98P9Q4.

Profile

Manna is the dried exudation from the bark of the European flowering ash, *Fraxinus ornus* (Oleaceae), containing about 40 to 60% of mannitol (p. 1427.3). It has been used as an osmotic laxative.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Pervivo; ***Cz.***: Dr Theiss Schweden Krauter†; ***Ger.***: florabio Manna-Feigen†; ***Hung.***: Bittner; ***Ital.***: Cumadren; ***Pol.***: Pervivo.

Mebeverine Hydrochloride

(BANM, USAN, rINNM)

CSAG-144; Hidrocloruro de mebeverina; Mebeverina, hidrocloruro de; Mébévérine, Chlorhydrate de; Mebeverini Hydrochloridum; Мебеверина Гидрохлорид.

4-[Ethyl(4-methoxy-α-methylphenethyl)amino]butyl veratrate hydrochloride.

$C_{25}H_{35}NO_5$,HCl=466.0

CAS — 3625-06-7 (mebeverine); 2753-45-9 (mebeverine hydrochloride).

ATC — A03AA04.

ATC Vet — QA03AA04.

UNII — 15VZ5AL4JN.

Pharmacopoeias. In *Br.*

BP 2014: (Mebeverine Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Uses and Administration

Mebeverine hydrochloride is an antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract. It is used in conditions such as irritable bowel syndrome (p. 1810.3) in a usual oral dose of 135 mg three times daily before meals; 100 mg three times daily has also been used. A modified-release preparation is also available, taken as 200 mg twice daily. The embonate is also used for oral liquid preparations in a dose equivalent to 150 mg of the hydrochloride three times daily.

For doses in children, see below.

Administration in children. Mebeverine is used in children for the symptomatic relief of gastrointestinal smooth muscle spasm. The *BNFC* suggests the following oral doses, expressed as mebeverine hydrochloride, given three times daily, preferably 20 minutes before meals:

- 3 to 4 years: 25 mg
- 4 to 8 years: 50 mg
- 8 to 10 years: 100 mg
- 10 to 18 years: adult doses may be given, see above

A modified-release formulation is also available; children from 12 years of age may be given adult doses, see above.

Adverse Effects and Precautions

Although adverse effects appear rare, gastrointestinal disturbances, dizziness, headache, insomnia, anorexia, and decreased heart rate have been reported in patients receiving mebeverine. Cases of hypersensitivity, including erythematous rash, urticaria, and angioedema, have also been reported. Mebeverine should be avoided in patients with paralytic ileus. Based on theoretical concerns, it should be used with care in patients with marked hepatic or renal impairment, and those with cardiac disorders such as heart block.

Cystic fibrosis. A 24-year-old man with cystic fibrosis, given mebeverine hydrochloride for lower abdominal pain and constipation, was found to have a perforated stercoral ulcer with generalised peritonitis.[1] It was suggested that mebeverine produced colonic stasis, which predisposed the patient to ulceration,[1] but the manufacturers[2] considered that the development of constipation and distal intestinal syndrome (meconium ileus equivalent) in this patient precipitated the development of stercoral ulceration. It was recommended[1] that antispasmodics such as mebeverine should not be used for the symptomatic treatment of distal intestinal syndrome in cystic fibrosis.

1. Hassan W, Keaney N. Mebeverine-induced perforated colon in distal intestinal syndrome of cystic fibrosis. *Lancet* 1990; **335:** 1225.
2. Whitehead AM. Perforation of colon in distal intestinal syndrome of cystic fibrosis. *Lancet* 1990; **336:** 446.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mebeverine as

probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Mebeverine is rapidly absorbed after oral doses with peak plasma concentrations occurring in 1 to 3 hours. It is 75% bound to albumin in plasma. Mebeverine is completely metabolised by hydrolysis to veratric acid and mebeverine alcohol, the latter of which may then be conjugated. The metabolites are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duspatalin; ***Austral.***: Colese; Colofac; ***Austria***: Colofac; ***Belg.***: Duspatalin; ***Braz.***: Duspatalin; ***Chile***: Doloverina; Duspatal; Evadol; Meditoina; ***China***: Duspatalin (杜适林); ***Cz.***: Duspatalin; ***Denm.***: Duspatalin; ***Fr.***: Colopriv†; Duspatalin; Spasmopriv†; ***Ger.***: Duspatal; ***Gr.***: Dolospasmo; Duspatalin; Gastromins; Trisolvetan; Yugorex; ***Hong Kong***: Duspatalin; ***Hung.***: Duspatalin; ***India***: Colospa; Libure; Mebaspa; Mebiz; Mebrin; Meva; Morease; ***Indon.***: Duspatalin; Irbosyd; ***Irl.***: Colofac; Mebecon; ***Israel***: Colotal; ***Ital.***: Duspatal; Duspatalin; ***Malaysia***: Duspatalin; Lezpain; Mebetin; ***Mex.***: Arluy; Duspatalin; ***Neth.***: Duspatal; Duspatalin; ***NZ***: Colofac; ***Philipp.***: Duspatalin; ***Pol.***: Duspatalin; ***Port.***: Duspatal; ***Rus.***: Duspatalin (Дюспаталин); Sparex (Спарекс); ***S.Afr.***: Bevispas; Colofac; ***Singapore***: Duspatalin; Mebetin; ***Spain***: Duspatalin; ***Switz.***: Duspatalin; ***Thai.***: Colofac; Duspatin; Farlotac; Menosor; ***Turk.***: Duspatalin; Duspaverin; Spasflex; ***UK***: Colofac; IBS Relief; ***Ukr.***: Duspatalin (Дуспаталин); Mebsin (Мебсин); Meverin (Меверин).

Multi-ingredient Preparations. ***India***: Mebasap-AL; Mebrin-AZ; Meva-C; Morease-I; ***Irl.***: Fybogel Mebeverine; ***UK***: Fybogel Mebeverine.

Pharmacopoeial Preparations
BP 2014: Mebeverine Tablets.

Mecloxamine Citrate *(rINNM)*

Citrato de mecloxamina; Mécloxamine, Citrate de; Mecloxamini Citras; Меклоксамина Цитрат.

2-[1-(4-Chlorophenyl)-1-phenylethoxy]-*N*,*N*-dimethyl-1-propanamine citrate.

$C_{19}H_{24}ClNO,C_6H_8O_7$=510.0

CAS — 5668-06-4 (mecloxamine); 56050-03-4 (mecloxamine citrate).

UNII — 26G46G752S.

Profile

Mecloxamine citrate is reported to have antimuscarinic properties and has been used for its antiemetic action in antimigraine preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Avamigran; ***Turk.***: Avmigran; ***Ukr.***: Nomigren (Номигрен).

Mepenzolate Bromide *(BAN, rINN)*

Bromuro de mepenzolato; Mepentsolaattibromidi; Mepenzolatbromid; Mépenzolate, Bromure de; Mepenzolate Methylbromide; Mepenzolati Bromidum; Mepenzolato, bromuro de; Mepenzolone Bromide; Мепензолата Бромид.

3-Benziloyloxy-1,1-dimethylpiperidinium bromide.

$C_{21}H_{26}BrNO_3$=420.3

CAS — 25990-43-6 (mepenzolate); 76-90-4 (mepenzolate bromide).

ATC — A03AB12.

ATC Vet — QA03AB12.

UNII — APX8D32IX1.

Pharmacopoeias. In *Jpn*.

Profile

Mepenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been used in the relief of gastrointestinal disorders associated with smooth muscle spasm and as an adjunct in the treatment of peptic ulcer disease. Up to 200 mg daily may be given orally in divided doses.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mepenzolate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Trancolon; ***USA***: Cantil.

Multi-ingredient Preparations. ***Jpn***: Trancolon P.

Mesalazine *(BAN, rINN)*

5-Aminosalicylic Acid; 5-ASA; Fisalamine; Mesalamine (USAN); Mesalatsiini; Mesalazin; Mesalazina; Mesalazinas; Mésalazine; Mesalazinum; Месалазин.

5-Amino-2-salicylic acid.

$C_7H_7NO_3$=153.1

CAS — 89-57-6.

ATC — A07EC02.

ATC Vet — QA07EC02.

UNII — 4Q81I59GXC.

NOTE. Distinguish from 4-aminosalicylic acid (Aminosalicylic Acid, p. 215.2) which is used in the treatment of tuberculosis.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Mesalazine). An almost white or light grey or light pink powder or crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid. Store in airtight containers. Protect from light.

USP 36: (Mesalamine). Light tan to pink needle-shaped crystals, odourless or with a slight characteristic odour. The colour may darken on exposure to air. Slightly soluble in water; very slightly soluble in dehydrated alcohol, in acetone, and in methyl alcohol; practically insoluble in butyl alcohol, in chloroform, in dichloromethane, in ether, in ethyl acetate, in *n*-hexane, and in propyl alcohol; soluble in dilute hydrochloric acid and in dilute alkali hydroxides. A 2.5% suspension in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Uses and Administration

Mesalazine is an anti-inflammatory drug structurally related to the salicylates and active in inflammatory bowel disease (p. 1808.3); it is considered to be the active moiety of sulfasalazine (p. 1890.1). Mesalazine is thought to act locally on the inflamed intestinal tissue, rather than systemically. Although its precise mechanism of action is uncertain, it may be due to inhibition of prostaglandin and leukotriene synthesis in the gastrointestinal mucosa.

Mesalazine is given orally or rectally in the treatment of *acute attacks* of mild to moderate ulcerative colitis, or the *maintenance of remission* of ulcerative colitis. Some products are also used for the *maintenance of remission* of Crohn's ileocolitis.

There are several differently formulated oral preparations of mesalazine available, and dosage recommendations vary. Recommended doses for some UK preparations are as follows:

- *Asacol 400 mg* tablets (*Warner Chilcott, UK*), *Ipocol* tablets (*Sandoz, UK*), *Mesren* tablets (*IVAX, UK*): acute attack, initially 2.4 g daily in divided doses; maintenance of remission, 1.2 to 2.4 g daily in divided doses.
- *Asacol 800 mg* tablets (*Warner Chilcott, UK*): mild acute exacerbations, 2.4 g daily in divided doses; moderate acute exacerbations, 4.8 g daily in divided doses; maintenance of remission, up to 2.4 g daily in divided doses
- *Mezavant* tablets (*Shire, UK*): acute attack, initially 2.4 to 4.8 g once daily; maintenance of remission, 2.4 g once daily
- *Pentasa* tablets (*Ferring, UK*): acute attack, initially up to 4 g daily in 2 or 3 divided doses; maintenance of remission, adjusted individually from an initial dose of 2 g once daily.
- *Pentasa* granules (*Ferring, UK*): acute attack, initially, up to 4 g daily in 2 to 4 divided doses; maintenance of remission, 2 g once daily.
- *Salofalk* tablets (*Falk, UK*): acute attack, initially 1.5 to 3 g daily in 3 divided doses; maintenance of remission, 1.5 g daily in 3 divided doses.
- *Salofalk* granules (*Falk, UK*): acute attack, initially 1.5 to 3 g daily, either once daily, or in 3 divided doses; maintenance of remission, 1.5 g daily in 3 divided doses.

Mesalazine may be given rectally, particularly when disease affects the sigmoid colon and rectum. Various formulations are available and the dose is usually given at night, but preparations do vary. Recommended doses for some UK preparations are as follows:

- *Asacol* suppositories (*Warner Chilcott, UK*): 0.75 to 1.5 g daily in divided doses
- *Asacol* foam enema (*Warner Chilcott, UK*): 1 g daily for disease affecting the rectosigmoid region; 2 g daily for disease involving the descending colon
- *Pentasa* suppositories and suspension enema (*Ferring, UK*): 1 g daily
- *Salofalk* suppositories (*Falk, UK*): 0.5 to 1 g given 2 or 3 times daily
- *Salofalk* foam enema and suspension enema (*Falk, UK*): 2 g daily

Similar preparations are available in other countries, and in the USA a suspension enema containing 4 g of mesalazine has been used.

For doses in children, see below.

References.

1. Clemett D, Markham A. Prolonged-release mesalazine: a review of its therapeutic potential in ulcerative colitis and Crohn's disease. *Drugs* 2000; **59:** 929–56.
2. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; **2:** 379–88.
3. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 01/06/07).
4. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
6. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **23:** 841–55.
7. van Bodegraven AA, Mulder CJ. Indications for 5-aminosalicylate in inflammatory bowel disease: is the body of evidence complete? *World J Gastroenterol* 2006; **12:** 6115–23.
8. Anonymous. Once-daily mesalamine (Lialda) for ulcerative colitis. *Med Lett Drugs Ther* 2007; **49:** 25–6.
9. McCormack PL, *et al*. Delayed-release Multi Matrix System (MMX) mesalazine: in ulcerative colitis. *Drugs* 2007; **67:** 2635–42.
10. Kale-Pradhan PB, *et al*. Multi-Matrix System Mesalamine: to use or not to use. *Ann Pharmacother* 2008; **42:** 265–9.

Administration. Because the release characteristics of different formulations of mesalazine vary, they should not be regarded as interchangeable.[1] This applies even to those formulations where the dosage is apparently similar.[2] However, a study in healthy subjects established that an oral once-daily regimen was bioequivalent to a twice-daily regimen of the same product (*Pentasa (Ferring, France)*),[3] and another study using a different product (*Salofalk granules (Falk, Germany)*) found that 8 weeks of once-daily dosing had similar safety and efficacy to a three-times daily regimen for inducing remission in patients with active ulcerative colitis.[4]

1. Forbes A, Chadwick C. Mesalazine preparations. *Lancet* 1997; **350:** 1329.
2. Benbow AG, Gould I. Mesalazine preparations. *Lancet* 1998; **351:** 68.
3. Gandia P, *et al*. Is once-daily mesalazine equivalent to the currently used twice-daily regimen? A study performed in 30 healthy volunteers. *J Clin Pharmacol* 2007; **47:** 334–42.
4. Kruis W, *et al*. International Salofalk OD Study Group. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009; **58:** 233–40.

Administration in children. Mesalazine may be given orally or rectally to children in the treatment of *acute attacks* of mild to moderate ulcerative colitis, or the *maintenance of remission* of ulcerative colitis.

There are several differently formulated oral preparations of mesalazine available, and dosage recommendations vary. The *BNFC* suggests the following oral doses for some UK preparations when used in children:

- *Asacol 400 mg* tablets (*Warner Chilcott, UK*): children aged 12 to 18 years may be given similar doses to adults, see above.
- *Ipocol* tablets (*Sandoz, UK*): children aged 6 to 18 years and weighing 40 kg or more may be given similar doses to adults.
- *Pentasa* tablets and granules (*Ferring, UK*) and *Salofalk* tablets and granules (*Falk, UK*): children aged 5 to 18 years and under 40 kg: acute attack, 30 to 60 mg/kg daily in 3 divided doses; maintenance of remission, 15 to 30 mg/kg daily in 2 or 3 divided doses. Children aged 5 to 18 years and over 40 kg may be given similar doses to adults.

  In addition, *Salofalk* granules may be given to children under 40 kg in a dose of 30 to 50 mg/kg once daily (preferably in the morning) for an acute attack.

Mesalazine may also be given rectally to children, particularly when disease affects the sigmoid colon and rectum. Various formulations are available and the dose is usually given at night, but preparations do vary. The *BNFC* suggests that children aged 12 to 18 years may be given similar doses to adults.

Diverticular disease. In a study involving 218 patients with a history of recurrent attacks of acute diverticulitis (p. 1806.2), half were assigned to treatment with oral

rifaximin 400mg twice daily for 7 days, and half received rifaximin plus a modified-release formulation of mesalazine 800 mg three times daily, again for 7 days. Courses were then repeated, with rifaximin at the same dose and mesalazine at 800 mg twice daily, for 7 days in each month, and patients followed for 12 months. The combination of rifaximin and mesalazine was significantly more effective in reducing symptomatic episodes and normalisation of bowel habit than rifaximin alone: 89 of 107 patients given the combination were symptom-free at 12 months, compared with 44 of 105 given just the antibacterial.[1] Similarly, the same group found that in patients with uncomplicated diverticular disease given 10 days of treatment with rifaximin and mesalazine (*Pentacol; Sofar, Ital.*) in the doses above, followed by mesalazine 1.6g daily for 8 weeks, 70 of 86 completing the study were completely asymptomatic, suggesting that daily mesalazine alone was an effective maintenance therapy, although longer-term studies were needed.[2] Mesalazine has also been investigated in combination with a probiotic preparation of lactic-acid-producing organisms.[3]

1. Tursi A, *et al*. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis* 2002; **34:** 510–15.
2. Brandimarte G, Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. *Med Sci Monit* 2004; **10:** PI70–PI73.
3. Tursi A, *et al*. Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. *J Clin Gastroenterol* 2006; **40:** 312–16.

Malignant neoplasms. The potential chemopreventive action of mesalazine against colorectal cancer, particularly in patients with inflammatory bowel disease, has been reviewed[1,2] but studies[3,4] have reached conflicting conclusions.

1. Stolfi C, *et al*. Molecular basis of the potential of mesalazine to prevent colorectal cancer. *World J Gastroenterol* 2008; **14:** 4434–9.
2. Lyakhovich A, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. *Aliment Pharmacol Ther* 2010; **31:** 202–9.
3. Ullman T, *et al*. Progression to colorectal neoplasia in ulcerative colitis: effect of mesalamine. *Clin Gastroenterol Hepatol* 2008; **6:** 1225–30.
4. Tang J, *et al*. Mesalamine protects against colorectal cancer in inflammatory bowel disease. *Dig Dis Sci* 2010; **55:** 1696–1703.

Adverse Effects and Precautions

Mesalazine may cause headache and gastrointestinal disturbances, such as nausea, diarrhoea, and abdominal pain. Hypersensitivity reactions may occasionally occur. Some patients may experience exacerbation of symptoms of colitis. There are some reports of myocarditis, pericarditis, pancreatitis, interstitial nephritis, nephrotic syndrome, allergic lung reaction, increased liver enzyme values, hepatitis, lupus-like syndrome, skin reactions, alopecia, peripheral neuropathy, myalgia, and arthralgia. There have been rare reports of blood disorders including aplastic anaemia, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, and methaemoglobinaemia.

Mesalazine should not be given to patients with severe renal or hepatic impairment, or salicylate hypersensitivity. It should be used with caution in the elderly, and in mild to moderate renal or hepatic impairment, active peptic ulceration, or sulfasalazine allergy.

If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. It is recommended that renal function is monitored before and during therapy (see Effects on the Kidneys, below).

Many of the adverse effects associated with sulfasalazine (sulfapyridine linked to mesalazine) therapy have been attributed to the sulfapyridine moiety and most patients unable to tolerate sulfasalazine because of hypersensitivity or adverse reactions can be transferred to mesalazine without adverse effects occurring.[1-4] However, a small number of patients also have adverse effects while taking mesalazine and these are often very similar to those seen with sulfasalazine.[1-4] They may include nausea, abdominal discomfort or pain, exacerbation of diarrhoea, headache, fever, and rashes. Mesalazine is not generally associated with sulfasalazine's adverse effects on sperm (although there has been a case of reversible male infertility attributed to mesalazine—see under Sulfasalazine, p. 1891.2). An analysis of adverse reactions reported to the UK CSM between 1991 and 1998 found no evidence of a significant difference in the frequency of serious adverse effects for mesalazine and sulfasalazine in the treatment of inflammatory bowel disease.[5] Reports of pancreatitis and interstitial nephritis were more common with mesalazine (but see Effects on the Kidneys, below). However, it has been pointed out that 80% of patients intolerant to sulfasalazine will tolerate mesalazine without problems.[6]

Mesalazine therapy should be started cautiously in patients with a history of sulfasalazine **hypersensitivity** and it should be withdrawn if signs of sensitivity develop or if there is diarrhoea or rectal bleeding. It has been suggested[2] that patients with a history of sulfasalazine hypersensitivity should be given test doses of mesalazine before starting a full course.

1. Dew MJ, *et al*. Treatment of ulcerative colitis with oral 5-aminosalicylic acid in patients unable to take sulphasalazine. *Lancet* 1983; **ii:** 801.
2. Campieri M, *et al*. 5-Aminosalicylic acid as rectal enema in ulcerative colitis patients unable to take sulphasalazine. *Lancet* 1984; **i:** 403.
3. Donald IP, Wilkinson SP. The value of 5-aminosalicylic acid in inflammatory bowel disease for patients intolerant or allergic to sulphasalazine. *Postgrad Med J* 1985; **61:** 1047–8.
4. Rao SS, *et al*. Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. *Scand J Gastroenterol* 1987; **22:** 332–6.
5. Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; **51:** 536–9.
6. D'Haens G, van Bodegraven AA. Mesalazine is safe for the treatment of IBD. *Gut* 2004; **53:** 155.

Breast feeding. The concentrations of mesalazine in maternal plasma and breast milk in a woman taking 500 mg three times daily, were 410 and 110 nanograms/mL respectively.[1] Although it was considered that the amount of mesalazine distributed into breast milk was small and that it was safe during breast feeding,[2,3] maternal use of mesalazine 500 mg suppositories twice daily has been associated with watery diarrhoea in a breast-fed infant[2] and for this reason the American Academy of Pediatrics considers that mesalazine should be given with caution to breast-feeding mothers.[4]

1. Jenss H, *et al*. 5-Aminosalicylic acid and its metabolite in breast milk during lactation. *Am J Gastroenterol* 1990; **85:** 331.
2. Nelis GF. Diarrhoea due to 5-aminosalicylic acid in breast milk. *Lancet* 1989; **i:** 383.
3. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. *Lancet* 1993; **342:** 618–19.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/02/06)

Effects on the blood. Although uncommon, mesalazine-associated adverse effects on the blood have been reported, including thrombocytopenia,[1,2] neutropenia,[3] severe aplastic anaemia,[4,5] and pancytopenia.[6] In July 1995 the UK CSM stated that it had been notified of 49 haematological reactions suspected of being associated with mesalazine,[7] including 5 reports of aplastic anaemia, 1 of agranulocytosis, 11 of leucopenia, and 17 of thrombocytopenia. There had been 3 fatalities. They recommended a blood count and immediate withdrawal of the drug if a dyscrasia was suspected. Intensive immunosuppressive treatment has been used in the management of mesalazine-associated aplastic anaemia.[5,8]

1. Daneshmend TK. Mesalazine-associated thrombocytopenia. *Lancet* 1991; **337:** 1297–8.
2. Farrell RJ, *et al*. Mesalamine-associated thrombocytopenia. *Am J Gastroenterol* 1999; **94:** 2304–6.
3. Wyatt S, *et al*. Filgrastim for mesalazine-associated neutropenia. *Lancet* 1993; **341:** 1476.
4. Abboudi ZH, *et al*. Fatal aplastic anaemia after mesalazine. *Lancet* 1994; **343:** 542.
5. Otsubo H, *et al*. Mesalazine-associated severe aplastic anemia successfully treated with antithymocyte globulin, cyclosporine and granulocyte colony-stimulating factor. *Int J Hematol* 1998; **68:** 445–8.
6. Kotanagi H, *et al*. Pancytopenia associated with 5-aminosalicylic acid use in a patient with Crohn's disease. *J Gastroenterol* 1998; **33:** 571–4.
7. CSM/MCA. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)
8. Laidlaw ST, Reilly JT. Antilymphocyte globulin for mesalazine-associated aplastic anaemia. *Lancet* 1994; **343:** 981–2.

Effects on the cardiovascular system. Myocarditis associated with chest pain and ECG abnormalities has been reported[1,2] in 2 patients taking mesalazine; 1 patient died in cardiogenic shock.[2] It has been suggested that mesalazine or sulfasalazine should be replaced by glucocorticoids if cardiac symptoms arise during treatment.[2] Pericarditis[3,4] with fever, rash, dyspnoea, pleural and pericardial effusions, and arthritis, has been described, and is considered to constitute a drug-induced lupus-like syndrome. Constrictive pericarditis with an absence of other lupus-like symptoms developed in a patient taking mesalazine for inflammatory bowel disease.[5] Based on reported cases of mesalazine-induced pericarditis, symptoms of this potentially life-threatening adverse effect have tended to arise 2 to 4 weeks after starting mesalazine, although symptom onset may be delayed by concurrent corticosteroid treatment.[6] Mesalazine cardiotoxicity presenting as an acute coronary syndrome, without myocarditis or pericarditis, has also been reported.[7]

1. Agnholt J, *et al*. Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i:** 1135.
2. Kristensen KS, *et al*. Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335:** 605.
3. Dent MT, *et al*. Mesalazine induced lupus-like syndrome. *BMJ* 1992; **305:** 159.
4. Lim AG, Hine KR. Fever, vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *BMJ* 1994; **308:** 113.
5. Oxentenko AS, *et al*. Constrictive pericarditis in chronic ulcerative colitis. *J Clin Gastroenterol* 2002; **34:** 247–51.
6. Waite RA, Malinowski JM. Possible mesalamine-induced pericarditis: case report and literature review. *Pharmacotherapy* 2002; **22:** 391–4.
7. Amin HE, *et al*. Mesalamine-induced chest pain: a case report. *Can J Cardiol* 2000; **16:** 667–9.

Effects on fertility. For a report of reversible male infertility occurring with mesalazine, see under Sulfasalazine, p. 1891.2.

Effects on the hair. For a report of accelerated loss of scalp hair in 2 patients receiving mesalazine enemas, see under Sulfasalazine, p. 1891.3.

Effects on the kidneys. Between February 1988 and December 1990 the UK CSM[1] received 9 reports of serious nephrotoxic reactions associated with the use of *Asacol*, a modified-release mesalazine preparation. The reactions included 4 cases of interstitial nephritis, 3 of severe renal failure, and 2 cases of nephrotic syndrome. A subsequent case report[2] indicated that by September 1998 the number of such reports for mesalazine totalled 104, including 35 cases of interstitial nephritis. The authors considered that monitoring of renal function was required in patients receiving mesalazine. A protocol for such monitoring was subsequently suggested,[3] and a similar protocol has been adopted in UK licensing information for mesalazine, with serum creatinine being estimated:

- before treatment
- every 3 months for the first year
- every 6 months for the next 4 years
- annually thereafter

The nephrotic syndrome[4] and interstitial nephritis[5] have also been reported with sulfasalazine, and interstitial nephritis with olsalazine (see p. 1867.1). A large UK epidemiologic study found no difference in risk of renal disease between mesalazine and sulfasalazine. The study also concluded that the risk of renal disease associated with mesalazine and related compounds is low and may be partly attributable to the underlying disease.[6] Overall nephrotoxicity has been estimated to occur in about 1 in 4000 UK patients per year taking aminosalicylate-based therapy.[7]

1. CSM. Nephrotoxicity associated with mesalazine (Asacol). *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024448&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Popoola J, *et al*. Late onset interstitial nephritis associated with mesalazine treatment. *BMJ* 1998; **317:** 795–7.
3. Corrigan G, Stevens PE. Review article: interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14:** 1–6.
4. Barbour VM, Williams PF. Nephrotic syndrome associated with sulphasalazine. *BMJ* 1990; **301:** 818.
5. Dwarakanath AD, *et al*. Sulphasalazine induced renal failure. *Gut* 1992; **33:** 1006–1007.
6. Van Staa TP, *et al*. 5-Aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology* 2004; **126:** 1733–9.
7. Muller AF, *et al*. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005; **21:** 1217–24.

Effects on the liver. A case of chronic hepatitis and liver fibrosis has been reported after prolonged use of mesalazine.[1] The authors considered that mesalazine should be stopped when liver dysfunction occurred.

1. Deltenre P, *et al*. Mesalazine (5-aminosalicylic acid) induced chronic hepatitis. *Gut* 1999; **44:** 886–8.

Effects on the nervous system. Peripheral neuropathy,[1] mainly affecting the legs, has occurred during mesalazine treatment. The symptoms resolved on stopping the drug. Mononeuritis multiplex was part of the presentation of an eosinophilic reaction attributed to mesalazine in an asthmatic patient;[2] Churg-Strauss syndrome developed after withdrawal of mesalazine, but the patient subsequently recovered without sequelae.

1. Woodward DK. Peripheral neuropathy and mesalazine. *BMJ* 1989; **299:** 1224.
2. Morice AH, *et al*. Mesalazine activation of eosinophil. *Lancet* 1997; **350:** 1105.

Effects on the pancreas. Pancreatitis has been reported as an adverse effect of mesalazine.[1-4] In 2 patients,[1,2] with abdominal pain and raised amylase activity, this reaction to mesalazine was confirmed by rechallenge and symptoms resolved on mesalazine withdrawal. By February 1994 the UK CSM had received 15 reports[3] of pancreatitis associated with mesalazine therapy. However, a case control study suggested that inflammatory bowel disease, rather than the use of mesalazine, may be associated with an increased risk of acute pancreatitis (see under Sulfasalazine, p. 1891.3)

1. Sachedina B, *et al*. Acute pancreatitis due to 5-aminosalicylate. *Ann Intern Med* 1989; **110:** 490–2.
2. Deprez P, *et al*. Pancreatitis induced by 5-aminosalicylic acid. *Lancet* 1989; **ii:** 445–6.
3. CSM. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)

4. Adachi E, *et al*. Acute pancreatitis secondary to 5-aminosalicylic acid therapy in a patient with ulcerative colitis. *Int J Pancreatol* 1999; **25:** 217–21.

Effects on the respiratory system. Pulmonary complications have been rarely reported with mesalazine. There have though been cases of interstitial lung disease, with features of hypersensitivity pneumonia.[1-3] Symptoms have included dyspnoea, cough, fever, and pleuritic chest pain, with the onset of symptoms varying from a few days to several years after starting mesalazine therapy. Although pulmonary complications can also be associated with inflammatory bowel disease itself, there has been a report[4] of eosinophilic pleural effusion in a patient who was given mesalazine in the absence of an established diagnosis of inflammatory bowel disease.

Pulmonary complications have also been reported with sulfasalazine (p. 1891.3), and pulmonary symptoms may also manifest as part of a broader lupus-like syndrome (see Effects on the Cardiovascular System, p. 1860.2).

1. Foster RA, *et al*. Mesalamine-related lung disease: clinical, radiographic, and pathologic manifestations. *Inflamm Bowel Dis* 2003; **9:** 308–15.
2. Lamsiah T, *et al*. Pneumopathie interstitielle induite par la mésalazine. *Gastroenterol Clin Biol* 2010; **34:** 224–6.
3. Jain N, *et al*. Mesalamine lung toxicity. *Conn Med* 2010; **74:** 265–7.
4. Trisolini R, *et al*. Eosinophilic pleural effusion due to mesalamine: report of a rare occurrence. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; **17:** 288–91.

Lupus. A lupus-like syndrome has been reported in 4 patients receiving mesalazine who developed antinuclear antibody (ANA)-positivity with at least one clinical feature of lupus, such as arthropathy, skin rashes, or acute inflammation unrelated to the underlying condition.[1] In all 4 cases symptoms resolved upon stopping mesalazine. For similar reports, see Effects on the Cardiovascular System, p. 1860.2.

1. Kirkpatrick AW, *et al*. Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease. *Can J Gastroenterol* 1999; **13:** 159–62.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mesalazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Pregnancy. Renal insufficiency in a neonate whose mother received oral mesalazine 2 to 4 g daily during the second trimester of pregnancy was suggested to be due to the drug,[1] although the proposed mechanism, inhibition of prostaglandin synthesis in the neonatal kidney, has been questioned.[2] A subsequent case-control study[3] found that use of oral mesalazine in 165 pregnant women with inflammatory bowel disease was not associated with a greater incidence of malformations. However, women treated with mesalazine were more likely to have preterm deliveries and newborns with decreased birth-weights, although the disease may have been a factor in this finding. A commentator on this study,[4] considered that active inflammatory bowel disease was a greater risk to pregnancy than drug treatment. In a further cohort of 123 pregnancies,[5] oral mesalazine at doses of 3 g daily or less did not increase the risk of fetal malformations or affect pregnancy outcome. The researchers concluded that further information was required on doses higher than 3 g daily. In another study,[6] all of 19 pregnancies in women receiving rectal mesalazine were full-term with no fetal abnormalities. A Danish cohort study[7] found an increased risk of still-birth and preterm birth in women who had been prescribed mesalazine or olsalazine during pregnancy, but no significant increased risk of malformations. The risk of still-birth was greatest in women with ulcerative colitis who were prescribed corticosteroids and either mesalazine or olsalazine, and the risk of preterm birth was greatest in women with ulcerative colitis who were prescribed either mesalazine or olsalazine alone. The authors acknowledged that it was difficult to distinguish between the increase in risk due to disease state, and the increase in risk due to medication.[7] For a discussion of sulfasalazine in pregnancy, see p. 1892.1.

1. Colombel J-F, *et al*. Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? *Lancet* 1994; **344:** 620–1.
2. Marteau P, Devaux CB. Mesalazine during pregnancy. *Lancet* 1994; **344:** 1708–9.
3. Diav-Citrin O, *et al*. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* 1998; **114:** 23–8.
4. Sachar D. Exposure to mesalamine during pregnancy increased preterm deliveries (but not birth defects) and decreased birth weight. *Gut* 1998; **43:** 316.
5. Marteau P, *et al*. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. *Aliment Pharmacol Ther* 1998; **12:** 1101–8.
6. Bell CM, Habal FM. Safety of topical 5-aminosalicylic acid in pregnancy. *Am J Gastroenterol* 1997; **92:** 2201–2.
7. Nørgård B, *et al*. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003; **52:** 243–7.

Interactions

Preparations formulated to release mesalazine in the colon should not be given with drugs, such as lactulose, that lower colonic pH as they may prevent the release of mesalazine (but see Gastrointestinal Drugs below).

Anticoagulants. For reference to a case of mesalazine reducing the effect of *warfarin*, see Gastrointestinal Drugs, p. 1534.1.

Antineoplastics. For mention of 5-aminosalicylates such as mesalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Gastrointestinal Drugs, p. 822.1.

Gastrointestinal drugs. Although it has been suggested that *lactulose* could delay the intestinal release of mesalazine from modified-release preparations, a study found no evidence that lactulose influenced the release or disposition of mesalazine.[1] Similarly, *omeprazole* did not appear to increase the likelihood of premature mesalazine release.

1. Hussain FN, *et al*. Mesalazine release from a pH dependent formulation: effects of omeprazole and lactulose co-administration. *Br J Clin Pharmacol* 1998; **46:** 173–5.

Pharmacokinetics

If given orally as conventional formulations, mesalazine would be extensively absorbed from the upper gastrointestinal tract, with little of the drug reaching the colon. Oral preparations are therefore generally formulated to release the drug in the terminal ileum and colon, where it is thought to exert a mainly local action. The specific release characteristics differ somewhat between formulations and this, together with interindividual variation, makes comparison of pharmacokinetic data between studies difficult. Even with modified-release preparations some 30 to 50% of an oral dose is thought to be lost to absorption in healthy subjects. Absorption from rectal dosage forms has also varied widely, with factors such as the dose, the formulation, and the pH also playing a role, but mean absorption of around 10 to 30% of a rectal dose has been reported.

The absorbed portion of mesalazine is almost completely acetylated in the gut wall and in the liver to acetyl-5-aminosalicylic acid. The rate of acetylation, and hence the concentration of parent drug and metabolite in the systemic circulation, may be dose dependent and subject to saturation. The acetylated metabolite is excreted mainly in urine by tubular secretion, with traces of the parent compound.

The plasma half-life of mesalazine is reported to be about 40 minutes and it is 40 to 50% bound to plasma proteins; the acetylated metabolite has a plasma half-life of 70 minutes and is about 80% bound to plasma proteins.

Only negligible quantities of mesalazine cross the placenta. Amounts distributed into breast milk are very small.

Reviews.

1. De Vos M. Clinical pharmacokinetics of slow release mesalazine. *Clin Pharmacokinet* 2000; **39:** 85–97.
2. Sandborn WJ, *et al*. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003; **17:** 29–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bufexan; Exotran; Mezavant; Pentasa; Rectocalm; Salofalk; Sekena; Suprimal; Xalazina; Yolecol; ***Austral.***: Mesasal; Mezavant; Pentasa; Salofalk; ***Austria***: Claversal; Mesagran; Mezavant; Pentasa; Salofalk; ***Belg.***: Claversal; Colitofalk; Mezavant; Pentasa; ***Braz.***: Asalit; Chron-ASA; Mesacol; ***Canad.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***Chile***: Pentasa; Salofalk; ***China***: Anjiesha (安洁莎); Etiasa (艾迪莎); Pentasa (颇得斯安); Salofalk (莎尔福); ***Cz.***: Asacol; Pentasa; Salofalk; Samezil†; ***Denm.***: Asacol; Lixacol†; Mesasal; Mesavancol; Mezavant; Pentasa; Quintasa; Salofalk; ***Fin.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***Fr.***: Fivasa; Pentasa; Rowasa; ***Ger.***: Asacol†; Asacolitin†; Claversal; Mezavant; Pentasa; Salofalk; ***Gr.***: Asacol; Asalazin; Crohnezine; Cronezil; Ectospasmol; Empenox; Enterin; Favorat; Laboxantryl; Mesagin; Mezavant; Pentasa; Prozylex; Salofalk; ***Hong Kong***: Asacol; Pentasa; Salofalk; ***Hung.***: Asacol†; Pentasa; Salofalk; Xalazin; ***India***: Asacol; Cosacol; Elmes; Etiasa; Mesacol; ***Indon.***: Midodrine; Salofalk; ***Irl.***: Asacolon; Mezavant; Pentasa; Salofalk; ***Israel***: Asacol; Pentasa; Rafassal; ***Ital.***: Asacol; Asalex; Asamax; Asavixin; Claversal; Enteraproct; Enterasin; Lextrasa; Mesaflor; Pentacol; Pentasa; Plimage; Proctasacol; ***Jpn***: Pentasa; ***Malaysia***: Pentasa; Salofalk; ***Mex.***: Asacol; Pentasa; Salofalk; Seramine; ***Neth.***: Asacol; Asamax†; Mesavancol; Mezavant; Pentasa; Salofalk; ***Norw.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***NZ***: Asacol; Asamax; Pentasa; ***Philipp.***: Pentasa; Salofalk; ***Pol.***: Asamax; Colitan; Crohnax; Jucolon; Pentasa; Salofalk; ***Port.***: Asacol; Claversal; Pentasa; Salofalk; ***Rus.***: Asacol (Асакол); Mesacol (Месакол); Pentasa (Пентаса); Salofalk (Салофальк); Samezil (Самезил); ***S.Afr.***: Asacol; Mesasal†; Pentasa; ***Singapore***: Asacol; Pentasa; Salofalk; ***Spain***: Claversal; Lixacol; Mezavant; Pentasa; Salofalk; ***Swed.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***Switz.***: Asacol; Asazine; Mesazine†; Pentasa; Salofalk; ***Thai.***: Mesacol; Pentasa; Salofalk; ***Turk.***: Asacol; Asocol; Pentasa; Salofalk; ***UK***: Asacol; Ipocol; Mesren†; Mezavant; Octasa; Pentasa; Salofalk; ***Ukr.***: Pentasa (Пентаса); Salofalk (Салофальк); ***USA***: Apriso; Asacol; Canasa; Delzicol; Lialda; Pentasa; Rowasa.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Mesalazine Tablets; Mesalazine Enema; Mesalazine Foam Enema; Mesalazine Suppositories; Prolonged-release Mesalazine Granules; Prolonged-release Mesalazine Tablets;

USP 36: Mesalamine Delayed-Release Tablets; Mesalamine Extended-Release Capsules; Mesalamine Rectal Suspension.

Methanthelinium Bromide *(BAN, pINN)*

Bromuro de metantelinio; Dixamonum Bromidum; Metantelinio, bromuro de; Methantheline Bromide; Methanthelinii Bromidum; Méthanthélinium, Bromure de; MTB-51; SC-2910; Метантеллиния Бромид.

Diethylmethyl[2-(xanthen-9-ylcarbonyloxy)ethyl]ammonium bromide.

$C_{21}H_{26}BrNO_3$=420.3

CAS — 5818-17-7 (methanthelinium); 53-46-3 (methanthelinium bromide).

ATC — A03AB07.

ATC Vet — QA03AB07.

UNII — 090519SAPF.

Profile

Methanthelinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease, in gastrointestinal disorders associated with smooth muscle spasm, and in the management of urinary incontinence. A usual oral dose in gastrointestinal disorders is 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Vagantin.

Methylbenactyzium Bromide *(rINN)*

Benactyzine Methobromide; Bromuro de metilbenacticio; Methylbenactyzii Bromidum; Méthylbénactyzium, Bromure de; Metilbenacticio, bromuro de; Метилбенактизия Бромид.

Diethyl(2-hydroxyethyl)methylammonium bromide benzilate.

$C_{21}H_{28}BrNO_3$=422.4

CAS — 3166-62-9.

UNII — M35Q3X4F69.

Pharmacopoeias. In *Jpn*.

Profile

Methylbenactyzium bromide, a derivative of benactyzine (p. 408.2), is an antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been given orally for the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Yi Er Ning (益尔宁).

Multi-ingredient Preparations. ***Austria***: Anxiolit plus.

Methylnaltrexone Bromide *(BAN, USAN, rINN)*

Bromure de Méthylnaltrexone; Bromuro de metilnaltrexona; Methylnaltrexonii Bromidum; MRZ-2663BR; Naltrexone Methobromide; Метилнальтрексон Бромид.

(17*RS*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide.

$C_{21}H_{26}BrNO_4$=436.3

CAS — 83387-25-1 (methylnaltrexone); 73232-52-7 (methylnaltrexone bromide).

ATC — A06AH01.

ATC Vet — QA06AH01.

UNII — RFO6IL3D3M.

Uses and Administration

Methylnaltrexone bromide is a selective peripherally acting antagonist of opioid μ-receptors that is used for the treatment of opioid-induced constipation in patients receiving palliative care for advanced illness, when response

to usual laxative therapy is insufficient. It is also being studied for treatment of opioid-induced constipation in patients with chronic pain, as well as for opioid-induced urinary retention and postoperative ileus.

For the treatment of opioid-induced constipation methylnaltrexone bromide may be given by subcutaneous injection in the following doses according to body-weight:

- less than 38 kg: 150 micrograms/kg
- 38 to 62 kg: 8 mg
- 62 to 114 kg: 12 mg
- more than 114 kg: 150 micrograms/kg

Doses are usually given once every 48 hours as needed, but no more frequently than once in 24 hours. For doses in renal impairment, see Administration in Renal Impairment, below.

An oral formulation is under investigation.

References.
1. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. *Ann Pharmacother* 2007; **41:** 984–93.
2. Reichle FM, Conzen PF. Methylnaltrexone, a new peripheral μ-receptor antagonist for the prevention and treatment of opioid-induced extracerebral side effects. *Curr Opin Investig Drugs* 2008; **9:** 90–100.
3. Thomas J, *et al*. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008; **358:** 2332–43.
4. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet* 2009; **373:** 1198–1206.
5. Clemens KE, Klaschik E. Managing opioid-induced constipation in advanced illness: focus on methylnaltrexone bromide. *Ther Clin Risk Manag* 2010; **6:** 77–82.
6. Garnock-Jones KP, McKeage K. Methylnaltrexone. *Drugs* 2010; **70:** 919–28.

Administration in renal impairment. Renal impairment reduces the clearance of methylnaltrexone and increases exposure, and although the usual dose (see Uses and Administration, p. 1861.3) may be given to those with mild or moderate impairment (creatinine clearance 30 mL/minute and above), dose reductions are advised in those with severe impairment (creatinine clearance less than 30 mL/minute). UK licensed product information recommends the following subcutaneous doses, usually given once every 48 hours as needed (but no more often than once in 24 hours), according to weight:

- 62 to 114 kg: 8 mg
- less than 62 kg or above 114 kg: 75 micrograms/kg

Methylnaltrexone is not recommended in those with end-stage renal impairment requiring dialysis due to a lack of data.

Similarly, US licensed product information recommends halving the usual dose in severe renal impairment.

Adverse Effects and Precautions

The most common adverse effects in patients treated with methylnaltrexone bromide are gastrointestinal disorders such as abdominal pain, nausea, flatulence, and diarrhoea. If severe or persistent diarrhoea occurs, therapy should be stopped. Dizziness, hyperhidrosis, and injection site reactions are also reported commonly with methylnaltrexone.

Gastrointestinal perforation has been reported rarely and methylnaltrexone should not be used in patients with gastrointestinal obstruction or acute surgical abdomen. Caution is advised in patients with lesions that affect the structural integrity of the gastrointestinal tract such as cancer or peptic ulcer. Caution is also recommended in those with a peritoneal catheter, colostomy, active diverticular disease, or faecal impaction as methylnaltrexone use has not been studied in these patients.

Methylnaltrexone is not recommended in patients with severe hepatic impairment or with end-stage renal disease requiring dialysis, due to a lack of data.

Pharmacokinetics

After subcutaneous injection methylnaltrexone bromide is absorbed rapidly, with peak plasma concentrations occurring at about 0.5 hours. It is only minimally bound to plasma proteins. Methylnaltrexone is eliminated mostly as unchanged drug; metabolites include methylnaltrexone sulfate and methyl-6-naltrexol isomers. Methyl-6-naltrexol isomers have less antagonist activity than methylnaltrexone bromide; methylnaltrexone sulfate is inactive. N-demethylation of methylnaltrexone to naltrexone is not significant. About half of the dose is excreted in the urine and less in the faeces. The terminal half-life is about 8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Relistor; ***Austral.***: Relistor; ***Austria***: Relistor; ***Belg.***: Relistor; ***Braz.***: Relistor; ***Canad.***: Relistor; ***Chile***: Relistor; ***Cz.***: Relistor; ***Denm.***: Relistor; ***Fr.***: Relistor; ***Ger.***: Relistor; ***Gr.***: Relistor; ***Hung.***: Relistor; ***Irl.***: Relistor; ***Ital.***: Relistor; ***Neth.***: Relistor; ***Norw.***: Relistor; ***Pol.***: Relistor; ***Port.***: Relistor; ***Spain***: Relistor; ***Swed.***: Relistor; ***Switz.***: Relistor; ***UK***: Relistor; ***USA***: Relistor.

Metoclopramide *(BAN, rINN)*

Metoclopramid; Metoclopramida; Métoclopramide; Metoclopramidum; Metoklopramid; Metoklopramidas; Metoklopramidi; Метоклопрамид.

4-Amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide.

$C_{14}H_{22}ClN_3O_2$=299.8

CAS — 364-62-5.

ATC — A03FA01.

ATC Vet — QA03FA01.

UNII — L4YEB44I46.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Metoclopramide). A white or almost white, fine powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble to slightly soluble in alcohol; slightly soluble in dichloromethane.

Metoclopramide Hydrochloride

(BANM, USAN, rINNM)

AHR-3070-C; DEL-1267; Hidrocloruro de metoclopramida; Metoclopramida, hidrocloruro de; Métoclopramide, chlorhydrate de; Metoclopramidhydrochlorid; Metoclopramidi Hydrochloridum; Metoclopramidi Hydrochloridum Monohydricum; Metoklopramid Hidroklorür; Metoklopramidhidroklorid; Metoklopramid-hydrochlorid monohydrát; Metoklopramidhydroklorid; Metoklopramidihydrokloridi; Metoklopramido hidrochloridas; Metoklopramidu chlorowodorek; MK-745; Метоклопрамида Гидрохлорид.

$C_{14}H_{22}ClN_3O_2$,HCl,H_2O=354.3

CAS — 7232-21-5 (anhydrous metoclopramide hydrochloride); 54143-57-6 (metoclopramide hydrochloride monohydrate); 2576-84-3 (anhydrous metoclopramide dihydrochloride).

ATC — A03FA01.

ATC Vet — QA03FA01.

UNII — 7B1QZY5SWZ (anhydrous metoclopramide hydrochloride); W1792A2RVD (metoclopramide hydrochloride monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Metoclopramide Hydrochloride). A white or almost white, crystalline powder or crystals. Very soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Metoclopramide Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder. Very soluble in water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether. Store in airtight containers. Protect from light.

Incompatibility. Proprietary preparations of metoclopramide hydrochloride are stated to be incompatible with cephalothin sodium, chloramphenicol sodium, and sodium bicarbonate.

Cisplatin, cyclophosphamide, doxorubicin hydrochloride, morphine hydrochloride, or diamorphine hydrochloride are stated to be compatible with metoclopramide hydrochloride but compatibility is dependent upon factors such as the particular formulation, drug concentration, and temperature.

Uses and Administration

Metoclopramide hydrochloride is a substituted benzamide used for its prokinetic and antiemetic properties. It stimulates the motility of the upper gastrointestinal tract without affecting gastric, biliary, or pancreatic secretion and increases gastric peristalsis, leading to accelerated gastric emptying and intestinal transit time. The resting tone of the gastro-oesophageal sphincter is increased and the pyloric sphincter is relaxed. Metoclopramide possesses parasympathomimetic activity as well as being a dopamine-receptor antagonist with a direct effect on the chemoreceptor trigger zone. It may have serotonin-receptor ($5\text{-}HT_3$) antagonist properties.

Metoclopramide is used in disorders of decreased gastrointestinal motility (p. 1805.2) such as gastroparesis or ileus; in gastro-oesophageal reflux disease (p. 1807.2) and dyspepsia (p. 1806.3); and in nausea and vomiting (p. 1811.3) associated with various gastrointestinal disorders, with migraine, after surgery, and with cancer therapy. It may be used to stimulate gastric emptying during radiographic examinations, to facilitate intubation of the small bowel, and in the management of aspiration syndromes (p. 1804.2).

In order to reduce the risks of neurological and other adverse effects, the EMA has restricted metoclopramide use to a maximum of 5 days and does not recommend its use for chronic conditions such as gastroparesis, dyspepsia, and gastro-oesophageal reflux disease, or as an adjunct in surgical or radiological procedures. The FDA also advises against chronic use unless the benefit of treatment outweighs the risk. The use of metoclopramide is restricted in children and young adults under 20 years of age (see Administration in Children, below).

It is usually given as the hydrochloride monohydrate with doses expressed as the anhydrous hydrochloride. In the USA, the strength of preparations of the hydrochloride monohydrate is usually expressed in terms of the base. Metoclopramide hydrochloride 10.5 mg is equivalent to about 10.0 mg of the anhydrous substance, which is equivalent to about 8.9 mg of the anhydrous base.

For most purposes the total daily dose should not exceed 500 micrograms/kg; dosage reduction is recommended in renal and perhaps hepatic impairment (see Administration in Hepatic or Renal Impairment, below).

- In the UK, the recommended dose, given orally, intramuscularly, or by slow intravenous injection (over at least 3 minutes), is 10 mg (expressed as anhydrous metoclopramide hydrochloride) three times daily.
- In the USA, the usual oral dose is 10 to 15 mg (expressed as the base) up to four times daily.
- Single doses of 10 to 20 mg (expressed as anhydrous base or anhydrous hydrochloride) may be given orally, intravenously, or intramuscularly when required, such as before a diagnostic procedure.

An intranasal formulation of metoclopramide is available in some countries.

The base, and salts including the dihydrochloride and the glycyrrhizate have also been used.

High-dose therapy. High doses of metoclopramide have been used, often with other drugs such as dexamethasone, in the treatment of the nausea and vomiting associated with cancer chemotherapy. In the UK, the loading dose of metoclopramide before cancer therapy is 2 to 4 mg/kg given as a continuous intravenous infusion over 15 to 20 minutes; it is followed by a maintenance dose of 3 to 5 mg/kg, again as a continuous intravenous infusion, given over 8 to 12 hours. Alternatively, initial doses of up to 2 mg/kg by intravenous infusion over at least 15 minutes may be given before cancer therapy and repeated every 2 hours. The total dosage by either continuous or intermittent infusion should not normally exceed 10 mg/kg in 24 hours. In the USA, dosing is started about 30 minutes before cancer chemotherapy; an initial dose of 2 mg/kg for highly emetogenic chemotherapy, or 1 mg/kg for less emetogenic chemotherapy, is given by intravenous infusion over at least 15 minutes. This dose is repeated every 2 hours for 2 doses, then every 3 hours for 3 doses.

Administration. *INTRANASAL.* References.

1. Ormrod D, Goa KL. Intranasal metoclopramide. *Drugs* 1999; **58:** 315–22. Commentaries. *ibid.*; 323–4.

Administration in children. In the EU the use of metoclopramide in children and young adults is restricted to a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and treatment of established postoperative nausea and vomiting. It may be used for up to 5 days in children aged 1 year and over. Usual oral and parenteral (intramuscular or intravenous) doses for all indications in the UK are:

- for those aged 15 to 19 years and weighing 60 kg and over: 10 mg three times daily
- 15 to 19 years (30 to 59 kg): 5 mg three times daily
- 9 to 14 years (30 kg and over): 5 mg three times daily
- 5 to 9 years (20 to 29 kg): 2.5 mg three times daily
- 3 to 5 years (15 to 19 kg): 2 mg two or three times daily
- 1 to 3 years (10 to 14 kg): 1 mg two or three times daily

An alternative dose for postoperative nausea and vomiting in those aged 1 to 20 years is 150 micrograms/kg given by slow intravenous injection. Further doses can be given 6 hours apart to a maximum of 500 micrograms/kg in 24 hours.

Where body-weight is below that specified for a given age group, the dose should reflect the weight rather than the age, so that a lower dose is chosen.

In the USA metoclopramide is licensed for use in children only to facilitate small bowel intubation in those resistant to conventional methods. A single intravenous dose, based on age, is recommended as follows:

- over 14 years: 10 mg
- 6 to 14 years: 2.5 to 5 mg
- under 6 years: 100 micrograms/kg

Administration in hepatic or renal impairment. Total clearance of metoclopramide is significantly reduced in patients with **renal impairment**[1-3] and the elimination half-life is prolonged to up to 19 hours.[2] This may be due to impaired metabolism[1,2] or to an alteration in enterohepatic circulation of metoclopramide.[1] Accumulation of metoclopramide could therefore occur in renal impairment with a possible increased risk of adverse effects. Dosage reductions of at least 50% have therefore been

recommended in patients with moderate to severe renal impairment.[1,2] US licensed product information recommends this dose reduction in those patients whose creatinine clearance is below 40 mL/minute; UK information advises dose reduction in significant renal impairment, but gives no guidance on appropriate doses.

Patients undergoing haemodialysis do not require dosage supplements since relatively little metoclopramide is cleared by this process.[2,3]

UK licensed product information also recommends that the dose of metoclopramide should be reduced in patients with clinically significant **hepatic impairment**, although again no recommendations on the size of the reduction are given; caution is advised in liver disease, due to loss of conjugation. The US product information notes that metoclopramide undergoes minimal hepatic metabolism and has been used safely in some patients with advanced liver disease (whose renal function was normal), and it makes no such recommendation for reduction of dose. Decreases in clearance and increases in half-life and area under the plasma concentration-time curve have been reported in patients with cirrhosis given metoclopramide.[4,5]

1. Bateman DN, *et al*. The pharmacokinetics of single doses of metoclopramide in renal failure. *Eur J Clin Pharmacol* 1981; **19:** 437–41.
2. Lehmann CR, *et al*. Metoclopramide kinetics in patients with impaired renal function and clearance by haemodialysis. *Clin Pharmacol Ther* 1985; **37:** 284–9.
3. Wright MR, *et al*. Effect of haemodialysis on metoclopramide kinetics in patients with severe renal failure. *Br J Clin Pharmacol* 1988; **26:** 474–7.
4. Hellstern A, *et al*. Absolute bioavailability of metoclopramide given orally or by enema in patients with normal liver function or with cirrhosis of the liver. *Arzneimittelforschung* 1987; **37:** 733–6.
5. Magueur E, *et al*. Pharmacokinetics of metoclopramide in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; **31:** 185–7.

Blood disorders. Responses to treatment with metoclopramide have been reported in patients with Diamond-Blackfan anaemia, probably through induction of prolactin release, although the mechanism by which prolactin affects erythropoiesis is unclear.[1,2] In a pilot study, 3 out of 9 evaluable patients responded after 12 to 15 weeks of therapy; high serum ferritin, pituitary dysfunction, male sex, and younger age may have contributed to the poor response to metoclopramide in other patients.[1] In another case, response was seen by the fourth week of treatment; at the time of the report, the patient had remained asymptomatic and transfusion independent for 8 months.[2]

1. Abkowitz JL, *et al*. Response of Diamond-Blackfan anemia to metoclopramide: evidence for a role for prolactin in erythropoiesis. *Blood* 2002; **100:** 2687–91.
2. Akiyama M, *et al*. Successful treatment of Diamond-Blackfan anemia with metoclopramide. *Am J Hematol* 2005; **78:** 295–8.

Gastroenteritis. For mention of the use of antiemetics such as metoclopramide to reduce vomiting in acute gastroenteritis, see Ondansetron, p. 1873.1.

Hiccup. Metoclopramide has been used in the management of intractable hiccup. For a discussion of hiccup and its management see p. 1046.3.

Lactation induction. Metoclopramide has been used[1,2] in doses of 10 mg three times daily for its dopamine antagonist properties to stimulate lactation in women who wish to breast feed and in whom mechanical stimulation of the nipple alone is inadequate, including mothers of adopted babies or babies born to surrogates.[3,4] However, pharmacological lactation induction should be viewed as adjunctive to mechanical methods and the duration of therapy should probably be limited to 7 to 14 days.[1,2] In addition, the efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.[5] Young women are at increased risk of extrapyramidal effects from metoclopramide—see under Adverse Effects, p. 1864.1. There has also been concern about the presence of the drug in breast milk. For a discussion of lactation inhibition and induction, see p. 2130.1.

1. Anderson PO, Valdés V. Increasing breast milk supply. *Clin Pharm* 1993; **12:** 479–80.
2. Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact* 2002; **18:** 274–9.
3. Cheales-Siebenaler NJ. Induced lactation in an adoptive mother. *J Hum Lact* 1999; **15:** 41–3.
4. Biervliet FP, *et al*. Induction of lactation in the intended mother of a surrogate pregnancy: case report. *Hum Reprod* 2001; **16:** 581–3.
5. Hansen WF, *et al*. Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol* 2005; **105:** 383–9.

Migraine. Metoclopramide is used in the treatment of migraine (p. 670.3) to alleviate nausea and vomiting and gastric stasis, which commonly develop as a migraine attack progresses and can lead to poor absorption of oral antimigraine preparations. It may also be given to counteract nausea and vomiting from the use of ergotamine. Metoclopramide is included in some combination analgesic preparations for the treatment of acute attacks of migraine. In one study, oral lysine aspirin with metoclopramide was as effective as oral sumatriptan in the treatment of migraine.[1] However, a review of combinations of oral metoclopramide plus an analgesic for migraine suggested that they were likely to be less effective than triptan monotherapy, although they might be an option for patients in whom triptans are contra-indicated or who could not tolerate triptans.[2] Metoclopramide with sumatriptan may be effective in patients unresponsive to a triptan alone.[3]

Parenteral metoclopramide has also been shown to be an effective treatment for acute migraine; it reduces pain, and to some extent nausea (although other antiemetics may be more effective), and a systematic review concluded that it should be considered a first-line treatment for migraine in the emergency department.[4] A later study found intravenous metoclopramide (with intermittent doses of diphenhydramine) to be comparable to subcutaneous sumatriptan in terms of pain relief at both 2 and 24 hours after treatment.[5]

1. Tfelt-Hansen P, *et al*. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346:** 923–6.
2. Azzopardi TD, Brooks NA. Oral metoclopramide as an adjunct to analgesics for the outpatient treatment of acute migraine. *Ann Pharmacother* 2008; **42:** 397–402.
3. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; **43:** 729–33.
4. Colman I, *et al*. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004; **329:** 1369–72.
5. Friedman BW, *et al*. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology* 2005; **64:** 463–8.

Orthostatic hypotension. Metoclopramide has been tried in the management of some patients with orthostatic hypotension, as mentioned on p. 1634.3.

Tourette's syndrome. A small, short-term study in children and adolescents with Tourette's syndrome (see Tics, p. 1030.1) or chronic tic disorders found that treatment with oral metoclopramide (up to 40 mg daily) significantly reduced tic score and severity compared with placebo.[1]

1. Nicolson R, *et al*. A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2005; **44:** 640–6.

Variceal haemorrhage. Metoclopramide 20 mg intravenously controlled bleeding from oesophageal varices within 15 minutes in 10 of 11 patients compared with 4 of 11 patients given placebo; all patients were treated by sclerotherapy.[1] Lower oesophageal sphincter pressure is increased by metoclopramide, thus reducing blood flow to varices and achieving haemostasis; another study[2] found use of metoclopramide with intravenous glyceryl trinitrate to be more effective than glyceryl trinitrate alone in reducing intravariceal pressure.

For a discussion of variceal haemorrhage and its management, see p. 2563.1.

1. Hosking SW, *et al*. Pharmacological constriction of the lower oesophageal sphincter: a simple method of arresting variceal haemorrhage. *Gut* 1988; **29:** 1098–1102.
2. Sarin SK, Saraya A. Effects of intravenous nitroglycerin and nitroglycerin and metoclopramide on intravariceal pressure: a double blind, randomized study. *Am J Gastroenterol* 1995; **90:** 48–53.

Adverse Effects

Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms (usually acute dystonic reactions); these are more common in children and young adults, and at daily doses above 500 micrograms/kg. Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients.

Other adverse effects affecting the CNS include restlessness, drowsiness, dizziness, anxiety, confusion, and tremor; hallucinations have been reported rarely. Depression has occurred and can be severe, with suicidal ideation and suicide reported. Hypotension, hypertension, gastrointestinal disturbances, dyspnoea, visual disturbances, urinary frequency and incontinence, and headache may also occur and there are isolated reports of blood disorders, hypersensitivity reactions (rash, bronchospasm, angioedema), and neuroleptic malignant syndrome. Disorders of cardiac conduction have been reported with intravenous metoclopramide and transient flushing of the face and upper body has followed high intravenous doses.

Metoclopramide stimulates prolactin secretion and may cause galactorrhoea or related disorders. Transient increases in plasma-aldosterone concentrations have been reported.

Effects on the blood. Agranulocytosis was associated with use of metoclopramide on 2 separate occasions.[1] Both episodes resolved within 2 to 3 weeks of withdrawing metoclopramide. Methaemoglobinaemia[2-4] and sulfhaemoglobinaemia[5,6] have also been reported. Methaemoglobinaemia (p. 1559.3) may be treated with methylthioninium chloride. In one case,[3] the patient died despite such treatment; blood samples taken before death were found to be haemolysed, and assays showed deficiency in G6PD activity (methylthioninium chloride should not be used in G6PD-deficient patients, see Adverse Effects of Methylthioninium Chloride, p. 1560.2).

1. Harvey RL, Luzar MJ. Metoclopramide-induced agranulocytosis. *Ann Intern Med* 1988; **108:** 214–15.
2. Grant SCD, *et al*. Methaemoglobinaemia produced by metoclopramide in an adult. *Eur J Clin Pharmacol* 1994; **47:** 89.
3. Karadsheh NS, *et al*. Metoclopramide-induced methemoglobinemia in a patient with co-existing deficiency of glucose-6-phosphate dehydrogenase and NADH-cytochrome b5 reductase: failure of methylene blue treatment. *Haematologica* 2001; **86:** 659–60.
4. Mérieau E, *et al*. Méthoclopramide et méthémoglobinémie néonatale. *Arch Pediatr* 2005; **12:** 438–41.
5. Van Veldhuizen PJ, Wyatt A. Metoclopramide-induced sulfhemoglobinemia. *Am J Gastroenterol* 1995; **90:** 1010–11.
6. Aravindhan N, Chisholm DG. Sulfhemoglobinemia presenting as pulse oximetry desaturation. *Anesthesiology* 2000; **93:** 883–4.

Effects on the cardiovascular system. There have been reports of hypotension,[1] hypertension,[2,3] and supraventricular tachycardia[4] associated with metoclopramide. Bradycardia followed by total heart block,[5] and sinus arrest,[6] have also been reported. It was suggested that metoclopramide may have contributed to a prolonged QT interval and torsade de pointes in a patient with heart failure and renal impairment.[7]

1. Park GR. Hypotension following metoclopramide administration during hypotensive anaesthesia for intracranial aneurysm. *Br J Anaesth* 1978; **50:** 1268–9.
2. Sheridan C, *et al*. Transient hypertension after high doses of metoclopramide. *N Engl J Med* 1982; **307:** 1346.
3. Filibeck DJ, *et al*. Metoclopramide-induced hypertensive crisis. *Clin Pharm* 1984; **3:** 548–9.
4. Bevacqua BK. Supraventricular tachycardia associated with postpartum metoclopramide administration. *Anesthesiology* 1988; **68:** 124–5.
5. Midttun M, Øberg B. Total heart block after intravenous metoclopramide. *Lancet* 1994; **343:** 182–3.
6. Malkoff MD, *et al*. Sinus arrest after administration of intravenous metoclopramide. *Ann Pharmacother* 1995; **29:** 381–3.
7. Siddique SM, *et al*. Metoclopramide as a possible cause of prolonged QT syndrome and torsade de pointes in a patient with heart failure and renal insufficiency. *Ann Intern Med* 2009; **150:** 502–4.

Effects on the endocrine system. *ALDOSTERONISM.* Metoclopramide has been reported to increase plasma-aldosterone concentrations in healthy individuals[1] and in patients with liver cirrhosis and ascites associated with secondary hyperaldosteronism.[2] Increased plasma aldosterone after metoclopramide use has also been associated with the development of oedema in a patient with congestive heart failure.[3] The metoclopramide-induced aldosterone response was blunted by giving neostigmine beforehand.[1]

1. Sommers DK, *et al*. Effect of neostigmine on metoclopramide-induced aldosterone secretion in man. *Eur J Clin Pharmacol* 1989; **36:** 411–13.
2. Mazzacca G, *et al*. Metoclopramide and secondary hyperaldosteronism. *Ann Intern Med* 1983; **98:** 1024–5.
3. Zumoff B. Metoclopramide and edema. *Ann Intern Med* 1983; **98:** 557.

HYPERPROLACTINAEMIA. Hyperprolactinaemia, galactorrhoea, and pituitary adenoma occurred in a 49-year-old woman with reflux oesophagitis who had received metoclopramide for 3 months.[1] Her plasma-prolactin concentrations fell to normal and her symptoms resolved over 4 months after withdrawal of metoclopramide. The pituitary tumour was considered to be incidental to, and not caused by, metoclopramide therapy. A 21-year-old female developed mastodynia, galactorrhoea, and hyperprolactinaemia after 2 days of treatment with metoclopramide;[2] she had previously taken domperidone intermittently without any problems. Her symptoms resolved rapidly on stopping therapy. Galactorrhoea has also been reported[3] in a neonate given metoclopramide.

1. Cooper BT, *et al*. Galactorrhoea, hyperprolactinaemia, and pituitary adenoma presenting during metoclopramide therapy. *Postgrad Med J* 1982; **58:** 314–15.
2. Bozzolo M, *et al*. Medikamentös induzierte Hyperprolaktinämie und Galaktorrhöe. *Schweiz Rundsch Med Prax* 1992; **81:** 1511–13.
3. Paturi B, *et al*. Galactorrhea with metoclopramide use in the neonatal unit. *J Perinatol* 2009; **29:** 391–2.

Effects on mental state. There are isolated reports of dose-related delirium, depression, and uncontrollable crying in patients treated with metoclopramide in doses of 40 to 80 mg daily.[1-3] Symptoms resolved on reducing the dose or withdrawing metoclopramide, and tolerance could be achieved by gradually increasing the dose. In another report,[4] a patient developed acute akathisia (see Extrapyramidal Effects p. 1864.1) shortly after starting metoclopramide 10 mg four times daily; this was accompanied by restlessness, anxiety, and irritability. Despite stopping the drug after 2 days, and treatment with paroxetine and lorazepam, the patient started to have panic attacks, which increased in frequency and severity; he also developed agoraphobia. Two months after taking metoclopramide he was diagnosed with major depressive disorder, which included intermittent suicidal ideation. Following aggressive therapy and hospitalisation, his symptoms gradually resolved.

Encephalopathy has been associated with intravenous metoclopramide in a patient with Parkinson's disease.[5]

Insomnia, with or without daytime drowsiness, has also been reported in patients taking metoclopramide 40 mg daily.[6]

Hypersensitivity psychosis has also been reported, shortly after stopping metoclopramide.[7] Symptoms included hallucinations, delusional experiences, anxiety, restlessness, and sleep disturbances; improvement and gradual resolution were noted after treatment with risperidone.

1. Bottner RK, Tullio CJ. Metoclopramide and depression. *Ann Intern Med* 1985; **103:** 482.
2. Adams CD. Metoclopramide and depression. *Ann Intern Med* 1985; **103:** 960.
3. Fishbain DA, Rogers A. Delirium secondary to metoclopramide hydrochloride. *J Clin Psychopharmacol* 1987; **7:** 281–2.
4. Anfinson TJ. Akathisia, panic, agoraphobia, and major depression following brief exposure to metoclopramide. *Psychopharmacol Bull* 2002; **36:** 82–93.
5. Messerschmidt KA, *et al*. Encephalopathy associated with metoclopramide use in a patient with Parkinson's disease. *Am J Health-Syst Pharm* 2012; **69:** 1303–6.
6. Saxe TG. Metoclopramide side effects. *Ann Intern Med* 1983; **98:** 674.
7. Lu M-L, *et al*. Metoclopramide-induced supersensitivity psychosis. *Ann Pharmacother* 2002; **36:** 1387–90.

Extrapyramidal effects. The Adverse Reactions Register of the UK CSM for the years 1967 to 1982 contained 479 reports of extrapyramidal reactions in which metoclopramide was the suspected drug: 455 were for dystonic-dyskinetic reactions, 20 for parkinsonism, and 4 for tardive dyskinesia.[1]

Acute **dystonic-dyskinetic** reactions occur most commonly in children and young adults[1-3] and about 70% of reactions are in females;[1,3] many are associated with doses above those recommended by the manufacturers.[1,3,4] Symptoms reported include oculogyric crisis,[4,5] opisthotonus,[6] torticollis,[5,7] trismus,[5,7] a tetanus-like reaction,[8] and blue coloration of the tongue;[6] akathisia after the use of metoclopramide alone,[9] or with droperidol[10] or haloperidol[9] has been reported (see also Effects on Mental State, p. 1863.3).

These effects usually occur within 72 hours of starting treatment[1] but have been reported within 30 minutes of receiving metoclopramide.[4] When metoclopramide is given intravenously, the rate may be important in determining the incidence of acute extrapyramidal reactions: a study indicated that akathisia was less frequent when the same dose was given as a 15-minute infusion rather than a 2-minute bolus injection.[11] Acute effects can occur in patients who have previously taken metoclopramide without complications[5,8,10] and may be precipitated by other drugs. Although generally self-limiting, deaths have occurred.[1,5] The reactions are readily reversed by an antihistamine such as diphenhydramine,[7] or an antimuscarinic such as benzatropine;[4,6] prophylactic use of diphenhydramine has been suggested for patients with a history of extrapyramidal reactions and in those less than 30 years of age.[7,8]

Metoclopramide-associated **parkinsonism** is thought to occur less commonly than the acute dystonias and is seen mainly in older patients. Symptoms usually appear several months after starting metoclopramide, but may occur within days or not for several years. Withdrawal of metoclopramide usually results in resolution of symptoms, although it may take several months.[1] A study has suggested that metoclopramide-induced parkinsonism (misdiagnosed as idiopathic Parkinson's disease) may be more common in the elderly than generally realised.[12]

Tardive dyskinesia may rarely be associated with use of metoclopramide. Development of this condition is directly related to the length of treatment with metoclopramide and the number of doses taken.[13] The reaction is usually confined to elderly patients after prolonged oral use,[14,15] but it has been reported with short-term high-dose parenteral use as an antiemetic in cancer chemotherapy,[16] and a case has been reported in an 8-year-old child treated with metoclopramide for gastro-oesophageal reflux disease in usual doses.[17] The average duration of treatment before the onset of symptoms was 14 months (range 4 to 44 months) in a report of 11 cases[15] and 26 months (range 8 to 60 months) in a report of 12 cases;[18] some patients did not have symptoms until after withdrawal of metoclopramide. Tardive dyskinesia is potentially irreversible and its management is difficult.[18] Some patients improve after withdrawal of metoclopramide but symptoms persisting during follow-up periods of up to 3 years have been reported.[14,15] The emphasis must be on prevention, hence the recommendation that metoclopramide should not be prescribed for the long-term treatment of minor symptoms, especially in elderly patients.[18] After analyses suggested that metoclopramide was the most common cause of drug-induced movement disorders and that about 20% of patients who used metoclopramide used it for longer than 3 months, the FDA recommended that chronic use of metoclopramide should be avoided in all patients unless the benefit of treatment is believed to outweigh the risk.[13] The EMA[19] has also restricted metoclopramide use to a maximum of five days and does not recommend its use for chronic conditions or as an adjunct in surgical or radiological procedures; its use in children is also restricted (see Administration in Children, p. 1862.3).

1. Bateman DN, *et al*. Extrapyramidal reactions with metoclopramide. *BMJ* 1985; **291:** 930–2.
2. Anonymous. Measuring therapeutic risk. *Lancet* 1989; **ii:** 139–40.
3. Adverse Drug Reactions Advisory Committee. Metoclopramide—choose the dose carefully. *Aust Adverse Drug React Bull* 1990; Feb.
4. Tait P, *et al*. Metoclopramide side effects in children. *Med J Aust* 1990; **152:** 387.
5. Pollera CF, *et al*. Sudden death after acute dystonic reaction to high-dose metoclopramide. *Lancet* 1984; **ii:** 460–1.
6. Alroe C, Bowen P. Metoclopramide and prochlorperazine: "the blue-tongue sign". *Med J Aust* 1989; **150:** 724–5.
7. Kris MG, *et al*. Extrapyramidal reactions with high-dose metoclopramide. *N Engl J Med* 1983; **309:** 433–4.
8. Della Valle R, *et al*. Metoclopramide-induced tetanus-like dystonic reaction. *Clin Pharm* 1985; **4:** 102–3.
9. Akagi H, Kumar TM. Akathisia: overlooked at a cost. *BMJ* 2002; **324:** 1506–7.
10. Barnes TRE, *et al*. Acute akathisia after oral droperidol and metoclopramide preoperative medication. *Lancet* 1982; **ii:** 48–9.
11. Regan LA, *et al*. Slower infusion of metoclopramide decreases the rate of akathisia. *Am J Emerg Med* 2009; **27:** 475–80.
12. Avorn J, *et al*. Increased incidence of levodopa therapy following metoclopramide use. *JAMA* 1995; **274:** 1780–2.
13. FDA. FDA requires boxed warning and risk mitigation strategy for metoclopramide-containing drugs (issued 26th February, 2009). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149533.htm (accessed 15/07/10)
14. Grimes JD, *et al*. Long-term follow-up of tardive dyskinesia due to metoclopramide. *Lancet* 1982; **ii:** 563.
15. Wiholm B-E, *et al*. Tardive dyskinesia associated with metoclopramide. *BMJ* 1984; **288:** 545–7.
16. Breitbart W. Tardive dyskinesia associated with high-dose intravenous metoclopramide. *N Engl J Med* 1986; **315:** 518.
17. Putnam PE, *et al*. Tardive dyskinesia associated with use of metoclopramide in a child. *J Pediatr* 1992; **121:** 983–5.
18. Orme ML'E, Tallis RC. Metoclopramide and tardive dyskinesia in the elderly. *BMJ* 1984; **289:** 397–8.
19. EMA. European Medicines Agency recommends changes to the use of metoclopramide: changes aim mainly to reduce the risk of neurological side effects (issued 26 July, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Metoclopramide_31/WC500146610.pdf (accessed 02/10/13)

Hypersensitivity. A patient given intravenous metoclopramide and butylhyoscine for gastrointestinal disturbances developed pruritus, generalised urticaria, hypotension, and loss of consciousness. She was treated with intravenous fluid, antihistamines, and corticosteroids. Skin prick tests revealed a response to metoclopramide, suggesting an IgE-mediated allergic reaction.[1]

1. Kerstan A, *et al*. Anaphylaxis during treatment of nausea and vomiting: IgE-mediated metoclopramide allergy. *Ann Pharmacother* 2006; **40:** 1889–90.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS, p. 1050.2) has occurred very rarely with metoclopramide. In a report of a case with a fatal outcome, it was noted that 17 additional cases had been published in the years 1978 to 1998, three of which resulted in death.[1] A case report in a 6-month-old female with Freeman-Sheldon syndrome[2] given metoclopramide suggested that pre-existing fever and myopathy may be predisposing factors. In another case,[3] a burns patient, there was some suggestion that the patient may have been susceptible to neuroleptic hyperthermic syndromes such as NMS and malignant hyperthermia. Metoclopramide should be stopped immediately if NMS occurs, and the patient treated urgently with bromocriptine.

1. Nonino F, Campomori A. Neuroleptic malignant syndrome associated with metoclopramide. *Ann Pharmacother* 1999; **33:** 644–5.
2. Stein MH, *et al*. Neuroleptic malignant syndrome induced by metoclopramide in an infant with Freeman-Sheldon syndrome. *Anesth Analg* 2006; **103:** 786–7.
3. Nachreiner R, *et al*. Neuroleptic malignant syndrome associated with metoclopramide in a burn patient. *J Burn Care Res* 2006; **27:** 237–41.

Precautions

Metoclopramide should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions, as in gastrointestinal haemorrhage, obstruction, perforation, or for a few days after surgery. There have been reports of hypertensive crises in patients with phaeochromocytoma given metoclopramide, thus its use is not recommended in such patients; caution is advised in patients with hypertension. Metoclopramide is also not recommended for use in patients with epilepsy as the frequency and severity of seizures may be increased.

Children, young adults, and the elderly should be treated with care as they are at increased risk of extrapyramidal reactions; the use of metoclopramide is restricted in children and young adults under 20 years (see Administration in Children, p. 1862.3). Prolonged therapy should generally be avoided (see Extrapyramidal Effects, above). Care should also be taken when metoclopramide is given to patients with renal or hepatic impairment, Parkinson's disease, or a history of depression, atopy (including asthma), or porphyria. Intravenous metoclopramide should be given with caution to patients at increased risk of cardiovascular reactions, including those with cardiac conduction abnormalities such as sick sinus syndrome.

Metoclopramide may cause drowsiness or impaired reactions; patients so affected should not drive or operate machinery.

Breast feeding. Metoclopramide is excreted into breast milk. The American Academy of Pediatrics[1] considers that the use of metoclopramide by mothers during breast feeding may be of concern, owing to its dopamine-receptor blocking activity. UK licensed product information states that problems in humans have not been reported.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)

Porphyria. Metoclopramide has been used successfully in the management of acute attacks of porphyria.[1] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metoclopramide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[2]

1. Elder GH, *et al*. Metoclopramide and acute porphyria. *Lancet* 1997; **350:** 1104.
2. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/11/11)

Pregnancy. Metoclopramide is often used to treat nausea and vomiting in pregnancy. A large retrospective cohort study confirmed that exposure to metoclopramide in the first trimester was not associated with adverse effects on the fetus including congenital malformations, perinatal death, and low birth-weight.[1]

1. Matok I, *et al*. The safety of metoclopramide use in the first trimester of pregnancy. *N Engl J Med* 2009; **360:** 2528–35.

Interactions

Increased toxicity may occur if metoclopramide is given with other centrally active drugs. Metoclopramide should be used with caution in patients taking other drugs that can also cause extrapyramidal reactions, such as the phenothiazines. It should also be used with care with other drugs acting at central dopamine receptors, such as pergolide. Combining metoclopramide with CNS depressant drugs can lead to increased sedative effects. Antimuscarinics and opioid analgesics antagonise the gastrointestinal effects of metoclopramide.

The absorption of other drugs may be affected by metoclopramide; it may either diminish absorption from the stomach (as with digoxin) or enhance absorption from the small intestine (for example, with alcohol, ciclosporin, levodopa, aspirin, or paracetamol). The absorption of food may be affected requiring adjustment of the insulin regimen in diabetic patients. Metoclopramide inhibits serum cholinesterase and may prolong neuromuscular blockade produced by suxamethonium (see p. 2040.1) and mivacurium (p. 2035.1). Metoclopramide may also increase prolactin blood concentrations and therefore interfere with drugs which have a hypoprolactinaemic effect such as bromocriptine (but see p. 899.1). The response to gonadorelin may be altered by metoclopramide, see p. 2282.2. Caution is required if metoclopramide must be given to patients receiving MAOIs and care is required when metoclopramide is given with drugs that affect cardiac conduction.

Antidepressants. For reference to extrapyramidal effects and other adverse effects suggestive of serotonin syndrome in patients taking metoclopramide with SSRIs or venlafaxine, see Gastrointestinal Drugs under Interactions for Fluoxetine (p. 424.3) and Venlafaxine (p. 457.1) respectively.

Carbamazepine. For a report of neurotoxicity associated with the use of metoclopramide with carbamazepine, see p. 517.3.

Hydroxyzine. Acute anxiety, rigidity, generalised tremor, opisthotonus, and hypertension developed in a 20-year-old man given metoclopramide 10 mg intravenously and hydroxyzine 100 mg intramuscularly.[1] The adverse effects occurred 30 minutes after giving hydroxyzine and it was suggested that hydroxyzine potentiated the onset of the reaction.

1. Fouilladieu JL, *et al*. Possible potentiation by hydroxyzine of metoclopramide's undesirable side effects. *Anesth Analg* 1985; **64:** 1227–8.

Pharmacokinetics

Metoclopramide is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses, although conditions such as vomiting or impaired gastric motility may reduce absorption. However, it undergoes hepatic first-pass metabolism, which varies considerably between subjects, and hence absolute bioavailability and plasma concentrations are subject to wide interindividual variation. On average, the bioavailability of oral metoclopramide is about 80%, but it varies between about 30 and 100%. Peak plasma concentrations of metoclopramide occur about 1 to 2 hours after an oral dose. Bioavailability is equally variable after rectal or intranasal doses, although it may be somewhat better if the drug is given intramuscularly.

Metoclopramide is weakly bound to plasma proteins (13 to 30%).

Metoclopramide is widely distributed in the body, and readily crosses the blood-brain barrier into the CNS. It also freely crosses the placenta, and has been reported to attain concentrations in fetal plasma about 60 to 70% of those in maternal plasma. Concentrations in breast milk may be higher than those in maternal plasma, particularly in the early puerperium, although concentrations decrease somewhat in the late puerperium.

Elimination of metoclopramide is biphasic, with a terminal elimination half-life of about 4 to 6 hours, although this may be prolonged in renal impairment, with consequent elevation of plasma concentrations. It is excreted in the urine, about 85% of a dose being eliminated in 72 hours, 20% as unchanged metoclopramide and the remainder as sulfate or glucuronide conjugates, or as metabolites. About 5% of a dose is excreted in faeces via the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Disgradon†; Fonderyl; Gastrocalm; Lizarona; Metoc; Midatenk; Novomit; Praux; Primavera-N; Primperil; Reliveran; Rilaquin; Rupemet; Saften; Sintegran; ***Austral.***: Maxolon; Pramin; ***Austria***: Gastrosil; Metogastron; Paspertin; ***Belg.***: Dibertil; Docmetoclo†; Primperan; ***Braz.***: Aristopramida; Emetic†; Eucil; Fluccil; Metoclosan; Metoclosantisa; Metoplamin†; Neolasil; No-Vomit†; Plabel; Plagex; Plamida†; Plamidasil; Plamivon; Plasil; Pramil; ***Canad.***: Apo-Metoclop; ***Chile***: Hemibe; Itan; ***Cz.***: Cerucal; Degan; MCP; ***Denm.***: Emperal; Gastro-Timelets; Primperan; ***Fin.***: Primperan; ***Fr.***: Anausin; Primperan; ***Ger.***: Cerucal; Gastronerton; MCP; Paspertin; ***Gr.***: Gaspalon; Geneprami-D; Lumania; Luv; Pharmyork; Primperan; ***Hong Kong***: Emeliv†; Maril; Martomide†; Maxolon†; Metolon†; Metomide†; Metram†; Pramin†; Primperan; Syntomide†; ***Hung.***: Cerucal; ***India***: Bacnorm; Donmet; Emenil; Emenorm; Labmet; Maxeron; Maxinorm; Metajex; Metarmin; Metoclop; Metocontin; Perinorm; Reglan; Tomid; Vominorm; ***Indon.***: Clopramel; Damaben; Emeran; Ethiferan; Gavistal; Lexapram; Meclam; Mepramide; Metolon†; Nilatika; Nofoklam; Normastin†; Obteran†; Opram; Piralen; Plasil; Praminal†; Primperan; Raclonid; Reguloop†; Sotatic; Tivomit; Tomit; Vertivom; Vilapon; Vomidex†; Vomipram; Vomitrol; Zumatrol†; ***Irl.***: Antimet†; Gastrobid Continus†; Maxolon; Metocyl†; ***Israel***: Pramin; ***Ital.***: Delipramil; Digestivo S Pellegrino; Isaprandil; Plasil; Pramidin; Randum; ***Jpn***: Primperan; ***Malaysia***: Malon; Maril; Maxolon†; Mexomide; Primperan; Pulin; ***Mex.***: Biopram; Carnotprim; Cirulan; Clorimet-Z; Conysmin; Dolmisin; Eudiges; Gigemet; Hopram; Meclomid; Midetol; Mipramid; Plasil; Polcotec; Pradex; Pramilem†; Primperan†; Propace; Raamfen; Synespramid; ***Mon.***: Prokinyl; ***Neth.***: Primperan; ***Norw.***: Afipran; ***NZ***: Maxolon; Metamide; ***Philipp.***: Biclomet; Clometide; Clomitene; Clozil; Metsil; Novom†; Plasil; Reglomar; Vitamet; Vomaine; ***Pol.***: Pramidin†; ***Port.***: Primperan; ***Rus.***: Apo-Metoclop (Апометоклоп)†; Cerucal (Церукал); Ceruglan (Церуглан); Cerulan (Церулан); Metamol (Метамол); Perinorm (Перинорм); ***S.Afr.***: Acumet†; Adco-Contromet; Betaclopramide; Clopamon; Maxolon; Metalon†; Perinorm†; Pramalon†; Setin; ***Singapore***: Apo-Metoclop; Emeliv; Maril; Metolon; Primperan; Pulin; Syntomide; ***Spain***: Primperan; ***Swed.***: Primperan; ***Switz.***: Paspertin; Primperan; ***Thai.***: Emetal; Gensil†; H-Peran; Hawkperan; KB Meta; Manosil; Maril; Met-Sil; Metoclor; Nausil; Nausin†; Plamide; Plamine; Plasil; R-J; Vomesea; ***Turk.***: Emoject; Metoklamide; Metpamid; Primperan; ***UAE***: Premosan; ***UK***: Maxolon; Primperan; ***Ukr.***: Cerucal (Церукал); Metucal (Метукал)†; ***USA***: Metozolv; Octamide†; Reclomide; Reglan; ***Venez.***: Clodoxin; Irtopan; Mepramida; Pramide; Primperan.

Multi-ingredient Preparations. ***Arg.***: Bil 13 Enzimatico; Bitecain AA; Digesplen; Facilgest; Factorine; Faradil Enzimatico†; Faradil; Migral Compositum; Pakinase; Pankreon Total; Tetralgin; Vacuobil Plus; ***Austral.***: Anagraine; Metomax; ***Austria***: Ceolat Compositum; ***Belg.***: Migpriv; ***Braz.***: Cefalium; Digeplus; Essen; Plagon†; Plasil Enzimatico; Sintozima†; ***Chile***: Aero Itan; Aerogastrol; Digespar; Garceptol; No-Ref; Pangastren; ***Cz.***: Migranerton; ***Fin.***: Migpriv†; ***Fr.***: Migpriv; ***Ger.***: Migraeflux MCP; Migralave + MCP; Migrane-Neuridal; Migranerton; ***Gr.***: Egityl; Premig; ***Hung.***: Migpriv; ***India***: Copar; Metadrate; Metoclop-P; Metopar; Metpar; Nausifar MPS; Okanorm Plus; Pacimol-M; Paramet; Paranorm; ***Indon.***: Primadol; Primperan Compositum; ***Irl.***: Paramax; ***Ital.***: Geffer; Migpriv; Migraprim; ***Mex.***: Antigram; Digenor Plus; Digenor; Espaven MD; Espraden; Plasil Enzimatico; Pramigel; Primpesasy†; ***Neth.***: Migrafin; ***NZ***: Paramax; ***Pol.***: Migpriv; ***Spain***: Aeroflat; Anti-Anorex Triple; Suxidina; ***Swed.***: Migpriv†; ***Switz.***: Migpriv†; ***Turk.***: Migprin; ***UK***: Migramax; Paramax.

Pharmacopoeial Preparations

BP 2014: Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets;

USP 36: Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets.

Metopimazine *(BAN, USAN, rINN)*

EXP-999; Metopimazina; Métopimazine; Metopimazinum; RP-9965; Метопимазин.

1-[3-(2-Methylsulphonylphenothiazin-10-yl)propyl]piperidine-4-carboxamide.

$C_{22}H_{27}N_3O_3S_2$=445.6

CAS — 14008-44-7.

ATC — A04AD05.

ATC Vet — QA04AD05.

UNII — 238S75V9AV.

Pharmacopoeias. In *Fr.*

Profile

Metopimazine, a phenothiazine dopamine antagonist, is an antiemetic with general properties similar to those of chlorpromazine (p. 1045.2). It is used in the management of nausea and vomiting, including that associated with cancer chemotherapy (p. 1811.3). It is given in usual oral doses of 15 to 30 mg daily, in up to 4 divided doses; similar daily doses have been given rectally in 3 divided doses. It has also been given by injection in a dose of 10 to 20 mg daily, usually intramuscularly but occasionally by the intravenous route. Higher doses of 30 to 50 mg daily in divided doses by intramuscular injection or intravenous infusion have been given for chemotherapy-induced nausea and vomiting; the first dose is given before chemotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vogalene; Vogalib; ***Gr.***: Vogalene.

Mosapride Citrate *(rINNM)*

AS-4370; Citrato de mosaprida; Mosaprida, citrato de; Mosapride, Citrate de; Mosapridi Citras; Rimopride Citrate; Мозаприда Цитрат.

(±)-4-Amino-5-chloro-2-ethoxy-*N*-{[4-(*p*-fluorobenzyl)-2-morpholinyl]methyl}benzamide citrate dihydrate.

$C_{21}H_{25}ClFN_3O_3,C_6H_8O_7,2H_2O$=650.1

CAS — 112885-41-3 (mosapride); 112885-42-4 (mosapride citrate).

UNII — MF497J489P (mosapride citrate); 73033I28Y6 (mosapride citrate dihydrate).

Profile

Mosapride is a substituted benzamide used for its prokinetic properties. It is reported to be an agonist at 5-HT_4 receptors, increasing acetylcholine release and stimulating gastrointestinal motility (see also Cisapride, p. 1832.1), as well as having 5-HT_3 antagonist properties. It is given orally as the citrate dihydrate, but doses are expressed as the anhydrous citrate, and are 5 mg three times daily before or after meals.

References.

1. Sakashita M, *et al.* Pharmacokinetics of the gastrokinetic agent mosapride citrate after single and multiple oral administrations in healthy subjects. *Arzneimittelforschung* 1993; **43:** 867–72.
2. Ruth M, *et al.* The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998; **12:** 35–40.
3. Ruth M, *et al.* The effect of mosapride on oesophageal motor function and acid reflux in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; **15:** 1115–21.
4. Asakawa H, *et al.* Effect of mosapride on glycemic control and gastric emptying in type 2 diabetes mellitus patients with gastropathy. *Diabetes Res Clin Pract* 2003; **61:** 175–82.
5. Liu Z, *et al.* Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. *Mov Disord* 2005; **20:** 680–6.
6. He M, *et al.* Mosapride citrate prolongs survival in stroke patients with gastrostomy. *J Am Geriatr Soc* 2007; **55:** 142–4.
7. Curran MP, Robinson DM. Mosapride: in gastrointestinal disorders. *Drugs* 2008; **68:** 981–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alprida†; Galopran; Gastrokin; Intesul; Levusid; Lostapride; Mosar; Vagantyl; ***China***: Bei Luo Na (贝络纳); Gasmotin (加斯清); Kuai Li (快力); Mei Wei Ning (美唯宁); RuiQi (瑞冀); Xinluona (新络纳); ***India***: Kinetix; M-Pride; Mic; Mopride; Mosadec; Mosafe; Mosakind; Mosap; Mosapid; Mosart; Mosiba; Mosid-MT; Mosid-OD; Moten Instab; Moza; Mozasef; Mozatone; Mozax; Musapro; Muzic; Normagut; Peripride†; ***Jpn***: Gasmotin; ***Mex.***: Dosier; ***Philipp.***: Gasmotin; ***Thai.***: Gasmotin.

Multi-ingredient Preparations. ***Arg.***: Mosar Enzimatico; Mosar Plus; ***India***: M-Pride-MPS; Mosid-MPS; Moza MPS; Moza Plus; Mozax-MPS; Pantec Plus.

Nabilone *(BAN, USAN, rINN)* ⊗

Compound 109514; Lilly-109514; Nabilon; Nabilona; Nabiloni; Nabilonum; Набилон.

(±)-(6a*R*,10a*R*)-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6*H*-benzo[c]chromen-9-one.

$C_{24}H_{36}O_3$=372.5

CAS — 51022-71-0.

ATC — A04AD11.

ATC Vet — QA04AD11.

UNII — 2N4O9L084N.

Uses and Administration

Nabilone, a synthetic cannabinoid with antiemetic properties, is used for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics (p. 1811.3).

The usual initial oral dose is 1 mg twice daily, increased to 2 mg twice daily if necessary. The first dose should be given the evening before starting chemotherapy, and the second dose 1 to 3 hours before the first dose of antineoplastic. Nabilone may be given throughout each cycle of chemotherapy and for 48 hours after the last dose of chemotherapy, if required. The dose of nabilone should not exceed 6 mg daily, given in 3 divided doses.

Reviews.

1. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; **323:** 16–21.
2. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Invest Drugs* 2008; **17:** 85–95.

Multiple sclerosis. There is a report of reduction in spasticity and nocturia, and improvement in mood and well-being, in a patient with multiple sclerosis (p. 996.3) who received nabilone 1 mg every second day.[1] A subsequent small crossover study[2] in patients with chronic upper motor neurone syndrome found that oral nabilone 1 mg daily reduced spasticity-related pain in this group. There are also anecdotal reports of improvement in symptoms in patients with multiple sclerosis who took cannabis, however, a review[3] considered evidence of efficacy to be lacking.

1. Martyn CN, *et al.* Nabilone in the treatment of multiple sclerosis. *Lancet* 1995; **345:** 579.
2. Wissel J, *et al.* Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol* 2006; **253:** 1337–41.
3. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.

Adverse Effects

Nabilone may produce adverse effects similar to those of cannabis (see p. 2468.2). The most common adverse effects are drowsiness, vertigo, and dry mouth. Neurological effects have included ataxia, confusion, disorientation, dizziness, euphoria, dysphoria, hallucinations, psychosis, depression, headache, decreased concentration, blurred vision, sleep disturbances, decreased coordination, and tremors. Adverse cardiovascular reactions including hypotension, orthostatic hypotension, and tachycardia have occurred. Gastrointestinal disturbances, decreased appetite, and abdominal pain have also been reported.

Precautions

Nabilone is extensively metabolised and largely excreted in bile, and therefore is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with a history of psychiatric disorders or depression, or those with hypertension or heart disease.

Because of the possibility of CNS depression, patients should be warned not to drive or operate machinery.

The possibility of dependence similar to that of cannabis should be borne in mind.

Interactions

Nabilone has been shown to have an additive CNS depressant effect when given with alcohol, codeine, diazepam, or other CNS depressants.

Pharmacokinetics

Nabilone is well absorbed from the gastrointestinal tract and is rapidly and extensively metabolised; one or more of the metabolites may be active. The major excretory pathway is the biliary system; about 65% of a dose is excreted in the faeces and about 20% in the urine. The elimination half-life of nabilone is about 2 hours, but the half-life of its combined metabolites is about 35 hours after an oral dose.

References.

1. Rubin A, *et al.* Physiologic disposition of nabilone, a cannabinol derivative, in man. *Clin Pharmacol Ther* 1977; **22:** 85–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cesamet; ***Canad.***: Cesamet; ***Mex.***: Cesamet; ***USA***: Cesamet.

Nizatidine *(BAN, USAN, rINN)*

LY-139037; Nitsatidiini; Nizatidin; Nizatidina; Nizatidinas; Nizatidinum; ZL-101; Низатидин.

4-[2-(1-Methylamino-2-nitrovinylamino)ethylthiomethyl]thiazol-2-ylmethyl(dimethyl)amine; *N*-[2-(2-Dimethylaminomethylthiazol-4-ylmethylthio)ethyl]-*N'*-methyl-2-nitrovinylidenediamine.

$C_{12}H_{21}N_5O_2S_2$=331.5

CAS — 76963-41-2.

ATC — A02BA04.

ATC Vet — QA02BA04.

UNII — P41PML4GHR.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nizatidine). An almost white or slightly brownish, crystalline powder. Sparingly soluble in water; soluble in methyl alcohol. A 1% solution in water has a pH of 8.5 to 10.0.

USP 36: (Nizatidine). An off-white to buff crystalline solid. Sparingly soluble in water; freely soluble in chloroform; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Nizatidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p. 1827.2).

In the management of benign **gastric** and **duodenal ulceration** (p. 1813.2), and NSAID-associated ulceration, a daily oral dose of nizatidine 300 mg is given either as a single dose at bedtime or in 2 divided doses, for 4 to 8 weeks. Where appropriate a maintenance dose of 150 mg daily may be given at night.

In **gastro-oesophageal reflux disease** (p. 1807.2) an oral dose of 150 to 300 mg twice daily is recommended for up to 12 weeks.

For the short-term symptomatic relief of **dyspepsia** an oral dose of 75 mg, repeated if necessary, up to a maximum of 150 mg daily may be taken for up to 14 days.

Nizatidine has also been given intravenously by continuous or intermittent infusion.

Doses of nizatidine should be reduced in patients with renal impairment (see below). For doses in children, see below.

Administration in children. Nizatidine is given to children for oesophagitis and gastro-oesophageal reflux disease in the USA; an oral dose of 150 mg twice daily for up to 8 weeks is licensed in those 12 years of age or over.

Administration in renal impairment. The dosage of nizatidine should be reduced in patients with renal impairment according to creatinine clearance (CC). Licensed product information recommends the following oral doses in renal impairment:

- CC 20 to 50 mL/minute: doses should be reduced by 50%, *or* where the standard dose would be 150 mg daily, 150 mg may be given on alternate days
- CC less than 20 mL/minute: doses should be reduced by 75%, *or* where the standard dose would be 300 mg daily, 150 mg may be given on alternate days, and where the standard dose would be 150 mg daily, 150 mg may be given every third day

Adverse Effects

As for Cimetidine, p. 1828.3. Some patients taking nizatidine may experience excessive sweating and urticaria; anaemia may also occur.

Nizatidine is considered to have no anti-androgenic activity although there are isolated reports of gynaecomastia and impotence.

Precautions

As for Cimetidine, p. 1830.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nizatidine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Unlike cimetidine (p. 1830.3) nizatidine does not inhibit cytochrome P450 isoenzymes, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of drugs whose absorption is dependent on an acid gastric pH.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p. 1735.2).

Antacids. For discussion of the effect of antacids on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Sucralfate. For information on the effect of sucralfate on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Pharmacokinetics

Nizatidine is readily absorbed from the gastrointestinal tract with peak plasma concentrations about 0.5 to 3 hours after an oral dose. The bioavailability of nizatidine exceeds 70% and may be slightly increased by the presence of food. It is widely distributed and is about 35% bound to plasma proteins.

The elimination half-life of nizatidine is 1 to 2 hours and is prolonged in renal impairment. A small amount is metabolised in the liver: nizatidine *N*-2-oxide, nizatidine *S*-oxide, and *N*-2-monodesmethylnizatidine have been identified, the latter having about 60% of the activity of nizatidine.

More than 90% of a dose of nizatidine is excreted in the urine, in part by active tubular secretion, within 12 hours, about 60% as unchanged drug. Less than 6% is excreted in the faeces. Nizatidine is distributed into breast milk.

References.

1. Callaghan JT, *et al.* A pharmacokinetic profile of nizatidine in man. *Scand J Gastroenterol* 1987; **22** (suppl 136): 9–17.
2. Abdel-Rahman SM, *et al.* Single-dose pharmacokinetics of nizatidine (Axid) in children. *J Clin Pharmacol* 2002; **42:** 1089–96.
3. Blum RA, *et al.* Pharmacokinetics and pharmacodynamics of a novel nizatidine controlled-release formulation in healthy subjects. *J Clin Pharmacol* 2003; **43:** 74–83.
4. Abdel-Rahman SM, *et al.* Developmental pharmacokinetics and pharmacodynamics of nizatidine. *J Pediatr Gastroenterol Nutr* 2004; **38:** 442–51.

Bioavailability. The bioequivalence of 3 oral liquid formulations of nizatidine was investigated relative to a commercially available nizatidine capsule. Of the 3 liquid formulations, one was a commercially available oral syrup (15 mg/mL), and 2 others were extemporaneously prepared, one as a solution in apple juice (1.2 mg/mL) and another as a suspension in an infant formula (*Enfamil; Ross, USA*; 15 mg/mL). Nizatidine in apple juice showed markedly less bioavailability, whereas the other 2 formulations were considered to be bioequivalent to the reference capsule.[1]

1. Abdel-Rahman SM, *et al.* The bioequivalence of nizatidine (Axid) in two extemporaneously and one commercially prepared oral liquid formulations compared with capsule. *J Clin Pharmacol* 2003; **43:** 148–53.

Distribution into breast milk. About 0.1% of an oral dose of nizatidine was secreted in breast milk in a study in lactating women.[1] The milk to serum ratio varied (from 1:1 to 4.9:1) with the time of samples.

1. Obermeyer BD, *et al.* Secretion of nizatidine into human breast milk after single and multiple doses. *Clin Pharmacol Ther* 1990; **47:** 724–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nizac; Tacidine; Tazac; ***Braz.***: Axid; ***Canad.***: Axid; ***Chile***: Nizaxid; ***China***: Axid (爱希); Ni Ting (妮停); Sai Fa Lei (赛法雷); ***Fr.***: Nizaxid; ***Gr.***: Axid; Elkofen; Flectar; Flexidon; Fterosan; Ozeltan; Peptodin; Ulcogastrin; ***Hung.***: Naxidin; ***Indon.***: Axid†; ***Irl.***: Axid; ***Ital.***: Cronizat; Nizax; ***Mex.***: Axid†; ***Neth.***: Axid; ***Philipp.***: Axid†; Nolcer; ***Port.***: Nizaxid†; Prospaxid; ***S.Afr.***: Antizid†; ***Spain***: Distaxid†; ***Thai.***: Axid; ***Turk.***: Axid; ***UK***: Axid†; ***USA***: Axid†; Axid; Axid.

Pharmacopoeial Preparations
BP 2014: Nizatidine Infusion;
USP 36: Nizatidine Capsules.

Octatropine Methylbromide *(BAN, rINN)*

Anisotropine Methobromide; Anisotropine Methylbromide (USAN); Metilbromuro de octatropina; Octatropina, metilbromuro de; Octatropine, Méthylbromure d'; Octatropini Methylbromidum; Октатропина Метилбромид.

(1*R*,3*r*,5*S*)-8-Methyl-3-(2-propylvaleryloxy)tropanium bromide.

$C_{17}H_{32}BrNO_2$=362.4

CAS — 80-50-2.

UNII — 62M960DHIL.

Pharmacopoeias. In *It.*

Profile

Octatropine methylbromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease and to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Espasmo Dioxadol; ***Chile***: Bufacyl; Valpin; ***Ital.***: Valpinax.

Olsalazine Sodium *(BANM, USAN, rINNM)*

Azodisal Sodium; CI Mordant Yellow 5; CJ-91B; Colour Index No. 14130; Natrii Olsalazinum; Olsalatsiininatrium; Olsalazin disodná sůl; Olsalazin-Natrium; Olsalazin Sodyum; Olsalazina sódica; Olsalazine Sodique; Olsalazinnatrium; Olsalazino natrio druska; Olsalazinum Dinatricum; Olsalazinum natricum; Olszalazin-nátrium; Sodium Azodisalicylate; Натрий Ольсалазин.

Disodium 5,5'-azodisalicylate.

$C_{14}H_8N_2Na_2O_6$=346.2

CAS — 6054-98-4.

ATC — A07EC03.

ATC Vet — QA07EC03.

UNII — Y7JEW0XG7I.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Olsalazine Sodium). A yellow, fine, crystalline powder; it exhibits polymorphism. Sparingly soluble in water; soluble in dimethyl sulfoxide; very slightly soluble in methyl alcohol.

Uses and Administration

Olsalazine consists of two molecules of mesalazine (p. 1859.2) linked with an azo bond. It is activated in the colon where the active mesalazine is released. It is given orally as the sodium salt in the management of acute mild ulcerative colitis and for the maintenance of remission (see Inflammatory Bowel Disease, p. 1808.3). The usual initial dose of olsalazine sodium is 1 g daily in divided doses and this is gradually increased, if necessary, over one week, to a maximum dose of 3 g daily. The usual dose for the maintenance of remission is 500 mg twice daily. Doses should be taken after meals and a single dose should not exceed 1 g. For doses in children, see below.

Administration in children. Although not licensed in the UK for use in children under 12 years, the *BNFC* suggests an oral dose of olsalazine for children aged 2 years and over; the adult dose may be given for an acute attack of mild ulcerative colitis (see Uses and Administration, above), and for maintenance of remission, a dose of 250 to 500 mg may be given twice daily, after food.

Adverse Effects and Precautions

As for Mesalazine, p. 1860.1. The most common adverse effects associated with olsalazine sodium are diarrhoea, arthralgia, and skin rashes. Diarrhoea may be watery in some patients; it may resolve with dosage reduction but can be severe enough to require withdrawal of treatment. Diarrhoea is less likely if the drug is taken after meals. There have been a few reports of blood dyscrasias. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Incidence of adverse effects. In an open study[1] of oral olsalazine 1 g daily involving 160 patients with active ulcerative colitis and a history of sulfasalazine intolerance, 103 (64.4%) patients had no adverse effects; 29 patients reported only minor adverse effects: gastrointestinal disturbances in 22 patients, transient skin rash in 3, and headache, increased salivation, cough, and irritability each in one patient. The most common adverse effect was frequent loose stools which affected 25 patients, 20 of whom had to stop treatment. This adverse effect occurred early in treatment, within 10 hours of the first dose in 13 patients. Severe diarrhoea was more frequent in patients with widespread disease, but the incidence of diarrhoea did not correlate with disease severity.

A subsequent study[2] in healthy subjects has shown that olsalazine has a significant inhibitory effect on water and electrolyte absorption in the small intestine, which may account, at least in part, for the induction of diarrhoea. Patients with extensive colitis have reduced colonic absorptive function and may be less able to assimilate the increased colonic inflow volumes.

1. Sandberg-Gertzén H, *et al.* Azodisal sodium in the treatment of ulcerative colitis: a study of tolerance and relapse-prevention properties. *Gastroenterology* 1986; **90:** 1024–30.
2. Raimundo AH, *et al.* Effects of olsalazine and sulphasalazine on jejunal and ileal water and electrolyte absorption in normal human subjects. *Gut* 1991; **32:** 270–4.

Breast feeding. A study[1] involving a 39-year-old woman with Crohn's disease found that olsalazine did not appear to present a clinically significant risk to the breast-fed infant. Olsalazine was undetectable in the breast milk for 48 hours after a single oral 500-mg dose, and although small amounts of the metabolite acetylated 5-aminosalicylic acid were detected in breast milk the infant showed no adverse effects during the 3 weeks afterwards in which the mother continued taking olsalazine.

1. Miller LG, *et al.* Disposition of olsalazine and metabolites in breast milk. *J Clin Pharmacol* 1993; **33:** 703–6.

Effects on the blood. As of July 1995, the UK CSM had received 4 reports of blood dyscrasias associated with olsalazine, none of them fatal.[1] It was recommended that a blood count be performed and the drug stopped immediately if there was suspicion of a dyscrasia. See also under Mesalazine, p. 1860.2.

1. CSM/MCA. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)

Effects on the kidneys. A report of nephrotoxicity, characterised by interstitial nephritis, was associated with the use of olsalazine.[1] Symptoms resolved on stopping of the drug. See also under Mesalazine, p. 1860.3.

1. Wilcox GM, *et al.* Nephrotoxicity associated with olsalazine. *Am J Med* 1996; **100:** 238–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies olsalazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Interactions

Antineoplastics. For mention of 5-aminosalicylates such as olsalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Gastrointestinal Drugs, p. 822.1.

Pharmacokinetics

Very little of an oral dose of olsalazine is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 2 molecules of 5-aminosalicylic acid (mesalazine). Some mesalazine is absorbed and acetylated (see p. 1861.2) but systemic concentrations of mesalazine and its metabolite are lower than after comparable oral doses of mesalazine, perhaps because there is less release of mesalazine in the small intestine, where absorption is better. Mesalazine concentrations in the colon after a dose of olsalazine are stated to be about 1000 times greater than systemic concentrations.

The small amounts (1 to 2% of the dose or less) of intact olsalazine that are absorbed are excreted mainly in urine; the elimination half-life after an intravenous dose has been calculated at about 1 hour. Some olsalazine is metabolised by sulfate conjugation in the liver: the elimination half-life of the metabolite is reported to be about 7 days.

References.

1. Ryde EM. Pharmacokinetic aspects of drugs targeted for the colon, with special reference to olsalazine. *Acta Pharm Suec* 1988; **25:** 327–8.
2. Laursen LS, *et al.* Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 1990; **31:** 1271–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dipentum; ***Austria***: Dipentum; ***Canad.***: Dipentum; ***Chile***: Dipentum†; ***China***: Chang Mei (畅美); ***Denm.***: Dipentum; ***Fin.***: Dipentum; ***Fr.***: Dipentum; ***Ger.***: Dipentum; ***Gr.***: Dipentum; ***Hong Kong***: Dipentum; ***Irl.***: Dipentum; ***Neth.***: Dipentum; ***Norw.***: Dipentum; ***NZ***: Dipentum; ***Port.***: Dipentum†; ***S.Afr.***: Dipentum; ***Swed.***: Dipentum; ***Switz.***: Dipentum†; ***Turk.***: Dipentum†; ***UK***: Dipentum; ***USA***: Dipentum.

Omeprazole *(BAN, USAN, rINN)*

H-168/68; Omepratsoli; Omeprazol; Omeprazolas; Oméprazole; Omeprazolo; Omeprazolum; Омепразол.

(*RS*)-5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridylmethylsulphinyl)benzimidazole.

$C_{17}H_{19}N_3O_3S$=345.4

CAS — 73590-58-6.

ATC — A02BC01.

ATC Vet — QA02BC01.

UNII — KG60484QX9.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Omeprazole). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature between 2 degrees and 8 degrees. Protect from light.

USP 36: (Omeprazole). A white to off-white powder. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from moisture.

Omeprazole Magnesium *(BANM, USAN, rINNM)*

Magnesii Omeprazolum; Omeprazol magnésico; Omeprazol-Magnesium; Oméprazole Magnesique; Oméprazole magnésique; Omeprazolum magnesicum; Магния Омепразол.

$C_{34}H_{36}MgN_6O_6S_2$=713.1

CAS — 95382-33-5.

ATC — A02BC01.

ATC Vet — QA02BC01.

UNII — 426QFE7XLK.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Omeprazole Magnesium). A white or almost white, hygroscopic powder. Very slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 36: (Omeprazole Magnesium). A white to off-white powder. Very soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Omeprazole Sodium *(BANM, USAN, rINNM)*

Natrii Omeprazolum; Omepratsolinatrium; Omeprazol-Natrium; Omeprazol sódico; Omeprazol sodná sůl monohydrát; Oméprazole sodique; Omeprazolnatrium; Omeprazol-nátrium; Omeprazolo natrio druska; Omeprazolum natricum; Omeprazolum Natricum Monohydricum; Натрий Омепразол.

$C_{17}H_{18}N_3NaO_3S$=367.4

CAS — 95510-70-6.

ATC — A02BC01.

ATC Vet — QA02BC01.

UNII — KV03YZ6QLW.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Omeprazole Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane; soluble in propylene glycol. The pH of a 2% solution in water is 10.3 to 11.3. Store in airtight containers. Protect from light.

Uses and Administration

Omeprazole is a proton pump inhibitor. It suppresses secretion of gastric acid by inhibiting the enzyme system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase), the 'proton pump' of the gastric parietal cell. It is used in conditions where inhibition of gastric acid secretion may be beneficial, including aspiration syndromes (p. 1804.2), dyspepsia (p. 1868.1), gastro-oesophageal reflux disease (p. 1807.2), peptic ulcer disease (p. 1813.2), and the Zollinger-Ellison syndrome (p. 1814.3).

Esomeprazole (p. 1841.1), an isomer of omeprazole, is also used.

Omeprazole may be given orally as the base or magnesium salt, or intravenously as the sodium salt. Doses are expressed in terms of the base. Omeprazole magnesium 10.32 mg and omeprazole sodium 10.64 mg are each equivalent to about 10 mg of omeprazole.

For the relief of acid-related **dyspepsia** omeprazole is given in usual doses of 10 or 20 mg daily orally for 2 to 4 weeks.

The usual dose for the treatment of **gastro-oesophageal reflux disease** is 20 mg orally once daily for 4 weeks, followed by a further 4 to 8 weeks if not fully healed. In refractory oesophagitis, a dose of 40 mg daily may be used. Maintenance therapy after healing of oesophagitis is 20 mg once daily, and for acid reflux is 10 mg daily. For dosage in children see below.

In the management of **peptic ulcer disease** a single daily dose of 20 mg orally, or 40 mg in severe cases, is given. Treatment is usually continued for 4 weeks for duodenal ulcer and 8 weeks for gastric ulcer. Where appropriate, a dose of 10 to 20 mg once daily may be given for maintenance.

For the eradication of *Helicobacter pylori* in peptic ulceration omeprazole may be combined with antibacterials in dual or triple therapy. Effective **triple therapy** regimens include omeprazole 20 mg twice daily or 40 mg once daily combined with: amoxicillin 500 mg and metronidazole 400 mg, both three times daily; clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) both twice daily; or with amoxicillin 1 g and clarithromycin 500 mg, both twice daily. These regimens are given for 7 or 10 days. **Dual therapy** regimens such as omeprazole 40 mg daily with clarithromycin 500 mg three times daily are licensed but are much less effective and must be given for 2 weeks. Omeprazole monotherapy may be continued after dual or triple therapy in patients with ulceration at the start of therapy; antisecretory therapy can be continued after triple therapy in those with large ulcers or complications.

Doses of 20 mg daily orally are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients with a history of gastroduodenal lesions who require continued NSAID treatment.

The initial recommended dosage for patients with the **Zollinger-Ellison syndrome** is 60 mg orally once daily, adjusted as required. The majority of patients are effectively controlled by doses in the range 20 to 120 mg daily, but doses up to 120 mg three times daily have been used. Daily doses above 80 mg should be given as divided doses (usually 2).

Omeprazole is also used for the prophylaxis of **acid aspiration** during general anaesthesia, in a dose of 40 mg the evening before surgery and a further 40 mg two to six hours before the procedure.

The dose of omeprazole may need to be reduced in patients with hepatic impairment (see p. 1868.1).

PARENTERAL DOSAGE.

In patients who are unsuited to receive oral therapy omeprazole sodium may be given on a short-term basis by intravenous infusion, in a usual dose equivalent to 40 mg of the base over a period of 20 to 30 minutes in 100 mL of sodium chloride 0.9% or glucose 5%. It may also be given by slow intravenous injection. Higher intravenous doses have been given to patients with Zollinger-Ellison syndrome, with a usual initial dose of 60 mg daily.

Although unlicensed in the UK for major peptic bleeding after endoscopy, the *BNF* suggests that omeprazole 80 mg can be infused intravenously over 40 to 60 minutes, followed by a continuous infusion of 8 mg/hour for 72 hours; treatment can then be continued orally.

General reviews.

1. Langtry HD, Wilde MI. Omeprazole: a review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs. *Drugs* 1998; **56:** 447–86.
2. Berardi RR, Welage LS. Proton-pump inhibitors in acid-related diseases. *Am J Health-Syst Pharm* 1998; **55:** 2289–98.
3. Erstad BL. Proton-pump inhibitors for acute peptic ulcer bleeding. *Ann Pharmacother* 2001; **35:** 730–40.
4. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003; **63:** 2739–54.
5. Dekel R, *et al.* The role of proton pump inhibitors in gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 277–95.
6. Anonymous. Proton pump inhibitors for GERD in children. *Med Lett Drugs Ther* 2007; **49:** 17–18.
7. Boparai V, *et al.* Guide to the use of proton pump inhibitors in adult patients. *Drugs* 2008; **68:** 925–47.
8. Lazzaroni M, Porro GB. Management of NSAID-induced gastrointestinal toxicity: focus on proton pump inhibitors. *Drugs* 2009; **69:** 51–69.
9. Bardou M, *et al.* Intravenous proton pump inhibitors: an evidence-based review of their use in gastrointestinal disorders. *Drugs* 2009; **69:** 435–48.

Administration. Omeprazole is given orally as tablets or capsules containing enteric-coated pellets or granules, which should be swallowed whole and not crushed or chewed. In children or patients with swallowing difficulties, UK licensed product information (*Losec; AstraZeneca*) states that the tablet be dispersed in water and then mixed with fruit juice (with a pH less than 5) or yogurt before swallowing without chewing. Similarly the contents of the capsules can be mixed with water, fruit juice (with a pH less than 5) or yogurt and swallowed without chewing. An oral suspension is available in some countries.

Administration in children. Licensed UK *oral* doses of omeprazole for the treatment of gastro-oesophageal reflux disease or reflux oesophagitis in children 1 year of age and over are determined by body-weight as follows:

- 10 to 20 kg: 10 mg once daily
- over 20 kg: 20 mg once daily

These doses may be doubled if necessary. Treatment may be given for 2 to 4 weeks for gastro-oesophageal reflux disease and for 4 to 8 weeks for reflux oesophagitis. Similar doses

are licensed in the USA, where an oral dose of 5 mg daily is included for children weighing from 5 kg up to 10 kg.

For gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including NSAID-associated ulceration, prophylaxis of acid aspiration, Zollinger-Ellison syndrome, and to reduce the degradation of pancreatic enzyme supplements in children with cystic fibrosis, the *BNFC* recommends an oral dose of 700 micrograms/kg once daily in neonates and children 1 month to 2 years of age. If needed, doses may be increased in neonates after 7 to 14 days, to 1.4 mg/kg once daily; some neonates may require up to 2.8 mg/kg once daily. In children up to 2 years of age, doses may be increased up to 3 mg/kg (to a maximum of 20 mg) once daily.

For *parenteral* dosage in children the *BNFC* recommends an intravenous dose of 500 micrograms/kg (to a maximum of 20 mg) once daily in children aged 1 month to 12 years; this may be increased to 2 mg/kg (to a maximum of 40 mg) once daily if needed.

For the eradication of *Helicobacter pylori* licensed oral doses in the UK for children from 4 years of age are omeprazole 10 mg in those weighing 15 to 30 kg or omeprazole 20 mg in those weighing over 30 kg, given twice daily with amoxicillin and clarithromycin for 1 week. In children from 1 to 12 years of age, the *BNFC* recommends an oral dose of omeprazole 1 to 2 mg/kg (to a maximum dose of 40 mg) once daily. This is given with antibacterial therapy under specialist supervision.

For administration of the tablets or capsules to children, see Administration, p. 1867.3.

A systematic review found that evidence was insufficient to support the efficacy and safety of proton pump inhibitors for the treatment of gastro-oesophageal disease in children and adolescents, although short-term use was well tolerated; proton pump inhibitors were found to be ineffective for infants.[1]

1. van der Pol RJ, *et al*. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics* 2011; **127:** 925–35.

Administration in hepatic impairment. Bioavailability and half-life of omeprazole can increase in patients with hepatic impairment. UK licensed product information suggests that a daily oral or intravenous dose of 10 to 20 mg may be sufficient for these patients.

Dyspepsia. Although earlier UK guidelines on the use of proton pump inhibitors in dyspepsia (p. 1806.3) suggested that they should not be used routinely in non-ulcer dyspepsia,[1] subsequent guidelines on its general management in both the UK[2] and the USA[3] consider that a 1-month empirical course in patients aged under 55 without symptoms suggestive of more serious disease is a valid first-line treatment.

1. NICE. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia (issued July 2000). Available at: http://www.nice.org.uk/nicemedia/pdf/proton.pdf (accessed 11/02/08)
2. NICE. Dyspepsia: management of dyspepsia in adults in primary care (Clinical Guideline 17: issued August 2004, updated June 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/CG017NICEguideline.pdf (accessed 11/02/08)
3. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005; **129:** 1753–5. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508505018172.pdf (accessed 11/02/08)

Inflammatory bowel disease. There are a few reports[1-3] of responses to omeprazole in patients with inflammatory bowel disease (p. 1808.3). Combination of omeprazole with mesalazine has also been tried.[2]

1. Heinzow U, Schlegelberger T. Omeprazole in ulcerative colitis. *Lancet* 1994; **343:** 477.
2. Dickinson JB. Is omeprazole helpful in inflammatory bowel disease? *J Clin Gastroenterol* 1994; **18:** 317–19.
3. Guslandi M, Tittobello A. Symptomatic response to omeprazole in inflammatory bowel disease. *J Clin Gastroenterol* 1996; **22:** 159–60.

Scleroderma. Gastro-oesophageal reflux is one of the gastrointestinal manifestations of systemic sclerosis, and proton pump inhibitors such as omeprazole play a major role in the management of such gastrointestinal disease.[1] For a discussion of the broader management of the condition see p. 1938.3.

1. Williamson DJ. Update on scleroderma. *Med J Aust* 1995; **162:** 599–601.

Adverse Effects

Proton pump inhibitors are generally well tolerated, and adverse effects are relatively infrequent. The adverse effects reported most often with omeprazole and other proton pump inhibitors have been headache, gastrointestinal disturbances, and rash; they have sometimes been severe enough to require stopping treatment.

Other effects include pruritus, dizziness, fatigue, cough, back or abdominal pain, arthralgia and myalgia, urticaria, and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, and Stevens-Johnson syndrome have occurred; toxic epidermal necrolysis has sometimes been fatal. Systemic hypersensitivity reactions, including fever, bronchospasm, angioedema, and anaphylaxis have been reported. Effects on the CNS include occasional insomnia, somnolence, aggression, and vertigo; reversible confusional states, agitation, depression, and hallucinations have occurred in severely ill patients. Raised liver enzymes, and isolated cases of hepatitis, jaundice, and hepatic encephalopathy have been reported; fatalities have occurred from hepatic failure or necrosis.

Other adverse effects reported rarely include gastrointestinal (including oesophageal) candidiasis, muscular weakness, paraesthesia, blurred vision, alopecia, stomatitis, increased sweating, taste disturbances, peripheral oedema, malaise, hyponatraemia, hypomagnesaemia, blood disorders (including agranulocytosis, leucopenia, and thrombocytopenia), gynaecomastia, impotence, and interstitial nephritis. Cardiovascular effects may occur, including angina, tachycardia or bradycardia. Pancreatitis (sometimes fatal) has been reported, as have tinnitus, urinary disorders, and eye disorders.

Proton pump inhibitors may increase the risk of gastrointestinal infections because of their acid suppressive effects. The absorption of some vitamins and minerals may be reduced.

Early toxicological studies identified carcinoid-like tumours of the gastric mucosa in *rats* given very high doses of omeprazole over long periods (see under Gastrointestinal Tumours, p. 1869.3).

References.

1. Yang Y-X, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology* 2010; **139:** 1115–27.
2. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 2011; **56:** 931–50.
3. Abraham NS. Proton pump inhibitors: potential adverse effects. *Curr Opin Gastroenterol* 2012; **28:** 615–20.

Incidence of adverse effects. Prescription-event monitoring for 16 205 patients prescribed omeprazole, 17 329 prescribed lansoprazole, and 11 541 prescribed pantoprazole indicated that adverse events were reported infrequently, with the most common being gastrointestinal disturbances and headache. The incidences of diarrhoea, the most commonly reported event, per 1000 days of exposure, were 0.18 for omeprazole, 0.39 for lansoprazole, and 0.23 for pantoprazole. Despite the inherent biases of such a cohort study, there did seem to be some evidence that lansoprazole might be associated with a somewhat greater risk of diarrhoea, particularly in the elderly.[1]

1. Martin RM, *et al*. The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. *Br J Clin Pharmacol* 2000; **50:** 366–72.

Effects on the blood. There have been rare cases of leucopenia, agranulocytosis, thrombocytopenia, and pancytopenia, with omeprazole and other proton pump inhibitors such as lansoprazole and pantoprazole.[1-4] Auto-immune haemolytic anaemia has also been reported with omeprazole.[5]

1. Holt TL, *et al*. Neutropenia associated with omeprazole. *Med J Aust* 1999; **170:** 141–2.
2. Zlabek JA, Anderson CG. Lansoprazole-induced thrombocytopenia. *Ann Pharmacother* 2002; **36:** 809–11.
3. Watson TD, *et al*. Pantoprazole-induced thrombocytopenia. *Ann Pharmacother* 2006; **40:** 758–61.
4. Thakor AS, *et al*. Toxic epidermal necrolysis and neutropaenia: complications of omeprazole. *Australas J Dermatol* 2009; **50:** 207–10.
5. Butt MI, *et al*. Autoimmune haemolytic anaemia associated with use of omeprazole. *Br J Hosp Med* 2007; **68:** 108.

Effects on the cardiovascular system. Results and preliminary analyses from 2 studies raised concerns about a possible increased risk of myocardial infarction, cardiac failure, and cardiac-related sudden death in patients taking *omeprazole* or *esomeprazole* compared with patients who had surgery for gastro-oesophageal reflux disease.[1,2] However, an FDA safety review found that patients who had surgery tended to be younger and less likely to have a history of cardiac problems or cardiac risk factors than those given such drugs.[2] The FDA concluded that long-term use of these drugs is not likely to be associated with an increased risk of cardiac problems.[3] However, while Health Canada[4] considered that there was no evidence to support such an increased risk with long-term use of esomeprazole they were unable to make such a definitive conclusion for omeprazole.

There is a possible increased risk of cardiovascular events when proton pump inhibitors are used with clopidogrel, see Proton Pump Inhibitors, under Interactions of Clopidogrel, p. 1344.2. However, patients given proton pump inhibitors after myocardial infarction were found to have an increased risk for adverse cardiovascular outcomes in a retrospective cohort study,[5] an effect which was independent of clopidogrel use.

1. FDA. Early communication about an ongoing safety review: omeprazole (Prilosec) esomeprazole (Nexium) (issued 9th August 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm072497.htm (accessed 15/07/10)
2. FDA. Follow-up to the August 9, 2007, communication about the ongoing safety review of omeprazole and esomeprazole (issued 10th December 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143258.htm (accessed 15/07/10)
3. FDA. FDA's safety reviews of Prilosec and Nexium find no evidence of increased rates of cardiac events (issued 10th December 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109037.htm (accessed 15/07/10)
4. Health Canada. Health Canada completes safety review of Losec (omeprazole) and Nexium (esomeprazole) (issued 27 February 2008). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_34-eng.php (accessed 09/07/08)
5. Charlot M, *et al*. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med* 2010; **153:** 378–86.

Effects on electrolytes. Electrolyte disturbances have been reported with proton pump inhibitors, including hyponatraemia, with *omeprazole*,[1] *esomeprazole*,[2] *lansoprazole*,[3] and *pantoprazole*.[4] Refractory hypomagnesaemia with hypocalcaemia and hypokalaemia has been reported in 2 patients given omeprazole. Both patients were also taking other medicines that can affect electrolyte balance; however all abnormalities resolved when omeprazole was stopped.[5] In another case, severe hypomagnesaemia with hypocalcaemia and hypokalaemia occurred after prolonged treatment with omeprazole; electrolytes recovered when treatment with ranitidine was substituted, but fell again when pantoprazole and then lansoprazole therapy were tried.[6] The FDA reviewed 61 reports of hypomagnesaemia associated with proton pump inhibitors when used for at least 3 months and generally for more than 1 year. Serious adverse events included tetany, arrhythmias, and seizures. In about a quarter of cases, magnesium supplementation did not improve concentrations and the proton pump inhibitor had to be stopped. The mechanism responsible for proton pump inhibitors causing hypomagnesaemia is unknown; however, long-term use of proton pump inhibitors may cause changes in intestinal absorption of magnesium. Measurement of magnesium concentrations should be considered in patients starting long-term proton pump inhibitor treatment, those taking digoxin, or those taking other medicines which may cause hypomagnesaemia.[7]

1. Colls BM, Menzies OH. Hyponatraemia, fever, vomiting, severe abdominal pain, and weight loss associated with omeprazole. *N Z Med J* 2005; **118:** U1263.
2. Mennecier D, *et al*. Hyponatremia with consciousness disturbance associated with esomeprazole. *Ann Pharmacother* 2005; **39:** 774–5.
3. Fort E, *et al*. Hyponatrémie sous lansoprazole. *Gastroenterol Clin Biol* 2000; **24:** 686.
4. Hamilton DV, Lewis HRA. A rare cause of hyponatraemia? *Br J Hosp Med* 2009; **70:** 663.
5. Shabajee N, *et al*. Omeprazole and refractory hypomagnesaemia. Abridged version: *BMJ* 2008; **337:** 173–5. Full version: http://www.bmj.com/cgi/content/full/337/jul10_3/a425 (accessed 17/06/09)
6. Broeren MAC, *et al*. Hypomagnesemia induced by several proton-pump inhibitors. *Ann Intern Med* 2009; **151:** 755–6. Correction. *ibid*. 2010; **152:** 268.
7. FDA. Low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs) (issued 2nd March 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm (accessed 26/09/11)

Effects on the endocrine system. Up to December 1991, WHO had received 30 reports of impotence or gynaecomastia which might have been due to omeprazole;[1] of these reports 15 were of impotence, 13 of gynaecomastia in men, and 2 of breast enlargement in women. The Spanish Pharmacovigilance System reported 24 cases of gynaecomastia associated with the use of proton pump inhibitors, including lansoprazole and rabeprazole, between January 1982 and July 2006. In most of the cases, gynaecomastia improved after stopping the drug.[2] For reference to a case-control study showing no statistical link between gynaecomastia and omeprazole, see under Cimetidine, p. 1829.2.

1. Lindquist M, Edwards IR. Endocrine adverse effects of omeprazole. *BMJ* 1992; **305:** 451–2.
2. Carvajal A, *et al*. Gynaecomastia associated with proton pump inhibitors: a case series from the Spanish Pharmacovigilance System. *Drug Safety* 2007; **30:** 527–31.

Effects on the eyes. Visual disturbances associated with the use of omeprazole have included 6 cases of irreversible blindness or visual impairment in severely ill patients given the drug intravenously, and 13 cases of visual disturbances associated with oral use.[1] As a result of concern about these effects the availability of intravenous omeprazole was restricted in Germany; however, the consensus appears to be that a causal link has not been established. Suggestions that visual (and also auditory[2]) impairment could follow drug-induced vasculitis[2-4] appear to be contentious.[1,5-7] A cohort study involving 140 128 patients given antisecretory therapy, 33 988 of whom received omeprazole, found no evidence that any of the drugs used was associated with a major increase in risk of vascular or inflammatory disorders of the eye;[8] however, the statistical power of this study was not high.[9]

1. Creutzfeldt WC, Blum AL. Safety of omeprazole. *Lancet* 1994; **343:** 1098.
2. Schönhöfer PS. Intravenous omeprazole and blindness. *Lancet* 1994; **343:** 665.

3. Schönhöfer PS. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343:** 1369–70.
4. Schönhöfer PS, *et al*. Ocular damage associated with proton pump inhibitors. *BMJ* 1997; **314:** 1805.
5. Colin-Jones D. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343:** 1369.
6. Lessell S. Omeprazole and ocular damage. *BMJ* 1998; **316:** 67.
7. Sachs G. Omeprazole and ocular damage. *BMJ* 1998; **316:** 67–8.
8. García Rodríguez LA, *et al*. A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.
9. Merlo J, Ranstam J. Ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1997; **43:** 449.

Effects on the gastrointestinal tract. Treatment with a proton pump inhibitor has been associated with rebound acid hypersecretion on withdrawal. In healthy subjects without gastric acid-related disease or symptoms, withdrawal of oral esomeprazole after 8 weeks treatment induced acid-related symptoms such as heartburn, acid regurgitation, and dyspepsia.[1]

1. Reimer C, *et al*. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009; **137:** 80–7.

Effects on the kidneys. A systematic review of proton pump inhibitor-associated interstitial nephritis included 47 cases with omeprazole, 6 with pantoprazole, 3 with esomeprazole, 2 with lansoprazole, and 2 with rabeprazole. Although there was insufficient evidence to conclude that proton pump inhibitors caused this reaction, there was a low-prevalence association between their use and the development of interstitial nephritis.[1]

A 2011 report by the Australian Therapeutic Goods Administration[2] stated that acute interstitial nephritis should be considered a class effect of proton pump inhibitors. There have been reports associated with all the proton pump inhibitors, although the incidence is unknown and may vary between individual drugs. Patients had usually presented with non-specific symptoms such as fever, anorexia, weight loss, fatigue, nausea, and vomiting; pyuria, proteinuria, and/or haematuria may also be noted. In some reports[3,4] of interstitial nephritis with omeprazole the condition was associated with rash and eosinophilia, and an allergic mechanism has been postulated.[4]

1. Sierra F, *et al*. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther* 2007; **26:** 545–53.
2. Anonymous. Proton pump inhibitors and acute interstitial nephritis. *Aust Prescriber* 2011; **34:** 190. Also available at: http://www.tga.gov.au/pdf/msu-2011-06.pdf (accessed 10/09/13)
3. Ruffenach SJ, *et al*. Acute interstitial nephritis due to omeprazole. *Am J Med* 1992; **93:** 472–3.
4. Christensen PB, *et al*. Renal failure after omeprazole. *Lancet* 1993; **341:** 55.

Effects on the liver. Raised liver enzymes have occurred with omeprazole and other proton pump inhibitors, and there have been isolated cases of hepatotoxicity. For a study comparing the incidence of acute liver injury in patients receiving omeprazole or histamine H_2-antagonists, see Cimetidine, p. 1829.3.

References.

1. Jochem V, *et al*. Fulminant hepatic failure related to omeprazole. *Am J Gastroenterol* 1992; **87:** 523–5.
2. Kourg SI, *et al*. Omeprazole and the development of acute hepatitis. *Eur J Emerg Med* 1998; **5:** 467–9.

Effects on the musculoskeletal system. Progressive muscular weakness suggestive of *myopathy* developed in a 78-year-old patient given oral omeprazole.[1] After 4 weeks of treatment the patient required assistance in walking and rising from squatting. Weakness resolved on withdrawal of the drug, but returned on rechallenge. Acute myopathy has also been reported after a single infusion of omeprazole.[2] Analysis of the WHO adverse drug reaction database in March 2005 revealed 868 reports associating proton pump inhibitors with *myalgia*, of which 292 cases had symptoms indicative of muscle disorders including *polymyositis* and *rhabdomyolysis*.[3] Reports implicated omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole, and it was suggested that myopathy was probably a class effect. The mechanism might involve induction of auto-immune antibodies.

A report of 5 cases of *arthralgia*, sometimes associated with swelling of the affected joints, in patients receiving omeprazole,[4] also noted that some reported cases of omeprazole-associated headache were accompanied by arthralgia or myalgia. In another case[5] arthralgia in a patient with a hereditary myopathy receiving omeprazole appeared to represent one aspect of a drug-induced *lupus* syndrome, being accompanied by malaise, fever, Raynaud's phenomenon, raised antinuclear antibody titres, and anticardiolipin and antihistone antibodies. Symptoms resolved on withdrawal of the drug.

A case of *eosinophilia* and myalgia related to lansoprazole treatment has been reported.[6]

There has also been a report of 2 cases of acute *gout* associated with omeprazole;[7] in one patient symptoms, which resolved on withdrawal, recurred on rechallenge. However, case control studies have failed to show an increased risk of polyarthralgia[8] or gout[9] associated with omeprazole use.

An FDA review[10] found an increased risk of *fractures* of the hip, wrist, or spine in 6 out of 7 epidemiological studies, in which patients took proton pump inhibitors for 1 to 12 years; the one study that did not find an association limited the study population to those without major risk factors for fracture. Patients in most studies were 50 years of age or older, and the increased risk was mainly in this age group, with treatment for one year or more. Two studies reported an increase in fractures with higher doses, and 2 reported an increase with longer duration of use. These data suggest patients taking proton pump inhibitors may be at an increased risk of fractures. However, factors that might influence this conclusion such as history of osteoporosis, smoking status, alcohol use, and BMI cannot be accounted for in epidemiological studies and 3 studies found no consistent association between chronic proton pump inhibitor use and bone mineral density; it is therefore unclear if proton pump inhibitor use causes an increased risk of fractures. A subsequent meta-analysis[11] of 11 observational studies (including 6 of the studies in the above FDA review) found that proton pump inhibitors modestly increased the risk of hip, spine, and fractures at any site. The MHRA[12] has also reported that meta-analyses of epidemiological studies suggest the risk of fracture is increased by 10 to 40% above baseline, although the studies varied in the extent to which they adjusted for confounders. It has been suggested that calcium malabsorption secondary to acid suppression may explain the association.[13]

1. Garrote FJ, *et al*. Subacute myopathy during omeprazole therapy. *Lancet* 1992; **340:** 672.
2. Tuccori M, *et al*. Acute severe myopathy following a single infusion of omeprazole. *Ann Pharmacother* 2006; **40:** 352–3.
3. Clark DWJ, Strandell J. Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol* 2006; **62:** 473–9.
4. Beutler M, *et al*. Arthralgias and omeprazole. *BMJ* 1994; **309:** 1620.
5. Sivakumar K, Dalakas MC. Autoimmune syndrome induced by omeprazole. *Lancet* 1994; **344:** 619–20.
6. Smith JD, *et al*. Possible lansoprazole-induced eosinophilic syndrome. *Ann Pharmacother* 1998; **32:** 196–200.
7. Kraus A, Flores-Suárez LF. Acute gout associated with omeprazole. *Lancet* 1995; **345:** 461–2.
8. Meier CR, Jick H. Omeprazole, H_2 blockers, and polyarthralgia: case-control study. *BMJ* 1997; **315:** 1283.
9. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br J Clin Pharmacol* 1997; **44:** 175–8.
10. FDA. FDA drug safety communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors (issued 25th May, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm (accessed 26/09/11)
11. Yu EW, *et al*. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med* 2011; **124:** 519–26.
12. MHRA. Proton pump inhibitors in long-term use: recent epidemiological evidence of increased risk of fracture. *Drug Saf Update* 2012; **5** 9: A2. Also available at: http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con149785.pdf (accessed 10/09/13)
13. Yang Y-X, *et al*. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; **296:** 2947–53. Correction. *ibid*. 2007; **297:** 470.

Effects on the nervous system. Ataxia has been reported in a patient given omeprazole;[1] symptoms resolved on stopping the drug. A patient given rabeprazole developed marked anxiety with panic attacks, episodic night terrors, confusion, and attention deficit.[2] Her symptoms resolved 2 days after stopping therapy. A month later, she was given esomeprazole, with no adverse neuropsychiatric symptoms. The authors hypothesised that rabeprazole use had resulted in significantly greater plasma gastrin concentrations than esomeprazole, which may have affected gastrin receptors in the brain.

1. Varona L, *et al*. Gait ataxia during omeprazole therapy. *Ann Pharmacother* 1996; **30:** 192.
2. Polimeni G, *et al*. Rabeprazole and psychiatric symptoms. *Ann Pharmacother* 2007; **41:** 1315–17.

Effects on the respiratory system. An intractable, dry, non-productive cough started abruptly in a 42-year-old non-smoker given omeprazole for gastro-oesophageal reflux disease (GORD). The cough was initially thought to be related to the GORD and treatment was continued for 4 months, without any cessation in the cough. Omeprazole was stopped, and the cough ceased abruptly, with no recurrence during a 2-year follow-up.[1]

For discussion of a possible increased risk of respiratory infection and pneumonia in patients taking proton pump inhibitors see Infection, p. 1870.1.

1. Howaizi M, Delafosse C. Omeprazole-induced intractable cough. *Ann Pharmacother* 2003; **37:** 1607–9.

Effects on the skin. An extensive blistering erythematous rash in an elderly woman given omeprazole[1] was characteristic of acute disseminated epidermal necrosis. The UK CSM had received 223 reports of cutaneous reactions to omeprazole up to August 1992, including 6 of erythema multiforme, but none of this severity. Other severe reactions that have subsequently been reported include a toxic bullous skin reaction,[2] exfoliative dermatitis,[3,4] erythema multiforme,[4] toxic erythema,[4] and dermatomyositis.[5] One patient developed exfoliative dermatitis with both omeprazole and lansoprazole.[4] The authors of this report noted that by January 1998 a total of 1296 skin reactions to omeprazole, 500 to lansoprazole, and 44 to pantoprazole, had been reported to the CSM. Most were non-specific rashes, pruritus, urticaria, erythematous rashes, and photosensitive eruptions. A lichenoid reaction that occurred in a patient taking omeprazole cleared after ceasing the drug, but recurred during treatment with both lansoprazole and pantoprazole.[6] Proton pump inhibitors, including esomeprazole, have been reported to worsen vitiligo.[7]

For a report of urticaria and angioedema possibly associated with the formulation of omeprazole see Hypersensitivity, p. 1870.1. For the association of rash with interstitial nephritis, see Effects on the Kidneys, above.

1. Cox NH. Acute disseminated epidermal necrosis due to omeprazole. *Lancet* 1992; **340:** 857.
2. Stenier C, *et al*. Bullous skin reaction induced by omeprazole. *Br J Dermatol* 1995; **133:** 343–4.
3. Epelde Gonzalo FD, *et al*. Exfoliative dermatitis related to omeprazole. *Ann Pharmacother* 1995; **29:** 82–3.
4. Cockayne SE, *et al*. Severe erythrodermic reactions to the proton pump inhibitors omeprazole and lansoprazole. *Br J Dermatol* 1999; **141:** 173–5.
5. Pan Y, *et al*. Omeprazole-induced dermatomyositis. *Br J Dermatol* 2006; **154:** 557–8.
6. Bong JL, *et al*. Lichenoid drug eruption with proton pump inhibitors. *BMJ* 2000; **320:** 283.
7. Schallreuter KU, Rokos H. From the bench to the bedside: proton pump inhibitors can worsen vitiligo. *Br J Dermatol* 2007; **156:** 1371–3.

Fever. Fever, associated with severe myalgia and headache, was seen in a 64-year-old man on 2 occasions, several hours after taking a dose of esomeprazole.[1] Although it was suggested[2] that the patient's hyperpyrexia was due to a hypersensitivity reaction, the authors argued[3] that esomeprazole may have interfered with the hypothalamic regulatory centres of body temperature.[1,3]

1. Grattagliano I, *et al*. Esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 757–60.
2. Su SS, *et al*. Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 1764.
3. Grattagliano I. Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 1765.

Gastrointestinal tumours. Early toxicological studies in *rats* given high doses of omeprazole over 2 years identified carcinoid tumours of the gastric mucosa associated with complete block of gastric acid secretion leading to *hypergastrinaemia and hyperplasia of enterochromaffin-like cells*.[1] This has been the main issue concerning the safety of omeprazole and other proton pump inhibitors and initially led to restrictions in use and duration of treatment. A drug manufacturer, *Glaxo*, developed a new test to detect genotoxicity of antisecretory drugs which indicated that a genotoxic effect of omeprazole could not be discounted.[2] This study was heavily criticised; more established genotoxicity tests have been reported to be negative for omeprazole,[3-5] and other groups have not been able to replicate the findings with the new test.[6] The lowest doses at which *Glaxo* found[2] a genotoxic effect of omeprazole were 10 to 20 mg/kg and the clinical significance of their results was questioned.[3] Long-term studies of omeprazole in patients with Zollinger-Ellison syndrome have found no increase in fasting serum-gastrin concentrations and no evidence of gastric carcinoid tumours.[7,8] For mention of the risk of proton pump inhibitors delaying the diagnosis of gastric carcinoma, see under Precautions, p. 1870.2. Hypergastrinaemia can occur with both short- and long-term omeprazole therapy,[9] and may be higher in patients with *Helicobacter pylori* infection.[10,11] Patients who had *H. pylori* eradicated before long-term omeprazole treatment had lower gastrin concentrations than those who did not, since *H. pylori* eradication reduced the pretreatment gastrin concentrations.[12]

H. pylori is also a cause of *atrophic gastritis*, another risk factor for stomach cancer, and one study found that omeprazole increased the risk of atrophic gastritis in *H. pylori*-positive patients with gastro-oesophageal reflux disease.[13] However, the results of this study require confirmation since it was nonrandomised and retrospective. Nevertheless, some have suggested that it may be appropriate to eradicate *H. pylori* before long-term treatment with a proton pump inhibitor.[12,13] Conversely, there is some evidence that *H. pylori* may be protective in gastro-oesophageal reflux disease.[14]

There has been a report of *gastric polyps* developing in 3 of 8 patients after receiving omeprazole 20 or 40 mg daily for one year.[15] In a subsequent report it was noted that these omeprazole-induced fundic gland polyps had remained asymptomatic and non-malignant for up to five years after their onset.[16]

The possible association between acid suppressing drugs and risk of gastric cancer has been studied (see also Cimetidine, under Carcinogenicity, p. 1828.3). A small increase in the risk of gastric cancer has been reported with the use of proton pump inhibitors, although the authors of this case control study suggested that confounding by indication was the most likely explanation.[17]

Further long-term studies of omeprazole may be needed before a realistic risk assessment can be made.

1. Ekman L, *et al*. Toxicological studies on omeprazole. *Scand J Gastroenterol* 1985; **20** (suppl 108): 53–69.
2. Burlinson B, *et al*. Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; **335:** 419.
3. Ekman L, *et al*. Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; **335:** 419–20.
4. Wright NA, Goodlad RA. Omeprazole and genotoxicity. *Lancet* 1990; **335:** 909–10.
5. Helander HF, *et al*. Omeprazole and genotoxicity. *Lancet* 1990; **335:** 910–11.
6. Goodlad RA. Acid suppression and claims of genotoxicity: what have we learned? *Drug Safety* 1994; **10:** 413–19.
7. Lloyd-Davies KA, *et al*. Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. *Aliment Pharmacol Ther* 1988; **2:** 13–32.
8. Maton PN, *et al*. Long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. *Gastroenterology* 1989; **97:** 827–36.
9. Koop H, *et al*. Serum gastrin levels during long-term omeprazole treatment. *Aliment Pharmacol Ther* 1990; **4:** 131–8.
10. Sanduleanu S, *et al*. Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. *Aliment Pharmacol Ther* 1999; **13:** 145–53.
11. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. *Gut* 2006; **55:** 1217–21.
12. El-Nujumi A, *et al*. Eradicating Helicobacter pylori reduces hypergastrinaemia during long term omeprazole treatment. *Gut* 1998; **42:** 159–65.
13. Kuipers EJ, *et al*. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996; **334:** 1018–22.
14. Labenz J, Malfertheiner P. Helicobacter pylori in gastro-oesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997; **41:** 277–80.
15. Graham JR. Gastric polyposis: onset during long-term therapy with omeprazole. *Med J Aust* 1992; **157:** 287–8.
16. Graham JR. Gastric acne: omeprazole-induced fundic gland polyposis. *Med J Aust* 1998; **168:** 93.
17. Tamim H, *et al*. Association between use of acid-suppressive drugs and risk of gastric cancer: a nested case-control study. *Drug Safety* 2008; **31:** 675–84.

Hypersensitivity. Cases of anaphylactic reactions after treatment with omeprazole, lansoprazole, and pantoprazole, have been reported in the literature and to WHO.[1] Cross-sensitivity to pantoprazole was reported[2] on skin-testing in 4 of 9 patients sensitive to omeprazole; oral challenge tests with pantoprazole in 3 patients, 2 of whom were negative on skin testing, produced pruritus and urticaria in all 3. However, none of the patients had a reaction to skin tests with lansoprazole, and 8 of the 9 tolerated oral challenge with lansoprazole without problems; the other developed widespread urticaria one hour after a therapeutic dose was reached.

Urticaria, facial angioedema, and bronchospasm in a patient given omeprazole capsules did not recur when the patient was given omeprazole granules and the reaction might have been precipitated by the ingredients of the capsule shell.[3]

See also under Effects on the Kidney and Effects on the Musculoskeletal System, p. 1869.1.

1. Natsch S, *et al*. Anaphylactic reactions to proton-pump inhibitors. *Ann Pharmacother* 2000; **34:** 474–6.
2. Lobera T, *et al*. Nine cases of omeprazole allergy: cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2009; **19:** 57–60.
3. Haeney MR. Angio-oedema and urticaria associated with omeprazole. *BMJ* 1992; **305:** 870.

Infection. Gastric-acid suppressing drugs such as proton pump inhibitors and H_2-antagonists have been linked to an increased risk of infection. A systematic review[1] found an increased risk of enteric infections such as *Salmonella, Campylobacter, Shigella,* or *Clostridium difficile* in patients taking acid suppressing drugs, although there was considerable heterogeneity between studies. Increased rates of sepsis[2] and necrotising enterocolitis[3] have also been reported in infants given H_2-antagonists. It has been suggested that the increased rate of infection could be due to the rise in gastric pH after acid suppressive treatment, resulting in increased microbial colonisation of the upper gastrointestinal tract.[1-3]

Results from studies into the risk of developing community-acquired pneumonia with the use of acid suppressants have been inconsistent. Increased rates of pneumonia have been reported with current use of acid suppressants in case-control and cohort studies,[4-7] whereas an industry-sponsored analysis of pooled adverse effect data on esomeprazole did not support an association between its use and respiratory-tract infections, including pneumonia.[8] A case control study found no overall increase in the risk of community-acquired pneumonia with current use of proton pump inhibitors, although unexpectedly, an increased risk was noted when proton pump inhibitors had been started in the previous month.[9] A systematic review also failed to find an association between use of proton pump inhibitors (esomeprazole, rabeprazole, pantoprazole and omeprazole) and respiratory infections, although it noted a trend towards an association.[10]

1. Leonard J, *et al*. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; **102:** 2047–56.
2. Bianconi S, *et al*. Ranitidine and late-onset sepsis in the neonatal intensive care unit. *J Perinat Med* 2007; **35:** 147–50.
3. Guillet R, *et al*. National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; **117:** e137–e142. Also available at: http://pediatrics.aappublications.org/cgi/reprint/117/2/e137 (accessed 09/04/08)
4. Laheij RJF, *et al*. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292:** 1955–60.
5. Canani RB, *et al*. Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; **117:** e817–e820. Available at: http://pediatrics.aappublications.org/cgi/reprint/117/5/e817 (accessed 01/04/09)
6. Herzig SJ, *et al*. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; **301:** 2120–8.
7. Eurich DT, *et al*. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med* 2010; **123:** 47–53.
8. Estborn L, Joelson S. Occurrence of community-acquired respiratory tract infection in patients receiving esomeprazole: retrospective analysis of adverse events in 31 clinical trials. *Drug Safety* 2008; **31:** 627–36.
9. Sarkar M, *et al*. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med* 2008; **149:** 391–8.
10. Sultan N, *et al*. Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. *Can J Gastroenterol* 2008; **22:** 761–6.

Lupus syndrome. For a report of drug-induced lupus syndrome associated with omeprazole therapy, see Effects on the Musculoskeletal System, p. 1869.1.

Malabsorption. Omeprazole has been reported to result in a substantial reduction in *cyanocobalamin* (vitamin B_{12}) absorption,[1] probably related to the increase in gastric pH, and indicating a potential risk of vitamin deficiency with long-term therapy.[2] UK licensed product information recommends that severely ill children, who may have borderline body stores of cyanocobalamin, should have serum vitamin B_{12} concentrations monitored if they require long-term therapy. Omeprazole has also been reported to impair the bioavailability of dietary *vitamin C*.[3] *Fat* malabsorption, secondary to increased deconjugation of bile acids caused by bacterial overgrowth in the jejunum, has also been reported with omeprazole treatment.[4] For the suggestion that proton pump inhibitors can cause *calcium* malabsorption, see Effects on the Musculoskeletal System, p. 1869.1.

1. Marcuard SP, *et al*. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B_{12}). *Ann Intern Med* 1994; **120:** 211–15.
2. Termanini B, *et al*. Effect of long-term gastric acid suppressive therapy on serum vitamin B_{12} levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998; **104:** 422–30.
3. Henry EB, *et al*. Proton pump inhibitors reduce the bioavailability of dietary vitamin C. *Aliment Pharmacol Ther* 2005; **22:** 539–45.
4. Shindo K, *et al*. Omeprazole induces altered bile acid metabolism. *Gut* 1998; **42:** 266–71.

Overdosage. A report of 2 cases of overdosage with omeprazole.[1] The major clinical features were drowsiness, headache (possibly due to a metabolite), and tachycardia. Both patients recovered uneventfully without specific treatment.

1. Ferner RE, Allison TR. Omeprazole overdose. *Hum Exp Toxicol* 1993; **12:** 541–2.

Precautions

Before giving omeprazole or other proton pump inhibitors to patients with gastric ulcers the possibility of malignancy should be excluded since these drugs may mask symptoms and delay diagnosis. Omeprazole and other proton pump inhibitors should be used with caution in hepatic impairment and dose adjustment may be required.

Breast feeding. Omeprazole is excreted in human milk. After a single oral dose, peak concentrations of omeprazole in breast milk were reported to be less than 7% of the peak serum concentration.[1]

1. Marshall JK, *et al*. Omeprazole for refractory gastroesophageal reflux disease during pregnancy and lactation. *Can J Gastroenterol* 1998; **12:** 225–7.

Gastric carcinoma. Proton pump inhibitors relieve dyspeptic symptoms associated with gastric carcinoma and can therefore delay its diagnosis. In addition, there is some evidence that they may also endoscopically 'heal' early gastric carcinoma so that the diagnosis is missed.[1] Consequently, some commentators recommend that proton pump inhibitors should not be prescribed for symptom control before endoscopy in patients at risk for gastric carcinoma.[2]

1. Wayman J, *et al*. The response of early gastric cancer to proton-pump inhibitors. *N Engl J Med* 1998; **338:** 1924–5.
2. Griffin SM, Raimes SA. Proton pump inhibitors may mask early gastric cancer: dyspeptic patients over 45 should undergo endoscopy before these drugs are started. *BMJ* 1998; **317:** 1606–7.

Helicobacter infection. Treatment with proton pump inhibitors may cause false-negative results in the urea breath test for *Helicobacter pylori* infection. In one study in patients with *H. pylori* infection, lansoprazole 30 mg daily for 4 weeks caused 33% of patients to have negative urea breath tests.[1] The breath test became positive again in all patients within 2 weeks of stopping lansoprazole therapy. In a similar study, 52% of patients had negative urea breath tests for *H. pylori* while receiving omeprazole 20 mg daily, and the breath test became positive again in all patients within 2 to 6 days of stopping treatment.[2] The manufacturers of the urea breath test for *H. pylori* recommend that it should not be performed for at least 2 weeks after stopping treatment with an antisecretory drug.

For a discussion of the link between proton pump inhibitors, *H. pylori*, and gastritis, see under Gastrointestinal Tumours p. 1869.3.

1. Laine L, *et al*. Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. *Ann Intern Med* 1998; **129:** 547–50.
2. Connor SJ, *et al*. The effect of dosing with omeprazole on the accuracy of the ^{13}C-urea breath test in Helicobacter pylori-infected subjects. *Aliment Pharmacol Ther* 1999; **13:** 1287–93.

Hepatic impairment. In patients with cirrhosis an increase in omeprazole bioavailability, and elimination half-life has been reported.[1] For dosage adjustment in hepatic impairment see Administration in Hepatic Impairment, p. 1868.1.

1. Andersson T, *et al*. Pharmacokinetics of [^{14}C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; **24:** 71–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies omeprazole as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Pregnancy. Proton pump inhibitors are not generally licensed for use during pregnancy (although the UK has licensed omeprazole for such use), but a meta-analysis[1] of 5 studies of exposure to proton pump inhibitors during the first trimester, involving 593 exposed infants, found the relative risk of major abnormalities associated with such exposure to be only 1.18, with a 95% confidence interval ranging from 0.72 to 1.94. Meta-analysis of exposures to omeprazole (from 4 studies only) gave a relative risk of 1.05 (95% confidence interval 0.59 to 1.85). It was concluded that exposure to proton pump inhibitors, and omeprazole in particular, did not pose an important teratogenic risk. A retrospective epidemiological study of data from the Swedish Medical Birth Registry, which identified 955 exposed infants, also found no evidence of significant risk after exposure to omeprazole during pregnancy,[2] a finding confirmed by a subsequent meta-analysis.[3] Additionally, a cohort study[4] into the use of proton pump inhibitors in the first trimester did not find an increased risk of major birth defects.

1. Nikfar S, *et al*. Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002; **47:** 1526–9.
2. Källén BAJ. Use of omeprazole during pregnancy–no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001; **96:** 63–8.
3. Gill SK, *et al*. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol* 2009; **104:** 1541–5.
4. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med* 2010; **363:** 2114–23.

Interactions

Omeprazole and other proton pump inhibitors are metabolised by the cytochrome P450 system, mainly by isoenzyme CYP2C19, and to a smaller extent by CYP3A4. Inhibitors or inducers of these isoenzymes may affect exposure to omeprazole and other proton pump inhibitors. In turn, proton pump inhibitors may alter the metabolism of some drugs metabolised by these enzymes. Omeprazole also inhibits CYP2C19 and may prolong the elimination of cilostazol, diazepam, phenytoin, and warfarin (but see below). Omeprazole and other proton pump inhibitors can affect the absorption of drugs such as dasatinib, erlotinib, posaconazole, ketoconazole, and itraconazole, whose absorption is dependent on an acid gastric pH. With voriconazole, the plasma concentration of both drugs may be increased (for further information, see p. 1871.1). Other proton pump inhibitors may be similarly affected by voriconazole. Omeprazole and other proton pump inhibitors should not be used with atazanavir or nelfinavir, as it substantially reduces exposure to the HIV-protease inhibitor.

The decrease in gastric activity with proton pump inhibitors may give false positive results in diagnostic investigations for neuroendocrine tumours and treatment should be stopped before such investigations.

Omeprazole is mainly metabolised by the cytochrome P450 isoenzyme CYP2C19 (see Metabolism, p. 1871.2) and therefore may interact with diazepam (see under Gastrointestinal Drugs, p. 1069.3). Some metabolism of phenytoin (see p. 544.3), tolbutamide, and the *R*-enantiomer of warfarin (see p. 1534.1) also takes place by CYP2C19, but the effects seen have been minor.[1] Although some induction of CYP1A2, which metabolises caffeine and

theophylline (p. 1236.1), has been reported this does not appear to be clinically significant.[2] While some consider the effect of omeprazole on CYP3A4 activity to be insignificant,[3] others have noted increasing evidence that competitive inhibition of intestinal CYP3A4 by omeprazole may affect the first-pass metabolism of several drugs.[4] A review concluded that, while omeprazole and possibly esomeprazole have a considerable potential for drug interactions, lansoprazole, pantoprazole and rabeprazole are associated with a lower incidence of drug interactions.[4]

For a study *in vitro* suggesting that omeprazole affected CYP3A4 metabolism of tacrolimus, see under Interactions of Tacrolimus, p. 1972.3. For more on the effect of proton pump inhibitors on tacrolimus, see Gastrointestinal Drugs, p. 1973.3. Proton pump inhibitors, including omeprazole, may also affect exposure to mycophenolate, see p. 1965.1.

For reference to the possibility of enhanced digoxin absorption with omeprazole, see p. 1357.3. For a study suggesting that omeprazole reduces the absorption of cyanocobalamin and vitamin C, see Malabsorption, p. 1870.2, and for its effect on calcium absorption see p. 1825.1. For reference to possible interactions between methotrexate and omeprazole, see p. 828.1.

1. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996; **31:** 9–28.
2. Rizzo N, *et al*. Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions. *Eur J Clin Pharmacol* 1996; **49:** 491–5.
3. Tateishi T, *et al*. Omeprazole does not affect measured CYP3A4 activity using the erythromycin breath test. *Br J Clin Pharmacol* 1995; **40:** 411–12.
4. Blume H, *et al*. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Safety* 2006; **29:** 769–84.

Clarithromycin. Studies in healthy subjects have indicated that use of omeprazole with clarithromycin results in an approximate 30% increase in peak plasma concentrations of omeprazole, and an increase in its mean half-life from 1.2 to 1.6 hours.[1] At the same time, plasma concentrations of clarithromycin were also modestly increased, as were local concentrations in gastric tissue and mucus.[1] Clarithromycin inhibits[2] the metabolism of omeprazole mediated by the cytochrome P450 isoenzyme CYP3A4. The interaction may contribute to the benefits of combined therapy for *Helicobacter pylori* infection.

1. Gustavson LE, *et al*. Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; **39:** 2078–83.
2. Furuta T, *et al*. Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* 1999; **66:** 265–74.

Clopidogrel. For recommendations that the use of proton pump inhibitors such as omeprazole with clopidogrel should be discouraged, see p. 1344.2.

Fluvoxamine. Omeprazole and other proton pump inhibitors are metabolised mainly by cytochrome P450 isoenzyme CYP2C19, which shows genetically determined polymorphism, yielding extensive metabolisers and poor metabolisers. Fluvoxamine increased exposure to omeprazole, lansoprazole, and rabeprazole in patients who were extensive metabolisers, but had no effect on pharmacokinetic parameters in poor metabolisers.[1-3] Dose reductions may need to be considered in patients treated with fluvoxamine and proton pump inhibitors.

1. Yasui-Furukori N, *et al*. Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol* 2004; **57:** 487–94.
2. Yasui-Furukori N, *et al*. Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. *J Clin Pharmacol* 2004; **44:** 1223–9.
3. Uno T, *et al*. Different effects of fluvoxamine on rabeprazole pharmacokinetics in relation to CYP2C19 genotype status. *Br J Clin Pharmacol* 2006; **61:** 309–14.

Voriconazole. When omeprazole is given with voriconazole, exposure to both drugs is increased. UK licensed product information for omeprazole states that a dose adjustment of omeprazole is not routinely indicated, unless patients have severe hepatic impairment and long-term therapy is indicated. However, UK licensed product information for voriconazole states that, while no dosage adjustment is considered necessary for voriconazole, when patients already receiving omeprazole are started on voriconazole, the dose of omeprazole should be halved. Other proton pump inhibitors may be similarly affected by voriconazole.

Pharmacokinetics

Omeprazole is rapidly but variably absorbed after oral doses. Absorption is not significantly affected by food. Omeprazole is acid-labile and the pharmacokinetics of the various formulations developed to improve oral bioavailability may vary. The absorption of omeprazole also appears to be dose-dependent; increasing the dosage above 40 mg has been reported to increase the plasma concentrations in a non-linear fashion because of saturable first-pass hepatic metabolism. In addition, bioavailability is higher after long-term use.

Bioavailability of omeprazole may be increased in elderly patients, in some ethnic groups such as Chinese, and in patients with hepatic impairment, but is not markedly affected in patients with renal impairment.

On absorption, omeprazole is almost completely metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2C19 to form hydroxy-omeprazole, and to a small extent by CYP3A4 to form omeprazole sulfone. The metabolites are inactive, and are excreted mostly in the urine and to a lesser extent in bile. The elimination half-life from plasma is reported to be about 0.5 to 3 hours. Omeprazole is about 95% bound to plasma proteins.

References.

1. Andersson T, *et al*. Pharmacokinetics of various single intravenous and oral doses of omeprazole. *Eur J Clin Pharmacol* 1990; **39:** 195–7.
2. Andersson T, Regårdh C-G. Pharmacokinetics of omeprazole and metabolites following single intravenous and oral doses of 40 and 80 mg. *Drug Invest* 1990; **2:** 255–63.
3. Ching MS, *et al*. Oral bioavailability of omeprazole before and after chronic therapy in patients with duodenal ulcer. *Br J Clin Pharmacol* 1991; **31:** 166–70.
4. Landahl S, *et al*. Pharmacokinetic study of omeprazole in elderly healthy volunteers. *Clin Pharmacokinet* 1992; **23:** 469–76.
5. Andersson T, *et al*. Pharmacokinetics of [^{14}C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; **24:** 71–8.
6. Jacqz-Aigrain E, *et al*. Pharmacokinetics of intravenous omeprazole in children. *Eur J Clin Pharmacol* 1994; **47:** 181–5.
7. Litalien C, *et al*. Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* 2005; **44:** 441–66.
8. Fock KM, *et al*. Proton pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? *Clin Pharmacokinet* 2008; **47:** 1–6.

Metabolism. The major enzyme involved in omeprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are poor metabolisers of omeprazole. This occurs in about 3% of Caucasians and 15% of Chinese, Japanese, and Koreans. These individuals have markedly higher plasma concentrations of omeprazole, and they may require dosage adjustment. Some omeprazole is metabolised by CYP3A4, and some by CYP2D6 to form desmethylomeprazole.

References.

1. Andersson T, *et al*. Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993; **36:** 521–30.
2. Caraco Y, *et al*. Ethnic and genetic determinants of omeprazole disposition and effect. *Clin Pharmacol Ther* 1996; **60:** 157–67.
3. Karam WG, *et al*. Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos* 1996; **24:** 1081–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acimed; Aziatop; Brux; Buscasan; Danlox; Faboacid Plus; Fabrazol; Fendiprazol; Gastec; Gastroprazol; Gastrotem; Klomeprax; Lafeprazol; Losec; Lyncis 24; Mucoxol; Nexoprazol; Oblisec; Omefar; Omeprasec; Pepticus; Pravil; Procelac; Prysma; Regulacid; Sedigastrol; Stomacine; Timezol; Ulcozol; Ulsanol†; Veroprazol; Zoltenk; ***Austral.***: Acimax; Losec; Maxor; Meprazol; Omepral; Ozmep; Pemzo; Probitor; ***Austria***: Gastrobene; Gastroplex†; Losec; Omec; Omepralan; ***Belg.***: Docomepra†; Logastric†; Losec; Sedacid; ***Braz.***: Estomepe; Eupept; Gasec†; Gaspiren; Gastrium; Gastrocimet; Gastrozol; Klispel; Loprazol; Losec; Lozeprel; Meprazan; Mesopran; Neoprazol; Neprazol; Omegastrol; Omenax; Omep; Omepramed; Omeprazin; Omeprotec; Omezolon; Omoprel; Oprazon; Peprazol; Pepsicaps†; Prazolex; Prazolol; Prazonil†; Ulcefor†; Uniprazol; Victrix; ***Canad.***: Losec; ***Chile***: Lomex; Losec; Micromex; Omeprax; Togran; Ulc-Out; Ulcelac†; Ulcizole; Ulcrux; Zatrol; Zomepral; ***China***: Ai Ni (爱尼); Ao Ke (奥克); Ao Li Ya (奥立雅); Ao Si Tan (奥斯坦); Ao Wei Kang (奥韦康); Aomeizhen (奥美真); Aoqi (奥齐); Aoxikang (奥西康); Haibaike (海百克); Ji Li (吉立); Jin Ao Kang (金奥康); Ke Di Sheng (克迪圣); Kun Li Yu (坤丽雨); Ledi (乐迪); Li Ao Jia (丽奥佳); Li Wei Ting (利韦廷); Losec (洛赛克); Luodan (罗丹); Luokai (洛凯); Novek (礼先); Pi Si Ke (彼司克); Ping Fang Shu (苹芳淑); Ramezol; Sai Ao (赛奥); Shenliyu (绅丽雨); Tianlong Taike (天龙泰克); ***Cz.***: Apo-Ome; Asilar; Gasec; Helicid; Lomac; Losec†; LosecPro; Loseprazol; Omepirex†; Omeprol†; Omolin†; Onprelen; Ortanol; Sinomenorm; Tulzol; Ultop; ***Denm.***: Losec; Omelix†; Omestad; Ortanol; ***Fin.***: Gastrostad; Losec; Omestad; ***Fr.***: Mopral; Mopralpro; Omediprol; Zoltum; ***Ger.***: Antra; Buscogast; Gastracid†; Ome TAD†; Ome-nerton; Ome-Puren†; Ome-Q†; Omebeta; Omedoc†; Omegamma†; OmeHennig†; OmeLich†; Omep†; Ulcozol; Ulnor†; ***Gr.***: Acromon; Alcerelief; Alevior; Assoprol; Belifax; Benzol; Candazol; Comoprazol; Diorium; Efrozin; Elcodrop; Elcofar; Elcontrol; Elibactin; Elkostop; Elkotheran; Eselan; Esopraz; Ezipol; Flusal; Gastronorm; Gertalgin; Gerxus; Glaveral; Inhiplex; Kerlofin; Lanex; Lenar; Lexigor; Lodrec; Lomezec; Loproc; Lordin; Losec; Lozaprin; Lyopraz; Malortil; Meprolen; Nedopron; Novek; Odamesol; Odasol; Ofnimarex; Olark; Omeprol; Omerane; Omezalin; Oprazium; Ortanol; Palser; Penrazol; Pip Acid; Prazolin; Probitor; Rukuz; Rythmogastryl; Sedacid; Sieral; Silato; Sodeprol; Spezato; Ufonitren; Vamac; Veralox; Zolandil; Zolelcon; Zolldenol; Zolmach; ***Hong Kong***: Losec; ***Hung.***: Losec; Ludea; Omegen; Omep; Omeprawin†; Ulzol†; ***India***: Abcid; Acichek; Acidof; Acigone; Aciom; Acitec; Adprazole; Adzole; Atozol; Avizol; Azol; Biocid; Biomac; Brocid; C-Praz; Capcid; Capocid; CG Mez; CGMag; Cinom; Coszol; Coz; Cozep; Cucid; Cuzole; DGR; Diocid; Dorcan; E-Zole; Elome; Elpra; Ezol; Forzole; Hariom; Hocid; Icer; Jotac; Lexcid; Litom; Lokit; Lomac; Lomecid; Lopra; Loress; Losec; Lupome; Menzol; Nilsec; Niszol; Nitpep; Nogacid; Novacid; O-Bit; Ocid; Ocimax; Ocinil; Odizol; Ogestrel; Okacid; Olicap; Olit; Olla-MT; Omag; Omalcer; Omapin; Ombel; Ombest; Omcare; Omcid; Omcure; Ome-PPI; Omecer; Omecid; Omecip; Omecos; Omega; Omegold; Omegord; Omejel; Omel; Omelax; Omen; Omenat; Omep; Omeplus; Omepral; Omepraz; Omepren; Omepromp; Omeraze; Omeris; Omesun; Omesym; Ometab; Omevar; Omey; Omez-FF; Omez; Omezol; Omezole; Omfact; Omicap; Omicas; Omicool; Omig; Omilee; Omind; Omitive; Omizac; Omizol; Omkair; Omlink; Omlo; Ommac; Omnilup; Omore; Ompep; Ompirol; Ompli; Ompraz; Omracap; Omriz; Omsy; Omtec; Omven; Omzee; Onazole; Op-Zole; Opaz; Opel; Opep; Opera; Oraz; Orole; Osec; Oskar; Ospicid; Ossum; OTG; Otto; Ozed; OZL; Ozo-D; Ozo; Ozol; Promisec; Ulzol; ***Indon.***: Contral; Dudencer; Inhipump; Lokev; Loklor†; Losec; Meisec; Norsec; Omevell; OMZ; Onic; Opm; Oprezol; Ozid; Prilos; Prohibit; Promezol; Protop; Pumpitor; Redusec; Regasec; Rindopump; Rocer; Socid; Stomacer; Ulpraz; Ulzol; Zepral; Zeprazol; Zolacap; Zollocid; ***Irl.***: Bentome†; BySec; Davliet†; Kalgriff†; Lopraz; Losamel; Losapol†; Losec; Losepine; Mylcer†; Pugritex; Romep; Sedacid; Tulzol†; Ulcid; ***Israel***: Losec; Omepra; Omepradex; Omeprix; ***Ital.***: Alsidol; Anadir; Antra; Arpezol; Cletus; Ibimezolo; Komezol; Kruxagon; Limnos; Losec; Maricrio; Mepral; Nansen; Omeprazen; Omolin; Protec; Ulcezol; Zaprol; ***Jpn***: Omepral; ***Malaysia***: Gasec; Losec; Medoprazole; Omelon; Omesec; Omez; Omezol; Omezole; Probitor; Risek; Romesec; Zenpro; Zimor; ***Mex.***: Alboz; Aleprozil; Apopraza; Azoran†; Danovag; Domer; Gerdex; Grizol; Haitrax; Hitrax†; Ibax; Ibemiral; Inhibitron; Logazil; Lopram; Losec; Medral; Melet; Mopral; Mornin; Olexin; Omecaps; Ometec; Opramid; Osiren; Ozoken; Panzer; Pastrizol; Pentren; Prazidec; Prazolit; Promezal; Reux; Sarox; Silopral; Solcer; Suifac; Tarzol; Ucetal; Ulsen; Ultizol; Ultromep†; Usaltron; Vulcasid; Zolufen; Zoral; Zulmedx; ***Neth.***: Buscozol; Ipegen; Itomed†; Kruidvat maagzuuremmer Omeprazole; Loprilin; Losec; Losecosan; Moprilic; Novek†; Omolin; Omoquis; Prazigast†; Romisan; ***Norw.***: Losec; ***NZ***: Losec; Omezol; ***Philipp.***: Acifre; Acipres; Aizole; Farmazol; Flazomel; Frazole; Gastriloc; Hovizol; Hycid; Lokit; Lomezek; Lopep; Loprezol; Losec; Megapraz†; Mepracid; Mepralin; Mepraz; Nocid; Omebloc; Omed; Omelon; Omenole; Omepron; Omeptas; Omez; Omizac; Omlek; OMZ; Opehex†; Opraz; Peptisolv; Perazole; Pleom; Plosek; Pramiz; Premio; Prexon; Promesec†; Prosec; Protonix; Puroxel; Risek; Somecid; Sydenprazole; Tansinel; Ulsek; Viprazo; Wilom; Zefxon; Zegacid; Zolmep; Zomep; Zosec; Zyom; ***Pol.***: Agastin; Bioprazol; Gasec; Helicid; Losec; Loseprazol; Notis; Omar†; Ortanol; Polprazol; Prazigast; Prazol; Progastim; Tulzol; Ultop; Ulzol†; ***Port.***: Albosan; Balzoprem; Belmazol; Bloprazol†; Eczop†; Eugastrim; Gasec; Losec; Luzina; Megazol†; Mepraz; Nems; Novek†; Omegrim†; Omepra; Omeratio†; Omerax; Ometon; Omezolan; Prazentol; Prazex; Prazolene; Proclor; Proton; ***Rus.***: Cisagast (Цисагаст); Gastrozol (Гастрозол); Helicid (Хелицид); Helol (Хелол); Lomac (Ломак); Losec (Лосек); Ocid (Оцид); Omecaps (Омекапс); Omez (Омез); Omipix (Омипикс); Omitox (Омитокс); Omizac (Омизак); Pleom (Плеом); Promes (Промез); Romesec (Ромесек); Sopral (Сопрал); Ulcozol (Улкозол); Ultop (Ультоп); Ulzol (Улзол)†; Zerocid (Зероцид); ***S.Afr.***: Altosec; Lokit; Losec; Nozer; Omez; Omiloc†; Ulzec†; ***Singapore***: Gasec; Losec; Ocid; Olit; Omesec; Omezol; Omezole; Omicap; Opizole; Penrazole; Proceptin; Pumpitor; Ramezol; Romesec; Zefxon; Zenpro; Zimor; ***Spain***: Arapride; Audazol; Aulcer; Belmazol; Ceprandal; Dolintol; Elgam†; Emeproton; Gastrimut; Indurgan†; Ipirasa†; Losec; Miol; Norpramin†; Novek; Nuclosina; Omapren; Ompranyt; Parizac; Pepticum; Prazipar†; Prysma; Sanamidol†; Ulceral; Ulcesep; Zimor; ***Swed.***: Losec; Omecat; ***Switz.***: Antra†; Antramups; AntraPro; Omed; Omeprax; Omezol; Oprazol†; ***Thai.***: Airomet; Amnopra; Desec; Dosate; Duogas; Duosolin; Eselan; Eucid; Gaster; Gomec; Lokit; Lomac; Lomicid; Losec; Madiprazole; Meiceral†; Metsec; Miracid; Moprix; Mosec; Nocid; O-Sid; Ocid; Olit†; Omeman; Omepac; Omeprol; Omesec; Omez†; Omezol; Omezole; Omicap†; Omlek; Opramed; Oprazole†; Prazole; Probitor†; Sanosec; Seto-o; Stomec; Ulpracid; Ulprazole; Zecid†; Zefxon; Zigacap; ***Turk.***: Demeprazol; Erbolin; Eselan; Gastromax; Losec; Omegast; Omeprazid; Omeprol; Omesek; Prosek; ***UAE***: Risek; ***UK***: Heartburn Relief; Losec; Mezzopram; Zanprol; ***Ukr.***: Cerol (Церол)†; Gasec (Гасек); Loseprazol (Лосепразол); Omep (Омеп); Omez (Омез); Oprazol (Опразол); Ultop (Ультоп); ***USA***: Prilosec; ***Venez.***: Fordex; Gastronol; Losec; Omebloc; Omevax; Omezul; Parsolen; Probitor; Promezol.

Multi-ingredient Preparations. ***Arg.***: Danlox Rapido; Gastec Rapido; ***Austral.***: Klacid HP 7; Losec Hp 7†; Probitor Hp7; ***Braz.***: Erradic; Omepramix; ***Canad.***: Losec 1-2-3 A; Losec 1-2-3 M; ***India***: Abcid-D; Abcool-D; Acio; Acitec-D; Adprazole-D; Adzole-DM; Atozol-D; Avizol-D; Azinorm O; Azo-O; Bemez-D; Biomac-D; Brozol-D; C-Praz-D; Capcid-D; Capocid-DM; Coöl Zone D; Coszol-D; Coz-D; Cucid-DM; Cuzole-D; Demo D; DGR-Plus; Dic-OM; Diocid-D; Diopra; Domci; Domepraz; Domeway; Domezol; Domizol-DS; Domocid; Domped-OZ; Domperon-O; Dompra; Domsin-O; Domstal-O; Domstal-RD; Domz; Dorcan-D; Drag-D; E-Zole-D; Elpra-D; Emidon-OM; Emopaz-D; Forzole-D; GI Kit; Ginac; GR8; Helibact; Helikit; Helipac; HP Kit; Icer-D; Jotac-D; L-Cot; Lexcid-DM; Litom-D; Lokit-Kit; Lomecid-D; Lopra-D; Lupome-D; Miliom-D; Minisec-AR; Netom-D; Neutral-O; Nitpep-D; Nogacid D; Novacid-D; O & D; O-Bit-DM; Ocid-D; Ocinil-D; Od; Odoman; Ogestrel-D; Okacid D; Olicap-D; Olla-D; Ombel-D; Ombest-D; Omcare-D; Omcure-D;

Omdom; Omecer-D; Omecid-D; Omecid-RD; Omecip-D; Omecos-D; Omeezol-D; Omejel-DM; Omelax-D; Omen-D; Omepraz-HP Kit; Omeraze-D; Omeris-D; Omesun-D; Omesym-D; Omevar-D; Omez Insta; Omez-D; Omfact-D; Omibase-D; Omic-D; Omicas-D; Omicool-D; Omidec; Omidip; Omidom; Omiflux; Omig-DM; Omilee-D; Omitive-D; Omitop-DM; Omitop; Omizol-D; Omkair-D; Omlink-D; Omlo-D; Ommac Plus; Omore-D; Omoxitin; Ompli-D; Ompraz-D; Omprest-D; Omracap-DM; Omriz-D; Omven-D; Omzee-D; Onazole-DP; Onazole-RD; Oned; Onto-D; Op-Zole D; Opaz-DM; Opel-D; Opera-D; Oraz-D; Orole-D; Ospicid-D; Ossum-D; OTC HP Kit; OTG-D; Otto-D; Ozed-D; Ozodom; Ozol-D; Pacidom-O; ***Malaysia***: Pylobact Combi; ***Mex.***: Pridamiral Pack; ***NZ***: Losec Hp7; ***Philipp.***: OAC Hp7†; ***Rus.***: Domstal-O (Домстал-О); Omez D (Омез Д); Pylobact (Пилобакт); ***Ukr.***: Limzer (Лімзер); Omez-D (Омез-Д); Pylobact Neo (Пилобакт Нео); ***USA***: Omeclamox-Pak; Zegerid.

Used as an adjunct in:. ***Arg.***: Dioxaflex Protect; ***Philipp.***: Skelan Protect; ***UK***: Axorid.

Pharmacopoeial Preparations
BP 2014: Gastro-resistant Omeprazole Capsules; Gastro-resistant Omeprazole Tablets; Omeprazole Oral Suspension;
USP 36: Omeprazole Delayed-Release Capsules; Omeprazole Oral Suspension.

Ondansetron *(BAN, rINN)*

GR-38032; Ondansetrón; Ondansétron; Ondansetroni; Ondansetronum; Ондансетрон.

(±)-1,2,3,9-Tetrahydro-9-methyl-3-(2-methylimidazol-1-ylmethyl)-carbazol-4(9*H*)-one.

$C_{18}H_{19}N_3O$=293.4

CAS — 99614-02-5; 116002-70-1.

ATC — A04AA01.

ATC Vet — QA04AA01.

UNII — 4AF302ESOS.

Pharmacopoeias. In *US*.

USP 36: (Ondansetron). A white to off-white powder. Sparingly soluble in water; very soluble in acid solutions. Store in airtight containers. Protect from light.

Ondansetron Hydrochloride

(BANM, USAN, rINNM)

GR-38032F; GR-C507-75; GR-C507/75; Hidrocloruro de ondansetrón; Odanserin; Ondansétron, chlorhydrate d'; Ondansetrón, hidrocloruro de; Ondansetron hydrochlorid; Ondansetronhydroklorid; Ondansetroni hydrochloridum; Ondansetronihydrokloridi; Ondansetrono hidrochloridas; Ondanstroni Hydrochloridum; Ondánszetronhidroklorid; SN-307; Ондансетрона Гидрохлорид.

$C_{18}H_{19}N_3O$,HCl,$2H_2O$=365.9

CAS — 99614-01-4; 103639-04-9.

ATC — A04AA01.

ATC Vet — QA04AA01.

UNII — NMH84OZK2B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Ondansetron Hydrochloride Dihydrate). A white or almost white powder. Sparingly soluble in water and in alcohol; slightly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 36: (Ondansetron Hydrochloride). A white to off-white powder. Sparingly soluble in water and in alcohol; very slightly soluble in acetone, in chloroform, and in ethyl acetate; slightly soluble in dichloromethane and in isopropyl alcohol; soluble in methyl alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Ondansetron hydrochloride and dexamethasone sodium phosphate were not compatible when high concentrations were combined in polypropylene syringes.[1] Lower concentrations (up to 640 micrograms/mL of ondansetron and 400 micrograms/mL of dexamethasone phosphate) were stable in 50 mL containers of infusion fluid for 30 days under refrigeration. Compatibility has been reported for 24 hours in plastic syringes at 4 degrees or 23 degrees with a variety of other drugs,[2] and with several antineoplastics (cytarabine, dacarbazine, doxorubicin, etoposide, or methotrexate) in PVC infusion bags for 48 hours at room temperature.[3]

1. Hagan RL, *et al.* Stability of ondansetron hydrochloride and dexamethasone sodium phosphate in infusion bags and syringes for 32 days. *Am J Health-Syst Pharm* 1996; **53:** 1431–5.
2. Stewart JT, *et al.* Stability of ondansetron hydrochloride and 12 medications in plastic syringes. *Am J Health-Syst Pharm* 1998; **55:** 2630–4.
3. Stewart JT, *et al.* Stability of ondansetron hydrochloride and five antineoplastic medications. *Am J Health-Syst Pharm* 1996; **53:** 1297–1300.

Uses and Administration

Ondansetron is a 5-HT_3 antagonist (5-HT_3-receptor antagonist) with antiemetic activity. It is used in the management of **nausea and vomiting** induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. For the management of nausea and vomiting, and the important role of 5-HT_3 antagonists, see p. 1811.3.

Ondansetron is given by intramuscular or slow intravenous injection or infusion as the hydrochloride, orally as the hydrochloride or base, or rectally as the base. Doses are expressed in terms of the base. Ondansetron hydrochloride 4.99 mg is equivalent to about 4 mg of ondansetron base.

Numerous dosing schedules of ondansetron have been used; some typical examples are cited below.

For *highly emetogenic* **chemotherapy** the following dose schedules appear to be equally effective in *preventing* acute emesis:

- a single dose of 8 mg by slow intravenous or intramuscular injection immediately before treatment

or

- 8 mg by slow intravenous or intramuscular injection immediately before treatment, either followed by a continuous intravenous infusion of 1 mg/hour for up to 24 hours, or by a further two doses of 8 mg two to four hours apart

or

- a single dose of 16 mg given by intravenous infusion over at least 15 minutes immediately before treatment, which can be followed by a further 2 doses of 8 mg by slow intravenous or intramuscular injection four hours apart

or

- 150 micrograms/kg (maximum 16 mg) by intravenous infusion over 15 minutes, beginning 30 minutes before chemotherapy, followed by a further 2 doses four hours apart

or

- a 16-mg suppository rectally, given 1 to 2 hours before treatment

or

- a single oral dose of 24 mg taken 30 minutes before the start of single-day chemotherapy

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by giving intravenous dexamethasone sodium phosphate 20 mg before chemotherapy.

Similar regimens to those given above are used for preventing acute emesis with *less emetogenic chemotherapy* and/or **radiotherapy** and also include:

- 8 mg given orally or by slow intravenous injection up to 2 hours before treatment, followed by an oral dose of 8 mg given 8 to 12 hours later

To protect against delayed emesis these regimens are followed by oral ondansetron 8 mg twice daily, or 16 mg rectally once daily, for up to 5 days after the end of a course of chemotherapy.

To *prevent* **postoperative nausea and vomiting** the following doses may be given:

- 16 mg orally an hour before anaesthesia

or

- 8 mg orally an hour before anaesthesia followed by 2 further doses of 8 mg at 8-hour intervals

or

- a single dose of 4 mg by slow intravenous or intramuscular injection at induction of anaesthesia

For the *treatment* of postoperative nausea and vomiting a single dose of 4 mg by intramuscular or slow intravenous injection is recommended.

For dosing in children, elderly patients, or those with hepatic impairment, see below.

Reviews.

1. Perez EA. A risk-benefit assessment of serotonin 5-HT_3 receptor antagonists in antineoplastic therapy-induced emesis. *Drug Safety* 1998; **18:** 43–56.
2. Gregory RE, Ettinger DS. 5-HT_3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting: a comparison of their pharmacology and clinical efficacy. *Drugs* 1998; **55:** 173–89.
3. Lindley C, Blower P. Oral serotonin type 3-receptor antagonists for prevention of chemotherapy-induced emesis. *Am J Health-Syst Pharm* 2000; **57:** 1685–97.
4. Culy CR, *et al.* Ondansetron: a review of its use as an antiemetic in children. *Paediatr Drugs* 2001; **3:** 441–79.
5. Gridelli C. 5-HT_3-receptor antagonists in the control of delayed-onset emesis. *Anticancer Res* 2003; 23: 2773–82.
6. Constenla M. 5-HT_3 receptor antagonists for prevention of late acute-onset emesis. *Ann Pharmacother* 2004; **38:** 1683–91.
7. Aapro M. 5-HT_3-receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. *Oncology* 2005; **69:** 97–109.
8. Anonymous. 5HT_3-receptor antagonists as antiemetics in cancer. *Drug Ther Bull* 2005; **43:** 57–62.

Administration. Ondansetron has been successfully used by continuous *subcutaneous* infusion to control intractable nausea and vomiting.[1] Despite concern about the low pH of ondansetron injection there was no problem with the skin at the infusion site. An *oral* protocol for chemotherapy-induced emesis in children has been described;[2] efficacy was similar to intravenous use.

1. Mulvenna PM, Regnard CFB. Subcutaneous ondansetron. *Lancet* 1992; **339:** 1059.
2. Walker PC, *et al.* Promoting the use of oral ondansetron in children receiving cancer chemotherapy. *Am J Health-Syst Pharm* 2001; **58:** 598–602.

Administration in children. Ondansetron is used in children for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. Ondansetron is given by slow intravenous injection or infusion as the hydrochloride, or orally as the hydrochloride or base. Doses are expressed in terms of the base.

In the USA a licensed regimen for **chemotherapy**-induced nausea and vomiting in children over 6 months of age is ondansetron 150 micrograms/kg by intravenous infusion 30 minutes before moderately to highly emetogenic chemotherapy, repeated 4 and 8 hours after the first dose. Alternatively, for children aged 4 to 11 years, an oral dose of 4 mg may be given 30 minutes before the start of moderately emetogenic chemotherapy, with subsequent 4-mg doses given 4 and 8 hours thereafter. An oral dose of 4 mg three times daily may be given for 1 to 2 days after the end of chemotherapy.

In the UK, ondansetron is licensed for use in children aged from 6 months and doses are calculated using body-weight or body-surface; weight-based dosing results in higher daily doses compared with those based on body-surface. In a typical regimen based on body-surface, an intravenous dose of ondansetron 5 mg/m^2 (maximum 8 mg) is infused (over at least 15 minutes) immediately before chemotherapy and followed after 12 hours by oral dosing for up to 5 days:

- children aged from 6 months and less than 0.6 m^2 body-surface: 2 mg every 12 hours
- from 6 months and 0.6 m^2 and over: 4 mg every 12 hours

When using body-weight, an intravenous dose of ondansetron 150 micrograms/kg (maximum 8 mg) is given immediately before chemotherapy and repeated every 4 hours for up to 3 doses. This is followed after 12 hours by oral dosing for up to 5 days:

- body-weight 10 kg and less: 2 mg every 12 hours
- over 10 kg: 4 mg every 12 hours

The daily dose of ondansetron by any route should not exceed 32 mg.

While ondansetron is not licensed in the UK for **radiotherapy**-induced nausea and vomiting in children, the *BNFC* recommends the same doses as those used for chemotherapy-induced nausea and vomiting (above).

A protocol for oral ondansetron dosage, with similar efficacy to intravenous use, has also been described, see Administration, above.

For the prevention and treatment of **postoperative nausea and vomiting** in children aged from 1 month, 100 micrograms/kg may be given by slow intravenous injection, up to a maximum dose of 4 mg.

Administration in the elderly. Most licensed product information for ondansetron states that dose adjustments for patients over 65 years of age are not necessary. However, the product information for one preparation (*Zofran; GSK, UK*) recommends that patients over 75 years of age are given an initial dose of 8 mg by intravenous infusion over 15 minutes for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy; this may be followed by a further 2 infusions of 8 mg given at least four hours apart.

Administration in hepatic impairment. Licensed product information recommends that the dose of ondansetron should not exceed 8 mg daily in patients with moderate or severe hepatic impairment. When this dose was given intravenously to patients with hepatic impairment, those with severe impairment showed an increase in the area under the plasma concentration/time curve and in the terminal plasma half-life, and a decrease in plasma clearance.[1] The authors of this study, some of whom worked for the manufacturers (*Glaxo*), considered that ondansetron should be restricted to once daily dosage in severe hepatic impairment.

1. Blake JC, *et al.* The pharmacokinetics of intravenous ondansetron in patients with hepatic impairment. *Br J Clin Pharmacol* 1993; **35:** 441–3.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment of bulimia nervosa. Preliminary reports have indicated

that ondansetron may be of benefit in the treatment of this disorder.[1,2]

1. Faris PL, *et al*. Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomised, double-blind trial. *Lancet* 2000; **355:** 792–7.
2. Fung SM, Ferrill MJ. Treatment of bulimia nervosa with ondansetron. *Ann Pharmacother* 2001; **35:** 1270–3.

Fatigue. Preliminary results indicated that treatment with 5-HT_3 antagonists such as ondansetron and tropisetron may be of benefit in patients with chronic fatigue.[1] Oral ondansetron 4 mg twice daily was reported[2] to resolve fatigue in a woman with chronic hepatitis C. In a randomised study in 36 patients with chronic hepatitis C, this dose of ondansetron given for 1 month significantly improved fatigue scores at day 15 and day 60 (beyond the treatment period) when compared with placebo.[3] The authors noted that patient awareness that constipation was a possible effect of active treatment may have potentially unblinded the study. Further confirmation by larger studies is needed.

1. Späth M, *et al*. Treatment of chronic fatigue syndrome with 5-HT_3 receptor antagonists—preliminary results. *Scand J Rheumatol* 2000; **113** (suppl): 72–7.
2. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet* 1999; **354:** 397.
3. Piche T, *et al*. Effect of ondansetron, a 5-HT_3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut* 2005; **54:** 1169–73.

Gastroenteritis. Antiemetics such as ondansetron have been tried to reduce vomiting during acute gastroenteritis in children. Reviews[1-3] have found that ondansetron (given orally or intravenously) reduces the risk of persistent vomiting, the need for intravenous fluids, and hospital admissions; an increased incidence of diarrhoea was seen, but further research was considered necessary to determine its clinical significance.[2] Metoclopramide was also effective in reducing the number of vomiting episodes and hospital admissions, although it was less often used because of its potentially serious adverse effects.[3]

1. DeCamp LR, *et al*. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2008; **162:** 858–65.
2. Phillips B. Towards evidence based medicine for paediatricians. *Arch Dis Child* 2010; **95:** 945–7.
3. Fedorowicz Z, *et al*. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2011 (accessed 05/10/11).

Pain. Preliminary results from a small crossover study[1] indicated that oral ondansetron was more effective than paracetamol in relieving the pain of fibromyalgia, a chronic disorder that responds poorly to conventional analgesics. A single bolus of ondansetron given to patients with chronic neuropathic pain significantly reduced pain scores 2 hours after injection in a placebo-controlled study;[2] this effect may be due to an action on 5-HT_3 receptors in the spinal cord.

Other 5-HT_3 antagonists such as granisetron[3-5] and tropisetron[6-8] have also been investigated in various painful syndromes.

1. Hrycaj P, *et al*. Pathogenetic aspects of responsiveness to ondansetron (5-hydroxytryptamine type 3 receptor antagonist) in patients with primary fibromyalgia syndrome—a preliminary study. *J Rheumatol* 1996; **23:** 1418–23.
2. McCleane GJ, *et al*. Does a single intravenous injection of the 5HT3 receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study. *Anesth Analg* 2003; **97:** 1474–8.
3. Voog O, *et al*. Immediate effects of the serotonin antagonist granisetron on temporomandibular joint pain in patients with systemic inflammatory disorders. *Life Sci* 2000; **68:** 591–602.
4. Dubey PK, Prasad SS. Pain on injection of propofol: the effect of granisetron pretreatment. *Clin J Pain* 2003; **19:** 121–4.
5. Ernberg M, *et al*. Effects on muscle pain by intramuscular injection of granisetron in patients with fibromyalgia. *Pain* 2003; **101:** 275–82.
6. Farber L, *et al*. Short-term treatment of primary fibromyalgia with the 5-HT3-receptor antagonist tropisetron: results of a randomized, double-blind, placebo-controlled multicenter trial in 418 patients. *Int J Clin Pharmacol Res* 2001; **21:** 1–13.
7. Stratz T, *et al*. Local treatment of tendinopathies: a comparison between tropisetron and depot corticosteroids combined with local anesthetics. *Scand J Rheumatol* 2002; **31:** 366–70.
8. Spath M, *et al*. Efficacy and tolerability of intravenous tropisetron in the treatment of fibromyalgia. *Scand J Rheumatol* 2004; **33:** 267–70.

Pruritus. There are several case reports[1,2] of cholestatic pruritus (p. 1687.3) responding to intravenous or oral ondansetron, including one in pregnancy.[3] However, results from controlled studies[4-6] have been mixed. It is similarly unclear if ondansetron is of benefit in pruritus due to renal failure,[7-9] and results have been conflicting from controlled studies evaluating its use in opioid-induced pruritus.[10-15] There are reports of ondansetron ameliorating the pruritus associated with some skin disorders.[16] Other 5-HT_3 antagonists such as tropisetron[9] and dolasetron[14] have also been investigated.

1. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. *Lancet* 1993; **341:** 1277.
2. Raderer M, *et al*. Ondansetron for pruritus due to cholestasis. *N Engl J Med* 1994; **330:** 1540.
3. Schumann R, Hudcova J. Cholestasis of pregnancy, pruritus and 5-hydroxytryptamine 3 receptor antagonists. *Acta Obstet Gynecol Scand* 2004; **83:** 861–2.
4. Müller C, *et al*. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. *Eur J Gastroenterol Hepatol* 1998; **10:** 865–70.
5. O'Donohue JW, *et al*. A controlled trial of ondansetron in the pruritus of cholestasis. *Aliment Pharmacol Ther* 2005; **21:** 1041–5.
6. Jones EA, *et al*. Ondansetron and pruritus in chronic liver disease: a controlled study. *Hepatogastroenterology* 2007; **54:** 1196–9.
7. Balaskas EV, *et al*. Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. *Nephron* 1998; **78:** 395–402.
8. Murphy M, *et al*. A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. *Br J Dermatol* 2003; **148:** 314–7.
9. Weisshaar E, *et al*. Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol* 2004; **13:** 298–304.
10. Borgeat A, Stirnemann H-R. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. *Anesthesiology* 1999; **90:** 432–6.
11. Korhonen AM, *et al*. Ondansetron does not prevent pruritus induced by low-dose intrathecal fentanyl. *Acta Anaesthesiol Scand* 2003; **47:** 1292–7.
12. Wells J, *et al*. Intrathecal fentanyl-induced pruritus during labour: the effect of prophylactic ondansetron. *Int J Obstet Anesth* 2004; **13:** 35–9.
13. Waxler B, *et al*. Prophylactic ondansetron does not reduce the incidence of itching induced by intrathecal sufentanil. *Can J Anesth* 2004; **51:** 685–9.
14. Iatrou CA, *et al*. Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2005; **101:** 1516–20.
15. Siddik-Sayyid SM, *et al*. Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? *Anesth Analg* 2007; **104:** 421–4.
16. Zenker S, *et al*. Behandlung von Pruritus als Symptom von Hauterkrankungen mit dem Serotonin-Rezeptorantagonisten Ondansetron. *J Dtsch Dermatol Ges* 2003; **1:** 705–10.

Psychiatric disorders. Ondansetron has been tried experimentally in several psychiatric disorders including schizophrenia,[1-3] and psychosis in patients with parkinsonism,[4] and may be of value in moderating tardive dyskinesia.[5] A reduction in tic severity in Tourette's syndrome (see Tics, p. 1030.1) has been reported,[6] and preliminary results have suggested benefit in obsessive-compulsive disorder,[7] and bulimia nervosa (see p. 1872.3). It is also reported to be under investigation in the management of panic attacks (p. 1029.1). For the more conventional management of schizophrenia, parkinsonism, and obsessive-compulsive disorder see p. 1031.3, p. 889.1, and p. 1028.2, respectively.

1. White A, *et al*. Ondansetron in the treatment of schizophrenia. *Lancet* 1991; **337:** 1173.
2. Adler LE, *et al*. Improved P50 auditory gating with ondansetron in medicated schizophrenia patients. *Am J Psychiatry* 2005; **162:** 386–8.
3. Levkovitz Y, *et al*. The effect of ondansetron on memory in schizophrenic patients. *Brain Res Bull* 2005; **65:** 291–5.
4. Zoldan J, *et al*. Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT_3 receptor antagonist. *Neurology* 1995; **45:** 1305–8.
5. Sirota P, *et al*. Use of the selective serotonin 3 receptor antagonist ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. *Am J Psychiatry* 2000; **157:** 287–9.
6. Toren P, *et al*. Ondansetron treatment in Tourette's disorder: a 3-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 499–503.
7. Pallanti S, *et al*. Ondansetron augmentation in treatment-resistant obsessive-compulsive disorder: a preliminary, single-blind, prospective study. *CNS Drugs* 2009; **23:** 1047–55.

Substance dependence. Ondansetron is being studied in the management of alcohol dependence (p. 1734.1). However, in one study[1] a significant reduction in alcohol consumption was found only in lighter drinkers after subgroup analysis. Another study[2] found a reduction in alcohol consumption by patients with early-onset alcoholism (onset before age 25) who took ondansetron compared with placebo. No such effect was seen, however, in patients with late-onset alcoholism. Further study found that ondansetron also effectively ameliorated mood disturbances including symptoms of depression, anxiety, and hostility, in early-onset alcoholics.[3] Self-reported alcohol consumption also reduced in adolescents (between ages 14 and 20) with alcohol dependence who were given ondansetron in an open study.[4]

1. Sellers EM, *et al*. Clinical efficacy of the 5-HT_3 antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res* 1994; **18:** 879–85.
2. Johnson BA, *et al*. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients. *JAMA* 2000; **284:** 963–71.
3. Johnson BA, *et al*. Ondansetron reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. *Alcohol Clin Exp Res* 2003; **27:** 1773–9.
4. Dawes MA, *et al*. A prospective, open-label trial of ondansetron in adolescents with alcohol dependence. *Addict Behav* 2005; **30:** 1077–85.

Adverse Effects and Precautions

Ondansetron and other 5-HT_3 antagonists may cause headache, a sensation of flushing or warmth, hiccups, and constipation. A transient rise in liver enzymes has occasionally occurred. There have been rare reports of immediate hypersensitivity reactions, including anaphylaxis. Chest pain, arrhythmias, hypotension, tachycardia, and bradycardia have been reported rarely. Dizziness and transient visual disturbances such as blurred vision (or very rarely, transient blindness) have been reported during rapid intravenous injection. Transient ECG changes including QT interval prolongation have occurred very rarely, mainly with intravenous ondansetron. Seizures and movement disorders, including extrapyramidal reactions such as dystonia, dyskinesia, and oculogyric crisis have been reported. Rashes and urticaria have also occurred. Injection site reactions may develop, and local burning sensations are common after insertion of suppositories.

5-HT_3 antagonists should generally not be used in patients who have had a hypersensitivity reaction to a member of this drug class. They should be used with care in patients with signs of subacute intestinal obstruction or ileus. Ondansetron should be given in reduced doses to patients with moderate to severe hepatic impairment.

Effects on carbohydrate metabolism. Hypoglycaemia associated with dystonia and seizures developed in a four-year-old child after ondansetron treatment for vomiting.[1] Blood glucose concentrations returned to normal with intravenous glucose. Indirect inhibition of stress-induced corticotropin and cortisol secretion via the effects of ondansetron on serotonergic pathways was suggested as a possible cause for the hypoglycaemia. For more reports of extrapyramidal effects and seizures, see Effects on the Nervous System, p. 1874.1.

1. Patel A, *et al*. Ondansetron-induced dystonia, hypoglycemia, and seizures in a child. *Ann Pharmacother* 2011; **45:** e7.

Effects on the cardiovascular system. In 1992 chest pain and/or cardiac arrhythmias that might have been associated with ondansetron were reported[1] in 4 patients, 2 of whom died. In 3 subsequent patients who developed severe chest or anginal pain, treatment with ondansetron was stopped.

The manufacturers (*Glaxo*) had at that time no evidence of a causal relationship between ondansetron and episodes of chest pain and cardiac abnormalities.[2] Giving ondansetron or granisetron intravenously produced no clinically important cardiovascular changes in a study in 12 healthy subjects.[3] Since then, however, hypotension, coronary vasospasm, and atrial fibrillation have been reported with ondansetron,[4] and myocardial ischaemia has been reported with both ondansetron[5] and dolasetron;[6] in the latter case this led to an acute myocardial infarction. Supraventricular tachycardia reported with dolasetron was attributed to an interaction with sevoflurane.[7] Dolasetron-induced torsade de pointes has also occurred,[8] and overdose of dolasetron has produced prolongation of the QT_c interval and hypotension.[9] Another study in healthy subjects found that dolasetron mainly altered ECG parameters indicative of ventricular depolarisation, whereas ondansetron affected mainly ventricular repolarisation.[10] However, ECG changes were transient and asymptomatic. Studies of high-dose intravenous granisetron[11-13] found no significant adverse effects on pulse, blood pressure, or ECG measurements. A review[14] of the electrocardiographic and cardiovascular effects of the 5-HT_3 antagonists concluded that although this class of drugs may cause small, transient ECG changes, the clinical benefits of the drugs outweighed the small theoretical risk of any clinically significant cardiovascular events. Nonetheless, the use of dolasetron in children has been contra-indicated in some countries (see Administration in Children, p. 1837.3).

1. Ballard HS, *et al*. Ondansetron and chest pain. *Lancet* 1992; **340:** 1107.
2. Palmer JBD, Greenstreet YL. Ondansetron and chest pain. *Lancet* 1992; **340:** 1410.
3. Boike SC, *et al*. Cardiovascular effects of i.v. granisetron at two administration rates and of ondansetron in healthy adults. *Am J Health-Syst Pharm* 1997; **54:** 1172–6.
4. Havrilla PL, *et al*. Coronary vasospasm and atrial fibrillation associated with ondansetron therapy. *Ann Pharmacother* 2009; **43:** 532–6.
5. Bosek V, *et al*. Acute myocardial ischemia after administration of ondansetron hydrochloride. *Anesthesiology* 2000; **92:** 885–7.
6. Arole A, *et al*. Coronary vasospasm leading to an acute myocardial infarction after the administration of dolasetron. *J Clin Anesth* 2005; **17:** 72–4.
7. Higgins DJ, Bunker NJ. Dolasetron and peri-operative cardiac arrhythmia. *Anaesthesia* 2005; **60:** 936–7.
8. Turner S, *et al*. Dolasetron-induced torsades de pointes. *J Clin Anesth* 2007; **19:** 622–5.
9. Rochford M, *et al*. Dolasetron overdose resulting in prolonged QTc interval and severe hypotension: a case report and literature review. *Emerg Med J* 2007; **24:** 515–7.
10. Benedict CR, *et al*. Single-blind study of the effects of intravenous dolasetron mesylate versus ondansetron on electrocardiographic parameters in normal volunteers. *J Cardiovasc Pharmacol* 1996; **28:** 53–9.
11. Carmichael J, Harris AL. High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: cardiac safety and tolerability. *Anticancer Drugs* 2003; **14:** 739–44.
12. Carmichael J, Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. *Cancer Chemother Pharmacol* 2004; **53:** 123–8.
13. Aapro M, Bourke JP. Rapid intravenous administration of granisetron prior to chemotherapy is not arythmogenic [sic]: results of a pilot study. *Eur J Cancer* 2003; **39:** 927–31.
14. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine$_3$ receptor antagonists. *Ann Pharmacother* 2003; **37:** 1276–86.

Effects on the eyes. Blurring followed by transient loss of vision has been reported after rapid intravenous injection of ondansetron.[1] Oculogyric crisis may occur as part of

extrapyramidal reactions seen with ondansetron, see Effects on the Nervous System, below.

1. Cherian A, Maguire M. Transient blindness following intravenous ondansetron. *Anaesthesia* 2005; **60:** 938–9.

Effects on the liver. Although disturbances in liver enzyme values have been reported in patients given ondansetron,[1] more severe symptoms of liver disorder appear to be very rare; however, there is a report of severe jaundice associated with ondansetron as an antiemetic for chemotherapy.[2] Symptoms did not recur when the patient received granisetron.

1. Lewandowski MJ, Chapman SA. Ondansetron-induced aminotransferase level elevation: case report and review of the literature. *Pharmacotherapy* 2008; **28:** 1542–6.
2. Verrill M, Judson I. Jaundice with ondansetron. *Lancet* 1994; **344:** 190–1.

Effects on the nervous system. Tonic-clonic movements and frothing at the mouth occurred in a patient 90 minutes after an infusion of ondansetron;[1] the patient responded to diazepam intravenously. The manufacturers had seen 10 patients who developed *seizures* during initial clinical studies, but considered that, unlike this case, all these patients had predisposing factors. Hypotension and generalised tonic-clonic seizures were reported in a patient with metastatic breast cancer given ondansetron as an intravenous bolus.[2] Although seizures might have been due to brain metastases, the authors concluded that ondansetron had been the likely cause, since the patient had no further problems when antiemetic therapy was changed to metoclopramide. A seizure associated with palonosetron therapy has also been reported.[3] *Extrapyramidal reactions* in patients given ondansetron as part of a chemotherapy regimen[4,5] and for postoperative nausea and vomiting[6-8] have also been reported. In one case,[8] transient multifocal encephalopathy developed. Clinical manifestations such as clonus, oculogyric crisis, and oromandibular and limb dystonia resembled those of structural brain injury, and response to diphenhydramine was poor; despite this, the patient made a full neurological recovery over the course of 12 hours. For reference to seizures and dystonia associated with hypoglycaemia in an ondansetron-treated child see Effects on Carbohydrate Metabolism, p. 1873.3. Ondansetron and related drugs can induce *headache*; it has sometimes been confused with post-dural puncture headache.[9]

1. Sargent AI, *et al*. Seizure associated with ondansetron. *Clin Pharm* 1993; **12:** 613–15.
2. Sharma A, Raina V. Generalised seizures following ondansetron. *Ann Oncol* 2001; **12:** 131–2.
3. Zambelli A, *et al*. Seizure associated with palonosetron. *Support Care Cancer* 2009; **17:** 217.
4. Krstenansky PM, *et al*. Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1994; **28:** 280.
5. Mathews HG, Tancil CG. Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1996; **30:** 196.
6. Stonell C. An extrapyramidal reaction to ondansetron. *Br J Anaesth* 1998; **81:** 658.
7. Tolan MM, *et al*. Perioperative extrapyramidal reactions associated with ondansetron. *Anesthesiology* 1999; **90:** 340–1.
8. Ritter MJ, *et al*. Ondansetron-induced multifocal encephalopathy. *Mayo Clin Proc* 2003; **78:** 1150–2.
9. Sharma R, Panda A. Ondansetron-induced headache in a parturient mimicking postdural puncture headache. *Can J Anaesth* 2010; **57:** 187–8.

Hypersensitivity. Anaphylactoid reactions have been reported in patients given ondansetron injections. The FDA stated in October 1993 that it had received 24 reports of such reactions,[1] mostly occurring after the first ondansetron dose of the second or third chemotherapy cycle, and characterised by urticaria, angioedema, hypotension, bronchospasm, and dyspnoea. Similar effects have been reported in a patient with no prior exposure to ondansetron.[2] A protocol for skin testing has been documented.[3]

Cross-sensitivity between 5-HT_3 antagonists has been reported;[4] 2 patients who had had a mild hypersensitivity reaction to one 5-HT_3 antagonist developed a more severe reaction after exposure to another. In the first case severe acute asthma, cyanosis, and loss of consciousness developed after ondansetron in a patient who had previously had an asthmatic reaction after tropisetron. The second patient had developed pruritus after a tropisetron injection and urticaria after ondansetron, and subsequently developed anaphylactic shock 5 minutes after a further dose of tropisetron. It was recommended that another 5-HT_3 antagonist should not be given as a replacement to patients who developed a hypersensitivity reaction to a drug of this class. However, there are reports of the successful use of granisetron in patients sensitive to ondansetron[5] and vice versa.[6]

1. Chen M, *et al*. Anaphylactoid-anaphylactic reactions associated with ondansetron. *Ann Intern Med* 1993; **119:** 862.
2. Weiss KS. Anaphylactic reaction to ondansetron. *Arch Intern Med* 2001; **161:** 2263.
3. Fernando SL, Broadfoot AJ. Ondansetron anaphylaxis: a case report and protocol for skin testing. *Br J Anaesth* 2009; **102:** 285–6.
4. Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine$_3$-receptor antagonists: a class effect? *Lancet* 1996; **347:** 584–5.
5. Bousquet PJ, *et al*. Isolated urticaria to ondansetron and successful treatment with granisetron. *Allergy* 2005; **60:** 543–4.
6. Kanny G, *et al*. IgE-mediated allergy to granisetron and safe use of ondansetron. *J Allergy Clin Immunol* 2001; **108:** 1059–60.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ondansetron as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Ondansetron does not appear to induce or inhibit the cytochrome P450 isoenzyme system, but it is itself metabolised by multiple hepatic isoenzymes, including CYP3A4, CYP2D6, and CYP1A2. US licensed product information states that inducers or inhibitors of these isoenzymes may change the clearance and half-life of ondansetron, but that on the basis of available data, no dose adjustments are recommended. UK licensed product information states that enzyme inhibition of one isoenzyme is usually compensated for by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement. Potent inducers of CYP3A4, such as phenytoin, carbamazepine, and rifampicin, have been reported to increase ondansetron clearance and reduce ondansetron plasma concentrations.

Because of the reports of transient ECG changes in some patients taking 5-HT_3 antagonists (see p. 1873.3), there is a theoretical need for caution if given with drugs that prolong QT-interval or cardiotoxic drugs such as anthracyclines; however, clinical evidence of a significant interaction seems to be mostly lacking.

Analgesics. For evidence of reduced analgesic efficacy of *tramadol* in patients also given 5-HT_3-receptor antagonists, such as ondansetron, see p. 140.3.

Antibacterials. *Rifampicin* pretreatment reduced the area under the plasma concentration-time curve of oral ondansetron by 65% and of intravenous ondansetron by 48% in healthy subjects.[1] Use of rifampicin, or other potent inducers of cytochrome P450 isoenzyme CYP3A4, with ondansetron may reduce antiemetic efficacy.

1. Villikka K, *et al*. The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* 1999; **65:** 377–81.

Antineoplastics. For mention of retrospective studies suggesting a change of pharmacokinetic parameters of high-dose cyclophosphamide and cisplatin when given with an ondansetron-containing antiemetic regimen, see Gastrointestinal Drugs, p. 773.3.

Pharmacokinetics

Peak plasma concentrations of ondansetron occur about 1.5 hours after an oral dose of 8 mg, and about 6 hours after a rectal dose. The absolute bioavailability is about 60%, mainly because of hepatic first-pass metabolism. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower, presumably due to reduced hepatic first-pass metabolism.

Ondansetron is extensively distributed in the body; about 70 to 75% of the drug in plasma is protein bound. It is metabolised in the liver through multiple enzymatic pathways; ondansetron is a substrate for cytochrome P450 isoenzymes, primarily CYP3A4, but also CYP1A2 and CYP2D6. Less than 5% of a dose is excreted unchanged in the urine.

The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal use. The terminal elimination half-life is prolonged to about 5 hours in the elderly and in those with renal impairment. These differences are not considered sufficient to warrant dosage adjustment. However, in patients with severe hepatic impairment, bioavailability may approach 100% and clearance is markedly reduced, with elimination half-lives of 15 to 32 hours; dosage restriction is advisable (see Administration in Hepatic Impairment, p. 1872.3). In general, children have a higher clearance than adults, although age-related reductions in clearance have also been reported, with younger children having lower clearances. Use of weight-based doses compensates for these changes and normalises exposure in paediatric patients.

References.
1. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **29:** 95–109.
2. Figg WD, *et al*. Pharmacokinetics of ondansetron in patients with hepatic insufficiency. *J Clin Pharmacol* 1996; **36:** 206–15.
3. Van Den Berg CM, *et al*. Pharmacokinetics of three formulations of ondansetron hydrochloride in healthy volunteers: 24-mg oral tablet, rectal suppository, and iv infusion. *Am J Health-Syst Pharm* 2000; **57:** 1046–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cetron; Dantenk; Dismolan; Espasevit; Finaber; Finoxi†; Tiosalis; Zofran; ***Austral.***: Ondaz; Onsetron; Zofran; ***Austria***: Ondensan; Zofran; Zotrix†; ***Belg.***: Avessa†; Avessaron; Zofran; ***Braz.***: Ansentron; Injectrax; Modifical; Nausedron; Ondantril; Ontrax; Vonau; Zofran; ***Canad.***: Zofran; ***Chile***: Amilene; Gardoton; Izofran; Levrox; Odanex†; Oncoemet†; Trorix†; ***China***: An Si Xin (安斯欣); Aoyimai (奥一麦); Di Li Xin (地力昕); En Fu De (恩复德); En Nuo Ping (恩诺平); Fu Mi Ting (富米汀); Kang Da Li Te (康达立特); Lu Wei Sen (路维森); Ou Bei (欧贝); Shi Tai (时泰); Wei Ze (维泽); Yi Feng (奕丰); Yi Shu Ning (益舒宁); Zofran (枢复宁); Zudan (枢丹); ***Cz.***: Danemet†; Emeset; Novetron; Ondemet; Setronon†; Zofran; ***Denm.***: Setofilm; Setrogen; Zofran; Zotrix†; ***Fin.***: Zofran; ***Fr.***: Setofilm; Zophren; ***Ger.***: Axisetron; cellondan; Zofran; ***Gr.***: Biosetron; Cruzafen; Dentron; Fedral; Jodol; Nofail; Odasen; Odnatron; Onda; Ondameton; Ondaren; Ondaseprol; Ondeton; Otredil; Setrodan; Trondamet; Vefron; Zetron; Zodatron; Zofron; Zophralen; ***Hong Kong***: Zofran; ***Hung.***: Antivom; Emetron; Ondagen; Zofran; ***India***: Adom-O; Afon MD; Ansecare; Anset; Back2Norm; C-Tron; Dan set; Dasin; Dentron; Doin; Domi-Up; Donset; Donsetron; Doran-O; Dotson; Dutron; E-On; Eldon; Emeran; Emeset; Emestal-O; Emestop; Emigo; Emitino; Emitus; Emnil; Emsetron; Emstal; Emtron; Flatron; Flexi; Fodino; Gendem-MD; Glendan; Glotron; K-Tron; Kanset; Keron; Lupisetron; Monda; Myset; Mytic; Naucet; Naucid; Neomit; Nitron; Nosirid; Novatron; Nuset; O-Set; Odanse; Olex Tab; Ominil; Omit; Onbit; Oncare; Oncoden; Oncon; Ond; Ondace; Ondai; Ondansetran; Ondanz; Ondar; Ondarom; Ondas; Ondavom; Ondax; Ondem; Ondemet-MD; Ondet; Ondigo; Onditron; Ondocil; Ondocos; Ondorise; Ondosia; Ondosym; Ondot; Ondrea; Ondron; Ondrovit; Onest; Ongone; Oniz; Onkam; Onlex; Ono; Onriz; Onsat; Onset; Onsett; Onstal; Onstar; Ontek; Ontic; Ontil; Ontiz; Ontome; Onv; Onvin; Onzy; Oralis; Orio-DT; Oset; Osetron; Otron; Periset; Vomiof; ***Indon.***: Cedantron; Ceteron; Dantroxal; Entron; Frazon; Invomit; Kliran; Lametic; Narfoz; Odanostin; Ondavell; Onetic; Trovensis; Vomceran; Vometraz; Vometron; Zantron; Zofran; ***Irl.***: Emital†; Emizof; Ondatab; Ondran; Setofilm; Zofran; ***Israel***: Zofran; ***Ital.***: Zofran; ***Malaysia***: Osetron; Setronax; Zofran; ***Mex.***: Danac; Dosatron; Modifical; Nalisen; Nodanton†; Onancen; Ondal; Precirux; Vosrym; Zofran; ***Neth.***: Setofilm; Zofran; ***Norw.***: Zofran; ***NZ***: Ondanaccord; Onsetron†; Zofran; ***Philipp.***: Emistop; Emodan; Nozuca; Onset; Vometron; Zofran; ***Pol.***: Atossa; Emetron; Ondagen; OndaLEK; Setronon; Zofran; ***Port.***: Emetron; Morpar; Nausiend†; Olmar; Otobrol; Zofran; ***Rus.***: Domegan (Домеган); Emeset (Эмесет); Emetron (Эметрон); Latran (Латран); Ondasol (Ондасол); Osetron (Осетрон); Setronon (Сетронон); Zofran (Зофран); ***S.Afr.***: Alepet; Danset; Dantron; Nausetron; Vomiz; Zofer; Zofran; ***Singapore***: Osetron; Setronax; Zofran; ***Spain***: Carvyx†; Setofilm; Yatrox; Zofran; ***Swed.***: Zofran; Zotrix†; ***Switz.***: Zofran; ***Thai.***: Dantron; Emeset; Emistop; Ondavell; Onsia; Zetron; Zofran; ***Turk.***: Zofer; Zofran; Zoltem; Zontron; Zophralen; ***UK***: Ondemet; Setofilm; Zofran; ***Ukr.***: Emetron (Эметрон); Osetron (Осетрон); Setronon (Сетронон); Zofran (Зофран); Zoltem (Золтем); ***USA***: Zofran; Zuplenz; ***Venez.***: Dismolan; Emeset; Tructum; Zofran.

Multi-ingredient Preparations. ***India***: Acidom-O; Alcirid-O; Alotac; Doran-O; Lupisetron Plus; Ond-R.

Pharmacopoeial Preparations
BP 2014: Ondansetron Injection; Ondansetron Tablets;
USP 36: Ondansetron Hydrochloride Oral Suspension; Ondansetron Injection; Ondansetron Oral Solution; Ondansetron Orally Disintegrating Tablets; Ondansetron Tablets.

Oxapium Iodide *(rINN)*

Ciclonium Iodide; Cyclonium Iodide; Ioduro de oxapio; Oxapii Iodidum; Oxapium, Iodure d'; SH-100; Оксапия Йодид.

1-(2-Cyclohexyl-2-phenyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium iodide.

$C_{22}H_{34}INO_2$=471.4

CAS — 6577-41-9.

UNII — 682380CG4N.

NOTE. Distinguish from Ciclonium Bromide, p. 1827.1, an unrelated antispasmodic.

Pharmacopoeias. In *Jpn*.

Profile

Oxapium iodide is an antimuscarinic that has been used as an antispasmodic in the treatment of gastrointestinal disorders and renal calculi.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Esperan.

Oxyphencyclimine Hydrochloride

(BANM, rINNM)

Hidrocloruro de oxifenciclimina; Oksifensiklimin Hidroklorür; Oxifenciclimina, hidrocloruro de; Oxyphencyclimine, Chlorhydrate d'; Oxyphencyclimini Hydrochloridum; Оксифенциклимина Гидрохлорид.

1,4,5,6-Tetrahydro-1-methylpyrimidin-2-ylmethyl α-cyclohexylmandelate hydrochloride.

$C_{20}H_{28}N_2O_3$,HCl=380.9

CAS — 125-53-1 (oxyphencyclimine); 125-52-0 (oxyphencyclimine hydrochloride).

ATC — A03AA01.

ATC Vet — QA03AA01.

UNII — GWO1432WOU.

Profile

Oxyphencyclimine hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease and for the relief of smooth muscle spasms in gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Daricon; ***Thai.***: KB Duode; Oxyno†; Proclimine; Weicon.

Multi-ingredient Preparations. ***China***: Rudd-U (立愉); ***Hong Kong***: Aluvit-U†; ***Thai.***: Bismocane; ***Turk.***: Spazmo-Valibrin.

Oxyphenonium Bromide *(BAN, rINN)*

Bromuro de oxifenonio; Oksyfenoniowy bromek; Oxifenonio, bromuro de; Oxphenonii Bromidum; Oxyphenonii Bromidum; Oxyphenonium Bromatum; Oxyphénonium, Bromure d'; Оксифенония Бромид.

2-(α-Cyclohexylmandeloyloxy)ethyldiethylmethylammonium bromide.

$C_{21}H_{34}BrNO_3$=428.4

CAS — 14214-84-7 (oxyphenonium); 50-10-2 (oxyphenonium bromide).

ATC — A03AB03.

ATC Vet — QA03AB03.

UNII — S9421HWB3Z.

Pharmacopoeias. In *Pol.*

Profile

Oxyphenonium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been given orally in a usual dose of 5 to 10 mg three or four times daily to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Antrenyl; ***Pol.***: Spasmophen†.

Palonosetron Hydrochloride

(USAN, rINNM)

Hidrocloruro de palonosetrón; Palonosétron, Chlorhydrate de; Palonosetrón, hidrocloruro de; Palonosetroni Hydrochloridum; RS-25259-197; Палоносетрона Гидрохлорид.

(3a*S*)-2,3,3a,4,5,6-Hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one hydrochloride.

$C_{19}H_{24}N_2O$,HCl=332.9

CAS — 135729-56-5 (palonosetron); 135729-55-4 (palonosetron hydrochloride); 135729-62-3 (palonosetron hydrochloride).

ATC — A04AA05.

ATC Vet — QA04AA05.

UNII — 23310D4I19.

Stability. The stability of palonosetron hydrochloride at concentrations of 5 and 30 micrograms/mL was assessed in PVC bags of the following 4 infusion solutions: glucose 5%, sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, and glucose 5% in lactated Ringer's solution. All solutions were considered to be physically and chemically stable for at least 48 hours at room temperature exposed to light, and for 14 days under refrigeration.[1]

Palonosetron 50 micrograms/mL (as palonosetron hydrochloride) was found to be physically and chemically stable during simulated Y-site administration with the following drugs:[2,3]

- atropine sulfate 400 micrograms/mL
- famotidine 2 mg/mL
- fentanyl citrate 50 micrograms/mL
- heparin sodium 100 units/mL
- hydromorphone hydrochloride 500 micrograms/mL
- lidocaine hydrochloride 10 mg/mL
- morphine sulfate 15 mg/mL
- pethidine hydrochloride 10 mg/mL
- potassium chloride 100 mmol/litre
- sufentanil 12.5 micrograms/mL (as sufentanil citrate)

1. Trissel LA, Xu QA. Physical and chemical stability of palonosetron HCl in 4 infusion solutions. *Ann Pharmacother* 2004; **38:** 1608–11.
2. Trissel LA, *et al.* Physical and chemical stability of palonosetron hydrochloride with five opiate agonists during simulated Y-site administration. *Am J Health-Syst Pharm* 2007; **64:** 1209–13.
3. Kupiec TC, *et al.* Physical and chemical stability of palonosetron hydrochloride with five common parenteral drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2008; **65:** 1735–9.

Uses and Administration

Palonosetron is a 5-HT_3 antagonist used in the prevention of nausea and vomiting induced by cytotoxic chemotherapy and for the prevention of postoperative nausea and vomiting. Palonosetron is given as the hydrochloride but doses are expressed in terms of the base; 280.8 micrograms of palonosetron hydrochloride is equivalent to about 250 micrograms of palonosetron.

For the prevention of acute and delayed **nausea and vomiting** associated with initial and repeat courses of moderately or highly emetogenic cancer **chemotherapy**, a dose of 250 micrograms is given intravenously over 30 seconds about 30 minutes before chemotherapy. Palonosetron can also be given orally to prevent acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. A dose of 500 micrograms is given about 1 hour before the start of chemotherapy.

For the prevention of **postoperative** nausea and vomiting, for up to 24 hours after surgery, a single dose of 75 micrograms is given intravenously over 10 seconds immediately before the induction of anaesthesia. Efficacy beyond 24 hours has not been shown.

Reviews

1. Siddiqui MAA, Scott LJ. Palonosetron. *Drugs* 2004; **64:** 1125–32.
2. Tonini G, *et al.* New drugs for chemotherapy-induced nausea and vomiting: focus on palonosetron. *Expert Opin Drug Metab Toxicol* 2005; **1:** 143–9.
3. Celio L, *et al.* Clinical update on palonosetron in the management of chemotherapy-induced nausea and vomiting. *Tumori* 2008; **94:** 447–52.
4. Yang LPH, Scott LJ. Palonosetron: in the prevention of nausea and vomiting. *Drugs* 2009; **69:** 2257–78.
5. Navari RM. Palonosetron: a second generation 5-hydroxytryptamine 3 receptor antagonist. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1577–86.
6. Ruhlmann C, Herrstedt J. Palonosetron hydrochloride for the prevention of chemotherapy-induced nausea and vomiting. *Expert Rev Anticancer Ther* 2010; **10:** 137–48.
7. Saito M, Tsukuda M. Review of palonosetron: emerging data distinguishing it as a novel 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting. *Expert Opin Pharmacother* 2010; **11:** 1003–14. Correction. *ibid.*; 1231.

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2, although no dosage reduction is considered necessary in hepatic impairment. Diarrhoea, fatigue, and abdominal pain may also occur. Patients with a history of constipation or signs of subacute intestinal obstruction should be monitored if given palonosetron.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Effects on the nervous system. For mention of a seizure associated with palonosetron see under Ondansetron, p. 1874.1.

Interactions

As for Ondansetron, p. 1874.2.

Pharmacokinetics

Palonosetron is well absorbed after oral dosing, with an absolute bioavailability of about 97%. Peak plasma concentrations occur about 5 hours after an oral dose. Palonosetron has a volume of distribution of around 7 to 8 litres/kg; plasma protein binding is about 62%. About 50% of a dose is metabolised in the liver by cytochrome P450 isoenzymes (notably CYP2D6, but also CYP3A4 and CYP1A2). About 80% of a dose is recovered in the urine within 144 hours, as palonosetron and its metabolites. The mean terminal elimination half-life is reported to be about 40 hours.

References.

1. Hunt TL, *et al.* Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol* 2005; **45:** 589–96.
2. Shah A, *et al.* Pharmacokinetic evaluation and safety profile of a 15-minute versus 30-second infusion of palonosetron in healthy subjects. *J Clin Pharmacol* 2006; **46:** 1139–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Aloxi; ***Belg.***: Aloxi; ***Braz.***: Onicit; ***Chile***: Onicit; ***China***: Jiouting (吉欧停); Zhiruo (止若); ***Cz.***: Aloxi; ***Denm.***: Aloxi; ***Ger.***: Aloxi; ***Gr.***: Aloxi; ***Hung.***: Aloxi; ***India***: Palnox; Palonew; Palzen; ***Indon.***: Paloxi; ***Irl.***: Aloxi; ***Israel***: Paloxi; ***Ital.***: Aloxi; ***Jpn***: Aloxi; ***Mex.***: Onicit; ***Neth.***: Aloxi; ***Norw.***: Aloxi; ***Pol.***: Aloxi; ***Port.***: Aloxi; ***S.Afr.***: Onicit; ***Singapore***: Aloxi; ***Spain***: Aloxi; ***Swed.***: Aloxi; ***Switz.***: Aloxi; ***Thai.***: Aloxi; ***Turk.***: Aloxi; ***UK***: Aloxi; ***USA***: Aloxi; ***Venez.***: Onicit.

Pantoprazole *(BAN, USAN, rINN)*

BY-1023; Pantopratsoli; Pantoprazol; Pantoprazolum; SKF-96022; Пантопразол.

5-Difluoromethoxybenzimidazol-2-yl 3,4-dimethoxy-2-pyridylmethyl sulphoxide.

$C_{16}H_{15}F_2N_3O_4S$=383.4

CAS — 102625-70-7.

ATC — A02BC02.

ATC Vet — QA02BC02.

UNII — D8TST4O562.

Pantoprazole Sodium *(BANM, USAN, rINNM)*

Natrii Pantoprazolum; Pantoprazol sódico; Pantoprazole Sodique; Pantoprazolum natricum; Натрий Пантопразол.

Pantoprazole sodium sesquihydrate.

$C_{16}H_{14}F_2N_3NaO_4S$,1½H_2O=432.4

CAS — 13B786-67-1 (anhydrous pantoprazole sodium); 164579-32-2 (pantoprazole sodium sesquihydrate).

ATC — A02BC02.

ATC Vet — QA02BC02.

UNII — 6871619Q5X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Pantoprazole Sodium Sesquihydrate). A white or almost white powder. Freely soluble in water and in alcohol; practically insoluble in hexane. Protect from light.

USP 36: (Pantoprazole Sodium). A white to off-white powder. Freely soluble in water, in dehydrated alcohol, and in methyl alcohol; practically insoluble in dichloromethane and in hexane. Protect from light.

Stability. A suspension of pantoprazole 2 mg/mL in sterile water and sodium bicarbonate was deemed to be physically and chemically stable[1] in amber polyethylene terephthalate bottles for 62 days at 2 degrees to 8 degrees.

1. Dentinger PJ, *et al.* Stability of pantoprazole in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; **59:** 953–6.

Uses and Administration

Pantoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p. 1867.2). It is given as the sodium salt but doses are expressed in terms of the base. Pantoprazole sodium 11.28 mg is equivalent to about 10 mg of pantoprazole.

In the treatment of **gastro-oesophageal reflux disease** (p. 1807.2), the usual oral dose is 20 to 40 mg once daily, which may be increased up to 80 mg daily. Treatment is usually given for 4 weeks, increased to 8 weeks if necessary; in the USA, up to 16 weeks of therapy is permitted for healing of erosive oesophagitis. For maintenance therapy, treatment can be continued with 20 to 40 mg daily. Alternatively, for recurring symptoms, an on-demand regimen of 20 mg daily may be given.

The usual dose for the treatment of **peptic ulcer disease** (p. 1813.2) is 40 mg once daily, increased up to 80 mg daily if needed. Treatment is usually given for 2 to 4 weeks for duodenal ulceration, or 4 to 8 weeks for benign gastric ulceration. For the eradication of *Helicobacter pylori* pantoprazole may be combined with two antibacterials in a 1-week **triple therapy** regimen. Effective regimens include pantoprazole 40 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily.

Patients who require prophylaxis for **NSAID-associated ulceration** may take 20 mg daily.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p. 1814.3), the initial dose is 80 mg daily in a single dose or 2 divided doses, adjusted as required; up to 240 mg daily has been used. Daily doses greater than 80 mg should be given in 2 divided doses.

PARENTERAL DOSAGE.

Pantoprazole may also be given intravenously, as the sodium salt, over 2 to 15 minutes, either as a slow injection or a short-term infusion. For peptic ulceration or gastro-oesophageal reflux disease, the recommended dose is 40 mg

daily. A dose of 80 mg once or twice daily may be used for Zollinger-Ellison syndrome; up to 240 mg daily may be given in divided doses. Patients should be switched to oral therapy as soon as possible.

For use in children, see below. Doses of pantoprazole may need to be reduced in patients with hepatic impairment (see below).

The magnesium salt and *S*-isomer of pantoprazole have also been used.

Reviews.

1. Anonymous. Pantoprazole—a third proton pump inhibitor. *Drug Ther Bull* 1997; **35:** 93–4.
2. Poole P. Pantoprazole. *Am J Health-Syst Pharm* 2001; **58:** 999–1008.
3. Cheer SM, *et al*. Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. *Drugs* 2003; **63:** 101–32.
4. Gisbert JP, *et al*. Pantoprazole based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2004; **16:** 89–99.
5. Lehmann FS, Beglinger C. Role of pantoprazole in the treatment of gastro-oesophageal reflux disease. *Expert Opin Pharmacother* 2005; **6:** 93–104.

Administration. Bioequivalence has been shown for pantoprazole granules (*Protonix, Wyeth*) given *orally* mixed with either apple juice or apple sauce, or when mixed with apple juice and given through a size 16 French nasogastric tube.[1]

The safety and tolerability profiles of *intravenous* pantoprazole given in 10 mL of sodium chloride 0.9% over 2 minutes were similar to those given over 15 minutes in 100 mL.[2]

A study[3] comparing two different infusion regimens of adjunctive pantoprazole for peptic ulcer bleeding found that clinical outcomes were similar if an intravenous bolus injection of pantoprazole 80 mg was followed by either a continuous intravenous infusion of 192 mg daily (given at 8 mg/hour which is usual practice), or 160 mg daily (given as 40 mg every 6 hours), both for 3 days.

1. Tammara B, *et al*. Bioequivalence among three methods of administering pantoprazole granules in healthy subjects. *Am J Health-Syst Pharm* 2009; **66:** 1923–8.
2. Micalizzi M, *et al*. Comparative tolerability of 2-and 15-minute intravenous infusions of pantoprazole. *Am J Health-Syst Pharm* 2007; **64:** 1822–6.
3. Hsu Y-C, *et al*. A randomized controlled trial comparing two different dosages of infusional pantoprazole in peptic ulcer bleeding. *Br J Clin Pharmacol* 2010; **69:** 245–51.

Administration in children. Pantoprazole is licensed in the USA for oral use in children from 5 years of age with gastro-oesophageal reflux disease. Children weighing 15 kg up to 40 kg are given 20 mg once daily, and those weighing 40 kg and over are given 40 mg once daily, for up to 8 weeks for erosive oesophagitis.

For findings from a review regarding the efficacy and safety of proton pump inhibitors in infants, children, and adolescents, see Administration in Children, under Omeprazole, p. 1867.3.

Administration in hepatic impairment. Dosage of pantoprazole may need to be reduced in severe hepatic impairment. UK licensed product information recommends a maximum dose of 20 mg daily orally or intravenously; however, US licensed product information suggests that doses up to 40 mg daily can be used. Doses above 40 mg daily have not been studied in patients with hepatic impairment. Liver enzymes should be monitored during therapy, and pantoprazole should be stopped if elevations occur.

Administration in renal impairment. Most studies have not found the pharmacokinetics of pantoprazole to be altered in patients with renal impairment[1] and licensed product information in the UK and USA generally does not recommend dosage adjustment in this group; however some UK sources, including the *BNF*, suggest that a maximum oral dose of 40 mg daily should be observed.

1. Cheer SM, *et al*. Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. *Drugs* 2003; **63:** 101–132.

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1. Dosage may need to be reduced in severe hepatic impairment; liver function should be monitored regularly, and therapy stopped if liver enzymes are elevated.

Incidence of adverse effects. In a postmarketing surveillance study of the 6-month period after the launch of pantoprazole in England (UK), the adverse effects reported most frequently were diarrhoea, nausea, and headache. Other effects included malaise or lassitude, rash, other gastrointestinal disturbances, myalgia, and oedema.[1]

1. Wilton LV, *et al*. The pharmacovigilance of pantoprazole: the results of postmarketing surveillance on 11 541 patients in England. *Drug Safety* 2003; **26:** 121–32.

Effects on the blood. For a report of thrombocytopenia with pantoprazole, see under Omeprazole, p. 1868.2.

Effects on electrolytes. For mention of a fall in blood-electrolytes during treatment with proton pump inhibitors including pantoprazole, see Omeprazole, p. 1868.3.

Effects on the kidneys. For reports of interstitial nephritis associated with pantoprazole see p. 1869.1.

Effects on the skin. For mention of skin reactions to pantoprazole, see p. 1869.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pantoprazole as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Interactions

As for Omeprazole, p. 1870.3.

For reference to a lack of effect of pantoprazole on diazepam, see Gastrointestinal Drugs, p. 1069.3, and for a lack of effect on theophylline, see p. 1236.1. Licensed product information states that there are reports of increased prothrombin time in patients taking pantoprazole and warfarin, but for reports suggesting a lack of effect on warfarin, see p. 1534.1. For a report of severe generalised myalgia and bone pain attributed to the use of methotrexate with pantoprazole, see Gastrointestinal Drugs, p. 828.1. Proton pump inhibitors, including pantoprazole, may affect exposure to mycophenolate, see p. 1965.1.

Pharmacokinetics

Pantoprazole is rapidly absorbed and peak plasma-pantoprazole concentrations occur about 2 to 2.5 hours after an oral dose. The oral bioavailability is about 77% with the enteric-coated tablet formulation, and does not vary after single or multiple doses. Pantoprazole is about 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19, to desmethylpantoprazole; small amounts are also metabolised by CYP3A4, CYP2D6, and CYP2C9. Metabolites are excreted mainly (about 80%) in the urine, with the remainder being excreted in faeces via the bile. The terminal elimination half-life is about 1 hour, and is prolonged in hepatic impairment; the half-life in patients with cirrhosis was 3 to 6 hours. Although the elimination half-life has been reported to be 3.5 to 10 hours in slow metabolisers (see also Metabolism under Omeprazole, p. 1871.2), minimal accumulation occurs with once-daily dosing.

References.

1. Pue MA, *et al*. Pharmacokinetics of pantoprazole following single intravenous and oral administration to healthy male subjects. *Eur J Clin Pharmacol* 1993; **44:** 575–8.
2. Kearns GL, *et al*. Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. *J Clin Pharmacol* 2008; **48:** 1356–65.
3. Pettersen G, *et al*. Population pharmacokinetics of intravenous pantoprazole in paediatric intensive care patients. *Br J Clin Pharmacol* 2009; **67:** 216–27.
4. Knebel W, *et al*. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. *J Clin Pharmacol* 2011; **51:** 333–45.
5. Ward RM, *et al*. A multicenter, randomized, open-label, pharmacokinetics and safety study of pantoprazole tablets in children and adolescents aged 6 through 16 years with gastroesophageal reflux disease. *J Clin Pharmacol* 2011; **51:** 876–87.

Bioavailability. A suspension of pantoprazole in sodium bicarbonate solution was rapidly absorbed, and peak plasma concentrations were comparable to that of the tablet. However, bioavailability of the suspension was about 25% lower than that of the tablet; the amount of sodium bicarbonate used may affect the bioavailability.[1]

1. Ferron GM, *et al*. Oral bioavailability of pantoprazole suspended in sodium bicarbonate solution. *Am J Health-Syst Pharm* 2003; **60:** 1324–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gastromax; Pampar; Pangest; Pantaltius†; Pantocas; Pantomed; Pantop; Pantus; Peptazol; Sipar; Supracam; Uldoral; ***Austral.***: Ozpan; Salpraz; Somac; Sozol; ***Austria***: Azidex; Gastroloc; Gastrozol; Genepan; Panprabene; Pantip; Pantoloc; Pantozol; Prazopant; Zurcal; ***Belg.***: Pantomed; Pantozol; Zurcale; Zurcamed; ***Braz.***: Gastropan; Pantasun; Pantocal; Pantopaz; Pantox; Pantozol; Pantrat; Tecta; Ziprol; Zurcal; ***Canad.***: Panto; Pantoloc; Tecta; ***Chile***: Ulcemex; Zurcal; ***China***: Fu Shi Tan (富诗坦); Jian Lang Chen (健朗晨); Luoxu (罗旭); Nuosen (诺森); Panlisu (泮立苏); Panmeilu (潘美路); Pantoloc; Tai Mei Ni Ke (泰美尼克); Wei Di (韦迪); Wei Ke An (卫可安); ***Cz.***: Adozole; Apo-Panto; Controloc; Gastrolan; Gastronorm; Loxanto; Nolpaza; Panogastin; Pantecta; Pantoloc; Pantomyl; Pantozol; Pantul; Somac; Supracid; Ulprix; ***Denm.***: Contracid†; Magamyl; Olypan†; Panrazol; Pantelke†; Pantoloc; Pantomyl†; PantoNyco; PantoNycomed; Prazomyl; Sigilamyl†; Ulprix; Zanlytab; Zaprym†; ***Fin.***: Giasemin; Panzor; Somac; ***Fr.***: Eupantol; Inipepsia; Inipomp; Ipraalox; Pantopan†; Pantozol; ***Ger.***: Gastrozol; Pantoprem; Pantozol; Rifun; ***Gr.***: Controloc; Gastroprozal; Noxadif; Ozepran; Pantium; Pantosec; Praz-Up; Roxitrol; Ulcened; Ulceron; Verneg; Zurcazol; ***Hong Kong***: Panrazol; Pantoloc; ***Hung.***: Controloc; Gerprazol; Noacid; Nolpaza; Pafenon; Panogastin; Pantacid; Pantomed†; Pazolexa; Zeladrol; Zimpax; ***India***: Achpilori; Aciban; Acidopent; Acihalt; Ampen; Anzop; Apanta; Apentral; Aripan; Arloc; Asipan; Avopan; Bus; Canozol; Caspan; CGPan; Concid; Controsec; Cool Pan; Culex; Cupan; Cypan; Digene Total; Domocid-PX; Dupent; E-Pento; Eracid; Fozole; Fulpan; Gasopep; Genpen; Gerdopan; Glopan; Hypa; Hyzole-P; Inpan; Intapan; Ipant; Isopan; Kapyl; Kenta; Klenz; Kurepane; Leetop; Lupipan; Medipent; Newpan; Nexpan; Nitzole; Normocid; Nupan; Omentum; Orapan; Oritop; Oxypan; Pacid; Pagero; Palgic; Palin; Palio; Pan-OD; Pan; Panbloc; Pancas; Pandat; Pandon; Pandosun; Pandry; Panfast; Pangy; Pankai; Panloc; Panmint; Pano; Panocid; Panopaz; Panor; Panpac; Panpari; Panpra; Panpro; Panprozole; Panpure; Pansa; Pansafe; Pansaul; Pansoft; Panstrike; Pansure; Pantab; Pantabit; Pantacin; Pantact; Pantadal; Pantagon; Pantakind; Pantamax; Pantamep; Pantanib; Pantaz; Pantazol; Pantec; Pantest; Pantif; Pantin-RD; Pantin; Pantium; Panto; Pantocaf; Pantocar; Pantocid; Pantocip; Pantocos; Pantodac; Pantoday; Pantofer; Pantofin; Pantol; Pantolex; Pantoloc; Pantolup; Pantom; Pantomas; Pantomax; Pantomore; Pantonid; Pantonis; Pantop; Pantopan; Pantopep; Pantopik; Pantopril; Pantosec; Pantosh; Pantosig; Pantosol; Pantotab; Pantotive; Pantovar; Pantox; Pantoz; Pantozol; Pantra; Pantric; Pantroz; Pantry; Pantz; Panum; Panwell; Panz; Panzac; Pentaloc; Praize; ***Indon.***: Caprol; Panso; Pantozol; Pepzol; ***Irl.***: Controloc Control; Freestom; Gastrolief; Nolpaza; Pantecta; Pantium; Pantoflux; Pantoloc; Pantosec; Pantozol Control; Pantup; Protium; Protizole; Somac; Zolepant; ***Israel***: Controloc; Pantoavenir; ***Ital.***: Pantecta; Pantopan; Pantorc; Peptazol; ***Malaysia***: Controloc; Toprazole; ***Mex.***: Panmicid; Pantozol; Peucetol; Prazolan; Protocord; Supacid; Tecta; Tevozol; Zolpeptid; Zolpra; Zoltum; Zurcal; ***Neth.***: Controloc Control; Empaflun; Ipraalox; Nolpaza†; Panore; Pantecta; Pantogerolan; Pantoloc Control; Pantorc†; Pantozol; Previfect; Somac Control; ***Norw.***: Pantoloc Control; Somac; ***NZ***: Pantocid; Somac†; ***Philipp.***: Domelong; Pantazol; Pantocar; Pantoloc; Pantopraz; Pantoprix; Pantor; Pantozim; Pantozol; Pentowin; Ulcepraz; ***Pol.***: Anesteloc; Contix; Contracid; Controloc; IPP; Noacid; Nolpaza; Panogastin; Panprazox; Pantecta; Pantogen; Pantozol Control; Panzol; Ranloc; Somac Control; Xotepic; ***Port.***: Apton; Controloc Control; Panbrabene; Panrazol; Pantecta; Pantoc; Panzat; Pranzol; Praoz†; Prazomyl†; Rarozol†; Somac Control; Zamol; Zamotil; Zipantol; Zurcal; ***Rus.***: Controloc (Контролок); Nolpaza (Нольпаза); Panum (Панум); Peptazol (Пептазол); Sunpraz (Санпраз); Zipantola (Зипантола); ***S.Afr.***: Conoran; Controloc†; Gastriwin; Pantocid; Pantoloc; Pentoz; Peploc; Topzole; ***Singapore***: Controloc; Peptazol; ***Spain***: Alapanzol; Anagastra; Citrel; Nolpaza; Normogastrol; Panproton; Pantecta; Pantoloc; Ulcotenal; ***Swed.***: Pantoloc; ***Switz.***: Contraflux; Gastrowell†; Panprax; Pantozol; Zurcal; ***Thai.***: Controloc; Pantocid; Pantoprol; ***Turk.***: Gastrazol; Pandev; Panref; Panthec; Panto; Pantpas; Protech; Protinum; Protonex; Pulcet; Ulcoreks; ***UK***: Pantoloc Control; Protium; ***Ukr.***: Controloc (Контролок); Nolpaza (Нольпаза); Pantokar (Пантокар); Pantosandoz (Пантосандоз)†; Penta (Пента)†; Proxium (Проксиум); Pulcet (Пульцет); Tecta Control (Текта Контрол); Ultera (Ультера)†; ***USA***: Protonix; ***Venez.***: Pantop.

Multi-ingredient Preparations. ***Austral.***: Somac-MA†; ***Ger.***: Zac-Pac; ***India***: Achpilori-D; Aciban-DSR; Acidopent-DSR; Aldepraz-D; Alizole-DSR; Anzop-D; Apentral-D; Aripan-D; Arloc-D; Armcid D; Asipan-D; Avopan-D; Bus-D; Canozol-D; Cazole-D; Concid-DM; Concid-DSR; Cupan-DSR; Cypan-D; Dazole-D; Deepen-D; Depam; Domocid-PX; Dompan; Domtac; Domtec-P; Dufex; Dupent-D; Dyoflux; E-Pento-D; Eracid-D; Eupanta D; FB; Fozole-D; Fulpan-D; Ganaton Total; Genpen-D; Gerdom; Gi-Fri; Glopan-D; GR8-OD; Hypa-D; Hyzole-DP; Inpan-D; Intapan-D; IPD; Kapyl-D; Kenta-D; Klenz-D; Kurepane-D; Latop-D; Leetop-D; Medipent-D; Moza Plus; Multipan-D; Nitzole-D; Nupan-D; Odipan-D; Odipep; Omentum-D; Orapan-D; Oritop-D; Oxypan-D; Paleo-ISR; Palgic-D; Palin-D; Palio-D; Palzic-D; Pan-D; Pancas-D; Pandat-D; Pandiff; Pandom; Pandostal; Pandosun-D; Pandry D; Panfast-D; Pangy-DM; Pankai-D; Panlee-D; Panmint-D; Pano-D; Panopaz-D; Panor-D; Panpac-D; Panpari-D; Panpra-D; Panpro-D; Panrole-D; Pansa-D; Pansafe-D; Pansaul-D; Pansi-SD; Pansoft-D; Panstrike-D; Pantabit-D; Pantabol-D; Pantact-D; Pantadal-D; Pantadom; Pantagon-DM; Pantamep-D; Pantanib-D; Pantanib-IT; Pantapil-D; Pantec Plus; Pantec-D; Pantest-D; Pantin-D; Pantium-D; Panto-D; Pantocar-D; Pantocid-D; Pantocid-HP; Pantocid-IT; Pantocos-D; Pantodac-D; Pantoday-D; Pantofer-D; Pantoflux; Pantol-D; Pantolex-D; Pantom-D; Pantomas-D; Pantomed-D; Pantomore-D; Pantonid-D; Pantop-D; Pantop-HP Kit; Pantop-HP; Pantopik-D; Pantosec D; Pantosh D; Pantosig-D; Pantosym-D; Pantotive-D; Pantovar-D; Pantovom; Pantox-D; Pantoz-D; Pantozol-D; Pantra-D; Pantry-D; Pantz-D; Pantz-DM; Panum-D; Panz-D; Panz-SR; Panzac-D; Panzo-D; Praize-D; ***Malaysia***: Klacid HP 7; ***Neth.***: PantoPAC; ***Switz.***: GastroPant; ***Ukr.***: β-Klatinol (β-КЛАТИНОЛ).

Pharmacopoeial Preparations

USP 36: Pantoprazole Oral Suspension; Pantoprazole Sodium Delayed-Release Tablets.

Pargeverine Hydrochloride *(rINNM)*

Pargeverina, hidrocloruro de; Pargévérine, Chlorhydrate de; Pargeverini Hydrochloridum; Propinox Hydrochloride; Пареверина Гидрохлорид.

2-(Dimethylamino)ethyldiphenyl(2-propynyloxy)acetate hydrochloride.

$C_{21}H_{23}NO_3$,HCl=373.9

CAS — 13479-13-5 (pargeverine); 2765-97-1 (pargeverine hydrochloride).

UNII — XT63P694CJ.

Profile

Pargeverine is reported to possess antimuscarinic and smooth-muscle relaxant properties and has been used in the treatment of gastrointestinal and smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Becebuen Gotas; Nova Paratropina; Sertal; ***Chile***: Bevitex; Bramedil; Plazolit; Viadil; Viplan; Viproxil; ***Mex.***: Bipasmin; Plidan; ***Port.***: Vagopax; ***Venez.***: Plidan.

Multi-ingredient Preparations. ***Arg.***: Antispasmina Compuesto; Apasmo Compuesto; Becebuen Compuesto; Binvex; Espasmo Dolex; Nova Paratropina Compositum; Propalgin; Sertal Compuesto; ***Chile***: Bramedil Compuesto; Scopanil; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; ***Mex.***: Firac Plus; Plidan Compuesto; ***Venez.***: Dologinex; Plidan Compuesto.

Pentaerythritol

Pentaeritritol; Tetramethylolmethane; Пентаэритритол.

2,2-Bis(hydroxymethyl)propane-1,3-diol.

$C_5H_{12}O_4$=136.1

CAS — 115-77-5.

ATC Vet — QA06AD14.

UNII — SU420W1S6N.

Profile

Pentaerythritol is an osmotic laxative used in the treatment of constipation (p. 1804.3) in oral doses of 5 to 15 g daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Auxitrans.

Peppermint Leaf

Black Mint; Borsosmentalevél; Hoja de Menta; Hortelã-Pimenta; List máty peprné; Liść mięty pieprzowej; Menta piperita, hoja de; Menth. Pip.; Mentha Piperita; Menthae Piperitae Folium; Menthe Poivrée; Menthe poivrée, feuille de; Pepparmyntblad; Peppermint; Pfefferminzblätter; Piparmintunlehti; Pipirmėčių lapai; White Mint; Листья Мяты Перечной.

*ATC Herb — HA03AW5039 (*Mentha x piperita*: leaf).*

UNII — A389O33LX6.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract. Also in *USNF.*

Ph. Eur. 8: (Peppermint Leaf). The whole or cut dried leaves of *Mentha X piperita*, containing not less than 1.2% v/w of essential oil if whole, or not less than 0.9% v/w if cut. It has a characteristic and penetrating odour and a characteristic aromatic taste. Protect from light.

USNF 31: (Peppermint). The dried leaf and flowering top of *Mentha piperita* (Labiatae). It has an aromatic, characteristic odour and a pungent taste, and produces a cooling sensation in the mouth.

Peppermint Oil

Aceite esencial de menta; Borsosmentaolaj; Essence de Menthe Poivrée; Essência de Hortelã-Pimenta; Menta piperita, aceite esencial de; Menthae Piperitae Aetheroleum; Menthae Piperitae Etheroleum; Menthe poivrée, huile essentielle de; Minzöl; Nane Yağı; Ol. Menth. Pip.; Olejek miętowy; Oleum Menthae Piperitae; Pepparmyntolja; Pfefferminzöl; Piparminttuöljy; Pipirmėčių eterinis aliejus; Silice máty peprné; Масло Мяты Перечной.

CAS — 8006-90-4.

*ATC Herb — HD04AW5002 (*Mentha x piperita*: essential oil); HA03AW5038 (*Mentha x piperita*: essential oil).*

UNII — AV092KU4JH.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Peppermint Oil). It is obtained by steam distillation from the fresh overground parts of the flowering plant of *Mentha X piperita*. It contains 30.0 to 55.0% menthol, 14.0 to 32.0% menthone, and 2.8 to 10.0% menthyl acetate, 3.5 to 8.0% 1,8-cineole, 1.5 to 10.0% isomenthone, 1.0 to 8.0% menthofuran, 1.0 to 3.5% limonene, not more than 3.0% pulegone, and not more than 1.0% carvone; the ratio of 1,8-cineole content to limonene content is not less than two.

It is a colourless, pale yellow, or pale greenish-yellow liquid with a characteristic odour and taste followed by a sensation of cold. Miscible with alcohol and with dichloromethane. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees.

USNF 31: (Peppermint Oil). The volatile oil distilled with steam from the fresh overground parts of the flowering plant *Mentha piperita* (Labiatae), rectified by distillation, and neither partially nor wholly dementholised. It yields not less than 5% of esters calculated as menthyl acetate and not less than 50% of total menthol, free and as esters.

It is a colourless or pale yellow liquid with a strong, penetrating, characteristic odour and a pungent taste, followed by a sensation of cold when air is drawn into the mouth. Soluble 1 in 3 of alcohol (70%) with not more than slight opalescence. Store in airtight containers at a temperature not exceeding 40 degrees.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that PVC bottles softened and distorted fairly rapidly in the presence of peppermint oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastic medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Uses and Administration

Peppermint oil is an aromatic carminative that relaxes gastrointestinal smooth muscle and relieves flatulence and colic. Enteric-coated capsules containing peppermint oil are used for the relief of symptoms of the irritable bowel syndrome or gastrointestinal spasm secondary to other disorders. Usual oral doses are 0.2 mL three times daily, (increased to 0.4 mL three times daily if necessary) for up to 2 to 3 months. The capsules should be taken before food and swallowed whole, not chewed.

Peppermint oil is used as a flavour and with other volatile agents in preparations for respiratory-tract disorders. It is also used in aromatherapy.

Peppermint leaf, the source of the oil, has also been used for its carminative and flavouring properties.

Gastrointestinal disorders. Menthol (p. 2553.2), the major constituent of peppermint oil, has properties similar to those of calcium-channel blockers on smooth muscle such as that in the human gut.[1] Reviews[2,3] of the use of peppermint oil in irritable bowel syndrome (p. 1810.3) concluded that there was some evidence of its benefit.

The relaxant effect of peppermint oil on the gastrointestinal tract has been used to reduce spasm during endoscopy by giving solubilised peppermint oil directly into the lumen, through the accessory channel of the endoscope. It has been described as effective during colonoscopy[4] and may be more effective than intramuscular hyoscine butylbromide during upper gastrointestinal endoscopy.[5] Addition of peppermint oil to barium enema has also been tried and appears to reduce spasm[6,7] and the need for intravenous antispasmodics.[6]

1. Grigoleit H-G, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. *Phytomedicine* 2005; **12:** 612–16.
2. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. *Am J Gastroenterol* 1998; **93:** 1131–5.
3. Grigoleit H-G, Grigoleit P. Peppermint oil in irritable bowel syndrome. *Phytomedicine* 2005; **12:** 601–6.
4. Asao T, *et al.* An easy method for the intraluminal administration of peppermint oil before colonoscopy and its effectiveness in reducing colonic spasm. *Gastrointest Endosc* 2001; **53:** 172–7.
5. Hiki N, *et al.* Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. *Gastrointest Endosc* 2003; **57:** 475–82.
6. Sparks MJW, *et al.* Does peppermint oil relieve spasm during barium enema? *Br J Radiol* 1995; **68:** 841–3.
7. Asao T, *et al.* Spasmolytic effect of peppermint oil in barium during double-contrast barium enema compared with Buscopan. *Clin Radiol* 2003; **58:** 301–5.

Sore nipples. There is some evidence[1] that topical application of peppermint water after each feed may help prevent nipple cracks and soreness in breast-feeding mothers.

1. Sayyah Melli M, *et al.* Effect of peppermint water on prevention of nipple cracks in lactating primiparous women: a randomized controlled trial. *Int Breastfeed J* 2007; **2:** 7.

Adverse Effects and Precautions

Peppermint oil can be irritant and may rarely cause hypersensitivity reactions. Reported reactions include erythematous skin rash, headache, bradycardia, muscle tremor, and ataxia. Heartburn has also been reported.

Effects on the cardiovascular system. Idiopathic atrial fibrillation occurred in 2 patients addicted to 'peppermints'. Normal rhythm was restored when peppermint-sucking ceased.[1]

1. Thomas JG. Peppermint fibrillation. *Lancet* 1962; **i:** 222.

Hypersensitivity. Exacerbation of asthma, with wheezing and dyspnoea, was associated with the use of paste-based toothpastes containing peppermint or wintergreen as a flavouring.[1]

1. Spurlock BW, Dailey TM. Shortness of (fresh) breath—toothpaste-induced bronchospasm. *N Engl J Med* 1990; **323:** 1845–6.

Interactions

Adverse effects may be more likely if peppermint oil is taken with alcohol. Enteric-coated capsules containing peppermint oil should not be taken immediately after food or with antacids. There is some evidence that peppermint oil can inhibit the cytochrome P450 isoenzyme CYP3A4, and may affect the clearance of drugs whose metabolism is mediated by this enzyme.

References.

1. Dresser GK, *et al.* Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. *Clin Pharmacol Ther* 2002; **72:** 247–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mintec; Origins IBS Relief; ***Austria***: Colpermin; Medicalm; ***Braz.***: Mentaliv; ***Cz.***: Colpermin; Matovy; Nat Maty Peprne†; ***Fr.***: Locabiotal; ***Ger.***: Euminz; Inspirol Heilpflanzenol†; spasmo gallo sanol N; Wildkrauterol spezial N; ***Gr.***: Colpermin; ***Hong Kong***: Colpermin; ***Hung.***: China-Oil; Mentil; ***Irl.***: Colpermin; ***Israel***: China Oel; Colpermin; Po Sum On Medicated Oil†; ***Ital.***: Carmint; Mintoil; ***Neth.***: Tempocol; ***Norw.***: Chiana; ***NZ***: Mintec; ***Port.***: Colominte; ***S.Afr.***: Pepermentdruppels†; ***Singapore***: Colpermin; ***Switz.***: Colpermin; ***Thai.***: Colpermin; Sahakarn Peppermint; ***Turk.***: China Oel†; Colpermin; ***UK***: Apercap; Colpermin; Equilon Herbal; Mintec; Obbekjaers.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Canad.***: Cynara Complex†; Lemon Balm†; ***Fr.***: Carominthe; Poconeol no 59†; ***UK***: Catarrh Cream; Laxadoron; Medicinal Gargle; Oleum Rhinale.

Pharmacopoeial Preparations

BP 2014: Concentrated Peppermint Emulsion; Gastro-resistant Peppermint Oil Capsules; Peppermint Spirit;
USNF 31: Peppermint Water;
USP 36: Peppermint Spirit.

Phenolphthalein *(BAN, rINN)*

Dihydroxyphthalophenone; Fenolftalein; Fenolftaleína; Fenolftaleinas; Fenoliftaleiini; Fenoloftaleina; Phénolphtaléine; Phenolphtaleinum; Phenolphthaleinum; Фенолфталеин.

3,3-Bis(4-hydroxyphenyl)phthalide.

$C_{20}H_{14}O_4$=318.3

CAS — 77-09-8.

ATC — A06AB04.

ATC Vet — QA06AB04.

UNII — 6QK969R2IF.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Phenolphthalein). A white or almost white powder. Practically insoluble in water; soluble in alcohol. Protect from light.

Uses and Administration

Phenolphthalein is a diphenylmethane stimulant laxative that has been used for the treatment of constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. It has been withdrawn in many countries because of concern over its carcinogenic potential after reports of tumours in *rodents.*

It has been given in pills or tablets, and as an emulsion with liquid paraffin. Yellow phenolphthalein, an impure form, has been used similarly.

Adverse Effects and Precautions

As for Bisacodyl, p. 1821.2. Hypersensitivity reactions, usually as skin rashes or eruptions, have occurred with phenolphthalein. Phenolphthalein may cause pink discoloration of alkaline urine.

Tumours have occurred in *rats* and *mice* given very high doses of phenolphthalein; there does not appear to be evidence of carcinogenicity in humans, but phenolphthalein-containing products have been withdrawn in many countries because of concerns about long-term safety.

Effects on the skin. Reports of skin reactions associated with phenolphthalein include fixed drug eruptions,[1,2] erythema multiforme reactions,[1,3] and toxic epidermal necrolysis.[4,5]

1. Baer RL, Harris H. Types of cutaneous reactions to drugs. *JAMA* 1967; **202:** 710–13.
2. Savin JA. Current causes of fixed drug eruptions. *Br J Dermatol* 1970; **83:** 546–9.
3. Shelley WB, *et al.* Demonstration of intercellular immunofluorescence and epidermal hysteresis in bullous fixed drug eruption due to phenolphthalein. *Br J Dermatol* 1972; **86:** 118–25.
4. Kar PK, *et al.* Toxic epidermal necrolysis in a patient induced by phenolphthalein. *J Indian Med Assoc* 1986; **84:** 189–93.
5. Artymowicz RJ, *et al.* Phenolphthalein-induced toxic epidermal necrolysis. *Ann Pharmacother* 1997; **31:** 1157–9.

Overdosage. The most likely consequence of phenolphthalein overdosage is excessive purgation, which may require fluid and electrolyte replacement. However, a possible association with acute pancreatitis occurred in a 34-year-old man who inadvertently ingested phenolphthalein 2 g. There was complete recovery with no sequelae from the pancreatitis.[1] Widespread organ failure with disseminated intravascular coagulation, massive liver damage, pulmonary oedema, renal failure, and myocardial damage in a second patient[2] were attributed to self-poisoning with an unknown quantity of phenolphthalein-containing laxative, although the diagnosis was problematic. The patient died despite intensive support.

1. Lambrianides AL, Rosin RD. Acute pancreatitis complicating excessive intake of phenolphthalein. *Postgrad Med J* 1984; **60:** 491–2.
2. Sidhu PS, *et al.* Fatal phenolphthalein poisoning with fulminant hepatic failure and disseminated intravascular coagulation. *Hum Toxicol* 1989; **8:** 381–4.

Pharmacokinetics

Up to 15% of phenolphthalein given orally is subsequently excreted in the urine. Enterohepatic circulation occurs and the glucuronide is excreted in the bile. Elimination may take several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fructines; ***India***: Jaglax; ***Israel***: Easylax; ***S.Afr.***: Brooklax†; Dr Mackenzies Veinoids†; Laxador†; Laxene†; SB Strong-Lax†; Super-Tabs†; Surget†; ***Thai.***: Phenolax; Regulim†; ***Turk.***: Alin; Laksafenol.

Multi-ingredient Preparations. ***Arg.***: Cascara Sagrada Bouzen; Cascara Sagrada Puler; Genolaxante; Veracolate†; ***Austral.***: Ford Pills†; ***Austria***: Waldheim Abfuhrdragees forte†; ***Chile***: Agarol†; Bulgarolax†; Fenokomp 39; Oblax A-1-1; ***India***: Coslax; Jetomisol-P; ***Indon.***: Laxadine; ***Israel***: Laxative Compound; ***Port.***: Doce Alivio; ***S.Afr.***: Brooklax Pills†; SB 3 Triple Action Pills†; ***Singapore***: Beagarol; ***Spain***: Laxante Bescansa Aloico†; ***Switz.***: Paragar; ***Thai.***: Anson; Emulax; Heroanson; Patarcolate; Taeniacide; Veracolate†; Zenda; ***Turk.***: Fenolaks; Karboseptin; Musilaks; ***UK***: Fam-Lax; ***USA***: Agoral.

Pipenzolate Bromide *(BAN, rINN)*

Bromuro de pipenzolato; Pipenzolat Bromür; Pipenzolate, Bromure de; Pipenzolate Methylbromide; Pipenzolati Bromidum; Pipenzolato, bromuro de; Пипензолата Бромид.

3-Benziloyloxy-1-ethyl-1-methylpiperidinium bromide.

$C_{22}H_{28}BrNO_3$=434.4

CAS — 13473-38-6 (pipenzolate); 125-51-9 (pipenzolate bromide).

ATC — A03AB14.

ATC Vet — QA03AB14.

UNII — JPX41DUS2B.

Profile

Pipenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of gastrointestinal disorders characterised by smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Cholspas†; ***Hong Kong***: Uni-Zolate†; ***Mex.***: Expal†; Pipzen; ***Turk.***: Piptalin.

Multi-ingredient Preparations. ***Chile***: Baldmin; Gasorbol; Sinpasmon; ***Hong Kong***: Infant-Sed†; ***Indon.***: Piptal; ***Mex.***: Espasal; Expal Compuesto; Finprob; ***Turk.***: Asilon; Libkol.

Piperidolate Hydrochloride *(BANM, rINNM)*

Hidrocloruro de piperidolato; Pipéridolate, Chlorhydrate de; Piperidolati Hydrochloridum; Piperidolato, hidrocloruro de; Пиперидолата Гидрохлорид.

1-Ethyl-3-piperidyl diphenylacetate hydrochloride.

$C_{21}H_{25}NO_2$,HCl=359.9

CAS — 82-98-4 (piperidolate); 129-77-1 (piperidolate hydrochloride).

ATC — A03AA30.

ATC Vet — QA03AA30.

UNII — 57UA660ILV.

Profile

Piperidolate hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been given in the symptomatic treatment of smooth muscle spasm associated with gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Dactiran; ***Mex.***: Dactil OB.

Multi-ingredient Preparations. ***Braz.***: Dactil OB.

Pipethanate Ethobromide *(rINNM)*

Ethylpipethanate Bromide; Etobromuro de pipetanato; Piperilate Ethobromide; Pipetanato, etobromuro de; Pipéthanate, Ethobromure de; Pipethanati Ethobromidum; Пипетаната Этобромид.

1-(2-Benziloyloxyethyl)-1-ethylpiperidinium bromide.

$C_{23}H_{30}BrNO_3$=448.4

CAS — 4546-39-8 (pipethanate); 23182-46-9 (pipethanate ethobromide).

Profile

Pipethanate ethobromide is an antimuscarinic with actions similar to those of atropine (p. 1312.1). It has been used in the symptomatic treatment of visceral spasms in oral doses of up to 160 mg daily in divided doses. Pipethanate ethobromide has been given intramuscularly or intravenously in doses of 10 to 20 mg daily; it has also been given rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Nospasmin; ***Ital.***: Spasmodil; ***Venez.***: Flespan.

Multi-ingredient Preparations. ***Chile***: Nospasmin Compuesto.

Pirenzepine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de pirenzepina; LS-519 (pirenzepine); LS-519-Cl2; Pirentsepiinidihydrokloridimonohydraatti; Pirenzepina, hidrocloruro de; Pirenzepin-dihidrokloridmonohidrát; Pirenzepin-dihydrochlorid monohydrát; Pirenzepindihydrokloridmonohydrat; Pirenzépine, Chlorhydrate de; Pirenzépine (dichlorhydrate de) monohydraté; Pirenzepini dihydrochloridum monohydricum; Pirenzepini Hydrochloridum; Pirenzepino dihidrochloridas monohidratas; Пирензепина Гидрохлорид.

5,11-Dihydro-11-(4-methylpiperazin-1-ylacetyl)pyrido[2,3-*b*][1,4]benzodiazepin-6-one dihydrochloride monohydrate.

$C_{19}H_{21}N_5O_2$,2HCl,H_2O=442.3

CAS — 28797-61-7 (pirenzepine); 29868-97-1 (pirenzepine hydrochloride).

ATC — A02BX03.

ATC Vet — QA02BX03.

UNII — 10YM403FLS.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Pirenzepine Dihydrochloride Monohydrate; Pirenzepine Hydrochloride BP 2014). A white or yellowish crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane; slightly soluble in methyl alcohol. A 10% solution in water has a pH of 1.0 to 2.0. Protect from light.

Uses and Administration

Pirenzepine is a selective M_1 tertiary amine antimuscarinic that displays a preferential action on the gastric mucosa thus causing a reduction in the secretion of gastric acid; it also reduces the secretion of pepsin. At therapeutic doses it has few other antimuscarinic actions.

Pirenzepine hydrochloride has been used in the management of peptic ulcer disease (p. 1813.2) in a usual oral dose of 50 mg two or three times daily for 4 to 6 weeks. It has also been given by slow intravenous or intramuscular injection in a dose of 10 mg every 12 hours.

Myopia. Pirenzepine ophthalmic gel has been investigated[1-4] in children for its potential in slowing the progression of myopia. In a study[3] involving 353 children with myopia, pirenzepine 2% gel given once or twice daily into the lower eyelid for 1 year was associated with reduced progression: at 12 months myopia had progressed by a mean of 0.7 and 0.47 dioptres in children assigned to once and twice daily dosage respectively, compared with 0.84 dioptres in those given placebo. The gel was generally well tolerated, the most frequent adverse effects being development of papillae or follicles, or abnormalities of accommodation such as mydriasis or cycloplegia. Of 55 patients who failed to complete the study, 31 did so as a result of adverse effects.

1. Bartlett JD, *et al.* A tolerability study of pirenzepine ophthalmic gel in myopic children. *J Ocul Pharmacol Ther* 2003; **19:** 271–9.
2. Siatkowski RM, *et al.* US Pirenzepine Study Group. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol* 2004; **122:** 1667–74.
3. Tan DTH, *et al.* Asian Pirenzepine Study Group. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology* 2005; **112:** 84–91.
4. Siatkowski RM, *et al.* U.S. Pirenzepine Study Group. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *J AAPOS* 2008; **12:** 332–9.

Adverse Effects and Precautions

Antimuscarinic adverse effects such as dry mouth and blurred vision have been reported but are less common with pirenzepine than with atropine (see p. 1312.1). Pirenzepine should be used with caution in patients with renal impairment, particularly those with end-stage renal failure.

Effects on the blood. Thrombocytopenia in one patient and agranulocytosis in another was probably associated with the use of pirenzepine.[1]

1. Stricker BHC, *et al.* Blood disorders associated with pirenzepine. *BMJ* 1986; **293:** 1074.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Pirenzepine is absorbed from the gastrointestinal tract but the bioavailability is reported to be only about 20 to 30%, and is decreased to about 10 to 20% when taken with food. Very little pirenzepine is metabolised. About 10% of an oral dose is excreted unchanged in the urine, the remainder being excreted in the faeces.

Pirenzepine has an elimination half-life of about 12 hours and is about 12% bound to plasma proteins. Diffusion across the blood-brain barrier is poor and only minimal amounts are present in breast milk.

Renal impairment. The renal clearance and total plasma clearance of pirenzepine may be significantly reduced in patients with renal impairment,[1,2] with clearance decreasing proportionately with the degree of renal impairment. The half-life of pirenzepine is increased with reported values ranging from 14 to 20 hours.[1-3] Plasma concentrations of pirenzepine may be reduced by up to about 50% during haemodialysis.[2,3]

1. Krakamp B, *et al.* Steady-state intravenous pharmacokinetics of pirenzepine in patients with hepatic insufficiency and combined renal- and hepatic insufficiency. *Eur J Clin Pharmacol* 1989; **36:** 71–3.
2. Krakamp B, *et al.* Steady-state intravenous pharmacokinetics of pirenzepine in patients with differing degrees of renal dysfunction. *Eur J Clin Pharmacol* 1989; **36:** 75–8.
3. MacGregor T, *et al.* Oral pharmacokinetics of pirenzepine in patients with chronic renal insufficiency, failure, and maintenance haemodialysis. *Eur J Clin Pharmacol* 1990; **38:** 405–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Gastrozepin; ***Ger.***: Gastrozepin; ***Gr.***: Gastrozepin; Threptin; ***Jpn***: Gastrozepin; ***Rus.***: Gastrozepin (Гастроцепин); ***Thai.***: Cevanil; ***Ukr.***: Gastrozepin (Гастроцепин).

Platyphylline Acid Tartrate

Platyphylline Bitartrate; Platyphyllini Hydrotartras; Платифиллина Битартрат.

1,2-Dihydro-12-hydroxysenecionan-11,16-dione hydrogen tartrate.

$C_{18}H_{27}NO_5$,$C_4H_6O_6$=487.5

CAS — 480-78-4 (platyphylline); 1257-59-6 (platyphylline acid tartrate).

UNII — 6SXK0Y9D98.

Profile

Platyphylline acid tartrate is a pyrrolizidine alkaloid occurring in *Senecio platyphyllus* and other *Senecio* spp. It has antimuscarinic actions and has been given alone or with papaverine in antispasmodic preparations.

Plaunotol *(rINN)*

CS-684; Plaunotolum; Плаунотол.
(2*Z*,6*E*)-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-6-methyl-2,6-octadiene-1,8-diol.
$C_{20}H_{34}O_2$=306.5
CAS — 64218-02-6.
UNII — MV715X4634.

Profile

Plaunotol is a complex aliphatic alcohol extracted from the Thai medicinal plant plau-noi (*Croton sublyratus* (Euphorbiaceae)). It is reported to possess cytoprotective properties and has been used in the treatment of gastritis and peptic ulcer disease in an oral dose of 80 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Kelnac; ***Thai.***: Kelnac†.

Polaprezinc *(rINN)*

Polaprézinc; Polaprezincum; Z-103; Zinc-L-carnosine; Полапрезинк.
catena-Poly{zinc-μ-[β-alanyl-L-histidinato(2-)-*N*,N^N,*O*:N^π]}.
$(C_9H_{12}N_4O_3Zn)_n$
CAS — 107667-60-7.

Profile

Polaprezinc is a cytoprotective agent used in the treatment of peptic ulcer disease and as a zinc supplement. It is under investigation as a treatment for taste disorders.

Poldine Metilsulfate *(BAN, pINN)*

IS-499; McN-R-726-47; Metilsulfato de poldina; Poldina, metilsulfato de; Poldine Methosulphate; Poldine Methylsulfate (USAN); Poldine Methylsulphate; Poldine, Métilsulfate de; Poldini Metilsulfas; Польдина Метилсульфат.
(*RS*)-2-Benziloyloxymethyl-1,1-dimethylpyrrolidinium methylsulphate.
$C_{21}H_{26}NO_3.CH_3O_4S$=451.5
CAS — 596-50-9 (poldine); 545-80-2 (poldine metilsulfate).
ATC — A03AB11.
ATC Vet — QA03AB11.
UNII — 564C0W9848.

Pharmacopoeias. In *Br.*

BP 2014: (Poldine Metilsulfate). A white odourless or almost odourless crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. A 1% solution in water has a pH of 5.0 to 7.0.

Profile

Poldine metilsulfate is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1) and has been used in the management of gastrointestinal disorders, including peptic ulcer disease.

Preparations

Pharmacopoeial Preparations
BP 2014: Poldine Tablets.

Polycarbophil *(BAN, rINN)*

Policarbofilo; Polycarbophile; Polycarbophilum; Поликарбофил.
CAS — 9003-97-8.
UNII — W25LM17A4W.

Pharmacopoeias. In *US.*

USP 36: (Polycarbophil). It is polyacrylic acid cross-linked with divinyl glycol. White to creamy-white granules, with a characteristic, ester-like odour. Swells in water to a range of volumes, depending primarily on the pH. Insoluble in water, in common organic solvents, and in dilute acids and alkalis. A 1% mixture in water has a pH of not more than 4.0. Store in airtight containers.

Polycarbophil Calcium *(BANM, rINNM)*

AHR-3260B; Calcii Polycarbophilum; Calcium Polycarbophil (USAN); HSR-237; Policarbofilo cálcico; Polycarbophile Calcique; Polycarbophilum Calcii; Polykarbofiilikalsium; Polykarbofilkalcium; Polykarbophilum Calcicum; WI-140; Кальций Поликарбофил.
CAS — 126040-58-2.
ATC — A06AC08.
ATC Vet — QA06AC08.
UNII — 8F049NKY49.

Pharmacopoeias. In *US.*

USP 36: (Calcium Polycarbophil). A white to creamy-white powder. Insoluble in water, in common organic solvents, and in dilute acids and alkalis. It loses not more than 10% of its weight on drying and contains not less than 18% and not more than 22% of calcium, calculated on the dried basis. Store in airtight containers.

Uses and Administration

Polycarbophil calcium has similar properties to ispaghula (p. 1849.2) and is used as a bulk laxative and for adjusting faecal consistency. After ingestion calcium ions are replaced by hydrogen ions from gastric acid and the resultant polycarbophil exerts a hydrophilic effect in the intestines.

It is given orally in a usual dose equivalent to 1 g of polycarbophil up to four times daily, as necessary. Doses should be taken with at least 250 mL of water.

Polycarbophil is used topically as a vaginal moisturiser and as an ocular lubricant.

References.

1. Danhof IE. Pharmacology, toxicology, clinical efficacy, and adverse effects of calcium polycarbophil, an enteral hydrosorptive agent. *Pharmacotherapy* 1982; **2:** 18–28.
2. Toskes PP, *et al.* Calcium polycarbophil compared with placebo in irritable bowel syndrome. *Aliment Pharmacol Ther* 1993; **7:** 87–92.
3. Chiba T, *et al.* Colonic transit, bowel movements, stool form, and abdominal pain in irritable bowel syndrome by treatments with calcium polycarbophil. *Hepatogastroenterology* 2005; **52:** 1416–20.

Adverse Effects and Precautions

As for Ispaghula, p. 1849.2. Polycarbophil calcium releases calcium ions in the gastrointestinal tract and should be avoided by patients who must restrict their calcium intake.

There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such bulk laxatives are swallowed dry. Therefore, they should always be taken with sufficient fluid and should not be taken immediately before going to bed. They should be avoided by patients who have difficulty swallowing.

Interactions

The calcium component of polycarbophil calcium may produce interactions typical of calcium salts (p. 1786.1), such as reducing the absorption of tetracyclines from the gastrointestinal tract; it should not be taken within 2 hours of the antibacterial. Polycarbophil calcium has also been reported to decrease the absorption of ciprofloxacin and mycophenolate mofetil.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Replens; ***Braz.***: Benestare; Muvinor; ***Canad.***: Equalactin†; Fiber-on-Tablet; Fibre Laxative; Prodiem Bulk Fibre; Replens; ***Chile***: Edubel; Hidrogel; ***Ger.***: Rephresh; Replens; ***Gr.***: Fibercon; ***India***: Calibs; Fibotab; ***Ital.***: Modula; Replens; ***Jpn***: Colonel; ***Mex.***: Replens; ***Singapore***: RepHresh; Replens†; ***Swed.***: Replens; ***USA***: Equalactin; FiberLax; Fibercon; FiberNorm†; Replens.

Multi-ingredient Preparations. ***Philipp.***: Mithra-Intim; ***UK***: Feminesse.

Potassium Acid Tartrate

E336; Hydrogenvinan draselný; Kalii Hydrogenotartras; Kaliovandenilio tartratas; Kalium Hydrotartaricum; Káliumhidrogén-tartarát; Kaliumhydrogentartrat; Kaliumvätetartrat; Kaliumvetytartraatti; Potassium Bitartrate (USAN); Potassium Hydrogen Tartrate; Potassium, hydrogénotartrate de; Potasu wodorowinian; Purified Cream of Tartar; Tartarus Depuratus; Tartrato ácido de potasio; Weinstein; Кислый Виннокислый Калий.
$C_4H_5KO_6$=188.2
CAS — 868-14-4.
ATC — A12BA03.
ATC Vet — QA12BA03.
UNII — NPT6P8P3UU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Potassium Hydrogen Tartrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

USP 36: (Potassium Bitartrate). Colourless or slightly opaque crystals or a white, crystalline powder. Slightly soluble in water; soluble in boiling water; very slightly soluble in alcohol. A saturated solution is acid to litmus. Store in airtight containers.

Profile

Potassium acid tartrate is given with sodium bicarbonate as a suppository for the treatment of constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. Carbon dioxide gas is produced in the rectum, which stimulates defaecation within 5 to 30 minutes.

Potassium acid tartrate is used as a food additive and pharmaceutical aid.

Potassium acid tartrate has been used as an ingredient of preparations for potassium supplementation, although other potassium salts are usually preferred. For the general properties of potassium salts, see p. 1793.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Lecicarbon; ***Ital.***: Potassion; ***Jpn***: Circanetten; ***Mon.***: Eductyl; ***Swed.***: Relaxit; ***Thai.***: Circanetten; ***USA***: Ceo-Two.

Homoeopathic Preparations. ***Ger.***: Phonix Silybum spag; Phonix Urtica-Arsenicum spag.

Pharmacopoeial Preparations
BPC 1968: Effervescent Potassium Tablets.

Potassium Sodium Tartrate

E337; Kalii Natrii Tartras; Kalio-natrio tartratas; Kalium Natrium Tartaricum; Kálium-nátrium-tartarát; Kaliumnatriumtartraatti; Kaliumnatriumtartrat; Potassium et de sodium, tartrate de; Rochelle Salt; Seignette Salt; Sodii et Potassii Tartras; Sodium Potassium Tartrate; Sodu potasu winian; Tartarus Natronatus; Tartrato de potasio y de sodio; Vinan draselno-sodný; Виннокислый Калий-натрий.
$C_4H_4KNaO_6.4H_2O$=282.2
CAS — 304-59-6 (anhydrous sodium potassium tartrate); 6381-59-5 (sodium potassium tartrate tetrahydrate); 6100-16-9 (sodium potassium tartrate tetrahydrate).
UNII — QH257BPV3J.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Potassium Sodium Tartrate Tetrahydrate). A white or almost white, crystalline powder or colourless transparent crystals. Very soluble in water; practically insoluble in alcohol.

USP 36: (Potassium Sodium Tartrate). Colourless crystals or a white, crystalline powder, with a cooling, saline taste. It effloresces slightly in warm dry air, the crystals often being coated with a white powder. Soluble 1 in 1 of water; practically insoluble in alcohol. Store in airtight containers.

Profile

Potassium sodium tartrate has been used as an osmotic laxative (p. 1804.1). It is also used as a food additive.

For the general properties of potassium salts, see p. 1793.1, and of sodium salts, see p. 1795.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Trigolax; Trilax.

Multi-ingredient Preparations. ***Austria***: Laxalpin†; ***Denm.***: Samarin; ***Fr.***: Romarene†; ***Hung.***: Samarin; ***Philipp.***: Castoria; ***Swed.***: Samarin; Samarin; ***UK***: Jaaps Health Salt.

Pharmacopoeial Preparations
BPC 1973: Compound Effervescent Powder.

Prifinium Bromide *(rINN)*

Bromuro de prifinio; PDB; Prifinii Bromidum; Prifinio, bromuro de; Prifinium, Bromure de; Pyrodifenium Bromide; Прифиния Бромид.
3-Diphenylmethylene-1,1-diethyl-2-methylpyrrolidinium bromide.
$C_{22}H_{28}BrN$=386.4
CAS — 10236-81-4 (prifinium); 4630-95-9 (prifinium bromide).
ATC — A03AB18.
ATC Vet — QA03AB18.
UNII — 3B7O9ZC520.

Profile

Prifinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It is structurally related to diphemanil metilsulfate (p. 2494.3).

Prifinium bromide is used to relieve smooth muscle spasms. Oral doses usually range from 90 to 180 mg daily in 3 divided doses. It can also be given by subcutaneous, intramuscular, or intravenous injection in a dose of 15 mg given 2 to 4 times daily. It has been given rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Riabal; ***Jpn***: Padrin; ***Mex.***: Anespas†; ***Rus.***: Riabal (Риабал); ***Ukr.***: Riabal (Риабал).

Proglumide *(BAN, USAN, rINN)*

CR-242; Proglumida; Proglumidum; W-5219; Xylamide; Проглумид.

(±)-4-Benzamido-*N*,*N*-dipropylglutaramic acid.

$C_{18}H_{26}N_2O_4$=334.4

CAS — 6620-60-6.

ATC — A02BX06.

ATC Vet — QA02BX06.

UNII — EPL8W5565D.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Proglumide is a cholecystokinin antagonist with an inhibitory effect on gastric secretion. It has been given orally or by intramuscular or intravenous injection in the treatment of peptic ulcer disease (p. 1813.2) and other gastrointestinal disorders.

Propantheline Bromide *(BAN, rINN)*

Bromuro de propantelina; Propanteliinibromidi; Propantelin Bromür; Propantelina, bromuro de; Propantelinbromid; Propantelin-bromid; Propantelino bromidas; Propanthelin-bromid; Propanthéline, Bromure de; Propanthelini bromidum; Propanthelinii Bromidum; Propanthelinium-bromid; Пропантелина Бромид.

Di-isopropylmethyl[2-(xanthen-9-ylcarbonyloxy)ethyl] ammonium bromide.

$C_{23}H_{30}BrNO_3$=448.4

CAS — 298-50-0 (propantheline); 50-34-0 (propantheline bromide).

ATC — A03AB05.

ATC Vet — QA03AB05.

UNII — UX9Z118X9F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Propantheline Bromide). A white or yellowish-white, slightly hygroscopic powder. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USP 36: (Propantheline Bromide). White or practically white, odourless, crystals. Very soluble in water, in alcohol, and in chloroform; practically insoluble in ether and in benzene.

Uses and Administration

Propantheline bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an antispasmodic (p. 1803.3) for conditions associated with gastrointestinal spasm, and as an adjunct in the treatment of peptic ulcer disease (p. 1813.2). The usual initial oral dose is 15 mg three times daily, 30 to 60 minutes before meals, and 30 mg at bedtime; doses of up to 120 mg daily may be needed in some patients. In elderly patients, doses of 7.5 mg three times daily may be sufficient. For doses in children, see below.

Propantheline bromide has been used in the treatment of adult enuresis or urinary incontinence, and in hyperhidrosis (see below), in doses similar to those given above.

Administration in children. Propantheline bromide is used in children for the symptomatic relief of gastrointestinal smooth muscle spasm. The *BNFC* suggests children from 1 month to 12 years may be given an oral dose of 300 micrograms/kg (maximum 15 mg) three or four times daily, at least 1 hour before food. Older children may be given the adult dose, see above.

Hyperhidrosis. Some antimuscarinics, including propantheline, have been applied topically in the treatment of hyperhidrosis (p. 1685.1). Adverse effects of antimuscarinics given orally generally preclude their use by this route, although oral propantheline was used successfully to control excessive sweating in 2 patients with spinal cord injuries,[1] and it is sometimes used in palliative care to control night sweats. The *BNF* notes that propantheline may be used for gustatory sweating in patients with diabetic neuropathy.

1. Canaday BR, Stanford RH. Propantheline bromide in the management of hyperhidrosis associated with spinal cord injury. *Ann Pharmacother* 1995; **29:** 489–92.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that propantheline should not be recommended for the treatment of urinary incontinence (p. 2349.2) or overactive bladder in women; other antimuscarinics are preferred.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40fullguideline.pdf (accessed 03/07/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Contact dermatitis has been reported after topical application of propantheline bromide.

Buccal and oesophageal ulceration. Severe buccal mucosal ulceration has been reported[1] in a 95-year-old woman as a result of retaining emepronium bromide tablets in her mouth, and recurred on giving propantheline bromide tablets.

1. Huston GJ, *et al.* Anticholinergic drugs, buccal ulceration and mucosal potential difference. *Postgrad Med J* 1978; **54:** 331–2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Propantheline bromide is incompletely absorbed from the gastrointestinal tract and bioavailability is reported to be reduced by food; it is extensively metabolised in the small intestine before absorption. The plasma elimination half-life after a single oral dose has been reported to be about 2 to 3 hours. Propantheline is eliminated mainly in the urine as metabolites and less than 10% as unchanged drug. The duration of action is about 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Pro-Banthine; ***Canad.***: Pro-Banthine†; ***Denm.***: Ercoril; ***Gr.***: Pro-Banthine; ***Hong Kong***: Panbro†; ***India***: Pro-Banthine; ***Indon.***: Pro-Banthine†; ***Irl.***: Pro-Banthine; ***NZ***: Pro-Banthine; ***S.Afr.***: Pro-Banthine; ***Singapore***: Panbro; Pro-Banthine; ***UK***: Pro-Banthine; ***USA***: Pro-Banthine†.

Multi-ingredient Preparations. ***Gr.***: Pro-Alusin-L; ***Indon.***: Methaphyllin†; ***Ital.***: Lexil.

Pharmacopoeial Preparations
BP 2014: Propantheline Tablets;
USP 36: Propantheline Bromide Tablets.

Prucalopride *(BAN, USAN, rINN)*

Prucaloprida; Prucalopridum; R-093877 (prucalopride or prucalopride hydrochloride); Прукалоприд.

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidyl]-7-benzofurancarboxamide.

$C_{18}H_{26}ClN_3O_3$=367.9

CAS — 179474-81-8.

ATC — A06AX05.

ATC Vet — QA06AX05.

UNII — 0A09IUW5TP.

Prucalopride Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de prucaloprida; Prucalopride, Chlorhydrate de; Prucalopridi Hydrochloridum; R-093877 (prucalopride or prucalopride hydrochloride); R-93877; Прукалоприда Гидрохлорид.

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidyl]-7-benzofurancarboxamide hydrochloride.

$C_{18}H_{26}ClN_3O_3$,HCl=404.3

CAS — 179474-80-7.

ATC — A06AX05.

ATC Vet — QA06AX05.

UNII — M8IYX9Z79V.

Prucalopride Succinate *(BAN, USAN, rINNM)*

Prucalopride, Succinate de; Prucalopridi Succinas; R-108512; Succinato de prucaloprida; Прукалоприда Суксинат.

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidyl]-7-benzofurancarboxamide succinate (1:1).

$C_{18}H_{26}ClN_3O_3$,$C_4H_6O_4$=486.0

CAS — 179474-85-2.

ATC — A06AX05.

ATC Vet — QA06AX05.

UNII — 4V2G75E1CK.

Uses and Administration

Prucalopride is a selective 5-HT_4 receptor agonist with prokinetic properties that is used in the treatment of women with chronic constipation where laxatives have failed to provide relief; efficacy in men has not been established. It is given as the succinate but doses are expressed as the base; prucalopride succinate 1.32 mg is equivalent to about 1 mg of prucalopride. The usual oral dose in women aged over 18 years is prucalopride 2 mg once daily. In elderly patients aged over 65 years, an initial dose of 1 mg once daily can be given, increased up to 2 mg once daily if required. For doses of prucalopride in hepatic and renal impairment, see below.

References.
1. Camilleri M, *et al.* A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008; **358:** 2344–54.
2. Quigley EM, *et al.* Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation–a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009; **29:** 315–28.
3. Tack J, *et al.* Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut* 2009; **58:** 357–65.
4. Frampton JE. Prucalopride. *Drugs* 2009; **69:** 2463–76.
5. Camilleri M, Deiteren A. Prucalopride for constipation. *Expert Opin Pharmacother* 2010; **11:** 451–61.

Administration in hepatic impairment. Due to a lack of data in patients with hepatic impairment, licensed product information for prucalopride recommends a reduced oral dose of 1 mg once daily in those with severe impairment (defined as Child-Pugh class C); no dose adjustments are considered necessary for those with mild to moderate impairment.

Administration in renal impairment. The main route of excretion of prucalopride is renal. Although no dosage adjustments are considered necessary in patients with mild to moderate renal impairment, licensed product information recommends a reduced oral dose of prucalopride 1 mg once daily in those with severe impairment (defined as a glomerular filtration rate of less than 30 mL/minute per 1.73 m^2). Prucalopride is not recommended for those on dialysis.

Adverse Effects and Precautions

The most frequently reported adverse effects during prucalopride treatment are headache and gastrointestinal disturbances such as abdominal pain, nausea, or diarrhoea. These usually occur at the start of therapy and resolve within a few days of continued treatment. Other common adverse effects include dizziness, pollakiuria (the frequent passing of small quantities of urine), and fatigue. Tremors, palpitations, anorexia, and fever have also been reported.

Due to a lack of study data, prucalopride should be used cautiously in patients with significant unstable comorbidities, particularly arrhythmias or ischaemic heart disease. It is not recommended in those with intestinal perforation or obstruction.

Interactions

In vitro data indicate that prucalopride does not affect the cytochrome P450 isoenzyme system, but may be a weak substrate of P-glycoprotein; ketoconazole, a potent P-glycoprotein inhibitor, increases exposure to prucalopride by about 40%, although this is not considered clinically relevant.

Pharmacokinetics

Oral prucalopride is rapidly absorbed and peak plasma concentrations occur after 2 to 3 hours. Absolute bioavailability is greater than 90%, and is not affected by food. Prucalopride is extensively distributed with low plasma-protein binding (about 30%). Metabolism in the liver is very slow and the main metabolite accounts for less than 4% of an excreted dose. Renal excretion of unchanged drug involves both passive filtration and active secretion. About 60% of a dose is excreted as unchanged drug via the urine and at least 6% via the faeces. Terminal elimination half-life is about 1 day. Prucalopride is excreted into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Resolor; ***Canad.***: Resotran; ***Cz.***: Resolor; ***Denm.***: Resolor; ***Fr.***: Resolor; ***Ger.***: Resolor; ***Gr.***: Resolor; ***Irl.***: Resolor; ***Neth.***: Resolor; ***Pol.***: Resolor; ***Port.***: Resolor; ***Singapore***: Resolor; ***Spain***: Resolor; ***Switz.***: Resolor; ***Thai.***: Resolor; ***UK***: Resolor.

Prune

Ameixa; Ciruela; Prunus; Слива Домашняя (*Prunus domestica*).
UNII — 58O0119YLZ.

Profile

Prune is the dried ripe fruits of the plum *Prunus domestica* and some other species of *Prunus* (Rosaceae). It has laxative and demulcent properties.

References.

1. Stacewicz-Sapuntzakis M, *et al*. Chemical composition and potential health effects of prunes: a functional food? *Crit Rev Food Sci Nutr* 2001; **41:** 251–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cirulaxia; Laxiruela; Mermelax; ***Austral.***: Neo-Cleanse; ***Chile***: Tamarine; ***Fr.***: Complexe Assistance†; Resource Prunogil†; Transifine; ***Ital.***: Fibranorm; ***Mex.***: Ciruelax Jalea; Laxacaps; ***UK***: Pure Plan.

Rabeprazole Sodium

(BANM, USAN, rINNM)

E-3810; LY-307640; Natrii Rabeprazolum; Rabeprazol sódico; Rabeprazol Sodyum; Rabéprazole Sodique; Rabeprazolum natricum; Sodium Pariprazole; Натрий Рабепразол.
2-({[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)-1*H*-benzimidazole sodium.
$C_{18}H_{20}N_3NaO_3S$=381.4
CAS — 117976-89-3 (rabeprazole); 117976-90-6 (rabeprazole sodium).
ATC — A02BC04.
ATC Vet — QA02BC04.
UNII — 3L36P16U4R.

Uses and Administration

Rabeprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p. 1867.2). It is given orally as rabeprazole sodium in the form of enteric-coated tablets. It is normally taken in the morning.

In the treatment of severe (erosive or ulcerative) **gastro-oesophageal reflux disease** (p. 1807.2), the usual dose of rabeprazole sodium is 20 mg once daily for 4 to 8 weeks; in the USA, a further 8-week course is permitted for healing of erosive oesophagitis. Thereafter, maintenance therapy can be continued with 10 or 20 mg daily depending on the response. For symptomatic disease without erosive or ulcerative oesophagitis a dose of 10 or 20 mg may be given once daily for 4 weeks; in the USA, a further 4-week course is permitted. Once symptoms have resolved, a dose of 10 mg once daily may be given as necessary.

For the treatment of active **peptic ulcer disease** (p. 1813.2), 20 mg daily is given for 4 to 8 weeks for duodenal ulcer and 6 to 12 weeks for gastric ulcer. For the eradication of *Helicobacter pylori* rabeprazole sodium may be combined with two antibacterials in a 1-week **triple therapy** regimen. Effective regimens include 20 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily.

For **Zollinger-Ellison syndrome** (p. 1814.3), the starting dose is 60 mg once daily, adjusted according to response. Doses up to 120 mg daily have been given; when the daily dose is more than 100 mg it should be given in 2 divided doses.

For doses in children, see below.

Dexrabeprazole, the dextrorotatory isomer of rabeprazole, and its sodium salt have also been used.

Reviews.

1. Prakash A, Faulds D. Rabeprazole. *Drugs* 1998; **55:** 261–7.
2. Anonymous. Rabeprazole. *Med Lett Drug Ther* 1999; **41:** 110–12.
3. Carswell CI, Goa KL. Rabeprazole: an update of its use in acid-related disorders. *Drugs* 2001; **61:** 2327–2356.
4. Pace F, *et al*. A review of rabeprazole in the treatment of acid-related diseases. *Ther Clin Risk Manag* 2007; **3:** 363–79.
5. Pallotta S, *et al*. Rabeprazole: a second-generation proton pump inhibitor in the treatment of acid-related disease. *Expert Rev Gastroenterol Hepatol* 2008; **2:** 509–22.
6. Dadabhai A, Friedenberg FK. Rabeprazole: a pharmacologic and clinical review for acid-related disorders. *Expert Opin Drug Safety* 2009; **8:** 119–26.
7. Baldwin CM, Keam SJ. Rabeprazole: a review of its use in the management of gastric acid-related diseases in adults. *Drugs* 2009; **69:** 1373–1401.

Administration in children. Rabeprazole sodium is licensed for use in children in the USA. For short-term treatment of gastro-oesophageal reflux disease, oral doses are given according to age and weight:

- 1 to 11 years and < 15 kg: 5 mg once daily, increased up to 10 mg once daily if needed, for up to 12 weeks
- 1 to 11 years and ⩾ 15 kg: 10 mg once daily for up to 12 weeks
- 12 years and older: 20 mg once daily for up to 8 weeks

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

Effects on the endocrine system. For cases of gynaecomastia associated with rabeprazole see Omeprazole, p. 1868.3.

Effects on the kidneys. For reports of interstitial nephritis associated with rabeprazole see p. 1869.1.

Effects on the nervous system. For a report of neuropsychiatric symptoms associated with rabeprazole, see p. 1869.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rabeprazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Interactions

As for Omeprazole (p. 1870.3) but because the cytochrome P450 isoenzyme system is a minor route of metabolism for rabeprazole, clinically significant interactions with diazepam, phenytoin, theophylline, or warfarin have not been found in healthy subjects.

Pharmacokinetics

Rabeprazole is rapidly absorbed and peak plasma concentrations occur about 3.5 hours after an oral dose. The oral bioavailability is about 52% with the enteric-coated tablet formulation, because of first-pass metabolism, and does not appear to vary after single or repeated doses. Rabeprazole is about 97% bound to plasma proteins. It is mainly metabolised via nonenzymatic reduction and, to a lesser extent, via the cytochrome P450 isoenzymes CYP2C19 and CYP3A4. Metabolites are excreted principally in the urine (about 90%) with the remainder in the faeces. The plasma half-life is about 1 to 2 hours, increased at least two to threefold in hepatic impairment, 1.6 times in CYP2C19 slow metabolisers (see also Metabolism under Omeprazole, p. 1871.2), and by 30% in the elderly.

References.

1. Yasuda S, *et al*. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4-hydroxylation status. *Clin Pharmacol Ther* 1995; **58:** 143–54.
2. Keane WF, *et al*. Rabeprazole: pharmacokinetics and tolerability in patients with stable, end-stage renal failure. *J Clin Pharmacol* 1999; **39:** 927–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pariet; Rabec; ***Austral.***: Pariet; ***Austria***: Pariet; ***Belg.***: Pariet; ***Braz.***: Pariet; ***Canad.***: Pariet; ***Chile***: Gastrodine; ***China***: An Si Fei (安斯菲); Pariet (波利特); Rui Bo Te (瑞波特); Xin Wei An (信卫安); Yu Tian Qing (雨田青); ***Cz.***: Rabebir; Rabecole; Rapoxol; Zulbex; ***Denm.***: Pariet; ***Fin.***: Pariet; ***Fr.***: Pariet; ***Ger.***: Pariet; ***Gr.***: Pariet; ***Hong Kong***: Pariet; ***Hung.***: Pariet; Rabeman; RabirEP; Rabyprex; ***India***: Abra; Acistal; Affirab; Albera; Algibra; Antuc; Aribzol; Asalt; Asirab; B-Joy; Bizo; Brazo; Cinrab; Coolx; Cyra; D-Rabibit; Depump; Desprazole; Dexicool; Dexpure; Dirab; Durab; Elrab; Furab-IT; Furab; Gasorab; Gastrazole; Genrab; Happi; Helirab; Hirabezole; Jeprab; Konzol; Koolzon; Mepraz; Nicid; Novorab; Nura; Odirab; Once; Oppi-R; Orpro; Rabeloc; Rabicip; ***Indon.***: Pariet; ***Irl.***: Pariet; Rabiclon; Razole; ***Ital.***: Pariet; ***Jpn***: Pariet; ***Malaysia***: Pariet; ***Mex.***: Pariet; ***Neth.***: Berizar; Beryx; Fardole; Jelgrad; Pariet; Praber; Prabexol; Rapespes; Rodesa; ***Philipp.***: Pariet; ***Pol.***: Pariet; ***Port.***: Pariet; ***Rus.***: Pariet (Париет); ***S.Afr.***: Pariet; ***Singapore***: Pariet; ***Spain***: Aciphex; Gelbra; Pariet; ***Swed.***: Pariet; ***Switz.***: Pariet; ***Thai.***: Pariet; ***Turk.***: Pariet; Prabex; Raneks; ***UK***: Pariet; ***Ukr.***: Barol (Барол); Razo (Разо)†; ***USA***: Aciphex; ***Venez.***: Pariet.

Multi-ingredient Preparations. ***India***: Abra-D; Ace-Proxyvon; Acera; Acistal-D; Adec; Affirab-D; Antuc DSR; Antuc-IT; Aptase-DSR HG; Aribzol-D; Asalt-D; Asirab-D; B-Joy Plus; Bizo-D; Bizo-IT; Brazo-D; Brazo-IT; Brozole-D; Cidrid; Comvine; Cool Rab-It; Curab-D; Cyclochek; Cyra-D; D-Kool; D-Rabibit-D; Degurge-D; Dexrobel-D; Digerab-D; Dirab-D; Domrab; Domzole-R; Dorafem; Drab; Dynapar PPI; Elrab-D; Esoga-RD; Furab-D; Gasorab-D; Gasorab-T; Gastrazole-D; Genrab-D; Happi-D; Helirab-D; Hurtiz-DSR; Itoplus; Itopraz; Itorab; Itorbe; Jeprab-D; Konzol-D; Kurab-D; Kurab; Mac-IT; Mac-RD; Mepraz-D; Novorab-D; Nucid-D; Nuloc-D; Nura-D; Nura-IT; Once-D; Ond-R; Oshzol-D; ***Ukr.***: Onristat (Оріністат)†; Rabiril (Рабирил).

Racecadotril *(BAN, rINN)*

Acetorphan; Racécadotril; Racecadotrilo; Racecadotrilum; Рацекадотрил.
(±)-*N*-[2-[(Acetylthio)methyl]-1-oxo-3-phenylpropyl]glycine phenylmethyl ester; *N*-[(*R,S*)-3-acetylthio-2-benzylpropanoyl] glycine benzyl ester; (±)-*N*-[α-(Mercaptomethyl)hydrocinnamoyl]glycine benzyl ester acetate.
$C_{21}H_{23}NO_4S$=385.5
CAS — 81110-73-8.
ATC — A07XA04.
ATC Vet — QA07XA04.
UNII — 76K53XP4TO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Racecadotril). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane.

Profile

Racecadotril is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thus reducing intestinal secretions. It is given orally in doses of 100 mg three times daily before meals for up to 7 days for the symptomatic management of acute diarrhoea (p. 1805.2).

The *S*-form of racecadotril (sinorphan, ecadotril—see Natriuretic Peptides, p. 1444.1) has been investigated for hypertension and heart failure.

References.

1. Baumer P, *et al*. Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea. *Gut* 1992; **33:** 753–8.
2. Roge J, *et al*. The enkephalinase inhibitor, acetorphan, in acute diarrhoea: a double-blind, controlled clinical trial versus Loperamide. *Scand J Gastroenterol* 1993; **28:** 352–4.
3. Beaugerie L, *et al*. Treatment of refractory diarrhoea in AIDS with acetorphan and octreotide: a randomized crossover study. *Eur J Gastroenterol Hepatol* 1996; **8:** 485–9.
4. Salazar-Lindo E, *et al*. Racecadotril in the treatment of acute watery diarrhea in children. *N Engl J Med* 2000; **343:** 463–7.
5. Matheson AJ, Noble S. Racecadotril. *Drugs* 2000; **59:** 829–35.
6. Alam NH, *et al*. Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial. *Gut* 2003; **52:** 1419–23.
7. Wang H-H, *et al*. A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. *World J Gastroenterol* 2005; **11:** 1540–3.
8. Szajewska H, *et al*. Systematic review: racecadotril in the treatment of acute diarrhoea in children. *Aliment Pharmacol Ther* 2007; **26:** 807–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Tiorfix; ***Braz.***: Tiorfan; ***Chile***: Hidrasec; Resorcal; ***China***: Du La Bao (杜拉宝); Feng Hai Ting (丰海停); Hidrasec (海兰赛); Mo Ni Ka (莫尼卡); ***Fr.***: Diarfix; Tiorfan; Tiorfanor; Tiorfast; ***Ger.***: Tiorfan†; ***Gr.***: Hidrasec; ***India***: Ad-DT; Ad-Sachet; Ad; Aquasec; Cadotril; Dirasec; Dotril; Enuff; Floradot; Hydral; Lomorest; Nodi; ***Indon.***: Hidrasec†; ***Ital.***: Tiorfix; ***Mex.***: Hidrasec; ***Neth.***: Hidrasec; ***Philipp.***: Hidrasec; ***Port.***: Tiorfan; ***Spain***: Tiorfan; ***Thai.***: Hidrasec; ***UK***: Hidrasec; ***Venez.***: Hidrasec.

Multi-ingredient Preparations. ***India***: Aidia; Dotvil; Editor; Enuff Xtra.

Ramosetron Hydrochloride *(rINNM)*

Hidrocloruro de ramosetrón; Ibsetron Hydrochloride; Ramosétron, Chlorhydrate de; Ramosetrón, hidrocloruro de; Ramosetroni Hydrochloridum; YM-060; Рамосетрона Гидрохлорид.
(-)-(*R*)-1-Methylindol-3-yl 4,5,6,7-tetrahydro-5-benzimidazolyl ketone hydrochloride.
$C_{17}H_{17}N_3O.HCl$=315.8
CAS — 132036-88-5 (ramosetron); 132907-72-3 (ramosetron hydrochloride).
UNII — 9551LHD87E.

Profile

Ramosetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p. 1872.1). Ramosetron hydrochloride is given for its antiemetic properties in the management of nausea and vomiting induced by cancer chemotherapy in a usual oral dose of 100 micrograms once daily. Alternatively, it may be given intravenously in a usual dose of 300 micrograms once daily; an additional dose of 300 micrograms may be given if needed, to a maximum daily dose of 600 micrograms. Ramosetron is also under

investigation in the management of diarrhoea-predominant irritable bowel syndrome.

Diarrhoea. Ramosetron has been tried with some success in a case of diabetic diarrhoea that had not responded to conventional antidiarrhoeals.[1]

1. Murao S, Hosokawa H. Serotonin 5-HT3 receptor antagonist for treatment of severe diabetic diarrhea. *Diabetes Care* 2010; **33:** e38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ai Ke An (艾可安); Lei Mai Xin (雷迈欣); Nasea (奈西雅); Shan Cheng (善成); Wei Yi Shu (维意舒); ***Indon.***: Nasea; ***Jpn***: Nasea; ***Philipp.***: Nasea; ***Thai.***: Irribow; Nasea.

Ranitidine *(BAN, USAN, rINN)*

AH-19065; Ranitidiini; Ranitidin; Ranitidina; Ranitidinum; Ранитидин.

NN-Dimethyl-5-[2-(1-methylamino-2-nitrovinylamino) ethylthiomethyl]furfurylamine.

$C_{13}H_{22}N_4O_3S$=314.4

CAS — 66357-35-5.

ATC — A02BA02.

ATC Vet — QA02BA02.

UNII — 884KT10YB7.

Ranitidine Hydrochloride *(BANM, rINNM)*

AH-19065; Hidrocloruro de ranitidina; Ranitidiinihydrokloridi; Ranitidin Hidroklorür; Ranitidina, hidrocloruro de; Ranitidine, chlorhydrate de; Ranitidin-hidroklorid; Ranitidinhydrochlorid; Ranitidin-hydrochlorid; Ranitidinhydroklorid; Ranitidini hydrochloridum; Ranitidino hidrochloridas; Ranitydyny chlorowodorek; Ранитидина Гидрохлорид.

$C_{13}H_{22}N_4O_3S,HCl$=350.9

CAS — 66357-59-3.

ATC — A02BA02.

ATC Vet — QA02BA02.

UNII — BK76465IHM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ranitidine Hydrochloride). A white or pale yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water; sparingly soluble or slightly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Ranitidine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. It is sensitive to light and to moisture. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Incompatibility and stability. References.

1. Chilvers MR, Lysne JM. Visual compatibility of ranitidine hydrochloride with commonly used critical-care medications. *Am J Hosp Pharm* 1989; **46:** 2057–8.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.
3. Williams MF, *et al.* In vitro evaluation of the stability of ranitidine hydrochloride in total parenteral nutrition mixtures. *Am J Hosp Pharm* 1990; **47:** 1574–9.
4. Galante LJ, *et al.* Stability of ranitidine hydrochloride at dilute concentration in intravenous infusion fluids at room temperature. *Am J Hosp Pharm* 1990; **47:** 1580–4.
5. Galante LJ, *et al.* Stability of ranitidine hydrochloride with eight medications in intravenous admixtures. *Am J Hosp Pharm* 1990; **47:** 1606–10.
6. Stewart JT, *et al.* Stability of ranitidine in intravenous admixtures stored frozen, refrigerated, and at room temperature. *Am J Hosp Pharm* 1990; **47:** 2043–6.
7. Montoro JB, Pou L. Comment on stability of ranitidine hydrochloride in total nutrient admixtures. *Am J Hosp Pharm* 1991; **48:** 2384.
8. Stewart JT, *et al.* Stability of ranitidine hydrochloride and seven medications. *Am J Hosp Pharm* 1994; **51:** 1802–7.
9. Crowther RS, *et al.* In vitro stability of ranitidine hydrochloride in enteral nutrient formulas. *Ann Pharmacother* 1995; **29:** 859–62.
10. Allwood MC, Martin H. Factors influencing the stability of ranitidine in TPN mixtures. *Clin Nutr* 1995; **14:** 171–6.

Uses and Administration

Ranitidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (p. 1827.2).

Ranitidine may be given orally or parenterally by the intravenous or intramuscular routes. Although most preparations contain ranitidine hydrochloride, strengths and doses are expressed in terms of the base. Ranitidine hydrochloride 111.6 mg is equivalent to about 100 mg of ranitidine. Doses of ranitidine may need to be adjusted in patients with renal impairment, and in children. For discussion of dosage in children and renal impairment, see below.

In the management of benign **gastric** and **duodenal ulceration** (p. 1813.2) a single daily oral dose of 300 mg at bedtime or 150 mg twice daily (in the morning and at bedtime) is given initially for at least 4 weeks. Up to 300 mg twice daily may be used if necessary. Where appropriate a maintenance dose of 150 mg daily may be given at bedtime. To treat ulcers associated with NSAID therapy, ranitidine 150 mg twice daily or 300 mg at bedtime may be given for 8 to 12 weeks; for duodenal ulcers, a higher dose of 300 mg twice daily for 4 weeks has also been used. (To *prevent* NSAID-associated ulcers, UK licensed product information recommends an oral dose of 150 mg twice daily given with NSAID treatment; although unlicensed, the *BNF* suggests a higher dose of 300 mg twice daily may be used.)

For duodenal ulcer associated with *Helicobacter pylori* infection, ranitidine in a usual oral dose of 300 mg once daily at bedtime or 150 mg twice daily may be given as part of triple therapy with amoxicillin 750 mg and metronidazole 500 mg, both given orally, three times daily, for 2 weeks. Therapy with ranitidine should then be continued for a further 2 weeks.

In **gastro-oesophageal reflux disease** (p. 1807.2) the oral dose is 150 mg twice daily or 300 mg at bedtime for up to 8 weeks or, if required, 12 weeks. This may be increased to 150 mg four times daily for up to 12 weeks in severe cases. In the maintenance of healing erosive oesophagitis, a dose of 150 mg twice daily may be used. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, (p. 1814.3) the initial oral dose is usually 150 mg twice or three times daily and may be increased if necessary; doses of up to 6 g daily have been used. Alternatively, an intravenous infusion may be given, initially at a rate of 1 mg/kg per hour; the rate may be increased by increments of 500 micrograms/kg per hour, beginning after 4 hours, if required. Intravenous doses up to 2.5 mg/kg per hour and infusion rates up to 220 mg/hour have been used.

For the management of patients at risk from **stress ulceration** of the upper gastrointestinal tract, parenteral therapy may be given as a slow intravenous injection of a 50-mg priming dose followed by a continuous intravenous infusion of 125 to 250 micrograms/kg per hour. Oral doses of 150 mg twice daily may be given once oral feeding is resumed.

In patients at risk of developing the **acid aspiration syndrome** (p. 1804.2) during general anaesthesia, an oral dose of 150 mg may be given 2 hours before the induction of anaesthesia and preferably also 150 mg the previous evening. Alternatively, a dose of 50 mg may be given by intramuscular or slow intravenous injection 45 to 60 minutes before the induction of anaesthesia. In obstetric patients at the start of labour, an oral dose of 150 mg may be given and may be repeated at intervals of 6 hours if required.

In patients with chronic episodic **dyspepsia** (p. 1806.3), a dose of 150 mg twice daily orally for up to 6 weeks may be given. For the short-term symptomatic relief of dyspepsia a dose of 75 mg, repeated if necessary up to a maximum of 4 doses daily, may be taken. Treatment should be restricted to a maximum of 2 weeks of continuous use at one time.

PARENTERAL DOSAGE.

The usual dose of ranitidine by intramuscular or intravenous injection is 50 mg, which may be repeated every 6 to 8 hours; the intravenous injection should be given slowly over not less than 2 minutes and should be diluted to contain 50 mg in 20 mL. For an intermittent intravenous infusion the recommended dose in the UK is 25 mg/hour given for 2 hours which may be repeated every 6 to 8 hours. A rate of 6.25 mg/hour has been suggested for continuous intravenous infusion although higher rates may be used for conditions such as Zollinger-Ellison syndrome or in patients at risk from stress ulceration (see above).

Administration in children. Ranitidine is used in children to heal duodenal and gastric ulcers and to prevent stress ulceration in critically ill patients. It is licensed in children, although indications, age ranges, and doses may vary from country to country. When given orally, ranitidine is licensed from ages 3 to 11 years and over 30 kg bodyweight in the UK, and from 1 month to 16 years in the USA.

In the treatment of duodenal and gastric ulcers, a usual oral dose of 4 to 8 mg/kg daily in 2 divided doses is given, to a maximum of 300 mg ranitidine daily, for 4 to 8 weeks. For maintenance US licensed product information recommends a dose of 2 to 4 mg/kg daily, to a maximum of 150 mg ranitidine daily.

In the treatment of gastro-oesophageal reflux disease, a usual oral dose of 5 to 10 mg/kg daily in 2 divided doses is given, to a maximum of 600 mg daily.

The *BNFC* suggests the same oral doses for 3 to 12 year olds as those licensed in the UK, but includes doses for younger children, for any indication:

- neonates: 2 mg/kg three times daily, although absorption can be unreliable, and a maximum dose of 3 mg/kg three times daily
- 1 to 6 months: 1 mg/kg three times daily; maximum 3 mg/kg three times daily
- 6 months to 3 years: 2 to 4 mg/kg twice daily

It also suggests adult doses for children aged 12 to 18 years, see Uses and Administration above.

Ranitidine may also be given intravenously to children when oral treatment is not possible. UK licensed product information recommends the following doses in children aged 6 months to 11 years:

Treatment of peptic ulcer and gastro-oesophageal reflux disease:

- initially 2 or 2.5 mg/kg (maximum 50 mg) as a slow intravenous injection over 10 minutes followed by intermittent infusion of 1.5 mg/kg every 6 to 8 hours
  or
- a loading dose of 450 micrograms/kg as a slow intravenous injection over at least 2 minutes followed by a continuous infusion of 150 micrograms/kg per hour

Prophylaxis of stress ulceration:

- 1 mg/kg (maximum 50 mg) as a slow intravenous injection over at least 2 minutes, every 6 to 8 hours
  or
- 125 to 250 micrograms/kg per hour as a continuous infusion

The *BNFC* also suggests intravenous doses for children according to age, for all indications:

- neonate: 0.5 to 1 mg/kg by slow intravenous injection every 6 to 8 hours
- 1 month to 18 years: 1 mg/kg (to a maximum of 50 mg) every 6 to 8 hours, either by slow intravenous injection or by intermittent infusion at a rate of 25 mg/hour

In the USA, ranitidine is given intravenously to treat children from 1 month to 16 years of age with duodenal ulcer. A dose of 2 to 4 mg/kg daily in 3 or 4 divided doses at 6 to 8 hourly intervals (maximum of 50 mg per dose) is given either by slow intravenous injection over 5 minutes, or by intermittent infusion over 20 minutes.

Administration in renal impairment. A study in patients with varying degrees of renal impairment[1] found that the mean terminal half-life of ranitidine was increased from 2.09 hours in subjects with normal renal function to between 4.23 and 8.45 hours in patients with renal impairment, the degree of prolongation being proportional to the degree of impairment as measured by glomerular filtration rate. As a result of these findings it was recommended that the dose of ranitidine should be halved in patients with a glomerular filtration rate of 20 mL/minute or less. Licensed product information therefore recommends that dosage of ranitidine be reduced in patients with severe renal impairment.

For patients with a creatinine clearance of less than 50 mL/minute, an *oral* dose of 150 mg daily at bedtime is recommended. This may be cautiously increased to 150 mg every 12 hours if needed and reduced back to 150 mg daily if maintenance treatment is required.

For *parenteral* use, licensed recommendations vary between countries. In the UK, individual doses may be reduced to 25 mg, while the frequency is adjusted in the USA to give a recommended usual dose of 50 mg every 18 to 24 hours, which may be cautiously increased to every 12 hours or more often if necessary.

Ranitidine 150 mg daily provided adequate serum concentrations without excessive accumulation in 20 patients undergoing regular haemodialysis.[2] The serum-ranitidine concentrations fell by about 50% during a 4-hour haemodialysis session but less than 3% of the dose was removed and supplemental doses after dialysis were considered unnecessary. Licensed product information in the UK and USA recommends that the timing of doses is adjusted so that they are given at the end of dialysis.

1. Dixon JS, *et al.* The effect of renal function on the pharmacokinetics of ranitidine. *Eur J Clin Pharmacol* 1994; **46:** 167–71.
2. Comstock TJ, *et al.* Ranitidine accumulation in patients undergoing chronic hemodialysis. *J Clin Pharmacol* 1988; **28:** 1081–5.

Cystic fibrosis. A comparative study involving 29 patients with cystic fibrosis (p. 177.2) found that ranitidine was more effective than cisapride in improving dyspeptic symptoms and gastric emptying and distension.[1] Antisecretory drugs are also used in this condition to decrease the inactivation of oral pancreatic enzyme therapy.

1. Cucchiara S, *et al.* Ultrasound measurement of gastric emptying time in patients with cystic fibrosis and effect of ranitidine on delayed gastric emptying. *J Pediatr* 1996; **128:** 485–8.

Immunomodulation. Like cimetidine (see p. 1827.3), ranitidine has been proposed to have immunoregulatory effects. However, ranitidine 300 mg twice daily had no effect on absolute CD4 cell counts or plasma HIV RNA in patients with HIV infection in a placebo-controlled study.[1] Similarly, ranitidine had no significant benefit in patients with gastric cancer (see Malignant Neoplasms, p. 1828.1).

1. Bartlett JA, *et al.* A placebo-controlled trial of ranitidine in patients with early human immunodeficiency virus infection. *J Infect Dis* 1998; **177:** 231–4.

Skin disorders. As with cimetidine (p. 1828.2), ranitidine has been tried in various skin disorders. Oral ranitidine 300 mg twice daily for up to 16 weeks has been reported to be of benefit as an adjuvant to local treatment with corticosteroids and a moisturising ointment in patients with *atopic dermatitis*.[1] There are reports of improvements in *psoriasis* after use of ranitidine,[2-4] although this is a field that is notoriously difficult to evaluate because of the chronic relapsing and remitting nature of the disease, and others have failed to show benefit.[5]

1. Veien NK, *et al.* Ranitidine treatment of hand eczema in patients with atopic dermatitis: a double-blind placebo-controlled trial. *J Am Acad Dermatol* 1995; **32:** 1056–7.
2. Witkamp L, *et al.* An open prospective clinical trial with systemic ranitidine in the treatment of psoriasis. *J Am Acad Dermatol* 1993; **28:** 778–81.
3. Smith KC. Ranitidine useful in the management of psoriasis in a patient with acquired immunodeficiency syndrome. *Int J Dermatol* 1994; **33:** 220–1.
4. Kristensen JK, *et al.* Systemic high-dose ranitidine in the treatment of psoriasis: an open prospective clinical trial. *Br J Dermatol* 1995; **133:** 905–8.
5. Çetin L, *et al.* High-dose ranitidine is ineffective in the treatment of psoriasis. *Br J Dermatol* 1997; **137:** 1021–2.

Adverse Effects

As for Cimetidine, p. 1828.3. Unlike cimetidine, ranitidine has little or no anti-androgenic effect, despite isolated reports of gynaecomastia and impotence.

General references.

1. Wormsley KG. Safety profile of ranitidine: a review. *Drugs* 1993; **46:** 976–85.
2. Mills JG, *et al.* The safety of ranitidine in over a decade of use. *Aliment Pharmacol Ther* 1997; **11:** 129–37.

Meningitis. A 30-year-old man developed aseptic meningitis on 3 occasions after use of ranitidine.[1] In each case symptoms resolved rapidly on withdrawal of the drug.

1. Durand JM, *et al.* Ranitidine and aseptic meningitis. *BMJ* 1996; **312:** 886. Correction. *ibid.*; 1392.

Precautions

As for Cimetidine, p. 1830.2.

Allergy testing. For mention of the effect of ranitidine on allergy testing, see Cimetidine, p. 1830.2.

Helicobacter pylori testing. For reference to the effect of ranitidine on the urea breath test for *Helicobacter pylori*, see p. 1830.2.

Hepatic impairment. For a report of increased resistance to H_2-antagonists in patients with liver cirrhosis, see Cimetidine, p. 1830.3.

Porphyria. Although licensed product information recommends that ranitidine should be avoided in patients with a history of acute porphyria, reports of porphyria associated with its use have been rare and inconclusive. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ranitidine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For information on the use of H_2-antagonists during pregnancy, see Cimetidine, p. 1830.3.

Renal impairment. For evidence of reduced clearance of ranitidine in patients with renal impairment see Administration in Renal Impairment, p. 1882.3.

Interactions

Unlike cimetidine (p. 1830.3), ranitidine does not seem to affect cytochrome P450 isoenzymes to any great extent, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists, its effects on gastric pH may alter the absorption of drugs whose absorption is dependent on an acid gastric pH.

A review comparing the drug interactions of ranitidine with those of cimetidine.[1]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p. 1735.2).

Antacids. For discussion of the effect of antacids on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Cisapride. For mention of the effect of cisapride on the bioavailability of ranitidine, see Cimetidine, p. 1831.1.

Sucralfate. For information on the effect of sucralfate on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Pharmacokinetics

Ranitidine is readily absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 2 to 3 hours after oral doses. Food does not significantly impair absorption. The bioavailability of ranitidine after oral doses is about 50%. Ranitidine is rapidly absorbed after intramuscular injection, with peak plasma concentrations occurring in about 15 minutes. It is weakly bound, about 15%, to plasma proteins.

The elimination half-life is about 2 to 3 hours and is increased in renal impairment. A small proportion of ranitidine is metabolised in the liver to the *N*-oxide, the *S*-oxide, and desmethylranitidine; the *N*-oxide is the major metabolite but accounts for only about 4 to 6% of a dose. About 30% of an oral dose and 70% of an intravenous dose is excreted unchanged in the urine in 24 hours, primarily by active tubular secretion; there is some excretion in the faeces. Ranitidine crosses the placental barrier and is distributed into breast milk.

Distribution into breast milk. A study in a mother given multiple doses of ranitidine showed higher concentrations in breast milk than in serum; the minimum milk concentration occurred between 1 and 2 hours after a dose and the highest concentration was towards the end of the 12-hour dosing interval.[1] The amount that would be ingested by the infant could not be reliably estimated because of the variable milk to serum ratio.

1. Kearns GL, *et al.* Appearance of ranitidine in breast milk following multiple dosing. *Clin Pharm* 1985; **4:** 322–4.

Enterohepatic recycling. Some individuals have a second peak in the plasma concentration of ranitidine, which could be due to enterohepatic recirculation. However, only 0.7 to 2.6% and 0.3 to 1.0% of a dose of ranitidine was excreted into the bile of 3 patients in 24 hours after 50 mg given intravenously or 300 mg given orally respectively, indicating that significant recirculation did not occur.[1]

1. Klotz U, Walker S. Biliary excretion of H_2-receptor antagonists. *Eur J Clin Pharmacol* 1990; **39:** 91–2.

Neonates. Renal function is limited in the first month of life, and reduced clearance of ranitidine would be expected. Blood samples taken from 27 full-term neonates given a single intravenous dose of ranitidine 2.4 mg/kg revealed the following pharmacokinetic data: elimination half-life, 3.45 hours; total volume of distribution, 1.52 litres/kg; total plasma clearance, 5.02 mL/kg per minute.[1] None of the infants had renal or hepatic impairment. In another study[2] in 13 full-term neonates undergoing extracorporeal membrane oxygenation, the elimination half-life was increased to 6.61 hours after an intravenous dose of 2 mg/kg ranitidine. A sustained increase in gastric pH was seen with this dose, and the authors suggested that a dosage interval of 12 hours or longer may be sufficient for intermittent intravenous use in this population. Alternatively, a continuous infusion of ranitidine 2 mg/kg daily was recommended to maintain the initial increase in pH. See also Administration in Children, p. 1882.2.

1. Fontana M, *et al.* Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993; **68:** 602–3.
2. Wells TG, *et al.* Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998; **38:** 402–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acidex; Adesial†; Alivian; Dualid; Espaven; Faboacid R; Fendibina; Gastrial; Gastrolets; Gastrosedol; Gastrozac; Labsidex; Lorbitidina; Luvier; Notrab; Prednocris; Ranimed; Ranitic†; Ranitral; Ranitul; Raticina; Reco; Reflux; Sustac; Taural; Teogrand; Tomag; Ulcotenk; Urgis†; Vingional; Vizerul; Zantac; ***Austral.***: Ausran; Mylanta 12 Hour Action; Rani 2; Ranihexal†; Ranitic†; Ranoxyl; Ulcaid; Zantac; ***Austria***: Ranic; Raninorm; Ulsal; Zantac; ***Belg.***: Docraniti†; Gastran†; Ranitimed†; Zantac; ***Braz.***: Antagon; Antak; Antidin; Aziliv; Label; Logat; Neosac; Randine; Raniblok; Raniclor†; Ranidin; Ranidina; Ranidine†; Raniflex; Ranitil; Ranitin†; Ranitinol; Ranition; Ranitrat; Tekadin; Ulceridina†; Ulcerocin; Ulcoren; Ultidin; Zadine; Zylium; ***Canad.***: Acid Reducer; Maximum Strength Acid Reducer; Novo-Ranidine†; Nu-Ranit; Zantac; ***Chile***: Ranicel†; Ranitax†; Tipac; Zantac; ***China***: Ai Ke Ting (艾克汀); Ai Ke Wei (艾可谓); De Te Li Er (德特利尔); Dong Yi (东易); FuWei (孚卫); Histac (西斯塔); Jing Lu (菁璐); JinWeiHe (津卫和); Jiu Ao (九奥); Ke Ao Si (可奥斯); Lanbaixing (兰百幸); Ou Hua Da (欧化达); Pu Er Tai (普而太); Qi Di (奇迪); Shan De Kang (善得康); Yi Zhen Kang (依真慷); Zantac (善卫得); ***Cz.***: Histac†; Ranisan; Ranital; Ulcosan; Zantac†; ***Denm.***: Acikure; Kuracid; Ranicodan; Syrex; Zantac; ***Fin.***: Inside; Ranicur†; Ranimex†; Ranisan; Ranixal; Zantac; ***Fr.***: Azantac; Raniplex; ***Ger.***: Junizac†; Ran Lich†; Rani-nerton†; Rani-Puren†; Raniberl†; Ranibeta; Ranicux; Raniprotect; Ranitic†; Ranitidoc†; Sostril†; Zantic; ***Gr.***: Alphadine; Aova; Baroxal; Bindazac; Blumol; Brixoral; Ceftrinal; Epadoren; Ezopta; Galebiron; Gaproxen; Gertocalm; Lomadryl; Lumaren; Narigen; Nipodur; Nitised; Odanet; Ptinolin; Raniclon; Ranizac; Restopon; Ribolin; Rothonal; Semuele; Smaril; Soredine; Specinor; Sveltanet; Synthomanet; Tupast; Ulcomet; Verlost; Yara; Zantac; Zoliden; Zurfix; ***Hong Kong***: Hyzan; LAtac†; Lumeran; Novo-Ranidine†; Radin†; Randac†; Ranidine†; Raniplex†; Ranital; Ranolta; Simetac†; Synitidine†; Ulticer; Uni-Rantac†; Zantac; Zendhin; ***Hung.***: Histac; Ranitic; Ulceran; Ulcosin†; Umaren; Zantac; ***India***: Aciloc; Actiran; Aztec; Becotac; Consec; Din; Emtec; Entac; Giran; Healcer; Helkoss; Histac; Hytide; Intac; Kamtac; Lantac; Lydin; Manotac; Meditin; Nilcer; Nitin; R-Loc; Rantac; Ultac; Zinetac; ***Indon.***: Acran; Aldin†; Anitid; Chopintac; Conranin; Fordin; Gastridin; Getidin; Hexer; Radin; Rancus; Ranicare; Ranilex; Ranin; Ranivell; Ranticid; Rantin; Ratan; Ratinal; Renatac; Scanarin; Titan; Tricker; Tyran; Ulceranin; Wiacid; Xeradin; Zantac; Zantadin; Zantifar; Zenti; Zumaran†; ***Irl.***: Bellran†; Gertac; Ranitic; Ranopine; Xanomel†; Zantac; ***Israel***: Zanidex†; Zantac; Zaridex; ***Ital.***: Dolilux; Raniben; Ranibloc; Ranidex†; Ranidil; Sensigard; Ulcex; Zantac; ***Jpn***: Zantac; ***Malaysia***: Arnetin; Gastril; Histac; Hyzan†; Vesyca; X'tac; Zantac; Zendhin; ***Mex.***: Acloral; Agrisen†; Aldivina; Anistal; Anticina†; Avintac; Azantac; Bio-Gast; Cauteridol†; Credaxol; Dinaxin; Driges; Flatmed; Galidrin; Gastrec; Gastridin; Histac†; Iqfadina; Katalem; Microtid; Midaven; Neugal†; Offentina†; Phartidine; Radyn; Ranepal; Ranifarm; Ranifur; Raniger; Ranisen; Ranulin; Raudil; Redacid; Sarcitec; Serranit; Serviradine; Sinhcloran; Syngasy; Terodul; Tianak; Ulcevit; Ulgastrin; Ulkodin; Ulmodhyl; Ulsaven; Ultran; Unitin; ***Neth.***: Azantac†; Kruidvat maagzuurremmer ranitidine; Zantac; ***Norw.***: Inside Brus†; Zantac; ***NZ***: H_2RA; Peptisoothe; Zantac; ***Philipp.***: Aceptin; Aciloc; Aciran; Alisazim; Ameket; Ceranid†; Clodine; Contracid; Dalycrid; Danitin; Diranite; Entac; Equaline; Eu-Ran†; Gastrone; Ildecep; Incid; Increph; Intac; Loracid; Microtec; Mordek; Normaxid; Pep-Bloc; Peptica; RA Bloc; Ramadine; Ranae; Randin; Ranisan; Ranitab; Ranitac; Ranitalis; Ranitein; Ranivint; Rantizec; Rapidin; Raxide; Renfort; Rentsan; Ulcedrug; Ulcemed; Ulcepac; Ulceragon; Ulceral†; Ulcergo; Ulcerix; Ulci-Cure; Ulcin; Ulran; Zantac; Zantol; Zeltac; Zeptag; Zerdin; Zidaxim; ***Pol.***: Gastranin Zdrovit; Novo-Ranidine†; Raniberl; Ranic; Ranigast; Ranimax; Ranisan; Ranitin†; Riflux; Solvertyl; Zantac; ***Port.***: Bloculcer; Efective†; Gastridina; Gastrolav; Gastrulcer; Pep-Rani; Peptab; Peptifar†; Ranitine; Stacer; Tecradina; Zantac; ***Rus.***: Aciloc (Ацилок); Histac (Гистак); Ranigast (Ранигаст); Ranisan (Ранисан); Ranitine (Ранитин); Rantac (Рантак); Ulcodin (Улкодин); Ulran (Ульран); Zantac (Зантак); Zantin (Зантин); Zoran (Зоран); ***S.Afr.***: Austac; GI-Tak; Histak; R-Loc; Ranihexal; Ranit; Ulcaid†; Ultak; Zantac; ***Singapore***: Aciloc; Beatac; Gastril; Histac; Hyzan; Lumaren; Neoceptin-R; Ranidine; Ratic; SP-Gastril; Vesyca; Xanidine; Zantac; Zendhin; Zynol; ***Spain***: Alquen; Aracidina†; Arcid†; Ardoral; Coralen; Denulcer†; Fagus†; Leiracid; Ranidin†; Ranuber†; Tanidina; Terposen; Zantac; ***Swed.***: Artonil†; Inside; Rani-Q; Stomacid; Zantac; ***Switz.***: Ranimed; Ulcidine†; Zantic; ***Thai.***: Acicare; Aciloc; Histac; R-Loc; Ramag; Ranicid; Ranid; Ranidine; Ranin; Ranit-VC; Rantac; Rantodine; Ratic; Ratica; Utac†; Xanidine; Zanamet; Zantac; Zantidon; Zardil†; ***Turk.***: Ranitab; Ranitine; Raniver; Ranobel; Rozon†; Santanol†; Ulcuran; Zandid; Zantac; ***UAE***: Rantag; ***UK***: Gavilast; Ranitic; Ranitil; Rantec; Ranzac; Zantac; ***USA***: Zantac; ***Venez.***: Aplom; Enteral; Gastac; Ranibloc; Retamin; Vizerul; Zantac.

Multi-ingredient Preparations. ***Arg.***: Euciton Reflux; Gastrosedol Plus; Megalex; ***China***: Ge Lai Shi (格来士); Yi Shuang Bi (易双必); Yilishu (宜立舒); ***India***: Acidom-O; Acidom; Aciloc RD; Actiran-D; Actispas-R; Alcirid-O; Alotac; Avispas; Aztec-D; Doran-O; Gaspaz; Helkoss-D; Manotac Plus; Meditin Plus; Mefar-PD; Normaxin-RT; ***Mex.***: Ergex; Pepti-Max.

Pharmacopoeial Preparations

BP 2014: Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets;

USP 36: Ranitidine in Sodium Chloride Injection; Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets.

Ranitidine Bismuth Citrate *(BAN, USAN)*

GR-122311X; Ranitidin Bizmut Sitrat; Ranitidin Bizmutreks; Ranitidina y bismuto, citrato de; Ranitidine Bismutrex; Ранитидин Висмут Цитрат.

N-[2-({5-[(Dimethylamino)methyl]furfuryl}thio)-ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, compound with bismuth (3+) citrate (1:1).

$C_{13}H_{22}N_4O_3S,C_6H_5BiO_7$=712.5

CAS — 128345-62-0.

ATC — A02BA07.

ATC Vet — QA02BA07.

UNII — 7AJ51I17KG.

Profile

Ranitidine bismuth citrate is a combination of ranitidine and a bismuth citrate complex, which dissociates in the stomach and releases ranitidine and bismuth; it therefore possesses both the actions of the bismuth compounds (p. 1822.2) and of ranitidine (p. 1882.1). It has been used in the management of peptic ulcer disease (p. 1813.2), and has

been given with antibacterials for the eradication of *Helicobacter pylori* infection and the prevention of relapse of peptic ulcer disease.

Blackening of the tongue and faeces is common with ranitidine bismuth citrate, and gastrointestinal disturbances, headache, mild anaemia, and altered liver enzyme values have been reported. Rarely, hypersensitivity reactions (including anaphylaxis), have occurred. It was not suitable for long-term or maintenance therapy because of the risk of bismuth accumulation.

Reviews.
1. Anonymous. Pylorid, H. pylori and peptic ulcer. *Drug Ther Bull* 1996; **34:** 69–70.
2. Chiba N, *et al.* Ranitidine bismuth citrate. *Can J Gastroenterol* 2001; **15:** 389–98.

Peptic ulcer disease. Although proton pump inhibitor-based *Helicobacter pylori* eradication regimens are more commonly used (see p. 1813.2), regimens containing ranitidine bismuth citrate have also been tried as alternatives with some success.[1]

1. Gisbert JP, *et al.* Systematic review and meta-analysis: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics in Helicobacter pylori eradication. *Helicobacter* 2005; **10:** 157–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Pylorisin†; ***Braz.***: Pylorid; ***China***: Jindele (金得乐); Ruibei (瑞倍); Shu Wei (舒威); Si Fu Si (斯伏丝); ***Fin.***: Pylorid†; ***Gr.***: Pylorid; ***Mex.***: Azanplus†; ***Philipp.***: Pylorid; ***Singapore***: Pylorid; ***Thai.***: Pylorid†; ***Turk.***: Pylorid; ***Venez.***: Pylorid.

Multi-ingredient Preparations. ***Austral.***: Pylorid-KA†.

Rebamipide *(rINN)*

Rebamipida; Rébamipide; Rebamipidum; Ребамипид.
(±)-α-(*p*-Chlorobenzamido)-1,2-dihydro-2-oxo-4-quinolinepropionic acid.
$C_{19}H_{15}ClN_2O_4$=370.8
CAS — 90098-04-7; 111911-87-6.

Profile

Rebamipide is stated to possess cytoprotective properties and is used in the treatment of peptic ulcer disease (p. 1813.2) and gastritis in usual oral doses of 100 mg three times daily. It has also been used rectally for the treatment of intestinal inflammation. Rebamipide eye drops are under investigation in the treatment of dry eye.

References.
1. Makiyama K, *et al.* Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. *Dig Dis Sci* 2005; **50:** 2323–9.
2. Miyata M, *et al.* Successful treatment of severe pouchitis with rebamipide refractory to antibiotics and corticosteroids: a case report. *World J Gastroenterol* 2006; **12:** 656–8.
3. Miwa H, *et al.* Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia: a double-blind placebo-controlled study in Japan. *J Gastroenterol Hepatol* 2006; **21:** 1826–31.
4. Terano A, *et al.* Rebamipide Clinical Study Group. Rebamipide, a gastroprotective and anti-inflammatory drug, promotes gastric ulcer healing following eradication therapy for Helicobacter pylori in a Japanese population: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol* 2007; **42:** 690–3.
5. Park SH, *et al.* Comparison of prevention of NSAID-induced gastrointestinal complications by rebamipide and misoprostol: a randomized, multicenter, controlled trial—STORM STUDY. *J Clin Biochem Nutr* 2007; **40:** 148–55.
6. Du Y, *et al.* Anti-inflammatory effects of rebamipide according to Helicobacter pylori status in patients with chronic erosive gastritis: a randomized sucralfate-controlled multicenter trial in China—STARS study. *Dig Dis Sci* 2008; **53:** 2886–95.
7. Sugai S, *et al.* Efficacy and safety of rebamipide for the treatment of dry mouth symptoms in patients with Sjögren's syndrome: a double-blind placebo-controlled multicenter trial. *Mod Rheumatol* 2009; **19:** 114–24.
8. Naito Y, Yoshikawa T. Rebamipide: a gastrointestinal protective drug with pleiotropic activities. *Expert Rev Gastroenterol Hepatol* 2010; **4:** 261–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Huining (惠宁); Mucosta (膜固思达); ***Indon.***: Becantex; Mucosta; ***Jpn***: Mucosta; ***Malaysia***: Mucosta; ***Philipp.***: Gastrix; Mucosta; ***Thai.***: Mucosta.

Renzapride *(BAN, rINN)*

ATL-1251; AZM-112 (renzapride hydrochloride); BRL-24924A; Renzaprida; Renzapridum; Рензаприд.
(±)-*endo*-4-Amino-*N*-(1-azabicyclo[3.3.1]non-4-yl)-5-chloro-*o*-anisamide.
$C_{16}H_{22}ClN_3O_2$=323.8
CAS — 88721-77-1; 112727-80-7.
UNII — 9073C0W4E9.

Profile

Renzapride is a substituted benzamide with prokinetic actions on gastrointestinal motility. It also has 5-HT_4 agonist and 5-HT_3 antagonist activity. It has been investigated for the management of gastrointestinal disorders including irritable bowel syndrome.

References.
1. Tack J, *et al.* Pilot study of the efficacy of renzapride on gastrointestinal motility and symptoms in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2006; **23:** 1655–65.
2. George AM, *et al.* Clinical trial: renzapride therapy for constipation-predominant irritable bowel syndrome—multicentre, randomized, placebo-controlled, double-blind study in primary healthcare setting. *Aliment Pharmacol Ther* 2008; **27:** 830–7.
3. Lembo AJ, *et al.* Clinical trial: renzapride treatment of women with irritable bowel syndrome and constipation - a double-blind, randomized, placebo-controlled, study. *Aliment Pharmacol Ther* 2010; **31:** 979–90.

Reslizumab *(USAN, rINN)*

Reslizumabum; Sch-55700; Реслизумаб.
CAS — 241473-69-8.

NOTE. The name Cinquil has been used as a trade mark for reslizumab.

Profile

Reslizumab is a humanised monoclonal antibody that is under investigation for the treatment of paediatric eosinophilic oesophagitis, hypereosinophilic syndrome, and asthma.

References.
1. Walsh GM. Reslizumab, a humanized anti-IL-5 mAb for the treatment of eosinophil-mediated inflammatory conditions. *Curr Opin Mol Ther* 2009; **11:** 329–36.
2. Walsh GM. Reslizumab for pediatric eosinophilic esophagitis. *Immunotherapy* 2010; **2:** 461–5.

Revaprazan *(rINN)*

Revaprazán; Révaprazan; Revaprazanum; Ревапразан.
N-(4-Fluorophenyl)-4,5-dimethyl-6-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine.
$C_{22}H_{23}FN_4$=362.5
CAS — 199463-33-7.
UNII — 5P184180P5.

Revaprazan Hydrochloride *(USAN, rINNM)*

Hidrocloruro de revaprazán; Révaprazan, Chlorhydrate de; Revaprazani Hydrochloridum; SB-641257A; YH-1885; Ревапразана Гидрохлорид.
N-(4-Fluorophenyl)-5,6-dimethyl-4-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine hydrochloride.
$C_{22}H_{23}FN_4$,HCl=398.9
CAS — 178307-42-1.
UNII — 4DQ6T10R64.

Profile

Revaprazan is a proton pump inhibitor that is under investigation for the management of gastric and duodenal ulceration, functional dyspepsia, and gastro-oesophageal reflux disease.

References.
1. Sorbera LA, *et al.* Revaprazan hydrochloride. *Drugs Of The Future* 2004; **29:** 455.
2. Yu K-S, *et al.* Pharmacokinetic and pharmacodynamic evaluation of a novel proton pump inhibitor, YH1885, in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 73–82.

Rhubarb

Chinese Rhubarb; Korzeń rzewienia; Rabarbarų šaknys; Rabarbaro; Rabarberrot; Raparperinjuuri; Ravent; Rebarbaragyökértörzs; Reveňový kořen; Rhabarber; Rhabarberwurzel; Rhei Radix; Rhei Rhizoma; Rheum; Rhubarb Rhizome; Rhubarbe; Ruibarbo; Ревень Аптечный.
ATC Herb — HA06AB5015 (Rheum palmatum: *root*).
UNII — A47JP5ZG9M (Rheum officinale *root*).

Description. Indian rhubarb (Himalayan rhubarb) consists of the dried rhizome and roots of *Rheum emodi*, *R. webbianum*, or some other related species of *Rheum*.

Rhapontic rhubarb (Chinese rhapontica) consists of the dried rhizomes of *R. rhaponticum*. It may occur as an adulterant of rhubarb, and pharmacopoeias specify a test to confirm its absence. Garden rhubarb, of which the leafstalks are used as food, is derived from *R. rhaponticum*.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. *Chin.* and *Jpn* also permit *Rheum tanguticum*, and *Jpn* also permits *R. coreanum*.

Ph. Eur. 8: (Rhubarb). The whole or cut, dried underground parts of *Rheum palmatum* or of *R. officinale* or of hybrids of these two species or of a mixture. The underground parts are often divided; the stem and most of the bark with the rootlets are removed. It contains not less than 2.2% of hydroxyanthracene derivatives, expressed as rhein ($C_{15}H_8O_6$ = 284.2), calculated with reference to the dried drug. Protect from light.

Uses and Administration

Rhubarb is an anthraquinone stimulant laxative used similarly to senna (p. 1885.2). It also exerts an astringent action due to the presence of gallic acid derivatives and tannins.

Homoeopathy

Rhubarb has been used in homoeopathic medicines under the following names: Rheum; Rhei radix; Rheum palmatum; Rheum officinale.

Adverse Effects and Precautions

As for Senna, p. 1885.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Femi-loges; Phyto-Strol; ***Pol.***: Laxitab; Radirex; Rzewex†.

Multi-ingredient Preparations. ***Arg.***: LX-30†; Oralsone Topic; Parodium; Pyralvex; Wunderbalsam; ***Austral.***: Betaine Digestive Aid; Burdock Complex; Neo-Cleanse; ***Austria***: Eucarbon; Phytovir; Pyralvex; Silberne†; ***Belg.***: Pyralvex; ***Braz.***: Camomila; Eparema; Gotas Preciosas; ***Canad.***: Herbal Laxative†; Herbolax†; Laxanat; Laxatil; Laxolax Phyto†; Melange de Plantes Formula Ll Laxatif†; Stomach Ease; Ultra-Lax†; ***Chile***: Parodium; ***Cz.***: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Eucarbon; Pyralvex†; Species Cholagogae Planta†; Zlucnikova Cajova Smes; ***Fr.***: Depuratum; Parodium; Pyralvex; Resource Rhubagil†; Tisane D'Ars†; ***Ger.***: Pyralvex†; ***Gr.***: Pyralvex; ***Hong Kong***: Hepatofalk†; Pyralvex†; ***Hung.***: Bano Svedkeseru; Bolus Laxans; Eucarbon; ***India***: Agloliv; ***Indon.***: Pyralvex†; ***Israel***: Eucarbon; Novicarbon†; ***Ital.***: Alosen†; Amaro Medicinale; Caramelle alle Erbe Digestive; Colax†; Dis-Cinil Complex; Eparema-Levul; Eparema; Eucarbon; Eupatol; Lactolas; Lassativi Vetegali†; Pyralvex; ***Jpn***: Bofutsushosan; Choijokito; Daijokito; Daiobotampito; Daiokanzoto; Daisaikoto; Inchinkoto; Jidabokuippo; Jizusoippo; Junchoto; Keishikashakuyakudaioto; Mashiningan; Otsujito; San'oshashinto; Tokakujokito; Tsudosan; ***Malaysia***: Eucarbon Herbal; Eucarbon; ***Neth.***: Pyralvex; ***Philipp.***: Boie Carminative (Carminasen); Pyralvex; ***Pol.***: Betasol; Diges-Tonic; Laxantol†; Rhelax; ***Port.***: Pyralvex; ***Rus.***: Parodium (Пародиум); ***S.Afr.***: Eucarbon†; Helmontskruie†; Lewensessens; Moultons Herbal Extract†; Pyralvex; Wonderkroonessens; ***Singapore***: Pyralvex; Sankaijo; ***Spain***: Crislaxo; Laxante Bescansa Aloico†; Pyralvex; Solucion Schoum; ***Switz.***: Padma-Lax; Padmed Laxan; Parsenn Creme pour herpes; Phytovir; Pyralvex; Schweden-Mixtur H; ***Thai.***: Pyralvex; Rheum; Sahakarn Mist Stomachic; ***Turk.***: Eucarbon; Karboseptin; Piraldyne; Pyralvex; ***UK***: Acidosis; Digestive; Fam-Lax Senna; Fam-Lax; HRI Golden Seal Digestive; Indian Brandee; Jacksons Herbal Laxative; Pegina; Pyralvex; Rhuaka; Stomach Mixture; Wind & Dyspepsia Relief; ***Ukr.***: Eucarbon (Эукарбон); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***USA***: Black-Draught; ***Venez.***: Cynascool; Natrossil; Pinvex; Rheu-Tarx 1.

Homoeopathic Preparations. ***Austral.***: Snore Eze; ***Canad.***: Essigen†; Vegetal Tonic; ***Fr.***: Camilia; Momordica Complexe No 109†; Tonique Vegetal; ***Switz.***: Camilia.

Pharmacopoeial Preparations

BP 2014: Compound Rhubarb Tincture.

Roxatidine Acetate Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de acetato de roxatidina; Hoe-062 (roxatidine); Hoe-760; Pifatidine Hydrochloride; Roxatidina, hidrocloruro de acetato de; Roxatidine, Acétate Chlorhydrique de; Roxatidini Acetati Hydrochloridum; TZU-0460; Роксатидина Ацетат Гидрохлорид.
N-{3-[(α-Piperidino-*m*-tolyl)oxy]propyl}glycolamide acetate monohydrochloride.
$C_{17}H_{26}N_2O_3$,C_2H_2O,HCl=384.9
CAS — 78273-80-0 (roxatidine); 97900-88-4 (roxatidine hydrochloride); 78628-28-1 (roxatidine acetate); 93793-83-0 (roxatidine acetate hydrochloride).
ATC — A02BA06.
ATC Vet — QA02BA06.
UNII — 60426GOR1E.

Pharmacopoeias. In *Jpn*.

Stability. The stability of roxatidine acetate hydrochloride in parenteral nutrition solutions was influenced by storage temperature and amino acid content and composition.[1]

1. Oh J, *et al.* Stability of roxatidine acetate in parenteral nutrient solutions containing different amino acid formulations. *Am J Health-Syst Pharm* 2005; **62:** 289–91.

Uses and Administration

Roxatidine acetate hydrochloride is an H_2-antagonist with actions and uses similar to those of cimetidine (p. 1827.2).

In the management of **peptic ulcer disease** the oral dose is 150 mg at bedtime or 75 mg twice daily for 4 to 6 weeks. Where appropriate a maintenance dose of 75 mg at bedtime may be given to prevent the recurrence of ulcers. In **gastro-oesophageal reflux disease** the recommended dose is 150 mg at bedtime or 75 mg twice daily for 6 to 8 weeks. Gastritis has been managed with 75 mg once daily in the evening, and a dose of 75 mg twice daily has been used for **Zollinger-Ellison** syndrome.

When used as a **pre-anaesthetic** medication, a dose of roxatidine acetate hydrochloride 75 mg is given 1 hour before anaesthesia by slow intravenous injection. Alternatively, an oral dose of 75 mg is given in the evening on the day before surgery and repeated 2 hours before the induction of anaesthesia; alternatively a single dose of 150 mg may be given the night before surgery.

Roxatidine acetate hydrochloride may also be given intravenously for the treatment of **upper gastrointestinal tract haemorrhage** in a dose of 75 mg twice daily by slow intravenous injection or by intravenous infusion.

For dosage in renal impairment, see below.

Reviews.

1. Murdoch D. Roxatidine acetate: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic potential in peptic ulcer disease and related disorders. *Drugs* 1991; **42:** 240–60.

Administration in renal impairment. The dosage of roxatidine acetate hydrochloride should be reduced in patients with renal impairment. Suggested oral doses for peptic ulcer disease or gastro-oesophageal reflux disease are based on creatinine clearance (CC):

- CC 20 to 50 mL/minute: 75 mg once daily
- CC less than 20 mL/minute: 75 mg every 2 days

However, results in 6 patients with chronic renal failure and CC less than 20 mL/minute indicated that giving the recommended dose of roxatidine acetate hydrochloride, 75 mg every other day, was inadequate to maintain gastric pH above 4 for more than 6 hours. Subsequent study in 8 patients showed that a dose of 75 mg daily was well tolerated and effective.[1]

For prophylaxis of peptic ulcers, the following oral doses have been suggested based on CC:

- CC 20 to 50 mL/minute: 75 mg every 2 days
- CC less than 20 mL/minute: 75 mg twice weekly

1. Gladziwa U, *et al.* Pharmacokinetics and pharmacodynamics of roxatidine in patients with renal insufficiency. *Br J Clin Pharmacol* 1995; **39:** 161–7.

Adverse Effects and Precautions

As for Cimetidine, p. 1828.3. Unlike cimetidine, roxatidine has little or no anti-androgenic effect, despite isolated reports of reductions in libido.

Interactions

Unlike cimetidine (p. 1830.3) roxatidine does not appear to affect cytochrome P450 isoenzymes, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists its effects on gastric pH may alter the absorption of drugs whose absorption is dependent on an acid gastric pH.

Pharmacokinetics

Roxatidine acetate hydrochloride is rapidly and almost completely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 1 to 4 hours after oral doses. It is rapidly hydrolysed to the active desacetyl metabolite, roxatidine, by esterases in the liver, small intestine, and serum.

Over 90% of a dose is excreted in the urine as roxatidine and other metabolites. The elimination half-life of roxatidine is about 4 to 6 hours and is prolonged in renal impairment.

Roxatidine crosses the placenta and small amounts have been reported to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Roxane; ***India***: Rotane; ***Ital.***: Gastralgin; Neo H2; Roxit; ***Jpn***: Altat; ***Spain***: Zarocs†.

Senna

Alexandriai szenna termés (senna pods, Alexandrian); Listek senesu (senna leaf); Plod kasie ostrolisté (senna pods, Alexandrian); Plod kasie úzkolisté (senna pods, Tinnevelly); Sen; Senų lapai (senna leaf); Senų vaisiai (senna pods, Alexandrian); Séné de Khartoum ou d'Alexandrie, fruit de (senna pods, Alexandrian); Séné de l'Inde ou de Tinnevelly, fruit de (senna pods, Tinnevelly); Séné, feuille de (senna leaf); Sennabalja, alexandrinsk (senna pods, Alexandrian); Sennabalja, Tinnevelley- (senna pods, Tinnevelley); Sennae folium (senna leaf); Sennae fructus acutifoliae (senna pods, Alexandrian); Sennae fructus angustifoliae (senna pods, Tinnevelly); Sennanpalko, Aleksandrian (senna pods, Alexandrian); Sennanpalko, Tinnevelleyn (senna pods, Tinnevelley); Sennový list (senna leaf); Siauralapių senų vaisiai (senna pods, Tinnevelly); Sinameki; Szennalevél (senna leaf); Tinevelly szenna termés (senna pods, Tinnevelly); Кассия Остролистная (Alexandrian senna); Александрийский Лист (Alexandrian senna leaf); Сенна Остролистная (Alexandrian senna).

CAS — 8013-11-4.

ATC — A06AB06.

ATC Vet — QA06AB06.

*ATC Herb — HA06AB5017 (*Senna alexandrina*: fruit); HA06AB5018 (*Senna alexandrina*: leaf).*

Description. Senna obtained commercially from *Cassia senna* (*C. acutifolia*) (Leguminosae) is known as Alexandrian senna or Khartoum senna and that from *Cassia angustifolia* (Leguminosae) as Tinnevelly senna.

Pharmacopoeias. Senna fruit, from Alexandrian and Tinnevelly senna is included in *Eur.* (see p. vii), *Int.*, and *US*. Senna leaf, from Alexandrian or Tinnevelly senna or both, is included in *Chin., Eur., Int., Jpn,* and *US.*

Ph. Eur. 8: (Senna Pods, Alexandrian; Sennae Fructus Acutifoliae; Alexandrian Senna Fruit BP 2014). The dried fruit of *Cassia senna* (*Cassia acutifolia*) containing not less than 3.4% of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$ = 862.7) with reference to the dried drug. Protect from light and moisture.

Ph. Eur. 8: (Senna Pods, Tinnevelly; Sennae Fructus Angustifoliae; Tinnevelly Senna Fruit BP 2014). The dried fruit of *Cassia angustifolia* containing not less than 2.2% of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$ = 862.7) with reference to the dried drug. Protect from light and moisture.

Ph. Eur. 8: (Senna Leaf; Sennae Folium). The dried leaflets of *Cassia senna* (=*Cassia acutifolia*), known as Alexandrian or Khartoum senna, or *Cassia angustifolia*, known as Tinnevelly senna, or a mixture of the two species. It contains not less than 2.5% of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$ = 862.7) with reference to the dried drug. Protect from light and moisture.

USP 36: (Senna Leaf). The dried leaflet of *Cassia acutifolia*, known in commerce as Alexandria senna, or *Cassia angustifolia*, known in commerce as Tinnevelly senna (Leguminosae). Protect from moisture and from light.

USP 36: (Senna Pods). The dried ripe fruit of *Cassia acutifolia* (Alexandrian senna) or *Cassia angustifolia* (Tinnevelly senna) containing not less than 3.4% or 2.2% respectively of anthraquinone glucosides, calculated as sennosides, on the dried basis. Protect from moisture and from light.

Sennosides

Senósidos; Сеннозиды.

CAS — 81-27-6 (sennoside A); 128-57-4 (sennoside B); 52730-36-6 (sennoside A, calcium salt); 52730-37-7 (sennoside B, calcium salt).

UNII — 1B5FPI42EN (sennosides A and B); 2F1O30GVXH (sennoside A); F887D1637W (sennoside B); 3FYP5M0IJX (calcium sennosides).

Pharmacopoeias. In *US.*

USP 36: (Sennosides). A partially purified natural complex of anthraquinone glucosides found in senna, isolated from *Cassia acutifolia* or *Cassia angustifolia* as calcium salts. It is a brownish powder. Soluble 1 in 35 of water, 1 in 2100 of alcohol, 1 in 3700 of chloroform, and 1 in 6100 of ether. A 10% solution in water has a pH of 6.3 to 7.3. Store at a temperature of 20 degrees to 25 degrees. Protect from moisture and from light.

Uses and Administration

Senna is an anthraquinone stimulant laxative (p. 1804.1) that is used to treat constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. The active anthraquinones are liberated into the colon from the sennoside glycosides by colonic bacteria and an effect usually occurs within 6 to 12 hours of an oral dose.

For constipation, senna is usually given as tablets, granules, or syrup. In some countries it is available as suppositories. In the UK, doses of senna preparations are usually expressed in terms of total sennosides calculated as sennoside B. The usual adult oral dose is 15 to 30 mg as a single dose at bedtime. (For doses in children see Administration in Children, below.) In the USA, the usual adult dose is 15 to 30 mg once or twice daily, expressed in terms of total sennosides.

For bowel evacuation before investigational procedures, a dose of 105 to 157.5 mg of sennosides may be given orally as a liquid preparation on the day before the procedure (but see Colonic Perforation under Precautions, p. 1886.1).

The purified sennosides (sennosides A and B), and their calcium salts (calcium sennoside A and calcium sennoside B) are used similarly to senna.

Homoeopathy

Senna leaf has been used in homoeopathic medicines under the following names: Senna; Senna folium.

Administration in children. In the UK, the following oral doses of sennosides are licensed for use for constipation in children:

- aged 2 to 6 years: 3.75 to 7.5 mg once daily in the morning
- aged 6 to 12 years: 7.5 to 15 mg once daily at night or in the morning
- 12 years and over: 15 to 30 mg once daily, usually at bedtime

In addition, although not licensed for use in children under 2 years, the *BNFC* allows for an oral dose of syrup (containing sennosides 7.5 mg per 5 mL) of 2.5 to 10 mL once daily in those aged 1 month to 4 years.

Adverse Effects

Senna may cause mild abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Anthraquinone derivatives may colour the urine yellowish-brown at acid pH, and red at alkaline pH. Reversible melanosis coli has been reported after chronic use.

Abuse. Prolonged use or abuse of senna laxatives has been associated with finger clubbing,[1-5] hypokalaemia[3] and tetany,[1] hypertrophic osteoarthropathy,[4,5] intermittent urinary excretion of aspartylglucosamine,[2] hypogammaglobulinaemia,[3] reversible cachexia,[3] and hepatitis[6] or hepatic failure.[7] In one case, nephrocalcinosis was attributed to hypercalcaemia caused by excessive ingestion of calcium sennosides.[5]

1. Prior J, White I. Tetany and clubbing in patient who ingested large quantities of senna. *Lancet* 1978; **ii:** 947.
2. Malmquist J, *et al.* Finger clubbing and aspartylglucosamine excretion in a laxative-abusing patient. *Postgrad Med J* 1980; **56:** 862–4.
3. Levine D, *et al.* Purgative abuse associated with reversible cachexia, hypogammaglobulinaemia, and finger clubbing. *Lancet* 1981; **i:** 919–20.
4. Armstrong RD, *et al.* Hypertrophic osteoarthropathy and purgative abuse. *BMJ* 1981; **282:** 1836.
5. Lim AKH, *et al.* Anorexia nervosa and senna misuse: nephrocalcinosis, digital clubbing and hypertrophic osteoarthropathy. *Med J Aust* 2008; **188:** 121–2.
6. Beuers U, *et al.* Hepatitis after chronic abuse of senna. *Lancet* 1991; **337:** 372–3.
7. Vanderperren B, *et al.* Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. *Ann Pharmacother* 2005; **39:** 1353–7.

Effects on the liver. Hepatitis has been reported in a patient drinking herbal tea containing senna. The patient was found to be a poor metaboliser for hepatic detoxification reactions; the authors cautioned against even small doses of herbal preparations in such patients.[1]

Hepatitis and hepatic failure have also been reported after abuse of senna laxatives, see Abuse, above.

1. Seybold U, *et al.* Senna-induced hepatitis in a poor metabolizer. *Ann Intern Med* 2004; **141:** 651.

Hypersensitivity. Hypersensitivity reactions manifesting as asthma and rhinoconjunctivitis have been reported in those manufacturing[1] or dispensing[2] senna products. However, a study of 125 workers involved in the manufacture of laxatives found only 4 cases of occupational asthma, although sensitisation to senna or ispaghula dust was present in 18 and 9 of the workers respectively, and other airway, eye, and skin symptoms were relatively frequent.[3]

A 2-year history of pruritic scaly erythematous plaques on the palmoplantar surfaces was reported[4] by a patient who had taken a sennoside laxative for 20 years. The lesions subsided over about 6 weeks on stopping the drug, and reappeared over the course of 8 weeks on restarting sennoside. However, patch testing and lymphocyte stimulation tests for sennoside were negative.

1. Helin T, Mäkinen-Kiljunen S. Occupational asthma and rhinoconjunctivitis caused by senna. *Allergy* 1996; **51:** 181–4.
2. Baggaley P. A shared allergy. *Pharm J* 1997; **259:** 724.
3. Marks GB, *et al.* Asthma and allergy associated with occupational exposure to ispaghula and senna products in a pharmaceutical work force. *Am Rev Respir Dis* 1991; **144:** 1065–9.
4. Fujita Y, *et al.* A case of interstitial granulomatous drug reaction due to sennoside. *Br J Dermatol* 2004; **150:** 1035–7.

Precautions

Senna should not be given to patients with nausea or vomiting, undiagnosed abdominal pain, or intestinal obstruction; care should also be taken in patients with

inflammatory bowel disease. Prolonged use should generally be avoided.

Although anthraquinone derivatives may be distributed into breast milk the concentration achieved after usual maternal dosage is thought to be insufficient to affect the nursing infant (see also below).

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving senna, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 21/11/06)

Colonic perforation. There were early reports of colonic perforation with faecal peritonitis,[1,2] in one case fatal,[1] after use of a senna preparation containing total sennosides 142 mg for bowel preparation before barium enema. In 1985, the strength of the UK preparation was halved to contain 72 mg of total sennosides; it was subsequently withdrawn, although a similar preparation, at the higher strength, remains available in some countries. To reduce the risk of colonic perforation, patients with suspected stricture, inflammatory bowel disease, or impending obstruction should not receive a bowel stimulant.[2]

1. Galloway D, *et al*. Faecal peritonitis after laxative preparation for barium enema. *BMJ* 1982; **284:** 472.
2. Cave-Bigley D. Faecal peritonitis after laxative preparation for barium enema. *BMJ* 1982; **284:** 740.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies senna as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. A retrospective case-control study involving 22 843 infants with congenital abnormalities and 38 151 healthy matched controls (of whom 506 and 937 respectively had mothers who had taken senna for constipation during pregnancy) found no association between abnormality and maternal use of senna.[1]

1. Ács N, *et al*. Senna treatment in pregnant women and congenital abnormalities in their offspring—a population-based case-control study. *Reprod Toxicol* 2009; **28:** 100–4.

Pharmacokinetics

There is some absorption of anthraquinone laxatives after oral doses. Absorbed anthraquinones are metabolised in the liver. Unabsorbed senna is hydrolysed in the colon by bacteria to release the active free anthraquinones. Anthraquinones are excreted in urine and faeces and distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ciruela Fibra†; Laxiruela Ciruela Fibra; Laxiruela; Laxuave Sen; ***Austral.***: Bekunis Tea†; Laxettes; Sennetabs; Senokot; ***Austria***: Bekunis; Colonorm; Darmol; Pursennid; X-Prep; ***Belg.***: Darlin†; Fuca; Grains de Vals Senna; Midro; Prunasine; Senokot; ***Braz.***: Senan; Sene†; Sennalax; ***Canad.***: Agarol Extra†; Agarol with Sennosides†; Bekunis; Ex-Lax; Experience; Formula Tl Tea†; Herbal Laxative†; Laxative Pills; Senokot; Swiss Kriss†; ***Chile***: Cholax; Naturlax; ***Cz.***: Caj z Listu Senny; List Senny; Senalax; Sennove Lusky; ***Denm.***: Thea Bona; ***Fin.***: Exprep†; Pursennid; ***Fr.***: Grains de Vals; Pursennide; Senokot; Tisane des Familles†; Tisane Franklin†; X-Prep; ***Ger.***: Bekunis Instant; Bekunis-Krautertee N; Depuran†; Midro Abfuhr; Midro Tee; Neda Fruchtewurfel†; Ramend; ***Gr.***: Bekunis; Pursennid; X-Prep; ***Hong Kong***: Senokot; Senoside; ***Hung.***: Darmol; Regulax; Tisasen; X-Prep; ***India***: Glaxenna; Senade; Senalax; ***Irl.***: Ex-Lax†; Senokot; ***Israel***: Bekunis; Ex-Lax†; Florilax†; Jungborn; Laxikal Forte; ***Ital.***: Falquilax; Pursennid; Tisana Kelemata; X-Prep; ***Malaysia***: Senokot; ***Mex.***: Arsen†; Bekunis; C-Motil; Ciruelax Comp; Ciruelax TE†; Lagenbach; Senokot; X-Prep; ***Neth.***: Bekunis Plantaardig†; Bekunis Senna†; Fuca excellent; Sennocol; X-Praep; ***Norw.***: Pursennid; Senokot†; X-Prep†; ***NZ***: Senokot; ***Philipp.***: Laxen; Senalax; Senokot; ***Pol.***: Bekunis; Figura 1; Regulax; Senalax; Senefol; X-Prep†; Xenna; ***Port.***: Bekunis Laxante Natural; Bekunis; Pursennide; Senolax; X-Prep; ***Rus.***: Glaxenna (Глаксенна); Herbion Laksana (Гербион Лаксана); Regulax (Регулакс); Senade (Сенаде); Senadexin (Сенадексин); Senalex (Сеналекс); Tisasen (Тисасен); ***S.Afr.***: Black Forest†; Depuran; Gal†; Hamburg Tea; Laxador Senna; Sennalax†; Senokot; Soflax; X-Prep; ***Singapore***: Bekunis; Senokot; ***Spain***: Arkocapsulas Sen; Bekunis; Justelax†; Laxante Bescansa Normal†; Laxante Olan; Laxante Salud; Neholis; X-Prep; ***Swed.***: Linella; Pursennid; ***Switz.***: Bekunis; Darmol; Fuca N†; Grains de Vals Nouvelle formule; Knobel Comprimes N†; Midro; Pursennide; X-Prep; ***Thai.***: Emulax Senna; Senokot; ***Turk.***: Pursennid; Roha-Lax; Sennalax; Senokot; X-M; ***UAE***: Laxal; ***UK***: Ex-Lax; Nylax with Senna; Senokot; Sure-Lax; ***Ukr.***: Regulax (Регулакс); Senadex (Сенадекс)†; ***USA***: Black-Draught†; Dosaflex; Dr Edwards Olive; Evac-U-Gen; Ex-Lax; Fletchers Castoria; Lax Pills; Little Tummys Laxative; Maximum Relief Ex-Lax; Pedia-Lax; Senexon; Senna Smooth; Senna-Gen; Senokot; Senokotxtra; X-Prep†; ***Venez.***: Laxovar; Senlax; Senokot.

Multi-ingredient Preparations. ***Arg.***: Agiolax; Candilax†; Cirulaxia; Delgacin; Gelax; Laxiruela; LX-30†; Medilaxan; Rapilax Fibras; Yuyo; ***Austral.***: Agiolax; Chemists Own Natural Laxative with Softener; Colon Care; Coloxyl with Senna; Combilax†; Detox Program; Neo-Cleanse; Sennesoft; Soflax; ***Austria***: Abfuhrtee St Severin; Agiolax; Carilax; Entschlackender Abfuhrtee EF-EM-ES; Eucarbon; Frugelletten; Laxalpin†; Mag Kottas Krauterexpress Abfuhrtee; Midro Tee; Neda Fruchtewurfel; Planta Lax; The Chambard-Tee; ***Belg.***: Agiolax; Herbesan; ***Braz.***: Agiolax; Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; ***Canad.***: Bekunis†; Control†; Doulax; Eliminex; Fiber Plus; Formula B-1†; Herba Tone†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Herbal Tabs†; Herbolax†; Laxanat; Laxolax; Linoforce; Melange de Plantes Formula Ll Laxatif†; Metab Herbs No 1†; Metab Herbs†; Senna-S; Senokot-S; Stomach Ease; Traditional Herbal Laxative†; Ultra-Lax†; ***Chile***: Bilaxil; Instalax; Mielax†; Naturlax†; Tamarine; Te Laxante†; ***China***: Agiolax (艾者思); ***Cz.***: Agiolax†; Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Eucarbon; Projimava; Reduktan; ***Denm.***: Dix†; ***Fin.***: Agiolax; ***Fr.***: Afra†; Agiolax; Boldoflorine; Boldoflorine; Boribel Tisane No 13†; Herbesan; Ideolaxyl; Laxilo†; Mediflor Contre la Constipation Passagere No 7; Modane; Mucinum a l'Extrait de Cascara; Olivalax; Santane C_6†; Tamarine†; Tisane D'Ars†; Tisane Garfield†; Tisane Provencale no 1; Tisane Saint-Urbain†; Ultratransit; Yerbalaxa; ***Ger.***: Agiolax; Alasenn; ***Gr.***: Agiolax; Tamarine; ***Hong Kong***: Agiolax; Mucinum†; ***Hung.***: Agiolax; Bano Svedkeseru; Bolus Laxans; Eucarbon; Herbalax; Super Colon Cleanse; ***India***: Bolax; Constricare; Evacuol; ***Irl.***: Agiolax; ***Israel***: Agiolax; Eucarbon; Jungborn†; Lido Tea†; Midro-Tea; Novicarbon†; ***Ital.***: Agiolax; Alosen†; Colax†; Combilax; Confetti Lassativi CM; Cuscutine†; Eucarbon; Fibrolax Complex; Lactolas; Midro; Miracolon; Ortisan; Tamarine; Tisana Kelemata; ***Jpn***: Circanetten; ***Malaysia***: Agiolax; Eucarbon Herbal; Eucarbon; ***Mex.***: Agiolax; Ciruelax Jalea; Fruticoline; Jarabe de Manzanas; Laxacaps; MD Lax; Naturetti; ***Neth.***: Agiolax; Herbesan†; Prunacolon; Prunasine; ***Norw.***: Agiolax†; ***NZ***: Coloxyl with Senna; Laxsol; ***Philipp.***: Boie Carminative (Carminasen); Castoria; ***Pol.***: Agiolax; Laxamix†; Melisana Klosterfrau; Normosan†; Senalax K; ***Port.***: Agiolax; Bekunis; Mucinum; Xarope de Macas Reinetas; ***Rus.***: Proctophytol (Проктофитол); ***S.Afr.***: Agiolax; Clairo†; Eucarbon†; ***Singapore***: Sankaijo; ***Spain***: Agiolax; Bekunis Complex; Crislaxo; Docuxen†; Farmasul; Jarabe Manceau; Laxante Sanatorium†; LinoMed; Modane; Pruina; Puntual; Puntualex; Pursenid; ***Swed.***: Agiolax†; ***Switz.***: Agiolax; Dragees aux figues avec du sene; Fruttasan†; Lapidar 10; Linoforce; LinoMed; Midro Tee; Phyto-Laxia†; Schweden-Mixtur H; Tisane laxative; Tisane Provencale no 1; Valverde Constipation dragees; Valverde Constipation sirop; ***Thai.***: Agiolax; Circanetten; Hemorrhoid Relief; ***Turk.***: Bekunis; Eucarbon; Karboseptin; ***UK***: Athera; Califig; Califig; Cassilax; Cleansing Herbs; Dual-Lax Extra Strong; Dual-Lax Normal Strength; Fam-Lax Senna; Fibre Plus; Jacksons Herbal Laxative; Kas-Bah; Laxative Tablets; Linoforce; Lion Cleansing Herbs; Lustys Herbalene; Manevac; Modern Herbals Laxative; Modern Herbals Menopause; Natural Herb Tablets; Out-of-Sorts; Pripsen†; Rhuaka; Senokot Dual Relief; Skin Cleansing; Tabritis; ***Ukr.***: Eucarbon (Эукарбон); Picosen (Пикосен); Softovak (Софтовак); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***USA***: Black-Draught; Dok Plus; Ex-Lax Gentle Strength†; Laxacin; Perdiem†; Peri-Colace; Senna Plus; Senna Prompt; Senna-S; Senokot-S; X-Prep Bowel Evacuant Kit-1†; ***Venez.***: Agiolax; Rheu-Tarx 1; Senokot con Docusato.

Homoeopathic Preparations. ***UK***: Laxadoron.

Pharmacopoeial Preparations
BP 2014: Senna Liquid Extract; Senna Tablets; Standardised Senna Granules;
Ph. Eur.: Senna Leaf Dry Extract, Standardised;
USP 36: Senna Fluidextract; Senna Syrup; Sennosides Tablets.

Simeticone *(BAN, rINN)*

Activated Dimethicone; Activated Dimethylpolysiloxane; Activated Dimeticone; Antifoam A; Antifoam AF; Simethicone (USAN); Simeticon; Simeticona; Siméticone; Simeticonum; Simetikon; Simetikonas; Simetikoni; Szimetikon; Симетикон.

CAS — 8050-81-5.

NOTE. Do not confuse with Dimeticone (p. 2209.3).

Compounded preparations of simeticone may be represented by the following names:

- Co-simalcite *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Simeticone). It is prepared by incorporation of 4 to 7% silica into poly(dimethylsiloxane) with a degree of polymerisation between 20 and 400. It contains 90.5 to 99.0% of poly(dimethylsiloxane). It is a greyish-white, opalescent, viscous liquid. Practically insoluble in water and in methyl alcohol; very slightly soluble to practically insoluble in dehydrated alcohol; partly miscible with dichloromethane, with ethyl acetate, with methyl ethyl ketone, and with toluene.

USP 36: (Simeticone). A mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilised with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, and silicon dioxide. It contains not less than 90.5% and not more than 99% of polydimethylsiloxane and not less than 4% and not more than 7% of silicon dioxide. A translucent, grey, viscous fluid. Insoluble in water, in alcohol, and in dehydrated alcohol; the liquid phase is soluble 1 in 10 of chloroform, of ether, and of benzene, leaving a residue of silicon dioxide. Store in airtight containers.

Profile

Simeticone is a mixture of liquid dimeticones containing finely divided silicon dioxide to enhance the defoaming properties of the silicone. It lowers surface tension and when given orally causes bubbles of gas in the gastrointestinal tract to coalesce, thus aiding their dispersion.

Simeticone is used for the relief of flatulence and abdominal discomfort due to excess gastrointestinal gas in disorders such as dyspepsia (p. 1806.3) and gastro-oesophageal reflux disease (p. 1807.2). Doses of 100 to 250 mg three or four times daily have been given. For many gastrointestinal disorders, it is given with an antacid.

For doses in children, see below

Simeticone is also used as a defoaming agent in radiography or endoscopy of the gastrointestinal tract.

Administration in children. Simeticone can be given orally to infants to relieve symptoms of colic (see Gastrointestinal Spasm, p. 1807.1); 20 to 40 mg is given before feeds.

Gastrointestinal disorders. A brief review of the use of simeticone for gastrointestinal symptoms concluded that although it was commonly prescribed with an antacid, there was no good evidence that this provided additional benefit. When used alone simeticone probably helped to relieve minor postoperative and postprandial symptoms and was a useful aid in upper gastrointestinal endoscopy.[1] However, some considered there was no convincing evidence that simeticone, alone or with antacids, was effective for the treatment of eructation, flatulence, or other signs or symptoms of excess gastrointestinal gas.[2]

1. Anonymous. Dimethicone for gastrointestinal symptoms? *Drug Ther Bull* 1986; **24:** 21–2.
2. Anonymous. Simethicone for gastrointestinal gas. *Med Lett Drugs Ther* 1996; **38:** 57–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies silicones when used for gastrointestinal disorders as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aesim; Aflat; Carbogasol Forte; Carbogasol; Espaven Antigas; Factor AG; Metiorisan; Minicidez; Mylanta Gas; Simecon; ***Austral.***: De-Gas; Gasbusters; Infacol; ***Austria***: Antiflat; Disflatyl†; Lefaxin; SAB Simplex; ***Belg.***: Imonogas; ***Braz.***: Dimetiliv; Dimezin; Espasmo Flatol; Finigas; Flagass; Flatex; Flaticona; Flatol; Flucolic; For Gas; Gastroflat; Gazyme; Lufisan; Luftal; Meticone†; Mylanta Plus; Mylicon; Sanagas; Silidron; ***Canad.***: Gas Relief; Gas-X; Infacol; Little Tummys Gas Relief; Ovol; Pediacol; Phazyme; Siligaz; Ultra Strength Gas Relief; Ultra Strength Ovol; Ultra Strength Phazyme; ***Chile***: Flapex; Gasoff; ***China***: Espumisan (柏西); Gascon (咖斯康); ***Cz.***: AeroOM; Espumisan; Lefax; SAB Simplex; ***Denm.***: Aeropax; Imogas; Mylicon; ***Fin.***: Cuplaton; Disflatyl; Minifom; ***Fr.***: Imonogas; Polysilane; Siligaz; ***Ger.***: Additiva†; Ceolat; Elugan; Endo-Paractol; Espumisan; Ilio-Funkton; Imogas; Lefax; SAB Simplex; ***Gr.***: Ceolat; Infacol; Infacolic; ***Hong Kong***: Air-X; Dentinox Colic Drops†; Disflatyl†; Gascon; Gasteel; Infacol; Ovol†; ***Hung.***: Espumisan; Infacol; SAB Simplex; ***India***: Dicon-I; Dimol; Tricaine-MPS; ***Indon.***: Aeroson†; Disflatyl; Flatunic†; Neolanta; ***Irl.***: Dentinox Colic; Imogas; Infacol; ***Israel***: Gazim X; Simicol; ***Ital.***: Imogas; Meteosim; Mylicon; Mylicongas; Simecrin; Simetic; ***Malaysia***: Cuplaton; Dentinox Colic Drops; Disflatyl; Gascoal; Gastyl; ***Mex.***: Espaven Pediatrico; Liberan; ***Neth.***: Aero-Om; Aeropax; ***Norw.***: Imogas; Minifom; Siloxan; ***NZ***: De-Gas; Infacol; ***Philipp.***: Disflatyl; Restime; ***Pol.***: Bobotic; Espumisan; Esputicon; Gastrosil; Infacol; Manti Gastop; Simet†; Ulgix; ***Port.***: Aero-Om; Disflat; Imogas; ***Rus.***: Bobotik (Боботик); Disflatyl (Дисфлатил); Espumisan (Эспумизан); SAB Simplex (САБ Симплекс); Simicol (Симикол); ***S.Afr.***: Telament; ***Singapore***: Cuplaton†; Gascoal; Infacol†; Rid-Wind; Simcone; ***Spain***: Aero Red; Disolgas; Enterosilicona; Imonogas; ***Swed.***: Imogaze; Minifom; ***Switz.***: Aero-Om; Disflatyl; Flatulex; Meteor†; Polysilane†; ***Thai.***: Air-X; Airrox†; Blow-X; Bubble Drops; Degas; Dioxzye; Disflatyl; Fa-x; Gas-

mad†; Gas-Med; Gas-MM; Gas-X; Gassi; Gastyl; Logastin; Mylom; Ovol†; Semeth; Sigas; Simcone; Simecon; Simetyl; Sitic-on†; V cap; Vin; ***Turk.***: Antiflat; Ceolat; Flatsil; Metsil; ***UAE***: Salinal; ***UK***: Dentinox Colic Drops; Infacol; Wind-Eze; ***Ukr.***: Bobothic (Боботик); Cuplaton (Куплатон); Disflatyl (Дисфлатил); Espumisan (Эспумизан); Infacol (Інфакол); SAB Simplex (Саб Симплекс); ***USA***: Baby Gas-X; Bicarsim; Colicon; Extra Strength Mintox Plus; Flatulex; Gas Relief; Gas-X; Major-Con; Mylanta Gas; Mylicon; Phazyme; SonoRx†; ***Venez.***: Antifom; Flatoril.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Austria***: Prontobario; ***Canad.***: Polibar Liquid†; Polibar Plus†; ***Spain***: Bario Dif†.

Pharmacopoeial Preparations
BP 2014: Simeticone for Oral Use; Simeticone Suspension for Infants;
USP 36: Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets; Magaldrate and Simethicone Oral Suspension; Magaldrate and Simethicone Tablets; Simethicone Capsules; Simethicone Emulsion; Simethicone Oral Suspension; Simethicone Tablets.

Smectites

Смектиты.
ATC — A07BC05 (diosmectite).
ATC Vet — QA07BC05 (diosmectite).

Profile

Smectites are natural mineral clays composed mainly of aluminium silicates and include aluminium magnesium silicate (p. 2168.2), bentonite (p. 2170.3), and Fuller's earth (p. 1553.2). They have adsorbent properties and some, such as dioctahedral smectite (diosmectite), have been used in the management of diarrhoea. They are also used as pharmaceutical excipients and in industry.

References.
1. Szajewska H, *et al.* Meta-analysis: smectite in the treatment of acute infectious diarrhoea in children. *Aliment Pharmacol Ther* 2006; **23:** 217–27.
2. Yen ZS, Lai MS. Smectite for acute diarrhoea in children. *Emerg Med J* 2006; **23:** 65–6.
3. Guarino A, *et al.* Clinical role of diosmectite in the management of diarrhea. *Expert Opin Drug Metab Toxicol* 2009; **5:** 433–40.
4. Dupont C, Vernisse B. Anti-diarrheal effects of diosmectite in the treatment of acute diarrhea in children: a review. *Paediatr Drugs* 2009; **11:** 89–99.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi Qi (必奇); Ken Te Ling (肯特令); Li Xie (立榭); Sai Li Mai (赛立迈); Si Ke Te (思克特); Si Mai Te (司迈特); ***Cz.***: Smecta; ***Fr.***: Smecta; ***Ger.***: Colina; ***Gr.***: Smecta; ***Hong Kong***: Smecta; ***Hung.***: Smecta; ***Ital.***: Diosmectal; Nodia; ***Malaysia***: Smecta; ***Pol.***: Smecta; ***Rus.***: Neosmektine (Неосмектин); Smecta (Смекта); ***Singapore***: Smecta; ***Thai.***: Smecta; ***Ukr.***: Smecta (Смекта).

Multi-ingredient Preparations. ***Belg.***: Barexal; ***Fr.***: Diozinac KS; Diozinac; ***Ger.***: Colina Spezial; ***Irl.***: Smecta; ***Ukr.***: Sorbex Baby (Сорбекс Малыш).

Sodium Gualenate *(rINN)*

Azulene Sodium Sulfonate; Azulene Soluble; Guaiazulene Sodium Sulphonate; Guaiazulene Soluble; Gualénate de Sodium; Gualenate Sodium; Gualenato de sodio; Natrii Gualenas; Натрия Гуаленат.
Sodium 5-isopropyl-3,8-dimethyl-1-azulene sulfonate.
$C_{15}H_{17}NaO_3S$=300.3
CAS — 6223-35-4.
UNII — 19WSH095WP.

Profile

Sodium gualenate is the 3-sodium sulfonate salt of guaiazulene, a substance isolated from chamomile oil. Sodium gualenate has anti-inflammatory effects and is used orally, usually with glutamine, to treat peptic ulcer disease and gastritis. Sodium gualenate hydrate is used as an oral rinse or gargle to treat mouth and throat disorders including pharyngitis, tonsillitis, stomatitis, gingivitis, and glossitis. Sodium gualenate hydrate eye drops are used to treat eye disorders including conjunctivitis, keratitis, blepharitis, and scleritis.

References.
1. Ogata J, *et al.* Gargling with sodium azulene sulfonate reduces the postoperative sore throat after intubation of the trachea. *Anesth Analg* 2005; **101:** 290–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Abodars; Azotesin; Azugaguru; Azulavine; Azulemic; Azulene; Azulene; Azuleone; Azunol; Azurinse†; Emagen; Nozlen; Vowlo.

Multi-ingredient Preparations. ***Jpn***: AZ Combination; Azulemin; Azulene.Glutamine; Hachiazule; Manamin GA; Mesadorin S; Podonin-S; Ruefrien; Sedagaston; Towazuren; Youzuren S.

Sodium Picosulfate *(BAN, USAN, rINN)*

DA-1773; LA-391; Natrii Picosulfas; Natrii Picosulfas Monohydricus; Natrio pikosulfatas; Natriumpicosulfat; Natriumpikosulfaatti; Natriumpikosulfat; Nátrium-pikoszulfát; Picosulfate de Sodium; Picosulfato de sodio; Picosulphol; Pikosíran sodný monohydrát; Sodium, picosulfate de; Sodium Picosulphate; Натрия Пикосульфат.
Disodium 4,4′-(2-pyridylmethylene)di(phenyl sulphate).
$C_{18}H_{13}NNa_2O_8S_2,H_2O$=499.4
CAS — 10040-45-6 (anhydrous sodium picosulfate); 1307301-38-7 (sodium picosulfate monohydrate).
ATC — A06AB08.
ATC Vet — QA06AB08.
UNII — LR57574HN8.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Sodium Picosulfate). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol.

Uses and Administration

Sodium picosulfate is a stimulant laxative related to bisacodyl (p. 1821.1) used for the treatment of constipation (p. 1804.3) and for evacuation of the colon before investigational procedures or surgery. When taken orally it is metabolised by colonic bacteria to an active form that stimulates bowel movements. It is usually effective within 6 to 12 hours although when used with magnesium citrate for bowel evacuation an effect may be seen within 3 hours.

For constipation it is given as a single oral dose of 5 to 10 mg, usually at bedtime. (For doses in children see below.)

For bowel evacuation, a dose of sodium picosulfate 10 mg with magnesium citrate (p. 1857.1) is given in the morning and again in the afternoon of the day before examination.

References.
1. Hoy SM, *et al.* Sodium picosulfate/magnesium citrate: a review of its use as a colorectal cleanser. *Drugs* 2009; **69:** 123–36.

Administration in children. In the UK, the following oral doses of sodium picosulfate have been recommended for children in the treatment of **constipation**; the dose is usually given at night:
- 1 month to 4 years: 250 micrograms/kg (maximum 5 mg)
- 4 to 10 years: 2.5 to 5 mg
- over 10 years: 5 to 10 mg

Most UK licensed product information gives similar doses to those above for **bowel cleansing**. Alternatively, some recommend that children may be given the following doses of a sachet containing sodium picosulfate 10 mg (with magnesium citrate):
- 1 to 2 years: ¼ sachet in the morning and ¼ sachet in the afternoon
- 2 to 4 years: ½ sachet in the morning and ½ sachet in the afternoon
- 4 to 9 years: 1 sachet in the morning and ½ sachet in the afternoon
- over 9 years: 1 sachet in the morning and 1 sachet in the afternoon

Adverse Effects and Precautions

As for Bisacodyl, p. 1821.2.

Bowel evacuation. The National Patient Safety Agency in the UK released a warning[1] about oral bowel cleansing preparations after reports of fatalities and harm from the improper use of these products. Particularly highlighted were electrolyte imbalance or dehydration due to inappropriate fluid intake or use of these products despite a clinical contra-indication. In Australia, the Adverse Drug Reactions Advisory Committee has also warned that low volume sodium picosulfate solutions may cause marked dehydration, hyponatraemia, other electrolyte abnormalities, and associated complications. Patients at particular risk include infants, the elderly, the frail, and those with congestive heart failure or with renal impairment.[2] It may be appropriate to carry out bowel preparation in hospital for those at risk.[1,3,4] Accumulation of magnesium may occur in patients with severe renal impairment given some magnesium-containing preparations, and an alternative should be used. Bowel cleansing preparations may affect the absorption of oral medicines given at the same time. Caution is also advised when these preparations are given with other medicines that affect fluid and electrolyte balance.[1]

A grand mal seizure in a 64-year-old female given sodium picosulfate with magnesium citrate was assumed to have been caused by hyponatraemia; the patient had normal electrolyte concentrations in the period before taking the bowel preparation. Care is needed when sodium picosulfate solutions are used in those with a low seizure threshold or potential sodium depletion.[5]

Although caution is advised with the use of bowel cleansing preparations in patients with inflammatory bowel disease, sodium picosulfate with magnesium citrate was considered a safe and effective bowel cleansing agent in adults[6] and children[7] with these problems. They tolerated the preparation as well as patients with other colonic disorders with no adverse effect on their disease symptoms. Patients should be kept well hydrated and this treatment should not be used in suspected toxic dilatation of the colon.

1. National Patient Safety Agency. Rapid Response Report: reducing risk of harm from oral bowel cleansing solutions (issued 19th February, 2009). Available at: http://www.npsa.nhs.uk/nrls/alerts-and-directives/rapidrr/reducing-risk-of-harm-from-oral-bowel-cleansing-solutions/ (accessed 08/06/09)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with sodium picosulphate bowel cleansing products. *Aust Adverse Drug React Bull* 2002; **21:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0202.pdf (accessed 03/07/08)
3. Lewis M, *et al.* Bowel preparation at home in elderly people. *BMJ* 1997; **314:** 74.
4. Hanning CD. Bowel preparation at home in elderly people. *BMJ* 1997; **314:** 74.
5. Prizelle FA, *et al.* Hyponatremia and seizures after bowel preparation: report of three cases. *Dis Colon Rectum* 2005; **48:** 393–6.
6. McDonagh AJG, *et al.* Safety of Picolax (sodium picosulphate-magnesium citrate) in inflammatory bowel disease. *BMJ* 1989; **299:** 776–7.
7. Evans M, *et al.* Safety of Picolax in inflammatory bowel disease. *BMJ* 1989; **299:** 1101–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium picosulfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Like bisacodyl (p. 1821.2), sodium picosulfate is metabolised by colonic bacteria to the active compound bis(*p*-hydroxyphenyl)pyridyl-2-methane. Only a small amount of sodium picosulfate is absorbed after an oral dose; this is subsequently excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agarol; Chicle; Cirulaxia; Dagol; Dulcolax; Factor Laxante; Feen-A-Mint; Gotalax; Granulax; Kritel; Laxamin; Modaton; Opalino; Rapilax; Trali; Verilax; Yodolin; ***Austral.***: Dulcolax SP; ***Austria***: Agaffin; Agiopic†; Guttalax; Laxasan; ***Belg.***: Dulcolax Picosulphate; Fructines; Laxoberon; Picolaxine; ***Braz.***: Cronoplex; Diltin; Forlax†; Guttalax; Rapilax; ***Chile***: Aguala; Cronolax; Dulcolax; Guttalax; Laxantil; Laxoberal†; ***Cz.***: Agiolax Pico†; Guttalax; Laxygal; Progut†; Regulax Pikosulfat; ***Denm.***: Actilax; Laxoberal; Picolon; ***Fin.***: Laxoberon; ***Fr.***: Fructines; ***Ger.***: Agiolax Pico; Darmol Pico; Dulcolax NP; Laxans-ratiopharm Pico; Laxoberal; Liquidepur mit Natriumpicosulfat†; Regulax Picosulfat; ***Gr.***: Guttalax; Laxatol; ***Hong Kong***: Sur-Lax; ***Hung.***: Guttalax; Laxygal; ***India***: Asilax Plus; Colax; Coso; Cremalax; Dyrset-Eze; Laxatab; Laxicare; Laxkair; Laxopic; Laxsure; Novalax Plus; Oslax; ***Indon.***: Laxoberon; ***Irl.***: Agiolax Pico†; Dulcolax; Laxoberal†; ***Ital.***: Euchessina CM; Falquigut; Gocce Lassative Aicardi; Guttalax; ***Jpn***: Laxoberon; ***Mex.***: Anara; Laxoberon; Motilaxil; ***Neth.***: Dulcodruppels; Dulcopearls; Pico-Salax; ***Norw.***: Laxoberal; ***Philipp.***: Dulcolax SP; Laxoberal†; ***Port.***: Dulcogotas; Fructines; Guttalax; Laxodal; Picolax; ***Rus.***: Guttalax (Гутталакс); Laxigal (Лакигал); Regulax Picosulphate (Регулакс Пикосульфат); Slabicap (Слабикап); Slabilen (Слабилен); ***Spain***: Contumax; Evacuol; Ezor; Gutalax†; Lubrilax; Skilax†; ***Swed.***: Cilaxoral; Laxoberal; ***Switz.***: Dulcolax Picosulfat; Fructines; Laxoberon; ***Turk.***: Dulcolax; ***UK***: Dulcolax; ***Ukr.***: Agiolax Pico (Агиолакс Пико)†; Guttalax (Гутталакс); Picolax (Пиколакс); ***Venez.***: Lasoberon.

Multi-ingredient Preparations. ***Arg.***: Agarol; Cascara Sagrada Oligoplex; Natulax Plus; ***Austral.***: Colonprep; PicoPrep; Prep Kit-C; ***Belg.***: Pilules de Vichy†; ***Braz.***: Agarol; ***Canad.***: Pico-Salax; Picodan; Purg-Odan; ***Chile***: Agarol; ***Cz.***: Picoprep; ***Denm.***: Citra-Fleet; Picoprep; ***Fin.***: CitraFleet; Picoprep; ***Fr.***: CitraFleet; Picoprep; ***Ger.***: CitraFleet; Picoprep; ***Hong Kong***: Picolax; ***Hung.***: Picoprep; ***India***: Cremaffin Plus; Daffolac-P; Gudlax-Plus; Laxicare; Laxit Plus; Momplus; ***Irl.***: CitraFleet; Picolax; ***Israel***: Pico-Salax; ***Malaysia***: Picoprep†; ***Neth.***: Picoprep; ***Norw.***: CitraFleet; Picoprep; ***NZ***: Picoprep; Prepkit-C; ***Port.***: CitraFleet; ***S.Afr.***: Picoprep†; ***Spain***: CitraFleet; Emuliquen Laxante; ***Swed.***: CitraFleet; Picoprep; ***Switz.***: Laxasan; Picoprep; ***UK***: CitraFleet; Picolax; ***Ukr.***: Picosen (Пикосен); ***USA***: Prepopik.

Pharmacopoeial Preparations
BP 2014: Compound Sodium Picosulfate Powder for Oral Solution; Sodium Picosulfate Oral Solution.

Anhydrous Sodium Sulfate

Anhydrous Sodium Sulphate; Dried Sodium Sulphate; Exsiccated Sodium Sulphate; Natrii Sulfas; Natrii sulfas anhydricus; Natrio sulfatas, bevandenis; Natrium Sulfuricum Siccatum; Natriumsulfaatti, vedetön; Natriumsulfat, vattenfritt; Síran sodný; Sodium (sulfate de) anhydre; Sodu siarczan bezwodny; Sulfato de sodio anhidro; Vízmentes nátrium-szulfát; Безводный Сульфат Натрия.

Na_2SO_4=142.0

CAS — 7757-82-6.
ATC — A06AD13; A12CA02.
ATC Vet — QA06AD13; QA12CA02.
UNII — 36KCS0R750.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Viet.*

US includes a single monograph for both the anhydrous form and the decahydrate.

Ph. Eur. 8: (Sodium Sulfate, Anhydrous). A white or almost white, hygroscopic powder. Freely soluble in water. Store in airtight containers.

USP 36: (Sodium Sulfate). It contains 10 molecules of water of hydration or is anhydrous. The decahydrate loses between 51 and 57% of its weight on drying and the anhydrous form loses not more than 0.5% of its weight. Large, colourless, odourless, transparent crystals or a granular powder. It effloresces rapidly in air, liquefies in its water of hydration at about 33 degrees, and loses all of its water of hydration at about 100 degrees. Freely soluble in water; insoluble in alcohol; soluble in glycerol. Store in airtight containers, preferably at a temperature not exceeding 30 degrees.

Sodium Sulfate

E514; Glauber's Salt; Natrii Sulfas Decahydricus; Natrii Sulphas; Natrio sulfatas dekahidratas; Natrium Sulfuricum Crystallisatum; Natriumsulfaattidekahydraatti; Natriumsulfat-Decahydrat; Natriumsulfatdekahydrat; Nátrium-szulfát-dekahidrát; Síran sodný dekahydrát; Sodium (sulfate de) décahydraté; Sodium Sulphate; Sodium Sulphate Decahydrate; Sodu siarczan dziesięciowodny; Sulfato de sodio; Глауберова Соль; Сульфат Натрия.

$Na_2SO_4.10H_2O$=322.2

CAS — 7727-73-3 (sodium sulfate decahydrate).
ATC — A06AD13; A12CA02.
ATC Vet — QA06AD13; QA12CA02.
UNII — 0YPR65R21J.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Viet.*

US includes a single monograph for both the anhydrous form and the decahydrate.

Ph. Eur. 8: (Sodium Sulfate Decahydrate; Sodium Sulfate BP 2014). A white or almost white, crystalline powder or colourless, transparent crystals. Freely soluble in water; practically insoluble in alcohol. It partly dissolves in its own water of crystallisation at about 33 degrees. It loses between 52.0 and 57.0% of its weight on drying.

USP 36: (Sodium Sulfate). It contains 10 molecules of water of hydration or is anhydrous. The decahydrate loses between 51 and 57% of its weight on drying and the anhydrous form loses not more than 0.5% of its weight. Large, colourless, odourless, transparent crystals or a granular powder. It effloresces rapidly in air, liquefies in its water of hydration at about 33 degrees, and loses all of its water of hydration at about 100 degrees. Freely soluble in water; insoluble in alcohol; soluble in glycerol. Store in airtight containers, preferably at a temperature not exceeding 30 degrees.

Profile

Sodium sulfate has been used as an osmotic laxative (p. 1804.1). It is also given in dilute solution (about 0.5%) with a high molecular weight macrogol for prompt bowel evacuation before investigational procedures or surgery (see Macrogols, p. 2548.1).

Sodium sulfate is also used as a n additive in foods.

For the general properties of sodium salts, see p. 1795.1.

Preparations

Proprietary Preparations (details are given i n Volume B)

Single-ingredient Preparations. ***Austral.***: Celloids SS 69†; ***China***: Chang Le (畅乐); ***Israel***: Moviprep.

Multi-ingredient Preparations. ***Arg.***: Magnesia Phosphorica I Oligoplex; Tractoclin; ***Austral.***: Duo Celloids SPSS†; Duo Celloids SSMP†; Duo Celloids SSPC†; Duo Celloids SSS†; Magnesium Compound; ***Austria***: Moviprep; ***Belg.***: Moviprep; ***Canad.***: Lithines du Dr Gustin†; Moviprep; Normo Gastryl†; ***China***: ZhengQing (正清); ***Cz.***: Fortrans; ***Denm.***: Moviprep; ***Fin.***: Moviprep; ***Fr.***: Actisoufre; Digedryl; Fortrans; Hepargitol; Maalox Digestion Difficile; Moviprep; Oxyboldine; Sel D; Tisane D'Ars†; ***Gr.***: Izetafin; ***Hong Kong***: Fortrans; ***Irl.***: Moviprep; ***Ital.***: Moviprep; ***Malaysia***: Fortrans; ***Mex.***: Cholal Modificado; ***Neth.***: Moviprep; ***Norw.***: Moviprep; ***NZ***: Moviprep; Prepkit-C; ***Philipp.***: Neutrazid; ***Pol.***: Fortrans; Sal Carolinum Factitium; Sal Ems Artificiale; Sal Ems Factitium; Sal Vichy Factitium; ***Port.***: Fortrans; ***Rus.***: Fortrans (Фортранс); ***Singapore***: Fortrans; ***Spain***: Darmen Salt; Leberetic†; Lebersal; Moviprep; Salcedol; ***Switz.***: Moviprep; Padma-Lax; Padmed Laxan; ***Thai.***: Ulgastrin; ***UK***: Moviprep; ***Ukr.***: Fortrans (Фортранс); ***USA***: Suclear; Suprep Bowel Prep; Triv.

Homoeopathic Preparations. ***Austral.***: IBS Eze; ***Austria***: Galstena; Lobelia Med Complex; Lymphomyosot; Tartephedreel; ***Canad.***: Bioactiv N†; Combinaison†; Cynara Complex†; Diamite; Homeo-Form P†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Ikoplex 14†; Lympatox; Melange†; Minerals+; Nuage Bioplasma†; Osteel†; Rexorubia†; Sore Throat L39†; ***Chile***: Bioactiv N; Ikoplex No 10; Ikoplex No 13; Ikoplex No 14; Ikoplex No 17; Ikoplex No 2; Ikoplex No 7; Ikoplex No 8; Similibus; ***Cz.***: Lymphomyosot; ***Fr.***: Berberis Complexe No 83; Hepatocynesine†; Mercurius Solubilis Complexe No 39; Rexorubia; Sulfur Complexe No 12; ***Ger.***: A-Bomin; Anovin; Drufusan N†; Drufusan; Flenin; Galloselect; Hepar-Hevert; Infihepan; Lymphomyosot N; Lymphomyosot; ***Hung.***: Lymphomyosot; Osteoheel; ***Neth.***: Lymfelite; Rhodolith-Gastreu R46; ***Rus.***: Atma (Атма); Galstena (Галстена); ***S.Afr.***: Lymphomyosot; ***Switz.***: Osteoheel; ***Ukr.***: Atma (Атма); Galstena (Галстена); Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations
USP 36: PEG 3350 and Electrolytes for Oral Solution; Sodium Sulfate Injection.

Sodium Tartrate

Dinátrium-tartarát; Disodium L-Tartrate; E335 (sodium tartrate or monosodium tartrate); Natriumtartrat; Sodu winian; Tartrato de sodio; Tartrato di sodio; Виннокислый Натрий.

Disodium 2,3-dihydroxybutanedioate.

$C_2H_4O_2(CO_2Na)_2.2H_2O$=230.1

CAS — 868-18-8 (anhydrous sodium tartrate); 6106-24-7 (sodium tartrate dihydrate).
ATC — A06AD21.
ATC Vet — QA06AD21.
UNII — QTO9JB4MDD.

Pharmacopoeias. In *USNF.*

USNF 31: (Sodium Tartrate). Transparent, colourless, odourless crystals. Freely soluble in water; insoluble in alcohol. pH of a 10% solution in water is between 7 and 9. Store in airtight containers.

Sodium Bitartrate

E335 (sodium tartrate or monosodium tartrate); Monosodium Tartrate; Sodium Acid Tartrate; Sodium Hydrogen Tartrate.

Sodium 2,3-dihydroxybutanedioate.

$C_4H_5NaO_6$=172.1

CAS — 526-94-3.
UNII — 75E63I9H07.

Profile

Sodium tartrate has been used as an osmotic laxative. It is used as a food additive. Sodium bitartrate is used as an acidity regulator.

For the general properties of sodium salts, see p. 1795.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Limonade Asepta; ***Gr.***: Alka-Coup.

Multi-ingredient Preparations. ***Austral.***: Amosan†.

Sofalcone *(pINN)*

Sofalcona; Sofalconum; SU-88; Софалькон.

{5-[(3-Methyl-2-butenyl)oxy]-2-{*p*-[(3-methyl-2-butenyl)oxy] cinnamoyl}phenoxy}acetic acid.

$C_{27}H_{30}O_6$=450.5

CAS — 64506-49-6.
UNII — 2B668TJX8E.

Profile

Sofalcone is reported to possess cytoprotective properties and is used in the treatment of gastritis and peptic ulcer disease (p. 1813.2). An oral dose of 100 mg is given 3 times daily.

References.

1. Isomoto H, *et al.* Sofalcone, a mucoprotective agent, increases the cure rate of Helicobacter pylori infection when combined with rabeprazole, amoxicillin and clarithromycin. *World J Gastroenterol* 2005; **11:** 1629–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Solon.

Sterculia

E416; Goma esterculia; Goma Karaya; Indian Tragacanth; Karaya; Karaya Gum; Sterculia Gum; Sterkülia; Tragacanto indio; Камедь Карайи; Стеркулия Жгучая (*Sterculia urens*).

CAS — 9000-36-6.
ATC — A06AC03.
ATC Vet — QA06AC03.
ATC Herb — HA06AC5011 (Sterculia urens: *gum*).
UNII — 73W9IQY50Q.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Sterculia). The gum obtained from *Sterculia urens* and other species of *Sterculia*. Irregular or vermiform pieces, greyish-white with a brown or pink tinge, with an odour resembling that of acetic acid. It contains not less than 14.0% of volatile acid (or not less than 10.0% if supplied in powdered form), calculated as acetic acid. Sparingly soluble in water, but swells into a homogeneous, adhesive, gelatinous mass; practically insoluble in alcohol. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Sterculia is used similarly to ispaghula (p. 1849.2) as a bulk laxative and for adjusting faecal consistency. It has also been used as an aid to appetite control in the management of obesity (p. 2315.1) but there is little evidence of efficacy. It is usually taken in the form of granules containing sterculia 62%; the dose is 1 to 2 sachets or 1 to 2 heaped 5 mL spoonfuls orally once or twice daily after meals. (For a dose in children see below.) The granules are washed down without chewing with plenty of water. They may also be taken sprinkled onto soft foods such as yogurt.

Sterculia is used topically, as a paste or powder, for skin protection and sealing in the fitting of ileostomy and colostomy appliances. It has also been used in dental fixative powders, and as an emulsifier and stabiliser in foods.

Administration in children. In the UK, the recommended oral dose of granules, containing sterculia 62%, for constipation in children aged 6 to 12 years is ½ to 1 sachet, or ½ to one 5 mL spoonful, once or twice daily after meals. Children over 12 years may be dosed as for adults, see Uses and Administration, above. The granules are washed down without chewing with plenty of water. They may also be taken sprinkled onto soft foods such as yogurt.

Adverse Effects and Precautions

As for Ispaghula, p. 1849.2. There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such compounds are swallowed dry. Therefore they should always be taken with sufficient fluid and should not be taken immediately before going to bed. They should be avoided by patients who have difficulty swallowing.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sterculia as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Normafibe; ***Belg.***: Normacol; ***Braz.***: Corega; ***Canad.***: Normacol; ***Fr.***: Normacol; ***Hong Kong***: Normacol†; ***Irl.***: Normacol; ***Ital.***: Normacol; ***Neth.***: Normacol; ***NZ***: Normacol; ***S.Afr.***: Normacol; ***Singapore***: Normacol; ***Swed.***: Inolaxol; ***Switz.***: Colosan mite; Colosan travel; Inolaxine†; Normacol; ***UK***: Normacol.

Multi-ingredient Preparations. ***Austral.***: Normacol Plus; ***Fr.***: Kaologeais†; Karayal; Laxilo†; Poly-Karaya; ***Gr.***: Normacol Plus; ***Hong Kong***: Normacol Plus†; ***India***: Evacuol; Kanormal†; ***Irl.***: Normacol Plus; ***NZ***: Granocol†; Normacol Plus; ***Port.***: Normacol Plus; ***S.Afr.***: Normacol Plus; ***Singapore***: Normacol Plus; ***Switz.***: Colosan plus; ***UK***: Normacol Plus.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox.

Pharmacopoeial Preparations
BP 2014: Sterculia Granules.

Sucralfate *(BAN, USAN, rINN)*

Sucralfato; Sucralfatum; Sukralfaatti; Sükralfat; Sukralfat; Сукральфат.

Sucrose hydrogen sulphate basic aluminium salt; Sucrose octakis(hydrogen sulphate) aluminium complex; β-D-Fructofuranosyl-α-D-glucopyranoside octakis (hydrogen sulphate) aluminium complex.

$C_{12}H_mAl_{16}O_nS_8$

CAS — 54182-58-0.

ATC — A02BX02.

ATC Vet — QA02BX02.

UNII — XX73205DH5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sucralfate). A white or almost white, amorphous powder. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

USP 36: (Sucralfate). The hydrous basic aluminium salt of sucrose octasulfate. Store in airtight containers.

Uses and Administration

Sucralfate is a cytoprotective drug that, under acid gastrointestinal conditions, forms an adherent complex with proteins that coats the gastric mucosa and is reported to have a special affinity for ulcer sites. It also inhibits the action of pepsin and adsorbs bile salts.

Sucralfate has been used in the treatment of peptic ulcer disease (p. 1813.2) and chronic gastritis. It is given orally and should be taken on an empty stomach before meals and at bedtime. The usual dose is 1 g four times daily or 2 g twice daily for 4 to 8 weeks; if necessary the dose may be increased to a maximum of 8 g daily. If longer-term therapy is required sucralfate may be given for up to 12 weeks. Where appropriate a maintenance dose of 1 g twice daily may be given to prevent the recurrence of duodenal ulcers.

For prophylaxis of gastrointestinal haemorrhage from stress ulceration the usual dose of sucralfate is 1 g six times daily; a dose of 8 g daily should not be exceeded. For children's doses see below.

Administration in children. Although sucralfate is not licensed in the UK for use in children under 15 years, the *BNFC* recommends the following oral doses for the treatment of peptic ulcer disease, or the prophylaxis of stress ulceration in children in intensive care (but see also under Bezoar Formation, below):

- 1 month to 2 years: 250 mg four to six times daily
- 2 to 12 years: 500 mg four to six times daily
- 12 to 15 years: 1 g four to six times daily
- 15 to 18 years: adult doses may be given, see above

The oral suspension blocks fine-bore feeding tubes and tablets should be crushed and dispersed in water instead.

Gastrointestinal bleeding. Sucralfate is an effective drug for the prophylaxis and management of stress-induced gastrointestinal bleeding in severely ill patients but whether it should be chosen over an H_2-antagonist has been subject to debate. One study suggested it might reduce the risk of late-onset pneumonia compared with ranitidine.[1] Another study[2] found ranitidine to be more effective than sucralfate in reducing the risk of gastrointestinal bleeding; while there was a trend towards a lower rate of pneumonia among patients receiving sucralfate, the difference was not significant. However, meta-analyses[3] found an increased risk of pneumonia with ranitidine compared with sucralfate, but no difference in the rate of pneumonia with sucralfate and placebo; insufficient data were available to conduct a meta-analysis of sucralfate's efficacy in terms of rates of bleeding, and a re-assessment of recommendations for the prophylaxis of stress ulcers was called for. Later guidelines[4] concluded that the use of sucralfate did not influence the incidence of ventilator-associated pneumonia compared with placebo. For further discussion of stress ulceration and bleeding, including the use of sucralfate, see under Peptic Ulcer Disease, p. 1813.2. There is also some evidence from a study[5] that sucralfate reduces gastrointestinal bleeding associated with NSAID use, although it does not prevent drug-induced gastric erosion.

In a study to assess whether oral prophylactic sucralfate could ameliorate the symptoms of acute radiation proctitis, sucralfate was found to increase the incidence of rectal bleeding compared with placebo; the cause of this increased bleeding was unclear.[6]

1. Prod'hom G, *et al.* Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. *Ann Intern Med* 1994; **120:** 653–62.
2. Cook D, *et al.* A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; **338:** 791–7.
3. Messori A, *et al.* Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; **321:** 1103–6.
4. Dodek P, *et al.* Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004; **141:** 305–13.
5. Hudson N, *et al.* Effect of sucralfate on aspirin induced mucosal injury and impaired haemostasis in humans. *Gut* 1997; **41:** 19–23.
6. Kneebone A, *et al.* The effect of oral sucralfate on the acute proctitis associated with prostate radiotherapy: a double-blind, randomized trial. *Int J Radiat Oncol Biol Phys* 2001; **51:** 628–35.

Gastro-oesophageal reflux disease. Although sucralfate has been tried for gastro-oesophageal reflux disease (p. 1807.2) the results of studies have been inconsistent.[1-3] However, if lifestyle or dietary measures prove insufficient for the management of heartburn in pregnancy, sucralfate may be considered for first-line therapy.

1. Orlando RC. Sucralfate therapy and reflux esophagitis: an overview. *Am J Med* 1991; **91** (suppl 2A); 123S–124S.
2. Klinkenberg-Knol EC, *et al.* Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995; **49:** 695–710.
3. Simon B, *et al.* Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1996; **10:** 441–6.

Mouth ulceration. Sucralfate has been investigated as a mouth rinse in the treatment and prophylaxis of stomatitis induced by cancer chemotherapy[1-3] although evidence of benefit for any drug is ambiguous (see Mucositis, p. 732.1). One study[2] in 40 patients found a significant reduction in symptoms among 23 evaluable patients given sucralfate prophylactically. Seven patients withdrew due to aggravation of chemotherapy-induced nausea. It was suggested that to overcome this problem, the suspension should have a neutral taste, should not be swallowed after rinsing, and that rinsing should not be started until nausea had stopped. However, another study[4] involving 80 patients treated with fluorouracil for colorectal cancer found no significant difference in self-reported mucositis symptoms between patients given sucralfate suspension and those given placebo.

Sucralfate has also been reported to be of benefit in patients with recurrent aphthous stomatitis (mouth ulceration—p. 1811.2). A study involving 21 such patients over 2 years found that topical application of sucralfate suspension 4 times daily was superior to treatment with an antacid (aluminium hydroxide with magnesium hydroxide) or placebo.[5]

In patients with Behçet's syndrome (p. 1601.1), topical sucralfate suspension significantly decreased the frequency, healing time, and pain of oral ulceration, as well as the healing time and pain of genital ulceration,[6] when compared with placebo.

1. Pfeiffer P, *et al.* A prospective pilot study on the effect of sucralfate mouth-swishing in reducing stomatitis during radiotherapy of the oral cavity. *Acta Oncol* 1990; **29:** 471–3.
2. Pfeiffer P, *et al.* Effect of prophylactic sucralfate suspension on stomatitis induced by cancer chemotherapy: a randomized, double-blind cross-over study. *Acta Oncol* 1990; **29:** 171–3.
3. Allison RR, *et al.* Symptomatic acute mucositis can be minimized or prophylaxed [sic] by the combination of sucralfate and fluconazole. *Cancer Invest* 1995; **13:** 16–22.
4. Nottage M, *et al.* Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Support Care Cancer* 2003; **11:** 41–7.
5. Rattan J, *et al.* Sucralfate suspension as a treatment of recurrent aphthous stomatitis. *J Intern Med* 1994; **236:** 341–3.
6. Alpsoy E, *et al.* The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. *Arch Dermatol* 1999; **135:** 529–32.

Skin ulceration. Sucralfate is of interest for its actions on epithelial wound healing,[1] and has reportedly been applied topically with some success to treat bleeding skin ulcers (p. 1690.1) associated with malignancy,[2] and to promote the healing of chronic venous ulcers.[3,4] It has been suggested that sucralfate promotes angiogenesis by binding to, and preventing degradation of, basic fibroblast growth factor (bFGF).[3] Topical sucralfate 7% cream was also reported to decrease pain and speed healing of the wound after open surgical removal of haemorrhoids.[5]

1. Masuelli L, *et al.* Topical use of sucralfate in epithelial wound healing: clinical evidences and molecular mechanisms of action. *Recent Pat Inflamm Allergy Drug Discov* 2010; **4:** 25–36.
2. Regnard CFB. Control of bleeding in advanced cancer. *Lancet* 1991; **337:** 974.
3. Tsakayannis D, *et al.* Sucralfate and chronic venous stasis ulcers. *Lancet* 1994; **343:** 424–5.
4. Tumino G, *et al.* Topical treatment of chronic venous ulcers with sucralfate: a placebo controlled randomized study. *Int J Mol Med* 2008; **22:** 17–23.
5. Gupta PJ, *et al.* Topical sucralfate decreases pain after hemorrhoidectomy and improves healing: a randomized, blinded, controlled study. *Dis Colon Rectum* 2008; **51:** 231–4.

Adverse Effects and Precautions

Constipation is the most frequently reported adverse effect of sucralfate although diarrhoea, nausea, vomiting, flatulence, or gastric discomfort may also occur. Other adverse effects include dry mouth, dizziness, drowsiness, headache, vertigo, back pain, and skin rashes. Hypersensitivity reactions such as pruritus, oedema, urticaria, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported.

Great caution is needed in patients with renal impairment (below) as absorption and accumulation of aluminium may cause adverse effects.

Bezoar formation. As of March 1999, the UK CSM was aware of 7 reports worldwide of bezoar formation associated with sucralfate use in intensive care patients.[1] It advised caution in the use of sucralfate in seriously ill patients because of the risks of bezoar formation and intestinal obstruction.[1] Patients with delayed gastric emptying or receiving concomitant enteral feeds may be at increased risk. A report by the French Pharmacovigilance System at about the same time made similar recommendations but also contra-indicated the use of sucralfate in premature and immature neonates.[2]

1. CSM/MCA. Bezoar formation with sulcralfate [sic] (Antepsin). *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232356&RevisionSelectionMethod=LatestReleased (accessed 07/11/06)
2. Guy C, Ollagnier M. Sucralfate et bézoard: bilan de l'enquête officielle de pharmacovigilance et revue de la littérature. *Therapie* 1999; **54:** 55–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sucralfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Renal impairment. Sucralfate under acid conditions can release aluminium ions that may be absorbed systemically. Significant increases in the urinary excretion of aluminium have been seen in healthy subjects given sucralfate 4g daily,[1,2] reflecting gastrointestinal absorption of aluminium; aluminium concentrations in serum and urine were significantly higher in patients with chronic renal impairment than in subjects with normal renal function,[3] and similar serum increases have been seen in children with acute renal failure.[4] Aluminium toxicity in patients with normal renal function receiving sucralfate would not be expected, but seizures, muscle weakness, bone pain,[1] and severe aluminium encephalopathy[5] have been reported in patients with end-stage renal disease requiring dialysis. Sucralfate should be used with caution in patients with renal impairment, especially if other aluminium-containing agents are also taken, and such patients should be monitored for signs of aluminium toxicity.[4,6]

1. Robertson JA, *et al.* Sucralfate, intestinal aluminium absorption, and aluminium toxicity in a patient on dialysis. *Ann Intern Med* 1989; **111:** 179–81.
2. Allain P, *et al.* Plasma and urine aluminium concentrations in healthy subjects after administration of sucralfate. *Br J Clin Pharmacol* 1990; **29:** 391–5.
3. Burgess E, *et al.* Aluminum absorption and excretion following sucralfate therapy in chronic renal insufficiency. *Am J Med* 1992; **92:** 471–5.
4. Thorburn K, *et al.* Aluminum accumulation in critically ill children on sucralfate therapy. *Pediatr Crit Care Med* 2001; **2:** 247–9.
5. Withers DJ, *et al.* Encephalopathy in patient taking aluminium-containing agents, including sucralfate. *Lancet* 1989; **ii:** 674.
6. Hemstreet BA. Use of sucralfate in renal failure. *Ann Pharmacother* 2001; **35:** 360–4.

Interactions

Sucralfate may interfere with the absorption of other drugs and it has been suggested that there should be an interval of 2 hours between giving sucralfate and other non-antacid medication. Some of the drugs reported to be affected by sucralfate include cimetidine, ranitidine, digoxin, fluoroquinolone antibacterials, ketoconazole, levothyroxine, phenytoin, tetracycline, quinidine, theophylline, and possibly warfarin. The recommended interval between sucralfate and antacids is 30 minutes. An interval of 1 hour should elapse between giving sucralfate and enteral feeding.

Pharmacokinetics

Sucralfate is only slightly absorbed from the gastrointestinal tract after oral doses. However, there can be some release of aluminium ions and of sucrose sulfate; small quantities of sucrose sulfate may then be absorbed and excreted, primarily in the urine; some absorption of aluminium may also occur (see Renal Impairment, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antepsin; Gastromed; Netunal; Sucralmax; ***Austral.***: Carafate; Ulcyte; ***Austria***: Sucralan; Sucralbene†; Sucramed; Ulcogant; ***Belg.***: Ulcogant†; ***Braz.***: Sucrafilm; ***Canad.***: Novo-Sucralate†; Sulcrate; ***Chile***: Mulcatel; Sulcran; ***China***: Disuo (迪索); Dixian (迪先); Hua Di (华迪); Shu Ke Jie (舒可捷); Shukefei (舒克菲); Sucrate (素可立); SuShun (速顺); Weidi (卫迪); WeiYi (渭帏); ***Cz.***: Sucralan†; Ulcogant; Venter; ***Denm.***: Antepsin; ***Fin.***: Alsucral; Antepsin; ***Fr.***: Keal; Ulcar; ***Ger.***: Sucrabest; Ulcogant; ***Gr.***: Dolisec; Melicide;

The symbol † denotes a preparation no longer actively marketed

Peptonorm; Sucrate; Ufarene; ***Hong Kong***: Sucari; Sucrate; Ulsanic; ***Hung.***: Alusulin; Ulcogant; Venter; ***India***: Acicot; Acral; Alfate†; Alifate; Bluegel-SF; Crasia; Cural; Daffocid; Erocot; Gard Plus; Lacrate; Magalcid-S; Sucrase; ***Indon.***: Inpepsa; Musin; Neciblok; Profat; Propepsa; Ulcumaag; Ulsafate; Ulsicral; Ulsidex; ***Irl.***: Antepsin; ***Israel***: Ulsanic; ***Ital.***: Antepsin; Citogel; Crafilm; Escudo; Gastrogel; Sucralfin; Sucramal; Sucrate; Sucroril; Sugar; Sugast; Suril; Ulcrast; ***Jpn***: Ulcerlmin; ***Malaysia***: Alsucral†; Ulcertec†; ***Mex.***: Apo-Lato; Discral; Duodenel; Metixane; Ulsicral; Unival; ***Neth.***: Ulcogant; ***Norw.***: Antepsin; ***NZ***: Carafate; ***Philipp.***: Iselpin; ***Pol.***: Ulgastran; Venter; ***Port.***: Calfate†; Cinebil; Ulcermate; Ulcermin; Ulcimer; ***Rus.***: Sucrat (Сукрат); Venter (Вентер); ***S.Afr.***: Ulcetab†; Ulsanic; ***Singapore***: Alsucral†; Ulcertec†; ***Spain***: Urbal; ***Swed.***: Andapsin; ***Switz.***: Ulcogant; ***Thai.***: Sucral; Sucrate; Ulcefate; Ulcrafate; Ulsanic; ***Turk.***: Antepsin†; ***UAE***: Sucralose; ***UK***: Antepsin; ***Ukr.***: Venter (Вентер); ***USA***: Carafate; Orafate; ProThelial; ***Venez.***: Cicalfate; Dip; Exinol; Ulciram; Ulcon.

Multi-ingredient Preparations. ***Arg.***: Cicalfate; ***Chile***: Cicalfate; ***Fr.***: Cicalfate; ***Gr.***: Profenil Complex; ***India***: Acicot-O; Acicral-O; Acral-O; Alcocid; Crasia-O; Daffocid-O; Erocot-O; Esfate-O; Focri-O; Greycid; Kulent-O; Kulfi; Lacrate-O; Lorcus-O; Oxefate-O.

Used as an adjunct in:. ***Gr.***: Vofen; ***Ital.***: Ketodol.

Pharmacopoeial Preparations
USP 36: Sucralfate Tablets.

Sulfasalazine *(BAN, USAN, rINN)*

Salatsosulfapyridiini; Salazosulfapyridin; Salazosulfapyridine; Salazosulfapyridinum; Salicylazosulfapyridine; SI-88; Sulfasalatsiini; Sülfasalazin; Sulfasalazin; Sulfasalazina; Sulfasalazinas; Sulfasalazinum; Sulfasalazyna; Sulphasalazine; Szulfaszalazin; Сульфасалазин.

4-Hydroxy-4′-(2-pyridylsulphamoyl)azobenzene-3-carboxylic acid.

$C_{18}H_{14}N_4O_5S$=398.4

CAS — 599-79-1.

ATC — A07EC01.

ATC Vet — QA07EC01.

UNII — 3XC8GUZ6CB.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Sulfasalazine). A bright yellow or brownish-yellow, fine powder. Practically insoluble in water and in dichloromethane; very slightly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Sulfasalazine). A fine odourless bright yellow or brownish-yellow powder. Practically insoluble in water, in chloroform, in ether, and in benzene; soluble 1 in 2900 of alcohol, and 1 in 1500 of methyl alcohol; soluble in aqueous solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Uses and Administration

Sulfasalazine is a compound of a sulfonamide, sulfapyridine, with 5-aminosalicylic acid (mesalazine). Its activity is generally considered to lie in the 5-aminosalicylic acid moiety, which is released in the colon by bacterial metabolism, although intact sulfasalazine has some anti-inflammatory properties in its own right.

In inflammatory bowel disease (p. 1808.3) it is used alone or as an adjunct to corticosteroids in the treatment of active ulcerative colitis and is effective in maintaining remission. Sulfasalazine may also be effective in the treatment of active Crohn's disease, particularly of the colon, but it does not appear to be of value in maintaining remissions. Sulfasalazine is also used as a disease modifying drug in the treatment of severe or progressive rheumatoid arthritis (below).

In **inflammatory bowel disease** the usual initial dose of sulfasalazine is 1 to 2 g orally 4 times daily in the UK. However, doses over 4 g daily are associated with an increased risk of toxicity, and in the USA, therefore, the usual dose is 1 g given 3 or 4 times daily, and an initial dose of 500 mg every 6 to 12 hours may be recommended to lessen gastrointestinal adverse effects. Enteric-coated tablets are also claimed to reduce the incidence of adverse gastrointestinal effects. The overnight interval between doses should not exceed 8 hours. On remission the dose in patients with ulcerative colitis is gradually reduced to 2 g daily and then generally continued indefinitely.

Sulfasalazine is also given rectally, as suppositories, initially at a dose of 1 g at night and in the morning. After three weeks the dosage is gradually reduced according to response. Rectal sulfasalazine can be given as 0.5 to 1 g night and morning as an adjunct to treatment by mouth.

In **rheumatoid arthritis** treatment is usually started with an oral dose of 500 mg daily, as enteric-coated tablets, for the first week; dosage is then increased by 500 mg daily each week to a maximum of 3 g daily given in 2 to 4 divided doses according to tolerance and response.

For doses in children, see below.

Administration in children. In children with inflammatory bowel disease, sulfasalazine can be used alone or as an adjunct to corticosteroids to treat active ulcerative colitis and to maintain remission. Sulfasalazine may also be used to treat active Crohn's disease, particularly of the colon, but it does not appear to be of value in maintaining remissions. Sulfasalazine is also used as a disease modifying drug in the treatment of juvenile rheumatoid arthritis.

To treat active **inflammatory bowel disease**, children 2 years of age or older may be given oral sulfasalazine 40 to 60 mg/kg daily in divided doses. This can be reduced to 20 to 30 mg/kg daily to maintain remission in ulcerative colitis.

Sulfasalazine can also be given rectally as suppositories; the *BNFC* suggests the following doses for children according to age:

- 5 to 8 years: 500 mg twice daily
- 8 to 12 years: 500 mg in the morning and 1 g at night
- 12 to 18 years: 0.5 to 1 g twice daily

Sulfasalazine has also been used for polyarticular **juvenile rheumatoid arthritis** (see also below). US licensed product information recommends that children aged 6 years and older who have not responded adequately to salicylates or other NSAIDs may be given an oral dose of 30 to 50 mg/kg daily in two divided doses, to a maximum of 2 g daily. To reduce adverse gastrointestinal effects, an enteric-coated tablet is used and the initial dose should be a quarter to a third of the planned maintenance; it is then increased weekly to reach the maintenance dose after one month.

Although sulfasalazine is not licensed for juvenile rheumatoid arthritis in the UK, the *BNFC* suggests that children aged 2 to 18 years may be given an initial oral dose of 5 mg/kg twice daily for 1 week. The dose is then increased to 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, and maintained on a dose of 20 to 25 mg/kg twice daily. For children aged 2 to 12 years the maximum dose suggested is 2 g daily, and 3 g daily for children aged 12 to 18 years.

Psoriasis. In a double-blind placebo-controlled study involving 50 patients with moderate to severe plaque-type psoriasis (p. 1688.1), sulfasalazine 3 to 4g daily produced a significantly greater clinical improvement than placebo after 4 weeks of treatment with a further improvement at 8 weeks.[1]

See also Psoriatic Arthritis, below.

1. Gupta AK, *et al.* Sulfasalazine improves psoriasis: a double-blind analysis. *Arch Dermatol* 1990; **126:** 487–93.

Pyoderma gangrenosum. Sulfasalazine is licensed in some countries for the treatment of pyoderma gangrenosum (p. 1688.3), a condition that may be associated with inflammatory bowel disease, although published evidence of benefit is scanty.

References.

1. Shenefelt PD. Pyoderma gangrenosum associated with cystic acne and hidradenitis suppurativa controlled by adding minocycline and sulfasalazine to the treatment regimen. *Cutis* 1996; **57:** 315–9.

Rheumatoid arthritis. Sulfasalazine is considered to be a useful disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (p. 13.2). Studies have found a beneficial clinical effect of sulfasalazine, compared with placebo, on tender and swollen joints, pain, and erythrocyte sedimentation rate.[1,2] Meta-analyses[3,4] of generally short-term comparative studies suggest that sulfasalazine is roughly comparable in efficacy to methotrexate, intramuscular gold (sodium aurothiomalate), and penicillamine. Other reviews[2,5] have also suggested that it may have similar efficacy to hydroxychloroquine and leflunomide. Although there are regional differences in the prescription of DMARDs, sulfasalazine has been widely used for initial therapy, especially of less severe disease.[5] In an open study[6] of 200 patients with rheumatoid arthritis who were randomly allocated to treatment with sulfasalazine or auranofin, 31% of the sulfasalazine recipients were still taking the drug after 5 years compared with 15% of auranofin recipients. Improvement over baseline was still significant at 5 years for those patients receiving sulfasalazine but not in those treated with auranofin. Although one study[7] failed to find convincing evidence that using sulfasalazine with methotrexate was more effective than either drug alone, other studies have shown that combination treatment with sulfasalazine plus methotrexate and hydroxychloroquine was more effective than methotrexate alone or with sulfasalazine or hydroxychloroquine or the combination of sulfasalazine with hydroxychloroquine.[8-10] A review of sulfasalazine use in the management of rheumatoid arthritis concluded that combination therapy may be of benefit in patients with early or advanced rheumatoid arthritis but that there is still a need for studies to determine the efficacy and tolerability of various combinations.[5]

1. Suarez-Almazor ME, *et al.* Sulfasalazine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 28/02/06).
2. Weinblatt ME, *et al.* Sulfasalazine treatment for rheumatoid arthritis: a metaanalysis of 15 randomized trials. *J Rheumatol* 1999; **26:** 2123–30.
3. Felson DT, *et al.* The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; **33:** 1449–61.
4. Capell HA, *et al.* Second line (disease modifying) treatment in rheumatoid arthritis: which drug for which patient? *Ann Rheum Dis* 1993; **52:** 423–8.
5. Plosker GL, Croom KF. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. *Drugs* 2005; **65:** 1825–49.
6. McEntegart A, *et al.* Sulfasalazine has a better efficacy/toxicity profile than auranofin—evidence from a 5 year prospective, randomized trial. *J Rheumatol* 1996; **23:** 1887–90.
7. Dougados M, *et al.* Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; **58:** 220–5.
8. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; **334:** 1287–91.
9. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1164–70.
10. Dale J, *et al.* Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. *Nat Clin Pract Rheumatol* 2007; **3:** 450–8.

JUVENILE IDIOPATHIC ARTHRITIS. Juvenile idiopathic arthritis (p. 12.1) is generally managed similarly to rheumatoid arthritis, but there is limited experience with the use of some antirheumatic drugs in children. Sulfasalazine has produced significant improvement in studies of patients with juvenile chronic arthritis; a literature review found that it was consistently reported to be of benefit.[1] Adverse effects were reported to be similar to those in adults, with the exception of a serum-sickness-like reaction which was mostly seen in systemic onset patients and may be unique to juvenile rheumatoid arthritis.[1] For doses see Administration in Children, above.

1. Brooks CD. Sulfasalazine for the management of juvenile rheumatoid arthritis. *J Rheumatol* 2001; **28:** 845–53.

Spondyloarthropathies. *ANKYLOSING SPONDYLITIS.* Sulfasalazine has been found to be effective[1] in the treatment of active ankylosing spondylitis (p. 14.3), but there is evidence that it is more useful in the treatment of active disease and peripheral articular manifestations than in the management of chronic long-standing disease.[2-4] The active moiety appears to be sulfapyridine rather than mesalazine.[5] Sulfasalazine was no better than placebo for the treatment of inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis, but it was more effective than placebo in a subgroup of patients with no peripheral arthritis.[6]

1. Ferraz MB, *et al.* Meta-analysis of sulfasalazine in ankylosing spondylitis. *J Rheumatol* 1990; **17:** 1482–6.
2. Clegg DO, *et al.* Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis: a Department of Veterans Affairs Cooperative study. *Arthritis Rheum* 1996; **39:** 2004–12.
3. Clegg DO, *et al.* Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondyloarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999; **42:** 2325–9.
4. Chen J, Liu C. Sulfasalazine for ankylosing spondylitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 28/02/06).
5. Taggart A, *et al.* Which is the active moiety of sulfasalazine in ankylosing spondylitis? A randomized, controlled study. *Arthritis Rheum* 1996; **39:** 1400–5.
6. Braun J, *et al.* Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006; **65:** 1147–53.

PSORIATIC ARTHRITIS. A systematic review[1] of interventions for psoriatic arthritis (see Spondyloarthropathies, p. 14.3) concluded that sulfasalazine was one of only two drugs with published evidence of well proven efficacy in psoriatic arthritis (the other being high-dose parenteral methotrexate).

See also under Psoriasis, above.

1. Jones G, *et al.* Interventions for treating psoriatic arthritis. Available in The Cochrane Database of Systematic Reviews, Issue 3. Chichester: John Wiley; 2000 (accessed 29/04/05).

Adverse Effects and Precautions

Since sulfasalazine is metabolised to sulfapyridine and 5-aminosalicylic acid (mesalazine), its adverse effects and precautions are similar to those of sulfonamides (see Sulfamethoxazole, p. 365.3) and of mesalazine (p. 1860.1). Many adverse effects have been attributed to the sulfapyridine moiety and appear to be more common if serum-sulfapyridine concentrations are greater than 50 micrograms/mL, if the daily dose of sulfasalazine is 4 g or more, or in slow acetylators of sulfapyridine.

The most commonly reported adverse effects include nausea and vomiting, abdominal discomfort, anorexia, headache, fever, and skin rash.

Adverse effects can be broadly divided into 2 groups:

- dose-related effects are dependent on acetylator phenotype, and largely predictable; this group includes nausea and vomiting, headache, haemolytic anaemia, and methaemoglobinaemia

- hypersensitivity reactions are essentially unpredictable and usually occur at the start of treatment; this group includes aplastic anaemia, hepatic and pulmonary dysfunction, vasculitis, auto-immune haemolysis, and rash such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug rash with eosinophilia and systemic symptoms (DRESS).

Oligospermia, reversible on withdrawal of sulfasalazine, has also been reported. Sulfasalazine treatment may result in yellow-orange discoloration of skin, urine, and other body fluids. Some soft contact lenses may be stained. Adverse effects on the CNS include insomnia, depression, hallucinations, vertigo, convulsions, aseptic meningitis, ataxia, encephalopathy, peripheral neuropathy, and tinnitus.

Sulfasalazine should not be given to patients with a history of sensitivity to sulfonamides or salicylates. Use in children under 2 years of age is contra-indicated because of the risk of kernicterus. Use in children with juvenile rheumatoid arthritis may result in a serum sickness-like reaction. Caution is required when used in patients with severe allergy or asthma.

Blood counts should be performed at the start of therapy and frequently thereafter, particularly during the first 3 months of treatment. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, jaundice, bruising or bleeding develop. Care is advisable in patients with G6PD deficiency because of the risk of haemolytic anaemia.

Sulfasalazine should be used with caution in hepatic or renal impairment. Liver function tests should be carried out at monthly intervals for the first 3 months of treatment. Periodic monitoring of kidney function has also been recommended.

The adverse effects associated with the use of sulfasalazine in patients with inflammatory bowel disease[1] or rheumatoid arthritis have been reviewed.[2,3] The type and incidence of adverse effects appear to be similar in both groups of patients.[2] Although most reactions are minor and patients may continue therapy at the same or reduced dosage, some patients stop treatment because of adverse effects and in these cases a hyposensitisation regimen may be considered.[1,4,5] **Hyposensitisation** should not be attempted in patients with a history of a serious adverse effect such as agranulocytosis, toxic epidermal necrolysis, erythema multiforme, frank haemolysis, or a severe hypersensitivity reaction.[1,4,5] An alternative to hyposensitisation in patients with inflammatory bowel disease who cannot tolerate sulfasalazine is to try a drug that supplies the active 5-aminosalicylic acid component without sulfapyridine, as the latter is thought to be responsible for many of the adverse effects. Examples include balsalazide, mesalazine, and olsalazine; however, some patients still experience hypersensitivity, see under Mesalazine, p. 1860.1.

1. Taffet SL, Das KM. Sulfasalazine: adverse effects and desensitization. *Dig Dis Sci* 1983; **28:** 833–42.
2. Amos RS, *et al*. Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years. *BMJ* 1986; **293:** 420–3.
3. Farr M, *et al*. Side effect profile of 200 patients with inflammatory arthritides treated with sulphasalazine. *Drugs* 1986; **32** (suppl 1): 49–53.
4. Purdy BH, *et al*. Desensitization for sulfasalazine skin rash. *Ann Intern Med* 1984; **100:** 512–14.
5. Bax DE, Amos RS. Sulphasalazine in rheumatoid arthritis: desensitising the patient with a skin rash. *Ann Rheum Dis* 1986; **45:** 139–40.

Breast feeding. Small amounts of sulfasalazine and its sulfapyridine metabolites are excreted in breast milk; the concentrations of sulfasalazine and total sulfapyridine may be up to 30% and 50% of maternal serum concentrations respectively.[1] Bloody diarrhoea in a breast-fed infant whose mother was taking sulfasalazine 3 g daily has been reported.[2] The mother was a slow acetylator with a relatively high blood concentration of sulfapyridine, which contributed to the appearance of the drug in the infant's blood. Based on this report, the American Academy of Pediatrics[3] considers that sulfasalazine should be given with caution to breast-feeding mothers. However, others consider that continued treatment with sulfasalazine can generally be recommended to breast-feeding mothers of healthy infants.[4] A small study initially involving 17 mother-child pairs concluded sulfasalazine treatment could continue throughout pregnancy and lactation. The study found negligible amounts of sulfasalazine, and its main metabolite sulfapyridine, were transferred to the child via breast feeding. The authors did however warn that this conclusion could not be applied to a prematurely born child or a child with haemolytic disease.[5]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2:** 1553.
2. Branski D, *et al*. Bloody diarrhea—a possible complication of sulfasalazine transferred through human breast milk. *J Pediatr Gastroenterol Nutr* 1986; **5:** 316–17.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/02/06)
4. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27:** 260–5.
5. Esbjörner E, *et al*. Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. *Acta Paediatr Scand* 1987; **76:** 137–42.

Effects on the blood. Blood disorders constitute 19% of all reactions reported with sulfasalazine.[1] As of June 1993 the UK CSM was aware of 191 reports of neutropenia, leucopenia, or agranulocytosis (22 fatal), 44 reports of bone marrow depression or aplastic anaemia (13 fatal) and 30 reports of thrombocytopenia (1 fatal).[1]

Although blood dyscrasias were initially thought to be caused by the sulfapyridine moiety, subsequent experience has shown that the aminosalicylates can also cause haematological reactions (see Mesalazine, p. 1860.2). The risk of blood dyscrasias with sulfasalazine has been estimated at 0.6 per 1000 in those given the drug for inflammatory bowel disease, but about 10 times greater in patients receiving sulfasalazine for rheumatoid arthritis.[2]

Sulfasalazine inhibits folic acid absorption, interferes with its metabolism, and can increase folic acid requirements through haemolysis of red blood cells.[3,4] These effects are not usually significant in patients with inflammatory bowel disease unless there are additional factors causing folate deficiency, such as intercurrent illness or an exacerbation of bowel disease.[3,4] However, clinical folate deficiency with macrocytosis, megaloblastic anaemia, or pancytopenia has been reported rarely.[3,4] Macrocytic anaemia associated with sulfasalazine may occur more commonly in patients with rheumatoid arthritis; it was found in 7 of 50 patients within 3 to 4 months of starting treatment with sulfasalazine.[5] The effects of sulfasalazine on folic acid metabolism appear to be dose-related and respond to withdrawal or dosage reduction, and folic acid supplements;[3-5] intravenous folinic acid may sometimes be needed.[4] Although the effects may be potentially serious, they are not a contra-indication to continuing sulfasalazine treatment.[4,5]

Patients with a history of leucopenia associated with gold therapy for rheumatoid arthritis should not be given sulfasalazine since a similar reaction may occur.[6]

1. CSM/MCA. Sulphasalazine and fatal blood dyscrasias. *Current Problems* 1993; **19:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. CSM/MCA. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
3. Swinson CM, *et al*. Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut* 1981; **22:** 456–61.
4. Logan ECM, *et al*. Sulphasalazine associated pancytopenia may be caused by acute folate deficiency. *Gut* 1986; **27:** 868–72.
5. Prouse PJ, *et al*. Macrocytic anaemia in patients treated with sulphasalazine for rheumatoid arthritis. *BMJ* 1986; **293:** 1407.
6. Bliddal H, *et al*. Gold-induced leucopenia may predict a similar adverse reaction to sulphasalazine. *Lancet* 1987; **i:** 390.

Effects on the cardiovascular system. Reports include Raynaud's syndrome with sulfasalazine[1] and myocarditis with sulfasalazine and with mesalazine.[2] Myocarditis leading to fatal cardiogenic shock has been reported in a patient receiving mesalazine and it has been recommended that sulfasalazine or mesalazine should be replaced by glucocorticoids if cardiac symptoms arise.[3] See also under Mesalazine, p. 1860.2, and under Balsalazide, p. 1820.3.

1. Reid J, *et al*. Raynaud's phenomenon induced by sulphasalazine. *Postgrad Med J* 1980; **56:** 106–7.
2. Agnholt J, *et al*. Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i:** 1135.
3. Kristensen KS, *et al*. Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335:** 605.

Effects on fertility. Although successful pregnancies have been reported in the partners of men taking sulfasalazine,[1,2] male infertility is a well recognised complication of sulfasalazine treatment. Untreated inflammatory bowel disease is not associated with abnormal seminal quality or infertility, but oligospermia, reduced sperm motility, and an increase in morphological abnormalities are seen after treatment with sulfasalazine which may lead to infertility.[1-4] Oligospermia has been reported in 86% of men with inflammatory bowel disease treated with sulfasalazine.[1] Seminal characteristics and fertility return to normal within 2 to 3 months of withdrawing sulfasalazine and successful pregnancies have been reported after withdrawal.[1-3] The mechanism involved is thought to be a direct toxic effect on immature and developing spermatozoa, possibly due to the sulfapyridine moiety.[2-4] Improvement in seminal characteristics and successful pregnancies have been reported following substitution of mesalazine[4,5] or balsalazide[6] for sulfasalazine in patients with ulcerative colitis. However, reversible infertility, similar to that caused by sulfasalazine, has also been reported with mesalazine.[7]

1. Birnie GG, *et al*. Incidence of sulphasalazine-induced male infertility. *Gut* 1981; **22:** 452–5.
2. Riley SA, *et al*. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut* 1987; **28:** 1008–12.
3. Toovey S, *et al*. Sulphasalazine and male infertility: reversibility and possible mechanism. *Gut* 1981; **22:** 445–51.
4. Ó'Moráin C, *et al*. Reversible male infertility due to sulphasalazine: studies in man and rat. *Gut* 1984; **25:** 1078–84.
5. Cann PA, Holdsworth CD. Reversal of male infertility on changing treatment from sulphasalazine to 5-aminosalicylic acid. *Lancet* 1984; **i:** 1119.
6. McIntyre PB, Lennard-Jones JE. Reversal with balsalazide of infertility caused by sulphasalazine. *BMJ* 1984; **288:** 1652–3.
7. Chermesh I, Eliakim R. Mesalazine-induced reversible infertility in a young male. *Dig Liver Dis* 2004; **36:** 551–2.

Effects on the gastrointestinal tract. Sulfasalazine-induced exacerbations of ulcerative colitis have been reported[1,2] and are probably caused by the salicylate moiety rather than sulfapyridine.[3] Other reported effects include intestinal villous atrophy.[4]

1. Schwartz AG, *et al*. Sulfasalazine-induced exacerbation of ulcerative colitis. *N Engl J Med* 1982; **306:** 409–12.
2. Ring FA, *et al*. Sulfasalazine-induced colitis complicating idiopathic ulcerative colitis. *Can Med Assoc J* 1984; **131:** 43–5.
3. Shanahan F, Targan S. Sulfasalazine and salicylate-induced exacerbation of ulcerative colitis. *N Engl J Med* 1987; **317:** 455.
4. Smith MA, *et al*. Angioimmunoblastic lymphadenopathy, sulphasalazine exposure and villous atrophy. *Postgrad Med J* 1985; **61:** 337–8.

Effects on the hair. Alopecia occurred on 2 occasions[1] after starting sulfasalazine 2 or 3 g daily in a patient with ulcerative colitis. On both occasions normal hair growth returned after treatment was stopped, and the patient was later successfully desensitised. However, alopecia that developed in another patient during sulfasalazine treatment did not recur on rechallenge.[2] In this case postpartum alopecia was considered to be the cause and these authors doubted whether sulfasalazine causes alopecia at all. Hair loss has been reported in 2 patients receiving mesalazine enemas.[3] However, remission of alopecia universalis has been reported during sulfasalazine treatment of rheumatoid arthritis.[4]

1. Breen EG, Donnelly S. Alopecia associated with sulphasalazine (Salazopyrin). *BMJ* 1986; **292:** 802.
2. Fich A, Eliakim R. Does sulfasalazine induce alopecia? *J Clin Gastroenterol* 1988; **10:** 466.
3. Kutty PK, *et al*. Hair loss and 5-aminosalicylic acid enemas. *Ann Intern Med* 1982; **97:** 785–6.
4. Jawad ASM, Scott DGI. Remission of alopecia universalis during sulphasalazine treatment for rheumatoid arthritis. *BMJ* 1989; **298:** 675.

Effects on the kidneys. UK licensed product information advises that adequate fluid intake and avoidance of urinary acidifiers may reduce the incidence of crystalluria and stone formation. For reports of nephrotic syndrome and of interstitial nephritis associated with sulfasalazine treatment, see under Mesalazine, p. 1860.3.

Effects on the pancreas. The UK CSM had received 6 reports of pancreatitis associated with sulfasalazine as of February 1994.[1] There had been further reports associated with mesalazine (see p. 1860.3). However, a large Danish population-based case-control study concluded neither sulfasalazine nor mesalazine was associated with an increased risk of pancreatitis, and that any increased risk might be associated with inflammatory bowel disease itself.[2]

1. CSM/MCA. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Munk EM, *et al*. Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. *Am J Gastroenterol* 2004; **99:** 884–8.

Effects on the respiratory system. Although one study reviewed 50 cases of sulfasalazine-induced pulmonary complications, pulmonary toxicity remains a rare adverse effect.[1] Most reports include dyspnoea, cough, pulmonary infiltrates, fever, and eosinophilia, usually developing in the first few months of treatment although they may occur after several years.[1-3] Symptoms are generally readily reversible on withdrawal of sulfasalazine, although death due to fibrosing alveolitis has been reported,[2] and the need for corticosteroid therapy remains debatable.[1] These effects have also occurred with mesalazine, p. 1861.1; they have been reported in patients with a history of sensitivity to salicylates, sulfonamides, or with no known sensitivity to these drugs.[2,3] Bronchiolitis obliterans organising pneumonia has been reported in a patient with rheumatoid arthritis receiving sulfasalazine;[4] clinical improvement occurred after sulfasalazine was stopped and corticosteroid therapy started.

1. Parry SD, *et al*. Sulphasalazine and lung toxicity. *Eur Respir J* 2002; **19:** 756–64.
2. Wang KK, *et al*. Pulmonary infiltrates and eosinophilia associated with sulfasalazine. *Mayo Clin Proc* 1984; **59:** 343–6.
3. Jordan A, Cowan RE. Reversible pulmonary disease and eosinophilia associated with sulphasalazine. *J R Soc Med* 1988; **81:** 233–5.
4. Ulubaş B, *et al*. Bronchiolitis obliterans organizing pneumonia associated with sulfasalazine in a patient with rheumatoid arthritis. *Clin Rheumatol* 2004; **23:** 249–51.

Effects on taste. Metallic taste has occurred in patients taking sulfasalazine for ulcerative colitis,[1] although diseases causing changes in gastrointestinal absorption may lead to zinc deficiency, which has itself been associated with a metallic taste. There has also been a report of two patients developing a reversible taste dysfunction, while taking sulfasalazine for rheumatoid arthritis.[2]

1. Ogburn RM. Sulfamethazine-related dysgeusia. *JAMA* 1979; **241:** 837.
2. Marcus RW. Sulfasalazine induced taste disturbances. *J Rheumatol* 1991; **18:** 634–5.

Lupus. A study in 11 patients with sulfasalazine-induced lupus found that induction of disease was more likely in patients who were slow acetylators of sulfapyridine, and who had HLA haplotypes associated with idiopathic SLE.[1] Furthermore, the risk of developing persistent SLE and lupus nephritis increased with duration of treatment and cumulative dose of sulfasalazine. Lupus-like syndrome has also occurred with mesalazine (p. 1861.1).

1. Gunnarsson I, *et al.* Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. *Br J Rheumatol* 1997; **36:** 1089–94.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulfasalazine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 03/10/11)

Pregnancy. Sulfasalazine and its sulfapyridine metabolites readily cross the placenta resulting in similar concentrations in the cord serum and maternal serum at delivery.[1,2] The concentration of the 5-aminosalicylic acid component of sulfasalazine in both cord serum and maternal serum is negligible.[1] There have been isolated reports of congenital abnormalities associated with use of sulfasalazine during pregnancy including coarctation of the aorta with a ventricular septal defect,[3,4] and genito-urinary disorders.[4] There is also a theoretical risk of kernicterus in the neonate if sulfasalazine is given close to delivery (see p. 366.2). However, given the concentrations of sulfasalazine and its metabolites found in cord blood, the risk of kernicterus from maternal use is considered minimal.[2] There have been many successful and uncomplicated pregnancies during sulfasalazine therapy and the general consensus favours continuing sulfasalazine throughout pregnancy when indicated.[1,3-6] (See also Mesalazine, p. 1861.1.) The minimum effective dose should be used and since sulfasalazine may precipitate folate deficiency (see Effects on the Blood, p. 1891.2), folic acid supplements are recommended.[7]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2:** 1553.
2. Järnerot G, *et al.* Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. *Scand J Gastroenterol* 1981; **16:** 693–7.
3. Hoo JJ, *et al.* Possible teratogenicity of sulfasalazine. *N Engl J Med* 1988; **318:** 1128.
4. Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. *Med J Aust* 1983; **1:** 528–9.
5. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27:** 260–5.
6. Korelitz BI. Commentary: observations on sulfasalazine in Crohn's disease and ulcerative colitis. *J Clin Pharmacol* 1987; **27:** 265–6.
7. Byron MA. Treatment of rheumatic diseases. *BMJ* 1987; **294:** 236–8.

Interactions

Giving sulfasalazine with antibacterial therapy may reduce conversion of sulfasalazine to its active metabolite (see below).

Sulfasalazine has been reported to interfere with the absorption of digoxin (p. 1357.3) or folic acid (see Effects on the Blood, p. 1891.2) from the gastrointestinal tract.

Antibacterials. Since the effects of sulfasalazine depend on release of 5-aminosalicylic acid by bacterial metabolism in the gut, any drug that reduces the intestinal microflora may reduce the production of active metabolite. Evidence for this has been seen in patients also given *rifampicin* and *ethambutol*,[1] or in subjects also given *ampicillin*.[2] However, a decrease in clinical effect does not seem to have been seen.

1. Shaffer JL, Houston JB. The effect of rifampicin on sulphapyridine plasma concentrations following sulphasalazine administration. *Br J Clin Pharmacol* 1985; **19:** 526–8.
2. Houston JB, *et al.* Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol* 1982; **14:** 395–8.

Antineoplastics. For mention of 5-aminosalicylates such as sulfasalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Gastrointestinal Drugs, p. 822.1.

Pharmacokinetics

About 15% of an oral dose of sulfasalazine is absorbed from the small intestine, although some of this is subsequently returned to the intestine in bile via enterohepatic circulation. The great majority of the dose reaches the colon where the azo bond is cleaved by the action of the intestinal flora, producing sulfapyridine and 5-aminosalicylic acid (mesalazine). Results in patients who have undergone colectomy suggest that between 60 and 90% of the total dose is metabolised in this way, but the degree of metabolism depends both on the activity of the intestinal flora and the speed of intestinal transit; colonic metabolism is reduced in patients with diarrhoea (for example, in active inflammatory bowel disease).

The small amount of intact sulfasalazine that is absorbed is extensively protein bound and subsequently excreted unchanged in urine. It crosses the placenta and is found in breast milk.

After cleavage of the sulfasalazine molecule about 60 to 80% of available sulfapyridine is absorbed, and undergoes extensive metabolism by acetylation, hydroxylation, and glucuronidation. Peak steady-state concentrations of sulfapyridine are higher in slow acetylators than fast acetylators after similar doses and the former are 2 to 3 times more likely to have adverse effects. Some 60% of the original dose of sulfasalazine is excreted in urine as sulfapyridine and its metabolites. As with sulfasalazine, absorbed sulfapyridine crosses the placenta and is found in breast milk.

The 5-aminosalicylic acid (5-ASA) moiety is much less well absorbed. About one-third of liberated 5-ASA is absorbed and almost all of this is acetylated and excreted in urine. For further details of the pharmacokinetics of 5-aminosalicylic acid see under Mesalazine, p. 1861.2.

Reviews.

1. Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. *Clin Pharmacokinet* 1985; **10:** 285–302.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Azulfidine; Flogostop; ***Austral.***: Pyralin; Salazopyrin; ***Austria***: Salazopyrin; ***Belg.***: Salazopyrine; ***Braz.***: Azulfin; Salazoprin; ***Canad.***: Salazopyrin; ***Chile***: Azulfidine; ***China***: Chang Jian Ning (长建宁); Salazopyrin; Weiliufen (维柳芬); ***Cz.***: Salazopyrin; ***Denm.***: Salazopyrin; ***Fin.***: Salazopyrin; ***Fr.***: Salazopyrine; ***Ger.***: Azulfidine; Colo-Pleon; Pleon RA; ***Gr.***: Salopyrine; ***Hong Kong***: Salazopyrin; ***Hung.***: Salazopyrin; ***India***: Iwata; Saaz; Salazar; Sazo; ***Indon.***: Lazafin; Sulcolon; ***Irl.***: Salazopyrin; ***Israel***: Salazopyrin; ***Ital.***: Salazopyrin; ***Jpn***: Azulfidine; ***Malaysia***: Salazopyrin; ***Mex.***: Azulfidina; ***Neth.***: Salazopyrine; ***Norw.***: Salazopyrin; ***NZ***: Salazopyrin; ***Pol.***: Salazopyrin; ***Port.***: Salazopirina; ***S.Afr.***: Salazopyrin; ***Singapore***: Salazopyrin; ***Spain***: Salazopyrina; ***Swed.***: Salazopyrin; ***Switz.***: Salazopyrin; ***Thai.***: Salazine; Salazopyrin; Saridine; ***Turk.***: Salazopyrin; ***UK***: Salazopyrin; Sulazine; ***Ukr.***: Salazopyrin (Салазопирин); ***USA***: Azulfidine; ***Venez.***: Azulfidine.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Sulfasalazine Tablets; Sulfasalazine Tablets;

USP 36: Sulfasalazine Delayed-release Tablets; Sulfasalazine Tablets.

Sulglicotide *(BAN, rINN)*

Sulglicotida; Sulglicotidum; Sulglycotide; Сульгликотид.

CAS — 54182-59-1.

ATC — A02BX08.

ATC Vet — QA02BX08.

Profile

Sulglicotide is a sulfated glycopeptide with cytoprotective properties extracted from pig duodenum. It has been used in the treatment of peptic ulcer disease and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Gliptide†.

Tamarind

Tamarindo; West Indian Tamarind; Плоды Тамаринда; Индийский Финик; Тамаринд.

ATC Herb — HA06AC5012 (Tamarindus indica: fruit).

UNII — 2U9H66X7VX.

Pharmacopoeias. In *Fr.*

Profile

Tamarind is the fruits of *Tamarindus indica* (Leguminosae) freed from the brittle outer part of the pericarp and preserved with sugar or syrup. It contains tartaric, citric, and malic acid and their salts. Tamarind is used as a laxative with senna.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Delabarre.

Multi-ingredient Preparations. ***Arg.***: Laxiruela; ***Austria***: Frugelletten; ***Braz.***: Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; ***Chile***: Bebe Dep; Tamarine; ***Fr.***: Tamarine†; Transifine; Ultratransit; ***Gr.***: Tamarine; ***Hung.***: Tamarinlax; ***Ital.***: Ortisan; Tamarine; ***Mex.***: MD Lax; Naturetti; ***Spain***: Dentomicin†; Pruina; ***UK***: Pure Plan.

Homoeopathic Preparations. ***Fr.***: Tamarindus Complexe No 95†.

Teduglutide *(BAN, USAN, rINN)*

ALX-0600; [2-Glycine]-1-33-glucagon-like Peptide II; Teduglutida; Téduglutide; Teduglutidum; Тедуглутид.

$C_{164}H_{252}N_{44}O_{55}S$=3752.1

CAS — 287714-30-1.

UNII — 7M19191IKG.

Uses and Administration

Teduglutide is an analogue of endogenous human glucagon-like peptide 2 (GLP-2) that acts as an agonist at GLP-2 receptors in the distal intestine. It increases intestinal and portal blood flow, inhibits gastric acid secretion, decreases intestinal motility, and promotes repair of the intestinal mucosa. Teduglutide is used in the management of patients with short bowel syndrome. A dose of 50 micrograms/kg is given by subcutaneous injection once daily. This initial dose may be titrated to a lower dose if necessary to improve tolerability. Doses should be reduced in moderate to severe renal impairment, see Administration in Renal Impairment, below.

Teduglutide is under investigation in Crohn's disease.

References.

1. Jeppesen PB. Teduglutide, a novel glucagon-like peptide 2 analog, in the treatment of patients with short bowel syndrome. *Therap Adv Gastroenterol* 2012; **5:** 159–71.
2. Nørholk LM, *et al.* Treatment of adult short bowel syndrome patients with teduglutide. *Expert Opin Pharmacother* 2012; **13:** 235–43.
3. Burness CB, McCormack PL. Teduglutide: a review of its use in the treatment of patients with short bowel syndrome. *Drugs* 2013; **73:** 935–47.

Administration in renal impairment. Exposure to teduglutide is increased in renal impairment and the usual dose (see Uses and Administration, above) should be reduced by 50% in patients with moderate to severe impairment (creatinine clearance < 50 mL/minute) or end-stage renal disease.

Adverse Effects and Precautions

The most common adverse effects associated with teduglutide include injection site reactions, abdominal pain and distension, nausea and vomiting, headaches, peripheral oedema, and upper respiratory-tract infections. Other adverse effects include flatulence, hypersensitivity reactions, changes to appetite, sleep disturbances, cough, skin haemorrhage, arthralgia, renal colic, chest pain, and night sweats. Patients with a stoma reported a higher incidence of stoma complications. Teduglutide enhances fluid absorption, and fluid overload and congestive heart failure have been seen during treatment. Intestinal obstruction has been reported; teduglutide should be withheld until it has resolved.

Teduglutide has the potential to cause hyperplastic changes including neoplasia and should not be used in patients with active gastrointestinal malignancy. In those at increased risk of malignancy or with an active non-gastrointestinal malignancy, the benefits and risks of treatment should be considered. Patients should be monitored for small bowel neoplasia. Colorectal polyps may develop during teduglutide therapy; before starting treatment a colonoscopy should be carried out and any polyps removed. Subsequently, a colonoscopy should be carried out at least every 5 years.

Cholecystitis, cholangitis, and cholelithiasis have been reported, and there have been adverse effects on the pancreas such as pancreatitis. Monitoring of the function of the gallbladder and pancreas should be carried out before and during treatment.

Antibodies to teduglutide have developed in some patients, and may cross-react with endogenous glucagon-like peptide-2. Concentrations of C-reactive protein increased when teduglutide therapy was started and then gradually declined with ongoing treatment. The long term impact of these changes is unknown.

Interactions

Teduglutide can increase the absorption of other drugs such as benzodiazepines; increased concentrations of prazepam were noted when teduglutide was started, which led to

deterioration of mental status. Caution is required when teduglutide is used with drugs that require titration or have a narrow therapeutic index.

Pharmacokinetics

Subcutaneous injection of teduglutide has an absolute bioavailability of 88% in healthy subjects, with peak plasma concentrations reached between 3 to 5 hours after a dose. No accumulation is seen after repeated doses. The metabolic pathway of teduglutide is unknown, but it is expected to be degraded into small peptides and amino acids via catabolic pathways, in a similar manner to endogenous glucagon-like peptide-2. Teduglutide is mainly cleared by the kidneys; plasma clearance has a similar value to the glomerular filtration rate. The mean terminal half-life is about 2 hours in healthy subjects and 1.3 hours in patients with short bowel syndrome. Exposure to teduglutide is reduced in patients with moderate hepatic impairment. In those with moderate to severe renal impairment or end-stage renal disease, exposure to teduglutide increases with the degree of impairment. Exposure is increased by a factor of 2.6 in patients with end-stage renal disease compared with healthy subjects.

References.

1. Marier J-F, *et al.* Pharmacokinetics, safety, and tolerability of teduglutide, a glucagon-like peptide-2 (GLP-2) analog, following multiple ascending subcutaneous administrations in healthy subjects. *J Clin Pharmacol* 2008; **48:** 1289–99.
2. Marier J-F, *et al.* Population pharmacokinetics of teduglutide following repeated subcutanenous [sic] administrations in healthy participants and in patients with short bowel syndrome and Crohn's disease. *J Clin Pharmacol* 2010; **50:** 36–49.
3. Nave R, *et al.* Pharmacokinetics of teduglutide in subjects with renal impairment. *Eur J Clin Pharmacol* 2013; **69:** 1149–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Gattex.

Tegaserod Maleate *(BANM, USAN, rINNM)*

HTF-919; Maleato de tegaserod; SDZ-HTF-919; Tégasérod, Maléate de; Tegaserod, maleato de; Tegaserodi Maleas; Тегасерода Малеат.

1-{[(5-Methoxyindol-3-yl)methylene]amino}-3-pentylguanidine maleate.

$C_{16}H_{23}N_5O,C_4H_4O_4$=417.5

CAS — 145158-71-0 (tegaserod); 189188-57-6 (tegaserod maleate).

ATC — A06AX06.

ATC Vet — QA06AX06.

UNII — E5XNT3RF5A.

Stability and compatibility. Crushed tablets of tegaserod were found to be stable in water, and apple juice; the latter may mask the taste of the drug. Orange juice, milk, or yogurt were not recommended as vehicles because of incomplete dissolution or uncertainty about stability.[1]

1. Carrier M-N, *et al.* Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. *Am J Health-Syst Pharm* 2004; **61:** 1135–42.

Uses and Administration

Tegaserod is a partial agonist at 5-HT_4 receptors and has prokinetic properties. Although it has been withdrawn in most countries because of an apparent high incidence of cardiovascular ischaemic events (see Effects on the Heart, below), it is still licensed in some for use in women below the age of 55 for the short-term treatment of irritable bowel syndrome (p. 1810.3), particularly the constipation-predominant form. It is also used for the treatment of chronic idiopathic constipation (p. 1804.3) in women less than 55 years of age. Efficacy in men and the elderly has not been established.

Tegaserod is given orally as the maleate but doses are expressed in terms of the base; 8.31 mg of tegaserod maleate is equivalent to about 6 mg of tegaserod. It is given in a dose of 6 mg twice daily before food. For irritable bowel syndrome, it is given for a maximum of 12 weeks; treatment should be stopped if no response is seen after 4 weeks.

References.

1. Evans BW, *et al.* Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 17/03/08).

Adverse Effects and Precautions

The most common adverse effects of tegaserod have been gastrointestinal disturbances including abdominal pain, diarrhoea, nausea, vomiting, and flatulence. Diarrhoea generally occurs within the first week of treatment and is usually transient but may be severe. Ischaemic colitis has been reported. Headache, dizziness, migraine, insomnia, fatigue, leg or back pain, and arthropathy have also been commonly reported.

Serious and sometimes fatal cardiovascular ischaemic events such as myocardial infarction, unstable angina pectoris, and stroke have occurred with tegaserod, and have led to its withdrawal from the market in most of the world. Cardiovascular adverse effects may also include hypotension and arrhythmias. Other adverse effects have included effects on the nervous system such as depression, and other gastrointestinal effects including cholelithiasis and dyspepsia.

Treatment has been contra-indicated in patients with a history of cardiovascular disease, bowel obstruction or biliary disease, abdominal adhesions, or diarrhoea, as well as in those with severe renal or moderate to severe hepatic impairment.

References.

1. Hasler WL, Schoenfeld P. Safety profile of tegaserod, a 5-HT_4 receptor agonist, for the treatment of irritable bowel syndrome. *Drug Safety* 2004; **27:** 619–31.
2. Quigley EM, *et al.* Safety and tolerability of tegaserod in patients with chronic constipation: pooled data from two phase III studies. *Clin Gastroenterol Hepatol* 2006; **4:** 605–13.

Effects on the gastrointestinal tract. Severe diarrhoea, leading to hypovolaemia, hypotension, and syncope has been seen occasionally in patients receiving tegaserod. Some patients required hospitalisation for rehydration, and patients should be advised to stop taking the drug and seek medical attention if severe diarrhoea or associated dizziness or lightheadedness develop. In addition, ischaemic colitis has been reported rarely, and the drug should be stopped immediately in patients who develop symptoms such as rectal bleeding, bloody diarrhoea, or new and worsening abdominal pain.[1] The FDA noted that it had received 20 reports of ischaemic colitis in patients taking tegaserod between August 2002 and March 2004; in 3 cases, the effect only developed after several months (7 to 13) of therapy.[2] However, in reply the manufacturer (*Novartis*) suggested that there was no evidence from post-marketing surveillance to support an increased rate of ischaemic colitis over that normally seen in patients with irritable bowel syndrome, who are at increased risk of this diagnosis, nor any obvious pharmacological mechanism for such an adverse effect.[3]

1. Novartis, Canada. Important safety update: diarrhea and ischemic colitis in patients using Zelnorm (tegaserod hydrogen maleate) (issued 28/04/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_e.pdf (accessed 07/07/06)
2. Brinker AD, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351:** 1361–3.
3. Joelsson BE, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351:** 1363–4.

Effects on the heart. In an analysis of pooled data from 29 studies, 13 out of 11 614 patients taking tegaserod had serious cardiovascular ischaemic events, compared with 1 out of 7031 patients taking placebo. Events included unstable angina pectoris, stroke, and myocardial infarction, one of which was fatal.[1-3] Most of these patients had at least one cardiovascular risk factor, but for some, no cardiovascular disease or risk had been diagnosed at the onset of treatment with tegaserod.[2] Patients taking tegaserod should seek medical attention if they have severe chest pain, dyspnoea, dizziness, sudden onset of weakness, difficulty walking or talking, or any other symptoms suggestive of myocardial infarction or stroke.[1] However, a large observational cohort study[4] involving over 55 000 patients in US general practice could not find any increased risk of cardiovascular event or stroke in users of tegaserod compared with matched controls.

1. FDA Public Health Advisory. Tegaserod maleate (marketed as Zelnorm) (issued 30th March 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm051284.htm (accessed 15/07/10)
2. Novartis, Canada. Health Canada endorsed important safety information on Zelnorm (tegaserod hydrogen maleate) (issued 30th March 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_2_e.pdf (accessed 31/05/07)
3. Novartis, USA. Urgent: marketing and sales suspension notice for Zelnorm tablets, 2-mg and 6-mg all lots within expiry (issued 30th March 2007). Available at: http://www.zelnorm.com/Dr_Doctor_Letter.pdf (accessed 31/05/07)
4. Loughlin J, *et al.* Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. *J Cardiovasc Pharmacol Ther* 2010; **15:** 151–7.

Pharmacokinetics

Tegaserod is rapidly absorbed from the gastrointestinal tract and peak plasma levels occur after about 1 hour. The absolute bioavailability of an oral dose is 10%; this is reduced by the presence of food. Tegaserod is widely distributed into the tissues and is about 98% bound to plasma proteins. Presystemic acid-catalysed hydrolysis in the stomach, and then oxidation and glucuronidation, produces the main metabolite, which is inactive; direct systemic glucuronidation also occurs. Two-thirds of an oral dose is excreted unchanged in the faeces and one-third excreted in the urine primarily as the main metabolite. The terminal half-life of tegaserod is about 11 hours.

Reviews.

1. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT_4 receptor partial agonist with promotile activity. *Clin Pharmacokinet* 2002; **41:** 1021–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Altezerod; Coloserod; Procinet; Tegarod; Zelmac; ***Braz.***: Zelmac; ***Chile***: Colonaid; Distimax†; Tegasir†; Ther†; Zelmac†; ***China***: Chang Luo Ning (常罗宁); Kai Le Ning (开乐宁); Zelmac (泽马可); ***Hong Kong***: Zelmac†; ***India***: Ibsinorm; Irbez; Tegibs; Tegod; ***Indon.***: Zelmac†; ***Mex.***: Zelmac; ***NZ***: Zelmac; ***Philipp.***: Zelnorm†; ***Rus.***: Zelmac (Зелмак); ***S.Afr.***: Zelnorm†; ***Singapore***: Zelmac; ***Thai.***: Zelmac†; ***Turk.***: Zelmac; ***Venez.***: Zelmac.

Tenatoprazole *(rINN)*

Benatoprazole; Enatoprazole; Tenatoprazol; Ténatoprazole; Tenatoprazolum; TU-199; Тенатопразол.

(±)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}-1*H*-imidazo[4,5-*b*]pyridine.

$C_{16}H_{18}N_4O_3S$=346.4

CAS — 113712-98-4.

UNII — RE0689TX2K.

Profile

Tenatoprazole is a proton pump inhibitor that is under investigation for the treatment of gastro-oesophageal reflux disease.

Teprenone *(rINN)*

E-671; Geranylgeranylacetone (5*E*,9*E*,13*E* isomer); Teprenona; Téprénone; Teprenonum; Тепренон.

6,10,14,18-Tetramethyl-5,9,13,17-nonadecatetraen-2-one, mixture of (5*E*,9*E*,13*E*) and (5*Z*,9*E*,13*E*) isomers.

$C_{23}H_{38}O$=330.6

CAS — 6809-52-5 (teprenone); 3796-63-2 (5E,9E,13E isomer); 3796-64-3 (5Z,9E,13E isomer).

UNII — S858451A4O.

Profile

Teprenone is a cytoprotective drug that is used in the treatment of gastritis and peptic ulcer disease (p. 1813.2) in a usual oral dose of 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Selbex (施维舒); ***Indon.***: Purubex; ***Jpn***: Selbex; ***Philipp.***: Selbex; ***Thai.***: Selbex.

Tiemonium Iodide *(BAN, rINN)*

Ioduro de tiemonio; TE-114; Tiemonii Iodidum; Tiemonio, Ioduro de; Tiémonium, Iodure de; Тиемония Йодид.

4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium iodide.

$C_{18}H_{24}INO_2S$=445.4

CAS — 6252-92-2 (tiemonium); 144-12-7 (tiemonium iodide).

ATC — A03AB17.

ATC Vet — QA03AB17.

UNII — FZ2LZ7U304.

Tiemonium Metilsulfate

Tiemonio, metilsulfato de; Tiemonium Methylsulphate; Тиемония Метилсульфат.

4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methyl-morpholinium methylsulphate.

$C_{19}H_{27}NO_6S_2$=429.5

CAS — 6504-57-0.

Profile

Tiemonium iodide and tiemonium metilsulfate are quaternary ammonium antimuscarinics with peripheral effects similar to those of atropine (p. 1312.1) and are used in the relief of visceral spasms.

Tiemonium metilsulfate is given in an oral dose of 100 to 300 mg daily in divided doses. It has also been given by intramuscular or slow intravenous injection or rectally as a suppository.

Tiemonium iodide has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Visceralgine; ***Indon.***: Visceralgine.

Multi-ingredient Preparations. ***Belg.***: Asodal†; ***Fr.***: Colchimax.

Timepidium Bromide *(rINN)*

Bromuro de timepidio; SA-504; Timepidii Bromidum; Timepidio, bromuro de; Timépidium, Bromure de; Тимепидия Бромид.

3-[Di-(2-thienyl)methylene]-5-methoxy-1,1-dimethylpiperidinium bromide monohydrate.

$C_{17}H_{22}BrNOS_2,H_2O$=418.4

CAS — 35035-05-3.

ATC — A03AB19.

ATC Vet — QA03AB19.

UNII — 8R9E4766V4.

Pharmacopoeias. In *Jpn.*

Profile

Timepidium bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been given for the symptomatic treatment of visceral spasms in usual oral doses of 30 mg three times daily. It has also been given by subcutaneous, intramuscular, and intravenous injection in a dose of 7.5 mg.

Urinary metabolites of timepidium may cause a reddish coloration of the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Sesden; ***Jpn***: Sesden; ***Singapore***: Sesden†.

Tiquizium Bromide *(pINN)*

Bromuro de tiquizio; HSR-902; Tiquizii Bromidum; Tiquizio, bromuro de; Tiquizium, Bromure de; Тихизия Бромид.

trans-3-(Di-2-thienylmethylene)octahydro-5-methyl-2*H*-quinolizinium bromide.

$C_{19}H_{24}BrNS_2$=410.4

CAS — 71731-58-3.

UNII — 659K6049SF.

Profile

Tiquizium bromide is an antimuscarinic with actions similar to those of atropine (p. 1312.1). It is used as an antispasmodic (p. 1803.3) in the treatment of gastrointestinal spasm, biliary tract disease, and urolithiasis; a suggested oral dose is 5 to 10 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Thiaton.

Tropisetron *(BAN, rINN)*

Tropisetrón; Tropisétron; Tropisetroni; Tropisetronum; Трописетрон.

1a*H*,5a*H*-Tropan-3a-yl indole-3-carboxylate.

$C_{17}H_{20}N_2O_2$=284.4

CAS — 89565-68-4.

ATC — A04AA03.

ATC Vet — QA04AA03.

UNII — 6I819NIK1W.

Tropisetron Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tropisetrón; ICS-205-930; Tropisétron, Chlorhydrate de; Tropisetrón, hidrocloruro de; Tropisetronhydrochlorid; Tropisetroni hydrochloridum; Трописетрона Гидрохлорид.

$C_{17}H_{20}N_2O_2$,HCl=320.8

CAS — 105826-92-4.

ATC — A04AA03.

ATC Vet — QA04AA03.

UNII — A19338Q2YO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tropisetron Hydrochloride). A white or almost white powder. Freely soluble or soluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane.

Uses and Administration

Tropisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p. 1872.2). It is used in the prevention of nausea and vomiting induced by cytotoxic therapy and in the treatment and prevention of postoperative nausea and vomiting (p. 1811.3).

Tropisetron is given as the hydrochloride by slow intravenous injection or infusion, or orally. Doses are expressed in terms of tropisetron base; 5.64 mg of tropisetron hydrochloride is equivalent to about 5 mg of tropisetron base.

For the *prophylaxis* of acute **nausea and vomiting** associated with cytotoxic **chemotherapy** a single dose of 5 mg may be given by slow intravenous injection or infusion on the day of treatment, shortly before chemotherapy. The injection is given over not less than 1 minute; it may be given into a running infusion. For infusion, it is diluted into 100 mL of a suitable infusion fluid (such as sodium chloride 0.9% or glucose 5%), and given over 15 minutes. Subsequent doses of 5 mg daily are given orally, in the morning at least one hour before food, for a further 5 days.

For the *treatment* of **postoperative** nausea and vomiting 2 mg may be given by slow intravenous injection (over not less than 30 seconds), or by infusion (over 15 minutes), within 2 hours of the end of anaesthesia. For *prophylaxis*, the same dose may be given shortly before induction of anaesthesia.

For doses in children, see below.

References.

1. Lee CR, *et al.* Tropisetron: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. *Drugs* 1993; **46:** 925–43.
2. Simpson K, *et al.* Tropisetron: an update of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2000; **59:** 1297–1315.
3. Kranke P, *et al.* Tropisetron zur Prophylaxe von Übelkeit und Erbrechen in der postoperativen Phase: eine quantitative systematische Übersicht. *Anaesthesist* 2002; **51:** 805–14.

Administration in children. Tropisetron hydrochloride is used in children to prevent nausea and vomiting induced by cytotoxic chemotherapy; doses are expressed in terms of tropisetron base. Children over 2 years of age have been given tropisetron 200 micrograms/kg (maximum dose 5 mg) before chemotherapy, by intravenous injection over at least 1 minute, or by infusion (at a concentration of 50 micrograms/mL in a suitable infusion fluid, over about 15 minutes). In children weighing less than 25 kg the same dose may be given intravenously once daily for up to a further 4 days as required. In those weighing more than 25 kg, a dose of 5 mg may be given orally once daily for up to a further 5 days; if oral dosage is not possible, 5 mg may be given intravenously.

Fatigue. Tropisetron has been reported to be of benefit in patients with chronic fatigue, see under Uses and Administration of Ondansetron, p. 1873.1.

Pain. For reference to the use of tropisetron in various painful syndromes, see under Uses and Administration of Ondansetron, p. 1873.1.

Pruritus. Tropisetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p. 1873.1).

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2. Fatigue, abdominal pain, and diarrhoea may also occur. Visual hallucinations, and an increase in blood pressure in patients with pre-existing hypertension, have been noted at high repeated doses. ECG changes such as prolongation of QT interval have been noted with high-dose intravenous tropisetron. The drug should therefore be used with caution in patients with cardiac rhythm or conduction disturbances. Care should be taken when driving or operating machinery. No dosage reduction is considered necessary in renal or hepatic impairment despite possible reductions in clearance.

Carcinogenicity. The manufacturer (*Novartis, UK*) has reported an increased incidence of hepatic neoplasms in male *mice* given high doses of tropisetron but it is suggested that these effects are both species and sex specific.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tropisetron as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Drugs that induce or inhibit hepatic enzymes may affect plasma concentrations of tropisetron. Licensed product information considers that any changes are usually unlikely to be clinically relevant with the recommended doses.

Tropisetron should be used with caution with antiarrhythmics, beta blockers, or drugs likely to prolong the QT interval, including those likely to cause electrolyte disturbances (see Ondansetron, p. 1874.2).

Pharmacokinetics

Tropisetron is well absorbed after oral doses. Peak plasma concentrations occur within 3 hours. Absolute bioavailability depends on the dose since first-pass metabolism is saturable. It is 71% bound to plasma proteins. Tropisetron is metabolised by hydroxylation and conjugation, and metabolites are excreted mainly in the urine with a small amount in the faeces. The cytochrome P450 isoenzyme CYP2D6 is involved in tropisetron metabolism, and shows genetic polymorphism. The elimination half-life is about 8 hours in extensive metabolisers and up to 45 hours in poor metabolisers. Clearance is also reduced in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Navoban; ***Austral.***: Navoban; ***Austria***: Navoban; ***Belg.***: Novaban; ***Chile***: Navoban†; ***China***: Di Ou Ping (迪欧平); Gai Ge En (盖格恩); Guang Di (广迪); He Tai (和太); Luo Ting (罗亭); Navoban (欧必亭); NiTai-Mei (尼泰美); Pu Luo Lin (普洛林); Qi Qiong (齐琼); Que Zhi Du (确芝杜); Rui Qi Tai (瑞齐泰); Sai Ge En (赛格恩); Shu Ji (纾吉); Tuo Li Shi Ning (妥立士宁); Wei Rui Te (维瑞特); Xin Bei (欣贝); Xin Shun Er (欣顺尔); YanDi (岩迪); ***Denm.***: Navoban; ***Fr.***: Navoban†; ***Ger.***: Navoban†; ***Gr.***: Navoban; ***Hong Kong***: Navoban; ***Hung.***: Navoban; ***Indon.***: Navoban; Setrovel; ***Ital.***: Navoban; ***Jpn***: Navoban; ***Malaysia***: Navoban; ***Mex.***: Navoban; ***Neth.***: Novaban; ***Norw.***: Navoban; ***NZ***: Navoban; ***Philipp.***: Hensetron; Navoban; ***Pol.***: Navoban†; ***Port.***: Navoban; ***Rus.***: Navoban (Навобан); Tropindol (Тропиндол); ***S.Afr.***: Navoban†; ***Spain***: Navoban†; Saronil†; ***Swed.***: Navoban; ***Switz.***: Navoban; ***Thai.***: Navoban†; ***Turk.***: Navoban; ***Ukr.***: Navoban (Навобан); ***Venez.***: Navoban.

Troxipide *(rINN)*

Troxipida; Troxipidum; Троксипид.

(±)-3,4,5-Trimethoxy-*N*-3-piperidylbenzamide.

$C_{15}H_{22}N_2O_4$=294.4

CAS — 30751-05-4.

ATC — A02BX11.

ATC Vet — QA02BX11.

UNII — W6QJX1Q00Z.

Profile

Troxipide is used for its cytoprotective properties in the treatment of gastritis and peptic ulcer disease (p. 1813.2) in a usual oral dose of 100 mg three times daily, after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ke Fen Qi (科芬奇); Shuqi (殊奇); ***Jpn***: Aplace.

Urogastrone

Anthelone; EGF-URO; Epidermal Growth Factor; Murodermina; Uroanthelone; Uroenterone; Urogastrona; Уроастрон.

CAS — 9010-53-1.

UNII — TZK30RF92W.

Pharmacopoeias. *Chin.* includes monographs for recombinant human epidermal growth factor suitable for external use.

Profile

Urogastrone is a polypeptide first isolated from human urine. Two forms have been identified, β and γ urogastrone. The β form consists of 53 amino acids and is distinguishable from the γ form by an additional terminal arginine residue. The β form is reported to be identical to human epidermal growth factor and this term is widely used in the literature.

Urogastrone inhibits gastric acid secretion and has been tried in the treatment of peptic ulcer disease and other gastrointestinal disorders but its rapid destruction in the stomach has limited its clinical use.

It is a potent stimulator of cellular proliferation and has also been used as an aid to wound healing.

Reviews.
1. Grazul-Bilska AT, *et al.* Wound healing: the role of growth factors. *Drugs Today* 2003; **39:** 787–800.
2. Klenkler B, Sheardown H. Growth factors in the anterior segment: role in tissue maintenance, wound healing and ocular pathology. *Exp Eye Res* 2004; **79:** 677–88.

Gastrointestinal disorders. Intravenous infusion of urogastrone 250 nanograms/kg over 1 hour has been reported[1,2] to reduce the secretion of gastric acid in patients with duodenal ulcer (p. 1813.2) or the Zollinger-Ellison syndrome (p. 1814.3). Ulcer pain was relieved 30 to 60 minutes after the start of the infusion.[2] A dose of 100 nanograms/kg per hour by intravenous infusion has been used with partial success in an infant with microvillous atrophy[3] and was apparently beneficial in an infant with necrotising enteritis.[4]

Human epidermal growth factor has also shown some promise in the treatment of active ulcerative colitis. In a small study,[5] patients received daily enemas containing either recombinant human epidermal growth factor (5 micrograms in 100 mL) or placebo; all patients also received oral mesalazine. Ten of the 12 patients in the urogastrone group were in remission after 2 weeks treatment compared with 1 of the 12 patients in the placebo group, and this benefit was maintained for up to 12 weeks.

1. Koffman CG, *et al.* Effect of urogastrone on gastric secretion and serum gastrin concentration in patients with duodenal ulceration. *Gut* 1982; **23:** 951–6.
2. Elder JB, *et al.* Effect of urogastrone in the Zollinger-Ellison syndrome. *Lancet* 1975; **ii:** 424–7.
3. Walker-Smith JA, *et al.* Intravenous epidermal growth factor/urogastrone increases small-intestinal cell proliferation in congenital microvillous atrophy. *Lancet* 1985; **ii:** 1239–40.
4. Sullivan PB, *et al.* Epidermal growth factor in necrotising enteritis. *Lancet* 1991; **338:** 53–4.
5. Sinha A, *et al.* Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003; **349:** 350–7.

Wound healing. For a general discussion of the management of wounds and ulcers, see p. 1690.1.

In a randomised double-blind study in 61 patients with diabetic foot ulcers, adding human epidermal growth factor 0.04% to an ulcer cream containing protein-free bovine blood extract was shown to significantly enhance wound healing and reduce healing time compared with either the cream alone or the cream plus human epidermal growth factor 0.02%.[1] Topical application of recombinant human epidermal growth factor 0.02% has also been reported to reduce pain and promote healing of exfoliated skin lesions in a patient with drug-induced Stevens-Johnson syndrome.[2]

The effect on the rate of wound healing of a cream containing sulfadiazine silver plus recombinant human epidermal growth factor (10 micrograms/mL) was compared with sulfadiazine silver alone in 12 patients each requiring skin grafts at 2 donor sites.[3] The cream containing epidermal growth factor accelerated the rate of epidermal regeneration in all patients and reduced the average time to 100% healing by about 1.5 days. Patients were followed up for a maximum of 1 year after cessation of therapy and no complications or clinical evidence of neoplasia at the healed donor sites occurred.

In contrast, recombinant human epidermal growth factor as an ophthalmic solution containing 30 or 100 micrograms/mL was investigated in patients who had undergone keratoplasty, but the weaker solution had no effect on the rate of re-epithelialisation, and the more concentrated one was actually associated with slower healing.[4]

1. Tsang MW, *et al.* Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; **26:** 1856–61.
2. Tsang MW, *et al.* The use of recombinant human epidermal growth factor (rhEGF) in a gentleman with drug-induced Steven Johnson syndrome. *Dermatol Online J* 2004; **10:** 25.
3. Brown GL, *et al.* Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; **321:** 76–9.
4. Dellaert MMMJ, *et al.* Influence of topical human epidermal growth factor on postkeratoplasty re-epithelialisation. *Br J Ophthalmol* 1997; **81:** 391–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Regen-D.

Multi-ingredient Preparations. ***Chile***: FCE; ***Ukr.***: Ebermin (Эбермин).

Valethamate Bromide

Valetamat Bromür; Valetamato, bromuro de; Валетамата бромид.

Diethylmethyl[2-(3-methyl-2-phenylvaleryloxy)ethyl] ammonium bromide.

$C_{19}H_{32}BrNO_2$=386.4

CAS — 16376-74-2 (valethamate); 90-22-2 (valethamate bromide).

UNII — 6XFR940M2A.

Profile

Valethamate bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been given orally, by injection or rectally in the symptomatic treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Epidosin; Osdil; Valosin; ***Indon.***: Epidosin; ***Turk.***: Epidosin.

Multi-ingredient Preparations. ***Turk.***: Epidosin Compozitum.

Vedolizumab *(USAN, rINN)*

LDP-02; MLN-0002; MLN-02; Védolizumab; Vedolizumabum; Ведолизумаб.

Immunoglobulin G1, anti-(human integrin LPAM-1 (lymphocyte Peyer's patch adhesion molecule 1))(human-*Mus musculus* heavy chain), disulfide with human-*Mus musculus*κ-chain, dimer.

CAS — 943609-66-3.

UNII — 9RV78Q2002.

Profile

Vedolizumab is a humanised monoclonal antibody under investigation for the treatment of inflammatory bowel disease.

References.
1. Feagan BG, *et al.* Treatment of active Crohn's disease with MLN0002, a humanized antibody to the α4β7 integrin. *Clin Gastroenterol Hepatol* 2008; **6:** 1370–7.
2. Soler D, *et al.* The binding specificity and selective antagonism of vedolizumab, an anti-α4β7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther* 2009; **330:** 864–75.

Zaldaride *(rINN)*

CGS-9343B (zaldaride maleate); Zaldarida; Zaldaridum; Зальдарид.

(±)-1-{1-[(4-Methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidyl}-2-benzimidazolinone.

$C_{26}H_{28}N_4O_2$=428.5

CAS — 109826-26-8 (zaldaride); 109826-27-9 (zaldaride maleate).

UNII — GH66PET653.

Profile

Zaldaride is a calmodulin antagonist that has been investigated as the maleate for the treatment of diarrhoea.

Diarrhoea. Studies in patients with travellers' diarrhoea (p. 1805.2) have indicated that zaldaride in oral doses of 20 mg as the maleate four times daily is an effective antidiarrhoeal.[1,2] It was somewhat less effective than loperamide when given without a loading dose,[2] but a regimen of 40 mg initially, followed by 20 mg, about every 6 hours was as effective as loperamide 4 mg initially followed by 2 mg after each unformed stool.[3]

1. DuPont HL, *et al.* Zaldaride maleate, an intestinal calmodulin inhibitor, in the therapy of travelers' diarrhea. *Gastroenterology* 1993; **104:** 709–15.
2. Okhuysen PC, *et al.* Zaldaride maleate (a new calmodulin antagonist) versus loperamide in the treatment of traveler's diarrhea: randomized, placebo-controlled trial. *Clin Infect Dis* 1995; **21:** 341–4.
3. Silberschmidt G, *et al.* Treatment of travellers' diarrhoea: zaldaride compared with loperamide and placebo. *Eur J GastroenterolHepatol* 1995; **7:** 871–5.

General Anaesthetics

This chapter includes drugs used for the induction and maintenance of general anaesthesia. General anaesthetics are given either by inhalation or by intravenous or occasionally intramuscular injection (see Table 1, below).

Table 1. Classification of general anaesthetics.

Injectable	Inhalational
Barbiturate	*Halogenated*
Methohexital	Chloroform
Thiamylal	Desflurane
Thiopental	Enflurane
	Halothane
Miscellaneous	Isoflurane
Alfadolone	Methoxyflurane
Alfaxolone	Sevoflurane
Etomidate	Trichloroethylene
Ketamine	*Miscellaneous*
Propanidid	Cyclopropane
Propofol	Anaesthetic Ether
Sodium Oxybate	Nitrous Oxide
Tiletamine	Xenon

Uses of General Anaesthetics

General anaesthetics depress the CNS and cause loss of consciousness associated with an inability to perceive pain. An ideal anaesthetic would produce unconsciousness, analgesia, and muscle relaxation suitable for all surgical procedures and would be metabolically inert and rapidly eliminated. No anaesthetic fulfils all these requirements in safe concentrations and it is customary to use several drugs to achieve the required conditions while minimising the risk of toxicity.

The activity of any anaesthetic is dependent on its ability to reach the brain. With inhalational anaesthetics there has to be a transfer from the alveolar space to the blood, then to the brain; recovery is a function of the removal of the anaesthetic from the brain. With injectable anaesthetics their activity is similarly dependent on their ability to penetrate the blood-brain barrier and recovery in turn is governed by their redistribution and excretion. The potency of inhalational anaesthetics is often expressed in terms of *minimum alveolar concentrations*, known as MAC values. The MAC of an anaesthetic is the concentration at 1 atmosphere that will produce immobility in 50% of subjects exposed to a noxious stimulus. Values given under the individual monographs are based on use without nitrous oxide as the latter can reduce the MAC. Other factors including age, body temperature, and concurrent medication such as premedicants and opioid analgesics can also affect MAC values.

General references.

1. Royston D, Cox F. Anaesthesia: the patient's point of view. *Lancet* 2003; **362:** 1648–58.
2. García-Miguel FJ, *et al.* Preoperative assessment. *Lancet* 2003; **362:** 1749–57.
3. Buhre W, Rossaint R. Perioperative management and monitoring in anaesthesia. *Lancet* 2003; **362:** 1839–46.
4. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; **362:** 1921–8.
5. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.
6. Stachnik J. Inhaled anesthetic agents. *Am J Health-Syst Pharm* 2006; **63:** 623–34. Correction. *ibid.*; 2436.
7. Nathan N, Odin I. Induction of anaesthesia: a guide to drug choice. *Drugs* 2007; **67:** 701–23.
8. Lerman J. Inhalation agents in pediatric anaesthesia—an update. *Curr Opin Anaesthesiol* 2007; **20:** 221–6.
9. Bovill JG. Inhalation anaesthesia: from diethyl ether to xenon. In: Schüttler J, Schwilden H, eds. *Handb Exp Pharmacol: Modern Anesthetics*. Berlin: Springer-Verlag, 2008; **182** (II): 121–42.
10. Ekstein M, *et al.* Monitored anaesthesia care in the elderly: guidelines and recommendations. *Drugs Aging* 2008; **25:** 477–500.
11. Pietrini D, *et al.* New trends in pediatric anesthesia. *Minerva Anestesiol* 2009; **75:** 191–9.
12. Landoni G, *et al.* Halogenated anaesthetics and cardiac protection in cardiac and non-cardiac anaesthesia. *Ann Card Anaesth* 2009; **12:** 4–9.
13. Torri G. Inhalation anesthetics: a review. *Minerva Anestesiol* 2010; **76:** 215–28.
14. Sneyd JR, Rigby-Jones AE. New drugs and technologies, intravenous anaesthesia is on the move (again). *Br J Anaesth* 2010; **105:** 246–54.

Anaesthesia. Many drugs are involved in achieving and maintaining conditions suitable for surgery. Conventional general anaesthesia may be divided into several stages including:

- premedication
- induction
- muscle relaxation and intubation
- maintenance
- analgesia
- reversal

A brief outline of the drugs typically used in each stage follows.

For **premedication**, benzodiazepines such as diazepam, lorazepam, midazolam, or temazepam, and some phenothiazines such as promethazine or alimemazine, may be given to sedate and relieve *anxiety* in apprehensive patients. Butyrophenones such as droperidol have also been used. The benzodiazepines have useful amnestic and muscle-relaxant properties and short-acting oral forms are common in current regimens. The phenothiazines and butyrophenones are rarely used now although their antiemetic actions may be useful to control *postoperative nausea and vomiting* (p. 1811.3). Cloral hydrate is still used in some countries for pre-operative sedation, particularly in children. The use of barbiturates has largely ceased. For sedation of children the oral route is often preferred to injections, or the rectal route may be used in exceptional circumstances.

Antimuscarinics such as atropine, glycopyrronium, and hyoscine may be given to inhibit excessive *bronchial* and *salivary secretions* induced by intubation, upper airway surgery, and some anaesthetics, although such use is less common nowadays. Antimuscarinics are also given as premedicants to reduce the intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol or by vagal stimulation. Hyoscine also provides some degree of amnesia.

Opioids, including morphine and its derivatives, papaveretum and pethidine, have been widely used before surgery to reduce anxiety, smooth induction of anaesthesia, reduce overall anaesthetic requirements, and provide pain relief during and after surgery. The routine use of opioids as premedicants is now rare and generally restricted to patients already in pain. However, they continue to find a role at induction (below).

Patients may also be given drugs that reduce the danger from regurgitation and *aspiration* of gastric contents (see Aspiration Syndromes, p. 1804.2), such as the histamine H_2-antagonists, cimetidine and ranitidine, and the proton pump inhibitor, omeprazole. Other drugs used include sodium citrate to neutralise gastric acidity and metoclopramide to stimulate gastric emptying. Cardiovascular drugs may be needed during surgery to control *blood pressure* and counteract *arrhythmias*.

The aim of **induction** is to produce anaesthesia rapidly and smoothly. Induction may be achieved with intravenous or inhalational anaesthetics but intravenous induction may be more pleasant for the patient. Intravenous drugs used include the barbiturate thiopental, the benzodiazepine midazolam, and other anaesthetics such as etomidate, propofol, or ketamine. Small doses of short-acting opioids, for example alfentanil, fentanyl, or remifentanil, given before or at induction allow the use of smaller induction doses of some drugs used for anaesthesia, and this technique is particularly suitable for poor-risk patients.

After induction, **muscle relaxation** with a rapidly acting depolarising neuromuscular blocker such as suxamethonium aids **intubation** of the patient. Longer acting, competitive neuromuscular blockers may then be given to allow procedures such as abdominal surgery to be carried out under lighter anaesthesia. For more detail, see Anaesthesia, p. 2028.1.

Maintenance of anaesthesia may be achieved with an inhalational anaesthetic, an intravenous anaesthetic, or an intravenous opioid, either alone or in combination.

Opioid analgesics may also be given for **analgesia** as supplements during general anaesthesia (see also Balanced Anaesthesia, under Anaesthetic Techniques, below). Long-acting opioids such as morphine or papaveretum may cause postoperative respiratory depression. The short-acting opioid fentanyl, and its congeners alfentanil and sufentanil, appear to produce fewer circulatory changes and may be preferred to other opioids, especially in cardiovascular surgery; remifentanil may be valuable for its very short duration of action. Various combinations of analgesic techniques, including the use of pre-emptive analgesia, are used or are being investigated for the management of surgical pain (see Postoperative Analgesia, p. 6.1).

At the end of surgery drugs are sometimes given to accelerate recovery by **reversal** of the effects of the various agents used during anaesthesia. The *neuromuscular block* produced by competitive neuromuscular blockers may be reversed with anticholinesterases such as neostigmine and edrophonium but atropine or glycopyrronium are also needed to prevent bradycardia and other muscarinic actions developing. The selective relaxant binding agent, sugammadex, is also used for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. The opioid antagonist naloxone has been given to reverse opioid-induced *respiratory depression*. However, it may antagonise the analgesic effects of the opioids in the control of postoperative pain and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use. Flumazenil is a benzodiazepine antagonist that is used to reverse the *central sedative effects* of benzodiazepines in anaesthetic procedures.

ANAESTHETIC TECHNIQUES. A balanced combination of drugs with different actions is often used to provide the various components of general anaesthesia including unconsciousness, muscle relaxation, and analgesia. This technique, termed **balanced anaesthesia**, has been reported to minimise intra-operative cardiovascular depression, to facilitate a rapid return of consciousness, and to have a low incidence of postoperative adverse effects such as nausea and vomiting, and excitation. Typically an opioid is given before or with induction and anaesthesia is induced using nitrous oxide and an intravenous barbiturate such as thiopental. The opioid is then given in small incremental doses to achieve and maintain adequate analgesia during surgery. Opioid analgesics commonly used in this technique include morphine, fentanyl, sufentanil, and alfentanil; buprenorphine and nalbuphine have also been used.

In **total intravenous anaesthesia** (TIVA), induction and maintenance of anaesthesia is achieved with one or more anaesthetics given intravenously. This allows high inspired oxygen concentrations in situations where hypoxaemia may otherwise occur, and is advantageous in surgery where delivery of inhaled anaesthetic may be difficult (for example in bronchoscopy). Combinations used in TIVA include propofol with alfentanil or fentanyl, and midazolam with alfentanil. Neuromuscular blockers are given to produce muscle relaxation but there can be difficulty in assessing the depth of anaesthesia in patients who are paralysed for mechanical ventilation, and there have been reports of awareness during procedures under TIVA (see also Intraoperative Awareness, under Precautions, p. 1897.3). Target-controlled infusion (TCI) systems are used in some countries to control the speed of induction and depth of anaesthesia by specifying target blood concentrations.

Although now largely obsolete, use of a neuroleptic with an opioid analgesic produces an altered state of consciousness known as **neuroleptanalgesia** in which the patient is calm and indifferent to the surroundings yet is responsive to commands. The technique was used for diagnostic or therapeutic procedures such as minor surgery, endoscopy, and changing dressings. Neuroleptanalgesia can be converted to **neuroleptanaesthesia** by the concurrent administration of nitrous oxide in oxygen; a muscle relaxant may also be included. Neuroleptanaesthesia is particularly useful if the patient's cooperation is required, as consciousness soon returns once the nitrous oxide is stopped. The neuroleptic most commonly used was droperidol and it was usually given with fentanyl although other opioids have also been used. These procedures have since evolved into **conscious sedation** and **monitored anaesthesia care** techniques using newer drugs such as propofol or remifentanil, with or without midazolam.

Ketamine used alone can produce a state of **dissociative anaesthesia** similar to that of neuroleptanalgesia in which the patient may appear to be awake but is unconscious. Marked analgesia and amnesia are produced, but there may be an increase in muscle tone and emergence reactions. Dissociative anaesthesia is considered suitable for use in various diagnostic procedures, dressing changes, and in minor surgery not requiring muscle relaxation.

Techniques using **local anaesthetics** are discussed on p. 1977.2.

Adverse Effects of General Anaesthetics and their Treatment

The complex regimens used in general anaesthesia may produce complications both during and after the procedure. Adverse effects that may occur with general anaesthesia include involuntary muscle movements, hiccup, coughing, bronchospasm, laryngospasm, apnoea, respiratory depression, hypotension, cardiac arrhythmias, and mild hypothermia. Regurgitation and aspiration of gastric contents (Mendelson's syndrome) is a potential cause of morbidity

and mortality associated with general anaesthesia, especially in obstetrics and in emergency surgery (see Aspiration Syndromes, p. 1804.2).

After general anaesthesia many patients will be drowsy and mental performance may be impaired for at least 24 hours. Postoperative nausea with or without vomiting is common in the absence of antiemetic prophylaxis; nausea may last for 2 days but vomiting seldom persists beyond the first day (for details of postoperative vomiting and its management, see p. 1811.3). Other relatively common postanaesthetic effects include anorexia, malaise, fatigue, dizziness, and headache. Delirium has been noted in at least 10% of elderly general surgical patients and in up to 50% of elderly patients undergoing hip fracture repair.

Sore throat is frequent in patients who have been intubated or have had a throat pack inserted. Dry mouth as a result of premedication can add to the patient's discomfort. Manipulations for the maintenance of a clear airway may result in postoperative jaw pain.

Muscle pain, typically involving the neck, shoulders, and upper abdomen, may occur if the neuromuscular blocker suxamethonium has been given. It is usually worse on the second postoperative day and may last up to 6 days. Shoulder ache after laparoscopy resolves after 24 hours; it is due to accumulation of carbon dioxide under the diaphragm. Backache may occur after epidural or spinal anaesthesia. Urinary retention may follow regional block, cystoscopic or gynaecological surgery, or when there is prostatism.

Malignant hyperthermia (malignant hyperpyrexia—see under Dantrolene, p. 2024.1) is a rare but potentially fatal complication of general anaesthesia that may be induced by inhalational anaesthetics (mainly halogenated hydrocarbons).

Hepatotoxicity may occur in patients who are sensitised to halogenated anaesthetics; halothane has been associated with severe hepatotoxicity and is largely superseded by newer agents.

Sensitisation of the myocardium to beta-adrenergic stimulation occurs with some anaesthetics.

There has been concern over the possible danger to anaesthetists, dentists, and other personnel from exposure to volatile anaesthetics.

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Effects on neurodevelopment. There has been some concern[1,2] that exposure to anaesthetics might have adverse effects on neurological and cognitive development of neonates and young children. Results of studies have been conflicting, and further research is needed; however, it has been suggested that elective procedures using general anaesthesia should be avoided below the age of 3 years.[2]

1. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. *Anesth Analg* 2008; **106:** 1681–1707.
2. Rappaport B, *et al.* Defining safe use of anesthesia in children. *N Engl J Med* 2011; **364:** 1387–90.

Hypersensitivity. Type I hypersensitivity reactions related to various aspects of the procedure have occurred during general anaesthesia.[1-4] In most patients the release of histamine and other mediators such as prostaglandins and leukotrienes is of no clinical importance but in a few susceptible individuals anaphylaxis may result; the mortality rate is estimated to range from 3 to 9%. Anaphylaxis may occur at any time, with 90% of reactions appearing at induction of anaesthesia.[4]

Neuromuscular blockers are associated with the highest (50 to 70%) incidence of anaphylaxis, followed by latex (12 to 20%) and antibacterials (15%).[4,5] (For details of hypersensitivity reactions associated with neuromuscular blockers, see under Adverse Effects of Suxamethonium, p. 2038.2.) Anaphylactic reactions to the general anaesthetics thiopental and propofol are uncommon, with an estimated incidence of 1 in 30 000 and 1 in 60 000, respectively; reactions to etomidate and ketamine are very rare and there appear to be no published reports associated with halogenated volatile anaesthetics.[3-6] Other agents used during general anaesthesia that are rarely associated with anaphylaxis include local anaesthetics, opioid analgesics, NSAIDs, colloids, contrast media, and disinfectants.[3-6]

Many factors to identify those at risk have been proposed over the years along with suggested modifications for anaesthetic management. Routine prophylaxis with histamine H_1- and histamine H_2-antagonists has been advocated by some as part of anaesthetic management but others recommend such use only in susceptible patients with known risk factors;[7] however, there is no evidence that prophylactic treatment with H_1-and H_2-antagonists and corticosteroids actually decreases the severity of anaphylaxis.[5,7,8] Preventing re-exposure to implicated agents and avoiding other known causes of histamine release are the mainstay of prophylaxis in susceptible patients.[5,8]

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7. Liccardi G, *et al.* Cardarelli Hospital Radiocontrast Media and Anesthetic-Induced Anaphylaxis Prevention Working Group. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. *J Investig Allergol Clin Immunol* 2008; **18:** 1–11.
8. Fisher MM, Doig GS. Prevention of anaphylactic reactions to anaesthetic drugs. *Drug Safety* 2004; **27:** 393–410.

Nausea and vomiting. For a discussion on postoperative nausea and vomiting and its management, see p. 1811.3.

Shivering and its treatment. Postoperative shivering, also referred to as spontaneous postanaesthetic tremor, can occur in up to 65% of patients recovering from general anaesthesia;[1,2] its aetiology and relationship to thermoregulation is unclear.[1,3,4] Postoperative shivering may be part of a more generalised neurological disturbance associated with anaesthesia.[1] It also occurs after regional anaesthesia, especially when given epidurally, but this is probably produced by different mechanisms.[3] Muscular activity during shivering greatly increases metabolic rate, oxygen consumption, and cardiac output and may cause complications in patients with cardiac or respiratory disorders. It can also strain surgical sutures, raise intra-ocular pressure, and impede haemodynamic monitoring.

Although the relationship between postoperative shivering, body temperature, and heat loss is unclear, patients may respond to **warming** their environment and the use of blankets.[1,3,5] Postoperative shivering may sometimes be an appropriate thermoregulatory response to a low body temperature,[3] and it is important before starting therapy to check the patient's temperature and take suitable steps to avoid hypothermia.[1]

Many **drugs** have been tried for the management of postoperative shivering including the central and respiratory stimulant doxapram, the α_2-agonist clonidine, and the opioid analgesic pethidine.[2,4,6,7] Reviews have discussed[1-4,7] other opioids that have been tried including morphine, alfentanil, butorphanol, fentanyl, and sufentanil but studies suggest that not all opioids are effective or that some may only be effective when given epidurally. However, this may be due to the use of insufficient doses rather than a true difference between opioids.[8] Tramadol and nefopam have also been tried.[2,6,7] Neuromuscular blockers have been used after cardiac surgery in order to reduce cardiovascular stress.[9] Vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.[10] However, as profound neuromuscular block is required to inhibit shivering, repeated or higher doses of vecuronium might be required to prevent recurrence. Other drugs that have been investigated include ketanserin,[2] ketamine,[11,12] and magnesium sulfate.[2]

1. Crossley AWA. Postoperative shivering. *Br J Hosp Med* 1993; **49:** 204–8.
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11. Dal D, *et al.* Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; **95:** 189–92.
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Precautions for General Anaesthetics

Patients with impaired function of the adrenal cortex, for example, those who are being treated, or have recently been treated, with corticosteroids, may develop hypotension with the stress of anaesthesia. Treatment with corticosteroids, pre-operatively and postoperatively, may be necessary. Patients taking other long-term medication such as antiplatelet drugs, oral anticoagulants, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, oestrogens, MAOIs, or lithium may need to change their dosage or therapy, or stop altogether, before major elective surgery.

Patients with chronic diseases such as diabetes or hypertension, or who are taking antivirals for HIV infection, may need adjustment to their therapy before anaesthesia. Anaesthetics should be used with caution in patients with cardiac, respiratory, renal, or hepatic impairment and care may be needed in elderly or obese patients.

Patients should not undertake hazardous tasks such as driving for at least 24 hours after a general anaesthetic; alcohol should also be avoided.

Children. For concerns about the potential effects of general anaesthesia on neurodevelopment in young children, see under Adverse Effects and Treatment, above.

Intraoperative awareness. Intraoperative awareness during general anaesthesia, defined as consciousness and explicit memory of surgical events, has a reported incidence of 0.1 to 0.2% in adults[1,2] and 0.8% in children.[3,4] Risk factors include light anaesthesia and a history of awareness.[1] Neuromuscular blockade-induced paralysis may also contribute by preventing the patient giving signs of awareness.[2] Recommended preventive measures include premedication with sedative or amnestic drugs, induction with sufficient doses of intravenous anaesthetic, the use of effective analgesic techniques during surgery, avoiding or minimising the use of neuromuscular blockers, the use of potent inhalational anaesthetics instead of total intravenous anaesthesia, and ensuring adequate concentrations of inspired anaesthetic gas.[2] The use of brain function monitors to determine depth of anaesthesia is controversial, since none has been proven to be uniformly reliable;[2] some authorities[5,6] advocate against their routine use, and instead recommend the use of clinical techniques (such as checking purposeful or reflex movement) and conventional monitoring systems (such as ECG, blood pressure, heart rate, end-tidal anaesthetic concentration, and capnography).

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Interactions of General Anaesthetics

Sensitisation of the myocardium to beta-adrenergic stimulation occurs with some anaesthetics and ventricular fibrillation may occur if *sympathomimetics* such as adrenaline and isoprenaline are also used. Enhanced hypotensive effects may result when anaesthetics are given with *ACE inhibitors*, *tricyclic antidepressants* (which may also increase the risk of arrhythmias), *MAOIs* (see also Anaesthesia, under Precautions for Phenelzine, p. 444.1), *antihypertensives*, *antipsychotics*, or *beta blockers*. The effects of *competitive neuromuscular blockers* may be increased by inhalational anaesthetics. The use of anaesthetics with other *CNS depressant drugs* such as those used for premedication may produce synergistic effects on the CNS and, in some cases, a smaller dose of general anaesthetic should be given.

Reviews.

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Alfadolone Acetate *(BANM, rINNM)*

Acetato de alfadolona; Alfadolona, acetato de; Alfadolone, Acétate d'; Alfadoloni Acetas; Alphadolone Acetate; GR-2/1574; Альфадолона Ацетат.

3α,21-Dihydroxy-5α-pregnane-11,20-dione 21-acetate.

$C_{23}H_{34}O_5$=390.5

CAS — 14107-37-0 (alfadolone); 23930-37-2 (alfadolone acetate).

UNII — 00TN4GS00S.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Alfadolone Acetate). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfadolone acetate has been used to enhance the solubility of alfaxalone (below). It possesses some anaesthetic properties and is considered to be about half as potent as alfaxalone.

Alfaxalone *(BAN, rINN)*

Alfaksaloni; Alfaxalon; Alfaxalona; Alfaxalonum; Alphaxalone; GR-2/234; Альфаксалон.

3α-Hydroxy-5α-pregnane-11,20-dione.

$C_{21}H_{32}O_3$=332.5

CAS — 23930-19-0.

ATC — N01AX05.

ATC Vet — QN01AX05.

UNII — BD07M97B2A.

NOTE. The name Saffan has been used as a trade mark for mixtures of alfadolone acetate with alfaxalone.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Alfaxalone). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfaxalone was formerly used with alfadolone acetate (above) 'Althesin', as an intravenous anaesthetic for induction and maintenance of general anaesthesia.

Adverse reactions associated with polyoxyl castor oil (present as a vehicle) led to the general withdrawal of alfaxalone with alfadolone acetate from human use. It is still used in veterinary medicine.

Chloroform

Chloroforme; Chloroformio; Chloroformium Anesthesicum; Chloroformum; Chloroformum pro Narcosi; Cloroform; Clorofórmio; Cloroformo; Formil tricloruro; Hloroforms; Kloroform; Kloroformi; Trichlorometano; Trichlorométhane; Tricloruro de metano; Tricloruro de metilo; Трихлорметан; Хлороформ.

Trichloromethane.

$CHCl_3$=119.4

CAS — 67-66-3.

ATC — N01AB02.

ATC Vet — QN01AB02.

UNII — 7V31YC746X.

Pharmacopoeias. In *Br.*, *Chin.*, and *Viet.*

BP 2014: (Chloroform). A colourless volatile liquid with a characteristic odour. Not more than 5.0% v/v distils below 60 degrees and the remainder distils at 60 degrees to 62 degrees. It contains 1.0 to 2.0% v/v of ethyl alcohol; amylene 50 micrograms/mL is permitted as an alternative to ethyl alcohol.

Slightly soluble in water; miscible with dehydrated alcohol, with ether, with fixed and volatile oils, and with most other organic solvents. Store in containers with glass stoppers or other suitable closures. Protect from light. The label should state whether it contains ethyl alcohol or amylene.

Stability. The addition of a small percentage of alcohol greatly retards the gradual oxidation that occurs when chloroform is exposed to air and light, and which results in its becoming contaminated with the very poisonous carbonyl chloride (phosgene) and with chlorine; the alcohol also serves to decompose any carbonyl chloride that may have been formed.

From a study[1] of chloroform losses from chloroform water and from 6 typical BPC mixtures under various conditions of storage the following shelf-lives were recommended:

- chloroform solutions and non-sedimented mixtures could be stored in well-closed well-filled containers for 2 months at ambient temperatures
- when stored in partially-filled containers and periodically opened the shelf-life should not exceed 2 weeks
- sedimented mixtures could be stored for 2 months in well-closed well-filled containers, but because loss of chloroform could be expected in containers periodically opened such mixtures should be prepared as required or packed in their final containers
- for chloroform-containing mixtures in the home a shelf-life of 2 weeks was suggested

1. Lynch M, *et al.* Chloroform as a preservative in aqueous systems: losses under "in-use" conditions and antimicrobial effectiveness. *Pharm J* 1977; **219:** 507–10.

Storage. It has been recommended[1] that if the period of use would exceed 6 weeks, PVC bottles should not be used for storing or dispensing: Chloroform and Morphine Tincture, or aqueous mixtures containing more than 5% thereof; mixtures or dispersions in which chloroform is present in excess of its aqueous solubility; aqueous mixtures containing chloroform and high concentrations of electrolytes; or of mixtures containing chloroform water.

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Uses and Administration

Chloroform is a volatile halogenated anaesthetic that was used by inhalation, but safer drugs are now preferred in general anaesthesia.

Chloroform is used as a carminative and as a flavouring agent and preservative. For these purposes it is usually employed as Chloroform Spirit (BP 2014) or Double-strength Chloroform Water (BP 2014) but doubts have been cast on the safety of the long-term use of chloroform in mixtures.

Externally, chloroform has a rubefacient action.

Chloroform is also used as a solvent.

Anaesthesia. An historical review of the use of chloroform in clinical anaesthesia.[1]

1. Payne JP. Chloroform in clinical anaesthesia. *Br J Anaesth* 1981; **53:** 11S–15S.

Adverse Effects and Precautions

Chloroform depresses respiration and produces hypotension. Cardiac output is reduced and arrhythmias may develop. Poisoning can lead to respiratory depression and cardiac arrest. Delayed hepatotoxic and nephrotoxic reactions have occurred 6 to 24 hours after a dose; symptoms may include abdominal pain, vomiting, and, at a later stage, jaundice.

Liquid chloroform is irritant to the skin and mucous membranes and may cause burns if spilt on them. Suitable precautions should be taken to avoid skin contact with chloroform as it can penetrate skin and produce systemic toxicity. Chloroform is not flammable. Care should be taken not to vaporise chloroform in the presence of a flame because of the production of toxic gases.

In the UK medicinal products are limited to a chloroform content of not more than 0.5% (w/w or v/v as appropriate) of chloroform. Exceptions include supply by a doctor or dentist, or in accordance with his prescription, to a particular patient, and supply for anaesthetic purposes.

In the USA the FDA has banned the use of chloroform in medicines and cosmetics, because of reported carcinogenicity in *animals*. It has also been withdrawn from systemic use in other countries.

The sale within or import into England and Wales and Scotland of food containing any added chloroform is prohibited.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving chloroform, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Poisoning. There has been a report[1] of a 19 year-old man who drank about 75 mL of chloroform in an attempted suicide; he recovered after supportive care and intravenous acetylcysteine therapy. Another report[2] described a 46 year-old woman with chronic alcoholism who developed acute liver failure and rhabdomyolysis after chloroform inhalation and binge drinking; she died despite supportive care.

1. Dell'Aglio DM, *et al.* Acute chloroform ingestion successfully treated with intravenously administered N-acetylcysteine. *J Med Toxicol* 2010; **6:** 143–6.
2. Lionte C. Lethal complications after poisoning with chloroform – case report and literature review. *Hum Exp Toxicol* 2010; **29:** 615–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Dentophar†; ***India***: Eltuss; ***Ital.***: Sekumatic†; ***Rus.***: Eludril (Элюдрил); Espol (Эспол); ***S. Afr.***: Diphenhydramine Expectorant Syrup†; Mrs Johnsons American Soothing Syrup†; SB Toothache Drops†; Tandpyndruppels†; Vicks Acta Plus†.

Pharmacopoeial Preparations

BP 2014: Chloroform and Morphine Tincture; Chloroform Spirit; Double-strength Chloroform Water.

Cyclopropane *(rINN)*

Ciclopropano; Cikloprópán; Ciklopropāns; Cyclopropaan; Cyclopropan; Cyclopropanum; Cyklopropan; Sikloprópan; Syklopropaani; Trimethylene; Trimetileno; Циклопропан.

C_3H_6=42.08

CAS — 75-19-4.

UNII — 99TB643425.

Pharmacopoeias. In *US.*

USP 36: (Cyclopropane). A colourless highly flammable gas with a characteristic odour and pungent taste. Freely soluble in alcohol; soluble in fixed oils. One volume dissolves in about 2.7 volumes of water at 15 degrees.

Stability. CAUTION. Mixtures of cyclopropane with oxygen or air at certain concentrations are explosive. Cyclopropane should not be used in the presence of an open flame or of any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage and supply. Cyclopropane is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Uses and Administration

Cyclopropane is an anaesthetic that has been given by inhalation for analgesia and induction and maintenance of general anaesthesia. It produces skeletal muscle relaxation, is non-irritant, and induction and recovery are rapid, but it is difficult to use and handle and other anaesthetics are generally preferred. Because of the risk of explosion, it has usually been given by means of a closed circuit. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 9.2%.

Adverse Effects and Precautions

Cyclopropane depresses respiration to a greater extent than many other anaesthetics. Laryngospasm, cardiac arrhythmias, or hepatic injury may occur. Cyclopropane increases the sensitivity of the heart to sympathomimetic amines. Malignant hyperthermia has also been reported. Postoperative nausea, vomiting, and headache are frequent.

Cyclopropane should be used with caution in patients with bronchial asthma and cardiovascular disorders. Premedication with atropine may be advisable to reduce vagal tone.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Abuse. Two of 4 deaths from abuse of volatile anaesthetics in operating rooms were attributed to cyclopropane.[1]

1. Bass M. Abuse of inhalation anesthetics. *JAMA* 1984; **251:** 604.

Malignant hyperthermia. Malignant hyperthermia has been associated with cyclopropane.[1]

1. Lips FJ, *et al.* Malignant hyperthermia triggered by cyclopropane during cesarean section. *Anesthesiology* 1982; **56:** 144–6.

Interactions

Care is advised if adrenaline or other sympathomimetics are given during cyclopropane anaesthesia. Potentiation of competitive neuromuscular blockers occurs after use of cyclopropane.

See also Interactions for General Anaesthetics, p. 1897.3.

Desflurane *(BAN, USAN, rINN)*

Desfluraan; Desfluraani; Desfluran; Desflurano; Desfluranum; Dezflurán; I-653; Десфлуран.

(±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether.
$C_3H_2F_6O$=168.0
CAS — 57041-67-5.
ATC — N01AB07.
ATC Vet — QN01AB07.
UNII — CRS35BZ94Q.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Desflurane). A clear, colourless, mobile, heavy liquid. B.p. about 22 degrees. Practically insoluble in water; miscible with anhydrous alcohol. Store in a glass bottle fitted with a polyethylene-lined cap. Before opening the bottle, cool the contents to below 10 degrees.

USP 36: (Desflurane). Store in airtight containers at a temperature of 20 to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Replace cap securely after each use. Protect from light.

Uses and Administration

Desflurane is a volatile halogenated anaesthetic given by inhalation. It is structurally similar to isoflurane and has anaesthetic actions similar to those of halothane (p. 1902.2). The minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranges from about 6% in the elderly to about 11% in infants. It is non-flammable and non-explosive in clinical concentrations but, because of its low boiling-point, it must be delivered by a special vaporiser, preferably within a closed circuit system.

Desflurane is used for induction and maintenance of general anaesthesia (p. 1896.1), but because of its pungency is not recommended for induction in children. Concentrations of 4 to 11% v/v have been used for induction and usually produce surgical anaesthesia in 2 to 4 minutes. Concentrations of 2 to 6% v/v with nitrous oxide or 2.5 to 8.5% v/v in oxygen or oxygen-enriched air may be used to maintain anaesthesia. Higher concentrations of desflurane have been used but it is important to ensure adequate oxygenation; concentrations in excess of 17% v/v are not recommended. For concentrations used in patients with hepatic or renal impairment, see below.

As with other volatile halogenated anaesthetics supplemental neuromuscular blockers may be required. Recovery from anaesthesia is reported to be more rapid than with other halogenated anaesthetics.

Administration in children. Although desflurane is not recommended for induction of anaesthesia in children, it is used for the maintenance of anaesthesia in this group; concentrations given are as for adults (see Uses and Administration, above).

Administration in hepatic or renal impairment. Desflurane concentrations of 1 to 4% v/v in oxygen and nitrous oxide have been used in patients with chronic renal or hepatic impairment and during renal transplantation surgery.

Anaesthesia. The characteristics of desflurane have been reviewed.[1-6] Its advantages are considered to include rapid induction and emergence from anaesthesia, and minimal metabolism makes end-organ toxicity unlikely. Emergence from anaesthesia and recovery of psychomotor and cognitive skills with desflurane is more rapid than after anaesthesia with other halogenated volatile anaesthetics such as isoflurane and possibly than after the intravenous anaesthetic propofol. This is considered to be of particular advantage for outpatient treatment, but studies so far have found no difference in time to discharge with desflurane or other general anaesthetics. Furthermore, the incidence of nausea and vomiting with desflurane is significantly greater than after the use of propofol. Desflurane's pungency may also limit its use for induction especially in children, although it is suitable for maintenance in this group and may be particularly suitable for neonates.[4]

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; **27:** 6–18.
2. Patel SS, Goa KL. Desflurane: a review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anaesthesia. *Drugs* 1995; **50:** 742–67.
3. Young CJ, Apfelbaum JL. Inhalational anesthetics: desflurane and sevoflurane. *J Clin Anesth* 1995; **7:** 564–77.
4. Hatch DJ. New inhalation agents in paediatric anaesthesia. *Br J Anaesth* 1999; **83:** 42–9.
5. Umbrain V, *et al.* Desflurane: a reappraisal. *Acta Anaesthesiol Belg* 2002; **53:** 187–91.
6. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.

Status epilepticus. For mention of the use of desflurane in the management of refractory status epilepticus, see p. 510.2.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias may occur. Desflurane may rarely precipitate malignant hyperthermia in susceptible individuals; patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with desflurane. It appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Nausea and vomiting have been reported in the postoperative period.

Desflurane is irritant to the airways and may provoke breath holding, apnoea, coughing, increased salivation, and laryngospasm. It is therefore not recommended for induction of anaesthesia in paediatric patients.

Desflurane may increase CSF pressure and should therefore be used with caution in patients with, or at risk of, raised intracranial pressure. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as desflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p. 1896.3 and p. 1897.3.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. A review[1] of *animal* and human studies concluded that the cardiorespiratory effects of desflurane were similar to those of isoflurane but that there might be better control of arterial pressure with desflurane during stressful stimuli. A study[2] in patients undergoing coronary artery bypass surgery showed that a state of haemodynamic stability suitable for patients at risk of myocardial ischaemia could be maintained when desflurane was used with the opioid analgesic fentanyl.

1. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesth Analg* 1992; **75:** S17–S31.
2. Parsons RS, *et al.* Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery. *Br J Anaesth* 1994; **72:** 430–8.

Effects on the liver. Although considered to be less hepatotoxic than some other halogenated anaesthetics (see under Adverse Effects of Halothane, p. 1902.3), delayed hepatotoxicity occurred in a 65-year-old woman after maintenance anaesthesia involving desflurane.[1] She had received halothane on two previous occasions which may have caused sensitisation. A fatal case[2] of acute liver failure associated with desflurane anaesthesia has been reported in a 53-year-old woman. She had significantly raised serum-alanine aminotransferase concentrations on first exposure but this was attributed to antibacterial toxicity; however, on second exposure 10 days later, she developed acute liver failure 96 hours after surgery and died despite supportive treatment. Hepatotoxicity has also been reported[3] after desflurane anaesthesia in a 15-month-old boy who had previously received isoflurane on two occasions, although it has been suggested[4] that this was more likely due to concomitant paracetamol therapy. Investigation of hepatocellular integrity (by measuring glutathione transferase alpha) in 30 women given desflurane indicated a mild subclinical disturbance.[5]

1. Martin JL, *et al.* Hepatotoxicity after desflurane anesthesia. *Anesthesiology* 1995; **83:** 1125–9.
2. Chin MW, *et al.* Desflurane-induced acute liver failure. *Med J Aust* 2008; **189:** 293–4.
3. Côté G, Bouchard S. Hepatotoxicity after desflurane anesthesia in a 15-month-old child with Mobius syndrome after previous exposure to isoflurane. *Anesthesiology* 2007; **107:** 843–5.
4. Her C. Acetaminophen-induced, not desflurane-induced, hepatotoxicity. *Anesthesiology* 2008; **109:** 570–1.
5. Tiainen P, *et al.* Changes in hepatocellular integrity during and after desflurane or isoflurane anaesthesia in patients undergoing breast surgery. *Br J Anaesth* 1998; **80:** 87–9.

Effects on the respiratory tract. The irritant effect of desflurane on the lungs limits its role in the induction of anaesthesia, especially in children. Pre-operative use of nebulised lidocaine 4% failed to alleviate the response[1] although pretreatment with intravenous opioids may reduce the irritation.[2]

1. Bunting HE, *et al.* Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *Br J Anaesth* 1995; **75:** 631–3.
2. Kong CF, *et al.* Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85:** 364–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desflurane as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by desflurane (see p. 2032.3). Lower doses of desflurane are required in those receiving opioids, benzodiazepines or other sedatives. Care is advised if adrenaline or other sympathomimetics are given to patients during desflurane anaesthesia.

See also Interactions of General Anaesthetics, p. 1897.3.

References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; **9:** 105–17.

Pharmacokinetics

Desflurane has a low blood/gas partition coefficient and on inhalation its absorption, distribution, and elimination are reported to be more rapid than for other halogenated anaesthetics such as isoflurane or halothane. It is excreted mainly unchanged through the lungs. A small amount diffuses through the skin. About 0.02% of inhaled desflurane is metabolised in the liver and trichloroacetic acid has been detected in the serum and urine of patients given desflurane.

References.

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; **27:** 6–18.
2. Eger EI. Physicochemical properties and pharmacodynamics of desflurane. *Anaesthesia* 1995; **50** (suppl): 3–8.
3. Wissing H, *et al.* Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane. *Br J Anaesth* 2000; **84:** 443–9.
4. Lu CC, *et al.* Pharmacokinetics of desflurane uptake into the brain and body. *Anaesthesia* 2004; **59:** 216–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Suprane; ***Austral.***: Suprane; ***Austria***: Suprane; ***Belg.***: Suprane; ***Canad.***: Suprane; ***Chile***: Suprane; ***China***: Suprane (优宁); ***Cz.***: Suprane; ***Denm.***: Suprane; ***Fin.***: Suprane; ***Fr.***: Suprane; ***Ger.***: Suprane; ***Gr.***: Suprane; ***Hong Kong***: Suprane; ***Hung.***: Suprane; ***Indon.***: Suprane; ***Irl.***: Suprane; ***Israel***: Sulorane; ***Ital.***: Suprane; ***Jpn***: Suprane†; ***Malaysia***: Suprane; ***Neth.***: Suprane; ***Norw.***: Suprane; ***NZ***: Suprane; ***Philipp.***: Suprane; ***Pol.***: Suprane; ***Port.***: Suprane; ***S.Afr.***: Suprane; ***Singapore***: Suprane; ***Spain***: Suprane; ***Swed.***: Suprane; ***Switz.***: Suprane; ***Thai.***: Suprane; ***Turk.***: Suprane; ***UK***: Suprane; ***USA***: Suprane.

Enflurane *(BAN, USAN, rINN)*

Anaesthetic Compound No. 347; Compound 347; Enfluraan; Enfluraani; Enfluran; Enflurano; Enfluranum; Methylflurether; NSC-115944; Энфлуран.
2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether; 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane.
$C_3H_2ClF_5O$=184.5
CAS — 13838-16-9.
ATC — N01AB04.
ATC Vet — QN01AB04.
UNII — 91169L5AYS.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Enflurane). A clear colourless volatile liquid having a mild sweet odour. Non-flammable. Distilling range 55.5 degrees to 57.5 degrees. Slightly soluble in water; miscible with organic solvents, with fats, and with oils. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Enflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of isoflurane. It has anaesthetic actions similar to those of halothane (p. 1902.2). Enflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 1.7% in middle age to 2.5% in children. Enflurane is given using a calibrated vaporiser for induction and maintenance of general anaesthesia (p. 1896.1); it is also used in

subanaesthetic doses to provide analgesia in obstetrics and other painful procedures (below).

To avoid CNS excitement a short-acting barbiturate or other intravenous induction agent is recommended before the inhalation of enflurane. Anaesthesia may be induced using enflurane alone with oxygen or in nitrous oxide-oxygen mixtures. In general, enflurane concentrations of 2 to 4.5% v/v produce surgical anaesthesia in 7 to 10 minutes. Anaesthesia may be maintained with a concentration of 0.5 to 3% v/v of enflurane; a concentration of 3% v/v should not be exceeded. Although enflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Postoperative analgesia may be necessary.

Concentrations of 0.25 to 1% v/v of enflurane are used to provide analgesia for vaginal delivery during childbirth and of 0.5 to 1% v/v to supplement other general anaesthetics during caesarean section.

Pain. Enflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures although a study[1] was unable to confirm that it had an analgesic effect at subanaesthetic concentrations.

1. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70:** 684–6.

Adverse Effects

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias have been reported although the incidence of arrhythmias is lower with enflurane than with halothane. It sensitises the myocardium to sympathomimetics to a lesser extent than halothane. Compared with halothane, enflurane has a stimulant effect on the CNS and convulsions may occur when concentrations of enflurane are high or hypocapnia is present. Malignant hyperthermia has also been reported. Asthma and bronchospasm may occur. There have been reports of elevated serum-fluoride concentrations although resulting renal damage appears to be rare. There have been changes in measurements of hepatic enzymes and several reports of liver damage. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on the blood. The development of carboxyhaemoglobinaemia in patients anaesthetised with volatile anaesthetics is discussed under Precautions, below.

Effects on the kidneys. The nephrotoxicity of volatile anaesthetics has been reviewed.[1] Although enflurane released inorganic fluoride it appeared to be safe in patients with normal renal function. It had also been given to patients with mild to moderate renal impairment without any further deterioration. There was an increase in serum-fluoride concentrations when enflurane was given to a group of patients who had been receiving isoniazid, but there was no change in kidney function. Pretreatment of patients with a single dose of disulfiram before anaesthesia was found to produce a consistent and almost complete inhibition of enflurane metabolism as shown by substantial reductions in plasma-fluoride concentrations and urinary excretion of fluoride.[2]

1. Mazze RI. Nephrotoxicity of fluorinated anaesthetic agents. *Clin Anaesthesiol* 1983; **1:** 469–83.
2. Kharasch ED, *et al.* Clinical enflurane metabolism by cytochrome P450 2E1. *Clin Pharmacol Ther* 1994; **55:** 434–40.

Effects on the liver. A review[1] of 58 cases of suspected enflurane hepatitis considered enflurane to be the likely cause of the liver damage in 24. There was biochemical evidence of liver damage in 23 of these cases. Histology reports were available for 15 patients and all showed some degree of hepatocellular necrosis and degeneration.

While the incidence of liver damage from enflurane seemed to be lower than from halothane, the character of the injury was similar.

Another review[2] of the same cases plus an additional 30 (88 in all) came to different conclusions; the main author was a consultant to the manufacturer of enflurane. Of the 88 patients with suspected enflurane hepatitis, 30 were rejected because of insufficient evidence and 43 were considered to have other factors known to produce liver injury. This left 15 possible cases of enflurane hepatitis compared with the 24 identified by the first review. While agreeing that in the rare patient unexplained liver damage follows enflurane anaesthesia, it was considered that the incidence was too small to suggest an association. No consistent histological pattern was identified in this study.

See also under Adverse Effects in Halothane, p. 1902.3.

1. Lewis JH, *et al.* Enflurane hepatotoxicity: a clinicopathologic study of 24 cases. *Ann Intern Med* 1983; **98:** 984–92.
2. Eger EI, *et al.* Is enflurane hepatotoxic? *Anesth Analg* 1986; **65:** 21–30.

Effects on respiration. Overall, enflurane is considered to produce more respiratory depression than halothane or isoflurane.[1,2]

1. Quail AW. Modern inhalation anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; **150:** 95–102.
2. Merrett KL, Jones RM. Inhalational anaesthetic agents. *Br J Hosp Med* 1994; **52:** 260–3.

Precautions

Enflurane should be used with caution in patients with convulsive disorders. High concentrations of enflurane may cause uterine relaxation. In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as enflurane (see below).

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with enflurane. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Report[1] of a fatality in a 29-year-old student nurse anaesthetist who had applied enflurane to the herpes simplex lesions of her lower lip. She was found with an empty 250 mL bottle of enflurane.

1. Lingenfelter RW. Fatal misuse of enflurane. *Anesthesiology* 1981; **55:** 603.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232306&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies enflurane as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients during enflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by enflurane (see p. 2032.3).

See also Interactions of General Anaesthetics, p. 1897.3.

Antibacterials. For the effects of *isoniazid* on enflurane defluorination, see Effects on the Kidneys under Adverse Effects, above.

Antidepressants. It appeared likely that the enflurane-induced seizure activity seen in 2 patients could have been enhanced by *amitriptyline*.[1] It may be advisable to avoid the use of enflurane in patients requiring tricyclic antidepressants, especially when the patient has a history of seizures or when hyperventilation or high enflurane concentrations are a desired part of the anaesthetic technique.

1. Sprague DH, Wolf S. Enflurane seizures in patients taking amitriptyline. *Anesth Analg* 1982; **61:** 67–8.

Disulfiram. For the effect of disulfiram on the metabolism of enflurane, see Effects on the Kidneys under Adverse Effects, above.

Pharmacokinetics

Enflurane is absorbed on inhalation. The blood/gas partition coefficient is low. It is mostly excreted unchanged through the lungs. Up to 10% of inhaled administered enflurane is metabolised in the liver, mainly to inorganic fluoride.

References.
1. Bengtson JP, *et al.* Uptake of enflurane and isoflurane during spontaneous and controlled ventilation. *Anaesth Intensive Care* 1992; **20:** 191–5.
2. Devchand D, *et al.* The uptake of enflurane during anaesthesia. *Anaesthesia* 1995; **50:** 491–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Enforan; ***Austria***: Ethrane†; ***Braz.***: Enfluthane; Enuran; Etrane; ***China***: Alyrane (应力美); Ethrane (易使宁); ***Indon.***: Ethrane†; ***Irl.***: Ethrane†; ***Israel***: Alyrane†; ***Ital.***: Ethrane; ***Mex.***: Enfran†; Ethrane†; ***Philipp.***: Alyrane†; Endurane; Ethrane; ***S.Afr.***: Ethrane; ***Turk.***: Ethrane; ***USA***: Ethrane; ***Venez.***: Ethrane.

Anaesthetic Ether

Aether ad Narcosin; Aether Anaestheticus; Aether pro Narcosi; Aether Purissimus; Altatáshoz való éter; Anestesiaeetteri; Anestesiaeetteri, Narkoosieetteri; Anestetinis eteris; Diethyl Ether; Dietil-éter; Dietilèter; Dietiletere; Dietileteris; Dietilêteris; Dietüüleeter; Dietyleter; Eeter; Êter; Éter anestésico; Eter dietylowy; Eter do narkozy; Éter etílico; Eter etylowy; Éter Puríssimo; Etere Dietilico; Etere Etilico; Ether; Ether Anesthesicus; Éther anesthésique; Ether Anestheticus; Éther diéthylique; Ether Ethylicus; Ether Ethylicus pro Narcosi; Ether k narkóze; Ethyl Ether; Etoksüetaan; Etossietano; Etoxietano; Etüüleeter; Narkoosieetteri; Narkoseter.

$(C_2H_5)_2O$=74.12

CAS — 60-29-7.

ATC — N01AA01.

ATC Vet — QN01AA01.

NOTE. Some synonyms applied to anaesthetic ether may also be used for solvent ether (p. 2212.3). Care should be taken to differentiate between the two grades of ether.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of anaesthetic ether:

Sweet Vitriol.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ether, Anaesthetic). Diethyl ether to which an appropriate quantity of a non-volatile antoxidant may have been added. It contains not more than 2 g/litre of water. A clear, colourless, volatile, highly flammable, and very mobile liquid. Distillation range 34 degrees to 35 degrees.

Soluble 1 in 15 of water; miscible with alcohol and with fatty oils. Store at a temperature of 8 degrees to 15 degrees in airtight containers. Protect from light. Ether remaining in a partly used container may deteriorate rapidly. The label should state the name and concentration of any added non-volatile antoxidant.

USP 36: (Ether). It consists of 96 to 98% of $C_4H_{10}O$, the remainder consisting of alcohol and water. Ether for anaesthetic use contains not more than 0.2% of water. It is a colourless, mobile, highly flammable, highly volatile liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. Its vapour, when mixed with air and ignited, may explode. B.p. about 35 degrees.

Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly-filled, airtight containers, remote from fire and at a temperature not exceeding 40 degrees. Protect from light. Ether to be used for anaesthesia must be preserved in airtight containers of not more than 3 kg capacity and is not to be used for anaesthesia if it has been removed from the original container longer than 24 hours.

Labelling. The label should state that it is suitable for use as an anaesthetic.

Stability. Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that free ether, even in low concentrations, caused softening of PVC bottles and was associated with loss by permeation.[1]

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Uses and Administration

Ether is an anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 1.92%. Ether is still used in some countries for the induction and maintenance of general anaesthesia although it has been replaced in many other countries by the halogenated anaesthetics. It possesses a respiratory stimulant effect in all but the deepest planes of

anaesthesia. Ether also possesses analgesic and muscle relaxant properties. Premedication with an antimuscarinic such as atropine is necessary to reduce salivary and bronchial secretions.

Solvent ether is described on p. 2212.3.

Adverse Effects

Ether has an irritant action on the mucous membrane of the respiratory tract; it stimulates salivation and increases bronchial secretion. Laryngeal spasm may occur. Ether causes vasodilatation which may lead to a severe fall in blood pressure and it reduces blood flow to the kidneys; it also increases capillary bleeding. The bleeding time is unchanged but the prothrombin time may be prolonged. Ether may cause malignant hyperthermia in certain individuals. Alterations in kidney and liver function have been reported. Convulsions occasionally occur. Hyperglycaemia due to gluconeogenesis has been noted.

Recovery is slow from prolonged ether anaesthesia and postoperative vomiting is common. Acute overdosage of ether is characterised by respiratory failure and cardiac arrest.

Dependence on ether or ether vapour has been reported. Prolonged contact with ether spilt on any tissue produces necrosis.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Precautions

Ether anaesthesia is contra-indicated in patients with diabetes mellitus, impaired kidney function, raised CSF pressure, and severe liver disease. Its use is not advisable in hot and humid conditions in patients with fever, as convulsions are liable to occur, particularly in children and in patients who have been given atropine.

See also Precautions for General Anaesthetics, p. 1897.3.

Interactions

Ether enhances the action of competitive neuromuscular blockers to a greater degree than most other anaesthetics. However, it does not potentiate the arrhythmogenic effect of sympathomimetics, including adrenaline, as much as other inhalational anaesthetics.

See also Interactions of General Anaesthetics, p. 1897.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Hoffmans Druppels.

Homoeopathic Preparations. ***Fr.***: Strophantus Compose; ***Ger.***: Angioton H; Angioton S†; Corselect N; Crataegus comp; Diacard.

Etomidate *(BAN, USAN, rINN)*

Etomidaat; Etomidaatti; Etomidat; Etomidát; Etomidatas; Étomidate; Etomidato; Etomidatum; R-16659; R-26490 (etomidate sulfate); Этомидат.

R-(+)-Ethyl 1-(α-methylbenzyl)imidazole-5-carboxylate.

$C_{14}H_{16}N_2O_2$=244.3

CAS — 33125-97-2.

ATC — N01AX07.

ATC Vet — QN01AX07.

UNII — Z226288598.

NOTE. Do not confuse with edetate; see Inappropriate Administration under Sodium Edetate, p. 1551.2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Etomidate). A white or almost white powder. M.p. about 68 degrees. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Etomidate). A white or almost white powder. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Uses and Administration

Etomidate is an intravenous anaesthetic used for the induction of general anaesthesia (p. 1896.1). Anaesthesia is rapidly induced and may last for 6 to 10 minutes with a single usual dose. Recovery is usually rapid without hangover effect. Etomidate has no analgesic activity.

For the induction of anaesthesia, etomidate is available as a conventional or an emulsion injection formulation. The usual dose is 300 micrograms/kg of etomidate given slowly, preferably into a large vein in the arm, although a lower dose of 150 micrograms/kg of the emulsion formulation may be sufficient. An initial dose of 150 to 200 micrograms/kg is recommended in the elderly, subsequently adjusted according to effects (see also below). Dosage should also be reduced in hepatic cirrhosis. Children may require up to 30% more than the usual adult dose (i.e. up to 400 micrograms/kg). Opioid analgesics or benzodiazepines as premedication reduce myoclonic muscle movements; opioids also reduce injection site pain. A neuromuscular blocker is necessary if intubation is required.

Administration in children. Etomidate is used in children for the induction of anaesthesia; for details of doses, which may be proportionately larger than in adults, see Uses and Administration, above. US licensed product information does not recommend the use of etomidate below 10 years of age. In the UK, etomidate emulsion is licensed for use in those aged over 6 months, although it may be given to younger patients in emergencies, and other formulations do not specify a minimum age; the *BNFC* suggests all etomidate products may be used for induction from 1 month of age.

Administration in the elderly. A study[1] in elderly patients has shown that although reducing the rate of intravenous injection of etomidate reduces the speed of induction, the dosage required is also reduced. Giving etomidate 0.2% solution at a rate of 10 mg/minute induced anaesthesia in a mean of 89.6 seconds and required a mean dose of 110 micrograms/kg. Corresponding values for a rate of 40 mg/minute were 47.7 seconds and 260 micrograms/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Anaesthesia. Etomidate might be useful for induction if rapid tracheal intubation is required with a competitive neuromuscular blocker as it has been shown to reduce the time to onset of block with vecuronium.[1,2] Indeed, etomidate has been suggested[2,3] by some to be the agent of choice for rapid sequence induction of anaesthesia in emergency settings; advantages include rapid onset and short duration of action, predictable clinical effect, and haemodynamic stability. However, there is considerable controversy about its use in critically-ill patients, see Effects on the Endocrine System, below.

1. Gill RS, Scott RPF. Etomidate shortens the onset time of neuromuscular block. *Br J Anaesth* 1992; **69:** 444–6.
2. Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med* 1997; **15:** 221–30.
3. Nestor NB, Burton JH. ED use of etomidate for rapid sequence induction. *Am J Emerg Med* 2008; **26:** 946–50.

Cushing's syndrome. There have been reports[1-4] of benefit with the use of etomidate for acute control of hypercortisolaemia associated with Cushing's syndrome (p. 2559.1), particularly if the oral route is not available.

1. Greening JE, *et al.* Efficient short-term control of hypercortisolaemia by low-dose etomidate in severe paediatric Cushing's disease. *Horm Res* 2005; **64:** 140–3.
2. Johnson TN, Canada TW. Etomidate use for Cushing's syndrome caused by an ectopic adrenocorticotropic hormone-producing tumor. *Ann Pharmacother* 2007; **41:** 350–3.
3. Dabbagh A, *et al.* Etomidate infusion in the critical care setting for suppressing the acute phase of Cushing's syndrome. *Anesth Analg* 2009; **108:** 238–9.
4. Mettauer N, Brierley J. A novel use of etomidate for intentional adrenal suppression to control severe hypercortisolemia in childhood. *PediatrCrit Care Med* 2009; **10:** e37–e40.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used, but other anaesthetics including etomidate have also been tried[1] for intractable convulsive status epilepticus. However, like several other anaesthetics there have been reports of seizures associated with its use in anaesthesia,[2,3] especially in patients with epilepsy.

1. Yeoman P, *et al.* Etomidate infusions for the control of refractory status epilepticus. *Intensive Care Med* 1989; **15:** 255–9.
2. Nicoll K, Callender J. Etomidate-induced convulsion prior to electroconvulsive therapy. *Br J Psychiatry* 2000; **177:** 373.
3. Sen H, *et al.* Epileptic seizure during anaesthesia induction with etomidate. *Middle East J Anesthesiol* 2010; **20:** 723–5.

Adverse Effects and Precautions

Excitatory phenomena (especially involuntary myoclonic muscle movements, which are sometimes severe) are common after injection of etomidate, but may be reduced by giving an opioid analgesic or a short-acting benzodiazepine beforehand. Pain on injection may be reduced by giving etomidate into a large vein in the arm rather than into the hand, or, again, by premedication with an opioid analgesic. Convulsions may occur rarely, as may laryngospasm and cardiac arrhythmias. Hypersensitivity reactions including anaphylaxis have been reported. Etomidate is associated with less hypotension than other drugs commonly used for induction.

Because etomidate inhibits adrenocortical function during maintenance anaesthesia (see below) its use is limited to induction of anaesthesia. Supplementary corticosteroid therapy should be considered in at-risk patients, particularly those with adrenocortical dysfunction.

Etomidate should be used with care in the elderly, who may be more prone to cardiac depression; lower doses may be required. The dose of etomidate should also be reduced in patients with hepatic cirrhosis. Caution may be appropriate in patients with pre-existing epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Effects on the endocrine system. Etomidate used for sedation in an intensive care unit was implicated in an increase in mortality.[1] However, there is considerable controversy about the effects of etomidate on mortality in critically-ill patients (such as those with severe trauma or sepsis) when given as a single bolus dose for induction.[2] One systematic review[3] concluded that the use of etomidate for rapid tracheal intubation in critically-ill patients was associated with an increased risk of mortality; however, another review[4] that included patients receiving routine surgical anaesthesia found this effect to be statistically insignificant.

The UK CSM agreed that etomidate could cause a significant fall in circulating plasma-cortisol concentrations, unresponsive to corticotropin stimulation.[5] Other regulators have taken similar views in restricting the use of etomidate, which is now not given by prolonged infusion, essentially limiting its licensed use to induction of anaesthesia. Licensed product information advises that the postoperative rise in serum-cortisol concentration, which has been noted after thiopental induction, is delayed for about 3 to 6 hours when etomidate is used for induction.

A study comparing the effects of etomidate with those of methohexital on the adrenocortical function of neonates borne by mothers who received these agents for induction of anaesthesia before caesarean section indicated that there was no evidence to preclude the use of etomidate in such patients. However, regardless of which anaesthetic agent was used, early feeding was recommended to avoid neonatal hypoglycaemia.[6]

The inhibitory effect of etomidate on adrenocortical function has been used to control episodes of hypercortisolaemia; for details, see Cushing's Syndrome, above.

1. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; **i:** 1270.
2. Kulstad EB, *et al.* Etomidate as an induction agent in septic patients: red flags or false alarms? *West J Emerg Med* 2010; **11:** 161–72.
3. Albert SG, *et al.* The effect of etomidate on adrenal function in critical illness: a systematic review. *Intensive Care Med* 2011; **37:** 901–10.
4. Hohl CM, *et al.* The effect of a bolus dose of etomidate on cortisol levels, mortality, and health services utilization: a systematic review. *Ann Emerg Med* 2010; **56:** 105–13.e5.
5. Goldberg A. Etomidate. *Lancet* 1983; **ii:** 60.
6. Crozier TA, *et al.* Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate. *Br J Anaesth* 1993; **70:** 47–53.

Hypersensitivity. Reactions involving immediate widespread cutaneous flushing or urticaria attributed to etomidate have been described.[1] There have also been reports[2,3] of anaphylactic reactions after injection of etomidate.

1. Watkins J. Etomidate: an 'immunologically safe' anaesthetic agent. *Anaesthesia* 1983; **38** (suppl): 34–8.
2. Krumholz W, *et al.* Ein fall von anaphylaktoider reaktion nach gabe von etomidat. *Anaesthesist* 1984; **33:** 161–2.
3. Sold M, Rothhammer A. Lebensbedrohliche anaphylaktoide reaktion nach etomidat. *Anaesthesist* 1985; **34:** 208–10.

Interactions

A reduced dose of etomidate may be necessary in patients who have received antipsychotics, sedatives, or opioids. The hypnotic effect of etomidate has been potentiated by other sedative drugs.

See also Interactions of General Anaesthetics, p. 1897.3.

Calcium-channel blockers. Prolonged anaesthesia and Cheyne-Stokes respiration after etomidate injection has been reported in 2 patients also given *verapamil*.[1]

1. Moore CA, *et al.* Potentiation of etomidate anesthesia by verapamil: a report of two cases. *Hosp Pharm* 1989; **24:** 24–5.

General anaesthetics. For a report of synergy between *propofol* and etomidate, see p. 1912.2.

Pharmacokinetics

After injection, etomidate is rapidly redistributed from the CNS to other body tissues, and undergoes rapid metabolism in the liver and plasma. Pharmacokinetics are complex and have been described by both 2- and 3-compartment models. Etomidate is about 76% bound to plasma proteins. It is mainly excreted in the urine, but some is excreted in the bile. It may cross the placenta and is distributed into breast milk.

References.

1. Levron JC, Assoune P. Pharmacocinétique de l'étomidate. *Ann Fr Anesth Reanim* 1990; **9:** 123–6.
2. Sfez M, *et al.* Comparaison de la pharmacocinétique de l'étomidate chez l'enfant et chez l'adulte. *Ann Fr Anesth Reanim* 1990; **9:** 127–31.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69:** 586–8.
4. Kaneda K, *et al.* Population pharmacokinetics and pharmacodynamics of brief etomidate infusion in healthy volunteers. *J Clin Pharmacol* 2011; **51:** 482–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Hypnomidate; ***Belg.***: Hypnomidate; ***Braz.***: Hypnomidate; ***China***: Fu Er Li (福尔利); ***Cz.***: Hypnomidate; ***Fr.***: Hypnomidate; ***Ger.***: Hypnomidate; ***Gr.***: Hypnomidate; ***Mex.***: Hypnomidate; ***Neth.***: Hypnomidate; ***Pol.***: Hypnomidate; ***Port.***: Hypnomidato; ***S.Afr.***: Hypnomidate; ***Spain***: Hypnomidate; ***Turk.***: Hypnomidate; ***UK***: Hypnomidate; ***USA***: Amidate.

Pharmacopoeial Preparations
USP 36: Etomidate Injection.

Fospropofol Sodium *(rINNM)*

Fospropofol Disodium (USAN); Fospropofol sódico; Fospropofol Sodique; GPI-15715; Natrii Fospropofolum; PQ-1002; Натрий Фоспропофол.

[2,6-Bis(1-methylethyl)phenoxy]methyl disodium phosphate.

$C_{13}H_{19}Na_2O_5P$=332.2

CAS — 258516-89-1 (fospropofol); 258516-87-9 (fospropofol sodium).

UNII — 30868AY0IF.

Profile

Fospropofol is a prodrug of propofol (p. 1909.3) that is given intravenously as the sodium salt for sedation (p. 1032.2) in adult patients undergoing diagnostic or therapeutic procedures. In those aged under 65 years, and who are healthy or have mild systemic disease, an initial bolus injection of 6.5 mg/kg (minimum: 385 mg, maximum: 577.5 mg) may be followed by supplemental doses of 1.6 mg/kg (minimum: 105 mg, maximum: 140 mg) given no more frequently than every 4 minutes. Patients aged 65 years and older, or those with severe systemic disease, should be given 75% of the usual initial (minimum: 297.5 mg, maximum: 437.5 mg) and supplemental (minimum: 70 mg, maximum: 105 mg) doses.

References.

1. Fechner J, *et al.* Pharmacokinetics and pharmacodynamics of GPI 15715 or fospropofol (Aquavan injection): a water-soluble propofol prodrug. In: Schüttler J, Schwilden H, eds. *Handb Exp Pharmacol: Modern Anesthetics.* Berlin: Springer-Verlag, 2008; **182** (III): 253–66.
2. Levitzky BE, Vargo JJ. Fospropofol disodium injection for the sedation of patients undergoing colonoscopy. *Ther Clin Risk Manag* 2008; **4:** 733–8.
3. Silvestri GA, *et al.* A phase 3, randomized, double-blind study to assess the efficacy and safety of fospropofol disodium injection for moderate sedation in patients undergoing flexible bronchoscopy. *Chest* 2009; **135:** 41–7.
4. Garnock-Jones KP, Scott LJ. Fospropofol. *Drugs* 2010; **70:** 469–77.
5. Gan TJ, *et al.* Safety evaluation of fospropofol for sedation during minor surgical procedures. *J Clin Anesth* 2010; **22:** 260–7.
6. Pergolizzi JV, *et al.* Perspectives on the role of fospropofol in the monitored anesthesia care setting. *Anesthesiol Res Pract* 2011; **2011:** 458920.
7. Bengalorkar GM, *et al.* Fospropofol: clinical pharmacology. *J Anaesthesiol Clin Pharmacol* 2011; **27:** 79–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Lusedra†.

Halothane *(BAN, rINN)*

Alotano; Halotaani; Halotan; Halotán; Halotanas; Halotano; Halothan; Halothanum; Phthorothanum; Галотан.

(RS)-2-Bromo-2-chloro-1,1,1-trifluoroethane.

$CHBrCl.CF_3$=197.4

CAS — 151-67-7.

ATC — N01AB01.

ATC Vet — QN01AB01.

UNII — UQT9G45D1P.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Halothane). A clear, colourless, mobile, dense, non-flammable liquid. Distillation range 49 degrees to 51 degrees. Slightly soluble in water; miscible with dehydrated alcohol and with trichloroethylene. Halothane contains 0.01% w/w of thymol. Store at a temperature not greater than 25 degrees in airtight containers. Protect from light.

USP 36: (Halothane). A colourless, mobile, non-flammable, heavy liquid having a characteristic odour resembling that of chloroform. It contains not less than 0.008% and not more than 0.012% of thymol, by weight, as a stabiliser. It should contain not more than 0.03% of water. Distillation range 49 degrees to 51 degrees.

Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not greater than 40 degrees. Protect from light. Dispense only in the original container.

Incompatibility. In the presence of moisture, halothane reacts with many metals. Rubber and some plastics deteriorate when in contact with halothane vapour or liquid.

Stability. Halothane contains 0.01% w/w of thymol as a stabiliser; some commercial preparations may also contain up to 0.00025% w/w of ammonia. Thymol does not volatilise with halothane and therefore accumulates in the vaporiser. It may give a yellow colour to any remaining liquid; halothane that has discoloured should be discarded.

Uses and Administration

Halothane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 0.64% in the elderly to 1.08% in infants. It is non-flammable and is not explosive when mixed with oxygen at normal atmospheric pressure. It is not irritant to the skin and mucous membranes and does not produce necrosis when spilt on tissues. It suppresses salivary, bronchial, and gastric secretions and dilates the bronchioles. However, its use has diminished due to the risk of hepatotoxicity; in the UK, it is only available on a named-patient basis and in other countries, such as the USA, it has been withdrawn from the market.

Halothane is used for the induction and maintenance of general anaesthesia (p. 1896.1) and is given using a calibrated vaporiser to provide close control over the concentration of inhaled vapour.

Anaesthesia may be induced initially with 0.5% v/v of halothane in oxygen or mixtures of nitrous oxide and oxygen, and increased gradually, according to response, to a concentration of 2 to 4% v/v. It takes up to about 5 minutes to attain surgical anaesthesia and halothane produces little or no excitement in the induction period. The more usual practice is to induce anaesthesia with an intravenous agent. Anaesthesia is maintained with concentrations of 0.5 to 2% v/v depending on the flow rate used; the lower concentration is usually suitable for the elderly.

Adequate muscle relaxation is only achieved with deep anaesthesia so a neuromuscular blocker is given to increase muscular relaxation if necessary.

Administration in children. Halothane has been used for the induction and maintenance of general anaesthesia in children; however, in the UK, it is now mainly used by specialist anaesthetists to manage difficult airways. Doses are as for adults (see Uses and Administration, above).

Status asthmaticus. Inhalational anaesthetics such as halothane, isoflurane, and sevoflurane, have occasionally been used in the management of life-threatening acute severe asthma (p. 1195.2) unresponsive to standard measures.

References.

1. Restrepo RD, *et al.* Halothane, an effective infrequently used drug, in the treatment of pediatric status asthmaticus: a case report. *J Asthma* 2005; **42:** 649–51.
2. Shankar V, *et al.* Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med* 2006; **32:** 927–33.
3. Thomson H, *et al.* Use of the AnaConDa™ anaesthetic delivery system to treat life-threatening asthma. *Anaesthesia* 2007; **62:** 295–6.
4. Burburan SM, *et al.* Anaesthetic management in asthma. *Minerva Anestesiol* 2007; **73:** 357–65.
5. Watanabe K, *et al.* Prolonged sevoflurane inhalation therapy for status asthmaticus in an infant. *Pediatr Anesth* 2008; **18:** 543–5.
6. Vaschetto R, *et al.* Inhalational anesthetics in acute severe asthma. *Curr Drug Targets* 2009; **10:** 826–32.
7. Tobias JD. Inhalational anesthesia: basic pharmacology, end organ effects, and applications in the treatment of status asthmaticus. *J Intensive Care Med* 2009; **24:** 361–71.

Adverse Effects

As with other halogenated anaesthetics, halothane has a depressant action on the cardiovascular system and reduces blood pressure; signs of overdosage are bradycardia and profound hypotension. It is also a respiratory depressant and can cause cardiac arrhythmias; there have been instances of cardiac arrest. The sensitivity of the heart to sympathomimetic amines is increased.

Adverse effects on the liver have limited its use in recent years (see below); these effects range from liver dysfunction to fatal hepatitis and necrosis and are more frequent following repeated use.

Halothane can produce nausea, vomiting, and shivering. Malignant hyperthermia has been reported.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Review.

1. Kharasch ED. Adverse drug reactions with halogenated anesthetics. *Clin Pharmacol Ther* 2008; **84:** 158–62.

Effects on the cardiovascular system. The incidence of cardiac arrhythmias is higher with halothane than with enflurane or isoflurane; also the arrhythmogenic threshold with injected adrenaline is lower with halothane than isoflurane or enflurane.

Arrhythmias are considered to be very common in children anaesthetised with halothane and in the UK it is recommended that it should not be used for dental procedures outside hospital in those under 18 years old.

A review[1] of the mechanisms involved suggested that at physiologically relevant concentrations, halogenated anaesthetics interact mainly with the repolarising potassium channels hERG and I_{Ks}, as well as with calcium and sodium channels at slightly higher concentrations. Inhibition of these produces proarrhythmic changes such as slowing of repolarisation and conduction. Other mechanisms, including alteration of catecholamine-induced signal transduction and possibly effects on neuronal pathways may also contribute to arrhythmogenesis.

1. Himmel HM. Mechanisms involved in cardiac sensitization by volatile anesthetics: general applicability to halogenated hydrocarbons? *Crit Rev Toxicol* 2008; **38:** 773–803.

Effects on the kidneys. Renal failure has been reported after halothane anaesthesia,[1,2] sometimes with concurrent liver failure.[2]

1. Cotton JR, *et al.* Acute renal failure following halothane anesthesia. *Arch Pathol Lab Med* 1976; **100:** 628–9.
2. Gelman ML, Lichtenstein NS. Halothane-induced nephrotoxicity. *Urology* 1981; **17:** 323–7.

Effects on the liver. Liver damage has been recognised as an adverse effect of halothane for many years[1-3] and continues to be reported.[4] It may be severe, and associated with a high mortality.

Two types of hepatotoxicity are recognised; in **type I** there is a minor disturbance in liver function shown by increases in liver enzyme values; this may occur in up to 30% of patients given halothane,[5] or more if activity is measured by glutathione-S-transferase rather than serum aminotransferase.[6] Subsequent re-exposure to halothane is not necessarily associated with liver damage.[2,7]

Type II hepatotoxicity, which is rarer, involves massive liver cell necrosis; reported incidences[2] range from 1 in 2500 to 1 in 36 000. Type II liver toxicity is characterised by several clinical features: non-specific gastrointestinal upset, delayed pyrexia, jaundice, eosinophilia, serum autoantibodies, rash, and arthralgia.[1,3] Biochemical tests of liver function show changes typical of hepatocellular damage; histological features are typified by centrilobular necrosis.[3] Several **risk factors** for development of serious toxicity have become apparent;[1-3] they include repeated exposure, previous adverse reactions to halothane (jaundice, pyrexia), female gender, obesity, middle age, genetic predisposition, enzyme induction, and a history of drug allergy.

The **causes** of halothane hepatotoxicity have been debated. Type I reactions may result from toxic products of halothane metabolism, possibly influenced by genetic factors or from an imbalance between hepatic oxygen supply and demand. Changes in cellular calcium homoeostasis may also be involved. Type II reactions are most likely immune-mediated.[2,3] It has been suggested[5] that metabolism of halothane produces a reactive metabolite which binds covalently to proteins in the endoplasmic reticulum of hepatocytes. In susceptible patients it is believed that these metabolite-modified proteins provoke an immune response which is responsible for the liver damage. Findings[8,9] have implicated the cytochrome P450 isoenzyme CYP2E1 as having a major role in the metabolism of halothane and patients with high levels of this isoenzyme may be predisposed to developing immune-medicated liver damage after halothane exposure.

The UK CSM,[10] after receiving 84 further reports of hepatotoxicity between 1978 and 1985, issued the following **guidelines** on **precautions** to be taken before using halothane:

- a careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane
- repeated exposure to halothane within a period of at least 3 months should be avoided unless there are overriding clinical circumstances. An opinion has been expressed that the 3-month interval between exposures would be unlikely to prevent hepatotoxicity[2]
- a history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contra-indication to its future use in that patient

These guidelines were reiterated in 1997 after the CSM was notified of a further 15 cases of acute liver failure all requiring transplantation.[11]

The problem of patients sensitised to halothane who require **subsequent anaesthesia** with a volatile anaesthetic has been discussed.[5] Although the incidence of hepatotoxicity produced by *enflurane* appears to be less than with halothane, it is of a similar nature and there have been reports of several patients who apparently had cross-sensitivity to both. Hepatotoxicity with *isoflurane* appears to be rare and it was suggested that for the majority of patients sensitised to halothane, isoflurane would be likely to be free

from hepatotoxic effects. However, there has been a report[12] of a patient who had had two previous exposures to isoflurane and subsequently developed liver function abnormalities after receiving halothane. Hepatotoxicity with *desflurane* (see p. 1899.2) might also be associated with sensitisation to halothane or isoflurane.

1. Rosenak D, *et al*. Halothane and liver damage. *Postgrad Med J* 1989; **65:** 129–35.
2. Neuberger JM. Halothane and hepatitis: incidence, predisposing factors and exposure guidelines. *Drug Safety* 1990; **5:** 28–38.
3. Ray DC, Drummond GB. Halothane hepatitis. *Br J Anaesth* 1991; **67:** 84–99.
4. Eghtesadi-Araghi P, *et al*. Halothane hepatitis in Iran: a review of 59 cases. *World J Gastroenterol* 2008; **14:** 5322–6.
5. Kenna JG, Neuberger JM. Immunopathogenesis and treatment of halothane hepatitis. *Clin Immunother* 1995; **3:** 108–24.
6. Allan LG, *et al*. Hepatic glutathione S-transferase release after halothane anaesthesia: open randomised comparison with isoflurane. *Lancet* 1987; **i:** 771–4.
7. Neuberger J, Williams R. Halothane anaesthesia and liver damage. *BMJ* 1984; **289:** 1136–9.
8. Kharasch ED, *et al*. Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. *Lancet* 1996; **347:** 1367–71.
9. Kenna JC, *et al*. Formation of the $C[F]_3CO$-protein antigens implicated in the pathogenesis of halothane hepatitis is catalyzed in human liver microsomes in vitro by CYP 2E1. *Br J Clin Pharmacol* 1997; **43:** 209.
10. CSM. Halothane hepatotoxicity. *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024425&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
11. CSM/MCA. Safety issues in anaesthesia: reminder: hepatotoxicity with halothane. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
12. Slayter KL, *et al*. Halothane hepatitis in a renal transplant patient previously exposed to isoflurane. *Ann Pharmacother* 1993; **27:** 101.

Precautions

The risk of halothane hepatitis led the UK CSM to issue guidelines on its use (see Effects on the Liver, under Adverse Effects, p. 1902.3). It is also recommended that patients be informed of any reactions and that this be done in addition to the updating of the patients' medical records.

It is recommended in the UK that halothane should not be used for dental procedures outside hospital in patients under 18 years old.

Halothane reduces uterine muscle tone during pregnancy and generally its use is not recommended in obstetrics because of the increased risk of postpartum haemorrhage.

Premedication with atropine has been recommended to reduce vagal tone and to prevent bradycardia and severe hypotension.

Measures may need to be taken to counteract any increase in CSF pressure or in cerebral blood flow. Halothane should be used with caution in patients with phaeochromocytoma.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with halothane. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. A brief review[1] of abuse of volatile anaesthetics found that of 14 patients who had ingested or sniffed halothane 10 had died. Another patient who had injected halothane intravenously also died. There has also been another report[2] of fatalities resulting from acute pulmonary oedema after intravenous injection of halothane.

1. Yamashita M, *et al*. Illicit use of modern volatile anaesthetics. *Can Anaesth Soc J* 1984; **31:** 76–9.
2. Berman P, Tattersal M. Self-poisoning with intravenous halothane. *Lancet* 1982; **i:** 340.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving halothane, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

Trace amounts of halothane have been detected in the breast milk of an anaesthetist exposed to environmental halothane in the operating theatre.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)
2. Coté CJ, *et al*. Trace concentrations of halothane in human breast milk. *Br J Anaesth* 1976; **48:** 541–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies halothane as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Adrenaline and most other sympathomimetics, and theophylline should be avoided during halothane anaesthesia since they can produce cardiac arrhythmias; the risk of arrhythmias is also increased if halothane is used in patients receiving dopaminergics. The effects of competitive neuromuscular blockers such as atracurium, and of ganglion blockers such as trimetaphan are enhanced by halothane and if required they should be given in reduced dosage. Morphine increases the depressant effects of halothane on respiration. Chlorpromazine also enhances the respiratory depressant effect of halothane. The effects of both ergometrine and oxytocin on the parturient uterus are diminished by halothane.

See also Interactions of General Anaesthetics, p. 1897.3.

Antiepileptics. For a case of *phenytoin* intoxication associated with halothane anaesthesia, see p. 542.2.

Benzodiazepines. *Midazolam* has been reported to potentiate the anaesthetic action of halothane.[1]

1. Inagaki Y, *et al*. Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–17.

General anaesthetics. For a report that halothane increases serum concentrations of *propofol*, see p. 1912.2.

Neuromuscular blockers. For the potentiation of the neuromuscular blockade of neuromuscular blockers such as *atracurium* by halothane, see p. 2032.3. For increased toxicity during halothane anaesthesia, see *suxamethonium* p. 2039.3.

Trichloroethane. Evidence of chronic cardiotoxicity was seen in 2 patients after repeated exposure to trichloroethane.[1] In both cases there was circumstantial evidence of a deterioration after routine anaesthetic use of halothane.

1. McLeod AA, *et al*. Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *BMJ* 1987; **294:** 727–9.

Xanthines. For references to increased cardiotoxicity when patients taking *theophylline* were anaesthetised with halothane, see p. 1236.2.

Pharmacokinetics

Halothane is absorbed on inhalation. It has a relatively low solubility in blood and is more soluble in the neutral fats of adipose tissue than in the phospholipids of brain cells. Up to 80% of inhaled halothane is excreted unchanged through the lungs. Up to 20% is metabolised by the liver by oxidative and, under hypoxic conditions, reductive pathways. Urinary metabolites include trifluoroacetic acid and bromide and chloride salts (oxidative pathway) and fluoride salts (reductive pathway). Halothane diffuses across the placenta and has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ineltano; ***Austral.***: Fluothane†; ***Braz.***: Fluothane; ***Cz.***: Narcotan†; ***Gr.***: Fluothane; ***Hung.***: Narcotan†; ***India***: Fluothane; Hypnothane; ***Indon.***: Fluothane†; ***NZ***: Fluothane; ***Pol.***: Narcotan†; ***Rus.***: Narcotan (Наркотан); ***Turk.***: Fluothane.

Multi-ingredient Preparations. ***Braz.***: Tanohalo.

Isoflurane *(BAN, USAN, rINN)*

Compound 469; Isofluraani; Isofluran; Isoflurano; Isofluranum; Izofluran; Izoflurán; Izofluranas; Изофлуран.

1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane.

$C_3H_2ClF_5O$=184.5

CAS — 26675-46-7.

ATC — N01AB06.

ATC Vet — QN01AB06.

UNII — CYS9AKD70P.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Isoflurane). A clear, colourless, mobile, heavy liquid. B.p. about 48 degrees. It is non-flammable. Practically insoluble in water; miscible with dehydrated alcohol and with trichloroethylene. Store in airtight containers. Protect from light.

USP 36: (Isoflurane). A clear, colourless, volatile liquid having a slight odour. B.p. about 49 degrees. Insoluble in water; miscible with common organic solvents and with fats and oils. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Isoflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of enflurane and has anaesthetic actions similar to those of halothane (p. 1902.2). Isoflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 1.05% in the elderly to 1.87% in infants. It is used in the induction and maintenance of general anaesthesia (p. 1896.1) although induction is more often carried out using an intravenous anaesthetic. Isoflurane is also used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures.

Isoflurane is given using a calibrated vaporiser. If it is used for induction then it is given with oxygen or oxygen and nitrous oxide mixtures and induction should start with an isoflurane concentration of 0.5% v/v increased to 1.5 to 3% v/v which generally produces surgical anaesthesia within 10 minutes. Its pungency may limit the rate of induction. Anaesthesia may be maintained with a concentration of 1 to 2.5% v/v with oxygen and nitrous oxide mixtures; 1.5 to 3.5% v/v may be required if used only with oxygen. Isoflurane 0.5 to 0.75% v/v with oxygen and nitrous oxide mixtures is suitable to maintain anaesthesia for caesarean section. Although isoflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Recovery is rapid.

Administration in children. Isoflurane is used for the induction and maintenance of general anaesthesia in children; doses are as for adults (see Uses and Administration, above).

Anaesthesia. *CAESAREAN SECTION.* Isoflurane 0.8% v/v has been found to be a suitable supplement to nitrous oxide-oxygen anaesthesia for patients undergoing caesarean section.[1] It has been suggested[2] that an overpressure technique might be of use to further reduce awareness in such patients. Giving isoflurane at a concentration of 2% v/v for 5 minutes followed by concentrations of 1.5% v/v for the next 5 minutes and 0.8% v/v thereafter produced higher arterial concentrations of isoflurane in patients undergoing caesarean section than when it was given at a concentration of 1% v/v throughout.[2]

1. Dwyer R, *et al*. Uptake of halothane and isoflurane by mother and baby during Caesarean section. *Br J Anaesth* 1995; **74:** 379–83.
2. McCrirrick A, *et al*. Overpressure isoflurane at Caesarean section: a study of arterial isoflurane concentrations. *Br J Anaesth* 1994; **72:** 122–4.

Pain. Isoflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures but studies[1,2] have been unable to confirm that it had an analgesic effect at subanaesthetic concentrations. The use of isoflurane 0.2 or 0.25% v/v in a mixture of nitrous oxide 50% v/v and oxygen 50% v/v has been studied.[3,4]

1. Tomi K, *et al*. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70:** 684–6.
2. Roth D, *et al*. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials. *Br J Anaesth* 1996; **76:** 38–42.
3. Wee MYK, *et al*. Isoflurane in labour. *Anaesthesia* 1993; **48:** 369–72.
4. Bryden FM, *et al*. Isoflurane for removal of chest drains after cardiac surgery. *Br J Anaesth* 1994; **73:** 712P–713P.

Sedation. *INTENSIVE CARE.* The various drugs used to provide sedation in intensive care are discussed on p. 1033.1. Isoflurane is not usually considered for such a purpose but in a comparative 24-hour study[1] in 60 patients requiring mechanical ventilation, isoflurane 0.1 to 0.6% v/v in an air-oxygen mixture produced satisfactory sedation for a greater proportion of time than did the continuous infusion of midazolam 10 to 200 micrograms/kg per hour. Patients given isoflurane also recovered more rapidly. Isoflurane has also been used successfully for sedation over 5 days in a 3-year-old infant who required ventilation for pneumonia, a complication of the child's myasthenia gravis.[2] However, there has been some concern over high plasma fluoride concentrations after prolonged use of isoflurane (see under Metabolism in Pharmacokinetics, p. 1904.3).

1. Kong KL, *et al*. Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* 1989; **298:** 1277–80.
2. McBeth C, Watkins TGL. Isoflurane for sedation in a case of congenital myasthenia gravis. *Br J Anaesth* 1996; **77:** 672–4.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used. Despite rare reports of seizures associated with the use of isoflurane in anaesthetic procedures (see Effects on the Nervous System, under Adverse Effects and Precautions, p. 1904.2) it has been used successfully,[1-3] typically

in concentrations of 0.5 to 1% v/v, to control refractory convulsive status epilepticus. Although some[4] consider that isoflurane-induced coma may be more easy to control than barbiturate-induced coma, the use of isoflurane may be limited by the need for special anaesthetic equipment and continuous EEG monitoring. Magnetic resonance imaging (MRI) signal abnormalities have been reported[5] with prolonged (up to 85 days) use of isoflurane in high concentrations (up to 2.5% v/v) for refractory status epilepticus; the authors suggested that these MRI findings may be indicative of neurotoxicity.

1. Meeke RI, *et al*. Isoflurane for the management of status epilepticus. *DICP Ann Pharmacother* 1989; **23:** 579–81.
2. Hilz MJ, *et al*. Isoflurane anaesthesia in the treatment of convulsive status epilepticus. *J Neurol* 1992; **239:** 135–7.
3. Mirsattari SM, *et al*. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 2004; **61:** 1254–9.
4. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
5. Fugate JE, *et al*. Prolonged high-dose isoflurane for refractory status epilepticus: is it safe? *Anesth Analg* 2010; **111:** 1520–4.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, arrhythmias, and malignant hyperthermia have been reported; patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with isoflurane. Isoflurane differs from halothane and enflurane in that it produces less cardiac depression than either drug and heart rate may be increased. Also isoflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane and enflurane. The incidence of cardiac arrhythmias is lower with isoflurane than with halothane. Shivering, nausea, and vomiting have been reported in the postoperative period.

Induction with isoflurane is not as smooth as with halothane and this may be connected with its pungency; breath holding, coughing, and laryngospasm may occur. It has been reported to increase the cerebrospinal pressure and should be used with caution in patients with raised intracranial pressure. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period. Isoflurane relaxes the uterine muscle; increased blood loss may occur after curettage or termination of pregnancy.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as isoflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p. 1896.3 and p. 1897.3.

A comparison[1] of isoflurane and halothane for outpatient dental anaesthesia in children considered that isoflurane would produce fewer arrhythmias than halothane, but that the ease of induction and the quality of anaesthesia was inferior to that with halothane. Others[2] also found a higher incidence of coughing, salivation, and laryngospasm with isoflurane than halothane, but felt that it could be used as an alternative.

Further information on the adverse effects profile of isoflurane can be obtained from the report of and commentaries on an extensive multicentre study of patients undergoing anaesthesia with this agent.[3,4]

1. Cattermole RW, *et al*. Isoflurane and halothane for outpatient dental anaesthesia in children. *Br J Anaesth* 1986; **58:** 385–9.
2. McAteer PM, *et al*. Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. *Br J Anaesth* 1986; **58:** 390–3.
3. Forrest JB, *et al*. A multi-centre clinical evaluation of isoflurane. *Can Anaesth Soc J* 1982; **29** (suppl): S1–S69.
4. Levy WJ. Clinical anaesthesia with isoflurane: a review of the multicentre study. *Br J Anaesth* 1984; **56:** 101S–112S.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. Isoflurane is considered to produce less cardiovascular depression than halothane. However, the results of a study[1] suggest that while this may be true for young patients, in elderly patients isoflurane appears to have a cardiac depressant effect similar to that of halothane.

1. McKinney MS, *et al*. Cardiovascular effects of isoflurane and halothane in young and elderly adult patients. *Br J Anaesth* 1993; **71:** 696–701.

CEREBRAL BLOOD FLOW. Autoregulation of cerebral blood flow appears to be impaired at higher concentrations of isoflurane. A study[1] in healthy subjects found that increasing isoflurane anaesthesia from a concentration of 1 to 2 minimum alveolar concentration (MAC) increased cerebral blood flow and reduced cerebral oxygen metabolism.

1. Olsen KS, *et al*. Effect of 1 or 2 MAC isoflurane with or without ketanserin on cerebral blood flow autoregulation in man. *Br J Anaesth* 1994; **72:** 66–71.

CORONARY CIRCULATION. Halothane, enflurane, and isoflurane decrease coronary perfusion pressure, coronary blood flow, ventricular function, and myocardial oxygen demand. Halothane and enflurane have a variable effect on coronary vascular resistance, but isoflurane dilates coronary vessels.[1] There has been concern over the potential of isoflurane to produce coronary steal and whether this effect is detrimental in patients with ischaemic heart disease.[2] However, despite conflicting results of individual studies[3-6] an early review[7] concluded that isoflurane could be used safely even in high-risk patients with coronary artery disease provided that blood pressure and heart rate were maintained close to baseline concentrations. A subsequent review[8] considered that more recent evidence supported the use of isoflurane as the anaesthetic agent of choice in patients with coronary heart disease.

1. Quail AW. Modern inhalational anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; **150:** 95–102.
2. Stoelting RK. Anesthesiology. *J AMA* 1991; **265:** 3103–5.
3. Buffington CW, *et al*. The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: an analysis of the coronary artery surgery study registry. *Anesthesiology* 1988; **69:** 721–7.
4. Inoue K, *et al*. Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? A clinical study of 1178 patients. *Anesth Analg* 1990; **71:** 469–74.
5. Slogoff S, *et al*. Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. *Anesth Analg* 1991; **72:** 22–7.
6. Stühmeier KD, *et al*. Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery. *Br J Anaesth* 1992; **69:** 602–6.
7. Hogue CW, *et al*. Anesthetic-induced myocardial ischemia: the isoflurane-coronary steal controversy. *Coron Artery Dis* 1993; **4:** 413–19.
8. Agnew NM, *et al*. Isoflurane and coronary heart disease. *Anaesthesia* 2002; **57:** 338–47.

Effects on the kidneys. See under Metabolism in Pharmacokinetics, below.

Effects on the liver. Of 45 cases of isoflurane-associated hepatotoxicity reported to the FDA between 1981 and 1984 there was some other cause for the liver damage in 29. While isoflurane might have been one of the causes of the damage in the other 16 cases, there was not a reasonable likelihood of an association between isoflurane and postoperative liver impairment.[1] Subsequent rare cases of hepatotoxicity,[2-8] sometimes fatal,[2,5,7,8] have suggested that isoflurane may induce hepatitis, though much less frequently than halothane, and that there may be cross-sensitisation with other halogenated anaesthetics.

See also under the Adverse Effects of Halothane, p. 1902.3.

1. Stoelting RK, *et al*. Hepatic dysfunction after isoflurane anesthesia. *Anesth Analg* 1987; **66:** 147–53.
2. Carrigan TW, Straughen WJ. A report of hepatic necrosis and death following isoflurane anesthesia. *Anesthesiology* 1987; **67:** 581–3.
3. Sinha A, *et al*. Isoflurane hepatotoxicity: a case report and review of the literature. *Am J Gastroenterol* 1996; **91:** 2406–9.
4. Hasan F. Isoflurane hepatotoxicity in a patient with a previous history of halothane-induced hepatitis. *Hepatogastroenterology* 1998; **45:** 518–22.
5. Turner GB, *et al*. Fatal hepatotoxicity after re-exposure to isoflurane: a case report and review of the literature. *Eur J Gastroenterol Hepatol* 2000; **12:** 955–9.
6. Malnick SDH, *et al*. Acute cholestatic hepatitis after exposure to isoflurane. *Ann Pharmacother* 2002; **36:** 261–3.
7. Ihtiyar E, *et al*. Fatal isoflurane hepatotoxicity without re-exposure. *Indian J Gastroenterol* 2006; **25:** 41–2.
8. Kusuma HR, *et al*. Fulminant hepatic failure after repeated exposure to isoflurane. *Indian J Anaesth* 2011; **55:** 290–2.

Effects on the nervous system. Seizures associated with induction of anaesthesia with isoflurane have been reported in patients without known neurological abnormalities and not undergoing neurosurgery.[1,2] However, data from a retrospective analysis of patients undergoing intracranial surgery indicated that when convulsions occurred postoperatively in these conditions, it was the neurosurgical procedures rather than the anaesthetics that were responsible.[3]

See also Status Epilepticus, under Uses and Administration, p. 1903.3.

1. Poulton TJ, Ellingson RJ. Seizure associated with induction of anesthesia with isoflurane. *Anesthesiology* 1984; **61:** 471–6.
2. Hymes JA. Seizure activity during isoflurane anesthesia. *Anesth Analg* 1985; **64:** 367–8.
3. Christys AR, *et al*. Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia. *Br J Anaesth* 1989; **62:** 624–7.

Effects on the respiratory tract. A study[1] conducted mainly in adults found that humidification of anaesthetic mixtures containing isoflurane could reduce respiratory complications such as coughing, laryngospasm, and breath holding that were usually associated with the use of isoflurane for induction. However, a similar study[2] in children failed to confirm these findings.

For a report of occupational asthma associated with exposure to isoflurane and sevoflurane, see Occupational Exposure, under Precautions of Sevoflurane, p. 1913.3.

1. van Heerden PV, *et al*. Effect of humidification on inhalation induction with isoflurane. *Br J Anaesth* 1990; **64:** 235–7.
2. McAuliffe GL, *et al*. Effect of humidification on inhalation induction with isoflurane in children. *Br J Anaesth* 1994; **73:** 587–9.

Effects on the skin. There have been rare reports of contact dermatitis to isoflurane in anaesthetists.[1,2]

1. Caraffini S, *et al*. Isoflurane: an uncommon cause of occupational airborne contact dermatitis. *Contact Dermatitis* 1998; **38:** 286.
2. Muncaster A, *et al*. Allergic contact dermatitis to isoflurane. *Br J Dermatol* 1999; **141:** (suppl 55): 96–7.

Hypersensitivity. For a report of hypersensitivity reactions, including asthma, angioedema, and dermatitis, associated with occupational exposure to isoflurane and sevoflurane, see Occupational Exposure, under Precautions of Sevoflurane, p. 1913.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isoflurane as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by isoflurane (see p. 2032.3). Care is advised if adrenaline and other sympathomimetics are given during isoflurane anaesthesia.

See also Interactions of General Anaesthetics, p. 1897.3.

Antineoplastics. Prolongation of the QT_c interval to above 440 milliseconds has been seen during anaesthesia with isoflurane 0.5% v/v in women who had received *anthracycline*-based (doxorubicin or epirubicin) chemotherapy for breast cancer.[1]

1. Owczuk R, *et al*. Is prolongation of the QTc interval during isoflurane anaesthesia more prominent in women pretreated with anthracyclines for breast cancer? *Br J Anaesth* 2004; **92:** 658–61.

General anaesthetics. For a report that isoflurane increases serum concentrations of *propofol*, see p. 1912.2.

Pharmacokinetics

Isoflurane is absorbed on inhalation. The blood/gas partition coefficient is lower than that of enflurane or halothane. It is mostly excreted unchanged through the lungs. About 0.2% of inhaled isoflurane is metabolised, mainly to inorganic fluoride.

Metabolism. In 26 patients sedated with isoflurane for 24 hours, plasma fluoride ion concentration increased from a mean of 4.03 nanomol/mL to 13.57 nanomol/mL in 12 hours after stopping sedation.[1] These fluoride concentrations were considered to be too low to cause clinical renal dysfunction. In 30 patients sedated with isoflurane for up to 127 hours (mean duration was 36 hours), mean plasma fluoride ion concentration increased[2] to 20.01 nanomol/mL during sedation and continued rising for 16 hours after stopping isoflurane to a maximum mean concentration of 25.34 nanomol/mL; thereafter, levels gradually declined to normal values by the fifth day. Despite the increased plasma fluoride ion concentrations, no biochemical or clinical evidence of deterioration in renal function was found. Giving isoflurane for 34 days to a patient with tetanus who required sedation to facilitate mechanical ventilation resulted[3] in sustained fluoride ion concentrations of 50 nanomol/mL and a peak concentration of 87 nanomol/mL. Although such concentrations are considered to be potentially nephrotoxic no clinical effect on renal function was found.

1. Kong KL, *et al*. Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects. *Br J Anaesth* 1990; **64:** 159–62.
2. Spencer EM, *et al*. Plasma inorganic fluoride concentrations during and after prolonged (>24h) isoflurane sedation: effect on renal function. *Anesth Analg* 1991; **73:** 731–7.
3. Stevens JJWM, *et al*. Prolonged use of isoflurane in a patient with tetanus. *Br J Anaesth* 1993; **70:** 107–109.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Forane; Zuflax; ***Austral.***: AErrane; Forthane†; ***Austria***: Forane; ***Belg.***: Forene; ***Braz.***: For-

ane; Isoforine; Isoran; ***Canad.***: AErrane; Forane; ***Chile***: Forene; ***China***: AErrane (艾思美); Forane (活宁); Ning Fen (宁芬); Terrell (宝龄托利儿); Yi Mei Ning (怡美宁); ***Cz.***: AErrane; Forane; ***Denm.***: Forene†; ***Fin.***: Forene†; ***Fr.***: AErrane; Forene; ***Ger.***: Forene; ***Gr.***: Forenium; ***Hong Kong***: AErrane†; Forane†; ***Hung.***: AErrane; Forane; ***India***: AErrane; Forane; Isorane; ***Indon.***: AErrane; Forane†; Terrell; ***Irl.***: AErrane; Forane; ***Israel***: AErrane; Forane; ***Ital.***: AErrane; Forane; ***Malaysia***: Forane; ***Mex.***: Forane; Sofloran†; ***Neth.***: AErrane†; Forene†; ***Norw.***: Forene; ***NZ***: AErrane; Forane†; Forthane; ***Philipp.***: AErrane; Florane; Forane; ***Pol.***: AErrane; Forane; ***Port.***: Forene; ***Rus.***: AErran (Аерран); Forane (Форан); ***S.Afr.***: AErrane†; Forane; Isofor; ***Singapore***: AErrane; Forane; ***Spain***: AErrane; Forane; ***Swed.***: Forene; ***Switz.***: Forene; ***Thai.***: AErrane; Forane; ***Turk.***: AErrane; Forane; Isofludem; ***UK***: AErrane; Forane; ***USA***: Forane; Terrell; ***Venez.***: Forene.

Ketamine Hydrochloride

(BANM, USAN, rINNM)

CI-581; CL-369; CN-52372-2; Hidrocloruro de ketamina; Ketamiinihydrokloridi; Ketamin Hidroklorür; Ketamina, hidrocloruro de; Kétamine, chlorhydrate de; Ketaminhidroklorid; Ketaminhydrochlorid; Ketamin-hydrochlorid; Ketaminhydroklorid; Ketamini Hydrochloridum; Ketamino hidrochloridas; Ketaminy chlorowodorek; Кетамина Гидрохлорид; Кетамин Хидрохлорид.

(±)-2-(2-Chlorophenyl)-2-methylaminocyclohexanone hydrochloride.

$C_{13}H_{16}ClNO,HCl$=274.2

CAS — 6740-88-1 (ketamine); 1867-66-9 (ketamine hydrochloride).

ATC — N01AX03.

ATC Vet — QN01AX03.

UNII — O18YUO0I83.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of ketamine:

Animal trank; Animal tranquilizer; Bump; Cat tranquilizer; Cat valium; Elephant tranquilizer; Green; Honey oil; Horse tranquilizer; Jet; Jet fuel; K; "K"; K wire; Kay Jay; K-blast; Keets; Keezy; Keller; Kellys day; Kenny; Ket; Keta; Ketaset; KFC; Kit kat; Kit-Kat; Kitty; KKK; Klarko K Kat; Klarky Kat; Kustard; Lady K; Naughty horsey; Old Man; Property of Sir John; Purple; Regretamine; Special K; Special "K"; Special la coke; Super acid; Super C; Super K; Tranquilizer; Triple K; Vetamine; Vitamin K; Wonky.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ketamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.1. Protect from light.

USP 36: (Ketamine Hydrochloride). A white crystalline powder having a slight characteristic odour. Soluble 1 in 4 of water, 1 in 14 of alcohol, 1 in 60 of dehydrated alcohol and of chloroform, and 1 in 6 of methyl alcohol; practically insoluble in ether. pH of a 10% solution in water is between 3.5 and 4.1. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Ketamine hydrochloride is incompatible with soluble barbiturates. US licensed product information recommends that when use of diazepam and ketamine is required they should be given separately and not mixed in the same giving equipment.

Esketamine Hydrochloride *(BANM, rINNM)*

Esketamiinihydrokloridi; Esketamina, hidrocloruro de; Eskétamine, Chlorhydrate d'; Eskétamine, chlorhydrate de; Esketaminhydrochlorid; Esketamin-hydrochlorid; Esketaminhydroklorid; Esketamini hydrochloridum; Esketamino hidrochloridas; Hidrocloruro de esketamina; *S*-Ketamine Hydrochloride; Эскетамина Гидрохлорид.

CAS — 33643-46-8 (esketamine).

ATC — N01AX14.

ATC Vet — QN01AX14.

UNII — L8P1H35P2Z.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Esketamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methylalcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.5. Protect from light.

Uses and Administration

Ketamine is an anaesthetic given by intravenous injection, intravenous infusion, or intramuscular injection. It produces dissociative anaesthesia characterised by a trance-like state, amnesia, and marked analgesia which may persist into the recovery period. There is often an increase in muscle tone and the patient's eyes may remain open for all or part of the period of anaesthesia. Ketamine is used in general anaesthesia for diagnostic or short surgical operations that do not require skeletal muscle relaxation, for the induction of anaesthesia to be maintained with other drugs, and as a supplementary anaesthetic (see p. 1896.1). It also has good analgesic properties in subanaesthetic doses. It is considered to be of particular value in children requiring frequent repeated anaesthesia. Recovery is relatively slow.

Ketamine is given as the hydrochloride but doses are expressed in terms of the equivalent amount of base; ketamine hydrochloride 1.15 mg is equivalent to about 1 mg of ketamine. The following doses have been used in adults and children:

- For induction, the dose given by *intravenous injection* may range from the equivalent of 1 to 4.5 mg/kg of ketamine; a dose of 2 mg/kg given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds of the end of the injection and lasting for 5 to 10 minutes.
- The initial *intramuscular* dose may range from 6.5 to 13 mg/kg; an intramuscular dose of 10 mg/kg usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes. For diagnostic or other procedures not involving intense pain an initial intramuscular dose of 4 mg/kg has been used.
- Additional intravenous or intramuscular doses, ranging from half to the full induction dose, may be given for maintenance.
- For induction by *intravenous infusion* a total dose of 0.5 to 2 mg/kg is usually given at an appropriate infusion rate. Maintenance is achieved with 10 to 45 micrograms/kg per minute, the infusion rate being adjusted according to response.

Use should be preceded by atropine or another suitable antimuscarinic. Diazepam or another benzodiazepine may be given before surgery or as an adjunct to ketamine to reduce the incidence of emergence reactions.

The *S*-isomer, esketamine, is also given for similar uses in anaesthesia.

Reviews.

1. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996; **77:** 441–4.
2. Wolff K, Winstock AR. Ketamine: from medicine to misuse. *CNS Drugs* 2006; **20:** 199–218.
3. Sinner B, Graf BM. Ketamine. In: Schüttler J, Schwilden H, eds. *Handb Exp Pharmacol: Modern Anesthetics.* Berlin: Springer-Verlag, 2008; **182** (III): 313–33.
4. Aroni F, *et al*. Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. *J Clin Pharmacol* 2009; **49:** 957–64.
5. Persson J. Wherefore ketamine? *Curr Opin Anaesthesiol* 2010; **23:** 455–60.

Administration. Although ketamine hydrochloride is usually given intravenously or intramuscularly, oral[1,2] and rectal[3] dosage has been used successfully in children. Intranasal use of ketamine with midazolam in a neonate requiring anaesthesia has also been reported.[4] Unfortunately the onset of sedation with these three routes is too slow for emergency procedures and therefore a jet-injector of ketamine was developed[5] to provide non-traumatic, painless, and rapid anaesthesia in children. Intranasal and transdermal use may be useful in the management of pain (below); oral, rectal, and subcutaneous routes have also been tried.[6]

1. Tobias JD, *et al*. Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* 1992; **90:** 537–41.
2. Gutstein HB, *et al*. Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; **76:** 28–33.
3. Lökken P, *et al*. Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res* 1994; **102:** 274–80.
4. Louon A, *et al*. Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; **77:** 529–30.
5. Zsigmond EK, *et al*. A new route, jet-injection for anesthetic induction in children–ketamine dose-range finding studies. *Int J Clin Pharmacol Ther* 1996; **34:** 84–8.
6. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; **16:** 27–35.

Administration in children. Ketamine is used in general anaesthesia in children; for details of doses, see Uses and Administration, above.

Nonketotic hyperglycinaemia. Ketamine was tried with strychnine in a neonate with severe nonketotic hyperglycinaemia (p. 2623.2) and resulted in neurological improvement, although motor development remained unsatisfactory.[1] It was thought that ketamine might act by blocking NMDA receptors, which are activated in the CNS by glycine.

1. Tegtmeyer-Metadorf H, *et al*. Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154:** 649–53.

Pain. For a discussion of pain and its management, see p. 4.1. Ketamine is used for its analgesic action in neuropathic or other pain unresponsive to conventional analgesics. (For mention of its use for outpatient procedures in children, see p. 5.2.) Reviews have found the evidence for such use to be limited,[1-4] and have also differed on its value for postoperative pain.[5-7] Some have suggested[1,3,4] that ketamine is a reasonable third-line option for pain where standard analgesics have failed; however, such use may be limited by its adverse effects. Subcutaneous, intramuscular, intravenous, epidural, intrathecal, intranasal, transdermal, rectal, and oral routes have all been tried.[1,8] Ketamine has also been used topically.[9]

1. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 2003; **97:** 1730–9.
2. Bell RF, *et al*. Ketamine as an adjuvant to opioids for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/06/05).
3. Ben-AriA, *et al*. Chronic administration of ketamine for analgesia. *J Pain Palliat Care Pharmacother* 2007; **21:** 7–14.
4. Blonk MI, *et al*. Use of oral ketamine in chronic pain management: a review. *Eur J Pain* 2010; **14:** 466–72.
5. Subramaniam K, *et al*. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; **99:** 482–95.
6. Elia N, Tramèr MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain* 2005; **113:** 61–70.
7. Bell RF, *et al*. Perioperative ketamine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
8. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; **16:** 27–35.
9. Finch PM, *et al*. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain* 2009; **146:** 18–25.

Psychiatric disorders. A small preliminary randomised placebo-controlled study reported[1] rapid reductions in severity of depression after an intravenous infusion of ketamine hydrochloride 500 micrograms/kg was given to patients with treatment-resistant depression (see Depression, p. 398.1); the effect began within 2 hours, and was sustained for up to 1 week after infusion. Single infusions of the same dose have also improved suicidal ideation in those with treatment-resistant depression[2] and reduced severity of depression as an adjunct in those with treatment-resistant bipolar depression (see Bipolar Disorder, p. 397.2).[3] The role of ketamine, an NMDA antagonist, and the glutamatergic system in the treatment of mood disorders has been reviewed.[4,5]

1. Zarate CA, *et al*. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; **63:** 856–64.
2. DiazGranados N, *et al*. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 2010; **71:** 1605–11.
3. Diazgranados N, *et al*. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010; **67:** 793–802.
4. Machado-Vieira R, *et al*. Ketamine and the next generation of antidepressants with a rapid onset of action. *Pharmacol Ther* 2009; **123:** 143–50.
5. Zarate C, *et al*. Glutamatergic modulators: the future of treating mood disorders? *Harv Rev Psychiatry* 2010; **18:** 293–303.

Status epilepticus. There have been isolated reports[1-3] of the successful use of ketamine in the control of refractory status epilepticus (p. 510.2).

1. Prüss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res* 2008; **82:** 219–22.
2. Hsieh CY, *et al*. Terminating prolonged refractory status epilepticus using ketamine. *Clin Neuropharmacol* 2010; **33:** 165–7.
3. Yeh PS, *et al*. Oral ketamine controlled refractory nonconvulsive status epilepticus in an elderly patient. *Seizure* 2011. Available at: http://dx.doi.org/10.1016/j.seizure.2011.06.001 (accessed 28/09/11)

Adverse Effects

Emergence reactions are common during recovery from ketamine anaesthesia and include vivid often unpleasant dreams, confusion, hallucinations, and irrational behaviour. Children and elderly patients appear to be less sensitive. Patients may also develop increased muscle tone, sometimes resembling seizures. Blood pressure and heart rate may be temporarily increased by ketamine; hypotension, arrhythmias, and bradycardia have occurred rarely.

Respiration may be depressed after rapid intravenous injection or with high doses. Apnoea and laryngospasm have occurred. Diplopia and nystagmus may occur. Nausea and vomiting, lachrymation, hypersalivation, and raised intra-ocular and CSF pressure have also been reported. Transient rashes and pain at the site of injection may occur.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on the cardiovascular system. Ketamine has been advocated by some for maintaining or increasing cardiovascular performance in selected patients during induction of anaesthesia as it may increase blood pressure and heart rate.[1] However, there have been reports of reduced cardiac and pulmonary performance in severely ill patients[1] and of arrhythmias.[2]

Some of the cardiovascular effects of ketamine may be attenuated by premedication with diazepam[2] or clonidine.[3]

1. Waxman K, *et al*. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 1980; **59:** 355–8.

2. Cabbabe EB, Behbahani PM. Cardiovascular reactions associated with the use of ketamine and epinephrine in plastic surgery. *Ann Plast Surg* 1985; **15:** 50–2.
3. Tanaka M, Nishikawa T. Oral clonidine premedication attenuates the hypertensive response to ketamine. *Br J Anaesth* 1994; **73:** 758–62.

Effects on the liver. Changes in liver enzyme values have occurred after ketamine in an initial dose of 1 mg/kg followed by continuous infusion as a 0.1% solution.[1]

1. Dundee JW, *et al.* Changes in serum enzyme levels following ketamine infusions. *Anaesthesia* 1980; **35:** 12–16.

Effects on mental state. Mental disturbances after ketamine anaesthesia may vary in incidence from less than 5% to greater than 30%,[1] but a subsequent review[2] assessed the general frequency at 10 to 20%; sedating drugs are effective at preventing and terminating such emergence reactions. Episodes of vomiting are generally associated with emergence from dissociative states. See also Abuse, below.

1. White PF, *et al.* Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56:** 119–36.
2. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; **26:** 985–1028.

Effects on the skin. Harlequin-like colour skin changes were reported[1] in a 9-month-old boy during anaesthesia with ketamine 15 mg. A transient patchy erythematous rash is seen on the upper torso in about 5 to 20% of adult patients given ketamine;[2] it disappears without treatment within about 20 minutes, and does not recur with further doses of the drug.

1. Wagner DL, Sewell AD. Harlequin color change in an infant during anesthesia. *Anesthesiology* 1985; **62:** 695.
2. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; **26:** 985–1028.

Malignant hyperthermia. Malignant hyperthermia has been reported in a patient given ketamine.[1]

1. Rasore-Quartino A, *et al.* Forma atipica di ipertermia maligna: osservazione di un caso da ketamina. *Pathologica* 1985; **77:** 609–17.

Precautions

Ketamine is contra-indicated in patients in whom elevation of blood pressure would be a serious hazard including those with hypertension, eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident, or cerebral trauma. Cardiac function should be monitored in patients found to have hypertension or cardiac decompensation. Ketamine should be used with caution in patients with elevated CSF pressure. It can raise intra-ocular pressure and should not be used in the presence of eye injury or increased intra-ocular pressure.

Ketamine does not reliably suppress pharyngeal and laryngeal reflexes and mechanical stimulation of the pharynx should be avoided unless a muscle relaxant is used.

Ketamine should be used with caution in patients with neurotic traits or psychiatric disorders. Verbal, tactile, and visual stimuli should be kept to a minimum during recovery in an attempt to reduce the risk of emergence reactions.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Healthcare workers in the USA were alerted to the dangers associated with the abuse of ketamine as long ago as 1979.[1] Similar concern had also been voiced in the UK[2] over the abuse of ketamine at social gatherings where it has been taken intranasally or orally; it has also been injected intramuscularly.[3] A WHO expert committee[4] considered in 2006 that the available information on ketamine was not sufficient to warrant international control. Studies in *animals* have shown that ketamine can produce dependence, however, reports of dependence in humans are limited (see below). Although tolerance may occur there is no evidence of a withdrawal syndrome (but see below). Ketamine abuse has been reported in several countries.

Ketamine produces a state of psychological dissociation resulting in hallucinations and out of body or near death experiences. It can induce a state of helplessness in which the user loses awareness of the environment and this with severe loss of coordination and pronounced analgesia can put the user at great risk. Furthermore, some users experience a state in which they are unconcerned about whether they live or die. Ketamine has the potential for compulsive repeated use and there have been reports of users self-injecting ketamine several times daily for prolonged periods. Dependency may develop[5,6] and withdrawal symptoms requiring detoxification can occur.[6] Frequent use may produce long-lasting memory impairment.[7,8] Other adverse effects include a report[9] of an acute dystonic reaction in a 20-year old man following self-administration of ketamine intravenously.

In one case series[10] of 20 patients presenting to hospital after ketamine abuse the most common symptoms included anxiety, chest pain, and palpitations. Frequent complications included agitation and rhabdomyolysis. Symptoms were generally short lived with most patients discharged within 5 hours. A more recent retrospective case-note review[11] of 233 patients, also presenting to hospital after ketamine abuse, found the most common presenting symptoms to be impaired consciousness, increased blood pressure, tachycardia, abdominal pain or tenderness, hyperthermia, and dizziness. Symptoms resolved with supportive treatment in most of these patients and none had developed major complications.

Some[2] suggest that patients seeking medical attention are best placed in a quiet darkened room to recover with diazepam being given for unresponsive panic attacks while others advocate that such patients should be admitted to an intensive care unit for close monitoring.[12] The use of intravenous fluids to prevent rhabdomyolysis has also been recommended.[10]

Long-term and frequent abuse of ketamine has been associated with adverse effects on the urinary tract;[13-16] time to onset was reported[17] to range from 1 month to several years. Patients may present with symptoms of dysuria, frequency, urgency, urinary incontinence, suprapubic pain, and haematuria. Examination has shown in some cases a contracted shrunken bladder and ulcerative cystitis. Complications have included hydronephrosis and renal impairment. Dilated common bile duct, presenting as epigastric pain, and abnormal liver function tests have also been reported[18,19] with long-term abuse.

Ketamine is tasteless, odourless, and colourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[6]

1. Anonymous. Ketamine abuse. *FDA Drug Bull* 1979; **9:** 24.
2. Jansen KLR. Non-medical use of ketamine. *BMJ* 1993; **306:** 601–2.
3. National Institute on Drug Abuse. Club drugs (GHB, Ketamine, and Rohypnol) (updated July 2010). Available at: http://www.drugabuse.gov/pdf/infofacts/ClubDrugs10.pdf (accessed 28/03/11)
4. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)
5. Jansen KLR, Darracot-Cankovic R. The nonmedical use of ketamine, part two: a review of problem use and dependence. *J Psychoactive Drugs* 2001; **33:** 151–8.
6. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
7. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001; **96:** 749–60.
8. Morgan CJA, *et al.* Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction* 2010; **105:** 121–33. Correction. *ibid.*; 766.
9. Felser JM, Orban DJ. Dystonic reaction afterketamine abuse. *Ann Emerg Med* 1982; **11:** 673–5.
10. Weiner AL, *et al.* Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med* 2000; **18:** 447–51.
11. Ng SH, *et al.* Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. *Hong Kong Med J* 2010; **16:** 6–11.
12. Gill PA. Non-medical use of ketamine. *BMJ* 1993; **306:** 1340.
13. Chu PSK, *et al.* Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007; **13:** 311–13.
14. Shahani R, *et al.* Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007; **69:** 810–12.
15. Cottrell AM, *et al.* Urinary tract disease associated with chronic ketamine use. *BMJ* 2008; **336:** 973.
16. Chu PS-K, *et al.* The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* 2008; **102:** 1616–22.
17. Tsai T-H, *et al.* Ketamine-associated bladder dysfunction. *Int J Urol* 2009; **16:** 826–9.
18. Wong SW, *et al.* Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. *Hong Kong Med J* 2009; **15:** 53–6.
19. Ng SH, *et al.* Dilated common bile ducts in ketamine abusers. *Hong Kong Med J* 2009; **15:** 157.

Neurosurgery. Although the idea that ketamine should not be used in patients at risk from rises in intracranial pressure has limited its use in neurosurgical patients, a review[1] considered that if used with controlled ventilation and a GABA receptor agonist, and without nitrous oxide, it did not appear to have adverse effects in this group; there is evidence suggesting that it may have neuroprotective properties in some circumstances.[1,2]

1. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg* 2005; **101:** 524–34.
2. Hudetz JA, Pagel PS. Neuroprotection by ketamine: a review of the experimental and clinical evidence. *J Cardiothorac Vasc Anesth* 2010; **24:** 131–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketamine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Inhalational anaesthetics, such as ether and halothane, and other cerebral depressants may prolong the effect of ketamine and delay recovery. Prolonged recovery has also occurred when barbiturates and/or opioids have been given with ketamine. It has been recommended that ketamine should not be used with ergometrine.

See also Interactions of General Anaesthetics, p. 1897.3.

Neuromuscular blockers. For the enhancement of the effect of *tubocurarine* or *atracurium* by ketamine, see p. 2032.3.

Thyroid drugs. For a reference to increased cardiovascular adverse effects with *levothyroxine*, see p. 2342.1.

Xanthines. For a reference to seizures and tachycardia attributed to an interaction between ketamine and *theophylline*, see p. 1236.2.

Pharmacokinetics

After intravenous boluses, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents ketamine's anaesthetic action, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite norketamine. Other metabolic pathways include hydroxylation of the cyclohexone ring and conjugation with glucuronic acid. The beta phase half-life is about 2.5 hours. Ketamine is excreted mainly in the urine as metabolites. It crosses the placenta.

References.

1. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981; **53:** 27–30.
2. Grant IS, *et al.* Pharmacokinetics and analgesic effects of IM and oral ketamine. *Br J Anaesth* 1981; **53:** 805–9.
3. Grant IS, *et al.* Ketamine disposition in children and adults. *Br J Anaesth* 1983; **55:** 1107–11.**14:** 144P.
4. Geisslinger G, *et al.* Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* 1993; **70:** 666–71.
5. Malinovsky J-M, *et al.* Ketamine and norketamine plasma concentrations after iv, nasal and rectal administration in children. *Br J Anaesth* 1996; **77:** 203–7.
6. Hijazi Y, *et al.* Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. *Br J Anaesth* 2003; **90:** 155–60.
7. Weber F, *et al.* S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. *Pediatr Anesth* 2004; **14:** 983–8.
8. Sigtermans M, *et al.* S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. *Anesthesiology* 2009; **111:** 892–903.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cost; Inducmina; Ketalar†; Ketanest; ***Austral.***: Ketalar; ***Austria***: Ketanest; ***Belg.***: Ketalar; ***Braz.***: Clortamina; Ketalar; ***Canad.***: Ketalar; ***Cz.***: Calypsol; Narkamon; ***Fin.***: Ketalar; Ketanest; ***Ger.***: Ketanest; ***Gr.***: Ketalar; Ketanest; ***Hong Kong***: Ketalar; ***Hung.***: Calypsol; ***India***: Aneket; Hypnoket; Keta; Ketafast; Ketajex; Ketalar; Ketam; Ketamax; Ketmin; Ketsia; Kmin; ***Indon.***: Anesject; Ivanes; Ketalar; KTM; ***Irl.***: Ketalar; ***Israel***: Ketalar; ***Malaysia***: Kanox; Ketava; ***Mex.***: Ketalin; ***Neth.***: Ketanest; ***Norw.***: Ketalar; ***NZ***: Ketalar; ***Philipp.***: Ketacor; Ketaject†; Ketamax; Ketazol; Quetanex†; ***Pol.***: Calypsol†; Ketanest; ***Port.***: Ketalar; ***Rus.***: Calypsol (Калипсол); ***S.Afr.***: Brevinaze†; ***Spain***: Ketolar; ***Swed.***: Ketalar; ***Switz.***: Ketalar; ***Thai.***: Calypsol; Ketalar; ***Turk.***: Ketalar; ***UK***: Ketalar; ***Ukr.***: Calypsol (Калипсол)†; ***USA***: Ketalar; ***Venez.***: Keiran.

Pharmacopoeial Preparations
BP 2014: Ketamine Injection;
USP 36: Ketamine Hydrochloride Injection.

Methohexital *(BAN, rINN)*

Méthohexital; Methohexitalum; Methohexitone; Metoheksitaali; Metohexital; Метогекситал.

(±)-5-Allyl-1-methyl-5-(1-methylpent-2-ynyl)barbituric acid; 1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione.

$C_{14}H_{18}N_2O_3$=262.3

CAS — 151-83-7; 18652-93-2.

ATC — N01AF01; N05CA15.

ATC Vet — QN01AF01; QN05CA15.

UNII — ESB8ND5IPE.

Pharmacopoeias. In *US*.

USP 36: (Methohexital). A white to faintly yellowish-white crystalline odourless powder. M.p. 92 degrees to 96 degrees but the range between beginning and end of melting does not exceed 3 degrees. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, and in dilute alkalis.

Methohexital Sodium *(BANM, rINNM)*

Compound 25398; Enallynymalnatrium; Méthohexital Sodique; Methohexitone Sodium; Metohexital sódico; Natrii Methohexitalum; Натрий Метогекситал.

$C_{14}H_{17}N_2NaO_3$=284.3

CAS — 309-36-4; 22151-68-4; 60634-69-7.

ATC — N01AF01; N05CA15.

ATC Vet — QN01AF01; QN05CA15.

UNII — 60200PNZ7Q.

Pharmacopoeias. *US* includes Methohexital Sodium for Injection.

USP 36: (Methohexital Sodium for Injection). A freeze-dried sterile mixture of methohexital sodium and anhydrous sodium carbonate as a buffer, prepared from an aqueous solution of methohexital, sodium hydroxide, and sodium carbonate. It is a white to off-white, essentially odourless, hygroscopic powder. pH of a 5% solution in water is between 10.6 to 11.6.

Incompatibility. Solutions of methohexital sodium are incompatible with acidic substances including some antibacterials, antipsychotics, neuromuscular blockers, antimuscarinics, and analgesics. Compounds commonly listed as incompatible include atropine sulfate, pethidine hydrochloride, metocurine iodide, fentanyl citrate, morphine sulfate, pentazocine lactate, silicones, suxamethonium chloride, tubocurarine chloride, and compound sodium lactate injection. Only preservative-free diluents should be used to reconstitute methohexital sodium; precipitation may occur if a diluent containing a bacteriostatic agent is used.

Stability. Solutions of methohexital sodium in Water for Injections are stable for at least 6 weeks at room temperature; however reconstituted solutions should be stored no longer than 24 hours as they contain no bacteriostatic agent. Solutions in glucose or sodium chloride injections are stable only for about 24 hours.

Uses and Administration

Methohexital is a short-acting barbiturate anaesthetic that has actions similar to those of thiopental (p. 1915.2) but it is about 2 to 3 times more potent. It is given as the sodium salt and has similar uses to thiopental in anaesthesia. Induction of anaesthesia is less smooth than with thiopental and there may be excitatory phenomena. It has a shorter duration of action than thiopental and recovery after an induction dose occurs within 5 to 7 minutes although drowsiness may persist for some time.

As with other barbiturate anaesthetics the dose of methohexital required varies greatly according to the state of the patient and the nature of other drugs also being used (see under Precautions of Thiopental, p. 1916.2, and Interactions of Thiopental, p. 1916.2, for further details). Methohexital sodium is usually given intravenously as a 1% solution. Higher concentrations may markedly increase the incidence of adverse effects. A typical dose for induction of anaesthesia is 50 to 120 mg (usual range 1 to 1.5 mg/kg) given at a rate of about 10 mg (1 mL of a 1% solution) every 5 seconds. For the maintenance of general anaesthesia methohexital sodium may be given by intravenous injection in doses of 20 to 40 mg every 4 to 7 minutes as required or it may be given as a 0.2% solution by continuous intravenous infusion at a rate of 3 mL/minute.

For dosage in children, see below.

Administration in children. Although intravenous use is considered preferable in adults, in the USA methohexital sodium has been licensed for use in children aged over 1 month only by the intramuscular and rectal routes: usual doses for the induction of anaesthesia are 6.6 to 10 mg/kg intramuscularly, as a 5% solution, or 25 mg/kg rectally, as a 1% solution. In some countries methohexital sodium has also been given intravenously to children.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients has shown that although reducing the rate of intravenous dosage reduces the speed of induction, the dosage required is also reduced. Giving methohexital sodium 0.5% at a rate of 25 mg/minute induced anaesthesia in a mean of 83.8 seconds and required a mean dose of 560 micrograms/kg. Corresponding values for a rate of 100 mg/minute were 43.6 seconds and 1 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Dental sedation. Some anaesthetics are used as sedatives in dental procedures (see p. 1032.2). Methohexital has been tried for patient-controlled sedation in oral surgery under local anaesthesia.[1] In a group of 42 patients, results with 2.5 mg of methohexital compared favourably with those obtained in patients receiving 5 mg of propofol on demand, although patients in the methohexital group had a greater degree of postoperative drowsiness.

1. Hamid SK, *et al.* Comparison of patient-controlled sedation with either methohexitone or propofol. *Br J Anaesth* 1996; **77:** 727–30.

Adverse Effects and Precautions

As for Thiopental Sodium, p. 1916.1.

Excitatory phenomena are more common and induction less smooth with methohexital than with thiopental. Methohexital should be used with caution, if at all, in patients with a history of epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Incidence of adverse effects. In a study of 4379 uses of methohexital in 2722 dental patients the total intravenous dose ranged from 20 mg to 560 mg (with a mean of 151 mg), and the duration of treatment was 8 to 32 minutes.[1] Complications included: restlessness not controlled by diazepam (292 cases), respiratory complications (214), uncontrollable crying during recovery (73), pain along vein (45) with thrombophlebitis (5), jactitations (22), and allergic reactions (10).

1. McDonald D. Methohexitone in dentistry. *Aust Dent J* 1980; **25:** 335–42.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving methohexital, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

In a study[2] of 9 breast-feeding women undergoing general anaesthesia, it was estimated that the exposure of a breast-fed infant to methohexital would be less than 1% of the maternal dose after induction with methohexital. Breast feeding was not interrupted during the study and none of the infants appeared drowsy or sedated.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Borgatta L, *et al.* Clinical significance of methohexital, meperidine, and diazepam in breast milk. *J Clin Pharmacol* 1997; **37:** 186–92.

Effects on the nervous system. Two case reports of seizures induced by methohexital in children with seizure disorders.[1] Seizures are considered a rare adverse effect of methohexital. In 48 000 patients given methohexital, only 3 developed clonic-type seizures.[2]

A case of a tonic-clonic seizure possibly due to an interaction between paroxetine and methohexital is discussed below.

1. Rockoff MA, Goudsouzian NG. Seizures induced by methohexital. *Anesthesiology* 1981; **54:** 333–5.
2. Metriyakool K. Seizures induced by methohexital. *Anesthesiology* 1981; **55:** 718.

Pain on injection. Methohexital is associated with severe pain particularly if veins on the back of the hands are used. The incidence of pain on injection may be reduced by using a forearm vein or by pre-injection with lidocaine.

Porphyria. Licensed product information contra-indicates the use of methohexital in patients with latent or manifest porphyria.

Rebound anaesthesia. Rebound of anaesthesia with abolition of reflexes and depression of respiration occurred in a 6-year-old boy[1] 100 minutes after anorectal induction with 27.6 mg/kg methohexital.

1. Kaiser H, Al-Rafai S. Wie sicher ist die rektale Narkoseeinleitung mit Methohexital in der Kinderanaesthesie? *Anaesthesist* 1985; **34:** 359–60.

Interactions

As for Thiopental Sodium, p. 1916.2.

Antidepressants. A 42-year-old woman[1] had a generalised tonic-clonic seizure immediately after being anaesthetised with methohexital for the last in a series of 6 electroconvulsive therapies. She had been receiving *paroxetine* throughout the series. A previous course, without concurrent paroxetine, had been uneventful.

1. Folkerts H. Spontaneous seizure after concurrent use of methohexital anesthesia for electroconvulsive therapy and paroxetine: a case report. *J Nerv Ment Dis* 1995; **183:** 115–16.

Pharmacokinetics

Methohexital is less lipid soluble than thiopental but concentrations sufficient to produce anaesthesia are attained in the brain within 30 seconds of an intravenous dose. Methohexital is also absorbed when given rectally, producing an effect within about 5 to 15 minutes. Recovery from anaesthesia occurs quickly as a result of rapid metabolism and redistribution into other body tissues. Methohexital does not appear to concentrate in fatty tissues to the same extent as other barbiturate anaesthetics. Protein binding has been reported to be about 73%. Methohexital is rapidly metabolised in the liver through demethylation and oxidation. The terminal half-life ranges from 1.5 to 6 hours. Methohexital diffuses across the placenta and has been detected in breast milk.

References.

1. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; **12:** 79–110.
2. Le Normand Y, *et al.* Pharmacokinetics and haemodynamic effects of prolonged methohexitone infusion. *Br J Clin Pharmacol* 1988; **26:** 589–94.
3. Redke F, *et al.* Pharmacokinetics and clinical experience of 20-h infusions of methohexitone in intensive care patients with postoperative pyrexia. *Br J Anaesth* 1991; **66:** 53–9.
4. van Hoogdalem EJ, *et al.* Pharmacokinetics of rectal drug administration, part I: general considerations and clinical applications of centrally acting drugs. *Clin Pharmacokinet* 1991; **21:** 11–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Brietal†; ***Austria***: Brietal; ***Neth.***: Brietal; ***Pol.***: Brietal†; ***Rus.***: Brietal (Бриетал); ***USA***: Brevital.

Pharmacopoeial Preparations

USP 36: Methohexital Sodium for Injection.

Methoxyflurane *(BAN, USAN, rINN)*

Methoxyfluran; Méthoxyflurane; Methoxyfluranum; Metoksifluraani; Metoxifluran; Metoxiflurano; NSC-110432; Метоксифлуран.

2,2-Dichloro-1,1-difluoro-1-methoxyethane; 2,2-Dichloro-1,1-difluoroethyl methyl ether.

$C_3H_4Cl_2F_2O$=165.0

CAS — 76-38-0.

ATC — N02BG09.

ATC Vet — QN02BG09.

UNII — 30905R8O7B.

Pharmacopoeias. In *US.*

USP 36: (Methoxyflurane). A clear, practically colourless, mobile liquid having a characteristic odour. It may contain a suitable stabiliser. B.p. about 105 degrees. Soluble 1 in 500 of water; miscible with alcohol, with acetone, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Methoxyflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 0.16%, but because of its low vapour pressure, induction of general anaesthesia with methoxyflurane is slow. In recommended concentrations it is non-flammable and not explosive when mixed with oxygen. Methoxyflurane possesses good analgesic properties. It does not produce appreciable skeletal muscle relaxation at the concentrations used. Methoxyflurane does not relax the uterus and has little effect on uterine contractions during labour. It is used in subanaesthetic doses to provide analgesia for painful procedures and trauma. In anaesthetic doses, it has been used mainly for maintenance of general anaesthesia (p. 1896.1), but safer anaesthetics are preferred because of its nephrotoxicity.

Concentrations of about 0.2 to 0.7% v/v are used to provide analgesia to conscious patients. The recommended maximum total dose for intermittent self-administration is 6 mL of liquid daily or 15 mL weekly; use on consecutive days is not recommended.

References.

1. Babl FE, *et al.* Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* 2006; **18:** 404–10.
2. Babl F, *et al.* A pilot study of inhaled methoxyflurane for procedural analgesia in children. *Pediatr Anesth* 2007; **17:** 148–53.
3. Buntine P, *et al.* Prehospital analgesia in adults using inhaled methoxyflurane. *Emerg Med Australas* 2007; **19:** 509–14.
4. Grindlay J, Babl FE. Review article: efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. *Emerg Med Australas* 2009; **21:** 4–11.

Adverse Effects

As with other halogenated anaesthetics respiratory depression, hypotension, and malignant hyperthermia have been reported. Methoxyflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane; arrhythmias appear to be rare.

Methoxyflurane impairs renal function in a dose-related manner that is thought to be due to the effect of the released fluoride on the distal tubule (but see under Pharmacokinetics, p. 1908.1) and may cause polyuric or oliguric renal failure, oxaluria being a prominent feature. Nephrotoxicity is greater with methoxyflurane than with other halogenated anaesthetics because of slower metabolism over several days resulting in prolonged production of fluoride ions, and metabolism to other potentially nephrotoxic substances.

There have also been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis. Cardiac hypotension, gastrointestinal adverse effects, euphoria, drowsiness, agitation, headache, dizziness, and amnesia have been reported, as have coughing and choking. Blurred vision, diplopia, and nystagmus have been noted.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Precautions

The use of methoxyflurane is limited because of its potential to cause nephrotoxicity and its use as a general anaesthetic is no longer recommended. Methoxyflurane should not be used daily for analgesia and is contra-indicated in the presence of renal impairment.

As with other halogenated anaesthetics it is advisable not to give methoxyflurane to patients who have shown signs of liver damage or fever after previous anaesthesia involving halogenated anaesthetics. Patients with known, or suspected, susceptibility to malignant hyperthermia should not be given methoxyflurane. When used for analgesia, methoxyflurane is also contra-indicated in those with cardiovascular instability, respiratory depression, and head injury or loss of consciousness; it should be used with caution in the elderly.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. A 27-year-old nurse suffered from progressive renal disease and painful diffuse and multifocal periostitis, which had developed as a probable consequence of intermittent self-exposure to methoxyflurane possibly over a 9-year period.[1] There has also been a report[2] of hepatitis in a 39-year-old physician who repeatedly self-administered subanaesthetic concentrations of methoxyflurane for insomnia. Inhalation of about 2 mL of methoxyflurane had occurred once or twice almost every day for 6 weeks. A 125-mL bottle of methoxyflurane had been consumed in about 1 month.

1. Klemmer PJ, Hadler NM. Subacute fluorosis: a consequence of abuse of an organofluoride anesthetic. *Ann Intern Med* 1978; **89:** 607–11.
2. Okuno T, *et al*. Hepatitis due to repeated inhalation of methoxyflurane in subanaesthetic concentrations. *Can Anaesth Soc J* 1985; **32:** 53–5.

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients also receiving methoxyflurane. The effects of competitive neuromuscular blockers are enhanced by methoxyflurane. The chronic use of hepatic enzyme-inducing drugs, such as barbiturates, may enhance the metabolism of methoxyflurane thereby increasing the risk of nephrotoxicity. Use of nephrotoxic drugs, including certain antibacterials, with methoxyflurane should be avoided; fatal nephrotoxicity has been reported when used with tetracycline.

See also Interactions of General Anaesthetics, p. 1897.3.

Pharmacokinetics

Methoxyflurane is absorbed on inhalation. The blood/gas partition coefficient is high. Methoxyflurane is metabolised to a greater extent than other inhalational anaesthetics. About 50 to 70% of absorbed methoxyflurane undergoes metabolism in the liver to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Methoxyflurane is very soluble in adipose tissue and excretion may be slow. Peak plasma concentrations of fluoride occur 2 to 4 days after a dose. Methoxyflurane crosses the placenta.

Metabolism. Although fluoride has been thought to be the nephrotoxic metabolite formed during biotransformation of methoxyflurane, studies[1,2] *in vitro* and in *rats* have suggested that dichloroacetic acid, formed with fluoride by *O*-demethylation, may contribute to the nephrotoxic effect.

1. Kharasch ED, *et al*. New insights into the mechanism of methoxyflurane nephrotoxicity and implications for anesthetic development (part 1): identification of the nephrotoxic metabolic pathway. *Anesthesiology* 2006; **105:** 726–36.
2. Kharasch ED, *et al*. New insights into the mechanism of methoxyflurane nephrotoxicity and implications for anesthetic development (part 2): identification of nephrotoxic metabolites. *Anesthesiology* 2006; **105:** 737–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Penthrox; ***NZ***: Penthrox; ***Ukr.***: Pentrox (Пентрокс).

Nitrous Oxide

Azot oksit; Azote, Protoxyde d'; Azoto Protossido; Azotu(I) tlenek; Diazoto oksidas; Dikväveoxid; Dilämmastikoksiid; Dinitrogen Oxide; Dinitrogenii Oxidum; Dinitrogenoksid; Dinitrogenoxid; Dinitrogén-oxid; Distickstoffmonoxid; Distikstofmonoxide; Dityppioksidi; Dušik suboksid; E942; Gas hilarante; Gaz ilariant; Ilokaasu; Kvælstofforilte; Lachgas; Lattergas; Laughing Gas; Lystgass; Monossido di diazoto; Monóxido de dinitrógeno; Monóxido de nitrógeno; Nitrogen Monoxide; Nitrogen Oxide; Nitrogenii Monoxidum; Nitrogenii Oxidum; Nitrogenium Oxydulatum; Ossido di diazoto; Oxid dusný; Òxid nitrós; Óxido nitroso; Oxidul de azot; Oxyde Nitreux; Oxydum Nitrosum; Podtlenek azotu; Protossido di azoto; Protoxid de azot; Protóxido de ázoe; Protóxido de nitrógeno; Stickoxydul; Stikstofoxidule; Диазотен оксид; Закись азота.

N_2O=44.01

CAS — 10024-97-2.

ATC — N01AX13.

ATC Vet — QN01AX13.

UNII — K50XQU1029.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nitrous oxide:

Bulb; Buzz bomb; Cartridges; Fall down; Gas; Going to the dentist; Grocery store high; Hippy crack; Hysteria; Laughing gas; Nang; Nie; Nigh; Nitro; Nitrogen; Nitrous; Noss; Pan; Shoot the breeze; Tanks; Whippet; Whippets; Wippets.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Nitrous Oxide). A colourless gas. One vol. measured at a pressure of 101 kPa dissolves, at 20 degrees, in about 1.5 vol. of water. Store liquefied under pressure in suitable containers complying with the legal regulations.

The BP 2014 directs that Nitrous Oxide should be kept in approved metal cylinders which are painted blue and carry a label stating 'Nitrous Oxide'. In addition, 'Nitrous Oxide' or the symbol 'N_2O' should be stencilled in paint on the shoulder of the cylinder.

USP 36: (Nitrous Oxide). A colourless gas, without appreciable odour or taste. One litre at 0 degrees and at a pressure of 760 mmHg weighs about 1.97 g. One volume dissolves in about 1.4 volumes of water at 20 degrees and at a pressure of 760 mmHg; freely soluble in alcohol; soluble in ether and in oils.

Flammability. Nitrous oxide supports combustion.

Storage and supply. Nitrous oxide is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Cylinders containing 50% nitrous oxide and 50% oxygen should be protected from the cold to prevent separation of the gases. Before use, cylinders should be maintained at a temperature above 10 degrees for at least 24 hours to ensure mixing; cylinders containing up to 700 litres of gas may be used immediately if inverted 3 times beforehand.

Uses and Administration

Nitrous oxide is an anaesthetic given by inhalation. It is a weak anaesthetic with a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 110%. It has strong analgesic properties, but produces little muscle relaxation. Nitrous oxide must be given with oxygen, otherwise hypoxia will occur.

Nitrous oxide with oxygen has been used in the induction and maintenance of general anaesthesia (p. 1896.1). However, it is now mainly used as an adjuvant to other inhalational or intravenous anaesthetics, permitting them to be used at significantly lower concentrations. It is also used, with oxygen, in subanaesthetic concentrations for analgesia and sedation in emergency care and obstetric and other painful procedures, including dental procedures (see p. 1032.2).

For maintenance of anaesthesia a mixture containing 50 to 66% nitrous oxide with oxygen is commonly used. Recovery is usually rapid from nitrous oxide anaesthesia.

Nitrous oxide usually 50% v/v with oxygen is used for analgesia; cylinders containing premixed nitrous oxide 50% v/v and oxygen 50% v/v are available in some countries.

Nitrous oxide has also been used occasionally as an insufflating gas for laparoscopy and as a refrigerant in cryosurgery.

Administration in children. Nitrous oxide with oxygen is used in general anaesthesia and for analgesia in children; doses are as for adults (see Uses and Administration, above).

Alcohol withdrawal syndrome. The symptoms of acute alcohol withdrawal (p. 1734.1) are usually managed with benzodiazepines; nitrous oxide has been tried but results have been equivocal.[1,2] More recently, a systematic review[3] found that although nitrous oxide may be a rapidly effective treatment for mild to moderate cases, there was no strong evidence in favour of its use over sedatives due to the small sample sizes of the included studies.

1. Gillman MA, Lichtigfeld FJ. Analgesic nitrous oxide for alcohol withdrawal: a critical appraisal after 10 years' use. *Postgrad Med J* 1990; **66:** 543–6.
2. Alho H, *et al*. Long-term effects of and physiological responses to nitrous oxide gas treatment during alcohol withdrawal: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2002; **26:** 1816–22.
3. Gillman MA, *et al*. Psychotropic analgesic nitrous oxide for alcoholic withdrawal states. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 14/01/10).

Pain. A mixture of nitrous oxide 50% v/v and oxygen 50% v/v can provide good relief of pain (see Choice of Analgesic, p. 4.2) without loss of consciousness and is suitable for self-administration. It has been widely used for analgesia and sedation during dental procedures. It is also used for short procedures such as dressing changes,[1,2] venepuncture and biopsy,[3] for pain relief during childbirth,[4] in the management of postoperative pain,[1] as an aid to postoperative physiotherapy, and for acute pain in emergency situations such as in ambulances and in the hospital setting.[3,5-7] It has also been tried successfully for colonoscopy,[8] and bronchoscopy.[9,10] Continuous inhalation of nitrous oxide-oxygen has been tried for periods longer than 24 hours in the management of pain in terminal cancer.[11] However, such a practice is not usually otherwise recommended[1] as it may result in megaloblastic bone-marrow changes.

1. Hull CJ. Control of pain in the perioperative period. *Br Med Bull* 1988; **44:** 341–56.
2. Gaukroger PB. Pediatric analgesia: which drug, which dose? *Drugs* 1991; **41:** 52–9.
3. Boulland P, *et al*. Mélange équimolaire oxygène-protoxyde d'azote (MEOPA): rappels théoriques et modalités pratiques d'utilisation. *Ann Fr Anesth Reanim* 2005; **24:** 1305–12.
4. Brownridge P. Treatment options for the relief of pain during childbirth. *Drugs* 1991; **41:** 69–80.
5. O'Sullivan Í, Benger J. Nitrous oxide in emergency medicine. *Emerg Med J* 2003; **20:** 214–17.
6. Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? *Emerg Med J* 2005; **22:** 901–8.
7. Babl FE, *et al*. Limited analgesic efficacy of nitrous oxide for painful procedures in children. *Emerg Med J* 2008; **25:** 717–21.
8. Aboumarzouk OM, *et al*. Nitrous oxide for colonoscopy. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2011 (accessed 22/08/11).
9. Fauroux B, *et al*. The efficacy of premixed nitrous oxide and oxygen for fiberoptic bronchoscopy in pediatric patients: a randomized, double-blind, controlled study. *Chest* 2004; **125:** 315–21.
10. Atassi K, *et al*. Prefixed equimolar nitrous oxide and oxygen mixture reduces discomfort during flexible bronchoscopy in adult patients: a randomized, controlled, double-blind trial. *Chest* 2005; **128:** 863–8.
11. Fosburg MT, Crone RK. Nitrous oxide analgesia for refractory pain in the terminally ill. *JAMA* 1983; **250:** 511–13.

Adverse Effects

The main complications after use of nitrous oxide are those due to varying degrees of hypoxia. Prolonged use has been followed by megaloblastic anaemia and myeloneuropathy. Depression of white cell formation may also occur. There is a risk of increased pressure and volume from the diffusion of nitrous oxide into air-containing cavities; prolonged exposure may lead to bowel distension, middle ear damage, and rupture of the ear drum. Malignant hyperthermia has been reported rarely.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Reviews.

1. Louis-Ferdinand RT. Myelotoxic, neurotoxic and reproductive adverse effects of nitrous oxide. *Adverse Drug React Toxicol Rev* 1994; **13:** 193–206.
2. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: an update. *Br Dent J* 1995; **178:** 95–100.
3. Weimann J. Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol* 2003; **17:** 47–61.
4. Collado V, *et al*. A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. *Expert Opin Drug Safety* 2007; **6:** 559–71.
5. Sanders RD, *et al*. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology* 2008; **109:** 707–22.

Effects on the blood. Nitrous oxide inactivates vitamin B_{12}, a cofactor for methionine synthase (which converts homocysteine to methionine), thereby increasing plasma-homocysteine concentrations and depleting methionine and tetrahydrofolate. The interference with folate metabolism and DNA synthesis prevents production of both leucocytes and red blood cells by the bone marrow. Megaloblastic changes in bone marrow and impaired granulocyte production are found in patients exposed to anaesthetic concentrations of nitrous oxide for 24 hours. In patients with normal bone marrow, stores of mature granulocytes will normally be adequate to prevent leucopenia during exposure for up to 3 days; in patients exposed to nitrous oxide for longer periods of time, leucopenia will develop and exposure for 4 days or longer can result in agranulocytosis. In general, healthy surgical patients can be given nitrous oxide for up to 24 hours without harm. In situations where nitrous oxide is used for more than 24 hours, folinic acid 30 mg twice daily has been given to protect the haematopoietic system. Repeat exposure to nitrous oxide at intervals of less than 3 days will have a cumulative effect on DNA synthesis and megaloblastic marrow changes have been reported following multiple short-term exposure.[1]

Depletion of methionine has been implicated in the neurological deficit (see Effects on the Nervous System,

p. 1909.1) seen mainly after chronic use of nitrous oxide. It may also account for the fetotoxicity seen in *rats*, see Pregnancy, under Precautions, below. For discussion of the effects of hyperhomocysteinaemia, see Effects on the Cardiovascular System, below.

Assessment of vitamin B_{12} levels should be considered before giving nitrous oxide anaesthesia to patients with risk factors for deficiency.[2]

1. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B_{12}. *Br J Anaesth* 1987; **59:** 3–13.
2. MHRA/CHM. Nitrous oxide: neurological and haematological toxic effects, especially with prolonged use. *Drug Safety Update* 2008; **2** (5): 2. Also available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con033504.pdf (accessed 20/09/11)

Effects on the cardiovascular system. Nitrous oxide is associated with a dose-dependent increase in plasma-homocysteine concentrations due to the inactivation of vitamin B_{12}, a cofactor for methionine synthase which converts homocysteine to methionine (see also Effects on the Blood and the Nervous System, p. 1908.3 and below, respectively). Acute nitrous oxide-induced hyperhomocysteinaemia has been shown[1] to impair endothelial function in patients with cardiovascular disease undergoing noncardiac surgery. A multicentre randomised controlled study[2] in patients undergoing noncardiac surgery found that the incidence of major postoperative complications, including postoperative fever, wound infection, pneumonia, pulmonary atelectasis, and severe nausea and vomiting, was reduced in the nitrous oxide-free group, but not the length of hospital stay. The authors also noted a possible association between nitrous oxide and postoperative myocardial infarction although this was statistically insignificant. (A substudy[3] on some of the patients identified hyperhomocysteinaemia as an independent risk factor for major postoperative complications, attributed to increased rates of cardiovascular complications.) Follow-up[4] after a median of 3.5 years suggested that nitrous oxide anaesthesia was associated with a marginal increase in the long-term risk of myocardial infarction, but not of death or stroke.

Measures to protect against nitrous oxide-induced hyperhomocysteinaemia have been tried. A randomised study[5] found that oral vitamin B-complex given daily for one week before surgery inhibited the increase in postoperative plasma-homocysteine concentrations; however, differences in clinical outcome were not measured. A later randomised placebo-controlled study[6] concluded that a single pre-operative intravenous infusion of vitamin B_{12} and folate did not prevent nitrous oxide-induced hyperhomocysteinaemia.

1. Myles PS, *et al.* Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. *Anesthesiology* 2008; **109:** 657–63.
2. Myles PS, *et al.* ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 2007; **107:** 221–31.
3. Myles PS, *et al.* Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. *Br J Anaesth* 2008; **100:** 780–6.
4. Leslie K, *et al.* Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. *Anesth Analg* 2011; **112:** 387–93.
5. Badner NH, *et al.* Preoperative oral B vitamins prevent nitrous oxide-induced postoperative plasma homocysteine increases. *Anesth Analg* 2001; **93:** 1507–10.
6. Rao LK, *et al.* Pre-operative vitamin B infusion and prevention of nitrous oxide-induced homocysteine increase. *Anaesthesia* 2010; **65:** 710–15.

Effects on the nervous system. Neurological disorders (mainly myeloneuropathies and neuropathies) have occurred in chronic abusers of nitrous oxide;[1-3] severe myeloneuropathy has been reported after acute use of a high dose.[4] Similar effects have been noted after repeated use of nitrous oxide in hospitalised patients. These neurological effects are considered to be due to nitrous oxide-induced methionine deficiency (see Effects on the Blood and the Cardiovascular System, p. 1908.3 and above, respectively). However, neurological effects can occur without preceding overt haematological changes. Psychosis, responsive to treatment with vitamin B_{12}, has also been reported in a patient abusing nitrous oxide.[5]

In patients with undiagnosed subclinical deficiency of vitamin B_{12} (a cofactor involved in methionine synthesis) neurological manifestations, including those consistent with subacute combined degeneration of the spinal cord, have occurred after a single exposure to nitrous oxide for anaesthesia.[6-8] A literature review[9] of 18 cases found that the onset of symptoms after exposure to nitrous oxide varied from immediately after surgery to about 2 months later; duration of exposure ranged from 60 minutes to 11 hours, at concentrations of 40 to 66%. Acute paralysis, due to degeneration of the spinal cord, has also been reported in a malnourished patient who had been abusing nitrous oxide for 10 days for the self-treatment of a painful sprained ankle.[10]

1. Miller MA, *et al.* Nitrous oxide "whippit" abuse presenting as clinical B12 deficiency and ataxia. *Am J Emerg Med* 2004; **22:** 124.
2. Doran M, *et al.* Toxicity after intermittent inhalation of nitrous oxide for analgesia. *BMJ* 2004; **328:** 1364–5.
3. Richardson PG. Peripheral neuropathy following nitrous oxide abuse. *Emerg Med Australas* 2010; **22:** 88–90.
4. Alt RS, *et al.* Severe myeloneuropathy from acute high-dose nitrous oxide (N_2O) abuse. *J Emerg Med* 2010. Available at: doi:10.1016/j.jemermed.2010.04.020
5. Sethi NK, *et al.* Nitrous oxide "whippit" abuse presenting with cobalamin responsive psychosis. *J Med Toxicol* 2006; **2:** 71–4.
6. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12}-deficient subjects? *JAMA* 1986: **255:** 1605–6.
7. Nestor PJ, Stark RJ. Vitamin B_{12} myeloneuropathy precipitated by nitrous oxide anaesthesia. *Med J Aust* 1996; **165:** 174.
8. Renard D, *et al.* Subacute combined degeneration of the spinal cord caused by nitrous oxide anaesthesia. *Neurol Sci* 2009; **30:** 75–6.
9. Singer MA, *et al.* Reversible nitrous oxide-induced myeloneuropathy with pernicious anemia: case report and literature review. *Muscle Nerve* 2008; **37:** 125–9.
10. Cartner M, *et al.* Paralysis caused by "nagging". *Med J Aust* 2007; **187:** 366–7.

Malignant hyperthermia. An 11-year-old girl whose father had died from malignant hyperthermia after anaesthesia developed hyperthermia after anaesthesia with nitrous oxide and oxygen.[1]

1. Ellis FR, *et al.* Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. *BMJ* 1974; **4:** 270–1.

Precautions

Hypoxic anaesthesia is dangerous and nitrous oxide should always be given with at least 21 to 30% oxygen. Nitrous oxide diffuses into gas-filled body cavities and is contra-indicated in patients with any condition where the expansion of trapped gas may be dangerous, such as head injuries with impairment of consciousness, pneumothorax, air embolism, decompression sickness, severe bullous emphysema, gross abdominal distension, intoxication, maxillofacial injuries, and after air encephalography or recent intra-ocular injection of gas. Nitrous oxide should not be used for more than a total of 24 hours, or more frequently than every 4 days, without close supervision and haematological monitoring. Oxygen should be given during emergence from prolonged anaesthesia with nitrous oxide to prevent diffusion hypoxia where the alveolar oxygen concentration is diminished. See also Precautions for General Anaesthetics, p. 1897.3.

Nitrous oxide has been subject to abuse.

Abuse. 'Recreational' use or abuse of nitrous oxide has been referred to as "nagging" or "nanging". For some of the resulting adverse effects of nitrous oxide abuse, see Effects on the Nervous System, above.

Driving. A slight but quantifiable impairment in driving ability was found up to 30 minutes after 15 minutes' inhalation of nitrous oxide/oxygen mixtures for analgesia and sedation;[1] indeed, licensed product information recommends against driving or operating machinery until at least 30 minutes after administration. Similarly, such activities should be avoided until 12 hours after nitrous oxide anaesthesia.

1. Moyes DG, *et al.* Driving after anaesthetics. *BMJ* 1979; **1:** 1425.

Epidural anaesthesia. Nitrous oxide diffuses into gas-filled body cavities and can increase the size of any air bubbles injected into the epidural space to determine placement of the needle in epidural anaesthesia.[1] This could result in uneven spread of the local anaesthetic and produce inadequate analgesia. The volume of air injected should be limited or another technique used to determine placement of the needle if nitrous oxide is to be given subsequently.

1. Stevens R, *et al.* Fate of extradural air bubbles during inhalation of nitrous oxide. *Br J Anaesth* 1994; **72:** 482P–483P.

Occupational exposure. A scavenging system and effective ventilation may be necessary to control the nitrous oxide pollution that can occur when this gas is used for analgesia or anaesthesia. Risk areas include, in addition to operating theatres, delivery rooms and dental surgeries.[1-3] Occupational exposure can lead to serious toxicity with bone-marrow and neurological impairment.[1,2] Reduced fertility has been reported in female dental workers exposed to high concentrations of nitrous oxide;[4] such women also appear to have a higher rate of spontaneous abortion.[5] It has been suggested that nitrous oxide can also affect male fertility;[6] in one study a dose-related increase in the incidence of spontaneous abortion was found in the wives of men with occupational exposure to nitrous oxide.[7] A later review[8] concluded that although there is some evidence of a causal link between exposure to nitrous oxide and spontaneous abortion and infertility, this evidence was limited. The author noted that most of the studies were conducted before scavenging was widely used, and none included ambient gas sampling, and that most of the data were obtained by questionnaire.

1. Brodsky JB, *et al.* Exposure to nitrous oxide and neurologic disease among dental professionals. *Anesth Analg* 1981; **60:** 297–301.
2. Sweeney B, *et al.* Toxicity of bone marrow in dentists exposed to nitrous oxide. *BMJ* 1985; **291:** 567–9.
3. Munley AJ, *et al.* Exposure of midwives to nitrous oxide in four hospitals. *BMJ* 1986; **293:** 1063–4. Correction. *ibid.*; 1280.
4. Rowland AS, *et al.* Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992; **327:** 993–7.
5. Rowland AS, *et al.* Nitrous oxide and fertility. *N Engl J Med* 1993; **328:** 284.
6. Brodsky JB. Nitrous oxide and fertility. *N Engl J Med* 1993; **328:** 284–5.
7. Cohen EN, *et al.* Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc* 1980; **101:** 21–31.
8. Olfert SM. Reproductive outcomes among dental personnel: a review of selected exposures. *J Can Dent Assoc* 2006; **72:** 821–5.

Pregnancy. Nitrous oxide is fetotoxic in *rats*.[1] However, retrospective reviews,[2] and individual case reports[3] have not shown nitrous oxide anaesthesia to be fetotoxic in humans. See also Occupational Exposure, above.

1. Lane GA, *et al.* Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. *Science* 1980; **210:** 899–901.
2. Aldridge LM, Tunstall ME. Nitrous oxide and the fetus: a review and the results of a retrospective study of 175 cases of anaesthesia for insertion of Shirodkar suture. *Br J Anaesth* 1986; **58:** 1348–56.
3. Park GR, *et al.* Normal pregnancy following nitrous oxide exposure in the first trimester. *Br J Anaesth* 1986; **58:** 576–7.

Vitamin B_{12} deficiency. For reports of neurological dysfunction associated with the use of nitrous oxide in patients with undiagnosed subclinical vitamin B_{12} deficiency, see Effects on the Nervous System, above.

Interactions

Use of nitrous oxide in a high concentration with an inhalational anaesthetic accelerates the uptake of the latter from the lungs. This phenomenon is known as the *second gas effect*. It is due to the disproportionate absorption of nitrous oxide into the blood resulting in an increased alveolar concentration of the second gas.

The use of high doses of opioids such as fentanyl with nitrous oxide may result in a drop in heart rate and cardiac output.

See also Interactions for General Anaesthetics, p. 1897.3.

Methotrexate. Combined use of nitrous oxide and methotrexate may increase some of the adverse effects of methotrexate therapy, see p. 828.2.

Pharmacokinetics

Nitrous oxide is rapidly absorbed on inhalation. The blood/gas partition coefficient is low and most of the inhaled nitrous oxide is rapidly eliminated unchanged through the lungs though small amounts diffuse through the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Niontix; ***Denm.***: Niontix; ***Fin.***: Niontix; ***Fr.***: Kinox; ***Ger.***: Niontix; ***Israel***: Maxicool; ***Neth.***: Niontix; ***Norw.***: Niontix; ***Swed.***: Niontix.

Multi-ingredient Preparations. ***Belg.***: Kalinox; ***Canad.***: Alnox; Entonox; Liqui-Med; ***Cz.***: Entonox; ***Denm.***: Kalinox; Livopan; Medimix; ***Fin.***: Livopan; ***Fr.***: Antasol; Entonox; Kalinox; Oxynox; ***Ger.***: Livopan; ***Irl.***: Entonox; ***Neth.***: Donopa; Relivopan; ***Pol.***: Entonox; ***S.Afr.***: Entonox; ***Spain***: Entonox; Kalinox; ***Swed.***: Livopan; Medimix; ***Switz.***: Entonox; Kalinox; Medimix†; ***UK***: Entonox; Equanox.

Propanidid *(BAN, USAN, rINN)*

Bayer-1420; FBA-1420; Propanidide; Propanididum; TH-2180; WH-5668; Пропанидид.

Propyl 4-diethylcarbamoylmethoxy-3-methoxyphenylacetate.

$C_{18}H_{27}NO_5$=337.4

CAS — 1421-14-3.

ATC — N01AX04.

ATC Vet — QN01AX04.

UNII — AO82L471NS.

Profile

Propanidid has been used as an intravenous anaesthetic for rapid induction and for maintenance of general anaesthesia of short duration.

Commercial preparations of propanidid were provided as a liquid in polyoxyl castor oil. Anaphylactoid reactions associated with the vehicle led to the general withdrawal of propanidid from use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Progray; ***Mex.***: Panitol.

Propofol *(BAN, USAN, rINN)*

Disoprofol; ICI-35868; Propofoli; Propofolis; Propofolum; Пропофол.

2,6-Di-isopropylphenol; 2,6-Bis(1-methylethyl)phenol.
$C_{12}H_{18}O$=178.3
CAS — 2078-54-8.
ATC — N01AX10.
ATC Vet — QN01AX10.
UNII — YI7VU623SF.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Propofol). A colourless or very light yellow, clear liquid. Very slightly soluble in water; miscible with hexane and with methyl alcohol. Store under an inert gas. Protect from light.

USP 36: (Propofol). A clear, colourless to slightly yellowish liquid. Very slightly soluble in water; very soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in cyclohexane and in isopropyl alcohol. Store under an inert gas in airtight containers. Protect from light.

Uses and Administration

Propofol is a short-acting anaesthetic given intravenously for the induction and maintenance of general anaesthesia (p. 1896.1). It is also used for sedation (p. 1032.2) in adult patients undergoing diagnostic procedures, in those undergoing surgery with local or regional anaesthesia, and in ventilated adult patients under intensive care. When used for anaesthesia, induction is rapid, as is recovery. Propofol has no analgesic activity and supplementary analgesia may be required.

Propofol is available as a 1 or 2% emulsion. The 1% emulsion may be given by intravenous injection or infusion, but the 2% emulsion is for infusion only. Infusions and injections should be prepared using aseptic techniques, see Administration, below.

Induction of **anaesthesia** is generally carried out by giving propofol by injection or infusion at a rate of 40 mg every 10 seconds; a rate of 20 mg every 10 seconds may be used in high-risk patients including elderly, neurosurgical, and debilitated patients. Most adults under 55 years of age can be anaesthetised by a dose of 1.5 to 2.5 mg/kg; high-risk patients usually require a dose of 1 to 1.5 mg/kg.

When used for maintenance propofol is infused at a rate of between 4 to 12 mg/kg per hour (or 3 to 6 mg/kg per hour for elderly and debilitated patients); alternatively intermittent bolus injections of 20 to 50 mg may be given; rapid bolus doses should be avoided in high-risk patients.

For dosage in children, see below.

A novel delivery system is also available for the induction and maintenance of anaesthesia in adults. The Diprifusor target-controlled infusion system allows the speed of induction and depth of anaesthesia to be controlled by specifying target blood concentrations of propofol. Initial target concentrations for induction range from 4 to 8 micrograms/mL for patients under 55 years of age; lower initial target concentrations should be used in older and debilitated patients and should be increased gradually thereafter in steps of 0.5 to 1 microgram/mL at intervals of 1 minute to achieve a gradual induction of anaesthesia. Target concentrations for maintenance are 3 to 6 micrograms/mL.

For **sedation** in diagnostic and surgical procedures in adults an initial infusion of 6 to 9 mg/kg per hour may be given for 3 to 5 minutes; alternatively 0.5 to 1 mg/kg may be injected slowly over 1 to 5 minutes. An infusion of 1.5 to 4.5 mg/kg per hour may be used for maintenance of sedation. High-risk patients usually require a 20% reduction in the maintenance dose.

For the sedation of ventilated adults propofol can be given by intravenous infusion in a dose of 0.3 to 4 mg/kg per hour. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored.

Reviews.

1. Langley MS, Heel RC. Propofol: a review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs* 1988; **35:** 334–72.
2. Larijani GE, *et al.* Clinical pharmacology of propofol: an intravenous anesthetic agent. *DICP Ann Pharmacother* 1989; **23:** 743–9.
3. Bryson HM, *et al.* Propofol: an update of its use in anaesthesia and conscious sedation. *Drugs* 1995; **50:** 513–59.
4. Fulton B, Sorkin EM. Propofol: an overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. *Drugs* 1995; **50:** 636–57.
5. Singh H, *et al.* Propofol for sedation during colonoscopy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 15/01/10).
6. Vasileiou I, *et al.* Propofol: a review of its non-anaesthetic effects. *Eur J Pharmacol* 2009; **605:** 1–8.
7. Lundström S, *et al.* Propofol. *J Pain Symptom Manage* 2010; **40:** 466–70.

Administration. Propofol is formulated as an oil-in-water emulsion for injection. Strict aseptic techniques must be maintained when handling propofol as, in some countries, the parenteral product contains no antimicrobial preservatives and the vehicle can support rapid growth of microorganisms. Aseptic techniques must also be applied to formulations, such as those available in the UK and USA, that contain the microbial-retarding agent disodium edetate, as microbial growth is still possible. An emulsion containing 1% of propofol may be diluted with glucose 5% immediately before use but it should not be diluted to a concentration of less than 2 mg/mL. An emulsion containing 2% of propofol should not be diluted. The use of a 5-micrometre filter needle to withdraw propofol emulsion from an ampoule does not cause significant loss of drug.[1] A reduction in concentration of propofol can occur when the diluted emulsion is run through PVC intravenous tubing.[1] Propofol 1 or 2% may be given into a running intravenous infusion through a Y-site close to the injection site and under these circumstances it is compatible with glucose 5%, sodium chloride 0.9%, lactated Ringer's solution, and glucose with sodium chloride or with lactated Ringer's solution.

Because injection of propofol can be painful, it may be mixed with alfentanil or lidocaine before use. UK licensed product information advises mixing lidocaine 0.5 or 1% injection (without preservatives) in a ratio of 1:20 with propofol injection 1% immediately before use; similarly, alfentanil injection 500 micrograms/mL may be mixed in a ratio of 1:20 to 1:50 with propofol 1%. It advises against mixing the 2% emulsion of propofol with other drugs.

1. Bailey LC, *et al.* Effect of syringe filter and I.V. administration set on delivery of propofol emulsion. *Am J Hosp Pharm* 1991; **48:** 2627–30.

Administration in children. In the UK, children aged 1 month and over may be given propofol for the induction and maintenance of anaesthesia. The dose should be adjusted for weight and age, and given slowly until the onset of anaesthesia. Most children aged over 8 years require an induction dose of 2.5 mg/kg; younger children may require a higher dose within the range of 2.5 to 4 mg/kg. Doses of 9 to 15 mg/kg per hour by intravenous infusion or intermittent bolus injections are suitable for maintenance. The 2% emulsion formulation of propofol should only be used in children aged 3 years and over. In the USA, children aged 3 years and over may be given propofol for the induction of anaesthesia; those aged 2 months and over may receive propofol for maintenance of anaesthesia. Doses are similar to those used in the UK.

Propofol is contra-indicated for sedation in children aged 16 years or less. A systematic review[1] found only 1 study of the use of propofol in neonates; although there was some evidence of benefit the numbers were insufficient to establish its role and safety.

1. Shah PS, Shah VS. Propofol for procedural sedation/anaesthesia in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 14/04/11).

Nausea and vomiting. It is commonly believed that propofol is associated with less postoperative nausea and vomiting than some other anaesthetics.[1,2] However, a review[3] concluded that any reduction in nausea and vomiting when using propofol anaesthesia may be short term and clinically relevant only for maintenance anaesthesia in procedures with an inherent risk of nausea and vomiting.

There are also reports[4-9] indicating that propofol may have some intrinsic antiemetic action when used in subhypnotic doses although a study[10] of the effect of sedative and non-sedative (sub-hypnotic) doses against apomorphine-induced vomiting has suggested that any antiemetic effect is probably due to sedation.

1. McCollum JSC, *et al.* The antiemetic action of propofol. *Anaesthesia* 1988; **43:** 239–40.
2. Woodward WM, *et al.* Comparison of post-operative nausea and vomiting after thiopentone/isoflurane or propofol infusion for 'bat-ear' correction in children. *Br J Anaesth* 1994; **72** (suppl 1): 92.
3. Tramèr M, *et al.* Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997; **78:** 247–55.
4. Borgeat A, *et al.* Adjuvant propofol for refractory cisplatin-associated nausea and vomiting. *Lancet* 1992; **340:** 679–80.
5. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73:** 411–12.
6. Borgeat A, *et al.* Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer. *Can J Anaesth* 1994; **41:** 1117–19.
7. Ewalenko P, *et al.* Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *Br J Anaesth* 1996; **77:** 463–7.
8. Gan TJ, *et al.* Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. *Anesthesiology* 1997; **87:** 779–84.
9. Unal Y, *et al.* Comparison of the efficacy of propofol and metoclopramide in preventing postoperative nausea and vomiting after middle ear surgery. *Saudi Med J* 2009; **30:** 778–82.
10. Thörn S-E, *et al.* Propofol effects upon apomorphine induced vomiting. *Br J Anaesth* 1994; **72** (suppl 1): 90.

Pruritus. Propofol is one of many drugs that have been tried in the management of pruritus (p. 1687.3). Sub-hypnotic doses of propofol appear to have an antipruritic action. It has produced conflicting results in the treatment and prophylaxis of pruritus associated with epidural and intrathecal morphine[1-4] although it appears to be able to relieve cholestasis-associated pruritus.[5] It has been suggested that propofol might act by suppression of the spinal transmission of pruritic signals.

1. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76:** 510–12.
2. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73:** 411–12.
3. Warwick JP, *et al.* The effect of subhypnotic doses of propofol on the incidence of pruritus after intrathecal morphine for caesarean section. *Anaesthesia* 1997; **52:** 270–5.
4. Beilin Y, *et al.* Subhypnotic doses of propofol do not relieve pruritus induced by intrathecal morphine after cesarean section. *Anesth Analg* 1998; **86:** 310–3.
5. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus associated with liver disease. *Gastroenterology* 1993; **104:** 244–7.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used. Propofol is also used[1-7] although good controlled studies of its efficacy are lacking; in addition, it has caused seizures when used in anaesthesia (see CNS Effects, under Precautions, p. 1912.1) and should be given with caution to patients with epilepsy. The risks of respiratory and cerebral depression, lipid overload with prolonged therapy, and propofol infusion syndrome should also be borne in mind. It may induce involuntary movements and care is required to distinguish these from seizures. Nonetheless, it has a rapid onset of action and its effects are maintained while the infusion is maintained; recovery is rapid on stopping. Some guidelines[7] recommend giving an initial intravenous bolus of 2 to 3 mg/kg, with further boluses of 1 to 2 mg/kg until seizures are controlled, followed by a continuous infusion of 4 to 10 mg/kg per hour guided by EEG monitoring. A lower initial bolus dose of 1 mg/kg has also been used.[4] The dose should be gradually reduced and the infusion tapered 12 to 24 hours after seizure activity is halted. Lower doses should be used in the elderly. A study[8] comparing propofol with high-dose barbiturates in patients with refractory status epilepticus concluded that recurrent seizures were common when propofol infusions were suddenly stopped but not when the infusions were gradually tapered.

1. Rossetti AO, *et al.* Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia* 2004; **45:** 757–63.
2. Marik PE, Varon J. The management of status epilepticus. *Chest* 2004; **126:** 582–91.
3. van Gestel JPJ, *et al.* Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005; **65:** 591–2.
4. Kälviäinen R, *et al.* Refractory generalised convulsive status epilepticus: a guide to treatment. *CNS Drugs* 2005; **19:** 759–68.
5. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia* 2007; **48** (suppl 8): 52–5. Correction. *ibid.*; 2383.
6. Parviainen I, *et al.* Propofol and barbiturates for the anesthesia of refractory convulsive status epilepticus: pros and cons. *Neurol Res* 2007; **29:** 667–71.
7. Meierkord H, *et al.* European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; **17:** 348–55.
8. Stecker MM, *et al.* Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998; **39:** 18–26.

Tetanus. Sedation with propofol has been used in the treatment of tetanus (p. 2029.2) to control spasms and rigidity.

Adverse Effects

Early studies with propofol used a preparation formulated with polyoxyl castor oil. Because of anaphylactoid reactions the preparation was reformulated with a vehicle of soya oil and purified egg phosphatide. Adverse effects with this preparation include pain on injection, especially if the injection is into a small vein. Local pain may be reduced by injection into a large vein or by injection of intravenous lidocaine. Apnoea may be frequent; apnoea lasting longer than 60 seconds has been reported to occur in 12% of patients. There are isolated reports of pulmonary oedema. Cardiovascular effects include a reduction in blood pressure and bradycardia. There have been reports of convulsions (sometimes delayed in onset) and involuntary movements. Fever and pancreatitis have occurred very rarely. Anaphylactoid reactions have been reported. Discoloration of urine has been reported after prolonged use. Nausea, vomiting, and headache may occur during recovery.

Children given propofol for prolonged sedation have suffered severe reactions and there have been fatalities, and a life-threatening infusion syndrome has also been seen in adults, see Incidence of Adverse Effects, below.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Incidence of adverse effects. In May 1989 the UK CSM commented on the 268 reports of adverse reactions to propofol that it had received since propofol was introduced to the UK market, during which period about 2 million patients had been anaesthetised with the drug.[1] These included reports of:

- seizures (37 cases, 13 in known epileptics)
- involuntary movements (16 cases)
- opisthotonus (10 cases)
- anaphylactic reactions (32 cases)
- cardiac arrest (13 cases)
- delayed recovery (8 cases)

In 1992 the CSM pointed to the risk of **delayed convulsions** with propofol and its particular importance

for day-case surgery.[2] While the incidence of convulsions was low (170 reports), 31% of the reports described the convulsions as delayed.

In June 1992 the CSM commented on the dangers of propofol for the **sedation of children** in intensive care,[3] a use for which it is contra-indicated in the UK. (This prohibition does not apply to its use for the sedation of ventilated adults—but see below—or to propofol's use as an *anaesthetic* in children. Sedation in children undergoing surgical and diagnostic procedures is not contra-indicated but is an unlicensed use, and is not recommended.[4])

The CSM reported that there had been 66 reports worldwide of serious adverse effects in children sedated with propofol, and some fatalities had ensued. The children had suffered neurological, cardiac, and renal effects, hyperlipidaemia, hepatomegaly, and metabolic acidosis. Five deaths had been reported to the CSM. These 5 children[5] were aged 4 weeks to 6 years and doses of propofol ranged from 4 to 10.7 mg/kg per hour. They developed metabolic acidosis, bradyarrhythmia, and progressive myocardial failure resistant to treatment. The latter has been reported by others to be significantly associated with the use of long-term, **high-dose** propofol infusions.[6]

Similar adverse effects resulting in fatalities have also been reported in **adult** patients with head injuries who received high doses of propofol infusion (greater than 5 mg/kg per hour) for long-term sedation.[7] The CSM subsequently reminded prescribers that the recommended dose range for sedation (up to 4 mg/kg per hour) should not be exceeded.[8] There has also been a report of death in a patient with a closed head injury who received propofol infusion at an average dose of 4.1 mg/kg per hour for long-term sedation.[9] Other fatalities reported included an adult patient with a spinal injury who was sedated with a maximum dose of 2.6 mg/kg per hour (mean 1.9 mg/kg per hour) for about 85 hours[10] and an adult patient with multiple fractures who received doses of 1.4 to 5.1 mg/kg per hour for 88 hours.[11]

The Australian Adverse Drug Reactions Advisory Committee[12] stated in December 2004 that it had received a report of lactic acidosis and another of torsade de pointes in adult patients receiving lower doses of propofol infusion, 30 and 100 mg/hour, respectively, for about 24 hours.

The term **propofol infusion syndrome** is used to describe the life-threatening adverse reaction that is characterised by metabolic acidosis, rhabdomyolysis, acute renal failure, hepatomegaly, hyperlipidaemia, and cardiac dysfunction.[13-16] A prospective observational study[17] of 1017 adult intensive care patients receiving propofol for at least 24 hours found that propofol infusion syndrome developed in 11 patients after an average of 3 days post infusion. Of these 11 patients, 2 died and 2 had received a dose of more than 4.98 mg/kg per hour of propofol (one of whom died). However, one commentator[18] has questioned the findings of this study, noting that they were at odds with most published literature and that the authors did not establish a dose-dependent association. It has also been suggested that concomitant use of glucocorticoids or vasopressive catecholamines are risk factors for development of the syndrome.[16]

Recent recommendations[19-21] on the safe use of propofol have reiterated that it should only be used by professionals trained in the provision of general anaesthesia and given in medical settings where resuscitation facilities are available.

1. CSM. Propofol—convulsions, anaphylaxis and delayed recovery from anaesthesia. *Current Problems 26* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024442&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
2. CSM. Propofol and delayed convulsions. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
3. CSM. Serious adverse effects and fatalities in children associated with the use of propofol (Diprivan) for sedation. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
4. CSM/MCA. Clarification: propofol (Diprivan) infusion contraindication. *Current Problems* 2002; **28:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074546&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
5. Parke TJ, *et al*. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992; **305:** 613–16.
6. Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; **8:** 491–9.
7. Cremer OL, *et al*. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; **357:** 117–18.
8. CSM/MCA. Long term, high dose propofol (Diprivan) infusion. *Current Problems* 2001; **27:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074586&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
9. Ernest D, French C. Propofol infusion syndrome: report of an adult fatality. *Anaesth Intensive Care* 2003; **31:** 316–19.
10. Merz TM, *et al*. Propofol infusion syndrome—a fatal case at a low infusion rate. *Anesth Analg* 2006; **103:** 1050.
11. Eriksen J, Povey HMR. A case of suspected non-neurosurgical adult fatal propofol infusion syndrome. *Acta Anaesthesiol Scand* 2006; **50:** 117–19.
12. Adverse Drug Reactions Advisory Committee (ADRAC). Propofol: danger of prolonged and high infusion rates in ICU. *Aust Adverse Drug React Bull* 2004; **23:** 23–4. Also available at: http://www.tga.gov.au/pdf/aadrb-0412.pdf (accessed 20/09/11)
13. Fodale V, La Monaca E. Propofol infusion syndrome: an overview of a perplexing disease. *Drug Safety* 2008; **31:** 293–303.
14. Orsini J, *et al*. Propofol infusion syndrome: case report and literature review. *Am J Health-Syst Pharm* 2009; **66:** 908–15.
15. Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and pathophysiology. *Minerva Anestesiol* 2009; **75:** 339–44.
16. Laquay N, *et al*. Le syndrome de perfusion du propofol. *Ann Fr Anesth Reanim* 2010; **29:** 377–86.
17. Roberts RJ, *et al*. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care* 2009; **13:** R169. Available at: http://ccforum.com/content/13/5/R169 (accessed 07/04/11)
18. Cremer OL. The propofol infusion syndrome: more puzzling evidence on a complex and poorly characterized disorder. *Crit Care* 2009; **13:** 1012. Available at: http://ccforum.com/content/13/6/1012 (accessed 07/04/11)
19. American Society of Anesthesiologists. Statement on safe use of propofol (approved 27th October, 2004; amended 21st October, 2009). Also available at: http://www.asahq.org/For-Members/Clinical-Information/~/media/For%20Members/documents/Standards%20Guidelines%20Stmts/Safe%20Use%20of%20Propofol.ashx (accessed 20/09/11)
20. Vargo JJ, *et al*. American Association for the Study of Liver Diseases, American College of Gasteroenterology, American Gastroenterological Association. Position statement: nonanesthesiologist administration of propofol for GI endoscopy. *Gastroenterology* 2009; **137:** 2161–7. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508509017454.pdf (accessed 26/09/11)
21. Dumonceau JM, *et al*. NAAP Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology guideline: non-anaesthesiologist administration of propofol for GI endoscopy. *Eur J Anaesthesiol* 2010; **27:** 1016–30.

Effects on the cardiovascular system. The main effect of propofol on the cardiovascular system is a fall in both systolic and diastolic blood pressure of 20 to 30%. The compensatory tachycardia seen after a fall in arterial pressure with other intravenous anaesthetics is not usually seen with propofol. Propofol can also decrease systemic vascular resistance, cardiac output, myocardial blood flow, and myocardial oxygen consumption. Bradycardia can occur even in those premedicated with antimuscarinics, and can occasionally be profound and lead to asystole.[1] Despite these cardiodepressant effects propofol in doses of 1.5 to 2.5 mg/kg does not generally cause unacceptable haemodynamic changes in patients with a healthy cardiovascular system although concern has been expressed about its safety in cardiac surgical patients.[2]

Patients (especially children) given propofol for continuous sedation in intensive care units have suffered adverse cardiac reactions with bradyarrhythmia, progressive myocardial failure, and death—see Incidence of Adverse Effects, p. 1910.3.

1. Tramèr MR, *et al*. Propofol and bradycardia: causation, frequency and severity. *Br J Anaesth* 1997; **78:** 642–51.
2. Ginsberg R, Lippmann M. Haemodynamic effects of propofol. *Br J Anaesth* 1994; **72:** 370–1.

Effects on lipids. Prolonged infusion of propofol may be associated with increases in serum triglycerides. In one patient this was believed to have been the cause of necrotising pancreatitis.[1]

1. Metkus AP, *et al*. A firefighter with pancreatitis. *Lancet* 1996; **348:** 1702.

Effects on mental function. There have been anecdotal reports[1] of disinhibited behaviour or sexually orientated hallucinations associated with the use of propofol, but a study using subanaesthetic doses found no evidence that propofol produced euphoria or other mood changes.[2]

1. Canaday BR. Amorous, disinhibited behaviour associated with propofol. *Clin Pharm* 1993; **12:** 449–51.
2. Whitehead C, *et al*. The subjective effects of low-dose propofol. *Br J Anaesth* 1994; **72** (suppl 1): 89.

Effects on the nervous system. See under Precautions, p. 1912.1.

Effects on respiration. See under Precautions, p. 1912.1.

Hypersensitivity. Anaphylactic reactions associated with polyoxyl castor oil used in propofol preparations had prompted a change to the use of soya oil and egg phosphatide in the formulation. A group of workers have reported a patient who had anaphylactic shock when given the reformulated emulsion.[1] A possible case of anaphylaxis to this formulation has also been reported in a child with allergies to egg and peanut oil.[2] Indeed, licensed product information contra-indicates its use in patients with peanut, soya, or egg allergy. However, some[3] have attributed such reactions to propofol itself, in particular its isopropyl and phenol groups.

1. Laxenaire MC, *et al*. Anaphylactic shock due to propofol. *Lancet* 1988; **ii:** 739–40.
2. Hofer KN, *et al*. Possible anaphylaxis after propofol in a child with food allergy. *Ann Pharmacother* 2003; **37:** 398–401.
3. Bradley AED, *et al*. Use of propofol in patients with food allergies. *Anaesthesia* 2008; **63:** 439.

Infection. Between June 1990 and February 1993, 62 cases of postsurgical infections identified in 7 hospitals in the USA were attributed to improper handling of propofol.[1] The infusion was not prepared aseptically and the syringes used in the infusion pumps were reused for several patients. Propofol is formulated as a soybean fat emulsion and the injection contains no antimicrobial preservative although, in the UK and USA, the formulation now contains the microbial-retarding agent, disodium edetate (see Administration, p. 1910.1). However, either formulation still has the potential to support microbial growth. Licensed product information now warns of the importance of aseptic technique in the preparation and use of propofol. Microbial multiplication did not appear to be clinically significant when propofol infusions were prepared and given using conventional aseptic techniques.[2]

1. Bennett SN, *et al*. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med* 1995; **333:** 147–54.
2. Farrington M, *et al*. Do infusions of midazolam and propofol pose an infection risk to critically ill patients? *Br J Anaesth* 1994; **72:** 415–17.

Malignant hyperthermia. From an *in-vitro* study it was concluded that propofol does not trigger malignant hyperthermia.[1] There is a report of the safe use of propofol in 19 patients considered susceptible to malignant hyperthermia.[2]

1. Denborough M, Hopkinson KC. Propofol and malignant hyperpyrexia. *Lancet* 1988; **i:** 191.
2. Harrison GG. Propofol in malignant hyperthermia. *Lancet* 1991; **337:** 503.

Pain on injection. Product information suggests the use of lidocaine or alfentanil to reduce the pain associated with injection of conventional formulations of propofol (see Administration, p. 1910.1); alternatively, the larger veins in the forearm and antecubital fossa can be used. Studies indicate that metoclopramide[1] might also be effective. The pain is thought to be caused by the proportion of the propofol dose that is present in the aqueous rather than the oily phase of the emulsion. It has been suggested[2] that the analgesic effect of lidocaine, and possibly metoclopramide, is due to a pH-lowering effect, causing more propofol to be present in the oily phase, but a study showing that lidocaine given by iontophoresis also reduces pain[3] suggests this is not the only mechanism. In another attempt to reduce pain by decreasing the amount of aqueous propofol, a formulation containing a mixture of medium-chain and long-chain triglycerides (*Propofol-Lipuro*), assumed to improve distribution into the lipid phase, has been introduced in some countries. However, studies in adults[4] and children[5] suggest that the reduction in pain with the newer formulation is not as great as that achieved by mixing lidocaine with the conventional long-chain formulation. Licensed product information for this formulation makes similar recommendations for reducing injection pain to those of the conventional formulation. Although some studies in adults[6] and children[7] have suggested that mixing lidocaine with *Propofol-Lipuro* resulted in less injection pain than mixing lidocaine with the conventional formulation, another study in children[8] had found the incidence and intensity of the pain to be similar with both methods. A systematic review and meta-analysis[9] of 177 randomised controlled studies found that about 60% of patients develop pain on injection of propofol alone, and that using an antecubital vein, or pretreating the hand vein with lidocaine along with venous occlusion, were most effective in reducing injection pain. The authors also recommended routine use of a small dose of opioids before induction unless contra-indicated.

1. Ganta R, Fee JPH. Pain on injection of propofol: comparison of lignocaine with metoclopramide. *Br J Anaesth* 1992; **69:** 316–17.
2. Eriksson M, *et al*. Effect of lignocaine and pH on propofol-induced pain. *Br J Anaesth* 1997; **78:** 502–6.
3. Sadler PJ, *et al*. Iontophoretically applied lidocaine reduces pain on propofol injection. *Br J Anaesth* 1999; **82:** 432–4.
4. Adam S, *et al*. Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. *Anesth Analg* 2004; **99:** 1076–9.
5. Nyman Y, *et al*. Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. *Br J Anaesth* 2005; **95:** 222–5.
6. Mallick A, *et al*. Lidocaine is more efficient than the choice of propofol formulations to reduce incidence of pain on induction. *Eur J Anaesthesiol* 2007; **24:** 403–7.
7. Rochette A, *et al*. Avoiding propofol injection pain in children: a prospective, randomized, double-blinded, placebo-controlled study. *Br J Anaesth* 2008; **101:** 390–4.
8. Varghese E, *et al*. Does the newer preparation of propofol, an emulsion of medium/long chain triglycerides cause less injection pain in children when premixed with lignocaine? *Pediatr Anesth* 2010; **20:** 338–42.
9. Jalota L, *et al*. Prevention of pain on injection of propofol: systematic review and meta-analysis. Abstract: *BMJ* 2011; **342:** 694. Full version: http://www.bmj.com/content/342/bmj.d1110.full.pdf (accessed 12/04/11)

Urine discoloration. A case report of dark green urine in a 16-year-old during a prolonged infusion of propofol.[1] Pink urine that also contained a uric acid precipitate was collected from an obese surgical patient after propofol anaesthesia.[2]

1. Bodenham A, *et al*. Propofol infusion and green urine. *Lancet* 1987; **ii:** 740.
2. Stern AB, *et al*. Pink urine after propofol anesthesia. *Kidney Int* 2010; **78:** 1193.

Precautions

Propofol should not be given to patients known to be allergic to it, or who have peanut, soya, or egg allergy (see Hypersensitivity, p. 1911.2). Propofol should be used with caution in patients with hypovolaemia, epilepsy, or lipid metabolism disorders, and in the elderly. Since there have been reports of delayed convulsions associated with the use of propofol it is recommended that special care should be taken when propofol is used for day-case surgery. When used in patients with increased intracranial pressure it should be given slowly to avoid a substantial decrease in mean arterial pressure and a resultant decrease in cerebral perfusion pressure. It is also recommended that propofol should not be used with ECT. Premedication with an antimuscarinic may be advisable since propofol does not cause vagal inhibition.

Propofol is used to provide continuous sedation for ventilated adult patients under intensive care. Account should be taken of increasing the patient's lipid load. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored. Children aged 16 years or less should not be sedated in this manner with propofol (see Incidence of Adverse Effects, p. 1910.3). Propofol is not recommended for use in obstetrics including caesarean section.

See also Precautions for General Anaesthetics, p. 1897.3.

For the need for aseptic handling of propofol see Administration, p. 1910.1 and Infection, p. 1911.2.

Abuse. References[1-6] to the abuse of propofol.

1. Kranioti EF, *et al*. Lethal self administration of propofol (Diprivan): a case report and review of the literature. *Forensic Sci Int* 2007; **167:** 56–8.
2. Wischmeyer PE, *et al*. A survey of propofol abuse in academic anesthesia programs. *Anesth Analg* 2007; **105:** 1066–71.
3. Roussin A, *et al*. Pharmacological and clinical evidences on the potential for abuse and dependence of propofol: a review of the literature. *Fundam Clin Pharmacol* 2007; **21:** 459–66.
4. Wilson C, *et al*. The abuse potential of propofol. *Clin Toxicol* 2010; **48:** 165–70.
5. Levy RJ. Clinical effects and lethal and forensic aspects of propofol. *J Forensic Sci* 2011; **56** (suppl 1): S142–S147.
6. Monroe T, *et al*. The misuse and abuse of propofol. *Subst Use Misuse* 2011; **46:** 1199–1205.

Breast feeding. A patient reported that the first breast milk expressed 8 hours after surgery, performed under an anaesthetic regimen that included propofol, had a bluish-green colour that changed to green on standing. The exact compound responsible for the discoloration could not be identified and any potential risk to a breast-fed infant was unknown.

1. Birkholz T, *et al*. Green breast milk after propofol administration. *Anesthesiology* 2009; **111:** 1168–9.

CNS effects. Epileptic activity was seen[1] on the EEGs of 3 patients given propofol and it was suggested that it might be useful in ECT, but others[2,3] found that the duration of seizures was less with propofol anaesthesia than with methohexital anaesthesia. It has been suggested[4] that propofol should not be used with ECT and this is the advice in UK licensed product information.

Some consider that abnormal movements induced by propofol are not associated with cortical seizure activity.[5,6] These appear to be more frequent with low doses of propofol[6] and can be abolished in children by increasing the induction dose of propofol from 3 to 5 mg/kg.

1. Hodkinson BP, *et al*. Propofol and the electroencephalogram. *Lancet* 1987; **ii:** 1518.
2. Simpson KH, *et al*. Seizure duration after methohexitone or propofol for induction of anaesthesia for electroconvulsive therapy (ECT). *Br J Anaesth* 1987; **59:** 1323P–1324P.
3. Rampton AJ, *et al*. Propofol and electroconvulsive therapy. *Lancet* 1988; **i:** 296–7.
4. Anonymous. Addendum: propofol better avoided with ECT at present. *Drug Ther Bull* 1990; **28:** 72.
5. Borgeat A, *et al*. Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation. *Br J Anaesth* 1993; **70:** 459–61.
6. Borgeat A, *et al*. Propofol and epilepsy: time to clarify. *Anesth Analg* 1994; **78:** 198–9.

Impaired respiration. The manufacturer has stated[1] that some patients who have received propofol for sedation in regional anaesthesia have had bradypnoea or hypoxaemia, or both. A reduction in oxygen saturation has also been noted in other patients sedated for endoscopy.[2] Licensed product information therefore recommends that oxygen saturation should be monitored and that oxygen supplementation should be readily available.

1. Arnold BDC. Sedation with propofol during regional anaesthesia. *Br J Anaesth* 1993; **70:** 112.
2. Patterson KW, *et al*. Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *Br J Anaesth* 1991; **67:** 108–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propofol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

The use of propofol with other CNS depressants, including those used in premedication, may increase the sedative, anaesthetic, and cardiorespiratory depressant effects of propofol. It is recommended that propofol is given after opioids so that the dose of propofol can be carefully titrated against the response. The dosage of propofol should be reduced if used with nitrous oxide or halogenated anaesthetics. Although propofol does not potentiate the effects of neuromuscular blockers, bradycardia and asystole have occurred after use of propofol with atracurium or suxamethonium (but see under Adverse Effects, p. 1911.2 for the effects of propofol itself on the cardiovascular system).

See also Interactions of General Anaesthetics, p. 1897.3.

Benzodiazepines. Propofol and *midazolam* have been reported to act synergistically.[1-3]

1. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
2. McClune S, *et al*. Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
3. Teh J, *et al*. Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.

Catecholamines. For the suggestion that use of catecholamines increases the risk of developing the propofol infusion syndrome see Incidence of Adverse Effects, p. 1910.3.

Clonidine. Premedication with clonidine has been reported[1] to reduce intraoperative requirements of propofol.

1. Guglielminotti J, *et al*. Effects of premedication on dose requirements for propofol: comparison of clonidine and hydroxyzine. *Br J Anaesth* 1998; **80:** 733–6.

Corticosteroids. For the suggestion that use of *glucocorticoids* increases the risk of developing the propofol infusion syndrome see Incidence of Adverse Effects, p. 1910.3.

Gastrointestinal drugs. The dose of propofol required for induction is reduced in patients given *metoclopramide*.[1]

1. Page VJ, Chhipa JH. Metoclopramide reduces the induction dose of propofol. *Acta Anaesthesiol Scand* 1997; **41:** 256–9.

General anaesthetics. Use with *halothane* or *isoflurane* has been reported to increase serum concentrations of propofol.[1] Synergy has been reported between propofol and *etomidate*.[2]

1. Grundmann U, *et al*. Propofol and volatile anaesthetics. *Br J Anaesth* 1994; **72** (suppl 1): 88.
2. Drummond GB, Cairns DT. Do propofol and etomidate interact kinetically during induction of anaesthesia? *Br J Anaesth* 1994; **73:** 272P.

Local anaesthetics. A reduction in the amount of propofol required to provide adequate hypnosis[1] or sedation[2] has been reported after *bupivacaine*[1] or *lidocaine*.[1,2] However, lidocaine is often added to propofol emulsions to reduce the pain of injection, see Administration, p. 1910.1.

1. Ben-Shlomo I, *et al*. Hypnotic effect of iv propofol is enhanced by im administration of either lignocaine or bupivacaine. *Br J Anaesth* 1997; **78:** 375–7.
2. Mallick A, *et al*. Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation. *Br J Anaesth* 1996; **77:** 731–4.

Opioids. In a study mean blood concentrations of propofol were higher in patients pretreated with *fentanyl* compared with patients maintained only on nitrous oxide.[1] However, others[2] were unable to confirm this interaction.

1. Cockshott ID, *et al*. Pharmacokinetics of propofol in female patients. *Br J Anaesth* 1987; **59:** 1103–10.
2. Dixon J, *et al*. Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol. *Br J Anaesth* 1990; **64:** 142–7.

Pharmacokinetics

The pharmacokinetics of propofol are best described by a 3-compartment model. After a single bolus dose, two distribution phases are seen. The first phase has a half-life of 2 to 4 minutes. This is followed by a second phase with a half-life of 30 to 60 minutes during which significant metabolism of propofol occurs, and then by a slower redistributive phase. The terminal half-life ranges from 3 to 12 hours; with prolonged use, the terminal half-life may be longer. The termination of anaesthetic effect after a single intravenous bolus or maintenance infusion is due to extensive redistribution from the brain to other tissues and to metabolic clearance.

Propofol is over 95% bound to plasma proteins. It undergoes extensive hepatic metabolism to conjugates which are eliminated in the urine. The pharmacokinetics of propofol do not appear to be altered by gender, chronic hepatic cirrhosis, or chronic renal impairment. Propofol crosses the placental barrier and is distributed into breast milk.

References.

1. Saint-Maurice C, *et al*. Pharmacokinetics of propofol in young children after a single dose. *Br J Anaesth* 1989; **63:** 667–70.
2. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet* 1989; **17:** 308–26.
3. Gin T, *et al*. Pharmacokinetics of propofol in women undergoing elective caesarean section. *Br J Anaesth* 1990; **64:** 148–53.
4. Servin F, *et al*. Pharmacokinetics of propofol infusions in patients with cirrhosis. *Br J Anaesth* 1990; **65:** 177–83.
5. Jones RDM, *et al*. Pharmacokinetics of propofol in children. *Br J Anaesth* 1990; **65:** 661–7.
6. Morgan DJ, *et al*. Pharmacokinetics of propofol when given by intravenous infusion. *Br J Clin Pharmacol* 1990; **30:** 144–8.
7. Gin T, *et al*. Disposition of propofol at caesarean section and in the postpartum period. *Br J Anaesth* 1991; **67:** 49–53.
8. Bailie GR, *et al*. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth* 1992; **68:** 486–91.
9. Altmayer P, *et al*. Propofol binding in human blood. *Br J Anaesth* 1994; **72** (suppl 1): 86.
10. Oei-Lim VLB, *et al*. Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment. *Br J Anaesth* 1998; **80:** 324–31.
11. Dawidowicz AL, *et al*. Free and bound propofol concentrations in human cerebrospinal fluid. *Br J Clin Pharmacol* 2003; **56:** 545–50.
12. Hiraoka H, *et al*. Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. *Br J Clin Pharmacol* 2005; **60:** 176–82.
13. Nitsun M, *et al*. Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.
14. Peeters MYM, *et al*. Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery. *Anesthesiology* 2006; **104:** 466–74.
15. Kim K-M, *et al*. Pharmacokinetics and pharmacodynamics of propofol microemulsion and lipid emulsion after an intravenous bolus and variable rate infusion. *Anesthesiology* 2007; **106:** 924–34.
16. Allegaert K, *et al*. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *Br J Anaesth* 2007; **99:** 864–70.
17. Bleeker C, *et al*. Recovery and long-term renal excretion of propofol, its glucuronide, and two di-isopropylquinol glucuronides after propofol infusion during surgery. *Br J Anaesth* 2008; **101:** 207–12.
18. Peeters MYM, *et al*. Disease severity is a major determinant for the pharmacodynamics of propofol in critically ill patients. *Clin Pharmacol Ther* 2008; **83:** 443–51.
19. Han T-H, *et al*. Propofol clearance and volume of distribution are increased in patients with major burns. *J Clin Pharmacol* 2009; **49:** 768–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diprivan; Fresofol; Gobbifol; Oleo-Lax; ***Austral.***: Diprivan; Fresofol; Recofol†; ***Austria***: Diprivan; ***Belg.***: Diprivan; Propolipid; ***Braz.***: Diprivan; Porpovan†; Profolen; Propoabbott†; Propotil; Propovan; ***Canad.***: Diprivan; ***Chile***: Anefol; Diprivan; ***China***: Di Shi Ning (迪施宁); Diprivan (得普利麻); Le Wei Jing (乐维静); Li Meng Xin (力蒙欣); Recofol (瑞可富); ***Cz.***: Diprivan†; Recofol†; ***Denm.***: Diprivan; Propolipid; Recofol; ***Fin.***: Propolipid; Recofol†; ***Fr.***: Diprivan; ***Ger.***: Disoprivan; ***Gr.***: Diprivan; Morpheas; Propogen; Recofol; ***Hong Kong***: Diprivan; Fresofol; ***Hung.***: Diprivan†; ***India***: Celofol; Cleofol; Critifol; Diprivan; Fresofol; Hypro; ***Indon.***: Diprivan; Fresofol; Proanes; Recofol; Safol; Trivam; ***Irl.***: Diprivan; Propoven; ***Israel***: Diprivan; Diprofol; Propofol Lipuro; Recofol; ***Ital.***: Diprivan; ***Malaysia***: Diprivan; Fresofol†; ***Mex.***: Cryotol; Diprivan; Fresofol; Indufol; Provive†; Recofol; ***Neth.***: Curtega; Diprivan; Recofol; Ripol; ***Norw.***: Diprivan†; Propolipid; ***NZ***: Diprivan; Fresofol; Provive; ***Philipp.***: Diprifol; Diprivan; Fresofol; IV-Pro; Lipuro; ***Pol.***: Abbofol†; Diprivan; Plofed; ***Port.***: Diprivan; Provive; ***Rus.***: Diprivan (Диприван); Propovan (Пропован); Recofol (Рекофол); ***S.Afr.***: Diprivan; Recofol†; ***Singapore***: Diprivan†; Fresofol; Recofol; ***Spain***: Diprivan; Recofol; ***Swed.***: Diprivan; Propolipid; ***Switz.***: Disoprivan; ***Thai.***: Anepol; Anesvan; Fresofol; Pofol; Profol; Recofol†; ***Turk.***: Diprivan; Pofol; Recofol; ***UK***: Diprivan; Propoven; ***Ukr.***: Diprivan (Диприван); Diprofol (Дипрофол); ***USA***: Diprivan; Propoven; ***Venez.***: Anespro; Diprivan; Profol.

Pharmacopoeial Preparations

BP 2014: Propofol Injection;
USP 36: Propofol Injectable Emulsion.

Sevoflurane *(BAN, USAN, rINN)*

BAX-3084; MR-654; Sevofluraan; Sevofluraani; Sevofluran; Sévoflurane; Sevoflurano; Sevofluranum; Sewofluran; Szevoflurán; Севофлуран.

Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether; 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)-propane.

$C_4H_3F_7O$=200.1

CAS — 28523-86-6.
ATC — N01AB08.
ATC Vet — QN01AB08.
UNII — 38LVP0K73A.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sevoflurane). A clear, colourless, volatile, non-flammable liquid. Slightly soluble in water; miscible with alcohol. Store in airtight, stainless-steel containers. Protect from light.

USP 36: (Sevoflurane). A clear, colourless, volatile, non-flammable liquid. Slightly soluble in water; miscible

with alcohol, with chloroform, and with ether. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Sevoflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 1.4% in the elderly to 3.3% in neonates. It is used for the induction and maintenance of general anaesthesia (p. 1896.1). It is non-flammable. Sevoflurane has a nonpungent odour and does not cause respiratory irritation. It also has muscle relaxant properties which may be sufficient for some surgical procedures to be performed without a neuromuscular blocker. However, it has been reported to possess no analgesic properties (but see Pain, below).

Sevoflurane is given using a calibrated vaporiser. A short-acting barbiturate or other intravenous induction agent may be given before inhaling sevoflurane. For induction in premedicated patients, sevoflurane is given in concentrations of up to 5% v/v in adults, with oxygen or a mixture of oxygen and nitrous oxide; concentrations of up to 7% v/v may be used in children. For induction in unpremedicated patients, concentrations of up to 8% v/v may be used. Induction with sevoflurane is rapid (surgical anaesthesia in less than 2 minutes) and smooth because of its nonpungent odour. Maintenance of anaesthesia is achieved with a concentration of 0.5 to 3% v/v with or without nitrous oxide.

Reviews.

1. Patel SS, Goa KL. Sevoflurane: a review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. *Drugs* 1996; **51:** 658–700.
2. Smith I, *et al.* Sevoflurane—a long-awaited volatile anaesthetic. *Br J Anaesth* 1996; **76:** 435–45.
3. Grounds RM, Newman PJ. Sevoflurane. *Br J Hosp Med* 1997; **57:** 43–6.
4. Goa KL, *et al.* Sevoflurane in paediatric anaesthesia: a review. *Paediatr Drugs* 1999; **1:** 127–53.
5. Ghatge S, *et al.* Sevoflurane: an ideal agent for adult day-case anesthesia? *Acta Anaesthesiol Scand* 2003; **47:** 917–31.
6. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.

Administration in children. Sevoflurane is used for the induction and maintenance of general anaesthesia in children; for details of doses, see Uses and Administration, above.

Pain. Two small, open-label studies[1,2] found self-administered sevoflurane 0.8% v/v in oxygen to be effective for pain relief during childbirth although an earlier study[3] was unable to confirm that it had an analgesic effect at subanaesthetic concentrations.

1. Yeo ST, *et al.* Analgesia with sevoflurane during labour: I. Determination of the optimum concentration. *Br J Anaesth* 2007; **98:** 105–9.
2. Yeo ST, *et al.* Analgesia with sevoflurane during labour: II. Sevoflurane compared with Entonox for labour analgesia. *Br J Anaesth* 2007; **98:** 110–15.
3. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70:** 684–6.

Adverse Effects

As with other halogenated anaesthetics sevoflurane may cause cardiorespiratory depression, hypotension, and malignant hyperthermia. However, the effects of sevoflurane on heart rate have only been seen at higher concentrations and it appears to have little effect on heart rhythm in comparison to other halogenated anaesthetics. Sevoflurane appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Other effects seen with sevoflurane include agitation, especially in children, laryngospasm, and increased cough and salivation. Urinary retention and acute renal failure have also been noted, as have changes in liver enzyme values and reports of liver damage. Seizures have occurred in children and young adults, as well as older adults, with and without predisposing risk factors; dystonic movements have also been seen in children. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on the cardiovascular system. The cardiovascular effects of sevoflurane are similar to those of isoflurane (see p. 1904.1) but it does not produce coronary steal. Also sevoflurane produces less tachycardia than isoflurane suggesting that it may be preferable in those predisposed to myocardial ischaemia.

Effects on the kidneys. Investigations[1] of the nephrotoxic potential of sevoflurane have found no evidence of renal function impairment despite peak plasma-fluoride ion concentrations greater than 50 nanomol/mL (a level considered to be nephrotoxic) being recorded in some patients at the end of sevoflurane anaesthesia,[2] and clinical experience would tend to support this.[3] The lack of renal toxicity with sevoflurane may be due to low concentrations of intrarenally generated fluoride ions;[4] in comparison, methoxyflurane defluorination in the kidney is much greater, and other metabolites may contribute to its known nephrotoxicity (see p. 1908.1).

Compound A, formed by the degradation of sevoflurane by carbon dioxide absorbents (see under Precautions, below), is nephrotoxic in *rats*.[1] However, studies in humans undergoing sevoflurane anaesthesia have detected no renal impairment postoperatively even when compound A was detected in the anaesthetic circuits.

1. Malan TP. Sevoflurane and renal function. *Anesth Analg* 1995; **81:** S39–S45.
2. Kobayashi Y, *et al.* Serum and urinary inorganic fluoride concentrations after prolonged inhalation of sevoflurane in humans. *Anesth Analg* 1992; **74:** 753–7.
3. Gentz BA, Malan TP. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs* 2001; **61:** 2155–62.
4. Kharasch ED, *et al.* Human kidney methoxyflurane and sevoflurane metabolism: intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. *Anesthesiology* 1995; **82:** 689–99.

Effects on the liver. There have been signs of hepatotoxicity in *animal* studies but in studies in humans, markers for hepatocellular dysfunction were no greater after sevoflurane anaesthesia than those after isoflurane.[1] The metabolism of sevoflurane differs from other halogenated anaesthetics in such a way that metabolites implicated in liver toxicity are not formed (see Pharmacokinetics, p. 1914.1). Nevertheless, licensed product information states that there have been postmarketing reports of hepatitis, and fatal cases of hepatic failure[2] and necrosis[3] have been reported. The production of compound A (see Carbon Dioxide Absorbents, under Precautions, below), increased cytosolic free calcium, and activation of free radical metabolising enzymes have been proposed as possible mechanisms of sevoflurane hepatotoxicity.[4]

1. Darling JR, *et al.* Comparison of the effects of sevoflurane with those of isoflurane on hepatic glutathione-S-transferase concentrations after body surface surgery. *Br J Anaesth* 1994; **73:** 268P.
2. Lehmann A, *et al.* Case report: fatal hepatic failure after aortic valve replacement and sevoflurane exposure. *Can J Anesth* 2007; **54:** 917–21.
3. Turillazzi E, *et al.* A fatal case of fulminant hepatic necrosis following sevoflurane anesthesia. *Toxicol Pathol* 2007; **35:** 780–5.
4. Singhal S, *et al.* Sevoflurane hepatotoxicity: a case report of sevoflurane hepatic necrosis and review of the literature. *Am J Ther* 2010; **17:** 219–22.

Effects on the nervous system. Sevoflurane has been shown to have a dose-related epileptogenic effect although the mechanism is unknown.[1] Tonic-clonic seizure-like movements associated with induction of anaesthesia using sevoflurane have been reported particularly in children[1-3] with or without a personal and/or family history of epilepsy or seizures, including an infant[4] with a history of tonic-clonic seizures. To minimise the risk, some have suggested[1] using a maximum of 1.5 times the minimum alveolar concentration (MAC) sevoflurane for maintenance of anaesthesia, and avoiding hypocapnia and monitoring cortical activity during the procedure.

1. Constant I, *et al.* Sevoflurane and epileptiform EEG changes. *Pediatr Anesth* 2005; **15:** 266–74.
2. Åkeson J, Didriksson I. Convulsions on anaesthetic induction with sevoflurane in young children. *Acta Anaesthesiol Scand* 2004; **48:** 405–7.
3. Yano T, *et al.* Two cases with past and family history of febrile convulsion developed seizure-like movements during sevoflurane anesthesia. *Anesthesiology* 2008; **109:** 571.
4. Rewari V, Sethi D. Recurrence of focal seizure activity in an infant during induction of anaesthesia with sevoflurane. *Anaesth Intensive Care* 2007; **35:** 788–91.

Hypersensitivity. For a report of hypersensitivity reactions, including asthma, associated with occupational exposure to isoflurane and sevoflurane, see under Precautions, below.

Precautions

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with sevoflurane. It should also not be used in those with a history of moderate or severe hepatic impairment associated with halogenated anaesthetics and should be used with caution in those with underlying liver disease. Sevoflurane reduces uterine muscle tone during pregnancy and should be used with caution in obstetrics because of the increased risk of uterine bleeding. Although the effects of sevoflurane on cerebral pressure are minimal in normal patients, safety in those with raised intracranial pressure has not been established and therefore sevoflurane should be used with caution together with techniques to lower intracranial pressure. As emergence and recovery are particularly rapid with sevoflurane patients may require early postoperative pain relief. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Fatalities have been reported[1-3] with the abuse of sevoflurane. Autopsy revealed pulmonary oedema and frothing in the lung of one victim, suggesting death by asphyxia,[1] and cardiac arrhythmias were considered the cause of death in another 2 victims.[2,3]

1. Rosales CM, *et al.* Sevoflurane concentrations in blood, brain, and lung after sevoflurane-induced death. *J Forensic Sci* 2007; **52:** 1408–10.
2. Levine B, *et al.* A fatality from sevoflurane abuse. *J Anal Toxicol* 2007; **31:** 534–6.
3. Cantrell FL. A fatal case of sevoflurane abuse. *Clin Toxicol* 2008; **46:** 918–19.

Carbon dioxide absorbents. During anaesthesia given by circle breathing systems, the degradation of sevoflurane by carbon dioxide absorbents (such as soda lime) results in the formation of pentafluoroisopropenyl fluoromethyl ether (PIFE; compound A), and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether (PMFE; Compound B). The degree of degradation, absorption, and solubility of volatile anaesthetics is affected by the water content of carbon dioxide absorbents. In the case of sevoflurane, patients may inhale significant amounts of degradation products when the soda lime dries out. Compound A has been shown to be nephrotoxic in *rats* (see under Effects on the Kidneys, above). Even during short exposure times, as required for induction of anaesthesia, use of moist soda lime is important to minimise sevoflurane degradation, which is also aggravated by a high potassium hydroxide content of the soda lime.[1] Licensed product information states that the problem of compound A formation may be greater if barium hydroxide lime is used as a carbon dioxide absorbent rather than soda lime. Newer carbon dioxide absorbents that contain no, or reduced amounts of, potassium and/or sodium hydroxide have been developed and subsequently shown[2-4] to reduce the degradation of sevoflurane.

The use of desiccated carbon dioxide absorbents with sevoflurane has also been associated with rare cases of extreme heat and smoke or fire developing in the anaesthetic apparatus.[5]

1. Funk W, *et al.* Dry soda lime markedly degrades sevoflurane during simulated inhalation induction. *Br J Anaesth* 1999; **82:** 193–8.
2. Kobayashi S, *et al.* Amsorb Plus and Drägersorb Free, two new-generation carbon dioxide absorbents that produce a low compound A concentration while providing sufficient CO_2 absorption capacity in simulated sevoflurane anesthesia. *J Anesth* 2004; **18:** 277–81.
3. Keijzer C, *et al.* Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. *Acta Anaesthesiol Scand* 2007; **51:** 31–7.
4. Marini F, *et al.* Compound A, formaldehyde and methanol concentrations during low-flow sevoflurane anaesthesia: comparison of three carbon dioxide absorbers. *Acta Anaesthesiol Scand* 2007; **51:** 625–32.
5. Abbott Laboratories, Canada. Important safety information regarding the use of Sevorane AF (sevoflurane) in conjunction with anesthesia machines (issued 17th November, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/sevorane_hpc-cps-eng.pdf (accessed 08/08/08)

Occupational exposure. Hypersensitivity reactions, manifesting as asthma, angioedema, or dermatitis, associated with occupational exposure to isoflurane and sevoflurane have been reported[1] in 3 healthcare workers. Of these, one worker with positive response on bronchial provocation testing subsequently had an anaphylactic reaction to sevoflurane during general anaesthesia; indirect exposure to sevoflurane resulted in a late asthmatic reaction in another, and exposure to isoflurane resulted in a rash in the third.

1. Vellore AD, *et al.* Occupational asthma and allergy to sevoflurane and isoflurane in anaesthetic staff. *Allergy* 2006; **61:** 1485–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sevoflurane as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Care is advised if adrenaline or other sympathomimetics are given during sevoflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by sevoflurane (see p. 2032.3). The metabolism, and hence toxicity, of sevoflurane may be increased by drugs or compounds that induce cytochrome P450 isoenzyme CYP2E1 including isoniazid and alcohol.

See also Interactions of General Anaesthetics, p. 1897.3.

References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; **9:** 105–17.

Pharmacokinetics

Sevoflurane is absorbed on inhalation. The blood/gas partition coefficient is low. Up to 5% of the absorbed dose of sevoflurane is metabolised in the liver by the cytochrome P450 isoenzyme CYP2E1 and defluorinated to its major metabolites hexafluoroisopropanol (HFIP), inorganic fluoride, and carbon dioxide. HFIP is rapidly conjugated with glucuronic acid and eliminated in the urine. Sevoflurane crosses the placenta.

References.
1. Behne M, *et al.* Clinical pharmacokinetics of sevoflurane. *Clin Pharmacokinet* 1999; **36:** 13–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Eraldin; Sevocristalia; Sevorane; ***Austral.***: Sevorane†; ***Austria***: Sevorane; ***Belg.***: Sevorane; ***Braz.***: Anesevo; Sevocris; Sevorane; ***Canad.***: Sevorane; ***Chile***: Sevorane; ***China***: Kai Te Li (凯特力); QiFuMei (奇弗美); Sevofrane (喜保福宁); Ultane (悦坦); ***Cz.***: Sevorane; ***Denm.***: Sevorane; ***Fin.***: Sevorane; ***Fr.***: Sevorane; ***Ger.***: Sevorane; ***Gr.***: Sevorane; ***Hong Kong***: Sevorane; ***Hung.***: Sevorane; ***Indon.***: Sevorane; Sojourn; ***Irl.***: Sevorane; ***Israel***: Sevorane; Sojourn; ***Ital.***: Sevorane; ***Malaysia***: Sevorane; ***Mex.***: Floves; Sevorane; Sovener; ***Neth.***: Sevorane; ***Norw.***: Sevorane; ***NZ***: Sevorane; ***Philipp.***: Sevo; Sevorane; ***Pol.***: Sevorane; ***Port.***: Sevorane; ***Rus.***: Sevorane (Севоране); ***S.Afr.***: Sojourn; Ultane; ***Singapore***: Sevorane; ***Spain***: Sevorane; ***Swed.***: Sevorane; ***Switz.***: Sevorane; ***Thai.***: Sefether; Sevorane; Sojourn; ***Turk.***: Sevorane; Sojourn; ***USA***: Sojourn; Ultane; ***Venez.***: Sevorane.

Sodium Oxybate *(USAN)*

JZP-6; NSC-84223; Ossibato di Sodio; Oxibato sódico; Sodium Gamma-hydroxybutyrate; Wy-3478; Натрия Оксибат; Натрия Оксибутират.

Sodium 4-hydroxybutyrate.

$C_4H_7NaO_3$=126.1

CAS — 502-85-2.

UNII — 7G33012534.

NOTE. The name Rekinla has been used as a trade mark for sodium oxybate.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of sodium oxybate or gamma-hydroxybutyrate:

Blue nitro; Blue verve; Caps; Cherry Meth; Date rape drug; Drogue Du Cambriolage Sexuel Parfait; Easy lay; Everclear; EZLay; Fantasy; G; Gamma Oh; Gamma-OH; GBH; Georgia home boy; GHB; Goop; Great hormones at bedtime; Grievous bodily harm; G-riffic; Jib; Liquid E; Liquid ecstacy; Liquid ecstasy; Liquid G; Liquid X; Organic quaalude; Salty water; Scoop; Sleep; Sleep-500; Soap; Somatomax; Somatomax PM; Vita-G; Water.

Pharmacopoeias. In *Chin.*

Uses and Administration

Sodium oxybate has hypnotic properties and, in its endogenous form, gamma-hydroxybutyrate (a catabolite of gamma-aminobutyric acid), increases dopamine concentrations in the brain. It is given intravenously usually with an opioid analgesic and a neuroleptic to produce general anaesthesia (p. 1896.1). Skeletal muscle relaxants may also be necessary. Sodium oxybate given orally is used in the treatment of cataplexy in patients with narcolepsy (below); in the USA it is also indicated for the excessive daytime sleepiness associated with narcolepsy.

In general anaesthesia a solution of sodium oxybate equivalent to 20% of the acid is given slowly by intravenous injection, usually in a dose of 60 mg/kg; in children 100 mg/kg may be used. For maintenance, a further dose that is half of the initial dose may be given.

For the management of narcolepsy in adults, sodium oxybate is given in initial oral doses of 4.5 g daily, as two equally-divided doses. The first dose should be taken at bedtime while in bed and at least 2 to 3 hours after food; the second dose should be taken 2.5 to 4 hours later also while sitting in bed. Both doses should be prepared before going to bed: each dose should be diluted with 60 mL of water. The initial dose may be increased in steps of 1.5 g (0.75 g per dose) every 1 to 2 weeks to a maximum dose of 9 g daily. If therapy has been stopped for more than 14 consecutive days, titration should be restarted at the lowest dose. Reduced doses are recommended in patients with hepatic impairment (see below).

References.
1. Fuller DE, *et al.* The Xyrem risk management program. *Drug Safety* 2004; **27:** 293–306.
2. Snead OC, Gibson KM. γ-Hydroxybutyric acid. *N Engl J Med* 2005; **352:** 2721–32. Correction. *ibid.* 2006; **354:** 537.
3. Pardi D, Black J. γ-Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs* 2006; **20:** 993–1018.
4. Castelli MP. Multi-faceted aspects of gamma-hydroxybutyric acid: a neurotransmitter, therapeutic agent and drug of abuse. *Mini Rev Med Chem* 2008; **8:** 1188–1202.
5. Benarroch EE. γ-Hydroxybutyric acid and its relevance in neurology. *Neurology* 2009; **72:** 282–6.

Administration in children. Sodium oxybate is used in general anaesthesia in children; for details of doses, see Uses and Administration, above.

Administration in hepatic impairment. The recommended initial oral dose of sodium oxybate (see Uses and Administration, above) should be halved in patients with hepatic impairment. Subsequent increases should be monitored against effect.

Alcohol withdrawal syndrome. A systematic review[1] of 13 randomised controlled studies involving 648 patients concluded that oral sodium oxybate 50 mg/kg daily is effective, when compared with placebo, in reducing symptoms of alcohol withdrawal (p. 1734.1) and in helping to prevent relapse for up to 3 months thereafter. It also appeared to be as effective as the benzodiazepines and clomethiazole in the treatment of alcohol withdrawal syndrome, and as effective as naltrexone and disulfiram in the maintenance of abstinence. The most commonly reported adverse effects were dizziness and vertigo. However, the risk of addiction, misuse, and/or abuse of the drug is of concern with this patient group.

1. Leone MA, *et al.* Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 17/03/11).

Cluster headache. Sodium oxybate has been investigated[1] in the management of patients with cluster headache (p. 670.1).

1. Khatami R, *et al.* Long-term efficacy of sodium oxybate in 4 patients with chronic cluster headache. *Neurology* 2011; **77:** 67–70.

Fibromyalgia. Studies[1-3] of the efficacy of sodium oxybate in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p. 14.2), showed some benefit in the perception of pain and fatigue, and in improving sleep.

1. Russell IJ, *et al.* Oxybate SXB-26 Fibromyalgia Syndrome Study Group. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum* 2009; **60:** 299–309.
2. Moldofsky H, *et al.* Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. *J Rheumatol* 2010; **37:** 2156–66.
3. Russell IJ, *et al.* Sodium Oxybate 06-008 FM Study Group. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. *Pain* 2011; **152:** 1007–17.

Narcoleptic syndrome. Sodium oxybate[1-7] given at night is used to improve cataplexy and excessive daytime sleepiness in patients with narcoleptic syndrome (p. 2314.3).

For a reference to the pharmacokinetics of sodium oxybate in narcoleptic patients, see p. 1915.1.

1. US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 2002; **25:** 42–9.
2. US Xyrem Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003; **26:** 31–5.
3. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med* 2005; **6:** 415–21.
4. Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med* 2005; **1:** 391–7.
5. Lemon MD, *et al.* Sodium oxybate for cataplexy. *Ann Pharmacother* 2006; **40:** 433–40.
6. Robinson DM, Keating GM. Sodium oxybate: a review of its use in the management of narcolepsy. *CNS Drugs* 2007; **21:** 337–54.
7. Black J, *et al.* The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J Clin Sleep Med* 2010; **6:** 596–602.

Adverse Effects

When used in general anaesthesia adverse effects with sodium oxybate include abnormal muscle movements during the induction period and nausea and vomiting. Occasional emergence delirium has been reported. Bradycardia frequently occurs. Respiration may be slowed and hypokalaemia has been reported.

The most common adverse reactions seen in patients taking sodium oxybate orally for the management of narcolepsy are dizziness, headache, and, particularly in women, nausea. Other common reactions include anorexia, vomiting, diarrhoea, peripheral oedema, abnormal dreams and nightmares, sleepwalking, confusion, depression, anxiety, insomnia, paraesthesia, somnolence, tremor, amnesia, blurred vision, sweating, muscle cramps, nocturnal enuresis, urinary incontinence, asthenia, and fatigue. Blood pressure may also be increased. Psychosis, convulsions, hallucinations, agitation, hypersensitivity, and faecal incontinence are less common; rarely, respiratory depression has been reported.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on electrolyte balance. A report of severe metabolic disorders occurring during therapy with sodium oxybate and tetracosactide in 4 patients with severe head injuries.[1] The disorders consisted of hypernatraemia, hypokalaemia, and metabolic acidosis.

1. Béal JL, *et al.* Troubles métaboliques induits par l'association gamma-hydroxy butyrate de sodium et tétracosactide chez le traumatisé crânien. *Therapie* 1983; **38:** 569–71.

Precautions

In general anaesthesia, sodium oxybate should not be given to patients with severe hypertension, bradycardia, conditions associated with defects of cardiac conduction, epilepsy, eclampsia, renal impairment, or alcohol abuse.

Treatment with oral sodium oxybate is contra-indicated in patients with succinic semialdehyde dehydrogenase deficiency, an enzyme involved in its metabolism to succinic acid. Its use is also contra-indicated in patients with epilepsy as safety and efficacy have not been established; convulsions have been reported with sodium oxybate use.

Patients with a history of depression or suicide attempt should be carefully monitored for depressive symptoms while taking sodium oxybate. The high sodium content of sodium oxybate (0.75 g of sodium in a 4.5 g daily dose) should be considered in patients with heart failure, hypertension, or impaired renal function.

Rebound symptoms with an increased frequency of cataplexy may be seen when sodium oxybate is stopped. There have also been rare reports of withdrawal symptoms such as insomnia, headache, dizziness, anxiety, hallucinations, and psychotic disorders following the illicit use of sodium oxybate (see Abuse, below).

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Reports[1] of acute poisoning with oral sodium oxybate after illicit use led the FDA to issue warnings[2] about its potential for abuse. It is usually supplied illicitly as the sodium salt under a variety of names (see Street Names, above) and has been promoted for body building, weight loss, as a psychedelic substance, and as a sleep aid. Sodium oxybate has also been abused at social gatherings.[3,4] Adverse effects include vomiting, drowsiness, amnesia, hypotonia, vertigo, respiratory depression, and involuntary movements. Seizure-like activity, bradycardia, hypotension, and respiratory arrest have also been reported. Resolution of symptoms occurs spontaneously over 2 to 96 hours. However, some patients have required hospitalisation and respiratory support; deaths have been reported in several countries.[5-9] Severity of symptoms depends on the dose of sodium oxybate and the presence of other drugs such as alcohol, benzodiazepines, cannabis, or amfetamines; however, fatalities associated with the ingestion of sodium oxybate alone have been reported.[9] Prolonged use of large doses may lead to a withdrawal syndrome on stopping.[3,4,10-12]

Sodium oxybate is available in tasteless and odourless forms, and has occasionally been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[3,4,13]

Its precursors gamma-butyrolactone (GBL) and 1,4-butanediol are abused similarly.[3,4,7,11] Withdrawal symptoms have also been associated with stopping these 2 substances in abusers.[12]

1. CDC. Multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. *JAMA* 1991; **265:** 447–8.
2. FDA. Warning about GHB. *JAMA* 1991; **265:** 1802.
3. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
4. National Institute on Drug Abuse. Club drugs (GHB, Ketamine, and Rohypnol) (updated July 2010). Available at: http://www.drugabuse.gov/pdf/infofacts/ClubDrugs10.pdf (accessed 28/03/11)
5. Anonymous. GBH death indicates increasing problem. *Pharm J* 1996; **256:** 441.
6. CDC. Gamma hydroxy butyrate use—New York and Texas, 1995–1996. *JAMA* 1997; **277:** 1511.
7. Caldicott DGE, *et al.* Fatalities associated with the use of γ-hydroxybutyrate and its analogues in Australasia. *Med J Aust* 2004; **181:** 310–13.
8. Knudsen K, *et al.* Twenty-three deaths with γ-hydroxybutyrate overdose in western Sweden between 2000 and 2007. *Acta Anaesthesiol Scand* 2010; **54:** 987–92.
9. Zvosec DL, *et al.* Case series of 226 γ-hydroxybutyrate-associated deaths: lethal toxicity and trauma. *Am J Emerg Med* 2011; **29:** 319–32.
10. Galloway GP, *et al.* Physical dependence on sodium oxybate. *Lancet* 1994; **343:** 57.
11. Wojtowicz JM, *et al.* Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM* 2008; **10:** 69–74.
12. van Noorden MS, *et al.* GHB-afhankelijkheid enonthoudingssyndroom: diagnostiek en behandeling. *Ned Tijdschr Geneeskd* 2010; **154:** A1286.

13. Németh Z, *et al.* The involvement of gamma-hydroxybutyrate in reported sexual assaults: a systematic review. *J Psychopharmacol* 2010; **24:** 1281–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium oxybate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

In anaesthesia, sodium oxybate enhances the effects of opioid analgesics, barbiturates, and competitive neuromuscular blockers. The CNS depressant effects of sodium oxybate may be potentiated by alcohol, sedative-hypnotics, and other CNS depressants. The risk of respiratory depression may also be increased by benzodiazepines.

See also Interactions of General Anaesthetics, p. 1897.3.

Pharmacokinetics

After oral doses sodium oxybate is rapidly but incompletely absorbed from the gastrointestinal tract; absolute bioavailability is about 25%. Peak concentrations are reached within 0.5 to 2 hours. Absorption may be delayed and decreased following a high fat meal. Protein binding is less than 1%. Sodium oxybate is metabolised in the liver via GHB dehydrogenase to succinic semialdehyde, which is then converted to succinic acid via another enzyme, succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle and is metabolised to carbon dioxide, which is expired, and water. Less than 5% of unchanged drug appears in the urine; faecal excretion is also negligible.

References.

1. Palatini P, *et al.* Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol* 1993; **45:** 353–6.
2. Scharf MB, *et al.* Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. *Sleep* 1998; **21:** 507–14.
3. Borgen LA, *et al.* The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J Clin Pharmacol* 2003; **43:** 59–65.
4. Borgen LA, *et al.* The pharmacokinetics of sodium oxybate oral solution following acute and chronic administration to narcoleptic patients. *J Clin Pharmacol* 2004; **44:** 253–7.
5. Brenneisen R, *et al.* Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol* 2004; **28:** 625–30.
6. Haller C, *et al.* GHB urine concentrations after single-dose administration in humans. *J Anal Toxicol* 2006; **30:** 360–4.
7. Abanades S, *et al.* Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. *Ann N Y Acad Sci* 2006; **1074:** 559–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Alcover; Xyrem; ***Belg.***: Xyrem; ***Canad.***: Xyrem; ***Cz.***: Xyrem; ***Denm.***: Xyrem; ***Fr.***: Gamma-OH; Xyrem; ***Ger.***: Somsanit; Xyrem; ***Irl.***: Xyrem; ***Ital.***: Alcover; Xyrem; ***Neth.***: Xyrem; ***Norw.***: Xyrem; ***Pol.***: Xyrem; ***Port.***: Xyrem; ***Spain***: Xyrem; ***Swed.***: Xyrem; ***Switz.***: Xyrem; ***UK***: Xyrem; ***USA***: Xyrem.

Thiamylal Sodium

Tiamilal sódico.
Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate.
$C_{12}H_{17}N_2NaO_2S$=276.3
CAS — 77-27-0 (thiamylal); 337-47-3 (thiamylal sodium).
UNII — T4L2P3KH7K.

Pharmacopoeias. In *Jpn*.

Profile

Thiamylal sodium is a short-acting intravenous barbiturate anaesthetic. It is possibly slightly more potent than thiopental sodium (below) and has similar actions and uses. It has been used for the production of complete anaesthesia of short duration, for the induction of general anaesthesia, or for inducing a hypnotic state.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Citosol; Isozol.

Thiopental Sodium *(BANM, rINN)*

Natrium Isopentylaethylthiobarbituricum (cum Natrio Carbonico); Penthiobarbital Sodique; Sodyum Tiopental; Sodyum Tiopenton; Soluble Thiopentone; Thiomebumalnatrium cum Natrii Carbonate; Thiopental et carbonate sodiques; Thiopental-Natrium; Thiopental Sodique; Thiopental Sodium and Sodium Carbonate; Thiopental sodná sůl a uhličitan sodný; Thiopentalum Natricum; Thiopentalum natricum et natrii carbonas; Thiopentobarbitalum Solubile; Thiopentone Sodium; Tiopentaalinatrium; Tiopentaalinatrium ja natriumkarbonaatti; Tiopental sódico; Tiopentalio natrio druska ir natrio karbonatas; Tiopentalnatrium; Tiopentál-nátrium és nátrium-karbonát; Tiopentalnatrium och natriumkarbonat; Тиопентал Натрий.

Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.
$C_{11}H_{17}N_2NaO_2S$=264.3
CAS — 76-75-5 (thiopental); 71-73-8 (thiopental sodium).
ATC — N01AF03; N05CA19.
ATC Vet — QN01AF03; QN05CA19.
UNII — 49Y44QZL70.

NOTE. The name thiobarbital has been applied to thiopental and has also been used to describe a barbiturate of different composition.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some include thiopental sodium with, some without, anhydrous sodium carbonate; some only include a sterile mixture for injection.

Ph. Eur. 8: (Thiopental Sodium and Sodium Carbonate; Thiopental Sodium BP 2014). A yellowish-white hygroscopic powder. It contains 84 to 87% thiopental and 10.2 to 11.2% sodium. Freely soluble in water; partly soluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 36: (Thiopental Sodium). A white to off-white crystalline powder, or yellowish-white to pale greenish-yellow hygroscopic powder. May have a disagreeable odour. Its solutions are alkaline to litmus, decompose on standing, and on boiling, precipitation occurs. Soluble in water and in alcohol; insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers.

Incompatibility. Solutions of thiopental sodium are incompatible with acidic and oxidising substances including some antibacterials, neuromuscular blockers and analgesics. Compounds commonly listed as incompatible include amikacin sulfate, benzylpenicillin salts, cefapirin sodium, codeine phosphate, ephedrine sulfate, fentanyl citrate, glycopyrronium bromide, morphine sulfate, pentazocine lactate, prochlorperazine edisilate, suxamethonium salts, and tubocurarine chloride. Solutions decompose on standing and precipitation occurs on boiling.

Stability. Loss of thiopental in PVC and cellulose propionate delivery systems has been reported,[1,2] but in another study,[3] no loss of potency was noted. Adsorption has been reported[4] not to occur in polyolefin infusion bags.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
3. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.

Uses and Administration

Thiopental is a short-acting barbiturate anaesthetic. It is given intravenously, usually for the induction of general anaesthesia (p. 1896.1), but may be used as the sole anaesthetic to maintain anaesthesia for short procedures with minimal painful stimuli. It is also used in anaesthesia as a supplement to other anaesthetics and as a hypnotic in balanced anaesthesia. Thiopental sodium may also be used intravenously in the control of refractory tonic-clonic status epilepticus and in neurosurgical patients to reduce increased intracranial pressure. It has also been given rectally for basal anaesthesia or basal narcosis.

Thiopental does not usually produce excitation and induction of anaesthesia is usually smooth. It has poor muscle relaxant properties and a muscle relaxant must be given before intubation is attempted. Thiopental also has poor analgesic properties and small doses may even lower the pain threshold. Recovery from moderate doses usually occurs within 10 to 30 minutes, but the patient may remain sleepy or confused for several hours. Large doses, repeated smaller doses, or continuous use may markedly delay recovery.

In **anaesthesia**, the dosage of thiopental varies greatly according to the state of the patient and the nature of other drugs being used concurrently (see under Precautions p. 1916.2 and Interactions p. 1916.2 for further details). Thiopental is usually given intravenously as the sodium salt as a 2.5% solution but a 5% solution is occasionally used. UK licensed product information states that a typical dose for inducing anaesthesia is 100 to 150 mg injected over 10 to 15 seconds, repeated after 30 to 60 seconds according to response. It also recommends that the total dosage used should not exceed 500 mg; in pregnant patients the total maximum dose is 250 mg. In some other countries, it has been recommended that induction begin with a test dose of 25 to 75 mg; thereafter, a dose of 50 to 75 mg may be given at intervals of 20 to 40 seconds according to response. Once anaesthesia has been established, additional doses of 25 to 50 mg may be given as necessary. When thiopental is used as the sole anaesthetic, anaesthesia can be maintained by repeat doses as needed or by continuous intravenous infusion of a 0.2 or 0.4% solution.

To **reduce elevations of intracranial pressure** in neurological patients, thiopental sodium is licensed for use as intermittent bolus injections of 1.5 to 3 mg/kg if adequate ventilation is provided (but see also Cerebrovascular Disorders, below). Higher doses have been tried.

For suggested doses in refractory tonic-clonic **status epilepticus**, see Status Epilepticus, p. 1916.1.

For dosage in *children* and the *elderly*, see also below.

References.

1. Russo H, Bressolle F. Pharmacodynamics and pharmacokinetics of thiopental. *Clin Pharmacokinet* 1998; **35:** 95–134.

Administration in children. For the *induction of anaesthesia* in children, UK licensed product information recommends that thiopental sodium is given by slow intravenous injection (over 10 to 15 seconds) in a dose of 2 to 7 mg/kg; the dose may be repeated after 1 minute. Intravenous injections are normally given as a 2.5% solution.

In the treatment of prolonged *status epilepticus* (see p. 1916.1), the *BNFC* recommends an initial dose of up to 2 mg/kg in neonates or up to 4 mg/kg in children aged 1 month to 18 years, given as a slow intravenous injection; for all patients, this should then be followed by a continuous intravenous infusion of up to 8 mg/kg per hour, adjusted according to response.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients showed that although reducing the rate of intravenous injection reduced the speed of induction, the dosage required was also reduced. Giving thiopental sodium 2.5% solution at a rate of 125 mg/minute induced anaesthesia in a mean of 90.8 seconds and required a mean dose of 2.8 mg/kg. Corresponding values for a rate of 500 mg/minute were 40.8 seconds and 5 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Anaesthesia. Some of the adverse effects of the neuromuscular blocker suxamethonium may be reduced when thiopental is used as part of the anaesthetic regimen. For a suggestion that thiopental may help to counteract the rise in intra-ocular pressure associated with the use of suxamethonium for intubation, see under Anaesthesia, p. 2028.1.

Cerebrovascular disorders. Barbiturates have been considered as suitable anaesthetics for use in patients with or at risk of raised intracranial pressure. Barbiturate-induced coma (commonly with pentobarbital or thiopental) has been used, both therapeutically and prophylactically, to protect the brain from ischaemia resulting from neurological insults including head injury, stroke, Reye's syndrome, and hepatic encephalopathy.[1-3] Rationale includes the ability of barbiturates to reduce intracranial pressure and to reduce metabolic demands of cerebral tissues. Although thiopental protected patients against the neuropsychiatric complications of cardiopulmonary bypass,[4] the Brain Resuscitation Clinical Trial I Study Group[5] found no cerebral benefit from thiopental in comatose survivors of cardiac arrest. Nor did others[6] observe any benefit from thiopental-induced coma in infants with severe birth asphyxia. A review in 1989 considered that there was no convincing evidence of improvement in neurological outcome to justify the risks of the procedure in conditions causing global ischaemia, although use of barbiturates without necessarily inducing coma might have a limited role in reduction of raised intracranial pressure refractory to other therapy. Use of barbiturates in the setting of regional cerebral ischaemia, including use during cardiopulmonary bypass to prevent focal neurological complications, remained controversial.[1] A systematic review[7] came to similar conclusions, pointing out that although the barbiturates may reduce intracranial pressure their hypotensive effects are likely to offset any beneficial action on cerebral perfusion, perhaps accounting for the lack of evidence for any clinical benefit. In addition, there have been individual case reports of effects on blood-potassium associated with thiopental-induced coma (see Effects on Electrolytes, under Adverse Effects and Treatment, p. 1916.1).

For a discussion of the treatment of raised intracranial pressure, including a mention of the use of barbiturates, see p. 1271.3.

1. Rogers MC, Kirsch JR. Current concepts in brain resuscitation. *JAMA* 1989; **261:** 3143–7.

2. Lyons MK, Meyer FB. Cerebrospinal fluid physiology and the management of increased intracranial pressure. *Mayo Clin Proc* 1990; **65:** 684–707.
3. Woster PS, LeBlanc KL. Management of elevated intracranial pressure. *Clin Pharm* 1990; **9:** 762–72.
4. Nussmeier NA, *et al*. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; **64:** 165–70.
5. Abramson NS, *et al*. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med* 1986; **314:** 397–403.
6. Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986; **61:** 1084–9.
7. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 16/06/05).

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used.

Doses of thiopental sodium in the treatment of status epilepticus appear to vary widely and may be defined by local clinical protocols. Licensed product information and the *BNF* recommend a dose of 75 to 125 mg intravenously as a 2.5% solution. Other regimens advocate an initial loading dose followed by further intermittent doses or a continuous infusion. European guidelines for the management of status epilepticus in adults suggest thiopental is started with a bolus of 3 to 5 mg/kg, then further boluses of 1 to 2 mg/kg every 2 to 3 minutes until seizures are controlled, followed by continuous intravenous infusion at a rate of 3 to 7 mg/kg per hour, titrated against EEG burst suppression, which should be maintained for at least 24 hours.[1] Recovery may be prolonged.[2]

For the dose of thiopental in children, see Administration in Children, p. 1915.3.

1. Meierkord H, *et al*. European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; **17:** 348–55.
2. Parviainen I, *et al*. High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. *Neurology* 2002; **59:** 1249–51.

Adverse Effects and Treatment

As for Phenobarbital, p. 536.3.

Excitatory phenomena such as coughing, hiccuping, sneezing, and muscle twitching or jerking may occur with any of the barbiturate anaesthetics, particularly during induction, but they occur more frequently with methohexital than with thiopental. Symptoms of laryngeal spasm or bronchospasm including cough and sneezing may also occur during induction. The intravenous injection of concentrated solutions of thiopental sodium such as 5% may result in thrombophlebitis. Extravasation of barbiturate anaesthetics may cause tissue necrosis. Intra-arterial injection causes severe arterial spasm with burning pain and may cause prolonged blanching of the forearm and hand and gangrene of digits. Hypersensitivity reactions have been rarely reported. Barbiturate anaesthetics can cause respiratory depression. They depress cardiac output and often cause an initial fall in blood pressure, and overdosage may result in circulatory failure. Arrhythmias may occur. Excessive doses are associated with hypothermia and profound cerebral impairment. Postoperative vomiting is infrequent but shivering may occur and there may be persistent drowsiness, confusion, and amnesia. Other relatively common postoperative effects include anorexia, malaise, fatigue, and dizziness; delirium has been seen in elderly patients. Headache has also been reported.

See also under Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on electrolytes. Although barbiturate-induced coma with intravenous thiopental is used in the management of raised intracranial pressure, it has been associated with reports of hypokalaemia and severe rebound hyperkalaemia.[1-3] Frequent monitoring of serum-potassium concentrations during the first 24 hours after stopping thiopental infusion,[1] and tapering the dose,[2] have been recommended by some.

1. Bouchard PM, *et al*. Thiopental-associated dyskalemia in severe head trauma. *J Trauma* 2008; **64:** 838–42.
2. Neil MJE, Dale MC. Hypokalaemia with severe rebound hyperkalaemia after therapeutic barbiturate coma. *Anesth Analg* 2009; **108:** 1867–8.
3. Jung JY, *et al*. Sequential occurrence of life-threatening hypokalemia and rebound hyperkalemia associated with barbiturate coma therapy. *Clin Nephrol* 2009; **71:** 333–7.

Hypersensitivity. Anaphylactic reactions to thiopental have been reported[1,2] although such reactions are rare. There has also been a report of haemolytic anaemia and renal failure with the development of an anti-thiopental antibody in a patient who had undergone general anaesthesia induced by thiopental.[3]

1. Westacott P, *et al*. Anaphylactic reaction to thiopentone: a case report. *Can Anaesth Soc J* 1984; **31:** 434–8.
2. Moneret-Vautrin DA, *et al*. Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
3. Habibi B, *et al*. Thiopental-related immune hemolytic anemia and renal failure: specific involvement of red-cell antigen I. *N Engl J Med* 1985; **312:** 353–5. Correction. *ibid.*; 1136.

Intra-arterial injection. Accidental intra-arterial injection of thiopental sodium produces severe arterial spasm with intense burning pain. Anaesthesia, paresis, paralysis, and gangrene may occur. Therapy has concentrated on dilution of injected thiopental, prevention and treatment of arterial spasm, prophylaxis of thrombosis, thrombectomy and other measures to sustain good blood flow. There has been a report[1] of the successful use of urokinase intra-arterially in the management of one patient accidentally given thiopental intra-arterially.

1. Vangerven M, *et al*. A new therapeutic approach to accidental intra-arterial injection of thiopentone. *Br J Anaesth* 1989; **62:** 98–100.

Precautions

Barbiturate anaesthetics are contra-indicated in severe shock, dystrophia myotonica, and when there is dyspnoea or respiratory obstruction such as in acute severe asthma or when maintenance of an airway cannot be guaranteed.

Barbiturate anaesthetics should be used with caution in patients with dehydration, hypovolaemia, severe haemorrhage, burns, severe anaemia, hyperkalaemia, toxaemia, myasthenia gravis, myxoedema and other metabolic disorders, or severe renal disease. Caution is also required in those with cardiovascular disease, adrenocortical insufficiency, cachexia, or increased intracranial pressure or blood urea. Reduced doses are required in the elderly and in severe hepatic disease.

See also Precautions for General Anaesthetics, p. 1897.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers received thiopental, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

In two groups of 8 women undergoing induction with thiopental, the milk-to-plasma ratio was less than 1 in both groups and it was considered that the effects of thiopental on breast-fed infants would be negligible.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Andersen LW, *et al*. Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiol Scand* 1987; **31:** 30–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiopental as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

Producing anaesthesia with the usual dose of barbiturate anaesthetics in patients accustomed to taking alcohol or other CNS depressants may be difficult; additional anaesthetics may be necessary. Patients being treated with phenothiazine antipsychotics may develop increased hypotension. Some phenothiazines, especially promethazine, may also increase the incidence of excitatory phenomena produced by barbiturate anaesthetics; cyclizine may possibly have a similar effect. Opioid analgesics can potentiate the respiratory depressant effect of barbiturate anaesthetics and the dose of the anaesthetic may need to be reduced. Use with nitrous oxide greatly reduces the dose of barbiturate anaesthetics required for anaesthesia. Reduced doses of thiopental may be required in patients receiving sulfafurazole.

See also Interactions of General Anaesthetics, p. 1897.3.

Antidepressants. Potentiation of barbiturate anaesthesia may be expected in patients receiving *tricyclic antidepressants* or *MAOIs* (see Anaesthesia under Precautions of Amitriptyline, p. 404.3 and for Phenelzine, p. 444.1, respectively).

Antipsychotics. For mention of the effect of *droperidol* on thiopental see Gastrointestinal Drugs, below.

Aspirin. Pretreatment with aspirin, a highly protein-bound drug, has been shown to potentiate thiopental anaesthesia.[1]

1. Dundee JW, *et al*. Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.

Gastrointestinal drugs. *Metoclopramide* profoundly reduced the dose of thiopental required to produce hypnosis in female patients; *droperidol* had a similar effect.[1]

1. Mehta D, *et al*. Metoclopramide decreases thiopental hypnotic requirement. *Anesth Analg* 1993; **77:** 784–7.

Probenecid. Pretreatment with probenecid, a highly protein-bound drug, potentiates thiopental anaesthesia.[1]

1. Dundee JW, *et al*. Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.

Pharmacokinetics

Thiopental is highly lipid soluble and when it is given intravenously as the sodium salt, concentrations sufficient to produce unconsciousness occur in the brain within 30 seconds. Onset of action occurs within 8 to 10 minutes when thiopental sodium is given rectally but absorption may be unpredictable if a suspension rather than a solution is used. Recovery from anaesthesia is also rapid due to redistribution to other tissues, particularly fat. About 80% of thiopental may be bound to plasma proteins, although reports show a wide range of figures. Thiopental is metabolised almost entirely in the liver, but as it is only released slowly from lipid stores this occurs at a very slow rate.

It is mostly metabolised to inactive metabolites but a small amount is desulfurated to pentobarbital. Repeated or continuous use can lead to accumulation of thiopental in fatty tissue and this can result in prolonged anaesthesia and respiratory and cardiovascular depression. Elimination of thiopental after bolus injection can be described by a triexponential curve. The terminal elimination half-life has been reported to be 10 to 12 hours in adults and about 6 hours in children. However, values of 26 to 28 hours have been reported in obese patients and pregnant patients at term. Thiopental readily diffuses across the placenta and is distributed into breast milk.

References.
1. Gaspari F, *et al*. Elimination kinetics of thiopentone in mothers and their newborn infants. *Eur J Clin Pharmacol* 1985; **28:** 321–5.
2. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; **12:** 79–110.
3. Esener Z, *et al*. Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69:** 586–8.
4. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75:** 344–51.
5. Norman E, *et al*. Placental transfer and pharmacokinetics of thiopentone in newborn infants. *Arch Dis Child Fetal Neonatal Ed* 2010; **95:** F277–F282.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bensulf; Hipnopento; ***Austral.***: Pentothal†; ***Belg.***: Pentothal†; ***Braz.***: Thionembutal; Thiopentax; ***Canad.***: Pentothal†; ***Denm.***: Pentothal; ***Fin.***: Pentocur; Pentothal; ***Fr.***: Pentothal†; ***Ger.***: Trapanal; ***Gr.***: Pentothal; ***Hong Kong***: Pentothal†; ***India***: Anesthal; Intraval Sodium; ***Indon.***: Pentothal; ***Ital.***: Farmotal; Pentothal; ***Malaysia***: Pentotex; ***Mex.***: Pentarim; Pentothal; Sodipental†; ***Neth.***: Pentothal; ***Norw.***: Pentothal†; ***NZ***: Intraval†; ***Philipp.***: Pentazol; Penthal; Pentobrim; Pentothal; ***Singapore***: Pentothal; ***Spain***: Pentothal; Tiobarbital; ***Swed.***: Pentothal†; ***Switz.***: Pentothal; ***Thai.***: Pentothal†; Thiopen; ***Turk.***: Ekipental; Pental; Pentothal†; ***USA***: Pentothal†.

Pharmacopoeial Preparations
BP 2014: Thiopental Injection;
USP 36: Thiopental Sodium for Injection.

Tiletamine Hydrochloride *(BANM, USAN, rINNM)*

CI-634; CL-399; CN-54521-2; Hidrocloruro de tiletamina; Tiletamina, hidrocloruro de; Tilétamine, Chlorhydrate de; Tiletamini Hydrochloridum; Тилетамина Гидрохлорид.

2-Ethylamino-2-(2-thienyl)cyclohexanone hydrochloride.

$C_{12}H_{17}NOS,HCl=259.8$

CAS — 14176-49-9 (tiletamine); 14176-50-2 (tiletamine hydrochloride).

UNII — 99TAQ2QWJI.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Tiletamine Hydrochloride). A white to off-white crystalline powder. Freely soluble in water; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol; freely soluble in 0.1N hydrochloric acid. pH of a 10% solution in water is between 3.0 and 5.0. Store in airtight containers.

Profile

Tiletamine has similar properties to ketamine (p. 1905.1). It is used as the hydrochloride with zolazepam (p. 1116.2) for general anaesthesia in veterinary medicine.

References.
1. Lee CC, *et al*. Movement disorder caused by abuse of veterinary anesthesia containing tiletamine. *Am J Emerg Med* 2009; **27:** 1022.e5–6.

Trichloroethylene *(rINN)*

Trichlorethylene; Trichlorethylenum; Trichloroethene; Trichloroéthylène; Trichloroethylenum; Trichloroetylen; Tricloroetileno; Трихлороэтилен.

$CHCl:CCl_2$=131.4

CAS — 79-01-6.

ATC — N01AB05.

ATC Vet — QN01AB05.

UNII — 290YE8AR51.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of trichloroethylene:

Trichlo.

Stability. NOTE. Trichloroethylene used for anaesthetic purposes contains thymol 0.01% w/v as a stabiliser and is coloured blue for identification. It is non-flammable.

Uses and Administration

Trichloroethylene is a volatile halogenated anaesthetic given by inhalation. It has been used in some countries for the maintenance of light anaesthesia (p. 1896.1) but it has weak anaesthetic properties compared with other halogenated anaesthetics and poor muscle relaxant activity, and safer anaesthetics are generally preferred. It has also been used to supplement anaesthesia with nitrous oxide-oxygen or halothane. Trichloroethylene is a potent analgesic and has been used in subanaesthetic concentrations to provide analgesia for obstetrics, emergency management of trauma, and other acutely painful procedures.

Trichloroethylene is used in industry as a solvent for oils and fats, for degreasing metals, and for dry cleaning. It has also been used in type correction fluids but is no longer included in most brands.

Adverse Effects and Precautions

Trichloroethylene increases the rate and decreases the depth of respiration and may be followed by apnoea. The sensitivity of the heart to beta-adrenergic activity may increase, possibly with ventricular arrhythmias.

Acute exposure to trichloroethylene may be followed by dizziness, lightheadedness, lethargy, nausea, and vomiting; hepatic and renal dysfunction may follow. Fatalities have occurred, although temporary unconsciousness is a more common manifestation.

Chronic poisoning may result in visual disturbances, intolerance to alcohol as manifested by transient redness of the face and neck (degreasers' or trichloroethylene flush), impairment of performance, hearing defects, neuralgia, and mild liver dysfunction. Prolonged contact with trichloroethylene can cause dermatitis, eczema, burns, and conjunctivitis.

Dependence has been reported in medical personnel and factory workers who regularly inhale trichloroethylene vapour.

If trichloroethylene is used as an anaesthetic it should not be used in closed-circuit apparatus since there is a reaction with soda lime to produce a toxic end product that may cause cranial nerve paralysis and possibly death.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Reviews[1-4] of the toxicity of trichloroethylene.

1. Health and Safety Executive. Trichloroethylene. *Toxicity Review* 6. London: HMSO, 1982.
2. WHO. Trichloroethylene. *Environmental Health Criteria 50*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc50.htm (accessed 26/05/04)
3. Davidson IWF, Beliles RP. Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. *Drug Metab Rev* 1991; **23:** 493–599.
4. Tabrez S, Ahmad M. Toxicity, biomarkers, genotoxicity, and carcinogenicity of trichloroethylene and its metabolites: a review. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2009; **27:** 178–96.

Abuse. Toxicity associated with inhalation of volatile substances including trichloroethylene has been reviewed.[1,2] Trichloroethylene can damage the kidney, liver, heart, and lung. However, in young healthy subjects, organ toxicity becomes apparent only with intensive and protracted abuse of volatile substances and fatalities have been reported.[3,4]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Anonymous. Solvent abuse: little progress after 20 years. *BMJ* 1990; **300:** 135–6.
3. Jones GR, Singer PP. An unusual trichloroethanol fatality attributed to sniffing trichloroethylene. *J Anal Toxicol* 2008; **32:** 183–6.
4. Takaki A, *et al*. A 27-year-old man who died of acute liver failure probably due to trichloroethylene abuse. *J Gastroenterol* 2008; **43:** 239–42.

Carcinogenicity. The use of trichloroethylene in foods, drugs, and cosmetics was banned by the FDA after studies found that hepatocellular carcinomas could be induced in *mice* by chronic exposure to very high doses. However, similar effects have not been found in *rats* and larger species and several epidemiologic studies have failed to show an increased incidence of liver tumours, total mortality, or mortality due to cancer in workers exposed to trichloroethylene. Suggestions that the carcinogenicity of trichloroethylene is due to one of its intermediate metabolites, cloral hydrate, have raised concern over the continuing use of cloral hydrate as a medicine. For further details, see p. 1056.1.

Effects on the liver. References[1,2] to hepatotoxicity after occupational exposure to trichloroethylene. See also Carcinogenicity, above, and Effects on the Skin, below.

1. McCunney RJ. Diverse manifestations of trichloroethylene. *Br J Ind Med* 1988; **45:** 122–6.
2. Schattner A, Malnick SDH. Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad Med J* 1990; **66:** 730–1.

Effects on the skin. A hypersensitivity syndrome comprising rashes, fever, hepatitis, and lymphadenopathy has been associated with occupational exposure to trichloroethylene, as have severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[1-3] Carriers of the HLA allele HLA-B*1301, which occurs almost exclusively in persons of Asian ancestry, have been suggested to be at increased risk for developing such reactions.[4]

Scleroderma has been reported[5] in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Kamijima M, *et al*. Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. *Int Arch Occup Environ Health* 2007; **80:** 357–70.
2. Kamijima M, *et al*. Trichloroethylene causes generalized hypersensitivity skin disorders complicated by hepatitis. *J Occup Health* 2008; **50:** 328–38.
3. Xu X, *et al*. Severe hypersensitivity dermatitis and liver dysfunction induced by occupational exposure to trichloroethylene. *Ind Health* 2009; **47:** 107–12.
4. Li H, *et al*. HLA-B*1301 as a biomarker for genetic susceptibility to hypersensitivity dermatitis induced by trichloroethylene among workers in China. *Environ Health Perspect* 2007; **115:** 1553–6.
5. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Poisoning. There has been a report[1] of a fatal self-poisoning in a 47-year-old woman with severe anorexia nervosa who ingested 500 mL of trichloroethylene and an unknown quantity of benzodiazepines. Coma developed shortly after ingestion, followed by abdominal distension, perforation, and necrosis, and multiple organ failure.

1. Liotier J, *et al*. A rare cause of abdominal compartment syndrome: acute trichlorethylene overdose. *Clin Toxicol* 2008; **46:** 905–7.

Interactions

The arrhythmogenic effects of trichloroethylene may be potentiated by sympathomimetics such as adrenaline. Alcohol consumption after chronic exposure to trichloroethylene may result in a reddening of the skin (see Adverse Effects and Precautions, above).

See also Interactions of General Anaesthetics, p. 1897.3.

Pharmacokinetics

Trichloroethylene is rapidly absorbed by inhalation and ingestion. Percutaneous absorption can occur. Some of the inhaled trichloroethylene is slowly eliminated through the lungs; trichloroethylene is metabolised mainly in the liver, cloral hydrate (see p. 1055.2) being the first stable major metabolite formed; most is then metabolised to trichloroethanol and trichloroacetic acid which are excreted in the urine. The latter may be used as an indicator of industrial exposure. Trichloroethylene diffuses across the placenta.

Xenon

Ksenon; Ksenonas; Ksenons; Ksenoon; Senon; Xeanón; Xenó; Xeno; Xenón; Xénon; Xenônio; Xenonum; Ксенон.

Xe=131.293

ATC — N01AX15.

ATC Vet — QN01AX15.

UNII — 3H3U766W84.

Profile

Xenon is a non-explosive gas. Mixtures of 60 or 70% v/v xenon with oxygen have been tried as a general anaesthetic.

References.

1. Rossaint R, *et al*. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003; **98:** 6–13.
2. Sanders RD, *et al*. Xenon: no stranger to anaesthesia. *Br J Anaesth* 2003; **91:** 709–17.
3. Bedi A, *et al*. Use of xenon as a sedative for patients receiving critical care. *Crit Care Med* 2003; **31:** 2470–7.
4. Preckel B, Schlack W. Xenon—cardiovascularly inert? *Br J Anaesth* 2004; **92:** 786–9.
5. Sanders RD, *et al*. Xenon: elemental anaesthesia in clinical practice. *Br Med Bull* 2005; **71:** 115–35.
6. Baskar N, Hunter JD. Xenon as an anaesthetic gas. *Br J Hosp Med* 2006; **67:** 658–61.
7. Derwall M, *et al*. Xenon: recent developments and future perspectives. *Minerva Anestesiol* 2009; **75:** 37–45.
8. Bronco A, *et al*. Xenon anaesthesia produces better early postoperative cognitive recovery than sevoflurane anaesthesia. *Eur J Anaesthesiol* 2010; **27:** 912–16.
9. Jordan BD, Wright EL. Xenon as an anesthetic agent. *AANA J* 2010; **78:** 387–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: LENOXe; ***Fr.***: LENOXe; ***Neth.***: LENOXe; ***Port.***: LENOXe; ***Spain***: LENOXe.

Growth Hormone and its Modulators

Human growth is under a complex system of hormonal controls. Growth hormone is produced by specialised cells (somatotropes) in the anterior pituitary; production and secretion are under a system of double regulation by a release-inhibiting hormone, somatostatin, and a growth hormone-releasing hormone, somatorelin, both produced in the hypothalamus. These in turn are modulated by various stimuli: dopamine, serotonin, hypoglycaemia, stress or emotional excitement, and ingestion of protein-rich meals all stimulate growth hormone release, whereas glucose, free fatty acids, insulin-like growth factor and growth hormone itself all suppress it.

The effects of growth hormone in the body rely on its interaction with a distinct growth hormone receptor; some effects, such as stimulation of lipolysis and gluconeogenesis, are direct but others, including its anabolic and growth-promoting effects, are mediated by induction of insulin-like growth factors (somatomedins).

Included in this chapter are growth hormone itself, now generally given as recombinant somatropin (p. 1919.3) or its synthetic methionyl analogue somatrem (p. 1919.3), and somatomedins such as mecasermin (p. 1929.2). Also included are the hypothalamic releasing hormone, somatorelin (p. 1930.1), and its analogue sermorelin (p. 1930.1); the hypothalamic inhibiting hormone, somatostatin (p. 1930.3), and its analogues such as lanreotide (p. 1923.2) and octreotide (p. 1924.1); the growth hormone release stimulant pralmorelin (p. 1929.1); and the growth hormone-receptor antagonist pegvisomant (p. 1928.2). Their use in acromegaly and growth retardation is discussed in more detail below.

Acromegaly and gigantism

Acromegaly and gigantism are syndromes of excess growth hormone secretion, usually associated with a secretory pituitary adenoma (somatropinoma).

Excessive growth hormone secretion in childhood, while the epiphyses of the long bones are open, results in ***gigantism***,[1,2] with a proportional growth spurt and skeletal enlargement. Other common features include obesity, coarse facial features, and disproportionately large hands and feet with thick fingers and toes. Puberty, with the increase in sex hormone secretion that leads to epiphyseal fusion, may be delayed by concomitant hypogonadism, leading to attainment of an even greater ultimate height. If growth hormone excess persists into adulthood, features of acromegaly may be superimposed on gigantism.[1] Treatment is similar to that used in acromegaly, as described below, although radiotherapy is used less often in gigantism because of the potential long-term consequences, such as hypopituitarism, for relatively young patients.[2] There is also more urgency to control the condition and avoid potentially irreversible musculoskeletal deformities and excessively tall stature.

When excess growth hormone secretion develops first in adulthood the condition is known as ***acromegaly***. Signs and symptoms tend to develop slowly and may be missed, sometimes for years. Growth hormone concentrations, and hence those of insulin-like growth factor I (IGF-I), which is produced in the liver in response to growth hormone, are elevated, sometimes markedly. The facial features become coarser, the jaw enlarges (prognathism), and hands and feet become enlarged. Peripheral neuropathy and carpal tunnel syndrome due to nerve entrapment, arthropathy, osteoarthritis, and muscle weakness, abnormal glucose tolerance, hypertension and left ventricular hypertrophy are all common, as is nodular goitre. Daytime somnolence may occur due to sleep apnoea. Acromegalics have an increased mortality if left untreated, largely due to cardiovascular disease.

Diagnosis and monitoring. The biochemical goal of treatment is to normalise growth hormone and IGF-I concentrations in order to reduce some of the signs and symptoms of acromegaly and to reverse the increased risk of mortality.[2,3] Growth hormone may be measured after an oral glucose tolerance test (OGTT); this suppresses growth hormone concentrations in healthy subjects, but not in patients with acromegaly. A growth hormone concentration below 400 nanograms/litre after an OGTT may be used to exclude acromegaly at the initial diagnosis, and in the assessment of surgical efficacy. Growth hormone concentrations taken as random samples may be used during the long-term monitoring of medical therapy for acromegaly; in such circumstances a target concentration below 1 microgram/litre is often used.[2,3] However, the target concentrations that have been suggested have changed over time with the development of more sensitive assays, and results must be interpreted in the context of the method used.[2-4] Random IGF-I concentrations should fall to normal for age and sex.[2,3]

Treatment. As for most pituitary tumours, **surgery** is the mainstay of treatment.[2,5] The success rate depends on surgical expertise and the size and extension of the mass, with success rates higher for microadenomas (75 to 95%) than macroadenomas (40 to 68%) depending on criteria.[5]

Drug therapy for acromegaly is indicated for patients who refuse surgery, have a low probability of a surgical cure, are at increased risk from surgery, have active disease after surgery, or are awaiting the effects of radiotherapy (see below).[2,5]

The *somatostatin analogues*, octreotide and lanreotide, reduce growth hormone secretion in most patients, but not all will have persistent suppression and normalisation of growth hormone levels.[6,7] Reported response rates vary, but effective growth hormone suppression occurs in about 50 to 55% of patients, and IGF-I is normalised in about 50 to 65%. Somatostatin analogues also produce tumour shrinkage, reducing tumour size by more than 20% in about 75% of patients,[5] and improve signs and symptoms of acromegaly, including improvements in cardiac structure and function.[8] Octreotide and lanreotide appear to have similar efficacy in the control of growth hormone and IGF-I concentrations based on limited data, but comparative studies of tumour shrinkage are lacking.[7,9]

There has been increasing interest in the use of somatostatin analogues for primary therapy, but when there is visual or neurological compromise then surgery is preferred because drug therapy may not provide enough tumour shrinkage to relieve pressure on the optic chiasm.[6,10] Guidelines[2,5] consider somatostatin analogues only suitable as first-line treatment for patients with a low likelihood of surgical cure or at high surgical risk. There are some data that suggest pre-operative use of somatostatin analogues could improve cardiovascular, respiratory, and metabolic functions and hence reduce morbidity associated with surgery, but further study is needed.[2,5,7,11] Pre-operative use might also improve surgical remission rates, particularly in patients with macroadenomas, but again further study is needed.[2,7,11]

Dopaminergics can produce a paradoxical reduction in growth hormone secretion in some patients with acromegaly, providing symptomatic relief. Cabergoline may be more effective than bromocriptine, but they are both less effective than somatostatin analogues. They are generally added to somatostatin analogue therapy, but may be considered alone for medical therapy in patients with modest IGF-I elevations when oral therapy is preferred.[2,5]

Pegvisomant is a growth hormone-receptor antagonist that may be used when other therapies have failed or are inappropriate.[2,5,7,12] It is reported[13,14] to lower IGF-I concentrations, improve signs and symptoms of acromegaly, and be well tolerated. Pegvisomant does not reduce growth hormone concentrations so these patients must be monitored by IGF-I measurement.[2,4] The addition of pegvisomant has also been reported to normalise IGF-I concentrations in patients with persistently elevated levels during somatostatin analogue therapy.[2,15]

Tumour regression induced by **radiotherapy** is a possible alternative, usually when surgical and/or medical therapy have failed.[2,5] Although it reduces growth hormone concentrations in most patients, its effects are slow and it often produces hypopituitarism. Since it may take several years for growth hormone concentrations to fall, drug therapy is also given until the effects of radiation therapy are satisfactory.

1. Eugster EA, Pescovitz OH. Gigantism. *J Clin Endocrinol Metab* 1999; **84:** 4379–84.
2. Katznelson L, *et al*. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. *Endocr Pract* 2011; **17** (suppl 4): 1–44. Also available at: https://www.aace.com/sites/default/files/AcromegalyGuidelines.pdf (accessed 13/09/11)
3. Giustina A, *et al*. Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab* 2010; **95:** 3141–8.
4. Growth Hormone Research Society, Pituitary Society. Biochemical assessment and long-term monitoring in patients with acromegaly: statement from a joint consensus conference of the Growth Hormone Research Society and the Pituitary Society. *J Clin Endocrinol Metab* 2004; **89:** 3099–3102. Also available at: http://jcem.endojournals.org/cgi/reprint/89/7/3099.pdf (accessed 24/10/05)
5. Melmed S, *et al*. Acromegaly Consensus Group. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab* 2009; **94:** 1509–17. Also available at: http://jcem.endojournals.org/content/94/5/1509.full.pdf (accessed 18/10/11)
6. Freda PU. Somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 2002; **87:** 3013–18.
7. Feelders RA, *et al*. Medical therapy of acromegaly: efficacy and safety of somatostatin analogues. *Drugs* 2009; **69:** 2207–26.
8. Maison P, *et al*. Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. *J Clin Endocrinol Metab* 2007; **92:** 1743–7.
9. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. *J Clin Endocrinol Metab* 2008; **93:** 2957–68.
10. Sheppard MC. Primary medical therapy for acromegaly. *Clin Endocrinol (Oxf)* 2003; **58:** 387–99.
11. Ben-Shlomo A, Melmed S. The role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab* 2003; **88:** 963–8.
12. Clemmons DR, *et al*. Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. *J Clin Endocrinol Metab* 2003; **88:** 4759–67.
13. Trainer PJ, *et al*. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med* 2000; **342:** 1171–7.
14. van der Lely AJ, *et al*. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001; **358:** 1754–9.
15. Neggers SJCMM, *et al*. Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. *J Clin Endocrinol Metab* 2007; **92:** 4598–4601.

Growth retardation

Stature follows a normal (bell-shaped) distribution within the population. Short stature has been defined as a height more than 2 standard deviations below the population mean, but there may be some difficulty in deciding at what point short stature becomes abnormal and to some extent this is determined by cultural as well as physiological norms.

Certain disorders are associated with well-defined deficiencies of growth which may be severe enough to warrant the description ***dwarfism***. Some forms are associated with disorders of bone or cartilage growth (skeletal dysplasias), and many of these result additionally in disproportionate growth, as in the short-limbs and large head characteristic of achondroplasia. Other genetic conditions that feature short stature include Noonan syndrome and SHOX (short stature homeobox-containing gene) deficiency. Other important causes of dwarfism include inadequate production of growth hormone (idiopathic growth hormone deficiency), either alone (isolated growth hormone deficiency) or combined with other pituitary hormone deficiencies as part of hypopituitarism; resistance to circulating growth hormone, as in Laron-type dwarfism, where there is a mutation of the growth hormone receptor; or defects in somatomedin synthesis.

Some other endocrine causes of short stature include hypothyroidism, Cushing's syndrome, and Turner's syndrome. Severe chronic disease in childhood such as asthma, chronic renal failure, or liver disorders can result in some growth retardation as can inadequate nutrition due to malabsorption syndromes such as coeliac disease.

Endocrine causes of growth retardation are significant because they may be treatable by appropriate replacement therapy. Isolated growth hormone deficiency, or growth hormone and gonadotrophin deficiencies, are the commonest congenital forms of hypopituitarism. Since most children with short stature will not have growth hormone deficiency and deficiency is rarely complete, care is required in its **diagnosis**. Although provocative growth hormone tests, which use non-physiological means to stimulate growth hormone secretion, have long been considered the gold standard for diagnosis of growth hormone deficiency they have limitations and some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) or their binding proteins to be more useful.[1] Different assays may give different results, and it has been advised that therapeutic decisions should be based on a combination of comprehensive clinical and height assessments, biochemical tests, and radiological evaluation.[2,3]

In children with confirmed **growth hormone deficiency** replacement therapy is appropriate, and is given by subcutaneous injections of synthetic human *growth hormone* (somatropin) or its methionyl analogue (somatrem). Treatment improves bone density[4,5] and growth velocity;[6,7] final adult height is also increased but the extent of the benefit is unclear.

A cohort study of French children registered to receive growth hormone between 1973 and 1993 suggested that the eventual outcome was not as good as expected, and treated individuals remained short.[8] However, a large American cohort that included more than 11 000 growth-hormone deficient patients found that although treated patients remained below target heights, many did achieve heights within the normal range for chronological age.[9] Maximum growth rates occurred in the first year of treatment and fell progressively thereafter, with no significant difference between growth rates after 4 years compared with pretreatment rates. A further cohort study[10] from the same French register for 1987 to 1996 found that adult heights were similar whether patients completed treatment or stopped before reaching adult height, and that patients

with severe growth hormone deficiency may respond better than those with less severe deficiency.

Growth hormone treatment regimens have changed over the years, and it appears that with optimal treatment it may be possible for some growth-hormone deficient children to achieve their genetic height potential.[7] An important prognostic factor is age, and for optimum results treatment should be started as early as possible in an attempt to maximise height before the onset of puberty.[2,7]

In patients with multiple pituitary hormone deficiencies, genetic defects in growth hormone synthesis, or severe organic growth hormone deficiency, growth hormone therapy should be continued into adulthood. In other patients, growth hormone deficiency may or may not persist into adult life, and retesting should be done after the patient reaches adult height and after 1 to 3 months without therapy.[2,11-13] In those patients who need continued treatment, the dose of growth hormone should be gradually reduced in order to maintain IGF-I concentrations within the normal range.[11,12]

Somatorelin (*growth hormone-releasing hormone*) or its analogue sermorelin have also been tried to boost growth hormone secretion in patients with growth hormone deficiency. Although there have been reports of improved growth rates, there are limited data directly comparing these with growth hormone. One large study[14] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer.

In patients with Laron dwarfism (**growth hormone resistance or insensitivity**), conventional growth hormone therapy is ineffective because of defects in the growth hormone receptors. However, replacement therapy with *mecasermin*, the recombinant form of insulin-like growth factor-I, may be of substantial benefit in the treatment of this disorder.[15]

The use of growth hormone in **short stature** other than that due to indisputable growth hormone deficiency is controversial. Benefit has been reported from growth hormone therapy in children with chronic renal failure,[16-18] juvenile idiopathic arthritis[19] (p. 12.1), cystic fibrosis (see also p. 1921.1)[20,21] in girls with Turner's syndrome (but see p. 2254.3), in young children (6 months to 3 years of age) with Down's syndrome,[22,23] and in Prader-Willi syndrome[24,25] (p. 2315.2), all of which are associated with marked growth retardation. However, many commentators see such interventions as essentially cosmetic. The treatment of idiopathic short stature in particular, for which no underlying disorder can be identified, poses problems as the risks and also the benefits in terms of final height are uncertain.[26-28] Children who are born small for gestational age usually experience catch-up growth by 2 years of age. In those who do not achieve this, growth hormone therapy can induce catch-up growth and improve childhood height scores; data on adult height are limited, however.[29,30] Guidelines suggest that therapy is justifiable in chronic renal insufficiency,[3,6,31] Turner's syndrome,[3,6,31] Prader-Willi syndrome,[3,31] and for children born small for gestational age.[3,31,32] However, sufficient evidence of benefit is lacking for other disorders including non-growth hormone deficient short stature and growth retardation associated with Down's syndrome, and some[6] consider that growth hormone should not be given to children with constitutional delay of growth.

More recently, growth hormone therapy has improved growth rate and height in children with SHOX deficiency.[31,33] Mutations and deletions of the SHOX gene, a gene involved in bone and cartilage formation, are associated with various short stature conditions such as Léri-Weill dyschondrosteosis, and are now understood to play a role in the short stature of Turner's syndrome and in some cases of idiopathic short stature. Growth hormone therapy can also improve height in children with Noonan syndrome.[34,35] As in other forms of growth retardation, starting treatment early before the onset of puberty might produce better results.

Although *sex hormones* have effects on growth they may also cause premature closure of the epiphyses when given to prepubertal or pubertal children, and this has limited their use. Nonetheless, anabolic drugs such as testosterone and oxandrolone have been used in boys, and oestrogen in girls, who have constitutional delay of growth associated with delayed puberty (see p. 2252.1). Oestrogens are not generally used for growth promotion in girls with Turner's syndrome, but as replacement therapy to promote puberty (see p. 2254.3).

Several *other drugs* have been investigated in growth retardation. Clonidine, which can promote growth hormone-releasing hormone release, has been given to children with growth hormone deficiency as well as to short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[36-38] Gonadorelin analogues have also been given with growth hormone to short girls with or without growth hormone deficiency, in an attempt to slow bone maturation and delay puberty, thereby improving adult height.[39,40] However, a decrease in bone mineral density may outweigh any modest increase in height.[41] Where growth retardation is associated with zinc deficiency, zinc supplementation may be useful (see p. 2127.2).

1. Rosenfeld RG, *et al*. Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab* 1995; **80:** 1532–40.
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41. Yanovski JA, *et al*. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 2003; **348:** 908–17.

Growth Hormone *(BAN)* ⊗

GH; Groeihormoon; Hormon wzrostu; Hormona del crecimiento; Hormone de croissance; Hormônio do crescimento; Kasvuhormoni; Kasvuhormoon; Növekedési hormon; Ormone della crescita; Phyone; Růstový hormon; Somatotrophin; Somatotropiini; Somatotropin; Somatotropina; Somatotropine; STH; Tillväxthormon; Veksthormon; Wachstumshormon; Гормон Роста; Растежен Хормон; Соматотропин.

CAS — 9002-72-6.

Somatrem *(BAN, USAN, pINN)* ⊗

Met-HGH; Methionyl Human Growth Hormone; Somatremum; Соматрем.

$C_{995}H_{1537}N_{263}O_{301}S_8$=22256.3

CAS — 82030-87-3.

ATC — H01AC02.

ATC Vet — QH01AC02.

UNII — CU8D464EDW.

Description. Somatrem is an analogue of somatropin containing an additional (methionyl) amino-acid residue. It may be produced in bacteria from recombinant DNA. Sometribove (*BAN*) is methionyl bovine growth hormone. Sometripor (*BAN*) is methionyl porcine growth hormone.

Somatropin *(BAN, USAN, rINN)* ⊗

CB-311; HGH; Human Growth Hormone; LY-137998; Somatropiini; Somatropina; Somatropinas; Somatropine; Somatropinum; Szomatropin; Соматропин.

$C_{990}H_{1528}N_{262}O_{300}S_7$=22125.1

CAS — 12629-01-5.

ATC — H01AC01.

ATC Vet — QH01AC01.

UNII — NQX9KB6PCL.

Description. Somatropin is synthetic human growth hormone having the normal structure of the major (22K) component of natural human pituitary growth hormone. It consists of a single polypeptide chain of 191 amino acids with disulfide linkages between positions 53 and 165 and between 182 and 189. For labelling purposes, the name may carry in parentheses an approved code in lower case letters indicative of the method of production: (epr) indicates production by enzymatic conversion of a precursor produced by a bacterium genetically modified by recombinant DNA technology; (rbe) indicates production from bacteria genetically modified by recombinant DNA technology; (rmc) indicates production from genetically engineered and transformed mammalian (mouse) cells.

Somidobove (*BAN*) is synthetic bovine growth hormone.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Somatropin). A protein having the structure (191 amino acid residues) of the major component of growth hormone produced by the human pituitary. A white or almost white powder, containing not less than 2.5 units/mg. Store at 2 degrees to 8 degrees in airtight containers.

Ph. Eur. 8: (Somatropin Concentrated Solution). A clear or slightly turbid, colourless solution. It may contain buffer

salts and other auxiliary substances. Store at -20 degrees in airtight containers. Avoid repeated freezing and thawing.

USP 36: (Somatropin). A protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced as a lyophilised powder or bulk solution by methods based on recombinant DNA technology. The lyophilised powder contains not less than 910 micrograms of somatropin per mg, calculated on the anhydrous basis. The bulk solution contains not less than 910 micrograms of somatropin per mg of total protein.

Store at -25 degrees to -10 degrees in airtight containers.

Units

4.4 units of human growth hormone (somatropin) are contained in 1.75 mg of freeze-dried purified human growth hormone, with 20 mg of glycine, 2 mg of mannitol, 2 mg of lactose, and 2 mg of sodium bicarbonate, in one ampoule of the first International Standard (1987).

The second International Standard for Somatropin (2000), rDNA-derived human growth hormone, has a defined content of 1.95 mg of protein per ampoule, with a specific activity of 3.0 units/mg. One mg of anhydrous Somatropin USP is equivalent to 3.0 USP Somatropin Units. Commercial preparations vary somewhat in the number of units/mg.

Uses and Administration

Growth hormone is an anabolic hormone secreted by the anterior lobe of the pituitary, varying in size and amino-acid sequence between animal species. It promotes growth of skeletal, muscular, and other tissues, stimulates protein anabolism, and affects fat and mineral metabolism. The hormone has a diabetogenic action on carbohydrate metabolism. Secretion is pulsatile and dependent on neural and hormonal influences including a hypothalamic release-inhibiting hormone (see Somatostatin, p. 1930.3), and a hypothalamic releasing hormone (see Somatorelin, p. 1930.1). Sleep, hypoglycaemia, and physical or emotional stress result in increased secretion of growth hormone. The effects of growth hormone on skeletal growth are mediated by the somatomedins (see p. 1929.1). Somatropin is synthetic human growth hormone and somatrem its methionyl analogue.

Somatropin is given to children with open epiphyses for the treatment of short stature due to growth hormone deficiency (pituitary dwarfism) following assessment of pituitary function. Somatrem has been used similarly but is no longer generally available. Somatropin is also used in children with some other forms of growth retardation, such as that associated with Turner's syndrome, Noonan syndrome, SHOX (short stature homeobox-containing gene) deficiency, or chronic renal insufficiency, in short children born small for gestational age, and in idiopathic short stature. In Prader-Willi syndrome, somatropin is given to improve growth and body composition (but see also under Adverse Effects and Precautions, p. 1922.3). In adults, somatropin is given for confirmed growth hormone deficiency. It is also used in the management of wasting or cachexia associated with AIDS. In short bowel syndrome, somatropin is used to increase intestinal absorption of water, electrolytes, and nutrients from specialised nutritional support.

Doses in **growth retardation** should be individualised for each patient. Manufacturers vary somewhat in their estimates of the number of units/mg for somatropin and although some countries specify labelling in mg, others require labelling in units or both.

- In *children with growth hormone deficiency*, the usual daily dose in the UK is 25 to 35 micrograms/kg (0.07 to 0.1 units/kg), or 0.7 to 1 mg/m^2(2 to 3 units/m^2). Doses are usually given by subcutaneous injection although some preparations are also licensed for intramuscular use; needle-free delivery systems are also available. Some licensed product information also suggests that doses should be given in the evening. Similar doses are used in other countries, where the total weekly dose may be divided into 3, 6, or 7 doses.
  When children with growth hormone deficiency reach their final height they should be re-assessed for the need to continue therapy, usually after at least 4 weeks without treatment. During *transition into adulthood* a subcutaneous dose of 200 to 500 micrograms daily may be used, and adjusted as required to maintain IGF-I concentrations in the normal range.
- In *Turner's syndrome* (gonadal dysgenesis), a subcutaneous daily dose of 45 to 50 micrograms/kg (0.14 units/kg), or 1.4 mg/m^2(4.3 units/m^2), is generally used, although higher doses of up to 67 micrograms/kg daily may be needed.
- Doses of up to 66 micrograms/kg daily have been used for growth retardation related to *Noonan syndrome*.
- Daily doses of 45 to 50 micrograms/kg may be used in children with growth retardation due to *chronic renal insufficiency* or *SHOX deficiency*.
- In children with growth retardation who were *born small for gestational age*, the licensed daily dose in the UK is 35 micrograms/kg by subcutaneous injection (0.1 units/kg), or 1 mg/m^2 (3 units/m^2). In the USA, the licensed dose is somewhat higher, at 480 micrograms/kg weekly, divided into 6 or 7 doses.
- In children with *idiopathic short stature* somatropin is given subcutaneously in a weekly dose of up to 300 to 470 micrograms/kg divided into 6 or 7 doses.
- In children with *Prader-Willi syndrome*, a daily dose of about 35 micrograms/kg, or 1 mg/m^2, is given subcutaneously; daily doses should not exceed 2.7 mg.

In patients with **adult-onset growth hormone deficiency** lower doses are recommended. The initial dose is not more than 6 micrograms/kg (0.018 units/kg) subcutaneously daily. The dose can then be gradually increased according to patient response, to a usual maximum of 12.5 micrograms/kg daily. Alternatively, an initial dose in the range of 100 to 300 micrograms daily (0.3 to 0.9 units) in the evening is increased gradually at monthly intervals, based on clinical response, to a maintenance dose that is usually no more than 1 mg daily. Dosage requirements may decline with increasing age. In the UK, it has been recommended that treatment should be re-assessed 9 months after starting therapy.

In the treatment of **HIV-associated wasting or cachexia** somatropin is given in doses of 100 micrograms/kg daily by subcutaneous injection at bedtime, to a maximum of 6 mg daily. A starting dose of 100 micrograms/kg on alternate days may be considered for patients who are at increased risk of adverse effects.

In **short bowel syndrome** somatropin is given subcutaneously in a dose of about 100 micrograms/kg daily (to a maximum of 8 mg daily) for 4 weeks.

Sustained-release injections and inhalation formulations of growth hormone are also under investigation.

Administration in children. For details of somatropin doses in children with growth retardation, see Uses and Administration, above. See also below for doses that have been tried in those with severe burns.

Administration in adults. Growth hormone continues to be secreted in adult life, although secretion and activity gradually decline with increasing age, and it appears to play a role in maintaining skeletal and lean body-mass amongst other things. In adults with growth hormone deficiency (usually secondary to pituitary adenoma or its treatment) replacement therapy with growth hormone is reported to decrease body fat and abdominal adiposity, increase lean body-mass, and improve lipid profiles.[1-5] It may also increase bone density,[1,3] but many studies have been uncontrolled and of short duration, and any beneficial effect on bone density appears to be small.[6] Strength[7] and exercise capacity[8] can also be improved, although prolonged growth hormone therapy and physical training may be required to increase muscle performance.[3] Cardiac structure and function can be adversely affected by growth hormone deficiency, and replacement therapy in adults can have a positive effect on some cardiac parameters.[9] There are also some reports of improvements in quality of life;[3] although a study[10] using general standardised psychometric tests found no benefit, another[11] using a questionnaire developed for adults with hypopituitarism reported long-term benefits. Long-term data are not yet available to determine whether growth hormone therapy reduces the mortality rate in this group of patients, but it may provide some protection against myocardial infarction.[12] Guidelines on the use of growth hormone in adults with growth hormone deficiency have been issued.[13-16]

Less well established is the use of growth hormone in otherwise healthy elderly patients. Considerable controversy has attended suggestions that growth hormone therapy may retard or reverse some of the metabolic effects of ageing, and there is some concern that these patients may be at increased risk of adverse effects.[17] Studies[18] have shown that growth hormone can increase lean body-mass and decrease body fat, but functional ability does not necessarily improve and common adverse effects include peripheral oedema, carpal tunnel syndrome, arthralgias, and gynaecomastia.

Other uses for growth hormone in adult patients are discussed below. For mention of managing the transition to adulthood of children with growth hormone deficiency, see above and under Growth Retardation, p. 1918.3.

1. Götherström G, *et al.* A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab* 2001; **86:** 4657–65.
2. Attanasio AF, *et al.* Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status—3-year results from the HypoCCS Database. *J Clin Endocrinol Metab* 2002; **87:** 1600–6.
3. Verhelst J, Abs R. Long-term growth hormone replacement therapy in hypopituitary adults. *Drugs* 2002; **62:** 2399–2412.
4. Maison P, *et al.* Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab* 2004; **89:** 2192–9.
5. Götherström G, *et al.* A 10-year, prospective study of the metabolic effects of growth hormone replacement in adults. *J Clin Endocrinol Metab* 2007; **92:** 1442–5.
6. Davidson P, *et al.* Growth hormone replacement in adults and bone mineral density: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2004; **60:** 92–8.
7. Götherström G, *et al.* Ten years of growth hormone (GH) replacement normalizes muscle strength in GH-deficient adults. *J Clin Endocrinol Metab* 2009; **94:** 809–16.
8. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *J Clin Endocrinol Metab* 2008; **93:** 4413–17.
9. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003; **108:** 2648–52.
10. Baum HBA, *et al.* Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *J Clin Endocrinol Metab* 1998; **83:** 3184–9.
11. Rosilio M, *et al.* Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). *J Clin Endocrinol Metab* 2004; **89:** 1684–93.
12. Svensson J, *et al.* Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab* 2004; **89:** 3306–12.
13. NICE. Human growth hormone (somatropin) in adults with growth hormone deficiency: Technology Appraisal 64 (issued August 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA64_HGHadults_fullguidance.pdf (accessed 20/08/08)
14. Ho KKY. 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol* 2007; **157:** 695–700. Also available at: http://www.ghresearchsociety.org/files/2007_Consensus_AGHD.pdf (accessed 08/12/08)
15. Cook DM, *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients—2009 update. *Endocr Pract* 2009; **15** (suppl 2): 1–29. Also available at: https://www.aace.com/sites/default/files/GrowthHormoneGuidelines.pdf (accessed 26/09/11)
16. Molitch ME, *et al.* Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96:** 1587–1609. Also available at: http://www.endo-society.org/guidelines/upload/Evaluation-treatment-of-Adult-Growth-Hormone-Deficiency-Clinical-Practice-Guideline-NonCME.pdf (accessed 26/09/11)
17. VanceML. Can growth hormone prevent aging? *N Engl J Med* 2003; **348:** 779–80.
18. Liu H, *et al.* Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 2007; **146:** 104–15.

Burns. Growth hormone has been studied as a possible treatment to increase the rate of wound healing after severe burns. In a small study[1] of children with severe burns requiring skin grafts, subcutaneous somatropin 100 micrograms/kg daily, given from the first autograft until donor-site healing, was ineffective. However, a higher dose of somatropin 200 micrograms/kg daily by intramuscular injection, given throughout hospitalisation, reduced donor-site healing times and the length of hospital stay. There has been some concern that growth hormone therapy might increase hypertrophic scar formation, but studies[2,3] of subcutaneous somatropin given daily from hospital discharge until 1 year after burning have not found this. Somatropin treatment given during hospitalisation has also been reported to ameliorate burn-induced growth delays in such children; those injured during non-growth-spurt years may benefit most.[4,5] Long-term therapy given for 1 year after wound healing may also improve weight, linear growth, lean body-mass, and bone mineral content.[3,6] However, the manufacturers have recommended that somatropin should not be used to treat acute catabolic states in critically ill and burn patients, as there is some evidence in adults that mortality may be increased.[7] The management of burns is described on p. 1683.1.

1. Herndon DN, *et al.* Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990; **212:** 424–9.
2. de Oliveira GV, *et al.* Growth hormone effects on hypertrophic scar formation: a randomized controlled trial of 62 burned children. *Wound Repair Regen* 2004; **12:** 404–11.
3. Branski LK, *et al.* Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Ann Surg* 2009;**250:** 514–23.
4. Low JFA, *et al.* Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. *Lancet* 1999; **354:** 1789.
5. Low JFA, *et al.* The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. *Burns* 2001; **27:** 447–52.
6. Hart DW, *et al.* Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg* 2001; **233:** 827–34.
7. Takala J, *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341:** 785–92.

Cachexia and lipodystrophy. Treatment with subcutaneous growth hormone has been reported to reverse weight loss and improve body wasting in subjects with HIV disease (p. 959.1).[1,2] It can have beneficial effects on

physical function, body-weight, lean body-mass, and measures of health-related quality of life.

Some benefit has been reported[3] with growth hormone therapy in HIV-associated lipodystrophy. However, the optimal dose of growth hormone for these patients has yet to be found. Studies using subcutaneous doses of 6 mg daily, although very effective in reducing visceral adipose fat, led to supraphysiological levels of IGF-I and treatment-limiting adverse effects in particular decreased insulin sensitivity. The use of lower doses such as 4 mg on alternate days had a more favourable adverse effect profile and produced acceptable decreases in visceral fat; physiological doses of growth hormone (about 1 mg daily) did not adversely affect insulin sensitivity but had modest effects on body composition. Furthermore, the effect of growth hormone on visceral fat is not sustained once treatment is withdrawn.

Growth hormone therapy has also been reported to improve metabolic indicators of malnutrition in some[4] but not other[5] studies of patients undergoing haemodialysis.

1. Goldsmith DR, Wagstaff AJ. Mammalian cell-derived somatropin: a review of its use in the management of HIV-associated wasting. *Drugs* 2006; **66:** 387–401.
2. Gelato M, *et al.* Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. *Clin Ther* 2007; **29:** 2269–88.
3. Stanley TL, Grinspoon SK. GH/GHRH axis in HIV lipodystrophy. *Pituitary* 2009; **12:** 143–52.
4. Johannsson G, *et al.* Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. *Am J Kidney Dis* 1999; **33:** 709–17.
5. Kotzmann H, *et al.* One-year growth hormone therapy improves granulocyte function without major effects on nutritional and anthropometric parameters in malnourished hemodialysis patients. *Nephron Clin Pract* 2003; **93:** c75–82.

Cardiovascular disorders. A few small uncontrolled studies have reported improvements in heart failure (p. 1262.3) with the use of growth hormone.[1] A meta-analysis[2] of 12 studies using growth hormone in adults with chronic heart failure, including 8 placebo-controlled studies, also found evidence for improvement in several cardiovascular measures; however, individual results have been mixed and further study of long-term high-dose therapy is needed. A small underpowered study[3] of 6 months of treatment in children with dilated cardiomyopathy found only a trend towards improved cardiac function. Retrospective analysis[4] of a group of childhood cancer survivors found that growth hormone used to treat deficiency had some beneficial effects on anthracycline-induced left ventricular dysfunction, but that these diminished when growth hormone therapy was stopped.

1. Volterrani M, *et al.* Role of growth hormone in chronic heart failure: therapeutic implications. *Drugs* 2000; **60:** 711–19.
2. Le Corvoisier P, *et al.* Cardiac effects of growth hormone treatment in chronic heart failure: a meta-analysis. *J Clin Endocrinol Metab* 2007; **92:** 180–5.
3. McElhinney DB, *et al.* Recombinant human growth hormone treatment for dilated cardiomyopathy in children. Abstract: *Pediatrics* 2004; **114:** 1074–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/114/4/e452 (accessed 16/09/05)
4. Lipshultz SE, *et al.* Cardiac changes associated with growth hormone therapy among children treated with anthracyclines. *Pediatrics* 2005; **115:** 1613–22.

Cystic fibrosis. The use of growth hormone has been investigated in several small studies in patients with cystic fibrosis (p. 177.2). A review[1] of studies in children, adolescents, and young adults found improvements in measures of pulmonary function, height, and weight in those treated with growth hormone, usually without a comparator. However, further study is needed to determine whether there are significant effects on pulmonary exacerbations or infections, bone fractures, or death. The typical dose used was 300 micrograms/kg per week [subcutaneously], and treatment was generally given for 6 months to 1 year.

1. Phung OJ, *et al.* Recombinant human growth hormone in the treatment of patients with cystic fibrosis. Abstract: *Pediatrics* 2010; **126:** 1000. Full version: http://pediatrics.aappublications.org/cgi/reprint/126/5/e1211 (accessed 22/03/11)

Fibromyalgia. Symptomatic improvement after daily subcutaneous growth hormone injection has been reported in women with fibromyalgia,[1-3] a painful form of soft-tissue rheumatism (p. 14.2), and low levels of insulin-like growth factor I (IGF-I).

1. Bennett RM, *et al.* A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med* 1998; **104:** 227–31.
2. Cuatrecasas G, *et al.* Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels: a pilot study. *BMC Musculoskelet Disord* 2007; **8:** 119. Available at: http://www.biomedcentral.com/content/pdf/1471-2474-8-119.pdf (accessed 08/04/09)
3. Cuatrecasas G. Fibromyalgic syndromes: could growth hormone therapy be beneficial? *Pediatr Endocrinol Rev* 2009; **6** (suppl 4): 529–33.

Growth retardation. Growth hormone is a mainstay of the management of growth retardation (see p. 1918.3).

Reviews.

1. Harris M, *et al.* Growth hormone treatment in children: review of safety and efficacy. *Pediatr Drugs* 2004; **6:** 93–106.
2. Richmond E, Rogol AD. Current indications for growth hormone therapy for children and adolescents. *Endocr Dev* 2010; **18:** 92–108.
3. Collett-Solberg PF. Update in growth hormone therapy of children. *J Clin Endocrinol Metab* 2011; **96:** 573–9.

Infertility. Growth hormone appears to sensitise the ovary to stimulation by gonadotrophins and it has been suggested that somatropin may have a role in the management of female infertility. However, studies of somatropin added to gonadotrophin regimens have generally been small, used different treatment protocols and outcome measures, and studied mixed groups of women in terms of the cause of infertility. Studies in women with poor response to ovarian stimulation have shown mixed results, and response may depend on the cause of infertility. Mixed results have also been reported in women with polycystic ovary syndrome. Benefits may be most likely in women with hypogonadotrophic hypogonadism,[1] or those considered to be poor responders,[2] but there is no additional benefit for women who have a normal ovarian response to gonadotrophins.[1,2] UK guidelines[3] for the treatment of infertility do not recommend its use. Growth hormone has also been tried similarly to enhance spermatogenesis in infertile men unresponsive to conventional therapy, but studies have been small, and despite some encouraging reports[4] others have found no benefit.[5,6]

For a discussion of infertility and the more usual drugs used in its management, see p. 2253.1.

1. Artini PG, *et al.* Growth hormone cotreatment with gonadotropins in ovulation induction. *J Endocrinol Invest* 1996; **19:** 763–79.
2. Duffy JMN, *et al.* Growth hormone for in vitro fertilization. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 28/04/10).
3. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)
4. Shoham Z, *et al.* Cotreatment with growth hormone for induction of spermatogenesis in patients with hypogonadotropic hypogonadism. *Fertil Steril* 1992; **57:** 1044–51.
5. Ovesen PG. *et al.* Vaekshormonbehandling af maend med nedsat saedkvalitet. *Ugeskr Laeger* 1998; **160:** 176–80.
6. Giagulli VA. Absence of effect of recombinant growth hormone to classic gonadotropin treatment on spermatogenesis of patients with severe hypogonadotropic hypogonadism. *Arch Androl* 1999; **43:** 47–53.

Osteogenesis imperfecta. For reference to possible benefit from growth hormone therapy in patients with osteogenesis imperfecta, see p. 1167.3.

Osteomalacia. As mentioned on p. 1168.1, there has been some interest in the use of growth hormone in children with hypophosphataemic rickets.

Prader-Willi syndrome. Growth hormone treatment may be of benefit in the management of children with Prader-Willi syndrome (p. 2315.2). It increases growth velocity and improves body composition, by reducing fat mass and increasing muscle mass. However, there is limited information about long-term efficacy, and the effect on growth velocity is reported to wane after 1 to 3 years of therapy. There are also specific contra-indications and precautions relating to the use of growth hormone in these patients (see under Adverse Effects and Precautions, p. 1922.3). Growth hormone treatment may also improve body composition in adults with Prader-Willi syndrome.

References.

1. Carrel AL, *et al.* Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: a controlled study. *J Pediatr* 1999; **134:** 215–21.
2. Myers SE, *et al.* Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr* 2000; **137:** 42–9.
3. Burman P, *et al.* Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 2001; **22:** 787–99.
4. Carrel AL, *et al.* Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab* 2002; **87:** 1581–5.
5. Whitman BY, *et al.* The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: a 2-year, controlled study. Abstract: *Pediatrics* 2002; **109:** 308–9. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e35 (accessed 16/09/05)
6. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; **88:** 283–5.
7. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; **145:** 744–9.
8. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; **65:** 178–85.
9. Myers SE, *et al.* Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. *Am J Med Genet A* 2007; **143:** 443–8.
10. Mogul HR, *et al.* Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab* 2008; **93:** 1238–45.
11. de Lind van Wijngaarden RFA, *et al.* Efficacy and safety of long-term continuous growth hormone treatment in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2009; **94:** 4205–15.
12. Carrel AL, *et al.* Long-term growth hormone therapy changes the natural history of body composition and motor function in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2010; **95:** 1131–6.
13. Sode-Carlsen R, *et al.* One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2010; **95:** 4943–50.

Short bowel syndrome. A combination of growth hormone, glutamine, and dietary modification may improve intestinal absorption of fluid, electrolytes, and other nutrients, and thus reduce parenteral nutrition requirements in patients with short bowel syndrome.[1] However, studies have produced conflicting results, and benefit may depend on several factors including the type and length of remaining bowel, the presence or absence of mucosal disease, and the doses of somatropin and glutamine.[2] Additionally the beneficial effects may be short-lived, returning to baseline if therapy is stopped.[3]

1. Keating GM, Wellington K. Somatropin (Zorbtive®) in short bowel syndrome. *Drugs* 2004; **64:** 1375–81.
2. Matarese LE, *et al.* Growth hormone, glutamine, and modified diet for intestinal adaptation. *J Am Diet Assoc* 2004; **104:** 1265–72.
3. Wales PW, *et al.* Human growth hormone and glutamine for patients with short bowel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 08/12/10).

Veterinary and agricultural use. Bovine growth hormone or bovine somatotrophin (bovine somatotropin; BST) can increase milk yield in dairy cows. There has been considerable debate about both animal welfare and human food safety, and although it is approved in the USA[1] its use is banned in the EU.

1. FDA. CVM Update. Update on human safety of BST (issued 5th February, 1999). Available at: http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm130356.htm (accessed 12/08/10)

Adverse Effects and Precautions

Antibodies to growth hormone have been formed in some patients but these rarely seem to affect growth. There may be redness, itching, lumps, or lipoatrophy at the site of injection. Transient dose-related fluid retention with peripheral oedema and carpal tunnel syndrome has occurred; headache, muscle and joint pain, paraesthesia, and cases of benign intracranial hypertension have been reported. Although growth hormone has diabetogenic effects, high acute dosage has been associated with hypoglycaemia followed by hyperglycaemia. Growth hormone therapy may further increase the risk of ear disorders and otitis media in patients with Turner's syndrome, who are already at increased risk of ear and hearing disorders.

Growth hormone therapy is contra-indicated in patients with active neoplasms or intracranial lesions and should be stopped if evidence of tumour growth develops. Growth hormones should not be used for growth promotion in patients with closed epiphyses. Patients with scoliosis should be monitored during growth hormone therapy because of the risk of progression of scoliosis that can occur with rapid growth. Because of the diabetogenic effect of growth hormone it should be given with care to patients with diabetes mellitus; adjustment of antidiabetic therapy may be necessary. Somatropin is contra-indicated in patients with proliferative or preproliferative diabetic retinopathy. Hypothyroidism may develop during treatment, and may result in suboptimal response. Secondary hypoadrenalism may be unmasked by somatropin treatment, requiring glucocorticoid replacement therapy (see also Interactions, p. 1923.1). Growth hormone should not be used in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see also p. 1922.3). For the suggestion that growth hormone should not be used to treat acute catabolic states, as in patients with severe burns or who are otherwise critically ill, see Burns, under Uses and Administration, p. 1920.3.

Reviews.

1. Growth Hormone Research Society. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. *J Clin Endocrinol Metab* 2001; **86:** 1868–70.
2. Quigley CA, *et al.* Safety of growth hormone treatment in pediatric patients with idiopathic short stature. *J Clin Endocrinol Metab* 2005; **90:** 5188–96.
3. Bolar K, *et al.* Long-term safety of recombinant human growth hormone in Turner syndrome. *J Clin Endocrinol Metab* 2008; **93:** 344–51.
4. Poduval A, Saenger P. Safety and efficacy of growth hormone treatment in small for gestational age children. *Curr Opin Endocrinol Diabetes Obes* 2008; **15:** 376–82.
5. Bell J, *et al.* Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab* 2010; **95:** 167–77.

Abuse. Growth hormone has been subject to abuse in sport for its anabolic effects.[1,2] Limited study data suggest that it may increase lean body-mass,[3,4] however, it has minimal effect on strength and athletic performance, and may worsen exercise capacity.[3]

1. Ehrnborg C, Rosén T. Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports. *Asian J Androl* 2008; **10:** 373–83.
2. Holt RIG. Is human growth hormone an ergogenic aid? *Drug Test Anal* 2009; **1:** 412–18.
3. Liu H, *et al.* Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med* 2008; **148:** 747–58.
4. Meinhardt U, *et al.* The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. *Ann Intern Med* 2010; **152:** 568–77.

Benign intracranial hypertension. Benign intracranial hypertension (pseudotumor cerebri) has been described[1,2] in patients given growth hormone treatment. In an analysis[3] of a postmarketing surveillance database (1985 to 2000) of almost 40 000 children and adolescents who had been treated with growth hormone for various conditions, benign intracranial hypertension was more common than in the general paediatric population. The incidence in new patients starting growth hormone therapy was estimated to be about 30 in 100 000, and it had occurred more frequently in patients with renal failure or Turner's syndrome. Headache and papilloedema were the most common symptom and sign, but these did not occur in all patients, and most cases had an onset of a few months. The condition was effectively managed by stopping growth hormone. A small number of patients were rechallenged after the benign intracranial hypertension had resolved, and most could be treated with doses that were 25 to 50% of the original dose. Another surveillance database[4] of nearly 58 000 children and adolescents found an overall incidence of 27.7 per 100 000 treatment years; the incidence was highest in patients with chronic renal impairment, and lowest in those with idiopathic growth hormone deficiency. The median onset of benign intracranial hypertension also varied between diagnostic groups, ranging from about 4 days to 1.3 years. Headache alone is a commonly reported adverse effect of growth hormone treatment, and this study found an incidence of 793.5 per 100 000 treatment years. It has been pointed out that diagnosis of benign intracranial hypertension may be complicated by the occurrence of headaches, which usually resolve spontaneously.[5]

1. Malozowski S, *et al.* Growth hormone, insulin-like growth factor I, and benign intracranial hypertension. *N Engl J Med* 1993; **329:** 665–6.
2. Malozowski S, *et al.* Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. *J Pediatr* 1995; **126:** 996–9.
3. Reeves GD, Doyle DA. Growth hormone treatment and pseudotumor cerebri: coincidence or close relationship? *J Pediatr Endocrinol Metab* 2002; **15** (suppl 2): 723–30.
4. Darendeliler F, *et al.* Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. *Horm Res* 2007; **68** (suppl 5): 41–7.
5. Price DA, *et al.* Benign intracranial hypertension induced by growth hormone treatment. *Lancet* 1995; **345:** 458–9.

Carcinogenicity. Despite fears to the contrary, studies in children given growth hormone after cranial irradiation for brain tumours or CNS leukaemia have found no evidence that therapy with growth hormone increased the *relapse* rate.[1-3]

Cases of acute *leukaemia* have been reported among patients treated with growth hormones. An international workshop convened in 1988 to review known leukaemia cases in patients treated with growth hormones in Europe, North America, Japan, and Australia since 1959 found the incidence of leukaemia in growth hormone-treated patients represented a twofold increase over the expected rate.[4] It was concluded that there may be a small increase in leukaemia incidence associated with growth hormone treatment of growth hormone-deficient patients, but that it was not clear that this was actually attributable to growth hormone. A later study involving 6284 patients treated with growth hormone between 1963 and 1985 in the USA confirmed an increase of about 2.5-fold in the incidence of leukaemia in this population, but noted that many of the patients had other risk factors for leukaemia.[5] It has been suggested that growth hormone deficiency is itself a risk factor for leukaemia and that perhaps this, rather than growth hormone treatment, is related to the increased incidence of leukaemia in these patients.[6] If there is any risk it is relatively small, and in view of the essential nature of growth hormone therapy in growth hormone-deficient children it was considered inappropriate and unwise to withhold it.[4] Further large cohort studies of survivors of childhood cancers[3] or patients treated for idiopathic growth hormone deficiency[7] have found that the use of growth hormone was not associated with an increased risk of leukaemia.

There is some evidence to suggest that growth hormone may increase the risk of *solid tumours*. The risk of secondary solid tumours was increased in a cohort of childhood cancer survivors, but the authors considered that the risk was probably quite small compared with the benefits of growth hormone therapy in these patients.[3] Extended follow-up of this group also suggested that the elevation of risk diminished with time.[8] Another cohort of patients who had been treated for idiopathic growth hormone deficiency showed increased risks in the incidence and mortality of colorectal cancer.[7]

Further reports of malignancies associated with growth hormone therapy include two children with Bloom's syndrome (a rare chromosomal disorder affecting DNA replication), one of whom developed B-cell non-Hodgkin's lymphoma and the other stem-cell leukaemia.[9]

Continued surveillance of patients who have received growth hormone therapy has been encouraged.[10,11]

1. Packer RJ, *et al.* Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. *J Clin Oncol* 2001; **19:** 480–7.
2. Swerdlow AJ, *et al.* Growth hormone treatment of children with brain tumors and risk of tumor recurrence. *J Clin Endocrinol Metab* 2000; **85:** 4444–9.
3. Sklar CA, *et al.* Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 2002; **87:** 3136–41.
4. Fisher DA, *et al.* Leukaemia in patients treated with growth hormone. *Lancet* 1988; **i:** 1159–60.
5. Fradkin JE, *et al.* Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 1993; **270:** 2829–32.
6. Rapaport R, *et al.* Relationship of growth hormone deficiency and leukemia. *J Pediatr* 1995; **126:** 759–61.
7. Swerdlow AJ, *et al.* Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. *Lancet* 2002; **360:** 273–7.
8. Ergun-Longmire B, *et al.* Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *J Clin Endocrinol Metab* 2006; **91:** 3494–8.
9. Brock PR, *et al.* Malignant disease in Bloom's syndrome children treated with growth hormone. *Lancet* 1991; **337:** 1345–6.
10. Ogilvy-Stuart AL, Gleeson H. Cancer risk following growth hormone use in childhood: implications for current practice. *Drug Safety* 2004; **27:** 369–82.
11. Jenkins PJ, *et al.* Does growth hormone cause cancer? *Clin Endocrinol (Oxf)* 2006; **64:** 115–21.

Creutzfeldt-Jakob disease. Reports in 1985 of a small number of deaths from Creutzfeldt-Jakob disease in patients under 40 years of age who had received growth hormone extracted from human pituitary glands resulted in the suspension of the distribution of pituitary-derived growth hormone by the licensing authorities in a number of countries, including Australia, Canada, the Netherlands, the UK, and the USA. Preparations of non-pituitary-derived growth hormone are now available that are free from contamination with Creutzfeldt-Jakob agent. However, because of the long incubation period of the disease, cases have been reported in patients who had received pituitary-derived growth hormone years previously.[1-5]

1. Brown P, *et al.* Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000; **55:** 1075–81.
2. Croes EA, *et al.* Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone. *J Neurol Neurosurg Psychiatry* 2002; **72:** 792–3.
3. Swerdlow AJ, *et al.* Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003; **61:** 783–91.
4. Hirst C. Iatrogenic Creutzfeldt-Jakob disease presenting 24 years after human growth hormone administration. *Br J Hosp Med* 2005; **66:** 592–3.
5. Furtner M, *et al.* Iatrogenic Creutzfeldt-Jakob disease 22 years after human growth hormone therapy: clinical and radiological features. *J Neurol Neurosurg Psychiatry* 2008; **79:** 229–31.

Effects on carbohydrate metabolism. A retrospective analysis[1] of data from a pharmacoepidemiological survey of children treated with growth hormone found a higher incidence of type 2 diabetes, compared with that found in untreated children. The researchers speculated that growth hormone treatment might precipitate the onset of type 2 diabetes in predisposed patients, and proposed that patients with risk factors for diabetes, including Turner's syndrome, Prader-Willi syndrome, or intra-uterine growth retardation, be monitored. Studies of growth hormone have reported rises in serum concentrations of insulin, fasting and postprandial blood-glucose, and glycosylated haemoglobin, although these changes were generally small.[2] It has been noted that these effects appear to regress during treatment, but not always, and in some patients glucose intolerance or diabetes mellitus are not reversible after withdrawal of growth hormone.

Nonketotic hyperglycaemia developed within weeks of beginning growth hormone therapy in a 22-month-old child, leading to convulsions and metabolic acidosis; the patient died despite correction of the hyperglycaemia.[3]

1. Cutfield WS, *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* 2000; **355:** 610–13.
2. Jeffcoate W. Growth hormone therapy and its relationship to insulin resistance, glucose intolerance and diabetes mellitus: a review of recent evidence. *Drug Safety* 2002; **25:** 199–212.
3. Garg AK, Hyperglycemia during replacement growth hormone therapy. *J Pediatr* 1994; **125:** 329.

Effects on immune function. Growth hormone is generally considered to interact with the immune system although there is a lack of evidence that this is clinically significant.[1-4] There has been a report of acute renal transplant rejection in 2 children receiving treatment for growth retardation with somatropin.[5] In both children renal function of the transplant was stable for several years before somatropin was started, and growth hormone therapy had continued for some months before rejection occurred. It was suggested that during the first months of growth hormone therapy in transplant recipients, immunosuppressive therapy should be increased and transplant function carefully monitored. However, in subsequent studies[6,7] the use of growth hormone did not affect the incidence of rejection.

1. Church JA, *et al.* Immune functions in children treated with biosynthetic growth hormone. *J Pediatr* 1989; **115:** 420–3.
2. Rapaport R, Oleske J. Immune function during growth hormone therapy. *J Pediatr* 1990; **116:** 669–70.
3. Rekers-Mombarg LTM, *et al.* Immunologic studies in children with idiopathic short stature before and during growth hormone therapy. *Horm Res* 1995; **44:** 203–7.
4. Lebl J, *et al.* Immune system in adults with childhood-onset growth hormone deficiency: effect of growth hormone therapy. *Endocr Regul* 2000; **34:** 169–73.
5. Tydén G, *et al.* Acute renal graft rejection after treatment with human growth hormone. *Lancet* 1990; **336:** 1455–6.
6. Maxwell H, Rees L. Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. *Arch Dis Child* 1998; **79:** 481–7.
7. Maxwell H, *et al.* Growth hormone and markers of immune function in children with renal transplants. *Pediatr Nephrol* 2000; **14:** 473–5.

Effects on mortality. The EMEA[1] and FDA[2] are conducting safety reviews of growth hormone after a long-term French epidemiological study of patients who had received treatment during childhood for short stature showed an increased mortality risk for patients given growth hormone compared with the general population. Until the reviews have been completed somatropin should be used according to licensed indications and doses, and the EMEA has issued a reminder that the recommended daily dose of 50 micrograms/kg should not be exceeded.[1]

1. EMEA. Update on somatropin-containing medicines (issued 16th December, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/12/WC500099936.pdf (accessed 22/09/11)
2. FDA. Safety review update of recombinant human growth hormone (somatropin) and possible increased risk of death (issued 4th August, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm265865.htm (accessed 22/09/11)

Effects on the pancreas. A report of acute pancreatitis on starting growth hormone treatment in a patient with pseudohypoparathyroidism and growth hormone deficiency.[1] Ten further cases of acute pancreatitis associated with growth hormone treatment had been reported to the FDA at the time of writing.

1. Malozowski S, *et al.* Acute pancreatitis associated with growth hormone therapy for short stature. *N Engl J Med* 1995; **332:** 401–2.

Effects on skeletal muscle. Mild inflammatory myositis, with myalgia and muscle weakness, has been reported in 2 patients receiving growth hormone therapy.[1] It was suggested that the effect might be due to *m*-cresol used as a preservative in the preparation.

1. Yordam N. Myositis associated with growth hormone therapy. *J Pediatr* 1994; **125:** 671.

Gynaecomastia. A report of 22 cases of prepubertal gynaecomastia diagnosed during growth hormone treatment.[1]

1. Malozowski S, Stadel BV. Prepubertal gynecomastia during growth hormone therapy. *J Pediatr* 1995; **126:** 659–61.

Hypersensitivity. Generalised urticaria in a patient given somatropin was overcome by a desensitisation regimen.[1] The patient was subsequently maintained uneventfully on daily injections of somatropin.

1. Walker SB, *et al.* Systemic reaction to human growth hormone treated with acute desensitization. *Pediatrics* 1992; **90:** 108–9.

Iron deficiency. The view has been expressed[1] that given the increased production of haemoglobin and the prevalence of iron deficiency in patients treated with growth hormone, supplementation with iron should be considered in patients receiving growth hormone treatment.

1. Vihervuori E, *et al.* Increases in hemoglobin concentration and iron needs in response to growth hormone treatment. *J Pediatr* 1994; **125:** 242–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies somatropin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Prader-Willi syndrome. Somatropin is used in children diagnosed with Prader-Willi syndrome to improve growth and body composition (see Uses and Administration, p. 1920.1). One US manufacturer of somatropin (*Pharmacia*) has stated that as of April 2003 it was aware of 7 reports of death in children with Prader-Willi syndrome treated with growth hormone.[1] The patients shared one or more of the following risk factors: severe obesity, a history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. It was recommended that patients with Prader-Willi syndrome should be evaluated for upper airway obstruction, before beginning treatment, and if signs of such obstruction, for example snoring, developed during treatment therapy should be suspended. Somatropin was considered contra-indicated in these patients if

1. Pharmacia Ltd. Genotropin: Prader-Willi syndrome. Letter to healthcare professionals, 2003.

they were severely obese or had severe respiratory impairment; licensed product information had been amended accordingly. Early diagnosis and aggressive treatment of respiratory infections was also recommended. A few cases have been described in the literature.[2-4]

Children with Prader-Willi syndrome appear to have a higher incidence of respiratory problems such as sleep apnoea, hypoventilation, and infections than healthy children.[5] A prospective study[6] of 25 patients reported that sleep-disordered breathing had actually improved in most of them after 6 weeks of growth hormone therapy. However, there was a subgroup of 6 patients in which obstructive sleep apnoea and hypopnoea worsened; 4 of them had developed upper respiratory-tract infections and enlarged tonsils, and 2 had high serum concentrations of insulin-like growth factor I (IGF-I) and enlarged tonsils.

1. Pharmacia, USA. Safetyalert: Genotropin (somatropin [rDNA origin] for injection) (issued May 2003). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm168411.htm (accessed 12/08/10)
2. Eiholzer U, *et al*. Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment: a case report. *Horm Res* 2002; **58** (suppl 3): 24–6.
3. Van Vliet G, *et al*. Sudden death in growth hormone-treated children with Prader-Willi syndrome. *J Pediatr* 2004; **144:** 129–31.
4. Craig ME, *et al*. Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; **65:** 178–85.
5. Eiholzer U. Deaths in children with Prader-Willi syndrome: a contribution to the debate about the safety of growth hormone treatment in children with PWS. *Horm Res* 2005; **63:** 33–9.
6. Miller J, *et al*. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2006; **91:** 413–17.

Interactions

High doses of corticosteroids may inhibit the growth promoting effects of growth hormone. For the effects of growth hormone on corticosteroids, see p. 1620.2. Doses of growth hormone may need to be increased in women receiving oral oestrogen replacement therapy, and may require adjustment if the route of oestrogen administration is changed.

Pharmacokinetics

Somatropin is well absorbed after subcutaneous or intramuscular injection with a bioavailability varying from about 60 to 80%; peak serum concentrations may not be achieved for several hours. After intravenous injection it has a half-life of about 20 to 30 minutes but after subcutaneous or intramuscular doses serum concentrations decline with a half-life of 3 to 5 hours, due to more prolonged release from the injection site. It is metabolised in the liver and kidneys and excreted in bile.

Absorption. Studies of the pharmacokinetics of somatropin after transdermal jet injection from 2 devices in healthy subjects suggested that absorption was more rapid and peak serum concentration higher than after conventional subcutaneous injection of the same dose.[1,2] However, this did not seem to result in any difference in the total amount absorbed, nor in the biological effect. Other needle-free devices[3,4] provided have similar concentration-time profiles for somatropin compared with conventional injection in healthy subjects. When studied in children with growth hormone deficiency, however, one device[3] was considered to cause more bleeding, pain, soreness, and bruising at the injection site than a needle-injection pen device.

1. Verhagen A, *et al*. Pharmacokinetics and pharmacodynamics of a single dose of recombinant human growth hormone after subcutaneous administration by jet-injection: comparison with conventional needle-injection. *Eur J Clin Pharmacol* 1995; **49:** 69–72.
2. Agersø H, *et al*. Pharmacokinetics and pharmacodynamics of a new formulation of recombinant human growth hormone administered by ZomaJet 2 Vision, a new needle-free device, compared to subcutaneous administration using a conventional syringe. *J Clin Pharmacol* 2002; **42:** 1262–8.
3. Dörr HG, *et al*. Are needle-free injections a useful alternative for growth hormone therapy in children? Safety and pharmacokinetics of growth hormone delivered by a new needle-free injection device compared to a fine gauge needle. *J Pediatr Endocrinol Metab* 2003; **16:** 383–92.
4. Brearley C, *et al*. Pharmacokinetics of recombinant human growth hormone administered by cool.click 2, a new needle-free device, compared with subcutaneous administration using a conventional syringe and needle. *BMC Clin Pharmacol* 2007; **7:** 10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biotropin; Genotropin; HHT; Hutrope; Norditropin; Saizen; ***Austral.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; SciTropin; Zomacton; ***Austria***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Belg.***: Genotonorm; Humatrope; Norditropin; NutropinAq; Omnitrope; Zomacton; ***Braz.***: Eutropin; Genotropin; Hormotrop; Humatrope; Norditropin; Omnitrope; Saizen; Somatrop; ***Canad.***: Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Serostim; ***Chile***: Genotonorm; HHT; Humatrope; Hutrope; Norditropin; Saizen; ***China***: An Su Meng (安苏萌); Genheal (珍怡); Genotropin (健豪宁); Hai Zhi Yuan (海之元); Humatrope (优猛苗); Jintropin (赛增); Norditropin (诺泽); Sai Gao Lu (赛高路); Saizen (思真); ***Cz.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin†; Zomacton; ***Denm.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Zomacton; ***Fin.***: Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Fr.***: Genotonorm; Maxomat†; Norditropine; NutropinAq; Omnitrope; Saizen; Umatrope; Zomacton; ***Ger.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Gr.***: Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; ***Hong Kong***: GenLei Jintropin; Genotropin; Humatrope†; Norditropin†; Saizen; SciTropin†; Serostim†; Zomacton; ***Hung.***: Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; ***India***: Genotropin; Humatrope; LG Eutropin; Norditropin; Saizen; ***Indon.***: Eutropin; Genotropin; Norditropin; Saizen; ***Irl.***: Genotropin; Norditropin; Nutropin; Omnitrope; Saizen; Valtropin†; Zomacton; ***Israel***: Bio-Tropin; Genotropin; Norditropin; Nutropin; Saizen†; ***Ital.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Jpn***: Growject; Norditropin; ***Malaysia***: Genotropin; Norditropin; Saizen; ***Mex.***: Cryo-Tropin; Genotropin; HHT†; Humatrope; Norditropin; Saizen; Serostim†; Xerendip; ***Neth.***: Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Zomacton; ***Norw.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***NZ***: Genotropin; Norditropin; Saizen; ***Philipp.***: GenHeal; Humatrope†; Norditropin; Saizen; SciTropin; ***Pol.***: Genotropin; Norditopin; NutropinAq; Omnitrope; Valtropin†; ***Port.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin†; Zomacton; ***Rus.***: Genotropin (Генотропин); Humatrope (Хуматроп); Jintropine (Джинтропин); Norditropin (Нордитропин); Rastan (Растан); Saizen (Сайзен); ***S.Afr.***: Genotropin; Humatrope; Norditropin; ***Singapore***: Genotropin; Norditropin; Saizen; SciTropin; ***Spain***: Genotonorm; Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Zomacton; ***Swed.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Switz.***: Genotropin; Humatrope; Norditropine; Omnitrope; Saizen; ***Thai.***: Eutropin; GenHeal; Genotropin; Norditropin; Saizen; ***Turk.***: Genotropin; Humatrope; Norditropin; Saizen; Zomacton; ***UK***: Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Zomacton; ***Ukr.***: Biorostan (Биоростан); Genotropin (Генотропин); Norditropin (Нордитропин); ***USA***: Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Serostim; Tev-Tropin; Zorbtive; ***Venez.***: Genotropin; Humatrope; Saizen.

Multi-ingredient Preparations. ***Ukr.***: Nutropin (Нутропин Aq).

Pharmacopoeial Preparations
BP 2014: Somatropin Injection;
Ph. Eur.: Somatropin for Injection;
USP 36: Somatropin for Injection.

Lanreotide *(BAN, rINN)*

Angiopeptin; BIM-23014; BN-52030; DC-13-116; Lanreotid; Lanreotida; Lanréotide; Lanreotidi; Lanreotidum; Lanreotyd; Ланреотид.

3-(2-Naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide cyclic (2→7)-disulfide.

$C_{54}H_{69}N_{11}O_{10}S_2$=1096.3

CAS — 108736-35-2.
ATC — H01CB03.
ATC Vet — QH01CB03.
UNII — 0G3DE8943Y.

Lanreotide Acetate *(BANM, USAN, rINNM)*

Acetato de lanreotida; BIM-23014C; Lanreotida, acetato de; Lanréotide, Acétate de; Lanreotidi Acetas; Ланреотида Ацетат.

$C_{54}H_{69}N_{11}O_{10}S_2.x\ (C_2H_4O_2)$

CAS — 127984-74-1.
ATC — H01CB03.
ATC Vet — QH01CB03.
UNII — IEU56G3J9C.

Uses and Administration

Lanreotide is a somatostatin analogue with similar properties to those of octreotide (p. 1924.1). It is given, as a long-acting depot injection, in the treatment of acromegaly (p. 1918.1) and thyrotrophic adenoma, as well as in the symptomatic management of neuroendocrine tumours, particularly carcinoid syndrome (p. 716.3).

Lanreotide is given as the acetate, but doses are usually expressed in terms of the base. The usual starting dose of one **intramuscular** depot injection (*Somatuline LA; Ipsen, UK*) is equivalent to lanreotide 30 mg every 14 days. In acromegaly and symptomatic neuroendocrine tumours, this may be increased if necessary to 30 mg every 7 to 10 days; in thyrotrophic adenoma it may be increased to 30 mg every 10 days.

An alternative preparation (*Somatuline Autogel; Ipsen, UK*) for acromegaly and symptomatic neuroendocrine tumours may be given by deep **subcutaneous** injection.

In acromegaly, an initial dose of 60 mg once every 28 days may be used in treatment-naive patients. For patients already receiving the intramuscular formulation, the same total dose of lanreotide that would have been given over 28 or 30 days may be replaced by a single dose of the subcutaneous preparation once every 28 days. In patients who respond to treatment, lanreotide may be gradually reduced to subcutaneous maintenance doses of 120 mg given at intervals of up to 56 days. In those who are not adequately controlled, a maximum dose of 120 mg once every 28 days may be used. Doses are adjusted according to symptoms and concentrations of growth hormone and IGF-I.

In patients with neuroendocrine tumours, the preparation for deep subcutaneous injection may be given in doses of 60 to 120 mg once every 28 days, and adjusted according to symptomatic relief.

In the USA, a preparation for deep subcutaneous injection (*Somatuline Depot; Tercica, USA*) may be given for acromegaly in initial doses of 90 mg once every 28 days for 3 months, then adjusted to between 60 and 120 mg every 28 days as necessary. Alternatively, for maintenance therapy a dose of 120 mg every 42 or 56 days may be appropriate.

For doses in hepatic and renal impairment, see below.

Lanreotide has been tried for the prevention of restenosis in coronary blood vessels following angioplasty (see Reperfusion and Revascularisation Procedures, p. 1259.2).

References.
1. Wymenga ANM, *et al*. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol* 1999; **17:** 1111–17.
2. Kuhn JM, *et al*. Evaluation of the treatment of thyrotropin-secreting pituitary adenomas with a slow release formulation of the somatostatin analog lanreotide. *J Clin Endocrinol Metab* 2000; **85:** 1487–91.
3. Ruszniewski P, *et al*. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004; **80:** 244–51.
4. Freda PU, *et al*. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 4465–73.
5. Croxtall JD, Scott LJ. Lanreotide Autogel: a review of its use in the management of acromegaly. *Drugs* 2008; **68:** 711–23.
6. Khan MS, *et al*. Long-term results of treatment of malignant carcinoid syndrome with prolonged release lanreotide (Somatuline Autogel). *Aliment Pharmacol Ther* 2011; **34:** 235–42.

Administration in hepatic and renal impairment. The clearance of lanreotide, given by intravenous bolus, was significantly reduced in patients with severe chronic renal impairment requiring haemodialysis.[1] However, the authors of this study suggested that considering the wide therapeutic window of lanreotide, depot formulations may be given at the usual initial dose, with further doses adjusted according to response. Clearance of lanreotide was only slightly reduced in patients with moderate to severe hepatic impairment (Child-Pugh category B and C).[2]

The UK licensed product information for one depot **subcutaneous** formulation (*Somatuline Autogel; Ipsen, UK*) given every 28 days recommends that dose adjustment is not necessary in renal or hepatic impairment. Product information for a similar US preparation (*Somatuline Depot; Tercica, USA*) advises that in moderate and severe renal or hepatic impairment, an initial dose of 60 mg instead of 90 mg should be given by deep subcutaneous injection once every 28 days for 3 months, then adjusted as needed. Product information for another preparation (*Somatuline LA; Ipsen, UK*) usually given **intramuscularly** every 14 days suggests that it is not necessary to adjust the starting dose in hepatic or renal impairment.

1. Barbanoj M, *et al*. Pharmacokinetics of the somatostatin analog lanreotide in patients with severe chronic renal insufficiency. *Clin Pharmacol Ther* 1999; **66:** 485–91.
2. Tomlinson B, *et al*. Pharmacokinetic profile of the somatostatin analogue lanreotide in individuals with chronic hepatic insufficiency. *Clin Pharmacokinet* 2006; **45:** 1003–11.

Adverse Effects and Precautions

As for Octreotide Acetate, p. 1927.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lanreotide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for Octreotide Acetate, p. 1927.3.

Pharmacokinetics

After intravenous injection lanreotide has a terminal half-life of about 2.5 hours. Lanreotide is available as injectable depot preparations, and after subcutaneous or intramuscular use of these an initial rapid liberation of the drug is followed by more prolonged release with an apparent half-

life of about 5 to 30 days. The absolute bioavailability is stated to range from about 55 to 80%, depending on the product.

References.
1. Hu M, Tomlinson B. Pharmacokinetic evaluation of lanreotide. *Expert Opin Drug Metab Toxicol* 2010; **6:** 1301–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Somatuline; ***Austral.***: Somatuline; ***Austria***: Somatuline; ***Belg.***: Somatuline; ***Canad.***: Somatuline; ***China***: Somatuline (索马杜林); ***Cz.***: Somatuline; ***Denm.***: Ipstyl; ***Fin.***: Somatuline; ***Fr.***: Somatuline; ***Ger.***: Somatuline; ***Gr.***: Somatuline; ***Hong Kong***: Somatuline; ***Hung.***: Somatuline; ***Irl.***: Somatuline; ***Israel***: Somatuline; ***Ital.***: Ipstyl; ***Jpn***: Somatuline; ***Neth.***: Somatuline; ***Norw.***: Ipstyl; ***Pol.***: Somatuline; ***Port.***: Somatulina; ***Rus.***: Somatuline (Соматулин); ***Singapore***: Somatuline; ***Spain***: Somatulina; ***Swed.***: Somatuline; ***Switz.***: Somatuline; ***Turk.***: Somatuline; ***UK***: Somatuline; ***Ukr.***: Somatuline (Соматулин); ***USA***: Somatuline.

Octreotide Acetate *(BANM, USAN, rINNM)*

Acetato de octreotida; Octreotida, acetato de; Octréotide, Acétate d'; Octreotidi Acetas; SMS-201-995 (octreotide); Октреотида Ацетат.

2-(D-Phenylalanyl-L-cystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cystyl)-(2*R*,3*R*)-butane-1,3-diol acetate; D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7) disulphide acetate.

$C_{49}H_{66}N_{10}O_{10}S_2.xC_2H_4O_2$=1019.2 (octreotide)

CAS — 83150-76-9 (octreotide); 79517-01-4 (octreotide acetate).

ATC — H01CB02.

ATC Vet — QH01CB02.

UNII — 75R0U2568I.

Incompatibility. Apparent loss of insulin has been reported from a total parenteral nutrient solution containing octreotide; there may be an incompatibility.[1] Also the manufacturers had suggested that octreotide might be adsorbed onto plastics. However, a solution containing octreotide 200 micrograms/mL as the acetate was reported to be stable at 5 degrees or -20 degrees for up to 60 days when stored in polypropylene syringes.[2]

1. Rosen GH. Potential incompatibility of insulin and octreotide in total parenteral nutrient solutions. *Am J Hosp Pharm* 1989; **46:** 1128.
2. Ripley RG, *et al*. Stability of octreotide acetate in polypropylene syringes at 5 and -20 degreesC. *Am J Health-Syst Pharm* 1995; **52:** 1910–11.

Uses and Administration

Octreotide is an octapeptide analogue of somatostatin (p. 1930.3) with similar properties but a longer duration of action.

It is used as the acetate in the symptomatic management of neuroendocrine tumours such as carcinoid tumours, VIPomas, and glucagonomas. Octreotide acetate is also used in the treatment of acromegaly and the prevention of complications after pancreatic surgery, and may be used in the treatment of other disorders including variceal haemorrhage and HIV-associated diarrhoea. It has also been investigated in a variety of other disorders.

In the management of **secretory neoplasms** octreotide acetate is given subcutaneously in an initial dose equivalent to 50 micrograms of octreotide once or twice daily gradually increased, according to response, to up to 600 micrograms daily in 2 to 4 divided doses. Higher doses have been used. If there is no benefit within a week of starting treatment for carcinoid tumour, continued therapy is not recommended.

Where a rapid response is required, the initial dose may be given by the intravenous route. In the UK, licensed product information states that it should be diluted not less than 1 in 1 or not more than 1 in 9 in sodium chloride 0.9%, but in the USA, product information permits the use of the undiluted solution as an intravenous bolus in emergencies; alternatively, the dose may be given by intermittent infusion over 15 to 30 minutes, diluted in 50 to 200 mL of sodium chloride 0.9% or glucose 5%.

Once control has been established maintenance therapy with a depot preparation may be possible; initially 20 mg by intramuscular injection every 4 weeks is suggested. Subcutaneous injection with a rapid-acting preparation should be continued for 2 weeks after the first depot injection to provide symptomatic cover, and may be added to therapy when necessary thereafter. Maintenance doses of the depot preparation may be adjusted after 2 or 3 months to between 10 and 30 mg every 4 weeks, as necessary.

In **acromegaly**, the usual dose is the equivalent of 100 to 200 micrograms of octreotide three times daily by subcutaneous injection. In the USA it is suggested that dosage begin with 50 micrograms three times daily in order to minimise gastrointestinal disturbance. If there is no relevant reduction in growth hormone concentrations and no improvement in clinical symptoms within 3 months of starting treatment, octreotide should be stopped. Once control has been established maintenance therapy with a depot preparation is possible; an initial dose equivalent to 20 mg of octreotide given intramuscularly once every 4 weeks has been recommended for patients with acromegaly, adjusted after 3 months to between 10 and 30 mg every 4 weeks. For patients who are not adequately controlled on 30 mg, the dose may be further increased to 40 mg every 4 weeks. The depot preparation may also be used for short-term treatment before pituitary surgery, but the last dose should be given at least 3 to 4 weeks before surgery to ensure successful endocrine testing for tumour removal 5 to 6 weeks after surgery.

For the prevention of complications after **pancreatic surgery** the equivalent of 100 micrograms of octreotide may be given three times daily by subcutaneous injection of a rapid-acting preparation; treatment is given for 7 consecutive days, beginning at least 1 hour before laparotomy on the day of operation.

In the management of **variceal haemorrhage** in patients with cirrhosis, octreotide is given as a continuous intravenous infusion at a dose equivalent to octreotide 25 micrograms/hour for 48 hours. Doses up to 50 micrograms/hour have been used. Patients at high risk of rebleeding may continue treatment for up to 5 days. For octreotide doses in oesophageal or gastric variceal bleeding in children, see below.

HIV-associated diarrhoea may be treated with an initial dose of octreotide 100 micrograms three times daily, given subcutaneously. If the diarrhoea is not controlled after a week, the dose may be increased to 250 micrograms three times daily, but if this is not effective after one further week then octreotide therapy should be stopped.

For doses in hepatic and renal impairment, see below.

General reviews of octreotide.

1. Anthony L, Freda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. *Curr Med Res Opin* 2009; **25:** 2989–99.

Administration in children. Although octreotide is not licensed in the UK for oesophageal or gastric variceal bleeding in children, the *BNFC* includes a dose of 1 microgram/kg per hour by continuous intravenous infusion for children aged from 1 month to 18 years. Higher doses may be needed initially, to a maximum dose of 50 micrograms/hour. The dose should be reduced gradually over 24 hours once there is no active bleeding.

For other uses of octreotide in children see Chylous Effusion, below, Hyperinsulinism, p. 1926.1, and Obesity, p. 1926.3.

Administration in hepatic and renal impairment. The clearance of octreotide may be reduced in patients with hepatic or renal impairment. US licensed product information suggests that intramuscular depot therapy should be started at a dose of octreotide 10 mg once every 4 weeks in patients with established liver cirrhosis or renal failure requiring dialysis. Patients with lesser degrees of renal impairment may be given normal doses (see above).

Acromegaly. Although surgery remains the most important method of treatment, octreotide has a useful role in the management of acromegaly (p. 1918.1), particularly as adjuvant therapy when there is still active disease after surgery, as primary therapy when surgery is not possible, or while awaiting the full effects of radiotherapy. Octreotide can reduce growth hormone concentrations, normalise IGF-I concentrations, reduce tumour size, and improve signs and symptoms.[1] There is also some evidence that it may improve cardiac function, which is usually compromised in these patients.[1,2] Octreotide can be given subcutaneously and this route is generally used initially to determine patient response and tolerance, but it must be given three times daily making it unattractive for long-term use. Intramuscular sustained-release octreotide is effective for maintenance therapy. There is also increasing interest in the role of octreotide for primary therapy of acromegaly, instead of surgery[2-5] and a meta-analysis[6] suggested that tumour shrinkage was greatest when somatostatin analogues were given as primary rather than secondary therapy. Additionally, pre-operative treatment with octreotide might improve surgical cure rates in patients with macroadenomas.[7]

1. Yang LPH, Keating GM. Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. *Drugs* 2010; **70:** 1745–69.
2. Colao A, *et al*. Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels, tumor shrinkage, and cardiovascular disease: a prospective study. *J Clin Endocrinol Metab* 2009; **94:** 3746–56.
3. Bevan JS, *et al*. Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab* 2002; **87:** 4554–63.
4. Cozzi R, *et al*. Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. *J Clin Endocrinol Metab* 2006; **91:** 1397–1403.
5. Colao A, *et al*. Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. *Clin Endocrinol (Oxf)* 2009; **70:** 757–68.
6. Freda PU, *et al*. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 4465–73.
7. Carlsen SM, *et al*. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *J Clin Endocrinol Metab* 2008; **93:** 2984–90.

Cardiovascular disorders. There have been reports of benefit from octreotide in patients with postprandial hypotension and orthostatic hypotension (p. 1634.3) associated with autonomic neuropathy.[1-6] Octreotide has also produced cardiac improvement in patients with acromegaly (see above). Promising results have been reported in patients with primary hypertrophic cardiomyopathy.[7,8] Benefit has also been reported in a few patients with dilated cardiomyopathy.[9] For the usual management of cardiomyopathies, see p. 1261.3.

1. Hoeldtke RD, *et al*. Treatment of autonomic neuropathy with a somatostatin analogue SMS-201-995. *Lancet* 1986; **ii:** 602–5.
2. Hoeldtke RD, Israel BC. Treatment of orthostatic hypotension with octreotide. *J Clin Endocrinol Metab* 1989; **68:** 1051–9.
3. Woo J, *et al*. Treatment of severe orthostatic hypotension with the somatostatin analogue octreotide. *Aust N Z J Med* 1990; **20:** 822–3.
4. Bordet R, *et al*. Octreotide in the management of orthostatic hypotension in multiple system atrophy: pilot trial of chronic administration. *Clin Neuropharmacol* 1994; **17:** 380–3.
5. Hoeldtke RD, *et al*. Treatment of orthostatic hypotension with midodrine and octreotide. *J Clin Endocrinol Metab* 1998; **83:** 339–43.
6. Hoeldtke RD, *et al*. Treatment of autonomic neuropathy, postural tachycardia and orthostatic syncope with octreotide LAR. *Clin Auton Res* 2007; **17:** 334–40.
7. Günal AI, *et al*. Short term reduction of left ventricular mass in primary hypertrophic cardiomyopathy by octreotide injections. *Heart* 1996; **76:** 418–21.
8. Demirtaş E, *et al*. Effects of octreotide in patients with hypertrophic obstructive cardiomyopathy. *Jpn Heart J* 1998; **39:** 173–81.
9. Eryol NK, *et al*. The effects of octreotide in dilated cardiomyopathy: an open-label trial in 12 patients. *Jpn Heart J* 2004; **45:** 613–21.

Chylous effusion. Chylous effusion results in accumulation of a milky lymphatic fluid containing raised concentrations of white blood cells, triglycerides, and cholesterol. Chylothorax, when the effusion affects the pleural cavity, is generally a complication of malignancy or chest surgery, or may be idiopathic. Treatment usually involves catheter drainage and dietary modification; surgery is used when these measures fail. Octreotide has been used successfully in several cases to treat chylothorax,[1-5] although there are also reports of it being ineffective.[6] Doses have generally been 50 to 100 micrograms subcutaneously 3 times daily. Octreotide has also been used for treating chylothorax in paediatric patients, particularly after cardiothoracic surgery. Doses noted in reviews[7-9] have ranged from 7 to 240 micrograms/kg daily by intravenous infusion, or around 4 to 40 micrograms/kg daily by subcutaneous injection. Octreotide has also been used in chyloperitoneum[10-15] and for cervical chylous fistula.[16]

1. Demos NJ, *et al*. Somatostatin in the treatment of chylothorax. *Chest* 2001; **119:** 964–6.
2. Demos NJ. Octreotide in the treatment of chylothorax. *Chest* 2002; **121:** 2080–1.
3. Evans J, *et al*. Chylous effusions complicating lymphoma: a serious event with octreotide as a treatment option. *Hematol Oncol* 2003; **21:** 77–81.
4. Makrilakis K, *et al*. Successful octreotide treatment of chylous pleural effusion and lymphedema in the yellow nail syndrome. *Ann Intern Med* 2004; **141:** 246–7.
5. Mincher L, *et al*. The successful treatment of chylous effusions in malignant disease with octreotide. *Clin Oncol (R Coll Radiol)* 2005; **17:** 118–21.
6. Mikroulis D, *et al*. Octreotide in the treatment of chylothorax. *Chest* 2002; **121:** 2079–80.
7. Roehr CC, *et al*. Somatostatin or octreotide as treatment options for chylothorax in young children: a systematic review. *Intensive Care Med* 2006; **32:** 650–7.
8. Helin RD, *et al*. Octreotide therapy for chylothorax in infants and children: a brief review. *Pediatr Crit Care Med* 2006; **7:** 576–9.
9. Caverly L, *et al*. Octreotide treatment of chylothorax in pediatric patients following cardiothoracic surgery. *Congenit Heart Dis* 2010; **5:** 573–8.
10. Bhatia C, *et al*. Octreotide therapy: a new horizon in treatment of iatrogenic chyloperitoneum. *Arch Dis Child* 2001; **85:** 234–5.
11. Leong RWL, *et al*. Chylous ascites caused by portal vein thrombosis treated with octreotide. *J Gastroenterol Hepatol* 2003; **18:** 1211–13.
12. Hwang J-B, *et al*. Resolution of refractory chylous ascites after Kasai portoenterostomy using octreotide. *J Pediatr Surg* 2004; **39:** 1806–7.
13. Qi J, *et al*. Management of postoperative chyloretroperitoneum in adults. *Singapore Med J* 2009; **50:** e338–e341.
14. Zhou DX, *et al*. The effectiveness of the treatment of octreotide on chylous ascites after liver cirrhosis. *Dig Dis Sci* 2009; **54:** 1783–8.
15. Soylu A, *et al*. Resolution of chyloperitoneum in a preterm with octreotide, diet and cessation of dialysis. *Pediatr Nephrol* 2010; **25:** 363–6.
16. Suver DW, *et al*. Somatostatin treatment of massive lymphorrhea following excision of a lymphatic malformation. *Int J Pediatr Otorhinolaryngol* 2004; **68:** 845–50.

Cushing's syndrome. Cushing's syndrome (p. 2559.1) can be caused by excessive secretion from an ectopic ACTH-secreting tumour. Many of these ectopic tumours express somatostatin receptors and it has been suggested that octreotide may be useful in the diagnosis, and possibly the treatment, of selected patients.[1] However, there are 5

types of somatostatin receptor,[2,3] and responses to octreotide have been variable,[4] even in the same patient.[3,5]

1. de Herder WW, Lamberts SWJ. Is there a role for somatostatin and its analogs in Cushing's syndrome? *Metabolism* 1996; **45** (suppl): 83–5.
2. de Herder WW, Lamberts SWJ. Octapeptide somatostatin-analogue therapy of Cushing's syndrome. *Postgrad Med J* 1999; **75:** 65–6.
3. Uwaifo GI, *et al*. Is there a therapeutic role for octreotide in patients with ectopic Cushing's syndrome? *J Endocrinol Invest* 2003; **26:** 710–17.
4. Woodhouse NJY, *et al*. Acute and long-term effects of octreotide in patients with ACTH-dependent Cushing's syndrome. *Am J Med* 1993; **95:** 305–8.
5. Gill GV, *et al*. Carcinoid-associated ectopic ACTH syndrome with variable response to octreotide. *Postgrad Med J* 1999; **75:** 98–101.

Diabetes mellitus. Although octreotide has been reported to impair glucose tolerance, and even precipitate frank diabetes (see Effects on Carbohydrate Metabolism, under Adverse Effects, p. 1927.2), its variable effects on blood glucose and insulin have led to investigations[1,2] of its ability to induce beta cell rest in patients with diabetes mellitus (p. 458.2) who still have residual insulin secretion. There is also some suggestion that it may be of benefit in the treatment or prevention of diabetic nephropathy[3,4] and retinopathy.[5-7] Benefit has been reported from the use of octreotide in patients with diabetic diarrhoea—see Diarrhoea, under Gastrointestinal Disorders, below.

1. Björk E, *et al*. Induction of β-cell rest in type 1 diabetes. *Diabetes Care* 1998; **21:** 427–30.
2. Vondra K, *et al*. Somatostatin: beneficial effects on remission in young adult patients with newly diagnosed diabetes mellitus type 1. *Physiol Res* 2004; **53:** 115–17.
3. Serri O, *et al*. Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *JAMA* 1991; **265:** 888–92.
4. Clemens A, *et al*. Octreotide (somatostatin analog) treatment reduces endothelial cell dysfunction in patients with diabetes mellitus. *Metabolism* 1999; **48:** 1236–40.
5. Grant MB, *et al*. The efficacy of octreotide in the therapy of severe nonproliferative and early proliferative diabetic retinopathy: a randomized controlled trial. *Diabetes Care* 2000; **23:** 504–9.
6. Boehm BO, *et al*. Octreotide reduces vitreous hemorrhage and loss of visual acuity risk in patients with high-risk proliferative diabetic retinopathy. *Horm Metab Res* 2001; **33:** 300–306.
7. Grant MB, Caballero S. Somatostatin analogues as drug therapies for retinopathies. *Drugs Today* 2002; **38:** 783–91.

Diagnosis and testing. Radiolabelled octreotide or other somatostatin analogues such as pentetreotide and depreotide may be used to visualise various malignant neoplasms which express somatostatin receptors.[1-5]

Octreotide may also have a role in the diagnosis of Cushing's syndrome, see p. 1924.3.

1. Basu S, *et al*. PET imaging in neuroendocrine tumors: current status and future prospects. *Minerva Endocrinol* 2008; **33:** 257–75.
2. Kwekkeboom DJ, *et al*. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with ^{111}In-pentetreotide. *Neuroendocrinology* 2009; **90:** 184–9. Also available at: http://www.enets.org/d.f.52.pdf (accessed 19/10/11)
3. Kwekkeboom DJ, *et al*. Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer* 2010; **17:** R53–R73.
4. Bombardieri E, *et al*. Oncology Committee of the EANM. ^{111}In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 2010; **37:** 1441–8. Also available at: http://www.eanm.org/publications/guidelines/EJNMMI_111In-Pentetreotide_GL.pdf (accessed 19/10/11)
5. Virgolini I, *et al*. Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE. *Eur J Nucl Med Mol Imaging* 2010; **37:** 2004–10. Also available at: http://www.eanm.org/publications/guidelines/gl_Ga68DOTA-X.pdf (accessed 19/10/11)

Eye disorders. There are reports of response to octreotide in patients with cystoid macular oedema, a refractory form of retinal oedema.[1-4] The problem recurred when octreotide was withdrawn[1,3,4] but responded to resumption of octreotide therapy.[1]

1. Kuijpers RWAM, *et al*. Treatment of cystoid macular edema with octreotide. *N Engl J Med* 1998; **338:** 624–6.
2. Hernaez-Ortega MC, *et al*. Sandostatin LAR for cystoid diabetic macular edema: a 1-year experience. *Diabetes Res Clin Pract* 2004; **64:** 71–2.
3. Missotten T, *et al*. Octreotide long-acting repeatable for the treatment of chronic macular edema in uveitis. *Am J Ophthalmol* 2007; **144:** 838–843.
4. Hogewind BF, *et al*. Octreotide acetate in dominant cystoid macular dystrophy. *Eur J Ophthalmol* 2008; **18:** 99–103.

Gastrointestinal disorders. Somatostatin inhibits gastric and intestinal secretion and the production of various active substances in the gastrointestinal tract. It also reduces splanchnic arterial blood flow and portal and gastric mucosal blood flow. These properties are made use of, usually in the form of octreotide, in the management of several gastrointestinal disorders including bleeding, refractory diarrhoea, fistulae, dumping syndrome, and nausea and vomiting secondary to bowel obstruction (see below).

Octreotide is used particularly in the treatment of carcinoid syndrome arising from endocrine tumours (see Neuroendocrine Tumours, p. 716.3).

BLEEDING. There have been mixed results with octreotide in the treatment of **nonvariceal** upper gastrointestinal bleeding. Although a large multicentre study[1] showed that octreotide had no benefit compared with placebo in the management of bleeding upper gastrointestinal ulcers, a meta-analysis that included somatostatin and octreotide suggested there might be some benefit.[2] Nevertheless, a later study[3] found that octreotide, given as an adjunct to endoscopic haemostasis using noradrenaline, did not seem to provide any additional benefit, and it is not recommended in the management of nonvariceal bleeding associated with peptic ulcer (p. 1813.2). A review suggested that octreotide was useful in patients with acquired gastrointestinal angiodysplasia with refractory bleeding, and might be considered for use particularly in those with inaccessible lesions or at high risk from other interventions.[4]

Octreotide may be used in the management of **variceal haemorrhage** (see under Monoethanolamine, p. 2563.1). There is some evidence that octreotide is as effective as sclerotherapy in the control of acute bleeding.[5] A meta-analysis[6] of studies comparing octreotide with other therapies (including vasopressin, terlipressin, sclerotherapy, or balloon tamponade) for the control of acute variceal bleeding found that octreotide had a similar effect to sclerotherapy in the prevention of rebleeding and was more effective and associated with fewer major complications than vasopressin or terlipressin. However, there was no evidence of mortality benefit associated with octreotide use. A systematic review[7] of studies comparing somatostatin or its analogues with either placebo or no drug treatment also found that although there was a small benefit in controlling bleeding, it was doubtful whether this benefit was worthwhile, and that deaths were not reduced. A third systematic review[8] found that sclerotherapy was associated with more frequent and severe adverse effects than drug therapy, including octreotide.

Controlled studies have suggested that *combination* of octreotide infusion for 5 days with endoscopic ligation[9] or sclerotherapy[10,11] reduces the risk of rebleeding. In another study,[12] sclerotherapy with 48 hours of octreotide infusion was more effective at controlling bleeding than sclerotherapy alone, and octreotide was as effective as sclerotherapy in those with evidence of recent bleeding. However, another study[13] found that octreotide given subcutaneously for up to 29 days after sclerotherapy did not affect the rate of early rebleeding. Octreotide has also produced some benefit (combined with regular sclerotherapy), in the long-term management of patients with cirrhotic portal hypertension.[14]

1. Christiansen J, *et al*. Placebo-controlled trial with the somatostatin analogue SMS 201-995 in peptic ulcer bleeding. *Gastroenterology* 1989; **97:** 568–74.
2. Imperiale TF, Birgisson S. Somatostatin or octreotide compared with H_2 antagonists and placebo in the management of acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Ann Intern Med* 1997; **127:** 1062–71. Correction. *ibid*. 1998; **128:** 245.
3. Nikolopoulou VN, *et al*. The effect of octreotide as an adjunct treatment in active nonvariceal upper gastrointestinal bleeding. *J Clin Gastroenterol* 2004; **38:** 243–7.
4. Brown C, *et al*. Somatostatin analogues in the treatment of recurrent bleeding from gastrointestinal vascular malformations: an overview and systematic review of prospective observational studies. *Dig Dis Sci* 2010; **55:** 2129–34.
5. Jenkins SA, *et al*. A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut* 1997; **41:** 526–33.
6. Corley DA, *et al*. Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology* 2001; **120:** 946–54.
7. Gøtzsche PC, Hróbjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 21/08/08).
8. D'Amico G, *et al*. Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 28/04/10).
9. Sung JJY, *et al*. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995; **346:** 1666–9.
10. Besson I, *et al*. Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* 1995; **333:** 555–60.
11. Zuberi BF, Baloch Q. Comparison of endoscopic variceal sclerotherapy alone and in combination with octreotide in controlling acute variceal hemorrhage and early rebleeding in patients with low-risk cirrhosis. *Am J Gastroenterol* 2000; **95:** 768–71.
12. Freitas DS, *et al*. Octreotide in acute bleeding esophageal varices: a prospective randomized study. *Hepatogastroenterology* 2000; **47:** 1310–14.
13. Primignani M, *et al*. Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: a randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 1995; **21:** 1322–7.
14. Jenkins SA, *et al*. Randomised trial of octreotide for long term management of cirrhosis after variceal haemorrhage. *BMJ* 1997; **315:** 1338–41.

DIARRHOEA. Octreotide has been tried for its effects on gastrointestinal secretion and intestinal transit time in the management of severe refractory diarrhoea associated with a variety of conditions. A review[1] found that studies were generally small, and that although there appeared to be an overall benefit associated with the use of octreotide, response was influenced by the cause of diarrhoea. There are reports of octreotide controlling diarrhoea associated with amyloidosis,[2-4] diabetes mellitus,[5-11] and bone marrow transplantation.[12,13] Although octreotide was reported to be useful in a case of microvillous atrophy,[14] others have not found it to be effective.[15] There have been reports of benefit in refractory AIDS-associated diarrhoea,[16] and it has been licensed for this use in some countries, but a double-blind, controlled study found octreotide to be no more beneficial than placebo.[17] Octreotide has also been used successfully for symptomatic treatment of chronic diarrhoea associated with cytomegalovirus colitis.[18] In patients with the short bowel syndrome and jejunostomies or ileostomies, octreotide may be useful in decreasing faecal mass[19] or jejunal efflux,[20] and increasing small bowel transit time.[21] Octreotide has also been used with some benefit in refractory diarrhoea associated with chemotherapy, particularly with regimens that include fluorouracil[22,23] and irinotecan.[24] In a small series of patients[25] the use of depot octreotide controlled most episodes of diarrhoea, and allowed the continuation of chemotherapy in some cases.

1. Szilagyi A, Shrier I. Systematic review: the use of somatostatin or octreotide in refractory diarrhoea. *Aliment Pharmacol Ther* 2001; **15:** 1889–97.
2. O'Connor CR, O'Dorisio TM. Amyloidosis, diarrhea, and a somatostatin analogue. *Ann Intern Med* 1989; **110:** 665–6.
3. Gilanders IA, *et al*. Octreotide therapy for diarrhoea. *Postgrad Med J* 1997; **73:** 62.
4. Jeong Y-S, *et al*. Successful treatment of protein-losing enteropathy due to AA amyloidosis with somatostatin analogue and high dose steroid in ankylosing spondylitis. *Clin Exp Rheumatol* 2000; **18:** 619–21.
5. Tsai S-T, *et al*. Diabetic diarrhea and somatostatin. *Ann Intern Med* 1986; **104:** 894.
6. Michaels PE, Cameron RB. Octreotide is cost-effective therapy in diabetic diarrhea. *Arch Intern Med* 1991; **151:** 2469.
7. Mourad FH, *et al*. Effective treatment of diabetic diarrhoea with somatostatin analogue, octreotide. *Gut* 1992; **33:** 1578–80.
8. Nakabayashi H, *et al*. Marked improvement of diabetic diarrhea with the somatostatin analogue octreotide. *Arch Intern Med* 1994; **154:** 1863–7.
9. Virally-Monod ML, *et al*. Variable efficacy of octreotide in diabetic diarrhea. *Diabetes Metab* 1996; **22:** 356–8.
10. Murao S, *et al*. Severe diabetic diarrhea successfully treated with octreotide, a somatostatin analogue. *Endocr J* 1999; **46:** 477–8.
11. Meyer C, *et al*. Octreotide treatment of severe diabetic diarrhoea. *Intern Med J* 2003; **33:** 617–8.
12. Crouch MA, *et al*. Octreotide acetate in refractory bone marrow transplant-associated diarrhea. *Ann Pharmacother* 1996; **30:** 331–6.
13. Ippoliti C, *et al*. Use of octreotide in the symptomatic management of diarrhea induced by graft-versus-host disease in patients with hematological malignancies. *J Clin Oncol* 1997; **15:** 3350–4.
14. Couper RTL, *et al*. Clinical response to the long acting somatostatin analogue SMS 201-995 in a child with congenital microvillus atrophy. *Gut* 1989; **30:** 1020–4.
15. Beck NS, *et al*. Microvillus inclusion disease in two Korean infants. *J Korean Med Sci* 1997; **12:** 452–6.
16. Montaner JSG, *et al*. Octreotide therapy in AIDS-related, refractory diarrhea: results of a multicentre Canadian-European study. *AIDS* 1995: **9:** 209–10.
17. Simon DM, *et al*. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome–associated diarrhea. *Gastroenterology* 1995; **108:** 1753–60. Correction. *ibid*.; **109:** 1024.
18. Bartels MC, Mergenhagen KA. Octreotide for symptomatic treatment of diarrhea due to cytomegalovirus colitis. *Ann Pharmacother* 2011; **45:** e4.
19. Ladefoged K, *et al*. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. *Gut* 1989; **30:** 943–9.
20. Nightingale JMD, *et al*. Jejunal efflux in short bowel syndrome. *Lancet* 1990; **336:** 765–8.
21. Nehra V, *et al*. An open trial of octreotide long-acting release in the management of short bowel syndrome. *Am J Gastroenterol* 2001; **96:** 1494–8.
22. Goumas P, *et al*. Octreotide acetate in the treatment of fluorouracil-induced diarrhea. *Oncologist* 1998; **3:** 50–3.
23. Zidan J, *et al*. Octreotide in the treatment of severe chemotherapy-induced diarrhea. *Ann Oncol* 2001; **12:** 227–9.
24. Barbounis V, *et al*. Control of irinotecan-induced diarrhea by octreotide after loperamide failure. *Support Care Cancer* 2001; **9:** 258–60.
25. Rosenoff S. Resolution of refractory chemotherapy-induced diarrhea (CID) with octreotide long-acting formulation in cancer patients: 11 case studies. *Support Care Cancer* 2004; **12:** 561–70.

FISTULAE. Octreotide has been used in the management of postoperative small-bowel fistulae. There have been mixed reports, but some have found reduced fistula output,[1,2] with the time to spontaneous fistula closure either reduced[1] or unchanged.[2] Octreotide has also been reported to accelerate healing of pancreatic cutaneous fistulae of various causes,[3] but others[4] have found no benefit from octreotide in preventing pancreatic fistula formation after pancreaticoduodenectomy. A systematic review[5] of controlled studies commented on the variation in study methods and conflicting results, but concluded that there is probably benefit in giving octreotide pre-operatively to prevent complications of pancreatic surgery, and that in established postoperative fistulae it may have a limited role in reducing fistula output and reducing the time to fistula closure. In a series of 5 patients[6] with Crohn's disease who were treated for 8 weeks with high-dose octreotide, enterocutaneous fistulae closed in 4 cases.

1. Nubiola-Calonge P, *et al*. Blind evaluation of the effect of octreotide (SMS 201-995), a somatostatin analogue, on small-bowel fistula output. *Lancet* 1987; **ii:** 672–4.
2. Alivizatos V, *et al*. Evaluation of the effectiveness of octreotide in the conservative treatment of postoperative enterocutaneous fistulas. *Hepatogastroenterology* 2002; **49:** 1010–12.
3. Prinz RA, *et al*. Treatment of pancreatic cutaneous fistulas with a somatostatin analog. *Am J Surg* 1988; **155:** 36–42.
4. Barnett SP, *et al*. Octreotide does not prevent postoperative pancreatic fistula or mortality following pancreaticoduodenectomy. *Am Surg* 2004; **70:** 222–7.
5. Li-Ling J, Irving M. Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials. *Br J Surg* 2001; **88:** 190–9.
6. Lavy A, Yasin K. Octreotide for enterocutaneous fistulas of Crohn's disease. *Can J Gastroenterol* 2003; **17:** 555–8.

OTHER GASTROINTESTINAL DISORDERS. Further gastrointestinal disorders in which octreotide might be useful include

dumping syndrome[1-3] (p. 1806.2). One report[4] suggested that preprandial subcutaneous doses produce higher peak serum concentrations and might therefore be more effective than a long-acting intramuscular formulation. Other disorders include reactive (or postprandial) hypoglycaemia,[5] and protein-losing enteropathy associated with intestinal lymphangiectasia.[6,7] Nausea and vomiting secondary to bowel obstruction in patients terminally ill with cancer may also be relieved by octreotide.[8,9] The *BNF* states that in palliative care a dose of 250 to 500 micrograms (sometimes up to 750 micrograms or occasionally higher) may be given by subcutaneous infusion over 24 hours to reduce intestinal secretions and to reduce vomiting due to bowel obstruction.

1. Vecht J, *et al*. Long-term results of octreotide-therapy in severe dumping syndrome. *Clin Endocrinol (Oxf)* 1999; **51:** 619–24.
2. Li-Ling J, Irving M. Therapeutic value of octreotide for patients with severe dumping syndrome—a review of randomised controlled trials. *Postgrad Med J* 2001; **77:** 441–2.
3. Arts J, *et al*. Efficacy of the long-acting repeatable formulation of the somatostatin analogue octreotide in postoperative dumping. *Clin Gastroenterol Hepatol* 2009; **7:** 432–7.
4. Didden P, *et al*. Octreotide therapy in dumping syndrome: analysis of long-term results. *Aliment Pharmacol Ther* 2006; **24:** 1367–75.
5. Lehnert H, *et al*. Treatment of severe reactive hypoglycemia with a somatostatin analogue (SMS 201-995). *Arch Intern Med* 1990; **150:** 2401–2.
6. Klingenberg RD, *et al*. Type I intestinal lymphangiectasia treated successfully with slow-release octreotide. *Dig Dis Sci* 2003; **48:** 1506–9.
7. Lee HL, *et al*. Successful treatment of protein-losing enteropathy induced by intestinal lymphangiectasia in a liver cirrhosis patient with octreotide: a case report. *J Korean Med Sci* 2004; **19:** 466–9.
8. Ripamonti C, *et al*. The role of somatostatin and octreotide in bowel obstruction: pre-clinical and clinical results. *Tumori* 2001; **87:** 1–9.
9. Mystakidou K, *et al*. Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double-blind, controlled clinical trial. *Anticancer Res* 2002; **22:** 1187–92.

Hypercalcaemia. There have been individual reports of hypercalcaemia associated with raised plasma concentrations of parathyroid hormone-related protein (hypercalcaemia of malignancy—p. 1167.2) being successfully controlled with octreotide in patients with malignant pancreatic endocrine tumours[1-3] and adrenal phaeochromocytoma.[4] Octreotide also resolved hypercalcaemia occurring in a patient with VIPoma and vasoactive intestinal peptide concentrations declined.[5] In 2 patients with a parathyroid hormone-related protein secreting carcinoid tumour, octreotide reduced protein concentrations in both patients[6,7] but controlled hypercalcaemia in only one.[7] Octreotide also normalised calcium concentrations in a patient with hypercalcaemia related to B cell lymphoma.[8] In many of these cases, hypercalcaemia had previously been resistant to treatment with bisphosphonates.

1. Wynick D, *et al*. Treatment of a malignant pancreatic endocrine tumour secreting parathyroid hormone related protein. *BMJ* 1990; **300:** 1314–15.
2. Dodwell D, *et al*. Treatment of a pancreatic tumour secreting parathyroid hormone related protein. *BMJ* 1990; **300:** 1653.
3. Müssig K, *et al*. Somatostatin receptor expression in a parathyroid hormone-related peptide-secreting pancreatic neuroendocrine tumour causing severe hypercalcaemia. *Eur J Gastroenterol Hepatol* 2007; **19:** 719–23.
4. Harrison M, *et al*. Somatostatin analogue treatment for malignant hypercalcaemia. *BMJ* 1990; **300:** 1313–14. Correction. *ibid.*; **301:** 97 [dosage error].
5. Venkatesh S, *et al*. Somatostatin analogue: use in the treatment of vipoma with hypercalcaemia. *Am J Med* 1989; **87:** 356–7.
6. Mantzoros CS, *et al*. Intractable hypercalcaemia due to parathyroid hormone-related peptide secretion by a carcinoid tumour. *Clin Endocrinol (Oxf)* 1997; **46:** 373–5.
7. Barhoum M, *et al*. Intractable hypercalcemia due to a metastatic carcinoid secreting parathyroid hormone-related peptide and interleukin-6: response to octreotide. *Am J Med Sci* 1999; **318:** 203–5.
8. Pezzilli R, *et al*. Octreotide for the treatment of hypercalcemia related to B cell lymphoma. *Oncology* 1997; **54:** 517–18.

Hyperinsulinism. As well as reactive hypoglycaemia (see under Other Gastrointestinal Disorders, p. 1925.3), octreotide has been used to control inappropriate insulin secretion, both in the short-term and long-term, in children with hypoglycaemia of infancy,[1-4] or nesidioblastosis.[5-7] Although not licensed in the UK for children, the *BNFC* includes a dose of octreotide for persistent hyperinsulinaemic hypoglycaemia (p. 1554.3) unresponsive to diazoxide and glucose. For neonates an initial dose of 2 to 5 micrograms/kg may be given every 6 to 8 hours subcutaneously and adjusted according to response. For children aged from 1 month to 18 years, an initial dose of 1 to 2 micrograms/kg every 4 to 6 hours may be used. Doses up to 7 micrograms/kg every 4 hours may be required in rare cases.

Octreotide has also been used to treat a patient with hyperinsulinaemia induced by quinine.[8,9] For mention of investigations of octreotide for the reverse effect, see Diabetes Mellitus, p. 1925.1.

1. Kirk JMW, *et al*. Somatostatin analogue in short term management of hyperinsulinism. *Arch Dis Child* 1988; **63:** 1493–4.
2. DeClue TJ, *et al*. Linear growth during long-term treatment with somatostatin analog (SMS 201-995) for persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr* 1990; **116:** 747–50.
3. Thornton PS, *et al*. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993; **123:** 637–43.
4. Aynsley-Green A, *et al*. Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.
5. Hindmarsh P, Brook CGD. Short-term management of nesidioblastosis using the somatostatin analogue SMS 201-995. *N Engl J Med* 1987; **316:** 221–2.
6. Delemarre-van de Waal HA, *et al*. Long-term treatment of an infant with nesidioblastosis using a somatostatin analogue. *N Engl J Med* 1987; **316:** 222–3.
7. Behrens R, *et al*. Unusual course of neonatal hyperinsulinaemic hypoglycaemia (nesidioblastosis). *Arch Dis Child* 1998; **78:** F156.
8. Phillips RE, *et al*. Effectiveness of SMS 201-995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia. *Lancet* 1986; **i:** 713–16.
9. Phillips RE, *et al*. Hypoglycaemia and counterregulatory hormone responses in severe falciparum malaria: treatment with Sandostatin. *Q J Med* 1993; **86:** 233–40.

Malignant neoplasms. See also Neuroendocrine Tumours, below. For mention of the use of octreotide to treat nausea and vomiting associated with malignant gastrointestinal obstruction see under Other Gastrointestinal Disorders, p. 1925.3. Octreotide has also proved of benefit in some patients with cancer pain (see Pain, below). An unconventional regimen using octreotide or somatostatin with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was investigated in patients with a variety of advanced malignancies and found to be ineffective.[1,2]

1. Italian Study Group for the Di Bella Multitherapy Trials. Evaluation of an unconventional cancer treatment (the Di Bella multitherapy): results of phase II trials in Italy. *BMJ* 1999; **318:** 224–8.
2. Buiatti E, *et al*. Results from a historical survey of the survival of cancer patients given Di Bella multitherapy. *Cancer* 1999; **86:** 2143–9.

HEPATOCELLULAR CARCINOMA. In a study in 58 patients with advanced hepatocellular carcinoma (p. 709.3) treatment with octreotide was associated with prolongation of survival compared with no treatment.[1] In a further case report[2] cancer regression occurred in a patient given octreotide, and a study[3] found better survival in patients treated with octreotide and tamoxifen compared with fluorouracil and mitomycin. However, other studies of octreotide in patients with advanced hepatocellular carcinoma failed to show any benefit.[4-7] A systematic review of randomised studies[8] concluded that octreotide did not improve survival.

1. Kouroumalis E, *et al*. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998; **42:** 442–7.
2. Siveke JT, *et al*. Complete regression of advanced HCC with long acting octreotide. *Gut* 2003; **52:** 1531. Correction. *ibid.*; 1800.
3. Pan D-Y, *et al*. Tamoxifen combined with octreotide or regular chemotherapeutic agents in treatment of primary liver cancer: a randomized controlled trial. *Hepatobiliary Pancreat Dis Int* 2003; **2:** 211–15.
4. Yuen M-F, *et al*. A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002; **36:** 687–91.
5. Lersch C, *et al*. Treatment of HCC with pravastatin, octreotide, or gemcitabine - a critical evaluation. *Hepatogastroenterology* 2004; **51:** 1099–1103.
6. Becker G, *et al*. HECTOR Study Group. Long-acting octreotide versus placebo for treatment of advanced HCC: a randomized controlled double-blind study. *Hepatology* 2007; **45:** 9–15.
7. Verset G, *et al*. Efficacy of the combination of long-acting release octreotide and tamoxifen in patients with advanced hepatocellular carcinoma: a randomised multicentre phase III study. *Br J Cancer* 2007; **97:** 582–8.
8. Jia W-D, *et al*. Octreotide therapy for hepatocellular carcinoma: a systematic review of the evidence from randomized controlled trials. *Hepatogastroenterology* 2010; **57:** 292–9.

MENINGIOMA. Octreotide has been reported to suppress headaches and visual disturbances associated with meningioma in a small number of patients.[1-3] Doses were generally started at 100 micrograms three times daily subcutaneously, but were increased to 500 micrograms three times daily in some cases because of tolerance. Although it was thought that octreotide may have had a beneficial effect on the meningioma size in one case,[1] others found no evidence of tumour shrinkage.[2,3] A pilot study[4] examined the effects of octreotide in 16 patients with recurrent meningioma that overexpressed somatostatin receptors. There were 5 partial responses, 5 cases of stable disease, and 6 cases of progressive disease after the first 3 treatment cycles; progression-free survival at 6 months was 44% (7 patients).

1. Rünzi MW, *et al*. Successful treatment of meningioma with octreotide. *Lancet* 1989; **i:** 1074.
2. García-Luna PP, *et al*. Clinical use of octreotide in unresectable meningiomas: a report of three cases. *J Neurosurg Sci* 1993; **37:** 237–41.
3. Jaffrain-Rea M-L, *et al*. Visual improvement during octreotide therapy in a case of episellar meningioma. *Clin Neurol Neurosurg* 1998; **100:** 40–3.
4. Chamberlain MC, *et al*. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 2007; **69:** 969–73. Correction. *ibid.* 2008; **70:** 325.

NEUROENDOCRINE TUMOURS. For a discussion of neuroendocrine tumours and other secretory neoplasms, including reference to the role of octreotide, see p. 716.3.

References.

1. Öberg K, *et al*. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004; **15:** 966–73.
2. Delaunoit T, *et al*. Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors. *Mayo Clin Proc* 2005; **80:** 502–6.
3. Kwekkeboom DJ, *et al*. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. *Neuroendocrinology* 2009; **90:** 220–6.
4. Colao A, *et al*. Somatostatin analogues: treatment of pituitary and neuroendocrine tumors. *Prog Brain Res* 2010; **182:** 281–94.
5. Öberg KE, *et al*. Role of somatostatins in gastroenteropancreatic neuroendocrine tumor development and therapy. *Gastroenterology* 2010; **139:** 742–53.

THYMOMA. A patient with thymoma and pure red cell aplasia, in whom corticosteroids alone failed to control anaemia, had complete remission after treatment with octreotide and prednisone, and subsequently remained well on long-term maintenance therapy with octreotide 500 micrograms twice daily subcutaneously and prednisone 200 micrograms/kg daily.[1] In a study[2] that included 32 patients with thymoma and a positive octreotide scan, octreotide therapy alone (500 micrograms subcutaneously three times daily for up to 1 year) or with prednisone (600 micrograms/kg daily) had modest activity; there were 2 complete and 10 partial responses overall.

1. Palmieri G, *et al*. Successful treatment of a patient with a thymoma and pure red-cell aplasia with octreotide and prednisone. *N Engl J Med* 1997; **336:** 263–5. Correction. *ibid.*; 1039.
2. Loehrer PJ, *et al*. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group phase II trial. *J Clin Oncol* 2004; **22:** 293–9. Correction. *ibid.*; 2261.

Nesidioblastosis. For reference to the use of octreotide in nesidioblastosis, see Hyperinsulinism, above.

Obesity. Hypothalamic obesity can be a complication of hypothalamic damage caused by insults such as head trauma, brain tumours, and cranial surgery or irradiation. Octreotide has improved body-weight, body-mass index, and regulation of insulin secretion in small studies of children with hypothalamic obesity.[1-3] Additionally octreotide has produced a small amount of weight loss in some obese adults with insulin hypersecretion.[4,5] Octreotide is also under investigation in the treatment of Prader-Willi syndrome (p. 2315.2).[6]

1. Lustig RH, *et al*. Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr* 1999; **135:** 162–8.
2. Lustig RH, *et al*. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003; **88:** 2586–92.
3. Tzotzas T, *et al*. Use of somatostatin analogues in obesity. *Drugs* 2008; **68:** 1963–73.
4. Velasquez-Mieyer PA, *et al*. Suppression of insulin secretion is associated with weight loss and altered macronutrient intake and preference in a subset of obese adults. *Int J Obes Relat Metab Disord* 2003; **27:** 219–26.
5. Lustig RH, *et al*. A multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of a long-acting formulation of octreotide in promoting weight loss in obese adults with insulin hypersecretion. *Int J Obes (Lond)* 2006; **30:** 331–41.
6. Haqq AM, *et al*. Circulating ghrelin levels are suppressed by meals and octreotide therapy in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2003; **88:** 3573–6.

Pain. Octreotide 120 to 480 micrograms daily was given by continuous intrathecal infusion to 6 patients with cancer pain that had been poorly controlled by opioid analgesics.[1] All patients obtained good pain relief, 3 reporting pain to be totally absent. Sustained decrease in incapacitating bone pain has also been reported in a patient with skeletal metastasis of a gastrinoma who was given subcutaneous octreotide 100 micrograms three times daily.[2] The pain of hypertrophic pulmonary osteoarthropathy (a paraneoplastic syndrome of periostitis, arthropathy, and gynaecomastia seen particularly with squamous cell lung cancer) has also been reported to respond to octreotide.[3] However, a controlled study of octreotide in cancer pain found that it was no better than placebo in most patients.[4] (General guidelines for the management of cancer pain are discussed on p. 7.1.) Octreotide has also been reported to ease headache associated with meningioma (above), and pituitary adenoma (see Acromegaly, p. 1924.2, and Pituitary Adenoma, p. 1927.1).

The use of intrathecal octreotide has also been described[5] in 2 patients with severe intractable non-malignant pain. During 5 years of treatment, octreotide provided a beneficial degree of pain relief and allowed a reduction in opioid dosage. However, the dose of octreotide had to be gradually increased, suggesting tolerance to the analgesic effect; one patient was receiving a daily dose of 648 micrograms.

1. Penn RD, *et al*. Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain* 1992; **49:** 13–19.
2. Burgess JR, *et al*. Effective control of bone pain by octreotide in a patient with metastatic gastrinoma. *Med J Aust* 1996; **164:** 725–7.
3. Johnson SA, *et al*. Treatment of resistant pain in hypertrophic pulmonary osteoarthropathy with subcutaneous octreotide. *Thorax* 1997; **52:** 298–9.
4. De Conno F, *et al*. Subcutaneous octreotide in the treatment of pain in advanced cancer patients. *J Pain Symptom Manage* 1994; **9:** 34–8.
5. Paice JA, *et al*. Intrathecal octreotide for relief of intractable nonmalignant pain: 5-year experience with two cases. *Neurosurgery* 1996; **38:** 203–7.

Pancreatic disorders. Octreotide has been tried in the treatment of acute pancreatitis, but was found to be ineffective.[1] Prophylactic octreotide has also been studied for the prevention of pancreatitis following endoscopic retrograde cholangiopancreatography with some positive results,[2,3] but a meta-analysis concluded that it was ineffective.[4] Others[5,6] have suggested that it might only be

effective at total doses of more than 500 micrograms, although the optimal route and timing are unclear.[5] For reference to the use of octreotide in the management of pancreatic endocrine tumours, see under Neuroendocrine Tumours (p. 716.3); for its use in pancreatic fistulae, see under Gastrointestinal Disorders, p. 1925.3.

1. Uhl W, *et al.* A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999; **45:** 97–104.
2. Thomopoulos KC, *et al.* Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. *Gastrointest Endosc* 2006; **64:** 726–31.
3. Li Z-S, *et al.* Effect of octreotide administration in the prophylaxis of post-ERCP pancreatitis and hyperamylasemia: a multicenter, placebo-controlled, randomized clinical trial. *Am J Gastroenterol* 2007; **102:** 46–51.
4. Bai Y, *et al.* Prophylactic octreotide administration does not prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. *Pancreas* 2008; **37:** 241–6.
5. Zhang Y, *et al.* Meta-analysis: octreotide prevents post-ERCP pancreatitis, but only at sufficient doses. *Aliment Pharmacol Ther* 2009; **29:** 1155–64.
6. Omata F, *et al.* Meta-analysis: somatostatin or its long-acting analogue, octreotide, for prophylaxis against post-ERCP pancreatitis. *J Gastroenterol* 2010; **45:** 885–95.

Pituitary adenoma. Octreotide has a role in the management of pituitary adenomas that cause acromegaly (see p. 1924.2). It has also been used in the management of rare tumours such as thyrotropin-secreting pituitary adenomas, usually when surgery or radiotherapy have failed. Octreotide may reduce concentrations of thyrotropin and normalise thyroid hormones in most patients; tumour shrinkage also occurs in at least a third of cases.[1-4] Octreotide has also been tried in the management of other rare adenomas such as clinically nonfunctioning adenomas, but results have been mixed; in a few cases there has been relief of symptoms such as headache without any change in tumour volume.[5]

1. Chanson P, *et al.* Octreotide therapy for thyroid-stimulating hormone-secreting pituitary adenomas: a follow-up of 52 patients. *Ann Intern Med* 1993; **119:** 236-40.
2. Caron P, *et al.* Efficacy of the long-acting octreotide formulation (octreotide-Lar) in patients with thyrotropin-secreting pituitary adenomas. *J Clin Endocrinol Metab* 2001; **86:** 2849–53.
3. Beck-Peccoz P, Persani L. Medical management of thyrotropin-secreting pituitary adenomas. *Pituitary* 2002; **5:** 83–8.
4. Socin HV, *et al.* The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol* 2003; **148:** 433–42.
5. Colao A, *et al.* Somatostatin analogs in treatment of non-growth hormone–secreting pituitary adenomas. *Endocrine* 2003; **20:** 279–83.

Polycystic kidney and liver diseases. Octreotide[1-3] and lanreotide[4] have been investigated in autosomal dominant polycystic kidney and liver diseases. Small studies, usually lasting 6 or 12 months, suggest that treatment may slow the rate of increase in kidney volume and may decrease liver volume.

1. Ruggenenti P, *et al.* Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int* 2005; **68:** 206–16.
2. Hogan MC, *et al.* Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol* 2010; **21:** 1052–61.
3. Caroli A, *et al.* Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. *Clin J Am Soc Nephrol* 2010; **5:** 783–9.
4. van Keimpema L, *et al.* Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2009; **137:** 1661–8.

Pretibial myxoedema. Pretibial myxoedema (deposition of glycosaminoglycans in the subcutaneous tissue of the shins) is associated with Graves' disease (see Hyperthyroidism, p. 2332.2). There are reports of apparent benefit from the use of octreotide for this condition. In one case,[1,2] octreotide given for 6 months after surgical removal of the myxoedematous tissue may have prevented its recurrence. In another,[3] octreotide injected intralesionally was reported to improve and control the condition. However, in other cases[4] subcutaneous octreotide has been ineffective.

1. Derrick EK, *et al.* Successful surgical treatment of severe pretibial myxoedema. *Br J Dermatol* 1995; **133:** 317–18.
2. Felton J, *et al.* Successful combined surgical and octreotide treatment of severe pretibial myxoedema reviewed after 9 years. *Br J Dermatol* 2003; **148:** 825–6.
3. Shinohara M, *et al.* Refractory pretibial myxoedema with response to intralesional insulin-like growth factor 1 antagonist (octreotide): downregulation of hyaluronic acid production by the lesional fibroblasts. *Br J Dermatol* 2000; **143:** 1083–6.
4. Rotman-Pikielny P, *et al.* Lack of effect of long-term octreotide therapy in severe thyroid-associated dermopathy. *Thyroid* 2003; **13:** 465–70.

Raised intracranial pressure. For reference to octreotide being tried in idiopathic intracranial hypertension, see p. 1271.3.

Sulfonylurea overdose. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia (see Treatment of Adverse Effects, p. 502.1).

Adverse Effects and Precautions

There may be a transient local reaction at the site of injection of octreotide. Systemic adverse effects are mainly gastrointestinal and may include anorexia, nausea, vomiting, diarrhoea and steatorrhoea, abdominal discomfort, and flatulence. Use between meals or at bedtime may reduce these gastrointestinal effects. Hypersensitivity reactions and hair loss have been reported rarely.

Gallstones may develop on long-term therapy; there have been isolated reports of hepatic dysfunction and of biliary colic associated with drug withdrawal. Checks should be made for gallstones before prolonged therapy and at 6- to 12-month intervals during treatment. There have also been isolated reports of pancreatitis and of hepatic dysfunction without cholestasis. Hypoglycaemia may occur, especially in patients with insulinomas, but there is also a risk of hyperglycaemia or impaired glucose tolerance. Thyroid function should be monitored during octreotide therapy because of the possibility of hypothyroidism. Pituitary tumours that secrete growth hormone can expand during treatment, causing serious complications; patients should be monitored for signs of tumour expansion, such as visual field defects. Cardiac rhythm should be monitored during intravenous use of octreotide. Doses may need to be adjusted in patients with liver cirrhosis or end-stage renal failure, in whom the clearance of octreotide is reduced.

In women with acromegaly, the normalisation of growth hormone and IGF-I concentrations by octreotide may restore fertility. Licensed product information for octreotide advises that contraception be used during treatment, but see also Pregnancy, below.

Effects on the biliary tract. Octreotide has an inhibitory effect on gallbladder motility and bile secretion, accounting for the development of gallstones and biliary colic.[1-6]

1. Redfern JS, Fortuner WJ. Octreotide-associated biliary tract dysfunction and gallstone formation: pathophysiology and management. *Am J Gastroenterol* 1995; **90:** 1042–52.
2. Tauber JP, *et al.* The impact of continuous subcutaneous infusion of octreotide on gallstone formation in acromegalic patients. *J Clin Endocrinol Metab* 1995; **80:** 3262–6.
3. Hussaini SH, *et al.* Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. *Gut* 1996; **38:** 775–83.
4. Trendle MC, *et al.* Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer* 1997; **79:** 830–4.
5. Moschetta A, *et al.* Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* 2001; **15:** 181–5.
6. Hofmann AF. Increased deoxycholic acid absorption and gall stones in acromegalic patients treated with octreotide: more evidence for a connection between slow transit constipation and gall stones. *Gut* 2005; **54:** 575–8.

Effects on carbohydrate metabolism. Changes in glucose tolerance may occur in patients with acromegaly who are treated with somatostatin analogues. A meta-analysis of studies of the use of octreotide or lanreotide in acromegaly concluded that somatostatin analogues had a marginal impact on glucose homoeostasis. There was evidence for a decrease in fasting plasma-insulin, but without significant effect on fasting plasma-glucose or glycated haemoglobin ($HbA1_c$). Nevertheless, a significant adverse effect may occur in individual patients and glycaemic monitoring was recommended.[1]

There has been a report of deterioration in glucose tolerance leading to death from diabetic ketoacidosis when octreotide treatment was stopped in a patient with acromegaly and insulin-resistant diabetes mellitus.[2]

See also Diabetes Mellitus and Hyperinsulinism under Uses and Administration, p. 1925.1 and p. 1926.1.

1. Mazziotti G, *et al.* Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. *J Clin Endocrinol Metab* 2009; **94:** 1500–8.
2. Abrahamson MJ. Death from diabetic ketoacidosis after cessation of octreotide in acromegaly. *Lancet* 1990; **336:** 318–19.

Effects on the hair. Diffuse loss of scalp hair has been reported in 4 of 7 women who received octreotide; after withdrawal of octreotide in 3 of the women there was a complete recovery of scalp hair.[1] Other similar cases have also been reported. In one case, diffuse alopecia in a male patient was completely reversed when octreotide was replaced with lanreotide.[2]

1. Jönsson A, Manhem P. Octreotide and loss of scalp hair. *Ann Intern Med* 1991; **115:** 913.
2. Lami M-C, *et al.* Hair loss in three patients with acromegaly treated with octreotide. *Br J Dermatol* 2003; **149:** 655–6.

Effects on the liver. Hepatitis occurred in 2 acromegalic patients treated with octreotide 300 micrograms daily subcutaneously.[1,2] In both cases liver enzyme values returned to normal within 1 to 2 months of withdrawing octreotide, and recurred on rechallenge.

1. Arosio M, *et al.* Acute hepatitis after treatment of acromegaly with octreotide. *Lancet* 1988; **ii:** 1498.
2. González-Martín JA, *et al.* Acute liver injury and octreotide. *Am J Gastroenterol* 1996; **91:** 2434–5.

Effects on mental function. A woman with acromegaly developed manic symptoms on 2 separate occasions 2 months after starting treatment with octreotide.[1]

1. Fernández-Real J-M, *et al.* Octreotide-induced manic episodes in a patient with acromegaly. *Ann Intern Med* 2006; **144:** 704.

Effects on the pancreas. There have been reports of pancreatitis associated with octreotide[1-4] and lanreotide.[4] It has been suggested that octreotide-induced pancreatitis may result from spasm of the sphincter of Oddi, resulting in retention of activated pancreatic enzymes due to outflow obstruction.[3]

1. Fredenrich A, *et al.* Acute pancreatitis after short-term octreotide. *Lancet* 1991; **338:** 52–3.
2. Sadoul J-L, *et al.* Acute pancreatitis following octreotide withdrawal. *Am J Med* 1991; **90:** 763–4.
3. Bodemar G, Hjortswang H. Octreotide-induced pancreatitis: an effect of increased contractility of Oddi sphincter. *Lancet* 1996; **348:** 1668–9.
4. Cannavò S, *et al.* Octreotide and lanreotide treatment in active acromegaly. *J Clin Endocrinol Metab* 1997; **82:** 2376–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies octreotide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. There have been reports of women given lanreotide[1,2] or octreotide[2-7] during pregnancy. Most were being treated for acromegaly, although there is also a report[6] of octreotide use during pregnancy in a woman treated for nesidioblastosis. In most cases, the somatostatin analogue was stopped early in the pregnancy, but in some cases octreotide was continued to term. No maternal complications or congenital anomalies were described, although several cases[2] of babies born small for gestational age have been seen.

1. de Menis E, *et al.* Uneventful pregnancy in an acromegalic patient treated with slow-release lanreotide: a case report. *J Clin Endocrinol Metab* 1999; **84:** 1489.
2. Caron P, *et al.* Acromegaly and pregnancy: a retrospective multicenter study of 59 pregnancies in 46 women. *J Clin Endocrinol Metab* 2010; **95:** 4680–7.
3. Neal JM. Successful pregnancy in a woman with acromegaly treated with octreotide. *Endocr Pract* 2000; **6:** 148–50.
4. Fassnacht M, *et al.* Octreotide LAR treatment throughout pregnancy in an acromegalic woman. *Clin Endocrinol (Oxf)* 2001; **55:** 411–15.
5. Mikhail N. Octreotide treatment of acromegaly during pregnancy. *Mayo Clin Proc* 2002; **77:** 297–8.
6. Boulanger C, *et al.* Normal pregnancy in a woman with nesidioblastosis treated with somatostatin analog octreotide. *J Endocrinol Invest* 2004; **27:** 465–70.
7. Maffei P, *et al.* Effects of octreotide exposure during pregnancy in acromegaly. *Clin Endocrinol (Oxf)* 2010; **72:** 668–77. Correction. *ibid.*; 856.

Interactions

Octreotide has been associated with alterations in nutrient absorption and there is a theoretical possibility that it may affect the oral absorption of other drugs. Patients receiving insulin or oral hypoglycaemics may require dose adjustments of these drugs if octreotide is also used. The bioavailability of bromocriptine is increased by octreotide. It has been suggested that dosage of beta blockers, calcium-channel blockers, or drugs to control fluid and electrolyte balance may also need to be adjusted.

Ciclosporin. For a reference to octreotide reducing serum concentrations of ciclosporin, see p. 1954.3.

Pharmacokinetics

Octreotide is rapidly absorbed after subcutaneous injection, with peak plasma concentrations reached about 25 to 40 minutes after a dose, and is distributed to body tissues. About 40 to 65% of the octreotide in the circulation is bound to plasma proteins. It is said to show non-linear pharmacokinetics, with reduced clearance at high doses. Octreotide has a plasma elimination half-life of about 1.5 hours; half-life is prolonged in elderly patients, renal impairment, and liver cirrhosis. About a third of a dose is excreted unchanged in the urine. Octreotide diffuses across the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sandostatin; ***Austral.***: Sandostatin; ***Austria***: Sandostatin; ***Belg.***: Sandostatine; ***Braz.***: Octride; Sandostatin; ***Canad.***: Sandostatin; ***Chile***: Sandostatin; ***China***: Jin Di Lin (金迪林); Li Er Ning (力尔宁); Li Te Xin (力特辛); Octride (启文); PeiXin (培新); Sandostatin (善宁); Sheng Ao Ding (生奥定); Tai Ruo Tan (太若坦); Xing An Yi (星安忆); Yi Pu Bi Shan (依普比善); Yi Pu Ning (益谱柠); ***Cz.***: Sandostatin; ***Denm.***: Sandostatin; ***Fin.***: Sandostatin; ***Fr.***: Sandostatine; Siroctid; ***Ger.***: Bendatreotid†; Sandostatin; ***Gr.***: Sandostatin; ***Hong Kong***: Sandostatin; ***Hung.***: Sandostatin; ***India***: Actide; Octate; Octide; Octride; Octronis; Okeron; Otide; Sandostatin; ***Indon.***: Sandostatin; ***Irl.***: Sandostatin; ***Israel***:

Sandostatin; ***Ital.***: Longastatina; Samilstin; Sandostatina; ***Malaysia***: Sandostatin; ***Mex.***: Acroken; Cryostatin; Proclose; Sandostatina; ***Neth.***: Sandostatine; ***Norw.***: Sandostatin; ***NZ***: Sandostatin; ***Philipp.***: Sandostatin; ***Pol.***: Sandostatin; Siroctid; ***Port.***: Octrayne; Sandostatina; ***Rus.***: Genfastat (Генфастат); Octride (Октрид); Sandostatin (Сандостатин); ***S.Afr.***: Sandostatin; ***Singapore***: Sandostatin; ***Spain***: Oktidel; Sandostatin; ***Swed.***: Sandostatin; ***Switz.***: Sandostatine; ***Thai.***: Octride; Sandostatin; ***Turk.***: Sandostatin; ***UK***: Sandostatin; ***Ukr.***: Octra (Октра); Octrestatin (Октрестатин); Octrin (Октрин); Sandostatin (Сандостатин); ***USA***: Sandostatin; ***Venez.***: Sandostatin.

Pasireotide *(USAN, rINN)*

Pasireotida; Pasiréotide; Pasireotidum; SOM-230; Пасиреотид.

Cyclo[(4*R*)-4-(2-aminoethylcarbamoyloxy)-L-prolyl-L-phenylglycyl-D-tryptophyl-L-lysyl-4-*O*-benzyl-L-tyrosyl-L-phenylalanyl-].

$C_{58}H_{66}N_{10}O_9$=1047.2

CAS — 396091-73-9 (pasireotide); 396091-76-2 (pasireotide acetate).

ATC — H01CB05.

ATC Vet — QH01CB05.

UNII — 98H1T17066.

Pasireotide Aspartate *(rINNM)*

Aspartato de pasireotida; Pasireotide L-aspartate; Pasiréotide, Aspartate de; Pasireotidi Aspartas; SOM-230B; Пасиреотида Аспартат.

$C_{58}H_{66}N_{10}O_9.xC_4H_7NO_4$

CAS — 396091-77-3 (pasireotide x aspartate).

ATC — H01CB05.

ATC Vet — QH01CB05.

Uses and Administration

Pasireotide is a somatostatin analogue that binds to 4 of the 5 human somatostatin (hsst) receptors, especially hsst-5 which is expressed at high levels in corticotropin (ACTH)-producing adenomas. The resulting inhibition of ACTH secretion is used in the treatment of Cushing's disease (p. 2559.1), particularly when surgery is not an option or has failed.

It is given as the diaspartate ($C_{58}H_{66}N_{10}O_9.2C_4H_7NO_4$ = 1313.4) but doses are expressed in terms of the base; 125 micrograms of pasireotide diaspartate is equivalent to about 100 micrograms of pasireotide. An initial dose equivalent to 600 micrograms of pasireotide is given twice daily by subcutaneous injection. Clinical benefit should be assessed after two months and the dose may be increased to 900 micrograms twice daily if necessary, according to the reduction in urinary free cortisol. If no response is seen after two months, treatment discontinuation should be considered. Adverse effects may be managed by a temporary reduction in dose by decrements of 300 micrograms twice daily. For doses in hepatic impairment, see below.

Pasireotide is also under investigation in the treatment of acromegaly and carcinoid tumours.

References.
1. Boscaro M, *et al.* Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. *J Clin Endocrinol Metab* 2009; **94:** 115–22.
2. Petersenn S, *et al.* Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. *J Clin Endocrinol Metab* 2010; **95:** 2781–9.
3. Feelders RA, *et al.* Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *N Engl J Med* 2010; **362:** 1846–8.
4. Colao A, *et al.* Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med* 2012; **366:** 914–24. Correction. *ibid.*; **367:** 780.

Administration in hepatic impairment. Higher exposure to pasireotide has been seen in subjects with moderate and severe hepatic impairment.[1] Licensed product information suggests that dose adjustment is not required in mild hepatic impairment (Child-Pugh class A). For patients with moderate hepatic impairment (Child-Pugh class B) the initial dose of subcutaneous pasireotide should be 300 micrograms twice daily with a maximum dose of 600 micrograms twice daily. Pasireotide should not be used in severe hepatic impairment (Child-Pugh class C).

1. Horsmans Y, *et al.* Effect of hepatic impairment on the pharmacokinetics of pasireotide (SOM230): results from a multicenter phase I study. *J Clin Pharmacol* 2012; **52:** 552–8.

Adverse Effects, Treatment, and Precautions

As for Octreotide Acetate, p. 1927.1. Other common adverse effects include anaemia, headache, hypotension, myalgia and arthralgia, and fatigue.

Hyperglycaemia is very commonly reported in patients given pasireotide for the management of Cushing's disease. Glycated haemoglobin (HbA_{1c}) has been reported to increase significantly and stabilise during therapy, then decrease but not return to baseline values after stopping pasireotide. Fasting plasma glucose and HbA_{1c} should be assessed before starting pasireotide then monitored weekly for the first 2 to 3 months of therapy and periodically thereafter. Fasting plasma glucose should be measured 4 weeks, and HbA_{1c} at 3 months, after stopping treatment. If hyperglycaemia remains uncontrolled by antidiabetic therapy, the dose of pasireotide should be adjusted or it should be stopped.

Mild transient elevations of liver enzymes commonly occur in patients given pasireotide. Rare cases of more significant increases in liver enzymes and bilirubin have been reported, usually developing within 10 days of starting therapy, with full recovery after stopping pasireotide. Monitoring of liver function is recommended before using pasireotide, after 1, 2, 4, 8, and 12 weeks during treatment, and thereafter as clinically indicated.

Bradycardia and QT prolongation have been reported and it is recommended that ECG should be monitored before and 1 week after starting pasireotide treatment, and thereafter as clinically indicated. Hypokalaemia and/or hypomagnesaemia should be corrected before treatment and monitored periodically during therapy.

Pasireotide causes rapid suppression of corticotropin (ACTH) secretion in Cushings' disease, and complete or near-complete suppression can cause transient adrenocortical insufficiency. Dose reduction or withdrawal of pasireotide with glucocorticoid replacement therapy may be needed. Pasireotide may also inhibit other pituitary hormones, and monitoring of pituitary function is recommended.

Interactions

Pasireotide is a P-glycoprotein (PgP) substrate so there is potential for strong PgP inhibitors to increase the concentrations of pasireotide; however, the clinical implications are unknown. Pasireotide should be used with caution with other drugs that prolong the QT interval or have bradycardic effects. Dose adjustment of insulin and other antidiabetic medicines may be required in patients given pasireotide.

Pharmacokinetics

Pasireotide is rapidly absorbed after subcutaneous injection, with peak plasma concentrations reached about 15 to 30 minutes after a dose. Pasireotide is mostly distributed in the plasma and plasma protein binding is about 88%. Pasireotide is eliminated mainly by hepatic clearance and is mostly found, unchanged, in the faeces (48%) and urine (8%). The half-life in healthy subjects is about 12 hours and increases in hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Signifor; ***Fr.***: Signifor; ***Neth.***: Signifor; ***Norw.***: Signifor; ***Switz.***: Signifor; ***UK***: Signifor; ***USA***: Signifor.

Pegvisomant *(BAN, USAN, rINN)*

B2036-PEG; Pegvisomanto; Pegvisomantti; Pegvisomantum; Pegwisomant; Пегвизомант.

18-L-Aspartic acid-21-L-asparagine-120-L-lysine-167-L-asparagine-168-L-alanine-171-L-serine-172-L-arginine-174-L-serine-179-L-threonine growth hormone (human), reaction product with polyethylene glycol.

CAS — 218620-50-9.

ATC — H01AX01.

ATC Vet — QH01AX01.

UNII — N824AOU5XV.

Uses and Administration

Pegvisomant is a protein of recombinant DNA origin to which several polyethylene glycol polymers are covalently bound. It is an analogue of human growth hormone that acts as an antagonist at growth hormone receptors, and is used in the treatment of acromegaly (below). A loading dose of 40 or 80 mg is given subcutaneously, followed by 10 mg daily. Further dose adjustments, in increments of 5 mg, are made according to serum concentrations of IGF-I, which should be measured every 4 to 6 weeks. The maintenance dose should not exceed 30 mg daily.

Reviews.
1. Muller AF, *et al.* Growth hormone receptor antagonists. *J Clin Endocrinol Metab* 2004; **89:** 1503–11.
2. Thankamony GN, *et al.* Pegvisomant: current and potential novel therapeutic applications. *Expert Opin Biol Ther* 2009; **9:** 1553–63.

Administration in children. For administration of pegvisomant in children with pituitary gigantism, see below.

Acromegaly. Pegvisomant may be used in patients with acromegaly (p. 1918.1) who have not responded adequately to surgery, radiotherapy, or somatostatin analogues, or when these therapies are unsuitable or not tolerated. The combination of pegvisomant with a somatostatin analogue is also under investigation in patients whose response to a somatostatin analogue alone is inadequate. Pegvisomant has also been tried in a small number of younger patients with gigantism (see below).

References.
1. Trainer PJ, *et al.* Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med* 2000; **342:** 1171–7.
2. van der Lely AJ, *et al.* Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001; **358:** 1754–9.
3. Feenstra J, *et al.* Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. *Lancet* 2005; **365:** 1644–6. Correction. *ibid.*; 1620.
4. Jehle S, *et al.* Alternate-day administration of pegvisomant maintains normal serum insulin-like growth factor-I levels in patients with acromegaly. *J Clin Endocrinol Metab* 2005; **90:** 1588–93.
5. Colao A, *et al.* Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. *Eur J Endocrinol* 2006; **154:** 467–77.
6. Pivonello R, *et al.* Treatment with growth hormone receptor antagonist in acromegaly: effect on cardiac structure and performance. *J Clin Endocrinol Metab* 2007; **92:** 476–82. Correction. *ibid.*; 1605.
7. Neggers SJCMM, *et al.* Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. *J Clin Endocrinol Metab* 2007; **92:** 4598–4601.
8. Ghigo E, *et al.* Comparison of pegvisomant and long-acting octreotide in patients with acromegaly naïve to radiation and medical therapy. *J Endocrinol Invest* 2009; **32:** 924–33.
9. Trainer PJ. ACROSTUDY: the first 5 years. *Eur J Endocrinol* 2009; **161** (suppl): S19–S24.

Gigantism. Several case reports have described the use of pegvisomant in children and adolescents in the treatment of pituitary gigantism (p. 1918.1).[1-4] The condition had been previously uncontrolled by other treatments (surgery, octreotide, or dopamine agonists). Generally daily subcutaneous injections of pegvisomant 10 mg were given initially, and the youngest patient[3] was aged 5 years and 6 months.

1. Rix M, *et al.* Pegvisomant therapy in pituitary gigantism: successful treatment in a 12-year-old girl. *Eur J Endocrinol* 2005; **153:** 195–201.
2. Müssig K, *et al.* Pegvisomant treatment in gigantism caused by a growth hormone-secreting giant pituitary adenoma. *Exp Clin Endocrinol Diabetes* 2007; **115:** 198–202.
3. Goldenberg N, *et al.* Treatment of pituitary gigantism with the growth hormone receptor antagonist pegvisomant. *J Clin Endocrinol Metab* 2008; **93:** 2953–6.
4. Bergamaschi S, *et al.* Eight-year follow-up of a child with a GH/prolactin-secreting adenoma: efficacy of pegvisomant therapy. *Horm Res Paediatr* 2010; **73:** 74–9.

Adverse Effects and Precautions

Adverse effects commonly reported with the use of pegvisomant include gastrointestinal disturbances, elevated liver function tests, flu-like symptoms, fatigue, injection site reactions, arthralgia, myalgia, peripheral oedema, headache, dizziness, somnolence, tremor, sweating, pruritus, rash, sleep disorders, hypercholesterolaemia, weight gain, hyperglycaemia, hunger, and hypertension.

Liver function should be tested before starting pegvisomant, then every 4 to 6 weeks for the first 6 months of therapy. US licensed product information recommends that further testing take place twice in the next 6 months and then twice in the following year.

Pegvisomant is structurally similar to growth hormone and may cause assays to overestimate growth hormone concentrations.

Breast feeding. The distribution of pegvisomant into breast milk has been examined (see Pregnancy, below).

Effects on the skin. Lipohypertrophy has been described in patients who have consistently injected pegvisomant into the same subcutaneous area.[1-3] Lipohypertrophy regressed on stopping the drug.[3] The efficacy of pegvisomant was also reduced in one case, but lipohypertrophy resolved and pegvisomant efficacy improved when the patient used the recommended technique of injection site rotation.[2] Licensed product information recommends that a different injection site is used daily to help prevent lipohypertrophy.

1. Maffei P, *et al.* Lipohypertrophy in acromegaly induced by the new growth hormone receptor antagonist pegvisomant. *Ann Intern Med* 2006; **145:** 310–12.
2. Marazuela M, *et al.* Pegvisomant-induced lipohypertrophy: report of a case with histopathology. *Ann Intern Med* 2007; **147:** 741–3.
3. Bonert VS, *et al.* Lipodystrophy in patients with acromegaly receiving pegvisomant. *J Clin Endocrinol Metab* 2008; **93:** 3515–18.

Pregnancy. A women receiving pegvisomant for acromegaly continued therapy during pregnancy.[1] The dose of pegvisomant needed to be increased from 15 mg subcutaneously daily to 20 mg daily one month after conception, and to 25 mg daily at 3 months of gestation. Normal fetal growth milestones were achieved and a normal child was delivered at week 40 by caesarean section. The baby girl

was reported to be healthy and normal at 6 months of age. Transplacental passage of pegvisomant was considered to be either absent or minimal, based on samples of maternal and cord blood. There was also no evidence of substantial secretion into breast milk, and the authors suggested that any that might be ingested would be likely to undergo rapid gastric hydrolysis.

There is also a report of a woman who continued to receive pegvisomant during a single cycle of IVF and until a positive pregnancy test, with no apparent adverse effect on the fetus. The child was reported to be normal at 1 year of age.[2]

1. Brian SR, *et al.* Treatment of acromegaly with pegvisomant during pregnancy: maternal and fetal effects. *J Clin Endocrinol Metab* 2007; **92:** 3374–7.
2. Qureshi A, *et al.* IVF/ICSI in a woman with active acromegaly: successful outcome following treatment with pegvisomant. *J Assist Reprod Genet* 2006; **23:** 439–42.

Interactions

Pegvisomant may increase insulin sensitivity. In patients with diabetes, doses of insulin or oral hypoglycaemics may need to be decreased because of the increased risk of hypoglycaemia. Patients taking opioid analgesics may require higher serum concentrations of pegvisomant to achieve appropriate IGF-I suppression.

Pharmacokinetics

Pegvisomant is absorbed slowly after subcutaneous injection, and peak serum concentrations occur after about 33 to 77 hours. It is slowly eliminated from serum, with a half-life estimated to range from 74 to 172 hours. Renal clearance of pegvisomant is negligible.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Somavert; ***Austria***: Somavert; ***Belg.***: Somavert; ***Braz.***: Somavert; ***Canad.***: Somavert; ***Cz.***: Somavert; ***Denm.***: Somavert; ***Fin.***: Somavert; ***Fr.***: Somavert; ***Ger.***: Somavert; ***Gr.***: Somavert; ***Hung.***: Somavert; ***Irl.***: Somavert; ***Israel***: Somavert; ***Ital.***: Somavert; ***Mex.***: Somavert; ***Neth.***: Somavert; ***Norw.***: Somavert; ***Pol.***: Somavert; ***Port.***: Somavert; ***Singapore***: Somavert; ***Spain***: Somavert; ***Swed.***: Somavert; ***Switz.***: Somavert; ***Turk.***: Somavert; ***UK***: Somavert; ***Ukr.***: Somavert (Сомаверт)†; ***USA***: Somavert.

Pralmorelin Dihydrochloride *(USAN, rINNM)* ⊗

Dihidrocloruro de pralmorelina; GHRP-2 (pralmorelin); Growth Hormone-releasing Peptide-2 (pralmorelin); KP-102 (pralmorelin); Pralmoréline, Dichlorhydrate de; Pralmorelini Dihydrochloridum; WAY-GPA-748; Пральморелина Дигидрохлорид.

D-Alanyl-3-(2-naphthyl)-D-alanyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide dihydrochloride.

$C_{45}H_{55}N_9O_6.2HCl$=890.9

CAS — 158861-67-7 (pralmorelin); 158827-34-0 (pralmorelin dihydrochloride).

UNII — R4AVR27MM8.

Profile

Pralmorelin is a small synthetic peptide that stimulates the release of growth hormone. It is used in the diagnosis of growth hormone deficiency; it has also been tried in the treatment of growth retardation (p. 1918.3).

References.

1. Mericq V, *et al.* Effects of eight months treatment with graded doses of a growth hormone (GH)-releasing peptide in GH-deficient children. *J Clin Endocrinol Metab* 1998; **83:** 2355–60.
2. Mahajan T, Lightman SL. A simple test for growth hormone deficiency in adults. *J Clin Endocrinol Metab* 2000; **85:** 1473–6.
3. Gondo RG, *et al.* Growth hormone-releasing peptide-2 stimulates GH secretion in GH-deficient patients with mutated GH-releasing hormone receptor. *J Clin Endocrinol Metab* 2001; **86:** 3279–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: GHRP.

Somatomedins ⊗

Fattori di crescita insulino-simili; IGFs; Insuliininkaltaiset kasvutekijät; Insulinähnliche Wachstumsfaktoren; Insuline-achtige groeifactoren; Insulin-like Growth Factors; Somatomedinas; Somatomedine; Somatomediner; Sulphation Factors; Соматомедины.

Description. Somatomedins are a group of polypeptide hormones related to insulin and usually known individually as insulin-like growth factors (IGFs), with molecular weights of about 7000 to 8000. They are synthesised in the liver, kidney, muscle, and other tissues.

Mecasermin *(BAN, USAN, rINN)* ⊗

CEP-151; FK-780; IGF-1; IGF-I; Insulin-like growth factor I (human); Mecasermina; Mécasermine; Mecaserminum; rhIGF-1; Somatomedin C; Somatomedina C; Меказермин.

$C_{331}H_{512}N_{94}O_{101}S_7$=7648.7

CAS — 68562-41-4; 67763-96-6.

ATC — H01AC03.

ATC Vet — QH01AC03.

UNII — 7GR9I2683O.

Mecasermin Rinfabate *(USAN, rINN)* ⊗

Mecasermina rinfabato; Mécasermine Rinfabate; Mecaserminum Rinfabas; rhIGF-I/rhIGFBP-3; Меказермин Ринфабат.

A complex of insulin-like growth factor I (human) with insulin-like growth factor-binding protein IGFBP-3 (human).

CAS — 478166-15-3.

ATC — H01AC05.

ATC Vet — QH01AC05.

UNII — NZ8M50KKRG.

Uses and Administration

The somatomedins are a group of polypeptide hormones, some of which are involved in mediating the effects of growth hormone in the body. Insulin-like growth factor I (IGF-I) is believed to be responsible for many of the anabolic effects of growth hormone. It is secreted primarily by the liver, regulated principally by growth hormone and insulin secretion; IGF-I may also be secreted in other tissues, where it may exert local hormonal (paracrine) effects. In the circulation, IGF-I is almost completely protein bound; 6 binding proteins have been identified and production of some of these is also under the control of growth hormone. In addition to its anabolic effects IGF-I, which is structurally related to insulin, also has potent hypoglycaemic properties.

IGF-I is available as mecasermin, a product of recombinant DNA technology. It is used in the treatment of growth failure in children and adolescents with severe primary IGF-I deficiency or with growth hormone gene deletion who have developed neutralising antibodies to growth hormone (see Growth Retardation, below). However, it is not recommended for children less than 2 years of age because of a lack of data. The starting dose of mecasermin is 40 to 80 micrograms/kg twice daily by subcutaneous injection. After 1 week, if this dose is tolerated, it may be increased by 40 micrograms/kg per dose to a maximum of 120 micrograms/kg twice daily. Mecasermin should be given within 20 minutes before or after food, to minimise hypoglycaemia. The dose should be reduced if hypoglycaemia occurs with recommended doses despite adequate food intake. If the patient is unable to eat for any reason, the dose of mecasermin should be withheld.

Mecasermin rinfabate is a recombinant protein complex of IGF-I and its most abundant binding protein, insulin-like growth factor binding protein-3 (IGFBP-3). It has been investigated for the management of amyotrophic lateral sclerosis and myotonic muscular dystrophy. It is also under investigation in the prevention of complications in preterm neonates that may be associated with low endogenous concentrations of IGF-I, such as retinopathy of prematurity.

IGF-II (IGF-2) is thought to play an important role in fetal growth, although its function in adults is uncertain. It is closely related in structure to IGF-I, but is not under the control of growth hormone.

General reviews.

1. Laron Z. Somatomedin-1 (insulin-like growth factor-I) in clinical use: facts and potential. *Drugs* 1993; **45:** 1–8.
2. Bondy CA, *et al.* Clinical uses of insulin-like growth factor I. *Ann Intern Med* 1994; **124:** 593–601.
3. Le Roith D. Insulin-like growth factors. *N Engl J Med* 1997; **336:** 633–40.
4. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. *Mol Pathol* 2001; **54:** 311–16.
5. Kemp SF, *et al.* Efficacy and safety of mecasermin rinfabate. *Expert Opin Biol Ther* 2006; **6:** 533–8.
6. Keating GM. Mecasermin. *BioDrugs* 2008; **22:** 177–88.

Administration in children. For details of mecasermin doses in children see Uses and Administration, above and Growth Retardation, below.

Diabetes mellitus. Patients with type 1 diabetes mellitus (p. 459.1) have low circulating levels of insulin-like growth factor I (IGF-I), and there has been considerable interest in the therapeutic potential of mecasermin in these patients.[1] Randomised studies[2,3] have found that mecasermin 40 micrograms/kg once or twice daily by subcutaneous injection improves metabolic control in the short term when added to insulin therapy. Insulin doses can also be reduced in some patients.[3] However, the role of IGF-I in the development of diabetic complications is unclear and there has been some concern about its proliferative effect in diabetic retinopathy.[1] Optic disc swelling and worsening of retinopathy have been reported with higher doses of mecasermin.[3] Mecasermin rinfabate has been tried in an attempt to limit adverse effects such as oedema, jaw pain, headache, Bells' palsy, and retinal oedema.[4]

Mecasermin has also been reported to improve insulin sensitivity and to lower concentrations of insulin, glucose, and C-peptide in patients with syndromes of severe insulin resistance or type 2 diabetes mellitus.[1]

1. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility. *Diabetes Technol Ther* 2000; **2:** 69–80.
2. Acerini CL, *et al.* Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997; **350:** 1199–1204.
3. Thrailkill KM, *et al.* Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. *Diabetes Care* 1999; **22:** 585–92.
4. Clemmons DR, *et al.* The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab* 2000; **85:** 1518–24.

Growth retardation. Mecasermin is used in the treatment of growth retardation (p. 1918.3) including Laron-type dwarfism (growth hormone resistance or insensitivity). It is given to children and adolescents with severe primary IGF-I deficiency, which includes patients with mutations in the growth hormone receptor or post-growth hormone receptor signalling pathway, and IGF-I gene defects. They have low concentrations of IGF-I and normal or elevated concentrations of growth hormone; they are not growth hormone deficient and cannot be expected to respond to growth hormone therapy. It is also used in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone. Mecasermin has stimulated linear growth and normalised biochemical abnormalities in these patients.[1] One study[2] found the effect on growth velocity in the first year to be dose dependent. The beneficial effect persisted during up to 8 years of treatment, but growth velocity gradually declined over this time. During long-term use, growth hormone and insulin are persistently suppressed, preventing hypoglycaemia and stabilising blood-glucose concentrations.[3] There is also an increase in the production of the insulin-like growth factor binding protein-3, which prolongs the half-life of mecasermin so that a progressive dose reduction is needed to avoid overdosage and adverse effects.[3]

Some children with idiopathic short stature have a low concentration of IGF-I of no apparent cause, which is less severe than IGF-I deficiency from genetic causes. It has been suggested that these patients, who have normal concentrations of growth hormone, might have a degree of growth hormone insensitivity, and a study[4] of IGF-I treatment reported improvements in height velocity, dependent on dose and age. However, this premise for IGF-I therapy has been criticised and a role for IGF-I treatment in idiopathic short stature requires further study.[5]

1. Laron Z. The essential role of IGF-I: lessons from the long-term study and treatment of children and adults with Laron syndrome. *J Clin Endocrinol Metab* 1999; **84:** 4397–4404.
2. Chernausek SD, *et al.* GH Insensitivity Syndrome Collaborative Group. Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. *J Clin Endocrinol Metab* 2007; **92:** 902–10.
3. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89:** 1031–44.
4. Midyett LK, *et al.* Recombinant insulin-like growth factor (IGF)-I treatment in short children with low IGF-I levels: first-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2010; **95:** 611–19.
5. Collett-Solberg PF, Misra M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. The role of recombinant human insulin-like growth factor-I in treating children with short stature. *J Clin Endocrinol Metab* 2008; **93:** 10–18.

Motor neurone disease. Mecasermin has been investigated for the management of amyotrophic lateral sclerosis, a form of motor neurone disease (p. 2605.2). A review of 2 studies concluded that there was not enough evidence to assess the clinical efficacy of mecasermin.[1] A later study found no benefit from mecasermin.[2]

1. Mitchell JD, *et al.* Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/08/08).
2. Sorenson EJ, *et al.* Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. *Neurology* 2008; **71:** 1770–5.

Osteoporosis. Mecasermin[1] and mecasermin rinfabate[2] have been investigated as stimulants of bone formation in osteoporosis (p. 1168.1). Some beneficial effects on bone density have been reported.

1. Grinspoon S, *et al.* Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. *J Clin Endocrinol Metab* 2002; **87:** 2883–91.
2. Boonen S, *et al.* Musculoskeletal effects of the recombinant human IGF-I/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab* 2002; **87:** 1593–9.

Adverse Effects and Precautions

Since the somatomedins are considered to be responsible for many of the actions of growth hormone similar adverse effects (see p. 1921.3) might be expected, and have been seen with mecasermin. Hypoglycaemia is common but symptoms can generally be avoided if mecasermin is given within 20 minutes of food. Tonsillar hypertrophy can develop; patients should be monitored for complications such as snoring, sleep apnoea, and chronic middle ear effusions. Thickening of the soft tissues of the face can also occur. Cardiomegaly and valvulopathy have been reported in a few patients. Although a relationship between cardiac changes and mecasermin therapy has not been confirmed, echocardiogram monitoring has been recommended. Injection site hypertrophy may occur, but can be avoided or resolved by proper rotation of injection sites. Cases of hypersensitivity, urticaria, pruritus, and erythema have also been reported.

Effects on the eyes. For concerns about an increased risk of retinopathy in diabetic patients receiving mecasermin, see under Diabetes Mellitus, p. 1929.2.

Intravenous administration. Syncope in the absence of hypoglycaemia has been reported in patients given mecasermin by intravenous bolus, accompanied in some cases by convulsions, asystole, bradycardia, hypotension, or dizziness.[1] Reports appear to have ceased since recommendations that mecasermin should not be given intravenously at rates greater than 24 micrograms/kg per hour. Arthralgia, nerve palsies, and hypophosphataemia and dyspnoea have been associated with high-dose intravenous bolus therapy.[2] Mecasermin is now given by subcutaneous injection (see Uses and Administration, p. 1929.2).

1. Malozowski S, Stadel B. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121:** 549.
2. Usala A-L. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121:** 550.

Pharmacokinetics

After subcutaneous injection, mecasermin has a bioavailability of almost 100% in healthy subjects. In the circulation it is bound to 6 binding proteins, with more than 80% bound to binding protein 3 (IGFBP-3). However, IGFBP-3 is greatly reduced in patients with severe primary IGF-I deficiency, such that there is an increase in the clearance of mecasermin. Mecasermin is metabolised in the liver and the kidney, and has a terminal half-life of about 6 hours in children with severe primary IGF-I deficiency.

After subcutaneous injection of mecasermin rinfabate in children with severe primary IGF-I deficiency, the half-life of free IGF-I is prolonged to about 13 hours and IGFBP-3 has a half-life of about 54 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Increlex; ***Belg.***: Increlex; ***Cz.***: Increlex; ***Denm.***: Increlex†; ***Fr.***: Increlex; ***Ger.***: Increlex; ***Gr.***: Increlex; ***Irl.***: Increlex; ***Israel***: Increlex; ***Ital.***: Increlex; ***Neth.***: Increlex; ***Norw.***: Increlex; ***Pol.***: Increlex; ***Port.***: Increlex; ***Spain***: Increlex; ***Swed.***: Increlex; ***UK***: Increlex; ***USA***: Increlex.

Somatorelin *(rINN)* ⊗

GHRF; GHRH; GRF; GRF-44; Growth Hormone-releasing Factor (Human); Growth Hormone-releasing Hormone; Hormone de libération de l'hormone de croissance; Somatocrinina; Somatocrinine; Somatokrinin; Somatoliberin; Somatolibérine; Somatoliberyna; Somatoreliini; Somatorelina; Somatoréline; Somatorelinum; Wachstumshormon-Releasing-Hormon; Соматотропин-освобождающ Хормон; Соматорелин.

$C_{215}H_{358}N_{72}O_{66}S$=5039.7

CAS — 83930-13-6.

ATC — V04CD05.

ATC Vet — QV04CD05.

Sermorelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de sermorelina; GRF(1-29)NH_2 (sermorelin); Growth Hormone-releasing Factor (Human)-(1-29)-peptide Amide (sermorelin); Sermorelina, acetato de; Sermoréline, Acétate de; Sermorelini Acetas; Серморелина Ацетат.

Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 acetate hydrate.

$C_{149}H_{246}N_{44}O_{42}S.xC_2H_4O_2.yH_2O$=3357.9 (sermorelin)

CAS — 86168-78-7 (sermorelin); 114466-38-5 (sermorelin acetate).

ATC — H01AC04; V04CD03.

ATC Vet — QH01AC04; QV04CD03.

UNII — 00IBG871QW.

Uses and Administration

Somatorelin is a peptide, secreted by the hypothalamus, that promotes the release of growth hormone from the anterior pituitary. It exists as 44-, 40-, and 37-amino acid peptides; the 44-amino acid form may possibly be converted to the smaller forms but all are reported to be active, the activity residing in the first 29 amino acid residues. Sermorelin is a synthetic peptide corresponding to the 1–29 amino acid sequence of somatorelin.

Somatorelin acetate is used for the diagnosis of growth hormone deficiency. The usual dose is the equivalent of somatorelin 50 micrograms by intravenous injection, given after the patient has fasted. In highly overweight adults and in children, a dose of 1 microgram/kg is given. Plasma or serum concentrations of growth hormone are measured before the dose of somatorelin and usually 30 minutes after, but additional measurements may be taken at 15, 45, 60, and 90 minutes for a better assessment of growth hormone release. The test can distinguish between pituitary and hypothalamic disorders but is not suitable as a screening test for growth hormone deficiencies.

Sermorelin acetate has been used similarly for the diagnosis of growth hormone deficiency. It has also been used for the treatment of growth retardation in children with growth hormone deficiency (see below).

Sermorelin has also been tried as an adjunct to gonadotrophin therapy in the induction of ovulation and has been investigated in the treatment of HIV-associated wasting.

Diagnostic use. Somatorelin (in its 40- or 44-amino acid forms) has been used in the assessment of growth hormone deficiency.[1-3] It has usually been given as a single intravenous injection in doses of 1 microgram/kg or total doses of up to 200 micrograms. Subsequent normal or exaggerated increases in serum-growth hormone concentrations have occurred in healthy subjects,[1,2] and in patients with hypothalamic tumours[3] or acromegaly,[2] but not in patients with hypopituitarism.[2] A synthetic 29-amino-acid sequence of somatorelin, sermorelin acetate has also been used for the diagnosis of growth hormone deficiency. However, it has been suggested that the test is not useful for screening as it does not test the hypothalamic-pituitary axis, and that it should not be used in routine clinical practice.[4] The use of sermorelin with the synthetic hexapeptide growth-hormone-releasing peptide-6 has also been reported.[5,6]

1. Thorner MO, *et al.* Human pancreatic growth-hormone-releasing factor selectively stimulates growth-hormone secretion in man. *Lancet* 1983; **i:** 24–8. Correction. *ibid.;* 256.
2. Wood SM, *et al.* Abnormalities of growth hormone release in response to human pancreatic growth hormone releasing factor (GRF (1-44)) in acromegaly and hypopituitarism. *BMJ* 1983; **286:** 1687–91.
3. Grossman A, *et al.* Growth-hormone-releasing factor in growth hormone deficiency: demonstration of a hypothalamic defect in growth hormone release. *Lancet* 1983; **ii:** 137–8.
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
5. Popovic V, *et al.* GH-releasing hormone and GH-releasing peptide-6 for diagnostic testing in GH-deficient adults. *Lancet* 2000; **356:** 1137–42.
6. Leal A, *et al.* A single growth hormone (GH) determination is sufficient for the diagnosis of GH-deficiency in adult patients using the growth hormone releasing hormone plus growth hormone releasing peptide-6 test. *Clin Endocrinol (Oxf)* 2002; **57:** 377–84.

Growth retardation. Sermorelin has been studied in children with growth hormone deficiency (p. 1918.3), usually in doses of 30 micrograms/kg subcutaneously daily. Although there have been reports of improved growth rates,[1-3] there are few direct comparisons with growth hormone. One large study[4] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer.

1. Neyzi O, *et al.* Growth response to growth hormone-releasing hormone (1—29)-NH_2 compared with growth hormone. *Acta Paediatr Suppl* 1993; **388:** 16–21.
2. Lanes R, *et al.* Long term therapy with a single daily subcutaneous dose of growth hormone releasing hormone (1-29) in prepubertal growth hormone deficient children. *J Pediatr Endocrinol* 1994; **7:** 303–8.
3. Ogilvy-Stuart AL, *et al.* Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone. *Clin Endocrinol (Oxf)* 1997; **46:** 571–8.
4. Thorner M, *et al.* Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. *J Clin Endocrinol Metab* 1996; **81:** 1189–96.

Lipodystrophy. In a placebo-controlled study[1] of 31 men with HIV-related lipodystrophy, insulin-like growth factor I (IGF-I) concentrations and body composition measures were improved in those given sermorelin 1 mg twice daily subcutaneously for 12 weeks.

1. Koutkia P, *et al.* Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. *JAMA* 2004; **292:** 210–18.

Adverse Effects and Precautions

Adverse effects of somatorelin acetate injection for diagnostic use include a transient sense of warmth or flushing of the head, neck, and upper body. There may also be taste and smell disturbances. Similar effects have been reported with sermorelin, as well as pain at the injection site, headache, nausea and vomiting, and tightness in the chest. Antibodies to somatorelin often develop on repeated use of sermorelin.

Uncontrolled thyroid disorders, obesity, hyperglycaemia, or elevated plasma fatty acids may impair response to somatorelin or sermorelin. Sermorelin should also be used with care in patients with epilepsy. Sermorelin should not be used to treat growth retardation in children whose growth hormone response to stimulation tests is inadequate. Treatment should cease once the epiphyses have closed.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sermorelin for diagnostic use as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Drugs that affect the secretion of growth hormone may interfere with the diagnostic efficacy of somatorelin or sermorelin; these include growth hormone itself (which should be stopped at least 1 week before testing), somatostatin and its analogues, insulin, corticosteroids, and cyclo-oxygenase inhibitors such as aspirin and indometacin. Growth hormone concentrations may be raised by clonidine and levodopa. The response to somatorelin or sermorelin may also be reduced by antimuscarinic drugs such as atropine, and by antithyroid drugs such as propylthiouracil.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: GHRH; ***Fr.***: Stimu-GH; ***Ger.***: GHRH; ***Gr.***: Esfarase; Geref; ***Irl.***: Geref†; ***Ital.***: Geref†; GHRH; ***Neth.***: GHRH; ***Spain***: GHRH; ***Switz.***: GHRH; ***UK***: GHRH; ***USA***: Geref†.

Somatostatin *(BAN, rINN)*

GH-RIF; GHRIH; Growth-hormone-release-inhibiting Hormone; Somatostatiini; Somatostatina; Somatostatinas; Somatostatine; Somatostatinum; Somatostatyna; Somatotrophin-release-inhibiting Factor; Szomatosztatin; Соматостатин.

Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys cyclic (3→14) disulphide.

$C_{76}H_{104}N_{18}O_{19}S_2$=1637.9

CAS — 38916-34-6.

ATC — H01CB01.

ATC Vet — QH01CB01.

UNII — 6E20216Q0L.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Somatostatin). A cyclic tetradecapeptide having the structure of the hypothalamic hormone that inhibits the release of human growth hormone. It is produced by chemical synthesis and contains not more than 15% w/w of acetic acid. A white amorphous powder. Freely soluble in water and in acetic acid; practically insoluble in dichloromethane. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light and moisture.

Somatostatin Acetate *(BANM, rINNM)*

Acetato de somatostatina; Somatostatiiniasetaatti; Somatostatin Asetat; Somatostatinacetat; Somatostatine, Acétate de; Somatostatini Acetas; Соматостатина Ацетат.

ATC — H01CB01.

ATC Vet — QH01CB01.

Uses and Administration

Somatostatin is a polypeptide obtained from the hypothalamus or by synthesis. The naturally occurring form has a cyclic structure. Although somatostatin derived from the hypothalamus is a 14-amino-acid peptide, a longer, 28-amino-acid form also exists in some tissues. Five different receptors for somatostatin have been identified. Somatostatin inhibits the release of growth hormone (p. 1919.3) from the anterior pituitary. It also inhibits the release of thyrotrophin (p. 2346.1) and corticotropin (p. 1628.3) from the pituitary, glucagon and insulin from the pancreas, and appears to have a role in the regulation of duodenal and

gastric secretions. In the CNS it appears to play a role in the perception of pain.

It has been tried in a variety of disorders such as upper gastrointestinal haemorrhage including variceal haemorrhage (see under Monoethanolamine, p. 2563.1), insulin resistance, and the management of hormone-secreting tumours and other hypersecretory disorders. However, it has a very short duration of action and several analogues of somatostatin have been produced in an attempt to prolong its activity as well as making its inhibitory effects more specific. Octreotide (p. 1924.1) and lanreotide (p. 1923.2) are such analogues.

Somatostatin is usually given as the acetate. In the treatment of gastrointestinal haemorrhage, such as acute bleeding from oesophageal varices, somatostatin acetate equivalent to somatostatin 250 micrograms has been given by intravenous bolus over 3 to 5 minutes, followed by a continuous infusion of 250 micrograms/hour (about 3.5 micrograms/kg per hour) until the bleeding has stopped, which is usually within 12 to 24 hours. The infusion may then be continued for a further 48 to 72 hours to prevent recurrent bleeding. In some cases, the infusion may be continued to a maximum of 120 hours.

Malignant neoplasms. Somatostatin given with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was ineffective in the treatment of advanced malignancies (see Malignant Neoplasms, under Uses and Administration of Octreotide, p. 1926.2).

Adverse Effects and Precautions

Abdominal discomfort, flushing, nausea, and bradycardia have been associated with too rapid infusion. Because of the short half-life of somatostatin adverse effects are generally transitory on stopping or reducing the infusion. Giving with parenteral nutrition has been suggested because of the inhibitory effects of somatostatin on intestinal absorption; blood glucose should be monitored since somatostatin may interfere with the secretion of insulin and glucagon. Allergic reactions have also been reported.

Effects on the kidneys. Somatostatin has been reported to have an inhibitory effect on renal function[1,2] and severe water retention and hyponatraemia have been reported.[3]

1. Walker BJ, *et al*. Somatostatin and water excretion. *Lancet* 1983; **i:** 1101–2.
2. Vora JP, *et al*. Effect of somatostatin on renal function. *BMJ* 1986; **292:** 1701–2.
3. Halma C, *et al*. Life-threatening water intoxication during somatostatin therapy. *Ann Intern Med* 1987; **107:** 518–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Somatin; ***Braz.***: Stilamin; ***Canad.***: Stilamin†; ***China***: Etaxene (忆太欣); Hening (赫宁); Lizhixue (丽枝雪); Modustatine (赛得); Shishitai (时士太); Stilamin (思他宁); ***Fr.***: Modustatine†; ***Gr.***: Atostan; Eklivan; Sadolin; Somabion; Somargen; Somaritin; Somastin; Sonafrine; Stilamin; ***Hong Kong***: Stilamin; ***India***: Ikestatina; Somastin; Stilamin; ***Indon.***: Stilamin; ***Ital.***: Etaxene; Ikestatina; Modustatina; Nastoren; Resurmide; Stilamin; ***Malaysia***: Stilamin; ***S.Afr.***: Stilamin; ***Singapore***: Stilamin; ***Spain***: Somonal†; ***Switz.***: Stilamin; ***Thai.***: Etaxene†; Stilamin; ***Turk.***: Somatosan; Stilamin†; ***Venez.***: Ikestatina; Stilamin.

Tesamorelin Acetate *(USAN, rINNM)*

Acetato de tesamorelina; Tésamoréline, Acétate de; Tesamorelini Acetas; TH-9507; Тезаморелина Ацетат.

(3*E*)-Hex-3-enoylsomatoliberin (human) acetate.

$C_{221}H_{366}N_{72}O_{67}S,xC_2H_4O_2$=5135.9 (tesamorelin)

CAS — 901758-09-6.

UNII — LGW5H38VE3.

Uses and Administration

Tesamorelin is a synthetic analogue of somatorelin (p. 1930.1) used for the reduction of excess abdominal fat in HIV-associated lipodystrophy. It is given subcutaneously as the acetate in a dose equivalent to 2 mg of tesamorelin daily.

References.

1. Falutz J, *et al*. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med* 2007; **357:** 2359–70.
2. Falutz J, *et al*. Effects of tesamorelin, a growth hormone-releasing factor, in HIV-infected patients with abdominal fat accumulation: a randomized placebo-controlled trial with a safety extension. *J Acquir Immune Defic Syndr* 2010; **53:** 311–22.
3. Falutz J, *et al*. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab* 2010; **95:** 4291–4304.
4. Dhillon S. Tesamorelin: a review of its use in the management of HIV-associated lipodystrophy. *Drugs* 2011; **71:** 1071–91.
5. Spooner LM, Olin JL. Tesamorelin: a growth hormone-releasing factor analogue for HIV-associated lipodystrophy. *Ann Pharmacother* 2012; **46:** 240–7.
6. Stanley TL, *et al*. Reduction in visceral adiposity is associated with an improved metabolic profile in HIV-infected patients receiving tesamorelin. *Clin Infect Dis* 2012; **54:** 1642–51.

Adverse Effects and Precautions

Tesamorelin may cause hypersensitivity reactions such as rash and urticaria and adverse effects associated with released growth hormone such as arthralgia, extremity pain, peripheral oedema, hyperglycaemia, and carpal tunnel syndrome may occur. Additionally, injection site reactions can include erythema, pruritus, pain, urticaria, irritation, swelling, and haemorrhage.

Tesamorelin is contra-indicated in active malignancy and any pre-existing malignancy should be inactive and treatment complete before starting tesamorelin. It is also contra-indicated in patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumour or surgery, head irradiation, or head trauma. Tesamorelin is contra-indicated in pregnancy.

Insulin-like growth factor I should be monitored and tesamorelin stopped if the former becomes persistently elevated. Impaired glucose metabolism has been reported and therefore also requires monitoring. Stopping tesamorelin should be considered in the event of critical illness.

References.

1. Falutz J, *et al*. Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. *AIDS* 2008; **22:** 1719–28.

Interactions

Since tesamorelin stimulates growth hormone production, they may have similar interactions (see p. 1923.1).

Pharmacokinetics

The absolute bioavailability of tesamorelin after a 2-mg subcutaneous dose was less than 4% in healthy adults. The mean elimination half-life of tesamorelin was 26 minutes in healthy subjects and 38 minutes in HIV-infected patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Egrifta.

Vapreotide *(BAN, USAN, rINN)*

BMY-41606; RC-160; Vapreotida; Vapréotide; Vapreotidum; Вапреотид.

D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2→7)-disulfide.

$C_{57}H_{70}N_{12}O_9S_2$=1131.4

CAS — 103222-11-3.

ATC — H01CB04.

ATC Vet — QH01CB04.

UNII — 2PK59M9GFF.

Vapreotide Acetate *(BANM, USAN, rINNM)*

Acetato de vapreotida; BMY-41606; DP-05-094; RC-160; Vapréotide, Acétate de; Vapreotidi Acetas; Вапреотида Ацетат.

D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2→7)-disulfide acetate salt (1:*n*).

$C_{57}H_{70}N_{12}O_9S_2,nC_2H_4O_2$

CAS — 849479-74-9.

ATC — H01CB04.

ATC Vet — QH01CB04.

UNII — 5562377HFV.

NOTE. The names Docrised, Octastatin, and Sanvar have been used as trade marks for vapreotide acetate.

Profile

Vapreotide is a somatostatin analogue similar to octreotide (p. 1924.1). It has been investigated in the management of various disorders, including bleeding oesophageal varices, gastrointestinal and pancreatic fistulas, acromegaly, carcinoid tumours, and for the prevention of postoperative complications after pancreatic surgery.

References.

1. Eriksson B, *et al*. The use of new somatostatin analogues, lanreotide and octastatin, in neuroendocrine gastro-intestinal tumours. *Digestion* 1996; **57** (suppl 1): 77–80.
2. Calès P, *et al*. Early administration of vapreotide for variceal bleeding in patients with cirrhosis. *N Engl J Med* 2001; **344:** 23–8.
3. Anonymous. Vapreotide: BMY 41606, RC 160, Sanvar. *Drugs R D* 2003; **4:** 326–30.
4. Fortune BE, *et al*. Vapreotide: a somatostatin analog for the treatment of acute variceal bleeding. *Expert Opin Pharmacother* 2009; **10:** 2337–42.

Immunosuppressants

Asthma, p. 1932
Blood disorders, p. 1932
Diabetes mellitus, p. 1932
Gastrointestinal disorders, p. 1932
Inflammatory bowel disease, p. 1932
Liver disorders, p. 1932
Lung disorders, p. 1932
Interstitial lung disease, p. 1932
Neurological disorders, p. 1932
Multiple sclerosis, p. 1932
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Ocular disorders, p. 1932
Organ and tissue transplantation, p. 1932
Corneal transplantation, p. 1933
Haematopoietic stem cell transplantation, p. 1933
Heart transplantation, p. 1934
Intestinal transplantation, p. 1935
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Lung transplantation, p. 1937
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Renal disorders, p. 1938
Rheumatoid arthritis, p. 1938
Sarcoidosis, p. 1938
Scleroderma, p. 1938
Skin and connective tissue disorders, p. 1939

The compounds described in this chapter are used in diseases considered to have an auto-immune component, and in organ and tissue transplantation. Some other important drugs used for their immunosuppressant properties are described under Antineoplastics, p. 691.1 and Corticosteroids, p. 1597.1. The choice of an immunosuppressant is discussed below.

Choice of Immunosuppressant

Asthma

Immunosuppressant drugs do not play a role in the regular management of asthma (p. 1195.2). In individual patients requiring oral corticosteroids for chronic severe asthma immunosuppressants have however been investigated for their anti-inflammatory and corticosteroid-sparing properties.

Blood disorders

For the use of immunosuppressants in aplastic anaemia, see p. 1121.3.

Diabetes mellitus

For mention of the use of immunosuppressants in recent-onset type 1 diabetes, see Prevention of Diabetes Mellitus, p. 460.3. See also Pancreatic Transplantation, p. 1938.1.

Gastrointestinal disorders

Inflammatory bowel disease. A number of immunosuppressants have been tried in inflammatory bowel disease (p. 1808.3), with some success, but the mainstays of drug therapy remain the aminosalicylates and the corticosteroids. Immunosuppressants may be valuable in some circumstances for their corticosteroid-sparing effect and for chronic active disease refractory to other treatments.

Liver disorders

For a discussion of the role of immunosuppressants, and particularly azathioprine, in the management of chronic active hepatitis, see p. 1602.3. For the use of immunosuppressants in primary biliary cirrhosis see under Ursodeoxycholic Acid, p. 2638.3.

Lung disorders

Interstitial lung disease. Corticosteroids have been used with azathioprine (or occasionally cyclophosphamide), for the treatment of various forms of interstitial lung disease (p. 1607.1).

Neurological disorders

Multiple sclerosis. Immunosuppressants have been tried in the treatment of multiple sclerosis (p. 996.3), although in some studies the benefit obtained may have been outweighed by toxicity.

Myasthenia gravis. Patients with myasthenia gravis (p. 684.1) who require immunosuppression are usually treated with corticosteroids. Other immunosuppressants such as azathioprine, ciclosporin, mycophenolate mofetil, and tacrolimus have been tried mainly for their corticosteroid-sparing effect but may also be of use when corticosteroids are contra-indicated or when response to their use alone is insufficient.

Ocular disorders

Immunosuppressants have been used with some success in ocular disorders with inflammatory or immunological components. In *scleritis* and *uveitis* (see p. 1612.3 and p. 1615.1) corticosteroids, given topically, intra-ocularly, or systemically are widely used when treatment is needed, but in unresponsive disease, or in patients with unacceptable adverse effects, immunosuppressants such as azathioprine, ciclosporin, or mycophenolate mofetil, may be given. Daclizumab, leflunomide, sirolimus, and tacrolimus have also been tried in uveitis. Immunosuppressants may be valuable in the management of *Behçet's disease*, *rheumatoid arthritis*, or *Wegener's granulomatosis*, (see p. 1601.1, p. 13.2, and p. 1615.2, respectively), including their associated ocular lesions. Ciclosporin or azathioprine have been used with corticosteroids in the management of both ocular and vascular symptoms of *Cogan's syndrome* (p. 1603.2). Ciclosporin has also been used topically in corneal ulceration, see p. 1947.1.

Ciclosporin or methotrexate may be options in the treatment of *Graves' ophthalmopathy* (see under Hyperthyroidism, p. 2332.2).

Reviews.

1. McCluskey PJ, *et al.* Management of chronic uveitis. *BMJ* 2000; **320:** 555–8.
2. Jabs DA, *et al.* Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000; **130:** 492–513.
3. Kulkarni P. Review: uveitis and immunosuppressive drugs. *J Ocul Pharmacol Ther* 2001; **17:** 181–7.
4. Dunn JP. Review of immunosuppressive drug therapy in uveitis. *Curr Opin Ophthalmol* 2004; **15:** 293–8.
5. Hemady RK, *et al.* Immunosuppressive agents and nonsteroidal anti-inflammatory drugs for ocular immune and inflammatory disorders. *Ophthalmol Clin North Am* 2005; **18:** 511–28.
6. Jap A, Chee S-P. Immunosuppressive therapy for ocular diseases. *Curr Opin Ophthalmol* 2008; **19:** 535–40.

Organ and tissue transplantation

Although surgical techniques suitable for the removal of organs and tissues from a donor, and their engraftment into a host, have existed for many years, such grafts would not normally survive for long. The host's CD4+ T-cells recognise foreign antigens from donor cells. A CD4+ cell is then activated by antigen-presenting cells to secrete interleukin-2 and induce T-cell proliferation. Activated T-cells mediate a rejection response, by increasing the activity and function of B-cells, cytotoxic CD8+ T-cells, and macrophages, either directly, or by cytokine release. Only from the 1960s with the development of drugs capable of attenuating or suppressing this response, did transplantation start to become a feasible mode of treatment.

The drugs available vary in their mechanisms of action, and are often combined for optimum effect. **Corticosteroids** (glucocorticoids) act at several points in the immune cascade, including antigen recognition and production of lymphokines. The **calcineurin inhibitors** ciclosporin and tacrolimus prevent formation of cytotoxic T-cells by inhibiting calcineurin activation, an important step in the release of interleukin-2 from helper T-cells, while polyclonal or monoclonal **antibodies** such as antilymphocyte immunoglobulins and muromonab-CD3 bind to and deplete T-cell populations. Basiliximab and daclizumab function as **interleukin-2 receptor antagonists**. **Antiproliferative drugs** such as azathioprine and mycophenolate mofetil act by preventing cell division of lymphocytes. Sirolimus and everolimus are **proliferation signal inhibitors** that inhibit the T-cell response to cytokines.

Immunosuppressant regimens may be divided into those aimed at:

- prevention of rejection in the early period after transplantation
- long-term maintenance prophylaxis
- treatment of acute episodes of rejection.

In haematopoietic stem cell transplantation, where an immunologically competent tissue is transplanted, it is the donor cells which attack host tissues (graft-versus-host disease), and immunosuppression is required for prophylaxis of this condition.

Because of the critical nature of the early stage, when the organ or tissue must recover normal function, and perhaps to permit better long-term tolerance, initial immunosuppressant regimens tend to use higher doses than maintenance therapy. Standard protocols are usually based around ciclosporin or tacrolimus, combined with corticosteroids and an anti-proliferative agent (triple therapy). Where appropriate, a course of monoclonal or polyclonal antibodies is added to the standard regimen for induction (quadruple therapy). This is usually only required in individuals at increased risk of acute rejection, such as children or patients with a previous transplant or pregnancy, multiple blood transfusions, or a poor HLA-matching. However, it also enables delayed introduction of ciclosporin or tacrolimus in patients at risk of nephrotoxicity, and the use of low-dose regimens, allowing for withdrawal of corticosteroids.

No one immunosuppressive regimen has been identified as being superior to others in pregnancy, and although there are known theoretical risks to mother and fetus, successful pregnancies are now common in transplant recipients. The incidence of structural malformation has not been noted to be increased compared with the general population, but newer regimens have yet to be evaluated.

Since immunosuppressant therapy must in most cases be given for the lifetime of the graft, in long-term maintenance the toxicity of the drugs used, and the risks of infection, neoplasia, post-transplant diabetes mellitus, gout, hyperlipidaemia, and osteoporosis, must be considered. Doses and numbers of drugs used tend to be reduced, and in particular there is a tendency to taper or even eliminate the doses of corticosteroids used in maintenance regimens because of the potential sequelae of prolonged corticosteroid use. Post-transplant cardiovascular disease is a leading cause of death and graft loss. The risk varies between types of transplant, and specific recommendations for prophylaxis may differ.

The use of less intensive maintenance regimens must be balanced against the risk of an acute rejection episode, and the likelihood of its responding to therapy. High-dose corticosteroids and polyclonal or monoclonal antibodies often play a role in the rescue therapy of patients with acute rejection episodes, although much depends upon the severity of the reaction, and whether such episodes have occurred previously.

The management of immunosuppression for the transplantation of particular organs is discussed in more detail below. With the use of suitable immunosuppressant regimens long-term graft survival can be obtained after transplantation. Ultimately, however, the complications of chronic rejection are likely to lead to loss of the graft: the induction of specific tolerance to the donor organ remains the goal of much research. In allogeneic haematopoietic stem cell transplantation, where the aim of immunosuppression is prevention of graft-versus-host disease rather than rejection, immunosuppressant therapy can often be tapered off and eventually withdrawn.

Much interest has been aroused by the possibility of organ transplants from *animals* genetically modified to reduce complement-mediated hyperacute rejection. It is not clear whether such xenotransplantation will require modified immunosuppressive regimens.

General reviews on immunosuppression and transplantation.

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6. Golshayan D, Pascual M. Tolerance-inducing immunosuppressive strategies in clinical transplantation: an overview. *Drugs* 2008; **68:** 2113–30.

7. Tredger JM, *et al*. Calcineurin inhibitor sparing in paediatric solid organ transplantation: managing the efficacy/toxicity conundrum. *Drugs* 2008; **68:** 1385–1414.
8. Calne RY. Transplantation: current developments and future directions. *Rev Neurosci* 2009; **20:** 267–73.
9. Urschel S, *et al*. Immunosuppression armamentarium in 2010: mechanistic and clinical considerations. *Pediatr Clin North Am* 2010; **57:** 433–57.
10. Ekser B, Cooper DK. Overcoming the barriers to xenotransplantation: prospects for the future. *Expert Rev Clin Immunol* 2010; **6:** 219–30.

Some **reviews** of the adverse effects and precautions associated with transplantation, and their management.

1. Chan SE, *et al*. Treatment of hepatitis C in solid organ transplantation. *Drugs* 2004; **64:** 489–98.
2. Slifkin M, *et al*. Viral prophylaxis in organ transplant patients. *Drugs* 2004; **64:** 2763–92.
3. Buell JF, *et al*. Malignancy after transplantation. *Transplantation* 2005; **80** (suppl 2): S254–S264.
4. Stamp L, *et al*. Gout in solid organ transplantation: a challenging clinical problem. *Drugs* 2005; **65:** 2593–2611.
5. Smith JM, McDonald RA. Emerging viral infections in transplantation. *Pediatr Transplant* 2006; **10:** 838–43.
6. McKay DB, Josephson MA. Pregnancy in recipients of solid organs—effects on mother and child. *N Engl J Med* 2006; **354:** 1281–93.
7. Wheeler DC, Krentz AJ. New-onset diabetes after transplantation. *Br J Hosp Med* 2007; **68:** 190–4.
8. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs* 2007; **67:** 1167–98.
9. Morrissey PE, *et al*. Medication noncompliance and its implications in transplant recipients. *Drugs* 2007; **67:** 1463–81.
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References to some experimental procedures.

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3. Ruan D, *et al*. Intervertebral disc transplantation in the treatment of degenerative spine disease: a preliminary study. *Lancet* 2007; **369:** 993–9.
4. Shores JT, *et al*. Composite tissue allotransplantation: hand transplantation and beyond. *J Am Acad Orthop Surg* 2010; **18:** 127–31.

Corneal transplantation. For reference to the use of immunosuppressants to treat graft rejection after corneal transplant see Corneal Graft Rejection, p. 1603.3.

Haematopoietic stem cell transplantation. Haematopoietic stem cell transplantation (HSCT) is used in the treatment of a variety of malignancies, notably leukaemias and lymphomas; to permit the use of very high-dose chemotherapy in the management of some solid tumours (bone marrow rescue); and to treat some other serious disorders affecting the bone marrow, such as aplastic anaemia and the haemoglobinopathies.[1,2]

HSCT may be **autologous**, in which case the patient's own stem cells are harvested or **allogeneic**, where stem cells are harvested from a healthy donor matched as closely as possible for HLA type.[3,4] The haematopoietic stem cells themselves may be derived from:

- bone marrow (classical bone marrow transplantation, BMT)
- peripheral blood (peripheral blood stem cell transplantation, PBSCT)
- umbilical cord blood

PBSCT is convenient as collection does not require hospitalisation or general anaesthesia for the donor, and clinical studies have shown more rapid engraftment of neutrophils and platelets compared with BMT.[2,5-7] However, allogeneic PBSCT appears to increase the risk of graft-versus-host disease[1,2,6-10] (see below). Allogeneic PBSCT was associated with decreased relapse rates and improved disease-free survival but similar overall survival in adults, when compared with BMT.[6] However, in children, allogeneic PBSCT was associated with higher mortality and treatment failure than BMT although relapse rates were similar; advanced disease status and use of colony-stimulating factor were also associated with poorer outcome.[7] Use of umbilical cord blood is associated with slightly delayed engraftment,[2,11-13] and hence, perhaps, an increased risk of fatal infection,[2,11] but a lower risk[2,12,14] of graft-versus-host disease (see below). A meta-analysis[15] confirmed these findings, but found a similar relapse rate, and equivalent survival for cord blood transplantation compared with unrelated BMT. It has mainly been used for transplants in children, since the total number of stem cells in a donation often falls short of the levels deemed necessary for engraftment in an adult.[1,2,5,13] However, cord blood is increasingly used for transplants in adults.[16] Since cell dose correlated with outcome in most studies, strategies have been developed to increase progenitor cell numbers in the cord blood units; techniques include pooled or sequential cord blood transplantation, or expansion of the cord blood cells with cytokines. Combination cord blood and bone marrow transplants, and reduced intensity regimens are under investigation.[16-18]

With autologous HSCT problems of **compatibility** do not arise, but if abnormal cell clones are present in the marrow (as in leukaemia) or stem cells they may be transferred back into the patient and cause disease relapse.[1] Allogeneic HSCT requires immunosuppression for about 6 months[19] to prevent graft-versus-host disease (see below) until a new immunological balance is achieved.

The patient is normally prepared by **conditioning** with total body irradiation, or myeloablative chemotherapy with drugs such as cyclophosphamide or busulfan, or more often both, in order to destroy host bone marrow cells.[5,20] In autologous procedures, harvesting of bone marrow or peripheral blood must be carried out before conditioning. Bone marrow is aspirated from the donor, and infused into the recipient via an indwelling catheter or directly into a peripheral vein. Peripheral blood stem cells are collected by cell separation after mobilisation, which is best achieved by a combination of chemotherapy and granulocyte or granulocyte-macrophage colony-stimulating factor.[1,2,5] Infection is a major cause of morbidity and mortality after transplantation, so prophylactic cover with antimicrobials[2,21,22] and normal immunoglobulins has been recommended,[21] although the value of the latter has been questioned.[23] A subsequent systematic review[24] found no advantage for immunoglobulin prophylaxis in terms of survival or infection prevention; they increased the risk for veno-occlusive disease (VOD), but decreased the rate of interstitial pneumonitis. The authors concluded the evidence did not support the routine use of immunoglobulin prophylaxis for HSCT. Granulocyte colony-stimulating factors are sometimes used after allogeneic transplants to hasten haematopoietic recovery. While a meta-analysis found no evidence for an increase in risk for acute or chronic graft-versus-host disease,[25] a large study found delayed platelet engraftment, increased graft-versus-host disease, and increased mortality in those given growth factors after allogeneic bone marrow transplants; these effects were not seen in patients given allogeneic PBSCT.[26]

In addition to such supportive care, patients who have received allogeneic transplants require immunosuppressive therapy aimed at the prevention of **graft-versus-host disease** (GVHD). GVHD is usually characterised as *acute* or *chronic* depending on the manifestations, and the time of presentation[1,4,5,10,27-30] (by convention acute disease occurs within a hundred days of transplantation, and chronic disease after this time, although in practice there is considerable overlap).

The organ systems mainly affected are skin, liver, lung, and gastrointestinal tract. Both forms are marked by maculopapular rashes, which in severe disease may progress to bullous lesions and epidermal necrolysis. Liver disease may include cholestatic jaundice (usually in the acute form) and hepatitis; symptoms may need to be distinguished from the VOD which sometimes complicates bone marrow transplantation and is due to the pre-transplant conditioning regimen (VOD may respond to treatment with antithrombin III[31] or defibrotide[32,33]). Ursodeoxycholic acid has been found to be of benefit for the prophylaxis of hepatic complications.[34] The main symptom of gastrointestinal GVHD is diarrhoea, often severe and painful. In patients with chronic GVHD other manifestations may include arthritis, mucositis, lung disease (bronchiolitis obliterans), and scleroderma.

Most modern regimens for the *prophylaxis* of GVHD after allogeneic HSCT are based on ciclosporin. Although GVHD still occurs in many ciclosporin-treated patients, morbidity is much reduced and survival improved. Combination regimens have been tried for prophylaxis, particularly ciclosporin or tacrolimus with methotrexate, but also combinations with other drugs including antilymphocyte immunoglobulins, corticosteroids, mycophenolate mofetil, and sirolimus.[9,19,35] After allogeneic myeloablative HSCT, adding corticosteroids to the prophylactic regimen has been found to reduce the incidence of moderately severe acute GVHD, but no benefit has been noted for survival.[36] Monoclonal antibodies have been used to produce T-cell depletion or reduce the effects of circulating cytokines,[9,28] and it has been suggested that RNA interference may have a potential role.[37]

Acute GVHD is usually *treated* mainly by the addition of corticosteroids (usually methylprednisolone) to the existing regimen until symptoms are controlled, followed by gradual tapering of the dose. Mycophenolate mofetil, antilymphocyte immunoglobulins, interleukin-2 receptor antibodies, etanercept, and infliximab have also been tried.[2,9,19,38-40] PUVA therapy and extracorporeal photopheresis have been used[2,9,30] and infusion of mesenchymal stem cells is also under investigation.[9,30,41]

Chronic GVHD has no specific standard therapy; most centres use a combination of corticosteroids and a calcineurin inhibitor (ciclosporin or tacrolimus).[2,10,19,30,42,43] Drugs that have been tried for salvage therapy include mycophenolate mofetil, sirolimus, daclizumab, thalidomide, pentostatin, etanercept, infliximab, and rituximab.[10,19,39,42] PUVA therapy with extracorporeal photopheresis has also been used, with good response rates,[10,42] and recommendations for use have been published in the UK.[44] Mesenchymal stem cell infusion may be a potential therapy.[10] Octreotide is recommended for the symptomatic treatment of diarrhoea.[45]

Donor T-cells reactive to recipient minor histocompatibility antigens can inhibit the growth of abnormal cells, and may also target aberrantly expressed proteins, provoking a 'graft-versus-tumour' effect, which reduces relapse, both after allogeneic transplantation and among patients in whom GVHD develops.[1] Indeed, many leukaemia patients who relapse after allogeneic transplant can be reinduced into remission by an additional infusion of donor lymphocytes.[2] Consequently, too effective an immunosuppressant regimen may not always be desirable, and leukaemic patients given bone marrow transplants purged of T-cells, which virtually abolishes GVHD, do not have a better survival rate than those given conventional prophylaxis (engraftment too is reduced in the absence of all T-cells). Specific donor marrow T-cell depletion has been investigated as the sole form of GVHD prophylaxis.[46] In a multicentre randomised study, marrow T-cell depletion was found to reduce but not abolish the incidence of acute GVHD, accelerate neutrophil recovery and reduce toxicity compared with transplantation with T-cell replete marrow; however, disease-free survival at 3 years did not differ due to higher rates of relapse in some patients, and a higher incidence of serious infection in T-cell depleted marrow recipients.[47] The observation of graft-versus-malignancy effects has led to the development of low-dose non-myeloablative conditioning regimens (with or without donor lymphocyte infusions) for elderly or more sensitive patients who might have been unable to receive the standard aggressive therapy.[1-3,15,48-52] Fludarabine is commonly used in reduced-intensity conditioning regimens, often combined with other drugs such as busulfan or melphalan, or with low-dose total body irradiation.[53] Safety and efficacy of these reduced-intensity regimens has led to wider application;[1] however, the lower mortality rate may be offset by a higher relapse rate,[1] and poor engraftment.[2]

An uncommon complication of HSCT is **transplantation-associated thrombotic microangiopathy** which is a thrombotic thrombocytopenic purpura that presents as a microangiopathic haemolytic anaemia. Calcineurin inhibitors have been linked to its development, and initial treatment involves replacing ciclosporin or tacrolimus with alternative immunosuppressants. Improvement has been reported when daclizumab has replaced a calcineurin inhibitor; defibrotide and rituximab have also been used in small numbers of patients.[54]

The combination of irradiation, chemotherapy, and immunosuppression can cause the development of **secondary malignancies** in long-term survivors of HSCT.[1,55-58]

Intracoronary injection of haematopoietic stem cells into the heart is under investigation for cardiac disease,[59] **intramuscular** injection has also been investigated in peripheral vascular disease.[60] There is also interest in HSCT in some auto-immune disorders.[60]

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Heart transplantation. Marked improvements have been seen in the outcome of heart transplantation since the introduction of ciclosporin, which has resulted in a reduced incidence and severity of rejection episodes.[1] The 1-year survival rate is about 80%.[1,2]

A common **immunosuppressive regimen** consists of triple therapy with ciclosporin or tacrolimus, azathioprine or mycophenolate, and corticosteroids.[3-6] Some centres also use induction therapy with antilymphocyte immunoglobulins (polyclonal antibodies) or muromonab-CD3.[4,7]

Induction therapy increases the risk of infection and lymphoproliferative disorders, but does delay the first rejection episode and allows transplantation in higher risk groups. It also enables calcineurin inhibitor use to be delayed in patients with initial poor renal function[7] and corticosteroids to be stopped as maintenance therapy in some groups of patients.[8] Muromonab-CD3 may be associated with a higher incidence of adverse reactions than polyclonal antibodies. Sensitisation to muromonab-CD3 is strongly associated with vascular rejection, and this and the dose-related propensity for lymphoproliferative disease with muromonab-CD3 have led to a decline in its use; some consider it should be abandoned in favour of polyclonal preparations.[7,9] The interleukin-2 receptor antibodies basiliximab and daclizumab have also been used for induction therapy.[2,7,10,11] However, daclizumab use has been associated with an increased risk of death due to infection, mostly in patients given additional immunosuppressive treatment with antilymphocyte drugs for early postoperative complications.[11] The interleukin-2 receptor antibodies have not as yet been associated with an additional risk of malignancies.[7] Alemtuzumab is under investigation for induction therapy in heart transplantation.[7,9]

There does not seem to be any great clinical benefit of tacrolimus over ciclosporin in heart transplant patients,[9,12,13] although some have reported reduced rates of histological rejection,[14,15] and there is evidence that patients of Afro-Caribbean origin in particular may be more prone to acute rejection with ciclosporin than with tacrolimus.[16] It has been suggested that tacrolimus be substituted for ciclosporin in those patients suffering persistent rejection, or adverse effects associated with ciclosporin,[17] or with hyperlipidaemia or hypertension.[18] Microemulsifying ciclosporin may be associated with less rejection than the oil-based formulation.[19]

The use of mycophenolate mofetil instead of azathioprine in triple therapy has been shown to reduce mortality and rejection in the first year after heart transplantation,[20] and a retrospective review[21] concluded that the advent of mycophenolate mofetil has contributed to improved survival in cardiac transplant recipients. Although lower mycophenolic acid (MPA) concentrations may be associated with an increased allograft rejection,[22] there appears to be no benefit in monitoring MPA concentrations beyond the first year in heart transplant recipients,[23] and MPA levels may be affected by concomitant immunosuppression, see Immunosuppressants under Interactions of Mycophenolate, p. 1964.2.

Many variations of regimens exist, and different drugs have been substituted or used adjunctively in order to decrease the doses, and thus alleviate the adverse effects associated with calcineurin inhibitors and/or corticosteroids. Substituting cyclophosphamide for azathioprine for 6 weeks after transplantation is reported to reduce the development of anti-muromonab-CD3 antibodies from induction therapy.[24] Substitution of mycophenolate mofetil with intravenous pulse cyclophosphamide for 4 months post-transplantation appeared to decrease the risk of rejection in a small, non-randomised study in sensitised allograft recipients.[25]

Alternative adjunctive therapies are the proliferation signal inhibitors, sirolimus and everolimus,[2,9] which allow for use of lower doses of calcineurin inhibitors, thus preserving renal function; however, long-term data are limited, and there is little experience with these drugs in paediatric patients. Use of sirolimus with ciclosporin and corticosteroids markedly reduced the incidence of acute rejection in a small open-label study.[26] However, the use of sirolimus with mycophenolate mofetil was associated with a higher than expected incidence of acute rejection in cardiac transplant patients switched from calcineurin inhibitors to this combination.[27]

It has been suggested that the high doses of corticosteroids used increase the risk of cardiac adverse events in the longer term, and protocols that wean patients from corticosteroids after 6 months postoperatively have been used,[28,29] without apparent increases in infection or rejection. Corticosteroid avoidance or early withdrawal regimens are feasible in many, if not most, paediatric heart transplant recipients.[9]

In the early post-transplant period, the most significant **causes of morbidity** are infection and rejection episodes.[8,9] Other complications post-transplant include right ventricular failure and cardiac arrhythmias.[30] Co-trimoxazole is used to protect against *Pneumocystis jirovecii* infection, and ganciclovir as prophylaxis against CMV.[3] Rejection is usually treated with corticosteroids, but other drugs have been used for corticosteroid-resistant cases,[8] including antilymphocyte immunoglobulins and muromonab-CD3.[4,29] In repetitive rejection, tacrolimus may be substituted for ciclosporin, and mycophenolate mofetil for azathioprine.[4,5] Adjunctive methotrexate, total lymphoid irradiation and photopheresis have all been tried.[8]

In the late post-transplant period, malignancy and coronary artery disease are the most significant problems.[3,7,8] About 5% of paediatric heart transplant recipients have been reported to develop post-transplant lymphoproliferative disease (PTLD).[2,31] The strongest risk factor for PTLD is the development of primary Epstein-Barr virus infection after transplantation although children who are seropositive for the virus are not necessarily protected from this complication.[2,9] Despite treatment with chemotherapy or a reduction in immunosuppression, PTLD is associated with significant morbidity and mortality; acute rejection may occur in those whose immunosuppression is reduced.[2] Rituximab and cellular immunotherapy are novel therapeutic approaches for PTLD.[9] Cardiac allograft vasculopathy (also termed coronary artery vasculopathy, or chronic rejection) is a major cause of death and prevention of its progression is a major therapeutic goal.[2,3,9,32,33] It is thought to be mainly an immunological response, but can be accelerated by recipient risk factors such as age, gender, obesity, hyperlipidaemia, hypertension, smoking, diabetes mellitus, pretransplant heart disease, postoperative CMV infection, and immunosuppression itself as well as donor risk factors such as age, gender, and hypertension.[3,6,8,34,35] Long-term use of calcineurin inhibitors is associated with renal dysfunction and also contributes to hypertension and hyperlipidaemia, all of which may exacerbate cardiac allograft vasculopathy.[33] Calcium-channel blockers have been used to decrease the incidence of coronary artery disease, but it has remained a difficult complication to treat.[34] HMG-CoA reductase inhibitors such as pravastatin and simvastatin are recommended[36,37] for the treatment of hyperlipidaemia; pravastatin or atorvastatin have been used in paediatric heart transplant patients.[2] There is evidence that statin therapy substantially improves survival.[38] Fibric acid derivatives may be considered in those patients with hypertriglyceridaemia not controlled by diet alone.[37] Supplementation with antioxidant vitamins such as C or E may reduce the progression of arteriosclerosis after transplantation,[39] and a small study[40] found that omega-3 fatty acids improved blood pressure control in hypertensive transplant recipients. There is some suggestion that sirolimus[26,41] and everolimus[42] may be of benefit in preventing cardiac allograft vasculopathy in adults; data are lacking in paediatric patients.[2,9] Retransplantation for graft failure due to cardiac allograft vasculopathy may be necessary.[33]

Improved surgical techniques and the use of ciclosporin have also made possible successful combined *heart-lung* transplants, although these may require enhanced or modified immunosuppression to prevent obliterative bronchiolitis, a possible manifestation of chronic rejection.[43] Early rejection after transplantation is the most important risk factor for the development of bronchiolitis obliterans syndrome although pathogenesis is unclear.[44] Lung infection,[43] or oxidative stress and lack of glutathione[44] may be factors in the aggravation or onset of bronchiolitis obliterans syndrome.

Donor-specific tolerance, whereby the patient permanently accepts their graft without the need for long-term immunosuppression, while remaining immunocompetent, remains the ultimate goal in cardiac transplantation.[6,9]

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Intestinal transplantation. Transplantation of the *small bowel* is becoming more common, especially in children.[1] There are 3 types of intestinal allograft: the isolated intestine, combined liver and intestine, and the multivisceral graft, which can also include the pancreas, stomach, liver, and kidneys.[2-5] Combined liver and small intestine transplants are used for patients dependent on parenteral nutrition and with irreversible intestinal and hepatic failure, while intestine-only transplants tend to be used for intestinal failure in patients with severe progressive complications of parenteral nutrition, such as recurring sepsis and impending loss of central venous access.[1,5-8] Multivisceral transplants are most common in patients with diffuse gastrointestinal motility disorders.[3,4] Transplantation of the *colon* is avoided because of poorer outcomes and increased risk of sepsis.[9] Overall patient and graft survival varies according to the type of intestinal allograft, and between transplant centres, but is reported to be about 50% at 5 years post-transplant;[1,10] more recent 1-year survival rates of over 90% at the most experienced centres may translate into improved longer-term survival.[10]

Tacrolimus and tapered corticosteroid doses[1,2,9,11-14] are the basis of the standard immunosuppressive regimen. In some centres, corticosteroid-free protocols are used, with induction therapy, and tacrolimus alone as maintenance.[5,14] Prostaglandins[8,9] such as alprostadil may also be given to augment mucosal immunosuppression, and improve splanchnic and renal blood flow. Induction therapy with antilymphocyte immunoglobulins or the interleukin-2 receptor antibodies basiliximab and daclizumab is used to prevent rejection.[1,9,12,14-16] Alemtuzumab has also been used.[13,14,16]

Adjunctive immunosuppressants have been added to the maintenance regimen. Azathioprine has been used.[5,12] Sirolimus has also been tried,[1,4,8,9,15] but combining tacrolimus with sirolimus does not have additional benefit over tacrolimus alone.[16] Sirolimus maintenance monotherapy, after induction, is increasingly favoured.[16] Any role for mycophenolate mofetil in intestinal transplantation is questionable,[13,15,17] owing to its gastrointestinal toxicity and poor absorption in intestinal transplant recipients, particularly during rejection.

Substantial morbidity occurs with intestinal transplants and acute rejection, manifested by diarrhoea, fever, and ileus, is common.[1,2,5,9] Initial treatment is with corticosteroids, and most centres increase the dose of tacrolimus as well. Antilymphocyte immunoglobulins or muromonab-CD3 may be used for severe or corticosteroid-unresponsive episodes.[1,2,7,9,14,16] Azathioprine, sirolimus, or mycophenolate mofetil have also been used adjunctively for treatment of rejection,[1,7] although concerns persist about the use of mycophenolate in intestinal transplantation (see above). Chronic rejection, a common cause of late graft dysfunction, is more difficult to treat.[1,9,17] Infliximab has been tried.[18]

Bacterial, viral, and fungal infections are also common post-transplant,[1,2,9,17] and may be confused with rejection.[4,17] Protocols for antimicrobial prophylaxis and treatment are similar to those used for other solid organ transplants. Selective gastrointestinal decontamination with non-absorbable oral antibacterials is usually performed during the first fortnight after transplantation, and during moderate to severe rejection episodes.[11,12] The high level of immunosuppression necessary in intestinal transplantation makes recipients particularly susceptible to post-transplant lymphoproliferative disease associated with Epstein-Barr virus infection.[1,2,4,6,17] Controlling rejection by more potent immunosuppression is difficult because of these complications, so the induction of immune tolerance through adjunctive bone marrow infusion is being investigated.[1,2,13,15] Graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1933.1) may occur and there may be a recurrence of the original disease.[2]

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Kidney transplantation. The transplantation of kidneys is now established as the ultimate therapy for end-stage renal disease. There is no single generally accepted immunosuppressant regimen, and different centres have achieved good results with a variety of strategies.[1] Therapy should be tailored to the individual patient. Several factors affect the intensity of immunotherapy required, including the donor source (living or cadaveric) and degree of HLA histocompatibility, and the age, race and panel reactive antibody titre of the recipient.[1]

A widely used approach consists of **triple therapy** with a *calcineurin inhibitor* (ciclosporin or tacrolimus), an *antiproliferative* (azathioprine or mycophenolate mofetil), and a *corticosteroid* (prednisolone).[2,3] Triple therapy is popular because it allows the use of lower doses of nephrotoxic calcineurin inhibitors, and the eventual tapering or even elimination of corticosteroids in some patients.[1]

Many variations of triple therapy regimens have been used.

- Azathioprine has largely been replaced by mycophenolate mofetil, which lowers the incidence of acute rejection and reduces the risk of chronic allograft failure.[4-6] This has been challenged, however, by a study[7] in which mycophenolate mofetil was found to be no better than azathioprine in prevention of acute rejection. The drugs were given with microemulsifying ciclosporin and corticosteroids, and ciclosporin dosage was targeted to plasma trough concentrations. The authors noted that previous studies attesting greater efficacy with mycophenolate mofetil had been carried out using the older standard ciclosporin formulation, and that the possibility of better activity with mycophenolate mofetil could not be excluded in patients in whom target ciclosporin concentrations are not achieved.
- Tacrolimus has been substituted for ciclosporin because it appeared to be more effective in preventing acute rejection than either the older oil-based formulation,[4] or the newer microemulsifying formulation.[8,9] Although it has been suggested that this does not lead to improved survival of either patients or grafts,[10] a systematic review[11] concluded that use of tacrolimus did improve graft survival, with a 44% reduction in graft loss within the first 6 months of transplantation; acute rejection was reduced by almost a third and severe rejection by half. The benefit in graft survival diminished with higher concentrations of tacrolimus. However, although tacrolimus may have a better cardiovascular risk profile than ciclosporin,[8,12,13] patients are two to three times more likely to develop diabetes and to have neurological adverse effects.[11] Choice of calcineurin inhibitor is therefore strongly influenced by adverse effect profiles.[10,14,15]
- There is some evidence of synergism between sirolimus and ciclosporin[16] and *addition* of sirolimus to ciclosporin-based regimens may reduce the incidence of acute rejection.[4,17] Combining sirolimus with tacrolimus instead of ciclosporin may be even more effective.[4] However, sirolimus may augment the nephrotoxicity of both ciclosporin[2] and tacrolimus,[5] and its use with full-dose calcineurin inhibitors has been associated with significantly reduced rates of allograft survival.[18] In an attempt to reduce the chronic allograft nephropathy (see below) associated particularly with calcineurin inhibitors, sirolimus has been given with azathioprine or mycophenolate mofetil, as an *alternative* to ciclosporin-based protocols. Comparable rejection rates and better renal function have been reported, although the use of sirolimus may increase the risk of cardiovascular-related morbidity and mortality, and safety has not been established.

Sequential quadruple therapy, in which antibody-based induction therapy is given postoperatively, in addition to triple therapy,[2,14] is also used. The antibodies are usually stopped once good graft function is achieved.[1] The regimen may improve long-term graft survival in patients with delayed graft function.[19]

Polyclonal lymphocyte-depleting antibodies are associated with a low incidence of rejection but evidence of their benefit in terms of graft survival is lacking; rabbit antilymphocyte immunoglobulin appears to be better than that of equine origin. Use of muromonab-CD3 has declined because of poor tolerability and an increased risk of lymphoproliferative disease.[20] The more specific interleukin-2 receptor antibodies basiliximab and daclizumab are widely used and appear to reduce the incidence of rejection episodes without increased toxicity.[4-6,19-22] Alemtuzumab has also been used, but data for this drug are comparatively limited.[20,23,24]

Some consider the interleukin-2 receptor antibodies to be the first-line choice for induction therapy because of their superior safety profile.[6] While there appears to be no difference between rabbit antilymphocyte immunoglobulins and interleukin-2 receptor antibodies in terms of efficacy, acute rejection in high-risk patients appears to occur less often with rabbit antilymphocyte immunoglobulins, which may be the preferred choice in patients who are highly sensitised or receiving a second transplant.[20] Basiliximab or daclizumab, used as part of a ciclosporin-based regimen, are recommended in the UK as options for induction therapy in children and adolescents undergoing renal transplantation, irrespective of immunological risk.[15]

As immunosuppressant regimens have developed the role of corticosteroids has come to be questioned, mainly because of the adverse effects associated with their prolonged use.[4,10,25,26] Studies indicate that corticosteroid

withdrawal is feasible in many patients initially given triple therapy,[1,27] and complete avoidance of corticosteroids may be possible with induction therapy using interleukin-2 receptor antibodies.[26] There has been debate about the long-term consequences of this for graft survival,[4,26,28,29] with a possible increased risk of acute or chronic rejection, and a high proportion of patients who need to resume corticosteroid therapy. A 2009 systematic review of 30 studies[30] found no increase in mortality or graft loss with corticosteroid avoidance or withdrawal strategies despite an increase in acute rejection. The authors concluded that safe corticosteroid avoidance or elimination may be feasible a few days after kidney transplantation if antibody induction treatment is used, or after 3 to 6 months if such induction is not used. However, it is crucial to individualise therapy, and caution is advised for high-risk patients, such as African Americans, sensitised, previously transplanted patients, or those with previous acute rejection episodes. Some consider the best approach to rapid corticosteroid withdrawal to be induction therapy (with antilymphocyte immunoglobulins in high-risk patients), calcineurin inhibitors, and mycophenolate mofetil.[26] Protocols that withdraw, minimise, or avoid calcineurin inhibitors have also been investigated.[29,31-35] Ciclosporin withdrawal is considered by some[32] to be more feasible for patients treated with mycophenolate mofetil than those given azathioprine. However, the most effective regimen in terms of patient and graft survival benefit, and minimisation of rejection and adverse effects, remains to be determined.[29] Data on long-term outcomes are lacking.[29,31,33]

Where an **acute rejection** episode occurs treatment is likely to be with high-dose corticosteroids, or with drugs such as antilymphocyte immunoglobulins, or muromonab-CD3, which are potent and effective reversers of rejection.[1,2,14] European guidelines recommend that the antibody preparations be reserved for corticosteroid-resistant rejection or more severe episodes,[19] but approaches remain varied.[1] Some guidelines[6] suggest tacrolimus should be substituted for ciclosporin; mycophenolate mofetil,[4] sirolimus,[36] and gusperimus[3,23] have also been effective in reversing acute rejection episodes. Ciclosporin and azathioprine are ineffective in treating established rejection. Interleukin-2 receptor antibodies have not been shown to reverse established rejection episodes.[3] There has also been evidence that asymptomatic CMV infection may be associated with episodes of late acute rejection;[37] ganciclovir is reported to improve graft function in such circumstances. However, augmented or rescue immunosuppressive therapy predisposes the patient to infections such as CMV, which may itself mimic late acute rejection, and contribute to chronic rejection.[38]

Severe, recurrent, late episodes of acute rejection are considered to be a major risk factor for the development of **chronic rejection**. Manifested clinically by declining renal function, hypertension, and low-grade proteinuria, the term chronic allograft nephropathy is used.[4] Long-term calcineurin inhibitor treatment and inadequate immunosuppression may contribute to this, but there is some suggestion that the addition of mycophenolate mofetil can delay this process.[4] Protocols that use sirolimus to reduce or replace calcineurin inhibitors have been investigated;[18,39-41] improved renal function has been reported, but use of sirolimus may increase the risk of coronary artery disease, and long-term results are lacking.

Although newer drugs have decreased the incidence of acute rejection, there is only limited evidence that this has improved longer-term **graft survival**.[42-44] The one-year cadaveric graft survival is about 88% and about 60% at 10 years.[45] Recurrence of the original disease or *de novo* renal disease may also cause graft failure.[46] Pentoxifylline[47] and gusperimus[48] may improve graft survival.

Cardiovascular disease is a major cause of **death** in renal transplant patients.[49] Corticosteroids and ciclosporin can impair endothelial function, cause hypertension, and hyperlipidaemia. Sirolimus has also been implicated in hyperlipidaemia.[49] Dyslipidaemia occurs in about 60% of patients after renal transplantation;[13,49] HMG-CoA reductase inhibitors (statins) and dietary modification have been recommended as first-line treatment by some,[13] whereas others[50] recommend drug treatment with various lipid-lowering drugs only if lifestyle changes are insufficient. Modification of the immunosuppressive protocols, as discussed above, may also be effective.[13] Hypertension affects up to 75% of kidney transplant recipients and is associated with premature death and graft loss. Calcium-channel blockers have been reported to reduce the risk of graft loss by about 25% compared with placebo or no treatment, and patients taking calcium-channel blockers also had a higher glomerular filtration rate on average. These effects appeared to be independent of hypertension and so it has been suggested that calcium-channel blockers should be considered for all patients after kidney transplantation. There is less evidence for ACE inhibitors in kidney transplant patients, and results from studies are inconclusive. A reduced risk of graft failure in patients taking an ACE inhibitor and/or an angiotensin receptor antagonist has been reported, and some have suggested that early treatment with an ACE inhibitor in patients without signs of glomerulosclerosis may have a beneficial effect on kidney function. However, treatment of proteinuria with an ACE inhibitor may not be effective in those with existing renal damage,[51] and a systematic review noted ACE inhibitors have some detrimental effects on graft function when compared with calcium-channel blockers.[52]

Hyperuricaemia is a common problem among renal transplant recipients;[53] the use of ciclosporin is an independent risk factor for new-onset gout after transplantation.[54] Use of sirolimus is also associated with an increased risk, whereas use of tacrolimus and mycophenolate mofetil carries a lower risk. Hyperuricaemia, besides having direct deleterious effects on the graft, may potentiate chronic renal dysfunction induced by calcineurin inhibitors, and contribute to chronic allograft nephropathy.[53] New-onset gout after transplantation may also be associated with hypertension, cardiovascular disease, and death.[54]

Morbidity and mortality have improved with reductions in cardiac, vascular and infectious complications, but there has been no decrease in death from **malignancy**, and the risk of developing cancer has been estimated to be about 100% by 30 years post-transplant.[55] Compared with the general population, renal transplant recipients have a three- to fivefold higher risk of malignancy; cancers tend to be more aggressive in transplant recipients, and solid organ tumours have a poorer prognosis. The most common malignancies include non-melanoma skin cancers and post-transplant lymphoproliferative disease (PTLD).[56,57] While not all malignancies are a consequence of transplantation or immunosuppressive therapy,[56] both the duration and intensity of immunosuppression have been linked to this increased incidence.[57] Other risk factors include increasing age, male gender,[58] sun exposure, and cigarette smoking.[56]

It is difficult to assess the impact of individual drugs on cancer risk.[56] Some studies have found an increased incidence in patients given muromonab-CD3 or calcineurin inhibitors;[58,59] azathioprine is not thought to be as carcinogenic as the calcineurin inhibitors.[59] Data are conflicting on the carcinogenic effects of mycophenolate.[56,59] Proliferation signal inhibitors such as sirolimus and everolimus have been reported to carry less of a risk, possibly as a result of their mode of action.[56-60] Although long-term data are needed, some have suggested that conversion from calcineurin inhibitors to proliferation signal inhibitors should be considered in high-risk patients,[57,58,60] or those with Kaposi's sarcoma.[6]

Nonmyeloablative conditioning regimens allowing for the development of immunological **tolerance** specific to the donor remain the ultimate goal of renal transplantation.[4,61] There are reports of the development of chimerism and tolerance allowing withdrawal of all immunosuppression in a few patients in whom kidney transplants were combined with haematopoietic stem cell transplantation.[62,63]

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Liver transplantation. Marked improvements have occurred in the outcome and reliability of liver transplan-

All cross-references refer to entries in Volume A

tation and it is now seen as standard therapy for acute and chronic hepatic failure, regardless of aetiology,[1-3] and some metabolic disorders.[4] The 1-year patient and graft survival rates[2,4,5] are about 90%.

The liver induces some tolerance and liver transplant recipients usually require less immunosuppression than other solid organ transplant patients.[6] **Immunosuppressive regimens** generally combine a calcineurin inhibitor (ciclosporin or tacrolimus) with a corticosteroid and azathioprine or mycophenolate mofetil; such triple therapy prevents acute rejection episodes in the majority of cases.[7-9] Double therapy with ciclosporin or tacrolimus and corticosteroids is also used,[8,10] and monotherapy with a calcineurin inhibitor alone has also been used, allowing for complete corticosteroid withdrawal or avoidance.[10]

A review of corticosteroid-free strategies in liver transplantation concluded that up to 50% of patients can avoid corticosteroids with little modification of their maintenance immunosuppressive regimen; adding mycophenolate mofetil and/or induction therapy with antibodies can increase this percentage, although over-immunosuppression may be a problem. Although data are weak and limited, corticosteroid avoidance is not advised with calcineurin inhibitor monotherapy, nor with calcineurin inhibitors and azathioprine; it may be feasible with tacrolimus and mycophenolate mofetil, or with calcineurin inhibitors and antibodies. Benefits of corticosteroid avoidance are seen in growth rates in children, diabetes mellitus, dyslipidaemia, CMV infection, and possibly other infections.[11] A meta-analysis of 19 studies[12] found that corticosteroid-free regimens did not increase the risk of death, graft loss, or bacterial infection compared with corticosteroid-based regimens. When corticosteroids were replaced with another immunosuppressant such as an interleukin-2 receptor antibody, antilymphocyte immunoglobulin, or mycophenolate mofetil, the risk of diabetes and rejection was markedly lower with the corticosteroid-free regimens. Patients with underlying auto-immune hepatitis or inflammatory bowel disease may be relatively refractory to corticosteroid withdrawal.[13]

Although some consider the evidence for one calcineurin inhibitor over another to be equivocal,[14] a systematic review concluded that tacrolimus is better than ciclosporin at preventing acute rejection in liver transplantation. It is also marginally better at preventing patient death and graft loss, but it increases the risk of post-transplant diabetes.[15] Studies of different formulations of ciclosporin found a reduced incidence of rejection with the microemulsifying formulation compared with the older oil-based product.[5]

The use of azathioprine in liver transplant patients has been limited due to its possible hepatotoxicity.[10] Mycophenolate mofetil has been used in place of azathioprine, to reduce the dose of the calcineurin inhibitor or corticosteroid used, and possibly prevent rejection.[2,8] Calcineurin inhibitors have been replaced with mycophenolate mofetil in an attempt to improve renal function,[10] although small studies have suggested that this monotherapy carries a high risk of rejection.[14] The long-term efficacy of calcineurin inhibitor minimisation or avoidance has yet to be determined.[16] The role of sirolimus in liver transplantation has yet to be evaluated.[3] There have been reports of efficacy when used with a calcineurin inhibitor,[1,9] which might allow dose reduction[9] or withdrawal of therapy[5] in patients with toxicity from tacrolimus or ciclosporin, but excess mortality, graft loss, and hepatic artery thrombosis has been associated with such use. A regimen of everolimus, a sirolimus derivative, and reduced-dose tacrolimus, plus a corticosteroid, has similar efficacy and better renal function that a standard -dose tacrolimus regimen.[17]

Induction therapy with antilymphocyte immunoglobulins or muromonab-CD3 is associated with a high incidence of infection and lymphoproliferative disease, and they have been generally reserved for the treatment of corticosteroid-resistant acute rejection.[2,4,8,9] However, interest in the use of antilymphocyte immunoglobulins as induction therapy has increased as it allows avoidance of calcineurin inhibitors early after transplantation, improving renal function without increasing rejection risk.[14] The use of interleukin-2 receptor antibodies, basiliximab, and daclizumab, is also increasing;[10] initial studies suggest they reduce the number of rejection episodes.[8,9] It has been suggested that they may be of benefit in those with pre-transplant renal impairment by allowing for delayed introduction or lower doses of calcineurin inhibitors,[18] although complete withdrawal of calcineurin inhibitors has been reported to lead to high rates of rejection.[14] The use of alemtuzumab has also been investigated.[10,14,16]

The induction of complete immune **tolerance** remains the ultimate goal in liver transplantation.[10,19,20] It may be feasible to reduce or stop all immunosuppression in long-term stable liver transplant patients.[6,21] The term 'operational tolerance' is used to define stable graft function without features of rejection and without immunosuppressive treatment; 'prope tolerance' refers to stable graft function in patients with minimal immunosuppression.[10,21] Although it is not uncommon for rejection to eventually occur in those withdrawn from immunosuppression, this may be reversed by resumption of therapy, with a small rate of graft loss. Favourable markers for successful withdrawal appear to be at least 2 years of post-transplant follow-up, low incidence of previous rejection episodes, non-autoimmune primary liver disease, and possibly minimal post-transplant immunosuppression.[21]

Most **acute rejection** episodes occur during the first 3 to 6 months of therapy.[13] Early acute rejection does not affect patient or graft survival[6,22,23] and, if mild, may be associated with increased survival.[1] Late acute rejection, occurring after 30 days post-transplant may be related to reduction or withdrawal of immunosuppressive therapy.[24] It has a worse prognosis, with reports of up to half of patients developing graft loss.[23] Corticosteroids are used in the first-line treatment of acute rejection.[11,25] For corticosteroid-resistant rejection, muromonab-CD3 or antilymphocyte immunoglobulins are used, and increasing the dose of tacrolimus, or conversion from ciclosporin to tacrolimus, may also be effective.[2,4,9] Interleukin-2 receptor antibodies may also be used. Mycophenolate mofetil or sirolimus have been added to treat recurrent acute rejection.[25] **Chronic rejection** is almost always preceded by one or more episodes of corticosteroid-resistant acute rejection,[23,24] and although its incidence has decreased[5,23-25] to less than 5%, it remains difficult to treat. Corticosteroids are generally ineffective; conversion from ciclosporin to tacrolimus has been reported to be effective,[23] as has addition of mycophenolate mofetil to tacrolimus, followed by interleukin-2 receptor antibodies, and then sirolimus in non-responsive patients.[25]

The main **complications** encountered with liver transplants are infection in the early post-transplant period, vascular and biliary complications, recurrent disease (particularly viral recurrence), and adverse effects due to immunosuppressants.[4,6,24,25]

Sepsis is an important cause of death in the early post-transplant period.[6,26,27] Patients at increased risk, including those with malnutrition, fulminant liver failure, or renal insufficiency, require particularly cautious immunosuppression and more aggressive antibacterial and antifungal prophylaxis regimens.

Recurrence of hepatitis B infection is common.[28] Although the introduction of hepatitis B immunoglobulins and lamivudine have improved the prospects for these patients, combination antiviral therapy and a modified immunosuppression protocol are usually needed.[3,6,7,22,23] Hepatitis C recurrence is almost universal in infected patients,[11,23,29] with a probable reduction in long-term graft survival.[7,22,23] The use of corticosteroids and muromonab-CD3 appears to be associated with more severe recurrence of hepatitis C. Treatment with interferon alfa plus ribavirin appears promising.[28-30]

Nephrotoxicity from ciclosporin or tacrolimus can be a significant problem after long-term therapy.[31] Long-term renal function is affected by the function in the early post-transplant period, so serum creatinine concentrations at 1 and 3 months are often used to predict toxicity.[7] Cardiovascular complications may follow metabolic abnormalities such as diabetes mellitus, hypertension, hyperlipidaemia, and obesity. Dose reduction or change of the calcineurin inhibitor used, corticosteroid withdrawal, or use of statins could minimise the cardiovascular risk post-transplantation.[32-34] Malignancy may occur after prolonged immunosuppression.[4,22,25]

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Lung transplantation. Lung transplantation has become accepted therapy[1-4] for end-stage pulmonary disease such as pulmonary hypertension, cystic fibrosis, emphysema, and pulmonary fibrosis, with a 1-year survival of 70% or more.[2] The rate of death is highest in the first year after transplantation, with infection and primary graft failure the leading causes of early death.[1,5]

Immunosuppressant therapy is usually with a triple therapy regimen of ciclosporin or tacrolimus, azathioprine or, increasingly, mycophenolate mofetil, and a corticosteroid.[1-12] Some centres also use induction therapy with polyclonal or monoclonal antibodies, although its use is controversial.[10,12] While induction therapy may reduce the incidence and severity of acute rejection, and allow for a delay in calcineurin inhibitor therapy, there is an increased risk of infection and of post-transplant lymphoproliferative disease.[2,3,5,13] Antilymphocyte immunoglobulins and muromonab-CD3 have been used; the interleukin-2 receptor antibodies basiliximab and daclizumab are increasingly used,[1,2,13] although experience with these drugs in lung transplantation is limited.[14] Alemtuzumab is under investigation for induction;[1,2,10,11,13,14] preliminary results are promising. Corticosteroids remain a mainstay in lung transplantation,[5,10,11,13-15] although corticosteroid-free regimens have been investigated, with promising results, and further study is warranted.[14,15] Sirolimus has been investigated in lung transplantation, but its early use as a primary immunosuppressant is not recommended[1,2,11] due to its potent antifibrotic effects; sirolimus may also induce pulmonary toxicity.[10,11,13] Cases of fatal anastomotic dehiscence have been reported, and concerns about wound healing complications have led to recommendations to only use sirolimus after initial airway bronchial wound healing is completed, or not until at least 3 months after transplant.[12,13] Everolimus is also under investigation for adjunctive use in lung transplantation.[11-14]

Acute rejection occurs more frequently with lung transplants than with other solid organ transplants;[1,16] from early reports in 60 to 100% of cases, incidence has apparently decreased to about 35% in those receiving induction therapy and about 45% in those without induction therapy,[13] although some centres have reported figures as high as 85%.[16] High doses of intravenous corticosteroids are generally used to control acute episodes of rejection.[3,7,13,16] Corticosteroid-refractory rejection demands further intervention, although no consensus exists. Evidence supports the conversion of ciclosporin to tacrolimus for patients with persistent acute rejection.[13] Other therapies include the use of monoclonal or polyclonal antibodies, plasmapheresis, and total lymphoid irradiation.[13,16] Inhaled ciclosporin has also been used to treat refractory acute rejection.[1,13]

Lung transplant recipients are at high risk of **infection** as a result of impaired pulmonary defence mechanisms, and post-transplant antibacterial prophylaxis is routine.[2] Patients at risk for CMV should be given ganciclovir.[2,7,15] There is no consensus on standard antifungal prophylaxis after lung transplant, but some centres use oral azole therapy or inhaled amphotericin.[2] Respiratory viruses pose a substantial risk to the lung allograft,[2,4,15] and may contribute to chronic rejection. The main complication encountered in the long term and major cause of late mortality is **chronic rejection** manifesting as bronchiolitis

obliterans syndrome (obliterative bronchiolitis).[1,2,7,16] This is characterised by progressive airway obstruction and may be present in up to 40% of patients at 2 years, and in 60 to 70% who survive for 5 years.[7] Young children and living donor lung transplant recipients may have a lower risk for the development of this syndrome.[5] The frequency and severity of acute rejection episodes are the main risk factors for the development of bronchiolitis obliterans, but CMV infection, airway ischaemia and HLA mismatching may also play a part.[1,4,6,7,15-18] There are no proven effective therapies,[4] and the prognosis is poor, with 40% mortality within 3 years of diagnosis.[7] Augmentation of immunosuppression is often tried, but may exacerbate the risk of infection.[4] Some centres change the maintenance regimen, converting ciclosporin to tacrolimus, and azathioprine to mycophenolate mofetil, along with a short course of high-dose corticosteroids.[13,16] Inhaled ciclosporin has also been used, with reports of a trend towards survival benefit.[13] Improvement in pulmonary function has been seen with maintenance azithromycin.[13,16,18] Statins may decrease the risk of developing bronchiolitis obliterans syndrome,[12] and promising results have been reported with the use of total lymphoid irradiation.[16] Re-transplantation may be necessary.[4,16]

Post-transplant lymphoproliferative disorders (PTLD) occur in lung transplant recipients, often in association with a primary Epstein-Barr virus infection.[3,4,15] The incidence is high in paediatric patients, ranging from 13 to 20%. Initial treatment involves a reduction in immunosuppression, or chemotherapy with rituximab.[3,15]

The induction of immune tolerance remains the ultimate goal in lung transplantation.[1,14]

Combined *heart-lung* transplants have also been performed, see under Heart Transplantation, p. 1934.2.

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Pancreatic transplantation. Transplantation of the pancreas may be considered in some diabetic patients. In the vast majority of cases, pancreatic grafts have been transplanted with a kidney (simultaneous pancreas-kidney or SPK) in patients with end-stage diabetic nephropathy, which has produced better graft survival than transplanting the pancreas alone.[1-3] However, pancreas transplants after renal allografting (PAK), or solitary pancreatic transplantation (PTA), are becoming more common,[3] and approaching comparable survival rates.[2,4] Advances in surgical and preservation techniques, and new immunosuppressants, have helped to improve survival.[1] Overall patient survival has been estimated to be about 98% at 1 year, with graft survival of about 78%.[5]

The pancreas is a highly immunogenic organ, so extensive **immunosuppression** is required. Standard treatment often consists of quadruple therapy.[2,6,7] Induction therapy is followed by maintenance therapy with a calcineurin inhibitor (ciclosporin or tacrolimus), corticosteroids, and azathioprine or mycophenolate mofetil.[2,7,8] Induction therapy reduces rejection rates, and may allow for corticosteroid withdrawal, but patient or graft survival is not altered.[6,7] The use of induction therapy varies between centres,[9] and may be dependent on the type of pancreatic transplant.[10] The interleukin-2 receptor antibodies basiliximab and daclizumab are increasingly favoured. Rabbit antilymphocyte immunoglobulins are also used, but the use of muromonab-CD3 has declined.[7] Alemtuzumab is under investigation.[5]

Tacrolimus is usually preferred to ciclosporin[2-4,6-8,10] as it appears to allow for rapid tapering or even complete withdrawal of corticosteroids, causes less rejection, and may increase graft survival and reduce the risk of pancreatic thrombosis. Mycophenolate mofetil is now preferred to azathioprine,[2,6,7,9,10] as it decreases rejection rates, although patient and graft survival rates are comparable.[6,7,10] Early withdrawal of corticosteroids appears to be safe and feasible in pancreatic transplantation,[6,7] without an increase in rejection rates; patients may, however, require slightly higher doses of calcineurin inhibitors, which increases the risk of nephrotoxicity.[7] Although the precise role of sirolimus in pancreatic transplantation has yet to be defined, it may be used with a low-dose calcineurin inhibitor, thus mitigating renal dysfunction,[2] or as a substitute for an antimetabolite,[7,10] or as the chief drug in a calcineurin inhibitor-free maintenance protocol, or for episodes of rejection.[7] Sirolimus used with tacrolimus may allow for rapid withdrawal of corticosteroids.[10]

Episodes of rejection are treated with corticosteroids or antilymphocyte immunoglobulins.[2,7] Conversion to tacrolimus from ciclosporin is used, and for those patients on tacrolimus, sirolimus has been tried.[2]

Pancreatic transplantation facilitates normal carbohydrate metabolism and has the potential to improve patient survival and reduce the incidence of diabetic nephropathy. However, there has been concern over the long-term **complications** of immunosuppression,[11] and whether islet-cell autoantibodies might produce diabetes in the transplanted graft (although this is certainly not inevitable with adequate immunosuppression).[12] The incidence of hyperglycaemia induced by immunosuppressive regimens after transplantation appears to be less in pancreatic transplants than in recipients of other organs.[5] Explanations for the absence of a higher diabetogenic effect of tacrolimus after pancreatic transplantation compared with other solid organ transplants may include a more cautious dose of tacrolimus in diabetic patients, the use of tacrolimus with corticosteroid-free protocols, and the use of pancreatic grafts from young donors who may be more resistant to a diabetogenic effect.[10]

One possible alternative to complete pancreatic transplantation is an **islet-cell** graft. These have rarely been successful,[1,13] with insulin independence at 1 year[3] only in about 10% of cases. However, the use of carefully prepared islet cells from more than one donor and a modified immunosuppressant protocol[14] has produced greatly improved results. In this 'Edmonton Protocol', corticosteroids were completely avoided because of diabetogenic effects. Induction therapy with daclizumab was used, followed by maintenance with sirolimus and low-dose tacrolimus.[14] Short-term follow-up data indicated that patients with unstable type I diabetes benefited in terms of glucose control from islet transplantation.[15] Reported insulin independence was 80% at 1 year after use of the 'Edmonton protocol'[16] and 10% at 5 years post-transplant.[17] Thus, engrafting an adequate beta-cell mass appears to be the critical factor for transplant success.[9] Insulin independence has been reported with single organs from cadaveric donors.[18] Further study of the 'Edmonton protocol' confirmed that islet-cell transplantation may successfully restore endogenous insulin production and glycaemic stability in patients with type I diabetes mellitus. Insulin independence is gradually lost again in most cases, but persistent islet function without insulin independence confers benefit in terms of glycaemic control, provided the patient can tolerate the immunosuppressive regimen. Islet transplantation may be best for highly selected patients with severe hypoglycaemia or labile type I diabetes mellitus, provided all other attempts to stabilise glycaemic control have been tried. For patients seeking long-term insulin independence, whole pancreas transplantation is a better option at present.[19] See also under Management of Diabetes Mellitus, p. 459.1.

The induction of tolerance,[3,5,11,20] the possibility of neogenesis of beta cells from pancreatic stem or precursor cells,[11,20,21] less toxic immunosuppressive therapy, and enhanced islet engraftment[19] remain focuses of investigation in islet transplantation.

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Renal disorders

Corticosteroids and immunosuppressants are commonly used in the treatment of glomerular kidney disease (p. 1604.3).

Rheumatoid arthritis

Disease-modifying antirheumatic drugs (DMARDs) including immunosuppressants may be given to patients with rheumatoid arthritis (p. 13.2) in an attempt to modify the course of the disease. Ciclosporin appears to be effective, but adverse effects have been a problem. The use of low-dose regimens may help to minimise nephrotoxicity. Use of ciclosporin with methotrexate has produced clinical improvement in patients who had only partial responses to methotrexate alone, but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy. Tacrolimus is licensed in some countries for use in refractory rheumatoid arthritis.

Azathioprine has been used, with beneficial short-term effects, but is reported to be no more effective than other DMARDs and significantly more toxic; it may however be useful with prednisone in rheumatoid vasculitis. Mycophenolate mofetil may be effective in rheumatoid arthritis, but further studies are needed.

References.

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2. Kitahara K, Kawai S. Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. *Curr Opin Rheumatol* 2007; **19:** 238–45.

Sarcoidosis

Where drug therapy is required for sarcoidosis (p. 1612.2), corticosteroids are the usual treatment. In patients in whom these are ineffective or poorly tolerated, immunosuppressants have been given, with variable results.

Scleroderma

The term scleroderma has been used for both systemic sclerosis, an uncommon multisystem disease characterised by collagen proliferation and fibrosis throughout the body, and for localised fibrotic changes of the skin (morphea) which rarely progresses to involve other organs. In systemic sclerosis, Raynaud's syndrome secondary to vascular involvement usually precedes skin changes; oedema is followed by thickening and tightening of the skin of hands and face, and sometimes limbs and trunk, before progressing to atrophy and contractures. Cutaneous changes may be limited or take a more aggressive diffuse form. Decreased gastrointestinal motility, dysphagia and gastro-oesophageal reflux, arthritis, muscle weakness, and cardiac involvement may occur. Among the most serious potential symptoms, which may result in death, are pulmonary disease and renal failure with malignant hypertension.[1-8]

Many treatments have been tried for localised scleroderma.[4,5] Symptomatic therapies include emollients and topical and systemic antipruritics. Topical, intralesional, and systemic corticosteroids may be useful, especially in early inflammatory stages. Other treatments include topical and systemic vitamin D analogues, topical tacrolimus, and imiquimod cream. Oral therapies used include ciclosporin, colchicine, hydroxychloroquine, interferon gamma, penicillamine, phenytoin, and methotrexate. Phototherapy with UV light, with or without psoralens, has also been reported to be of benefit.

There is a paucity of adequately controlled studies for systemic scleroderma; no treatment has been clearly shown to affect the progression of the disease, and much management is essentially symptomatic. Immunosuppres-

sants are probably appropriate in the early oedematous stages of diffuse scleroderma.[1,6,9,10] Antilymphocyte immunoglobulins have been tried as an induction therapy in early stages of the disease.[9] Ciclosporin has been found to be beneficial, both for skin and visceral manifestations, but its use has been limited by nephrotoxicity and hypertension.[1,3,9,11,12] Tacrolimus has also been tried, though again adverse effects limit its benefit.[9,11,12] Mycophenolate mofetil has been tried after antilymphocyte immunoglobulins with reports of significant skin improvement.[12] Cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilise pulmonary function, and increase survival, especially in early disease, in some studies,[7] but a meta-analysis[13] considered that there was no evidence of a clinically significant improvement in lung function in patients with interstitial lung disease caused by systemic sclerosis. Other novel immunosuppressive strategies include bone marrow ablation followed by peripheral blood stem cell transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1),[1,3,5,9,10] photopheresis with a psoralen, and the induction of oral tolerance with native bovine type I collagen.[9] Rituximab is under investigation.[10,12]

Penicillamine has been widely used as an antifibrotic drug, but with variable effects. Observational studies have reported improvements in skin, renal, cardiac, and pulmonary symptoms;[14] however, others have found that usual doses of penicillamine were no more effective than lower doses,[1,9,15] and it is considered by some to be no more effective than placebo.[5] Interferons alfa and gamma have also produced variable results;[5,9] the latter is under investigation for pulmonary fibrosis.[3] Some other drugs have been investigated for their antifibrotic properties, including halofuginone, minocycline and relaxin.[9,15] There is some evidence that oxidative stress is involved in the pathogenesis of scleroderma, so antoxidants like probucol may also be useful.[9] Other drugs that have been investigated include imatinib,[10] potassium aminobenzoate, and thymopentin.

Many patients will require therapy for organ-specific symptoms.

- *Skin* flexibility may be maintained by emollients,[16] and systemic antihistamines can relieve itching, an early feature of diffuse cutaneous scleroderma.[9] Methotrexate has been used with some benefit.[1,3,5,7,9,15]
- Most progress has been made in the management of *vascular* symptoms. ACE inhibitors are considered to be the standard treatment for patients with renal ischaemia,[3,5,6,17] although some 30% of patients will still eventually require renal replacement therapy.[9] For patients who develop pulmonary arterial hypertension the prostaglandins epoprostenol, iloprost, or treprostinil may be given intravenously;[1,3,5,6,9] some have also been investigated subcutaneously[6] or by inhalation.[3,5,6] Sildenafil, bosentan or ambrisentan are also used.[3,5-7,10,18] There is some evidence that epoprostenol and bosentan may be associated with improved survival as well as symptomatic improvement.[3]
  Treatment of Raynaud's syndrome (see under Vasospastic Arterial Disorders, p. 1275.3) unresponsive to nonpharmacological therapy involves the use of calcium-channel blockers such as nifedipine or diltiazem.[1,3,16] Topical nitrates have been used, and intravenous epoprostenol or iloprost are used in acute attacks.[1,3,6,9] Oral iloprost has been tried with variable results.[6] Bosentan can prevent the development of new digital ulcers but may not speed the healing of existing ones.[3] Calcitonin gene-related peptide is being investigated as an alternative to iloprost.[1] Because elevated levels of serotonin have been found in patients with Raynaud's phenomenon, SSRIs and ketanserin have been used.[1] Atorvastatin[6] and sildenafil[10,17] have been reported to be helpful. Dietary supplementation with antoxidant vitamins, fish oils, and evening primrose oil has been of anecdotal benefit.[1,9,19] Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome.[6,19]
  Cardiac involvement may be underdiagnosed;[9] ACE inhibitors or digoxin may be used.[1]
- *Lung* fibrosis is usually treated with cyclophosphamide,[1,3,5,9,20] with or without a corticosteroid such as prednisolone. There is no evidence for corticosteroids alone in lung scleroderma, and high dose may precipitate scleroderma renal crisis, leading to irreversible renal failure.[7] As mentioned above, interferon gamma is under investigation.
- In patients with *gastrointestinal* disease, proton pump inhibitors such as omeprazole, sometimes with prokinetic drugs, are extremely effective for oesophageal involvement, and broad spectrum antibacterials are helpful for small bowel bacterial overgrowth.[1,8,9]

NSAIDs and corticosteroids must be used with care in scleroderma because of the risk of exacerbating renal and other problems.[1,9]

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17. Moore SC, Hermes DeSantis ER. Treatment of complications associated with systemic sclerosis. *Am J Health-Syst Pharm* 2008; **65:** 315–21.
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20. Tashkin DP, *et al.* Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354:** 2655–66.

Skin and connective tissue disorders

Immunosuppressants are used in various skin and connective tissue disorders, including Behçet's syndrome (p. 1601.1), eczema (p. 1684.1), pemphigus and pemphigoid (p. 1687.1), polymyositis (p. 1611.1), psoriasis (p. 1688.1), SLE (p. 1613.3), and the various vasculitic syndromes (p. 1615.2). See also Scleroderma, p. 1938.3.

Antilymphocyte Immunoglobulins

Inmunoglobulinas antilinfocitarias; Иммуноглобулины Антилимфоцитарные.

ATC — L04AA03 (antilymphocyte immunoglobulin, horse); L04AA04 (antilymphocyte immunoglobulin, rabbit).

ATC Vet — QL04AA03 (antilymphocyte immunoglobulin, horse); QL04AA04 (antithymocyte immunoglobulin, rabbit).

UNII — 475247QF1Z (equine thymocyte immunoglobulin); D7RD81HE4W (lapine thymocyte immunoglobulin).

Description. Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes produced by the purification of sera from appropriately immunised animals. The term antilymphocyte immunoglobulin (ALG; lymphocyte immune globulin) implies a product raised against all lymphocyte subsets. The term antithymocyte immunoglobulin (antithymocyte gammaglobulin; antithymocyte globulin; ATG) implies specificity for T-cells (thymus lymphocytes or thymocytes). However, in practice the nomenclature does not seem to be used consistently, and both terms tend to be used for antibodies raised against T-cells. Nomenclature normally includes an indication of the animal source of the immunoglobulin e.g. antithymocyte immunoglobulin (horse), or antithymocyte immunoglobulin (rabbit).

In addition to the purified immunoglobulins the native sera (antilymphocyte serum and antithymocyte serum, sometimes referred to as lymphocytic antiserum and thymitic antiserum) have also been used as immunosuppressants.

Pharmacopoeias. *Eur.* (see p. vii) includes an anti-T lymphocyte immunoglobulin.

Ph. Eur. 8: (Anti-T Lymphocyte Immunoglobulin for Human Use, Animal; Immunoglobulinum Anti-T Lymphocytorum ex Animale ad Usum Humanum). A sterile liquid or freeze-dried preparation containing immunoglobulins, obtained from serum or plasma of animals, mainly rabbits or horses, immunised with human lymphocytic antigens. It has the property of diminishing the number and function of immunocompetent cells, in particular T-lymphocytes. It contains principally immunoglobulin G, and may contain antibodies against other lymphocyte subpopulations and against other cells. It is intended for intravenous administration, after dilution with a suitable diluent where applicable. It may contain excipients such as stabilisers. Protect from light.

Uses and Administration

Antilymphocyte immunoglobulins are antibodies, raised in *animals*, which act against lymphocytes, and in particular against T-cells, to produce suppression of cell-mediated immunity.

They may be added to existing immunosuppressant regimens to treat acute rejection episodes in patients who have undergone organ or tissue transplantation. Alternatively, they may be given prophylactically as part of a combination immunosuppressant regimen with several other agents. For discussion of the role of antilymphocyte immunoglobulins in transplantation, see p. 1932.2 *et seq.*

Antilymphocyte immunoglobulins are also used in the treatment of aplastic anaemia (p. 1121.3) in patients unsuitable for bone marrow transplantation, and have been tried in other immunological disorders. They are under investigation for the treatment of myelodysplastic syndromes (p. 694.3). The dose used in **transplantation** depends on the indication and the combination of immunosuppressants used and may vary between countries.

In the UK, *rabbit* antilymphocyte immunoglobulin is used at the following doses for:

- prophylaxis of rejection after heart transplantation: 1 to 2.5 mg/kg daily for 3 to 5 days
- prophylaxis of rejection after kidney transplantation: 1 to 1.5 mg/kg daily for 3 to 9 days
- treatment of corticosteroid-resistant renal graft rejection: 1.5 mg/kg daily for 7 to 14 days

In the USA, *rabbit* antilymphocyte immunoglobulin is used at the following dose for:

- treatment of acute renal graft rejection: 1.5 mg/kg daily for 7 to 14 days

The *rabbit* product is diluted in sodium chloride 0.9% or glucose 5% (usually using 50 mL per vial, to obtain a total volume ranging from 50 to 500 mL), and given by intravenous infusion using a 0.22 micrometre in-line filter, into a vein with rapid blood flow. The first dose is given over at least 6 hours, and over at least 4 hours on subsequent occasions.

In the USA and Canada, *horse* antilymphocyte immunoglobulin is used at the following doses for:

- prophylaxis of renal graft rejection: 15 mg/kg daily for 14 days, then every other day for 14 days, to a total of 21 doses in 28 days; the first dose is given within 24 hours before or after the transplant
- treatment of renal graft rejection: 10 to 15 mg/kg daily for 14 days; additional alternate-day therapy, up to a total of 21 doses, can be given

For the treatment of **aplastic anaemia**, the recommended dose of *horse* antilymphocyte immunoglobulin is 10 to 20 mg/kg daily for 8 to 14 days; additional alternate-day therapy, up to a total of 21 doses, can be given.

The *horse* product is diluted in an appropriate infusion solution (including sodium chloride 0.9% or glucose 5% plus sodium chloride at either 0.225% or 0.45%); the final concentration should not exceed 4 mg/mL. The infusion is given over at least 4 hours, via an in-line filter (0.2 to 1 micrometre), into a vein with rapid blood flow. A skin sensitivity test is recommended before the first infusion, see Adverse Effects, Treatment, and Precautions, p. 1940.2.

For children's doses, see Administration in Children, below.

Administration in children. Although data in children are limited, licensed product information in the USA states that doses of *horse* antilymphocyte immunoglobulin for renal graft rejection in paediatric **transplantation** patients have ranged from 5 to 25 mg/kg daily. The children's dose for *rabbit* antilymphocyte immunoglobulin is the same as for adults, see above.

For **aplastic anaemia**, doses of *horse* antilymphocyte immunoglobulin have also been comparable to those used in adults, see above.

Aplastic anaemia. The British Committee for Standards in Haematology (BCSH) issued an alert[1] in July 2011 to haematologists concerning the unexpectedly low response rate and survival seen in a study[2] of aplastic anaemia patients treated with *rabbit* antilymphocyte immunoglobulin for the first course of immunosuppressive therapy. In 2007, the *horse* product had been withdrawn in the UK and replaced by the rabbit product, which had previously been used for a second course of therapy in patients who had relapsed or were refractory to a first course of horse antilymphocyte immunoglobulin. The European Blood and Marrow Transplant Severe Aplastic Anaemia Working Party (EBMT SAAWP) requested that the horse antilymphocyte immunoglobulin be made available in Europe,

and offered the following guidance, supported by the BCSH:

- *horse* antilymphocyte immunoglobulin is recommended as first-line immunosuppressive therapy for aplastic anaemia patients ineligible for HLA-identical sibling haematopoietic stem cell transplantation (HSCT)
- if *horse* antilymphocyte immunoglobulin is unavailable, treatment with the *rabbit* product may be considered. The EBMT SAAWP recommended a lower intravenous dose, of 2.5 mg/kg daily for 5 days (instead of 3.75 mg/kg for 5 days) until more data were available, and that the *rabbit* product only be used in experienced centres
- alternative first-line options include ciclosporin monotherapy; data with alemtuzumab as first-line therapy in aplastic anaemia are limited
- early unrelated donor HSCT using fludarabine-based conditioning regimens may also be an option, and may be considered as first-line treatment in children

1. Marsh J, *et al.* Guidance from the BCSH Aplastic Anaemia Writing Committee relating to recent prospective studies of rabbit antithymocyte globulin (ATG) used for a first course of immunosuppressive therapy (IST) in aplastic anaemia (issued July 2011). Available at: http://www.bcshguidelines.com/documents/Use_of_rabbit_ATG_July_2011.pdf (accessed 14/07/11)
2. Scheinberg P, *et al.* Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. *N Engl J Med* 2011; **365:** 430–8.

Organ and tissue transplantation. The use of antilymphocyte immunoglobulins in organ and tissue transplantation has been reviewed.[1] Although antilymphocyte immunoglobulin products may be derived from various species, much of the experience in transplantation seems to be with a product of *rabbit* origin. In kidney transplantation (p. 1935.2), rabbit antilymphocyte immunoglobulin is considered effective for both prevention and treatment of acute graft rejection. It has been found to be more effective than the *horse* product in treating acute rejection and preventing recurrent rejection in adults; graft survival rates and the incidence of infection did not differ significantly. Induction therapy with rabbit antilymphocyte immunoglobulin has been used successfully in both adults[2,3] and paediatric[4,5] renal transplant recipients. In children, the incidence of acute rejection was lower in rabbit immunoglobulin recipients than in those given the horse product;[6] however, rates of Epstein-Barr virus (EBV) infection were higher with the rabbit product. Patient and graft survival rates, incidence of chronic rejection, EBV lymphoma, or other infection did not differ significantly between the 2 groups.

In adult renal transplant recipients considered to be at high risk for acute rejection or delayed graft function, induction with rabbit antilymphocyte immunoglobulin reduced the incidence and severity of acute rejection (but not the incidence of delayed graft function) compared with basiliximab induction. Patients receiving antilymphocyte immunoglobulin had a greater incidence of infection but a lower incidence of CMV disease; patient and graft survival were similar in the 2 groups after 1 year.[7] After 5 years, the antilymphocyte immunoglobulin group was found to have a lower incidence of acute rejection, and of the combined end-point of acute rejection, graft loss, and death; rates of CMV infection also remained lower in this group.[8]

Induction therapy with antilymphocyte immunoglobulins has also been shown to be beneficial in other solid organ transplants, with lower rates of rejection reported in liver (p. 1936.3), pancreas (p. 1938.1), kidney-pancreas, heart (p. 1934.2), and heart-lung transplantation. Use in lung transplantation remains controversial due to a higher incidence of CMV infection.[9] Induction protocols differ between institutions.

In haematopoietic stem cell transplant recipients (p. 1933.1), those given rabbit antilymphocyte immunoglobulin before a matched unrelated donor (MUD) transplant had comparable outcomes to those given matched related donor (MRD) transplants but no antilymphocyte immunoglobulin; the authors supposed that the use of antilymphocyte immunoglobulin caused MUD recipients to behave clinically like MRD recipients.[10] A review of the use of antilymphocyte immunoglobulins in haematopoietic stem cell transplantation concluded that it significantly reduces the severity and incidence of acute graft-versus-host disease (GVHD) and chronic GVHD. This protective effect is dependent on the dose, the timing of infusion, and the brand used. However, antilymphocyte immunoglobulin induction therapy delays immune reconstitution and there is an increased risk of infection; the use of an antilymphocyte immunoglobulin is a risk factor for EBV reactivation.[11]

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Adverse Effects, Treatment, and Precautions

Common adverse effects of *rabbit* and *horse* antilymphocyte immunoglobulins include fever, chills, myalgia, arthralgia, and skin reactions including rash, pruritus, and urticaria. Premedication with antihistamines and/or corticosteroids may prevent or reduce the intensity of adverse effects. Leucopenia and thrombocytopenia are also common. Although usually transient, dose adjustment may be needed if they become severe or prolonged. Platelet infusions may be needed in aplastic anaemia patients. Other common effects are gastrointestinal disturbances, headache, dyspnoea, hypotension, and pain. Hypertension, tachycardia, oedema, dizziness, malaise, and weakness can also occur. Infusion site reactions include pain, swelling, or redness; thrombophlebitis can be avoided by infusion into a vein with rapid blood flow.

As with other immunosuppressive drugs, infection (including CMV), reactivation of infection, and secondary malignancies (including lymphoma and post-transplant lymphoproliferative disease) have been reported.

Manifestations of serum sickness can occur, especially in aplastic anaemia patients; prophylaxis or treatment with corticosteroids may decrease the frequency of this reaction. Anaphylaxis is uncommon but serious; fatalities have been reported. The infusion should be stopped immediately and the patient managed accordingly (see p. 1293.2).

Aside from anaphylaxis, other serious immune-mediated reactions have been reported with ***rabbit*** antilymphocyte immunoglobulins including acute infusion-associated reactions, which have been attributed to the release of cytokines and can be fatal; premedication and reducing the infusion rate may minimise reaction incidence and intensity, and the first dose should be infused over a minimum of 6 hours into a vein with rapid blood flow. Hyperkalaemia has also been reported with the *rabbit* product.

To identify those at risk of anaphylaxis with ***horse*** antilymphocyte immunoglobulin, a skin sensitivity test is recommended before the first infusion, although the predictive value of this test is clinically unproven and reactions can occur after a negative test. However, if the test is positive, alternative therapy should be considered. Respiratory distress may indicate an anaphylactoid reaction, in which case the infusion should be stopped.

Other adverse effects that can occur with the *horse* product commonly include stomatitis, chest and/or back pain, and night sweats. Arteriovenous fistulas may clot. Fulminant haemolysis has been reported rarely; erythrocyte transfusion and appropriate treatment may be necessary, and the infusion stopped if haemolysis is severe or unremitting. Other adverse effects include laryngospasm, lymphadenopathy, paraesthesia, bradycardia, myocarditis, congestive heart failure, hepatosplenomegaly, seizures, toxic epidermal necrolysis, and wound dehiscence. Iliac vein obstruction, renal artery or deep-vein thrombosis, abnormal renal and/or liver function tests, acute renal failure, and proteinuria can also occur. A burning sensation in the soles or palms, soreness of the mouth or throat, and abnormal involuntary movements, tremor, or rigidity have also been reported.

Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should generally be avoided for the same reason.

For the suggestion that use of *rabbit* rather than *horse* antilymphocyte immunoglobulins in the treatment of aplastic anaemia may be associated with reduced survival, and precautions for such use, see under Uses and Administration, p. 1939.3.

Effects on the kidneys. Acute renal failure has been reported after the use of antilymphocyte immunoglobulins.[1,2] Prolonged anuria requiring haemodialysis has occurred.[2]

1. Levine JM, *et al.* Antithymocyte globulin-induced acute renal failure. *Am J Kidney Dis* 1999; **34:** 1155.
2. Barakat RK, *et al.* Prolonged renal failure secondary to antithymocyte globulin treatment in severe aplastic anemia. *Ann Pharmacother* 2007; **41:** 895–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies *rabbit* antilymphocyte immunoglobulin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. *Horse* antilymphocyte immunoglobulin is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Linfoglobulina†; Timoglobulina; ***Austral.***: Atgam; ***Austria***: Thymoglobuline; ***Belg.***: ATG; Thymoglobuline; ***Braz.***: Thymoglobuline; ***Canad.***: Atgam; Thymoglobulin; ***Chile***: Linfoglobulina†; Thymogam; Timoglobulina; ***China***: ATG (抗人T); Thymoglobuline (即复宁); ***Cz.***: ATG; Thymoglobuline; ***Denm.***: Thymoglobuline; ***Fin.***: Thymoglobuline; ***Fr.***: Lymphoglobuline†; Thymoglobuline; ***Ger.***: Thymoglobulin; ***Gr.***: ATG; Lymphoglobuline; Thymoglobuline; ***Hong Kong***: ATG; Atgam; Thymoglobuline; ***Hung.***: ATG; Thymoglobulin; ***India***: Atgam; Lymphoglobuline; Thymoglobuline; ***Irl.***: ATG; Thymoglobulin; ***Israel***: ATG; Lymphoglobuline†; Thymoglobuline; ***Ital.***: Thymoglobuline; ***Jpn***: Thymoglobuline; ***Malaysia***: Atgam; Thymoglobuline; ***Mex.***: Atgam; Tecelac†; ***Neth.***: ATG; Lymphoglobuline†; Thymoglobuline; ***Norw.***: Thymoglobuline; ***NZ***: Atgam; ***Philipp.***: Thymogam; Thymoglobuline; ***Pol.***: ATG; Lymphoglobuline†; Tecelac†; Thymoglobuline; ***Port.***: Timoglobulina; ***Rus.***: Antilipholine (Антилимфолин); ATG (АТГ); Atgam (Атгам); Thymoglobulin (Тимоглобулин); ***S.Afr.***: Atgam†; Lymphoglobuline†; Thymoglobuline†; ***Singapore***: ATG; Atgam; Thymoglobuline; ***Spain***: Atege; Timoglobulina; ***Swed.***: ATG; Thymoglobuline; ***Switz.***: ATG; Lymphoglobuline†; Thymoglobuline; ***Thai.***: ATG; Thymoglobuline; ***Turk.***: ATG; Lymphoglobuline; Thymoglobuline; ***UK***: Thymoglobuline; ***Ukr.***: Atgam (Атгам)†; Thymoglobuline (Тимоглобулин)†; ***USA***: Atgam; ***Venez.***: Atgam.

Pharmacopoeial Preparations

Ph. Eur.: Anti-T Lymphocyte Immunoglobulin for Human Use, Animal.

Azathioprine *(BAN, USAN, rINN)*

Atsatiopriini; Azathioprin; Azathioprinum; Azatioprin; Azatioprina; Azatioprinas; Azatiopryna; BW-57322; NSC-39084; Азатиоприн.

6-(1-Methyl-4-nitroimidazol-5-ylthio)purine.

$C_9H_7N_7O_2S$=277.3

CAS — 446-86-6.

ATC — L04AX01.

ATC Vet — QL04AX01.

UNII — MRK240IY2L.

NOTE. The abbreviation AZT, which has sometimes been used for azathioprine, has also been used to denote the antiviral zidovudine.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8 (Azathioprine). A pale yellow powder. Practically insoluble in water and in alcohol; soluble in dilute solutions of alkali hydroxides; sparingly soluble in dilute mineral acids. Protect from light.

USP 36: (Azathioprine). A pale yellow, odourless powder. Insoluble in water; very slightly soluble in alcohol and in chloroform; sparingly soluble in dilute mineral acids; soluble in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Uses and Administration

Azathioprine is an immunosuppressive antimetabolite with similar actions to those of mercaptopurine (p. 820.3), to which it is converted in the body. Its effects may not be seen for several weeks after a dose. It is given orally, but where this is not feasible it may be given by slow intravenous injection or by infusion as azathioprine sodium. If given by infusion, the required dose should be diluted to a concentration of 0.25 to 2.5 mg/mL in sodium chloride 0.9% or glucose 5%, and infused over 30 to 60 minutes.

Azathioprine is mainly used as an immunosuppressant for the prevention of rejection in **organ and tissue transplantation** (p. 1932.2). The dose for this purpose, given orally or intravenously, varies from 1 to 5 mg/kg daily and depends partly on the regimen used; the higher doses are used initially, adjusted according to clinical response and haematological tolerance.

Azathioprine is also used in diseases with an **autoimmune or inflammatory** component, see below. The usual dose of azathioprine, given orally or intravenously, in these conditions is in the range of 1 to 3 mg/kg daily. If no improvement is seen after 3 to 6 months, therapy may be stopped.

For doses in children, see Administration in Children, p. 1941.1.

Use of azathioprine with a corticosteroid (p. 1597.3) may have a corticosteroid-sparing effect.

Blood counts should be carried out regularly during treatment and azathioprine withdrawn or the dosage reduced at the first indication of bone-marrow depression. Measurement of thiopurine methyltransferase (TPMT) activity may be used to identify patients at risk of haematological toxicity, although this cannot substitute for blood count monitoring.

Administration in children. UK licensed product information for azathioprine allows for the same doses in children as those used in adults (see Uses and Administration, p. 1940.3), both in organ and tissue transplantation and for diseases with an auto-immune or inflammatory component. The *BNFC* recommends that children aged 1 month to 18 years be given an oral or intravenous maintenance dose of 1 to 3 mg/kg once daily for suppression of **transplant rejection**; alternatively, the total daily dose may be given in 2 divided doses. For **severe ulcerative colitis and Crohn's disease**, the *BNFC* states that azathioprine may be given to children aged 2 to 18 years in an oral dose of 2 mg/kg (if necessary increased up to 2.5 mg/kg) once daily. For diseases with an **auto-immune** component such as SLE and vasculitis, the *BNFC* advises that azathioprine is usually used when corticosteroids alone are ineffective; children from 1 month to 18 years of age are given oral azathioprine in similar doses to those used in adults.

Administration in hepatic or renal impairment. UK licensed product information states that controlled studies have not supported the suggestion that toxicity of azathioprine might be enhanced in the presence of renal impairment. Nevertheless, doses used should be at the lower end of the normal range, and haematological response should be carefully monitored. US licensed product information also recommends low doses, while stating that relatively oliguric patients, especially those with tubular necrosis in the immediate post-cadaveric transplant period, may have delayed clearance of azathioprine and/or its metabolites.

UK licensed product information states that the metabolism of azathioprine may be impaired in patients with hepatic dysfunction; regular blood counts and liver function tests should be performed and the dosage of azathioprine reduced if hepatic or haematological toxicity occurs.

Blood disorders. Immunosuppressants such as azathioprine are occasionally tried in auto-immune haemolytic anaemia (p. 1122.2) refractory to other treatment and may permit reduction of corticosteroid dosage. Similarly in patients with immune thrombocytopenia (p. 1606.1), azathioprine may be tried as a second-line treatment option. Azathioprine with a corticosteroid has been tried in the rare condition of acquired haemophilia (p. 1126.3).

Cogan's syndrome. Azathioprine has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p. 1603.2).

Connective tissue and muscular disorders. Azathioprine is one of many drugs tried for disease control in Behçet's syndrome[1] (p. 1601.1) and SLE[2] (p. 1613.3). In polymyositis (p. 1611.1), combined therapy with azathioprine and a corticosteroid has been found to be better than a corticosteroid alone for maintenance long-term.[3] However, there is also some evidence that methotrexate may be more effective in refractory polymyositis than azathioprine.[4]

1. Yazici H, *et al.* A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990; **322:** 281–5.
2. Abu-Shakra M, Shoenfeld Y. Azathioprine therapy for patients with systemic lupus erythematosus. *Lupus* 2001; **10:** 152–3.
3. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. *Arthritis Rheum* 1981; **24:** 45–8.
4. Joffe MM, *et al.* Drug therapy of the idiopathic inflammatory myopathies; predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. *Am J Med* 1993; **94:** 379–87.

Inflammatory bowel disease. Azathioprine, or its metabolite mercaptopurine, is used to induce remission in chronically active inflammatory bowel disease (p. 1808.3), and to maintain remission, particularly in Crohn's disease.[1-3] They have a useful corticosteroid-sparing effect. Azathioprine may also be useful as a postoperative maintenance treatment in Crohn's disease.[4] In patients with ulcerative colitis, azathioprine may be an effective maintenance therapy for those who are refractory to or intolerant of mesalazine or sulfasalazine; it may also be useful for patients who require repeated courses of corticosteroids.[5]

Continuation of azathioprine therapy beyond 4 years has had conflicting results in terms of relapse rates and flare incidence. A randomised study in patients with Crohn's disease and in clinical remission, having been treated with azathioprine for at least 42 months, found that relapse rates were higher in those patients continued on placebo compared with those continued on azathioprine.[6] In another study of patients with corticosteroid-dependent Crohn's disease, a breakthrough of symptoms during continuous therapy was common, particularly after 48 months on azathioprine.[7] In an analysis of 1176 patients with inflammatory bowel disease, the authors concluded that stopping azathioprine therapy may be considered after 3 to 4 years in Crohn's disease patients in complete remission and without corticosteroid requirements but that continuation appears beneficial in all other Crohn's disease patients and for patients with ulcerative colitis.[8]

The onset of benefit from oral azathioprine may be delayed for several months.[1] One study[9] reported that a more rapid response could be achieved with an intravenous loading dose but a later study failed to confirm this.[10]

1. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 14/07/10).
2. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 06/10/09).
3. Fraser AG, *et al.* The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50:** 485–9.
4. Myrelid P, *et al.* Azathioprine as a postoperative prophylaxis reduces symptoms in aggressive Crohn's disease. *Scand J Gastroenterol* 2006; **41:** 1190–5.
5. Timmer A, *et al.* Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
6. Lémann M, *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128:** 1812–18.
7. Chebli JM, *et al.* Long-term results with azathioprine therapy in patients with corticosteroid-dependent Crohn's disease: open-label prospective study. *J Gastroenterol Hepatol* 2007; **22:** 268–74.
8. Holtmann MH, *et al.* Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006; **51:** 1516–24.
9. Sandborn WJ, *et al.* An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology* 1995; **109:** 1808–17.
10. Sandborn WJ, *et al.* Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease: North American Azathioprine Study Group. *Gastroenterology* 1999; **117:** 527–35.

Leprosy. For mention of the use of azathioprine as a corticosteroid-sparing agent in the management of type 1 lepra reactions, see p. 188.3.

Liver disorders. Azathioprine has been widely used with corticosteroids to produce and maintain remission of chronic active hepatitis (p. 1602.3); such combination therapy, which also permits a reduction in corticosteroid dosage, is generally thought to be more effective than azathioprine alone. Patients successfully maintained in remission for at least a year on azathioprine with a corticosteroid can subsequently be maintained on azathioprine (at a dose of 2 mg/kg daily) alone.[1] Results in patients with primary biliary cirrhosis (p. 2638.3) have been more equivocal, and initial studies did not indicate much benefit from azathioprine, although a later study did seem to indicate improved survival and disease retardation.[2]

1. Johnson PJ, *et al.* Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995; **333:** 958–63.
2. Christensen E, *et al.* Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: final results of an international trial. *Gastroenterology* 1985; **89:** 1084–91.

Lung disorders. Corticosteroids remain the mainstay of treatment for the various forms of interstitial lung disease (p. 1607.1). In idiopathic pulmonary fibrosis there is weak evidence that combined therapy with azathioprine has some benefits,[1] but expert collaborative guidelines have suggested[2] that although prednisolone with azathioprine (in a dose of 2 to 3 mg/kg daily, up to a maximum of 150 mg daily) was previously recommended, this regimen should now only be considered when combined with oral acetylcysteine, and the regimen should be regarded as experimental pending further evidence.

1. Raghu G, *et al.* Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; **144:** 291–6.
2. Wells AU, *et al.* Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; **63** (suppl 5): v1–v58. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/DPLD/Guidelines/Thorax%20Sept%2008.pdf (accessed 12/01/10)

Neuromuscular disorders. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for myasthenia gravis (p. 684.1). It may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient. Azathioprine is not usually used alone because it may be several months before any beneficial effect is seen. Some studies have also indicated modest benefit from azathioprine in patients with multiple sclerosis (p. 996.3). It has been suggested that the benefits are too slight to justify the toxicity of the required doses, but it has also been pointed out that in terms of relapse reduction azathioprine appears as effective as newer treatments such as interferon beta. For a recommendation that the cumulative dose of azathioprine should not exceed 600 g, see under Carcinogenicity, p. 1942.1.

Ocular disorders. For mention of the use of azathioprine in various disorders characterised by ocular lesions such as scleritis or uveitis, see p. 1932.1.

Polymyalgia rheumatica. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for polymyalgia rheumatica (p. 1610.3) and in whom withdrawal is difficult.

Psoriatic arthritis. Azathioprine may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p. 14.3) when the arthritis is not controlled by physical therapy and NSAIDs.

Retroperitoneal fibrosis. There are reports[1,2] of success with azathioprine and corticosteroids in the treatment of retroperitoneal fibrosis (p. 1612.1).

1. Moroni G, *et al.* Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches. *Nephrol Dial Transplant* 2006; **21:** 2485–90.
2. Kisiel B, *et al.* Idiopathic retroperitoneal fibrosis: case report. *Pol Arch Med Wewn* 2009; **119:** 677–8.

Rheumatoid arthritis. Although azathioprine may be beneficial in rheumatoid arthritis (p. 13.2) in the short-term, its toxicity is significantly more severe than other disease-modifying antirheumatic drugs (DMARDs).[1] It may, however, be useful in patients with severe disease unresponsive to other DMARDs especially in those with extra-articular manifestations such as vasculitis.[2]

1. Suarez-Almazor ME, *et al.* Azathioprine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).
2. Heurkens AHM, *et al.* Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991; **151:** 2249–54.

Sarcoidosis. Cytotoxic immunosuppressants such as azathioprine have been tried in patients with sarcoidosis (p. 1612.2) who do not respond to or cannot tolerate corticosteroids.

Skin disorders. Like other immunosuppressants, azathioprine has been tried in various refractory skin disorders, notably in pemphigus and pemphigoid[1,2] (see p. 1942.1). Other conditions in which it has been tried include atopic eczema,[3-8] nodular prurigo,[9] chronic actinic dermatitis,[3,6] pyoderma gangrenosum,[4] erythema multiforme,[4,10] pompholyx, and plaque psoriasis,[6] as well as in the skin manifestations of systemic disorders such as dermatomyositis and lupus erythematosus.[2] Guidelines for the use of azathioprine in dermatology have been developed.[1] The recommended dose for azathioprine in dermatological disorders is 1 to 3 mg/kg daily, adjusted according to response. Treatment should be withdrawn if no response is seen within 3 months. Azathioprine should not be used in dermatology patients with very low or absent thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, p. 1943.2), due to the danger of prolonged and severe myelosuppression (see Effects on the Blood, p. 1942.2). If azathioprine is given to patients with low TPMT activity, doses of 0.5 to 1 mg/kg daily should be used, with monitoring for myelosuppression. Patients with normal to high TPMT activity should be started on doses at the higher end of the range of 1 to 3 mg/kg daily; in those who do not respond, and have not had adverse effects, doses above this range may be considered for a trial period.

1. Anstey AV, *et al.* British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004; **151:** 1123–32. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Azathioprine.pdf (accessed 15/01/08)
2. Patel AA, *et al.* Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol* 2006; **55:** 369–89.
3. YoungerIR, *et al.* Azathioprine in dermatology. *J Am Acad Dermatol* 1991; **25:** 281–6.
4. Tan BB, *et al.* Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* 1997; **136:** 351–5.
5. Lear JT, *et al.* A retrospective review of the use of azathioprine in severe atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 47): 38.
6. Scerri L. Azathioprine in dermatological practice: an overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv Exp Med Biol* 1999; **455:** 343–8.
7. Murphy L-A, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147:** 308–15.
8. Meggitt SJ, *et al.* Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367:** 839–46.
9. Lear JT, *et al.* Nodular prurigo responsive to azathioprine. *Br J Dermatol* 1996; **134:** 1151.
10. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p. 1687.1). Other immunosuppressants may be added to maintain disease control and allow a reduction in corticosteroid dosage, and azathioprine is commonly used in this way in pemphigus vulgaris.[1] There is limited evidence to suggest that azathioprine may also be effective as monotherapy to induce remission in mild pemphigus.[1] Azathioprine has been used similarly in bullous pemphigoid, but there is some disagreement about its efficacy,[2] and guidelines suggest that it should only be considered if the corticosteroid cannot be reduced to an acceptable dose.[3]

1. Harman KE, *et al*. British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Pemphigus%20Vulgaris.pdf (accessed 15/01/08)
2. Walsh SRA, *et al*. Bullous pemphigoid: from bench to bedside. *Drugs* 2005; **65:** 905–26.
3. Wojnarowska F, *et al*. British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bullous%20Pemphigoid.pdf (accessed 15/01/08)

Vasculitic syndromes. Azathioprine has been tried in vasculitic syndromes, including giant cell arteritis (p. 1604.2), microscopic polyangiitis (p. 1610.2), Churg-Strauss syndrome (p. 1603.1), Takayasu's arteritis (p. 1614.3), and Wegener's granulomatosis (p. 1615.2). In general it is most useful in maintenance for its corticosteroid-sparing effect. Cyclophosphamide tends to be preferred where a more aggressive regimen is required, as in some combinations for induction of remission.

Adverse Effects

Dose-related bone-marrow depression is common with use of azathioprine; this may be manifested as leucopenia or, less often, thrombocytopenia or anaemia, and rarely, as agranulocytosis, pancytopenia, or aplastic anaemia. Myelosuppression is generally reversible, and may occasionally be delayed. Macrocytic, including megaloblastic, anaemia has occurred. Patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) may be at increased risk of myelotoxicity. Azathioprine has also been associated with the development of liver damage; it has been suggested that cholestatic symptoms may be due to the mercaptopurine moiety. Rarely, delayed and potentially fatal veno-occlusive liver disease has occurred.

Other adverse effects associated with azathioprine include gastrointestinal disturbances, reversible alopecia, and symptoms including rashes, muscle and joint pains, fever, rigors, pneumonitis, pancreatitis, tachycardia, renal dysfunction, and hypotension, some or all of which may represent hypersensitivity reactions. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely.

Solutions for injection are irritant.

References.

1. Lawson DH, *et al*. Adverse effects of azathioprine. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 161–71.

Carcinogenicity. Immunosuppression, including that with azathioprine, may be associated with an increased risk of certain neoplasms such as lymphomas and skin cancers in transplant recipients,[1] in patients with inflammatory bowel disease,[2-4] and in patients with rheumatoid arthritis.[5-7] Partly because of lower doses of immunosuppressants used in inflammatory bowel disease, the risk of lymphoma in these patients appears to be less than that associated with transplant recipients.[8] The hazard ratio in patients with inflammatory bowel disease treated with a thiopurine such as azathioprine has been estimated at just over 5 times that in patients who did not receive thiopurines;[4] however, the absolute cumulative risk over 10 years in young patients remained below 1% and was not considered to alter the positive risk-benefit ratio of such treatment. Rheumatic diseases may themselves be associated with an increased risk of malignancy that is independent of treatment, but one study[6] concluded that there is a further risk related to the duration of exposure to immunosuppressive drugs, including azathioprine. A recent systematic review[9] of the use of azathioprine for multiple sclerosis concluded that, when the balance between the benefits and harms were considered, azathioprine was a reasonable alternative to interferon beta in patients who frequently relapse and require corticosteroids. Other evidence in the literature suggested that the long-term risk of malignancy may be related to use for longer than 10 years and a cumulative dose above 600 g and the reviewers recommended that this dose should not be exceeded. Others have suggested an increased risk at cumulative doses in excess of 140 g; it was also suggested that the development of unexpected cytopenias in patients stabilised on long-term therapy may be a sign of increased risk of myelodysplasia or leukaemia.[10]

Skin cancer may be a particular risk in immunosuppressed patients with a history of high sun exposure.[8] Azathioprine treatment has been reported to cause photosensitisation of skin to UVA light, which could contribute to the development of skin cancers;[11] limiting exposure to UV light and use of sunscreens is recommended during azathioprine treatment.

1. Kinlen LJ, *et al*. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 1979; **2:** 1461–6.
2. Kandiel A, *et al*. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54:** 1121–5.
3. Kwon JH, Farrell RJ. The risk of lymphoma in the treatment of inflammatory bowel disease with immunosuppressive agents. *Crit Rev Oncol Hematol* 2005; **56:** 169–78.
4. Beaugerie L, *et al*. CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; **374:** 1617–25.
5. Silman AJ, *et al*. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. *Ann Rheum Dis* 1988; **47:** 988–92.
6. Asten P, *et al*. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; **26:** 1705–14.
7. Patel P, *et al*. Azathioprine induced Hodgkin lymphoma: a case report and review of literature. *Am J Clin Oncol* 2005; **28:** 427–8.
8. Boyle J, *etal*. Cancer, warts, and sunshine in renal transplant patients: a case-control study. *Lancet* 1984; **i:** 702–5.
9. Casetta I, *et al*. Azathioprine for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
10. Kwong Y-L. Azathioprine: association with therapy-related myelodysplastic syndrome and acute myeloid leukemia. *J Rheumatol* 2010; **37:** 485–90.
11. Perrett CM, *et al*. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. *Br J Dermatol* 2008; **159:** 198–204.

Effects on the blood. Neutropenia in patients receiving mercaptopurine has been reported to correlate negatively with the concentration of the metabolite tioguanine nucleotide in erythrocytes,[1] and it has been suggested that measurement of metabolite concentrations in erythrocytes,[2] or activity of the enzyme thiopurine methyltransferase (TPMT),[3-6] permits prediction of those individuals likely to develop severe bone-marrow toxicity with mercaptopurine and the related drugs tioguanine and azathioprine. However, not all studies have found such correlations,[7] and effects on the bone marrow with this class of drugs are probably multifactorial;[8,9] low activity of other enzymes such as lymphocyte 5-nucleotidase,[10] and other factors, may contribute to toxicity. A review[9] of studies investigating TPMT activity in patients with Crohn's disease concluded that measurement of TPMT activity on starting azathioprine has a role in identifying those at risk of severe myelosuppression. Lower TPMT activities correlate with low neutrophil counts in the initial 4 months of thiopurine therapy; identification of the heterozygote might allow for safer management (see Therapeutic Drug Monitoring, p. 1943.2). However, in those patients established on therapy, TPMT did not predict clinical response or toxicity. Life-threatening myelotoxicity developed in a patient with normal TPMT activity who was treated with azathioprine for atopic eczema; myelosuppression was initially undetected despite a profound decrease in blood counts within the first 2 weeks of treatment.[11]

For the suggestion that unexpected cytopenias may be a warning sign of future malignant transformation see Carcinogenicity, above.

Pure red cell aplasia occurs rarely with use of azathioprine; reported cases have all been in renal transplant recipients. In one such case,[12] reduction of the dose and use of erythropoietin was ineffective; however, the patient recovered within weeks of stopping azathioprine.

1. Lennard L, *et al*. Childhood leukaemia: a relationship between intracellular 6-mercaptopurine metabolites and neutropenia. *Br J Clin Pharmacol* 1983; **16:** 359–63.
2. Maddocks JL, *et al*. Azathioprine and severe bone marrow depression. *Lancet* 1986; **i:** 156.
3. Schütz E, *et al*. Azathioprine-induced myelosuppression in thiopurine methyltransferase deficient heart transplant recipient. *Lancet* 1993; **341:** 436.
4. Lennard L, *et al*. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993; **69:** 577–9.
5. Jackson AP, *et al*. Thiopurine methyltransferase levels should be measured before commencing patients on azathioprine. *Br J Dermatol* 1997; **136:** 133–4.
6. Black AJ, *etal*. Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. *Ann Intern Med* 1998; **129:** 716–18.
7. Boulieu R, *et al*. Intracellular thiopurine nucleotides and azathioprine myelotoxicity in organ transplant patients. *Br J Clin Pharmacol* 1997; **43:** 116–18.
8. Soria-Royer C, *et al*. Thiopurine-methyl-transferase activity to assess azathioprine myelotoxicity in renal transplant recipients. *Lancet* 1993; **341:** 1593–4.
9. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002; **51:** 143–6.
10. Kerstens PJSM, *et al*. 5-Nucleotidase and azathioprine-related bone-marrow toxicity. *Lancet* 1993; **342:** 1245–6.
11. Wee JS, *et al*. Life threatening myelotoxicity secondary to azathioprine in a patient with atopic eczema and normal thiopurine methyltransferase activity. *BMJ* 2011; **342:** d1417.
12. Agrawal A, *et al*. Azathioprine-induced pure red cell aplasia: case report and review. *Transplant Proc* 2004; **36:** 2689–91.

Effects on the liver. A review[1] of drug-related hepatotoxicity noted that azathioprine has been associated with hepatocanalicular cholestasis, in which the interference with bile flow is combined with hepatocyte damage, and with several hepatic vascular disorders, including focal sinusoidal dilatation, peliosis, and veno-occlusive disease. A later review[2] grouped reported cases into three syndromes: hypersensitivity, idiosyncratic cholestatic reaction, and presumed endothelial cell injury, with the imidazole and 6-mercaptopurine components of azathioprine playing different roles in pathogenesis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Romagnuolo J, *et al*. Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. *Can J Gastroenterol* 1998; **12:** 479–83.

Hypersensitivity. In 2 of 5 renal transplant recipients with acute allergic reactions associated with azathioprine, the symptoms (interstitial nephritis) were initially mistaken for acute rejection episodes.[1] In another report,[2] shock, fever, and acute renal insufficiency in a patient led to an initial mistaken diagnosis of sepsis, and it was recommended that a hypersensitivity reaction be considered as a cause if any of these symptoms occurred within 4 weeks of azathioprine ingestion. Other reported features of hypersensitivity include malaise, gastrointestinal disturbances, myalgia, arthralgia, fever, headache and raised liver enzymes.[3,4] Skin lesions have been reported, with maculopapular erythema occurring most frequently; purpura, urticaria, and erythema nodosum-like lesions have also been described.[4,5] Skin biopsies often showed features of leucocytoclastic vasculitis.[4] Sweet syndrome (acute febrile neutrophilic dermatosis)[6,7] and Stevens-Johnson syndrome[5] have also been reported. In some cases, skin patch testing for azathioprine was negative;[3,5] a drug-induced lymphocyte stimulation test (which evaluates the antigen specific reactivity of lymphocytes by measuring the proliferation of peripheral blood lymphocytes exposed to the suspected drug) has been proposed as a sensitive and reliable test for azathioprine hypersensitivity.[5]

Indirect hypersensitivity has also been reported; allergic contact dermatitis occurred on the genitals of a man whose wife had been taking azathioprine. During her treatment, vaginal secretions were noted to be yellow, indicating secretion of the drug or its metabolites. The husband, but not the wife, reacted to azathioprine patch tests.[8]

1. Parnham AP, *et al*. Acute allergic reactions associated with azathioprine. *Lancet* 1996; **348:** 542–3.
2. Fields CL, *et al*. Hypersensitivity reaction to azathioprine. *South Med J* 1998; **91:** 471–4.
3. Hinrichs R, *et al*. Azathioprine hypersensitivity in a patient with peripheral demyelinating polyneuropathy. *Br J Dermatol* 2003; **148:** 1076–7.
4. Sinico RA, *et al*. Azathioprine hypersensitivity: report of two cases and review of the literature. *J Nephrol* 2003; **16:** 272–6.
5. Mori H, *et al*. Drug eruption caused by azathioprine: value of using the drug-induced lymphocytes stimulation test for diagnosis. *J Dermatol* 2004; **31:** 731–6.
6. el-Azhary RA, *et al*. Sweet syndrome as a manifestation of azathioprine hypersensitivity. *Mayo Clin Proc* 2008; **83:** 1026–30.
7. Yiasemides E, Thom G. Azathioprine hypersensitivity presenting as a neutrophilic dermatosis in a man with ulcerative colitis. *Australas J Dermatol* 2009; **50:** 48–51.
8. Cooper HL, *et al*. A case of conjugal azathioprine-induced contact hypersensitivity. *N Engl J Med* 2008; **359:** 1524–6.

Precautions

Regular monitoring of blood counts is required. Patients with renal or hepatic impairment require more frequent monitoring of blood counts and may need reduced doses; liver function tests should be performed in hepatic impairment. Consideration should be given to testing patients for thiopurine methyltransferase (TPMT) activity. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Azathioprine should generally be avoided in pregnancy (see p. 1943.1).

For a recommendation that the cumulative dose of azathioprine should not exceed 600 g in patients with multiple sclerosis, see under Carcinogenicity, above.

Breast feeding. Low concentrations of mercaptopurine have been found in human colostrum and breast milk of patients taking azathioprine.[1] Breast feeding by these patients has not been recommended because of the potential risk of immunosuppression in the infant.[1-3] However, there are reports[1,2] of 3 breast-fed infants, whose mothers had been taking doses of 75 or 100 mg of azathioprine daily, in whom no evidence of immunosuppression was found. All 3 had normal blood counts, no increase in infections, and above average growth rate. In one case, the levels of mercaptopurine were determined at 2 days and after 2 weeks of breast feeding,[1] and in the other 2 cases, no levels were determined.[2] In a third report, 31 breast-milk samples were collected from 10 breast-feeding

women (taking from 75 to 150mg azathioprine daily);[3] low concentrations of mercaptopurine were only detected in one case. The neonates were followed for up to 28 days, and showed no signs of immunosuppression, nor were mercaptopurine and tioguanine nucleotides detectable in their red blood cells. The authors concluded that breast feeding should not be withheld in infants of mothers receiving azathioprine. However, they cautioned that there were no data on the effect of thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, below) on metabolite concentrations in breast milk, and expressed concern as to whether a TPMT-deficient infant, unable to inactivate mercaptopurine absorbed into the breast milk, will be exposed to significant blood levels of the drug. In a study of 4 mothers and their infants,[4] all of whom had the wild-type TPMT genotype (with normal TPMT activity), infant exposure to azathioprine through breast milk was undetectable. The authors also cautioned that mothers taking higher doses or those with decreased TPMT activity might transfer more drug to the infant. It has been noted[5] that many breast-fed infants would have already been exposed to potentially much higher concentrations of mercaptopurine *in utero*.

A study[6] evaluating the long-term development of children exposed to thiopurines during pregnancy and breast feeding, found that none of the 9 children who were breast fed had any differences in development compared with 21 formula-fed children; no adverse effects on development or immune function were seen in any children due to *in utero* exposure.

1. Coulam CB, *et al*. Breast-feeding after renal transplantation. *Transplant Proc* 1982; **14:** 605–9.
2. Grekas DM, *et al*. Immunosuppressive therapy and breast-feeding after renal transplantation. *Nephron* 1984; **37:** 68.
3. Sau A, *et al*. Azathioprine and breastfeeding—is it safe? *Br J Obstet Gynaecol* 2007; **114:** 498–501.
4. Gardiner SJ, *et al*. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006; **62:** 453–6.
5. Moretti ME, *et al*. Breast-feeding during maternal use of azathioprine. *Ann Pharmacother* 2006; **40:** 2269–72.
6. de Meij TG, *et al*. The Dutch Initiative on Crohn and Colitis. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38:** 38–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azathioprine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pregnancy. Azathioprine and/or its metabolites have been found in low concentrations in fetal blood after maternal use of azathioprine.[1] Azathioprine is teratogenic in *animals*, and congenital abnormalities, chromosomal aberrations,[2] fetal growth retardation,[3,4] low birth-weight, and spontaneous abortion have been reported in the offspring of pregnant women taking azathioprine. Neonatal leucopenia and thrombocytopenia have also been reported after maternal exposure.[5] Cohort studies have found an increased risk of congenital abnormalities, perinatal mortality, and preterm births after maternal or paternal exposure to azathioprine.[6,7] However, adverse birth outcomes may be related to the underlying disease rather than use of azathioprine or mercaptopurine,[8] and some consider its use in inflammatory bowel disease to be safe and not associated with an increased risk of congenital malformations.[9-11] There was no effect on long-term development or immune function in a 6 year follow-up of children exposed *in utero*.[11] A meta-analysis[12] of studies in inflammatory bowel disease also found no increase in congenital malformations with thiopurines, but noted a higher risk of preterm birth.

The UK Teratology Information Service[13] considers that the data suggests azathioprine and mercaptopurine are safe in pregnancy, with no overall increased risk of an adverse pregnancy outcome. Although premature delivery and intra-uterine growth abnormalities have been reported following thiopurine use in pregnancy, the severity of maternal conditions and frequent use of multiple medications makes it difficult to attribute these outcomes to maternal use of thiopurines. It also noted that there were theoretical concerns about the effect maternal immunosuppression with thiopurines might have on the development of the neonatal immune system.

1. de Boer NKH, *et al*. Azathioprine use during pregnancy: unexpected intrauterine exposure to metabolites. *Am J Gastroenterol* 2006; **101:** 1390–2.
2. The Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. *Br J Obstet Gynaecol* 1980; **87:** 839–45.
3. Pirson Y, *et al*. Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; **313:** 328.
4. Hou S. Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; **313:** 328.
5. Davison JM, *et al*. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. *Br J Obstet Gynaecol* 1985; **92:** 233–9.
6. Nørgård B, *et al*. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. *Aliment Pharmacol Ther* 2003; **17:** 827–34.
7. Nørgård B, *et al*. The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; **19:** 679–85.
8. Langagergaard V, *et al*. Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; **25:** 73–81.
9. Alstead EM, *et al*. Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology* 1990; **99:** 443–6.
10. Coelho J, *et al*. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011; **60:** 198–203.
11. de Meij TG, *et al*. The Dutch Initiative on Crohn and Colitis. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38:** 38–43.
12. Akbari M, *et al*. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19:** 15–22.
13. UK Teratology Information Service. Use of azathioprine/6-mercaptopurine in pregnancy (issued December 2010). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Azathioprine%202010.pdf (accessed 30/05/13)

Interactions

The effects of azathioprine are enhanced by allopurinol and the dose of azathioprine should be reduced to one-third to one-quarter of the usual dose when allopurinol is given. A further dose reduction or alternative therapy should be considered in those patients with low or absent thiopurine methyltransferase (TPMT) activity.

In addition to being affected by allopurinol, azathioprine may itself affect other drugs including the following:

- competitive neuromuscular blockers (antagonism, see under Immunosuppressants on p. 2033.1)
- vaccines (reduced response or generalised infection, see p. 2375.3)
- warfarin (inhibition, see Immunosuppressants p. 1534.2).

Gastrointestinal drugs. For mention of *5-aminosalicylates* inhibiting the metabolism of thiopurines such as azathioprine, and increasing their toxicity, see Mercaptopurine, p. 822.1.

Mercaptopurine. The Institute for Safe Medication Practices in the USA reported a case in which a patient with a history of Crohn's disease was prescribed azathioprine and mercaptopurine by separate practitioners. The patient developed profound myelosuppression, severe sepsis, and died. Many drug information software programs were found to not warn of this possible therapeutic duplication.[1]

1. Institute for Safe Medication Practices. Duplication with azathioprine and mercaptopurine (issued 29 June, 2006). Available at: http://www.ismp.org/Newsletters/acutecare/articles/20060629_3.asp?ptr=y (accessed 15/01/08)

Pharmacokinetics

Azathioprine is well absorbed from the gastrointestinal tract when given orally. After oral or intravenous doses it disappears rapidly from the circulation and is extensively metabolised to mercaptopurine (which is then further metabolised—see p. 822.1). Both azathioprine and mercaptopurine are about 30% bound to plasma proteins. About 10% of a dose of azathioprine is reported to be split between the sulfur and the purine ring to give 1-methyl-4-nitro-5-thioimidazole. The proportion of different metabolites is reported to vary between patients. Metabolites and small amounts of unchanged azathioprine and mercaptopurine are eliminated in the urine. Azathioprine is distributed into breast milk in low concentrations.

Therapeutic drug monitoring. Although plasma concentrations of 6-thiouric acid (the inactive product of mercaptopurine, and hence of azathioprine) can be readily measured in patients who have been receiving azathioprine, they are of little value in therapeutic drug monitoring.[1] The active moieties are the tioguanine nucleotides (6-TGN) formed intracellularly, which appear to have extremely long half-lives,[2] and mean erythrocyte concentrations of which appear to vary considerably between individuals.[2] The formation of other inactive metabolites is catalysed by thiopurine methyltransferase (TPMT) and its activity is genetically determined, with a trimodal distribution in the general population; 0.3% have low activity of TPMT, 11% have intermediate activity, and 89% have normal or high activity. Patients with low or intermediate activity appear to shift metabolism toward production of 6-TGN.

Because excess concentrations of 6-TGN have been associated with leucopenia, it has been suggested[3] that:

- patients with normal or high TPMT activity receive standard doses of azathioprine or mercaptopurine
- those with intermediate TPMT activity have reduced doses
- those with low activity not be treated with either drug

However, these recommendations remain controversial.[4] Haematological toxicity is not always explained by TPMT status, and other factors may be involved[5] (see also Effects on the Blood, p. 1942.2). Some consider that TPMT deficiency is not a contra-indication to thiopurine therapy; an initial dose reduction to 10 to 15% of the standard azathioprine dose has been used in TPMT-deficient patients with inflammatory bowel disease.[5] There are a proportion of patients in whom TPMT activity is very high; these patients appear to respond less well to standard doses, and higher-than-standard doses have been recommended.[6] While recommendations for pretreatment measurement of TPMT status remain controversial,[4,5] some consider the avoidance of potentially fatal toxicity a compelling argument for TPMT assessment before thiopurine therapy is started;[6] although becoming more common in the UK, there may be differences between medical specialties in the frequency with which testing is used.[7] However, TPMT units and normal ranges vary between laboratories depending on the methodology used,[6] and TPMT genotype or phenotype testing is not a surrogate for monitoring of complete blood counts.[4]

Because low concentrations of erythrocyte 6-TGN have been associated with disease relapse in lymphomas and leukaemias, a small study[8] of patients with inflammatory bowel disease attempted to define a therapeutic window of drug efficacy. Without monitoring TPMT genotype, treatment efficacy was found to correlate with erythrocyte 6-TGN levels. It was concluded that patients who remain symptomatic despite apparently therapeutic 6-TGN concentrations should be treated with adjunctive or alternative immunosuppression or surgery. However, a large study[9] did not confirm disease correlation with 6-TGN concentrations, and concluded that therapeutic drug monitoring of 6-TGN may be premature. It was noted that methodological differences, such as assay technique, existed between their study and others. As the role of routine monitoring of 6-TGN remains controversial,[4,10,11] it has been suggested that selective monitoring, such as in those with low or intermediate TPMT activity, be considered.[3] Some consider the measurement of 6-TGN useful to assess treatment compliance, or in cases of malabsorption.[4]

1. Chan GLC, *et al*. Pharmacokinetics of 6-thiouric acid and 6-mercaptopurine in renal allograft recipients after oral administration of azathioprine. *Eur J Clin Pharmacol* 1989; **36:** 265–71.
2. Chan GLC, *et al*. Azathioprine metabolism: pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. *J Clin Pharmacol* 1990; **30:** 358–63.
3. Sandborn WJ. Rational dosing of azathioprine and 6-mercaptopurine. *Gut* 2001; **48:** 591–2.
4. Lichtenstein GR. Use of laboratory testing to guide 6-mercaptopurine/azathioprine therapy. *Gastroenterology* 2004; **127:** 1558–64.
5. Teml A, *et al*. Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. *Clin Pharmacokinet* 2007; **46:** 187–208.
6. Sanderson J, *et al*. Thiopurine methyltransferase: should it be measured before commencing thiopurine drug therapy? *Ann Clin Biochem* 2004; **41:** 294–302.
7. Anonymous. TPMT testing before azathioprine therapy? *Drug Ther Bull* 2009; **47:** 9–12.
8. Cuffari C, *et al*. Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut* 2001; **48:** 642–6.
9. Lowry PW, *et al*. Measurement of thiopurine methyltransferase activity and azathioprine metabolites in patients with inflammatory bowel disease. *Gut* 2001; **49:** 665–70.
10. Dubinsky MC. Monitoring of AZA/6-MP treatment in children with IBD is necessary. *Inflamm Bowel Dis* 2003; **9:** 386–8.
11. Griffiths AM. Monitoring of azathioprine/6-mercaptopurine treatment in children with IBD is not necessary. *Inflamm Bowel Dis* 2003; **9:** 389–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Imuran; ***Austral.***: Azahexal†; Azamun; Azapin; Imuran; Thioprine; ***Austria***: Azaglax†; Immunoprin; Imurek; ***Belg.***: Imuran; ***Braz.***: Imunen; Imuran; ***Canad.***: Imuran; ***Chile***: Imuran; ***China***: Imuran (依木兰); ***Cz.***: Azaprine; Immunoprin; Imuran; ***Denm.***: Azathiodura; Azathioregio; Immunoprin; Imurel; ***Fin.***: Azamun; Imurel; ***Fr.***: Imurel; ***Ger.***: Aza-Q†; Azafalk; Azaimun; Colinsan†; Imurek; Zytrim†; ***Gr.***: Azapress; Imuran; ***Hong Kong***: Imuprin; Imuran; ***Hung.***: Imuran; ***India***: Azap; Azimune; Azoprine; Azoran; Imuran; Imuzat; Transimune; ***Indon.***: Imuran; ***Irl.***: Imuger; Imuran; ***Israel***: Azopi; Imuran; ***Ital.***: Azafor; Immunoprin; ***Malaysia***: Azamun; Imuran; ***Mex.***: Azatrilem; Imuran; ***Neth.***: Azafalk; Immunoprin; Imuran; ***Norw.***: Imurel; ***NZ***: Azamun; Imuprine; Imuran; Thioprine†; ***Philipp.***: Imuran; ***Pol.***: Imuran; ***Port.***: Imuran; ***Rus.***: Imuran (Имуран); ***S.Afr.***: Azamun; Azapress; Imuran; Zaprine; ***Singapore***: Azafrine; Imuran; ***Spain***: Imurel; ***Swed.***: Immunoprin; Imurel; ***Switz.***: Azaimun; Azarek; Imurek; ***Thai.***: Azadus; Imuprin; Imuran; Zinothin; ***Turk.***: Imuran; ***UK***: Imuran; ***USA***: Azasan; Imuran; ***Venez.***: Azaprin.

Multi-ingredient Preparations. ***Ger.***: Azamedac.

Pharmacopoeial Preparations
BP 2014: Azathioprine Oral Suspension; Azathioprine Tablets; **USP 36:** Azathioprine Oral Suspension; Azathioprine Sodium for Injection; Azathioprine Tablets.

Basiliximab *(BAN, USAN, rINN)*

Basiliksimab; Basiliksimabi; Basiliximabum; chRFT5; SDZ-CHI-621; Базиликсимаб.

Immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), disulfide with human-mouse monoclonal CHI621 light chain, dimer.

CAS — 179045-86-4.
ATC — L04AC02.
ATC Vet — QL04AC02.
UNII — 9927MT646M.

Uses and Administration

Basiliximab is a chimeric murine/human monoclonal antibody similar to daclizumab (p. 1957.1) that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection episodes in patients undergoing renal transplantation, and is given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids; azathioprine or mycophenolate mofetil may also be added to the regimen. Doses are given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes. The recommended dose for adults is 20 mg, given within 2 hours before transplant surgery and repeated once after 4 days. (For children's doses, see Administration in Children, below). The second dose should be withheld if graft loss or a severe hypersensitivity reaction occurs.

Administration in children. Licensed product information recommends the following intravenous doses of basiliximab in children over 1 year of age, for prophylaxis of acute rejection in allogeneic renal transplantation, as part of an immunosuppressive regimen containing ciclosporin and corticosteroids:

- body-weight under 35 kg: 10 mg within 2 hours before transplantation surgery; 10 mg 4 days after surgery
- body-weight 35 kg or more: 20 mg within 2 hours before transplantation surgery; 20 mg 4 days after surgery (same as adults, see Uses and Administration, above)

Doses may be given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes.

Organ and tissue transplantation. Basiliximab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p. 1935.2), including paediatric renal transplant recipients; it is usually given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. A small study found that basiliximab significantly reduced the occurrence of rejection episodes in those treated with dual therapy (calcineurin inhibitor and corticosteroids) but not in those given triple therapy (including mycophenolate).[1] In a study of paediatric renal transplant recipients, addition of basiliximab to a tacrolimus-based regimen was safe, but did not result in a lower incidence of rejection episodes.[2] There is some suggestion that antilymphocyte immunoglobulins may be more effective than basiliximab in reduction of acute rejection in adult renal transplant patients,[3,4] although some consider basiliximab to offer improved clinical efficacy over antilymphocyte immunoglobulin induction in paediatric patients,[5] and others have commented[6] that graft survival at 12 months has been similar with each drug. Reviews[7-9] have concluded that the use of basiliximab in renal transplantation is safe and effective, with reduced rates of acute rejection, but no long-term benefit in terms of graft survival; basiliximab appears to allow the safe withdrawal of corticosteroids or the use of corticosteroid-free immunosuppressive regimens.

There is a short report suggesting that the use of a single dose is as effective as the standard 2-dose regimen in renal transplantation in terms of the incidence of acute rejection.[10]

Basiliximab has also been investigated in liver transplantation (p. 1936.3). Given with dual therapy to adult patients, it was found to reduce the incidence of acute rejection episodes in the first year when compared with placebo, including patients positive for hepatitis C.[11] Basiliximab with dual therapy also reduced the incidence of acute graft rejection in small paediatric studies.[12,13] In paediatric liver transplantation, corticosteroid-free immunosuppressive regimens using basiliximab and tacrolimus have been associated with significantly lower rejection rates at 1 year than corticosteroid-based regimens.[14,15]

Basiliximab has been investigated for the prevention of rejection in heart,[16,17] lung,[18,19] and pancreatic transplantation (see p. 1934.2, p. 1937.3, and p. 1938.1, respectively). It has been reported to be effective[20] in the treatment of corticosteroid-refractory acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p. 1933.1).

1. Lee BM, *et al.* Effect o f basiliximab on renal allograft rejection within 1 year after transplantation. *Transplant Proc* 2006; **38:** 2025–8.
2. Grenda R, *et al.* A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006; **6:** 1666–72.
3. Heilman RL, *et al.* Acute rejection risk in kidney transplant recipients on steroid-avoidance immunosuppression receiving induction with either antithymocyte globulin or basiliximab. *Transplant Proc* 2006; **38:** 1307–13.
4. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355:** 1967–77.
5. Clark G, *et al.* Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 1304–9.
6. Josephson MA. Rabbit antithymocyte globulin or basiliximab for induction therapy? *N Engl J Med* 2006; **355:** 2033–5.
7. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs* 2003; **63:** 2803–35.
8. Boggi U, *et al.* A benefit-risk assessment of basiliximab in renal transplantation. *Drug Safety* 2004; **27:** 91–106.
9. McKeage K, McCormack PL. Basiliximab: a review of its use as induction therapy in renal transplantation. *BioDrugs* 2010; **24:** 55–76.
10. Baquero A, *et al.* Basiliximab: a comparative study between the use of the recommended two doses versus a single dose in living donor kidney transplantation. *Transplant Proc* 2006; **38:** 909–10.
11. Neuhaus P, *et al.* Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. *Liver Transpl* 2002; **8:** 132–42.
12. Ganschow R, *et al.* First experience with basiliximab in pediatric liver graft recipients. *Pediatr Transplant* 2001; **5:** 353–8.
13. Ganschow R, *et al.* Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant* 2005; **9:** 741–5.
14. Reding R, *et al.* Steroid-free liver transplantation in children. *Lancet* 2003; **362:** 2068–70.
15. Spada M, *et al.* Randomized trial of basiliximab induction versus steroid therapy in pediatric liver allograft recipients under tacrolimus immunosuppression. *Am J Transplant* 2006; **6:** 1913–21.
16. Segovia J, *et al.* A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. *Transplantation* 2006; **81:** 1542–8.
17. Mattei MF, *et al.* Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. *J Heart Lung Transplant* 2007; **26:** 693–9.
18. Hachem RR, *et al.* A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant* 2005; **24:** 1320–6.
19. Borro JM, *et al.* Comparative study of basiliximab treatment in lung transplantation. *Transplant Proc* 2005; **37:** 3996–8.
20. Funke VAM, *et al.* Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. *Bone Marrow Transplant* 2006; **37:** 961–5.

Skin disorders. There are a few case reports of successful treatment with basiliximab in psoriasis[1-4] (p. 1688.1), chronic atopic dermatitis[5] (see Eczema, p. 1684.1), lichen planus,[6] and epidermolysis bullosa acquisita[7] (p. 1684.3).

1. Salim A, *et al.* Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). *Br J Dermatol* 2000; **143:** 1121–2.
2. Mrowietz U, *et al.* Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. *Arch Dermatol* 2000; **136:** 675–6.
3. Owen CM, Harrison PV. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. *Clin Exp Dermatol* 2000; **25:** 195–7.
4. Bell HK, Parslew RAG. Use of basiliximab as a cyclosporin-sparing agent in palmoplantar pustular psoriasis with myalgia as an adverse effect. *Br J Dermatol* 2002; **147:** 606–7.
5. Kägi MK, Heyer G. Efficacy of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in a patient with severe chronic atopic dermatitis. *Br J Dermatol* 2001; **145:** 350–1.
6. Rebora A, *et al.* Basiliximab is effective for erosive lichen planus. *Arch Dermatol* 2002; **138:** 1100–1.
7. Haufs MG, Haneke E. Epidermolysis bullosa acquisita treated with basiliximab, an interleukin-2 receptor antibody. *Acta Derm Venereol (Stockh)* 2001; **81:** 72.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with basiliximab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, sneezing, hypotension, tachycardia, cardiac failure, wheezing, dyspnoea, bronchospasm, pulmonary oedema, and respiratory failure. Capillary leak syndrome and cytokine release syndrome have been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Patients in whom other immunosuppression was prematurely stopped, after initial therapy with basiliximab, appear to be at increased risk of hypersensitivity reactions. Therapy should be permanently stopped if a severe reaction occurs.

Giving basiliximab as a bolus may cause nausea, vomiting, and local reactions, including pain.

It is generally recommended that basiliximab is avoided during pregnancy or breast feeding; contraception is recommended before starting, during, and up to 4 months after treatment.

Effects on glucose tolerance. It has been suggested[1] that use of basiliximab in immunosuppressant regimens for kidney transplantation may be associated with the development of impaired glucose homoeostasis.

1. Aasebø W, *et al.* Impaired glucose homeostasis in renal transplant recipients receiving basiliximab. *Nephrol Dial Transplant* 2010; **25:** 1289–93.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies basiliximab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pharmacokinetics

Basiliximab has a terminal half-life of about 7 days in adults and about 9 days in children.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Simulect; ***Austral.***: Simulect; ***Belg.***: Simulect; ***Braz.***: Simulect; ***Canad.***: Simulect; ***Chile***: Simulect; ***China***: Simulect (舒莱); ***Cz.***: Simulect; ***Denm.***: Simulect; ***Fin.***: Simulect; ***Fr.***: Simulect; ***Ger.***: Simulect; ***Gr.***: Simulect; ***Hong Kong***: Simulect; ***Hung.***: Simulect; ***Indon.***: Simulect; ***Irl.***: Simulect; ***Israel***: Simulect; ***Ital.***: Simulect; ***Malaysia***: Simulect; ***Mex.***: Simulect; ***Neth.***: Simulect; ***Norw.***: Simulect; ***NZ***: Simulect; ***Philipp.***: Simulect; ***Pol.***: Simulect; ***Port.***: Simulect; ***Rus.***: Simulect (Симулект); ***S.Afr.***: Simulect; ***Singapore***: Simulect; ***Spain***: Simulect; ***Swed.***: Simulect; ***Switz.***: Simulect; ***Thai.***: Simulect; ***Turk.***: Simulect; ***UK***: Simulect; ***Ukr.***: Simulect (Симулект); ***USA***: Simulect; ***Venez.***: Simulect.

Belatacept *(USAN, rINN)*

Bélatacept; Belatacepte; Belataceptum; BMS-224818; LEA-29Y; Белатацепт.

CAS — 706808-37-9.
ATC — L04AA28.
ATC Vet — QL04AA28.
UNII — E3B2GI648A.

Uses and Administration

Belatacept is a derivative of abatacept (p. 15.2). It is a fusion protein and co-stimulation blocker that prevents T-cell activation. Belatacept is used for the prevention of organ rejection in adults undergoing kidney transplantation (p. 1935.2), and who are seropositive for the Epstein-Barr virus. It is used with basiliximab induction, mycophenolate mofetil, and corticosteroids.

Belatacept is reconstituted with a suitable diluent (sterile water for injection, sodium chloride 0.9%, or glucose 5%) using a silicone-free syringe. For intravenous infusion, it is further diluted in a suitable infusion fluid (sodium chloride 0.9% or glucose 5%) to a final concentration ranging from 2 mg/mL to 10 mg/mL (typically, 100 mL will be appropriate, although total infusion volumes range from 50 mL to 250 mL). Belatacept is infused over 30 minutes, via an infusion set with a non-pyrogenic, low-protein-binding filter (0.2 to 1.2 micrometres).

The total infusion dose of belatacept is based on the body-weight of the patient at the time of transplantation and should not be modified during the course of therapy, unless there is a change in body-weight of greater than 10%. The dosing for the *initial* phase is as follows:

- day 1 (day of transplantation, before implantation): 10 mg/kg
- day 5 (about 96 hours after day 1 dose): 10 mg/kg
- end of week 2 and week 4: 10 mg/kg
- end of week 8 and week 12: 10 mg/kg

Dosing in the *maintenance* phase is:

- end of week 16 and every 4 weeks (±3 days) thereafter: 5 mg/kg

The dose prescribed for the patient must be evenly divisible by 12.5 mg, in order for the dose to be prepared accurately using the reconstituted solution and the silicone-free syringe. *For example: if a patient weighs 64 kg, the dose at 10 mg/kg equals 640 mg; the closest dose divisible by 12.5 mg is 637.5 mg, which is then prescribed.*

References.

1. Vincenti F, *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; **353:** 770–81.
2. Emamaullee J, *et al.* Costimulatory blockade with belatacept in clinical and experimental transplantation - a review. *Expert Opin Biol Ther* 2009; **9:** 789–96.
3. Vincenti F, *et al.* A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010; **10:** 535–46.
4. Durrbach A, *et al.* A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transplant* 2010; **10:** 547–57.
5. Vincenti F, *et al.* Five-year safety and efficacy of belatacept in renal transplantation. *J Am Soc Nephrol* 2010; **21:** 1587–96.

6. Larsen CP, *et al*. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation* 2010; **90:** 1528–35.
7. Martin ST, *et al*. Belatacept: a novel biologic for maintenance immunosuppression after renal transplantation. *Pharmacotherapy* 2011; **31:** 394–407.
8. Vanrenterghem Y, *et al*. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). *Transplantation* 2011; **91:** 976–83.

Adverse Effects, Treatment, and Precautions

The most common adverse effects associated with belatacept are anaemia, leucopenia, gastrointestinal disturbances, urinary-tract infections, peripheral oedema, hypertension, fever, cough, headache, and hypokalaemia or hyperkalaemia.

Patients taking immunosuppressants are at increased risk for the development of secondary malignancies. Post-transplant lymphoproliferative disorder (PTLD), mainly involving the CNS, has been reported; the risk of PTLD was higher in patients who were seronegative for the Epstein-Barr virus (EBV), and these patients, or those whose EBV serostatus is unknown, should not be given belatacept. Other risk factors for PTLD include CMV infection and T-cell depleting therapy; CMV prophylaxis is recommended for at least 3 months after transplantation, and T-cell depleting therapy to treat acute rejection should be used with caution. Non-melanoma skin cancer has also been reported, and exposure to sunlight or UV light should be limited; the use of protective clothing and sunscreen is advised.

Serious, and potentially fatal, infections can occur with immunosuppressants, and antibacterial prophylaxis is recommended after transplantation. Progressive multifocal leukoencephalopathy, caused by the JC virus, has been reported rarely, especially at higher cumulative doses or more frequent dosing of belatacept. Cases of polyoma virus-associated nephropathy have also been reported.

Other adverse effects include electrolyte disturbances, increased creatinine, dyslipidaemia, dyspnoea, hypotension, dizziness, tremor, anxiety, insomnia, acne, alopecia, hyperhidrosis, arthralgia, musculoskeletal pain, haematoma, and lymphocele. Atrial fibrillation may occur. Renal and urinary disorders include haematuria, proteinuria, dysuria, renal tubular necrosis, renal impairment (including acute renal failure), urinary incontinence, and hydronephrosis.

Live vaccines should not be given with belatacept.

Interactions

For precations about the use of live vaccines with belatacept, see Adverse Effects, Treatment, and Precautions, above.

Pharmacokinetics

Belatacept is reported to have linear pharmacokinetics at usual dosages. Steady-state concentrations occur by week 8 in the initial phase after transplantation and by month 6 during the maintenance phase (see Uses and Administration, p. 1944.3). After repeated intravenous doses of 10 mg/kg and 5 mg/kg belatacept in renal transplant patients, its mean terminal half-life is about 9.8 days and about 8.2 days, respectively. There is a trend towards higher clearance of belatacept with increasing body-weight.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Nulojix; ***Fr.***: Nulojix; ***Ger.***: Nulojix; ***Irl.***: Nulojix; ***Israel***: Nulojix; ***Ital.***: Nulojix; ***Neth.***: Nulojix; ***Norw.***: Nulojix; ***Swed.***: Nulojix; ***Switz.***: Nulojix; ***UK***: Nulojix; ***USA***: Nulojix.

Belimumab *(USAN, rINN)*

Bélimumab; Belimumabum; Белимумаб.

Immunoglobulin G1, anti-(human cytokine BAFF) (human monoclonal LymphoStat-B heavy chain), disulfide with human monoclonal LymphoStat-B λ-chain, dimer.

CAS — 356547-88-1.
ATC — L04AA26.
ATC Vet — QL04AA26.
UNII — 73B0K5S26A.

NOTE. The name LymphoStat-B has been used as a trade mark for belimumab.

Uses and Administration

Belimumab is a human monoclonal antibody (p. 2561.1) that inhibits B-lymphocyte stimulator (BLyS; BAFF; TNFSF13B; a naturally occurring protein required for B lymphocyte development). Belimumab is used for the treatment of adults with active, autoantibody-positive SLE (p. 1613.3) who are receiving standard therapy. As experience is lacking, use is not recommended in patients with severe active lupus nephritis or severe active CNS disease. The recommended dose is 10 mg/kg intravenously every 2 weeks for the first 3 doses, and every 4 weeks thereafter. The dose is diluted in 250 mL of sodium chloride 0.9% and infused over 1 hour. Belimumab is under investigation for other auto-immune diseases such as rheumatoid arthritis.

References.
1. Ding C. Belimumab, an anti-BLyS human monoclonal antibody for potential treatment of inflammatory autoimmune diseases. *Expert Opin Biol Ther* 2008; **8:** 1805–14.
2. Wallace DJ, *et al*. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009; **61:** 1168–78.
3. Jacobi AM, *et al*. Effect of long-term belimumab treatment on B cells in systemic lupus erythematosus: extension of a phase II, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2010; **62:** 201–10.
4. Navarra SV, *et al*. BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; **377:** 721–31.
5. Thanou-Stavraki A, Sawalha AH. An update on belimumab for the treatment of lupus. *Biologics* 2011; **5:** 33–43.
6. Sanz I, *et al*. Belimumab. *Nat Rev Drug Discov* 2011; **10:** 335–6.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with belimumab are nausea, diarrhoea, fever, insomnia, pain in extremities, and migraine. Depression is common, and can be serious, especially in those with a history of depressive or psychiatric disorders; suicide has been reported, although it is unknown whether belimumab therapy is associated with an increased risk for suicidal behaviour.

Serious and sometimes fatal infections, including pneumonia, urinary-tract infections, cellulitis, and bronchitis, have been reported in patients treated with belimumab, and treatment should not be started in those with chronic infections; belimumab should be stopped if a patient develops an infection. Other common infections include upper respiratory-tract infection, nasopharyngitis, sinusitis, and influenza.

The signs and symptoms of hypersensitivity reactions and infusion reactions are similar, and these are common on the day of belimumab infusion, despite premedication. Manifestations include rash, urticaria, pruritus, hypotension, dyspnoea, angioedema, bradycardia, myalgia, and headache. Anaphylaxis has also been reported.

Secondary malignancies can occur after immunosuppressive treatment and malignancies including non-melanoma skin cancer have been reported rarely after belimumab treatment. Live vaccines should not be given with belimumab, or for 30 days before treatment.

Interactions

For precautions about the use of live vaccines with belimumab, see Adverse Effects, Treatment, and Precautions, above.

Pharmacokinetics

After intravenous use, serum belimumab concentrations decline in a bi-exponential manner, with a distribution half-life of about 40 hours and a terminal half-life of about 19 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Benlysta; ***Canad.***: Benlysta; ***Denm.***: Benlysta; ***Ger.***: Benlysta; ***Israel***: Benlysta; ***Neth.***: Benlysta; ***Norw.***: Benlysta; ***Spain***: Benlysta; ***Swed.***: Benlysta; ***Switz.***: Benlysta; ***UK***: Benlysta; ***USA***: Benlysta.

Ciclosporin *(BAN, rINN)*

27-400; Ciclosporina; Ciclosporina A; Ciclosporine; Ciclosporinum; Ciklosporin; Ciklosporinas; Cyclosporin; Cyclosporin A; Cyclosporine (USAN); Cyklosporin; OL-27-400; Siklosporiini; Siklosporin; Циклоспорин.

Cyclo{-[4-(*E*)-but-2-enyl-*N*,4-dimethyl-L-threonyl]-L-homoalanyl-(*N*-methylglycyl)-(*N*-methyl-L-leucyl)-L-valyl-(*N*-methyl-L-leucyl)-L-alanyl-D-alanyl-(*N*-methyl-L-leucyl)-(*N*-methyl-L-leucyl)-(*N*-methyl-L-valyl)-}.

$C_{62}H_{111}N_{11}O_{12}$=1202.6

CAS — 59865-13-3.
ATC — L04AD01; S01XA18.
ATC Vet — QL04AD01; QS01XA18.
UNII — 83HN0GTJ6D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ciclosporin). A substance produced by *Beauveria nivea* (=*Tolypocladium inflatum* Gams) or obtained by any other means. A white or almost white powder; practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Cyclosporine). A white to almost white powder. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, in dichloromethane, in ether, and in methyl alcohol; slightly soluble in saturated hydrocarbons. Store in airtight containers. Protect from light.

Incompatibility. The plasticiser diethylhexyl phthalate, which is a possible carcinogen, was leached from PVC containers by ciclosporin preparations containing polyoxyl castor oil.[1] Such preparations should not be given through PVC tubing nor stored in PVC containers. Polysorbate 80, which is an excipient in other ciclosporin preparations, also leached plasticiser from PVC,[1] and similar precautions would apply to preparations so formulated. UK licensed product information further recommends that containers and stoppers be free of silicone oil and fatty substances.

For reported incompatibility between ciclosporin and mycophenolate, see Incompatibility, under Mycophenolate, p. 1961.2.

1. Pearson SD, Trissel LA. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. *Am J Hosp Pharm* 1993; **50:** 1405–9.

Stability. Ciclosporin was stable over 72 hours after dilution in glucose 5% or glucose/amino-acid solutions and storage at room temperature in the dark; similar stability was seen after dilution in lipid emulsion, but dilutions in sodium chloride 0.9% were considered to be stable only for 8 hours.[1] In all cases miscibility in the diluent was poor and vigorous shaking was required after addition to produce even distribution of ciclosporin. An extemporaneously compounded paste produced from ciclosporin oral solution (*Sandimmun*) in an oral gel base was found to be stable[2] for at least 31 days in aluminium-lined ointment tubes stored at 2 degrees to 37 degrees.

1. McLeod HL, *et al*. Stability of cyclosporin in dextrose 5%, NaCl 0.9%, dextrose/amino acid solution, and lipid emulsion. *Ann Pharmacother* 1992; **26:** 172–5.
2. Ghnassia LT, *et al*. Stability of cyclosporine in an extemporaneously compounded paste. *Am J Health-Syst Pharm* 1995; **52:** 2204–7.

Uses and Administration

Ciclosporin is a powerful immunosuppressant that appears to act specifically on lymphocytes, mainly helper T-cells. It forms a complex with the receptor protein cyclophilin; this complex binds to and inhibits the activation of calcineurin, an important step in the production of lymphokines, including interleukin-2, and results in a depression of cell-mediated immune response. Unlike cytotoxic immunosuppressants such as cyclophosphamide it has little effect on bone marrow.

Ciclosporin is used, usually with corticosteroids (and often with other immunosuppressants), in organ and tissue transplantation for the prophylaxis of graft rejection, or in the management of graft rejection in patients previously treated with other immunosuppressants. It is also used in severe forms of atopic dermatitis, psoriasis, or rheumatoid arthritis, usually when conventional therapy is ineffective or inappropriate, and is used in nephrotic syndrome.

Ciclosporin has been tried in other diseases considered to have an auto-immune component, as indicated by the cross-references given below; they include aplastic anaemia, asthma, Behçet's syndrome, chronic active hepatitis, multiple sclerosis, myasthenia gravis, sarcoidosis, scleritis or uveitis, scleroderma, and various skin disorders.

Ciclosporin is given orally as liquid-filled capsules or as an oily solution, which may be diluted with milk or fruit juice (not grapefruit) immediately before use to improve palatability. Microemulsifying formulations with improved bioavailability are available in several countries. For advice on changing between oral formulations see Administration, Oral, p. 1946.2. The daily dose of ciclosporin is taken in 2 divided doses, although the conventional formulation is sometimes given as a single daily dose.

In **organ transplantation** the usual initial oral dose of ciclosporin is 10 to 15 mg/kg daily, beginning 4 to 12 hours before transplantation, and continued for 1 to 2 weeks; lower initial doses may be given with other immunosuppressants (e.g. with corticosteroids or as part of 'triple' or 'quadruple' therapy). Dosage may subsequently be reduced gradually to a daily maintenance dose of 2 to 6 mg/kg.

Kidney function and blood pressure should be monitored regularly, as well as blood concentrations of ciclosporin (see Therapeutic Drug Monitoring, p. 1956.1), and dosage should be adjusted as necessary. (For specific recommendations on adjustment when given with everolimus see Administration with Everolimus, p. 1946.3). Hepatic function should also be monitored.

Ciclosporin may also be given intravenously, at one-third of the oral dose, in patients in whom oral dosage is not feasible. It is given by slow intravenous infusion over 2 to 6 hours, the 5% concentrate being diluted 1:20 to 1:100 in sodium chloride 0.9% or glucose 5%, to give a 0.05 to

0.25% solution of ciclosporin. Because of the risk of anaphylactoid reactions, which have been attributed to the polyoxyl castor oil vehicle, patients should be transferred to oral therapy as soon as possible.

For the prevention of graft rejection in **bone marrow transplantation**, and prevention and treatment of graft-versus-host disease, an initial dose of 3 to 5 mg/kg daily by the intravenous route is recommended, starting the day before transplantation and continuing for up to 2 weeks until oral maintenance, in doses of 12.5 mg/kg daily can be instituted. If oral treatment is used to begin therapy the recommended dose is 12.5 to 15 mg/kg daily followed by 12.5 mg/kg daily for maintenance. The maintenance dose is continued for at least 3 to 6 months, then gradually reduced until ciclosporin is withdrawn altogether; this may take up to a year after transplantation.

Ciclosporin given by inhalation is under investigation for the prevention and treatment of graft rejection after lung transplantation in some countries.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

In the treatment of **psoriasis**, ciclosporin may be given in usual initial oral doses of 2.5 mg/kg daily (a maximum of 5 mg/kg daily is recommended in the UK and 4 mg/kg daily in the USA), in 2 divided doses, reduced once remission is achieved to the lowest effective maintenance dose. Treatment should usually be stopped if there is insufficient response to the maximum dose within 6 weeks; overall, it has been recommended that ciclosporin should be given for about 3 months before being considered ineffective. A similar dosage range may be given for a maximum of 8 weeks in the treatment of severe **atopic dermatitis**.

In **rheumatoid arthritis** oral ciclosporin may be given in initial daily doses of 2.5 mg/kg, divided into two doses, for a period of 6 or 8 weeks. If the clinical effect is insufficient dosage may then be gradually increased to a maximum of 4 mg/kg daily; if there is no response after 3 to 4 months, treatment should be stopped.

For **nephrotic syndrome** secondary to glomerular kidney disease (minimal change nephropathy, focal glomerulosclerosis, or membranous nephropathy) dosage of ciclosporin depends on age and renal function. To induce remission in patients with normal renal function 5 mg/kg daily may be given to adults, in 2 divided doses orally. In patients with renal impairment the initial dose should not exceed 2.5 mg/kg daily. Treatment may be stopped if there is no response after 3 months (or 6 months in patients with membranous nephropathy). In patients who do respond, maintenance doses should be gradually reduced to the minimum effective value.

For doses in children, see Administration in Children, below.

Eye drops containing ciclosporin 0.05% are used in the management of **dry eye** associated with ocular inflammation. A topical emulsion of ciclosporin is under investigation for the treatment of vernal keratoconjunctivitis, a severe form of chronic allergic conjunctivitis.

Ciclosporin can inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, and has been given with antineoplastics to raise their intracellular concentrations. Nonimmunosuppressive ciclosporin analogues such as valspodar (p. 2641.3) are also being investigated for their ability to reverse multidrug resistance.

Administration. It has been suggested that calculating doses in mg/kg may not be the best way to achieve the desired blood concentrations of ciclosporin.[1] (See also Therapeutic Drug Monitoring, p. 1956.1) Retrospective study of 1071 renal transplant recipients indicated that blood ciclosporin concentrations were not significantly correlated with patient weight, the best prediction of trough blood concentration being given by the formula:

$$\text{Blood concentration (nanograms/mL)} = \frac{\text{dose in mg/day}}{(1.34 + 0.00011 \times \text{days after transplant} - 0.0049 \times \text{height in cm})}$$

This formula appeared useful in predicting blood concentrations in prospective studies; from the seventh day after transplantation target trough concentrations could be expected to be about 0.3 times the daily ciclosporin dose in mg.

1. Bock HA, *et al.* Weight-independent dosing of cyclosporine—an alternative to the mg/kg doctrine. *Transplantation* 1994; **57:** 1484–9.

INHALATION. Aerosolised ciclosporin given by inhalation has proved effective[1,2] in the management of acute graft rejection in lung transplantation (p. 1937.3). Doses were up to 300 mg daily via a nebuliser, in either propylene glycol or ethanol solvents.[3] Pulmonary delivery of ciclosporin has been reviewed.[3,4] A positive association between deposited aerosolised ciclosporin dose and improvement in lung function was found in 15 subjects treated over 2 years postoperatively.[5] In a case-control study,[6] aerosolised ciclosporin improved survival among lung transplant recipients with bronchiolitis obliterans. In a randomised controlled study, inhaled ciclosporin given prophylactically did not improve the rate of acute rejection, but it did improve chronic rejection-free survival and overall survival.[7]

A dry powder formulation of ciclosporin for inhalation use has been developed in order to overcome problems of local irritation with propylene glycol; feasibility and efficacy studies with this new formulation are needed.[8]

1. Keenan RJ, *et al.* Efficacy of inhaled cyclosporine in lung transplant recipients with refractory rejection: correlation of intragraft cytokine gene expression with pulmonary function and histologic characteristics. *Surgery* 1995; **118:** 385–91.
2. Iacono AT, *et al.* Dose-related reversal of acute lung rejection by aerosolized cyclosporine. *Am J Respir Crit Care Med* 1997; **155:** 1690–8.
3. Klyashchitsky BA, Owen AJ. Nebulizer-compatible liquid formulations for aerosol pulmonary delivery of hydrophobic drugs: glucocorticoids and cyclosporine. *J Drug Target* 1999; **7:** 79–99.
4. Corcoran TE. Inhaled delivery of aerosolized cyclosporine. *Adv Drug Deliv Rev* 2006; **58:** 1119–27.
5. Corcoran TE, *et al.* Preservation of post-transplant lung function with aerosol cyclosporin. *Eur Respir J* 2004; **23:** 378–83.
6. Iacono AT, *et al.* Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. *Eur Respir J* 2004; **23:** 384–90.
7. Iacono AT, *et al.* A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med* 2006; **354:** 141–50.
8. Zijlstra GS, *et al.* Characterization of a cyclosporine solid dispersion for inhalation. *AAPS J* 2007; **9:** E190–E199.

OCULAR. Topical ciclosporin, in strengths ranging from 0.05 to 2% has been shown to be effective[1,2] in the treatment of various ocular surface disorders, particularly dry eye (see p. 1947.1) and atopic keratoconjunctivitis. It has also been used for corneal ulcers, glaucoma (see p. 1947.1 and p. 1947.2, respectively), as adjunctive therapy in corneal allograft rejection, and for the ocular manifestations of graft-versus-host disease.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

1. Tatlipinar S, Akpek EK. Topical ciclosporin in the treatment of ocular surface disorders. *Br J Ophthalmol* 2005; **89:** 1363–7.
2. Foulks GN. Topical cyclosporine for treatment of ocular surface disease. *Int Ophthalmol Clin* 2006; **46:** 105–22.

ORAL. The microemulsifying formulation of ciclosporin has been reviewed.[1,2] Different oral formulations of ciclosporin are not considered interchangeable without careful monitoring, to avoid changes in bioavailability. When switching to a different formulation, ciclosporin blood concentration and graft function should be measured and the patient monitored for adverse effects.[3] The *BNF* recommends prescribing by trade name to avoid unintended changes.

After development of the oral microemulsifying formulation of ciclosporin patients were switched from the old formulation on a 1:1 basis by weight initially, with monitoring of resultant ciclosporin concentrations and subsequent dosage adjustment. Results were generally good, despite some reports of nephrotoxicity or rejection in previously stable grafts,[4-7] and a meta-analysis[8] concluded that of *de novo* transplant recipients, those receiving the microemulsifying formulation had significantly fewer instances of rejection, and, in liver transplant recipients, significantly fewer adverse events. Licensed product information for the original microemulsifying formulation (*Neoral*) recommends transfer on this 1:1 basis by dose for patients stabilised on the conventional formulation, with monitoring of blood-ciclosporin concentrations, serum creatinine, and blood pressure, and subsequent dose adjustment as appropriate.

1. Noble S, Markham A. Cyclosporin: a review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral). *Drugs* 1995; **50:** 924–41.
2. Dunn CJ, *et al.* Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral) in organ transplantation. *Drugs* 2001; **61:** 1957–2016.
3. MHRA/CHM. Drug safety advice. Ciclosporin: must be prescribed and dispensed by brand name. *Drug Safety Update* 2009; **3** (5): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON065445&RevisionSelectionMethod=LatestReleased (accessed 11/06/10)
4. Bennett WM, *et al.* Which cyclosporin formulation? *Lancet* 1996; **348:** 205.
5. Olyaei AJ, *et al.* Switching between cyclosporin formulations: what are the risks? *Drug Safety* 1997; **16:** 366–73.
6. Filler G, Ehrich J. Which cyclosporin formulation? *Lancet* 1996; **348:** 1176–7.
7. Gennery A, *et al.* Which cyclosporin formulation? *Lancet* 1996; **348:** 1177.
8. Shah MB, *et al.* A meta-analysis to assess the safety and tolerability of two formulations of cyclosporine: Sandimmune and Neoral. *Transplant Proc* 1998; **30:** 4048–53.

Administration in children. UK licensed product information states that, while experience with ciclosporin in children is limited, **transplant** patients from 3 months of age have received the drug at the same doses recommended for adults (see Uses and Administration, p. 1945.3). However, at doses above the recommended range, children seem to be more susceptible to fluid retention, convulsions, and hypertension. These effects respond to dose reduction.

In contrast, US licensed product information states that, while data in children are lacking, transplant recipients as young as 6 months and 1 year have received the standard formulation and microemulsifying formulation, respectively, with no unusual adverse effects, and that children have generally required and tolerated higher doses of the standard formulation than those used in adults.

The *BNFC* advises to consult local treatment protocols for details of use in organ transplantation.

For the treatment of **psoriasis** and **atopic dermatitis** doses recommended by the *BNFC* for children from 1 month of age are the same as for adults (see Uses and Administration, p. 1945.3).

In the treatment of **nephrotic syndrome** UK licensed product information states that children may be given 6 mg/kg daily orally, in 2 divided doses, if renal function is normal. The dose should not exceed 2.5 mg/kg daily in patients with impaired renal function. The *BNFC* specifies use from 1 month of age.

Although ciclosporin is not licensed in the UK for use in **ulcerative colitis**, the *BNFC* recommends the following initial doses in refractory disease in children, which are then adjusted according to ciclosporin blood concentrations and response:

- orally in those aged 2 to 18 years: 2 mg/kg twice daily (maximum 5 mg/kg twice daily)
- by intravenous infusion in those aged 3 to 18 years: 0.5 to 1 mg/kg twice daily

A dose regimen with an initial fixed dose and further adjustment depending on the area under the concentration-time curve has also been suggested, see Children, under Pharmacokinetics, p. 1955.3.

Administration with everolimus. Everolimus is given with ciclosporin and corticosteroids to prevent graft rejection in renal or cardiac transplantation. Exposure to ciclosporin should be reduced from 1 month after transplantation. Because ciclosporin interacts with everolimus, and the dose adjustments of ciclosporin will affect exposure to everolimus, licensed product information for everolimus recommends that concentrations of *both* drugs be monitored to minimise the risk of graft rejection. Before dose reduction of ciclosporin, everolimus whole blood concentrations should be at least 3 nanograms/mL (see Therapeutic Drug Monitoring, p. 1956.1, and under Everolimus, p. 1959.2).

In renal transplantation, ciclosporin doses may be adjusted according to either ciclosporin concentrations taken 2 hours after a dose (C_2) or trough concentrations (C_0). The following ciclosporin C_2 target ranges have been suggested:

- weeks 0 to 4: 1000 to 1400 nanograms/mL
- weeks 5 to 8: 700 to 900 nanograms/mL
- weeks 9 to 12: 550 to 650 nanograms/mL
- weeks 13 to 52: 350 to 450 nanograms/mL

Alternatively, the following ciclosporin target trough concentrations (C_0) have been suggested:

- month 1: 100 to 200 nanograms/mL
- months 2 to 3: 75 to 150 nanograms/mL
- months 4 to 5: 50 to 100 nanograms/mL
- months 6 to 12: 25 to 50 nanograms/mL

In cardiac transplantation the following ciclosporin target trough concentrations have been suggested:

- month 1: 200 to 350 nanograms/mL
- month 2: 150 to 250 nanograms/mL
- months 3 to 4: 100 to 200 nanograms/mL
- months 5 to 6: 75 to 150 nanograms/mL
- months 7 to 12: 50 to 100 nanograms/mL

Asthma. Ciclosporin is being considered as a potential treatment for some cases of refractory asthma (p. 1195.2). A controlled study[1] in patients with chronic severe asthma requiring long-standing oral corticosteroid treatment found that addition of ciclosporin in an initial dose of 5 mg/kg daily to their regimen resulted in significant improvement in lung function and a reduced frequency of disease exacerbation, compared with placebo. The results were interesting because of the improvement in what had been considered 'irreversible' airflow obstruction. A subsequent study[2] from the same centre involving 39 patients with severe corticosteroid-dependent asthma found that low-dose oral ciclosporin (an initial dose of 5 mg/kg daily) permitted a reduction in the daily dosage of prednisolone, from a median of 10 to 3.5 mg daily. However, a systematic review[3] considered that, given the adverse effects of ciclosporin, any clinical benefit was debatable.

1. Alexander AG, *et al.* Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992; **339:** 324–8.
2. Lock SH, *et al.* Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996; **153:** 509–14.
3. Evans DJ, *et al.* Cyclosporin as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).

Behçet's syndrome. Ciclosporin has been tried in Behçet's syndrome, see p. 1601.1.

Blood disorders. In primary acquired red cell aplasia (see Normocytic-normochromic Anaemia, p. 1123.1), ciclosporin is considered as effective at inducing remission as corticosteroid monotherapy, or corticosteroids plus cyclophosphamide, and some consider it first-line treatment for relapsed disease.[1]

Ciclosporin, usually combined with antilymphocyte immunoglobulin, is used in patients with aplastic anaemia when bone marrow transplantation is unsuitable (see p. 1121.3).

1. Sawada K, *et al.* Acquired pure red cell aplasia: updated review of treatment. *Br J Haematol* 2008; **142:** 505–14.

Cogan's syndrome. Ciclosporin has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p. 1603.2).

Corneal ulcer. Ciclosporin 1% eye drops, with lamellar keratoplasty, proved effective in treating Mooren's ulcer, a possibly auto-immune corneal disease that is difficult to manage and can lead to blindness.[1] Treatment with topical ciclosporin alone may also be useful[2] in patients with sterile corneal ulcers associated with rheumatoid disease.

1. Chen J, *et al.* Mooren's ulcer in China: a study of clinical characteristics and treatment. *Br J Ophthalmol* 2000; **84:** 1244–9.
2. Gottsch JD, Akpek EK. Topical cyclosporin stimulates neovascularization in resolving sterile rheumatoid central corneal ulcers. *Trans Am Ophthalmol Soc* 2000; **98:** 81–90.

Dermatomyositis. See Polymyositis and Dermatomyositis, p. 1948.1.

Diabetes mellitus. Immunosuppressants have been used in attempts to prolong the so called 'honeymoon period' in recently diagnosed diabetics (p. 460.3). Ciclosporin has apparently produced modest benefits in such a context,[1-3] but its use is limited by concerns about toxicity.[4]

1. Bougneres PF, *et al.* Factors associated with early remission of type 1 diabetes in children treated with cyclosporine. *N Engl J Med* 1988; **318:** 663–70.
2. The Canadian-European Randomized Control Trial Group. Cyclosporin-induced remission of IDDM after early intervention: association of 1 yr of cyclosporin treatment with enhanced insulin secretion. *Diabetes* 1988; **37:** 1574–82.
3. Carel JC, *et al.* Cyclosporine delays but does not prevent clinical onset in glucose intolerant pre-type 1 diabetic children. *J Autoimmun* 1996; **9:** 739–45.
4. Parving H-H, *et al.* Cyclosporine nephrotoxicity in type 1 diabetic patients: a 7-year follow-up study. *Diabetes Care* 1999; **22:** 478–83.

Dry eye. Topical ciclosporin has been used,[1-3] with apparent benefit, for keratoconjunctivitis sicca (dry eye—see p. 2190.1). Studies[4,5] found ciclosporin 0.05% and 0.1% to be the most appropriate formulations since no additional benefit was found with higher concentrations[4] and both were significantly better than placebo.[5]

Topical ciclosporin has also been reported to be beneficial for patients with dry eyes secondary to graft-versus-host disease.[6]

1. Laibovitz RA, *et al.* Pilot trial of cyclosporine 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca. *Cornea* 1993; **12:** 315–23.
2. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. *Ophthalmology* 2007; **114:** 76–9.
3. Ridder WH. Ciclosporin use in dry eye disease patients. *Expert Opin Pharmacother* 2008; **9:** 3121–8.
4. Stevenson D, *et al.* Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. *Ophthalmology* 2000; **107:** 967–74.
5. Sall K, *et al.* Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology* 2000; **107:** 631–9.
6. Lelli GJ, *et al.* Ophthalmic cyclosporine use in ocular GVHD. *Cornea* 2006; **25:** 635–8.

Eczema. Ciclosporin is effective in atopic eczema (atopic dermatitis),[1-3] where it is used as adjunctive therapy (see p. 1684.1). It is generally reserved for short-term treatment (up to 8 weeks) in patients with severe disease unresponsive to all conventional therapies, although reports have described long-term use in adult patients.[4] It has also been suggested[5] that long-term remission is possible, even in those treated with short courses. Ciclosporin has been used for both short courses[6,7] and continuous therapy in children.[8] A systematic review and meta-analysis[9] that incorporated most of these studies concluded that the mean clinical improvement in disease severity after 6 to 8 weeks of ciclosporin treatment is about 55%; however, the true benefit may be somewhat lower due to publication bias. Higher initial doses of 4 to 5 mg/kg led to a more rapid response, and the mean benefit after 2 weeks at this dose was about 40%. In a small, open, crossover study,[10] the microemulsifying form was considered equivalent or superior in tolerability and efficacy when compared with the conventional formulation. Responses have also been reported in severe eczematisation associated with Darier's disease[11] (p. 1683.2).

1. van Joost T, *et al.* Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol* 1994; **130:** 634–40.
2. Munro CS, *et al.* Maintenance treatment with cyclosporin in atopic eczema. *Br J Dermatol* 1994; **130:** 376–80.
3. Granlund H, *et al.* Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995; **132:** 106–12.
4. Berth-Jones J, *et al.* Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. *Br J Dermatol* 1997; **136:** 76–81.
5. Granlund H, *et al.* Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol (Stockh)* 1998; **78:** 40–3.
6. Zaki I, *et al.* Treatment of severe atopic dermatitis in childhood with cyclosporin. *Br J Dermatol* 1996; **135** (suppl 48): 21–4.
7. Berth-Jones J, *et al.* Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* 1996; **34:** 1016–21.
8. Harper JI, *et al.* Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; **142:** 52–8.
9. Schmitt J, *et al.* Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21:** 606–19.
10. Chawla M, *et al.* Comparison of the steady state pharmacokinetics of two formulations of cyclosporin in patients with atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 48): 9–14.
11. Shahidullah H, *et al.* Darier's disease: severe eczematization successfully treated with cyclosporin. *Br J Dermatol* 1994; **131:** 713–16.

Glaucoma. Topical ciclosporin has produced some encouraging results[1] when used as an adjunct to reduce formation of scar tissue and improve outcome of glaucoma filtering surgery. It has been suggested[2] that topical ciclosporin 0.5% may be substituted for topical corticosteroids in the treatment of postkeratoplasty glaucoma.

1. Turaçli E, *et al.* A comparative clinical trial of mitomycin C and cyclosporin A in trabeculectomy. *Eur J Ophthalmol* 1996; **6:** 398–401.
2. Perry HD, *et al.* Topical cyclosporin A in the management of postkeratoplasty glaucoma. *Cornea* 1997; **16:** 284–8.

Glomerular kidney disease. Ciclosporin has been tried in various forms of glomerular kidney disease (p. 1604.3) but use has been cautious because of fears about nephrotoxicity. Nonetheless, responses have been seen in patients with corticosteroid-resistant minimal change nephropathy,[1,2] focal glomerulosclerosis,[1-3] and membranous nephropathy.[4-6] An international workshop[7] considered that ciclosporin therapy was effective at inducing a sustained remission from proteinuria, and preserved renal function long-term in corticosteroid-dependent or -resistant minimal change nephropathy and corticosteroid-resistant focal glomerulosclerosis in both adults and children. There was evidence to support its use as a first-line option in membranous nephropathy and focal glomerulosclerosis, and after a 12-week course of cytotoxic therapy has failed in minimal change nephropathy.

1. Nyrop M, Olgaard K. Cyclosporin A treatment of severe steroid resistant nephrotic syndrome in adults. *J Intern Med* 1990; **227:** 65–8.
2. Niaudet P, *et al.* Steroid-resistant idiopathic nephrotic syndrome and ciclosporin. *Nephron* 1991; **57:** 481.
3. Chishti AS, *et al.* Long-term treatment of focal segmental glomerulosclerosis in children with cyclosporine given as a single daily dose. *Am J Kidney Dis* 2001; **38:** 754–60.
4. Cattran DC, *et al.* A controlled trial of cyclosporine in patients with progressive membranous nephropathy. *Kidney Int* 1995; **47:** 1130–5.
5. Cattran DC, *et al.* Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int* 2001; **59:** 1484–90.
6. Goumenos DS. What have we learned from the use of ciclosporin A in the treatment of nephrotic patients with idiopathic membranous nephropathy? *Expert Opin Pharmacother* 2008; **9:** 1695–1704.
7. Cattran DC, *et al.* Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. *Kidney Int* 2007; **72:** 1429–47.

Hepatitis. In chronic active hepatitis (p. 1602.3), some evidence suggests that ciclosporin may offer an alternative therapy in patients with severe auto-immune (non-viral) disease where corticosteroids alone or with azathioprine do not suffice.

Histiocytic syndromes. Ciclosporin has been tried in patients with advanced Langerhans-cell histiocytosis (p. 692.1).

Inflammatory bowel disease. Ciclosporin has been tried with variable success as a second-line drug in inflammatory bowel disease (p. 1808.3). Intravenous high-dose ciclosporin has shown some efficacy in refractory ulcerative colitis,[1] and a review[2] concluded that intravenous ciclosporin should be offered to selected patients as an alternative to surgery. Treatment should be started at 2 mg/kg daily, as it appears to be as effective as 4 mg/kg daily. A systematic review,[3] which included only 2 studies, concluded that short-term ciclosporin may be used where surgery is the only option, but that this is not based on strong evidence.

Benefit from ciclosporin in Crohn's disease is less clear. A systematic review[4] concluded that low dose (5 mg/kg daily) oral ciclosporin is not effective for induction of remission in Crohn's disease. While some studies suggest that higher oral doses or intravenous ciclosporin might be beneficial, these are not considered to be useful alternatives for long-term management due to the risk of nephrotoxicity and the availability of other proven therapy.

1. Loftus CG, *et al.* Cyclosporin for refractory ulcerative colitis. *Gut* 2003; **52:** 172–3.
2. Pham CQD, *et al.* Cyclosporine for severe ulcerative colitis. *Ann Pharmacother* 2006; **40:** 96–101.
3. Shibolet O, *et al.* Cyclosporine A for induction of remission in severe ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 15/01/08).
4. McDonald JWD, *et al.* Cyclosporine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/01/08).

Interstitial lung disease. There are reports of benefit from the use of ciclosporin in idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1607.1), although data are too limited to support its use.

Leprosy. For mention of the use of ciclosporin in the management of type 1 lepra reactions in patients with leprosy, see p. 188.3.

Lichen planus. Lichen planus is a skin disorder generally controlled with corticosteroids (see p. 1685.2), although ciclosporin has also been used. Ciclosporin has been given successfully in relatively low doses (3 to 5 mg/kg orally) to produce remission of severe lichen planus,[1] but such therapy may be associated with the development of hypertension and impairment of renal function. Use of topical ciclosporin for oral lichen planus has been tried, but results have been variable.[2-8] One such study failed to note any benefit long-term from either ciclosporin mouthwash or corticosteroid oral paste.[7]

1. Pigatto PD, *et al.* Cyclosporin A for treatment of severe lichen planus. *Br J Dermatol* 1990; **121:** 121–3.
2. Eisen D, *et al.* Cyclosporin wash for oral lichen planus. *Lancet* 1990; **335:** 535–6.
3. Eisen D, *et al.* Effect of topical cyclosporine rinse on oral lichen planus: a double-blind analysis. *N Engl J Med* 1990; **323:** 290–4.
4. Levell NJ, *et al.* Lack of effect of cyclosporin mouthwash in oral lichen planus. *Lancet* 1991; **337:** 796–7.
5. Ho VC, Conklin RJ. Effect of topical cyclosporine rinse on oral lichen planus. *N Engl J Med* 1991; **325:** 435.
6. Porter SR, *et al.* The efficacy of topical cyclosporin in the management of desquamative gingivitis due to lichen planus. *Br J Dermatol* 1993; **129:** 753–5.
7. Sieg P, *et al.* Topical cyclosporin in oral lichen planus: a controlled, randomized prospective trial. *Br J Dermatol* 1995; **132:** 790–4.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; **154:** 139–45.

Lupus nephritis. Ciclosporin has been investigated for SLE (p. 1613.3), particularly lupus nephritis. Significant reductions in proteinuria have been reported,[1-6] although controlled studies are needed.

1. Fu LW, *et al.* Clinical efficacy of cyclosporin A Neoral in the treatment of paediatric lupus nephritis with heavy proteinuria. *Br J Rheumatol* 1998; **37:** 217–21.
2. Tam LS, *et al.* Long-term treatment of lupus nephritis with cyclosporin A. *Q J Med* 1998; **91:** 573–80.
3. Hallegua D, *et al.* Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. *Lupus* 2000; **9:** 241–51.
4. Fujinaga S, *et al.* Treatment of steroid-resistant membranous lupus nephritis with plasmapheresis and low-dose cyclosporine. *Pediatr Nephrol* 2007; **22:** 616–17.
5. Rihova Z, *et al.* Treatment of lupus nephritis with cyclosporine—an outcome analysis. *Kidney Blood Press Res* 2007; **30:** 124–8.
6. Ogawa H, *et al.* Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. *Mod Rheumatol* 2007; **17:** 92–7.

Multiple sclerosis. As noted on p. 996.3, immunosuppressants, including ciclosporin, have produced modest benefit in patients with multiple sclerosis. However, it has been concluded that the scanty benefits of therapy are outweighed by the toxicity of the doses required.

Muscular dystrophies. A study in 15 boys with Duchenne muscular dystrophy (p. 1608.1) given oral ciclosporin 5 mg/kg daily in divided doses, adjusted according to trough serum concentrations of ciclosporin, found that muscular force generation was improved during treatment, but declined again once treatment ceased.[1] The clinical significance, if any, is unknown.

1. Sharma KR, *et al.* Cyclosporine increases muscular force generation in Duchenne muscular dystrophy. *Neurology* 1993; **43:** 527–32.

Myasthenia gravis. Ciclosporin may be of use as an alternative to azathioprine in the management of myasthenia gravis (p. 684.1) for its corticosteroid-sparing effect[1] or when patients are intolerant of or unresponsive to corticosteroids and azathioprine.[2-4] It appears to be of similar efficacy to azathioprine[5] with a more rapid effect but serious adverse effects such as nephrotoxicity may limit its use.

1. Tindall RSA, *et al.* A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Ann N Y Acad Sci* 1993; **681:** 539–51.
2. Bonifati DM, Angelini C. Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. *J Neurol* 1997; **244:** 542–7.
3. Ciafaloni E, *et al.* Retrospective analysis of the use of cyclosporine in myasthenia gravis. *Neurology* 2000; **55:** 448–50.
4. Lavrnic D, *et al.* Cyclosporine in the treatment of myasthenia gravis. *Acta Neurol Scand* 2005; **111:** 247–52.
5. Schalke BCG, *et al.* Ciclosporin A vs azathioprine in the treatment of myasthenia gravis: final results of a randomized, controlled double-blind clinical trial. *Neurology* 1988; **38** (suppl 1): 135.

Organ and tissue transplantation. Ciclosporin has greatly improved the prospects for successful organ and tissue transplantation, and is a mainstay of regimens used to prevent rejection of solid organ grafts as well as being used for the prevention of graft-versus-host disease in bone

marrow transplantation. For more detailed discussion of organ and tissue transplantation and the role of ciclosporin, see p. 1932.2. Ciclosporin has also occasionally been used for corneal graft rejection (p. 1603.3) in high-risk patients, where corticosteroids alone are insufficient. An ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation. Inhaled ciclosporin is under investigation in lung transplantation, see p. 1937.3 and under Administration, p. 1946.1.

A few selected references to the use of ciclosporin in transplantation are given below.

1. Frei UA, *et al*. Randomized, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. *Transplantation* 1998; **65:** 1455–60.
2. Eisen HJ, *et al*. Safety, tolerability, and efficacy of cyclosporine microemulsion in heart transplant recipients: a randomized, multicenter, double-blind comparison with the oil-based formulation of cyclosporine—results at 24 months after transplantation. *Transplantation* 2001; **71:** 70–78.
3. Thervet E, *et al*. Benefit-risk assessment of ciclosporin withdrawal in renal transplant recipients. *Drug Safety* 2004; **27:** 457–76.
4. Hesselink DA, *et al*. The use of cyclosporine in renal transplantation. *Transplant Proc* 2004; **36** (suppl): 99S–106S.
5. Pape L, *et al*. Cyclosporine in pediatric kidney transplantation. *Transplant Proc* 2004; **36** (suppl): 203S–207S.
6. Banner NR, Yacoub MH. Cyclosporine in thoracic organ transplantation. *Transplant Proc* 2004; **36** (suppl): 302S–308S.
7. Patel JK, Kobashigawa JA. Cardiac transplant experience with cyclosporine. *Transplant Proc* 2004; **36** (suppl): 323S–330S.
8. Johnston A, *et al*. Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients. *Eur J Clin Pharmacol* 2004; **60:** 389–95.
9. Schrem H, *et al*. Update on liver transplantation using cyclosporine. *Transplant Proc* 2004; **36:** 2525–31.
10. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **38:** 169–74.

Pemphigus. Although pemphigus is usually treated with corticosteroids (see p. 1687.1), ciclosporin has also been tried in a few patients with pemphigus vulgaris, with variable results.[1-4] A small, randomised study[5] found that use of corticosteroids with ciclosporin had no advantage over corticosteroids alone.

1. Luisi AF, Stoukides CA. Cyclosporine for the treatment of pemphigus vulgaris. *Ann Pharmacother* 1994; **28:** 1183–5.
2. Vardy DA, Cohen AD. Cyclosporine therapy should be considered for maintenance of remission in patients with pemphigus. *Arch Dermatol* 2001; **137:** 505.
3. Gooptu C, Staughton RCD. Use of topical cyclosporin in oral pemphigus. *J Am Acad Dermatol* 1998; **38:** 860–1.
4. Olszewska M, *et al*. Efficacy and safety of cyclophosphamide, azathioprine, and cyclosporine (ciclosporin) as adjuvant drugs in pemphigus vulgaris. *Am J Clin Dermatol* 2007; **8:** 85–92.
5. Ioannides D, *et al*. Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus. *Arch Dermatol* 2000; **136:** 868–72.

Polymyositis and dermatomyositis. Ciclosporin may be of benefit[1,2] in refractory polymyositis and dermatomyositis (see p. 1611.1).

1. Qushmaq KA, *et al*. Cyclosporin A in the treatment of refractory adult polymyositis/dermatomyositis: population based experience in 6 patients and literature review. *J Rheumatol* 2000; **27:** 2855–9.
2. Kim H-J, *et al*. Dermatomyositis, complicated with pneumomediastinum, successfully treated with cyclosporine A: a case report and review of literature. *Rheumatol Int* 2009; **29:** 1101–4.

Primary biliary cirrhosis. In primary biliary cirrhosis (p. 2638.3) some benefit has been reported with ciclosporin, but there are problems with toxicity. A systematic review[1] concluded that, despite improvements in pruritus and liver biochemical variables, ciclosporin did not delay the progression of the disease, and that its use outside of clinical studies could not be recommended.

1. Gong Y, *et al*. Cyclosporin A for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 15/01/08).

Psoriasis. Ciclosporin is used to induce remission or prevent relapse in severe refractory psoriasis (p. 1688.1). Response to ciclosporin has been reported for virtually all the clinical manifestations of the disease,[1] including pustular psoriasis of pregnancy.[2-4] Benefit has also been reported in children with severe refractory psoriasis,[1,5] although exposure should be limited in view of the potential for cumulative toxicity.

Doses of 2.5 to 5 mg/kg daily given for up to 12 weeks produced marked improvement in the majority of patients with severe plaque psoriasis.[6] This intermittent therapy allows for a lower cumulative dose of ciclosporin and in turn decreases the risk of nephrotoxicity or hypertension.[7] Recommendations have been made in the UK for the use of ciclosporin in the management of psoriasis;[8] for those with severe stable disease, an initial starting dose of 2.5 mg/kg daily is suggested, with dose increases of 0.5 to 1 mg/kg daily made at intervals of 2 to 4 weeks, according to clinical response, and up to a maximum of 5 mg/kg daily. Treatment is given for about 12 weeks, and use of adjunctive topical therapy is recommended. Ciclosporin should be stopped once remission is achieved, and restarted at the previous effective dose if the patient relapses. In acute flares of the disease, ciclosporin may be started at higher doses (maximum 5 mg/kg daily) and titrated down as symptoms improve. The patient's renal function and blood pressure should be monitored before and during treatment. In a minority of patients requiring long-term continuous therapy, the duration of treatment should be limited to a maximum of 2 years, and an annual assessment of the patient's glomerular filtration rate is recommended. In most studies, maintenance doses were less than 3.5 mg/kg daily.

Reviews[1,9] have concluded that patients on short-term ciclosporin therapy for psoriasis do not require routine therapeutic drug monitoring (see under Pharmacokinetics, p. 1956.1). However, some consider that monitoring of trough concentrations is necessary in those treated with greater than 3 mg/kg daily, or in those at risk of renal impairment.[9] Monitoring may also be useful when compliance is questionable, or drug interactions are suspected.[1]

1. Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatol Treat* 2005; **16:** 258–77.
2. Edmonds EVJ, *et al*. Pustular psoriasis of pregnancy treated with ciclosporin and high-dose prednisolone. *Clin Exp Dermatol* 2005; **30:** 709–10.
3. Kura MM, Surjushe AU. Generalized pustular psoriasis of pregnancy treated with oral cyclosporin. *Indian J Dermatol Venereol Leprol* 2006; **72:** 458–9.
4. Kapoor R, Kapoor JR. Cyclosporine resolves generalized pustular psoriasis of pregnancy. *Arch Dermatol* 2006; **142:** 1373–5.
5. Pereira TM, *et al*. Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20:** 651–6.
6. Faerber L, *et al*. Cyclosporine in severe psoriasis: results of a meta-analysis in 579 patients. *Am J Clin Dermatol* 2001; **2:** 41–7.
7. Ho VC. The use of ciclosporin in psoriasis: a clinical review. *Br J Dermatol* 2004; **150** (suppl. 67): 1–10.
8. Griffiths CEM, *et al*. Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol* 2004; **150** (suppl. 67): 11–23.
9. Heydendael VMR, *et al*. Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147:** 122–9.

Psoriatic arthritis. One study[1] has shown that low-dose ciclosporin effectively improves joint complaints in psoriatic arthritis (see under Spondyloarthropathies, p. 14.3), and another[2] found ciclosporin to be more effective than sulfasalazine. Its use in psoriatic arthritis has been reviewed.[3]

1. Mahrle G, *et al*. Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis: a prospective multicentre study. *Br J Dermatol* 1996; **135:** 752–7.
2. Salvarani C, *et al*. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; **28:** 2274–82.
3. Salvarani C, *et al*. Multidisciplinary focus on cyclosporin A. *J Rheumatol Suppl* 2009; **83:** 52–5.

Pyoderma gangrenosum. There have been reports[1-6] of responses to ciclosporin in patients with pyoderma gangrenosum (p. 1688.3).

1. Sassolas B, *et al*. Pyoderma gangrenosum with pathergic phenomenon in pregnancy. *Br J Dermatol* 2000; **142:** 827–8.
2. Vena GA, Cassano N. Can we still suggest the topical cyclosporin treatment in cutaneous disorders? *J Eur Acad Dermatol Venereol* 2001; **15:** 18–19.
3. Schöfer H, Baur S. Successful treatment of postoperative pyoderma gangrenosum with cyclosporin. *J Eur Acad Dermatol Venereol* 2002; **16:** 148–51.
4. Patrone P, *et al*. Pyoderma gangrenosum of the scalp treated with cyclosporine A. *Int J Dermatol* 2002; **41:** 916–18.
5. Park H-J, *et al*. Recalcitrant oral pyoderma gangrenosum in a child responsive to cyclosporine. *J Dermatol* 2003; **30:** 612–16.
6. Hasselmann DO, *et al*. Pyoderma gangrenosum: clinical presentation and outcome in 18 cases and review of the literature. *J Dtsch Dermatol Ges* 2007; **5:** 560–4.

Reperfusion and revascularisation procedures. Ciclosporin has been investigated as an adjunct to limit reperfusion injury (p. 1259.2) in acute myocardial infarction. A controlled pilot study[1] in which patients received ciclosporin before undergoing percutaneous coronary intervention, reported a reduced infarct size as measured by creatine kinase release and magnetic resonance imaging; troponin release was not affected.

1. Piot C, *et al*. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 2008; **359:** 473–81.

Retroperitoneal fibrosis. There is a report[1] of response to ciclosporin in a patient with retroperitoneal fibrosis (p. 1612.1).

1. Marzano A, *et al*. Treatment of idiopathic retroperitoneal fibrosis using cyclosporin. *Ann Rheum Dis* 2001; **60:** 427–8.

Rheumatoid arthritis. Various disease-modifying antirheumatic drugs (DMARDs) are used in rheumatoid arthritis (p. 13.2) in an attempt to modify the disease process. Ciclosporin has produced responses in active disease,[1-4] and there is some evidence that it can slow radiological progression of disease[4] as well as providing symptomatic relief; a systematic review[5] has concluded it has an important clinical benefit in the short-term (up to one year) treatment of progressive disease. There has been some concern about associated nephrotoxicity,[1] but the use of low-dose regimens may help to minimise this.

Ciclosporin has also been combined with other DMARDs. Use with methotrexate has reportedly produced responses in patients unresponsive to methotrexate alone,[6] but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy.[7] Others consider that ciclosporin monotherapy is of limited benefit, but that combination therapy with methotrexate is one of the best options to control aggressive disease.[8]

International consensus recommendations for the use of ciclosporin in rheumatoid arthritis[9] suggested that it might be considered in patients who are candidates for DMARDs and who did not have risk factors such as malignancy, uncontrolled hypertension, renal dysfunction, cytopenias, or marked disorder of liver function. They recommended a starting dose of between 2.5 and 3 mg/kg daily, increased if necessary after 4 to 8 weeks, in increments of 0.5 or 1 mg/kg at 1 to 2 month intervals, up to a maximum of 5 mg/kg daily, particular care being taken at doses over 4 mg/kg daily. Once the patient's disease had been stable for at least 3 months the daily dose should be decreased monthly or bimonthly in decrements of 500 micrograms/kg to the lowest effective dose. If it was only partially effective after 3 months at the maximum tolerable dose another medication should be considered instead or in addition; if there was no response to the maximum tolerable dose after 3 months, ciclosporin should be stopped. Patients should be carefully monitored before and during therapy.

Ciclosporin has been shown to have a corticosteroid-sparing effect and control the fever of juvenile idiopathic arthritis.[10] In patients with refractory juvenile idiopathic arthritis, adding ciclosporin to methotrexate therapy has been reported to elicit significant clinical improvement.[11]

1. Yocum DE, *et al*. Cyclosporin A in severe, treatment-refractory rheumatoid arthritis: a randomized study. *Ann Intern Med* 1988; **109:** 863–9.
2. Tugwell P, *et al*. Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. *Lancet* 1990; **335:** 1051–5.
3. Landewé RBM, *et al*. A randomized, double-blind, 24-week controlled study of low-dose cyclosporine versus chloroquine for early rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 637–43.
4. Førre Ø, *et al*. Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: results of a 48-week multicenter study comparing low-dose cyclosporine with placebo. *Arthritis Rheum* 1994; **37:** 1506–12.
5. Wells GA, *et al*. Cyclosporine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 15/01/08).
6. Tugwell P, *et al*. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; **333:** 137–41.
7. Proudman SM, *et al*. Treatment of poor-prognosis early rheumatoid arthritis. *Arthritis Rheum* 2000; **43:** 1809–19.
8. Gremese E, Ferraccioli GF. Benefit/risk of cyclosporine in rheumatoid arthritis. *Clin Exp Rheumatol* 2004; **22** (suppl 35): S101–S107.
9. Panayi GS, Tugwell P. The use of cyclosporin A microemulsion in rheumatoid arthritis: conclusions of an international review. *Br J Rheumatol* 1997; **36:** 808–11.
10. Gerloni V, *et al*. Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis: results of a 10-year prospective study. *Rheumatology (Oxford)* 2001; **40:** 907–13.
11. Ravelli A, *et al*. Combination therapy with methotrexate and cyclosporine A in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002; **20:** 569–72.

Sarcoidosis. Corticosteroids are the usual therapy for symptomatic sarcoidosis (p. 1612.2), and other agents are very much second-line; ciclosporin is one of several immunosuppressants that have been tried with variable results.

Scleritis. Ciclosporin is used alone or with corticosteroids in the treatment of scleritis (see p. 1612.3).

Scleroderma. There are a few reports of responses to ciclosporin in patients with scleroderma (p. 1938.3).

Toxic epidermal necrolysis. Ciclosporin has been reported to be of benefit in toxic epidermal necrolysis;[1-4] it has been given both enterally[1] and intravenously,[2] often combined with corticosteroids.[3,4]

1. Arévalo JM, *et al*. Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000; **48:** 473–8.
2. Hashim N, *et al*. Early cyclosporine treatment of incipient toxic epidermal necrolysis induced by concomitant use of lamotrigine and sodium valproate. *Acta Derm Venereol* 2004; **84:** 90–1.
3. Aihara Y, *et al*. Toxic epidermal necrolysis in a child successfully treated with cyclosporin A and methylprednisolone. *Pediatr Int* 2007; **49:** 659–62.
4. Rai R, Srinivas CR. Suprapharmacologic doses of intravenous dexamethasone followed by cyclosporine in the treatment of toxic epidermal necrolysis. *Indian J Dermatol Venereol Leprol* 2008; **74:** 263–5.

Uveitis. Ciclosporin is used in uveitis, see p. 1615.1.

Vasculitic syndromes. For the use of ciclosporin in Takayasu's arteritis and Wegener's granulomatosis, see p. 1614.3 and p. 1615.2, respectively.

Adverse Effects and Treatment

Nephrotoxicity, manifesting as raised serum creatinine and urea, is the major adverse effect of ciclosporin. It is related to drug-plasma concentrations and is usually reversible on reduction of the dose. In renal graft recipients episodes of nephrotoxicity may be difficult to distinguish from graft

rejection. Interstitial fibrosis may develop during long-term therapy.

Other frequent adverse effects include hypertension, gastrointestinal disturbances, fatigue, hepatotoxicity, hypertrichosis, gum hyperplasia, tremor, headaches, hyperlipidaemias, hyperkalaemia, hypomagnesaemia, hyperuricaemia, paraesthesia, and muscle cramps and myalgia. Less commonly, anaemia, thrombocytopenia, rashes, weight increase, oedema, pancreatitis, myopathy, neuropathy, and hyperglycaemia have been reported. Glomerular capillary thrombosis has occurred, and may progress to graft failure. Encephalopathy, manifest as convulsions, confusion, visual disturbances including blindness, movement disorders, or psychiatric disturbances, has been reported. Optic disc oedema, including papilloedema with possible visual impairment secondary to benign intracranial hypertension, has occurred rarely.

Anaphylactoid reactions have occurred after intravenous use; it has been suggested that these represent a reaction to the polyoxyl castor oil vehicle of the intravenous preparation.

Immunosuppression, including ciclosporin treatment, is associated with an increased incidence of lymphoma and other malignancies, particularly those of the skin, and excess exposure to UV light should be avoided during treatment. There is also an increased risk of infection, including activation of latent viral infections. These include BK virus-associated nephropathy that can lead to renal graft loss.

Alopecia. Although ciclosporin is more often associated with reports of hypertrichosis, there have been cases of alopecia areata developing in patients given ciclosporin,[1] sometimes with complete hair loss (alopecia universalis).[2,3]

1. Davies MG, Bowers PW. Alopecia areata arising in patients receiving cyclosporin immunosuppression. *Br J Dermatol* 1995; **132:** 835–6.
2. Monti M, *et al*. Alopecia universalis in liver transplant patients treated with cyclosporin. *Br J Dermatol* 1995; **133:** 663–4.
3. Parodi A, *et al*. Alopecia universalis and cyclosporin A. *Br J Dermatol* 1996; **135:** 657.

Calcineurin inhibitor-induced pain syndrome. Calcineurin inhibitor-induced pain syndrome is reported rarely after organ or tissue transplantation and is associated with the use of ciclosporin, and less frequently tacrolimus. Symptoms vary from deep, aching rest pain to the sudden onset of severe, periarticular bone pain.[1] In some cases the pain resembled an electric shock, and was accompanied or preceded by intense pruritus;[2,3] progression to allodynia has been reported in one patient. Weight-bearing areas are commonly affected, particularly the lower limbs and pain is generally bilateral and symmetrical. Onset has been associated with high trough concentrations of calcineurin inhibitors. The mechanism of the syndrome is unclear, but it has been suggested that calcineurin inhibitors cause vascular changes that disturb bone perfusion and permeability, leading to vasoconstriction and bone marrow oedema.[1,4] Elevation of the feet, and dose reduction or withdrawal of calcineurin-inhibitor treatment are reported to relieve pain;[1] switching from one calcineurin inhibitor to another has had variable results.[4] Response to usual analgesia is often poor, but calcium-channel blockers such as nifedipine have been used with some success.[1,4]

1. Elder GJ. From marrow oedema to osteonecrosis: common paths in the development of post-transplant bone pain. *Nephrology (Carlton)* 2006; **11:** 560–7.
2. Noda Y, *et al*. Calcineurin-inhibitor-induced pain syndrome after bone marrow transplantation. *J Anesth* 2008; **22:** 61–3.
3. Kida A, *et al*. Incapacitating lower limb pain syndrome in cord blood stem cell transplant recipients with calcineurin inhibitor. *Pathol Oncol Res* 2004; **10:** 204–6.
4. Lavoratore SR, *et al*. Cyclosporine-induced pain syndrome in a child undergoing hematopoietic stem cell transplant. *Ann Pharmacother* 2009; **43:** 767–71.

Carcinogenicity. The use of ciclosporin in **organ transplant** recipients is associated with an increased incidence of malignancy, notably lymphoma,[1] and also skin cancer and Kaposi's sarcoma. The manufacturers have stated that of an estimated 5550 transplant patients who had been treated with ciclosporin by February 1984, lymphoproliferative disorders had been reported in 40; this represented an overall incidence of 0.7%, varying from 0.2 to 8% in different series.[2] In 1991, a report of 12 cases of lymphoproliferative disorders among 132 paediatric liver graft recipients estimated the incidence at about 2.8% per year for the first 6 years after transplantation, giving a cumulative risk of nearly 20% after 7 years.[3] There is evidence that the incidence of malignancy is related to dose,[2,4] and is greater when ciclosporin is used with other potent immunosuppressants.[2] In addition, the incidence of malignancy varies geographically, possibly reflecting environmental triggers and genetic susceptibility.[5]

It has been suggested that these lymphomas represent proliferation of B-cells under the influence of Epstein-Barr virus, a process normally prevented by the T-cells which are specifically inhibited by ciclosporin.[3] The resultant, usually polyclonal, lymphoproliferative tumours appear to regress on prompt excision of the affected tissue and reduction or withdrawal of the immunosuppressant regimen, in most cases without graft loss.[6] However, the need for vigilance and rapid response to these conditions has been stressed, since the responsive polyclonal disorder may evolve into a monoclonal, frankly malignant form; where the presentation is indistinguishable from a classic non-Hodgkins lymphoma the prognosis is much less good.[3] Interestingly, use of lower dose ciclosporin regimens appears to maintain normal elimination of Epstein-Barr virus-infected B-cells by specific T-cells,[7] and may lead to a reduced incidence of malignancy compared with earlier results.[4,7]

The risk of skin cancers in ciclosporin recipients is further increased by the exposure to sunlight.[8] Prophylactic retinoid therapy may prevent skin cancer in patients with renal transplants.[9]

There is no clear evidence that ciclosporin is associated with an increased incidence of malignancy compared with other immunosuppressants, although in one study dysplastic skin lesions were found in 14 of 64 transplant patients receiving ciclosporin compared with 3 of 33 previous similar patients who had received azathioprine.[10] However, such comparisons are difficult, not least because many transplant patients tend to have received multiple immunosuppressant agents. The safety of ciclosporin in **dermatology** patients has been reviewed.[11] Despite reports of lymphomas and other malignancies in dermatology patients treated with ciclosporin, a 5-year cohort study showed no increased risk of lymphoma or internal malignancies. While there was an increased risk of non-melanoma skin cancers, especially squamous cell carcinoma, many patients had been previously exposed to PUVA, methotrexate, or other immunosuppressants. Adjusting for these variables, more than 2 years of cumulative treatment with ciclosporin was estimated to increase the risk of non-melanoma skin cancer by a factor of 3.3 when compared with less than 2 years of cumulative treatment.

1. Penn I. Cancers following cyclosporine therapy. *Transplantation* 1987; **43:** 32–5.
2. Beveridge T, *et al*. Lymphomas and lymphoproliferative lesions developing under cyclosporin therapy. *Lancet* 1984; **i:** 788.
3. Malatack JJ, *et al*. Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: a growing concern. *J Pediatr* 1991; **118:** 667–75.
4. Dantal J, *et al*. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351:** 623–8.
5. Newstead CG. Assessment of risk of cancer after renal transplantation. *Lancet* 1998; **351:** 610–11.
6. Starzl TE, *et al*. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984; **i:** 583–7.
7. Crawford DH, Edwards JMB. Immunity to Epstein-Barr virus in cyclosporin A-treated renal allograft recipients. *Lancet* 1982; **i:** 1469–70.
8. Stockfleth E, *et al*. Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res* 2002; **160:** 251–8.
9. Bavinck JN, *et al*. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995; **13:** 1933–8.
10. Shuttleworth D, *et al*. Epidermal dysplasia and cyclosporine therapy in renal transplant patients: a comparison with azathioprine. *Br J Dermatol* 1989; **120:** 551–4.
11. Behnam SM, *et al*. Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. *J Drugs Dermatol* 2005; **4:** 189–94.

Dysmorphic changes. There was pronounced coarsening of facial features in 11 children who were treated with prednisone and ciclosporin for renal transplantation and followed up for more than 6 months.[1] The changes resembled those seen with phenytoin therapy. In a 13-year-old patient given ciclosporin as part of an immunosuppressive regimen after lung transplantation, facial dysmorphism, which developed along with follicular disturbances, later improved upon conversion to tacrolimus.[2] Similarly, lip hypertrophy associated with ciclosporin use in 2 paediatric patients resolved after therapy was changed to tacrolimus.[3] A 58-year-old renal transplant recipient on long-term ciclosporin therapy developed progressive facial changes, including swelling and distortion of the nose (rhinophyma);[4] surgery or physical ablation of excess tissue may provide cosmetic improvement.

1. Reznik VM, *et al*. Changes in facial appearance during cyclosporin treatment. *Lancet* 1987; **i:** 1405–7.
2. Chastain MA, Millikan LE. Pilomatrix dysplasia in an immunosuppressed patient. *J Am Acad Dermatol* 2000; **43:** 118–22.
3. Cansick JC, Hulton S-A. Lip hypertrophy secondary to cyclosporin treatment. *Pediatr Nephrol* 2003; **18:** 710–11.
4. Brown S, *et al*. Minerva picture]. *BMJ* 2005; **330:** 1218.

Effects on the blood. Erythraemia[1,2] and thrombocytosis[3] have both been reported with ciclosporin treatment, both of which may contribute to **thromboembolic complications.** One retrospective study reported 17 thromboembolic events (pulmonary embolism, renal-vein or deep-vein thrombosis, or haemorrhoidal thrombosis) in 13 of 90 renal allograft recipients treated with ciclosporin and corticosteroids, compared with only 1 episode of superficial thrombophlebitis in 90 similar patients treated with an azathioprine-based regimen.[4] However, other authors dispute that the incidence of thromboembolic events is any greater after ciclosporin than azathioprine,[5-7] and one group found the reverse.[8]

Other effects that have been associated with ciclosporin therapy include cases of the haemolytic-uraemic syndrome,[9] and thrombocytopenia,[10] or leucopenia.[11] Post-transplant thrombotic microangiopathy has also been reported.[12,13] This syndrome can include haemolytic anaemia and thrombocytopenia, and must be distinguished from rejection in renal transplant recipients. In those patients with a history of thrombotic microangiopathy, the risk of recurrence is high, irrespective of ciclosporin treatment.

1. Tatman AJ, *et al*. Erythraemia in renal transplant recipients treated with cyclosporin. *Lancet* 1988; **i:** 1279.
2. Innes A, *et al*. Cyclosporin and erythraemia. *Lancet* 1988; **ii:** 285.
3. Itami N, *et al*. Thrombocytosis after cyclosporin therapy in child with nephrotic syndrome. *Lancet* 1988; **ii:** 1018.
4. Vanrenterghem Y, *et al*. Thromboembolic complications and haemostatic changes in cyclosporin-treated cadaveric kidney allograft recipients. *Lancet* 1985; **i:** 999–1002.
5. Bergentz S-E, *et al*. Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 101–2.
6. Zazgornik J, *et al*. Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 102.
7. Choudhury N, *et al*. Thromboembolic complications in cyclosporin-treated kidney allograft recipients. *Lancet* 1985; **ii:** 606.
8. Allen RD, *et al*. Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 1004.
9. Bonser RS, *et al*. Cyclosporin-induced haemolytic uraemic syndrome in liver allograft recipient. *Lancet* 1984; **ii:** 1337.
10. Dejong DJ, Sayler DJ. Possible cyclosporine-associated thrombocytopenia. *DICP Ann Pharmacother* 1990; **24:** 1007.
11. Michel F, *et al*. Bone marrow toxicity of cyclosporin in a kidney transplant patient. *Lancet* 1986; **ii:** 394.
12. Pisoni R, *et al*. Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Safety* 2001; **24:** 491–501.
13. Bren A, *et al*. Follow-up of kidney graft recipients with cyclosporine-associated hemolytic-uremic syndrome and thrombotic microangiopathy. *Transplant Proc* 2005; **37:** 1889–91.

Effects on the cardiovascular system. The principal cardiovascular adverse effect of ciclosporin is **hypertension.** This may be severe,[1,2] appears to be dose-related,[1-3] and is particularly common in recipients of cardiac or heart-lung grafts.[4,5] There may be an association with low serum-magnesium concentrations.[6] Mechanisms that may contribute to ciclosporin-induced hypertension include impaired sodium excretion,[7] enhanced sympathetic nervous activity,[4,8] effects on renal prostaglandin metabolism,[3] and direct damage to endothelial cells[9] with release of the potent vasoconstrictor endothelin,[10] all of which may be due to calcineurin inhibition.[11] Thus hypertension may occur independently of nephrotoxicity,[3,8] and may be difficult to treat with conventional antihypertensive regimens.[7] Calcium-channel blockers are the preferred class of antihypertensives for hypertension that develops after transplantation.[1,12] It is important to choose one that does not interact with ciclosporin (see Cardiovascular Drugs under Interactions, p. 1953.3).[1] Beta blockers may also be used. Diuretics are usually avoided.[12] For mention of the ability of calcium-channel blockers to ameliorate the nephrotoxic effects of ciclosporin, see Transplantation, under Diltiazem, p. 1360.1, Nifedipine, p. 1450.2, and Verapamil, p. 1523.3 Occasionally, hypertension may be irreversible.[3,13]

Raynaud's syndrome has been reported with ciclosporin.[14] Conversely, use of ciclosporin has also reportedly caused erythromelalgia, with painful inflammatory vasodilatation of the extremities.[15] For a discussion of possible thromboembolic complications, see Effects on the Blood, above.

1. Textor SC, *et al*. Cyclosporine-induced hypertension after transplantation. *Mayo Clin Proc* 1994; **69:** 1182–93.
2. Robert N, *et al*. Effect of cyclosporine on blood pressure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 15/07/10).
3. Porter GA, *et al*. Cyclosporine-associated hypertension. *Arch Intern Med* 1990; **150:** 280–3.
4. Scherrer U, *et al*. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990; **323:** 693–9.
5. Weidle PJ, Vlasses PH. Systemic hypertension associated with cyclosporine: a review. *Drug Intell Clin Pharm* 1988; **22:** 443–51.
6. June CH, *et al*. Correlation of hypomagnesemia with the onset of cyclosporine-associated hypertension in marrow transplant patients. *Transplantation* 1986; **41:** 47–51.
7. Weinman EJ. Cyclosporine-associated hypertension. *Am J Med* 1989; **86:** 256–7.
8. Mark AL. Cyclosporine, sympathetic activity, and hypertension. *N Engl J Med* 1990; **323:** 748–50.
9. Zaal MJW, *et al*. Is cyclosporin toxic to endothelial cells? *Lancet* 1988; **ii:** 956–7.
10. Deray G, *et al*. Increased endothelin level after cyclosporine therapy. *Ann Intern Med* 1991; **114:** 809.
11. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; **72:** S9–12.
12. Taler SJ, *et al*. Cyclosporin-induced hypertension: incidence, pathogenesis and management. *Drug Safety* 1999; **20:** 437–49.
13. Sennesael JJ, *et al*. Hypertension and cyclosporine. *Ann Intern Med* 1986; **104:** 729.
14. Deray G, *et al*. Cyclosporin and Raynaud phenomenon. *Lancet* 1986; **ii:** 1092–3.
15. Thami GP, Bhalla M. Erythromelalgia induced by possible calcium channel blockade by ciclosporin. *BMJ* 2003; **326:** 910.

Effects on the gastrointestinal tract. There have been reports[1,2] of severe non-specific colitis associated with both elevated[1] and therapeutic[2] blood or serum concentrations of ciclosporin.

1. Innes A, *et al*. Cyclosporin toxicity and colitis. *Lancet* 1988; **ii:** 957. Correction. *ibid.*; 1094.
2. Bowen JRC, Sahi S. Cyclosporin induced colitis. *BMJ* 1993; **307:** 484.

Effects on glucose tolerance. Ciclosporin, particularly in high doses, may be associated with reduced insulin production,[1] impaired glucose tolerance,[2] and occasional overt diabetes mellitus,[3,4] although ciclosporin has also been tried, with some apparent benefit, in the treatment of recent-onset diabetes mellitus (see under Uses and Administration, p. 1947.1). The incidence of fasting hyperglycaemia has been estimated at about 8% in ciclosporin-treated renal transplant recipients, compared with about 5% in those given an azathioprine-based regimen.[4]

1. Scott JP, Higenbottam TW. Adverse reactions and interactions of cyclosporin. *Med Toxicol* 1983; **3:** 107–27.
2. Gunnarsson R, *et al*. Deterioration in glucose metabolism in pancreatic transplant recipients given cyclosporin. *Lancet* 1983; **ii:** 571–2.
3. Bending JJ, *et al*. Diabetogenic effect of cyclosporin. *BMJ* 1987; **294:** 401–2.
4. Yagisawa T, *et al*. Deterioration in glucose metabolism in cyclosporine-treated kidney transplant recipients and rats. *Transplant Proc* 1986; **18:** 1548–51.

Effects on the kidneys. Ciclosporin nephrotoxicity comprises 2 distinct forms of renal injury.[1,2]

Acute nephrotoxicity is dose-related, and reversible.[1-4] It occurs shortly after starting ciclosporin and often presents as an asymptomatic increase in serum creatinine, which improves quickly on dosage adjustment or drug withdrawal.[2,5] It may be difficult to distinguish ciclosporin nephrotoxicity from acute graft rejection after kidney transplantation.[5] Extremely high intravenous doses of ciclosporin (21 mg/kg per 24 hours for 60 hours) have been associated with fatal acute tubular necrosis;[6] in another patient given an overdose of 30 mg/kg per 24 hours, the error was detected after 18 hours, and the necrosis deemed to be partially reversible.[7]

Acute ciclosporin nephrotoxicity appears to be related to a renal imbalance of vasoconstrictor and vasodilator mediators, leading to intense vasoconstriction within the kidney.[1,2] Stimulation of the renin-angiotensin system,[5] free radical damage,[1,2] and activation of the sympathetic nervous system[1,5] have been suggested to play a role; numerous vasoactive mediators, including prostaglandins, thromboxanes, nitric oxide, and endothelin-1, may be implicated.[2,3] However, studies with therapies affecting vasoactive factors have produced equivocal results.[1-3]

Chronic nephrotoxicity is related to long-term exposure to ciclosporin.[2] It may be difficult to distinguish between chronic ciclosporin nephrotoxicity and chronic allograft rejection or nephropathy.[4,5] There is a decline in glomerular filtration rate, which may be irreversible or only partially reversible in transplant patients;[3] Some cardiac transplant patients given higher doses than those used in renal transplantation have developed end-stage renal failure.[3] One study[8] in paediatric heart transplant patients found that the decline in renal function correlated with early exposure to ciclosporin. However, in non-transplant patients, renal function impairment has been reported to be reversible after stopping ciclosporin.[3,9] Long-term follow-up has not shown progressive loss of renal function in these patients.[3] Chronic nephrotoxicity is also associated with typical irreversible histological changes, such as interstitial fibrosis.[1-3] which may occur as a result of ischaemic damage secondary to the prolonged alterations in intrarenal haemodynamics.[3] The mechanism is not completely understood, and chronic nephrotoxicity can occur independently of acute renal dysfunction, dosage, or ciclosporin blood concentrations.[4]

Acquired cystic kidney disease developed in 24 of 89 paediatric liver transplant patients treated with ciclosporin compared with 2 of 146 patients treated with tacrolimus in a retrospective study; this difference became evident after 5 to 10 years of follow-up. Those with renal impairment were also found to be at increased risk. However, factors such as renal injury during transplantation, hypertension, or exposure to other nephrotoxic drugs could have contributed to the difference in cyst formation between ciclosporin and tacrolimus. Patients taking ciclosporin were also followed for more than twice as many years as those taking tacrolimus, allowing more time for cysts to develop. Ciclosporin-induced interstitial fibrosis was suggested as a possible mechanism for the effect.[10]

Drugs tried to *ameliorate* the nephrotoxic effects of ciclosporin in patients who have undergone transplantation include calcium-channel blockers (see Transplantation, under Diltiazem, p. 1360.1, Nifedipine, p. 1450.2, and Verapamil, p. 1523.3), clonidine, codergocrine,[11-13] omega-3 triglycerides,[14] misoprostol and other prostaglandin analogues,[15,16] and cilastatin.[17] Although benefits have been reported with some of these, hydration, careful monitoring of ciclosporin concentrations, and the use where possible of low-dose or intermittent regimens of ciclosporin appear to remain the major means of minimising nephrotoxicity. Calcium-channel blockers are used if hypertension occurs (see Effects on the Cardiovascular System, p. 1949.3).

1. Burdmann EA, *et al*. Cyclosporine nephrotoxicity. *Semin Nephrol* 2003; **23:** 465–76.
2. Cattaneo D, *et al*. Nephrotoxic aspects of cyclosporine. *Transplant Proc* 2004; **36** (suppl): 234S–239S.
3. Leaker B, Cairns HS. Clinical aspects of cyclosporin nephrotoxicity. *Br J Hosp Med* 1994; **52:** 529–34.
4. Vítko Š, Viklický O. Cyclosporine renal dysfunction. *Transplant Proc* 2004; **36** (suppl): 243S–247S.
5. Busauschina A, *et al*. Cyclosporine nephrotoxicity. *Transplant Proc* 2004; **36** (suppl): 229S–233S.
6. Shechter P. Acute tubular necrosis following high-dose cyclosporine A therapy. *Eur J Clin Pharmacol* 1996; **49:** 521–3.
7. Dussol B, *et al*. Acute tubular necrosis induced by high level of cyclosporine A in a lung transplant. *Transplantation* 2000; **70:** 1234–6.
8. Hornung TS, *et al*. Renal function after pediatric cardiac transplantation: the effect of early cyclosporin dosage. *Pediatrics* 2001; **107:** 1346–50.
9. Powles AV, *et al*. Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol* 1998; **138:** 443–9.
10. Calvo-Garcia MA, *et al*. Acquired renal cysts after pediatric liver transplantation: association with cyclosporine and renal dysfunction. *Pediatr Transplant* 2008; **12:** 666–71.
11. Heinrichs DA, *et al*. The effects of co-dergocrine on cyclosporin A pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1987; **24:** 117–18.
12. Nussenblatt RB, *et al*. Hydergine and cyclosporin nephrotoxicity. *Lancet* 1986; **i:** 1220–1.
13. Kho TL, *et al*. Hydergine and reversibility of cyclosporin nephrotoxicity. *Lancet* 1986; **ii:** 394–5.
14. Stoof TJ, *et al*. Does fish oil protect renal function in cyclosporin-treated psoriasis patients? *Br J Dermatol* 1990; **123:** 535.
15. Moran M, *et al*. Prevention of acute graft rejection by the prostaglandin E_1 analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; **322:** 1183–8.
16. Di Palo FQ, *et al*. Role of a prostaglandin E_1 analogue in the prevention of acute graft rejection by cyclosporine. *N Engl J Med* 1990; **323:** 832.
17. Tejedor A, *et al*. Cilastatin protection against cyclosporin A-induced nephrotoxicity: clinical evidence. *Curr Med Res Opin* 2007; **23:** 505–13.

Effects on lipids. Marked hyperlipidaemia has been associated with ciclosporin therapy, with notable increases reported in low-density lipoprotein cholesterol,[1,2] and triglycerides. An increase in lipoprotein(a) has been reported,[3] but this was disputed.[4-6] Ciclosporin has been reported to have greater effects on lipids than azathioprine[7] or tacrolimus[8] post-transplantation. The use of corticosteroids with ciclosporin appears to have an additive adverse effect on lipids.[9] Lipid regulating drugs are used to decrease hypercholesterolaemia in transplant patients.

1. Luke DR, *et al*. Longitudinal study of cyclosporine and lipids in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1990; **30:** 163–9.
2. Ballantyne CM, *et al*. Effects of cyclosporine therapy on plasma lipoprotein levels. *JAMA* 1989; **262:** 53–6.
3. Webb AT, *et al*. Does cyclosporin increase lipoprotein(a) concentrations in renal transplant recipients? *Lancet* 1993; **341:** 268–70.
4. Kronenberg F, *et al*. Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; **341:** 765.
5. Segarra A, *et al*. Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; **341:** 766.
6. Hunt BJ, *et al*. Does cyclosporin affect lipoprotein(a) concentrations? *Lancet* 1994; **343:** 119–20.
7. Van den Dorpel MA, *et al*. Conversion from cyclosporine A to azathioprine treatment improves LDL oxidation in kidney transplant recipients. *Kidney Int* 1997; **51:** 1608–12.
8. Taylor DO, *et al*. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. *J Heart Lung Transplant* 1999; **18:** 336–45.
9. Moore R, *et al*. Calcineurin inhibitors and post-transplant hyperlipidaemias. *Drug Safety* 2001; **24:** 755–66.

Effects on the nervous system. Adverse effects of ciclosporin on the CNS include tremor,[1-4] ataxia,[1-3] confusion[1,2,5] or agitation,[2] mental depression,[3] headache,[2,5] sleep disturbances,[2] lethargy,[1,2,6,7] or coma[2,5-7] (in one case coma persisted for 44 days),[8] convulsions,[2,3,5,9-13] leukoencephalopathy,[2,8,9,13] cortical blindness,[2,9] diplopia,[14] and spasticity or paralysis of the limbs.[1,2] Opsoclonus (an involuntary eye movement disorder) has also been reported.[13] In one reported case of posterior leukoencephalopathy, the patient developed irreversible abulia (impairment of ability to perform voluntary actions or make decisions; reduction in speech, movement, thought, and emotional reaction);[15] the patient initially presented with subtle symptoms of decreased appetite and reduced activity. Convulsions have sometimes been associated with hypertension and fluid retention,[11] but this is by no means always the case.[9,10]

Although neurotoxicity usually manifests within a month of beginning treatment, it may be delayed, and in one case occurred only after 3 years of ciclosporin therapy.[16] Severe CNS toxicity has been stated to vary in incidence from 0.1% in renal transplant patients to about 1.6% in bone marrow transplant recipients.[12] There is some evidence for an association of serious neurological effects with low total serum-cholesterol concentrations,[2] and the use of the intravenous formulation.[2] Neurotoxicity may also be associated with the use of lipid solutions.[17] An association with hypomagnesaemia has also been proposed[3] but may just represent concomitant nephrotoxicity.[18] Convulsions may be more likely or more severe in patients with a familial history of epilepsy,[19] subclinical aluminium overload,[20] or in those also given high-dose corticosteroids.[5,21,22]

The mechanism of toxicity is unknown but may be associated with disturbance of the blood-brain barrier;[10,12,23] it has been suggested that the metabolite M-17, or possibly other metabolites, are responsible for neurotoxicity.[6] Ciclosporin may be selectively toxic for glial cells, and alteration of sympathetic outflow by calcineurin inhibition may also mediate neurotoxicity.[24]

For reports of calcineurin inhibitor-induced pain syndrome which has sometimes been associated with use of ciclosporin, see p. 1949.1.

1. Atkinson K, *et al*. Cyclosporine-associated central-nervous-system toxicity after allogeneic bone-marrow transplantation. *N Engl J Med* 1984; **310:** 527.
2. de Groen PC, *et al*. Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. *N Engl J Med* 1987; **317:** 861–6.
3. Thompson CB, *et al*. Association between cyclosporin neurotoxicity and hypomagnesaemia. *Lancet* 1984; **ii:** 1116–20.
4. Munhoz RP, *et al*. Movement disorders secondary to long-term treatment with cyclosporine A. *Arq Neuropsiquiatr* 2005; **63:** 592–6.
5. Taque S, *et al*. Central neurotoxicity of cyclosporine in two children with nephrotic syndrome. *Pediatr Nephrol* 2004; **19:** 276–80.
6. Kunzendorf U, *et al*. Cyclosporin metabolites and central-nervous-system toxicity. *Lancet* 1988; **i:** 1223.
7. Lischke R, *et al*. Cyclosporine-related neurotoxicity in a patient after bilateral lung transplantation for cystic fibrosis. *Transplant Proc* 2004; **36:** 2837–9.
8. Berden JHM, *et al*. Severe central-nervous-system toxicity associated with cyclosporin. *Lancet* 1985; **i:** 219–20.
9. Hughes RL. Cyclosporine-related central nervous system toxicity in cardiac transplantation. *N Engl J Med* 1990; **323:** 420–1.
10. Gottrand F, *et al*. Cyclosporine neurotoxicity. *N Engl J Med* 1991; **324:** 1744–5.
11. Joss DV, *et al*. Hypertension and convulsions in children receiving cyclosporin A. *Lancet* 1982; **i:** 906.
12. Krupp P, *et al*. Encephalopathy associated with fat embolism induced by solvent for cyclosporin. *Lancet* 1989; **i:** 168–9.
13. Marchiori PE, *et al*. Cyclosporine A-induced ocular opsoclonus and reversible leukoencephalopathy after orthotopic liver transplantation: brief report. *Clin Neuropharmacol* 2004; **27:** 195–7.
14. Openshaw H. Eye movement abnormality associated with cyclosporin. *J Neurol Neurosurg Psychiatry* 2001; **70:** 809.
15. Nishie M, *et al*. Posterior encephalopathy subsequent to cyclosporin A presenting as irreversible abulia. *Intern Med* 2003; **42:** 750–5.
16. Welge-Lüssen UC, Gerhartz HH. Late onset of neurotoxicity with cyclosporin. *Lancet* 1994; **343:** 293.
17. De Klippel N. Cyclosporin leukoencephalopathy induced by intravenous lipid solution. *Lancet* 1992; **339:** 1114.
18. Allen RD, *et al*. Cyclosporin and magnesium. *Lancet* 1985; **i:** 1283–4.
19. Velu T, *et al*. Cyclosporin-associated fatal convulsions. *Lancet* 1985; **i:** 219.
20. Nordal KP, *et al*. Aluminium overload, a predisposing condition for epileptic seizures in renal-transplant patients treated with cyclosporin. *Lancet* 1985; **ii:** 153–4.
21. Durrant S, *et al*. Cyclosporin A, methylprednisolone, and convulsions. *Lancet* 1982; **ii:** 829–30.
22. Boogaerts MA, *et al*. Cyclosporin, methylprednisolone, and convulsions. *Lancet* 1982; **ii:** 1216–17.
23. Sloane JP, *et al*. Disturbance of blood-brain barrier after bone-marrow transplantation. *Lancet* 1985; **ii:** 280–1.
24. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13:** 313–26.

Effects on skeletal muscle. Ciclosporin has occasionally been associated with myopathy.[1-6] The manufacturer noted that 29 cases had been reported by December 1990, which appeared to be divided into cases of toxic or non-specific myopathy or mild sensory motor neuropathy, which were generally dose-related; and rhabdomyolysis, often, but not always, when used with lovastatin or colchicine.[7] Rhabdomyolysis has also been reported when other statins were used with ciclosporin, see Lipid Regulating Drugs, under Interactions, p. 1954.1.

1. Noppen M, *et al*. Cyclosporine and myopathy. *Ann Intern Med* 1987; **107:** 945–6.
2. Goy J-J. Myopathy as possible side-effect of cyclosporin. *Lancet* 1989; **i:** 1446–7.
3. Grezard O, *et al*. Cyclosporin-induced muscular toxicity. *Lancet* 1990; **335:** 177.
4. Fernandez-Sola J, *et al*. Reversible cyclosporin myopathy. *Lancet* 1990; **335:** 362–3.
5. Wahie S, Meggitt SJ. Myotoxicity occurring with ciclosporin in a patient with atopic dermatitis. *Br J Dermatol* 2005; **153:** 1238.
6. Khan S, *et al*. Musculoskeletal and myotoxic side-effects in a patient treated for psoriasis. *Br J Dermatol* 2006; **155:** 481.
7. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; **337:** 915.

Hyperplasia. Ciclosporin is well known to be associated with the development of gingival hyperplasia or gingival overgrowth: one review[1] has estimated the incidence at about 30% in transplant patients, while noting that reported values in the literature range from about 7 to 70%. A large study[2] found dosage and serum concentration of ciclosporin to be the most significant risk factors in the development of gingival hyperplasia. The presence of dental plaque may exacerbate the response, and good oral hygiene is important in preventing or minimising of gingival overgrowth.[1] Use with nifedipine (which can itself produce hyperplasia) may exacerbate overgrowth;[3] a cohort study[4] of renal transplant recipients found that amlodipine was associated with a greater prevalence of overgrowth than nifedipine. Overgrowth is generally reversible after dosage reduction or withdrawal of ciclosporin; where this is not feasible, surgical excision is recommended.[1] However, improvement or resolution of the overgrowth may

also be produced by a course of azithromycin.[5-7] Similar benefit has been reported for metronidazole in some[8,9] but not all patients.[10] There are reports[11,12] of marked improvement in hyperplasia after changing treatment from ciclosporin to tacrolimus, including a case apparently resistant to azithromycin.[13]

Enlargement of the papillae of the tongue[14] and sebaceous gland hyperplasia[15] have also occurred in association with ciclosporin.

1. Brunet L, *et al.* Gingival enlargement induced by drugs. *Drug Safety* 1996; **15:** 219–31.
2. Thomas DW, *et al.* Risk factors in the development of cyclosporine-induced gingival overgrowth. *Transplantation* 2000; **69:** 522–6.
3. Slavin J, Taylor J. Cyclosporin, nifedipine, and gingival hyperplasia. *Lancet* 1987; **ii:** 739.
4. James JA, *et al.* The calcium channel blocker used with cyclosporin has an effect on gingival overgrowth. *J Clin Periodontol* 2000; **27:** 109–15.
5. Jucglà A, *et al.* The use of azithromycin for cyclosporin-induced gingival overgrowth. *Br J Dermatol* 1998; **138:** 198–9.
6. Nash MM, Zaltzman JS. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 1998; **65:** 1611–15.
7. Citterio F, *et al.* Azithromycin treatment of gingival hyperplasia in kidney transplant recipients is effective and safe. *Transplant Proc* 2001; **33:** 2134–5.
8. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343:** 986.
9. Cecchin E, *et al.* Treatment of cyclosporine-induced gingival hypertrophy. *Ann Intern Med* 1997; **126:** 409–10.
10. Aufricht C, *et al.* Oral metronidazole does not improve cyclosporine A-induced gingival hyperplasia. *Pediatr Nephrol* 1997; **11:** 552–5.
11. Thorp M, *et al.* The effect of conversion from cyclosporine to tacrolimus on gingival hyperplasia, hirsutism and cholesterol. *Transplantation* 2000; **69:** 1218–20.
12. James JA, *et al.* Reduction in gingival overgrowth associated with conversion from cyclosporin A to tacrolimus. *J Clin Periodontol* 2000; **27:** 144–8.
13. Vallejo C, *et al.* Resolution of cyclosporine-induced gingival hyperplasia resistant to azithromycin by switching to tacrolimus. *Haematologica* 2001; **86:** 110.
14. Silverberg NB, *et al.* Lingual fungiform papillae hypertrophy with cyclosporin A. *Lancet* 1996; **348:** 967.
15. Boschnakow A, *et al.* Ciclosporin A-induced sebaceous gland hyperplasia. *Br J Dermatol* 2003; **149:** 198–200.

Hypersensitivity. Anaphylactoid reactions in 5 of 21 patients given intravenous ciclosporin infusions were found to be associated with improper mixing of the ciclosporin concentrate, which had a polyoxyl castor oil vehicle, with the infusion solution.[1] It was concluded that this had led to an initial bolus of polyoxyl castor oil that had triggered the anaphylactic reactions. Subsequent study indicated that peak concentrations of up to 9 times the intended concentration of ciclosporin and polyoxyl castor oil were present in the first 10 minutes of a poorly mixed infusion.[2] Anaphylactic shock after ingestion of ciclosporin capsules has been reported. The microemulsifying base containing corn oil and polyoxyl 40 hydrogenated castor oil, which is related to the polyoxyl castor oil vehicle used in the intravenous formulation, was considered to be the likely cause.[3]

1. Liau M, *et al.* High incidence of anaphylactoid reactions to i v cyclosporin A caused by improper dissolution of Cremophor EL. *Clin Pharmacol Ther* 1995; **57:** 209.
2. Liau-Chu M, *et al.* Mechanism of anaphylactoid reactions: improper preparation of high-dose intravenous cyclosporine leads to bolus infusion of Cremophor EL and cyclosporine. *Ann Pharmacother* 1997; **31:** 1287–91.
3. Kuiper RAJ, *et al.* Cyclosporine-induced anaphylaxis. *Ann Pharmacother* 2000; **34:** 858–61.

Hyperuricaemia. Ciclosporin therapy may be associated with marked hyperuricaemia,[1-3] which may lead (mainly in male patients[1]) to episodes of severe gouty arthritis.[1-3] It has been suggested that ciclosporin specifically reduces urate clearance by the kidney independently of its effects on glomerular filtration,[4,5] but this has been disputed.[6] Treatment of ciclosporin-induced gout can be difficult since interactions with NSAIDs may lead to enhanced renal toxicity[5] and patients who are also receiving azathioprine may have increased bone-marrow toxicity if given allopurinol.[7] Benzbromarone appears to be an alternative[8] for treating hyperuricaemia in renal transplant recipients with a creatinine clearance greater than 25 mL/minute.

1. Lin H-Y, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1989; **321:** 287–92.
2. Kahl LE, *et al.* Gout in the heart transplant recipient: physiologic puzzle and therapeutic challenge. *Am J Med* 1989; **87:** 289–94.
3. Burack DA, *et al.* Hyperuricemia and gout among heart transplant recipients receiving cyclosporine. *Am J Med* 1992; **92:** 141–6.
4. Noordzij TC, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; **322:** 335.
5. Farge D, *et al.* Hyperuricemia and gouty arthritis in heart transplant recipients. *Am J Med* 1990; **88:** 553.
6. Zürcher RM, *et al.* Hyperuricaemia in cyclosporin-treated patients: a GFR-related effect. *Nephrol Dial Transplant* 1996; **11:** 153–8.
7. Figg WD. Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; **332:** 334–5.
8. Zürcher RM, *et al.* Excellent uricosuric efficacy of benzbromarone in cyclosporin-A-treated renal transplant patients: a prospective study. *Nephrol Dial Transplant* 1994; **9:** 548–51.

Overdosage. Anxiety, diarrhoea, vomiting, and perspiration, with weak and irregular pulse, occurred in a patient accidentally injected with 250 mg (estimated 6.25 mg/kg) of ciclosporin.[1] The patient subsequently developed atrial fibrillation, which was treated with digoxin, and in the next 36 hours showed signs of slight renal insufficiency. Two days later no adverse effects were apparent. Atrial fibrillation also developed in another patient accidentally given 1 g of microemulsifying oral ciclosporin.[2] No adverse renal, hepatic, or neurological effects were seen in a third patient[3] who took 25 g of ciclosporin over 8 days. There was a mild increase in blood pressure and other symptoms included burning sensations in the mouth and the extremities, dysgeusia, facial flushing, and gastrointestinal disturbances. Symptoms resolved within 2 weeks of stopping ciclosporin.

A patient accidentally given intravenous ciclosporin at 30 mg/hour for 13 hours, developed massive intracerebral oedema and brainstem compression and died despite stopping the infusion.[4]

Although ciclosporin is only minimally dialysable, whole blood exchange (therapeutic erythrocytapheresis followed by plasma exchange) has been used in the management of a patient inadvertently given 3.5 g of ciclosporin orally; the overdose was discovered too late for the use of activated charcoal or gastric lavage, and plasma exchange alone was considered unsuitable because of the partitioning of ciclosporin between plasma and erythrocytes. The patient, who had signs of nephrotoxicity and hepatotoxicity, recovered without long-term sequelae.[5]

For reference to tubular necrosis after extremely high intravenous doses of ciclosporin, see under Effects on the Kidneys, p. 1950.1.

1. Wallemacq PE, Lesne ML. Accidental massive IV administration of cyclosporine in man. *Drug Intell Clin Pharm* 1985; **19:** 29–30.
2. LoVecchio FA, Goltz HR. Atrial fibrillation following acute overdose with oral cyclosporine. *Ann Pharmacother* 2000; **34:** 405.
3. Baumhefner RW, *et al.* Huge cyclosporin overdose with favourable outcome. *Lancet* 1987; **ii:** 332.
4. de Perrot M, *et al.* Massive cerebral edema after i.v. cyclosporin overdose. *Transplantation* 2000; **70:** 1259–60.
5. Kwon SU, *et al.* Successful whole blood exchange by apheresis in a patient with acute cyclosporine intoxication without long-term sequelae. *J Heart Lung Transplant* 2006; **25:** 483–5.

Precautions

Regular monitoring of renal and hepatic function, blood pressure, and serum electrolytes (chiefly potassium and magnesium) is required in patients receiving ciclosporin. Serum lipids should also be monitored. Monitoring of plasma ciclosporin concentrations is mandatory in transplant patients. Dosage adjustment is often necessary in patients with renal impairment or other factors affecting plasma ciclosporin concentrations. Care is required in patients with hyperuricaemia, and intravenous formulations should be given cautiously to those who have previously received parenteral drugs formulated in polyoxyl castor oil, or to those with a history of allergic reactions.

Ciclosporin should not be used to treat atopic dermatitis, psoriasis, or rheumatoid arthritis in patients with persistently raised creatinine, uncontrolled hypertension, uncontrolled infections, or malignancy. An exception is patients with treated malignant or pre-malignant lesions of the skin who may receive ciclosporin as a last resort for psoriasis. Psoriatic patients should not be given concomitant ultraviolet irradiation and should avoid excessive sun exposure. Ciclosporin may increase the risk of benign intracranial hypertension.

The commercially available oral formulations of ciclosporin differ in their bioavailability, and patients should not be transferred from one to another without appropriate monitoring (see Administration, Oral, p. 1946.2). Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Immunosuppressants may reduce the response to vaccines and use with live vaccines should generally be avoided as there is a possibility of generalised infection, see Vaccines, p. 1955.1.

Breast feeding. The American Academy of Pediatrics considers that ciclosporin may possibly suppress the immune system in a nursing infant.[1] However, a study[2] in the breast-fed infants of 7 women given ciclosporin found that the amounts ingested by the infant produced undetectable blood concentrations. In another case it was estimated that a breast-fed infant received less than 100 micrograms/kg of ciclosporin daily.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/01/08)
2. Nyberg G, *et al.* Breast feeding during treatment with cyclosporine. *Transplantation* 1998; **65:** 253–5.
3. Thiru Y, *et al.* Successful breast feeding while mother was taking cyclosporin. *BMJ* 1997; **315:** 463.

Porphyria. There have been reports of patients with acute intermittent porphyria given ciclosporin pre- and post-transplant with no exacerbation of symptoms.[1,2] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ciclosporin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[3]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; **41:** 113–15.
2. Warholm C, Wilczek H. Renal transplantation in a case of acute intermittent porphyria. *J Clin Pharmacol* 2003; **43:** 1158–60.
3. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pregnancy. Ciclosporin has been used successfully in pregnant women. However, in common with other immunosuppressants, fetal growth retardation may be a significant problem.[1-4] Patients with hypertension or graft dysfunction are more likely to have adverse outcomes, so patients should have stable graft function and be on maintenance therapy before considering pregnancy.[1,2] Serum ciclosporin concentrations may fall during pregnancy,[2,3,5] but although frequent monitoring is necessary, the altered immune state of pregnancy may protect against rejection episodes.[5] Ciclosporin should be used at the lowest possible dose to maintain efficacy, and one review[3] has recommended that the daily dose should be kept below 5 mg/kg.

One case of osseous malformation, resulting in hypoplasia of the right leg has been reported in an infant born to a ciclosporin-treated mother.[6]

1. Armenti VT, *et al.* Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation* 1995; **59:** 476–9.
2. Armenti VT, *et al.* National Transplantation Pregnancy Registry (NTPR): cyclosporine dosing and pregnancy outcome in female renal transplant recipients. *Transplant Proc* 1996; **28:** 2111–12.
3. Huynh LA, Min DI. Outcomes of pregnancy and the management of immunosuppressive agents to minimize fetal risks in organ transplant patients. *Ann Pharmacother* 1994; **28:** 1355–6.
4. Lamarque V, *et al.* Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. *Transplant Proc* 1997; **29:** 2480.
5. Thomas AG, *et al.* The effect of pregnancy on cyclosporine levels in renal allograft patients. *Obstet Gynecol* 1997; **90:** 916–19.
6. Pujals JM, *et al.* Osseous malformation in baby born to woman on cyclosporin. *Lancet* 1989; **i:** 667.

Interactions

Ciclosporin is extensively metabolised in the liver and plasma-ciclosporin concentrations may be affected by inducers or competitive inhibitors of hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4. For example, use of carbamazepine, nevirapine, phenytoin, phenobarbital, rifampicin, St John's wort, and other inducers of hepatic enzymes may lead to lower plasma concentrations of ciclosporin, and increased plasma concentrations have been reported with some antifungals, macrolide antibacterials, HIV-protease inhibitors, the NNRTI delavirdine, some calcium-channel blockers, sex hormones, corticosteroids and grapefruit juice. In transplant patients frequent measurement of plasma ciclosporin and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of other drugs.

Concurrent use of statins may increase the risk of myopathy and rhabdomyolysis. Potassium-sparing diuretics should be avoided because of the risk of hyperkalaemia, and patients taking ciclosporin should avoid a high dietary intake of potassium. The risk of gingival hyperplasia may be increased by amlodipine or nifedipine.

During treatment with ciclosporin, vaccination may be less effective, and the use of live vaccines should generally be avoided.

Care should be taken when ciclosporin is given with other nephrotoxic drugs.

Reviews of the interactions of ciclosporin.

1. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin. *Clin Pharmacokinet* 1990; **19:** 319–32 and 400–15.
2. Lake KD, Canafax DM. Important interactions of drugs with immunosuppressive agents used in transplant recipients. *J Antimicrob Chemother* 1995; **36** (suppl B): 11–22.
3. Campana C, *et al.* Clinically significant drug interactions with cyclosporin: an update. *Clin Pharmacokinet* 1996; **30:** 141–79.
4. Chan L-N. Drug-nutrient interactions in transplant recipients. *J Parenter Enteral Nutr* 2001; **25:** 132–41.

Antibacterials. *AMINOGLYCOSIDES.* Increased nephrotoxicity has been reported after the use of aminoglycosides with ciclosporin.[1,2] However, a retrospective analysis in 21 patients given ciclosporin for allogeneic bone marrow transplant, in whom aminoglycosides were used if fever and neutropenia developed, showed no greater incidence of nephrotoxicity than in 20 autologous bone marrow recipients who did not receive ciclosporin, suggesting that these drugs can be given together provided careful monitoring is maintained.[3]

1. Termeer A, *et al.* Severe nephrotoxicity cause by the combined use of gentamicin and cyclosporine in renal allograft recipients. *Transplantation* 1986; **42:** 220–1.
2. Morales JM, *et al.* Reversible acute renal toxicity by toxic sinergic effect between gentamicin and cyclosporine. *Clin Nephrol* 1988; **29:** 272.
3. Chandrasekar PH, Cronin SM. Nephrotoxicity in bone marrow transplant recipients receiving aminoglycoside plus cyclosporine or aminoglycoside alone. *J Antimicrob Chemother* 1991; **27:** 845–9.

CHLORAMPHENICOL. Marked rises in plasma-ciclosporin concentrations have been reported when chloramphenicol was given.[1-3] Ciclosporin trough concentrations should be monitored if these drugs are used together.[3]

1. Steinfort CL, McConachy KA. Cyclosporin-chloramphenicol drug interaction in a heart-lung transplant recipient. *Med J Aust* 1994; **161:** 455.
2. Bui LL, Huang DD. Possible interaction between cyclosporine and chloramphenicol. *Ann Pharmacother* 1999; **33:** 252–3.
3. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; **4:** 169–74.

FLUOROQUINOLONES. Several reports have indicated that the quinolone *ciprofloxacin* has no effect on the pharmacokinetics of ciclosporin.[1-3] However, there is a report of enhanced nephrotoxicity without a change in ciclosporin concentrations in a patient given ciprofloxacin,[4] and another report showing both enhanced nephrotoxicity and increased ciclosporin concentrations.[5] Furthermore, a small case-control study suggested an increase in transplant rejection with ciprofloxacin.[6] *Norfloxacin* has been reported to decrease clearance and increase blood concentrations of ciclosporin in paediatric patients,[7] probably by inhibition of ciclosporin metabolism. *Levofloxacin* did not alter ciclosporin pharmacokinetics in healthy subjects,[8] but a study in renal transplant patients found that levofloxacin partially inhibited the metabolism of ciclosporin;[9] no adverse effects and no supratherapeutic concentrations of ciclosporin were seen.

1. Hooper TL, *et al.* Ciprofloxacin: a preferred treatment for legionella infections in patients receiving cyclosporin A. *J Antimicrob Chemother* 1988; **22:** 952–3.
2. Tan KKC, *et al.* Co-administration of ciprofloxacin and cyclosporin: lack of evidence for a pharmacokinetic interaction. *Br J Clin Pharmacol* 1989; **28:** 185–7.
3. Krüger HU, *et al.* Investigation of potential interaction of ciprofloxacin with cyclosporine in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1990; **34:** 1048–52.
4. Elston RA, Taylor J. Possible interaction of ciprofloxacin with cyclosporin A. *J Antimicrob Chemother* 1988; **21:** 679–80.
5. Nasir M, *et al.* Interaction between ciclosporin and ciprofloxacin. *Nephron* 1991; **57:** 245–6.
6. Wrishko RE, *et al.* Investigation of a possible interaction between ciprofloxacin and cyclosporine in renal transplant patients. *Transplantation* 1997; **64:** 996–9.
7. McLellan RA, *et al.* Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation. *Clin Pharmacol Ther* 1995; **58:** 322–7.
8. Doose DR, *et al.* Levofloxacin does not alter cyclosporine disposition. *J Clin Pharmacol* 1998; **38:** 90–93.
9. Federico S, *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; **45:** 169–75.

LINCOSAMIDES. Decreased plasma-ciclosporin concentrations, requiring increases in the daily dose, were seen in 2 lung transplant patients given oral *clindamycin* for lung infection. In both cases, the original doses of ciclosporin were resumed once clindamycin had been stopped. The authors suggested close monitoring of plasma-ciclosporin levels if this combination were used.[1]

1. Thurnheer R, *et al.* Possible interaction between clindamycin and cyclosporin. *BMJ* 1999; **319:** 163.

MACROLIDES. Markedly raised blood concentrations of ciclosporin have been reported in patients also given *erythromycin.*[1-4] The mechanism involved appears to be a combination of decreased hepatic metabolism of ciclosporin and increased gastrointestinal absorption.[5] Similar elevations of ciclosporin concentrations have been noted after use with other macrolide antibacterials, including *clarithromycin,*[6-8] *josamycin,*[9,10] *midecamycin,*[11] *midecamycin acetate,*[12] and the structurally-related streptogramins, *pristinamycin*[13] and *quinupristin/dalfopristin.*[14] Small increases in ciclosporin concentrations have been seen with *roxithromycin.*[15] Increases in ciclosporin concentrations were attributed to *azithromycin* in 2 patients,[16,17] but a study in 6 patients found no effect.[18] *Spiramycin* does not appear to affect the pharmacokinetics of ciclosporin.[19,20]

1. Ptachcinski RJ, *et al.* Effect of erythromycin on cyclosporine levels. *N Engl J Med* 1985; **313:** 1416–17.
2. Martell R, *et al.* The effects of erythromycin in patients treated with cyclosporine. *Ann Intern Med* 1986; **104:** 660–1.
3. Wadhwa NK, *et al.* Interaction between erythromycin and cyclosporine in a kidney and pancreas allograft recipient. *Ther Drug Monit* 1987; **9:** 123–5.
4. Gupta SK, *et al.* Cyclosporin-erythromycin interaction in renal transplant patients. *Br J Clin Pharmacol* 1989; **27:** 475–81.
5. Ignoffo RJ, Kim LE. Erythromycin and cyclosporine drug interaction. *DICP Ann Pharmacother* 1991; **25:** 30–1.
6. Ferrari SL, *et al.* The interaction between clarithromycin and cyclosporine in kidney transplant recipients. *Transplantation* 1994; **58:** 725–7.
7. Treille S, *et al.* Kidney graft dysfunction after drug interaction between clarithromycin and cyclosporin. *Nephrol Dial Transplant* 1996; **11:** 1192–3.
8. Sádaba B, *et al.* Concurrent clarithromycin and cyclosporin A treatment. *J Antimicrob Chemother* 1998; **42:** 393–5.
9. Kreft-Jais C, *et al.* Effect of josamycin on plasma cyclosporine levels. *Eur J Clin Pharmacol* 1987; **32:** 327–8.
10. Azanza JR, *et al.* Possible interaction between cyclosporine and josamycin: a description of three cases. *Clin Pharmacol Ther* 1992; **51:** 572–5.
11. Alfonso I, *et al.* Interaction between cyclosporine A and midecamycin. *Eur J Clin Pharmacol* 1997; **52:** 79–80.
12. Couet W, *et al.* Effect of ponsinomycin on cyclosporin pharmacokinetics. *Eur J Clin Pharmacol* 1990; **39:** 165–7.
13. Garraffo R, *et al.* Pristinamycin increases cyclosporin blood levels. *Med Sci Res* 1987; **15:** 461.
14. Stamatakis MK, Richards JG. Interaction between quinupristin/dalfopristin and cyclosporine. *Ann Pharmacother* 1997; **31:** 576–8.
15. Billaud EM, *et al.* Interaction between roxithromycin and cyclosporin in heart transplant patients. *Clin Pharmacokinet* 1990; **19:** 499–502.
16. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. *Nephron* 1995; **70:** 130.
17. Page RL, *et al.* Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy* 2001; **21:** 1436–43.
18. Gómez E, *et al.* Interaction between azithromycin and cyclosporin? *Nephron* 1996; **73:** 724.
19. Vernillet L, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1989; **27:** 789–94.
20. Kessler M, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1990; **29:** 370–1.

PENICILLINS. Decreased plasma-ciclosporin concentrations and effect were seen in a patient given *nafcillin.*[1] Conversely, another study reported increased nephrotoxicity from the use of ciclosporin with nafcillin but no apparent increase in ciclosporin concentrations.[2] Raised plasma-ciclosporin concentrations have been reported in a patient after receiving treatment with *ticarcillin.*[3]

1. Veremis SA, *et al.* Subtherapeutic cyclosporine concentrations during nafcillin therapy. *Transplantation* 1987; **43:** 913–15.
2. Jahansouz F, *et al.* Potentiation of cyclosporine nephrotoxicity by nafcillin in lung transplant recipients. *Transplantation* 1993; **55:** 1045–8.
3. Lambert C, *et al.* Interaction ciclosporine-ticarcilline chez un transplanté rénal. *Presse Med* 1989; **18:** 230.

RIFAMYCINS. Use with *rifampicin* has been associated with marked decreases in blood-ciclosporin concentrations,[1-5] and has resulted in graft rejection.[1,3] Although it has been assumed that this effect represents induction of the hepatic metabolism of ciclosporin by rifampicin, there is some suggestion that rifampicin may decrease the absorption of ciclosporin or induce intestinal metabolism, resulting in reduced bioavailability.[6] Topical application of *rifamycin* has also been associated with a decrease in blood-ciclosporin concentrations in another patient;[7] ciclosporin concentrations rose immediately after withdrawal of rifamycin, suggesting that the effect was not due to enzyme induction.

1. Langhoff E, Madsen S. Rapid metabolism of cyclosporin and prednisone in kidney transplant patient receiving tuberculostatic treatment. *Lancet* 1983; **ii:** 1031.
2. Daniels NJ, *et al.* Interaction between cyclosporin and rifampicin. *Lancet* 1984; **ii:** 639.
3. Allen RDM, *et al.* Cyclosporin and rifampicin in renal transplantation. *Lancet* 1985; **i:** 980.
4. Freitag VL, *et al.* Effect of short-term rifampin on stable cyclosporine concentrations. *Ann Pharmacother* 1999; **33:** 871–2.
5. Zelunka EJ. Intravenous cyclosporine-rifampin interaction in a pediatric bone marrow transplant recipient. *Pharmacotherapy* 2002; **22:** 387–90.
6. Hebert MF, *et al.* Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. *Clin Pharmacol Ther* 1992; **52:** 453–7.
7. Renoult E, *et al.* Effect of topical rifamycin SV treatment on cyclosporin A blood levels in a renal transplant recipient. *Eur J Clin Pharmacol* 1991; **40:** 433–4.

STREPTOGRAMINS. Increased plasma concentrations of ciclosporin have occurred after therapy with *pristinamycin* and *quinupristin/dalfopristin* (see Macrolides, above).

SULFONAMIDES. Intravenous, but not oral, therapy with *sulfadimidine* and *trimethoprim* has been associated with falls in ciclosporin concentrations to subtherapeutic values.[1,2] Oral *sulfadiazine* has had a similar effect.[3] Conversely, *trimethoprim* and *co-trimoxazole* can cause rises in serum creatinine, and therefore may contribute to ciclosporin-induced nephrotoxicity.[4,5]

1. Wallwork J, *et al.* Cyclosporin and intravenous sulphadimidine and trimethoprim therapy. *Lancet* 1983; **i:** 366–7.
2. Jones DK, *et al.* Serious interaction between cyclosporin A and sulphadimidine. *BMJ* 1986; **292:** 728–9.
3. Spes CH, *et al.* Sulfadiazine therapy for toxoplasmosis in heart transplant recipients decreases cyclosporine concentration. *Clin Investig* 1992; **70:** 752–4.
4. Thompson JF, *et al.* Nephrotoxicity of trimethoprim and cotrimoxazole in renal allograft recipients treated with cyclosporine. *Transplantation* 1983; **36:** 204–6.
5. Ringden O, *et al.* Nephrotoxicity by co-trimoxazole and cyclosporin in transplanted patients. *Lancet* 1984; **i:** 1016.

TIGECYCLINE. Marked increases in the serum concentration of ciclosporin occurred in a renal transplant patient during antibacterial treatment with tigecycline;[1] the patient developed signs of nephrotoxicity and the ciclosporin dose had to be reduced by 50% and omitted for one day. Three days after antibacterial therapy was complete, ciclosporin had to be increased again to the previous dose in order to maintain therapeutic concentrations.

1. Stumpf AN, *et al.* High serum concentrations of ciclosporin related to administration of tigecycline. *Eur J Clin Pharmacol* 2009; **65:** 101–3.

Antidepressants. Giving *fluoxetine* to a patient receiving ciclosporin as part of an immunosuppressant regimen after cardiac transplantation was associated with a subsequent marked increase in ciclosporin trough blood concentrations to about twice their original value, necessitating a reduction in ciclosporin dosage.[1] After withdrawal of fluoxetine, ciclosporin concentrations fell, and dosage had to be increased. However, a study in 13 other patients given ciclosporin with fluoxetine failed to find any evidence of altered ciclosporin concentrations.[2] A nearly ten-fold increase in ciclosporin concentration was seen in a cardiac transplant patient after use of *nefazodone,*[3] and there are 2 case reports[4] of ciclosporin toxicity due to interactions with nefazodone and *fluvoxamine* in renal transplant recipients. Ciclosporin concentrations decreased in a 10-year-old African American heart transplant recipient 22 days after starting *bupropion.* Despite an increase in ciclosporin dosage, ciclosporin concentrations decreased even further, necessitating another increase in ciclosporin dose, and withdrawal of bupropion.[5]

1. Horton RC, Bonser RS. Interaction between cyclosporin and fluoxetine. *BMJ* 1995; **311:** 422.
2. Strouse TB, *et al.* Fluoxetine and cyclosporine in organ transplantation: failure to detect significant drug interactions or adverse clinical events in depressed organ recipients. *Psychosomatics* 1996; **37:** 23–30.
3. Wright DH, *et al.* Nefazodone and cyclosporine drug-drug interaction. *J Heart Lung Transplant* 1999; **18:** 913–15.
4. Vella JP, Sayegh MH. Interactions between cyclosporine and newer antidepressant medications. *Am J Kidney Dis* 1998; **31:** 320–3.
5. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; **11:** 193–8.

ST JOHN'S WORT. Ciclosporin plasma levels are reduced by St John's wort.[1] This has led to acute rejection episodes in transplant patients,[2] and the two drugs should not be used together.[3]

1. Bauer S, *et al.* Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br J Clin Pharmacol* 2003; **55:** 203–11.
2. Ernst E. St John's wort supplements endanger the success of organ transplantation. *Arch Surg* 2002; **137:** 316–19.
3. CSM/MCA Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074626&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)

Antidiabetics. Use of *glibenclamide* with ciclosporin in 6 patients was associated with a mean 57% increase in the steady-state plasma concentration of ciclosporin, suggesting that dosage adjustment may be necessary when both drugs are given.[1]

For the effect of ciclosporin on *repaglinide*, see under Interactions of Repaglinide, p. 496.1.

1. Islam SI, *et al.* Possible interaction between cyclosporine and glibenclamide in posttransplant diabetic patients. *Ther Drug Monit* 1996; **18:** 624–6.

Antiepileptics. Use with the antiepileptics *carbamazepine,*[1-3] *phenobarbital,*[4] and *phenytoin,*[5] which are all inducers of hepatic cytochrome P450, has been associated with a reduction in blood-ciclosporin concentrations. *Oxcarbazepine* also decreased ciclosporin trough concentrations in a kidney transplant recipient with epilepsy; concentrations were corrected by an increase in ciclosporin dose. The dose of oxcarbazepine also had to be reduced due to hyponatraemia, and ciclosporin concentrations remained stable thereafter.[6] *Valproate* has been successfully used in ciclosporin-treated patients without apparent interaction.[1,2]

1. Hillebrand G, *et al.* Valproate for epilepsy in renal transplant recipients receiving cyclosporine. *Transplantation* 1987; **43:** 915–16.
2. Schofield OMV, *et al.* Cyclosporin A in psoriasis: interaction with carbamazepine. *Br J Dermatol* 1990; **122:** 425–6.
3. Cooney GF, *et al.* Effects of carbamazepine on cyclosporine metabolism in pediatric renal transplant recipients. *Pharmacotherapy* 1995; **15:** 353–6.
4. Carstensen H, *et al.* Interaction between cyclosporin A and phenobarbitone. *Br J Clin Pharmacol* 1986; **21:** 550–1.
5. Freeman DJ, *et al.* Evaluation of cyclosporin-phenytoin interaction with observations on cyclosporin metabolites. *Br J Clin Pharmacol* 1984; **18:** 887–93.
6. Rösche J, *et al.* Possible oxcarbazepine interaction with cyclosporine serum levels: a single case study. *Clin Neuropharmacol* 2001; **24:** 113–16.

Antifungals. The imidazole *ketoconazole* is a potent inhibitor of hepatic cytochrome P450 and markedly increased blood-ciclosporin concentrations have resulted when conventional formulations of the latter were given with the antifungal.[1-4] The interaction has been used, similarly to the calcium-channel blockers (see p. 1953.3), to permit therapeutic blood concentrations of ciclosporin to be achieved at lower doses;[5-8] however, this method may result in considerable variations in ciclosporin pharmacokinetics, and has been criticised on several grounds.[9] It was noted[10] that this improved bioavailability of ciclosporin was not seen when the microemulsifying formulation (see Absorption under Pharmacokinetics, p. 1955.2) was given with ketoconazole, suggesting that bioavailability was already maximal. Increased ciclosporin concentrations have also been reported with *itraconazole,*[11,12] and it has also been suggested[13] that use be made of this interaction, similarly to ketoconazole, to allow for decreased ciclosporin doses. *Voriconazole* also increases exposure to ciclosporin, and ciclosporin concentrations should be closely monitored.[14,15] There is a single report of increased ciclosporin plasma concentrations with use of *miconazole.*[16] However, although such an interaction has also been reported with *fluconazole,*[17,18] a small study has failed to note any significant interaction;[19,20] it has been suggested that an interaction may take place only at high doses of fluconazole,[21] or that sex and ethnicity may play a role.[18]

Increased nephrotoxicity may occur if ciclosporin is used with *amphotericin B,*[22,23] while liposomal amphotericin B has

been reported possibly to exacerbate ciclosporin neurotoxicity.[24] There is a report of decreased ciclosporin concentrations in a patient after addition of *griseofulvin* to therapy.[25] Modest decreases have also been seen in ciclosporin concentrations when *terbinafine* was given.[26] *Micafungin* modestly inhibits ciclosporin metabolism; however, in a minority of patients it may cause a significant increase in ciclosporin concentrations.[27]

1. Ferguson RM, *et al.* Ketoconazole, cyclosporin metabolism, and renal transplantation. *Lancet* 1982; **ii:** 882–3.
2. Dieperink H, Møller J. Ketoconazole and cyclosporin. *Lancet* 1982; **ii:** 1217.
3. Shepard JH, *et al.* Cyclosporine-ketoconazole: a potentially dangerous drug-drug interaction. *Clin Pharm* 1986; **5:** 468.
4. Gomez DY, *et al.* The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 15–19.
5. First MR, *et al.* Concomitant administration of cyclosporin and ketoconazole in renal transplant recipients. *Lancet* 1989; **ii:** 1198–1201.
6. Keogh A, *et al.* Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. *N Engl J Med* 1995; **333:** 628–33.
7. El-Husseini A, *et al.* Concomitant administration of cyclosporine and ketoconazole in idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2004; **19:** 2266–71.
8. El-Husseini A, *et al.* Co-administration of cyclosporine and ketoconazole in idiopathic childhood nephrosis. *Pediatr Nephrol* 2004; **19:** 976–81.
9. Frey FJ. Concomitant cyclosporin and ketoconazole. *Lancet* 1990; **335:** 109–10.
10. Akhlaghi F, *et al.* Pharmacokinetics of cyclosporine in heart transplant recipients receiving metabolic inhibitors. *J Heart Lung Transplant* 2001; **20:** 431–8.
11. Kramer MR, *et al.* Cyclosporine and itraconazole interaction in heart and lung transplant recipients. *Ann Intern Med* 1990; **113:** 327–9.
12. Leather H, *et al.* Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12:** 325–34.
13. Florea NR, *et al.* Beneficial pharmacokinetic interaction between cyclosporine and itraconazole in renal transplant recipients. *Transplant Proc* 2003; **35:** 2873–7.
14. Romero AJ, *et al.* Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. *Clin Pharmacol Ther* 2002; **71:** 226–34.
15. Groll AH, *et al.* Pharmacokinetic interaction between voriconazole and ciclosporin A following allogeneic bone marrow transplantation. *J Antimicrob Chemother* 2004; **53:** 113–14.
16. Horton CM, *et al.* Cyclosporine interactions with miconazole and other azole-antimycotics: a case report and review of the literature. *J Heart Lung Transplant* 1992; **11:** 1127–32.
17. Collignon P, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; **i:** 1262.
18. Mathis AS, *et al.* Sex and ethnicity may chiefly influence the interaction of fluconazole with calcineurin inhibitors. *Transplantation* 2001; **71:** 1069–75.
19. Krüger HU, *et al.* Absence of significant interaction of fluconazole with cyclosporin. *J Antimicrob Chemother* 1989; **24:** 781–6.
20. Ehninger G, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; **ii:** 104–5.
21. López-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? *Ann Pharmacother* 1993; **27:** 427–30.
22. Kennedy MS, *et al.* Acute renal toxicity with combined use of amphotericin B and cyclosporine after marrow transplantation. *Transplantation* 1983; **35:** 211–15.
23. Furrer K, *et al.* Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogenic stem cell transplantation. *Swiss Med Wkly* 2002; **132:** 316–20.
24. Ellis ME, *et al.* Is cyclosporin neurotoxicity enhanced in the presence of liposomal amphotericin B? *J Infect* 1994; **29:** 106–7.
25. Abu-Romeh SH, *et al.* Ciclosporin A and griseofulvin: another drug interaction. *Nephron* 1991; **58:** 237.
26. Lo ACY, *et al.* The interaction of terbinafine and cyclosporine A in renal transplant patients. *Br J Clin Pharmacol* 1997; **43:** 340–1.
27. Hebert MF, *et al.* Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45:** 954–60.

Antigout drugs. A patient who had been receiving maintenance doses of ciclosporin for some years, with consistent whole-blood trough concentrations of around 130 nanograms/mL at doses of 175 mg twice daily had a rise in ciclosporin concentrations to 410 nanograms/mL after 2 months of treatment with *allopurinol* 200 mg daily.[1] Ciclosporin concentrations returned to their previous levels over several weeks after stopping allopurinol, and rose again on rechallenge. Dosage of ciclosporin was then reduced. For a report of a low dose of allopurinol being added to a ciclosporin-containing immunosuppressive regimen, see Organ and Tissue Transplantation, p. 601.2.

UK licensed product information states that *colchicine* may increase ciclosporin concentrations.

In a report of 120 heart transplant recipients with hyperuricaemia, *sulfinpyrazone* reduced ciclosporin concentrations, and 2 patients needed treatment for acute rejection.[2]

1. Gorrie M, *et al.* Allopurinol interaction with cyclosporin. *BMJ* 1994; **308:** 113.
2. Caforio ALP, *et al.* Sulfinpyrazone reduces cyclosporine levels: a new drug interaction in heart transplant recipients. *J Heart Lung Transplant* 2000; **19:** 1205–8.

Antimalarials. A large rise in serum-ciclosporin concentration was seen on 2 occasions in a renal graft recipient when *chloroquine* was added to his medication for malaria prophylaxis.[1] *Quinine* has been reported to reduce ciclosporin concentrations.[2]

1. Finielz P, *et al.* Interaction between cyclosporin and chloroquine. *Nephron* 1993; **65:** 333.
2. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singapore Med J* 1991; **32:** 189–90.

Antineoplastics. Elevated plasma-ciclosporin concentrations and an increased incidence of nephrotoxic effects and hypertension have been reported in patients receiving ciclosporin for psoriasis who had been previously,[1] or concurrently,[2] treated with *methotrexate*. Conversely, methotrexate has been used effectively with reduced-dose ciclosporin in graft-versus-host disease.[3] Severe renal failure has been reported when standard oral doses of ciclosporin were given after high-dose intravenous *melphalan* (used as a bone marrow conditioning agent before allogeneic bone marrow transplantation).[4] A retrospective analysis of allogeneic haematopoietic stem cell transplant patients taking ciclosporin found that, in those given a conditioning regimen containing *cyclophosphamide*, mean serum-ciclosporin concentrations were reduced; no effect on the incidence of graft-versus-host disease could be established.[5]

UK licensed product information states that *imatinib* may increase ciclosporin concentrations.

Ciclosporin increases plasma-*doxorubicin* concentrations and toxicity (see p. 785.3), and has been used to increase oral absorption of *paclitaxel* (see p. 842.2). For the effects of ciclosporin on the pharmacokinetics of *teniposide* and *etoposide*, see p. 867.2 and p. 792.1, respectively.

Ciclosporin and its analogues have been given with antineoplastics for their ability to inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, thus resulting in raised intracellular concentrations of the other drug.

1. Powles AV, *et al.* Cyclosporin toxicity. *Lancet* 1990; **i:** 610.
2. Korstanje MJ, *et al.* Cyclosporine and methotrexate: a dangerous combination. *J Am Acad Dermatol* 1990; **23:** 320–1.
3. Stockschlaeder M, *et al.* A pilot study of low-dose cyclosporin for graft-versus-host prophylaxis in marrow transplantation. *Br J Haematol* 1992; **80:** 49–54.
4. Morgenstern GR, *et al.* Cyclosporin interaction with ketoconazole and melphalan. *Lancet* 1982; **ii:** 1342.
5. Nagamura F, *et al.* Effect of cyclophosphamide on serum cyclosporine levels at the conditioning of hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **32:** 1051–8.

Antiobesity drugs. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported[1-3] in transplant recipients given *orlistat*. It was postulated[2] that the interaction was a result of reduced absorption of ciclosporin in the presence of orlistat and that at least 2 hours should elapse between doses of these two drugs. However, despite this dosing interval, there has been a further report[3] of subtherapeutic plasma levels of ciclosporin. The patient had had severe diarrhoea, and the subsequent decreased absorption of fats was thought to have decreased the absorption of ciclosporin.

An increase in ciclosporin trough concentrations occurred when a renal transplant patient was given *sibutramine*;[4] both drugs are metabolised by cytochrome P450 isoenzyme 3A4.

1. Nägele H, *et al.* Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. *Eur J Clin Pharmacol* 1999; **55:** 667–9.
2. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. *N Engl J Med* 2000; **342:** 1141–2.
3. Barbaro D, *et al.* Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature. *Endocr Pract* 2002; **8:** 124–6.
4. Clerbaux G, *et al.* Interaction between sibutramine and cyclosporine. *Am J Transplant* 2003; **3:** 906.

Antivirals. For a report of mutual elevations in the area under the plasma concentration-time curves for ciclosporin and the HIV-protease inhibitor *saquinavir*, see Indinavir, p. 988.2.

Bifendate. In 2 patients given maintenance doses of ciclosporin, trough whole-blood concentrations decreased from 97.7 nanograms/mL to 49.0 nanograms/mL and from 127.5 nanograms/mL to 45.0 nanograms/mL respectively when bifendate was given. Ciclosporin concentrations returned to pre-treatment levels over several weeks once bifendate was stopped.[1]

1. Kim YS, *et al.* The effect of diphenyl-dimethyl-dicarboxylate on cyclosporine-A blood level in kidney transplants with chronic hepatitis. *Korean J Intern Med* 1997; **12:** 67–9.

Cardiovascular drugs. *ACE INHIBITORS.* There may be an increased risk of hyperkalaemia when ACE inhibitors are used with ciclosporin. Acute renal failure, associated with use of *enalapril*, has been reported in 2 patients given ciclosporin after renal transplantation.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; **16:** 66–9.

ANTIARRHYTHMICS. Marked rises in serum-ciclosporin concentrations despite reductions in dose have been noted in recipients of organ transplants after treatment with *amiodarone*.[1-3] A rise in serum ciclosporin has similarly been seen in a patient given both ciclosporin and *propafenone*.[4]

1. Mamprin F, *et al.* Amiodarone-cyclosporine interaction in cardiac transplantation. *Am Heart J* 1992; **123:** 1725–6.
2. Egami J, *et al.* Increase in cyclosporine levels due to amiodarone therapy after heart and heart-lung transplantation. *J Am Coll Cardiol* 1993; **21:** 141A.
3. Chitwood KK, *et al.* Cyclosporine-amiodarone interaction. *Ann Pharmacother* 1993; **27:** 569–71.
4. Spes CH, *et al.* Ciclosporin-propafenone interaction. *Klin Wochenschr* 1990; **68:** 872.

ANTICOAGULANTS. Treatment with *warfarin* for deep-vein thrombosis in a patient maintained on ciclosporin for pure red cell aplasia resulted in a relapse of the latter and a significant fall in ciclosporin blood concentrations.[1] Increase in the ciclosporin dose restored control of the aplasia but resulted in a marked increase in prothrombin activity requiring an increase in warfarin dosage. The results suggest that each drug interferes with the activity of the other. The influence of the patient's other medications (including phenobarbital and folic acid), if any, is unknown, although it has been suggested[2,3] that the phenobarbital had enhanced the metabolism of both drugs. In another report,[2] a patient on long-term warfarin for deep-vein thrombosis was started on ciclosporin for lymphoma relapse, and subsequently required larger doses of warfarin. During use of *acenocoumarol* with ciclosporin, the dose of ciclosporin had to be increased[3] in one patient and both drugs decreased[4] in another. It appears that the interaction between ciclosporin and anticoagulants is unpredictable[3] and dependent on the anticoagulant used.[2]

1. Snyder DS. Interaction between cyclosporine and warfarin. *Ann Intern Med* 1988; **108:** 311.
2. Turri D, *et al.* Oral anticoagulants and cyclosporin A. *Haematologica* 2000; **85:** 893–4.
3. Borrás-Blasco J, *et al.* Interaction between cyclosporine and acenocoumarol in a patient with nephrotic syndrome. *Clin Nephrol* 2001; **55:** 338–40.
4. Campistol JM, *et al.* Interaction between ciclosporin A and Sintrom. *Nephron* 1989; **53:** 291–2.

ANTIPLATELET DRUGS. Ticlopidine decreased serum-ciclosporin concentrations in isolated cases,[1-3] but a study in 20 heart transplant patients failed to show any interaction between ciclosporin and low-dose ticlopidine.[4] For reports of rhabdomyolysis occurring in patients stabilised on ciclosporin and a statin when *clopidogrel* was added to their treatment, see Statins, p. 1344.3.

1. Birmelé B, *et al.* Interaction of cyclosporin and ticlopidine. *Nephrol Dial Transplant* 1991; **6:** 150–1.
2. Verdejo A, *et al.* Probable interaction between cyclosporin A and low dose ticlopidine. *BMJ* 2000; **320:** 1037.
3. Feriozzi S, *et al.* Treatment with ticlopidine is associated with reduction of cyclosporin A blood levels. *Nephron* 2002; **92:** 249–50.
4. Boissonnat P, *et al.* A drug interaction study between ticlopidine and cyclosporin in heart transplant recipients. *Eur J Clin Pharmacol* 1997; **53:** 39–45.

BETA BLOCKERS. Ciclosporin plasma concentrations increased when *carvedilol* was added to treatment regimens of renal[1] and cardiac[2] transplant patients. Considerable interindividual variation was seen in one study,[1] so it is recommended that ciclosporin concentrations should be monitored carefully if the drugs are used together.

1. Kaijser M, *et al.* Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients. *Clin Transplant* 1997; **11:** 577–81.
2. Bader FM, *et al.* The effect of β-blocker use on cyclosporine level in cardiac transplant recipients. *J Heart Lung Transplant* 2005; **24:** 2144–7.

ENDOTHELIN RECEPTOR ANTAGONISTS. There is a complex interaction between ciclosporin and bosentan. If the drugs are given together reduced ciclosporin concentrations and increased bosentan concentrations may occur; further details are given on p. 1328.1. For information on ciclosporin increasing exposure to ambrisentan, see p. 1298.3.

CALCIUM-CHANNEL BLOCKERS. The calcium-channel blockers *diltiazem*,[1-3] *lercanidipine*, *nicardipine*,[4,5] and *verapamil*[6,7] have all been associated with increases in ciclosporin blood concentrations. It has been suggested that such an interaction can be used to obtain effective ciclosporin concentrations with lower doses.[8] In addition, there is some evidence of mitigation of ciclosporin-induced nephrotoxicity when calcium-channel blockers are given (see Effects on the Kidneys, p. 1950.1), and they are useful for ciclosporin-induced hypertension (see Effects on the Cardiovascular System, p. 1949.3). However, some caution is required: one report has pointed out that diltiazem does not increase ciclosporin concentrations in all cases,[9] while others have found that use together alters the pattern of ciclosporin metabolites, and that pharmacokinetic changes are greater in female than in male patients.[10] Therefore, some prefer a calcium-channel blocker that does not alter ciclosporin pharmacokinetics for hypertension and renal protection. *Nifedipine* has not been shown to increase blood-ciclosporin concentrations.[6] For a report of increased nifedipine toxicity with ciclosporin see Immunosuppressants, p. 1454.1. Other calcium-channel blockers that do not appear to affect ciclosporin pharmacokinetics include *felodipine*[7,11] and *isradipine*.[7,12] Ciclosporin concentrations have been reported to increase or to remain unchanged with *amlodipine*.[13] Use of amlodipine or nifedipine with ciclosporin may exacerbate the problem of gingival hyperplasia—see Hyperplasia under Adverse Effects, p. 1950.3.

1. Brockmöller J, *et al.* Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; **38:** 237–42.
2. Bourge RC, *et al.* Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; **90:** 402–4.

3. Åsberg A, *et al.* Pharmacokinetic interactions between microemulsion formulated cyclosporine A and diltiazem in renal transplant recipients. *Eur J Clin Pharmacol* 1999; **55:** 383–7.
4. Todd P, *et al.* Nicardipine interacts with cyclosporin. *Br J Dermatol* 1989; **121:** 820.
5. Kessler M, *et al.* Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; **36:** 637–8.
6. Tortorice KL, *et al.* The effects of calcium channel blockers on cyclosporine and its metabolites in renal transplant patients. *Ther Drug Monit* 1990; **12:** 321–8.
7. Yildiz A, *et al.* Interaction between cyclosporine A and verapamil, felodipine, and isradipine. *Nephron* 1999; **81:** 117–18.
8. Sketris IS, *et al.* Effect of calcium-channel blockers on cyclosporine clearance and use in renal transplant patients. *Ann Pharmacother* 1994; **28:** 1227–31.
9. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; **42:** 642–4.
10. Bleck JS, *et al.* Diltiazem increases blood concentrations of cyclized cyclosporine metabolites resulting in different cyclosporine metabolite patterns in stable male and female renal allograft recipients. *Br J Clin Pharmacol* 1996; **41:** 551–6.
11. Cohen DJ, *et al.* Influence of oral felodipine on serum cyclosporine concentrations. *Clin Transplant* 1994; **8:** 541–5.
12. Endresen L, *et al.* Lack of effect of the calcium antagonist isradipine on cyclosporine pharmacokinetics in renal transplant patients. *Ther Drug Monit* 1991; **13:** 490–5.
13. Schrama YC, Koomans HA. Interactions of cyclosporin A and amlodipine: blood cyclosporin A levels, hypertension and kidney function. *J Hypertens* 1998; **16** (suppl): S33–S38.

CARDIAC GLYCOSIDES. For reference to the effect of ciclosporin on serum-digoxin concentrations, see Immunosuppressants, under Interactions of Digoxin, p. 1357.3.

CLONIDINE. Addition of clonidine to the regimen of a 3-year-old child who had developed hypertension after a renal transplant resulted in a marked increase in whole blood ciclosporin concentrations, despite a reduction in ciclosporin dose.[1] Ciclosporin concentrations fell rapidly on withdrawal of clonidine.

1. Gilbert RD, *et al.* Interaction between clonidine and cyclosporine A. *Nephron* 1995; **71:** 105.

DIURETICS. Enhanced nephrotoxicity, without apparent change in ciclosporin blood concentrations, has been seen in individual patients after addition of *metolazone*[1] or *amiloride* with *chlorothiazide*[2] to their regimen. Severe nephrotoxicity, resulting in loss of graft function, has been seen in a renal transplant patient given *mannitol* with ciclosporin;[3] graft function recovered on withdrawal of the diuretic.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; **294:** 578.
2. Deray G, *et al.* Enhancement of cyclosporin nephrotoxicity by diuretic therapy. *Clin Nephrol* 1989; **32:** 47.
3. Brunner FP, *et al.* Mannitol potentiates cyclosporine nephrotoxicity. *Clin Nephrol* 1986; **25** (suppl 1): S130–6.

LIPID REGULATING DRUGS. A study in 10 renal transplant recipients indicated that use of ciclosporin with *probucol* markedly reduced the whole blood and plasma concentrations of the former in 9 of them, compared with use of ciclosporin alone.[1] *Bezafibrate* has been reported to increase blood concentrations of ciclosporin, with resultant nephrotoxicity.[2] However, other studies with bezafibrate have found a small decrease in ciclosporin concentrations,[3] or no effect,[4,5] despite an increase in serum creatinine in each study. Conflicting effects have also been reported with other fibrates: decreased[6] and unchanged[7] ciclosporin concentrations have occurred with *fenofibrate*, and both a decrease[8] and lack of effect[9] have also occurred with *gemfibrozil*.

In 1 study, *simvastatin* increased the unbound fraction of ciclosporin in the blood, resulting in a modest increase in apparent ciclosporin clearance.[10] In renal transplant recipients, *atorvastatin* increased ciclosporin blood concentrations in 4 out of 10 patients in one study[11] but was deemed to have minimal clinical effect in others.[12,13] Ciclosporin concentrations were unaffected by *cerivastatin*,[11,14] *fluvastatin*,[15] *lovastatin*,[16] and *pravastatin*.[16,17] A literature review concluded that the statins do not interact with ciclosporin to a clinically relevant degree. However, given the narrow therapeutic range of ciclosporin, the increase in systemic exposure to statins, and reports of rhabdomyolysis when used together, the authors advise that ciclosporin levels be monitored when starting statin therapy, and that lower doses of statins be used.[18] For the effects of ciclosporin on plasma levels of statins and reports of rhabdomyolysis, see Immunosuppressants, under Interactions of Simvastatin, p. 1495.3.

1. Gallego C, *et al.* Interaction between probucol and cyclosporine in renal transplant patients. *Ann Pharmacother* 1994; **28:** 940–3.
2. Hirai M, *et al.* Elevated blood concentrations of cyclosporine and kidney failure after bezafibrate in renal graft recipient. *Ann Pharmacother* 1996; **30:** 883–4.
3. Barbir M, *et al.* Maxepa versus bezafibrate in hyperlipidemic cardiac transplant recipients. *Am J Cardiol* 1992; **70:** 1596–1601.
4. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; **341:** 371.
5. Jespersen B, Tvedegaard E. Bezafibrate induced reduction of renal function in a renal transplant recipient. *Nephrol Dial Transplant* 1995; **10:** 702–3.
6. Boissonnat P, *et al.* The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. *Transplantation* 1994; **58:** 245–7.
7. de Lorgeril M, *et al.* Pharmacokinetics of cyclosporine in hyperlipidaemic long-term survivors of heart transplantation: lack of interaction with the lipid-lowering agent, fenofibrate. *Eur J Clin Pharmacol* 1992; **43:** 161–5.
8. Fehrman-Ekholm I, *et al.* Decreased cyclosporine levels during gemfibrozil treatment of hyperlipidemia after kidney transplantation. *Nephron* 1996; **72:** 483.
9. Pisanti N, *et al.* Lack of effect of gemfibrozil on cyclosporine blood concentrations in kidney-transplanted patients. *Am J Nephrol* 1998; **18:** 199–203.
10. Akhlaghi F, *et al.* Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant recipients. *Br J Clin Pharmacol* 1997; **44:** 537–42.
11. Renders L, *et al.* Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. *Nephrol Dial Transplant* 2001; **16:** 141–6.
12. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; **1:** 382–6.
13. Taylor PJ, *et al.* Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother* 2004; **38:** 205–8.
14. Mück W, *et al.* Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. *Clin Pharmacol Ther* 1999; **65:** 251–61.
15. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; **62:** 1559–64.
16. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; **62:** 311–21.
17. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; **25:** 2732–4.
18. Åsberg A. Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. *Drugs* 2003; **63:** 367–78.

Colchicine. Use of ciclosporin with colchicine may result in myopathy or rhabdomyolysis—see Effects on Skeletal Muscle, under Adverse Effects, p. 1950.3. For reports of adverse effects and increased serum-ciclosporin concentrations when given with colchicine, see also p. 606.3.

Corticosteroids. It has been suggested that use of ciclosporin with corticosteroids increases plasma concentrations of both drugs, but not all studies support this—see Immunosuppressants, p. 1620.2.

Gastrointestinal drugs. Giving *cisapride*[1] or *metoclopramide*[2] to renal transplant recipients receiving ciclosporin has been reported to increase peak ciclosporin concentrations and increase the speed of absorption. *Cimetidine*,[3,4] *ranitidine*,[3] or *famotidine*,[4] do not appear to affect ciclosporin pharmacokinetics. A literature review[5] noted that although there are reports of cimetidine influencing peak concentrations of ciclosporin, there is no support for a pharmacokinetic interaction. A pharmacodynamic interaction between ciclosporin and histamine H_2-receptor antagonists, resulting in a potentiation of nephrotoxicity, is also unlikely.

1. Finet L, *et al.* Effects of cisapride on the intestinal absorption of cyclosporine in renal transplant recipients. *Gastroenterology* 1991; **100:** A209.
2. Wadhwa NK, *et al.* The effect of oral metoclopramide on the absorption of cyclosporine. *Transplant Proc* 1987; **19:** 1730–3.
3. Barri YM, *et al.* Cimetidine or ranitidine in renal transplant patients receiving cyclosporine. *Clin Transplant* 1996; **10:** 34–8.
4. Shaefer MS, *et al.* Evaluation of the pharmacokinetic interaction between cimetidine or famotidine and cyclosporine in healthy men. *Ann Pharmacother* 1995; **29:** 1088–91.
5. Lewis SM, McCloskey WW. Potentiation of nephrotoxicity by H_2-antagonists in patients receiving cyclosporine. *Ann Pharmacother* 1997; **31:** 363–5.

Grapefruit juice. Grapefruit juice increases the bioavailability of oral ciclosporin,[1-4] including the microemulsion formulation,[5] leading to marked increases in blood-ciclosporin concentrations; intravenous ciclosporin is unaffected. The effect appears to be due to inhibition of cytochrome P450 enzymes in the gut wall by substances present in grapefruit juice,[3] resulting in transiently reduced ciclosporin metabolism. Although it has been suggested that the effect might be used similarly to that of calcium-channel blockers or ketoconazole in reducing the required dose of ciclosporin,[2] others have pointed out that grapefruit juice is not standardised and its effects are variable.[6]

Pomelo juice has also reportedly increased ciclosporin bioavailability; pomelo is a citrus fruit closely related to grapefruit.[7]

1. Proppe DG, *et al.* Influence of chronic ingestion of grapefruit juice on steady-state blood concentrations of cyclosporine A in renal transplant patients with stable graft function. *Br J Clin Pharmacol* 1995; **39:** 337–8.
2. Yee GC, *et al.* Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; **345:** 955–6.
3. Hollander AAMJ, *et al.* The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. *Clin Pharmacol Ther* 1995; **57:** 318–24.
4. Ducharme MP, *et al.* Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. *Clin Pharmacol Ther* 1995; **57:** 485–91.
5. Ku Y-M, *et al.* Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? *J Clin Pharmacol* 1998; **38:** 959–65.
6. Johnston A, Holt DW. Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; **346:** 122–3.
7. Grenier J, *et al.* Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. *Clin Pharmacol Ther* 2006; **79:** 255–62.

Immunosuppressants. There has been a report of altered ciclosporin requirements in paediatric renal graft patients treated with *basiliximab*,[1] but others have failed to note such an effect,[2] and whether an interaction exists is unclear.

Treatment of acute rejection of kidney grafts in 10 patients using *muromonab-CD3* resulted in increases in mean trough ciclosporin concentrations, despite a reduction in ciclosporin dosage.[3] Once muromonab-CD3 was withdrawn the dosage of ciclosporin had to be increased again to provide adequate concentrations. In a retrospective study[4] of renal transplant recipients given ciclosporin and either muromonab-CD3 or antilymphocyte immunoglobulin, ciclosporin trough concentrations were found to be raised on day 5 postoperatively in the patients receiving muromonab-CD3. Although no differences were found in trough concentrations on days 7 and 10, the doses of ciclosporin had by then been adjusted based on the levels obtained on day 5.

For the effects of ciclosporin on the pharmacokinetics of *everolimus*, *mycophenolate mofetil*, and *sirolimus*, see p. 1959.1, p. 1964.2, and p. 1968.1 respectively.

Tacrolimus inhibits ciclosporin metabolism *in vitro*[5] but did not alter the pharmacokinetics of intravenous ciclosporin in 7 liver transplant patients.[6] However, there is a possibility of increased nephrotoxicity when the drugs are used together, so licensed product information contra-indicates such use.

1. Strehlau J, *et al.* Interleukin-2 receptor antibody-induced alterations of ciclosporin dose requirements in paediatric transplant recipients. *Lancet* 2000; **356:** 1327–8.
2. Vester U, *et al.* Basiliximab in paediatric liver-transplant recipients. *Lancet* 2001; **357:** 388–9.
3. Vrahnos D, *et al.* Cyclosporin levels during OKT3 treatment of acute renal allograft rejection. *Pharmacotherapy* 1991; **11:** 278.
4. Vasquez EM, Pollak R. OKT3 therapy increases cyclosporine blood levels. *Clin Transplant* 1997; **11:** 38–41.
5. Venkataramanan R, *et al.* Pharmacokinetics of FK 506 in transplant patients. *Transplant Proc* 1991; **23:** 2736–40.
6. Jain AB, *et al.* Pharmacokinetics of cyclosporine and nephrotoxicity in orthotopic liver transplant patients rescued with FK 506. *Transplant Proc* 1991; **23:** 2777–9.

Methoxsalen. In a pharmacokinetic study, a single oral dose of methoxsalen significantly increased the oral bioavailability of ciclosporin.[1]

1. Rheeders M, *et al.* Drug-drug interaction after single oral doses of the furanocoumarin methoxsalen and cyclosporine. *J Clin Pharmacol* 2006; **46:** 768–75.

Methylphenidate. Methylphenidate led to an increase in ciclosporin concentrations in a 10-year-old African American boy, necessitating reduction of the ciclosporin dose.[1] The patient had previously had to stop bupropion because of decreased ciclosporin concentrations.

1. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; **11:** 193–8.

NSAIDs. Raised serum-ciclosporin trough concentrations and small increases in serum creatinine and BUN concentrations, followed the use of *sulindac* in a previously-stabilised renal graft recipient taking an immunosuppressive regimen including ciclosporin.[1] Increased renal impairment was seen when sulindac or *naproxen* were added to ciclosporin therapy in patients with rheumatoid arthritis.[2] Nephrotoxicity, in the absence of significantly raised blood-ciclosporin concentrations, has been reported in other patients given *diclofenac* with ciclosporin.[3] Ciclosporin may also increase plasma-diclofenac concentrations, see p. 50.2. In general, because of the known potential of NSAIDs to adversely affect renal function, careful monitoring of renal function is advised if these drugs are added to ciclosporin therapy or their dosages altered.

1. Sesin GP, *et al.* Sulindac-induced elevation of serum cyclosporine concentration. *Clin Pharm* 1989; **8:** 445–6.
2. Altman RD, *et al.* Interaction of cyclosporine A and nonsteroidal anti-inflammatory drugs on renal function in patients with rheumatoid arthritis. *Am J Med* 1992; **93:** 396–402.
3. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337:** 252.

Octreotide. A marked reduction in ciclosporin serum concentrations was seen in 10 diabetic patients with pancreatic transplants when octreotide was also given;[1] it was suggested that if these 2 drugs are used together the oral dosage of ciclosporin needs to be increased on average by 50%.

1. Landgraf R, *et al.* Effect of somatostatin analogue (SMS 201-995) on cyclosporine levels. *Transplantation* 1987; **44:** 724–5.

Quercetin. In a small study in healthy males, pre-treatment with the flavonoid quercetin significantly increased the peak concentration and bioavailability of ciclosporin.[1]

1. Choi JS, *et al.* Effect of quercetin on the pharmacokinetics of oral cyclosporine. *Am J Health-Syst Pharm* 2004; **61:** 2406–9.

Retinoids. After a report of increased whole-blood ciclosporin concentrations and nephrotoxicity in a patient given *etretinate* with ciclosporin, *in-vitro* results indicated that

etretinate inhibited hepatic microsomal metabolism of ciclosporin, as did *acitretin* and *isotretinoin*.[1] However, a study failed to find evidence of such an interaction *in vitro*.[2]

1. Shah IA, *et al*. The effects of retinoids and terbinafine on the human hepatic microsomal metabolism of cyclosporin. *Br J Dermatol* 1993; **129:** 395–8.
2. Webber IR, Back DJ. Effect of etretinate on cyclosporin metabolism in vitro. *Br J Dermatol* 1993; **128:** 42–4.

Sevelamer. Although sevelamer did not appear to affect ciclosporin concentrations in one study,[1] a case report[2] described a reduction in ciclosporin trough concentrations after sevelamer was started, an effect that was seen again upon rechallenge. It was suggested that sevelamer may bind with bile acids in the gut, affecting ciclosporin absorption,[2] or bind to ciclosporin, thereby reducing ciclosporin absorption directly.[3] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Pieper A-K, *et al*. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004; **19:** 2630–3.
2. Guillen-Anaya M-A, Jadoul M. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2004; **19:** 515.
3. Wauters J-P, *et al*. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2005; **20:** 660–1.

Sex hormones. Raised ciclosporin concentrations in blood have been seen when therapy with *danazol*,[1] *methyltestosterone*,[2] or *norethisterone*[1] was given with ciclosporin, and clinical evidence of both nephrotoxicity[1,2] and hepatotoxicity[2] has been seen. Severe hepatotoxicity and raised plasma-ciclosporin trough values also resulted when an oral contraceptive containing *levonorgestrel* and *ethinylestradiol* was taken by a woman receiving ciclosporin;[3] she had taken the same contraceptive before beginning ciclosporin without ill-effects.

1. Ross WB, *et al*. Cyclosporin interaction with danazol and norethisterone. *Lancet* 1986; **i:** 330.
2. Møller BB, Ekelund B. Toxicity of cyclosporine during treatment with androgens. *N Engl J Med* 1985; **313:** 1416.
3. Deray G, *et al*. Oral contraceptive interaction with cyclosporin. *Lancet* 1987; **i:** 158.

Tolvaptan. For the effect of ciclosporin on tolvaptan concentrations, see p. 2633.1.

Ursodeoxycholic acid. In a heart transplant patient with short bowel syndrome, ursodeoxycholic acid increased the trough concentrations of ciclosporin by enhancing its absorption.[1] In an attempt to determine whether this interaction would aid the attainment of therapeutic ciclosporin concentrations after heart transplantation, a patient with a jejunoileal bypass was given ciclosporin both with and without ursodeoxycholic acid; no difference was noted in the bioavailability of ciclosporin.[2] Small studies in liver transplant recipients found no alteration in ciclosporin pharmacokinetics when given single doses of ursodeoxycholic acid,[3] nor any difference in ciclosporin requirements between patients given ursodeoxycholic acid and those given placebo.[4] Another study in 12 liver transplant patients, 6 of whom had cholestatic liver dysfunction, found that ursodeoxycholic acid increased the rate of absorption of ciclosporin, but that peak concentrations and bioavailability did not change significantly.[5] In a study using microemulsifying ciclosporin in liver transplant recipients, ursodeoxycholic acid reduced the absorption rate and bioavailability of ciclosporin in 9 patients without cholestasis, but increased absorption rate and bioavailability in 3 cholestatic patients.[6] UK licensed product information for the microemulsifying formulation states that ursodeoxycholic acid increases ciclosporin concentrations.

1. Gutzler F, *et al*. Ursodeoxycholic acid enhances the absorption of cyclosporine in a heart transplant patient with short bowel syndrome. *Transplant Proc* 1992; **24:** 2620–1.
2. Kino KJ, Wittkowsky AK. Influence of bile acid replacement on cyclosporine absorption in a patient with jejunoileal bypass. *Pharmacotherapy* 1995; **15:** 350–2.
3. Maboundou CW, *et al*. A single dose of ursodiol does not affect cyclosporine absorption in liver transplant patients. *Eur J Clin Pharmacol* 1996; **50:** 335–7.
4. Söderdahl G, *et al*. Ursodeoxycholic acid increased bile flow and affects bile composition in the early postoperative phase following liver transplantation. *Transpl Int* 1998; **11** (suppl): S231–S238.
5. Al-Quaiz MN, *et al*. Variable effect of ursodeoxycholic acid on cyclosporin absorption after orthotopic liver transplantation. *Transpl Int* 1994; **7:** 190–4.
6. Caroli-Bosc F-X, *et al*. Ursodeoxycholic acid modulates cyclosporin A oral absorption in liver transplant recipients. *Fundam Clin Pharmacol* 2000; **14:** 601–9.

Vaccines. Efficacy of immunoprophylaxis may be expected to be reduced during ciclosporin therapy, and use of live virus vaccines, in particular, is contra-indicated in immunocompromised patients;[1] there has also been concern that vaccine antigens given during ciclosporin therapy might induce tolerance and result in increased rather than decreased susceptibility to diseases.

1. Grabenstein JD, Baker JR. Comment: cyclosporine and vaccination. *Drug Intell Clin Pharm* 1985; **19:** 679–80.

Vitamins. For reference to increased absorption of ciclosporin when given with a water-soluble macrogol derivative of *vitamin E*, see Absorption, under Pharmacokinetics, below.

Pharmacokinetics

The pharmacokinetics of ciclosporin are variable and difficult to determine. Results vary depending on the assay used, and values obtained by different methods are not strictly comparable.

Absorption of conventional formulations of ciclosporin from the gastrointestinal tract is variable and incomplete. An oral microemulsifying formulation with improved absorption characteristics is available and is more rapidly and completely absorbed, with peak concentrations achieved about 1.5 to 2 hours after a dose.

Ciclosporin is widely distributed throughout the body. Distribution in the blood is concentration-dependent, with between 41 and 58% in erythrocytes and 10 to 20% in leucocytes; the remainder is found in plasma, about 90% protein-bound, mostly to lipoprotein. Because of distribution into blood cells whole blood concentrations are higher than, and not comparable with, plasma concentrations; where peak plasma concentrations are reported to be about 1 nanogram/mL (by specific HPLC assay) for each mg of oral ciclosporin, whole blood concentrations for each mg range from about 1.4 to 2.7 nanograms/mL. Ciclosporin is reported to cross the placenta, and to be distributed into breast milk.

Clearance from the blood is biphasic. The terminal elimination half-life of an oral dose is reported to range from about 5 to 20 hours; clearance in children is more rapid.

Ciclosporin is extensively metabolised in the liver and mainly excreted in faeces via the bile. About 6% of a dose is reported to be excreted in urine, less than 0.1% unchanged.

References.

1. Mendonza AE, *et al*. Blood and plasma pharmacokinetics of ciclosporin in diabetic kidney transplant recipients. *Clin Pharmacokinet* 2008; **47:** 733–42.
2. Xiaoli D, Qiang F. Population pharmacokinetic study of cyclosporine in patients with nephrotic syndrome. *J Clin Pharmacol* 2009; **49:** 782–8.

Absorption. Ingestion of conventional *oral* formulations of ciclosporin with food may increase its bioavailability, although the effect only appears to be significant when the meal is high in fat;[1] ingestion with food and added bile acids may also increase absorption moderately.[2] A micelle-forming macrogol derivative of vitamin E (tocofersolan) has also been reported to markedly increase ciclosporin absorption.[3,4]

Because of the problems of variable oral absorption, an oral microemulsifying formulation has been developed that offers greatly improved and more predictable bioavailability,[5-8] particularly in liver transplant patients with impaired bile flow.[5] It should be noted that the formulation of this product in fact includes a vitamin E compound.

However, a study[9] has suggested that contrary to previous assumptions, conventional formulations of ciclosporin are quite well absorbed, and that the low bioavailability is due to extensive cytochrome-mediated metabolism in the gut wall (see also Metabolism, p. 1956.1). If this were the case, the improved bioavailability seen with the microemulsifying formulation is presumably less to do with improved absorption than with protection from such metabolism.

Very little drug is absorbed after application to the *eye*; ciclosporin accumulates on the ocular surface and cornea, achieving concentrations considered suitable for local immunomodulation. Corneal concentrations are affected by the choice of vehicle, but intra-ocular penetration is low. Little or no ocular metabolism is considered to occur in humans.[10]

1. Gupta SK, *et al*. Effect of food on the pharmacokinetics of cyclosporine in healthy subjects following oral and intravenous administration. *J Clin Pharmacol* 1990; **30:** 643–53.
2. Lindholm A, *et al*. The effect of food and bile acid administration on the relative bioavailability of cyclosporin. *Br J Clin Pharmacol* 1990; **29:** 541–8.
3. Sokol RJ, *et al*. Improvement of cyclosporin absorption in children after liver transplantation by means of water-soluble vitamin E. *Lancet* 1991; **338:** 212–15.
4. Chang T, *et al*. The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 1996; **59:** 297–303.
5. Trull AK, *et al*. Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion. *Br J Clin Pharmacol* 1995; **39:** 627–31.
6. van den Borne BEEM, *et al*. Relative bioavailability of a new oral form of cyclosporin A in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1995; **39:** 172–5.
7. Friman S, Bäckman L. A new microemulsion formulation of cyclosporin: pharmacokinetic and clinical features. *Clin Pharmacokinet* 1996; **30:** 181–93.
8. Schädeli F, *et al*. Population pharmacokinetic model to predict steady-state exposure to once-daily cyclosporin microemulsion in renal transplant recipients. *Clin Pharmacokinet* 2002; **41:** 59–69.
9. Wu C-Y, *et al*. Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 492–7.
10. Tang-Liu DD-S, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. *Clin Pharmacokinet* 2005; **44:** 247–61.

Children. A pharmacokinetic study in paediatric renal transplant recipients found that clearance of ciclosporin (when adjusted for body weight) was about 25% higher in children 8 years old or less than in older children or adults; clearance was highest in children between 4 months and 2 years of age and declined steadily thereafter, reaching adult values by about 12 years. As bioavailability and the volume of distribution (as adjusted for body weight) was similar in all age groups, the half-life was estimated to be 20% shorter in younger patients. The authors suggested that children up to 8 years of age may need a higher dose of ciclosporin per body weight and a shorter dosage interval to achieve similar exposure to older patients.[1]

In a study[2] in paediatric haematopoietic stem cell transplant recipients, however, no relationship was found between body weight, length, age, or glomerular filtration rate and clearance or volume of distribution. This led the authors to question commonly-used dosing strategies using an initial dose based on body weight and then adjusted according to trough ciclosporin concentrations (see also Administration in Children, p. 1946.2). They suggested initial intravenous doses (ciclosporin 40 mg daily for children weighing between 10 and 20 kg, 60 mg daily for those weighing 20 to 35 kg, and 80 mg daily for those weighing 35 to 60 kg), should then be adjusted according to the calculated area under the concentration-time curve (AUC) using 2 blood ciclosporin concentrations (a trough concentration and another 2 to 3 hours later). Although an optimum AUC for prophylaxis of graft-versus-host disease has not been determined, a target AUC of about 3.5 hours/mg per litre was thought to be appropriate.[2] For further discussion of strategies for monitoring ciclosporin concentrations, see p. 1956.1.

1. Fanta S, *et al*. Developmental pharmacokinetics of ciclosporin—a population pharmacokinetic study in paediatric renal transplant candidates. *Br J Clin Pharmacol* 2007; **64:** 772–84. Correction. *ibid*. 2008; **65:** 973.
2. Willemze AJ, *et al*. Ciclosporin kinetics in children after stem cell transplantation. *Br J Clin Pharmacol* 2008; **66:** 539–45.

Distribution. The distribution characteristics of ciclosporin are clinically important; binding in blood and plasma is of importance in determining immunosuppressive activity after organ transplantation.[1] The unbound concentration of ciclosporin may have a closer association with both renal and cardiac allograft rejection than the total (bound plus unbound) concentration.

1. Akhlaghi F, Trull AK. Distribution of cyclosporin in organ transplant recipients. *Clin Pharmacokinet* 2002; **41:** 615–37.

Ethnicity and sex. Gender-dependent racial differences in the pharmacokinetics of ciclosporin have been suggested.[1] African American women showed larger clearances of intravenous and oral ciclosporin (microemulsifying formulation) than African American men, and white women. There were no significant differences in clearance between men of different ethnic origin, or between white men and women. Overall bioavailability was also lower in African Americans compared with white subjects. However, other studies[2,3] found no differences in relative bioavailability between races.

Differences in hepatic cytochrome P450 isoenzyme CYP3A and intestinal P-glycoprotein activity may account for interindividual variability in ciclosporin disposition, and it has been speculated that polymorphic CYP3A5 expression might contribute to interracial differences.[4] However, most studies[5,6] have found little or no association between CYP3A4 or CYP3A5 genotype and ciclosporin pharmacokinetics, although one study found that patients with a CYP3A4 variant allele had a small but significantly higher oral clearance of ciclosporin.[7] However, black and Asian transplant recipients were found to have a reduced oral clearance in this study, independent of their CYP3A genotype, and in apparent contradiction to the literature. The authors commented that most of the studies had been conducted with the older oil-based products, and use of the microemulsifying formulation had not been associated with significant differences in ciclosporin pharmacokinetics between ethnic groups.[7] Genotyping of transplant recipients was considered unlikely to be of use in optimising ciclosporin dosage in clinical practice.[6,7]

1. Min DI, *et al*. Gender-dependent racial difference in disposition of cyclosporine among healthy African American and white volunteers. *Clin Pharmacol Ther* 2000; **68:** 478–86.
2. Stein CM, *et al*. Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects. *Clin Pharmacol Ther* 2001; **69:** 317–23.
3. Pollak R, *et al*. Cyclosporine bioavailability of Neoral and Sandimmune in white and black de novo renal transplant recipients. *Ther Drug Monit* 1999; **21:** 661–3.
4. Yates CR, *et al*. The effect of CYP3A5 and MDR1 polymorphic expression on cyclosporine oral disposition in renal transplant patients. *J Clin Pharmacol* 2003; **43:** 555–64.

5. Hesselink DA, *et al*. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; **74:** 245–54.
6. Anglicheau D, *et al*. CYP3A5 and MDR1 genetic polymorphisms and cyclosporine pharmacokinetics after renal transplantation. *Clin Pharmacol Ther* 2004; **75:** 422–33.
7. Hesselink DA, *et al*. Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin Pharmacol Ther* 2004; **76:** 545–56.

Metabolism. *In vitro*[1] and *in vivo*[2-4] evidence indicates that the low oral bioavailability of ciclosporin is due to first-pass metabolism in the gastrointestinal tract rather than the liver.

1. Tjia JF, *et al*. Cyclosporin metabolism by the gastrointestinal mucosa. *Br J Clin Pharmacol* 1991; **31:** 344–6.
2. Kolars JC, *et al*. First-pass metabolism of cyclosporin by the gut. *Lancet* 1991; **338:** 1488–90.
3. Hoppu K, *et al*. Evidence for pre-hepatic metabolism of oral cyclosporine in children. *Br J Clin Pharmacol* 1991; **32:** 477–81.
4. Wu C-Y, *et al*. Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 492–7.

Therapeutic drug monitoring. Considerable debate has attended the necessity for therapeutic monitoring of ciclosporin concentrations and also on the questions of which assay methods to use and whether to measure drug concentrations in whole blood or plasma.

Before the introduction of specific monoclonal radioimmunoassay the high performance liquid chromatography (HPLC) assay for ciclosporin had the advantage of being specific for the parent compound, and some suggested it to be the method of choice.[1,2] However, it is a more complex procedure, is not universally available, and is slower to perform than radio-immunoassay.[1,3-5] Specific monoclonal radio-immunoassays are now widely available; a comparative study of specific and non-specific radio-immunoassays, HPLC, and polyclonal fluorescence polarisation immunoassay (FPIA) found that the specific assays, used on whole blood samples, gave the best correlation with clinical events.[6]

Because the distribution of ciclosporin between blood cells and plasma is temperature-dependent,[7] plasma concentrations may be twice as high at 37 degrees as at 21 degrees. The temperature at which samples are stored and processed may therefore considerably influence results. In consequence, measurement of drug concentrations in whole blood is to be preferred.[1,3,4,8] However, many, particularly early, clinical studies have given plasma or serum concentrations, which makes comparison of literature data difficult. This problem is compounded by a considerable degree of variation between laboratories,[9,10] even when the same technique is used,[10] and by circadian variations in ciclosporin metabolism which mean that samples should be taken at the same time of day.[11] Since ciclosporin concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[12]

Because of the variability in results caused by difficulties in monitoring it has proved difficult to determine precisely the ciclosporin concentrations associated with therapeutic benefit and toxicity,[1,3-5] and it has been suggested that measurement of the therapeutic concentrations is unnecessary (provided the patient's clinical condition and renal function are monitored) when low-dose ciclosporin is being given (for example, in psoriasis).[13] However, others consider that it is always critical that ciclosporin blood trough concentrations are regularly measured,[14] in addition to other monitoring. A study in paediatric haematopoietic stem cell transplant recipients found a significant relationship between ciclosporin blood trough concentrations and the severity of acute graft-versus-host disease (GVHD); with lower trough concentrations, GVHD was more severe during the early post-transplantation period.[15] It has been suggested[16] that trough ciclosporin concentrations (C_0), measured by a specific method in whole blood, should not be less than 150 nanograms/mL during the first month after renal transplantation, although lower concentrations are subsequently acceptable; trough concentrations of 250 to 300 nanograms/mL are recommended in the 3 months after liver transplantation.

Other methods of monitoring ciclosporin therapy include monitoring the area under the concentration-time curve (AUC), limited sampling strategies, and Bayesian forecasting.[14,17-22] However, these methods also have limitations, often requiring several samples at inconvenient times for the patient, and can involve complex calculations.

Maximum calcineurin inhibition occurs in the first 1 to 2 hours after ciclosporin dosing, and it was hypothesised that AUC in the first 4 hours after a dose, or the blood concentration at 2 hours after a dose (C_2) might better predict immunosuppressive efficacy than trough concentrations (C_0) or AUC over 12 hours.[23] A large study[24] in liver transplant recipients found that measuring C_2 was superior to C_0 monitoring, resulting in a reduction of the incidence and severity of rejection. It was pointed out that these results could not necessarily be extrapolated to different transplant groups and that analysis when sampling high ciclosporin concentrations needed to be extremely accurate.[25] Data from lung transplant recipients found measurements of C_0 but not C_2 or C_6 to be associated with the risk of acute lung allograft rejection.[26] However, there was some suggestion that C_2 predicted rejection better than C_0 in renal[27] and heart[28] transplant recipients also. In paediatric renal transplant recipients,[23] C_2 monitoring was found to be a better predictor of ciclosporin exposure during the absorption phase than C_0.

C_2 is widely considered to be the best time-point predictor of exposure to ciclosporin during the first 4 hours postdose. This was based on data from studies in adult renal, liver, heart, and lung transplant recipients, as well as in paediatric renal and liver transplant patients; patients had received microemulsifying ciclosporin.[29-31] C_2 monitoring was also able to identify high, intermediate, or low absorbers of ciclosporin. Additional monitoring beyond the C_2 time point was considered necessary in low absorbers to identify true low absorbers from slow absorbers.[29,30] Target C_2 concentrations at various times post-transplantation were recommended by an international consensus group for adult renal and liver transplant patients receiving ciclosporin microemulsion.[29]

For adult renal transplant recipients:

- 1 month post-transplant: C_2 1.5 to 2 micrograms/mL (this should be achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 2 months post-transplant: C_2 1.5 micrograms/mL;
- 3 months post-transplant: C_2 1.3 micrograms/mL;
- 4 to 6 months post-transplant: C_2 1.1 micrograms/mL;
- 7 to 12 months post-transplant: C_2 900 nanograms/mL;
- 12 months post-transplant or more: C_2 800 nanograms/mL

For adult liver transplant recipients:

- 0 to 6 months post-transplant: C_2 1 microgram/mL (initially achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 6 to 12 months post-transplant: C_2 800 nanograms/mL;
- more than 12 months post-transplant: C_2 600 nanograms/mL

Data on long-term clinical benefit of monitoring in terms of rejection prophylaxis and overall safety profile were lacking, and target levels were not established for other transplant groups. A 15-minute 'window of opportunity' before and after the 2-hour time point was considered to provide an acceptable (10%) margin of error, during which time the C_2 sample could be taken.[29] Findings from a 3-year prospective study of C_2 monitoring in stable renal transplant recipients suggested that this method offered clinical benefits in terms of control of hypertension and dyslipidaemia, and protection against chronic renal allograft dysfunction.[32] A subsequent study of C_2 monitoring in heart transplant patients[33] found that higher C_2 concentrations were associated with less episodes of acute cellular rejection. However, in renal transplant patients,[34,35] C_2 concentrations did not predict rejection. A multicentre, retrospective French study[36] determined that, in renal transplant patients monitored on C_0, most patients had C_2 concentrations below the target ranges recommended by the international consensus group; the authors suggested that lower C_2 ranges might be targeted in the early- and long-term post-transplantation periods for those given interleukin-2 receptor antibodies, and that optimal therapeutic windows for ciclosporin monitoring based on C_2 needed more definition. A review of limited sampling strategies in liver transplant patients[37] concluded that, while C_2 monitoring might be better than C_0 monitoring to improve acute rejection rate in the early post-transplantation period, the evidence was not strong, and that further well-designed studies were needed. A review of ciclosporin monitoring after allogeneic stem cell transplantation[38] acknowledged that C_2 monitoring might be preferable to trough concentration monitoring in these patients, but also stated that optimal strategies remained to be defined and that randomised studies were needed.

There has been concern that differences in blood ciclosporin results from various assay systems would necessitate assay-specific target ranges for monitoring. Most transplant centres have developed target ciclosporin ranges that reflect the methodology in use. A study[39] of 5 different assay methods, including radio-immunoassay, HPLC, and FPIA, found that when measuring C_0, this would indeed be the case, but that with C_2 monitoring, differences in the results from the various assay methods were not statistically significant, and were unlikely to be of clinical significance. Different proportions of parent ciclosporin and metabolites were thought to be the reason for this disparity at the two time points. The authors considered that a single target therapeutic range could be adopted when monitoring C_2 concentrations, regardless of the assay method used.

For suggested C_0 and C_2 values used to adjust ciclosporin dosage when given with everolimus, see Administration with Everolimus, p. 1946.3.

1. Ptachcinski RJ, *et al*. Cyclosporine concentration determinations for monitoring and pharmacokinetic studies. *J Clin Pharmacol* 1986; **26:** 358–66.
2. Varghese Z, *et al*. How to measure cyclosporin. *Lancet* 1984; **i:** 1407–8.
3. Faynor SM, *et al*. Therapeutic drug monitoring of cyclosporine. *Mayo Clin Proc* 1984; **59:** 571–2.
4. Burkle WS. Cyclosporine pharmacokinetics and blood level monitoring. *Drug Intell Clin Pharm* 1985; **19:** 101–5.
5. Rodighiero V. Therapeutic drug monitoring of cyclosporin: practical applications and limitations. *Clin Pharmacokinet* 1989; **16:** 27–37.
6. Lindholm A, *et al*. A prospective study of cyclosporine concentration in relation to its therapeutic effect and toxicity after renal transplantation. *Br J Clin Pharmacol* 1990; **30:** 443–52.
7. Dieperink H. Temperature dependency of cyclosporin plasma levels. *Lancet* 1983; **i:** 416.
8. Bandini G, *et al*. Measuring cyclosporin in plasma. *Lancet* 1983; **i:** 762.
9. Moyer TP. Measurement of cyclosporine: a challenge to the professional laboratory organizations. *Ther Drug Monit* 1985; **7:** 123–4.
10. Johnston A, *et al*. The United Kingdom Cyclosporin Quality Assessment Scheme. *Ther Drug Monit* 1986; **8:** 200–204.
11. Venkataramanan R, *et al*. Diurnal variation in cyclosporine kinetics. *Ther Drug Monit* 1986; **8:** 380–1.
12. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; **45:** 775–88.
13. Heydendael VMR, *et al*. Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147:** 122–9.
14. Dumont RJ, Ensom MHH. Methods for clinical monitoring of cyclosporin in transplant patients. *Clin Pharmacokinet* 2000; **38:** 427–47.
15. Martin P, *et al*. Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. *Bone Marrow Transplant* 2003; **32:** 777–84.
16. Lindholm A. Therapeutic monitoring of cyclosporin—an update. *Eur J Clin Pharmacol* 1991; **41:** 273–83.
17. David O, Johnston A. Limited sampling strategies. *Clin Pharmacokinet* 2000; **39:** 311–13.
18. Leger F, *et al*. Maximum A Posteriori Bayesian estimation of oral cyclosporin pharmacokinetics in patients with stable renal transplants. *Clin Pharmacokinet* 2002; **41:** 71–80.
19. Bourgoin H, *et al*. Bayesian estimation of cyclosporin exposure for routine therapeutic drug monitoring in kidney transplant patients. *Br J Clin Pharmacol* 2005; **59:** 18–27.
20. Tokui K, *et al*. Dose adjustment strategy for oral microemulsion formulation of cyclosporine: population pharmacokinetics-based analysis in kidney transplant patients. *Ther Drug Monit* 2004; **26:** 287–94.
21. Saint-Marcoux F, *et al*. Patient characteristics influencing ciclosporin pharmacokinetics and accurate Bayesian estimation of ciclosporin exposure in heart, lung and kidney transplant patients. *Clin Pharmacokinet* 2006; **45:** 905–22.
22. Willemze AJ, *et al*. Ciclosporin kinetics in children after stem cell transplantation. *Br J Clin Pharmacol* 2008; **66:** 539–45.
23. Weber LT, *et al*. Cyclosporin A absorption profiles in pediatric renal transplant recipients predict the risk of acute rejection. *Ther Drug Monit* 2004; **26:** 415–24.
24. Levy G, *et al*. Improved clinical outcomes for liver transplant recipients using cyclosporine monitoring based on 2-hr post-dose levels (C_2). *Transplantation* 2002; **73:** 953–9.
25. Holt DW. Cyclosporine monitoring based on C_2 sampling. *Transplantation* 2002; **73:** 840–1.
26. Trull A, *et al*. Randomized, trough blood cyclosporine concentration-controlled trial to compare the pharmacodynamics of Sandimmune and Neoral in de novo lung transplant recipients. *Ther Drug Monit* 1999; **21:** 17–26.
27. Pescovitz MD, *et al*. Two-hour post-dose cyclosporine level is a better predictor than trough level of acute rejection of renal allografts. *Clin Transplant* 2002; **16:** 378–82.
28. Solari SG, *et al*. Cyclosporine monitoring with 2-hour postdose levels in heart transplant recipients. *Ther Drug Monit* 2005; **27:** 417–21.
29. Levy G, *et al*. Patient management by Neoral C_2 monitoring: an international consensus statement. *Transplantation* 2002; **73** (suppl): S12–S18.
30. Nashan B, *et al*. Use of Neoral C_2 monitoring: a European consensus. *Transpl Int* 2005; **18:** 768–78.
31. Trevillian P. Caring for Australians with Renal Impairment (CARI). The CARI guidelines. Calcineurin inhibitors in renal transplantation: therapeutic drug monitoring. *Nephrology (Carlton)* 2007; **12** (suppl 1): S57–S65.
32. Citterio F, *et al*. Results of a three-year prospective study of C_2 monitoring in long-term renal transplant recipients receiving cyclosporine microemulsion. *Transplantation* 2005; **79:** 802–6.
33. Delgado DH, *et al*. Monitoring of cyclosporine 2-hour post-dose levels in heart transplantation: improvement in clinical outcomes. *J Heart Lung Transplant* 2005; **24:** 1343–6.
34. Gotti E, *et al*. Blood cyclosporine level soon after kidney transplantation is a major determinant of rejection: insights from the Mycophenolate Steroid-Sparing Trial. *Transplant Proc* 2005; **37:** 2037–40.
35. Einecke G, *et al*. Limitations of C_2 monitoring in renal transplant recipients. *Nephrol Dial Transplant* 2005; **20:** 1463–70.
36. Loichot C, *et al*. Cyclosporine monitoring in renal transplant recipients with induction therapy: C_2 levels in patients monitored on C_0. *Fundam Clin Pharmacol* 2006; **20:** 91–6.
37. Marin JG, *et al*. Is C2 monitoring or another limited sampling strategy superior to C0 monitoring in improving clinical outcomes in adult liver transplant recipients? *Ther Drug Monit* 2006; **28:** 637–42.
38. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **38:** 169–74.
39. Johnston A, *et al*. Monitoring cyclosporin in blood: between-assay differences at trough and 2 hours post-dose (C2). *Ther Drug Monit* 2003; **25:** 167–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cermox; Lacrinmune; Restasis; Sandimmun; Sigmasporin; ***Austral.***: Cicloral; Cysporin†; Neoral; Sandimmun; ***Austria***: Cicloralhexal; Neoimmun; Sandimmun; ***Belg.***: Neoral-Sandimmun; Sandimmun; ***Braz.***: Gengraf; Restasis; Sandimmun; Sigmasporin; ***Canad.***: Neoral; Restasis; Sandimmune; ***Chile***: Equoral; Gengraf†; Modusik-A; Restasis; Sandimmun; ***China***: Gengraf (金格福); Implanta (因普兰他); Lizhu Huanming (丽珠环明); Neoral (新山地明); Saisip-

ing (赛斯平); Tianke (田可); Xin Sai Si Ping (新赛斯平); *Cz.*: Cyclaid; Equoral; Sandimmun; Sigmasporon; ***Denm.***: Deximune; Sandimmun; ***Fin.***: Sandimmun; ***Fr.***: Neoral; Sandimmun; ***Ger.***: Cicloral†; Deximune; Immunosporin; Sandimmun; ***Gr.***: Imunofar; Neoral; Restasis; Sandimmun; ***Hong Kong***: Gengraf†; Restasis; Sandimmun; ***Hung.***: Sandimmun; ***India***: Cyclomune; Cyclophil ME; Cyrin; Graftin; Immusol; Imusporin; Panimun Bioral; Sandimmun; ***Indon.***: Sandimmun; ***Irl.***: Deximune; Neoral; Sandimmun; ***Israel***: Deximune; Restasis; Sandimmun; Sangcya†; ***Ital.***: Sandimmun; ***Jpn***: Papilock; ***Malaysia***: Gengraf†; Restasis; Sandimmun; ***Mex.***: Immulem†; Modusik-A; Restasis; Sandimmun; Supremunn; ***Neth.***: Neoral; Sandimmune; ***Norw.***: Sandimmun; ***NZ***: Gengraf†; Neoral; Sandimmun; ***Philipp.***: Arpimune; Cyrin; Osporin; Restasis; Sandimmun; ***Pol.***: Cyclaid; Equoral; Sandimmun; ***Port.***: Ciclostar; Sandimmun; ***Rus.***: Ciclopren (Циклопрен); Consupren (Консупрен)†; Cycloral (Циклорал); Equoral (Экорал); Imusporin (Имуспорин); Orgasporin (Оргаспорин); Panimun Bioral (Панимун Биорал); Sandimmun (Сандиммун); ***S.Afr.***: Ciclohexal†; Sandimmun; ***Singapore***: Gengraf; Sandimmun; ***Spain***: Sandimmun; ***Swed.***: Sandimmun; ***Switz.***: Ciclosol†; Sandimmun; ***Thai.***: Consupren†; Equoral; Gengraf†; Kasporin; Panimun Bioral†; Restasis; Sanda; Sandimmun; ***Turk.***: Gengraf; Restasis; Sandimmun; ***UAE***: Sigmasporin; ***UK***: Capimune; Capsorin; Deximune; Neoral; Sandimmun; ***Ukr.***: Equoral (Екворал); Restasis (Рестасис); Sandimmun (Сандиммун Неорал); ***USA***: Gengraf; Neoral; Restasis; Sandimmune; ***Venez.***: Imusporin; Restasis; Sandimmun.

Pharmacopoeial Preparations
BP 2014: Ciclosporin Eye Drops;
USP 36: Cyclosporine Capsules; Cyclosporine Injection; Cyclosporine Oral Solution.

Daclizumab *(BAN, USAN, rINN)*

Dacliximab; Daclizumabum; Daklitsumabi; Daklizumab; Humanised Anti-Tac Antibody; Ro-24-7375; Даклизумаб.
Immunoglobulin G 1, (human-mouse monoclonal 1H4 γ-chain, anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer.
CAS — 152923-56-3.
ATC — L04AC01.
ATC Vet — QL04AC01.
UNII — CUJ2MVI71Y.

Uses and Administration

Daclizumab is a humanised monoclonal murine antibody that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen, Tac subunit) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection after kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. It is given in a dose of 1 mg/kg intravenously over 15 minutes within 24 hours before surgery and repeated at intervals of 2 weeks for a total of 5 doses. The required dose is diluted in 50 mL of sodium chloride 0.9%, and may be infused either centrally or peripherally. Daclizumab is also under investigation for its immunosuppressant properties in other forms of transplantation (see below) and in various diseases with an auto-immune component.

Administration in children. The dose for daclizumab in children aged 1 year and over is the same as in adults (see Uses and Administration, above).

Multiple sclerosis. Daclizumab has been tried[1-8] (alone or with interferon beta) in patients with relapsing-remitting or secondary progressive multiple sclerosis; clinical benefit and a reduction in new lesions on MRI has been reported.

1. Bielekova B, *et al.* Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon β. *Proc Natl Acad Sci U S A* 2004; **101:** 8705–8.
2. Rose JW, *et al.* Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* 2004; **56:** 864–7.
3. Rose JW, *et al.* Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology* 2007; **69:** 785–9.
4. Martin R. Humanized anti-CD25 antibody treatment with daclizumab in multiple sclerosis. *Neurodegener Dis* 2008; **5:** 23–6.
5. Ali EN, *et al.* Daclizumab in treatment of multiple sclerosis patients. *Multiple Sclerosis* 2009; **15:** 272–4.
6. Kim SE. Daclizumab treatment for multiple sclerosis. *Pharmacotherapy* 2009; **29:** 227–35.
7. Bielekova B, *et al.* Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. *Arch Neurol* 2009; **66:** 483–9.
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Ocular disorders. There have been reports of benefit with daclizumab in ocular inflammatory disorders[1] including scleritis, ocular cicatricial pemphigoid, and uveitis, all of which had been resistant to conventional therapy.

1. Papaliodis GN, *et al.* Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003; **110:** 786–9.

Organ and tissue transplantation. Daclizumab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p. 1935.2);[1-4] it is usually given as part of an immunosuppressive regimen that includes a calcineurin inhibitor and corticosteroids.

There are reports of successful corticosteroid withdrawal and corticosteroid-free regimens using daclizumab.[5] An attempt at using daclizumab to avoid use of ciclosporin after renal transplantation was unsuccessful, with a high rate of overall acute rejection in the daclizumab group.[6] However, prolonged monotherapy with daclizumab has been used to avoid rejection in patients non-adherent to standard maintenance regimens.[7]

Daclizumab has also been investigated for the prevention of acute rejection after heart,[8] liver,[9,10] and lung[11] transplantation (see p. 1934.2, p. 1936.3, and p. 1937.3, respectively) but increased mortality has followed its use in patients receiving heart grafts[12] (see also Effects on Mortality, below).

Daclizumab has also been tried in the management of acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p. 1933.1). While some consider it a viable alternative for corticosteroid-refractory acute GVHD,[13] others found that when daclizumab was used with corticosteroids to treat acute GVHD, this combination had a significantly deleterious effect on patient survival.[14]

Controlled studies that directly compare 2 doses of daclizumab with the standard 5-dose regimen in kidney transplantation are lacking; despite this, many centres use a 2-dose regimen.[15] In a small, retrospective analysis[16] of simultaneous kidney-pancreas transplant recipients (see Pancreatic Transplantation, p. 1938.1), patients given 1 to 3 doses of daclizumab in addition to triple therapy had a significantly higher incidence of rejection than those given 4 to 5 doses. There was no difference in patient or graft survival. A larger multicentre study[17,18] found that simultaneous kidney-pancreas recipients given daclizumab 2 mg/kg every 14 days for 2 doses had a similar incidence of rejection to those given the standard 5-dose regimen; mean time to onset of rejection was delayed in the 2-dose regimen but there was no beneficial effect of daclizumab on graft survival at 3 years. A small comparative study[19] in heart transplant recipients found 2 doses of daclizumab to be at least as effective as the 5-dose regimen; no significant differences were seen for mortality. A novel 3-dose regimen has been investigated in liver transplantation.[20]

1. Vincenti F, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med* 1998; **338:** 161–5.
2. Nashan B, *et al.* Reduction of acute renal allograft rejection by daclizumab. *Transplantation* 1999; **67:** 110–15.
3. Bumgardner GL, *et al.* Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001; **72:** 839–45.
4. Ciancio G, *et al.* Daclizumab induction, tacrolimus, mycophenolate mofetil and steroids as an immunosuppression regimen for primary kidney transplant recipients. *Transplantation* 2002; **73:** 1100–6.
5. ter Meulen CG, *et al.* Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor α therapy: a prospective, randomized, multicenter study. *Am J Transplant* 2004; **4:** 803–10.
6. Åsberg A, *et al.* Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006; **82:** 62–8.
7. Chaudhuri A, *et al.* Extended daclizumab monotherapy for rejection-free survival in non-adherent adolescent recipients of renal allografts. *Pediatr Transplant* 2009; **13:** 927–32.
8. Beniaminovitz A, *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med* 2000; **342:** 613–19.
9. Niemeyer G, *et al.* Long-term safety, tolerability and efficacy of daclizumab (Zenapax) in a two-dose regimen in liver transplant recipients. *Am J Transplant* 2002; **2:** 454–60.
10. Figueras J, *et al.* Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. *Transpl Int* 2006; **19:** 641–8.
11. Garrity ER, *et al.* Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation* 2001; **71:** 773–7.
12. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.
13. Bordigoni P, *et al.* Daclizumab, an efficient treatment for steroid-refractory acute graft-versus-host disease. *Br J Haematol* 2006; **135:** 382–5.
14. Lee SJ, *et al.* Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood* 2004; **104:** 1559–64.
15. van Gelder T, *et al.* Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? *Drugs* 2004; **64:** 1737–41.
16. Bruce DS, *et al.* Multicenter survey of daclizumab induction in simultaneous kidney-pancreas transplant recipients. *Transplantation* 2001; **72:** 1637–43.
17. Stratta RJ, *et al.* One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. *Transplant Proc* 2004; **36:** 1080–1.
18. Stratta RJ, *et al.* A prospective, randomized, multicenter study evaluating the safety and efficacy of two dosing regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. *Transplant Proc* 2005; **37:** 3531–4.
19. Ortiz V, *et al.* Induction therapy with daclizumab in heart transplantation—how many doses? *Transplant Proc* 2006; **38:** 2541–3.
20. Washburn WK, *et al.* A novel three-dose regimen of daclizumab in liver transplant recipients with hepatitis C: a pharmacokinetic and pharmacodynamic study. *Liver Transpl* 2006; **12:** 585–91.

Skin disorders. There are reports of successful treatment with daclizumab in psoriasis (p. 1688.1),[1,2] pemphigus vulgaris,[3] bullous pemphigoid[4] (see Pemphigus and Pemphigoid, p. 1687.1), and epidermolysis bullosa acquisita[5] (p. 1684.3). Cutaneous manifestations of adult T-cell leukaemia/lymphoma have also been reported to respond to daclizumab.[6]

1. Wohlrab J, *et al.* Treatment of recalcitrant psoriasis with daclizumab. *Br J Dermatol* 2001; **144:** 209–10.
2. Dichmann S, *et al.* Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. *J Am Acad Dermatol* 2002; **47:** 635–6.
3. Renkl A, *et al.* A novel therapeutic option in pemphigus vulgaris: humanized monoclonal anti-CD25 antibody. *Br J Dermatol* 2004; **150:** 1220–2.
4. Mockenhaupt M, *et al.* Daclizumab: a novel therapeutic option in severe bullous pemphigoid. *Acta Derm Venereol* 2005; **85:** 65–6.
5. Egan CA, *et al.* Treatment of epidermolysis bullosa acquisita with the humanised anti-Tac mAb daclizumab. *Clin Immunol* 2001; **101:** 146–51.
6. Osborne GEN, *et al.* Novel treatment of Sézary-like syndrome due to adult T-cell leukaemia/lymphoma with daclizumab (humanized anti-interleukin-2 receptor α antibody). *Br J Dermatol* 2006; **155:** 617–20.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with daclizumab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, hypotension, hypoxia, tachycardia, cardiac arrest, wheezing, dyspnoea, bronchospasm, pulmonary oedema, peripheral oedema, laryngeal oedema, and respiratory failure. Injection site reactions have also been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Therapy should be permanently stopped if a severe reaction occurs.

Effects on the heart. A report of sinus bradycardia[1] associated with the use of daclizumab.

1. Bassily-Marcus A, *et al.* Sinus bradycardia associated with daclizumab in liver transplant recipients: report of 3 cases. *Exp Clin Transplant* 2008; **6:** 80–3.

Effects on mortality. Increased mortality was reported in cardiac transplant recipients given an immunosuppressive regimen of daclizumab with ciclosporin, mycophenolate mofetil, and corticosteroids. Some deaths were associated with severe infection and use with antilymphocyte immunoglobulins.[1,2]

1. Roche, USA. Zenapax (daclizumab) (issued August 2003). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm168401.htm (accessed 05/08/10)
2. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies daclizumab as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pharmacokinetics

The recommended regimen of daclizumab (see above) should result in serum concentrations sufficient to saturate interleukin-2 receptors for about 90 days post-transplantation in adult patients, and 120 days in paediatric patients. The terminal elimination half-life of daclizumab has ranged from 11 to 38 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zenapax; ***Austral.***: Zenapax†; ***Austria***: Zenapax†; ***Belg.***: Zenapax; ***Braz.***: Zenapax; ***Canad.***: Zenapax†; ***Chile***: Zenapax; ***China***: Zenapax (赛尼哌); ***Cz.***: Zenapax†; ***Denm.***: Zenapax†; ***Fin.***: Zenapax†; ***Fr.***: Zenapax†; ***Ger.***: Zenapax†; ***Gr.***: Zenapax; ***Hong Kong***: Zenapax†; ***Hung.***: Zenapax; ***Irl.***: Zenapax†; ***Israel***: Zenapax†; ***Ital.***: Zenapax†; ***Mex.***: Zenapax; ***Neth.***: Zenapax†; ***NZ***: Zenapax†; ***Philipp.***: Zenapax; ***Pol.***: Zenapax†; ***Rus.***: Zenapax (Зенапакс); ***S.Afr.***: Zenapax†; ***Singapore***: Zenapax; ***Spain***: Zenapax†; ***Swed.***: Zenapax†; ***Switz.***: Zenapax†; ***Thai.***: Zenapax†; ***Turk.***: Zenapax; ***UK***: Zenapax†; ***USA***: Zenapax†; ***Venez.***: Zenapax.

Everolimus *(BAN, USAN, rINN)*

Everolimo; Everolimús; Évérolimus; Everolimusum; Ewerolimus; NVP-RAD-001; RAD-001; SDZ-RAD; SDZ-RAD-666; Эверолимус.
(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone.
$C_{53}H_{83}NO_{14}$=958.2
CAS — 159351-69-6.

The symbol † denotes a preparation no longer actively marketed

ATC — L01XE10; L04AA18.
ATC Vet — QL01XE10; QL04AA18.
UNII — 9HW64Q8G6G.

Uses and Administration

Everolimus is a derivative of sirolimus (p. 1966.2). It is used as a proliferation signal inhibitor in the prevention of graft rejection episodes in patients undergoing heart or kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin (microemulsifying) and corticosteroids, or in patients undergoing liver transplantation as part of a regimen that includes tacrolimus and corticosteroids. It is also used for the treatment of advanced renal cell carcinoma (p. 708.3) after failure of therapies such as sunitinib or sorafenib that target vascular endothelial growth factor. In postmenopausal women with advanced hormone-receptor positive HER2-negative breast cancer (p. 702.1), everolimus is used with exemestane after treatment with a nonsteroidal aromatase inhibitor such as letrozole or anastrozole has failed. Everolimus is also used for the treatment of progressive neuroendocrine tumours of pancreatic origin (p. 716.3) in patients with unresectable, locally advanced, or metastatic disease. Everolimus is used in the treatment of subependymal giant-cell astrocytoma (see Malignant Neoplasms of the Brain, p. 701.2) associated with tuberous sclerosis in patients who are unable to have surgery. Patients with renal angiomyolipoma associated with tuberous sclerosis who are at risk of complications but not needing immediate surgery may also be treated with everolimus.

For immunosuppression in patients undergoing **heart or kidney transplantation**, the recommended oral dose is everolimus 750 micrograms twice daily, begun as soon as possible after transplantation, and given at the same time as ciclosporin. Whole blood concentrations of both everolimus and ciclosporin should be monitored, see Administration with Everolimus, p. 1946.3. In **liver transplantation** the recommended oral dose of everolimus is 1 mg twice daily, begun about 4 weeks after transplantation, and given at the same time of day as tacrolimus.

In advanced **renal cell carcinoma**, advanced **breast cancer**, advanced **neuroendocrine tumours**, and **renal angiomyolipoma**, the recommended oral dose is everolimus 10 mg once daily. If toxicity occurs, the dose may be reduced to 5 mg once daily, or withheld and restarted at 5 mg once daily. Dose adjustments are required when everolimus is given with some other drugs, see Administration with Other Drugs, below.

In subependymal **giant-cell astrocytoma** the initial oral dose of everolimus, given once daily, is based on body-surface. US licensed product information recommends a dose of 4.5 mg/m^2 for adults and children aged 1 year and older. UK information provides a more specific regimen licensed for use in adults and children aged 3 years and older:

- up to 1.2 m^2: 2.5 mg
- 1.3 to 2.1 m^2: 5 mg
- 2.2 m^2 or over: 7.5 mg

Everolimus whole blood trough concentrations should be measured about 2 weeks after starting treatment and doses adjusted to attain a concentration of 5 to 15 nanograms/mL. In patients whose trough concentrations are below 5 nanograms/mL or above 15 nanograms/mL, dose adjustments may be made in steps of 2.5 mg (or 2 mg for dispersible tablets) every 2 weeks to achieve the target range. If a dose reduction is required in a patient taking 2.5 mg daily, alternate day dosing should be used. Treatment may be withheld and/or the dose temporarily reduced for severe adverse effects. Trough concentrations should be measured about 2 weeks after adjusting the dose of everolimus or starting/adjusting the dose of other drugs that may affect everolimus concentrations (see Administration with Other Drugs, below).

Dose adjustments may be required when everolimus is used in patients with hepatic impairment, see below.

Everolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

Administration in children. For doses of everolimus used in children with subependymal giant-cell astrocytoma associated with tuberous sclerosis, see Uses and Administration, above.

Administration in hepatic impairment. The clearance of everolimus was significantly reduced in patients with moderate hepatic impairment.[1] When used orally for immunosuppression in patients undergoing **heart, kidney, or liver transplantation**, licensed product information for everolimus suggests the following reductions to the usual initial daily dose:

- mild impairment (Child Pugh class A): reduce by one-third
- moderate impairment (Child Pugh class B): reduce by one-half
- severe impairment (Child Pugh class C): reduce by at least one-half

Further titration of the dose is based on therapeutic drug monitoring (see Therapeutic Drug Monitoring, under Pharmacokinetics, p. 1959.2).

In some countries where everolimus is licensed for heart and kidney transplantation, the dose should be reduced to about one-half of the usual recommended dose if 2 of the following parameters occur in patients with mild or moderate hepatic impairment:

- bilirubin > 34 micromoles/litre
- albumin < 35 g/litre
- INR > 1.3

When used for **renal cell carcinoma**, **breast cancer**, **neuroendocrine tumours** of pancreatic origin, or **renal angiomyolipoma** associated with tuberous sclerosis, the recommended oral dose of everolimus is 7.5 mg daily in patients with mild hepatic impairment and 5 mg once daily in moderate impairment. In those with severe hepatic impairment, everolimus may be used to a maximum dose of 2.5 mg daily.

In the treatment of subependymal **giant-cell astrocytoma** associated with tuberous sclerosis, US licensed product information suggests that no dose adjustment is needed in patients with mild or moderate hepatic impairment, but that in severe impairment the starting dose of everolimus should be reduced by one-half. UK licensed product information does not recommend the use of everolimus in patients younger than 18 years old who have hepatic impairment. In those aged 18 and older, it recommends that 75% of the usual starting dose should be given to patients with mild impairment, 25% of the usual dose in moderate impairment, and that it should be avoided in severe impairment. It also recommends whole blood trough concentrations for everolimus of 3 to 15 nanograms/mL. For usual doses, see Uses and Administration, above.

1. Kovarik JM, *et al.* Influence of hepatic impairment on everolimus pharmacokinetics: implications for dose adjustment. *Clin Pharmacol Ther* 2001; **70:** 425–30.

Administration with other drugs. Exposure to everolimus may be affected by inducers or inhibitors of the cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein. The oral dose of everolimus may need to be modified if given with such drugs and whole blood everolimus concentrations should be monitored (see Therapeutic Drug Monitoring, p. 1959.2). Strong CYP3A4 inhibitors should not be given with everolimus.

In **heart, kidney, or liver transplantation** use of strong CYP3A4 inducers or inhibitors with everolimus is not recommended. For guidance on adjusting *ciclosporin* doses when the two drugs are given together for transplantation see Administration with Everolimus, under Ciclosporin, p. 1946.3.

Strong CYP3A4 inducers should also be avoided if possible in **renal cell carcinoma**, **breast cancer**, **neuroendocrine tumours**, and **renal angiomyolipoma**, but if they must be used, the dose of everolimus may be increased up to 20 mg once daily in 5 mg increments, (usually four and eight days after starting the inducer). Once the inducer is stopped everolimus should be reduced to the original dose. When moderate CYP3A4 inhibitors or P-glycoprotein inhibitors are to be used, the dose of everolimus may be reduced to 2.5 to 5 mg once daily (or 5 mg every other day) with close monitoring for adverse effects. About 2 or 3 days after the inhibitor is stopped, everolimus should be increased to the original dose.

If strong CYP3A4 inducers need to be used in **giant-cell astrocytoma** UK licensed product information recommends titrating the dose to ensure everolimus concentrations remain in the target range (see Uses and Administration, above); US information suggests doubling the dose initially, and then making further adjustments as necessary. Once the inducer is stopped everolimus should be reduced to the original dose. When moderate CYP3A4 inhibitors or P-glycoprotein inhibitors are to be used, the everolimus dose should initially be reduced by about 50% and then adjusted further as necessary. Once the inhibitor is stopped everolimus should be increased to the original dose 2 or 3 days later.

Malignant neoplasms. References.

1. Motzer RJ, *et al.* RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372:** 449–56.
2. Oudard S, *et al.* Everolimus (RAD001): an mTOR inhibitor for the treatment of metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2009; **9:** 705–17.
3. Garnock-Jones KP, Keating GM. Everolimus: in advanced renal cell carcinoma. *Drugs* 2009; **69:** 2115–24.
4. Yao JC, *et al.* Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 2010; **28:** 69–76.
5. Grgic T, *et al.* Everolimus: a new mammalian target of rapamycin inhibitor for the treatment of advanced renal cell carcinoma. *Ann Pharmacother* 2011; **45:** 78–83.
6. Yao JC, *et al.* RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364:** 514–23.
7. Pavel ME, *et al.* Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011; **378:** 2005–12.
8. Baselga J, *et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; **366:** 520–9.
9. Thompson LA, *et al.* Everolimus: a new treatment option for advanced pancreatic neuroendocrine tumors. *Ann Pharmacother* 2012; **46:** 1212–19.
10. Dhillon S. Everolimus in combination with exemestane: a review of its use in the treatment of patients with postmenopausal hormone receptor-positive, HER2-negative advanced breast cancer. *Drugs* 2013; **73:** 475–85.

Organ and tissue transplantation. References.

1. Eisen HJ, *et al.* Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; **349:** 847–58.
2. Vitko S, *et al.* Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *Am J Transplant* 2004; **4:** 626–35.
3. Nashan B, *et al.* Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. *Transplantation* 2004; **78:** 1332–40.
4. Lorber MI, *et al.* Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation* 2005; **80:** 244–52.
5. Vitko S, *et al.* Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2005; **5:** 2521–30. Correction. *ibid.* 2006; **6:** 243.
6. Pascual J. Everolimus in clinical practice—renal transplantation. *Nephrol Dial Transplant* 2006; **21** (suppl 3): iii18–iii23.
7. Webster AC, *et al.* Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
8. Dunn C, Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs* 2006; **66:** 547–70.
9. Snell GI, *et al.* Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant* 2006; **6:** 169–77.
10. Levy G, *et al.* Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; **12:** 1640–8.
11. Chapman JR, *et al.* Proliferation signal inhibitors in transplantation: questions at the cutting edge of everolimus therapy. *Transplant Proc* 2007; **39:** 2937–50.
12. Vigano M, *et al.* RAD B253 Study Group. Prevention of acute rejection and allograft vasculopathy by everolimus in cardiac transplants recipients: a 24-month analysis. *J Heart Lung Transplant* 2007; **26:** 584–92.
13. Hill JA, *et al.* A lower incidence of cytomegalovirus infection in de novo heart transplant recipients randomized to everolimus. *Transplantation* 2007; **84:** 1436–42.
14. Chan L, *et al.* CRADUS09 Study Group. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. *Transplantation* 2008; **85:** 821–6.
15. Salvadori M, *et al.* Everolimus with very low-exposure cyclosporine a in de novo kidney transplantation: a multicenter, randomized, controlled trial. *Transplantation* 2009; **88:** 1194–1202.
16. Koch M. Everolimus in liver and lung transplantation. *Drugs Today* 2009; **45:** 11–20.

Polycystic kidney disease. Autosomal dominant polycystic kidney disease is a slowly progressive hereditary disorder in which renal cysts develop, usually leading to end-stage renal disease. In a controlled 2-year study, everolimus slowed the increase in total kidney volume over the first year, but did not slow the progression of renal impairment.[1]

1. Walz G, *et al.* Everolimus in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2010; **363:** 830–40. Correction. *ibid.*; 1190 and 1977.

Psoriasis. A patient with psoriasis and a poor response to conventional therapy was treated with everolimus and ciclosporin. All manifestations improved after 4 weeks of therapy, but treatment had to be stopped after the patient developed leucopenia.[1]

1. Frigerio E, *et al.* Severe psoriasis treated with a new macrolide: everolimus. *Br J Dermatol* 2007; **156:** 372–4.

Reperfusion and revascularisation procedures. References to the use of everolimus-eluting stents.

1. Zhang F, *et al.* Clinical safety and efficacy of everolimus-eluting stents compared to paclitaxel-eluting stents in patients with coronary artery disease. *Ann Med* 2011; **43:** 75–9.
2. de Waha A, *et al.* Everolimus-eluting versus sirolimus-eluting stents: an updated meta-analysis of randomized trials. *Clin Res Cardiol* 2012; **101:** 461–7.
3. Palmerini T, *et al.* Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; **379:** 1393–1402.
4. Palmerini T, *et al.* Stent thrombosis with everolimus-eluting stents: meta-analysis of comparative randomized controlled trials. *Circ Cardiovasc Interv* 2012; **5:** 357–64.
5. Townsend JC, *et al.* Everolimus-eluting stents in interventional cardiology. *Vasc Health Risk Manag* 2012; **8:** 393–404.
6. Park KW, *et al.* Safety and efficacy of second-generation everolimus-eluting Xience V stents versus zotarolimus-eluting resolute stents in real-world practice: patient-related and stent-related outcomes from the multicenter prospective EXCELLENT and RESOLUTE-Korea registries. *J Am Coll Cardiol* 2013; **61:** 536–44.

Tuberous sclerosis complex. References.

1. Krueger DA, *et al.* Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med* 2010; **363:** 1801–11.

2. Curran MP. Everolimus: in patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. *Paediatr Drugs* 2012; **14:** 51–60.
3. Franz DN, *et al*. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2013; **381:** 125–32.
4. Bissler JJ, *et al*. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2013; **381:** 817–24.

Adverse Effects and Precautions

As for Sirolimus, see p. 1967.2.

Other adverse effects that have been reported with everolimus include dehydration, fatigue, diabetes mellitus, chest pain, heart failure, dysgeusia, insomnia, conjunctivitis, nail disorders, haemoptysis, dyspnoea, and skin disorders such as pruritus, palmar-plantar erythrodysesthesia syndrome, and acneform dermatitis.

Renal function, fasting glucose concentrations, and full blood count should be measured at baseline and periodically during treatment.

Effects on the lungs. Pulmonary toxicity is a well-known adverse effect in patients given sirolimus (p. 1967.3) and similar toxicity has occurred[1-4] in patients given everolimus.

1. Expósito V, *et al*. Everolimus-related pulmonary toxicity in heart transplant recipients. *J Heart Lung Transplant* 2008; **27:** 797–800.
2. Otton J, *et al*. Everolimus-associated pneumonitis in 3 heart transplant recipients. *J Heart Lung Transplant* 2009; **28:** 104–6.
3. Vandewiele B, *et al*. Diffuse alveolar hemorrhage induced by everolimus. *Chest* 2010; **137:** 456–9.
4. Depuydt P, *et al*. Fatal acute pulmonary injury associated with everolimus. *Ann Pharmacother* 2012; **46:** e7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies everolimus as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

Everolimus is a substrate of cytochrome P450 isoenzyme CYP3A4 and a substrate and moderate inhibitor of P-glycoprotein. Plasma concentrations of everolimus may be affected by inducers or competitive inhibitors of CYP3A4 or P-glycoprotein. Exposure to everolimus is increased when given with the CYP3A4/P-glycoprotein inhibitors ciclosporin, ketoconazole, erythromycin, and verapamil. Licensed product information advises avoiding the use of everolimus with CYP3A4 or P-glycoprotein inhibitors; dosage reductions have been suggested if use with a moderate CYP3A4 inhibitor is necessary. Substances that are potent inducers of CYP3A4 or P-glycoprotein may decrease exposure to everolimus; dosage increases have been suggested if use together cannot be avoided. For dose adjustments, see Uses and Administration, p. 1958.1.

In vitro results suggest that systemic concentrations of everolimus after usual oral doses are unlikely to inhibit P-glycoprotein, CYP3A4, or CYP2D6, but theoretically, everolimus may affect the bioavailability of CYP3A4 or P-glycoprotein substrates when given together.

Use with live vaccines should be avoided.

References.

1. Kovarik JM, *et al*. Everolimus drug interactions: application of a classification system for clinical decision making. *Biopharm Drug Dispos* 2006; **27:** 421–6.

Immunosuppressants. The bioavailability of everolimus was significantly increased when given with *ciclosporin*,[1] and dose adjustment of everolimus may be necessary if the ciclosporin dose is altered (see Administration with Everolimus, p. 1946.3).

In contrast, results from a small study implied that *tacrolimus* appeared to have a minimal effect on everolimus blood concentrations, and the dose of everolimus, when used with tacrolimus, may need to be higher than that given with ciclosporin in order to achieve therapeutic everolimus blood concentrations.[2]

1. Kovarik JM, *et al*. Differential influence of two cyclosporine formulations on everolimus pharmacokinetics: a clinically relevant pharmacokinetic interaction. *J Clin Pharmacol* 2002; **42:** 95–9.
2. Kovarik JM, *et al*. Differential pharmacokinetic interaction of tacrolimus and cyclosporine on everolimus. *Transplant Proc* 2006; **38:** 3456–8.

Ketoconazole. In a pharmacokinetic study in 12 healthy subjects,[1] ketoconazole increased the maximum concentration of everolimus by an average of 3.9-fold; area under the concentration-time curve was also increased by about 15-fold. The half-life of everolimus was significantly prolonged, and its clearance reduced. Since ketoconazole inhibits both cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, the authors supposed that both pathways might have contributed to this interaction. The interaction was deemed to be clinically relevant and they advised against use of these 2 drugs together.

1. Kovarik JM, *et al*. Blood concentrations of everolimus are markedly increased by ketoconazole. *J Clin Pharmacol* 2005; **45:** 514–18.

Rifampicin. In a pharmacokinetic study,[1] rifampicin increased the clearance of everolimus, decreasing exposure to everolimus by about 63%.

1. Kovarik JM, *et al*. Effect of rifampin on apparent clearance of everolimus. *Ann Pharmacother* 2002; **36:** 981–5.

Verapamil. Verapamil increased the bioavailability of everolimus; the half-life of everolimus was essentially unchanged. The dose of everolimus should be reduced when these two drugs are given together, but the amount should be determined by blood concentrations and clinical monitoring. Verapamil concentrations may also be affected by everolimus, but the mechanism is unclear; any dose adjustment of verapamil should be guided by blood pressure monitoring.[1]

1. Kovarik JM, *et al*. Pharmacokinetic interaction between verapamil and everolimus in healthy subjects. *Br J Clin Pharmacol* 2005; **60:** 434–7.

Pharmacokinetics

Peak plasma concentrations of everolimus occur about 1 to 2 hours after an oral dose. Plasma protein binding is about 74%. Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall, and is a substrate of P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Most metabolites are excreted in the faeces with small amounts found in urine. The mean elimination half-life of everolimus is about 30 hours.

References.

1. Kovarik JM, *et al*. Clinical development of an everolimus pediatric formulation: relative bioavailability, food effect, and steady-state pharmacokinetics. *J Clin Pharmacol* 2003; **43:** 141–7.
2. Kirchner GI, *et al*. Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* 2004; **43:** 83–95.
3. Moes DJAR, *et al*. Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients. *Clin Pharmacokinet* 2012; **51:** 467–80.

Therapeutic drug monitoring. Licensed product information recommends routine monitoring of whole blood everolimus concentrations when used as an immunosuppressant for transplantation, or for giant-cell astrocytoma.

In heart, kidney, and liver **transplantation** patients with everolimus trough levels of 3 nanograms/mL or greater have been found to have a lower incidence of acute rejection; an upper limit of 8 nanograms/mL is recommended. Monitoring is considered especially important in those with hepatic impairment (see under Uses and Administration, p. 1958.1) and if ciclosporin formulation or dosage is changed (see Administration with Everolimus, under Ciclosporin, p. 1946.3).

In **giant-cell astrocytoma** doses should be adjusted to attain everolimus trough concentrations of 5 to 15 nanograms/mL (see under Uses and Administration, p. 1958.1).

Use of everolimus with some other drugs may affect trough concentrations, see Administration with Other Drugs, p. 1958.2.

Further references.

1. Kovarik JM, *et al*. Exposure-response relationships for everolimus in de novo kidney transplantation: defining a therapeutic range. *Transplantation* 2002; **73:** 920–5.
2. Kovarik JM, *et al*. Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. *Ther Drug Monit* 2004; **26:** 499–505.
3. Starling RC, *et al*. Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. *Am J Transplant* 2004; **4:** 2126–31.
4. Lorber MI, *et al*. Therapeutic drug monitoring for everolimus in kidney transplantation using 12-month exposure, efficacy, and safety data. *Clin Transplant* 2005; **19:** 145–52.
5. Mabasa VH, Ensom MH. The role of therapeutic monitoring of everolimus in solid organ transplantation. *Ther Drug Monit* 2005; **27:** 666–76.
6. Kovarik JM, *et al*. Everolimus in pulmonary transplantation: pharmacokinetics and exposure-response relationships. *J Heart Lung Transplant* 2006; **25:** 440–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Certican; ***Austral.***: Afinitor; Certican; ***Austria***: Afinitor; Certican; ***Belg.***: Afinitor; Certican; ***Braz.***: Afinitor; Certican; ***Canad.***: Afinitor; ***Chile***: Certican; ***Cz.***: Afinitor; Certican; ***Denm.***: Afinitor; Certican; Votubia; ***Fin.***: Certican; ***Fr.***: Afinitor; Certican; Votubia; ***Ger.***: Afinitor; Certican; Votubia; ***Gr.***: Afinitor; Certican; ***Hong Kong***: Afinitor; Certican; ***Hung.***: Certican; ***India***: Certican; ***Indon.***: Certican; ***Irl.***: Afinitor; Votubia; ***Israel***: Afinitor; Certican; ***Ital.***: Certican; ***Jpn***: Afinitor; Certican; ***Malaysia***: Afinitor; Certican; ***Mex.***: Certican; ***Neth.***: Afinitor; Certican; Votubia; ***Norw.***: Afinitor; Certican; Votubia; ***NZ***: Afinitor; ***Philipp.***: Afinitor; Certican; ***Pol.***: Afinitor; Certican; ***Port.***: Afinitor; Certican; ***Rus.***: Afinitor (Афинитор); Certican (Сертикан); ***S.Afr.***: Certican; ***Singapore***: Afinitor; Certican; ***Spain***: Afinitor; Certican; Votubia; ***Swed.***: Afinitor; Certican; Votubia; ***Switz.***: Afinitor; Certican; Votubia; ***Thai.***: Afinitor; Certican; ***Turk.***: Afinitor; Certican; ***UK***: Afinitor; Votubia; ***Ukr.***: Afinitor (Афинитор); Certican (Сертикан); Sertikan (Сертикан)†; ***USA***: Afinitor; Zortress; ***Venez.***: Certican.

Gusperimus Hydrochloride *(rINNM)*

BMS-181173; BMY-42215-1; 15-Deoxyspergualin Hydrochloride; Deoxyspergualin Hydrochloride; Guspérimus, Chlorhydrate de; Gusperimús, hidrocloruro de; Gusperimus Trihydrochloride (USAN); Gusperimusi Hydrochloridum; Hidrocloruro de gusperimús; NKT-01; NSC-356894; Гусперимуса Гидрохлорид.

(±)-*N*-[({4-[(3-Aminopropyl)amino]butyl}carbamoyl)hydroxymethyl]-7-guanidinoheptanamide trihydrochloride.

$C_{17}H_{37}N_7O_3,3HCl=496.9$

CAS — 104317-84-2 (gusperimus); 89149-10-0 (gusperimus); 85468-01-5 (gusperimus hydrochloride).

ATC — L04AA19.

ATC Vet — QL04AA19.

UNII — QZS4144I00.

Profile

Gusperimus is a guanidine derivative that inhibits both cell-mediated and antibody-mediated immunity. It is used in the treatment of renal graft rejection, and has been investigated in the management of graft-versus-host disease and Wegener's granulomatosis. For mention of its role in reversing acute graft rejection in kidney transplantation, see p. 1935.2.

Gusperimus is used as the hydrochloride. A dose of 3 to 5 mg/kg of gusperimus hydrochloride given daily for 7 days, by intravenous infusion over 3 hours, has been suggested in the treatment of acute renal graft rejection. Treatment may be continued for a further 3 days if required.

Adverse effects reported with gusperimus include bone-marrow depression, numbness of face and extremities, headache, gastrointestinal disturbances, alterations in liver enzyme values, and facial flushing. Rapid injection should be avoided as an acute increase in plasma concentration may produce respiratory depression.

References.

1. Ramos EL, *et al*. Deoxyspergualin: mechanism of action and pharmacokinetics. *Transplant Proc* 1996; **28:** 873–5.
2. Tanabe K, *et al*. Effect of deoxyspergualin on the long-term outcome of renal transplantation. *Transplant Proc* 2000; **32:** 1745–6.
3. Amada N, *et al*. Prophylactic use of deoxyspergualin improves long-term graft survival in living related renal transplant recipients transfused with donor-specific blood. *Transplant Proc* 2001; **33:** 2256–7.
4. Birck R, *et al*. 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003; **14:** 440–7.
5. Schmitt WH, *et al*. Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol Dial Transplant* 2005; **20:** 1083–92.
6. Amada N, *et al*. Deoxyspergualin prophylaxis with tacrolimus further improves long-term graft survival in living-related renal-transplant recipients transfused with donor-specific blood. *Transplant Proc* 2005; **37:** 927–9.
7. Nojima M, *et al*. Combined therapy of deoxyspergualin and plasmapheresis: a useful treatment for antibody-mediated acute rejection after kidney transplantation. *Transplant Proc* 2005; **37:** 930–3.
8. Kawagishi N, *et al*. Usage of deoxyspergualin on steroid-resistant acute rejection in living donor liver transplantation. *Tohoku J Exp Med* 2006; **208:** 225–33.
9. Flossmann O, *et al*. Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. *Ann Rheum Dis* 2009; **68:** 1125–30.
10. Flossmann O, Jayne DRW. Long-term treatment of relapsing Wegener's granulomatosis with 15-deoxyspergualin. *Rheumatology (Oxford)* 2010; **49:** 556–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Spanidin; ***Jpn***: Spanidin.

Inolimomab *(rINN)*

BT-563; Inolimomabum; Инолимомаб.

Immunoglobulin G1, anti-(human interleukin 2 receptor α-chain) (mouse monoclonal B-B10 γ1-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer.

CAS — 152981-31-2.

Profile

Inolimomab is a murine/human monoclonal antibody similar to daclizumab (p. 1957.1) that acts as an interleukin-2 receptor antagonist at the alpha chain (CD25) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is under investigation for the treatment of graft-versus-host disease after organ transplantation.

References.

1. Winkler M. Inolimomab (OPi). *Curr Opin Investig Drugs* 2002; **3:** 1464–7.
2. Wabbijn M, *et al*. Ten-year follow-up of recipients of a kidney or heart transplant who received induction therapy with a monoclonal antibody against the interleukin-2 receptor. *Exp Clin Transplant* 2004; **2:** 201–7.
3. Bay JO, *et al*. Inolimomab in steroid-refractory acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation: retrospective analysis and comparison with other interleukin-2 receptor antibodies. *Transplantation* 2005; **80:** 782–8.

4. Bonaros N, *et al.* Ten-year follow-up of a prospective, randomized trial of BT563/bb10 versus anti-thymocyte globulin as induction therapy after heart transplantation. *J Heart Lung Transplant* 2006; **25:** 1154–63.
5. Piñana JL, *et al.* Encouraging results with inolimomab (anti-IL-2 receptor) as treatment for refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2006; **12:** 1135–41.
6. Dartois C, *et al.* Exposure-effect population model of inolimomab, a monoclonal antibody administered in first-line treatment for acute graft-versus-host disease. *Clin Pharmacokinet* 2007; **46:** 417–32.

Mizoribine *(rINN)*

HE-69; Mizoribina; Mizoribinum; Мизорибин.
5-Hydroxy-1-β-D-ribofuranosylimidazole-4-carboxamide.
$C_9H_{13}N_3O_6$=259.2
CAS — 50924-49-7.
UNII — 4JR41A10VP.

Pharmacopoeias. In *Jpn.*

Profile

Mizoribine is an oral immunosuppressant that is used for the management of rejection in kidney transplantation, for nephrotic syndrome associated with primary glomerular disease, for lupus nephritis, and for rheumatoid arthritis.

Adverse effects include myelosuppression, hyperuricaemia, gastrointestinal disturbances, and hypersensitivity reactions. Stevens-Johnson syndrome has also been reported.

Administration. Although oral doses of mizoribine of 1 to 3 mg/kg daily have been recommended in renal transplantation, higher doses (above 5 mg/kg daily) have been widely used. Similarly, an oral dose of 50 mg three times daily has been recommended for patients with nephrotic syndrome associated with primary glomerular disease or lupus nephritis, and in rheumatoid arthritis, but high-dose regimens have been investigated.

Further references.

1. Tanabe K, *et al.* Long-term results in mizoribine-treated renal transplant recipients: a prospective, randomized trial of mizoribine and azathioprine under cyclosporine-based immunosuppression. *Transplant Proc* 1999; **31:** 2877–9.
2. Yoshioka K, *et al.* A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. *Kidney Int* 2000; **58:** 317–24.
3. Yokota S. Mizoribine: mode of action and effects in clinical use. *Pediatr Int* 2002; **44:** 196–8.
4. Takei S. Mizoribine in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. *Pediatr Int* 2002; **44:** 205–9.
5. Honda M. Nephrotic syndrome and mizoribine in children. *Pediatr Int* 2002; **44:** 210–6.
6. Nagaoka R, *et al.* Mizoribine treatment for childhood IgA nephropathy. *Pediatr Int* 2002; **44:** 217–23.
7. Tsuzuki K. Role of mizoribine in renal transplantation. *Pediatr Int* 2002; **44:** 224–31.
8. Shibasaki T, *et al.* A randomized open-label comparative study of conventional therapy versus mizoribine onlay therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clin Exp Nephrol* 2004; **8:** 117–26.
9. Akiyama T, *et al.* Mizoribine in combination therapy with tacrolimus for living donor renal transplantation: analysis of a nationwide study in Japan. *Transplant Proc* 2005; **37:** 843–5.
10. Tanaka H, *et al.* Long-term mizoribine intermittent pulse therapy for young patients with flare of lupus nephritis. *Pediatr Nephrol* 2006; **21:** 962–6.
11. Tanaka E, *et al.* Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. *Mod Rheumatol* 2006; **16:** 214–19.
12. Sugitani A, *et al.* Revival of effective and safe high-dose mizoribine for the kidney transplantation. *Clin Transplant* 2006; **20:** 590–5.
13. Kawasaki Y, *et al.* Efficacy of single dose of oral mizoribine pulse therapy two times per week for frequently relapsing nephrotic syndrome. *J Nephrol* 2007; **20:** 52–6.
14. Stypinski D, *et al.* Safety, tolerability and pharmacokinetics of higher-dose mizoribine in healthy male volunteers. *Br J Clin Pharmacol* 2007; **63:** 459–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bredinin (布累迪宁); ***Jpn***: Bredinin.

Muromonab-CD3 *(USAN, rINN)*

Muromonabum-CD3; OKT3; Муромонаб-CD3.
ATC — L04AA02.
ATC Vet — QL04AA02.
UNII — JGA39ICE2V.

Description. A murine monoclonal antibody comprising a purified IgG_{2a} immunoglobulin with a heavy chain having a molecular weight of about 50 000 daltons and a light chain with a molecular weight of about 25 000 daltons.

Pharmacopoeias. In *Chin.*

Uses and Administration

Muromonab-CD3 is a murine monoclonal antibody to the T3 (CD3) antigen of human T-lymphocytes, which is essential to antigen recognition and response; the antibody thus specifically blocks T-cell generation and function, to exert an immunosuppressant effect without affecting the bone marrow.

It is used in the treatment of acute allograft rejection in organ transplant recipients, in doses of 5 mg daily by intravenous injection for 10 to 14 days. For children's doses, see Administration in Children, below. The dose of any other immunosuppressant therapy may need to be reduced. Patients should be monitored closely after the first few doses of muromonab-CD3 because of the risk of cytokine release syndrome and hypersensitivity reactions. The first dose may be preceded by intravenous methylprednisolone sodium succinate, in a dose of 8 mg/kg, 1 to 4 hours before muromonab-CD3. Paracetamol and antihistamines may also be given with muromonab-CD3 to reduce early reactions.

Muromonab-CD3 has also been given experimentally as part of regimens for the prophylaxis of graft rejection. For further details of the use of muromonab-CD3 in the treatment and prophylaxis of graft rejection see Organ and Tissue Transplantation, p. 1932.2, *et seq.*

References.

1. ten Berge IJM, *et al.* Guidelines for optimal use of muromonab CD3 in transplantation. *BioDrugs* 1999; **11:** 277–84.
2. Flechner SM. A randomized prospective trial of low-dose OKT3 induction therapy to prevent rejection and minimize side effects in recipients of kidney transplants. *Transplantation* 2000; **69:** 2374–81.
3. Henry ML, *et al.* A randomized prospective trial of OKT3 induction in the current immunosuppression era. *Clin Transplant* 2001; **15:** 410–14.
4. Benfield MR, *et al.* A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. *Pediatr Transplant* 2005; **9:** 282–92.
5. Knop S, *et al.* OKT3 muromonab as second-line and subsequent treatment in recipients of stem cell allografts with steroid-resistant acute graft-versus-host disease. *Bone Marrow Transplant* 2005; **36:** 831–7.
6. Sevmis S, *et al.* OKT3 treatment for steroid-resistant acute rejection in kidney transplantation. *Transplant Proc* 2005; **37:** 3016–18.
7. Wilmot I, *et al.* OKT3 treatment in refractory pediatric heart transplant rejection. *J Heart Lung Transplant* 2005; **24:** 1793–7.
8. Knop S, *et al.* Treatment of steroid-resistant acute GVHD with OKT3 and high-dose steroids results in better disease control and lower incidence of infectious complications when compared to high-dose steroids alone: a randomized multicenter trial by the EBMT Chronic Leukemia Working Party. *Leukemia* 2007; **21:** 1830–3.

Administration. *ORAL* Oral muromonab-CD3 has been investigated in doses of 0.2 to 5 mg daily (with or without the glycolipid beta-glucosylceramide), and appears to have some activity.[1]

1. Ilan Y, *et al.* Oral administration of OKT3 monoclonal antibody to human subjects induces a dose-dependent immunologic effect in T cells and dendritic cells. *J Clin Immunol* 2010; **30:** 167–77.

Administration in children. The initial recommended doses in children given muromonab-CD3 for acute allograft rejection are as follows:

- those weighing 30 kg or less: 2.5 mg daily
- those weighing more than 30 kg: 5 mg daily

Doses are given by intravenous injection for 10 to 14 days.

Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require doses to be titrated upwards. The initial dose may be subsequently adjusted in 2.5 mg increments to achieve T-cell clearance (CD3-positive cells less than 25 cells/mm^3) and ensure therapeutic serum concentrations of muromonab-CD3 (of 800 nanograms/mL or greater, see Therapeutic Drug Monitoring, p. 1961.1).

Adverse Effects, Treatment, and Precautions

An acute cytokine release syndrome occurs in most patients, typically 30 to 60 minutes after the first few doses of muromonab-CD3 (although it may occur later). Frequency and severity tend to decrease with successive doses, while prophylactic corticosteroids may reduce initial adverse reactions (see Uses and Administration, above). The syndrome ranges from a more frequently reported, mild, self-limiting, flu-like illness to a less common, severe, and life-threatening, shock-like reaction, which may include serious cardiovascular and CNS manifestations. Typical clinical manifestations of the cytokine release syndrome include high fever, chills or rigors, headache, tremor, gastrointestinal disturbances, myalgia, and generalised weakness. Rash and pruritus may also occur. Cardiorespiratory findings may include apnoea, dyspnoea, bronchospasm or wheezing, tachypnoea, respiratory arrest or failure, acute respiratory distress syndrome, angina, myocardial infarction, chest pain or tightness, tachycardia, hypertension, hypotension, cardiac failure, pulmonary oedema, hypoxaemia, and arrhythmias. Reversible impairment of renal function may also be associated with the syndrome.

Other reported effects of muromonab-CD3 include encephalopathy, cerebral oedema, and a syndrome resembling aseptic meningitis, with headache, fever, stiff neck, and photophobia; seizures have also occurred. Hypersensitivity reactions, including fatal anaphylaxis, have been reported and may be difficult to distinguish from the cytokine release syndrome.

As with other potent immunosuppressants, treatment with muromonab-CD3 may increase the risk of serious infections and the development of certain malignancies. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason.

Muromonab-CD3 should not be given to patients with uncontrolled hypertension, or in patients hypersensitive to products of murine origin. It should be avoided in patients with a history of seizures. Because fluid overload is associated with an increased risk of pulmonary oedema due to the cytokine release syndrome, muromonab-CD3 is contra-indicated in patients who have undergone a more than 3% weight gain in the week preceding therapy, or who have radiographic evidence of fluid overloading. Repeated courses of muromonab-CD3 may be less effective because of the development of antibodies to the drug. Paediatric patients may be at increased risk of serious adverse effects following muromonab-CD3 therapy.

Effects on the blood. *THROMBOEMBOLISM.* Intragraft thromboses developed in 9 of 93 consecutive kidney transplant recipients given high-dose muromonab-CD3 (10 mg daily) as part of their immunosuppressive regimen.[1] In one patient the thrombosis was in the renal artery, and in 3 in the renal vein; the remainder had thromboses in the glomerular capillaries and thrombotic microangiopathy similar to that of haemolytic-uraemic syndrome. The authors suggested that muromonab-CD3 has procoagulant effects, perhaps mediated by released tumour necrosis factor; these effects had also been seen in 3 patients receiving muromonab-CD3 at conventional doses (5 mg daily). Another group[2] has also reported an apparently increased incidence of acute vascular thrombosis in patients given muromonab-CD3 at conventional doses, but in the experience of others,[3] despite evidence of activation of coagulation by the drug, treatment of acute rejection with 5 mg daily was not associated with thromboembolic complications. US licensed product information states that the relationship to dose remains unclear, but that the relative risk appears to be greater with doses above the recommended dose.

1. Abramowicz D, *et al.* Induction of thromboses within renal grafts by high-dose prophylactic OKT3. *Lancet* 1992; **339:** 777–8.
2. Gomez E, *et al.* Main graft vessels thromboses due to conventional-dose OKT3 in renal transplantation. *Lancet* 1992; **339:** 1612–13.
3. Raasveld MHM, *et al.* Thromboembolic complications and dose of monoclonal OKT3 antibody. *Lancet* 1992; **339:** 1363–4.

Effects on the ears. Bilateral sensorineural hearing loss has occurred after muromonab-CD3 therapy. In one case series, 5 out of 7 patients were affected, showing a mean hearing loss of 18 decibels.[1] Tinnitus may also occur.[1,2] Although symptoms are generally reversible,[1,2] one patient still showed a deficit in hearing after 6 months.[3]

1. Hartnick CJ, *et al.* Reversible sensorineural hearing loss following administration of muromonab-CD3 (OKT3) for cadaveric renal transplant immunosuppression. *Ann Otol Rhinol Laryngol* 2000; **109:** 45–7.
2. Hartnick CJ, *et al.* Reversible sensorineural hearing loss after renal transplant immunosuppression with OKT3 (muromonab-CD3). *Ann Otol Rhinol Laryngol* 1997; **106:** 640–2.
3. MichalsM, *et al.* Hearing loss associated with muromonab-CD3 therapy. *Clin Pharm* 1988; **7:** 867–8.

Effects on the nervous system. Generalised seizures were reported in 2 uraemic kidney-graft recipients given muromonab-CD3.[1] Delayed graft function may result in the accumulation of uraemic toxins which combine with cytokines released by the immunosuppressant to produce the effects on the CNS. Seizures and encephalopathy were reported in siblings given muromonab-CD3 after renal transplantation, and appeared to predispose one of them to develop ciclosporin neurotoxicity.[2] A neurological syndrome characterised by akinetic mutism, blepharospasm, anomic aphasia, and delirium, occurred in a heart transplant patient given muromonab-CD3; symptoms resolved after stopping therapy.[3]

The manufacturers have warned that children treated with muromonab-CD3 may be at increased risk of nervous system complications, notably cerebral oedema that may result in fatal cerebral herniation. Since 1986, and as of May 2004, 9 cases of cerebral oedema had been reported worldwide in children, resulting in 6 deaths. Cerebral herniation had occurred within a few hours to 1 day after injection. Signs include the sudden appearance of severe headache, seizures, impaired mental function, drowsiness and lethargy, and coma.[4]

1. Seifeldin RA, *et al.* Generalized seizures associated with the use of muromonab-CD3 in two patients after kidney transplantation. *Ann Pharmacother* 1997; **31:** 586–9.
2. Thaisetthawatkul P, *et al.* Muromonab-CD3-induced neurotoxicity: report of two siblings, one of whom had subsequent cyclosporin-induced neurotoxicity. *J Child Neurol* 2001; **16:** 825–31.
3. Pittock SJ, *et al.* OKT3 neurotoxicity presenting as akinetic mutism. *Transplantation* 2003; **75:** 1058–60.

4. Janssen-Ortho, Canada. Important new safety information on Orthoclone OKT*3 (muromonab-CD3) (issued 17 May 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/orthoclone_okt3_pa-ap-eng.pdf (accessed 18/02/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies muromonab-CD3 as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pharmacokinetics

Therapeutic drug monitoring. US licensed product information states that serum concentrations of muromonab-CD3 are measurable using an enzyme-linked immunosorbent assay (ELISA). Studies in organ transplant recipients found that patients less than 10 years of age had higher concentrations than patients aged 10 to 50 years. Subsequent clinical experience has shown that serum concentrations of muromonab-CD3 greater than or equal to 800 nanograms/mL block the function of T-cells. Reduced T-cell clearance or low plasma concentrations of muromonab-CD3 provide a basis for adjusting muromonab dosage or stopping therapy.

In adults, periodic monitoring to ensure plasma muromonab-CD3 concentrations of 800 nanograms/mL or greater, or CD3-positive cells less than 25 cells/mm^3 is recommended. Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require increased doses of muromonab-CD3 to achieve similar depletion of CD3-positive cells and therapeutic serum concentrations; both T-cell clearance and plasma muromonab-CD3 should be monitored daily in children.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Orthoclone OKT3†; ***Belg.***: Orthoclone OKT3; ***Braz.***: Orthoclone OKT3; ***China***: Ior T3 (爱欧山); ***Fin.***: Orthoclone OKT3†; ***Fr.***: Orthoclone OKT3†; ***Ger.***: Orthoclone OKT3†; ***Gr.***: Orthoclone; ***Israel***: Orthoclone OKT3; ***Ital.***: Orthoclone OKT3; ***Mex.***: Ior-T3†; Orthoclone OKT3; ***Neth.***: Orthoclone OKT3†; ***Norw.***: Orthoclone OKT3†; ***NZ***: Orthoclone OKT3; ***Port.***: Orthoclone OKT3; ***S.Afr.***: Orthoclone†; ***Singapore***: Orthoclone OKT3; ***Swed.***: Orthoclone OKT3†; ***Switz.***: Orthoclone OKT3†; ***Turk.***: Orthoclone OKT3†; ***USA***: Orthoclone OKT3†; ***Venez.***: OKT3.

Mycophenolate

ATC — L04AA06.
ATC Vet — QL04AA06.

Mycophenolic Acid *(BAN, USAN, rINN)*

Acide Mycophénolique; Ácido micofenólico; Acidum Mycophenolicum; Lilly-68618; MPA; NSC-129185; Микофеноловая Кислота.

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoic acid.

$C_{17}H_{20}O_6$=320.3

CAS — 24280-93-1.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — HU9DX48N0T.

Mycophenolate Mofetil *(BANM, USAN, rINNM)*

Micofenolato de mofetilo; Mikofenolat Mofetil; Mikofenolato mofetilis; Mofetilis Mycophenolas; Mofetil-mykofenolát; Mofetilo, micofenolato de; Mycophenolas Mofetil; Mycophenolas Mofetilum; Mycophenolas-mofetil; Mycophénolate mofétil; Mycophénolate, Mofétil de; Mycophenolate Morpholinoethyl; Mycophenolatmofetil; Mykofenolaattimofetiili; Mykofenolatmofetil; RS-61443; Микофеноловаяа Мофетил.

2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate.

$C_{23}H_{31}NO_7$=433.5

CAS — 115007-34-6; 128794-94-5.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — 9242ECW6R0.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mycophenolate Mofetil). A white or almost white, crystalline powder. M.p. about 96 degrees. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. Protect from light.

USP 36: (Mycophenolate Mofetil). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in acetone. Store in airtight containers.

Mycophenolate Mofetil Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro del micofenolato de mofetilo; Mycophénolate, Mofétil Chlorhydrate de; Mycophenolati Mofetili Hydrochloridum; RS-61443-190; Микофеноловой Мофетила Гидрохлорид.

2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate hydrochloride.

$C_{23}H_{31}NO_7$,HCl=470.0

CAS — 116680-01-4.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — UXH81S8ZVB.

Incompatibility. Solutions of mycophenolate mofetil hydrochloride were found to be physically compatible and chemically stable with solutions containing clinically relevant concentrations of cefepime, dopamine, noradrenaline, tacrolimus, and vancomycin, for up to 4 hours of simulated Y-site administration. However, combining ciclosporin and mycophenolate resulted in effervescence and chemical instability.[1]

1. Cochran BG, *et al.* Physical compatibility and chemical stability of mycophenolate mofetil during simulated Y-site administration with commonly coadministered drugs. *Am J Health-Syst Pharm* 2007; **64:** 1410–14.

Stability. UK and US licensed product information states that, after reconstitution of *mycophenolate mofetil oral suspension*, it may be stored at room temperature (15 degrees to 30 degrees) or in a refrigerator (2 degrees to 8 degrees) for up to 60 days; it should not be frozen.

UK licensed product information for *mycophenolate mofetil hydrochloride solution for infusion* states that the infusion should be started within 3 hours of reconstitution and dilution; solutions may be kept at room temperature (15 degrees to 30 degrees). A study found that solutions of mycophenolate mofetil hydrochloride in concentrations equivalent to mycophenolate mofetil 1, 5, or 10 mg/mL were stable for 7 days when stored at 4 degrees or 25 degrees in PVC infusion bags.[1] However, it was noted that a progressive discoloration occurred in bags unprotected from light and stored at 25 degrees; further study was required to determine the source of the discoloration.

1. Certain E, *et al.* Stability of i.v. mycophenolate mofetil in 5% dextrose injection in polyvinyl chloride infusion bags. *Am J Health-Syst Pharm* 2002; **59:** 2434–9.

Mycophenolate Sodium *(BANM, USAN, rINNM)*

ERL-080; Micofenolato sódico; Mycophénolate de Sodium; Natrii Mycophenolas; Натрий Микофеноловая.

Sodium 4(*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

$C_{17}H_{19}NaO_6$=342.3

CAS — 37415-62-6.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — WX877SQI1G.

Uses and Administration

Mycophenolic acid is an immunosuppressant derived from *Penicillium stoloniferum.* It is a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibits purine synthesis, with potent cytostatic effects on both T- and B-lymphocytes. It is given with other immunosuppressants, for the prevention of graft rejection, and has also been tried in diseases with an auto-immune or immune-mediated inflammatory component.

It has been used mainly as the morpholinoethyl derivative, mycophenolate mofetil, or its hydrochloride salt; doses of both are expressed as mycophenolate mofetil. 1.08 g of mycophenolate mofetil hydrochloride is equivalent to about 1 g of mycophenolate mofetil. An enteric-coated formulation of mycophenolate sodium (the sodium salt of mycophenolic acid) is also available in some countries. Doses are expressed in terms of the acid; mycophenolate sodium 769 mg is equivalent to about 720 mg of mycophenolic acid.

In patients to whom oral therapy cannot initially be given, mycophenolate mofetil may be given for up to 14 days by intravenous infusion. Infusions are given as the hydrochloride salt. It is dissolved in glucose 5% to a final concentration equivalent to mycophenolate mofetil 6 mg/mL, and given over 2 hours through either a central or peripheral vein.

In the prophylaxis of acute **renal** graft rejection in adults, the conventional formulation of mycophenolate mofetil is given orally in doses of 1 g twice daily, usually within 72 hours of transplantation; the equivalent dose may be given by intravenous infusion, but is usually started within 24 hours after transplantation.

The enteric-coated formulation of mycophenolate sodium is also given for the prophylaxis of acute renal graft rejection to adults in a dose equivalent to mycophenolic acid 720 mg twice daily; the two formulations cannot be indiscriminately interchanged or substituted.

In the prophylaxis of **cardiac** graft rejection in adults, mycophenolate mofetil 1.5 g twice daily is given orally, within 5 days after transplantation, or by intravenous infusion at an equivalent dose.

For use in the prophylaxis of rejection in **hepatic** transplantation in adults, the equivalent of mycophenolate mofetil 1 g twice daily is given by intravenous infusion for the first 4 days after transplantation, with subsequent conversion to 1.5 g twice daily orally as soon as it can be tolerated.

For doses of mycophenolate used for organ transplantation in children see Administration in Children, below.

Patients should undergo regular blood counts; if neutropenia develops consideration should be given to interrupting mycophenolate treatment, reducing the dose, or stopping therapy.

Administration in children. Oral mycophenolate mofetil is licensed from the age of 2 years in the UK, and from 3 months of age in the USA. For prevention of **renal** graft rejection in patients up to 18 years of age, the recommended oral dose of mycophenolate mofetil is 600 mg/m^2 twice daily, up to a maximum of 1 g twice daily. Patients with a body-surface of 1.25 to 1.5 m^2 may be given 750 mg twice daily, whereas those with a body-surface of greater than 1.5 m^2 may be given the same dose as adults (see Uses and Administration, above). In the UK, the *BNFC* allows for use from 1 month to 18 years at 600 mg/m^2 twice daily orally or by intravenous infusion when used with ciclosporin and corticosteroids, but recommends 300 mg/m^2 twice daily when used with tacrolimus and corticosteroids; the maximum in both cases is 2 g daily.

UK licensed product information states that no data are available for paediatric cardiac and hepatic transplant patients. However, for prophylaxis of rejection in **hepatic** transplantation, the *BNFC* recommends mycophenolate mofetil 10 mg/kg twice daily, orally or by intravenous infusion, for children aged from 1 month to 18 years. This may be increased to 20 mg/kg twice daily, to a maximum of 2 g daily. The dose is the same whether used with either ciclosporin and corticosteroids, or tacrolimus and corticosteroids.

Mycophenolate mofetil is used in paediatric **haematopoietic stem cell** transplant (HSCT) recipients, often with a calcineurin inhibitor such as ciclosporin. Dosing guidelines for paediatric HSCT patients are lacking, but exposure to mycophenolic acid has been found to differ compared with other transplant recipients, see under Pharmacokinetics, p. 1965.2.

Mycophenolate mofetil is also used for severe refractory eczema in children, see p. 1962.1.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dose adjustments of *mycophenolate mofetil* are needed for renal transplant recipients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are necessary for those with hepatic disease of differing aetiology. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

UK licensed product information states that no dose adjustments are needed for *mycophenolate sodium* in renal transplant patients with hepatic impairment.

Administration in renal impairment. US licensed product information states that exposure to mycophenolic acid (MPA) is increased in patients with severe chronic renal impairment. Although mean MPA concentrations in patients with delayed renal graft function were comparable to those transplant patients without delayed renal graft function, there is a potential for a transient increase in MPA concentrations if renal graft function is delayed. However, dose adjustment does not appear to be necessary in these patients. Both US and UK licensed product information state that in renal transplant patients with severe chronic renal impairment (GFR less than 25 mL/minute per 1.73 m^2), oral or intravenous doses of *mycophenolate mofetil* above 1 g twice daily should be avoided; UK product information recommends that the daily dose of *mycophenolate sodium* in these patients should not exceed 1.44 g. No dose adjustments of mycophenolate are needed in those with delayed renal graft function. No data are available for cardiac or hepatic transplant recipients with severe chronic renal impairment.

Chronic active hepatitis. Mycophenolate mofetil may be of benefit in patients with auto-immune hepatitis

(p. 1602.3) who are intolerant of or unresponsive to azathioprine or other standard therapy.[1-5]

1. Richardson PD, *et al.* Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. *J Hepatol* 2000; **33:** 371–5.
2. Devlin SM, *et al.* Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. *Can J Gastroenterol* 2004; **18:** 321–6.
3. Inductivo-Yu I, *et al.* Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. *Clin Gastroenterol Hepatol* 2007; **5:** 799–802.
4. Hennes EM, *et al.* Mycophenolate mofetil as second line therapy in autoimmune hepatitis? *Am J Gastroenterol* 2008; **103:** 3063–70.
5. Aw MM, *et al.* Mycophenolate mofetil as rescue treatment for autoimmune liver disease in children: a 5-year follow-up. *J Hepatol* 2009; **51:** 156–60.

Eczema. Mycophenolate mofetil has been reported to be safe and effective in the treatment of moderate-to-severe, refractory eczema (p. 1684.1). Typical oral doses are 1 to 2 g daily in adults, and 30 to 50 mg/kg (or 1.2 g/m^2) daily in children.[1-3]

1. Neuber K, *et al.* Treatment of atopic eczema with oral mycophenolate mofetil. *Br J Dermatol* 2000; **143:** 385–91.
2. Grundmann-Kollmann M, *et al.* Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol* 2001; **137:** 870–3.
3. Heller M, *et al.* Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007; **157:** 127–32.

Eye disorders. Retrospective evaluations of treatment outcomes in patients with chronic inflammatory eye disease treated with mycophenolate mofetil found that it was effective in controlling inflammation and had a useful corticosteroid-sparing effect.[1,2] Mycophenolate mofetil, used either alone or adjunctively, has been reported[3-8] to be of benefit in refractory uveitis (p. 1615.1). Oral doses of 600 mg/m^2 twice daily or 1 g twice daily have been used in children; the latter dose has also been used in adults with uveitis. There was some suggestion mycophenolate might be less effective in those patients initially unresponsive to azathioprine.[5] For mention of its use in uveitis associated with sarcoidosis see p. 1963.1.

1. Baltatzis S, *et al.* Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. *Ophthalmology* 2003; **110:** 1061–5.
2. Thorne JE, *et al.* Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology* 2005; **112:** 1472–7.
3. Zierhut M, *et al.* Immunsuppressive Therapie mit Mycophenolat Mofetil (CellCept) in der Behandlung der Uveitis. *Ophthalmologe* 2001; **98:** 647–51.
4. Greiner K, *et al.* Effizienz von Mycophenolat-Mofetil bei der Therapie der intermediären und posterioren Uveitis. *Ophthalmologe* 2002; **99:** 691–4.
5. Lau CH, *et al.* Long-term efficacy of mycophenolate mofetil in the control of severe intraocular inflammation. *Clin Experiment Ophthalmol* 2003; **31:** 487–91.
6. Siepmann K, *et al.* Mycophenolate mofetil is a highly effective and safe immunosuppressive agent for the treatment of uveitis: a retrospective analysis of 106 patients. *Graefes Arch Clin Exp Ophthalmol* 2006; **244:** 788–94.
7. Doycheva D, *et al.* Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol* 2007; **91:** 180–4.
8. Teoh SC, *et al.* Mycophenolate mofetil for the treatment of uveitis. *Am J Ophthalmol* 2008; **146:** 752–60.

Glomerular kidney disease. Mycophenolate mofetil, in usual adult oral doses of 1 to 2 g daily, has been reported[1-10] to be of benefit in various forms of glomerular kidney disease (p. 1604.3); in childhood nephrotic syndrome, it was reported to have a significant corticosteroid-sparing effect, reduce relapse rates,[5,11] and benefit renal function.[8,12]

1. Choi MJ, *et al.* Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int* 2002; **61:** 1098–1114.
2. Karim MY, Abbs IC. Mycophenolate mofetil in nonlupus glomerulonephropathy. *Lupus* 2005; **14** (suppl): s39–s41.
3. Segarra A, *et al.* Efficacy and safety of 'rescue therapy' with mycophenolate mofetil in resistant primary glomerulonephritis—a multicenter study. *Nephrol Dial Transplant* 2007; **22:** 1351–60.
4. Moudgil A, *et al.* Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: current status and future directions. *Pediatr Nephrol* 2005; **20:** 1376–81.
5. Hogg RJ, *et al.* Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 2006; **1:** 1173–8.
6. Afzal K, *et al.* Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2007; **22:** 2059–65.
7. Okada M, *et al.* Mycophenolate mofetil therapy for children with intractable nephrotic syndrome. *Pediatr Int* 2007; **49:** 933–7.
8. Cailliez M, *et al.* Le mycophénolate mofétil améliore la fonction rénale et l'imprégnation cortisonique au cours du syndrome néphrotique corticodépendant de l'enfant. Une étude de cohorte. *Nephrol Ther* 2008; **4:** 15–20.
9. Dorresteijn EM, *et al.* Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. *Pediatr Nephrol* 2008; **23:** 2013–20.
10. Fujinaga S, *et al.* Mycophenolate mofetil therapy for childhood-onset steroid dependent nephrotic syndrome after long-term cyclosporine: extended experience in a single center. *Clin Nephrol* 2009; **72:** 268–73.
11. Bagga A, *et al.* Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 2003; **42:** 1114–20.
12. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil. *Pediatr Nephrol* 2004; **19:** 101–4.

Immune thrombocytopenia. Mycophenolate mofetil has been reported[1-4] to be of benefit in small numbers of patients with refractory immune thrombocytopenia (p. 1606.1).

1. Howard J, *et al.* Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anaemia and auto-immune thrombocytopenia purpura. *Br J Haematol* 2002; **117:** 712–15.
2. Hou M, *et al.* Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. *Eur J Haematol* 2003; **70:** 353–7.
3. Kotb R, *et al.* Efficacy of mycophenolate mofetil in adult refractory autoimmune cytopenias: a single center preliminary study. *Eur J Haematol* 2005; **75:** 60–64.
4. Provan D, *et al.* Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. *Am J Hematol* 2006; **81:** 19–25.

Inflammatory bowel disease. Mycophenolate mofetil has been investigated as an alternative to azathioprine in Crohn's disease (see Inflammatory Bowel Disease, p. 1808.3). A randomised study in 70 patients compared therapy with corticosteroids plus mycophenolate mofetil or azathioprine in patients with moderate or severe Crohn's disease. The authors concluded that the mycophenolate regimen produced a clinical response earlier than the azathioprine regimen, and that mycophenolate should be considered in patients allergic or unresponsive to azathioprine or mercaptopurine.[1] However, it has been suggested[2] that the study may have been too short to draw definite conclusions, given the known delayed therapeutic effect of azathioprine. A beneficial effect for 5 out of 6 patients with severe Crohn's disease was reported[3] after 3 months of therapy with oral mycophenolate mofetil 1 g twice daily, but this effect was not sustained beyond 6 months.[4] Others have also noted relapse or lack of response to be relatively common;[5,6] while mycophenolate may have a role in those who cannot tolerate, or are refractory to, azathioprine,[7,8] the latter remains the immunosuppressant of choice due to its greater ability to prevent flare-ups.[2]

1. Neurath MF, *et al.* Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. *Gut* 1999; **44:** 625–8.
2. Miehsler W, *et al.* Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? *Am J Gastroenterol* 2001; **96:** 782–7.
3. Florin THJ, *et al.* Treatment of steroid refractory inflammatory bowel disease (IBD) with mycophenolate mofetil (MMF). *Aust N Z J Med* 1998; **28:** 344–5.
4. Radford-Smith GL, *et al.* Mycophenolate mofetil in IBD patients. *Lancet* 1999; **354:** 1386–7.
5. Ford AC, *et al.* Mycophenolate mofetil in refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **17:** 1365–9.
6. Wenzl HH, *et al.* Mycophenolate mofetil for Crohn's disease: short-term efficacy and long-term outcome. *Aliment Pharmacol Ther* 2004; **19:** 427–34.
7. Palaniappan S, *et al.* Mycophenolate mofetil therapy for refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13:** 1488–92.
8. Tan T, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. *World J Gastroenterol* 2009; **15:** 1594–9.

Multiple sclerosis. In a small open-label study, 5 out of 7 patients with multiple sclerosis (p. 996.3) benefited from mycophenolate mofetil; 3 of these patients reported improved movement.[1] A retrospective review[2] of mycophenolate mofetil treatment (given either adjunctively or as monotherapy) in 79 patients, reported subjective improvements in 12 patients given adjunctive therapy. It has been tried as combination therapy with interferon beta-1a.[3]

1. Ahrens N, *et al.* Mycophenolate-mofetil in the treatment of refractory multiple sclerosis. *J Neurol* 2001; **248:** 713–14.
2. Frohman EM, *et al.* Mycophenolate mofetil in multiple sclerosis. *Clin Neuropharmacol* 2004; **27:** 80–83.
3. Vermersch P, *et al.* G-SEP (Groupe septentrional d'études et de prise en charge de la sclérose en plaques). Combination of IFN β -1a (Avonex) and mycophenolate mofetil (Cellcept) in multiple sclerosis. *Eur J Neurol* 2007; **14:** 85–9.

Myasthenia gravis. Mycophenolate mofetil has been investigated in the treatment of myasthenia gravis (p. 684.1) but did not appear to be of benefit in controlled studies.[1,2]

1. Sanders DB, *et al.* An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology* 2008; **71:** 400–6.
2. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology* 2008; **71:** 394–9.

Organ and tissue transplantation. Mycophenolate mofetil is used for the prophylaxis of graft rejection in kidney (p. 1935.2), heart (p. 1934.2), and liver transplantation (p. 1936.3), and has also been used after transplantation of the lung (p. 1937.3), pancreas (p. 1938.1), and intestines (p. 1935.1). It has been used as an alternative to, or replacement for, azathioprine, and may result in fewer rejections. However, in a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression. It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1).

A few selected references to the use of mycophenolate mofetil in transplantation are given below.

1. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; **345:** 1321–5.
2. Halloran P, *et al.* Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 1997; **63:** 39–47. Correction. *ibid.*; 618.
3. Mathew TH. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years. *Transplantation* 1998; **65:** 1450–4. Correction. *ibid.*; **66:** 817.
4. Oh JM, *et al.* Comparison of azathioprine and mycophenolate mofetil for the prevention of acute rejection in recipients of pancreas transplantation. *J Clin Pharmacol* 2001; **41:** 861–9.
5. Salvadori M, *et al.* Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2003; **4:** 231–6.
6. Sollinger HW. Mycophenolates in transplantation. *Clin Transplant* 2004; **18:** 485–92.
7. Remuzzi G, *et al.* Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial. *Lancet* 2004; **364:** 503–12.
8. Budde K, *et al.* Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. *Transplant Proc* 2005; **37:** 912–15.
9. Curran MP, Keating GM. Mycophenolate sodium delayed release: prevention of renal transplant rejection. *Drugs* 2005; **65:** 799–805.
10. Manzia TM, *et al.* Use of mycophenolate mofetil in liver transplantation: a literature review. *Transplant Proc* 2005; **37:** 2616–17.
11. Ciancio G, *et al.* Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005; **80** (suppl 2): S191–S200.
12. Srinivas TR, *et al.* The impact of mycophenolate mofetil on long-term outcomes in kidney transplantation. *Transplantation* 2005; **80** (suppl 2): S211–S220.
13. Kobashigawa JA, Meiser BM. Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. *Transplantation* 2005; **80** (suppl 2): S235–S243.
14. Kaplan B. Enteric-coated mycophenolate sodium (Myfortic): an overview of current and future use in transplantation. *Drugs* 2006; **66** (suppl 2): 1–8.
15. Kobashigawa JA, *et al.* Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, Myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. *J Heart Lung Transplant* 2006; **25:** 935–41.
16. Zimmerhackl LB, *et al.* Mycophenolate mofetil (Cellcept) in pediatric renal transplantation. *Transplant Proc* 2006; **38:** 2038–40.
17. Schmeding M, *et al.* Mycophenolate mofetil in liver transplantation—is monotherapy safe? *Clin Transplant* 2006; **20** (suppl 17): 75–9.
18. Sanford M, Keating GM. Enteric-coated mycophenolate sodium: a review of its use in the prevention of renal transplant rejection. *Drugs* 2008; **68:** 2505–33.

Pemphigus and pemphigoid. Mycophenolate mofetil has been used successfully in the treatment of pemphigus and pemphigoid (p. 1687.1), both with prednisolone[1-3] and alone.[4] In randomised, non-blinded studies, adjuvant mycophenolate mofetil was found to be as effective as adjuvant azathioprine in pemphigus (vulgaris and foliaceus)[5] and pemphigoid;[6] corticosteroid-sparing effects were similar and there was a trend towards fewer adverse effects with mycophenolate.

1. Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; **135:** 54–6.
2. Williams JV, *et al.* Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. *Br J Dermatol* 2000; **142:** 506–8.
3. Powell AM, *et al.* An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol* 2003; **149:** 138–45.
4. Bredlich R-O, *et al.* Mycophenolate mofetil monotherapy for pemphigus vulgaris. *Br J Dermatol* 1999; **141:** 934.
5. Beissert S, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; **142:** 1447–54.
6. Beissert S, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007; **143:** 1536–42.

Polymyositis and dermatomyositis. Mycophenolate mofetil has been reported to be of benefit in refractory cases of polymyositis and dermatomyositis (p. 1611.1), allowing for tapering of corticosteroid doses.[1-3] Despite benefit in 6 out of 10 patients in another study,[4] 3 patients developed opportunistic infection, which was fatal in 1 case. While acknowledging that other factors may have had a role in this, the authors advised caution in the use of mycophenolate in dermatomyositis.

1. Gelber AC, *et al.* Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. *J Rheumatol* 2000; **27:** 1542–5.
2. Majithia V, Harisdangkul V. Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. *Rheumatology (Oxford)* 2005; **44:** 386–9.
3. Edge JC, *et al.* Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol* 2006; **142:** 65–9.
4. Rowin J, *et al.* Mycophenolate mofetil in dermatomyositis: is it safe? *Neurology* 2006; **66:** 1245–7.

Primary biliary cirrhosis. Despite initial reports[1] of benefit with mycophenolate mofetil in the treatment of primary biliary cirrhosis (p. 2638.3), a small study found no clinical benefit when it was given to patients with incomplete responses to ursodeoxycholic acid.[2]

1. Jones EA. Rationale for trials of long-term mycophenolate mofetil therapy for primary biliary cirrhosis. *Hepatology* 2002; **35:** 258–62.

2. Talwalkar JA, *et al*. Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2005; **39:** 168–71.

Psoriasis. Mycophenolate mofetil has proved successful in some cases of psoriasis (p. 1688.1) refractory to conventional therapies,[1-3] although a comparative study found it to be less effective than ciclosporin.[4] Topical application (as a 2% cream) has been investigated.[5]

1. Grundmann-Kollmann M, *et al*. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 2000; **42:** 835–7.
2. Geilen CC, *et al*. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001; **144:** 583–6.
3. Zhou Y, *et al*. Mycophenolate mofetil (CellCept) for psoriasis: a two-center, prospective, open-label clinical trial. *J Cutan Med Surg* 2003; **7:** 193–7.
4. Beissert S, *et al*. A comparison of mycophenolate mofetil with ciclosporine for the treatment of chronic plaque-type psoriasis. *Dermatology* 2009; **219:** 126–32.
5. Wohlrab J, *et al*. Topical application of mycophenolate mofetil in plaque-type psoriasis. *Br J Dermatol* 2001; **144:** 1263–4.

Retroperitoneal fibrosis. There are several reports[1-5] of success with mycophenolate mofetil and corticosteroids in the treatment of retroperitoneal fibrosis (p. 1612.1).

1. Jois RN, *et al*. Mycophenolate mofetil for maintenance of remission in idiopathic retroperitoneal fibrosis. *Rheumatology (Oxford)* 2007; **46:** 717–18.
2. Adler S, *et al*. Successful mycophenolate mofetil therapy in nine patients with idiopathic retroperitoneal fibrosis. *Rheumatology (Oxford)* 2008; **47:** 1535–8.
3. Swartz RD, *et al*. Idiopathic retroperitoneal fibrosis: a role for mycophenolate mofetil. *Clin Nephrol* 2008; **69:** 260–8.
4. Witschi M, *et al*. Treatment of mediastinal fibrosis with mycophenolate mofetil. *Respiration* 2009; **78:** 330–3.
5. Scheel PJ, *et al*. Combined prednisone and mycophenolate mofetil treatment for retroperitoneal fibrosis: a case series. *Ann Intern Med* 2011; **154:** 31–6.

Rheumatoid arthritis. Mycophenolate mofetil has been tried in rheumatoid arthritis (p. 13.2); reports suggest it may effectively suppress synovial inflammation.[1]

1. McMurray RW, Harisdangkul V. Mycophenolate mofetil: selective T cell inhibition. *Am J Med Sci* 2002; **323:** 194–6.

Sarcoidosis. Mycophenolate mofetil has been used as an adjunct in the successful treatment of patients with mucocutaneous sarcoidosis (p. 1612.2)[1] and neurosarcoidosis.[2,3] It was reported to have a significant corticosteroid-sparing effect in an adolescent with renal involvement,[4] and was effective in a case of severe, relapsing, corticosteroid-dependent gastrointestinal sarcoidosis.[5] It has also been used in sarcoidosis-associated uveitis.[6]

1. Kouba DJ, *et al*. Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *Br J Dermatol* 2003; **148:** 147–8.
2. Chaussenot A, *et al*. Neurosarcoïdose et mycophénolate mofétil. *Rev Neurol (Paris)* 2007; **163:** 471–5.
3. Moravan M, Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. *Neurology* 2009; **72:** 337–40.
4. Moudgil A, *et al*. Successful steroid-sparing treatment of renal limited sarcoidosis with mycophenolate mofetil. *Pediatr Nephrol* 2006; **21:** 281–5.
5. O'Connor AS, *et al*. Pancreatitis and duodenitis from sarcoidosis: successful therapy with mycophenolate mofetil. *Dig Dis Sci* 2003; **48:** 2191–5.
6. Bhat P, *et al*. Mycophenolate mofetil therapy for sarcoidosis-associated uveitis. *Ocul Immunol Inflamm* 2009; **17:** 185–90.

Scleroderma. There are reports of response to mycophenolate in patients with scleroderma (p. 1938.3).

References.
1. Nihtyanova SI, *et al*. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis. *Rheumatology (Oxford)* 2007; **46:** 442–5.
2. Vanthuyne M, *et al*. A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. *Clin Exp Rheumatol* 2007; **25:** 287–92.
3. Shenin M, *et al*. The use of mycophenolate mofetil for the treatment of systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2008; **8:** 11–14.

Systemic lupus erythematosus. Oral mycophenolate mofetil plus prednisolone, given for 12 months, was found to be as effective as oral cyclophosphamide plus prednisolone, for 6 months, followed by azathioprine plus prednisolone for 6 months,[1] in the treatment of Chinese patients with diffuse proliferative *lupus nephritis* (see Systemic Lupus Erythematosus, p. 1613.3). However, some[2,3] have cautioned about generalising these findings to other patients since mycophenolate was compared with oral and not intravenous pulsed cyclophosphamide, which is considered the standard of care in those with diffuse proliferative disease. Patients with poorer prognoses were also considered to have been excluded or underrepresented in the study, and follow-up was short. However, in a 24-week unblinded study[4] oral mycophenolate mofetil was more effective in inducing complete remission than intermittent intravenous cyclophosphamide when used as induction therapy for active lupus nephritis and appeared to be better tolerated. Also, there have been reports of benefit with mycophenolate mofetil in patients with various forms of refractory lupus nephritis, including proliferative disease and membranous nephropathy,[5-7] and some consider it a good therapeutic alternative.[8,9] A review[10] concluded that limited data support induction with cyclophosphamide followed by maintenance with azathioprine or mycophenolate; in selected patients induction with mycophenolate is a reasonable alternative. Meta-analyses concluded that daily oral mycophenolate mofetil, in average or median doses of 1 to 2 g, was more effective than pulsed intravenous or oral cyclophosphamide,[11] and that mycophenolate reduced the risk of failure to induce remission during induction therapy when compared with cyclophosphamide.[12] However, the role of racial and ethnic differences in lupus remain poorly understood, and enrolment of varying ethnic populations in studies can significantly affect results of therapy.[13] Furthermore, it has been pointed out that subjects in studies included in one meta-analysis had relatively preserved renal function, and results cannot be generalised to patients with moderate to severe renal impairment and rapidly progressive glomerulonephritis.[14] While acknowledging data of mycophenolate use in children are limited, another review[15] concluded that from data in adults, mycophenolate is an acceptable alternative to intravenous cyclophosphamide in the induction phase for newly diagnosed patients with mild to moderate nephritis and intact renal function; it may also be suitable if there is concern about a patient's future fertility. However, the optimal dose and length of induction treatment with mycophenolate are still unknown.

Mycophenolate mofetil has been used to control extra-renal manifestations of SLE,[16,17] although it was ineffective in a small number of patients with severe refractory cutaneous disease.[18] Oral mycophenolate sodium 1.44 g daily has been reported to be effective in the treatment of patients with subacute cutaneous lupus erythematosus resistant to standard therapy.[19]

1. Chan TM, *et al*. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; **343:** 1156–62.
2. Falk RJ. Treatment of lupus nephritis—a work in progress. *N Engl J Med* 2000; **343:** 1182–3.
3. Karassa FB, Isenberg DA. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2001; **344:** 382–3. Correction. *ibid.*; 1176.
4. Ginzler EM, *et al*. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; **353:** 2219–28.
5. Kingdon EJ, *et al*. The safety and efficacy of MMF in lupus nephritis: a pilot study. *Lupus* 2001; **10:** 606–11.
6. Kapitsinou PP, *et al*. Lupus nephritis: treatment with mycophenolate mofetil. *Rheumatology (Oxford)* 2004; **43:** 377–80.
7. Spetie DN, *et al*. Mycophenolate therapy of SLE membranous nephropathy. *Kidney Int* 2004; **66:** 2411–15.
8. Ginzler EM, Aranow C. Mycophenolate mofetil in lupus nephritis. *Lupus* 2005; **14:** 59–64.
9. Pisoni CN, *et al*. Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. *J Rheumatol* 2005; **32:** 1047–52.
10. Lenz O, *et al*. Defining the role of mycophenolate mofetil in the treatment of proliferative lupus nephritis. *Drugs* 2005; **65:** 2429–36.
11. Moore RA, Derry S. Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis. *Arthritis Res Ther* 2006; **8:** R182.
12. Walsh M, *et al*. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2007; **2:** 968–75.
13. Dooley MA. Mycophenylate [sic] mofetil: what role in the treatment of lupus? *Lupus* 2006; **15:** 179–82.
14. Contreras G, Sosnov J. Role of mycophenolate mofetil in the treatment of lupus nephritis. *Clin J Am Soc Nephrol* 2007; **2:** 879–82.
15. Paredes A. Can mycophenolate mofetil substitute cyclophosphamide treatment of pediatric lupus nephritis? *Pediatr Nephrol* 2007; **22:** 1077–82.
16. Karim MY, *et al*. Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. *Rheumatology (Oxford)* 2002; **41:** 876–82.
17. Pisoni CN, *et al*. Mycophenolate mofetil and systemic lupus erythematosus: an overview. *Lupus* 2005; **14** (suppl): s9–s11.
18. Pisoni CN, *et al*. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. *Clin Exp Rheumatol* 2005; **23:** 393–6.
19. Kreuter A, *et al*. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol* 2007; **156:** 1321–7.

Vasculitic syndromes. Mycophenolate mofetil has been tried in various vasculitic syndromes, including Churg-Strauss syndrome (p. 1603.1), polyarteritis nodosa and microscopic polyangiitis (p. 1610.2), Takayasu's arteritis (p. 1614.3), and Wegener's granulomatosis (p. 1615.2).

Adverse Effects, Treatment, and Precautions

Mycophenolate is associated with gastrointestinal disturbances, particularly diarrhoea and vomiting; gastrointestinal ulceration, haemorrhage, and perforation have occurred. Immunosuppression, including mycophenolate treatment, is associated with an increased incidence of lymphoma and other malignancies, particularly those of the skin, and excess exposure to UV light should be avoided during treatment. There is also an increased risk of infection, including activation of latent viral infections. These include JC virus-associated progressive multifocal leukoencephalopathy (fatalities have been reported), and BK virus-associated nephropathy which can lead to renal graft loss. Leucopenia, thrombocytopenia, and anaemia are common and there have been reports of aplastic anaemia and bone-marrow depression, sometimes fatal. Pure red cell aplasia has also occurred. Regular full blood counts are recommended during therapy, and treatment may need to be stopped if severe neutropenia develops. Isolated cases of abnormal neutrophil morphology without impaired function, including acquired Pelger-Huët anomaly, have been reported. Other reported adverse effects include asthenia, fever, pain, headache, renal impairment, hypertension or hypotension, hyperglycaemia, disturbances of electrolytes and blood lipids, peripheral oedema, pleural effusion, dyspnoea, cough, acne, rash, alopecia, dizziness, insomnia or somnolence, paraesthesia, and tremor. Agitation, depression, anxiety, tachycardia, and arthralgia are also common. Abnormal hepatic function tests have also been reported. Hypersensitivity reactions, including angioedema and anaphylaxis, have occurred. Pancreatitis, hepatitis, colitis, and gingival hyperplasia have been reported. There are rare reports of interstitial lung disorders, including fatal pulmonary fibrosis. Mycophenolate is teratogenic in *animals*; malformations, especially of the external ear, and other facial abnormalities, have been reported in infants after maternal exposure to mycophenolate (see p. 1964.1).

Mycophenolate should be given with care to patients with severe renal impairment or active disorders of the gastrointestinal tract. Intra-uterine devices should be used with caution in those given immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided in these patients for the same reason.

Mycophenolate mofetil and mycophenolate sodium should not be indiscriminately interchanged or substituted because of their differing pharmacokinetic profiles.

Effects on the blood. Mycophenolate mofetil has been associated with pure red cell aplasia; as of April 2009, 41 cases had been reported worldwide.[1] Some patients were also taking other medicines that could have contributed to the development of pure red cell aplasia. The condition resolved in 16 patients when the dose of mycophenolate mofetil was reduced or withdrawn.

1. MHRA/CHM. Mycophenolate mofetil: pure red cell aplasia. *Drug Safety Update* 2009; **2** (12): 8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON051771&RevisionSelectionMethod=LatestReleased (accessed 14/10/09)

Effects on the gastrointestinal tract. The adverse effects of mycophenolate mofetil on the gastrointestinal tract appeared to be mostly of an irritative nature and included diarrhoea, abdominal pain, nausea and vomiting, anorexia, dyspepsia, and occasionally gastrointestinal haemorrhage or perforation.[1] Paediatric patients tended to have a higher incidence of adverse gastrointestinal events than adults. There was some evidence that adverse effects were related to peak plasma concentrations of the drug.

A review comparing the adverse effect profile of enteric-coated mycophenolate sodium with that of mycophenolate mofetil found a similar incidence of gastrointestinal adverse effects with the two formulations. It was noted that the pathophysiology of the gastrointestinal disturbances seen with mycophenolate is complex and not fully understood. An increased incidence of diarrhoea has been seen with higher mycophenolic acid (MPA) concentrations, possibly due to a direct effect of MPA on intestinal enterocytes, caused by its inhibitory effect on inosine monophosphate dehydrogenase. While exposure to MPA may be higher with the enteric-coated formulation, studies have not shown an appreciable increase in gastrointestinal adverse effects with mycophenolate sodium; the enteric coating might have diminished the direct effect of MPA on enterocytes in the upper gastrointestinal tract.[2] Two studies found that gastrointestinal adverse effects decreased after patients were switched from mycophenolate mofetil to enteric-coated mycophenolate sodium.[3,4]

1. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: aetiology, incidence and management. *Drug Safety* 2001; **24:** 645–63.
2. Behrend M, Braun F. Enteric-coated mycophenolate sodium: tolerability profile compared with mycophenolate mofetil. *Drugs* 2005; **65:** 1037–50.
3. Calvo N, *et al*. Renal transplant patients with gastrointestinal intolerability to mycophenolate mofetil: conversion to enteric-coated mycophenolate sodium. *Transplant Proc* 2006; **38:** 2396–7.
4. Boswell A, *et al*. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in patients with gastrointestinal side effects: case studies. *Prog Transplant* 2006; **16:** 138–40.

Handling. The UK licensed product information for film-coated gastro-resistant tablets of mycophenolate sodium (*Myfortic, Novartis*) warns that if it is necessary to crush the tablets, inhalation of the powder or direct contact of the powder with the skin or mucous membranes should be avoided.

Infection. The use of mycophenolate mofetil was not found to increase the risk of CMV infection in 2 small studies.[1,2] However, it did appear to be associated with an increased frequency[1] and severity[2] of CMV disease (defined as CMV infection plus evidence of viral syndrome). The number of organs affected in patients with CMV disease was also higher in those treated with mycophenolate mofetil.[2]

A retrospective study[3] found that the use of a protocol containing mycophenolate mofetil and tacrolimus was an independent risk factor for the development of CMV disease, but that the dose of mycophenolate mofetil was not. The authors interpreted this to mean that either the combination of mycophenolate mofetil and tacrolimus had an overall stronger immunosuppressive effect than other regimens, or that this protocol bore a specific risk for the development of CMV disease. The pharmacokinetics of mycophenolic acid (MPA), a metabolite of mycophenolate mofetil, and its interaction with tacrolimus, must be considered, with further studies taking MPA levels into account (see Immunosuppressants, under Interactions, below).

In contrast to these findings, another retrospective study[4] found that, although no patient developed CMV disease, the use of mycophenolate mofetil was an independent risk factor for the development of CMV infection in those patients initially seropositive for the CMV antigen.

In a study comparing the adverse effects of mycophenolate mofetil and enteric-coated mycophenolate sodium in renal transplant patients, the overall incidence of infections was similar. However, patients receiving mycophenolate sodium had significantly fewer serious infections. The incidence of CMV infection was very low and similar in both groups.[5]

In February 2008 the manufacturer in agreement with the EMEA warned[6] that isolated cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, had been reported in patients receiving mycophenolate mofetil (*CellCept, Roche*) for transplant rejection or SLE; a diagnosis of PML should be considered in patients who develop neurological symptoms while receiving mycophenolate mofetil. It was also recommended that consideration should be given to reducing the total immunosuppression in patients who develop PML but with a reminder that such a reduction may place the graft at risk in transplant patients.

Regimens containing mycophenolate, particularly with tacrolimus, have been associated with an increased risk of BK-virus nephropathy,[7] although the association may be with intensive immunosuppression rather than mycophenolate itself.[8,9]

1. ter Meulen CG, *et al.* The influence of mycophenolate mofetil on the incidence and severity of primary cytomegalovirus infections and disease after renal transplantation. *Nephrol Dial Transplant* 2000; **15:** 711–14.
2. Sarmiento JM, *et al.* Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. *Clin Transplant* 2000; **14:** 136–8.
3. Kuypers DRJ, *et al.* Role of immunosuppressive drugs in the development of tissue-invasive cytomegalovirus infection in renal transplant recipients. *Transplant Proc* 2002; **34:** 1164–70.
4. Hambach L, *et al.* Increased risk of complicated CMV infection with the use of mycophenolate mofetil in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2002; **29:** 903–6.
5. Budde K, *et al.* Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *Am J Transplant* 2003; **4:** 237–43.
6. Roche, UK. Reports of progressive multifocal leukoencephalopathy (PML) in CellCept (mycophenolate mofetil) treated patients (issued 18th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014106&RevisionSelectionMethod=Latest (accessed 19/05/08)
7. Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. *Transpl Infect Dis* 2009; **11:** 290–7.
8. Hirsch HH, *et al.* Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation* 2005; **79:** 1277–86.
9. Manitpisitkul W, *et al.* Maintenance immunosuppressive agents as risk factors for BK virus nephropathy: a case-control study. *Transplantation* 2009; **88:** 83–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mycophenolate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pregnancy. There have been reports of spontaneous abortions and structural malformations in infants born to women taking mycophenolate.[1-3] The manufacturers of mycophenolate mofetil (*Roche, USA*) have warned that use of the drug during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, oesophagus, and kidney.[1] Women of child-bearing potential should have a negative pregnancy test within 1 week of starting mycophenolate therapy. Women taking mycophenolate should use effective contraception, from at least 4 weeks before starting therapy, and until 6 weeks after stopping mycophenolate.

1. Roche, USA. Important changes in the CellCept (mycophenolate mofetil) prescribing information—use of CellCept is associated with increased pregnancy loss and congenital malformations/change from pregnancy category C to pregnancy category D (issued October 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM154077.pdf (accessed 05/08/10)
2. Anderka MT, *et al.* Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. *Am J Med Genet A* 2009; **149A:** 1241–8.
3. Merlob P, *et al.* Tetrada of the possible mycophenolate mofetil embryopathy: a review. *Reprod Toxicol* 2009; **28:** 105–8.

Interactions

Mycophenolate may compete with other drugs that undergo active renal tubular secretion, resulting in increased concentrations of either drug. Antacids, polycarbophil calcium, sevelamer, or colestyramine may reduce absorption of mycophenolate. Rifampicin decreases exposure to mycophenolate (in patients not also taking ciclosporin); mycophenolic acid (MPA) concentrations should be monitored when rifampicin and mycophenolate are used together. See p. 1963.2 for precautions about use with live vaccines.

Antacids. Although giving mycophenolate mofetil with an antacid mixture (aluminium and magnesium hydroxides) or food both resulted in reductions in peak plasma concentrations of mycophenolic acid (MPA), the differences were small compared with interindividual variation, and were considered unlikely to be clinically significant.[1]

UK licensed product information for mycophenolate sodium states that, although magnesium- or aluminium-containing antacids decrease MPA exposure and peak plasma concentrations, they may be used intermittently for the treatment of occasional dyspepsia; chronic use of antacids is not recommended.

1. Bullingham R, *et al.* Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients. *Br J Clin Pharmacol* 1996; **41:** 513–16.

Antibacterials. A selective bowel decontamination regimen of *tobramycin, cefuroxime*, and the antifungal *nystatin*, apparently inhibited the enterohepatic recycling of mycophenolic acid (MPA), thereby reducing the bioavailability of mycophenolate in liver transplant recipients.[1] *Norfloxacin, metronidazole*, or a combination of the two, reduced exposure to MPA and mycophenolic acid glucuronide (see Metabolism, p. 1965.2) when given to healthy subjects receiving mycophenolate mofetil. The effect of the antibacterials appeared to be additive.[2] Rapid reductions in MPA concentrations were seen after renal transplant patients stabilised on mycophenolate were given either *ciprofloxacin* or *amoxicillin with clavulanic acid*; MPA concentrations recovered to baseline within 3 days of stopping antibacterial therapy, and the effect was seen to wane with continued dosage of antibacterials for 14 days.[3] *Rifampicin* markedly reduced exposure to MPA in a heart-lung transplant recipient, possibly through induction of mycophenolate glucuronidation.[4] A study in renal transplant recipients given rifampicin confirmed this reduction in MPA exposure, concluding that the mechanism was induction of glucuronidation and inhibition of enterohepatic circulation.[5]

1. Schmidt LE, *et al.* The effect of selective bowel decontamination on the pharmacokinetics of mycophenolate mofetil in liver transplant recipients. *Liver Transpl* 2001; **7:** 739–42.
2. Naderer OJ, *et al.* The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. *J Clin Pharmacol* 2005; **45:** 219–26.
3. Borrows R, *et al.* The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil-based renal transplantation. *Ther Drug Monit* 2007; **29:** 122–6.
4. Kuypers DRJ, *et al.* Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate-glucuronosyltransferase. *Clin Pharmacol Ther* 2005; **78:** 81–8.
5. Naesens M, *et al.* Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. *Clin Pharmacol Ther* 2006; **80:** 509–21.

Immunosuppressants. Stopping *ciclosporin* therapy in renal transplant recipients was found to increase serum concentrations of mycophenolic acid (MPA),[1,2] leading to the hypothesis that ciclosporin inhibits the enterohepatic circulation of MPA. In contrast,[3,4] *tacrolimus* therapy increased serum concentrations of MPA, apparently by inhibiting conversion to mycophenolic acid glucuronide (MPAG). While the studies have been criticised,[5] it has been pointed out that an interaction cannot be excluded.[6] An increased incidence of CMV disease has been reported in renal transplant recipients given a triple therapy regimen containing tacrolimus and mycophenolate mofetil.[7] Based on a study[8] in children it has been recommended that mycophenolate mofetil be given in initial doses of 600 mg/m^2 twice daily with ciclosporin but 300 mg/m^2 twice daily with tacrolimus; 500 mg/m^2 twice daily was suggested if no calcineurin inhibitor was given. It is also recommended that dose adjustments are made using therapeutic drug monitoring. However, changes to MPA concentrations may be dose-dependent; a pharmacokinetic study[9] suggested that the ciclosporin dosing schedule used (standard-dose, low-dose, or initial low-dose treatment withdrawn after 6 months) influenced exposure, with MPA exposure tending to increase as ciclosporin exposure decreased. Changes in MPA exposure with tacrolimus have been shown to vary with the dose of mycophenolate mofetil used, an effect that was not adequately reflected by MPA trough concentrations (see Therapeutic Drug Monitoring, p. 1965.2).[10] Another study found marked interindividual variability in MPA and MPAG pharmacokinetics when patients were given ciclosporin microemulsion or tacrolimus in the early stages after renal transplantation. This variability was greater in those given ciclosporin than in those given tacrolimus, and mean total MPA concentrations were about half that of patients in the tacrolimus group.[11] A randomised crossover study compared the effect of ciclosporin microemulsion or tacrolimus on the pharmacokinetics of MPA when each of these were given with enteric-coated mycophenolate sodium to stable renal transplant recipients.[12] In comparison with use with ciclosporin, giving mycophenolate sodium with tacrolimus resulted in a moderate increase in the total exposure of MPA and decreased maximum concentrations and total exposure to the metabolites MPAG and the acyl glucuronide. The results were not statistically significant, and the authors suggested that on this basis, doses of mycophenolate sodium need not be adjusted when converting stable renal transplant patients from one calcineurin inhibitor to the other. However, they recommended that mycophenolate sodium dose adjustments should be based on both the pharmacokinetic data and the clinical situation.

UK licensed product information has stated that ciclosporin reduces MPA exposure, and may decrease MPA concentrations when these two drugs are given together. The exact extent of the decrease is not known for mycophenolate sodium, but may be about 20%, extrapolated from data for mycophenolate mofetil. However, since efficacy studies used this combination, no dose adjustment of mycophenolate is considered necessary. If concomitant ciclosporin therapy is interrupted or stopped, an increase in MPA of about 30% is to be expected, and dosage should be re-evaluated depending on the immunosuppressive regimen. While not commenting on dose adjustment when used with tacrolimus, UK licensed product information for mycophenolate sodium stated that stable renal transplant patients showed increased MPA exposure and decreased MPAG when tacrolimus was substituted for ciclosporin.

Pharmacokinetic analyses found that use of *sirolimus* with mycophenolate led to greater MPA exposure,[13,14] but lower MPAG exposure,[15] when compared with ciclosporin plus mycophenolate. Therapeutic drug monitoring of MPA is recommended in transplant recipients given both mycophenolate and sirolimus;[13,14] guidelines are needed when switching patients from ciclosporin to sirolimus, since the same dose of mycophenolate mofetil would lead on average to a 50% increase in MPA exposure in patients receiving sirolimus compared with ciclosporin.[14]

1. Smak Gregoor PJH, *et al.* Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999; **68:** 1603–6.
2. Shipkova M, *et al.* Effect of cyclosporine withdrawal on mycophenolic acid pharmacokinetics in kidney transplant recipients with deteriorating renal function: preliminary report. *Ther Drug Monit* 2001; **23:** 717–21.
3. Zucker K, *et al.* Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. *Transpl Immunol* 1997; **5:** 225–32.
4. Hübner GI, *et al.* Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 1999; **21:** 536–9.
5. van Gelder T, *et al.* Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 2000; **22:** 639.
6. Hübner GI, Sziegoleit W. Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 2000; **22:** 498–9.
7. Kuypers DRJ, *et al.* Role of immunosuppressive drugs in the development of tissue-invasive cytomegalovirus infection in renal transplant recipients. *Transplant Proc* 2002; **34:** 1164–70.
8. Filler G, *et al.* Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. *Pediatr Nephrol* 2000; **14:** 100–104.
9. Kuypers DR, *et al.* Mycophenolic acid exposure after administration of mycophenolate mofetil in the presence and absence of ciclosporin in renal transplant recipients. *Clin Pharmacokinet* 2009; **48:** 329–41.
10. Kuypers DRJ, *et al.* Long-term changes in mycophenolic acid exposure in combination with tacrolimus and corticosteroids are dose dependent and not reflected by trough plasma concentration: a prospective study in 100 de novo renal allograft recipients. *J Clin Pharmacol* 2003; **43:** 866–80.
11. Atcheson BA, *et al.* Mycophenolic acid pharmacokinetics and related outcomes early after renal transplant. *Br J Clin Pharmacol* 2005; **59:** 271–80.
12. Kaplan B, *et al.* Randomized calcineurin inhibitor cross over study to measure the pharmacokinetics of co-administered enteric-coated mycophenolate sodium. *Clin Transplant* 2005; **19:** 551–8.
13. Büchler M, *et al.* Higher exposure to mycophenolic acid with sirolimus than with cyclosporine cotreatment. *Clin Pharmacol Ther* 2005; **78:** 34–42.
14. Picard N, *et al.* A comparison of the effect of ciclosporin and sirolimus on the pharmokinetics [sic] of mycophenolate in renal transplant patients. *Br J Clin Pharmacol* 2006; **62:** 477–84.
15. Pescovitz MD, *et al.* Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. *Br J Clin Pharmacol* 2007; **64:** 758–71.

Iron. Absorption of mycophenolate mofetil after oral doses was markedly reduced by iron preparations in a study in 7 healthy subjects:[1] mean peak serum concentrations of mycophenolic acid were reduced from 20.1 to 1.3 micrograms/mL. However, in contrast, a study in 16 healthy subjects found no interaction between iron supplements and mycophenolate mofetil,[2] and 2 studies in renal transplant patients found no significant effect of oral iron supplements on the absorption of mycophenolate mofetil.[3,4]

1. Morii M, *et al*. Impairment of mycophenolate mofetil absorption by iron ion. *Clin Pharmacol Ther* 2000; **68:** 613–6.
2. Ducray PS, *et al*. Absence of an interaction between iron and mycophenolate mofetil absorption. *Br J Clin Pharmacol* 2005; **62:** 492–5.
3. Mudge DW, *et al*. The effect of oral iron admiinistration [sic] on mycophenolate mofetil absorption in renal transplant recipients: a randomized, controlled trial. *Transplantation* 2004; **77:** 206–9.
4. Lorenz M, *et al*. Ferrous sulfate does not affect mycophenolic acid pharmacokinetics in kidney transplant patients. *Am J Kidney Dis* 2004; **43:** 1098–1103.

Proton pump inhibitors. Proton pump inhibitors increase gastric pH and may affect the bioavailability of mycophenolate salts. A prospective case-control study[1] found that *pantoprazole* reduced exposure to mycophenolate mofetil in heart transplant recipients. *Omeprazole*[2] and pantoprazole[3] have been reported to reduce the absorption of mycophenolate mofetil but not enteric-coated mycophenolate sodium in healthy subjects.

1. Kofler S, *et al*. Proton pump inhibitors reduce mycophenolate exposure in heart transplant recipients-a prospective case-controlled study. *Am J Transplant* 2009; **9:** 1650–6.
2. Kees MG, *et al*. Omeprazole impairs the absorption of mycophenolate mofetil but not of enteric-coated mycophenolate sodium in healthy volunteers. *J Clin Pharmacol* 2011;.
3. Rupprecht K, *et al*. Bioavailability of mycophenolate mofetil and enteric-coated mycophenolate sodium is differentially affected by pantoprazole in healthy volunteers. *J Clin Pharmacol* 2009; **49:** 1196–1201.

Sevelamer. Exposure to mycophenolate mofetil was reduced after the use of sevelamer in renal transplant patients, an effect that was thought to be due to sevelamer reducing the absorption of mycophenolate.[1] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Pieper A-K, *et al*. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004; **19:** 2630–3.

Pharmacokinetics

Mycophenolate mofetil is rapidly and extensively absorbed from the gastrointestinal tract; enteric-coated mycophenolate sodium is also extensively absorbed. Mycophenolate undergoes presystemic metabolism to active mycophenolic acid (MPA). MPA undergoes enterohepatic recirculation and secondary increases in plasma MPA concentrations are seen; these have been reported at between 6 to 12 hours after a dose of mycophenolate mofetil, and at between 6 to 8 hours after a dose of mycophenolate sodium. MPA is metabolised by glucuronidation to the inactive mycophenolic acid glucuronide. The majority of a dose of mycophenolate is excreted in the urine as this glucuronide, with negligible amounts of MPA; about 6% of a dose is recovered in faeces. MPA is 97% bound to plasma albumin. The mean half-life of MPA after oral and intravenous doses of mycophenolate mofetil has been reported to be 17.9 hours and 16.6 hours, respectively; an MPA half-life of about 12 hours has been reported for mycophenolate sodium.

References.
1. Bullingham RES, *et al*. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 1998; **34:** 429–55.
2. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet* 2007; **46:** 13–58.
3. Filler G, *et al*. Pharmacokinetics of mycophenolate mofetil and sirolimus in children. *Ther Drug Monit* 2008; **30:** 138–42.
4. Lévesque E, *et al*. Pharmacokinetics of mycophenolate mofetil and its glucuronide metabolites in healthy volunteers. *Pharmacogenomics* 2008; **9:** 869–79.
5. de Winter BCM, *et al*. Population pharmacokinetics of mycophenolic acid: a comparison between enteric-coated mycophenolate sodium and mycophenolate mofetil in renal transplant recipients. *Clin Pharmacokinet* 2008; **47:** 827–38.
6. Sam W-J, *et al*. Population pharmacokinetics of mycophenolic acid and its 2 glucuronidated metabolites in kidney transplant recipients. *J Clin Pharmacol* 2009; **49:** 185–95.
7. Barraclough KA, *et al*. Pharmacogenetic influences on mycophenolate therapy. *Pharmacogenomics* 2010; **11:** 369–90.

Bioavailability. A study in renal transplant patients found single doses of mycophenolate sodium 640 mg and 720 mg to be bioequivalent to mycophenolate mofetil 1 g. The 720-mg dose most closely approximated the mycophenolic acid (MPA) exposure of the mycophenolate mofetil dose.[1] The authors noted that since the study was conducted in patients given ciclosporin, bioequivalence of MPA exposure between these two formulations could not be assumed for patients receiving other immunosuppressants. A meta-analysis of 3 studies in stable renal transplant recipients concluded that mycophenolate mofetil and enteric-coated mycophenolate sodium give equivalent mycophenolate exposure in these patients.[2]

1. Arns W, *et al*. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Transplant* 2005; **19:** 199–206.
2. Johnston A, *et al*. Bioequivalence of enteric-coated mycophenolate sodium and mycophenolate mofetil: a meta-analysis of three studies in stable renal transplant recipients. *Transplantation* 2006; **82:** 1413–18.

Haematopoietic stem cell transplantation. Pharmacokinetic studies have suggested that exposure to mycophenolic acid is lower in adult[1] and paediatric[2] haematopoietic stem cell transplant (HSCT) recipients taking mycophenolate mofetil compared with reference values from renal transplant recipients. Children were found to have similar exposure to mycophenolic acid as adults, despite a 33% higher daily dose.[2]

1. van Hest RM, *et al*. Pharmacokinetics of mycophenolate mofetil in hematopoietic stem cell transplant recipients. *Ther Drug Monit* 2007; **29:** 353–60.
2. Jacobson P, *et al*. Higher mycophenolate dose requirements in children undergoing hematopoietic cell transplant (HCT). *J Clin Pharmacol* 2008; **48:** 485–94.

Metabolism. Mycophenolate mofetil is rapidly de-esterified in the body to active mycophenolic acid (MPA), which is subsequently converted to inactive mycophenolic acid glucuronide (MPAG) in the gastrointestinal tract, liver and possibly kidney. This conversion to MPAG is considered to be the most important and rate limiting step.[1] MPA undergoes enterohepatic circulation, with MPAG formed in the liver being excreted into bile and converted back to MPA in the gastrointestinal tract. A further metabolite, the acyl glucuronide, has been shown to be active *in vitro*, inhibiting human inosine monophosphate dehydrogenase,[1,2] and may have implications in therapeutic drug monitoring (see below). MPA is extensively bound to albumin in patients with normal renal and hepatic function, but this binding may be affected in transplant patients by several factors such as hypoalbuminaemia, hyperbilirubinaemia, and uraemia. Accumulation of MPAG leads to an increase in unbound MPA, and a subsequent increase in MPA clearance.[2]

A crossover study to compare the metabolism of mycophenolate mofetil with mycophenolate sodium[3] found that the onset of MPA absorption was delayed with mycophenolate sodium, consistent with its enteric-coated formulation. However, MPA exposure was considered to be bioequivalent, and MPA metabolism did not differ significantly between the two formulations. MPAG was confirmed as being the principal metabolite of MPA, and the authors considered that acyl glucuronide exposure was of a sufficient magnitude to potentially contribute to immunosuppression and toxicity.

1. Shaw LM, *et al*. Pharmacokinetic, pharmacodynamic, and outcome investigations as the basis for mycophenolic acid therapeutic drug monitoring in renal and heart transplant patients. *Clin Biochem* 2001; **34:** 17–22.
2. Shaw LM, *et al*. Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* 2001; **23:** 305–15.
3. Tedesco-Silva H, *et al*. Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. *Transplant Proc* 2005; **37:** 852–5.

Therapeutic drug monitoring. Mycophenolic acid (MPA) concentration appears to correlate with efficacy and toxicity.[1] Patients with low MPA concentrations may be at increased risk of transplant rejection,[2-5] or graft-versus-host disease,[5] and there is some evidence that a high MPA concentration correlates with increased adverse effects.[4,6] Fixed doses of mycophenolate mofetil have been reported to lead to variable MPA exposure,[7,8] and other immunosuppressants can affect MPA concentrations, see under Interactions, p. 1964.2. Therapeutic drug monitoring of mycophenolate mofetil is therefore considered necessary.[1]

Assay procedures to measure MPA concentrations include HPLC and an enzyme-multiplied immunoassay technique (EMIT). However, the acyl glucuronide metabolite of MPA (see Metabolism, above) may cross-react with the latter method, leading to higher measured concentrations than with HPLC.[8,9] This overestimation of MPA exposure using EMIT was reported to be about 24 to 35%, with the greatest bias seen in kidney recipients early after transplantation. However, in paediatric renal transplant patients, EMIT showed comparable diagnostic efficacy to HPLC, and is an acceptable assay for MPA in this population.[8] Another suggested approach is to measure inosine monophosphate dehydrogenase activity directly, (see Metabolism, above) but this has produced variable results.[10]

A review[9] concluded that while some studies show a correlation between MPA trough concentration (C_0) and acute allograft rejection, MPA area under the concentration-time curve (AUC) is predictive of the risk for rejection, and that both have limitations. An abbreviated AUC involving more practical blood sampling regimens may be more appropriate, and a trough concentration between 1 and 3.5 mg/litre has been proposed. For paediatric transplant recipients, a predose trough concentration, as measured by EMIT assay, of between 1.6 and 3.5 mg/litre has been recommended.[11] However, it has been pointed out[12] that the therapeutic range may be different at different time points after transplantation, and among different patient populations; concomitant drugs may also influence this range. The following target concentrations have been recommended for transplant patients taking mycophenolate mofetil:[13]

- MPA AUC 30 to 60 mg X hours/litre as determined by HPLC in the first 30 days post-transplantation
- for renal transplant recipients on a ciclosporin-based regimen, MPA C_0 greater than or equal to 1.3 mg/litre, as measured by HPLC
- for renal transplant recipients on a tacrolimus-based regimen, MPA C_0 greater than or equal to 1.9 mg/litre, as measured by HPLC
- for cardiac transplant recipients, MPA C_0 greater than or equal to 2 mg/litre, as measured by EMIT, or 1.2 to 3.5 mg/litre as measured by HPLC
- for liver transplant recipients, target concentrations could not be definitively recommended; similar targets to renal transplantation were suggested until more data are available

Some have stated that the contribution of MPA trough level monitoring during mycophenolate mofetil therapy is unproven, given the lack of data in paediatric renal transplant patients, and in cardiac and liver transplantation, and that adherence to recommended target ranges for MPA cannot ensure an improved clinical outcome.[14]

It has also been pointed out that, because of differing pharmacokinetic profiles, algorithms developed for mycophenolate mofetil cannot be used for patients treated with mycophenolate sodium.[15]

Measurements of unbound MPA concentrations may be of benefit in patients with renal or hepatic impairment, as factors such as hypoalbuminaemia and renal dysfunction affect the binding of MPA.[9] In liver transplant patients, plasma protein binding of MPA increased as albumin concentration increased and as bilirubin concentration decreased, leading to decreased unbound fraction of MPA, and contributing to large intra- and interindividual pharmacokinetic variability.[16] A population pharmacokinetic study considered the complexity in determining MPA pharmacokinetics to be underestimated.[17] Bayesian forecasting using only 3 samples has been reported to accurately predict MPA exposure.[18-20]

A study in 6 patients with psoriasis concluded that MPA trough concentrations (measured by EMIT) did not predict efficacy or toxicity, but instead were useful to evaluate compliance.[21]

For the view that MPA trough concentrations may not adequately reflect exposure in patients also receiving tacrolimus, see Immunosuppressants, under Interactions, p. 1964.2.

1. Mourad M, *et al*. Therapeutic monitoring of mycophenolate mofetil in organ transplant recipients: is it necessary? *Clin Pharmacokinet* 2002; **41:** 319–27.
2. van Gelder T, *et al*. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; **68:** 261–6.
3. DeNofrio D, *et al*. Mycophenolic acid concentrations are associated with cardiac allograft rejection. *J Heart Lung Transplant* 2000; **19:** 1071–6.
4. Tredger JM, *et al*. Monitoring mycophenolate in liver transplant recipients: toward a therapeutic range. *Liver Transpl* 2004; **10:** 492–502.
5. Jacobson P, *et al*. Relationship of mycophenolic acid exposure to clinical outcome after hematopoietic cell transplantation. *Clin Pharmacol Ther* 2005; **78:** 486–500.
6. Mourad M, *et al*. Correlation of mycophenolic acid pharmacokinetic parameters with side effects in kidney transplant patients treated with mycophenolate mofetil. *Clin Chem* 2001; **47:** 88–94.
7. David-Neto E, *et al*. The need of mycophenolic acid monitoring in long-term renal transplants. *Clin Transplant* 2005; **19:** 19–25.
8. Jeong H, Kaplan B. Therapeutic monitoring of mycophenolate mofetil. *Clin J Am Soc Nephrol* 2007; **2:** 184–91.
9. Shaw LM, *et al*. Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* 2001: **23:** 305–15.
10. Shaw LM, *et al*. Monitoring of mycophenolic acid in clinical transplantation. *Ther Drug Monit* 2002; **24:** 68–73.
11. Filler G. Value of therapeutic drug monitoring of MMF therapy in pediatric transplantation. *Pediatr Transplant* 2006; **10:** 707–11.
12. Venkataramanan R, Shaw LM. Therapeutic monitoring of mycophenolic acid in liver transplant patients. *Liver Transpl* 2004; **10:** 503–5.
13. van Gelder T, *et al*. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* 2006; **28:** 145–54.
14. Kaplan B. Mycophenolic acid trough level monitoring in solid organ transplant recipients treated with mycophenolate mofetil: association with clinical outcome. *Curr Med Res Opin* 2006; **22:** 2355–64.
15. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
16. Pisupati J, *et al*. Intraindividual and interindividual variations in the pharmacokinetics of mycophenolic acid in liver transplant patients. *J Clin Pharmacol* 2005; **45:** 34–41.
17. Shum B, *et al*. Population pharmacokinetic analysis of mycophenolic acid in renal transplant recipients following oral administration of mycophenolate mofetil. *Br J Clin Pharmacol* 2003; **56:** 188–97.
18. Le Guellec C, *et al*. Population pharmacokinetics and Bayesian estimation of mycophenolic acid concentrations in stable renal transplant patients. *Clin Pharmacokinet* 2004; **43:** 253–66.

19. Zahr N, *et al*. Pharmacokinetic study of mycophenolate mofetil in patients with systemic lupus erythematosus and design of Bayesian estimator using limited sampling strategies. *Clin Pharmacokinet* 2008; **47:** 277–84.
20. Saint-Marcoux F, *et al*. Pharmacokinetic modelling and development of Bayesian estimators for therapeutic drug monitoring of mycophenolate mofetil in reduced-intensity haematopoietic stem cell transplantation. *Clin Pharmacokinet* 2009; **48:** 667–75.
21. Daudén E, *et al*. Plasma trough levels of mycophenolic acid do not correlate with efficacy and safety of mycophenolate mofetil in psoriasis. *Br J Dermatol* 2004; **150:** 132–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: CellCept; Imuxgen; Metocris; Munotras†; Mycoldosa; Myfortic; ***Austral.***: CellCept; Imulate; Myfortic; ***Austria***: CellCept; Myfortic; ***Belg.***: CellCept; Myfenax; Myfortic; ***Braz.***: CellCept; Myfortic; ***Canad.***: CellCept; Myfortic; ***Chile***: CellCept; Myfortic; ***China***: Myfortic (米芙); Saikeping (赛可平); Shun You (顺友); ***Cz.***: CellCept; Limfocept; Mofimutral; Mometil; Mophecen; Myclausen; Mycofenor; Myfenax; Myfortic; Mygref; Trixin; ***Denm.***: CellCept; Myclausen; Myfenax; Myfortic; ***Fin.***: CellCept; Myfortic; ***Fr.***: CellCept; Myfortic; ***Ger.***: CellCept; Mycopheno-cell; Myfortic; ***Gr.***: CellCept; Mycofen; Myfenax; Myfetil; Myfortic; ***Hong Kong***: CellCept; Micocept; Myfortic; ***Hung.***: CellCept; Mofimutral; Myfenax; Myfortic; Presumin; ***India***: Baxmune; CellCept; Cellmune; MMF; Mofetyl; Mofilet; Mycept; Mycofit; Mycophen; Myfortic; Mygraft; Myotec; ***Indon.***: CellCept; Myfortic; ***Irl.***: CellCept; Myclausen; Mycolat; Myfenax; Myfortic; ***Israel***: CellCept; Mefetil; Myfortic; ***Ital.***: CellCept; Myfortic; Rigenol; Rimmunos; ***Jpn***: CellCept; ***Malaysia***: CellCept; Myfortic; ***Mex.***: CellCept; Celprot; Lanfetil; Myfortic; Tevacept; ***Neth.***: CellCept; Myclausen; Myfortic; ***Norw.***: CellCept; Myfenax; Myfortic; ***NZ***: CellCept; Ceptolate; Myaccord; ***Philipp.***: CellCept; Mofilet; Mycept; Myfetil; Myfortic; Renocell; ***Pol.***: CellCept; Myclausen; Myfenax; Myfortic; ***Port.***: CellCept; Myclausen; Myfenax; Myfortic; ***Rus.***: CellCept (Селлсепт); Myfortic (Майфортик); Mysept (Майсепт); Supresta (Супреста); ***S.Afr.***: CellCept; Myfortic; ***Singapore***: CellCept; Myfortic; Refrat; ***Spain***: CellCept; Myfenax; Myfortic; ***Swed.***: CellCept; Myclausen; Myfenax; Myfortic; ***Switz.***: CellCept; Myfortic; ***Thai.***: CellCept; Myfortic; ***Turk.***: CellCept; Mofecept; Myfortic; ***UK***: Arzip; CellCept; Myfortic; ***Ukr.***: CellCept (Селлсепт); Myfenax (Мифенакс); Myfortic (Мифортик); ***USA***: CellCept; Myfortic; ***Venez.***: CellCept; Myfortic.

Pharmacopoeial Preparations
USP 36: Mycophenolate Mofetil Capsules; Mycophenolate Mofetil for Injection; Mycophenolate Mofetil for Oral Suspension; Mycophenolate Mofetil Tablets.

Remestemcel-L *(USAN)*

JR-0301.
Allogeneic human mesenchymal stem cells.

NOTE. The name Prochymal has been used as a trade mark for remestemcel-L.

Profile

Remestemcel-L contains *ex-vivo* cultured allogeneic human mesenchymal stem cells, and is used in the treatment of acute graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1933.1). It is also under investigation in the management of acute radiation syndrome, Crohn's disease, myocardial infarction, pulmonary disease, and type 1 diabetes mellitus.

References.
1. Kebriaei P, *et al*. Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2009; **15:** 804–11.
2. Hare JM, *et al*. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal) after acute myocardial infarction. *J Am Coll Cardiol* 2009; **54:** 2277–86.
3. Prasad VK, *et al*. Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal®) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. *Biol Blood Marrow Transplant* 2011; **17:** 534–41.
4. Mannon PJ. Remestemcel-L: human mesenchymal stem cells as an emerging therapy for Crohn's disease. *Expert Opin Biol Ther* 2011; **11:** 1249–56.

Reparixin *(USAN, rINN)*

DF-1681Y; Reparixina; Réparixine; Reparixinum; Repertaxin; Репариксин.
(2*R*)-2-[4-(2-Methylpropyl)phenyl]-*N*-methylsulfonylpropanamide.
$C_{14}H_{21}NO_3S$=283.4
CAS — 266359-83-5.
UNII — U604E1NB3K.

Reparixin Lysine *(rINNM)*

Reparixin L-Lysine; Reparixina lisina; Réparixine Lysine; Reparixinum Lysinum; Repertaxin L-lisina; Repertaxin L-Lysine; Репариксин Лизин.
Reparixin compound with L-lysine (1:1).
$C_{14}H_{21}NO_3S,C_6H_{14}N_2O_2$=429.6
CAS — 266359-93-7.

Profile

Reparixin is an inhibitor of interleukin-8. Reparixin and reparixin lysine have been investigated for the prevention of delayed graft function in organ transplantation.

Sirolimus *(BAN, USAN, rINN)*

AY-022989; AY-22989; NSC-226080; Rapamicina; Rapamycin; Sirolimús; Sirolimusum; Sirolimuusi; Wy-090217; Сиролимус.
(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone.
$C_{51}H_{79}NO_{13}$=914.2
CAS — 53123-88-9.
ATC — L04AA10.
ATC Vet — QL04AA10.
UNII — W36ZG6FT64.

Uses and Administration

Sirolimus is a macrolide compound obtained from *Streptomyces hygroscopicus* and has potent immunosuppressant properties. Sirolimus binds to a protein (FK binding protein-12; FKBP-12; FKPB-12) and this complex inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase for cell cycle progression thus suppressing cytokine-driven T-cell proliferation.

Sirolimus is used for the prevention of graft rejection in kidney transplantation (p. 1935.2), and is being investigated for induction of remission in some auto-immune diseases. Sirolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement. They are also used in the treatment of severe claudication and critical limb ischaemia of infrapopliteal lesions (which is the most severe form of arterial disease in the leg).

For prevention of graft rejection, sirolimus is given with ciclosporin and corticosteroids as soon as possible after transplantation. A loading dose of 6 mg is given orally, followed by a maintenance dose of 2 mg daily, 4 hours after ciclosporin. In patients 13 years of age or more who weigh less than 40 kg a loading dose of 3 mg/m^2, followed by initial maintenance doses of 1 mg/m^2 daily, is recommended. It is recommended that the dose of sirolimus should be adjusted to obtain whole blood trough concentrations of 4 to 12 nanograms/mL (by chromatographic assay), and the doses of ciclosporin and corticosteroids gradually reduced. After 2 to 3 months, ciclosporin should be gradually stopped over 4 to 8 weeks, and the dose of sirolimus adjusted to obtain trough concentrations of about 12 to 20 nanograms/mL. In the USA, ciclosporin may be continued for up to 4 months; sirolimus trough concentrations of 16 to 24 nanograms/mL have been recommended for the first year after transplantation; thereafter, the concentrations should be 12 to 20 nanograms/mL. In patients at high immunological risk (defined as black [Afro-Caribbean] patients and/or repeat renal transplant patients and/or patients with high panel-reactive antibodies), sirolimus may be used with ciclosporin and corticosteroids for the first year after transplantation. A loading dose of up to 15 mg is suggested, followed by an initial maintenance dose of 5 mg daily; adjustments thereafter are made on the basis of whole blood trough concentrations. In patients in whom ciclosporin withdrawal is unsuccessful or cannot be attempted, sirolimus should not be used for more than 3 months after transplantation.

For further information on use in children, and for doses in hepatic impairment, see below.

Sirolimus has been shown to possess antifungal and antineoplastic properties. It is under investigation for gene regulation in gene therapy.

Administration. A study in renal transplant recipients judged the tablet and oral solution formulations of sirolimus to be therapeutically equivalent.[1] Licensed product information states that while 2 mg of oral solution has been shown to be clinically equivalent to 2 mg of the oral tablet formulation, and the two are hence interchangeable, it is unknown whether higher doses of the oral solution are clinically equivalent to the same doses as tablets. When switching patients between formulations, it is recommended to give the same dose and verify the sirolimus trough concentrations 1 to 2 weeks later; verification of trough concentrations is also recommended when switching between different tablet strengths.

1. Mathew TH, *et al*. A comparative study of sirolimus tablet versus oral solution for prophylaxis of acute renal allograft rejection. *J Clin Pharmacol* 2006; **46:** 76–87.

Administration in children. In the USA, sirolimus is not licensed for use in children under 13 years of age. For doses in children aged 13 years or older, and weighing under 40 kg, see Uses and Administration, above. In the UK, sirolimus is licensed from 18 years of age, and the *BNFC* recommends local treatment protocols be consulted for details of doses to be used in children; official guidance from NICE recommends that sirolimus be used as a component of immunosuppressive regimens in children and adolescents only if intolerance necessitates the withdrawal of a calcineurin inhibitor.[1]

1. NICE. Immunosuppressive therapy for renal transplantation in children and adolescents (Technology Appraisal 99, issued April 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA099guidance.pdf (accessed 07/02/08)

Administration in hepatic impairment. Exposure to sirolimus and half-life are both increased in patients with mild to moderate hepatic impairment (Child-Pugh category A or B). Licensed product information states that in patients with hepatic impairment, it is not necessary to modify the loading dose of sirolimus, but whole blood trough concentrations should be closely monitored in these patients. US licensed product information states that the maintenance dose should be reduced by about one-third in patients with mild to moderate hepatic impairment; both US and UK licensed product information recommend reducing the dose by about one-half in patients with severe hepatic impairment. A study[1] involving 9 patients with severe hepatic impairment (Child-Pugh category C) indicated that an initial dosage reduction of about 60% followed by therapeutic drug monitoring might be suitable in these patients.

1. Zimmerman JJ, *et al*. Pharmacokinetics of sirolimus (rapamycin) in subjects with severe hepatic impairment. *J Clin Pharmacol* 2008; **48:** 285–92.

Inflammatory bowel disease. Sirolimus was added to treatment for severe Crohn's disease in a patient who was losing response to infliximab. An initial oral dose of sirolimus 2 mg daily was adjusted to maintain serum trough concentrations at 5 nanograms/mL; this was achieved on a dose of 4 mg daily. Infliximab infusions continued to be given every 6 weeks. A marked improvement in symptoms, inflammatory markers, and endoscopic appearance was noted after 8 weeks of sirolimus, and after 12 weeks of treatment the interval between infliximab infusions was able to be increased to 8 weeks. Sirolimus was stopped after 6 months and remission maintained with 8-weekly infliximab infusions.[1]

1. Massey DCO, *et al*. Use of sirolimus (rapamycin) to treat refractory Crohn's disease. *Gut* 2008; **57:** 1294–6.

Kaposi's sarcoma. Transplant recipients are susceptible to the development of Kaposi's sarcoma (p. 718.1) as a result of long-term immunosuppressive therapy. In 15 renal transplant recipients with biopsy-proven Kaposi's sarcoma, therapy with ciclosporin and mycophenolate was stopped, and sirolimus started. After 1 month, cutaneous lesions had regressed in 12 patients and after 6 months biopsy specimens were negative for Kaposi's sarcoma.[1] While stopping ciclosporin or mycophenolate has led to remission of Kaposi's sarcoma,[2] sirolimus may have an antineoplastic action independent of its immunosuppressive effect.[1] In renal transplant recipients, those who received sirolimus-based therapy after ciclosporin withdrawal at month 3 had a reduced incidence of both skin and non-skin (including Kaposi's sarcoma) malignancies at 5 years after transplantation, compared with those who continued with sirolimus and ciclosporin therapy.[3]

1. Stallone G, *et al*. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352:** 1317–23.
2. Dantal J, Soulillou J-P. Immunosuppressive drugs and the risk of cancer after organ transplantation. *N Engl J Med* 2005; **352:** 1371–3.
3. Campistol JM, *et al*. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17:** 581–9.

Lymphangioleiomyomatosis. Improvements in left lung function have been noted in a patient with lymphangioleiomyomatosis treated with sirolimus after transplantation of the right lung.[1] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p. 2288.3.

1. Egan JJ, *et al*. Sirolimus for lymphangioleiomyomatosis lesions. *N Engl J Med* 2008; **358:** 1963–4.

Organ and tissue transplantation. Sirolimus is used for the prophylaxis of graft rejection in kidney transplantation (p. 1935.2), initially as an adjunct to calcineurin inhibitor-based regimens. It is increasingly used for corticosteroid or calcineurin inhibitor withdrawal, although long-term data

are lacking, and the safety of ciclosporin withdrawal in high-risk patients has not been adequately studied and is not recommended. Sirolimus has been investigated for liver (p. 1936.3), heart (p. 1934.2), pancreas (p. 1938.1), and lung (p. 1937.3) transplantation, although safety has not been established, see Adverse Effects and Precautions below. In *de novo* renal transplant patients, there was an increased risk of rejection in those given sirolimus and mycophenolate and corticosteroids with an interleukin-2 receptor antibody, compared with those not given an interleukin-2 receptor antibody. In a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression.

A few selected references to the use of sirolimus in transplantation are given below.

1. Vasquez EM. Sirolimus: a new agent for prevention of renal allograft rejection. *Am J Health-Syst Pharm* 2000; **57:** 437–51.
2. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000; **356:** 194–202.
3. Ingle GR, *et al*. Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother* 2000; **34:** 1044–55.
4. Johnson RW. Sirolimus (Rapamune) in renal transplantation. *Curr Opin Nephrol Hypertens* 2002; **11:** 603–7.
5. Radovancevic B, Vrtovec B. Sirolimus therapy in cardiac transplantation. *Transplant Proc* 2003; **35** (suppl): 171S–176S.
6. Trotter JF. Sirolimus in liver transplantation. *Transplant Proc* 2003; **35** (suppl): 193S–200S.
7. MacDonald AS. Rapamycin in combination with cyclosporine or tacrolimus in liver, pancreas, and kidney transplantation. *Transplant Proc* 2003; **35** (suppl): 201S–208S.
8. Neff GW, *et al*. Ten years of sirolimus therapy in orthotopic liver transplant recipients. *Transplant Proc* 2003; **35** (suppl): 209S–216S.
9. Dupont P, Warrens AN. The evolving role of sirolimus in renal transplantation. *Q J Med* 2003; **96:** 401–9.
10. Kahan BD. Sirolimus: a ten-year perspective. *Transplant Proc* 2004; **36:** 71–5.
11. Lo A, *et al*. Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004; **77:** 1228–35.
12. Kuypers DRJ. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Safety* 2005; **28:** 153–81.
13. Mehrabi A, *et al*. The role and value of sirolimus administration in kidney and liver transplantation. *Clin Transplant* 2006; **20** (Suppl 17): 30–43.
14. Mulay AV, *et al*. Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. *Transplantation* 2006; **82:** 1153–62.
15. Augustine JJ, *et al*. Use of sirolimus in solid organ transplantation. *Drugs* 2007; **67:** 369–91.
16. House AA, *et al*. Sirolimus use in recipients of expanded criteria donor kidneys. *Drugs* 2008; **68** (suppl 1): 41–9.
17. Kahan BD. Fifteen years of clinical studies and clinical practice in renal transplantation: reviewing outcomes with de novo use of sirolimus in combination with cyclosporine. *Transplant Proc* 2008; **40** (suppl): S17–S20.
18. Campistol JM, *et al*. Practical recommendations for the early use of m-TOR inhibitors (sirolimus) in renal transplantation. *Transpl Int* 2009; **22:** 681–7.
19. Flechner SM. Sirolimus in kidney transplantation indications and practical guidelines: de novo sirolimus-based therapy without calcineurin inhibitors. *Transplantation* 2009; **87** (8 suppl): S1–S6.
20. Patel SJ, *et al*. Considerations in sirolimus use in the early and late post-transplant periods. *Expert Opin Drug Safety* 2009; **8:** 421–34.

Psoriasis. Sirolimus has been investigated both systemically[1,2] and topically[3,4] in the treatment of psoriasis (p. 1688.1).

1. Reitamo S, *et al*. A double-blind study in patients with severe psoriasis to assess the clinical activity and safety of rapamycin (sirolimus) alone or in association with a reduced dose of cyclosporine. *Br J Dermatol* 1999; **141:** 978–9.
2. Reitamo S, *et al*. Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; **145:** 438–45.
3. Ormerod AD, *et al*. Penetration, safety and efficacy of the topical immunosuppressive sirolimus in psoriasis. *Br J Dermatol* 1999; **141:** 975.
4. Ormerod AD, *et al*. Treatment of psoriasis with topical sirolimus: preclinical development and a randomized, double-blind trial. *Br J Dermatol* 2005; **152:** 758–64.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Coronary stents that elute sirolimus effectively reduce restenosis[1-8] and have been widely used. There is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis,[9-14] although not all studies have noted differences.[15] The risk of late stent thrombosis may be increased with drug eluting stents,[16] although the evidence is controversial,[17] and their role in complex interventions is not yet established.[18,19] Oral sirolimus may also be effective in preventing restenosis.[20-23]

1. Morice M-C, *et al*. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346:** 1773–80.
2. Moses JW, *et al*. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349:** 1315–23.
3. Lemos PA, *et al*. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003; **41:** 2093–9.
4. Vishnevetsky D, *et al*. Sirolimus-eluting coronary stent. *Am J Health-Syst Pharm* 2004; **61:** 449–56.
5. Cheng-Lai A, Frishman WH. Sirolimus-eluting coronary stents: novel devices for the management of coronary artery disease. *Am J Ther* 2004; **11:** 218–28.
6. Spaulding C, *et al*. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 989–97.
7. Kastrati A, *et al*. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 1030–9.
8. Weisz G, *et al*. Five-year follow-up after sirolimus-eluting stent implantation: results of the SIRIUS (sirolimus-eluting stent in de-novo native coronary lesions) trial. *J Am Coll Cardiol* 2009; **53:** 1488–97.
9. Windecker S, *et al*. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; **353:** 653–62.
10. Dibra A, *et al*. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353:** 663–70.
11. Hofma SH, *et al*. One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
12. Stettler C, *et al*. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; **370:** 937–48.
13. Lee S-W, *et al*. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus: 2-year clinical outcomes of the DES-DIABETES trial. *J Am Coll Cardiol* 2009; **53:** 812–13.
14. Zhang F, *et al*. Meta-analysis of five randomized clinical trials comparing sirolimus- versus paclitaxel-eluting stents in patients with diabetes mellitus. *Am J Cardiol* 2010; **105:** 64–8.
15. Gallø AM, *et al*. SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 2008; **299:** 409–16.
16. Stone GW, *et al*. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356:** 998–1008.
17. Mauri L, *et al*. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; **356:** 1020–9.
18. Beohar N, *et al*. Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297:** 1992–2000.
19. Win HK, *et al*. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297:** 2001–9.
20. Hausleiter J, *et al*. Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation* 2004; **110:** 790–5.
21. Waksman R, *et al*. Oral rapamycin to inhibit restenosis after stenting of de novo coronary lesions: the Oral Rapamune to Inhibit Restenosis (ORBIT) study. *J Am Coll Cardiol* 2004; **44:** 1386–92.
22. Rodriguez AE, *et al*. ORAR II Investigators. Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the Prospective, Randomized Oral Rapamycin in Argentina (ORAR II) Study. *J Am Coll Cardiol* 2006; **47:** 1522–9.
23. Rodriguez AE, *et al*. Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). *Heart* 2005; **91:** 1433–7.

Uveitis. Sirolimus has been reported to be effective in the treatment of patients with refractory uveitis.[1]

1. Shanmuganathan VA, *et al*. The efficacy of sirolimus in the treatment of patients with refractory uveitis. *Br J Ophthalmol* 2005; **89:** 666–9.

Adverse Effects and Precautions

Commonly reported adverse effects of sirolimus include peripheral oedema, lymphocele, hypokalaemia, hypophosphataemia, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, hyperglycaemia, tachycardia, venous thromboembolism, gastrointestinal disturbances, stomatitis, arthralgia, epistaxis, acne, rash, bone necrosis, fever, hypertension, headache, and pain including abdominal pain. Anaemia, thrombocytopenia, neutropenia or leucopenia are also common.

Immunosuppression, including sirolimus treatment, is associated with an increased incidence of lymphoma and other malignancies, particularly those of the skin, and excess exposure to UV light should be avoided during treatment. There is also an increased risk of infection, including activation of latent viral infections. These include JC virus-associated progressive multifocal leukoencephalopathy (PML), and BK virus-associated nephropathy that can lead to renal graft loss. Antimicrobial prophylaxis is recommended against pneumocystis pneumonia for the first year after transplantation and against CMV for the first 3 months after transplantation.

Thrombotic thrombocytopenic purpura and the haemolytic-uraemic syndrome may occur, as may hypersensitivity, including anaphylactic reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. There are reports of fluid accumulation, including lymphoedema, pleural effusions, and pericardial effusions. Pulmonary embolism, pulmonary haemorrhage, pancreatitis, and alveolar proteinosis may occur rarely. Renal impairment, proteinuria, focal glomerulosclerosis, or nephrotic syndrome may develop; renal function should be monitored, especially when given with ciclosporin. In patients with delayed graft function, sirolimus may delay recovery of renal function. There are reports of hepatotoxicity, and rarely, fatal hepatic necrosis. Excess mortality, graft loss, and hepatic artery thrombosis has been associated with the use of sirolimus in immunosuppressive regimens in liver transplant recipients and therefore use in such patients is not recommended. Interstitial lung disease has been reported, including some fatalities, although other cases resolved on stopping or reducing the dose of sirolimus. Abnormal wound healing after transplant surgery has been reported with the use of sirolimus, especially in those with a BMI greater than 30 kg/m^2; bronchial anastomotic dehiscence, including some fatal cases, has occurred in lung transplant recipients and use in these patients is not recommended.

Sirolimus may have adverse effects on sperm production azoospermia and infertility have been reported. These effects are usually reversible on stopping sirolimus.

Immunosuppressants may reduce the response to vaccines, and the use of live vaccines should be avoided. Intra-uterine devices should be used with caution during immunosuppressive therapy, as there is an increased risk of infection.

Hypersensitivity reactions and subacute thrombosis have occurred with use of the sirolimus-eluting stent; fatalities have been reported.

Effects on the kidneys. Proteinuria and renal dysfunction have been associated with sirolimus. A review[1] concluded that the vast majority of evidence suggested that proteinuria was mediated by glomerular haemodynamic mechanisms due to withdrawal of other immunosuppressants in kidneys with chronic glomerular injury, as in those transplant patients with chronic allograft dysfunction. Whether sirolimus directly causes proteinuria and/or mediates direct glomerular toxicity remains to be resolved and further studies are needed.

1. Rangan GK. Sirolimus-associated proteinuria and renal dysfunction. *Drug Safety* 2006; **29:** 1153–61.

Effects on the liver. A retrospective review of 488 patients noted an increased incidence of veno-occlusive disease of the liver when sirolimus was included in the regimen for prophylaxis against graft-versus-host disease after myeloablative allogeneic stem cell transplant. Incidence was increased further if sirolimus was given with methotrexate after a conditioning regimen using cyclophosphamide and total body irradiation, and was excessively high when sirolimus was used with a busulfan-based conditioning regimen.[1]

1. Cutler C, *et al*. Sirolimus is associated with veno-occlusive disease of the liver after myeloablative allogeneic stem cell transplantation. *Blood* 2008; **112:** 4425–31.

Effects on the lungs. Pulmonary toxicity, including interstitial pneumonitis,[1-9] and alveolar haemorrhage,[5,10,11] has been reported with sirolimus. There was some suggestion in one series that the incidence of interstitial pneumonitis might be higher in patients who switched from calcineurin inhibitors to sirolimus than in those who were started on sirolimus after transplantation.[6] Possible risk factors include giving a loading dose, late use of sirolimus compared with initial therapy, and higher sirolimus dose and trough concentrations; additional risk factors include allograft dysfunction, hypervolaemia, and male gender.[7] Acute respiratory distress has been reported in a 1-year-old heart transplant recipient 3 days after starting sirolimus.[12] Pulmonary alveolar proteinosis has also been reported in a renal transplant patient 2 years after starting sirolimus; symptoms resolved markedly upon stopping sirolimus.[13]

Similar toxicity has occurred with everolimus (p. 1959.1).

1. Morelon E, *et al*. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; **343:** 225–6.
2. Singer SJ, *et al*. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; **343:** 1815–16.
3. Morelon E, *et al*. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001; **72:** 787–90.
4. Lennon A, *et al*. Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation* 2001; **72:** 1166–7.
5. Pham P-T T, *et al*. Sirolimus-associated pulmonary toxicity. *Transplantation* 2004; **77:** 1215–20.
6. Champion L, *et al*. Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Ann Intern Med* 2006; **144:** 505–9.
7. Morath C, *et al*. Four cases of sirolimus-associated interstitial pneumonitis: identification of risk factors. *Transplant Proc* 2007; **39:** 99–102.
8. García-Luque A, *et al*. Sirolimus-associated pneumonitis in heart transplant recipients. *Ann Pharmacother* 2008; **42:** 1143–5.
9. Feagans J, *et al*. Interstitial pneumonitis in the transplant patient: consider sirolimus-associated pulmonary toxicity. *J La State Med Soc* 2009; **161:** 166–72.
10. Vlahakis NE, *et al*. Sirolimus-associated diffuse alveolar hemorrhage. *Mayo Clin Proc* 2004; **79:** 541–5.
11. Khalife WI, *et al*. Sirolimus-induced alveolar hemorrhage. *J Heart Lung Transplant* 2007; **26:** 652–7.
12. Das BB, *et al*. Acute sirolimus pulmonary toxicity in an infant heart transplant recipient: case report and literature review. *J Heart Lung Transplant* 2007; **26:** 296–8.
13. Pedroso SL, *et al*. Pulmonary alveolar proteinosis: a rare pulmonary toxicity of sirolimus. *Transpl Int* 2007; **20:** 291–6.

Effects on the nervous system. Posterior reversible encephalopathy syndrome (a neurotoxic condition involving oedema of the white matter in the posterior parts of the brain and characterised by headache, confusion, and

visual disturbances) has been reported after use of sirolimus.[1,2]

1. Bodkin CL, Eidelman BH. Sirolimus-induced posterior reversible encephalopathy. *Neurology* 2007; **68:** 2039–40.
2. Moskowitz A, *et al.* Posterior reversible encephalopathy syndrome due to sirolimus. *Bone Marrow Transplant* 2007; **39:** 653–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sirolimus as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Thrombosis. There was an apparent clustering of reports of subacute thrombosis associated with the use of the sirolimus-eluting stent soon after its marketing approval in 2003.[1] However, subsequent studies[2] and additional data from 2063 patients[3] suggest that use of the sirolimus-eluting stent is not associated with an excess risk of subacute thrombosis compared with bare-metal stents.

1. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; **351:** 1593–5.
2. Jeremias A, *et al.* Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004; **109:** 1930–2.
3. FDA. FDA public health web notification: final update of information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the Cordis CYPHER® sirolimus-eluting coronary stent (issued 18th October 2004). Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062120 (accessed 05/08/10)

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, HIV-protease inhibitors, the NNRTI delavirdine, and diltiazem may increase plasma concentrations of sirolimus. Conversely, inducers of this isoenzyme, such as nevirapine and rifampicin, may reduce plasma concentrations of sirolimus. Use of sirolimus with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein is not recommended. Grapefruit juice should not be taken with sirolimus. Ciclosporin can affect the rate and extent of sirolimus absorption and it is recommended that these drugs be given 4 hours apart. Use of sirolimus with a calcineurin inhibitor may also increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, or thrombotic microangiopathy. Use of sirolimus with an ACE inhibitor may increase the risk of developing angioedema. See p. 1967.2 for precautions about use with live vaccines.

Immunosuppressants. Concentrations of sirolimus, and area under the concentration-time curve were significantly higher when sirolimus and *ciclosporin* were given together than when the 2 drugs were given 4 hours apart,[1,2] and a synergistic effect has been suggested.[3] This effect may allow for lower doses[4] or early withdrawal[5] of ciclosporin, resulting in improved renal function and less nephrotoxicity. However, for the risk of increased thrombotic reactions see Interactions, above.

Sirolimus may decrease blood concentrations of *tacrolimus*.

1. Kaplan B, *et al.* The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. *Clin Pharmacol Ther* 1998; **63:** 48–53.
2. Zimmerman JJ, *et al.* Pharmacokinetic interactions between sirolimus and microemulsion cyclosporine when orally administered jointly and 4 hours apart in healthy volunteers. *J Clin Pharmacol* 2003; **43:** 1168–76.
3. Kahan BD, Kramer WG. Median effect analysis of efficacy versus adverse effects of immunosuppressants. *Clin Pharmacol Ther* 2001; **70:** 74–81.
4. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; **145:** 438–45.
5. Johnson RWG, *et al.* Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; **72:** 777–86.

Pharmacokinetics

Sirolimus is rapidly absorbed after doses of the oral solution, with a time to peak concentration of about 2 hours. Absorption is variably affected by food, especially high-fat meals. Sirolimus is extensively bound to plasma proteins. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Metabolism occurs by demethylation or hydroxylation, and the majority of a dose is excreted via the faeces, with only about 2% excreted in the urine. In healthy subjects, the bioavailability of a single dose of the tablet formulation is about 27% higher than the oral solution, bioavailability of which is only about 14%. However, this difference is less marked in renal transplant recipients, and when switching between formulations, licensed product information recommends giving the same dose, with trough concentrations verified 1 to 2 weeks later. The terminal half-life in stable renal transplant patients after multiple oral doses has been reported to be about 62 hours; the half-life in men was reported to be significantly longer than in women (about 72 hours compared with about 61 hours).

References.

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; **40:** 573–85.

Genetic factors. Renal transplant recipients with at least one CYP3A5*1 allele had lower exposure to sirolimus than those patients homozygous for CYP3A5*3, and patients with CYP3A5*1/*1 and *1/*3 genotypes required significantly higher sirolimus daily dosage to achieve the same blood concentrations at steady state as the *3/*3 genotypes.[1] Determination of this cytochrome P450 isoenzyme polymorphism could be useful for individualising doses of sirolimus.

1. Le Meur Y, *et al.* CYP3A5*3 influences sirolimus oral clearance in de novo and stable renal transplant recipients. *Clin Pharmacol Ther* 2006; **80:** 51–60.

Therapeutic drug monitoring. The immunosuppressive efficacy and the occurrence and severity of adverse effects of sirolimus correlate with blood concentrations.[1] There is also a good correlation between sirolimus trough concentrations and the area under the concentration-time curve (AUC); the trough concentration is therefore a useful surrogate marker for sirolimus exposure.[2] When sirolimus is used with ciclosporin, whole blood trough concentrations of sirolimus between 4 and 12 nanograms/mL are associated with protection from acute rejection episodes and adverse events. Black patients may require higher doses of sirolimus to achieve a similar exposure to non-black patients; trough concentrations in the higher end of the range are recommended to reduce the risk of rejection.[3] When ciclosporin therapy is stopped, a target trough concentration of sirolimus of about 12 to 20 nanograms/mL is recommended (see also Uses and Administration, p. 1966.2).

Daily monitoring of sirolimus is not necessary due to the relatively long half-life of the drug (about 60 hours). Furthermore, sirolimus concentrations are variable early after transplantation due to physiological changes from surgery and concurrent dose adjustments in other immunosuppressants. The first sample should be taken about 4 days or more after the initial loading dose, and then weekly for the first month and every 2 weeks for the second month.[3] Monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing.[2,3]

After the first 2 months of dose titration, routine therapeutic drug monitoring is not considered necessary in all patients, although it is considered warranted in patients receiving concurrent CYP3A4 and/or P-glycoprotein inducers or inhibitors. Monitoring may also be needed in those at high risk of rejection, those displaying signs of toxicity, or those in whom compliance is a problem.[3] Patients with liver disease, hyperlipidaemia, or leucopenia should also have their sirolimus blood concentrations determined,[2] and concentrations in children should be monitored.[3] Licensed product information states that the recommended 24-hour trough concentrations for sirolimus are based on chromatographic assay methods, and that these values are not interchangeable with immunoassay methods.

Limited sampling strategies based on two time points within 4 hours after dosing were found to be useful predictors of sirolimus exposure in kidney transplant recipients on calcineurin inhibitor-free immunosuppressive regimens;[4] Bayesian forecasting has also been proposed as an accurate predictor of sirolimus pharmacokinetics.[5,6]

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; **40:** 573–85.
2. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
3. Stenton SB, *et al.* Sirolimus: the evidence for clinical pharmacokinetic monitoring. *Clin Pharmacokinet* 2005; **44:** 769–86.
4. Cattaneo D, *et al.* Limited sampling strategies for the estimation of sirolimus daily exposure in kidney transplant recipients on a calcineurin inhibitor-free regimen. *J Clin Pharmacol* 2009; **49:** 773–81.
5. Dansirikul C, *et al.* A Bayesian approach for population pharmacokinetic modelling of sirolimus. *Br J Clin Pharmacol* 2006; **62:** 420–34.
6. Djebli N, *et al.* Sirolimus population pharmacokinetic/pharmacogenetic analysis and Bayesian modelling in kidney transplant recipients. *Clin Pharmacokinet* 2006; **45:** 1135–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rapamune; ***Austral.***: Rapamune; ***Austria***: Rapamune; ***Belg.***: Rapamune; ***Braz.***: Rapamune; ***Canad.***: Rapamune; ***Chile***: Rapamune; ***China***: Rapamune (雷帕鸣); Rui Pa Ming (瑞帕明); Saimosi (赛莫司); Yixinke (宜欣可); ***Cz.***: Rapamune; ***Denm.***: Rapamune; ***Fin.***: Rapamune; ***Fr.***: Rapamune; ***Ger.***: Rapamune; ***Gr.***: Rapamune; ***Hong Kong***: Rapamune; ***Hung.***: Rapamune; ***India***: Rapamune; ***Irl.***: Rapamune; ***Israel***: Rapamune; ***Ital.***: Rapamune; ***Malaysia***: Rapamune; ***Mex.***: P-Hysplan; Rapamune; Renacept; ***Neth.***: Rapamune; ***Norw.***: Rapamune; ***NZ***: Rapamune; ***Philipp.***: Rapamune; ***Pol.***: Rapamune; ***Port.***: Rapamune; ***Rus.***: Rapamune (Рапамун); ***S.Afr.***: Rapamune; ***Singapore***: Rapamune; ***Spain***: Rapamune; ***Swed.***: Rapamune; ***Switz.***: Rapamune; ***Thai.***: Rapamune; ***Turk.***: Rapamune; ***UK***: Rapamune; ***USA***: Rapamune; ***Venez.***: Rapamune.

Tacrolimus *(BAN, USAN, rINN)*

FK-506; FR-900506; Tacrolimús; Tacrolimusum; Takrolimus; Takrolimuusi; Tsukubaenolide; Такролимус.

(-)-(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-{(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl}-14,16,-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone monohydrate.

$C_{44}H_{69}NO_{12}.H_2O$=822.0

CAS — 104987-11-3 (anhydrous tacrolimus); 109581-93-3 (tacrolimus monohydrate).

ATC — D11AH01; L04AD02.

ATC Vet — QD11AH01; QL04AD02.

UNII — WM0HAQ4WNM (tacrolimus); Y5L2157C4J (anhydrous tacrolimus).

Pharmacopoeias. In *US*.

USP 36: (Tacrolimus). Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Tacrolimus is a potent macrolide (macrolactam) immunosuppressant derived from *Streptomyces tsukubaensis*, and has actions similar to those of ciclosporin (see p. 1945.3). Tacrolimus binds to an intracellular protein, FKBP-12, and then forms a complex with calcium, calmodulin, and calcineurin, which inhibits the activity of calcineurin. This interferes with the production of lymphokines such as interleukin-2 and inhibits T-lymphocyte activation, resulting in immunosuppression.

Tacrolimus is used to prevent or treat rejection in patients receiving organ transplants, as indicated by the cross-references given in Organ and Tissue Transplantation, p. 1970.2. Tacrolimus has been tried in a few patients with refractory auto-immune or immune-mediated disorders; in some countries it is licensed for use in myasthenia gravis, in rheumatoid arthritis that is unresponsive to conventional therapy, in lupus nephritis where corticosteroids are ineffective or contra-indicated, and in corticosteroid-refractory ordependent ulcerative colitis. Tacrolimus is also applied topically in the management of moderate to severe atopic eczema. Tacrolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

UK licensed product information recommends that oral tacrolimus should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximum absorption. Different oral formulations of tacrolimus are not considered interchangeable and should be prescribed by brand name, see Oral Formulations, p. 1969.2.

For **prevention of rejection** after organ transplantation, in adult patients in the UK, the initial ***oral*** daily doses, to be given as an immediate-release formulation in 2 divided doses, are:

- *liver* transplantation: 100 to 200 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 200 to 300 micrograms/kg, starting within 24 hours of completion of surgery
- *heart* transplantation: 75 micrograms/kg, after antibody induction, and within 5 days of completion of surgery, and when the patient is stable

  Alternatively, tacrolimus has been given within 12 hours of transplantation, in patients without other organ dysfunction, at an initial oral dose of 2 to 4 mg daily, with mycophenolate mofetil and corticosteroids, or with sirolimus and corticosteroids

If the patient's condition does not permit oral use, therapy may be given ***intravenously***, by continuous 24-hour infusion, for up to 7 days; suggested initial adult daily doses are:

- *liver* transplantation: 10 to 50 micrograms/kg
- *kidney* transplantation: 50 to 100 micrograms/kg
- *heart* transplantation: 10 to 20 micrograms/kg

For **treatment of rejection**, increased tacrolimus doses, supplemental corticosteroid therapy, and short courses of monoclonal or polyclonal antibodies have been used. In patients being converted to tacrolimus from another immunosuppressant for the treatment of rejection after liver or kidney transplantation, treatment should begin with the initial oral dose recommended for primary immunosuppression. For heart transplant patients converted to tacrolimus, an initial oral dose of 150 micrograms/kg daily, in 2 divided doses, is recommended. UK dose recommendations for rejection therapy in other allografts are based on

limited data. The following initial ***oral*** daily doses of tacrolimus have been used:
- *lung* transplantation: 100 to 150 micrograms/kg
- *pancreatic* transplantation: 200 micrograms/kg
- *intestinal* transplantation: 300 micrograms/kg

In the USA, the following initial ***oral*** daily doses, given in 2 divided doses, are recommended for adult patients for the **prevention of rejection**:
- *liver* transplantation: 100 to 150 micrograms/kg, starting no sooner than 6 hours after transplantation
- *kidney* transplantation: 200 micrograms/kg when used with azathioprine, or 100 micrograms/kg when used with mycophenolate mofetil and an interleukin-2 receptor antagonist, starting within 24 hours of transplantation, but delayed if necessary until renal function has recovered
- *heart* transplantation: 75 micrograms/kg, starting no sooner than 6 hours after transplantation

For most transplant patients, initial oral therapy is recommended. If ***intravenous*** tacrolimus therapy is needed, the recommended starting daily doses, to be given as a continuous infusion, are:
- *liver* transplantation: 30 to 50 micrograms/kg, starting no sooner than 6 hours after transplantation
- *kidney* transplantation: 30 to 50 micrograms/kg, starting within 24 hours of transplantation, but delayed if necessary until renal function has recovered
- *heart* transplantation: 10 micrograms/kg, starting no sooner than 6 hours after transplantation

Tacrolimus doses are usually reduced in the post-transplant period; in some cases other immunosuppressant therapy can be stopped, leading to tacrolimus monotherapy or tacrolimus-based dual therapy. Maintenance dosage should be adjusted according to whole-blood trough concentrations in individual patients: it is suggested that most patients can be satisfactorily maintained at whole-blood trough concentrations below 20 nanograms/mL (for details see Therapeutic Drug Monitoring, p. 1974.2).

A prolonged-release ***oral*** formulation of tacrolimus is also available in the UK for the prevention of rejection in adult liver or kidney transplantation, and the treatment of allograft rejection (*Advagraf, Astellas*). The same initial daily dose as that recommended for the UK twice-daily immediate-release formulation is given once daily in the morning using prolonged-release capsules. Patients maintained on the twice-daily immediate-release formulation may also be converted to once-daily prolonged-release capsules at the same total daily dose. However, immediate-release and prolonged-release formulations are not considered interchangeable, and tacrolimus trough concentrations should be monitored to ensure similar systemic exposure is maintained. In the USA, a prolonged-release formulation is licensed for the prevention of rejection in kidney transplantation (*Astagraf, Astellas*). When used with basiliximab induction an initial oral dose of 150 micrograms/kg once daily is given before or within 48 hours of the transplant, but may be delayed until renal function has recovered. When basiliximab induction is not used, a pre-operative dose of 100 micrograms/kg is given within 12 hours before reperfusion; an initial postoperative dose of 200 micrograms/kg once daily is given at least 4 hours after the pre-operative dose and within 12 hours of reperfusion.

For doses used in paediatric transplant recipients, see Administration in Children, below.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, ***topical*** tacrolimus may be applied thinly to the affected areas twice daily as a 0.03 or 0.1% ointment; an attempt should be made to use the lower strength or reduce the frequency of application when possible. For treatment in children, see Administration in Children, below. US licensed product information suggests treatment should be continued only until resolution of signs and symptoms. If clinical manifestations do not improve within 6 weeks, diagnosis of atopic eczema should be confirmed through re-examination. UK licensed product information recommends that if no signs of improvement are seen after 2 weeks of treatment, further treatment options should be considered.

In the UK, tacrolimus is also licensed for maintenance treatment; patients who have responded to up to 6 weeks of twice-daily treatment may thinly apply tacrolimus 0.1% ointment to areas usually affected by eczema twice weekly with 2 to 3 days between applications, for up to 12 months. During a flare, twice-daily treatment may be restarted.

Reviews.

1. Winkler M, Christians U. A risk-benefit assessment of tacrolimus in transplantation. *Drug Safety* 1995; **12:** 348–57.
2. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. *Drugs* 2000; **59:** 323–89.
3. Skaehill PA. Tacrolimus in dermatologic disorders. *Ann Pharmacother* 2001; **35:** 582–8.
4. Woo DK, James WD. Topical tacrolimus: a review of its uses in dermatology. *Dermatitis* 2005; **16:** 6–21.
5. Simpson D, Noble S. Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions. *Drugs* 2005; **65:** 827–58.
6. First MR, Fitzsimmons WE. Modified release tacrolimus. *Yonsei Med J* 2004; **45:** 1127–31.
7. Wente MN, *et al*. Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
8. Chisholm MA, Middleton MD. Modified-release tacrolimus. *Ann Pharmacother* 2006; **40:** 270–5.
9. Cross SA, Perry CM. Tacrolimus once-daily formulation: in the prophylaxis of transplant rejection in renal or liver allograft recipients. *Drugs* 2007; **67:** 1931–43.
10. First MR. First clinical experience with the new once-daily formulation of tacrolimus. *Ther Drug Monit* 2008; **30:** 159–66.

Administration. The mean dose of tacrolimus required to produce a standard trough concentration of 10 to 15 nanograms/mL was reported to be 96% higher in 7 black renal graft recipients than in 20 such patients of white or Asian descent.[1] (For mention of the effect of ethnicity on the bioavailability of tacrolimus see under Pharmacokinetics, p. 1974.1.)

Children generally require relatively higher doses than adults to achieve the same blood concentrations (see Administration in Children, below). There is limited evidence that children with hepatitis C required on average one-third of the dose of tacrolimus needed by children without the virus.[2]

1. Andrews PA, *et al*. Racial variation in dosage requirements of tacrolimus. *Lancet* 1996; **348:** 1446.
2. Moreno M, *et al*. Monitoring of tacrolimus as rescue therapy in pediatric liver transplantation. *Ther Drug Monit* 1998; **20:** 376–9.

ORAL FORMULATIONS. Tacrolimus has a narrow therapeutic index and even minor differences in blood concentrations have the potential to affect immunosuppression or cause adverse effects; inadvertent switching between different oral formulations has led to acute rejection and toxicity. Additionally, conventional preparations are immediate-release, twice-daily formulations, and these are not interchangeable with, nor licensed for quite the same indications as, the prolonged-release, once daily formulations available in some countries. The two formulations fulfil regulatory criteria for bioequivalence; however, studies in transplant recipients have shown reduced exposure to tacrolimus, with higher rates of acute rejection, on conversion from the conventional preparation to the prolonged-release formulation.[1]

The UK Commission on Human Medicines has advised that all oral tacrolimus products should be prescribed by brand name only.[2]

1. Barraclough KA, *et al*. Once- versus twice-daily tacrolimus: are the formulations truly equivalent? *Drugs* 2011; **71:** 1561–77.
2. MHRA/CHM. Oral tacrolimus products: prescribe and dispense by brand name only, to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection. *Drug Safety Update* 2012; **5**(11): A1. Available at: http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con157116.pdf (accessed 06/06/13)

Administration in children. For **prevention of rejection** after organ transplantation in paediatric patients in the UK, tacrolimus is given in the following initial ***oral*** daily doses, in 2 divided doses:
- *liver* transplantation: 300 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 300 micrograms/kg, starting within 24 hours of completion of surgery; a lower dose of 200 micrograms/kg has been used in adolescents to prevent very high trough concentrations
- *heart* transplantation, *after antibody induction*: 100 to 300 micrograms/kg, starting within 5 days of the completion of surgery, and when the patient is stable

If the patient's condition does not allow for oral use, therapy may be started ***intravenously***, by continuous 24-hour infusion; intravenous therapy may be given for up to 7 days, but should be converted to oral therapy as soon as clinically possible. Suggested daily doses are:
- *liver* transplantation: 50 micrograms/kg
- *kidney* transplantation: 75 to 100 micrograms/kg

For *heart* transplantation *without antibody induction*, patients may be started on intravenous doses of 30 to 50 micrograms/kg daily, as a continuous 24-hour infusion. The first oral dose should be started 8 to 12 hours after stopping intravenous infusion, at a dose of 300 micrograms/kg daily, given in 2 divided doses.

For **treatment of rejection**, increased tacrolimus doses, supplemental corticosteroid therapy, and short courses of monoclonal or polyclonal antibodies have been used. In children being converted to tacrolimus from another immunosuppressant for the treatment of rejection after *liver* or *kidney* transplantation, treatment should begin with the initial oral dose recommended for primary immunosuppression. For paediatric *heart* transplant patients converted to tacrolimus, an initial oral dose of 200 to 300 micrograms/kg daily, in 2 divided doses, is recommended.

In the USA, the following ***oral*** daily doses, given in 2 divided doses, are recommended for children for the **prevention of rejection**:
- *liver* transplantation: 150 to 200 micrograms/kg, starting about 6 hours after transplantation

The ***intravenous*** dose is as for adults (see Uses and Administration, p. 1968.3).

Doses are adjusted according to whole-blood trough concentrations (see Therapeutic Drug Monitoring, p. 1974.2); children generally require doses per kg 1½ to 2 times higher than adults to achieve the same concentrations. Different oral formulations of tacrolimus are not considered interchangeable and should be prescribed by brand name, see Oral Formulations, above.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, tacrolimus may be used ***topically*** in children aged 2 to 16 years as a 0.03% ointment applied thinly to the affected areas twice daily, for up to 3 weeks. In the UK this is then reduced to once daily until lesions clear. The 0.1% ointment is not licensed for use in children under 16, although it has been used (see Eczema, below). Initial treatment duration is as for adults (see Uses and Administration, p. 1968.3).

In the UK, tacrolimus is also licensed for maintenance treatment; children aged 2 to 16 years who have responded to up to 6 weeks of initial treatment may thinly apply tacrolimus 0.03% ointment to the areas commonly affected by eczema twice weekly with 2 to 3 days between applications, for up to 12 months. During a flare, twice-daily treatment may be restarted.

For reference to the development of lentigines in children given long-term treatment with the higher strength preparation see Effects on the Skin under Adverse Effects, p. 1972.2.

Children aged 16 years and older are treated as for adults (see Uses and Administration, p. 1968.3).

Eczema. Topical tacrolimus has been found to be safe and effective[1-4] for short-term use in the treatment of moderate to severe atopic eczema (p. 1684.1). In adult patients, 0.1% tacrolimus ointment applied to all affected areas was shown to have similar efficacy to 0.1% hydrocortisone butyrate ointment,[5] and be more effective than fluticasone 0.005% ointment (applied to the face),[6] or a combination of 0.1% hydrocortisone butyrate ointment (applied to the trunk and extremities) and 1% hydrocortisone acetate ointment (applied to the head and neck).[7] In 18 of 19 patients with facial atopic eczema resistant to 0.03% tacrolimus ointment,[8] there was significant improvement upon application of a 0.03% lotion formulation, and 6 patients were positive to a patch test for white petrolatum, an ingredient of the commercial ointment. A meta-analysis concluded that topical tacrolimus 0.1% was as effective as potent topical corticosteroids and more effective than mild topical corticosteroids for the treatment of eczema; however, tacrolimus was significantly more likely to cause skin burning than corticosteroids.[9] Another meta-analysis[10] found that 0.03% and 0.1% tacrolimus ointment were both more effective than topical hydrocortisone acetate 1% or pimecrolimus 1% in effecting remission of eczema in paediatric patients. However, there was no significant difference in efficacy between the two strengths of tacrolimus.

Results from a small, open-label study suggest that long-term intermittent use of tacrolimus ointment may reverse the skin atrophy induced by topical corticosteroids.[11] In other studies,[12,13] adult and paediatric patients (2 to 15 years of age) with atopic eczema were treated continuously or intermittently with twice-daily tacrolimus 0.1% ointment for up to 4 years. Although about half of the patients withdrew from the studies early, there was no indication of an increased risk of adverse effects with the long-term use of tacrolimus, nor was there an indication of an increased risk for any cutaneous infection with increased duration of exposure to tacrolimus.

Maintenance treatment with tacrolimus ointment 0.03% applied two or three times weekly has also been shown to be effective in preventing eczema exacerbations in children for up to 12 months.[14,15]

In general, however, long-term use of topical tacrolimus should be avoided because of concerns about potential carcinogenicity (see under Adverse Effects, p. 1971.2).

1. Gianni LM, Sulli MM. Topical tacrolimus in the treatment of atopic dermatitis. *Ann Pharmacother* 2001; **35:** 943–6.
2. Allen BR. Tacrolimus ointment: its place in the therapy of atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 401–3.
3. Anonymous. Topical tacrolimus—a role in atopic dermatitis? *Drug Ther Bull* 2002; **40:** 73–5.
4. Fleischer AB, Boguniewicz M. An approach to pruritus in atopic dermatitis: a critical systematic review of the tacrolimus ointment literature. *J Drugs Dermatol* 2010; **9:** 488–98.
5. Reitamo S, *et al*. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 547–55.
6. Doss N, *et al*. Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. *Br J Dermatol* 2009; **161:** 427–34.
7. Reitamo S, *et al*. A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults

with moderate to severe atopic dermatitis. *Br J Dermatol* 2005; **152:** 1282–9.
8. Sugiura H, *et al*. An open study of a lotion formulation to improve tolerance of tacrolimus in facial atopic dermatitis. *Br J Dermatol* 2001; **145:** 795–8.
9. Ashcroft DM, *et al*. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; **330:** 516–22.
10. Yan J, *et al*. Meta-analysis of tacrolimus ointment for atopic dermatitis in pediatric patients. *Pediatr Dermatol* 2008; **25:** 117–20.
11. Kyllönen H, *et al*. Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. *Br J Dermatol* 2004; **150:** 1174–81.
12. Hanifin JM, *et al*. US Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *J Am Acad Dermatol* 2005; **53** (suppl 2): S186–S194.
13. Reitamo S, *et al*. 0.1% Tacrolimus Ointment Long-term Follow-up Study Group. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol* 2008; **159:** 942–51.
14. Thaçi D, *et al*. European Tacrolimus Ointment Study Group. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* 2008; **159:** 1348–56.
15. Paller AS, *et al*. US Tacrolimus Ointment Study Group. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics* 2008; **122:** e1210–e1218.

Encephalitis. Compared with historical untreated controls, 7 patients with Rasmussen encephalitis (a progressive neurological disorder thought to have an auto-immune origin) had a superior outcome in terms of neurological function and progression rate of cerebral hemiatrophy after treatment with tacrolimus, but no better seizure outcome.[1] The control patients had more severe disease, but since only 1 patient on tacrolimus showed a cognitive decline, and none became eligible for hemispherectomy, the authors concluded prospective studies would be useful.

1. Bien CG, *et al*. An open study of tacrolimus therapy in Rasmussen encephalitis. *Neurology* 2004; **62:** 2106–9.

Glomerular kidney disease. Tacrolimus has been reported[1-5] to be effective in inducing remission in patients with glomerular kidney disease (p. 1604.3); it has been used as monotherapy from first presentation, as well as in patients refractory to standard therapy, and in those with corticosteroid-dependent disease. However, a small, longitudinal study[6] in children with severe corticosteroid-dependent nephrotic syndrome given tacrolimus after inadequate response to ciclosporin, reported no better management of disease with tacrolimus, although it was beneficial for some children.

1. Segarra A, *et al*. Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002; **17:** 655–62.
2. Duncan N, *et al*. Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004; **19:** 3062–7.
3. Westhoff TH, *et al*. Tacrolimus in steroid-resistant and steroid-dependent nephrotic syndrome. *Clin Nephrol* 2006; **65:** 393–400.
4. Bhimma R, *et al*. Management of steroid-resistant focal segmental glomerulosclerosis in children using tacrolimus. *Am J Nephrol* 2006; **26:** 544–51.
5. Praga M, *et al*. Grupo Español de Estudio de la Nefropatía Membranosa. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. *Kidney Int* 2007; **71:** 924–30.
6. Sinha MD, *et al*. Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. *Nephrol Dial Transplant* 2006; **21:** 1848–54.

Hepatitis. In auto-immune chronic active hepatitis (p. 1602.3), some evidence suggests that tacrolimus may offer an alternative therapy when corticosteroids alone or with azathioprine do not suffice.

Ichthyosis. For mention of the use of tacrolimus in ichthyosis see p. 1685.1.

Inflammatory bowel disease. There are reports of response to tacrolimus in patients with inflammatory bowel disease (IBD; p. 1808.3). Tacrolimus has been given orally,[1-4] intravenously,[1] or topically,[5,6] in the treatment of ulcerative colitis[1,3,4] and Crohn's disease,[1-3,5,6] refractory to standard therapy. A systematic review[7] of 23 reports of tacrolimus use in 286 patients concluded that oral tacrolimus was a reasonable and effective alternative for fistulising Crohn's disease, although the evidence base was poor and comparative studies with infliximab were needed. Tacrolimus was also a possible alternative in IBD cases unresponsive to corticosteroids. Intravenous use was not deemed to confer any advantage over oral dosage; topical tacrolimus might be an option in certain cases.

1. Fellermann K, *et al*. Tacrolimus: a new immunosuppressant for steroid refractory inflammatory bowel disease. *Transplant Proc* 2001; **33:** 2247–8.
2. Ierardi E, *et al*. Oral tacrolimus long-term therapy in patients with Crohn's disease and steroid resistance. *Aliment Pharmacol Ther* 2001; **15:** 371–7.
3. Bousvaros A, *et al*. Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000; **137:** 794–9.
4. Ogata H, *et al*. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55:** 1255–62. Correction. *ibid.*; 1684. [dosage error in abstract]
5. Casson DH, *et al*. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47:** 436–40.
6. Hart AL, *et al*. Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; **13:** 245–53.
7. Gonzalez-Lama Y, *et al*. The role of tacrolimus in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2006; **51:** 1833–40.

Myasthenia gravis. Tacrolimus has been reported to be effective in the management of myasthenia gravis (p. 684.1) in patients resistant to conventional therapy, or for whom standard therapy is contra-indicated.[1,2] In an open-label study, 79 patients with myasthenia gravis, who had undergone thymectomy and were on high doses of prednisone and ciclosporin, were switched from ciclosporin to tacrolimus. Initial doses of tacrolimus were 100 micrograms/kg daily, given in 2 divided doses. Dosage was subsequently adjusted to achieve plasma concentrations between 7 and 8 nanograms/mL; tacrolimus doses of 6 to 10 mg daily were needed. After 1 year doses were reduced to achieve concentrations of about 6 nanograms/mL. Doses of prednisone were reduced, and finally withdrawn in all but 2 patients; 73 patients received tacrolimus for more than 3 years. All patients were able to resume normal daily activities.[3] Tacrolimus is licensed for use for myasthenia gravis in some countries, in a usual oral dose of 3 mg once daily. In these doses it was reported to reduce corticosteroid use in another small study; treatment was continued long-term and efficacy was maintained for up to 3 years.[4] There is some suggestion that tacrolimus may be more effective in thymomatous myasthenia gravis than in non-thymomatous disease.[5]

Tacrolimus has also been used as first-line adjunctive therapy with prednisolone; it was reported to decrease the daily prednisolone dose, and the need for plasmapheresis and high-dose intravenous methylprednisolone.[6]

1. Evoli A, *et al*. Successful treatment of myasthenia gravis with tacrolimus. *Muscle Nerve* 2002; **25:** 111–14.
2. Shimojima Y, *et al*. Tacrolimus in refractory patients with myasthenia gravis: coadministration and tapering of oral prednisolone. *J Clin Neurosci* 2006; **13:** 39–44.
3. Ponseti JM, *et al*. Long-term results of tacrolimus in cyclosporine- and prednisone-dependent myasthenia gravis. *Neurology* 2005; **64:** 1641–3.
4. Tada M, *et al*. Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis. *J Neurol Sci* 2006; **247:** 17–20.
5. Mitsui T, *et al*. Beneficial effect of tacrolimus on myasthenia gravis with thymoma. *Neurologist* 2007; **13:** 83–6.
6. Nagane Y, *et al*. Efficacy of low-dose FK506 in the treatment of Myasthenia gravis—a randomized pilot study. *Eur Neurol* 2005; **53:** 146–50.

Ocular disorders. For mention of the use of tacrolimus in various disorders characterised by ocular lesions such as uveitis, see p. 1932.1.

Organ and tissue transplantation. Tacrolimus has been used both for primary immunosuppression and for the control of graft rejection. Much of the initial experience with the drug was for liver grafts, (p. 1936.3), but it is also used in the transplantation of heart (p. 1934.2), kidney (p. 1935.2), lung (p. 1937.3), pancreas (p. 1938.1), and intestines (p. 1935.1). It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1).

A few selected references to the use of tacrolimus in transplantation are given below.

1. European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; **344:** 423–8.
2. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; **331:** 1110–15.
3. Gruessner RW. Tacrolimus in pancreas transplantation: a multicenter analysis. *Clin Transplant* 1997; **11:** 299–312.
4. Gruessner RWG, *et al*. Suggested guidelines for the use of tacrolimus in pancreas/kidney transplantation. *Clin Transplant* 1998; **12:** 260–2.
5. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; **359:** 741–6.
6. O'Grady JG, *et al*. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360:** 1119–25.
7. Scott LJ, *et al*. Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs* 2003; **63:** 1247–97.
8. Kelly D, *et al*. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet* 2004; **364:** 1054–61.
9. Webster AC, *et al*. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005; **331:** 810–14.
10. McCormack PL, *et al*. Tacrolimus: in heart transplant recipients. *Drugs* 2006; **66:** 2269–79.
11. Haddad E, *et al*. Cyclosporin versus tacrolimus for liver transplanted patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/03/08).
12. Wente MN, *et al*. Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
13. Patel JK, Kobashigawa JA. Tacrolimus in heart transplant recipients: an overview. *BioDrugs* 2007; **21:** 139–43.
14. Joseph A, *et al*. Tacrolimus immunosuppression in high-risk corneal grafts. *Br J Ophthalmol* 2007; **91:** 51–5.
15. Bowman LJ, Brennan DC. The role of tacrolimus in renal transplantation. *Expert Opin Pharmacother* 2008; **9:** 635–43.
16. Wallemacq P, *et al*. Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. *Ther Drug Monit* 2009; **31:** 139–52.
17. Fortune K, Couriel D. Tacrolimus in hematopoietic stem cell transplantation. *Expert Opin Drug Metab Toxicol* 2009; **5:** 835–41.

Psoriasis. Tacrolimus has been shown to be effective in the treatment of psoriasis (p. 1688.1) when used orally[1] or topically.[2-7]

1. The European FK 506 Multicentre Psoriasis Study Group. Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996; **132:** 419–23.
2. Remitz A, *et al*. Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol* 1999; **141:** 103–7.
3. Clayton TH, *et al*. Topical tacrolimus for facial psoriasis. *Br J Dermatol* 2003; **149:** 419–20.
4. Brune A, *et al*. Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. *Pediatr Dermatol* 2007; **24:** 76–80.
5. Liao YH, *et al*. Comparison of cutaneous tolerance and efficacy of calcitriol 3 $\mu g\ g^{-1}$ ointment and tacrolimus 0.3 $mg\ g^{-1}$ ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. *Br J Dermatol* 2007; **157:** 1005–12.
6. Vissers WHPM, *et al*. Topical treatment of mild to moderate plaque psoriasis with 0.3% tacrolimus gel and 0.5% tacrolimus cream: the effect on SUM score, epidermal proliferation, keratinization, T-cell subsets and HLA-DR expression. *Br J Dermatol* 2008; **158:** 705–12.
7. Bissonnette R, *et al*. Efficacy and tolerability of topical tacrolimus ointment for the treatment of male genital psoriasis. *J Cutan Med Surg* 2008; **12:** 230–4.

Pyoderma gangrenosum. There are reports of response to tacrolimus, given orally,[1-3] or topically,[4-9] or both,[10,11] in patients with pyoderma gangrenosum (p. 1688.3). A small study[12] found topical tacrolimus 0.3% in carmellose sodium paste to be more effective than clobetasol propionate 0.05% for peristomal pyoderma gangrenosum.

Systemic absorption, resulting in tacrolimus blood concentrations equivalent to oral dosing, has been reported in patients with pyoderma gangrenosum in whom tacrolimus was applied directly onto ulcerated areas;[13,14] therapeutic drug monitoring has been suggested for patients treated with topical tacrolimus over large skin areas or with impaired skin barriers.

1. Abu-Elmagd K, *et al*. Resolution of severe pyoderma gangrenosum in a patient with streaking leukocyte factor disease after treatment with tacrolimus (FK 506). *Ann Intern Med* 1993; **119:** 595–8.
2. D'Incà R, *et al*. Tacrolimus to treat pyoderma gangrenosum resistant to cyclosporine. *Ann Intern Med* 1998; **128:** 783–4.
3. Lyon CC, *et al*. Recalcitrant pyoderma gangrenosum treated with systemic tacrolimus. *Br J Dermatol* 1999; **140:** 562–4.
4. Schuppe H-C, *et al*. Topical tacrolimus for pyoderma gangrenosum. *Lancet* 1998; **351:** 832.
5. Reich K, *et al*. Topical tacrolimus for pyoderma gangrenosum. *Br J Dermatol* 1998; **139:** 755–7.
6. Vidal D, Alomar A. Successful treatment of periostomal pyoderma gangrenosum using topical tacrolimus. *Br J Dermatol* 2004; **150:** 387–8.
7. Lally A, *et al*. Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; **141:** 1175–6.
8. Chiba T, *et al*. Topical tacrolimus therapy for pyoderma gangrenosum. *J Dermatol* 2005; **32:** 199–203.
9. Kontos AP, *et al*. An open-label study of topical tacrolimus ointment 0.1% under occlusion for the treatment of pyoderma gangrenosum. *Int J Dermatol* 2006; **45:** 1383–5.
10. Jolles S, *et al*. Combination oral and topical tacrolimus in therapy-resistant pyoderma gangrenosum. *Br J Dermatol* 1999; **140:** 564–5.
11. Deckers-Kocken JM, Pasmans SG. Successful tacrolimus (FK506) therapy in a child with pyoderma gangrenosum. *Arch Dis Child* 2005; **90:** 531.
12. Lyon CC, *et al*. Topical tacrolimus in the management of peristomal pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 13–17.
13. Ghislain P-D, *et al*. Efficacy and systemic absorption of topical tacrolimus used in pyoderma gangrenosum. *Br J Dermatol* 2004; **150:** 1052–3.
14. Pitarch G, *et al*. Systemic absorption of topical tacrolimus in pyoderma gangrenosum. *Acta Derm Venereol* 2006; **86:** 64–5.

Reperfusion and revascularisation procedures. References to the use of tacrolimus-eluting stents.

1. García-Tejada J, *et al*. Carbo-stent liberador de tacrolimus Janus: resultados inmediatos y seguimiento clínico a medio plazo. *Rev Esp Cardiol* 2007; **60:** 197–200.
2. Han Y-L, *et al*. Midterm outcomes of prospective, randomized, single-center study of the Janus tacrolimus-eluting stent for treatment of native coronary artery lesions. *Chin Med J (Engl)* 2007; **120:** 552–6.
3. Tamburino C, *et al*. Real world safety and efficacy of the Janus Tacrolimus-Eluting stent: long-term clinical outcome and angiographic findings from the Tacrolimus-Eluting STent (TEST) registry. *Catheter Cardiovasc Interv* 2009; **73:** 243–8.
4. Onuma Y, *et al*. MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in de novo coronary stenoses. *Eur Heart J* 2009; **30:** 1477–85.

Rheumatoid arthritis. In a small, open-label study[1] of 12 patients with rheumatoid arthritis (p. 13.2) refractory to other disease-modifying antirheumatic drugs including ciclosporin, 7 had significant response to tacrolimus after treatment for 6 months, with 4 of these patients maintaining this response after 2 years of therapy. In a larger controlled study,[2] tacrolimus improved disease activity in patients with rheumatoid arthritis resistant to methotrexate. Similarly, an open-label multicentre study involving 80 patients with active disease inadequately responsive to methotrexate alone, addition of oral tacrolimus 3 mg daily to methotrexate therapy produced a clinical improvement in about half. The regimen was considered to be generally well tolerated.[3] Tacrolimus in an oral dose of 3 mg once daily has been licensed for use in refractory

rheumatoid arthritis in some countries; elderly patients may be given 1.5 mg once daily.[4,5]

1. Gremillion RB, *et al*. Tacrolimus (FK506) in the treatment of severe, refractory rheumatoid arthritis: initial experience in 12 patients. *J Rheumatol* 1999; **26:** 2332–6.
2. Furst DE, *et al*. Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* 2002; **46:** 2020–8.
3. Kremer JM, *et al*. Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a six-month, open-label study. *Arthritis Rheum* 2003; **48:** 2763–8.
4. Curran MP, Perry CM. Tacrolimus: in patients with rheumatoid arthritis. *Drugs* 2005; **65:** 993–1001.
5. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. *Rheumatology (Oxford)* 2006; **45:** 441–4.

Scleroderma. There are reports of response to tacrolimus in patients with scleroderma (p. 1938.3).

Skin disorders. Topical tacrolimus has been used to treat various skin disorders. Aside from its licensed use in eczema (p. 1969.3), and use in psoriasis and pyoderma gangrenosum (see p. 1970.3), there are reports of benefit in granuloma annulare,[1,2] lichen sclerosus,[3] lichen striatus,[4] pityriasis alba,[5] pityriasis lichenoides,[6] seborrhoeic dermatitis,[7] as well as the skin manifestations of angiolymphoid hyperplasia,[8] pruritus due to primary biliary cirrhosis,[9] and facial cutaneous lupus erythematosus.[10]

1. Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150:** 792–4.
2. Jain S, Stephens CJM. Successful treatment of disseminated granuloma annulare with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1042–3.
3. Hengge UR, *et al*. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. *Br J Dermatol* 2006; **155:** 1021–8.
4. Sorgentini C, *et al*. Lichen striatus in an adult: successful treatment with tacrolimus. *Br J Dermatol* 2004; **150:** 776–7.
5. Rigopoulos D, *et al*. Tacrolimus ointment 0.1% in pityriasis alba: an open-label, randomized, placebo-controlled study. *Br J Dermatol* 2006; **155:** 152–5.
6. Simon D, *et al*. Successful treatment of pityriasis lichenoides with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1033–5.
7. Braza TJ, *et al*. Tacrolimus 0.1% ointment for seborrhoeic dermatitis: an open-label pilot study. *Br J Dermatol* 2003; **148:** 1242–4.
8. Mashiko M, *et al*. A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. *Br J Dermatol* 2006; **154:** 803–4.
9. Aguilar-Bernier M, *et al*. Successful treatment of pruritus with topical tacrolimus in a patient with primary biliary cirrhosis. *Br J Dermatol* 2005; **152:** 808–9.
10. Tzung T-Y, *et al*. Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. *Br J Dermatol* 2007; **156:** 191–2.

Adverse Effects, Treatment, and Precautions

The most common adverse effects after **systemic** use of tacrolimus include tremor, headache, paraesthesias, nausea and diarrhoea, hypertension, insomnia, and renal impairment. Disturbances of serum electrolytes, notably hyperkalaemia, and hyperglycaemic conditions, including diabetes mellitus, occur frequently. Hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia are common. Anaemia, leucopenia, and thrombocytopenia also occur commonly. Other common adverse effects include mood changes, anxiety, confusion, dizziness, tinnitus and hearing loss, visual disturbances, peripheral neuropathies, and convulsions; constipation, dyspepsia, gastrointestinal perforation and ulceration, and gastrointestinal haemorrhage; dyspnoea, parenchymal lung disorders, pleural effusions, pharyngitis, cough, nasal congestion and inflammation; alopecia, acne, skin rashes, and pruritus; and arthralgia, muscle cramps, asthenia, febrile disorders, oedema, ascites and liver dysfunction.

Thromboembolic and ischaemic events, and tachycardia are common; ventricular arrhythmias, cardiac arrest, heart failure, palpitations, and ECG changes are less frequent. Tacrolimus may prolong the QT interval. Cardiomyopathies, including ventricular hypertrophy have also been reported; most cases have been reversible, and occurred mainly with tacrolimus blood concentrations much higher than the recommended maximum levels. Coagulation disorders, neutropenia, and pancytopenia have occurred, as have asthma, acute respiratory distress syndrome, hypoproteinaemia, dysmenorrhoea, uterine bleeding, deep limb venous thrombosis, paralytic ileus, acute and chronic pancreatitis, peritonitis, and haemolytic uraemic syndrome. There are rare reports of thrombotic thrombocytopenic purpura, hypoprothrombinaemia, and hirsutism. Toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic artery thrombosis, and veno-occlusive liver disease have also occurred rarely.

CNS adverse effects including coma, paralysis, CNS haemorrhage, amnesia, and speech and language abnormalities have been reported with tacrolimus. Posterior reversible encephalopathy syndrome (PRES) has also developed during treatment; symptoms include headache, altered mental status, seizures, and visual disturbances. Magnetic resonance imaging should be carried out in patients with symptoms of PRES, and if diagnosed, tacrolimus treatment should be stopped. Most patients have recovered with supportive treatment such as blood pressure control.

Tacrolimus injection is formulated with polyoxyl castor oil and anaphylactoid reactions have occurred; prophylactic antihistamines may reduce the risk. When given orally, it is important to distinguish controlled-release from immediate-release formulations; serious adverse effects have resulted from confusion between the two.

Dosage reduction may be necessary in patients with hepatic impairment. Care is also required in patients with pre-existing renal impairment, and dosage reduction may prove advisable in such patients. Monitoring of blood concentrations of tacrolimus is recommended in all patients, especially during episodes of diarrhoea as concentrations may be significantly affected. Renal and hepatic function, blood pressure, blood glucose, electrolytes, haematological and cardiac function, as well as neurological and visual status, coagulation values, and plasma protein should be monitored regularly.

Immunosuppression, including tacrolimus treatment, is associated with an increased incidence of EBV-associated lymphoproliferative disorders, lymphoma, and other malignancies, particularly those of the skin. Excess exposure to UV light should be avoided during treatment, particularly with topical tacrolimus (see below). There is also an increased risk of infection, including activation of latent viral infections. These include JC virus-associated progressive multifocal leukoencephalopathy and BK virus-associated nephropathy that can lead to serious or fatal outcomes. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Immunosuppressants may reduce the response to vaccines and the use of live vaccines should be avoided. Tacrolimus may affect visual or neurological function, and patients so affected should not drive or operate dangerous machinery.

Topical tacrolimus has been associated with local irritation such as burning sensations and pruritus, and skin disorders including acne, rosacea, and an increased incidence of herpes simplex and zoster infections, folliculitis, and impetigo. Lymphadenopathy, headache and 'flu-like' symptoms have also been reported. Facial flushing and skin irritation has been reported after consumption of alcohol. Exposure of the skin to sunlight should be minimised and the use of artificial sources of ultraviolet light avoided.

Skin infections should be treated before starting therapy with topical tacrolimus. It should not be used in immunocompromised patients or those with conditions that might increase systemic absorption of tacrolimus. It must also not be applied to pre-malignant or malignant skin conditions; some malignant skin conditions may mimic eczema.

Breast feeding. Tacrolimus is distributed into breast milk. Tacrolimus concentrations were measured in milk from a liver transplant recipient on a dose of 100 micrograms/kg daily. The authors estimated that the infant would ingest only 0.06% (60 nanograms/kg daily) of the mother's weight-adjusted dose. No adverse effects were noted in the infant at 2.5 months of age.[1]

Licensed product information recommends that women should avoid breast feeding while taking tacrolimus.

1. French AE, *et al*. Milk transfer and neonatal safety of tacrolimus. *Ann Pharmacother* 2003; **37:** 815–18.

Calcineurin inhibitor-induced pain syndrome. For discussion of the calcineurin inhibitor-induced pain syndrome, see Ciclosporin, p. 1949.1.

Carcinogenicity. The systemic use of tacrolimus increases the risk of malignancy.

Carcinogenicity studies in *animals* have also reported an increase in the incidence of malignancies associated with the topical calcineurin inhibitors, tacrolimus and pimecrolimus. As of December 2004 the FDA had received reports of 19 cases of lymphoma or cutaneous tumours associated with topical tacrolimus, of which 4 cases were a recurrence or aggravation of a pre-existing malignancy, and 3 other cases were confounded by other possible risk factors. At this same date, the FDA had also received reports of 10 cases of malignancy in patients treated with topical pimecrolimus, including 6 cutaneous tumours. Although the potential for systemic immunosuppression from topical use was unknown and the role of the drug in these cases was uncertain, the FDA recommended that topical calcineurin inhibitors should only be used as a second-line drug for short-term and intermittent treatment of eczema, and that they should not be used in immunocompromised patients or in children younger than 2 years of age.[1,2] Similar warnings have been issued in the European Union.[3] However, there has been some debate about the risk of malignancy associated with the topical use of these drugs, and several groups[4-6] have examined the evidence used by the FDA. They found that after topical application in humans the serum concentrations of these drugs were usually low or undetectable, that there was no evidence of systemic immunosuppression as measured by response to childhood immunisation and delayed hypersensitivity, no evidence of an increase in malignancy in clinical studies or compared with the general population, and that none of the reported lymphoma cases resembled the usual presentation and histology seen with systemic immunosuppression-associated lymphoma. They concluded that based on available data the risk of cancer from topical calcineurin inhibitors was theoretical and unknown. A review[7] of skin cancer risk found that there was no conclusive evidence from *rodent* studies to suggest that topical calcineurin inhibitors were associated with an increase in skin cancers, or a potentiation of UV-associated immunosuppression and carcinogenicity. There was also no evidence of an increased risk of skin cancer in human studies. In general, there seems to be agreement that long-term data are still needed to determine the carcinogenic risk, if there is any, from topical tacrolimus and pimecrolimus. Until long-term safety data are available some[8] consider that it would be prudent if topical calcineurin inhibitors were:

- not used in children under 2 years of age
- not used continuously for more than 6 weeks, with an application-free period of up to 2 weeks
- avoided in immunocompromised patients
- avoided in patients with neoplasia
- avoided in those with skin disorders liable to lead to increased systemic absorption

Patients should also be encouraged to use a broad-spectrum sunscreen daily on all sunlight-exposed skin.

1. FDA. Information for healthcare professionals: tacrolimus (marketed as Protopic) (issued June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126497.htm (accessed 05/08/10)
2. FDA. Alert for healthcare professionals: pimecrolimus (marketed as Elidel) (issued June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm153525.htm (accessed 05/08/10)
3. CSM/MHRA. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): reports of malignancies. *Current Problems* 2006; **31:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Fonacier L, *et al*. Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2005; **115:** 1249–53.
5. Bieber T, *et al*. Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology* 2005; **211:** 77–8.
6. Berger TG, *et al*. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006; **54:** 818–23.
7. Ring J, *et al*. Review of the potential photo-cocarcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. *J Eur Acad Dermatol Venereol* 2005; **19:** 663–71.
8. Ring J, *et al*. The US FDA 'black box' warning for topical calcineurin inhibitors: an ongoing controversy. *Drug Safety* 2008; **31:** 185–98.

Effects on the blood. Severe anaemia due to selective depression of erythropoiesis in a patient given tacrolimus resolved when tacrolimus was replaced with ciclosporin.[1] More generalised bone marrow suppression,[2] post-transplant thrombotic microangiopathy,[3] and red cell aplasia[4] have also been reported. Hypoplasia occurring in a liver transplant recipient,[5] was characterised by a slow but complete recovery after substituting tacrolimus with ciclosporin.

1. Winkler M, *et al*. Anaemia associated with FK 506 immunosuppression. *Lancet* 1993; **341:** 1035–6.
2. de-la-Serna-Higuera C, *et al*. Tacrolimus-induced bone marrow suppression. *Lancet* 1997; **350:** 714–15.
3. Trimarchi HM, *et al*. FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation* 1999; **67:** 539–44.
4. Misra S, *et al*. Red cell aplasia in children on tacrolimus after liver transplantation. *Transplantation* 1998; **65:** 575–7.
5. Nosari A, *et al*. Bone marrow hypoplasia complicating tacrolimus (FK506) therapy. *Int J Hematol* 2004; **79:** 130–2.

Effects on carbohydrate metabolism. The development of diabetes mellitus after solid organ transplantation is common,[1,2] which may be attributed to the diabetogenic effects of immunosuppressive drugs. Incidence has appeared to be increased in both adult[3] and paediatric[4] renal transplant recipients given tacrolimus. However, a retrospective review[2] found no significant difference in incidence between patients receiving tacrolimus or ciclosporin but found instead a correlation between the absence of an antiproliferative agent and the development of diabetes. A retrospective study of liver transplant recipients found that, although those given tacrolimus had a greater incidence of diabetes mellitus, hepatitis C infection was the only factor predictive of its development.[1] In contrast, a meta-analysis[5] found the incidence of new-onset diabetes mellitus (NODM) to be significantly higher among patients receiving tacrolimus compared with those receiving ciclosporin after solid organ transplantation. An observational study[6] confirmed this finding, and found it to be unrelated to corticosteroid dosage, although relatively high doses of corticosteroids were used across the study. A

retrospective study[7] found tacrolimus to be significantly more diabetogenic than ciclosporin, even when corticosteroid dosing was lower with tacrolimus. An analysis of data for 8839 patients[8] found the risk of NODM to be greatest with high tacrolimus doses, but the increased risk versus ciclosporin was sustained even with lower tacrolimus doses. Higher corticosteroid doses potentiated the diabetogenic effect of tacrolimus, but even the lowest dosage group for tacrolimus and corticosteroids had higher rates of NODM than all ciclosporin groups; there was no association between corticosteroid dose and NODM for any dosage of ciclosporin. In a small, retrospective study,[9] conversion from tacrolimus to ciclosporin resulted in marked improvement of glucose metabolism, and even reversal of diabetes mellitus in a significant proportion of patients.

1. AlDosary AA, *et al*. Post-liver transplantation diabetes mellitus: an association with hepatitis C. *Liver Transpl* 2002; **8:** 356–61.
2. First MR, *et al*. Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. *Transplantation* 2002; **73:** 379–86.
3. Pirsch JD, *et al*. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997; **63:** 977–83.
4. Al-Uzri A, *et al*. Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation* 2001; **72:** 1020–4.
5. Heisel O, *et al*. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004; **4:** 583–95.
6. Kamar N, *et al*. Diapason Study Group. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007; **22:** 1986–93.
7. Hoitsma AJ, Hilbrands LB. Relative risk of new-onset diabetes during the first year after renal transplantation in patients receiving tacrolimus or cyclosporine immunosuppression. *Clin Transplant* 2006; **20:** 659–64.
8. Burroughs TE, *et al*. Influence of early posttransplantation prednisone and calcineurin inhibitor dosages on the incidence of new-onset diabetes. *Clin J Am Soc Nephrol* 2007; **2:** 517–23.
9. Bouchta NB, *et al*. Conversion from tacrolimus to cyclosporin is associated with a significant improvement of glucose metabolism in patients with new-onset diabetes mellitus after renal transplantation. *Transplant Proc* 2005; **37:** 1857–60.

Effects on the cardiovascular system. Hypertrophic cardiomyopathy, and in some cases heart failure, has been described in paediatric patients receiving tacrolimus after organ grafting (small bowel or liver).[1] Symptoms largely resolved on stopping or reducing dosage. A similar case had been found *post mortem* in an adult,[2] and the UK CSM[3] was aware of 29 reported cases worldwide as of July 1995. Echocardiographic monitoring of patients receiving tacrolimus has been recommended, with dose reduction or withdrawal in those who developed hypertrophic changes.[3] However, echocardiographic abnormalities may be quite common after orthotopic liver transplantation in adults, with no obvious relationship to the use of tacrolimus,[4] and a retrospective analysis concluded that tacrolimus is not a risk factor for hypertrophic cardiomyopathy in adult transplant recipients.[5]

Severe hypertension was documented in 5 out of 10 paediatric patients who received intravenous tacrolimus after renal transplant surgery. All patients responded to intravenous labetalol. By contrast none of 11 children who received ciclosporin at the same institution developed hypertension.[6] However, a review[7] concluded that tacrolimus causes less hypertension than ciclosporin, resulting in a better cardiovascular risk profile in renal transplant recipients, and possibly ultimately prolonging graft survival.

1. Atkison P, *et al*. Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet* 1995; **345:** 894–6.
2. Natazuka T, *et al*. Immunosuppressive drugs and hypertrophic cardiomyopathy. *Lancet* 1995; **345:** 1644.
3. CSM/MCA. Tacrolimus (Prograf) and hypertrophic cardiomyopathy in transplant patients. *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20156196&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Dollinger MM, *et al*. Tacrolimus and cardiotoxicity in adult liver transplant recipients. *Lancet* 1995; **346:** 507.
5. Coley KC, *et al*. Lack of tacrolimus-induced cardiomyopathy. *Ann Pharmacother* 2001; **35:** 985–9.
6. Booth CJ, *et al*. Intravenous tacrolimus may induce severe hypertension in renal transplant recipients. *Arch Dis Child* 1999; **80** (suppl 1): A27.
7. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; **72** (suppl): S9–12.

Effects on the kidneys. A comparison in patients who had undergone liver transplantation suggested that nephrotoxicity was more of a problem in those receiving tacrolimus than in those given a ciclosporin-based regimen.[1] In particular intravenous tacrolimus during the first week after transplantation was associated with acute renal failure in 4 of 20 patients. Furthermore, on follow-up for 1 year, GFR was somewhat lower in the tacrolimus-treated group. A small study compared GFR and effective renal plasma flow (ERPF), at various stages after transplantation, in renal and liver transplant recipients given tacrolimus.[2] In renal transplant patients, the GFR, although lower than normal, was increased after transplant, and remained stable over 3 months. ERPF, however, was significantly lower at 3 months. In liver transplant recipients, despite being lower than normal, GFR and ERPF were unchanged at 1 year post-transplant.

1. Porayko MK, *et al*. Nephrotoxic effects of primary immunosuppression with FK-506 and cyclosporine regimens after liver transplantation. *Mayo Clin Proc* 1994; **69:** 105–11.
2. Agarwala S, *et al*. Evaluation o f renal function i n transplant patients on tacrolimus therapy. *J Clin Pharmacol* 2002; **42:** 798–805.

Effects on the nervous system. Although many of the symptoms of neurotoxicity induced by tacrolimus are similar to those of ciclosporin (p. 1950.2), some symptoms such as headaches, tremor, and sleep disturbances, appear to be more prevalent with tacrolimus, and the incidence of tacrolimus-induced neurotoxicity appears to be higher in liver transplant recipients.[1]

Severe peripheral neuropathy with signs of cerebral dysfunction has been reported in 2 patients receiving tacrolimus.[2] Among other central effects, tacrolimus has also been associated with speech disorders, including severe dysarthria and mutism;[3-6] some degree of speech dysfunction, in the form of an apparent Norwegian accent in one case,[3] may persist long-term.[3,5]

Encephalopathy, sometimes occurring within the reversible posterior leukoencephalopathy syndrome (RPLS), has been reported with use of tacrolimus.[7-11] Presenting symptoms included acute severe headache, seizures, cortical blindness, disorientation, and hypertension.

Miller Fisher syndrome, a variant of Guillain-Barré syndrome, has been attributed to tacrolimus use in a liver transplant recipient.[12] Clinical manifestations included ataxia, ophthalmoplegia, and areflexia.

1. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13:** 313–26.
2. Ayres RCS, *et al*. Peripheral neurotoxicity with tacrolimus. *Lancet* 1994; **343:** 862–3.
3. Boeve BF, *et al*. Dysarthria and apraxia of speech associated with FK-506 (tacrolimus). *Mayo Clin Proc* 1996; **71:** 969–72.
4. Bronster DJ, *et al*. Tacrolimus-associated mutism after orthotopic liver transplantation. *Transplantation* 2000; **70:** 979–82.
5. Sokol DK, *et al*. Tacrolimus (FK506)-induced mutism after liver transplant. *Pediatr Neurol* 2003; **28:** 156–8.
6. Chegounchi M, *et al*. Progressive neurological disease induced by tacrolimus in a renal transplant recipient: case presentation. *BMC Nephrol* 2006; **7:** 7.
7. Kiemeneij IM, *et al*. Acute headache as a presenting symptom of tacrolimus encephalopathy. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1126–7.
8. Nakazato T, *et al*. Reversible posterior leukoencephalopathy syndrome associated with tacrolimus therapy. *Intern Med* 2003; **42:** 624–5.
9. Frühauf NR, *et al*. Late onset of tacrolimus-related posterior leukoencephalopathy after living donor liver transplantation. *Liver Transpl* 2003; **9:** 983–5.
10. Schuuring J, *et al*. Severe tacrolimus leukoencephalopathy after liver transplantation. *Am J Neuroradiol* 2003; **24:** 2085–8.
11. Lavigne CM, *et al*. Tacrolimus leukoencephalopathy: a neuropathologic confirmation. *Neurology* 2004; **63:** 1132–3.
12. Kaushik P, *et al*. Miller Fisher variant of Guillain-Barré syndrome requiring a cardiac pacemaker in a patient on tacrolimus after liver transplantation. *Ann Pharmacother* 2005; **39:** 1124–7.

Effects on skeletal muscle. Severe acute rhabdomyolysis, leading to fatal acute renal failure, developed in an 18-month-old child given tacrolimus after bone marrow transplantation.[1] Seizures, severe rhabdomyolysis, and acute renal failure were reported in a renal transplant patient taking tacrolimus and a monoclonal antibody.[2]

1. Hibi S, *et al*. Severe rhabdomyolysis associated with tacrolimus. *Lancet* 1995; **346:** 702.
2. Fontana I, *et al*. Severe rhabdomyolysis and acute renal failure in a kidney transplant patient treated with tacrolimus and chimaeric CD25 monoclonal antibody. *Transplant Proc* 2004; **36:** 711–2.

Effects on the skin. Three children developed lentigines (small pigmented macules) while receiving long-term (9 months to 4 years) treatment with topical tacrolimus 0.1% for eczema. The lesions developed mainly in the areas where tacrolimus had been applied. Despite withdrawal of tacrolimus, the lentigines still persisted at review 6 to 18 months later. The authors noted that use of tacrolimus was outside the product's licensed indications, and that the clinical implications of their findings remained uncertain.[1]

1. Hickey JR, *et al*. Does topical tacrolimus induce lentigines in children with atopic dermatitis? A report of three cases. *Br J Dermatol* 2005; **152:** 152–4.

Hepatitis. For the suggestion that dosage requirements of tacrolimus may be reduced in children with hepatitis C see Administration, p. 1969.2.

Infection. For a report of an increased incidence of CMV disease in renal transplant recipients given a regimen combining tacrolimus and mycophenolate mofetil see under Interactions, p. 1964.2.

Overdosage. A report[1] of 12 cases of acute overdose with tacrolimus described overdoses of up to 30 times the prescribed dose. Three patients were asymptomatic, while 7 showed mild transient renal and hepatic impairment, nausea, and mild hand tremors. One patient suffered renal failure, histoplasmosis, and sepsis 48 hours after admission for the overdose. The outcome was unknown in one patient. All 8 symptomatic patients recovered when tacrolimus concentrations returned to normal. No specific treatment regimen has been recommended, but patients have been treated with gastric lavage, oral activated charcoal, and phenytoin. The latter is used both to prevent seizures and to enhance tacrolimus metabolism by stimulation of cytochrome P450. Patients should be closely monitored for known signs and symptoms of tacrolimus toxicity. In a further series of 5 cases,[2] acute ingestion of tacrolimus was reported to be well tolerated, and adequately managed with conservative treatment.

1. Curran CF, *et al*. Acute overdoses of tacrolimus. *Transplantation* 1996; **62:** 1376.
2. Mrvos R, *et al*. Tacrolimus (FK 506) overdose: a report of five cases. *J Toxicol Clin Toxicol* 1997; **35:** 395–9.

Porphyria. Data are limited on the use of tacrolimus in patients with porphyria. There has been a report of a patient with acute intermittent porphyria given tacrolimus for 5 days before renal transplantation, and maintenance tacrolimus post-transplantation, without exacerbation of symptoms.[1] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tacrolimus as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[2]

1. Barone GW, *et al*. The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; **41:** 113–5.
2. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pregnancy. Tacrolimus crosses the placenta. Licensed product information states that, although *systemic* tacrolimus has shown abortifacient and teratogenic properties in *animal* studies, limited data in humans show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy compared with other immunosuppressants. However, use of tacrolimus has been associated with neonatal hyperkalaemia, which appears to normalise spontaneously, and neonatal renal dysfunction; the neonate should be monitored for potential adverse effects.

There are no adequate data from the use of *topical* tacrolimus in pregnancy.

Further references.

1. Kainz A, *et al*. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000; **70:** 1718–21.
2. Jain AB, *et al*. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003; **76:** 827–32.
3. Baumgart DC, *et al*. Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. *Gut* 2005; **54:** 1822–3.

Interactions

Increased nephrotoxicity may result if tacrolimus is given with other potentially nephrotoxic drugs: use with ciclosporin should be avoided for this reason. Similarly, concurrent use with neurotoxic drugs should be avoided. High potassium intake or potassium-sparing diuretics should also be avoided in patients receiving tacrolimus. Tacrolimus is extensively bound to plasma proteins and so has the potential to interact with other drugs that are highly protein bound.

Tacrolimus is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme system, such as azole antifungals, bromocriptine, calcium-channel blockers, cimetidine, some corticosteroids, ciclosporin, danazol, HIV-protease inhibitors, macrolide antibacterials, and metoclopramide, may produce increased blood concentrations of tacrolimus. The metabolism of tacrolimus may also be inhibited by grapefruit juice and they should not be taken together. Equally, inducers of this enzyme system (such as carbamazepine, phenobarbital, phenytoin, rifampicin, and St John's wort) may reduce blood concentrations of tacrolimus. Sirolimus can also decrease blood concentrations of tacrolimus. Corticosteroids may increase or decrease tacrolimus concentrations. Nevirapine and the NNRTI delavirdine may also affect tacrolimus concentrations. For a warning concerning the use of live vaccines in patients receiving immunosuppressants see Adverse Effects and Precautions, p. 1971.1.

Facial flushing or skin irritation may occur if alcohol is consumed by patients using topical tacrolimus.

The cytochrome P450 isoenzyme subfamily CYP3A, and P-glycoprotein, are involved in the pharmacokinetic pathways of tacrolimus.[1] Drugs that interact with these systems will probably affect tacrolimus concentrations, mainly by influencing oral bioavailability rather than clearance.[2] A study[3] *in vitro* found that metabolism of tacrolimus by CYP3A in human liver microsomes was inhibited by bromocriptine, corticosterone, dexamethasone, ergotamine, erythromycin, ethinylestradiol, josamycin, ketoconazole, miconazole, midazolam, nifedipine, omeprazole, tamoxifen, troleandomycin, and verapamil. No effect on tacrolimus metabolism was seen with aspirin, amphotericin B, captopril, cefotaxime, ciprofloxacin, diclofenac, diltiazem, doxycycline, furosemide, glibenclamide,

imipramine, lidocaine, paracetamol, prednisolone, progesterone, ranitidine, sulfamethoxazole, trimethoprim, or vancomycin.

1. van Gelder T. Drug interactions with tacrolimus. *Drug Safety* 2002; **25:** 707–12.
2. Christians U, *et al*. Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet* 2002; **41:** 813–51.
3. Christians U, *et al*. Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; **41:** 187–90.

Antibacterials. Increased concentrations of tacrolimus in plasma have been reported with *erythromycin*;[1] the interaction was accompanied by some evidence of nephrotoxicity. A similar interaction has been reported between tacrolimus and *clarithromycin*.[2,3] For reference to the effects of macrolides on tacrolimus metabolism *in vitro* see p. 1972.3.

Treatment with *rifampicin* has been found to substantially decrease tacrolimus concentrations.[4,5] A pharmacokinetic study found that rifampicin induces metabolism of tacrolimus in both the liver and intestine, probably by induction of the cytochrome P450 isoenzyme subfamily CYP3A and P-glycoprotein.[6] Both *metronidazole*[7,8] and *chloramphenicol*[9,10] increased the blood concentrations of tacrolimus. This is probably due to inhibition of metabolism, and dosage reduction of the immunosuppressant may be necessary when either drug is given with tacrolimus. A pharmacokinetic study[11] found that *levofloxacin* partially inhibited the metabolism of tacrolimus, and recommended that drug concentrations be monitored when these 2 drugs are used together.

Plasma concentrations of tacrolimus are also increased by *quinupristin/dalfopristin*.

1. Jensen C, *et al*. Interaction between tacrolimus and erythromycin. *Lancet* 1994; **344:** 825.
2. Wolter K, *et al*. Interaction between FK 506 and clarithromycin in a renal transplant patient. *Eur J Clin Pharmacol* 1994; **47:** 207–8.
3. Ibrahim RB, *et al*. Tacrolimus-clarithromycin interaction in a patient receiving bone marrow transplantation. *Ann Pharmacother* 2002; **36:** 1971–2.
4. Furlan V, *et al*. Interactions between FK506 and rifampicin or erythromycin in pediatric liver recipients. *Transplantation* 1995; **59:** 1217–18.
5. Chenhsu R-Y, *et al*. Renal allograft dysfunction associated with rifampin-tacrolimus interaction. *Ann Pharmacother* 2000; **34:** 27–31.
6. Hebert MF, *et al*. Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 1999; **39:** 91–6.
7. Herzig K, Johnson DW. Marked elevation of blood cyclosporin and tacrolimus levels due to concurrent metronidazole therapy. *Nephrol Dial Transplant* 1999; **14:** 521–3.
8. Page RL, *et al*. Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother* 2005; **39:** 1109–13.
9. Schulman SL, *et al*. Interaction between tacrolimus and chloramphenicol in a renal transplant recipient. *Transplantation* 1998; **65:** 1397–8.
10. Mathis AS, *et al*. Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; **4:** 169–74.
11. Federico S, *et al*. Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; **45:** 169–75.

Antidepressants. Tacrolimus trough concentrations reduced sharply in a patient who took *St John's wort*, and returned to previous levels on stopping the St John's wort.[1] St John's wort induces cytochrome P450 isoenzyme CYP3A4, enhancing the metabolism of tacrolimus. A pharmacokinetic study[2] confirmed this, finding an increase in tacrolimus clearance; the authors concluded that potential consequences of this interaction in transplant recipients are rejection and graft loss.

1. Bolley R, *et al*. Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* 2002; **73:** 1009.
2. Hebert MF, *et al*. Effects of St. John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 89–94.

Antiepileptics. For the effect of tacrolimus on *phenytoin* plasma concentrations, see Immunosuppressants in Phenytoin, p. 545.1.

Antifungals. Elevated plasma-tacrolimus concentrations have been reported in patients given *clotrimazole*,[1] *fluconazole*,[2] or *voriconazole*[3]; a reduction in the dose of tacrolimus was likely to be necessary if it were given with an azole antifungal. A study involving tacrolimus and *ketoconazole* suggested that an increase in the oral bioavailability of tacrolimus from a mean of 14 to 30% when given with the azole was probably due to decreased cytochrome P450 isoenzyme CYP3A4 metabolism in the gut wall, or improved absorption due to inhibition of P-glycoprotein mediated efflux, rather than an effect on hepatic metabolism.[4] Similarly, a 50% reduction in tacrolimus dosage was found to be necessary when the drug was given with *itraconazole*.[5] It has been suggested that the interaction could be exploited to reduce the cost of immunosuppressant regimens.[6] In another study of itraconazole with tacrolimus,[7] 1 patient required a 20% increase in the dose of tacrolimus, 3 patients required no dose adjustment, and 5 patients required tacrolimus dose reductions, ranging from 20 to 76.5%. The authors concluded that the magnitude of the dose reduction is dependent on the initial tacrolimus serum concentration and the final target concentration.

1. Mieles L, *et al*. Interaction between FK506 and clotrimazole in a liver transplant recipient. *Transplantation* 1991; **52:** 1086–7.
2. Mañez R, *et al*. Fluconazole therapy in transplant recipients receiving FK506. *Transplantation* 1994; **57:** 1521–3.
3. Venkataramanan R, *et al*. Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. *Antimicrob Agents Chemother* 2002; **46:** 3091–3.
4. Floren LC, *et al*. Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. *Clin Pharmacol Ther* 1997; **62:** 41–9.
5. Capone D, *et al*. Effects of itraconazole on tacrolimus blood concentrations in a renal transplant recipient. *Ann Pharmacother* 1999; **33:** 1124–5.
6. Kramer MR, *et al*. Dose adjustment and cost of itraconazole prophylaxis in lung transplant recipients receiving cyclosporine and tacrolimus (FK506). *Transplant Proc* 1997; **29:** 2657–9.
7. Leather H, *et al*. Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12:** 325–34.

Antivirals. Ten- to fiftyfold reductions in tacrolimus dosage were necessary to maintain therapeutic tacrolimus trough concentrations, in 6 HIV-positive liver transplant recipients receiving tacrolimus-based immunosuppressive therapy, when antiretroviral therapy including an HIV-protease inhibitor was started postoperatively.[1] This effect was more pronounced with *nelfinavir* than *indinavir*. In contrast, 4 HIV-positive kidney transplant recipients given antiretroviral therapy without HIV-protease inhibitors required only conventional doses of tacrolimus. The authors caution that some HIV-protease inhibitors can act as both inducers and inhibitors of the cytochrome P450 isoenzyme CYP3A4. While the inhibitory effect appears to predominate when given with tacrolimus, if the HIV-protease inhibitor is withdrawn suddenly the CYP3A4 system may remain induced, and a sudden decrease in tacrolimus concentration may occur; this had occurred in one case. For this reason, they concluded that great caution and frequent tacrolimus monitoring are necessary when HIV-protease inhibitors are introduced or withdrawn in transplant recipients receiving tacrolimus.

The potential interaction between tacrolimus and *atazanavir* in an HIV-positive renal transplant recipient was managed by monitoring serum concentrations of tacrolimus and modifying the tacrolimus dose accordingly; metabolism and elimination of tacrolimus were impaired in the presence of atazanavir.[2]

Dramatic increases in tacrolimus blood concentrations have been reported after addition of *lopinavir/ritonavir* in HIV-positive liver transplant recipients.[3-5] Some patients did not need further tacrolimus for up to 3 weeks, even with normal hepatic function; with hepatic dysfunction, 1 mg of tacrolimus provided a therapeutic concentration for up to 5 weeks, and in one patient the tacrolimus concentration increased for the next few days with the introduction of lopinavir/ritonavir without any additional dose of tacrolimus. The authors recommended a pre-emptive decrease in tacrolimus dose by at least 50% one day before starting therapy with lopinavir/ritonavir, and withholding tacrolimus for the next few days; therapy should then be guided by therapeutic drug monitoring of tacrolimus blood concentrations.[4] The usual dose of tacrolimus while a patient is on lopinavir/ritonavir is expected to be about 0.5 to 1 mg weekly.[3,4] In contrast, *efavirenz* did not appreciably affect tacrolimus pharmacokinetics.[5]

1. Jain AKB, *et al*. The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl* 2002; **8:** 841–5.
2. Tsapepas DS, *et al*. Managing the atazanavir-tacrolimus drug interaction in a renal transplant recipient. *Am J Health-Syst Pharm* 2011; **68:** 138–42.
3. Schonder KS, *et al*. Tacrolimus and lopinavir/ritonavir interaction in liver transplantation. *Ann Pharmacother* 2003; **37:** 1793–6.
4. Jain AB, *et al*. Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl* 2003; **9:** 954–60.
5. Teicher E, *et al*. Effect of highly active antiretroviral therapy on tacrolimus pharmacokinetics in hepatitis C virus and HIV co-infected liver transplant recipients in the ANRS HC-08 study. *Clin Pharmacokinet* 2007; **46:** 941–52.

Calcium-channel blockers. Dosage requirements for tacrolimus were substantially reduced in 22 liver graft recipients who also received *nifedipine*, compared with 28 patients given tacrolimus alone, in a 1-year retrospective study.[1]

Tacrolimus toxicity has been reported in a liver transplant patient shortly after starting *diltiazem*.[2]

1. Seifeldin RA, *et al*. Nifedipine interaction with tacrolimus in liver transplant recipients. *Ann Pharmacother* 1997; **31:** 571–5.
2. Hebert MF, Lam AY. Diltiazem increases tacrolimus concentrations. *Ann Pharmacother* 1999; **33:** 680–2.

Danazol. Nephrotoxicity and tremors associated with elevated concentrations of tacrolimus developed in a patient given danazol with the immunosuppressant.[1] The effect might have been due to inhibition of the metabolism of tacrolimus.

1. Shapiro R, *et al*. FK 506 interaction with danazol. *Lancet* 1993; **341:** 1344–5.

Deoxyschizandrin. Mean blood concentrations of tacrolimus in 12 healthy subjects rose from 22.2 to 66.4 nanograms/mL after they had received 13 days of treatment with SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin.[1] During the study the area under the concentration-time curve (AUC) of tacrolimus also rose by 164.2% while oral clearance fell by 49%. It was suggested that constituents of *Schisandra sphenanthera* may act as inhibitors of the cytochrome P450 isoenzyme CYP3A4 and/or P-glycoprotein.

1. Xin H-W, *et al*. Effects of *Schisandra sphenanthera* extract on the pharmacokinetics of tacrolimus in healthy volunteers. *Br J Clin Pharmacol* 2007; **64:** 469–75.

Gastrointestinal drugs. In 2 renal transplant recipients, tacrolimus trough concentrations increased markedly after introduction of *lansoprazole* and returned to normal after it was stopped.[1,2] One of the patients was later given *rabeprazole* with no effect on tacrolimus concentration.[2] The same effects were apparent in a study of healthy subjects,[3] with lansoprazole increasing the concentration and decreasing the clearance of tacrolimus, but the degree of interaction was found to depend, at least partly, upon the genetic status of the patients. The authors supposed that certain ethnic groups might be at higher risk for this interaction. In contrast, rabeprazole appears less affected by genotypic status, and had minimal effect on tacrolimus pharmacokinetics; the authors considered it a safer proton pump inhibitor than lansoprazole for those with cytochrome P450 isoenzyme CYP2C19 gene mutation who were receiving tacrolimus. An *in-vitro* study suggested that omeprazole inhibited the metabolism of tacrolimus.[4] Despite a study reporting no clinically relevant interaction between omeprazole and tacrolimus in renal transplant recipients,[5] increased tacrolimus concentrations were reported when a paediatric liver transplant patient was started on omeprazole.[6]

1. Takahashi K, *et al*. Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann Pharmacother* 2004; **38:** 791–4.
2. Homma M, *et al*. Effects of lansoprazole and rabeprazole on tacrolimus blood concentration: case of a renal transplant recipient with CYP2C19 gene mutation. *Transplantation* 2002; **73:** 303–4.
3. Itagaki F, *et al*. Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. *J Pharm Pharmacol* 2004; **56:** 1055–9.
4. Christians U, *et al*. Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; **41:** 187–90.
5. Pascual J, *et al*. Interaction between omeprazole and tacrolimus in renal allograft recipients: a clinical-analytical study. *Transplant Proc* 2005; **37:** 3752–3.
6. Moreau C, *et al*. Interaction between tacrolimus and omeprazole in a pediatric liver transplant recipient. *Transplantation* 2006; **81:** 487–8.

Immunosuppressants. *Sirolimus* may decrease blood concentrations of tacrolimus; in stable renal transplant recipients given both drugs, mean exposure and trough concentrations of tacrolimus decreased by about 30% relative to tacrolimus alone. Tacrolimus may inhibit *ciclosporin* metabolism *in vitro*, with the possibility of increased nephrotoxicity (see under Ciclosporin, p. 1954.3). Tacrolimus may also increase concentrations of mycophenolic acid, a metabolite of *mycophenolate mofetil* (see under Mycophenolate Mofetil, p. 1964.2), and the risk of infection may be increased if used together.

Sevelamer. There was a progressive reduction in tacrolimus concentrations in a renal transplant patient after starting sevelamer, which was thought to be due to binding of tacrolimus in the gut.[1] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Merkle M, *et al*. The effect of sevelamer on tacrolimus target levels. *Transplantation* 2005; **80:** 707.

Pharmacokinetics

Absorption of tacrolimus after oral doses is reported to be erratic. Oral bioavailability varies very widely; the mean value is in the range of 20 to 25%. The rate and extent of absorption of tacrolimus is decreased by the presence of food, with the effect most pronounced after a high-fat meal. There is little or no systemic exposure to tacrolimus after topical use (but see Absorption, p. 1974.1). After intravenous doses it is widely distributed to the tissues; it is extensively bound to erythrocytes in the blood, and variations in red cell binding account for much of the variability in pharmacokinetics. The portion in plasma is about 99% bound to plasma proteins. Tacrolimus is extensively metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4, and excreted, primarily in bile,

almost entirely as metabolites. Considerable metabolism also occurs in the intestinal wall. Whole-blood elimination half-life has been reported to average 43 hours in healthy subjects, and to range from about 12 to 16 hours in transplant patients.

References.

1. Gruber SA, *et al*. Pharmacokinetics of FK506 after intravenous and oral administration in patients awaiting renal transplantation. *J Clin Pharmacol* 1994; **34:** 859–64.
2. Jusko WJ, *et al*. Pharmacokinetics of tacrolimus in liver transplant patients. *Clin Pharmacol Ther* 1995; **57:** 281–90.
3. Venkataramanan R, *et al*. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 1995; **29:** 404–30.
4. Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. *Clin Pharmacokinet* 2001; **40:** 283–95.
5. Bekersky I, *et al*. Comparative tacrolimus pharmacokinetics: normal versus mildly hepatically impaired subjects. *J Clin Pharmacol* 2001; **41:** 628–35.
6. Reding R, *et al*. Efficacy and pharmacokinetics of tacrolimus oral suspension in pediatric liver transplant recipients. *Pediatr Transplant* 2002; **6:** 124–6.
7. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004; **43:** 623–53.
8. Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. *Drug Metab Pharmacokinet* 2007; **22:** 328–35.
9. Antignac M, *et al*. Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients. *Br J Clin Pharmacol* 2007; **64:** 750–7.
10. Undre NA, *et al*. Skin and systemic pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol* 2009; **160:** 665–9.
11. Reitamo S, *et al*. The pharmacokinetics of tacrolimus after first and repeated dosing with 0.03% ointment in infants with atopic dermatitis. *Int J Dermatol* 2009; **48:** 348–55.
12. Zhao W, *et al*. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clin Pharmacol Ther* 2009; **86:** 609–18.
13. Benkali K, *et al*. Tacrolimus population pharmacokinetic-pharmacogenetic analysis and Bayesian estimation in renal transplant recipients. *Clin Pharmacokinet* 2009; **48:** 805–16.
14. Zheng S, *et al*. Pharmacokinetics of tacrolimus during pregnancy. *Ther Drug Monit* 2012; **34:** 660–70.
15. Guy-Viterbo V, *et al*. Population pharmacokinetic analysis of tacrolimus in the first year after pediatric liver transplantation. *Eur J Clin Pharmacol* 2013; **69:** 1533–42.

Absorption. A single topical application of a 0.1% tacrolimus ointment to an infant for the treatment of chronic dermatitis, resulted in high serum-tacrolimus concentrations (24 nanograms/mL). Tacrolimus levels decreased over 7 days, after which another smaller, single application of 0.03% tacrolimus ointment again resulted in high serum concentrations. The authors cautioned against its use in young children and diseases with decreased skin barrier function.[1] In another report,[2] elevated blood tacrolimus concentrations were seen after application of 0.1% tacrolimus ointment to a large area of the body of a patient with erythroderma; again, caution in conditions where the skin barrier is disrupted was advised.

1. Kameda G, *et al*. Unexpected high serum levels of tacrolimus after a single topical application in an infant. *J Pediatr* 2003; **143:** 280. Correction. *ibid.*; 462.
2. Teshima D, *et al*. Increased topical tacrolimus absorption in generalized leukemic erythroderma. *Ann Pharmacother* 2003; **37:** 1444–7.

Bioavailability. Bioavailability of tacrolimus appears to be influenced by the type and timing of meals. Food, particularly high-fat meals, significantly reduced bioavailability, compared with the fasting state.[1] Ingestion of tacrolimus up to 1.5 hours after a meal also considerably reduced absorption.[2] UK licensed product information states that tacrolimus should be taken on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. Gastrointestinal metabolism of tacrolimus is thought to be extensive, significantly affecting its bioavailability,[3] and differences in this metabolism may account for apparent differences in availability according to ethnic origin.[4]

1. Bekersky I, *et al*. Effect of low- and high-fat meals on tacrolimus absorption following 5 mg single oral doses to healthy human subjects. *J Clin Pharmacol* 2001; **41:** 176–82.
2. Bekersky I, *et al*. Effect of time of meal consumption on bioavailability of a single oral 5 mg tacrolimus dose. *J Clin Pharmacol* 2001; **41:** 289–97.
3. Tuteja S, *et al*. The effect of gut metabolism on tacrolimus bioavailability in renal transplant recipients. *Transplantation* 2001; **71:** 1301–7.
4. Mancinelli LM, *et al*. The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. *Clin Pharmacol Ther* 2001; **69:** 24–31.

Genetic factors. Renal transplant recipients homozygous for CYP3A5*3 required lower doses to reach target trough concentrations of tacrolimus compared with CYP3A5*1 allele carriers;[1] the latter group can be expected to have a tacrolimus clearance 25 to 45% greater than that of homozygotes.[2] Determination of the cytochrome P450 isoenzyme genotype before transplantation may identify patients at risk for underimmunosuppression or toxicity.

1. Hesselink DA, *et al*. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; **74:** 245–54.
2. Utecht KN, *et al*. Effects of genetic polymorphisms on the pharmacokinetics of calcineurin inhibitors. *Am J Health-Syst Pharm* 2006; **63:** 2340–8.

Therapeutic drug monitoring. There is a good correlation between tacrolimus trough concentrations and systemic exposure, and analysis at other time points is not considered to offer any advantage.[1] However, since tacrolimus concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[2]

Microparticle enzyme immunoassay (MEIA) and enzyme-linked immunosorbent assay (ELISA) have both been used to measure tacrolimus whole blood concentrations. A study[3] of liver transplant recipients found that increasing trough tacrolimus concentrations, as measured by the ELISA, correlated with decreasing risk of acute rejection, but increasing risk of nephrotoxicity. The authors suggested a trough blood concentration of less than 15 nanograms/mL to minimise nephrotoxicity. While several studies have shown that adverse effects are more closely correlated with tacrolimus concentrations than with dose, the correlation between concentrations and allograft rejection has not been established. There is some suggestion that measuring the unbound concentration of tacrolimus may be a better correlate for rejection than whole blood concentrations.[4]

Licensed product information states that blood trough concentrations of tacrolimus should be monitored during the post-transplantation period; blood should be drawn just before the next dose. Samples which are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept for longer they may be frozen at -20 degrees for up to 6 months. The frequency of monitoring is based on clinical need; about twice-weekly during the early post-transplant period is recommended, followed by periodic monitoring during maintenance therapy. Trough concentrations should also be monitored after dose adjustment, although it may take several days before changes become apparent. Monitoring is also recommended when signs of toxicity or acute rejection are seen, after changes in the immunosuppressive regimen, or when other drugs are given which may alter tacrolimus blood concentrations. The majority of patients can be successfully managed if blood concentrations are maintained below 20 nanograms/mL. In practice, in the early post-transplant period, whole blood trough concentrations have generally been in the range of 5 to 20 nanograms/mL in liver transplant recipients, and 10 to 20 nanograms/mL in kidney and heart transplant recipients. A higher target range of 15 to 25 nanograms/mL is recommended in children after heart transplantation, when tacrolimus is given intravenously and antibody induction is not used. During maintenance therapy, blood concentrations have generally been between 5 and 15 nanograms/mL in liver, kidney, and heart transplant patients, although when tacrolimus is used with everolimus in liver transplantation, a lower tacrolimus target range of 3 to 5 nanograms/mL is recommended.

Bayesian forecasting[5,6] and limited sampling strategies (with samples taken 1.5 hours postdose and immediately predose)[7] have also been used to predict exposure to tacrolimus.

Licensed product information states that the relationship between tacrolimus trough concentrations and systemic exposure is similar for the standard formulation (*Prograf, Astellas*) and the prolonged-release formulation (*Advagraf* or *Astagraf, Astellas*), although they are not interchangeable (see Oral Formulations, p. 1969.2).

1. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
2. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; **45:** 775–88.
3. Venkataramanan R, *et al*. Clinical utility of monitoring tacrolimus blood concentrations in liver transplant patients. *J Clin Pharmacol* 2001; **41:** 542–51.
4. Zahir H, *et al*. Factors affecting variability in distribution of tacrolimus in liver transplant recipients. *Br J Clin Pharmacol* 2004; **57:** 298–309.
5. Fukudo M, *et al*. Forecasting of blood tacrolimus concentrations based on the Bayesian method in adult patients receiving living-donor liver transplantation. *Clin Pharmacokinet* 2003; **42:** 1161–78.
6. Fukudo M, *et al*. Prospective evaluation of the Bayesian method for individualizing tacrolimus dose early after living-donor liver transplantation. *J Clin Pharmacol* 2009; **49:** 789–97.
7. Mathew BS, *et al*. A limited sampling strategy for tacrolimus in renal transplant patients. *Br J Clin Pharmacol* 2008; **66:** 467–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Litacro; Prograf; Protopic; Tacraf†; Tacro-Tic; Tacroinmun; ***Austral.***: Prograf; ***Austria***: Advagraf; Prograf; Protopic; ***Belg.***: Advagraf; Prograft; Protopic; ***Braz.***: Prograf; Protopic; ***Canad.***: Advagraf; Prograf; Protopic; ***Chile***: Cromidin; Prograf; Protopic; T-Inmun; ***China***: Advagraf (新普乐可复); Prograf (普乐可复); Protopic (普特彼); ***Cz.***: Advagraf; Gecrol; Lecron; Modigraf; Prograf; Protopic; Tacni; ***Denm.***: Advagraf; Prograf; Protopic; ***Fin.***: Prograf; Protopic; Tacni; ***Fr.***: Advagraf; Modigraf; Prograf; Protopic; ***Ger.***: Advagraf; Modigraf; Prograf; Protopic; Tacpan; Tacro-cell; ***Gr.***: Advagraf; Prograf; Protopic; ***Hong Kong***: Advagraf; Prograf; Protopic; ***Hung.***: Advagraf; Prograf; Protopic; ***India***: Crolim; Mustopic; Olmis; PanGraf; Tacroz; ***Indon.***: Prograf; Protopic; ***Irl.***: Advagraf; Modigraf; Prograf; Protopic; Tacni; ***Israel***: Prograf; Protopic; Tacrocel; ***Ital.***: Advagraf; Lecron; Prograf; Protopic; ***Jpn***: Graceptor; Prograf; Protopic; ***Malaysia***: Prograf; Protopic; ***Mex.***: Framebin; Limustin; Lytomi-C; Octralin; Proalid; Prograf; Protopic; Traderma; ***Neth.***: Advagraf; Modigraf; Prograf; Prograft; Protopic; Tacni; ***Norw.***: Advagraf; Modigraf; Prograf; Protopic; Tacni; ***NZ***: Prograf; ***Philipp.***: Prograf; Protopic; Tacrocin; Tagraf; Vingraf; ***Pol.***: Advagraf; Modigraf; Prograf; Protopic; ***Port.***: Advagraf; Modigraf; Prograf; Protopic; ***Rus.***: Advagraf (Адвараф); Prograf (Програф); Protopic (Протопик); ***S.Afr.***: Prograf; Protopic; ***Singapore***: Prograf; Protopic; ***Spain***: Adoport; Advagraf; Modigraf; Prograf; Protopic; Tartrime; ***Swed.***: Advagraf; Prograf; Protopic; Tacni; ***Switz.***: Advagraf; Prograf; Protopic; ***Thai.***: Advagraf; Prograf; Protopic; ***Turk.***: Prograf; Protopic; ***UK***: Adoport; Advagraf; Capexion; Modigraf; Perixis; Prograf; Protopic; Tacni; ***Ukr.***: Prograf (Програф); Protopic (Протопик); ***USA***: Astagraf; Prograf; Protopic; ***Venez.***: Prograf.

Pharmacopoeial Preparations

USP 36: Tacrolimus Capsules; Tacrolimus Oral Suspension.

Umirolimus *(USAN, rINN)*

Biolimus; TRM-986; Umirolimús; Umirolimusum; Биолимус; Умиролимус.

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-Ethoxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-octadecahydro-23,27-epoxy-5*H*-pyrido[2,1-*c*][1,4]oxazacyclohentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone.

$C_{55}H_{87}NO_{14}$=986.3

CAS — 851536-75-9.

NOTE. The names Biolimus A9 and BA9 have been used as trade marks for umirolimus.

Profile

Umirolimus is an analogue of sirolimus (p. 1966.2). A umirolimus-eluting stent has been developed to reduce restenosis after coronary artery stent placement.

References.

1. Windecker S, *et al*. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008; **372:** 1163–73.
2. Ostojic M, *et al*. The pharmacokinetics of Biolimus A9 after elution from the Nobori stent in patients with coronary artery disease: the NOBORI PK study. *Catheter Cardiovasc Interv* 2008; **72:** 901–8.
3. Verheye S, *et al*. 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. *J Am Coll Cardiol* 2009; **53:** 1031–9.
4. Wykrzykowska JJ, *et al*. Biolimus-eluting biodegradable polymer versus sirolimus-eluting permanent polymer stent performance in long lesions: results from the LEADERS multicentre trial substudy. *EuroIntervention* 2009; **5:** 310–17.
5. Wykrzykowska JJ, *et al*. Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer: the LEADERS trial substudy. *JACC Cardiovasc Interv* 2009; **2:** 861–70.

Voclosporin *(USAN, rINN)*

ISA-247; ISATX-247; LX-211; R-1524; Voclosporina; Voclosporine; Voclosporinum; Вокльоспорин.

Cyclo{L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl]-(2*S*)-2-aminobutanoyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl}.

$C_{63}H_{111}N_{11}O_{12}$=1214.6

CAS — 515814-01-4.

ATC — L04AD03.

ATC Vet — QL04AD03.

UNII — 2PN063X6B1.

NOTE. The name Luveniq has been used as a trade mark for voclosporin.

Profile

Voclosporin is an analogue of ciclosporin (p. 1945.2) that is under investigation for the treatment of uveitis, psoriasis, and for the prevention of rejection in organ transplantation.

References.

1. Dumont FJ. ISAtx-247 (Isotechnika/Roche). *Curr Opin Investig Drugs* 2004; **5:** 542–50.

2. Anonymous. ISA 247: trans-ISA 247, trans-R 1524, ISA(TX)247, ISAtx 247, ISATx247, LX 211, LX211, R 1524, R-1524. *Drugs R D* 2007; **8:** 103–12.
3. Papp K, *et al*. Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; **371:** 1337–42.
4. Anglade E, *et al*. A new agent for the treatment of noninfectious uveitis: rationale and design of three LUMINATE (Lux Uveitis Multicenter Investigation of a New Approach to Treatment) trials of steroid-sparing voclosporin. *Clin Ophthalmol* 2008; **2:** 693–702.
5. Deuter CME. Systemisches Voclosporin bei Uveitis. *Ophthalmologe* 2010; **107:** 672–5.

Zotarolimus *(USAN, rINN)*

ABT-578; Zotarolimusum; Зотаролимус.

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-Dihydroxy-10,21-dimethoxy-3-{(2*R*)-1-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]propan-2-yl}-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-octadecahydro-5*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazahentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone.

$C_{52}H_{79}N_5O_{12}$=966.2

CAS — 221877-54-9.

UNII — H4GXR80IZE.

Profile

Zotarolimus is an analogue of sirolimus (p. 1966.2) that is used in the form of a drug-eluting stent to reduce the risk of restenosis after percutaneous coronary stenting.

Reperfusion and revascularisation procedures. References to the use of zotarolimus-eluting stents.

1. Burke SE, *et al*. Zotarolimus (ABT-578) eluting stents. *Adv Drug Deliv Rev* 2006; **58:** 437–46.
2. Fajadet J, *et al*. ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006; **114:** 798–806.
3. Kandzari DE, Leon MB. Overview of pharmacology and clinical trials program with the zotarolimus-eluting endeavor stent. *J Interv Cardiol* 2006; **19:** 405–13.
4. Korovesis S, *et al*. Subacute thrombosis following implantation of zotarolimus-eluting stent. *Hellenic J Cardiol* 2006; **47:** 310–2.
5. Kandzari DE, *et al*. ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2006; **48:** 2440–7.
6. Chen Y-W, *et al*. Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. *J Cardiovasc Pharmacol* 2007; **49:** 228–35.
7. Gershlick A, *et al*. ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol* 2007; **100** (suppl 2): S45–S55.
8. Meredith IT, *et al*. Four-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, the first-in-human study. *Am J Cardiol* 2007; **100** (suppl 2): S56–S61.
9. Jain AK, *et al*. Real-world safety and efficacy of the endeavor zotarolimus-eluting stent: early data from the E-Five Registry. *Am J Cardiol* 2007; **100** (suppl 2): S77–S83.
10. Brugaletta S, *et al*. Zotarolimus for the treatment of coronary artery disease: pathophysiology, DES design, clinical evaluation and future perspective. *Expert Opin Pharmacother* 2009; **10:** 1047–58.
11. Meredith IT, *et al*. RESOLUTE Investigators. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. *J ACC Cardiovasc Interv* 2009; **2:** 977–85.
12. Meredith IT, *et al*. ENDEAVOR I Investigators. Five-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, first-in-human study. *Catheter Cardiovasc Interv* 2009; **74:** 989–95.

Local Anaesthetics

Local anaesthetics produce reversible loss of function or sensation by preventing or diminishing the conduction of nerve impulses near to the site of their application or injection. Because their mode of action is to decrease permeability of the nerve cell membrane to sodium ions, they also have a membrane stabilising effect.

Most clinically useful local anaesthetics have the same general chemical configuration of an amine portion joined to an aromatic residue by an ester or amide link. The type of linkage is important in determining the properties of the drug.

For a classification of local anaesthetics, see Table 1, below.

Table 1. Classification of local anaesthetics.

Amide type	**Ester type**
Articaine	*Esters of benzoic acid*
Bupivacaine	Amylocaine
Cinchocaine	Cocaine
Ethyl parapiperidino-acetylaminobenzoate	Propanocaine
Levobupivacaine	*Esters of meta-aminobenzoic acid*
Lidocaine	Proxymetacaine
Mepivacaine	*Esters of para-aminobenzoic acid*
Oxetacaine	Benzocaine
Prilocaine	Butyl aminobenzoate
Ropivacaine	Chloroprocaine
Tolycaine	Oxybuprocaine
Trimecaine	Procaine
Miscellaneous	Propoxycaine
Dyclonine	Tetracaine
Ethyl chloride	Tricaine
Ketocaine	
Myrtecaine	
Pramocaine	
Quinisocaine	

Uses and Administration

Local anaesthetics act by preventing the generation and transmission of impulses along nerve fibres and at nerve endings; depolarisation and ion-exchange are inhibited. The effects are reversible. They are used for the local relief of painful conditions, and to prevent pain and discomfort of various medical and surgical procedure (see below). In general, loss of pain (analgesia) occurs before loss of sensory and autonomic function (anaesthesia) and loss of motor function (paralysis), but this may depend on the drug used and the site into which it is given.

Local anaesthetics vary in their potency and speed of onset and duration of action. The anaesthetic must penetrate the lipoprotein nerve sheath in its unionised form before it can act and therefore drugs with high lipid-solubility tend to have a greater potency and duration of action and a faster onset than drugs with low lipid-solubility. The most protein-bound drugs tend to have the longest duration of action.

The potency of local anaesthetics is traditionally compared against that of procaine, which is low; chloroprocaine, lidocaine, mepivacaine, and prilocaine are similar or somewhat more potent; bupivacaine and ropivacaine highly potent, and tetracaine extremely potent.

Speed of onset and duration of action also depend on the technique used (see Local Anaesthetic Techniques, p. 1977.2), the type of block, and the site of administration.

The speed of onset and duration of action of local anaesthetics may be increased by the addition of a vasoconstrictor, which has the effect of reducing the uptake of the local anaesthetic into the circulation from the injection site. Solutions containing adrenaline 1 in 200 000 are generally advocated, although higher concentrations such as 1 in 80 000 may be used in dentistry where the total dose is small. The total amount of adrenaline injected should not exceed 500 micrograms although the amount of adrenaline absorbed varies considerably with the site of injection; some consider that the maximum dose should be 200 micrograms. Other vasoconstrictors including noradrenaline are also used, but the 2002 *Dental Practitioners' Formulary* in the UK considered that noradrenaline should not be used since it presented no advantages and when given at relatively high concentrations had occasionally been associated with severe hypertensive episodes. Vasoconstrictors should not be used when producing a nerve block in an appendage such as a digit, as gangrene may occur. Vasoconstrictors have been added to injections for spinal block, but their use is not recommended because of the danger of reducing the blood supply to the spinal cord.

Local anaesthetics are generally given as acidic solutions of the water-soluble hydrochloride salts; alkalinisation of these solutions or formulation as a carbonated base may increase the speed of onset (below).

The dosage of individual local anaesthetics depends on the injection site and the procedure used. The smallest effective dose and the lowest effective concentration should be used. Smaller doses are usually needed in the elderly, in children, in debilitated patients, and in cardiac disease. Doses should also be reduced in the presence of hepatic disease. Meticulous attention to technique is essential particularly in nerve block and spinal procedures. Injections for central nerve blocks, such as epidural (including caudal block) and spinal block should not contain preservatives.

Action. The intrinsic vasoactivity of a local anaesthetic can influence its rate of removal from the site of action and therefore its duration of action. Ester-type local anaesthetics such as tetracaine and procaine are more likely to produce vasodilatation than amide-type local anaesthetics such as cinchocaine, lidocaine, mepivacaine, and prilocaine after intradermal doses.[1] However, cocaine differs from other ester-type local anaesthetics in that it produces vasoconstriction. The amide-type local anaesthetics can produce vasoconstriction but, apart from prilocaine, their vasoconstrictor activity has generally been found to decline with increasing concentration,[1,2] and, in a study, lidocaine and bupivacaine produced more vasodilatation than vasoconstriction at the higher concentrations tested.[2] Mepivacaine has produced greater and more consistent vasoconstriction than lidocaine, cinchocaine, or prilocaine after intradermal injection[1] but this greater vasoactivity is not always evident.[3]

1. Willatts DG, Reynolds F. Comparison of the vasoactivity of amide and ester local anaesthetics: an intradermal study. *Br J Anaesth* 1985; **57:** 1006–11.
2. Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lignocaine. *Br J Anaesth* 1976; **48:** 1171–4.
3. Goebel WM, *et al.* Comparative circulatory levels of 2 per cent mepivacaine and 2 per cent lignocaine. *Br Dent J* 1980; **148:** 261–4.

Administration. Systemic toxic effects of local anaesthetics are related to blood concentrations and, as absorption varies considerably according to the site of injection, it has been suggested[1,2] that recommendation of a single maximum dose without regard to the site of the procedure is meaningless. If a plasma-lidocaine concentration of 5 micrograms/mL were required for toxicity then this would be achieved by injection of 300 mg in the intercostal area, 500 mg epidurally, 600 mg in the region of the brachial plexus, or 1 g subcutaneously. The reduction of peak concentrations obtained by the addition of adrenaline was also dependent on the site of injection. Furthermore, most cases of severe toxicity did not result from overdosage but from inadvertent intravascular injection or too rapid injection.

1. Scott DB. "Maximum recommended doses" of local anaesthetic drugs. *Br J Anaesth* 1989; **63:** 373–4.
2. Scott DB. Safe use of lignocaine. *BMJ* 1989; **299:** 56.

CARBONATED SOLUTIONS. The use of carbonated solutions of local anaesthetics instead of the usual hydrochloride salts has been discussed in several reviews.[1-3] Although some early studies indicated that carbonated solutions of bupivacaine, lidocaine, or prilocaine produced earlier onset of anaesthesia and improved the quality of epidural or brachial plexus blocks not all subsequent studies have confirmed these results. A method for preparing carbonated solutions has been published[4] but proprietary preparations of such solutions of bupivacaine or lidocaine may be available in some countries.

1. Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986; **58:** 701–16.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
3. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; **65:** 225–33.
4. Bromage PR. Improved conduction blockade in surgery and obstetrics: carbonated local anesthetics. *Can Med Assoc J* 1967; **97:** 1377–84.

PH OF SOLUTIONS. The pain associated with infiltration of local anaesthetics can be reduced by buffering the solution to physiological pH with sodium bicarbonate.[1,2] Although buffering itself does not appear to compromise the efficacy of anaesthesia,[2] alkalinisation of the solution may reduce the solubility of the local anaesthetic and cause precipitation.[2-4] To enhance stability local anaesthetic solutions are usually prepared at an acidic pH and it is therefore recommended that if solutions are buffered they should be used immediately.[2] (Solutions containing adrenaline require an acidic pH.)

Similar pH adjustments of solutions for intravenous regional anaesthesia have been reported to reduce the amount of local venous irritation and thrombophlebitis[5] and to increase the speed of onset and the duration of the block.[6] However, it has been noted that at alkaline pH lidocaine can lower surface tension, thereby altering drop size and potentially resulting in a decreased dose if such solutions are infused via a drop counting device rather than a volume pump.[7] Alkalinisation of a solution used for epidural block for caesarean section has been reported to result in a more rapid onset of action and denser block.[8]

Alkalinisation has also been used to hasten the onset of peripheral nerve block[9] by increasing the proportion of the lipid-soluble nonionised free base but the effect in epidural block has been inconsistent.[10,11]

1. McKay W, *et al.* Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. *Anesth Analg* 1987; **66:** 572–4.
2. Cristoph RA, *et al.* Pain reduction in local anesthetic administration through pH buffering. *Ann Emerg Med* 1988; **17:** 117–20.
3. Nakano NI. Temperature-dependent aqueous solubilities of lidocaine, mepivacaine, and bupivacaine. *J Pharm Sci* 1979; **68:** 667–8.
4. Bourget P, *et al.* Factors influencing precipitation of pH-adjusted bupivacaine solutions. *J Clin Pharm Ther* 1990; **15:** 197–204.
5. Yudenfreund SM, *et al.* pH-Buffered 2-chloroprocaine for intravenous regional anesthesia. *DICP Ann Pharmacother* 1989; **23:** 614–15.
6. Armstrong P, *et al.* Effect of alkalinization of prilocaine on IV regional anaesthesia. *Br J Anaesth* 1989; **63:** 625P–626P.
7. Leor R, *et al.* The influence of pH on the intravenous delivery of lidocaine solutions. *Eur J Clin Pharmacol* 1990; **39:** 521–3.
8. Fernando R, Jones HM. Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural caesarean section. *Br J Anaesth* 1991; **67:** 699–703.
9. Coventry DM, Todd JG. Alkalinization of bupivacaine for sciatic nerve blockade. *Br J Anaesth* 1989; **62:** 227P.
10. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
11. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; **65:** 225–33.

Anorectal disorders. See under Surface Anaesthesia, p. 1977.3.

Cough. Drugs such as lidocaine or bupivacaine have been given by inhalation in severe intractable cough (p. 1651.2), including cough caused by malignant neoplasms.[1-4] Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, nebulised local anaesthetics should be used in controlled circumstances only; there may also be temporary loss of the swallowing reflex.

Intravenous lidocaine has also been tried for the prevention of fentanyl-induced cough.[5-7]

1. Howard P, *et al.* Lignocaine aerosol and persistent cough. *Br J Dis Chest* 1977; **71:** 19–24.
2. Stewart CJ, Coady TJ. Suppression of intractable cough. *BMJ* 1977; **i:** 1660–1.
3. Sanders RV, Kirkpatrick MB. Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. *JAMA* 1984; **252:** 2456–7.
4. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1741.
5. Lin C-S, *et al.* Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. *Can J Anesth* 2004; **51:** 654–9.
6. Pandey CK, *et al.* Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. *Anesth Analg* 2004; **99:** 1696–8.
7. Pandey CK, *et al.* Intravenous lidocaine 0.5 mg.kg^{-1} effectively suppresses fentanyl-induced cough. *Can J Anesth* 2005; **52:** 172–5.

Endoscopy. Local anaesthetics such as lidocaine are sometimes used before endoscopy to improve patient comfort and facilitate passage of the endoscope. As mentioned in the discussion on drugs used in endoscopy (see p. 1032.3) some consider that the use of local anaesthetics for procedures such as gastrointestinal endoscopy should probably be reserved for those patients who prefer not to be sedated as their use in addition to premedication with opioids or benzodiazepines appears to serve little purpose.

References.

1. Chuah SY, *et al.* Topical anaesthesia in upper gastrointestinal endoscopy. *BMJ* 1991; **303:** 695.
2. Jameson JS, *et al.* Topical anaesthesia improves toleration for upper gastrointestinal endoscopy. *Gut* 1992; **33** (suppl): S51.
3. Randell T, *et al.* Topical anaesthesia of the nasal mucosa for fibreoptic airway endoscopy. *Br J Anaesth* 1992; **68:** 164–7.

Mouth ulceration. For the role of local anaesthetics in the management of mouth ulceration, see p. 1811.2.

Pain. Pain and its general management are discussed on p. 4.1. Local anaesthetics are used in a variety of situations for the management of pain. They are usually given by local injection or applied topically but are sometimes used intravenously in techniques such as intravenous regional anaesthesia, which involves the continuous infusion of local anaesthetics such as lidocaine to produce general

analgesia. However, the technique is potentially dangerous and seldom used.

NERVE BLOCKS. Nerve blocks produce analgesia by interrupting the nervous transmission of pain signals either by temporary inhibition of conduction or by destruction of the nerve. Nerve blocks may be used alone or with analgesics in the management of acute or chronic pain associated with a well-defined anatomical site, especially when the pain is unresponsive to or not adequately controlled by conventional therapy. The route of administration and method used depend on the site to be blocked but may include peripheral nerve block, autonomic nerve blocks such as sympathetic nerve blocks and coeliac plexus block, and central nerve blocks such as epidural (including caudal) and spinal block. **Local anaesthetics** are used when a temporary effect is required. **Neurolytics** such as phenol or alcohol or freezing of the nerve (cryoanalgesia) produce more prolonged block, but even so the effects may last no more than a few months, and the variable and non-selective neural damage produced correlates poorly with pain relief; some consider the risk of complications to outweigh the benefits obtained.[1]

The use of nerve blocks in the *management of cancer* (see Cancer Pain, p. 7.1) has declined following the refinement of the use of conventional analgesics. Some consider that their value may be limited to patients with a life expectancy of 3 months or less[2] and that the main benefit of nerve blocks in cancer is to produce maximum pain relief rapidly. However, others consider that chemical and thermal neurolysis can provide long-term control of severe cancer pain without a substantial incidence of adverse effects.[3] Neurolytic blocks may be of particular value in cancer pain syndromes involving the viscera or the torso, but are rarely applicable in the management of extremity pain.[4] Neuropathic pain is rarely helped by somatic neural block and may even be aggravated,[1] but block of the splanchnic nerves or coeliac plexus with alcohol or phenol is reputed to be effective in relieving severe intractable pain caused by cancer of the pancreas, stomach, small intestine, gallbladder, or other abdominal viscera, especially when the cancer has not spread to the parietal peritoneum.[5]

Similar neurolytic blocks preceded by a local anaesthetic have also been used in patients with *severe intractable pain* of chronic pancreatitis, postcholecystectomy syndrome, or other chronic abdominal visceral diseases unrelieved by medical or surgical therapy.

Central nerve blocks using local anaesthetics with or without **opioids** are used for the *management of acute pain* such as labour pain (p. 8.3) and postoperative pain (p. 6.1) including that in children (p. 5.2); they are also sometimes used for cancer pain.[1,6]

Sympathetic nerve blocks using repeated injections of local anaesthetics or neurolytics have been used for sympathetically maintained pain. Intravenous regional sympathetic block is an alternative when a single limb is involved;[1] guanethidine is one of the drugs that has been used.[7]

Injections of local anaesthetics with or without **corticosteroids** are often used for blocks of localised painful joints. Nerve blocks are also used to block localised painful trigger areas[8] such as postoperative or post-traumatic neuroma formation and for focal muscle pain.

For the role of nerve blocks in the management of low back pain, see p. 9.2.

1. Hanks GW, Justins DM. Cancer pain: management. *Lancet* 1992; **339:** 1031–6.
2. WHO. Cancer pain relief and palliative care: report of a WHO expert committee. *WHO Tech Rep Ser 804*,1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_804.pdf (accessed 11/08/08)
3. American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section. Practice guidelines for cancer pain management. *Anesthesiology* 1996; **84:** 1243–7. Also available at: http://www.asahq.org/publicationsAndServices/cancer.html (accessed 11/08/08)
4. Marshall KA. Managing cancer pain: basic principles and invasive treatments. *Mayo Clin Proc* 1996; **71:** 472–7.
5. Bonica JJ. Management of pain with regional analgesia. *Postgrad Med J* 1984; **60:** 897–904.
6. Hunt R, Massolino J. Spinal bupivacaine for the pain of cancer. *Med J Aust* 1989; **150:** 350.
7. Hannington-Kiff JG. Relief of causalgia in limbs by regional intravenous guanethidine. *BMJ* 1979; **2:** 367–8.
8. Foley KM. The treatment of cancer pain. *N Engl J Med* 1985; **313:** 84–95.

Postherpetic neuralgia. For the role of local anaesthetics in the management of postherpetic neuralgia, see p. 10.3.

Premature ejaculation. A cream containing lidocaine 2.5% and prilocaine 2.5% has been applied topically to the penis for a desensitising effect in the management of premature ejaculation (p. 2350.2). The cream is usually applied to the penis and covered with a condom for a period of time, then washed off before sexual intercourse. It has been reported to increase intravaginal ejaculatory latency time compared with a placebo cream,[1] and a study[2] of different application times found 20 minutes to be the optimum. Longer application times were associated with erection loss because of numbness of the penis, and delayed ejaculation. Decreased vaginal sensitivity in female partners, from residual anaesthetic, has also been reported.[1]

1. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int* 2004; **93:** 1018–21.
2. Atikeler MK, *et al.* Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia* 2002; **34:** 356–9.

Soft-tissue rheumatism. For the adjunctive use of local anaesthetics in the management of soft-tissue rheumatism, see p. 14.2.

Spasticity. The management of spasticity (p. 2014.2) involves physiotherapy and the use of antispastic drugs. Other approaches to treatment include nerve blocks with local anaesthetics; these can improve spasticity but should generally only be used when further muscle relaxation would not increase disability.

Stuttering. Local anaesthetics have been tried in the treatment of stuttering (p. 1078.1).

Local Anaesthetic Techniques

Local anaesthetics are used in several techniques. In order of increasing level of anaesthesia they are:

- surface or topical anaesthesia
- infiltration anaesthesia
- regional nerve block, including peripheral nerve block, sympathetic nerve block, and central nerve block, which includes epidural and spinal (intrathecal or subarachnoid) block

Local anaesthetics may also be given intravenously for regional anaesthesia in the extremities.

Infiltration anaesthesia

Infiltration anaesthesia is produced by injection of a local anaesthetic such as lidocaine or bupivacaine directly into and around the field of operation without attempting to identify individual nerves. The drug used should not be absorbed too rapidly otherwise the anaesthesia will wear off too quickly for practical use; some local anaesthetics require the addition of a vasoconstrictor in low concentrations, which can increase the duration of infiltration anaesthesia and reduce peak plasma concentrations of the local anaesthetic. Infiltration anaesthesia is extensively used in dentistry.

Anaesthesia of small areas by infiltration techniques requires a relatively large amount of local anaesthetic, which is not a problem for minor surgery but would be for more extensive areas that required anaesthesia. The amount of local anaesthetic used can be reduced and the duration of anaesthesia increased by blocking specific nerves that innervate the area. This may be carried out at several levels. In *field block* anaesthesia subcutaneous injection of a local anaesthetic close to the nerves around the area to be anaesthetised blocks sensory nerve paths. This is a form of infiltration anaesthesia, but the technique requires less drug for a given area to be anaesthetised.

Intravenous regional anaesthesia

Intravenous regional anaesthesia (Bier's block) involves injection of a dilute solution of local anaesthetic into a suitable limb vein after exsanguination and application of a tourniquet, in order to produce anaesthesia distal to it. Arterial flow must remain occluded for at least 20 minutes after injection and adrenaline should not be used. Intravenous regional anaesthesia may be used for short procedures where postoperative pain is not marked, such as manipulation of fractures and minor surgical procedures to the limbs. Although a safe procedure when performed correctly, complications have arisen; there have been fatalities associated with the use of bupivacaine, and prilocaine is the drug of choice. Facilities for resuscitation should be available.

Regional nerve block

Regional nerve block anaesthesia involves specific blocks at the levels of major nerves or spinal roots, and may include peripheral nerve block, sympathetic nerve block, and central nerve block including epidural and spinal block. For a discussion of the use of nerve blocks in the management of pain, see Nerve Blocks, above.

Central nerve block. Central nerve block includes epidural and spinal block.

Epidural block (also referred to as *extradural* or *peridural block*) is widely used to provide analgesia or anaesthesia in surgical and obstetric procedures. It involves injecting a local anaesthetic such as lidocaine, bupivacaine, or ropivacaine, alone or with a small dose of an opioid analgesic into the epidural space in the lumbar, sacral (*caudal block*), thoracic, or cervical regions. Introduction of a cannula into the epidural space enables prolonged analgesia or anaesthesia (epidural anaesthesia) to be provided through the use of 'top-up' doses or continuous infusion of the drugs. A vasoconstrictor is sometimes added to reduce systemic exposure to the local anaesthetic. A test dose at the intended injection site is recommended before starting epidural anaesthesia to ensure that the main dose is not accidentally injected intravascularly or into the subarachnoid space.

Spinal block (also referred to as *subarachnoid* or *intrathecal block*) is produced by injecting a solution of a suitable drug such as bupivacaine within the spinal subarachnoid space, causing temporary paralysis of the nerves with which it comes into contact. It may be used, for example, to produce spinal anaesthesia in surgical procedures on the lower body. Vasoconstrictors have been added to prolong the duration of the block but the effect is not always clinically useful and there is a danger of restricting the blood supply to the spinal cord; therefore this practice is not recommended. The somatic level at which anaesthesia occurs depends on many factors including the specific gravity or baricity of the anaesthetic solution used and the positioning of the patient.

For the adverse effects of and precautions for central block, see p. 1978.1 and p. 1979.2, respectively.

Peripheral nerve block. Peripheral nerve block anaesthesia involves injection into or around a peripheral nerve or plexus supplying the part to be anaesthetised; motor fibres may be blocked as well as sensory fibres. *Brachial plexus block* is widely used for procedures involving the arm; lower limb blocks are less simple although *sciatic* and *femoral blocks* may be combined to permit surgery below the knee. Other peripheral nerve blocks such as those for the head and neck, or *intercostal* or *paravertebral blocks* for local anaesthesia of the trunk, are mostly highly specialised techniques. Lidocaine, prilocaine, bupivacaine, or ropivacaine have all been widely used for peripheral nerve blocks. Adrenaline is often added as a vasoconstrictor.

Pudendal block (usually with prilocaine) may be useful in obstetrics before forceps delivery, but as mentioned under Labour Pain on p. 8.3, the technique of *paracervical local anaesthetic block* has largely fallen out of favour because of the high incidence of serious adverse effects on the fetus.

Sympathetic nerve block. Sympathetic nerve block such as *stellate ganglion blockade* and *lumbar sympathectomy* is used in the management of a range of painful conditions and vascular diseases (see under Complex Regional Pain Syndrome on p. 8.1). Temporary block is obtained using local anaesthetics such as lidocaine or bupivacaine but permanent block may be produced with use of neurolytic agents such as phenol (see Pain, p. 1764.1) or alcohol (see Pain, p. 1733.2).

Surface anaesthesia

Surface or topical anaesthesia blocks the sensory nerve endings in the skin or mucous membranes. Many local anaesthetics are effective surface anaesthetics, a notable exception being procaine. Penetration of intact skin by most local anaesthetics is poor whereas absorption through mucous membranes may be rapid. However, reliable percutaneous anaesthesia can be achieved by application of a eutectic mixture of lidocaine and prilocaine to intact skin (see under Surface Anaesthesia in Lidocaine, p. 1989.3). Eutectic mixtures may be of value in providing surface anaesthesia for various minor medical or surgical procedures. Tetracaine also provides reliable percutaneous anaesthesia. Other methods of dermal delivery of local anaesthetics include a transdermal patch of lidocaine (either alone or with tetracaine), and an iontophoretic drug delivery system incorporating lidocaine and adrenaline. Anaesthesia of the skin and subcutaneous tissues is also discussed under Infiltration Anaesthesia, above.

There are several special uses of topical anaesthesia including anaesthetising the cornea during ophthalmological procedures, and the throat and larynx before intubation and bronchoscopy. Absorption from the respiratory tract is rapid and care is essential to avoid giving a toxic dose. Great care is also necessary when using local anaesthetics to anaesthetise the urethra; if trauma has occurred, rapid absorption of the drug may occur and give rise to serious adverse effects.

Local anaesthetics have been included in topical preparations to relieve the pain of haemorrhoids (p. 1808.1) but good evidence of their efficacy is lacking. Similar uses include pain relief in pruritus ani and anal fissure. Excessive application of local anaesthetics to the rectal mucosa should be avoided as absorption can occur; use for periods of no longer than a few days is recommended to prevent sensitisation of the anal skin. Local anaesthetics are sometimes included in topical preparations for the relief of pruritus (p. 1687.3). However, they are only marginally effective and can very occasionally cause sensitisation. The use of local anaesthetics in rubefacient and topical analgesic preparations is mentioned on p. 6.3.

Adverse Effects

Adverse effects apparent after local anaesthesia may be caused by the anaesthetic or errors in technique, or may be the result of blockade of the sympathetic nervous system. Local anaesthetics may produce systemic adverse effects as a result of raised plasma concentrations that occur when the rate of uptake into the circulation exceeds the rate of breakdown, for example, after

- accidental intravascular injection
- excessive or too rapid doses
- absorption of large amounts through mucous membranes or damaged skin
- absorption of large amounts from inflamed or highly vascular areas

The systemic toxicity of local anaesthetics mainly involves the CNS and the cardiovascular system. Excitation of the CNS may be manifested by restlessness, excitement, nervousness, paraesthesias, dizziness, tinnitus, blurred vision, nausea and vomiting, muscle twitching and tremors, and convulsions. Numbness of the tongue and perioral region, and lightheadedness followed by sedation may appear as early signs of systemic toxicity. Excitation when it occurs may be transient and followed by depression with drowsiness, respiratory failure, and coma. There may be effects on the cardiovascular system with myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; arrhythmias and cardiac arrest may occur. Hypotension often accompanies spinal and epidural anaesthesia; inappropriate positioning of the patient may be a contributory factor for women in labour.

Hypersensitivity reactions are rare and generally limited to local anaesthetics of the ester type. There appears to be no cross-sensitivity between ester- and amide-type local anaesthetics. Idiosyncrasy to local anaesthetics has been reported. Hypersensitivity reactions to preservatives in local anaesthetic preparations have also occurred.

Some local anaesthetics cause methaemoglobinaemia.

Fetal intoxication has occurred after the use of local anaesthetics in labour, either as a result of transplacental diffusion or after accidental injection of the fetus.

Prolonged use of topical anaesthetics in the eye causes corneal damage.

Adverse effects may also be caused by vasoconstrictors given with the anaesthetic.

Reviews.

1. McCaughey W. Adverse effects of local anaesthetics. *Drug Safety* 1992; **7:** 178–189.
2. Berde CB. Toxicity of local anesthetics in infants and children. *J Pediatr* 1993; **122** (suppl): S14–S20.
3. Naguib M, *et al.* Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Safety* 1998; **18:** 221–50.
4. Dalens BJ, Mazoit J-X. Adverse effects of regional anaesthesia in children. *Drug Safety* 1998; **19:** 251–68.
5. Cox B, *et al.* Toxicity of local anaesthetics. *Best Pract Res Clin Anaesthesiol* 2003; **17:** 111–36.
6. Fuzier R, *et al.* French Association of Regional Pharmacovigilance Centres. Adverse drug reactions to local anaesthetics: a review of the French pharmacovigilance database. *Drug Safety* 2009; **32:** 345–56.

Adverse effects of central block. Central nerve block (see under Local Anaesthetic Techniques, p. 1977.2), comprising spinal or epidural block, is very widely used and certain adverse effects are particularly associated with the technique. Systemic effects (see Adverse Effects, above) are more likely with epidural than with spinal block, because of the larger doses used.

Total spinal anaesthesia from extreme spread of a block or accidental penetration of the dura during an epidural block produces unconsciousness, hypotension, and respiratory arrest. Less extensive spread to the cervical region is usually associated with nausea, agitation, and hypotension.

Hypotension (associated with venodilatation and decreased cardiac output secondary to sympathetic block) is the **cardiovascular** effect most often associated with the technique, and may be especially problematic in pregnancy. Other cardiovascular complications may include bradycardia or heart block; cardiac arrest has also been reported unexpectedly after spinal anaesthesia.

Post-dural puncture headache (see under Treatment of Adverse Effects, p. 1979.1) is probably the most common **neurological complication** related to these procedures and may be accompanied by tinnitus or photophobia. Headache after spinal block may rarely be caused by meningitis. Backache is a frequent postoperative complication of epidural, spinal, or general anaesthesia. Cranial nerve lesions and reversible loss of hearing in the low frequency range, usually affecting both ears, have been reported rarely following spinal block. Neurological complications associated with these blocks may also rarely include paraplegia caused by arachnoiditis, or trauma or compression of the spinal cord after development of a haematoma or abscess. Transient radicular irritation involving the lower back, buttocks, and thighs may develop within 24 hours of spinal block; recovery is usually within 1 week. Cauda equina syndrome, the symptoms of which include urinary retention, loss of perineal sensation, loss of sexual function, and faecal incontinence, is also a rare complication which can present many months after spinal block. There is some evidence that, although still rare, the incidence of neurotoxic complications after spinal anaesthesia is greater with lidocaine than with other commonly used local anaesthetics such as bupivacaine and tetracaine. The incidence of persistent lumbosacral neuropathy may be as high as 1 in 200 after continuous spinal anaesthesia with lidocaine.

Perioperative shivering has been associated with epidural block.

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1. Kalmanovitch DVA, Simmons P. Post-anaesthetic complications in the home. *Prescribers' J* 1988; **28:** 124–31.
2. Wildsmith JAW, Lee JA. Neurological sequelae of spinal anaesthesia. *Br J Anaesth* 1989; **63:** 505–7.
3. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anaesthesia. *Drug Safety* 1990; **5:** 179–94.
4. Anonymous. Perioperative shivering. *Lancet* 1991; **338:** 547–8.
5. Broome IJ. Hearing loss and dural puncture. *Lancet* 1993: **341:** 667–8.
6. Russell R, *et al.* Assessing long term backache after childbirth. *BMJ* 1993; **306:** 1299–1303.
7. Harding SA, *et al.* Meningitis after combined spinal-extradural anaesthesia in obstetrics. *Br J Anaesth* 1994; **73:** 545–7.
8. Gielen M. Spinal anaesthesia: hearing loss, failure, transient radicular irritation. *Anaesthesia* 1998; **53** (suppl 2): 23–5.
9. Horlocker TT, Wedel DJ. Neurologic complications of spinal and epidural anesthesia. *Reg Anesth Pain Med* 2000; **25:** 88–98.
10. Johnson ME. Potential neurotoxicity of spinal anesthesia with lidocaine. *Mayo Clin Proc* 2000; **75:** 921–32.
11. Zaric D, Pace NL. Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 24/12/09).

Effects on the ears. Symptoms such as vertigo, nausea, and nystagmus, which have been reported after the use of local anaesthetics in the external[1] or middle ear,[2] may result from penetration of the local anaesthetic into the inner ear. For reference to hearing disturbances associated with spinal block, see under Adverse Effects of Central Block, above.

1. Raine NMN, Whittet HB. Emla cream and induced vertigo. *Br J Hosp Med* 1994; **51:** 614–15.
2. Blair Simmons F, *et al.* Lidocaine in the middle ear: a unique cause of vertigo. *Arch Otolaryngol* 1973; **98:** 42–3.

Effects on the joints. Between 2006 and 2008, the FDA[1] received 35 reports of chondrolysis (mainly in the shoulder) occurring in postoperative patients after the unlicensed use of continuous intra-articular infusions of local anaesthetics via elastomeric infusers. Of these, 30 had received bupivacaine (with or without adrenaline), 2 had received bupivacaine and ropivacaine, and 2 had received bupivacaine as a single injection with an intra-articular infusion of lidocaine. The average infusion time was between 48 and 72 hours. Symptoms of chondrolysis appeared as early as 2 months (median of 5 months), and diagnosed within a median of 8.5 months, after infusion. A further 4 reports have subsequently been received. Similar reports have also been received by Health Canada.[2]

1. FDA. Information for healthcare professionals: chondrolysis reported with continuously infused local anesthetics (marketed as bupivacaine, chlorprocaine, lidocaine, mepivacaine, procaine and ropivacaine) (issued 13th November, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190302.htm (accessed 06/08/10)
2. Health Canada. Local anesthetic infusion with postoperative pain pumps and articular chondrolysis. *Can Adverse React News* 2009; **19** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n1-eng.php#ar1 (accessed 24/12/09)

Effects on wound healing. A review of the literature[1] found evidence that local infiltration of local anaesthetics can have detrimental effects on the first two stages of wound healing. The size of the effect on mature wound strength remains to be determined.

1. Brower MC, Johnson ME. Adverse effects of local anesthetic infiltration on wound healing. *Reg Anesth Pain Med* 2003; **28:** 233–40.

Hypersensitivity. Local anaesthetics may provoke types I and IV hypersensitivity reactions. Type I reactions (e.g. anaphylaxis) to local anaesthetics are generally rare. They occur more often with the ester-type than with the amide-type drugs, probably because of the metabolism of the former to para-aminobenzoic acid (PABA). Nevertheless, severe or fatal reactions have been associated not only with ester-type local anaesthetics such as tetracaine[1] and procaine[2] but also with the amide-type local anaesthetics lidocaine[3-7] and prilocaine.[3] Intolerance may also have been the cause of death in a patient who received mepivacaine for paracervical anaesthesia.[8] Hypotension during dental anaesthesia is usually a vasovagal response unrelated to the type of local anaesthetic used and may be prevented by the use of diazepam. Patients sensitised by topical application may then develop anaphylactic reactions when treated systemically.[9] The use of drugs such as benzocaine or tetracaine in lozenges or throat sprays may also sensitise patients.[10]

Some patients diagnosed as being hypersensitive to local anaesthetics may have reacted to preservatives in the preparations.[11] Cross-hypersensitivity reactions may also occur between some ester-type local anaesthetics and topical preparations, such as sunscreens, that contain PABA or related compounds.[12]

Skin testing may be of benefit in patients who will require future local anaesthesia and when a patient's history does not rule out a possible allergic reaction. However, testing itself can cause severe or anaphylactic reactions.[9,13]

Type IV reactions (i.e. delayed reactions) to local anaesthetics have also been reported, albeit rarely.[14-17]

For reports of the incidence of allergy to local anaesthetics determined by patch testing, see under individual monographs.

1. Moriwaki K, *et al.* A case report of anaphylactic shock induced by tetracaine used for spinal anesthesia. *Masui* 1986; **35:** 1279–84.
2. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; **i:** 355.
3. Fisher MM, Pennington JC. Allergy to local anaesthesia. *Br J Anaesth* 1982; **54:** 893–4.
4. Howard JJ, *et al.* Adult respiratory distress syndrome following administration of lidocaine. *Chest* 1982; **81:** 644–5.
5. Promisloff RA, DuPont DC. Death from ARDS and cardiovascular collapse following lidocaine administration. *Chest* 1983; **83:** 585.
6. Ruffles SP, Ayres JG. Fatal bronchospasm after topical lignocaine before bronchoscopy. *BMJ* 1987; **294:** 1658–9.
7. Ball IA. Allergic reactions to lignocaine. *Br Dent J* 1999; **186:** 224–6.
8. Grimes DA, Cates W. Deaths from paracervical anesthesia used for first-trimester abortion, 1972–1975. *N Engl J Med* 1976; **295:** 1397–9.
9. Mulvey PM. Allergy to local anaesthetics. *Med J Aust* 1980; **1:** 386.
10. Verbov J. Drug eruptions. *Practitioner* 1979; **222:** 400–9.
11. Wildsmith JAW, *et al.* Alleged allergy to local anaesthetic drugs. *Br Dent J* 1998; **184:** 507–10.
12. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anesthesia. *Drug Safety* 1990; **5:** 179–94.
13. Brown DT, *et al.* Allergic reaction to an amide local anaesthetic. *Br J Anaesth* 1981; **53:** 435–7.
14. Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. *Contact Dermatitis* 1991; **25:** 45–8.
15. Craft DV, Good RP. Delayed hypersensitivity reaction of the knee after injection of arthroscopy portals with bupivacaine (Marcaine). *Arthroscopy* 1994; **10:** 305–8.
16. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; **34:** 387–9.
17. Ban M, Hattori M. Delayed hypersensitivity due to epidural block with ropivacaine. *BMJ* 2005; **330:** 229.

Methaemoglobinaemia. Methaemoglobinaemia has been reported with several local anaesthetics including tetracaine,[1] benzocaine,[1-6] and lidocaine[1,7] but is more commonly associated with the use of prilocaine.[8-11] It may occur after local injection or topical use. It has been suggested that the effect is due to the presence of an aniline group in the structure or, in the case of lidocaine and prilocaine, metabolism to an aniline-like structure. Methaemoglobinaemia may result from the use of usual doses as well as exposure to toxic concentrations of local anaesthetic;[1,10] with prilocaine doses of 8 mg/kg or more [above recommended maxima] usually produce symptoms.[12]

Methaemoglobinaemia has occurred after the topical application of a eutectic preparation of prilocaine and lidocaine.[8,11] Although increases in methaemoglobin concentrations are generally small after the use of this mixture in infants[13,14] and children,[15] some infants may be particularly susceptible to induced methaemoglobinaemia during the first 3 months of life probably due to their limited enzyme capacity.[13] In some countries, including the UK and USA, the cream is licensed for limited use in neonates (see also Surface Anaesthesia under Lidocaine, p. 1989.3).

Use with drugs such as sulfonamides[8] or antimalarials[12] may predispose to methaemoglobinaemia. Patients with haemoglobinopathies or G6PD deficiency may also be at greater risk.[1]

1. Olson ML, McEvoy GK. Methemoglobinemia induced by local anesthetics. *Am J Hosp Pharm* 1981; **38:** 89–93.
2. Rodriguez LF, *et al.* Benzocaine-induced methemoglobinemia: report of a severe reaction and review of the literature. *Ann Pharmacother* 1994; **28:** 643–9.
3. Tush GM, Kuhn RJ. Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother* 1996; **30:** 1251–4.
4. LeClaire AC, *et al.* Methemoglobinemia secondary to topical benzocaine use in a lung transplant patient. *Ann Pharmacother* 2005; **39:** 373–6.
5. FDA. FDA Public Health Advisory: benzocaine sprays marketed under different names, including Hurricaine, Topex, and Cetacaine (issued 10th February, 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124350.htm (accessed 06/08/10)
6. Dahshan A, Donovan GK. Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. Abstract: *Pediatrics* 2006; **117:** 1415–16. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/4/e806 (accessed 24/12/09)
7. Karim A, *et al.* Methemoglobinemia complicating topical lidocaine used during endoscopic procedures. *Am J Med* 2001; **111:** 150–3.
8. Jakobson B, Nilsson A. Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole: a case report. *Acta Anaesthesiol Scand* 1985; **29:** 453–5.
9. Mandel S. Methemoglobinemia following neonatal circumcision. *JAMA* 1989; **261:** 702.
10. Knobeloch L, *et al.* CDC. Prilocaine-induced methemoglobinemia—Wisconsin, 1993. *MMWR* 1994; **43:** 655–7.
11. Parker JF, *et al.* EMLA toxicity after application for allergy skin testing. *Pediatrics* 2004; **113:** 410–11.
12. Reynolds F. Adverse effects of local anaesthetics. *Br J Anaesth* 1987; **59:** 78–95.
13. Nilsson A, *et al.* Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth* 1990; **64:** 72–6.

14. Brisman M, *et al.* Methaemoglobin formation after the use of EMLA cream in term neonates. *Acta Paediatr* 1998; **87:** 1191–4.
15. Frayling IM, *et al.* Methaemoglobinaemia in children treated with prilocaine-lignocaine cream. *BMJ* 1990; **301:** 153–4.

Pregnancy. As mentioned under Adverse Effects of Central Block, p. 1978.1, hypotension may be particularly problematic for patients receiving epidural or spinal block for analgesia during labour. In addition it has been suggested that patients receiving epidural analgesia during labour may have an increased risk of pyrexia, which can lead to fetal compromise.[1]

The use of paracervical block has fallen out of favour because of serious adverse effects on the fetus.

1. Fusi L, *et al.* Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; **i:** 1250–2.

Treatment of Adverse Effects

At the first signs of local anaesthetic toxicity from parenteral dosage, the injection should be stopped; in some cases it may also be possible to apply a tourniquet to limit further systemic absorption. Subsequent management, regardless of the route, is supportive. If systemic reactions develop, steps should be taken to maintain the circulation and respiration and to control convulsions. A patent airway must be established and oxygen given, with assisted ventilation if necessary. The circulation should be maintained with infusions of intravenous fluids. Vasopressors have been suggested in the treatment of marked hypotension although their use is accompanied by a risk of CNS excitation. Ephedrine is preferred for the management of hypotension associated with spinal or epidural block, particularly in pregnancy. Cardiotoxicity, particularly with some local anaesthetics such as bupivacaine, may be refractory (for the suggested use of lipid emulsions see Soya Oil, p. 2093.1). Vasopressors should not be given to patients receiving oxytocic drugs. Convulsions may be controlled with intravenous benzodiazepines such as diazepam although these drugs may also depress respiration and the circulation. Intravenous phenobarbital is used for persistent convulsions.

Methaemoglobinaemia may be treated with intravenous methylthioninium chloride.

Post-dural puncture headache. Headache after puncture of the dura mater during procedures such as lumbar puncture or central nerve blocks is thought to be caused by subsequent leakage of CSF. The incidence of such post-dural puncture headache is significantly reduced by the use of small, blunt needles, which produce a smaller hole in the dura and separate its fibres rather than cutting them.

When treatment is necessary conservative therapy such as analgesics and hydration will relieve symptoms in the majority of patients with mild post-dural puncture headache within 1 to 2 days. Bed rest does not reduce the incidence but once headache develops the patient may feel some relief when recumbent. If the headache persists for a further 24 hours measures such as epidural saline or dextran 40 or the use of intravenous caffeine and sodium benzoate may be effective; oral caffeine has also been shown to be of benefit. However, perhaps the most widely favoured measure, despite a lack of good evidence, is the epidural injection of autologous blood to form a blood patch over the dural puncture. There have been anecdotal reports of success using corticotropin or tetracosactide but such reports of relief with sumatriptan were not confirmed by a controlled study.

References.

1. Choi A, *et al.* Pharmacologic management of postdural puncture headache. *Ann Pharmacother* 1996; **30:** 831–9.
2. Broadley SA, Fuller GN. Lumbar puncture needn't be a headache. *BMJ* 1997; **315:** 1324–5.
3. Serpell MG, *et al.* Prevention of headache after lumbar puncture: questionnaire survey of neurologists and neurosurgeons in United Kingdom. *BMJ* 1998; **316:** 1709–10.
4. Evans RW, *et al.* Assessment: prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2000; **55:** 909–14. Also available at: http://www.neurology.org/cgi/reprint/55/7/909.pdf (accessed 11/08/08)
5. Boonmak P, Boonmak S. Epidural blood patching for preventing and treating post-dural puncture headache. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 06/08/10).
6. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth* 2003; **91:** 718–29.
7. Armon C, Evans RW. Addendum to assessment: prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005; **65:** 510–12. Also available at: http://www.neurology.org/cgi/reprint/65/4/510.pdf (accessed 11/08/08)

Precautions

As with any drug local anaesthetics are contra-indicated in patients with known hypersensitivity. However, it might be possible to avoid reactions by using a local anaesthetic of the alternative chemical type. Facilities for resuscitation should be available when local anaesthetics are given parenterally.

Local anaesthetics should not be used in patients with complete heart block. They should be given cautiously to the elderly, to the debilitated, to children, and to patients with epilepsy, impaired cardiac conduction or respiratory function, shock, or hepatic impairment; patients with myasthenia gravis are particularly susceptible to the effects of local anaesthetics. Ester-type local anaesthetics are contra-indicated in patients with low plasma-cholinesterase concentrations. Techniques such as epidural or spinal block should not be used in patients with cerebrospinal diseases, cardiogenic or hypovolaemic shock, or altered coagulation status. Because of the risk of transmitting infection into the CNS these techniques should not be employed where there is pyogenic infection of the skin at or adjacent to the injection site.

Because of the risk of systemic adverse effects when local anaesthetics are absorbed too rapidly, they should not be injected into or applied to inflamed or infected tissues or to damaged skin or mucosa. For similar reasons, the rate of injection should not be too rapid and great care must be taken to avoid inadvertent intravascular injection. The risk of adverse effects from the uptake of local anaesthetics into the circulation may be reduced by the inclusion of adrenaline to produce vasoconstriction, but the lowest effective concentration of adrenaline should be used. Solutions containing adrenaline should not, however, be used for producing anaesthesia in appendages such as digits, because the profound ischaemia that follows may lead to gangrene. Mepivacaine and prilocaine tend to produce less vasodilatation at low concentrations than other local anaesthetics and may be useful where the addition of vasoconstrictors is contra-indicated (but see also under Action, p. 1976.2).

When used in the mouth or throat, local anaesthetics may impair swallowing and increase the risk of aspiration. Patients who have received local anaesthetics for procedures such as laryngoscopy or tracheoscopy should be cautioned not to eat or drink for at least 3 to 4 hours after the anaesthetic.

The cornea may be damaged by prolonged topical application of local anaesthetics, particularly cocaine. Patients should be warned not to rub or touch the eye while anaesthesia persists and the anaesthetised eye should be protected from dust and bacterial contamination.

Local anaesthetics may be ototoxic and should not be instilled into the middle ear.

The application of local anaesthetics to the skin for prolonged periods or to extensive areas should be avoided.

Precautions for central block. Epidural or spinal block may rarely result in paraplegia caused by an induced haematoma or abscess, and have thus been considered unsuitable in patients with pre-existing neurological disease, infection at the puncture site, or blood disorders, or in those receiving aspirin or full-dose anticoagulant therapy. Such therapy may be stopped at an appropriate time before surgery if central block is planned. It is necessary to balance the risk of withholding anticoagulation against the risk of bleeding in the individual patient. Epidural or spinal block in patients given low-dose anticoagulant therapy to prevent postoperative deep-vein thrombosis is still controversial. For further discussion and recommendations see Spinal Anaesthesia, p. 1400.1.

A study in the USA[1] involving 891 patients found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia compared with placebo; it was considered that the recommendation to stop aspirin 7 to 10 days before delivery was unjustified.

1. Sibai BM, *et al.* Low-dose aspirin in correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; **172:** 1553–7.

Inappropriate use. The FDA[1] has expressed concern over the inappropriate use of topical local anaesthetics, such as lidocaine gel, which can lead to excessive systemic absorption and cause life-threatening adverse effects such as irregular heartbeat, seizures, breathing difficulties, and coma. Such use may include applying too much, applying to a large area of skin or to irritated or broken skin, or covering the skin with a wrap or using a heating pad after application. The FDA[2] has also warned against the use of standardised compounded creams that often contain high doses, and/or a combination, of local anaesthetics after 2 deaths due to improper use of a compounded lidocaine and tetracaine cream before laser hair removal were reported.[3]

For details of inappropriate intra-articular use, see Effects on the Joints, p. 1978.2.

1. FDA. Public Health Advisory: potential hazards of skin products containing numbing ingredients for relieving pain from mammography and other medical tests and conditions (issued 16th January, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm110625.htm (accessed 26/05/10)
2. FDA. News Release: FDA warns five firms to stop compounding topical anesthetic creams (issued 5th December, 2006). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108793.htm (accessed 26/05/10)
3. FDA. Public Health Advisory: life-threatening side effects with the use of skin products containing numbing ingredients for cosmetic procedures (issued 6th February, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm054718.htm (accessed 26/05/10)

Tachyphylaxis. The effect of successive epidural injections of 2% solutions of lidocaine, mepivacaine, or prilocaine was reduced by 25 to 30% with each injection when the interval between the disappearance of analgesia and re-injection was more than 10 minutes but anaesthesia was augmented if this interval was less than 10 minutes.[1] Such tachyphylaxis, associated with the prolonged epidural use of all local anaesthetics, has also been reviewed.[2]

1. Bromage PR, *et al.* Tachyphylaxis in epidural analgesia 1: augmentation and decay of local anesthesia. *J Clin Pharmacol* 1969; **9:** 30–8.
2. Mogensen T. Tachyphylaxis to epidural local anaesthetics. *Dan Med Bull* 1995; **42:** 141–6.

Test dose. A test dose is recommended in epidural block to check for accidental intravenous or intrathecal injection but negative results should be treated with caution.[1] Accidental intravenous placement of the needle is notoriously more difficult to detect than inadvertent subarachnoid placement. Adrenaline has been added to the test solution to aid detection of intravenous injection but is considered by some to be of little value.[2,3]

1. Scott DB. Test doses in extradural block. *Br J Anaesth* 1988; **61:** 129–30.
2. Thornburn J. Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia. *Br J Anaesth* 1989; **62:** 578–81.
3. Narchi P, *et al.* Heart rate response to a niv test dose of adrenaline and lignocaine with and without atropine pretreatment. *Br J Anaesth* 1991; **66:** 583–6.

Interactions

The metabolism of ester-type local anaesthetics may be inhibited by anticholinesterases, increasing the risk of systemic toxicity.

Ester derivatives such as tetracaine, benzocaine, or procaine that are hydrolysed to para-aminobenzoic acid may antagonise the activity of aminosalicylic acid or sulfonamides. Ester-type local anaesthetics such as procaine and cocaine that are hydrolysed by plasma cholinesterase may competitively enhance the neuromuscular blocking activity of suxamethonium; the amide local anaesthetic, lidocaine may have a similar effect.

There is an increased risk of myocardial depression when amide-type local anaesthetics such as bupivacaine, levobupivacaine, lidocaine, or ropivacaine are given with antiarrhythmics.

If local anaesthetics containing adrenaline are given for epidural or paracervical block during labour the use of an oxytocic drug post partum may lead to severe hypertension. Although there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and MAOIs or tricyclic antidepressants, great care should nevertheless be taken to avoid inadvertent intravenous doses of the local anaesthetic preparation.

For further details of interactions between local anaesthetics and other drugs, see under individual monographs.

Pharmacokinetics

Most local anaesthetics are readily absorbed through mucous membranes, and through damaged skin. Local anaesthetics are weak bases and at tissue pH can diffuse through connective tissue and cellular membranes to reach the nerve fibre where ionisation can occur.

Anaesthetics of the ester type are hydrolysed by esterases in the plasma and, to a lesser extent, in the liver. The effect of spinal anaesthetics lasts until the drug is taken up into the blood circulation since there is little esterase in the spinal fluid.

Amide-type anaesthetics are metabolised in the liver and, in some cases, the kidneys. While there is little protein binding with most ester-type anaesthetics, the amide types are considerably bound.

References.

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
3. Smith C. Pharmacology of local anaesthetic agents. *Br J Hosp Med* 1994; **52:** 455–60.
4. Mazoit J-X, Dalens BJ. Pharmacokinetics of local anaesthetics in infants and children. *Clin Pharmacokinet* 2004; **43:** 17–32.

Amylocaine Hydrochloride *(BANM)*

Amilocaína, hidrocloruro de; Amyleinii Chloridum; Amylocain. Hydrochlor.; Chlorhydrate d'Amyléine; Амилокаина Гидрохлорид.

(*RS*)-1-(Dimethylaminomethyl)-1-methylpropyl benzoate hydrochloride.

$C_{14}H_{21}NO_2$,HCl=271.8

CAS — 532-59-2 (amylocaine hydrochloride); 644-26-8 (amylocaine hydrochloride).
UNII — 224EF0K14Q.

Profile

Amylocaine, a benzoic acid ester, is a local anaesthetic (p. 1976.1) used mainly as the hydrochloride in a range of preparations for application to the skin or mucous membranes. It has also been used in preparations for the relief of painful anorectal conditions and has been included in oral mixtures for the relief of coughs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Dolodent.

Multi-ingredient Preparations. ***Belg.***: Dentophar†; Rectovasol; ***Braz.***: Fonergin; Hemodotti†; ***Cz.***: Avenoc†; ***Fr.***: Avenoc; Dentobaume; Elenol†; Paracamf; Pulmoll†; Sedaplaie†; ***Hong Kong***: Frazoline†; ***Ital.***: Dentinale; Proctosedyl; ***Mon.***: Bronchodermine; ***Thai.***: Bacal; Basina; Citacin; Izac; Lobacin; Medcin†; Mybacin; Novacin; Thrody.

Homoeopathic Preparations. ***Canad.***: Avenoc†; ***Port.***: Avenoc†.

Articaine Hydrochloride *(BANM, USAN, rINNM)*

40045; Articaína, hidrocloruro de; Articaïne, Chlorhydrate d'; Articainhydrochlorid; Articaini Hydrochloridum; Artikaiinihydrokloridi; Artikain Hidroklorür; Artikain-hidroklorid; Artikainhydrochlorid; Artikainhydroklorid; Artikaino hidrochloridas; Carticaine Hydrochloride; Carticaini Hydrochloridum; Hidrocloruro de articaína; Hoe-045; Karticainhydroklorid; Kartikaiinihydrokloridi; Kartikain Hidroklorür; Артикаина Гидрохлорид.

Methyl 4-methyl-3-(2-propylaminopropionamido)thiophene-2-carboxylate hydrochloride.

$C_{13}H_{20}N_2O_3S,HCl$=320.8

CAS — 23964-58-1 (articaine); 23964-57-0 (articaine hydrochloride).
ATC — N01BB08.
ATC Vet — QN01BB08.
UNII — QS9014Q792.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Articaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Articaine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol. Protect from light.

Profile

Articaine hydrochloride is an amide local anaesthetic (p. 1976.1). It has been used as a 1 or 2% solution with or without adrenaline for infiltration and regional anaesthesia. A 4% solution of articaine hydrochloride with adrenaline is used similarly in dentistry. A hyperbaric solution of articaine hydrochloride with glucose has been used for spinal block.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies articaine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bucanest; Deltazine; Septanest; ***Austria***: Septanest; Sopira Citocartin; Ubistesin; Ultracain Dental; ***Canad.***: Astracaine†; Septanest; Ultracaine D-S; Zorcaine; ***China***: Primacaine Adrenaline (必兰); ***Cz.***: Septanest S; Supracain; Ubistesin; ***Denm.***: Dentocaine; Septanest; Septocaine; Sopira Citocartin; Ubistesin; ***Fin.***: Dentocaine; Septocaine; Ubistesin; Ultracain D-Suprarenin; ***Fr.***: Alphacaine; Articadent; Artinibsa; Bucanest†; Deltazine; Primacaine; Septanest; Ubistesin Adrenalinee; ***Ger.***: Sopira Citocartin; Ubistesin; Ultracain D-S; Ultracain Suprarenin; Ultracain; ***Gr.***: Artikamine; Septanest; Ubistesin; ***Hong Kong***: Ubistesin; ***Hung.***: Ubistesin; Ultracain D-S; ***Irl.***: Espestesin; ***Israel***: Septanest; Ubistesin; ***Ital.***: Alfacaina; Cartidont; Citocartin; Sarticain; Septanest; Ubistesin; ***Neth.***: Citocartin; Loncarti; Septanest; Ubistesin; Ultracain D-S; ***Norw.***: Septocaine; ***NZ***: Septanest; Ubistesin; ***Port.***: Alphacaine†; Artinibsa; Artinostrum; Meganest; Septanest; Ubistesin; ***Rus.***: Alphacaine (Альфакаин); Artifrin (Артифрин); Brilocaine (Брилокаин); Citocartin (Цитокартин); Primacaine Adrenaline (Примакаин С Адреналином); Septanest (Септанест); Ubistesin (Убистезин); Ultracain (Ультракаин); ***Singapore***: Ubistesin; ***Spain***: Artinibsa; Meganest; Septanest; Ubistesin; Ultracain; ***Swed.***: Septocaine; Ubistesin; ***Switz.***: Alphacaine; Rudocain; Septanest; Ubistesin; Ultracaine D-S; ***Turk.***: Ultracain; ***UK***: Septanest; ***Ukr.***: Artifrin (Артифрин); Ultracain D-S (Ультракаин Д-С); ***USA***: Orabloc; Septocaine.

Pharmacopoeial Preparations
USP 36: Articaine Hydrochloride and Epinephrine Injection.

Benzocaine *(BAN, rINN)*

Anaesthesinum; Anestezin; Anesthamine; Bensokain; Bentsokaiini; Benzocain; Benzocaína; Benzocaïne; Benzocainum; Benzokain; Benzokaina; Benzokainas; Ethoform; Éthoforme; Ethyl Aminobenzoate; Ethylis Aminobenzoas; Бензокаин.

Ethyl 4-aminobenzoate.

$C_9H_{11}NO_2$=165.2

CAS — 94-09-7.
ATC — C05AD03; D04AB04; N01BA05; R02AD01.
ATC Vet — QC05AD03; QD04AB04; QN01AX92; QN01BA05; QR02AD01.
UNII — U3RSY48JW5.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of benzocaine:

Coco snow; Procrystal; Pro-crystal.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Benzocaine). Colourless crystals or a white or almost white, crystalline powder. M.p. 89 degrees to 92 degrees. Very slightly soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Benzocaine). Small, white crystals or a white odourless crystalline powder. M.p. 88 degrees to 92 degrees. Soluble 1 in 2500 of water, 1 in 5 of alcohol, 1 in 2 of chloroform, 1 in 4 of ether, and 1 in 30 to 50 of almond oil or olive oil; dissolves in dilute acids.

Uses and Administration

Benzocaine, a para-aminobenzoic acid ester, is a local anaesthetic used for surface anaesthesia (p. 1977.3); it has low potency and low systemic toxicity. It is used, often with other drugs such as analgesics, antiseptics, antibacterials, antifungals, and antipruritics, for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, haemorrhoids, anal pruritus, and ear pain.

Lozenges containing benzocaine in usual doses of up to 10 mg are used for the relief of sore throat. Gels, pastes, solutions, and sprays containing benzocaine in concentrations of up to 20% have been used for surface anaesthesia of the mouth and throat.

Benzocaine is used in ear drops, creams, ointments, lotions, solutions, sprays, gels, and suppositories in concentrations of up to 20% for topical analgesia and anaesthesia.

Benzocaine has also been used as the hydrochloride.

Obesity. It has been reported[1] that despite the inclusion of benzocaine in some over-the-counter appetite suppressants there is no good evidence of its value in obesity (p. 2315.1).

1. Anonymous. A nasal decongestant and a local anesthetic for weight control? *Med Lett Drugs Ther* 1979; **21:** 65–6.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1.

Abuse. Benzocaine has been used as an adulterant or 'cutting' agent in the preparation of cocaine for illicit use and adverse effects such as methaemoglobinaemia have been seen after cocaine overdosage as a result of the benzocaine content.[1]

1. McKinney CD, *et al.* Benzocaine-adultered street cocaine in association with methemoglobinemia. *Clin Chem* 1992; **38:** 596–7.

Hypersensitivity. The incidence of positive reactions in patients patch tested with benzocaine has ranged from 3.3 to 5.9%.[1,2] Patch testing with benzocaine has been recommended by The International Contact Dermatitis Research Group as an indicator of contact hypersensitivity to local anaesthetics. However, it was found that of 40 patients who had had positive reactions to benzocaine with tetracaine and cinchocaine, 21 were not allergic to benzocaine alone.[3]

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83:** 543–5.
2. Bandmann H-J, *et al.* Dermatitis from applied medicaments. *Arch Dermatol* 1972; **106:** 335–7.
3. Beck MH, Holden A. Benzocaine—an unsatisfactory indicator of topical local anaesthetic sensitization for the UK. *Br J Dermatol* 1988; **118:** 91–4.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

See under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lodoc; ***Austral.***: Applicaine†; ***Austria***: Anaestherit; ***Braz.***: Solarcaine; ***Canad.***: Anbesol Baby; Anbesol Extra Strength; Anbesol; Baby Orajel; Comfortcaine†; Dermine†; First Aid Spray; ManDelay†; Oragard-B; Orajel; Swabplus Insect Bite Relief†; Swabplus Mouth Pain Relief†; Swabplus Teething pain Relief†; Ultracare; ***Chile***: Anbesol†; BBdent Gel Topico; Dentispray†; Foille; Kalmafta; ***China***: Ou Ji (欧吉); ***Cz.***: Babydent†; ***Fr.***: Prothyl†; Topex; ***Ger.***: Anaesthesin N†; Anaesthesin; Labocane†; ***Hung.***: Babydent†; ***India***: Mamdew Baby Gel; ManDelay; Mucopain; ***Irl.***: Burneze; Lanacane; ***Israel***: Anadent; Baby Gel; Hurricaine; Lanacane†; Maintain; Oramed†; UltraCare; ***Mex.***: Auralyt; Gomas Garde B; Graneodin B; ***NZ***: Solarcaine†; ***Pol.***: Baby Orajel†; Orajel†; ***Port.***: Dentispray; Topigel; ***Rus.***: Relief Advance (Релиф Адванс); ***S.Afr.***: Kiddigum†; ***Spain***: Dentispray; Gartricin; Hurricaine; Lanacane; Nani Pre Dental; Topispray; ***Turk.***: Undo-Pate; ***UK***: AAA; Burneze; Lanacane; Orajel; Ultra Chloraseptic; Ultracare; ***Ukr.***: Babydent (Бебидент)†; ***USA***: Americaine First Aid; Americaine; Anbesol Jr; Baby Anbesol; Baby Orajel; Benzo-O-Sthetic; Benzodent; Cepacol Dual Relief Sore Throat Spray; Cepacol Fizzlers; Chigger-Tox†; Dent's Extra Strength Toothache Gum; Dent's Maximum Strength Toothache Drops; Dent-O-Kain; Dermoplast; Detane†; Hurricaine; Ivy-Rid; Kank-A Soothing Beads; Lanacane; Medicone†; Mycinettes; Orabase Baby; Orabase Dental; Orabase-B; Orajel; Oral Pain Relief; Ora-Magic Plus; Otocain; Pinnacaine; SensoGARD; Trocaine; Zilactin-B Medicated.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
USP 36: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Benzocaine and Menthol Topical Aerosol; Benzocaine Cream; Benzocaine Gel; Benzocaine Lozenges; Benzocaine Ointment; Benzocaine Otic Solution; Benzocaine Topical Aerosol; Benzocaine Topical Solution; Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution.

Bupivacaine *(BAN, USAN, rINN)*

Bupivacaína; Bupivacaïne; Bupivacainum; Bupivakaiini; Bupivakain; SKY-0402; Бупивакаин.

(±)-(1-Butyl-2-piperidyl)formo-2′,6′-xylidide.

$C_{18}H_{28}N_2O$=288.4

CAS — 2180-92-9; 38396-39-3.
ATC — N01BB01.
ATC Vet — QN01BB01.
UNII — Y8335394RO.

Bupivacaine Hydrochloride

(BANM, USAN, rINNM)

AH-2250; Bupivacaína, hidrocloruro de; Bupivacaïne, Chlorhydrate de; Bupivacainhydrochlorid; Bupivacaini Hydrochloridum; Bupivacaini Hydrochloridum Monohydricum; Bupivakaiinihydrokloridi; Bupivakain Hidroklorür; Bupivakain-hidroklorid; Bupivakain-hydrochlorid monohydrát; Bupivakainhydroklorid; Bupivakaino hidrochloridas; Bupiwakainy chlorowodorek; Hidrocloruro de bupivacaína; LAC-43; Win-11318; Бупивакаина Гидрохлорид.

$C_{18}H_{28}N_2O,HCl,H_2O$=342.9

CAS — 18010-40-7 (anhydrous bupivacaine hydrochloride); 14252-80-3 (bupivacaine hydrochloride monohydrate); 73360-54-0 (bupivacaine hydrochloride monohydrate).
ATC — N01BB01.
ATC Vet — QN01BB01.
UNII — 7TQO7W3VT8.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Bupivacaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Bupivacaine Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in acetone and in chloroform. A 1% solution in water has a pH of 4.5 to 6.0.

Stability of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

For reference to the stability of admixtures of bupivacaine and fentanyl in solution, with or without adrenaline, see under Fentanyl, p. 60.1.

Uses and Administration

Bupivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It has a slow onset and a long duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor, and absorption into the circulation from the site of injection is reduced. Slow accumulation occurs with repeated doses. It is used mainly for infiltration anaesthesia and regional nerve blocks, particularly epidural block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is contra-indicated for epidural block in obstetrics. (Local anaesthetic techniques are discussed on p. 1977.2.) At high doses bupivacaine produces surgical anaesthesia, whereas at lower doses it is used for the management of acute pain such as labour pain (below) and in postoperative analgesia (p. 6.1).

Bupivacaine is a racemic mixture but the *S* (-)-isomer levobupivacaine (see p. 1987.2) is also used. A carbonated solution of bupivacaine is available for injection in some countries (see p. 1976.2). An injectable liposomal formulation of bupivacaine is also used for postoperative analgesia (see below).

In recommended doses bupivacaine produces complete sensory blockade but the concentration of bupivacaine solution used affects the extent of motor blockade achieved. A 0.25% solution generally produces incomplete motor block, a 0.5% solution will usually produce motor block and some muscle relaxation, and complete motor block and muscle relaxation can be achieved with a 0.75% solution.

The dosage of bupivacaine used depends on the site of injection and the procedure used, as well as the status of the patient. Bupivacaine is usually given as the hydrochloride monohydrate salt although doses are expressed in terms of the anhydrous hydrochloride; bupivacaine hydrochloride monohydrate 10.55mg is equivalent to about 10mg anhydrous bupivacaine hydrochloride. Bupivacaine is also given as the base in a liposomal suspension; however, different formulations are not bioequivalent and doses cannot be directly converted from any other formulation to the liposomal suspension.

In the UK the suggested general **maximum single dose** of bupivacaine hydrochloride is 150mg with or without adrenaline followed if necessary by doses of up to 50mg every 2 hours. In the USA the recommended maximum single dose is 175mg of the plain preparation or 225mg when given with adrenaline; doses may be repeated at intervals of not less than 3 hours but the total daily dose should not exceed 400mg. The dose should be reduced in the elderly, in children (see also below), in debilitated patients, and in cardiac or hepatic disease.

A test dose of bupivacaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Subsequent doses should be given in small increments.

Solutions with or without adrenaline may be used for most **local anaesthetic techniques** and procedures apart from dental infiltration, when adrenaline is added to the solution (see below).

- For **surgical anaesthesia**, bupivacaine hydrochloride is given by *infiltration* as a 0.25% solution in doses up to the recommended maximum (see above). When a longer duration of anaesthesia is required, as in dental or surgical procedures of the maxillary and mandibular area, a 0.5% solution with adrenaline 1 in 200 000 has been used but a total dose of 90mg (18mL) should not be exceeded over a single dental sitting.
- For *peripheral nerve block* the usual dose is 12.5mg (5mL) as a 0.25% solution or 25mg (5mL) as a 0.5% solution, although doses up to the recommended maximum single dose (see above) may also be given. A 0.375% solution is also available. A 0.75% solution has been used for *retrobulbar block* in ophthalmic surgery in a dose of 15 to 30mg (2 to 4mL).
- For *sympathetic nerve block* 50 to 125mg (20 to 50mL) as a 0.25% solution is recommended.
- For *lumbar epidural block* in surgery a 0.25% solution of bupivacaine hydrochloride may be used in a dose of 25 to 50mg (10 to 20mL) or as a 0.5% solution in a dose of 50 to 100mg (10 to 20mL). A 0.75% solution is also used for induction of lumbar epidural block in non-obstetric surgery in a single dose of 75 to 150mg (10 to 20mL). For *caudal block* in surgery 37.5 to 75mg (15 to 30mL) as a 0.25% solution or 75 to 150mg (15 to 30mL) as a 0.5% solution may be used.
- Hyperbaric solutions of bupivacaine hydrochloride without adrenaline may be used for *spinal block*. Preparations containing 0.5% are available and are given in doses of 10 to 20mg (2 to 4mL).
- In the management of **acute pain** bupivacaine may be given as an epidural bolus or by continuous infusion. For analgesia during *labour*, doses of 15 to 30mg (6 to 12mL) as a 0.25% solution, 22.5 to 45mg (6 to 12mL) as a 0.375% solution, or 30 to 60mg (6 to 12mL) as a 0.5% solution have been recommended as a bolus for lumbar block. Alternatively, when given as an infusion, a dose of 10 to 15mg (10 to 15mL) per hour as a 0.1% solution or 10 to 15mg (8 to 12mL) per hour as a 0.125% solution has been recommended for lumbar block. Bupivacaine may also be given as a bolus caudal injection for labour pain; doses of 25 to 50mg (10 to 20mL) as a 0.25% solution, 37.5 to 75mg (10 to 20mL) as a 0.375% solution, or 50 to 100mg (10 to 20mL) as a 0.5% solution are recommended.
- For *postoperative pain* bupivacaine may be given as an epidural infusion in doses of 4 to 15mg (4 to 15mL) per hour as a 0.1% solution or 5 to 15mg (4 to 12mL) per hour as a 0.125% solution. A liposomal suspension containing bupivacaine 1.3% is available for local infiltration into the surgical site to produce post-surgical analgesia; the recommended dose is based on the site and the volume required to cover the area. For bunionectomy, a single dose of 106mg (8mL) is given: 7mL into the tissues surrounding the osteotomy and 1mL into the subcutaneous tissue. For haemorrhoidectomy, a single dose of 266mg (20mL) is diluted to 30mL with preservative-free sodium chloride 0.9% for injection and infiltrated around the anal sphincter in 6 equally divided portions.

Action. Addition of potassium chloride 0.2mmol to 40mL of bupivacaine 0.25% solution resulted in a more rapid onset of sensory loss than the same dose of plain bupivacaine in patients undergoing brachial plexus block for forearm or hand surgery.[1]

Hyaluronidase did not increase the speed of onset of brachial plexus block produced by bupivacaine 0.5%, with or without adrenaline, but did reduce the duration of anaesthesia.[2]

Bupivacaine encapsulated in liposomes can prolong postsurgical analgesic action without motor block.[3,4]

For a comparison of the vasoactivity of bupivacaine and some other local anaesthetics, see p. 1976.2.

1. Parris MR, Chambers WA. Effects of the addition of potassium to prilocaine or bupivacaine: studies on brachial plexus blockade. *Br J Anaesth* 1986; **58:** 297–300.
2. Keeler JF, *et al*. Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth* 1992; **68:** 68–71.
3. Boogaerts S, *et al*. Epidural administration of liposomal bupivacaine for the management of postsurgical pain. *Br J Anaesth* 1993; **70:** (suppl 1): 104.
4. Boogaerts JG, *et al*. Pharmacokinetic-pharmacodynamic specific behaviour of liposome-associated bupivacaine in humans. *Br J Anaesth* 1995; **74** (suppl 1): 74.

Administration in children. The *BNFC* recommends that the dose of bupivacaine in children should be adjusted according to physical status and the nature of the procedure.

Bupivacaine 0.25%, injected intra-operatively at the wound site, up to a maximum dose of 1.5mg/kg with adrenaline has been used in infants for the control of postoperative pain due to pyloromyotomy and appears to attenuate some of the cardiac and respiratory effects associated with the use of general anaesthesia alone.[1] Doses of 2.5mg of bupivacaine for each year of age, as a 0.5% solution, have been used for ilioinguinal nerve block in children undergoing herniotomy.[2] A study[3] in infants undergoing abdominal surgery found that an epidural infusion of bupivacaine produced comparable analgesia to an intravenous infusion of morphine. It was considered that bupivacaine might be preferable to morphine in neonates and young infants who are particularly prone to respiratory depression, but older children might require additional sedation or analgesia to prevent postoperative restlessness.

1. McNicol LR, *et al*. Peroperative bupivacaine for pyloromyotomy pain. *Lancet* 1990; **335:** 54–5.
2. Smith BAC, Jones SEF. Analgesia after herniotomy in a paediatric day unit. *BMJ* 1982; **285:** 1466.
3. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extradural bupivacaine. *Br J Anaesth* 1993; **70:** 10–16.

Headache. Small amounts of bupivacaine 0.5% have been injected into the lower cervical paraspinal muscles for the emergency treatment of headache.[1,2]

1. Mellick LB, *et al*. Treatment of headaches in the ED with lower cervical intramuscular bupivacaine injections: a 1-year retrospective review of 417 patients. *Headache* 2006; **46:** 1441–9.
2. Mellick LB, Pleasant MR. Do pediatric headaches respond to bilateral lower cervical paraspinous bupivacaine injections? *Pediatr Emerg Care* 2010; **26:** 192–6.

Labour pain. For a discussion of the management of labour pain, including mention of the use of local anaesthetics, see p. 8.3.

Early experience in nearly 1000 patients suggested that 8mL of a 0.5% solution of bupivacaine with adrenaline was the optimum dose for epidural block during labour;[1] pain relief lasted for about 2 hours. Decreasing the concentration of the final dose to 0.25% reduced the persistence of sensory and motor nerve block after delivery. Others[2] found that bupivacaine 0.375% was the most suitable concentration for epidural analgesia when using a regimen of regular 'top-up' doses of 500 micrograms/kg about every 90 minutes. However, the use of low doses of bupivacaine 0.25% for epidural analgesia in primiparous women was associated with a lower incidence of forceps delivery and oxytocin augmentation.[3] Although an even lower concentration of bupivacaine (0.0625%) used with sufentanil[4] produced analgesia similar to that with 0.125% bupivacaine used alone, the duration of the second stage of labour and the incidence of instrumental and surgical delivery were not reduced. Similar results were obtained using bupivacaine 0.0625% with diamorphine 0.005%; in addition pruritus and drowsiness produced by diamorphine were considered to be troublesome in many patients.[5] However, a large UK study[6,7] compared a traditional epidural regimen using 10mL boluses of bupivacaine 0.25% given up to every hour, with two lower-dose regimens using bupivacaine 0.1% with fentanyl 2 micrograms/mL, and found the lower dose techniques were at least as effective and were associated with a lower incidence of instrumental delivery.

Combined spinal-epidural blocks, in which an initial intrathecal injection of bupivacaine or bupivacaine with an opioid is given before starting the epidural, are also used,[6-9] and have been found to give excellent results,[7] although they may have no advantages over a low-dose epidural technique.[10]

Intrathecal injections containing bupivacaine have also been given alone[11,12] for the management of labour pain but the use of this route alone is usually associated with anaesthesia and management of postoperative pain in caesarean section. Bupivacaine has also been tried with lidocaine for epidural anaesthesia in caesarean section in order to reduce the dose of bupivacaine and minimise cardiotoxicity.[13]

1. Crawford JS. Lumbar epidural block in labour: a clinical analysis. *Br J Anaesth* 1972; **44:** 66–74.
2. Purdy G, *et al*. Continuous extradural analgesia in labour: comparison between "on demand" and regular "top-up" injections. *Br J Anaesth* 1987; **59:** 319–24.
3. Turner MJ, *et al*. Primiparous women using epidural analgesia. *BMJ* 1990; **300:** 123.
4. Auroy Y, Benhamou D. Extradural analgesia for labour: 0.125% bupivacaine vs 0.0625% bupivacaine with 0.2 micrograms mL^{-1} sufentanil. *Br J Anaesth* 1995; **74** (suppl 1): 105–6.
5. Bailey CR, *et al*. Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001; **358:** 19–23.
7. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Randomized controlled trial comparing traditional with two "mobile" epidural techniques: anesthetic and analgesic efficacy. *Anesthesiology* 2002; **97:** 1567–75.
8. Stacey RGW, *et al*. Single space combined spinal-extradural technique for analgesia in labour. *Br J Anaesth* 1993; **71:** 499–502.
9. Collis RE, *et al*. Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345:** 1413–16.
10. Simmons SW, *et al*. Combined spinal-epidural versus epidural analgesia in labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/02/08).
11. Kestin IG, *et al*. Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
12. McHale S, *et al*. Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour. *Br J Anaesth* 1992; **69:** 634–6.
13. Howell P, *et al*. Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *Br J Anaesth* 1990; **65:** 648–53.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1 and p. 1979.1.

Bupivacaine appears to be more cardiotoxic than other local anaesthetics. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and a successful outcome may require prolonged resuscitative efforts. For reports suggesting that infusion of a lipid emulsion may be of benefit, and a suggested protocol for its use, see Cardiotoxicity, under Soya Oil, p. 2093.1.

For reference to the toxic threshold for bupivacaine plasma concentrations, see Absorption under Pharmacokinetics, p. 1982.2.

Effects on the cardiovascular system. Bupivacaine[1,2] appears to be more cardiotoxic than most other commonly used local anaesthetics and marked cardiovascular depression may occur at plasma concentrations only slightly above those for CNS toxicity.[2] Fatalities have occurred. Simultaneous seizures and cardiovascular collapse may develop rapidly on inadvertent intravascular injection and even prompt oxygenation and blood pressure support might not prevent cardiac arrest.[2] Ventricular fibrillation which is very resistant to normal methods of defibrillation may develop. Since lidocaine and the other local anaesthetics have additive effects on the CNS bretylium may be preferable to lidocaine for the treatment of induced arrhy-

thmias.[1] Seizures and life-threatening ventricular fibrillation have also been reported after systemic absorption of bupivacaine solutions in an adolescent patient undergoing wound debridement.[3] Fatal cardiotoxicity has occurred after the use of bupivacaine in intravenous regional anaesthesia, possibly due to leakage past the tourniquet, and the use of bupivacaine in this technique should be avoided.[1] Fatalities have also been associated with the use of 0.75% solutions for epidural anaesthesia in obstetric patients and this strength is no longer recommended for obstetric anaesthesia. See also Labour Pain under Uses and Administration, p. 1981.2.

1. Anonymous. Cardiotoxicity of local anaesthetic drugs. *Lancet* 1986; **ii:** 1192–4.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51:** 285–7.
3. Yan AC, Newman RD. Bupivacaine-induced seizures and ventricular fibrillation in a 13-year-old girl undergoing wound debridement. *Pediatr Emerg Care* 1998; **14:** 354–5.

Effects on the eyes. Bilateral retinal haemorrhages developed in a 47-year-old woman[1] after receiving a caudal block with bupivacaine 0.5%. The haemorrhages cleared and her usual vision returned by 3 months.

1. Ling C, *et al.* Bilateral retinal haemorrhages following epidural injection. *Br J Ophthalmol* 1993; **77:** 316–17.

Prolonged block. Use of bupivacaine in regional anaesthesia may result in prolonged block.[1,2]

1. Pathy GV, Rosen M. Prolonged block with recovery after extradural analgesia for labour. *Br J Anaesth* 1975; **47:** 520–2.
2. Brockway MS, *et al.* Prolonged brachial plexus block with 0.42% bupivacaine. *Br J Anaesth* 1989; **63:** 604–5.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Bupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is contra-indicated for epidural block in obstetrics.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bupivacaine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Renal impairment. Spinal block was more rapid in onset and of shorter duration in patients with chronic renal failure given 3 mL of bupivacaine 0.75% than in control patients.[1]

1. Orko R, *et al.* Subarachnoid anaesthesia with 0.75% bupivacaine in patients with chronic renal failure. *Br J Anaesth* 1986; **58:** 605–9.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Antiarrhythmics. There is an increased risk of myocardial depression when bupivacaine and antiarrhythmics are given together.

Beta blockers. *Propranolol* reduced the clearance of bupivacaine by 35% in 6 healthy subjects.[1] There is a risk of increased bupivacaine toxicity if these drugs are used together.

1. Bowdle TA, *et al.* Propranolol reduces bupivacaine clearance. *Anesthesiology* 1987; **66:** 36–8.

Calcium-channel blockers. There is a theoretical risk that the adverse effects of bupivacaine on the heart might be enhanced in patients taking calcium-channel blockers, but evidence of a clinical problem is lacking.

Histamine H_2-antagonists. Studies of the effect of H_2-antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While a group of workers[1] found that pretreatment with *cimetidine* decreased the clearance of bupivacaine, others have failed to find any significant pharmacokinetic effects.[2,3] Similarly, pretreatment with *ranitidine* has either increased plasma concentrations of bupivacaine[4] or had no significant effect.[3]

1. Noble DW, *et al.* Effects of H-2 antagonists on the elimination of bupivacaine. *Br J Anaesth* 1987; **59:** 735–7.
2. Pihlajamäki KK. Lack of effect of cimetidine on the pharmacokinetics of bupivacaine in healthy subjects. *Br J Clin Pharmacol* 1988; **26:** 403–6.
3. Flynn RJ, *et al.* Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *Br J Anaesth* 1989; **62:** 87–91.
4. Wilson CM. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. *Br J Anaesth* 1986; **58:** 1330P–1331P.

Local anaesthetics. For reference to the effect of bupivacaine on the protein binding of *lidocaine* and *mepivacaine*, see p. 1991.2 and p. 1992.3, respectively.

Pharmacokinetics

Bupivacaine is about 95% bound to plasma proteins. Reported half-lives are from 1.5 to 5.5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine mainly as metabolites with only 5 to 6% as unchanged drug.

Bupivacaine is distributed into breast milk in small quantities. It crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the CSF.

See also under Local Anaesthetics, p. 1979.3.

Absorption. The toxic threshold for bupivacaine plasma concentrations is considered by some[1] to lie in the range of 2 to 4 micrograms/mL and in the UK the maximum single recommended dose for anhydrous bupivacaine hydrochloride is 150 mg (equivalent to about 2 mg/kg). Giving bupivacaine for *regional anaesthesia* of the head and neck in a mean total dose of 3.4 mg/kg has produced mean peak plasma concentrations of 3.56 micrograms/mL (with adrenaline) and 4.95 micrograms/mL (without adrenaline), without producing toxicity.[2] Similarly, *intrapleural* bupivacaine 0.5% in a dose of 2.5 mg/kg has produced mean peak plasma concentrations of 2.57 and 3.22 micrograms/mL (with or without adrenaline, respectively) without producing toxicity.[3] A further study[4] in which a 72-hour interpleural infusion of bupivacaine hydrochloride with adrenaline was given to cholecystectomy patients showed appreciable interpatient variability in steady-state plasma drug concentrations (range 1.3 to 3.2 micrograms/mL; mean 2.1 micrograms/mL); no patient suffered any adverse effects. Bilateral *intercostal* nerve blocks using bupivacaine 2 mg/kg have also produced concentrations within the presumed toxic range without adverse effects but the use of adrenaline with this block did not reliably reduce peak plasma-bupivacaine concentrations.[5]

Stellate ganglion block with bupivacaine 0.25% has produced a mean peak plasma concentration of 340 and 470 nanograms/mL after doses of 10 or 20 mL, respectively.[6] Giving bupivacaine 0.5% in a dose of 3 mg/kg with or without adrenaline for *sciatic* and *femoral nerve block* produced mean peak plasma concentrations below 800 nanograms/mL.[7]

Intra-articular bupivacaine is rapidly absorbed from the synovial membrane of the knee during arthroscopy but plasma concentrations did not exceed 350 nanograms/mL after controlled pressure-irrigation with isotonic solutions containing up to 200 mg.[8] Although a group of workers found that the peak plasma concentrations of bupivacaine after intra-articular injection of 30 mL of a 0.5% solution for arthroscopy was 875 nanograms/mL they suggested that adrenaline should probably be added to minimise absorption.[9]

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *Br J Anaesth* 1984; **56:** 485–92.
3. Gin T, *et al.* Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. *Br J Anaesth* 1990; **64:** 662–6.
4. Kastrissios H, *et al.* The disposition of bupivacaine following a 72h interpleural infusion in cholecystectomy patients. *Br J Clin Pharmacol* 1991; **32:** 251–4.
5. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *Br J Anaesth* 1990; **64:** 436–41.
6. Hardy PAJ, Williams NE. Plasma concentrations of bupivacaine after stellate ganglion block using two volumes of 0.25% bupivacaine plain solution. *Br J Anaesth* 1990; **65:** 243–4.
7. Misra U, *et al.* Plasma concentrations of bupivacaine following combined sciatic and femoral 3 in 1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; **66:** 310–13.
8. Debruyne D, *et al.* Monitoring serum bupivacaïne levels during arthroscopy. *Eur J Clin Pharmacol* 1985; **27:** 733–5.
9. Butterworth JF, *et al.* Effect of adrenaline on plasma concentrations of bupivacaine following intra-articular injection of bupivacaine for knee arthroscopy. *Br J Anaesth* 1990; **65:** 537–9.

SURFACE ANAESTHESIA. Studies of the absorption of bupivacaine after surface application.

1. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; **17:** 61–6.

Pregnancy. Bupivacaine crosses the placenta to a lesser degree than lidocaine or mepivacaine after maternal injection. Values of 0.2 to 0.4 have been reported[1,2] for the ratio of fetal to maternal concentrations for bupivacaine compared with values of 0.5 to 0.7 quoted[2,3] for lidocaine and mepivacaine. The greater degree of protein-binding of bupivacaine compared with these other drugs not only limits the amount of bupivacaine available to cross the placenta but also reduces the relative amount of free drug in the fetal circulation[2] (see also under Protein Binding, below). Addition of adrenaline to the injection does not appear to affect the placental transfer rate of bupivacaine.[4] Measurement of a beta-phase half-life of 25 hours in the neonate compared with 1.25 hours in mothers suggests that the neonate is less able to metabolise bupivacaine.[5]

1. Denson DD, *et al.* Serum bupivacaine concentrations in term parturients following continuous epidural analgesia for labor and delivery. *Ther Drug Monit* 1984; **6:** 393–8.
2. Blogg CE, Simpson BR. Obstetric analgesia and the newborn baby. *Lancet* 1974; **i:** 1283.
3. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; **47:** 322–7.
4. Reynolds F, *et al.* Effect of time and adrenaline on the feto-maternal distribution of bupivacaine. *Br J Anaesth* 1989; **62:** 509–14.
5. Caldwell J, *et al.* Pharmacokinetics of bupivacaine administered epidurally during childbirth. *Br J Clin Pharmacol* 1976; **3:** 956P–957P.

Protein binding. The two major binding proteins for bupivacaine in the blood are α_1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations. Reduction in pH from 7.4 to 7.0 decreases the affinity of the α_1-acid glycoprotein for bupivacaine but has no effect on albumin affinity.[1] Binding of bupivacaine is reduced during pregnancy but it is considered that the increase in free bupivacaine concentrations is unlikely to cause a clinically significant increase in the risk of CNS or cardiovascular toxicity.[2]

As fetal plasma contains little α_1-acid glycoprotein the binding capacity for bupivacaine is reduced and this may contribute to the difference between maternal and fetal plasma concentration at delivery[3] (see also under Pregnancy, above).

Ageing, uncomplicated by disease, does not affect the protein binding of bupivacaine.[4]

1. Denson D, *et al.* Alpha$_1$-acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther* 1984; **35:** 409–15.
2. Denson DD, *et al.* Bupivacaine protein binding in the term parturient: effects of lactic acidosis. *Clin Pharmacol Ther* 1984; **35:** 702–9.
3. Petersen MC, *et al.* Relationship between the transplacental gradients of bupivacaine and α_1-acid glycoprotein. *Br J Clin Pharmacol* 1981; **12:** 859–62.
4. Veering BT, *et al.* Age does not influence the serum protein binding of bupivacaine. *Br J Clin Pharmacol* 1991; **32:** 501–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bupicaina; Bupigobbi; Bupinex; Caina G; Duracaine; ***Austral.***: Marcain; ***Austria***: Bucain; Carbostesin; Dolanaest; ***Belg.***: Marcaine; ***Braz.***: Bupiabbott Plus; Bupiabbott; Bupstesic; Dorcaina; Marcaina; Neocaina; ***Canad.***: Marcaine; Sensorcaine; Vivacaine; ***Cz.***: Marcaine; ***Denm.***: Marcain; ***Fin.***: Bicain; Marcain; ***Fr.***: Bupiforan†; ***Ger.***: Bucain; Carbostesin; Dolanaest; ***Gr.***: Marcaine; ***Hong Kong***: Marcain; ***Hung.***: Bucain; Marcain; ***India***: Anawin; Bupivan; Marcain; Sensorcaine; ***Indon.***: Bucain; Bunascan; Buvanest; Decain; Marcain; Recain; Regivell; ***Irl.***: Marcain; ***Israel***: Kamacaine; Marcaine; ***Ital.***: Bupibil; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Marcaina; ***Malaysia***: Marcain; ***Mex.***: Buvacaina†; ***Neth.***: Marcaine; ***Norw.***: Marcain; ***NZ***: Marcain; ***Philipp.***: Ascain; Marcaine; Senpicaine; Senpivac; Sensorcaine; ***Pol.***: Marcaine; ***Port.***: Bupinostrum; Marcaina; ***Rus.***: Anekain (Анекаин)†; BloccoC (БлоккоС); Marcain (Маркаин); ***S.Afr.***: Macaine; Regibloc†; ***Singapore***: Marcain; ***Spain***: Inibsacain; ***Swed.***: Marcain; ***Switz.***: Carbostesin; Duracain†; ***Thai.***: Marcaine; Regivell; ***Turk.***: Marcaine; ***UK***: Marcain; ***Ukr.***: Bucain (Букаин); Marcaine (Маркаин); Omnikain (Омникаин); ***USA***: Exparel; Marcaine; Sensorcaine; ***Venez.***: Duracaina.

Multi-ingredient Preparations. ***Austral.***: Marcain with Fentanyl; ***Fin.***: Solomet c bupivacain hydrochlorid; ***NZ***: Bupafen; Marcain with Fentanyl; ***UK***: Bufyl; ***USA***: Duocaine.

Pharmacopoeial Preparations

BP 2014: Bupivacaine and Adrenaline Injection; Bupivacaine and Diamorphine Injection; Bupivacaine and Fentanyl Injection; Bupivacaine Heavy Injection; Bupivacaine Injection;
USP 36: Bupivacaine Hydrochloride in Dextrose Injection; Bupivacaine Hydrochloride Injection.

Butyl Aminobenzoate

Butamben (USAN); Butilaminobenzoato; Butoforme; Бутиламинобензоат.

Butyl 4-aminobenzoate.

$C_{11}H_{15}NO_2$=193.2

CAS — 94-25-7.

UNII — EFW857872Q.

Pharmacopoeias. In *Fr.* and *US*.

USP 36: (Butamben). A white, odourless, crystalline powder. M.p. 57 degrees to 59 degrees. Soluble 1 in 7000 of water; soluble in alcohol, in ether, in chloroform, in fixed oils, and in dilute acids. It slowly hydrolyses when boiled with water.

Butyl Aminobenzoate Picrate

Abbott-34842; Butamben Picrate (USAN); Butilaminobenzoato, picrato de.

$(C_{11}H_{15}NO_2)_2C_6H_3N_3O_7$=615.6

CAS — 577-48-0.
UNII — D4ZFB7ZH5Y.

Profile

Butyl aminobenzoate, a para-aminobenzoic acid ester, is a local anaesthetic (p. 1976.1) that has been used for surface anaesthesia of the skin and mucous membranes. It has also been used for relief of pain and pruritus associated with anorectal disorders. A suspension of butyl aminobenzoate 5 or 10% has been given epidurally.

Butyl aminobenzoate picrate has been applied to the skin as an ointment.

References.
1. Korsten HH, *et al.* Long-lasting epidural sensory blockade by n-butyl-p-aminobenzoate in the terminally ill intractable cancer pain patient. *Anesthesiology* 1991; **75:** 950–60.
2. Armstrong DG, Kanat IO. Analgesic efficacy of topical butamben picrate. *J Am Podiatr Med Assoc* 1995; **85:** 738–40.
3. Shulman M, *et al.* Nerve blocks with 5% butamben suspension for the treatment of chronic pain syndromes. *Reg Anesth Pain Med* 1998; **23:** 395–401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Unguento Picrato de Butesin.

Multi-ingredient Preparations. ***Canad.***: Cetacaine; ***Chile***: Butesin†; ***Fr.***: Nestosyl†; Nestosyl; ***India***: Proctosedyl; ***Ital.***: Prurex; ***Rus.***: Proctosedyl (Проктоседил); Proctosedyl M (Проктоседил М); ***Spain***: Alvogil†; ***Switz.***: Alvogyl; ***USA***: Cetacaine.

Pharmacopoeial Preparations
USP 36: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Erythromycin Ethylsuccinate Injection.

Chloroprocaine Hydrochloride *(rINNM)*

Chloroprocaïne, Chlorhydrate de; Chloroprocaini Hydrochloridum; Cloroprocaína, hidrocloruro de; Hidrocloruro de cloroprocaína; Хлоропрокаина Гидрохлорид.

2-Diethylaminoethyl 4-amino-2-chlorobenzoate hydrochloride.

$C_{13}H_{19}ClN_2O_2,HCl$=307.2

CAS — 133-16-4 (chloroprocaine); 3858-89-7 (chloroprocaine hydrochloride).
ATC — N01BA04.
ATC Vet — QN01BA04.
UNII — LT7Z1YW11H.

Pharmacopoeias. In *US*.

USP 36: (Chloroprocaine Hydrochloride). A white odourless crystalline powder. Soluble 1 in 20 of water and 1 in 100 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Solutions are acid to litmus.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Uses and Administration

Chloroprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It has properties similar to those of procaine (p. 1994.3). It has a rapid onset (6 to 12 minutes) and short duration (one hour) of action.

Chloroprocaine is used as the hydrochloride for infiltration, peripheral nerve block, and central nerve block including lumbar and caudal epidural blocks. It may be given, if necessary, with adrenaline 1 in 200 000 to delay absorption and reduce toxicity. Chloroprocaine is not an effective surface anaesthetic. It should not be used for spinal anaesthesia. (Local anaesthetic techniques are discussed on p. 1977.2.)

The dosage of chloroprocaine used depends on the site of injection and the procedure used. In adults the **maximum single dose** of chloroprocaine hydrochloride without adrenaline should not exceed 800 mg; when given with adrenaline 1 in 200 000 the maximum single dose should not exceed 1 g. A test dose of chloroprocaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Doses for various procedures include:

- *mandibular nerve block*: 40 to 60 mg (2 to 3 mL) as a 2% solution
- *infra-orbital nerve block*: 10 to 20 mg (0.5 to 1 mL) as a 2% solution
- *brachial plexus block*: 600 to 800 mg (30 to 40 mL) as a 2% solution
- *digital nerve block*: 30 to 40 mg (3 to 4 mL) as a 1% solution without adrenaline
- in obstetrics a dose of 200 mg (10 mL) per side as a 2% solution is suggested for *pudendal block* and for a *paracervical block* a 1% solution in a dose of 30 mg (3 mL) at each of 4 sites
- *lumbar epidural block*: 40 to 50 mg (2 to 2.5 mL) as a 2% solution or 60 to 75 mg (2 to 2.5 mL) as a 3% solution for each segment to be anaesthetised, the usual total dose being 300 to 750 mg with smaller repeat doses being given at intervals of 40 to 50 minutes
- *caudal block*: 300 to 500 mg (15 to 25 mL) as a 2% solution or 450 to 750 mg (15 to 25 mL) as a 3% solution may be given and repeated at intervals of 40 to 60 minutes

Dosages should be reduced in children, elderly or debilitated patients, and those with cardiac or liver disease. For children concentrations of 0.5 to 1% are suggested for infiltration and 1 to 1.5% for nerve block procedures.

Administration in children. For brief details on the use of chloroprocaine hydrochloride in children, see above.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1. Chloroprocaine is said to be unsuitable for intravenous regional anaesthesia (Bier's block) because of a high incidence of thrombophlebitis associated with such use. It is also contra-indicated in spinal anaesthesia due to potential neurotoxicity.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

Chloroprocaine is hydrolysed rapidly in the circulation by plasma cholinesterase. It has a half-life of 19 to 26 seconds in adults. It is excreted in the urine mainly as metabolites.

See also under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Nesacaine; ***China***: Kai Ning (凯宁); Ke Pu Nuo (可谱诺); ***Switz.***: Ivracain; ***UK***: Ampres; ***USA***: Nesacaine.

Pharmacopoeial Preparations
USP 36: Chloroprocaine Hydrochloride Injection.

Cinchocaine *(BAN, rINN)*

Cincainum; Cinchocaïne; Cinchocainum; Cincocaína; Cinkokain; Dibucaine; Sinkokaiini; Цинхокаин.

2-Butoxy-*N*-(2-diethylaminoethyl)cinchoninamide; 2-Butoxy-*N*-(2-diethylaminoethyl)quinoline-4-carboxamide.

$C_{20}H_{29}N_3O_2$=343.5

CAS — 85-79-0.
ATC — C05AD04; D04AB02; N01BB06; S01HA06.
ATC Vet — QC05AD04; QD04AB02; QN01BB06; QS01HA06.
UNII — L6JW2TJG99.

Pharmacopoeias. In *US*.

USP 36: (Dibucaine). A white to off-white powder, with a slight characteristic odour. M.p. 62.5 degrees to 66 degrees. Soluble 1 in 4600 of water, 1 in 0.7 of alcohol, 1 in 0.5 of chloroform, and 1 in 1.4 of ether; soluble in 1N hydrochloric acid. It darkens on exposure to light. Store in airtight containers. Protect from light.

Cinchocaine Hydrochloride *(BANM, rINNM)*

Cincaini Chloridum; Cinchocaïne, Chlorhydrate de; Cinchocainhydrochlorid; Cinchocaini hydrochloridum; Cinchokainhidroklorid; Cinchokain-hydrochlorid; Cinchokaino hidrochloridas; Cincocaína, hidrocloruro de; Cinkokainhydroklorid; Dibucaine Hydrochloride; Dibucainium Chloride; Hidrocloruro de cincocaína; Percainum; Sinkokaiinihydroklorid; Sinkokain Hidroklorür; Sovcainum; Цинхокаина Гидрохлорид.

$C_{20}H_{29}N_3O_2,HCl$=379.9

CAS — 61-12-1.
ATC — C05AD04; D04AB02; N01BB06; S01HA06.
ATC Vet — QC05AD04; QD04AB02; QN01BB06; QS01HA06.
UNII — Z97702A5DG.

NOTE. This compound was originally marketed under the name Percaine, but accidents occurred owing to the confusion of this name with procaine.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cinchocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals; it is hygroscopic. It agglomerates very easily. Very soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. A 2% solution in water has a pH of 5.0 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Dibucaine Hydrochloride). Colourless or white to off-white crystals or white to off-white, crystalline powder. It is odourless, somewhat hygroscopic, and darkens on exposure to light. Freely soluble in water, in alcohol, in acetone, and in chloroform. Its solutions have a pH of about 5.5. Store in airtight containers. Protect from light.

Profile

Cinchocaine is an amide local anaesthetic (p. 1976.1) that is now generally only used for surface anaesthesia. It is one of the most potent and toxic of the long-acting local anaesthetics and its parenteral use was restricted to spinal anaesthesia.

For surface anaesthesia cinchocaine has been used, as the base or hydrochloride, in creams and ointments containing up to 1% and in suppositories for the temporary relief of pain and itching associated with skin and anorectal conditions. Cinchocaine benzoate has also been used topically.

Action. For a comparison of the vasoactivity of cinchocaine and some other local anaesthetics, see p. 1976.2.

Plasma cholinesterase deficiency. For mention of the use of cinchocaine in the determination of plasma cholinesterase activity, see under Precautions of Suxamethonium Chloride, p. 2039.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cinchocaine as not porphyrinogenic when used for surface anaesthesia of the cornea; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Nupercainal; ***Canad.***: Nupercainal; ***Denm.***: Cincain; ***Fin.***: Orodrops; ***Ger.***: DoloPosterine N; ***Gr.***: Nupercainal; ***India***: Nupercainal†; ***Port.***: Nupercainal; ***Swed.***: Cincain; ***UK***: Nupercainal; ***USA***: Nupercainal.

Multi-ingredient Preparations. ***Arg.***: Procto Venart; Proctyl; Scheriproct; Ultraproct; ***Austral.***: Proctosedyl; Rectinol HC†; Rectinol; Scheriproct; Ultraproct†; ***Austria***: Scheriproct; ***Belg.***: Scheriproct; Trihistalex; Ultraproct; ***Braz.***: Proctox-H; Proctyl; Ultraproct; ***Canad.***: Nupercainal; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; ***Chile***: Scheriproct; Ultraproct; ***Cz.***: Faktu; Otobacid N; Spofax; ***Denm.***: Proctosedyl; ***Fin.***: Proctosedyl; Scheriproct; ***Fr.***: Deliproct; Ultraproct; ***Ger.***: Faktu†; Otobacid N; ***Gr.***: Hemorrocort; Proctosedyl-N; Scheriproct Neo; ***Hong Kong***: Borraginol-N†; Decatylen; Faktu; ***India***: Faktu; Otogesic; ***Indon.***: Borraginol-N; Faktu; Ultraproct†; ***Irl.***: Proctosedyl; Scheriproct; Ultraproct; ***Ital.***: Ultraproct; ***Jpn***: Una A Gel†; Una A; ***Malaysia***: Decatylen; Proctosedyl; ***Mex.***: Proctoacid; Scheriproct; Ultraproct; ***Neth.***: Proctosedyl; ***Norw.***: Proctosedyl; Scheriproct; ***NZ***: Proctosedyl; Ultraproct; ***Philipp.***: Faktu; Proctosedyl; Ultraproct; ***Pol.***: Proctosone†; Proktosedon; ***Port.***: Decatyleno; Faktu; Scheriproct; ***Rus.***: Ultraproct (Ультрапрокт); ***S.Afr.***: Medi-Keel A; Proctosedyl; Scheriproct; ***Singapore***: Decatylen; Faktu; Proctosedyl; ***Spain***: Anestesia Local Braun S/A; Ruscus; ***Swed.***: Proctosedyl†; Scheriproct N; ***Switz.***: Decatylene Neo; Faktu; Locaseptil-Neo; Scheriproct; ***Thai.***: Proctosedyl; ***Turk.***: Ultraproct; ***UAE***: Supraproct-S; ***UK***: Proctosedyl; Scheriproct; Ultraproct; Uniroid-HC; ***Ukr.***: Decatylen (Декатилен); Ultraproct (Ультрапрокт); ***USA***: Corticaine†; ***Venez.***: Scheriproct.

Pharmacopoeial Preparations
USP 36: Dibucaine Cream; Dibucaine Hydrochloride Injection; Dibucaine Ointment.

Coca ⊗

Coca Leaves; Hoja de Coca; Кока.

Profile

Coca is the dried leaves of *Erythroxylum coca* (Bolivian or Huanuco leaf) or of *E. truxillense* (Peruvian or Truxillo leaf) (Erythroxylaceae), indigenous to Bolivia and Peru and cultivated in Colombia and Indonesia.

Coca leaves contain about 0.7 to 1.5% of total alkaloids, of which cocaine, cinnamyl-cocaine, and α-truxilline are the most important.

Coca was formerly used for its stimulant action and for the relief of gastric pain, nausea, and vomiting, but it has no place in modern medicine. The practice of coca leaf chewing still continues in South America.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Fr.*: Tabacum Compose.

Cocaine *(BANJ)* ⊗

Cocaina; Cocaína; Cocainum; Kokaiini; Kokain; Methyl Benzoylecgonine; Кокаин.

(1*R*,2*R*,3*S*,5*S*)-2-(Methoxycarbonyl)tropan-3-yl benzoate.

$C_{17}H_{21}NO_4$=303.4

CAS — 50-36-2.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

ATC Vet — QN01BC01; QR02AD03; QS01HA01; QS02DA02.

UNII — I5Y540LHVR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of cocaine:

24-7; 151; 256; A1-Yola; All-American drug; Angie; Apple jacks; Aspirin; Aunt; Aunt Nora; Baby T; Bad; Badrock; Bah-say; Baise; Ball; Balls Mahoney; Bane; Barbs; Basa; Base; Baseball; Basing; Basuco; Batman; Bazooka; Bazulco; Beak; Beam; Beamers; Beans; Beat; Beautiful boulders; Bebe; Beemers; Berni; Bernice; Bernie; Bernie's flakes; Bernie's gold dust; Big bloke; Big C; Big flake; Big rush; Bill blass; Billie hoke; Bing; Bing Crosby; Bings; Birdie powder; Biscuits; Bjs; BJ's; B.J.'s; Black rock; Blanca; Blanco; Blast; Blizzard; Blotter; Blow; Blowcaine; Blowout; Blue; Bobo; Bogota Bullion; Bolivian; Bolivian marching powder; Bollo; Bolo; Bomb; Bonecrusher; Bones; Booger; Booger Sugar; Boost; Booth; Bopper; Botray; Boubou; Boulder; Boulya; Bouncing powder; Boutros; Boy; Branco; Breakfast of champions; Brick; Brooke Shields; Bubble gum; Bugar sugar; Buger sugar; Bullia capital; Bullion; Bump; Bumper; Bunk; Burese; Burnese; Bush; Butler; Butter; Butter Sandwich; Butter Sandwiches; Butu; C; Cabello; Cadillac; Caine; Cakes; California cornflakes; Came; Candy; Candy C; Candy cane; Candy sugar; Candycaine; Cane; Cap; Caps; Capsula; Carnie; Carrie; Carrie Nation; Casper; Casper the ghost; Cat's pee; Caviar; CDs; C-dust; Cecil; C-game; Cha; Chabbie; Chach; Chalk; Champagne; Champagne of drugs; Chan; Chandi; Chang; Charlie; Charlie girl; Chaz; Cheap basing; Cheddar; Cheese; Chemical; Chewies; Chez; Chinese Sky Candy; Ching; Chippy; Choe; Cholly; Climax; Cloud; Cloud nine; Coc; Co-ca-ee-na; Coca; Coca-Cola; Coco; Coconut; Cokane; Coke; Cola; Colombian Dancing Dust; Colombian Foot Soldiers; Colombian Marching Powder; Colombo; Colorado; Combol; Cookie; Cookies; Coover; Coovers; Corine; Cornbread; Corrine; Corrinne; Crack; Crackers; Crank; Crib; Crill; Cristaux; Crow; Crumbs; Crunch & Munch; Crusty treats; Crystal; Cubes; Cuch; Dama blanca; Demo; Demolish; Devil drug; Devil's dandruff; Devilsmoke; Dice; Dime; Dime special; Dip; Dirty basing; Divits; DOA; Double bubble; Double yoke; Dream; Duct; Dust; Dutch Bliss; Eastside player; Egg; Eggs; El Perico; Electric kool-aid; Esnortiar; Eve; Everclear; Eye opener; Eye openers; Famous dimes; Farlopa; Fast white lady; Fat bags; Fifty-one; Fish scales; Flake; Flave; Florida snow; Foo Foo; Foo foo stuff; Foo-foo dust; Foolish powder; Freebase; Freeze; French fries; Fries; Friskie powder; Fry; Gak; Garbage rock; Gas; Gear; Geek; Get your own; Gift-of-the-sun; Gift-of-the-sun-god; Gin; Girl; Girlfriend; Glad stuff; Glo; Gold; Gold dust; Gold star; Golf ball; Golf balls; Gooka; Gravel; Green gold; Grit; Grits; Groceries; Gulosa; Gutter glitter; Hail; Half track; Hamburger; Hamburger helper; Hamburgers; Handball; Happy dust; Happy powder; Happy trails; Hard; Hard ball; Hard line; Hard rock; Hardball; Have a dust; Haven dust; Heaven; Heaven dust; Heavy stuff; Hell; Henry VIII; Her; Hit; Hocus-Pocus; Hollywood; Homer; Hooter; Hoove; Hotcakes; How do you like me now?; Hubba; Hubba, I am back; Hubbas; Hunter; I am back; Ice; Ice cube; Icing; Inca message; Incentive; Issues; Ivory flakes; Jam; Jejo; Jelly; Jelly beans; Jessica Simpson; "Jiffy"; Johnny; Johnson; Joy powder; Junk; Kangaroo; Kangoroo; Kate; Kibbles & Bits; King; King's habit; Kitty; Kokomo; Kryptonite; Kubba; Kubs; Kuff; Lady; Lady C; Lady caine; Lady snow; Late night; Leaf; Lido; Line; Lines; Liquid lady; Llello; Love; Love affair; Lucifer Left-Nostril; Ma'a; Mama coca; Marching dust; Marching powder; Mayo; Merca; Merck; Merk; Mighty white; Mix; Mixed jive; Mobbeles; Mojo; Monster; Mosquitos; Movie star drug; Mr. B.; Mujer; Munch; Neige; Neve; New addition; Nieve; Nighttrain; Nose; Nose candy; Nose powder; Nose stuff; Nuggets; Number 3; One-fifty-one; One-to-one; Oyster stew; Pala; Paradise; Paradise white; Pariba; Parlay; Partying; Pasta; Paste; Patico; Pearl; Pebbles; Pee Wee; Pepsi; Percia; Percio; Perico; Peruvian; Peruvian flake; Peruvian lady; Peruvian Marching Powder; P.F.; Picnic in Stevenage; Piece; Piedra; Piedras; Pile; Piles; Pimp; Polvo blanco; Pony; Pop; Powder; Powder diamonds; Press; Prime time; Primo; Product; Purple caps; Purple haze; Quick; Quik; Quill; Race horse Charlie; Racehorse Charlie; Railers; Rane; Raw; Ready rock; Real tops; Red caps; Regular "P"; Rest in peace; Ringer; Ringers; Roca; Rock; Rock attack; Rocks; Rocks of hell; Rocky III; Rooster; Rox; Roxanne; Royalty; Roz; Rush; Schmeck; Schoolboy; Schoolcraft; Scorpion; Scottie; Scotty; Scrabble; Scramble; Scruples; Serpico 21; Seven-Up; Sevenup; Shabu; Shake; She; Sherms; Shit; Shnazzle; Shneg; Shootin' Caine; Showbiz Sherbert; Shrile; Sightball; Skeeter; Skeezell; Slab; Sleet; Sleigh ride; Smack; Smoke; Snai; Sniff; Snort; Snow; Snow bird; Snow coke; Snow cone; Snow soke; Snow toke; Snow Train; Snow white; Snowcones; Soap; Society high; Soda; Soft; Soup; Space; Space dust; Speed; Speed boat; Square time Bob; Squares; Squib; Squirrel; Star; Star dust; Star-spangled powder; Stardust; Stone; Stones; Strawberry; Street Caviar; Studio fuel; Suga buga; Sugar; Sugar block; Sugar boogers; Super cloud; Sutta; Sweet stuff; Swell up; T; Talco; Tardust; Teenager; Teeth; Tension; The champagne of stimulants; The devil; The great white hope; Thing; Tissue; Tony; Toot; Tootie; Top gun; Topo; Tornado; Toss up; Toss-ups; Trails; Trey; Troop; Turkey; Turtle stuff; Tutti-frutti; Tweaks; Twenty rock; Twinkie; Ultimate; Uptown; Uzi; Wacky dust; Wash; Washed rock; Wave; Weasel dust; Whack; White; White ball; White boy; White cloud; White Devil; White dragon; White dust; White ghost; White girl; White horse; White lade; White lady; White Lion; White mosquito; White Pony; White powder; White stuff; White sugar; White tornado; Whites; Whiz bang; Window pane; Wings; Witch; Woolies; Wrecking crew; Yada; Yadidi; Yahoo; Yak; Yale; Yam; Yams; Ya Yo; Yao; Yay; Yayo; Yayoo; Yay-yo; Yeah-O; Yeaho; Yee Yoo; Yeo; Yeyo; Yimyom; Yiz; Yola; Zing; Zip; Zulu.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Cocaine). It may be obtained from the leaves of *Erythroxylum coca* and other spp. of *Erythroxylum*, or by synthesis. Colourless crystals or a white, crystalline powder. It is slightly volatile. M.p. 96 degrees to 98 degrees. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform; soluble in arachis oil; slightly soluble in liquid paraffin.

USP 36: (Cocaine). Colourless to white crystals or white, crystalline powder. M.p. 96 degrees to 98 degrees. Soluble 1 in 600 of water, 1 in 7 of alcohol, 1 in 1 of chloroform, 1 in 3.5 of ether, 1 in 12 of olive oil, and 1 in 80 to 100 of liquid paraffin. A saturated solution in water is alkaline to litmus. Protect from light.

Cocaine Hydrochloride *(BANM)* ⊗

Chloridrato de Cocaína; Cocaína, hidrocloruro de; Cocaïne, chlorhydrate de; Cocaine Hydrochlor.; Cocainhydrochlorid; Cocaini hydrochloridum; Cocainium Chloratum; Kokaiinihydrokloridi; Kokain-hidroklorid; Kokain-hydrochlorid; Kokain-hydroklorid; Kokaino hidrochloridas; Kokainy chlorowodorek.

$C_{17}H_{21}NO_4$,HCl=339.8

CAS — 53-21-4.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

ATC Vet — QN01BC01; QR02AD03; QS01HA01; QS02DA02.

UNII — XH8T8T6WZH.

NOTE. CCN is a code approved by the BP 2014 for use on single unit doses of eye drops containing cocaine hydrochloride where the individual containers may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cocaine Hydrochloride). Colourless crystals or a white or almost white crystalline powder. M.p. about 197 degrees with decomposition. Very soluble in water; freely soluble in alcohol. Protect from moisture and light.

USP 36: (Cocaine Hydrochloride). Colourless crystals or white, crystalline powder. Soluble 1 in 0.5 of water, 1 in 3.5 of alcohol, and 1 in 15 of chloroform; soluble in glycerol; insoluble in ether. Protect from light.

Stability in solutions. *ALKALIS.* Solutions of cocaine hydrochloride are adversely affected by alkalis.

PHENOL A stability study[1] was conducted in response to queries over conflicting data on the incompatibility of cocaine hydrochloride solutions and phenol. Some pharmacists had reported that cocaine hydrochloride eye drops preserved with phenol had shown no sign of physical incompatibility. The BPC 1973 states that cocaine hydrochloride is incompatible with phenol but suggests that cocaine hydrochloride solutions may be preserved with chlorocresol. The study found that there was no sign of physical incompatibility in aqueous solutions containing cocaine hydrochloride 5% and phenol 0.5% stored for a year at temperatures of 0 degrees to 37 degrees but there was a fall in pH, greatest at the higher temperatures, which was suggestive of chemical change. It was recommended that such solutions should be stored in a cool place.

1. *PSGB Lab Report P/75/14* 1975.

Uses and Administration

Cocaine, a benzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used as a surface anaesthetic but, because of systemic adverse effects and its abuse potential, its use is now almost entirely restricted to surgery of the ear, nose, and throat. It has been largely replaced by other drugs in ophthalmology because of its corneal toxicity, although it may still be useful in removal or debridement of the corneal epithelium. Cocaine also blocks the uptake of catecholamines at adrenergic nerve endings and potentiates the action of catecholamines. Its sympathomimetic actions cause tachycardia, peripheral vasoconstriction, a rise in blood pressure, and mydriasis. The use of cocaine with sympathomimetics such as adrenaline increases the risk of cardiac arrhythmias. Despite this hazard some use this combination in otolaryngology to improve the operative field and reduce absorption.

When applied to mucous membranes, surface anaesthesia develops rapidly and persists for 30 minutes or longer depending on the concentration of cocaine used, the dose, and on the vascularity of the tissue.

Cocaine hydrochloride is used in aqueous solutions; cocaine hydrochloride 1.12 g is equivalent to about 1 g of cocaine. Solutions containing up to 4% have been used in ophthalmology (but precautions for ophthalmic use should be considered, see p. 1986.2).

Solutions containing up to 10% of cocaine are applied to the nasal mucosa in otolaryngological procedures. Pastes containing up to 25% of cocaine have also been applied.

In order to avoid systemic effects, the usual maximum total dose recommended for application to the nasal mucosa in healthy adults is 1.5 mg/kg. It should be used only by those skilled in the precautions needed to minimise absorption and the consequent risk of arrhythmias.

Cocaine was used with diamorphine or morphine for the relief of severe pain, especially in terminal illness, but this use is now obsolete.

Cocaine solutions should *never* be given by injection; other local anaesthetics are equally effective and much safer.

References.

1. Middleton RM, Kirkpatrick MB. Clinical use of cocaine: a review of the risks and benefits. *Drug Safety* 1993; **9:** 212–17.
2. Latorre F, Klimek L. Does cocaine still have a role in nasal surgery? *Drug Safety* 1999; **20:** 9–13.

Adverse Effects

Because the therapeutic use of cocaine is now very restricted many reports of adverse effects occur in the context of abuse. However, both systemic and local effects have followed its use as a surface anaesthetic. Although some effects are similar to those of other local anaesthetics (p. 1978.1), cocaine differs in that it acts as a potent indirect-acting sympathomimetic. It stimulates the CNS causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hypertonia, and hyperreflexia. Convulsions, coma, and metabolic acidosis may develop. Symptoms of CNS stimulation and sympathetic overactivity are very marked in overdosage with cocaine. A single 1-g oral dose may be fatal, but some persons have a cocaine idiosyncrasy and severe toxicity may occur after doses of only 10 mg intravenously. Systemic absorption of small doses may slow the heart, but with increasing doses tachycardia, hypertension, and ventricular fibrillation occur.

High concentrations of cocaine should not be used topically as, in addition to risks of systemic toxicity after absorption, lasting local damage may occur.

Topical application of cocaine to the cornea can cause corneal damage with clouding, pitting, sloughing, and occasionally ulceration. Topical application to the nose or mouth has been reported to cause loss of smell and taste respectively.

Prolonged use of cocaine by nasal inhalation may cause mucosal damage or perforation of the nasal septum.

Abuse. Cocaine abuse and its effects have been reviewed.[1-6]

Cocaine abuse was once only in the form of chewing of coca leaves containing small amounts of cocaine, but processing of the leaves has led to abuse with a variety of more dangerous preparations containing higher concentrations of cocaine.[7] Coca paste, produced by maceration of the leaves with petrol and sulfuric acid, contains about 40 to 90% of cocaine sulfate and is smoked with tobacco or cannabis. Treatment of coca paste with hydrochloric acid produces cocaine hydrochloride, which is abused by intravenous injection, either alone or with diamorphine, or by sniffing to achieve nasal absorption. Alkaloidal cocaine (cocaine base; 'freebase'), which is abused by smoking, is produced by treating cocaine hydrochloride with alkali, followed either by heating (to form 'crack' cocaine) or by extracting the base from ether or another organic solvent. Other types of cocaine, which are prepared and consumed locally in South America and have a high content of contaminants such as car battery acid, lime, petrol, or kerosene, include 'Merla' and 'Oxi'.[8] The route by which cocaine is taken determines the rate and extent of its absorption, and hence the abuse potential, although once

absorbed, the pharmacokinetics are independent of route. Intravenous cocaine hydrochloride and smoked cocaine base have a greater potential for abuse than intranasal cocaine hydrochloride because of their greater rapidity and intensity of effects.

The psychological effects of cocaine abuse may be described by a cycle of initial euphoria followed by dysphoria and finally schizophreniform psychosis.[7,9] Euphoria may be accompanied by other symptoms of stimulation such as sexual arousal, anorexia, insomnia, hyperexcitability, loquacity, and grandiosity, and users may appear manic. After a short time these feelings are replaced by symptoms of dysphoria including considerable anxiety, fear, depression, apathy, irritability, and suspiciousness. Dysphoria may be ameliorated by repeated use, so the user develops the need to take the drug continuously to feel relatively well, but repeated use appears to diminish the intensity of the effects.[7] During euphoria and dysphoria users may develop varied physical symptoms including palpitations, headache, dizziness, gastrointestinal effects, hyperhidrosis, tremors, tachycardia, hypertension, fever, and myoclonic jerks. Seizures can also occur after repeated use. In chronic abusers psychological deterioration may eventually occur, resulting in loss of mental function, compulsive disorders, suicidal ideation, psychopathic disorders, and ultimately a psychosis resembling acute paranoid schizophrenia similar to that seen with amfetamines.[7,9] Symptoms may include paranoia, stereotyped behaviour, delusions, loss of impulse control, violence, and visual, olfactory, auditory, gustatory, and tactile hallucinations. Overdosage can result in death due to status epilepticus, hyperthermia, ventricular tachycardia, and cardiac or respiratory arrest.[7]

For further details of the adverse effects of cocaine abuse, including effects due to use during pregnancy, see below.

1. Johanson C-E, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989; **41:** 3–52.
2. Warner EA. Cocaine abuse. *Ann Intern Med* 1993: **119:** 226–35.
3. Strang J, *et al*. Cocaine in the UK—1991. *Br J Psychiatry* 1993; **162:** 1–13.
4. Das G. Cocaine abuse in North America: a milestone in history. *J Clin Pharmacol* 1993; **33:** 296–310.
5. Hatsukami DK, Fischman MW. Crack cocaine and cocaine hydrochloride: are the differences myth or reality? *JAMA* 1996; **276:** 1580–8.
6. Brownlow HA, Pappachan J. Pathophysiology of cocaine abuse. *Eur J Anaesthesiol* 2002; **19:** 395–414.
7. Arif A, ed. *Adverse health consequences of cocaine abuse*. Geneva: WHO, 1987.
8. Bastos FI, *et al*. Smoked crack cocaine in contemporary Brazil: the emergence and spread of 'oxi'. *Addiction* 2011; **106:** 1191–2.
9. Leikin JB, *et al*. Clinical features and management of intoxication due to hallucinogenic drugs. *Med Toxicol Adverse Drug Exp* 1989; **4:** 324–50.

ADULTERATION. For a report of methaemoglobinaemia as a result of the ingestion of cocaine adulterated with *benzocaine*, see Abuse under Adverse Effects of Benzocaine, p. 1980.2. For reports of severe neutropenia and agranulocytosis as a result of the abuse of cocaine adulterated with *levamisole*, see under Precautions of Levamisole, p. 158.2.

BREAST FEEDING. The American Academy of Pediatrics[1] has stated that, when used as a drug of abuse by breast-feeding mothers, cocaine has caused signs of intoxication in the infant, notably diarrhoea, vomiting, irritability, seizures, and tremulousness.

Acute intoxication has been reported in a breast-fed child whose mother was using cocaine intranasally.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)
2. Chasnoff IJ, *et al*. Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987; **80:** 836–8.

EFFECTS ON THE BLOOD. Severe thrombocytopenia has occurred in 6 males who abused cocaine;[1] 5 of the cases involved intravenous abuse while the sixth patient took by inhaling.

See also Adulteration, above.

1. Leissinger CA. Severe thrombocytopenia associated with cocaine use. *Ann Intern Med* 1990; **112:** 708–10.

EFFECTS ON THE CARDIOVASCULAR SYSTEM. There appears to be no relationship between underlying heart disease and the risk of cocaine-induced cardiac effects and cardiac events can occur regardless of the route of abuse.[1] Cardiovascular toxicity due to cocaine may be related to individual sensitivity and therefore may not be predictable or dose dependent.[2] Patients with plasma cholinesterase deficiency are particularly at risk for sudden death.[3] Other risk factors for cardiovascular disease, such as cigarette smoking or pre-existing atherosclerosis, may exacerbate the cardiotoxicity of cocaine.[4-6] Cocaine blocks reuptake of catecholamines at adrenergic nerve endings and thus produces sympathetic stimulation of the cardiovascular system. Accumulation of catecholamines predisposes the myocardium to arrhythmias,[7] and sinus tachycardia, supraventricular or ventricular tachyarrhythmias, myocarditis, and sudden arrhythmic death may occur.[7-9] Severe hypertension can lead to cerebrovascular accidents and stroke has occurred even in young adults without other predisposing conditions.[10,11] However, the exact mechanism of cocaine-induced stroke remains unclear and other implicated effects include vasospasm, cerebral vasculitis, enhanced platelet aggregation, and cardioembolism.[12] Aortic dissection and rupture of the aorta have also occurred.[6] Up to 25% of emergency admissions to US urban hospitals with nontraumatic chest pain have detectable amounts of cocaine or its metabolites in their urine, but only a minority of these have myocardial infarction,[6] as chest pain without signs of myocardial infarction also commonly occurs.[8] Asymptomatic myocardial ischaemia manifesting as episodes of ST-segment elevation has also been reported during withdrawal of cocaine.[13] The mechanism for these changes is probably multifactorial, including increased myocardial oxygen demand, coronary vasoconstriction, and enhanced platelet aggregation and thrombus formation.[6,14] The immediate vasoconstrictor effect of cocaine may be followed by delayed or recurrent vasoconstriction due to its active metabolites, benzoylecgonine and ethyl methyl ecgonine.[6]

Vasoconstriction may also produce ischaemia in the fingers, toes, spinal cord,[8] spleen,[15] and intestines.[16] Renal ischaemia and infarction may also occur.[17,18] Other reported cardiovascular effects include dilated cardiomyopathy and premature atherosclerosis.[6]

Guidance[19] has been issued on the management of cocaine-associated chest pain and myocardial infarction.

1. VanDette JM, Cornish LA. Medical complications of illicit cocaine use. *Clin Pharm* 1989; **8:** 401–11.
2. Thadani PV. Cardiovascular toxicity of cocaine: underlying mechanisms. *J Appl Cardiol* 1990; **5:** 317–20.
3. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315:** 1495–1500.
4. Moliterno DJ, *et al*. Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *N Engl J Med* 1994; **330:** 454–9.
5. Higgins ST, *et al*. Influence of cocaine use on cigarette smoking. *JAMA* 1994; **272:** 1724.
6. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001; **345:** 351–8. Correction. *ibid.*; 1432.
7. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; **4:** 174–85.
8. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1990; **32:** 92–4.
9. Bauman JL, *et al*. Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994; **34:** 902–11.
10. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med* 1990; **113:** 821–7.
11. Levine SR, *et al*. Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N Engl J Med* 1990; **323:** 699–704.
12. Treadwell SD, Robinson TG. Cocaine use and stroke. *Postgrad Med J* 2007; **83:** 389–94.
13. Nademanee K, *et al*. Myocardial ischemia during cocaine withdrawal. *Ann Intern Med* 1989; **111:** 876–80.
14. Rezkalla SH, Kloner RA. Cocaine-induced acute myocardial infarction. *Clin Med Res* 2007; **5:** 172–6.
15. Novielli KD, Chambers CV. Splenic infarction after cocaine use. *Ann Intern Med* 1991; **114:** 251–2.
16. Freudenberger RS, *et al*. Intestinal infarction after intravenous cocaine administration. *Ann Intern Med* 1990; **113:** 715–16.
17. Sharff JA. Renal infarction associated with intravenous cocaine use. *Ann Emerg Med* 1984; **13:** 1145–7.
18. Bemanian S, *et al*. Cocaine-induced renal infarction: report of a case and review of the literature. *BMC Nephrol* 2005; **6:** 10. Available at: http://www.biomedcentral.com/1471-2369/6/10 (accessed 22/06/06)
19. McCord J, *et al*. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation* 2008; **117:** 1897–1907. Also available at: http://www.circ.ahajournals.org/cgi/reprint/117/14/1897 (accessed 21/12/09)

EFFECTS ON THE CNS. Severe CNS depression with deep coma has been seen in a few cocaine abusers after prolonged binges.[1]

1. Roberts JR, Greenberg MI. Cocaine washout syndrome. *Ann Intern Med* 2000; **132:** 679–80.

EFFECTS ON THE KIDNEYS. For reference to renal failure following rhabdomyolysis associated with cocaine abuse, see under Effects on the Muscles, below. There has been a report[1] of acute renal failure occurring in a 16-year-old girl secondary to cocaine abuse but without evidence of rhabdomyolysis.

For reference to renal ischaemia and infarction due to cocaine abuse, see under Effects on the Cardiovascular System, above.

1. Leblanc M, *et al*. Cocaine-induced acute renal failure without rhabdomyolysis. *Ann Intern Med* 1994; **121:** 721–2.

EFFECTS ON THE LUNGS. Smoking the free base has resulted in pulmonary complications not seen with other methods of abuse for cocaine. Associated adverse effects have included pulmonary oedema, hypersensitivity pneumonitis, pulmonary haemorrhage, obliterative bronchiolitis, abnormalities of pulmonary function, pneumomediastinum, and pneumothorax.[1] Severe or life-threatening exacerbations of asthma have also been reported.[2]

1. Ettinger NA, *et al*. A review of the respiratory effects of smoking cocaine. *Am J Med* 1989; **87:** 664–8.
2. Rubin RB, Neugarten J. Cocaine-associated asthma. *Am J Med* 1990; **88:** 438–9.

EFFECTS ON THE MOUTH. Abuse of cocaine can produce several adverse effects in the oral cavity including perforation of the palate (usually after perforation of the nasal septum), gingival lesions, and erosions of the teeth.[1]

1. Brand HS, *et al*. Cocaine and oral health. *Br Dent J* 2008; **204:** 365–9.

EFFECTS ON THE MUSCLES. Rhabdomyolysis, sometimes progressing to renal failure, has been associated with free-base smoking or injection of cocaine hydrochloride.[1-3]

1. Roth D, *et al*. Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; **319:** 673–7.
2. Herzlich BC, *et al*. Rhabdomyolysis related to cocaine abuse. *Ann Intern Med* 1988; **109:** 335–6.
3. Pogue VA, Nurse HM. Cocaine-associated acute myoglobinuric renal failure. *Am J Med* 1989; **86:** 183–6.

EFFECTS ON SEXUAL FUNCTION. While the initial euphoria of cocaine abuse may be accompanied by sexual arousal, sexual dysfunction can occur[1] and male infertility has been reported.[2] Priapism associated with cocaine abuse has also occurred.[3]

1. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315:** 1495–1500.
2. Bracken MB, *et al*. Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril* 1990; **53:** 315–22.
3. Altman AL, *et al*. Cocaine associated priapism. *J Urol* 1999; **161:** 1817–18.

EFFECTS ON THE SKIN. Urticarial vasculitis occurred in a young man after intranasal abuse of cocaine.[1]

1. Hofbauer GFL, *et al*. Uritcarial vasculitis following cocaine use. *Br J Dermatol* 1999; **141:** 600–601.

OVERDOSAGE. References to fatal overdosage from cocaine abuse.

1. Greenland VC, *et al*. Vaginally administered cocaine overdose in a pregnant woman. *Obstet Gynecol* 1989; **74:** 476–7.
2. Peretti FJ, *et al*. Cocaine fatality: an unexplained blood concentration in a fatal overdose. *Forensic Sci Int* 1990; **48:** 135–8.
3. Karch SB, *et al*. Relating cocaine blood concentrations to toxicity–an autopsy study of 99 cases. *J Forensic Sci* 1998; **43:** 41–5.

PREGNANCY. The effects of cocaine abuse during pregnancy have been reviewed.[1-4] Women who abuse cocaine during pregnancy appear to have an increased risk of spontaneous abortion,[5] abruptio placentae[6,7] and associated stillbirths,[8] premature labour,[9-11] and other birth complications.[9-11] These effects may be due to vasoconstriction by cocaine increasing maternal blood pressure and reducing placental blood flow.[12] Uterine rupture[13] during pregnancy and rupture of ectopic pregnancies[14] have also been associated with cocaine. Neonates born to mothers abusing cocaine have an increased risk of intra-uterine growth retardation and may have lower birth-weight, smaller head size, and shorter length.[6,8-10,15-17] Cocaine is possibly teratogenic and congenital abnormalities associated with abuse include cardiovascular abnormalities,[9,18,19] limb reduction defects,[20] intestinal atresia or infarction,[20] skull defects,[8] and genito-urinary tract anomalies.[21] Neurobehavioural impairment[22] and signs of transient CNS irritability[23] may also occur. Some workers[24,25] have found effects on cognition and motor delays while others have found effects on arousal and attention regulation rather than cognitive processes.[26,27] Cocaine can increase neonatal cerebral blood flow[28] and cerebral infarction and associated seizures have occurred in neonates whose mothers took cocaine near to the onset of labour.[29] Evidence on the risk of intraventricular haemorrhage is conflicting.[7,25]

1. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol* 1992; **79:** 778–89.
2. Volpe JJ. Effects of cocaine use on the fetus. *N Engl J Med* 1992; **327:** 399–407. Correction. *ibid.*; 1039.
3. Wiggins RC. Pharmacokinetics of cocaine in pregnancy and effects on fetal maturation. *Clin Pharmacokinet* 1992; **22:** 85–93.
4. Fajemirokun-Odudeyi O, Lindow SW. Obstetric implications of cocaine use in pregnancy: a literature review. *Eur J Obstet Gynecol Reprod Biol* 2004; **112:** 2–8.
5. Chasnoff IJ, *et al*. Cocaine use in pregnancy. *N Engl J Med* 1985; **313:** 666–9.
6. Dombrowski MP, *et al*. Cocaine abuse is associated with abruptio placentae and decreased birth weight, but not shorter labor. *Obstet Gynecol* 1991; **77:** 139–41.
7. Dusick AM, *et al*. Risk of intracranial hemorrhage and other adverse outcomes after cocaine exposure in a cohort of 323 very low birth weight infants. *J Pediatr* 1993; **122:** 438–45.
8. Bingol N, *et al*. Teratogenicity of cocaine in humans. *J Pediatr* 1987; **110:** 93–6.
9. Little BB, *et al*. Cocaine abuse during pregnancy: maternal and fetal implications. *Obstet Gynecol* 1989; **73:** 157–60.
10. Mastrogiannis DS, *et al*. Perinatal outcome after recent cocaine usage. *Obstet Gynecol* 1990; **76:** 8–11.
11. Spence MR, *et al*. The relationship between recent cocaine use and pregnancy outcome. *Obstet Gynecol* 1991; **78:** 326–9.
12. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
13. Gonsoulin W, *et al*. Rupture of unscarred uterus in primigravid woman in association with cocaine abuse. *Am J Obstet Gynecol* 1990; **163:** 526–7.
14. Thatcher SS, *et al*. Cocaine use and acute rupture of ectopic pregnancies. *Obstet Gynecol* 1989; **74:** 478–9.
15. Zuckerman B, *et al*. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; **320:** 762–8.
16. Chasnoff IJ, *et al*. Temporal patterns of cocaine use in pregnancy: perinatal outcome. *JAMA* 1989; **261:** 1741–4.
17. Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol* 1991; **77:** 361–4.
18. Lipshultz SE, *et al*. Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr* 1991; **118:** 44–51.
19. Shaw GM, *et al*. Maternal use of cocaine during pregnancy and congenital cardiac anomalies. *J Pediatr* 1991; **118:** 167–8.
20. Hoyme HE, *et al*. Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics* 1990; **85:** 743–7.
21. Chávez GF, *et al*. Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA* 1989; **262:** 795–8.
22. Singer LT, *et al*. Neurobehavioural sequelae of fetal cocaine exposure. *J Pediatr* 1991; **119:** 667–72.

23. Doberczak TM, *et al*. Neonatal neurologic and electroencephalographic effects of intrauterine cocaine exposure. *J Pediatr* 1988; **113:** 354–8.
24. Azuma SD, Chasnoff IJ. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. *Pediatrics* 1993; **92:** 396–402.
25. Singer LT, *et al*. Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr* 1994; **124:** 765–71.
26. Mayes LC, *et al*. Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine. *Pediatrics* 1995; **95:** 539–45.
27. Ackerman JP, *et al*. A review of the effects of prenatal cocaine exposure among school-aged children. *Pediatrics* 2010; **125:** 554–65.
28. van der Bor M, *et al*. Increased cerebral blood flow velocity in infants of mothers who abuse cocaine. *Pediatrics* 1990; **85:** 733–6.
29. Chasnoff IJ, *et al*. Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986; **108:** 456–9.

Treatment of Adverse Effects

As for Local Anaesthetics in general, p. 1979.1.

Cocaine overdosage. In the emergency management of overdosage with cocaine the general aims are to establish adequate ventilation and support the circulation. If oral ingestion of a large amount is suspected activated charcoal should be considered. A tourniquet may be applied to limit absorption if the drug was injected. Patients who have swallowed packages containing cocaine for the purpose of smuggling, may be given laxatives but surgical intervention may be required if signs of toxicity appear.

Sedation with intravenous diazepam may be sufficient to manage the symptoms of cocaine overdose. Sedation with benzodiazepines may also be appropriate initial therapy for hypertension or tachyarrhythmias since the excessive sympathetic tone is largely centrally mediated. If hypertension persists, intravenous nitrates should be given; calcium-channel blockers such as diltiazem, nifedipine, or verapamil are an alternative. Phentolamine or sodium nitroprusside may also be tried in patients with hypertension without any evidence of cardiac ischaemia. The use of pure beta blockers should be avoided because of the risk of paradoxical hypertension and coronary vasoconstriction, presumably due to unopposed α-adrenergic stimulation effects of cocaine. However, the beta blocker labetalol which has both α- and β-adrenergic effects may be considered. (For discussion on the use of beta blockers in cocaine-induced myocardial ischaemia, see Cocaine Toxicity under Precautions of Beta Blockers, p. 1320.3.) Chest pain should initially be treated with diazepam or buccal or sublingual nitrates; aspirin should also be given. Persistent pain may require treatment with calcium-channel blockers such as verapamil or intravenous nitrates. Verapamil may also be tried in narrow complex tachycardia. Broad complex tachycardia is treated with sodium bicarbonate; lidocaine may be tried in unresponsive patients. However, there is concern about the use of lidocaine for the treatment of cocaine-induced arrhythmias as lidocaine may enhance toxicity. Diazepam or lorazepam should be used to manage seizures but if they cannot be controlled, propofol or phenytoin can be tried. Hyperthermia should be treated with physical cooling but the use of dantrolene may also be necessary. Control of anxiety and agitation with benzodiazepines when combined with rapid cooling may also have the effect of decreasing heat production in hyperthermic patients. Metabolic acidosis should be monitored and treated where necessary. Short-acting barbiturates or benzodiazepines may be used for dysphoric agitation but drugs that lower the seizure threshold or aggravate hyperthermia such as phenothiazines or haloperidol should be avoided.

References.
1. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; **4:** 174–85.
2. Ramrakha P, Barton I. Drug smuggler's delirium. *BMJ* 1993; **306:** 470–1.
3. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1996; **38:** 43–6.
4. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
5. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; **333:** 1267–72.

Cocaine withdrawal syndrome. Cocaine can produce psychological dependence but does not produce a major physical withdrawal syndrome. The management of cocaine abuse and dependence has been reviewed.[1-3] There is no advantage to gradual withdrawal and it is best for the patient to stop the drug abruptly.[1,4] The three major psychiatric complications associated with cocaine withdrawal are dysphoric agitation, severe depression, and psychotic symptoms.[1] Such complications are initially managed with psychosocial treatments. However patients with more severe dependence or those who fail to respond to psychosocial treatments should be considered for drug therapies. Dysphoric agitation is best treated with diazepam; propranolol may also be used in more persistent cases. Depressive symptoms during the acute post-cocaine phase are usually transient and require no treatment other than close observation. Desipramine has been used with equivocal results; it appears to be of most benefit in patients who have antecedent or consequent symptoms of severe depression.[3] Trazodone and imipramine have also been tried but had more adverse effects than desipramine.[3] Furthermore, a systematic review has concluded that there was no evidence to support the use of antidepressants[5] in the treatment of cocaine dependence. Antipsychotics such as chlorpromazine, haloperidol, and promazine have been used to manage patients with psychotic symptoms associated with cocaine dependence.[1] However, a systematic review[6] of 7 small studies concluded that there was no evidence to support the use of antipsychotics in the treatment of cocaine dependence; the drugs studied were haloperidol, olanzapine, and risperidone.

Several drugs have been tried in the maintenance of abstinence from cocaine.[1] Lithium may be useful in patients with bipolar disorder or cyclothymic personality. Methylphenidate may be helpful in patients with attention deficit disorders but has potential for abuse itself. Phenothiazine derivatives have been tried in the control of impulsive behaviour and to decrease cocaine craving, although adverse effects may limit their acceptability. Carbamazepine has been reported to suppress the craving for cocaine although this has not been supported by subsequent studies.[3] Furthermore, a systematic review[7] has concluded that there was no evidence to support the use of anticonvulsants (i.e. carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and valproate) in the treatment of cocaine dependence. Buprenorphine has been investigated to suppress cocaine and opioid use in patients dependent on both drugs.[3] Anxiolytics or antidepressants are considered unlikely to be of benefit in maintaining abstinence.[3] MAOIs such as phenelzine have been used in a manner analogous to the use of disulfiram in alcohol abuse to provoke unpleasant reactions if patients relapse.[8] Disulfiram itself has also been tried with some success (see below).

There is evidence to suggest that cocaine use affects the dopaminergic modulation of CNS function, and several drugs that interact with the dopamine system have been tried in the treatment of cocaine abuse and dependence.[3,9] For most drugs the results have been disappointing or equivocal although disulfiram and selegiline may warrant further investigation.[9]

A vaccine is under investigation for the treatment of cocaine dependence.

1. Arif A, ed. *Adverse health consequences of cocaine abuse*. Geneva: WHO, 1987.
2. Kleber HD. Pharmacotherapy, current and potential, for the treatment of cocaine dependence. *Clin Neuropharmacol* 1995; **18** (suppl 1): S96–S109.
3. Mendelson JH, Mello NK. Management of cocaine abuse and dependence. *N Engl J Med* 1996; **334:** 965–72.
4. DoH (England) and the devolved administrations (2007). *Drug misuse and dependence: UK guidelines on clinical management* (updated September 2007). London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive. Also available at: http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf (accessed 06/08/10)
5. de Lima MS, *et al*. Antidepressants for cocaine dependence. [Withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 17/08/10).
6. Amato L, *et al*. Antipsychotic medications for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 21/12/09).
7. Minozzi S, *et al*. Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/12/09).
8. Brewer C. Cocaine and crack. *BMJ* 1989; **299:** 792.
9. Gorelick DA, *et al*. Agents in development for the management of cocaine abuse. *Drugs* 2004; **64:** 1547–73.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Since some patients have a marked sensitivity to cocaine, giving a test dose before use on mucous membranes has been suggested. Cocaine should not be applied to damaged mucosa because of the risk of systemic toxicity from enhanced absorption. Ophthalmic preparations of cocaine should not be applied to the eyes for prolonged periods as damage to the cornea may occur not only from the local action of cocaine, but also from loss of the protective eyelid reflexes. As with other mydriatics, there is also a risk of cocaine precipitating angle-closure glaucoma in patients predisposed to the condition. Patients receiving cocaine for surface anaesthesia should be monitored for possible cardiovascular effects. Cocaine should be used with great caution in patients with hypertension, cardiovascular disease, or thyrotoxicosis. It is not recommended for use during pregnancy or breast feeding.

Abuse. Cocaine is subject to abuse. See under Adverse Effects, p. 1984.3.

Gilles de la Tourette's syndrome. Gilles de la Tourette's syndrome, which had been well controlled for 10 years by haloperidol, was precipitated in a 27-year-old man after intranasal use of cocaine on one occasion.[1]

1. Mesulam M-M. Cocaine and Tourette's syndrome. *N Engl J Med* 1986; **315:** 398.

Myasthenia gravis. Report of a patient in whom cocaine abuse first unmasked and then exacerbated myasthenia gravis.[1]

1. Berciano J, *et al*. Myasthenia gravis unmasked by cocaine abuse. *N Engl J Med* 1991; **325:** 892.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Cocaine and adrenaline enhance each other's sympathomimetic effects and should preferably not be used together. Caution is needed if cocaine is used with other drugs that may also potentiate the action of catecholamines such as guanethidine or MAOIs.

Adrenaline. In a report[1] of 3 cases of arrhythmias associated with the use of a paste containing cocaine 25% and adrenaline 0.18% for local anaesthesia of the nasal mucosa, the amount of cocaine applied to the nasal mucosa ranged from about 2.5 to 4.5 mg/kg. The maximum recommended dose of cocaine alone in healthy adults is 1.5 mg/kg.

1. Nicholson KEA, Rogers JEG. Cocaine and adrenaline paste: a fatal combination? *BMJ* 1995; **311:** 250–1.

Alcohol. In the presence of alcohol, cocaine is metabolised to its ethyl homologue cocaethylene.[1] Cocaethylene appears to have the same stimulant effects as cocaine but it has a longer half-life and *animal* studies suggest that it is more toxic than the parent drug. However, a review of the literature concluded that the use of cocaine with alcohol did not cause more cardiovascular problems than expected from the additive effects of each drug.[2]

1. Randall T. Cocaine, alcohol mix in body to form even longer lasting, more lethal drug. *JAMA* 1992; **267:** 1043–4.
2. Pennings EJM, *et al*. Effects of concurrent use of alcohol and cocaine. *Addiction* 2002; **97:** 773–83.

Beta blockers. *Propranolol* potentiated cocaine-induced coronary vasoconstriction after intranasal dosage of cocaine in a placebo-controlled study.[1] Because of a possible risk of paradoxical hypertension associated with the use of propranolol to manage arrhythmias associated with cocaine overdosage some prefer the use of labetalol for this indication (see under Treatment of Adverse Effects, above).

1. Lange RA, *et al*. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990; **112:** 897–903.

Haloperidol. For the effect of haloperidol in cocaine abusers, see under Chlorpromazine, p. 1053.1.

Pharmacokinetics

Cocaine may be slowly absorbed from some sites because of the vasoconstriction it produces, but absorption occurs from all sites of application, including mucous membranes and the gastrointestinal tract, and may be enhanced when there is inflammation. Cocaine is rapidly absorbed when smoked.

Cocaine is rapidly metabolised by plasma esterases and hepatic esterases to ecgonine methyl ester. Benzoylecgonine, another major metabolite of cocaine, may be produced by spontaneous hydrolysis. Cocaine is also demethylated to the active metabolite norcocaine which is not excreted but undergoes further metabolism. There is considerable interindividual variation in the plasma half-life of cocaine possibly due to differences in esterase activity.

Cocaine and its metabolites are excreted in the urine, about 10% appearing as unchanged drug; they may be detectable in urine for several days or even weeks after use. Cocaine crosses the blood-brain barrier and accumulates within the CNS. It does not appear to undergo rapid metabolism within the brain and concentrations in the CNS after acute intoxication may greatly exceed those in plasma.

Cocaine crosses the placenta and the presence of its metabolites in neonatal hair has been used to indicate intrauterine exposure. Cocaine is distributed into breast milk.

See also under Local Anaesthetics, p. 1979.3.

References.
1. Busto U, *et al*. Clinical pharmacokinetics of non-opiate abused drugs. *Clin Pharmacokinet* 1989; **16:** 1–26.
2. Graham K, *et al*. Determination of gestational cocaine exposure by hair analysis. *JAMA* 1989; **262:** 3328–30.
3. Burke WM, Ravi NV. Urinary excretion of cocaine. *Ann Intern Med* 1990; **112:** 548–9.
4. Ravi NV, Burke WM. Cocaine and traffic accident fatalities in New York City. *JAMA* 1990; **263:** 2887.
5. Schenker S, *et al*. The transfer of cocaine and its metabolites across the term human placenta. *Clin Pharmacol Ther* 1993; **53:** 329–39.

Absorption. Cocaine is rapidly absorbed from the pulmonary vasculature when smoked and the speed of onset of its effects is similar to that obtained after intravenous injection.[1] Absorption from mucous membranes is delayed by vasoconstriction and peak plasma concentrations of up to 474 nanograms/mL have occurred 15 to 120 minutes after application of doses of 1.5 to 2 mg/kg to the nasal mucosa as a 10% cocaine hydrochloride solution;[2,3] coc-

aine may still be detectable in the nose several hours later and this may result in prolonged systemic absorption.[2] In a study it was estimated that only 5% of the total dose of cocaine hydrochloride used before nasal surgery was absorbed from the nasal mucosa after application of 500 mg of cocaine hydrochloride as a 25% paste with adrenaline or 200 mg as a 10% solution with adrenaline (Moffett's solution) and blood concentrations were well below those associated with toxicity[4] (but see also Adrenaline, under Interactions, p. 1986.3). Peak serum concentrations of cocaine have been obtained 50 to 90 minutes after oral use and are similar to those obtained with nasal application.[3]

1. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
2. Van Dyke C, *et al.* Cocaine: plasma concentrations after intranasal application in man. *Science* 1976; **191:** 859–61.
3. Van Dyke C, *et al.* Oral cocaine: plasma concentrations and central effects. *Science* 1978; **200:** 211–13.
4. Quiney RE. Intranasal topical cocaine: Moffett's method or topical cocaine paste? *J Laryngol Otol* 1986; **100:** 279–83.

Preparations

Pharmacopoeial Preparations
BP 2014: Adrenaline and Cocaine Intranasal Solution; Cocaine Eye Drops; Cocaine Paste;
USP 36: Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Cocaine Hydrochloride Tablets for Topical Solution.

Dyclonine Hydrochloride *(BANM, rINNM)*

Diclonina, hidrocloruro de; Dyclocaine Hydrochloride; Dyclocaini Chloridum; Dyclonine, Chlorhydrate de; Dyclonini Hydrochloridum; Hidrocloruro de diclonina; Диклонина Гидрохлорид.
4′-Butoxy-3-piperidinopropiophenone hydrochloride.
$C_{18}H_{27}NO_2$,HCl=325.9
CAS — 586-60-7 (dyclonine); 536-43-6 (dyclonine hydrochloride).
ATC — N01BX02; R02AD04.
ATC Vet — QN01BX02; QR02AD04.
UNII — ZEC193879Q.

Pharmacopoeias. In *US.*

USP 36: (Dyclonine Hydrochloride). White crystals or white crystalline powder, with a slight odour. Soluble 1 in 60 of water, 1 in 24 of alcohol, and 1 in 2.3 of chloroform; soluble in acetone; practically insoluble in ether and in hexane. A 1% solution in water has a pH of 4.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Dyclonine hydrochloride is a local anaesthetic (p. 1976.1) used topically for surface anaesthesia of the skin and mucous membranes. Lozenges containing up to 3 mg and throat sprays containing 0.1% of dyclonine hydrochloride have been used for the temporary relief of pain associated with sore throats or mouth irritation; a gel has also been used. It may cause irritation at the site of application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Cepacol Spray†; Sucrets for Kids; Sucrets Vapor†; Sucrets†; ***China***: Da Ji Su (达己苏); ***USA***: Sucrets Childrens Formula; Sucrets Original Formula Sore Throat Wild Cherry; Sucrets Throat Spray.

Multi-ingredient Preparations. ***Canad.***: Sucrets Complete; ***USA***: Cepacol Maximum Strength Sore Throat†; Skin Shield; Sucrets Complete; Sucrets Maximum Strength Sore Throat; Tanac.

Pharmacopoeial Preparations
USP 36: Dyclonine Hydrochloride Gel; Dyclonine Hydrochloride Topical Solution.

Ethyl Chloride

Ethyli Chloridum; Aethylium Chloratum; Chlorethyl; Cloruro de Etilo; Ethylis Chloridum; Etylklorid; Etylu chlorek; Etyylikloridi; Hydrochloric Ether; Monochlorethane; Этилхлорид; Хлористый Этил.
Chloroethane.
C_2H_5Cl=64.51
CAS — 75-00-3.
ATC — N01BX01.
ATC Vet — QN01BX01.
UNII — 46U771ERWK.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Ethyl Chloride). A colourless, mobile, very volatile liquid at low temperatures or under pressure, with a characteristic ethereal odour. B.p. 12 degrees to 13 degrees. Slightly soluble in water; freely soluble in alcohol and in ether. Store in airtight containers, preferably hermetically sealed.

Stability. Ethyl chloride is highly flammable and mixtures of the gas with 5 to 15% of air are explosive.

Uses and Administration

Owing to its low boiling-point and the intense cold produced by evaporation, ethyl chloride has been used as a local anaesthetic in minor surgery but such use is not generally recommended. It has also been used topically for the relief of pain and to test the efficacy of regional anaesthesia. Ethyl chloride was formerly used as an inhalational anaesthetic but has no place in modern anaesthetic practice.

Adverse Effects and Precautions

As for Chloroform, p. 1898.2.

Cutaneous sensitisation can occur rarely. Thawing of frozen tissue following surgery may be painful and prolonged spraying onto the skin can cause chemical frostbite. Freezing may also distort the histological structure of biopsy specimens. Ethyl chloride should not be applied to broken skin or mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: ShiBo (施博); ***Ger.***: Chloraethyl Dr Henning; ***Hong Kong***: WariActiv; ***Israel***: Chloraethyl Dr Henning; ***Mex.***: Traumazol; ***Spain***: Cloretilo Chemirosa; ***Switz.***: Chlorethyl†; ***UK***: Cryogesic.

Multi-ingredient Preparations. ***USA***: Fluro-Ethyl†.

Ethyl *p*-Piperidinoacetylaminobenzoate

EPAB; *p*-Piperidinoacetilaminobenzoato de etilo; SA-7.
4-[(1-Piperidinylacetyl)amino]benzoic acid ethyl ester.
$C_{16}H_{22}N_2O_3$=290.4
CAS — 41653-21-8.
UNII — 6M452G7O1F.

NOTE. The name Nichicaine has been used as a trade mark for ethyl *p*-piperidinoacetylaminobenzoate.

Profile

Ethyl *p*-piperidinoacetylaminobenzoate is an amide local anaesthetic (p. 1976.1) that has been given orally for the symptomatic relief of gastritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Sulcain.

Ketocaine Hydrochloride *(rINNM)*

Chetocaina Cloridrata; Hidrocloruro de ketocaína; Ketocaína, hidrocloruro de; Kétocaïne, Chlorhydrate de; Ketocaini Hydrochloridum; Кетокаина Гидрохлорид.
2′-(2-Di-isopropylaminoethoxy)butyrophenone hydrochloride.
$C_{18}H_{29}NO_2$,HCl=327.9
CAS — 1092-46-2 (ketocaine); 1092-47-3 (ketocaine hydrochloride).

Profile

Ketocaine hydrochloride is a local anaesthetic (p. 1976.1) that has been used as a surface anaesthetic in suppositories or ointments for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Proctolyn.

Levobupivacaine *(BAN, rINN)*

S (-)-Bupivacaine; Levobupivacaína; Lévobupivacaïne; Levobupivacainum; Levobupivakaiini; Levobupivakain; Левобупивакаин.
(*S*)-1-Butyl-2-piperidylformo-2′,6′-xylidide.
$C_{18}H_{28}N_2O$=288.4
CAS — 27262-47-1.
ATC — N01BB10.
ATC Vet — QN01BB10.
UNII — A5H73K9U3W.

Levobupivacaine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levobupivacaína; Levobupivacaína, hidrocloruro de; Lévobupivacaïne, Chlorhydrate de; Levobupivacaini Hydrochloridum; Levobupivakain Hidroklorür; Левобупивакаина Гидрохлорид.
$C_{18}H_{28}N_2O$,HCl=324.9
CAS — 27262-48-2.
ATC — N01BB10.
ATC Vet — QN01BB10.
UNII — J998RDZ51I.

Uses and Administration

Levobupivacaine is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is the *S*-enantiomer of bupivacaine (p. 1980.3). Levobupivacaine is given as the hydrochloride for infiltration anaesthesia and regional nerve blocks including epidural block; however, it is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is also contra-indicated for epidural blocks in obstetrics. (Local anaesthetic techniques are discussed on p. 1977.2.)

Levobupivacaine hydrochloride is available in solutions containing the equivalent of 0.0625 to 0.75% of levobupivacaine. The dosage depends on the site of injection and the procedure used as well as the status of the patient. The recommended **maximum single dose** is 150 mg. The total daily dose should not exceed 400 mg. A test dose of a suitable local anaesthetic, preferably with adrenaline, should be given before starting epidural block with levobupivacaine to detect inadvertent intravascular injection. Subsequent doses of levobupivacaine should be given in small increments. Levobupivacaine should be given in reduced doses to elderly, debilitated, or acutely ill patients.

- For **surgical anaesthesia** doses of levobupivacaine for *epidural block* are 50 to 100 mg (10 to 20 mL) as a 0.5% solution, or 75 to 150 mg (10 to 20 mL) as a 0.75% solution; for caesarean section, doses are 75 to 150 mg (15 to 30 mL) as a 0.5% solution. The dose for *spinal block* is 15 mg (3 mL) as a 0.5% solution.
- For *peripheral nerve blocks*, doses are 2.5 to 150 mg as a 0.25 or 0.5% solution; a volume of 40 mL should not be exceeded.
- For *infiltration anaesthesia* up to 150 mg (60 mL) as a 0.25% solution may be used. For peribulbar block in *ophthalmic* procedures 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution may be given. For ilioinguinal or iliohypogastric blocks in **children** under 12 years of age, doses of levobupivacaine are 0.625 to 2.5 mg/kg (0.25 to 0.5 mL/kg) as a 0.25 or 0.5% solution.
- In the management of **acute pain** levobupivacaine may be given as an epidural bolus or by continuous infusion. For pain relief during *labour* 15 to 50 mg (6 to 20 mL) as a 0.25% solution is given as a bolus. Alternatively, levobupivacaine may be given as an infusion in a dose of 5 to 12.5 mg per hour as a 0.125% solution (4 to 10 mL per hour) or as a 0.0625% solution (8 to 20 mL per hour). For *postoperative pain*, an epidural infusion may be given in a dose of 12.5 to 18.75 mg per hour as a 0.25% solution (5 to 7.5 mL per hour), a 0.125% solution (10 to 15 mL per hour), or a 0.0625% solution (20 to 30 mL per hour).

In some countries such as the UK, licensed product information recommends that a lower concentration such as the 0.125% solution should be used if other analgesics are also given for pain relief. When necessary, dilutions should be made with sodium chloride 0.9%.

Reviews

1. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs* 2000; **59:** 551–79.
2. Sanford M, Keating GM. Levobupivacaine: a review of its use in regional anaesthesia and pain management. *Drugs* 2010; **70:** 761–91.

Action. A comparison[1] of epidural bupivacaine with levobupivacaine in women in labour found that levobupivacaine had 98% of the potency of the racemate, a clinically insignificant difference. However it was pointed out that whereas the concentration of bupivacaine solutions was expressed in terms of the hydrochloride, solutions of levobupivacaine had their strength expressed in terms of the free base. When calculations were made in terms of molar equivalents levobupivacaine appeared to be 13% less potent than racemic bupivacaine. The difference in expression should be borne in mind when evaluating comparative studies.

1. Lyons G, *et al.* Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; **81:** 899–901.

Administration in children. The *BNFC* recommends that the dose of levobupivacaine in children should be adjusted

according to physical status and the nature of the procedure.

For the licensed dosage of levobupivacaine hydrochloride for ilioinguinal or iliohypogastric blocks in children, see p. 1987.3.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Levobupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is also contra-indicated for epidural block in obstetrics.

Effects on the cardiovascular system. It has been suggested[1] that levobupivacaine may have a lower risk of causing cardiotoxicity than bupivacaine (for the effects of bupivacaine on the cardiovascular system see p. 1981.3).

1. Mather LE, Chang DH. Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs* 2001; **61:** 333–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levobupivacaine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3. Plasma concentrations of levobupivacaine may be reduced by enzyme-inducing drugs such as rifampicin. Levobupivacaine is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP1A2 and there is a theoretical possibility that substrates for or inhibitors of these isoenzymes may adversely alter plasma concentrations of levobupivacaine.

Pharmacokinetics

The pharmacokinetics of levobupivacaine are similar to those of the racemic form, bupivacaine (p. 1982.2). Levobupivacaine is at least 97% bound to plasma proteins. After intravenous doses the mean half-life is about 80 minutes. Levobupivacaine is extensively metabolised and excreted as its metabolites mainly in the urine, with smaller amounts appearing in the faeces. 3-Hydroxylevobupivacaine is a major metabolite and its formation is mediated by the cytochrome P450 isoenzyme CYP1A2; the isoenzyme CYP3A4 is also involved in the metabolism of levobupivacaine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Chirocaine; ***Austria***: Chirocaine; ***Belg.***: Chirocaine; ***Braz.***: Novabupi; ***Chile***: Chirocaina; ***China***: Ao Gui Ren (奥桂仁); Chirocaine (凯乐); Su Ka (速卡); Yi Jie Ka (伊捷卡); ***Cz.***: Chirocaine; ***Fin.***: Chirocaine; ***Fr.***: Chirocaine; ***Gr.***: Chirocaine; ***Hong Kong***: Chirocaine; ***Hung.***: Chirocaine†; ***Irl.***: Chirocaine; ***Ital.***: Chirocaine; ***Jpn***: Popscaine; ***Mex.***: Quirocaine†; ***Neth.***: Chirocaine; ***Philipp.***: SensiBloq; ***Port.***: Chirocaine; ***S.Afr.***: Chirocaine; ***Singapore***: Chirocaine; ***Spain***: Chirocane; ***Swed.***: Chirocaine; ***Switz.***: Chirocaine; ***Thai.***: Chirocaine; ***Turk.***: Chirocaine; ***UK***: Chirocaine; ***Venez.***: Chirocaina.

Lidocaine *(BAN, rINN)*

Lidocain; Lidocaína; Lidocaïne; Lidocainum; Lidokaiini; Lidokain; Lidokaina; Lidokainas; Lignocaína; Lignocaine; Лидокаин.

2-Diethylaminoaceto-2′,6′-xylidide.

$C_{14}H_{22}N_2O$=234.3

CAS — 137-58-6.

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

UNII — 98PI200987.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Lidocaine). A white or almost white, crystalline powder. M.p. 66 degrees to 70 degrees. Practically insoluble in water; very soluble in alcohol and in dichloromethane.

USP 36: (Lidocaine). A white to slightly yellow crystalline powder with a characteristic odour. M.p. 66 degrees to 69 degrees. Practically insoluble in water; very soluble in alcohol and in chloroform; freely soluble in ether and in benzene; dissolves in oils.

Eutectic mixture. Lidocaine forms a mixture with prilocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Lidocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lidocaína; Hidrocloruro de lignocaína; Lidocaína, hidrocloruro de; Lidocaïne, Chlorhydrate de; Lidocainhydrochlorid; Lidocaini hydrochloridum; Lidocaini Hydrochloridum Monohydricum; Lidokaiinihydrokloridi; Lidokain Hidroklorür; Lidokain-hidroklorid; Lidokain-hydrochlorid monohydrát; Lidokainhydroklorid; Lidokaino hidrochloridas; Lidokainy chlorowodorek; Lignoc. Hydrochlor.; Lignocaine Hydrochloride; Lignokain Hidroklorür; Лидокаина Гидрохлорид.

$C_{14}H_{22}N_2O,HCl,H_2O$=288.8

CAS — 73-78-9 (anhydrous lidocaine hydrochloride); 6108-05-0 (lidocaine hydrochloride monohydrate).

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

UNII — V13007Z41A (lidocaine hydrochloride monohydrate); EC2CNF7XFP (anhydrous lidocaine hydrochloride).

NOTE. LIDFLN is a code approved by the BP 2014 for use on single unit doses of eye drops containing lidocaine hydrochloride and fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Lidocaine Hydrochloride). A white, or almost white, crystalline powder. M.p. 74 degrees to 79 degrees. Very soluble in water; freely soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 36: (Lidocaine Hydrochloride). A white, odourless, crystalline powder. M.p. 74 degrees to 79 degrees. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Incompatibility. Lidocaine hydrochloride has been reported to be incompatible in solution with amphotericin B,[1] sulfadiazine sodium,[2] methohexital sodium,[2] cefazolin sodium,[3] or phenytoin sodium.[4]

Acid stable drugs such as adrenaline hydrochloride, noradrenaline acid tartrate, or isoprenaline may begin to deteriorate within several hours of admixture with lidocaine hydrochloride as lidocaine solutions may raise the pH of the final solution above the maximum pH for their stability. Such extemporaneous mixtures should be used promptly after preparation.[5]

1. Whiting DA. Treatment of chromoblastomycosis with high local concentrations of amphotericin B. *Br J Dermatol* 1967; **79:** 345–51.
2. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28:** 228–40.
3. Kleinberg ML, *et al.* Stability of antibiotics frozen and stored in disposable hypodermic syringes. *Am J Hosp Pharm* 1980; **37:** 1087–8.
4. Kirschenbaum HL, *et al.* Stability and compatibility of lidocaine hydrochloride with selected large-volume parenterals and drug additives. *Am J Hosp Pharm* 1982; **39:** 1013–15.
5. Parker EA. Xylocaine hydrochloride 2% injection. *Am J Hosp Pharm* 1971; **28:** 805.

pH of solutions. For the effect pH has on the surface tension and administration of lidocaine solutions by infusion, see under Administration in Uses and Administration, p. 1976.2. For its effect on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Stability. Although there was no decrease in the lidocaine content of lidocaine hydrochloride and adrenaline injection during transport and storage under tropical conditions, the content of adrenaline fell to almost zero in some samples after several months; supply of the injection as a dry powder and separate solvent should be considered for the tropics.[1]

The lidocaine content of buffered cardioplegic solutions has been reported[2] to decrease when stored in PVC containers at ambient temperature, but not when stored at 4 degrees. This loss appeared to result from pH-dependent sorption of lidocaine onto the plastic and did not occur when lidocaine solutions were stored in glass bottles.

1. Abu-Reid IO, *et al.* Stability of drugs in the tropics: a study in Sudan. *Int Pharm J* 1990; **4:** 6–10.
2. Lackner TE, *et al.* Lidocaine stability in cardioplegic solution stored in glass bottles and polyvinyl chloride bags. *Am J Hosp Pharm* 1983; **40:** 97–101.

Uses and Administration

Lidocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is used for infiltration anaesthesia and regional nerve blocks. It has a rapid onset of action and anaesthesia is obtained within a few minutes; it has an intermediate duration of action. The speed of onset and duration of action of lidocaine are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced. It is generally given as the hydrochloride. Lidocaine hydrochloride monohydrate 1.23 g or anhydrous lidocaine hydrochloride 1.16 g are both equivalent to about 1 g of lidocaine. A carbonated solution of lidocaine is also available in some countries for injection (see p. 1976.2). Lidocaine is also a useful surface anaesthetic but it may be rapidly and extensively absorbed following topical application to mucous membranes, and systemic effects may occur. Hyaluronidase (p. 2527.2) has been added to preparations of lidocaine used for surface and infiltration anaesthesia but may enhance systemic absorption. (Local anaesthetic techniques are discussed on p. 1977.2.)

Lidocaine is included in some injections, such as depot corticosteroids, to prevent pain, itching, and other local irritation. Lidocaine sodium has also been included in intramuscular injections of some antibacterials to reduce the pain on injection.

Lidocaine is also a class Ib antiarrhythmic used in the treatment of ventricular arrhythmias, especially after myocardial infarction. It has been given by intravenous infusion in the treatment of refractory status epilepticus.

USE IN LOCAL ANAESTHESIA.

The dose of lidocaine hydrochloride used for local anaesthesia depends on the site of injection and the procedure used. Specific doses for individual procedures are not always available in UK licensed product information, although US product information often includes them (see below). When given with adrenaline, the suggested general **maximum single dose** of lidocaine hydrochloride is 500 mg; without adrenaline, the recommended maximum single dose in the UK is 200 mg and in the USA, 300 mg, except for spinal anaesthesia (see below). Lidocaine hydrochloride solutions containing adrenaline 1 in 200 000 are used for infiltration anaesthesia and nerve blocks including epidural block; higher concentrations of adrenaline are seldom necessary, except in dentistry, where solutions of lidocaine hydrochloride with adrenaline 1 in 80 000 are widely used. Doses should be reduced in children, the elderly, and in debilitated patients. A test dose, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular or subarachnoid dosage.

The following doses have been recommended for individual **local anaesthetic procedures** in the USA:

- For percutaneous *infiltration anaesthesia*, 5 to 300 mg (1 to 60 mL of a 0.5% solution, or 0.5 to 30 mL of a 1% solution).
- The dosage in *peripheral nerve block* depends on the route. For brachial plexus block 225 to 300 mg (15 to 20 mL) as a 1.5% solution is used; for dental nerve block a 2% solution may be used in doses of 20 to 100 mg (1 to 5 mL); for intercostal nerve block 30 mg (3 mL) is given as a 1% solution; for paracervical block a 1% solution is used in a dose of 100 mg (10 mL) on each side, repeated not more frequently than every 90 minutes; for paravertebral block a 1% solution may be used in doses of 30 to 50 mg (3 to 5 mL); a 1% solution is recommended for pudendal block in doses of 100 mg (10 mL) on each side; for retrobulbar block a 4% solution may be used in doses of 120 to 200 mg (3 to 5 mL).
- For *sympathetic nerve block* a 1% solution is recommended; doses are 50 mg (5 mL) for cervical block and 50 to 100 mg (5 to 10 mL) for lumbar block.
- For *epidural anaesthesia* 2 to 3 mL of solution is needed for each dermatome to be anaesthetised but usual total doses and recommended concentrations are: lumbar epidural 250 to 300 mg (25 to 30 mL) as a 1% solution for analgesia and 225 to 300 mg (15 to 20 mL) as a 1.5% solution or 200 to 300 mg (10 to 15 mL) as a 2% solution for anaesthesia, and for thoracic epidural a 1% solution may be used at doses of 200 to 300 mg (20 to 30 mL). In obstetric caudal analgesia 200 to 300 mg (20 to 30 mL) is used as a 1% solution and in surgical caudal anaesthesia a 1.5% solution may be used in doses of 225 to 300 mg (15 to 20 mL). For continuous epidural or caudal anaesthesia, the maximum doses should not be repeated more frequently than every 90 minutes.
- A hyperbaric solution of 1.5% or 5% lidocaine hydrochloride in glucose 7.5% solution is available for *spinal anaesthesia*; adrenaline should not be used. Doses of up to 50 mg (1 mL) as a 5% solution and 9 to 15 mg (0.6 to 1 mL) as a 1.5% solution have been used during labour for a normal vaginal delivery. Up to 75 mg (1.5 mL) as the 5% solution has been used for caesarean section and 75 to 100 mg (1.5 to 2 mL) for other surgical procedures.
- For *intravenous regional anaesthesia* a 0.5% solution without adrenaline has been used in doses of 50 to 300 mg (10 to 60 mL); a maximum dose of 4 mg/kg has been recommended for adults.

Lidocaine may be used in a variety of formulations for **surface anaesthesia**.

- Lidocaine ointment is used for *anaesthesia of skin and mucous membranes* with a maximum recommended total

dose of 20 g of 5% ointment (equivalent to 1 g of lidocaine base) in 24 hours.

- A 4% foam may be applied to the skin up to 3 or 4 times daily for the *relief of pain* caused by minor cuts or burns, abrasions, sunburn, and insect bites.
- Gels are used for *anaesthesia of the urinary tract* and the dose used varies in different countries. UK licensed product information recommends instilling about 120 to 220 mg (6 to 11 mL) of lidocaine hydrochloride as a 2% gel into the urethra several minutes before examination. The doses used in the USA are as follows: in females 60 to 100 mg of lidocaine hydrochloride as a 2% gel is inserted into the urethra several minutes before examination; in males 100 to 200 mg is used before catheterisation and 600 mg before sounding or cystoscopy.
  A 2% gel may also be used as *anaesthetic lubrication for endotracheal intubation*; a moderate amount is applied to the external surface of the endotracheal tube shortly before use.
  A eutectic gel containing lidocaine base 2.5% and prilocaine base 2.5% is used for *anaesthesia of the periodontal pockets* during dental scaling and/or root planing. Typically, 1.7 g of gel, or less, will be sufficient for one quadrant of dentition; the maximum recommended quantity per treatment session is 8.5 g.
- Topical solutions are used for *surface anaesthesia of mucous membranes of the mouth, throat, and upper gastrointestinal tract*. For painful conditions of the mouth and throat a 2% solution may be used: 300 mg (15 mL) may be rinsed and ejected or, for pharyngeal pain, the solution is gargled and swallowed if necessary; it should not be used more frequently than every 3 hours to a maximum daily dose of 2.4 g. Doses of 40 to 200 mg as a 4% solution (1 to 5 mL) are used before bronchoscopy, bronchography, laryngoscopy, oesophagoscopy, endotracheal intubation, and biopsy in the mouth and throat. Lidocaine in a strength of 10% has also been used as a spray for application to mucous membranes for the prevention of pain during various procedures including use in otorhinolaryngology, dentistry, introduction of instruments into the respiratory and gastrointestinal tracts, and in obstetrics. The dose depends on the extent of the site to be anaesthetised; 10 to 50 mg is generally sufficient for dentistry and otorhinolaryngology; for other procedures, the maximum dose in a 24-hour period is 200 mg. For laryngotracheal anaesthesia 160 mg of lidocaine hydrochloride as a 4% solution is sprayed or instilled as a single dose into the lumen of the larynx and trachea.
- Lidocaine is used *rectally* as suppositories, sprays, ointments, and creams in the treatment of haemorrhoids and other painful perianal conditions.
- *Eye drops* containing lidocaine hydrochloride 4% with fluorescein are used in tonometry.
  An *ophthalmic gel* containing lidocaine hydrochloride 3.5% is used for surface anaesthesia during ophthalmological procedures.
- A *eutectic mixture* containing lidocaine base 2.5% and prilocaine base 2.5% is applied as a cream under an occlusive dressing to produce *surface anaesthesia of the skin* before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts (see also under Surface Anaesthesia, below).
- Other methods of dermal delivery include a *transdermal patch* of lidocaine 5% for the symptomatic relief of neuropathic pain associated with postherpetic neuralgia, and an *iontophoretic drug delivery system* incorporating lidocaine and adrenaline. A transdermal patch containing lidocaine 70 mg with tetracaine 70 mg is also available for surface anaesthesia.

USE IN ARRHYTHMIAS.

For the treatment of **ventricular arrhythmias** lidocaine is given *intravenously* as the hydrochloride. It may be used in advanced cardiac life support for cardiac arrest due to ventricular fibrillation and pulseless ventricular tachycardia when direct current shocks (together with adrenaline) have failed to restore a normal rhythm. For adults, a usual dose of 1 to 1.5 mg/kg can be given and repeated as necessary to a maximum total dose of 3 mg/kg. The *endotracheal* route has been used when intravenous access cannot be obtained, although doses should probably be larger than those given intravenously; the precise endotracheal dose has not yet been established, however.

Lidocaine is also used in other ventricular arrhythmias in which the patient is in a more stable condition. In these circumstances lidocaine hydrochloride is usually given as a loading dose followed by an infusion. Usual doses are 50 to 100 mg or 1 to 1.5 mg/kg as a direct *intravenous injection* at a rate of 25 to 50 mg/minute. If no effect is seen within 5 to 10 minutes of this loading dose, it may be repeated once or twice to a maximum dose of 200 to 300 mg in 1 hour. A *continuous intravenous infusion* is usually started after loading, at a dose of 1 to 4 mg/minute. It is rarely necessary to continue this infusion for longer than 24 hours, but in the event that a longer infusion is required, the dose may need to be reduced to avoid potential toxicity resulting from an increase in the half-life. Dosage may need to be reduced in the elderly and in patients with heart failure or liver disorders.

In emergency situations, lidocaine hydrochloride has also been given for arrhythmias by *intramuscular* injection into the deltoid muscle in a dose of 300 mg, repeated if necessary after 60 to 90 minutes.

Action. For a comparison of the vasoactivity of lidocaine and some other local anaesthetics, see p. 1976.2.

Administration in children. The *BNFC* recommends that the dose of lidocaine in children should be adjusted according to physical status and the nature of the procedure.

Burns. Lidocaine given intravenously has been reported to have produced pain relief in a few patients with second-degree burns.[1]

1. Jönsson A, *et al.* Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991; **338:** 151–2.

Cardiac arrhythmias. Lidocaine is classified as a class Ib antiarrhythmic drug (p. 1243.1) and may be used in the treatment of ventricular arrhythmias, including those associated with cardiac arrest and myocardial infarction, although other drugs are usually preferred (see Cardiac Arrhythmias, p. 1266.1). It is usually given intravenously (see p. 1988.2). Lidocaine may also be used during advanced cardiac life support (see Cardiac Arrest, p. 1268.3).

Lidocaine has been considered for the *prophylaxis* of ventricular fibrillation in patients with proven or suspected myocardial infarction. However, while some studies have identified a protective effect of lidocaine,[1,2] in others it was not shown to reduce mortality and might even have increased it,[3,4] and thus is no longer generally recommended.

It has been suggested that the increased mortality sometimes seen with lidocaine might be associated with the duration of treatment; a study[5] found that patients who received a bolus dose of lidocaine followed by a 40-hour continuous infusion for prophylaxis of ventricular arrhythmias had more episodes of heart failure than patients who received the bolus dose followed by an 8-hour infusion.

1. Horwitz RI, Feinstein AR. Improved observational method for studying therapeutic efficacy: suggestive evidence that lidocaine prophylaxis prevents death in acute myocardial infarction. *JAMA* 1981; **246:** 2455–9.
2. Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985; **313:** 1105–10.
3. MacMahon S, *et al.* Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA* 1988; **260:** 1910–16.
4. Hine LK, *et al.* Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. *Ann Intern Med* 1989; **149:** 2694–8.
5. Pharand C, *et al.* Lidocaine prophylaxis for fatal ventricular arrhythmias after acute myocardial infarction. *Clin Pharmacol Ther* 1995; **57:** 471–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Lidocaine is one of a large number of drugs that has been tried in the treatment of hiccups without strong evidence of their efficacy. It has been given intravenously, or in the form of a 2% viscous solution taken orally. Nebulised lidocaine has also been tried.[1]

1. Neeno TA, Rosenow EC. Intractable hiccups: consider nebulized lidocaine. *Chest* 1996; **110:** 1129–30.

Intubation. Lidocaine has produced conflicting results when used to attenuate the pressor response and rise in intra-ocular pressure induced by procedures such as tracheal intubation.[1-5] For an overall discussion of this problem, see under Anaesthesia, p. 2028.1.

1. Tam S, *et al.* Attenuation of circulatory responses to endotracheal intubation using intravenous lidocaine: a determination of the optimal time of injection. *Can Anaesth Soc J* 1985; **32:** S65.
2. Murphy DF, *et al.* Intravenous lignocaine pretreatment to prevent intraocular pressure rise following suxamethonium and tracheal intubation. *Br J Ophthalmol* 1986; **70:** 596–8.
3. Drenger B, Pe'er J. Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine. *Br J Ophthalmol* 1987; **71:** 546–8.
4. Miller CD, Warren SJ. IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. *Br J Anaesth* 1990; **65:** 216–19.
5. Mostafa SM, *et al.* Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation. *Br J Anaesth* 1990; **64:** 515–17.

Migraine and cluster headache. Despite periodic interest, lidocaine has so far failed to find an accepted role in the management of migraine (p. 670.3) or cluster headache (p. 670.1). Lidocaine has been tried for the emergency parenteral treatment of migraine, but in a comparative study with dihydroergotamine or chlorpromazine it was found to be less effective than either.[1] While some workers have found that intranasal instillation of lidocaine has produced rapid relief of headache in some patients with acute migraine (though early relapse was common)[2] others have found it to be ineffective.[3] It has also been reported to be effective in aborting individual attacks of headache during cluster periods in patients with cluster headache.[4,5] However, most patients do not appear to obtain complete pain relief.

1. Bell R, *et al.* A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* 1990; **19:** 1070–82.
2. Maizels M, *et al.* Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* 1996; **276:** 319–21.
3. Blanda M, *et al.* Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. *Acad Emerg Med* 2001; **8:** 337–42.
4. Kittrelle JP, *et al.* Cluster headache: local anesthetic abortive agents. *Arch Neurol* 1985; **42:** 496–8.
5. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995; **35:** 83–4.

Neuropathic pain syndromes. Lidocaine may be useful in the management of some types of neuropathic pain syndromes (p. 10.1). The pain of *postherpetic neuralgia* has been significantly reduced by the application of lidocaine 5% transdermal patches[1-3] although a systematic review[4] found insufficient evidence to recommend its use as first-line therapy; intravenous lidocaine[5] and a eutectic mixture of lidocaine and prilocaine (see Surface Anaesthesia below) have also been of benefit. Other syndromes where intravenous lidocaine therapy has been tried include *diabetic neuropathy*[6] and *central neuropathic pain* associated with stroke or spinal cord injury.[7]

1. Rowbotham MC, *et al.* Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; **65:** 39–44.
2. Comer AM, Lamb HM. Lidocaine patch 5%. *Drugs* 2000, **59:** 245–9.
3. Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drugs* 2004; **64:** 937–47.
4. Khaliq W, *et al.* Topical lidocaine for the treatment of postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 22/04/08).
5. Attal N, *et al.* Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004; **62:** 218–25.
6. Kastrup J, *et al.* Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *BMJ* 1986; **292:** 173.
7. Attal N, *et al.* Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; **54:** 564–74.

Pleurodesis. Lidocaine has been instilled intrapleurally as a 1% solution in doses of up to 300 mg to relieve the severe chest pain associated with the use of tetracycline for pleurodesis.[1-3] While the larger doses were significantly more effective[2] toxic plasma concentrations were less likely to occur if a dose of 3 mg/kg or less was used.[3]

1. Harbecke RG. Intrapleurally given tetracycline with lidocaine. *JAMA* 1980; **244:** 1899–1900.
2. Sherman S, *et al.* Optimum anesthesia with intrapleural lidocaine during chemical pleurodesis with tetracycline. *Chest* 1988; **93:** 533–6.
3. Wooten SA, *et al.* Systemic absorption of tetracycline and lidocaine following intrapleural instillation. *Chest* 1988; **94:** 960–3.

Status epilepticus. Lidocaine hydrochloride may be used to control status epilepticus (p. 510.2) resistant to more conventional treatment, particularly in those with respiratory disease. It has a rapid onset of action but its effect is short-lived and continuous infusion may be necessary.[1] It should also be noted that doses producing high plasma concentrations of lidocaine can result in CNS toxicity including seizures.[1] Recurrence of seizures associated with the withdrawal of prolonged lidocaine therapy may be due to its accumulated metabolites exerting an excitatory effect on the nervous system when the inhibitory effect of lidocaine is being reduced.[2]

Lidocaine was used instead of diazepam for 42 episodes of status epilepticus in 36 patients who either had limited pulmonary reserve or who had not responded to intravenous diazepam.[3] Lidocaine 1.5 to 2 mg/kg (usually a dose of 100 mg) was given as a single intravenous dose over 2 minutes. This dose was repeated once if there was no positive response to the first dose (11 episodes) or if the seizures recurred (19 episodes). Subsequently a continuous infusion of lidocaine at a rate of 3 to 4 mg/kg per hour was given in the 7 episodes that recurred after the second dose; 5 of these showed a positive response. The 11 episodes not responding to the first dose did not respond to the second dose or to a continuous infusion. In a retrospective analysis[4] of 37 children with status epilepticus, lidocaine was effective in only 19 of 53 episodes; however, in a few cases it was effective where other drugs had failed, and those patients who responded did so rapidly (within 5 minutes of being given the drug).

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
2. Wallin A, *et al.* Lidocaine treatment of neonatal convulsions, a therapeutic dilemma. *Eur J Clin Pharmacol* 1989; **36:** 583–6.
3. Pascual J, *et al.* Role of lidocaine (lignocaine) in managing status epilepticus. *J Neurol Neurosurg Psychiatry* 1992; **55:** 49–51.
4. Hamano S-I, *et al.* Intravenous lidocaine for status epilepticus during childhood. *Dev Med Child Neurol* 2006; **48:** 220–2.

Surface anaesthesia. *EUTECTIC MIXTURES.* A cream containing lidocaine 2.5% and prilocaine 2.5% as a eutectic mixture can produce local anaesthesia when applied topically to intact skin. It appears to be of value in *adults* and *chil-*

dren,[1-3] in minor medical or surgical procedures such as venepuncture, intravenous or arterial cannulation, retrobulbar injections, lumbar puncture, curettage of molluscum contagiosum lesions, genital wart removal, split skin grafting, laser treatment, extracorporeal shock wave therapy, separation of preputial adhesions, and circumcision. It has also been tried as an anaesthetic for the ear drum in preparation for otological procedures such as myringotomy and grommet insertion but is potentially ototoxic and should not be used in the presence of a perforation. Postherpetic neuralgia (p. 10.3) has also been treated with some success.[4,5]

The eutectic cream is usually applied to skin under an occlusive dressing for at least 60 minutes although it has been suggested that for children aged 1 to 5 years 30 minutes may be sufficient.[6] The manufacturers suggest a maximum application time of 5 hours. The onset and duration of the effect may be affected by the site of application.[2] When used for the removal of genital warts an occlusive dressing is not necessary and the application time recommended by the manufacturer is 5 to 10 minutes. The level of anaesthesia begins to decline after 10 to 15 minutes when applied to the genital mucosa and any procedure should be started immediately.

Eutectic mixtures of lidocaine and prilocaine have also been used in *neonates* to reduce the pain of puncture procedures[7] and for circumcision,[8] and appear to be safe and effective. However, there has been concern that excessive absorption (particularly of prilocaine) might lead to methaemoglobinaemia (see p. 1978.3). Nonetheless, in some countries, including the UK and USA, the cream is licensed for use in neonates provided that their gestational age is at least 37 weeks, and that methaemoglobin values are monitored in those aged 3 months or less; it should not be used in infants under 1 year who are receiving methaemoglobin-inducing drugs.

Systemic absorption of both drugs from the eutectic cream appears to be minimal across intact skin[6] even after prolonged or extensive use.[9] However, it should not be used on wounds or mucous membranes except for genital warts in adults. It should not be applied to or near the eyes because it causes corneal irritation, and it should not be instilled in the middle ear. It should be used with caution in patients with atopic dermatitis, anaemia, or congenital or acquired methaemoglobinaemia. Transient paleness, redness, and oedema may occur following application.

Some studies suggest that a topical gel formulation of tetracaine 4% can produce longer and more rapid anaesthesia than the above lidocaine with prilocaine cream (see Surface Anaesthesia, under Uses and Administration of Tetracaine, p. 1997.1). It has also been suggested[10] that topical tetracaine may have practical advantages over the eutectic mixture of lidocaine and prilocaine, which has to be applied for at least one hour, and causes vasoconstriction at the site of application which can make venepuncture difficult.

For reference to the use of a eutectic mixture of lidocaine and prilocaine for the management of premature ejaculation in adults, see p. 1977.1.

1. Lee JJ, Rubin AP. Emla cream and its current uses. *Br J Hosp Med* 1993; **50:** 463–6.
2. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream: a review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). *Drugs* 1993; **46:** 126–51.
3. Koren G. Use of the eutectic mixture of local anesthetics in young children for procedure-related pain. *J Pediatr* 1993; **122** (suppl): S30–S35.
4. Litman SJ, *et al*. Use of EMLA cream in the treatment of post-herpetic neuralgia. *J Clin Anesth* 1996; **8:** 54–7.
5. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med* 1996; **335:** 32–42.
6. Hanks GW, White I. Local anaesthetic creams. *BMJ* 1988; **297:** 1215–16.
7. Gourrier E, *et al*. Use of EMLA cream in a department of neonatology. *Pain* 1996; **68:** 431–4.
8. Brady-Fryer, B *et al*. Pain relief for neonatal circumcision. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 16/06/05).
9. Scott DB. Topical anaesthesia of intact skin. *Br J Parenter Ther* 1986; **7:** 134–5.
10. Russell SCS, Doyle E. Paediatric anaesthesia. *BMJ* 1997; **314:** 201–3.

Tinnitus. Tinnitus is the perception of a noise that arises or appears to arise within the head.

Objective tinnitus may be audible to others and arises from lesions outside the auditory system. Subjective tinnitus (tinnitus aurium) originates from sites within the auditory system and is perceived only by the patient. A simple and remediable cause of tinnitus can be impacted ear wax. Tinnitus is often associated with head injury, vertigo, and hearing loss, including age-related and noise-induced hearing loss. It may also be a symptom of an underlying disorder such as Ménière's disease, may be associated with anxiety or depressive disorders, or may be a manifestation of drug toxicity (for example with aspirin or quinine). In such cases, treatment of the underlying disorder or removal of the offending drug can resolve the tinnitus.

Treatment of tinnitus is difficult although reassurance and counselling are often effective in helping patients to tolerate their condition. Maskers or, if the tinnitus is associated with hearing loss, hearing aids are also used; surgery is rarely indicated. Intravenous lidocaine has proven to be effective in reducing or eliminating tinnitus but the effect only lasts for a few hours and is, therefore, impractical for most patients. Efforts to find an effective oral analogue of lidocaine have not, so far, been successful. Other drugs that have been tried include acamprosate, benzodiazepines such as alprazolam and clonazepam, the antiepileptics carbamazepine and phenytoin, tricyclic antidepressants, and the loop diuretic furosemide, but adverse effects limit their use. Ginkgo biloba has been tried but there are doubts about its value.

References.

1. Luxon LM. Tinnitus: its causes, diagnosis, and treatment. *BMJ* 1993; **306:** 1490–1.
2. Robson AK, Birchall JP. Management of tinnitus. *Prescribers' J* 1994; **34:** 1–7.
3. Coles RRA. Drug treatment of tinnitus in Britain. In: Reich GE, Vernon JA, eds. *Proceedings of the fifth international tinnitus seminar*. Portland: American Tinnitus Association, 1995.
4. Vesterager V. Tinnitus—investigation and management. *BMJ* 1997; **314:** 728–31.
5. Simpson JJ, Davies WE. Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999; **20:** 12–18.
6. Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope* 1999; **109:** 1202–11.
7. Lockwood AH, *et al*. Tinnitus. *N Engl J Med* 2002; **347:** 904–10.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1 and p. 1979.1.

Effects on the CNS. Suspected psychotic reactions have been reported in 6 patients given intravenous lidocaine for the treatment of cardiac disorders.[1] In another case,[2] 2 patients developed signs of cerebral ataxia after topical use of lidocaine for endoscopy.

When compared with other local anaesthetics, lidocaine may be associated with an increased risk of neurotoxic complications when used for spinal anaesthesia, (see under Adverse Effects of Central Block, p. 1978.1).

1. Turner WM. Lidocaine and psychotic reactions. *Ann Intern Med* 1982; **97:** 149–50.
2. Perney P, *et al*. Transitory ataxia related to topically administered lidocaine. *Ann Pharmacother* 2004; **38:** 828–30.

Effects on the skin. Erythema and pigmentation of the upper lip in a child after local dental infiltration of lidocaine was attributed to a type of fixed drug eruption.[1] Erythema may also occur after topical use of some lidocaine formulations, such as transdermal patches, while transient blanching of the skin is frequent after application of eutectic lidocaine/prilocaine mixtures to the skin.[2] Erythema nodosum and erythema multiforme occurring simultaneously after the use of lidocaine spray and further exacerbated by local lidocaine injection has been reported.[3]

True hypersensitivity reactions, including dermatitis, are rare (see also Hypersensitivity, p. 1978.2) but can occur.[4]

1. Curley RK, *et al*. An unusual cutaneous reaction to lignocaine. *Br Dent J* 1987; **162:** 113–14.
2. Villada G, *et al*. Local blanching after epicutaneous application of EMLA cream: a double-blind randomized study among 50 healthy volunteers. *Dermatologica* 1990; **181:** 38–40.
3. Rodríguez-Carreón AA, *et al*. Simultaneous erythema nodosum and erythema multiforme after local lidocaine injection. *Ann Pharmacother* 2008; **42:** 127–30.
4. Bircher AJ, *et al*. Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; **34:** 387–9.

Overdosage. The most serious effects of lidocaine intoxication are on the CNS and cardiovascular system and overdosage can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death. Intoxication with lidocaine is relatively common and can occur as a result of acute overdosage after poor control of intravenous maintenance infusions or accidental injection of concentrated solutions. However, it more commonly results from inadvertent intravascular dosage during regional anaesthesia, or from too rapid injection of antiarrhythmic doses, particularly in patients with circulatory insufficiency, or when clearance is reduced due to heart failure, liver disease, old age, or through interaction with other drugs.[1] Seizures have also been reported after excessive doses given subcutaneously.[2] Although the bioavailability of lidocaine is low it may be sufficient to result in significant toxicity when swallowed[1] and there have been reports of CNS effects, seizures, and death in children[3-7] and adults[8-10] after the ingestion of topical solutions and after the use of viscous preparations in the mouth. Death has also ensued after gargling with a 4% lidocaine solution.[11] Lidocaine is absorbed from mucous membranes and serious toxicity has been reported after urethral[12] or rectal[13] instillation of lidocaine preparations.

1. Denaro CP, Benowitz NL. Poisoning due to class 1B antiarrhythmic drugs: lignocaine, mexiletine and tocainide. *Med Toxicol Adverse Drug Exp* 1989; **4:** 412–28.
2. Pelter MA, *et al*. Seizure-like reaction associated with subcutaneous lidocaine injection. *Clin Pharm* 1989; **8:** 767–8.
3. Sakai RI, Lattin JE. Lidocaine ingestion. *Am J Dis Child* 1980; **134:** 323.
4. Rothstein P, *et al*. Prolonged seizures associated with the use of viscous lidocaine. *J Pediatr* 1982; **101:** 461–3.
5. Mofenson HC, *et al*. Lidocaine toxicity from topical mucosal application. *Clin Pediatr (Phila)* 1983; **22:** 190–2.
6. Giard MJ, *et al*. Seizures induced by oral viscous lidocaine. *Clin Pharm* 1983; **2:** 110.
7. Amitai Y, *et al*. Death following accidental lidocaine overdose in a child. *N Engl J Med* 1986; **314:** 182–3.
8. Fruncillo RJ, *et al*. CNS toxicity after ingestion of topical lidocaine. *N Engl J Med* 1982; **306:** 426–7.
9. Parish RC, *et al*. Seizures following oral lidocaine for esophageal anesthesia. *Drug Intell Clin Pharm* 1985; **19:** 199–201.
10. Geraets DR, *et al*. Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; **26:** 1380–1.
11. Zuberi BF, *et al*. Lidocaine toxicity in a student undergoing upper gastrointestinal endoscopy. *Gut* 2000; **46:** 435.
12. Dix VW, Tresidder GC. Collapse after use of lignocaine jelly for urethral anaesthesia. *Lancet* 1963; **i:** 890.
13. Pottage A, Scott DB. Safety of "topical" lignocaine. *Lancet* 1988; **i:** 1003.

Pregnancy. Serious adverse effects of epidural anaesthesia are rare but lidocaine may have transient effects on the neonatal auditory system.[1]

1. Bozynski MEA, *et al*. Effect of prenatal lignocaine on auditory brain stem evoked response. *Arch Dis Child* 1989; **64:** 934–8.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

In general lidocaine should not be given to patients with hypovolaemia, heart block or other conduction disturbances, and should be used with caution in patients with congestive heart failure, bradycardia, or respiratory depression. Lidocaine is metabolised in the liver and must be given with caution to patients with hepatic impairment. The plasma half-life of lidocaine may be prolonged in conditions that reduce hepatic blood flow such as cardiac and circulatory failure. Metabolites of lidocaine may accumulate in patients with renal impairment.

The intramuscular injection of lidocaine may increase creatine phosphokinase concentrations that can interfere with the diagnosis of acute myocardial infarction.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving lidocaine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Cerebrovascular disorders. Lidocaine 5 mg/kg by intravenous infusion over 30 minutes was associated with a 12% reduction in cerebral blood flow in healthy subjects although this returned to normal within 60 minutes.[1] Cerebral blood flow in patients with diabetes was lower than in healthy subjects, but was unaffected by lidocaine infusion, indicating reduced cerebrovascular reactivity.

1. Kastrup J, *et al*. Intravenous lidocaine and cerebral blood flow: impaired microvascular reactivity in diabetic patients. *J Clin Pharmacol* 1990; **30:** 318–23.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lidocaine as probably not porphyrinogenic when used in local anaesthetic procedures, for surface anaesthesia of the skin and mucous membranes, and as an antiarrhythmic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Renal impairment. The pharmacokinetics of lidocaine and its metabolite monoethylglycinexylidide appear to be unaffected in patients with renal failure on chronic haemodialysis except that accumulation of the metabolite glycinexylidide may occur during infusions of 12 hours or more.[1] A later pharmacokinetic study[2] of lidocaine in healthy subjects, patients with moderate or severe renal impairment, and anephric patients undergoing haemodialysis found that the clearance of lidocaine was decreased by an average of 18 and 49% in those with moderate and severe impairment, respectively, but was unchanged in those undergoing haemodialysis; there was, however, considerable interindividual variation in the clearance of lidocaine in patients with renal impairment. The authors suggested starting lidocaine infusions at the lower end of the usual dose range with close monitoring for toxicity; no reduction in loading doses appeared necessary. Data to predict the amount of lidocaine and glycinexylidide removed during haemodialysis have been provided.[3,4] Lidocaine does not appear to be removed during haemofiltration.[5]

1. Collinsworth KA, *et al*. Pharmacokinetics and metabolism of lidocaine in patients with renal failure. *Clin Pharmacol Ther* 1975; **18:** 59–64.

2. De Martin S, *et al*. Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. *Clin Pharmacol Ther* 2006; **80:** 597–606.
3. Gibson TP, Nelson HA. Drug kinetics and artificial kidneys. *Clin Pharmacokinet* 1977; **2:** 403–26.
4. Lee CC, Marbury TC. Drug therapy in patients undergoing haemodialysis: clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1984; **9:** 42–66.
5. Saima S, *et al*. Negligible removal of lidocaine during arteriovenous hemofiltration. *Ther Drug Monit* 1990; **12:** 154–6.

Smoking. The effects of smoking on lidocaine therapy are unclear. Studies in a limited number of patients have found reduced systemic bioavailability suggestive of induction of drug-metabolising activity[1] and an inconsistent effect on protein binding.[2,3]

1. Huet P-M, Lelorier J. Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. *Clin Pharmacol Ther* 1980; **28:** 208–15.
2. McNamara PJ, *et al*. Effect of smoking on binding of lidocaine to human serum proteins. *J Pharm Sci* 1980; **69:** 749–51.
3. Davis D, *et al*. The effects of age and smoking on the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1985; **19:** 261–5.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

The clearance of lidocaine may be reduced by propranolol and cimetidine (see below). The cardiac depressant effects of lidocaine are additive with those of beta blockers and of other antiarrhythmics. Additive cardiac effects may also occur when lidocaine is given with intravenous phenytoin; however, the long-term use of phenytoin and other enzyme-inducers may increase dosage requirements of lidocaine (see Antiepileptics, below). Hypokalaemia produced by acetazolamide, loop diuretics, and thiazides antagonises the effect of lidocaine.

Antiarrhythmics. Lidocaine toxicity, arising from the use of an oral preparation containing lidocaine, has been reported[1] in a patient who was receiving *mexiletine*. There are individual reports of seizures or heart failure and cardiac arrest in patients who received intravenous lidocaine with *ajmaline*,[2] *amiodarone*,[3,4] or *tocainide*.[5] Delirium has been reported in a patient who received lidocaine with *procainamide*.[6]

1. Geraets DR, *et al*. Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; **26:** 1380–1.
2. Bleifeld W. Side effects of antiarrhythmic drugs. *Naunyn Schmiedebergs Arch Pharmacol* 1971; **269:** 282–97.
3. Siegmund JB, *et al*. Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol* 1993; **21:** 513–15.
4. Keidar S, *et al*. Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. *Am Heart J* 1982; **104:** 1384–5.
5. Forrence E, *et al*. A seizure induced by concurrent lidocaine-tocainide therapy—is it just a case of additive toxicity? *Drug Intell Clin Pharm* 1986; 20: 56–9.
6. Ilyas M, *et al*. Delirium induced by a combination of anti-arrhythmic drugs. *Lancet* 1969; **ii:** 1368–9.

Antiepileptics. Studies in healthy subjects and patients with epilepsy[1,2] suggest that long-term use of drugs such as *phenytoin* or *barbiturates* may increase dosage requirements for lidocaine due to induction of drug-metabolising microsomal enzymes. Phenytoin can also increase plasma concentrations of α_1-acid glycoprotein and thereby reduce the free fraction of lidocaine in plasma.[3]

The cardiac depressant effects of lidocaine may be dangerously enhanced by intravenous phenytoin.[4]

1. Heinonen J, *et al*. Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. *Acta Anaesthesiol Scand* 1970; **14:** 89–95.
2. Perucca E, Richens A. Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. *Br J Clin Pharmacol* 1979; **8:** 21–31.
3. Routledge PA, *et al*. Lignocaine disposition in blood in epilepsy. *Br J Clin Pharmacol* 1981; **12:** 663–6.
4. Wood RA. Sinoatrial arrest: an interaction between phenytoin and lignocaine. *BMJ* 1971; **1:** 645.

Beta blockers. Significant increases in plasma-lidocaine concentrations have occurred with *propranolol*,[1-4] owing to a reduction in the clearance of lidocaine from plasma. A similar interaction has occurred with *nadolol*[3] and *metoprolol*,[2] although in another study[5] metoprolol did not alter the pharmacokinetics of lidocaine. The hepatic metabolism of lidocaine may be reduced as a result of a fall in hepatic blood flow associated with reduced cardiac output or it may be caused by direct inhibition of hepatic microsomal enzymes.[6] Significant impairment of lidocaine clearance would therefore be most likely to occur with those drugs that lack intrinsic sympathomimetic activity and have a greater effect on cardiac output or with the more lipid-soluble drugs that have greater effects on microsomal oxygenases. The reduction in clearance produced by propranolol seems to be mainly by direct inhibition of metabolism rather than by lowering of hepatic blood flow.[4]

Although some licensed product information suggest a reduction in the dosage of lidocaine injection when used with beta blockers, others consider that potentially toxic plasma concentrations occur when lidocaine is given in repeated high doses and such an interaction should be of no clinical significance after short-term treatment with lidocaine at recommended doses.

1. Ochs HR, *et al*. Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N Engl J Med* 1980; **303:** 373–7.
2. Conrad KA, *et al*. Lidocaine elimination: effects of metoprolol and of propranolol. *Clin Pharmacol Ther* 1983; **33:** 133–8.
3. Schneck DW, *et al*. Effects of nadolol and propranolol on plasma lidocaine clearance. *Clin Pharmacol Ther* 1984; **36:** 584–7.
4. Bax NDS, *et al*. The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. *Br J Clin Pharmacol* 1985; **19:** 597–603.
5. Miners JO, *et al*. Failure of 'therapeutic' doses of β-adrenoceptor antagonists to alter the disposition of tolbutamide and lignocaine. *Br J Clin Pharmacol* 1984; **18:** 853–60.
6. Tucker GT, *et al*. Effects of β-adrenoceptor antagonists on the pharmacokinetics of lignocaine. *Br J Clin Pharmacol* 1984; **17** (suppl 1): 21S–28S.

H_2-antagonists. The interaction between *cimetidine* and lidocaine has been considered[1-4] but differences between the studies make interpretation of the overall clinical significance of the results difficult. Cimetidine appears to reduce the hepatic metabolism of lidocaine; it may also reduce its clearance by decreasing hepatic blood flow. Significant increases in plasma-lidocaine concentrations have been reported. Changes in protein binding are not generally important but patients with myocardial infarction who have increased levels of α_1-acid glycoprotein may be partially protected from increases in concentrations of free lidocaine.[5] Since it is not possible to identify those patients at risk all patients receiving both drugs should be closely monitored for signs of toxicity. Some licensed product information suggest a reduction in the dosage of lidocaine injection when used with cimetidine; however, others consider that potentially toxic plasma concentrations occur when lidocaine is given in repeated high doses and such an interaction should be of no clinical significance after short-term treatment with lidocaine at recommended doses.

The use of other H_2-antagonists may be preferable. In studies in healthy subjects *ranitidine* either had no effect on lidocaine kinetics[6] or produced changes consistent with small reductions in hepatic blood flow.[7]

1. Feely J, *et al*. Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med* 1982; **96:** 592–4.
2. Knapp AB, *et al*. The cimetidine-lidocaine interaction. *Ann Intern Med* 1983; **98:** 174–7.
3. Bauer LA, *et al*. Cimetidine-induced decrease in lidocaine metabolism. *Am Heart J* 1984; **108:** 413–15.
4. Patterson JH, *et al*. Influence of a continuous cimetidine infusion on lidocaine plasma concentrations in patients. *J Clin Pharmacol* 1985; **25:** 607–9.
5. Berk SI, *et al*. The effect of oral cimetidine on total and unbound serum lidocaine concentrations in patients with suspected myocardial infarction. *Int J Cardiol* 1987; **14:** 91–4.
6. Feely J, Guy E. Lack of effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1983; **15:** 378–9.
7. Robson RA, *et al*. The effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1985; **20:** 170–3.

Local anaesthetics. Although several drugs were shown to reduce the amount of lidocaine bound to α_1-acid glycoprotein only the displacement produced by *bupivacaine* was considered to be of possible clinical significance.[1]

There is concern about the use of lidocaine to treat *cocaine*-induced arrhythmias as lidocaine may enhance toxicity.[2]

1. Goolkasian DL, *et al*. Displacement of lidocaine from serum α_1-acid glycoprotein binding sites by basic drugs. *Eur J Clin Pharmacol* 1983; **25:** 413–17.
2. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; **333:** 1267–72.

Neuromuscular blockers. The possible interaction between neuromuscular blockers and antiarrhythmics including lidocaine is discussed under Atracurium, p. 2031.3.

Oral contraceptives. For mention of the effect of oral contraceptives on the protein binding of lidocaine, see under Protein Binding in Pharmacokinetics, below.

Pharmacokinetics

Lidocaine is readily absorbed from the gastrointestinal tract, from mucous membranes, and through damaged skin. Absorption through intact skin is poor. It is rapidly absorbed from injection sites including muscle.

After an intravenous dose lidocaine is rapidly and widely distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. Lidocaine is bound to plasma proteins, including α_1-acid glycoprotein (AAG). The extent of binding is variable but is about 66%. Plasma protein binding of lidocaine depends in part on the concentrations of both lidocaine and AAG. Any alteration in the concentration of AAG can greatly affect plasma concentrations of lidocaine (see under Protein Binding, below).

Plasma concentrations decline rapidly after an intravenous dose with an initial half-life of less than 30 minutes; the elimination half-life is 1 to 2 hours but may be prolonged if infusions are given for longer than 24 hours or if hepatic blood flow is reduced.

Lidocaine is largely metabolised in the liver and any alteration in liver function or hepatic blood flow can have a significant effect on its pharmacokinetics and dosage requirements. First-pass metabolism is extensive and bioavailability is about 35% after oral doses. Metabolism in the liver is rapid and about 90% of a given dose is dealkylated to form monoethylglycinexylidide and glycinexylidide. Both of these metabolites may contribute to the therapeutic and toxic effects of lidocaine and since their half-lives are longer than that of lidocaine, accumulation, particularly of glycinexylidide, may occur during prolonged infusions. Further metabolism occurs and metabolites are excreted in the urine with less than 10% of unchanged lidocaine. Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Drugs that alter hepatic blood flow or induce drug-metabolising microsomal enzymes can also affect the clearance of lidocaine (see Interactions, above). Renal impairment may affect the clearance of lidocaine (see p. 1990.3); accumulation of its active metabolites can also occur.

Lidocaine crosses the placenta and blood-brain barrier; it is distributed into breast milk.

See also under Local Anaesthetics, p. 1979.3.

References.

1. Nattel S, *et al*. The pharmacokinetics of lignocaine and β-adrenoceptor antagonists in patients with acute myocardial infarction. *Clin Pharmacokinet* 1987; **13:** 293–316.

Absorption. *SURFACE APPLICATION.* Serum-lidocaine concentrations were usually so low as to be unmeasurable in patients who gargled and expectorated 15 mL (300 mg) of a 2% viscous solution before endoscopy[1] and mean peak serum concentrations of lidocaine were below those associated with toxicity following endotracheal application of 100 mg of lidocaine by spray.[2] The relative bioavailability of lidocaine has been found to be higher when applied to the upper respiratory tract than after administration to the lower respiratory tract.[3] Acceptably low plasma-lidocaine concentrations were noted with the following regimen used before bronchoscopy: a 4% lidocaine solution gargled for 30 seconds, a 2% solution sprayed onto the oropharynx, a 2% jelly applied to the oropharynx and nasal passages, and a 1% solution injected through a bronchoscope.[4] However, a fatality has been reported following the use of lidocaine as a gargle (see Overdosage, p. 1990.2); the absorption of intranasal lidocaine can also be highly variable.[5] For bronchoscopy, inhalation of lidocaine from a nebuliser rather than a direct spray may result in lower peak serum concentrations.[6]

Absorption of lidocaine is generally poor through intact skin. However, there is some evidence that absorption may be greater after application to the skin of preterm infants.[7]

1. Fazio A, *et al*. Lidocaine serum concentrations following endoscopy. *Drug Intell Clin Pharm* 1987; **21:** 752–3.
2. Scott DB, *et al*. Plasma lignocaine concentrations following endotracheal spraying with an aerosol. *Br J Anaesth* 1976; **48:** 899–902.
3. McBurney A, *et al*. Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; **17:** 61–6.
4. Ameer B, *et al*. Systemic absorption of topical lidocaine in elderly and young adults undergoing bronchoscopy. *Pharmacotherapy* 1989; **9:** 74–81.
5. Scavone JM, *et al*. The bioavailability of intranasal lignocaine. *Br J Clin Pharmacol* 1989; **28:** 722–4.
6. Labedzki L, *et al*. Reduced systemic absorption of intrabronchial lidocaine by high-frequency nebulization. *J Clin Pharmacol* 1990; **30:** 795–7.
7. Barrett DA, Rutter N. Percutaneous lignocaine absorption in newborn infants. *Arch Dis Child* 1994; **71:** F122–F124.

Protein binding. Lidocaine is markedly bound to α_1-acid glycoprotein (AAG), a plasma protein which is increased after trauma, surgery, burns, myocardial infarction, in chronic inflammatory disorders such as Crohn's disease, and in cancer. Protein binding may therefore be greatly increased in these conditions and reduced in neonates, the nephrotic syndrome, and in liver disease when AAG concentrations are lower than normal. This can result in an eightfold variation in the free fraction of lidocaine between these conditions.[1] Measurement of free drug concentrations may be a better guide to dosage requirements than measurement of total plasma concentrations.[2] AAG concentrations may also be reduced by oestrogens[3] leading to a higher free fraction of lidocaine in women than in men and the free fraction is further increased during pregnancy and in women taking oral contraceptives.[3,4] Protein binding may also be affected by other concomitant drug therapy or smoking (for further details, see Antiepileptics under Interactions, above, and Precautions, Smoking, above).

1. Routledge PA. Pharmacological terms: protein binding. *Prescribers' J* 1988; **28:** 34–5.

2. Shand DG. α_1-Acid glycoprotein and plasma lidocaine binding. *Clin Pharmacokinet* 1984; **9** (suppl 1): 27–31.
3. Routledge PA, *et al*. Sex-related differences in the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1981; **11**: 245–50.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α_1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; **29**: 522–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fidecaina; Gobbicaina; Indican; Lafecaina; Larjancaina; Lidanest; LMX 4; Regiocaina; Solvente Indoloro; Xylocaina; ***Austral.***: Nurocain†; Stud 100; Xylocaine Special Adhesive; Xylocaine; Xylocard; ***Austria***: Lidocorit; Neo-Xylestesin; Versatis; Xylanaest; Xylocain; Xylocard†; Xyloneural; ***Belg.***: Linisol; Otalgan; Otipax; Otocalmine; Versatis; Xylocaine Visqueuse; Xylocaine; Xylocaine; Xylocard; ***Braz.***: Dermomax; Gel-Lido†; Labcaina; Lidial; Lidocabbott; Lidoflex†; Lidogel; Lidojet; Lidopass; Lidospray; Lidoston; Xylestesin; Xylocaina; ***Canad.***: After Sun; Afterburn; Banana Boat Soothacaine†; Band-Aid Antiseptic; Betacaine; Burn Cream; Burn Relief; Caribbean Breeze Burn Relief; Hawaiian Tropic After Sun; Lidodan; Lidomax; Maxilene; Octocaine; Pre-Wax†; Preattached; Safetec Burn; Safetec Sting Relief; Smartshield After Sun; Solarcaine Lidocaine; Soothing Gel; Stallion; Water-Jel; Xylocaine; Xylocard; ***Chile***: Bebegesic; Dentaliv†; Dimecaina; Exido; Gelcain; Odongel; Prolong; Solin; Versatis; Xylocaina; ***China***: Ke Ze Pu (克泽普); Li Shu Ka (利舒卡); ***Cz.***: Trachisan; Versatis; Xylocaine; ***Denm.***: Versatis; Xylocain; Xyloplyin; ***Fin.***: Lidocard; Xylocain; ***Fr.***: Biodicaine†; Dynexan; Dynexangival; Lidrian†; Mesocaine; Pressicaine N†; Pressicaine; Versatis; Xylocaine; Xylocard; Xylocontact; Xylonor; Xylorolland; Ziacaine; ***Ger.***: Acoin; Gelicain†; Haemo-Exhirud Bufexamac†; Heweneural; Licain; Lidesthesin†; Lidocard; Lidoject†; LidoPosterine†; Posterisan akut; Trachilid; Trachisan Halsschmerztabletten†; Versatis; Xylocain (Kardiologie); Xylocain; Xylocitin cor; Xylocitin; Xyloneural; ***Gr.***: Akten; Ecocain; Lidocosil; Lidoderm; Lidonet; Lignospan; Narcodon; Neo-Lidocaton; Osagel; Sensolid; Trachilid; Utiblack; Versatis; Xylestesin-A; Xylestesin-S Special; Xylestesin; Xylocaine; Xylol; Xylonor Noradrenaline; Xylozan; ***Hong Kong***: Lidocaton†; Xylestesin-A; Xylocaine; ***India***: Gesicain; Lignocad; Lignocip; Lignodent; Lignoloc; Lignosafe; Lignox; Lox; Loxicard; Nummit; Otidrop; Tivision†; Xylocaine; Xylocard; ***Indon.***: Extracaine†; Garianes†; Lidodex; Lidonest†; Pehacain; Xylocaine; ***Irl.***: Lignospan; Versatis; Xylocaine; ***Israel***: After Burn; Betacaine†; Esracain; Lidocadren; Lignospan; Octocaine; Stud 100; Xylocaine; Xylonor Noradrenaline; ***Ital.***: Basicaina; Ecocain; Lident Adrenalina; Lident Adrenor; Lidofast; Lidosen; Lidrian; Luan; Ortodermina; Xilo-Mynol; Xylocaina; Xylonor; Xyloplyina; ***Jpn***: Penles; ***Malaysia***: Denkan; Lakan; Xylocaine; ***Mex.***: Betacaine†; Hipoden; Pharmacaine; Pisacaina†; Sensipharma; Sunicaine; Undorlan; Unicaine; Uvega; Xylocaina; ***Neth.***: Dentinox; Lignospan; Nolaid; Otalgan; Trachisan; Unguentum contra haemorrhoides PCH†; Xylocaine; ***Norw.***: Versatis; Xylocain; ***NZ***: Virasolve; Xylestesin-A; Xylocaine; Xylocard; ***Philipp.***: Dentocaine; Enducaine; Epicaine; Lygnonex; Nobucaine; Xepacaine; Xylocaine; Xylocard†; ***Pol.***: Lidoposterin; Xylocaine; ***Port.***: Lambdalina; Lidoject; Lidonostrum; Lincaina; Octocaine; Vessatis; Xilonibsa; Xylocaina; ***Rus.***: Dynexan A (Динексан А); Gelicain (Геликаин); Licaine (Ликаин); Lidochlor (Лидохлор); Luan (Луан); Versatis (Версатис); ***S.Afr.***: Peterkaien†; Remicaine; Remicard; Xylocaine; Xylotox; ***Singapore***: Gesicain; Lakan; Lignopad; Xylestesin-A; Xylocaine; Xylocard; ***Spain***: Dermovagisil; Lambdalina; Octocaine; Versatis; Xilonibsa; Xylocaina†; Xylonor 2% Sin Vasoconst†; Xylonor Especial; ***Swed.***: Versatis; Xylocain; Xylocard; ***Switz.***: Dynexan; Kenergon; Neo-Sinedol; Neurodol Tissugel; Rapidocaine; Sedagul†; Solarcaine; Xylesine; Xylocain; Xylocard†; Xyloneural; ***Thai.***: Docaine; Drocanil-A; LD-Caine†; Lidocation; Locana; Medicaine; Udocaine; Xylocaine; ***Turk.***: Anestol; Aritmal; Jetmonal; Jetokain; Jetosel; Ksilidin; Laconest; Lidestol; Lidobag; Lidosel; Locanest-A; Lokalen; Monocain; Xylocain; ***UAE***: Ecocain; ***UK***: Dequaspray; Laryng-O-Jet; LMX4; Premjact; Stud; Vagisil; Versatis; Xylocaine; Xylocaine; ***Ukr.***: Versatis (Версатис); ***USA***: Akten; AneCream; Anestacon; Anestafoam†; Dentipatch†; Dilocaine; Dr Scholl's Cracked Heel Relief; Duo-Trach Kit; L-M-X; LC-4; LC-5; LidaMantle†; Lidoderm; LidoPen; Lidosite†; LTA; Nervocaine; Octocaine; RectiCare; Regenecare; Topicaine; Xolido; Xylocaine; Zingo†; ***Venez.***: Cifarcaina; Farmacaina; Nenedent.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Arg.***: Adaxil; Amplibenzatin Bronquial; Artrilase; Bago Bl B6 B12; Cefalomicina; Cefamezin; Mecanyl; Pen di Ben; Rivacefin; Tunik B12; Tunik; Vartalon Complemento; Zienam; ***Austral.***: Zyderm†; Zyplast†; ***Austria***: Rheumesser; Rocephin; Zienam; ***Belg.***: Kefzol; Rocephine; ***Braz.***: Butazolidina; Cefoxin†; Ceftriax; Cianotrat-Dexa; Gripsay; Injeflex; Neocefitriona; Olfen†; Rocefin; Terramicina; Tetrapulmo†; Vitatonus Dexa; Voltaflan; ***Canad.***: Neo-Bex; ***Chile***: Bioflex†; Cidoten Rapilento; Cronolevel; Depo-Medrol; Dolotol 12; Neurobionta; Prevepen Forte; Tol 12 Plus; ***China***: Olfen (奥尔芬); ***Cz.***: Dona; Olfen; ***Fin.***: Rocephalin; ***Fr.***: Cefaloject†; Claforan; Rocephine; Unacim; Zinnat; ***Ger.***: Ambene; Keltican N†; Medivitan; Pendysin; Rocephin; ***Gr.***: Apotel; ***Hong Kong***: Olfen; Tapain; ***Hung.***: Cefam†; Claforan; Dona; Milgamma N; Mydeton; Rocephin; ***India***: Calcindon; Oxytetra; Terramycin; ***Indon.***: Bioneuron; Neurobiovit; Neurophil; Neurotrat; ***Ital.***: Acef; Aminomal; Ateroid; Aximad; Axobat; Batixim; Bethacil; Biotassina; Bioticic†; Bixon; Cefam; Cefamezin; Cefazil; Cefociclin; Cefodie; Cefomit; Cefoplus; Cefoprim†; Cefrag; Cemado†; Chefir; Cilpier; Clody; Coxanturenasi; Dardum; Davixon; Daycef; Daytrix; Deixim; Delius; Diaxone; Diezime; Dona; Ecosette; Eftry; Emidoxin; Eposerin; Eraxitron; Farecef†; Farecillin; Fidato; Fonicid; Fosforilasi; Frineg; Glicero-Valerovit; Imipem; Kocefan; Krucef†; Lirgosin; Lisa; Loricin; Mancef; Maxid†; Mefoxin; Metafar; Metax; Mionevrasi; Modiem; Modivid; Monobiotic; Monoxar; Necid; Nefazol; Neurol; Niklod; Nilson; Nokid; Panatrix; Pantoxon; Peracil; Picillin; Piperital; Pipersal; Pipertex; Praticef†; Ragex; Raikocef; Refotax; Reparcillin; Rifocin; Rocefin; Roxiden; Salocef; Semipenil; Setriox; Sintocef; Sirtap; Sofarcid; Spectrocef; Supero; Surgamyl; Taxime; Tazobac; Tazocin; Tienam; Timecef; Tricortin; Trinevrina B6; Unasyn; Valecid†; Valexime; Zariviz; Zimanel; ***Jpn***: Cefamezin; Cefmetazon; Cefoperazin; Pentcillin; ***Mex.***: Benaxona; Bonadoxina; Butazolidina; Cefaxona; Ceftrex; Ceftrilem; Centrifal; Claforan; Dexabion; Forvin; Fosfocil; Fot-Amsa; Fotexina; Gadital; Kedacillin†; Limiprol; Megapenil Forte†; Megion; Rocephin; Terbac†; Terramicina; Tiaminal B_{12}; Tirotax; Triaken; Tribe 12; Viken†; ***NZ***: Rocephin†; Zyderm; Zyplast; ***Pol.***: Dicloratio; Milgamma N; Mydocalm; Neoton; Olfen; ***Port.***: Monocid; Rocephin; ***Rus.***: Ambene (Амбене); Combilipen (Комбилипен); CompligamV (КомплигамВ); Milgamma (Мильгамма); Mydocalm (Мидокалм); Trigamma (Тригамма); Vitagamma (Витагамма); ***Singapore***: CosmoDerm; CosmoPlast; Juvederm; Olfen; ***Spain***: Claforan; Fosfocina; Gobemicina Retard†; Inzitan; Kurgan; Monocid; Neurodavur Plus; Neuromade; Retarpen; Rocefalin†; Tecfazolina; ***Swed.***: Rocephalin; ***Switz.***: Ancopir; Butadion†; Olfen; Rocephin; ***Thai.***: Fenacaine; Juvederm Ultra XC; Neo-Pyrazol†; Nivagin†; Olan-Gin†; Paramol TP; Paranal-L†; Umeda Para-J; Utofin; Vetamol; Viartril S; ***Turk.***: Alfasid; Baktisef; Cefaks; Cefamezin; Cefizox; Cefozin; Cephaxon; Combicid; Desefin; Duobaktam; Duocid; Equiceft; Equizolin; Forsef; Iesef; Iespor; Maksiporin; Mefoxim; Neurogriseovit; Nevakson; Nobecid; Novosef; Rifocin; Rocephin; Sefamax; Sefazol; Sulcid; Sulperazon; Tienam; Triaxon; Unacefin; ***Ukr.***: Diclocain (Диклокаин); Dona (Дона); Megafen Plus (Мегафен Плюс)†; Milgamma (Мильгамма); Olfen (Олфен); Tolperil (Толперил); Vitaxon (Витаксон); ***USA***: Perlane; Restylane; ***Venez.***: Briomet; Cefacidal; Complejo B Compositum; Deca-Lentermina Complex; Lentermina Complex; Mega-Neubion; Miovit; Neuribe; Rocephin; Rubrinal; Rubrinex.

Pharmacopoeial Preparations

BP 2014: Lidocaine and Adrenaline Injection; Lidocaine and Chlorhexidine Gel; Lidocaine Gel; Lidocaine Injection; Lidocaine Ointment; Sterile Lidocaine Solution;

USP 36: Lidocaine and Prilocaine Cream; Lidocaine Hydrochloride and Dextrose Injection; Lidocaine Hydrochloride and Epinephrine Injection; Lidocaine Hydrochloride Injection; Lidocaine Hydrochloride Jelly; Lidocaine Hydrochloride Oral Topical Solution; Lidocaine Hydrochloride Topical Solution; Lidocaine Ointment; Lidocaine Oral Topical Solution; Lidocaine Topical Aerosol; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment.

Mepivacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de mepivacaína; Mepivacaína, hidrocloruro de; Mépivacaïne, Chlorhydrate de; Mepivacainhydrochlorid; Mepivacaini Chloridum; Mepivacaini Hydrochloridum; Mepivakaiinihydrokloridi; Mepivakain-hidroklori d; Mepivakain-hydrochlorid; Mepivakainhydroklorid; Mepivakaino hidrochloridas; Мепивакаина Гидрохлорид.

(1-Methyl-2-piperidyl)formo-2′,6′-xylidide hydrochloride.

$C_{15}H_{22}N_2O,HCl=282.8$

CAS — 96-88-8 (mepivacaine); 22801-44-1 ((±)-mepivacaine); 1722-62-9 (mepivacaine hydrochloride).

ATC — N01BB03.

ATC Vet — QN01BB03.

UNII — 4VFX2L7EM5.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Mepivacaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.0.

USP 36: (Mepivacaine Hydrochloride). A white, odourless, crystalline solid. Freely soluble in water and in methyl alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of about 4.5.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Uses and Administration

Mepivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is mainly used for infiltration anaesthesia, peripheral nerve block, and epidural block. (Local anaesthetic techniques are discussed on p. 1977.2.) Mepivacaine has a rapid onset and an intermediate duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced.

The dosage of mepivacaine hydrochloride varies with the site of injection and the type of **local anaesthetic procedure**. In adults, the **maximum single dose** of mepivacaine hydrochloride should not generally exceed 400 mg and the total dose in 24 hours should not exceed 1 g. Doses should be reduced in the elderly, in debilitated patients, and in those with cardiac or hepatic impairment. Concentrations of less than 2% should be used in children under 3 years or weighing less than about 14 kg (30 pounds); the dose in children should not exceed 5 to 6 mg/kg.

- For *infiltration anaesthesia* up to 400 mg as a 1% (40 mL) or 0.5% (80 mL) solution is used. For *dental infiltration and nerve block* a 2% solution with a vasoconstrictor or a 3% plain solution is used. For anaesthesia at a single site in the jaw a dose of 36 mg (1.8 mL) as a 2% solution or 54 mg (1.8 mL) as a 3% solution is used. For anaesthesia of the entire oral cavity 180 mg (9 mL) as a 2% solution or 270 mg (9 mL) as a 3% solution is used. Some recommend that no more than 400 mg should be given at a single dental sitting.
- For *peripheral nerve blocks*, namely *cervical, brachial plexus, intercostal,* and *pudendal blocks*, 1 or 2% solutions may be used in doses of 50 to 400 mg (5 to 40 mL) as a 1% solution, or 100 to 400 mg (5 to 20 mL) as a 2% solution. For pudendal block half of the dose is injected on each side. For *paracervical block* a dose of up to 100 mg (10 mL) as a 1% solution on each side has been suggested allowing an interval of 5 minutes between sides. This may be repeated at an interval of not less than 90 minutes, and for a combined paracervical and pudendal block up to 150 mg (15 mL) as a 1% solution is injected on each side. For therapeutic nerve block in the management of pain 10 to 50 mg (1 to 5 mL) as a 1% solution or 20 to 100 mg (1 to 5 mL) as a 2% solution may be given.
- For *epidural block* usual doses are: 150 to 300 mg (15 to 30 mL) as a 1% solution, 150 to 375 mg (10 to 25 mL) as a 1.5% solution, or 200 to 400 mg (10 to 20 mL) as a 2% solution. Hyperbaric solutions of mepivacaine hydrochloride without adrenaline have also been used for *spinal block*.

Mepivacaine has been included in the intramuscular injections of other drugs to minimise the pain produced at the injection site.

Mepivacaine has also been used as a surface anaesthetic but other local anaesthetics such as lidocaine are more effective.

Action. For a comparison of the vasoactivity of mepivacaine and some other local anaesthetics, see p. 1976.2.

Administration in children. For uses and dosage of mepivacaine hydrochloride in children, see above.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mepivacaine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Local anaesthetics. Studies *in vitro* showed that *bupivacaine* dramatically reduced the binding of mepivacaine to α_1-acid glycoprotein.[1]

1. Hartrick CT, *et al*. Influence of bupivacaine on mepivacaine protein binding. *Clin Pharmacol Ther* 1984; **36**: 546–50.

Pharmacokinetics

Mepivacaine is about 78% bound to plasma proteins. The plasma half-life has been reported to be about 2 to 3 hours in adults and about 9 hours in neonates. It is rapidly metabolised in the liver and less than 10% of a dose is reported to be excreted unchanged in the urine. Over 50% of a dose is excreted as metabolites into the bile but these probably undergo enterohepatic circulation as only small amounts appear in the faeces. Several metabolites are also excreted via the kidneys and include glucuronide conjugates of hydroxy compounds and an *N*-demethylated compound, 2′,6′-pipecoloxylidide. Mepivacaine crosses the placenta.

See also under Local Anaesthetics, p. 1979.3.

Pregnancy. There is considerable transfer of mepivacaine across the placenta after maternal doses and the ratio of fetal to maternal concentrations[1] is about 0.7. Although neonates have a very limited capacity to metabolise mepivacaine it appears they are able to eliminate the drug.[2]

1. Lurie AO, Weiss JB. Blood concentration of mepivacaine and lidocaine in mother and baby after epidural anesthesia. *Am J Obstet Gynecol* 1970; **106:** 850–6.
2. Meffin P, *et al*. Clearance and metabolism of mepivacaine in the human neonate. *Clin Pharmacol Ther* 1973; **14:** 218–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mepigobbi; ***Austral.***: Carbocaine†; ***Austria***: Mepinaest; Scandicain†; Scandonest; ***Belg.***: Scandicaine; ***Canad.***: Carbocaine; Isocaine; Polocaine; Scandonest; ***China***: Scandonest (斯康杜尼); ***Cz.***: Mepivastesin; Scandonest†; ***Denm.***: Carbocain; Scandonest; ***Fin.***: Scandonest; ***Fr.***: Carbocaine; Scandicaine; ***Ger.***: Meaverin; Mecain; Mepi-Welk; Mepihexal†; Mepivastesin; Scandicain; ***Gr.***: Mepivakate; Mepivastesin; Optocain; Scandonest; Tevacaine; ***Hong Kong***: Mepicaton†; Mepivastesin; ***Irl.***: Scandonest; ***Israel***: Isocaine; Mepicaton†; Mepivastesin; Scandicaine; ***Ital.***: Carbocaina; Carboplyina; Carbosen; Mepi-Mynol; Mepibil; Mepicain; Mepident; Mepiforan; Mepisolver; Mepivamol; Mepivirgi; Optocain; Pericaina; Scandonest; ***Neth.***: Scandicaine†; Scandonest; ***Norw.***: Carbocain; Scandonest; ***Port.***: Isogaine; Mepivastesin; Scandinibsa; Scandonest; ***Rus.***: Mepivastesin (МЕПИВАСТЕЗИН); ***S. Afr.***: Carbocaine; Scandonest; ***Singapore***: Mepivastesin; ***Spain***: Isogaine; Scandinibsa; Scandonest; ***Swed.***: Carbocain; Scandonest; ***Switz.***: Scandicain; Scandonest; ***Thai.***: Mepicaton; ***USA***: Carbocaine with Neo-Cobefrin; Carbocaine; Isocaine; Polocaine; Scandonest.

Multi-ingredient Preparations.

Used as an adjunct in:. ***Austria***: Estradurin; ***Belg.***: Estradurine†; ***Denm.***: Estradurin; ***Fin.***: Estradurin; ***Jpn***: Amasulin; Bestcall; Pansporin; Takesulin†; ***Norw.***: Estradurin†; ***Singapore***: Nevramin; ***Swed.***: Estradurin; ***Switz.***: Estradurin; ***Thai.***: Nevramin; ***Ukr.***: Estradurin (Эстрадурин)†.

Pharmacopoeial Preparations

USP 36: Mepivacaine Hydrochloride and Levonordefrin Injection; Mepivacaine Hydrochloride Injection.

Myrtecaine *(rINN)*

Mirtecaína; Myrtécaïne; Myrtecainum; Nopoksamin; Nopoxamine; Миртекаин.

2-[2-(10-Norpin-2-en-2-yl)ethoxy]triethylamine.

$C_{17}H_{31}NO$=265.4

CAS — 7712-50-7.

UNII — 9902116282.

Profile

Myrtecaine is a local anaesthetic (p. 1976.1) used topically as the base or laurilsulfate in rubefacient preparations for the treatment of muscle and joint pain. Myrtecaine laurilsulfate is also used in preparations with antacids for the symptomatic relief of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Algesal; ***Austria***: Acidrine; Algesal; Latesyl; Rheugesal†; Traumasal; ***Chile***: Sinacid†; ***Cz.***: Algesal; ***Fr.***: Acidrine; Algesal Suractive; ***Ger.***: Algesal†; ***Gr.***: Algesal Suractive; ***Hung.***: Algesal; ***Indon.***: Acidrine; Algesal Superactive; ***Ital.***: Acidrine; ***Neth.***: Algesal Forte†; ***Port.***: Algesal; Latesil; ***Spain***: Algesal; ***Turk.***: Acidrine; Algesal Suractive; ***Venez.***: Lemazol.

Oxetacaine *(BAN, rINN)*

Oksetakaiini; Oksetakain; Oxetacaína; Oxétacaïne; Oxetacainum; Oxetakain; Oxethazaine (USAN); Oxethazaine; Wy-806; Оксетакаин.

2,2′-(2-Hydroxyethylimino)bis[*N*-(αα-dimethylphenethyl)-*N*-methylacetamide].

$C_{28}H_{41}N_3O_3$=467.7

CAS — 126-27-2 (oxetacaine); 13930-31-9 (oxetacaine hydrochloride).

ATC — C05AD06.

ATC Vet — QC05AD06.

UNII — IP8QT76V17.

Pharmacopoeias. In *Br.* and *Jpn*.

BP 2014: (Oxetacaine). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol; very soluble in chloroform; soluble in ethyl acetate.

Profile

Oxetacaine is an amide anaesthetic (p. 1976.1) that is stated to have a prolonged action. It is used orally with antacids for the symptomatic relief of gastro-oesophageal reflux disease (p. 1807.2). It has also been used as the hydrochloride in ointments and suppositories for the relief of pain associated with haemorrhoids.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Tricaine-MPS; ***Ital.***: Emoren; ***Jpn***: Strocain.

Multi-ingredient Preparations. ***Arg.***: Mucaine; ***Austral.***: Mucaine†; ***Austria***: Tepilta; ***Braz.***: Droxaine; ***Canad.***: Mucaine; ***Fr.***: Mutesa†; ***Ger.***: Tepilta; ***Gr.***: Oxaine-M; ***Hong Kong***: Antacaine; Gastrocaine; Mucaine†; Oxema Improved; Strocain; ***India***: Acicot-O; Acicral-O; Acinil-O; Acral-O; Alcaine; Alcocid; Belief; Bestocid-O; Bluegel-O; Coligon-O; Crasia-O; Daffocid-O; Depcid-O; Dicaine; Digiflux-A; Disocain; Erocot-O; Esfate-O; Focri-O; Gastromax-O; Graster; Greycid; Jevacain; Kaicid-O; Kulent-O; Kulfi; Lacrate-O; Lorcus-O; Maxicain; Merigel-A; Mucaine; Newcain; Nubase; OAM; Oshrid; Oxefate-O; Oxycane; Pepticaine; ***Philipp.***: Geltazine; ***S.Afr.***: Mucaine; ***Singapore***: Strocain; ***Spain***: Roberfarin; ***Thai.***: Mucaine†; Strocain; ***Turk.***: Mucaine.

Oxybuprocaine Hydrochloride

(BANM, rINNM)

Benoxinate Hydrochloride; Hidrocloruro de oxibuprocaína; Oksibuprokaiinihydrokloridi; Oksibuprokain Hidroklorür; Oksibuprokaino hidrochloridas; Oxibuprocaína, hidrocloruro de; Oxibuprokain-hidroklorid; Oxibuprokainhydroklorid; Oxybuprocaïne, Chlorhydrate d'; Oxybuprocainhydrochlorid; Oxybuprocaini Hydrochloridum; Oxybuprokain hydrochlorid; Оксибупрокаина Гидрохлорид.

2-Diethylaminoethyl 4-amino-3-butoxybenzoate hydrochloride.

$C_{17}H_{28}N_2O_3$,HCl=344.9

CAS — 99-43-4 (oxybuprocaine); 5987-82-6 (oxybuprocaine hydrochloride).

ATC — D04AB03; S01HA02.

ATC Vet — QD04AB03; QS01HA02.

UNII — 0VE4U49K15.

NOTE. OXB, formerly BNX, is a code approved by the BP 2014 for use on single unit doses of eye drops containing oxybuprocaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Oxybuprocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Benoxinate Hydrochloride). White or slightly off-white, crystals or crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 0.8 of water, 1 in 2.6 of alcohol, and 1 in 2.5 of chloroform; insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.0.

Uses and Administration

Oxybuprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used for surface anaesthesia (p. 1977.3) and is reported to be less irritant than tetracaine when applied to the conjunctiva in therapeutic concentrations.

Oxybuprocaine is used as the hydrochloride in a 0.4% solution in short ophthalmological procedures. One drop instilled into the conjunctival sac anaesthetises the surface of the eye sufficiently to allow tonometry after 60 seconds and a further drop after 90 seconds provides adequate anaesthesia for the fitting of contact lenses. Three drops at 90-second intervals produces sufficient anaesthesia after 5 minutes for removal of a foreign body from the corneal epithelium, or for incision of a Meibomian cyst through the conjunctiva. The sensitivity of the cornea is normal again after about 1 hour.

A 1% solution of oxybuprocaine hydrochloride is used for surface anaesthesia of the ear, nose, and throat.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Effects on the eyes. Fibrinous iritis and moderate corneal swelling occurred in 2 patients after the use of a 0.4% or 1% solution of oxybuprocaine hydrochloride for topical anaesthesia of the eye for minor surgery.[1] The effects may have been due to inadvertent entry of the drug into the anterior chamber of the eye.

1. Haddad R. Fibrinous iritis due to oxybuprocaine. *Br J Ophthalmol* 1989; **73:** 76–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxybuprocaine as not porphyrinogenic when used for surface anaesthesia in ophthalmological procedures; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Benoxinat; Novain; ***Belg.***: Unicaine; ***Braz.***: Oxinest; ***China***: Benoxil (倍诺喜); ***Cz.***: Benoxi; Novesin†; ***Fin.***: Oftan Obucain; ***Fr.***: Cebesine; ***Ger.***: Conjuncain-EDO; Novesine; ***Hung.***: Humacain; ***India***: Bendzon†; ***Israel***: Localin; ***Ital.***: Novesina; ***Philipp.***: Oxyben†; ***Port.***: Anestocil; ***Rus.***: Benoxi (Бенокси); Inokain (Инокаин); ***S.Afr.***: Novesin; ***Spain***: Prescaina; ***Switz.***: Cebesin†; Novesin; ***Thai.***: Novesin†; ***Turk.***: Benoxinate; Novesin; ***Ukr.***: Inokain (Инокаин).

Multi-ingredient Preparations. ***Austral.***: Fluress†; ***Austria***: Flurekain†; ***Canad.***: Fluress; ***Fin.***: Oftan Flurekain; ***Fr.***: Collu-Blache†; Desomedine; ***Ger.***: Thilorbin; ***Gr.***: Collu-Blache; ***Mex.***: Mentalgina; ***Port.***: Fluotest; Mebocaina; ***Rus.***: Grammidin with Anesthetic Neo (Граммидин с АнестетикОм Нео); ***Spain***: Anestesico Doble; Fluotest; ***Swed.***: Fluress; ***Switz.***: Collu-Blache; Mebucaine; ***UAE***: B-Cool; ***Ukr.***: Grammidin with Anaesthetic Neo (Граммидин С Анестетиком Нео); ***USA***: Fluorox; Flurate†; Fluress; Flurox.

Pharmacopoeial Preparations

BP 2014: Oxybuprocaine Eye Drops;

USP 36: Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution.

Pramocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pramocaína; Pramocaína, hidrocloruro de; Pramocaïne, Chlorhydrate de; Pramocaini Hydrochloridum; Pramoksiinihydrokloridi; Pramoxine Hydrochloride; Pramoxinhydroklorid; Pramoxini Hydrochloridum; Pramoxinium Chloride; Прамокаина Гидрохлорид.

4-[3-(4-Butoxyphenoxy)propyl]morpholine hydrochloride.

$C_{17}H_{27}NO_3$,HCl=329.9

CAS — 140-65-8 (pramocaine); 637-58-1 (pramocaine hydrochloride).

ATC — C05AD07; D04AB07.

ATC Vet — QC05AD07; QD04AB07.

UNII — 88AYB867L5.

Pharmacopoeias. In *US*.

USP 36: (Pramoxine Hydrochloride). A white or almost white crystalline powder; it may have a faint aromatic odour. Freely soluble in water and in alcohol; soluble 1 in 35 of chloroform; very slightly soluble in ether. A 1% solution in water has a pH of about 4.5. Store in airtight containers.

Profile

Pramocaine hydrochloride is a local anaesthetic (p. 1976.1) used for surface anaesthesia. It is used alone or with corticosteroids and other drugs, usually in a concentration of 1%, in many formulations for the relief of pain and itching associated with minor skin conditions and anorectal disorders. Initial burning or stinging may occur following topical application. It should not be used for the nose or eyes. The base has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Dermoplast Poison Ivy Treatment; ***Fr.***: Tronothane; ***Israel***: Sarmed; ***Ital.***: Tronotene; ***S. Afr.***: Anugesic; ***Spain***: Balsabit†; Denutraxan; ***Thai.***: Primoly; ***USA***: Campho-Phenique Cold Sore Treatment & Scab Relief; Fleet Pain Relief; Ivy Wash; Pramox; Prax; Proctofoam; Sarna Sensitive Anti-Itch; Tronothane; Vagisil.

Multi-ingredient Preparations. ***Arg.***: Anusol Duo S; Anusol Duo; Anusol-A; Milorix†; Tocorectal; ***Belg.***: Nestosyl; ***Canad.***: Anugesic-HC; Anusol Plus; Anuzinc HC Plus; Anuzinc Plus; Aveeno Anti-Itch; Caladryl†; Gold Bond Anti-Itch; Gold Bond Medicated; Hemorrhoid Ointment; Hemorrhoidal Ointment; Onguent Hemorrhoidal†; Polysporin Itch Relief; Polysporin Lip Treatment; PrameGel; Pramox HC; Proctodan-HC; Proctofoam-HC; Sarna-P; ***Chile***: Caladryl Clear; ***Irl.***: Anugesic-HC; Anugesic-HC; Proctofoam-HC; ***Israel***: Epifoam; Hemorid†; Proctofoam-HC; ***Ital.***: Proctofoam-HC; ***Mex.***: Caladryl Clear; Soyaloid Apruri; ***Neth.***: Nestosyl; ***S.Afr.***: Anugesic†; ***Turk.***: Hipokort Arti; ***UK***: Anugesic-HC†; Anugesic-HC; Proctofoam-HC; ***USA***: 1 + 1-F; AmLactin AP†; Analpram E; Analpram-HC;

Anusol; Aveeno Anti-Itch†; Bacitraycin Plus; Bite & Itch Lotion; Calaclear; Caladryl Clear; Caladryl; Calagesic; Callergy Clear; Cortamox†; Cortane-B; Cortic ND; Cyotic; EndaRoid; Enzone; Epifoam; Gold Bond Intensive Healing; HC Pram; HC Pramoxine; Hemorid For Women; Mediotic-HC; Neosporin + Pain Relief; Neosporin + Pain Relief; Novacort; Oticin HC; Oticin; Oto-End; Otomar-HC; Phicon-F; Phicon; Pram-HCA; Pram-Cort; PrameGel; Pramosone; PramOtic; Preparation H; ProCort; Proctofoam-HC; Sarna Ultra†; Summer's Eve Anti-Itch; Tri-Biozene; Tronolane; Tucks; Zinotic†; Zone-A; Zoto-HC; ZyPram.

Pharmacopoeial Preparations
USP 36: Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Jelly.

Prilocaine *(BAN, USAN, rINN)*

Prilocain; Prilocaína; Prilocaïne; Prilocainum; Prilokaiini; Prilokain; Prilokainas; Прилокаин.

2-Propylaminopropiono-*o*-toluidide.

$C_{13}H_{20}N_2O$=220.3

CAS — 721-50-6.

ATC — N01BB04.

ATC Vet — QN01BB04.

UNII — 046O35D44R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Prilocaine). A white or almost white, crystalline powder. M.p. 36 degrees to 39 degrees. Slightly soluble in water; very soluble in alcohol and in acetone.

USP 36: (Prilocaine). A white or almost white powder or crystal aggregates. M.p. 36 degrees to 39 degrees. Slightly soluble in water; very soluble in alcohol and in acetone. Store at a temperature below 25 degrees.

Eutectic mixture. Prilocaine forms a mixture with lidocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Prilocaine Hydrochloride *(BANM, USAN, rINNM)*

Astra-1512; Hidrocloruro de prilocaína; L-67; Prilocaína, hidrocloruro de; Prilocaïne, Chlorhydrate de; Prilocainhydrochlorid; Prilocaini Hydrochloridum; Prilokaiinihydrokloridi; Prilokain Hidroklorür; Prilokain hydrochlorid; Prilokainhidroklorid; Prilokainhydroklorid; Prilokaino hidrochloridas; Propitocaine Hydrochloride; Прилокаина Гидрохлорид.

$C_{13}H_{20}N_2O$,HCl=256.8

CAS — 721-50-6 (prilocaine); 1786-81-8 (prilocaine hydrochloride).

ATC — N01BB04.

ATC Vet — QN01BB04.

UNII — MJW015BAPH.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Prilocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. M.p. 168 degrees to 171 degrees. Freely soluble in water and in alcohol; very slightly soluble in acetone.

USP 36: (Prilocaine Hydrochloride). A white odourless crystalline powder. Freely soluble in water and in alcohol; slightly soluble in chloroform; very slightly soluble in acetone; practically insoluble in ether.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Uses and Administration

Prilocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It has a similar anaesthetic potency to lidocaine. However, it has a slower onset of action, less vasodilator activity, and a slightly longer duration of action; it is also less toxic. Prilocaine hydrochloride is used for infiltration anaesthesia and nerve blocks in solutions of 0.5%, 1%, and 2%. A 1% solution is also used for epidural analgesia and a 2% solution is used for epidural anaesthesia; for intravenous regional anaesthesia 0.5% solutions are used. A 3% solution with the vasoconstrictor felypressin (p.2502.3) or a 4% solution without are used for dental procedures. A 4% solution with adrenaline 1 in 200 000 is also used for dentistry in some countries. Carbonated solutions of prilocaine have also been tried in some countries in epidural and brachial plexus nerve blocks (see under Administration, p. 1976.2). Prilocaine is used for surface anaesthesia in a eutectic mixture with lidocaine. (Local anaesthetic techniques are discussed on p. 1977.2.)

The dosage used in various **local anaesthetic procedures** varies with the site of injection and the procedure used. The recommended **maximum single dose** in adults for prilocaine hydrochloride is 400 mg if used alone, or 300 mg if used with felypressin. Doses should be reduced in elderly or debilitated patients. The dose for children over 6 months of age is up to 5 mg/kg. For *dental infiltration* or *dental nerve blocks*, the usual adult dose of prilocaine hydrochloride without felypressin is 40 to 80 mg (1 to 2 mL) as a 4% solution; children under 10 years generally require about 40 mg (1 mL). Similar doses of the 4% solution with adrenaline (1:200 000) may be used for most routine dental procedures. The usual adult dose of prilocaine hydrochloride with felypressin 0.03 international units/mL is 30 to 150 mg (1 to 5 mL) as a 3% solution; children under 10 years generally require 30 to 60 mg (1 to 2 mL).

A eutectic mixture of prilocaine base 2.5% and lidocaine base 2.5% (see Surface Anaesthesia, under Lidocaine, p. 1989.3) is applied as a cream under an occlusive dressing to produce *surface anaesthesia* of the skin before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts. It is also used as a eutectic gel for *anaesthesia of the periodontal pockets* during dental scaling and/or root planing. Typically, 1.7 g of gel, or less, will be sufficient for one quadrant of dentition; the maximum recommended quantity per treatment session is 8.5 g.

Action. For a comparison of the vasoactivity of prilocaine and some other local anaesthetics, see p. 1976.2.

Administration in children. The *BNFC* recommends that the dose of prilocaine in children should be adjusted according to physical status and the nature of the procedure.

For uses and dosage of prilocaine hydrochloride in children, see above.

Infiltration anaesthesia. Addition of felypressin at a concentration of 0.03 international units/mL to prilocaine 3% injection did not reduce plasma concentrations of prilocaine after infiltration of a 60-mg dose into the upper premolar region.[1]

1. Cannell H, Whelpton R. Systemic uptake o f prilocaine after injection of various formulations of the drug. *Br Dent J* 1986; **160:** 47–9.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Prilocaine has relatively modest toxicity compared with most amide-type local anaesthetics. However, dose-related methaemoglobinaemia and cyanosis, attributed to the metabolite *o*-toluidine, appear to occur more frequently with prilocaine than with other local anaesthetics (see Methaemoglobinaemia, p. 1978.3). Symptoms usually occur when doses of prilocaine hydrochloride exceed about 8 mg/kg but the very young may be more susceptible. Methaemoglobinaemia has been seen in neonates whose mothers received prilocaine shortly before delivery and it has also been reported after prolonged topical application of a prilocaine/lidocaine eutectic mixture in children. (See Surface Anaesthesia in Lidocaine, p. 1989.3 for precautions to be observed with such a eutectic mixture.) Methaemoglobinaemia may be treated by giving oxygen followed, if necessary, by an injection of methylthioninium chloride.

Prilocaine is contra-indicated for paracervical block in obstetrics.

Prilocaine should be avoided in patients with anaemia, congenital or acquired methaemoglobinaemia, cardiac or ventilatory failure, or hypoxia.

Effects on the CNS. For reference to the prilocaine serum concentrations associated with CNS toxicity, see Absorption under Pharmacokinetics, below.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prilocaine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Methaemoglobinaemia may occur at lower doses of prilocaine in patients receiving therapy with other drugs known to cause such conditions (e.g. sulfonamides such as sulfamethoxazole in co-trimoxazole).

Neuromuscular blockers. For a possible interaction between *mivacurium* and prilocaine, see under Atracurium, p. 2033.1.

Pharmacokinetics

Prilocaine is reported to be 55% bound to plasma proteins. It is rapidly metabolised mainly in the liver and also in the kidneys and is excreted in the urine mainly as metabolites. One of the principal metabolites excreted in the urine is *o*-toluidine, which is believed to cause the methaemoglobinaemia seen after large doses. Prilocaine crosses the placenta and during prolonged epidural anaesthesia may produce methaemoglobinaemia in the fetus. It is distributed into breast milk.

See also under Local Anaesthetics, p. 1979.3.

Absorption. Peak serum concentrations of prilocaine hydrochloride attained after the use of 8.5 mL of a 1% solution for retrobulbar and facial nerve block were well below the concentration of 20 micrograms/mL associated with CNS toxicity due to prilocaine.[1]

1. Goggin M, *et al.* Serum concentrations of prilocaine following retrobulbar block. *Br J Anaesth* 1990; **64:** 107–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Citanest; ***Belg.***: Citanest; ***Braz.***: Citanest com Octapressin; Citocaina; ***Canad.***: Citanest; ***Denm.***: Citanest Octapressin; ***Fin.***: Citanest Octapressin; ***Ger.***: Takipril; Xylonest; ***Hong Kong***: Citanest Octapressin†; ***Mex.***: Pristesin F; ***Neth.***: Citanest Octapressine; Citanest; ***Norw.***: Citanest Octapressin; ***NZ***: Citanest; ***Singapore***: Citanest Octapressin; ***Swed.***: Citanest Octapressin; Citanest; ***Switz.***: Xylonest; ***Turk.***: Citanest Octapressin†; Citanest; ***UK***: Citanest with Octapressin; Citanest; Prilotekal; ***USA***: Citanest.

Multi-ingredient Preparations. ***Arg.***: Emla; ***Austral.***: Emla; ***Austria***: Emla; Oraqix; ***Belg.***: Emla; ***Braz.***: Emla; Medicaina; ***Canad.***: Emla; ***Chile***: Eutecaina; ***China***: Emla (恩纳); ***Cz.***: Emla; ***Denm.***: Emla; Oraqix; Tapin; ***Fin.***: Emla; Oraqix; Tapin; ***Fr.***: Anesderm; Emla; Emlapatch; Oraqix; ***Ger.***: Anesderm; Emla; Oraqix; ***Gr.***: Emla; Funis; Opralix; Prinex; Xylocream; ***Hong Kong***: Emla; Lidiprine; ***India***: Asthesia; Emlap; ***Indon.***: Dolones; Emla; Estesia; Topsy; ***Irl.***: Emla; Oraqix; ***Israel***: Duo-Caine; Emla; ***Ital.***: Emla; Oraqix; ***Jpn***: EMLA; ***Malaysia***: Emla; Lipro; ***Mex.***: Emla; ***Neth.***: Emla; Oraqix; ***Norw.***: Emla; Oraqix; Tapin; ***NZ***: Emla; Oraqix; ***Philipp.***: Emla; Emlocaine; ***Pol.***: Emla; ***Port.***: Emla; Oraqix; ***Rus.***: Emla (Эмла); ***S.Afr.***: Emla; Topla; ***Singapore***: Emla; ***Spain***: Emla; Oraqix; ***Swed.***: Emla; Oraqix; Tapin; ***Switz.***: Anesderm; Emla; Oraqix; ***Thai.***: Emla; Liprikaine; ***Turk.***: Emla; ***UK***: Emla; Oraqix; ***Ukr.***: Emla (Эмла); ***USA***: Emla; Oraqix.

Pharmacopoeial Preparations
BP 2014: Prilocaine Injection;
USP 36: Lidocaine and Prilocaine Cream; Prilocaine and Epinephrine Injection; Prilocaine Hydrochloride Injection.

Procaine Hydrochloride *(BANM, rINNM)*

Allocaine; Ethocaine Hydrochloride; Hidrocloruro de procaína; Novocainum; Procaína, hidrocloruro de; Procaïne, Chlorhydrate de; Procainhydrochlorid; Procaini Hydrochloridum; Procainii Chloridum; Procainium Chloride; Prokaiinihydrokloridi; Prokain Hidroklorür; Prokain-hidroklorid; Prokain-hydrochlorid; Prokainhydroklorid; Prokaino hidrochloridas; Prokainy chlorowodorek; Syncaine; Прокаина Гидрохлорид.

2-Diethylaminoethyl 4-aminobenzoate hydrochloride.

$C_{13}H_{20}N_2O_2$,HCl=272.8

CAS — 59-46-1 (procaine); 51-05-8 (procaine hydrochloride).

ATC — C05AD05; N01BA02; S01HA05.

ATC Vet — QC05AD05; QN01BA02; QS01HA05.

UNII — 95URV01IDQ.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Procaine Hydrochloride). A white or almost white crystalline powder or colourless crystals. Very soluble in water; soluble in alcohol. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 36: (Procaine Hydrochloride). Odourless, small, white crystals or white, crystalline powder. Soluble 1 in 1 of water and 1 in 15 of alcohol; slightly soluble in chloroform; practically insoluble in ether.

Incompatibility. Procaine hydrochloride has been reported to be incompatible with aminophylline, barbiturates, magnesium sulfate, phenytoin sodium, sodium bicarbonate, and amphotericin B.

Stability of solutions. Degradation of procaine in a cardioplegic solution containing magnesium, sodium, potassium, and calcium salts was found to be temperature dependent.[1] At a storage temperature of 6 degrees the shelf-life of the solution was 5 weeks and this was increased to 9 weeks when the storage temperature was -10 degrees.

Using carbon dioxide instead of nitrogen in the head space did not affect stability of procaine.

1. Synave R, *et al.* Stability of procaine hydrochloride in a cardioplegic solution containing bicarbonate. *J Clin Hosp Pharm* 1985; **10:** 385–8.

Uses and Administration

Procaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. Because of its poor penetration of intact mucous membranes, procaine is ineffective for surface application and has been chiefly used by injection, although in general it has been replaced by lidocaine and other local anaesthetics. It has a slow onset of action and a short duration of action. It has vasodilator activity and therefore a vasoconstrictor may be added to delay absorption and increase the duration of action. Procaine has mainly been used for infiltration anaesthesia, peripheral nerve blocks, and spinal block. (Local anaesthetic techniques are discussed on p. 1977.2.) It has also been used in cardioplegic solutions to protect the myocardium during cardiac surgery.

Procaine hydrochloride is given in concentrations of 0.5 to 2%. The dosage depends on the site of injection and the procedure used, as well as the status of the patient.

Procaine hydrochloride has been used with propoxycaine in dentistry.

Procaine forms poorly soluble salts or conjugates with some drugs, for example penicillin, and is used to prolong their action after injection. It may also reduce the pain of injection.

Procaine-*N*-glucoside hydrochloride has been included in a preparation for gastrointestinal disorders, and procaine ascorbate has been included in a multivitamin preparation.

Action. For a comparison of the vasoactivity of procaine and some other local anaesthetics, see p. 1976.2.

Dementia. Procaine hydrochloride has been used for many years for its anti-ageing effects including the prevention of dementia (p. 388.1) and cognitive impairment but its value is not established. A systematic review[1] found no evidence of its benefit; some serious adverse effects were associated with long-term use.

1. Szatmári S, Bereczki D. Procaine treatments for cognition and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 23/12/09).

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Effects on the cardiovascular system. Severe hypotension leading to cardiac arrest and death developed in a patient after an infusion of 600 mg of procaine for malignant hyperthermia.[1]

1. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; **i:** 355.

Hypersensitivity. Of 600 persons with dermatitis or eczema submitted to patch testing with 2% aqueous solution of procaine hydrochloride, 4.8% gave a positive reaction.[1]

For reports of hypersensitivity including anaphylactic reactions associated with procaine and other local anaesthetics, see under Adverse Effects of Local Anaesthetics, p. 1978.2.

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83:** 543–5.

Systemic lupus erythematosus. The limited theoretical risk from using procaine for local anaesthesia in patients who have had procainamide-induced SLE was aired some years ago.[1-3]

1. Dubois EL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; **238:** 2201.
2. Alarcón-Segovia D. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; **238:** 2201.
3. Lee SL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; **238:** 2201.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Diuretics. Use with *acetazolamide* extends the plasma half-life of procaine.[1]

1. Calvo R, *et al.* Effects of disease and acetazolamide on procaine hydrolysis by red blood cell enzymes. *Clin Pharmacol Ther* 1980; **27:** 179–83.

Pharmacokinetics

Procaine is poorly absorbed from mucous membranes and is usually given parenterally. It is rapidly hydrolysed by plasma cholinesterase to para-aminobenzoic acid and diethylaminoethanol; some may also be metabolised in the liver. Only about 6% is bound to plasma proteins. About 80% of the para-aminobenzoic acid is excreted unchanged or conjugated in the urine. About 30% of the diethylaminoethanol is excreted in the urine, the remainder being metabolised in the liver.

See also under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Endocaina; Fadacaina; Procanest; ***Austria***: Geroaslan H3†; Gerovital H3†; Novanaest; ***Canad.***: Novocain†; ***Ger.***: Hewedolor Procain; Lophakomp-Procain; Pasconeural-Injektopas; ***Hong Kong***: Gerovital H3†; ***Ital.***: Lenident; ***Singapore***: Procanol; ***USA***: Novocain†; ***Venez.***: Artrocel; Bioquel; Genaplex.

Multi-ingredient Preparations. ***Arg.***: 6-Copin; Dastonil; Gingeron; KH3†; Levantol Procaina; Longevital; Otalex G; Otonorthia; ***Austral.***: Cardioplegia Concentrate; ***Austria***: KH3; ***Braz.***: Aftine; Bismu-Jet; Claudemor; Colutoide; Dentisan†; Fonergin; Otoloide; Oturga; ***Chile***: Biocord-E; Biocord; Diltotal; Infor; Pantiban†; ***China***: Compound Anisodine (复方樟柳碱); Jinquan (金泉); ***Cz.***: Solutio Thomas cum Procaino; ***Denm.***: Kardioplex†; ***Fr.***: Otylol; ***Ger.***: Gero H3 Aslan†; Hewedolor plus Coffein†; Otalgan; ***Gr.***: Cardioplegia; KH3; ***Hong Kong***: Cardioplegia; KH3; ***Hung.***: Hemorid; Hemorid; ***India***: Cardiplegin; Florocid; KP-Plegia; ***Indon.***: Cardioplegia; ***Irl.***: Cardioplegia; ***Ital.***: Dentosedina; Ginvapast; Neo-Ustiol; Otalgan; Otomidone; Otopax; Ustiosan; ***Malaysia***: Cardioplegia; ***NZ***: KH3; ***Rus.***: Menovasin (Меновазин); Ottoslavin (Оттославин); Solutan (Солутан)†; ***S. Afr.***: Universal Earache Drops†; ***Singapore***: Cardioplegia; ***Spain***: Anestesia Local Braun S/A; Co Bucal; Coliriocilina Adren Astr†; Eupnol; Kanafosal Predni†; Kanafosal†; Neocolan†; Nulacin Fermentos†; Oftalmol Ocular; Otosedol†; ***Switz.***: Anaestalgin†; Ginvapast; Otalgan; Otosan; ***Thai.***: Cardioplegia; KH3†; ***Ukr.***: Menovasan (Меновазан).

Used as an adjunct in:. ***Arg.***: Betametasona B12; ***Braz.***: Dexacobal; Dexador; Dexagil; Dexaneurin; ***Ger.***: Eukalisan N†.

Homoeopathic Preparations. ***Ger.***: NeyChon Nr 68; NeyGero Nr 64; NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations
USP 36: Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Procaine Hydrochloride and Epinephrine Injection; Procaine Hydrochloride Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Propanocaine Hydrochloride *(rINNM)*

467D$_3$; Hidrocloruro de propanocaína; Propanocaína, hidrocloruro de; Propanocaïne, Chlorhydrate de; Propanocaini Hydrochloridum; Пропанокаина Гидрохлорид.

3-Diethylamino-1-phenylpropyl benzoate hydrochloride.

$C_{20}H_{25}NO_2$,HCl=347.9

CAS — 493-76-5 (propanocaine); 1679-79-4 (propanocaine hydrochloride).

Profile

Propanocaine hydrochloride, a benzoic acid ester, is a local anaesthetic (p. 1976.1) that has been used topically for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Detraine†.

Propoxycaine Hydrochloride *(rINNM)*

Hidrocloruro de propoxicaína; Propoxicaína, hidrocloruro de; Propoxycaïne, Chlorhydrate de; Propoxycaini Hydrochloridum; Propoxycainium Chloride; Пропоксикаина Гидрохлорид.

2-Diethylaminoethyl 4-amino-2-propoxybenzoate hydrochloride.

$C_{16}H_{26}N_2O_3$,HCl=330.9

CAS — 86-43-1 (propoxycaine); 550-83-4 (propoxycaine hydrochloride).

UNII — K490D39G46.

Pharmacopoeias. In *US*.

USP 36: (Propoxycaine Hydrochloride). A white odourless crystalline solid. It discolours on prolonged exposure to light and air. Soluble 1 in 2 of water, 1 in 10 of alcohol, and 1 in 80 of ether; practically insoluble in acetone and in chloroform. A 2% solution in water has a pH of about 5.4. Protect from light.

Profile

Propoxycaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic (p. 1976.1). It has been used with procaine hydrochloride and a vasoconstrictor for infiltration anaesthesia and nerve block in dental procedures. Propoxycaine has a more rapid onset and a longer duration of action than that of procaine.

Preparations

Pharmacopoeial Preparations
USP 36: Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proxymetacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de proximetacaína; Proksimetakain Hidroklorür; Proparacaine Hydrochloride; Proparakain Hidroklorür; Proximetacaína, hidrocloruro de; Proxymétacaïne, Chlorhydrate de; Proxymetacaini Hydrochloridum; Проксиметакаина Гидрохлорид.

2-Diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride.

$C_{16}H_{26}N_2O_3$,HCl=330.9

CAS — 499-67-2 (proxymetacaine); 5875-06-9 (proxymetacaine hydrochloride).

ATC — S01HA04.

ATC Vet — QS01HA04.

UNII — U96OL57GOY.

NOTE. PROX is a code approved by the BP 2014 for use on single unit doses of eye drops containing proxymetacaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PROXFLN is a similar code approved for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Proxymetacaine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Soluble in water and in chloroform; very soluble in dehydrated alcohol; practically insoluble in ether. A 1% solution in water has a pH of 5.7 to 6.4. Protect from light.

USP 36: (Proparacaine Hydrochloride). A white to off-white, or faintly buff-coloured, odourless, crystalline powder. Soluble in water, in warm alcohol, and in methyl alcohol; insoluble in ether and in benzene.

Uses and Administration

Proxymetacaine hydrochloride, a meta-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used for surface anaesthesia (p. 1977.3) in ophthalmology in a concentration of 0.5%. Proxymetacaine is of similar potency to tetracaine in equal concentrations and induces anaesthesia within about 20 seconds. The duration of action may be 15 minutes or longer. Instillation of 1 or 2 drops permits tonometry after 30 seconds. For removal of foreign bodies or sutures from the cornea 1 or 2 drops are instilled every 5 to 10 minutes for up to 3 applications, or 1 or 2 drops are instilled 2 to 3 minutes before the procedure. For deeper anaesthesia such as needed for cataract extraction 1 drop is instilled every 5 to 10 minutes to a total of 5 to 7 applications.

Trigeminal neuralgia. There have been anecdotal reports that proxymetacaine eye drops relieved trigeminal neuralgia (p. 11.2) refractory to carbamazepine.[1,2] However, a controlled study failed to show any benefit.[3]

1. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by ophthalmic anesthetic. *JAMA* 1991; **265:** 2807.
2. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by optical anesthesia. *JAMA* 1991; **266:** 1649.
3. Kondziolka D, *et al.* The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia: a randomized double-blind placebo-controlled trial. *J Neurosurg* 1994; **80:** 993–7.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

A severe immediate-type corneal reaction to proxymetacaine may rarely occur. Allergic contact dermatitis has also been reported.

Effects on the skin. Exacerbation of Stevens-Johnson syndrome has been reported[1] in a woman after ophthalmic anaesthesia with proxymetacaine hydrochloride.

1. Ward B, *et al.* Dermatologic reaction in Stevens-Johnson syndrome after ophthalmic anesthesia with proparacaine hydrochloride. *Am J Ophthalmol* 1978; **86:** 133–5.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

See under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anestalcon; Poencaina; ***Austral.***: Alcaine; ***Belg.***: Alcaine; ***Braz.***: Anestalcon; Visonest; ***Canad.***: Ak-Taine; Alcaine; Diocaine; Ophthetic†; ***Chile***: Anestalcon; ***China***: Alcaine (爱尔凯因); ***Ger.***: Proparakain-POS; ***Gr.***: Alcaine; ***Hong Kong***: Alcaine; ***India***: Paracain; ***Malaysia***: Alcaine; ***Mex.***: Alcaine; ***Norw.***: Alcaine; ***NZ***: Ophthetic†; ***Philipp.***: Alcaine; ***Pol.***: Alcaine; ***Rus.***: Alcaine (Алкаин)†; ***Singapore***: Alcaine†; Primax; ***Switz.***: Alcaine; ***Turk.***: Alcaine; Opticaine†; ***Ukr.***: Alcain (Алкаин); ***USA***: Ak-Taine; Alcaine; Ocu-Caine; Ophthetic; Parcaine; ***Venez.***: Alcaine; Poencaina.

Multi-ingredient Preparations. ***Canad.***: Fluoracaine†; ***USA***: Fluoracaine; Fluorocaine.

Pharmacopoeial Preparations
BP 2014: Proxymetacaine Eye Drops;
USP 36: Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Proparacaine Hydrochloride Ophthalmic Solution.

Quinisocaine Hydrochloride *(BANM, rINNM)*

Chinisocainum Hydrochloride; Dimethisoquin Hydrochloride (USAN); Dimethisoquinium Chloride; Hidrocloruro de quinisocaína; Quinisocaína, hidrocloruro de; Quinisocaïne, Chlorhydrate de; Quinisocaini Hydrochloridum; Хинизокаина Гидрохлорид.

2-(3-Butyl-1-isoquinolyloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{17}H_{24}N_2O,HCl=308.8$

CAS — 86-80-6 (quinisocaine); 2773-92-4 (quinisocaine hydrochloride).
ATC — D04AB05.
ATC Vet — QD04AB05.
UNII — SMP2689462.

Profile

Quinisocaine hydrochloride is a local anaesthetic (p. 1976.1) that has been used as a surface anaesthetic in the form of an ointment or cream in a concentration of 0.5% for the relief of pruritus, anogenital or anorectal irritation, and minor skin conditions. It has also been used as suppositories.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Quotane; ***Ger.***: Haenal akut; ***Switz.***: Isochinol.

Multi-ingredient Preparations. ***Fr.***: Rectoquotane.

Ropivacaine Hydrochloride

(BANM, rINNM)

AL-281; Hidrocloruro de ropivacaína; Ropivacaína, hidrocloruro de; Ropivacaïne, Chlorhydrate de; Ropivacaini Hydrochloridum; Ropivakaiinihydrokloridi; Ropivakain Hidroklorür; Ropivakainhydroklorid; Ропивакаина Гидрохлорид.

(*S*)-2′,6′-Dimethyl-1-propylpiperidine-2-carboxanilide hydrochloride monohydrate.

$C_{17}H_{26}N_2O,HCl,H_2O=328.9$

CAS — 84057-95-4 (ropivacaine); 98717-15-8 (anhydrous ropivacaine hydrochloride); 132112-35-7 (ropivacaine hydrochloride monohydrate).
ATC — N01BB09.
ATC Vet — QN01BB09.
UNII — V910P86109 (ropivacaine hydrochloride monohydrate); 35504LBE2T (anhydrous ropivacaine hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ropivacaine Hydrochloride Monohydrate). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. pH of a 2% solution in water is 4.5 to 6.0.

USP 36: (Ropivacaine Hydrochloride). A white crystalline powder. Soluble in water. A 1% solution in water has a pH of 4.5 to 6.0.

Uses and Administration

Ropivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is a long-acting local anaesthetic, although onset and duration of action are dependent upon the site of injection; the presence of a vasoconstrictor such as adrenaline has no effect. Ropivacaine is used for epidural block, peripheral nerve block, and infiltration anaesthesia and field block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). (Local anaesthetic techniques are discussed on p. 1977.2.) At high doses ropivacaine produces surgical anaesthesia, whereas at lower doses it is used for the management of acute pain such as labour pain (p. 8.3) and in postoperative analgesia (p. 6.1).

Like bupivacaine (p. 1980.3), ropivacaine has a differential blocking effect on nerve fibres and, at the lowest concentration used, there is good differentiation between sensory and motor block. The onset and duration of sensory block produced by ropivacaine is generally similar to that obtained with bupivacaine but the motor block is often slower in onset, shorter in duration, and less intense.

Ropivacaine hydrochloride is given in concentrations of 0.2 to 1%. The dosage depends on the site of injection and the procedure used, as well as the status of the patient. The dose of ropivacaine should be reduced in the elderly, and in acutely ill or debilitated patients. A test dose of lidocaine with adrenaline should be given before starting epidural block with ropivacaine to detect inadvertent intravascular administration.

- For **surgical anaesthesia**, doses of ropivacaine hydrochloride for *lumbar epidural block* are 75 to 150 mg (15 to 30 mL) as a 0.5% solution, or 112.5 to 187.5 mg (15 to 25 mL) as a 0.75% solution, or 150 to 200 mg (15 to 20 mL) as a 1% solution; for caesarean section, doses are 100 to 150 mg (20 to 30 mL) as a 0.5% solution or 112.5 to 150 mg (15 to 20 mL) as a 0.75% solution. Doses for *thoracic epidural block* to establish a block for postoperative pain relief are 25 to 75 mg (5 to 15 mL) as a 0.5% solution or 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution; the actual dose used depends on the level of the injection.
- For *peripheral nerve block* of major nerves such as the brachial plexus, typical doses are 175 to 250 mg (35 to 50 mL) as a 0.5% solution; 225 to 300 mg (30 to 40 mL) as a 0.75% solution has also been recommended for brachial plexus block.
- For *infiltration anaesthesia* and *field block* up to 200 mg (40 mL) as a 0.5% solution or up to 225 mg (30 mL) as a 0.75% solution may be used.
- In the management of **acute pain** ropivacaine hydrochloride is used as a 0.2% solution for epidural block (0.5% solutions may be used for infiltration). Doses for *lumbar epidural block* are 20 to 40 mg (10 to 20 mL) as an initial bolus followed by 20 to 30 mg (10 to 15 mL) at intervals of not less than 30 minutes. Alternatively, 12 to 20 mg (6 to 10 mL) per hour may be given as a continuous epidural infusion; if additional pain relief is required, doses of up to 28 mg (14 mL) per hour may be given. Doses for *thoracic epidural block* are 12 to 28 mg (6 to 14 mL) per hour as a continuous infusion.
- For *infiltration anaesthesia* doses are 2 to 200 mg (1 to 100 mL) as a 0.2% solution or 5 to 200 mg (1 to 40 mL) as a 0.5% solution.
- In neonates, infants, and children aged up to 12 years, ropivacaine hydrochloride may be used for the management of peri- and postoperative pain. A 0.2% solution is given in a dose of 2 mg/kg (1 mL/kg) to achieve a *caudal epidural block*.

References.
1. Markham A, Faulds D. Ropivacaine: a review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; **52:** 429–49.
2. McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76:** 300–307.
3. Morton C. Ropivacaine. *Br J Hosp Med* 1997; **58:** 97–100.
4. Stienstra R. The place of ropivacaine in anesthesia. *Acta Anaesthesiol Belg* 2003; **54:** 141–8.
5. Zink W, Graf BM. Benefit-risk assessment of ropivacaine in the management of postoperative pain. *Drug Safety* 2004; **27:** 1093–1114.
6. Simpson D, *et al*. Ropivacaine: a review of its use in regional anaesthesia and acute pain management. *Drugs* 2005; **65:** 2675–2717.

Administration in children. The *BNFC* recommends that the dose of ropivacaine in children should be adjusted according to physical status and the nature of the procedure.

For uses and dosage of ropivacaine hydrochloride in children, see above.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Ropivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics.

Effects on the cardiovascular system. Ropivacaine is structurally related to bupivacaine, but data from extensive *animal* studies suggest that ropivacaine may be less cardiotoxic than bupivacaine.[1] Results from a study[2] in 12 healthy male subjects support these data; at doses producing CNS symptoms cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine than with bupivacaine.

1. Cederholm I. Preliminary risk-benefit analysis of ropivacaine in labour and following surgery. *Drug Safety* 1997; **16:** 391–402.
2. Knudsen K, *et al*. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78:** 507–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ropivacaine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Giving ropivacaine with general anaesthetics, opioid analgesics, or drugs structurally related to amide-type local anaesthetics (e.g. certain antiarrhythmics) may result in potentiation of adverse effects.

The metabolism of ropivacaine is mediated by the cytochrome P450 isoenzyme CYP1A2 and the potential exists for interactions between ropivacaine and other drugs that inhibit or act as a substrate for this isoenzyme. Prolonged use of ropivacaine should be avoided in patients treated with potent CYP1A2 inhibitors, such as fluvoxamine. Plasma concentrations of ropivacaine may be reduced by enzyme-inducing drugs such as rifampicin.

Pharmacokinetics

Ropivacaine is about 94% bound to plasma proteins. The terminal elimination half-life has been reported to be 1.8 hours. It is extensively metabolised in the liver, mainly by aromatic hydroxylation which is mediated by the cytochrome P450 isoenzyme CYP1A2; the isoenzyme CYP3A4 plays a minor role in the metabolism of ropivacaine. The metabolites are excreted mainly in the urine; about 1% of a dose is excreted as unchanged drug. Some metabolites also have a local anaesthetic effect but less than that of ropivacaine. Ropivacaine crosses the placenta.

See also under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Naropin; ***Austral.***: Naropin; ***Austria***: Naropin; ***Belg.***: Naropin; ***Braz.***: Naropin; Ropi; ***Canad.***: Naropin; ***Chile***: Naropin†; ***China***: Heng Luo (恒洛); Naropin (耐乐品); Zhuo Tan (卓坦); ***Cz.***: Naropin†; ***Denm.***: Naropin; ***Fin.***: Naropin; ***Fr.***: Naropeine; ***Ger.***: Naropin; ***Gr.***: Naropeine; ***Hong Kong***: Naropin; ***Hung.***: Naropin; ***Indon.***: Naropin; ***Irl.***: Naropin; ***Israel***: Naropin; ***Ital.***: Naropina; ***Malaysia***: Naropin; ***Mex.***: Naropin; Ropiconest; ***Neth.***: Naropin; ***Norw.***: Naropin; ***NZ***: Naropin; ***Philipp.***: Naropin; ***Pol.***: Naropin; Ropimol; ***Port.***: Naropeine; ***Rus.***: Naropin (Наропин); ***S.Afr.***: Naropin; ***Singapore***: Naropin; ***Spain***: Naropin; ***Swed.***: Narop; ***Switz.***: Naropin; ***Thai.***: Naropin; ***Turk.***: Naropin; ***UK***: Naropin; ***Ukr.***: Naropin (Наропин); ***USA***: Naropin.

Multi-ingredient Preparations. ***Austral.***: Naropin with Fentanyl; ***NZ***: Naropin with Fentanyl.

Pharmacopoeial Preparations
USP 36: Ropivacaine Hydrochloride Injection.

Tetracaine *(BAN, rINN)*

Amethocaine; Tetracaína; Tétracaïne; Tetracainum; Tetrakaiini; Tetrakain; Тетракаин.

2-Dimethylaminoethyl 4-butylaminobenzoate.

$C_{15}H_{24}N_2O_2=264.4$

CAS — 94-24-6.
ATC — C05AD02; D04AB06; N01BA03; S01HA03.
ATC Vet — QC05AD02; QD04AB06; QN01BA03; QS01HA03.
UNII — 0619F35CGV.

Pharmacopoeias. In *US*.

USP 36: (Tetracaine). A white or light yellow waxy solid. M. p. 41 degrees to 46 degrees. Very slightly soluble in water; soluble 1 in 5 of alcohol and 1 in 2 of chloroform or of ether; soluble in benzene. Store in airtight containers. Protect from light.

Tetracaine Hydrochloride *(BANM, rINNM)*

Amethocaine Hydrochloride; Dicainum; Hidrocloruro de tetracaína; Tetracaina, hidrocloruro de; Tétracaïne, Chlorhydrate de; Tetracainhydrochlorid; Tetracaini Hydrochloridum; Tetracainii Chloridum; Tetrakaiinihydrokloridi; Tetrakain Hidroklorür; Tetrakain hydrochlorid; Tetrakainhidroklorid; Tetrakainhydroklorid; Tetrakaino hidrochloridas; Tetrakainy chlorowodorek; Тетракаина Гидрохлорид.

$C_{15}H_{24}N_2O_2$,HCl=300.8
CAS — 136-47-0.
ATC — C05AD02; D04AB06; N01BA03; S01HA03.
ATC Vet — QC05AD02; QD04AB06; QN01BA03; QS01HA03.
UNII — 5NF5D4OPCI.

NOTE. TET is a code approved by the BP 2014 for use on single unit doses of eye drops containing tetracaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Tetracaine Hydrochloride). A white or almost white, slightly hygroscopic, polymorphic, crystalline powder. Freely soluble in water; soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Tetracaine Hydrochloride). A fine, white, odourless, hygroscopic, polymorphic, crystalline powder. Very soluble in water; soluble in alcohol; insoluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Tetracaine, a para-aminobenzoic acid ester, is a potent local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used for surface anaesthesia and spinal block; its use in other local anaesthetic techniques is restricted by its systemic toxicity.

Tetracaine is generally used as the hydrochloride in solutions and creams, and as the base in gels or ointments.

For *anaesthesia of the eye*, solutions containing 0.5 to 1% tetracaine hydrochloride have been used; ointments have also been used. Instillation of a 0.5% solution produces anaesthesia within 25 seconds that lasts for 15 minutes or longer and is suitable for use before minor surgical procedures.

For *topical anaesthesia*, a 4% gel is used as a *percutaneous local anaesthetic* before *venepuncture or venous cannulation.* The gel is applied to the centre of the area to be anaesthetised and covered with an occlusive dressing. In some circumstances such as where cannulation is difficult anaesthesia of more than one site may be necessary. Children aged 5 years and over and adults may receive a maximum of 5 tubes (about 5 g) at a single time applied to separate sites; younger children should only receive the contents of one tube at a single time but this can be applied to separate sites. Gel and dressing are removed after 30 minutes for venepuncture and after 45 minutes for venous cannulation. A single application generally provides anaesthesia for 4 to 6 hours. Licensed product information states that this method is not suitable for premature infants or those less than 1 month of age; however, the *BNFC* recommends that such a method may be used in neonates. A transdermal patch containing tetracaine 70 mg with lidocaine 70 mg is available for surface anaesthesia of intact skin in connection with *needle puncture* and in cases of *superficial surgical procedures.* A cream or an ointment has been used for painful conditions of the *anus or rectum.*

Tetracaine hydrochloride has also been used in the *mouth* in sprays and lozenges.

Tetracaine hydrochloride has also been used for *spinal block* usually as a 0.5% solution.

Action. For a comparison of the vasoactivity of tetracaine with some other local anaesthetics, see p. 1976.2.

Administration in children. For the use of tetracaine hydrochloride as a percutaneous local anaesthetic in children, see above. See also Surface Anaesthesia, below

Spinal block. A study[1] in 40 patients indicated that for patients undergoing caesarean section with spinal anaesthesia (see Central Nerve Block, p. 1977.2) doses of 12 or 14 mg of tetracaine provided better intraoperative analgesia than doses of 8 or 10 mg without leading to excessive spread of the block.

1. Hirabayashi Y, *et al.* Visceral pain during Caesarean section: effect of varying dose of spinal amethocaine. *Br J Anaesth* 1995; **75:** 266–8.

Surface anaesthesia. A topical gel formulation of tetracaine 4% appears to provide more rapid and prolonged surface anaesthesia (see p. 1977.3) than a eutectic mixture of lidocaine and prilocaine.[1,2] In a double-blind placebo-controlled study[3] the tetracaine gel formulation was significantly better than the eutectic mixture in reducing pain caused by laser treatment of portwine stains. Similar findings were also seen in a comparative study[4] and a systematic review[5] in children requiring venous cannulation, although others have questioned the efficacy of tetracaine gel in peripheral insertion of a central catheter.[6] The same formulation appears to be effective when incorporated into a transdermal patch.[7] Patches containing a mixture of lidocaine and tetracaine have also been tried[8,9] and are licensed in some countries for surface anaesthesia of intact skin in connection with needle puncture and in cases of superficial surgical procedures.

There have been reports of seizures and death in children after the use of a mixture of tetracaine, adrenaline, and cocaine on mucosal surfaces;[10] application of preparations of tetracaine to highly vascular surfaces is contra-indicated. A gel containing a mixture of lidocaine, adrenaline, and tetracaine has been found to be an effective alternative to the cocaine-containing preparation.[11]

Tetracaine has also been incorporated into a mucosa-adhesive polymer film to relieve the pain of oral lesions resulting from radiation and antineoplastic therapy.[12] Liposome-encapsulated tetracaine has also been shown to provide adequate surface anaesthesia.[13]

1. McCafferty DF, *et al.* In vivo assessment of percutaneous local anaesthetic preparations. *Br J Anaesth* 1989; **62:** 17–21.
2. Rømsing J, *et al.* Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. *Br J Anaesth* 1999; **82:** 637–8.
3. McCafferty DF, *et al.* Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth* 1997; **78:** 286–9.
4. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child* 2000; **82:** 309–10.
5. Lander JA, *et al.* EMLA and amethocaine for reduction of children's pain associated with needle insertion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/04/08).
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Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1 and p. 1979.1.

Tetracaine has high systemic toxicity. Absorption of tetracaine from mucous membranes is rapid and adverse reactions can occur abruptly without the appearance of prodromal signs or convulsions; fatalities have occurred.

A stinging sensation may occur when tetracaine is used in the eye. Mild erythema at the site of application is frequently seen with topical use; slight oedema or pruritus occur less commonly. Blistering of the skin may occur.

Urethral stricture. There has been a report[1] of a sudden increase in the incidence of urethral stricture after transurethral surgery, which may have been due to an increase in the concentration of tetracaine hydrochloride in the lubricant gel from 0.1 to 3%.

1. Pansadoro V. Role of local anaesthetics in urethral strictures after transurethral surgery. *Lancet* 1990; **336:** 64.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Tetracaine should not be applied to inflamed, traumatised, or highly vascular surfaces. It should not be used to provide anaesthesia for bronchoscopy or cystoscopy, as lidocaine is a safer alternative.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetracaine as not porphyrinogenic when used for surface anaesthesia in ophthalmological procedures; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

See under Local Anaesthetics, p. 1979.3. Tetracaine is reported to be about 15% bioavailable after application of a 4% gel to intact skin, with a mean absorption and elimination half-life of about 75 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tray-Te†; ***Braz.***: Anestesico; ***Canad.***: Ametop; Pontocaine; Viractin; ***Fr.***: Solutricine Maux de Gorge; ***Ger.***: Ophtocain N; ***Gr.***: Tetravisc; ***Irl.***: Ametop; ***Mex.***: Ponti; ***Philipp.***: Pontocaine; ***Port.***: Lubrificante Anestesico; ***S.Afr.***: Anethaine; Covostet; ***Spain***: Anestesia Topi Braun C/A†; Anestesia Topi Braun S/A; Anestesico; Hemonet†; Lubricante Urologico; ***Swed.***: Tetrakain; ***UK***: Ametop; Anethaine; ***USA***: Cepacol Viractin Cold Sore Treatment†; Pontocaine.

Multi-ingredient Preparations. ***Arg.***: Bagociletas con Anestesia†; Clevosan; Drill; ***Austria***: Dynexan; Herviros; ***Belg.***: Hexomedine†; ***Braz.***: Hexomedine; Oto-Betnovate; ***Canad.***: Cetacaine; Denti-Care Denti-Freeze; Denti-Care Topical; One Touch; ZAP; ***Cz.***: Drill; Rapyden; ***Denm.***: Ralydan; ***Fr.***: Aphtoral; Cantalene; Doli Mal de Gorge; Drill; Eludril; Ergix mal de gorge; Otylol; Rapydan†; Solutricine Maux de Gorge†; ***Ger.***: Gingicain D; ***Gr.***: Buccasept†; Rapydan; ***Hung.***: Drill†; Faringopront; ***Irl.***: Rapydan; ***Israel***: Anaesthetic Ear Drops; Otidin; ***Ital.***: Donalg; Odongi; Ralydan; Recto-Reparil; Ruscoroid; ***Neth.***: Pliaglis; Rapydan; ***Norw.***: Rapydan; ***NZ***: Topicaine; ***Pol.***: Ruskorex; ***Port.***: Anucet; Drill; Hemofissural; Rapydan; ***Rus.***: Anti-Angin (Анти-Ангин); Drill (Дрилл)†; Novosept (Новосепт Форте); ***S.Afr.***: Dynexan; ***Spain***: Anestesico Doble; Blastoestimulina†; Dentikrisos†; Otogen Calmante; Pliaglis; Resorborina; Vinciseptil Otico; ***Swed.***: Rapydan; ***Switz.***: Angidine†; Eludril†; Mucosan†; Tyrothricine + Gramicidine†; ***Turk.***: Dervanol; Hemoralgine; Otimisin; ***UK***: Eludril; Pliaglis; Rapydan†; ***USA***: Cetacaine; Pliaglis; Stypto-Caine; Synera.

Pharmacopoeial Preparations
BP 2014: Tetracaine Eye Drops;
USP 36: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Tetracaine and Menthol Ointment; Tetracaine Hydrochloride Cream; Tetracaine Hydrochloride for Injection; Tetracaine Hydrochloride in Dextrose Injection; Tetracaine Hydrochloride Injection; Tetracaine Hydrochloride Ophthalmic Solution; Tetracaine Hydrochloride Topical Solution; Tetracaine Ointment; Tetracaine Ophthalmic Ointment.

Tolycaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tolicaína; Tolicaína, hidrocloruro de; Tolycaïne, Chlorhydrate de; Tolycaini Hydrochloridum; Толикаина Гидрохлорид.

Methyl 2-(2-diethylaminoacetamido)-*m*-toluate hydrochloride.

$C_{15}H_{22}N_2O_3$,HCl=314.8
CAS — 3686-58-6 (tolycaine); 7210-92-6 (tolycaine hydrochloride).

Profile

Tolycaine hydrochloride is an amide local anaesthetic (p. 1976.1) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations.

Used as an adjunct in:. ***Ger.***: Tardocillin.

Tricaine Mesilate

Metacaine Mesylate; Tricaína, mesilato de; Tricaine Mesylate; TS-222.

Ethyl 3-aminobenzoate methanesulphonate.

$C_{10}H_{15}NO_5S$=261.3
CAS — 886-86-2.
ATC Vet — QN01AX93.
UNII — 971ZM8IPK1.

Profile

Tricaine mesilate is a derivative of an isomer of benzocaine (see p. 1980.2) and although it has been used as a local anaesthetic in human medicine it is now mainly used as an anaesthetic and tranquilliser for fish and other cold-blooded animals.

Trimecaine Hydrochloride *(rINNM)*

Hidrocloruro de trimecaína; Trimecaína, hidrocloruro de; Trimécaïne, Chlorhydrate de; Trimecaini Hydrochloridum; Trimecainium Chloratum; Trimekain-hydrochlorid; Тримекаина Гидрохлорид.

2-Diethylamino-2′,4′,6′-trimethylacetanilide hydrochloride.
$C_{15}H_{24}N_2O,HCl$=284.8
CAS — 616-68-2 (trimecaine); 1027-14-1 (trimecaine hydrochloride).
UNII — 5491FXS1NB.

Profile

Trimecaine hydrochloride is an amide local anaesthetic (p. 1976.1). It has been used topically and by injection and has been included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Mesocain.

Multi-ingredient Preparations. *Cz.*: Mesocain; Septonex Plus; ***Rus.***: Levosin (Левосин); Simetrid (Симетрид).

Miotics Mydriatics and Antiglaucoma Drugs

Glaucoma and ocular hypertension, p. 1999
Mydriasis and cycloplegia, p. 2000
Reversal of mydriasis, p. 2000
Strabismus, p. 2000

Included in this chapter are a variety of drugs used in the eye to alter accommodation and produce mydriasis or cycloplegia, or in the treatment of glaucoma. Some drugs used for these purposes, or in other ocular disorders, but with other primary uses, may be found elsewhere in *Martindale*.

Glaucoma and ocular hypertension

Intra-ocular pressure rises when there is an imbalance between production and drainage of aqueous humour in the eye. Aqueous humour is secreted by the ciliary body and flows into the posterior chamber of the eye. It then passes through the pupil into the anterior chamber from where about 75% drains from the eye through the trabecular meshwork into Schlemm's canal and then into the episcleral veins. The remainder is removed by the uveoscleral route, passing through the ciliary muscle and finally into the episcleral tissues.

The term **ocular hypertension** is used to describe intra-ocular pressure above an upper normal value of 21 mmHg when there are no signs of optic nerve damage. The term **glaucoma** is used to describe a group of conditions characterised by cupping (excavation) of the optic disc and damage of the optic nerve leading to gradual but irreversible visual loss; glaucoma is one of the most common causes of blindness.

Raised intra-ocular pressure is an important risk factor for glaucoma, and as it is the only one that can be altered, current therapy for glaucoma is directed at lowering it. The aim is not just to reduce intra-ocular pressure to a normal value but to a level at which damage to the optic nerve ceases.[1-7] Some patients may have raised intra-ocular pressure for many years without evidence of glaucoma. Whether these patients would receive long-term benefit from a reduction in intra-ocular pressure has been a matter of debate. However, randomised studies[8,9] have shown that topical ocular hypotensive treatment was effective in preventing or delaying the onset of open-angle glaucoma in patients with raised intra-ocular pressure. In addition, another study[10,11] has found that lowering intra-ocular pressure slows the progression of glaucoma. A meta-analysis[12] has also confirmed that lowering intra-ocular pressure reduces the risk of visual field loss in the long term in patients with ocular hypertension or newly-diagnosed glaucoma. Similarly, a systematic review[13] concluded that topically lowering intra-ocular pressure had a protective effect on the visual field. Some,[14] including NICE[15] in the UK, consider that only high-risk patients with raised intra-ocular pressure should be treated; such risk factors include thin central corneal thickness measurement, large cup-to-disc ratio, older age, intra-ocular pressure fluctuation, and a family history of blindness. In practice, many ophthalmologists consider that therapy is indicated if the intra-ocular pressure is higher than 30 mmHg. Glaucoma can also occur and progress in patients with an intra-ocular pressure within the normal range (normal tension glaucoma).

Raised intra-ocular pressure associated with glaucoma is usually due to reduced outflow of aqueous humour from the eye. Glaucoma is described as open-angle or angle-closure depending on the mechanism of the obstruction of drainage and may be acute or chronic. Glaucoma may also be referred to as primary or secondary. **Primary glaucoma** is usually associated with a direct disturbance of outflow whereas **secondary glaucoma** develops as a consequence of some diseases or of trauma.

The most common form of glaucoma is **chronic open-angle glaucoma** (simple glaucoma; wide-angle glaucoma), which is due to blockage in drainage through the trabecular meshwork. Intra-ocular pressure increases gradually, and the condition is usually asymptomatic until well advanced and severe damage has occurred. Usually, both eyes are affected. Risk factors include old age, diabetes, Afro-Caribbean race, a family history of glaucoma, and myopia. A '**steroid glaucoma**' may be produced, after a few weeks of treatment with eye drops containing corticosteroids, in patients predisposed to open-angle glaucoma; the risk with systemic corticosteroids appears to be less.

In contrast, **angle-closure glaucoma** (closed-angle glaucoma; narrow-angle glaucoma) usually occurs as an acute emergency. Patients present with a painful red eye, sweating, and nausea and vomiting as a result of a rapid rise in intra-ocular pressure. This can result from blockage of the flow of aqueous humour into the anterior chamber. The resulting rise in intra-ocular pressure bows the iris against the trabecular meshwork, restricting outflow and thereby further raising intra-ocular pressure. It usually occurs in patients with hypermetropia who have a shallow anterior chamber and a narrow filtration angle. The use of mydriatics in such patients is generally considered to be contra-indicated on the grounds that dilatation of the pupil could precipitate an acute attack of angle-closure glaucoma, but see Glaucoma, under Tropicamide, p. 2012.3.

ANTIGLAUCOMA DRUGS.

Drugs used in the treatment of glaucoma[1,3-5,16-18] lower intra-ocular pressure by a variety of mechanisms and their effects are often additive. Most are used topically although a few are given by systemic routes.

- ***Beta blockers*** inhibit beta receptors in the ciliary epithelium and thereby reduce the secretion of aqueous humour. They have traditionally been the drugs of first choice for initial and maintenance treatment of open-angle and other chronic glaucomas and of ocular hypertension; other drugs are used with them when further reductions in intra-ocular pressure are required. Advantages over miotics (below) include a lack of effect on pupil size and accommodation; in addition they can be given once or twice daily which may improve compliance. They are also better tolerated than miotics but can produce systemic effects, and their safety, particularly in the elderly, has been questioned.[19,20] Cardioselective beta blockers may cause fewer pulmonary adverse effects, such as bronchoconstriction, than non-selective beta blockers. Studies suggest that individual topical beta blockers are probably equally effective in reducing intra-ocular pressure but if a non-selective beta blocker is used an additional reduction in pressure may not be obtained with adrenaline (see below). However, a meta-analysis has suggested that timolol may be more effective than betaxolol.[21]
- Topical ***prostaglandin analogues*** or ***prostamides***, such as bimatoprost, latanoprost, tafluprost, and travoprost, lower intra-ocular pressure by increasing uveoscleral outflow. They are increasingly a first choice, alone or as adjuncts, in the treatment of ocular hypertension or open-angle glaucoma. A meta-analysis of the efficacy of common antiglaucoma drugs found bimatoprost, travoprost, and latanoprost to be the most effective in lowering intra-ocular pressure.[21] They are given once daily and appear to be well-tolerated. They do not affect pupil size or accommodation, but may cause a potentially irreversible increase in brown pigmentation of the iris; the long-term significance of this effect is unknown. Unoprostone, which needs to be used twice daily, appears to be less effective than the other prostaglandin analogues.[22]
- ***Parasympathomimetic miotics*** help trabecular drainage by constricting the pupil and pulling open the trabecular meshwork. However, this can cause blurred vision and browache, especially in younger patients, and the small pupil may cause problems if central vision is already limited. Parasympathomimetic miotics also reduce uveoscleral outflow and this can cause a paradoxical increase in intra-ocular pressure in patients with a recessed anterior angle. They should not be used in the presence of inflammation as adhesions may form between the pupil and the lens (posterior synechiae). Topical miotics were once the mainstay of glaucoma treatment but their ocular adverse effects and multiple dosing regimens have limited their use. Pilocarpine is the most frequently used miotic and is indicated in the treatment of open-angle glaucoma and other chronic glaucomas. It is often added to treatment with other drugs when further reductions in intra-ocular pressure are required. Carbachol is sometimes used when resistance or intolerance to pilocarpine develops. Physostigmine is more potent than pilocarpine but is poorly tolerated and is rarely used now; it was used with pilocarpine but rarely alone. Stronger or longer-acting anticholinesterase miotics such as ecothiopate can cause pupillary block and induce angle-closure glaucoma. They are usually only used in patients refractory to other antiglaucoma treatment or in those in whom the lens of the eye has been removed (aphakic patients). Pilocarpine is also used in the emergency treatment of angle-closure glaucoma before surgery or laser therapy.
- ***Carbonic anhydrase inhibitors*** such as acetazolamide reduce production of aqueous humour by a mechanism independent of their diuretic action. They are used as part of the emergency treatment of angle-closure glaucoma to produce a rapid reduction in intra-ocular pressure before surgery or laser therapy. Systemic doses may also be added to treatment in open-angle glaucoma and other chronic glaucomas in patients refractory to standard treatment but many patients are unable to tolerate prolonged therapy. Topical carbonic anhydrase inhibitors, such as dorzolamide or brinzolamide, have a lower potential to produce adverse effects. They are used similarly to other topical drugs either alone or as an adjunct in patients resistant to or intolerant of first-line drugs.
- Topical ***alpha$_2$-adrenoceptor agonists*** such as apraclonidine and brimonidine lower intra-ocular pressure by reducing production of aqueous humour. Apraclonidine is used alone or as an adjunct to other drugs in the control of intra-ocular pressure associated with ocular surgery or in the short-term to delay laser treatment or surgery for patients with glaucoma not adequately controlled with other drugs; tachyphylaxis and ocular irritation limit its long-term use. Brimonidine is used similarly. Clonidine has also been used in some countries.
- Other topical ***sympathomimetics*** such as dipivefrine increase outflow of aqueous humour through the trabecular meshwork and the uveoscleral route and may also reduce its rate of production. They are used in open-angle glaucoma and other chronic glaucomas usually when further reductions in intra-ocular pressure are required in patients receiving beta blockers (but may not produce an additive effect if used with a non-selective beta blocker).[23] As they produce pupillary dilatation they can induce an acute attack if used in angle-closure glaucoma. Adrenaline can cause eye irritation and produce systemic effects; it is now rarely used. Dipivefrine is converted into adrenaline by corneal esterases and ocular adverse effects are usually less than with adrenaline itself although, again, it is rarely used. Guanethidine, an adrenergic neurone blocker, reduces aqueous humour secretion and is used either alone or in combination to enhance and prolong the effect of adrenaline; prolonged use can cause fibrosis and corneal changes.
- ***Osmotic diuretics*** reduce vitreous volume and can produce a marked reduction in intra-ocular pressure. They are used in the short-term management of glaucoma when a rapid reduction in intra-ocular pressure is required before surgery. Mannitol and urea are both given intravenously and have a faster onset than glycerol or isosorbide given orally.
- Several ***other drugs*** are used topically in glaucoma and ocular hypertension. The alpha-adrenergic antagonist dapiprazole is used in some countries.

DIAGNOSIS OF GLAUCOMA.

Open-angle glaucoma is asymptomatic in its early stages and the use of screening methods for detecting early disease is of great importance.[24] Measurement of intra-ocular pressure alone is a poor diagnostic tool and direct examination of the optic nerve together with visual field examination and intra-ocular pressure tonometry is considered to be more reliable.[1,3-5] Provocative tests such as placing the patient prone in a dark room are sometimes used to identify eyes suffering from or at risk of *angle-closure glaucoma*. Short-acting mydriatics have also been used but are not without risk. Long-term follow-up of patients whose treatment had been determined by the use of a provocative test using phenylephrine with pilocarpine has suggested that this test is neither sensitive nor specific.[25]

TREATMENT OF GLAUCOMA.

Open-angle glaucoma or *ocular hypertension* are frequently treated first with a topical beta blocker or, increasingly, a prostaglandin analogue. It may be necessary to combine

these drugs or add others such as a topical alpha$_2$-adrenoceptor agonist or a topical carbonic anhydrase inhibitor to control intra-ocular pressure. Miotics are usually reserved for third-line use. It has been suggested that each type of drug should be tried alone first before resorting to combination therapy.

If further reduction of intra-ocular pressure is required a systemic carbonic anhydrase inhibitor may be used but long-term treatment is poorly tolerated. If this is unsuccessful, surgery (trabeculectomy) or laser treatment (trabeculoplasty) is usually indicated. Laser treatment appears to be as effective as topical drug therapy[26] although its effects may be short-lived.[27] It has been suggested that it might be of use in the initial treatment of older patients who cannot use eye drops or when surgery needs to be postponed or is contra-indicated.[1] Some also recommend that laser treatment is tried before a miotic or an oral carbonic anhydrase inhibitor, because of the potential adverse effects associated with these drugs.[5] Surgery with fluorouracil or mitomycin augmentation (see below) should be offered to those who are at risk of progressing to vision loss despite topical treatment or those with advanced disease.[15] Initial studies in the UK also suggested that early surgery was superior to drug or laser treatment in reducing intra-ocular pressure and preserving vision;[27] however, a later study[28] showed no difference in the progression of visual field loss in patients with newly-diagnosed glaucoma after the initial use of surgery or drug treatment. A systematic review has also found that in early mild open-angle glaucoma progression of the disease over 5 years was no different if first treatment was with medication or trabeculectomy but trabeculectomy was associated with more eye discomfort, an increased risk of cataract, and reduction in visual acuity.[29] The early use of surgery was often advocated in Europe, especially in younger patients, although it is now rarely used as the primary form of treatment.[4]

It is essential to start treatment for an *acute attack of angle-closure glaucoma* within 24 to 48 hours. If treatment is delayed adhesions may form between the iris and the cornea (peripheral anterior synechiae) and the trabecular meshwork may be damaged. *Chronic angle-closure glaucoma* may then develop with permanently raised intra-ocular pressure which ultimately leads to total loss of vision (absolute glaucoma). The initial treatment aims to produce a rapid reduction in intra-ocular pressure. A miotic such as pilocarpine is used topically to constrict the pupil while a carbonic anhydrase inhibitor such as acetazolamide is given orally or by intravenous injection. Osmotic diuretics such as mannitol or urea given intravenously or glycerol or isosorbide given orally may also be used. When intra-ocular pressure has been reduced sufficiently, laser therapy or surgery is performed on both eyes to increase drainage of aqueous humour. If further topical treatment is required after surgery, treatment is usually as for open-angle glaucoma. Beta blockers, with or without adrenaline, are preferred to pilocarpine as there is a risk of posterior synechiae forming when pilocarpine is used.

Glaucoma filtering surgery such as trabeculectomy can be highly effective in reducing intra-ocular pressure, but in some groups of patients, such as children, Afro-Caribbeans, or those who have had previous ocular surgery, there is a high failure rate, usually due to formation of scar tissue.[30] The scar formation is associated with proliferation of fibroblasts; subconjunctival injection of antiproliferative drugs such as fluorouracil has been shown to reduce the failure rate of surgery but at a cost of increased epithelial toxicity and conjunctival wound leaks.[30] A study group[31] reporting on the long-term follow-up of patients treated with fluorouracil recommended that fluorouracil should still be used in the surgical management of glaucoma in patients with a history of ocular surgery, but in view of the increased incidence of late-onset conjunctival wound leaks at the dosage they employed, suggested caution in its use in eyes with good prognoses. Single intraoperative doses of mitomycin have been applied topically as an alternative to the regimen of multiple injections required with fluorouracil. Rates of success comparable with those for fluorouracil have been achieved but there is a risk of adverse effects that could affect vision;[32] long-term safety of antiproliferative drugs remains to be determined.

Postoperative ocular hypertension may occur after surgery on the anterior chamber of the eye or procedures such as trabeculoplasty. Acetylcholine or carbachol instilled directly into the anterior chamber of the eye (intracameral instillation) are used intra-operatively to reduce early postoperative rises in intra-ocular pressure in procedures such as cataract extraction. The short action of acetylcholine can be an advantage as prolonged miosis is associated with severe postoperative pain. However, some consider carbachol to be the more effective drug;[33,34] standard antiglaucoma drugs including beta blockers, pilocarpine, apraclonidine, and carbonic anhydrase inhibitors have also been used for prophylaxis of postoperative ocular hypertension.

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Mydriasis and cycloplegia

Drugs that dilate the pupil (mydriatics) and paralyse accommodation (cycloplegics) are used topically in the examination of the eye and other ophthalmic procedures. They are also used in the management of inflammatory conditions of the eye to treat or prevent the formation of adhesions between the lens and the iris (see Uveitis, p. 1615.1) and in strabismus (below).

Mydriasis requires either paralysis of the pupillary constrictor muscles, which can be achieved with antimuscarinics, or stimulation of the dilator muscles, as produced by sympathomimetics. Cycloplegia results from paralysis of the ciliary muscles (antimuscarinics, but not sympathomimetics, have this effect).

Antimuscarinics used in ophthalmology vary in onset and duration of action. *Atropine* can take up to 40 minutes or more to produce mydriasis, which persists for at least 7 days; it takes 1 to 3 hours to produce cycloplegia and 6 to 12 days for recovery of accommodation. *Hyoscine* has a shorter duration of action than atropine, although the effects may still persist for 3 to 7 days. For ophthalmic procedures, antimuscarinics such as *homatropine*, *cyclopentolate*, or *tropicamide*, with a more rapid onset and shorter duration of action than atropine, may be preferable. Recovery occurs up to 6 hours after tropicamide, and up to 24 hours after cyclopentolate; after homatropine it may take up to 3 days. Cycloplegia with homatropine may be incomplete, and particularly for young children (who are often resistant to the action of homatropine) cyclopentolate or atropine may be preferred.

The most common topical sympathomimetic is *phenylephrine*, but *hydroxyamfetamine* is also used in some countries. They are often used with an antimuscarinic to enhance mydriasis, especially in patients who might respond poorly to antimuscarinics alone, such as those with dark irides or diabetes, or those who are receiving prolonged miotic therapy. *Adrenaline* has been used for maintenance of mydriasis during ophthalmic surgery.

The local anaesthetic *cocaine* also has an independent mydriatic effect but because of concern over corneal toxicity it is now little used in ophthalmology.

Miosis (pupil constriction) resistant to conventional mydriatics often develops during ocular surgery, possibly due to the release of prostaglandins and other substances associated with trauma. *NSAIDs* are prostaglandin synthetase inhibitors and have been tried before ocular surgery to prevent or reduce intra-operative miosis. They do not possess intrinsic mydriatic properties.

Reversal of mydriasis

Topical miotics (mydriolytics) are sometimes used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but do not appear to be in routine clinical use. *Pilocarpine* can counteract the mydriatic effect of topical sympathomimetics, such as phenylephrine and hydroxyamfetamine, but is ineffective against mydriasis produced by antimuscarinics, such as homatropine, and may impair vision further when used with tropicamide. Furthermore, there is also the risk that pilocarpine might precipitate angle-closure glaucoma in susceptible patents. *Dapiprazole* appears to be safer than pilocarpine when used to reverse sympathomimetic-induced mydriasis and is effective to some degree against tropicamide-induced mydriasis. It also appears to enhance recovery of accommodation after the use of cycloplegics.

The rate of reversal of mydriasis is generally slower in patients with dark irides than in those with lighter irides.

Strabismus

Strabismus, sometimes referred to as a squint or cast, is a lack of coordination of the visual axes of the eyes so that the eyes are usually either turned towards (convergent strabismus; esotropia) or away (divergent strabismus; exotropia) from each other. It can arise from a physical defect of the attachment of the extra-ocular muscles to the eye or from paralysis, spasms, or overactivity affecting the extra-ocular muscles of one of the eyes. In young children strabismus or other conditions that prevent a clear image being formed on the retina can result in visual impairment (amblyopia) in the affected eye if not treated.

Treatment for strabismus often consists of eye exercises, and methods to force preferential use of the affected eye by restricting vision through the healthy eye. This is accomplished either by using an eye patch or by penalisation with glasses or the cycloplegic drug *atropine*. However, as prolonged use of atropine eye drops may be required there is a risk of systemic toxicity. Surgery may sometimes be necessary. Extra-ocular injection of *botulinum A toxin* has been used to weaken an overactive extra-ocular eye muscle as an aid to eye realignment; repeated injections may be required. Long-acting parasympathomimetic miotics such as *demecarium*, *dyflos*, and *ecothiopate* have been used in the diagnosis and management of convergent strabismus due to excessive accommodation. Centrally-acting drugs such as *levodopa* and *citicoline* have also been investigated. With any form of treatment care has to be taken not to induce amblyopia in the healthy eye.

References.

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2:** 91–100.
2. Donahue SP. Pediatric strabismus. *N Engl J Med* 2007; **356:** 1040–7.

Aceclidine *(USAN, rINN)*

Aceclidina; Acéclidine; Aceclidinum; Ацеклидин.

1-Azabicyclo[2.2.2]octan-3-ol acetate; 3-Quinuclidinol acetate; 3-Acetoxyquinuclidine.

$C_9H_{15}NO_2$=169.2

CAS — 827-61-2.

ATC — S01EB08.

ATC Vet — QS01EB08.

UNII — 0578K3ELIO.

Aceclidine Hydrochloride (rINNM)

Acéclidine, Chlorhydrate d'; Aceclidini Hydrochloridum; Hidrocloruro de aceclidina; Ацеклидина Гидрохлорид.

$C_9H_{15}NO_2$,HCl=205.7

CAS — 6109-70-2.

ATC — S01EB08.

ATC Vet — QS01EB08.

UNII — 3B22O325Q6.

Profile

Aceclidine hydrochloride is a parasympathomimetic miotic (see Pilocarpine, p. 2010.2) that is a cholinergic agonist. It has been used in eye drops to lower intra-ocular pressure in patients with glaucoma.

Use. Aceclidine has been tried for the management of disturbances of night vision after laser refractive surgery.[1]

1. Randazzo A, *et al.* Pharmacological management of night vision disturbances after refractive surgery: results of a randomized clinical trial. *J Cataract Refract Surg* 2005; **31:** 1764–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Glaucostat†; Glaunorm; ***Ital.***: Glaunorm.

Multi-ingredient Preparations. ***Ital.***: Glautimol.

Acetazolamide (BAN, rINN) ⊗

Acetazolam; Acetazolamid; Acetazolamida; Acetazolamidas; Acétazolamide; Acetazolamidum; Asetatsoliamidi; Asetazolamid; Ацетазоламид.

5-Acetamido-1,3,4-thiadiazole-2-sulphonamide; *N*-(5-Sulphamoyl-1,3,4-thiadiazol-2-yl)acetamide.

$C_4H_6N_4O_3S_2$=222.2

CAS — 59-66-5.

ATC — S01EC01.

ATC Vet — QS01EC01.

UNII — O3FX965V0I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Acetazolamide). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Acetazolamide). A white to faintly yellowish-white, odourless, crystalline powder. Very slightly soluble in water; sparingly soluble in practically boiling water; slightly soluble in alcohol. Store in airtight containers.

Acetazolamide Sodium (BANM, rINNM) ⊗

Acetazolamida sódica; Acétazolamide Sodique; Natrii Acetazolamidum; Sodium Acetazolamide; Натрий Ацетазоламид.

$C_4H_5N_4NaO_3S_2$=244.2

CAS — 1424-27-7.

ATC — S01EC01.

ATC Vet — QS01EC01.

UNII — 429ZT169UH.

Stability. Solutions of acetazolamide sodium in glucose 5% and sodium chloride 0.9% were stable for 5 days at 25 degrees with a loss of potency of less than 7.2%.[1] At 5 degrees the loss of potency in both solutions was less than 6% after 44 days of storage. Small reductions in pH were recorded, possibly due to the formation of acetic acid during the decomposition of acetazolamide. At -10 degrees the loss in potency after 44 days of storage was less than 3% in both solutions. Results were similar in samples thawed in tap water and in a microwave oven.

An oral suspension of acetazolamide 25 mg/mL prepared from tablets with the aid of sorbitol solution 70% was stable for at least 79 days at 5 degrees, 22 degrees, and 30 degrees. It was recommended that the formulation be maintained at pH 4 to 5 and stored in amber glass bottles.[2]

1. Parasrampuria J, *et al.* Stability of acetazolamide sodium in 5% dextrose or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1987; **44:** 358–60.
2. Alexander KS, *et al.* Stability of acetazolamide in suspension compounded from tablets. *Am J Hosp Pharm* 1991; **48:** 1241–4.

Uses and Administration

Acetazolamide is an inhibitor of carbonic anhydrase with weak diuretic activity and is used mainly in the management of glaucoma (below). Other indications include epilepsy (below) and high-altitude disorders (below).

By inhibiting carbonic anhydrase in the eye acetazolamide decreases the formation of aqueous humour and so decreases intra-ocular pressure. It is used in the preoperative management of angle-closure **glaucoma**, or as an adjunct in the treatment of open-angle glaucoma. In the treatment of glaucoma the usual oral dose is 250 mg to 1 g daily; divided doses should be used for amounts greater than 250 mg daily. Modified-release preparations are also available.

Acetazolamide is also used, either alone or with other antiepileptics, for the treatment of various forms of **epilepsy** in oral doses of 250 mg to 1 g daily in divided doses.

When oral dosing is impracticable, acetazolamide may be given parenterally as the sodium salt; acetazolamide sodium 275 mg is equivalent to about 250 mg of acetazolamide. It may be given by intramuscular injection but the intravenous route is preferred due to the alkalinity of the solution. Doses are similar to those given orally.

Acetazolamide is also used to prevent or ameliorate the symptoms of **high-altitude disorders**. Prompt descent will still be necessary if severe symptoms such as cerebral oedema or pulmonary oedema occur. The usual oral dose is 500 mg to 1 g daily in divided doses, preferably starting 24 to 48 hours before ascent and continuing for at least 48 hours while at high altitude as necessary to control symptoms. It may also be given as a modified-release preparation.

For details of doses in children, see below.

Acetazolamide also increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, by inhibiting the reaction catalysed by carbonic anhydrase in the renal tubules, and so promotes an alkaline diuresis. When given orally as an immediate-release preparation, its effect begins within 60 to 90 minutes and lasts for 8 to 12 hours. However, continuous use is associated with metabolic acidosis and an accompanying loss of diuretic activity. Therefore, although acetazolamide has been used as a diuretic, it has largely been superseded by drugs such as the thiazides or furosemide. For **diuresis** the usual oral dose is 250 to 375 mg and is given either once daily or on alternate days; intermittent therapy is required for a continued effect. Similar doses have also been given parenterally.

Administration in children. Acetazolamide is used, either alone or with other antiepileptics, for the treatment of various forms of **epilepsy** in children. UK licensed product information recommends giving 8 to 30 mg/kg (maximum of 750 mg) orally daily in divided doses. Alternatively, the *BNFC* suggests an initial dose of 2.5 mg/kg 2 or 3 times daily in neonates and children up to 12 years of age; this may then be increased to a maintenance dose of 5 to 7 mg/kg 2 or 3 times daily (maximum of 750 mg daily). Older children may be given the usual adult dose (see above).

Although unlicensed, the *BNFC* suggests that acetazolamide may be used in the management of open-angle and secondary **glaucoma**, or perioperatively in angle-closure glaucoma. Those aged 1 month to 12 years may be given oral doses of 5 mg/kg 2 to 4 times daily, adjusted according to response to a maximum of 750 mg daily; older children may be given the usual adult dose (see above).

The *BNFC* also suggests that acetazolamide may be used to reduce **raised intracranial pressure** in children aged 1 month to 12 years; an initial dose of 8 mg/kg may be given 3 times daily, increased as necessary to a maximum of 100 mg/kg daily.

When oral dosing is impractical, the aforementioned doses may be given by slow intravenous injection.

Administration in the elderly. For the suggestion that reduced doses may be required in elderly patients see under Precautions, p. 2002.3.

Epilepsy. Acetazolamide may be used in the treatment of epilepsy (p. 506.1) as an alternative or adjunct to first-line drugs for refractory partial seizures with or without secondary generalisation. It is also effective in some other refractory forms of epilepsy including atypical absence, tonic, atonic, myoclonic, and menstruation-related seizures (catamenial epilepsy).[1-5] It is believed to act by inhibition of carbonic anhydrase in glial cells in the CNS.[6] The major drawback to the chronic use of acetazolamide is the rapid development of tolerance,[6] but this may be delayed or prevented by using it as an adjunct to other antiepileptics. Acetazolamide has been successfully used in management of seizures in children from 1 year of age.[5]

1. Resor SR, Resor LD. Chronic acetazolamide monotherapy in the treatment of juvenile myoclonic epilepsy. *Neurology* 1990; **40:** 1677–81.
2. Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. *Ann Pharmacother* 1996; **30:** 514–19.
3. Hoddevik GH. Acetazolamid—verdt en renessanse i epilepsibehandlingen? *Tidsskr Nor Laegeforen* 2000; **120:** 1042–5.
4. Lim LL, *et al.* Acetazolamide in women with catamenial epilepsy. *Epilepsia* 2001; **42:** 746–9.
5. Katayama F, *et al.* Long-term effectiveness and side effects of acetazolamide as an adjunct to other anticonvulsants in the treatment of refractory epilepsies. *Brain Dev* 2002; **24:** 150–4.
6. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacol Rev* 1990; **42:** 223–86.

Glaucoma. Acetazolamide may be given orally or parenterally in the acute management of angle-closure glaucoma (p. 1999.1) and to minimise rises in intra-ocular pressure associated with ocular surgery.[1,2] It may also be given orally in the long-term management of primary and secondary open-angle glaucoma but is usually used as a second-line drug and added to topical beta blockers. However, up to 50% of patients are unable to tolerate oral therapy because of adverse effects[3] although topical carbonic anhydrase inhibitors such as dorzolamide may be better tolerated. Attempts have been made to reduce the adverse effects of acetazolamide by modifying the dosage schedule. A single-dose study[4] showed that doses of acetazolamide greater than 63 mg produced no greater reductions in intra-ocular pressure in patients with ocular hypertension. Another study[5] reported that acetazolamide 250-mg tablets twice daily controlled intra-ocular pressure adequately while producing fewer adverse effects than 250 mg four times daily and it was suggested that there was no advantage in using the modified-release capsule formulation (500 mg twice daily). A study in patients with open-angle glaucoma[6] found that most patients were adequately controlled by a single night-time dose of acetazolamide 500 mg either as tablets or modified-release capsules. The night-time dose also reduced the severity of adverse effects compared with the same dose given in the morning, and could aid compliance.

1. Ladas ID, *et al.* Prophylactic use of acetazolamide to prevent intraocular pressure elevation following Nd-YAG laser posterior capsulotomy. *Br J Ophthalmol* 1993; **77:** 136–8.
2. Edmunds B, Canning CR. The effect of prophylactic acetazolamide in patients undergoing extensive retinal detachment repair. *Eye* 1996; **10:** 328–30.
3. Hurvitz LM, *et al.* New developments in the drug treatment of glaucoma. *Drugs* 1991; **41:** 514–32.
4. Friedland BR, *et al.* Short-term dose response characteristics of acetazolamide in man. *Arch Ophthalmol* 1977; **95:** 1809–12.
5. Ledger-Scott M, Hurst J. Comparison of the bioavailability of two acetazolamide formulations. *Pharm J* 1985; **235:** 451.
6. Joyce PW, Mills KB. Comparison of the effect of acetazolamide tablets and sustets on diurnal intraocular pressure in patients with chronic simple glaucoma. *Br J Ophthalmol* 1990; **74:** 413–16.

High-altitude disorders. Acetazolamide is the most frequently used drug for the prophylaxis of high-altitude disorders (p. 1276.2). It accelerates the process of acclimatisation, thus reducing the incidence of acute mountain sickness and associated symptoms such as headache, nausea, vomiting, and lethargy. The optimum dose is not clear. A systematic review[1] concluded that 750 mg daily effectively prevented acute mountain sickness, but that a dose of 500 mg daily was not effective. However, these conclusions have been criticised, and a subsequent controlled study[2] found that a dose of 125 mg twice daily reduced the incidence of acute mountain sickness by about 50%. Acetazolamide may also have some benefit in relieving symptoms once they have developed although experience is limited. It does not prevent or protect against pulmonary or cerebral oedema.

1. Dumont L, *et al.* Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; **321:** 267–72.
2. Basnyat B, *et al.* Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt Med Biol* 2003; **4:** 45–52.

Macular oedema. For mention of the use of acetazolamide to treat macular oedema associated with uveitis, see Uveitis, p. 1615.1.

Ménière's disease. In Ménière's disease (p. 611.2) high concentrations of carbonic anhydrase are found in the labyrinth, and acetazolamide, a carbonic anhydrase inhibitor, has been tried for both diagnosis and treatment.[1] A dose of 500 mg by intravenous injection has been suggested for diagnosis of fluctuating Ménière's disease.[1] Oral treatment with the drug, however, has not been particularly effective and has been associated with a high incidence of adverse effects.[2]

1. Brookes GB. Ménière's disease: a practical approach to management. *Drugs* 1983; **25:** 77–89.
2. Brookes GB, Booth JB. Oral acetazolamide in Ménière's disease. *J Laryngol Otol* 1984; **98:** 1087–95.

Neuromuscular disorders. Acetazolamide may be of benefit in some neuromuscular disorders, including hypokalaemic periodic paralysis (p. 1777.3). Doses of 375 to 500 mg daily were effective in 2 patients with severe paralysis and were well tolerated.[1] Preliminary observations in 5 other patients showed a striking improvement in 3. In a further 12 patients,[2] doses of 125 mg were given three times daily to children and 250 mg two to six times daily to adults. There was dramatic improvement in 10 of the 12 and this lasted for up to 43 months. Chronic weakness between attacks in 10 patients was improved in 8.

Acetazolamide may reduce the frequency of attacks in patients with hyperkalaemic periodic paralysis (p. 1777.2). It has also been used in episodic ataxia.[3]

1. Resnick JS, *et al.* Acetazolamide prophylaxis in hypokalemic periodic paralysis. *N Engl J Med* 1968; **278:** 582–6.

2. Griggs RC, *et al*. Acetazolamide treatment of hypokalemic periodic paralysis: prevention of attacks and improvement of persistent weakness. *Ann Intern Med* 1970; **73:** 39–48.
3. Melberg A, *et al*. Loss of control after a cup of coffee. *Lancet* 1997; **350:** 1220.

Raised intracranial pressure. Acetazolamide has been used to reduce raised intracranial pressure (p. 1271.3). It has a role in the management of idiopathic intracranial hypertension. It has also been tried in the treatment of immunocompromised patients with chronically raised intracranial pressure due to cryptococcal meningitis,[1] although a controlled study[2] was terminated early due to serious adverse events possibly due to additive toxicity with amphotericin. However, acetazolamide was used successfully for long-term treatment in 2 immunocompetent patients[3] with raised intracranial pressure following fungal meningitis.

1. Johnston SRD, *et al*. Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infect* 1992; **24:** 185–9.
2. Newton PN, *et al*. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis* 2002; **35:** 769–72.
3. Patel S, *et al*. Acetazolamide therapy and intracranial pressure. *Clin Infect Dis* 2002; **36:** 538.

Adverse Effects

Common adverse effects of acetazolamide are malaise, fatigue, depression, excitement, headache, weight loss, and gastrointestinal disturbances. Drowsiness and paraesthesia involving numbness and tingling of the face and extremities are also common with high doses in particular. Diuresis can be troublesome, but generally abates after a few days of continuous therapy. Acidosis may develop during treatment and is generally mild but severe metabolic acidosis has occasionally been reported, especially in elderly or diabetic patients or those with renal impairment. Electrolyte imbalances including hyponatraemia and hypokalaemia may occasionally occur; hypokalaemia is generally transient and rarely clinically significant.

Blood dyscrasias occur rarely and may include aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, and thrombocytopenic purpura. Acetazolamide can give rise to crystalluria, renal calculi, and renal colic; renal lesions, possibly due to a hypersensitivity reaction, have also been reported.

Other adverse reactions include allergic skin reactions, fever, thirst, dizziness, ataxia, irritability, confusion, reduced libido, haematuria, glycosuria, renal failure, abnormal liver function tests, loss of appetite, alterations in taste, transient myopia, and tinnitus and hearing disturbances. Rare reactions include photosensitivity, hepatitis or cholestatic jaundice, flaccid paralysis, and convulsions.

Intramuscular injections are painful owing to the alkalinity of the solution.

Effects on the blood. Severe, often fatal, blood dyscrasias have been reported in patients taking acetazolamide. By 1989, the National Registry of Drug-Induced Ocular Side Effects in the USA[1] had received reports of haematological reactions possibly due to carbonic anhydrase inhibitors in 139 patients, of which 50 cases (36%) were fatal. Most deaths were due to aplastic anaemia. Over half the reactions occurred during the first 6 months of therapy. The value of periodic blood analysis in patients taking carbonic anhydrase inhibitors for prolonged periods has been debated[2-7] but is advised by licensed product information. The US National Registry has recommended[8] that initial and 6-monthly blood analysis should be undertaken.

1. Fraunfelder FT, Bagby GC. Possible hematologic reactions associated with carbonic anhydrase inhibitors. *JAMA* 1989; **261:** 2257.
2. Alm A, *et al*. Monitoring acetazolamide treatment. *Acta Ophthalmol (Copenh)* 1982; **60:** 24–34.
3. Miller RD. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 745–6.
4. Johnson T, Kass MA. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1986; **101:** 128–9.
5. Zimran A, Beutler E. Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts? *Am J Ophthalmol* 1987; **104:** 654–8.
6. Lichter PR. Carbonic anhydrase inhibitors, blood dyscrasias, and standard-of-care. *Ophthalmology* 1988; **95:** 711–12.
7. Mogk LG, Cyrlin MN. Blood dyscrasias and carbonic anhydrase inhibitors. *Ophthalmology* 1988; **95:** 768–71.
8. Fraunfelder FT, *et al*. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 79–81.

Effects on electrolyte balance. Acetazolamide has been reported to cause symptomatic metabolic acidosis in the elderly, in diabetic patients, and in those with renal impairment.[1-6] Raised plasma-acetazolamide concentrations have been reported in elderly patients, probably attributable to reduced renal function, and in 6 of 9 glaucoma patients this was associated with hyperchloraemic metabolic acidosis.[7] A single-dose study[8] in 4 elderly patients found that reduced acetazolamide clearance correlated with renal function. Urea and electrolyte concentrations should be measured before and during treatment with acetazolamide, particularly in the elderly and in other patients, such as diabetics, who may have renal impairment.

1. Maisey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1981; **283:** 1527–8.
2. Goodfield M, *et al*. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; **284:** 422.
3. Reid W, Harrower ADB. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; **284:** 1114.
4. Heller I, *et al*. Significant metabolic acidosis induced by acetazolamide: not a rare complication. *Arch Intern Med* 1985; **145:** 1815–17.
5. Parker WA, Atkinson B. Acetazolamide therapy and acid-base disturbance. *Can J Hosp Pharm* 1987; **40:** 31–4.
6. Zaidi FH, Kinnear PE. Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes. *Br J Ophthalmol* 2004; **88:** 714–15.
7. Chapron DJ, *et al*. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.
8. Chapron DJ, *et al*. Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.

Effects on endocrine function. Hirsutism occurred in a 2½-year-old girl after treatment for 16 months with acetazolamide for congenital glaucoma.[1] There was no evidence of virilisation.

1. Weiss IS. Hirsutism after chronic administration of acetazolamide. *Am J Ophthalmol* 1974; **78:** 327–8.

Effects on the kidneys. Large reductions in glomerular filtration rate occurred during treatment with carbonic anhydrase inhibitors in 3 type 1 diabetics with nephropathy and glaucoma.[1] Kidney function improved when the drug was withdrawn.

1. Skøtt P, *et al*. Effect of carbonic anhydrase inhibitors on glomerular filtration rate in diabetic nephropathy. *BMJ* 1987; **294:** 549.

Effects on the liver. For a report of liver damage associated with use of acetazolamide, see Hypersensitivity, below.

Effects on the skin. Rashes, including severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported during acetazolamide therapy; the fact that acetazolamide is a sulfonamide-derivative has been suggested as a cause for these reactions. Photosensitivity has also been noted rarely.

Severe exacerbation of rosacea occurred in a patient taking acetazolamide for glaucoma; the rosacea improved on withdrawal of acetazolamide and relapsed again on its reintroduction.[1]

1. Shah P, *et al*. Severe exacerbation of rosacea by oral acetazolamide. *Br J Dermatol* 1993; **129:** 647–8.

Extravasation. Extravasation was reported in a patient after intravenous acetazolamide and led to severe ulceration requiring surgery to repair the skin defect.[1] It was recommended that 1 to 2 mL of sodium citrate 3.8% should be injected subcutaneously near the site of extravasation in order to neutralise the alkaline effects of the acetazolamide injection.

1. Callear A, Kirkby G. Extravasation of acetazolamide. *Br J Ophthalmol* 1994; **78:** 731.

Hypersensitivity. A 54-year-old man with glaucoma who was treated with acetazolamide 500 mg daily for 26 days developed a generalised erythematous rash and became delirious, dehydrated, markedly jaundiced, with peripheral circulatory failure, and died from cholestatic jaundice with hepatic coma and anuria.[1] Drug-induced hypersensitivity and hepatitis due to acetazolamide was suspected.

Anaphylaxis has also been reported[2] after a single oral dose in a patient who had not previously received acetazolamide. However, the patient was hypersensitive to sulfonamides and the reaction may have been caused by cross-sensitivity (see also Precautions, below).

1. Kristinsson A. Fatal reaction to acetazolamide. *Br J Ophthalmol* 1967; **51:** 348–9.
2. Tzanakis N, *et al*. Anaphylactic shock after a single oral intake of acetazolamide. *Br J Ophthalmol* 1998; **82:** 588.

Precautions

Acetazolamide is contra-indicated in the presence of sodium or potassium depletion, in hyperchloraemic acidosis, in conditions such as Addison's disease and adrenocortical insufficiency, and in marked hepatic or renal impairment. Encephalopathy may be precipitated in patients with hepatic dysfunction. It should not be used in chronic angle-closure glaucoma since it may mask deterioration of the condition. Since acetazolamide is a sulfonamide derivative, it should not be used in patients with a history of sulfonamide hypersensitivity, but see also further information on cross-reactivity between sulfonamides under Sulfamethoxazole, p. 365.3.

Acetazolamide should be given with care to patients likely to develop acidosis or with diabetes mellitus; severe metabolic acidosis may occur in the elderly, and in patients with renal impairment, pulmonary obstruction, or emphysema. Acetazolamide may increase the risk of hyperglycaemia in diabetic patients.

Periodic monitoring of plasma electrolytes and blood count is recommended during long-term therapy and patients should be cautioned to report any unusual rashes. Acetazolamide is teratogenic in *animals*.

Some adverse effects such as drowsiness and myopia may affect a patient's ability to perform skilled tasks including driving.

Breast feeding. Acetazolamide has been detected in breast milk.[1] However, there have been no reports of adverse effects in breast-fed infants whose mothers were receiving acetazolamide and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Söderman P, *et al*. Acetazolamide excretion into human breast milk. *Br J Clin Pharmacol* 1984; **17:** 599–600.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 17/03/06)

Diabetes mellitus. For a brief discussion of metabolic acidosis in patients with diabetes, see Effects on Electrolyte Balance, above.

For a report of deterioration in renal function in patients with diabetic nephropathy who were given carbonic anhydrase inhibitors, see Effects on the Kidneys, above.

The elderly. A retrospective review[1] of 222 patients with glaucoma reported that those aged 40 years or less tolerated treatment with carbonic anhydrase inhibitors much better than older patients. A single-dose study[2] of acetazolamide in 4 elderly subjects found that the capacity to clear acetazolamide from plasma correlated with creatinine clearance and was thus reduced in the elderly. They also had reduced plasma protein binding and the combination of these factors predisposed the elderly to enhanced accumulation of acetazolamide in erythrocytes.

Plasma-acetazolamide concentrations exceeded the **therapeutic range** (5 to 10 micrograms/mL) in 9 of 12 elderly patients receiving acetazolamide for glaucoma or metabolic alkalosis.[3] Hyperchloraemic metabolic acidosis was detected in 6 of 9 glaucoma patients. The excessive plasma concentrations were attributed to age-related reductions in renal function. It was suggested that elderly patients may require reduced doses of acetazolamide.

For reports of symptomatic metabolic acidosis associated with use of acetazolamide in the elderly, see Effects on Electrolyte Balance, above.

1. Shrader CE, *et al*. Relationship of patient age and tolerance to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1983; **96:** 730–3.
2. Chapron DJ, *et al*. Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.
3. Chapron DJ, *et al*. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.

Interference with laboratory estimations. Acetazolamide interfered with an HPLC method of assay for theophylline[1] resulting in an unnecessary dose reduction and worsening apnoea in an infant. Other workers[2] pointed out that the interference depended on the solvent used in the extraction, and presented evidence to suggest that acetazolamide may not interfere with other assay methods for theophylline.

1. Mecrow IK, Goldie BP. Acetazolamide interferes with theophylline assay. *Lancet* 1987; **i:** 558.
2. Kelsey HC, *et al*. Interference by acetazolamide in theophylline assay depends on the method. *Lancet* 1987; **ii:** 403.

Renal impairment. For a brief discussion of metabolic acidosis in patients with renal impairment, see Effects on Electrolyte Balance, above.

Interactions

By rendering the urine alkaline acetazolamide reduces the urinary excretion, and so may enhance the effects, of drugs such as amfetamines, ephedrine, and quinidine; conversely, urinary alkalinisation can reduce the effects of methenamine and its compounds. Acetazolamide may enhance antiepileptic-induced osteomalacia. Use of acetazolamide with aspirin may result in severe acidosis and increase CNS toxicity. Acetazolamide may affect fluid and electrolyte balance leading to interactions similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Unlike thiazides, however, acetazolamide may increase the excretion of lithium.

Antacids. *Sodium bicarbonate* therapy enhances the risk of renal calculus formation in patients taking acetazolamide.[1]

1. Rubenstein MA, Bucy JG. Acetazolamide-induced renal calculi. *J Urol (Baltimore)* 1975; **114:** 610–12.

Antiepileptics. For severe osteomalacia in patients taking acetazolamide with *phenytoin* and other antiepileptics, see

Diuretics, p. 544.3. Acetazolamide may increase serum concentrations of *carbamazepine*, see Diuretics, p. 517.3.

Antineoplastics. Alkalinisation of the urine by acetazolamide increases the solubility of *methotrexate* in the urine and also increases its excretion. This effect has been exploited therapeutically to reduce the nephrotoxicity of methotrexate (see Effects on the Kidneys, p. 825.2).

Benzodiazepines. Ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of *triazolam* by acetazolamide.[1]

1. Masuyama S, *et al*. Ondine's Curse': side effect of acetazolamide? *Am J Med* 1989; **86:** 637.

Local anaesthetics. For the effect of acetazolamide on *procaine*, see p. 1995.1.

Salicylates. Salicylates displace acetazolamide from plasma protein binding sites and reduce its renal clearance,[1] leading to elevated plasma-acetazolamide concentrations. In addition acidosis produced by acetazolamide may increase salicylate toxicity by enhancing salicylate tissue penetration.[2] Severe metabolic acidosis has been reported[3] in patients with normal renal function given acetazolamide with salicylates.

Use of salicylates with acetazolamide should be avoided if possible, particularly if renal dysfunction is present. If the combination is used, patients should be carefully monitored for symptoms of CNS toxicity such as lethargy, confusion, somnolence, tinnitus, and anorexia.

1. Sweeney KR, *et al*. Toxic interaction between acetazolamide and salicylate: case report and a pharmacokinetic explanation. *Clin Pharmacol Ther* 1986; **40:** 518–24.
2. Anderson CJ, *et al*. Toxicity of combined therapy with carbonic anhydrase inhibitors and aspirin. *Am J Ophthalmol* 1978; **86:** 516–19.
3. Cowan RA, *et al*. Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function. *BMJ* 1984; **289:** 347–8.

Pharmacokinetics

Acetazolamide is fairly rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after oral doses. It has been estimated to have a plasma half-life of about 3 to 6 hours. It is tightly bound to carbonic anhydrase and high concentrations are present in tissues containing this enzyme, particularly red blood cells and the renal cortex; it is highly bound to plasma proteins. It is excreted unchanged in the urine and has been detected in breast milk.

References.

1. Lehmann B, *et al*. The pharmacokinetics of acetazolamide in relation to its use in the treatment of glaucoma and to its effects as an inhibitor of carbonic anhydrases. *Adv Biosci* 1969; **5:** 197–217.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diamox; Hydroftal; Matro; ***Austral.***: Diamox; ***Austria***: Diamox; ***Belg.***: Diamox; ***Braz.***: Diamox; Zolamox; ***Canad.***: Diamox†; ***Cz.***: Diluran; ***Denm.***: Diamox; ***Fin.***: Diamox†; Odemin; ***Fr.***: Defiltran; Diamox; ***Ger.***: Acemit; Diamox; Glaupax; ***Gr.***: Diamox; Edemox; ***Hong Kong***: Diamox†; ***Hung.***: Huma-Zolamide; ***India***: Acetamide; Acetamin; Acetariv; Avva; Diamox; Iopar; ***Indon.***: Diamox†; Glauseta; ***Irl.***: Diamox; ***Israel***: Uramox; ***Ital.***: Diamox; ***Mex.***: Acetazolamida; Diamox; Diazol†; Akezol; ***Neth.***: Diamox; ***Norw.***: Diamox; ***NZ***: Diamox; Glaumox; ***Philipp.***: Cetamid; Diamox†; Optamide; Zolmide; ***Pol.***: Diuramid; ***Port.***: Carbinib; ***Rus.***: Diacarb (Диакарб); ***S.Afr.***: Azomid; Diamox; ***Singapore***: Diamox; ***Spain***: Edemox; ***Swed.***: Diamox; ***Switz.***: Diamox; Glaupax; ***Thai.***: Diamox; Medene; ***Turk.***: Diazomid; ***UK***: Diamox; ***Ukr.***: Diacarb (Диакарб); Diuremid (Диуремид); ***USA***: Diamox.

Pharmacopoeial Preparations

BP 2014: Acetazolamide Oral Suspension; Acetazolamide Tablets;

USP 36: Acetazolamide for Injection; Acetazolamide Tablets.

Acetylcholine Chloride *(BAN, rINN)*

Aceticholino chloridas; Acetilcolina, cloruro de; Acetilkolinklorid; Acetylcholin chlorid; Acetylcholinchlorid; Acétylcholine, chlorure d'; Acetylcholini Chloridum; Acetylkolinklorid; Acetylocholiny chlorek; Asetilkolin Klorür; Asetyylikoliinikloridi; Cloruro de acetilcolina; Ацетилхолина Хлорид.

(2-Acetoxyethyl)trimethylammonium chloride.

$C_7H_{16}ClNO_2$=181.7

CAS — 51-84-3 (acetylcholine); 60-31-1 (acetylcholine chloride).

ATC — S01EB09.

ATC Vet — QS01EB09.

UNII — AF73293C2R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Jpn includes Acetylcholine Chloride for Injection.

Ph. Eur. 8: (Acetylcholine Chloride). A very hygroscopic, white or almost white crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Acetylcholine Chloride). White or off-white crystals or crystalline powder. Very soluble in water; freely soluble in alcohol; insoluble in ether. It is decomposed by hot water and by alkalis. Store in airtight containers.

Uses and Administration

Acetylcholine is an endogenous chemical transmitter with a very wide range of actions in the body (see below). It is used as a miotic to reduce postoperative rises in intra-ocular pressure associated with cataract surgery, penetrating keratoplasty, iridectomy, and other anterior segment surgery (see p. 1999.1) but is ineffective when applied topically as it is hydrolysed more rapidly than it can penetrate the cornea. Doses of 0.5 to 2 mL of a freshly prepared 1% solution of acetylcholine chloride are therefore instilled directly into the anterior chamber of the eye (intracameral instillation). Miosis occurs within seconds and lasts for about 20 minutes. A second application may be made if prolonged miosis is required.

Action. Acetylcholine is a powerful quaternary ammonium parasympathomimetic but its action is transient as it is rapidly destroyed by cholinesterase. It is released from postganglionic parasympathetic nerves and also from some postganglionic sympathetic nerves to produce peripheral actions which correspond to those of muscarine. It is accordingly a vasodilator and cardiac depressant, a stimulant of the vagus and the parasympathetic nervous system, and it has a tonic action on smooth muscle. It also increases lachrymal, salivary, and other secretions. All the muscarinic actions of acetylcholine are abolished by atropine.

Acetylcholine also has actions that correspond to those of nicotine and is accordingly a stimulant of skeletal muscle, the autonomic ganglia, and the adrenal medulla. The nicotinic actions of acetylcholine on skeletal muscle are blocked by competitive neuromuscular blockers; they are also inhibited by massive doses or discharge of acetylcholine itself, which has clinical application in relation to the mode of action of suxamethonium (p. 2037.2).

Drugs that mimic or enhance the actions of acetylcholine in the body are known as **parasympathomimetics** and may be classified into 2 distinct pharmacological groups:

- **cholinergic agonists**, such as bethanechol, carbachol, methacholine, and pilocarpine which act directly on effector cells to mimic the effects of acetylcholine. They are sometimes referred to as cholinomimetics or true parasympathomimetics; some such as bethanechol, carbachol, and methacholine are choline esters
- **anticholinesterases** (cholinesterase inhibitors) which inhibit the enzymic hydrolysis of acetylcholine by acetylcholinesterase and other cholinesterases, thereby prolonging and enhancing its actions in the body. They may be classified by the length of time taken to restore active enzyme following binding of enzyme to drug. The 'reversible' anticholinesterases such as ambenonium, neostigmine, physostigmine, and pyridostigmine generally produce enzyme inhibition for a few hours, whereas 'irreversible' anticholinesterases such as dyflos and ecothiopate produce extremely prolonged inhibition, and return of cholinesterase activity depends on synthesis of new enzyme. Centrally acting reversible anticholinesterases include donepezil, galantamine, rivastigmine, and tacrine

Drugs such as fampridine and guanidine, which enhance the release of acetylcholine from nerve terminals, also have similar effects.

Diagnosis and testing. *AUTONOMIC FAILURE.* Acetylcholine has been used in a sweat-spot test for autonomic neuropathy in diabetic patients.[1] An area on the dorsum of the foot is painted with iodine and starch, followed by intradermal injection of acetylcholine into the centre of the area. Sweat produced in response to acetylcholine reacts with the iodine and starch to produce fine black dots corresponding to the pores of the sweat glands; a normal response is indicated by a uniform distribution of dark spots whereas in diabetic autonomic neuropathy this pattern is lost to a varying degree. A similar test has been carried out[2] to assess sympathetic nerve function and therefore predict the success of lumbar sympathectomy in patients with critical limb ischaemia.

1. Ryder REJ, *et al*. Acetylcholine sweatspot test for autonomic denervation. *Lancet* 1988; **i:** 1303–5.
2. Altomare DF. Acetylcholine sweat test: an effective way to select patients for lumbar sympathectomy. *Lancet* 1994; **344:** 976–8.

Adverse Effects

Because it is rapidly hydrolysed in the body by cholinesterases the toxicity of acetylcholine is normally relatively low.

Systemic adverse effects of the choline esters include nausea and vomiting, abdominal pain, flushing, sweating, salivation, lachrymation, rhinorrhoea, eructation, diarrhoea, urinary frequency, headache, bradycardia, peripheral vasodilatation leading to hypotension, and bronchoconstriction.

Ocular adverse effects after local application of choline esters to the eye include corneal oedema, clouding, and decompensation, persistent bullous keratopathy, retinal detachment, and postoperative iritis.

Treatment of Adverse Effects

Atropine sulfate may be given intravenously, intramuscularly, or subcutaneously to control the muscarinic and most nicotinic effects of the choline esters. Supportive treatment may be required.

Precautions

Choline esters are generally contra-indicated for *systemic use* in intestinal or urinary obstruction or where increased muscular activity of the urinary or gastrointestinal tract is liable to be harmful. They are also contra-indicated in asthma and obstructive airways disease, in cardiovascular disorders including bradycardia or heart block and recent myocardial infarction, and in hypotension, vagotonia, epilepsy, parkinsonism, hyperthyroidism, peptic ulceration, and pregnancy. Choline esters should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse effects are liable to occur, calling for emergency treatment with atropine.

Although acetylcholine is normally rapidly hydrolysed in the body, systemic effects have followed *topical application* of choline esters to the eye, albeit rarely, and caution is advisable in the above conditions.

Interactions

As for Neostigmine, p. 688.3. Acetylcholine is hydrolysed in the body by cholinesterase and its effects are markedly prolonged and enhanced if given after anticholinesterases.

Beta blockers. Severe bronchospasm with subsequent pulmonary oedema was reported[1] after intra-ocular injection of acetylcholine chloride in a patient also receiving oral *metoprolol*.

1. Rasch D, *et al*. Bronchospasm following intraocular injection of acetylcholine in a patient taking metoprolol. *Anesthesiology* 1983; **59:** 583–5.

NSAIDs. According to licensed product information for acetylcholine chloride ophthalmic preparations, there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Miochol; ***Belg.***: Miocholе; ***Canad.***: Miochol-E; Miogan†; ***Fin.***: Miochol-E; ***Fr.***: Miocholе; ***Ger.***: Miochol-E; ***Gr.***: Miochol-E; ***Hong Kong***: Miochol-E; ***Indon.***: Miochol-E; ***Irl.***: Miochol-E; ***Israel***: Miochol; ***Ital.***: Miochol-E†; Miovisin; ***Mex.***: Iloc; ***Neth.***: Miochol; ***NZ***: Miochol; ***Port.***: Miochol; ***S.Afr.***: Covochol; Miochol; ***Swed.***: Miochol-E; ***Switz.***: Miochol; ***Turk.***: Miochol-E; ***UK***: Miochol; Miphtel; ***USA***: Miochol.

Pharmacopoeial Preparations

USP 36: Acetylcholine Chloride for Ophthalmic Solution.

Apraclonidine Hydrochloride

(BANM, USAN, rINNM)

AL-02145 (apraclonidine); *p*-Aminoclonidine Hydrochloride; Aplonidine Hydrochloride; Apraclonidina, hidrocloruro de; Apraclonidine, chlorhydrate d'; Apraclonidini Hydrochloridum; Hidrocloruro de aminoclonidina; Hidrocloruro de aplonidina; Hidrocloruro de apraclonidina; NC-14; Апраклонидина Гидрохлорид.

2-[(4-Amino-2,6-dichlorophenyl)imino]imidazolidine hydrochloride; 2,6-Dichloro-N^1-imidazolidin-2-ylidene-*p*-phenylenediamine hydrochloride.

$C_9H_{10}Cl_2N_4HCl$=281.6

CAS — 66711-21-5 (apraclonidine); 73218-79-8 (apraclonidine hydrochloride).

ATC — S01EA03.

ATC Vet — QS01EA03.

UNII — D2VW67N38H.

NOTE. APR is a code approved by the BP 2014 for use on single unit doses of eye drops containing apraclonidine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *US.*

USP 36: (Apraclonidine Hydrochloride). A white to off-white, odourless to practically odourless powder. Soluble 1 in 34 of water, 1 in 74 of alcohol, and 1 in 13 of methyl alcohol; insoluble in chloroform, in ethyl acetate, and in hexanes. pH of a 1% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Uses and Administration

Apraclonidine is an alpha$_2$-adrenoceptor agonist derived from clonidine (p. 1339.1). It reduces intra-ocular pressure when instilled into the eye and is used in patients undergoing eye surgery, and as an adjunct in the management of glaucoma (p. 1999.1). The reduction in intra-ocular pressure begins within an hour of instillation and is maximal after about 3 to 5 hours.

Apraclonidine is used as the hydrochloride, but the strength of an ophthalmic solution is usually expressed in terms of the base. Apraclonidine hydrochloride 11.5 mg is equivalent to about 10 mg of apraclonidine.

To control or prevent a postoperative increase in intra-ocular pressure in patients undergoing anterior segment laser surgery, a 1% solution is instilled into the eye one hour before surgery and again immediately upon completion of surgery.

For short-term adjunctive therapy in patients with raised intra-ocular pressure not controlled by conventional therapy, a 0.5% solution may be instilled three times daily.

There is a loss of effect over time (tachyphylaxis) with apraclonidine and the benefit in most patients lasts for less than a month.

Adverse Effects and Precautions

Adverse effects after perioperative instillation of apraclonidine into the eye include hyperaemia, lid retraction, and mydriasis. Some patients may develop an exaggerated reduction in intra-ocular pressure. On regular instillation an ocular intolerance reaction may occur, characterised by hyperaemia, ocular pruritus, increased lachrymation, ocular discomfort, and oedema of the lids and conjunctiva; treatment should be stopped if these symptoms occur. Other adverse effects reported include dry mouth and nose, conjunctivitis, conjunctival blanching, blurred vision, asthenia, headache, and taste disturbances.

Systemic absorption can occur after application to the eye and may result in adverse effects similar to those of clonidine (p. 1341.2). Cardiovascular effects have been reported; therefore apraclonidine should be used with caution in patients with severe cardiovascular disease, including hypertension, and in patients with a history of vasovagal attacks. Drowsiness may also occur; if affected, patients should not drive or operate machinery. Depression has rarely been associated with use of apraclonidine and it should be used with caution in depressed patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies apraclonidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Systemic absorption may occur after topical application of apraclonidine to the eye and there is a theoretical possibility of interactions similar to those reported with clonidine (p. 1342.1). Since the effects of apraclonidine on circulating catecholamines are unknown, licensed product information recommends that MAOIs should not be given with apraclonidine; tricyclic and related antidepressants and systemic sympathomimetics should also be avoided or used with caution.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Iopidine; ***Austria***: Iopidine; ***Belg.***: Iopidine; ***Canad.***: Iopidine; ***China***: Chen Ze (辰泽); ***Denm.***: Iopidine; ***Fin.***: Iopidine; ***Fr.***: Iopidine; ***Ger.***: Iopidine; ***Gr.***: Iopidine; ***Hong Kong***: Iopidine; ***India***: Alfadrops; ***Irl.***: Iopidine; ***Israel***: Iopidine; ***Ital.***: Iopidine; ***Jpn***: Iopidine; ***Mex.***: Iopidine; ***Neth.***: Iopidine; ***Norw.***: Iopidine; ***NZ***: Iopidine; ***Port.***: Iopidine; ***S.Afr.***: Iopidine; ***Singapore***: Iopidine†; ***Spain***: Iopimax; ***Swed.***: Iopidine; ***Switz.***: Iopidine; ***Thai.***: Iopidine; ***Turk.***: Iopidine; ***UK***: Iopidine; ***USA***: Iopidine.

Pharmacopoeial Preparations
USP 36: Apraclonidine Ophthalmic Solution.

Befunolol Hydrochloride *(rINNM)* ⊗

Béfunolol, Chlorhydrate de; Befunolol, hidrocloruro de; Befunololi Hydrochloridum; BFE-60; Hidrocloruro de befunolol; Бефунолола Гидрохлорид.
7-[2-Hydroxy-3-(isopropylamino)propoxy]-2-benzofuranyl methyl ketone hydrochloride.
$C_{16}H_{21}NO_4$,HCl=327.8
CAS — 39552-01-7 (befunolol); 39543-79-8 (befunolol hydrochloride).
ATC — S01ED06.
ATC Vet — QS01ED06.
UNII — B03Z2VY37I.

Profile

Befunolol is a beta blocker (p. 1316.3). It is used as the hydrochloride in the management of ocular hypertension and open-angle glaucoma (p. 1999.1). Eye drops containing befunolol hydrochloride 0.25%, 0.5%, or 1% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Thilonium; ***Ital.***: Betaclar†; ***Jpn***: Bentos.

Bimatoprost *(BAN, USAN, rINN)*

AGN-192024; Bimatoprostum; Биматопрост.
(*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl}-*N*-ethyl-5-heptenamide.
$C_{25}H_{37}NO_4$=415.6
CAS — 155206-00-1.
ATC — S01EE03.
ATC Vet — QS01EE03.
UNII — QXS94885MZ.

Uses and Administration

Bimatoprost is a synthetic prostamide, a fatty-acid amide that is structurally related to dinoprost (prostaglandin $F_{2\alpha}$). It is used to reduce intra-ocular pressure in the treatment of open-angle glaucoma and ocular hypertension (p. 1999.1). Reduction in pressure starts about 4 hours after instillation and is maximal within 8 to 12 hours; the effect lasts for at least 24 hours. It is given once daily in the evening as a 0.01% or 0.03% ophthalmic solution.

Bimatoprost is also used in the treatment of hypotrichosis of the eyelashes; one drop of a 0.03% ophthalmic solution is applied to each eye once nightly along the skin of the upper eyelid margin at the base of the eyelashes.

References.
1. Williams RD, *et al.* Bimatoprost Study Group. Long-term efficacy and safety of bimatoprost for intraocular pressure lowering in glaucoma and ocular hypertension: year 4. *Br J Ophthalmol* 2008; **92:** 1387–92.
2. Patil AJ, *et al.* Bimatoprost - a review. *Expert Opin Pharmacother* 2009; **10:** 2759–68.
3. Katz LJ, *et al.* Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol* 2010; **149:** 661–671.

Adverse Effects and Precautions

As for Latanoprost, p. 2008.2. Ocular pruritus is common. Hypertension and headache also commonly occur. There have been reports of bradycardia or hypotension and bimatoprost should be used with caution in patients predisposed to a low heart rate or blood pressure. Reactivation of previous corneal infiltrates or ocular infections has also been reported rarely; it should be used with caution in those with a history of significant ocular viral infections, such as herpes simplex, or uveitis or iritis.

Pharmacokinetics

Small amounts of bimatoprost are absorbed from eye drops and peak blood concentrations occur within 10 minutes of dosing. Bimatoprost is metabolised by oxidation, de-ethylation, and glucuronidation, and is excreted mainly in the urine with about 25% appearing in the faeces. The elimination half-life is 45 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lumigan; ***Austral.***: Lumigan; ***Austria***: Lumigan; ***Belg.***: Lumigan; ***Braz.***: Glamigan; Lumigan; ***Canad.***: Latisse; Lumigan; ***Chile***: Lumigan; ***China***: Lumigan (卢美根); ***Cz.***: Lumigan; ***Denm.***: Lumigan; ***Fin.***: Lumigan; ***Fr.***: Lumigan; ***Ger.***: Lumigan; ***Gr.***: Lumigan; ***Hong Kong***: Lumigan; ***Hung.***: Lumigan; ***India***: Careprost; Lumigan; ***Irl.***: Lumigan; ***Israel***: Latisse; Lumigan; ***Ital.***: Lumigan; ***Jpn***: Lumigan; ***Malaysia***: Lumigan; ***Mex.***: Lumigan; ***Neth.***: Lumigan; ***Norw.***: Lumigan; ***NZ***: Lumigan; ***Philipp.***: Lumigan; ***Pol.***: Lumigan; ***Port.***: Lumigan; ***S.Afr.***: Lumigan; ***Singapore***: Latisse; Lumigan; ***Spain***: Lumigan; ***Swed.***: Lumigan; ***Switz.***: Lumigan; ***Thai.***: Lumigan; ***Turk.***: Lumigan; ***UK***: Lumigan; ***USA***: Latisse; Lumigan; ***Venez.***: Lumigan.

Multi-ingredient Preparations. ***Arg.***: Ganfort; ***Austral.***: Ganfort; ***Austria***: Ganfort; ***Braz.***: Ganfort; ***Chile***: Ganfort; ***Cz.***: Ganfort; ***Denm.***: Ganfort; ***Fr.***: Ganfort; ***Ger.***: Ganfort; ***Gr.***: Ganfort; ***Hong Kong***: Ganfort; ***Hung.***: Ganfort; ***India***: Careprost Plus; Ganfort; ***Irl.***: Ganfort; ***Israel***: Ganfort; ***Ital.***: Ganfort; ***Malaysia***: Ganfort; ***Mex.***: Ganforti; ***Neth.***: Ganfort; ***Norw.***: Ganfort; ***NZ***: Ganfort; ***Philipp.***: Ganfort; ***Pol.***: Ganfort; ***Port.***: Ganfort; ***Singapore***: Ganfort; ***Spain***: Ganfort; ***Swed.***: Ganfort; ***Switz.***: Ganfort; ***Thai.***: Ganfort; ***Turk.***: Ganfort; ***UK***: Ganfort; ***Ukr.***: Ganfort (Ганфорт).

Brimonidine Tartrate *(BANM, USAN, rINNM)*

AGN-190342-LF; Brimonidin Tartrat; Brimonidina, tartrato de; Brimonidine, Tartrate de; Brimonidini Tartras; Tartrato de brimonidina; UK-14304-18; Бримонидина Тартрат.
5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate.
$C_{11}H_{10}BrN_5$,$C_4H_6O_6$=442.2
CAS — 59803-98-4 (brimonidine); 79570-19-7 (brimonidine tartrate).
ATC — S01EA05.
ATC Vet — QS01EA05.
UNII — 4S9CL2DY2H.

Uses and Administration

Brimonidine is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of apraclonidine (above). It is used to lower intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (below), as an alternative or adjunct to topical beta blocker therapy. It may also be used as adjunctive therapy in patients with raised intra-ocular pressure not controlled by topical monotherapy with other drugs such as latanoprost and travoprost. The reduction in intra-ocular pressure is maximal about 2 hours after topical use.

In the management of glaucoma or ocular hypertension, eye drops containing brimonidine tartrate 0.1, 0.15, or 0.2% are instilled two or three times daily.

Glaucoma. References[1-4] to the use of brimonidine in glaucoma and ocular hypertension (p. 1999.1).

1. Frampton JE. Topical brimonidine 0.2%/timolol 0.5% ophthalmic solution: in glaucoma and ocular hypertension. *Drugs Aging* 2006; **23:** 753–61.
2. Fung AT, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; **91:** 62–8.
3. Katz LJ, *et al.* Efficacy and safety of brimonidine and dorzolamide for intraocular pressure lowering in glaucoma and ocular hypertension. *Curr Med Res Opin* 2007; **23:** 2971–83.
4. Fudemberg SJ, *et al.* Efficacy, safety, and current applications of brimonidine. *Expert Opin Drug Safety* 2008; **7:** 795–9.

Adverse Effects and Precautions

As for Apraclonidine Hydrochloride, above.

In children. Systemic adverse effects, occasionally severe,[1] have been reported in children treated with brimonidine eye drops. In one study[2] adverse effects were reported in 70 of 83 children given adjunctive brimonidine, the most common effects being lethargy and excessive sleepiness; other effects included ocular irritation and blurred vision. Hypothermia occurred in a few cases, mainly in older children. Effects suggesting CNS depression, such as cyanosis and breathing difficulty, were rare, and were most likely in children less than 6 years of age or weighing less than 20 kg. Alternative medication should be considered in this group. In the UK, licensed product information contra-indicates use in neonates and infants under 2 years of age; use in children under 12 years of age is not recommended.

1. Sztajnbok J. Failure of naloxone to reverse brimonidine-induced coma in an infant. *J Pediatr* 2002; **140:** 485–6.
2. Al-Shahwan S, *et al.* Side-effect profile of brimonidine tartrate in children. *Ophthalmology* 2005; **112:** 2143–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies brimonidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Apraclonidine Hydrochloride, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alphagan; Brimo-Klonal; Brimopress; Oftalmotonil; ***Austral.***: Alphagan; Enidin; ***Austria***: Alphagan; ***Belg.***: Alphagan; ***Braz.***: Alphabrin; Alphagan; Bri-

moftal; Glaub; ***Canad.***: Alphagan; ***Chile***: Agglad Ofteno; Alphagan; Brimopress; ***China***: Alphagan (阿法根); Brimocon (沐利汀); Mu Xin (沐欣); ***Cz.***: Alphagan; Luxfen; ***Denm.***: Alphagan; Alphastad; Brimoratio; Glaudin; ***Fin.***: Alphagan; Glaudin†; ***Fr.***: Alphagan; ***Ger.***: Alphagan; Brimo Ophtal; Brimozept; ***Gr.***: Alphagan; Benil; Brimodine; Brimogan; Brimontal; Brinal; Brinidin; Corneax; Glaucoval; Pharmexin; ***Hong Kong***: Alphagan; ***India***: Alphagan; Brimochek; Brimodin; Brimopress; Brimosun; Iobrim; ***Irl.***: Alphagan; Brimon; ***Israel***: Alphagan; ***Ital.***: Alphagan; ***Jpn***: Aiphagan; ***Malaysia***: Alphagan; ***Mex.***: Agglad; Alphagan; Briop; Nor-Tenz; ***Neth.***: Alphagan; Briglau; ***Norw.***: Alphagan; Brimoratio; ***NZ***: Alphagan; ***Philipp.***: Alphagan; ***Pol.***: Alphagan; Brimoteva; Luxfen; ***Port.***: Alphagan; Bglau; ***S.Afr.***: Alphagan; ***Singapore***: Alphagan; ***Spain***: Alfadina; Alphagan; ***Swed.***: Alphagan; Brimoratio; Glaudin; ***Switz.***: Alphagan; ***Thai.***: Alphagan; ***Turk.***: Alphagan; ***UK***: Alphagan; Brymont; ***Ukr.***: Alphagan (Альфаган); Luxfen (Люксфен); ***USA***: Alphagan; Mirvaso; ***Venez.***: Agglad Ofteno; Alphagan.

Multi-ingredient Preparations. ***Arg.***: Combigan; Timobrim; ***Austral.***: Combigan; ***Austria***: Combigan; ***Belg.***: Combigan; ***Braz.***: Combigan; ***Canad.***: Combigan; ***Chile***: Combigan; ***Cz.***: Combigan; ***Denm.***: Combigan; ***Fin.***: Combigan; ***Fr.***: Combigan; ***Ger.***: Combigan; ***Gr.***: Combigan; ***Hong Kong***: Combigan; ***Hung.***: Combigan; ***India***: Brimochek-T; Brimocom; Brimolol; Combigan; ***Irl.***: Combigan; ***Israel***: Combigan; ***Ital.***: Combigan; ***Malaysia***: Combigan; ***Mex.***: Combigan-D; Krytantek; ***Neth.***: Combigan; ***Norw.***: Combigan; ***NZ***: Combigan; ***Philipp.***: Combigan; ***Pol.***: Combigan; ***Port.***: Combigan; ***S.Afr.***: Combigan; ***Singapore***: Combigan; ***Spain***: Combigan; ***Swed.***: Combigan; ***Switz.***: Combigan; ***Thai.***: Combigan; ***Turk.***: Combigan; ***UK***: Combigan; ***Ukr.***: Combigan (Комбиган); ***USA***: Combigan; Simbrinza.

Brinzolamide *(BAN, USAN, rINN)* ⊗

AL-4862; Brintsolamidi; Brinzolamid; Brinzolamida; Brinzolamidum; Бринзоламид.

(*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide.

$C_{12}H_{21}N_3O_5S_3$=383.5

CAS — 138890-62-7.

ATC — S01EC04.

ATC Vet — QS01EC04.

UNII — 9451Z89515.

Pharmacopoeias. In *US.*

USP 36: (Brinzolamide). A white or almost white powder. Insoluble in water; slightly soluble in alcohol and in methyl alcohol.

Uses and Administration

Brinzolamide is a carbonic anhydrase inhibitor with actions and uses similar to those of dorzolamide (p. 2006.3). It is used to reduce intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p. 1999.1), either alone or as adjunctive therapy with a topical beta blocker or prostaglandin analogue. A 1% suspension is instilled into the eye two or three times daily.

Glaucoma. References.

1. Cvetkovic RS, Perry CM. Brinzolamide: a review of its use in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 2003; **20:** 919–47.
2. Iester M. Brinzolamide. *Expert Opin Pharmacother* 2008; **9:** 653–62.

Adverse Effects and Precautions

As for Dorzolamide, p. 2007.1.

Effects on the eyes. Corneal oedema has been noted in the eyes of 2 patients after the long-term use of brinzolamide 1% eye drops;[1] both patients recovered after brinzolamide was stopped.

1. Zhao JC, Chen T. Brinzolamide induced reversible corneal decompensation. *Br J Ophthalmol* 2005; **89:** 389–90.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies brinzolamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Azopt; ***Austral.***: Azopt; ***Austria***: Azopt; ***Belg.***: Azopt; ***Braz.***: Azopt; ***Canad.***: Azopt; ***Chile***: Azopt; ***China***: Azopt (派立明); ***Cz.***: Azopt; ***Denm.***: Azopt; ***Fin.***: Azopt; ***Fr.***: Azopt; ***Ger.***: Azopt; ***Gr.***: Azopt; ***Hong Kong***: Azopt; ***Hung.***: Azopt; ***Indon.***: Azopt; ***Irl.***: Azopt; ***Israel***: Azopt; ***Ital.***: Azopt; ***Malaysia***: Azopt; ***Mex.***: Azopt; ***Neth.***: Azopt; ***Norw.***: Azopt; ***NZ***: Azopt; ***Philipp.***: Azopt; ***Pol.***: Azopt; ***Port.***: Azopt; ***Rus.***: Azopt (Азопт); ***S.Afr.***: Azoptic; ***Singapore***: Azopt; ***Spain***: Azopt; ***Swed.***: Azopt; ***Switz.***: Azopt; ***Thai.***: Azopt; ***Turk.***: Azopt; ***UK***: Azopt; ***Ukr.***: Azopt (Азопт); ***USA***: Azopt; ***Venez.***: Azopt.

Multi-ingredient Preparations. ***Arg.***: Azarga; ***Austral.***: Azarga; ***Austria***: Azarga; ***Belg.***: Azarga; ***Canad.***: Azarga; ***Chile***: Azarga; ***Cz.***: Azarga; ***Denm.***: Azarga; ***Fr.***: Azarga; ***Ger.***: Azarga; ***Gr.***: Azarga; ***Hung.***: Azarga; ***Irl.***: Azarga; ***Ital.***: Azarga; ***Malaysia***: Azarga; ***Neth.***: Azarga; ***Norw.***: Azarga; ***NZ***: Azarga; ***Pol.***: Azarga; ***Port.***: Azarga; ***Rus.***: Azarga (Азарга); ***Singapore***: Azarga; ***Spain***: Azarga; ***Swed.***: Azarga; ***Switz.***: Azarga; ***Thai.***: Azarga; ***Turk.***: Azarga; ***UK***: Azarga; ***USA***: Simbrinza.

Pharmacopoeial Preparations

USP 36: Brinzolamide Ophthalmic Suspension.

Carbachol *(BAN, rINN)*

Carbach.; Carbacholi Cloridum; Carbacholine; Carbacholum; Carbacholum Chloratum; Carbacol; Choline Chloride Carbamate; Karbachol; Karbacholis; Karbakol; Karbakoli; Karbaminocholiny chlorek; Карбахол.

O-Carbamoylcholine chloride; (2-Carbamoyloxyethyl)trimethylammonium chloride.

$C_6H_{15}ClN_2O_2$=182.6

CAS — 51-83-2.

ATC — N07AB01; S01EB02.

ATC Vet — QA03AB92; QN07AB01; QS01EB02.

UNII — 8Y164V895Y.

NOTE. CAR is a code approved by the BP 2014 for use on single unit doses of eye drops containing carbachol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Carbachol). A white or almost white, crystalline, hygroscopic powder. Very slightly soluble in water; sparingly soluble in alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Carbachol). A white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Chlorocresol (0.025 to 0.1%) and chlorobutanol (0.5%) were both found to be incompatible with a solution of carbachol (0.8%) and sodium chloride (0.69%), very slight precipitates forming on heating and increasing on standing.[1]

1. *PSGB Lab Report No.911* 1962.

Uses and Administration

Carbachol, a choline ester, is a quaternary ammonium parasympathomimetic with the muscarinic and nicotinic actions of acetylcholine (p. 2003.2). It is not inactivated by cholinesterases so its actions are more prolonged than those of acetylcholine.

Carbachol has a miotic action and is usually given intraocularly to produce miosis in ocular surgery and to reduce postoperative rises in intra-ocular pressure; up to 0.5 mL of a 0.01% solution is instilled into the anterior chamber of the eye (intracameral instillation). The maximum degree of miosis is usually obtained within 2 to 5 minutes of intraocular instillation and miosis lasts for 24 hours.

Eye drops containing up to 3% of carbachol have also been used to lower intra-ocular pressure in glaucoma, usually three times daily with other miotics (see below). Miosis occurs within 10 to 20 minutes of instillation and lasts for 4 to 8 hours; reduction in intra-ocular pressure lasts for 8 hours.

Carbachol has been used for the treatment of urinary retention including postoperative urinary retention. It has also been used in some countries for the treatment of decreased gastrointestinal motility.

Dry mouth. Carbachol has been used as an alternative to pilocarpine in the treatment of radiation-induced xerostomia.[1] The overall treatment of dry mouth is discussed on p. 2175.3.

1. Joensuu H. Treatment for post-irradiation xerostomia. *N Engl J Med* 1994; **330:** 141–2.

Glaucoma and ocular hypertension. Carbachol is sometimes used as an alternative to pilocarpine in the management of glaucoma (p. 1999.1) when resistance or intolerance to pilocarpine develops. It is also instilled into the anterior chamber of the eye (intracameral instillation) to minimise postoperative rises in intra-ocular pressure associated with ocular surgery, and some[1,2] have found it to be more effective than acetylcholine.

1. Ruiz RS, *et al.* Effects of carbachol and acetylcholine on intramuscular pressure after cataract extraction. *Am J Ophthalmol* 1989; **107:** 7–10.
2. Hollands RH, *et al.* Control of intraocular pressure after cataract extraction. *Can J Ophthalmol* 1990; **25:** 128–32.

Adverse Effects, Treatment, and Precautions

As described for choline esters under Acetylcholine Chloride, p. 2003.2. Carbachol has substantial nicotinic activity which may be unmasked by the use of atropine to counteract muscarinic effects.

Carbachol also produces adverse effects and requires precautions similar to those of other miotics such as pilocarpine (p. 2011.2) when used in the eye, but may produce more ciliary spasm than pilocarpine.

Effects on the gastrointestinal tract. Fatal oesophageal rupture has been reported[1] after subcutaneous injection of carbachol to relieve urinary retention.

1. Cochrane P. Spontaneous oesophageal rupture after carbachol therapy. *BMJ* 1973; **1:** 463–4.

Overdosage. Life-threatening attacks of profuse sweating, intestinal cramps, explosive defaecation, hypothermia, hypotension, and bradycardia occurred in a 36-year-old man after deliberate poisoning with 30 to 40 mg of carbachol.[1] The patient's 10-year-old son had died after poisoning with a similar dose of carbachol.

1. Sangster B, *et al.* Two cases of carbachol intoxication. *Neth J Med* 1979; **22:** 27–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carbachol for ophthalmic use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

NSAIDs. Licensed UK product information for acetylcholine chloride ophthalmic preparations states that there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Miostat; ***Austral.***: Miostat; ***Belg.***: Miostat; ***Canad.***: Miostat; ***Cz.***: Miostat; ***Fr.***: Miostat; ***Ger.***: Carbamann†; ***Hung.***: Miostat; ***Israel***: Miostat; ***Ital.***: Mioticol; ***Malaysia***: Miostat; ***Neth.***: Miostat; ***NZ***: Miostat; ***Philipp.***: Miostat; ***Pol.***: Miostat; ***Singapore***: Miostat; ***Swed.***: Isopto Karbakolin†; Miostat; ***Switz.***: Miostat; ***Thai.***: Miostat; ***Turk.***: Miostat; ***USA***: Carbastat†; Miostat.

Pharmacopoeial Preparations

USP 36: Carbachol Intraocular Solution; Carbachol Ophthalmic Solution.

Cyclopentolate Hydrochloride

(BANM, rINNM)

Ciclopentolato, hidrocloruro de; Ciklopentolát-hidroklorid; Ciklopentolato hidrochloridas; Cloridrato de Ciclopentolato; Cyclopentolate, Chlorhydrate de; Cyclopentolathydrochlorid; Cyclopentolati Hydrochloridum; Cyklopentolát hydrochlorid; Cyklopentolathydroklorid; Hidrocloruro de ciclopentolato; Siklopentolat Hidroklorür; Syklopentolaattihydrokloridi; Циклопентолата Гидрохлорид.

2-Dimethylaminoethyl 2-(1-hydroxycyclopentyl)-2-phenylacetate hydrochloride.

$C_{17}H_{25}NO_3$,HCl=327.8

CAS — 512-15-2 (cyclopentolate); 5870-29-1 (cyclopentolate hydrochloride).

ATC — S01FA04.

ATC Vet — QS01FA04.

UNII — 736I6971TE.

NOTE CYC is a code approved by the BP 2014 for use on single unit doses of eye drops containing cyclopentolate hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PHNCYC is a similar code approved for eye drops containing phenylephrine hydrochloride and cyclopentolate hydrochloride.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Cyclopentolate Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 36: (Cyclopentolate Hydrochloride). A white crystalline powder, which develops a characteristic odour on standing. Very soluble in water; freely soluble in alcohol; insoluble in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store at a temperature not exceeding 8 degrees in airtight containers.

Uses and Administration

Cyclopentolate hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used to produce mydriasis and cycloplegia (p. 2000.2) for ophthalmic diagnostic procedures and also in the treatment of uveitis and iritis (p. 1615.1). It acts more quickly than atropine and has a shorter duration of action; the maximum mydriatic effect is produced 30 to 60 minutes after instillation, and may persist for up to 24 hours or longer in some patients; the maximum cycloplegic effect is produced within 25 to 75 minutes and accommodation recovers within 6 to 24 hours.

For diagnostic procedures, instillation of a 0.5% ophthalmic solution of cyclopentolate hydrochloride, repeated after about 5 to 15 minutes if necessary, is usually sufficient. Higher strengths have been used.

In the treatment of uveitis and iritis, a 0.5% ophthalmic solution of cyclopentolate hydrochloride is instilled into the eye up to four times daily.

Deeply pigmented eyes are more resistant to pupillary dilatation and may require the use of a 1% solution.

For details of doses in children, see below.

Administration in children. For diagnostic procedures in children, instillation of a 1% ophthalmic solution of cyclopentolate hydrochloride, repeated after about 5 to 15 minutes if necessary, is usually sufficient. Higher strengths have been used. However, some recommend that strengths greater than 0.5% should not be used in infants and that cyclopentolate should not be used at all during the first 3 months of life.

In the treatment of uveitis, the *BNFC* suggests that a 0.5% ophthalmic solution of cyclopentolate hydrochloride may be instilled into the eye 2 to 4 times daily; a 1% solution should be used for deeply pigmented eyes.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Eye drops of cyclopentolate hydrochloride may cause temporary irritation.

Abuse. Cyclopentolate eye drops have been abused.[1] One of 2 patients who did so had been instilling 200 to 400 drops of cyclopentolate into both eyes daily for about 4 months, presumably for its CNS effects, and had intense nausea, vomiting, weakness, and tremors on withdrawal.

1. Sato EH, *et al.* Abuse of cyclopentolate hydrochloride (Cyclogyl) drops. *N Engl J Med* 1992; **326:** 1363–4.

Hypersensitivity. Two children developed hypersensitivity reactions shortly after the instillation of 1% cyclopentolate hydrochloride eye drops into each eye.[1] Both children initially had a facial rash but in one of them the rash later spread to include the arms and legs and was accompanied by mild breathlessness.

1. Jones LWJ, Hodes DT. Possible allergic reactions to cyclopentolate hydrochloride: case reports with literature review of uses and adverse reactions. *Ophthalmic Physiol Opt* 1991; **11:** 16–21.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclopentolate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Systemic toxicity. Ten of 66 patients (29 males and 37 females) who received one drop of 2% cyclopentolate in each eye developed mild to moderate systemic toxicity; 9 of the 10 were female.[1] Toxic signs included physical weakness, nausea, lightheadedness, changes in emotional attitude, unprovoked weeping, and loss of equilibrium; tachycardia was always present but changes in blood pressure were insignificant. Spontaneous recovery occurred within 1 hour to several days.

As with atropine, it has been recommended that cyclopentolate eye drops should not be used during the first 3 months of life because of the possible association with development of amblyopia. Systemic toxicity has also been reported in neonates given ocular cyclopentolate.[2]

A 4-year-old boy with cerebral palsy and paraplegia suffered tonic-clonic seizures, facial flushing, and tachycardia 70 minutes after one drop of a 1% cyclopentolate solution was instilled into each eye to dilate his pupils.[3] The child had no history of convulsions and had received 1% cyclopentolate eye drops on 2 previous occasions without incident. In a more recent case,[4] a 23-month-old boy had a tonic-clonic seizure lasting 30 minutes after the use of cyclopentolate 1% and phenylephrine 10% eye drops. One drop of each was instilled into both eyes every 5 minutes for 3 doses; the seizure occurred 45 minutes after the last dose. The child was found to have low pseudocholinesterase activity, an enzyme likely to be involved in the metabolism of cyclopentolate.

1. Awan KJ. Adverse systemic reactions of topical cyclopentolate hydrochloride. *Ann Ophthalmol* 1976; **8:** 695–8.
2. Bauer CR, *et al.* Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant. *J Pediatr* 1973; **92:** 501–5.
3. Fitzgerald DA, *et al.* Seizures associated with 1% cyclopentolate eyedrops. *J Paediatr Child Health* 1990; **26:** 106–7.
4. Demayo AP, Reidenberg MM. Grand mal seizure in a child 30 minutes after Cyclogyl (cyclopentolate hydrochloride) and 10% Neo-Synephrine (phenylephrine hydrochloride) eye drops were instilled. Abstract: *Pediatrics* 2004; **113:** 1390–1. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/5/e499 (accessed 24/11/05)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ciclopenal; ***Austral.***: Cyclogyl; ***Belg.***: Cyclogyl; ***Braz.***: Ciclolato; Ciclopegico; ***Canad.***: Ak-Pentolate; Cyclogyl; Diopentolate; ***Chile***: Cyclogyl; ***China***: Cyclogyl (赛飞杰); ***Denm.***: Cyclogyl; ***Fin.***: Oftan Syklo; ***Fr.***: Skiacol; ***Ger.***: Zykolat-EDO; ***Gr.***: Cyclogyl; ***Hong Kong***: Cyclogyl; ***Hung.***: Humapent; ***India***: Bell Pentolate†; Cyclate; Cyclogik; Cyclogyl; Cyclopent; Dilate; ***Irl.***: Mydrilate; ***Ital.***: Ciclolux; ***Malaysia***: Colircusi Cicloplejico; Cyclogyl; ***Mex.***: Refractyl; ***Neth.***: Cyclogyl; ***NZ***: Cyclogyl; ***Port.***: Cicloplegicedol; Midriodavi; ***Rus.***: Cyclomed (Цикломед); Cycloptic (Циклоптик); ***S.Afr.***: Cyclogyl; ***Singapore***: Cyclogyl†; ***Spain***: Ciclopegic; Cicloplejico; ***Swed.***: Cyclogyl; ***Switz.***: Cyclogyl; ***Thai.***: Cyclogyl; ***Turk.***: Siklomid; Sikloplejin; ***UK***: Mydrilate; ***Ukr.***: Cyclomed (Цикломед); ***USA***: Ak-Pentolate; Cyclogyl; Ocu-Pentolate; Pentolair†; ***Venez.***: Cyclogyl.

Multi-ingredient Preparations. ***India***: Cycdex; Cyclogyl-D; Cyclopent Plus; Cyclopent-DM; ***Malaysia***: Cyclomydril; ***S.Afr.***: Cyclomydril; ***Singapore***: Cyclomydril†; ***USA***: Cyclomydril.

Pharmacopoeial Preparations
BP 2014: Cyclopentolate Eye Drops;
USP 36: Cyclopentolate Hydrochloride Ophthalmic Solution.

Dapiprazole Hydrochloride *(USAN, rINNM)*

AF-2139; Dapiprazol, hidrocloruro de; Dapiprazole, Chlorhydrate de; Dapiprazoli Hydrochloridum; Hidrocloruro de dapiprazol; Дапипразола Гидрохлорид.

5,6,7,8-Tetrahydro-3-[2-(4-*o*-tolyl-1-piperazinyl)ethyl]-*s*-triazolo[4,3-*a*]pyridine monohydrochloride.

$C_{19}H_{27}N_5$,HCl=361.9

CAS — 72822-12-9 (dapiprazole); 72822-13-0 (dapiprazole hydrochloride).
ATC — S01EX02.
ATC Vet — QS01EX02.
UNII — DS9UJN110X.

Profile

Dapiprazole hydrochloride is an alpha blocker given as eye drops to reverse mydriasis; it is also used in some countries in the management of glaucoma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Benglau†; ***Gr.***: Glamidolo; ***Ital.***: Glamidolo; ***USA***: Rev-Eyes†.

Demecarium Bromide *(BAN, rINN)*

BC-48; Bromuro de demecario; Demecarii Bromidum; Demecario, bromuro de; Démécarium, Bromure de; Demekariumbromid; Demekariumbromidi; Демекария Бромид.

N,N'-Decamethylenebis(*N,N,N*-trimethyl-3-methylcarbamoyloxyanilinium) dibromide.

$C_{32}H_{52}Br_2N_4O_4$=716.6

CAS — 16505-84-3 (demecarium); 56-94-0 (demecarium bromide).
ATC — S01EB04.
ATC Vet — QS01EB04.
UNII — 61D5V4OKTP.

Pharmacopoeias. In *US*.

USP 36: (Demecarium Bromide). A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in acetone; soluble in ether. pH of a 1% solution in water is between 5.0 and 7.0. Store in airtight containers. Protect from light.

Profile

Demecarium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase with a long duration of action similar to that of ecothiopate iodide (p. 2007.2). It has been used as a 0.125 or 0.25% ophthalmic solution in the treatment of open-angle glaucoma and in the diagnosis and management of accommodative convergent strabismus.

Preparations

Pharmacopoeial Preparations
USP 36: Demecarium Bromide Ophthalmic Solution.

Diclofenamide *(BAN, rINN)* ⊗

Dichlorphenamide; Diclofenamida; Diclofénamide; Diclofenamidum; Diklofenamid; Diklofenamidi; Диклофенамид.

4,5-Dichlorobenzene-1,3-disulphonamide.

$C_6H_8Cl_2N_2O_4S_2$=305.1

CAS — 120-97-8.
ATC — S01EC02.
ATC Vet — QS01EC02.
UNII — VVJ6673MHY.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

Profile

Diclofenamide is an inhibitor of carbonic anhydrase with properties similar to those of acetazolamide (p. 2001.1). When given orally its effect begins within 1 hour and lasts for 6 to 12 hours.

Diclofenamide is used to reduce intra-ocular pressure in glaucoma (p. 1999.1). The usual initial oral dose is 100 mg every 6 to 12 hours until the desired response is obtained, followed by a maintenance dose of 50 mg every 8 hours. Diclofenamide sodium has been given by injection.

Diclofenamide may be of benefit in hyper- and hypokalaemic periodic paralysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Oratrol; ***Ital.***: Antidrasi†; Fenamide; ***Spain***: Glauconide†.

Pharmacopoeial Preparations
USP 36: Dichlorphenamide Tablets.

Dorzolamide Hydrochloride

(BANM, USAN, rINNM) ⊗

Dorzolamid Hidroklorür; Dorzolamida, hidrocloruro de; Dorzolamide, Chlorhydrate de; Dorzolamidhydrochlorid; Dorzolamidi hydrochloridum; Hidrocloruro de dorzolamida; L-671152 (dorzolamide); MK-0507; MK-507; Дорзоламида Гидрохлорид.

(4*S*,6*S*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulphonamide 7,7-dioxide hydrochloride.

$C_{10}H_{16}N_2O_4S_3$,HCl=360.9

CAS — 120279-96-1 (dorzolamide); 130693-82-2 (dorzolamide hydrochloride).
ATC — S01EC03.
ATC Vet — QS01EC03.
UNII — QZO5366EW7.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Dorzolamide Hydrochloride). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in anhydrous alcohol; slightly soluble in methyl alcohol. It exhibits polymorphism.

USP 36: (Dorzolamide Hydrochloride). A white to off-white crystalline powder. Soluble in water. Store at 15 degrees to 30 degrees. Protect from light.

Uses and Administration

Dorzolamide is a carbonic anhydrase inhibitor with actions similar to those of acetazolamide (p. 2001.1). It is used in the management of open-angle glaucoma, pseudo-exfoliative glaucoma, and ocular hypertension (p. 1999.1), either alone or as an adjunct to a topical beta blocker.

Dorzolamide is given as eye drops containing dorzolamide hydrochloride equivalent to 2% of the base. For monotherapy it is usually given three times daily; a twice-daily regimen is recommended when used with a beta blocker.

References.

1. Lesk MR, *et al.* Effectiveness and safety of dorzolamide-timolol alone or combined with latanoprost in open-angle glaucoma or ocular hypertension. *Ann Pharmacother* 2008; **42:** 498–504.
2. Katz LJ, *et al.* Efficacy and safety of brimonidine and dorzolamide for intraocular pressure lowering in glaucoma and ocular hypertension. *Curr Med Res Opin* 2007; **23:** 2971–83.

Adverse Effects and Precautions

Local ocular adverse effects may occur with dorzolamide eye drops and include conjunctivitis, keratitis, burning or stinging, eyelid inflammation or irritation, and blurred vision. Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery. There is also an increased potential for developing corneal oedema in those with low endothelial cell counts. Hence, dorzolamide eye drops should be used with caution in these patient groups. Dorzolamide may be absorbed systemically, resulting in adverse effects and precautions similar to those of acetazolamide (see p. 2002.1). Other adverse effects reported are headache, bitter taste, epistaxis, fatigue, and nausea.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dorzolamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Systemic absorption may occur after topical application of dorzolamide to the eye and there is a theoretical possibility of interactions similar to those reported with acetazolamide (see p. 2002.3).

Pharmacokinetics

Systemic absorption occurs after topical application of dorzolamide to the eye. It accumulates in red blood cells during chronic dosing due to binding to carbonic anhydrase and is about 33% bound to plasma proteins. Dorzolamide forms a single *N*-desethyl metabolite that is less active and also accumulates in red blood cells where it binds mainly to the less active isoenzyme of carbonic anhydrase. Although dorzolamide is mainly excreted unchanged in the urine, its metabolite is also excreted in the urine.

References.

1. Martens-Lobenhoffer J, Banditt P. Clinical pharmacokinetics of dorzolamide. *Clin Pharmacokinet* 2002; **41:** 197–205.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dorlamida; Trusopt; ***Austral.***: Trusopt; ***Austria***: Trusopt; ***Belg.***: Trusopt; ***Braz.***: Glalfital; Ocupress; Trusopt; ***Canad.***: Trusopt; ***Chile***: Glaucotensil; Trusopt; ***Cz.***: Oftidor; Trusopt; ***Denm.***: Trusopt; ***Fin.***: Trusopt; ***Fr.***: Trusopt; ***Ger.***: Dorzo-Vision; Trusopt; ***Gr.***: Dorolad; Optodrop; Trusopt; ***Hong Kong***: Trusopt; ***Hung.***: Trusopt; ***India***: Dortas; Dorzox; Ocudor; ***Irl.***: Trusopt; ***Israel***: Trusopt; ***Ital.***: Trusopt; ***Malaysia***: Trusopt; ***Mex.***: Piobaj; Trusopt; ***Neth.***: Dorzostill; Trusopt; ***Norw.***: Trusopt; ***NZ***: Trusopt; ***Philipp.***: Trusopt; ***Pol.***: Dorzostill; Rozalin; Trusopt; ***Port.***: Proglau; Trusopt; ***Rus.***: Trusopt (Трусопт); ***S.Afr.***: Trusopt; ***Singapore***: Trusopt; ***Spain***: Trusopt; ***Swed.***: Trusopt; ***Switz.***: Dorzo-Vision; Trusopt; ***Thai.***: Trusopt; ***Turk.***: Trusopt; ***UK***: Trusopt; ***Ukr.***: Dorsamed (Дорзамед); ***USA***: Trusopt; ***Venez.***: Dorzol; Glaucotensil D; Trusopt.

Multi-ingredient Preparations. ***Arg.***: Aliviapres; Cosopt; Dor-Timolol; Dorlamida T; Glaucotensil TD; Timed D; Zopirol DM; ***Austral.***: Cosopt; ***Austria***: Cosopt; ***Belg.***: Cosopt; ***Braz.***: Cosopt; Glaucoftal; ***Canad.***: Cosopt; ***Chile***: Cosopt; Dorsof T; Dorzine; Glaucotensil T; Glausolets Plus; Tiof Plus; ***Cz.***: Cosopt; ***Denm.***: Cosopt; Timosopt†; ***Fin.***: Cosopt; Glaukostad; ***Fr.***: Cosopt; ***Ger.***: Cosopt; Dorzo Plus T; Dorzolamid comp; ***Gr.***: Cosopt; Dorzoptic Plus; Dorzotim; Dotiz; Optodrop-Co; Tesol; ***Hong Kong***: Cosopt; ***Hung.***: Cosopt; Glamzolid; ***India***: Misopt; Ocudor-T; ***Irl.***: Clar-opt; Cosopt; Dortim; ***Israel***: Cosopt; ***Ital.***: Cosopt; ***Malaysia***: Cosopt; ***Mex.***: Anhigot; Cosopt; Krytantek; Trovost; ***Neth.***: Cosopt; Dortim; ***Norw.***: Cosopt; ***NZ***: Cosopt; ***Philipp.***: Cosopt; ***Pol.***: Cosopt; Dotiteva; Rozacom; ***Port.***: Cosopt; Timosopt†; ***Rus.***: Cosopt (Косопт); Dorzopt (Дорзопт); ***S.Afr.***: Cosopt; ***Singapore***: Cosopt; ***Spain***: Cosopt; ***Swed.***: Cosopt; Costad; ***Switz.***: Co-Dorzolamid; Cosopt; ***Thai.***: Cosopt; ***Turk.***: Cosopt; ***UK***: Cosopt; ***USA***: Cosopt; ***Venez.***: Cosopt; Dobet; Glaucotensil T.

Pharmacopoeial Preparations

BP 2014: Dorzolamide and Timolol Eye Drops; Dorzolamide Eye Drops;

USP 36: Dorzolamide Hydrochloride Ophthalmic Solution.

Dyflos *(BAN)*

DFP; Diflos; Difluorophate; Di-isopropil fluorofosfato; Di-isopropyl Fluorophosphate; Di-isopropylfluorophosphonate; Fluostigmina; Fluostigmine; Isoflurofato; Isoflurophate.

Di-isopropyl phosphorofluoridate.

$C_6H_{14}FO_3P$=184.1

CAS — 55-91-4.

ATC — S01EB07.

ATC Vet — QS01EB07.

UNII — 12UHW9R67N.

Pharmacopoeias. In *US.*

USP 36: (Isoflurophate). A clear, colourless, or faintly yellow liquid. Specific gravity about 1.05. Sparingly soluble in water; soluble in alcohol and in vegetable oils. It is decomposed by moisture with the evolution of hydrogen fluoride. Store at 8 degrees to 15 degrees in sealed containers.

Profile

Dyflos is an irreversible inhibitor of cholinesterases with actions similar to those of ecothiopate iodide (below). It has been used mainly in the treatment of open-angle glaucoma, particularly in aphakic patients and when other drugs have proved inadequate; it has usually been given as a 0.025% ophthalmic ointment. It was also used in the diagnosis and management of accommodative convergent strabismus.

Handling. The vapour of dyflos is very toxic. The eyes, nose, and mouth should be protected when handling dyflos, and contact with the skin should be avoided. Dyflos can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Preparations

Pharmacopoeial Preparations

USP 36: Isoflurophate Ophthalmic Ointment.

Ecothiopate Iodide *(BAN, rINN)*

Echothiophate Iodide; Ecostigmine Iodide; Écothiopate, Iodure d'; Ecothiopati Iodidum; Ecotiopato, ioduro de; Ekotiopaattijodidi; Ekotiopatjodid; Ioduro de ecotiopato; MI-217; Экотиопата Йодид.

(2-Diethoxyphosphinylthioethyl)trimethylammonium iodide.

$C_9H_{23}INO_3PS$=383.2

CAS — 6736-03-4 (ecothiopate); 513-10-0 (ecothiopate iodide).

ATC — S01EB03.

ATC Vet — QS01EB03.

UNII — BA9QH3P00T.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Echothiophate Iodide). A white, crystalline, hygroscopic solid having a slight mercaptan-like odour. Soluble 1 in 1 of water, 1 in 25 of dehydrated alcohol, and 1 in 3 of methyl alcohol; practically insoluble in other organic solvents. Its solutions in water have a pH of about 4. Store in airtight containers preferably at a temperature below 0 degrees. Protect from light.

Uses and Administration

Ecothiopate is an irreversible inhibitor of cholinesterase; its actions are similar to those of neostigmine (p. 687.2) but much more prolonged. Its miotic action begins within 1 hour of its application and may persist for 1 to 4 weeks; it causes a reduction in intra-ocular pressure, which is maximal after 24 hours and may persist for days or weeks.

Ecothiopate iodide is used mainly in the treatment of open-angle glaucoma (p. 1999.1), particularly in aphakic patients and when other drugs have proved inadequate. It is usually given as drops of a 0.125% ophthalmic solution. Licensed product information states that 2 daily doses are preferred to allow for diurnal variations in intra-ocular pressure, although it has also been given once daily or on alternate days. It is advisable to give the single dose or one of the 2 daily doses at bedtime.

Ecothiopate iodide eye drops are also used in the diagnosis and management of accommodative convergent strabismus.

Adverse Effects

As for Neostigmine, p. 688.2. For adverse effects of miotics, see also Pilocarpine, p. 2011.2.

Ecothiopate is an irreversible cholinesterase inhibitor; its action, and hence its adverse effects, may be prolonged.

Plasma and erythrocyte cholinesterases may be reduced by treatment with eye drops of ecothiopate or other long-acting anticholinesterases, and systemic toxicity occurs more frequently than with shorter-acting miotics. Acute iritis, retinal detachment, or precipitation of acute glaucoma may occasionally occur, and iris cysts (especially in children) or lens opacities may develop on prolonged treatment.

Treatment of Adverse Effects

To treat the systemic effects of poisoning, atropine sulfate may be given parenterally with pralidoxime chloride as for intoxication with organophosphorus insecticides (see p. 1571.2); subconjunctival injection of pralidoxime has been used to reverse severe ocular adverse effects. Supportive treatment, including assisted ventilation, should be given as necessary.

To prevent or reduce development of iris cysts in patients receiving ecothiopate eye drops, phenylephrine eye drops may be given simultaneously.

Precautions

As for Neostigmine, p. 688.3. For precautions of miotics, see also under Pilocarpine, p. 2011.2. In general, as with other long-acting anticholinesterases, ecothiopate should be used only where therapy with other drugs has proved ineffective. Ecothiopate iodide should not be used in patients with iodine hypersensitivity.

Interactions

As for Neostigmine, p. 688.3. The possibility of an interaction remains for a considerable time after stopping long-acting anticholinesterases such as ecothiopate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Phospholine Iodide.

Pharmacopoeial Preparations

USP 36: Echothiophate Iodide for Ophthalmic Solution.

Homatropine *(BAN)*

Homatropiini; Homatropin; Homatropina; Homatropinum.

(1*R*,3*r*,5*S*)-Tropan-3-yl (*RS*)-mandelate.

$C_{16}H_{21}NO_3$=275.3

CAS — 87-00-3.

ATC — S01FA05.

ATC Vet — QS01FA05.

UNII — 8QS6WCL55Z.

Homatropine Hydrobromide *(BANM)*

Homatr. Hydrobrom.; Homatropiinihydrobromidi; Homatropina, hidrobromuro de; Homatropine, bromhydrate d'; Homatropin-hidrobromid; Homatropin-hydrobromid; Homatropinhydrobromid; Homatropini hydrobromidum; Homatropinium Bromide; Homatropino hidrobromidas; Homatropinum Bromatum; Homatropiny bromowodorek; Omatropina Bromidrato; Oxtolyltropine Hydrobromide; Tropyl Mandelate Hydrobromide.

$C_{16}H_{21}NO_3$,HBr=356.3

CAS — 51-56-9.

ATC — S01FA05.

ATC Vet — QS01FA05.

UNII — BEW7469QZ0.

NOTE. HOM is a code approved by the BP 2014 for use on single unit doses of eye drops containing homatropine hydrobromide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Homatropine Hydrobromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 36: (Homatropine Hydrobromide). White crystals or a white crystalline powder. Soluble 1 in 6 of water, 1 in 40 of alcohol, and 1 in 420 of chloroform; insoluble in ether. pH of a 2% solution in water is between 5.7 and 7.0. Store in airtight containers. Protect from light.

Homatropine Methylbromide *(BANM, rINN)*

Homatropiinimetyylibromidi; Homatropina, metilbromuro de; Homatropine Methobromide; Homatropine, Méthylbromure d'; Homatropini Methylbromidum; Homatropin-methylbromid; Homatropin-methylbromid; Homatropin-metilbromid; Homatropinmetylbromid; Homatropino metilbromidas; Methylhomatropinium Bromatum; Methylhomatropinium Bromide; Metilbromuro de homatropina; Гоматропина Метилбромид.

(1*R*,3*r*,5*S*)-3-[(±)-Mandeloyloxy]-8-methyltropanium bromide.

$C_{16}H_{21}NO_3$,CH_3Br=370.3

CAS — 80-49-9.

UNII — 68JRS2HC1C.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Homatropine Methylbromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.5 to 6.5. Protect from light.

USP 36: (Homatropine Methylbromide). A white, odourless, powder that slowly darkens on exposure to light. Very soluble in water; freely soluble in alcohol and in acetone containing about 20% of water; practically insoluble in acetone and in ether. pH of a 5% solution in water is between 4.5 and 6.5. Store in airtight containers. Protect from light.

Uses and Administration

Homatropine is a tertiary amine antimuscarinic with effects similar to those of atropine (p. 1310.3). It is used as the hydrobromide, also a tertiary amine, to produce mydriasis and cycloplegia (p. 2000.2); its actions are more rapid and of shorter duration than those of atropine, but it is less potent and has a relatively weak cycloplegic effect. In general, onset of action is between 30 and 60 minutes, and recovery within 1 to 3 days. Homatropine hydrobromide is generally used as a 1, 2, or 5% ophthalmic solution. For the determination of refraction, instillation may be repeated if necessary 5 to 10 minutes later. In the treatment of uveitis (p. 1615.1), the eye drops should be instilled two or three times daily, or up to every 3 to 4 hours if required.

For details of doses in children, see below.

Homatropine has also been used as the quaternary ammonium methobromide derivative in the treatment of gastrointestinal spasm and as an adjunct in peptic ulcer disease; the methobromide has also been included in preparations used for the treatment of coughs.

Administration in children. The *BNFC* suggests that eye drops containing 0.5% homatropine hydrobromide may be instilled once daily or on alternate days, adjusted according to response, for uveitis in children aged 3 months to 2 years; older children may use 0.5 or 1% eye drops instilled twice daily, adjusted according to response.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Ophthalmic use. Antimuscarinic toxicity (including ataxia, restlessness, excitement, hallucinations) has been reported in children[1] and the elderly[2,3] given homatropine eye drops.

1. Hoefnagel D. Toxic effects of atropine and homatropine eyedrops in children. *N Engl J Med* 1961; **264:** 168–71.
2. Reid D, Fulton JD. Tachycardia precipitated by topical homatropine. *BMJ* 1989; **299:** 795–6.
3. Tune LE, *et al.* Anticholinergic delirium caused by topical homatropine ophthalmologic solution: confirmation by anticholinergic radioreceptor assay in two cases. *J Neuropsychiatr Clin Neurosci* 1992; **4:** 195–7.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antiespasmodico; Dallapasmo; Espasmotropin; Paratropina; ***Braz.***: Espasmo Flatol; Novatropina; ***Gr.***: Nopar; ***India***: Homarin; Homide; ***Mex.***: Homogrin; Infafren Simple†; Pasmolit†; ***Philipp.***: Lesopen; ***Singapore***: Hemasol; ***Spain***: Homatrop†; ***Venez.***: Litropina.

Multi-ingredient Preparations. ***Arg.***: Antispasmina; Asestor; Bellatotal; Bibol Leloup; Carbon Tabs; Colistop; Dimaval; Espasmo Ibuprofeno; Espasmofin; Factor AG Antiespasmodico; Hepatodirectol; Ibufem; Ibupirac Fem; Opoenterol; Paratropina Antigas; Paratropina Compuesta; Sumal; Teprix Fem; Zimerol; ***Braz.***: Espasmo Dimetiliv; Espasmo Luftal; Flagass Baby; Migrane; Sedalene; Sedalin†; Spasmotropin; Tropinal; ***Chile***: Codelasa; ***Gr.***: Colik; ***Hung.***: Neo-Bilagit; Troparinum; ***Mex.***: Bontal; Coralzul; Dialgin†; Facetin-D; Neopecsul; Neoxil; Threchop†; Yodozona; ***Philipp.***: Creamalin HM; ***Thai.***: Diaropect; Polyenzyme-I†; ***USA***: Hycodan†; Hydromet; Hydropane; Tussigon.

Pharmacopoeial Preparations

BP 2014: Homatropine Eye Drops;
USP 36: Homatropine Hydrobromide Ophthalmic Solution; Homatropine Methylbromide Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets.

Latanoprost *(BAN, USAN, rINN)*

Latanoprosti; Latanoprostum; PhXA-41; XA-41; Латанопрост.

Isopropyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl}-5-heptenoate.

$C_{26}H_{40}O_5$=432.6

CAS — 130209-82-4.

ATC — S01EE01.

ATC Vet — QS01EE01.

UNII — 6Z5B6HVF6O.

Pharmacopoeias. In *US.*

USP 36: (Latanoprost). A colourless to slightly yellow oil. Practically insoluble in water; freely soluble in acetone, in alcohol, in ethyl acetate, in isopropyl alcohol, in methyl alcohol, and in octanol; very soluble in acetonitrile. Store at a temperature of -25 degrees to 8 degrees. Protect from light.

Uses and Administration

Latanoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) that is used to reduce intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension (p. 1999.1). Reduction of intra-ocular pressure starts about 3 to 4 hours after instillation and is maximal after 8 to 12 hours; pressure reduction lasts for at least 24 hours. A 0.005% ophthalmic solution is instilled once daily, preferably in the evening.

References.

1. Patel SS, Spencer CM. Latanoprost: a review of its pharmacological properties, clinical efficacy and tolerability in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 1996; **9:** 363–78.
2. Einarson TR, *et al.* Meta-analysis of the effect of latanoprost and brimonidine on intraocular pressure in the treatment of glaucoma. *Clin Ther* 2000; **22:** 1502–15.
3. Zhang WY, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001; **85:** 983–90.
4. Feldman RM. An evaluation of the fixed-combination of latanoprost and timolol for use in open-angle glaucoma and ocular hypertension. *Expert Opin Pharmacother* 2004; **5:** 909–21.
5. Bayer A, *et al.* Clinical predictors of latanoprost treatment effect. *J Glaucoma* 2005; **14:** 260–3.
6. Nagar M, *et al.* A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. *Br J Ophthalmol* 2005; **89:** 1413–17.
7. Diestelhorst M, Larsson LI. European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. *Ophthalmology* 2006; **113:** 70–6.
8. Fung AT, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; **91:** 62–8.
9. Varma R, *et al.* Using diurnal intraocular pressure fluctuation to assess the efficacy of fixed-combination latanoprost/timolol versus latanoprost or timolol monotherapy. *Br J Ophthalmol* 2010; **94:** 80–4.

Adverse Effects and Precautions

Latanoprost eye drops may produce a gradual increase in the amount of brown pigment in the iris, due to increased melanin content of melanocytes. This change in eye colour is most evident in patients with mixed colour irises, and may be permanent in some patients. The onset of iris pigmentation is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. Darkening, thickening, and lengthening of eyelashes may occur and are reversible upon stopping treatment. Darkening of the palpebral skin has been reported rarely. Ocular irritation, conjunctival hyperaemia, transient punctate epithelial erosions and eyelid oedema may occur; there have also been rare reports of iritis and/or uveitis, and macular oedema. Systemic effects may also occur, see below for further details. Dizziness, headache, arthralgia, and myalgia have also been reported.

Effects on the eyes. Latanoprost has been associated with various adverse effects on the eyes, including case reports of cystoid macular oedema[1] and bilateral optic disc oedema.[2] Licensed product information states that reports of macular oedema have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with risk factors for cystoid macular oedema such as those with diabetic retinopathy or retinal vein occlusion.

Herpes simplex dendritic keratitis developed in 2 patients during latanoprost therapy.[3] The author suggested that the biochemical changes in the cornea caused by latanoprost may predispose to herpes keratitis.

1. Wardrop DRA, Wishart PK. Latanoprost and cystoid macular oedema in a pseudophake. *Br J Ophthalmol* 1998; **82:** 843–4.
2. Stewart O, *et al.* Bilateral optic disc oedema associated with latanoprost. *Br J Ophthalmol* 1999; **83:** 1092–3.
3. Ekatomatis P. Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma. *Br J Ophthalmol* 2001; **85:** 1008–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies latanoprost as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Systemic effects. The use of latanoprost eye drops has been associated with systemic adverse reactions. In a case report[1] of 2 patients with latanoprost-associated hypertension the authors mentioned that other events including peripheral and facial oedema, dyspnoea, exacerbation of asthma, tachycardia, and chest pain or angina pectoris had been reported. Another case report[2] also referred to exacerbation of angina. Although a study[3] involving 24 stable asthmatics found that latanoprost eye drops had no effect on pulmonary function or asthma symptoms, UK licensed product information recommends caution in patients with asthma.

1. Peak AS, Sutton BM. Systemic adverse effects associated with topically applied latanoprost. *Ann Pharmacother* 1998; **32:** 504–5.
2. Mitra M, *et al.* Exacerbation of angina associated with latanoprost. *BMJ* 2001; **323:** 783.
3. Hedner J, *et al.* Latanoprost and respiratory function in asthmatic patients: randomized, double-masked, placebo-controlled crossover evaluation. *Arch Ophthalmol* 1999; **117:** 1305–9.

Interactions

Paradoxical increases in intra-ocular pressure have been reported after the concomitant ophthalmic use of 2 prostaglandin analogues. UK licensed product information states that the use of 2 or more prostaglandin analogues or derivatives is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Glaucogesic; Glaucostat; Klonaprost; Latanoflax†; Louten; Ocuprost; Oftal-Mix; Paraiop†; Tanamof; Xalatan; ***Austral.***: Xalatan; ***Austria***: Xalatan; ***Belg.***: Xalatan; ***Braz.***: Drenatan; Xalatan; ***Canad.***: Xalatan; ***Chile***: Gaap Ofteno; Gaax; Latof; Louten; Para Iop; Xalatan; ***China***: Latoprost (拉坦前列素); Xalatan (适利达); ***Cz.***: Arulatan; Glaucotens; Latalux; Solusin; Unilat; Xalatan; Xaloptic; ***Denm.***: Xalatan; ***Fin.***: Monoprost; Oftastad; Xalatan; ***Fr.***: Xalatan; ***Ger.***: Xalatan; ***Gr.***: Joxar; Latandrops; Lataneau; Lataz; X-Iop; Xalaprost; Xalatan; ***Hong Kong***: Xalatan; ***Hung.***: Lanotan; Latapres; Xalatan; ***India***: 9PM; Ioprost; Ioptame; Latochek; Latodrops; Latoprost; ***Indon.***: Xalatan; ***Irl.***: Latacris; Latop; Proxal; Xalatan; Zanopro Plus; Zanopro; ***Israel***: Glautan; Xalatan; ***Ital.***: Xalatan; ***Malaysia***: Xalatan; ***Mex.***: Algun; Gaap Ofteno; Kevixkeni; Latsol; Pioprost; Xalatan; ***Neth.***: Arulatan†; Exprosol; Exsolut; Eylasol; Latusol; Monoprost; Optopress; Prolasol†; Soleye†; Sollat; Solusin; Xalatan; ***Norw.***: Glauprost; Xalatan; ***NZ***: Eyeprost; Hysite; Xalatan†; ***Philipp.***: Xalatan; ***Pol.***: Ocumer; Xalatan; Xaloptic; ***Port.***: Xalatan; ***Rus.***: Glauprost (Глаупрост); Xalatan (Ксалатан); ***S.Afr.***: Ocuprost; Xalatan; ***Singapore***: Xalatan; ***Spain***: Arulatan; Tonlit; Xalatan; Xalavista; Xelor; ***Swed.***: Xalatan; ***Switz.***: Latano-Vision; Latanomed; Monoprost; Xalatan; Xalos; ***Thai.***: Xalatan; ***Turk.***: Oftagen; Xalatan; ***UK***: Monopost; Xalatan; ***Ukr.***: Lanotan (Ланотан); Latanox (Латанокс); Xalatan (Ксалатан); ***USA***: Xalatan; ***Venez.***: Gaap Ofteno; Laprost; Latanopress; Xalatan.

Multi-ingredient Preparations. ***Arg.***: Glaucostat T; Latimodorf; Louten T; Ocuprostim; Xalacom; ***Austral.***: Xalacom; ***Austria***: Xalacom; ***Belg.***: Xalacom; ***Braz.***: Xalacom; ***Canad.***: Xalacom; ***Chile***: Gaax T; Latof-T; Xalacom; ***China***: Xalacom (适利加); ***Cz.***: Xalacom; ***Denm.***: Alatopran; Latanostad Comp; Latiotim; Xalacom†; Xalcom; ***Fin.***: Latiotim; Oftastad Comp; Xalcom; ***Fr.***: Xalacom; ***Ger.***: Xalacom; ***Gr.***: Tinoprost; Xalacom; ***Hong Kong***: Xalacom; ***Hung.***: Xalacom; ***India***: Laprost Plus; Latim; Latochek-T; Latocom; ***Indon.***: Xalacom; ***Irl.***: Codalux; Glaucotima; Lataneau Plus; Timlatan; Xalacom; Xaloptic Combi; ***Israel***: Xalacom; ***Ital.***: Tavu; Xalacom†; ***Malaysia***: Xalacom; ***Mex.***: Xalacom; ***Neth.***: Latim-POS; Xalacom; ***Norw.***: Latiotim; Xalcom; ***NZ***: Xalacom; ***Philipp.***: Xalacom; ***Pol.***: Xalacom; ***Port.***: Tavu; Xalacom; ***Rus.***: Xalacom (Ксалаком); ***S.Afr.***: Xalacom; ***Singapore***: Xalacom; ***Spain***: Latimvista; Xalacom; ***Swed.***: Latiotim; Xalcom; ***Switz.***: Co-Latanoprost; Xalacom; ***Thai.***: Xalacom; ***Turk.***: Xalacom; ***UK***: Xalacom; ***Ukr.***: Lanotan T (Ланотан Т); Xalacom (Ксалаком); ***Venez.***: Xalacom.

Levobunolol Hydrochloride

(BANM, USAN, rINNM) ⊗

(-)-Bunolol Hydrochloride; *l*-Bunolol Hydrochloride; Hidrocloruro de levobunolol; Lévobunolol, Chlorhydrate de; Levobunolol, hidrocloruro de; Levobunolol Hidroklorür; Levobunololhydroklorid; Levobunololi Hydrochloridum; Levobunololihydrokloridi; W-7000A; Левобунолола Гидрохлорид.

(-)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride.

$C_{17}H_{25}NO_3$,HCl=327.8

CAS — 47141-42-4 (levobunolol); 27912-14-7 (levobunolol hydrochloride).

ATC — S01ED03.

ATC Vet — QS01ED03.

UNII — O90S49LDHH.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Levobunolol Hydrochloride). A white or pinkish-white crystalline powder. Freely soluble in water; sparingly

soluble in alcohol. A 5% solution in water has a pH of between 4.5 and 6.5. Protect from light.

USP 36: (Levobunolol Hydrochloride). A white odourless crystalline powder. Soluble in water and in methyl alcohol; slightly soluble in alcohol and in chloroform. A 5% solution in water has a pH between 4.5 and 6.5.

Uses and Administration

Levobunolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Levobunolol is used as the hydrochloride to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension (p. 1999.1). It begins to act 1 hour after instillation with maximal effect seen between 2 and 6 hours; the effect may be maintained for up to 24 hours. Levobunolol hydrochloride is usually used as a 0.5% ophthalmic solution instilled once or twice daily; alternatively a 0.25% solution may be instilled twice daily.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Some systemic absorption is reported to occur after topical application to the eye. After oral doses levobunolol is rapidly and almost completely absorbed from the gastrointestinal tract. It is extensively metabolised in the liver; the principal metabolite, dihydrolevobunolol, is reported to possess beta-blocking activity. The metabolites and some unchanged drug are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Betagan; Levunolol; ***Austral.***: Betagan†; ***Austria***: Vistagan; ***Belg.***: Betagan; ***Braz.***: B-Tablock; Betagan; ***Canad.***: Betagan; ***Chile***: Betagen; ***China***: Betagan (贝他根); ***Cz.***: Vistagan; ***Fr.***: Betagan; ***Ger.***: Vistagan; ***Gr.***: Bunolol; Pentila; Vistagan; ***Hong Kong***: Betagan; ***Hung.***: Vistagan; ***India***: Betagan; ***Irl.***: Betagan; ***Ital.***: Vistagan; ***Malaysia***: Betagan; ***Mex.***: Betagan; ***Neth.***: Betagan; ***NZ***: Betagan; ***Port.***: Betagan; ***S.Afr.***: Betagan; ***Singapore***: Betagan; ***Spain***: Betagan; ***Switz.***: Vistagan; ***Thai.***: Betagan; ***Turk.***: Betagan; ***UK***: Betagan; ***USA***: Ak-Beta; Betagan†; ***Venez.***: Vistagan.

Multi-ingredient Preparations. ***Canad.***: Probeta†.

Pharmacopoeial Preparations
BP 2014: Levobunolol Eye Drops;
USP 36: Levobunolol Hydrochloride Ophthalmic Solution.

Methazolamide *(BAN, rINN)* ⊗

Metazolamida; Méthazolamide; Methazolamidum; Метазоламид.

N-(4-Methyl-2-sulphamoyl-Δ^2-1,3,4-thiadiazolin-5-ylidene) acetamide.

$C_5H_8N_4O_3S_2$=236.3

CAS — 554-57-4.

ATC — S01EC05.

ATC Vet — QS01EC05.

UNII — W733B0S9SD.

Pharmacopoeias. In *US.*

USP 36: (Methazolamide). A white or faintly yellow crystalline powder with a slight odour. Very slightly soluble in water and in alcohol; slightly soluble in acetone; soluble in dimethylformamide. Protect from light.

Uses and Administration

Methazolamide is an inhibitor of carbonic anhydrase with actions similar to those of acetazolamide (p. 2001.1). It is used in the treatment of glaucoma (p. 1999.1) in oral doses of 50 to 100 mg two or three times daily. Its action is less prompt but of longer duration than that of acetazolamide, lasting for 10 to 18 hours.

The diuretic activity of methazolamide is less pronounced than that of acetazolamide.

Adverse Effects and Precautions

As for Acetazolamide, p. 2002.1.

Hypersensitivity. Cholestatic hepatitis with jaundice, rash, and subsequent pure red cell aplasia was associated with methazolamide in a patient.[1] Drug-induced hypersensitivity was suspected as the cause of the reaction.

1. Krivoy N, *et al.* Methazolamide-induced hepatitis and pure RBC aplasia. *Arch Intern Med* 1981; **141:** 1229–30.

Pharmacokinetics

Methazolamide is absorbed from the gastrointestinal tract more slowly than acetazolamide. It has been reported not to be extensively bound to plasma proteins, and to have a half-life of about 14 hours. About 15 to 30% of the dose is excreted in the urine; the fate of the remainder is unknown.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ni Mu Ke Si (尼目克司); ***Thai.***: Neptazane; ***USA***: Neptazane.

Pharmacopoeial Preparations
USP 36: Methazolamide Tablets.

Metipranolol *(BAN, USAN, rINN)* ⊗

BMOI-004; Methypranolol; Métipranolol; Metipranololum; VUAB-6453 (SPOFA); VUFB-6453; Метипранолол.

1-(4-Acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol; 4-(2-Hydroxy-3-isopropylaminopropoxy)-2,3,6-trimethylphenyl acetate.

$C_{17}H_{27}NO_4$=309.4

CAS — 22664-55-7.

ATC — S01ED04.

ATC Vet — QS01ED04.

UNII — X39AL81KEB.

NOTE. MPR is a code approved by the BP 2014 for use on single unit doses of eye drops containing metipranolol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Br.*

BP 2014: (Metipranolol). A white crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; dissolves in dilute mineral acids. The filtrate of a 2.5% suspension in water has a pH of 9.0 to 10.0. Protect from light.

Uses and Administration

Metipranolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to be largely lacking in intrinsic sympathomimetic activity and membrane-stabilising properties.

Metipranolol is used to reduce raised intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p. 1999.1). Eye drops usually containing metipranolol 0.1 or 0.3% are used twice daily.

Metipranolol has also been given orally in the management of cardiovascular disorders.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Conjunctivitis, conjunctival leucoplakia, transient stinging, as well as other ocular adverse effects have been reported with metipranolol eye drops. Granulomatous anterior uveitis has been reported rarely; a high incidence reported in the UK may have been associated with changes induced by radiation sterilisation of metipranolol eye drops in their final container, but this preparation is no longer available.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Beta-Ophtiole; ***Belg.***: Beta-Ophtiole; ***Braz.***: Beta-Ophtiole; ***Cz.***: Trimepranol; ***Ger.***: Betamann; ***Ital.***: Turoptin; ***Mon.***: Betanol; ***Neth.***: Beta-Ophtiole; ***Philipp.***: Beta-Ophtiole; ***Pol.***: Betamann; ***Port.***: Beta-Ophtiole†; ***S.Afr.***: Beta-Ophtiole; ***Singapore***: Beta-Ophtiole; ***Turk.***: Turoptin; ***USA***: OptiPranolol.

Multi-ingredient Preparations. ***Austria***: Betacarpin; ***Belg.***: Normoglaucon†; ***China***: Normoglaucon (啫高康); ***Ger.***: Normoglaucon; ***Gr.***: Beta Opthiole; Ripix; ***Neth.***: Normoglaucon†; ***Pol.***: Normoglaucon; ***Port.***: Normoglaucon†.

Pharmacopoeial Preparations
BP 2014: Metipranolol Eye Drops.

Nipradilol *(rINN)* ⊗

K-351; Nipradilolum; Nipradolol; Нипрадилол.

8-[2-Hydroxy-3-(isopropylamino)propoxy]-3-chromanol 3-nitrate.

$C_{15}H_{22}N_2O_6$=326.3

CAS — 81486-22-8.

UNII — FVM336I71Y.

Profile

Nipradilol is a non-cardioselective beta blocker (p. 1316.3). It is also reported to have direct vasodilating activity. It is used in the management of glaucoma and ocular hypertension (p. 1999.1); eye drops containing nipradilol 0.05% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Hypadil.

Physostigmine *(BAN)*

Eserina; Eserine; Fisostigmina; Fysostigmiini; Fysostigmin; Physostigminum.

(3a*S*,8a*R*)-1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl methylcarbamate.

$C_{15}H_{21}N_3O_2$=275.4

CAS — 57-47-6.

ATC — S01EB05; V03AB19.

ATC Vet — QA03AX90; QA03FA90; QS01EB05; QV03AB19.

UNII — 9U1VM840SP.

Description. An alkaloid obtained from the calabar bean (ordeal bean; chopnut), the seed of *Physostigma venenosum* (Leguminosae).

Pharmacopoeias. In *US.*

USP 36: (Physostigmine). An alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum* (Leguminosae). It is a white, odourless, microcrystalline powder which acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals. M.p. not lower than 103 degrees. Slightly soluble in water; freely soluble in alcohol; very soluble in chloroform and in dichloromethane; soluble in fixed oils and in benzene. Store in airtight containers. Protect from light.

Physostigmine Salicylate *(BANM)*

Eserine Salicylate; Ésérine, salicylate d'; Eserini Salicylas; Ezerino salicilatas; Fisostigmina, salicilato de; Fizostigmino salicilatas; Fizostygminy salicylan; Fizosztigmin-szalicilát; Fysostigmiinisalisylaatti; Fysostigminsalicylat; Fysostigmin-salicylát; Physostig. Sal.; Physostigmine Monosalicylate; Physostigmini Salicylas; Physostigminsalicylat.

$C_{15}H_{21}N_3O_2$,$C_7H_6O_3$=413.5

CAS — 57-64-7.

ATC — S01EB05; V03AB19.

ATC Vet — QS01EB05; QV03AB19.

UNII — 2046ZRO9VU.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Physostigmine Salicylate). Colourless or almost colourless crystals. It becomes red on exposure to air and light; the colour develops more quickly in the presence of moisture. Sparingly soluble in water; soluble in alcohol. A 0.9% solution in water has a pH of 5.1 to 5.9. Store in airtight containers. Protect from light. Aqueous solutions are unstable.

USP 36: (Physostigmine Salicylate). White, shining, odourless, crystals or white powder. It acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 75 of water, 1 in 16 of alcohol, 1 in 6 of chloroform, and 1 in 250 of ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Stability. See p. 2010.1.

Physostigmine Sulfate *(BANM)*

Ésérine, sulfate d'; Eserine Sulphate; Eserini Sulfas; Ezerino sulfatas; Fisostigmina, sulfato de; Fizostigmino sulfatas; Fizosztigmin-szulfát; Fysostigmiinisulfaatti; Fysostigminsulfat; Fysostigmin-sulfát; Physostig. Sulph.; Physostigmine Sulphate; Physostigmini Sulfas; Physostigminsulfat; Sulfato de eserina.

$(C_{15}H_{21}N_3O_2)_2,H_2SO_4$=648.8

CAS — 64-47-1.

ATC — S01EB05; V03AB19.

ATC Vet — QS01EB05; QV03AB19.
UNII — G63V2J2N71.

Pharmacopoeias. In *US.*

USP 36: (Physostigmine Sulfate). A white, odourless, microcrystalline powder. It is deliquescent in moist air, and acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 4 of water, 1 in 0.4 of alcohol, and 1 in 1200 of ether. Store in airtight containers. Protect from light.

Stability. In aqueous solutions physostigmine is hydrolysed to eseroline and subsequently oxidised to the red compound rubreserine and other coloured products. Solutions for injection or ophthalmic use should not be used if more than slightly discoloured.

Uses and Administration

Physostigmine is a reversible tertiary amine inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2). Physostigmine has been used, alone or more usually with other miotics such as pilocarpine, to decrease intra-ocular pressure in glaucoma; it has been given as eye drops containing the salicylate or as an ophthalmic ointment containing the sulfate. Physostigmine is a more potent miotic than pilocarpine but is rarely tolerated for prolonged periods.

Physostigmine crosses the blood-brain barrier and has been used parenterally to reverse the central as well as the peripheral effects of agents with antimuscarinic actions after overdosage but such treatment is not usually recommended.

Antimuscarinic poisoning. As physostigmine penetrates the blood-brain barrier it has been used to reverse the central effects of poisoning with agents that have antimuscarinic actions including tricyclic antidepressants, antihistamines, some antiemetics, some antiparkinsonian drugs, and phenothiazines. However, reviewers agree that in general such use is inappropriate and hazardous. Physostigmine does not appear to affect the mortality rate in tricyclic antidepressant poisoning[1] and its use can lead to severe cardiac[2,3] and respiratory effects[2,3] and to convulsions.[2,4]

1. Aquilonius S-M, Hedstrand U. The use of physostigmine as an antidote in tricyclic anti-depressant intoxication. *Acta Anaesthesiol Scand* 1978; **22:** 40–5.
2. Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA* 1975; **231:** 941–3.
3. Caine ED. Anticholinergic toxicity. *N Engl J Med* 1979; **300:** 1278.
4. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.

Baclofen overdosage. For references to the use of physostigmine in the treatment of baclofen overdosage, see p. 2016.1.

Cerebellar ataxias. Double-blind controlled studies indicate that physostigmine[1,2] can produce symptomatic improvement in some patients with cerebellar ataxia including those with hereditary forms of spinocerebellar degeneration such as Friedreich's ataxia. However, another study did not show any significant improvement in patients given physostigmine for cerebellar ataxia.[3]

1. Rodriguez-Budelli MM, *et al.* Action of physostigmine on inherited ataxias. *Adv Neurol* 1978; **21:** 195–202.
2. Aschoff JC, *et al.* Physostigmin in der Behandlung von Kleinhirnataxien. *Nervenarzt* 1996; **67:** 311–18.
3. Wessel K, *et al.* Double-blind crossover study with physostigmine in patients with degenerative cerebellar diseases. *Arch Neurol* 1997; **54:** 397–400.

Dementia. Physostigmine has been studied in the symptomatic management of Alzheimer's disease (see Dementia, p. 388.1). However, a systematic review concluded that the evidence of its efficacy was limited and the benefits shown were not convincing.[1] Small early studies with oral physostigmine in Alzheimer's disease were inconclusive; a larger multicentre study[2] using controlled-release physostigmine found that it produced some improvement in cognitive and global function, but gastrointestinal adverse effects were common and led to a high drop-out rate.

1. Coelho Filho JM, Birks J. Physostigmine for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 17/03/06).
2. Thal LJ, *et al.* A 24-week randomized trial of controlled-release physostigmine in patients with Alzheimer's disease. *Neurology* 1999; **52:** 1146–52.

Adverse Effects, Treatment, and Precautions

Systemic effects as for Neostigmine, p. 688.2, although usually more severe. Physostigmine crosses the blood-brain barrier and may therefore produce CNS effects.

For adverse effects and precautions for topical miotics see also under Pilocarpine, p. 2011.2. Physostigmine is not well tolerated when used in the eyes for long periods and may produce follicles in the conjunctiva; hypersensitivity reactions are also common. Prolonged use of ophthalmic ointments containing physostigmine may cause depigmentation of the lid margins in dark-skinned patients.

Overdosage. Symptomatic and supportive treatment, including the use of diazepam and atropine where necessary, is generally recommended for systemic toxicity due to physostigmine. However, in an early report, the use of atropine in a patient who had taken 1 g of physostigmine had to be abandoned after it produced tachycardia and multifocal ventricular ectopic beats.[1] In a similar case of severe poisoning a slow intravenous injection of propranolol 5 mg reduced the high pulse rate and controlled pulse irregularities permitting frequent intravenous doses of atropine.[2]

1. Cumming G, *et al.* Treatment and recovery after massive overdosage of physostigmine. *Lancet* 1968; **ii:** 147–9.
2. Valero A. Treatment of severe physostigmine poisoning. *Lancet* 1968; **ii:** 459–60.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Physostigmine is readily absorbed from the gastrointestinal tract, subcutaneous tissues, and mucous membranes. It is largely destroyed in the body by hydrolysis of the ester linkage by cholinesterases; a parenteral dose is claimed to be destroyed within 2 hours. It crosses the blood-brain barrier. Little is excreted in the urine.

Small studies suggest marked interindividual differences in the absorption and metabolism of physostigmine salicylate after oral doses of up to 4 mg, perhaps because of saturable presystemic metabolism.[1-3] Oral bioavailability ranged from 5.2 to 11.7% in 3 of 5 subjects.[3]

In a study[4] of a single application of a physostigmine (base) transdermal system in 6 subjects, the mean absolute bioavailability was 36% (range 12.6 to 53.2%); the interindividual variability in absolute bioavailability was decreased by about 30% in comparison with an oral solution of physostigmine salicylate. There was continued absorption of physostigmine after removal of the transdermal system, indicating a drug reservoir in the skin.

In a study[5] of 9 patients with Alzheimer's disease, a mean elimination half-life for physostigmine of 16.4 minutes was reported with intravenous physostigmine salicylate. Cholinesterase inhibition was more prolonged than suggested by its elimination half-life.

1. Gibson M, *et al.* Physostigmine concentrations after oral doses. *Lancet* 1985; **i:** 695–6.
2. Sharpless NS, Thal LJ. Plasma physostigmine concentrations after oral administration. *Lancet* 1985; **i:** 1397–8.
3. Whelpton R, Hurst P. Bioavailability of oral physostigmine. *N Engl J Med* 1985; **313:** 1293–4.
4. Walker K, *et al.* Pharmacokinetics of physostigmine in man following a single application of a transdermal system. *Br J Clin Pharmacol* 1995; **39:** 59–63.
5. Asthana S, *et al.* Clinical pharmacokinetics of physostigmine in patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; **58:** 299–309.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Anticholium; ***Cz.***: Anticholium; ***Ger.***: Anticholium; ***Gr.***: Anticholium; ***Singapore***: Antilirium.

Multi-ingredient Preparations. ***India***: Bi-Miotic†.

Pharmacopoeial Preparations
USP 36: Physostigmine Salicylate Injection; Physostigmine Salicylate Ophthalmic Solution; Physostigmine Sulfate Ophthalmic Ointment.

Pilocarpine *(BAN)*

Pilocarpina; Pilocarpinum; Pilokarpiini; Pilokarpin.
(3*S*,4*R*)-3-Ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl) methyl]furan-2(3*H*)-one.
$C_{11}H_{16}N_2O_2$=208.3
CAS — 92-13-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.
UNII — 01MI4Q9DI3.

Description. An alkaloid obtained from the leaves of jaborandi, *Pilocarpus microphyllus* (Rutaceae) and other species of *Pilocarpus.*

Pharmacopoeias. In *US.*

USP 36: (Pilocarpine). A viscous, exceedingly hygroscopic, oily liquid or crystals. M.p. about 34 degrees. Soluble in water, in alcohol, and in chloroform; sparingly soluble in ether and in benzene; practically insoluble in petroleum spirit. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Pilocarpine Borate

Pilocarpina, borato de.
$C_{11}H_{16}N_2O_2.xBH_3O_3$
CAS — 16509-56-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

Pilocarpine Hydrochloride *(BANM)*

Pilocarp. Hydrochlor.; Pilocarpina, hidrocloruro de; Pilocarpine, chlorhydrate de; Pilocarpine Monohydrochloride; Pilocarpinhydrochlorid; Pilocarpini Chloridum; Pilocarpini hydrochloridum; Pilocarpinium Chloratum; Pilokarpiinihydrokloridi; Pilokarpin Hidroklorür; Pilokarpin-hidroklorid; Pilokarpin-hydrochlorid; Pilokarpinhydroklorid; Pilokarpino hidrochloridas; Pilokarpiny chlorowodorek.
$C_{11}H_{16}N_2O_2$,HCl=244.7
CAS — 54-71-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.
UNII — 0WW6D218XJ.

NOTE. PIL is a code approved by the BP 2014 for use on single unit doses of eye drops containing pilocarpine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Pilocarpine Hydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. M.p. about 203 degrees. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Pilocarpine Hydrochloride). Colourless, translucent, odourless, hygroscopic crystals. Soluble 1 in 0.3 of water, 1 in 3 of alcohol, and 1 in 360 of chloroform; insoluble in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. Pilocarpine hydrochloride oral solution, prepared from powder or eye drops and buffered at pH 5.5, was found[1] to be stable for 60 days at 25 degrees and for 90 days at 4 degrees.

1. Fawcett JP, *et al.* Formulation and stability of pilocarpine oral solution. *Int J Pharm Pract* 1994; **3:** 14–18.

Pilocarpine Nitrate *(BANM)*

Pilocarp. Nit.; Pilocarpina, nitrato de; Pilocarpine Mononitrate; Pilocarpine, nitrate de; Pilocarpini Nitras; Pilocarpinii Nitras; Pilocarpinium Nitricum; Pilocarpinnitrat; Pilokarpiininitraatti; Pilokarpinnitrat; Pilokarpin-nitrát; Pilokarpino nitratas.
$C_{11}H_{16}N_2O_2$,HNO_3=271.3
CAS — 148-72-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.
UNII — M20T465H6J.

NOTE. PIL is a code approved by the BP 2014 for use on single unit doses of eye drops containing pilocarpine nitrate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US,* and *Viet.*

Ph. Eur. 8: (Pilocarpine Nitrate). Colourless crystals, or white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Protect from light.

USP 36: (Pilocarpine Nitrate). Shining white crystals. Soluble 1 in 4 of water and 1 in 75 of alcohol; insoluble in chloroform and in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Pilocarpine is a direct-acting tertiary amine parasympathomimetic that has the muscarinic effects of acetylcholine (p. 2003.2). It is used mainly in the treatment of glaucoma (p. 1999.1) and in the treatment of dry eye (p. 2190.1) or dry mouth (p. 2011.1); it has also been used as a diaphoretic in diagnostic tests for cystic fibrosis and leprosy (p. 2011.1). Topical application of pilocarpine to the eye produces miosis (pupil constriction) by contraction of the iris sphincter muscle; contraction of the ciliary muscle results in increased accommodation. Constriction of the pupil also pulls open the trabecular meshwork in the eye and this in turn facilitates drainage of aqueous humour and reduction of intra-ocular pressure. After the use of eye drops, miosis occurs in about 10 to 30 minutes and lasts 4 to 8 hours while peak reduction in intra-ocular pressure occurs within 75 minutes and the reduction usually persists for 4 to 14 hours.

Pilocarpine is used in the treatment of open-angle **glaucoma** (but see also Glaucoma, under Adverse Effects, p. 2011.2) and is commonly given with topical beta blockers

or sympathomimetics. It is used as the hydrochloride or the nitrate, usually as 0.5 to 4% eye drops instilled up to 4 times daily, adjusted according to response. Solutions containing up to 6% of the hydrochloride may also be available and the higher strengths may sometimes be required in patients with heavily pigmented irides. A 4% ophthalmic gel has also been used. Pilocarpine may be used before surgery as part of the emergency treatment of acute attacks of angle-closure glaucoma.

The miotic action of pilocarpine has been used to antagonise the effects of sympathomimetic mydriatics on the eye and in surgical procedures on the eye. Pilocarpine borate has been used similarly in ophthalmology to the hydrochloride and nitrate.

Pilocarpine hydrochloride is used in the treatment of **dry mouth** following radiotherapy for malignant neoplasms of the head and neck. It increases salivary flow only in patients with residual salivary gland function. The initial oral dose is 5 mg three times daily with or immediately after meals, increased gradually if necessary after 4 weeks until an adequate response is obtained, up to a maximum of 10 mg three times daily. Oral doses of 5 mg four times daily are used to treat **dry eye** or mouth in patients with Sjögren's syndrome; this dose may be increased to a maximum of 30 mg daily. Treatment should be stopped if no improvement occurs after 3 months of use. For doses in patients with hepatic impairment, see below.

Administration in hepatic impairment. UK licensed product information recommends that daily doses of *oral* pilocarpine should be reduced in patients with moderate to severe cirrhosis. The dose may gradually be increased to 5 mg three times daily if tolerated.

In the USA, licensed information suggests that the starting oral dose of pilocarpine should be 5 mg twice daily in patients with moderate hepatic impairment (Child-Pugh category B); it is not recommended in those with severe impairment (Child-Pugh category C) because of a lack of pharmacokinetic studies in these patients.

Diagnosis and testing. *CYSTIC FIBROSIS.* The fact that individuals with cystic fibrosis have abnormally high concentrations of sodium and chloride in their sweat has been used in the diagnosis of this condition and pilocarpine iontophoresis has been used to promote sweating as part of that test.[1] Despite the fact that neonatal genetic screening for cystic fibrosis-causing mutations is now possible, sweat testing using pilocarpine iontophoresis remains the gold standard for diagnosis, and can help avoid the small likelihood of diagnostic error.[2,3] US guidelines[3] note that sweat electrolytes may be transiently elevated during the first 24 hours of life, but sweat testing may be performed from 48 hours onward if an adequate sample can be obtained.

1. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959; **23:** 545–9.
2. Parad RB, *et al.* Sweat testing infants detected by cystic fibrosis newborn screening. *J Pediatr* 2005; **147** (suppl): S69–S72.
3. LeGrys VA, *et al.* Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. *J Pediatr* 2007; **151:** 85–9.

LEPROSY. The induction of sweat secretion by intradermal injection of pilocarpine nitrate has been used to assess the functional status of dermal nerves in patients with leprotic skin lesions.[1]

1. Joshi PB. Pilocarpine test in assesment of therapeutic efficacy in maculoanaesthetic leprosy. *Lepr India* 1976; **48:** 55–60.

Dry mouth. Pilocarpine is used as a sialogogue in the treatment of dry mouth (p. 2175.3) after radiotherapy of the head and neck,[1,2] although benefit may not be entirely related to preservation of salivation.[3,4] A systematic review[5] based on 3 studies found limited evidence to support such use; although about half of the patients responded to pilocarpine, response did not occur in some for up to 12 weeks and adverse effects were common. Pilocarpine may also be of use in the management of drug-induced oral dryness,[6,7] and is used as a treatment for dry mouth and dry eye in the auto-immune disease, Sjögren's syndrome.[1,8–11]

1. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. *Drugs* 1995; **49:** 143–55.
2. Taylor SE. Efficacy and economic evaluation of pilocarpine in treating radiation-induced xerostomia. *Expert Opin Pharmacother* 2003; **4:** 1489–97.
3. Gorsky M, *et al.* The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97:** 190–5.
4. Gornitsky M, *et al.* Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98:** 45–52.
5. Davies AN, Shorthose K. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 10/06/08).
6. Götrick B, *et al.* Oral pilocarpine for treatment of opioid-induced oral dryness in healthy adults. *J Dent Res* 2004; **83:** 393–7.
7. Masters KJ. Pilocarpine treatment of xerostomia induced by psychoactive medications. *Am J Psychiatry* 2005; **162:** 1023.
8. Nelson JD, *et al.* Oral pilocarpine for symptomatic relief of keratoconjunctivitis sicca in patients with Sjögren's syndrome. *Adv Exp Med Biol* 1998; **438:** 979–83.
9. Vivino FB, *et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. *Arch Intern Med* 1999; **159:** 174–81.
10. Tsifetaki N, *et al.* Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis* 2003; **62:** 1204–7.
11. Baudouin C, *et al.* Traitements actuels de la xérophtalmie dans le syndrome de Gougerot-Sjögren. *Rev Med Interne* 2004; **25:** 376–82.

Reversal of mydriasis. Pilocarpine has been used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but other miotics may be preferred (see p. 2000.3). It counteracts the mydriatic effects of sympathomimetics, such as phenylephrine and hydroxyamfetamine,[1] but is ineffective against mydriasis produced by antimuscarinics, such as homatropine,[1] and may impair vision further when used with tropicamide.[2] Furthermore, there is also the risk of pilocarpine precipitating angle-closure glaucoma in susceptible patients (see Glaucoma, under Precautions, below and also Glaucoma, in Tropicamide, p. 2012.3).

1. Anastasi LM, *et al.* Effect of pilocarpine in counteracting mydriasis. *Arch Ophthalmol* 1968; **79:** 710–15.
2. Nelson ME, Orton HP. Counteracting the effects of mydriatics: does it benefit the patient? *Arch Ophthalmol* 1987; **105:** 486–9.

Adverse Effects, Treatment, and Precautions

Systemic effects and cautions are as for Neostigmine, p. 688.2.

With the *oral* use of pilocarpine, sweating is a common problem; caution is needed to avoid dehydration in patients who may sweat excessively and who cannot maintain an adequate fluid intake. Paradoxical hypertension and constipation, confusion, and increased urinary frequency have also been reported. Licensed product information states that it should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision or dizziness may affect the performance of skilled tasks including driving. In addition pilocarpine should be given with care to those with cognitive or psychiatric disturbances, with renal calculi or renal impairment, or with biliary-tract disorders. Dosage should be reduced in patients with hepatic impairment (see Administration in Hepatic Impairment, above).

After *ocular* use pilocarpine is usually better tolerated than the anticholinesterases, but in common with other miotics may produce ciliary spasm, ocular pain and irritation, blurred vision, lachrymation, myopia, and browache. Conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage, and increased pupillary block have been reported. Lens opacities have occurred after prolonged use. Treatment with miotics should be stopped if symptoms of systemic toxicity develop.

Miotics are contra-indicated in conditions where pupillary constriction is undesirable such as acute iritis, acute uveitis, anterior uveitis, and some forms of secondary glaucoma. They should be avoided in acute inflammatory disease of the anterior segment of the eye. If possible, treatment with long-acting miotics should be stopped before surgery on the eye as there is an increased risk of hyphaema. Miotics should be used with extreme caution in patients with a history of retinal detachment and in young patients with myopia. Care is also needed in patients with corneal or conjunctival damage. Miosis may cause blurred vision and difficulty with dark adaptation and caution is necessary with night driving or when hazardous tasks are undertaken in poor illumination. Miotics should not be used by patients wearing soft contact lenses.

Asthma. A reminder that topical miotics can precipitate bronchospasm in susceptible patients.[1] However, the severity of the reaction induced by carbachol has been reported to be less than that produced by timolol. Bronchospastic complications are much less likely to occur with pilocarpine but have nevertheless been reported. As inhalations of methacholine are used to induce bronchospasm in the diagnosis of latent asthma, the risk of exacerbating asthma should be considered before methacholine is used in the eye.

1. Prakash UBS, *et al.* Pulmonary complications from ophthalmic preparations. *Mayo Clin Proc* 1990; **65:** 521–9.

Dementia. In patients with dementia of Alzheimer type, CNS symptoms may be induced or exacerbated by the use of pilocarpine eye drops.[1,2]

1. Reyes PF, *et al.* Mental status changes induced by eye drops in dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1987; **50:** 113–15.
2. Fraunfelder FT, Morgan R. The aggravation of dementia by pilocarpine. *JAMA* 1994; **271:** 1742–3.

Glaucoma. Miotics usually lower intra-ocular pressure by decreasing the resistance to outflow of aqueous humour from the anterior chamber through the trabecular network. However, they appear to reduce uveoscleral outflow and this may cause a paradoxical rise in intra-ocular pressure in patients with severely compromised trabecular outflow as was reported in a patient with post-traumatic angle-recession glaucoma.[1] It has been recommended that pilocarpine should be avoided after drainage operations for glaucoma because its miotic effect can increase the occurrence of posterior pupillary synechiae; a topical beta blocker is usually adequate if control of intra-ocular pressure is required.[2] Pilocarpine-induced miosis was shown to cause a significant deterioration in visual field in patients with chronic open-angle glaucoma.[3] It was suggested that this should be an important consideration when choosing therapy for glaucoma, particularly in cases where field loss approaches the permitted legal minimum for driving. Of 53 patients receiving long-term therapy with pilocarpine gel, 15 developed a corneal haze, which persisted for at least 2 years in 13; although the patients remained asymptomatic the long-term effects were unknown.[4] Many patients using the gel also developed superficial punctate keratitis which usually cleared spontaneously during treatment.

1. Bleiman BS, Schwartz AL. Paradoxical intraocular pressure response to pilocarpine: a proposed mechanism and treatment. *Arch Ophthalmol* 1979; **97:** 1305–6.
2. Phillips CI, *et al.* Posterior synechiae after glaucoma operations: aggravation by shallow anterior chamber and pilocarpine. *Br J Ophthalmol* 1987; **71:** 428–32.
3. Webster AR, *et al.* The effect of pilocarpine on the glaucomatous visual field. *Br J Ophthalmol* 1993; **77:** 721–5.
4. Johnson DH, *et al.* Corneal changes during pilocarpine gel therapy. *Am J Ophthalmol* 1986; **101:** 13–15.

Hypersensitivity. Contact urticaria involving the eyelids has been reported[1] in a patient after treatment with pilocarpine eye drops for glaucoma.

1. O'Donnell BF, Foulds IS. Contact allergic dermatitis and contact urticaria due to topical ophthalmic preparations. *Br J Ophthalmol* 1993; **77:** 740–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pilocarpine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Retinal detachment. The use of miotics has been implicated in many reports as a cause of retinal detachment but reviews of the subject have concluded that there is little factual evidence to support the association.[1,2] However, there is circumstantial evidence that retinal detachment is more likely to occur with strong miotics. Furthermore, patients with myopia or pre-existing retinal damage appear to be at greater risk and there is the possibility that even low concentrations of relatively mild miotics such as 1% pilocarpine might precipitate retinal detachment.

1. Alpar JJ. Miotics and retinal detachment: a survey and case report. *Ann Ophthalmol* 1979; **11:** 395–401.
2. Beasley H, Fraunfelder FT. Retinal detachments and topical ocular miotics. *Ophthalmology* 1979; **86:** 95–8.

Systemic absorption. Systemic adverse effects after the ophthalmic use of pilocarpine are thought to be rare and reports of toxicity mainly involve elderly patients treated for acute angle-closure glaucoma before surgery and given relatively high doses.[1,2] It may not be feasible to stop the miotic in these circumstances. In a report of psychotic reaction in such a patient,[2] pilocarpine was continued but the patient was instructed on how to minimise absorption by closing the lachrymal canal; an atypical antipsychotic with minimal antimuscarinic effects (risperidone) was also given.

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
2. Sirois FJ. Pilocarpine psychosis. *Psychosomatics* 2005; **46:** 88.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Mean elimination half-lives for pilocarpine have been reported to be 0.76 and 1.35 hours after repeated oral doses of 5 and 10 mg of the hydrochloride, respectively. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. About 30% of an oral dose is excreted in the urine as pilocarpine and its inactive metabolites, including pilocarpic acid; the fate of the remaining 70% is unknown. Data from *animal* studies indicate that pilocarpine is distributed into breast milk at concentrations similar to those in the plasma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Isopto Carpina; Klonocarpina; Omaclopil; Pilocarpol†; Pilomed†; Sonadryl; Tensiocap†; Wetol; Xao Pil†; ***Austral.***: Isopto Carpine; Pilopt†; PV Carpine†;

Austria: Pilorcarpin Puroptal; Salagen; ***Belg.***: Isopto Carpine; Pilo; Salagen; ***Braz.***: Isopto Carpine; Pilocan; Pilosol; ***Canad.***: Akarpine; Diocarpine; Isopto Carpine; Pilopine HS; Salagen; ***Chile***: Pilogel; ***China***: Rui Er Xin (瑞尔欣); Zhenrui (真瑞); ***Cz.***: Pilogel; Pilopos†; ***Fin.***: Isopto Carpine; Salagen; ***Fr.***: Pilo; Salagen; ***Ger.***: Pilomann-Ol; Pilomann; Pilopos†; Salagen; Spersacarpin; ***Gr.***: Cidren; Dispercarpine; Isopto Carpine; Pilocollyre; Pilofar; Pilogel; Pilotina; Prothenol; Saglion; Salagen; Saliviral; Sumario; Ugetin; Xerocarp; ***Hong Kong***: Isopto Carpine; Salagen; ***Hung.***: Humacarpin; Salagen; ***India***: Andre Carpine; Carpine; Carpinol; Carpo-Miotic†; Carporen; Locarp; Pilocar; ***Indon.***: Miokar; ***Irl.***: Pilogel†; Salagen†; ***Israel***: Mi-Pilo; Salagen; ***Ital.***: Dropilton; Salagen; ***Malaysia***: Isopto Carpine; ***Mex.***: Caliprene†; Pil; Pilo; ***Neth.***: Pilogel†; Salagen; ***Norw.***: Isopto Carpine†; ***NZ***: Ocusert†; Pilopt; ***Philipp.***: Isopto Carpine; ***Port.***: Salagen; ***Rus.***: Oftan Pilocarpin (Офтан Пилокарпин); ***S.Afr.***: Isopto Carpine; Pilogel; ***Singapore***: Isopto Carpine†; Opticar; Pilogel†; Salagen; ***Spain***: Isopto Carpina; Salagen; ***Swed.***: Salagen; ***Switz.***: Salagen; Spersacarpine; ***Thai.***: Isopto Carpine; Salagen†; ***Turk.***: Pilogel; Pilokarsol; Pilosed; Salagen; ***UK***: Pilogel†; Salagen; ***USA***: Adsorbocarpine†; Akarpine†; Isopto Carpine; Ocu-Carpine†; Pilocar†; Pilopine HS; Piloptic†; Pilopto-Carpine†; Pilostat†; Salagen; ***Venez.***: Pilocar.

Multi-ingredient Preparations. ***Arg.***: Amplus; Glaucotensil; Pilotim; ***Austral.***: Timpilo†; ***Austria***: Betacarpin; Fotil; Normastigmin mit Pilocarpin; Thiloadren†; ***Belg.***: Carteopil†; Normoglaucon†; ***China***: Normoglaucon (嗪高康); ***Cz.***: Fotil; ***Denm.***: Fotil; ***Fin.***: Fotil; ***Fr.***: Carpilo†; Pilobloq†; ***Ger.***: Fotil; Glauko Biciron; Normoglaucon; TP-Ophtal; ***Gr.***: Dropiltim; Fotil; Ripix; Ryvina; T+P; Thilocombin; Timpilo; Yvano; ***Hong Kong***: Timpilo†; ***Hung.***: Fotil; ***India***: Bi-Miotic†; Iotim-Plus; ***Israel***: Timpilo†; ***Ital.***: Equiton; Pilobloc; Timicon; ***Neth.***: Fotil†; Normoglaucon†; ***Norw.***: Fotil; ***NZ***: Timpilo; ***Philipp.***: Fotil; ***Pol.***: Fotil†; Normoglaucon; ***Port.***: Normoglaucon†; Timoglau Plus†; ***Rus.***: Fotil (Фотил); Pilotimol (Пилотимол); Proxocarpine (Проксокарпин); ***Swed.***: Fotil; ***Switz.***: Arteopilo†.

Pharmacopoeial Preparations
BP 2014: Pilocarpine Hydrochloride Eye Drops; Pilocarpine Nitrate Eye Drops;
USP 36: Pilocarpine Hydrochloride Ophthalmic Solution; Pilocarpine Hydrochloride Tablets; Pilocarpine Nitrate Ophthalmic Solution; Pilocarpine Ocular System.

Tafluprost *(BAN, USAN, rINN)*

AFP-168; DE-085; MK-2452; Tafluprostum; Тафлупрост.
Isopropyl (5*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-3,3-difluoro-4-phenoxybut-1-enyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.
$C_{25}H_{34}F_2O_5$=452.5
CAS — 209860-87-7.
ATC — S01EE05.
ATC Vet — QS01EE05.
UNII — 1O6WQ6T7G3.

Profile

Tafluprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) that is used to reduce intra-ocular pressure in the treatment of open-angle glaucoma and ocular hypertension (p. 1999.1), either alone or as adjunctive therapy with a topical beta blocker. Reduction of intra-ocular pressure starts about 2 to 4 hours after instillation and is maximal after 12 hours; pressure reduction lasts for at least 24 hours. A 0.0015% ophthalmic solution is instilled once daily, preferably in the evening.

References.

1. Hamacher T, *et al*. Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from a pharmacodynamics analysis. *Acta Ophthalmol Suppl (Oxf)* 2008; **242:** 14–19.
2. Egorov E, *et al*. Adjunctive use of tafluprost with timolol provides additive effects for reduction of intraocular pressure in patients with glaucoma. *Eur J Ophthalmol* 2009; **19:** 214–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Saflutan; ***Belg.***: Saflutan; ***Braz.***: Saflutan; ***Cz.***: Taflotan; ***Denm.***: Taflotan; ***Fin.***: Taflotan; ***Fr.***: Saflutan; ***Ger.***: Taflotan; ***Hong Kong***: Taflotan; ***Irl.***: Saflutan; ***Israel***: Saflutan; ***Neth.***: Saflutan; ***Norw.***: Taflotan; ***Pol.***: Taflotan; ***Singapore***: Taflotan; ***Spain***: Saflutan; ***Swed.***: Taflotan; ***Switz.***: Saflutan; ***Thai.***: Taflotan; ***UK***: Saflutan; ***USA***: Zioptan.

Travoprost *(BAN, USAN, rINN)*

AL-6221; Travoprosti; Travoprostum; Травопрост.
Isopropyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[α,α,α-trifluoro-*m*-tolyl]oxy]-1-butenyl}cyclopentyl)-5-heptenoate.
$C_{26}H_{35}F_3O_6$=500.6
CAS — 157283-68-6.
ATC — S01EE04.
ATC Vet — QS01EE04.
UNII — N0A3Z5XTC6.

NOTE. TRO is a code approved by the BP 2014 for use on single unit doses of eye drops containing tropicamide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Tropicamide). A white or almost white, crystalline powder. M.p. 95 degrees to 98 degrees. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Travoprost). A clear, colourless, viscous oil. Insoluble in water. Store at -25 degrees to -15 degrees under nitrogen in airtight containers. Protect from light.

Uses and Administration

Travoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used in the treatment of open-angle glaucoma and ocular hypertension (p. 1999.1), as a 0.004% ophthalmic solution instilled once daily, preferably in the evening. The reduction in pressure starts about 2 hours after instillation and is maximal after 12 hours; the effect is maintained for at least 24 hours.

References.

1. Ang GS, *et al*. The effect of travoprost on daytime intraocular pressure in normal tension glaucoma: a randomised controlled trial. *Br J Ophthalmol* 2008; **92:** 1129–33.
2. Kammer JA, *et al*. Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3-month, randomised, masked-evaluator, multicentre study. *Br J Ophthalmol* 2010; **94:** 74–9.

Adverse Effects and Precautions

As for Latanoprost, p. 2008.2.

Effects on the eyes. Severe iritis and corneal oedema developed in an elderly woman 3 weeks after restarting travoprost after eye surgery;[1] rechallenge was positive. The authors commented that the UK MHRA was aware of one other case of uveitis associated with travoprost.

1. Kumarasamy M, Desai SP. Anterior uveitis is associated with travoprost. *BMJ* 2004; **329:** 205.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies travoprost as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arvo; Glaucoprost; Glauno; Travatan; ***Austral.***: Travatan; ***Austria***: Travatan; ***Belg.***: Travatan; ***Braz.***: Travamed; Travatan; ***Canad.***: Travatan; ***Chile***: Travatan; ***China***: Travatan (苏为坦); ***Cz.***: Travatan; ***Denm.***: Travatan; ***Fin.***: Travatan; ***Fr.***: Travatan; ***Ger.***: Travatan; ***Gr.***: Travatan; ***Hong Kong***: Travatan; ***Hung.***: Travatan; ***India***: Lupitros; ***Indon.***: Travatan; ***Irl.***: Travatan; ***Israel***: Travatan; ***Ital.***: Travatan; ***Malaysia***: Travatan; ***Mex.***: Travatan; ***Neth.***: Travatan; ***Norw.***: Travatan; ***NZ***: Travatan; ***Philipp.***: Travatan; ***Pol.***: Travatan; ***Port.***: Travatan; ***Rus.***: Travatan (Траватан); ***S.Afr.***: Travatan; ***Singapore***: Travatan; ***Spain***: Travatan; ***Swed.***: Travatan; ***Switz.***: Travatan; ***Thai.***: Travatan; ***Turk.***: Travatan; ***UK***: Travatan; ***Ukr.***: Travatan (Траватан); ***USA***: Travatan; ***Venez.***: Travatan.

Multi-ingredient Preparations. ***Arg.***: DuoTrav; Neoprost; ***Austria***: DuoTrav; ***Belg.***: DuoTrav; ***Canad.***: DuoTrav; ***Chile***: DuoTrav; ***Cz.***: DuoTrav; ***Denm.***: DuoTrav; ***Fr.***: DuoTrav; ***Ger.***: DuoTrav; ***Gr.***: DuoTrav; ***Hong Kong***: DuoTrav; ***Hung.***: DuoTrav; ***Irl.***: DuoTrav; ***Israel***: DuoTrav; ***Ital.***: DuoTrav; ***Malaysia***: DuoTrav; ***Neth.***: DuoTrav; ***Norw.***: DuoTrav; ***NZ***: DuoTrav; ***Philipp.***: DuoTrav; ***Pol.***: DuoTrav; ***Port.***: DuoTrav; ***S.Afr.***: DuoTrav; ***Singapore***: DuoTrav; ***Spain***: DuoTrav; ***Swed.***: DuoTrav; ***Switz.***: DuoTrav; ***Thai.***: DuoTrav; ***Turk.***: DuoTrav; ***UK***: DuoTrav.

Pharmacopoeial Preparations
USP 36: Travoprost Ophthalmic Solution.

Tropicamide *(BAN, USAN, rINN)*

Bistropamide; Ro-1-7683; Tropicamid; Tropicamida; Tropicamidum; Tropikamid; Tropikamidas; Tropikamidi; Тропикамид.
N-Ethyl-*N*-(4-pyridylmethyl)tropamide; (2*RS*)-*N*-Ethyl-3-hydroxy-2-phenyl-*N*-(pyridin-4-ylmethyl)propanamide.
$C_{17}H_{20}N_2O_2$=284.4
CAS — 1508-75-4.
ATC — S01FA06.
ATC Vet — QS01FA06.
UNII — N0A3Z5XTC6.

USP 36: (Tropicamide). A white or practically white crystalline powder, odourless or having not more than a slight odour. M.p. 96 degrees to 100 degrees. Slightly soluble in water; freely soluble in chloroform and in solutions of strong acids. Store in airtight containers. Protect from light.

Uses and Administration

Tropicamide is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used as eye drops to produce mydriasis and cycloplegia (p. 2000.2). It has a more rapid onset and a shorter duration of effect than atropine: mydriasis is produced within 20 to 40 minutes of use and usually lasts for about 6 hours; cycloplegia is maximal within about 30 minutes and is short-lasting, with complete recovery of accommodation normally within 6 hours. Tropicamide has been reported to be inadequate for cycloplegia in children.

To produce **mydriasis**, a 0.5% ophthalmic solution is instilled 15 to 20 minutes before examination of the eye. To produce **cycloplegia** a 1% solution is used and repeated after 5 minutes; a further instillation may be necessary to prolong the effect after 20 to 30 minutes.

Dementia. Tropicamide has been studied for use in the differential diagnosis of Alzheimer's disease (see Dementia, p. 388.1). Excessive pupil dilatation in response to tropicamide eye drops occurred in patients with signs and symptoms of Alzheimer's disease.[1] However, a double-blind placebo-controlled study[2] in similar patients and healthy subjects indicated that this was not a reliable diagnostic test for Alzheimer's disease.

1. Gómez-Tortosa E, *et al*. Pupil response to tropicamide in Alzheimer's disease and other neurodegenerative disorders. *Acta Neurol Scand* 1996; **94:** 104–9.
2. Graff-Radford NR, *et al*. Tropicamide eyedrops cannot be used for reliable diagnosis of Alzheimer's disease. *Mayo Clin Proc* 1997; **72:** 495–504.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

References.
1. Vuori M-L, *et al*. Systemic absorption and anticholinergic activity of topically applied tropicamide. *J Ocul Pharmacol* 1994; **10:** 431–7.

Glaucoma. The use of mydriatics is considered liable to provoke an acute attack in patients with glaucoma or a tendency to glaucoma; licensed product information generally contra-indicates their use in such patients. However, a systematic review concluded that in fact a history of open-angle glaucoma did not predispose to acute angle closure under mydriasis, and that mydriasis with tropicamide in particular appeared to be safe and should be recommended in all patients when thorough retinal examination was indicated.[1] In contrast, the use of pilocarpine to reverse mydriatics was potentially harmful.

1. Pandit RJ, Taylor R. Mydriasis and glaucoma: exploding the myth. A systematic review. *Diabet Med* 2000; **17:** 693–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tropicamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mydril; ***Austral.***: Mydriacyl; ***Austria***: Mydriaticum; ***Belg.***: Mydriacyl; Tropicol; ***Braz.***: Ciclomidrin; Mydriacyl; Tropinom; ***Canad.***: Diotrope; Mydriacyl; Tropicacyl; ***Chile***: Mydriacyl; ***China***: Mydrin-M (美多丽满); Runzheng (润正); ***Cz.***: Mydrum†; Unitropic; ***Denm.***: Mydriacyl; ***Fr.***: Mydriaticum; ***Ger.***: Mydriaticum; Mydrum; ***Gr.***: Tropixal; ***Hong Kong***: Mydriacyl; ***Hung.***: Mydrum†; ***India***: Meptrop; Optimide; Tmide; Tropico†; ***Indon.***: Midric; ***Irl.***: Mydriacil†; ***Israel***: Mydramide; ***Ital.***: Tropimil; Visumidriatic; ***Malaysia***: Mydriacyl; ***Mex.***: Myriacyl; ***NZ***: Mydriacyl; ***Philipp.***: Mydriacyl; ***Port.***: Tropicil Top; ***Rus.***: Mydriacyl (Мидриацил); Mydrum (Мидрум); ***S.Afr.***: Mydriacyl; Mydriaticum; ***Singapore***: Mydriacyl†; Triacyl; ***Swed.***: Mydriacyl; ***Switz.***: Mydriaticum; ***Thai.***: Mydriacyl; ***Turk.***: Tropamid; ***UK***: Mydriacyl; ***Ukr.***: Mydriacil (Мидриацил); ***USA***: Mydral; Mydriacyl; Ocu-Tropic; Opticyl; Tropicacyl; ***Venez.***: Mydriacyl.

Multi-ingredient Preparations. ***Arg.***: Fotorretin; Midria Phoenix; Midriax-T; Sensu; Tropioftal F; ***Belg.***: Mydriasert; ***Canad.***: Diophenyl-T; Phenyltrope; ***China***: Mydrin-P (美多丽); ***Denm.***: Mydriasert; ***Fin.***: Mydriasert; ***Fr.***: Mydriasert; ***Ger.***: Mydriasert; ***Hong Kong***: Mydrin-P; ***India***: Drosyn-T; Itrop Plus; Meptrop-P; Optimide Plus; Tropico Plus†; ***Ital.***: Mydriasert; Visumidriatic Fenilefrina; ***Mex.***: Augex; ***Neth.***: Mydriasert; ***Philipp.***: Sanmyd-P;

Port.: Mydriasert; ***Spain***: Mydriasert; ***Swed.***: Mydriasert; ***Switz.***: Mydriasert; ***UK***: Mydriasert; ***USA***: Paremyd; ***Venez.***: Fotorretin.

Pharmacopoeial Preparations
BP 2014: Tropicamide Eye Drops;
USP 36: Tropicamide Ophthalmic Solution.

Unoprostone Isopropyl *(rINNM)*

Isopropyl Lunoprostone; Isopropyl Unoprostone; UF-021; Unoprostona de isopropilo; Unoprostone, Isopropyle d'; Unoprostoni Isopropylas; Унопростона Изопропил.

Isopropyl (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate.

$C_{25}H_{44}O_5$=424.6

CAS — 120373-36-6 (unoprostone); 120373-24-2 (unoprostone isopropyl).

ATC — S01EE02.

ATC Vet — QS01EE02.

UNII — 5M161S5O5P.

Profile

Unoprostone, like latanoprost (p. 2008.1), is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as the isopropyl ester for the treatment of glaucoma and ocular hypertension (p. 1999.1). Ophthalmic solutions containing unoprostone isopropyl 0.12 or 0.15% may be instilled twice daily.

References.

1. de Arruda Mello PA, *et al.* Safety of unoprostone isopropyl as mono- or adjunctive therapy in patients with primary open-angle glaucoma or ocular hypertension. *Drug Safety* 2002; **25:** 583–97.
2. Chiba T, *et al.* Comparison of iridial pigmentation between latanoprost and isopropyl unoprostone: a long term prospective comparative study. *Br J Ophthalmol* 2003; **87:** 956–9.
3. Stewart WC, *et al.* The safety and efficacy of unoprostone 0.15% versus brimonidine 0.2%. *Acta Ophthalmol Scand* 2004; **82:** 161–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rescula; ***Braz.***: Rescula; ***Chile***: Rescula†; ***Cz.***: Rescula†; ***Hung.***: Rescula†; ***Jpn***: Rescula; ***Mex.***: Rescula; ***Philipp.***: Rescula; ***Rus.***: Rescula (Рескула); ***Thai.***: Rescula†; ***USA***: Rescula; ***Venez.***: Rescula.

Muscle Relaxants

The muscle relaxants included in this chapter are used in the management of musculoskeletal and neuromuscular disorders. There are 2 main types:

- **centrally acting relaxants**—these generally have a selective action on the CNS and are principally used for relieving painful muscle spasms or spasticity occurring in musculoskeletal and neuromuscular disorders. Their mechanism of action may be due to their CNS-depressant activity. Baclofen and tizanidine are two examples.
- **directly acting relaxants**—dantrolene is a drug that has a direct action on skeletal muscle and is used for the relief of spasticity associated with a variety of conditions.

Also included in this chapter are **botulinum toxins A and B**, which inhibit the release of acetylcholine at the motor nerve terminals.

Some benzodiazepines are also used in the treatment of muscle spasms; further details may be found under Diazepam, p. 1063.2.

Other drugs that block transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia are discussed in the chapter on Neuromuscular Blockers, p. 2028.1.

Drugs used to relax *smooth muscle* include the various antispasmodics (p. 1803.3) used for their antimuscarinic or direct smooth-muscle relaxant effects in the management of gastrointestinal disorders, as well as some other drugs such as papaverine (p. 2362.2).

Muscle spasm

Spasm is a painful involuntary contraction of muscle that can cause involuntary movement, interfere with function, and cause distortion. It is a symptom of many muscular and other types of disorders and treatment should mainly be aimed at the underlying cause. Centrally acting muscle relaxants and benzodiazepines are used to treat muscle spasms such as *splinting* that occur in response to local trauma or musculoskeletal and joint disorders. Splinting is a reflex muscular spasm that produces muscular rigidity and acts as a protective mechanism to prevent movement and further damage of the affected part. Short courses of muscle relaxants may be considered in the management of acute low back pain (p. 9.2).

Cramps are muscle spasms of abrupt onset that occur at rest and usually last for a few seconds or minutes. They are often precipitated by dehydration and hyponatraemia produced by vigorous exercise, excessive sweating, diarrhoea, and vomiting, or may be associated with drug therapy or haemodialysis (see Haemodialysis-induced Cramp, p. 1779.3). Pregnant women, the elderly, and those with peripheral vascular disease, appear to be particularly susceptible to night cramps of the feet or legs, the cause of which is not well understood.

The management of muscle cramps has been reviewed.[1-4] Quinine has traditionally been used for *nocturnal cramps* but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. Meta-analyses[5,6] have indicated that although quinine was modestly effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind; patients should be closely monitored over a period of at least 4 weeks while the efficacy of quinine was assessed. In the UK, it is recommended that treatment should be stopped every 3 months to see whether it is still needed.[7] In the USA, the FDA has ruled that quinine products should no longer be used for the management of nocturnal cramps.[8,9] There is little convincing evidence to support the use of other drugs.[1-4,8]

A systematic review[10] concluded that magnesium (as the lactate and citrate) is modestly effective in the treatment of *leg cramps in pregnancy*; calcium salts were ineffective, and although early evidence suggested benefit with sodium chloride, high doses were required with their attendant cardiovascular risks.

1. McGee SR. Muscle cramps. *Arch Intern Med* 1990; **150:** 511–18.
2. Butler JV, *et al*. Nocturnal leg cramps in older people. *Postgrad Med J* 2002; **78:** 596–8.
3. Katzberg HD, *et al*. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; **74:** 691–6. Also available at: http://www.neurology.org/cgi/reprint/74/8/691.pdf (accessed 09/07/10)
4. Guay DR. Are there alternatives to the use of quinine to treat nocturnal leg cramps? *Consult Pharm* 2008; **23:** 141–56.
5. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
6. Man-Son-Hing M, *et al*. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
7. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; **34:** 7–8.
8. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
9. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; **123:** 86.
10. Young GL, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 16/06/05).

Spasticity

The term spasticity has been loosely applied to various disorders of motor control resulting from CNS disease and marked by effects such as increased muscle tone, exaggerated stretch reflexes, impaired voluntary movement, weakness, loss of dexterity, abnormal posture, and often disturbed gait. In some patients muscle spasm and pain may be more distressing than impaired movement. Other complications may include contractures, pressure sores, and infection. Spasticity is a feature of neurological conditions such as multiple sclerosis, cerebral palsy, head injury, and stroke, particularly if there are spinal lesions.

Spasticity is disabling and difficult to treat when severe, but mild or moderate forms may be effectively managed by conservative treatment. Some patients may even rely on spasticity to provide a means of posture control and care should be taken that treatment does not lead to increased disability.

Various discussions on the management of spasticity have been published.[1-11] The mainstay of management is physiotherapy and antispastic drugs, although the evidence for the latter is rather scanty.[9,12,13] Baclofen, dantrolene, diazepam, and tizanidine are the drugs most often used. These 4 drugs act via different mechanisms, which are not fully understood.

Baclofen is thought to act at the spinal cord level but may also have supraspinal sites of action. It is a powerful neuronal depressant and may exert its inhibitory effects by acting as an agonist at GABA (gamma aminobutyric acid) receptors. *Diazepam* is also thought to act centrally by enhancing the response to GABA. In contrast, *dantrolene* acts directly on muscles, possibly by interfering with the release of calcium from muscular sarcoplasmic reticulum needed for contraction. *Tizanidine* is a centrally acting relaxant and α-adrenergic agonist; it is thought to act at spinal and supraspinal levels by inhibiting the presynaptic activity of excitatory interneurones.[7] It can produce additive effects with baclofen, allowing a reduction in the dosage of both drugs; use with benzodiazepines is not recommended because of the potential for interactions. All these are usually given orally but baclofen may also be given intrathecally in severe chronic spasticity.[10,14,15] Injection directly into the spinal subarachnoid space allows immediate delivery to the site of action in the spinal cord and the use of considerably lower doses than those given orally. It has been reported[16] that some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity reappearing, and that others have been able to reduce the dosage required.

Other drugs that may produce some benefit or are being studied in spasticity include *other benzodiazepines*, *clonidine*, *gabapentin*, and *memantine*.

Alternative approaches to treatment include nerve blocks using *local anaesthetics*; they should generally only be used when further muscle relaxation would not increase disability. *Chemical neurolysis* using alcohol or phenol is only considered when there is intractable continuous pain. Local injections of *botulinum A toxin* have produced some encouraging results in the management of limb spasticity in post-stroke or spinal injury patients and in children with cerebral palsy;[17-19] its temporary effect may be an advantage over chemical neurolysis but the need for regular injections may limit acceptability in children.[17] In children with cerebral palsy, a systematic review[20] has found insufficient evidence to support or refute such use in those with lower limb spasticity; however, another systematic review[21] has found the use of botulinum A toxin as an adjunct to occupational therapy to be effective in the management of upper limb spasticity.

Nondrug treatments have included electrical stimulation techniques such as transcutaneous nerve stimulation and dorsal column stimulation; vibration applied to agonist spastic muscles to improve voluntary movement; cooling to decrease afferent inputs from peripheral receptors; and orthopaedic surgery or neurosurgery.

1. Young RR. Spasticity: a review. *Neurology* 1994; **44** (suppl 9): S12–S20.
2. Ko CK, Ward AB. Management of spasticity. *Br J Hosp Med* 1997; **58:** 400–5.
3. Kita M, Goodkin DE. Drugs used to treat spasticity. *Drugs* 2000; **59:** 487–95.
4. Anonymous. The management of spasticity. *Drug Ther Bull* 2000; **38:** 44–6.
5. Bhakta BB. Management of spasticity in stroke. *Br Med Bull* 2000; **56:** 476–85.
6. Burchiel KJ, Hsu FPK. Pain and spasticity after spinal cord injury: mechanisms and treatment. *Spine* 2001; **26** (suppl): S146–S160.
7. Ward AB. A summary of spasticity management – a treatment algorithm. *Eur J Neurol* 2002; **9** (suppl 1): 48–52.
8. Abbruzzese G. The medical management of spasticity. *Eur J Neurol* 2002; **9** (suppl 1): 30–4.
9. Montané E, *et al*. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. *Neurology* 2004; **63:** 1357–63.
10. Verrotti A, *et al*. Pharmacotherapy of spasticity in children with cerebral palsy. *Pediatr Neurol* 2006; **34:** 1–6.
11. Delgado MR, *et al*. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010; **74:** 336–43. Also available at: http://www.neurology.org/cgi/reprint/74/4/336.pdf (accessed 09/07/10)
12. Taricco M, *et al*. Pharmacological interventions for spasticity following spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/06/05).
13. Shakespeare DT, *et al*. Anti-spasticity agents for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 16/06/05).
14. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; **49:** 262–7.
15. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; **36:** 21–2.
16. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; **60:** 168–73.
17. Neville B. Botulinum toxin in the cerebral palsies. *BMJ* 1994; **309:** 1526–7.
18. Fried GW, Fried KM. Spinal cord injury and use of botulinum toxin in reducing spasticity. *Phys Med Rehabil Clin N Am* 2003; **14:** 901–10.
19. Preiss RA, *et al*. The effects of botulinum toxin (BTX-A) on spasticity of the lower limb and on gait in cerebral palsy. *J Bone Joint Surg Br* 2003; **85:** 943–8.
20. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
21. Hoare BJ, *et al*. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 28/01/10).

Afloqualone *(rINN)*

Aflocualona; Afloqualonum; HQ-495; Афлоквалон.

6-Amino-2-fluoromethyl-3-o-tolylquinazolin-4(3*H*)-one.

$C_{16}H_{14}FN_3O$=283.3

CAS — 56287-74-2.

UNII — CO4U2C8ORZ.

NOTE. The names Aflozon, Airomate, Anapolet, Anmetolon, Arostowa, and Ohsiat have been used as trade marks for afloqualone.

Pharmacopoeias. In *Jpn*.

Profile

Afloqualone is a centrally acting skeletal muscle relaxant that has been given orally for the treatment of muscle spasm associated with musculoskeletal conditions. Photosensitivity reactions have been reported.

References.

1. Ishikawa T, *et al*. Photoleukomelanodermatitis (Kobori) induced by afloqualone. *J Dermatol* 1994; **21:** 430–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Arofuto.

Baclofen *(BAN, USAN, rINN)*

Aminomethyl Chlorohydrocinnamic Acid; Ba-34647; Baclofène; Baclofeno; Baclofenum; Baklofeeni; Baklofen; Baklofén; Baklofenas; Баклофен.

β-Aminomethyl-*p*-chlorohydrocinnamic acid; (*RS*)-Amino-3-(4-chlorophenyl)butyric acid.

$C_{10}H_{12}ClNO_2$=213.7

CAS — 1134-47-0.

ATC — M03BX01.

ATC Vet — QM03BX01.

UNII — H789N3FKE8 (baclofen); NYU6UTW25B (R-baclofen); 3OHN4989XM (S-baclofen).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Baclofen). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 36: (Baclofen). A white to off-white, odourless or practically odourless, crystalline powder. Slightly soluble in water; very slightly soluble in methyl alcohol; insoluble in chloroform. Store in airtight containers.

Uses and Administration

Baclofen, an analogue of gamma-aminobutyric acid (p. 2509.2), is a centrally acting skeletal muscle relaxant. It interferes with the release of excitatory neurotransmitters and inhibits monosynaptic and polysynaptic transmission at the spinal cord level. It may also act at supraspinal sites producing CNS depression. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of conditions.

Baclofen is given *orally* in divided doses, preferably with or after food or milk. The initial dose of baclofen is 15 mg daily, increased gradually according to response. A suggested regimen is 5 mg three times daily for 3 days, increased to 10 mg three times daily for 3 days, then in similar increments and intervals until either a dose of 20 mg three times daily is reached or until the desired therapeutic effect is obtained. Higher doses have been used: doses of more than 80 to 100 mg daily are not generally recommended although doses of up to 150 mg daily have been given to carefully supervised patients.

Elderly patients should receive lower initial doses, although final maintenance doses may be in the same range as younger adults. For dosage in renal impairment, see below.

If no benefit is apparent within 6 weeks of achieving the maximum dosage, therapy should probably be gradually withdrawn.

Baclofen is also given *by continuous intrathecal infusion* in the treatment of spasticity in patients intolerant of, or unresponsive to, oral antispastic therapy including baclofen. Before beginning the intrathecal regimen any existing antispastic therapy should be gradually withdrawn to avoid overdosage or drug interactions. Intrathecal test doses are given initially to determine if there is going to be any benefit before implanting a controlled infusion pump. It is important that patients are monitored closely in experienced centres during screening and immediately after implantation of the infusion pump and that resuscitation equipment is available for immediate use.

Test doses start at 25 or 50 micrograms given over at least 1 minute and are increased by 25 micrograms at intervals of not less than 24 hours until a dose of 100 micrograms is reached or a positive response of about 4 to 8 hours is obtained. Patients who fail to respond to a test dose of 100 micrograms are considered to be unsuitable for intrathecal treatment.

For patients showing a positive response lasting for longer than 8 to 12 hours, the test dose that was required to produce the response can then be given as a 24-hour infusion; if the response to the test dose lasted 8 to 12 hours or less, then a dose equivalent to twice the test dose is given. Daily dosage can then be adjusted as required. Maintenance doses range from about 12 micrograms to 2 mg daily in those with spasticity of spinal origin, with most patients being adequately maintained on 300 to 800 micrograms daily. In those with spasticity of cerebral origin, maintenance doses range from about 22 micrograms to 1.4 mg daily, with a mean of 276 micrograms daily at 12 months and 307 micrograms daily at 24 months.

For details of dosage in children, see below.

Administration in children. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of conditions in children. UK licensed product information recommends, in children from birth to 18 years of age, an initial *oral* dose of 300 micrograms/kg daily, preferably in 4 divided doses, increased gradually at intervals of about 1 week until the desired therapeutic effect is obtained; maintenance doses range from 750 micrograms/kg to 2 mg/kg daily. The total daily dose should not exceed 40 mg in children under 8 years of age and 60 mg in those aged from 8 to 18 years.

Baclofen is also given *by continuous intrathecal infusion* in the treatment of severe chronic spasticity of spinal or cerebral origin in children intolerant of, or unresponsive to, oral antispastic therapy including baclofen. An initial test dose of 25 to 50 micrograms is recommended in children aged 4 to 18 years (see above for further dosing details); initial maintenance doses range from 25 to 200 micrograms daily (median daily dose 100 micrograms).

Administration in renal impairment. Doses of baclofen should be reduced in renal impairment or in patients undergoing chronic haemodialysis; oral doses of 5 mg daily have been suggested in UK licensed product information (but see also under Precautions, p. 2016.3).

Alcohol withdrawal and abstinence. Reviews[1-3] of baclofen in both the treatment of alcohol withdrawal syndrome and maintenance of abstinence (p. 1734.1) have shown promising results and that it was well tolerated; however, the optimal dose and duration have yet to be established. Increased sedation may occur when baclofen is used in patients likely to ingest alcohol (see Interactions, p. 2016.3), however, a study[4] found that performance was not impaired to a greater extent with concomitant use than with the use of baclofen or alcohol alone.

1. Leggio L, *et al.* Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol Disord Drug Targets* 2010; **9:** 33–44.
2. Liu J, Wang L. Baclofen for alcohol withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2011 (accessed 03/04/12).
3. Muzyk AJ, *et al.* Defining the role ofbaclofen for the treatment of alcohol dependence: a systematic review of the evidence. *CNS Drugs* 2012; **26:** 69–78.
4. Evans SM, Bisaga A. Acute interaction of baclofen in combination with alcohol in heavy social drinkers. *Alcohol Clin Exp Res* 2009; **33:** 19–30.

Dystonias. There have been reports of improvement in patients with various forms of dystonia (p. 903.3) treated with baclofen[1-5] although there has also been a report[6] of a patient whose condition deteriorated during baclofen therapy.

1. Narayan RK, *et al.* Intrathecal baclofen for intractable axial dystonia. *Neurology* 1991; **41:** 1141–2.
2. Greene PE, Fahn S. Baclofen in the treatment of idiopathic dystonia in children. *Mov Disord* 1992; **7:** 48–52.
3. van Hilten BJ, *et al.* Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000; **343:** 625–30.
4. Albright AL, *et al.* Intrathecal baclofen for generalized dystonia. *Dev Med Child Neurol* 2001; **43:** 652–7.
5. Jaffe MS, Nienstedt LJ. Intrathecal baclofen for generalized dystonia: a case report. *Arch Phys Med Rehabil* 2001; **82:** 853–5.
6. Silbert PL, Stewart-Wynne EG. Increased dystonia after intrathecal baclofen. *Neurology* 1992; **42:** 1639–40.

Gastro-oesophageal reflux disease. Baclofen has been tried in the treatment of gastro-oesophageal reflux disease (p. 1807.2) in adults[1,2] and children.[3] It may control gastro-oesophageal reflux by inhibiting transient sphincter relaxation. Although a reduction in the number of reflux episodes was reported,[1-3] there was no effect on acid reflux symptoms.[1,2] However, another study[4] has shown a positive effect on the symptoms of acid reflux. It has been suggested that although baclofen may be of benefit, its adverse CNS effects mean that new oral selective GABA-B agonists should be developed for this indication.[5]

1. Van Herwaarden MA, *et al.* The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. *Aliment Pharmacol Ther* 2002; **16:** 1655–62.
2. Zhang Q, *et al.* Control of transient lower oesophageal sphincter relaxations and reflux by the $GABA_B$ agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; **50:** 19–24.
3. Omari TI, *et al.* Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. *J Pediatr* 2006; **149:** 468–74.
4. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the $GABA_B$ agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. *Gut* 2003; **52:** 464–70.
5. Tonini M, *et al.* Progress with novel pharmacological strategies for gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 347–61.

Hiccup. Baclofen has been given orally in doses ranging from 10 to 80 mg daily for the management of intractable hiccup (p. 1046.3) poorly controlled by other drugs. It has also been combined with gabapentin.

References.

1. Burke AM, *et al.* Baclofen for intractable hiccups. *N Engl J Med* 1988; **319:** 1354.
2. Lance JW, Bassil GT. Familial intractable hiccup relieved by baclofen. *Lancet* 1989; **ii:** 276–7.
3. Yaqoob M, *et al.* Baclofen for intractable hiccups. *Lancet* 1989; **ii:** 562–3.
4. Ramirez FC, Graham DY. Treatment of intractable hiccup with baclofen: results of a double-blind randomized, controlled, cross-over study. *Am J Gastroenterol* 1992; **87:** 1789–91.
5. Ramirez FC, Graham DY. Hiccups, compulsive water drinking, and hyponatremia. *Ann Intern Med* 1993; **118:** 649.
6. Walker P, *et al.* Baclofen, a treatment for chronic hiccup. *J Pain Symptom Manage* 1998; **16:** 125–32.
7. Hernández JL, *et al.* Gabapentin for intractable hiccup. *Am J Med* 2004; **117:** 279–81.

Migraine and cluster headache. The efficacy of baclofen in conditions such as trigeminal neuralgia or various types of neuropathic pain suggested that it may be useful in migraine or cluster headache. Pilot studies confirmed these hypotheses with baclofen proving useful for prophylaxis[1] in migraine (p. 670.3) and for treatment[2] in cluster headache (p. 670.1).

1. Hering-Hanit R. Baclofen for prevention of migraine. *Cephalalgia* 1999; **19:** 589–91.
2. Hering-Hanit R, Gadoth N. The use of baclofen in cluster headache. *Curr Pain Headache Rep* 2001; **5:** 79–82.

Pain. Like some other muscle relaxants baclofen is used in the management of painful conditions associated with muscle spasm or spasticity (see below). The use of muscle relaxants for conditions such as acute low back pain is referred to on p. 9.2. Baclofen does not appear to possess conventional analgesic activity[1] but may potentiate the analgesia produced by opioid analgesics,[2] and has been used as an adjuvant in neuropathic pain,[3,4] notably trigeminal neuralgia[5] (p. 11.2).

1. Terrence CF, *et al.* Is baclofen a n analgesic? *Clin Neuropharmacol* 1983; **6:** 241–5.
2. Panerai AE, *et al.* Baclofen prolongs the analgesic effect of fentanyl in man. *Br J Anaesth* 1985; **57:** 954–5.
3. Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 1994; **9:** 500–9.
4. Slonimski M, *et al.* Intrathecal baclofen in pain management. *Reg Anesth Pain Med* 2004; **29:** 269–76.
5. Fromm GH, *et al.* Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol* 1984; **15:** 240–4.

Spasticity. Baclofen is one of the main drugs used in the management of spasticity (see p. 2014.2). It is used to reduce muscle spasm and pain especially in spinal cord lesions in conditions such as multiple sclerosis or paraplegia. Baclofen is also used for spasticity of cerebral origin. However, some consider that there are insufficient data to refute or support the use of oral or continuous intrathecal baclofen in the management of spasticity in children or adolescents with cerebral palsy.[1]

Oral doses of 30 to 80 mg daily are usually quite well tolerated,[2] but patients with severe spasticity often require high doses of baclofen before a response occurs and, consequently, some may fail to respond because adverse effects limit increases in dosage. Intrathecal baclofen is therefore sometimes tried as this produces much higher concentrations in the CNS than oral doses.[2-4] It may be given intrathecally by bolus injection or by continuous infusion; infusion is probably preferred[5] to minimise the risk of overdosage. Because patients are screened for response before beginning continuous infusion, results have generally been good.[2] There is a large interindividual variation in the intrathecal dose required to produce improvement in spasticity (see Uses and Administration, above). An increased dose of baclofen may be given at night to prevent spasms that interfere with sleep.

Although reports of tolerance to the effect of intrathecal baclofen have raised doubt[6] over whether long-term benefit can be maintained, long-term efficacy has been achieved.[7-10] Furthermore, some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity re-appearing and others have been able to reduce the dosage required.[11]

1. Delgado MR, *et al.* Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010; **74:** 336–43. Also available at: http://www.neurology.org/cgi/reprint/74/4/336.pdf (accessed 09/07/10)
2. Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. *Drug Safety* 2004; **27:** 799–818.
3. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; **49:** 262–7.
4. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; **36:** 21–2.
5. Penn RD, Kroin JS. Intrathecal baclofen. *N Engl J Med* 1989; **321:** 1414–15.
6. Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. *Ann Pharmacother* 1993; **27:** 767–74.
7. Penn RD, *et al.* Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* 1989; **320:** 1517–21.
8. Azouvi P, *et al.* Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. *Arch Phys Med Rehabil* 1996; **77:** 35–9.
9. Dario A, *et al.* Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. *Acta Neurol Scand* 2002; **105:** 83–7.
10. Campbell WM, *et al.* Long-term safety and efficacy of continuous intrathecal baclofen. *Dev Med Child Neurol* 2002; **44:** 660–5.
11. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; **60:** 168–73.

Stiff-man syndrome. There have been anecdotal case reports[1] of benefit with intrathecal baclofen in a patient with stiff-man syndrome (see under Muscle Spasm, p. 1064.3) inadequately controlled with other drugs or oral baclofen. However, in a double-blind placebo-controlled study[2] clinical improvement was evident in only 1 of 3 patients given intrathecal baclofen.

1. Stayer C, *et al.* Intrathecal baclofen therapy for stiff-man syndrome and progressive encephalomyelopathy with rigidity and myoclonus. *Neurology* 1997; **49:** 1591–7.
2. Silbert PL, *et al.* Intrathecal baclofen therapy in stiff-man syndrome: a double-blind, placebo-controlled trial. *Neurology* 1995; **45:** 1893–7.

Tardive dyskinesia. Baclofen is one of many drugs that have been tried in antipsychotic-induced tardive dyskinesia (see Extrapyramidal Disorders, p. 1049.2) but its efficacy is unclear. A systematic review[1] found the effects of baclofen, and other gamma-aminobutyric acid agonists to be inconclusive and unconvincing in the management of antipsychotic-induced tardive dyskinesia. The review also pointed out that the adverse effects caused by use of these drugs might outweigh any benefits.

1. Rathbone J, *et al.* Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 20/10/05).

Tetanus. The management of tetanus is described on p. 2029.2 and p. 209.2. Beneficial responses have been seen with baclofen by continuous intrathecal infusion,[1-5] usually in doses of 1 to 2 mg daily.[1,5] However, the therapeutic range of intrathecal baclofen in severe tetanus may be very narrow and deep coma with loss of spontaneous respiration and reflexes has been reported[6] after an increase in dosage from 1.2 mg to 2 mg daily. This adverse effect could be fatal in the absence of ventilatory support. To avoid the risk of secondary infection from an indwelling intraspinal catheter intermittent intrathecal baclofen has also been used.[7,8]

1. Müller H, *et al*. Intrathecal baclofen in tetanus. *Lancet* 1986; **i:** 317–18.
2. Dressnandt J, *et al*. Intrathecal baclofen in tetanus: four cases and a review of reported cases. *Intensive Care Med* 1997; **23:** 896–902.
3. Engrand N, *et al*. The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology* 1999; **90:** 1773–6.
4. Boots RJ, *et al*. The treatment of tetanus with intrathecal baclofen. *Anaesth Intensive Care* 2000; **28:** 438–42.
5. Santos ML, *et al*. Intrathecal baclofen for the treatment of tetanus. *Clin Infect Dis* 2004; **38:** 321–8.
6. Romijn JA, *et al*. Reversible coma due to intrathecal baclofen. *Lancet* 1986; **ii:** 696.
7. Demaziere J, *et al*. Intermittent intrathecal baclofen for severe tetanus. *Lancet* 1991; **337:** 427.
8. Saissy JM, *et al*. Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med* 1992; **18:** 241–4.

Tourette's syndrome. Improvement was noted in children with Tourette's syndrome (see Tics, p. 1030.1) treated with baclofen compared with placebo in a small study.[1]

1. Singer HS, *et al*. Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. *Neurology* 2001; **56:** 599–604.

Urinary incontinence. Baclofen has been used with some benefit in the management of urinary incontinence and retention (p. 2349.2) secondary to lesions of the spinal cord.

References.
1. Hachen HJ, Krucker V. Clinical and laboratory assessment of the efficacy of baclofen (Lioresal) on urethral sphincter spasticity in patients with traumatic paraplegia. *Eur Urol* 1977; **3:** 237–40.
2. Leyson JFJ, *et al*. Baclofen in the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol (Baltimore)* 1980; **124:** 82–4.
3. Kurns JJM, Delhaas EM. Intrathecal baclofen infusion in patients with spasticity and neurogenic bladder disease. *World J Urol* 1991; **9:** 153–6.

Adverse Effects

Adverse effects associated with baclofen such as sedation, somnolence, and nausea are often transient and dose-related. They may be minimised by increasing doses gradually or controlled by a reduction in dosage.

Other common adverse effects include dizziness, lassitude, lightheadedness, confusion, fatigue, muscular pain and weakness, and hypotension. Other adverse effects include euphoria, hallucinations, depression, headache, tinnitus, convulsions, paraesthesias, slurred speech, dry mouth, taste alterations, vomiting, diarrhoea or constipation, ataxia, nystagmus, tremors, insomnia, visual disturbances, rashes, pruritus, increased sweating, urinary disturbances, respiratory or cardiovascular depression, blood sugar changes, alterations in liver function values, and a paradoxical increase in spasticity. Hypothermia has been reported rarely. Problems with erection and ejaculation have also been reported with intrathecal baclofen; these are usually reversible on withdrawal of therapy.

Overdosage may lead to muscular hypotonia, hypothermia, drowsiness, respiratory depression, coma, and convulsions (see also below).

Stopping baclofen abruptly may result in a withdrawal syndrome (see under Precautions, below).

Effects on the nervous system. Epilepsy, progressing to status epilepticus, has been associated with the use of baclofen in a patient who had had no history of seizures.[1] Baclofen had been given in a dose of 80 mg daily and symptoms had resolved after gradual withdrawal and the use of antiepileptics.

1. Rush JM, Gibberd FB. Baclofen-induced epilepsy. *J R Soc Med* 1990; **83:** 115–16.

Treatment of Adverse Effects

Treatment of baclofen overdosage is symptomatic. The value of gastric decontamination in the management of overdosage with baclofen is unclear but oral activated charcoal may be considered if given within 1 hour of ingesting more than 3 mg/kg. Haemodialysis or haemofiltration should be considered in severe cases. Observation should continue for at least 6 hours after ingestion. For the use of physostigmine salicylate in the treatment of intrathecal baclofen overdosage, see below.

Overdosage. Atropine sulfate 600 micrograms intravenously[1] was used to treat a patient who had ingested 420 mg of baclofen and had failed to improve after gastric lavage and induced diuresis. Bradycardia, hypotension, hypothermia, and respiratory depression all improved and no further treatment was needed. The clinical course and management of acute intoxication in 8 adolescents, who ingested estimated amounts of baclofen ranging from 60 to more than 600 mg, has also been described.[2]

Accidental *intrathecal* overdosage has caused respiratory depression, decreased alertness, coma, muscle weakness, and vomiting.[3] Mild intrathecal bolus overdoses of baclofen in patients without cardiac compromise have been treated using physostigmine although the use of physostigmine in poisoning is now generally considered hazardous (see Antimuscarinic Poisoning, p. 2010.1). Physostigmine salicylate was given intravenously in a dose of 1 to 2 mg over 5 minutes and repeated if necessary at intervals of 30 to 60 minutes.[3,4] Physostigmine was ineffective in a patient who accidentally received 10 mg of baclofen intrathecally;[5] in such severe overdosage, respiratory support and time to recover is needed.[4] A lumbar tap to remove about 30 to 50 mL of CSF may help to reduce the intrathecal concentration of baclofen if implemented soon after the overdose.

1. Ferner RE. Atropine treatment for baclofen overdose. *Postgrad Med J* 1981; **57:** 580–1.
2. Perry HE, *et al*. Baclofen overdose: drug experimentation in a group of adolescents. *Pediatrics* 1998; **101:** 1045–8.
3. Müller-Schwefe G, Penn RD. Physostigmine in the treatment of intrathecal baclofen overdose. *J Neurosurg* 1989; **71:** 273–5.
4. Penn RD, Kroin JS. Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322:** 1533–4.
5. Saltuari L, *et al*. Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322:** 1533.

Precautions

Baclofen stimulates gastric acid secretion and should be used with caution in patients with a history of peptic ulcer and avoided in those with active peptic ulcer disease. It should also be used with caution in patients with severe psychiatric disorders or epilepsy or convulsive disorders since these disorders may be exacerbated by baclofen. Liver function should be monitored in patients with liver disease. Baclofen should be used with caution in patients with renal impairment; a reduced dose should be given (see also Renal Impairment, below). Baclofen should also be used with caution in patients with respiratory impairment. Observations of increased blood sugar concentrations suggest caution in patients with diabetes mellitus. Care is also required in the elderly, in whom adverse effects may be more common, and in patients with cerebrovascular disease (who tolerate baclofen poorly). It should be used with caution in patients who use their spasticity to maintain posture or to increase function. Urine retention may be exacerbated in patients with hypertonic bladder sphincters. Baclofen may cause drowsiness; patients affected should not drive or operate machinery.

Abrupt withdrawal of baclofen may result in a withdrawal syndrome and exacerbation of spasticity; dosage should be reduced gradually over at least 1 to 2 weeks, or longer if symptoms occur.

Anaesthesia. Acute bradycardia and hypotension occurred after rib retraction in 3 patients given baclofen 30 mg orally 90 minutes before thoracic surgery under general anaesthesia, but not in a further 3 patients given placebo.[1] Giving atropine and ephedrine relieved bradycardia and hypotension in 2 patients, but a brief cardiac arrest occurred in 1. Baclofen may disturb autonomic control of the circulation during general anaesthesia and surgery.

1. Sill JC, *et al*. Bradycardia and hypotension associated with baclofen used during general anaesthesia. *Anesthesiology* 1986; **64:** 255–8.

Breast feeding. The concentrations of baclofen found in breast milk are small[1] and UK licensed product information states that no undesirable effects are to be expected in breast-fed infants. The American Academy of Pediatrics also considers that baclofen is usually compatible with breast feeding; no adverse effects have been seen in breast-feeding infants whose mothers were receiving baclofen.[2]

1. Eriksson G, Swahn C-G. Concentrations of baclofen in serum and breast milk from a lactating woman. *Scand J Clin Lab Invest* 1981; **41:** 185–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 23/06/04)

Peptic ulcer. Results of a study of baclofen-stimulated gastric acid secretion in 10 healthy subjects given 600 micrograms/kg intravenously suggested that patients on baclofen might be at risk from baclofen-induced hyperacidity.[1]

1. Pugh S, *et al*. Clinical and experimental significance of the newly discovered activity of baclofen (PCP-GABA) as a stimulant of gastric acid secretion. *Gut* 1985; **26:** A545.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies baclofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy and the neonate. Two successful pregnancies have been reported[1] in a woman receiving intrathecal baclofen; there was no evidence of teratogenicity, and neurodevelopmental outcome in the children seemed normal. However, convulsions were seen in a week-old infant whose mother had taken oral baclofen during pregnancy.[2] The convulsions, which were refractory to antiepileptics, lidocaine, and pyridoxine, ceased within 30 minutes of giving baclofen to the infant.

1. Calderón Muñoz F, *et al*. Pregnancy outcome in a woman exposed to continuous intrathecal baclofen infusion. *Ann Pharmacother* 2000; **34:** 956.
2. Ratnayaka BDM, *et al*. Neonatal convulsions after withdrawal of baclofen. *BMJ* 2001; **323:** 85.

Renal impairment. There have been reports of baclofen toxicity in patients with severe renal impairment.[1] Most patients had received oral doses of 15 mg or more of baclofen daily although some dialysis patients still developed toxic symptoms after having received the manufacturer's suggested dose of 5 mg daily for only 4 days or after a cumulative dose of only 15 mg. The most common symptom of toxicity was impaired consciousness which often occurred within 12 hours of ingestion.

1. Su W, *et al*. Reduced level of consciousness from baclofen in people with low kidney function. *BMJ* 2009; **339:** b4559. Available at: http://www.bmj.com/content/339/bmj.b4559?view=long&pmid=20044395 (accessed 29/03/12)

Respiratory disorders. Baclofen might precipitate bronchoconstriction in susceptible individuals. A patient with asthma developed symptomatic bronchoconstriction after taking baclofen on two separate occasions.[1] Another patient who had a history of exercise-induced dyspnoea and wheezing was found to have bronchial hyperresponsiveness to methacholine only after taking baclofen.

1. Dicpinigaitis PV, *et al*. Baclofen-induced bronchoconstriction. *Ann Pharmacother* 1993; **27:** 883–4.

Withdrawal. Psychiatric reactions including hallucinations, paranoia, delusions, psychosis, anxiety, confusion, and agitation have been reported[1-5] on abrupt withdrawal of oral baclofen; symptoms generally resolved on restarting. Convulsions have also been reported.[6] The abrupt withdrawal of intrathecal baclofen may also result in high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity which in rare cases has advanced to rhabdomyolysis, multiple organ failure, and death.[7-9]

Except for serious adverse reactions, the dose of oral baclofen should be gradually reduced: the UK CSM recommends reduction over at least 1 to 2 weeks or longer if symptoms occur. Similarly, the FDA has advised against the abrupt withdrawal of intrathecal baclofen.[9]

1. Lees AJ, *et al*. Hallucinations after withdrawal of baclofen. *Lancet* 1977; **i:** 858.
2. Stein R. Hallucinations after sudden withdrawal of baclofen. *Lancet* 1977; **ii:** 44–5.
3. Harrison SA, Wood CA. Hallucinations after preoperative baclofen discontinuation in spinal cord injury patients. *Drug Intell Clin Pharm* 1985; **19:** 747–9.
4. CSM/MCA. Severe withdrawal reactions with baclofen. *Current Problems* 1997; **23:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Leo RJ, Baer D. Delirium associated with baclofen withdrawal: a review of common presentations and management strategies. *Psychosomatics* 2005; **46:** 503–7.
6. Barker I, Grant IS. Convulsions after abrupt withdrawal of baclofen. *Lancet* 1982; **ii:** 556–7.
7. Grenier B, *et al*. Hyperthermie grave liée à un sevrage brutal de baclofène administré de façon continue par voie intrathécale. *Ann Fr Anesth Reanim* 1996; **15:** 659–62.
8. Green LB, Nelson VS. Death after acute withdrawal of intrathecal baclofen: case report and literature review. *Arch Phys Med Rehabil* 1999; **80:** 1600–4.
9. Coffey RJ [Medtronic]. Important drug warning (issued April 2002). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM170907.pdf (accessed 22/01/10)

Interactions

Alcohol and other CNS depressants may exacerbate the CNS effects of baclofen and should be avoided; severe aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium. There may be increased weakness if baclofen is given to patients taking a tricyclic antidepressant and there may be an increased hypotensive effect if it is given to patients receiving antihypertensive therapy. Ibuprofen (see NSAIDs, p. 2017.1) and other drugs that produce renal insufficiency may reduce baclofen excretion leading to toxicity.

Dopaminergics. For reports of patients with Parkinson's disease taking *levodopa* who have had adverse effects when given baclofen, see under Levodopa, on p. 907.3.

NSAIDs. There has been a report of an elderly patient who developed baclofen toxicity after *ibuprofen* therapy was also started.[1] It appeared that acute renal insufficiency caused by ibuprofen had impaired baclofen excretion.

1. Dahlin PA, George J. Baclofen toxicity associated with declining renal clearance after ibuprofen. *Drug Intell Clin Pharm* 1984; **18:** 805–8.

Pharmacokinetics

Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract after an oral dose. Peak plasma concentrations occur about 0.5 to 3 hours after ingestion, but the rate and extent of absorption vary between patients, and may vary inversely with the dose. After oral doses some baclofen crosses the blood-brain barrier, with concentrations in CSF about 12% of those in the plasma. About 30% of baclofen is bound to plasma proteins. About 70 to 80% of a dose is excreted in the urine mainly as unchanged drug; about 15% is metabolised in the liver. The elimination half-life of baclofen is about 3 to 4 hours in plasma and about 1 to 5 hours in the CSF. Baclofen crosses the placenta and is distributed into breast milk.

Absorption. A crossover study in 5 healthy subjects given baclofen 20 mg orally after an overnight fast or a standardised breakfast showed that baclofen was rapidly absorbed in both cases, and the rate and extent of absorption were not significantly altered by the presence of food.[1] There is no need to modify the current practice of giving baclofen with food to minimise gastrointestinal adverse effects.

1. Peterson GM, *et al*. Food does not affect the bioavailability of baclofen. *Med J Aust* 1985; **142:** 689–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Baclodox†; Bafen; Lioresal; ***Austral.***: Baclo†; Clofen; Lioresal; Stelax; ***Austria***: Lioresal; ***Belg.***: Lioresal; ***Braz.***: Baclon; Lioresal; ***Canad.***: Lioresal; Nu-Baclo; ***Chile***: Cetril; Lioresyl; ***China***: Lioresal (力奥来素); Spinax (郝智); Zufen (枢芬); ***Denm.***: Lioresal; ***Fin.***: Lioresal; ***Fr.***: Lioresal; ***Ger.***: Lebic†; Lioresal; ***Gr.***: Glasbor; Jofen; Lioresal; Miorel; Vioridon; ***Hong Kong***: Clofen†; Lioresal; Stelax; ***Hung.***: Lioresal; ***India***: Baclan; Bacmax; Chinofen; Liofen; Lioresal; Parafon DSC; ***Indon.***: Lioresal; ***Irl.***: Baclopar; Lioresal; ***Israel***: Baclosal; Lioresal; ***Ital.***: Lioresal; ***Malaysia***: Clofen†; Lioresal; ***Neth.***: Lioresal; ***Norw.***: Lioresal; ***NZ***: Lioresal; Pacifen; ***Philipp.***: Lioresal; Onelaxant-R; ***Pol.***: Lioresal; ***Port.***: Lioresal; ***Rus.***: Baclosan (Баклосан); ***S.Afr.***: Lioresal; ***Singapore***: Colmifen; Lioresal; ***Spain***: Lioresal; ***Swed.***: Lioresal; ***Switz.***: Lioresal; ***Thai.***: Baclosal; Fenisal; Liobac; Lioresal; ***Turk.***: Lioresal; ***UK***: Lioresal; Lyflex; ***USA***: Gablofen; Kemstro†; Lioresal; ***Venez.***: Lioresal.

Pharmacopoeial Preparations
BP 2014: Baclofen Oral Solution; Baclofen Tablets;
USP 36: Baclofen Oral Suspension; Baclofen Tablets.

Botulinum Toxins

Toxinas botulínicas.
ATC — M03AX01.
ATC Vet — QM03AX01.

Description. Botulinum toxins A and B are neurotoxins produced by *Clostridium botulinum*. They are proteins comprising a heavy chain thought to be responsible for binding to the target cells and translocation of the toxin across the cell membrane, linked by a disulfide bond to a light chain responsible for the toxic activity.

Botulinum A Toxin

Botuliinitoksiini tyyppi A; Botulinum A Toksini; Toxin typ A mot botulism; Toxina botulínica A; Toxine botulinique type A; Toxinum botulinicum typum A.
UNII — E21KPY694.

Pharmacopoeias. *Eur.* (see p. vii) includes the injection.

Ph. Eur. 8: (Botulinum Toxin Type A for Injection; Toxinum Botulinicum Typum A ad Iniectabile). A dried preparation containing purified botulinum neurotoxin type A, which may be present in the form of a complex with haemagglutinins and non-toxic proteins, prepared from a suitable strain of *Clostridium botulinum* type A.

Botulinum B Toxin

Botulinum B Toksini; Botulinum Toxin Type B; Toxina botulínica B.
UNII — 0Y70779M1F.

Pharmacopoeias. *Eur.* (see p. vii) includes the injection.

Ph. Eur. 8: (Botulinum Toxin Type B for Injection; Toxinum Botulinicum B ad Iniectabile). A liquid preparation containing purified botulinum neurotoxin type B, which may be present in the form of a complex with haemagglutinins and non-toxic proteins, prepared from a suitable strain of *Clostridium botulinum* type B.

Units

The dose of preparations containing botulinum toxins A or B is expressed in terms of units, but the available preparations are used at different doses for the same indications, and the units of one preparation cannot be considered to apply to another.

Uses and Administration

Botulinum toxins cause neuromuscular blockade by inhibiting the calcium-ion mediated release of acetylcholine at the motor nerve terminals, resulting in a diminished endplate potential and subsequent flaccid paralysis of the affected muscles. The paralysis persists until new nerve terminals form, usually within 2 to 4 months.

Botulinum A toxin is given by local injection in the treatment of hemifacial spasm, blepharospasm, spasmodic torticollis, lower limb spasticity in children with cerebral palsy, and upper limb spasticity associated with stroke in adults. Botulinum A toxin is also used for the management of strabismus and hyperhidrosis, and has also been approved for the treatment of glabellar (frown) lines in adults up to 65 years of age. It is being investigated for use in the management of several other disorders. The following preparations of botulinum A toxin are available in the UK and the USA:

- *Azzalure* (*Galderma, UK*): described as botulinum A toxin-haemagglutinin complex
- *Botox* (*Allergan, UK*): described as botulinum A toxin protein complex
- *Botox/Botox Cosmetic* (*Allergan, USA*): described as onabotulinumtoxinA
- *Dysport* (*Ipsen, UK*): described as botulinum A toxin-haemagglutinin complex
- *Dysport* (*Ipsen, USA*): described as abobotulinumtoxinA
- *Vistabel* (*Allergan, UK*): described as botulinum A toxin
- *Xeomin* (*Merz, UK*): described as botulinum A toxin
- *Xeomin* (*Merz, USA*): described as incobotulinumtoxinA

Botulinum B toxin is used in the management of spasmodic torticollis and, being antigenically distinct, it has the potential for use in patients who develop resistance to treatment due to the development of antibodies to type A toxin. The following preparations of botulinum B toxin are available in the UK and the USA:

- *Myobloc* (*Solstice, USA*): described as rimabotulinumtoxinB
- *NeuroBloc* (*Eisai, UK*): described as botulinum B toxin

Doses of botulinum toxins A and B are expressed in terms of units, which have not been standardised between preparations (see under Units, above). Doses are therefore specific to each individual preparation; details are given under each indication, below, where relevant.

Botulinum F toxin is under investigation for the treatment of similar neuromuscular disorders.

Reviews.

1. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; **11:** 145–52.
2. Hughes AJ. Botulinum toxin in clinical practice. *Drugs* 1994; **48:** 888–93.
3. Cheng CM, *et al*. Unlabeled uses of botulinum toxins: a review, part 1. *Am J Health-Syst Pharm* 2006; **63:** 145–52.
4. Cheng CM, *et al*. Unlabeled uses of botulinum toxins: a review, part 2. *Am J Health-Syst Pharm* 2006; **63:** 225–32.
5. Simpson DM, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review)—report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; **70:** 1699–1706.
6. Naumann M, *et al*. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; **70:** 1707–14.

Achalasia. The treatment of choice for achalasia (see Oesophageal Motility Disorders, p. 1813.2) is mechanical dilatation of the lower oesophageal sphincter, or if necessary surgery, but more recently injection of botulinum A toxin[1-3] has been found to be effective. However, a systematic review[4] found that one year after treatment only 11 of 43 (26%) patients who received botulinum A toxin were in symptomatic remission compared with 33 of 47 (70%) patients treated with mechanical dilatation. It has been recommended that its use would be better reserved for patients thought to be at risk from mechanical dilatation or surgery.[3,5] Another study[6] showed that intrasphincteric injection of botulinum toxin A was safe and effective for the treatment of achalasia in the short and medium term, although only a weak correlation with dose emerged.

1. Pasricha PJ, *et al*. Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; **332:** 774–8. Correction. *ibid.*; **333:** 75.
2. Cuillière C, *et al*. Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin. *Gut* 1997; **41:** 87–92.
3. da Silveira EBV, Rogers AI. Treatment of achalasia with botulinum A toxin. *Am J Ther* 2002; **9:** 157–61.
4. Leyden JE, *et al*. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/01/10).
5. Spiess AE, Kahrilas PJ. Treating achalasia: from whalebone to laparoscope. *JAMA* 1998; **280:** 638–42.
6. Annesse V, *et al*. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut* 2000; **46:** 597–600.

Anal fissure. Anal fissure is a superficial tear in the mucosa of the distal anal canal characterised by pain on defaecation, rectal bleeding, and spasm of the anal sphincter. Healing, which is usually uneventful, may be helped by conservative management with bran and bulk laxatives and topical local anaesthetics for pain relief. Surgical treatment has been used for patients who develop a chronic condition but has been associated with high rates of long-term incontinence and recurrence. Although systematic reviews considered that surgery was more effective than alternative medical therapies,[1,2] some of these have been investigated.[3-6] As hypertonicity of the internal anal sphincter may be involved in the pathophysiology of chronic anal fissure, local injections of botulinum A toxin have been used to produce paresis of this sphincter.[7-9] The duration of the effect appears to be long enough to allow complete healing of the fissure in most patients although some may relapse; a long-term, follow-up study[10] involving 57 completely healed patients, noted a high recurrence rate (41.5%) once the effects of botulinum toxin disappeared. Temporary incontinence had been the only adverse effect reported during treatment.

Topical application of nitrates can relax the anal sphincter; benefit from topical application of glyceryl trinitrate has been reported,[11-13] although a high rate of spontaneous resolution with placebo has cast doubt over the degree of advantage in some studies.[1,12] Follow-up[14] of patients treated with glyceryl trinitrate indicated that after 24 to 38 months most had not had further problems or had had occasional recurrences which in the majority of cases had responded to further topical treatment. Isosorbide dinitrate ointment has also been tried, and may be of benefit with botulinum A toxin.[15]

Topical calcium antagonists also seem to be effective. Both diltiazem[16-18] and nifedipine[19,20] seem to be of benefit and there is evidence that they may be a better choice than topical glyceryl trinitrate.[19,20] Nifedipine has been combined with botulinum toxin;[20] it has also been given orally.[21]

1. Nelson R. A systematic review of medical therapy for anal fissure. *Dis Colon Rectum* 2004; **47:** 422–31.
2. Nelson R. Non surgical therapy for anal fissure. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/05/08).
3. Cook TA, *et al*. The pharmacology of the internal anal sphincter and new treatments of ano-rectal disorders. *Aliment Pharmacol Ther* 2001; **15:** 887–98.
4. American Gastroenterological Association. American Gastroenterological Association medical position statement: diagnosis and care of patients with anal fissure. *Gastroenterology* 2003; **124:** 233–4.
5. Madoff RD, Fleshman JW. AGA technical review on the diagnosis and care of patients with anal fissure. *Gastroenterology* 2003; **124:** 235–45.
6. Wray D, *et al*. Anal fissure: a review. *Br J Hosp Med* 2008; **69:** 455–8.
7. Jost WH, Schimrigk K. Botulinum toxin in therapy of anal fissure. *Lancet* 1995; **345:** 188–9.
8. Maria G, *et al*. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med* 1998; **338:** 217–20.
9. Jost WH. Ten years' experience with botulin toxin in anal fissure. *Int J Colorectal Dis* 2002; **17:** 298–302.
10. Minguez M, *et al*. Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. *Gastroenterology* 2002; **123:** 112–17.
11. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; **349:** 11–14. Correction. *ibid.*: 656.
12. Bailey HR, *et al*. Fissure Study Group. A study to determine the nitroglycerin ointment dose and dosing interval that best promote the healing of chronic anal fissures. *Dis Colon Rectum* 2002; **45:** 1192–9.
13. Scholefield JH, *et al*. A dose finding study with 0.1 %, 0.2%, and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures. *Gut* 2003; **52:** 264–9.
14. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; **352:** 1681.
15. Lysy J, *et al*. Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure. *Gut* 2001; **48:** 221–4.
16. Jonas M, *et al*. A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.
17. Jonas M, *et al*. Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; **45:** 1091–5.
18. Bielecki K, Kolodziejczak M. A prospective randomized trial of diltiazem and glyceryltrinitrate ointment in the treatment of chronic anal fissure. *Colorectal Dis* 2003; **5:** 256–7.
19. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; **46:** 805–8.
20. Tranqui P, *et al*. Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. *Can J Surg* 2006; **49:** 41–5.
21. Cook TA, *et al*. Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; **86:** 1269–73.

Anismus. Anismus is a condition in which inappropriate contraction of the anal sphincters occurs when bowel evacuation is attempted; it seems to be a form of dystonia.

Treatment with botulinum A toxin was investigated in 7 patients with intractable constipation due mainly to anismus.[1] The toxin was injected bilaterally into the puborectalis muscle using an electromyographically guided needle; patients were allowed to continue with their laxatives throughout the study if required. Symptoms improved in all but one of the patients, although two patients could not be regarded as treatment successes

because they developed faecal incontinence; four patients had an excellent clinical outcome. However, another study involving 24 patients found the clinical efficacy of botulinum A toxin to be limited.[2]

1. Hallan RI, *et al.* Treatment of anismus in intractable constipation with botulinum A toxin. *Lancet* 1988; **ii:** 714–17.
2. Ron Y, *et al.* Botulinum toxin type-A in therapy of patients with anismus. *Dis Colon Rectum* 2001; **44:** 1821–6.

Blepharospasm. Blepharospasm is a focal dystonia characterised by repeated involuntary blinking caused by spasms of the orbicularis oculi muscle of the eye, and can result in functional blindness. Blepharospasm is often associated with other dystonias of the head and neck, such as Meige syndrome, in which patients also suffer from involuntary contractures of the muscles around the mouth. Oral drug treatment as used for dystonias in general (see p. 903.3) is usually ineffective, and surgery (facial nerve avulsion) is often followed by recurrent spasm.[1] Local injections of botulinum A toxin into the orbicularis oculi muscle mimic the effect of surgical denervation of the muscle and are reported[2-6] to have been effective in over 70% of patients; they are now generally considered[7] to be the treatment of choice. Symptomatic improvement has been reported to last from about 9 to 15 weeks; no increase in duration of effect is apparent after multiple injections. In one retrospective study in patients with blepharospasm and Meige syndrome, treatment with botulinum A toxin was still effective in most patients 11 years after the start of therapy.[4]

For blepharospasm botulinum A toxin is injected into the orbicularis oculi of the upper and lower lids; injection into additional sites in the brow area and upper facial area may be indicated if the spasms interfere with vision. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*:

- The preparation *Botox* (*Allergan, UK*) is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 3 days and reaches a peak after 1 to 2 weeks; each treatment lasts for about 3 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit. *Botox* (*Allergan*) is also available in the USA and given in similar doses, although higher cumulative doses of up to 200 units are allowed in a 30-day period.
- The preparation *Xeomin (Merz, UK)* is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 4 days; each treatment lasts for about 3 to 4 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit. *Xeomin* (*Merz*) is also available in the USA for use in patients who have previously been treated with *Botox*; the total initial dose in both eyes should not exceed 70 units.
- For the preparation *Dysport* (*Ipsen, UK*) the initial dose is a total of 120 units per eye given as subcutaneous injections of 20 and 40 units per site. Subsequently the total dose may need to be reduced to 60 to 80 units per eye. With this preparation the relief of symptoms may begin within 2 to 4 days with a maximum effect being obtained within 2 weeks. Injections of *Dysport* should be repeated every 12 weeks or as required.

1. Kennedy RH, *et al.* Treatment of blepharospasm with botulinum toxin. *Mayo Clin Proc* 1989; **64:** 1085–90.
2. Grandas F. Blepharospasm: a review of 264 patients. *J Neurol Neurosurg Psychiatry* 1988; **51:** 767–72.
3. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; **239:** 5–8.
4. Mauriello JA, *et al.* Treatment selections of 239 patients with blepharospasm and Meige syndrome over 11 years. *Br J Ophthalmol* 1996; **80:** 1073–6.
5. Defazio G, Livrea P. Primary blepharospasm: diagnosis and management. *Drugs* 2004; **64:** 237–44.
6. Costa J, *et al.* Botulinum toxin type A therapy for blepharospasm. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 28/03/06).
7. Hallett M, *et al.* Update on blepharospasm: report from the BEBRF International Workshop. *Neurology* 2008; **71:** 1275–82.

Cosmetic use. Botulinum A toxin has been used for the cosmetic treatment of facial lines and wrinkles and age-related neck degeneration.[1-5]

For the temporary improvement in appearance of moderate to severe glabellar (frown) lines two doses of botulinum A toxin are injected into each of the corrugator muscles (not closer than 1 cm above the central eyebrow) and one dose into the procerus muscle. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*:

- The preparation *Botox Cosmetic* (*Allergan, USA*) is given in a dose of 4 units into each of 5 sites to a total dose of 20 units. An effect is obtained in 1 to 2 days which increases in intensity in the first week; each treatment lasts for about 3 to 4 months. More frequent dosing is not recommended as safety and efficacy have not been evaluated. A preparation with a similar dosage regimen (*Vistabel; Allergan, UK*) is available in the UK.
- The preparation *Dysport* (*Ipsen, USA*) is given in a dose of 10 units into each of 5 sites to a total dose of 50 units. Each treatment may last for up to 4 months and it should be given no more frequently than every 3 months.
- The preparation *Azzalure* (*Galderma, UK*) is also available for such use. A dose of 10 units is given into each of 5 sites to a total dose of 50 units. Each treatment lasts for up to 4, in some cases 5, months. The treatment interval should be no more frequent than every 3 months.

1. Olver JM. Botulinum toxin A treatment of overactive corrugator supercilii in thyroid eye disease. *Br J Ophthalmol* 1998; **82:** 528–33.
2. Song KH. Botulinum toxin type A injection for the treatment of frown lines. *Ann Pharmacother* 1998 **32:** 1365–7.
3. Anonymous. Cosmetic use of botulinum toxin. *Med Lett Drugs Ther* 1999; **41:** 63–4.
4. Anonymous. Botulinum toxin (Botox Cosmetic) for frown lines. *Med Lett Drugs Ther* 2002; **44:** 47–8.
5. Carruthers A. Botulinum toxin type A: history and current cosmetic use in the upper face. *Dis Mon* 2002; **48:** 299–322.

Gastric motility disorders. Some benefit has been reported from the use of botulinum A toxin injection in gastric motility disorders (p. 1805.2). In an open-label study[1] 6 diabetic patients with gastroparesis had an improvement in gastric emptying after treatment with botulinum A toxin. A literature search[2] was only able to find case reports, case series, and open-label studies on the use of botulinum A toxin for gastroparesis.

1. Ezzeddine D, *et al.* Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002; **55:** 920–3.
2. DeSantis ERH, Huang S. Botulinum toxin type A for treatment of refractory gastroparesis. *Am J Health-Syst Pharm* 2007; **64:** 2237–40.

Hand dystonia. Hand dystonia, or hand cramp, is a type of focal dystonia (p. 903.3). It is more commonly reported in people who perform repetitive movements with their hands, such as writers, keyboard operators, and musicians. Treatment was traditionally with antimuscarinics, although with limited success, but botulinum toxin has increasingly become the first-line option.[1] A double-blind study reported that 8 out of 10 patients had greater subjective improvement in focal hand dystonia, compared with placebo, after treatment with intramuscular botulinum A toxin; objective improvement in muscle strength was seen in 6 patients.[2] However, pain and severe weakness in the shoulder region resembling neuralgic amyotrophy has been reported[3] in 2 patients injected with botulinum A toxin for writer's cramp. It was considered that if unexplained pain occurred in the shoulder or upper arm after a first injection of botulinum A toxin further injections were contra-indicated.

1. Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. *Mov Disord* 2004; **19** (suppl 8): S116–S119.
2. Cole R, *et al.* Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord* 1995; **10:** 466–71.
3. Sheean GL, *et al.* Pain and remote weakness in limbs injected with botulinum toxin A for writer's cramp. *Lancet* 1995; **346:** 154–6.

Headache. The therapeutic effect of botulinum A toxin in headache was first seen as a coincidental side effect in patients receiving the drug for hyperfunctional facial lines. A review[1] of subsequent studies concluded that efficacy could be shown for the prophylaxis of migraine (p. 670.3); a small number of patients who received treatment during the acute phase of a migraine attack also had pain relief. However, other reviews[2,3] have concluded that, despite promising initial results, there was limited evidence from controlled studies to support the use of botulinum toxins in the management of migraine. More recently, studies using stricter inclusion criteria have shown positive results with botulinum A toxin in patients with chronic migraine.[4] In the UK, botulinum A toxin as the preparation *Botox* (*Allergan, UK*) is licensed for the prophylaxis of headaches in adults with chronic migraine; this is defined as headaches on at least 15 days each month of which at least 8 days are with migraine. The recommended total dose, given intramuscularly, is 155 to 195 units which should be divided across 7 specific head and neck muscle areas: frontalis: total of 20 units over 4 sites; corrugator: total of 10 units over 2 sites; procerus: total of 5 units at one site; occipitalis: total of 30 to 40 units over 6 to 8 sites; temporalis: total of 40 to 50 units over 8 to 10 sites; trapezius: total of 30 to 50 units over 6 to 10 sites; cervical paraspinal muscle group: total of 20 units over 4 sites. Injections may be repeated every 12 weeks. *Botox* (*Allergan*) is also available in the USA for the management of chronic migraine; it is given in a similar manner.

Contradictory results had been reported in the studies evaluating tension-type headache (p. 671.3).[2,5-7] However, in the original review[1] it was emphasised that an important finding had been the need to inject botulinum A toxin at the site of the pain or trigger points and not on a standardised basis, and that this should be considered in future studies. Improvement had been noted in individual cases of cluster headache (p. 670.1) and in some patients with headache attributed to disorders of the neck.

Some benefit has also been seen with botulinum B toxin in the treatment of migraine and tension-type headaches.[8]

1. Göbel H, *et al.* Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. *J Neurol* 2001; **248** (suppl 1): 34–8.
2. Schulte-Mattler WJ, Martinez-Castrillo JC. Botulinum toxin therapy of migraine and tension-type headache: comparing different botulinum toxin preparations. *Eur J Neurol* 2006; **13** (suppl 1): 51–4.
3. Gupta VK. Botulinum toxin a treatment for migraine? A systematic review. *Pain Med* 2006; **7:** 386–94.
4. Ashkenazi A. Botulinum toxin type a for chronic migraine. *Curr Neurol Neurosci Rep* 2010; **10:** 140–6.
5. Ondo WG, *et al.* Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia* 2004; **24:** 60–5.
6. Schulte-Mattler WJ, *et al.* Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain* 2004; **109:** 110–14.
7. Rozen D, Sharma J. Treatment of tension-type headache with Botox: a review of the literature. *Mt Sinai J Med* 2006; **73:** 493–8.
8. Fadeyi MO, Adams QM. Use of botulinum toxin type B for migraine and tension headaches. *Am J Health-Syst Pharm* 2002; **59:** 1860–2.

Hemifacial spasm. Hemifacial spasm is characterised by involuntary unilateral synchronous contractions of muscles innervated by the facial nerve. The spasms usually begin with twitching of muscles around the eye or mouth but as the disease progresses their frequency increases and they spread to involve the rest of the facial muscles. Hemifacial spasm may be improved by surgery but there is a risk of irreversible paralysis. Few drugs are effective for hemifacial spasm but carbamazepine has been reported to have been of help on occasions. Reports suggest that injections of botulinum A toxin may be effective in relieving symptoms in at least 75% of patients but there do not appear to be any studies comparing it against other treatments. Repeat injections are required by most patients every 3 to 4 months but long-term efficacy appears to be maintained. Dosage regimens of botulinum A toxin used in hemifacial spasm are similar to those used for blepharospasm (see above) although an electromyographically guided needle may be required to identify small muscles around the mouth.

References.

1. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; **239:** 5–8.
2. Chen R-S, *et al.* Botulinum toxin A injection in the treatment of hemifacial spasm. *Acta Neurol Scand* 1996; **94:** 207–11.
3. Boghen DR, Lesser RL. Blepharospasm and hemifacial spasm. *Curr Treat Options Neurol* 2000; **2:** 393–400.
4. Jost WH, Kohl A. Botulinum toxin: evidence-based medicine criteria in blepharospasm and hemifacial spasm. *J Neurol* 2001; **248** (suppl 1): 21–4.
5. Defazio G, *et al.* Botulinum toxin A treatment for primary hemifacial spasm: a 10-year multicenter study. *Arch Neurol* 2002; **59:** 418–20.
6. Costa J, *et al.* Botulinum toxin type A therapy for hemifacial spasm. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).

Hyperhidrosis. Various drugs and surgical techniques have been used in the treatment of hyperhidrosis (p. 1685.1). Botulinum A toxin is used in the management of focal hyperhidrosis because of its ability to block cholinergic transmission at nerve terminals innervating the sweat glands. Encouraging results have been obtained in patients with severe resistant focal hyperhidrosis using intradermal[1,2] or subcutaneous[3,4] injections and results from two larger multicentre studies[5,6] confirm that intradermal injection of botulinum A is effective and well-tolerated for the treatment of axillary hyperhidrosis. In the UK, it is given for this purpose as the preparation *Botox* (*Allergan, UK*), by intradermal injection in doses of 50 units to each axilla, evenly distributed in multiple sites about 1 to 2 cm apart. Clinical improvement generally occurs within a week of injection, and may last for 4 to 7 months; repeat injections may be given once the effects of the previous injection have subsided. *Botox* (*Allergan*) is also available in the USA for the treatment of axillary hyperhidrosis; it is given in similar doses.

Some workers[7] prefer to use intradermal injections for palmar hyperhidrosis in order to minimise the risk of reversible weakness of the small muscles of the hand reported with subcutaneous injection.

1. Naumann M, *et al.* Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. *Arch Dermatol* 1998; **134:** 301–4.
2. Schnider P, *et al.* Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; **145:** 289–93.
3. Schnider P, *et al.* Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *Br J Dermatol* 1997; **136:** 548–52.
4. Schnider P, *et al.* Uses of botulinum toxin. *Lancet* 1997; **349:** 953.
5. Heckmann M, *et al.* Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; **344:** 488–93.
6. Naumann M, *et al.* Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. *BMJ* 2001; **323:** 596–9.
7. Heckmann M, *et al.* Optimizing botulinum toxin therapy for hyperhidrosis. *Br J Dermatol* 1998; **138:** 553–4.

Hyperlachrymation. Botulinum A toxin may be of benefit[1,2] in the management of hyperlachrymation ('crocodile tears').

1. Riemann R, *et al.* Successful treatment of crocodile tears by injection of botulinum toxin into the lacrimal gland: a case report. *Ophthalmology* 1999; **106:** 2322–4.
2. Keegan DJ, *et al.* Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. *Br J Ophthalmol* 2002; **86:** 43–6.

Laryngeal dystonias. Botulinum A toxin has been tried in the treatment of spasmodic dysphonia,[1-3] focal laryngeal dystonia,[4] and dysfunctional spasm after total laryngectomy.[5] Botulinum B toxin has also been used.[6]

1. Whurr R, *et al.* Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review of 22 studies. *Int J Lang Commun Disord* 1998; **33** (suppl): 327–9.
2. Gibbs SR, Blitzer A. Botulinum toxin for the treatment of spasmodic dysphonia. *Otolaryngol Clin North Am* 2000; **33:** 879–94.
3. Watts C, *et al.* Botulinum toxin injections for the treatment of spasmodic dysphonia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 07/05/08).
4. Marion M-H, *et al.* Stridor and focal laryngeal dystonia. *Lancet* 1992; **339:** 457–8.
5. Crary MA, *et al.* Using botulinum toxin A to improve speech and swallowing function following total laryngectomy. *Arch Otolaryngol Head Neck Surg* 1996; **122:** 760–3.
6. Sataloff RT, *et al.* Botulinum toxin type B for treatment of spasmodic dysphonia: a case report. *J Voice* 2002; **16:** 422–4.

Micturition disorders. Preliminary results[1] suggest that injection of botulinum A toxin into the detrusor muscle can increase functional bladder capacity and restore continence in patients with urinary incontinence (p. 2349.2) after spinal cord injury who are resistant to antimuscarinics. Similar results[2] have been found in children with detrusor hyperreflexia caused by myelomeningocele.

Botulinum A toxin has also been tried in other bladder dysfunctions.[3,4] Reviews[5,6] have concluded that although there is some evidence that injection of botulinum toxins into the detrusor wall can improve symptoms of overactive bladder syndrome, further studies are warranted.

In a few small studies[7,8] the injection of botulinum A toxin into the prostate gland has been reported to relieve the symptoms of urinary retention associated with benign prostatic hyperplasia (p. 2347.1).

1. Schurch B, *et al.* Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol (Baltimore)* 2000; **164:** 692–7.
2. Schulte-Baukloh H, *et al.* Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *Urology* 2002; **59:** 325–7.
3. Phelan MW, *et al.* Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. *J Urol (Baltimore)* 2001; **165:** 1107–10.
4. Smith CP, *et al.* Botulinum toxin in urology: evaluation using an evidence-based medicine approach. *Nat Clin Pract Urol* 2004; **1:** 31–7.
5. Schurch B. Botulinum toxin for the management of bladder dysfunction. *Drugs* 2006; **66:** 1301–18.
6. Duthie J, *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).
7. Maria G, *et al.* Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003; **62:** 259–65.
8. Kuo H-C. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005; **65:** 670–4.

Nystagmus. Surgery, corrective spectacles, and drug therapy have all been tried for the treatment of nystagmus (rapid involuntary movement of the eyeball). Retrobulbar injection of botulinum A toxin has produced improvement in patients with acquired or congenital nystagmus.[1-4] In 6 patients with acquired nystagmus visual acuity was improved, and the amplitude of the nystagmus was reduced, but the frequency was generally unchanged and the need for repeated injections and adverse effects such as diplopia limited patient acceptability.[1]

1. Repka MX, *et al.* Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; **112:** 1320–4.
2. Carruthers J. The treatment of congenital nystagmus with Botox. *J Pediatr Ophthalmol Strabismus* 1995; **32:** 306–8.
3. Lennerstrand G, *et al.* Treatment of strabismus and nystagmus with botulinum toxin type A: an evaluation of effects and complications. *Acta Ophthalmol Scand* 1998; **76:** 27–37.
4. Stahl JS, *et al.* Medical treatment of nystagmus and its visual consequences. *J R Soc Med* 2002; **95:** 235–7.

Ocular surgery. Ptosis is a common adverse effect of botulinum A toxin but therapeutic ptosis induced with botulinum toxin has been described as a useful adjunct in the management of patients undergoing epikeratoplasty since it promoted stabilisation of the epithelium on the graft.[1]

1. Freegard T, *et al.* Therapeutic ptosis with botulinum toxin in epikeratoplasty. *Br J Ophthalmol* 1993; **77:** 820–2.

Pain. There have been anecdotal reports of the use of botulinum A toxin in the treatment of painful disorders such as postcholecystectomy pain associated with sphincter of Oddi dysfunction,[1] and relief of orofacial pain associated with temporomandibular joint dysfunction[2] and facial arthromyalgia.[3] Promising results have been obtained from an open study[4] investigating botulinum toxin as a treatment for chronic refractory tennis elbow in 14 patients. Its efficacy in relieving pain in other chronic conditions such as low back pain, and myofascial pain, in addition to improving function, has also been shown in individual studies.[5] A small pilot study[6] found that botulinum A toxin reduced diabetic neuropathic pain in the feet. The general management of pain is discussed on p. 4.2 with separate sections on biliary and renal colic (p. 6.3), diabetic neuropathy (p. 8.2), low back pain (p. 9.2), orofacial pain (p. 10.2), and soft-tissue rheumatism (p. 14.2).

1. Pasricha PJ, *et al.* Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. *Gut* 1994; **35:** 1319–21.
2. Girdler NM. Use of botulinum toxin to alleviate facial pain. *Br J Hosp Med* 1994; **52:** 363.
3. Girdler NM. Uses of botulinum toxin. *Lancet* 1997; **349:** 953.
4. Morré HHE, *et al.* Treatment of chronic tennis elbow with botulinum toxin. *Lancet* 1997; **349:** 1746.
5. Lang AM. Botulinum toxin therapy for myofascial pain disorders. *Curr Pain Headache Rep* 2002; **6:** 355–60.
6. Yuan R-Y, *et al.* Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. *Neurology* 2009; **72:** 1473–8.

Sialorrhoea. Botulinum toxins may be effective in the treatment of sialorrhoea and drooling associated with conditions such as cerebral palsy[1] and Parkinson's disease.[2] A review[3] found botulinum toxin A to be safe and effective in the treatment of sialorrhoea; however, further studies are warranted.

1. Jongerius PH, *et al.* Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. *Pediatrics* 2004; **114:** 620–7.
2. Ondo WG, *et al.* A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. *Neurology* 2004; **62:** 37–40.
3. Benson J, Daugherty KK. Botulinum toxin A in the treatment of sialorrhea. *Ann Pharmacother* 2007; **41:** 79–85.

Spasmodic torticollis. Spasmodic torticollis (cervical dystonia) is a focal dystonia (p. 903.3) characterised by spasmodic rotation of the head as a result of dystonic spasm of the neck muscles. The head may turn to one side (torticollis), extend (retrocollis), or flex (antecollis). Spasms may be repetitive or sustained. Response of spasmodic torticollis to drug therapy is usually poor and surgery has been associated with potentially serious complications. Intramuscular injections of botulinum toxins can be effective but dysphagia, which can have severe consequences (see under Adverse Effects, p. 2021.1) occurs in a significant number of patients. Other adverse effects have included lethargy, local weakness, vertigo, and dysphonia.

When injecting botulinum toxins localisation of the involved muscles with electromyographic guidance may be useful. Multiple injection sites allow more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. Bilateral injection of the sternocleidomastoid muscle is not recommended as there is an increased risk of adverse effects, especially dysphagia. Reduced doses may be required for patients with reduced muscle mass.

Doses of botulinum toxins, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation.*

In the UK the usual initial dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 500 units injected in divided doses into the two or three most active neck muscles:

- for *rotational torticollis*, 350 units is given initially into the splenius capitis muscle (ipsilateral to the direction of the chin/head rotation) and 150 units into the sternocleidomastoid muscle (contralateral to rotation)
- for *laterocollis*, 350 units is given initially into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternocleidomastoid muscle; if associated with *shoulder elevation*, ipsilateral trapezoid or levator scapulae muscles may also require treatment; if 3 muscles need treatment, 300 units are injected into the splenius capitis muscle, 100 units into the sternocleidomastoid muscle, and 100 units into the third muscle
- for *retrocollis*, 250 units is given into each of the splenius capitis muscles which may be followed after 6 weeks by bilateral trapezius injections in a dose of up to 250 units per muscle; bilateral splenii injections may increase the risk of neck muscle weakness

Subsequent doses may range from 250 to 1000 units, although the higher doses may be accompanied by an increase in adverse effects such as dysphagia; doses above 1000 units are not recommended. An initial effect is usually seen within 1 week; injections usually need to be repeated every 12 weeks or as required. A preparation with a similar dosage regimen (*Dysport; Ipsen, USA*) is also available in the USA.

In the UK, botulinum A toxin as the preparation *Xeomin (Merz, UK)* is indicated for spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements. In practice, the maximum total dose is usually not more than 200 units but up to 300 units may be given. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia. An initial effect is usually observed within 1 week; each treatment lasts for about 3 to 4 months and injections may be repeated if necessary after at least 10 weeks. *Xeomin* (*Merz*) is also available in the USA for the treatment of spasmodic torticollis.

Recommended doses in the UK for botulinum A toxin as the preparation *Botox* (*Allergan, UK*) are listed below but licensed product information states that in practice the maximum total dose is not usually more than 200 units. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia.

- *Type I* (head rotated toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 50 to 100 units divided amongst at least 2 sites; levator scapulae: total of 50 units amongst 1 or 2 sites; scalene: total of 25 to 50 units amongst 1 or 2 sites; splenius capitis: total of 25 to 75 units amongst 1 to 3 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type II* (head rotation only)—sternocleidomastoid muscle: total dosage of 25 to 100 units divided amongst at least 2 sites if more than 25 units is given
- *Type III* (head tilted toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 25 to 100 units at posterior border divided amongst at least 2 sites if more than 25 units is given; levator scapulae: total of 25 to 100 units amongst at least 2 sites; scalene: total of 25 to 75 units amongst at least 2 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type IV* (bilateral posterior cervical muscle spasm with elevation of the face)—splenius capitis and splenius cervicis: a total dosage of 50 to 200 units divided amongst 2 to 8 sites and which include both sides of the neck

Botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is also available in the USA for the treatment of spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements.

In the UK the usual initial dose of botulinum B toxin as the preparation *NeuroBloc* (*Eisai, UK*) is 5000 to 10 000 units given by intramuscular injection in divided doses into the two to four most affected muscles.

Botulinum B toxin as the preparation *Myobloc* (*Solstice, USA*) is also available in the USA. The initial dose is 2500 to 5000 units given by intramuscular injection divided between the affected muscles. Licensed product information recommends that patients with no history of tolerating botulinum injections should be started on a lower initial dose.

References.

1. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1990; **53:** 640–3.
2. Greene P, *et al.* Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990; **40:** 1213–18.
3. Anderson TJ, *et al.* Botulinum toxin treatment of spasmodic torticollis. *J R Soc Med* 1992; **85:** 524–9.
4. Brans JWM, *et al.* Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. *Neurology* 1996; **46:** 1066–72.
5. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1431–8.
6. Brashear A, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1439–46.
7. Velickovic M, *et al.* Cervical dystonia: pathophysiology and treatment options. *Drugs* 2001; **61:** 1921–43.
8. Figgitt DP, Noble S. Botulinum toxin B: a review of its therapeutic potential in the management of cervical dystonia. *Drugs* 2002; **62:** 705–22.
9. Dressler D, *et al.* Botulinum toxin type B in antibody-induced botulinum toxin type A therapy failure. *J Neurol* 2003; **250:** 967–9. Correction. *ibid.*; 1263–5.
10. Walker FO. Botulinum toxin therapy for cervical dystonia. *Phys Med Rehabil Clin N Am* 2003; **14:** 749–66.
11. Lew MF. Duration of effectiveness of botulinum toxin type B in the treatment of cervical dystonia. *Adv Neurol* 2004; **94:** 211–15.
12. Jankovic J. Treatment of cervical dystonia with botulinum toxin. *Mov Disord* 2004; **19** (suppl 8): S109–S115.
13. Costa J, *et al.* Botulinum toxin type B for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 28/03/06).
14. Costa J, *et al.* Botulinum toxin type A therapy for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).
15. Comella CL, *et al.* Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology* 2005; **65:** 1423–9.
16. Costa J, *et al.* Botulinum toxin type A versus anticholinergics for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 07/05/08).

Spasticity. The mainstay of management of spasticity, as discussed on p. 2014.2, is physiotherapy and antispastic drugs. Chemical neurolysis should only be considered when there is intractable continuous pain. Local injections of botulinum A toxin, as an alternative to chemical neurolysis, have been used in the management of limb spasticity in multiple sclerosis,[1] and in post-stroke patients,[1-6] and children with cerebral palsy.[7-14] In children with cerebral palsy, a systematic review[15] has found insufficient evidence to support or refute such use in those with lower

limb spasticity; however, another systematic review[16] has found the use of botulinum A toxin as an adjunct to occupational therapy to be effective in the management of upper limb spasticity. Botulinum B toxin has also been tried.[12,17]

Doses of botulinum A toxin, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation:* Botulinum A toxin is used in the management of dynamic equinus foot deformity associated with spasticity in children with cerebral palsy.

- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Botox* (*Allergan, UK*) is 4 units/kg injected into each of 2 sites in the medial and lateral heads of the gastrocnemius muscle. When both lower limbs are to be injected on the same occasion this total dose should be divided between the 2 limbs. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 2 months.
- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 10 to 30 units/kg divided between both calf muscles, mainly targeted to the gastrocnemius muscle. The maximum dose administered should not exceed 1000 units per patient. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 12 weeks.

Botulinum A toxin is also used in the treatment of upper limb spasticity in adults.

- In the treatment of upper limb spasticity associated with stroke, the exact dosage and number of injection sites of botulinum A toxin as the preparation *Botox* (*Allergan, UK*) should be tailored to the individual based on the muscles involved, the severity of the spasticity, and the presence of local weakness. The manufacturer recommends a total dose of 50 units into the flexor digitorum profundus, the flexor digitorum sublimis, the flexor carpi radialis, or the flexor carpi ulnaris, and a total dose of 20 units into the adductor pollicis or flexor pollicis longus. In clinical studies, cumulative doses did not exceed 360 units at any treatment session. Botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is also available in the USA for the treatment of upper arm spasticity. Doses should be tailored to meet individual patient requirements.
- The preparation *Xeomin* (*Merz, UK*) is used in the treatment of post-stroke upper arm spasticity. Initial doses range from 10 to 80 units and should be tailored to the individual; a total dose of 400 units should not be exceeded at a given session. Clinical improvement is seen within 4 weeks. Treatment may be repeated after a minimum of 12 weeks.
- In the treatment of focal spasticity of the arm, the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 1000 units divided into: a dose of 150 units into the flexor digitorum profundus, the flexor carpi ulnaris, and the flexor carpi radialis; 150 to 250 units into the flexor digitorum superficialis; and 300 to 400 units into the biceps brachii. All muscles should be injected at one site except the biceps brachii which should be injected at 2 sites. Lower doses are recommended in patients whose target muscles are small, where the biceps brachii is not to be injected, or in patients receiving multi-level injections. Clinical improvement generally occurs within the first 2 weeks.

1. Sheean G. Botulinum toxin treatment of adult spasticity: a benefit-risk assessment. *Drug Safety* 2006; **29:** 31–48.
2. Simpson DM, *et al.* Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996; **46:** 1306–10.
3. Bhakta BB, *et al.* Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatry* 1996; **61:** 30–5.
4. Burbaud P, *et al.* A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. *J Neurol Neurosurg Psychiatry* 1996; **61:** 265–9.
5. Brashear A, *et al.* Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; **347:** 395–400.
6. Shaw L, Rodgers H. Botulinum toxin type A for upper limb spasticity after stroke. *Expert Rev Neurother* 2009; **9:** 1713–25.
7. Zelnik N, *et al.* The role of botulinum toxin in the treatment of lower limb spasticity in children with cerebral palsy—a pilot study. *Isr J Med Sci* 1997; **33:** 129–33.
8. Carr LJ, *et al.* Position paper on the use of botulinum toxin in cerebral palsy. *Arch Dis Child* 1998; **79:** 271–3.
9. Fehlings D, *et al.* An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. *J Pediatr* 2000; **137:** 331–7.
10. Ubhi T, *et al.* Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. *Arch Dis Child* 2000; **83:** 481–7.
11. Koman LA, *et al.* Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics* 2001; **108:** 1062–71.
12. Berweck S, Heinen F. Use of botulinum toxin in pediatric spasticity (cerebral palsy). *Mov Disord* 2004; **19** (suppl 8): S162–S167.
13. Bjornson K, *et al.* Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. *Pediatrics* 2007; **120:** 49–58.
14. Moore AP, *et al.* Two-year placebo-controlled trial of botulinum toxin A for leg spasticity in cerebral palsy. *Neurology* 2008; **71:** 122–8.
15. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
16. Hoare BJ, *et al.* Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 27/01/10).
17. Brashear A, *et al.* Botulinum toxin type B in upper-limb poststroke spasticity: a double-blind, placebo-controlled trial. *Arch Phys Med Rehabil* 2004; **85:** 705–9.

Stiff-man syndrome. A patient with stiff-man syndrome (see Muscle Spasm, p. 1064.3) had marked improvement of ambulation and cessation of pain after injection of botulinum A toxin into affected paraspinal muscles.[1] In another case report, improvement in rigidity and muscle spasm was reported[2] in 2 patients after botulinum treatment; muscle spasms reduced within 3 days of treatment. It was also found that there was an increase in the duration of effect of botulinum A toxin after each subsequent injection and only a gradual return of painful spasm.

1. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. *Mov Disord* 1993; **8:** 371–3.
2. Liguori R, *et al.* Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. *Mov Disord* 1997; **12:** 1060–3.

Strabismus. Botulinum A toxin has been used to weaken overactive extra-ocular muscles as an alternative or adjunct to surgery in the correction of strabismus (p. 2000.3). Not all patients respond to botulinum A toxin and many patients who do respond require more than one injection to maintain improvement. Botulinum A toxin does not appear to offer a better degree of correction than traditional surgery, and it has been suggested that it should be reserved for use in patients unresponsive to, or unsuitable for, surgery. In the USA botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is indicated for the treatment of strabismus in patients 12 years of age or older. Depending on the direction and degree of deviation to be corrected the recommended initial dose of Botox to be injected into any one extra-ocular muscle ranges from 1.25 to 5 units. Paralysis is usually seen within the first 2 days and increases in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a further 2 to 6 weeks. It is recommended that patients are re-examined 7 to 14 days after injection to assess the effect of the dose given. If treatment is required for residual or recurrent strabismus, patients are either given treatment at the previous dosage if response was judged to have been adequate or up to twice the previous dose if paralysis had been incomplete; no more than 25 units should be injected into any one muscle. Repeat injections should not be given until the effects of the previous dose have dissipated. Injections should be diluted with unpreserved 0.9% sodium chloride solution so that the volume given per muscle is between 0.05 mL and 0.15 mL. Injections should also be made using an electromyographically guided needle to aid location of the target muscle.

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2. Carruthers JDA, *et al.* Botulinum vs adjustable suture surgery in the treatment of horizontal misalignment in adult patients lacking fusion. *Arch Ophthalmol* 1990; **108:** 1432–5.
3. Lyons CJ, *et al.* Botulinum toxin therapy in dysthyroid strabismus. *Eye* 1990; **4:** 538–42.
4. McNeer KW. An investigation of the clinical use of botulinum toxin A as a postoperative adjustment procedure in the therapy of strabismus. *J Pediatr Ophthalmol Strabismus* 1990; **27:** 3–9.
5. Scott AB, *et al.* Botulinum treatment of childhood strabismus. *Ophthalmology* 1990; **97:** 1434–8.
6. Petitto VB, Buckley EG. Use of botulinum toxin in strabismus after retinal detachment surgery. *Ophthalmology* 1991; **98:** 509–13.
7. Elston J. Is botulinum toxin helpful in squint management? *Br J Ophthalmol* 1998; **82:** 105.
8. Tejedor J, Rodríguez JM. Early retreatment of infantile esotropia: comparison of reoperation and botulinum toxin. *Br J Ophthalmol* 1999; **83:** 783–7.
9. Dawson EL, Lee JP. Does botulinum toxin have a role in the treatment of small-angle esotropia? *Strabismus* 2004; **12:** 257–60.
10. Dawson EL, *et al.* Does botulinum toxin have a role in the treatment of secondary strabismus? *Strabismus* 2005; **13:** 71–3.
11. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 27/01/10).

Stuttering. Botulinum toxin may be of benefit in the treatment of stuttering (p. 1078.1).[1,2]

1. Brin MF, *et al.* Laryngeal botulinum toxin injections for disabling stuttering in adults. *Neurology* 1994; **44:** 2262–6.
2. Cordivari C, *et al.* New therapeutic indications for botulinum toxins. *Mov Disord* 2004; **19** (suppl 8): S157–S161.

Tourette's syndrome. Improvement in tics was noted in patients with Tourette's syndrome (see Tics, p. 1030.1) treated with botulinum A toxin.[1,2]

1. Kwak CH, *et al.* Botulinum toxin in the treatment of tics. *Arch Neurol* 2000; **57:** 1190–3.
2. Marras C, *et al.* Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001; **56:** 605–10.

Tremor. Local injection of botulinum A toxin[1-4] has been tried in patients with essential tremor (p. 1318.3) that fails to respond to conventional treatment. Botulinum A toxin injection has also been successfully used to treat essential palatal tremor[5-7] and associated symptoms such as uncomfortable ear clicking.

1. Henderson JM, *et al.* Botulinum toxin A in non-dystonic tremors. *Eur Neurol* 1996; **36:** 29–35.
2. Jankovic J, *et al.* A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord* 1996; **11:** 250–6.
3. Pacchetti C, *et al.* Botulinum toxin treatment for functional disability induced by essential tremor. *Neurol Sci* 2000; **21:** 349–53.
4. Brin MF, *et al.* A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology* 2001; **56:** 1523–8.
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6. Jamieson DRS, *et al.* Ear clicks in palatal tremor caused by activity of the levator veli palatini. *Neurology* 1996; **46:** 1168–9.
7. Cho JW, *et al.* Case of essential palatal tremor: atypical features and remarkable benefit from botulinum toxin injection. *Mov Disord* 2001; **16:** 779–82.

Vaginismus. Report[1] of one patient who had relief of vaginismus (painful involuntary spasm of the vaginal or perianal muscles severe enough to prevent intercourse) for more than 24 months after injection of botulinum toxin into the vaginal wall muscles.

1. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. *Lancet* 1997; **349:** 252–3.

Adverse Effects

Injections of botulinum toxins have been associated with a transient burning sensation, bruising at the injection site, and local weakness. Adverse reactions related to the spread of botulinum toxins distant to the site of injection have been reported and sometimes this was associated with significant debility or a fatal outcome in very rare cases. Exaggerated muscle weakness may occur with therapeutic doses. Deep or misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles. Overdosage can produce a widespread paralysis.

There have been occasional reports of hypersensitivity reactions such as rashes and flu-like symptoms. There have also been rare reports of cardiovascular adverse effects, including arrhythmia and myocardial infarction, and of seizures or convulsions, particularly in predisposed patients.

- The most common adverse effects **after injection into muscles around the eye**, such as in the management of blepharospasm, hemifacial spasm, or strabismus, are ptosis, lachrymation, photophobia, ocular irritation, and facial swelling. Some patients may be unable to close the eyelid completely. Other adverse effects that have been reported include ectropion and entropion, and diplopia. Blinking may be reduced and this can lead to dry eye, keratitis, and corneal damage. Angle-closure glaucoma has been reported. Vertical deviation has also occurred in patients treated for horizontal strabismus. Needle penetrations of the eye during treatment of strabismus have resulted in vitreous and retrobulbar haemorrhages.
- Dysphagia is the most common adverse effect **after injection into neck muscles** in the treatment of spasmodic torticollis and there may be pooling of saliva with risk of aspiration in severely affected patients (*important*, see also Precautions, p. 2021.2). Dry mouth, paralysis of the vocal cords, and weakness of the neck muscles may also occur. Generalised weakness, malaise, nausea, and visual disturbances have occasionally been reported. Other effects which have occurred rarely include drowsiness, numbness, stiffness, ptosis, and headache. Respiratory difficulties, associated with the use of large doses, have occurred on rare occasions.
- Adverse effects most frequently associated with **injection into the lower limbs** in the treatment of cerebral palsy include falling, leg pain, and local and general weakness; lethargy and leg cramps have also been reported.
- Common adverse effects **after injection into the upper limb** in the treatment of spasticity associated with stroke are arm pain, dysphagia, muscle weakness, and hypertonia. A perceived increase in non-axillary sweating, within one month of the injection, has been reported after treatment for hyperhidrosis of the axillae; rarely, mild transient weakness of the arms has also occurred.
- Headache is the most frequent adverse effect **after injection into the muscles around the forehead** in the treatment of glabellar (frown) lines. Other adverse effects frequently reported include ptosis, facial pain, muscle weakness, and nausea.

Reviews.

1. Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Dis Mon* 2002; **48:** 336–56.

Incidence of adverse effects. It has been suggested that the difference between botulinum A toxin preparations may not be confined to just a numerical dosage adjust-

ment.[1] Reviews of the literature have suggested that there may also be a difference in the incidence of adverse effects. The reported frequency of dysphagia for *Dysport* (28% and 44%) in patients with spasmodic torticollis was greater than that for *Botox* (9.5 to 17%). This variation might relate to differences in bioactivity not recognised by the mouse lethality bioassay that is used to determine the potency of preparations.

In February 2009, the Australian Adverse Drug Reactions Advisory Committee[2] reported that since mid-1994 it had received 45 reports of adverse effects associated with botulinum A toxin in 36 females and 9 males, whose age ranged from 2 to 79 years (median: 45 years); none were fatal. The most common reaction (16 cases) was muscle weakness at sites adjacent to, or distant from, the injected area; of these, there were 8 reports of dysphagia, 3 of respiratory failure or dyspnoea, and 7 of generalised muscle weakness. Other reactions included rash or other allergic reaction (10 reports), diplopia (6 reports), and fatigue (4 reports).

1. Borodic G. Therapeutic botulinum toxin. *Lancet* 1994; **344:** 1370.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Adverse reactions with botulinum toxin A (Botox, Dysport). *Aust Adverse Drug React Bull* 2009; **28:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0902.pdf (accessed 27/01/10)

Angiosarcoma. It has been suggested[1] that botulinum A toxin injection might have acted as a triggering factor for angiosarcoma in a 66-year-old patient being treated for blepharospasm.

1. Kárpáti S, *et al*. Human herpesvirus type 8-positive facial angiosarcoma developing at the site of botulinum toxin injection for blepharospasm. *Br J Dermatol* 2000; **143:** 660–2.

Antibody formation. Neutralising antibodies that reduce or abolish the beneficial effects of treatment have been found after prolonged treatment with botulinum A toxin.[1] A review[2] in 1994 considered that there was growing concern over the development of antibodies after repeated injections, as many of the conditions for which botulinum toxin is indicated require indefinite treatment. Antibody formation was reported to be more common with high doses (as in spasmodic torticollis) than after low doses (as for blepharospasm). The occurrence of antibodies appeared to correlate with the dose per injection, the quantity of botulinum protein given per injection, the number of injections given, and the frequency of injections.

Antibodies have also developed after the use of botulinum B toxin. However, botulinum toxin B is antigenically distinct from botulinum A toxin, and may be of value in patients who develop resistance to treatment associated with antibody formation to type A toxin.[3] Botulinum F toxin is also antigenically distinct and is being studied in a similar way.

1. Hambleton P, *et al*. Antitoxins and botulinum toxin treatment. *BMJ* 1992; **304:** 959–60.
2. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; **11:** 145–52.
3. Brin MF, *et al*. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1431–8.

Biliary colic. A 43-year-old woman with no history of gallbladder disease had single episodes of biliary colic after each of 3 sessions of treatment with botulinum A toxin for blepharospasm.[1] Botulinum A toxin might have exerted a systemic effect to block acetylcholine release leading to gallbladder hypomotility with delayed emptying and stasis.

1. Schnider P, *et al*. Gallbladder dysfunction induced by botulinum A toxin. *Lancet* 1993; **342:** 811–12.

Dysphagia. By November 1993, the UK CSM had received 4 reports of severe dysphagia with choking in patients given injections of botulinum A toxin into the neck muscles as a treatment for torticollis.[1] The dysphagia developed 5 to 7 days after the injection and in one patient it was persisting 6 weeks after the injection. The dysphagia led to aspiration of the stomach contents into the lungs and one patient with a history of poor lung function died from bronchopneumonia. Dysphagia is also reported to be a common adverse effect in patients with spasmodic torticollis being treated with botulinum B toxin.[2]

See also Incidence of Adverse Effects and Systemic Effects, p. 2020.3 and below, respectively, for further reference to dysphagia as an adverse effect.

1. CSM/MCA. Reminder: botulinum type A toxin (Dysport)—severe dysphagia with unlicensed route of administration. *Current Problems* 1993; **19:** 11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Lew MF, *et al*. The safety and efficacy of botulinum toxin type B in the treatment of patients with cervical dystonia: summary of three controlled clinical trials. *Neurology* 2000; **55** (suppl 5): S29–S35.

Effects on the eyes. Acute angle-closure glaucoma has been reported[1] in an 83-year-old woman after a series of injections of botulinum A toxin for the treatment of blepharospasm. Permanent extra-ocular muscle damage after botulinum A toxin injection into the left inferior rectus muscle has been reported[2] in a 70-year-old man.

1. Corridan P, *et al*. Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. *Br J Ophthalmol* 1990; **74:** 309–10.
2. Mohan M, *et al*. Permanent extraocular muscle damage following botulinum toxin injection. *Br J Ophthalmol* 1999; **83:** 1309–10.

Systemic effects. In February 2008, the FDA[1] reported that it had received reports of systemic adverse reactions associated with the spread of botulinum toxin from the injected area. Symptoms described include dysphagia, ptosis, weakness and numbness of the lower extremities, and respiratory insufficiency. The most serious cases, resulting in hospitalisation and death, occurred mostly in children with cerebral palsy who were being treated for limb spasticity; doses used ranged from 6.25 to 32 units/kg of a botulinum A toxin preparation *Botox*, and 388 to 625 units/kg of a botulinum B toxin preparation *Myobloc*. No deaths had been reported in adults; doses used ranged from 100 to 700 units of *Botox*, and 10 000 to 20 000 units of *Myobloc*.

In April 2009, a follow-up report[2] from the FDA added that the majority of such case reports in adults occurred in those being treated for spasticity or spasmodic torticollis. The FDA was aware of several deaths in adults; however, causality to botulinum toxin use could not be established due to the patients' pre-existing conditions. No definitive reports of serious adverse reactions associated with the spread of botulinum toxin had been identified with the use of *Botox* in the treatment of glabellar (frown) lines or severe primary axillary hyperhidrosis.

Similar cases have also been reported in other countries.[3] See also Incidence of Adverse Effects and Dysphagia, p. 2020.3 and above, respectively.

1. FDA. Early communication about an ongoing safety review of Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B) (issued 8th February, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070366.htm (accessed 28/01/10)
2. FDA. Follow-up to the February 8, 2008, early communication about an ongoing safety review of Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B) (issued April 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm143819.htm (accessed 28/01/10)
3. Health Canada. Botulinum toxin type A (Botox) and distant toxin spread. *Can Adverse React News* 2008; **18**(4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_vl8n4-eng.pdf (accessed 28/01/10)

Treatment of Adverse Effects

The use of artificial tears may relieve keratitis and dry eye. In the event of overdosage general supportive care is required. The patient should be monitored for several days for signs of paralysis and artificial respiration may be necessary. Since the effects of botulinum toxins are irreversible once bound to nerve terminals, it is doubtful that specific botulinum antitoxin (p. 2380.2) will be of value unless given very rapidly after overdosage.

Precautions

Botulinum toxin is contra-indicated in generalised disorders of muscle activity such as myasthenia gravis. As with other biological products, the potential for botulinum toxin to cause anaphylaxis should be considered. Botulinum toxins should be given with extreme caution to patients with neurological disorders or a history of dysphagia or aspiration. Patients or their carers should be advised to seek immediate medical attention if problems with swallowing or speech, or respiratory disorders develop.

Botulinum toxins should only be used by appropriately qualified and trained specialists. Injections must be made with great care, especially those into the neck, to avoid unintended paralysis; the relevant anatomy, and any alterations due to previous surgery, must be understood before injection. Botulinum toxins should not be given if there is any infection at the proposed injection site.

The effects of botulinum toxins in pregnancy are unknown; fetal malformations and abortion have been reported in *rabbits*, and licensed product information recommends that botulinum toxins should not be given to pregnant women. Breast feeding is also considered a contra-indication: it is not clear whether the toxin is distributed into breast milk.

When **injected into the muscles around the eyes**, as for the treatment of blepharospasm, hemifacial spasm, or strabismus, reduced blinking can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with seventh cranial nerve disorders. Corneal sensation should be carefully tested in previously treated eyes, injection into the lower eyelid area avoided, and any resulting epithelial defect vigorously treated.

Handling. Residual botulinum A toxin or spillages should be inactivated by autoclaving or use of a dilute hypochlorite solution (0.5%). Botulinum B toxin may be decontaminated in a similar manner; a strong caustic solution may also be used.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies botulinum toxins as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/10/11)

Interactions

The effect of botulinum toxins may theoretically be potentiated by aminoglycosides or spectinomycin. Interactions may also occur with other drugs that have neuromuscular blocking activity, including lincosamides, polymyxins, tetracyclines, and muscle relaxants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Botox; Dysport; Xeomin; ***Austral.***: Botox; Dysport; ***Austria***: Azzalure; Botox; Dysport; NeuroBloc; Xeomin; ***Belg.***: Azzalure; Botox; Dysport; Vistabel; ***Braz.***: Botox; Botulift; Dysport; Prosigne; Xeomin; ***Canad.***: Botox; Xeomin; ***Chile***: Dysloṛt; ***China***: Botox (保妥适); ***Cz.***: Botox; Dysport; NeuroBloc; Vistabel; ***Denm.***: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Fin.***: Azzalure; Bocouture; Botox; Dysport; Vistabel; Xeomin; ***Fr.***: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Ger.***: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Gr.***: Botox; Dysport; NeuroBloc; Vistabel; ***Hong Kong***: Botox; BTXA; Dysport; ***Hung.***: Botox; Dysport; NeuroBloc; Vistabel; ***India***: Botox; ***Indon.***: Botox; Lanzox; ***Irl.***: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; ***Israel***: Botox; Dysport; ***Ital.***: Botox; Dysport; NeuroBloc; Vistabex; Xeomin; ***Jpn***: Botox; NerBloc; ***Malaysia***: Botox; Dysport; ***Mex.***: Antipar; Botox; Dysport; Xeomeen; ***Neth.***: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; ***Norw.***: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***NZ***: Botox; Dysport; ***Philipp.***: Botox; Dysport; ***Pol.***: Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Port.***: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Rus.***: Botox (Ботокс); Dysport (Диспорт); Lantox (Лантокс); Xeomin (Ксеомин); ***S.Afr.***: Botox; Dysport; ***Singapore***: Botox; Dysport; ***Spain***: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Swed.***: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Switz.***: Botox; Dysport; Vistabel; ***Thai.***: Botox; Botulax; Dysport; Zentox; ***Turk.***: Botox; Dysport; ***UK***: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Ukr.***: Botox (Ботокс); Dysport (Диспорт); ***USA***: Botox; Dysport; Myobloc; Xeomin; ***Venez.***: Botox; Dysport.

Pharmacopoeial Preparations

Ph. Eur.: Botulinum Toxin Type A for Injection; Botulinum Toxin Type B for Injection.

Carisoprodol *(BAN, rINN)*

Carisoprodolum; Isopropylmeprobamate; Karisoprodol; Karisoprodoli; Karizoprodol; Karizoprodolis; Каризопродол.

2-Methyl-2-propyltrimethylene carbamate isopropylcarbamate.

$C_{12}H_{24}N_2O_4$=260.3

CAS — 78-44-4.

ATC — M03BA02.

ATC Vet — QM03BA02.

UNII — 21925K482H.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Carisoprodol). A white or almost white fine powder. M.p. 92 degrees to 95 degrees. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.

USP 36: (Carisoprodol). A white crystalline powder having a mild characteristic odour. M.p. 91 degrees to 94 degrees. Soluble 1 in 2083 of water, 1 in 2.5 of alcohol and of acetone, and 1 in 2.3 of chloroform. Store in airtight containers.

Uses and Administration

Carisoprodol is a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions. After oral doses its effects begin within about 30 minutes and last for 4 to 6 hours. It is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. A usual oral dose is 250 to 350 mg given three or four times daily for up to 2 to 3 weeks. Elderly patients may require half the usual dose or less. It is also given with analgesics in compound preparations.

The EMEA and some other authorities have recommended for carisoprodol to be suspended from the market due to the increased risk of abuse and addiction, as well as

the risk of altered mental state and psychomotor impairment.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Meprobamate, p. 1084.1.

The most common adverse effects reported with carisoprodol are drowsiness, dizziness, and headache. Sedation may affect the performance of skilled tasks and affected patients should not drive or operate machinery. Poor metabolisers, deficient in the cytochrome P450 isoenzyme CYP2C19, may be at greater risk of drowsiness.

Idiosyncratic reactions may occur within minutes of a dose in patients who have not previously received carisoprodol. Such reactions have been reported rarely and include anaphylactic shock, syncope, tachycardia, confusion, transient quadriplegia, and bronchospasm. Cross-reactivity can occur with its metabolite meprobamate.

Overdosage may result in seizures, stupor, coma, shock, respiratory depression, and rarely death.

Carisoprodol should be used with caution in patients with impaired hepatic or renal function.

Cases of dependence and abuse have been reported with the prolonged use of carisoprodol, particularly in patients with a history of addiction; withdrawal reactions have also occurred when treatment is suddenly stopped after prolonged use or the use of high doses. The increased risk of abuse and addiction with carisoprodol, as well as the risk of altered mental state and psychomotor impairment, has led the EMEA and some other authorities to recommend that it is suspended from the market; in the USA, however, it is recommended that use is limited to 2 to 3 weeks.

Abuse. Analysis[1] of data from the Norwegian Prescription Database found that carisoprodol was used in higher doses than recommended indicating its potential as a drug of abuse. Subsequently, the Norwegian Medicines Agency and the EMEA have recommended for its suspension (see above).

There have been isolated reports[2,3] of amnestic states associated with abuse of carisoprodol.

1. Bramness JG, *et al.* Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2007; **64:** 210–18.
2. Hussain HM, *et al.* Carisoprodol-induced amnestic state and nocturnal blackouts. *Aust N Z J Psychiatry* 2008; **42:** 909–11.
3. Gupta A, *et al.* Carisoprodol-induced amnestic state. *Indian J Psychiatry* 2008; **50:** 72–3.

Breast feeding. Carisoprodol is distributed into breast milk, achieving concentrations 2 to 4 times those in maternal plasma. In a case report,[1] except for mild sedation, no other adverse effects were seen in an infant whose mother received carisoprodol 2.8 g daily before and throughout gestation, and during 1 month of exclusive breast feeding; the maximum infant dose of carisoprodol and meprobamate was 6.9% of the mother's weight-adjusted dose during breast feeding.

US licensed product information states that carisoprodol should be used with caution in breast-feeding mothers.

1. Briggs GG, *et al.* High-dose carisoprodol during pregnancy and lactation. *Ann Pharmacother* 2008; **42:** 898–901.

Dependence. There are reports[1,2] of carisoprodol dependence, probably due to its metabolism to meprobamate (see p. 1084.1). Symptoms of abrupt withdrawal have included chills, tremors, myalgia, muscle twitching, insomnia, irritability, anxiety, and hallucinations.[1,3] In one case[1] the patient had symptoms of meprobamate withdrawal that resolved with a dose-reducing schedule of meprobamate.

Dependence may occur more often when carisoprodol is given in high doses and for prolonged periods, especially in patients with a history of alcohol or drug dependence or in those with marked personality disorders. One group[2] found that patients with a history of substance abuse were twice as likely to use carisoprodol in larger doses to those prescribed than those with no such history.

The risk of dependence with carisoprodol has led the EMEA and some other authorities to recommend its suspension from the market (see above).

1. Luehr JG, *et al.* Mail-order (veterinary) drug dependence. *JAMA* 1990; **263:** 657.
2. Reeves RR, *et al.* Carisoprodol (Soma): abuse potential and physician unawareness. *J Addict Dis* 1999; **18:** 51–6.
3. Reeves RR, Burke RS. Carisoprodol: abuse potential and withdrawal syndrome. *Curr Drug Abuse Rev* 2010; **3:** 33–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carisoprodol as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

The CNS effects of carisoprodol may be potentiated by alcohol or other CNS depressants. Carisoprodol may cause hepatic enzyme induction and it may therefore affect the metabolism of some drugs. The metabolism of carisoprodol is mediated by the cytochrome P450 isoenzyme CYP2C19; use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of carisoprodol, however, there is a lack of data.

Pharmacokinetics

Carisoprodol is absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1.5 to 2 hours. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C19, which shows genetic polymorphism, and excreted in urine as metabolites, including meprobamate (p. 1083.3). The terminal elimination half-life of carisoprodol is about 2 hours. It is distributed in substantial amounts into breast milk.

References.

1. Olsen H, *et al.* Carisoprodol elimination in humans. *Ther Drug Monit* 1994; **16:** 337–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Listaflex; ***Gr.***: Artifar; Soma; ***India***: Carisoma; ***Mex.***: Somacid; ***Thai.***: Somagin†; ***USA***: Soma.

Multi-ingredient Preparations. ***Arg.***: Algiseda Plus; Algiseda; Flexicamin A; Flexicamin B12; Flexicamin; Flogiatrin B12; Flogiatrin; Listaflex Forte; Naprontag Flex; Naprux Disten; Rumisedan Fuerte; Solocalm Plus; Solocalm-Flex; ***Braz.***: Algi-Tanderil; Beserol; Diclofetamol; Dorilax; Flexalgin; Infralax; Mio-Citalgan; Mioflex A; Mioflex; Mionevrix; Sanilax; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Tandrotamol; Torsilax; Trilax; ***Gr.***: Relacton; ***India***: Carisoma Compound; Somaflam; ***Indon.***: New Skelan; Somadril Compound; ***Mex.***: Blocacid†; Caridoxen; Caxidol; Contraxen; Dolaren; Dorsal; Duoflex; Empatil; Naxodol†; Profenlax†; Somalgesic; ***Thai.***: Alaxan†; Asialax†; Cariso-Co†; Caritasone; Cenpadol†; Muscelax†; Myophen†; Pasodol†; Polixan†; Raxsoma†; ***USA***: Sodol Compound; ***Venez.***: Praxona.

Pharmacopoeial Preparations

USP 36: Carisoprodol and Aspirin Tablets; Carisoprodol Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets.

Chlorphenesin Carbamate

(BANM, USAN, pINNM)

Carbamato de clorfenesina; Chlorphénésine, Carbamate de; Chlorphenesini Carbamatum; Clorfenesina, carbamato de; U-19646; Хлорфенезина Карбамат.

3-(4-Chlorophenoxy)propane-1,2-diol 1-carbamate.

$C_{10}H_{12}ClNO_4$=245.7

CAS — 104-29-0 (chlorphenesin); 886-74-8 (chlorphenesin carbamate).

UNII — 57U5YI11WP.

Pharmacopoeias. In *Jpn*.

Profile

Chlorphenesin carbamate is a centrally acting skeletal muscle relaxant related to mephenesin (p. 2025.2). Its mode of action may be related to general depressant effects on the CNS. It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual initial oral dose is 250 mg three times daily, adjusted according to response. It has been recommended that chlorphenesin carbamate should not be given for longer than 8 weeks.

Chlorphenesin base (p. 575.3) is used as an antifungal.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Rinlaxer.

Chlorzoxazone *(BAN, rINN)*

Chlorobenzoxazolinone; Chlorzoxazonum; Clorzoxazona; Klooritsoksatsoni; Klorzoksazon; Klorzoxazon; Хлорзоксазон.

5-Chlorobenzoxazol-2(3*H*)-one.

$C_7H_4ClNO_2$=169.6

CAS — 95-25-0.

ATC — M03BB03.

ATC Vet — QM03BB03.

UNII — H0DE420U8G.

Pharmacopoeias. In *US*.

USP 36: (Chlorzoxazone). A white or practically white, practically odourless, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in methyl alcohol; soluble in solutions of alkali hydroxides and ammonia. Store in airtight containers.

Uses and Administration

Chlorzoxazone is a centrally acting skeletal muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect mainly at the level of the spinal cord and subcortical areas of the brain. Its effects begin within an hour of an oral dose and last for 3 to 4 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual oral dose is 250 mg three or four times daily. For severe muscle spasms, an initial dose of 500 mg three or four times daily may be given; the dose can often be reduced subsequently, although doses of up to 750 mg three or four times daily may be given if necessary. Chlorzoxazone is also given with analgesics in compound preparations.

Adverse Effects and Treatment

The most common adverse effects of chlorzoxazone are drowsiness and dizziness. There may occasionally also be gastrointestinal irritation and gastrointestinal bleeding has been reported rarely. Other effects that have occurred are headache, overstimulation, and rarely sensitivity reactions including rashes, petechiae, ecchymoses, urticaria and pruritus; very rarely, angioedema or anaphylactoid reactions may occur. Some patients taking chlorzoxazone have developed jaundice and liver damage suspected to be caused by the drug.

After overdosage there may be gastrointestinal disturbances, drowsiness, dizziness, headache, malaise, and sluggishness followed by marked loss of muscle tone, hypotension, and respiratory depression. Emptying the stomach by lavage should be considered, followed by activated charcoal and supportive therapy.

Effects on the liver. Hepatotoxicity, sometimes fatal, has been associated with chlorzoxazone treatment.[1]

1. Powers BJ, *et al.* Chlorzoxazone hepatotoxic reactions: a n analysis o f 21 identified o r presumed cases. *Arch Intern Med* 1986; **146:** 1183–6.

Overdosage. Overdosage and coma occurred on 2 occasions in a patient taking chlorzoxazone; on the second occasion, the patient responded to intravenous flumazenil.[1]

1. Roberge RJ, *et al.* Two chlorzoxazone (Parafon forte) overdoses and coma in one patient: reversal with flumazenil. *Am J Emerg Med* 1998; **16:** 393–5.

Torticollis. There has been a report of a patient with a spasmodic torticollis-like syndrome, consisting of tonic deviation of the head to the right, clenching of the teeth, and dysarthria, which developed repeatedly within 2 hours of ingesting chlorzoxazone for low back pain.[1] Intravenous injection of benzatropine mesilate 1 mg gave rapid relief of symptoms.

1. Rosin MA. Chlorzoxazone-induced spasmodic torticollis. *JAMA* 1981; **246:** 2575.

Precautions

Chlorzoxazone should not be given to patients with impaired liver function and should be stopped if signs of liver toxicity appear. Patients should be advised to report to their doctor any signs or symptoms of possible liver toxicity such as fever, rash, jaundice, dark urine, anorexia, nausea, vomiting, or right upper quadrant pain. Chlorzoxazone may cause drowsiness; patients affected should not drive or operate machinery.

The urine of patients taking chlorzoxazone may be coloured orange or reddish-purple by a phenolic metabolite.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorzoxazone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

The CNS effects of chlorzoxazone may be enhanced by alcohol and other CNS depressants.

Disulfiram. A study[1] of the efficacy of disulfiram as an inhibitor of the cytochrome P450 isoenzyme CYP2E1 (an enzyme involved in the metabolism of chlorzoxazone) found that a single 500-mg dose of disulfiram reduced plasma clearance of chlorzoxazone by 85%, resulting in a doubling of the latter's peak plasma concentrations and

prolongation of its elimination half-life from a mean of 0.92 to 5.1 hours.

1. Kharasch ED, *et al.* Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther* 1993; **53:** 643–50.

Isoniazid. Isoniazid inhibited the clearance of chlorzoxazone by 56% when given to 10 slow acetylator subjects resulting in an increase in sedation, headache, and nausea.[1] Two days after stopping isoniazid there had been a rebound increase in the clearance of chlorzoxazone by 56% over the pre-isoniazid clearance value. Similar but less pronounced effects have also been reported[2] in rapid acetylators with chlorzoxazone's pharmacokinetic parameters returning to baseline values in 2 days.

1. Zand R, *et al.* Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. *Clin Pharmacol Ther* 1993; **54:** 142–9.
2. O'Shea D, *et al.* Modulation of CYP2E1 activity by isoniazid in rapid and slow N-acetylators. *Br J Clin Pharmacol* 1997; **43:** 99–103.

Pharmacokinetics

Chlorzoxazone is reported to be completely absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is rapidly metabolised in the liver via the cytochrome P450 isoenzyme CYP2E1, mainly to 6-hydroxychlorzoxazone, and excreted in the urine mainly as the glucuronide metabolite. The elimination half-life of chlorzoxazone is about 1 hour.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Solaxin; ***Hung.***: Myoflexin; ***India***: Bio Flexic; Divorel Plus; New Panazox; Ontac Plus; ***Indon.***: Solaxin; ***S.Afr.***: Paraflex†; ***Swed.***: Paraflex; ***Thai.***: Chlorzox; ***Turk.***: Paraflex; ***USA***: Lorzone; Paraflex; Parafon Forte DSC; Remular-S.

Multi-ingredient Preparations. ***Arg.***: Ibupirac Flex; Paraflex AN; Paraflex Plus; Rucaten Forte; Vefren Flex; ***Braz.***: Paralon; ***Canad.***: Acetazone Forte C8; Acetazone Forte; Back-Aid; ***Chile***: Beserol-S; Brevex; Desdol; Flectadol; Tonoflex; Winasorb Flex; ***China***: Lunan Beite (鲁南贝特); ***Gr.***: Parafon; ***India***: Abate-CZ; Aceclo-MR; Aceforce-MR; Acemiz-MR; Acemove-MR; Acent-MR; Acepar-MR; Acetuff-MR; Aci-MR; Aclog-CX; Aclozox; Actizox; Adenim-MR; Adnac-MR; Afesan-CZ; Agile-MR; Arflur-MR; Armdic MR; Artigesic-MR; Asonac Forte; Aspa Plus; Aspa; Avifem-MR; Avinim-MR; Balzox; Brenlax; Brufamol-M; Bufex-C; Bufex-CD; C-MR; Cadiflam; Cep-MR; Chlorizok; Cipzox; Clopar MR; Clopar Plus; Clopar-K; Combinac-MR; Cuzox-MR; Cynac-MR; Decizox; Delock-MR; Demo-MR; Diazox-MR; Dicloat-CZ; Diclofalm Forte; Diclofast-P; Dicloflam MR; Diclomove-MR; Diclonac-MR; Diclonet-Forte; Diclonij-KMR; Diclonij-Super; Diclonova MR; Dicloriz; Diclovar-CZ; Dicnac MR; Dicnac Plus; Dicnap-MR; Dicol-MR; Dicoliv-MR; Dicron-C; Dicyclozed; Diczone Plus; Diczone-MR; Difisal Relax; Diflac Plus; Dikul MR; Dilofen-CZ; Dion MR; Dipclo-MR; Diplofen-MR; Divexx-MR; Dizox; Dodo-MR; Doloban; Dolocide MR; Dolokind-MR; Dolomed-MR; Dolostat-MR; Dolowin-MR; Dolozox; Don-MR; DP Gesic MR; Dpazox; Dual Gesic Plus; Duodil; E-Fen-CZ; Elaxic; Elfenac-MR; Fenadec MR; Fenaplus-MR†; Fenbest MR; Fenzone Forte; Fenzoxe Forte; Flamace-MR; Flamar-MX; Flamese-KR; Flexicam; Flexigesic-MR; Flexon-MR; Forgesic-MR; Fornac-CZ; Frenac-MR; Hifenac-MR; Icobit-Plus; Imflamol-ZX; Intagesic-MR; Intragesic-MR; KMR; Larigox; Lebec-MR; Lipcy-MR; Litonac-MR; Lobak; Lupisulide MR; Magadol-SP; Maxigesic-MR; Maxoflam-MR; Mezonac; Micronac-MR; Minidolo; Mobifen; Mobiflam; Mobisox; Mobizox; Mofax; Morcet-MR; Mumo; Muscodac; Muskel; Muzox; Mydic-MR; Myofan; Myospaz Forte; Myospaz; Naclomol-MR; Nacpo; Namplus; Nelsid Fort; Neulab-MR; New Mezonac; Nicip MR; Nifen MR; Nile-CZ; Nim-MR; Nimkul-CZ; Nimkul-MR; Nimucet-MR; Nimuflex-MR; Nimuflex; Nimvista-MR; Niplonac-MR; Novil; Novozox; Numol-MR; Nusaid-MR; Onafen-CZ; Orthodac MR; Osdip-MR; Osteoflam-MR; Ostizox; Pacizox; Paclo-MR; Painkair-MR; Paradic-C; Paradic-MR; Paraflax; Parafon; Paratel-ACP; Parazox-D; ***Malaysia***: Paras; ***Mex.***: Parafon Forte; Reumophan Alka; Reumophan Vit; Tafirol Flex; ***Philipp.***: Parafon†; ***S.Afr.***: Parafon†; ***Thai.***: Cezox; Falfon†; MP Fon; Myora†; Neofon†; Parafon; Vorafon; ***Turk.***: Mepadol; Muskazon; Parafon; ***USA***: Flexaphen†.

Pharmacopoeial Preparations
USP 36: Chlorzoxazone Tablets.

Cyclobenzaprine Hydrochloride

(USAN, rINNM)

Ciclobenzaprina, hidrocloruro de; Cyclobenzaprine, Chlorhydrate de; Cyclobenzaprini Hydrochloridum; Hidrocloruro de ciclobenzaprina; MK-130 (cyclobenzaprine); Proheptatriene Hydrochloride; Ro-4-1557 (cyclobenzaprine); RP-9715 (cyclobenzaprine); Циклобензаприна Гидрохлорид.

3-(5*H*-Dibenzo[*a,d*]cycloheptен-5-ylidene)-*NN*-dimethylpropylamine hydrochloride.

$C_{20}H_{21}N,HCl$=311.9

CAS — 303-53-7 (cyclobenzaprine); 6202-23-9 (cyclobenzaprine hydrochloride).

ATC — M03BX08.
ATC Vet — QM03BX08.
UNII — 0VE05JYS2P.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of cyclobenzaprine hydrochloride:

Cyclo; Cyclone.

Pharmacopoeias. In *US*.

USP 36: (Cyclobenzaprine Hydrochloride). A white to off-white, odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and in dichloromethane; insoluble in hydrocarbons.

Uses and Administration

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle relaxant, related to the tricyclic antidepressants. It acts mainly at the brain stem to decrease tonic somatic motor activity influencing both alpha and gamma motor systems. Additional activity at spinal cord sites may be involved. Effects begin within 1 hour of an oral dose; the effects of a single dose have been reported to last as long as 12 to 24 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual oral dose is 5 mg three times daily, increased if necessary to 10 mg three times daily. Treatment for more than 2 or 3 weeks is not recommended. A starting dose of 5 mg with less frequent dosing is recommended for elderly patients. For doses in patients with hepatic impairment, see below. A modified-release preparation of cyclobenzaprine hydrochloride is also available for once-daily dosing.

Administration in hepatic impairment. A starting oral dose of 5 mg of cyclobenzaprine hydrochloride, and perhaps less frequent dosing than usual (see Uses and Administration, above), is recommended for those with mild hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

Back pain. A meta-analysis[1] of 14 studies concluded that cyclobenzaprine hydrochloride, in the short term, improves low back pain (p. 9.2). Doses given to patients were titrated and ranged from 10 to 60 mg daily with a median dose of 30 mg daily. Patients improved moderately in the first 4 days of treatment, with the effects of cyclobenzaprine hydrochloride gradually declining with time although there was some evidence of continued improvement at 2 weeks. Further studies are needed to determine the optimal length of use in the management of acute back pain. Adverse effects were common, occurring in at least 53% of patients.

1. Browning R, *et al.* Cyclobenzaprine and back pain: a meta-analysis. *Arch Intern Med* 2001; **161:** 1613–20.

Fibromyalgia. Studies of the efficacy of cyclobenzaprine in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p. 14.2), have produced conflicting results but a meta-analysis[1] of 5 such studies suggested that cyclobenzaprine had some modest benefit in the condition. Patients were more likely to report overall improvement and moderate reductions in individual symptoms, particularly sleep, while taking the drug.

1. Tofferi JK, *et al.* Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum* 2004; **51:** 9–13.

Adverse Effects, Treatment, and Precautions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and shares their adverse effects and precautions (see Amitriptyline, p. 402.3). Cyclobenzaprine should be used with caution in the elderly and patients with hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

It may cause drowsiness; patients affected should not drive or operate machinery.

The elderly. Symptoms of toxicity[1] (hallucinations, insomnia, and restlessness) were seen in a 76-year-old patient taking cyclobenzaprine at therapeutic doses. US licensed product information states that the elderly may be more likely to have adverse effects such as hallucinations and confusion..

In another study[2] the mean elimination half-life of cyclobenzaprine in the elderly was longer than in younger subjects and clearance was reduced. It was suggested that it should be used in a reduced dose or frequency in the elderly.

1. Douglass MA, Levine DP. Hallucinations in an elderly patient taking recommended doses of cyclobenzaprine. *Arch Intern Med* 2000; **160:** 1373.
2. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Neuroleptic malignant syndrome. Report of a neuroleptic malignant-like syndrome associated with cyclobenzaprine in a 36-year-old man.[1] It was not clear whether the syndrome was due to an idiosyncratic reaction or to an overdose.

1. Theoharides TC, *et al.* Neuroleptic malignant-like syndrome due to cyclobenzaprine. *J Clin Psychopharmacol* 1995; **15:** 79–81.

Overdosage. Treatment of cyclobenzaprine overdose is mainly symptomatic and supportive. A large retrospective study[1] found that cyclobenzaprine hydrochloride overdoses of up to 1 g rarely present with the serious cardiovascular and neurological effects seen with tricyclic antidepressant overdoses. There were no reports of seizures, life-threatening arrhythmias, or fatalities. However, 150 patients required treatment in the intensive care unit, 13 patients needed assisted ventilation, and 8 were unresponsive to stimuli. It was noted that observation may be sufficient for overdoses of under 50 mg in children.

Rhabdomyolysis, associated with cyclobenzaprine overdosage has been reported.[2]

1. Spiller HA, *et al.* Five-year multicentre retrospective review of cyclobenzaprine toxicity. *J Emerg Med* 1995; **13:** 781–5.
2. Chabria SB. Rhabdomyolysis: a manifestation of cyclobenzaprine toxicity. *J Occup Med Toxicol* 2006; **1:** 16.

Interactions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and may be subject to similar interactions (see Amitriptyline, p. 406.1). The CNS effects of cyclobenzaprine may be enhanced by alcohol or other CNS depressants.

Antidepressants. A patient who already had QT prolongation associated with use of cyclobenzaprine and *fluoxetine*, developed torsade de pointes, progressing into ventricular fibrillation, when given *droperidol* as premedication before surgery.[1] QT abnormalities resolved on stopping cyclobenzaprine.

1. Michalets EL, *et al.* Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* 1998; **32:** 761–5.

Antipsychotics. For a report of an interaction between cyclobenzaprine and *droperidol*, see Antidepressants above.

Pharmacokinetics

Cyclobenzaprine hydrochloride is readily and almost completely absorbed from the gastrointestinal tract, although plasma concentrations vary considerably among individuals given the same dose. About 93% is bound to plasma proteins and has a reported effective half-life of 8 to 37 hours. It is extensively metabolised, mainly to glucuronide conjugates, and excreted in the urine. Cytochrome P450 isoenzymes CYP3A4, CYP1A2, and to a lesser extent CYP2D6 mediate its demethylation. Some unchanged drug appears in the bile and is excreted in the faeces.

References.

1. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Cizax; Miofibrax; Miosan; Mirtax; Musculare; Muscuprina; ***Canad.***: Novo-Cycloprine; ***Chile***: Ciclamil; Fibrox; Flexin; Iphsaflex; Masterelax; Medarex; Mio-Relax; Nostaden; Reflexan; Relexil; Tensamon; Tensiomax; Tensodox; Tonalgen; Ziclob; ***India***: Mobrine-IR; ***Israel***: Amrixal; ***Ital.***: Flexiban; ***Port.***: Flexiban; ***Spain***: Yurelax; ***USA***: Amrix; Fexmid; Flexeril†.

Multi-ingredient Preparations. ***Arg.***: Dorixina Relax; ***Braz.***: Dolamin Flex; ***Mex.***: Dorixina Relax; Yuredol; ***Venez.***: Dorixina Flex.

Pharmacopoeial Preparations
USP 36: Cyclobenzaprine Hydrochloride Tablets.

Dantrolene Sodium *(BANM, USAN, rINNM)*

Dantrolène Sodique; Dantroleno sódico; F-368 (dantrolene); F-440; Natrii Dantrolenum; Sodyum Dantrolen; Натрий Дантролен.

The hemiheptahydrate of the sodium salt of 1-[5-(4-nitrophenyl)furfurylideneamino]imidazolidine-2,4-dione.

$C_{14}H_9N_4NaO_5,3½H_2O$=399.3

CAS — 7261-97-4 (dantrolene); 14663-23-1 (anhydrous dantrolene sodium); 24868-20-0 (dantrolene sodium, hemiheptahydrate).

ATC — M03CA01.

ATC Vet — QM03CA01.
UNII — 287M0347EV.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Dantrolene Sodium). A yellowish-orange to orange crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in acetone; sparingly soluble in methyl alcohol.

USP 36: (Dantrolene Sodium). A fine orange to orange-brown powder. Sparingly soluble in dimethylformamide and in glycerol; sparingly soluble to practically insoluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Dantrolene sodium is a muscle relaxant with a direct action on skeletal muscle. It uncouples muscular contraction from excitation, probably by interfering with the release of calcium from the sarcoplasmic reticulum.

It is used orally, for the symptomatic relief of chronic, severe spasticity (p. 2014.2). It is also given, usually by intravenous injection, for the treatment of malignant hyperthermia.

For **spasticity**, the initial oral dose is 25 mg daily increased gradually as necessary, at 7-day intervals, over about 7 weeks to a maximum dose of 100 mg four times daily. If no response is achieved within 45 days treatment should be stopped.

In the treatment of **malignant hyperthermia**, dantrolene sodium is given, with supportive measures, in an initial dose of 1 mg/kg by rapid intravenous injection, repeated, if necessary, to a total dose of 10 mg/kg. An average dose of 2.5 mg/kg is usually effective. If a relapse or recurrence occurs, dantrolene should be given again at the last effective dose. In the USA, doses of 1 to 2 mg/kg orally four times daily have also been recommended for up to 3 days after the crisis to prevent recurrence, and similar doses have been given for 1 to 2 days before surgery in individuals thought to be at risk of developing the syndrome. Prophylactic doses may also be given intravenously; 2.5 mg/kg has been recommended, infused over about 60 minutes, starting about 75 minutes before anticipated anaesthesia, with further doses during anaesthesia and surgery if signs of malignant hyperthermia develop.

For details of doses in children, see below.

Administration in children. Dantrolene may be given orally for the symptomatic relief of chronic, severe spasticity in children. Although not licensed in the UK, the *BNFC* suggests that children aged 5 to 12 years may initially be given 500 micrograms/kg once daily, increased to 500 micrograms/kg 3 times daily after 7 days, and those aged 12 to 18 years may initially be given 25 mg once daily, increased to 3 times daily after 7 days. For all age groups, further increases may be made in steps of 500 micrograms/kg every 7 days until a satisfactory response is achieved, to a maximum dose of 2 mg/kg 3 or 4 times daily (400 mg daily). Similar doses have been given in US licensed product information.

Dantrolene may also be given for the treatment of malignant hyperthermia in children. In the UK, the *BNFC* suggests that those aged 1 month to 18 years may be given an initial dose of 2 to 3 mg/kg by rapid intravenous injection, then 1 mg/kg repeated as necessary to a total dose of 10 mg/kg. US licensed product information suggests that children may be given the usual adult doses (see Uses and Administration, above) for the prevention and treatment of malignant hyperthermia.

Hyperthermia. Dantrolene is used in the treatment of hyperthermia associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, which occurs in the neuroleptic malignant syndrome (see below and p. 1050.2) and in malignant hyperthermia (see below). There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents such as carbon monoxide,[1] MAOIs,[2] and ethyltenamfetamine.[3] However, after suggestions that it might also be of use in cocaine intoxication, the manufacturers[4] warned physicians that they should not regard dantrolene as an effective treatment for all types of hyperthermia and rigidity accompanying poisoning.

Dantrolene has been tried as part of treatment for heat stroke (see under Fever and Hyperthermia, p. 11.3) but does not appear to affect outcome.[5]

1. Ten Holter JBM, Schellens RLLAM. Dantrolene sodium for treatment of carbon monoxide poisoning. *BMJ* 1988; **296:** 1772–3.
2. Kaplan RF, *et al.* Phenelzine overdose treatment with dantrolene sodium. *JAMA* 1986; **255:** 642–4.
3. Tehan B. Ecstasy and dantrolene. *BMJ* 1993; **306:** 146.
4. Fox AW. More on rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1989; **321:** 1271.
5. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002; **346:** 1978–88.

MALIGNANT HYPERTHERMIA. Malignant hyperthermia (malignant hyperpyrexia) is a rare but potentially fatal syndrome associated with general anaesthesia, in which a sudden increase in the concentration of calcium in muscle cytoplasm initiates a series of metabolic disturbances. The disorder appears to be genetically determined and is more common in males. In susceptible individuals a reaction may be induced by inhalation anaesthetics (mainly halogenated hydrocarbons), suxamethonium, prolonged anaesthesia, pre-operative exercise, muscle trauma, fever, or anxiety. However, many reactions occur in individuals who have had uneventful general anaesthesia previously. Early signs and symptoms of the syndrome include tachycardia, unstable blood pressure, hypercapnia, rising temperature, and hyperventilation followed by metabolic acidosis and hyperkalaemia. Muscle rigidity develops in many patients and later there may be evidence of muscle damage including raised serum concentrations of creatine phosphokinase and other enzymes, myoglobinaemia, and myoglobinuria. Hyperthermia develops relatively late. Other late complications may include renal failure, intravascular coagulopathy, and pulmonary oedema.

Treatment should be started as soon as possible after symptoms appear with dantrolene being given by rapid intravenous injection until symptoms disappear.[1-3] Supportive treatment must also be given including immediate withdrawal of anaesthesia, giving oxygen, correction of acidosis with sodium bicarbonate, control of hyperkalaemia with insulin, and cooling procedures (see p. 11.3).

The incidence of reactions in susceptible individuals can be reduced by avoiding triggering agents. Dantrolene has also been given prophylactically, but a high incidence of adverse effects has been reported,[4] and such use is not generally recommended.[3] Susceptibility to malignant hyperthermia can be detected by histological examination of muscle fibres obtained by biopsy and study of their response to caffeine and/or halothane *in vitro*. Although such testing remains the gold standard for determining susceptibility, genetic testing is also being developed as an alternative.[5]

Dantrolene has been suggested[6] for use as a secondary drug in the treatment of a related and potentially fatal syndrome that has developed in some children after induction of anaesthesia with halothane and suxamethonium (see also Children, under Precautions of Suxamethonium, p. 2039.1).

1. Britt BA. Dantrolene. *Can Anaesth Soc J* 1984; **31:** 61–75.
2. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.
3. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
4. Wedel DJ, *et al.* Clinical effects of intravenously administered dantrolene. *Mayo Clin Proc* 1995; **70:** 241–6.
5. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA* 2005; **293:** 2918–24.
6. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; **77:** 1054.

Neuroleptic malignant syndrome. Dantrolene has been used, usually alone or with bromocriptine, in the treatment of neuroleptic malignant syndrome (p. 1050.2), although some workers have not found it to be of use,[1] and evidence from controlled studies is lacking.[2] Doses reported for dantrolene have varied greatly.[3,4] For those patients unable to swallow and when rapid control of symptoms is required, doses of 1 mg/kg or more have been given initially by intravenous injection. Oral doses of up to 600 mg daily have been given in divided doses.

1. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.
2. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
3. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.
4. Harpe C, Stoudemire A. Aetiology and treatment of neuroleptic malignant syndrome. *Med Toxicol* 1987; **2:** 166–76.

Tetanus. Dantrolene has effectively controlled muscle spasms in the treatment of tetanus (see p. 2029.2). It has also been used as an adjunct[1] to neuromuscular blockade; there are conflicting reports[2,3] of its value in avoiding mechanical ventilation.

1. Tidyman M, *et al.* Adjunctive use of dantrolene in severe tetanus. *Anesth Analg* 1985; **64:** 538–40.
2. Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. *Anaesthesia* 1993; **48:** 969–71.
3. Possamai C, *et al.* Dantrolene infusion in severe tetanus. *Anaesthesia* 1997; **52:** 610.

Adverse Effects

Adverse effects associated with dantrolene sodium tend to occur at the start of treatment, but are often short lived and can be controlled by adjusting the dose. The most common adverse effects are drowsiness, dizziness, fatigue, weakness, and general malaise. Diarrhoea may be severe enough to require withdrawal. If diarrhoea recurs on restarting dantrolene, then treatment should probably be stopped permanently. Other adverse effects reported include nausea and vomiting, anorexia, constipation, abdominal cramps, gastrointestinal bleeding, tachycardia, unstable blood pressure, dyspnoea, rashes (often acneform), pruritus, chills and fever, headache, myalgia, nervousness, insomnia, confusion, visual disturbances, mental depression, dysphagia and speech disturbances, and seizures. Haematuria, crystalluria, urinary frequency and retention, and incontinence may occur. Rare but serious adverse effects include hepatotoxicity which may be fatal (see below) and pleural effusion with pericarditis.

Serious adverse effects do not appear to be a problem with the short-term use of intravenous dantrolene sodium in the treatment of malignant hyperthermia.

Effects on the liver. Dantrolene has caused hepatotoxicity with raised liver enzyme values, jaundice, and hepatitis;[1-3] fatalities have been reported.[1,3] Not all patients had symptoms such as anorexia, nausea, or abdominal discomfort before the onset of disease and the severity of hepatic injury was unrelated to clinical presentation. In the first report[1] the 14 fatalities occurred with doses in excess of 200 mg daily; a later review[3] found the mean dose associated with 27 fatalities to be 582 mg daily, while reports of non-fatal liver toxicity (95 cases) were associated with a mean dose of 263 mg daily. The onset of hepatic injury was usually between 1 and 6 months after starting treatment and fatalities were not reported in the first 2 months. Only rarely did injury develop before 45 days of treatment. Females appeared to be at greater risk of serious liver injury and the severity of reaction appeared to be age-related with most fatalities occurring in patients over 30 years of age. The liver injury was usually hepatocellular and might include ascending cholangitis; there was little evidence of hypersensitivity.

1. Utili R, *et al.* Dantrolene-associated hepatic injury: incidence and character. *Gastroenterology* 1977; **72:** 610–16.
2. Wilkinson SP, *et al.* Hepatitis from dantrolene sodium. *Gut* 1979; **20:** 33–6.
3. Chan CH. Dantrolene sodium and hepatic injury. *Neurology* 1990; **40:** 1427–32.

Effects on the lungs. Pulmonary oedema associated with heart failure,[1] and pleural effusions with eosinophilia[2-4] have been reported rarely in patients receiving dantrolene. These reactions generally resolve on withdrawal of the drug but resolution may take several months; corticosteroid therapy may be of benefit in dantrolene-related eosinophilic pleural effusion.[3]

1. Robillart A, *et al.* Insuffisance cardiaque par surdosage en dantrolène. *Ann Fr Anesth Reanim* 1986; **5:** 617–19.
2. Mahoney JM, Bachtel MD. Pleural effusion associated with chronic dantrolene administration. *Ann Pharmacother* 1994; **28:** 587–9.
3. Felz MW, Haviland-Foley DJ. Eosinophilic pleural effusion due to dantrolene: resolution with steroid therapy. *South Med J* 2001; **94:** 502–4.
4. Le-Quang B, *et al.* Dantrolene and pleural effusion: case report and review of literature. *Spinal Cord* 2004; **42:** 317–20.

Lymphomas. A case of fatal lymphocytic lymphoma was associated with prolonged dantrolene therapy (600 mg daily) for progressive spastic paraplegia.[1]

1. Wan HH, Tucker JS. Dantrolene and lymphocytic lymphoma. *Postgrad Med J* 1980; **56:** 261–2.

Precautions

It is recommended that dantrolene sodium should not be given to patients with active liver disease. Liver-function tests should be performed in all patients before and during treatment; if abnormal values are found, treatment should generally be stopped. The risk of liver injury may be increased in patients over 30 years of age, in females (especially those taking oestrogens), in those with a history of liver disease, and with doses above 400 mg daily (see under Effects on the Liver, above). Dantrolene sodium should be used with caution in patients with cardiac or pulmonary disorders. It should not be given to patients who use their spasticity to maintain posture or function or to patients with acute muscle spasm.

Dantrolene sodium may cause drowsiness; patients affected should not drive or operate machinery.

Interactions

The CNS effects of dantrolene sodium may be enhanced by alcohol or other CNS depressants. Use with other potentially hepatotoxic drugs such as oestrogens may possibly increase the risk of liver damage and should be avoided.

Calcium-channel blockers. Severe hyperkalaemia and myocardial depression occurred with intravenous dantrolene for prophylaxis of malignant hyperthermia in a patient also taking *verapamil* for angina.[1] The peak serum-potassium concentration was 7.1 mmol/litre 2.5 hours after the dantrolene infusion. *Nifedipine* was substituted for verapamil in a subsequent operation and only a small

increase in serum potassium occurred after dantrolene. Ventricular fibrillation and cardiovascular collapse associated with hyperkalaemia have been seen with this combination in *animal* studies, and the manufacturers recommend that calcium-channel blockers and intravenous dantrolene should not be used together.

Severe hyperkalaemia has also been noted in a patient taking *diltiazem* after a dantrolene infusion was started.[2]

1. Rubin AS, Zablocki AD. Hyperkalaemia, verapamil, and dantrolene. *Anesthesiology* 1987; **66:** 246–9.
2. Yoganathan T, *et al.* Dantrolene-induced hyperkalemia in a patient treated with diltiazem and metoprolol. *J Cardiothorac Anesth* 1988; **2:** 363–4.

Pharmacokinetics

Dantrolene sodium is slowly and almost completely absorbed from the gastrointestinal tract after oral doses. It is metabolised in the liver mainly to the hydroxylated metabolite, which is nearly as potent as dantrolene sodium, and the acetamide metabolite which has weak muscle relaxant activity. It is excreted in the urine, mainly as metabolites with a small amount of unchanged dantrolene; some is excreted in the bile. Dantrolene is bound extensively to plasma proteins. The elimination half-life of oral dantrolene is about 9 hours, although half-lives of up to 12 hours have been reported after intravenous use. Dantrolene crosses the placenta and has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dantrium; ***Belg.***: Dantrium; ***Braz.***: Dantrolen; ***Canad.***: Dantrium; ***Chile***: Dantrium; ***Denm.***: Dantrium; ***Fr.***: Dantrium; ***Ger.***: Dantamacrin; ***Gr.***: Dantrium; Dantrolen†; ***Irl.***: Dantrium; ***Israel***: Dantrium; ***Ital.***: Dantrium; ***Neth.***: Dantrium; ***NZ***: Dantrium; ***S. Afr.***: Dantrium; ***Switz.***: Dantamacrin; ***UK***: Dantrium; ***USA***: Dantrium; Revonto.

Pharmacopoeial Preparations
BP 2014: Dantrolene Oral Suspension;
USP 36: Dantrolene Sodium Capsules; Dantrolene Sodium for Injection.

Eperisone Hydrochloride *(rINNM)*

Eperisona, hidrocloruro de; Épérisone, Chlorhydrate d'; Eperisoni Hydrochloridum; Hidrocloruro de eperisona; Эперизона Гидрохлорид.
4′-Ethyl-2-methyl-3-piperidinopropiophenone hydrochloride.
$C_{17}H_{25}NO,HCl$=295.9
CAS — 64840-90-0 (eperisone); 56839-43-1 (eperisone hydrochloride).
ATC — M03BX09.
ATC Vet — QM03BX09.
UNII — U38O8U7P6X.

Pharmacopoeias. In *Jpn.*

Profile

Eperisone is a centrally acting skeletal muscle relaxant that has been used in the symptomatic treatment of muscle spasm (p. 2014.1) and spasticity (p. 2014.2). It may also have a vasodilator action. Eperisone hydrochloride has been given in usual oral doses of 50 mg three times daily after food.

Effects on the skin. A non-pigmenting fixed drug eruption developed in a 42-year-old woman after taking oral diclofenac sodium and eperisone hydrochloride.[1] There was no residual hyperpigmentation and the rash and accompanying itching and burning sensation resolved within 7 days after stopping both drugs. On rechallenge with eperisone, an erythematous plaque developed at the same site within a couple of hours. The lesion disappeared within 5 days with no sequelae.

1. Choonhakarn C. Non-pigmenting fixed drug eruption: a new case due to eperisone hydrochloride. *Br J Dermatol* 2001; **144:** 1288–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bei Li Si (贝力斯); Beigesi (贝格斯); Myonal (妙纳); Yi Yu (宜宇); Zuo Ning (佐宁); ***Indon.***: Eprinoc; Epsonal; Estalex; Forelax; Forres; Lional; Myobat; Myoman; Myonal; Myonep; Myori; Permyo; Plexion; Rizonax; Zonal; ***Ital.***: Expose; Myonal; ***Jpn***: Myonal; ***Malaysia***: Myonal; ***Philipp.***: Myonal; Perispa; ***Singapore***: Myonal; ***Thai.***: Espenal; Musolax; Myonal; Ralexa.

Idrocilamide *(rINN)*

Idrocilamida; Idrocilamidum; LCB-29; Идроциламид.
N-(2-Hydroxyethyl)cinnamamide.
$C_{11}H_{13}NO_2$=191.2
CAS — 6961-46-2.
ATC — M02AX05.
ATC Vet — QM02AX05.
UNII — 6C816LUB1O.

Profile

Idrocilamide is a centrally acting muscle relaxant. It is reported to have local muscle relaxant and anti-inflammatory effects and is now mainly used topically.

Adverse effects. When given orally idrocilamide was reported to produce abdominal pain, nausea, and drowsiness. Excitement, euphoria and hallucinations, and depression may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Srilane; ***Switz.***: Talval.

Mephenesin *(BAN, rINN)*

Cresoxydiol; Glykresin; Mefenesiini; Mefenesin; Mefenesina; Méphénésine; Mephenesinum; Мефенезин.
3-(*o*-Tolyloxy)propane-1,2-diol.
$C_{10}H_{14}O_3$=182.2
CAS — 59-47-2.
ATC — M03BX06.
ATC Vet — QM03BX06.
UNII — 7B8PIR2954.

NOTE. The name tolynol has been applied to both mephenesin and *p*,α-dimethylbenzyl alcohol (p. 2493.3).

Pharmacopoeias. In *It.*

Profile

Mephenesin is a centrally acting skeletal muscle relaxant used for the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. Its clinical usefulness is considered to be limited by its brief duration of action. It is given orally in doses of 1.5 to 3 g daily in divided doses. It is also applied topically, usually with rubefacients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Decontractyl; ***Ger.***: DoloVisano M†.

Multi-ingredient Preparations. ***Belg.***: Algipan; ***Fr.***: Algipan†; Decontractyl; Traumalgyl†; ***India***: Acks†; Capsigyl-D; Capsigyl; Diclowin; Dolomed; Ethnorub; Flamar†; Inflazone; Medicreme; Neurophen; Relaxyl; Systaflam; ***Ital.***: Relaxar; ***S.Afr.***: Spasmend.

Mephenoxalone *(rINN)*

AHR-233; Mefenoksalon; Mefenoxalona; Méphénoxalone; Mephenoxalonum; Methoxadone; OM-518; Мефеноксалон.
5-(2-Methoxyphenoxymethyl)oxazolidin-2-one.
$C_{11}H_{13}NO_4$=223.2
CAS — 70-07-5.
ATC — N05BX01.
ATC Vet — QN05BX01.
UNII — CZ87T54W8W.

Profile

Mephenoxalone has actions similar to those of meprobamate (p. 1083.3). It has been given orally in a dose of 200 to 400 mg three times daily as a muscle relaxant in the treatment of muscle spasm (p. 2014.1). It has also been given for the treatment of anxiety.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Dimexol; Dorsiflex; ***Neth.***: Dorsiflex†; ***Turk.***: Dorsiflex.

Multi-ingredient Preparations. ***Turk.***: Dorsilon.

Metaxalone *(BAN, USAN, rINN)*

AHR-438; Metaxalona; Métaxalone; Metaxalonum; Метаксалон.
5-(3,5-Xylyloxymethyl)oxazolidin-2-one.
$C_{12}H_{15}NO_3$=221.3
CAS — 1665-48-1.
UNII — 1NMA9J598Y.

Uses and Administration

Metaxalone is a centrally acting skeletal muscle relaxant. Its mode of action may be related to its sedative properties.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual oral dose is 800 mg three or four times daily.

Adverse Effects, Treatment, and Precautions

As for Chlorzoxazone, p. 2022.3.

Metaxalone may cause drowsiness; patients affected should not drive or operate machinery.

Patients taking metaxalone excrete in the urine a metabolite which gives a false positive reaction to copper sulfate-based tests for glycosuria.

Overdosage. The most common symptoms in a series of 142 adults with metaxalone ingestion reported to Texas poison centres during 2000 to 2006 were drowsiness or lethargy, tachycardia, nausea, dizziness or vertigo, agitation, slurred speech, and tremor; doses of up to 44 g had been taken.[1] The severity of the final medical outcome was judged to be none (49.3% of patients), minor (35.2%), moderate (13.4%), and major (2.1%); no deaths were reported.

1. Forrester MB. Adult metaxalone ingestions reported to Texas poison control centers, 2000-2006. *Hum Exp Toxicol* 2010; **29:** 55–62.

Interactions

The CNS effects of metaxalone may be enhanced by alcohol and other CNS depressants.

Pharmacokinetics

Metaxalone is absorbed from the gastrointestinal tract, metabolised in the liver, and excreted in urine as metabolites. The plasma elimination half-life is about 2 to 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Flexura; ***USA***: Skelaxin.

Multi-ingredient Preparations. ***India***: Fenaplus-RX; Flexura-D; Metadol; Mobiswift-D.

Methocarbamol *(BAN, rINN)*

Guaiphenesin Carbamate; Méthocarbamol; Methocarbamolum; Metocarbamol; Metokarbamol; Metokarbamoli; Метокарбамол.
2-Hydroxy-3-(2-methoxyphenoxy)propyl carbamate.
$C_{11}H_{15}NO_5$=241.2
CAS — 532-03-6.
ATC — M03BA03.
ATC Vet — QM03BA03.
UNII — 125OD7737X.

Pharmacopoeias. In *US.*

USP 36: (Methocarbamol). A white powder, odourless or having a slight characteristic odour. M.p. about 94 degrees or, if previously ground to a fine powder, about 90 degrees. Soluble 1 in 40 of water at 20 degrees; sparingly soluble in chloroform; soluble in alcohol only with heating; insoluble in *n*-hexane and in benzene. Store in airtight containers.

Uses and Administration

Methocarbamol is a centrally acting skeletal muscle relaxant whose action may be due to general depressant effects on the CNS.

Methocarbamol is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. It is sometimes given with analgesics in compound preparations for the treatment of musculoskeletal pain.

The usual initial oral dose for muscle spasm is 1.5 g four times daily, reduced to a maintenance dose of about 4 g daily after 2 to 3 days. A dose of 750 mg three times daily may be sufficient for a therapeutic effect. Half the maximum daily dose or less may be sufficient for elderly patients.

Methocarbamol has also been given intravenously at a rate of not more than 300 mg/minute, by slow injection or by infusion in sodium chloride 0.9% or glucose 5% injection. The parenteral route should not be used for more than 3 consecutive days and the dose should not exceed 3 g daily. The patient should remain lying down during, and for

10 to 15 minutes after, intravenous doses. The US manufacturers state that the injection is hypertonic and extravasation should be avoided. However, it may also be given by intramuscular injection in a dose of up to 500 mg into each gluteal region at intervals of 8 hours.

Adverse Effects

Adverse effects reported with methocarbamol include nausea, vomiting, anorexia, lightheadedness, dizziness, lassitude, drowsiness, restlessness, anxiety, confusion, tremor, vertigo, blurred vision, fever, headache, convulsions, and hypersensitivity reactions such as rashes, pruritus, urticaria, angioedema, and conjunctivitis with nasal congestion.

After injection patients may have flushing and a metallic taste; incoordination, diplopia, nystagmus, vertigo, syncope, hypotension, bradycardia, and anaphylaxis have been reported. There may be sloughing and thrombophlebitis at the site of injection.

Precautions

Methocarbamol is contra-indicated in coma or pre-coma states, brain damage, myasthenia gravis, or in patients with a history of epilepsy. Caution is advisable in renal or hepatic impairment. Methocarbamol may cause drowsiness; patients affected should not drive or operate machinery.

Preparations for injection may contain, as a solvent, a macrogol which could increase existing acidosis and urea retention in patients with renal impairment; such preparations should not be used in patients with known or suspected renal disease.

Abnormal coloration. Methocarbamol has been reported to cause brown to black or green discoloration of the urine on standing.[1]

1. Baran RB, Rowles B. Factors affecting coloration of urine and feces. *J Am Pharm Assoc* 1973; **NS13:** 139–42.

Interactions

The CNS effects of methocarbamol may be potentiated by alcohol or other CNS depressants. Methocarbamol has also been reported to potentiate the effects of anorectics and antimuscarinics, and to inhibit the effect of pyridostigmine.

Pharmacokinetics

Methocarbamol is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Its plasma half-life is reported to be about 1 to 2 hours. It is metabolised by dealkylation and hydroxylation and is excreted in urine mainly as the glucuronide and sulfate conjugates of its metabolites. A small amount is excreted in faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Robaxin; ***Fr.***: Lumirelax; ***Ger.***: DoloVisano Methocarbamol; Ortoton; ***Gr.***: Robaxin; Trolar; ***Hong Kong***: Myomethol; ***India***: Robinax; ***Mex.***: Remisol†; Rexivin; ***S.Afr.***: Robaxin; ***Spain***: Robaxin; ***Thai.***: Laxan; Mannix; Manobaxine; Mebaxin; Methamol; Musxan; Myomethol†; Polyxan; ***UK***: Robaxin; ***USA***: Robaxin.

Multi-ingredient Preparations. ***Canad.***: Analgesic and Muscle Relaxant Caplets; Aspirin Night-Time†; Dodds Back Ease†; Extra Strength Muscle & Back Pain ASA; Extra Strength Muscle & Back Pain Relief; Methoxacet-C; Methoxacet; Methoxisal-C; Methoxisal; Midol Night-Time; Muscle & Back Pain Relief Extra Strength; Muscle & Back Pain Relief-8; Muscle & Back Pain Relief; Relaxophen; Robax Platinum; Robaxacet-8; Robaxacet; Robaxisal-C; Robaxisal; Spasmhalt-ASA; Spasmhalt; Summit Ultra; Tylenol Back Pain; ***Gr.***: Robaxisal; ***India***: Asolt-AT; Flexinol; Ibugesic-M; Neuromol-MR; Robiflam; Robinaxol; ***Mex.***: Ardosons; Artridol; Carbafen; Carbager-Plus; Carbamox; Dolocam Plus; Flexamol†; Malival Compuesto; Morlan; Remisol-Plus; Retoflam F; Reupat; Robaxifen; Robaxisal; ***S.Afr.***: Robaxisal†; ***Spain***: Robaxisal Compuesto; ***Thai.***: Sancago; ***Turk.***: Miyorel; ***Venez.***: Beseroldos; Robaxifen; Robaxisal.

Pharmacopoeial Preparations
USP 36: Methocarbamol Injection; Methocarbamol Tablets.

Pridinol Mesilate *(rINNM)*

C-238 (pridinol); Mesilato de pridinol; Pridinol, Mésilate de; Pridinol, mesilato de; Pridinol Mesylate; Pridinoli Mesilas; Придинола Мезилат.

1,1-Diphenyl-3-piperidinopropan-1-ol methanesulphonate.

$C_{20}H_{25}NO,CH_3SO_3H$=391.5

CAS — 511-45-5 (pridinol); 968-58-1 (pridinol hydrochloride); 6856-31-1 (pridinol mesilate).

ATC — M03BX03.

ATC Vet — QM03BX03.

Profile

Pridinol mesilate is a centrally acting muscle relaxant used in the symptomatic treatment of muscle spasm (p. 2014.1). The usual initial oral dose is 2 to 8 mg three times daily, reduced to 4 to 8 mg daily for maintenance treatment. It has also been given by intramuscular or intravenous injection or rectally, and has been applied in compound topical preparations.

Pridinol has been used as the hydrochloride for its antimuscarinic properties in the management of parkinsonism (p. 889.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prinil; Relaxedan; ***Ger.***: Myoson; ***Ital.***: Lyseen; ***Pol.***: Polmesilat.

Multi-ingredient Preparations. ***Arg.***: Aldoron Flex; Blokium Flex; Bronax Flex; Curinflam Plus; Diclofenac Flex; Diclogesic Relax; Diclolabsa Relax; Diclomar Flex; Diclonex Flex; Diclonex R; Dioxaflex Plus; Dolvan Flex; Doxtran Flex; Flexidol Relax; Iglodine Flex; Metaflex Plus NF; Mextran Flex; Mio Aldoron NF; Mio-Virobron NF; Nalgiflex Relax; Oxa Sport; Oxadisten; Pancloflex; Prifec; Rodinac Flex; Silfox Flex; Tenaron Flex; Tomanil Flex; Valuca Flex; Vesalion Flex; Viartril Flex; Vimultisa Flex; Voltaren Flex; Xedenol Flex.

Thiocolchicoside *(rINN)*

Thiocolchicosidum; Tiocolchicósido; Tiyokolşikozid; Тиокольхикозид.

3,10-Di(demethoxy)-3-glucopyranosyloxy-10-methylthiocolchicine.

$C_{27}H_{33}NO_{10}S$=563.6

CAS — 602-41-5.

ATC — M03BX05.

ATC Vet — QM03BX05.

UNII — T1X8S697GT.

Pharmacopoeias. In *Fr.*

Profile

Thiocolchicoside is a muscle relaxant that has been claimed to possess GABA-mimetic and glycinergic actions. It is used in the symptomatic treatment of painful muscle spasm (p. 2014.1). The usual initial oral dose is 16 mg daily given in 2 divided doses. It has also been given intramuscularly in a usual dose of 8 mg daily given in 2 divided doses, or applied as cream or ointment. Photosensitivity reactions may occur.

References.

1. Tüzün F, *et al.* Multicenter, randomized, double-blinded, placebo-controlled trial of thiocolchicoside in acute low back pain. *Joint Bone Spine* 2003; **70:** 356–61.
2. Guarneri C, *et al.* Embolia cutis medicamentosa following thiocolchicoside injection. *J Eur Acad Dermatol Venereol* 2008; **22:** 1005–6.
3. Giavina-Bianchi P, *et al.* Epileptic seizure after treatment with thiocolchicoside. *Ther Clin Risk Manag* 2009; **5:** 635–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Molagar; ***Braz.***: Coltrax; Muscoril; ***Cz.***: Muscoril; ***Fr.***: Colthiozid; Coltramyl; Miorel; Myoplege; ***Gr.***: Dirulan; Disintryl; Haliver; Izinor; Klesidren; Lamepon; Musclide; Musco-ril; Relief; Thiacomin; ***India***: Colchico; Muscodol; Myoril; ***Ital.***: Decontril; Miostart; Miotens; Muscoflex; Muscoril; Sciomir; Strialisin; Teraside; Tiorilene†; Tioside; ***Pol.***: Muscoril†; ***Port.***: Coltramyl; Relmus; ***Turk.***: Adeleks; Dynaxon; Kenfix; Maxthio; Muscoflex; Muscoril; Myal; Myodin; Recoside; Thiospa; Tiorelax; Tyoflex; ***Venez.***: Biocolchid; Coltrax; Colval; Eusilen; Lampral; Tiochax.

Multi-ingredient Preparations. ***India***: Lorchek-MR; Lupiflex; Nucoxia-MR; ***Ital.***: Muscoril Trauma; ***Mex.***: Neuroflax; ***Port.***: Adalgur N; ***Spain***: Adalgur; ***Venez.***: Colfene.

Tizanidine Hydrochloride

(BANM, USAN, rINNM)

AN-021; DS-103-282; DS-103-282-ch; Hidrocloruro de tizanidina; Tizanidina, hidrocloruro de; Tizanidine, Chlorhydrate de; Tizanidini Hydrochloridum; Тизанидина Гидрохлорид.

5-Chloro-*N*-(2-imidazolin-2-yl)-2,1,3-benzothiadiazol-4-ylamine hydrochloride.

$C_9H_8ClN_5S,HCl$=290.2

CAS — 51322-75-9 (tizanidine); 64461-82-1 (tizanidine hydrochloride).

ATC — M03BX02.

ATC Vet — QM03BX02.

UNII — B53E3NMY5C.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Tizanidine Hydrochloride). Store in airtight containers.

Uses and Administration

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant. It is an α_2-adrenergic agonist structurally related to clonidine (p. 1339.1) and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurones. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions.

Tizanidine hydrochloride is given orally, usually in divided doses; doses are expressed in terms of the base. Tizanidine hydrochloride 1.14 mg is equivalent to about 1 mg of tizanidine. The usual initial daily dose in the UK in the management of spasticity is the equivalent of 2 mg of the base given as a single dose. The dose may be increased thereafter according to response in steps of 2 mg at intervals of at least 3 to 4 days, usually up to 24 mg daily given in 3 or 4 divided doses. A similar schedule, with an initial daily dose of 4 mg, increased as required in steps of 2 to 4 mg, is used in the USA. The maximum recommended dose is 36 mg daily. Maintenance doses have been given in some countries in the form of modified-release preparations. For dosage in renal impairment, see below.

In the treatment of painful muscle spasm tizanidine hydrochloride is given in doses equivalent to 2 to 4 mg of the base three times daily.

Administration in renal impairment. UK licensed product information recommends that in patients with renal insufficiency, oral treatment with tizanidine hydrochloride should be started with the equivalent of 2 mg of the base once daily; thereafter it advises a slow increase in the once-daily dose before increasing the frequency of administration. Similar recommendations are made in US product information.

Headache. Results from an open-label study[1] and a later controlled study[2] suggested that tizanidine might be of value in the prophylaxis of chronic daily headache. However, an earlier controlled study[3] failed to show any significant advantage over placebo in the treatment of chronic tension-type headache. In another study[4] tizanidine was also effective when given with a long-acting NSAID as part of a detoxification regimen for patients with chronic daily headaches induced by analgesic overuse.

1. Saper JR, *et al.* An open-label dose-titration study of the efficacy and tolerability of tizanidine hydrochloride tablets in the prophylaxis of chronic daily headache. *Headache* 2001; **41:** 357–68.
2. Saper JR, *et al.* Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002; **42:** 470–82.
3. Murros K, *et al.* Modified-release formulation of tizanidine in chronic tension-type headache. *Headache* 2000; **40:** 633–7.
4. Smith TR. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* 2002; **42:** 175–7.

Premedication. The value of tizanidine as a premedicant has been studied.[1] An oral dose of tizanidine 12 mg appears to have sedative and sympatholytic effects comparable with oral clonidine 150 micrograms.

1. Meittinen TJ, *et al.* The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg* 1996; **82:** 817–20.

Spasticity. The efficacy of tizanidine for spasticity (p. 2014.2) associated with cerebral and spinal disorders[1,2] has been shown in several placebo-controlled studies and in comparative studies it has produced similar improvements in muscle tone to baclofen or diazepam. Carefully titrated doses of tizanidine and baclofen used together may have additive beneficial effects[1,2] but use with benzodiazepines is not recommended because of potential interactions.[1] It was considered that tizanidine might have the advantage of being better tolerated than baclofen.

1. Wagstaff AJ, Bryson HM. Tizanidine: a review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997; **53:** 435–52.
2. Kamen L, *et al.* A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. *Curr Med Res Opin* 2008; **24:** 425–39.

Adverse Effects and Precautions

Tizanidine hydrochloride may cause drowsiness; patients affected should not drive or operate machinery. Other adverse effects include dry mouth, fatigue, dizziness or vertigo, muscle pain and weakness, insomnia, anxiety, headache, bradycardia, nausea, and gastrointestinal disturbances. Hallucinations have occurred on rare occasions. Many adverse effects have been found to be dose related and slow titration of doses appears to reduce the frequency of occurrence. Hypotension may occur.

Increases in liver enzymes and rarely acute hepatitis have been associated with tizanidine and it is contra-indicated in patients with severe hepatic dysfunction. In the UK it is recommended that liver function should be monitored monthly in all patients for the first 4 months

and in those who develop symptoms suggestive of hepatic dysfunction; similarly, in the USA baseline assessment and monitoring at 1, 3, and 6 months is advised. Treatment should be stopped if liver enzymes are persistently raised.

Caution is required in the elderly and in patients with renal insufficiency.

Interactions

Tizanidine is metabolised by the cytochrome P450 isoenzyme CYP1A2 and use with ciprofloxacin or fluvoxamine, both potent inhibitors of this isoenzyme, is contra-indicated. Use with other more moderate inhibitors of CYP1A2 (such as other quinolone antibacterials, cimetidine, and antiarrhythmics such as amiodarone, mexiletine, propafenone, and verapamil) should be avoided unless clinically necessary. The CNS effects of tizanidine may be enhanced by alcohol or other CNS depressants. There may be an additive hypotensive effect when tizanidine is used in patients receiving antihypertensive therapy; bradycardia may also be enhanced if given with beta blockers or digoxin. Caution should be exercised when tizanidine is given with drugs known to increase the QT interval. The clearance of tizanidine has been reported to be lower in women receiving hormonal contraceptives.

Antibacterials. In a study of healthy subjects,[1] *ciprofloxacin*, an inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to elevate the plasma concentrations of tizanidine thereby potentiating its hypotensive and sedative effects.

1. Granfors MT, *et al.* Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* 2004; **76:** 598–606.

Antidepressants. In a study[1] in 10 healthy subjects, *fluvoxamine*, a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to increase tizanidine's peak plasma concentrations and elimination half-life twelvefold and threefold, respectively. An increased incidence of adverse effects associated with tizanidine such as hypotension, bradycardia, drowsiness, and dizziness was noted in these subjects.

A 70-year-old woman receiving fluvoxamine 150 mg daily and other medications developed bradycardia, dry mouth, urinary retention, and a low body temperature when given tizanidine 3 mg daily;[2] the patient improved when tizanidine was stopped. In a retrospective survey of medical records, the authors reported adverse effects associated with tizanidine in 6 of 23 patients also receiving fluvoxamine.

1. Granfors MT, *et al.* Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. *Clin Pharmacol Ther* 2004; **75:** 331–41.
2. Momo K, *et al.* Drug interaction of tizanidine and fluvoxamine. *Clin Pharmacol Ther* 2004; **76:** 509–10.

Antiepileptics. For reference to an interaction between tizanidine and *phenytoin*, see p. 545.1.

Cardiovascular drugs. Severe hypotension, occurring 2 hours after treatment with tizanidine, has been reported in a patient receiving antihypertensives, including *lisinopril*, and other medications.[1] The patient improved after tizanidine and antihypertensives were stopped; they were later resumed without lisinopril, and caused no problems.

1. Kao C-D, *et al.* Hypotension due to interaction between lisinopril and tizanidine. *Ann Pharmacother* 2004; **38:** 1840–3.

Oral contraceptives. Mean peak plasma concentrations after a single 4-mg dose of tizanidine were 3 times greater in 15 women using an oral contraceptive containing *ethinylestradiol* and *gestodene* than in controls;[1] the elimination half-life was not, however, significantly different. The effect appeared to be due to inhibition of the cytochrome P450 isoenzyme CYP1A2 by the contraceptive, resulting in reduced presystemic metabolism of tizanidine. Because the therapeutic range of tizanidine is narrow, care should be exercised if it is given to patients taking oral contraceptives.

1. Granfors MT, *et al.* Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2. *Clin Pharmacol Ther* 2005; **78:** 400–11.

Pharmacokinetics

Tizanidine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after oral doses. It is about 30% bound to plasma proteins. Tizanidine undergoes extensive first-pass metabolism in the liver mainly via the cytochrome P450 isoenzyme CYP1A2 and is excreted mainly in the urine as inactive metabolites. Elimination half-lives of 2 to 4 hours have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sirdalud; Tizanidal; ***Austria***: Sirdalud; ***Belg.***: Sirdalud; ***Braz.***: Sirdalud; ***Canad.***: Zanaflex; ***Chile***: Sirdalud; ***China***: Chang Bang (畅邦); KaiLaiTong (凯莱通); ***Cz.***: Sirdalud; ***Denm.***: Sirdalud; Zanic; ***Fin.***: Sirdalud; ***Ger.***: Sirdalud; ***Gr.***: Sirdalud; ***Hong Kong***: Sirdalud†; ***Hung.***: Sirdalud; ***India***: DTN 52; Emsulide-MR; Nimcom; Nimeb-T; Nimuflex-T; Nixia; Sirdalud; ***Indon.***: Myores; Sirdalud; Tizacom; Zitanid; ***Irl.***: Tizaflex; Zanaflex; ***Ital.***: Navizan; Sirdalud; ***Jpn***: Ternelin; ***Mex.***: Sirdalud; ***Neth.***: Sirdalud; ***Philipp.***: Sirdalud; Ternelax; ***Pol.***: Sirdalud; TizaniTeva; Tizanor; ***Port.***: Sirdalud; ***Rus.***: Sirdalud (Сирдалуд); Tisalud (Тизалуд); ***Spain***: Sirdalud; ***Switz.***: Sirdalud; ***Thai.***: Sirdalud; Tidar; Tizan; ***Turk.***: Devalud; Sirdalud; ***UK***: Zanaflex; ***Ukr.***: Sirdalud (Сирдалуд); Tizalud (Тизалуд); ***USA***: Zanaflex; ***Venez.***: Sirdalud.

Multi-ingredient Preparations. ***India***: Accetiz-P; Acent-TZ; Acicloflex-MR; Acota-MR; Alsolide-MR; Antipen-T; Asflam; Avisera-MR; Bestogesic MR; Brufen-MR; Canmet-MR; Carnil MR; Cipzone-TN; Citanz; Dicloran-MR; Diplonim-MR; Doloflam-MR; Etiza; Gesnim-MR; Gonim; Icobit-MR; Ingesic-MR; Itzgon; Jusgo-MR; Kinectine-MR†; Leofenac-MR; Lumbril-T; Mef-T; Meftal-MR; Minipar-TZ; Mortrin-T; Movon-MR; Nelsid-MR; Neomol-MR; Niciflex-T; Nicip T; Nile-TZ; Nimat-MR; Nimdin; Nimeril-T; Nimetiz; Nimi-LB; Nimitiz; Nimofen-T; Nimotiz MR; Nimpain T; Nimsaid-T; Nimtiz-MR; Nimudin; Nimulid MR; Nimvar-MR; Nimven-T; Nise-MR; Nizapas-MR; Nizi; Nizox-MR; Nobel-MR; Novolid-MR; Onalide-MR; Opel-MR; Orthobid-MR; Orthodex-MR; Zerodol-MR.

Pharmacopoeial Preparations
USP 36: Tizanidine Tablets.

Tolperisone Hydrochloride *(BANM, rINNM)*

AV-650; Hidrocloruro de tolperisona; N-553; Tolperisona, hidrocloruro de; Tolpérisone, Chlorhydrate de; Tolperisoni Hydrochloridum; Тольперизона Гидрохлорид.

2,4′-Dimethyl-3-piperidinopropiophenone hydrochloride.

$C_{16}H_{23}NO,HCl$=281.8

CAS — 728-88-1 (tolperisone); 3644-61-9 (tolperisone hydrochloride).

ATC — M03BX04.

ATC Vet — QM03BX04.

UNII — 8Z075K2TIG.

Pharmacopoeias. In *Jpn.*

Profile

Tolperisone hydrochloride is a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity (p. 2014.2) and muscle spasm (p. 2014.1), in usual oral doses of 50 to 150 mg three times daily. It has also been given by injection.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Miodom; ***Austria***: Mydocalm; ***Cz.***: Mydocalm; ***Ger.***: Mydocalm; Viveo†; ***Hong Kong***: Mydocalm; Quali-Docalm; ***Hung.***: Miderizone; Myderison†; Mydeton; ***Jpn***: Muscalm; ***Pol.***: Mydocalm; Tolperis; ***Rus.***: Mydocalm (Мидокалм); ***Switz.***: Mydocalm; Tolflex; ***Thai.***: Biocalm; Musocalm; Mydocalm; Mydono†; Mydosone; Myoxan; Risocalm; Soneriper; Spamus; Tanderon; Usocalm; ***Ukr.***: Mydocalm (Мидокалм); Tolperil (Толперил).

Multi-ingredient Preparations. ***Mex.***: Mydocalm-A.

Neuromuscular Blockers

Anaesthesia, p. 2028
Intensive care, p. 2028
Tetanus, p. 2029

Neuromuscular blockers (myoneuronal blockers) affect transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia, particularly to enable adequate muscle relaxation to be achieved with light anaesthesia. There are 2 main types of neuromuscular blockers: competitive (non-depolarising neuromuscular blockers) and depolarising neuromuscular blockers (see Table 1, below).

Table 1. Classification of neuromuscular blockers.

Competitive		Depolarising
Aminosteroidal	*Benzylisoquinolinium*	Suxamethonium
Pancuronium	Alcuronium	
Pipecuronium	Atracurium	
Rocuronium	Cisatracurium	
Vecuronium	Gallamine	
	Mivacurium	
	Tubocurarine	

- **Competitive neuromuscular blockers** act by competing with acetylcholine for receptors on the motor end-plate. Their action can be opposed by increasing the local concentration of acetylcholine, for example by giving an anticholinesterase such as neostigmine (p. 687.1). Tubocurarine (p. 2040.1) was formerly the standard reference drug of this type but its use has declined, therefore details of the actions and uses of competitive neuromuscular blockers are discussed under Atracurium, p. 2030.1.
- **Depolarising neuromuscular blockers** act by depolarising the motor end-plate to prevent the normal response to acetylcholine; their action is not reversed by anticholinesterases. Suxamethonium (p. 2037.1) is the standard reference drug of this type.

Other drugs that have muscle relaxant properties and which are used in the management of musculoskeletal and neuromuscular disorders are discussed in the chapter on Muscle Relaxants, p. 2014.1.

General references.

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Anaesthesia

Neuromuscular blockers are used in general anaesthesia for their muscle relaxant effects to facilitate intubation at induction and to provide continued relaxation during maintenance. Their use is determined partly by their onset and duration of action (see Table 2, below), but both onset and duration are dose-dependent and can therefore vary. Generally, *competitive neuromuscular blockers*, due to their slower onset and longer duration of action, are used in major operations, while the *depolarising neuromuscular blockers* (usually suxamethonium), with a much faster onset and shorter duration, are used for minor operations or manipulations and particularly for intubation. After use of suxamethonium to aid intubation, a longer-acting competitive drug may then be given to maintain muscle relaxation throughout the operation. Competitive neuromuscular blockers with a short to intermediate duration of action, such as atracurium and vecuronium, are more widely used than those with a longer duration of action such as pancuronium.

Suxamethonium has been widely used after induction of anaesthesia to aid **intubation**; however, because of the adverse effects such as myalgia associated with suxamethonium (see also below), alternative neuromuscular blockers have been investigated for intubation and some questioned the use of suxamethonium for *elective* procedures,[1] especially in day-case patients.[2] Some competitive blockers such as vecuronium have a relatively rapid onset of action and have been used for intubation during routine, planned surgery. However, they act too slowly to enable rapid intubation in an *emergency*, when suxamethonium remains the drug of choice. Although rocuronium, a competitive blocker, is only slightly slower in onset, and may be suitable in emergencies if suxamethonium is contra-indicated,[3-5] it has a much longer duration of action, and needs to be given with an opioid such as alfentanil,[6] or with propofol,[4] to obtain equivalent intubating conditions.

In attempting to create more favourable conditions for rapid intubation with competitive neuromuscular blockers and thus provide an alternative to suxamethonium, anaesthetists have tried using large doses[3] or combinations[7] of competitive blockers. Other methods tried include giving competitive neuromuscular blockers in divided doses in an attempt to shorten the onset to paralysis.[3,8] This so-called *priming principle* involves giving a small initial dose, termed the priming dose, followed by a large paralysing dose. Priming may be with 2 doses of the same competitive relaxant or a combination of 2 different relaxants which may then show synergism. However, some consider[8] that priming techniques are associated with unacceptable adverse effects such as muscle weakness and aspiration, and that they are not safe, especially in the elderly.[3] In another technique, a single large dose of a neuromuscular blocker is given, followed by the induction anaesthetic as soon as the patient complains of weakness.[3] This is called the *timing principle* and although it has been successfully used with some neuromuscular blockers, problems such as perceived muscle weakness or shortness of breath may occur if the anaesthetic is not injected at the right moment.

The use of anaesthetic regimens that avoid or reduce the need for a neuromuscular blocker during intubation has also been investigated. The anaesthetic propofol with a short-acting opioid such as alfentanil has often been tried. In addition to its use alone, such a regimen has been combined successfully with low doses of suxamethonium[9] or rocuronium,[10] or standard doses of vecuronium,[11] to produce suitable conditions for intubation.

Procedures such as intubation can cause **complications**: an undesirable pressor response may occur, resulting in increased heart rate and arterial blood pressure. There may also be an increase in intracranial pressure and intra-ocular pressure. Furthermore, the use of suxamethonium to aid intubation is itself associated with a transient increase in intra-ocular pressure. Small doses of a competitive neuromuscular blocker have been given before suxamethonium[12] to prevent this rise in intra-ocular pressure, although some consider such a measure ineffective.[13] Opioids such as alfentanil and fentanyl appear to be effective in attenuating both the pressor response[14-16] and the rise in intra-ocular pressure[17,18] associated with intubation, but the use of lidocaine has produced conflicting results.[19-23] Many anaesthetics, with the exception of ketamine, reduce intra-ocular pressure to some extent and giving thiopental beforehand may help to counteract the effect of suxamethonium.[24]

Table 2. Relative speed of onset and duration of action of neuromuscular blockers.

Neuromuscular blocker	Onset*	Duration†
Alcuronium	Intermediate	Intermediate
Atracurium	Intermediate	Short/Intermediate
Cisatracurium	Intermediate	Short/Intermediate
Gallamine	Rapid	Intermediate
Mivacurium	Intermediate	Short
Pancuronium	Rapid	Long
Pipecuronium	Intermediate	Intermediate/Long
Rocuronium	Rapid	Intermediate
Suxamethonium	Ultra-rapid	Ultra-short
Tubocurarine	Intermediate/Slow	Intermediate
Vecuronium	Rapid	Intermediate

**Onset:*
Ultra-rapid, less than 1 minute
Rapid, 1 to 2 minutes
Intermediate, 2 to 4 minutes
Slow, more than 4 minutes

†Duration:
Ultra-short, less than 8 minutes
Short, 8 to 20 minutes
Intermediate, 20 to 50 minutes
Long, more than 50 minutes

Onset and duration of action are dose-dependent

Other drugs that have been used or tried in the prevention of the haemodynamic response to intubation include magnesium sulfate[25] and propofol.[26,27]

Competitive neuromuscular blockers are usually used to provide muscle relaxation during **maintenance** anaesthesia. Patients given a neuromuscular blocker generally require less anaesthetic permitting a state of 'lighter anaesthesia' and hence reducing the adverse effects of the anaesthetic. At the end of the procedure any residual block should be reversed, either with an anticholinesterase or the selective relaxant binding agent sugammadex if appropriate, and the patient should be monitored until spontaneous respiration has resumed. For further details see Anaesthesia under Uses of General Anaesthetics, p. 1896.1.

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Intensive care

The use of neuromuscular blockers in patients requiring mechanical ventilation as part of intensive care has been discussed in reviews[1-3] and guidelines.[4] Neuromuscular blockers are used to provide additional relaxation and facilitate ventilatory support in patients who fail to respond to sedation alone. It is important to ensure that such patients are adequately sedated and relatively pain free

All cross-references refer to entries in Volume A

before these drugs are used. Patients who are considered most likely to benefit are those with spontaneous respiration that is counterproductive to mechanical ventilation. Patients with little inherent respiratory muscle activity are less likely to obtain an improvement in oxygenation. Neuromuscular blockers may also improve control of intracranial pressure in patients with intracranial hypertension, including prevention of rises in intracranial pressure associated with routine tracheobronchial suction.

Pancuronium has been widely used as a neuromuscular blocker in intensive care because of its tendency to increase arterial pressure and the majority of patients requiring a neuromuscular blocker can be adequately managed with pancuronium; however, its long duration of action may be a problem in some circumstances, and its vagolytic activity can also produce tachycardia. Vecuronium, atracurium, and cisatracurium have relatively few cardiovascular effects, but there has been some concern over the ability of the atracurium metabolite laudanosine to accumulate in the CNS (see Biotransformation, under Pharmacokinetics, p. 2033.3). Atracurium and cisatracurium may also be more suitable in patients with hepatic or renal impairment as their metabolism does not lead to the accumulation of active metabolites. Other neuromuscular blockers that have been used in intensive care include doxacurium, pipecuronium, and rocuronium.

Close monitoring of neuromuscular blockade is recommended since the pharmacodynamics and pharmacokinetics of neuromuscular blockers may be altered in patients in intensive care;[1-4] this should also allow the lowest effective neuromuscular blocking dose to be used, and reduce adverse events. Prolonged neuromuscular blockade has been related to dosage.

Other factors that may potentiate neuromuscular blockade include drug interactions, electrolyte imbalance, hypothermia, or changes in acid–base balance.[1,3] Conversely, dosage requirements may be increased in patients with burns or in those receiving prolonged therapy. Tachyphylaxis has occurred with some neuromuscular blockers, but may resolve on switching to another blocker.

Prolonged neuromuscular blockade has been associated with adverse effects and should be avoided when possible. Recovery after withdrawal of prolonged treatment may be longer than pharmacologically predicted due to the accumulation of active metabolites; this is a particular problem for neuromuscular blockers with a long duration of action and for patients with hepatic or renal impairment. An acute myopathy has also followed prolonged use, most commonly with aminosteroid neuromuscular blockers (see Table 1, p. 2028); there are case reports suggesting that use of corticosteroids might increase the risk.[4,5]

When rapid reversal of paralysis is necessary an anticholinesterase such as neostigmine may be used, but relatively little is known about the efficacy of anticholinesterases in reversing prolonged paralysis.[6]

Neonatal intensive care. Neuromuscular blockers such as pancuronium bromide are used in neonatal intensive care to obtain muscle relaxation during mechanical ventilation in infants with severe pulmonary disease, especially in those whose respiratory efforts are out of phase with the ventilator.[7] They are only used in infants at high risk of complications such as *pneumothorax* or *intraventricular haemorrhage*; their routine use in all ventilated neonates is not recommended.[8]

Abolition of spontaneous respiration during mechanical ventilation has had variable effects on the incidence of *pneumothorax* in infants with respiratory distress syndrome. Although a reduced incidence was found in one study[9] involving infants of less than 33 weeks' gestation, in another study[10] the incidence was reduced only in infants with a gestational age of 27 to 32 weeks; no reduction was obtained in those below 26 weeks' gestation. Paralysis also failed to reduce the incidence of pneumothorax or interstitial emphysema in a study[11] of infants with hyaline membrane disease but did appear to speed recovery of lung function.

The aetiology of *intraventricular haemorrhage* remains obscure but there is a well recognised association with gestational age;[12] less mature neonates are more susceptible and the incidence decreases sharply after 30 weeks' gestation. There appears to be an association between fluctuating cerebral blood-flow velocity in the first day of life and subsequent development of intraventricular haemorrhage.[13] Respiratory paralysis from the first day of life until 72 hours of age has been reported[14] to stabilise both cerebral and arterial blood-flow velocity and to produce a decrease in the incidence and severity of intraventricular haemorrhage in infants with respiratory distress syndrome. However, respiratory paralysis has also been reported to have no effect on the development of intraventricular haemorrhage.[9,10]

The use of neuromuscular blockers in the newborn is not without complications. Multiple joint contractures, possibly potentiated by use of aminoglycosides or phenobarbital, have been reported[15,16] in infants given pancuronium, and regular passive limb movements should be performed during paralysis. Marked oedema, severe disturbances of fluid balance, renal failure and death have been reported in 2 neonates.[17] Hypoxaemia may develop after induction of paralysis unless a significant increase in ventilator support is made;[9,13,18] hypotension may also occur.[19] Drugs such as pancuronium which are metabolised in the liver and excreted in the urine have a prolonged action in premature infants.[7] As with adults (see above), continuous use of neuromuscular blockers in neonates has been associated with prolonged neuromuscular block on withdrawal.[20]

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Tetanus

The clinical manifestations of tetanus after infection with *Clostridium tetani* are caused by the highly potent neurotoxin tetanospasmin produced by its germinating spores.

The muscular symptoms of generalised tetanus include trismus (lockjaw), glottal spasm, generalised muscle spasm, opisthotonus (spasm of the back muscles resulting in backward arching of the body), respiratory spasm, and paralysis. Other complications include electrolyte disturbances and autonomic dysfunction leading to cardiovascular effects such as hypertension, tachycardia, and peripheral vasoconstriction. Patients may have a milder form in which the twitching and muscle spasms are limited to the area near the site of the injury, but such localised tetanus is rare and can progress to the generalised form.

The goal of treatment is to relieve muscle spasm, prevent respiratory and metabolic complications, neutralise unbound or circulating toxin, and eliminate the source of toxin. For the **antibacterial treatment** of tetanus and neutralisation of tetanospasmin, see p. 209.2. The mainstay of treatment for **rigidity and spasms** is sedation with *benzodiazepines* such as diazepam or midazolam; they may also reduce patient anxiety. *Opioid analgesics* can be added to treatment to provide analgesia and additional sedation; in addition, *fentanyl*, *morphine*, and *sufentanil* may control autonomic overactivity. *Antiepileptics*, particularly phenobarbital, may also provide additional sedation. *Chlorpromazine* is sometimes used with benzodiazepines to minimise rigidity and muscle spasms. Sedation with *propofol* may also control spasms and rigidity without the need for an additional relaxant; however, mechanical ventilation is required. Centrally acting muscle relaxants have also been tried to control muscle spasms. *Baclofen* has been given by the intrathecal route, but its therapeutic range in severe tetanus may be very narrow and deep coma and loss of spontaneous respiration has been reported. *Dantrolene* has also been reported to be effective. When muscle spasms are severe or interfere with respiration, *competitive neuromuscular blockers* have been used in addition to benzodiazepine sedation, to control spasms and to induce therapeutic paralysis so mechanical ventilation can be started.

Control of **autonomic overactivity** may be achieved with sedation; benzodiazepines, antiepileptics, and opioid analgesics have all been used (see above). *Beta blockers* such as propranolol have also been used; however, they are no longer recommended because of the potential for severe cardiovascular effects. Labetalol has both alpha- and beta-blocking activity but offers no advantage over propranolol. More recently, *esmolol*, a short-acting beta blocker, has been used. *Magnesium sulfate* has been found to minimise autonomic disturbance in ventilated patients and controls spasms in non-ventilated patients, but there is need for further investigation. **Electrolyte disturbance** is corrected with calcium and magnesium salts.

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6. Okoromah CN, Lesi FE. Diazepam for treating tetanus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 18/05/06).

Alcuronium Chloride *(BAN, USAN, rINN)*

Alcuronii Chloridum; Alcuronio, cloruro de; Alcuronium, chlorure d'; Alcuroniumchlorid; Alkuronio chloridas; Alkuronium-chlorid; Alkurónium-klorid; Alkuroniumklorid; Alkuroniumkloridi; Allnortoxiferin Chloride; Cloruro de alcuronio; Diallylnortoxiferine Dichloride; Diallyltoxiferine Chloride; Dicloruro de dialilnortoxiferina; Ro-4-3816; Алкурония Хлорид.

NN'-Diallylbisnortoxiferinium dichloride.

$C_{44}H_{50}Cl_2N_4O_2$=737.8

CAS — 23214-96-2 (alcuronium); 15180-03-7 (alcuronium chloride).

ATC — M03AA01.

ATC Vet — QM03AA01.

UNII — 490DW6501Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Ph. Eur. & (Alcuronium Chloride). A white or slightly greyish-white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; practically insoluble in cyclohexane. Store under nitrogen in an airtight container. Protect from light.

Profile

Alcuronium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1) that is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1). It can induce histamine release to some degree. Anaphylactoid reactions have been associated with the use of alcuronium. It has some vagolytic action and may produce tachycardia; hypotension may also occur.

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial dose of 150 to 250 micrograms/kg has been given intravenously. Muscle relaxation occurs after about 2 minutes and the effect lasts for about 20 to 30 minutes. Supplementary doses of 30 micrograms/kg have been given to provide additional periods of muscle relaxation.

Pregnancy. Alcuronium crosses the placenta. No evidence of neuromuscular block was seen in any of the neonates born to 12 women who received alcuronium 15 to 30 mg by intravenous injection, 5 to 10.5 minutes before delivery[1] but caution was advised if alcuronium was given in obstetrics in high doses or for a prolonged period.

1. Ho PC, *et al*. Caesarean section and placental transfer of alcuronium. *Anaesth Intensive Care* 1981; **9:** 113–18.

Renal impairment. Alcuronium is excreted mainly by the kidneys and accumulation, with prolonged paralysis, may therefore be expected in patients with renal impairment given large or repeated doses. A prolonged elimination half-life has been reported in anuria.[1] However, doses of 160 micrograms/kg have been used without any problems in patients with chronic renal failure undergoing renal transplantation.[2] The average duration of action of this dose was 37 minutes and any residual neuromuscular blockade at the end of surgery was successfully reversed using atropine and neostigmine.

1. Raaflaub J, Frey P. Zur Pharmakokinetik von Diallyl-nor-toxiferin beim Menschen. *Arzneimittelforschung* 1972; **22:** 73–8.
2. Kaushik S, *et al*. Use of alcuronium in patients undergoing renal transplantation. *Br J Anaesth* 1984; **56:** 1229–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Alloferin†; ***S.Afr.***: Alloferin; ***Ukr.***: Alloferin (Аллоферин)†.

Atracurium Besilate *(BAN, rINN)*

33A74; Atracurii Besilas; Atracurio, besilato de; Atracurium, Bésilate d'; Atracurium Besylate (USAN); Atracurium Besylate; Atracuriumbesilat; Atrakurio besilatas; Atrakuriumbesilaatti; Atrakuriumbesilat; Atrakurium-besylát; Atrakuryum Besilat; Besilato de atracurio; BW-33A; Атракурия Безилат.

2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) di(benzenesulphonate).

$C_{53}H_{72}N_2O_{12}.2C_6H_5O_3S$=1243.5

CAS — 64228-81-5.

ATC — M03AC04.

ATC Vet — QM03AC04.

UNII — 40AX66P76P.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Atracurium Besilate). A white to yellowish-white, slightly hygroscopic powder. It contains 55.0 to 60.0% of the *cis-cis* isomer, 34.5 to 38.5% of the *cis-trans* isomer, and 5.0 to 6.5% of the *trans-trans* isomer. Soluble in water; very soluble in alcohol, in acetonitrile, and in dichloromethane. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Atracurium Besylate). A white to off-white solid. It contains not less than 5.0% and not more than 6.5% of the *trans-trans* isomer, not less than 34.5% and not more than 38.5% of the *cis-trans* isomer, and not less than 55.0% and not more than 60.0% of the *cis-cis* isomer. It is unstable at room temperature. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Cisatracurium Besilate *(BAN, rINN)*

51W89 (cisatracurium); Bésilate de Cisatracurium; Besilato de cisatracurio; BW-51W (cisatracurium); BW-51W89 (cisatracurium); Cisatracurii Besilas; Cisatracurio, besilato de; Cisatracurium, Bésilate de; Cisatracurium Besylate; Sisatrakuryum Bezilat; Цисатракурия Безилат.

(1*R*,1′*R*,2*R*,2′*R*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene) bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.

CAS — 96946-42-8.

ATC — M03AC11.

ATC Vet — QM03AC11.

UNII — 80YS8O1MBS.

Incompatibility. Neuromuscular blockers are generally incompatible with alkaline solutions, for example barbiturates such as thiopental sodium. It is good practice not to give neuromuscular blockers in the same syringe, or simultaneously through the same needle, as other drugs.

Licensed product information states that cisatracurium is incompatible with ketorolac trometamol or propofol emulsion; in addition, lactated Ringer's injection with glucose 5% or lactated Ringer's solution should not be used as a diluent when preparing solutions of cisatracurium for infusion.

Stability. In a stability study,[1] solutions of cisatracurium (as the besilate) in concentrations of 2 or 10 mg/mL were stable for at least 90 days when stored in the original vials at 4 degrees either exposed to or protected from light; similar solutions stored at 23 degrees were stable for at least 45 days. Solutions of 2 mg/mL stored in plastic syringes at 4 degrees or 23 degrees were stable for at least 30 days. Solutions of 0.1, 2, or 5 mg/mL in 5% glucose injection or 0.9% sodium chloride injection in PVC minibags were stable for at least 30 days stored at 4 degrees; the 5 mg/mL solution was also stable for at least 30 days stored at 23 degrees.

1. Xu QA, *et al.* Stability of cisatracurium besylate in vials, syringes, and infusion admixtures. *Am J Health-Syst Pharm* 1998; **55:** 1037–41.

Uses and Administration

Competitive neuromuscular blockers act by competing with acetylcholine for receptors on the motor end-plate of the neuromuscular junction to produce blockade. The muscles that produce fine rapid movements such as those of the face are the first to be affected, followed by those of the limbs and torso; the last to be affected are those of the diaphragm. The paralysis is reversible with recovery occurring in reverse order. Restoration of normal neuromuscular function can be hastened by increasing the concentration of acetylcholine at the motor end-plate by giving an anticholinesterase such as neostigmine.

Atracurium and cisatracurium are competitive benzylisoquinolinium neuromuscular blockers. The commercial preparation of atracurium is a mixture of 10 stereoisomers of which cisatracurium constitutes about 15%. Cisatracurium, the *R-cis,1′R-cis*-isomer of atracurium, is about 3 times more potent than the mixture of isomers of atracurium. After an intravenous dose of atracurium, muscle relaxation begins in about 2 minutes and lasts for 15 to 35 minutes; onset may be slightly slower for cisatracurium.

Atracurium besilate and cisatracurium besilate are used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage.

For **atracurium besilate**, in the UK, the usual initial dose for adults and children over 1 month of age is 300 to 600 micrograms/kg by intravenous injection. Subsequent doses of 100 to 200 micrograms/kg may be given as necessary, typically every 15 to 25 minutes for maintenance in prolonged procedures. It is recommended that in patients with cardiovascular disease the initial dose should be given over a period of 60 seconds.

Atracurium besilate may also be given by continuous intravenous infusion at a rate of 5 to 10 micrograms/kg per minute to maintain neuromuscular block during prolonged procedures. Somewhat higher infusion rates may be used in patients undergoing controlled ventilation in intensive care.

Although unlicensed in the UK, the *BNFC* suggests that neonates may be given atracurium in doses similar to those used in older children (see above).

Cisatracurium is given as the besilate but doses are expressed as the base. Cisatracurium 1 mg is equivalent to about 1.34 mg of cisatracurium besilate. In the UK, the usual initial dose for intubation of adults and children over 1 month of age is 150 micrograms/kg by intravenous injection. In adults, the neuromuscular block may be extended with maintenance doses of 30 micrograms/kg (each dose provides about 20 minutes of additional block). In children aged 2 years and over, the neuromuscular block may be extended with maintenance doses of 20 micrograms/kg (each dose provides about 9 minutes of additional block). The *BNFC* suggests that a maintenance dose of 30 micrograms/kg, repeated about every 20 minutes, may be given to younger children aged 1 month and over; however, such use is unlicensed in the UK.

Cisatracurium besilate may also be given by continuous intravenous infusion to adults and children over 2 years of age at an initial rate equivalent to cisatracurium 3 micrograms/kg per minute followed by a rate of 1 to 2 micrograms/kg per minute after stabilisation.

Similar doses of atracurium and cisatracurium are used in the USA.

Reviews.

1. Bryson HM, Faulds D. Cisatracurium besilate: a review of its pharmacology and clinical potential in anaesthetic practice. *Drugs* 1997; **53:** 848–66.

Administration in children. Children generally require larger doses of competitive neuromuscular blockers on a weight basis than adolescents or adults to achieve similar degrees of neuromuscular blockade and may recover more quickly. In contrast, neonates and infants under 1 year of age are more sensitive and usual doses may produce prolonged neuromuscular blockade (see also Uses and Administration, above for some suggested doses).

References.

1. Brandom BW, Fine GF. Neuromuscular blocking drugs in pediatric anesthesia. *Anesthesiol Clin North America* 2002; **20:** 45–58.

ECT. Competitive neuromuscular blockers have been used to reduce the intensity of muscle contractions and minimise trauma in patients receiving ECT, but suxamethonium (p. 2037.3) is generally preferred because of its short duration of action.

Intravenous regional anaesthesia. Competitive neuromuscular blockers and/or opioid analgesics have been added to the local anaesthetic used in intravenous regional anaesthesia (p. 1977.2) to improve the quality of anaesthesia. However atracurium (see Tourniquets under Precautions, p. 2031.3) and mivacurium (see Tourniquets, p. 2035.1) might be unsuitable for such use.

Shivering. Various drugs have been tried in the treatment of postoperative shivering (p. 1897.2). There are reports of neuromuscular blockers being used to treat shivering after cardiac surgery in order to reduce cardiovascular stress;[1] one study[2] has suggested that vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.

1. Cruise C, *et al.* Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; **39:** 563–8.
2. Dupuis J-Y, *et al.* Pancuronium or vecuronium for the treatment of shivering after cardiac surgery. *Anesth Analg* 1994; **79:** 472–81.

Tetanus. For mention of the role of competitive neuromuscular blockers in the management of muscle spasms caused by tetanus, see p. 2029.2.

Adverse Effects

The adverse effects of competitive neuromuscular blockers are generally similar although they differ in their propensity to cause histamine release and associated cardiovascular effects. The latter appear to be rare with the aminosteroidal blockers and the benzylisoquinolinium blocker cisatracurium (see below). Competitive neuromuscular blockers with vagolytic activity may produce tachycardia and a rise in blood pressure. The use of blockers that lack an effect on the vagus will not counteract the bradycardia produced during anaesthesia by the other drugs employed or by vagal stimulation. Reduction in blood pressure with compensatory tachycardia may occur with some competitive neuromuscular blockers, in part because of sympathetic ganglion blockade or the release of histamine. Reduction in gastrointestinal motility and tone may occur as a result of ganglionic blockade.

Histamine release may also lead to wheal-and-flare effects at the site of injection, flushing, occasionally bronchospasm, and rarely anaphylactoid reactions.

Malignant hyperthermia has been associated rarely with competitive neuromuscular blockers.

Some competitive neuromuscular blockers such as pancuronium, tubocurarine, and vecuronium can cause a decrease in the partial thromboplastin time and prothrombin time.

In overdosage there is prolonged apnoea due to paralysis of the intercostal muscles and diaphragm, with cardiovascular collapse and the effects of histamine release.

Atracurium and its isomer cisatracurium have no significant vagal or ganglionic blocking activity at recommended doses. Unlike atracurium, cisatracurium does not induce histamine release and is therefore associated with greater cardiovascular stability.

For possible risks from their major metabolite laudanosine, see Biotransformation, under Pharmacokinetics, p. 2033.3.

Effects on body temperature. Competitive neuromuscular blockers are not considered to be a trigger factor for malignant hyperthermia; however, there have been rare case reports of apparent association. Two cases of mild malignant hyperthermia have been reported[1] where tubocurarine was probably the triggering drug. Each episode developed in a member of a family known to be susceptible to malignant hyperthermia, despite preventive measures such as prophylactic cooling, and avoidance of potent inhalation anaesthetics and depolarising neuromuscular blockers. Another case[2] was associated with the use of pancuronium.

1. Britt BA, *et al.* Malignant hyperthermia induced by curare. *Can Anaesth Soc J* 1974; **21:** 371–5.
2. Waterman PM, *et al.* Malignant hyperthermia: a case report. *Anesth Analg* 1980; **59:** 220–1.

Effects on the muscles. For reference to acute myopathy and prolonged muscle weakness after withdrawal of long-term continuous infusions of competitive neuromuscular blockers, see Intensive Care, p. 2028.3.

Hypersensitivity. There have been reports of severe anaphylactoid reactions after use of atracurium[1,2] or cisatracurium.[3-5] For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Suxamethonium Chloride, p. 2038.2.

1. Stirton-Hopkins C. Life-threatening reaction to atracurium. *Br J Anaesth* 1988; **60:** 597–8.
2. Oh TE, Horton JM. Adverse reactions to atracurium. *Br J Anaesth* 1989; **62:** 467–8.
3. Briassoulis G, *et al.* Persistent anaphylactic reaction after induction with thiopentone and cisatracurium. *Paediatr Anaesth* 2000; **10:** 429–34.
4. Legros CB, *et al.* Severe anaphylactic reaction to cisatracurium in a child. *Anesth Analg* 2001; **92:** 648–9.
5. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005; **33:** 816–19.

Treatment of Adverse Effects

It is essential to maintain assisted respiration in patients who have received a competitive neuromuscular blocker until spontaneous breathing is fully restored; in addition a cholinesterase inhibitor such as neostigmine is usually given intravenously, with atropine or glycopyrronium, to hasten reversal of the neuromuscular block. Patients need to be closely monitored after reversal of block to ensure that muscle relaxation does not return.

Severe hypotension may require intravenous fluid replacement and cautious use of a pressor agent; the patient should be positioned to facilitate venous return from the muscles.

Giving an antihistamine before induction of neuromuscular blockade may help to prevent histamine-induced adverse effects in patients with asthma or those susceptible to bronchospasm.

Reversal of neuromuscular blockade. For a discussion of the use of anticholinesterases for reversal of residual neuromuscular block produced by intermediate- or short-acting blockers after surgical or similar procedures, see under Neostigmine, p. 688.1.

Precautions

Patients who have received a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Atracurium and other competitive neuromuscular blockers should be used with great care, if at all, in respiratory insufficiency or pulmonary disease and in the dehydrated or severely ill patient. The response to neuromuscular blockers is often unpredictable in patients with neuromuscular disorders and they should be used with great care in these patients (see below). Caution is also needed in patients with a history of conditions such as asthma where release of histamine would be a hazard. Care is also required in patients with a history of hypersensitivity to any neuromuscular blocker because high rates of cross-sensitivity have been reported. For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Adverse Effects of Suxamethonium Chloride, p. 2038.2.

Resistance to the effects of competitive neuromuscular blockers may occur in patients with burns (see below). The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment: resistance appears to occur to some, such as doxacurium, metocurine, pancuronium, and tubocurarine, while dosage of others, including mivacurium and rocuronium, may need to be reduced because of a prolonged action.

Competitive neuromuscular blockers excreted mainly in the urine should be used with caution in renal impairment; a reduction in dosage may be necessary. Doses may need to be reduced in infants and neonates because of increased sensitivity to competitive muscle relaxants. Doses in obese patients should usually be based upon the patient's ideal body-weight rather than actual body-weight.

The effects of competitive neuromuscular blockers are increased by metabolic or respiratory acidosis and hypokalaemia, hypermagnesaemia, hypocalcaemia, and hypophosphataemia and dehydration. Competitive neuromuscular blockade may also be enhanced by raised body temperature and reduced in hypothermia.

In contrast to other competitive neuromuscular blockers, reduction in body temperature may necessitate a dosage reduction for *atracurium and its isomer cisatracurium* since cooling reduces the rate of inactivation of atracurium and cisatracurium, but physiological variations in body temperature and pH will not significantly affect their action.

Burns. The dose requirements of competitive neuromuscular blockers are increased in patients with burns,[1-3] the dose correlating with both the extent of the burn and time after injury. This resistance is usually not seen in patients with less than 10% body-surface burns but if more than 40% of the body-surface is affected the dose of competitive blocker may need to be up to five times higher than in patients without burns. Resistance peaks about 2 weeks after injury, persists for many months in patients with major burns, and decreases gradually with healing of the burn. The mechanism of resistance is multifactorial but may be partly explained by increased protein binding, increased volume of distribution, and increased numbers of acetylcholine receptors at the motor end-plate requiring more muscle relaxant to produce a given effect. Despite the high doses of competitive relaxants that are required, recovery from neuromuscular blockade is not seriously impaired and their effects can be reversed with usual doses of an anticholinesterase.

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; **26:** 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; **ii:** 1003–4.
3. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; **16:** 409–18.

Cardiopulmonary bypass. The effect of cardiopulmonary bypass on the pharmacokinetics and pharmacodynamics of competitive neuromuscular blockers can be complex but generally their dosage may need to be reduced. Although the intensity of neuromuscular blockade of most competitive neuromuscular blockers is reduced by hypothermia[1] used during cardiopulmonary bypass, their use during this procedure is associated with rises in plasma concentrations, reduced clearance, and prolongation of the elimination half-life.[2-6] Various mechanisms, including reduced distribution to highly perfused tissues such as the lungs, have been proposed to explain this effect.[2] For atracurium, it appears that it is a reduction in the temperature-dependent inactivation by Hofmann elimination during hypothermia that enables lower doses to be used.[7]

1. Buzello W, *et al.* Unequal effects of cardiopulmonary bypass-induced hypothermia on neuromuscular blockade from constant infusion of alcuronium, d-tubocurarine, pancuronium, and vecuronium. *Anesthesiology* 1987; **66:** 842–6.
2. Walker JS, *et al.* Alcuronium kinetics in patients undergoing cardiopulmonary bypass surgery. *Br J Clin Pharmacol* 1983; **15:** 237–44.
3. Walker JS, *et al.* Altered d-tubocurarine disposition during cardiopulmonary bypass surgery. *Clin Pharmacol Ther* 1984; **35:** 686–94.
4. Wierda JMKH, Agoston S. Pharmacokinetics of vecuronium during hypothermic bypass. *Br J Anaesth* 1989; **63:** 627P–628P.
5. Smeulers NJ, *et al.* Hypothermic cardiopulmonary bypass influences the concentration-response relationship and the biodisposition of rocuronium. *Eur J Anaesthesiol* 1995; **12** (suppl 11): 91–4.
6. Asokumar B, *et al.* Pharmacokinetics of doxacurium during normothermic and hypothermic cardiopulmonary bypass surgery. *Can J Anaesth* 1998; **45:** 515–20.
7. Flynn PJ, *et al.* Use of atracurium in cardiac surgery involving cardiopulmonary bypass with induced hypothermia. *Br J Anaesth* 1984; **56:** 967–72.

Hepatic impairment. The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment (see Precautions, above) but alterations in the pharmacokinetics of atracurium and cisatracurium in patients with hepatic impairment (see Biotransformation, under Pharmacokinetics, p. 2033.3) do not appear to be clinically significant and a reduction in dosage is not generally recommended.

Neuromuscular disorders. Caution is needed if competitive neuromuscular blockers are given to patients with neuromuscular disease since severe complications have been reported.[1] Increased response may be seen in patients with paraplegia or quadriplegia, but resistance has been reported in patients with hemiplegia. Increased response also may occur in patients with amyotrophic lateral sclerosis, neurofibromatosis, and poliomyelitis; this is of little concern unless the respiratory muscles are involved when prolonged apnoea may occur. Patients with myasthenia gravis usually show increased sensitivity to competitive neuromuscular blockers although small doses have been given without complications. During remission of myasthenia gravis a normal response is usual but since remission is often incomplete, small intermittent doses are advised. A significantly greater exaggeration of response is seen in patients with the myasthenic syndrome. Both normal and increased responses have been reported in patients with myotonias or muscular dystrophies but exquisite sensitivity occurs in patients with ocular muscular dystrophy. A normal response to competitive relaxants may be expected in patients with multiple sclerosis, muscular denervation, Parkinson's disease, and tetanus.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61:** 173–87.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atracurium as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Cisatracurium is classed as not porphyrinogenic and may also be used as a drug of first choice with no precautions needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. A review[1] of the pharmacokinetics of neuromuscular blockers in pregnancy concluded that atracurium and mivacurium are the best choice in pregnancy since their actions are predictable; their duration of action is either unchanged or only slightly prolonged. Atracurium also has a low umbilical to maternal vein concentration (uv/mv) ratio. In general, it is advisable[1] to choose a neuromuscular blocker with a low uv/mv ratio and a short duration of action, and to inject the lowest dose required to produce adequate surgical conditions.

Atracurium 300 micrograms/kg given to 26 women undergoing caesarean section, with subsequent incremental doses of 100 or 200 micrograms/kg if necessary, produced good surgical relaxation in all patients without any complications.[2] Of the 26 neonates delivered, respiration was established within 90 seconds in 21, with an Apgar score of 10 at 5 minutes. The remaining 5 neonates were delivered by caesarean section because of fetal distress and were slower to start breathing.

A study[3] of 22 women in the immediate postpartum period found the onset and duration of cisatracurium to be significantly shorter when compared with nonpregnant patients.

1. Guay J, *et al.* Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. *Clin Pharmacokinet* 1998; **34:** 483–96.
2. Frank M, *et al.* Atracurium in obstetric anaesthesia: a preliminary report. *Br J Anaesth* 1983; **55:** 113S-114S.
3. Pan PH, Moore C. Comparison of cisatracurium-induced neuromuscular blockade between immediate postpartum and nonpregnant patients. *J Clin Anesth* 2001; **13:** 112–17.

Renal impairment. Although some differences in the pharmacokinetics of atracurium and cisatracurium have been reported in patients with renal impairment (see Biotransformation, under Pharmacokinetics, p. 2033.3), duration of their neuromuscular blocking action is not significantly dependent on renal function and usual doses may be given to such patients.[1,2] Atracurium has been given by infusion to patients with end-stage renal failure[3] when the initial dose required for induction of neuromuscular block was 37% higher than that required by patients without renal impairment. The increase could be explained by the larger extracellular fluid volume in patients with chronic renal failure.

Although the pharmacokinetics of atracurium and cisatracurium are not appreciably different in renal impairment, those of their metabolites may be (see Biotransformation, under Pharmacokinetics, p. 2033.3) and therefore it has been suggested that neuromuscular function should be monitored during use of atracurium.[4]

1. Hunter JM, *et al.* Use of the muscle relaxant atracurium in anephric patients: preliminary communication. *J R Soc Med* 1982; **75:** 336–340.
2. Boyd AH, *et al.* Pharmacodynamics of the 1R cis-1′R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; **74:** 400–404.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.
4. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; **19:** 230–40.

Resistance. The aetiology of resistance to competitive blockers is not clear but might be due to pharmacodynamic or pharmacokinetic alterations associated with disease states such as burn injuries (see above) or hepatic impairment (see above) or therapy with other drugs (see Interactions, below). One review[1] noted that there had been several case reports of resistance to competitive neuromuscular blockers; most had been associated with use of single doses or short-term intermittent therapy, but more recent reports had documented resistance during continuous infusions in 9 patients of whom 7 had received atracurium and 2 rocuronium. Resistance to atracurium had followed 2 different patterns. Patients had required either usual or raised doses for initial control but both groups had subsequently required progressive increases. Most patients with resistance to atracurium were successfully managed by transfer to pancuronium or doxacurium.

1. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; **16:** 409–18.

Tourniquets. Atracurium might be unsuitable for neuromuscular blockade of a limb that has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] Atracurium undergoes non-enzymatic degradation in plasma and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; **73:** 726.

Interactions

Some drugs may influence neuromuscular transmission and thus interfere with the action of both competitive and depolarising neuromuscular blockers, resulting in potentiation or antagonism of neuromuscular block. Some interactions may be advantageous, such as the reversal of competitive neuromuscular block by anticholinesterases. In general, adverse interactions are potentially more serious in patients with impaired neuromuscular function (see Neuromuscular Disorders, above, and under Suxamethonium Chloride, p. 2039.1).

Drug interactions affecting neuromuscular blockers of either type (competitive and depolarising) as well as those specific for competitive neuromuscular blockers are discussed below. For drug interactions specific to depolarising neuromuscular blockers see under Interactions of Suxamethonium Chloride, p. 2039.2.

Reviews.

1. Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. *Drug Safety* 1996; **15:** 261–73.
2. Cammu G. Interactions of neuromuscular blocking drugs. *Acta Anaesthesiol Belg* 2001; **52:** 357–63.

Antiarrhythmics. *Lidocaine, procainamide, quinidine,* and *verapamil* all have some neuromuscular blocking activity and may enhance the block produced by neuromuscular blockers. Large doses of lidocaine may reduce the release of acetylcholine and act directly on the muscle membrane. Quinidine has a curare-like action at the neuromuscular

junction and depresses the muscle action potential. If given during recovery from neuromuscular block it can result in muscle weakness and apnoea and it should be avoided, if possible, in the immediate postoperative period. For details regarding interactions with calcium-channel blockers, see below.

Antibacterials. Some antibacterials in very high concentration can produce a muscle paralysis that may be additive to or synergistic with that produced by neuromuscular blockers. The neuromuscular block produced by antibacterials may be enhanced in patients with intracellular potassium deficiency, low plasma-calcium concentration, neuromuscular disease, or a tendency to a high plasma-antibacterial concentration, for example after large doses or in renal impairment. The interaction appears to be more important for competitive neuromuscular blockers. The antibacterials most commonly implicated are aminoglycosides, lincosamides, polymyxins, and, more rarely, tetracyclines.

The *aminoglycosides* reduce release of, and sensitivity to, acetylcholine and their effect can be reversed, at least in part, by calcium, fampridine, or an anticholinesterase. The interaction can occur with aminoglycosides given by most routes. There are reports of potentiation of neuromuscular blockade occurring with many different aminoglycoside-neuromuscular blocker combinations[1-6] and all aminoglycosides should be used with extreme caution during surgery and in the postoperative period.

The *lincosamides* (*clindamycin* and *lincomycin*) can prolong the action of muscle relaxants producing a neuromuscular block that may be difficult to reverse with calcium or anticholinesterases.[7-9] Patients should be monitored for prolonged paralysis.

There have been reports of prolonged apnoea[1,4,8] after use of *polymyxins* (*colistin, polymyxin B*) with a neuromuscular blocker. The block is difficult to reverse; calcium may be partially successful, but neostigmine may increase the block.

Tetracyclines have weak neuromuscular blocking properties; potentiation of neuromuscular block has been reported in patients with myasthenia gravis.[1] Reversal of the block may be partly achieved with calcium, but the value of anticholinesterases is questionable.

The *ureidopenicillins* (*azlocillin* and *mezlocillin*), and the closely related *piperacillin*, are reported to prolong the block produced by vecuronium.[10,11]

Vancomycin has been reported to increase neuromuscular blockade by vecuronium.[12] Prolonged paralysis and apnoea has occurred in a patient recovering from suxamethonium-induced blockade after being given vancomycin.[13]

1. Pittinger CB, *et al.* Antibiotic-induced paralysis. *Anesth Analg Curr Res* 1970; **49:** 487–501.
2. Hall DR, *et al.* Gentamicin, tubocurarine, lignocaine and neuromuscular blockade. *Br J Anaesth* 1972; **44:** 1329–32.
3. Waterman PM, Smith RB. Tobramycin-curare interaction. *Anesth Analg Curr Res* 1977; **56:** 587–8.
4. Giala MM, Paradelis AG. Two cases of prolonged respiratory depression due to interaction of pancuronium with colistin and streptomycin. *J Antimicrob Chemother* 1979; **5:** 234–5.
5. Regan AG, Perumbetti PPV. Pancuronium and gentamicin interaction in patients with renal failure. *Anesth Analg* 1980; **59:** 393.
6. Jedeikin R, *et al.* Prolongation of neuromuscular blocking effect of vecuronium by antibiotics. *Anaesthesia* 1987; **42:** 858–60.
7. Booij LHD, *et al.* Neostigmine and 4-aminopyridine antagonism of lincomycin-pancuronium neuromuscular blockade in man. *Anesth Analg* 1978; **57:** 316–21.
8. de Gouw NE, *et al.* Interaction of antibiotics on pipecuronium-induced neuromuscular blockade. *J Clin Anesth* 1993; **5:** 212–15.
9. Sloan PA, Rasul M. Prolongation of rapacuronium neuromuscular blockade by clindamycin and magnesium. *Anesth Analg* 2002; **94:** 123–4.
10. Tryba M. Wirkungsverstäkung nicht-depolarisierender Muskelrelaxantien durch Acylaminopenicilline: Untersuchungen am Beispiel von Vecuronium. *Anaesthesist* 1985; **34:** 651–5.
11. Tryba M, Klemm D. Wechselwirkungen zwischen Acylaminopenicillinen und nicht depolarisierenden Muskelrelaxantien. *Fortschr Antimikrob Antineoplast Chemother* 1985; **4–7:** 1827–33.
12. Huang KC, *et al.* Vancomycin enhances the neuromuscular blockade of vecuronium. *Anesth Analg* 1990; **70:** 194–6.
13. Albrecht RF, Lanier WL. Potentiation of succinylcholine-induced phase II block by vancomycin. *Anesth Analg* 1993; **77:** 1300–2.

Anticholinesterases. Anticholinesterases, including *ecothiopate, edrophonium, galantamine, neostigmine, pyridostigmine, rivastigmine*, and possibly *donepezil*, antagonise the effect of competitive neuromuscular blockers. Some anticholinesterases such as neostigmine inhibit both acetylcholinesterase and plasma cholinesterase, and are used clinically to antagonise competitive neuromuscular blockade. Conversely, anticholinesterases enhance the action of depolarising muscle relaxants such as suxamethonium thus prolonging neuromuscular block, although suxamethonium-induced phase II block can be reversed with an anticholinesterase. See also Interactions in Suxamethonium Chloride, p. 2039.3.

Antiepileptics. Resistance to competitive neuromuscular blockers has been reported in patients receiving chronic treatment with *carbamazepine*[1,2] or *phenytoin*[3,4] and rapid recovery from neuromuscular block may occur. In addition, children on chronic antiepileptic drugs (carbamazepine and/or phenytoin) were found to recover quicker from rocuronium-induced paralysis than those not on antiepileptics.[5] In a study[6] with cisatracurium, faster recovery rates were also recorded in patients receiving acute or chronic treatment with unspecified antiepileptics. However, atracurium[1] and mivacurium[7] appear to be unaffected by chronic carbamazepine therapy and the effect of chronic phenytoin treatment on atracurium has usually been minimal.[3] Although one study[8] did report that epileptic patients receiving one or more antiepileptics had significantly shorter times to recovery from atracurium, the authors pointed out that the patient populations were different from those in the previous studies.[1,3]

A report of sensitivity to vecuronium[9] has suggested that acute dosage of phenytoin may increase rather than decrease the effect of competitive neuromuscular blockers.

1. Ebrahim Z, *et al.* Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg* 1988; **67:** S55.
2. Whalley DG, Ebrahim Z. Influence of carbamazepine on the dose-response relationship of vecuronium. *Br J Anaesth* 1994; **72:** 125–6.
3. Ornstein E, *et al.* The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; **67:** 191–6.
4. Hernández-Palazón J, *et al.* Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. *J Neurosurg Anesthesiol* 2001; **13:** 79–81.
5. Soriano SG, *et al.* Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. *Paediatr Anaesth* 2000; **10:** 133–6.
6. Koenig HM, Edwards TL. Cisatracurium-induced neuromuscular blockade in anticonvulsant treated neurosurgical patients. *J Neurosurg Anesthesiol* 2000; **12:** 314–18.
7. Spacek A, *et al.* Chronic carbamazepine therapy does not influence mivacurium-induced neuromuscular block. *Br J Anaesth* 1996; **77:** 500–502.
8. Tempelhoff R, *et al.* Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg* 1990; **71:** 665–9.
9. Baumgardner JE, Bagshaw R. Acute versus chronic phenytoin therapy and neuromuscular blockade. *Anaesthesia* 1990; **45:** 493–4.

Antineoplastics. It has been recommended that atracurium should be used with care in patients receiving anti-oestrogenic drugs,[1] after a case of prolonged neuromuscular blockade with atracurium in a patient receiving *tamoxifen*. See also under Interactions of Suxamethonium Chloride, p. 2039.3.

1. Naguib M, Gyasi HK. Antiestrogenic drugs and atracurium—a possible interaction? *Can Anaesth Soc J* 1986; **33:** 682–3.

Aprotinin. After reports of apnoea, caution has been advised when aprotinin is used with neuromuscular blockers.[1,2]

1. Chasapakis G, Dimas C. Possible interaction between muscle relaxants and the kallikrein-trypsin inactivator "Trasylol". *Br J Anaesth* 1966; **38:** 838–9.
2. Marcello B, Porati U. Trasylol e blocco neuromuscolare: nota preventiva. *Minerva Anestesiol* 1967; **33:** 814–15.

Benzodiazepines. There are conflicting reports of the effect of *diazepam* on neuromuscular blockers; potentiation,[1,2] or antagonism[1] of neuromuscular block, and a lack of interaction[3-5] have all been reported.

1. Feldman SA, Crawley BE. Interaction of diazepam with the muscle-relaxant drugs. *BMJ* 1970; **2:** 336–8.
2. Yuan H-B, *et al.* The interaction of diazepam with vecuronium: a clinical study. *Chin Med J* 1994; **54:** 259–64.
3. Bradshaw EG, Maddison S. Effect of diazepam at the neuromuscular junction. *Br J Anaesth* 1979; **51:** 955–60.
4. Asbury AJ, *et al.* Effect of diazepam on pancuronium-induced neuromuscular blockade maintained by a feedback system. *Br J Anaesth* 1981; **53:** 859–63.
5. Driessen JJ, *et al.* Benzodiazepines and neuromuscular blocking drugs in patients. *Acta Anaesthesiol Scand* 1986; **30:** 642–6.

Beta blockers. There is conflicting evidence for the effect of beta blockers on the activity of neuromuscular blockers. Lack of effect on depolarising neuromuscular block[1] and antagonism[2,3] or enhancement[4,5] of both competitive and depolarising block have been reported. The exact mechanism of interaction is not clear. There have also been reports of some neuromuscular blockers such as atracurium[6,7] and alcuronium[8] increasing the hypotension and bradycardia associated with the use of anaesthesia in patients receiving beta blockers; these include reports in patients using beta blockers in eye drops.

1. McCammon RL, *et al.* The effect of esmolol on the onset and duration of succinylcholine-induced neuromuscular blockade. *Anesthesiology* 1985; **63:** A317.
2. Varma YS, *et al.* Effect of propranolol hydrochloride on the neuromuscular blocking action of d-tubocurarine and succinylcholine in man. *Indian J Med Res* 1972; **60:** 266–72.
3. Varma YS, *et al.* Comparative effect of propranolol, oxprenolol and pindolol on neuromuscular blocking action of d-tubocurarine in man. *Indian J Med Res* 1973; **61:** 1382–6.
4. Rozen MS, Whan FM. Prolonged curarization associated with propranolol. *Med J Aust* 1972; **1:** 467–8.
5. Murthy VS, *et al.* Cardiovascular and neuromuscular effects of esmolol during induction of anesthesia. *J Clin Pharmacol* 1986; **26:** 351–7.
6. Glynne GL. Drug Interaction? *Anaesthesia* 1984; **39:** 293.
7. Rowlands DE. Drug Interaction? *Anaesthesia* 1984; **39:** 1252.
8. Yate B, Mostafa SM. Drug Interaction? *Anaesthesia* 1984; **39:** 728.

Botulinum A toxin. Theoretically, the neuromuscular block induced by botulinum toxins may be enhanced by competitive neuromuscular blockers.

Calcium-channel blockers. Calcium-channel blockers such as diltiazem, nicardipine, nifedipine, and verapamil enhance the effect of competitive neuromuscular blockers.[1-6] *Verapamil* may interfere with the release of acetylcholine and prolonged use may lead to a reduction in intracellular calcium concentration. Potentiation of neuromuscular blockade has been reported[1,2] and the block may be resistant to reversal with neostigmine; edrophonium may be required. The dose requirement for vecuronium was reduced by as much as 50% in surgical patients receiving *diltiazem*.[4,6] A similar effect was seen with *nicardipine*,[5] which reduced the requirement for vecuronium in a dose-dependent fashion. The interaction of vecuronium with diltiazem appeared to be due to a pharmacodynamic mechanism[4] but nicardipine also reduced the plasma clearance of vecuronium, indicating a partial pharmacokinetic mechanism as well.[5] *Nifedipine* also caused an increase in the intensity and duration of action of atracurium and vecuronium when given during anaesthesia.[3]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; **63:** 155–7.
2. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; **64:** 1021–5.
3. Jelen-Esselborn S, Blobner M. Wirkungsverstärkung von nichtdepolarisierenden Muskelrelaxanzien durch Nifedipin i.v. in Inhalationsanaesthesie. *Anaesthesist* 1990; **39:** 173–8.
4. Sumikawa K, *et al.* Reduction in vecuronium infusion dose requirements by diltiazem in humans. *Anesthesiology* 1992; **77:** A939.
5. Kawabata K, *et al.* Decrease in vecuronium infusion dose requirements by nicardipine in humans. *Anesth Analg* 1994; **79:** 1159–64.
6. Takasaki Y, *et al.* Diltiazem potentiates the neuromuscular blockade by vecuronium in humans. *Jpn J Anesthesiol* 1995; **44:** 503–7.

Cardiac inotropes. Pancuronium or suxamethonium may interact with *cardiac glycosides*[1] resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; **58:** 567–9.

Corticosteroids. Antagonism of the neuromuscular blocking effects of pancuronium[1] and vecuronium[2] has been reported in patients taking corticosteroids. This interaction may occur only with long-term corticosteroid treatment and may be expected with all competitive neuromuscular blockers.

For reference to a suggestion that use of corticosteroids might increase the risk of acute myopathy associated with prolonged use of neuromuscular blockers, see Intensive Care, p. 2028.3.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; **29:** 280–2.
2. Parr SM, *et al.* Betamethasone-induced resistance to vecuronium: a potential problem in neurosurgery? *Anaesth Intensive Care* 1991; **19:** 103–5.

Diuretics. *Furosemide*, and possibly *mannitol*, have been reported to enhance tubocurarine neuromuscular block in patients with renal failure,[1] but antagonism of tubocurarine by furosemide has also occurred.[2] Small doses of furosemide (less than 100 micrograms/kg) may inhibit protein kinase, which inhibits muscle contraction and potentiates neuromuscular blockade, whereas high doses inhibit phosphodiesterase, increasing cAMP activity and resulting in antagonism of neuromuscular blockade. The potassium-depleting effect of diuretics may enhance the effect of competitive neuromuscular blockers.

1. Miller RD, *et al.* Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. *Anesthesiology* 1976; **45:** 442–5.
2. Azar I, *et al.* Furosemide facilitates recovery of evoked twitch response after pancuronium. *Anesth Analg* 1980; **59:** 55–7.

Ganglion blockers. Prolonged neuromuscular blockade has been reported[1,2] in patients given neuromuscular blockers and *trimetaphan*. Trimetaphan may have direct neuromuscular blocking activity and some activity against plasma cholinesterase.

1. Wilson SL, *et al.* Prolonged neuromuscular blockade associated with trimethaphan: a case report. *Anesth Analg Curr Res* 1976; **55:** 353–6.
2. Poulton TH, *et al.* Prolonged apnea following trimethaphan and succinylcholine. *Anesthesiology* 1979; **50:** 54–6.

General anaesthetics. Neuromuscular blockers are potentiated in a dose-dependent manner by inhalation anaesthetics.[1-5] The dose of neuromuscular blocker may need to be reduced by up to 70%[1] depending on the anaesthetic used and its concentration, and on the choice of blocker; the interaction is of greater clinical importance with competitive blockers. *Isoflurane, enflurane, desflurane*, and *sevoflurane* produce the greater potentiation, followed by *halothane* and *cyclopropane*. Reversal of competitive block with an anticholinesterase has been reported to be reduced.[6,7] See also under Interactions of Suxamethonium Chloride, p. 2039.3.

Potentiation of the neuromuscular blocking effects of tubocurarine[8] and atracurium[9] has been reported after the intravenous use of *ketamine*. Results from studies *in vitro* suggest that ketamine decreases sensitivity to acetylcholine

and it would therefore be expected to potentiate all neuromuscular blockers, but no interaction was reported for pancuronium.[8] Early data[10] suggesting that ketamine potentiates suxamethonium-induced blockade have not been confirmed by later studies.[8,11]

For incompatibility between neuromuscular blockers and alkaline solutions such as thiopental sodium, see under Incompatibility, p. 2030.1.

1. Cannon JE, *et al.* Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; **67:** 503–6.
2. Swen J, *et al.* Interaction between nondepolarizing neuromuscular blocking agents and inhalation anesthetics. *Anesth Analg* 1989; **69:** 752–5.
3. Ghourin AF, White PF. Comparative effects of desflurane and isoflurane on vecuronium-induced neuromuscular blockade. *J Clin Anesth* 1992; **4:** 34–8.
4. Vanlinthout LEM, *et al.* Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium. *Br J Anaesth* 1996; **76:** 389–95.
5. Wulf H, *et al.* Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia. *Br J Anaesth* 1998; **80:** 308–12.
6. Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *Br J Anaesth* 1982; **54:** 441–5.
7. Gill SS, *et al.* Edrophonium antagonism of atracurium during enflurane anaesthesia. *Br J Anaesth* 1990; **64:** 300–5.
8. Johnston RR, *et al.* The interaction of ketamine with d-tubocurarine, pancuronium, and succinylcholine in man. *Anesth Analg Curr Res* 1974; **53:** 496–501.
9. Toft P, Helbo-Hansen S. Interaction of ketamine with atracurium. *Br J Anaesth* 1989; **62:** 319–20.
10. Bovill JG, *et al.* Current status of ketamine anaesthesia. *Lancet* 1971; **i:** 1285–8.
11. Helbo-Hansen HS, *et al.* Ketamine does not affect suxamethonium-induced neuromuscular blockade in man. *Eur J Anaesthesiol* 1989; **6:** 419–23.

Histamine H_2-antagonists. There are conflicting reports of the effects of histamine H_2-antagonists on neuromuscular blockade. *Cimetidine* has been variously reported to prolong suxamethonium-induced paralysis[1] or to have no effect.[2] *Famotidine* and *ranitidine* have been reported[2] not to interact with suxamethonium. Cimetidine, but not ranitidine, has been reported[3] to delay recovery from vecuronium-induced neuromuscular block. Neither drug appeared to affect recovery after the use of atracurium.

1. Kambam JR, *et al.* Effect of cimetidine on duration of action of succinylcholine. *Anesth Analg* 1987; **66:** 191–2.
2. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; **63:** 348–50.
3. McCarthy G, *et al.* Effect of H2-receptor antagonist pretreatment on vecuronium- and atracurium-induced neuromuscular blockade. *Br J Anaesth* 1991; **66:** 713–15.

Immunosuppressants. Antagonism of the neuromuscular blocking effects of competitive neuromuscular blockers has been reported with *azathioprine*,[1] although the effect may not be clinically important. Azathioprine probably inhibits phosphodiesterase activity at the motor nerve terminal resulting in increased release of acetylcholine. There have been reports of prolonged neuromuscular blockade with atracurium, pancuronium, and vecuronium in some patients receiving *ciclosporin* intravenously.[2,3] This effect has been attributed to an interaction with polyoxyl castor oil used as the solvent for intravenous ciclosporin but a similar reaction has been reported in a patient receiving ciclosporin orally.[4]

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interaction with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.
2. Crosby E, Robblee JA. Cyclosporine-pancuronium interaction in a patient with a renal allograft. *Can J Anaesth* 1988; **35:** 300–302.
3. Sidi A, *et al.* Prolonged neuromuscular blockade and ventilatory failure after renal transplantation and cyclosporine. *Can J Anaesth* 1990; **37:** 543–8.
4. Ganjoo P, Tewari P. Oral cyclosporine-vecuronium interaction. *Can J Anaesth* 1994; **41:** 1017.

Lithium. There have been isolated reports of prolonged neuromuscular blockade after the use of neuromuscular blockers in patients receiving lithium.[1,2]

1. Borden H, *et al.* The use of pancuronium bromide in patients receiving lithium carbonate. *Can Anaesth Soc J* 1974; **21:** 79–82.
2. Hill GE, *et al.* Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. *Anesthesiology* 1976; **44:** 439–42.

Local anaesthetics. Healthy subjects who had undergone regional anaesthesia of the forearm had symptoms suggestive of local anaesthetic toxicity on deflation of the tourniquet cuff when mivacurium and *prilocaine* had been used together for anaesthesia;[1] giving prilocaine or mivacurium alone did not produce such an effect. The suggestion that mivacurium may alter vascular permeability, allowing a more rapid diffusion of prilocaine back into the blood from the tissues, should be investigated.[2]

The interaction between neuromuscular blockers and *lidocaine* is discussed in Antiarrhythmics p. 2031.3.

1. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; **78:** 222–3.
2. Torrance JM, *et al.* Interactions between mivacurium and prilocaine. *Br J Anaesth* 1997; **78:** 262.

Magnesium salts. Parenteral magnesium salts may potentiate the effects of competitive and depolarising neuromuscular blockers;[1] the neuromuscular block is deepened and prolonged and a reduction in the dose of the blocker may be needed. Magnesium salts should be used with caution in the postoperative period, as use shortly after recovery from neuromuscular block can lead to recurarisation.[2] Magnesium salts reduce release of and sensitivity to acetylcholine, thus contributing to neuromuscular blockade.

1. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. *Anesthesiology* 1970; **32:** 23–7.
2. Fuchs-Buder T, Tassonyi E. Magnesium sulphate enhances residual neuromuscular block induced by vecuronium. *Br J Anaesth* 1996; **76:** 565–6.

MAOIs. There appears to be a theoretical hazard with pancuronium in patients receiving MAOIs since it releases stored adrenaline;[1] alcuronium, atracurium, or vecuronium would appear to be suitable alternatives.

1. Stack CG, *et al.* Monoamine oxidase inhibitors and anaesthesia: a review. *Br J Anaesth* 1988; **60:** 222–7.

Neuromuscular blockers. A competitive neuromuscular blocker given shortly before a depolarising blocker such as suxamethonium antagonises the depolarising neuromuscular block. This interaction has been used clinically to reduce muscle fasciculations caused by suxamethonium (see Effects on the Muscles, p. 2038.1) and tried for other adverse effects associated with suxamethonium (see Effects on Plasma-potassium Concentration, p. 2038.2). To achieve this antagonism a small non-paralysing dose of a competitive blocker is given before suxamethonium. If a paralysing dose of a competitive blocker is followed some time later with a dose of suxamethonium, for example to facilitate abdominal closure, the resulting neuromuscular block is influenced by the competitive blocker used, the depth of residual block, the dose of suxamethonium, and whether an anticholinesterase is given; antagonism, enhancement, and a combination of the two have been seen.[1,2]

A competitive blocker is often given after the short-acting suxamethonium to maintain neuromuscular blockade during long procedures. The action of the competitive blocker has been reported to be considerably potentiated and prolonged in these circumstances,[3,4] and reduction in the dose of the competitive blocker may be appropriate.

Combination of competitive blockers may have additive or synergistic effects and the interaction may differ depending on which blocker is given first. Caution is needed if a small dose of a shorter-acting blocker is given near the end of an operation in which a long-acting blocker has been given previously, since the resulting block may be greater than expected and much longer than desired.[5-8]

1. Scott RPF, Norman J. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1988; **61:** 292–6.
2. Black AMS. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1989; **62:** 348–9.
3. d'Hollander AA, *et al.* Clinical and pharmacological actions of a bolus injection of suxamethonium: two phenomena of distinct duration. *Br J Anaesth* 1983; **55:** 131–4.
4. Ono K, *et al.* Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium. *Br J Anaesth* 1989; **62:** 324–6.
5. Rashkovsky OM, *et al.* Interaction between pancuronium bromide and vecuronium bromide. *Br J Anaesth* 1985; **57:** 1063–6.
6. Middleton CM, *et al.* Use of atracurium or vecuronium to prolong the action of tubocurarine. *Br J Anaesth* 1989; **62:** 659–63.
7. Kim KS, *et al.* Interactions between mivacurium and pancuronium. *Br J Anaesth* 1997; **79:** 19–23.
8. Motamed C, *et al.* Interaction between mivacurium and pancuronium: impact of the order of administration. *Eur J Clin Pharmacol* 2005; **61:** 175–7.

Sex hormones. Resistance to the neuromuscular blocking effects of suxamethonium and vecuronium in a patient was attributed to previous long-term therapy with *testosterone*,[1] although the exact mechanism could not be explained. See also under Interactions of Suxamethonium Chloride, p. 2040.1.

1. Reddy P, *et al.* Resistance to muscle relaxants in a patient receiving prolonged testosterone therapy. *Anesthesiology* 1989; **70:** 871–3.

Smoking. Smoking may affect the dose requirements for neuromuscular blockers. One study[1] found that smokers needed more vecuronium than non-smokers; it was considered that the effect might be explained at the receptor level, although increased metabolism of vecuronium could not be excluded. In contrast, an earlier study[2] found the amount of atracurium required was reduced in smokers.

1. Teiriä H, *et al.* Effect of smoking on dose requirements for vecuronium. *Br J Anaesth* 1996; **76:** 154–5.
2. Kroeker KA, *et al.* Neuromuscular blockade in the setting of chronic nicotine exposure. *Anesthesiology* 1994; **81:** A1120.

Sympathomimetics. Intravenous *salbutamol* has been reported to enhance the blockade obtained with pancuronium and vecuronium.[1] See also under Interactions of Suxamethonium Chloride, p. 2040.1.

1. Salib Y, Donati F. Potentiation of pancuronium and vecuronium neuromuscular blockade by intravenous salbutamol. *Can J Anaesth* 1993; **40:** 50–3.

Xanthines. Resistance to neuromuscular block with pancuronium, requiring an increase in dosage or transfer to vecuronium, has been reported in patients receiving *aminophylline* with[1] or without[2] corticosteroid therapy. It was suggested that this effect might be due to inhibition of phosphodiesterase by aminophylline resulting in increased release of acetylcholine at the nerve terminal.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; **29:** 280–2.
2. Daller JA, *et al.* Aminophylline antagonizes the neuromuscular blockade of pancuronium but not vecuronium. *Crit Care Med* 1991; **19:** 983–5.

Pharmacokinetics

On intravenous injection both atracurium besilate and cisatracurium besilate undergo spontaneous degradation via Hofmann elimination (a non-enzymatic breakdown process occurring at physiological pH and temperature) to produce laudanosine and other metabolites. There is also ester hydrolysis by non-specific plasma esterases. The metabolites have no neuromuscular blocking activity.

About 80% of atracurium besilate is bound to plasma proteins. Atracurium besilate and its metabolites cross the placenta in clinically insignificant amounts. Excretion of atracurium and cisatracurium is in urine and bile, mostly as metabolites. The elimination half-life has been reported to be about 20 minutes for atracurium and 22 to 29 minutes for cisatracurium but laudanosine has an elimination half-life of about 3 to 6 hours.

Reviews.

1. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. *Clin Pharmacokinet* 1999; **36:** 27–40.
2. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.
3. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; **54:** 526–34.

Biotransformation. Atracurium and cisatracurium are degraded by Hofmann elimination and metabolised by non-specific plasma esterases. Hofmann elimination is generally believed to be the main route of degradation but *in-vitro* work suggests ester hydrolysis is more important.[1] Both routes are independent of renal and hepatic function and no dosage reduction is recommended for elderly patients or those with impaired renal or hepatic function. However, the elimination half-life of atracurium has been found to be slightly longer in elderly patients[2] and in those with hepatic cirrhosis[3] compared with young and healthy patients, although others[4] have found no change in the pharmacokinetics of atracurium in the elderly. Renal and hepatic involvement in the metabolism of atracurium[2] may help to explain any tendency to reduced elimination but this does not appear to be clinically significant. Although clearance of cisatracurium has been reported to be reduced in patients with renal failure[5] this appears to have little significant effect on its pharmacodynamics.[6] Differences in the pharmacokinetics of cisatracurium in patients with hepatic impairment have been reported to be minor.[7]

The major biotransformation product of atracurium and cisatracurium is *laudanosine*; it has no clinical neuromuscular blocking activity but has been associated with CNS stimulation in *animal* studies. It is more lipid soluble than atracurium and cisatracurium and has a half-life of around 3 hours compared with one of about 20 minutes for atracurium. Higher plasma-laudanosine concentrations have been reported in patients with renal failure[5,8,9] than in patients with normal renal function. The elimination half-life of laudanosine was found to be significantly greater in patients with hepatic cirrhosis[3] and in elderly patients[2] compared with healthy and young patients respectively. High plasma-laudanosine concentrations were also seen in 10 critically ill patients with acute respiratory distress syndrome;[10] no adverse effects were noted.

Laudanosine crosses the blood-brain barrier in man. The concentration of laudanosine in the CSF increases during an infusion of atracurium and the CSF-to-plasma ratio gradually increases. A ratio of 0.14 was found at 125 to 140 minutes[11] during an infusion of atracurium at a mean rate of 510 micrograms/kg per hour. No evidence of CNS stimulation has been reported in man although patients given atracurium[12] had a 20% higher mean arterial-thiopental concentration at awakening compared with patients given vecuronium, suggesting that laudanosine may have had a minor stimulatory effect on the CNS. The blood-brain barrier appears to be effective in preventing a very high concentration of laudanosine from reaching the CNS and it is considered unlikely[13] that concentrations great enough to provoke seizures will be reached. Cisatracurium

may be associated with the production of less laudanosine than atracurium.[14]

1. Stiller RL, *et al.* In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1985; **57:** 1085–8.
2. Kent AP, *et al.* Pharmacokinetics of atracurium and laudanosine in the elderly. *Br J Anaesth* 1989; **63:** 661–6.
3. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *Br J Anaesth* 1989; **62:** 177–83.
4. d'Hollander AA, *et al.* Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology* 1983; **59:** 237–40.
5. Eastwood NB, *et al.* Pharmacokinetics of 1R-cis 1'R-cis atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. *Br J Anaesth* 1995; **75:** 431–5.
6. Boyd AH, *et al.* Pharmacodynamics of the 1R cis-1'R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; **74:** 400–404.
7. De Wolf AM, *et al.* Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. *Br J Anaesth* 1996; **76:** 624–8.
8. Fahey MR, *et al.* Effect of renal failure on laudanosine excretion in man. *Br J Anaesth* 1985; **57:** 1049–51.
9. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; **19:** 230–40.
10. Farenc C, *et al.* Pharmacokinetic-pharmacodynamic modeling of atracurium in intensive care patients. *J Clin Pharmacol* 2001; **41:** 44–50.
11. Eddleston JM, *et al.* Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma during intracranial surgery. *Br J Anaesth* 1989; **63:** 525–30.
12. Beemer GH, *et al.* Production of laudanosine following infusion of atracurium in man and its effects on awakening. *Br J Anaesth* 1989; **63:** 76–80.
13. Yate PM, *et al.* Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *Br J Anaesth* 1987; **59:** 211–17.
14. Boyd AH, *et al.* Comparison of the pharmacokinetics and pharmacodynamics of an infusion of cis-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit. *Br J Anaesth* 1996; **76:** 382–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gelolagar; Nimbium; Tracrium; Tracurix; Tracuron; ***Austral.***: Nimbex; Tracrium; ***Austria***: Nimbex; Tracrium; ***Belg.***: Nimbex; Tracrium; ***Braz.***: Abbottracurium; Besitrac; Nimbium; Tracrium; Tracur; ***Canad.***: Nimbex; ***Chile***: Nimbex; Tracrium; ***China***: Nimbex (赛机宁); Tracrium (卡肌宁); ***Cz.***: Nimbex; Tracrium; ***Denm.***: Nimbex; ***Fin.***: Nimbex; ***Fr.***: Nimbex; Tracrium; ***Ger.***: Nimbex; Tracrium†; ***Gr.***: Nimbex; Tracrium; ***Hong Kong***: Nimbex; Tracrium; ***Hung.***: Nimbex; Tracrium; ***India***: Acris; Artacil; Atcurium; Atcuron; Atracade; Atrakt; Atrelax; Tracrium; ***Indon.***: Farelax; Notrixum; Tracrium; Tramus; ***Irl.***: Nimbex; Tracrium; ***Israel***: Mycurium; Tracrium; ***Ital.***: Acurmil; Nimbex; Tracrium; ***Malaysia***: Atralex; Nimbex†; Tracrium; ***Mex.***: Nimbex; Relatrac†; Trablok†; Tracrium; ***Neth.***: Nimbex; Tracrium; ***Norw.***: Nimbex; ***NZ***: Tracrium; ***Philipp.***: Atracor; Trac; Tracrium; ***Pol.***: Abbocurium†; Nimbex; Tracrium; ***Port.***: Faulcurium; Nimbex; Tracrium; ***Rus.***: Nimbex (Нимбекс); Tracrium (Тракриум); ***S.Afr.***: Nimbex; Tracrium; ***Singapore***: Tracrium; ***Spain***: Nimbex; Tracrium; ***Swed.***: Nimbex†; Tracrium†; ***Switz.***: Nimbex; Tracrium; ***Thai.***: Atra; Nimbex; Notrixum; Tracrium; ***Turk.***: Dematrac; Nimbex; Tracrium; ***UK***: Nimbex; Tracrium; ***Ukr.***: Intuban (Интубан); Tracrium (Тракриум); ***USA***: Nimbex; Tracrium†.

Pharmacopoeial Preparations
USP 36: Atracurium Besylate Injection.

Gallamine Triethiodide *(BANM, rINN)*

Benzcurine Iodide; Galamin Trietiyodür; Galamina, trietioduro de; Galamino trietjodidas; Gallamiinitrietjodidi; Gallamine, Triéthiodure de; Gallamini triethiodidum; Gallamin-triethiodid; Gallamin-triethojodid; Gallamin-trietjodid; Gallamintrietjodid; Gallamone Triethiodide; Trietioduro de galamina; Галламина Триэтйодид.

2,2′,2″-(Benzene-1,2,3-triyltrioxy)tris(tetraethylammonium) tri-iodide.

$C_{30}H_{60}I_3N_3O_3$=891.5

CAS — 153-76-4 (gallamine); 65-29-2 (gallamine triethiodide).

ATC — M03AC02.

ATC Vet — QM03AC02.

UNII — Q3254X40X2.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Gallamine Triethiodide). A white, hygroscopic, odourless, amorphous powder. Very soluble in water; sparingly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 5.3 and 7.0. Store in airtight containers. Protect from light.

Profile

Gallamine triethiodide is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1). It has been used to provide muscle relaxation in general anaesthesia for surgical procedures and to aid controlled ventilation. Gallamine has some vagolytic action and may produce tachycardia; blood pressure may also be raised. It has a small effect on histamine release and occasionally anaphylactoid reactions have been reported.

Gallamine triethiodide has also been given intramuscularly, with or without hyaluronidase.

Renal impairment. Significantly prolonged elimination half-life and reduced clearance have been reported[1] in patients with chronic renal failure given gallamine triethiodide in initial doses of 2 mg/kg intravenously.

1. Ramzan MI, *et al.* Gallamine disposition in surgical patients with chronic renal failure. *Br J Clin Pharmacol* 1981; **12:** 141–7.

Preparations

Pharmacopoeial Preparations
BP 2014: Gallamine Injection;
USP 36: Gallamine Triethiodide Injection.

Mivacurium Chloride *(BAN, USAN, rINN)*

BW-B1090U; Cloruro de mivacurio; Mivacurii Chloridum; Mivacurio, cloruro de; Mivacurium, Chlorure de; Mivakuriumklorid; Mivakuriumkloridi; Mivakuryum Klorür; Мивакурия Хлорид.

A mixture of the stereoisomers of (*E*)-1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′-tetramethoxy-2,2′-dimethyl-1,1′-bis(3,4,5-trimethoxybenzyl)-2,2′-[oct-4-enedioylbis(oxytrimethylene)]di-isoquinolinium dichloride.

$C_{58}H_{80}Cl_2N_2O_{14}$=1100.2

CAS — 106861-44-3 (mivacurium chloride, total racemate).

ATC — M03AC10.

ATC Vet — QM03AC10.

UNII — 600ZG213C3.

Incompatibility. See under Atracurium, p. 2030.1 for details regarding the incompatibility of neuromuscular blockers.

Uses and Administration

Mivacurium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1).

On intravenous injection muscle relaxation occurs within 1.5 to 2.5 minutes, depending on the dose with a duration of action of about 10 to 20 minutes. It is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. Mivacurium is given as the chloride although doses are expressed in terms of mivacurium base. The initial dose by intravenous injection in adults and children over 12 years of age is 70 to 250 micrograms/kg. Doses up to 150 micrograms/kg may be given over 5 to 15 seconds but higher doses should be given over 30 seconds. In patients with asthma or cardiovascular disease, or those who are sensitive to falls in arterial blood pressure, it should be given over 60 seconds. To give a dose of 250 micrograms/kg for tracheal intubation, an injection of 150 micrograms/kg may be followed 30 seconds later by an injection of 100 micrograms/kg. Maintenance doses of 100 micrograms/kg may be given at intervals of 15 minutes. In children aged 2 to 6 months an initial dose of 150 micrograms/kg has been given; in children aged 7 months to 12 years, an initial dose of 200 micrograms/kg has been given. A maintenance dose of 100 micrograms/kg may be given every 6 to 9 minutes for children aged 2 months to 12 years.

Mivacurium chloride may also be given by continuous intravenous infusion for maintenance of block. For adults and children aged over 12 years the initial rate is 8 to 10 micrograms/kg per minute adjusted every 3 minutes if necessary by increments of 1 microgram/kg per minute to a usual rate of 6 to 7 micrograms/kg per minute; in children aged 2 months to 12 years the usual rate is 11 to 14 micrograms/kg per minute.

Reduced doses may be required in the elderly and in patients with hepatic or renal impairment (see below).

Reviews.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44:** 182–99.
2. Frampton JE, McTavish D. Mivacurium: a review of its pharmacology and therapeutic potential in general anaesthesia. *Drugs* 1993; **45:** 1066–89.
3. Feldman S. Mivacurium. *Br J Hosp Med* 1997; **57:** 199–201.

Action. Mivacurium has a shorter duration of action than most other competitive neuromuscular blockers. Studies[1-3] suggest that it is a useful alternative to suxamethonium for the production of neuromuscular block of short duration and has the advantage that its block can be reversed with an anticholinesterase. For a discussion of the choice of anticholinesterase for reversal of neuromuscular block produced by short-acting blockers such as mivacurium, see under Neostigmine, p. 688.1. Although its onset of action may be accelerated by giving a priming dose,[4] mivacurium has a slower onset than suxamethonium and so may not be a suitable alternative[5] when rapid intubation is required. For a general review of neuromuscular blockers, see Anaesthesia, p. 2028.1.

1. Brandom BW, *et al.* Comparison of mivacurium and suxamethonium administered by bolus and infusion. *Br J Anaesth* 1989; **62:** 488–93.
2. Caldwell JE, *et al.* Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth* 1989; **63:** 393–9.
3. Goldberg ME, *et al.* Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. *Anesth Analg* 1989; **69:** 93–9.
4. Haxby EJ, *et al.* Mivacurium priming intervals. *Br J Anaesth* 1994; **72:** 485P.
5. Anonymous. Mivacurium—a new neuromuscular blocker. *Med Lett Drugs Ther* 1992; **34:** 82.

Administration in children. For details of uses and dosage of mivacurium chloride in infants and children, see Uses and Administration, above.

Administration in the elderly. In a study[1] comparing the effects of mivacurium in elderly and young adults, the duration of neuromuscular effects was prolonged in elderly patients by about 30%. The mean infusion requirement in elderly patients was 3.67 micrograms/kg per minute compared with 5.5 micrograms/kg per minute in young adults.

Licensed product information states that elderly patients may require decreased infusion rates or smaller or less frequent maintenance bolus doses.

1. Maddineni VR, *et al.* Neuromuscular and haemodynamic effects of mivacurium in elderly and young adult patients. *Br J Anaesth* 1994; **73:** 608–12.

Administration in hepatic or renal impairment. The pharmacokinetics of mivacurium have been studied in patients with renal[1-3] or hepatic impairment.[1,4,5] The duration of relaxation produced by mivacurium was about 1.5 times greater than normal in patients with end-stage renal disease and up to about 3 times greater than normal in patients with end-stage liver disease. Reduced plasma-cholinesterase activity in the patients with hepatic impairment may have played an important part in this effect. Although an anticholinesterase such as neostigmine hastens recovery by only a few minutes in healthy subjects, its use may be indicated in patients in whom recovery is delayed.[2]

Licensed product information recommends that in patients with end-stage renal or liver disease, the dose should be adjusted according to individual clinical response.

1. Cook DR, *et al.* Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. *Br J Anaesth* 1992; **69:** 580–5.
2. Phillips BJ, Hunter JM. Use of mivacurium chloride by constant infusion in the anephric patient. *Br J Anaesth* 1992: **68:** 492–8.
3. Head-Rapson AG, *et al.* Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. *Br J Anaesth* 1995; **75:** 31–6.
4. Devlin JC, *et al.* Pharmacodynamics of mivacurium chloride in patients with hepatic cirrhosis. *Br J Anaesth* 1993; **71:** 227–31.
5. Head-Rapson AG, *et al.* Pharmacokinetics of the three isomers of mivacurium and pharmacodynamics of the chiral mixture in hepatic cirrhosis. *Br J Anaesth* 1994; **73:** 613–18.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3). Mivacurium chloride has no significant vagal or ganglion blocking activity at recommended doses. It may induce histamine release especially when given in large doses rapidly.

Mivacurium should be used with caution, if at all, in patients with plasma cholinesterase deficiency, since its duration of action will be prolonged in such patients.

Burns. In common with other competitive muscle relaxants patients with burns may develop resistance to mivacurium and require increased doses (see under Atracurium, p. 2031.1). However, as these patients may also have reduced plasma cholinesterase activity dosage requirements could also be reduced. Licensed product information recommends that such patients should be given a test dose of 15 to 20 micrograms/kg with subsequent dosage adjustments being guided by monitoring of the block.

Neuromuscular disorders. Neuromuscular blockade was successfully achieved with mivacurium in an obese elderly patient with myasthenia gravis requiring surgery.[1] Only about half the usual dose was required and even then recovery was delayed. See Atracurium, p. 2031.2 for a dis-

cussion of the use of competitive neuromuscular blockers in patients with neuromuscular disorders.

1. Seigne RD, Scott RPF. Mivacurium chloride and myasthenia gravis. *Br J Anaesth* 1994; **72:** 468–9.

Plasma cholinesterase deficiency. There have been reports of prolonged neuromuscular block produced by mivacurium in patients with plasma cholinesterase deficiency.[1-4] Time to full recovery varied; one patient required up to 8 hours.

1. Goudsouzian NG, *et al.* Prolonged neuromuscular block from mivacurium in two patients with cholinesterase deficiency. *Anesth Analg* 1993; **77:** 183–5.
2. Sockalingam I, Green DW. Mivacurium-induced prolonged neuromuscular block. *Br J Anaesth* 1995; **74:** 234–6.
3. Fox MH, Hunt PCW. Prolonged neuromuscular block associated with mivacurium. *Br J Anaesth* 1995; **74:** 237–8.
4. Zimmer S. Mivacurium and prolonged neuromuscular block. *Br J Anaesth* 1995; **75:** 823.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mivacurium as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Tourniquets. Mivacurium might be unsuitable for neuromuscular blockade of a limb which has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] It is largely inactivated by the enzymatic action of plasma cholinesterase and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated. However, as for other competitive neuromuscular blockers, the use of mivacurium to supplement regional anaesthesia has produced prolonged muscle weakness well beyond cuff deflation.[2] This suggests that mivacurium is not broken down in the ischaemic limb and that recovery is not dependent on plasma concentrations of mivacurium.

See also Local Anaesthetics, under Interactions of Atracurium, p. 2033.1, for a report of symptoms suggestive of local anaesthetic toxicity when prilocaine and mivacurium were used together.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; **73:** 726.
2. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; **78:** 222–3.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Metoclopramide. Metoclopramide, an inhibitor of plasma cholinesterase, was found to significantly prolong the duration of action of mivacurium in patients undergoing surgery, although in this study only marginal inhibition of plasma cholinesterase by metoclopramide occurred.[1]

1. Skinner HJ, *et al.* Influence of metoclopramide on plasma cholinesterase and duration of action of mivacurium. *Br J Anaesth* 1999; **82:** 542–5.

Pharmacokinetics

Mivacurium is a mixture of 3 stereoisomers, 2 of which (*cis-trans* and *trans-trans*) are considered to account for most of the neuromuscular blocking effect. All 3 isomers are inactivated by plasma cholinesterase. Renal and hepatic mechanisms are involved in their elimination with excretion in urine and bile.

Reviews.

1. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mivacron; ***Austral.***: Mivacron; ***Austria***: Mivacron; ***Belg.***: Mivacron; ***Chile***: Mivacron; ***China***: Mivacron (美维松); ***Cz.***: Mivacron; ***Denm.***: Mivacron; ***Fin.***: Mivacron; ***Fr.***: Mivacron; ***Ger.***: Mivacron; ***Gr.***: Mivacron; ***Hong Kong***: Mivacron; ***Hung.***: Mivacron; ***Irl.***: Mivacron; ***Ital.***: Mivacron; ***Malaysia***: Mivacron; ***Neth.***: Mivacron; ***Norw.***: Mivacron; ***NZ***: Mivacron; ***Pol.***: Mivacron; ***Port.***: Mivacron; ***Rus.***: Mivacron (Мивакрон); ***S.Afr.***: Mivacron; ***Singapore***: Mivacron; ***Spain***: Mivacron†; ***Swed.***: Mivacron; ***Switz.***: Mivacron; ***Turk.***: Mivacron; ***UK***: Mivacron.

Pancuronium Bromide *(BAN, USAN, rINN)*

Bromuro de pancuronio; NA-97; Org-NA-97; Pancuronii Bromidum; Pancuronio, bromuro de; Pancuronium, Bromure de; Pancuroniumbromid; Pankuronio bromidas; Pankuroniowy bromek; Pankuronium-bromid; Pankuroniumbromid; Pankuroniumbromidi; Pankuronyum Bromür; Панкурония Бромид.

1,1′-(3α,17β-Diacetoxy-5α-androstan-2β,16β-ylene)bis(1-methylpiperidinium) dibromide.

$C_{35}H_{60}Br_2N_2O_4$=732.7

CAS — 15500-66-0.

ATC — M03AC01.

ATC Vet — QM03AC01.

UNII — U9LY9Y75X2.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Pancuronium Bromide). White, yellowish-white, or slightly pink, hygroscopic crystalline powder. Very soluble to freely soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Pancuronium Bromide). A white, yellowish-white, or slightly pink, crystalline hygroscopic powder. Freely soluble in water, in alcohol, and in dichloromethane. Store in airtight containers. Protect from light and moisture.

Uses and Administration

Pancuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1). Muscle relaxation occurs within about 1.5 to 2 minutes of intravenous injection and lasts for about 45 to 60 minutes.

Pancuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The initial dose for intubation is usually 50 to 100 micrograms/kg by intravenous injection, with maintenance doses of 10 to 20 micrograms/kg. Children may be given similar doses. Some manufacturers recommend a reduction in the initial dose to 20 to 60 micrograms/kg when pancuronium is given following suxamethonium. Doses of 30 to 40 micrograms/kg initially have been recommended in neonates, with maintenance doses of 10 to 20 micrograms/kg as necessary. In the UK, the *BNFC* suggests that higher doses may be used in neonates for muscle relaxation in prolonged surgical procedures; an initial dose of 100 micrograms/kg, with maintenance doses of 50 micrograms/kg as necessary, has been suggested. In the USA, dosage based on an initial test dose of 20 micrograms/kg has been advocated for the neonate.

Adult patients under intensive care who require assisted ventilation for conditions such as intractable status asthmaticus or tetanus may be given 60 micrograms/kg intravenously every 1 to 1½ hours or less frequently.

Care should be taken when giving pancuronium to patients with hepatic or renal impairment, see below.

Administration in children. For details of uses and dosage of pancuronium bromide in infants and children, see Uses and Administration, above.

Administration in hepatic impairment. Prolonged neuromuscular blockade may occur in patients with liver disease given pancuronium bromide since increased elimination half-life with increased volume of distribution and reduced clearance has been reported.[1] However, the expanded distribution volume may necessitate an increase in the dose of pancuronium in these patients[1,2] and may be interpreted as resistance to the neuromuscular blocking effects of pancuronium.

1. Duvaldestin P, *et al.* Pancuronium pharmacokinetics in patients with liver cirrhosis. *Br J Anaesth* 1978; **50:** 1131–6.
2. Ward ME, *et al.* Althesin and pancuronium in chronic liver disease. *Br J Anaesth* 1975; **47:** 1199–1204.

Administration in renal impairment. Prolonged neuromuscular blockade may occur when pancuronium is given to patients with severe renal impairment. Pancuronium distributes rapidly into extracellular fluid after intravenous injection and the initial neuromuscular blockade produced will depend upon the peak drug concentration in this fluid. Since extracellular fluid volume is increased in chronic renal failure such patients may require a larger initial dose of pancuronium and a 45% increase in dose requirement has been reported[1] in patients with end-stage renal failure. Renal excretion is the main route of elimination and prolonged elimination half-life with reduced clearance may be expected in renal failure; total dose requirements may be reduced. The main infusion rate of pancuronium to maintain 90% blockade in patients with end-stage renal failure was reported to be 61.5% less than for patients with normal renal function.

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure. *Br J Anaesth* 1987; **59:** 995–1003.

Fetal paralysis. Pancuronium bromide 100 micrograms/kg of the estimated fetal-weight, given into the umbilical vein, produced fetal paralysis for about 40 minutes during intravascular exchange transfusion.[1] A dose of 200 to 300 micrograms/kg produced fetal paralysis for about 1 to 8 hours for more complicated transfusion procedures.[2] No adverse effects were reported.

1. Copel JA, *et al.* The use of intravenous pancuronium bromide to produce fetal paralysis during intravascular transfusion. *Am J Obstet Gynecol* 1988; **158:** 170–1.
2. Moise KJ, *et al.* Intravenous pancuronium bromide for fetal neuromuscular blockade during intrauterine transfusion for red-cell alloimmunization. *Obstet Gynecol* 1989; **74:** 905–8.

Neuroleptic malignant syndrome. Pancuronium is one of several drugs for which there have been isolated reports[1] of success in the management of neuroleptic malignant syndrome (p. 1050.2).

1. Sangal R, Dimitrijevic R. Neuroleptic malignant syndrome: successful treatment with pancuronium. *JAMA* 1985; **254:** 2795–6.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3).

Pancuronium has vagolytic and sympathomimetic action, which may cause tachycardia and hypertension, but does not produce ganglionic blockade. It has little histamine-releasing effect. Hypersensitivity reactions are relatively rare but bradycardia, bronchospasm, hypotension, and cardiovascular collapse have been reported. Pancuronium has been associated with excessive salivation in some patients.

Pancuronium should be used with caution in patients with raised catecholamine concentrations, or in those who are receiving drugs with sympathomimetic effects, as cardiovascular adverse effects are more likely in these patients.

Effects on the ears. A study[1] found that neonates who survived congenital diaphragmatic hernia were more likely to suffer from sensorineural hearing loss after prolonged use of pancuronium bromide during the neonatal period. However, the authors commented that the association is not necessarily causal and that further investigation is required.

1. Cheung P-Y, *et al.* Prolonged use of pancuronium bromide and sensorineural hearing loss in childhood survivors of congenital diaphragmatic hernia. *J Pediatr* 1999; **135:** 233–9.

Hypersensitivity. Reports[1-4] of anaphylactoid or anaphylactic reactions associated with pancuronium bromide.

See also under Suxamethonium Chloride, p. 2038.2.

1. Brauer FS, Ananthanarayan CR. Histamine release by pancuronium. *Anesthesiology* 1978; **49:** 434–5.
2. Patriarca G, *et al.* Pancuronium allergy: a case report. *Br J Anaesth* 1989; **62:** 210–12.
3. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
4. Sanchez-Guerrero IM, *et al.* Anaphylactoid reaction induced by pancuronium during general anaesthesia. *Eur J Anaesthesiol* 1998; **15:** 613–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pancuronium as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Postoperative complications. Because of its prolonged duration of action, pancuronium may be more likely than other neuromuscular blockers to produce residual neuromuscular block; such residual block is associated with an increased incidence of postoperative respiratory complications.[1,2]

1. Berg H, *et al.* Residual neuromuscular block is a risk factor for postoperative pulmonary complications: a prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41:** 1095–1103.
2. Bissinger U, *et al.* Postoperative residual paralysis and respiratory status: a comparative study of pancuronium and vecuronium. *Physiol Res* 2000; **49:** 455–62.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Pharmacokinetics

On intravenous injection pancuronium bromide is rapidly distributed into body tissues; about 80% may be bound to plasma proteins. A small proportion is metabolised in the liver to metabolites with weak neuromuscular blocking activity. It is largely excreted in urine as unchanged drug and metabolites; a small amount is excreted in bile. The

plasma elimination half-life is about 2 hours. It crosses the placenta in small amounts.

Pregnancy. In 15 patients undergoing caesarean section[1] given pancuronium bromide 100 micrograms/kg intravenously with other agents, mean maternal arterial and umbilical venous serum concentrations of pancuronium bromide and metabolites were 520 and 120 nanograms/mL, respectively at delivery (mean of 13 minutes after injection), giving a fetal to maternal ratio of 0.23.

1. Wingard LB, *et al.* Modified fluorometric quantitation of pancuronium bromide and metabolites in human maternal and umbilical serums. *J Pharm Sci* 1979; **68:** 914–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bemicin; Pancuron; Pavulon; Plumger; ***Austral.***: Pavulon†; ***Braz.***: Pancuron; Pavulon†; ***Chile***: Pavulon; ***China***: Pavulon (潘龙); ***Cz.***: Pavulon; ***Fin.***: Pavulon†; ***Fr.***: Pavulon†; ***Gr.***: Pavulon; ***Hong Kong***: Pavulon; ***India***: Neocuron; Panconium; Panuron; ***Indon.***: Pavulon; ***Israel***: Pavulon; ***Ital.***: Pavulon; ***Jpn***: Mioblock†; ***Malaysia***: Pavulon; ***Mex.***: Bromurex†; Panlem†; ***Neth.***: Pavulon†; ***Philipp.***: Pavulon†; ***Port.***: Pancurox; ***Rus.***: Pavulon (Павулон); ***S.Afr.***: Curon-B†; Pavulon†; ***Singapore***: Pavulon†; ***Swed.***: Pavulon†; ***Switz.***: Pavulon†; ***Thai.***: Pavulon†; ***Turk.***: Pavulon; ***Venez.***: Panuron; Pavulon; Pesium.

Pharmacopoeial Preparations
BP 2014: Pancuronium Injection;
USP 36: Pancuronium Bromide Injection.

Pipecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de pipecurio; Bromuro de pipecuronio; Pipecurium Bromide; Pipecuronii Bromidum; Pipecuronio, bromuro de; Pipécuronium, Bromure de; Pipekuroniumbromid; Pipekuroniumbromidi; RGH-1106; Пипекурония Бромид.

1,1,1′,1′-Tetramethyl-4,4′-(3α,17β-diacetoxy-5α-androstan-2β,16β-diyl)dipiperazinium dibromide.

$C_{35}H_{62}Br_2N_4O_4$=762.7

CAS — 52212-02-9 (anhydrous pipecuronium bromide); 68399-57-5 (pipecuronium bromide dihydrate).

ATC — M03AC06.

ATC Vet — QM03AC06.

UNII — R6ZTY81RE1.

Profile

Pipecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1). It has been used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures and to aid mechanical ventilation. Pipecuronium is reported to have no significant cardiovascular adverse effects or histamine-related effects.

Reviews and studies.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44:** 182–99.
2. Tassonyi E, *et al.* Pharmacokinetics of pipecuronium in infants, children and adults. *Eur J Drug Metab Pharmacokinet* 1995; **20:** 203–8.
3. Melloni C. Farmacologia clinica del pipecuronium; studio comparativo della sua durata clinica in anestesia bilanciata (propofol/fentanyl) vs isoflurano. *Minerva Anestesiol* 1995; **61:** 491–500.
4. Meretoja OA, Erkola O. Pipecuronium revisited: dose-response and maintenance requirement in infants, children, and adults. *J Clin Anesth* 1997; **9:** 125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Arduan (阿端); ***Cz.***: Arduan; ***Gr.***: Arduan; ***Hung.***: Arduan; ***India***: Arduan; ***Pol.***: Arduan; ***Rus.***: Aperomid (Апероми́д); Arduan (Ардуа́н); ***Ukr.***: Arduan (Ардуа́н).

Rocuronium Bromide *(BAN, USAN, rINN)*

Bromuro de rocuronio; Org-9426; Rocuronii Bromidum; Rocuronio, bromuro de; Rocuronium, Bromure de; Rocuroniumbromid; Rokuroniowy bromek; Rokuroniumbromid; Rokuronium-bromid; Rokuroniumbromidi; Rokuronyum Bromür; Рокурония Бромид.

1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide 17-acetate; 1-(17β-Acetoxy-3α-hydroxy-2β-morpholino-5α-androstan-16β-yl)-1-allylpyrrolidinium bromide.

$C_{32}H_{53}BrN_2O_4$=609.7

CAS — 119302-91-9.

ATC — M03AC09.

ATC Vet — QM03AC09.

UNII — I65MW4OFHZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Rocuronium Bromide). An almost white or pale yellow, slightly hygroscopic, powder. Freely soluble in water and in dehydrated alcohol; very soluble in dichloromethane. A 1.0% solution in water has a pH of 8.9 to 9.5. Store in airtight containers at a temperature below -15 degrees. Protect from light.

USP 36: (Rocuronium Bromide). An almost white or pale yellow, slightly hygroscopic powder. Freely soluble in water and in dehydrated alcohol. pH of a 1% solution in water is 8.9 to 9.5. Store in airtight containers at a temperature of -25 degrees to -10 degrees. Protect from light and moisture.

Uses and Administration

Rocuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1). After intravenous injection it produces muscle relaxation within 1 to 2 minutes with a duration of about 30 to 50 minutes. Rocuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. A usual initial dose in adults is 600 micrograms/kg by intravenous injection; however, higher doses of 1 mg/kg are recommended for intubation during rapid sequence induction of anaesthesia. Usual maintenance doses are 150 micrograms/kg by injection, although these should be reduced to 75 to 100 micrograms/kg if prolonged inhalational anaesthesia is planned. Maintenance may also be by infusion at a rate of 300 to 600 micrograms/kg per hour although higher rates have been suggested in US licensed product information. Similar doses to those used in adults have been used in the UK in children older than one month but maintenance doses may be required more frequently. In the USA, rocuronium is licensed for use in children from birth onwards; again doses are similar to those used in adults.

For obese patients weighing more than 30% over their ideal body-weight UK licensed product information recommends that doses should be calculated according to lean body-mass; in the USA it is recommended that dosage should be based on actual body-weight. UK product information also recommends reduced maintenance doses of 75 to 100 micrograms/kg by injection in the elderly. For doses in hepatic or renal impairment, see below.

Reviews and discussions.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44:** 182–9.
2. Hunter JM. Rocuronium: the newest aminosteroid neuromuscular blocking drug. *Br J Anaesth* 1996; **76:** 481–3.

Administration in children. In a study involving 70 children, conditions for intubation were judged to be good to excellent within one minute of intravenous doses of rocuronium 600 or 900 micrograms/kg, with a trend to better conditions with the higher dose[1] (see also Uses and Administration, above for recommended doses).

1. Fuchs-Buder T, Tassonyi E. Intubating conditions and time course of rocuronium-induced neuromuscular block in children. *Br J Anaesth* 1996; **77:** 335–8.

INTRAMUSCULAR ROUTE. Intramuscular injection of rocuronium 1 mg/kg into the deltoid muscle permitted tracheal intubation to be carried out in lightly anaesthetised infants after 2.5 minutes.[1] In children a dose of 1.8 mg/kg enabled tracheal intubation after 3 minutes. However, the mean time to initial recovery after these large doses was 57 minutes in infants and 70 minutes in children. This prolonged duration of action may limit intramuscular use for brief procedures, particularly in children.

1. Reynolds LM, *et al.* Intramuscular rocuronium in infants and children: dose-ranging and tracheal intubating conditions. *Anesthesiology* 1996; **85:** 231–9.

Administration in hepatic or renal impairment. Regardless of the anaesthetic technique used, UK licensed product information recommends an initial dose of rocuronium bromide 600 micrograms/kg by intravenous injection and a reduced maintenance dose of 75 to 100 micrograms/kg by intravenous injection, or 300 to 400 micrograms/kg per hour by continuous infusion, in patients with hepatic or biliary-tract disease, or renal failure.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3). Rocuronium is reported to have minimal cardiovascular and histamine-releasing effects. High doses (greater than 900 micrograms/kg of rocuronium bromide) have mild vagolytic activity. It should be used with caution in patients with biliary disease or hepatic or renal impairment.

Hepatic impairment. There have been conflicting reports of the pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic impairment. In contrast to earlier studies[1,2] one group of workers[3] found a significant reduction in the plasma clearance of rocuronium in patients with cirrhosis. The elimination half-life has been variously reported to be unchanged[1] or prolonged[2,3] with delayed recovery.[3] Some studies[2,3] found that the onset of action was not affected while one group of workers[1] reported a delay.

Licensed product information recommends that care should be taken when giving rocuronium to patients with clinically significant hepatic impairment (see also under Uses and Administration, above).

1. Khalil M, *et al.* Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. *Anesthesiology* 1994; **80:** 1241–7.
2. Magorian T, *et al.* The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg* 1995; **80:** 754–9.
3. van Miert MM, *et al.* The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. *Br J Clin Pharmacol* 1997; **44:** 139–44.

Hypersensitivity. Although rocuronium is considered to have minimal histamine-releasing effects, histaminoid reactions have been reported[1] on induction of anaesthesia in 3 patients who had been given rocuronium. An increased incidence of severe hypersensitivity reactions (particularly anaphylactic shock) has been reported with rocuronium compared with other neuromuscular blockers available in France.[2] Fatalities have occurred.[3]

See also the discussion of the relative risks of hypersensitivity associated with neuromuscular blockers, under Suxamethonium Chloride, p. 2038.2.

1. Neal SM, *et al.* Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84:** 108–11.
2. Mayer M. Information importante de pharmacovigilance: Esméron et manifestations allergiques. Available at: http://www.afssaps.fr/content/download/12056/143941/version/1/file/letesmer.pdf (accessed 12/02/10)
3. Baillard C, *et al.* Anaphylaxis to rocuronium. *Br J Anaesth* 2002; **88:** 600–602.

Pain on administration. Severe transient burning pain associated with injection of rocuronium was considered[1] to be responsible for the spontaneous movement sometimes seen in the arm or wrist into which rocuronium is given. It is recommended that rocuronium should be given only when a deep stage of unconsciousness has been achieved.

1. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? *Br J Anaesth* 1997; **79:** 382–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rocuronium as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Renal impairment. In a study[1] of the pharmacokinetics and neuromuscular effects of rocuronium, the clearance of rocuronium was reduced in patients with renal failure when compared with healthy subjects, but the accompanying increase in duration of clinical relaxation did not reach statistical significance. However, it was recommended that rocuronium should be used with caution in the presence of renal failure as there were large interpatient variations in both clinical response and pharmacokinetic parameters. It has been suggested[2] that chronic renal failure may have played a role in the prolongation of neuromuscular blockade in a 47-year-old woman given rocuronium 1 mg/kg. Although this dose is within the recommended adult dose range, it was criticised[3] as being excessive for a patient with renal impairment.

For recommendation that care should be taken when giving rocuronium to patients with renal failure, see under Uses and Administration, above.

1. Cooper RA, *et al.* Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (ORG 9426) during isoflurane anaesthesia in patients with and without renal failure. *Br J Anaesth* 1993; **71:** 222–6.
2. Lewis KS, *et al.* Prolonged neuromuscular blockade associated with rocuronium. *Am J Health-Syst Pharm* 1999; **56:** 1114–18.
3. Cozanitis DA, Booij HD. Muscle relaxants and renal failure. *Am J Health-Syst Pharm* 2000; **57:** 1713–14.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Pharmacokinetics

On intravenous use plasma concentrations of rocuronium follow a three-compartment open model. There is an initial

distribution phase with a half-life of 1 to 2 minutes followed by a slower distribution phase with a half-life of 14 to 18 minutes. It is reported to be about 30% bound to plasma proteins. The elimination half-life is about 1.2 to 1.4 hours. Up to 40% of a dose may be excreted in the urine within 24 hours; rocuronium is also excreted in the bile. The main metabolite of rocuronium, 17-desacetylrocuronium, is reported to have a weak neuromuscular blocking effect.

References.
1. Khuenl-Brady KS, Sparr H. Clinical pharmacokinetics of rocuronium bromide. *Clin Pharmacokinet* 1996; **31:** 174–83.
2. McCoy EP, *et al.* Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia. *Br J Anaesth* 1996: **76:** 29–33.
3. Wierda JMKH, *et al.* Pharmacokinetics and pharmacokinetic-dynamic modelling of rocuronium in infants and children. *Br J Anaesth* 1997; **78:** 690–5.
4. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.
5. Proost JH, *et al.* Urinary, biliary and faecal excretion of rocuronium in humans. *Br J Anaesth* 2000; **85:** 717–23.

Intensive care. The pharmacokinetics of rocuronium appear to differ between intensive care patients given prolonged dosage and surgical patients.[1] The volume of distribution at steady state may be increased, the plasma clearance decreased, and the terminal half-life prolonged. Recovery time on stopping may also be longer.

1. Sparr HJ, *et al.* Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients. *Br J Anaesth* 1997; **78:** 267–73.

Pregnancy. The mean concentration of rocuronium in venous plasma of 32 patients given a dose of 600 micrograms/kg before undergoing caesarean section was 2412 nanograms/mL at delivery;[1] the ratio of mean concentrations of rocuronium in umbilical venous plasma to maternal venous plasma at this time was 0.16. In 12 of these patients the mean concentration of rocuronium in umbilical arterial plasma was 271 nanograms/mL giving a ratio of 0.62 for the mean concentration of rocuronium in arterial to venous umbilical plasma. The concentration of 17-desacetylrocuronium in maternal venous plasma was 178 nanograms/mL and was less than 25 nanograms/mL in umbilical plasma.

1. Abouleish E, *et al.* Rocuronium (Org 9426) for Caesarean section. *Br J Anaesth* 1994; **73:** 336–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Esmeron; ***Austria***: Esmeron; ***Belg.***: Esmeron; ***Braz.***: Esmeron; Rocuron; Romeran; ***Canad.***: Zemuron; ***Chile***: Esmeron; ***China***: Esmeron (爱可松); ***Cz.***: Esmeron; ***Denm.***: Esmeron; ***Fin.***: Esmeron; ***Fr.***: Esmeron; ***Ger.***: Esmeron; ***Gr.***: Esmeron; ***Hong Kong***: Esmeron; ***Hung.***: Esmeron; ***India***: Esmeron; ***Indon.***: Esmeron; Roculax; ***Irl.***: Esmeron; ***Israel***: Esmeron; ***Ital.***: Esmeron; ***Jpn***: Eslax; ***Malaysia***: Esmeron; ***Mex.***: Esmeron; ***Neth.***: Esmeron; ***Norw.***: Esmeron; ***NZ***: Esmeron; ***Philipp.***: Esmeron; Rocuron; ***Pol.***: Esmeron; Roqurum; ***Port.***: Esmeron; ***Rus.***: Esmeron (Эсмерон); ***S.Afr.***: Esmeron; ***Singapore***: Esmeron; ***Spain***: Esmeron; ***Swed.***: Esmeron; ***Switz.***: Esmeron; ***Thai.***: Esmeron; ***Turk.***: Esmeron; ***UK***: Esmeron; ***Ukr.***: Esmeron (Эсмерон); ***USA***: Zemuron; ***Venez.***: Esmeron.

Suxamethonium Chloride (BAN, pINN)

Choline Chloride Succinate; Cloruro de succinilcolina; Cloruro de suxametonio; Succicurarium Chloride; Succinylcholine Chloride; Suksametonio chloridas; Suksametoniowy chlorek; Suksametoniumkloridi; Süksinilkolin Klorür; Suxamethonii Chloridum; Suxamethonii Chloridum Dihydricum; Suxamethonium chlorid dihydrát; Suxaméthonium, chlorure de; Suxamethoniumchlorid; Suxametonio, cloruro de; Suxametoniumklorid; Suxametonklorid; Szuxametóniumklorid; Суксаметония Хлорид.

2,2′-Succinyldioxybis(ethyltrimethylammonium) dichloride dihydrate.

$C_{14}H_{30}Cl_2N_2O_4,2H_2O$=397.3

CAS — 306-40-1 (suxamethonium); 55-94-7 (suxamethonium bromide); 71-27-2 (anhydrous suxamethonium chloride); 6101-15-1 (suxamethonium chloride dihydrate); 541-19-5 (suxamethonium iodide).

ATC — M03AB01.

ATC Vet — QM03AB01.

UNII — I9L0DDD30I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Suxamethonium Chloride). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Succinylcholine Chloride). A white, odourless, crystalline powder. The anhydrous form is hygroscopic. Soluble 1 in 1 of water and 1 in 350 of alcohol; slightly soluble in chloroform; practically insoluble in ether. Its solutions in water have a pH of about 4. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Incompatibilities of neuromuscular blockers are discussed under Atracurium, p. 2030.1.

Stability. A study of the loss of potency of suxamethonium chloride 20 mg/mL in water indicated that decomposition occurred at a considerably higher rate at 40 degrees than at 25 degrees and that the pH range of maximum stability was 3.75 to 4.50 for unbuffered solutions.[1] Assuming the usual conditions of manufacturing, transit, and storage the total loss of potency was estimated to be 7% and 9% respectively for injections kept at room temperature for 4 and 6 weeks. If unbuffered, suxamethonium chloride injection complying with USP 36 pH limits (3.0 to 4.5) must be stored at room temperature; it should not be kept for longer than 4 weeks.

1. Boehm JJ, *et al.* Shelf life of unrefrigerated succinylcholine chloride injection. *Am J Hosp Pharm* 1984; **41:** 300–2.

Uses and Administration

Suxamethonium is a depolarising neuromuscular blocker used to produce muscle relaxation. It combines with cholinergic receptors of the motor end-plate to produce depolarisation but is resistant to breakdown by acetylcholinesterase. This prevents repolarisation and subsequent depolarisation, and a flaccid muscle paralysis occurs. This initial depolarisation block is commonly known as a **phase I block.** The muscles that produce fine rapid movements such as those of the face are the first to be affected followed by those of the limbs, abdomen, and chest; the diaphragm is affected last. Recovery occurs in reverse order. When excessive amounts of suxamethonium accumulate at the neuromuscular junction, for example after high or prolonged dosage, the nature of the block may change to one with characteristics similar to competitive block. This is commonly termed **phase II block** or **dual block** and may be associated with prolonged neuromuscular blockade and apnoea.

After intravenous injection suxamethonium chloride acts in about 30 to 60 seconds and has a duration of action of about 2 to 6 minutes. After intramuscular injection it acts in 2 to 3 minutes and has a duration of action of about 10 to 30 minutes.

Suxamethonium is used in surgical and other procedures in which a rapid onset and brief duration of muscle relaxation is needed (see Anaesthesia, p. 2028.1), including intubation, endoscopies, and ECT. It is used as suxamethonium chloride, and is normally given by intravenous injection. The content of preparations of suxamethonium chloride may be described in terms of either the dihydrate or the anhydrous form, depending on the country of origin, and this should be borne in mind when evaluating the literature although the differences are small (anhydrous suxamethonium chloride 1 mg is equivalent to about 1.1 mg of the dihydrate).

Suxamethonium should be given after induction of general anaesthesia because paralysis is usually preceded by painful muscle fasciculations. A competitive neuromuscular blocker may sometimes be given before suxamethonium to try to reduce some of the adverse effects on the muscles (see Effects on the Muscles, p. 2038.1). Premedication with an antimuscarinic may be of value in reducing bradycardia and excessive salivation. Assisted ventilation is necessary.

An initial test dose of 100 micrograms/kg, or 5 to 10 mg, of suxamethonium chloride may be given intravenously if increased sensitivity is suspected. Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The response to suxamethonium varies considerably and the usual single dose of suxamethonium chloride for an adult is 0.3 to 1.1 mg/kg by intravenous injection. Supplementary doses of 50 to 100% of the initial dose may be given at 5 to 10 minute intervals if required but the total dose given by repeated intravenous injection or continuous infusion (see below) should not exceed 500 mg/hour. Infants and children are more resistant to suxamethonium than adults. A recommended intravenous dose for infants under 1 year of age is 2 mg/kg; a dose of 1 mg/kg is recommended for children 1 to 12 years old.

When a suitable vein is inaccessible suxamethonium chloride has been given by intramuscular injection in a dose of 3 to 4 mg/kg to a maximum total dose of 150 mg. The intramuscular dose for children aged under 1 year is up to 5 mg/kg and for older children is up to 4 mg/kg to a maximum total dose of 150 mg.

For prolonged procedures in adults sustained relaxation may be obtained by continuous intravenous infusion of a 0.1 to 0.2% solution. A rate of 2.5 to 4 mg/minute is usually adequate but may be adjusted as necessary. The total dose given by repeated intravenous injection (see above) or continuous infusion should not exceed 500 mg/hour.

Suxamethonium bromide and suxamethonium iodide have also been used.

Administration in children. For details of uses and dosage of suxamethonium chloride in infants and children, see Uses and Administration, above.

ECT. Suxamethonium chloride is used to decrease the muscular contractions associated with electrically induced convulsions. It temporarily paralyses muscles during ECT, preventing violent muscle contractions that can potentially result in broken bones and fractures.

Suxamethonium chloride remains the most commonly used neuromuscular blocker in ECT. However, patients with a history of malignant hyperthermia, neuroleptic malignant syndrome, catatonic schizophrenia, and organophosphate poisoning are more susceptible to adverse effects.[1] Mivacurium has been used, with satisfactory results, in at-risk-patients, although histamine release and hypotension may be a problem. Other competitive neuromuscular blockers tried include atracurium and vecuronium.

1. Ding Z, White PF. Anesthesia for electroconvulsive therapy. *Anesth Analg* 2002; **94:** 1351–64.

Adverse Effects

The neuromuscular blocking action of suxamethonium chloride is terminated by the enzyme plasma cholinesterase and prolonged apnoea may occur in patients with an atypical enzyme or with low enzyme activity. Apnoea may also occur following development of phase II block (see Uses and Administration, above) after high or repeated doses of suxamethonium chloride, although tachyphylaxis may also occur with repeated doses.

Transient fasciculations occur during the onset of depolarising block. Rhabdomyolysis, myoglobinaemia, and myoglobinuria have been reported and may be associated with muscle damage after fasciculations. Postoperative muscle pain occurs in some patients but is not directly related to the degree of fasciculation. A transient rise in intra-gastric pressure may occur secondary to fasciculation of abdominal muscles. A transient increase in intra-ocular pressure often occurs. Depolarisation of skeletal muscle produces an immediate increase in plasma-potassium concentration and this can have serious consequences in some patients (see p. 2038.2).

Stimulation of the vagus nerve and parasympathetic ganglia by suxamethonium chloride may be followed by bradycardia, other arrhythmias, and hypotension, and may be exacerbated by the raised plasma-potassium concentration; cardiac arrest has been reported. Tachycardia and an increase in blood pressure due to stimulation of sympathetic ganglia have also been reported.

Suxamethonium chloride may cause an increase in salivary, bronchial, and gastric secretion and other muscarinic effects. Salivary gland enlargement has occurred.

Direct release of histamine from mast cells occurs but this is not the main mechanism of hypersensitivity reactions (see Hypersensitivity, p. 2038.2). Flushing, rashes, bronchospasm, and shock have been reported.

Other reported effects include prolonged respiratory depression and apnoea.

Suxamethonium chloride is implicated in the development of malignant hyperthermia (p. 2024.1) in those patients with a genetic predisposition to the syndrome.

Reviews.
1. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **10:** 331–49.
2. Orebaugh SL. Succinylcholine: adverse effects and alternatives in emergency medicine. *Am J Emerg Med* 1999; **17:** 715–21.

Effects on intra-ocular pressure. Doses of suxamethonium are often followed 20 to 30 seconds later by a transient increase in intra-ocular pressure, which may be due in part to contracture of extra-ocular muscles. If suxamethonium is used during eye surgery after incision of the eyeball or in patients with a penetrating eye injury, there is a theoretical risk that any increase in intra-ocular pressure may result in extrusion of ocular contents and loss of sight. However, there appear to be few reports of vitreous extrusion associated with suxamethonium,[1] and a large retrospective study[2] has failed to find any evidence that suxamethonium caused additional eye damage in patients with penetrating eye injuries. Furthermore, the procedure of intubation itself is associated with a greater increase in intra-ocular pressure than that seen with suxamethonium. Nonetheless, some suggest that a rapid competitive neuromuscular blocker would be preferable to aid intubation in patients with penetrating eye injuries, after incision of the eyeball, and in glaucoma, although others consider that

the risk of a transient rise of intra-ocular pressure in these situations should be weighed against the need for rapid intubation.[1,3] For a discussion on the use of various drugs to counteract the rise in intra-ocular pressure associated with suxamethonium and intubation in general, see under Anaesthesia, p. 2028.1.

1. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **5:** 331–49.
2. Libonati MM, *et al.* The use of succinylcholine in open eye surgery. *Anesthesiology* 1985; **62:** 637–40.
3. Edmondson L. Intraocular pressure and suxamethonium. *Br J Anaesth* 1997; **79:** 146.

Effects on the muscles. Muscle fasciculations and postoperative muscle pain commonly follow use of suxamethonium. **Fasciculations** (generalised and desynchronised contractions of skeletal muscle fibres) occur during the onset of depolarising block in almost all patients given suxamethonium and may cause muscle damage. They are seen especially in the 'fine' muscles of the hands and face, and can be useful as an indication that suxamethonium is working. Attempts have been made to prevent their development with the aim of reducing postoperative muscle pain. However, there appears to be no direct correlation between the extent of visible fasciculations and muscle pain.[1,2] Slow infusion of suxamethonium[3] or giving divided doses[4] reduces fasciculations but not muscle pain.

Postoperative **muscle pain** is one of the most common adverse effects of suxamethonium and has been noted in about 50% of patients, although the reported incidence varies widely from around 1.5 to about 90%.[2] It usually occurs on the first postoperative day and lasts for 2 or 3 days, and most often affects muscles of the neck, shoulders, and upper abdomen.[2] The incidence and severity of muscle pain is increased in patients who are mobile soon after surgery and in females, but it occurs less often in children, pregnant women, and the elderly.[2]

The mechanism of suxamethonium-induced muscle pain is not fully understood; there have been many attempts to prevent it. Pretreatment with a small dose of a competitive neuromuscular blocker reduces both visible fasciculations and the incidence and severity of muscle pain,[1,2,5-8] but may delay the onset and alter the intensity of subsequent suxamethonium block[9] and impair conditions for intubation[1,9] (see Neuromuscular Blockers, under Interactions in Atracurium, p. 2033.2). In addition, larger doses of suxamethonium are required;[10] consequently the practice is considered controversial by some.[10,11] Pretreatment with a small dose (10 mg) of suxamethonium in a 'self-taming' technique appears to offer no protection against muscle pain.[1,2] The choice of anaesthetic induction agent has been suggested to be significant, as has the timing of doses, but despite claims for benefit with, for example, propofol, this remains questionable.[2] Pretreatment with benzodiazepines or NSAIDs has produced conflicting results.[2] Other drugs that have been tried include lidocaine, calcium gluconate, and vitamin C; there is some evidence that lidocaine may be the most effective pretreatment.[2] Not all methods have concentrated on drug treatment. A simple regimen of stretching exercises before premedication has reduced the incidence of both fasciculations and postoperative muscle pain.[12]

Suxamethonium may also produce an increase in **jaw tension** (masseter spasm or trismus)[13] in both adults[14] and children[15,16] during the onset of neuromuscular blockade. Tracheal intubation is greatly hindered in affected patients. It is not possible to predict which patients will show this response and the mechanism is unknown, although in about 50% of patients it may indicate the onset of malignant hyperthermia. Pretreatment with a paralysing dose of a competitive neuromuscular blocker prevents the response[16] but it is unknown whether this is clinically useful.

1. O'Sullivan EP, *et al.* Differential effects of neuromuscular blocking agents on suxamethonium-induced fasciculations and myalgia. *Br J Anaesth* 1988; **60:** 367–71.
2. Wong SF, Chung F. Succinylcholine-associated postoperative myalgia. *Anaesthesia* 2000; **55:** 144–52.
3. Feingold A, Velazquez JL. Suxamethonium infusion rate and observed fasciculations: a dose-response study. *Br J Anaesth* 1979; **51:** 241–5.
4. Wilson DB, Dundee JW. Failure of divided doses of succinylcholine to reduce the incidence of muscle pains. *Anesthesiology* 1980; **52:** 273–5.
5. Bennetts FE, Khalil KI. Reduction of post-suxamethonium pains by pretreatment with four non-depolarising agents. *Br J Anaesth* 1981; **53:** 531–6.
6. Erkola O, *et al.* Five non-depolarizing muscle relaxants in precurarization. *Acta Anaesthesiol Scand* 1983; **27:** 427–32.
7. Sosis M, *et al.* Comparison of atracurium and d-tubocurarine for prevention of succinylcholine myalgia. *Anesth Analg* 1987; **66:** 657–9.
8. Findlay GP, Spittal MJ. Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium. *Br J Anaesth* 1996; **76:** 526–9.
9. Pauca AL, *et al.* Inhibition of suxamethonium relaxation by tubocurarine and gallamine pretreatment during induction of anaesthesia in man. *Br J Anaesth* 1975; **47:** 1067–73.
10. McManus CM. Neuromuscular blockers in surgery and intensive care, part 2. *Am J Health-Syst Pharm* 2001; **58:** 2381–99.
11. Mencke T, *et al.* Pretreatment before succinylcholine for outpatient anesthesia? *Anesth Analg* 2002; **94:** 573–6.
12. Magee DA, Robinson RJS. Effect of stretch exercises on suxamethonium induced fasciculations and myalgia. *Br J Anaesth* 1987; **59:** 596–601.
13. Saddler JM. Jaw stiffness—an ill understood condition. *Br J Anaesth* 1991; **67:** 515–16.
14. Leary NP, Ellis FR. Masseteric muscle spasm as a normal response to suxamethonium. *Br J Anaesth* 1990; **64:** 488–92.
15. Van Der Spek AFL, *et al.* Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants. *Br J Anaesth* 1990; **64:** 21–7.
16. Smith CE, *et al.* Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children. *Br J Anaesth* 1990; **64:** 577–81.

Effects on plasma-potassium concentration. Suxamethonium causes depolarisation of motor end-plates in skeletal muscle, resulting in an immediate increase in plasma-potassium concentration. The rise is usually small, being about 0.5 mmol or less per litre, but suxamethonium is best avoided in patients whose plasma-potassium concentration is already high, such as those with renal impairment. An exaggerated response, with severe hyperkalaemia resulting in ventricular fibrillation and cardiac arrest, has been reported in patients with burns,[1,2] massive trauma, closed head injury, neuromuscular disease (see Neuromuscular Disorders, under Precautions, p. 2039.1), and severe long-lasting sepsis.[3] See also Children, under Precautions, p. 2039.1 for reference to fatal cardiac arrest associated with hyperkalaemia in children. With burns or trauma the period of greatest risk is from about 10 to 90 days after the injury, but may be further prolonged if there is delayed healing or persistent infection. These patients may still react abnormally to suxamethonium 2 years after the injury. In neuromuscular disease the greatest risk period is usually from 3 weeks to 6 months after onset, but severe hyperkalaemia may occur after 24 to 48 hours or later than 6 months. Patients with severe sepsis for more than a week should be considered at risk of hyperkalaemia and suxamethonium should not be given until the infection has cleared. The mechanism of this hyperkalaemic response appears to be a supersensitivity of acetylcholine receptors in which the entire muscle fibre membrane, rather than discrete motor end-plate sites, becomes directly excitable by depolarising drugs. Depolarisation by suxamethonium thus results in release of potassium over the entire muscle fibre membrane and hyperkalaemia results.

Various methods have been tried to attenuate the hyperkalaemia, including pretreatment with a small dose of a competitive neuromuscular blocker[3,4] or with suxamethonium itself.[5,6] No method is reliable enough to be used clinically.

Anaesthetics such as thiopental and halothane can increase the hyperkalaemic response.[4]

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; **26:** 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; **ii:** 1003–4.
3. Kohlschütter B, *et al.* Suxamethonium-induced hyperkalaemia in patients with severe intra-abdominal infections. *Br J Anaesth* 1976; **48:** 557–62.
4. Dhanaraj VJ, *et al.* A study of the changes in serum potassium concentration with suxamethonium using different anaesthetic agents. *Br J Anaesth* 1975; **47:** 516–19.
5. Magee DA, Gallagher EG. "Self-taming" of suxamethonium and serum potassium concentration. *Br J Anaesth* 1984; **56:** 977–9.
6. Plötz J, Schreiber W. Side effects induced by suxamethonium on the skeletal muscle and their prevention. *Br J Anaesth* 1985; **57:** 1044–5.

Hypersensitivity. Hypersensitivity reactions to neuromuscular blockers are more common in women than in men,[1,2] in atopic patients and those who have a history of asthma or allergy,[2] and in patients who have had a previous reaction to anaesthetic drugs.[2] Circulatory collapse, flushing, rash, urticaria, and bronchospasm have occurred in hypersensitivity reactions associated with suxamethonium;[1,3,4] deaths have been reported.[3,5]

Data from intradermal testing have been used to qualify the **risk** of allergic reactions associated with the neuromuscular blockers:[6]

- benzylisoquinolinium blockers *alcuronium* and *tubocurarine* and the depolarising blocker *suxamethonium* were considered to be associated with the highest risk
- benzylisoquinolinium blockers *atracurium, cisatracurium, gallamine*, and *mivacurium* and the aminosteroid *rocuronium* presented an intermediate risk
- the aminosteroids *pancuronium* and *vecuronium* were considered to have the lowest risk

A type I immediate hypersensitivity reaction involving IgE antibodies is considered to be the **mechanism** of most hypersensitivity reactions associated with neuromuscular blockers.[2,5,7,8] Antibodies reacting with neuromuscular blockers, including suxamethonium, have been noted.[5,8] The antibodies appear to be directed against quaternary or tertiary ammonium-ion groups which are present in neuromuscular blockers; such groups are also found in other drugs, cosmetics, disinfectants, and foods. Some have suggested that pholcodine consumption may cause sensitisation to neuromuscular blockers.[9] Such phenomena may help explain the cross-reactivity reported between different neuromuscular blockers[1,2,5,8,10] and how sensitisation occurs without prior exposure to any neuromuscular blocker.[2,5] At least 50% of patients sensitive to one neuromuscular blocker will react to one or more others[11] with some patients sensitive to most.[1] Intradermal skin tests are used to investigate and predict sensitivity to neuromuscular blockers, but their interpretation is controversial and it cannot be concluded that all patients with positive skin tests will have clinical sensitivity.[1,11] Although radioallergosorbent tests can detect antibodies to suxamethonium, alcuronium, and thiopental[3,12] some consider that their routine use is not justified as reactions could be avoided by taking an adequate patient history.[13]

However, neuromuscular blockers also have a direct effect on mast cells, releasing histamine without immunological involvement, and could cause anaphylactoid reactions. Histamine release associated with use of aminosteroidal blockers is rare compared with the benzylisoquinolinium blockers.[14] Tubocurarine is considered to be the most potent releaser of histamine, with pancuronium and vecuronium having only very weak activity. Suxamethonium is considered to have only 1% of the histamine-releasing activity of tubocurarine but is more likely to produce serious hypersensitivity reactions.

1. Youngmen PR, *et al.* Anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition? *Lancet* 1983; **ii:** 597–9.
2. Fisher MM, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983; **62:** 559–64.
3. Brahams D. Fatal reaction to suxamethonium: case for screening by radioallergosorbent test? *Lancet* 1989; **i:** 1400–1.
4. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
5. Fisher M, Baldo B. Adverse reactions to alcuronium: an Australian disease? *Med J Aust* 1983; **1:** 630–2.
6. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? *Br J Anaesth* 2001; **86:** 678–82.
7. Vervloet D. Anaphylactoid reactions to suxamethonium. *Lancet* 1983; **ii:** 1197.
8. Harle DG, *et al.* Detection of IgE antibodies to suxamethonium after anaphylactoid reactions during anaesthesia. *Lancet* 1984; **I:** 930–2.
9. Florvaag E, Johansson SGO. The pholcodine story. *Immunol Allergy Clin North Am* 2009; **29:** 419–27.
10. Harle DG, *et al.* Cross-reactivity of metocurine, atracurium, vecuronium and fazadinium with IgE antibodies from patients unexposed to these drugs but allergic to other myoneural blocking drugs. *Br J Anaesth* 1985; **57:** 1073–6.
11. Withington DE. Relevance of histamine to the anaesthetist. *Br J Hosp Med* 1988; **40:** 264–70.
12. Assem ESK. Anaphylactic anaesthetic reactions: the value of paper radioallergosorbent tests for IgE antibodies to muscle relaxants and thiopentone. *Anaesthesia* 1990; **45:** 1032–8.
13. Noble DW, Yap PL. Screening for antibodies to anaesthetics. *BMJ* 1989; **299:** 2.
14. Naguib M, *et al.* Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth* 1995; **75:** 588–92.

Treatment of Adverse Effects

Once suxamethonium chloride has been given assisted respiration should be maintained until spontaneous respiration has been fully restored. Transfusion of fresh frozen plasma or other source of plasma cholinesterase will help the destruction of the suxamethonium when prolonged paralysis is a result of atypical or low serum concentrations of plasma cholinesterase. Anticholinesterases should not normally be used since they potentiate the usual phase I block (see Uses and Administration, p. 2037.2). If the neuromuscular block ceases to be depolarising in type and acquires some features of a competitive block (phase II block) the cautious use of an anticholinesterase may be considered. A short-acting anticholinesterase such as edrophonium may be given intravenously and if an obvious improvement is maintained for several minutes, neostigmine may be given with atropine.

Severe hypersensitivity reactions should be treated promptly with supportive and symptomatic measures.

If malignant hyperthermia develops, it may be treated as described on p. 2024.1.

The muscarinic effects of suxamethonium chloride, such as bradycardia and excessive salivary secretion, may be reduced by giving an antimuscarinic such as atropine before suxamethonium. A small dose of a competitive neuromuscular blocker given before suxamethonium has been used to reduce some of the adverse effects of suxamethonium on the muscles (see Effects on the Muscles, above).

Precautions

Patients given a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Suxamethonium chloride is contra-indicated in patients with atypical plasma cholinesterase and should be used with caution in patients with reduced plasma cholinesterase activity (see p. 2039.1), which may occur in certain disease states and following exposure to certain drugs. Plasma cholinesterase concentrations fall during pregnancy and the puerperium and therefore maternal paralysis may be mildly prolonged. Suxamethonium is contra-indicated in patients with burns, massive trauma, renal impairment with a raised plasma-potassium concentration, severe long-lasting sepsis,

and severe hyperkalaemia, since suxamethonium-induced rises in plasma-potassium concentration can have serious consequences in such patients; patients who have been immobilised for prolonged periods may be at similar risk. It is contra-indicated in patients with a history of hypersensitivity to the drug and, because high rates of cross-sensitivity have been reported (see p. 2038.2), should be used with caution when hypersensitivity to any neuromuscular blocker has previously occurred. Suxamethonium should be avoided in patients with a penetrating eye injury, raised intra-ocular pressure or glaucoma, or those about to undergo incision of the eyeball in eye surgery, because of the risks from increased intra-ocular pressure (although see under Adverse Effects, p. 2037.3). Suxamethonium chloride produces muscle contractions before relaxation and should therefore be used with caution in patients with bone fractures. It is contra-indicated in patients with a personal or family history of malignant hyperthermia.

The response to suxamethonium chloride is often unpredictable in patients with neuromuscular disorders and it should be used with great caution in these patients (see below). Caution is also needed if it is given to a patient with cardiac or respiratory disease. Children may be at special risk from cardiac arrest associated with hyperkalaemia (see below).

Hypothermia may enhance the neuromuscular blocking effects of suxamethonium chloride and an increase in body temperature may reduce them.

Children. Reports of fatal cardiac arrests[1,2] in apparently healthy children and adolescents, who were subsequently found to have had undiagnosed myopathies, led to restrictions in the USA on the use of suxamethonium in this age group. Suxamethonium was contra-indicated except for emergency tracheal intubation or where an immediate securing of an airway was essential. Many anaesthetists disagreed[2] with this contra-indication and an FDA Committee advised[3] that it should be replaced by a warning about the possibility of cardiac arrest associated with hyperkalaemia with special attention being paid to male children who are considered to be at the highest risk. One British anaesthetist who questioned the rationale behind restricting the elective use of suxamethonium pointed out that alternatives to suxamethonium had not been shown to be as safe or effective for airway management.[4] The rare occurrence of cardiac arrest in children might be further reduced by taking a careful family history to exclude undiagnosed myopathies and by using an intravenous as opposed to inhalation induction when suxamethonium is to be used.[4] A survey had found that most cases of cardiac arrest in children in the UK associated with the use of suxamethonium had been caused by vagal overactivity in non-atropinised patients.

1. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; **77:** 1054.
2. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **10:** 331–49.
3. FDA. *FDC Reports Pink Sheet* 1994; June 13: 16.
4. Hopkins PM. Use of suxamethonium in children. *Br J Anaesth* 1995; **75:** 675–7.

Neuromuscular disorders. Caution is needed if suxamethonium is to be given to patients with neuromuscular disease, since severe complications have been reported.[1] Hyperkalaemia and cardiac arrhythmias or cardiac arrest have been reported after use of suxamethonium in patients with hemiplegia, diffuse intracranial lesions (head injury, encephalitis, ruptured cerebral aneurysm), tetanus, paraplegia, acute anterior horn cell disease, and muscular dystrophies. An exaggerated response to suxamethonium has been reported in the myasthenic syndrome but resistance may occur in patients with neurofibromatosis. Resistance may also occur in patients with myasthenia gravis, but uneventful use has also been reported, although early onset of phase II block is possible in these patients. Muscle contractures and hyperkalaemia may be expected in amyotrophic lateral sclerosis and muscular denervation. Suxamethonium should be avoided in patients with myotonias, as response is unpredictable. It is recommended that suxamethonium is also avoided in hemiplegia, paraplegia, muscular denervation, and muscular dystrophies.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61:** 173–87.

Plasma cholinesterase deficiency. Suxamethonium is normally rapidly hydrolysed by plasma cholinesterase and the clinical effects usually last for only several minutes. Activity of the enzyme varies between individuals and prolonged paralysis following suxamethonium is commonly due to a hereditary or acquired reduction in plasma cholinesterase activity. The genes involved in the control of plasma cholinesterase production are termed usual, atypical (dibucaine-resistant), fluoride-resistant, and silent. About 96% of the population are homozygous for the usual gene. The commonest variant in western populations is the atypical form with about 3 to 4% of the population being heterozygous for this variant. They have a slightly prolonged response to suxamethonium. Homozygotes for the atypical variant have a frequency of about 0.04%. They exhibit markedly prolonged apnoea after a standard dose of suxamethonium but can be readily identified by biochemical tests. The fluoride-resistant and silent variants occur very rarely. A measure of plasma cholinesterase activity can be obtained from the percentage inhibition of the enzyme by the local anaesthetic cinchocaine (commonly known in this context by its American name, dibucaine) to give the **dibucaine number**. Most normal people have a dibucaine number of about 80.

Acquired plasma cholinesterase deficiency is clinically less important than genetically determined deficiency. The enzyme is synthesised in the liver and **severe liver impairment** or malnutrition may cause abnormally low enzyme levels with some prolongation of suxamethonium activity. Reduced enzyme activity may also be found in severe anaemia, burns, cancer, collagen diseases, severe dehydration, severe infections, malnutrition, myocardial infarction, myxoedema, and renal impairment; plasmapheresis or plasma exchange removes significant amounts of plasma cholinesterase.

During **pregnancy** there is a rapid fall in plasma cholinesterase concentration that persists throughout pregnancy and for up to several weeks into the puerperium. The concentration of atypical plasma cholinesterase is also reduced in pregnancy and the puerperium. Some **drugs** reduce plasma cholinesterase synthesis or activity and may prolong suxamethonium paralysis as discussed under Interactions, below.

References.

1. Wood GJ, Hall GM. Plasmapheresis and plasma cholinesterase. *Br J Anaesth* 1978; **50:** 945–9.
2. Evans RT, Wroe JM. Plasma cholinesterase changes during pregnancy: their interpretation as a cause of suxamethonium-induced apnoea. *Anaesthesia* 1980; **35:** 651–4.
3. Lumley J. Prolongation of suxamethonium following plasma exchange. *Br J Anaesth* 1980; **52:** 1149–50.
4. Williams FM. Clinical significance of esterases in man. *Clin Pharmacokinet* 1985; **10:** 392–403.
5. Robson N, *et al.* Plasma cholinesterase changes during the puerperium. *Anaesthesia* 1986; **41:** 243–9.
6. Cherala SR, *et al.* Placental transfer of succinylcholine causing transient respiratory depression in the newborn. *Anaesth Intensive Care* 1989; **17:** 202–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies suxamethonium as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Renal impairment. Suxamethonium chloride may be given in usual doses to patients with renal failure[1,2] although it is usually recommended that it should be avoided if hyperkalaemia is also present (see Effects on Plasma-potassium Concentration p. 2038.2). However, in a retrospective review[3] of 38 patients with serum potassium levels greater than 5.5 mmol/litre given a standard intubation dose of suxamethonium, there were no reports of dysrhythmias or unexpected admissions to the intensive care unit.

Patients with renal failure given repeated doses of suxamethonium did not show an excessive increase in serum potassium; however sinus bradycardia commonly occurred and it was recommended that repeated injections should be avoided in such patients.[2] If necessary, pretreatment with glycopyrrolate or atropine to protect against bradycardia should be considered.

1. Ryan DW. Preoperative serum cholinesterase concentration in chronic renal failure. *Br J Anaesth* 1977; **49:** 945–9.
2. Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: an old question revisited. *Anesth Analg* 2000; **91:** 237–41.
3. Schow AJ, *et al.* Can succinylcholine be used safely in hyperkalemic patients? *Anesth Analg* 2002; **95:** 119–22.

Interactions

Some drugs may interact with depolarising neuromuscular blockers such as suxamethonium. The mechanisms of interaction can include a direct effect on neuromuscular transmission or an alteration of enzyme activity and may result in potentiation or antagonism of neuromuscular block. In general, such interactions are potentially more serious in patients with impaired neuromuscular function or reduced activity of plasma cholinesterase, who are more sensitive to suxamethonium's effects.

Interactions common to competitive and depolarising neuromuscular blockers are covered under Atracurium, p. 2031.3 whereas those specific for depolarising blockers are discussed below.

Antiarrhythmics. See under Atracurium, p. 2031.3.

Antibacterials. See under Atracurium, p. 2032.1.

Anticholinesterases. The action of suxamethonium may be markedly prolonged in patients using eye drops containing *ecothiopate*, a long-acting anticholinesterase that inhibits both acetylcholinesterase and plasma cholinesterase. After systemic absorption of ecothiopate, plasma cholinesterase activity may rapidly be reduced to 5% or less of normal and prolonged apnoea after use of suxamethonium has occurred. On stopping ecothiopate, enzyme activity remains depressed for 1 to 2 months. If a patient has used ecothiopate eye drops in the previous 2 months, suxamethonium should not be given unless normal plasma cholinesterase activity can be shown; a competitive neuromuscular blocker is preferable. Exposure to *organophosphorus insecticides* may also reduce plasma cholinesterase activity resulting in prolonged paralysis after use of suxamethonium; enzyme activity may be totally abolished. Anticholinesterases including *edrophonium*, *neostigmine*, *pyridostigmine*, *rivastigmine*, and possibly *donepezil* enhance the action of suxamethonium, although suxamethonium-induced phase II block can be reversed with an anticholinesterase. Care should be taken if there is a need to use suxamethonium for urgent short procedures after a competitive-neuromuscular-induced block has been antagonised with an anticholinesterase, as the resulting block may be greatly prolonged.[1]

1. Fleming NW, *et al.* Neuromuscular blocking action of suxamethonium after antagonism of vecuronium by edrophonium, pyridostigmine or neostigmine. *Br J Anaesth* 1996; **77:** 492–5.

Antiepileptics. The mean time to recovery from suxamethonium-induced neuromuscular block was 14.3 minutes in 9 patients receiving chronic treatment with *phenytoin* and/or *carbamazepine* compared with 10.0 minutes in 9 patients not receiving antiepileptics.[1]

1. Melton AT, *et al.* Prolonged duration of succinylcholine in patients receiving anticonvulsants: evidence for mild upregulation of acetylcholine receptors? *Can J Anaesth* 1993; **40:** 939–42.

Antineoplastics. *Cyclophosphamide* has been reported to prolong the neuromuscular block produced by suxamethonium through reduction of plasma cholinesterase activity, possibly by alkylation of the enzyme.[1] Since enzyme activity may be reduced by up to 70% for several days to several weeks, it was suggested[2] that suxamethonium should be avoided if possible in patients receiving cyclophosphamide. A more recent case report[3] would also support this suggestion. Other alkylating agents also reported to reduce plasma cholinesterase activity include *chlormethine*, *thiotepa*, and *tretamine*.[2]

1. Walker IR, *et al.* Cyclophosphamide, cholinesterase and anaesthesia. *Aust N Z J Med* 1972; **3:** 247–51.
2. Zsigmond EK, Robins G. The effect of a series of anti-cancer drugs on plasma cholinesterase activity. *Can Anaesth Soc J* 1972; **19:** 75–82.
3. Koseoglu V, *et al.* Acquired pseudocholinesterase deficiency after high-dose cyclophosphamide. *Bone Marrow Transplant* 1999; **24:** 1367–8.

Aprotinin. See under Atracurium, p. 2032.2.

Benzodiazepines. See under Atracurium, p. 2032.2.

Beta blockers. See under Atracurium, p. 2032.2.

Cardiac inotropes. See under Atracurium, p. 2032.3.

Ganglion blockers. See under Atracurium, p. 2032.3.

General anaesthetics. Tachyphylaxis and phase II block (see Uses and Administration, p. 2037.2) develop earlier, and after smaller total doses of suxamethonium, when inhalation anaesthetics are used. *Halothane* may increase the incidence of arrhythmias associated with suxamethonium and can potentiate suxamethonium-induced muscle damage.[1] Suxamethonium should be used with caution with other drugs that might produce additive cardiovascular effects. Severe bradycardia and asystole have occurred when used in anaesthetic regimens with *propofol* and opioids such as *fentanyl*.

See also under Interactions of Atracurium, p. 2032.3.

1. Laurence AS, Henderson P. Serum myoglobin after suxamethonium administration to children: effect of pretreatment before iv and inhalation induction. *Br J Anaesth* 1986; **58:** 126P.

Histamine H_2 antagonists. See under Atracurium, p. 2033.1.

Lithium. See under Atracurium, p. 2033.1.

Local anaesthetics. *Procaine*, *cocaine*, and *chloroprocaine* are ester-type local anaesthetics which are hydrolysed by plasma cholinesterase and may competitively enhance the neuromuscular blocking activity of suxamethonium. See also Antiarrhythmics under Atracurium, p. 2031.3.

Magnesium salts. See under Atracurium, p. 2033.2.

MAOIs. Reduction of plasma cholinesterase activity by *phenelzine* has been reported[1] to cause significant prolongation of suxamethonium paralysis. Enzyme activity may be reduced to 10% of normal and recovery can take up to a month. The dosage of suxamethonium may need to be substantially reduced or a competitive neuromuscular blocker used.

1. Bodley PO, *et al.* Low serum pseudocholinesterase levels complicating treatment with phenelzine. *BMJ* 1969; **3:** 510–12.

Metoclopramide. Dose-dependent prolongation of suxamethonium-induced neuromuscular blockade has been reported in patients given metoclopramide.[1,2] The potent inhibitory effect of metoclopramide on plasma cholinesterase may account for this interaction.

1. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; **63:** 348–50.
2. Kao YJ, *et al.* Dose-dependent effect of metoclopramide on cholinesterases and suxamethonium metabolism. *Br J Anaesth* 1990; **65:** 220–4.

Neuromuscular blockers. See under Atracurium, p. 2033.2.

Sex hormones. *Oestrogens* and oestrogen-containing *oral contraceptives* reduce plasma cholinesterase activity[1] possibly due to suppression of hepatic synthesis of the enzyme, but little prolongation of suxamethonium paralysis may be expected since activity is reduced by only about 20%. See also under Atracurium, p. 2033.2.

1. Robertson GS, Aberd MB. Serum protein and cholinesterase changes in association with contraceptive pills. *Lancet* 1967; **i:** 232–5.

Sympathomimetics. *Bambuterol* can inhibit plasma cholinesterase activity and so prolong the activity of suxamethonium.[1] Phase II block has been reported in some patients with abnormal plasma cholinesterase.[2]

1. Staun P, *et al.* The influence of 10 mg and 20 mg bambuterol on the duration of succinylcholine-induced neuromuscular blockade. *Acta Anaesthesiol Scand* 1990; **34:** 498–500.
2. Bang U, *et al.* The effect of bambuterol on plasma cholinesterase activity and suxamethonium-induced neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. *Acta Anaesthesiol Scand* 1990; **34:** 600–604.

Pharmacokinetics

After injection, suxamethonium is rapidly hydrolysed by plasma cholinesterase. One molecule of choline is split off rapidly to form succinylmonocholine which is then slowly hydrolysed to succinic acid and choline. About 10% of suxamethonium is excreted unchanged in the urine. Succinylmonocholine has weak muscle-relaxant properties mainly of a competitive nature.

The gene responsible for the expression of plasma cholinesterase exhibits polymorphism and enzyme activity varies between individuals (see Plasma Cholinesterase Deficiency, under Precautions, p. 2039.1).

Small amounts of suxamethonium cross the placenta.

Reviews.

1. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; **54:** 526–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actirelax; Fosfitone; Succi; ***Austral.***: Scoline†; ***Austria***: Lysthenon; ***Braz.***: Quelicin; Succitrat; Succnil Colin; ***Canad.***: Quelicin; ***Denm.***: Suxameton; ***Fin.***: Sukolin; ***Fr.***: Celocurine; ***Ger.***: Lysthenon; Pantolax; ***Gr.***: Lycitrope; Mioflex; ***India***: Entubate; Midarine; Myorelex; ***Indon.***: Quelicin; ***Irl.***: Anectine; ***Israel***: Succinyl; ***Ital.***: Midarine; ***Jpn***: Relaxin; ***Malaysia***: Ethicoline; ***Mex.***: Anectine†; Uxicolin†; ***Neth.***: Curalest; ***Norw.***: Curacit; ***Philipp.***: Anekcin; Anektil; Quelicin; ***Pol.***: Chlorsuccillin; ***Port.***: Mioflex; ***Rus.***: Dithylin (Дитилин); Lysthenon (Листенон); ***S.Afr.***: Scoline†; ***Singapore***: Ethicholine; ***Spain***: Anectine; Mioflex; ***Swed.***: Celocurin; ***Switz.***: Lysthenon; Midarine; Succinolin; ***Thai.***: Succinyl; ***Turk.***: Lysthenon; ***UK***: Anectine; ***USA***: Anectine; Quelicin.

Pharmacopoeial Preparations

BP 2014: Suxamethonium Chloride Injection;
USP 36: Succinylcholine Chloride for Injection; Succinylcholine Chloride Injection.

Tubocurarine Chloride *(BAN, rINN)*

Cloruro de tubocurarina; Tubocurarina, cloruro de; Tubocurarinchlorid; *d*-Tubocurarine Chloride; (+)-Tubocurarine Chloride Hydrochloride Pentahydrate; Tubocurarine, Chlorure de; Tubocurarini chloridum; Tubocurarinii Chloridum Pentahydricum; Tubokurariinikloridi; Tubokurarinium-chlorid pentahydrát; Tubokurarin-klorid; Tubokurarinklorid; Tubokurarino chloridas; Тубокурарина Хлорид.

(+)-7′,12′-Dihydroxy-6,6′-dimethoxy-2,2′,2′-trimethyltubocuraranium dichloride pentahydrate.

$C_{37}H_{42}Cl_2N_2O_6.5H_2O$=771.7

CAS — 57-95-4 (tubocurarine); 57-94-3 (anhydrous tubocurarine chloride); 6989-98-6 (tubocurarine chloride, pentahydrate).

ATC — M03AA02.

ATC Vet — QM03AA02.

UNII — 900961Z8VR.

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.

USP 36: (Tubocurarine Chloride). A white or yellowish-white to greyish-white, crystalline powder. Soluble 1 in 20 of water and 1 in 45 of alcohol. Store in airtight containers.

Profile

Tubocurarine is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1). It may be obtained from extracts of the stems of *Chondodendron tomentosum* (Menispermaceae) and is one of the active principles of curare, by which name it is sometimes referred to in anaesthetic literature. A transient fall in blood pressure commonly occurs after its use, due in part to ganglionic blockade and the release of histamine; there may also be an increase in heart rate. Tubocurarine chloride is the chloride of (+)-tubocurarine and has been used similarly to other competitive neuromuscular blockers to produce muscle relaxation in various procedures but has largely been replaced by other drugs with fewer cardiovascular effects and a lower potential for histamine release. Tubocurarine chloride has also been used to control the muscle spasms of tetanus (p. 2029.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Decurin†.

Pharmacopoeial Preparations

USP 36: Tubocurarine Chloride Injection.

Vecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de vecuronio; Org-NC-45; Vecuronii Bromidum; Vecuronio, bromuro de; Vécuronium, bromure de; Vecuroniumbromid; Vekuroniumbromid; Vekuronium-bromid; Vekuroniumbromidi; Vekuronyum Bromür; Wekuroniowy bromek; Векурония Бромид.

1-(3α,17β-Diacetoxy-2β-piperidino-5α-androstan-16β-yl)-1-methylpiperidinium bromide.

$C_{34}H_{57}BrN_2O_4$=637.7

CAS — 50700-72-6.

ATC — M03AC03.

ATC Vet — QM03AC03.

UNII — 7E4PHP5N1D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Vecuronium Bromide). White or almost white crystals or crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in acetonitrile; freely soluble in dichloromethane. Store in airtight containers. Protect from light and moisture.

USP 36: (Vecuronium Bromide). White or creamy white crystals, or a crystalline powder. Slightly soluble in water and in acetone; sparingly soluble in alcohol. Store in airtight containers.

Incompatibility. A solution containing vecuronium bromide 1 mg/mL was found to be visually incompatible with furosemide.[1] For incompatibilities of competitive neuromuscular blockers in general, see under Atracurium on p. 2030.1.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.

Stability. In a stability study,[1] solutions of vecuronium bromide 1 mg/mL in preservative-free sterile water for injection were stable for at least 21 days when stored in polypropylene syringes at 23 to 25 degrees or at 3 to 5 degrees.

1. Johnson CE, Cober MP. Stability of vecuronium in sterile water for injection stored in polypropylene syringes for 21 days. *Am J Health-Syst Pharm* 2007; **64:** 2356–8.

Uses and Administration

Vecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1).

After intravenous injection muscle relaxation occurs within about 1.5 to 2 minutes and lasts for about 20 to 30 minutes.

Vecuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The usual initial dose for intubation in adults is 80 to 100 micrograms/kg by intravenous injection, although reduced initial doses of 30 to 50 micrograms/kg are suggested after the use of suxamethonium. Higher initial doses ranging from 150 to 300 micrograms/kg have sometimes been used for other procedures. However, it is recommended that the dose should not exceed 100 micrograms/kg in caesarean section or neonatal surgery. Maintenance doses of 20 to 30 micrograms/kg may be given as required during prolonged procedures; in the USA a lower maintenance dose of 10 to 15 micrograms/kg is recommended. Neuromuscular blockade may also be maintained with an intravenous infusion given at a rate of 0.8 to 1.4 micrograms/kg per minute but should be preceded by an initial bolus injection of 80 to 100 micrograms/kg. UK licensed product information recommends that in obese patients the dosage of vecuronium should be reduced taking into account ideal body-weight.

Licensed product information recommends that, in general, children can be given adult doses:

- children up to 1 year may have a more rapid response and the high initial dose for intubation may not be necessary
- neonates and infants below 5 months of age may be more sensitive to vecuronium and it is recommended that they should be given an initial test dose of 10 to 20 micrograms/kg, followed by increments according to response
- the duration of action and recovery is longer in neonates and infants than in children and adults and they may require smaller maintenance doses given less frequently
- dose requirements in children aged 2 to 10 years are higher than for adults and neonates but usually within the ranges given above; the duration of action is also shorter in children and more frequent maintenance doses may be required

Administration in children. For details of uses and dosage of vecuronium bromide in infants and children, see Uses and Administration, above.

Administration in hepatic impairment. Although the manufacturers make no specific recommendations for dosage reduction in hepatic impairment, the duration of action of vecuronium was reported to be significantly prolonged in patients with cholestasis[1] or cirrhosis with oesophageal varices[2] given a dose of 200 micrograms/kg intravenously. Plasma clearance was significantly reduced and the elimination half-life significantly increased from a mean of 58 to 98 minutes.[1] A dose of 150 micrograms/kg was found to have a similar onset and duration of action in patients with hepatic impairment and healthy controls,[2] but a dose of 100 micrograms/kg had a slower onset and slightly shorter duration of action in those with liver disturbance.[3] After a dose of vecuronium, rapid and extensive hepatic uptake occurs, which largely determines its short duration of action. However, as the dose increases this mechanism becomes saturated, and hepatic elimination becomes more important in terminating activity. This would help to explain the variation in results seen with the different doses. Caution is needed if large single doses or repeated doses are given to patients with hepatic impairment.

1. Lebrault C, *et al.* Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. *Br J Anaesth* 1986; **58:** 983–7.
2. Hunter JM, *et al.* The use of different doses of vecuronium in patients with liver dysfunction. *Br J Anaesth* 1985; **57:** 758–64.
3. Bell CF, *et al.* Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985; **57:** 160–8.

Administration in renal impairment. As vecuronium bromide is excreted in urine only in small amounts, it may be given in usual doses to patients with renal failure.[1,2] No clinically significant difference in elimination half-life, clearance, or duration of action were reported[1] between patients with renal failure and those with normal renal function. The onset of neuromuscular block may be slightly slower in renal failure[2] and these patients may require an increase of around 20% in the initial dose of vecuronium.[3] However, the dosage requirement for maintenance of neuromuscular block may be reduced by about 20%[3] and slight prolongation of block may occur if dosage is not adjusted, but reversal of residual block with neostigmine is prompt and effective.[2]

Resistance to vecuronium has been reported[2] in 2 anephric patients. Total doses of 620 and 660 micrograms/kg produced maximum neuromuscular block of 77% and 36%, respectively but, despite the high doses used, there were no adverse effects or residual curarisation.

1. Fahey MR, *et al.* Pharmacokinetics of Org NC 45 (Norcuron) in patients with and without renal failure. *Br J Anaesth* 1981; **53:** 1049–53.

2. Hunter JM, *et al.* Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *Br J Anaesth* 1984; **56:** 941–51.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3).

Vecuronium bromide has little histamine-releasing activity although a local reaction at the site of injection has been reported; bronchospasm and anaphylactoid reactions have been rarely reported. It also has little vagolytic or ganglion-blocking activity and produces no significant adverse cardiovascular effects at usual doses.

Caution may be needed in patients with hepatic or renal impairment (see under Uses and Administration, p. 2040.3); dosage adjustments may be required in renal failure.

The elderly. It has been recommended that neuromuscular function should be monitored in elderly patients receiving vecuronium since there may be a risk of prolonged block.[1]

1. Slavov V, *et al.* Comparison of duration of neuromuscular blocking effect of atracurium and vecuronium in young and elderly patients. *Br J Anaesth* 1995; **74:** 709–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vecuronium as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. The proportion of vecuronium crossing the placenta after doses of 60 to 80 micrograms/kg was considered clinically insignificant and its use during obstetric anaesthesia was considered safe for the newborn.[1]

1. Demetriou M, *et al.* Placental transfer of Org NC 45 in women undergoing caesarean section. *Br J Anaesth* 1982; **54:** 643–5.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Pharmacokinetics

On intravenous injection vecuronium is rapidly distributed. It is taken up by the liver and partly metabolised; the metabolites have some neuromuscular blocking activity. It is excreted mainly in bile as unchanged drug and metabolites; some is also excreted in urine. The plasma elimination half-life is reported to range from about 30 to 80 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Galaren; Gobbicuronio; Rivecrum; Vecural; Vecuron; ***Austral.***: Norcuron; Vecure; ***Austria***: Norcuron; ***Belg.***: Norcuron; ***Braz.***: Norcuron†; Vecuron; ***Canad.***: Norcuron†; ***Chile***: Norcuron; ***China***: Norcuron (万可松); Xian Lin (仙林); ***Cz.***: Norcuron; ***Fin.***: Norcuron; ***Fr.***: Norcuron; ***Ger.***: Norcuron; ***Gr.***: Alnorcon; Norcuron; Vecurol; ***Hong Kong***: Norcuron; ***Hung.***: Norcuron; ***India***: Neovec; Norcuron; ***Indon.***: Ecron; Norcuron; ***Irl.***: Norcuron; ***Israel***: Norcuron; ***Ital.***: Norcuron; ***Jpn***: Musculax; ***Malaysia***: Norcuron; ***Mex.***: Bromivec; Curlem†; Nodescron; Norcuron; ***Neth.***: Norcuron; ***Norw.***: Norcuron; ***NZ***: Norcuron; ***Philipp.***: Norcuron; Noruvec; Vecuron; ***Pol.***: Norcuron; ***Port.***: Norcuron; ***Rus.***: Norcuron (Норкурон); ***S.Afr.***: Muscuron; Norcuron; ***Singapore***: Norcuron†; ***Spain***: Norcuron; ***Swed.***: Norcuron†; ***Switz.***: Norcuron; ***Thai.***: Norcuron; ***Turk.***: Blok-L; Norcuron; ***UK***: Norcuron; ***Ukr.***: Norcuron (Норкурон)†; ***USA***: Norcuron†; ***Venez.***: Prorelax; Vecuron.

Nutritional Agents and Vitamins

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The principal constituents of food are carbohydrates, fats, minerals, proteins, vitamins, indigestible fibre, and water. Energy is provided by the metabolism of carbohydrates, fats, surplus protein, and alcohol.

Carbohydrates found in foods may be classified according to their degree of polymerisation into three main groups, namely sugars, oligosaccharides, and polysaccharides; all of these are made up only of carbon, hydrogen, and oxygen. Sugars can be further subdivided into *monosaccharides* (single-molecule sugars), such as fructose and glucose, *disaccharides* (whose molecules consist of two monosaccharides joined together), such as lactose and sucrose, and *sugar alcohols* (polyols) such as sorbitol and mannitol. *Oligosaccharides* typically consist of 3 to 9 monosaccharides joined together, and include maltooligosaccharides such as maltodextrins. *Polysaccharides* consist of many monosaccharides joined together and include starches and non-starch polysaccharides such as cellulose. Non-starch polysaccharides are the major fraction of dietary fibre, and many authorities now consider this term to be preferable to dietary fibre.

Fats have the same elemental composition as carbohydrates, but with a lower proportion of oxygen. Dietary fat is usually in the form of triglycerides, esters of glycerol with three fatty acid molecules. Essential fatty acids are ones that cannot be made in the body and which must be supplied by the food.

Proteins are made up of carbon, hydrogen, oxygen, and nitrogen; most proteins also contain sulfur and some contain phosphorus. They are required for the regulation of body processes such as growth and tissue maintenance. Excess protein can be converted into carbohydrate and used to provide energy.

Proteins consist of chains of **amino acids** of which there are *essential* and *non-essential* types. Essential amino acids (indispensable amino acids) cannot be synthesised in sufficient amounts in the body and must therefore be present in food; non-essential amino acids can be synthesised in the body. There are eight essential amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Arginine and histidine are also essential for infant growth while synthesis of cysteine, taurine, and tyrosine may be inadequate in premature infants.

Several inorganic elements, or minerals, are essential dietary constituents; those which are required in relatively small amounts are known as **trace elements** (see p. 2045.3). Their main function is to act as essential cofactors in various enzyme systems.

Vitamins and their general role in health are described p. 2045.3.

Dietary Modification

Infants, children, elderly people, and pregnant or lactating women have particular nutritional requirements, but in most cases, provided that they are in good general health, adjustment to intake is all that is required rather than extensive modification or supplementation.

Dietary modification is important in the management of some disorders. Calorie restriction is fundamental to the management of obesity, although it may be difficult to motivate patients to accept long-term changes to their eating habits, and some fashionable diets are at best of little value.

The role of diet in the aetiology of cardiovascular disorders (such as salt intake in hypertension and fat intake in ischaemic heart disease) is recognised to be of importance and has lead to public health campaigns for healthier eating patterns.

Dietary modification is also an accepted part of the management of diabetes mellitus, while protein restriction is important in the management of uraemia or hepatic encephalopathy.

There are also metabolic disorders such as phenylketonuria, or forms of intolerance to dietary components, such as coeliac disease, in which the diet must be modified to exclude or drastically reduce certain food components.

Amino acid metabolic disorders. Various inborn errors of amino-acid metabolism are known. They are not common but their consequences are often serious or fatal. Although in some cases there is no effective treatment, early diagnosis is important as some conditions can be managed by dietary modification and/or the use of vitamins. Two of the better known syndromes, homocystinuria and phenylketonuria, are discussed briefly below. Cystinosis, another disorder of amino acid metabolism, is discussed on p. 2555.1. Urea cycle disorders are discussed under Hyperammonaemia on p. 2049.3.

Homocystinuria. Homocystinuria in its classical form is an autosomal recessive disorder in which a genetic deficiency of the enzyme cystathionine synthetase (cystathionine β-synthase), results in accumulation of homocysteine (oxidised extracellularly to homocystine).[1,2] Manifestations may include mental retardation, atherosclerosis, thromboembolism, osteoporosis, and ocular symptoms including lens dislocation, glaucoma, cataract, and retinal detachment.[2] Dietary restriction of methionine with cystine supplementation has been used for treatment; some patients may respond to treatment with B vitamins (pyridoxine, cobalamins, and folic acid),[1-3] or to betaine.[2-4] Compliance with betaine is often poor, however; choline, which is converted to betaine by the liver, has also been given, although experience with its use is limited.[3]

Phenylketonuria. Phenylketonuria is an autosomal recessive disorder that is usually due to a defect in the enzyme phenylalanine hydroxylase. This results in raised blood concentrations of phenylalanine in the neonate, and if untreated produces a syndrome of skin rash, depigmentation, hypertonia, seizures, and severe mental retardation.[5,6] Variants of phenylalanine hydroxylase deficiency include atypical or mild phenylketonuria and hyperphenylalaninaemia; some patients have an inherited defect in the metabolism of tetrahydrobiopterin causing a 'malignant phenylketonuria'.[7]

The disease is controlled by use of a diet very low in phenylalanine,[5,8,9] which if started early can permit relatively normal intellectual development. Protein substitutes are recommended, but the optimal dose remains to be determined; there is some evidence that phenylalanine tolerance increases, and blood phenylalanine levels decrease, when total protein intake from the protein substitute is increased.[10] Controversy exists as to whether dietary restrictions may eventually be relaxed,[7,9] and most consider lifelong metabolic control necessary.[5,11] Metabolic control is important in pregnant women as the consequences of fetal exposure to high phenylalanine concentrations include microcephaly, mental deficiency, and congenital heart disease.[5,12-14]

No consensus exists as to optimal blood concentrations of phenylalanine, although frequent monitoring is necessary. In the UK and USA, values between 2 and 6 mg per 100 mL are usually recommended for neonates, children up to age 12, and pregnant women; for patients over 12 years, concentrations between 2 and 10 mg per 100 mL have been advocated.[5]

High-dose tyrosine does not appear to be an effective alternative to a diet low in phenylalanine.[15-19] Sapropterin (p. 2610.2) is a synthetic form of tetrahydrobiopterin that has been used, with dietary phenylalanine restriction, neurotransmitter replacement, and folinic acid, to treat malignant phenylketonuria;[7,20] it has also shown some promise for the treatment of maternal phenylketonuria.[21,22] Some have suggested sapropterin may even replace a low-phenylalanine diet in certain patients.[23] Enzyme replacement or substitution are under investigation.[6,7,14,24]

1. Isherwood DM. Homocystinuria. *BMJ* 1996; **313:** 1025–6.
2. Yap S. Classical homocystinuria: vascular risk and its prevention. *J Inherit Metab Dis* 2003; **26:** 259–65.
3. Walter JH, *et al*. Strategies for the treatment of cystathionine β -synthase deficiency: the experience of the Willink Biochemical Genetics Unit over the past 30 years. *Eur J Pediatr* 1998; **157** (suppl): S71–S76.
4. Lawson-Yuen A, Levy HL. The use of betaine in the treatment of elevated homocysteine. *Mol Genet Metab* 2006; **88:** 201–7.
5. National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: screening and management, October 16-18, 2000. *Pediatrics* 2001; **108:** 972–82. Also available at: http://pediatrics.aappublications.org/cgi/reprint/108/4/972.pdf (accessed 13/01/06)
6. Kim W, *et al*. Trends in enzyme therapy for phenylketonuria. *Mol Ther* 2004; **10:** 220–4.
7. Hanley WB. Adult phenylketonuria. *Am J Med* 2004; **117:** 590–5.
8. Medical Research Council. Report of the Medical Research Council Working Party on Phenylketonuria. Recommendations on the dietary management of phenylketonuria. *Arch Dis Child* 1993; **68:** 426–7.
9. Poustie VJ, Wildgoose J. Dietary interventions for phenylketonuria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley: 2010 (accessed 24/05/10).
10. MacDonald A, *et al*. Protein substitutes for PKU: what's new? *J Inherit Metab Dis* 2004; **27:** 363–71.
11. Cederbaum S. Phenylketonuria: an update. *Curr Opin Pediatr* 2002; **14:** 702–6.
12. Rouse B, *et al*. Maternal phenylketonuria syndrome: congenital heart defects, microcephaly, and developmental outcomes. *J Pediatr* 2000; **136:** 57–61.
13. Rouse B, Azen C. Effect of high maternal blood phenylalanine on offspring congenital anomalies and developmental outcome at ages 4 and 6 years: the importance of strict dietary control preconception and throughout pregnancy. *J Pediatr* 2004; **144:** 235–9.
14. American Academy of Pediatrics, Committee on Genetics. Policy statement: maternal phenylketonuria. *Pediatrics* 2008; **122:** 445–9. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;122/2/445.pdf (accessed 20/04/09)
15. Pietz J, *et al*. Effect of high-dose tyrosine supplementation on brain function in adults with phenylketonuria. *J Pediatr* 1995; **127:** 936–43.
16. Smith ML, *et al*. Randomised controlled trial of tyrosine supplementation on neuropsychological performance in phenylketonuria. *Arch Dis Child* 1998; **78:** 116–21.
17. Poustie VJ, Rutherford P. Tyrosine supplementation for phenylketonuria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley: 1999 (accessed 13/01/06).
18. van Spronsen FJ, *et al*. Phenylketonuria: tyrosine supplementation in phenylalanine-restricted diets. *Am J Clin Nutr* 2001; **73:** 153–7.
19. van Spronsen FJ, *et al*. Phenylketonuria: tyrosine beyond the phenylalanine-restricted diet. *J Inherit Metab Dis* 2001; **24:** 1–4.
20. Michals-Matalon K. Sapropterin dihydrochloride, 6-R-L-erythro-5,6,7,8-tetrahydrobiopterin, in the treatment of phenylketonuria. *Expert Opin Invest Drugs* 2008; **17:** 245–51.
21. Trefz FK, Blau N. Potential role of tetrahydrobiopterin in the treatment of maternal phenylketonuria. *Pediatrics* 2003; **112:** 1566–9.
22. Koch R. Maternal phenylketonuria and tetrahydrobiopterin. *Pediatrics* 2008; **122:** 1367–8.
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24. Sarkissian CN, Gámez A. Phenylalanine ammonia lyase, enzyme substitution therapy for phenylketonuria, where are we now? *Mol Genet Metab* 2005; **86** (suppl 1): S22–S26.

Cardiovascular disease. Modification of the diet may be helpful in patients with, or at risk of, cardiovascular disease. In patients with hypertension (p. 1251.1), reduction in salt intake may be tried before starting drug therapy or used as an adjunct to such therapy. Reduction in the total intake of dietary fat, and in particular of saturated fatty acids, is considered important for both the general population and those considered at high risk of ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1). An increased intake of long chain n-3 polyunsaturated fatty acids has been recommended and also a restriction on *trans* fatty acids. Dietary cholesterol should be restricted although it may make less of a contribution to plasma cholesterol levels than dietary saturates.[1-3]

For discussion of the possibility that antoxidant vitamins may reduce the risk of ischaemic heart disease see under Vitamins, p. 2047.1. The link between folic acid,

homocysteine, and ischaemic heart disease is discussed on p. 2063.3.

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Coeliac disease. Coeliac disease (gluten-sensitive enteropathy; coeliac sprue) is an inflammatory disorder of the small intestine that results from an immunological reaction to the protein fraction of gluten (p. 2517.2). The inflammation leads to mucosal atrophy with subsequent malabsorption, although the extent and severity of mucosal inflammation varies widely, and some patients are asymptomatic. In adults, anaemia and mild gastrointestinal symptoms that may be confused with irritable bowel syndrome are the usual symptoms. In infants and children there may be growth retardation or failure to thrive, and gastrointestinal symptoms may be more marked. Other nutritional deficiencies, including calcium malabsorption leading to osteopenia, may also occur, and mouth ulcers are also common. Provisional diagnosis usually involves serological tests for IgA anti-transglutaminase 2 or antiendomysial antibodies, and multiple intestinal biopsies.

Treatment of coeliac disease involves a strict, life-long, gluten-free diet. Nutritional supplements may be necessary at the start of treatment but can usually be stopped once mucosal recovery has occurred. Diagnosis is confirmed by clinical improvement or normalisation of the mucosa on repeat biopsy after 3 to 4 months. Dermatitis herpetiformis (p. 1683.2) is a non-gastrointestinal manifestation of coeliac disease. Patients may have no gastrointestinal symptoms, although mucosal abnormalities are generally apparent on biopsy. These patients also respond to a gluten-free diet.

Coeliac disease is associated with other auto-immune diseases, including type 1 diabetes, thyroid disease, and IgA deficiency. Patients with coeliac disease have an increased incidence of small-bowel lymphoma and a slight increase in the incidence of some other gastrointestinal cancers. There is some evidence that this incidence is reduced in patients maintaining a strict diet.

Patients who do not respond to or relapse while on a strict gluten-free diet are considered to have refractory coeliac disease, which can be classified as type 1 or 2. Type 1 is responsive to corticosteroids and other immunosuppressants and only rarely evolves into enteropathy-associated T-cell lymphoma, whereas type 2 is considered a premalignant condition with about half of patients developing T-cell lymphoma within 5 years of diagnosis. Refractory type 2 coeliac disease and T-cell lymphoma is treated with cytotoxic chemotherapy (see Lymphomas, p. 695.3), although results have been disappointing; autologous haematopoietic bone marrow transplantation has induced remissions in some patients, although relapses have occurred.

Alternative or adjunctive treatments to a gluten-free diet are being investigated. Therapies with an intraluminal action aim to reduce gluten immunogenicity by modifying wheat strains or pretreating flour, or preventing the uptake of gluten by the intestinal epithelium. Another approach is to modify the immune response; in refractory disease or enteropathy-associated T-cell lymphoma, systemic T-cell or cytokine antagonists such as the CCR9 chemokine receptor inhibitor CCX-282 have been tried. Desensitisation or attempted restoration of tolerance to gluten is also being studied.

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Diabetes mellitus. Dietary control is important in both type 1 and type 2 diabetes mellitus (p. 459.1). The goals of dietary modification are to maintain glucose concentrations in the normal range or as close to normal as possible, and a lipid and lipoprotein profile and blood pressure that reduce the risk of macrovascular disease.

Fish odour syndrome. Fish odour syndrome (trimethylaminuria) is an inherited metabolic disorder in which there is impaired hepatic *N*-oxidation of trimethylamine. Trimethylamine is formed in the intestine by bacterial degradation of foods rich in choline and carnitine, and is readily absorbed from the gut. If not oxidised in the liver, it is excreted in the breath, urine, sweat, and vaginal secretions. It smells of rotting fish, and has a high olfactory potency. Treatment involves dietary modification to avoid choline-rich foods such as eggs, liver, peas, soya beans, and sea fish. Short-term treatments to reduce the intestinal flora, and thereby decrease the production of trimethylamine, are occasionally used; examples include metronidazole, neomycin, and lactulose.

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Hepatic encephalopathy. Restriction of dietary protein intake is a mainstay of the treatment of hepatic encephalopathy, but care is required to avoid malnutrition (see p. 1808.2).

Inflammatory bowel disease. In inflammatory bowel diseases (p. 1808.3) dietary modification or **supplementation** may often be necessary to maintain the nutritional status of the patient. Specific nutritional problems include protein deficiency, fluid and electrolyte depletion, iron deficiency, and deficiencies of certain minerals, vitamins and trace elements, such as magnesium, calcium and vitamin D, vitamin K, and folic acid.[1,2] Supplementation may be oral, nasogastric, or parenteral. In general, although they are considered to have equal efficacy,[3] enteral feeding is preferred to parenteral nutrition. The latter is generally reserved for those who cannot tolerate the enteral route, for perioperative use, or for specific clinical circumstances such as bowel obstruction or perforation.[4,5]

Improvement in nutritional status, elimination of dietary antigens, down-regulation of inflammatory cytokines or up-regulation of anti-inflammatory cytokines, or alteration in bacterial flora are also possible mechanisms whereby nutritional therapy may exert a **therapeutic** effect in inflammatory bowel disease.[5-7] Although controversial as primary therapy, enteral feeding, particularly with elemental diets, has been shown to be effective in the treatment of active *Crohn's disease*,[8] but probably less effective than corticosteroids.[9-11] It may also have some benefit in maintaining remission.[12] There are beneficial effects in children with growth failure, which is exacerbated by corticosteroids,[13,14] and some consider enteral nutrition the first choice of management in paediatric patients with Crohn's disease.[3] Combining an elemental diet with low-dose corticosteroids has also been suggested as a therapeutic approach in children, although it is as yet untested.[14] Adult patients with Crohn's disease who are considered candidates for enteral nutrition include those on potentially high cumulative corticosteroid doses, or who are corticosteroid-refractory or corticosteroid-intolerant, or those at high risk for osteoporosis.[5]

Data are considered insufficient to assess the efficacy of enteral nutrition in *ulcerative colitis*.[5,7]

The term **elemental diet** was originally coined to describe diets containing free amino acids and glucose and was often prefixed by the phrase 'chemically defined'. However, it came to embrace diets whose nitrogen sources included peptides and were often also called predigested diets. It was suggested[15] that the term elemental diet could be used for either type but that for those with an amino acid nitrogen source the term chemically defined elemental diet should be used whereas for those with a peptide nitrogen source predigested elemental diet was suitable. The term polymeric diet should be used for those diets with a whole protein nitrogen source (such as milk or soya).

There appears to be little difference between formulas in terms of therapeutic response, although compliance may be better with polymeric feeds due to the unpalatability of elemental diets.[3,5,13] Several different elemental diets are available; some contain long-chain triglycerides as the fat source, but for patients with impaired fat digestion, medium-chain triglycerides are considered preferable.[1] There is some suggestion that the effectiveness of enteral diets in treating active Crohn's disease might relate to the fat rather than nitrogen composition,[1,3,7] with less inflammation occurring with those containing the fewest long-chain triglycerides.[1]

Other potentially beneficial components of diets for Crohn's disease include omega-3 triglycerides, which may have beneficial effects on inflammatory processes, and in achieving remission;[4,14,16] no clinical benefit has been seen with fatty acid or dietary fish oil supplementation in active ulcerative colitis.[17] Short-chain fatty acids have been proposed as a means of increasing butyrate levels, which may have a direct anti-inflammatory effect on the colon; butyrate enemas have shown benefit in ulcerative colitis.[5,13,17] The use of a substrate ('pre-biotic') to deliver short-chain fatty acids, or directly delivering probiotics to the intestine, have also been proposed.[5,17] Glutamine has been suggested as being beneficial for epithelial integrity of the small intestine,[1,16] although useful data are lacking.[1,4,5]

Much interest also surrounds the use of **growth factors** in enteral formulas, such as epidermal growth factor or transforming growth factor-β, which may have anti-inflammatory actions on the gut mucosa.[7]

Elimination diets, whereby foods are slowly reintroduced once remission has been achieved, aim to reduce relapse rates in Crohn's disease, but the process is prolonged and complicated.[1,3] In a study of patients with ulcerative colitis in remission, consumption of red and processed meat, protein, or alcohol increased the likelihood of relapse;[18] these foods are rich sources of sulfur or sulfate, and sulfide toxicity may be important in the pathogenesis of ulcerative colitis.[17] There is also some suggestion that titanium may be harmful in Crohn's disease, and diets low in titanium have been advocated, with preliminary data suggesting a benefit.[3]

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Malignant neoplasms. For a discussion of the possible link between an increased intake of antoxidant vitamins and a reduced risk of developing malignancies, see under Vitamins, p. 2047.3.

Obesity. Obesity is relatively common in the developed world, and is accompanied by an increased risk of cardiovascular disease, diabetes, and other disorders. Methods such as dietary modification, behaviour therapy, and exercise with adjunctive drug therapy, where indicated (see p. 2315.1) can produce weight loss, but the essence of treatment is a reduction in calorific intake, usually by about 300 to 500 kcal daily in patients with a body-mass index (BMI) of 27 to 35, and 500 to 1000 kcal in those with a BMI greater than 35. This would be expected to produce a weight loss of about 0.25 to 1 kg weekly. Very low calorie diets (less than 600 to 800 kcal daily) should only be considered after the failure of determined attempts to lose weight by conventional calorie restriction. For weight loss to be achieved and sustained, eating behaviour must be permanently modified, which may pose difficulties. The proportion of calories from fat in particular, and also alcohol and sugars should be reduced and those from high carbohydrate foods increased. It is obviously important to maintain an adequate intake of essential nutrients.

Artificial sweeteners or other non-sucrose sweeteners are often used as part of weight-reducing diets.

Renal failure. Low-protein diets may be of value in preventing or slowing the progression of chronic renal failure (p. 1779.1). Patients with renal failure who adopt a protein-restricted diet have fewer symptoms of uraemia than those on a normal diet. Some results have also suggested that protein restriction can slow the progression of renal failure, but the value of low-protein diets in delaying the onset of end-stage renal disease has been the subject of much controversy.[1] Two large multicentre studies provided little evidence of a substantial benefit,[2,3] but a systematic review[4] provided support for dietary protein restriction in adults, although another such review[5] could not find evidence of benefit in children. *Animal* studies

suggest that modification of the protein source from animal to soya protein might slow renal disease progression, especially at high intakes.[6]

Generally, low-protein diets providing between 600 to 800 mg/kg daily have been recommended,[1,7-9] although a very low-protein diet providing 300 mg of vegetable origin protein, supplemented with a mixture of essential amino acids, has been recommended for highly motivated patients with advanced renal failure.[1]

Once the patient starts dialysis, however, protein losses through the dialysis membrane or peritoneum may require an increase of protein intake to between 1.2 and 1.3 g/kg daily.[7,9] Because energy intake needs to remain constant, food selection has to change qualitatively.[7] Sodium, potassium and phosphate intake also need to be controlled.[7,9] During dialysis, restricting dietary phosphate while maintaining sufficient protein intake may be difficult, and modification of the protein source may be necessary.[10]

After kidney transplantation, if renal function stabilises, protein restriction is again advisable;[7] between 1.3 and 1.5 g/kg daily is recommended initially, then 1 g/kg daily for maintenance.[9] However, adverse effects of immunosuppressant drugs may complicate the dietary targets, with the patient at risk of diabetes, dyslipidaemia, and possible hypertension.[7] The importance of salt restriction and reduction of the sodium dialysate content in controlling hypertension in renal patients has been emphasised.[11]

It has been suggested that the benefit of other interventions such as the use of ACE inhibitors,[12] as well as the difficulties in obtaining patient compliance with such a restrictive diet,[13] may have limited the benefits to be obtained from protein restriction, but there is also evidence that response and outcome vary depending on the cause of renal failure.[3,14]

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Enteral and Parenteral Nutrition

Malnutrition of varying degrees is not uncommon in hospitalised patients, and some form of nutritional support is important in patients who cannot eat an adequate normal diet. Such support should provide for the patient's requirements for energy, in the form of carbohydrate and fat, nitrogen as amino acids or protein, water and electrolytes; where appropriate, vitamins and trace elements should also be supplied. Indications for nutritional support may include unconsciousness, obstruction or inability to swallow, inflammatory bowel disease, fistula, short bowel syndrome, and weakness and malnutrition associated with trauma, surgery, or malignant disease. If possible, nutritional support should be by the enteral route; it is easier, more physiological, and less prone to complications than the parenteral route.

Enteral nutrition includes feeding by mouth, by nasogastric or nasoenteric tube, or directly into a gastrostomy or other enterostomy. It may be supplemental, if normal food intake is possible but inadequate, or total. Individual patients vary in their requirements according to age, size, and metabolic state, but a diet supplying 2000 to 3000 kcal of energy and 10 to 15 g of nitrogen (as 60 to 90 g of protein) in 2 to 3 litres of fluid is fairly typical; because absorption from the gastrointestinal tract is incomplete requirements are higher than by the parenteral route. Preparations containing whole protein (often derived from milk or soya) are generally preferred; elemental diets, in which nitrogen is supplied as amino acids or oligopeptides, are less well tolerated and less palatable, although they may have a role in impaired digestion or when a zero-residue diet is desired.

Although preferred to parenteral nutrition, enteral feeding is not without complications. Patients may be at risk of oesophagitis, aspiration, and regurgitation as a result of the tube insertion; other potential problems include diarrhoea, nausea and vomiting, gastric retention, hyperglycaemia, fluid and electrolyte disturbances, and microbial contamination of the feed regimen.

Parenteral nutrition is reserved for situations in which it is impossible to meet nutritional requirements by the enteral route. Like enteral nutrition it may be given supplementally or as the sole source of body requirements (total parenteral nutrition or TPN). It is normally given via a dedicated central venous catheter. However, peripheral veins are increasingly used for short-term feeding. This reduces some complications and insertion is less complex, but because of the risk of thrombophlebitis the feeds used should have low osmolality and neutral pH. Other measures to delay the development of peripheral thrombophlebitis are mentioned under Adverse Effects and Precautions, p. 2045.1.

The formulation of the nutritional solution must be adjusted according to the patient's requirements. The solution should supply sufficient energy to allow for the resting energy expenditure (around 25 kcal/kg in the average adult) but must also take into account any increased energy expenditure of illness. Conversely, starvation can reduce resting metabolism and energy requirements. Various formulae exist for the calculation of energy expenditure in patients. Energy is best supplied in the form of carbohydrate (at least 30%, and preferably 60% of energy requirements should be in this form) and fat. Glucose is the optimal carbohydrate energy source, while fat is supplied as a lipid emulsion, often of soya oil. Nitrogen is supplied as amino acids, but to ensure that these are used for protein synthesis rather than as sources of energy it is important to control the ratio of non-protein energy to nitrogen in the solution. A ratio of 150 to 200 kcal per g of nitrogen is usually considered optimal but in hypercatabolic patients (e.g. in sepsis) lower ratios of 120 kcal per g or less may be appropriate. All essential amino acids are supplied although there is some variation between solutions as to which non-essential amino acids are present.

Parenteral nutrition must also supply the patient's requirements for fluid, essential electrolytes such as sodium, potassium, magnesium, bicarbonate, and calcium (as well as phosphate, since glucose infusion may provoke hypophosphataemia), and, particularly if treatment is prolonged, vitamins and trace elements. If glucose loading produces signs of hyperglycaemia insulin may be added to correct it.

The major complication of parenteral nutrition is bacterial colonisation of the catheter, which can lead to septicaemia. Other problems may include venous thrombosis or air embolism, extravasation due to misplacement of the catheter tip, and metabolic disturbances. Adverse effects of overfeeding include respiratory and hepatic dysfunction. Complications of long-term total parenteral nutrition include gallbladder sludging, gallstones, cholestasis, and abnormal liver function tests.

Stability and compatibility. The complex nature of solutions for parenteral nutrition renders them susceptible to compatibility problems.[1-18] Stability is dependent upon several factors including pH and relative concentrations of the components. Amino acids exert a buffering effect on the overall pH of mixed solutions containing amino acids, glucose, and fat emulsions but amino acids with glucose undergo the Maillard reaction (browning) and the life of combined solutions is therefore limited. Solutions containing electrolytes, particularly divalent cations, are not stable, and aggregation will eventually occur. Additives should be added only if there is known compatibility, and any additions performed aseptically before the start of the infusion.

The most significant cause of precipitation is higher concentrations of calcium and phosphate,[13,18] and the most important factor governing calcium phosphate precipitation is the final pH of the mixture. The pH is itself determined by several factors, including the commercial source of the amino acid infusion, and the final amino acid and glucose concentrations. The use of organic phosphate compounds may reduce the likelihood of precipitation. Trace element precipitation may also occur and amino acid infusions can contain detectable quantities of trace elements as contaminants. The most significant cause of chemical instability is the degradation of specific vitamins, through exposure to light or binding with the plastic of the bag or giving sets. Two particular reactions, the oxidation of ascorbic acid, and the reduction of thiamine, are of concern.

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Uses. Parenteral and enteral nutrition now have an established place either for supplemental use or for providing total nutritional requirements in many conditions. General reviews as well as those pertaining to special groups of patients or disorders have been published.[1-26]

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Adverse effects and precautions. *ENTERAL NUTRITION.* Complications of enteral feeding can arise from mechanical, gastrointestinal, metabolic or other causes, such as infection or aspiration.[1] The most common nutritional complication of enteral feeding is failure to meet nutritional requirements, and overzealous feeding may lead to the 'refeeding syndrome' manifested by glucose intolerance, fluid retention, and electrolyte imbalances.[2-5] High-protein formulas with low water intake may also cause this syndrome.[1] These rapid *metabolic* and electrolyte changes can lead to severe or even fatal cardiopulmonary and neurological problems.[6] To avoid these problems, low levels of feeding for the first few days have been recommended; about 20 kcal/kg daily has been suggested but even this may be too high, especially in patients with existing

All cross-references refer to entries in Volume A

electrolyte abnormalities, and about 10 kcal/kg daily may be more suitable for high-risk patients;[3,7] UK guidelines[3] suggest that a maximum of 5 kcal/kg daily may be considered in extreme cases (e.g. patients with a BMI less than 14 kg/m^2 or negligible intake for more than 15 days). Mechanical or *physical complications* include displacement or clogging of the tube, or patient discomfort.[1,2,6-8] Many of the problems encountered can be avoided by using a fine bore tube, giving the feed by continuous infusion, and by careful monitoring of the patient for metabolic abnormalities.[9] However, tubes become clogged more often if the calibre of the tube is small, the tube is long, placed in the stomach, the feeding continuous, or if medication is given through the tube.[2,8] Inadequate flushing and protein precipitation may also occur.[6]

Positioning the tube in the small bowel rather than the stomach has been suggested to reduce the incidence of *aspiration*,[2,8,10] although few studies have been done comparing intraduodenal and intragastric feeding in terms of clinical outcomes, and there are concerns about appropriate placement, infection, and reflux.[11] A meta-analysis[12] failed to find any clinical benefit of post-pyloric feeding over gastric feeding in terms of the incidence of pneumonia, length of stay, and mortality; the study was limited by a relatively small number of patients, and did not include patients considered at high risk of aspiration. Prokinetic drugs such as metoclopramide, or erythromycin, have been used to promote gastric emptying and reduce residual gastric volumes.[10-12]

Complexation of the nutrients with aluminium-containing antacids, also given via the tube, may occur and this *deposition* of solid masses may cause oesophageal obstruction.[13]

Diarrhoea in patients receiving enteral nutrition may not necessarily be caused by the tube feeding itself;[14,15] malabsorption, infections and microbial contamination, underlying disease, and concomitant drug therapy can be possible contributors.[1,2,7,16,17] However, enteral feeding has been shown to be associated with increased colonic secretion, which can be reversed by infusion of short-chain fatty acids.[18] Because colonic microflora may play a role in the pathogenesis of diarrhoea associated with enteral feeds, manipulation of the microflora using pre- or probiotics has been suggested as a means of reducing the incidence, duration or severity thereof, and some enteral feeding formulas contain prebiotics. However, few studies have investigated the effect on diarrhoea, and further research is warranted.[17]

While enteral tube feeding and the presence of a nasogastric tube are risk factors for *infection*, optimal nourishment through enteral feeding in high-risk patients unable to tolerate oral nutrition may also improve their immune status.[19]

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PARENTERAL NUTRITION. A common complication of parenteral nutrition is *infection* of the intravenous feeding catheter site,[1-3] which can lead to septicaemia. Infection and colonisation of central venous catheters may be reduced if the catheter is tunnelled through subcutaneous tissue before emerging through the skin.[4] Strict aseptic techniques should be used[1] for changing the dressing or bags containing the nutrient fluids. Misplacement of the catheter has been reported.[3,5] Precipitation of minerals, lipids, and medications can cause line occlusion.[3]

Thrombophlebitis can occur after the use of either peripheral or central veins. Although it has been suggested that infusion of hyperosmolar solutions via a central line is less likely to produce thrombophlebitis, because the feed is immediately diluted by a large volume of blood, major thrombotic complications such as pulmonary embolism and right atrial thrombosis could be more common than hitherto recognised in children and adolescents receiving long term parenteral nutrition via central catheters.[6,7] The use of a fine-bore silicone catheter peripherally may avoid the need for central vein cannulation[8] and there is a lower incidence of thrombophlebitis when fine-bore silicone catheters rather than teflon ones are used for peripheral parenteral nutrition.[9] The use of giving sets with filters may decrease thrombophlebitis during peripheral infusion.[10,11] The addition of heparin or buffer solutions to the feed, and the use of local hydrocortisone and glyceryl trinitrate, have also been reported to prolong the survival of peripheral infusion sites.[11,12] Extravasation may also be a problem, particularly with hyperosmolar solutions, and has led to severe tissue damage; hyaluronidase or thiomucase may be used in the treatment of such extravasation.[13]

Parenteral nutrition may be associated with *atrophic changes* in the mucosal structure and enzymic activity of the intestine, leading to increased permeability with a possible increased risk of bacteraemia and endotoxaemia. These changes, which have been attributed to lack of glutamine (which is unstable in solution), can reportedly be prevented by addition of glutamine-releasing dipeptides to solutions for total parenteral nutrition—see p. 2070.3. Some have questioned the extent of this mucosal atrophy or bacterial translocation associated with parenteral feeding.[14,15]

Prolonged parenteral nutrition has been associated with *hepatobiliary complications*, especially in children;[16,17] cholelithiasis and cholestasis have been reported, with the latter sometimes progressing to liver failure.[18] Although the aetiology is considered multifactorial,[18] contamination of the solution with manganese (see Accumulation under Adverse Effects of Manganese, p. 2081.3) or aluminium[19] has been suggested as one possible cause of the cholestasis.

Aluminium toxicity has also been implicated in the *bone changes*, manifesting as osteomalacia, seen in patients on long-term parenteral nutrition.[3,17] Osteopenia and osteoporosis have also been reported;[17] possible mechanisms include calcium, phosphate, or magnesium deficiencies, vitamin D deficiency or toxicity, vitamin K deficiency, or excessive protein.[3] A review, however, considered the risk to be minimal, with little deleterious effect on cortical bone and an improvement on trabecular bone.[5] Other factors implicated in possible metabolic bone disease include calcium deficiency and vitamin D toxicity.[17]

Other metabolic complications associated with parenteral nutrition include hyperglycaemia, hypoglycaemia, hyperlipidaemia, hypercapnia, acid–base disturbances, and 'refeeding syndrome'.[20] Hyperglycaemia may be due to excessive glucose infusion, and can lead to immunodepression and an increased risk of infection; insulin therapy is indicated if it persists. Hypoglycaemia, although less common, may occur if parenteral nutrition is interrupted or as a result of an insulin overdose. Hyperlipidaemia is caused by excessive fatty acid synthesis from glucose, or impaired lipid clearance. The use of a mixture of medium-chain and long-chain triglycerides (rather than long-chain triglyceride emulsions alone) may result in fewer serum lipid abnormalities since medium-chain triglycerides are oxidised faster than long-chain triglycerides. Overfeeding of total calories and glucose can lead to hypercapnia which can cause acute respiratory acidosis.[20] While most acid–base disturbances are related to the underlying condition, excess chloride or acetate in the parenteral nutrition solution may cause metabolic acidosis or alkalosis, respectively.[17] The 'refeeding syndrome' can occur when severely malnourished patients are given rapid nutritional repletion, leading to fluid and electrolyte imbalances, glucose intolerance, and vitamin deficiencies. These may result in significant or even fatal cardiac, pulmonary, renal, gastrointestinal, and neuromuscular complications. Electrolyte disturbances include sodium retention, hypophosphataemia, hypokalaemia, and hypomagnesaemia; thiamine deficiency may lead to Wernicke's encephalopathy in malnourished patients or in thiamine-deficient patients given high carbohydrate loads.[20]

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Trace Elements

Trace elements are inorganic substances found in small amounts in the tissues and required for various metabolic processes; together with the vitamins (see below) they are sometimes referred to as micronutrients. The elements considered essential are chromium, copper, fluorine, iodine, iron, manganese, molybdenum, selenium, and zinc. Iron, in the form of haem, plays an essential role in oxygen transport while iodine is required by the thyroid for the formation of thyroid hormones; most of the other essential trace elements are cofactors for various enzymes. Boron, nickel, silicon, and vanadium may also be essential, and it has been suggested on the basis of *animal* studies that there might be a requirement for tin.

Well-defined deficiency syndromes exist for copper, iodine, iron, selenium, and zinc; although deficiency of other trace elements is possible, their deficiency syndromes are not well defined because of their ubiquity in the diet. Guidance concerning the intake of various trace elements has been published—see also Human Requirements under Vitamins, p. 2046.1.

References.

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Vitamins

Vitamins are organic substances required by the body in small amounts for various metabolic processes. Most are not synthesised in the body, or are synthesised in small or insufficient quantities. Vitamins are sometimes classified as fat soluble or water soluble. Substances in the vitamin A, D, E, and K groups are generally fat soluble, and biotin, folic acid, niacin, pantothenic acid, vitamins B_1, B_2, B_6, and B_{12}, and vitamin C substances are generally water soluble.

Vitamin deficiency may result from an inadequate diet, perhaps due to increased requirements such as during pregnancy, or may be induced by disease or drugs. Vitamins may be used clinically for the prevention and treatment of specific vitamin deficiency states and details of these uses are provided under the individual drug monographs.

Large doses of vitamins (megavitamin therapy) have been proposed for a variety of disorders, but adequate evidence of their value is lacking. Excessive intakes of most water-soluble vitamins have little effect due to their rapid excretion in urine, but excessive intakes of fat-soluble vitamins accumulate in the body and are potentially dangerous.

Stability. Water-soluble vitamins are liable to degrade in solution especially if exposed to light. Addition of vitamin mixtures to infusion solutions for parenteral nutrition should therefore be carried out as soon as possible before infusion. Solutions should be used within 24 hours of preparation and be protected from light.

Carcinogenicity. For mention of an increased risk of lung cancer in patients receiving betacarotene and vitamin A, and an increased incidence of second primary cancers in patients given vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p. 2047.3. For a dis-

cussion of possible carcinogenic effects in children given vitamin K intramuscularly, see Carcinogenicity, p. 2124.2.

Effects on mortality. Although vitamin supplements have been widely taken in the hope of improving mortality from various diseases, a large systematic review[1] concluded that there was no evidence that antoxidant vitamin supplements improved mortality, and some, such as vitamin A, betacarotene, and vitamin E, might increase it.

For mention of possible adverse effects on mortality with betacarotene supplementation, see Effects on Mortality, p. 2051.3.

For discussion on the effects on mortality with Vitamin A, see p. 2102.1.

For mention of possible beneficial effects of high serum ascorbic acid levels on all-cause mortality, see under Vitamin C, p. 2111.3.

For mention of beneficial effects on mortality with vitamin D supplementation in a mainly elderly population, see UK and US Recommended Dietary Intake, p. 2118.1.

For mention of possible dose-dependent adverse effects on mortality with use of vitamin E, see Effects on Mortality, p. 2121.2.

For discussion of the effects of various antoxidant vitamins on cardiovascular disease and cancer, see Prophylaxis of Ischaemic Heart Disease, p. 2047.1, and Prophylaxis of Malignant Neoplasms, p. 2047.3.

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Human requirements. Vitamins and trace elements are essential nutrients and in many countries guidance has been published concerning their intake.

In the UK various terms are used to define intake:[1]

- estimated average requirement (**EAR**) is used for the requirements of energy, proteins, vitamins, or minerals of a group of people and usually about half will need more and half less than the specified figure
- lower reference nutrient intake (**LRNI**) is applied to proteins, vitamins, or minerals and is that amount that is enough for only a few people who have low needs
- reference nutrient intake (**RNI**) is also applied to proteins, vitamins, or minerals and is an amount that is enough, or more than enough, for about 97% of people in a group
- a safe intake is used to indicate an intake or range of intakes where there is not enough information to estimate EAR, LRNI, or RNI, but rather it is an amount enough for almost everyone but is not so large as to cause undesirable effects
- dietary reference value (**DRV**) is used to cover EAR, LRNI, RNI, and safe intake.

It is emphasised in a 1991 report[1] that these intakes are not meant to be recommendations for any individual or group; they do not reflect either a recommendation that such an amount should be taken daily in the diet or as a supplement. They are intended rather as yardsticks for the assessment of dietary surveys and food supply statistics; to provide guidance on appropriate dietary composition and meal provision; or for food labelling purposes in which case it is envisaged that an EAR will be used.

An Expert Group on Vitamins and Minerals, established in the UK to review data on the safe intake of vitamins and minerals from food and food supplements, recommended the use of safe upper levels (**SULs**). These were the doses of vitamins and minerals that individuals could take daily on a lifelong basis without significant risk to health on the basis of available evidence.[2]

In the USA the National Academy of Sciences has traditionally set recommended dietary allowances (**RDAs**),[3] defined as the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged to be adequate to meet the known nutrient needs of practically all healthy persons. The allowances are amounts that are intended to be consumed as part of a normal diet. However, new dietary reference intakes (**DRIs**) have been developed,[4] which include 3 reference values in addition to the traditional RDA as follows:

- the EAR is the intake that meets the needs of half the individuals in a group
- the adequate intake is the mean intake level that appears to sustain a desired marker of health, and will be set when there is insufficient evidence to establish an RDA
- the tolerable upper intake level is the maximum intake that is not likely to adversely affect health.

WHO[5] has similar definitions for the EAR and the tolerable upper intake level, but uses the term recommended nutrient intake (**RNI**) for the daily intake which meets the nutrient requirements of almost all healthy individuals in an age- and sex-specific group (set at the EAR plus 2 standard deviations).

Information pertaining to the requirements of specific vitamins and minerals is provided under the individual monographs.

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3. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances.* 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
4. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes: applications in dietary assessment.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309071836 (accessed 21/07/08)
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Supplementation. An adequate dietary intake of vitamins is necessary for good health but whether vitamin supplementation in the absence of any demonstrable deficiency is beneficial or even worthwhile remains debatable.

It is generally considered that healthy persons eating a normal balanced diet should have no need for vitamin supplementation.[1,2] A review of the topic[1] pointed out that the vitamins that people chose for self medication are often not the ones that are actually present in inadequate amounts in their diets and that the commercial preparations available often do not make it clear whether the amounts they contain are near the physiological requirements or many times greater. Supplementation should concentrate on groups of people at risk of deficiency such as neonates, who need vitamin K; pregnant and lactating women, who need calcium, folic acid, and iron; and certain groups who need vitamin D; vegans and their infants may require vitamin B_{12} supplements. A multivitamin supplement might be considered for some groups such as the elderly and those with reduced calorie intake.[1,3] However, it might be difficult to find a good multivitamin preparation containing all 13 vitamins but no non-vitamins. Also with many of the multivitamin preparations the doses and ratios varied inexplicably.[1]

A review[4] of supplementation specifically in children concluded that, provided schoolchildren and adolescents eat a wide variety of foods, there was no need for vitamin supplementation. However, it was recommended that supplementation with vitamins A, C, and D should be given to those between the ages of 6 months and 2 years and preferably up to the age of 5 years. Several authorities in different countries have set upper safety limits for vitamins; these vary considerably.[5]

Vitamin and mineral supplementation has been investigated in various disorders (see below). However, a systematic review for the National Institutes of Health in the USA led to the consensus that evidence was insufficient to recommend either for or against the use of multivitamin and mineral supplements to prevent cancer and chronic disease.[6,7] (For a systematic review that concluded against use of antoxidant supplements see Effects on Mortality, above.)

1. Truswell S. Who should take vitamin supplements? *BMJ* 1990; **301:** 135–6. Correction. *ibid.*; 354.
2. Waine C. Vitamin and mineral supplements. *Pharm J* 2001; **267:** 352–4.
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7. NIH State-of-the-Science Panel. National Institutes of Health State-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med* 2006; **145:** 364–71.

EYE DISORDERS. Vitamin therapy has been investigated for the prophylaxis or treatment of various eye disorders. **Vitamin A** is used in the management of xerophthalmia, see p. 2101.1. There is some suggestion of benefit with vitamin A for retinitis pigmentosa, p. 2101.1; results with **vitamin E** are conflicting. Vitamin E has been used for the treatment of retinopathy of prematurity, p. 2120.3. For discussion of the effect of **vitamins C, E, betacarotene**, and **zinc** on age-related macular degeneration, see under Betacarotene, p. 2051.2.

HIV INFECTION AND AIDS. Low serum micronutrient concentrations are common in HIV-positive individuals, especially in the developing world; malabsorption, anorexia, diarrhoea, and increased energy demands contribute to malnutrition,[1,2] which in turn contributes to immune impairment and increased mortality. It is generally agreed that in the setting of poverty and lack of adequate nutrition, provision of food programs and/or some form of supplementation is vital,[3] as an adjunct to antiretroviral therapy,[1,2,4] but the specific benefits of vitamin supplementation are extremely unclear, and recommendations have therefore varied.[1,2,4,5]

Conflicting results have been seen in studies of **vitamin A** supplementation (see p. 2100.2). Other studies have suggested that **multivitamin** supplementation, with or without other micronutrients such as selenium and zinc, might have some benefits,[4] including increases in CD4+ and CD8+ cell counts,[6-8] in some cases with the suggestion that this delayed disease progression[8] or decreased adverse pregnancy outcomes.[7] However, an unexpected increase in genital shedding of HIV-1 has also been reported,[6] and a meta-analysis failed to show that multivitamin supplementation during pregnancy prevented vertical transmission or premature delivery, or improved childhood mortality at 1 year.[5] In contrast, a later systematic review[4] considered that the evidence did suggest some benefits to both pregnant and lactating women and their offspring from maternal multivitamin supplementation, and multivitamins might also be of benefit in patients co-infected with HIV and tuberculosis. However, antiretroviral therapy remained the one intervention that had consistently been shown to reduce morbidity and mortality and improve nutritional status in HIV-infected patients.

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4. Irlam JH, *et al.* Micronutrient supplementation in children and adults with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 22/12/10).
5. Mills EJ, *et al.* Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of randomized trial [sic] including more than 2800 women. *AIDS Res Ther* 2005; **2:** 4.
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8. Fawzi WW, *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; **351:** 23–32.

INFECTION. **Vitamin A** has an important role in the prevention of complications from measles (see p. 2100.3), but evidence for benefit in respiratory-tract infections is less compelling (see p. 2100.3). Some studies show evidence of benefit for **vitamin C** in treating the common cold (p. 951.1), but routine high-dose prophylaxis is not considered justified. **Vitamin E** has shown conflicting results in respiratory-tract infections, see p. 2120.3.

For a discussion of the role of vitamins in HIV infection and AIDS see above.

MENTAL FUNCTION. Giving vitamin and mineral supplements to children was reported in 1988 to increase non-verbal *intelligence*[1] and the topic has since remained highly controversial. In the next 2 years more studies were published but these failed to substantiate the earlier possible effect and concluded that vitamin supplementation did not improve mental functioning or reasoning in children.[2,3] Suggestions were made shortly after these publications that there might be a subset of children with poor nutritional status who would receive some benefit[4] but this again was disputed.[5]

In 1991 another study was published,[6] this time coinciding with the launch of the proprietary product used in the study, with the publication of a book on the subject, and with the showing on British television of a documentary concerning the study. This study purported to show that supplementation with exactly the recommended dietary allowances of vitamins improved the IQ of children, a finding that was said not to occur significantly with other quantities of vitamin supplementation. This view attracted extremely harsh criticism[7-9] from physicians, nutritionists, psychologists, and epidemiologists.

Despite conflicting data on the effect of **vitamin E** intake on cognitive decline, US guidelines have suggested that vitamin E be considered in patients with *Alzheimer's disease* in an attempt to slow progression of the disease. A subsequent meta-analysis found no evidence of efficacy of vitamin E in cognitive impairment (see Dementia, p. 2120.2). A cohort study found low **folate** concentrations to be the predominant risk factor for cognitive decline in elderly people.[10] Raised homocysteine concentrations have also been found in patients with cognitive decline and dementia.[11] While a 2-year controlled study in elderly patients without cognitive impairment found that daily homocysteine-lowering treatment with folate, **vitamin B_6**, and **vitamin B_{12}** did not improve cognitive performance,[12] another found that daily folic acid supplementation for 3 years significantly improved measures of cognitive function.[13] A meta-analysis,[14] which included the latter study, came to the conclusion that the few studies carried out provided no consistent evidence either way that folic acid, with or without vitamin B_{12}, had a beneficial effect on

the cognitive function of elderly people with or without dementia. A subsequent placebo-controlled study[15] in patients with mild to moderate Alzheimer's disease given folic acid, vitamin B_6, and vitamin B_{12} supplements to lower homocysteine concentrations did not show any slowing of cognitive decline. Depression was also reported more often in supplemented patients, a surprising result given the reported association between raised homocysteine levels and depression (see below). Routine supplementation was therefore not recommended for these patients in the absence of vitamin B deficiency.

Similarly, low folate concentrations and increased homocysteine concentrations have been implicated in *depression*, and supplementation has been proposed,[11] both as monotherapy, or as a means of augmenting antidepressant efficacy.[16] Although supplementation with folic acid, vitamin B_6, and vitamin B_{12} failed to show any benefit over placebo on the incidence or severity of depression in 299 elderly men, the study was underpowered and did not take into account use of antidepressants.[17]

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PREGNANCY. **Folic acid** protects against the development of neural tube defects (p. 2064.3) and supplementation during pregnancy is advised; **vitamin B_{12}** supplementation may also be warranted. Antenatal supplementation with **iron** plus folic acid or micronutrients may have further benefits for the child, see Iron-deficiency Anaemia, p. 2073.2. **Vitamin A**, however, may be teratogenic and maximum intakes in pregnancy have been recommended, see p. 2102.1. The risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to **vitamin D** therapy (see p. 2117.3). Systematic reviews[1,2] of supplementation in pregnancy lacked enough data to indicate whether **vitamin C** or **E**, alone or with other supplements, were of benefit. There was some suggestion of decreased risk of developing pre-eclampsia with either vitamin C or E; however, preterm births may have increased with vitamin C supplementation.

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PROPHYLAXIS OF ISCHAEMIC HEART DISEASE. Hypercholesterolaemia is a major risk factor for the development of atherosclerosis and consequently ischaemic heart disease. Since oxidation of lipids, particularly low-density-lipoprotein (LDL) cholesterol,[1] has been proposed as a factor in atherogenesis, the possibility of preventing atherosclerosis by the use of dietary antoxidants such as **vitamins E** and **C** and **betacarotene** has been investigated. A six-year study of supplementation with vitamins C and E in hypercholesterolaemic patients showed a slowing of atherosclerotic progression, especially in men.[2] Prospective epidemiological studies have revealed a reduced risk of ischaemic heart disease in individuals taking vitamin E supplements,[3,4] and those with a high carotene intake (particularly smokers).[3] In a further prospective cohort study,[5] dietary vitamin E consumption, but not vitamin E supplementation, was associated with decreased risk of death from ischaemic heart disease. Intake of vitamin C, however, did not appear to be associated with a decreased risk of ischaemic heart disease in these studies,[3-5] although another study[6] found a significantly lower risk in those taking vitamin C supplements. Data from some studies assessing serum or fat concentrations also provide evidence that high betacarotene concentrations are associated with decreased cardiovascular disease.[7-9]

However, despite these promising results, randomised placebo-controlled studies have failed to find any benefit for betacarotene supplements in the primary or secondary prevention of ischaemic heart disease, and those for vitamin E supplements are inconclusive. In the Alpha Tocopherol, Beta Carotene Cancer Prevention (ATBC) study, which monitored cardiovascular disease as a secondary end-point, vitamin E was not associated with a decreased incidence of ischaemic heart disease, and betacarotene was associated with a small increased risk.[10] In further analyses, neither supplement appreciably altered the incidence of angina pectoris,[11] nor showed any beneficial effect on cardiovascular deaths in the subset of men with previous myocardial infarction.[12] It has been suggested that the lack of effect of vitamin E in this study may be due to an insufficiently high dose of tocopherol. Similarly, neither the Betacarotene and Retinol Efficacy Trial (CARET)[13] nor the Skin Cancer Prevention Study[9] found an effect for betacarotene supplementation on the risk of death from cardiovascular disease.

In studies specifically on cardiovascular end-points, no benefit from betacarotene supplements was seen in a large, randomised, placebo-controlled study[14] in healthy men. Studies of supplementation with high-dose vitamin E in patients with evidence of ischaemic heart disease,[15] or after myocardial infarction,[16] failed to show any beneficial effect on cardiovascular deaths, although in one study[15] there was a reduction in non-fatal myocardial infarction and major cardiovascular events. The Heart Outcomes Prevention Evaluation (HOPE) study also showed that vitamin E treatment for 4 to 6 years had no effect on cardiovascular events in high-risk patients;[17] further follow-up[18] raised the possibility of an increased risk of heart failure with vitamin E. Long-term (7 to 10 years) vitamin E or vitamin C supplementation failed to reduce the incidence of cardiovascular events in low-risk patients in the Physicians' Health Study II;[19] although there was no difference in the rate of heart failure with either vitamin, an increase in haemorrhagic stroke was noted with vitamin E use. Another large-scale study, the Heart Protection Study, assessed the effect of a 'cocktail' of vitamin E, vitamin C, and betacarotene on the development of ischaemic heart disease in high-risk subjects, and again found no evidence of benefit.[20] Another study[21] using a similar cocktail in patients with established heart disease found no effect on clinical outcome. In view of the lack of evidence of benefit with vitamin supplements, it has been recommended that the emphasis should instead be on consuming a balanced diet including antoxidant-rich fruits, vegetables, and whole grains rather than vitamin supplements;[22,23] authors of a meta-analysis[24] of studies of antoxidant vitamins for the prevention of cardiovascular disease concluded that, in view of a possibly harmful effect of betacarotene and inefficacy of vitamin E, the use of these supplements be discouraged. It has been pointed out[25] that differences between the observational and clinical studies may be due to intrinsic differences between individuals who choose to take supplements and the high-risk populations studied in randomised studies, who may be less amenable to cardiovascular risk reduction with antoxidant supplementation. It has also been suggested[26] that high-dose antoxidants may only benefit patients who suffer from particularly high levels of oxidative stress. After 18 months of vitamin E supplementation, high-risk patients with diabetes mellitus and the haptoglobin 2-2 genotype (associated with reduced antoxidant protection) had a reduced incidence of cardiovascular events, particularly non-fatal myocardial infarction. A pharmacogenomic approach has been proposed to identify those who might benefit from treatment.

For a discussion of the possibility that **folic acid** and **vitamin B** may reduce ischaemic heart disease through a homocysteine-lowering effect, see p. 2063.3. For uncertainty about the value of **vitamin D** supplementation in preventing cardiovascular disease see p. 2115.1.

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PROPHYLAXIS OF MALIGNANT NEOPLASMS. There is evidence that a diet rich in fruit and vegetables is associated with a lower incidence of malignant disease, particularly of the respiratory and digestive tracts.[1] It has been hypothesised that some of the benefits of such a diet derive from the role of antoxidant vitamins such as the carotenoids and vitamins C and E in scavenging free radicals.[2,3] However, it is by no means certain that these are the only, or necessarily the most important, dietary components responsible for benefit, since components such as dietary fibre may also play a role. In addition, different antoxidants may vary in their properties and efficacy,[3,4] and the appropriate dosage remains largely conjectural, and perhaps as a result the evidence of benefit is often conflicting.

Several clinical studies of the use of **vitamin A** or **betacarotene** in the secondary or primary prevention of malignancy have been reported. Prolongation of disease-free interval in patients with various malignant neoplasms was reported in 1 study of betacarotene,[5] and others reported remission of oral leucoplakia (p. 750.3) in patients treated with betacarotene and vitamin A,[6,7] or betacarotene alone.[8] Vitamin A alone was reported to reduce the incidence of primary tobacco-related neoplasms in a study of patients treated surgically for lung cancer.[9] In a prospective, cohort study,[10] vitamin A intake, including preformed vitamin A and carotenoids, was associated with a reduced risk of breast cancer among smokers. However, other results have largely failed to substantiate any benefit for secondary prevention. No reduction in the incidence of new skin cancers,[11-13] or in malignant transformation of cervical dysplasia,[14] or in new colorectal adenomas[15] was reported in other studies. In a primary prevention study, a combination of betacarotene, vitamin E, and selenium was associated with a reduction in stomach and oesophageal cancers in a population at high risk of these cancers and with a diet low in micronutrients in China.[16] In contrast, other primary prevention studies have failed to show any benefit, and possibly some harm, from betacarotene supplements in well-nourished populations. A study in smokers[17-19] showed an increase in lung cancer and associated mortality in those receiving betacarotene, but not those receiving vitamin E. Similarly, an increased risk of

lung cancer was noted in recipients of betacarotene with vitamin A in another study in individuals at high risk of lung cancer, and this study was stopped early as a result.[20,21] In a 6-year follow-up,[22] this risk was found to persist, albeit at lower and not statistically significant levels. A third study in healthy men found no benefit or harm for betacarotene supplements in terms of incidence of malignant neoplasms, including those of the lung;[23] a subgroup analysis of this study suggested that supplementation may reduce the risk of prostate cancer in those men with low baseline betacarotene levels.[24] Among subjects with colorectal adenoma,[25] who neither smoked nor drank alcohol, betacarotene supplementation was associated with a decrease in the risk of recurrent adenoma, but risk was increased in those who smoked or drank alcohol. A meta-analysis[26] of studies of antoxidant supplementation found that betacarotene had no anticarcinogenic effects on gastrointestinal cancer, and that given alone, it increased mortality. When given with vitamin A and E, mortality increased further. A further systematic review and meta-analysis[27] found that betacarotene supplementation was associated with an increased incidence of cancer among smokers, but not among non-smokers. There was also a trend towards increased cancer mortality with betacarotene supplementation. A 24% increase in the risk of lung cancer was reported in current smokers taking betacarotene supplements in a meta-analysis of 4 studies in high-risk patients.[28]

Vitamin C has also been proposed for prevention of malignancy but there is no real evidence to justify it. It certainly appears to be ineffective as adjuvant therapy in the treatment of advanced malignancy,[29] and the incidence of prostate or total cancer was not reduced by vitamin C supplementation in a large, placebo-controlled study.[30] Combination with betacarotene and vitamin E also failed to show any effect in preventing colorectal adenoma.[15] At physiological concentrations vitamin C is an important antoxidant,[3] but while low serum ascorbic acid concentrations have been inversely related to cancer mortality,[31,32] supplementation is unlikely to be justified in anyone eating a balanced diet.[1]

There is epidemiological evidence that **vitamin D** has protective effects against the development of malignant neoplasms,[33] but it is still unclear whether supplementation, and if so to what degree, would be appropriate—see also p. 2116.1.

Vitamin E substances are also known to play an important antoxidant role in the body. *Animal* studies have suggested that they should inhibit tumour production, and the Chinese study mentioned above found combined antoxidant therapy including vitamin E to be of benefit in the primary prevention of stomach and oesophageal cancers.[16] Other studies in western populations have generally been disappointing; vitamin E had no effect on lung cancer incidence in those at risk,[17,18] and did not prevent the development of new colorectal adenomas.[15] In a study of patients with head and neck cancer, supplementation with vitamin E led to a higher incidence of second primary cancers and reduced cancer-free survival; patients on supplements had initially also been given betacarotene. While noting the fact that the study population were at high-risk for second primary cancers, the authors cautioned against the use of high-dose vitamin E supplements for cancer prevention.[34] There is also suggestion of increased all-cause mortality with high-dose vitamin E (see p. 2121.2). However, further analysis of the lung-cancer study[35] suggested that vitamin E may have protected against prostate cancer. Despite preliminary evidence that selenium (see p. 2087.2) or vitamin E supplementation may reduce the risk of prostate cancer, a large, randomised, controlled study[36] found no evidence of benefit with either selenium or vitamin E supplementation alone or vitamin E plus selenium. Similarly, vitamin E supplementation did not reduce the risk of prostate or total cancer in another large, placebo-controlled study.[30]

Results from the Nurses' Health Study have indicated that prolonged use of multivitamins was associated with reduced risk of developing cancer of the colon.[37] This effect was thought to be due to the **folate** component and could be demonstrated after 15 years of use, but not after shorter-term ingestion. Dietary folate was also associated with a modest reduction in risk for colon cancer, and folic acid intake might reduce the risk of breast cancer, especially in those regularly consuming alcohol.[38,39] Combined treatment with folic acid, vitamin B_6, and vitamin B_{12} had no effect on the overall risk of invasive cancer or breast cancer among women at high risk of cardiovascular disease.[40] For the suggestion that folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, under Folic Acid, p. 2065.3.

Concerns have been raised about the potential for antoxidants to protect tumour cells as well as healthy cells from oxidative damage generated by radiation therapy and some chemotherapy. Although data are limited and sometimes conflicting, some have suggested that the use of antoxidant supplements should be discouraged during radiotherapy or chemotherapy.[41]

While a diet involving frequent consumption of fruits and vegetables is likely to be beneficial,[1,42] others have also suggested that these associations may have been overstated, and that weight control and regular exercise should be prioritised.[38]

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Alanine *(BAN, USAN, rINN)*

A; Ala; Alaniini; Alanin; Alanina; L-Alanina; Alaninas; L-Alanine; Alaninum; NSC-206315; Аланин.

L-2-Aminopropionic acid.

$C_3H_7NO_2$=89.09

CAS — 56-41-7.

UNII — OF5P57N2ZX (L-alanine); 1FU7983T0U (DL-alanine).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Alanine). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Alanine). White, odourless, crystals or crystalline powder. Freely soluble in water; slightly soluble in 80% alcohol; insoluble in ether. pH of a 5% solution in water is between 5.5 and 7.0. Store in airtight containers.

Profile

Alanine is an aliphatic non-essential amino acid. It is used as a dietary supplement. The dipeptide *N* (2)-L-alanyl-L-glutamine is used similarly.

The isomeric compound β-alanine (3-aminopropionic acid), which does not have a chiral centre, is a precursor of the muscle peptide carnosine, and has been promoted for its possible benefits in decreasing fatigue and increasing exercise performance in athletes.

Hypoglycaemia. References to the investigational use of alanine in the management of insulin-induced hypoglycaemia.[1-5]

1. Wiethop BV, Cryer PE. Glycemic actions of alanine and terbutaline in IDDM. *Diabetes Care* 1993; **16:** 1124–30.
2. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; **16:** 1131–6.
3. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; **20:** 1231–6.
4. Evans ML, *et al.* Alanine infusion during hypoglycaemia partly supports cognitive performance in healthy human subjects. *Diabet Med* 2004; **21:** 440–6.
5. Porcellati F, *et al.* Effect of the amino acid alanine on glucagon secretion in non-diabetic and type 1 diabetic subjects during hyperinsulinaemic euglycaemia, hypoglycaemia and post-hypoglycaemic hyperglycaemia. *Diabetologia* 2007; **50:** 422–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Abufene; Betalane; ***Rus.***: Klimalanin (Клималанин); ***Singapore***: Abufene; ***Ukr.***: Abufene (Абъюфен).

Multi-ingredient Preparations. ***Arg.***: Normoprost Compuesto; ***China***: Pu Luo Si Tai (普罗司泰); ***Fr.***: ProstaSecurA; ***India***: Nerfit; ***Ital.***: Chetonex; ***Pol.***: Naturapia Prostata†; ***Spain***: Tebetane Compuesto.

Amino Acid Chelates

Amino Acid Complexes; Hydrolysed Protein Chelates; Proteinates; Vegetable Protein Complexes.

Profile

Chelation of minerals with amino acids is thought to improve their intestinal absorption and preparations containing minerals with either specific amino acids or hydrolysed proteins have been used as dietary supplements. Minerals and trace elements that have been given in this form include boron (p. 2052.3), calcium (p. 1783.1), chromium (p. 2055.3), iron (p. 2073.1), magnesium (p. 1786.3), manganese (p. 2081.2), molybdenum (p. 2082.3), nickel, potassium (p. 1793.1), and zinc (p. 2126.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bioglan Zinc Chelate†; ***Braz.***: Calato; Calcichell; Ferrini; Mag-Tab; Repocal; ***Ger.***: Zinkamin; ***Israel***: Light Iron; ***Ital.***: Tecnofer.

Multi-ingredient Preparations. ***Austral.***: AB Extra Bone-Care +; AB Oriostin; Antioxidant Forte Tablets†; Antioxidant Tablets†; Beta A-C; Beta A-C; Bio ACE Excell; Bio ACE; Bio Magnesium; Bio Zinc; Chelated Cal-Mag with Vitamin D; Citri Slim+Trim†; Echinacea 4000†; Echinacea ACE + Zinc; Echinacea Complex†; Enhance for Men; FAB; Fe-Max; Femme-F; Gluco Support; Homme-F; Iron Max; Joint Mobility†; Lyp-Sine; Machlor; Mag-

Oro; PM IQShield; PM Kids Intelligent; Prostate Care; Radiance; Skin Support; The Blue One†; Zinc Plus; Zinc Zenith; Zn-A-C†; ***Braz.***: Ceglen Zinco; Ferrini Folico; Folifer; ***Canad.***: Osteo-Guard†; Osteo-Life†; Phytopro†; ***Hung.***: Salus Herz-Schutz; ***India***: Enerjex; Probofex Caps; ***Indon.***: Carni Plus; ***Mex.***: Ferricol; Ferrivax F; Intrafer F-800; Intrafer TF; Intrafer; ***Singapore***: Arthro-Flex; Ruflex; ***USA***: CalMag Plus; Fosteum; Poly-Vi-Flor with Iron; REQ49+.

Arginine *(rINN)*

Arg; Arginiini; Arginin; Arginina; Argininas; L-Arginine; Argininum; R; Аргинин.

L-2-Amino-5-guanidinovaleric acid.

$C_6H_{14}N_4O_2$=174.2

CAS — 74-79-3.

UNII — 94ZLA3W45F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Arginine). A white or almost white crystalline powder, or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Arginine). White, practically odourless crystals. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Arginine Aspartate

Arginiiniaspartaatti; Arginina, aspartato de; Argininaspartat; Arginin-aspartát; Arginine, aspartate d'; Arginini aspartas; Arginino aspartatas; Asparginінum; Аргинина Аспартат.

(2*S*)-2-Amino-5-guanidinopentanoic acid (2*S*)-2-aminobutanedioate.

$C_{10}H_{21}N_5O_6$=307.3

CAS — 7675-83-4.

UNII — LZB1G2I725.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Arginine Aspartate). White or almost white granules or powder. Very soluble in water, practically insoluble in alcohol and in dichloromethane.

Arginine Glutamate *(BAN, USAN, rINNM)*

Arginina, glutamato de; Arginine, Glutamate d'; Arginini Glutamas; Glutamato de arginina; Аргинина Глутамат.

L-Arginine L-glutamate.

$C_6H_{14}N_4O_2.C_5H_9NO_4$=321.3

CAS — 4320-30-3.

ATC — A05BA01.

ATC Vet — QA05BA01.

UNII — TU1X77K34Q.

Arginine Hydrochloride *(USAN, rINNM)*

Arginiinihydrokloridi; Arginina, hidrocloruro de; Arginine, chlorhydrate d'; L-Arginine Monohydrochloride; Argininhidroklorid; Argininhydrochlorid; Arginin-hydrochlorid; Argininhydroklorid; Arginini Hydrochloridum; Arginino hidrochloridas; Hidrocloruro de arginina; Аргинина Гидрохлорид.

$C_6H_{14}N_4O_2$,HCl=210.7

CAS — 1119-34-2.

ATC — B05XB01.

ATC Vet — QB05XB01.

UNII — F7LTH1E20Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Arginine Hydrochloride). A white or almost white crystalline powder, or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Arginine Hydrochloride). White, practically odourless, crystals or crystalline powder. Freely soluble in water.

Uses and Administration

Arginine is a basic amino acid that is essential for growth. It is used as a **dietary supplement**, to treat or prevent deficiency, or to aid recovery during convalescence. It is given orally as the aspartate, glutamate, or hydrochloride; 1 g of arginine is equivalent to about 1.76 g of arginine aspartate, or 1.84 g of arginine glutamate, or 1.21 g arginine hydrochloride. A usual oral dose, expressed as arginine aspartate, is 2 to 5 g daily, given with or after food.

Arginine stimulates the release of growth hormone by the pituitary gland and may be used instead of, or in addition to, other tests such as insulin-induced hypoglycaemia, for the **evaluation of growth disorders**; false-positive and false-negative results are relatively common and evaluation therefore should not be made on the basis of a single arginine test. It is used as a 10% solution of the hydrochloride in usual doses of 30 g by intravenous infusion given over 30 minutes. A further test may be given after 24 hours.

For doses in children, see below.

Arginine is used in certain conditions accompanied by **hyperammonaemia**; for further details see below.

Arginine hydrochloride has also been used as an **acidifying agent**. In severe metabolic alkalosis intravenous doses have been calculated by the formula:

intravenous dose (in grams) =
desired decrease in plasma-bicarbonate concentration (mEq or mmol/litre)
X
[patient's body-weight (in kg)/9.6]

In forced acid diuresis to hasten drug elimination after overdose a suggested dose has been 10 g intravenously over 30 minutes. However, this has the potential to cause myoglobinuria with acute renal failure, and is rarely used.

Arginine may also be used in the form of the acetylasparaginate, citrate, malate, oxoglurate, tidiacicate (thiazolidine-2,4-dicarboxylate), and timonacicate (thiazolidine-4-carboxylate). Formulation as an arginine salt is used to improve the solubility of several drugs, notably analgesics and antibacterials.

References.

1. Tapiero H, *et al.* Arginine. *Biomed Pharmacother* 2002; **56:** 439–45.
2. Tong BC, Barbul A. Cellular and physiological effects of arginine. *Mini Rev Med Chem* 2004; **4:** 823–32.
3. Zhou M, Martindale RG. Arginine in the critical care setting. *J Nutr* 2007; **137** (suppl 2): 1687S–1692S.
4. Barbul A, Uliyargoli A. Use of exogenous arginine in multiple organ dysfunction syndrome and sepsis. *Crit Care Med* 2007; **35** (suppl): S564–S567.
5. Coman D, *et al.* New indications and controversies in arginine therapy. *Clin Nutr* 2008; **27:** 489–96.
6. Wu G, *et al.* Arginine metabolism and nutrition in growth, health and disease. *Amino Acids* 2009; **37:** 153–68.

Administration in children. Arginine is used in children as a **dietary supplement**, to treat or prevent deficiency, or to aid recovery during convalescence. Children from 6 years of age have been given an oral dose of arginine aspartate 1 g once or twice daily.

Arginine is also given intravenously for the **evaluation of growth disorders** in children. A usual dose of arginine hydrochloride 500 mg/kg is given as a 10% solution infused over 30 minutes in children weighing less than 60 kg; children weighing 60 kg or more may be given the adult dose (see above). A further test may be given after 24 hours.

For doses of arginine used in children with **hyperammonaemia**, see below.

Cardiovascular use. Arginine is the physiological precursor of nitric oxide and this has been suggested as an explanation for the **hypotensive effect** that has been reported in healthy subjects[1-3] and hypertensive patients[1,4] given infusions of arginine, although effects unrelated to nitric oxide generation cannot be excluded.[4]

Oral arginine has also been reported to significantly decrease mean systolic blood pressure in hypertensive patients,[5] in patients on haemodialysis, and in renal transplant recipients.[6] In patients with essential *hypertension*, a single oral dose of arginine had no effect on blood pressure, although it did improve endothelium-dependent flow-mediated dilatation of the brachial artery compared with placebo.[7] In patients with pulmonary hypertension, short-term use of arginine has reduced pulmonary arterial pressure.[8-10]

In pregnant women with *pre-eclampsia* (see Hypertension, p. 1251.1), plasma-arginine concentrations were found to be markedly reduced compared with control subjects.[11] Arginine infusions of 20 g, given to women with mild to moderate gestational hypertension,[12] and 30 g given to pre-eclamptic women,[13] significantly reduced systolic and diastolic blood pressure, with no adverse effect on fetal heart rate in the one study.[12] In a study of pre-eclamptic women given oral arginine 12 g daily for 2 days, no significant differences in diastolic blood pressure were seen compared with those receiving placebo.[14] However, in another study of pre-eclamptic women given oral arginine 3 g daily for 3 weeks, systolic, diastolic and mean arterial pressure were significantly reduced compared with those taking placebo.[15]

Because of apparent **improvement in endothelial function** with arginine,[16] some interest has surrounded its potential role in other cardiovascular diseases, such as *coronary artery disease* and *heart failure*.[17] Decrease in plasma-cholesterol concentrations has also been reported in 2 hypercholesterolaemic patients given arginine infusions.[18] However, long-term supplementation was found not to be helpful (and possibly harmful) in patients with *peripheral arterial disease*,[19] and arginine therapy has been implicated in increased mortality when given to patients after *myocardial infarction* (see under Adverse Effects and Precautions, p. 2050.2). Nonetheless, some interest in its possibilities continues.[16]

There are case reports[20] of successful use of arginine in the management of the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (*MELAS*), with a reduction in the frequency of major stroke-like attacks. A small study[21] in 24 patients with MELAS found that their plasma-arginine concentrations (during both the acute and interictal phases) were lower than those of controls. Arginine given intravenously in the acute phase of stroke-like attacks resulted in an improvement of symptoms within 24 hours in nearly all patients. Treatment with oral arginine was continued for 18 months in 6 patients, with a reduction in the frequency and severity of attacks.

1. Nakaki T, *et al.* L-arginine-induced hypotension. *Lancet* 1990; **336:** 696.
2. Hishikawa K, *et al.* L-arginine-induced hypotension. *Lancet* 1991; **337:** 683–4.
3. Petros AJ, *et al.* L-arginine-induced hypotension. *Lancet* 1991; **337:** 1044–5.
4. Pedrinelli R, *et al.* Pressor, renal and endocrine effects of L-arginine in essential hypertensives. *Eur J Clin Pharmacol* 1995; **48:** 195–201.
5. Palloshi A, *et al.* Effect of oral L-arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. *Am J Cardiol* 2004; **93:** 933–5.
6. Kelly BS, *et al.* Oral arginine improves blood pressure in renal transplant and hemodialysis patients. *J Parenter Enteral Nutr* 2001; **25:** 194–202.
7. Lekakis JP, *et al.* Oral L-arginine improves endothelial dysfunction in patients with essential hypertension. *Int J Cardiol* 2002; **86:** 317–23.
8. Mehta S, *et al.* Short-term pulmonary vasodilation with L-arginine in pulmonary hypertension. *Circulation* 1995; **92:** 1539–45.
9. Nagaya N, *et al.* Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. *Am J Respir Crit Care Med* 2001; **163:** 887–91.
10. Morris CR, *et al.* Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003; **168:** 63–9.
11. D'Aniello G, *et al.* Plasma L-arginine is markedly reduced in pregnant women affected by preeclampsia. *J Chromatogr B Biomed Sci Appl* 2001; **753:** 427–31.
12. Neri I, *et al.* Effects of acute L-arginine infusion on non-stress test in hypertensive pregnant women. *J Matern Fetal Neonatal Med* 2004; **16:** 23–6.
13. Facchinetti F, *et al.* L-Arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. *J Soc Gynecol Investig* 1999; **6:** 202–7.
14. Staff AC, *et al.* Dietary supplementation with L-arginine or placebo in women with pre-eclampsia. *Acta Obstet Gynecol Scand* 2004; **83:** 103–7.
15. Rytlewski K, *et al.* Effects of prolonged oral supplementation with L-arginine on blood pressure and nitric oxide synthesis in preeclampsia. *Eur J Clin Invest* 2005; **35:** 32–7.
16. Heffernan KS, *et al.* L-arginine as a nutritional prophylaxis against vascular endothelial dysfunction with aging. *J Cardiovasc Pharmacol Ther* 2010; **15:** 17–23.
17. Cheng JWM, Balwin SN. L-arginine in the management of cardiovascular diseases. *Ann Pharmacother* 2001; **35:** 755–64.
18. Korbut R, *et al.* Effect of L-arginine on plasminogen-activator inhibitor in hypertensive patients with hypercholesterolemia. *N Engl J Med* 1993; **328:** 287–8.
19. Wilson AM, *et al.* L-arginine supplementation in peripheral arterial disease: no benefit and possible harm. *Circulation* 2007; **116:** 188–95.
20. Geberhiwot T, *et al.* Case 36-2005: a woman with seizure, disturbed gait, and altered mental status. *N Engl J Med* 2006; **354:** 1096–7.
21. Koga Y, *et al.* L-arginine improves the symptoms of strokelike episodes in MELAS. *Neurology* 2005; **64:** 710–12.

Hyperammonaemia. Hyperammonaemia is a characteristic feature of inborn errors of the urea cycle, caused by defects in the enzymes carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (causing hyperargininaemia), or *N*-acetylglutamate synthase (NAGS).[1,2] During the urea cycle, waste ammonia, in the form of the ammonium ion, is normally condensed with bicarbonate and ATP to form carbamoyl phosphate which undergoes several more reactions, including one leading to the synthesis of arginine, and ultimate transformation to urea for excretion. Thus, in defects of this cycle ammonia accumulates and arginine synthesis is deficient.[3] Hyperammonaemia is most severe when the enzyme defect occurs in the early steps of the urea cycle, such as in CPS or OTC deficiency, and is less severe at later stages, as in ASL or arginase deficiency.[2] Hyperammonaemia is often associated with respiratory alkalosis in patients with urea cycle disorders.[3]

The basis of **treatment** is dietary protein restriction, to decrease the requirement for waste nitrogen synthesis,[4] and the use of drugs to stimulate alternative pathways of waste nitrogen excretion.[5,6] Such drugs include arginine, citrulline, sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. In the initial management of severe hyperammonaemia, haemodialysis is preferred over peritoneal dialysis because it is more effective.[3,7]

Arginine supplements are given except in hyperargininaemia.[5,7] *Citrulline* may be used in some cases instead;[8] it may be useful for CPS and OTC deficiency (in doses of about 170 mg/kg daily or 3.8 g/m^2 daily),[5,6,9] but it is not recommended for patients with ASS or ASL deficiency, as levels of citrulline are already elevated.[5,10] Some recommend citrulline with arginine in acute hyperammonaemia to aid additional removal of nitrogen.[9] For the treatment of acute hyperammonaemia, some recommend a loading dose of arginine 600 mg/kg over 90 minutes pending definitive diagnosis.[3,10] Alternatively, a loading dose of 200 mg/kg or 4 g/m^2 has been advocated for CPS or OTC deficiency,[6,9,10] and 600 mg/kg or 12 g/m^2 for ASS or

ASL deficiency.[6,9,10] The same dose as the loading dose is then given over 24 hours, as a constant maintenance infusion,[6,9,10] until conversion to oral medication is made.[10] For long-term management of ASS or ASL deficiency, doses of arginine ranging from 400 to 700 mg/kg daily have been recommended.[5,6,9,10] The *BNFC* suggests arginine doses for neonates and children up to 18 years of age, to be given under specialist supervision:

- For acute hyperammonaemia in CPS or OTC deficiency, an initial intravenous infusion of 200 mg/kg over 90 minutes, is followed by a continuous infusion of 8 mg/kg per hour; for maintenance, an oral dose of 100 mg/kg is given daily in 3 or 4 divided doses.
- For acute hyperammonaemia in citrullinaemia or arginosuccinic aciduria, an initial intravenous infusion of 600 mg/kg over 90 minutes, is followed by a continuous infusion of 25 mg/kg per hour; for maintenance, an oral dose of 100 to 175 mg/kg is given three or four times daily with food, and adjusted according to response.

Patients also receive treatment with *sodium benzoate* and *sodium phenylacetate*[6,10] or *sodium phenylbutyrate*.[5,6] ASL deficiency can be managed with protein restriction and arginine alone,[6,11] although some still advocate the use of sodium phenylbutyrate.[5,8] When sodium benzoate is conjugated with glycine and excreted as hippuric acid it provides an alternative pathway of nitrogen excretion, while sodium phenylacetate and sodium phenylbutyrate provide a second and even more effective pathway by conjugation with glutamine.[6,7,10] Some consider intravenous sodium benzoate and sodium phenylacetate the treatment of choice in acute hyperammonaemia; sodium phenylbutyrate is recommended for chronic management.[9] In a 25-year, open-label, uncontrolled study, intravenous therapy with sodium phenylacetate and sodium benzoate clearly improved survival in patients with acute hyperammonaemia, with an overall survival rate of 84%; survival was also related to peak plasma ammonium concentration and age. Haemodialysis was also used to control hyperammonaemia, especially in neonates and older patients who were less responsive to intravenous therapy.[12]

It has been suggested that *carnitine* supplementation (at 100 mg/kg daily[9] either orally or intravenously) should be added to minimise neurological symptoms and toxicity, but its value is uncertain.[4,13] Low carnitine levels are reportedly rare in patients with urea cycle disorders, and in patients treated with sodium benzoate benzoyl carnitine may form, negating any potential benefit from carnitine supplementation.[8]

Liver transplantation (p. 1936.3) may achieve long-term correction of urea cycle disorders, even in the very young patient, and *gene replacement* therapy is under investigation.[14]

Hyperammonaemia and hepatic encephalopathy (p. 1808.2) can also arise from other causes[7,13] for which arginine may not be advocated. *Carglumic acid* (p. 2471.1) is the treatment of choice for patients with hyperammonaemia arising from NAGS deficiency.

1. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S6–S10.
2. Shih VE. Alternative-pathway therapy for hyperammonemia. *N Engl J Med* 2007; **356:** 2321–2.
3. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S1–S5.
4. Leonard JV. The nutritional management of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S40–S45.
5. Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S56–S61.
6. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl): S46–S55.
7. Leonard JV, Morris AAM. Urea cycle disorders. *Semin Neonatol* 2002; **7:** 27–35.
8. Wilcken B. Problems in the management of urea cycle disorders. *Mol Genet Metab* 2004; **81** (suppl): S86–S91.
9. Kleppe S, *et al.* Urea cycle disorders. *Curr Treat Options Neurol* 2003; **5:** 309–19.
10. Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S30–S39.
11. Brusilow SW, *et al.* Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med* 1984; **310:** 1630–4.
12. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356:** 2282–92.
13. Leonard JV, Morris AAM. Inborn errors of metabolism around time of birth. *Lancet* 2000; **356:** 583–7.
14. Lee B, Goss J. Long-term correction of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S62–S71.

Necrotising enterocolitis. A systematic review[1] considered that although there was evidence suggesting that supplementation of the feed of premature neonates with arginine could prevent the development of necrotising enterocolitis (p. 185.1), it was insufficient to recommend the practice without further study.

1. Shah P, Shah V. Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 24/06/08).

Adverse Effects and Precautions

Nausea, vomiting, flushing, headache, numbness, and local venous irritation may occur if arginine solutions are infused too rapidly; extravasation leading to a burn-like reaction and/or skin necrosis has been reported. Hypersensitivity reactions including rash and anaphylaxis have occurred, and treatment should be stopped if these are serious. Arginine therapy has been associated with haematuria that sometimes occurred 1 or 2 days after dosing. There have also been isolated reports of a decrease in platelet count. Elevated plasma-potassium concentrations have been reported in uraemic patients and arginine should therefore be used with caution in patients with renal disease or anuria. Arginine hydrochloride should be given cautiously to patients with electrolyte disturbances as its high chloride content could lead to the development of hyperchloraemic acidosis.

Extravasation. Full-thickness skin necrosis has been reported[1,2] after extravasation of a 10% solution of arginine hydrochloride. Both osmotic and local hyperkalaemic effects have been proposed as a mechanism for the injury.[1]

1. Bowlby HA, Elanjian SI. Necrosis caused by extravasation of arginine hydrochloride. *Ann Pharmacother* 1992; **26:** 263–4.
2. Salameh Y, Shoufani A. Full-thickness skin necrosis after arginine extravasation—a case report and review of literature. *J Pediatr Surg* 2004; **39:** E9–E11.

Hyperkalaemia. Two alcoholic patients with severe liver disease and moderate renal insufficiency developed severe hyperkalaemia when given arginine hydrochloride and one died.[1] Both patients had received a total of 300 mg of spironolactone some time before arginine hydrochloride, but the contribution of spironolactone to the hyperkalaemia was not known. In a study to investigate the mechanism of metabolic changes due to arginine, plasma-potassium concentrations were found to be significantly higher in diabetic subjects than those for normal subjects, leading the authors to suppose that while arginine-induced hyperkalaemia may be promoted by low insulin blood levels, it could not be attributed to glucagon, pH changes, or aldosterone inhibition.[2]

In another fatal case due to an overdose of arginine,[3] a 21-month-old girl developed an acute metabolic acidosis with transient but severe hyponatraemia, and irreversible brain death; no hyperkalaemia was seen. Unlike the previously reported case, the patient had normal renal function, and the authors supposed the absence of hyperkalaemia to be due to a rapid increase in renal potassium excretion.

1. Bushinsky DA, Gennari FJ. Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 1978; **89:** 632–4.
2. Massara F, *et al.* The risk of pronounced hyperkalaemia after arginine infusion in the diabetic subject. *Diabete Metab* 1981; **7:** 149–53.
3. Gerard JM, Luisiri A. A fatal overdose of arginine hydrochloride. *J Toxicol Clin Toxicol* 1997; **35:** 621–5.

Hypersensitivity. Two reports of anaphylactic reactions that occurred shortly after the start of infusions of arginine 5 or 10% given to test growth-hormone output.[1,2]

1. Tiwary CM, *et al.* Anaphylactic reaction to arginine infusion. *N Engl J Med* 1973; **288:** 218.
2. Resnick DJ, *et al.* Case report of an anaphylactoid reaction to arginine. *Ann Allergy Asthma Immunol* 2002; **88:** 67–8.

Myocardial infarction. A placebo-controlled study investigated whether the addition of arginine to standard therapy after myocardial infarction would decrease vascular stiffness and improve left ventricular function. The study was stopped early due to an increased number of deaths in the arginine group. The authors commented that, while the results could be due to chance, nevertheless arginine should not be given to patients after a myocardial infarction.[1] This prompted Canadian health authorities (Health Canada) to issue similar advice and stipulate that all arginine products must carry a warning label to this effect.[2]

1. Schulman SP, *et al.* L-Arginine therapy in acute myocardial infarction: the Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* 2006; **295:** 58–64.
2. Health Canada. Advisory: Health Canada advises heart patients not to use products containing L-arginine (issued 16th May 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_30-eng.php (accessed 05/02/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lacorene; Multio; ***Austria***: Sangenor; ***Braz.***: Reforgan; Targifor; ***China***: Hua Shi Ai Er (华士艾尔); Jing Ning (净宁); Kang Si Ke Wei (康司科韦); Pu Luo Chuan (普洛川); Xian Ding (先丁); Xian Jing (先京); Xin Qi Bang (欣其邦); YiXin (逸欣); ***Fr.***: Dynamisan; Energitum†; Eucol†; Pargine; Sargenor; Tiadilon; ***Gr.***: Amargine; ***India***: Arginitric; Nitriga; ***Ital.***: Bioarginina; Dynamisan; Sargenor; ***Malaysia***: Arginitric; ***Port.***: Asparten; Bio-Energol Plus; Bioenergex; Pan-Astenico R; Sargenor; Sulfile†; ***Rus.***: Glutargin (Глутаргин); ***Spain***: Potenciator; Sargisthene; Sorbenor; ***Switz.***: Dynamisan; ***Ukr.***: Glutargin (Глутаргин); Tivortin (Тивортин); ***USA***: R-Gene.

Multi-ingredient Preparations. ***Arg.***: Acrea; ADX; Energizante Vital con ginseng; Energizante; Holomagnesio Vital; Potencil; Synapsys; Total Magnesiano Sport; Triconal; VNS 45; ***Austria***: Leberinfusion; ***Braz.***: Dinavital C; Energoplex; Estafan; Ornitargin; Targifor C; Taurargin; Viatop AM; ***Chile***: Dynamisan; Kerium Anticaspa -Caspa Seca; Ureadin 30; Ureadin Rx DB; Ureadin Rx RD; ***Fr.***: Arginotri-B; Citrarginine†; D-Stress; Fastenyl; Hepagrume; Hepargitol; Sargenor a la Vitamine C; ***Gr.***: Tonotil-N; ***Hong Kong***: Profile B Plus Fat Burner†; ***Hung.***: Glutarsin E; ***India***: Aminocal 500; Arg-9; Bio-10; Cavenor; Elnutra; Enduranz; Enlarge; Furtipil-L; Hi-Q; Hi-Q; Hyrase; Jivak; Lutamin; Lutivit; Lycobal Forte; Lytox; N-Care Forte; ***Indon.***: Asten; Aviter; Maxirex; Menolia†; Neo Hormoviton Greng; Neo Hormoviton; Reximax; Sirec; Viusid; ***Ital.***: Anasten Plus; Argidam; Edodes; Ipoazotal Complex; Isoram; Linfoflu; Linfoiodine†; Salovit; Sargenor Plus; Sargenor Sport†; Somatron; Vitalmix Fos; ***Jpn***: Q & P Gold; ***Mex.***: Zumba; ***Spain***: Dynamogen; Tomevit†; ***Switz.***: Vitasprint Complex†; ***UK***: Neurozan; ***Ukr.***: Citrarginine (Цитраргинин); Corargin (Кораргин); Energin (Энергин); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Cardiotek Rx; ***Venez.***: Brugesic Plus; Ocoxin; Viusid.

Pharmacopoeial Preparations

BP 2014: Arginine Hydrochloride Infusion; Arginine Hydrochloride Oral Solution;

USP 36: Arginine Capsules; Arginine Hydrochloride Injection; Arginine Tablets; Aztreonam for Injection; Aztreonam Injection; Cefepime for Injection.

Asparagine Monohydrate

L-α-Aminosuccinamic Acid Monohydrate; Asparagiinimonohydraatti; Asparagin monohydrát; Asparagin-Monohydrat; Asparagina, monohidrato de; Asparaginas monohidratas; L-Asparagine Monohydrate; Asparagine monohydratée; Asparaginmonohydrat; Asparaginum monohydricum; Asparamide; Aspartamic acid; Aspartic acid beta-amide; N (asparagine); NSC-82391; Аспарагин Моногидрат.

(2*S*)-2,4-Diamino-4-oxobutanoic acid monohydrate.

$C_4H_8N_2O_3,H_2O$=150.1

CAS — 70-47-3 (anhydrous asparagine); 5794-13-8 (asparagine monohydrate).

UNII — 2PD79VF521 (asparagine monohydrate); 5Z33R5TKO7 (l-asparagine); 7NG0A2TUHQ (anhydrous l-asparagine).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*, which specifies the anhydrous form or the monohydrate.

Ph. Eur. 8: (Asparagine Monohydrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.0.

USNF 31: (Asparagine). It is anhydrous or contains one molecule of water of hydration. A white, crystalline powder or white crystals. Soluble in water; practically insoluble in alcohol and in ether. Its solutions are acid to litmus. Protect from light.

Profile

Asparagine is a non-essential amino acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Acutil Fosforo; Neuralfa; Tiofort; ***Spain***: Agudil†.

Aspartic Acid *(USAN, rINN)*

Acide aspartique; Ácido aspártico; Acidum Asparticum; Asp; Asparagiinihappo; Asparaginic Acid; Asparaginsyra; L-Aspartic Acid; Aspártico, ácido; Asparginsäure; Asparto rūgštis; Aszparaginsav; D; Kwas asparaginowy; Kyselina asparagová; Аспарагиновая Кислота.

L-Aminosuccinic acid.

$C_4H_7NO_4$=133.1

CAS — 56-84-8.

UNII — 30KYC7MIAI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in ether; soluble in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Aspartic acid is a non-essential amino acid. It is used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Ubiten; ***China***: Ge Mei Nai Xin (格美乃欣); Hu Tian Bao (护天保); Jia He Mei (佳合美); Pai Ke Xin (派可欣); Piaojiamei (朴佳美); Qiang Pu Jin (强普金); Sheng Yi Ge (圣益格); Tian Jia Mei (天甲美); Tuo Qi (妥奇); Wan Pu Ding (万普定); Wei Fu De (维复德); Wei Le Nuo (威乐诺); Wei Ou Lu (维欧路); Wei Shuang (唯双); Xin Mei Jia (欣美佳); Yu Di Ning (玉迪宁); ***Hung.***: Reergin.

Betacarotene *(BAN, rINN)*

all-*trans*-β-Carotene; Beetakaroteeni; Beta Carotene (USAN); Bétacarotène; Betacaroteno; Betacarotenum; Betacarotin; Betakaroten; Betakarotenas; Bétakarotin; E160(a); Provitamin A; Provitamina A; Бетакаротен.

β,β-Carotene; (*all-E*)-1,1′-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis[2,6,6-trimethylcyclohexene].

$C_{40}H_{56}$=536.9

CAS — 7235-40-7.

ATC — A11CA02; D02BB01.

ATC Vet — QA11CA02; QA11HA90; QD02BB01.

UNII — 01YAE03M7J.

Description. Carotene exists in 3 isomeric forms, all of which are converted to some extent into vitamin A in the livers of man and *animals*. Of the 3 isomers of carotene, the *beta* compound is more active than the *alpha-* or *gamma-*isomers. The vitamin A activity of plants is due to the presence of *alpha-*, *beta-*, and *gamma-*carotenes and to kryptoxanthine; that of *animal* tissues is due to both vitamin A and carotene, while fish-liver oils contain vitamin A but no carotene.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Betacarotene). A brown-red or brownish-red crystalline powder. Practically insoluble in water and in dehydrated alcohol; slightly soluble in cyclohexane. It is sensitive to air, heat and light, especially in solution. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Beta Carotene). Red or reddish-brown to violet-brown crystals or crystalline powder. Insoluble in water, in acids, and in alkalis; practically insoluble in alcohol and in methyl alcohol; soluble in carbon disulfide, in chloroform, and in benzene; sparingly soluble in ether, in petroleum spirit, and in vegetable oils. Store in airtight containers. Protect from light.

Units

Vitamin A activity in foods is expressed in terms of retinol equivalents: 6 micrograms of betacarotene represents 1 retinol equivalent (or 10 of the former International units for provitamin A—see p. 2099.2).

Uses and Administration

Betacarotene is a carotenoid precursor of vitamin A (p. 2098.3). In the *treatment* of **vitamin A deficiency**, vitamin A is preferred to betacarotene. However, betacarotene has been used for the *prevention* of vitamin A deficiency at a dose of 6 to 15 mg daily.

Betacarotene may be given orally to reduce the severity of photosensitivity reactions in patients with **erythropoietic protoporphyria** (see also Porphyria, below). Doses are in the range of 30 to 300 mg daily, depending upon severity; they may be taken as either single daily doses or divided doses but should preferably be taken with meals. The protection offered by betacarotene is not total and generally 2 to 6 weeks of treatment resulting in a yellow coloration of palms and soles is necessary before patients should attempt to increase their exposure to sunlight.

For doses in children, see below.

Betacarotene and other carotenoids (alphacarotene and gammacarotene) are used as **colouring agents** for foods and medicinal products.

Betacarotene has **antoxidant** activity and has been studied for its possible protective benefit in a number of disorders (but see Effects on Mortality, below).

Administration in children. Betacarotene may be used in children for the management of photosensitivity reactions in erythropoietic protoporphyria (see also Porphyria, below). Although not licensed in the UK, the *BNFC* suggests oral doses for specialist use:

- 1 to 5 years: 60 to 90 mg daily
- 5 to 9 years: 90 to 120 mg daily
- 9 to 12 years: 120 to 150 mg daily
- 12 to 16 years: 150 to 180 mg daily
- 16 to 18 years: 180 to 300 mg daily

The daily dose may be given in single or divided doses. The protection offered by betacarotene is not total and generally 2 to 6 weeks of treatment is necessary before increasing exposure to sunlight. Doses should be adjusted according to levels of exposure.

For discussion of deficiency states in children, see below.

Age-related macular degeneration. A study in patients with age-related macular degeneration (p. 880.2) indicated that the risk of developing this disorder (a leading cause of irreversible blindness among elderly persons) was markedly decreased amongst those with the highest dietary carotenoid intake;[1] in particular, lutein and zeaxanthin, or green leafy vegetables (which contain high concentrations of these carotenoids) were associated with a lower risk. Increasing the dietary intake of these carotenoids may be of benefit in reducing the development of this disorder. Despite this, systematic reviews found no evidence that antoxidant vitamin and mineral supplementation would either prevent[2,3] or delay the onset of macular degeneration. However, one study[4] has shown modest benefit from vitamin C, vitamin E, betacarotene, and zinc supplementation in those with moderate to severe signs of the disease. A systematic review to assess the effects of antoxidant vitamin or mineral supplementation on the progression of age-related macular degeneration included this study, and noted that the generalisability of these findings to other populations (with differing nutritional status) was unknown. Long-term harm from supplementation could not be ruled out.[5]

1. Seddon JM, *et al.* Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA* 1994; **272:** 1413–20.
2. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 11/03/08).
3. Chong EW-T, *et al.* Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007; **335:** 755–9.
4. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no.8. *Arch Ophthalmol* 2001; **119:** 1417–36.
5. Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/08).

Deficiency states. A study in Senegalese children with vitamin A deficiency found that supplementation with betacarotene (in a single dose equivalent to 200 000 units of vitamin A) was as effective as a single 200 000 unit dose of vitamin A palmitate in reversing ocular changes.[1] Since betacarotene is less toxic than vitamin A itself it would have some advantages for supplementation, either as an oral supplement or by encouraging the consumption of carotenoid-rich fruit and vegetables. A study in anaemic Indonesian women found that a supplement containing betacarotene with iron, vitamin C, and folate improved vitamin A status, whereas an additional daily portion of dark-green leafy vegetables containing a similar amount of betacarotene did not.[2] However, others contended that consumption of food sources of carotenoids were effective in improving vitamin A status in deficiency states,[3,4] and that it might not be appropriate to extrapolate these findings in adults (not necessarily deficient in vitamin A) to vitamin A deficient children.[3,5] WHO policy was to promote dietary adjustment wherever vitamin A deficiency was endemic.[5] Despite further studies confirming improved vitamin A status among those given foods high in betacarotene,[6,7] (supplying around 6 mg of betacarotene daily in adults[6] or 3.5 mg daily in children[7]) a review[8] considered the bioavailability of betacarotene from plant foods to be low, and questioned the retinol equivalency determined by WHO (see Units, above). Another study[9] found that increasing dietary fat consumption and eliminating helminthic infection further increased serum retinol concentrations in children given food high in betacarotene.

For a study reporting improved vitamin A status with betacarotene plus zinc compared with betacarotene or zinc alone, and the suggestion that zinc may have a role in the conversion of betacarotene to retinol, see Vitamin A Deficiency, under Zinc, p. 2127.3.

For further discussion of vitamin A deficiency and the value of supplementation in various disease states, see under Vitamin A Substances, p. 2099.2.

1. Carlier C, *et al.* A randomised controlled trial to test equivalence between retinyl palmitate and β carotene for vitamin A deficiency. *BMJ* 1993; **307:** 1106–10.
2. de Pee S, *et al.* Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. *Lancet* 1995; **346:** 75–81.
3. Reddy V. Vitamin A status and dark green leafy vegetables. *Lancet* 1995; **346:** 1634–5.
4. Underwood BA. Vitamin A status and dark green leafy vegetables. *Lancet* 1995; **346:** 1635.
5. WHO. Vitamin A status: is dietary replacement practicable. *WHO Drug Inf* 1995; **9:** 141.
6. Ncube TN, *et al.* Supplementing lactating women with puréed papaya and grated carrots improved vitamin A status in a placebo-controlled trial. *J Nutr* 2001; **131:** 1497–1502.
7. Vuong LT, *et al.* Plasma β-carotene and retinol concentrations of children increase after a 30-d supplementation with the fruit Momordica cochinchinensis (gac). *Am J Clin Nutr* 2002; **75:** 872–9.
8. West CE, *et al.* Consequences of revised estimates of carotenoid bioefficacy for dietary control of vitamin A deficiency in developing countries. *J Nutr* 2002; **132** (suppl): 2920S–2926S.
9. Jalal F, *et al.* Serum retinol concentrations in children are affected by food sources of β-carotene, fat intake, and anthelmintic drug treatment. *Am J Clin Nutr* 1998; **68:** 623–9.

Ischaemic heart disease. There are results from epidemiological studies suggesting the potential benefits of dietary betacarotene in preventing ischaemic heart disease, particularly in smokers; however, randomised placebo-controlled studies of betacarotene supplements have failed to find any benefit, as discussed on p. 2047.1.

Malignant neoplasms. Some evidence from epidemiological studies suggested that higher dietary intakes of carotenoids and especially betacarotene had a protective effect against cancer. Consequently several randomised placebo-controlled studies examining the use of betacarotene supplements in the primary or secondary prevention of malignancy were instigated. However, the results of studies so far published have generally been disappointing. Moreover, some results suggest that supplementation with betacarotene may lack benefit or may actually be harmful (see Prophylaxis of Malignant Neoplasms, p. 2047.3 and Effects on Mortality, below).

Porphyria. Despite a lack of robust evidence,[1] betacarotene is the most widely used systemic drug for the management of erythropoietic protoporphyria,[2,3] a non-acute porphyria characterised by cutaneous photosensitivity (p. 1556.1). It has been given with canthaxanthin to reduce the skin discoloration caused by betacarotene alone.

1. Minder EI, *et al.* A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria. *Cell Mol Biol (Noisy-le-grand)* 2009; **55:** 84–97.
2. Todd DJ. Erythropoietic protoporphyria. *Br J Dermatol* 1994; **131:** 751–66.
3. Todd DJ. Therapeutic options for erythropoietic protoporphyria. *Br J Dermatol* 2000; **142:** 826.

Adverse Effects and Precautions

Loose stools may occasionally occur during treatment with betacarotene and the skin may assume a slightly yellow discoloration. Bruising, dizziness, and arthralgia have been reported rarely.

Excessive intake of betacarotene does not result in hypervitaminosis A (see Pharmacokinetics, p. 2052.1).

Carcinogenicity. For reference to studies finding an increased incidence of lung cancers in individuals given betacarotene supplements to protect against malignancy, see under Prophylaxis of Malignant Neoplasms, p. 2047.3.

Effects on mortality. A systematic review of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies found that betacarotene, used either singly or with other antoxidants, significantly increased all-cause mortality.[1] In another review and meta-analysis, betacarotene supplementation showed a trend towards increased cancer mortality.[2]

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
2. Bardia A, *et al.* Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clin Proc* 2008; **83:** 23–34.

Effects on the skin. Yellow pigmentation of the skin may result from an unusually high consumption of carrots or other source of carotene,[1] or from a defect in the enzyme that normally metabolises betacarotene to vitamin A.[2] Hypercarotenaemia can be distinguished from jaundice by the fact that the sclerae retain their normal white colour. Pigmentation occurs first on the palms and soles and may extend to the nasolabial folds. Although it has been stated that the condition is harmless,[1,3] as the body converts carotene to retinol only as required,[1] others consider that long-standing hypercarotenaemia can have clinical sequelae:[2] neutropenia[4] and amenorrhoea[5] have been reported to be associated with the condition.

1. Sharman IM. Hypercarotenaemia. *BMJ* 1985; **290:** 95.
2. Vaughan Jones SA, Black MM. Metabolic carotenaemia. *Br J Dermatol* 1994; **131:** 145.
3. McGowan R, *et al.* Carotenaemia in children is common and benign: most can stay at home. *Scott Med J* 2004; **49:** 82–4.
4. Shoenfeld Y, *et al.* Neutropenia induced by hypercarotenaemia. *Lancet* 1982; **i:** 1245.
5. Kemmann E, *et al.* Amenorrhoea associated with carotenemia. *JAMA* 1983; **249:** 926–9.

Pharmacokinetics

Gastrointestinal absorption of betacarotene depends on the presence of bile and is increased by dietary fat. About 20 to 60% of betacarotene is metabolised to retinol in the intestinal wall, and a small amount is converted to vitamin A in the liver. The proportion of betacarotene converted to vitamin A decreases as the intake of betacarotene increases, and high doses of betacarotene do not lead to abnormally high serum concentrations of vitamin A. Unchanged betacarotene is distributed to various tissues including fat, the adrenal glands, and ovaries.

References.

1. Wang X-D. Review: absorption and metabolism of β -carotene. *J Am Coll Nutr* 1994; **13:** 314–25.

Human Requirements

Carotenes, of which betacarotene has the highest activity, are major dietary sources of vitamin A—see p. 2102.2.

UK and US recommended dietary intake. There is currently no UK dietary reference value (see p. 2046.1) for betacarotene, and in the USA recommended dietary allowances or dietary reference intakes (see p. 2046.1) have not been set. However, the Expert Group on Vitamins and Minerals[1] has established a safe upper level (SUL) for betacarotene of 7 mg daily, or about 110 micrograms/kg daily for a 60-kg adult.

1. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 06/01/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: B-Caroteno; Bronce Sol; ***Austria***: Carotaben; ***Braz.***: Vitizin Beta; Zirvit Beta; ***China***: Bei Xi Di (贝西迪); Kaluo (卡洛); ***Cz.***: Carotaben; ***Ger.***: Carotaben; Carotinora; ***India***: Oxyma; ***Ital.***: Keratoplastica; Tannisol; ***Switz.***: Carotaben; ***Thai.***: Betacar; ***Turk.***: Acecap; Carovit; ***UK***: Biocarotine; ***USA***: Lumitene.

Multi-ingredient Preparations. ***Arg.***: Betabronze; Carotenos; Herbaccion Antioxidante; Hipersel; Indian Health - Urucum; Ipri V Plus; Ipri V Total; Ipri V; Krebs Plus; Krebs; Larotabe; Marathon Antioxidante; Natubrown; Para Sol SD; Perfect Sun; Piel Vital; Rominafort; Senexon Plus; Sigmasol; Sol Bronce Vital; Super Antioxidante; SX-22; Tonovital Antioxidante; Tonovital Plus Antioxidante; Vitamina C Plus; Zinc Antioxidante + Guarana; ***Austral.***: Antioxidant Forte Tablets†; Antioxidant Tablets†; Beta A-C; Beta A-C; Bilberry Plus Eye Health†; Bio ACE Excell; Bio ACE; Cholesterol Health; Eye Health Herbal Plus Formula 4†; Ocuvite PreserVision†; Radiance; Skin Support; Supercarotene C&E†; ***Austria***: Linola-Fett†; ***Braz.***: Licopene†; Livten Vit; Ocuvite PreserVision; ***Canad.***: Beta-C†; Ester Aces; Geri-Plus†; Liv-Gd; Liv-Gd; Phytopro†; Protect†; Super AO Factors; Super AO Formula†; Watkins Harvest†; ***Chile***: Balans†; Biodif†; Biofax†; Biotonus; Larotabe; Seresis; Unitone; Vitagenol; Vitotal†; ***China***: Bei Xi Yi (贝西伊); Difrarel (递法明); ***Fr.***: Anti-oxydant 200; Cledist; Difrarel; Imedeen Tan Optimizer†; Oxelio Topique; Oxelio; Photoderm; Superoxylase; ***Hong Kong***: Antioxidant Vita Tech†; Sanjukei Panax Ginseng; ***Hung.***: Cellactive; Memolife; ***India***: Actima; Ala-Plus; Alfaflavon; Alfatoz; Alfex-BT; Alpha B-Cal; Antoxid; Beta-Sclerobion; Bm-Vita; Carofit; Co-Q-Dent; Derantox; Dianuron; Ecome-LY; Elnutra-M; Elrox-AO; Exerge-HC; Fabulae; Flintoff; Freecad; Ginkoriv Plus; Glace; Horac; L-Bex; L-Vit-Z; Leclub; Lutamin; Lutivit; Luvion; Lycogreen; Lycominvit; Lyconerve; Lycosta; Lycozin; Lytox; Macugold; Natoz; NBOxid; Ocugold; Oiz; Orymax; Oxipre; Oxyban; Oxydex; Oxyeye; Oxytret; Oxyvit; ***Indon.***: Amaropo Plus; Antion; Antox; Artovit; Asten; Azvit; Bececar; Berry Vision; Beta-CE; Betafort; Bevita; Bevizil; Bioretin†; Brainvit; Colaskin; Curcuma Plus; Danzet; Entrap; Eyebright; Eyevit; Hemaviton Skin Nutrient; Kuminta; Lanavision Plus; Lanavision; Lesifit; Letropar; Lubire; Lutevit; Lycoten; Lycoxy; Matase; Matovit; Maxivit; My Caps; Nicaro; Nu-Derm Sunblock†; nutrivision; Nuvision; Ocu-V; Oculex; Oculex; Opibright; Optha-LL; Optimax Plus; Optimax; Oxcal; Oxypen; Oxyvit; Progence; Qutan-10; Radivit; Reticopen; Retivit Plus; Retivit; Retop; Scaven; Seleca; Selefit Plus; Seloxy AA; Seloxy; Univoxy; Vantiz; Viceten-Z; Viceten†; Vioxy-fm; Vioxy; Vitacore; Vitacur; Vitalene; Vitanox; Vitop; ***Irl.***: Seven Seas Active Sport†; ***Israel***: Opti-Safe Areds; Opti-Safe†; ***Ital.***: AMD; Anaribes Plus; Angstrom Viso; Angstrom Viso; Betaeffe Plus; Caresel; Carovit Forte; Carovit Repair; Carovit; Ecamannan; Eccarvit Plus; Keratolip; Konorderm; Mirtilene; Mirtivit; Riduton Ergo; Selenium-ACE†; Solecin†; Tannidin Plus; Tanwards Combi; Vitalux; Vitreolux; ***Malaysia***: Eurobio Bio-Vizmax; Seresis; ***Mex.***: Seresis; Unitone; ***Philipp.***: Carofit; Cristane; iiCare; Nutri-Aid; Polynerv-E with lecithin; Pynocare 40 Actisome; Zimuvite; ***Pol.***: Biovision; ***Port.***: Fortal Vision; Rilastil Anti-Oxidante; Rilastil Dermo Solar; ***Rus.***: Antioxycaps (Антиоксикапс); Antioxycaps with Iodine (Антиоксикапс с Йодом); Antioxycaps with Selenium (Антиоксикапс С Селеном); Antioxycaps with Zincum (Антиоксикапс с Цинком); Hematogen C Vita (Гематоген С Вита); Strix (Стрикс); Tri-V Plus (Три-Ви Плюс)†; Triovit (Триовит); ***Singapore***: Androlistica; Glutamine Plus; Scar Esthetique; Seresis†; ***Spain***: Aceite Acalorico; Mirtilus†; ***Switz.***: Visaline†; ***Ukr.***: Gold Ray (Голд Рей); Optix (Оптикс); Optix Forte (Оптикс Форте); OxyLic (ОксиЛик); Triovit (Триовит); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Vitrum Foreyes (Витрум Форайз); Vitrum Foreyes Forte (Вітрум Форайз Форте); ***USA***: Aces; ***Venez.***: Biocaps; Optibiol.

Pharmacopoeial Preparations

USP 36: Beta Carotene Capsules; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets.

Biotin *(rINN)*

Biotiini; Biotina; Biotinas; Biotine; Biotinum; Coenzyme R; Vitamin H; Биотин.

cis-5-(Hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-4-yl)valeric acid.

$C_{10}H_{16}N_2O_3S$=244.3

CAS — 58-85-5.

ATC — A11HA05.

ATC Vet — QA11HA05.

UNII — 6SO6U10H04.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Biotin). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water and in alcohol; practically insoluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Biotin). A practically white crystalline powder. Very slightly soluble in water and in alcohol; insoluble in other common organic solvents. Store in airtight containers.

Profile

Biotin is traditionally considered to be a vitamin B substance. It is an essential coenzyme in fat metabolism and in other carboxylation reactions. Biotin deficiency may result in the urinary excretion of organic acids and changes in skin and hair. Deficiency of biotin is very unlikely in man because of its widespread distribution in food. Egg-yolk and offal are especially good sources. Biotin deficiency has been reported however during long-term parenteral nutrition and in patients with biotinidase deficiency, an inherited metabolic disorder. For dosage in biotinidase or isolated carboxylase deficiency see below. A combination of biotin and chromium tripicolinate (p. 2056.1) has been promoted as an adjunct for the management of diabetes mellitus.

Biotin combines with avidin, a glycoprotein present in raw egg-white, to form an inactive compound.

Adverse effects. For reference to life-threatening eosinophilic pleuropericarditis in a patient receiving biotin and pantothenic acid see p. 2085.3.

Deficiency states. Biotin has been used to treat deficiency of biotinidase or holocarboxylase synthetase, enzymes responsible for the recycling and incorporation of biotin. In the UK, the *BNFC* suggests the following doses:

- for isolated carboxylase defects, biotin may be given to neonates in a dose of 5 mg once daily by mouth or slow intravenous injection, adjusted according to response; older patients may be given 10 mg daily. The usual maintenance dose ranges from 10 to 50 mg daily, though up to 100 mg daily may be needed
- for defects of biotin metabolism, 10 mg once daily may be given by mouth or slow intravenous injection, adjusted according to response. Usual maintenance doses are 5 to 20 mg daily but higher doses may be needed

References.

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Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p. 2046.1) has been set for biotin although it was considered that an intake of between 10 and 200 micrograms daily was both safe and adequate.[1] Similarly in the USA an adequate intake of 30 micrograms daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aminosam; Panabiotin; ***Austria***: Bio-H-Tin; Curatin; Medobiotin; Merzbiotin†; ***Chile***: Hvit; ***Cz.***: Deacura; ***Fin.***: Biotisan; ***Ger.***: Bio-H-Tin; Deacura; Gabunat; Natubiotin; ***Hung.***: Bio-H-Tin†; ***India***: Biosure; Btn; Cosmetin; H-Vit; ***Ital.***: Biodermatin; Diathynil; Nebiotin; ***Pol.***: Biotebal; ***Spain***: Medebiotin; ***Switz.***: Bio-H-Tin; Rombellin; ***Ukr.***: Medobiotin (Медобиотин); ***USA***: Appearex; Hard Nails.

Multi-ingredient Preparations. ***Arg.***: Cistidac; Cistimax Ungueal; Folimax B; HSN; Megaplus; Rain-LY; Valcatil Max; Valcatil Plus; ***Austral.***: Gluco Support; ***Braz.***: Eximia Fortalize; ***Canad.***: Glucoplex; ***Chile***: Anastim; Brolin; Vantux Plus; ***Fr.***: Forcapil; Zeniac LP; Zeniac; ***Hung.***: Forcapil; ***India***: Acmic-Alpha; Ameco Plus; B-9 Tetra; B7 Plus; Biofair; Derantox; E-Cod Plus; Mexivit; Pabatab-BZ; ***Indon.***: Aldovas; Alicron; Cerebrofort Gold; Neofer; Tiola; Vionin; ***Ital.***: Bioesse Plus; Biomineral 5-Alfa Shampoo; Biomineral 5-Alfa; ***Malaysia***: Evelle; ***Philipp.***: Diachrotin; Optigrow; ***Singapore***: Evelle; ***Spain***: Doctodermis; Lacerdermol†; ***UK***: Pilfood; ***Ukr.***: Fitoval Capsules (Фитовал капсулы); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; ***USA***: Blood Sugar Balance; PNV-Iron†; REQ49+; ***Venez.***: Anastim.

Pharmacopoeial Preparations

USP 36: Biotin Capsules; Biotin Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Boron

Bor; Bore; Borium; Boro; Бор.

B=10.81

CAS — 7440-42-8.

UNII — N9E3X5056Q.

Profile

Boron is a trace element that is widely distributed in nature, mainly in the form of borates. It appears to be essential for plant and animal health. Boron compounds such as borax and boric acid have been used as disinfectants although less toxic preparations are usually preferred. Boron has also been used in nutritional supplements for bone health.

Boron, in the form of injections of boron-10 containing compounds such as sodium borocaptate or boronophenylalanine, is being investigated in boron neutron capture therapy. Boron-10, a stable isotope, when irradiated with low-energy thermal neutrons undergoes nuclear capture and fissure reactions so that the high energy radiation released locally can be used to treat malignant neoplasms including high-grade gliomas, melanomas, and cerebral metastases.

References.

1. Newnham RE. Essentiality of boron for healthy bones and joints. *Environ Health Perspect* 1994; **102** (suppl 7): 83–5.
2. WHO. Boron. *Environmental Health Criteria 204.* Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/ehc/ehc/ehc204.htm (accessed 12/10/10)
3. Barth RF, *et al.* Boron neutron capture therapy of cancer: current status and future prospects. *Clin Cancer Res* 2005; **11:** 3987–4002.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Accelerex; Bone Builder; ***Chile***: Caprimida D Balance; ***India***: Bonjo Aid; Kelcer; Kibocal-M; Orbone Forte; Orbone; Ospical-M; Osteo-G; ***Indon.***: Biocal-95; Cal-95; Calplex; Caltron; Jointace; OA Plus; ***Ital.***: Osteo Complex; ***Malaysia***: Bio-Cal; ***Pol.***: Caltrate Plus; ***Singapore***: Shine Bio-Cal; ***Thai.***: Calvin Plus; ***UK***: Caltrate Plus; Estroven; Ostron; ***Ukr.***: Calcemin (Кальцемин); Calcemin Silver (Кальцемин Сильвер); ***USA***: Caltrate Plus; Prenate Chewable with Quatrefolic; TheraCal D.

Pharmacopoeial Preparations
USP 36: Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets.

Calcium Ferrous Citrate

Ferrous Calcium Citrate.
Dicalcium iron(2+) bis(2-hydroxypropane-1,2,3-tricarboxylate).
$C_{12}H_{10}Ca_2FeO_{14}$=514.2
CAS — 53684-61-0.
UNII — 4P1IZU59M5.

Profile

Calcium ferrous citrate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Singapore***: Raricap Combi; Raricap.

Calcium Fluoride

Fluoruro cálcico; Фторид Кальция.
CaF_2=78.07
CAS — 7789-75-5.
UNII — O3B55K4YKI.

Pharmacopoeias. In *Ger.*

Profile

Calcium fluoride is used as a fluoride supplement (see Sodium Fluoride, p. 2089.2) for the prevention of dental caries. Calcium fluoride is also used as a source of calcium.

Homoeopathy

Calcium fluoride has been used in homoeopathic medicines under the following names: Calcarea Fluorica; Calc. Fluor; Calcium Fluoratum; Cal. fl.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Calcifluor†.

Multi-ingredient Preparations. ***Austral.***: Duo Celloids SCF†; Duo Celloids SPCF†; ***Denm.***: Bifluorid; ***Fr.***: Bifluorid; ***India***: Calcinol; ***Pol.***: Bifluorid; ***Swed.***: Bifluorid; ***Thai.***: Calcinol-RB.

Homoeopathic Preparations. ***Austral.***: Celloids CF 43†; ***Austria***: Nebenhohlen-Tropfen Nr 26†; Zahnkugelchen; ***Canad.***: Combinaison†; Cutisitum†; Diamite; Formula CI 207†; Formula DE 226†; Formula PC 223†; Hylands Bioplasma; Hylands Hemorrhoids; Melange†; Nuage Bioplasma†; Optalia†; Phyto-Cal; Sinus Ease; Sinuspax†; Sorinoheel; Tyglan†; ***Chile***: Calcarea fluor Compuesta; Ikoplex No 10; Ikoplex No 15; Ikoplex No 1; Ikoplex No 24; Ikoplex No 4; Ikoplex No 6; ***Cz.***: Galium; ***Fr.***: Calcarea Compose; Homeodose 20†; Jenoverine†; Osteocynesine; Silicea Complexe No 11; Sinuspax; ***Ger.***: Cefalymphat†; Disco-cyl Ho-Len-Complex; Drufusan N†; Drufusan; Infiossan; Ranocalcin HM; Reproven N; Varicylum N; Venen-Komplex Ho-Fu-Complex; Veno-Injektopas; ***Neth.***: Jenoverine†; Kind 0-6 Caltrivat; Lymfelite; Myamolite; Osteocynesine†; Toxex; ***Port.***: Osteocynesine; ***Rus.***: Mastopol (Мастопол); Rhus-Plus (Рус-Плюс); ***Switz.***: Regenaplex Nr. 21c; Regenaplex Nr. 51c; Sinuspax†; ***UK***: Medicinal Gargle; New Era Elasto; ***Ukr.***: Immunokind (Иммунокинд).

Calcium Levomefolate

Calcium L-Methylfolate; Calcium (6S)-5-Methyltetrahydrofolate; Calcium L-5-Methyltetrahydrofolate; Levomefolate Calcium (USAN); Levomefolinate Calcium; LMCA; Кальция L-Метилфолат.
Calcium *N*-[4-({[(6*S*)-2-amino-5-methyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl}amino)benzoyl]-L-glutamate.
$C_{20}H_{23}CaN_7O_6$=497.5
CAS — 151533-22-1 (calcium levomefolate); 26560-38-3 (calcium methylfolate).
UNII — A9R10K3F2F.

NOTE. The names calcium levomefolinate and calcium mefolinate have been used for calcium levomefolate and calcium methylfolate respectively. Metafolin is a trade mark that has been used for calcium levomefolate.

Pharmacopoeias. In *US.*

USP 36: (Calcium L-5-methyltetrahydrofolate). It contains not more than 1.0% of calcium D-5-methyltetrahydrofolate calculated on the anhydrous and solvent-free basis. Store in airtight containers at a temperature between 8 degrees and 15 degrees in a dry place.

Profile

Calcium levomefolate is the calcium salt of the (*S*)-isomer of 5-methyltetrahydrofolate, the biologically active metabolite of folic acid (p. 2063.1). It is used as a food supplement and also has similar uses to folic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Prefolic; ***USA***: Deplin.

Multi-ingredient Preparations. ***USA***: ALZ-NAC; Beyaz; Cerefolin NAC; LMTHF/Pyridoxine HCl/Cyanocobalamin; Metanx; PNV-Iron†; Safyral; VitaCirc-B.

Carnitine Derivatives

Производные Карнитина.

Acetylcarnitine Hydrochloride

Acetilcarnitina, hidrocloruro de; Acetyl-L-carnitine Chloride; Levacecarnine Hydrochloride; Levocarnitinum acetilum hydrochloricum; ST-200; Ацетилкарнитина Гидрохлорид.
(3-Carboxy-2-hydroxypropyl)trimethylammonium acetate (ester) chloride.
$C_9H_{17}NO_4$,HCl=239.7
CAS — 5080-50-2.
ATC — N06BX12.
ATC Vet — QN06BX12.
UNII — NDW10MX58T.

Carnitine *(rINN)*

Carnitina; Carnitinum; Karnitin; ST-198; Vitamin B_T; Vitamina B_T; Карнитин.
(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; 3-Hydroxy-4-trimethylammoniobutyrate.
$C_7H_{15}NO_3$=161.2
CAS — 461-06-3.
UNII — S7UI8SM58A.

Levocarnitine *(BAN, USAN, rINN)*

L-Carnitina; L-Carnitine; L-Karnitin; Levocarnitin; Levocarnitina; Lévocarnitine; Levocarnitinum; Levokarnitiini; Levokarnitin; Levokarnitinas; Левокарнитин.
(*R*)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; (*R*)-3-Hydroxy-4-trimethylammoniobutyrate.
$C_7H_{15}NO_3$=161.2
CAS — 541-15-1.
ATC — A16AA01.
ATC Vet — QA16AA01.
UNII — 0G389FZZ9M.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Levocarnitine). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water; soluble in warm alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 6.5 to 8.5. Store in airtight containers.

USP 36: (Levocarnitine). White, hygroscopic, crystals or crystalline powder. Freely soluble in water and in hot alcohol; practically insoluble in acetone, in ether, and in benzene. pH of a 5% solution in water is between 5.5 and 9.5. Store in airtight containers.

Levocarnitine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocarnitina; Lévocarnitine, Chlorhydrate de; Levocarnitini Hydrochloridum; Левокарнитина Гидрохлорид.
(*R*)-3-Hydroxy-4-trimethylammoniobutyrate hydrochloride.
$C_7H_{15}NO_3$,HCl=197.7
CAS — 6645-46-1.
UNII — J3Y5E6IKS3.

Levocarnitine Propionate

L-Carnitine propionate; Lévocarnitine, Propionate de; Levocarnitini Propionas; Propionato de levocarnitina; L-Propionylcarnitine; Propionylcarnitine; Propionyl-L-carnitine; ST-261; Левокарнитина Пропионат.
$C_{10}H_{19}NO_4$=217.3
CAS — 20064-19-1.
UNII — 0HU2UI27HF.

Levocarnitine Propionate Hydrochloride *(USAN)*

Propionyl-L-carnitine Hydrochloride; STI-261.
(2*R*)-3-Carboxy-*N*,*N*,*N*-trimethyl-2-(propanoyloxy)propan-1-aminium chloride.
$C_{10}H_{20}ClNO_4$=253.7
CAS — 119793-66-7.
UNII — 12FW2YBF04.

Uses and Administration

Carnitine is an amino acid derivative that is an essential cofactor of fatty acid metabolism.

Carnitine is used in the treatment of primary carnitine deficiency and in carnitine deficiency secondary to a variety of defects of intermediary metabolism or other conditions such as haemodialysis. Both the L- and the DL-isomers have been used, but it is believed that only levocarnitine is effective and in addition, that DL-carnitine supplementation can lead to carnitine deficiency.

In the UK, depending on the condition, up to 200 mg/kg daily of levocarnitine is given orally, in 2 to 4 divided doses. Rarely, higher doses of up to 400 mg/kg daily may be needed. In the USA, lower doses up to about 3 g daily are recommended.

When given intravenously, up to 100 mg/kg daily is given in 3 to 4 divided doses by slow intravenous injection over 2 to 3 minutes. Higher intravenous doses have been given, but are associated with an increased incidence of adverse effects.

Similar doses are used in children, although initial dose recommendations may vary in different countries, see Administration in Children, below.

In patients with carnitine deficiency secondary to haemodialysis, the recommended dose of levocarnitine is 10 to 20 mg/kg intravenously after each dialysis session, adjusted according to plasma-carnitine concentrations. An oral maintenance dose of 1 g daily may be considered (but see Adverse Effects and Precautions, p. 2054.3).

Levocarnitine is under investigation for the treatment of zidovudine-induced mitochondrial myopathy. Carnitine derivatives have been used to treat conditions including cardiovascular disease, peripheral arterial disease, cerebrovascular insufficiency, peripheral neuropathies, and neurological disorders, see below.

Carnitine chloride, carnitine hydrochloride, carnitine orotate, carnitine tartrate, levocarnitine fumarate, levocarnitine tartrate, acetylcarnitine or its hydrochloride, and bicarnitine chloride have also been used.

Administration in children. In the treatment of primary and secondary carnitine deficiency and organic acidaemias in children, levocarnitine is given in doses similar to those used in adults, see Uses and Administration, above. In the USA, an initial oral dose of 50 mg/kg daily is suggested for infants and children, increased gradually if necessary to a maximum of 3 g daily. The *BNFC* suggests that carnitine may also be given to neonates and children up to 18 years of age by intravenous infusion for primary deficiency and organic acidaemias, diluted in sodium chloride 0.9%, or glucose 5 or 10%; an initial dose of 100 mg/kg over 30 minutes is followed by a continuous infusion of 4 mg/kg per hour.

Carnitine supplementation. Carnitine occurs as distinct L- and D-isomers although naturally-occurring carnitine is almost exclusively the L-isomer.[1] Carnitine is an essential co-factor of fatty acid metabolism in the heart, liver, and skeletal muscle.[1,2] It is normally synthesised in the liver, brain, and kidneys in sufficient quantities to meet human requirements but dietary sources such as meat and dairy products also provide carnitine.[1-4] In plasma and tissues carnitine is present in the free form and as acylated esters of which acetylcarnitine is the most abundant.

Although DL-carnitine is the form often present in over-the-counter preparations and dietary supplements, levocarnitine should be preferred, as the two isomers differ in their actions. Levocarnitine acts as a substrate for carnitine acetyltransferase while D-carnitine acts as a competitive inhibitor; also, levocarnitine-induced stimulation of palmitate oxidation is competitively inhibited by D-palmitoylcarnitine. Such differences are believed to account for findings of benefit only with the L-isomer, or unwanted effects when D-carnitine or DL-carnitine was used.[1,5]

Primary **carnitine deficiency** is a disorder of the membrane transport of carnitine and patients have presented with hypoglycaemia and encephalopathy, skeletal myopathy, and cardiomyopathy. Therapy with carnitine in these primary deficiency states is considered to have a rational basis.[2,4-6] Secondary carnitine deficiency occurs in many inherited metabolic disorders, especially in the organic acidurias and disorders of beta-oxidation. The value of carnitine for these conditions is controversial.[2,4,6-8]

Carnitine deficiency may also arise during the long-term use of **drugs** such as valproic acid,[5,9-11] pivampicillin,[12,13] or pivmecillinam,[12] which are conjugated with carnitine. Whether carnitine supplementation can prevent or reverse this type of deficiency is unclear: although treatment with carnitine raised plasma-carnitine concentrations, it had no more effect than placebo on the well-being of children receiving valproic acid therapy in one study,[14] but others have found levocarnitine supplementation of value in attenuating valproate-induced hyperammonaemia after a protein-rich meal,[15] and some paediatric neurologists consider supplementation justified in selected children with epilepsy,[16,17] including those with, or at risk of, valproate-induced hepatotoxicity and hyperammonaemic encephalopathy. There is some suggestion that carbamazepine and phenobarbital can also decrease carnitine concentrations.[10,11] Therapy with cisplatin[18] or ifosfamide[19] has been reported to cause increased urinary excretion of carnitine.

There is also some evidence[5,20] that carnitine supplements may be of benefit to low birth-weight preterm **infants**, but a double-blind study[21] failed to confirm this effect. A systematic review concluded that there are insufficient data to support the use of carnitine supplementation for the treatment of apnoea of prematurity, despite a plausible rationale for such treatment.[22] While some evidence of benefit exists for carnitine supplementation of neonates receiving parenteral nutrition,[5] a systematic review found no evidence of effect on weight gain, fat utilisation, or ketogenesis.[23]

Low concentrations of carnitine have also been reported to occur in a variety of other conditions (see below).

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CARDIOVASCULAR DISEASE. There is some evidence that carnitine supplementation may exert a cardioprotective role. Benefit in patients with *cardiomyopathies*,[1-3] reduction of infarct size in patients with *myocardial infarction*,[4] and increased exercise performance in patients with *angina*[5] or *intermittent claudication*,[6-9] have all been described in patients given carnitine. While variable effects on cholesterol and triglyceride plasma concentrations have been described,[5] studies in diabetic[10] and hyperlipoproteinaemic[11] patients have reported reductions in plasma lipoprotein(a) concentrations. However, carnitine supplementation in patients with chronic *heart failure* failed to increase exercise capacity,[12] and its value outside of actual deficiency is still considered uncertain.[5]

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7. Brevetti G, *et al*. European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999; **34:** 1618–24.
8. Wiseman LR, Brogden RN. Propionyl-L-carnitine. *Drugs Aging* 1998; **12:** 243–8.
9. Andreozzi GM. Propionyl L-carnitine: intermittent claudication and peripheral arterial disease. *Expert Opin Pharmacother* 2009; **10:** 2697–2707.
10. Derosa G, *et al*. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. *Clin Ther* 2003; **25:** 1429–39.
11. Sirtori CR, *et al*. L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). *Nutr Metab Cardiovasc Dis* 2000; **10:** 247–51.
12. The Investigators of the Study on Propionyl-L-Carnitine in Chronic Heart Failure. Study on propionyl-L-carnitine in chronic heart failure. *Eur Heart J* 1999; **20:** 70–6.

EXERCISE PERFORMANCE. Improved exercise performance in patients with angina or peripheral vascular disease has been described in patients given carnitine supplementation (see Cardiovascular Disease, above). However, evidence of benefit from the use of carnitine in healthy subjects in an attempt to improve athletic performance is lacking.[1,2] Nonetheless, interest in, and research into, the possible effects in healthy subjects and their mechanisms has continued.[3-6]

1. Tonda ME, Hart LL. N,N dimethylglycine and L-carnitine as performance enhancers in athletes. *Ann Pharmacother* 1992; **26:** 935–7.
2. Brass EP. Supplemental carnitine and exercise. *Am J Clin Nutr* 2000; **72** (suppl): 618S–623S.
3. Karlic H, Lohninger A. Supplementation of L-carnitine in athletes: does it make sense? *Nutrition* 2004; **20:** 709–15.
4. Brass EP. Carnitine and sports medicine: use or abuse? *Ann N Y Acad Sci* 2004; **1033:** 67–78.
5. Kraemer WJ, *et al*. L-carnitine supplementation: influence upon physiological function. *Curr Sports Med Rep* 2008; **7:** 218–23.
6. Broad EM, *et al*. Carbohydrate, protein, and fat metabolism during exercise after oral carnitine supplementation in humans. *Int J Sport Nutr Exerc Metab* 2008; **18:** 567–84.

FATIGUE. Placebo-controlled studies in elderly subjects found that levocarnitine supplementation significantly reduced physical and mental fatigue,[1,2] while an open study in patients with chronic fatigue syndrome reported improvement in mental fatigue with acetylcarnitine, and general fatigue improvement with propionylcarnitine.[3] In a crossover study with amantadine, patients with chronic fatigue syndrome given levocarnitine for 8 weeks showed improvement in 12 out of 18 parameters measuring fatigue; patients who were most ill at the start of the study improved the most.[4] There is also some suggestion that levocarnitine supplementation may be of benefit in alleviating fatigue induced by antineoplastic chemotherapy,[5] or interferon.[6] For reports of carnitine use for fatigue in multiple sclerosis patients, see Neurological Disorders, below.

1. Pistone G, *et al*. Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. *Drugs Aging* 2003; **20:** 761–7.
2. Malaguarnera M, *et al*. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 2007; **86:** 1738–44.
3. Vermeulen RCW, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* 2004; **66:** 276–82.
4. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* 1997; **35:** 16–23.
5. Graziano F, *et al*. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. *Br J Cancer* 2002; **86:** 1854–7.
6. Neri S, *et al*. L-carnitine decreases severity and type of fatigue induced by interferon-α in the treatment of patients with hepatitis C. *Neuropsychobiology* 2003; **47:** 94–7.

HAEMODIALYSIS. Carnitine homoeostasis is altered in renal failure[1] and a functional deficiency may develop in patients on dialysis.[2] This dialysis-related carnitine disorder manifests notably as anaemia, intradialytic hypotension, cardiomyopathy, and muscle weakness and fatigability. Treatment with intravenous levocarnitine 20 mg/kg after each dialysis session has been recommended. Clinical response should be evaluated at 3-monthly intervals, and treatment stopped if no improvement is seen within 9 to 12 months.[2] A systematic review suggested a beneficial effect of levocarnitine for the management of anaemia in haemodialysis patients.[3] Since carnitine supplementation has been associated with a reduction[4,5] in the incidence of haemodialysis-induced cramps (p. 1779.3) it has been suggested that these cramps might be due in part to carnitine deficiency. A meta-analysis[6] considered the evidence for benefit in cramp and hypotension to be suggestive, but not conclusive.

1. Matera M, *et al*. History of L-carnitine: implications for renal disease. *J Ren Nutr* 2003; **13:** 2–14.
2. Eknoyan G, *et al*. Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder: National Kidney Foundation Carnitine Consensus Conference. *Am J Kidney Dis* 2003; **41:** 868–76.
3. Hurot J-M, *et al*. Effects of L-carnitine supplementation in maintenance hemodialysis patients: a systematic review. *J Am Soc Nephrol* 2002; **13:** 708–14.
4. Ahmad S, *et al*. Multicenter trial of L-carnitine in maintenance hemodialysis patients II: clinical and biochemical effects. *Kidney Int* 1990; **38:** 912–18.
5. Sakurauchi Y, *et al*. Effects of L-carnitine supplementation on muscular symptoms in hemodialyzed patients. *Am J Kidney Dis* 1998; **32:** 258–64.
6. Lynch KE, *et al*. Effects of L-carnitine on dialysis-related hypotension and muscle cramps: a meta-analysis. *Am J Kidney Dis* 2008; **52:** 962–71.

HIV INFECTION. Carnitine deficiency has been reported in HIV-infected patients. Causes may include malabsorption or increased excretion due to a wasting syndrome commonly found in these patients, or toxicity from antiretroviral drugs causing metabolic changes or altered lipid metabolism in the patient.[1] Small, mostly uncontrolled studies have suggested benefit from supplementation with levocarnitine or acetylcarnitine in relieving complications of HIV infection and adverse effects of antiretroviral drugs,[2] notably toxic neuropathy.[3,4]

1. Vilaseca MA, *et al*. Low serum carnitine in HIV-infected children on antiretroviral treatment. *Eur J Clin Nutr* 2003; **57:** 1317–22.
2. Ilias I, *et al*. L-Carnitine and acetyl-L-carnitine in the treatment of complications associated with HIV infection and antiretroviral therapy. *Mitochondrion* 2004; **4:** 163–8.
3. Herzmann C, *et al*. Long-term effect of acetyl-L-carnitine for antiretroviral toxic neuropathy. *HIV Clin Trials* 2005; **6:** 344–50.
4. Osio M, *et al*. Acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study. *J Peripher Nerv Syst* 2006; **11:** 72–6.

MALE INFERTILITY. Increases in sperm motility have been reported in some infertile men treated with carnitine,[1-3] and some studies have reported improvements in pregnancy rates,[4] although clinical benefit needs to be further evaluated.[4,5]

1. Lenzi A, *et al*. Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. *Fertil Steril* 2003; **79:** 292–300.
2. Lenzi A, *et al*. A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril* 2004; **81:** 1578–84.
3. Vicari E, Calogero AE. Effects of treatment with carnitines in infertile patients with prostato-vesiculo-epididymitis. *Hum Reprod* 2001; **16:** 2338–42.
4. Zhou X, *et al*. Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. *Asia Pac J Clin Nutr* 2007; **16** (suppl 1): 383–90.
5. Agarwal A. Carnitines and male infertility. *Reprod Biomed Online* 2004; **8:** 376–84.

NEUROLOGICAL DISORDERS. A meta-analysis of 21 studies concluded that acetylcarnitine improved mild cognitive impairment and prevented deterioration in patients with mild *Alzheimer's disease*.[1] However, a systematic review of 11 of these trials concluded that, although some evidence of benefit on clinical global impression exists, use of acetylcarnitine could not be routinely recommended in the treatment of Alzheimer's disease.[2]

Although no differences were found in serum carnitine concentrations in *multiple sclerosis* patients with or without disabling fatigue,[3] there is some suggestion of benefit with acetylcarnitine treatment for those patients with fatigue,[4] although a systematic review[5] considered the evidence of benefit insufficient. Carnitine has been reported to be of benefit in other cases of fatigue (see above).

In *Rett syndrome*, a severe neurodevelopmental disorder, supplementation with levocarnitine led to improvements in sleep efficiency, energy levels, and communication skills.[6] Parental and medical assessment of patient well-being improved in another study;[7] girls with classical Rett syndrome also improved in motor behaviour as assessed medically.

1. Montgomery SA, *et al*. Meta-analysis of double-blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol* 2003; **18:** 61–71.
2. Hudson S, Tabet N. Acetyl-l-carnitine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 08/11/05).
3. Fukazawa T, *et al*. Serum carnitine and disabling fatigue in multiple sclerosis. *Psychiatry Clin Neurosci* 1996; **50:** 323–5.
4. Tomassini V, *et al*. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. *J Neurol Sci* 2004; **218:** 103–8.
5. Tejani AM, *et al*. Carnitine for fatigue in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 10/06/10).
6. Ellaway CJ, *et al*. Medium-term open label trial of L-carnitine in Rett syndrome. *Brain Dev* 2001; **23** (suppl): S85–S89.
7. Ellaway C, *et al*. Rett syndrome: randomized controlled trial of L-carnitine. *J Child Neurol* 1999; **14:** 162–7.

Adverse Effects and Precautions

Gastrointestinal disturbances such as nausea, vomiting, diarrhoea, and abdominal cramps have been reported after the use of levocarnitine. Body odour has also been noticed in some patients, possibly due to the formation of the metabolite trimethylamine (see Fish Odour Syndrome, p. 2043.2). Decreasing the dosage may reduce or eliminate these effects; oral levocarnitine should be consumed slowly to decrease gastrointestinal disturbances. Seizures have been reported.

Patients with severe renal impairment should not be given high oral doses of levocarnitine for long periods,

because of the accumulation of the metabolites trimethylamine and trimethylamine-*N*-oxide. This is said not to occur to the same extent after intravenous dosage. Diabetic patients given carnitine while receiving insulin or hypoglycaemic drugs should be monitored for hypoglycaemia.

Renal impairment. Of 30 patients given DL-carnitine intravenously after dialysis sessions 3 developed myasthenia-like symptoms but when these 3 were given only levocarnitine the symptoms did not occur.[1] It was considered that in anuric uraemic patients the D-isomer was not excreted adequately and that accumulation had blocked neuromuscular transmission. It was therefore suggested that levocarnitine, rather than the DL-form, should be used. (High and prolonged oral doses of levocarnitine should, however, be avoided—see p. 2054.3.)

1. Bazzato G, *et al*. Myasthenia-like syndrome after DL but not L-carnitine. *Lancet* 1981; **i:** 1209.

Pharmacokinetics

Oral doses of levocarnitine are absorbed slowly and incompletely from the small intestine. Bioavailability has been reported to be only about 10 to 15%, with peak plasma concentrations occurring about 3 to 4 hours after an oral dose. Plasma concentrations after oral doses represent the sum of endogenous and exogenous material. Levocarnitine does not appear to bind to plasma proteins. It is mainly eliminated by the kidneys, undergoing extensive tubular reabsorption. After intravenous doses, levocarnitine appears to undergo minimal metabolism. Levocarnitine given orally may undergo degradation in the gastrointestinal tract, leading to the formation of metabolites such as trimethylamine-*N*-oxide and γ-butyrobetaine, recovered in the urine and faeces, respectively.

References.
1. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. *Clin Pharmacokinet* 2003; **42:** 941–67.
2. Bain MA, *et al*. Disposition and metabolite kinetics of oral L-carnitine in humans. *J Clin Pharmacol* 2006; **46:** 1163–70.
3. Fornasini G, *et al*. A pharmacokinetic model for L-carnitine in patients receiving haemodialysis. *Br J Clin Pharmacol* 2007; **64:** 335–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Albicar; Fertilix; Laremide; Neurex; Neuroactil; ***Austria***: Nefrocarnit; ***Canad.***: Carnitor; ***Chile***: Actigeron; Carnicor†; ***China***: Ao Bei Li (奥贝利); Ao Shu Jie (澳枢捷); BoWei (博维); Carnitene (可益能); Cartan (卡尔特); Dongweili (东维力); Gai Lei (盖雷); Ke Fei (克非); Ke Ni You (可尼尤); Ke Pu Tuo (可谱妥); Lei ka (雷卡); Lv Ding Fang (律定方); Ni Di Duo (尼迪多); Ni Er (尼尔); Wei Le Rui (威乐瑞); Xin Neng (芯能); Yu Li (誉利); Zhuo Ka (卓卡); ***Fr.***: Levocarnil; ***Ger.***: Biocarn; L-Carn; Nefrocarnit; ***Gr.***: Aminocer; Aveptol; Bicarnesine; Bitobionil; Carniben; Carnidose; Carnil; Carniprol; Carnisac; Carnitop; Carnivit; Corubin; Duocarnic; Energocarnil; Ensial; Ergogen; Frutenor; Growart; Inestom; Intelecta; Koptilan; Lecarna; Levalastine; Levamin; Levars; Levicin; Levocarnil; Levocuor; Levosan; Lisefor; Listover; Locar; Lofostin; Lyzip; Maledrol; Medicardin; Merlit; Mevamyst; Minartine; Minoa; Oskana; Phacovit; Revotonine; Ridovet; Soludamin; Superamin; Tonovit; Trian; Trinalin; Vigorup; Xaritic; ***Hong Kong***: Carnitene; Carnitor; ***India***: Carnicle; Carnitor; L-Tine; Lencar; Nucarnit; ***Ital.***: Bio-Vis; Branigen; Branitil†; Carnitene; Carnovis; Dromos; Elleci; Eucar†; Eucarnil; Eufertil; Farnitin; Lefcar; Levocarvit; Medocarnitin; Megavis†; Miocardin; Miocor; Miotonal; Neo Cardiol†; Nicetile; Normobren; Zibren; ***Jpn***: L-Cartin FF; ***Mex.***: Cardispan; Lipovitasi D; Provicar; ***Neth.***: Nefrocarnit; ***Philipp.***: Cardimax; Carnicor; Cartine; Levocetile; ***Pol.***: Carnivit†; ***Port.***: Cartine†; Disocor; Lacetilina†; ***Rus.***: Carniten (Карнитен); Elcar (Элькар); ***Spain***: Carnicor; Secabiol; ***Turk.***: Carnitene; Nefro-Carnitin; ***UK***: Carnitor; ***USA***: Carnitor; VitaCarn; ***Venez.***: Carnisin; Kativil; Lixi; Provicar.

Multi-ingredient Preparations. ***Arg.***: Azodac; Biocell; Biomag Vital; Cistidac; Dermasolutions†; Desgras Burner Fat; Durgel; Garcinol Max; Herbaccion Diet; Metabolic; Natural Diet; Reductase; Redumax; Ripped Max; Silueta Plus†; ***Austral.***: Homme-F; Magnesium Powder; PM Kids Intelligent; ***Braz.***: Carnabol; Ferrotrat B12 Plus; Nutrimaiz SM; Trimetabol†; ***Chile***: Cellenergy; Peracon; Ubiten; ***Hung.***: Metabol; ***India***: Cardi-NRG; Cardistim; Carnit; Evion-LC; Exart; Hi-Q Plus; Hi-Q Plus; Hosit-L; Immunace; L-Nit; Lenova-MF; Levo-F; Levo-Forte; Maxoza; NE; Nu-Look; ***Indon.***: Betaslim; Bexicom Fit; Bioquinone; Canergy†; Car-Q; Carni Plus; Carnon; Co-vitala; Combes†; Corsel; DFM; Enercore; Galten; Immunace; Metsel; nu Qten Com; Procardio†; Vitaslim; ***Ital.***: Anasten Plus; Atlantis; Binfolipase; Briovitase Sostegno; Carfosid; Co-Carnetina B12; Creavit; Enercomplex; Linfolipase; Lipoenergy; Memovigor; Phototrop; Riduton Ergo; Salovit; Tripondil; ***Malaysia***: Hovid Q-10 SupraBio + L-Carnitine; Olivenol livin' Vigor†; ***Mex.***: Redumed; Slim-D†; ***Philipp.***: Fit-N-Trim; Fitrum; Godex†; Memorx IQ Plus; Mitodex; Nutrafit; Optigrow; Zeman; ***Pol.***: Kofevit†; ***Singapore***: Cardio-Essentials; Olivenol Livin' Vigor; ***Spain***: Hepadif; Malandil; Pranzo; ***Ukr.***: Cardonat (Кардонат); Hepadif (Гепадиф); Stifimol (Стифимол); Trimetabol (Триметабол); ***USA***: Cardio Tone.

Pharmacopoeial Preparations

USP 36: Levocarnitine Injection; Levocarnitine Oral Solution; Levocarnitine Tablets.

Casein

Kazeina.
CAS — 9000-71-9.
UNII — 48268V50D5.

Profile

Casein is a protein found in milk and has been used as a source of protein in preparations for enteral and parenteral nutrition; it may be used in the production of protein hydrolysate injection. Calcium caseinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Proteina 100; Proteinex Victus; Secalbum; Sumaprot 90; ***Israel***: Casec†; ***Mex.***: Calsein†; K-Sein; ***USA***: Casec†.

Multi-ingredient Preparations. ***India***: Bioferum Forte; Protone; Protone; ***Mex.***: Calciyodina; ***Switz.***: Cicafissan; Vitafissan N.

Choline Bitartrate

Bitartarato de Colina; Choline Acid Tartrate; Choline Hydrogen Tartrate; Cholinii Tartras; Colina, bitartrato de; Холина Битартрат.
2-Hydroxyethyltrimethylammonium hydrogen tartrate.
$C_9H_{19}NO_7$=253.3
CAS — 87-67-2.
UNII — 6K2W7T9V6Y.

Pharmacopoeias. In *US*.

USP 36: (Choline Bitartrate). A white, hygroscopic, crystalline powder; odourless or with a faint trimethylamine odour. Clear and colourless in solution. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 3.0 and 4.0.

Choline Chloride *(rINN)*

Choline, Chlorure de; Cholini Chloridum; Cholinii Chloridum; Choliny chlorek; Cloruro de colina; Colina, cloruro de; Koliinikloridi; Kolinklorid; Холина Хлорид.
2-Hydroxyethyltrimethylammonium chloride.
$C_5H_{14}ClNO$=139.6
CAS — 62-49-7 (choline); 67-48-1 (choline chloride).
UNII — 45I14D8O27.

Pharmacopoeias. In *Fr.* and *US*.

USP 36: (Choline Chloride). Hygroscopic, colourless or white crystals or crystalline powder, usually having a slight odour of trimethylamine. Clear and colourless in solution. Soluble in water and in alcohol. pH of a 10% solution in water is between 4.0 and 7.0.

Profile

Choline is an acetylcholine precursor. It is involved in lipid metabolism and acts as a methyl donor in various other metabolic processes. Choline has traditionally been considered to be a vitamin B substance although its functions do not justify its classification as a vitamin. Choline can be synthesised in the body. However, its absence in total parenteral nutrition causes hepatic steatosis, and it is also thought to be a requirement in the diet of neonates. Sources of choline, which occurs mostly as lecithin, include egg-yolk and vegetable and animal fat.

Choline is used as a dietary supplement and has been used to treat liver disorders such as fatty liver and cirrhosis. It has been tried in the management of Alzheimer's disease (see Dementia, p. 388.1) but without success. Choline is used as the dihydrogen citrate, and orotate salts as well as the bitartrate and the chloride.

Human requirements. In the USA, an adequate intake (see p. 2046.1) of 550 mg daily in men and 425 mg daily in women has been determined for choline.[1] The tolerable upper intake level for adults is 3.5 g daily.[1] There is evidence that dietary requirements may vary between individuals as a result of several genetic polymorphisms in metabolism;[2] premenopausal women also appear to have an increased capacity for choline synthesis, compared with postmenopausal women or with men.

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)
2. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. *Annu Rev Nutr* 2006; **26:** 229–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Bitoline; Cidalin; Hepastar; Livat-DS; Livodex.

Multi-ingredient Preparations. ***Arg.***: Energizante Vital con ginseng; Energizante; GB 100; Ripped Max; Skin Hair & Nails; ***Austral.***: For Women Multi Plus EPO†; KickStart Detox; Metabolift Fat Burner; PM Syrin; ***Austria***: Vita-Gerin; ***Braz.***: Abcler; Anekron; B-Vesil†; Biohepax†; Chofrafig; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Hepalin; Hepatox; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B6; Panvitrop; Xantinon B12; Xantinon Complex; ***Canad.***: Emulsi Factors; Formula 17605 Diaplex; Formula AO†; Hepaticol; Lipofactors & Niacin†; Liv-Gd; Liv-Gd; Live-Rite; Phyto-Marinex; T-BMP; ***Chile***: Hepabil; ***Fr.***: Citrocholine†; Cystichol†; Desintex-Choline†; Hepagrume; Memoptic; ***Ger.***: Vita-Gerin N; ***Hong Kong***: Anti-Stress Hi B Plus C†; B Complex 50; Executive Stress†; Mega-Antioxidant†; Super Vita Vim; Vita Stress†; Vitabex A†; Vitacymin†; ***India***: Al-Live; Anorexin Plus; Apel-G; Apirich; Apitus-TC; App-Up; Appe-Care; Appet; Appetidin; Asi-Liv; Atric Plus; Auz; Bio Cyp; C-Lysin; Cherrytone; Chocy; Cipliv; Clydin; Cyaptin; Cyp-L; Cypine-TS; Cypolin; Cypon DPS; Cypon-I; Cyprea-T; Cypro-L; Cypro; Cyprobit; Cyproz; Decyp-P; Delphicol†; Devlup; Forliv; Fortil; Gardian; Genoplex Forte; Growise; Hapeast; Hepa; Hepachol; Hepawin Plus; Hepoline; Hepsandinn; Homocyst; Hypetin; In-OZ; Karnatakaiv; Lecyp; Lederplex; Liveril; Livobion; Livobion; Livocip; Livpron; LSky; Lycostar-CM; Lycyp; M-Cyp; Maltviron; Mecolin; Morvit; Multivite Gold; Multivite Woman; NBTone; O-AP; Optifit; Oraxin; Orliv; Orovit; Sorbiline; Sorliv; ***Indon.***: Bio-Curliv; Carni Plus; Curliv Plus; Curliv; DFM; Growee; Hepabion†; Hepatin; Lipagent; Methicol; Methioson; Miniceronal†; Proliver; Vidaylin L; Vionin; Zamel; ***Irl.***: Ketovite; ***Ital.***: Lipoenergy; Nervocel†; Rischiaril; ***Malaysia***: Pharmaton†; Revital; Vi-Daylin; ***Philipp.***: Arcostrong†; BioSil†; Completia†; Energel; Enerzip; K-A Plus; Leginsol-E; Pharmaton; Rejuvenex; ***Pol.***: Methiovit†; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); Prohepar (Прогепар); ***S.Afr.***: Clusivol; Hepavite†; Neurotone; Prohep†; ***Singapore***: Essentials†; Groweе†; ***Switz.***: Vita-Gerin; Vitiron; ***Thai.***: Liporon; Vita Multicap; Vitop; ***UK***: Lipotropic Factors; Skin Care Nutrients; ***Ukr.***: Hepahealth (Гепахелс); PM Sirin (ПМ Сирин); Vitiron (Витирон); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Advanced Ear Health Formula; Alive Once Daily Womens 50+ Ultra Potency; Cholinoid†; Clinical Nutrients 50-Plus Men; Megavite Fruits & Veggies; One A Day Vitacraves; Solo; Tyler Prenatal; ***Venez.***: Hepasil.

Chondroitin Sulfate–Iron Complex

Chondroitin Sulphate–Iron Complex; Ferropolichondrum; Hierro y sulfato de condroitina, complejo de; Железа Сульфат-Хондроитина Комплекс.
CAS — 54391-57-0.
ATC — B03AB07.
ATC Vet — QB03AB07.

Profile

Chondroitin sulfate-iron complex is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 900 mg daily, equivalent to up to 90 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Isairon.

Chromium

Chrom; Chrome; Cromo; Хром.
Cr=51.9961
UNII — X1N4508KF1 (chromium ion); 0R0008Q3JB (chromium).

Chromium Trichloride

Chromic Chloride; Cromo, tricloruro de; Трёххлористый Хром; Хлористый Хром.
$CrCl_3,6H_2O$=266.4
CAS — 10025-73-7 (anhydrous chromium trichloride); 10060-12-5 (chromium trichloride hexahydrate).
UNII — KB1PCR9DMW (chromium trichloride); Z310X5O5RP (anhydrous chromium trichloride).

Pharmacopoeias. In *US*.

USP 36: (Chromic Chloride). Dark green, odourless, slightly deliquescent crystals. Soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Chromium Tripicolinate

Chromium Picolinate; Cromo, tripicolinato de; Пиколинат Хрома.

$C_{18}H_{12}N_3O_6Cr$=418.3

CAS — 14639-25-9.

UNII — S71T8B8Z6P.

Pharmacopoeias. In *US.*

USP 36: (Chromium Picolinate). Store in airtight containers.

Uses and Administration

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism. It exists in several oxidation states, of which the trivalent (3+) and hexavalent (6+) are the most important. Trivalent chromium compounds are nutritionally active and are discussed further below; hexavalent compounds have industrial uses and are generally more toxic (see Chromium Trioxide, p. 2476.2). Dietary sources rich in chromium include brewers' yeast, meat, whole grains, and nuts, and usually contain the trivalent form. Chromium trichloride has been given as a chromium supplement in total parenteral nutrition. Chromium tripicolinate is used as a chromium supplement, and is being investigated for improving glycaemic control in patients with diabetes mellitus. Chelates of chromium and nicotinic acid (chromium nicotinate; chromium polynicotinate; niacin-bound chromium) have also been used. One such product has been widely promoted under the name *ChromeMate* (*InterHealth Nutraceuticals, USA*).

Diabetes mellitus. A review[1] of trivalent chromium in the management of diabetes mellitus (p. 459.1) concluded that it may have an adjunctive role. A meta-analysis[2] found no effect of chromium on glucose or insulin concentrations in non-diabetic subjects; data for diabetic patients were inconclusive. A systematic review[3] found no significant effect with chromium supplementation on lipid or glucose metabolism in non-diabetic subjects, but that it might have a modest beneficial effect on glycaemia and dyslipidaemia in those patients with diabetes. Meta-analysis was hampered by the overall poor quality and heterogeneity of available studies,[3] and further research was considered necessary.[1-3]

1. Ryan GJ, *et al.* Chromium as adjunctive treatment for type 2 diabetes. *Ann Pharmacother* 2003; **37:** 876–85.
2. Althuis MD, *et al.* Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 2002; **76:** 148–55.
3. Balk EM, *et al.* Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. *Diabetes Care* 2007; **30:** 2154–63.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p. 2046.1) has been set for chromium although a safe and adequate intake was believed to be above 25 micrograms daily for adults.[1] Similarly, in the USA a recommended dietary allowance has not been published but the adequate intake was estimated to be 35 micrograms daily for young men and 25 micrograms daily for young women.[2] WHO considers that the minimum population mean intake likely to meet normal needs for chromium might be about 33 micrograms daily, and that supplementation of this element should not exceed 250 micrograms daily until more is known.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Chromium. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 155–60.

Obesity. Chromium picolinate has been promoted as a dietary supplement to assist in weight loss. However, a randomised placebo-controlled study involving 80 obese adults found that supplementation with oral chromium picolinate 1 mg daily for 24 weeks did not affect weight loss in this group.[1]

1. Yazaki Y, *et al.* A pilot study of chromium picolinate for weight loss. *J Altern Complement Med* 2010; **16:** 291–9.

Supplementation. Although a daily chromium intake of 200 nanograms/kg has been suggested in children given total parenteral nutrition (TPN), a study in 15 children[1] given long-term parenteral nutrition found that supplementation at about this level was associated with serum-chromium concentrations 4 to 42 times higher than the mean value in 15 children not receiving TPN. Raised serum-chromium concentrations were associated with a decrease in glomerular filtration rate; one year after stopping chromium supplementation, which reduced intake to 50 nanograms/kg daily (as contaminants of water and TPN solutions), chromium concentrations, although lower, were still higher than controls and renal function had not altered. The authors subsequently ceased chromium supplementation in both children and adults, since chromium contamination of TPN solutions appeared adequate to prevent deficiency, although it was acknowledged that signs of chromium deficiency might take some years to appear. The recommendations for chromium supplementation in parenteral nutrition have therefore been queried.[2] Chromium contamination in various preparations used in paediatric parenteral nutrition has been studied.[3]

1. Moukarzel AA, *et al.* Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 1992; **339:** 385–8.
2. Moukarzel A. Chromium in parenteral nutrition: too little or too much? *Gastroenterology* 2009; **137** (suppl): S18–S28.
3. Hak EB, *et al.* Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55:** 150–4.

Adverse Effects

Trivalent salts of chromium, such as chromium trichloride, are generally considered to produce few adverse effects. However, hexavalent forms of chromium are notably toxic (see under Chromium Trioxide, p. 2476.2).

Effects on the kidneys. Two cases of renal failure were attributed to ingestion of excessive doses of chromium tripicolinate in women with no history of renal dysfunction.[1,2] Acute renal failure with features of acute tubular necrosis, and requiring haemodialysis, has been reported after ingestion of a chromium picolinate-containing supplement. The amount of chromium in the supplement could not be determined.[3] For mention of decreases in glomerular filtration rate in children receiving chromium-supplemented total parenteral nutrition, see Supplementation, above.

1. Wasser WG, *et al.* Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 1997; **126:** 410.
2. Cerulli J, *et al.* Chromium picolinate toxicity. *Ann Pharmacother* 1998; **32:** 428–31.
3. Wani S, *et al.* Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. *Ann Pharmacother* 2006; **40:** 563–6.

Effects on the skin. There have been rare reports[1,2] of cutaneous reactions to oral chromium tripicolinate, including one of acute generalised exanthematous pustulosis.

1. Young PC, *et al.* Acute generalized exanthematous pustulosis induced by chromium picolinate. *J Am Acad Dermatol* 1999; **41:** 820–3.
2. Fowler JF. Systemic contact dermatitis caused by oral chromium picolinate. *Cutis* 2000; **65:** 116.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: NH4 Silhouette; Ripped Max; Sigmar Lipo; Tonekin; ***Austral.***: Chrome; ***Canad.***: Micro Cr; ***Chile***: Edul K-200; ***India***: CP; ***Israel***: Micro Cr; ***Ital.***: Croben; ***Mex.***: Cromotex; ***USA***: Chroma-Pak†.

Multi-ingredient Preparations. ***Arg.***: Centellacrom; Garcinia Cambogia Compuesta; Herbaccion Diet; IP6; Metabolic; Ripped Max; ***Austral.***: 3B Beer Belly Buster†; Citri Slim+Trim†; Digestaid; Gluco Support; Metabolift Fat Burner; ***Braz.***: Olig-Trat; ***Canad.***: Formula 7441†; Formula 7442†; Glucoplex; ***Fr.***: Expuryl; Gynalpha Plus†; Hydrastart; Optibiol; ***Hung.***: Dietet-In; Klimin; ***India***: Alcrin-M; Alcrin; Alphamix-BT; Alphamix; Beta-Sclerobion; Betonin-CZ; Carofit-D; Chromet; Cobadex-CZS; Cobalvit Plus; Cobanerve Plus; Cromoplex; D-Gard; Dianuron; Ecobal-Plus; Ecobal; Eldervit-ZC; Elmecob Plus; Exerge; Felicita-OD; Glim-C; Glycor-C; Horac; Kefive Plus; Me Plus; Me-Plus; Mecobion-OD; Mecoday Plus; Mintide Plus; Natrolip; Nervijen-D; Nervz-B; Neuractin Forte; Neuromin-EA; Neurotrat; Nocad; Nuroclad-Plus; Nurokind-More; Nutricobal Plus; Obedeuce; Optisulin; Optivision; Ostebon-M; Oxitra; Oxyglobin; Winofit; ***Indon.***: Aldovas; Alicron; Betaslim; Biocholes†; Combes†; F-Slim†; Fres Diab; Kitoles†; Lanavision Plus; nutrivision; Osfit; Tiola; Univoxy; Vitala; Vitaslim; ***Ital.***: Eccarvit Plus; ***Mex.***: Slim-D†; ***Mon.***: Evestrel Physio Profil†; Romarinex Chrome; ***Philipp.***: Diachrotin; Diamaxin; Glucontrol; Liposorb; Mordica; Nutrafit; ***Singapore***: Apple Cider Vinegar Diet; Chitosano; Multitrace-5; Nutrivision†; Optibiol; ***Thai.***: Biotrat; Diavit; ***Turk.***: Keten; ***UK***: Selenium Bonus; ***Ukr.***: Lipomin (Липомин); Stifimol (Стифимол); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; ***USA***: Blood Sugar Balance; Cro-Man-Zin; Dexatrim Max Daytime Appetite Control.

Pharmacopoeial Preparations

USP 36: Chromic Chloride Injection; Chromium Picolinate Tablets; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Citrulline

Citrulina; L-Citrulline; NSC-27425; N^5-(Aminocarbonyl)-L-ornithine; N^5-Carbamylornithine; Цитруллин.

α-Amino-δ-ureidovaleric acid.

$C_6H_{13}N_3O_3$=175.2

CAS — 372-75-8.

UNII — 29VT07BGDA.

Profile

Citrulline is a non-essential amino acid that is involved in the urea cycle. Citrulline and citrulline malate are used as dietary supplements.

Hyperammonaemia. Citrulline has been given as an alternative to arginine in the management of hyperammonaemia (p. 2049.3) due to **urea cycle disorders**.

Lysinuric protein intolerance is another condition associated with hyperammonaemia and similar neurological sequelae. In this condition there is no deficiency of urea-cycle enzymes but a deficiency of urea-cycle substrate, such as ornithine, which results in reduced synthesis of citrulline. Patients are treated with dietary protein restriction and citrulline supplementation, which improves protein tolerance and nutrition but only slightly ameliorates growth retardation. Osteoporosis may be severe in children with this disorder.[1] A child presenting with osteopenia and diagnosed with lysinuric protein intolerance was given large oral doses of citrulline (up to 5.7 g daily). Aside from a substantial increase in protein tolerance, a striking acceleration in linear growth and bone mass was reported.[2] Lysine deficiency may be implicated in growth retardation,[1] but lysine supplementation may precipitate diarrhoea and malabsorption.[2] Six patients with lysinuric protein intolerance and receiving oral citrulline were supplemented with oral lysine. Larger lysine doses of 0.55 mmol/kg and 1.1 mmol/kg given consecutively, caused profuse diarrhoea, but smaller doses of 0.05 mmol/kg, given three times daily (up to a maximum dose of 2.5 mmol) were well tolerated. Plasma lysine concentrations were normalised with no adverse effects on the urea cycle.[1]

1. Lukkarinen M, *et al.* Oral supplementation corrects plasma lysine concentrations in lysinuric protein intolerance. *Metabolism* 2003; **52:** 935–8.
2. Carpenter TO, *et al.* Lysinuric protein intolerance presenting as childhood osteoporosis: clinical and skeletal response to citrulline therapy. *N Engl J Med* 1985; **312:** 290–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: MyoCIT; Stimol; ***Indon.***: Stimol†; ***Port.***: Dynergum; ***Rus.***: Stimol (Стимол); ***Spain***: Stimol; ***Switz.***: Biostimol; ***Ukr.***: Stimol (Стимол).

Multi-ingredient Preparations. ***Arg.***: Total Magnesiano Sport; ***Braz.***: Ornitargin; ***Ital.***: Ipoazotal Complex; Promofort.

Cod-liver Oil *(BAN)*

Aceite de Hígado de Bacalao; Balık yağı; Cod Liver Oil; Csukamájolaj; Foie de morue, huile de; Huile de Foie de Morue; Iecoris aselli oleum; Kalanmaksaöljy; Lebertran; Menkių kepenų taukai; Ol. Morrh.; Óleo de Bacalhau; Oleum Jecoris Aselli; Oleum Morrhuae; Olio di Fegato di Merluzzo; Rybí olej; Torskleverolja; Тресковый Печёночный Жир.

CAS — 8001-69-2.

UNII — BBL281NWFG.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Eur. also includes farmed cod-liver oil.

Ph. Eur. 8: (Cod-liver Oil (Type A) and Cod-liver Oil (Type B)). Purified fatty oils obtained from the fresh livers of wild cod, *Gadus morhua* and other species of Gadidae, solid substances being removed by cooling and filtering. The oils contain 600 units (180 micrograms) to 2500 units (750 micrograms) of vitamin A per g and 60 units (1.5 micrograms) to 250 units (6.25 micrograms) of vitamin D_3(colecalciferol) per g. Antoxidants may be added.

Clear, yellowish liquids. Practically insoluble in water; slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Store under an inert gas if no antoxidant is added. Protect from light.

Ph. Eur. 8: (Cod-liver Oil, Farmed). Purified fatty oil obtained from the fresh livers of farmed cod, *Gadus morhua*, solid substances being removed by cooling and filtering. It contains 50 units (15 micrograms) to 500 units (150 micrograms) of vitamin A per gram and a maximum of 50 units (1.3 micrograms) of vitamin D_3 per gram. The sum of the contents of eicosapentaenoic acid and docosahexaenoic acid

(expressed as triglycerides) is 10.0 to 28.0%. Antoxidants may be added.

A clear, pale yellowish liquid. Practically insoluble in water; slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Store under an inert gas if no antoxidant is added. Protect from light.

USP 36: (Cod Liver Oil). The partially destearinated fixed oil obtained from the fresh livers of *Gadus morrhua* and other species of Gadidae. It contains not less than 600 units (180 micrograms) and not more than 2500 units (750 micrograms) of vitamin A per g and not less than 60 units (1.5 micrograms) and not more than 250 units (6.25 micrograms) of vitamin D per g. It may be flavoured by the addition of not more than 1% of a suitable flavour or a mixture of flavours. A suitable antoxidant may be added.

A thin, oily liquid, having a characteristic, slightly fishy but not rancid odour. Slightly soluble in alcohol; freely soluble in carbon disulfide, in chloroform, in ether, and in ethyl acetate. Store in airtight containers. It may be bottled or packaged in containers from which air has been expelled by the production of a vacuum or by an inert gas.

Profile

Cod-liver oil is a rich source of vitamin D (p. 2112.3) and a good source of vitamin A (p. 2098.3). It also contains several essential fatty acids.

Cod-liver oil dressings or ointment have been advocated to accelerate healing in burns, ulcers, pressure sores, and superficial wounds, but controlled observations have failed to substantiate claims of their value.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Adecaps†; ***Fr.***: Lactomorrhuol; ***Ger.***: Gelovital; Unguentolan; ***Gr.***: Seven Seas; ***Hong Kong***: Scott's Emulsion; ***India***: Eleven Seas; Elnocod; Seaking; ***Ital.***: Dermovitamina; ***Mex.***: Bacnutri; ***Pol.***: Letin-Tran†; Masc Tranowa; Naturkaps Tran; Tran; ***Spain***: Aceite Geve Concentrado; ***Switz.***: Morrhulan†; ***Turk.***: Seven Seas Pulse; ***Venez.***: Scott Tradicional; Supercod.

Multi-ingredient Preparations. ***Arg.***: Abanta; Atomoderma A-D; Atomoderma Plus; Cicatrex Baby; Clinal; Eryteal; Hipoglos con Hidrocortisona; Klorane Bebe Eryteal; ***Austral.***: Arthro-Eze; Covitol; Desitin Nappy Rash Ointment; Hypol Cherry; Hypol; ***Austria***: Dermilon; Dermowund†; Desitin; Leukichtan; Mirfulan; Nuri-Kapseln†; Pudan-Lebertran-Zinksalbe; Vulpuran; ***Belg.***: Mitosyl; Polyseptol; ***Braz.***: Emulsao Scott; Hiposan; Oxizinco†; Topiglos†; ***Canad.***: Desitin; ***Chile***: Cikavit; Deltisan; Desitin; Nenegloss†; Pediaderm; Vatanal; ***Fr.***: Fletagex; Magalite; ***Ger.***: Lebertran plus; Mirfulan Spray N; Mirfulan; Mitosyl N; Zinksalbe; ***Gr.***: Fissan-Pate; Fissan; ***Hong Kong***: Desitin†; Scott's Emulsion Orange†; Scott's Emulsion Original†; ***Hung.***: Klimin; ***India***: Codesoft; Codvit-E; E-Cod Omega; E-Cod Plus; Ecod; Ecoliv; Evitop-C; Seaking Plus; ***Indon.***: Biostrum; Caloma Plus; Calostrum; Co-Q-10; Curvit CL; Scott's Emulsion Vita; Scott's Emulsion; Seltifort Gold; Vidoran Emulsion Rasa; ***Irl.***: Caldease; Morhulin; ***Israel***: Desitin; Rekasitin†; Zincod; ***Ital.***: Fosfarsile Junior; Neo-Ustiol; Steril Zeta; Trofo 5; ***Mex.***: Capent; Desitin; Emulsion de Scott; Glossderm; ***Pol.***: Rectosec; Tranvit†; ***Port.***: Mitosyl; ***S.Afr.***: Achromide; Daromide†; SB Universal Ointment†; Ung Vernleigh; ***Singapore***: Robovites Multivitamins; Seven Seas JointCare High Strength; Seven Seas JointCare Max; ***Spain***: Avril; Carena; ***Switz.***: Unguentolan; Vita-Hexin; ***Turk.***: Derivit; ***UK***: Arheumacare; Clogar; Jointace; JointCare Max; M & M; Morhulin; ***Ukr.***: Vitrum Cardio (Вітрум Кардио); ***USA***: A+D Zinc Oxide Cream; Caldesene; Clocream; Desitin; Diaper Rash; Dyprotex.

Homoeopathic Preparations. ***Fr.***: Jenoverine†.

Pharmacopoeial Preparations
USP 36: Cod Liver Oil Capsules.

Copper

Cobre; Cuivre; Cuprum; Koppar; Kupari; Kupfer; Miedź; Медь.
Cu=63.546
CAS — 7440-50-8.
UNII — 789U1901C5.

Pharmacopoeias. *Eur.* (see p. vii) includes Copper for Homoeopathic Preparations.

Ph. Eur. 8: (Copper for Homoeopathic Preparations; Cuprum ad Praeparationes Homoeopathicae). A reddish-brown powder. Practically insoluble in water and in alcohol; soluble in hydrochloric acid and in nitric acid.

Calcium Copperedetate

Cuproedetato cálcico.
Calcium [ethylenediaminetetra-acetato(4–)-*N*,*N*′,*O*,*O*′]copper (II) dihydrate.
$C_{10}H_{12}CaCuN_2O_8.2H_2O$=427.9
CAS — 66317-91-7 (anhydrous calcium copperedetate).

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Calcium Copperedetate). A blue crystalline powder. It contains 9.1 to 9.7% of Ca and 14.4 to 15.3% of Cu. Freely soluble in water, the solution gradually precipitating the tetrahydrate; practically insoluble in alcohol.

Copper Chloride

Cobre, cloruro de; Cupric Chloride; Miedzi chlorek; Хлористая Медь.
$CuCl_2.2H_2O$=170.5
CAS — 7447-39-4 (anhydrous copper chloride); 10125-13-0 (copper chloride dihydrate).
UNII — S2QG84156O (cupric chloride dihydrate); P484053J2Y (anhydrous cupric chloride).

Pharmacopoeias. In *US*.

USP 36: (Cupric Chloride). Bluish-green, deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Copper Gluconate

Cobre, gluconato de; D-gluconato de cobre (1:2); Глюканат Меди.
Copper D-gluconate (1:2); Bis(D-gluconato-O^1,O^2) copper.
$C_{12}H_{22}CuO_{14}$=453.8
CAS — 527-09-3.
UNII — RV823G6G67.

Pharmacopoeias. In *US*.

Copper Sulfate

Cobre, sulfato de; Copper Sulph.; Copper Sulphate; Cuivre (Sulfate de); Cuivre, sulfate de; Cupri sulfas; Cupri Sulphas; Cupric Sulfate; Kopparsulfat; Kuparisulfaatti; Kupfersulfat; Miedzi(II) siarczan; Réz(II)-szulfát; Síran měďnatý; Sulfato de Cobre; Vario sulfatas; Медный Купорос; Сульфат Меди; Хальканит.
Copper (II) sulphate pentahydrate.
$CuSO_4.5H_2O$=249.7
CAS — 7758-98-7 (anhydrous copper sulfate); 7758-99-8 (copper sulfate pentahydrate).
ATC — V03AB20.
ATC Vet — QV03AB20.
UNII — KUW2Q3U1VV (anhydrous cupric sulfate); LRX7AJ16DT (cupric sulfate pentahydrate).

NOTE. Crude copper sulfate is sometimes known as 'blue copperas', 'blue stone', and 'blue vitriol'.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*

Eur. and *Viet.* also include anhydrous copper sulfate.

Ph. Eur. 8: (Copper Sulfate Pentahydrate). A blue crystalline powder or transparent blue crystals. Freely soluble in water; practically insoluble in alcohol; soluble in methyl alcohol.

Ph. Eur. 8: (Copper Sulfate, Anhydrous). A greenish-grey, very hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. Store in airtight containers.

USP 36: (Cupric Sulfate). Deep blue, triclinic crystals, or blue, crystalline granules or powder. It effloresces slowly in dry air. Soluble 1 in 3 of water, 1 in 0.5 of boiling water, 1 in 500 of alcohol, and 1 in 3 of glycerol. Its solutions are acid to litmus. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Copper is an essential trace element although severe copper deficiency, which is associated with anaemia, neutropenia, and bone demineralisation, is rare in humans. A copper salt such as the sulfate or chloride can be added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states. Doses that have been used for prophylaxis range from 0.5 to 1.5 mg (7.9 to 23.6 micromoles) of copper daily; up to 3 mg daily has been suggested in established deficiency. The dose should be governed by the serum-copper concentration, which in healthy adults ranges between 0.7 and 1.6 micrograms/mL (0.01 to 0.025 micromol/mL).

For doses in children, see Administration in Children, below.

Copper sulfate and other soluble salts of copper have an astringent action on mucous surfaces and in strong solutions they are corrosive. Copper nitrate has been used in preparations for the removal of warts. The uses of copper acetate are discussed on p. 2486.3.

Copper has a contraceptive effect when present in the uterus, and is added to some intra-uterine contraceptive devices (see Contraception, p. 2232.3); such devices are considered to be effective and safe for several years after insertion, and may be the most effective method for emergency contraception (p. 2233.2). Copper is also reported to have an antimicrobial action.

Copper sulfate has been used to prevent the growth of algae in reservoirs, ponds, and swimming pools and as a molluscicide in the control of fresh-water snails that act as intermediate hosts in the life-cycle of the parasites causing schistosomiasis.

Reagents containing copper sulfate are used in tests for reducing sugars.

In veterinary medicine calcium copperedetate, copper methionate, copper oxide, and cuproxoline are used for the prevention and treatment of copper deficiency.

Copper bracelets are worn as a folk remedy for rheumatic disorders: there is no good evidence to justify such a practice.

Homoeopathy

Copper has been used in homoeopathic medicines under the following names: Cuprum metallicum; Cuprum; Cuprum met.; Cup. met.

Copper chloride has been used in homoeopathic medicines under the following names: Cuprum muriaticum; Cuprum mur.

Copper sulfate has been used in homoeopathic medicines under the following names: Cuprum sulfuricum; Cuprum sulphuricum; Cup. s.; Cuprum sulph.

Copper tetraammine sulfate (tetraminecopper sulfate) has been used in homoeopathic medicines under the following names: Cuprum ammonio-sulphuricum; Cuprum am sulph.

General references.

1. Wang T, Guo Z. Copper in medicine: homeostasis, chelation therapy and antitumor drug design. *Curr Med Chem* 2006; **13:** 525–37.

Administration in children. A copper salt such as the chloride or sulfate may be added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states in children. A daily dose of 20 micrograms/kg (0.3 micromoles/kg) of copper has been suggested. In the USA, licensed product information recommends this dose for all children, whereas UK licensed product information suggests a maximum of 300 micrograms of copper daily for children weighing 40 kg or less, and adult doses in children over 40 kg (see above). Infants weighing less than 1.5 kg may have increased requirements due to their low body reserves and increased requirements for growth.

Deficiency states. Acquired copper deficiency is very rare and the small number of cases have usually involved patients on total parenteral nutrition or long-term enteral nutrition.[1] Copper deficiency may also be due to malnutrition,[2] malabsorption, or secondary to excessive zinc consumption.[3,4] Clinical manifestations of deficiency include hypocupraemia, hypoceruloplasminaemia, neutropenia, anaemia, osteoporosis, and fracture of the long bones.[2] However, cases may present with neurological signs resembling the subacute combined degeneration normally associated with vitamin B_{12} deficiency.[3,4] Effects on blood may be absent, and zinc concentrations normal;[3] however, hyperzincaemia may be seen even in the absence of exogenous zinc consumption.[4]

Menkes' disease is an X-linked genetic disorder associated with a defect in copper transport, which almost invariably results in death due to progressive cerebral degeneration by the age of 3 years.[5,6] Clinical features include skeletal abnormalities, severe mental retardation, thrombosis, hypothermia, arterial abnormalities, and characteristic facial features.[7] Early parenteral treatment with copper-histidine complex may be of benefit in such children.[5-8] Optimal response to copper therapy appears to occur only in patients who are identified in the newborn period and who have some residual copper-transport activity. More than 3 years of copper replacement therapy may not be necessary or desirable.[6]

1. Masugi J, *et al.* Copper deficiency anemia and prolonged enteral feeding. *Ann Intern Med* 1994; **121:** 386.
2. Cordano A. Clinical manifestations of nutritional copper deficiency in infants and children. *Am J Clin Nutr* 1998; **67** (suppl): 1012S–1016S.
3. Kumar N, *et al.* Copper deficiency myelopathy produces a picture like subacute combined degeneration. *Neurology* 2004; **63:** 33–9.
4. Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc* 2006; **81:** 1371–84.
5. Sarkar B, *et al.* Copper-histidine therapy for Menkes' disease. *J Pediatr* 1993; **123:** 828–30.
6. Kaler SG, *et al.* Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med* 2008; **358:** 605–14.
7. Kirodian BG, *et al.* Treatment of Menkes disease with parenteral copper histidine. *Indian Pediatr* 2002; **39:** 183–5.
8. Cox DW. Disorders of copper transport. *Br Med Bull* 1999; **55:** 544–55.

Human requirements. In the UK dietary reference values (see p. 2046.1) have been published for copper.[1] Although

an estimated average requirement (EAR) could not be derived a reference nutrient intake (RNI) of 1.2 mg (19 micromoles) daily was set for adults; RNIs of lower values were also specified for infants and children.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for copper of 160 micrograms/kg daily.

In the USA the recommended dietary allowance (RDA) for copper is 900 micrograms daily in adults, and the tolerable upper intake level is 10 mg daily.[3]

WHO has estimated a minimum population mean intake of 1.2 mg daily for women and 1.3 mg daily for men, and safe upper limits of population mean intakes of 10 mg daily for women and 12 mg daily for men;[4] values are also estimated for infants and children.

The difficulties of establishing guidelines for copper requirements have been reviewed.[5]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
4. WHO. Copper. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 123–43.
5. Stern BR. Essentiality and toxicity in copper health risk assessment: overview, update and regulatory considerations. *J Toxicol Environ Health A* 2010; **73:** 114–27.

Schistosomiasis. Although most control programmes for schistosomiasis (p. 148.1) use niclosamide as a molluscicide, and copper salts have largely been abandoned for snail control, WHO noted in 1993 that copper sulfate was still used for this purpose in Egypt.[1]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 21/07/08)

Adverse Effects and Treatment

Adverse effects from copper have tended to arise after absorption of the metal from cooking utensils and during dialysis. Ingestion of copper from cooking utensils is associated mainly with hepatotoxicity. Dialysis procedures may supply copper through the water supply or from parts of the equipment and when this happens patients may suffer haemolysis and other haematological reactions, kidney involvement, and hepatotoxicity; the toxicity is generally a result of poor equipment maintenance.

Adverse effects attributed to copper have been reported in women with copper-containing intra-uterine devices. There have been isolated case reports of various effects such as allergy and endometrial changes. However, it is difficult to separate adverse effects due solely to the copper from those due to the device.

The symptoms of Wilson's disease (hepatolenticular degeneration) (see p. 1567.3) are due to an accumulation of copper in various parts of the body.

Copper salts if ingested can produce severe gastrointestinal effects and there may be systemic absorption of copper leading to the effects discussed above. The use of sprays of copper salts in agriculture has been associated with lung changes. Treatment of copper poisoning is symptomatic and may involve the use of a chelating agent to remove any absorbed metal. Dialysis has been tried.

Effects on the liver. Cirrhosis and acute liver failure have been attributed to chronic excessive copper supplement ingestion.[1] Supplementation with 10 mg daily of copper (around the safe upper limit) for 2 months has been reported to be associated with transient mild increases in serum aminotransferase values.[2]

1. O'Donohue J, *et al.* Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur J Gastroenterol Hepatol* 1993; **5:** 561–2.
2. Araya M, *et al.* Supplementing copper at the upper level of the adult dietary recommended intake induces detectable but transient changes in healthy adults. *J Nutr* 2005; **135:** 2367–71.

Effects on the nervous system. It has been proposed[1-3] that both excess and deficiency of copper ions in the CNS may play a role in the development of Alzheimer's disease and dementia (p. 388.1).

1. Brewer GJ. The risks of copper toxicity contributing to cognitive decline in the aging population and to Alzheimer's disease. *J Am Coll Nutr* 2009; **28:** 238–42.
2. Quinn JF, *et al.* Copper in Alzheimer's disease: too much or too little? *Expert Rev Neurother* 2009; **9:** 631–7.
3. Hung YH, *et al.* Copper in the brain and Alzheimer's disease. *J Biol Inorg Chem* 2010; **15:** 61–76.

Interactions

Large doses of zinc supplements may inhibit the gastrointestinal absorption of copper.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Multiload†; ***Braz.***: Multiload; ***Canad.***: Micro Cu; ***Chile***: Diu-Safe Cu/375; Diuprotect†; Multiload; Safety T; ***China***: Multiload (莫迪司); ***Fr.***: Gynelle 375; Metacuprol†; Multiload; TT 380; UT 380; ***Ger.***: femena†; GyneFix; Multiload†; ***Hong Kong***: Flexi-T; Multiload; ***Hung.***: Feroglobin-B12; ***India***: Multiload; ***Indon.***: Copper-T; ***Israel***: Micro Cu; Mona-Lisa; ***Ital.***: Gravigard; Gynefix; Multiload; No-Gravid; UT 380; ***Malaysia***: Multiload; ***Mon.***: Algicuivre; ***NZ***: Multiload; ***S.Afr.***: Cuprocept CCL; Dalcept; Tricept; ***Singapore***: Multiload; ***Switz.***: Multiload; ***Thai.***: Multiload; ***Turk.***: Multiload†; ***UK***: Flexi-T; Gynefix; Multiload; ***USA***: Paragard T380A; ***Venez.***: Cicalfate; Multiload.

Multi-ingredient Preparations. ***Arg.***: Agua D'Alibour; Cicalfate; Dermalibour; Gingeron; Glucobefol†; Ipri V Total; Krebs Plus; Nova-T; Senexon Plus; Stress with Zinc; Tonovital Plus Antioxidante; Tricomax; Valeriana Compuesta; ***Austral.***: Ascoxal†; Bone Builder; Caltrate Plus; Haemo-Red; Macu-Vision; Ocuvite PreserVision†; ***Braz.***: Belagin†; Ferrotrat B12 Plus; Ocuvite PreserVision; Olig-Trat; Rubrargil; Stresstabs; Sulfato Ferroso Composto; Zincovit; ***Canad.***: Caltrate Plus; Nova-T; TLI; ***Chile***: Agua Sulfatada Picrica†; Biogenol; Caprimida D Balance; Cellvital†; Cicalfate; Cicaplast; Dermalibour; Larotabe; Sebium H2O†; ***China***: Nova T (新体); Solcoderm (思可得); ***Cz.***: Caltrate Plus; Feroglobin B_{12}; ***Fr.***: Actyferil; Alpharegul Femme; Atoderm moussant; Cicalfate; Cicaplast; Creme de Dalibour; Cu-Zn; Cuivramine; Decramp; Dermalibour; Dermalibour; Dermo-Sulfuryl; Dermocuivre; Dolores; Dynabiane; Eryase†; Naturophta Macula; Oligobiane Fe-Cu; Oligocure; Oligoderm†; Oligorhine; Photoderm; Ramet Dalibour; Ruboderm; Stimunal; Stimuplexe†; Synaptiv; Tot'Hema; Vitacuivre; ***Ger.***: Goldlily; Nova-T; Solco-Derman; ***Hong Kong***: Caltrate Plus; Nova-T†; Solcoderm†; ***Hung.***: Ferrocomp; Humet-R; Multicomp; ***India***: Advit-A; Alcalci-D; Ampucare; Anofer; Antoxid; Avitaz Plus; Aviton; Avpro; Beta-Sclerobion; Calmix; Carbosyl; Deferon; Deoxidant; Derantox; Eldervit-ZC; Elferri Plus; Elnutra; Elrox-AO; Exerge; Fabulae; Facicap; Fejet-OD; Fejet; Ferrimin; Fersolate-CM; Flintoff; Freecad; FRS; Geocal; Haem Up; Haem-Up Gems; Haem-Up; HB-Orange; Hemocare; Hemocare; Hepatoglobine†; I-Lute; Iron-Gold; Ironate; Kibocal-M; Kudamin; Logical-M; Lytox; Macuchek; Maxiferon; Maxo-FE; Menosoft; Mexivit; Moxafav; NBOxid; Nofro; Orbone Forte; Orbone; Ospical-M; Ostebon-M; Osteo-G; Oxi-Red; Oxidon; Oxipre; Oxy-V; Oxyban; Oxydex; Oxyeye; Oxytret; Siderfol; Softeron-Z; ***Indon.***: Adfer; Biosanbe; Caltron; Diabion; Emibion; Emineton; Feritrin; Feroglobin; Feroglobin; Ferokid; Habebion†; Hemafort; Inbion; Jointace; My Caps; Neogobion; Nichobion; Nonemi; Nova-T; Opibion; Osfit; Ossovit Plus; Pronita; Retivit Plus; Retivit; Sangobion; Sangofer; Sangovitin†; Solvitron; Steopor; Suprabion; Tropifer; Vantiz; Viliron; Vioxy-fm; Vioxy; Vitabion; Vitachol; Vitanox; Vitonal; Zevit Grow; Zinc Pharmacore; Zivon; ***Irl.***: Caltrate Plus†; ***Israel***: Nova-T; Stresstabs with Zinc†; ***Ital.***: Artrodue; Artrosulfur; Astar; Chiton; Cuprosodio Plus; Cuprosodio; Emmenoiasi; Flogovis; Inflamase; Linfonorm; Neosulfur†; Nevril; Nova-T; Osteo Complex; Rinogutt Atlantic; Sterimar Cu; Zincoral; ***Malaysia***: Caltrate Plus; Eurobio Bio-Vizmax; Nova-T; Opibion; ***Mex.***: Ascoxal†; Dalidome; Daribur; Drusen; Nova-T; ***Mon.***: Algicuivre; ***NZ***: Caltrate Plus; Nova-T†; ***Philipp.***: Caltrate Plus; Macrobee with Iron; Sangobion; ***Pol.***: Caltrate Plus; ***Port.***: Bioclin Sebo Care; Tot'Hema; ***Rus.***: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Complivit Oftalmo (Компливит Офтальмо); Ferrohematogen (Феррогематоген); Solcoderm (Солкодерм); Tot'Hema (Тотема); Tri-V Plus (Три-Ви Плюс)†; ***S.Afr.***: Dr Williams Pink Pills†; Ferrous Sulphate Compound†; Lotio Pruni Comp cum Cupro†; Muscle Rub†; Nova-T; ***Singapore***: Caltrate Plus; Floron; Hemacaps†; Hemoplex; Multitrace-5; Neogobion; Nova-T; Ocuvite Adult 50+; Opibion; Sangobion; ***Switz.***: Nova-T; Solcoderm; Venadoron; ***Thai.***: Caltrate Plus; Calvin Plus; Diavit; Glufer-C†; Mac-Q-Vis; Temaron; ***Turk.***: Eser Metaller; Nova-T†; ***UK***: Caltrate Plus; Feroglobin; Foresight Iron Formula; Nova-T; Ostron; Vitalux Plus; ***Ukr.***: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Calcemin Silver (Кальцемин Сильвер); Fitoval Capsules (Фитовал капсулы); Optix (Оптикс); Quadevit (Квадевит); Revalid (Ревалид); Solcoderm (Солкодерм); Tot'Hema (Тотема); Vimifor Multivitamin with Beta-Carotene (Вімі-фор Мультивітамін З Бета-каротином)†; Vitrum Foreyes (Витрум Форайз); Vitrum Osteomag (Витрум Остеомаг); ***USA***: Antioxidant Formula; Caltrate Plus; Feocyte; I-Vite Protect; Macular Vitamin Benefit; MacuTrition; NicAzel Forte; Nicomide†; ORA5; PNV-Iron†; Prenatal Plus; Preservision Eye Vitamin; REQ49+; Tri-zel; VP-Zel; ***Venez.***: Cianofer; Cobalfer; Ferroliver; Ferronorm; Folifer B-12; Hepafol con B-12; Nova-T.

Homoeopathic Preparations. ***Canad.***: Allergies; Brocosin; Cocyntal; Col 138†; Drosera Complex; Drosera Plex†; Formula FA 224†; Formula PC 223†; Hay Fever; Homeo-Form AL†; Kids Allergies; Snore No More; Spascupreel; ***Cz.***: Dolicoccil†; Drosetux; Spascupreel S†; ***Fr.***: Abbe Chaupitre no 19†; Abbe Chaupitre no 43†; Cina Compose; Drosera Compose; Drosetux; Homeofortil†; L 25; ***Ger.***: Allergie-Injektopas; Broncho-Injektopas; Drufusan N†; Infi-China; Infifer N; Monapax; Pectapas CPL; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Rufebran broncho†; Spascupreel; Zahnungstropfen Escatitona; ***Hung.***: Dolicoccil; Drosetux; Spascupreel; ***Neth.***: Emvita 11; Geovita; Homeocare Digesto; Phonix Hydrargyrum; Phonix Solidago comp; Spascupreel H; ***Switz.***: Drosetux; Regenaplex Nr. 12; Regenaplex Nr. 31a; ***Ukr.***: Kindinorm (Киндинорм).

Pharmacopoeial Preparations

USP 36: Calcium and Vitamin D with Minerals Tablets; Cupric Chloride Injection; Cupric Sulfate Injection; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Cysteine *(rINN)*

C; Cisteína; Cys; Cystéine; L-Cysteine; Cysteinum; E920; L-Cysteina; Цистеин.

L-2-Amino-3-mercaptopropionic acid.

$C_3H_7NO_2S$=121.2

CAS — 52-90-4.

UNII — K848JZ4886.

Pharmacopoeias. In *Ger.* and *Jpn.*

Cysteine Hydrochloride *(rINNM)*

Cisteína, hidrocloruro de; Cisteino hidrochloridas monohidratas; Cisztein-hidroklorid-monohidrát; Cys Hydrochloride; Cystéine, Chlorhydrate de; Cystéine (chlorhydrate de) monohydraté; L-Cysteine Hydrochloride Monohydrate; Cystein-hydrochlorid monohydrát; Cysteinhydrokloridmonohydrat; Cysteini Hydrochloridum; Cysteini Hydrochloridum Monohydricum; Hidrocloruro de cisteína; Kysteiinihydrokloridimonohydraatti; L-Cysteiny chlorowodorek; Цистеина Гидрохлорид.

L-2-Amino-3-mercaptopropionic acid hydrochloride monohydrate.

$C_3H_7NO_2S,HCl,H_2O$=175.6

CAS — 52-89-1 (anhydrous L-cysteine hydrochloride); 7048-04-6 (L-cysteine hydrochloride monohydrate).

UNII — A9U1687S1S (anhydrous cysteine hydrochloride); ZT934N0X4W (cysteine hydrochloride monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cysteine Hydrochloride Monohydrate; Cysteine Hydrochloride BP 2014). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Cysteine Hydrochloride). White crystals or crystalline powder. Soluble in water, in alcohol, and in acetone.

Profile

Cysteine is a non-essential amino acid. Cysteine and cysteine hydrochloride are used as dietary supplements.

Cysteine and cysteine hydrochloride are included in preparations used in ophthalmology; eye drops have been used to prevent corneal ulceration after chemical burns.

References.

1. Soghier LM, Brion LP. Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 24/06/08).
2. Riedijk MA, *et al.* Cysteine: a conditionally essential amino acid in low-birth-weight preterm infants? *Am J Clin Nutr* 2007; **86:** 1120–5.
3. Meduri A. *et al.* Role of cysteine in corneal wound healing after photorefractive keratectomy. *Ophthalmic Res* 2009; **41:** 76–82.

Precautions. Cysteine, like other sulfhydryl-containing drugs, could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes and suspected hepatocellular injury.[1]

1. Csako G, Elin RJ. Unrecognized false-positive ketones from drugs containing free-sulfhydryl group(s). *JAMA* 1993; **269:** 1634.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Fixcanat†.

Multi-ingredient Preparations. ***Arg.***: Cicatrex Biotic; Dial-ND; Homocisteon Compuesto; Icaps Plus; ***Austral.***: Cicatrin†; Natal Plus; ***Braz.***: Cicatrene; ***Chile***: Brolin Forte; Brolin; ***China***: BiFu (比孚); Bo Luo Ni (博罗尼); Gan Mu Shu (甘木舒); Gan Wei Xin (甘维欣); Gan You Lin (感佑林); Jun Qiang (君强); Kang Er Ning (康尔宁); LiWeiEr (里威尔); Neo-Minophagen C (美能); NuoHao (诺豪); Ruo Jing (若菁); Shu Kang Lin (抒康林); Tuo Di (妥迪); Wei Suan Su (卫算苏); Wei Yi Xing (卫伊兴); Xin-Kang (昕康); Ye Xin (业欣); Yi Nuo Wei (依诺维); Yi Xin (易新); YouNiDi (尤尼迪); Yu Li Sen (宇立森); ***Fr.***: Lobamine-Cysteine; Notrino†; Phakan†; ***Hong Kong***: Hepatofalk†; ***Hung.***: Antismoke; ***Indon.***: Lanavision Plus; Miniceronal†; ***Irl.***: Cicatrin†; ***Ital.***: Biophase Complex†; Cicatrene; Endoepatox; Lipoacid Combi; ***Port.***: Cicatrin; Lipoacid Combi; ***Rus.***: Prohepar

(Прогепар); ***S.Afr.***: Cicatrin†; Prohep†; ***Singapore***: Hepasil DTX†; Vitaton Gold; Vitaton; ***Switz.***: Cicatrex; ***UK***: Skin Care Nutrients; ***Ukr.***: Fakovit (Факовит)†; Oko-Health (Око-хелс); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***Venez.***: Ocoxin.

Pharmacopoeial Preparations
USP 36: Cysteine Hydrochloride Injection.

Cystine *(USAN, rINN)*

Cistina; Cistinas; Cisztin; Cystin; L-Cystine; Cystinum; Di(α-aminopropionic)-β-disulphide; Kystiini; L-Cystyna; Цистин; β,β′-Dithiodialanine.
L-3,3′-Dithiobis(2-aminopropionic acid).
$C_6H_{12}N_2O_4S_2$=240.3
CAS — 56-89-3.
UNII — 48TCX9A1VT.

Pharmacopoeias. In *Chin.*, *Eur* (see p. vii), and *US*.

Ph. Eur. 8: (Cystine). A white or almost white crystalline powder. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Cystine). Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Cystine is a non-essential amino acid. It is used as a dietary supplement.

Low-methionine diets with cystine supplementation have been used in the treatment of congenital homocystinuria (see Amino Acid Metabolic Disorders, p. 2042.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Gelucystine; ***Ital.***: Cistidil; Mavigen Sebo; ***Spain***: Crecil.

Multi-ingredient Preparations. ***Arg.***: Aminoterapia Capilar; Aminoterapia; Cistidac; Cistimax; Dial-ND; Formuly Piel; HSN; LOHP; Megacistin; Megaplus; Tricomax; Valcatil Max; Valcatil Plus; Valcatil; ***Austria***: Pantogar; Priorin; ***Braz.***: Pantogar; ***Chile***: Vantux Plus; Vantux; ***Cz.***: Merz Spezial†; ***Fr.***: Anacaps tri-Activ; Anacaps†; Cysticholt; Cystine B_6; Forcapil; Phaneres; Solacy; ***Ger.***: Pantovigar; ***Hong Kong***: Merz Spezial†; Pantogar; Perfectil; Pilfood; ***Hung.***: Forcapil; Merz Spezial; Revalid; ***Indon.***: Pantogar; ***Ital.***: Biomineral One; Biomineral Plus; Biomineral; Konorderm; ***Mex.***: Pantogar; ***Pol.***: Merz Spezial; Revalid; ***Port.***: Neo-Cystine; Onglinex; ***Rus.***: Eltacin (Элтацин); Merz Spezial Dragees (Специальное Драже Мерц); Pantovigar (Пантовигар); Perfectil (Перфектил); ***Singapore***: Pantogar; ***Switz.***: Pantogar; Priorin N; ***Thai.***: Genquin; ***Turk.***: Pantogar; Priorin; ***UK***: Pilfood; ***Ukr.***: Fitoval Capsules (Фитовал капсулы); Pantogar (Пантогар); Perfectil (Перфектил); Perfectil Plus (Перфектил Плюс); Revalid (Ревалид); ***USA***: Amino-Cerv.

Dectaflur *(USAN, rINN)*

Dectafluro; Dectaflurum; SKF-38094; Дектафлур.
9-Octadecenylamine hydrofluoride.
$C_{18}H_{38}NF$=287.5
CAS — 36505-83-6 (nonstereospecific); 1838-19-3 (9-octadecenylamine).
UNII — Q3B1Y93C1S.

Profile

Dectaflur is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) in the prevention of dental caries. For a report of stomatitis considered to be due to dectaflur, see Hypersensitivity, under Sodium Fluoride, p. 2091.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Elmex; Elmex.

Multi-ingredient Preparations. ***Austria***: Elmex; Elmex; ***Belg.***: Elmex; ***Cz.***: Elmex; Elmex; ***Fin.***: Elmex; Elmex; ***Ger.***: Elmex; Elmex; Ledermix Fluorid; Multifluorid†; ***Hung.***: Elmex; Elmex; ***Israel***: Elmex; ***Ital.***: Elmex; ***Neth.***: Elmex; Elmex; ***Switz.***: Elmex; Elmex; Paro aux fluorures d'amines Gelee.

Dextrin *(BAN)*

British Gum; Dekstriini; Dekstrinas; Dextrina; Dextrine; Dextrinum; Dextrinum Album; Starch Gum; Декстрин.
$[C_6H_{10}O_5]_n.xH_2O$
CAS — 9004-53-9.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Dextrin). Maize, potato, or cassava starch partially hydrolysed and modified by heating with or without the presence of acids, alkalis, or pH control agents. A white or almost white, free-flowing powder. Very soluble in boiling water forming a mucilaginous solution; slowly soluble in cold water; practically insoluble in alcohol. A 5% dispersion in water has a pH of 2.0 to 8.0.

USNF 31: (Dextrin). It is starch, or partially hydrolysed starch, modified by heating in a dry state, with or without acids, alkalis, or pH control agents. A white, yellow, or brown free-flowing powder. Its solubility in water varies; it is usually very soluble, but often contains an insoluble portion.

Icodextrin *(BAN, USAN, rINN)*

Icodextrina; Icodextrine; Icodextrinum; Ikodekstriini; Ikodextrin; Икодекстрин.
$[C_6H_{10}O_5]_n$
CAS — 337376-15-5.
UNII — 2NX48Z0A9G.

Profile

Dextrin, a glucose polymer, is (1→4)-α-D-glucan derived from the hydrolysis of starch. Icodextrin is dextrin with more than 85% of its molecules with molecular weights between 1640 and 45 000, and a weight-average molecular weight of about 20 000. Dextrin is a source of carbohydrate sometimes used in oral dietary supplements and tube feeding. Glucose is rapidly released in the gastrointestinal tract but because of the high average molecular weight of dextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on dextrin (such as maltodextrin p. 2080.3), and intended for dietary supplementation, usually have a low electrolyte content and are free of lactose and sucrose. Such preparations may be particularly useful in certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Dextrin is used as a tablet and capsule diluent, and as a binding, suspending, and viscosity-increasing agent. It has also been used as an adhesive and stiffening agent for surgical dressings.

Dextrin sulfate intravaginal gel has been investigated in the prophylaxis of HIV infection and AIDS.

Icodextrin is used in dialysis fluids as an alternative to glucose-based solutions (see also below). Icodextrin-based fluids are instilled intraperitoneally to reduce adhesions after gynaecological and other abdominal surgery. They have also been used as vehicles for drugs given via the peritoneal cavity.

Dialysis. Glucose-based solutions are commonly used in dialysis solutions for continuous ambulatory peritoneal dialysis (CAPD). However, there is rapid absorption of glucose across the peritoneal membrane, reducing the duration of ultrafiltration and leading to long-term metabolic complications such as hyperglycaemia, hyperinsulinaemia, hyperlipidaemia and obesity. Other osmotic agents have been investigated. One study reported results in 11 patients[1] receiving CAPD who had suffered repeated fluid overload from glucose-based dialysis solutions, and suggested that replacement of glucose with dextrin as the osmotic agent could reverse fluid overload and possibly reduce the frequency of exchange. However, others[2] considered that the proposed frequency of exchange would not provide adequate removal of urea, and that in addition to underdialysis there would be an accumulation of poorly-metabolisable glucose polymers in the blood.

Icodextrin is another alternative.[3-5] It is a glucose polymer, given in iso-osmolar solution. Studies supported by the manufacturers have found that it can be used in ultrafiltration for up to 12 hours, with lower transperitoneal absorption and potential calorie load than glucose solutions.[6,7] It can also be metabolised by amylases in the blood, so is less likely to accumulate than other glucose polymers if absorbed,[7] although the resultant concentrations of maltose (the primary metabolite) have resulted in falsely elevated blood-glucose measurements with some test methods,[8-11] leading to inappropriate insulin dosing and potentially life-threatening adverse effects. Licensed product information states that glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase based methods should not be used for this reason. In a study in CAPD patients, icodextrin was well-tolerated and produced at least equivalent ultrafiltration to glucose solutions.[6] Another study found that peritoneal dialysis patients on icodextrin lost weight and had improved fluid status compared with patients on glucose.[12] In a small study of peritoneal dialysis patients with fluid overload and due to be transferred to haemodialysis, substitution of icodextrin for one long-dwell exchange daily significantly increased ultrafiltration and extended technique survival-time.[13]

A combination of icodextrin and glucose has also been investigated as a means to reduce glucose exposure while increasing ultrafiltration.[14,15]

1. Stein A, *et al.* Glucose polymer for ultrafiltration failure in CAPD. *Lancet* 1993; **341:** 1159.
2. Martis L, *et al.* CAPD with dialysis solution containing glucose polymer. *Lancet* 1993; **342:** 176–7.
3. Frampton JE, Plosker GL. Icodextrin: a review of its use in peritoneal dialysis. *Drugs* 2003; **63:** 2079–2105.
4. Hamburger RJ, Kraus MA. Icodextrin fulfills unmet clinical need of PD patients: improved ultrafiltration. *Dialysis Transplant* 2003; **32:** 675–80.
5. Chhabra D, Nash K. Icodextrin: an alternative peritoneal dialysis fluid. *Expert Opin Drug Metab Toxicol* 2008; **4:** 1455–64.
6. Mistry CD, *et al.* A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. *Kidney Int* 1994; **46:** 496–503.
7. Peers E, Gokal R. Icodextrin provides long dwell peritoneal dialysis and maintenance of intraperitoneal volume. *Artif Organs* 1998; **22:** 8–12.
8. Riley SG, *et al.* Spurious hyperglycaemia and icodextrin in peritoneal dialysis fluid. *BMJ* 2003; **327:** 608–9.
9. MHRA. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 21/07/08)
10. Disse E, Thivolet C. Hypoglycemic coma in a diabetic patient on peritoneal dialysis due to interference of icodextrin metabolites with capillary blood glucose measurements. *Diabetes Care* 2004; **27:** 2279.
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Hypersensitivity. Skin reactions, sometimes severe and generalised, have occurred in patients given icodextrin.[1-5] Reactions have sometimes been delayed up to about 2 weeks after use.[3]

For the suggestion that recurrent sterile peritonitis in patients receiving icodextrin might be due to a hypersensitivity reaction, see below.

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3. Queffeulou G, *et al.* Allergy to icodextrin. *Lancet* 2000; **356:** 75.
4. Al-Hoqail IA, Crawford RI. Acute generalized exanthematous pustulosis induced by icodextrin. *Br J Dermatol* 2001; **145:** 1026–7.
5. Valance A, *et al.* Icodextrin cutaneous hypersensitivity: report of 3 psoriasiform cases. *Arch Dermatol* 2001; **137:** 309–10.

Peritonitis. Sterile peritonitis attributed to icodextrin has been reported.[1,2] Subsequently, several batches were withdrawn by the manufacturer in May 2002 because of bacterial contamination with high levels of peptidoglycan.[2,3] However, further incidents of peritonitis have been reported with icodextrin in patients previously exposed to the withdrawn batches,[4-6] prompting theories of sensitisation to icodextrin or peptidoglycans. Concerns were expressed regarding possible cross-sensitisation to dextran polymers in these patients,[6] as well as the possibility that even low levels of peptidoglycans might trigger peritonitis.[7] Histological changes similar to bacterial peritonitis have been found in patients with icodextrin-associated sterile peritonitis.[8] It was suggested that if cloudy dialysate reappeared upon rechallenge, icodextrin should be withdrawn.[8]

In an effort to determine the cause of the aseptic peritonitis, a manufacturer-sponsored analysis determined that recalled batches of dialysis solution were within product and pharmacopoeial specifications for content, safety, and sterility. However, both dialysate solution and icodextrin raw material caused increases in interleukin-6 response *in vitro*, suggesting a non-endotoxin contaminant as the cause of the aseptic peritonitis. Further analysis found peptidoglycan contamination of the raw icodextrin by *Alicyclobacillus acidocaldarius* to be the cause.[3]

A subsequent 2-year prospective multicentre cohort study involving 722 patients undergoing peritoneal dialysis found no evidence that use of icodextrin-based solutions altered rates of peritonitis.[9]

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3. Martis L, *et al.* Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. *Lancet* 2005; **365:** 588–94.
4. Basile C, *et al.* The impact of relapsing sterile icodextrin-associated peritonitis on peritoneal dialysis outcome. *J Nephrol* 2003; **16:** 384–6.

5. Povlsen JV, *et al*. Exposure to the peptidoglycan contaminant in icodextrin may cause sensitization of the patient maintained on peritoneal dialysis. *Perit Dial Int* 2003; **23:** 509–10.
6. Enia G, *et al*. Sterile icodextrin-associated peritonitis may induce hypersensitivity and recurrent peritonitis on re-challenge. *Nephrol Dial Transplant* 2003; **18:** 626.
7. Seow Y-YT, *etal*. Icodextrin-associated peritonitis among CAPD patients. *Nephrol Dial Transplant* 2003; **18:** 1951–2.
8. Goffin E, *et al*. Icodextrin-associated peritonitis: what conclusions thus far? *Nephrol Dial Transplant* 2003; **18:** 2482–5.
9. Vychytil A, *et al*. Extraneal Peritonitis Study Group. Icodextrin does not impact infectious and culture-negative peritonitis rates in peritoneal dialysis patients: a 2-year multicentre, comparative, prospective cohort study. *Nephrol Dial Transplant* 2008; **23:** 3711–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adept; ***Austral.***: Poly-Joule; ***Fr.***: Caloreen; ***Gr.***: Caloreen†; ***India***: Benefiber; ***Port.***: Extraneal; ***UK***: Adept; Caloreen; ***USA***: Benefiber.

Multi-ingredient Preparations. ***Arg.***: Extraneal; ***Austral.***: Extraneal; ***Belg.***: Extraneal; ***Canad.***: Extraneal; Polycose; ***Cz.***: Extraneal; ***Denm.***: Extraneal; ***Fin.***: Extraneal; ***Fr.***: Extraneal; ***Hong Kong***: Extraneal; ***Hung.***: Extraneal; ***Irl.***: Extraneal; ***Israel***: Extraneal; ***Ital.***: Extraneal; ***Neth.***: Extraneal; ***Norw.***: Extraneal; ***NZ***: Extraneal; ***Philipp.***: Extraneal; ***Rus.***: Extraneal (Экстранил); ***S.Afr.***: Extraneal†; ***Singapore***: Extraneal; ***Spain***: Extraneal; ***Swed.***: Extraneal; ***Switz.***: Extraneal; ***Thai.***: Extraneal; ***Turk.***: Extraneal; ***USA***: Extraneal.

Pharmacopoeial Preparations
USNF 31: Liquid Glucose.

Ferric Ammonium Citrate

381; Ammonium Ferric Citrate; Citrato amoniacal de hierro; Citrato amónico férrico; Citrato de hierro y amonio; Demir III Amonyum sitrat; Ferricum Citricum Ammoniatum; Iron and Ammonium Citrate; Аммония-Железа (III) Цитрат.
CAS — 1185-57-5.
ATC — V08CA07.
ATC Vet — QV08CA07.
UNII — UVP74NG1C5.

Pharmacopoeias. In *US*.

USP 36: (Ferric Ammonium Citrate). It contains between 16.5% and 18.5% of iron. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Profile

Ferric ammonium citrate is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is also used as a food additive, as an acidity regulator, anticaking agent, or source of iron. It has been used as a colouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fu Rui Ming (复锐明); ***Gr.***: Ferriseltz; ***India***: Rubraplex; ***Turk.***: Ferro; Nuklofer; Samson; Tonoferrin.

Multi-ingredient Preparations. ***Arg.***: ITE-B12 Forte; ***Braz.***: Ferrotrat B12 Plus; Hematiase B12; Rubrargil; ***Canad.***: Maltlevol; ***Gr.***: Hemovital†; ***Hong Kong***: Nutroplex†; ***Hung.***: China; ***India***: Acufer; Adfe; Adifer-Z; Atovit; Blosyn; Calphos; Calron; Cario; Chemofer-12; Cherifer; Cinred; Dexorange; Dexorange; Disiorange; Emorange; Exifol; Extrafer; Familykair; Feday; Fefo; Fekair; Femina; Fenna; Fephar; Ferglobin; Feric Grow; Feripro; Ferradol†; Ferricos; Ferril; Ferrimin; Ferrisun; Ferritop Iron Tonic; Ferritop Iron; Ferritop Paed; Ferrochelate; Ferrofit; Ferrolac; Fezza; Fruitovit; FV-Tone; Genfol; Glentona Plus; Globac-Z; Globac; Globifex; Globiron-Z; Haem Up; Haem-Up Gems; Haem-Up; Haematinga; Haemo-Z; Haemocare; HB-Act; HB-Norm; HB-Nova; HB-Orange; HB-Orange; Hb-Rich; HB-Up; HB-Up; Hembran-Fe; Hemex; Hemfer; Hemo-G; Hemsi; Hepatoglobine†; Hepatoglobine; Hepp Forte; Hevit; Ifycarb; Ind-Orange; Inpro; Iron-Gold; Irorange; Isofer; Liton; Lohtone; Maxo-FE; Minadex; Minigadine; Neurophosphates-Iron; Nodyfer; Oxi-Red; Sharkoferrol; Vitamon; ***Ital.***: Emopon; ***S.Afr.***: SB Blood Purifying Mixture†; ***UK***: Ironorm; ***Ukr.***: Haemoferon (Гемоферон); Ranferon-12 (Ранферон-12)†; ***USA***: Geritol; Geritonic; ***Venez.***: Beferron; Cianofer; Hepafol.

Pharmacopoeial Preparations
USP 36: Ferric Ammonium Citrate for Oral Solution.

Ferric Carboxymaltose *(BAN, USAN, rINN)*

Carboximaltosa férrica; Carboxymaltose Ferrique; Ferricum Carboxymaltosum; Iron Dextri-maltose; VIT-45; Железа Карбоксимальтоза.
Poly[D-glucopyranosyl(1→4)]-D-gluconic acid complex of hydrated iron (III) oxide.
CAS — 9007-72-1.
UNII — 6897GXD6OE.

Profile

Ferric carboxymaltose is used as a source of parenteral iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2) when oral iron therapy is ineffective or impractical. The total cumulative dose is calculated according to body-weight and iron deficit. In the UK, the maximum single dose is 1 g of iron and no more than 1 g of iron should be given each week. Ferric carboxymaltose may be given undiluted by intravenous injection; doses between 200 and 500 mg of iron should be injected at a rate of 100 mg/min while those above 500 mg should be given over 15 minutes. Alternatively, it can be diluted with sodium chloride 0.9% and given by intravenous infusion. It should not be given by intramuscular or subcutaneous injection. In patients on haemodialysis, a single maximum daily injection supplying 200 mg of iron may be given undiluted directly into the venous limb of the dialyser. For further information relating to the parenteral use of iron, see Iron Dextran, p. 2075.3.

References.

1. Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs* 2009; **69:** 739–56.
2. Moore RA, *et al*. Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. *BMC Blood Disord* 2011; **11:** 4. Available at: http://www.biomedcentral.com/content/pdf/1471-2326-11-4.pdf (accessed 11/04/12)

Hypersensitivity. Rash is common after injection of ferric carboxymaltose, but urticaria, pruritus, and anaphylactoid reactions are stated to be less so. For a discussion of whether dextran-free preparations may be safer than iron dextran, see p. 2076.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ferinject; ***Austria***: Ferinject; ***Belg.***: Injectafer; ***Cz.***: Ferinject; ***Denm.***: Ferinject; ***Fin.***: Ferinject; ***Fr.***: Ferinject; ***Ger.***: Ferinject; ***Gr.***: Ferinject; ***Irl.***: Ferinject; ***Israel***: Ferinject; ***Neth.***: Ferinject; ***Norw.***: Ferinject; ***Port.***: Ferinject; ***Singapore***: Ferinject; ***Spain***: Ferinject; ***Swed.***: Ferinject; ***Switz.***: Ferinject; ***UK***: Ferinject; ***USA***: Injectafer.

Ferric Pyrophosphate

Difosfato férrico; Férrico, pirofosfato; Iron Pyrophosphate; Пирофосфат Железа.
$Fe_4(P_2O_7)_3$=745.2
CAS — 10058-44-3.
UNII — QK8B99250F.

Profile

Ferric pyrophosphate is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Incremin Iron; ***India***: Incremin; ***Mex.***: Incremin Con Hierro; ***USA***: Vitafol; Vitalize.

Ferritin

Ferritina; Ферритин.

Profile

Ferritin is the major iron storage protein of vertebrates, found mainly in the liver, spleen, intestinal mucosa, and bone marrow and consisting of a soluble protein shell (apoferritin) with a core of crystalline ferric hydroxyphosphate complex. It has been given orally as a source of iron (p. 2073.1) in iron-deficiency anaemias (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Ferrivax; ***Port.***: Profer; ***Spain***: Ferroprotina; Kilor; Profer; Syron.

Ferrocholinate *(rINN)*

Ferrocholinatum; Ferrocolinato; Феррохолинат.
$C_{11}H_{20}FeNO_9,2H_2O$=402.2
CAS — 1336-80-7.
UNII — LWI5ZJ8WVL.

Profile

Ferrocholinate is a chelate prepared by reacting equimolar quantities of freshly precipitated ferric hydroxide with choline dihydrogen citrate. It is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Podertonic.

Multi-ingredient Preparations. ***India***: Alcezyme; Atpro; Avpro; C-Haem; Casiop; Haemoprotex; Hemral; Irex-12 Tonic; Irobex; Irona; Medifer; Nutra; Osprovit.

Ferrous Ascorbate

Ferroso, ascorbato; Железа Аскорбат.
$C_{12}H_{14}FeO_{12}$=406.1
CAS — 24808-52-4.
ATC — B03AA10.
ATC Vet — QB03AA10.

Profile

Ferrous ascorbate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in usual doses of up to 1.47 g daily (equivalent to about 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ascofer; ***India***: Aloha-XT DPS; Fericos-XT.

Multi-ingredient Preparations. ***Austria***: China-Eisenwein†; ***India***: Aloha-XT; Ascofit; Ascoliza; Barocal Forte; C-Rich; Cariz-XT; Corus-FA; CPink; Ep-Iron Fol; Ev-Syl-XT; Faroo-XT; Farris; Febate; Fephar; Feriena; Ferisym-XT; Ferolact; Ferolact; Feronia-XT; Feropic-XT; Ferosig; Ferulic; Fesu-XT; Fezon; Fezys-XT; Fresco; HB-Ron; Hemacor; Huntred-Z; Huntred; I-Fol; Ifyasco-Z; Iolebate; Ircor-FA; Irofur; Iromax; Irosol; Irosol; Irus; Levifer; Litron-XT; Nid-XT.

Ferrous Aspartate

Ferroso, aspartato; Железа Аспартат.
$C_8H_{12}FeN_2O_8,4H_2O$=392.1
ATC — B03AA09.
ATC Vet — QB03AA09.
UNII — Z56D82TX8V.

Profile

Ferrous aspartate is a source of iron (p. 2073.1) used in dietary supplements. It is given orally in a usual dose of 112 mg daily (equivalent to about 16 mg of iron daily). Higher doses were formerly given in the treatment of iron-deficiency anaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Spartocine†; ***USA***: FE Aspartate.

Ferrous Chloride

Ferroso, cloruro; Железа Хлорид.
Iron (II) chloride tetrahydrate.
$FeCl_2.4H_2O$=198.8
CAS — 7758-94-3 (anhydrous ferrous chloride); 13478-10-9 (ferrous chloride tetrahydrate).
ATC — B03AA05.
ATC Vet — QB03AA05.
UNII — S3Y25PHP1W.

Profile

Ferrous chloride is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in a usual dosage of about 350 to 700 mg daily in divided doses (equivalent to about 100 to 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Fer UCB; ***Pol.***: Hemofer; ***Switz.***: Ferrascorbin†.

Multi-ingredient Preparations. ***Switz.***: Ferrascorbin†.

Ferrous Fumarate

Demir Fumarat; Eisen(II)-fumarat; Ferrofumaraatti; Ferrofumarat; Ferrosi Fumaras; Ferroso, fumarato; Fumaran

železnatý; Fumarate ferreux; Geležies(II) fumaratas; Vas(II)-fumarát; Железа Фумарат.
$C_4H_2FeO_4$=169.9
CAS — 141-01-5.
ATC — B03AA02.
ATC Vet — QB03AA02; QB03AD02.
UNII — R5L488RY0Q.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Ferrous Fumarate). A fine, reddish-orange or reddish-brown powder. Slightly soluble in water; very slightly soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Ferrous Fumarate). A reddish-orange to red-brown, odourless powder, which may contain soft lumps that produce a yellow streak when crushed. Slightly soluble in water; very slightly soluble in alcohol. Its solubility in dilute hydrochloric acid is limited by the separation of fumaric acid.

Profile

Ferrous fumarate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in usual doses of up to 600 mg daily (equivalent to about 200 mg of iron daily); doses of up to 1.2 g daily (equivalent to about 400 mg of iron daily) may be used if necessary.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous fumarate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hemofer; Hemoferrol; ***Austria***: Ferretab; Ferrobet; ***Canad.***: Neo-Fer; Palafer; ***Cz.***: Ferronat†; ***Fr.***: Aloferal; Fumafer; ***Ger.***: Ferrum Hausmann; Rulofer N; ***Gr.***: Chrofer; ***Hung.***: Feroglobin-B12; ***Indon.***: Fercee; ***Irl.***: Fersaday†; Galfer; ***Mex.***: Biofuroso; Croferron; Fernadin; Ferro-Terapina; Ferval; Fumavit; Gestaferron; Medifer†; ***Norw.***: Nycoplus Neo-Fer; ***Rus.***: Heferol (Хеферол); ***Singapore***: Iron Beacons; ***Swed.***: Erco-Fer†; ***Switz.***: Ferrum Hausmann; Lufer†; ***Thai.***: Cebrin-Fe; F-Tab; Femarate; Ferdek; Fermasian; Fermate; I-RON; ***Turk.***: Feramat; ***UK***: Fersaday; Fersamal†; Galfer; ***USA***: Femiron; Ferretts; Ferro-Dok; Hemocyte; Nephro-Fer†; Vitron-C; ***Venez.***: Ferol; Ferroce.

Multi-ingredient Preparations. ***Arg.***: Anemidox-Ferrum; Anemidox-Solutab; Ferretab Compuesto; Ferrocebrina; Hemofer Folic; Hierro Folico; ***Austral.***: Bio Iron; Extralife PMS-Care†; Iron Max; Iron Plus; ***Austria***: Ferretab Comp; ***Belg.***: Gestiferrol; ***Braz.***: Betozone†; Folix-Mater†; Iloban; ***Canad.***: Ferro-C with B Complex; Formula C 36†; Liv-Gd; Neo-Fer CF; Palafer CF; ***Chile***: Confer; Fercovit; Ferranim; Ferro Vitaminico†; Folifer; Orlon; ***Cz.***: Feroglobin B_{12}; Ferretab Comp; Merz Spezial†; ***Denm.***: Jern C; ***Gr.***: Dicalets-M; ***Hong Kong***: Fortifer; ***Hung.***: Merz Spezial; ***India***: Adfe-C; Adfe; Adifer-Z; Aglon; Alamin-Fez; Anemidox; Astyfer-Z; Astyfer; Autrin; Aviton; Avpro; Blosyn; Blush; Calcefol; Calhem Plus; Calpro ZE; Capsovit; Chemofer-12; Choice; Cromofer-OD; Cromofer-Z; Deferon; Dumasules-Z; Dumasules; Elferri-Z; Enzofer-TR; Facicap; Fe-Z; Febex; Fekair; Femicontin; Fenna; Feritol; Ferozinc; Ferrimin; Ferritop; Ferro Hepatine; Ferrogen-Z; Ferrogen; Fezocaps; Fleefer; Globac-Z; Glohem TR; Haem Up-Z; Haem-Up Gems; Haematinga; Haemglow-Z; Haemglow; Haemplus; Hamozen-Z; HB Plus; HB-Act; HB-Norm; Hembran Plus; Hemfast; Hemforte; Hemofer-Z; Hemprovit-Fe; Hemral; Hemsi; Hemsyneral-TD; Hepasules-F; Hepasules†; Hepatoglobine†; Idiglobin; Irex-12; Ironate; Ironeed; Liton-Z; Livogen Captab; Livogen-Z; Medifer; Mefol; Myglo; Nid-XT; Nodyfer; Ossofez; Oxyglobin; Siderfol; Softeron-Z; Softeron; ***Indon.***: Bioferron; Bionemi; Calmin-AF; Dasabion; Emineton; Ferobion; Hemafort; Hemarate CE†; Hemobion; Lactacin; Natabion; Nichobion; Nonemi; Nufagrabion-GM; Nufagrabion; Odiron-C†; Prenamia; Prenatin-DF; Prohelic; Rejuvan†; Solvitral; Solvitron; Veroscan; Vitachol; Vitalex; Vitamam 2; Vitamam 3; Vitonal; ***Irl.***: Galfer FA; Givitol†; ***Israel***: Folex; Foric; ***Malaysia***: Ferrovit†; ***Mex.***: Autrin; Dialeli AF; Ferro Grin†; Ferrotemp; Fumarol†; Yemifer-HE; ***Philipp.***: Anemicon Plus; Anixon; Appebon with Iron; Azul; Beniforte; Blush; Charlize; Comvit FA; Essenfer; Femme; Fer-Essence; Fergesol; Ferlette; Feronerv; Ferosal; Ferroplex; Ferrovit; Foramefer; Fortifer FA; Fortifer; Fumiron + B; Harvifer; Hemarate; Hemobion; Hemovin; Heralink; Hi-Smart Teens; Iroplex; Macrobee with Iron; Micropil Plus; Molvite-OB; Multispec-E; Mulvitron; Nakaron; Natalbes; TLC Vita-OB; Trev-Iron Plus; Trev-Iron; TriHEMIC; Trust Pill; Usanatal; Zoiron; ***Rus.***: Ferretab Comp (Ферретаб Комп); Merz Spezial Dragees (Специальное Драже Мерц); ***S.Afr.***: Autrin†; Neurotone; Pregamal; ***Singapore***: Iron Melts; Odiron-C; Wanse; ***Spain***: Cinfavit Complex; Foliferron; ***Switz.***: Duofer Fol; Duofer; ***Thai.***: Adnemic-F; Biocalron; Boracap; FB Fer†; FBC Plus; FBC; Fer-200†; Fercalmin; Ferli-6; Ferosix; Ferplus-B; Ferrocine; Ferropro; Ferrovit; Foli-C; Hemarate†; Hemolax†; Intricon; Obimin-AZ; Polycolvit; Polyvit; Vita-Cal; ***Turk.***: Ferrozinc; Vi-Fer; ***UK***: Galfer FA; Meterfolic; Pregaday; ***Ukr.***: Hemsyneral-TD (Гемсинерал-ТД)†; Little Friend (Маленькие Друзья)†; Merz Special Dragees (Специальное Драже Мерц); Pregnalac (Прегналак)†; Pregnavit (Прегнавит); Ranferon-12 (Ранферон-12); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Vitrum Prenatal (Витрум Пренатал); ***USA***: ABC to Z; Albafort; Berocca Plus; Caltrate + Iron & Vitamin D; Certagen; Chromagen FA; Chromagen Forte; Chromagen†; Contrin; Diatx Fe; Estrostep Fe; Femcon Fe; Ferotrinsic; Ferrogels Forte; Fetrin; Formula B Plus; Fumatinic†; Geriot; Gevral T; Hem Fe; Hematinic Plus; Hematinic; Hemocyte Plus; Hemocyte-F; Junel Fe; Livitrinsic-f†; Lo Minastrin Fe; Loestrin Fe; Minastrin 24 FE; Multifol; Parvlex; Pronemia Hematinic; Repliva†; Tandem Plus; Tandem; Thera Hematinic; Theragenerix-H; Tilia Fe; Tolfrinic; Tri-Legest; TriHEMIC; Trinsicon†; Vitafol-OB; Vitafol; Wymzya Fe; Yelets; Zenchent Fe; Zodeac; ***Venez.***: Cobalfer; Fefol; Ferroliver; Ferronorm; Folifer B-12; Hepafol con B-12; Vitnatal.

Pharmacopoeial Preparations
BP 2014: Ferrous Fumarate and Folic Acid Tablets; Ferrous Fumarate Capsules; Ferrous Fumarate Oral Suspension; Ferrous Fumarate Tablets;
USP 36: Ferrous Fumarate and Docusate Sodium Extended-release Tablets; Ferrous Fumarate Tablets.

Ferrous Gluceptate

Ferroso, gluceptato; Ferrous Glucoheptonate; Glucoheptonato ferroso.
$Fe(C_7H_{13}O_8)_2$=506.2
CAS — 25126-38-9.
UNII — 13809H6DVG.

Profile

Ferrous gluceptate is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Unifer.

Multi-ingredient Preparations. ***Arg.***: Egestan Hierro; ***Spain***: Normovite Antianemico.

Ferrous Gluconate

E579; Eisen(II)-Gluconat; Ferroglukonaatti; Ferroglukonat; Ferrosi gluconas; Ferrosi Gluconas Hydricus; Ferroso, gluconato; Geležies(II) gliukonatas; Gluconate ferreux; Glukonan železnatý hydrát; Vas(II)-glükonát; Železa(II) glukonian; Железа Глюконат.
Iron (II) di(D-gluconate).
$C_{12}H_{22}FeO_{14}.xH_2O$
CAS — 299-29-6 (anhydrous ferrous gluconate); 12389-15-0 (ferrous gluconate dihydrate).
ATC — B03AA03.
ATC Vet — QB03AA03.
UNII — U1B11I423Z.

Pharmacopoeias. In *Eur.* (see p. vii).

Chin. and *US* specify the dihydrate.

Ph. Eur. 8: (Ferrous Gluconate). A greenish-yellow to grey powder or granules. It contains not less than 11.8% and not more than 12.5% of ferrous iron calculated with reference to the dried substance. Freely but slowly soluble in water producing a greenish-brown solution, more readily soluble in hot water; practically insoluble in alcohol. A 10% solution in water has a pH of 4.0 to 5.5 three to four hours after preparation. Protect from light.

USP 36: (Ferrous Gluconate). A yellowish-grey or pale greenish-yellow, fine powder or granules having a slight odour resembling that of burnt sugar. Soluble 1 in 5 of water; practically insoluble in alcohol. A 5% solution in water is acid to litmus. Store in airtight containers.

Profile

Ferrous gluconate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 1.8 g daily (equivalent to up to 210 mg of iron daily).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous gluconate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Losferron; ***Belg.***: Losferron; ***Canad.***: Novo-Ferrogluc†; ***Chile***: Glucoferro K; ***Cz.***: Losferron†; ***Denm.***: Fexin†; ***Ger.***: Eisen-Sandoz†; Ferrum Verla; Floradix mit Eisen; Losferron; Rulofer G†; Vitaferro†; ***Gr.***: Viofer; ***Israel***: Ferro-Nes; Ferro; Ferronal; ***Ital.***: Auxofer†; Bioferal; Bioglufer; Blustark†; Crom; Cromatonferro; Effegyn; Emoxiron†; Eritropiu; Ferro Complex; Ferrogyn; Gloros; Glucoferro; Losferron; Megafer; Monoferro†; Prontoferro; Sidervim; Sustemial; ***Neth.***: Losferron; ***Norw.***: Fexin†; ***Pol.***: Ascofer; ***Port.***: Bioferro; Hemototal; ***Rus.***: Ferronal (Ферронал)†; ***Spain***: Losferron; ***Swed.***: Fexim†; ***Switz.***: Lufer†; ***Turk.***: Losferron; ***Ukr.***: Megaferin (Мегаферін)†; ***USA***: Ferate Tabs; Fergon; ***Venez.***: Salfer; Yisafer.

Multi-ingredient Preparations. ***Canad.***: Floradix Formula; Floradix Tab†; Floravit†; Floravit; Liv-Gd; ***Chile***: Prenavit; ***Fr.***: Alpharegul Femme; Tot'Hema; ***Ger.***: Floradix Eisen-Folsaure; Floradix Krauterblut†; ***Hung.***: Floradix; ***India***: Ampiro; Beetone; Deferon; Elferri; Facicap; Febex; Ferrocin C B12 Plus; Fezee; Gynae-CVP; Gystat; Haemglow; Hemiphos; Hemolex; Hepp-Tone; Infaglobin; Ironate; JP Tone; Livogen Hemtonic; Marvita; Mefol; Mulmin Plus; Mulmin; Myglo; Mynberrys Compound; Osteoz-FR; ***Indon.***: Adfer; Biosanbe; Diabion; Emibion; Habebion†; Inbion; Maltiron; Muveron; Neogobion; Opibion; Pronita; Sangobion; Sangobion; Sangofer; Sangovitin†; Solvitron; Suprabion; Suprabion; Tropifer; Vitabion; ***Ital.***: Ergon; Ferromina; ***Malaysia***: Opibion; Sangobion; ***Philipp.***: Sangobion; Sangobion; ***Pol.***: Additiva Ferrum†; ***Port.***: Tot'Hema; ***Rus.***: Tot'Hema (Тотема); ***Singapore***: Chitosano; Hemacaps†; Hemoplex; Neogobion; Opibion; Sangobion; ***Switz.***: Duofer Fol; Duofer; Ferrascorbin†; ***Thai.***: Ferro-Be-Sian†; Ferromin; Glufer-C†; Sangobion†; ***Turk.***: Ferro-Vital†; ***UK***: Floradix; Foresight Iron Formula; ***Ukr.***: Tot'Hema (Тотема); ***USA***: Compete; Iromin-G; ***Venez.***: Bioglobina.

Homoeopathic Preparations. ***Ger.***: HanoOxygen E.

Pharmacopoeial Preparations
BP 2014: Ferrous Gluconate Tablets;
USP 36: Ferrous Gluconate Capsules; Ferrous Gluconate Elixir; Ferrous Gluconate Tablets.

Ferrous Glycine Sulfate

Aminoacetosulfato ferroso; Demir Glisin Sülfat; Ferroglycini Sulfas; Ferroglycinsulfat; Ferroglysiinisulfaatti; Ferroso de glicina, sulfato; Ferrous Aminoacetosulphate; Ferrous Glycine Sulphate; Железа Глицин Сульфат.
CAS — 14729-84-1.
ATC — B03AA01.
ATC Vet — QB03AA01.

Profile

Ferrous glycine sulfate is a chelate of ferrous sulfate and glycine used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in a usual dose containing the equivalent of 100 mg of iron daily; up to about 300 mg daily has been used in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Neutrofer Neonatal; Neutrofer; ***Chile***: Cheltin; ***Denm.***: Glycifer; Niferex; ***Fin.***: Obsidan; Spartofer; ***Ger.***: Ferro sanol duodenal; Ferro Sanol; ***Gr.***: Ferro Sanol; ***Hong Kong***: Ferro Sanol; ***Irl.***: Plesmet†; ***Ital.***: Niferex; ***Norw.***: Niferex; ***Port.***: Niferex; ***Spain***: Ferbisol; Ferro Sanol; Glutaferro; ***Swed.***: Niferex; ***Switz.***: Ferro sanol; ***Turk.***: Ferro Sanol; ***USA***: Gentle Iron; ***Venez.***: Herronduo.

Multi-ingredient Preparations. ***Arg.***: Anemidox Ultra; ***Braz.***: Neutrofer Folico; ***Chile***: Cheltin Folic; Pre Mat; ***Fin.***: Obsidan comp; ***Ger.***: Ferro sanol comp; Ferro sanol gyn; ***India***: Astyfer; Fecontin-F; Fecontin-Z†; Fereg-F; Fereg-Z; Ferinova; Fezocar; Glyciron; Hemfer-A; Hemfer; Hemfer; Hemocare; Hemocare; Mighty; ***Turk.***: Ferro Sanol B; ***UK***: Florisene; ***USA***: Repliva†; ***Venez.***: Herrongyn.

Ferrous Iodide

Ferrous Iodine; Iron Diiodide.
FeI_2=309.7
CAS — 7783-86-0.
ATC — B03AA11.
ATC Vet — QB03AA11.
UNII — F5452U54PN.

Profile

Ferrous iodide has been used as a source of iron (p. 2073.1) and iodine (p. 2336.3).

Homoeopathy

Ferrous iodide has been used in homoeopathic medicines under the following names: Eisenjodid; Eisenjodür; Ferr-i.; Ferrum iodatum; Ferrum jodatum; Iodide of iron; Jodeisen.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Lymphomyosot; ***Cz.***: Lymphomyosot; ***Fr.***: Aurum Complexe No 38†; ***Ger.***: Lymphomyosot N; Lymphomyosot; Rufebran thyreo†; Thyreo-Injektopas; ***Hung.***: Lymphomyosot; ***S.Afr.***: Lymphomyosot; ***Switz.***: Regenaplex Nr. 25c; ***Ukr.***: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Ferrous Lactate

E585; Ferroso, lactato; Iron Lactate; Молочнокислое Железо.

$C_6H_{10}FeO_6.3H_2O$=288.0

CAS — 5905-52-2 (anhydrous ferrous lactate); 6047-24-1 (ferrous lactate trihydrate).

UNII — 5JU4C2L5A0 (ferrous lactate); IEP40B1R5X (ferrous lactate trihydrate).

Profile

Ferrous lactate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Dan Zhu (丹珠); La Ke Fei (拉克菲); Tie Xin (貼鑫); You Ni Xue (尤尼雪); ***S.Afr.***: Ferro Drops L; ***Spain***: Cromatonbic Ferro.

Multi-ingredient Preparations. ***Austria***: Anthozym†; ***Pol.***: Multivitamol; ***Ukr.***: Gerovital Dr. Theiss (Геровитал Др. Тайсс); Multivitamol Dr Theiss (Мультивитамол Др. Тайсс).

Ferrous Oxalate

Ferroso, oxalato; Ferrum Oxalicum Oxydulatum; Iron Protoxalate; Protoxalato de hierro; Железа Оксалат.

$C_2FeO_4.2H_2O$=179.9

CAS — 516-03-0 (anhydrous ferrous oxalate); 6047-25-2 (ferrous oxalate dihydrate).

UNII — DZP4YV3ICV.

Profile

Ferrous oxalate has been used as a source of iron (p. 2073.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Disulone.

Ferrous Succinate

Ferroso, succinato; Железа Сукцинат.

$C_4H_4FeO_4$=171.9

CAS — 10030-90-7.

ATC — B03AA06.

ATC Vet — QB03AA06.

UNII — 818ZYK7N91.

Profile

Ferrous succinate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to about 600 mg daily (equivalent to up to about 200 mg of iron daily).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous succinate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ferdromaco; ***China***: Su Li Fei (速力菲); ***Fr.***: Inofer; ***Ger.***: Ferrlecit 2.

Multi-ingredient Preparations. ***India***: Hematrine; ***USA***: Iron Complex.

Ferrous Sulfate

Demir Sülfat; Eisen(II)-Sulfat; Ferreux (Sulfate); Ferrosi Sulfas; Ferrosi sulfas heptahydricus; Ferroso, sulfato; Ferrosulfaattiheptahydraatti; Ferrosulfatheptahydrat; Ferrous Sulphate; Ferrum Sulfuricum Oxydulatum; Geležies(II) sulfatas heptahidratas; Iron (II) Sulphate Heptahydrate; Iron Sulphate; Síran železnatý heptahydrát; Sulfate ferreux heptahydraté; Sulfato de hierro; Sulfato de hierro (II) heptahidrato; Vas(II)-szulfát; Żelaza(II) siarczan; Железа Сульфат.

$FeSO_4.7H_2O$=278.0

CAS — 7720-78-7 (anhydrous ferrous sulfate); 7782-63-0 (ferrous sulfate heptahydrate).

ATC — B03AA07.

ATC Vet — QB03AA07; QB03AD03.

UNII — 39R4TAN1VT.

NOTE. Crude ferrous sulfate is known as Green Vitriol or Green Copperas.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Swiss also includes ferrous sulfate sesquihydrate.

Ph. Eur. 8: (Ferrous Sulfate Heptahydrate). A light green crystalline powder or bluish-green crystals, efflorescent in air. It is oxidised in moist air, becoming brown. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

USP 36: (Ferrous Sulfate). Pale bluish-green, odourless, crystals or granules. It is efflorescent in dry air and oxidises readily in moist air to form brownish-yellow basic ferric sulfate. Soluble 1 in 1.5 of water and 1 in 0.5 of boiling water; insoluble in alcohol. A 10% solution in water is acid to litmus, having a pH of about 3.7. Store in airtight containers.

Dried Ferrous Sulfate *(USAN)*

Dried Ferrous Sulphate; Exsiccated Ferrous Sulphate; Ferreux (sulfate) desséché; Ferrosi sulfas desiccatus; Ferrosi Sulfas Exsiccatus; Ferroso desecado, sulfato; Sulfato ferroso seco.

CAS — 13463-43-9.

UNII — 2IDP3X9OUD (anhydrous ferrous sulfate); RIB00980VW (dried ferrous sulfate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Ferrous Sulfate, Dried). Hydrated ferrous sulphate deprived of part of its water of hydration by drying. A greyish-white powder which is oxidised in moist air, becoming brown. It contains 86.0 to 90.0% of $FeSO_4$. Slowly but freely soluble in water, very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

USP 36: (Dried Ferrous Sulfate). A greyish-white to buff-coloured powder consisting primarily of ferrous sulfate monohydrate with varying amounts of ferrous sulfate tetrahydrate. It contains 86.0 to 89.0% of $FeSO_4$. Slowly soluble in water; insoluble in alcohol.

Profile

Ferrous sulfate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally; the dried form is often used in solid dosage forms and the heptahydrate in liquid dosage forms. Usual doses of dried ferrous sulfate are up to 600 mg daily (equivalent to 180 to 195 mg of iron daily, this figure being somewhat variable depending on the purity and water content of the salt).

Ferrous sulfate oxidised with nitric and sulfuric acids yields ferric subsulfate solution, also known as Monsel's solution, which has been used as a haemostatic.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous sulfate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Eurofer; Factofer; Feklon; Fer-In-Sol; Ferricol; Ferrocebrina; Ferromas; Ferrometion; Hemofer; Hemoferrol; Iberol; Medifer; Siderblut; TGI; ***Austral.***: Ferro-Gradumet; Ferrograd C; ***Austria***: Aktiferrin; Ferro-Gradumet; Tardyferon; ***Belg.***: Fero-Grad; Fero-Gradumet; Tardyferon; ***Braz.***: Cimefer; Fer-In-Sol; Ferronil; Ferrosol†; Ferrototal; Iberol; Ironfer†; Sulfer Plus†; Sulferbel; Sulfergan Composto; Sulferro†; Sulferrol; Vitafer; ***Canad.***: Fer-In-Sol; Ferodan; Ferofate†; Novo-Ferrosulfate†; Slow-Fe; ***Chile***: Fer-In-Sol; Ferrigot; ***Cz.***: Aktiferrin; Sorbifer; Tardyferon; ***Denm.***: Ferro; ***Fin.***: Duroferon; Retafer; ***Fr.***: Fer AP-HP; Fero-Grad vitamine C; Timoferol; ***Ger.***: Aktiferrin N†; Ceferro; Dreisafer; Eisentabletten; Eryfer; Ferrogamma; Floradix Eisen; Haemoprotect; Hamatopan; Kendural C; Plastufer†; Plastulen†; Tardyferon; ***Gr.***: Cooperfer; Fer-In-Sol; Microfer; Resoferon; Tardyferon; ***Hong Kong***: Ferasul†; Ferisan†; Iron-200; Super-Fe†; ***Hung.***: Aktiferrin; Ferro-Gradumet; Sorbifer; Tardyferon; ***India***: Ferich; ***Indon.***: Sulfas Ferrosus; ***Irl.***: Feospan; Fer-In-Sol; Ferrograd C; Ferrograd; ***Israel***: Ferro-Gradumet; Slow-Fe†; Tardyferon; ***Ital.***: Fer-In-Sol; Ferrograd C; Ferrograd; ***Malaysia***: Retafer; ***Mex.***: Biofenor; Fer-In-Sol; Ferifer; Forcil†; Hemobion; Valdefer; ***Neth.***: Fero-Gradumet; Ferrograd; Protiferron; ***Norw.***: Duroferon; Ferromax; Nycoplus Ferro-Retard; ***NZ***: Ferro-Gradumet; Ferrograd C; ***Philipp.***: Brisofer; Feosol; Feovit†; Fer-In-Sol; Ferglobin; Ferosal; Sorbifer; United Home Fersulfate Iron; ***Pol.***: Ferro-Gradumet†; Hemofer; Sorbifer; Tardyferon; ***Port.***: Ferro-Gradumet; Tardyferon; ***Rus.***: Aktiferrin (Актиферрин); Ferro-Gradumet (Ферроградумет); Ferroplex (Ферроплекс); Hemofer (Гемофер); Sorbifer (Сорбифер); Tardyferon (Тардиферон); ***S.Afr.***: Fero-Grad†; Ferro Drops; Fesofor†; ***Spain***: Fero-Gradumet; Tardyferon; ***Swed.***: Duroferon; ***Switz.***: Aktiferrin; Ferro-Gradumet; ***Thai.***: Fer-In-Sol†; Ferrotabs; Kidiron; Pediron; ***Turk.***: Oroferon; Tardyferon; ***UAE***: Kdiron; ***UK***: Feospan; Ferrograd C; Ferrograd; Ironorm; ***Ukr.***: Aktiferrin (Актиферрин); Aktiferrin (Актиферрин); Sorbifer (Сорбифер); Tardyferon (Тардиферон); ***USA***: Enfamil Fer-In-Sol; Fe^{50}; Feosol; Fer-gen-sol†; Fer-Iron; Feratab†; Fero-Grad; Ferrous Drops; Irospan; Slow-Fe; ***Venez.***: Fer-In-Sol.

Multi-ingredient Preparations. ***Arg.***: Bifidosa; Cistidac; Factofer B12; Fefol; Ferro Folic; Ferrogalfol; Hierro Plus†; Iberol; Rubiron; Sideralce; Tardyferon; Vifortol Prenatal; ***Austral.***: Fefol; FGF Tabs; Irontona†; ***Austria***: Aktiferrin Compositum; Ferrograd Fol; Ferrum-Quarz; Kephalodoron; Tardyferon-Fol; ***Braz.***: Betozone†; Cobaldoze†; Combiron; Dobiron; Ferrocomplex; Ferroplex; Ferrotrat; Iberin Folico; Iberol; Novofer; Paratonico†; Sulfato Ferroso Composto; Vitonico; ***Canad.***: Pediavit Select; Slow-Fe Folic†; ***Chile***: Acomir con hierro†; Ferranem; Ferromalt; Iberol Folico†; Iberol†; ***China***: Yi Yuan Sheng (益源生); ***Cz.***: Aktiferrin Compositum; Ferro-Folgamma; Tardyferon-Fol; ***Fr.***: Oligobiane Fe-Cu; Tardyferon B_9; Tardyferon; Thalamag fer B_9; ***Ger.***: Eryfer comp†; Ferro-Folgamma; Ferro-Folsan; Hamatopan F; Kendural-Fol-500†; Plastulen Duo†; Tardyferon-Fol; ***Gr.***: Feofol; Fero-Folic; Gyno-Tardyferon; ***Hong Kong***: Iberet-Folic†; Iberet†; ***Hung.***: Ferro-Folgamma; Ferrograd Folic; Neo-Ferro Folgamma; Tardyferon-Fol; ***India***: Cofol; Conviron Forte; Conviron-TR; Durovit-Fez; Durovit; Elferri-TR; Fefol-Z; Fefol; Feonat-Z; Feonat; Ferobid-Z; Ferritop-SR; Ferro-Plan Kit; Ferrochelate-Z; Fersolate-CM; Ferz; Fesofor-Z; Fesovit; Fesovit; Festo-TR; Feton-Z-TR; Fezee; Haem-F; HB-Plan Kit; Hb-Rich 300; Iberol†; Iberol; Irex-TR; Ironifol-Z; Irosoft; JP Tone-TR†; Maxiferon; Mulmin-F; Plastules B-12; Protone; ***Indon.***: Befozi; Iberet-Folic; Iberet; ***Irl.***: Fefol; Ferrograd Folic; ***Israel***: Aktiferrin-F; Ferrograd Folic; Foliferrin; Slow-Fe Folic†; Tardyferon B9†; ***Ital.***: Ferrograd Folic; ***Malaysia***: Aktiferrin-F†; Iberet-Folic; ***Mex.***: Alpharexin†; Ferro Folico; Hemoinfant; Iberet†; Iberol†; Orafer Comp; Tardyferon-Fol; ***NZ***: Ferrograd Folic; ***Philipp.***: Ameciron; Appebon with Iron; Appetason; Appetason; Appetite OB; Appetite with Iron; Cuteplex; Drexabion OB; Dupharon; Femina; Ferlin; Ferlin; Ferosal; Ferro-Folsan Plus†; Foralivit; Hanizyn; Heltine; Hemiron; IBC; Iberet-Folic; Iberet; Imefer; Irobon; Magniferron; Mediferron-Vita; Meganerv-E; Micron-C; Molvite with Iron; Natalac FeFol; Propan with Iron; Regeron-E Plus; Terraferron; ***Pol.***: Ferrograd Folic†; Hemofer F†; Tardyferon-Fol; ***Port.***: Fefolato; Ferrograd Folico; Folifer; Tardyferon-Fol; ***Rus.***: Aktiferrin Compositum (Актиферрин Композитум); Biovital (Биовитал); Fenules (Фенюльс); Fenules Zinc (Фенюльс Цинк); Ferro-Folgamma (Ферро-Фольгамма); Ferrohematogen (Феррогематоген); Ferrovit (Ферровит); Gyno-Tardyferon (Гино-тардиферон); Hematogen C (Гематоген С); Hematogen C Vita (Гематоген С Вита); Hematogen Nova (Гематоген Новый); ***S.Afr.***: Dr Williams Pink Pills†; Fefol-Vit†; Fefol†; Fero-Folic; Ferrous Sulphate Compound†; Foliglobin; ***Singapore***: Aktiferrin-F†; Ferbeaplex; Iberet-Folic; Iberet; ***Spain***: Bialfer; ***Switz.***: Aktiferrin-F†; Fero-Folic; Gyno-Tardyferon; Kendural; Tardyferon; ***Thai.***: Ferro-BC; Iberet; Temaron; ***Turk.***: Gyno-Tardyferon; Gynoferon; Natabec†; ***UAE***: Folicron; ***UK***: Fefol; Ferrograd Folic; Ironorm; ***Ukr.***: Fenules (Фенюльс)†; Fersinol-Z (Ферсинол-3); Gyno-Tardyferon (Гино-Тардиферон); ***USA***: Aqua Ban Plus; Fero-Folic; Generet; Slow Fe with Folic Acid; ***Venez.***: Ferro-Folic; Ferroce B12; Iberol C.

Homoeopathic Preparations. ***Cz.***: Ferrum Homaccord†; ***S.Afr.***: Kephalodoron†; ***UK***: Bidor.

Pharmacopoeial Preparations

BP 2014: Ferrous Sulphate Tablets; Paediatric Ferrous Sulphate Oral Solution; Prolonged-release Ferrous Sulphate Tablets;

USP 36: Ferric Subsulfate Solution; Ferrous Sulfate Oral Solution; Ferrous Sulfate Syrup; Ferrous Sulfate Tablets.

Ferrous Tartrate

Ferrosi Tartras; Ferroso, tartrato; Железа Тартрат.

$C_4H_4FeO_6.2½H_2O$=249.0

CAS — 2944-65-2 (anhydrous ferrous tartrate).

ATC — B03AA08.

ATC Vet — QB03AA08.

UNII — ZRW631PTZD.

Profile

Ferrous tartrate has been used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Denm.*: Ferroplex-frangula.

Ferumoxytol *(USAN)*

Code 7228; Ферумокситол.
CAS — 1309-38-2.
UNII — CLH5FT6412 (ferumoxytol non-stoichiometric magnetite).

Uses and Administration

Ferumoxytol is a superparamagnetic iron oxide that is coated with a low-molecular-weight semisynthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. It is used as a source of iron for the treatment of iron-deficiency anaemia (p. 2073.2) in patients with chronic kidney disease. The dose is expressed in terms of elemental iron. An initial dose of 510 mg is given by intravenous injection at a rate of up to 30 mg/second. A second dose of 510 mg is given 3 to 8 days later. In patients receiving haemodialysis, ferumoxytol is given after at least one hour of haemodialysis has been completed and once the blood pressure is stable. Haematological response to therapy should be assessed at least one month after the second dose of ferumoxytol. Patients with persistent or recurrent iron-deficiency anaemia may receive further doses of ferumoxytol. Ferumoxytol may potentially be used as a contrast medium in magnetic resonance imaging (p. 1580.1).

References.

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2. Li W, *et al.* Lower extremity deep venous thrombosis: evaluation with ferumoxytol-enhanced MR imaging and dual-contrast mechanism—preliminary experience. *Radiology* 2007; **242:** 873–81.
3. Neuwelt EA, *et al.* The potential of ferumoxytol nanoparticle magnetic resonance imaging, perfusion, and angiography in central nervous system malignancy: a pilot study. *Neurosurgery* 2007; **60:** 601–11.
4. Spinowitz BS, *et al.* Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol* 2008; **19:** 1599–1605.
5. Singh A, *et al.* Safety of ferumoxytol in patients with anemia and CKD. *Am J Kidney Dis* 2008; **52:** 907–15.
6. Provenzano R, *et al.* Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clin J Am Soc Nephrol* 2009; **4:** 386–93.
7. Schwenk MH. Ferumoxytol: a new intravenous iron preparation for the treatment of iron deficiency anemia in patients with chronic kidney disease. *Pharmacotherapy* 2010; **30:** 70–9.

Adverse Effects and Precautions

As for Iron Dextran, p. 2076.1

Haematological response to ferumoxytol therapy should be monitored regularly. It should not be used in patients with evidence of iron overload or to treat anaemia not caused by iron deficiency.

The results of magnetic resonance imaging may be altered by ferumoxytol therapy, and the effects may persist for up to 3 months after the last dose.

Hypersensitivity. Ferumoxytol has not been directly compared with other intravenous iron preparations in terms of its safety profile. For a discussion of whether dextran-free preparations may be safer than iron dextran, see p. 2076.2.

Pharmacokinetics

Peak plasma concentrations of ferumoxytol occur about 20 minutes after intravenous injection. Plasma elimination half-life is about 15 hours. Ferumoxytol is not removed by haemodialysis.

References.

1. Landry R, *et al.* Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol* 2005; **25:** 400–10.
2. Pai AB, *et al.* Plasma pharmacokinetics of two consecutive doses of ferumoxytol in healthy subjects. *Clin Pharmacol Ther* 2010; **88:** 237–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Feraheme; ***Neth.***: Rienso; ***Norw.***: Rienso; ***Switz.***: Rienso; ***UK***: Rienso; ***USA***: Feraheme.

Folic Acid *(BAN, rINN)*

Acide Folique; Ácido fólico; Acidum Folicum; Folacin; Fólico, ácido; Folik Asit; Folinsyre; Folio rūgštis; Folsäure; Folsav; Folsyra; Foolihappo; Kwas foliowy; Kyselina listová; PGA; Pteroylglutamic Acid; Pteroylmonoglutamic Acid; Vitamin B_9; Vitamin B_{11}; Фолиевая Кислота.

N-[4-(2-Amino-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.
$C_{19}H_{19}N_7O_6$=441.4
CAS — 59-30-3 (folic acid); 6484-89-5 (sodium folate).
ATC — B03BB01.
ATC Vet — QB03BB01.
UNII — 935E97BOY8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Folic Acid). A yellowish or orange crystalline powder. Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions. Protect from light.

USP 36: (Folic Acid). A yellow, yellow-brownish, or yellowish-orange, odourless crystalline powder. Very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether. It readily dissolves in dilute solutions of alkali hydroxides and carbonates; soluble in hot, 3N hydrochloric acid and in hot, 2N sulfuric acid; soluble in hydrochloric acid and in sulfuric acid, yielding pale yellow solutions. Protect from light.

Uses and Administration

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions, and in the formation and utilisation of formate. Deficiency, which can result in megaloblastic anaemia (p. 2109.1), develops when the dietary intake is inadequate (as in malnutrition), when there is malabsorption (as in sprue), increased utilisation (as in pregnancy or conditions such as haemolytic anaemia), increased loss (as in haemodialysis), or as a result of the use of folate antagonists and other drugs that interfere with normal folate metabolism (see Interactions, p. 2066.2).

Folic acid is used in the treatment and prevention of the folate deficiency state. It does not correct folate deficiency due to dihydrofolate reductase inhibitors; calcium folinate (p. 2067.1) is used for this purpose, but see Antineoplastic Toxicity, below. Folic acid is also used in women of child-bearing potential and pregnant women to protect against neural tube defects in their offspring. This is discussed in more detail in Neural Tube Defects, p. 2064.3.

For the **treatment** of folate-deficient megaloblastic anaemia it is recommended in the UK that folic acid is given orally in doses of 5 mg daily for 4 months; up to 15 mg daily may be necessary in malabsorption states. Continued oral dosage with folic acid 5 mg every 1 to 7 days may be necessary in chronic haemolytic states such as thalassaemia major or sickle-cell anaemia, depending on the diet and rate of haemolysis; similar doses may be necessary in some patients receiving renal dialysis in order to prevent deficiency.

In the USA the usual recommended therapeutic dose for folate deficiency is oral folic acid 0.25 to 1 mg daily until a haematopoietic response has been obtained, although some patients require higher doses, especially in malabsorption states. The usual maintenance dose is 400 micrograms daily.

For doses in children, see below.

In the **prophylaxis** of megaloblastic anaemia of pregnancy, the usual dose is 500 micrograms daily in the UK.

For women of child-bearing potential at high risk of having a pregnancy affected by neural tube defect, the dose of folic acid is 4 or 5 mg daily starting before pregnancy (in the USA the recommendation is 4 weeks before) and continued through the first trimester. For other women of child-bearing potential the dose is 400 micrograms daily.

Folic acid may also be given by intramuscular, intravenous, or subcutaneous injection as the sodium salt.

Administration in children. The *BNFC* suggests the following oral doses of folic acid for children:

Folate supplementation in neonates

- preterm neonates: 50 micrograms once daily *or* 500 micrograms once weekly, given from 2 weeks of age until full-term corrected age is reached

Folate-deficient megaloblastic anaemia

- neonate to 1 year: initially 500 micrograms/kg daily (maximum 5 mg) for up to 4 months; up to 10 mg daily may be required in those aged from 1 month with malabsorption states
- 1 to 18 years: use adult doses, see above

Haemolytic anaemia, metabolic disorders

- 1 month to 12 years: 2.5 to 5 mg daily
- 12 to 18 years: 5 to 10 mg daily

Prophylaxis of folate deficiency in dialysis

- 1 month to 12 years: 250 micrograms/kg (maximum 10 mg) daily
- 12 to 18 years: 5 to 10 mg daily

For doses of folic acid used to prevent methotrexate adverse effects in juvenile idiopathic arthritis, see below.

Antineoplastic toxicity. Folinic acid does not require reduction by dihydrofolate reductase to its active form, and is used to reduce the toxicity of high-dose methotrexate antineoplastic therapy (folinic acid rescue, see p. 2067.1). In patients with mucosal or gastrointestinal adverse effects associated with the much lower weekly doses of methotrexate used in the treatment of autoimmune diseases such as rheumatoid arthritis or juvenile idiopathic arthritis, a weekly oral dose of folic acid has been used to reduce the frequency of adverse effects. Such supplementation, although widely favoured, particularly in the USA,[1] remains somewhat controversial, as some consider it may reduce the efficacy of methotrexate.[2] Nonetheless, although unlicensed in the UK, the following oral doses of folic acid have been suggested, usually given at least 24 hours after the methotrexate dose:

BNF

- adult over 18 years: 5 mg once weekly

BNFC

- 2 to 18 years: 1 mg daily or 5 mg once weekly

1. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004; **43:** 267–71.
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Cardiovascular disease. Epidemiological studies indicate that individuals with a low serum folate are at increased risk of fatal coronary heart disease,[1] and that those with a high intake of folate,[2] or folic acid and vitamin B_6,[3] from vitamin supplements or food, are at lower risk of ischaemic heart disease or stroke. Vitamin deficiency, especially folic acid deficiency, is a common cause of hyperhomocysteinaemia.[4,5] Elevated blood-homocysteine concentrations may be an independent risk factor for atherosclerosis (p. 1250.2) and ischaemic heart disease (p. 1254.2), venous thrombosis (p. 1274.1), and stroke (p. 1269.2).[4-8] Whether hyperhomocysteinaemia directly causes cardiovascular disease, as concluded by a meta-analysis,[9] or is a possible marker of increased vascular risk,[10] remains controversial.[11,12]

Folic acid reduces blood-homocysteine concentrations;[13-15] vitamin B_{12}, but not B_6, may have an additional effect.[14] The higher the baseline blood-homocysteine concentration, or the lower the baseline value of folate,[14] the greater the effect of folate supplements; reductions were similar with daily doses from 0.5 to 5 mg of folic acid,[14] although a randomised study[15] found greater effects with a daily 2-mg dose compared with a dose of 200 micrograms. A meta-analysis concluded that a daily dose of 800 micrograms or more was needed to achieve maximum reductions in homocysteine concentrations.[16]

Results of studies assessing cardiovascular risk versus folate intake have been variable. Although some have found the risk of hypertension,[17] or stroke[18] to be lower in patients with higher folate intakes (dietary or via supplementation), and there are suggestions that endothelial function is improved by folate supplementation,[19,20] others have reported no association between intake and cardiovascular risk.[21,22] A large open-label study[23] found that, while folic acid supplementation significantly reduced plasma homocysteine concentrations, it did not reduce recurrence of cardiovascular events in patients with stable coronary artery disease. (Most patients had been treated with lipid-lowering therapy, and the authors stated that this might have overshadowed any potential beneficial effects of folic acid.) Similarly, a randomised controlled study, the Vitamin Intervention for Stroke Prevention (VISP) study,[24] found that high daily doses of folic acid, vitamin B_6 and vitamin B_{12} modestly decreased total homocysteine concentrations compared with low daily doses, but had no treatment effect on recurrent stroke, myocardial infarction, or death. Three further large controlled studies (HOPE-2, NORVIT, and WENBIT) also found no significant beneficial effect of treatment with folic acid plus vitamin B_{12} and/or vitamin B_6 on cardiovascular disease risk, despite adequate homocysteine-lowering effects;[25-27] such therapy was even suggested to be harmful.[25] Results from meta-analyses have been conflicting; one[28] concluded that folic acid supplementation could effectively reduce the risk of stroke in patients without a history of stroke, whereas others found no reduction in the risk of cardiovascular events, stroke, or all-cause mortality in patients at risk of, or with pre-existing, cardiovascular disease given folic acid, vitamin B_6, and vitamin B_{12} (alone or in combination)[29] or in patients with pre-existing cardiovascular or renal disease given folic acid with or without additional B vitamins.[30] However, exclusion of the VISP study from the latter meta-analysis led to a significant protective effect of folic acid supplementation on stroke.[30]

Results of other ongoing studies are considered necessary before definite conclusions can be drawn as to the so-called

'homocysteine hypothesis' of atherothrombotic vascular disease; while some recommend against routine treatment,[4,31,32] others consider homocysteine-lowering treatment in high-risk patients to be justified.[33,34] A meta-analysis[35] of observational studies indicated that the relationship between hyperhomocysteinaemia and ischaemic heart disease and stroke risk in healthy individuals might not be as strong as had previously been suggested, with stronger associations found in retrospective studies than in prospective studies. The lack of effect in some studies also prompted the suggestion that homocysteine may be a biological marker of cardiovascular disease risk rather than a modifiable cause.[27] The American Heart Association has stated[7] that, until the results of more controlled studies become available, routine testing of plasma-homocysteine concentrations cannot be justified; all patients should, however, be encouraged to consume the recommended dietary allowance (RDA) of folate, vitamin B_6 and vitamin B_{12}.

Daily treatment with oral folic acid, vitamin B_6, and vitamin B_{12} significantly decreased restenosis and target-vessel revascularisation after percutaneous coronary angioplasty.[36] In contrast, in another study[37] folic acid, vitamin B_6, and vitamin B_{12}, increased restenosis and target-vessel revascularisation. The studies differed in dosage regimen, patient population, lesion length, and procedure used,[38,39] but the strong proliferative effect of folate on neointimal growth may exceed the positive effect of lowering homocysteine concentrations,[40] and it has been stated[38] that these vitamins should not be routinely used in patients receiving coronary stents.

Patients with renal impairment develop hyperhomocysteinaemia as a result of delayed elimination and altered metabolism; the prevalence of plasma homocysteine levels greater than 15 micromoles/L has been reported to be 80 to 90% in dialysis patients, compared with 5% in the general population. In haemodialysis patients with moderate to severe hyperhomocysteinaemia, intravenous folinic acid 10 mg three times weekly has been reported to dramatically decrease homocysteine concentrations, although normal levels of homocysteine were not attained.[41] In a small study in renal transplant recipients with hyperhomocysteinaemia, vitamin B_6 was effective in reducing post-methionine-loading plasma homocysteine concentrations, and folic acid plus vitamin B_{12} was effective in lowering fasting plasma-homocysteine concentrations. The authors concluded that all three of these B-group vitamins may have a role in reducing atherosclerotic outcomes in this patient group.[42]

There has been some suggestion that folic acid supplementation during pregnancy may reduce rates of congenital heart defects in infants. Although the dose-effect relationship between folic acid intake and congenital heart defects remains unclear, an analysis[43] of the prevalence of severe congenital heart defects before and after food fortification with folic acid (below), reported a 6.2% decrease per year in birth prevalence after the introduction of a fortification programme in Canada; birth prevalence did not change in the 8 years before fortification.

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6. Mangoni AA, Jackson SHD. Homocysteine and cardiovascular disease: current evidence and future prospects. *Am J Med* 2002; **112:** 556–65.
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9. Wald DS, *et al*. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002; **325:** 1202–6.
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12. Lewis SJ, *et al*. Meta-analysis of MTHFR 677C→T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? *BMJ* 2005; **331:** 1053–6.
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Deficiency states. Reviews of the use of folic acid in conditions associated with folate deficiency.

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Food fortification. Mandatory fortification of foods with folic acid has caused much controversy. Some advocate this measure as prevention against neural tube defects (below) and there is some suggestion it may also prevent other birth defects such as congenital heart defects (see Cardiovascular Disease, p. 2063.3). Others remain concerned about folic acid supplementation masking vitamin B_{12} deficiency (p. 2066.1) or having possible carcinogenic effects (p. 2065.3).

Further references.

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Hearing loss. Epidemiological studies have suggested an association between homocysteine and folate concentrations and hearing status. A 3-year controlled study in a country without folic acid food fortification found that supplementation slowed the decline in age-related hearing loss. Further studies were considered necessary to confirm these findings.[1]

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Mental function. For a discussion of the effects of folate supplementation on cognitive function and depression, see Mental Function, p. 2046.3.

Neural tube defects. Failure of the fetal neural tube to fuse normally during the first 4 weeks of pregnancy may result in one of several congenital defects. These include *anencephaly* (absence of the brain and cranial vault) and *spina bifida* (failure of the vertebrae to fuse).[1,2] The latter ranges from spina bifida occulta, where neurological abnormalities are rare, to meningocoele or meningomyelocoele, where the meninges, or meninges and spinal cord, herniate outwards through the vertebral defect and which may be associated with hydrocephalus and paralysis of the lower limbs and sphincters.

The reasons for this failure in normal development are not well understood and appear to include both environmental and genetic factors. The risk is increased in certain geographical areas, and in the offspring of parents with previous children who had neural tube defects, or of parents who themselves suffer from the condition.[1]

A defect in the methylenetetrahydrofolate reductase gene has been identified, which is estimated to occur in about 5 to 15% of white populations, and appears to result in an increased requirement for folates, and an increased risk of recurrent early pregnancy loss and neural tube defects.[3,4] Since the 1960s there has been some evidence that the mother's folate status was significant, and in the early 1980s two groups published evidence for claims that oral folic acid, with or without other vitamins, in the period around conception, reduced the incidence of neural tube defect in the offspring of mothers who had previously borne children with the defect.[5,6]

Although criticised on several grounds, the conclusions of these studies were borne out by a large multicentre study initiated by the UK Medical Research Council (MRC).[7] This study was terminated early because of overwhelming evidence that folic acid 4 mg daily taken from before conception until the twelfth week of gestation by women with a history of a previous pregnancy affected by a neural tube defect reduced the incidence of such defect by about two-thirds. Other studies and systematic reviews have since confirmed the benefits of supplementation.[8-10] Multivitamins alone (A, D, B_1, B_2, nicotinamide, B_6, and C) did not demonstrate a similar benefit.

Prevention of recurrence. In the light of the MRC study, it is recommended in the UK that in couples with spina bifida or a history of previous offspring with neural tube defect, all those women who may become pregnant should receive folic acid 5 mg daily (in the absence of a commercially-available 4-mg dosage form) until the twelfth week of pregnancy.[11] In the USA, recommendations are 4 mg of folic acid daily from at least 4 weeks before conception through the first 3 months of pregnancy.[12] It must be borne in mind that only about 60 to 70% of neural tube defects appear to be folate-sensitive, and parents should be counselled appropriately. Similar doses of folic acid have been recommended for women in intermediate- to high-risk categories for neural tube defects in Canada.[13]

The investigators in the MRC study acknowledged that a 4-mg dose may not be optimal, and both early[5,6] and later[14] studies imply that much lower doses of folic acid may reduce the risk of recurrence, but this has yet to be clearly shown. Furthermore, the optimum length of time that supplements should be given to these women before conception is unknown.

Prevention of occurrence. First occurrences of neural tube defects account for about 95% of cases, and there are obvious public health implications if the benefits of folate in mothers known to be at risk can be extended to the general population. A study in Hungary[15] indicated that folic acid 800 micrograms daily with multivitamins, taken for at least one month before conception and until the third month of gestation decreased the incidence of first occurrence of neural tube defects. A case control study in the USA[16] (where the normal incidence of neural tube defect is much lower than Hungary) suggested that a periconceptional folic acid intake of as little as 400 micrograms daily reduced the occurrence of the disorder by 60%.

With such results in mind the US Public Health Service has recommended that all women of child-bearing age who are capable of pregnancy should receive folic acid 400 micrograms daily.[1,17] A subsequent review by the US Preventive Services Task Force suggested that the dose of folic acid should be slightly higher at 400 to 800 micrograms daily.[18] Care should be taken to keep folate consumption below 1 mg daily except under medical supervision.[1,17] Such universal coverage would allow for the problem of unplanned pregnancies but would be difficult to achieve, other than by fortification of dietary staples with folate.

All cross-references refer to entries in Volume A

Food fortification has therefore been adopted in the USA, at a level of 140 micrograms of folic acid per 100 g of cereal-grain product. While this amount will probably be insufficient to provide maximum reduction in the incidence of neural tube defects,[19,20] there is some evidence of benefit,[21] and it was chosen to minimise the risk of masking vitamin B_{12} deficiency in the elderly.[22] Efforts to increase the use of folic acid supplements in women of child-bearing potential are still advocated. In Canada, where food fortification has been associated with a significant reduction in neural tube defects,[23] similar recommendations have been made.[13]

In the UK, the current recommendation is that all women planning a pregnancy should take an extra 400 micrograms of folic acid daily before conception and during the first 12 weeks of pregnancy, bringing the average folate intake to about 600 micrograms daily.[11] In unplanned pregnancies, supplementation should begin as soon as pregnancy is suspected. Some, however, consider this amount to be too low.[24] As in the USA, food fortification has been considered, and the Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that universal fortification of flour at 240 micrograms of folic acid per 100 g in food would significantly reduce the number of neural tube defects.[25] In May 2007, the UK Food Standards Agency agreed that mandatory fortification be introduced. However, there are concerns about possible carcinogenic effects (see Carcinogenicity, below) and results of further studies are awaited. Debate has continued as to the amount, if any, of fortification necessary.[24,26-31] The UK Scientific Advisory Committee on Nutrition reconfirmed[32] the COMA recommendation for fortification of flour but said that further consideration should be given to the amount and form of folate used and also called for better monitoring of vitamin B_{12} in those aged 65 and over. There has also been a renewed call for fortification of foods in Europe,[33-36] and Australia and New Zealand,[37,38] as issuing recommendations on folic acid use has not led to a substantial decrease in the incidence of neural tube defects, and efforts have not reached all the target population. Certainly, mandatory food fortification with folic acid has been shown to dramatically decrease the incidence of neural tube defects in Canada,[39] Chile,[40] and the USA.[21,41,42] Fears of masking vitamin B_{12} deficiency appear to have not been borne out (see Vitamin B_{12} Deficiency, p. 2066.1).

Patients receiving antiepileptic drugs are at increased risk of neural tube defect and it has been suggested that folic acid supplementation for such patients should be at the level used for prevention of recurrence,[43] i.e. 4 or 5 mg daily.

The mechanism by which folic acid protects against neural tube defects is unknown, but various theories have been postulated including a positive effect in promoting neural tube closure,[44] or a selective abortifacient effect on affected fetuses (terathanasia),[45] although the latter has been disputed.[46] There is some evidence that low maternal vitamin B_{12} concentrations are an independent risk factor for neural tube defects,[47,48] perhaps indicating a role for methionine synthase in their aetiology, and suggesting that additional supplementation with cobalamins may be warranted, or that methionine supplements could be investigated as an alternative to folic acid.[49,50] Some suggest that hyperhomocysteinaemia may be a cause of some neural tube defects and that they may be due to an inborn error of folate and/or homocysteine metabolism; furthermore, a dietary deficiency may trigger a genetic predisposition towards the development of neural tube defects.[2] Interestingly, the results from the Hungarian programme[51,52] and from other studies[53-55] suggest that multivitamin supplements (including folic acid) may also reduce the occurrence of other congenital abnormalities. Maternal folate deficiency has also been associated with an increased risk of adverse birth outcomes, apart from neural tube defects, such as preterm delivery, low infant birthweight, and fetal growth retardation.[56]

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Osteoporosis. Treatment with folate and vitamin B_{12} can reduce elevated plasma homocysteine concentrations and may subsequently decrease the risk of osteoporosis and hip fracture, see Osteoporosis, under Vitamin B_{12}, p. 2109.3.

Prophylaxis of malignant neoplasms. For reference to suggestions that folate supplements may be associated with reduced risk of certain cancers, see p. 2047.3. However, folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, below.

Adverse Effects

Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

Hypersensitivity. A woman had 3 episodes of hypersensitivity, including anaphylaxis, on exposure to synthetic folic acid. Intradermal testing with folic acid solution was positive and a blinded challenge to folic acid solution led to widespread urticaria. Sensitisation to folic acid may have occurred after supplementation with vitamin B, at which time she had recurrent episodes of urticaria. The patient appeared to tolerate dietary folates, and the authors suggested that foods fortified with folic acid be clearly labelled.[1]

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Precautions

Folic acid should never be given alone or with inadequate amounts of vitamin B_{12} for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B_{12} deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord (see also Vitamin B_{12} Deficiency, p. 2066.1).

Breast feeding. Folic acid is excreted into breast milk. No adverse effects have been seen in breast-fed infants whose mothers were receiving folic acid, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/01/06)

Carcinogenicity. Follow-up data from a large study of folate supplementation suggested a greater risk of death due to breast cancer in those women randomised to high doses; the association was not statistically significant and further studies were considered necessary.[1] In contrast, other studies suggest a reduced risk of some cancers with folate supplementation, see Prophylaxis of Malignant Neoplasms, p. 2047.3. A large study found that folic acid supplementation did not reduce colorectal adenoma risk; evidence for an increased risk of adenomas with supplementation was equivocal.[2]

Animal studies suggest that folic acid may have dual modulatory effects on carcinogenesis, depending on dose and timing of supplementation. Folate deficiency may inhibit, whereas supplementation may promote, the progression of established neoplasms. In normal tissue, however, folate deficiency can predispose towards neoplastic transformation and modest amounts of folate may suppress tumour development; supraphysiological doses may enhance tumour progression.[3,4] Thus, use of folate before the existence of preneoplastic lesions may prevent tumour development, whereas use once early lesions are established appears to increase tumorigenesis.[5] However, determining the presence of preneoplastic foci in the general population is almost impossible.[4] Given the tendency for cancer patients to consume more supplements than healthy subjects, the possibility of adverse effects of folic acid on cancer progression, recurrence, and metastasis should be borne in mind, and research on folate supplementation among patients with cancer is needed.[5]

Careful monitoring of the long-term effects of folic acid food fortification (p. 2064.2) is also advised,[3,4] and some have advocated against mandatory fortification on this basis.[6] Population-based observations[7] in Canada and the USA noted a temporal association between the introduction of folic acid fortification programmes and increased rates of colorectal cancer in North America. Although the explanation for the increase is unclear, improvements in cancer screening and higher intakes of folic acid may play a part. After reviewing the data regarding folic acid and the risk of cancer, the Scientific Advisory Committee on Nutrition[8] considered that although there are uncertainties, they still supported the recommendation for mandatory

fortification of flour in the UK, with controls to limit excessive folic acid intake. These included the restriction of voluntary fortification, and further guidance for at-risk population groups on the use of folic acid supplements: an intake from supplements not to exceed 200 micrograms daily is recommended in those with a history of colorectal adenomas, and in those aged over 50 years as the risk of developing colorectal cancer increases after this age.

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Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies folic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Vitamin B_{12} deficiency. The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects (see p. 2064.3) has created debate[1-7] on the amount of fortification and on the risks of masking vitamin B_{12} deficiency, particularly in the elderly. As mentioned in Precautions, p. 2065.3, folic acid should not be used in megaloblastic anaemia due to vitamin B_{12} deficiency, because it will not prevent the neurological manifestations of this deficiency, and may delay the diagnosis. Masking of vitamin B_{12} deficiency has been noted with daily doses of folic acid of 5 mg, but it is generally considered that very low doses do not have this effect. It has also been stated that folic acid may precipitate the neurological manifestations of vitamin B_{12} deficiency; however, a review of the evidence suggests this is unlikely.[8]

Nevertheless, concerns regarding neurological effects of vitamin B_{12} deficiency in the elderly have led to adoption of a level of folic acid fortification in the USA that is accepted not to provide optimum protection against neural tube defects, but that it is hoped will minimise any risks.[9] It has been suggested that fortification with vitamin B_{12} as well might also be a solution.[10-12] While some studies of food fortification show no evidence of a deterioration in vitamin B_{12} status in elderly patients,[13,14] there is concern[12,15] that individuals may be consuming folic acid in excess of the upper limit of 1 mg daily (see under UK and US Recommended Dietary Intake, below). Because several countries in the Americas fortify flour, but at varying levels, a technical consultation was convened by the Pan American Health Organization, the March of Dimes, and the CDC, in order to develop guidelines on fortification.[15] It was recommended[16] that all women of reproductive age consume 400 micrograms daily of synthetic folic acid in addition to dietary intake; a minimum additional intake of 200 micrograms daily of folic acid from fortified foods was proposed. A target mean intake of 1 microgram daily of vitamin B_{12} from food fortification was recommended in countries where data are consistent with vitamin B_{12} deficiency; this amount was considered sufficient since, unlike dietary sources of vitamin B_{12}, synthetic vitamin B_{12} is highly bioavailable.

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Interactions

Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, antituberculous drugs, alcohol, glucarpidase, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides. In some instances, such as during methotrexate or antiepileptic therapy, replacement therapy with folinic acid or folic acid may become necessary in order to prevent megaloblastic anaemia developing; folate supplementation has reportedly decreased serum-phenytoin concentrations in a few cases (see Vitamins, p. 545.2) and there is a possibility that such an effect could also occur with barbiturate antiepileptics.

Antiepileptic-associated folate deficiency is discussed further under Effects on the Blood in Phenytoin, p. 540.2.

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Pharmacokinetics

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver.

The principal storage site of folate is the liver; it is also actively concentrated in the CSF.

Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

Human Requirements

Body stores of folate in healthy persons have been reported as being between 5 to 10 mg, but may be much higher. In the UK about 150 to 200 micrograms of folate daily is considered a suitable average intake for all healthy persons except women of child-bearing potential and pregnant women who require additional folic acid to protect against neural tube defects in their offspring (see p. 2064.3). In the US the recommended dietary allowance is 400 micrograms of dietary folate equivalents (see below) in both men and women. Folate is present, chiefly combined with several L(+)-glutamic acid moieties, in many foods, particularly liver, kidney, yeast, and leafy green vegetables. The vitamin is readily oxidised to unavailable forms and is easily destroyed during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for folate.[1] In the USA recommended dietary allowances (RDAs) had been set, and were reviewed[2] under the programme to set Dietary Reference Intakes (see p. 2046.1). Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the Reference Nutrient Intake (RNI) for adult males and females is 200 micrograms daily and the Estimated Average Requirement (EAR) is 150 micrograms daily. In the USA the RDA is expressed in terms of dietary folate equivalents (DFEs) where 1 microgram DFE is equivalent to 1 microgram folate from natural sources, 0.5 micrograms of a folic acid supplement taken on an empty stomach, or 0.6 micrograms of folic acid from fortified food or as a supplement taken with meals. An RDA of 400 micrograms DFE daily for adult men and women has been set; the EAR is 320 micrograms DFE daily and the tolerable upper intake level is 1 mg daily.

Folate requirements are increased during pregnancy; an RNI of 300 micrograms daily has been suggested for pregnant women in the UK and an RDA of 600 micrograms daily in the USA. In view of the value of folate in preventing neural tube defects, it is now recommended that women planning a pregnancy receive supplemental folic acid before conception and during the first trimester (see Neural Tube Defects, p. 2064.3). To increase the intake in women of child-bearing age, folic acid fortification (p. 2064.2) of grain-based foods has been adopted in the USA, and advocated in other countries including the UK. However, there remains some debate over the appropriate level of fortification to optimise prevention of neural tube defects and to minimise the risks of possible carcinogenicity, or of masking underlying vitamin B_{12} deficiency in the elderly (see Carcinogenicity and Vitamin B_{12} deficiency, p. 2065.3 and above, respectively).

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2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acifol; Anemidox Folico; Anfolic; Arisfolic; Azolac Folico; Bernafolic; Biolfolic; Coflic; Conacid; Dupofol; Edulsan Folic†; Egestan Folico; Folacina; Folaport; Foliagen; Folimax; Folinemic; Galfol; Gynofol; Livifol; Medifol; Nexovital Folico; Ronfolic; Sojar Folico; Suprafol; ***Austral.***: Megafol; ***Austria***: Folsan; ***Belg.***: Folavit; ***Braz.***: Afopic; Endofolin; Enfol; Femme Folico; Folacin; Folantine; Folifolin; Folital; Folonin; Hipofol; Materfolic; Neo Folico; Pre-Folic; ***Canad.***: Novo-Folacid; ***Chile***: Folacid; Folifemin; Folisanin; Folvit; Miliser; ***China***: Mei Tian Fu (美天福); Pa Lai Xin (帕莱欣); Si Li An (斯利安); ***Denm.***: Folimet; ***Fin.***: Foliver; Folvite; ***Fr.***: Speciafoldine; ***Ger.***: DreisaFol; Fol Injekt†; Fol Lichtenstein†; Folarell; Folcur†; Folgamma Mono†; Folsan; Folverlan; Gravi-Fol†; Lafol†; ***Gr.***: Filicine; Folidex; ***Hong Kong***: Uni-Folic†; ***Hung.***: Feroglobin-B12; Folsav; Huma-Folacid; ***India***: Afol; B-9; B-Fol; C-Fol; Chewfol; Cobal Forte; Cufol; Elfol; F-5; FA; Facitab; Ferich; Fericos-XT; FH-12; Flolica-OD; Fol-B; Fol; Folacin; Folaid; Folat; Folbit; Foldivit; Folet; Folib; Folicare; Foliday; Foliden; Folimac; Folimust; Folistar; Folitas; Folix; Foliz; Folneu; Folson; Folvite; Foly; Forich; Ftol; Globin; Ingafol; Lik; Momfol; Neofol; Nicofer-F; Nutrilic; Rubraplex; Vitafol; ***Indon.***: Anelat; Folac; Folacite; Folacom; Folas; Folavit; Folaxin; Nufolic; ***Irl.***: Clonfolic; Preconceive; ***Israel***: Foli; ***Ital.***: Fertifol; Folidex; Folina; Folingrav; Serengrav; ***Mex.***: AF; Folivital; Materfol; Prinac Ac†; ***Norw.***: Nycoplus Folsyre; ***Philipp.***: Enhansid; Folacid; Folart; Foleq; Foliage; Folicard; Folicare; Folinc; Folisure; Maxifol; Purifol; ***Pol.***: Acifolik; Folacid; Folifem; Folik; Folimin†; Folovit; ***Port.***: Acfol; Dozefol; Folicil; Folidex; Fovital; ***Rus.***: Folacin (Фолацин); Mamifol (Мамифол); ***Spain***: Acfol; Bialfoli; Zolico; ***Swed.***: Folacin; Folvidon; ***Switz.***: Andreafol; Drossafol; Fertifol; Folvite; ***Thai.***: Cebrin-Fe; F-Min; Foliamin; Folicare†; Folimed; Folivit; ***Turk.***: Folbiol; ***UAE***: Folicum; ***UK***: Folicare; Lexpec; Preconceive; ***Ukr.***: Folacin (Фолацин); Tifol (Тифоль); Vitrum Folicum (ВитрумФоликум); ***USA***: Folvite; ***Venez.***: Afoklin; Folac.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Ferrous Fumarate and Folic Acid Tablets; Folic Acid Injection; Folic Acid Tablets;

USP 36: Folic Acid Injection; Folic Acid Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Folinic Acid *(BAN)*

Citrovorum Factor; Folínico, ácido; Leucovorin; Фолиновая Кислота.

5-Formyltetrahydropteroylglutamic acid; *N*-[4-(2-Amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

$C_{20}H_{23}N_7O_7$=473.4

CAS — 58-05-9.

UNII — Q5719DVLP.

Calcium Folinate *(BANM, rINN)*

Calcii Folinas; Calcii Folinas Hydricus; Calcium, folinate de; Calcium Folinate-SF; Calcium Leucovorin; Calciumfolinat; Folinate de Calcium; Folinato cálcico; Kalcio folinatas; Kalciumfolinat; Kalcium-folinát; Kalcium-folinát hydrát; Kalsiumfolinaatti; Kalsiyum Folinat; Kalsiyum Lökovorin; Leucovorin Calcium; NSC-3590; Кальция Фолинат.

The calcium salt of folinic acid (1:1).

$C_{20}H_{21}CaN_7O_7$=511.5

CAS — 1492-18-8 (anhydrous calcium folinate); 41927-89-3 (calcium folinate pentahydrate); 6035-45-6 (calcium folinate pentahydrate).
ATC — V03AF03.
ATC Vet — QV03AF03.
UNII — RPR1R4C0P4.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Chin. includes the pentahydrate ($C_{20}H_{21}CaN_7O_7$, $5H_2O = 601.6$).

Ph. Eur. 8: (Calcium Folinate). A white or light yellow, amorphous or crystalline, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone. A 2.5% solution in water has a pH of 6.8 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Leucovorin Calcium). A yellowish-white or yellow, odourless, powder. Very soluble in water; practically insoluble in alcohol. Protect from light.

Incompatibility. Calcium folinate and fluorouracil, with or without 5% glucose, were incompatible when mixed in various ratios and stored in PVC containers at various temperatures.[1]

1. Trissel LA, *et al.* Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.

Calcium Levofolinate *(BAN, rINN)*

Calcii Levofolinas; Calcii levofolinas pentahydricus; Kalcio levofolinatas; Kalciumlevofolinat; Kalcium-levofolinát pentahydrát; Kalcium-levofolinát-pentahidrát; Kalciumlevofolinat-pentahydrat; Kalsiumlevofolinaatti; Kalsiumlevofolinaattipentahydraatti; Levofolinate; Lévofolinate calcique pentahydraté; Lévofolinate de Calcium; Levofolinato de calcio; Levoleucovorin Calcium (USAN); Кальция Левофолинат.

The calcium salt of the isomer of *S*-folinic acid (1:1).
$C_{20}H_{21}CaN_7O_7,5H_2O = 601.6$
CAS — 80433-71-2 (anhydrous calcium levofolinate).
ATC — V03AF04.
ATC Vet — QV03AF04.
UNII — 778XL6VBS8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Calcium Levofolinate Pentahydrate). A white or light yellow, amorphous or crystalline, hygroscopic powder. Slightly soluble in water; practically insoluble in alcohol and in acetone. A 0.8% solution in water has a pH of 7.5 to 8.5. Store in airtight containers. Protect from light.

Sodium Folinate

Dinatrium folinat; Disodium folinate (BANM); Natrium folinat; Натрия Фолинат.
$C_{20}H_{21}N_2O_7Na_2 = 517.4$
CAS — 42476-21-1 (monosodium folinate).
ATC — V03AF06.
ATC Vet — QV03AF06.
UNII — 4MXU9LJS4Q.

Uses and Administration

Folinic acid is the 5-formyl derivative of tetrahydrofolic acid, the active form of folic acid. Folinic acid is used principally as an antidote to folic acid antagonists, such as methotrexate (p. 826.3), which block the conversion of folic acid to tetrahydrofolate by binding the enzyme dihydrofolate reductase. It does not block the antimicrobial action of folate antagonists such as trimethoprim or pyrimethamine, but may reduce their haematological toxicities. It is also used as an adjunct to fluorouracil in the treatment of colorectal cancer.

Folinic acid is given as calcium or sodium folinate, although doses are stated in terms of folinic acid. 1.08 mg of anhydrous calcium folinate, 1.27 mg of calcium folinate pentahydrate, or 1.09 mg of sodium folinate are each equivalent to about 1 mg of folinic acid. Calcium folinate can be given orally, by intramuscular injection, by intravenous infusion, or by intravenous injection; Intravenous injections should be given over several minutes because of their calcium content; the maximum recommended rate is equivalent to folinic acid 160 mg/minute. It has been recommended that oral doses should not be greater than 25 to 50 mg, since absorption is saturable. Calcium levofolinate, the active laevo-isomer, is used similarly to calcium folinate; it is given in doses half those recommended for the racemic form. Sodium folinate is given by intravenous injection or infusion; sodium levofolinate is used similarly.

In cases of inadvertent **overdosage of a folic acid antagonist**, folinic acid should be given as soon as possible and preferably within the first hour. Doses equal to or greater than the dose of *methotrexate* have been recommended. Alternatively it has been stated that for large doses or overdoses of methotrexate, calcium folinate may be given by intravenous infusion in a dose equivalent to 75 mg of folinic acid within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. Although *vincristine* is not a folic acid antagonist, folinic acid has also been proposed for some manifestations of vincristine toxicity overdosage—see p. 883.2.

Folinic acid is used with high-dose methotrexate antineoplastic therapy to reduce the toxicity of the methotrexate ('**folinic acid rescue**'; 'calcium leucovorin rescue'). Calcium folinate rescue is necessary when *methotrexate* is given at doses exceeding 500 mg/m² and should be considered with methotrexate doses of 100 to 500 mg/m². It may sometimes be considered in patients who have received lower doses.

Dosage and duration of folinic acid rescue must be adapted according to the methotrexate regimen and the patient's ability to clear the antineoplastic; many antineoplastic regimens include appropriate rescue protocols. In general, UK licensed product information recommends that the first dose of calcium folinate is the equivalent of 15 mg folinic acid (6 to 12 mg/m²) to be given 12 to 24 hours (usually the latter) after the beginning of methotrexate infusion. The same dose is given every 6 hours for 24 hours, initially by intramuscular injection or intravenous injection or infusion, but switching to the oral form after one or more parenteral doses. At the end of this time (48 hours after the start of the original methotrexate infusion) the residual methotrexate concentration should be measured. If this is *less* than a threshold concentration of 0.5 micromoles/litre, the same dose is continued usually for a further 48 hours. If it is *greater* than this value, further calcium folinate dosages should be adapted according to methotrexate concentration as follows, and given every 6 hours for a further 48 hours or until the serum-methotrexate concentration falls below 0.05 micromoles/litre (i.e. one-tenth of the threshold concentration):

- serum methotrexate > 0.5 micromoles/litre: calcium folinate equivalent to 15 mg/m² folinic acid
- serum methotrexate > 1 micromole/litre: calcium folinate equivalent to 100 mg/m² folinic acid
- serum methotrexate > 2 micromoles/litre: calcium folinate equivalent to 200 mg/m² folinic acid

The dose of sodium folinate in rescue therapy is also based on serum-methotrexate concentrations (as measured 24 to 30 hours after beginning methotrexate):

- serum methotrexate 0.01 to 1.5 micromoles/litre: sodium folinate equivalent to 10 to 15 mg/m² folinic acid every 6 hours for 48 hours
- serum methotrexate 1.5 to 5 micromoles/litre: sodium folinate equivalent to 30 mg/m² folinic acid every 6 hours until methotrexate concentration is less than 0.05 micromoles/litre
- serum methotrexate > 5 micromoles/litre: sodium folinate equivalent to 60 to 100 mg/m² folinic acid every 6 hours until methotrexate concentration is less than 0.05 micromoles/litre

In patients who have received doses of methotrexate below 100 mg, and in whom rescue therapy is considered appropriate, oral doses of folinic acid 15 mg every 6 hours for 48 to 72 hours may suffice.

In addition, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of rescue treatment. Renal function should be monitored daily.

To prevent *trimetrexate* toxicity, folinic acid is given during treatment and for 72 hours after the last trimetrexate dose. A usual dose is folinic acid 20 mg/m² given every 6 hours, either orally or by intravenous injection over 5 to 10 minutes; daily doses are adjusted according to toxicity. In trimetrexate toxicity (such as may occur when folinic acid has not been given with high trimetrexate doses), intravenous folinic acid can be given after trimetrexate has been stopped, in a dose of 40 mg/m² every 6 hours for 3 days.

For *trimethoprim* toxicity, folinic acid 3 to 10 mg daily is given intravenously or intramuscularly after the drug is stopped, until blood counts recover.

For *pyrimethamine* toxicity (such as may occur with prolonged low-dose therapy or with high doses), folinic acid 5 to 50 mg daily intravenously or intramuscularly is given during treatment, and adjusted according to blood counts.

Folinic acid is also used **with fluorouracil** to enhance the cytotoxic effect in advanced colorectal cancer. Both high-dose regimens (typically doses of folinic acid 200 mg/m², followed by fluorouracil) and low-dose regimens (20 mg/m²) have been used—for details, see Uses and Administration of Fluorouracil, p. 795.3. Sodium folinate has been used in similar doses. It may also be given at a dose equivalent to folinic acid 500 mg/m² by intravenous infusion over 2 hours. An intravenous injection of fluorouracil 600 mg/m² is given one hour after the start of the folinate infusion. Alternatively, a continuous infusion of fluorouracil 2.6 g/m² is given for 24 hours after the sodium folinate dose. Treatment is given weekly for 6 weeks, and may then be repeated after a 2-week interval; the number of cycles depends on the response of the tumour.

Folinic acid, like folic acid, is effective in the treatment of folate-deficient **megaloblastic anaemia** (see p. 2109.1). Oral doses of 15 mg daily have been suggested. If given intramuscularly a dose of up to 1 mg daily has been recommended on the grounds that higher doses have not been proven to be any more effective. It is unsuitable for megaloblastic anaemia secondary to vitamin-B_{12} deficiencies.

Cardiovascular disease. For a report of the use of intravenous folinic acid to reduce levels of homocysteine in haemodialysis patients, see Cardiovascular Disease, under Folic Acid, p. 2063.3.

Deficiency states. Cerebral folate deficiency has been defined as any neurological syndrome associated with low CSF concentrations of 5-methyltetrahydrofolate, the active metabolite of folic acid.[1-3] Neurodevelopmental disorders have been associated with this deficiency, manifest as irritability, sleep disturbances, cerebellar ataxia, spastic paraplegia, dyskinesia, epileptic seizures, and speech difficulties. Dramatic improvements in some symptoms have been noted with oral folinic acid;[1,2,4] 0.5 to 1 mg/kg folinic acid daily has been used.[1] Analysis of CSF folate metabolites is recommended for patients presenting with movement disorders, mental retardation, or autism.[2,4]

1. Ramaekers VT, Blau N. Cerebral folate deficiency. *Dev Med Child Neurol* 2004; **46:** 843–51.
2. Hansen FJ, Blau N. Cerebral folate deficiency: life-changing supplementation with folinic acid. *Mol Genet Metab* 2005; **84:** 371–3.
3. Gordon N. Cerebral folate deficiency. *Dev Med Child Neurol* 2009; **51:** 180–2.
4. Moretti P, *et al.* Cerebral folate deficiency with developmental delay, autism, and response to folinic acid. *Neurology* 2005; **64:** 1088–90.

HIV infection and AIDS. Calcium folinate has been used to reduce the toxicity of pyrimethamine and trimethoprim in patients with HIV infection. However, oral calcium folinate given to patients with AIDS receiving co-trimoxazole for the treatment of pneumocystis pneumonia was associated with a higher rate of therapeutic failure and a decrease in survival and did not reduce the frequency of dose-limiting co-trimoxazole toxicity.[1] Calcium folinate also did not reduce the toxicity of co-trimoxazole being used for the primary prophylaxis of PCP.[2] Vitamin B_{12} and folinic acid supplementation in patients with HIV infection did not prevent or reduce zidovudine-induced myelosuppression.[3]

1. Safrin S, *et al.* Adjunctive folinic acid with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. *J Infect Dis* 1994; **170:** 912–17.
2. Bozzette SA, *et al.* The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98:** 177–82.
3. Falguera M, *et al.* Study of the role of vitamin B_{12} and folinic acid supplementation in preventing hematologic toxicity of zidovudine. *Eur J Haematol* 1995; **55:** 97–102.

Adverse Effects

Occasional hypersensitivity, including anaphylactic reactions, has been reported; pyrexia has occurred rarely after injections. Gastrointestinal disturbances, insomnia, agitation, and depression have been reported rarely, after high doses.

Precautions

As for Folic Acid, p. 2065.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcium folinate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Sodium folinate is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for Folic Acid, p. 2066.2.

Folinic acid should not be used with a folic acid antagonist such as methotrexate unless the intention is to nullify the effect of the antagonist. It should not be given within 2 hours of a dose of glucarpidase, see p. 1555.2. Folinic acid enhances the toxicity, as well as the antineoplastic action, of fluorouracil, especially on the gastrointestinal tract.

Antineoplastics. For the suggestion of an interaction between *capecitabine* and intracellularly retained folate when capecitabine was given after a regimen of fluorouracil and folinic acid, see Administration, under Capecitabine, p. 758.1.

Pharmacokinetics

Calcium folinate is well absorbed after oral and intramuscular doses and, unlike folic acid (p. 2066.2), is rapidly converted to biologically active folates. The oral absorption of calcium folinate is saturable, with a bioavailability of about 97% for a 25 mg dose, 75% for 50 mg, and 37% for 100 mg. Peak plasma concentrations of folinic acid occur about 10 minutes after an intravenous dose; systemic availability is similar with intramuscular doses but peak serum concentrations are lower. Sodium folinate is considered to be bioequivalent to calcium folinate. Folate is concentrated in the liver and CSF although distribution occurs to all body tissues. The major metabolite of folinic acid is 5-methyl-tetrahydrofolic acid which is mainly produced in the liver and intestinal mucosa. The total terminal half-life of the active metabolites of parenteral calcium folinate is about 6 hours. Folates are mainly excreted in the urine, with small amounts in the faeces.

References.

1. McGuire BW, *et al*. Pharmacokinetics of leucovorin calcium after intravenous, intramuscular, and oral administration. *Clin Pharm* 1988; **7:** 52–8.
2. Wolfrom C, *et al*. Pharmacokinetic study of methotrexate, folinic acid and their serum metabolites in children treated with high-dose methotrexate and leucovorin rescue. *Eur J Clin Pharmacol* 1990; **39:** 377–83.
3. Zittoun J, *et al*. Pharmacokinetic comparison of leucovorin and levoleucovorin. *Eur J Clin Pharmacol* 1993; **44:** 569–73.
4. Mader RM, *et al*. Pharmacokinetics of rac-leucovorin vs [S]-leucovorin in patients with advanced gastrointestinal cancer. *Br J Clin Pharmacol* 1994; **37:** 243–8.
5. Schmitz JC, *et al*. Disposition of folic acid and its metabolites: a comparison with leucovorin. *Clin Pharmacol Ther* 1994; **55:** 501–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asovorin; Elvefocal†; Estroquin; Folinfabra; Leucocalcin; Novizet; Rontafor†; ***Austria***: FOLI-Cell†; Sodiofolin†; ***Belg.***: Elvorine; Folina-Cell†; Levofolic; Rescuvolin; VoriNa; ***Braz.***: Fauldleuco; Folicorin; Glencovorin; Legifol CS; Levorin; Prevax; Tecnovorin; Tevafolin; ***Canad.***: Folacal; ***Chile***: Covorit; ***China***: Ai Jie Kang (爱捷康); Ai Ru Xi (爱汝昔); Antrex (安曲希); Fu Neng (福能); Gai Er Qing (盖尔青); Kang Da Li Ping (康达利平); Kang Lai Er (康莱尔); Li Lei Te (力雷特); Likelin (立可林); Lu Wei Fen (路维芬); Ou Li (欧力); Quefuli (确呋力); Rescuvolin (惠仁复林); Shiming (世明); Si Min Le (司敏乐); Tong Ao (同奥); Ya Fu Xin (亚复欣); ***Cz.***: Levofolic; VoriNa; ***Denm.***: Isovorin; ***Fin.***: Antrex; Isovorin; Levofolic; ***Fr.***: Elvorine; Folinoral; Lederfoline; Osfolate†; ***Ger.***: Axifolin; Bendafolin; DeGalin; FOLI-Cell; Haemato-folin; Lederfolat; Neofolin†; Oncofolic; Rescuvolin; Ribofolin; Ribosofol; VoriNa; ***Gr.***: Buateron; Calcifolin; Calcivoran; Claro; Durofolin; Esvorin; Fedolen; Folical; Foliment; Folinacid; Folinato; Folivoran; Folmigor; Foxolin; Isovorin; Levofolic; Lizocalcio; Osimol; Refolinon; Reotan; Rescuvolin; Sanficinate; Sanovein; Veravorin; Vivalcid; Zamenit; Zenemia; ***Hong Kong***: Calciumfolinat; ***Hung.***: VoriNa†; ***India***: Biovorin; Cafonate; CCM; Covorin; Dalisol; Fastovorin; Leucorin; Lucal; Nyrin; ***Indon.***: Rescuvolin; ***Irl.***: Folicid; Lederfolin†; Sodiofolin; VoriNa; ***Israel***: Calciumfolinat; ***Ital.***: Calcifolin; Calfolex; Calinat†; Citofolin; Divifolin; Ecofol; Folanemin; Folaren; Foliben; Folidar; Lederfolin; Levofolene; Osfolato; Sanifolin; Sulton; Tonofolin; ***Jpn***: Uzel; ***Malaysia***: Nyrin†; Rescuvolin; ***Mex.***: Dalisol†; Ifavor†; Medsavorina; Precileucin; ***Neth.***: Ebefolin†; Rescuvolin; Ribofolin†; VoriNa; ***Norw.***: Isovorin†; ***Philipp.***: Folinoxan†; Litacor; Lovorin; Rescuvolin; VoriNa; ***Pol.***: Levofolic; ***Port.***: FOLI-Cell; Folinovo; Isovorin; Lederfoline; Levofolic; Medifolin; Raycept; Sodiofolin; VoriNa†; ***Rus.***: Natriofoline (Натриофолин); ***S.Afr.***: Isovorin; Rescuvolin; ***Singapore***: Nyrin; Rescuvolin; ***Spain***: Cromatonbic Folinico; Folaxin; Folidan†; Isovorin; Lederfolin; Sodiofolin†; ***Swed.***: Isovorin; ***Thai.***: Cafonate; Dalisol; Folina†; Rescuvolin; ***Turk.***: Antrex†; Rescuvolin; ***UK***: Isovorin; Refolinon; Sodiofolin; ***USA***: Fusilev; ***Venez.***: Leuconolver.

Multi-ingredient Preparations. ***Gr.***: Fysiofol; Legofolin; ***Ital.***: Carfosid; Emopon; Eparmefolin; Ferritin Complex; Ferrofolin; Hepa-Factor; Linfoflu; ***Rus.***: Ferlatum Fol (Ферлатум Фол); ***Turk.***: Komfer Fol.

Pharmacopoeial Preparations

BP 2014: Calcium Folinate Injection; Calcium Folinate Tablets; **USP 36:** Leucovorin Calcium Injection; Leucovorin Calcium Tablets.

Folitixorin *(rINN)*

Folitixorina; Folitixorine; Folitixorinum; 5,10-Methylenetetrahydrofolate; 5,10-Methylenetetrahydrofolic acid; Tetrahydromethylenefolate; Фолитиксорин.

N-{4-[(6a*RS*)-3-Amino-1-oxo-1,4,5,6,6a,7-hexhydroimidazo[1,5-*f*]pteridin-8(9*H*)-yl]benzoyl}-L-glutamic acid.

$C_{20}H_{23}N_7O_6$=457.4

CAS — 3432-99-3.

UNII — 0SXY5ET48B.

Profile

Folitixorin is an active metabolite of folinic acid. It is under investigation for use with fluorouracil in the treatment of pancreatic cancer and metastatic colorectal cancer.

Fructose

Azúcar de fruta; D-Fructosa; Fructosa; D-Fructose; Fructosum; Fruit Sugar; Fruktoosi; Fruktos; Fruktosa; Fruktozė; Fruktóz; Fruktoza; Laevulose; Laevulosum; Levulosa; Levulose; Фруктоза.

D-(-)-Fructopyranose.

$C_6H_{12}O_6$=180.2

CAS — 57-48-7.

ATC — V06DC02.

ATC Vet — QV06DC02.

UNII — 6YSS42VSEV (fructose); XY6UN3QB6S (high fructose corn syrup).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

USNF includes High Fructose Corn Syrup.

Ph. Eur. 8: (Fructose). A white or almost white, crystalline powder with a very sweet taste. Very soluble in water; soluble in alcohol.

USP 36: (Fructose). Colourless crystals or a white crystalline powder. Is odourless and has a sweet taste. Freely soluble in water; soluble 1 in 15 of alcohol and 1 in 14 of methyl alcohol.

USNF 31: (High Fructose Corn Syrup). A sweet, nutritive saccharide mixture prepared as a clear, aqueous solution from high-glucose-equivalent corn starch hydrolysate by the partial enzymatic conversion of glucose to fructose, using an insoluble glucose isomerase enzyme preparation. It is available in two types, 42% and 55%, based on fructose content. Store in airtight containers.

Uses and Administration

Fructose is sweeter than sucrose or sorbitol. It is used as a sweetener in foods for diabetics (although it is not clear it offers any advantage over sucrose); in the UK it has been advised that the intake of fructose be limited to 25 g daily in persons with diabetes mellitus.

Fructose has been used as an alternative to glucose in parenteral nutrition but its use is not recommended because of the risk of lactic acidosis. Use by intravenous infusion in the treatment of severe alcohol poisoning is also no longer recommended.

Solutions of fructose with glucose have been used in the treatment of nausea and vomiting (p. 1811.3) including vomiting of pregnancy. Fructose is also used as a dissolution enhancer and tablet diluent in pharmaceuticals.

Pain. Oral fructose solution was considered to be as effective as oral glucose solution (p. 2069.3) in alleviating mild pain in neonates.[1]

1. Akçam M. Oral fructose solution as an analgesic in the newborn: a randomized, placebo-controlled and masked study. *Pediatr Int* 2004; **46:** 459–62.

Adverse Effects

Large oral doses of fructose may cause flatulence, abdominal pain, and diarrhoea. Lactic acidosis and hyperuricaemia may follow intravenous infusions; fatalities have occurred.

Effects on metabolism. Fructose may increase serum concentrations of uric acid, especially in those with existing *hyperuricaemia* or gout. A large cohort study found that consumption of fructose was associated with an increased risk of gout in men. Fructose-rich fruits or fruit juice may also increase the risk.[1] It has been pointed out that fructose intake has increased in the USA, where soft drinks are usually sweetened with high fructose corn syrup (also known as isoglucose), whereas elsewhere they tend to be sweetened with sucrose.[2] The potential adverse metabolic effects of dietary fructose intake on *serum lipids*, and whether such intake is associated with the metabolic syndrome and a disproportionate risk of hyperlipidaemia, obesity, and consequent diabetes mellitus has been repeatedly reviewed,[3-10] although definitive evidence seems to be lacking.

1. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 2008; **336:** 309–12.
2. Underwood M. Sugary drinks, fruit, and increased risk of gout. *BMJ* 2008; **336:** 285–6.
3. Bray GA. Fructose: should we worry? *Int J Obes (Lond)* 2008; **32** (suppl 7): S127–SI31.
4. Angelopoulos TJ, *et al*. The effect of high-fructose corn syrup consumption on triglycerides and uric acid. *J Nutr* 2009; **139:** 1242S–1245S.
5. Johnson RJ, *et al*. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 2009; **30:** 96–116.
6. Schaefer EJ, *et al*. Dietary fructose and glucose differentially affect lipid and glucose homeostasis. *J Nutr* 2009; **139:** 1257S–1262S.
7. Dolan LC, *et al*. Evidence-based review on the effect of normal dietary consumption of fructose on development of hyperlipidemia and obesity in healthy, normal weight individuals. *Crit Rev Food Sci Nutr* 2010; **50:** 53–84.
8. Bray GA. Soft drink consumption and obesity: it is all about fructose. *Curr Opin Lipidol* 2010; **21:** 51–7.
9. Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* 2010; **90:** 23–46.
10. Stanhope KL, Havel PJ. Fructose consumption: recent results and their potential implications. *Ann N Y Acad Sci* 2010; **1190:** 15–24.

Hypersensitivity. Urticaria associated with the ingestion of certain foods by a patient was found to be caused by D-psicose, a minor constituent of the sweetener, high-fructose syrup.[1]

1. Nishioka K, *et al*. Urticaria induced by D-psicose. *Lancet* 1983; **ii:** 1417–18.

Precautions

Fructose should not be given to patients with hereditary fructose intolerance.

It should be given with caution to patients with impaired kidney function or severe liver damage.

Intravenous administration. Reiterations of the view that the use of intravenous infusions containing fructose and sorbitol, which remained popular in some countries, should be abandoned.[1,2] Not only could they lead to life-threatening build-up of lactic acid, they had led to fatalities in patients with undiagnosed hereditary fructose intolerance.

1. Collins J. Time for fructose solutions to go. *Lancet* 1993; **341:** 600.
2. CSM/MCA. Reminder: fructose and sorbitol containing parenteral solutions should not be used. *Current Problems* 2001; **27:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074566&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)

Pharmacokinetics

Fructose is absorbed from the gastrointestinal tract but more slowly than glucose. It is metabolised more rapidly than glucose, mainly in the liver where it is phosphorylated and a part is converted to glucose; other metabolites include lactic acid and pyruvic acid. Although the metabolism of fructose is not dependent on insulin, and insulin is not considered necessary for its removal from the blood, glucose is a metabolic product of fructose and requires the presence of insulin for its further metabolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Feng Hai Neng (丰海能); Gan Le Li (甘乐力); Hu Chuan (护川); Pu Li Kang (普利康); Wei Bei Xian (韦贝仙); Xing Ya (星雅); ***Hung.***: Fructosol; ***Ital.***: Fructan; Fructofin; Fructosil.

Multi-ingredient Preparations. ***Arg.***: Azodac; High Energy; ***Braz.***: Biofructose; Caviamina†; Dramin B6 DL; Energivit; Energoplex; Enervit; Frutoplex; Frutovena; Neo Cebetil; ***Canad.***: Pediatric Electrolyte; ***China***: Bu Rui De (布瑞得); Feng Hai Ping (丰海平); Ganruining (甘瑞宁); Hai Si Wei (海斯维); Nai Neng (耐能); Rui Qin Yuan (瑞秦源); Ying Fan Shu (英凡舒); ***Fr.***: Filigel†; ***India***: Maxoza; ***Indon.***: Gastro-Ad†; Trifluid; ***Irl.***: Rehidrat†; ***Israel***: Peptical; ***Ital.***: Api Baby; Eparema-Levul; Liozim; Litostop; Nerex; Nutrigel; The Ginseng King†; ***Jpn***: Trifluid; Triparen; ***USA***: Emetrol; Formula EM; Nausatrol; Nausetrol.

Pharmacopoeial Preparations

BP 2014: Fructose Infusion;
USP 36: Fructose and Sodium Chloride Injection; Fructose Injection.

Gleptoferron *(BAN, USAN, rINN)*

Gleptoferrón; Gleptoferronum; Iron Heptonate; Глептоферрон.

$C_7H_{14}O_8.(C_6H_{10}O_5)_n.FeOOH$

CAS — 57680-55-4.

ATC Vet — QB03AC91.

UNII — 898723IQHQ.

Profile

Gleptoferron is a macromolecular complex of ferric hydroxide and dextran-glucoheptonic acid. It is used for iron-deficiency anaemia in veterinary medicine. It is given by intramuscular injection.

Glucose

Glucosa; Glukoz; Glukoza; Глюкоза; Декстроза.

ATC — B05CX01; V04CA02; V06DC01.

ATC Vet — QB05CX01; QV04CA02; QV06DC01.

Anhydrous Glucose

Anhydrous Dextrose; Dextrosa anhidra; Dextrosum Anhydricum; Gliukozė, bevandenė; Glucosa anhidra; D-Glucose; Glucose anhydre; Glucosum; Glucosum anhydricum; Glukoosi, vedetön; Glukos, vattenfri; Glukosa; Glukoza bezwodna; Vízmentes glükóz; Безводная Глюкоза.

D-(+)-Glucopyranose.

$C_6H_{12}O_6$=180.2

CAS — 50-99-7.

UNII — 5SL0G7R0OK (anhydrous dextrose); IY9XDZ35W2 (dextrose).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*,and *Viet.*

Some pharmacopoeias include anhydrous glucose and/or glucose monohydrate as separate monographs whereas others permit the anhydrous and/or monohydrate under a single monograph.

Ph. Eur. 8: (Glucose, Anhydrous). A white or almost white, crystalline powder with a sweet taste. Freely soluble in water; sparingly soluble in alcohol.

The BP 2014 directs that when Glucose Intravenous Infusion is required as a diluent for official injections or intravenous infusions, Glucose Intravenous Infusion 5% should be used.

USP 36: (Dextrose). It contains one molecule of water of hydration or is anhydrous. Colourless crystals or white, crystalline or granular powder. It is odourless and has a sweet taste. Soluble 1 in 1 of water and 1 in 100 of alcohol; very soluble in boiling water; soluble in boiling alcohol.

Glucose Monohydrate

Dekstroz Monohidrat; Dextrosa monohidrato; Dextrosum Monohydridicum; Gliukozė monohidratas; D-Glucosa monohidrato; Glucosa monohidrato; Glucose-Monohydrat; D-Glucose Monohydrate; Glucose monohydraté; Glucosum monohydricum; Glukoosimonohydraatti; Glukosa monohydrát; Glukosmonohydrat; Glükóz-monohidrát; Glycosum; Grape Sugar; Глюкоза Моногидрат.

D-(+)-Glucopyranose monohydrate.

$C_6H_{12}O_6.H_2O$=198.2

CAS — 5996-10-1 (glucose monohydrate); 14431-43-7 (glucose monohydrate); 8027-56-3 (liquid glucose).

UNII — IY9XDZ35W2 (dextrose); LX22YL083G (dextrose monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Some pharmacopoeias include anhydrous glucose and/or glucose monohydrate as separate monographs whereas others permit the anhydrous and/or monohydrate under a single monograph.

Eur. includes Glucose, Liquid and Glucose, Liquid, Spray-dried. *USNF* includes Dextrose Excipient, Liquid Glucose, Corn Syrup, and Corn Syrup Solids.

Ph. Eur. 8: (Glucose Monohydrate; Glucose BP 2014). A white or almost white crystalline powder with a sweet taste. Freely soluble in water; sparingly soluble in alcohol.

Ph. Eur. 8: (Glucose, Liquid). A clear, colourless, or brown viscous liquid containing a mixture of glucose, oligosaccharides, and polysaccharides obtained by hydrolysis of starch, in aqueous solution. It contains not less than 70.0% of dry matter. Miscible with water. It may partly or totally solidify at room temperature, liquefying again on heating to 50 degrees.

Ph. Eur. 8: (Glucose, Liquid, Spray-dried). A white or almost white, slightly hygroscopic powder or granules. Freely soluble in water.

USP 36: (Dextrose). It contains one molecule of water of hydration or is anhydrous. Colourless crystals or white, crystalline or granular powder. It is odourless and has a sweet taste. Soluble 1 in 1 of water and 1 in 100 of alcohol; very soluble in boiling water; soluble in boiling alcohol.

USNF 31: (Dextrose Excipient). A sugar usually obtained by hydrolysis of starch. It contains one molecule of water of hydration. Colourless crystals or white, crystalline or granular powder. Freely soluble in water; very soluble in boiling water; slightly soluble in alcohol; sparingly soluble in boiling alcohol.

USNF 31: (Liquid Glucose). It is obtained by incomplete hydrolysis of starch; it consists chiefly of glucose, dextrins, maltose, and water. It is a colourless or yellowish, thick, syrupy, odourless or nearly odourless liquid. Miscible with water; sparingly soluble in alcohol.

USNF 31: (Corn Syrup). An aqueous solution of saccharides obtained by partial hydrolysis of edible corn starch by food grade acids and/or enzymes. It contains not less than 20% reducing sugar content (dextrose equivalent) expressed as D-glucose, calculated on the dried basis. A clear, white to light yellow, viscous liquid. Miscible in all proportions with water. Store in airtight containers.

USNF 31: (Corn Syrup Solids; Dried Glucose Syrup). A dried mixture of saccharides obtained by partial hydrolysis of edible corn starch by food grade acids and/or enzymes. It contains not less than 20% reducing sugar content (dextrose equivalent) expressed as D-glucose, calculated on the dried basis. A sweet, white to light yellow powder or granules. Soluble in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Uses and Administration

Glucose, a monosaccharide, is given orally or by intravenous infusion in the treatment of carbohydrate and fluid depletion. It is the preferred source of carbohydrate in parenteral nutrition regimens (p. 2044.1) and is used in oral rehydration solutions (p. 1780.1) for the prevention and treatment of dehydration due to acute diarrhoeal diseases (p. 1805.2).

Glucose is also used in the treatment of hypoglycaemia (see below) and is given orally in the glucose tolerance test as a diagnostic aid for diabetes mellitus (see p. 458.3).

The way in which the strengths of glucose solutions for intravenous use are expressed varies in different countries. Glucose Intravenous Infusion (BP 2014) may be prepared from either anhydrous glucose or glucose monohydrate but the potency is expressed in terms of anhydrous glucose whereas Dextrose Injection (USP 36) is prepared from glucose monohydrate and potency is expressed in terms of the monohydrate. Anhydrous glucose 900 mg is equivalent to about 1 g of glucose monohydrate. Thus, the term glucose 5% may represent, depending on origin, either 50 g/litre of anhydrous glucose (equivalent to about 55 g/litre of glucose monohydrate) or 50 g/litre of glucose monohydrate (equivalent to about 45 g/litre of anhydrous glucose). As the manner in which such preparations are referred to in the medical literature is sometimes ambiguous, it has not always been possible to state clearly in *Martindale* whether the strengths of glucose solutions mentioned relate to the anhydrous or hydrated form; however, in *Martindale*, unless otherwise specified, glucose injection is a 5% solution to distinguish it from more concentrated forms. For many practical purposes it is probably less important to know the exact way in which the strength of a given concentration is expressed than to avoid confusion between completely different strengths such as 5, 10, and 50% as the more concentrated forms are associated with particular adverse effects and precautions.

Solutions of glucose in water are iso-osmotic with blood at a concentration of anhydrous glucose 5.05% or glucose monohydrate 5.51%. Glucose solution 5% is therefore the strength often employed for fluid depletion; it may be given via a peripheral vein. Glucose solutions with a concentration greater than 5% are hyperosmotic and are generally used as a carbohydrate source; a 50% solution is often used in the treatment of severe hypoglycaemia (but see also Hypoglycaemia, below). Hyperosmotic solutions should generally be given via a central vein although the *American Hospital Formulary Service* suggests that concentrations up to 10% may be given via a large peripheral vein, with the injection site alternated daily if possible. In the emergency treatment of hypoglycaemia it may be necessary to use a peripheral vein but the solution should be given slowly; a suggested rate for glucose 50% in such circumstances is 3 mL/minute.

The dose of glucose is variable and is dependent on individual patient requirements; serum-glucose concentrations may need to be carefully monitored. The maximum rate of glucose utilisation has been estimated to be about 500 to 800 mg/kg per hour.

Strongly hyperosmotic glucose solutions (25 to 50%) have also been given to reduce cerebrospinal pressure see Raised Intracranial Pressure, (p. 1271.3) and cerebral oedema caused by delirium tremens or acute alcohol intoxication (see p. 1734.1) although they do not appear to be widely used. Glucose solution (25 to 50%) has also been used as a sclerosing agent in the treatment of varicose veins (p. 2564.1) and as an irritant to produce adhesive pleuritis in the management of pleural effusions and pneumothorax. Liquid glucose is used as a sweetener, binder, or granulating and coating agent in pharmaceuticals.

Ectopic pregnancy. Ectopic pregnancy is now recognised at earlier stages as a result of improved diagnostic techniques. Surgery remains the mainstay of treatment, but although conservative surgical techniques may be used in an attempt to preserve fertility, nonsurgical methods have been increasingly investigated. The best established therapy is with methotrexate (p. 823.3), but hyperosmolar glucose solutions have also been used. Local instillation of 5 to 20 mL of glucose 50% into the gestational sac (salpingocentesis) has been described.[1] It was reported to be more effective than expectant management of early tubal pregnancy[2] but another study was stopped because of a higher failure rate with glucose than local methotrexate.[3]

1. Natofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; **42:** 39–47.
2. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; **76:** 797–800.
3. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; **265:** 82–4.

Glycogen storage disease type I. Starch may be a more acceptable alternative to glucose in the control of the hypoglycaemia of type I glycogen storage disease, see p. 2095.3.

Haemodialysis-induced cramp. Suggestions that haemodialysis-induced cramps (p. 1779.3) are due to hypovolaemia are supported by the efficacy of volume expansion with hypertonic solutions in the management of such cramps. Intravenous infusion of 50 mL of glucose 50% solution has been used as an effective alternative to infusion of sodium chloride or mannitol.[1,2]

1. Milutinovich J, *et al.* Effect of hypertonic glucose on the muscular cramps of hemodialysis. *Ann Intern Med* 1979; **90:** 926–8.
2. Canzanello VJ, *et al.* Comparison of 50% dextrose water, 25% mannitol, and 23.5% saline for the treatment of hemodialysis-associated muscle cramps. *Trans Am Soc Artif Intern Organs* 1991; **37:** 649–52.

Hyperkalaemia. Insulin, together with glucose to prevent hypoglycaemia, is given to stimulate the cellular uptake of potassium in the emergency treatment of moderate to severe hyperkalaemia (p. 1777.1). Usually, 50 mL of glucose 50% is given.

Hypoglycaemia. Glucose is used to correct insulin-induced hypoglycaemia, as discussed on p. 484.3, either orally or by infusion of a hypertonic solution (20 or 50%). Glucose 5 or 10% may be used but larger volumes are required. Although 50% glucose solution has been generally used to correct hypoglycaemia in children, some consider that so concentrated a solution is associated with unacceptable morbidity and possible mortality, and that it should be replaced by the 10% solution for this purpose.[1] The *BNFC* recommends use of 5 mL/kg of glucose 10% intravenous infusion, given with care and through a large-gauge needle into a large vein; it states that a 50% solution of glucose should not be used, as it is very viscous and hypertonic. A 5 or 10% solution is used to prevent the hypoglycaemia associated with insulin infusion for the treatment of diabetic ketoacidosis, once blood-glucose concentrations have fallen to an acceptable level (see Diabetic Emergencies, p. 465.3).

1. Winrow AP, *et al.* Paediatric resuscitation: don't use 50% dextrose. *BMJ* 1993; **306:** 1612.

Myocardial infarction. The value of a glucose, insulin, and potassium combination in patients with myocardial infarction has been investigated (see p. 482.3).

Pain. Oral glucose solution or spray has been used similarly to sucrose solution (p. 2097.1) to alleviate mild pain in neonates,[1-6] and there is some suggestion it may be more effective than topically applied local anaesthetic, or an opioid.[6,7]

Glucose solutions have been injected for prolotherapy (the local injection of irritant solutions to stimulate proliferation)[8,9] in the management of painful musculoskeletal conditions such as low back pain[9] and groin strain.[10] The value of such treatment has been disputed.

1. Skogsdal Y, *et al.* Analgesia in newborns given oral glucose. *Acta Paediatr Scand* 1997; **86:** 217–20.
2. Carbajal R, *et al.* Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ* 1999; **319:** 1393–7.
3. Carbajal R, *et al.* Crossover trial of analgesic efficacy of glucose and pacifier in very preterm neonates during subcutaneous injections. *Pediatrics* 2002; **110:** 389–93.
4. Akçam M, Örmeci AR. Oral hypertonic glucose spray: a practical alternative for analgesia in the newborn. *Acta Paediatr* 2004; **93:** 1330–3.
5. Thyr M, *et al.* Oral glucose as an analgesic to reduce infant distress following immunization at the age of 3, 5 and 12 months. *Acta Paediatr* 2007; **96:** 233–6.
6. Axelin A, *et al.* Oral glucose and parental holding preferable to opioid in pain management in preterm infants. *Clin J Pain* 2009; **25:** 138–45.
7. Gradin M, *et al.* Pain reduction at venipuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics* 2002; **110:** 1053–7.
8. Rabago D, *et al.* A systematic review of prolotherapy for chronic musculoskeletal pain. *Clin J Sport Med* 2005; **15:** 376–80.
9. Dagenais S, *et al.* Prolotherapy injections for chronic low-back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/06/08).
10. Topol GA, *et al.* Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Arch Phys Med Rehabil* 2005; **86:** 697–702.

Adverse Effects and Precautions

Intravenous glucose solutions (particularly hyperosmotic solutions, which also have a low pH) may cause local pain, vein irritation, and thrombophlebitis, and tissue necrosis if extravasation occurs. Some of these reactions may be due to degradation products present after autoclaving or to poor

technique in giving the solution. Intravenous infusion can lead to fluid and electrolyte disturbances including hypokalaemia, hypomagnesaemia, and hypophosphataemia. Prolonged or rapid infusion of large volumes of isoosmotic solutions may cause oedema or water intoxication; conversely, prolonged or rapid use of hyperosmotic solutions may result in dehydration as a consequence of the induced hyperglycaemia.

The use of hyperosmotic glucose solutions is contra-indicated in patients with anuria, intracranial or intraspinal haemorrhage, and in delirium tremens where there is dehydration. They should be used with caution in patients with diabetes mellitus, as rapid infusion can lead to hyperglycaemia, as well as in those with malnutrition, thiamine deficiency, carbohydrate intolerance, sepsis, shock, or trauma.

It has been suggested that glucose solutions should not be used after acute ischaemic strokes as hyperglycaemia has been implicated in increasing cerebral ischaemic brain damage and in impairing recovery.

Glucose solutions should not be given through the same infusion equipment as whole blood as haemolysis and clumping can occur.

Pregnancy. Glucose solutions are commonly used as hydrating fluids and as vehicles for other drugs. If given during labour it has been suggested that the glucose load on the mother may lead to fetal hyperglycaemia, hyperinsulinaemia, and acidosis, with subsequent neonatal hypoglycaemia and jaundice.[1,2] Others[3] have found no evidence of such an effect, especially if the fetus is well-oxygenated,[4] and note that the number of patients included in such reports is often small and the selection criteria not homogeneous.

A placebo-controlled study[5] in healthy women scheduled for termination of pregnancy at mid-gestation found that giving 100 g of oral glucose 1 hour before termination had no adverse effect on fetal acid–base levels. Fetuses with malformations had been excluded. However, the authors cautioned that, at higher maternal glucose concentrations (as may be found in pregnant diabetics), changes consistent with fetal metabolic acidosis might occur, and that the glucose tolerance test might also be hazardous to fetuses with growth retardation. Late reactions to the acute glucose load could not be studied.

1. Kenepp NB, *et al*. Fetal and neonatal hazards of maternal hydration with 5% dextrose before caesarean section. *Lancet* 1982; **i:** 1150–2.
2. Singhi S, *et al*. Hazards of maternal hydration with 5% dextrose. *Lancet* 1982; **ii:** 335–6.
3. Piquard F, *et al*. Does fetal acidosis develop with maternal glucose infusion during normal labor? *Obstet Gynecol* 1989; **74:** 909–14.
4. Cerri V, *et al*. Intravenous glucose infusion in labor does not affect maternal and fetal acid-base balance. *J Matern Fetal Med* 2000; **9:** 204–8.
5. Weissman A, *et al*. Effect of the 100-g oral glucose tolerance test on fetal acid-base balance. *Prenat Diagn* 2003; **23:** 281–3.

Stroke. Hyperglycaemia may be caused by physiological stress during ischaemic stroke, and this worsens cerebral ischaemic damage and impairs recovery. During cerebral ischaemia, cellular hypoxia causes a shift from aerobic to anaerobic metabolism of glucose leading to intracellular lactic acidosis, which is toxic to the cell. Hyperglycaemia provides more glucose for anaerobic metabolism, further worsening intracellular acidosis. Blood-glucose concentrations should therefore be monitored and hyperglycaemia avoided or treated. Glucose infusions should not be used routinely after ischaemic stroke, unless specifically indicated. Hypoglycaemia must also be avoided and for patients who do require glucose, it should be given by continuous infusion, avoiding large infusions or boluses that can cause hyperglycaemia.[1]

1. Wass CT, Lanier WL. Glucose modulation o f ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc* 1996; **71:** 801–12.

Thiamine deficiency. Wernicke's encephalopathy (p. 2103.3) may be precipitated by giving intravenous glucose to thiamine-deficient patients.[1,2]

1. Watson AJ, *et al*. Acute Wernickes encephalopathy precipitated by glucose loading. *Ir J Med Sci* 1981; **150:** 301–3.
2. Koguchi K, *et al*. Wernicke's encephalopathy after glucose infusion. *Neurology* 2004; **62:** 512.

Pharmacokinetics

Glucose is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of glucose occur about 40 minutes after oral doses in hypoglycaemic patients. It is metabolised via pyruvic or lactic acid to carbon dioxide and water with the release of energy. All body cells are capable of oxidising glucose and it forms the principal source of energy in cellular metabolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Glucolin; Glucotem; Kissimin; Nutrosa; ***Canad.***: Dextroject; Glucodex; ***Cz.***: Ardeanutrisol G; ***Fin.***: Glucosteril; Selutrio; ***Ger.***: Accu-Chek Dextrose OGT; Glucosteril; ***Hung.***: Isodex; ***Indon.***: Infusan D; Otsu-D5; Wida; ***Ital.***: Energen; ***Pol.***: Maltan; ***Port.***: Glucosada; Glucosado; Glucosteril; ***Rus.***: Glucosteril (Глюкостерил); Rheopolyglukin (Реополиглюкин); ***Spain***: Apiroserum Glucosado; Flebobag Glucosada†; Fleboflex Glucosada†; Fleboplast Glucosada†; Freeflex Glucosa; Glucocemin; Glucosmon†; Meinvenil Glucosa†; Plast Apyr Glucosado; Suero Glucosado; ***Swed.***: Perfadex; ***UK***: Dextrogel; GlucoGel; Rapilose; ***USA***: Dex4 Glucose; Glutose; Insulin Reaction.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Ger.***: NeyArthrosome (Revitorgan-Dilution)†.

Pharmacopoeial Preparations

BP 2014: Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution; Glucose Infusion; Glucose Irrigation Solution; Potassium Chloride and Glucose Infusion; Potassium Chloride, Sodium Chloride and Glucose Infusion; Sodium Chloride and Glucose Infusion;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USNF 31: Dextrose Excipient; Liquid Glucose;
USP 36: Alcohol in Dextrose Injection; Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Bretylium Tosylate in Dextrose Injection; Bupivacaine Hydrochloride in Dextrose Injection; Dextran 40 in Dextrose Injection; Dextran 70 in Dextrose Injection; Dextrose and Sodium Chloride Injection; Dextrose Injection; Dobutamine in Dextrose Injection; Dopamine Hydrochloride and Dextrose Injection; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lidocaine Hydrochloride and Dextrose Injection; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Dextrose Injection Type 4; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Ringer's and Dextrose Injection; Sodium Chloride and Dextrose Tablets; Tetracaine Hydrochloride in Dextrose Injection.

Glucose-1-phosphate

Cori Ester; α-D-Glucopyranose-1-phosphate; α-Glucose-1-Phosphoric Acid; Glucose-1-(dihydrogen Phosphate).
α-D-Glucopyranose 1-(dihydrogen phosphate).
$C_6H_{13}O_9P$=260.1
CAS — 59-56-3 (glucose-1-phosphate); 18822-82-7 (arginine glucose-1-phosphate); 6997-09-7 (calcium glucose-1-phosphate); 17364-14-6 (monosodium glucose-1-phosphate); 56401-20-8 (disodium glucose-1-phosphate).
UNII — CIX3U01VAU.

NOTE. The name Arginil has been used to denote arginine glucose-1-phosphate.

Profile

Glucose-1-phosphate is an intermediate in both the synthesis and utilisation of glycogen and has been used as a source of glucose (p. 2068.3) and organic phosphorus. The sodium and calcium salts have been used as dietary supplements and the arginine salt has been used in liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Phocytan; ***Ital.***: Glu-Phos.

Glutamic Acid *(USAN, rINN)*

Acide Glutamique; Ácido glutámico; Acidum Glutamicum; E; E620; Glu; L-Glutamic Acid; Glutámico, ácido; Glutamiinihappo; Glutaminic Acid; Glutaminsäure; Glutaminsav; Glutaminsyra; Glutamo rūgštis; Kwas glutaminowy; Kyselina glutamová; Глутаминовая Кислота.
L-(+)-2-Aminoglutaric acid.
$C_5H_9NO_4$=147.1
CAS — 56-86-0.
UNII — 3KX376GY7L (L-glutamic acid); 61LJO5I15S (DL-glutamic acid).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Glutamic Acid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in boiling water; slightly soluble in cold water; practically insoluble in alcohol, in acetic acid, and in acetone. Protect from light.

USP 36: (Glutamic Acid). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Glutamic Acid Hydrochloride *(rINNM)*

Acide Glutamique, Chlorhydrate de; Acidum Glutamicum Hydrochloridum; Aciglumin; Glu Hydrochloride; Glutámico, hidrocloruro del ácido; Hidrocloruro del ácido glutámico; Глутаминовой Кислоты Гидрохлорид.
L-(+)-2-Aminoglutaric acid hydrochloride.
$C_5H_9NO_4$,HCl=183.6
CAS — 138-15-8.
ATC — A09AB01.
ATC Vet — QA09AB01.
UNII — M0C2SP444T.

Pharmacopoeias. In *Ger.* Also in *USNF*.

USNF 31: (L-Glutamic Acid, Hydrochloride). A white, crystalline powder. Soluble 1 in about 3 of water; almost insoluble in alcohol and in ether. Solutions are acid to litmus. Protect from light.

Glutamine *(USAN, rINN)*

Gln; Glutamina; L-Glutamina; L-Glutamine; Glutaminum; Levoglutamida; Levoglutamide; Lévoglutamide; Levoglutamidum; Q; Левоглутамид.
L-Glutamic acid 5-amide; L-(+)-2-Aminoglutaramic acid.
$C_5H_{10}N_2O_3$=146.1
CAS — 56-85-9.
ATC — A16AA03.
ATC Vet — QA16AA03.
UNII — 0RH81L854J.

Pharmacopoeias. In *Ger.*, *Jpn*, and *US*.

USP 36: (Glutamine). White crystals or crystalline powder. Soluble in water; practically insoluble in alcohol and in ether. Store at a mean temperature not exceeding 25 degrees.

Profile

Glutamic acid is a non-essential amino acid which is degraded readily in the body to form glutamine (levoglutamide). Glutamic acid and glutamine are used as dietary supplements. The dipeptides *N* (2)-L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln) are used similarly.

Glutamic acid hydrochloride, which releases hydrochloric acid in the stomach, has been used in the symptomatic treatment of achlorhydria or hypochlorhydria in usual oral doses of 250 to 750 mg with meals.

A glutamine-based oral suspension is under investigation for the treatment of oral mucositis.

Antineoplastic toxicity. Oral glutamic acid has been used in the reduction of vincristine neurotoxicity (see Administration Error, p. 883.2).

Oral supplementation with glutamine may also have a role in alleviating the diarrhoea associated with irinotecan (see Effects on the Gastrointestinal Tract, p. 813.2).

A glutamine-based oral suspension is under investigation for the treatment of oral mucositis associated with cancer chemotherapy (p. 732.1). In breast cancer patients with moderate to severe oral mucositis glutamine reduced both the incidence and severity of the mucositis.[1] A literature review[2] reported variable results with glutamine supplementation for chemotherapy-induced mucositis, but stated that higher doses may be beneficial.

Oral glutamine was found to be of no benefit in alleviating myalgias or arthralgias associated with paclitaxel therapy.[3]

1. Peterson DE, *et al*. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer* 2007; **109:** 322–31.
2. Savarese DMF, *et al*. Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treat Rev* 2003; **29:** 501–13.
3. Jacobson SD, *et al*. Glutamine does not prevent paclitaxel-associated myalgias and arthralgias. *J Support Oncol* 2003; **1:** 274–8.

Parenteral and enteral nutrition. Evidence that glutamine is involved in the regulation of muscle protein synthesis, maintenance of gut mucosal barrier function, and possibly enhanced immunological response has led to studies of supplementation with glutamine or more stable peptide derivatives in parenteral and enteral nutrition regimens for patients with injury and infection.[1] Although non-essential under normal circumstances, many consider glutamine to be a conditionally essential amino acid in patients with catabolic disease.[2,3]

Supplementation of parenteral nutrition regimens with glutamine has been shown to reduce clinical infection in patients who have undergone bone marrow transplantation[4] or who have suffered multiple trauma.[5] Improved survival has been reported among intensive-care patients given parenteral feeds supplemented with glutamine,[6,7] although a larger study found it difficult to show a benefit.[8] A systematic review,[9] including these studies, inferred that seriously ill patients, with gastrointestinal failure and

receiving parenteral nutrition, should receive glutamine supplements for at least 6 days and at a dose of greater than 200 mg/kg daily, in order to derive maximum benefit. Low plasma glutamine concentration upon admission to an intensive-care unit was considered to be an independent risk factor for mortality, and it has been suggested that plasma concentrations be used as an indicator for glutamine supplementation.[10]

In patients undergoing major uncomplicated surgery on the lower gastrointestinal tract, a significantly better postoperative nitrogen balance was achieved in those whose total parenteral nutrition regimen had been supplemented with about 20 g daily of glutamine coupled with alanine (L-alanyl-L-glutamine) (equivalent to about 12 g daily of glutamine) when compared with a control group.[11] Others[12] have shown that supplementation of total parenteral nutrition solutions with a glutamine dipeptide (glycyl-L-glutamine), in quantities equivalent to 230 mg/kg of glutamine daily, prevented the increased intestinal permeability and atrophic changes in the intestinal mucosa associated with unsupplemented solutions. Supplementation of total parenteral nutrition with α-ketoglutarate or a dipeptide, ornithine-α-ketoglutarate, reduced muscle protein depletion in one study,[13] suggesting that this may be a more physiological way of providing glutamine. Although recognising that clinical benefit in terms of infectious complications remained to be established, a review[14] of the use of ornithine-α-ketoglutarate stated that supplementation in the elderly improved clinical outcome in chronic malnutrition, by increasing appetite and body-weight gain and improving healing.

1. Sacks GS. Glutamine supplementation in catabolic patients. *Ann Pharmacother* 1999; **33:** 348–54.
2. Kelly D, Wischmeyer PE. Role of L-glutamine in critical illness: new insights. *Curr Opin Clin Nutr Metab Care* 2003; **6:** 217–22.
3. Melis GC, *et al*. Glutamine: recent developments in research on the clinical significance of glutamine. *Curr Opin Clin Nutr Metab Care* 2004; **7:** 59–70.
4. Ziegler TR, *et al*. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation: a randomized, double-blind, controlled study. *Ann Intern Med* 1992; **116:** 821–8.
5. Houdijk APJ, *et al*. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; **352:** 772–6.
6. Griffiths RD, *et al*. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997; **13:** 295–302.
7. Goeters C, *et al*. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; **30:** 2032–7.
8. Powell-Tuck J, *et al*. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut* 1999; **45:** 82–8.
9. Novak F, *et al*. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med* 2002; **30:** 2022–9.
10. Wernerman J. Glutamine and acute illness. *Crit Care* 2003; **9:** 279–85.
11. Stehle P, *et al*. Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. *Lancet* 1989; **i:** 231–3.
12. van der Hulst RRWJ, *et al*. Glutamine and the preservation of gut integrity. *Lancet* 1993; **334:** 1363–5.
13. Wernerman J, *et al*. α-Ketoglutarate and postoperative muscle catabolism. *Lancet* 1990; **335:** 701–3.
14. Blonde-Cynober F, *et al*. Use of ornithine α-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; **19:** 73–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glutamic acid hydrochloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Glutamine is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actyn-Myosyn; Alglutamin; Dipeptiven; ***Austria***: Dipeptiven; Neuroglutamin; ***Braz.***: Glutafora; ***Chile***: Dipeptiven; ***China***: An Kai Shu (安凯舒); Chong Tai (重太); Dipeptiven (力太); Pei Er Ji (培尔吉); Shi Lin (施林); Xin Kun Chang (欣坤畅); Xin Mai Lin (新麦林); Zhong Xin Tai (仲新太); Zi Wei (自维); ***Cz.***: Adamin-G; Dipeptiven; ***Denm.***: Dipeptiven; ***Fin.***: Dipeptiven; Hypochylin; ***Fr.***: Dipeptiven; ***Ger.***: Dipeptamin; Glutamin; Gluti-Agil mono; Pepsaletten N†; ***Gr.***: Aminol; Dipeptiven; Glutamol; ***Hong Kong***: Dipeptiven; ***Hung.***: Dipeptiven; ***India***: Convales; Elemune; ***Indon.***: Dipeptiven; Glutrop; ***Irl.***: Adamin-G†; Dipeptiven; ***Israel***: Dipeptiven; ***Ital.***: Dipeptiven; Glutaven; ***Malaysia***: Dipeptiven†; ***Mex.***: Dipeptiven; ***Neth.***: Dipeptiven; ***Norw.***: Dipeptiven; ***NZ***: Dipeptiven; ***Pol.***: Dipeptiven; ***Port.***: Dipeptiven; ***Rus.***: Dipeptiven (Дипептивен); ***S.Afr.***: Dipeptiven; ***Singapore***: Dipeptiven; ***Spain***: Dipeptiven; ***Swed.***: Dipeptiven; Hypochylin; ***Switz.***: Dipeptiven; ***Thai.***: Dipeptiven; ***Turk.***: Dipeptiven; ***UK***: Dipeptiven; ***Ukr.***: Dipeptiven (Дипептивен); ***USA***: NutreStore.

Multi-ingredient Preparations. ***Arg.***: Levoglutil Vitaminado; Memorex Vital; Normoprost Compuesto; Tuaplex; ***Austral.***: Aspartatol†; Digestive Zyme†; Mindac; ***Braz.***: Glutavigon; Libiplus; Memoriol B6; Nutrimaiz SM; Organoneuro Cerebral; ***Canad.***: Digest; ***Chile***: Dynamisan; Glutacyl Vitaminado; Hexalectol; ***China***: Gu Ao (谷奥); Pu Luo Si Tai (普罗司泰); She Lan (舍兰); Zi Mo (兹末); ***Fr.***: Bouillet; Phakan†; ProstaSecurA; Vita-Dermacide; Xal; YSE Glutamique†; ***Ger.***: Leferdivin†; ***Gr.***: Tonotil-N; ***Hong Kong***: Esafosfina Glutammica; ***Hung.***: Glutarsin E; Reergin; ***India***: Actovit; Ameco; Aminos; Aminut; Aneudox-12; B-Banc; Bavitam; Bcom-L; Betaneuron OD; Dayvital; Dipeptiven; Florablend; Glubex-Z; Glubex-Z; Glutammune; Glutazene; Kabimmune; Lycobel; Mecze-FL; Medineuron; Miol; Neuratab B6; Neurogard; Orovit; Orovit; Orovit; ***Indon.***: Asten; Cerebrofort AA+DHA; Cerebrofort Gold; Cerebrovit Senior; Cerebrovit X-Cel; Curbexon; Erpha Livita; Fortelysin†; Hemaviton Stamina Plus; Kuminta; Lanavision Plus; Pediagrow; Prefit; Proseval; Provital Plus; Provital; Stamino; Zamel; ***Ital.***: Acutil Fosforo; Fosfaserin; Fosfo Plus; Glutamin Fosforo; Memovit B12; Selene; ***Jpn***: Azulemin; Azulene.Glutamine; Manamin GA; Mesadorin S; Podonin-S; Ruefrien; Sedagaston; Towazuren; Youzuren S; ***Mex.***: Bigenol†; Glutacalcio; ***Philipp.***: Catarstat; Glutaphos; Spasmo-Canulase; ***Pol.***: Naturapia Prostata†; ***Port.***: Cebrotex Forte†; Espasmo Canulase†; Fosgluten Super Reforcado; Relavit Fosforo; ***Rus.***: Eltacin (Элтацин); ***S. Afr.***: Lentogesic; Spasmo-Canulase†; ***Singapore***: Glutamine Plus; NutraMX; Provital; ***Spain***: Agudil†; Dynamin; Fosgluten Reforzado†; Nucleserina; Tebetane Compuesto; ***Switz.***: Spasmo-Canulase; Tonoglutal; Vitasprint B12; Vitasprint Complex†; ***Turk.***: Pepzan; Seldiyet; ***Ukr.***: Fakovit (Факовит)†; Quadevit (Квадевит); ***USA***: Panplex 2-Phase; Sunnie; Tyler Prenatal; ***Venez.***: Glutapak-R; Glutapak.

Homoeopathic Preparations. ***Ger.***: NeyGeront Vitalkapsein A.

Glycine *(rINN)*

Ácido aminoacético; Acidum Aminoaceticum; Aminoacetic Acid; Aminoättiksyra; Aminoetikkahappo; E640 (glycine or glycine sodium); G; Glicin; Glicina; Glicinas; Glicocola; Glicolol; Glicyna; Gly; Glycin; Glycinum; Glycocoll; Glysiini; Sucre de Gélatine; Глицин.

$C_2H_5NO_2$=75.07

CAS — 56-40-6.

ATC — B05CX03.

ATC Vet — QB05CX03.

UNII — TE7660XO1C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Glycine). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 5.9 to 6.4.

USP 36: (Glycine). A white, odourless crystalline powder. Soluble 1 in 4 of water at 25 degrees, 1 in 2.6 at 50 degrees, 1 in 1.9 at 75 degrees, and 1 in 1.5 at 100 degrees; soluble 1 in 1254 of alcohol; very slightly soluble in ether. Its solutions are acid to litmus.

Uses and Administration

Glycine is a non-essential aliphatic amino acid. It is used as a dietary supplement.

Glycine is sometimes used with antacids in the treatment of gastric hyperacidity. It is also used as an ingredient of some aspirin preparations with the object of reducing gastric irritation. Glycine powder has been used as a debriding and polishing agent for dental hygiene.

Sterile solutions of glycine 1.5% in water, which are hypotonic and non-conductive, are used as urogenital irrigation solutions during certain surgical procedures, particularly transurethral resection of the prostate.

Glycine hydrochloride has also been used.

Adverse Effects and Precautions

Systemic absorption of glycine irrigation solutions can lead to disturbances of fluid and electrolyte balance and cardiovascular and pulmonary disorders (see below).

Glycine irrigation should be used cautiously in patients with hepatic impairment since any absorption and consequent metabolism may cause hyperammonaemia. The possible effects on fluid and electrolyte balance warrant cautious use in patients with cardiopulmonary or renal dysfunction; glycine irrigation is contra-indicated in anuric patients.

Systemic absorption. Absorption of glycine irrigation solution during surgical procedures can cause disturbances of the circulatory and nervous systems.[1-3] Often seen after transurethral resection of the prostate, these symptoms and signs have been referred to as the transurethral resection syndrome,[1] although they have also been described after other urological or gynaecological surgical procedures.[4,5] Hyponatraemia and glycine toxicity are thought to be responsible for the clinical manifestations.[1,2,5]

Symptoms and signs include chest pains, hypertension, hypotension, bradycardia, anuria, dyspnoea, nausea, vomiting, restlessness, confusion, apprehension, irritability, headache, and seizures.[1,3-5] Chills, diarrhoea, and abdominal pain have also been reported,[1] as have visual disturbances and blindness.[3,6] Myocardial infarction,[7,8] coma, and death may occur.[5,7]

Absorption may occur rapidly, through the intravascular route, or, more rarely, slowly via extravascular absorption.[1,2,4] Extravasation should be suspected when abdominal pain and swelling are apparent.[4,9] Ethanol has been added to the irrigation fluid, and ethanol breath tests performed regularly during procedures in order to detect and monitor absorption.[1,2,4,9] However, the syndrome has still occurred despite monitoring;[9] awareness of the pattern of ethanol changes and clinical symptoms associated with extravascular as well as intravascular absorption are considered essential.[4,9]

1. Olsson J, *et al*. Symptoms of the transurethral resection syndrome using glycine as the irrigant. *J Urol (Baltimore)* 1995; **154:** 123–8.
2. Tauzin-Fin P. Complication des liquides d'irrigation à base de glycocolle: le syndrome de résorption. *Therapie* 2002; **57:** 48–54.
3. Radziwill AJ, *et al*. Visual disturbances and transurethral resection of the prostate: the TURP syndrome. *Eur Neurol* 1997; **38:** 7–9.
4. Hahn RG. Transurethral resection syndrome after transurethral resection of bladder tumours. *Can J Anaesth* 1995; **42:** 69–72.
5. Siddiqui MA, *et al*. Glycine irrigant absorption syndrome following cystoscopy. *Clin Nephrol* 1996; **45:** 365–6.
6. Karci A, Erkin Y. Transient blindness following hysteroscopy. *J Int Med Res* 2003; **31:** 152–5.
7. Byard RW, *et al*. Glycine toxicity and unexpected intra-operative death. *J Forensic Sci* 2001; **46:** 1244–6.
8. Hahn RG, Persson P-G. Acute myocardial infarction after prostatectomy. *Lancet* 1996; **347:** 335.
9. Hahn RG. Life-threatening transurethral resection syndrome despite monitoring of fluid absorption with ethanol. *Eur J Anaesthesiol* 1995; **12:** 431–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Titralac; ***Fr.***: Derm Hydralin; Hydralin Gyn; ***Hong Kong***: Gyn-Hydralin; Titralac†; ***NZ***: Titralac; ***Rus.***: Prostatilen (Простатилен); ***S.Afr.***: Titralac†; ***Thai.***: Glycine-Tur; ***Ukr.***: Glicised (Глицисед-кмп).

Multi-ingredient Preparations. ***Arg.***: Cicatrex Biotic; Glicocalcio; Normoprost Compuesto; Novo Benitol; Synapsys; ***Austral.***: Cal Alkyline†; Cicatrin†; ***Austria***: Centramin; ***Braz.***: B-Vesil†; Cicatrene; ***Canad.***: Antacid 2†; ***Chile***: Dolotol 12; ***China***: BiFu (比孚); Bo Luo Ni (博罗尼); Gan Mu Shu (甘木舒); Gan Wei Xin (甘维欣); Gan You Lin (感佑林); Jun Qiang (君强); Kang Er Ning (康尔宁*); LiWeiEr (里威尔); Neo-Minophagen C (美能); Neo-Minophagen C (美能); NuoHao (诺豪); Pu Luo Si Tai (普罗司泰); Ruo Jing (若菁); Shu Kang Lin (抒康林); Tuo Di (妥迪); Wei Suan Su (卫算苏); Wei Yi Xing (卫伊兴); XinKang (昕康); Ye Xin (业欣); Yi Nuo Wei (帷诺维); Yi Xin (易新); YouNiDi (尤尼迪); ***Fr.***: Derm'Intim; Phakan†; ProstaSecurA; Pruriced; ***Gr.***: Titralac; ***India***: Astyfer-Z; Astyfer; Biospirin; Cotaryl; Fe-Z; Ferro Hepatine; ***Indon.***: Aviter; IsoCal; Viusid; ***Irl.***: Cicatrin†; ***Ital.***: Cicatrene; Detoxicon; Digestivo Antonetto; Omegadin Plus; ***Mex.***: Magnesium Glycocolle Lafarge; ***Philipp.***: Catarstat; ***Pol.***: Naturapia Prostata†; ***Port.***: Cicatrin; ***Rus.***: Eltacin (Элтацин); ***S.Afr.***: Cicatrin†; ***Spain***: Tebetane Compuesto; Tulgrasum Cicatrizante; ***Switz.***: Cicatrex; DAM Antacidum†; ***Thai.***: Genquin; ***Ukr.***: Fakovit (Факовит)†; Medichronal (Медихронал); Oko-Health (Око-хелс).

Used as an adjunct in:. ***Austral.***: Cardiprin; Disprin Direct; ***Cz.***: Godasal; ***Ger.***: Godamed; ***Gr.***: Junior Algon; ***Hong Kong***: Cardiprin; Glyprin; ***India***: Aspisol; ***Indon.***: Contrexyn; Inzana†; Minigrip; Proxime; ***Ital.***: Aspiglicina; ***Malaysia***: Cardiprin; Glyprin; ***Pol.***: Alka-Prim; Asprocard†; Asprocol; ***Rus.***: Alka-Prim (Алька-Прим); ***Singapore***: Cardiprin; Glyprin; ***Spain***: Okaldol con Cafeina; Okaldol; ***Thai.***: Caparin; Cardiprin; ***Ukr.***: Alka-Prim (Алька-Прим); Godasal (Годасал).

Pharmacopoeial Preparations
BP 2014: Glycine Irrigation Solution;
USP 36: Glycine Irrigation.

Halibut-liver Oil

Aceite de hígado de fletán; Aceite de Hígado de Hipogloso; Heilbuttleberöl; Ol. Hippogloss.; Oleum Hippoglossi; Oleum Jecoris Hippoglossi; Палтусовый Печёночный Жир.

CAS — 8001-46-5.

UNII — QMX76ZL97M.

Pharmacopoeias. In *Br.*

BP 2014: (Halibut-liver Oil). The fixed oil extracted from the fresh or suitably preserved liver of the halibut species belonging to the genus *Hippoglossus*. It contains not less than 30 000 units of vitamin A activity per g. Wt per mL 0.915 to 0.925 g. A pale to golden yellow liquid with a fishy, but not rancid, odour and taste. Practically insoluble in alcohol; miscible with chloroform, with ether and with petroleum spirit. Store in well-filled containers. Protect from light.

Profile

Halibut-liver oil is used as a means of giving vitamins A (p. 2098.3) and D (p. 2112.3); the proportion of vitamin A to vitamin D is usually greater in halibut-liver oil than in cod-liver oil (p. 2056.3). It is usually given in capsules.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pancutan Base†.

Multi-ingredient Preparations. ***Arg.***: Eryteal; Klorane Bebe Eryteal; Pancutan; ***Austria***: Nuri-Kapseln†; Vitawund; ***Chile***: Hipoglos; Mintaglos; Nistaglos; ***Port.***: Halibut.

Pharmacopoeial Preparations
BP 2014: Halibut-liver Oil Capsules.

Histidine *(BAN, USAN, rINN)*

H; His; Histidiini; Histidin; Histidina; Histidinas; L-Histidine; Histidinum; Hisztidin; NSC-137773; Гистидин.

L-2-Amino-3-(1*H*-imidazol-4-yl)propionic acid.

$C_6H_9N_3O_2$=155.2

CAS — 71-00-1.

UNII — 4QD397987E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Histidine). Colourless crystals or a white or almost white crystalline powder. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Histidine). White, odourless crystals. Soluble in water; very slightly soluble in alcohol; insoluble in ether. pH of a 2% solution in water is between 7.0 and 8.5.

Histidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de histidina; Histidiinihydrokloridimonohydraatti; Histidina, hidrocloruro; Histidine (chlorhydrate d') monohydraté; Histidine, Chlorhydrate de; Histidine Monohydrochloride; Histidin-hydrochlorid monohydrát; Histidinhydrokloridmonohydrat; Histidini Hydrochloridum; Histidini Hydrochloridum Monohydricum; Histidinium Chloride; Histidino hidrochloridas monohidratas; Histydyny monochlorowodorek; Hisztidin-hidroklorid-monohidrát; Гистидина Гидрохлорид.

L-Histidine hydrochloride monohydrate.

$C_6H_9N_3O_2$,HCl,H_2O=209.6

CAS — 645-35-2 (anhydrous histidine hydrochloride).

UNII — 1D5Q932XM6 (anhydrous histidine hydrochloride); X573657P6P (histidine hydrochloride monohydrate).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Histidine Hydrochloride Monohydrate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.0 to 5.0. Protect from light.

Profile

Histidine is a basic amino acid that is essential for infant growth and which may be essential for some other groups, such as patients with uraemia. Histidine and histidine hydrochloride are used as dietary supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Enhance for Men; ***Fr.***: Bion Restore; ***India***: Astyfer-Z; Astyfer; Astyfer; Doloral; ***Philipp.***: Biomix.

Honey

Bal; Clarified Honey; Gereinigter Honig; Honig; Honung; Hunaja; Madu; Med; Medus; Mel; Mel Depuratum; Mel Despumatum; Miel; Miel Blanc; Miel purificada; Purified Honey; Strained Honey; Мёд.

UNII — Y9H1V576FH (honey); Z9305QFA72 (dandelion honey); W44S7N2P8P (rape honey).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Honey; Mel). It is produced by bees (*Apis mellifera*) from the nectar of plants or from secretions of living parts of plants, which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store, and leave in the honey comb to ripen and mature. If the bee has been exposed to treatment to prevent or cure diseases or to any substance intended for preventing, destroying, or controlling any pest, unwanted species of plants or animals, appropriate steps are taken to ensure that the levels of residues are as low as possible. It is an almost white to dark brown, viscous liquid which may be partly crystalline.

USNF 31: (Purified Honey). It is obtained by purification of honey from the comb of the bee, *A. mellifera* and all subspecies of *A. mellifera*. The honey is extracted by centrifugation, pressure, or other suitable procedures. Specific gravity 1.400 and 1.435 at 20 degrees. Store in airtight containers. It is not intended for infants under one year of age unless it is free from *Clostridium* spp.

Profile

Honey, which contains about 70 to 80% of glucose and fructose, is used as a demulcent and sweetening agent, especially in linctuses and cough mixtures (see Cough p. 1651.2). Preparations containing honey are used in the management of skin ulcers, wounds, and burns.

Contamination. Honey has been identified as a source of *Clostridium botulinum* spores and thus recommendations have been made that honey should not be given to infants under 1 year because of the risk of causing infant botulism.[1,2]

Honey produced from certain species of *Rhodoendron* plants has been found to contain grayanotoxins. Grayanotoxin I is responsible for honey poisoning, manifest as bradycardia, cardiac arrhythmias, hypotension, gastrointestinal disturbances, dizziness, loss of consciousness, blurred vision, chills, cyanosis, sweating, and salivation.[3,4] Convulsions have also been reported.[4]

1. Arnon SS, *et al*. Honey and other environmental risk factors for infant botulism. *J Pediatr* 1979; **94:** 331–6.
2. Tanzi MG, Gabay MP. Association between honey consumption and infant botulism. *Pharmacotherapy* 2002; **22:** 1479–83.
3. Özhan H, *et al*. Cardiac emergencies caused by honey ingestion; a single centre experience. *Emerg Med J* 2004; **21:** 742–4.
4. Dilber E, *et al*. A case of mad honey poisoning presenting with convulsion: intoxication instead of alternative therapy. *Turk J Med Sci* 2002; **32:** 361–2.

Cough. Honey has a long history of use in the management of cough (p. 1651.2), particularly in children, but as with many traditional cough remedies, evidence of its value is largely lacking.[1,2]

1. Mulholland S, Chang AB. Honey and lozenges for children with non-specific cough. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 10/06/10).
2. Oduwole O, *et al*. Honey for acute cough in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 10/06/10).

Wounds. Anecdotal reports and traditional usage dating back to ancient Egypt suggest that honey may be of some value as a wound dressing (p. 1690.1). Its antibacterial properties are attributed both to high osmolality and the liberation of hydrogen peroxide, but may vary with the source:[1-4] in Europe, some of the best activity has been seen with lime-flower honey.[2] Manuka honey (p. 2550.1) has been found to have high concentrations of methylglyoxyl, which correspond to a greater antibacterial activity *in vitro* than other honeys.[5] Sterilised manuka honey was reported to heal a leg ulcer infected with meticillin-resistant *Staphylococcus aureus*,[6] although a randomised open-label study found no evidence that dressings impregnated with manuka honey improved the healing of venous leg ulcers at 12 weeks compared with usual care.[7] However, a systematic review[8] concluded that there was no evidence of benefit from adjuvant use of honey with compression dressings in the treatment of leg ulcers. In a preliminary study, honey obtained from the tea plant (see Xanthine-containing Beverages, p. 2648.2) significantly reduced the incidence of grade 3 and 4 radiation-induced oral mucositis.[9]

A group from India[10] has reported that the properties of honey offer a potentially simple and cheap means of preserving skin grafts in developing countries, with 100% uptake of reconstituted grafts stored for up to 6 weeks and 80% uptake of those stored for 7 to 12 weeks. In comparison with sulfadiazine silver, occlusive honey dressings were also found to be more effective for the treatment of superficial partial thickness thermal burns,[11] and systematic reviews[8,12] have tended to confirm its benefits in aiding the healing of burns.

However, concern has been expressed since honey may contain not only chemical contaminants but clostridial spores (see also above), and it has been suggested[2] that to be medically acceptable, honey must be sterile, residue-free, and of measured antibacterial activity.

Sugar has been used similarly to honey in treating wounds (see p. 2097.2).

1. Greenwood D. Honey for superficial wounds and ulcers. *Lancet* 1993; **341:** 90–1.
2. Postmes T, *et al*. Honey for wounds, ulcers, and skin graft preservation. *Lancet* 1993; **341:** 756–7.
3. Molan PC. Re-introducing honey in the management of wounds and ulcers - theory and practice. *Ostomy Wound Manage* 2002; **48:** 28–40.
4. Booth S. Are honey and sugar paste alternatives to topical antiseptics? *J Wound Care* 2004; **13:** 31–3.
5. Mavric E, *et al*. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. *Mol Nutr Food Res* 2008; **52:** 483–9.
6. Natarajan S, *et al*. Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. *J Dermatol Treat* 2001; **12:** 33–6.
7. Jull A, *et al*. Honey as Adjuvant Leg Ulcer Therapy trial collaborators. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg* 2008; **95:** 175–82.
8. Jull AB, *et al*. Honey as a topical treatment for wounds. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 10/06/10).
9. Biswal BM, *et al*. Topical application of honey in the management of radiation mucositis: a preliminary study. *Support Care Cancer* 2003; **11:** 242–8.
10. Subrahmanyam M. Storage of skin grafts in honey. *Lancet* 1993; **341:** 63–4.
11. Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns* 1998; **24:** 157–61.
12. Wijesinghe M, *et al*. Honey in the treatment of burns: a systematic review and meta-analysis of its efficacy. *N Z Med J* 2009; **122:** 47–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Antibacterial Honey Barrier†; Medihoney Antibacterial Wound Gel; ***Ger.***: Infecto-Honey; ***India***: Crack Free; ***Indon.***: SanoSkin Melladerm Plus; ***Ital.***: Oramil; ***Neth.***: Natterman Melrosum; ***Rus.***: Geptrong (Гептронг); Kriomelt (Криомелт); ***UK***: Medihoney Antibacterial Wound Gel; Mesitran.

Multi-ingredient Preparations. ***Arg.***: Expectosan Hierbas y Miel; Farinop; Laxiruela; ***Braz.***: Expectomel; Melagriao; Melxi; Peitoral Martel; ***Canad.***: Honey Blend Herbal Cough Syrup; Mielocol†; ***Chile***: Fray Romano; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil†; Mielax†; Mielito; Paltomiel Plus; Paltomiel; Paltomiel; Propolkit; Propolkit; Pulmosina; Timuss-Kit; ***Fr.***: Aromadetox†; Aromavital†; Aromazen†; Feromiel†; Olioseptil Gorge-Larynx; Olioseptil Gorge-Larynx; Pharyndol; Pharyndol; Taido; ***Ger.***: InfectoHoney Alginat†; ***Hung.***: Doppelherz Energie Tonikum N; ***India***: Britesite; Evaren; Honitus; Kofarest-H; Moiste; ***Indon.***: BioStrath; Pectum; Sirec; ***Irl.***: Lemsip Dry Cough; Venos Honey & Lemon; ***Ital.***: Alvear con Ginseng; Apiserum con Telergon 1†; Bebimix†; Bioton; Bron 6; Faringel; Liozim; Nepiros; Nerex; Nutrigel; The Ginseng King†; ***NZ***: Robitussin Honey Cough†; ***Pol.***: Babicum; Melis-Tonic; ***Rus.***: Bronchicum Husten (Бронхикум Сироп от Кашля)†; Doppelherz Energotonik (Доппельгерц Энерготоник); Evalar (Эвалар); Kliophyt (Клиофит); Prostopine (Простопин); ***S.Afr.***: Choats Extract of Lettuce Cough Mixture†; Enzian Anaemodoron Drops†; ***Singapore***: Arkopharma Propolis Spray; ***Spain***: Novogumil; ***UK***: Adult Meltus for Chesty Coughs & Catarrh; Beehive Balsam; Buttercup Syrup (Honey and Lemon flavour); Feroglobin; Herb and Honey Cough Elixir; Honey & Molasses; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets Medicated Linctus; Lockets; M & M; Meltus Expectorant; Meltus Honey & Lemon; Potters Children's Cough Pastilles; Potters Gees Linctus; Regina Royal Five; Sanderson's Throat Specific; Throaties Pastilles; Venos Honey & Lemon; Zubes Honey & Lemon; ***Ukr.***: Huato Pills (Болюсы Хуато); ***Venez.***: Jengimiel Sabila; Jengimiel; Jengimiel; Viusid.

Homoeopathic Preparations. ***Chile***: Drosemiel; ***UK***: Fragador.

Invert Sugar

Azúcar invertido; Инвертный Сахар.

CAS — 8013-17-0.

ATC — C05BB03.

ATC Vet — QC05BB03.

UNII — ED9595S6ACY (maize invert sugar).

Pharmacopoeias. *Br.* and *US* include preparations of invert sugar.

Profile

Invert sugar is an equimolecular mixture of glucose and fructose which may be prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar has similar actions and uses to those of glucose (p. 2068.3) and fructose (p. 2068.2). It has been used as a 10% solution as an alternative to glucose in parenteral nutrition but, as with fructose, such use cannot be recommended.

A syrup of invert sugar is used as a stabilising agent; when mixed with suitable proportions of sucrose-based syrup it will help to prevent crystallisation of the sucrose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Fructodex.

Multi-ingredient Preparations. ***Hung.***: Doppelherz Energie Tonikum N; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); ***S.Afr.***: Emex; ***USA***: Travert.

Pharmacopoeial Preparations
BP 2014: Invert Syrup;
USP 36: Invert Sugar Injection; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3.

Iron

Demir; Eisen; Fer; Ferro; Ferrum; Hierro; Ijzer; Järn; Rauta; Żelazo; Železo; Железо.

Fe=55.845

CAS — 7439-89-6.

UNII — E1UOL152H7.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Iron for Homoeopathic Preparations; Ferrum ad Praeparationes Homoeopathicae). A fine, blackish-grey powder, without metallic lustre, obtained by reduction or sublimation. Practically insoluble in water and in alcohol; it dissolves with heating in dilute mineral acids.

Uses and Administration

Iron is an essential constituent of the body, being necessary for haemoglobin formation and for the oxidative processes of living tissues. Iron deficiency results in defective erythropoiesis and anaemia. Iron and iron salts should only be given for the treatment or prophylaxis of iron-deficiency anaemias (see below). They should not be given for the treatment of other types of anaemia except where iron deficiency is also present. Iron-deficiency anaemias respond readily to iron therapy but the underlying cause of the anaemia should be determined and treated.

The preferred route for giving iron is oral, usually as soluble ferrous salts which are better absorbed than ferric salts. The usual adult dose for the treatment of iron-deficiency anaemia is 100 to 200 mg of iron daily in divided doses. The usual adult prophylactic dose is about 60 to 120 mg of iron daily. For doses in children, see Administration in Children, below. Therapy is generally continued until haemoglobin concentrations reach normal values, which may take some weeks, and then for a further 3 months or more to restore body-iron stores.

Further information concerning the dosage of iron salts and compounds used is provided in the individual monographs; this information, however, tends to reflect the amounts of iron contained in different salts or available commercial preparations and therefore, in some instances, may not be within the general range of iron dosages as quoted above.

The iron content of various iron salts is tabulated in Table 1, below.

Modified-release dosage forms of iron are claimed to result in reduced gastrointestinal adverse effects and have the advantage of once-daily dosage. The preparations are designed to release the iron gradually along the gut but in some instances the iron may not be released until the preparation reaches a part of the gut where absorption is poor thus resulting in sub-optimal dosing.

Iron can also be given parenterally in circumstances where oral therapy cannot be undertaken and such use is typified by iron dextran (see p. 2075.3).

Administration in children. Iron is given orally to children to treat and prevent iron-deficiency anaemia (see below). There are various recommendations for children's doses but up to 2 mg/kg of iron three times daily for treatment and 1 to 2 mg/kg (usually to a maximum of 30 mg) daily for prophylaxis has been used.

Administration in the elderly. Patients over 80 years of age with iron-deficiency anaemia (below) were randomised to elemental iron therapy in daily doses of 15 mg, 50 mg (as liquid ferrous gluconate), or 150 mg (as tablets of calcium ferrous citrate) and treated for 2 months.[1] Serum haemoglobin and ferritin concentrations increased significantly in all patients, without significant differences between the 3 doses. The authors concluded that, while these results may not apply to patients with iron deficiency due to malabsorption, chronic disease, or untreated *Helicobacter pylori* infection, low-dose therapy is an effective option for elderly patients with iron-deficiency anaemia, in whom the adverse effects of iron could cause considerable morbidity and impaired compliance. Younger patients could also probably be treated effectively with low-dose iron therapy.

1. Rimon E, *et al.* Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005; **118:** 1142–7.

Table 1. Approximate amounts of different iron salts that supply 60 mg of elemental iron.

Iron salt	Amount
Ferrous ascorbate (anhydrous)	437 mg
Ferrous aspartate (tetrahydrate)	422 mg
Ferrous chloride (tetrahydrate)	214 mg
Ferrous fumarate (anhydrous)	183 mg
Ferrous gluconate (dihydrate)	518 mg
Ferrous succinate (anhydrous)	185 mg
Ferrous sulfate (dried)	186 mg
Ferrous sulfate (heptahydrate)	300 mg

Anoxic seizures. Reductions in the frequency of breath-holding episodes in children treated with iron,[1] and especially in those with iron-deficiency anaemia,[2,3] suggest that there might be a relationship between reflex anoxic seizures (p. 1311.3) and iron deficiency.[4] A systematic review[5] confirmed the apparent benefit of iron supplementation (5 mg/kg daily of elemental iron for 16 weeks) in reducing frequency and severity of attacks, particularly in children with iron-deficiency anaemia, in whom there appeared to be a trend to parallel improvements in breath-holding and haemoglobin values.

1. Daoud AS, *et al.* Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997; **130:** 547–50.
2. Mocan H, *et al.* Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999; **81:** 261–2.
3. Pedersen KW, Knudsen FU. Skal børn med affektkramper behandles med jern? *Ugeskr Laeger* 2004; **166:** 2789–91.
4. Hannon DW. Breath-holding spells: waiting to inhale, waiting for systole, or waiting for iron therapy? *J Pediatr* 1997; **130:** 510–12.
5. Zehetner AA, *et al.* Iron supplementation for breath-holding attacks in children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 09/06/10).

Cough. In a small study[1] of 19 patients, iron supplementation with ferrous sulfate successfully reduced the cough associated with ACE inhibitors (see p. 1285.3). The authors hypothesised that this effect was due to the inhibition by iron of nitric oxide synthase. However, there are some concerns[2] about the effect of giving a nitric oxide synthase inhibitor to hypertensive patients, as it has been found to increase blood pressure in *animal* studies.

1. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
2. Lev I, Rian AJJT. Iron supplementation in ACE inhibition as a treatment for cough: is it really inoffensive? *Hypertension* 2001; **38:** e38.

Iron-deficiency anaemia. The iron content of the body is normally kept constant by regulation of the amount absorbed to balance the amount lost. If loss is increased, and/or intake inadequate, a negative iron-balance may lead by degrees to depletion of body iron stores, iron deficiency, and eventually to anaemia. Iron requirements are increased during infancy, puberty, pregnancy, and during menstruation, and iron-deficiency anaemias are most common in women and children; the most common cause in adult males and postmenopausal women is blood loss, usually from the gastrointestinal tract.

Iron deficiency usually results in a microcytic, hypochromic anaemia, but the diagnosis of iron deficiency should be confirmed, if there is any doubt, by measurement of serum ferritin, erythrocyte protoporphyrin, or total iron binding capacity (transferrin). Iron therapy can begin once deficiency is confirmed, but the underlying cause of the deficiency should still be sought and treated.

Treatment. The prevention and control of iron-deficiency anaemias has been reviewed.[1-4] Almost all iron-deficiency anaemias respond readily to treatment with iron. The treatment of choice is an oral ferrous salt (ferrous iron is better absorbed than ferric iron).[1] Many iron compounds have been used for this purpose, but do not offer any real advantage over the simple ferrous fumarate, gluconate, or sulfate salts. The usual adult dose is sufficient of these salts to supply about 100 to 200 mg of elemental iron daily (for the elemental iron content of various iron salts, see Table 1, above), with the aim of increasing haemoglobin concentrations by about 1 g/litre daily or about 20 g/litre every 3 weeks.[1] Haemoglobin response is greatest in the first few weeks of therapy and is proportional to the severity of the original anaemia. Once haemoglobin concentrations have risen to the normal range, iron therapy should be continued for a further 3 months to aid replenishment of iron stores.[1,3] For the view that low-dose iron therapy may be as effective as higher doses, see Administration in the Elderly, above.

Oral iron has been given with agents such as ascorbic acid to enhance iron absorption, and modified-release preparations have been used in patients intolerant of ordinary formulations of iron but the *BNF* considers them to have no therapeutic advantage.

Failure to respond to oral iron after about 3 weeks of therapy may be indicative of non-compliance, continued blood loss with inadequate replacement of iron, malabsorption, wrong diagnosis, or other complicating factors, and the treatment should be reassessed.

Parenteral iron therapy is rarely indicated, may produce severe adverse effects, and should be reserved for patients who are genuinely intolerant of oral iron, persistently non-compliant,[3] who have gastrointestinal disorders exacerbated by oral iron therapy, continuing blood loss too severe for oral treatment to provide sufficient iron, or for those unable to absorb iron adequately from the gastrointestinal tract. Patients with chronic renal failure on haemodialysis (and some on peritoneal dialysis) require regular iron. US guidelines[5] suggest that intravenous use is preferred in haemodialysis patients, but that iron may be given either intravenously or orally in predialysis and peritoneal dialysis patients. The most common parenteral forms are iron dextran, iron sorbitol, iron sucrose, and sodium ferric gluconate complex.

Exceptionally, in patients with profound anaemia, blood transfusion may be necessary to restore dangerously low concentrations of haemoglobin. This may be the case, for example, in cases of worsening angina or severe coexisting pulmonary disease.[1] However, transfusion should always be avoided if possible.

Prophylaxis. Prophylaxis may be desirable in some groups at risk of iron deficiency and consequent anaemia, and may include therapy with oral iron supplements, measures to improve dietary iron intake, fortification of food staples, or control of infection. For the possible problems associated with iron supplementation in those who are not deficient, see Effects in Non-deficient Subjects, under Precautions, p. 2074.3.

WHO[2] recommends that universal supplementation of iron and folic acid should be implemented for pregnant women, starting as soon as possible after gestation starts and continuing for the rest of the pregnancy. WHO also recommends that where anaemia prevalence is above 40%, women of child-bearing age and lactating women should be given 3 months of iron and folic acid supplementation. However, the US Preventive Services Task Force has reviewed the subject of iron supplementation during pregnancy,[6] and concluded that there was insufficient evidence for or against routine supplementation.[7] A systematic review[8] found that weekly or daily antenatal iron supplementation, with or without folic acid, was effective at preventing anaemia and iron deficiency at term, although data on maternal and neonatal adverse outcomes such as low birth-weight, preterm birth, or postpartum haemorrhage were limited. Adverse effects, particularly haemoconcentration, (Hb greater than 130 g/litre) were associated with the use of iron; the authors considered that current preventative antenatal iron doses for use in developing countries appeared to be excessive. However, antenatal iron supplements may help reduce neonatal mortality in developing countries; a study[9] carried out in rural China found that antenatal iron and folic acid increased the duration of gestation, reduced preterm delivery, and reduced early neonatal mortality compared with folic acid alone. Antenatal micronutrients (supplementation with 15 minerals and vitamins including folic acid and a lower dose of iron) increased birth-weight compared with folic acid alone, but did not affect early neonatal mortality.

Iron supplementation is accepted in menorrhagia, after gastrectomy, and in the management of low birth-weight infants such as the premature. Iron deficiency in infants and children may result in developmental delay or impairment of cognitive function.[2] Breast feeding should be encouraged during the first year of life.[1] WHO has suggested[2] that low birth-weight infants be given universal supplementation. Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%, iron supplementation should be given to all children between 6 and 23 months of age; for children aged 24 months and above, a 3-month course of iron supplementation should be given where the anaemia prevalence is above 40%.

The usual prophylactic dose in adults suggested by WHO is about 60 mg of elemental iron daily (see also Uses and Administration above). Doses of about 2 mg/kg of elemental iron daily (up to 30 mg) have been suggested for prophylaxis in children (see also Administration in Children, above).

Dietary measures, such as addition of vitamin-C-rich foods, or other enhancers of iron absorption including iron in the form of haem (found in meat or fish) to the diet, control of parasitic infections such as hookworm (which are responsible for considerable occult blood loss), and malaria prophylaxis are particularly important for the general community in developing countries. Fortification of food staples poses technical problems as iron salts react with food components and may produce rancidity or other undesirable changes on storage. Nonetheless, wheat or maize flour, rice, and milk products have been fortified in some countries, and consideration has also been given to fortification of salt or sugar.

1. Provan D. Iron deficiency anaemia. In: Provan D, ed. *ABC of clinical haematology*. 2nd ed. London: BMJ Books, 2003: 1–4.
2. WHO. *Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers*. Geneva: WHO, 2001. Available at: http://www.who.int/entity/nutrition/publications/en/ida_assessment_prevention_control.pdf (accessed 11/07/06)
3. British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia (issued May 2005). Available at: http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf (accessed 09/11/05)
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; **370:** 511–20.
5. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 2006; **47** (suppl 3): S16–S85. Correction. *ibid.*; **48:** 518. Also available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm (accessed 04/12/06)

6. US Preventive Services Task Force. Routine iron supplementation during pregnancy: review article. *JAMA* 1993; **270:** 2848–54.
7. US Preventive Services Task Force. Routine iron supplementation during pregnancy: policy statement. *JAMA* 1993; **270:** 2846–8.
8. Peña-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron +folic acid supplementation for women during pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 03/02/10).
9. Zeng L, *et al.* Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. Abridged version: *BMJ* 2008; **337:** 1211–15. Full version: http://www.bmj.com/cgi/reprint/337/nov07_4/a2001 (accessed 16/03/09) Correction. *ibid.* a2522.

Restless legs syndrome. Iron deficiency is present in about a quarter of people with restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2), particularly older people, and serum ferritin concentrations are inversely correlated with the severity of symptoms. Iron may have a role in the pathophysiology of the disorder, and treatment of iron deficiency may reduce symptoms.[1]

1. Medcalf P, Bhatia KP. Restless legs syndrome. *BMJ* 2006; **333:** 457–8.

Adverse Effects

The astringent action of **oral** iron preparations sometimes produces gastrointestinal irritation and abdominal pain with nausea and vomiting. These irritant adverse effects are usually related to the amount of elemental iron taken rather than the type of preparation. Other gastrointestinal effects may include either diarrhoea or constipation. Adverse effects can be reduced by giving it with or after food (rather than on an empty stomach) or by beginning therapy with a small dose and increasing gradually. Modified-release products are claimed to produce fewer adverse effects but this may only reflect the lower availability of iron from these preparations. Oral liquid preparations containing iron salts may blacken the teeth and should be drunk through a straw. The faeces of patients taking iron salts may be coloured black.

The adverse effects associated with iron given **parenterally** are described under iron dextran (see p. 2076.1).

Since absorbed iron is conserved by the body, **iron overload**, with increased storage of iron in various tissues (haemosiderosis), may occur as a result of excessive or mistaken therapy, especially parenteral therapy. Patients with pre-existing iron storage or absorption diseases are also at risk.

Acute iron **overdosage** can be divided into four stages.

- In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting and diarrhoea, predominates. Other effects may include cardiovascular disorders such as hypotension, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally progress past this first phase.
- The second phase, which is not always seen, may occur at 6 to 24 hours after ingestion and is characterised by a temporary remission or clinical stabilisation.
- In the third phase, 12 to 48 hours after ingestion, gastrointestinal toxicity recurs together with shock, metabolic acidosis, severe lethargy or coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and possible myocardial dysfunction.
- The fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damage.

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that toxicity is likely with doses containing more than the equivalent of about 60 mg/kg of iron; the equivalent of 200 to 250 mg/kg iron is considered potentially fatal. Serum-iron concentrations have also been used as an indication of the severity of overdosage, see below.

Effects on the cardiovascular system. For a suggestion that iron overload may contribute to ischaemic heart disease, see Effects in Non-deficient Subjects, below.

Effects on growth. Iron supplementation in iron-replete children has been reported to adversely affect their growth—see Effects in Non-deficient Subjects, below.

Hypersensitivity. Oral iron supplements have been associated with hypersensitivity reactions; reports to Health Canada have included anaphylaxis and skin reactions such as rash, pruritus, urticaria, oedema, and photosensitivity.[1]

1. Health Canada. Oral iron supplements: skin reactions and other hypersensitivity reactions. *Can Adverse React News* 2010; **20** (3): 4–5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n3-eng.pdf (accessed 02/12/13)

Iron overload. Because the body lacks a mechanism for the excretion of excess iron, abnormally high absorption or repeated blood transfusion will result in iron overload (p. 1545.2), leading eventually to haemochromatosis. The consequences of haemochromatosis include pigment deposition in skin and other organs, mild liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up can lead to death, mainly through heart failure or arrhythmia. Where iron overload is due to increased absorption, phlebotomy is the treatment of choice; however, if phlebotomy is not tolerated or in patients who are transfusion-dependent (as in β-thalassaemia—see p. 1124.1) treatment with iron chelators such as desferrioxamine is used to retard accumulation.

Treatment of Adverse Effects

In treating acute iron poisoning, speed is essential to reduce absorption of iron from the gastrointestinal tract. Activated charcoal is ineffective, but whole bowel irrigation should be considered in those who have ingested the equivalent of more than 20 mg/kg of elemental iron within 6 hours of presentation. Serum-iron concentrations may be an aid to estimating the severity of poisoning. Although these do not always correlate well with symptoms, the UK Poisons Information Service considers that concentrations taken about 4 hours after ingestion generally indicate the severity of poisoning as follows:

- less than 3 micrograms/mL, mild poisoning
- 3 to 5 micrograms/mL, moderate poisoning
- more than 5 micrograms/mL, severe poisoning

Peak iron concentrations occur about 4 to 6 hours after ingestion.

Chelation therapy with desferrioxamine (p. 1544.1) can be considered for moderate to severe poisoning, and is guided by iron concentrations and symptoms. Iron concentrations should be measured when the patient presents, before chelation therapy is started. In patients with severe poisoning and symptoms such as coma or shock, desferrioxamine is given without waiting for the results of iron measurements. Desferrioxamine may also be considered in patients who are symptomatic and have a iron concentration above 5 micrograms/mL within 6 hours of ingesting more than 20 mg/kg iron. In asymptomatic patients with severe poisoning, those with moderate poisoning, or those presenting more than 6 hours after ingestion, further measurements of iron concentration determine the need for chelation.

Other measures include symptomatic management and treatment for metabolic acidosis (p. 1775.2). Haemodialysis does not remove iron efficiently but may be useful in acute renal failure to help remove the iron-desferrioxamine complex.

Maternal treatment of iron overdose should be as for the non-pregnant patient.

General references.

1. Proudfoot AT, *et al.* Management of acute iron poisoning. *Med Toxicol* 1986; **1:** 83–100.
2. Mann KV, *et al.* Management of acute iron overdose. *Clin Pharm* 1989; **8:** 428–40.
3. Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am* 1994; **12:** 397–413.
4. Fine JS. Iron poisoning. *Curr Probl Pediatr* 2000; **30:** 71–90.

Overdosage. References highlighting the specific problem of iron overdose in children.[1-4] Child-resistant packaging and warning labels may be helpful in reducing the problem.

1. Anonymous. Iron-containing drugs and supplements: accidental poisoning. *WHO Drug Inf* 1995; **9:** 159–60.
2. Fitzpatrick R, Murray V. Iron toxicity: dietary supplements. *Pharm J* 1996; **256:** 666.
3. CSM/MCA. Oral iron supplements: accidental overdose may be fatal in children. *Current Problems* 2001; **27:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 08/11/05)
4. Singhi SC, *et al.* Acute iron poisoning: clinical picture, intensive care needs and outcome. *Indian Pediatr* 2003; **40:** 1177–82.

Overdosage in pregnancy. Limited data on the treatment of iron overdose in pregnancy from the UK National Teratology Information Service, suggested that treatment with desferrioxamine should not be withheld if clinically indicated.[1-3] Most pregnancies had a normal outcome. A literature review[4] of iron overdose in pregnant women found that women with peak serum-iron concentrations greater than or equal to 4 micrograms/mL were more frequently symptomatic, but that there was no relationship between peak iron level and frequency of spontaneous abortion, preterm delivery, congenital anomalies, or perinatal or maternal death. However, women with stage 3 iron toxicity, defined as those manifesting with hepatic, renal, or cardiac failure, were more likely to spontaneously abort, deliver preterm, or die.

1. McElhatton PR, *et al.* The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 1991; **10:** 251–9.
2. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; **12:** 579.
3. McElhatton PR, *et al.* The outcome of pregnancy following iron overdose by the mother. *Br J Clin Pharmacol* 1998; **45:** 212P–213P.
4. Tran T, *et al.* Intentional iron overdose in pregnancy—management and outcome. *J Emerg Med* 2000; **18:** 225–8.

Precautions

Iron compounds should not be given to patients receiving repeated blood transfusions or to patients with anaemias not produced by iron deficiency unless iron deficiency is also present. Oral and parenteral iron therapy should not be used together. Care should be taken in patients with iron-storage or iron-absorption diseases such as haemochromatosis, haemoglobinopathies, or existing gastrointestinal diseases such as inflammatory bowel disease, intestinal strictures and diverticulae.

Liquid preparations containing iron salts should be well diluted with water and swallowed through a straw to prevent discoloration of the teeth.

Effects in non-deficient subjects. There has been concern about the potential consequences of iron supplementation in individuals and groups who are not actually iron-deficient. Apart from the suggestion that certain populations may be at somewhat increased risk of microbial *infection* after supplementation (see Infections, below), there is some evidence that supplementation in children without iron deficiency may *retard their growth*.[1,2] It has also been proposed that iron may be associated with *ischaemic heart disease*, by modifying low-density lipoprotein in ways which increase its atherogenic potential and by sensitising the myocardium to ischaemic injury.[3,4] However, conclusions of a cohort study[5] and a systematic review[6] did not support any correlation between iron status and coronary heart disease. There is some suggestion that an excess of iron may be *carcinogenic*;[7,8] conclusive studies are lacking.

1. Idjradinata P, *et al.* Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994; **343:** 1252–4.
2. Dewey KG, *et al.* Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. *J Nutr* 2002; **132:** 3249–55.
3. Burt MJ, *et al.* Iron and coronary heart disease: iron's role is undecided. *BMJ* 1993; **307:** 575–6.
4. Sullivan JL. Iron and coronary heart disease: iron makes myocardium vulnerable to ischaemia. *BMJ* 1993; **307:** 1066–7.
5. Sempos CT, *et al.* Serum ferritin and death from all causes and cardiovascular disease: the NHANES II Mortality Study. *Ann Epidemiol* 2000; **10:** 441–8.
6. Danesh J, Appleby P. Coronary heart disease and iron status: meta-analyses of prospective studies. *Circulation* 1999; **99:** 852–4.
7. Deugnier Y. Iron and liver cancer. *Alcohol* 2003; **30:** 145–50.
8. Huang X. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res* 2003; **533:** 153–71.

INFECTIONS. Iron is not only an essential element for humans but is also essential for many micro-organisms. Thus, it has been suggested that persons with either adequate iron stores or iron overload may provide optimum conditions for microbial growth and therefore be susceptible to an increased incidence and severity of infection; conversely, iron-deficiency anaemia may offer some protection against infections. The topic has been reviewed[1,2] and although there is no evidence that small amounts of iron supplements or iron-fortified food in normal people will render them more prone to infection[3] there is some evidence that in populations with a high prevalence of endemic infectious disease such as malaria, iron therapy may be followed by a higher incidence of infectious complications or by a flare-up of existing low-grade disease. Therefore, the routine use of iron supplements in such communities has been questioned,[4,5] although an increasing number of studies failed to show a detrimental effect.[6-10] A subsequent systematic review[11] concluded that, while iron supplementation slightly increases the risk of developing diarrhoea, it has no apparent harmful effect on the overall incidence of infectious illnesses in children. More recently, a controlled study found that supplementation with iron and folic acid increased the risk of severe illness and death in pre-school children in a population with high rates of malaria. The authors concluded that, while iron-deficient children can benefit from supplementation in the presence of active prophylaxis and treatment of malaria, supplementation in non-deficient subjects might be harmful.[12] Data conflict on the association between parenteral iron and infection in dialysis patients; some consider that treatment with parenteral iron should be avoided during active infection.[13,14]

1. Hershko C, *et al.* Iron and infection. *BMJ* 1988; **296:** 660–4.
2. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. *J Nutr* 2001; **131** (suppl): 616S–633S.
3. Bullen JJ, Ward CG. Iron and infection. *BMJ* 1988; **296:** 1539.
4. Oppenheimer SJ, *et al.* Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1986; **80:** 603–12.

5. Smith AW, *et al*. The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Ann Trop Paediatr* 1989; **9:** 17–23.
6. Harvey PWJ, *et al*. The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *Am J Trop Med Hyg* 1989; **40:** 12–18.
7. Boele van Hensbroek M, *et al*. Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; **89:** 672–6.
8. van den Hombergh J, *et al*. Does iron therapy benefit children with severe malaria-associated anaemia? A clinical trial with 12 weeks supplementation of oral iron in young children from the Turiani Division, Tanzania. *J Trop Pediatr* 1996; **42:** 220–7.
9. Menendez C, *et al*. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997; **350:** 844–50.
10. Mebrahtu T, *et al*. Low-dose daily iron supplementation for 12 months does not increase the prevalence of malarial infection or density of parasites in young Zanzibari children. *J Nutr* 2004; **134:** 3037–41.
11. Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002; **325:** 1142.
12. Sazawal S, *et al*. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006; **367:** 133–43.
13. Brewster UC, Perazella MA. Intravenous iron and the risk of infection in end-stage renal disease patients. *Semin Dial* 2004; **17:** 57–60.
14. Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. *Ann Pharmacother* 2007; **41:** 1476–80.

Interference with diagnostic tests. Although studies *in vitro* found that iron (ferrous sulfate) caused a false-positive result in the Hemoccult test for blood in faeces, this did not occur *in vivo* in persons receiving oral iron therapy.[1-3] An explanation for the difference in these findings was that hydrogen peroxide in the Hemoccult developer converted ferrous ions in solution to ferric ions, which caused oxidation in the test, whereas *in vivo* the iron was probably eliminated in the faeces in the form of non-reactive insoluble iron precipitates.[2]

1. Kulbaski MJ, *et al*. Oral iron and the Hemoccult test: a controversy on the teaching wards. *N Engl J Med* 1989; **320:** 1500.
2. McDonnell M, Elta G. More on oral iron and the Hemocculttest. *N Engl J Med* 1989; **321:** 1684.
3. Anderson GD, *et al*. An investigation into the effects of oral iron supplementation on in vivo Hemoccult stool testing. *Am J Gastroenterol* 1990; **85:** 558–61.

Porphyria. Erythropoietic protoporphyria was exacerbated by oral iron therapy in 4 patients;[1] a further patient had a variable reaction to iron, being able to tolerate it on some occasions but suffering from exacerbation of porphyria on others.[2] Intravenous iron precipitated porphyria cutanea tarda in one patient on haemodialysis.[3]

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, offers classifications and recommendations for various iron preparations — see Ferrous Fumarate (p. 2061.1), Ferrous Gluconate (p. 2061.2), Ferrous Succinate (p. 2062.1), Ferrous Sulfate (p. 2062.2), and Iron Sucrose (p. 2078.2).

1. Milligan A, *et al*. Erythropoietic protoporphyria exacerbated by oral iron therapy. *Br J Dermatol* 1988; **119:** 63–6.
2. McClements BM, *et al*. Erythropoietic protoporphyria and iron therapy. *Br J Dermatol* 1990; **122:** 423–6.
3. McKane W, *et al*. Porphyria cutanea tarda precipitated by intravenous iron in a haemodialysis patient. *Nephrol Dial Transplant* 2001; **16:** 1936–8.

Interactions

Iron salts are not well absorbed orally, and food may further impair their absorption.

Compounds containing calcium and magnesium, including antacids and mineral supplements, and bicarbonates, carbonates, oxalates, or phosphates, may impair the absorption of iron by the formation of insoluble complexes. Zinc salts may also decrease the absorption of iron. The absorption of both iron salts and tetracyclines is diminished when taken together orally. If treatment with both drugs is required, a time interval of about 2 to 3 hours should be allowed between them. A suitable interval is also advised if an iron supplement is needed in patients given trientine. Iron is chelated by acetohydroxamic acid, reducing the absorption of both. Iron should not be given with dimercaprol as toxic complexes may form.

The response to iron may be delayed in patients receiving systemic chloramphenicol.

Some agents, such as ascorbic acid and citric acid, may actually increase the absorption of iron.

In addition to those already mentioned, iron salts can also decrease the absorption of other drugs and thus reduce their bioavailability and clinical effect. Drugs so affected include cefdinir, bisphosphonates, entacapone, fluoroquinolones, levodopa, methyldopa, mycophenolate mofetil, and penicillamine. Iron salts may reduce the efficacy of levothyroxine (p. 2342.1).

Interactions with parenteral iron are mentioned under Iron Dextran, p. 2077.1.

Reviews.

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; **31:** 251–5.

Pharmacokinetics

Iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and by some dietary acids (such as ascorbic acid) and occurs more readily when the iron is in the ferrous state or is part of the haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if the body stores are overloaded. Normally only about 5 to 15% of the iron ingested in food is absorbed.

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin; the remainder is contained within the storage forms, ferritin (p. 2060.2) or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin.

Only very small amounts of iron are excreted as the majority released after the destruction of the haemoglobin molecule is re-used. This conservation of body iron, and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive iron therapy or repeated transfusions.

General references.

1. Harju E. Clinical pharmacokinetics of iron preparations. *Clin Pharmacokinet* 1989; **17:** 69–89.

Human Requirements

The body contains about 4 g of iron most of which is present as haemoglobin.

Apart from haemorrhage, iron is mainly lost from the body in the faeces, urine, from skin, and sweat, but the total loss is very small. Iron is also lost in small amounts in breast milk and in menstrual blood. In healthy men and postmenopausal women the loss is replaced by the absorption of about 1 mg of iron daily; about 1.5 to 2 mg needs to be absorbed daily by premenopausal women. In childhood and adolescence, the need is proportionately greater because of growth. Iron absorption is variable but is usually between 5 and 15% and therefore a dietary allowance containing the equivalent of about 10 mg of iron daily is usually sufficient for men and postmenopausal women; up to 15 mg daily may be necessary for premenopausal women with normal menstrual blood losses; some authorities recommend higher amounts or supplements during pregnancy. For further details concerning dietary requirements, see below and for a discussion of prophylactic iron given during pregnancy, see Iron-deficiency Anaemia, under Uses and Administration, p. 2073.2.

Good dietary sources of haem-iron are animal products such as meat and fish; non-haem-iron is also found in animal products and in vegetable products such as legumes and some leafy vegetables, but some vegetable products with a high iron content also contain phosphates or phytates which inhibit absorption by the formation of unabsorbable complexes.

UK and US recommended dietary intake. In the UK, dietary reference values (DRV)[1] and in the USA, recommended dietary allowances (RDA)[2] have been published for iron.

In the UK the estimated average requirement (EAR) for adult males and postmenopausal females is 6.7 mg daily and the reference nutrient intake (RNI) is 8.7 mg daily; for premenopausal females, but without heavy menstrual blood losses, the EAR and RNI are 11.4 and 14.8 mg daily respectively. Amounts for infants, children, and adolescents, which are proportionately higher than those for adults, are also given. No increase is considered necessary during pregnancy or lactation.[1]

In the USA the RDA for adult males and postmenopausal females is 8 mg daily and that for premenopausal women is 18 mg. The tolerable upper intake level is 45 mg daily. Amounts for infants, children, and adolescents, again proportionately higher than for adults, are also provided. The RDA for pregnant women is 27 mg daily. An RDA of 9 mg for lactating adult women has been estimated from the EAR of non-menstruating women plus the average iron content of human milk.[2]

The Food and Agriculture Organization of the United Nations and the WHO have together published guidelines concerning iron requirements and these take into account many factors including bioavailability of iron in the diet.[3]

For the definitions of DRV, EAR, RNI, and RDA, see under Vitamins, p. 2046.1.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. FAO/WHO. *Requirements of vitamin A, iron, folate and vitamin B_{12}: report of a joint FAO/WHO expert consultation*. Rome: Food and Agriculture Organization of the United Nations, 1988.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Myrafer; ***Canad.***: Gento-Iron†; ***Hong Kong***: Hausmann Ferrum†; ***India***: Biofer; Eleron; Evaglow; Fegem; Fejet-IV; Ferisan-S; Feritin; Ferium; Feriz; Fesafe; Folinal Plus; HB Fast; Orofer; Phosfomin Iron; ***Indon.***: Ferromia†; ***Israel***: Ferrocal; ***Ital.***: Profer; ***Jpn***: Ferromia; ***Malaysia***: Ferrocyte; ***Mex.***: Unifer; ***Singapore***: Ferrocyte; ***Thai.***: Ferrocyte†; ***USA***: EZFE; Icar; iFerex; Ircon; ProFe; Wee Care.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Hangover Relief; ***Austria***: Dalektro; ***Canad.***: Formula FA 224†; ***Chile***: Ikoplex No 2; ***Cz.***: Ferrum Homaccord†; ***Fr.***: Ferrum Complexe No 29; ***Ger.***: Conva-cyl Ho-Len-Complex; Cranio-cyl Ho-Len-Complex; Delto-cyl Ho-Len-Complex; Nuxal comp; ***Neth.***: Biodoron; Emvita 11; Geovita.

Pharmacopoeial Preparations

USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Iron Dextran

Complejo de hierro dextrano; Demir Dekstran; Hierro dextrano; Iron-Dextran Complex; Железо-Декстрановый Комплекс.

CAS — 9004-66-4.

ATC Vet — QB03AB90; QB03AC90.

UNII — 95HR524N2M.

Pharmacopoeias. *Br.*, *Chin.*, and *US* include injections.

BP 2014: (Iron Dextran Injection). A sterile colloidal solution containing a complex of ferric hydroxide and dextrans of weight average molecular weight between 5000 and 7000. It contains 4.75 to 5.25% of iron and 17.0 to 23.0% of dextrans. pH 5.2 to 6.5.

USP 36: (Iron Dextran Injection). A sterile colloidal solution of ferric hydroxide in complex with partially hydrolysed dextran of low molecular weight. It may contain not more than 0.5% of phenol as a preservative. pH 5.2 to 6.5.

Uses and Administration

Iron dextran is given by injection, and should be used only in the treatment of proven iron-deficiency anaemia (p. 2073.2) where oral therapy is ineffective or impracticable.

For iron-deficiency anaemia, total dosage is **calculated** according to the haemoglobin concentration and body-weight of the patient; allowance is also made for additional iron to replenish iron stores. Iron dextran injection is usually supplied with a table from which the recommended dose can be obtained for patients of different weights and haemoglobin (Hb) status. There may be variations between countries in the doses obtained from such tables. Doses can also be calculated from various formulas. A typical formula used for a preparation containing the equivalent of 50 mg/mL of iron is:

$$\text{Dose in mL} = \{0.0442 \times \text{body-weight (kg)} \times [\text{desired Hb level (g/100 mL)} - \text{measured Hb level}]\} + (0.26 \times \text{body-weight})$$

In adults, the calculated lean body-weight should normally be used in this formula rather than the actual body-weight. Note that doses obtained from tables or the above formulas are for iron-deficiency anaemia, and are not suitable for iron replacement for simple blood loss.

Before starting therapy, some licensed product information recommend a **test** dose via the intended route with observation for adverse reactions, but see Hypersensitivity (p. 2076.2) for a discussion of the value of such doses.

The total dose requirement may be given as a series of **intramuscular** injections daily or once or twice weekly. It is given by deep intramuscular injection into the upper outer quadrant of the buttock; to prevent leakage along the injection track, the subcutaneous tissue is drawn to one side before the needle is inserted. Before the first therapeutic dose, a test dose may be given and the patient observed for at least 1 hour: a dose of 0.5 mL (25 mg) has been suggested.

Thereafter, up to 2 mL (100 mg) may be given daily until the required dose is reached.

Iron dextran is also given **intravenously** either by total-dose infusion (TDI) or as divided injections. US licensed product information recommends that a test dose of 25 mg is given before the first therapeutic dose and that the patient is observed for at least 1 hour; if no adverse reactions occur within that time, the remainder of the initial dose may be given. In the UK, the first portion of every dose is given more slowly than the remainder of the dose, during which time the patient is observed for adverse reactions; recommendations for the rate at which this is done may vary in different countries.

In total-dose infusion, the total dose calculated according to the haemoglobin concentration (as outlined above) is given by slow intravenous infusion in about 500 mL of sodium chloride 0.9% or glucose 5%; sodium chloride may be preferable because of the reduced incidence of thrombophlebitis. The first 25 mg of iron should be infused over 5 to 15 minutes. UK licensed product information recommends that if no adverse reaction has occurred during this time the rate of infusion may be increased progressively to 45 to 60 drops/minute; the infusion usually takes 4 to 6 hours.

For divided intravenous use, the total dose is also calculated according to the haemoglobin concentration. In the UK, the usual recommended dosage schedule is 100 to 200 mg of iron given 2 or 3 times weekly until the total dose has been given. It may be given diluted in 10 to 20 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given slowly over 1 to 2 minutes. If no adverse reactions occur within 15 minutes, the remaining portion of the dose is given. Alternatively, 100 to 200 mg may be diluted in 100 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given over 15 minutes and if no adverse reactions occur during this time, the remaining portion of the infusion is given at a rate of not more than 100 mL in 30 minutes. In the USA, the injection may be given undiluted at a rate not exceeding 50 mg iron (1 mL) per minute; maximum daily doses are similar to those given for intramuscular injection.

For use in children, see Administration in Children, below.

Administration in children. In some countries, including the USA, iron dextran is licensed in children from 4 months of age to treat iron-deficiency anaemia (p. 2073.2) when oral therapy is not possible or ineffective. The total dose is calculated according to the haemoglobin concentration and body-weight of the child. Licensed product information usually contains a table with doses for patients of different weights and haemoglobin status. A formula can also be used to calculate the dose; an example is given in Uses and Administration, p. 2075.3.

Iron dextran is usually given as a series of daily deep intramuscular injections until the required dose is reached, but it may also be given as a series of daily slow intravenous injections. A total dose intravenous infusion may be used in some countries. Before starting therapy, some licensed product information recommend a test dose given via the intended route and the child observed for adverse reactions, but see Hypersensitivity (below) for a discussion of the value of such doses. The following test doses have been suggested according to body-weight:

- less than 10 kg: 0.2 mL (10 mg)
- 10 to 20 kg: 0.3 mL (15 mg)
- over 20 kg: 0.5 mL (25 mg), as for adults

Provided no untoward reaction occurs a therapeutic dose may then be given. If a test dose is not given, the first portion of every dose is administered more slowly than the remainder, and the patient observed for adverse effects.

When giving iron dextran as a series of divided intravenous or intramuscular injections, the following daily doses have been suggested as a maximum, according to body-weight, continued until the total dose has been given:

- under 5 kg: 0.5 mL (25 mg)
- 5 up to 10 kg: 1 mL (50 mg)
- 10 kg or more: as for adults, p. 2075.3

Adverse Effects and Treatment

Severe anaphylactoid reactions may occur with iron dextran and fatalities have been reported. It is therefore recommended that it be given where there are facilities for the emergency treatment of such reactions and that certain precautions be observed; the value of a test dose has been questioned (see Precautions, below for further details).

Rapid intravenous use may be associated with vascular flushing and hypotension. Thrombophlebitis may occur at the site of injection, although the incidence can be reduced by giving iron dextran in sodium chloride 0.9% rather than glucose 5%. Intramuscular injection is associated with local reactions, pain, and staining at the site of injection; leakage along the injection track may occur unless the proper technique is used (see Uses and Administration, p. 2075.3). Cardiovascular effects such as chest pain or tightness, shock, myocardial infarction, hypertension, tachycardia, bradycardia, and arrhythmias may occur with either route. Rashes, urticaria, purpura, and pruritus have been reported. Other reactions include gastrointestinal disturbances, haematuria, dyspnoea, and taste disturbance.

Patients may also have delayed reactions 1 to 2 days after injection of iron dextran, such as backache, arthralgia, myalgia, lymphadenopathy, chills, fever, paraesthesia, dizziness, malaise, headache, nausea, and vomiting.

Overdose of parenteral iron is unlikely to be associated with any acute manifestations. Unwarranted parenteral iron therapy will result in iron overload and excess storage of iron (haemochromatosis) in the long term. The consequences of this include liver and endocrine dysfunction and heart disease (see Iron Overload, p. 2074.2), and possibly an increased risk of infection (see Infections, under Precautions for Iron, p. 2074.3). Iron overload may require chelation therapy with desferrioxamine (p. 1544.1).

Intramuscular injection of iron complexes such as iron dextran has resulted in sarcomas at the injection site in *animals*. There is some evidence that this may occur in humans.

Incidence of adverse effects. For information about the incidence of adverse effects and comparison of the safety profiles of different intravenous iron products, see Hypersensitivity, below.

Effects on the blood. A 1-year-old girl with Down's syndrome and iron-deficiency anaemia was given 3 intramuscular injections of iron dextran over 6 days (to a total of 30 mg/kg). Pancytopenia, which developed subsequently, reappeared when challenged with iron dextran. Tests indicated an allergic pathogenesis for the pancytopenia.[1] For further discussion of hypersensitivity reactions to iron dextran, see under Hypersensitivity, below.

Thrombocytopenia has also been reported after iron dextran[2] and iron sucrose[3] therapy.

1. Hurvitz H, *et al*. Pancytopenia caused by iron-dextran. *Arch Dis Child* 1986; **61:** 194–6.
2. Go RS, *et al*. Thrombocytopenia after iron dextran administration in a patient with severe iron deficiency anemia. *Ann Intern Med* 2000; **132:** 925.
3. Taskapan H, *et al*. Transient severe thrombocytopenia in a patient on CAPD after intravenous iron administration. *Perit Dial Int* 2003; **23:** 408–9.

Hypersensitivity. The Boston Collaborative Drug Surveillance Program monitored consecutively 32 812 medical inpatients. Drug-induced anaphylaxis occurred in 1 of 169 patients given iron dextran (route not stated).[1] An investigation of 481 persons given a total of 2099 intravenous injections of iron dextran found 3 life-threatening immediate anaphylactoid reactions; 8 severe delayed reactions were also observed, and many reactions of a less serious nature.[2] In a more recent series,[3] 10 of 573 patients had anaphylactoid reactions after intravenous iron dextran. Other serious reactions included 1 case of cardiac arrest, and 3 cases of dyspnoea, hypertension, or chest pain.

Licensed product information may recommend a test dose before giving a full therapeutic dose (see Uses and Administration, p. 2075.3); however, hypersensitivity reactions have still occurred when doses were previously tolerated, and the EMA does not consider a test dose a reliable way to predict how the patient will respond.[4] A desensitisation protocol has been used successfully in a patient who reacted to the test dose[5] and in a patient with a previous life-threatening reaction to iron infusion;[6] methylprednisolone 50 mg was given intravenously at 13 hours, 7 hours, and 1 hour before iron dextran, and diphenhydramine 50 mg and ephedrine 25 mg were given intramuscularly 1 hour before infusion. Dextran 1 (p. 1137.3) was given just before the iron dextran infusion. Approximately 2 g of iron was then given over a period of about 4 days.

It is not clear whether hypersensitivity to iron dextran is due to the dextran or the iron component.[7-9] When compared with lower molecular-weight iron dextran, a higher molecular-weight iron dextran was reported to be associated with significantly higher rates of adverse reactions,[8,10,11] including fatalities and anaphylactoid reactions;[10] some have called for the use of high-molecular-weight iron dextran to be abandoned.[12] Reviews[7,9,13,14] suggest that parenteral dextran-free iron compounds such as iron sucrose or sodium ferric gluconate complex may be safer alternatives to iron dextran. Iron sucrose has been reported to be well tolerated in patients previously intolerant to iron dextran, sodium ferric gluconate complex, or both.[15,16] Iron sucrose was considered to have the most favourable safety profile when compared with iron dextran and sodium ferric gluconate;[14] a comparison of adverse reaction rates found that iron sucrose and sodium ferric gluconate had much lower rates of adverse effects than iron dextran or ferumoxytol.[17] However, adverse reactions have still been reported in patients treated with dextran-free preparations,[9,18] and some have challenged the view that they are safer than iron dextran.[19,20]

In a report of a lupus-like disorder associated with use of iron dextran,[21] the illness resolved with appropriate treatment but recurred on rechallenge.

Due to the risk of severe hypersensitivity reactions, use of intravenous iron products is restricted during pregnancy, see Pregnancy, p. 2077.1.

For discussion of pancytopenia believed to have an underlying allergic pathogenesis, see Effects on the Blood, above.

1. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; **i:** 587–8.
2. Hamstra RD, *et al*. Intravenous iron dextran in clinical medicine. *JAMA* 1980; **243:** 1726–31.
3. Fishbane S, *et al*. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; **28:** 529–34.
4. EMA. New recommendations to manage the risk of allergic reactions with intravenous iron-containing medicines (issued 28th June, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf (accessed 02/12/13)
5. Monaghan MS, *et al*. Safe administration of iron dextran to a patient who reacted to the test dose. *South Med J* 1994; **87:** 1010–12.
6. Hickman MA, *et al*. Successful administration of iron dextran in a patient who experienced a life threatening reaction to intravenous iron dextran. *Ann Allergy Asthma Immunol* 2000; **84:** 262–3.
7. Fishbane S. Safety in iron management. *Am J Kidney Dis* 2003; **141** (suppl): S18–S26.
8. McCarthy JT, *et al*. Adverse events in chronic hemodialysis patients receiving intravenous iron dextran—a comparison of two products. *Am J Nephrol* 2000; **20:** 455–62.
9. Fishbane S, Kowalski EA. The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate. *Semin Dial* 2000; **13:** 381–4.
10. Chertow GM, *et al*. On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004; **19:** 1571–5.
11. Auerbach M, *et al*. Clinical update: intravenous iron for anaemia. *Lancet* 2007; **369:** 1502–4.
12. Auerbach M, Rodgers GM. Intravenous iron. *N Engl J Med* 2007; **357:** 93–4.
13. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol* 2004; **76:** 74–8.
14. Coppol E, *et al*. A comparative look at the safety profiles of intravenous iron products used in the hemodialysis population. *Ann Pharmacother* 2011; **45:** 241–7.
15. Charytan C, *et al*. Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; **96:** c63–c66.
16. Haddad A, *et al*. Use of iron sucrose in dialysis patients sensitive to iron dextran. *Saudi J Kidney Dis Transpl* 2009; **20:** 208–11.
17. Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health-Syst Pharm* 2012; **69:** 310–20.
18. Saadeh CE, Srkalovic G. Acute hypersensitivity reaction to ferric gluconate in a premedicated patient. *Ann Pharmacother* 2005; **39:** 2124–7.
19. Eichbaum Q, *et al*. Is iron gluconate really safer than iron dextran? *Blood* 2003; **101:** 3756–7.
20. Auerbach M, Al Talib K. Low-molecular weight iron dextran and iron sucrose have similar comparative safety profiles in chronic kidney disease. *Kidney Int* 2008; **73:** 528–30.
21. Oh VMS. Iron dextran and systemic lupus erythematosus. *BMJ* 1992; **305:** 1000.

Overdosage. A 29-year-old woman was given 32 mL iron dextran (*Imferon*) intravenously. Twenty-four hours later she developed muscle cramps, bilateral frontal headaches, with subsequent neck stiffness, and marked opisthotonia with photophobia.[1] The haemoglobin concentration did not rise after the infusion of iron which indicated there had been no iron deficiency. Thus, abnormally high concentrations of free iron had followed the iron therapy and this free iron was able to cross into the CSF and was responsible for the meningitic symptoms.

1. Shuttleworth D, *et al*. Meningism due to intravenous iron dextran. *Lancet* 1983; **ii:** 453.

Precautions

Iron dextran is contra-indicated in patients with severe liver damage or acute kidney infection. It is also contra-indicated in persons with a history of hypersensitivity to the preparation. Teratogenicity has been found in non-anaemic *animals* given the equivalent of about three times the maximum human dose and its use is restricted in pregnancy (see p. 2077.1).

Additionally, iron dextran should be given with caution to patients with a history of allergic disorders or asthma and in these patients the intramuscular, and not the intravenous, route should be used. Patients with rheumatoid arthritis may develop worsening of symptoms when given iron dextran intravenously. Patients with other inflammatory disorders may be at increased risk of delayed reactions. Large doses of iron dextran by infusion may lead to serum discoloration; this should not be mistaken as evidence of haemolysis. Oral iron salts should be stopped before giving parenteral iron.

Intravenous iron preparations should only be given when resuscitation facilities are available to treat allergic reactions immediately. Some licensed product information recommend a test dose before a full therapeutic dose (see Uses and Administration p. 2075.3), but see Hypersensitivity (above) for a discussion of the value of such doses.

Patients should be kept under observation for at least 30 minutes after intravenous doses.

Iron dextran formulated with phenol as a preservative is intended to be given by the intramuscular route only.

Pregnancy. Severe hypersensitivity reactions to intravenous iron products used during pregnancy can put both the mother and unborn child at risk, and the EMA recommends treatment should be confined to the second or third trimesters, provided the benefit outweighs the risk to the unborn child.[1]

1. EMA. New recommendations to manage the risk of allergic reactions with intravenous iron-containing medicines (issued 28th June, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf (accessed 02/12/13)

Interactions

As for Iron, p. 2075.1.

Enalapril. Enalapril may possibly potentiate the adverse systemic reactions seen with intravenous iron therapy.[1]

1. Rolla G, *et al.* Systemic reactions to intravenous iron therapy in patients receiving angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* 1994; **93:** 1074–5.

Pharmacokinetics

After intramuscular injection iron dextran is absorbed primarily through the lymphatic system: most is absorbed after 3 days and the remainder over 3 to 4 weeks. A variable portion may become fixed in the muscle for several weeks or months. After intravenous infusion, iron dextran is taken up by the cells of the reticuloendothelial cells, particularly in the liver and spleen. The reticuloendothelial cells gradually separate iron from the iron-dextran complex; the distribution and elimination of iron is described on p. 2075.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cosmofer; Fexiron; Intrafer; Yectafer; ***Austria***: Cosmofer; ***Belg.***: Fercayl; ***Canad.***: DexIron; Infufer; ***China***: CosmoFer (科莫非); ***Denm.***: Cosmofer; ***Fin.***: Cosmofer; ***Fr.***: Ferrisat; ***Ger.***: Cosmofer†; ***Gr.***: Cosmofer; Ironate; Multiferrum; ***India***: Ferri; Imferon; ***Indon.***: Cosmofer; Hibiron†; ***Irl.***: Cosmofer; ***Mex.***: Driken†; Ferrocel; Ferroin; Hidex; Irondex; ***Neth.***: Cosmofer; ***Norw.***: Cosmofer; ***Philipp.***: Cosmofer; ***Port.***: Cosmofer; ***S.Afr.***: Cosmofer; ***Spain***: Cosmofer; ***Swed.***: Cosmofer; ***Switz.***: Ferrum Hausmann; ***Thai.***: Cosmofer; Unodex; ***Turk.***: Cosmofer; ***UK***: Cosmofer; ***Ukr.***: Ferrolecum (Ферролек); ***USA***: DexFerrum; INFeD; ***Venez.***: Cosmofer.

Multi-ingredient Preparations. ***Arg.***: Yectafer Complex; ***India***: Imferon F-12.

Pharmacopoeial Preparations
BP 2014: Iron Dextran Injection;
USP 36: Iron Dextran Injection.

Iron Phosphate

Ferri Phosphas; Ferric Phosphate; Iron Orthophosphate; Железа Фосфат.

FePO4=150.8

CAS — 10045-86-0.

UNII — N6BAA189V1.

Pharmacopoeias.

Br. includes forms for homoeopathic preparations.

BP 2014: (Hydrated Iron(II) and Iron(III) Phosphate for Homoeopathic Preparations). A mixture of hydrated iron(II) phosphate and iron(III) phosphate and some hydrated oxides of iron. It contains not less than 16.0% of Fe^{2+}, equivalent to not less than 47.9% of $Fe_3(PO_4)_2$, $8H_2O = 501.6$. A slate blue amorphous powder. Insoluble in water; soluble in hydrochloric acid. Protect from light.

BP 2014: (Hydrated Iron(III) Phosphate for Homoeopathic Preparations). It consists of $FePO_4.4H_2O = 222.9$. A yellow to pale ochre powder. Insoluble in water; soluble in dilute mineral acids. Protect from light.

Profile

Iron phosphate is used as a source of iron in food supplements. It is also used as a molluscicide and is an ingredient in some fertilisers.

Homoeopathy

Iron phosphate has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Celloids IP 82†.

Multi-ingredient Preparations. ***Austral.***: Celloid Compounds Magcal Plus†; Celloid Compounds Sodical Plus†; Duo Celloids CPIP†; Duo Celloids PCIP†; Duo Celloids PPIP†; Duo Celloids SPIP†; Hernidisc; Irontona†; Prosta Balance; Vitatona†.

Homoeopathic Preparations. ***Austral.***: Earache Relief†; Pain & Fever Relief; Respatona Sore Throat; ***Austria***: Aflubin; China Med Complex; Ferrum Phosphoricum comp; Globuli gegen Fieber und Grippe Nr 1; Globuli gegen Grippe; Metavirulent; Osanit Zahnungskugelchen; Proagil; Rheuma; Zahnkugelchen; ***Canad.***: Artis-Heel†; Biochemic Phosphates; Calms Forte; Calnor†; Camilia; Combinaison†; Comp-Drops 5 Expectorant†; Den 141†; Diamite; Drosera Complex; Drosera Plex†; Earache; Homeovox; Hylands Bioplasma; Hylands Formula CF; Hylands Formula NT; Ikoplex 11 Digestion Aid†; Ikoplex 21†; Kids' Earache; Melange†; Minerals+; Nerve Tonic; Nuage Bioplasma†; Rexorubia†; Ton 1 Complex†; ***Chile***: Ikoplex No 11; Ikoplex No 18; Ikoplex No 19; Ikoplex No 21; Ikoplex No 22; Ikoplex No 23; Ikoplex No 7; Ikoplex No 8; Influk; ***Cz.***: Drosetux; Ferrum Homaccord†; Homeovox; ***Fr.***: Aconitum Compose†; Boripharm No 1†; Drosera Compose; Drosetux; Homeovox; Infludo; Ipeca Compose; Jenoverine†; Kalium Phosphoricum Complexe No 100; Rexorubia; Selenium Complexe No 99; Silicea Complexe No 11; ***Ger.***: Arthriplex; Cefasinu; Drufusan N†; Drufusan; Ferrum phosphoricum comp; Grippe-Gastreu S R6; Immunorell; Infifer N; metavirulent; Naranotox comp; Naranotox; Osanit; phono Gripp; Poly-Arthrisan M; Pulmosan Infekt; Ranocalcin HM; Refesan T; Secale-Gastreu; Sinfrontal; toxi-loges; ***Hung.***: Aflubin; Drosetux; Homeovox; ***Neth.***: Auriculite; Grippe-Gastreu R6; Hemorrolite; Homeovox; Jenoverine†; Kind 0-3 Chamodent; Kind 0-6 Kinditherm; Oteel H; Rhodolith-Gastreu R46; Rhumeel; ***Port.***: Homeovox; ***Rus.***: Aflubin (Афлубин); Anabar (Анабар); Homeovox (Гомеовокс); ***S.Afr.***: Ferrum Phos Comp†; ***Switz.***: Drosetux; Homeovox; Influaforce†; Lithiumeel; metavirulent; Omida comprimes homeopathiques pour la gorge; Regenaplex Nr 41a; Rheuma-Heel; Sinfrontal; Sinusin; ***UK***: Fragador; New Era Elasto; ***Ukr.***: Aflubin (Афлубин); Dentokind (Дентокинд); Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Homeovox (Гомеовокс); ***USA***: Preferred Remedies Cold & Flu.

Iron Polymaltose

Demir III Hidroksit Polimaltoz; Ferromaltose; Ferrum Polyisomaltose; Hierro polimaltosa; Железа (III) Гидроксид Полимальтозат.

UNII — UM5219H89V.

Profile

Iron polymaltose is a complex of ferric hydroxide and isomaltose. It is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in usual doses containing the equivalent of 100 mg of iron daily although up to 300 mg daily has been given in some countries. It is also given parenterally, the total dose being calculated and given by intravenous infusion or, preferably, as a series of intramuscular injections containing the equivalent of up to 200 mg of iron in a single day; injections are usually given only every few days. For further information relating to the parenteral use of iron, see Iron Dextran, p. 2075.3.

Iron isomaltoside 1000 is a complex of ferric iron and isomaltosides derived from the low-molecular-weight dextran fraction dextran 1 (p. 1137.3) that is given intravenously; it is used similarly to iron polymaltose for iron-deficiency anaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ferranin; Maltofer; Siderblut Poli; Siderblut; Vitalix; ***Austral.***: Ferrosig; Ferrum H; ***Braz.***: Endofer; Noripurum; Ultrafer; ***Chile***: Ferium; Ferroral; Ferzun; Hemoval; Maltofer; ***Cz.***: Ferrum†; Maltofer; ***Denm.***: Monofer; ***Fin.***: Maltofer; Monofer; ***Ger.***: Ferrum Hausmann; ***Gr.***: Antianem; Dextrifer; Feralice; Ferrata; Ferrobest; Ferrum Hausmann; Hemafer; Hydrofer-3; Monofer; Plus-Fer; Veltifer; ***Hong Kong***: Ferrum Hausmann; ***Hung.***: Maltofer; ***India***: Carbiran; Ferich; Fericip; Ferid; Ferigil; Feritas; Ferium; Ferocid; Feron; Ferose; Ferro Hepatine; Ferron; Ferst; Feton; Gilfer; Globiron; Haemarange; Hbron; Hemglo; Hemsub; Malto-Mix; Maltofer; Mumfer; Orofer; ***Indon.***: Maltofer; ***Irl.***: Ferrum Hausmann; Monover; ***Israel***: Ferripel; ***Ital.***: Intrafer; ***Malaysia***: Maltofer; Saferon; ***Mex.***: Ferranina; ***Neth.***: Monofer; ***Norw.***: Monofer; ***NZ***: Ferrosig; Ferrum H; ***Pol.***: Ferrum Lek; ***Port.***: Ferrum Hausmann; Maltofer; ***Rus.***: Fenules Complex (Фенюльс Комплекс); Ferri (Ферри); Ferrum Lek (Феррум Лек); Maltofer (Мальтофер); ***S.Afr.***: Ferrimed; ***Singapore***: Ferrum Hausmann; ***Spain***: Monoferro; ***Swed.***: Monofer; ***Switz.***: Maltofer; ***Thai.***: Eurofer-Iron; Ferium; ***Turk.***: Ferifer; Ferimax; Ferlos; Ferrum Hausmann; Maltofer; Santafer; Solufer; Veltifer; ***UK***: Monofer; ***Ukr.***: Fenules Baby (Фенюльс)†; Ferrum Lek (Феррум); Ferumbo (Ферумбо); Maltofer (Мальтофер); ***Venez.***: Intafer; Maltofer.

Multi-ingredient Preparations. ***Arg.***: Ferranin Complex; Hierro Dupofol†; Isis Fe; Maltofer Fol; Siderblut Complex; Siderblut Folic; Tenvic; Vitalix Complex; ***Braz.***: Noripurum Folico; Noripurum Vitaminado; ***Chile***: Ferroral Fol; Maltofer Fol Plus; Maltofer Fol†; ***Cz.***: Maltofer Fol; ***Gr.***: Dextrifer-Fol; Ferrum Fol Hausmann; Hemafer fol; ***Hong Kong***: Eurofer; Maltofer Fol; ***Hung.***: Maltofer Fol; ***India***: Biofer; Carbofen; Carzin-IPC; Cheri; Facer; Fefa; Fegem; Femed; Femed; Fered; Ferich; Fericip; Feritas; Feritin; Ferium-C; Ferium; Ferom Grow; Feron; Ferose; Ferrasia; Ferro; Ferro; Ferronova; Ferrum Fol; Ferst; Feton; Folinal Plus; Globac-PM; Globiron; Glowcarb; Growell-PM; Hbron; Hem; Hemglo; Hemsub; Hepofer; Infer-Z; Ironifol; Irozys; Mumfer-Z; Mumfer; New-Feripro; Orofer Kit; ***Indon.***: Feritrin; Maltofer Fol; ***Irl.***: Ferrum Fol; ***Israel***: Ferrifol; Tiptipot Ferripel + D; ***Malaysia***: Eurofer; Maltofer; Saferon; ***Mex.***: Ferranina Complex; Ferranina Fol; Ironfol; ***Philipp.***: Eurofer; Orofer; Restor; ***Port.***: Ferrum Fol; Maltoferfol†; ***Rus.***: Biofer (Биофер); Ferri-Fol (Ферри-Фол); Maltofer Fol (Мальтофер Фол); ***S.Afr.***: Ferrimed; ***Singapore***: Eurofer†; Floron; ***Switz.***: Maltofer Fol; ***Thai.***: Eurofer; Orofer; ***Turk.***: Ferlos; Ferrum Hausman Fort; Maltofer Fol; Santafer Fort; ***Ukr.***: Maltofer Fol (Мальтофер Фол); ***Venez.***: Intafer; Intaferfol; Maltoferfol.

Iron Sorbitol

Astra-1572; Demir Sorbitol; Hierro sorbitol; Iron Sorbitex (USAN); Iron-Sorbitol-Citric Acid Complex; Сорбитоловое Железо.

CAS — 1338-16-5.

ATC Vet — QB03AC03.

Pharmacopoeias. *US* includes an injection.

USP 36: (Iron Sorbitex Injection). A sterile solution of a complex of iron, sorbitol, and citric acid that is stabilised with the aid of dextrin and an excess of sorbitol. pH 7.2 to 7.9.

Profile

Iron sorbitol is a complex of ferric iron, sorbitol, and citric acid that has been given by deep intramuscular injection in the treatment of iron-deficiency anaemia (p. 2073.2); like iron dextran (p. 2076.1) its use is potentially hazardous and it should only be used where oral therapy is ineffective or impracticable.

Iron sorbitol should not be given intravenously.

Effects on the heart. Severe cardiac complications, including complete AV block, ventricular tachycardia, and atrial or ventricular fibrillation have occurred with iron sorbitol, and have sometimes proved fatal.

Of 3 patients with the malabsorption syndrome treated with intramuscular injections of iron sorbitol,[1] 2 died; in one, findings were consistent with anaphylaxis but in the other cardiac toxicity was considered to be due to a direct effect. In the third patient direct cardiac toxicity was also implicated. In another report,[2] a patient developed cardiac arrhythmia after his seventh injection of iron sorbitol. He was found to have a low serum concentration of alpha-tocopherol, supposed by the authors to be caused by the patient's malabsorption syndrome. This had apparently predisposed the patient to arrhythmia by contributing to myocardial cell sensitivity to lipid peroxidation, which is catalysed by ferrous ions. Insufficient alpha-tocopherol to scavenge the free radicals generated by the iron could also have led to loss of myocardial fatty acids, thereby disturbing membrane function. It was suggested that iron sorbitol was a less stable form of iron than iron dextran, and should be given with extreme caution to patients with malabsorption and low levels of alpha-tocopherol.

1. Karhunen P, *et al.* Reaction to iron sorbitol injection in three cases of malabsorption. *BMJ* 1970; **2:** 521–2.
2. Lindvall S, *et al.* Alpha-tocopherol and cardiac toxicity of iron. *Scand J Haematol* 1980; **25:** 331–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Jecktofer; ***Turk.***: Jectofer†.

Multi-ingredient Preparations. ***India***: Perimax; Jectocos Plus.

Pharmacopoeial Preparations
USP 36: Iron Sorbitex Injection.

Iron Succinyl-Protein Complex

Demir III Protein Süksinat; Ferro Proteinsuccinilato; Hierro succinil-proteína, complejo de; Iron Proteinsuccinylate; ITF-282; Proteinsuccilinato de hierro; Железа Протеин Сукцинилат.

CAS — 93615-44-2.

ATC — B03AB09.

ATC Vet — QB03AB09.

Profile

Iron succinyl-protein complex is a source of iron (p. 2073.1) used for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 1.6 g daily (equivalent to up to 80 mg of iron daily).

References.
1. Köpcke W, Sauerland MC. Meta-analysis of efficacy and tolerability data on iron proteinsuccinylate in patients with iron deficiency anemia of different severity. *Arzneimittelforschung* 1995; **45:** 1211–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ferplex; ***Chile***: Fisiofer; Legofer; ***China***: Ferplex (菲普利); ***Cz.***: Ferplex; ***Gr.***: Fysiofer; Legofer; ***India***: Ferplex; ***Ital.***: Ferlatum; Ferplex; Pernexin; Proteoferrina†; Rekord Ferro; Stratofer; ***Mex.***: Ferxal; ***Pol.***: Feroplex; ***Port.***: Fervit; Fetrival; Legofer; ***Rus.***: Ferlatum (Ферлатум); ***Spain***: Ferplex; Ferrocur; Lactoferrina; ***Turk.***: Ferplex; Komfer.

Multi-ingredient Preparations. ***Gr.***: Fysiofol; Legofolin; ***India***: Ferolact; ***Ital.***: Ferrofolin; ***Rus.***: Ferlatum Fol (Ферлатум Фол); ***Turk.***: Ferplex Fol; Komfer Fol.

Iron Sucrose *(BAN, USAN)*

Demir Sükroz; Eisenzucker; Ferri oxidum saccharatum; Ferric Hydroxide Sucrose; Ferric Oxide, Saccharated; Ferrique (oxyde) sucré; Ferrum Oxydatum Saccharatum; Hierro sacarosa; Iron (III) hydroxide-sucrose complex; Iron Saccharate; Oxyde de Fer Sucré; Saccharated ferric oxide; Saccharated Iron Oxide; XI-921; Железа Оксид Сахарат.

CAS — 8047-67-4.
ATC — B03AB02; B03AC02.
ATC Vet — QB03AB02; QB03AC02.
UNII — FZ7NYF5N8L.

Pharmacopoeias. In *Swiss.*

Br. and *US* include an injection.

BP 2014: (Iron Sucrose Injection). A sterile colloidal solution containing a complex of iron(III) hydroxide with sucrose of average molecular weight between 34 000 and 60 000. It contains 1.90 to 2.10% w/v of iron (Fe) and 27.0 to 33.0% w/v of sucrose. pH 10.5 to 11.0.

USP 36: (Iron Sucrose Injection). A sterile, colloidal solution of ferric hydroxide in complex with sucrose in water for injection. Sodium hydroxide may be added to adjust the pH. It contains no antimicrobial agent, chelating agent, dextran, gluconate, or other added substances. pH 10.5 to 11.1 at 20 degrees. It is intended for intravenous use only. When given by intravenous infusion, it should be diluted with 0.9% sodium chloride injection to a concentration of 0.5 to 2.0 mg of elemental iron/mL. Do not allow to freeze.

Uses and Administration

Iron sucrose is used as a source of iron (p. 2073.1) for adults with iron-deficiency anaemia (p. 2073.2), including those with chronic kidney disease. It is given when oral iron therapy is ineffective or impractical, by slow intravenous injection, or intravenous infusion; when used in haemodialysis patients, it may be given into the venous limb of the dialyser. The dose is calculated according to body-weight and iron deficit. In the UK, the maximum single dose must not exceed 200 mg of iron given not more than three times weekly. The dose is split if the total necessary dose exceeds the maximum single dose. The dose may be given undiluted at a rate of 20 mg/minute. Alternatively, it is diluted to a minimum concentration of 1 mg/mL in sodium chloride 0.9% and given at a rate not exceeding 50 mL per 15 minutes.

In the USA, for patients with chronic kidney disease and on haemodialysis, a dose of 100 mg may be given per consecutive haemodialysis session, either undiluted as a slow intravenous injection over 2 to 5 minutes, or diluted in up to 100 mL sodium chloride 0.9% and infused over at least 15 minutes. For peritoneal dialysis patients, two infusions of 300 mg over 1.5 hours are given 14 days apart, followed by an infusion of 400 mg over 2.5 hours 14 days later. The doses are diluted in a maximum of 250 mL of sodium chloride 0.9%. For patients with chronic kidney disease but not on dialysis, a dose of 1 g is given over a 14-day period, as a 200 mg slow undiluted intravenous injection over 2 to 5 minutes on 5 separate occasions within this time. Iron sucrose has also been given orally.

Anaemia of chronic renal failure. References.
1. Charytan C, *et al.* Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. *Am J Kidney Dis* 2001; **37:** 300–7.
2. Stoves J, *et al.* A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001; **16:** 967–74.
3. Chandler G, *et al.* Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001; **38:** 988–91.
4. Blaustein DA, *et al.* The safety and efficacy o fa n accelerated iron sucrose dosing regimen in patients with chronic kidney disease. *Kidney Int* 2003; (suppl): S72–S77.
5. Charytan C, *et al.* Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; **96:** 63–6.
6. Leijn E, *et al.* Intravenous iron supplementation in children on hemodialysis. *J Nephrol* 2004; **17:** 423–6.
7. Aronoff GR, *et al.* Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. *Kidney Int* 2004; **66:** 1193–8.
8. Van Wyck DB, *et al.* The United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; **68:** 2846–56.
9. Hollands JM, *et al.* Safety of high-dose iron sucrose infusion in hospitalized patients with chronic kidney disease. *Am J Health-Syst Pharm* 2006; **63:** 731–4.

Iron-deficiency anaemia. A treatment protocol consisting of alternate day iron sucrose infusions was reported to be well tolerated and effective in improving haemoglobin concentrations in patients with iron deficiency anaemia (and without severe chronic kidney disease).[1]

1. Wall GC, Pauly RA. Evaluation of total-dose iron sucrose infusions in patients with iron deficiency anemia. *Am J Health-Syst Pharm* 2008; **65:** 150–3.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p. 2076.1. Iron sucrose injection is strongly alkaline and must not be given subcutaneously or intramuscularly. UK (but not US) licensed product information contra-indicates its use in patients with a history of asthma, eczema, anaphylaxis, or other allergic disorders.

Effects on the blood. For a report of thrombocytopenia associated with iron sucrose, see under Iron Dextran, p. 2076.2.

Hypersensitivity. For a discussion of whether iron sucrose may be a safer alternative to iron dextran, see p. 2076.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iron sucrose as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Iron sucrose is rapidly cleared from the plasma after intravenous injection with a terminal half-life of about 6 hours. A competitive exchange of iron takes place from the iron sucrose complex to the iron-binding protein transferrin. About 5% of a dose is eliminated via the kidneys in the first 4 hours after a dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dixafer; Energavit; Ferive; Ferricrine†; Sucrox; Venofer; ***Austral.***: Venofer; ***Austria***: FerMed; Venofer; ***Belg.***: Venofer; ***Canad.***: Venofer; ***Chile***: Cheltin IV; Encifer; Rafofer; Sucrox; Venofer; ***China***: Venofer (维乐福); ***Cz.***: Ferion; FerroLogic; Ferrum†; Venofer; ***Denm.***: Venofer; ***Fin.***: Venofer; Venotrix; ***Fr.***: Fer Actavis; Fer Mylan; Fer Sandoz; Venofer; ***Ger.***: FerMed; Venofer; ***Gr.***: Alvofer; Anemifer; Dextrifer-S; Faremio; Felix; Ferrinemia; Ferroprol; Ferrovin; Hemafer-S; Intrafer; Ironcrose; Nephroferol; Reoxyl; Sucro-Fer; Sucroven; Veniron; Venofer; ***Hong Kong***: Venofer; ***Hung.***: Venofer; ***India***: Aviron; Encifer; Evron; Farris; Ferocorp; Ferosig; Feshia; Fesu; Fezza-S; Hemilift; Icor; Intrafer; Ircor; Irofer; Isest; Litron; Microfer; Nicofer; Omron; ***Indon.***: Nefrofer; Venofer; ***Irl.***: FerroLogic; Venofer; ***Israel***: Fermed; Ferrovin; Venofer; ***Ital.***: Ferrum Hausmann; Venofer; ***Malaysia***: Venofer; ***Mex.***: Venoferrum; ***Neth.***: Ferracin; FerroLogic; Venofer; ***Norw.***: Venofer; ***NZ***: Venofer; ***Philipp.***: Encifer; Feron; Ferrofer; Venofer; ***Pol.***: Ferion; Venofer; ***Port.***: Referen; Venofer; ***Rus.***: Venofer (Венофер); ***S.Afr.***: Venofer; ***Singapore***: Venofer; ***Spain***: Feriv; FerMed; Venofer; ***Swed.***: Venofer; ***Switz.***: Venofer; ***Thai.***: Encifer; Fe-Back; Ferrofer; Venofer; ***Turk.***: Ferroven; Inferose; Sukrofer; Venofer; ***UAE***: Feromax; ***UK***: Venofer; ***USA***: Venofer; ***Venez.***: Venofer.

Multi-ingredient Preparations. ***India***: Corus; Feristar.

Pharmacopoeial Preparations
BP 2014: Iron Sucrose Injection;
USP 36: Iron Sucrose Injection.

Isoleucine *(BAN, USAN, rINN)*

I; Ile; Isoleucin; Isoleucina; L-Isoleucine; Isoleucinum; Isoleusiini; Izoleucin; Izoleucinas; Изолейцин.

L-2-Amino-3-methylvaleric acid.

$C_6H_{13}NO_2$=131.2

CAS — 73-32-5.
UNII — 04Y7590D77.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Isoleucine). A white or almost white, crystalline powder or flakes. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Isoleucine). White, practically odourless crystals. Soluble in water; slightly soluble in hot alcohol; insoluble in ether. pH of a 1% solution in water is between 5.5 and 7.0.

Profile

Isoleucine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Falkamin; ***Ital.***: Isobranch; Isoram; Sargenor Sport†.

Isomalt *(BAN)*

Bay-i-3930; E953; Isomalta; Isomalti; Isomaltitol; Isomaltum; Izomalt; Izomaltas; Palatinit; Изомальт.

CAS — 64519-82-0.
UNII — S870P55O2W.

NOTE. The name Isomaltitol has also been applied to 6-*O*-α-D-glucopyranosyl-D-glucitol.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Isomalt). A mixture of 6-*O*-α-D-glucopyranosyl-D-glucitol ($C_{12}H_{24}O_{11}$ = 344.3) and 1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate ($C_{12}H_{24}O_{11}$,$2H_2O$ = 380.3) and neither of the two components is less than 3%, calculated with reference to the anhydrous substance. A white or almost white powder or granules. Freely soluble in water; practically insoluble in dehydrated alcohol.

USNF 31: (Isomalt). 6-*O*-α-D-Glucopyranosyl-D-glucitol (1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM), and neither of the two components is less than 3.0% of the mixture, calculated on the anhydrous basis.

Profile

Isomalt is a sugar alcohol (polyol) used as a bulk sweetener in foods. It is noncariogenic with about half the sweetness of sucrose. The ingestion of large quantities may produce flatulence and have a laxative effect.

Metabolism. Isomalt is partly metabolised in the small intestine to glucose, mannitol, and sorbitol and the remaining isomalt is completely metabolised by the flora of the large intestine.[1] The Australian manufacturers have commented that the hydrolysis and absorption is minimal and does not significantly affect blood-sugar or insulin concentrations; they consider isomalt to be suitable for use by diabetic patients.[2]

1. FAO/WHO. Evaluation of certain food additives and contaminants: twenty-ninth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 733* 1986. Available at: http://libdoc.who.int/trs/WHO_TRS_733.pdf (accessed 20/03/09)
2. Barnes JA. Martindale and isomalt. *Aust J Pharm* 1994; **75:** 183.

Lactose

Azúcar de la leche; Lactosa; Lactosum; Laktoosi; Laktos; Laktosa; Laktozė; Laktóz; Laktoza; Lattosio; Milk Sugar; Saccharum Lactis; Лактоза.

CAS — 63-42-3 (anhydrous lactose); 5989-81-1 (lactose monohydrate); 10039-26-6 (lactose monohydrate, cyclic); 64044-51-5 (lactose monohydrate, open form).
UNII — J2B2A4N98G (lactose); 3SY5LH9PMK (anhydrous lactose); EWQ57Q8I5X (lactose monohydrate).

Description. Lactose is a disaccharide obtained from the whey of milk. It may exist in a number of distinct forms depending upon the crystallisation and drying processes employed. The forms can vary in the contents of crystalline and amorphous lactose, the amounts of α-lactose (*O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose) and β-lactose (*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose), and in their hydration states. The α-form of lactose exists in either the anhydrous ($C_{12}H_{22}O_{11}$ = 342.3) or monohydrate ($C_{12}H_{22}O_{11}$,H_2O = 360.3) state whereas the β-form exists only in the anhydrous state. Commercial lactose is mainly the α-monohydrate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.* Also in *USNF.* Some pharmacopoeias include separate monographs for anhydrous lactose and lactose monohydrate.

Ph. Eur. 8: (Lactose, Anhydrous). It is β-lactose or a mixture of α-lactose and β-lactose. A white or almost white, crystalline powder. Freely but slowly soluble in water; practically insoluble in alcohol.

Ph. Eur. 8: (Lactose Monohydrate; Lactose BP 2014). It is the monohydrate of α-lactose. It may be modified as to its physical characteristics and may contain varying propor-

tions of amorphous lactose. A white or almost white, crystalline powder. Freely but slowly soluble in water; practically insoluble in alcohol. Store in airtight containers.

USNF 31: (Anhydrous Lactose). It is β-lactose or a mixture of α- and β-lactose. It is a white or almost white powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USNF 31: (Lactose Monohydrate). It is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety. It may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose. It is a white, free-flowing powder. Freely, but slowly soluble in water; practically insoluble in alcohol. Store in airtight containers.

Uses and Administration

Lactose, the carbohydrate component of milk, is less sweet than sucrose.

Lactose is widely used as an excipient in pharmaceutical manufacturing. In the production of capsules or tablets it may be used as a diluent, bulking agent, or filler, and in powders as a bulking agent. Lactose is also used as a carrier for drugs in dry powder inhalers. Characteristics such as particle size or flow characteristics make different grades of lactose suitable for different applications.

Adverse Effects and Precautions

Lactose intolerance occurs due to a deficiency of the intestinal enzyme lactase. Ingestion of lactose by patients with lactase deficiency leads to a clinical syndrome of abdominal pain, diarrhoea, distension, and flatulence; symptoms may also occur in persons without such a deficiency who have ingested excessive amounts of lactose.

Lactose is contra-indicated in patients with galactosaemia, the glucose-galactose malabsorption syndrome, or lactase deficiency.

Lactose intolerance. Reviews of lactose intolerance.[1-3] The capacity of the infant intestine to produce lactase, the enzyme responsible for digesting lactose, is retained into adulthood only by a minority of the world's population, mostly in those of north European descent; in Africa and Asia more than 90% of the population are lactase deficient. Because of the ubiquity of lactose in the diet and the consequent frequency of abdominal symptoms, attempts have been made to treat lactose intolerance by dietary exclusion (which need not be complete since lactase deficiency is rarely absolute). An alternative is enzyme replacement therapy with β-galactosidase from micro-organisms (see Tilactase, p. 2631.2), but the role of such therapy has yet to be fully determined. The findings of one study[4] suggested that, in adults with lactose intolerance, the use of lactose-digestive aids is unnecessary if lactose intake is limited to the equivalent of 240 mL of milk or less daily.

There has been concern that lactose might be contaminated with protein from milk, and it has been recommended that children with cow's milk allergy avoid lactose-containing foods. However, a small study[5] found that children allergic to cow's milk could still tolerate lactose.

For the use of soya in infants intolerant to cow's milk, see Food Intolerance, p. 2093.2.

1. Anonymous. Lactose intolerance. *Lancet* 1991; **338:** 663–4.
2. Vesa TH, *et al*. Lactose intolerance. *J Am Coll Nutr* 2000; **19** (suppl): 165S–175S.
3. Heyman MB. Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. *Pediatrics* 2006; **118:** 1279–86.
4. Suarez FL, *et al*. A comparison of symptoms after the consumption of milk or lactose-hydrolysed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995; **333:** 1–4.
5. Fiocchi A, *et al*. Clinical tolerance to lactose in children with cows' milk allergy. *Pediatrics* 2003; **112:** 359–62.

Pharmacokinetics

Lactose is hydrolysed by lactase in the small intestine to glucose and galactose, which are then absorbed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Novo-Plus†.

Multi-ingredient Preparations. ***Fr.***: Tavag†; ***Hung.***: Genia; ***India***: Osmowin.

Leucine *(BAN, USAN, rINN)*

α-Aminoisocaproic Acid; L; Leu; Leucin; Leucina; Leucinas; L-Leucine; Leucinum; Leucyna; Leusiini; Лейцин.

L-2-Amino-4-methylvaleric acid.

$C_6H_{13}NO_2$=131.2

CAS — 61-90-5.

UNII — GMW67QNF9C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Leucine). A white or almost white, crystalline powder or shiny flakes. Sparingly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Leucine). White, practically odourless crystals. Sparingly soluble in water; insoluble in ether. pH of a 1% solution in water is between 5.5 and 7.0.

Profile

Leucine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Revitalose; ***Ger.***: Falkamin; ***Ital.***: Isobranch; Isoram; Sargenor Sport†.

Lutein

E161(b); Xanthophyll; Лютеин.

(3*R*,3′*R*,6′*R*)-β,ε-Carotene-3,3′-diol.

$C_{40}H_{56}O_2$=568.9

CAS — 127-40-2.

UNII — X72A60C9MT.

Pharmacopoeias. In *US*.

US. also includes Lutein Preparation.

USP 36: (Lutein). A red crystalline powder. Soluble in dehydrated alcohol, in dichloromethane, and in ethyl acetate; partially soluble in hexane. Store at 8 degrees to 15 degrees in tightly-sealed, airtight containers. Protect from light and oxygen.

Profile

Lutein is a naturally occurring carotenoid that has been investigated for its supposed role in a number of conditions including age-related macular degeneration (p. 880.2), cataracts, cardiovascular disease, and cancer.

Lutein is also used as a colouring agent.

References.

1. Mares-Perlman JA, *et al*. The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; **132** (suppl): 518S–524S.
2. Granado F, *et al*. Nutritional and clinical relevance of lutein in human health. *Br J Nutr* 2003; **90:** 487–502.
3. Trumbo PR, Ellwood KC. Lutein and zeaxanthin intakes and risk of age-related macular degeneration and cataracts: an evaluation using the Food and Drug Administration's evidence-based review system for health claims. *Am J Clin Nutr* 2006; **84:** 971–4.
4. Cho E, *et al*. Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. *Am J Clin Nutr* 2008; **87:** 1837–43.
5. Roberts RL, *et al*. Lutein and zeaxanthin in eye and skin health. *Clin Dermatol* 2009; **27:** 195–201.
6. Carpentier S, *et al*. Associations between lutein, zeaxanthin, and age-related macular degeneration: an overview. *Crit Rev Food Sci Nutr* 2009; **49:** 313–26.
7. Berson EL, *et al*. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol* 2010; **128:** 403–11.
8. Stringham JM, *et al*. The influence of dietary lutein and zeaxanthin on visual performance. *J Food Sci* 2010; **75:** R24–R29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Y-Lut.

Multi-ingredient Preparations. ***Arg.***: Ocuvite DM; Ocuvite Omega3; Vitalux Plus; ***Austral.***: For Eyes; Multi+Vision; Radiance; ***Canad.***: ICaps Lutein and Zeaxanthin; Visionex; ***Chile***: Vision Tabs; ***Fr.***: Anti-oxydant 200; Bion 3 Seniors; Blue Berry; Corvitec; Difravision; Lero Pervulane; Macula; Naturophta Macula; Phytosolaire†; PreserVision; Reti-Nat†; Sun Vue; Trioptec; Visioprev; Vitalux Plus; Vitareds†; Vitrecor; ***Hong Kong***: Icaps; Ocuvite; Visionex†; ***India***: Absolut; Calorex; Dayvital; Ecome-LY; Elgrape; Elnutra-M; Elnutra; GV-24; I-Lute; I-Site; I-Zen; Imunolife; Izeal; L-Bex; Leclub; Lutamin; Lutivit; Luvion; Lycocare; Lycoden-M; Lycodric; Lycofact Plus; Lycominvit; Lyconerve; Lycosta; Lycozin; Lytox; Macuchek; Multivite Vision; Multizac; Natoz; Nervijen-D; Nislutin; Ocugold; One-Up; Optivision; Optivite; Orymax; Orymax; Oxired-L; Oxy-V; Oxyeye; ***Indon.***: Ervision; Eyebright; Eyevit; Kapset; Lubire; Lutevision Extra; Lutevision†; Lutevit; Lycoxy; Matoflam; Matovit AX; Matovit Fifty; Natureyes; nutrivision; Nuvision; Ocu-V; Ocugard; Oculex; Oculex; Optha-LL; Optimax Plus; Optimax; Oxypen; Proview; Reticopen; Retivit Plus; Retivit; Retop; Seltifort Gold; Vita-Vision; Vitalux Plus; Vitanox; ***Irl.***: Ocuvite†; ***Israel***: Multivitamin; Opti-Safe Areds; Opti-Safe†; Quantum; Vitalux Plus; ***Ital.***: AMD; Assist; Astar; Berart; Connivea; Euretin Duo; Ginkoret; Macvit; Meralut; PML Crono; Preservision Luteina; Troca Vit; Visu Q10; Visu-len; Visu-ton; VisuQ10; Vitalux Plus; ***Malaysia***: Eurobio Bio-Vizmax; Visionex†; Vitalux Plus; ***Mex.***: Drusen; Icaps; Optivision; Snelvit; Vitalux Plus; ***Philipp.***: Havitall; iiCare; Nutricap; Nutrof†; Nutrotal; Polynerv-E with lecithin; ***Port.***: Ever-Fit Dermo; Fortal Vision; ***Rus.***: Complivit Oftalmo (Компливит Офтальмо); Multimax (Мультимакс); Multimax for Eyes (Мультимакс Для Глаз); ***Singapore***: Essentials†; I-Vite; i-Vitein; Icaps; Nutrivision†; Ocuvite Adult 50+; Ocuvite Lutein; Optibiol; PreserVision; Visionex†; Visionex; Vitalux Plus; ***Thai.***: Icaps†; Ocuvite; Vitalux Plus; ***Turk.***: Per-Vital; ***UK***: Icaps; Vitalux Plus; ***Ukr.***: Centrum with Lutein (Центрум С Лютеином); Multimax (Мультимакс); Ocuvite Complete (Окювайт Комплит); Ocuvite Lutein Forte (Окювайт Лютеин форте); Oko-Health (Око-хелс); Optix (Оптикс); Optix Forte (Оптикс Форте); Perfectil Plus (Перфектил Плюс); Vitrum Foreyes (Витрум Форайз); Vitrum Foreyes Forte (Вітрум Форайз Форте); ***USA***: Alive Mens Energy; Alive Once Daily Womens 50+ Ultra Potency; Alive Womens 50+; Cardio Tone; Certavite Senior with Antioxidant Nutrients; Clinical Nutrients 50-Plus Men; Corvita; Corvite Free; Daily Betic; Fitness Tabs for Men; Fitness Tabs for Women; MacuTrition; Nutravance; Ocuvite Eye + Multi; Preservision Eye Vitamin; Preservision Lutein; REQ49+; ***Venez.***: Vilox; Vitalux Plus; Vitavision.

Pharmacopoeial Preparations

USP 36: Lutein Capsules.

Lysine *(BAN, USAN, rINN)*

K; Lisina; Lys; L-Lysine; Lysinum; Лизин.

L-2,6-Diaminohexanoic acid.

$C_6H_{14}N_2O_2$=146.2

CAS — 56-87-1.

ATC — B05XB03.

ATC Vet — QB05XB03.

UNII — K3Z4F929H6.

Pharmacopoeias. In *Ger.* as the monohydrate.

Lysine Acetate *(BANM, rINNM)*

Acetato de lisina; Lisina, acetato de; Lizino acetatas; Lizyny octan; Lys Acetate; Lysiiniasetaatti; Lysinacetat; Lysin-acetát; Lysine, Acétate de; L-Lysine Monoacetate; Lysini acetas; Лизина Ацетат.

L-2,6-Diaminohexanoic acid acetate.

$C_6H_{14}N_2O_2,C_2H_4O_2$=206.2

CAS — 57282-49-2.

UNII — TTL6G7LIWZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Lysine Acetate). A white or almost white, crystalline powder or colourless crystals. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Lysine Acetate). White, odourless crystals or crystalline powder. Freely soluble in water.

Lysine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de lisina; Lisina, hidrocloruro de; Lizin-hidroklorid; Lizino hidrochloridas; Lys Hydrochloride; Lysiinihydrokloridi; Lysine, chlorhydrate de; L-Lysine Monohydrochloride; Lysin-hydrochlorid; Lysinhydrochlorid; Lysin-hydroklorid; Lysini Hydrochloridum; Лизина Гидрохлорид.

L-2,6-Diaminohexanoic acid hydrochloride.

$C_6H_{14}N_2O_2$,HCl=182.6

CAS — 657-27-2.

UNII — JNJ23Q2COM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Lysine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Lysine Hydrochloride). A white, odourless powder. Freely soluble in water.

Profile

Lysine is a basic amino acid that is an essential constituent of the diet. Lysine acetate and lysine hydrochloride are used as dietary supplements.

Lysinuric protein intolerance. For mention of the use of lysine to correct lysine deficiency in lysinuric protein intolerance, see Hyperammonaemia, under Citrulline, p. 2056.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ai Xin Wei (爱欣威); An Wan Tong (安万彤); Bao Lin (包林); Beiyuan (倍援); Ci Xing (慈星); Gan Luo (甘络); Hai Jing Wu (海京吴); He An Si (荷安斯); Jun Ao (君傲); Lai An (莱安); Lang De (朗德); Li Da An (力达安); Lu Wei Tong (路维彤); Nuo Lai Xin (诺莱欣); Pi Luo

Tong (彼洛彤); Pu Le Kang (普乐康); Rui Shi Kang (瑞适康); Sai Luo Su (赛络苏); Shu Lang (舒朗); Si Fu Ti (思弗提); Si Li Jia (思力加); Tai Di Te (泰迪特); Tai Li Xing (泰利星); Tian Yi An (添亦安); Wei Sai Lai (威赛来); Xinjielin (新杰林); Ya Shu (雅抒); Yi Ning Shi (怡宁适); Yifu (亿复); You Ni Ming (尤尼明); Zhen Tong (镇通); Zhi Mai Xin (智迈欣).

Multi-ingredient Preparations. ***Arg.***: Cistidac; Ferona†; Kiddi; Latlas Fresh; Latlas; ***Austral.***: Accomin†; C Pal†; Calporo†; Incremin Iron; Lyp-Sine; Once Daily Mens Multi; Once Daily Womens Multi; Womens One-a-Day Multi; ***Braz.***: Betozone†; Buclimax†; Calcifluol; Carnabol; Ferrotrat B12 Plus; Gaballon; Glucal B12†; Pharmaton Kiddi; Profol; Propan; Suplevit; Trimetabol†; ***Chile***: Chicovit Pharmaton; Orodina; Peracon; Tonval†; ***China***: Diweijia (迪维佳); Kiddi (冠迪); ***Cz.***: Kiddi Pharmaton†; ***Fr.***: Curasten†; Revitalose; Sarvit a la lysine†; Stimuplexe†; Surfortan; ***Gr.***: Beceton; Issobevit; Set-Vit; Upsaton; Vivacton; ***Hong Kong***: Appezym; Biovite†; Calibo Calcium†; Champs C with Lysine; Champs M with Lysine; Conbo-BC†; Digezym; Kiddi Pharmaton†; Lysinevita†; Macro M†; Nutroplex with Iron & Lysine; Pantamin MV†; Tricavita†; Vi-Daylin with Lysine; Vita-Bo Calcium†; Vita-Bo Multivitamins†; Vitacymin Syrup with Lysine†; ***Hung.***: Epavir; ***India***: Abiphos; Absolut; Acmic-S; Actioner; Adrovit; Alcevit; Almal-Z; Aminocal 500; Aminocal; Anvital DPS; Arical; Arogyme; Asiplex; Astyfer-Z; Astyfer; Astyfer; Atovit; Aviton; Avm; Avpro; B Com; B-12; Bcom-L; Beco-Red-12; Betadex-12; Beth-P; Bethadoxin-12; Bethadoxin-P; Betonin-AST; Bevon; Bioferum Forte; Bonforte; C-Haem; C-Lysin; Cadbe; Calcefol; Calcila; Calcila; Calme; Calmix; Calnet; Calsal Plus; Calsat; Calsure; Caltac; Calvit-L; Cecal; Cherrytone; Cinred; Compicare; Cuplex-L; Cydine; Cypee; Cyprowal; Delvit; Diakair; Dicalciiplex; ECD3; Elferri Plus; Enerjex; Eugadine Lysine; Extrafer; Facicap; Familykair; Fe-Z; Ferrimin; Ferrisun; Ferritop Iron; Ferrochelate; Fibrotin; Forcal; Fortical; Fortox; Full-365; G-Calvit; G-Vit; Gromet-Z; Gromin; HB-Orange; Hemral; Hemsi; Hepachol; Ibelac; Ifycal-D3; Incremin; Inpro; Intabion; Irex-12 Tonic; Irona; Ironate; Irosol; Karibe; Kelcer; Kidicare; Kudamin; Lephos; Litcal; Liton; Livobion; Livobion; Logical; Lycal; Lycoden-M; Lycosta; Lycozin; Lysicon-V c Zinc; Lysicon-V; Lysoplex; M-Cal; Marvita; Meconerv; Medifer; Merical; Mexivit; Mincovit; Minero; Minitone Plus; Miproten; Momkair; Moreage; Multiphar; Mumcal; Mvimin; N-Care; N-Rich; Nervic; Nervion; Nestosule-MV; Neuragen; Neurobex; New Viminta; Nitical; Nor-B; Nucal; Nutra; Ob-Cal; Orovit; Ospical; Oxired; Oxitra; Pedic; Phosfomin; Polybion; Protone; Sioplex Lysine; Tonoferon; ***Indon.***: Abdelyn; Adebion; Adelysin; Alsine; Anabion Plus DHA; Anabion; Apialys; Asedas; Becombion Extra Lysine; Biokid†; Biolysin Smart; Biolysin; Bionutrion; Biostrum; Calcidol; Calostrum; Cavital; Champs C with Lysine; Champs M with Lysine; Corovit; Curmunos; Curviplex; Elkana; Erpha Livita; Ferobion; Ferofort; Feroglobin; Fitkom; Fortelysin†; Growee; Igastrum Plus; Imustrum; Incremin with Iron†; Kiddi Pharmaton; Kolivit; Kumina; Likurmin; Lisovit; Lybex; Lycalvit; Lysmin Plus; Lysmin; Lytacur; Lyvit; Mulsanol; Muveron; Osimax; Pediagrow; Pedilis; Picavit; Prefit; Prokids; Provital Plus; Provital; RaVita; Seltifort Kids; Solvita Baby; Solvita Plus; Truvit; Vialyn; Vidaylin L; Vidoran Plus; Viferron; Xanda; Zamel; ***Irl.***: Kiddi Pharmaton†; ***Israel***: Kiddi; ***Ital.***: Rinotrofina C; ***Malaysia***: Appeton; Junior Citrex; Kiddi Pharmaton; Nutroplex with Iron & Lysine†; Proviton; Shine Cutie; Shine Junior Multivitamin; Shine Multivitamin Plus†; Vi-Daylin; ***Mex.***: Aminoyodarsencal; Convifer con Hierro; Corpotasin CL; Incremin Con Hierro; Infavit; Integrovin; Kiddi Pharmaton; Medox ABC; Rocavit; Vita-Bel†; Vivioptal; ***NZ***: Incremin with Iron; ***Philipp.***: Appebon with Iron; Appebon; Appetason; Appetite Plus; Appetite with Iron; Bio-Termin Plus with Lecithin; Biomix; Bomvital; Brighser; Ceegeefer†; Celer C; Celermin†; Chlorvytol†; Crevytin†; Dreamvite; Ener A Plus; Enersel; Enouvim; EZ-Grow; Ferlette; Flexivit; Healthy Kidz; Heltine Plus; Hi-Smart Teens; Hi-Smart; Incremin; Jagaplex; K-A Plus; Kiddi Pharmaton; Kiddie Estamin; Kiddirel; Leginsol Vita; Lexivit; Lysadam Plus; Macrobee with Lysine; Medgivit; Medifcrron-Vita; Medifortan; Mcgavit; Memorx IQ Plus; Molvite with Iron; Multigen; Multigrow; Nerveplex; Nutrazinc; Nutri 10; Nutricaire; Nutrigrow Plus; Nutrigrow†; Nutrigrow; Nutrivita; Nutroplex with Iron & Lysine; Onevit; Optigrow; Pediafortan Forte-GE; Pediafortan Forte; Provital; Pryce-Kidz; Regeron Vita with Chlorella; Regeron Vita; Rejuvon; Restor; Revicon Forte (Improved); Sigiaton Plus; Strevit; Supplemin-C; Syplex; TLC Vita; Tropicee Plus; Ultravit-TL; United American Tiki Tiki Star; Vigorvit; Visymplex Plus; Vita SL Plus; Vita SL with lecithin†; Vita SL; Vitakids; Vitalivin-E Reformulated†; Vitaplex; Vitazinc; Z-Vita; ***Port.***: Belisina†; Tonice; ***Rus.***: Feroglobin-B12 (Фероглобин-В12); ***S.Afr.***: Activex 40 Plus†; Clusivol; ***Singapore***: Appelin-B12; Belvea Liquid Health Calcium; Champs C with Lysine†; Champs M†; Growee†; NutraMX; Pharmaton Kiddi; Provital; Vitaton Gold; Vitaton; ***Spain***: Malandil; Pranzo; Tomevit†; ***Switz.***: Pharmaton Kiddi Vita; ***Thai.***: Kiddi Pharmaton; Nutroplex Lysine; Osmo; Patarvit; Syn-O-Vits; Vitakid; ***UK***: Feroglobin; Florisene; ***Ukr.***: Cardonat (Кардонат); Energin (Энергин); Kiddi Pharmaton (Кидди Фарматон); Rotavit Royal (Ротавит Ройял); Trimetabol (Триметабол); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Biotect Plus; Herpetrol; Jets; Klorvess; Klorvess; Vitalize; ***Venez.***: Vitisival.

Pharmacopoeial Preparations

USP 36: Lysine Hydrochloride Tablets.

Magnesium Fluoride

Фторид Магния.

MgF_2=62.30

CAS — 7783-40-6.

UNII — 5N014C7IWU.

Profile

Magnesium fluoride is used as a fluoride supplement (see Sodium Fluoride, p. 2089.2) for the prevention of dental caries. Magnesium fluoride is also used as a source of magnesium.

Homoeopathy

Magnesium fluoride has been used in homoeopathic medicines under the following names: Magnesia Fluorata; Magnesium Fluoratum; Magnesia Fluoricum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Total Magnesiano.

Multi-ingredient Preparations. ***Arg.***: Total Magnesiano con Vitamina C; Total Magnesiano Limon; Total Magnesiano Sport; Total Magnesiano; Total Magnesiano; ***Spain***: Magnesium Pyre; Magnogene.

Homoeopathic Preparations. ***Ger.***: Maflurell; ***Hung.***: Toxex.

Maize Oil

Aceite de maíz; Corn Oil; Huile de Maïs, Kukoricamagolaj; Kukuričný olej; Kukurūzų aliejus; Maïs, huile de; Maissiõljy; Majsolja; Maydis Oleum; Ol. Mayd.; Olej kukurydziany; Oleum Maydis; Кукурузное Масло; Маисовое Масло.

CAS — 8001-30-7.

UNII — 8470G57WFM.

Pharmacopoeias. In *Chin.*, *Eur* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Maize Oil, Refined; Maydis Oleum Raffinatum). The refined fatty oil obtained from the seeds of *Zea mays*. A clear, light yellow or yellow oil. Practically insoluble in water and in alcohol; miscible with dichloromethane and with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Corn Oil). The refined fixed oil obtained from the embryos of *Zea mays* (Gramineae). A clear, light yellow, oily liquid having a faint characteristic odour. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Maize oil is a fixed oil with a high content of unsaturated acids, and has been used to replace saturated acids in the diets of patients with familial hypercholesterolaemia. It is also used as an oily vehicle in pharmaceutical formulations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Preservation; ***USA***: Lipomul†.

Malt Extract

Extractum Bynes; Malta, xtracto de; Экстракт Солода; Солодовый Экстракт.

UNII — R3NBG8914U (barley malt extract); 22P8DKP670 (barley malt syrup).

Profile

Malt extract contains 50% or more of maltose, with dextrin, glucose, and small amounts of other carbohydrates, and protein. It is prepared from malted grain of barley (*Hordeum distichon, H. vulgare*) or a mixture of this with not more than 33% of malted grain of wheat (*Triticum aestivum* or *T. turgidum*).

Malt extract has nutritive properties. It is chiefly used as a vehicle in preparations containing cod-liver oil (p. 2056.3) and halibut-liver oil (p. 2071.3). It is a useful flavouring agent for masking bitter tastes.

A product known as malt soup extract, obtained from barley grains, and containing 73% maltose with 12% other polymeric carbohydrates as well as small amounts of proteins, electrolytes, and vitamins, is sometimes used as a laxative.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Maltin; ***USA***: Maltsupex.

Multi-ingredient Preparations. ***Canad.***: Floradix Kindervital†; ***Chile***: Ferromalt; ***Fr.***: Effidigest; Galactogil; ***Ger.***: Weleda Hustenelixier; ***India***: Marvita; Sharkoferrol; Sharkomalt†; ***Indon.***: Bio-Strath; ***Jpn***: Hangebyakujutsutemmato; ***S.Afr.***: Cough Elixir†.

Maltitol *(BAN)*

E965; Hydrogenated Maltose; D-Maltitol; Maltitolo; Maltitolis; Maltitolum; Maltosa hidrogenada; Мальтит.

α-D-Glucopyranosyl-1,4-β-glucitol.

$C_{12}H_{24}O_{11}$=344.3

CAS — 585-88-6.

UNII — D65DG142WK.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Maltitol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol.

USNF 31: (Maltitol). A white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol.

Maltitol Syrup

E965; Hydrogenated Glucose Syrup; Hydrogenated High Maltose-glucose Syrup; Jarabe de glucosa hidrogenada; Jarabe de glucosa hidrogenada con alto contenido en maltosa; Liquid Maltitol; Maltitol clekly; Maltitol, flytande; Maltitol, Jarabe de; Maltitol liquide; Maltitol roztok; Maltitol Solution; Maltitoli, nestemäinen; Maltitolum liquidum; Maltitszirup; Skystasis maltitolis; Мальтитный Сироп.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Maltitol, Liquid). An aqueous solution of a hydrogenated, part hydrolysed starch, containing not less than 68.0% w/w and not more than 85.0% w/w of anhydrous substance composed of a mixture of mainly D-maltitol with D-sorbitol and hydrogenated oligo- and polysaccharides. It contains not less than 50.0% w/w of D-maltitol and not more than 8.0% w/w of D-sorbitol, both calculated with reference to the anhydrous substance. A clear, colourless, syrupy liquid. Miscible with water and with glycerol.

USNF 31: (Maltitol Solution). A water solution containing, on the anhydrous basis, not less than 50.0% of D-maltitol (w/w) and not more than 8.0% of D-sorbitol (w/w).

Nomenclature. Hydrogenated glucose syrup is a generic term encompassing products of widely varying composition and it was concluded that such products containing up to 90% of maltitol should more properly be called maltitol syrup.[1] This was subsequently amended to include products containing up to 98% maltitol.[2] Preparations containing a minimum of 98% of maltitol were assigned the title maltitol.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_776.pdf (accessed 20/03/09)
2. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_837.pdf (accessed 20/03/09)

Profile

Maltitol and maltitol syrup are bulk sweeteners used in foods and pharmaceuticals. They are considered to be noncariogenic and about as sweet as sucrose. The ingestion of large quantities may produce flatulence and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Singapore***: Arkopharma Propolis Spray.

Maltodextrin

Maltodekstriini; Maltodekstrinas; Maltodextrina; Maltodextrine; Maltodextrinum; Мальтодекстрин.

CAS — 9050-36-6.

UNII — 7CVR7L4A2D.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Maltodextrin). A mixture of glucose, disaccharides, and polysaccharides, obtained by the partial hydrolysis of starch. The degree of hydrolysis, expressed as dextrose equivalent (DE) is less than 20 (nominal value). A white or almost white, slightly hygroscopic powder or granules. Freely soluble in water.

USNF 31: (Maltodextrin). A nonsweet, nutritive saccharide mixture of polymers that consists of D-glucose units with a dextrose equivalent of less than 20. It is prepared by the partial hydrolysis of food grade starch with suitable acids and/or enzymes. White, hygroscopic powder or granules. Freely soluble or readily dispersible in water; slightly soluble to insoluble in dehydrated alcohol. pH of a 20% solution in water is between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 30 degrees and a relative humidity not exceeding 50%.

Profile

Maltodextrin, a glucose polymer (malto-oligosaccharide), is a source of carbohydrate often used in oral dietary supplements and tube feeding. It rapidly releases glucose in the gastrointestinal tract but because of the high average molecular weight of maltodextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on maltodextrin and intended for dietary supplementation usually have a low electrolyte content and are free of other sugars such as fructose, galactose, lactose, and sucrose. Such preparations may be particularly useful in certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Maltodextrin is also employed as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Carbohidrato 100; MC Modulo Calorico; Polimerosa; ***Austral.***: Maxijul†; ***Braz.***: Nidex; Oligossac; ***Chile***: Modulo Calorico; ***Cz.***: Fantomalt; ***Fin.***: Fantomalt; ***Hong Kong***: Fiber Basics; ***Ital.***: Energen; Fantomalt; Maltovis; Nidex; ***NZ***: Moducal; ***Pol.***: Fantomalt; ***Port.***: Fantomalt; ***USA***: Moducal; ***Venez.***: Fantomalt.

Multi-ingredient Preparations. ***Arg.***: Hidro-Energy; Invisifiber; ***Fr.***: Alhydrate†; Chondrosteo; Gumilk; Hydrigoz†; Pelvimag; Picolite; ***Indon.***: L-Bio; ***Ital.***: Combirice; Litostop; Selezime; ***Venez.***: Glutapak-R; Glutapak; Hermesetas Gold; Modulo Calorico; Multidex.

Maltose

Maltobiose; Maltosa; D-Maltose; Мальтоза.

4-*O*-α-D-Glucopyranosyl-β-D-glucopyranose.

$C_{12}H_{22}O_{11}$=342.3

CAS — 69-79-4 (anhydrous maltose); 6363-53-7 (maltose monohydrate).

UNII — XJ6S9RV06F (maltose); 66Y63L379N (anhydrous maltose); DM477EE40D (maltose monohydrate).

Pharmacopoeias. *Jpn* includes the monohydrate. *USNF* permits the anhydrous and monohydrate forms.

USNF 31: (Maltose). It contains one molecule of water of hydration or is anhydrous. A white, odourless, crystalline powder that has a sweet taste. Freely soluble in water; very soluble in dehydrated alcohol; practically insoluble in ether; slightly soluble in methyl alcohol. pH of a 10% solution in water is between 3.7 and 4.7 (anhydrous form) and between 4.0 and 5.5 (monohydrate form).

Profile

Maltose, a disaccharide composed of two glucose molecules, is less sweet than sucrose. It is obtained from starch by hydrolysis with amylase. Maltose is often present with other sugars in mixtures used as carbohydrate sources. It is also used as a pharmaceutical excipient.

Adverse effects. Hyponatraemia developed after intravenous infusion of normal immunoglobulin in 10% maltose in a patient with acute renal failure after liver transplantation.[1] The effect, which recurred on each of four successive infusions, resembled that of hyperglycaemia and was thought to be due to accumulation of maltose and other osmotically active metabolites in the extracellular fluid.

1. Palevsky PM, *et al.* Maltose-induced hyponatremia. *Ann Intern Med* 1993; **118:** 526–8.

Precautions. Preparations that contain, or are metabolised to, maltose may interfere with the results from glucose tests (p. 2516.3). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2] The problem may also occur with icodextrin, which produces maltose as a metabolite (see Dialysis, p. 2059.2).

1. MHRA. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005 and updated). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 22/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Infumal; Martos; ***Jpn***: Martos.

Multi-ingredient Preparations. ***Indon.***: Hydromal; Potacol-R; ***Jpn***: Actit; Potacol-R.

Pharmacopoeial Preparations
USNF 31: Liquid Glucose.

Manganese

Mangan; Manganèse; Manganeso; Manganum; Марганец.

Mn=54.938045

CAS — 7439-96-5.

UNII — H6EP7W5457 (manganese ion); 42Z2K6ZL8P (manganese).

Manganese Chloride

Manganeso, cloruro de; Марганца Хлорид.

$MnCl_2.4H_2O$=197.9

CAS — 7773-01-5 (anhydrous manganese chloride); 13446-34-9 (manganese chloride tetrahydrate).

UNII — 6YB4901Y90 (anhydrous manganese chloride); QQE170PANO (manganese chloride tetrahydrate).

Pharmacopoeias. In *US.*

USP 36: (Manganese Chloride). Large, irregular, pink, odourless, translucent crystals. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. pH of a 5% solution in water is between 3.5 and 6.0.

Manganese Gluconate

Manganèse, gluconate de; Manganeso, gluconato de; Mangangluconat; Mangani gluconas; Марганца Глюконат.

Bis(D-gluconato-O^1,O^2) manganese; Manganese D-gluconate.

$C_{12}H_{22}MnO_{14}$=445.2

CAS — 6485-39-8.

UNII — 9YY2F980SV (manganese gluconate); 7G09WJ8QIR (anhydrous manganese gluconate); 0O43J7044T (manganese gluconate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), which allows either anhydrous or hydrated forms, and in *US*, which allows either anhydrous or the dihydrate.

Ph. Eur. 8: (Manganese Gluconate). A white or pale pink, slightly hygroscopic, crystalline powder. Soluble in water; practically insoluble in anhydrous ethanol; insoluble in dichloromethane. Store in non-metallic, airtight containers.

USP 36: (Manganese Gluconate).

Manganese Sulfate

Mangaanisulfaattimonohydraatti; Manganèse (sulfate de) monohydraté; Manganese Sulphate; Manganeso, sulfato de; Mangani Sulfas; Mangani Sulfas Monohydricum; Mangán(II)-szulfát-monohidrát; Mangano sulfatas; Mangansulfatmonohydrat; Manganu siarczan; Síran manganatý; Марганца Сульфат.

Manganese (II) sulphate monohydrate.

$MnSO_4.H_2O$=169.0

CAS — 7785-87-7 (anhydrous manganese sulfate); 10034-96-5 (manganese sulfate monohydrate); 10101-68-5 (manganese sulfate tetrahydrate).

UNII — W00LYS4T26 (manganese sulfate); IGA15S9H40 (anhydrous manganese sulfate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Br.* and *Fr.* also include the tetrahydrate.

BP 2014: (Manganese Sulfate). The tetrahydrate occurs as pale pink, odourless or almost odourless, crystals or crystalline powder. Freely soluble in water; practically insoluble in alcohol.

Ph. Eur. 8: (Manganese Sulfate Monohydrate). It occurs as a pale pink, slightly hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol.

USP 36: (Manganese Sulfate). The monohydrate occurs as pale red, slightly efflorescent crystals, or as a purple, odourless powder. Soluble in water; insoluble in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Manganese is an essential trace element and small amounts of a salt such as the chloride or sulfate are sometimes added to solutions for TPN. Daily doses ranging from 150 to 800 micrograms (2.7 to 14.6 micromoles) of manganese have been suggested.

For doses in children, see Administration in Children, below.

Manganese compounds or salts that have been used in therapeutics in addition to those mentioned above include manganese amino acid chelate, manganese dioxide, manganese gluconate, and manganese hydrogen citrate.

Administration in children. A manganese salt such as the chloride or sulfate may be added to parenteral feeds as a source of manganese in the prophylaxis and treatment of deficiency states in children. US licensed product information suggests 2 to 10 micrograms/kg (36 to 180 nanomoles/kg) of manganese daily for all children. In the UK, licensed product information suggests a daily dose of 1 microgram/kg (up to a maximum of 15 micrograms) of manganese for children weighing 40 kg or less, and adult doses in children over 40 kg (see above). A low-dose regimen of not more than 1 microgram/kg manganese daily has been recommended in children given long-term parenteral nutrition to avoid accumulation (see Accumulation, below).

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p. 2046.1) has been set for manganese although a safe intake for adults was believed to lie above 1.4 mg (26 micromoles) daily.[1] Similarly, in the USA a recommended dietary allowance has not been published, although an adequate intake has been estimated to be 2.3 mg daily for men and 1.8 mg daily for women.[2] A tolerable upper intake level of 11 mg daily has also been set.[2] WHO has not proposed a safe range of mean population intakes for manganese since neither intakes resulting in deficiency nor threshold toxicity levels have been established.[3] Diets high in unrefined cereals, nuts, leafy vegetables, and tea will be high in manganese.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Manganese. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996; 163–7.

Adverse Effects and Precautions

Acute poisoning due to ingestion of manganese or manganese salts is rare. The main symptoms of chronic poisoning, either from injection or usually inhalation of manganese dust or fumes in air, include extrapyramidal effects which may be followed by progressive deterioration in the CNS. Parenteral manganese should be used cautiously in patients with reduced biliary excretion, especially in cholestatic liver disease. When the duration of total parenteral nutrition is likely to exceed 1 month, serum-manganese concentration and liver function should be checked before starting treatment and regularly during treatment; additives containing manganese should be stopped if serum-manganese concentrations are raised or cholestasis develops.

Accumulation. There are reports of cholestatic liver disease, and possibly changes in the basal ganglia, associated with hypermanganesaemia in children given long-term parenteral nutrition;[1,2] manganese accumulation may be secondary to impaired biliary excretion.[3] Manganese supplementation in such patients requires re-appraisal and whole blood manganese concentrations should be monitored regularly. A low-dose regimen of not more than 1 microgram/kg (18 nanomoles/kg) daily has been suggested,[2,3] a dose that was also recommended by the American Society for Parenteral and Enteral Nutrition.[4] Hypermanganesaemia and basal ganglia manganese deposition resolved over time in 2 children when the manganese dose in their parenteral nutrition was reduced.[5] Manganese accumulation in the basal ganglia has been seen in patients with liver cirrhosis,[6,7] and may be associated with parkinsonism[7-9] (for reference to the use of aminosalicylic acid in the treatment of manganese-induced parkinsonism, see p. 216.1). Concern has been expressed[10] at the high levels of manganese contained in infant formulas.

1. Reynolds AP, *et al.* Manganese in long term paediatric parenteral nutrition. *Arch Dis Child* 1994; **71:** 527–8.
2. Fell JME, *et al.* Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 1996; **347:** 1218–21.
3. Beath SV, *et al.* Manganese toxicity and parenteral nutrition. *Lancet* 1996; **347:** 1773–4. Correction. *ibid.* **348:** 416.

4. Mirtallo J, *et al*. American Society for Parenteral and Enteral Nutrition. Safe practices for parenteral nutrition. *J Parenter Enteral Nutr* 2004; **28:** S39–S70. Also available at: http://www.nutritioncare.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=574 (accessed 24/03/09)
5. Kafritsa Y, *et al*. Long term outcome of brain manganese deposition in patients on home parenteral nutrition. *Arch Dis Child* 1998; **79:** 263–5.
6. Krieger D, *et al*. Manganese and chronic hepatic encephalopathy. *Lancet* 1995; **346:** 270–4.
7. Burkhard PR, *et al*. Chronic parkinsonism associated with cirrhosis. *Arch Neurol* 2003; **60:** 521–8.
8. Zatta P, *et al*. The role of metals in neurodegenerative processes: aluminum, manganese, and zinc. *Brain Res Bull* 2003; **62:** 15–28.
9. Lucchini RG, *et al*. From manganism to manganese-induced parkinsonism: a conceptual model based on the evolution of exposure. *Neuromolecular Med* 2009; **11:** 311–21.
10. Hozyasz KK, Ruszczynska A. High manganese levels in milk-based infant formulas. *Neurotoxicology* 2004; **25:** 733.

Pharmacokinetics

Absorption of manganese from the gastrointestinal tract is variable, ranging from 3 to 50%. There is some evidence that the amount absorbed decreases as intake increases, suggesting a homoeostatic response. In the circulation, manganese is bound to transmanganin, a beta-1-globulin. Manganese is stored in the brain, kidneys, pancreas, and liver. It is excreted in bile, and undergoes enterohepatic circulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Micro Mn; ***India***: Infladase Forte; ***Israel***: Micro Mn; ***USA***: Mangimin.

Multi-ingredient Preparations. ***Arg.***: Gingeron; Glucobefol†; Ipri V Total; Krebs Plus; Senexon Plus; Tonovital Plus Antioxidante; ***Austral.***: AB Ausbiobone; Accelerex; Bone Builder; Caltrate Plus; Joint Formula Advanced; Nutribone; ***Braz.***: Ferrotrat B12 Plus; Olig-Trat; Xantinon B12; ***Canad.***: Caltrate Plus; Fibroplex; Formula CDC; Procosa; ***Chile***: Caprimida D Balance; Cicaplast; Larotabe; ***Cz.***: Caltrate Plus; ***Fr.***: Cicaplast; Kinesamine; Oligocure; Oligoderm†; Superoxylase; Tot'Hema; ***Hong Kong***: Caltrate Plus; Procosa II†; ***Hung.***: Dietet-In; Ferrocomp; Humet-R; Klimin; Multicomp; Obesmin; ***India***: Actima; Antoxid; Aviton; Avpro; Avpro; B7 Plus; Beta-Sclerobion; Bonjo Aid; Calmix; Calsuper Forte; Carbosyl; Cartifix; Cartispan; Cartivit; Cartiwel; Cartiz; Casiop; Cool-Joint; Cosantin; D-Gard; Derantox; Eldervit-ZC; Elnutra; Elrox-AO; Evepearl-PMS; Exerge-HC; Exerge; Fabulae; Fejet; Ferrimin; Fersolate-CM; Flintoff; Free M; Freecad; Furtipil-L; GC Flex; Gencart; Geocal; Glortho Forte; Glucomade; Glucovit Plus; Haem Up; Haem-Up Gems; Haem-Up; Hemocare; Hemocare; I-Lute; Intecar; Iron-Gold; Ironate; Kefive Plus; Logical-M; Lytox; Macuchek; Maxiferon; Maxo-FE; Mexivit; Minigadine; Necare; Neogadine SG; Nervitone; Nicy Days; Nofro; Nutra; Orbone Forte; Orbone; Ostebon-M; Osteo-G; Osteoflex; Ostop; Ostovit; Oxidon; Oxipre; Oxy-V; Oxyban; Oxydex; Oxyeye; Oxytret; Oxyvit; Winofit; ***Indon.***: Adfer; Artro Plus; Artro; Biosanbe; Calciviton; Caltron; Diabion; Emibion; Emineton; Eviprostat; Feroglobin; Fitbon Plus; Fripos; GCM; Habebion†; Hemafort; Inbion; Joint Care Plus; Joint Care; Jointace; Lavarix; Naturema; Neogobion; Nonemi; OA Forte; OA Plus; OA; Opibion; Osamin; Ossovit Plus; Oste; Ostela; Osteocal Plus; Osteoflam; Osteokom Forte; Osteokom; Osteonic; Osteor Plus; Osteor; Osteotin; Ostine; Osvion Plus; Pronita; Rebone; Rheumatin Forte; Rheumatin; Risteon; Sangobion; Sangofer; Sangovitin†; Solvitron; Steopor; Suprabion; Tonikum Bayer; Tonikum Bode; Tropifer; Viopor-M Forte; Viopor-M; Viopor; Viostin Com DS; Viostin Com; Viostin-X; Vioxyfm; Vioxy; Vitabion; Vitonal; ***Irl.***: Caltrate Plus†; ***Israel***: Mega Gluflex; ***Ital.***: Saniquiet; Sterimar Mn; Vertiginkgo; ***Malaysia***: Caltrate Plus; Opibion; ***Mex.***: Actiman; ***Norw.***: Tonipan†; ***NZ***: Caltrate Plus; ***Philipp.***: Caltrate Plus; Macrobee with Iron; Ruflex; Sangobion; ***Pol.***: Biovital†; Caltrate Plus; ***Port.***: Tot'Hema; ***Rus.***: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Tot'Hema (Тотема); ***S.Afr.***: Dr Williams Pink Pills†; Ferrous Sulphate Compound†; ProFLEX†; ***Singapore***: Caltrate Plus; Eviprostat; Floron; Hemacaps†; Hemoplex; Multitrace-5; Neogobion; Opibion; Procosa II†; Sangobion; ***Thai.***: Caltrate Plus; Calvin Plus; Glufer-C†; ***Turk.***: Eser Metaller; Ultimate; ***UK***: Calci-Plus; Caltrate Plus; Joint Action; Ostron; ***Ukr.***: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Calcemin Silver (Кальцемин Сильвер); Tot'Hema (Тотема); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Vitrum Osteomag (Витрум Остеомаг); ***USA***: Antioxidant Formula; Caltrate Plus; Cro-Man-Zin; REQ49+; ***Venez.***: Ocoxin; Vitalux.

Homoeopathic Preparations. ***Austria***: Dalektro; ***Canad.***: Formula DE 226†; Sinus Ease; Sinuspax†; ***Fr.***: Silicea Complexe No 11; Sinuspax; Uranium Compose†; Voxpax; ***Ger.***: Drufusan N†; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; ***Switz.***: Sinuspax†.

Pharmacopoeial Preparations

USP 36: Calcium and Vitamin D with Minerals Tablets; Manganese Chloride for Oral Solution; Manganese Chloride Injection; Manganese Sulfate Injection; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Medium-chain Triglycerides

Keskipitkäketjuiset tyydyttyneet triglyseridit; Triacylglyceroly střední nasycené; Trigliceridai, vidutinės grandinės; Trigliceridek, közepes szénláncú zsírsavaké; Triglicéridos de cadena media; Triglycerida saturata media; Triglycerider, medellångkedjiga; Triglycérides à chaîne moyenne; Среднецепочечные Триглицериды.

UNII — C9H2L21V7U.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Triglycerides, Medium-chain). The fatty acids are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis*. They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2 = 172.3$). They contain not less than 95% of saturated fatty acids with **8** and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in well-filled containers. Protect from light.

USNF 31: (Medium-Chain Triglycerides). They are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis*. They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2 = 172.3$). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Medium-chain triglycerides are used for enteral and parenteral nutrition (p. 2044.1) in conditions associated with malabsorption of fat, such as cystic fibrosis, enteritis, and steatorrhoea, and after intestinal resection. Medium-chain triglycerides are more readily hydrolysed than long-chain triglycerides and are not dependent upon biliary or pancreatic secretions for absorption from the gastrointestinal tract. They provide 35 kJ (8.3 kcal) per g. They do not provide essential fatty acids.

Medium-chain triglycerides have also been used as bases for pharmaceutical preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Teceeme; ***Austral.***: Liquigen; MCT Oil; ***Cz.***: MCT Oil; ***Denm.***: MCT Oil; ***Fin.***: Liquigen; MCT Oljy; ***Fr.***: Liquigen; ***Gr.***: MCT Oil; ***Hung.***: Structolipid†; ***Irl.***: Liquigen†; ***Israel***: MCT; ***Ital.***: MCT; Mytic 810; ***NZ***: Liquigen; MCT Oil; ***Port.***: MCT Oil; ***UK***: Alembicol D; Liquigen; MCT Oil; ***USA***: MCT.

Multi-ingredient Preparations. ***Arg.***: Lipofundin MCT/LCT-E†; Lipofundin MCT/LCT; Lipovenos MCT/LCT; ***Austral.***: Caprilon; MCT Duocal†; SMOFlipid; Visine Professional†; ***Austria***: Lipidem; Lipofundin mit MCT; SMOFlipid; Structolipid†; ***Belg.***: Lipoplus; Medialipide; Nutriflex Lipid; ***Chile***: Lipofundin MCT/LCT; Lipovenos MCT/LCT; ***China***: Lipofundin MCT/LCT (力保肪宁); Lipovenoes (力能); Structolipid (力文); ***Cz.***: Lipofundin MCT/LCT†; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Structolipid; ***Denm.***: Lipidem; Liquigen; MCT Duocal; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid†; Vasolipid; ***Fin.***: Lipoplus; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; ***Fr.***: Lipidem; Liprocil; Medialipide; Mednutriflex Lipide G; Nutriflex Lipide†; Reanutriflex Lipide; Reanutriflex Omega; SMOFKabiven; SMOFlipid; Structolipide†; ***Ger.***: Gleitgelen; Lipidem; Lipofundin MCT; Lipovenos MCT; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Visine Trockene Augen; ***Gr.***: Lipofundin MCT/LCT; Lipoplus; SMOFKabiven; SMOFlipid; Structolipid; ***Hong Kong***: Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; ***Hung.***: Lipofundin MCT†; SMOFlipid; ***India***: Celepid MCT-LCT; Lipofundin MCT/LCT; Nutrilex Lipid Peri; ***Indon.***: Hepabion†; Lipimix; Lipofundin MCT/LCT†; Lipomed MCT/LCT; ***Irl.***: Caprilon†; Lipidem; Lipofundin MCT/LCT†; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid†; ***Israel***: Lipofundin MCT/LCT; SMOFKabiven; SMOFlipid; ***Ital.***: Caprilon; Dicovit DK; Dicovit; Lipidem; Lipimix; Lipofundin MCT; Liquigen; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; SMOFlipid; Structolipid; Visine Dry Eyes†; ***Mex.***: Lipofundin MCT/LCT; ***Neth.***: Lipofundin MCT/LCT†; Lipoplus; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid; ***Norw.***: Lipidem; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Structolipid†; Vasolipid; ***NZ***: Structolipid; ***Pol.***: Lipofundin MCT/LCT; SMOFKabiven; SMOFlipid; ***Port.***: Lipofundina MCT/LCT; Lipoplus; Nutribraun; SMOFKabiven; SMOFlipid; Structolipid; ***Rus.***: Lipofundin MCT/LCT (Липофундин МСТ/ЛСТ); Lipoplus (Липоплюс); SMOFlipid (СМОФлипид); ***S. Afr.***: Lipofundin MCT/LCT†; ***Singapore***: Lipofundin MCT/LCT; ***Spain***: Lipofundina MCT/LCT; Lipomix; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Structolipid†; ***Swed.***: Lipoplus; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; ***Switz.***: Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SmofKabiven; SMOFlipid; Structolipid; ***Thai.***: Lipidem; Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; Structolipid†; ***Turk.***: Lipofundin MCT/LCT; SMOFlipid; ***UK***: Caprilon; Imuderm†; Lipidem; Lipofundin MCT/LCT; MCT Duocal; Nutriflex Lipid; NuTRIflex Omega; SMOFlipid; Structolipid; ***Ukr.***: Lipofundin MCT/LCT (Липофундин МСТ/ЛСТ); SMOFlipid (СМОФлипид); ***Venez.***: Lipofundin MCT/LCT.

Molybdenum

Molibdeno; Molibdenum; Molybdän; Molybdène; Молибден.

Mo=95.96

UNII — 81AH48963U.

Ammonium Molybdate

Amonowy molibdenian; Molibdato de amonio; Молибдат Аммония; Молибденовокислый Аммоний.

Hexaammonium molybdate tetrahydrate.

$(NH_4)_6Mo_7O_{24}.4H_2O = 1236.0$

CAS — 12054-85-2.

UNII — OGI154X474 (ammonium molybdate tetrahydrate); 21Y68J178E (anhydrous ammonium molybdate).

Pharmacopoeias. In *US.*

USP 36: (Ammonium Molybdate). Colourless or slightly greenish or yellowish crystals. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Sodium Molybdate

Molibdato de sodio; Molybdenan sodný dihydrát; Natrii Molybdas Dihydricus; Natrio molibdatas dihidratas; Nátrium-molibdenát-dihidrát; Natriummolybdaattidihydraatti; Natriummolybdatdihydrat; Sodium (molybdate de) dihydraté; Sodu molibdenian; Молибдат Натрия; Молибденовокислый Натрий.

$Na_2MoO_4.2H_2O = 242.0$

UNII — 948QAQ08I1.

Pharmacopoeias. In *Eur.* (see p. vii). *Ger.* also includes a monograph for the anhydrous substance.

Ph. Eur. 8: (Sodium Molybdate Dihydrate). A white or almost white powder or colourless crystals. Freely soluble in water.

Uses and Administration

Molybdenum is an essential trace element and small amounts, in the form of ammonium molybdate or sodium molybdate, are sometimes added to solutions for TPN. A suggested dose is about 20 to 120 micrograms (0.2 to 1.2 micromoles) elemental molybdenum daily.

Ammonium molybdate is used in veterinary medicine to treat copper poisoning in sheep.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p. 2046.1) has been set for molybdenum although a safe intake was believed to be between 50 and 400 micrograms (0.5 and 4 micromoles) daily for adults.[1] In the USA, the recommended dietary allowance is 45 micrograms daily for adults.[2] The tolerable upper intake level is 2 mg daily.[2] WHO make the suggestion that the adult basal requirement for molybdenum could be about 25 micrograms daily,[3] corresponding to approximately 400 nanograms/kg.

Foods contributing to dietary molybdenum include milk, beans, breads, and cereals; however, extreme regional variations occur in molybdenum contents of food crops due to soil differences.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Molybdenum. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 144–54.

Adverse Effects

Very high intakes of molybdenum, and associated increases in xanthine oxidase activity, may result in hyperuricaemia, and possibly gout. Molybdenum intoxication may impair the utilisation of copper.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Molybdene Injectable†; ***USA***: Molypen†.

Multi-ingredient Preparations. ***Canad.***: T-OS; ***Hung.***: Humet-R; ***Thai.***: Ferrovit; ***Ukr.***: Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†.

Pharmacopoeial Preparations

USP 36: Ammonium Molybdate Injection; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Nicotinamide Ascorbate *(BANM, rINNM)*

Ascorbato de nicotinamida; Niacinamide Ascorbate; Nicoscorbine; Nicotinamide, Ascorbate de; Nicotinamidi Ascorbas; Никотинамида Аскорбат.

$C_{12}H_{14}N_2O_7$=298.3

CAS — 1987-71-9.

UNII — JTL8B7TVW7.

Profile

Nicotinamide ascorbate is a complex of nicotinamide (below) with ascorbic acid (p. 2110.3) that is used in multivitamin preparations. It has also been given with betaine glucuronate and diolamine glucuronate for liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Jetepar†; ***Malaysia***: Jetepar; ***Philipp.***: Jetepar; ***Singapore***: Jetepar†.

Nicotinic Acid *(BAN, rINN)*

375; Acide Nicotinique; Ácido nicotínico; Acidum nicotinicum; Kwas nikotynowy; Kyselina nikotinová; Niacin; Niacina; Nicotínico, ácido; Nicotinsäure; Nikotiinihappo; Nikotinik Asit; Nikotino rūgštis; Nikotinsäure; Nikotinsav; Nikotinsyra; Никотиновая Кислота.

Pyridine-3-carboxylic acid.

$C_6H_5NO_2$=123.1

CAS — 59-67-6.

ATC — C04AC01; C10AD02.

ATC Vet — QC04AC01; QC10AD02.

UNII — 2679MF687A.

NOTE. Some published sources use the term niacin as a generic term to include both nicotinic acid and nicotinamide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Nicotinic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water and in boiling alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. Protect from light.

USP 36: (Niacin). White crystals or crystalline powder, odourless or has a slight odour. Soluble 1 in 60 of water; freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; practically insoluble in ether.

Nicotinamide *(BAN, rINN)*

Niacinamide; Nicotinamid; Nicotinamida; Nicotinamidum; Nicotinic Acid Amide; Nicotylamide; Nikotiiniamidi; Nikotinamid; Nikotinamidas; Nikotynamid; Vitamin B_3; Vitamin PP; Vitamina B_3; Vitamina PP; Никотинамид.

Pyridine-3-carboxamide.

$C_6H_6N_2O$=122.1

CAS — 98-92-0.

ATC — A11HA01.

ATC Vet — QA11HA01.

UNII — 25X51I8RD4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Nicotinamide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 6.0 to 7.5.

USP 36: (Niacinamide). A white crystalline powder, odourless or practically so. Soluble 1 in 1.5 of water, 1 in 10 of boiling water, and 1 in 5.5 of alcohol; soluble in glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Uses and Administration

Nicotinic acid and nicotinamide, the form that occurs naturally in the body, are water-soluble vitamin B substances that are converted to nicotinamide adenine dinucleotide (nadide, p. 2567.1) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain.

Nicotinic acid deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a syndrome known as pellagra, characterised by skin lesions, especially on areas exposed to sunlight, with hyperpigmentation and hyperkeratinisation. Other symptoms include diarrhoea, abdominal pain, glossitis, stomatitis, loss of appetite, headache, lethargy, and mental and neurological disturbances. Nicotinic acid deficiency may occur with other vitamin B-complex deficiency states, for example in alcoholism.

Nicotinic acid and nicotinamide are used in the treatment and prevention of **nicotinic acid deficiency**. Nicotinamide is preferred as it does not cause vasodilatation. They are usually given orally, the preferred route, but may also be given by the intramuscular route or by slow intravenous injection. Doses of up to 500 mg daily (of either compound) in divided doses have been recommended.

Nicotinic acid has been used for its **vasodilator** action in the treatment of a variety of disorders; its value is not considered to be established.

In high doses, nicotinic acid has beneficial effects on blood lipid profiles, and has been used, with dietary modification and often with other lipid regulating drugs, in **hyperlipidaemias** (see below). For the immediate-release preparations, an initial oral dose of 250 mg once daily is increased every 4 to 7 days until a dose of 1.5 to 2 g daily is reached or the desired effect is seen. If hyperlipidaemia is not controlled after 2 months at this dose, the dose can be increased at 2- to 4-week intervals to 3 g daily in 3 divided doses. Although US licensed product information suggests that doses up to 6 g daily may be required in some patients, the *National Heart, Lung, and Blood Institute* in the USA recommends a maximum dose of 4.5 g daily.

Alternatively, an initial dose of 500 mg at night has been given as a modified-release preparation and gradually increased according to response to a maintenance dose of 1 to 2 g at bedtime. The daily dose should not be increased by more than 500 mg in any 4-week period.

Topical nicotinamide is used in the treatment of mild to moderate inflammatory **acne** (see below), typically as a 4% gel applied twice daily.

Nicotinamide has been shown to inhibit the destruction of pancreatic beta cells *in vitro* and is therefore being investigated in the prevention and treatment of type 1 **diabetes mellitus** (see below).

Acne. Topical nicotinamide may be used in the treatment of inflammatory acne (p. 1682.2); nicotinamide 4% was as effective as clindamycin 1% when applied topically twice daily for 8 weeks.[1]

1. Shalita AR, *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34:** 434–7.

Diabetes mellitus. Nicotinic acid can affect glucose tolerance and should be used with care in established diabetes (see Effects on Glucose Tolerance, p. 2084.1). However, the drug has been used successfully in patients with diabetes. In the prevention of diabetes mellitus (p. 460.3) nicotinamide has been reported to induce remission in patients with newly diagnosed type 1 diabetes mellitus and may delay the onset of disease.[1,2] However, a randomised study found modified-release nicotinamide at 1.2 g/m^2 daily (to a maximum of 3 g daily) to be ineffective in preventing the onset of diabetes mellitus in first-degree relatives of patients with the disease.[3] Nicotinic acid can also raise high-density lipoprotein (HDL)-cholesterol concentrations (see below);[4,5] changes in glucose tolerance were mild enough for the drug to be considered as an alternative to statins and fibrates in diabetic patients. For further discussion of the role of nicotinic acid in the management of dyslipidaemias in diabetic patients, see under Diabetes-associated Cardiovascular Disease, p. 463.3.

1. Elliott RB, Chase HP. Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. *Diabetologia* 1991; **34:** 362–5.
2. Pozzilli P, *et al.* Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care* 1996; **19:** 1357–63.
3. European Nicotinamide Diabetes Intervention Trial Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type I diabetes. *Lancet* 2004; **363:** 925–31.
4. Elam MB, *et al.* Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *JAMA* 2000; **284:** 1263–70.
5. Grundy SM, *et al.* Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med* 2002; **162:** 1568–76.

Hyperlipidaemias. The first-line treatment for hyperlipidaemias remains dietary and lifestyle modification; where this fails, drug therapy may be considered (p. 1248.1). Nicotinic acid is reported to have a favourable effect on blood-lipid profiles, raising high-density lipoprotein (HDL)-cholesterol and lowering low-density lipoprotein (LDL)-cholesterol.[1-3] Nicotinic acid is used particularly in familial hypertriglyceridaemia, or in familial combined hyperlipidaemia when both triglyceride and cholesterol concentrations are similarly elevated. Nicotinic acid was less effective than lovastatin at reducing LDL-cholesterol in patients with primary hypercholesterolaemia, but more effective at increasing HDL-cholesterol; lovastatin was better tolerated.[4] A combination of nicotinic acid with lovastatin was found to be comparable to atorvastatin and more effective than simvastatin in reducing LDL-cholesterol, and more effective than either atorvastatin or simvastatin in increasing HDL-cholesterol, in a study of patients with dyslipidaemia.[5] Some have recommended that nicotinic acid be substituted for a statin to lower LDL-cholesterol when patients cannot tolerate a statin.[2] Combination therapy is recommended when the reduction in LDL-cholesterol is insufficient with statin monotherapy,[2,6] or when raising HDL-cholesterol would be beneficial,[7-9] as in patients with type 2 diabetes mellitus, or the metabolic syndrome.[8] The risk of muscle toxicity with this combination is not considered to be significantly different to that with statin monotherapy.[7,10] A combination preparation of nicotinic acid with laropiprant was developed in an attempt to reduce flushing, but this preparation was withdrawn when it was found to have no benefit over statin therapy and an increased risk of adverse effects.[11,12]

1. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271:** 672–7.
2. McKenney J. Niacin for dyslipidemia: considerations in product selection. *Am J Health-Syst Pharm* 2003; **60:** 995–1005.
3. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. *Drugs* 2005; **65:** 2719–40.
4. Illingworth DR, *et al.* Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. *Arch Intern Med* 1994; **154:** 1586–95.
5. Bays HE, *et al.* Comparison of once-daily, Niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; **91:** 667–72.
6. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003; **78:** 735–42.
7. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med* 2004; **164:** 697–705.
8. Chapman MJ, *et al.* Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; **20:** 1253–68.
9. Yim BT, Chong PH. Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. *Ann Pharmacother* 2003; **37:** 106–15.
10. Robinson JG. Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin. *Vasc Health Risk Manag* 2009; **5:** 31–43.
11. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013; **34:** 1279–91.
12. EMA. European Medicines Agency confirms recommendation to suspend Tredaptive, Pelzont and Trevaclyn: doctors should no longer prescribe these medicines and should review patients' treatment options (issued 18th January, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/01/WC500137453.pdf (accessed 03/12/13)

Pemphigus. Oral treatment with nicotinamide and a tetracycline[1-6] has controlled lesions in pemphigus and pemphigoid (p. 1687.1), including persistent pemphigoid gestationis,[5] and ocular cicatricial pemphigoid.[6]

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132:** 668–70.
2. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133:** 88–90.
3. Reiche L, *et al.* Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* 1998; **23:** 254–7.
4. Goon ATJ, *et al.* Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. *Singapore Med J* 2000; **41:** 327–30.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13:** 143–6.
6. Dragan L, *et al.* Tetracycline and niacinamide: treatment alternatives in ocular cicatricial pemphigoid. *Cutis* 1999; **63:** 181–3.

Adverse Effects and Treatment

Nicotinic acid has a vasodilator action and when given orally or by injection in therapeutic doses it may cause flushing, a sensation of heat, faintness, and a pounding in the head. Flushing may be accompanied by tingling, itching, headache, dizziness, tachycardia, palpitations, dyspnoea,

sweating, chills, or oedema. These symptoms are transient and various strategies have been proposed to reduce them (see Incidence of Adverse Effects, below). Nicotinamide does not have a vasodilator action.

Other adverse effects that have been reported, especially after high doses of nicotinic acid, include dryness of the skin, pruritus, hyperpigmentation, rash, cramps, cough, diarrhoea, nausea and vomiting, anorexia, activation of peptic ulcer, eye disorders including cystoid macular oedema and toxic amblyopia, decrease in glucose tolerance, hyperglycaemia, and hyperuricaemia. Most of these effects subside on withdrawal of the drug. Nicotinic acid has been associated with abnormal liver function tests and jaundice. Increases in liver transaminases are generally reversible on stopping treatment. Hypophosphataemia, a reduction in platelet counts, prolongation of prothrombin time, arrhythmias, and hypersensitivity reactions including angioedema have also been reported. Insomnia, myalgia, and hypotension may occur.

Topical nicotinamide may cause dryness of the skin and, less frequently, pruritus, erythema, burning sensation, and irritation. Frequency of application should be reduced if these effects occur.

References.
1. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007; **99** (suppl 1): S22–S31.

Incidence of adverse effects. Nicotinic acid produces frequent adverse effects, but they are not usually serious, tend to decrease with time, and some can be minimised by following appropriate instructions for use.[1,2] Dermal and gastrointestinal reactions are most common. Truncal and facial flushing are reported in 90 to 100% of treated patients in large clinical studies; they appear to be prostaglandin-mediated and can be reduced with aspirin 75 mg or 325 mg given shortly before the nicotinic acid, or simply by giving nicotinic acid with food, and by starting therapy with a low dose and gradually increasing this. It may also help to avoid eating spicy foods or drinking hot drinks or alcohol at the same time as taking nicotinic acid. Flushing may be less common with modified-release formulations;[2] furthermore, an analysis of serious adverse events reported to the FDA suggested that the incidence of such effects (including effects on the liver) with modified-release preparations of nicotinic acid was about one-sixth of that with conventional formulations.[3]

1. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987; **2:** 10–32.
2. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.
3. Alsheikh-Ali AA, Karas RH. The safety of niacin in the US Food and Drug Administration adverse event reporting database. *Am J Cardiol* 2008; **101** (suppl): 9B–13B.

Effects on the eyes. Retrospective survey of hyperlipidaemic patients suggested that dry eyes (sicca syndromes), blurred vision, and swollen eyelids might be associated with nicotinic acid therapy in some patients.[1] The effects appeared to be dose-related and reversible. In 2 patients treatment was stopped because of symptoms suggestive of cystoid macular oedema. Other cases of nicotinic acid maculopathy have been reported.[2,3]

1. Fraunfelder FW, *et al*. Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995; **79:** 54–6.
2. Callanan D, *et al*. Macular edema associated with nicotinic acid (niacin). *JAMA* 1998; **279:** 1702.
3. Spirn MJ, *et al*. Optical coherence tomography findings in nicotinic acid maculopathy. *Am J Ophthalmol* 2003; **135:** 913–14.

Effects on glucose tolerance. Nicotinic acid can reduce glucose tolerance, and this may be problematic in patients with diabetes mellitus,[1,2] although it has been investigated in the prevention of diabetes mellitus (see p. 2083.2). A review[3] of the effects of nicotinic acid on glucose control in patients with dyslipidaemia found that, although it is recognised that it can increase blood glucose concentrations, the effects were typically minor (about 4 to 5%) when given at daily doses of 2.5 g or less. In most patients with type 2 diabetes mellitus changes in blood glucose concentrations could be managed by adjusting antidiabetic therapy, and the cardiovascular benefits of nicotinic acid treatment might outweigh the risks.

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.
2. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97:** 313–16.
3. Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin Proc* 2008; **83:** 470–8.

Effects on the liver. Hepatotoxicity may occur with nicotinic acid.[1-6] Significant elevations of liver enzymes are occasionally seen with nicotinic acid therapy. They are more common in patients given large dosage increases over short periods of time, and in patients treated with modified-release formulations. It has been suggested[7] that since effects on liver function may in some instances lead to hepatic failure and are more common with modified-release dosage forms the use of crystalline immediate-release preparations should be preferred, a view shared by other commentators.[8] However, although studies appear to confirm a more frequent association of hepatotoxicity with modified-release dosage forms[4,9,10] it should be borne in mind that these effects can also occur with the immediate-release preparations, especially at high doses. Some manufacturers of modified-release preparations have stated that cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when patients have substituted modified-release dosage forms for immediate-release crystalline preparations at equivalent doses. There is also a suggestion that not all modified-release preparations are alike in their effects.[11] For a study indicating a lower incidence of reported serious adverse effects in patients given modified-release rather than conventional formulations, see Incidence of Adverse Effects, above.

1. Henkin Y, *et al*. Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. *JAMA* 1990; **264:** 241–3.
2. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. *JAMA* 1990; **264:** 181.
3. Etchason JA, *et al*. Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 1991; **66:** 23–8.
4. Rader JI, *et al*. Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92:** 77–81.
5. Coppola A, *et al*. Niacin-induced hepatotoxicity: unusual presentations. *South Med J* 1994; **87:** 30–2.
6. Gavilán JC, *et al*. Hepatitis inducida por niacina. *Med Clin (Barc)* 2002; **118:** 558.
7. Palumbo PJ. Rediscovery of crystalline niacin. *Mayo Clin Proc* 1991; **66:** 112–13.
8. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97:** 313–16.
9. McKenney JM, *et al*. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271:** 672–7.
10. Gray DR, *et al*. Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; **121:** 252–8.
11. Lavie CJ, Milani RV. Safety and side-effects of sustained-release niacin. *JAMA* 1994; **272:** 513–14.

Effects on the muscles. Myopathy has been noted with nicotinic acid.[1,2] Rhabdomyolysis has occurred when nicotinic acid was given with lovastatin (see Lipid Regulating Drugs, under Interactions of Simvastatin, p. 1495.3). However, an analysis of adverse events reported to the FDA with a combination of modified-release nicotinic acid and lovastatin suggested the incidence was no higher than with either drug alone, see Incidence of Adverse Effects, above.

1. Litin SC, Anderson CF. Nicotinic-acid associated myopathy: a report of three cases. *Am J Med* 1989; **86:** 481–3.
2. Gharavi AG, *et al*. Niacin-induced myopathy. *Am J Cardiol* 1994; **74:** 841–2.

Hyperuricaemia. Nicotinic acid decreases urinary excretion of uric acid, which may result in elevation of serum uric acid and exacerbation of pre-existing gout.[1]

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.

Precautions

Liver function should be tested before starting treatment with nicotinic acid, every 6 to 12 weeks for the first year, and periodically thereafter. A persistent increase in transaminases of 3 or more times the upper limit of normal requires treatment to be stopped. Nicotinic acid should not be used in patients with significant hepatic impairment, and treatment should be closely monitored in those with jaundice or other hepato-biliary disorders. Modified-release preparations should not be substituted for equivalent doses of immediate-release crystalline nicotinic acid preparations, as cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred.

Caution is required when using nicotinic acid in patients with active peptic ulcer disease or acute coronary syndrome, patients with or predisposed to gout, or in those who consume large amounts of alcohol. Nicotinic acid and its metabolites are excreted via the kidneys and caution is required in patients with renal impairment. Patients with diabetes mellitus should be monitored closely when taking nicotinic acid as increases in fasting blood glucose have occurred.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nicotinic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Nicotinamide is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Although some evidence suggests that combinations of nicotinic acid and statins can be given safely (see Incidence of Adverse Effects, above), there may be an increased risk of myopathy or rhabdomyolysis (see Lipid Regulating Drugs, under Interactions of Simvastatin, p. 1495.3). Nicotinic acid may increase the requirements for insulin or oral hypoglycaemics. Aspirin may reduce the clearance of nicotinic acid. *In vitro* studies suggest that colestipol and colestyramine may reduce the availability of nicotinic acid, and some licensed product information recommends an interval of at least 4 to 6 hours between giving nicotinic acid and bile-acid binding resins.

Antiepileptics. For the effect of nicotinamide on *carbamazepine*, see Vitamins, p. 517.3.

Nicotine. A patient started to have flushing and dizziness after her usual doses of nicotinic acid when transdermal nicotine patches were added to her therapy.[1] She had experienced such reactions 3 years previously on starting nicotinic acid therapy, but not since, and it was suggested that on this occasion an interaction might have been responsible.

1. Rockwell KA. Potential interaction between niacin and transdermal nicotine. *Ann Pharmacother* 1993; **27:** 1283–4.

Pharmacokinetics

Nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract after oral doses and widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to *N*-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

References.
1. Pieper JA. Overview of niacin formulations: differences in pharmacokinetics, efficacy, and safety. *Am J Health-Syst Pharm* 2003; **60** (Suppl 2): S9–14.

Human Requirements

The daily human requirement of nicotinic acid, though not definitely known, is probably about 15 to 20 mg. Yeast, meat, fish, potatoes, legumes, and wholemeal cereals are good sources of nicotinic acid and nicotinamide. However they may be present in a bound, unabsorbable form in cereals, especially maize. Nicotinic acid can also be obtained from the conversion of tryptophan in the body, 60 mg of dietary tryptophan being considered equivalent to 1 mg of dietary nicotinic acid, so requirements are influenced by dietary protein intake and if protein intake is adequate there is little need for any preformed vitamin in the diet. There is generally little loss of nicotinic acid from foods during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for nicotinic acid[1] and in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK the reference nutrient intake (RNI) is 6.6 mg niacin equivalent per 1000 kcal daily and the estimated average requirement (EAR) is 5.5 mg niacin equivalent per 1000 kcal daily for adult males and females. One niacin equivalent is equal to 1 mg of dietary nicotinic acid or 60 mg of dietary tryptophan. In the US the RDAs are also expressed in niacin equivalents and are 16 mg daily for adult males and 14 mg daily for adult females; the EAR is 12 mg daily in males and 11 mg daily in females. The tolerable upper intake level for adults is 35 mg daily.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: NB-3; Niaspan; ***Austral.***: Papulex; ***Austria***: Direktan; Niaspan; ***Belg.***: Ucemine PP; ***Braz.***: Acinic; Metri; Papuless; ***Canad.***: Ni-Odan; Niaspan; ***Chile***: Cotina; Niacex†; Niaspan; ***China***: Ben Yue (本悦); Gao Zi Ke (高兹克); Niaspan (诺之平); Pu Fu Lin (普扶林); Rui Zhi (锐旨); Shu Cheng (舒成); Tian Xin Shuang (天新爽); ***Fin.***: Niaspan†; ***Fr.***: Niaspan†; Nicobion; Papulex; ***Ger.***: Niaspan†; Nicobion†; ***Gr.***: Nicotivit; ***Hong Kong***: Niaspan; Nicocin†; ***India***: Neasyn; Nialip; Nicocin; ***Indon.***: Niacef; Niaspan; ***Irl.***: Niaspan; Nicam; Pelzont†; ***Israel***: Niaspan; ***Ital.***: Niaspanor; ***Mex.***: Hipocol; Nacro; Niaspan; Pepevit†; ***Neth.***: Niaspan†; ***Norw.***: Niaspan†; ***Philipp.***: Niaspan; ***Port.***: Niaspan; ***Rus.***: Enduracin (Эндурацин); Vita-Iodurol (Вита-иодурол); ***Singapore***: Niaspan; ***Swed.***: Niaspan†; ***Switz.***: Niaspan†; ***Thai.***: Niaspan; Nicotabs; ***Turk.***: Niascor; Niaspan; ***UK***: Freederm; Niaspan†; Nicam; ***USA***: Endur-acin; Niaspan; Slo-Niacin; ***Venez.***: Niaspan.

Multi-ingredient Preparations. *Arg.*: Anemidox; Atomo Ordenador; Centella Asiatica Compuesta; Cordaptive; IP6; Proavenal Omegatopic; *Austral.*: Dynamo†; Papulex; Sunsense Anti Ageing Face; *Austria*: Pelzont†; Tredaptive†; *Belg.*: Tredaptive†; Trihistalex; *Braz.*: Cordaptive; Fortevit; Frutoplex; Frutovena; Sadol†; *Canad.*: Advicor†; Formula 7441†; Formula 7442†; Inner Shade†; Lipofactors & Niacin†; Nia-Plex; TBV; *Chile*: Becomplina Fuerte†; Benutrex 1000†; Cicapost; Effaclar AI; Exomega; Kerium Anticaspa Intensivo; Perfungol†; Proaven; Rodepan; Ureadin Forte; Ureadin Rx PS; Ureadin Rx RD; *China*: Kai Yu (凯渝); *Cz.*: Pelzont†; Tredaptive†; Trevaclyn†; *Denm.*: Tredaptive†; *Fin.*: Neurovitan†; Vertipam†; *Fr.*: Actipur 3 en 1; Actipur Anti-imperfections; Actipur Stop; Dida; Papulex; Surelen†; Tone; Tredaptive†; Vita-Dermacide; *Ger.*: Eukalisan N†; Floradix Eisen-Folsaure; Floradix Krauterblut†; Tredaptive†; *Gr.*: Collyre Vitaphakol; Suprin; Tredaptive†; Vertigo-Vomex; *Hong Kong*: Tredaptive†; *Hung.*: Dietet-In; Klimin; Obesmin; Paniverin†; *India*: Aclin; Acmic; Adifer-Z; Aglozyme; Alfariz; Aloederm; Altrazyme; Alvit; Aneudox-12; Aneudox-12; Atpro; Avas Plus; Avpro; B-12; CB-12; Clin-3; Clinicare; Clinmide; Clinsoft; Diligan; Ecobal; Efcoba Plus; Exomega; Faceclin; Feast; Femcinol-A; Folcin-12 Combi; Folium; Folnet; Folvina; Fortox; Genprot; Globiron-Z; Hepa-Merz†; Hepasure; Hepawin; Kalzana; L-Bex; Lesstrol-N; Livogen; Livosil-B; Lornit; Mecona Plus; Mego-XL; Mericobal; Methoneuron-C; Methovit; N-Meedia; Neogadine SG; Neurophosphates†; Neurotrat; Neurotrat; Nicinal; Nicolin; Nisacne; Niyat; Nurokind Plus; Nurokind-More; Nutra; Nutrared; Nutrozyme; Oraflora; Ornipan; Pabatab-BZ; Sioneuron; *Indon.*: Baliin Q10; Biocholes†; Carni Plus; Cereton; Combiplex; Dansera; Dialac; Hemaviton Jreng; Kitoles†; Sangobion ActiFe; Sotens†; Tonikum Bayer; Vionin; Yeastafort; *Irl.*: Crampex; Effaclar AI; Effico; Quiet Life; Tredaptive†; Trevaclyn†; *Israel*: Babyzim; Tredaptive†; *Ital.*: AMD; Disepavit; Emopon; Epargriseovit; Epaviten; Folepar B12; Fosforilasi; Konorderm; Novostatin; Pineal; PML Crono; Solvobil†; Virman Plus; *Malaysia*: Dermaheal DeAkni; P-Trovite; *Mex.*: Cordaptive; *Mon.*: Monasens; Vitarutine; *Neth.*: Pelzont†; Tredaptive†; Trevaclyn†; *Norw.*: Tredaptive†; *NZ*: Tredaptive†; *Philipp.*: Hiruscar; Jetepar; Tredaptive†; *Pol.*: Dernilan; Pelzont†; Tredaptive†; Trevaclyn†; *Port.*: Cicapost; Pelzont†; Tredaptive†; Trevaclyn†; Ureadin Forte; *Rus.*: Cytoflavin (Цитофлавин); Doppelherz Ginseng Aktiv (Доппельгерц Женьшень Актив); Essliver Forte (Эссливер Форте); Lidevine (Лидевин); Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); Nicospan (НИКОШПАН); Oftan Catachrom (Офтан Катахром); Remaxol (Ремаксол); Unienzyme с MPS (Юниэнзим с МПС); *Singapore*: Beafort; Beaplex; Erase; Ferbeaplex; Hiruscar; Papulex Isocorrexion; Papulex Oil-Free; Papulex; Tredaptive†; *Spain*: Depurativo Richelet†; Enofosforina Vigor†; Tredaptive†; *Swed.*: Tredaptive†; *Switz.*: Tredaptive†; *Thai.*: B-100 Complex; *Turk.*: Epargriseovit; *UK*: Crampex; Effico; Quiet Life; S.P.H.P.; Tredaptive†; Vitalux Plus; *Ukr.*: B-Complex Multi-Tabs (В-Комплекс Мульти-Табс)†; Cocarnit (Кокарнит); Cytoflavin (Цитофлавин); Decamevit (Декамевит); Fenules (Фенюльс)†; Hepaforte (Гепафорте); Levasil (Левасил); Lidevin (Лидевин); Sedavit (Седавит); Vita-Iodurol (Вита-Йодурол)†; *USA*: Advicor; Integra F; NicAzel Forte; Nicomide†; REQ49+; Simcor; Trizel; VP-Zel.

Homoeopathic Preparations. *Ger.*: Infi-China; Infi-Symphytum; Infihepan.

Pharmacopoeial Preparations

BP 2014: Nicotinamide Tablets; Nicotinic Acid Tablets; Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 36: Niacin Extended-Release Tablets; Niacin Injection; Niacin Tablets; Niacinamide Injection; Niacinamide Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Olaflur *(BAN, USAN, rINN)*

Amine Fluoride 297; GA-297; Olaflurum; SKF-38095; Олафлур.

2,2′-(3-[*N*-(2-Hydroxyethyl)octadecylamino]propylimino) diethanol dihydrofluoride.

$C_{27}H_{60}F_2N_2O_3$=498.8

CAS — 6818-37-7.

ATC — A01AA03.

ATC Vet — QA01AA03.

UNII — 8NY9L8837D.

Profile

Olaflur is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) in the prevention of dental caries. For a report of stomatitis considered to be due to olaflur, see Hypersensitivity, under Sodium Fluoride, p. 2091.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Fluormex; *Port.*: Elmex; Elmex.

Multi-ingredient Preparations. *Austria*: Elmex; Elmex; *Belg.*: Elmex; *Cz.*: Elmex; Elmex; *Fin.*: Elmex; Elmex; *Ger.*: Elmex; Elmex; Ledermix Fluorid; Multifluorid†; *Hung.*: Elmex; Elmex; *Israel*: Elmex; Elmex; Meridol; *Ital.*: Elmex; *Neth.*: Elmex; Elmex; *Pol.*: Elmex; Fluormex; *Switz.*: Elmex; Elmex; Paro aux fluorures d'amines Gelee.

Ornithine *(rINN)*

Orn; L-Ornithine; Ornithinum; Ornitina; α,δ-Diaminovaleric Acid; Орнитин.

L-2,5-Diaminovaleric acid.

$C_5H_{12}N_2O_2$=132.2

CAS — 70-26-8.

UNII — E524N2IXA3.

Pharmacopoeias. *Ger.* includes Ornithine Aspartate and Ornithine Hydrochloride.

Profile

Ornithine is an aliphatic non-essential amino acid. It is used as a dietary supplement.

The aspartate, hydrochloride, and oxoglurate (ornithine ketoglutarate, see also Parenteral and Enteral Nutrition under Glutamic Acid, p. 2070.3) and phenylacetate have been used in various indications including the treatment of hyperammonaemia (p. 2049.3) and hepatic encephalopathy (p. 1808.2).

References.

1. Rapport L, Lockwood B. Ornithine ketoglutarate. *Pharm J* 2001; **266:** 688–90.
2. Coudray-Lucas C, *et al.* Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. *Crit Care Med* 2000; **28:** 1772–6.
3. Kircheis G, *et al.* Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab Brain Dis* 2002; **17:** 453–62.
4. Blonde-Cynober F, *et al.* Use of ornithine alpha-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; **19:** 73–5.
5. Jalan R, *et al.* L-Ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy. *Med Hypotheses* 2007; **69:** 1064–9.
6. Jiang Q, *et al.* L-Ornithine-l-aspartate in the management of hepatic encephalopathy: a meta-analysis. *J Gastroenterol Hepatol* 2009; **24:** 9–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Hepa; Hepasan; *Braz.*: Hepa-Merz; *China*: Hepa-Merz (雅博司); Rui Gan (瑞甘); *Fr.*: Cetornan; Ornicetil†; *Ger.*: Hepa-Merz KT†; Hepa-Merz; Hepa-Vibolex; *Hong Kong*: Hepa-Merz; *Hung.*: Hepa-Merz; *India*: Alnalive; Analiv; Arosi; Biohep; Hep-Zo; Hepa-Merz; Hepacor; Hepagard; Hepastar; Hepawin; Hepaze; Hepoline; Intraliv; Longliv; Lorni-S; Lornit; Nitlor; Nitoliv; Olson; *Indon.*: Hepa-Merz; Hevtin†; Livola; *Ital.*: Ornil KGF; Ornil; *Mex.*: Hepa-Merz; *Philipp.*: Hepa-Merz; *Pol.*: Hepa-Merz; Hepatil†; *Rus.*: Hepa-Merz (Гепа-Мерц); Ornicetil (Орницетил); *Thai.*: Hepa-Merz; *Turk.*: Hepa-Merz; *Ukr.*: Hepa-Merz (Гепа-Мерц).

Multi-ingredient Preparations. *Braz.*: Ornitargin; *Fr.*: Actigess†; *Hong Kong*: Profile B Plus Fat Burner†; *India*: Alcohep; Analiv; Arosi; Biohep; Hepa-Merz†; Hepa-Merz; Hepalon; Hepan-L; Hepasure; Hepasure; Hepator; Hepawin Plus; Hepawin; Hepawin; Kayliv; Livbel; Livopill; Livtop; Lornit; Nitlor Plus; Orniliv; Ornipan; Ornipan; *Ital.*: Ipoazotal Complex; Somatron.

Pantothenic Acid *(BAN)*

Pantoténico, ácido; Vitamin B_5; Vitamina B_5; Пантотеновая Кислота; Витамин B5.

(+)-(*R*)-3-(2,4-Dihydroxy-3,3-dimethylbutyramido)propionic acid.

$C_9H_{17}NO_5$=219.2

CAS — 79-83-4 (D-pantothenic acid); 599-54-2 (DL-pantothenic acid).

ATC — A11HA31; D03AX04.

ATC Vet — QA11HA31; QD03AX04.

UNII — 19F5HK2737.

Calcium Pantothenate *(BANM, rINN)*

Calcii Pantothenas; Calcium, pantothénate de; Calciumpantothenat; Dextro Calcium Pantothenate; Kalcio pantotenatas; Kalciumpantotenat; Kalcium-pantotenát; Kalsiumpantotenaatti; Pantotenato de calcio; Pantothenan vápenatý; Pantothénate de Calcium; Wapnia pantotenian; Кальция Пантотенат.

$(C_9H_{16}NO_5)_2Ca$=476.5

CAS — 137-08-6 (calcium D-pantothenate); 6381-63-1 (calcium DL-pantothenate).

ATC — A11HA31; D03AX04.

ATC Vet — QA11HA31; QD03AX04.

UNII — 568ET80C3D (calcium D-pantothenate); 2KC899R47Q (calcium DL-pantothenate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

US also has a monograph for Racemic Calcium Pantothenate.

Ger. also includes Sodium Pantothenate.

Ph. Eur. 8: (Calcium Pantothenate). A white or almost white, slightly hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution has a pH of 6.8 to 8.0. Store in airtight containers.

USP 36: (Calcium Pantothenate). The calcium salt of the dextrorotatory isomer of pantothenic acid. A white, odourless, slightly hygroscopic powder. Soluble 1 in 3 of water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Store in airtight containers.

USP 36: (Racemic Calcium Pantothenate). A mixture of the calcium salts of the dextrorotatory and laevorotatory isomers of pantothenic acid. The physiological activity of Racemic Calcium Pantothenate is about one-half that of Calcium Pantothenate. A white, slightly hygroscopic powder, having a faint characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Its solutions are neutral or alkaline to litmus. Store in airtight containers.

Uses and Administration

Pantothenic acid is traditionally considered to be a vitamin B substance. It is a component of coenzyme A which is essential in the metabolism of carbohydrate, fat, and protein.

Deficiency of pantothenic acid is unlikely in man because of its widespread distribution in food.

Pantothenic acid has no accepted therapeutic uses in human medicine, though it has been given orally as a nutritional supplement, often as the calcium salt and usually with other vitamins of the B group.

Adverse Effects

Pantothenic acid is reported to be generally non-toxic.

Eosinophilia. A report of life-threatening eosinophilic pleuropericarditis associated with the use of biotin and pantothenic acid.[1] Symptoms resolved on stopping the vitamins.

1. Debourdeau PM, *et al.* Life-threatening eosinophilic pleuropericardial effusion related to vitamins B_5 and H. *Ann Pharmacother* 2001; **35:** 424–6.

Pharmacokinetics

Pantothenic acid is readily absorbed from the gastrointestinal tract after oral doses. It is widely distributed in the body tissues and appears in breast milk. About 70% of pantothenic acid is excreted unchanged in the urine and about 30% in the faeces.

Human Requirements

Pantothenic acid is widely distributed in foods. Meat, legumes, and whole grain cereals are particularly rich sources; other good sources include eggs, milk, vegetables, and fruits.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) has been set (see p. 2046.1) for pantothenic acid although an intake of 3 to 7 mg daily for adults was believed to be adequate.[1] Similarly, in the USA a recommended dietary allowance has not been published but an adequate intake for adults was believed to be 5 mg daily, increased to 6 mg in pregnancy and 7 mg during lactation.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Pantonate†; *Denm.*: BiOrto Pantothensyre; *Ger.*: Kerato Biciron; *Mex.*: Span Plex†; *Rus.*: Zorex (Зорекс); *Switz.*: Pantothen.

Multi-ingredient Preparations. *Arg.*: Bifena; Cellskinlab Hydragel B5; Cidermex; Culuflex H†; Garcinia + Fucus; Guarana Diates†; Hairplus; Megaplus; Triconal; Valcatil Max; Valcatil Plus; Valeriana Relax Diates†; *Austral.*: Bio ACE Excell; Bio ACE; Otrivin

Saline Plus; Zn-A-C†; ***Austria***: Pantogar; Priorin; ***Belg.***: Sili-Met-San†; ***Braz.***: Gaballon; Pantevit; Pantogar; ***Canad.***: Femm†; Formula M†; ***Chile***: Becomplina Fuerte†; Foltene Research Anticaspa†; Hydragel B5 CKL; Hydrating B5 Gel†; Modane; ***China***: Kai Yu (凯渝); ***Fr.***: Forcapil; Modane; Navi Blef; ***Ger.***: Pantovigar; Regepithel; ***Hung.***: Forcapil; ***India***: Acmic; Admine; All-G; Ameco; Efcoba Plus; Endruff; Livosil-B; Neurotrat; Nurokind-More; Pabatab-BZ; Sioneuron; ***Indon.***: Aviter; Combiplex; Pantogar; Proimbus†; Provigor†; ***Ital.***: Nuleron; Silisan; ***Malaysia***: Vitamin C YSP; ***Mex.***: Espaven; Modaton; Pantogar; ***Mon.***: Cicaleine; ***Philipp.***: B-Prime Plus; Korgivit-E†; Lungcaire Plus; ***Rus.***: Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); Pantovigar (Пантовигар); ***Singapore***: Beafort; Pantogar; Vitamin C-500; ***Spain***: Calcio 20 Complex†; Lacerdermol†; Lupidon; Pulmofasa; Tri Hachemina†; ***Switz.***: Cortifluid N; Decasept N†; Pantogar; Priorin N; ***Turk.***: Pantogar; Pilo Cura; Priorin; ***UK***: Pilfood; ***Ukr.***: B-Complex Multi-Tabs (В-Комплекс Мульти-Табс)†; Fenules (Фенюльс)†; Fitoval Capsules (Фитовал капсулы); Levasil (Левасил); Pantogar (Пантогар); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Zorex (Зорекс); ***USA***: REQ49+.

Pharmacopoeial Preparations

USP 36: Calcium Pantothenate Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Phenylalanine *(USAN, rINN)*

α-Aminohydrocinnamic Acid; F; Fenilalanin; Fenilalanina; Fenilalaninas; Fenylalanin; Fenyloalanina; Fenyylialaniini; Phe; Phenylalanin; L-Phenylalanine; Phénylalanine; Phenylalaninum; Фенилаланин.

L-2-Amino-3-phenylpropionic acid.

$C_9H_{11}NO_2$=165.2

CAS — 63-91-2.

UNII — 47E5O17Y3R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Phenylalanine). A white or almost white, crystalline powder, or shiny, white flakes. Sparingly soluble in water; very slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Phenylalanine). White, odourless crystals. Sparingly soluble in water; very slightly soluble in alcohol, in methyl alcohol, and in dilute mineral acids. pH of a 1% solution in water is between 5.4 and 6.0.

Profile

Phenylalanine is an aromatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Phenylalanine intake should be restricted in patients with phenylketonuria (see Amino Acid Metabolic Disorders, p. 2042.2).

Vitiligo. There is no totally effective treatment for vitiligo (localised hypopigmentation, p. 1687.2). Oral or topical photochemotherapy with psoralens is generally considered to be the best available treatment, but experimental therapy includes UVA phototherapy with phenylalanine. Use of phenylalanine in oral doses of up to 100 mg/kg with UVA/sunlight led to beneficial results in more than 90% of 200 patients with vitiligo.[1] Greatest benefit was noted in early disease, but prolonged use still induced repigmentation in long-standing cases. Repigmentation occurred mainly in areas rich in follicles. Such therapy is contra-indicated in phenylketonuria and in pregnancy.

Similarly a further open study reported responses in 94 of 149 patients receiving 50 to 100 mg/kg daily of phenylalanine plus twice weekly UVA treatment.[2] However, only 22% of responders had repigmentation in more than 60% of the affected area. Higher doses did not seem to be more effective than 50 mg/kg daily. Another group reported on 6 years of experience of treatment of vitiligo using 50 or 100 mg/kg daily of phenylalanine, with application of 10% phenylalanine gel and daily sun exposure.[3] Although not ideal, they considered the treatment useful, especially for its ability to rapidly repigment the face. The same group performed an open study, adding topical 0.025% clobetasol propionate, and ultraviolet exposure during autumn and winter; 65.5% of patients achieved 100% repigmentation on the face.[4]

1. Cormane RH, *et al*. Treatment of vitiligo with L-phenylalanine and light. *Br J Dermatol* 1986; **115:** 587.
2. Siddiqui AH, *et al*. L-Phenylalanine and UVA irradiation in the treatment of vitiligo. *Dermatology* 1994; **188:** 215–18.
3. Camacho F, Mazuecos J. Treatment of vitiligo with oral and topical phenylalanine: 6 years of experience. *Arch Dermatol* 1999; **135:** 216–17.
4. Camacho F, Mazuecos J. Oral and topical L-phenylalanine, clobetasol propionate, and UVA/sunlight - a new study for the treatment of vitiligo. *J Drugs Dermatol* 2002; **2:** 127–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fenilup.

Multi-ingredient Preparations. ***Arg.***: Desgras; Fosfovita; KLB6 Fruit Diet; ***Fr.***: Revitalose.

Polysaccharide-Iron Complex

Polisacárido hierro, complejo.

Profile

Polysaccharide-iron complex is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses containing the equivalent of up to 300 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Ferricure; ***Canad.***: Fera-MAX; Triferexx; ***China***: Hong Yuan Da (红源达); Niferex (力蓝能); ***Hong Kong***: Niferex; ***UK***: Niferex; ***USA***: Duofer; Fe-Tinic†; Ferrex Plus; Ferrex; Myferon; Niferex; NovaFerrum 50; NovaFerrum Pediatric; Poly-Iron.

Multi-ingredient Preparations. ***USA***: Fe-Tinic Forte; Ferrex Forte Plus†; Ferrex Forte; Ferrex PC; Hemocyte-F; Niferex Forte; Novaferrum 125; Nu-Iron V; Poly-Iron Forte; Tandem Plus; Tandem.

Proline *(BAN, USAN, rINN)*

P; Pro; Proliini; Prolin; Prolina; Prolinas; L-Proline; Prolinum; Пролин.

L-Pyrrolidine-2-carboxylic acid.

$C_5H_9NO_2$=115.1

CAS — 147-85-3.

UNII — 9DLQ4CIU6V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Proline). Fermentation product, extract or hydrolysate of protein. A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Proline). White, odourless crystals. Freely soluble in water and in dehydrated alcohol; insoluble in butyl alcohol, in ether, and in isopropyl alcohol.

Profile

Proline is a cyclic non-essential amino acid. It is used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Calmobrul; ***Port.***: Creme Laser Hidrante†.

Protein Hydrolysate

CAS — 9015-54-7.

Profile

Protein hydrolysates are produced by enzymatic, physical, or chemical hydrolysis of proteins from animal or vegetable sources. They contain mixtures of free amino acids and peptides of differing lengths (including dipeptides, tripeptides, other oligopeptides, and polypeptides) depending on the method of hydrolysis.

Protein hydrolysates have been used as a nitrogen source in preparations for enteral and parenteral nutrition (p. 2044.1). They have also been used in dietary supplements and in infant feeds, although their benefits are not established. Some protein hydrolysates (peptones) have been used as choleretics and as test meals to stimulate gastrin production. They have also been used as culture media for bacteria and other cells.

References.

1. Osborn DA, Sinn JKH. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 17/08/11).
2. Manninen AH. Protein hydrolysates in sports nutrition. *Nutr Metab (Lond)* 2009; **6:** 38.
3. Schaafsma G. Safety of protein hydrolysates, fractions thereof and bioactive peptides in human nutrition. *Eur J Clin Nutr* 2009; **63:** 1161–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Drenocol; ***Austral.***: Nutramigen†; ***Canad.***: Alimentum; Colibyl†; ***Chile***: Cholinogo†; ***Hong Kong***: Pilfood; ***India***: Alcezyme; Altone; Aminozyme; Anzykair; Cydine; Cypee; Cyprowal; Genprot; Haemoprotex; Hemocare; Hemocare; Hemprovit-Fe; Hepatoglobine†; Hepatoglobine; Inpro; Kairase; Marpro-Z; Miproten; Neogadine SG; Nervitone; Newtrolax; Nodyfer; Osprovit; Oxyglobin; Prova; Santevini; ***Israel***: Hydrolac; ***Malaysia***: Alimentum; ***Mex.***: Chofabol; Peptochol; ***S.Afr.***: Fissan; ***Singapore***: Similac Alimentum; ***Switz.***: Pil-Food; ***UK***: Similac Alimentum; ***USA***: Alimentum; Nutramigen; ***Venez.***: Nutramigen.

Safflower Oil

Aceite de alazor; Aceite de cártamo; Carthame (huile de) raffinée; Carthami Oleum Raffinatum; Dygminų aliejus, rafinuotas; Saffrolja, raffinerad; Safloriöljy, puhdistettu; Světlicový olej čištěný; Сафлоровое Масло.

*ATC Herb — HB05BA5002 (*Carthamus tinctorius*: oil); HC10AW5003 (*Carthamus tinctorius*: oil).*

UNII — 65UEH262IS.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Chin., *Eur.* (see p. vii), and *Jpn* include Safflower, the flower of *Carthamus tinctorius*.

Ph. Eur. 8: (Safflower Flower; Carthami Flos). Dried flower of *Carthamus tinctorius*. It contains not less than 1% of total flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$=464.4), calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Safflower Oil, Refined). The fatty oil obtained from seeds of *Carthamus tinctorius* (type I) or from seeds of hybrids of *C. tinctorius* (type II), by expression and/or extraction followed by refining. Type II refined safflower oil is rich in oleic acid. It may contain a suitable antoxidant. A clear, viscous, yellow to pale yellow liquid. Relative density about 0.922 (type I) and about 0.914 (type II). Practically insoluble in alcohol; miscible with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store in well-filled airtight containers. Protect from light.

USP 36: (Safflower Oil). The refined fixed oil yielded from the seed of *Carthamus tinctorius* (Compositae). A light yellow oil. It thickens and becomes rancid on prolonged exposure to air. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers. Protect from light.

Profile

Safflower oil is the refined fixed oil obtained from the seeds of the safflower, or false (bastard) saffron, *Carthamus tinctorius* (Compositae). It contains about 75% of linoleic acid as well as various saturated fatty acids.

Safflower oil has similar actions and uses to those of soya oil, p. 2092.3. Emulsions containing a mixture of safflower oil 5% and soya oil 5%, or 10% and 10% respectively, are given as part of total parenteral nutrition regimens.

Adverse effects. For reference to the association of safflower oil-based emulsion, as part of a parenteral nutrition regimen, with the development of sinus bradycardia, see Effects on the Cardiovascular System, under Soya Oil, p. 2093.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Liposyn; Microlipid; ***India***: Dermamoist; ***Indon.***: Baliin Q10; ***Ital.***: Liposyn; ***Mex.***: Liposyn†; ***Rus.***: Vitamax (Витамакс)†; Wantong Artiplas (Ваньтун Артиплас); ***Singapore***: Life 2; ***Turk.***: Liposyn†; ***Ukr.***: Energin (Энергин); Farcovit B12 (Фарковит B12)†; ***USA***: Liposyn II; Microlipid.

Selenium

Seiléiniam; Seleen; Seleeni; Selen; Selenas; Seleni; Selèni; Selenij; Selenio; Selênio; Seleniu; Sélénium; Seleniwm; Selēns; Selenyòm; Selenyum; Shellainium; Silinyu; Szelén; Селен.

Se=78.96

UNII — H6241UJ22B.

Potassium Selenate

Selenato potásico; Селеновокислый Калий; Селенат Калия.

K_2SeO_4=221.2

CAS — 7790-59-2.

UNII — 99798PU7MI.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Potassium Selenate). Colourless crystals or a white crystalline powder. Freely soluble in water.

Selenious Acid

Kwas selenawy; Selenioso, ácido; Селенистая Кислота.
Monohydrated selenium dioxide .
H_2SeO_3=129.0
CAS — 7783-00-8.
UNII — F6A27P4Q4R.

Pharmacopoeias. In *US.*

USP 36: (Selenious Acid). Store in airtight containers.

Selenium Dioxide

Selenious Anhydride; Selenium Oxide.
SeO_2=111.0
CAS — 7446-08-4.
UNII — 9N3UK29E57.

Selenomethionine

Selenium Methionine; Selenomethionin; L-Selenomethionine; Sélénométhionine.
(*S*)-2-Amino-4-(methylselenyl)butyric acid.
$C_5H_{11}NO_2Se$=196.1
CAS — 3211-76-5 (L-selenomethionine); 1464-42-2 (DL-selenomethionine).
UNII — 964MRK2PEL.

Pharmacopoeias. In *US.*

Sodium Selenate

AI3-10625; CCRIS 1259; Disodium Selenate; Natriumseleniat; NSC-378348; Selenato sódico; Sodium Selenium Oxide; Селеновокислый Натрий; Селенат Натрия.
Na_2SeO_4=188.9
CAS — 13410-01-0.
ATC — A12CE01.
ATC Vet — QA12CE01.
UNII — 5DQP25600A (sodium selenate); 0CJN4029EB (sodium selenate decahydrate).

Sodium Selenite

Natrii Selenis Pentahydricus; Natrio selenitas pentahidratas; Natriumseleniittipentahydraatti; Natriumselenitpentahydrat; Seleničitan sodný pentahydrát; Selenito sódico; Sodium (sélénite de) pentahydraté; Sodu selenin pięciowodny; Sodyum Selenit; Селенистокислый Натрий; Селенит Натрия.
$Na_2SeO_3.5H_2O$=263.0
CAS — 10102-18-8.
ATC — A12CE02.
ATC Vet — QA12CE02.
UNII — HIW548RQ3W (sodium selenite); 0WV4L961ZV (sodium selenite pentahydrate).

Pharmacopoeias. In *Eur.* (see p. vii). *BP(Vet)* includes anhydrous sodium selenite.

Ph. Eur. 8: (Sodium Selenite Pentahydrate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP(Vet) 2014: (Sodium Selenite). A white to slightly greyish pink granular powder. Freely soluble in water; practically insoluble in alcohol and ether.

Uses and Administration

Selenium is an essential trace element. It is an integral part of the enzyme system glutathione peroxidase, which protects intracellular structures against oxidative damage. Deficiency of selenium has been associated with an endemic form of cardiomyopathy, Keshan disease, seen in certain areas of China. It has also been associated with Kaschin-Beck disease, an endemic osteoarthropathy, which causes a severe deformity of the joints. Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine and derivatives.

Selenious acid and its sodium salt, sodium selenite, are used as a source of selenium, especially for patients with deficiency states after prolonged parenteral nutrition. Suggested doses for addition to TPN range from 20 to 40 micrograms (0.25 to 0.5 micromoles) elemental selenium daily. Sodium selenate has also been used.

For doses added to parenteral nutrition for children, see Administration in Children, below.

For proven selenium deficiency that cannot be offset from food sources, selenium may be given orally, or by intramuscular or intravenous injection, usually in the form of sodium selenite pentahydrate, to provide doses of about 100 to 200 micrograms selenium daily; if necessary this can be increased to 500 micrograms daily.

Selenium and selenium salts have also been used in dietary supplements. Selenomethionine is thought to be more bioavailable than inorganic salts and has also been used; other organic selenium compounds that have been tried include methylselenocysteine (Se-methylselenocysteine; selenomethylselenocysteine).

Selenate and selenite salts are used for selenium deficiency states in veterinary medicine.

Action. References.
1. Rayman MP. The importance of selenium to human health. *Lancet* 2000; **356:** 233–41.

Administration in children. Selenious acid or sodium selenite may be added to parenteral feeds as a source of selenium in the prophylaxis and treatment of deficiency states in children. US licensed product information suggests a dose of 3 micrograms/kg (38 nanomoles/kg) of selenium daily for all children. In the UK, licensed product information suggests 2 micrograms/kg (to a maximum of 30 micrograms) of selenium daily for children weighing 40 kg or less, and adult doses in children over 40 kg (see above).

In preterm neonates, low selenium plasma concentrations have been suggested to be a potential risk factor for neonatal respiratory disorders and retinopathy of prematurity. A systematic review[1] found that supplementation with selenium, either enterally or parentally, did not reduce the incidence of these complications, nor is it associated with improved survival. However, it is associated with benefit in terms of reduction in the number of episodes of late-onset sepsis in very preterm infants. There was evidence that recommended doses in this group might be inadequate for some populations.

1. Darlow BA, Austin NC. Selenium supplementation to prevent short-term morbidity in preterm neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 18/02/09).

HIV infection and AIDS. A randomised controlled study found that oral supplementation with selenium 200 micrograms daily for 9 months suppressed the progression in HIV-1 viral load and provided indirect improvement of the CD4+ count.[1] For a study reporting increased CD4+ and CD8+ counts, but increased genital HIV-1 shedding with multivitamin plus selenium supplementation, see HIV Infection and AIDS, p. 2046.2.

1. Hurwitz BE, *et al.* Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. *Arch Intern Med* 2007; **167:** 148–54.

Human requirements. In the UK dietary reference values (see p. 2046.1)[1] and in the USA recommended dietary allowances (RDA)[2] have been published for selenium.

In the UK the reference nutrient intake for adults is 75 and 60 micrograms daily for men and women respectively; values are also given for infants and children of varying ages and for lactating women. The UK report also noted that there was no convincing evidence that high intakes protected against cancer or cardiovascular disease; indeed, there was even some evidence that high intakes disturbed selenium homoeostasis and it was recommended that the maximum safe intake from all sources should be set at 450 micrograms daily for adult males. The Expert Group on Vitamins and Minerals[3] have since established a safe upper level (SUL) for selenium of 450 micrograms daily.

In the USA, the RDA for adult males and females is 55 micrograms daily, and again values are also given for infants and children as well as pregnant and lactating women. The tolerable upper intake level is 400 micrograms daily.[2]

WHO have recommended a lower limit of the safe range of population mean intakes of dietary selenium of 40 micrograms daily for adult males and 30 micrograms daily for adult females.[4] A maximum daily safe dietary selenium intake of 400 micrograms was suggested for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
4. WHO. Selenium. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996; 105–22.

Prophylaxis of malignant neoplasms. Selenium supplementation did not protect against the development of new basal or squamous cell carcinomas of the skin in a study of patients with a history of these cancers.[1] Further follow-up data[2] showed a statistically significant increased risk of squamous cell carcinoma and of total non-melanoma skin cancer with selenium supplementation. However, analysis of secondary end-points at the first report indicated a reduced incidence of various other cancers in this study group.[1]

Subsequent study has suggested, in particular, an association between low selenium intake and the risk of prostate cancer; incidence was reduced by 63% in patients receiving the supplement.[3] Further follow-up confirmed this inverse association, but found that only men with low baseline selenium concentrations were likely to benefit.[4] Case-control studies have also reported that a higher selenium intake reduced the risk of advanced prostate cancer.[5,6] Higher pre-diagnostic selenium levels were associated with a lower risk of prostate cancer only for subjects with increased baseline prostate-specific antigen (PSA) concentrations (above 4 nanograms/mL). The authors hypothesised that selenium may slow tumour progression.[6] However, a large, randomised, controlled study[7] that used prostate cancer detection as the primary end-point, found no evidence of benefit with either selenium supplementation alone or selenium plus vitamin E, and prompted the suggestion that antoxidant supplements should not be recommended for preventing prostate cancer.[8] The possible value of selenium supplementation during conventional *treatment* of prostate cancer has also been reviewed.[9]

An inverse association between selenium concentrations and the risk of bladder cancer has been reported, although results from case-control studies are inconsistent. Controlled studies investigating the effect of selenium on bladder cancer recurrence and prognosis are planned.[10]

For a finding that selenium supplementation had no beneficial effect on overall mortality, see Effects on Mortality, below.

1. Clark LC, *et al.* Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA* 1996; **276:** 1957–63. Correction. *ibid.* 1997; **277:** 1520.
2. Duffield-Lillico AJ, *et al.* Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1477–81.
3. Clark LC, *et al.* Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998; **81:** 730–4.
4. Duffield-Lillico AJ, *et al.* Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int* 2003; **91:** 608–12.
5. Yoshizawa K, *et al.* Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998; **90:** 1219–24.
6. Li H, *et al.* A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* 2004; **96:** 696–703.
7. Lippman SM, *et al.* Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009; **301:** 39–51.
8. Gann PH. Randomized trials of antioxidant supplementation for cancer prevention: first bias, now chance—next, cause. *JAMA* 2009; **301:** 102–3.
9. Tabassum A, *et al.* Ingestion of selenium and other antioxidants during prostate cancer radiotherapy: a good thing? *Cancer Treat Rev* 2010; **36:** 230–4.
10. Brinkman M, *et al.* Use of selenium in chemoprevention of bladder cancer. *Lancet Oncol* 2006; **7:** 766–74.

Adverse Effects

Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea, dermatitis, metallic taste, garlic odour of breath, irritability, fatigue, and peripheral neuropathy.

Effects on glucose metabolism. A study into the effects of selenium on non-melanoma skin cancer found a higher rate of diabetes mellitus in those who received nearly 8 years of selenium supplements compared with placebo.[1] This prompted some to suggest that, until further studies show otherwise, people whose diets provide the recommended daily allowance of selenium should avoid supplements.[2]

1. Stranges S, *et al.* Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; **147:** 217–23.
2. Bleys J, *et al.* Selenium and diabetes: more bad news for supplements. *Ann Intern Med* 2007; **147:** 271–2.

Effects on mortality. A systematic review[1] of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies considered that selenium had no significant effect on mortality, either beneficial or harmful; however, it was recommended that future studies should be monitored closely for evidence of harm.

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Toxicity. *Chronic* exposure to high amounts of selenium has been reported to cause toxic effects on endocrine function, hepatotoxicity, gastrointestinal disturbances, and dermatological effects such as nail and hair loss and dermatitis. There has been some suggestion also of neurotoxicity, and a possible increased risk of amyotrophic lateral sclerosis. Studies have had conflicting results, and different inorganic and organic forms may vary greatly in biological activity, toxicity, and nutritional importance.[1]

Acute toxicity has also been reported; characteristic symptoms of selenium toxicity are garlicky or sour breath odour, vomiting and gastrointestinal disturbances, restlessness, hypersalivation, muscle spasms, haemolysis, liver necrosis, cerebral and pulmonary oedema, coma, and death.[1-3] A man who had taken vitamin tablets containing between 500 and 1000 times the amount of selenium labelled on the bottle developed generalised alopecia, changes in nail colour, diarrhoea, worsening fatigue, and paraesthesias. Two weeks after stopping the vitamins, early regrowth of hair and yellowish-white and red transverse lines on his nails were noted.[2] In another case, an elderly man who was concerned that he might have prostate cancer ingested 10 g of sodium selenite. He developed significant abdominal pain, vomiting and diarrhoea, hypotension, and ventricular tachycardia. Blood tests showed acidosis, hypokalaemia and an excessive selenium concentration. Despite symptomatic therapy, he suffered a cardiac arrest and died.[3] The FDA[4] found hazardous amounts of selenium in certain dietary supplements after receiving 43 reports of serious adverse effects in people using the products. Adverse effects usually started after 5 to 10 days of daily ingestion and included significant hair loss, muscle cramps, diarrhoea, joint pain, fatigue, deformation or loss of finger nails, and blistering skin. The daily dose taken by one patient was found to be about 24 mg, more than 400 times the US recommended daily allowance of 55 micrograms.[5]

1. Vinceti M, *et al*. Adverse health effects of selenium in humans. *Rev Environ Health* 2001; **16:** 233–51.
2. Clark RF, *et al*. Selenium poisoning from a nutritional supplement. *JAMA* 1996; **275:** 1087–8.
3. See KA, *et al*. Accidental death from acute selenium poisoning. *Med J Aust* 2006; **185:** 388–9.
4. FDA. FDA finds hazardous levels of selenium in samples of "Total Body Formula" and "Total Body Mega Formula": dietary supplement products linked to adverse reactions (issued 9th April 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116878.htm (accessed 22/07/10)
5. Sutter ME, *et al*. Selenium toxicity: a case of selenosis caused by a nutritional supplement. *Ann Intern Med* 2008; **148:** 970–1.

Pharmacokinetics

Selenium compounds are generally readily absorbed from the gastrointestinal tract. Selenium is stored in red blood cells, the liver, spleen, heart, and nails. It is converted in tissues to its metabolically active forms. Selenium is excreted in the urine, and to a lesser extent in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sele200; Selebound; ***Austral.***: Selemite-B†; Seleno Forte; ***Austria***: Selen; Selenase; ***Canad.***: Formula 2†; Micro Se; Selepen†; ***Cz.***: Selenase; ***Ger.***: Cefasel; Seleject†; Selen-loges; Selenase; Seltrans; Uniselen†; ***Gr.***: Selenase T; ***Hong Kong***: Selepen; ***Hung.***: Selen Plus; Selenor; Selesyn; ***Irl.***: Selesyn; ***Neth.***: Selenase; ***Port.***: Selenase; ***Switz.***: Selenase; ***Turk.***: Selenase; ***UK***: Selenase; ***Ukr.***: Cefasel (Цефаселя); Selenaza (Селеназа); ***USA***: Sele-Pak†; Selepen†.

Multi-ingredient Preparations. ***Arg.***: Antioxidante Plus; Centella Asiatica Compuesta; Fem Plus 50; Herbaccion Antioxidante; Hipersel; Ipri V Plus; Ipri V Total; Krebs Plus; Magnesio 102 Plus; Marathon Antioxidante; Parselenium E; Radite Plus; Selder; Senexon Plus; Super Antioxidante; Tonovital Antioxidante; ***Austral.***: Advanced Prostate Care; Bio ACE Excell; Femme-F; For Eyes; Homme-F; Lutein-Vision Advanced; Lutein-Vision; Prosta Balance; Prostate Care; Prostate Health Formula; Radiance; ResveratoX; ***Braz.***: Lymium; Ocuvite Lutein; ***Canad.***: DMTX; Ester Aces; Formula AO†; Formula PC†; Geri-Plus†; Prostaplex; Protect†; Super AO Factors; Super AO Formula†; Synergistic Selenium; Watkins Vision†; ***Chile***: Biofax†; Larotabe; Natursel-C; Reparex; Seresis; Vitagenol; ***Fr.***: Anti-oxydant 200; Anti-oxydant F4; Arbum; Bio-Selenium†; Cledist; Derm; Donalis; GliSODine Solaire; Gynalpha Plus†; Nat'Os; Naturophta Macula; Oxelio; Phytosolaire†; Proselem; Prostabiol; ProstaSecurA; Selenium + Zinc†; Selomega; Sun Vue; Superoxylase; Ultraselem; ***Hong Kong***: Ocuvite; ***Hung.***: Cellactive; Humet-R; ***India***: Actima; Adrovit; Advit-A; Alcored; Alphamix; Aminos; Aminut; Androvit; Antoxid; Aritom-L; Avitaz Plus; Aza Cap; B7 Plus; Beta-Sclerobion; Bio-10; Cad-11; Cadred; Cally Plus; Carbion; Carbona; Carfol-Z; Carofit-D; Carron; Cobadex-CZS; Cobal Plus; Cobalvit Plus; Cobanerve Plus; Cobanerve; Coq Forte; D-Gard; Delage; Deoxidant; Derantox; Dianuron; EC; Ecobal; Efcoba Forte; Eldervit-ZC; Elgrape; Elmecob Plus; Elnutra; Elonyl-Z; Elrox-AO; Enhance; Evica; Exerge-HC; Exerge; Exox; Fabulae; Fef-OD; Fejet-OD; Ferisis; Feronyl; Ferox; Ferox; Ferritop-Z; Festene; Fexid-Z; Fezec; Fifolar; Flintoff; Frednil; Freecad; Frezep; FRS; Furtipil-L; Gardian; Gatdor; Gencart; Glace; Glortho Forte; Hi-Q Plus; Hi-Q Plus; Hi-Q; Hi-Q; Homoxid; Horac; Hyrase; I-Lute; Inerve; Irocafe; Irossgold; Jivak; Joyce; Jstat; Kefive Plus; L-Bex; Lancitone-CS; Layo; Lizace; Luvion; Lyco-First; Lycobig; Lycodric; Lycolife; Lycomato; Lycomint; Lycostar-CM; Lycoswift; Lyto; Lytox; Macuchek; Maxoza; Me Plus; Me-Plus; Mecoday Plus; Medifer; Medifer; Megagin; Mexivit; Mufe; NBOxid; Nerwin-MD; Neuractin Forte; Nitizest; Nocad; Nofro; Nuromin; Ocufree; Omegachek; Optivision; Osfer; Ostebon-M; Ovista; Oxi-Red; Oxibet; Oxidon; Oxipre; Oxitra; Oxy-V; Oxyban; Oxydex; Oxyeye; Oxyla-AL; Oxytret; Oxyvit; Winofit; ***Indon.***: Antox; Artovit; Artro Plus; Azvit; Bevizil; Cerebrovit Active; Cerebrovit X-Cel; Colaskin; Danzet; Echinox; Eftian; Ekinase; Entrap; Erphacea; Ever E†; Eyebright; Eyevit; GCM; Hemaviton Brain Nutrient†; Hemaviton Skin Nutrient; Hepachol; Heparviton NF; Imulan; Imumax; Imunogard; Imunos; Imunos; Imunvit Plus; Joint Care Plus; Joint Care; Lanavision Plus; Lubire; Lutevision Extra; Lycoten; Lysmin Plus; Matoflam; Matovit AX; Maxivit; My Caps; Naturema; Neoboost Kids; Neoboost; Noros; Nufit; nutrivision; Nuvision; OA Forte; OA Plus; OA; Ocu-V; Oculex; Osteokom Forte; Osteokom; Osteor Plus; Osteor; Osvion Plus; Oxcal; Proliva; Qutan-10; Radiblock; Radivit; Reticopen; Retivit Plus; Retivit; Retop; Rheumatin Forte; Rheumatin; Risteon; Scaven; Selefit Plus; Seloxy AA; Seloxy; Stacare; Univoxy; Vantiz; Viceten-Z; Viopor-M Forte; Viopor-M; Viopor; Viostin Com; Vioxy-fm; Vioxy; Vitanox; ***Irl.***: Antox; Ocuvite†; ***Israel***: Colтect†; ***Ital.***: Betaeffe Plus; Bioesse Plus; Blunorm; Caresel; Euretin Duo; Fosfarsile Forte; Influ-Zinc; Konorderm; Longevital; Neomyrt Plus; Nolder†; Omegadin Plus; Ri-Donna; Salovit; Selene; Selenium-ACE†; Semel; Tannidin Plus; Tripondil; Valcap; Visu-len; ***Malaysia***: Bio-Cal; Eurobio Bio-Vizmax; Lycovid; Pharmaton with Selenium; Shine Bio ACE with Selenium; ***Mex.***: Alfavit-Eoxi†; ***Mon.***: Evestrel Jour Nuit†; ***Philipp.***: ALAnerv; Carofit; Nutrof†; Omnimune; Vigor-ACE; Zeman; ***Pol.***: Ekovit†; Rutinoscorbin Plus; ***Port.***: Ever-Fit Dermo; Fortal Vision; Rilastil Anti-Oxidante; Rilastil Dermo Solar; ***Rus.***: Complivit Oftalmo (Компливит Офтальмо); Tri-V Plus (Три-Ви Плюс)†; Triovit (Триовит); ***Singapore***: Glutamine Plus; Multitrace-5; Nutrivision†; Shine Bio-Cal; Vigor-Ace; ***Thai.***: Bio-Selenium Zinc; Ocuvite; ***Turk.***: ACE plus Selenyum; Prostamen; ***UK***: Antox; Aria; Betaimune; Estroven; GlucoSelene; NutriScience; Selene-Activ; Selenium Bonus; Silica-OK; Visio-Max; ***Ukr.***: Linex Immuno (Линекс Иммуно); Livonorm (Ливонорм); Ocuvite Lutein Forte (Окювайт Лютеин форте); Pravenor (Правенор); Triovit (Триовит); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін 3 Бета-каротином)†; Vitrum Cardio (Вітрум Кардио); Vitrum Foreyes Forte (Вітрум Форайз Форте); Vizivit (Визивит); Yohimbex-Garmonia (Йохимбекс-Гармония); ***USA***: Aces; Antioxidant Formula; AquADEKS; Immunicare; REQ49+; Udamin SP; Udamin; Vitaline Selenium; ***Venez.***: Kalsis; Uvagen.

Homoeopathic Preparations. ***Austral.***: Hangover Relief; ***Austria***: Crimax; Dalektro; Globuli gegen Hautausschlage; Selenium Med Complex; ***Canad.***: Acne; Adrisin†; Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Amphosca†; Cutisitum†; Fatigue; Formula FA 224†; Homeo-Form F†; Selenium Homaccord†; Ubicoenzyme; ***Chile***: Bioactiv I; ***Fr.***: Acidum Phosphoricum Compose†; Amphosca Orchitine; Amphosca Ovarine; Selenium Complexe No 99; ***Ger.***: Heweselen†; Infi-China; Schworocor A; Sedaselect; Selen-Wied; Selenarell; Selenokehl; Tondinel H; Tondinel; ***Neth.***: Dermalite; ***Switz.***: Omida comprimes homeopathiques pour la gorge; ***USA***: Preferred Remedies Fatigue.

Pharmacopoeial Preparations

USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Selenious Acid Injection; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules.

Serine *(BAN, USAN, rINN)*

β-Hydroxyalanine; S; Ser; Seriini; Serin; Serina; Serinas; L-Serine; Sérine; Serinum; Seryna; Szerin; Серин.

L-2-Amino-3-hydroxypropionic acid.

$C_3H_7NO_3$=105.1

CAS — 56-45-1 (serine); 302-84-1 (DL-serine).

UNII — 452VLY9402.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Serine). Fermentation product, extract or hydrolysate of protein. White or almost white crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. Protect from light.

USP 36: (Serine). White, odourless crystals. Soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Serine is a non-essential amino acid. It is used as a dietary supplement.

The racemic form (DL-serine) has been included in iron supplements to increase iron absorption.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Methyl Transfer.

Used as an adjunct in:. ***Austria***: Aktiferrin Compositum; Aktiferrin; ***Cz.***: Aktiferrin Compositum; Aktiferrin; ***Hung.***: Aktiferrin; ***Israel***: Aktiferrin-F; Foliferrin; ***Malaysia***: Aktiferrin-F†; ***Rus.***: Aktiferrin (Актиферрин); Aktiferrin Compositum (Актиферрин Композитум); ***Singapore***: Aktiferrin-F†; ***Switz.***: Aktiferrin-F†; Aktiferrin; ***Ukr.***: Aktiferrin (Актиферрин); Aktiferrin (Актиферрин).

Silicon

Křemík; Kiezel; Kisel; Krzem; Pii; Räni; Silicijs; Silici; Silício; Silicio; Silicis; Siliciu; Silicium; Silisium; Silisyum; Szilícium; Кремний; Силиций.

Si=28.085

CAS — 7440-21-3 (silicon); 2445-53-6 (monomethylsilanetriol).

UNII — Z4152N8IUI.

Silicic Acid

Acido Silícico; Hydrosilicic Acid; Kieselsäure; Kiezelzuur; Kiselsyre; Kyselina Křemičitá; Piihappo; Polysilicic Acid; Silicio Rūgštis; Silicon Hydroxide; Кремниевая Кислота.

CAS — 1343-98-2.

UNII — Y6O7T4G8P9.

Pharmacopoeias. *Jpn.* includes Light Anhydrous Silicic Acid.

Orthosilicic Acid

Monosilicic Acid; Silicon Tetrahydroxide; Tetrahydroxysilane.

$Si(OH)_4$=96.11

CAS — 10193-36-9.

UNII — 623B93YABH.

Profile

Silicon is a metalloid element that occurs widely in nature, mainly in the form of its compounds. It is an essential trace element and has been used in nutritional supplements, usually complexed with amino acids (silicon amino acid chelate; silicon hydrolysed vegetable protein chelate) to improve its bioavailability, or as its more soluble compounds, such as orthosilicic acid. Extracts of plants rich in silicon, such as equisetum (p. 2500.1) have been used similarly. Silicon also has industrial uses, particularly in electronics.

Silicic acids are compounds of silicon, oxygen, and hydrogen; when heated, they lose water to form silica gel (see Silicon Dioxide, p. 2208.3). Orthosilicic acid has been used as a source of silicon in nutritional supplements since it is the most bioavailable form of silicon (above). It is often given as choline-stabilised orthosilicic acid, a mixture with choline chloride (p. 2055.2).

Silicon compounds such as silicas (p. 2208.3) and silicones (p. 2209.2) also have pharmaceutical uses.

So called 'organic silicon' (monomethylsilanetriol) has been used in nutritional supplements. Organic silicon compounds have also been used topically for hair and skin disorders, including monomethylsilanetriol potassium citrate, methylsilanol mannuronate, a complex with hydroxyproline (methylsilanol hydroxyproline aspartate), and siloxanetriol alginate.

References.

1. Barel A, *et al*. Effect of oral intake of choline-stabilized orthosilicic acid on skin, nails and hair in women with photodamaged skin. *Arch Dermatol Res* 2005; **297:** 147–53.
2. Martin KR. The chemistry of silica and its potential health benefits. *J Nutr Health Aging* 2007; **11:** 94–7.
3. Wickett RR, *et al*. Effect of oral intake of choline-stabilized orthosilicic acid on hair tensile strength and morphology in women with fine hair. *Arch Dermatol Res* 2007; **299:** 499–505.
4. Spector TD, *et al*. Choline-stabilized orthosilicic acid supplementation as an adjunct to calcium/vitamin D3 stimulates markers of bone formation in osteopenic females: a randomized, placebo-controlled trial. *BMC Musculoskelet Disord* 2008; **9:** 85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Florasil; ***Fr.***: Dexsil Silicium.

Multi-ingredient Preparations. ***Arg.***: Bagovit Avant; Celu-Ikx; ***Austral.***: Advanced Bladder Care; ***Canad.***: Active Calcium; ***Fr.***: Cicactive; Dexsil Articulations; Dexsil Jambes Legeres; Dexsil Peau; Dexsil Sport; ***Hong Kong***: Active Calcium†; Procosa II†; ***India***: Orbone; ***Mex.***: Maxilene; ***Singapore***: Active Calcium†; Procosa II†; ***Switz.***: Venadoron; Wala Baume nasal doux; Wala Baume nasal.

Sodium Feredetate *(BAN, rINN)*

Ferédétate de Sodium; Feredetato sódico; Natrii Feredetas; Sodium Ironedetate; Натрия Фередетат.

The monohydrated iron chelate of the monosodium salt of ethylenediamine-*NNN'N'*-tetra-acetic acid; Iron (III) sodium ethylenediaminetetra-acetate monohydrate.

$C_{10}H_{12}FeN_2NaO_8.H_2O$=385.1

CAS — 15708-41-5 (anhydrous sodium feredetate).

ATC — B03AB03.

ATC Vet — QB03AB03.

UNII — 403J23EMFA.

Pharmacopoeias. In *Br.*

BP 2014: (Sodium Feredetate). A yellow or yellowish brown, hygroscopic, crystalline powder. A 1% solution in water has a pH of 4.0 to 6.5. Store in airtight containers.

Profile

Sodium feredetate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 1.42 g daily (equivalent to up to about 205 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ferrostrane; ***India***: Alfer; Barohem; Fearo-FD; Fedrer; Feranid; Ferfoz Plus; Ferofast; Icrate; Irex; Irored; Kiron-UP; ***Indon.***: FeRRIZ; ***Philipp.***: Ferrosmate; ***UK***: Sytron.

Multi-ingredient Preparations. ***India***: Alnaferon; Barohem; Calcinol; Carfer; Fearo-FD; Fenora-SF; Fepot; Feranid; Ferazin; Ferazin; Ferfoz Plus; Ferich; Ferimax; Ferimax; Ferimax; Ferisan; Feristar; Feriz-SF; Ferofast; Ferywel; Fesoft; Glozy; Haem-XT; Haemgrow; Irex; Irofact-SF; Kiron-UP; Melan; Melan; Mighty-SF; Oxi-Red.

Pharmacopoeial Preparations
BP 2014: Sodium Feredetate Oral Solution.

Sodium Ferric Gluconate Complex *(USAN)*

Ferric Sodium Gluconate; D-Gluconic acid, iron (3+) sodium salt; Hierro gluconato sódico, complejo de; Iron Gluconate; Natrii ferrigluconas; Sodium Ferric Gluconate; Sodium ferrigluconate; Sodium-Iron(III) Gluconate Complex.

$[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_x$

CAS — 34089-81-1.
ATC Vet — QB03AC07.
UNII — CC9149U2QX.

NOTE. Distinguish from Ferrous Gluconate.

Uses and Administration

Sodium ferric gluconate complex is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. The recommended dose for haemodialysis patients who are receiving epoetin therapy is 125 mg iron (10 mL) diluted in 100 mL sodium chloride 0.9%, and given as an intravenous infusion over 1 hour; it may also be given undiluted as a slow intravenous injection (at a rate of up to 12.5 mg/minute) during dialysis. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response.

For doses in children, see Administration in Children below.

Administration in children. Sodium ferric gluconate complex can be given to children to treat iron-deficiency anaemia (p. 2073.2). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. Children 6 years of age and older on haemodialysis and who are receiving epoetin therapy may be given 1.5 mg/kg of elemental iron (0.12 mL/kg), diluted in 25 mL sodium chloride 0.9% and infused over 1 hour, up to a maximum of 125 mg per dose. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response.

Anaemia of chronic renal failure. References.

1. Yorgin PD, *et al.* Sodium ferric gluconate therapy in renal transplant and renal failure patients. *Pediatr Nephrol* 2000; **15:** 171–5.
2. Fishbane S, Wagner J. Sodium ferric gluconate complex in the treatment of iron deficiency for patients on dialysis. *Am J Kidney Dis* 2001; **37:** 879–83.
3. Folkert VW, *et al.* Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher dose (> or =250 mg) administration. *Am J Kidney Dis* 2003; **41:** 651–7.
4. Michael B, *et al.* Sodium ferric gluconate complex in haemodialysis patients: a prospective evaluation of long-term safety. *Nephrol Dial Transplant* 2004; **19:** 1576–80.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p. 2076.1.

Hypersensitivity. For a discussion as to whether sodium ferric gluconate complex may be a safer alternative to iron dextran, see p. 2076.2.

Pharmacokinetics

Peak concentrations vary with the dose and rate at which sodium ferric gluconate complex is given. The volume of distribution does not appear to vary according to dose or rate. Elimination half-life varies by dose, and has been reported to be 0.85 hours for a dose of 62.5 mg and 1.45 hours for a dose of 125 mg; doses were given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Ferrlecit; ***Chile***: Pentaferr; ***Cz.***: Ferrlecit; ***Ger.***: Ferrlecit; ***Hung.***: Ferrlecit; ***India***: Efecient; ***Israel***: Ferrlecit; ***Ital.***: Extrafer; Ferlixit; Ferri-Emina; Ferritin Oti; Ferrosprint; Hemocromo; Rossepar; Sanifer†; ***Port.***: Ferritin Oti; ***USA***: Ferrlecit; Nulecit†.

Multi-ingredient Preparations. ***Ital.***: Ferritin Complex.

Sodium Fluoride

Fluorid sodný; Fluoruro sódico; Natrii Fluoridum; Natrio fluoridas; Natrium Fluoratum; Natriumfluorid; Nátriumfluorid; Natriumfluoridi; Sodium, fluorure de; Sodu fluorek; Sodyum Fluorür; Фторид Натрия.

NaF=41.99

CAS — 7681-49-4.
ATC — A01AA01; A12CD01.
ATC Vet — QA01AA01; QA12CD01.
UNII — 8ZYQ1474W7.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Sodium Fluoride). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol.

USP 36: (Sodium Fluoride). A white, odourless powder. Soluble 1 in 25 of water; insoluble in alcohol.

Uses and Administration

Sodium fluoride is used to prevent dental caries and may be used to increase bone density in osteoporosis (see p. 2090.1). Sodium fluoride is used as a source of fluoride in total parenteral nutrition.

The content of sodium fluoride is usually expressed in terms of the fluoride; 2.2 mg of sodium fluoride is equivalent to about 1 mg of fluoride. Fluoride content may also be expressed as ppm: fluoride 1 mg/litre equals 1 ppm. Each g of sodium fluoride provides about 23.8 mmol of sodium and fluoride.

For **dental caries prophylaxis**, sodium fluoride is used as an adjunct to diet and oral hygiene. It may render the enamel of teeth more resistant to acid, promote remineralisation, or reduce microbial acid production. Fluoride can be given by *fluoridation* of the public water supply (p. 2090.1) to achieve a usual fluoride concentration of 1 ppm in temperate regions. The concentration may vary from 0.6 to 1.2 ppm depending on the climatic temperature with the lower concentrations being used in hotter regions where more water is likely to be consumed. Fluoridation of salt at a minimum concentration of 200 mg of fluoride per kg of salt is an alternative. Fluoridation of milk has been tried in some countries.

Dental benefits from the use of *oral* fluoride supplements by adults are unsubstantiated. *Local application* of fluoride is effective; daily mouth-rinses of sodium fluoride 0.05% (about 227 ppm fluoride) or weekly mouth-rinses of sodium fluoride 0.2% (about 909 ppm) may be used. Sodium fluoride 2% (about 9090 ppm) solution is available for topical use, under professional supervision. Fluoridated toothpastes are now widely available and are a convenient source of fluoride. In the UK, the maximum permitted fluoride level in conventional toothpastes is sodium fluoride 0.33% (1500 ppm fluoride); higher concentrations of sodium fluoride 0.62 or 1.1% (2800 or 5000 ppm fluoride) are available under professional supervision. Sodium fluoride has also been applied topically as a varnish under professional supervision. Alternatively, sodium fluoride solutions or gels acidified with phosphoric acid (commonly known as acidulated phosphate fluoride preparations) may be used. These preparations are considered to increase the fluoride uptake by the enamel and protect the enamel from demineralisation. For maximum benefit, eating, drinking, or rinsing should be avoided for at least 15 to 30 minutes after topical fluoride application.

For uses and doses of sodium fluoride in children, see Administration in Children, below.

Other fluoride compounds used in oral hygiene products and toothpastes include aluminium fluoride, ammonium fluoride, calcium fluoride (p. 2053.1), dectaflur (p. 2059.1), magnesium fluoride (p. 2080.2) nicomethanol hydrofluoride, olaflur (p. 2085.1), potassium fluoride, sodium monofluorophosphate (p. 2091.3), and stannous fluoride (p. 2094.3). Other fluorides used in the fluoridation of water supplies include sodium silicofluoride (p. 2091.3).

Sodium fluoride has also been used, like some other fluoride compounds, in **rodenticides** and **insecticides**.

Administration in children. Sodium fluoride may be given as an *oral supplement* to children considered to be at high risk of caries. The daily dosage should be adjusted for the fluoride content of the drinking water, for fluorides ingested from other sources such as the diet, and for the age of the child. Guidelines in the USA and the UK both suggest that, where the drinking water contains less than 0.3 ppm of fluoride, children may be given the following doses according to age:

- under 6 months: not recommended
- 6 months to 3 years: sodium fluoride 550 micrograms (equivalent to 250 micrograms of fluoride) daily
- 3 to 6 years: 1.1 mg (equivalent to 500 micrograms of fluoride) daily
- 6 years and over: 2.2 mg (equivalent to 1 mg of fluoride) daily.

When drinking water contains 0.3 to 0.7 ppm (0.3 to 0.6 ppm in the USA) of fluoride lower doses should be considered. Specifically, it is recommended that no additional fluoride should be given to children less than 3 years of age and for older children the above doses should be halved. If the water contains more than 0.7 ppm (0.6 ppm in the USA) of fluoride, supplementation is not recommended. Tablets should be sucked or chewed before swallowing since the topical action of fluoride on enamel and plaque is considered to be more important than the systemic effect. The value of giving fluoride during pregnancy, to benefit the child, is not established.

Sodium fluoride may also be applied *locally* in children. As for adults, daily mouth-rinses of sodium fluoride 0.05% (about 227 ppm fluoride) or weekly mouth-rinses of sodium fluoride 0.2% (about 909 ppm) may be used, but are not recommended for children aged under 6 years because they are unable to effectively spit the rinse out after use. Fluoridated toothpastes may also be used by children, but the amount applied by children aged under 6 years should be supervised to avoid excessive use or ingestion. For children aged up to 3 years, a smear of toothpaste containing at least 0.22% sodium fluoride (1000 ppm fluoride) has been suggested, and for children aged from 3 to 6 years, a pea-sized amount of toothpaste containing about 0.3% sodium fluoride (1350 to 1500 ppm fluoride). If the water supply is fluoridated or if oral fluoride supplements are being given to children under the age of 7, then a toothpaste containing less than about 0.13% sodium fluoride (600 ppm fluoride) may be advisable. Toothpastes with higher concentrations may be prescribed for older children; 0.62% sodium fluoride (2800 ppm fluoride) in children over 10 years and 1.1% sodium fluoride (5000 ppm fluoride) in children over 16 years. Sodium fluoride may also be applied topically as a varnish or a gel, see Uses and Administration, above.

Dental caries prophylaxis. There is strong and consistent evidence in favour of the efficacy of fluoride in preventing or reducing the incidence of dental caries. However, there is no strong evidence that one form of topical fluoride is more effective than another.

References.

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3. Craig GC. Fluorides and the prevention of dental decay: a statement from the Representative Board of the British Dental Association. *Br Dent J* 2000; **188:** 654.
4. CDC. Recommendations for using fluoride to prevent and control dental caries in the United States. *MMWR* 2001; **50** (RR-14): 1–42. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5014.pdf (accessed 08/11/05)
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10. Marinho VCC, *et al.* One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 08/11/05).
11. Marinho VCC, *et al.* Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 08/11/05).
12. Petersson LG, *et al.* Professional fluoride varnish treatment for caries control: a systematic review of clinical trials. *Acta Odontol Scand* 2004; **62:** 170–6.
13. Twetman S, *et al.* Caries-preventive effect of sodium fluoride mouthrinses: a systematic review of controlled clinical trials. *Acta Odontol Scand* 2004; **62:** 223–30.
14. Jones S, *et al.* The effective use of fluorides in public health. *Bull WHO* 2005; **83:** 670–6.

15. WHO/FDI World Dental Federation/International Association for Dental Research. Beijing declaration: call to action to promote oral health by using fluoride in China and Southeast Asia (issued September 2007). Available at: http://www.fdiworldental.org/sites/default/files/media/Beijing_Declaration_English.pdf (accessed 22/07/10)
16. Azarpazhooh A, Main PA. Fluoride varnish in the prevention of dental caries in children and adolescents: a systematic review. *J Can Dent Assoc* 2008; **74:** 73–9.
17. Robinson C. Fluoride and the caries lesion: interactions and mechanism of action. *Eur Arch Paediatr Dent* 2009; **10:** 136–40.
18. Poulsen S. Fluoride-containing gels, mouth rinses and varnishes: an update of evidence of efficacy. *Eur Arch Paediatr Dent* 2009; **10:** 157–61.
19. Marinho VC. Cochrane reviews of randomized trials of fluoride therapies for preventing dental caries. *Eur Arch Paediatr Dent* 2009; **10:** 183–91.
20. Walsh T, *et al.* Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 10/06/10).
21. Hiiri A, *et al.* Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 10/06/10).

Fluoridation of water. Some countries add fluoride to water supplies to prevent dental caries. This has been the subject of much controversy.

References.
1. MRC. MRC working group report: water fluoridation and health (issued September 2002). Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002482 (accessed 10/03/08)
2. The British Fluoridation Society/The UK Public Health Association/The British Dental Association/The Faculty of Public Health. One in a million: the facts about water fluoridation. 2nd edition. Available at: http://www.bfsweb.org/onemillion/onemillion.htm (accessed 10/03/08)
3. Cheng KK, *et al.* Adding fluoride to water supplies. *BMJ* 2007; **335:** 699–702.
4. Yeung CA. A systematic review of the efficacy and safety of fluoridation. *Evid Based Dent* 2008; **9:** 39–43.
5. CDC. Populations receiving optimally fluoridated public drinking water—United States, 1992-2006. *MMWR* 2008; **57:** 737–41.

Human requirements. In the USA dietary reference intakes have been set for fluoride. These propose an adequate intake (see p. 2046.1) for dental caries prevention to be 4 mg daily in adult men and 3 mg in women;[1] lower values are suggested in children and adolescents, depending on age. The tolerable upper intake level is 10 mg daily in adults.[1]

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Osteoporosis. Fluoride has been given (usually as sodium fluoride or sodium monofluorophosphate) in the treatment of osteoporosis (p. 1168.1) to improve bone strength by inducing subclinical fluorosis. The main effect of fluoride on the skeleton is to stimulate osteoblasts and increase trabecular bone mass. Because antiresorptive drugs cannot restore lost bone mass, this is potentially valuable in the treatment of osteoporosis. However, too much fluoride can increase bone fragility, and the overall effect on the incidence of fracture has not been established. A systematic review[1] of 11 studies found that fluoride can increase bone mineral density (BMD) at the lumbar spine after 2 and 4 years of treatment, but did not reduce vertebral fractures. As the dose of fluoride increased, the risk of non-vertebral fractures and gastrointestinal adverse effects increased, without any effect on the vertebral fracture rate. Similar findings were reported in another review,[2] but an increased BMD in the hip was also reported, and although no effect was seen on the overall risk of fractures, a subgroup analysis found low daily doses of fluoride (20 mg or less) were associated with a reduction in vertebral and non-vertebral fracture risk. No difference was noted in the fracture risk reduction for either sodium fluoride or sodium monofluorophosphate. However, most studies in both reviews[1,2] also used calcium, making it difficult to assess the effect of fluoride alone on BMD or fracture risk. Fluoride is not considered first-line therapy for postmenopausal osteoporosis.[1]

1. Haguenauer D, *et al.* Fluoride for treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 07/04/10).
2. Vestergaard P, *et al.* Effects of treatment with fluoride on bone mineral density and fracture risk—a meta-analysis. *Osteoporos Int* 2008; **19:** 257–68.

Adverse Effects and Treatment

In the controlled amounts recommended for fluoridation of drinking water and at the recommended doses used in dentistry for caries prophylaxis, sodium fluoride has not been shown to have significant adverse effects.

In **acute** poisoning, sodium fluoride taken orally is corrosive, forming hydrofluoric acid in the stomach. Adverse effects include a salty or soapy taste, increased salivation, gastrointestinal disturbances, abdominal pain, weakness, drowsiness, faintness, and shallow breathing; more serious effects include hypocalcaemia, hypomagnesaemia, hyperkalaemia, tremors, hyperreflexia, tetany, convulsions, cardiac arrhythmias, shock, respiratory arrest, and cardiac failure. Death may occur within 2 to 4 hours.

Although there is much interindividual variation, a single oral dose of 5 to 10 g of sodium fluoride would be considered lethal in an untreated adult by most authorities. However, severe poisoning has been reported after oral doses of less than 1 g, and the minimum dose that can cause possibly fatal toxicity in children has been suggested to be 5 mg/kg of fluoride ion.

Treatment of acute poisoning involves gastric lavage with lime water or a weak solution of another calcium salt to precipitate fluoride, maintenance of high urine output, slow intravenous injections of calcium gluconate 10% for hypocalcaemia and tetany, and symptomatic and supportive measures. Magnesium sulfate may be given to correct hypomagnesaemia, and aluminium hydroxide may also reduce fluoride absorption. Haemodialysis may be considered.

Chronic fluoride poisoning may result in skeletal fluorosis, manifestations of which include increased density and coarsened trabeculation of bone and calcification in ligaments, tendons, and muscle insertions. Clinical signs are bone pain, stiffness, limited movement, and in severe cases, crippling deformities. Prolonged excessive intake by children during the period of tooth development before eruption can result in dental fluorosis characterised by mottled enamel. At fluoride concentrations in drinking water of 1 to 2 ppm (1 to 2 mg/litre) dental fluorosis is mild with white opaque flecks on the teeth. At higher concentrations, enamel defects become more severe with brown to black staining and the teeth have a pitted corroded appearance.

The **fluoridation** of water (above) has been a subject of considerable controversy. Suggestions that it increases the incidence of thyroid disorders, chromosome aberrations, and cancer have not been substantiated.

Reviews of the toxic effects of fluoride salts.

1. WHO. Fluorine and Fluorides. *Environmental Health Criteria 36.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc36.htm (accessed 08/11/05)
2. Whitford GM. The physiological and toxicological characteristics of fluoride. *J Dent Res* 1990; **69** (Spec Iss): 539–49.
3. Whitford GM. The metabolism and toxicity of fluoride. *Monogr Oral Sci* 1996; **16:** 1–153.
4. WHO. Fluorides. *Environmental Health Criteria 227.* Geneva: WHO, 2002. Available at: http://www.inchem.org/documents/ehc/ehc/ehc227.htm (accessed 08/11/05)
5. Dhar V, Bhatnagar M. Physiology and toxicity of fluoride. *Indian J Dent Res* 2009; **20:** 350–5.

Carcinogenicity. Based on comparisons of cancer mortality rates for communities residing in fluoridated and non-fluoridated cities, it was alleged that artificial fluoridation of water might be associated with an increased risk of cancer.[1] Re-examination of these data by others did not confirm the relationship, nor did further studies in a number of countries.[2] In Great Britain, the Working Party on Fluoridation of Water and Cancer[3] found nothing that could lead them to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, was capable of inducing cancer, or of increasing the mortality from cancer. In this respect, fluoridation of drinking water was considered safe. Further study in *animal* models by the USA National Toxicology Programme[4] found no evidence of carcinogenicity in female *rats* or in *mice* of either sex. A small number of osteosarcomas was found in male *rats* in the medium- and high-dose groups, although the association between sodium fluoride and the tumour was uncertain. A review of epidemiological evidence of possible carcinogens in drinking water stated that additional data gathered since 1990 did not support an association between the risk of osteosarcoma, or any other cancer, and the fluoride in drinking water.[5]

A cohort study of workers exposed to high levels of fluoride dust reported excess incidences of primary lung cancer and bladder tumours.[6]

1. Yiamouyiannis J, Burk D. Fluoridation and cancer: age-dependence of cancer mortality related to artificial fluoridation. *Fluoride* 1977; **10:** 102–25S.
2. Clemmesen J. The alleged association between artificial fluoridation of water supplies and cancer: a review. *Bull WHO* 1983; **61:** 871–83.
3. DHSS. *Fluoridation of water and cancer: a review of the epidemiological evidence: report of the working party.* London: HMSO, 1985.
4. Public Health Service report on fluoride benefits and risks. *JAMA* 1991; **266:** 1061–2, 1066–7.
5. Cantor KP. Drinking water and cancer. *Cancer Causes Control* 1997; **8:** 292–308.
6. Grandjean P, Olsen JH. Extended follow-up of cancer incidence in fluoride-exposed workers. *J Natl Cancer Inst* 2004; **96:** 802–3.

Effects on bones and joints. Exacerbation of **rheumatoid arthritis** in a 68-year-old woman was attributed to sodium fluoride given for osteoporosis.[1]

An increased risk of **hip fracture** in the elderly has been suggested as being associated with fluoridated water;[2] another study[3] reported that this association was confined to fluoride concentrations of more than 110 micrograms/litre. However, a large case-control study[4] found no increase in the risk of hip fracture for people ingesting fluoridated water at concentrations of about 1 mg/litre (1 ppm). Similarly, a large prospective study[5] in older white women found no increase in the risk of fractures with long-term exposure to fluoridated drinking water, and even a suggestion of a reduction in the risk of fractures of the hip and vertebrae, due to increased bone mineral density of the femoral neck and lumbar spine, in those women continuously exposed to fluoridation. An epidemiological study in a large rural Chinese population found that long-term fluoride exposure from drinking water containing 4.32 ppm or more increased the risk of overall fracture as well as hip fracture. Water containing 1 to 1.06 ppm decreased the risk of overall fractures relative to areas with negligible water fluoridation; a similar protective effect on the risk of hip fractures was not seen. Although the number of hip fractures were small, the authors suggested that this supported other findings that fluoride concentrations of about 1 ppm in drinking water do not increase the risk of hip fracture.[6] For comment on the influence of therapeutic doses of fluoride on the incidence of fractures, see above under Osteoporosis in Uses and Administration.

Use of fluoride, particularly in doses of 40 mg or more daily, may be associated with a **peripheral pain syndrome**, usually manifested as bone pain in the distal lower limbs, but sometimes involving the upper limbs and axial skeleton. The cause is uncertain: both stress fractures and increased bone growth at the site of pain have been proposed.[7]

Fluoride-related **bone disease** (skeletal fluorosis) manifesting as osteomalacia or osteosclerosis, has been reported after excessive consumption of tea (brewed, bottled, or iced).[8,9] Some bottled teas were found to have fluoride concentrations above the FDA's limit of 2.4 ppm for bottled beverages.[9]

1. Duell PB, Chesnut CH. Exacerbation of rheumatoid arthritis by sodium fluoride treatment of osteoporosis. *Arch Intern Med* 1991; **151:** 783–4.
2. Danielson C, *et al.* Hip fractures and fluoridation in Utah's elderly population. *JAMA* 1992; **268:** 746–8.
3. Jacqmin-Gadda H, *et al.* Fluorine concentration in drinking water and fractures in the elderly. *JAMA* 1995; **273:** 775–6.
4. Hillier S, *et al.* Fluoride in drinking water and risk of hip fracture in the UK: a case-control study. *Lancet* 2000; **355:** 265–9.
5. Phipps KR, *et al.* Community water fluoridation, bone mineral density, and fractures: prospective study of effects in older women. *BMJ* 2000; **321:** 860–4.
6. Li Y, *et al.* Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. *J Bone Miner Res* 2001; **16:** 932–9.
7. Jones G, Sambrook PN. Drug-induced disorders of bone metabolism: incidence, management and avoidance. *Drug Safety* 1994; **10:** 480–9.
8. Hallanger Johnson JE, *et al.* Fluoride-related bone disease associated with habitual tea consumption. *Mayo Clin Proc* 2007; **82:** 719–24. Correction. *ibid.*; 1017. [dosage error]
9. Whyte MP. Fluoride levels in bottled teas. *Am J Med* 2006; **119:** 189–90.

Effects on the kidneys. Nephrotoxicity has been associated with high plasma concentrations of fluoride during anaesthesia with fluorine-containing anaesthetics such as methoxyflurane (p. 1907.3). Elevated fluoride ion concentrations have also been noted in the plasma of patients receiving enflurane or isoflurane, although no clinical effect on renal function was found (see Effects on the Kidneys, p. 1900.1 and Metabolism, p. 1904.3).

Fluorosis. Discussions of chronic fluorosis.[1-5] In a 1994 report, WHO considered that in temperate climates, *teeth* seemed not to be affected if fluoride concentrations in drinking water were not greatly above 1 ppm; fluorosis affecting bone had not been detected at concentrations of 4 to 8 ppm in temperate regions, although it could occur at concentrations of more than 6 ppm in tropical areas.[6] However, a later systematic review[7] of the effects of water fluoridation, which included 214 studies worldwide, considered that at a concentration of 1 ppm, an estimated 12.5% of exposed people would develop sufficient fluorosis of their teeth to cause aesthetic concern. Swallowing of fluoridated toothpaste by young children has been implicated as a risk factor for fluorosis.[4,8] Higher concentrations of fluoride in toothpaste have been associated with less caries, but with higher levels of fluorosis,[9] and toothpastes with lower concentrations of fluoride have been recommended for use in children.[8,9] The use of infant formula feeds reconstituted with fluoridated water may result in ingestion of large amounts of fluoride[5] and subsequent fluorosis;[3] bottled water may also contain fluoride.[5]

Skeletal fluorosis associated with excess tea consumption has also been reported (see Effects on Bones and Joints, above).

1. Anonymous. Chronic fluorosis. *BMJ* 1981; **282:** 253–4.
2. Mason JO. A message to health professionals about fluorosis. *JAMA* 1991; **265:** 2939.
3. Horowitz HS. Proper use of fluoride products in fluoridated communities. *Lancet* 1999; **353:** 1462.
4. Whelton HP, *et al.* A review of fluorosis in the European Union: prevalence, risk factors and aesthetic issues. *Community Dent Oral Epidemiol* 2004; **32** (suppl): 9–18.
5. Levy SM. An update on fluorides and fluorosis. *J Can Dent Assoc* 2003; **69:** 286–91.
6. WHO. Fluorides and oral health: report of a WHO expert committee on oral health status and fluoride use. *WHO Tech Rep Ser 846* 1994. Available at: http://libdoc.who.int/trs/WHO_TRS_846.pdf (accessed 24/03/09)

7. McDonagh MS, *et al*. Systematic review of water fluoridation. *BMJ* 2000; **321:** 855–9.
8. Rock WP, Sabieha AM. The relationship between reported toothpaste usage in infancy and fluorosis of permanent incisors. *Br Dent J* 1997; **183:** 165–70.
9. Steiner M, *et al*. Effect of 1000 ppm relative to 250 ppm fluoride toothpaste: a meta-analysis. *Am J Dent* 2004; **17:** 85–8.

Gum disease. In the Davangere district of India, the fluoride concentration in the drinking water ranges from 1.5 to 3 ppm; there is virtually no dental care. In a study of patients with dental fluorosis in this district, a strong association was found between the occurrence of periodontal disease and the severity of fluorosis; periodontitis was also high in subjects with poor oral hygiene. Gingivitis reduced as the degree of fluorosis increased. Fluoride may have a role in the aetiology and pathogenesis of gum disease.[1]

1. Vandana KL, Reddy MS. Assessment of periodontal status in dental fluorosis subjects using community periodontal index of treatment needs. *Indian J Dent Res* 2007; **18:** 67–71.

Hypersensitivity. Dermatitis, urticaria, headaches, gastrointestinal reactions, stomatitis, and mouth ulcers have all been reported as hypersensitivity reactions after use of fluoride-containing toothpastes, tablets, drops or drinking water.[1] Topical treatment of the teeth with a sodium fluoride preparation has been reported to cause severe disseminated acute urticaria and facial angioedema, requiring hospitalisation.[2] However, 2 other cases of reaction to the same commercial preparation were considered to be due to colophony (p. 2484.2) contained in the preparation.[3] It has been suggested that, in cases of probable toothpaste allergy, lack of response to patch tests on the skin may be because fluoride crosses the oral mucous membrane more easily than the skin.[4]

Stomatitis has also been reported after use of gels containing olaflur and dectaflur.[5]

1. Mummery RV. Claimed fluoride allergy. *Br Dent J* 1984; **157:** 48.
2. Camarasa JG, *et al*. Contact urticaria from sodium fluoride. *Contact Dermatitis* 1993; **28:** 294.
3. Isaksson M, *et al*. Contact allergy to Duraphat. *Scand J Dent Res* 1993; **101:** 49–51.
4. Brun R. Recurrent benign aphthous stomatitis and fluoride allergy. *Dermatology* 2004; **208:** 181.
5. Ganter G, *et al*. Contact dermatitis and stomatitis due to amine fluoride. *Contact Dermatitis* 1997; **37:** 248.

Overdosage. References.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.
2. Gessner BD, *et al*. Acute fluoride poisoning from a public water system. *N Engl J Med* 1994; **330:** 95–9.
3. Arnow PM, *et al*. An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. *Ann Intern Med* 1994; **121:** 339–44.
4. Shulman JD, Wells LM. Acute fluoride toxicity from ingesting home-use dental products in children, birth to 6 years of age. *J Public Health Dent* 1997; **57:** 150–8.

Precautions

When considering fluoride supplementation, allowance should be made for fluorides ingested from other sources; fluoride supplements in children are not generally recommended when the fluoride content of drinking water is over 0.7 ppm (0.6 ppm in the USA) (see also Uses and Administration, p. 2089.2). Care should be taken to prevent children swallowing excessive fluoride after topical application to teeth.

Patients with impaired renal function may be particularly susceptible to fluorosis. Regular dialysis with fluoridated water may result in additional fluoride absorption; a maximum concentration of 0.2 ppm of fluoride in the dialysate has been recommended. Dialysis patients not using deionised water are at risk from changes in the fluoride content of the water supply.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium fluoride as not porphyrinogenic when used for caries prevention; it may be used as a drug of first choice and no precautions are needed. Sodium fluoride is not classified when used as a mineral supplement.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Aluminium, calcium, and magnesium salts may decrease the absorption of fluoride.

Pharmacokinetics

Sodium fluoride and other soluble fluorides are readily absorbed from the gastrointestinal tract. Inhaled fluorides (from industrial fumes and dusts) are absorbed through the lungs. Fluoride is deposited mainly in the bones and teeth. It is principally excreted in the urine but small amounts may also be excreted in faeces and sweat. It crosses the placenta and is present in saliva, nails, and hair. There is some evidence of distribution into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aquafresh Ultimate White; Elgydium Junior; Elgydium Proteccion Caries; Fluordent; Fluorogel; Fluoroplat; Naf Buches; Opalescence; ***Austral.***: Flurets†; NeutraFluor; ***Austria***: Duraphat; Fluodont†; Sensodyne Proschmelz; Zymafluor; ***Belg.***: Fluodontyl; Fluor; Z-Fluor; ***Braz.***: Fluotrat; ***Canad.***: Fluocal†; Fluor-A-Day; Nafrinse†; Oro-NaF†; PDF; Perfect Solutions†; Sensodyne ProNamel; Solu-Flur†; Xerolube†; ***Chile***: Caristop; Fluocaril Bi-Fluore†; Gengisyl†; Vitaflur; Vitis Orthodontic Pasta; Vitis Pasta; ***Cz.***: Zymafluor; ***Denm.***: Duraphat; Fluorolex; ***Fin.***: Duraphat; Fludent; Fluorilette†; ***Fr.***: Duraphat; Elgydium Protection Caries; Fluodontyl; Fluor†; Fluorex; Sanogyl; Zymafluor; ***Ger.***: Duraphat; Fluoretten; Ossin†; Sensodyne Proschmelz; Zymafluor†; ***Gr.***: Apoflux; Duraphat; Flurexil; ***Hung.***: Arthrofluor†; Dentocar; Zymafluor; ***India***: Denex-PF; Naf; Otoflour; ***Indon.***: Fluoricare; Listermint†; Vinafluor; ***Irl.***: Duraphat; ***Israel***: Duraphat; Fluvium†; Teeth Tough†; Zymafluor; ***Ital.***: AZ Verde†; Cleanicdent; Dentosan Extra Fluor†; Duraphat; Eburdent; Fluor-In†; Fluorinse; Listerine Difesa; Zymafluor; ***Mex.***: Audifluor; ***Neth.***: Dentigel; Duraphat; En-De-Kay; Zymafluor; ***Norw.***: Duraphat; Fluorette; Flux; ***Philipp.***: Infaflor; ***Pol.***: Fluossen†; Zymafluor†; ***Port.***: Duraphat; Elmex; Fluor-In; Maxfluor; Zymafluor; ***S.Afr.***: Listerfluor; Zymafluor; ***Spain***: Fluodontyl†; Fluor; ***Swed.***: Dentan; Dentirol Fluor; Duraphat; Fludent; Fluorette; Top dent fluor; ***Switz.***: Duraphat; Paro Fluor; Sensodyne Proemail Fluorid; Zymafluor; ***Thai.***: Flu-Ride; Zymafluor; ***Turk.***: Dentiflour; Fluoxytil; Zymafluor; ***UK***: Duraphat; En-De-Kay; Fluor-A-Day; Fluorigard; Sensodyne Mint; ***USA***: ACT; Denta Plus; DentaGel; Dry Mouth Relief; EtheDent; Fluor-a-day; Fluorigard; Fluorinse; Fluoritab; Flura; Karidium; Karigel-N; Karigel; Listerine Tooth Defense; Ludent; Luride; Minute-Gel; MouthKote F/R; NeutraGard Advanced; OrthoWash; Pediaflor†; Pharmaflur; Phos-Flur; Point-Two; Prevident; ReNaf; SF 5000 Plus; SF Gel; SodiPhluor; Thera-Flur.

Multi-ingredient Preparations. ***Arg.***: ADC Fluor; Aquafresh Sensitive; Bucal Hyper Sensitive; Bucal Tac Whitening Gel; Buclorhex; Cal-C-Vita Fluor; Desensyl; Elgydium Dientes Sensibles; Emoform Total; Esmedent con Fluor; Esmedent; Fluordent PX; Fluordent PX; Fluorogel 2001 para Dientes Sensibles; Fluorogel 2001; Kdesin; Ostelin F; Parodontax Fluor; Pervinox Extra Mint; Pervinox Fresh Mint; Pervinox Fruit; Revelplac 2001; Sensident; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Blanqueador; Sensodyne Cool; Sensodyne Proteccion Total; Sensodyne Rapido Alivio; Squam; Squam; Tac Fluor; Tri-Vi-Fluor; Vitasol F; ***Austral.***: Macleans Sensitive; ***Austria***: Elmex; Ossiplex†; ***Belg.***: Elmex; Fluocaril; Sedemol; Sulfa-Sedemol; ***Braz.***: Calci-Ped; Calciferol Composto; Calcifix B12; Calcifix Irradiado; Calcifluol; Calcigenol; Calcinol Complexo; Calciofar; Calferon; Calvita B12†; Deficical B12; Femme com Fluor; Kindcalcio†; Malvatricin Branqueador†; Malvatricin Natural†; Malvatricin; Malvatrikids F; Malvatrikids Junior; Natalins com Fluor; Nativit Fluor; Noplak Max; Poly-Vi-Fluor; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool†; Sensodyne Fresh Mint; Sensodyne Protecao Total; Tri-Vi-Fluor; ***Canad.***: Cepacol with Fluoride†; Gel-Kam Dentinbloc; Listerine Antiseptic with Fluoride; Oral-B Anti-Bacterial with Fluoride; Perfect Solutions 1-Minute†; Perfect Solutions In Office Rinse†; Sensodyne-F; Sensodyne; ***Chile***: Cariax; Caristop; Elgydium Dientes Sensibles; FKD; Fluorencil; Listermint Con Fluor†; Oralgene; Orthokin; Sensaid; Vitis Encias Pasta; Vitis Orthodontic Colutorio; ***Cz.***: Elmex; ***Denm.***: Bifluorid; ***Fin.***: Elmex; Xerodent; ***Fr.***: Bifluorid; Elgydium Dents Sensibiles; Elgydium Protection email; Fluocaril Bi-Fluore; Fluocaril blancheur†; Fluocaril dents sensibles†; Fluocaril Junior and Fluocaril Kids†; Fluoselgine; Fluosterol; Gum HaliControl; Listerine protection dents et gencives; Parogencyl prevention gencives†; Paroplak†; Sanogyl Fluo†; Sensigel; Zymaduo; ***Ger.***: D-Fluoretten; Elmex; Fluor-Vigantoletten; Gum SensiPro†; Ledermix Fluorid; Multifluorid†; Ossiplex†; Ossofortin Plus; Zymafluor D†; ***Gr.***: Fluocaril Bi-Fluore; ***Hong Kong***: Listerine Teeth and Gum Defence; Sensodyne Gentle†; ***Hung.***: Elmex; Klimin; ***India***: AM-PM Junior; AM-PM Special; Clohex Plus; Dentasep-F; Florocid; Fluoritop-MR; Garlin; HAA; Icee Mth Wsh; Kidodent; Me-Fresh; Nitra-OR; ***Indon.***: Hical; Osteocal Plus; Sensodyne Cool Gel; Solvita Baby; ***Irl.***: Colgate Total; ***Israel***: Elmex; Elmex; ***Ital.***: Actifluor; Actisens; Aqua Emoform; AZ Protezione Gengive; AZ Tartar Control; Benodent; Broxo al Fluoro; Colgate Total; Dentosan Junior; Dentosan Ortodontico; Dentosan Sensibile; Eburdent F; Elmex; Emoform Actisens; Emoform-Tat; Fluocaril Bi-Fluore; Fluocaril; Lacalut; Oral-B Collutorio Denti Gengive; Oral-B Denti Sensibili; Osteo Complex; Otofluor; Plax; Ridiodent; ***Mex.***: Arnident; Fluoxytil†; ***Neth.***: Elmex; Fluocaril Bi-Fluore†; ***Norw.***: Xerodent; ***NZ***: Listerine Teeth Defence; ***Philipp.***: Listerine Teeth & Gum Defense; Natalbes; Natalins-M; Poly-Vi-Flor; Xylorinse; ***Pol.***: Bifluorid; Elmex; Fluormex; Fluoro-zel; ***Port.***: Bexident; Fluocaril Bi-Fluore; ***Rus.***: Elgyfluor (Эльгифлуор); Parodontocide (Пародонтоцид); Sensigel (Сенсигель); ***S.Afr.***: Ossiplex†; ***Singapore***: 2Sensitive; Elgydium Sensitive; Elgyfluor†; Listerine Teeth & Gum Defense; Sensigel; ***Spain***: Vitagama Fluor†; ***Swed.***: Bifluorid; Xerodent; ***Switz.***: Elmex; Paro aux fluorures d'amines Gelee; ***Thai.***: FBC Plus; Poly-Vi-Flor†; ***Turk.***: D-Flor†; Kalsifluor; Nesgarin; Sensodyne Gel; Sensoral; Xialine; Zymaduo; ***UK***: AS Saliva Orthana; CB12; Dentyl pH; Hydrotab; Listermint with Fluoride; Macleans Mouthguard; Sensodyne-F; ***Ukr.***: Vitaftor (Вітафтор)†; ***USA***: ControlRx; Florical; Fluoridex Daily Defense Sensitivity Relief; Mulvidren-F Softab; Poly-Vi-Flor with Iron; Poly-Vi-Flor; Polytabs-F; Sensitivity Protection Crest; Sensodyne iso-active; Soluvite; Tri-A-Vite F; Tri-Vi-Flor; Tri-Vi-Floro; Trivitamin Fluoride Drops; Vi-Daylin/F; ***Venez.***: Sensodyne.

Pharmacopoeial Preparations

BP 2014: Sodium Fluoride Mouthwash; Sodium Fluoride Oral Drops; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets; **USP 36:** Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Sodium Fluoride and Acidulated Phosphate Topical Solution; Sodium Fluoride and Phosphoric Acid Gel; Sodium Fluoride Gel; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Sodium Monofluorophosphate

Fluorofosfato sódico; MFP Sodium; Monofluorofosfato sódico; Natrii Monofluorophosphas; Natriummonofluorfosfat; Natriummonofluorifosfaatti; Sodium Fluorophosphate; Монофторфосфат Натрия.

Disodium phosphorofluoridate.

Na_2PO_3F=143.9

CAS — 10163-15-2.

ATC — A01AA02; A12CD02.

ATC Vet — QA01AA02; QA12CD02.

UNII — C810JCZ56Q.

Pharmacopoeias. In *US*.

USP 36: (Sodium Monofluorophosphate). A white to slightly grey, odourless powder. Freely soluble in water. pH of a 2% solution in water is between 6.5 and 8.0.

Profile

Sodium monofluorophosphate is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) in toothpastes for the prevention of dental caries. It may also be given orally in the management of osteoporosis.

In the UK, the maximum permitted fluoride level in toothpastes is 1.14% of sodium monofluorophosphate (0.15% or 1500 ppm of fluoride). Formulations for children under 7 years of age typically contain sodium monofluorophosphate 0.38% (500 ppm fluoride); higher concentrations may be used, but the amount applied should be supervised to avoid excessive use or ingestion.

Other monofluorophosphate salts permitted for use in oral hygiene products and dentifrices include ammonium monofluorophosphate, calcium monofluorophosphate, and potassium monofluorophosphate. Glutamine monofluorophosphate has been used for osteoporosis.

Osteoporosis. For reference to the use of fluorides, including sodium monofluorophosphate, in the treatment of osteoporosis, see under Uses and Administration of Sodium Fluoride, p. 2090.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aquafresh Triple Proteccion; ***Austral.***: Fluorocare; ***Braz.***: Confident; Emoform AP; Malvatricin Antitartaro†; Unique Plus; ***Chile***: Fluocaril Bi-Fluore†; Gengisyl†; Oralfresh Proteccion; ***India***: Denex-PF; Inissiate; Kidodent; Magdent-R; ***Ital.***: Isifluor; Neo Fluostomygen; Platinum; ***USA***: Biotene Dry Mouth; ***Venez.***: Aquafresh.

Multi-ingredient Preparations. ***Arg.***: Adolcas; Desensyl; Emoform Total; Fluordent PX; Hexiben; Negaporosis; Sensodyne-F; Squam; ***Austria***: Fluocalcic†; ***Belg.***: Fluocaril; ***Braz.***: Emoform AT; Fluomint†; Malvatricin Antiplaca†; Malvatricin Branqueador†; Malvatricin Dentes Sensiveis†; Malvatricin Natural Organic†; Malvatricin Natural Soft†; Malvatricin Natural†; Malvatricin Plus†; Odontis-Rx; Sensodyne-F†; ***Chile***: Caristop Sensitive; Caristop; Fluorencil; ***Cz.***: Tridin; ***Fr.***: Emoform Dents Sensibles; Fluocaril Bi-Fluore; Fluocaril Junior and Fluocaril Kids†; Sanogyl Fluo†; ***Ger.***: Tridin Forte†; Tridin; ***Gr.***: Fluocaril Bi-Fluore; ***Hong Kong***: Tridin; ***Hung.***: Tridin; ***India***: Denoseal-F; Denpot-KF; Hydent K; Hydent; K-Dent-F; Klinit; Magdent-KF; Nitra; Nitrodent-KF; Nitrodent-R; ***Ital.***: Aqua Emoform; Biogreen; Broxo al Fluoro; Dentosan Junior; Emoform-Tat; Fluocaril Bi-Fluore; FluorD3†; Formedico; Neo Emoform; Neo-Stomygen; Periogard Plus; Stomygen; Tridin; ***Mex.***: Dentsiblen†; Fluoxytil†; Periodentyl; ***Neth.***: Fluocaril Bi-Fluore†; ***Pol.***: Fluoro-zel; ***Port.***: Fluocaril Bi-Fluore; ***Singapore***: Biotene; Oral-Seven; ***Switz.***: Emoform-F au fluor†; ***Turk.***: Sensodyne-F; ***USA***: Monocal; Optimoist; Sensodyne-F.

Sodium Silicofluoride

Fluorosilicato sódico; Fluosilicato sódico; Hexafluorosilicato sódico; Silicofluoruro sódico; Sodium Fluorosilicate; Sodium

Fluosilicate; Sodium Hexafluorosilicate; Кремнефтористый Натрий.
Na_2SiF_6=188.1
CAS — 16893-85-9.
UNII — 806AV2E065.

Profile

Sodium silicofluoride is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) for the fluoridation of drinking water. It has also been considered for inclusion in oral hygiene products.

Other silicofluoride (fluorosilicate) salts permitted for use in oral hygiene products include ammonium silicofluoride, magnesium silicofluoride, and potassium silicofluoride.

Sodium silicofluoride has also been used in insecticides.

Sorbitol

E420; D-Sorbitol; Sorbitoli; Sorbitolis; Sorbitolum; Szorbit; Сорбит; Сорбитол.
D-Glucitol.
$C_6H_{14}O_6$=182.2
CAS — 50-70-4.
ATC — A06AD18; A06AG07; B05CX02; V04CC01.
ATC Vet — QA06AD18; QA06AG07; QB05CX02; QV04CC01.
UNII — 506T60A25R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF.*

US includes only Sorbitol Solution.

Ph. Eur. 8: (Sorbitol). A white or almost white crystalline powder. It exhibits polymorphism. Very soluble in water; practically insoluble in alcohol.

USNF 31: (Sorbitol). White, odourless, hygroscopic powder, granules, or crystalline masses having a sweet taste with a cold sensation. Soluble 1 in 0.45 of water; sparingly soluble in alcohol; practically insoluble in solvent ether. pH of a 10% w/w solution in water is between 3.5 and 7.0.

Incompatibility. For reference to the incompatibility of sorbitol with hydroxybenzoates, see p. 1757.3.

Uses and Administration

Sorbitol is a polyhydric sugar alcohol (polyol) with about half the sweetening power of sucrose. It occurs naturally in many fruits and vegetables and is prepared commercially by the reduction of glucose.

It has been given as a 30% solution as an alternative to glucose in parenteral nutrition (p. 2044.1) but its use is not recommended because of the risk of lactic acidosis.

Sorbitol may be given as an osmotic laxative in the management of constipation (p. 1804.3); daily doses of about 14 to 42 g orally, or 30 to 36 g rectally have been used.

Solutions containing about 3% of sorbitol are used as irrigating fluids in transurethral surgical procedures.

Sorbitol was formerly given intravenously as a 50% solution as an osmotic diuretic.

Sorbitol also acts as a bulk sweetening agent. It is used in limited quantities as a sweetener in energy-reduced diabetic food products. It is also used as an alternative to sucrose in many sugar-free oral liquid preparations and in sugar-free foods as it is less likely to cause dental caries.

Sorbitol also has humectant and stabilising properties and is used in various pharmaceutical and cosmetic products including toothpaste.

Adverse Effects and Precautions

As for Fructose, p. 2068.2.

Effects on electrolyte balance. Sorbitol is used as a vehicle in some proprietary preparations of activated charcoal intended to reduce drug absorption after poisoning; the sorbitol increases the palatability of the preparation and also produces an osmotic diarrhoea that facilitates elimination of the activated charcoal and adsorbed drug. Repeated doses of such preparations are often advocated but there have been reports[1-3] of severe sorbitol-induced hypernatraemia in adults and children. In all cases, charcoal in a 70% sorbitol suspension had been given. It has been recommended that fluid and electrolyte balance be monitored closely, and that preparations with lower concentrations of sorbitol be used if possible.[2,3] For debate about such multiple dose therapy see Poisoning, under Activated Charcoal, p. 1538.1.

1. Gazda-Smith E, Synhavsky A. Hypernatraemia following treatment of theophylline toxicity with activated charcoal and sorbitol. *Arch Intern Med* 1990; **150:** 689 and 692.
2. Allerton JP, Strom JA. Hypernatremia due to repeated doses of charcoal-sorbitol. *Am J Kidney Dis* 1991; **17:** 581–4.
3. Farley TA. Severe hypernatremic dehydration after use of an activated charcoal-sorbitol suspension. *J Pediatr* 1986; **109:** 719–22.

Effects on the gastrointestinal tract. Sorbitol is often used as a sweetener in sugar-free preparations and the risk of sorbitol-induced diarrhoea associated with such products has been highlighted.[1-4] Chronic sorbitol-induced diarrhoea with associated pneumatosis intestinalis has been reported in a child given 21.7 g sorbitol daily in liquid medications.[5] Colonic and upper gastrointestinal necrosis, including some fatalities, have been reported after use of sodium polystyrene sulfonate in sorbitol, and may have been associated with the sorbitol component, see p. 1575.3.

It has also been suggested that sorbitol contributed to the morbidity in a patient who developed septicaemia as a complication of intestinal pseudo-obstruction, after the use of charcoal with sorbitol to treat self-poisoning with theophylline.[6] It was suggested that gaseous distension after bacterial metabolism of sorbitol had rendered the bowel wall ischaemic, facilitating passage of bacteria or of endotoxin into the systemic circulation.

1. Brown AM, Masson E. Hidden' sorbitol in proprietary medicines - a cause for concern? *Pharm J* 1990; **245:** 211.
2. Edes TE, *et al.* Diarrhea in tube-fed patients: feeding formula not necessarily the cause. *Am J Med* 1990; **88:** 91–3.
3. Johnston KR, *et al.* Gastrointestinal effects of sorbitol as an additive in liquid medications. *Am J Med* 1994; **97:** 185–91.
4. Bauditz J, *et al.* Severe weight loss caused by chewing gum. *BMJ* 2008; **336:** 96–7.
5. Duncan B, *et al.* Medication-induced pneumatosis intestinalis. *Pediatrics* 1997; **99:** 633–6.
6. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7:** 74–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sorbitol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Sorbitol is poorly absorbed from the gastrointestinal tract after oral or rectal use. It is metabolised mainly in the liver, to fructose (see p. 2068.3), a reaction catalysed by the enzyme sorbitol dehydrogenase. Some sorbitol may be converted directly to glucose by the enzyme aldose reductase.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Sorbilax; ***Braz.***: Minilax; ***Rus.***: Sorbit (Сорбит); ***Swed.***: Resulax.

Multi-ingredient Preparations. ***Arg.***: Humectante Bucal; Micronema; ***Austral.***: Aquae; Carbosorb XS; Fleet Micro-Enema†; Microlax; ***Austria***: Glandosane; Microklist; Yal; ***Belg.***: Microlax; Spagulax Sorbitol†; ***Braz.***: Anekron; Colachofra; Hepalin; Hepatox; ***Canad.***: Charac Tol; Charcodote; Microlax; Moi-Stir; ***Chile***: Secand; Solucion Irrigacion Vesical†; Tabletas Phillips; Ureadin Rx PS; ***Cz.***: Yal; ***Denm.***: Klyx; ***Fin.***: Klyx; Microlax; ***Fr.***: Actigess†; Apilaxe; Artisial; Cicatridine; Hepagrume; Hepargitol; Microlax; Nivabetol†; Parapsyllium; Schoum; Spagulax au Sorbitol†; SST†; ***Ger.***: Flacar; Freka-Drainjet Purisole†; Glandosane; Microklist; Saliva natura; Xerotin; Yal; ***Gr.***: Collyre Vitaphakol; Suprin; ***Hong Kong***: Glandosane; Microlax†; Osmofundin†; Salivart†; ***Hung.***: Balansol; Rehydrosol†; ***India***: Al-Live; Alkasol-P; Aminocore 5-S Plus; Aminofusion; Anorexin Plus; Aqwet; Bioferum Forte; Bioffin; Brofentol; Celemin; Celemix Combi; Cyaptin-SF; Cyaptin; Cyp-L; Cypine-TS; Cypolin; Cypon-I; Cyprea-T; Cyprobit; Decyp-P; Ferricos; Ferritop Iron Tonic; Ferrofit; Forliv; Fortil; Gastrozyme; Gelusil Plus; Growise; Haematinga; Hb-Rich; Hepachol; Hepoline; Hermin; Livocip; Mecolin; Siloxogene; Sorbiline; Sorliv; ***Indon.***: Aminofusin L; Aminovel; Amnorel; Celemin; Ferobion; Intrafusin SX-E; Laxarec; Microlax; Nutrisol-S; Pan Amin G; Pronita; Tutofusin LC; Tutofusin OpS; Valamin; ***Israel***: Biolax Protect; Biolax†; Charcodote; Spray Mint; ***Ital.***: Citroepatina†; Macrolax; Novilax; Sorbiclis; ***Jpn***: Lactec G; ***Mex.***: Clyss-Go; ***Neth.***: Klyx; Microlax; ***Norw.***: Klyx; Microlax; ***NZ***: Carbosorb XS; Microlax; ***Pol.***: Purisole SM†; Rektiolax; ***Port.***: Clyss-Go; Glandosane†; Purisole; ***Rus.***: Aminosol (Аминосол); Hepasol A (Гепасол А); Highmix (Хаймикс); Microlax (Микролакс); Reosorbilact (Реосорбилакт); Sorbilact (Сорбилакт); ***S.Afr.***: Agofell†; ***Singapore***: Charcodote; Microlax; Minica S; Osmofundin; ***Spain***: Sugarbil†; ***Swed.***: Klyx; Microlax; Omnilax; ***Switz.***: Agarol Soft†; Glandosane; Microklist; Microlax; Pursana; Yal; ***Thai.***: Glandosane; ***Turk.***: Charflo Sorbitol†; Kansilak; Libalaks; Sabalaks; Yal; ***UK***: Glandosane; Luborant†; Relaxit; Saliva Natura; SST; Xerotin; ***Ukr.***: Hepasol A (Гепасол А); Lactoprotein-C (Лактопротеин-С); Reosorbilact (Реосорбилакт); Rheosorbilact (Реосорбилакт); Sorbilact (Сорбилакт); Turusol (Турусол); ***USA***: Actidose with Sorbitol; Moi-Stir; Numoisyn; Plax; Salivart.

Pharmacopoeial Preparations

Ph. Eur.: Sorbitol, Liquid (Crystallising); Sorbitol, Liquid (Non-crystallising); Sorbitol, Liquid, Partially Dehydrated;

USNF 31: Noncrystallizing Sorbitol Solution;
USP 36: Sorbitol Solution.

Soya Bean

Habas de soja; Soja Bean; Soyabean; Soybean; Соевый Боб.
ATC Herb — HA10BX5002 (Glycine max: seed).
UNII — L7HT8F1ZOD.

Description. Soya bean is the seed of the soya plant *Glycine max* (*G. hispida*; *G. soja* (L.) Merr.). It is a source of soya oil and soya protein.*G.soja* Siebold & Zucc. is wild soybean.

Soya Oil

Aceite de soja; Soiae Oleum; Soijaöljy; Sojų aliejus; Soja Bean Oil; Soja, huile de; Sojae oleum; Sojaolja; Sójový olej; Soya Yağı; Soya-bean Oil; Soyabean Oil; Soybean Oil; Szójababolaj; Соевое Масло.
CAS — 8001-22-7.
ATC Herb — HD02WB5002 (Glycine max: oil); HB05BA5003 (Glycine max: oil).
UNII — 241ATL177A (soya oil); A2M91M918C (hydrogenated soya oil).

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*

Eur. (see p. vii) includes both hydrogenated and refined oils. *Ger.* also includes a partially hydrogenated oil. *USNF* includes the hydrogenated oil.

Ph. Eur. 8: (Soya-bean Oil, Refined; Soiae Oleum Raffinatum). It is the fatty oil obtained from seeds of *G. max* (*G. hispida*) by extraction and subsequent refining. It may contain a suitable antoxidant and is a clear, pale yellow liquid. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

The BP 2014 directs that when Soya Oil, Soyabean Oil, or Soya-bean Oil is demanded, Refined Soya Oil shall be supplied.

Ph. Eur. 8: (Soya-bean Oil, Hydrogenated; Soiae Oleum Hydrogenatum). It is obtained by refining, bleaching, hydrogenation, and deodorisation of soya oil. It consists mainly of triglycerides of palmitic and stearic acids and is a white or almost white mass or powder which melts to a clear, pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Protect from light.

USP 36: (Soybean Oil). The refined fixed oil obtained from the seeds of the soya plant *Glycine max* (Fabaceae). It may contain suitable antoxidants. A clear, pale yellow, oily liquid having a characteristic odour. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

USNF 31: (Hydrogenated Soybean Oil). The product obtained by refining, bleaching, hydrogenation, and deodorisation of oil obtained from seeds of the soya plant, *Glycine max* (Fabaceae). It consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. between 66 degrees and 72 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Store in airtight containers. Protect from light.

Incompatibility. For mention of the stability and compatibility of solutions and emulsions for parenteral nutrition see under Enteral and Parenteral Nutrition, p. 2044.2.

Uses and Administration

Emulsions of fractionated soya oil containing 10, 20, or 30% are given by slow intravenous infusion as part of total parenteral nutrition regimens (p. 2044.1), usually with amino acid and carbohydrate solutions. The solutions and emulsions may be given at separate sites, at the same site through a Y-connector, or combined in one admixture. Fat emulsions provide a high energy intake in a relatively small volume. They may also be used to prevent or correct essential fatty acid deficiency. When used as a calorie source the dose of the emulsion is determined by the energy requirements and clinical status of the patient; the amount of total carbohydrate, generally, should not comprise more than 60% of patients' total calorie intake. For the prevention and correction of fatty acid deficiency about 5 to 10% of total calorific intake should be as an intravenous fat emulsion.

The composition and dosage recommendations of commercial preparations do differ slightly but they should be started slowly. Suggested initial rates for the 10% and 20% products are 1 mL/minute and 0.5 mL/minute respectively for 15 to 30 minutes. The rate may then be increased and up to about 500 mL (or 10 mL/kg) of 10% or

250 mL (or 5 mL/kg) of 20% emulsion may be given on the first day. The total daily dosage may then be increased gradually on subsequent days; suggested daily dose ranges are 500 to 1500 mL of a 10% or 500 to 1000 mL of a 20% emulsion and suggested rates of infusion are 500 mL of a 10% emulsion over a period of not less than 3 hours, and 500 mL of a 20% emulsion over not less than 5 hours. Where a 30% emulsion is used, a dose of 333 mL or about 4.75 mL/kg has been recommended, given over 5 hours or more; the first dose should not exceed 3 mL/kg.

Soya oil also has emollient properties and is used as a bath additive in the treatment of dry skin conditions.

Preparations made from whole soya beans, containing soya oil and soya protein, are used as the basis of lactose-free vegetable milks for infants and patients with lactose or similar disaccharide intolerance or with an allergy to cow's milk protein (see also Food Intolerance, below).

Administration. It has been suggested[1] that it is the concentration of phospholipid solubilisers, and particularly the excess present as free phospholipid liposomes, that determines the effect of lipid emulsions on plasma-lipid concentrations. In 20 premature infants requiring parenteral nutrition, infusion of up to 4 g/kg of fat daily as a 20% emulsion had less effect on plasma lipid concentrations than 2 g/kg daily as a 10% emulsion; the difference was thought to be due to the fact that the 20% emulsion was relatively liposome-poor, with a ratio of phospholipids to triglycerides of 0.06, whereas the liposome-rich 10% emulsion had a ratio of 0.12. The authors suggested that the 10% emulsion should not be used in preterm infants. Others noted similar results;[2] a 10% lipid emulsion with a reduced phospholipid content has, however, been reported to be relatively well tolerated in premature infants.[3]

For mention of the risk of kernicterus if lipid infusions are given to hyperbilirubinaemic neonates, see under Precautions, p. 2094.2.

1. Haumont D, *et al.* Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition. *J Pediatr* 1992; **121:** 759–63.
2. Cairns PA, *et al.* Tolerance of mixed lipid emulsion in neonates: effect of concentration. *Arch Dis Child Fetal Neonatal Ed* 1996; **75:** F113–F116.
3. Gohlke BC, *et al.* Serum lipids during parenteral nutrition with a 10% lipid emulsion with reduced phospholipid emulsifier content in premature infants. *J Pediatr Endocrinol Metab* 1997; **10:** 505–9.

Cardiotoxicity. Intravenous infusion of lipid emulsions has been proposed for the treatment of refractory cardiotoxicity caused by lipophilic local anaesthetics such as bupivacaine,[1,2] possibly acting in part as a 'lipid sink' into which the drugs partition, removing them from the tissues. A patient in whom prolonged cardiac arrest, unresponsive to conventional management, developed after interscalene block with bupivacaine and mepivacaine, was given a 100 mL bolus of a 20% lipid emulsion via the peripheral intravenous catheter, which resulted in almost immediate resumption of sinus rhythm;[3] the patient was subsequently given an infusion of the emulsion at a rate of 0.5 mL/kg per minute over 2 hours, and remained in sinus rhythm. There was no evidence of complications related to the use of lipid emulsion over the following 2 weeks. A subsequent case of refractory asystole subsequent to brachial plexus block with ropivacaine[4] also responded to a 100 mL bolus of 20% lipid emulsion, followed by a continuous infusion at a rate of 0.2 mL/kg per minute (total dose 4 mL/kg).

Although there have been concerns about the longer term safety of a large lipid burden, and a lack of consensus about the appropriateness of the treatment given the scanty evidence base, a protocol has been suggested[1] on the basis of case reports and *animal* studies. Treatment, which is reserved for patients with local anaesthetic cardiotoxicity resistant to standard resuscitation, is to continue advanced cardiac life support measures (see Cardiac Arrest, p. 1268.3) plus:

- intravenous bolus of 20% lipid emulsion (*Intralipid*) at a dose of 1.5 mL/kg, *followed by*
- continuous infusion of the emulsion at a rate of 0.25 mL/kg per minute for 30 minutes; if blood pressure declines, rate may be increased to 0.5 mL/kg per minute. The infusion may be continued for up to an hour if appropriate, and may need to be restarted if blood pressure declines when it is stopped

If there is no response to the bolus it may be repeated once or twice; additional boluses are not likely to be required once sinus rhythm returns, even though ventricular ectopy or other arrhythmias may persist.

The technique may be appropriate for other lipophilic drugs that cause refractory cardiotoxicity—for mention of its use to treat verapamil toxicity after overdosage with a modified-release formulation, see p. 1524.2.

1. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. *Toxicol Rev* 2006; **25:** 139–45.
2. Leskiw U, Weinberg GL. Lipid resuscitation for local anesthetic toxicity: is it really lifesaving? *Curr Opin Anaesthesiol* 2009; **22:** 667–71.
3. Rosenblatt MA, *et al.* Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006; **105:** 217–18.
4. Litz RJ, *et al.* Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* 2006; **61:** 800–1.

Food intolerance. The American Academy of Pediatrics has recommended[1] that soya-based infant feeds are appropriate for use in galactosaemia and hereditary lactase deficiency, and may be an alternative for families who wish to avoid using infant feeds containing animal products. Extensively hydrolysed protein feeds should be considered for documented allergy to cow's milk protein, as 10 to 14% of these infants will also have a soy protein allergy. Infants with cow's milk-protein-induced enteropathy or enterocolitis are also very likely to be sensitive to soy protein, and should again receive a feed derived from hydrolysed protein, or synthetic amino acids. After rehydration for acute gastroenteritis, most previously healthy infants can continue to have human milk or cow milk feeds, but soy-based infant feeds may be indicated when secondary lactose intolerance occurs. The Academy concluded that soya-based infant feeds are not recommended for preterm infants and have no proven role in the prevention of atopic disease or in the management of infantile colic. In infants and children at high risk for developing food allergies or intolerance, a systematic review[2] found that there was no evidence that feeding with a soy formula compared with a cow's milk formula reduced the incidence of food allergies or intolerance.

The FDA has warned against the use of soya-based drinks intended for adults as the sole source for nutrition for infants.[3] It was stated that soya drinks can lead to severe protein and calorie malnutrition, multiple vitamin and mineral deficiency, and death in infants who receive no other source of nourishment, and should not be confused with soya-based infant formulas, which are specially formulated to meet the nutritional needs of infants.

For reference to the use of soya-based foods themselves causing allergic reactions, see under Hypersensitivity, p. 2094.1.

1. Bhatia J, Greer F. American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008; **121:** 1062–8. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/1062 (accessed 27/01/10)
2. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/11/05).
3. Nightingale S. Warnings issued about practices, products: soy drink warning. *JAMA* 1985; **254:** 1428.

Hyperlipidaemias. Soya protein has been tried in the treatment of hyperlipidaemia (p. 1248.1). Soya isoflavones such as genistein (p. 2620.3) and daidzein (p. 2620.3) can mimic oestrogen and should therefore have a beneficial effect on blood lipids.[1,2] Other constituents of soya protein, including fytic acid and saponins, may also contribute and thus intact soya protein may provide the maximum cholesterol-lowering effect.[2,3] A meta-analysis of controlled trials found that the substitution of soya protein for animal protein in the diet resulted in significant decreases in serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride concentrations.[4] A subsequent systematic review of studies reached similar conclusions,[1] and the FDA considered that a low-fat diet including 25 g daily of soya protein might reduce the risk of ischaemic heart disease.[2] A later analysis by the American Heart Association[5] considered that cardiovascular benefit was very modest and appeared only when large amounts of animal protein were substituted with soya protein. The effect appeared to be more to do with a broader modification of diet than any effect of soya isoflavones. Soya protein does not appear to have a cholesterol-lowering effect in subjects with normal cholesterol concentrations,[2] although a small study found it to be beneficial in type 2 diabetes patients with near-normal lipid concentrations.[6]

1. Costa RL, Summa MA. Soy protein in the management of hyperlipidemia. *Ann Pharmacother* 2000; **34:** 931–5.
2. Erdman JW. Soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. *Circulation* 2000; **102:** 2555–9.
3. Demonty I, *et al.* Role of isoflavones in the hypocholesterolemic effect of soy. *Nutr Rev* 2003; **61:** 189–203.
4. Anderson JW, *et al.* Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995; **333:** 276–82.
5. Sacks FM, *et al.* Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* 2006; **113:** 1034–44. Also available at: http://circ.ahajournals.org/cgi/reprint/113/7/1034.pdf (accessed 20/03/09)
6. Hermansen K, *et al.* Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. *Diabetes Care* 2001; **24:** 228–33.

Menopausal disorders. Soya contains phytoestrogens in the form of isoflavones, in particular daidzein (p. 2620.3) and genistein (p. 2620.3), which have been investigated for their oestrogen-modulating effects in the treatment of symptoms associated with menopausal disorders—see under Soya Isoflavones, p. 2620.3.

Osteoarthritis. For mention of the possible benefits of a mixture of avocado and soya oils (avocado-soybean unsaponifiables) for symptomatic relief in patients with osteoarthritis, see p. 2451.2.

Adverse Effects

Hypersensitivity reactions including fever and chills have been reported after the infusion of soya oil emulsion although they are considered to be fairly rare. Other rare immediate reactions include dyspnoea, cyanosis, hyperlipidaemia, hypercoagulability, nausea, vomiting, headache, and chest and back pain. Delayed reactions include hepatomegaly, splenomegaly, jaundice due to cholestasis, thrombocytopenia, leucopenia, and transient increases in liver function tests.

Prolonged or too rapid infusion of soya oil emulsion or its use in patients with impaired fat metabolism has been associated with the 'overload syndrome'. This is manifested by anaemia, leucocytopenia, thrombocytopenia, and impaired coagulation, hepatosplenomegaly, hyperlipidaemia, fever, focal seizures, shock, and coma. Metabolic acidosis has been associated with severe overdosage especially if carbohydrates are not also given. Pigmentation of tissues in the reticuloendothelial system after prolonged therapy with lipid emulsion infusions has also been reported.

Soya protein-based infant feeds can be antigenic and cause gastrointestinal adverse effects in sensitive individuals.

Bacteraemia. A strong association has been found between giving lipids through peripheral venous catheters made of Teflon and development of coagulase-negative staphylococcal bacteraemia in neonates.[1] It was suggested that investigation of catheters made of other materials, or other delivery systems, might reduce the opportunity for coagulase-negative staphylococci to adhere and come into contact with nutrient-rich growth media in the form of lipid emulsions. Others also took the view that this work should not lead to the abandonment of parenteral lipids in premature infants.[2]

1. Freeman J, *et al.* Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990; **323:** 301–8.
2. Klein JO. From harmless commensal to invasive pathogen: coagulase-negative staphylococci. *N Engl J Med* 1990; **323:** 339–40.

Effects on the cardiovascular system. Sinus bradycardia has been reported in a patient receiving total parenteral nutrition that included soya oil-based emulsion via a central line.[1] The authors suggested that it might be wise to give fat emulsion only through a peripheral vein. However, sinus bradycardia has been reported after a safflower oil-based emulsion given via a peripheral vein as part of a TPN regimen.[2]

1. Sternberg A, *et al.* Intralipid-induced transient sinus bradycardia. *N Engl J Med* 1981; **304:** 422–3.
2. Traub SL, *et al.* Sinus bradycardia associated with peripheral lipids and total parenteral nutrition. *J Parenter Enteral Nutr* 1985; **9:** 358–60.

Effects on the endocrine system. Soya bean is a rich source of phytoestrogens including isoflavones, and it has been found that infants fed soya-based formula have high serum concentrations of these substances,[1] which has brought the safety of soya-based formulas into question. *Animal* and *in vitro* data suggest that isoflavones such as genistein have pharmacological effects on growth and development.[2] However, genistein and daidzein are less potent than endogenous oestrogens and have less binding affinity to oestrogen receptors.[3] It is not known to what extent infants are able to metabolise and deconjugate soya isoflavones.[4] A small retrospective study[5] found no oestrogenic effects in children fed soya protein formula for at least 6 months. A larger retrospective cohort study[6] in adults observed no statistically significant differences between those who had been fed soya formula and those fed cow's milk formula as infants.

As yet, there is insufficient evidence of harm from soya-based formulas,[7] although further studies are deemed necessary to assess long-term effects.[2,4] The American Academy of Pediatrics[8] considers soya protein-based formulas to be safe and effective in healthy term infants, while providing no advantage over cow's milk protein-based formulas. However, soya-based formulas are not recommended for use in preterm infants because of concerns about poorer bone development compared with infants given formulas based on cow's milk protein.

Before their supplementation with iodine, there had been reports of hypothyroidism associated with soya formula feeds. Abnormal thyroid function tests have since been reported in infants fed with soya formulas, and a retrospective analysis of infants with congenital hypothyroidism found those fed with soya took longer for their thyroid stimulating hormone levels to normalise.[9]

1. Setchell KDR, *et al.* Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 1997; **350:** 23–7.

2. Chen A, Rogan WJ. Isoflavones in soy infant formula: a review of evidence for endocrine and other activity in infants. *Annu Rev Nutr* 2004; **24:** 33–54.
3. Miniello VL, *et al.* Soy-based formulas and phyto-oestrogens: a safety profile. *Acta Paediatr Suppl* 2003; **91:** 93–100.
4. Mendez MA, *et al.* Soy-based formulae and infant growth and development: a review. *J Nutr* 2002; **132:** 2127–30.
5. Giampietro PG, *et al.* Soy protein formulas in children; no hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab* 2004; **17:** 191–6.
6. Strom BL, *et al.* Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 2001; **286:** 807–14.
7. Tuohy PG. Soy infant formula and phytoestrogens. *J Paediatr Child Health* 2003; **39:** 401–5.
8. Bhatia J, Greer F. American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008; **121:** 1062–8. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/1062 (accessed 27/01/10)
9. Conrad SC, *et al.* Soy formula complicates management of congenital hypothyroidism. *Arch Dis Child* 2004; **89:** 37–40.

Effects on the nervous system. CNS disorders in 2 patients given infusions of fractionated soya emulsion included convulsions and coma; cortical blindness developed in one young woman.[1] A similar case was attributed to fat embolism,[2] but, occurring after what the manufacturers pointed out was a faster than recommended infusion,[3] may perhaps have represented a fat-overload syndrome. Neurological complications can be the presenting and principal signs of fat overload; focal and generalised seizures, weakness, and encephalopathy have been reported.[4]

Migraine with visual aura has also been reported in a 57-year old man taking soya beans, soya milk, and a soya protein supplement.[5]

1. Jellinek EH. Dangers of intravenous fat infusions. *Lancet* 1976; **ii:** 967.
2. Estebe JP, Malledant Y. Fat embolism after lipid emulsion infusion. *Lancet* 1991; **337:** 673.
3. McCracken M. Fat embolism after lipid emulsion infusion. *Lancet* 1991; **337:** 983.
4. Schulz PE, *et al.* Neurological complications from fat emulsion therapy. *Ann Neurol* 1994; **35:** 628–30.
5. Engel PA. New onset migraine associated with use of soy isoflavone supplements. *Neurology* 2002; **59:** 1289–90.

Hypersensitivity. Urticaria has been reported in 2 patients after the intravenous use of soya oil emulsions.[1,2] In one case the patient had previously received the emulsion for 19 days without ill-effect.[1]

Anaphylactic reactions have been documented after the ingestion of several foods or foodstuffs containing, or prepared from, soya beans, although the exact allergen remains unknown. In one patient who suffered anaphylactic attacks after eating such products a specific IgE-antibody response to the allergen Kunitz soybean trypsin inhibitor was demonstrated.[3] This was not, however, the only allergen present in soya beans as other patients who had a negative response to this allergen had positive responses in whole soya bean tests. A type I reaction to soya bean protein has been described in patients given parenteral lipid emulsions containing soya bean lecithin as the emulsifier.[4] A patient who ingested a soya protein drink experienced exercise-induced anaphylaxis; skin prick tests were positive to soya, but specific IgE antibodies to soya were undetectable.[5]

IgE antibodies to soya bean antigens have also been found in workers who suffered from asthma after handling soya beans[6,7] leading to the suggestion that an allergic mechanism had been responsible; the asthma was believed to have been due to the dust released during the handling of the beans.

1. Kamath KR, *et al.* Acute hypersensitivity reaction to Intralipid. *N Engl J Med* 1981; **304:** 360.
2. Hiyama DT, *et al.* Hypersensitivity following lipid emulsion infusion in an adult patient. *J Parenter Enteral Nutr* 1989; **13:** 318–20.
3. Moroz LA, Yang WH. Kunitz soybean trypsin inhibitor: a specific allergen in food anaphylaxis. *N Engl J Med* 1980; **302:** 1126–8.
4. Weidmann B, *et al.* Hypersensitivity reactions to parenteral lipid solutions. *Support Care Cancer* 1997; **5:** 504–5.
5. Taramarcaz P, *et al.* Soy anaphylaxis. *Allergy* 2001; **56:** 792.
6. Sunyer J, *et al.* Case-control study of serum immunoglobulin-E antibodies reactive with soybean in epidemic asthma. *Lancet* 1989; **i:** 179–82.
7. Hernando L, *et al.* Asthma epidemics and soybean in Cartagena (Spain). *Lancet* 1989; **i:** 502.

Pulmonary fat emboli. Pulmonary fat emboli or microemboli, sometimes fatal, have occurred in several infants who received infusions of fat emulsions based on soya oil.[1-3]

In one case[3] the patient's serum, which contained a high concentration of C-reactive protein, agglutinated the fat emulsion and this finding was considered to support the hypothesis that microemboli are formed by agglutination of fat emulsion in the blood by C-reactive protein. The authors of this report did not consider the precise pathogenesis to be clear, nor did they know whether the condition was preventable, but did suggest that it might be prudent either to ensure that the C-reactive protein concentration was normal (less than 10 mg/litre) or to perform a creaming test to determine which babies may embolise the infused fat emulsion. However, another study,[4] while not excluding a role of C-reactive protein in agglutination, failed to find any correlation between raised concentrations of this protein and the rate of agglutination. A review[5] classified fat embolism into those derived from direct entry of depot fat into the blood (e.g. after trauma), and those derived from agglutination of endogenous or exogenous fat. High concentrations of C-reactive protein were considered to be responsible for the agglutination of the liposomes of fat emulsions; chylomicrons and very low-density lipoproteins in the blood may also agglutinate, contributing to fat embolism.

1. Barson AJ, *et al.* Fat embolism in infancy after intravenous fat infusions. *Arch Dis Child* 1978; **53:** 218–23.
2. Levene MI, *et al.* Pulmonary fat accumulation after Intralipid infusion in the preterm infant. *Lancet* 1980; **ii:** 815–8.
3. Hulman G, Levene M. Intralipid microemboli. *Arch Dis Child* 1986; **61:** 702–3.
4. Zagara G, *et al.* C-reactive protein and serum agglutination in vivo of intravenous fat emulsions. *Lancet* 1989; **i:** 733.
5. Hulman G. The pathogenesis of fat embolism. *J Pathol* 1995; **176:** 3–9.

Precautions

Intravenous soya oil emulsion should not be given to patients with severe liver disease, acute shock, or severe or pathological hyperlipidaemia, or when the ability to metabolise fat may otherwise be impaired. Caution has also been advised in patients with pulmonary disease, renal insufficiency, uncompensated diabetes mellitus and other metabolic disorders, sepsis, anaemia, and some disorders of blood coagulation. If given to such patients, the elimination of fat should be monitored daily.

Intravenous soya oil emulsion may interfere with some laboratory tests if blood is taken before fat has adequately cleared; this may take 4 to 6 hours.

Egg-yolk phospholipids may be used as emulsifiers in some preparations, which should not be given to patients with severe egg allergy.

Fat emulsions may extract phthalate plasticisers from bags and giving sets and non-phthalate containing equipment should be used wherever possible.

Soya-based infant feeds should be avoided in infants with documented cow's milk protein-induced enteropathy or enterocolitis, as these infants are often also sensitive to soya protein.

Neonatal hyperbilirubinaemia. In neonates with hyperbilirubinaemia, intravenous lipid emulsions should be used with caution because of the risk of displacing bilirubin from albumin and the resulting risk of producing kernicterus. The risk appears to be higher in preterm infants,[1] at higher doses,[1] and with intermittent rather than continuous dosing.[2]

1. Spear ML, *et al.* The effect of 15-hour fat infusions of varying dosage on bilirubin binding to albumin. *J Parenter Enteral Nutr* 1985; **9:** 144–7.
2. Brans YW, *et al.* Influence of intravenous fat emulsion on serum bilirubin in very low birthweight neonates. *Arch Dis Child* 1987; **62:** 156–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ivelip; Lipofundin N; Lipovenos; Piascledine; Sojar Pro; Soyacal†; ***Austral.***: Intralipid; Ivelip; ***Austria***: Balneum; Intralipid; Olbad Cordes†; ***Belg.***: Gynosoya; ***Braz.***: Fisiogen; Soyfit; ***Canad.***: Intralipid; ***Chile***: Lipofundin; Lipovenos; ***China***: Intralipid (英脱利匹特); Intralipos (力基); Ivelip (意维利匹); ***Cz.***: Balneum Hermal; Intralipid; Lipovenoes†; Soyacal†; ***Denm.***: Intralipid; ***Fin.***: Intralipid; ***Fr.***: Endolipide†; Gynalpha; Intralipide; Ivelip; Phyto Soya; SANO-Gastril; ***Ger.***: Balneoconzen N; Balneovit; Balneum; Buer Lecithin Cholesterin Balance†; Deltalipid†; Lipidavit SL; Lipofundin N; Lipopharm; Lipostabil; Lipovenos; Olbad Cordes†; salvilipid†; Soyacal†; ***Gr.***: Intralipid; Lipovenoes; ***Hong Kong***: Intralipid; Lipofundin N†; ***Hung.***: Balneum; Intralipid; Structolipid†; ***India***: Celepid; Intralipid; ***Indon.***: Celepid; Glisopos; Intralipid; Intralipos; Ivelip; Lipovenoes; ***Irl.***: Balneum†; Intralipid; ***Israel***: Balneum; Intralipid; Ivelip; ***Ital.***: Balneum Hermal; Elolipid; Intralipid; Lipofundin S; Lipovenos; ***Jpn***: Intrafat; ***Malaysia***: Intralipid†; ***Mex.***: Lipofundin N; Lipovenoes; ***Mon.***: Evestrel†; ***Neth.***: Intralipid; Lipovenos†; ***Norw.***: Intralipid; ***NZ***: Intralipid; Ivelip; ***Philipp.***: Celepid; Soyacal; ***Pol.***: Balneum Hermal†; Intralipid; Ivelip†; Lipofundin N; Soya Meno†; Soyfem; ***Port.***: Banholeum; Emulsao de Lipidos; Endolipide†; Intralipid; Lipovenoes; Soyacal; ***Rus.***: Intralipid (Интралипид); Resalut Pro (Резалют Про); ***S.Afr.***: Intralipid; ***Singapore***: Intralipid; Intralipos; Ivelip; Lipofundin N; ***Spain***: Aquiflav†; Bluna†; Fitoladius; Flavodrei; Intralipid; Isodonna†; Malena; Menoclim†; Normosoy; Phyto Soya; Pleginer; Primsoja†; Ratiofemin†; Soyacal; ***Swed.***: Intralipid; ***Switz.***: Balmed Hermal Plus; Balmed Hermal; Intralipid†; Lipovenos†; ***Thai.***: Celepid†; Intralipid; Ivelip†; Lipofundin N†; Lipofundin S†; ***Turk.***: Intralipid; Ivelip; Lipovenos; ***UK***: Balneum; Intralipid; Ivelip; Lipofundin; Zeroneum; ***Ukr.***: Enerliv (Энерлив); Intralipid (Интралипид); Liventiale (Ливенциале)†; Onagris (Онагрис); ***USA***: Intralipid; Liposyn III; ***Venez.***: Ivelip.

Multi-ingredient Preparations. ***Arg.***: Clinoleic; Derrumal; Kabiven; Lecitina E; Lipofundin MCT/LCT-E†; Lipofundin MCT/LCT; Liposomas; Lipovenos MCT/LCT; Lipovenos PLR; Puraplus; Sigmafem; Sojar Plus-Calcio; Ukase Lulitis; ***Austral.***: Clinoleic; EFA Compound; Extralife Meno-Care†; GR² Control Appetite Reducer; Hypol; Kabiven; Mens Super Soy/Clover†; PhytoLife; PM H-Regulator; SMOFlipid; Soy Power Plus†; Treen-en; ***Austria***: Balneum Plus; Clinoleic; Kabiven†; Lipidem; Lipofundin mit MCT; Nutriflex Lipid; OliClinomel; PE-Mix†; PeriOlimel; SMOFlipid; Structolipid†; Vitromix; ZentroOlimel; ***Belg.***: Clinoleic; Lipoplus; Medialipide; Nutriflex Lipid; OliClinomel; Olimel; PeriOlimel; ***Braz.***: Borag; Emulsao Scott; Piascledine; Votag O6; ***Canad.***: Clinoleic; Liposyn; Olimel; PeriOlimel; ***Chile***: Cellenergy; Hyaluron; Kabiven; Lipofundin MCT/LCT; Lipovenos MCT/LCT; OliClinomel; Piascledine; ***China***: Lipofundin MCT/LCT (力保肪宁); Lipovenoes (力能); ***Cz.***: Balneum Hermal Plus; Clinoleic; Kabiven; Lipofundin MCT/LCT†; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Olimel; PeriOlimel; Piascledine; SMOFKabiven; SMOFlipid; ***Denm.***: Clinoleic; Kabiven; Lipidem; Numeta GE; Nutriflex Lipid; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; Vasolipid; ***Fin.***: Clinoleic; Kabiven; Lipoplus; Numeta GE; Nutriflex Lipid; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; ***Fr.***: Alpharegul Homme; Biopause; Clinoleic; Elteans; Fadiamone; Gynalpha Plus†; Kabiven; Kotor Meno; Lipidem; Medialipide; Mednutriflex Lipide G; Nutriflex Lipide†; OliClinomel; Olimel; Oxelio; Perikabiven; PeriOlimel; Pharyndol; Piascledine; Reanutriflex Lipide; Reanutriflex Omega; SMOFKabiven; SMOFlipid; StructoKabiven; Structolipide†; Synaptiv; Vitrimix†; ***Ger.***: Balneum Plus; Clinoleic; Kabiven; Lipidem; Lipofundin MCT; Lipovenos MCT; Numeta GE; Nutriflex Lipid; NuTRIflex Omega; Oleobal; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; ***Gr.***: Clinoleic; Clinomel; Compleven; Kabiven; Lipofundin MCT/LCT; Lipoplus; Multimel; Nutriflex Lipid; OliClinomel; SMOFKabiven; SMOFlipid; Trive-1000; ***Hong Kong***: Kabiven; Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; Vitrimix KV†; ***Hung.***: Allice; Balneum Hermal Plus; Kabiven; Lipofundin MCT†; OliClinomel; SMOFlipid; ***India***: Celepid MCT-LCT; Familykair; Gynerol; Hemofit; Kabiven; Lipofundin MCT/LCT; Nutrilex Lipid Peri; Osteoshield; ***Indon.***: Hepabion†; Kabiven; Lanaven; Lipofundin MCT/LCT†; Lipomed MCT/LCT; Maxitrin†; Vitrimix†; ***Irl.***: Balneum Plus†; Clinoleic†; KabiMix†; Kabiven; Lipidem; Lipofundin MCT/LCT†; Numeta GE; Nutriflex Lipid; OliClinomel; SMOFKabiven; SMOFlipid; Structolipid†; Triomel; Vitrimix KV†; ***Israel***: Balneum Plus; Clinoleic; Kabiven; Lipofundin MCT/LCT; OliClinomel; SMOFKabiven; SMOFlipid; ***Ital.***: Acumel; Anti-Ves; Assist; Bioestril Ginseng; Bioestril Valeriana; Biomineral 5-Alfa; Clinoleic; Demalit; Eavit Plus; Fitogen; Ginil; Kabiven; Lipidem; Lipimix; Lipofundin MCT; Liposyn; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; OliClinomel; Perismofven; Periven; Piascledine; Pluvio; Pulsalux; SMOFlipid; Soymen; Structolipid; ***Malaysia***: Kabiven†; ***Mex.***: Bano Coloide; Caltrate + S; Kabiven; Lipofundin MCT/LCT; Liposyn†; Piascledine; Prevefem Complex; Riban; Soyaloid Apruri; Soyaloid; Soydex; ***Mon.***: Evestrel Jour Nuit†; Evestrel Physio Profil†; ***Neth.***: Clinoleic; Kabiven; Lipofundin MCT/LCT†; Lipoplus; Numeta GE; Nutriflex Lipid; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid; Vitrimix KV†; ***Norw.***: Clinoleic; Kabiven; Lipidem; Numeta GE; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Vasolipid; ***NZ***: Clinoleic; Kabiven; OliClinomel; ***Philipp.***: Her Soy Plus; Kabiven; Livermin; ***Pol.***: Balneum Hermal Plus†; Clinoleic; Clinomel; Compleven†; Kabiven; Lipofundin MCT/LCT; Naturapia Menopauza; Piascledine; SMOFKabiven; SMOFlipid; ***Port.***: Banholeum Composto; Banholeum Gele; Clinoleic; Lipofundina MCT/LCT; Lipoplus; Nutribraun; Nutriplasmal†; OliClinomel; SMOFKabiven; SMOFlipid; Structolipid; Vitrimix; ***Rus.***: Kabiven (Кабивен); Lipofundin MCT/LCT (Липофундин МСТ/ЛСТ); Lipoplus (Липоплюс); Oliclinomel (ОлиКлиномель); Piascledine (Пиаскледин); SMOFlipid (СМОФлипид); ***S.Afr.***: Clinomel†; Lipofundin MCT/LCT†; ***Singapore***: Clinoleic; Kabiven; Lipofundin MCT/LCT; Pro-Gut; ***Spain***: Clinoleic; Fitogyn; Kabiven; Lipofundina MCT/LCT; Lipomix; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid†; ***Swed.***: Clinoleic; Kabiven; Lipoplus; Numeta GE; Nutriflex Lipid; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; ***Switz.***: Antidry; Clinoleic; Lipofundin MCT/LCT; Lipoplus; Numeta; Nutriflex Lipid; OliClinomel†; Olimel; PeriOlimel; SmofKabiven; SMOFlipid; Structolipid; ***Thai.***: Cal-ups-D-Soy; Clinoleic; Kabiven; Lipidem; Lipofundin MCT/LCT; Nutriflex Lipid; OliClinomel; SMOFlipid; Vitrimix†; ***Turk.***: Clinoleic; Lipofundin MCT/LCT; Liposyn†; SMOFlipid; Vitrimix; ***UK***: Balneum Plus; Clinoleic; Emustil; Kabiven; Lipidem; Lipofundin MCT/LCT; Nutriflex Lipid; NuTRIflex Omega; OliClinomel; Phytolife Plus; Skin Perfecting Oil; SMOFlipid; Structolipid; Ymea; Zerozole†; ***Ukr.***: Kabiven (Кабивен); Lipofundin MCT/LCT (Липофундин МСТ/ЛСТ); SMOFlipid (СМОФлипид); ***USA***: Clinolipid; Liposyn II; Tucks; ***Venez.***: Lipofundin MCT/LCT; Maternavit.

Pharmacopoeial Preparations

USP 36: Lipid Injectable Emulsion.

Stannous Fluoride

Fluoruro estañoso; Stannosi Fluoridum; Фторид Олова.

Tin fluoride.

SnF_2=156.7

CAS — 7783-47-3.

ATC — A01AA04.

ATC Vet — QA01AA04.

UNII — 3FTR44B32Q.

Pharmacopoeias. In *US*.

USP 36: (Stannous Fluoride). A white crystalline powder. Freely soluble in water; practically insoluble in alcohol, in

chloroform, and in ether. pH of a freshly prepared 0.4% solution in water is between 2.8 and 3.5.

Stability. Aqueous solutions of stannous fluoride decompose within a few hours with the formation of a white precipitate; they slowly attack glass.

Profile

Stannous fluoride is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) for the prophylaxis of dental caries. Dental gels containing concentrations of stannous fluoride 0.4% are available for daily use. Higher concentrations have been applied under professional supervision. Stannous fluoride has also been used in dentifrices and mouth rinses.

Stannous fluoride has an unpleasant taste.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Gel-Kam; Gelstan; Perfect Solutions in Office Rinse†; ***Fr.***: Emoform†; ***Ital.***: Fluorigard Gel-Kam; Gel-Kam; Oral-B Pasta Dentifricia Denti e Gengive†; ***UK***: Fluorigard Gel-Kam; ***USA***: Gel Kam; Gel-Kam; Gel-Tin; Just for Kids; PerioMed; Stop.

Multi-ingredient Preparations. ***Canad.***: Gel-Kam Dentinbloc; ***Denm.***: Amerscan Stannous†; ***Israel***: Meridol; ***Ital.***: Actifluor.

Pharmacopoeial Preparations
USP 36: Stannous Fluoride Gel.

Starch

Almidón; Amido; Amidon; Amidon de blé (wheat starch); Amidon de maïs (maize starch); Amidon de pomme de terre (potato starch); Amidon de riz (rice starch); Amidon prégélatinisé (pregelatinised starch); Amilo; Amylum; Amylum pregelificatum (pregelatinised starch); Bulvių krakmolas (potato starch); Burgonyakeményítő (potato starch); Búzakeményítő (wheat starch); Hidegenduzzadó keményítő (pregelatinised starch); Kukoricakeményítő (maize starch); Kukurūzų krakmolas (maize starch); Kviečių krakmolas (wheat starch); Maissitärkkelys (maize starch); Majsstärkelse (maize starch); Maydis amylum (maize starch); Oryzae amylum (rice starch); Perunatärkkelys (potato starch); Potatisstärkelse (potato starch); Pregelifikuotas krakmolas (pregelatinised starch); Pšeničný škrob (wheat starch); Riisitärkkelys (rice starch); Risstärkelse (rice starch); Rizskeményítő (rice starch); Ryžių krakmolas (rice starch); Škrob bramborový (potato starch); Škrob kukuřičný (maize starch); Škrob předbobtnalý (pregelatinised starch); Škrob rýžový (rice starch); Skrobia kukurydziana (maize starch); Skrobia pszeniczna (wheat starch); Skrobia ziemniaaczana (potato starch); Solani amylum (potato starch); Stärke; Tritici amylum (wheat starch); Vehnätärkkelys (wheat starch); Vetestärkelse (wheat starch); Крахмал.

CAS — 9005-25-8 (starch); 9005-82-7 (α-amylose); 9004-34-6 (β-amylose); 9037-22-3 (amylopectin).

UNII — O8232NY3SJ (corn starch); 8I089SAH3T (potato starch); 4DGK8B7I3S (rice starch); 24SC3U704I (tapioca starch); 79QS2MG2LP (wheat starch).

Description. Starch consists of polysaccharide granules obtained from the caryopsis of maize, *Zea mays*, rice, *Oryza sativa*, wheat, *Triticum aestivum* (*T. vulgare*), from the tubers of potato, *Solanum tuberosum* from the seeds (peas) of *Pisum sativum*, or from the rhizomes of cassava, *Manihot utilissima*. Maize starch is also known as corn starch. Starch contains amylose and amylopectin, both polysaccharides based on α-glucose.

Pharmacopoeias. Some or all of the starches described are included in *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*.

Chin. and *Eur.* also include Pregelatinised Starch, *Eur.* includes Pregelatinised Hydroxypropyl Starch. *USNF* also includes Pregelatinized Starch, Modified Starch, Pregelatinized Modified Starch, and Pregelatinized Hydroxypropyl Starch. *US* includes Absorbable Dusting Powder and Topical Starch.

Ph. Eur. 8: (Maize Starch; Maydis Amylum). It is obtained from the caryopsis of *Zea mays*. It is a matt, white to slightly yellowish, very fine powder that creaks when pressed between the fingers. The presence of granules with cracks or irregularities on the edge is exceptional. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 4.0 to 7.0.

Ph. Eur. 8: (Pea Starch). It is obtained from the seeds of *Pisum sativum*. A white or almost white, very fine powder. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 5.0 to 8.0.

Ph. Eur. 8: (Potato Starch; Solani Amylum). It is obtained from the tuber of *Solanum tuberosum*. It is a very fine, white or almost white powder which creaks when pressed between the fingers. It does not contain starch grains of any other origin but may contain a minute quantity, if any, of fragments of the tissue of the original plant. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 5.0 to 8.0. Store in airtight containers.

Ph. Eur. 8: (Rice Starch; Oryzae Amylum). It is obtained from the caryopsis of *Oryza sativa*. It is a tasteless, very fine, white or almost white powder which creaks when pressed between the fingers. The presence of granules with cracks or irregularities on the edge is exceptional. Practically insoluble in cold water and in alcohol. Store in airtight containers.

Ph. Eur. 8: (Wheat Starch; Tritici Amylum). It is obtained from the caryopsis of *Triticum aestivum* (*T. vulgare*). It is a very fine, white or almost white powder which creaks when pressed between the fingers. It does not contain starch grains of any other origin but may contain a minute quantity, if any, of fragments of the tissue of the original plant. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 4.5 to 7.0. Store in airtight containers.

Ph. Eur. 8: (Pregelatinised Starch; Amylum Pregelificatum). It is prepared from maize starch, potato starch, or rice starch by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics. It is a white or yellowish white powder that swells in cold water.

Ph. Eur. 8: (Starch, Hydroxypropyl; Amylum Hydroxypropylum). A partially substituted 2-hydroxypropylether of maize starch, potato starch, cassava starch, rice starch, or pea starch chemically modified by etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch with reduced viscosity. Mixing of starches from different botanical sources prior to chemical modification is not allowed. It contains 0.5% to 7.0% of hydroxypropyl groups. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

Ph. Eur. 8: (Starch, Hydroxypropyl, Pregelatinised; Amylum Hydroxypropylum Pregelificatum). It is prepared from hydroxypropyl starch by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying. It contains 0.5% to 7.0% of hydroxypropyl groups. pH of a 3.0% mixture in water is 4.5 to 8.0. A white or slightly yellowish powder.

BP 2014: (Tapioca Starch). It is obtained from the rhizomes of *Manihot utilissima*. It is a very fine powder which creaks when pressed between the fingers. Practically insoluble in cold water and in alcohol. Store in airtight containers.

The BP 2014 gives Cassava Starch as an approved synonym.

The BP 2014 directs that when starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch, or in tropical countries where these are not available, Tapioca Starch may be supplied or used.

USNF 31: (Corn Starch). It consists of the starch granules separated from the mature grain of corn, *Zea mays* (Gramineae). Irregular, angular, white masses or fine powder. Is odourless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 4.0 to 7.0.

USNF 31: (Pea Starch). It is obtained from the seeds of *Pisum sativum*. A white or almost white, very fine powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Potato Starch). It is obtained from the tuber of *Solanum tuberosum*. Irregular, angular, white masses or fine powder. Is odourless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 5.0 to 8.0.

USNF 31: (Rice Starch). It is obtained from the caryopsis of *Oryza sativa*. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 5.0 to 8.0.

USNF 31: (Tapioca Starch). Granules separated from the tubers of tapioca (cassava), *Manihot utilissima* (Euphorbiaceae). Irregular, angular, white to pale yellow masses or fine powder. Insoluble in cold water and in alcohol. A 20% slurry in water after 5 minutes of continuous agitation has a pH of 4.5 to 7.0.

USNF 31: (Wheat Starch). It is obtained from the caryopsis of *Triticum aestivum* (*T. vulgare*). Irregular, angular, white masses or fine powder. Is odourless and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 4.5 to 7.0.

USNF 31: (Hydroxypropyl Corn Starch). A partially substituted 2-hydroxypropylether obtained from corn starch by a chemical modification of etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch. It contains 2.0 to 7.0% of hydroxypropyl groups on the dried basis. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Hydroxypropyl Pea Starch). A partially substituted 2-hydroxypropylether obtained from pea starch by a chemical modification of etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch. It contains 2.0 to 7.0% of hydroxypropyl groups on the dried basis. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Hydroxypropyl Potato Starch). A partially substituted 2-hydroxypropylether obtained from potato starch by a chemical modification of etherification with propylene oxide. In addition, this starch may be partially hydrolysed using acids or enzymes to obtain thinned starch. It contains 2.0 to 7.0% of hydroxypropyl groups on the dried basis. pH of a 20% suspension in carbon-dioxide-free water, after standing for 15 minutes, is 4.5 to 8.0. A white or slightly yellowish powder. Practically insoluble in cold water and in alcohol.

USNF 31: (Pregelatinized Starch). It is starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. It may be modified to render it compressible and flowable.

USNF 31: (Modified Starch). It is starch modified by chemical means. Food starch may be acid-modified, bleached, oxidised, esterified, etherified, or treated enzymatically to change its functional properties. A 20% slurry in water, after 5 minutes stirring at a moderate rate, has a pH of 3.0 to 9.0.

USNF 31: (Pregelatinized Modified Starch). It is Modified Starch that has been chemically or mechanically processed, or both, to rupture all or part of the granules to produce a product that swells in cold water. Moderately coarse to fine, white to off-white powder. It is odourless and has a slight, characteristic taste. Slightly soluble to soluble in cold water; insoluble in alcohol.

USNF 31: (Pregelatinized Hydroxypropyl Corn Starch). Prepared from hydroxypropyl corn starch by mechanical processing in the presence of water, with or without heat, to rupture all or some of the starch granules, and subsequently dried. It contains 2.0% to 7.0% of hydroxypropyl groups on the dried basis. A white or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture.

USNF 31: (Pregelatinized Hydroxypropyl Pea Starch). Prepared from hydroxypropyl pea starch by mechanical processing in the presence of water, with or without heat, to rupture all or some of the starch granules, and subsequently dried. It contains 2.0% to 7.0% of hydroxypropyl groups on the dried basis. A white or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture.

USNF 31: (Pregelatinized Hydroxypropyl Potato Starch). Prepared from hydroxypropyl potato starch by mechanical processing in the presence of water, with or without heat, to rupture all or some of the starch granules, and subsequently dried. It contains 2.0% to 7.0% of hydroxypropyl groups on the dried basis. A white or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture.

Uses and Administration

Starch is absorbent and is widely used in dusting powders, either alone or mixed with zinc oxide or other similar substances. Starch is used as a surgical glove powder, but such use has been discouraged (see p. 2096.2). It is incorporated in many tablets as a binder, diluent, or disintegrating agent. Pregelatinised starch is used similarly as a tablet binder.

Starch mucilage is given by mouth in the treatment of iodine poisoning; it has been used topically as a skin emollient.

Rice-based solutions may be used in the prevention and treatment of dehydration due to acute diarrhoeal diseases (p. 1805.2).

Glycogen storage disease type I. Type I glycogen storage disease is an autosomal recessive metabolic disorder in

which glucose-6-phosphatase is not expressed, resulting in hypoglycaemia due to lack of glucose production. Accumulation of glycogen and other metabolic derangements can lead to complications including renal impairment, hepatomegaly and hepatic adenoma, hyperuricaemia, hyperlipidaemias, and lactic acidosis. The condition has been successfully managed by continuous nocturnal nasogastric infusion of glucose and frequent daytime feedings. However, such a regimen requires good patient compliance and monitoring of the night-time infusions.[1]

As an alternative, a more standard diet together with uncooked corn starch suspensions prepared with tap water at room temperature and taken every 6 hours in doses of 1.75 to 2.5 g/kg have been reported[2] to be very satisfactory in maintaining normoglycaemia. In one infant, in whom starch was unsatisfactory, the lack of response was considered to be due to inadequate pancreatic amylase activity and although it was subsequently reported[3] that addition of a pancreatic enzyme concentrate had produced some improvement, the response was still inadequate to maintain normoglycaemia for more than 2 hours. It was considered that other amylase preparations should be identified for possible use in such patients. A small study of 7 young adults with glycogen storage disease type I found that a single dose of uncooked corn starch maintained plasma glucose concentrations for 7 hours in 5 of the patients.[4]

A long-term study of the effects of corn starch therapy found fewer complications among patients with near normal metabolic control and in those having started therapy at a younger age, but other factors appeared to be involved in the pathogenesis.[5] Corn starch therapy has nonetheless been reported to have improved proximal renal tubular dysfunction in 3 patients who had previously only had frequent daytime feeding as therapy. In 16 other patients previously treated with corn starch or glucose infusions, such renal dysfunction was not identified, and it was considered that the rapid response to therapy may explain why renal tubular dysfunction is not found more frequently in these patients.[6]

Because optimal metabolic control reduces the risk of developing long-term complications, an attempt has been made to define guidelines for long-term management of the disease.[7] Continuous nocturnal nasogastric feeding with a glucose or glucose polymer or a sucrose-free maltodextrin formula low in lactose may be introduced in very young infants. Uncooked corn starch should not be started in patients under 1 year of age as pancreatic amylase activity may be immature. Thereafter, since no significant differences in growth or biochemical parameters have been found between the use of nocturnal nasogastric infusions and uncooked corn starch overnight, corn starch may be started at a dose of 250 mg/kg and increased slowly to prevent adverse effects. It is recommended that the corn starch be mixed with water in a ratio of 1:2 and that an uncooked corn starch tolerance test be performed to establish the duration of the fasting period. The total dietary plan should aim to provide 60 to 65% of the total energy intake from carbohydrates, 10 to 15% from protein, and the remainder from fat, preferably vegetable oils with a high linoleic acid content. Lactose, fructose, and sucrose should be restricted. Drug therapy for metabolic complications may be necessary, such as allopurinol for hyperuricaemia, and bicarbonate for correction of lactic acidosis.[7]

For mention of the possible role of starch in the management of glycogen storage disease type V, see under Sucrose, below.

For a brief description of glycogen storage disease type II, see under Acid Alpha Glucosidase, p. 2428.1.

1. Goldberg T, Slonim AE. Nutrition therapy for hepatic glycogen storage diseases. *J Am Diet Assoc* 1993; **93:** 1423–30.
2. Chen Y-T, *et al*. Cornstarch therapy in type 1 glycogen-storage disease. *N Engl J Med* 1984; **310:** 171–5.
3. Chen Y-T, Sidbury JB. Cornstarch therapy in type 1 glycogen-storage disease. *N Engl J Med* 1984; **311:** 128–9.
4. Wolfsdorf JI, Crigler JF. Cornstarch regimens for nocturnal treatment of young adults with type I glycogen storage disease. *Am J Clin Nutr* 1997; **65:** 1507–11.
5. Weinstein DA, Wolfsdorf JI. Effect of continuous glucose therapy with uncooked cornstarch on the long-term clinical course of type Ia glycogen storage disease. *Eur J Pediatr* 2002; **161** (suppl): S35–S39.
6. Chen Y-T, *et al*. Amelioration of proximal renal tubular dysfunction in type I glycogen storage disease with dietary therapy. *N Engl J Med* 1990; **323:** 590–3.
7. Rake JP, *et al*. Guidelines for management of glycogen storage disease type I - European study on glycogen storage disease type I (ESGSD I). *Eur J Pediatr* 2002; **161** (suppl): S112–S119.

Adverse Effects

Effects of cassava. In 1985 WHO added *malnutrition-related diabetes* (which included the type previously known as tropical diabetes) to its classification of diabetes mellitus.[1] Epidemiological evidence had suggested an association between fibrocalculous pancreatic diabetes (a subclass of malnutrition-related diabetes) and the consumption of cassava root (tapioca, manioc), which for many people living in tropical developing countries, where protein intake was low, was the main source of food energy.

Cassava root contains several cyanogenic substances and although food preparation and processing could reduce the cyanide content, there was the possibility that in persons with an inadequate protein intake, particularly if deficient in sulfur-containing amino acids which are involved in detoxification pathways, accumulation of cyanides might occur. WHO, however, did consider that further research was necessary to firmly establish any relation between this type of diabetes and high levels of cassava consumption. In a review that appeared in the following year[2] the cassava/malnutrition hypothesis was thought to be attractive, but unproven; also there was strong evidence against it being the only cause.

WHO deleted malnutrition-related diabetes from its 1998 report on the classification of diabetes.[3] Fibrocalculous pancreatic diabetes is now fibrocalculous pancreatopathy, a disease which may cause diabetic mellitus but is not considered a form of diabetes.

Konzo, an upper motor neurone disease characterised by spastic paraparesis,[4] and commonly associated with optic neuropathy,[5] has been reported to be caused by dietary exposure to cyanide after ingestion of cassava root. *Growth retardation* has also been associated with consumption of inadequately processed cassava.[6]

1. WHO. Diabetes mellitus: report of a WHO study group. *WHO Tech Rep Ser 727* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_727.pdf (accessed 20/03/09)
2. Abu-Bakare A, *et al*. Tropical or malnutrition-related diabetes: a real syndrome? *Lancet* 1986; **i:** 1135–8.
3. Alberti KGMM, Zimmet PZ. Definition, diagnosis, and classification of diabetes mellitus and its complications. Part I: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; **15:** 539–53.
4. Ernesto M, *et al*. Persistent konzo and cyanogen toxicity from cassava in northern Mozambique. *Acta Trop* 2002; **82:** 357–62.
5. Mwanza J-C, *et al*. Neuro-ophthalmologic findings in konzo, an upper motor neuron disorder in Africa. *Eur J Ophthalmol* 2003; **13:** 383–9.
6. Banea-Mayambu J-P, *et al*. Dietary cyanide from insufficiently processed cassava and growth retardation in children in the Democratic Republic of Congo (formerly Zaire). *Ann Trop Paediatr* 2000; **20:** 34–40.

Glove powder. The use of starch glove powders by surgeons has resulted in contamination of surgical wounds by starch and in the development of complications such as inflammation, adhesions, and granulomatous lesions. In addition, glove starch powder may be a risk factor in the development of latex allergy, and may act as a vector for bacterial pathogens. Because of these risks, it has been proposed that the use of powder in latex gloves be banned,[1-5] a step which has been taken in some countries.[5]

1. Haglund U, Junghanns K, eds. Glove powder—the hazards which demand a ban. *Eur J Surg* 1997; **163** (suppl 579): 1–55.
2. AAAAI and ACAAI joint statement concerning the use of powdered and non-powdered natural latex gloves. *Ann Allergy Asthma Immunol* 1997; **79:** 487.
3. Dave J, *et al*. Glove powder: implications for infection control. *J Hosp Infect* 1999; **42:** 282–5.
4. Edlich RF, Reddy VR. A call to ban glove cornstarch. *Arch Surg* 2001; **136:** 116.
5. Edlich RF, *et al*. Dangers of cornstarch powder on medical gloves: seeking a solution. *Ann Plast Surg* 2009; **63:** 111–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aptamil Feed Thickener; ***Fr.***: Magic Mix; ***India***: Bio-Sorb; ***Mex.***: Panaline; ***NZ***: Karicare Food Thickener.

Multi-ingredient Preparations. ***Arg.***: Ninderm; Talquisedan; ***Austral.***: Nucolox†; Summer's Eve Feminine; ZSC; ***Canad.***: Bum-Butt-R; ***Chile***: Talquisedan; ***Fr.***: Poudre du Marcheur†; Supro; Trigopax; ***India***: Derby Cool; Feel Chill†; ***Indon.***: L-Bio; ***Irl.***: Skin Clear†; ***Israel***: Baby Paste†; ***Ital.***: Glicerolax; Lenipasta; ***NZ***: Lamisil Odor Eze†; ***Port.***: Cuidaderma; ***S.Afr.***: SB Universal Ointment†; ***Turk.***: Alkagin; ***UK***: Herbheal Ointment; Psorasolv; Skin Clear; ***USA***: Balmex Baby; Desitin with Zinc Oxide; Diaparene Corn Starch; Mexsana; Paladin; Palomar E.

Pharmacopoeial Preparations

BP 2014: Compound Zinc Paste; Talc Dusting Powder;
USP 36: Absorbable Dusting Powder; Topical Starch.

Sucralose *(BAN)*

Sucralosa; Sucralosum; TGS; Trichlorogalactosucrose; Triclorogalactosucrosa; Сукралоза.

1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside.

$C_{12}H_{19}Cl_3O_8$=397.6

CAS — 56038-13-2.

UNII — 96K6UQ3ZD4.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sucralose). A white or almost white, crystalline powder. Freely soluble in water; soluble in anhydrous alcohol; slightly soluble in ethyl acetate.

USNF 31: (Sucralose). A white to off-white, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in ethyl acetate. Store in a cool, dry place at a temperature not exceeding 21 degrees.

Profile

Sucralose is used as a sweetening agent in foods, beverages, and pharmaceuticals. It has between about 300 and 1000 times the sweetening power of sucrose; this is not reduced by cooking. It has no food value and is noncariogenic.

References.

1. Anonymous. Sucralose—a new artificial sweetener. *Med Lett Drugs Ther* 1998; **40:** 67–8.
2. Roberts A, *et al*. Sucralose metabolism and pharmacokinetics in man. *Food Chem Toxicol* 2000; **38** (suppl): S31–S41.
3. Grotz VL, Munro IC. An overview of the safety of sucralose. *Regul Toxicol Pharmacol* 2009; **55:** 1–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Sugafor.

Sucrose

Azúcar; Azúcar de caña; Cane Sugar; Refined Sugar; Sacarosa; Saccharose; Saccharosum; Saccharum; Sacharosa; Sacharozė; Sacharoza; Sackaros; Sakkaroosi; Sucre; Sucrosum; Szacharóz; Zucker; Сахароза.

β-D-Fructofuranosyl-α-D-glucopyranoside.

$C_{12}H_{22}O_{11}$=342.3

CAS — 57-50-1.

UNII — C151H8M554 (sucrose); 8M707QY5GH (raw sugar).

Description. Sucrose is obtained from sugar-cane, *Saccharum officinarum* (Gramineae), sugar-beet, *Beta vulgaris* (Chenopodiaceae), and other sources.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF*.

Br. also contains Compressible Sugar.

Eur. also includes Sugar Spheres.

USNF also includes Compressible Sugar, Confectioner's Sugar, and Sugar Spheres.

Ph. Eur. 8: (Sucrose). A white or almost white, crystalline powder or shiny, colourless or white or almost white crystals. Very soluble in water; slightly soluble in alcohol; practically insoluble in dehydrated alcohol.

USNF 31: (Sucrose). A sugar obtained from *Saccharum officinarum* (Gramineae), *Beta vulgaris* (Chenopodiaceae), and other sources. White, crystalline powder or lustrous, dry, colourless or white crystals. Soluble 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 170 of alcohol; practically insoluble in dehydrated alcohol.

Incompatibility. Sucrose may be contaminated by traces of heavy metals or sulfites and this can lead to incompatibility with other ingredients when it is used as a pharmaceutical excipient. Syrup preserved with hydroxybenzoates has been reported to be incompatible with a range of compounds.

Uses and Administration

Sucrose, a disaccharide, is used as a sweetening agent. It is commonly used as household sugar. If the sweetness of sucrose is taken as 100, fructose has a value of about 173, glucose 74, maltose 32, galactose 32, and lactose 16.

Sucrose is used as a tablet excipient and lozenge basis, and as a suspending and viscosity-increasing agent. Syrups prepared from concentrated solutions of sucrose form the basis of many linctuses. Treacle (molasses), a byproduct of sugar production that contains sucrose and minerals, has also been used.

Sucrose 30% eye drops have been used as a hypertonic agent for clearing corneal oedema.

Cough. Sucrose syrups are used as demulcents in linctuses used for treating cough (p. 1651.2).

Diagnostic test for gastrointestinal damage. Sucrose is not absorbed from the healthy gastrointestinal tract. It has been proposed that the absorption of sucrose could be used as a diagnostic test of gastric damage.[1-3]

1. Sutherland LR, *et al*. A simple non-invasive marker of gastric damage: sucrose permeability. *Lancet* 1994; **343:** 998–1000.
2. Meddings JB, *et al*. Sucrose permeability: a novel means of detecting gastroduodenal damage noninvasively. *Am J Ther* 1995; **2:** 843–9.
3. Kawabata H, *et al*. Sucrose permeability as a means of detecting diseases of the upper digestive tract. *J Gastroenterol Hepatol* 1998; **13:** 1002–6.

Gastrointestinal spasm. For mention of a beneficial effect of sucrose solution in infant colic, see p. 1807.1.

Glycogen storage disease type V. Glycogen storage disease type V (McArdle's disease) is a rare autosomal recessive disorder characterised by mutations in the gene for myophosphorylase, an enzyme essential for glycogenoly-

sis.[1,2] Patients present with exercise-induced pain, cramps, fatigue, and myoglobinuria which, if severe, can cause acute renal failure.[2] Low-dose creatine supplementation (60 mg/kg daily) produced modest benefits during ischaemic exercise testing, but higher doses (150 mg/kg daily) worsened symptoms.[2] Sucrose 75 g by mouth improved exercise tolerance in 12 patients in a randomised crossover study.[1] Uncooked corn starch, either alone or with sucrose, has been suggested as an alternative in order to avoid any pronounced increase in serum insulin,[3] but this has been rejected on the basis that the necessary rapid increase in blood glucose will not be produced.[4]

1. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med* 2003; **349:** 2503–9.
2. Quinlivan R, *et al.* Pharmacological and nutritional treatment for McArdle's disease (glycogen storage disease type V). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).
3. Gaglia JL, Wolfsdorf JI. Oral sucrose and exercise tolerance in McArdle's disease. *N Engl J Med* 2004; **350:** 1575.
4. Vissing J, Haller RG. Oral sucrose and exercise tolerance in McArdle's disease. *N Engl J Med* 2004; **350:** 1575–6.

Hiccup. Giving a teaspoon of dry granulated sugar resulted in the immediate cessation of hiccup in 19 of 20 patients;[1] 12 of the patients had suffered from hiccup for less than 6 hours but in the remaining 8 persistent hiccup had been present for 24 hours to 6 weeks. The effect may be due to stimulation of the pharynx. An early protocol for the treatment of intractable hiccup (p. 1046.3) suggests that swallowing dry granulated sugar is one of the first treatments that should be tried.

1. Engleman EG, *et al.* Granulated sugar as treatment for hiccups in conscious patients. *N Engl J Med* 1971; **285:** 1489.

Pain. A systematic review[1] concluded that oral sucrose solutions could reduce physiological and behavioural indicators of stress and pain in neonates undergoing painful procedures although there had been some doubt expressed[2] over whether this indicated effective analgesia. The review[1] was unable to determine an optimal dose, but 1 mL of a 25% solution or 2 mL of a 50% solution has been reported to reduce crying time in premature[3] and full-term[4] infants, respectively, when given 2 minutes before heel-prick sampling. Similarly, in infants given intramuscular vaccines, 2 mL of a 75% sucrose solution by mouth reduced crying time,[5] and 2 mL of a 24% solution reduced pain scores;[6] 2 mL of oral sucrose 24% also reduced pain scores in premature infants undergoing eye examinations for retinopathy of prematurity.[7] One literature review[8] suggested that a dose of 500 mg sucrose provided effective analgesia for neonates. However, a randomised study found pacifiers (dummies) to have a better analgesic effect than 2 mL of a 30% sucrose solution; a synergistic effect was found with a combination of sucrose and pacifiers.[9] Another review[10] recommended that, along with a pacifier, 0.1 to 0.4 mL of a 24% sucrose solution be given to premature infants, and up to 2 mL be given to term infants. Others have recommended the use of 0.5 mL/kg of a 33% sucrose solution (about 170 mg/kg), stating that more dilute solutions carry a risk of bacterial contamination.[11] The route by which sucrose solution is given may also be important: a reduced pain response was only noted after intraoral doses; giving it via a nasogastric tube was ineffective.[12]

A study in preterm infants found that, while there were no differences on neurobehavioural developmental outcomes between infants given repeated sucrose analgesia or placebo, higher number of doses of sucrose predicted lower scores in motor development, vigour, alertness and orientation. The authors postulated that repeated stimulation by sucrose may interfere with normal functioning and maturation of the preterm infant's endogenous opiate system, and cautioned against the routine use of sucrose analgesia in this population.[13] For choice of analgesic in children, see p. 5.2.

1. Stevens B, *et al.* Sucrose for analgesia in newborn infants undergoing painful procedures. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 10/06/10).
2. Anonymous. Pacifiers, passive behaviour, and pain. *Lancet* 1992; **339:** 275–6.
3. Ramenghi LA, *et al.* Reduction of pain response in premature infants using intraoral sucrose. *Arch Dis Child* 1996; **74:** F126–F128.
4. Haouari N, *et al.* The analgesic effect of sucrose in full term infants: a randomised controlled trial. *BMJ* 1995; **310:** 1498–1500.
5. Lewindon PJ, *et al.* Randomised controlled trial of sucrose by mouth for the relief of infant crying after immunisation. *Arch Dis Child* 1998; **78:** 453–6.
6. Hatfield LA, *et al.* Analgesic properties of oral sucrose during routine immunizations at 2 and 4 months of age. *Pediatrics* 2008; **121:** e327–e334. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/2/e327 (accessed 03/03/09)
7. Gal P, *et al.* Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. *Ann Pharmacother* 2005; **39:** 1029–33.
8. Masters-Harte LD, Abdel-Rahman SM. Sucrose analgesia for minor procedures in newborn infants. *Ann Pharmacother* 2001; **35:** 947–52.
9. Carbajal R, *et al.* Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ* 1999; **319:** 1393–7.
10. Prince WL, *et al.* Treatment of neonatal pain without a gold standard: the case for caregiving interventions and sucrose administration. *Neonatal Netw* 2004; **23:** 33–45.
11. Shann F. Suckling and sugar reduce pain in babies. *Lancet* 2007; **369:** 721–3.
12. Ramenghi LA, *et al.* "Sucrose analgesia": absorptive mechanism or taste perception. *Arch Dis Child Fetal Neonatal Ed* 1999; **80:** F146–F147.
13. Johnston CC, *et al.* Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. *Pediatrics* 2002; **110:** 523–8.

Wound healing. Sugar, either in the form of granulated sugar[1-5] or pastes composed of caster sugar and icing sugar,[6,7] has been used successfully in the treatment of wounds (p. 1690.1) including mediastinitis after cardiac surgery,[1,3] large abscesses and bed sores,[6,7] diabetic ulcers,[2,4] and recurrent bone infections after surgical debridement in patients with leprosy.[5] Debridement of the wound is believed to be due partly to the osmotic effect of sugar and partly to the mechanical cleansing action but it is not known how sugar stimulates granulation tissue to form.[6,7] Once granulation tissue is well established and the wound is shrinking, an alternative wound preparation, such as an alginate, hydrocolloid, or hydrogel, should be used as sugar pastes cause bleeding.[8] Sugar is also effective at deodorising malodorous wounds. The use of the combined caster and icing sugar pastes, of which details of the formulas used are provided in the original publications,[6,7] has been advocated as a way to overcome the problems of possible non-sterility and contamination of commercial granulated sugar.[6,7]

Honey (p. 2072.2) has been used similarly.

1. Trouillet JL, *et al.* Use of granulated sugar in treatment of open mediastinitis after cardiac surgery. *Lancet* 1985; **ii:** 180–4.
2. Quatraro A, *et al.* Sugar and wound healing. *Lancet* 1985; **ii:** 664.
3. De Feo M, *et al.* Treatment of recurrent postoperative mediastinitis with granulated sugar. *J Cardiovasc Surg* 2000; **41:** 715–19.
4. Kilic A. Healing of diabetic ulcers with granulated sugar. *Plast Reconstr Surg* 2001; **108:** 585.
5. Grauwin MY, *et al.* Comment guérir les ostéites et ostéo-arthrites des extrémités des anciens malades de la lèpre par le sucre cristallisé alimentaire? *Acta Leprol* 1999; **11:** 147–52.
6. Gordon H, *et al.* Sugar and wound healing. *Lancet* 1985; **ii:** 663–4.
7. Middleton KR, Seal D. Sugar as an aid to wound healing. *Pharm J* 1985; **235:** 757–8.
8. Seal DV, Middleton K. Healing of cavity wounds with sugar. *Lancet* 1991; **338:** 571–2.

Adverse Effects and Precautions

Sucrose consumption increases the incidence of dental caries.

Sucrose use should be avoided in patients with the glucose-galactose malabsorption syndrome, fructose intolerance, or sucrase-isomaltase deficiency. The intake of sucrose from dietary and other sources must be controlled in patients with diabetes mellitus.

Dietary sugar. The Panel on Dietary Sugars reviewed the evidence relating to sugars in the diet and the health of the population in the UK.[1]

No evidence was found that the consumption of most sugars naturally incorporated into the cellular structure of foods (intrinsic sugars) represented a threat to health and consideration was therefore mainly directed towards the dietary use of sugars not so incorporated (extrinsic sugars), of which sucrose was the principal non-milk extrinsic sugar.

There was extensive evidence suggesting that sugars were the most important dietary factor in the cause of dental caries and it was recommended that consumption of non-milk extrinsic sugars should be decreased.

It was considered that dietary sugars may contribute to the development of obesity, a condition which plays an important part in the aetiology of many diseases. For the majority of the population, who had normal plasma lipids and normal glucose tolerance, the consumption of sugars within the present range carried no special metabolic risks but those persons consuming more than about 200 g daily should replace the excess with starch. It was, however, recommended that those with special medical problems such as diabetes or hypertriglyceridaemia should restrict non-milk extrinsic sugar to less than about 20 to 50 g daily unless otherwise instructed by their own physician or dietitian. It was also concluded that current consumption of sugars, particularly sucrose, played no direct causal role in the development of cardiovascular (atherosclerotic coronary, peripheral, or cerebral vascular) disease, essential hypertension, or diabetes mellitus, and also had no significant specific effects on behaviour or psychological function. Although links between sucrose intake and certain other diseases (such as colorectal cancer, renal and biliary calculi, and Crohn's disease) had been proposed it was not felt that the evidence was adequate to justify any general dietary recommendations.

The conclusions of a joint FAO/WHO consultation on carbohydrates in human nutrition[2] were broadly in agreement with the above. However, they noted that the terms intrinsic and extrinsic sugars had not gained wide acceptance, either in the UK or other countries in the world, and they recommended against the use of these terms. In the USA, the term added sugars has also been used to describe sugars and syrups which are added to foods during processing or preparation. Guidance on dietary intakes issued by the American Food and Nutrition Board suggested a maximum intake of 25% of energy from added sugars.[3] The American Heart Association[4] has also recommended a reduced intake of added sugars, and suggested a specific upper limit; most American women should eat or drink no more than 100 calories daily from added sugars, and no more than 150 calories daily from added sugars for most American men.

1. DoH. Dietary sugars and human disease: report of the panel on dietary sugars of the committee on medical aspects of food policy. *Report on health and social subjects 37.* London: HMSO, 1989.
2. FAO/WHO. *Carbohydrates in human nutrition: report of a joint FAO/WHO expert consultation. FAO Food and Nutrition 66.* Rome: Food and Agriculture Organization of the United Nations, 1998. Also available at: http://www.fao.org/docrep/W8079E/w8079e00.htm (accessed 20/03/09)
3. *et al.*. Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academy Press, 2005. Also available at: http://books.nap.edu/openbook.php?record_id=10490&page=R1 (accessed 12/02/09)
4. Johnson RK, *et al.* American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2009; **120:** 1011–20. Also available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192627 (accessed 11/02/10)

Effects on the kidneys. Acute renal failure with severe hyponatraemia has followed the use of granulated sugar to treat an infected pneumonectomy wound cavity.[1] It was noted that intravenous sucrose had long been known to be nephrotoxic in both *animal* models and man and that mild renal insufficiency before sucrose intoxication might have contributed to the nephrosis. Others, however, considered that the nephrotoxicity might have been caused by gentamicin, a solution of which had been used to irrigate the cavity before packing the wound.[2] Intravenous immunoglobulin preparations containing sucrose (as a stabilising agent) have also caused acute renal failure.[3,4]

1. Debure A, *et al.* Acute renal failure after use of granulated sugar in deep infected wound. *Lancet* 1987; **i:** 1034–5.
2. Archer H, *et al.* Toxicity of topical sugar. *Lancet* 1987; **i:** 1485–6.
3. Ahsan N, *et al.* Intravenous immunoglobulin-induced osmotic nephrosis. *Arch Intern Med* 1994; **154:** 1985–7.
4. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; **93:** 901–4.

Pharmacokinetics

Sucrose is hydrolysed in the small intestine by the enzyme sucrase to glucose and fructose, which are then absorbed. Sucrose is excreted unchanged in the urine when given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Gelodiet; Pacidol.

Multi-ingredient Preparations. ***Arg.***: Semble; ***Austral.***: Nyal Chesty Cough; ***Fr.***: Adiaril; Alhydrate†; Hydrigoz†; Picolite; ***Hung.***: Bittner; ***India***: A2-Z; Energy Plus; Lycosta; ***Irl.***: Rehidrat†; Venos Expectorant; ***Jpn***: U-Pasta; ***Philipp.***: Cholyte Plus With Zinc; Orhydrate†; SportsAde; ***S.Afr.***: Emetrol; Rehidrat; ***Thai.***: D-Lyte; ***UK***: Honey & Molasses; Venos Cough Mixture; Venos Expectorant.

Pharmacopoeial Preparations
BP 2014: Compressible Sugar; Syrup;
Ph. Eur.: Sugar Spheres;
USNF 31: Compressible Sugar; Confectioner's Sugar; Sugar Spheres; Syrup.

Sucrose Polyesters

Sacarosa, poliésteres de la; Полиэфиры Сахарозы.

Profile

A sucrose polyester that is a mixture of hexa-, hepta-, and octa-fatty acid esters of sucrose is used as a nondigestible fat substitute by the food industry. Fat substitutes have been promoted as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

Possible adverse effects of sucrose polyesters are flatulence, anal leakage, abdominal cramps, and loose bowel movements. They may also reduce the absorption of fat-soluble vitamins.

References.

1. Cotton JR, *et al.* Replacement of dietary fat with sucrose polyester: effects on energy intake and appetite control in non-obese males. *Am J Clin Nutr* 1996; **63:** 891–6.
2. Goldman P. Olestra: assessing its potential to interact with drugs in the gastrointestinal tract. *Clin Pharmacol Ther* 1997; **61:** 613–18.
3. Cheskin LJ, *et al.* Gastrointestinal symptoms following consumption of olestra or regular triglyceride potato chips: a controlled comparison. *JAMA* 1998; **279:** 150–2.

4. Sandler RS, *et al.* Gastrointestinal symptoms in 3181 volunteers ingesting snack foods containing olestra or triglycerides. *Ann Intern Med* 1999; **130:** 253–61.
5. Bray GA, *et al.* A 9-mo randomized clinical trial comparing fat-substituted and fat-reduced diets in healthy obese men: the Ole Study. *Am J Clin Nutr* 2002; **76:** 928–34.

Sunflower Oil

Aceite de girasol; Auringonkukkaöljy; Helianthi Annui Oleum; Helianthi Oleum; Huile de Tournesol; Napraforgóolaj; Olej słonecznikowy; Oleum Helianthi; Saulėgrąžų aliejus; Slunečnicový olej; Solrosolja; Sonnenblumenöl; Sunflowerseed Oil; Tournesol, huile de; Подсолнечное Масло.

ATC Herb — HA06AX5005 (Helianthus annuus: seed oil); HD02WB5003 (Helianthus annuus: oil).
UNII — 3W1JG795YI.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sunflower Oil, Refined; Helianthi Annui Oleum Raffinatum). The fatty oil obtained from the seeds of *Helianthus annuus* by mechanical expression or by extraction and then refined. A suitable antoxidant may be added. A clear, light yellow liquid. Practically insoluble in water and in alcohol; miscible with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store in well-filled airtight containers. Protect from light.

USNF 31: (Sunflower Oil). A refined fixed oil obtained from the seeds of the sunflower plant *Helianthus annuus* (Asteraceae alt. Compositae). Specific gravity between 0.914 and 0.924 at 20 degrees. Store in airtight containers. Protect from light.

Profile

Sunflower oil is the fixed oil expressed from the fruits of *Helianthus annuus*. It is used as a salad oil and in pharmaceutical preparations. It is rich in linoleic acid (p. 2509.2).

Multiple sclerosis. As discussed on p. 996.3, the role of dietary lipids in multiple sclerosis remains to be proven,[1] although many patients modify their diets and take supplements of sunflower and other oils. One study showed a reduction in severity and duration of relapse in patients taking linoleic acid supplements (as sunflower oil).[2] Another[3] reported benefit in patients who limited their intake of dietary saturated fatty acids and supplemented their diet with polyunsaturated fatty acids. A systematic review[4] of the relationship between dietary interventions (including linoleic acid given as sunflower oils) and multiple sclerosis concluded that there was insufficient evidence to determine their benefits or risks.

1. Anonymous. Lipids and multiple sclerosis. *Lancet* 1990; **336:** 25–6.
2. Millar JHD, *et al.* Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *BMJ* 1973; **1:** 765–8.
3. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 1990; **336:** 37–9.
4. Farinotti M, *et al.* Dietary interventions for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Singapore***: Lubrex†.

Multi-ingredient Preparations. ***Austria***: Pelsana Med; Piniment; ***Fr.***: Menolistica; Oropur; Trigopax; ***Ger.***: Kneipp Arnika Salbe S; ***Hong Kong***: Sanjukei Panax Ginseng; ***Hung.***: Pelsano Med; Pelsano Med; ***India***: Alovit-AF; ***Ital.***: DHA; ***NZ***: Snorenz; ***Philipp.***: Nutri-Aid; ***Singapore***: Snoreeze; ***Switz.***: Huile de millepertuis A. Vogel (huile de St. Jean); Pelsano; Pelsano; ***Turk.***: Snoreless; ***UK***: Goodnight StopSnore; Snor-Away.

Tagatose

D-*lyxo*-hexulose; D-Tagatose; Tagatosum; Tagatoza; Таратоза.
$C_6H_{12}O_6$=180.2
CAS — 87-81-0 (tagatose); 17598-81-1 (DL-tagatose).
UNII — T7A20Y888Y.

Pharmacopoeias. In *USNF.*

USNF 31: (Tagatose). Tagatose is a ketohexose, an epimer of fructose inverted at C-4. It is obtained from galactose by isomerisation under alkaline conditions in the presence of calcium. White or almost white crystals, having a sweet taste. Very soluble in water; very slightly soluble in alcohol.

Profile

Tagatose is a naturally occurring monosaccharide, produced commercially from lactose. It is 92% as sweet as sucrose, but contains fewer calories. It may be used as a sweetener in foods, beverages, toothpaste, mouthwashes, and medicines.

Threonine *(BAN, USAN, rINN)*

β-Methylserine; T; Thr; Threonin; L-Threonine; Thréonine; Threoninum; Treoniini; Treonin; Treonina; Treoninas; Треонин.
L-2-Amino-3-hydroxybutyric acid.
$C_4H_9NO_3$=119.1
CAS — 72-19-5 (L-threonine); 80-68-2 (DL-threonine).
UNII — 2ZD004190S.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Threonine). Fermentation product, extract or hydrolysate of protein. A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 2.5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 36: (Threonine). White, odourless crystals. Freely soluble in water; insoluble in dehydrated alcohol, in chloroform, and in ether. pH of a 5% solution in water is between 5.0 and 6.5.

Profile

Threonine is an amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Threonine has been investigated for the treatment of various spastic disorders.

DL-Threonine has been used in topical preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cicatrex Biotic; ***Austral.***: Cicatrin†; ***Braz.***: Cicatrene; ***Irl.***: Cicatrin†; ***Ital.***: Cicatrene; ***Port.***: Cicatrin; ***Rus.***: Biotredin (Биотредин); ***S.Afr.***: Cicatrin†; ***Switz.***: Cicatrex; ***Thai.***: Genquin.

Tricaprylin

AC-1202; Caprylic Acid Triglyceride; Caprylic Triglyceride; Caprylidene; Glycerin Tricaprylate; 1,2,3-Tricapryloylglycerol. Glyceryl trioctanoate; Propane-1,2,3-triyl trioctanoate.
$C_{27}H_{50}O_6$=470.7
CAS — 538-23-8.
UNII — 6P92858988.

NOTE. The name Ketasyn has been used as a trade mark for tricaprylin.

Profile

Tricaprylin is a medium-chain triglyceride which is metabolised to ketone bodies, providing an alternative energy substrate to glucose; it elevates serum-ketone levels and is promoted for use in the clinical dietary management of patients with Alzheimer's disease. It has been supplied as a powder formulation in 10 or 40 g sachets containing 5 or 20 g of tricaprylin, respectively. It is given as an oral dose of 20 g tricaprylin daily, preferably with or after a full meal (usually breakfast or lunch). The main adverse effects are gastrointestinal such as diarrhoea, flatulence, or dyspepsia. A starting dose of 5 g tricaprylin daily, increased gradually over 7 days as tolerated, may minimise these effects. It should be used with caution in patients at risk of ketoacidosis.

References.

1. Costantini LC, *et al.* Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neurosci* 2008; **9** (suppl 2): S16.
2. Henderson ST, *et al.* Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond)* 2009; **6:** 31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Axona.

Tuna-liver Oil

Tunny-liver Oil.

Profile

Tuna-liver oil is a source of vitamin D (p. 2112.3) and vitamin A (below). It also contains several essential fatty acids. It is used, similarly to cod-liver oil (p. 2056.3), as a nutritional supplement and has been used in skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Femme Plus†.

Tyrosine *(BAN, USAN, rINN)*

Tirosina; Tirozin; Tirozinas; Tyr; Tyrosiini; Tyrosin; L-Tyrosine; Tyrosinum; Tyrozyna; Y; Тирозин.
L-2-Amino-3-(4-hydroxyphenyl)propionic acid.
$C_9H_{11}NO_3$=181.2
CAS — 60-18-4.
UNII — 42HK56048U.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Tyrosine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Tyrosine). White, odourless crystals or crystalline powder. Very slightly soluble in water; insoluble in alcohol and in ether.

Profile

Tyrosine is an aromatic non-essential amino acid. It is used as a dietary supplement. The sodium salt has also been used.

Phenylketonuria. Tyrosine was not an effective alternative to a diet low in phenylalanine in patients with phenylketonuria, see under Amino Acid Metabolic Disorders, p. 2042.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Aussie Tan Pre-Tan†; PM LifePro Max for Men; PM LifePro Max for Women; Prosense for Men†; Prosense for Women†; Zellulean with Escin†; ***Fr.***: Dynabiane; Fibromyalgine Fort; Fibromyalgine; Phytozac; Silinovea; ***India***: Ipreg; Placentrex; ***Indon.***: Femosa; ***Port.***: Rilastil Dermo Solar; ***Ukr.***: Stifimol (Стифимол); ***USA***: Adrenoil.

Valine *(BAN, USAN, rINN)*

α-Aminoisovaleric Acid; V; Val; Valiini; Valin; Valina; Valinas; L-Valine; Valinum; Валин.
(*S*)-2-Amino-3-methylbutanoic acid.
$C_5H_{11}NO_2$=117.1
CAS — 72-18-4.
UNII — HG18B9YRS7.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Valine). Fermentation product, extract or hydrolysate of protein. A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Valine). White, odourless crystals. Soluble in water; practically insoluble in alcohol, in acetone, and in ether. pH of a 5% solution in water is between 5.5 and 7.0.

Profile

Valine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Revitalose; ***Ger.***: Falkamin; ***Ital.***: Isobranch; Isoram; Sargenor Sport†.

Vitamin A *(USAN)*

Antixerophthalmic Vitamin; A-vitamiini; A-vitamin; Axerophtholum; Oleovitamin A; Retinol (BAN); Retinol (rINN); Rétinol; Retinolum; Vitamin A Alcohol; Vitaminas A; Vitamine A; Vitaminum A; Witamina A; Ретинол.
15-Apo-β-caroten-15-ol; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraen-1-ol.
$C_{20}H_{30}O$=286.5
CAS — 68-26-8.
ATC — A11CA01; D10AD02; R01AX02; S01XA02.
ATC Vet — QA11CA01; QD10AD02; QR01AX02; QS01XA02.
UNII — 81G40H8B0T (vitamin A); G2SH0XKK91 (retinol).

Description. Vitamin A is generally used in the form of esters, such as the acetate, palmitate, and propionate.

Vitamin A Acetate. Retinol Acetate; Retinyl Acetate; $C_{22}H_{32}O_2$ = 328.5; CAS — 127-47-9

Vitamin A Palmitate. Retinol Palmitate; Retinyl Palmitate; $C_{36}H_{60}O_2$ = 524.9; CAS — 79-81-2

Vitamin A Propionate. Retinol Propionate; Retinyl Propionate; $C_{23}H_{34}O_2$ = 342.5; CAS — 7069-42-3.

Pharmacopoeias. In *Eur.* (see p. vii), *US,* and *Viet.*, which permit retinol or its esters.

Chin. includes a monograph for the acetate. *Jpn* includes monographs for the acetate and the palmitate.

Br. includes a monograph for a natural ester concentrate.

Eur. also includes monographs for synthetic concentrates in an oily form, a powder form, and a solubilisate/emulsion.

Int. includes an oily concentrated form.

The BP 2014 states that the term 'Retinol' is used within BP titles for preparations containing synthetic ester(s) and the term 'Vitamin A' within the BP title for the preparation containing material of natural origin.

Ph. Eur. 8: (Vitamin A). Under the name Vitamin A are included a number of substances of very similar structure (including (*Z*)-isomers) found in animal tissues and possessing similar activity. The principal and biologically most active substance is all-(*E*) retinol.

Vitamin A is generally used in the form of esters such as the acetate, propionate, and palmitate. Synthetic retinol ester refers to an ester (acetate, propionate, or palmitate) or a mixture of synthetic retinol esters.

Retinol acetate occurs as pale yellow crystals. M.p. about 60 degrees; once melted it tends to yield a supercooled melt. Retinol propionate occurs as a reddish-brown oily liquid. Retinol palmitate occurs as a fat-like, light yellow solid, or as a yellow oily liquid, if melted. M.p. about 26 degrees. All retinol esters are practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used should be protected by an atmosphere of inert gas.

Ph. Eur. 8: (Vitamin A Concentrate (Oily Form), Synthetic; Vitaminum A Densatum Oleosum; Synthetic Retinol Concentrate (Oily Form) BP 2014). It is prepared from synthetic retinol ester as is or by dilution with a suitable vegetable oil. It contains not less than 500 000 units of vitamin A per g. It is a yellow or brownish-yellow, oily liquid; practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents. Partial crystallisation may occur in highly concentrated solutions.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 8: (Vitamin A Concentrate (Powder Form), Synthetic; Vitaminum A Pulvis; Synthetic Retinol Concentrate (Powder Form) BP 2014). It is obtained by dispersing a synthetic retinol ester in a matrix of gelatin or acacia or other suitable material. It contains not less than 250 000 units of vitamin A per g. It is a yellowish powder usually in the form of particles of almost uniform size. Practically insoluble in water or may swell or form an emulsion, depending on formulation.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 8: (Vitamin A Concentrate (Solubilisate/Emulsion), Synthetic; Vitaminum A in Aqua Dispergibile; Synthetic Retinol Concentrate, Solubilisate/Emulsion BP 2014). It is a liquid form (water is generally used as solvent) of synthetic retinol ester and a suitable solubiliser. It contains not less than 100 000 units of vitamin A per g. It is a yellow or yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or take the form of a gel. A mixture of 1 g with 10 mL of water previously warmed to 50 degrees gives after cooling to 20 degrees, a uniform, slightly opalescent and slightly yellow dispersion.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

BP 2014: (Natural Vitamin A Ester Concentrate). It consists of a natural ester or a mixture of natural esters of retinol or of a solution of the ester or mixture of esters in arachis oil or other suitable vegetable oil. It contains not less than 485 000 units of vitamin A per g. It is a yellow oil or a mixture of oil and crystalline material, with a faint odour. Practically insoluble in water; soluble or partly soluble in alcohol; miscible with chloroform, with ether, and with petroleum spirit. Store in airtight containers at 8 degrees to 15 degrees. Protect from light.

USP 36: (Vitamin A). It may consist of retinol or its esters formed from edible fatty acids, principally acetic and palmitic acids. In liquid form, it is a light yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. It may be practically odourless or may have a mild fishy odour but no rancid odour or taste. It is unstable in air and light. In liquid form, it is insoluble in water and in glycerol; soluble in dehydrated alcohol and in vegetable oils; very soluble in chloroform and in ether. In solid form, may be dispersible in water. Store in airtight containers, preferably under an atmosphere of inert gas. Protect from light.

Units

The International Standards for vitamin A and for provitamin A were discontinued in 1954 and 1956 respectively but the International units for these substances have continued to be widely used. In 1960–1, the WHO Expert Committee on Biological Standardization stated that the International unit for vitamin A is equivalent to the activity of 0.000344 mg of pure all-*trans* vitamin A acetate and the International unit for provitamin A is equivalent to the activity of 0.0006 mg of pure all-*trans* β-carotene.

The activity of one International unit is contained in 0.0003 mg of all-*trans* retinol, in 0.00055 mg of all-*trans* retinol palmitate, and in 0.000359 mg of all-*trans* retinol propionate.

The USP 36 defines 1 USP unit as equal to the biological activity of 0.0003 mg of the all-*trans* isomer of retinol, and is equivalent to the International unit.

Vitamin A activity in foods is currently expressed in terms of retinol equivalents: 1 retinol equivalent is defined as 1 microgram of all-*trans* retinol, 6 micrograms of all-*trans* beta carotene, or 12 micrograms of other provitamin A carotenoids.

Uses and Administration

Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light. Vitamin A deficiency develops when the dietary intake is inadequate and is seen more frequently in young children than in adults. It is rare in developed countries but remains a major problem in many developing countries. Prolonged deficiency leads to xerophthalmia or 'dry eye', the initial symptom of which is night blindness which may progress to severe eye lesions and blindness. Other symptoms include changes in the skin and mucous membranes.

Vitamin A is used in the treatment and prevention of vitamin A deficiency. It may be given orally in an oil- or water-based form, the oil-based generally being the preferred type. It can also be given by intramuscular injection of a water-miscible form; oil-miscible preparations of vitamin A are poorly absorbed from injection sites after intramuscular injection and are not usually given by this route. For further details concerning vitamin A supplementation, including doses for the treatment and prophylaxis of xerophthalmia, see p. 2101.1.

Vitamin A supplements are often given to patients with primary biliary cirrhosis or chronic cholestatic liver disease as deficiencies are common in these disorders. An intramuscular dose of 100 000 units every 2 to 4 months has been suggested. For doses in children, see below.

Vitamins A and D have been used together in creams or ointments in the treatment of minor skin disorders including abrasions. Vitamin A has also been used alone to treat various skin disorders including acne and psoriasis. It has been tried in patients with retinitis pigmentosa to retard the decline in retinal function.

Administration in children. Vitamin A supplementation may be required in children with cholestatic liver disease; the *BNFC* suggests an intramuscular dose of 50 000 units once monthly in neonates and children aged up to 1 year to prevent deficiency in complete biliary obstruction.

For further details concerning vitamin A supplementation in deficiency states, see below.

Deficiency states. Vitamin A deficiency is relatively rare in developed countries and is usually only seen in certain medical conditions such as biliary cirrhosis or cholestatic jaundice. However, it is a continuing problem in many developing countries and children appear to be particularly vulnerable.

In **developing countries** where dietary intake is often less than desirable, infections such as measles, acute respiratory diseases, and diarrhoea can be major precipitating factors of vitamin A deficiency. Thus WHO have targeted elimination of vitamin A deficiency as an important strategy in child health,[1,2] and as part of the Expanded Programme on Immunization. They recommend the use of vitamin A supplements in the treatment of vitamin A deficiency and to prevent vitamin A deficiency where the periodic use of supplements is determined to be the most feasible and effective method of improving vitamin A status.

- In *universal distribution programmes*,[2,3] supplemental doses are given to all children up to the age of 5 at a dose of 200 000 units every 4 to 6 months, with infants between the ages of 6 and 12 months receiving half this dose. Infants aged less than 6 months may receive 50 000 units if they are not breast fed or if they are breast fed and their mothers have not received supplemental vitamin A. If clinical signs of vitamin A deficiency are evident at the time of routine supplementation, treatment should be given as described under Xerophthalmia, p. 2101.1. Mothers should receive 200 000 units within 6 weeks of delivery of a child.
- *Targeted distribution programmes* involve vitamin A supplementation to children and pregnant women in specific high-risk areas.[2] Doses used in children are similar to those used in universal programmes, but doses used in pregnant women should not exceed 10 000 units daily, or 25 000 units weekly.[2]

A number of studies have indicated that general supplementation with vitamin A decreases both mortality rates and morbidity among children in developing countries with a high prevalence of vitamin A deficiency.[4-7] Although not all studies have confirmed these findings,[8,9] two meta-analyses concur that the effect is likely to be genuine especially as regards measles infection,[10,11] (see Measles, p. 2100.3) and researchers and commentators have agreed that overall improvement of vitamin A status is worthwhile and necessary.[12-14] A study in children given half the dose of vitamin A recommended by WHO found that it provided equally good or better protection against mortality, but not against morbidity.[15] Supplementation with vitamin A 23 300 units weekly, or the equivalent amount of betacarotene, in women of child-bearing age reduced pregnancy-related mortality.[16] Studies have also evaluated mortality specifically in infants less than 6 months of age with varying results. Some have found no overall benefit on early infant mortality;[17,18] one study reported a tendency for the relative risk of mortality to increase with improved nutritional status.[17] A systematic review[19] also failed to find evidence of benefit. No sustained benefit was seen on vitamin A status or morbidity beyond the age of 6 months, in infants receiving vitamin A supplements with immunisation at 6, 10, and 14 weeks.[20] Another study in west Africa, noted variations in mortality rate between the sexes and according to the season in which the supplement was given, with an increased mortality in girls supplemented in the rainy season but a reduced mortality among boys supplemented in the dry season.[18] Others have reported overall decreases in mortality at 6 months[21] and 1 year[22] of age. A study in vitamin-A-deficient children has demonstrated abnormalities in T-cell subsets which are corrected by vitamin A supplementation,[23] and it has been proposed that the apparent effects of vitamin A on morbidity and mortality may be due to modulation of immune function (see also Effects on the Immune System, p. 2101.3). Discrepancies in results could be explained by inherent differences between the populations being studied, such as vitamin A deficiency status and infant mortality rates.[24]

In **other countries** in which vitamin A deficiency is not widespread some form of supplementation may still be considered. In the UK, the *BNFC* suggests the following oral doses, with or after food, according to age:

- neonates and infants up to 1 year: 5000 units daily
- 1 to 18 years: 10 000 units daily

Higher doses may be used initially for the treatment of severe deficiency. Preterm infants have low vitamin A status at birth, which may increase their risk of developing chronic lung disease.[25] A meta-analysis of studies in low birthweight infants found that vitamin A supplementation was associated with a reduced requirement for oxygen at 36 weeks postmenstrual age.[25] While studies of vitamin A supplementation to prevent chronic lung disease in very low birth-weight infants have had conflicting results,[26,27] some have commented that differences in patient population, postnatal therapies, and dosage of vitamin A could explain these discrepancies, and consider optimal supplementation necessary.[28] Others have called for further studies in preterm infants to define optimal dosage and mode of delivery of vitamin A; research should include quantification of hepatic stores, assessment of retinal function, and long-term clinical outcome.[29]

1. Potter AR. Reducing vitamin A deficiency: could save the eyesight and lives of countless children. *BMJ* 1997; **314:** 317–18.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 2nd ed. Geneva: WHO,1997.
3. WHO. Integration of vitamin A supplementation with immunization. *Wkly Epidem Rec* 1999; **74:** 1–6.
4. Rahmathullah L, *et al.* Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; **323:** 929–35.
5. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
6. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
7. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
8. Herrera MG, *et al.* Vitamin A supplementation and child survival. *Lancet* 1992; **340:** 267–71.
9. Gupta P, Indrayan A. Effect of vitamin A supplementation on childhood morbidity and mortality: critical review of Indian studies. *Indian Pediatr* 2002; **39:** 1099–1118.

10. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; **306:** 366–70.
11. Fawzi WW, *et al*. Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; **269:** 898–903.
12. Anonymous. Vitamin A and malnutrition/infection complex in developing countries. *Lancet* 1990; **336:** 1349–51.
13. Humphrey JH, Rice A L. Vitamin A supplementation of young infants. *Lancet* 2000; **356:** 422–4.
14. Villamor E, Fawzi WW. Vitamin A supplementation: implications for morbidity and mortality in children. *J Infect Dis* 2000; **182** (suppl): S122–S133.
15. Benn CS, *et al*. Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005; **331:** 1428–32.
16. West KP, *et al*. Double blind, cluster randomised trial of low dose supplementation with vitamin A or β carotene on mortality related to pregnancy in Nepal. *BMJ* 1999; **318:** 570–5. Correction. *ibid.*; 1386.
17. West KP, *et al*. Mortality of infants <6 mo of age supplemented with vitamin A: a randomized double-masked trial in Nepal. *Am J Clin Nutr* 1995; **62:** 143–8.
18. Benn CS, *et al*. Effect of 50 000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. *BMJ* 2008; **336:** 1416–20.
19. Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. *BMJ* 2009; **338:** b919.
20. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; **352:** 1257–63. Correction. *ibid*. 1999; **353:** 154.
21. Rahmathullah L, *et al*. Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. *BMJ* 2003; **327:** 254–7.
22. Humphrey JH, *et al*. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *J Pediatr* 1996; **128:** 489–96.
23. Semba RD, *et al*. Abnormal T-cell subset proportions in vitamin-A-deficient children. *Lancet* 1993; **341:** 5–8.
24. Tielsch JM. Vitamin A supplements in newborns and child survival. *BMJ* 2008; **336:** 1385–6.
25. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/07/08).
26. Tyson JE, *et al*. Vitamin A supplementation for extremely-low-birthweight infants. *N Engl J Med* 1999; **340:** 1962–8.
27. Wardle SP, *et al*. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F9–F13.
28. Shenai JP. Vitamin A supplementation in very low birth weight neonates: rationale and evidence. *Pediatrics* 1999; **104:** 1369–74.
29. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F103–F108.

ANAEMIA. A study among pregnant Indonesian women with nutritional anaemia (see Iron-Deficiency Anaemia, p. 2073.2) found a beneficial effect for vitamin A on haemoglobin when given with iron supplementation.[1] Similarly, in anaemic children given iron,[2] or adolescents given iron plus folic acid,[3] greater improvements in haemoglobin concentrations were seen with addition of vitamin A to supplementation. Vitamin A is considered essential for haematopoiesis; it has been suggested that vitamin A is required for the mobilisation and utilisation of iron for haemoglobin synthesis.[4] However, there are reports of anaemia caused by vitamin A supplementation, see Effects on the Blood, p. 2101.3.

1. Suharno D, *et al*. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993; **342:** 1325–8.
2. Mwanri L, *et al*. Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. *J Nutr* 2000; **130:** 2691–6.
3. Ahmed F, *et al*. Concomitant supplemental vitamin A enhances the response to weekly supplemental iron and folic acid in anemic teenagers in urban Bangladesh. *Am J Clin Nutr* 2001; **74:** 108–15.
4. van den Broek N. Anaemia and micronutrient deficiencies. *Br Med Bull* 2003; **67:** 149–60.

DIARRHOEA. Although oral rehydration therapy remains the mainstay of the management of diarrhoea (p. 1805.2) once it develops, it has been suggested that vitamin A supplementation may be of use in reducing the incidence and mortality of diarrhoea during childhood. Several large mortality studies reported that vitamin A supplementation was associated with reduced mortality attributed to diarrhoea,[1-3] although another did not.[4] The effect on morbidity from diarrhoea is even less clear. A reduction in the severity, but not the incidence, of diarrhoea has been noted in two studies.[5,6] However, in one study in children with subclinical vitamin A deficiency, there was an increased prevalence of diarrhoea for 2 weeks after vitamin A supplementation,[7] and in another study, vitamin A increased the incidence of diarrhoea in children aged less than 30 months.[8] A meta-analysis[9] concluded that vitamin A supplementation has no consistent overall protective effect on the incidence of diarrhoea. While severity was not examined, they noted that the decrease in diarrhoea mortality rates but not incidence can be reconciled if vitamin A reduces diarrhoea severity and not susceptibility to infection. This is possibly supported by a study that found that a single high-dose vitamin A supplement, given with standard antibacterial treatment, reduced the severity of acute shigellosis in children in Bangladesh.[10] One group[11] proposed that the inconsistent findings on morbidity of vitamin A supplementation may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. They found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone (see Vitamin A Deficiency, under Zinc, p. 2127.3).

1. West KP, *et al*. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
2. Daulaire NMP, *et al*. Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
4. Vijayaraghavan K, *et al*. Effect of massive dose of vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; **336:** 1342–5.
5. Barreto ML, *et al*. Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; **344:** 228–31.
6. Bhandari N, *et al*. Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; **309:** 1404–7.
7. Stansfield SK, *et al*. Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; **342:** 578–82.
8. Dibley MJ, *et al*. Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; **126:** 434–42.
9. Grotto I, *et al*. Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; **142:** 297–304.
10. Hossain S, *et al*. Single dose vitamin A treatment in acute shigellosis in Bangladeshi children: randomised double blind controlled trial. *BMJ* 1998; **316:** 422–6.
11. Rahman MM, *et al*. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314–18.

HIV INFECTION AND AIDS. A study in Malawi found that the rates of vertical transmission of HIV infection (birth of seropositive infants to seropositive mothers) were inversely related to maternal vitamin A status;[1] vitamin A deficiency during pregnancy was associated with a threefold to fourfold increased risk of mother-to-child transmission of HIV. This was not incompatible with the role of vitamin A in immunity and maintenance of mucosal surfaces, and since both HIV infection and pregnancy are risk factors for vitamin A deficiency, it was suggested that nutritional intervention to reduce vitamin A deficiency might help combat mother-to-child transmission. A South African study[2] found, in contrast, that supplementing HIV-infected pregnant women with vitamin A and betacarotene did not reduce the overall risk of vertical transmission to neonates. Supplementation did reduce the incidence of preterm births, and among these neonates, risk of perinatal HIV transmission was lower in those whose mothers had been supplemented. Vitamin A supplementation actually increased the risk of HIV transmission through breast feeding, with no effect on mortality at 24 months, in a Tanzanian trial.[3] Yet another study,[4] again in Tanzania, for which vertical transmission data were not available, found no evidence of an effect of vitamin A on birth outcomes in HIV-infected women and the authors pointed out that serum concentrations of vitamin A might be a marker of the stage of HIV disease rather than being causally related to outcome. The study did however find that multivitamin supplements reduced the risk of low birth-weight and size for age, and of premature birth, in the offspring of these women.[4] Interestingly, another trial in Tanzania found little difference between vitamin A supplementation and placebo on the progression of HIV disease and mortality. Multivitamin (excluding vitamin A) supplementation delayed disease progression and was associated with decreased mortality; addition of vitamin A to the multivitamin regimen reduced this benefit.[5] This is in contrast to 2 studies in Tanzania[6] and Uganda,[7] which found that vitamin A supplementation decreased mortality in children infected with HIV; however these results were not considered generalisable to communities with access to better healthcare and nutrition.

A systematic review and meta-analysis,[8] which included some of these conflicting studies, did not support the use of vitamin A supplementation to reduce the risk of vertical transmission and concluded that it may in fact increase the risk. Maternal vitamin A supplementation was not considered to decrease childhood mortality at 1 year. A further systematic review found no significant reduction in HIV progression in 6 studies of vitamin A or beta-carotene supplementation in adults. All-cause mortality was, however, halved in a meta-analysis of 3 studies in African children and short-term growth was improved in 1 study; the effect on diarrhoeal and respiratory morbidity was inconsistent.[9]

Means of reducing the risk of HIV infection in neonates are discussed under HIV Infection Prophylaxis, p. 959.1.

1. Semba RD, *et al*. Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* 1994; **343:** 1593–7.
2. Coutsoudis A, *et al*. Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. *AIDS* 1999; **13:** 1517–24.
3. Fawzi WW, *et al*. Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS* 2002; **16:** 1935–44.
4. Fawzi WW, *et al*. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T-cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998; **351:** 1477–82.
5. Fawzi WW, *et al*. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; **351:** 23–32.
6. Fawzi WW, *et al*. A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *Pediatr Infect Dis J* 1999; **18:** 127–33.
7. Semba RD, *et al*. Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: a controlled clinical trial. *Nutrition* 2005; **21:** 25–31.
8. Mills EJ, *et al*. Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of RCTs including more than 2800 women. *AIDS Res Ther* 2005; **2:** 4.
9. Irlam JH, *et al*. Micronutrient supplementation in children and adults with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 22/12/10).

MEASLES. Vitamin A supplementation has an important role in the prevention of complications from measles.[1,2] Two studies specifically addressing vitamin A status and measles have found that complications such as pneumonia and diarrhoea were less common in children who had received supplements at the time of diagnosis than in those given a placebo.[3,4] WHO has recommended treating children in populations where vitamin A deficiency is common with high-dose vitamin A supplements during episodes of measles as follows:[5]

- all children over 12 months of age: 200 000 units
- those between 6 and 12 months of age: 100 000 units
- infants less than 6 months of age: 50 000 units

Doses are given on 2 consecutive days and followed by a third dose at least 2 weeks later.

Studies in the USA have indicated that even among well-nourished children from a developed country, vitamin A deficiency in measles patients is not uncommon,[6,7] and vitamin A supplementation needs to be considered in children at risk.[8]

1. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; **306:** 366–70.
2. Fawzi WW, *et al*. Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; **269:** 898–903.
3. Barclay AJG, *et al*. Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987; **294:** 294–6.
4. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; **323:** 160–4.
5. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 2nd ed. Geneva: WHO,1997.
6. Arrieta AC, *et al*. Vitamin A levels in children with measles in Long Beach, California. *J Pediatr* 1992; **121:** 75–8.
7. Butler JC, *et al*. Measles severity and serum retinol (vitamin A) concentration among children in the United States. *Pediatrics* 1993; **91:** 1176–81.
8. Committee on Infectious Diseases of the American Academy of Pediatrics. Vitamin A treatment of measles. *Pediatrics* 1993; **91:** 1014–15.

PREMATURITY. The fetus accumulates vitamin A in the third trimester, and most premature infants have low plasma vitamin A concentrations. Inadequate vitamin A supplementation after birth may exacerbate the problem, and contribute to an increased risk of developing chronic lung disease. A systematic review found that supplementing very low birth-weight infants with vitamin A was associated with a reduction in death or oxygen requirement at 1 month of age.[1]

1. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 12/03/08).

RESPIRATORY-TRACT INFECTIONS. Mortality studies did not show a consistent impact for vitamin A supplementation on death from non-measles-related respiratory infections.[1-3] Similarly, other studies have found no benefit of vitamin A on subsequent respiratory morbidity.[4-6] A meta-analysis of studies reporting pneumonia morbidity and mortality found no overall benefit or harm from vitamin A supplementation.[7] However, an increased prevalence of symptoms of respiratory infections associated with vitamin A supplementation has been noted in two studies,[8,9] particularly in children with adequate nutritional status. A meta-analysis of the effect of vitamin A supplementation on childhood morbidity found an increased incidence of respiratory-tract infections; since most trials had excluded children with overt vitamin A deficiency, the authors speculated that high-dose vitamin A given to children with adequate vitamin A stores might cause a temporary decline in immune status, increasing their susceptibility to infection.[10] A systematic review concluded that vitamin A should not be given to all children for *prevention* of acute lower respiratory-tract infections, but noted that children with vitamin A deficiency or poor nutritional status might benefit from supplementation in this respect.[11]

Vitamin A was not effective for the *treatment* of childhood non-measles-related lower respiratory-tract infections[12] or pneumonia.[13] Similarly, there was no benefit from vitamin A in the treatment of RSV infection in children in 2 studies.[14,15] In one of these studies there was a tendency for vitamin A to improve outcomes in the subgroup of severely ill children,[14] and in the other there was a slight increase in duration of hospitalisation in low-risk children receiving vitamin A.[15] A meta-analysis found no evidence that adjunctive treatment with high-dose vitamin A alters the course of pneumonia in children.[16]

1. West KP, *et al*. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
2. Daulaire NMP, *et al*. Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.

3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
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6. Kartasasmita CB, *et al*. Plasma retinol level, vitamin A supplementation and acute respiratory infections in children of 1-5 years old in a developing country. *Tubercle Lung Dis* 1995; **76:** 563–9.
7. The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bull WHO* 1995; **73:** 609–19.
8. Stansfield SK, *et al*. Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; **342:** 578–82.
9. Dibley MJ, *et al*. Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; **126:** 434–42.
10. Grotto I, *et al*. Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; **142:** 297–304.
11. Chen H, *et al*. Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 12/03/08).
12. Kjolhede CL, *et al*. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr* 1995; **126:** 807–12.
13. Nacul LC, *et al*. Randomised, double blind, placebo controlled clinical trial of efficacy of vitamin A treatment in non-measles childhood pneumonia. *BMJ* 1997; **315:** 505–10.
14. Dowell SF, *et al*. Treatment of respiratory syncytial virus infection with vitamin A: a randomised placebo-controlled trial in Santiago, Chile. *Pediatr Infect Dis J* 1996; **15:** 782–6.
15. Bresee JS, *et al*. Vitamin A therapy for children with respiratory syncytial virus infection: a multicenter trial in the United States. *Pediatr Infect Dis J* 1996; **15:** 777–82.
16. Brown N, Roberts C. Vitamin A for acute respiratory infection in developing countries: a meta-analysis. *Acta Paediatr* 2004; **93:** 1437–42.

XEROPHTHALMIA. Vitamin A deficiency is responsible in many developing countries for visual problems that may culminate in xerophthalmia and blindness.[1] Supplementation with vitamin A as recommended by WHO and discussed under Deficiency states, p. 2099.2, will raise the vitamin A status of the individual and act prophylactically against the development of xerophthalmia. For the treatment of xerophthalmia (which includes night blindness, conjunctival xerosis with Bitot's spots, corneal xerosis, corneal ulceration, and keratomalacia) WHO have stated[2] that oral doses of vitamin A, preferably in an oil-based preparation, are the treatment of choice and should be given immediately the disorder is recognised in the following doses:

- patients over 1 year of age (with the exception of women of reproductive age): 200 000 units
- infants aged 6 to 12 months: 100 000 units
- those aged less than 6 months: 50 000 units

Doses should be repeated the next day, and again at least 2 weeks later.

In *women of reproductive age* there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant (see Pregnancy, p. 2102.1) with the serious consequences of xerophthalmia. WHO recommend that when there are severe signs of active xerophthalmia (i.e. acute corneal lesions) high-dose vitamin A treatment should be given as described above for those aged over 1 year. When only less severe signs are present (night blindness, Bitot's spots), women of reproductive age should receive a daily oral dose of 5000 to 10 000 units for at least 4 weeks. Alternatively, a weekly dose of not more than 25 000 units may be substituted.

Although xerophthalmia is far less common in developed countries, vitamin A deficiency should be considered in all patients with recurrent conjunctival or corneal disorders associated with gastrointestinal or liver disease.[3]

1. Smith J, Steinemann TL. Vitamin A deficiency and the eye. *Int Ophthalmol Clin* 2000; **40:** 83–91.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 2nd ed. Geneva: WHO,1997.
3. Watson NJ, *et al*. Vitamin A deficiency and xerophthalmia in the United Kingdom. *BMJ* 1995; **310:** 1050–1. Correction. *ibid.*: 1320.

Malignant neoplasms. Epidemiological studies suggest that antoxidant vitamins such as the vitamin A substances may play a role in preventing the development of malignancy but there is currently little evidence from prospective studies that supplementation is helpful, and even some evidence of harm (see p. 2047.3). Conversely, synthetic retinoids such as tretinoin (all-*trans*-retinoic acid) have an established role in treating some cancers (see p. 1725.3).

Retinitis pigmentosa. Retinitis pigmentosa is the name applied to a group of slowly progressive hereditary degenerative diseases of the retina[1] that often result in blindness in adulthood. The rod and cone photoreceptors in the retina are primarily affected and initial symptoms include night blindness and intolerance to light. Later signs include infiltration of pigment from the retinal pigmentary epithelium into the retinal layers. Various treatments have been tried but none appear to have any proven benefit. Results of one large double-blind study[2] suggest that whereas treatment with vitamin A might slow the decline in visual acuity treatment with vitamin E appears to have a deleterious effect on the rate of decline. Vitamin E did appear to delay the rate of vision decline in 3 patients with retinitis pigmentosa and a defect in α-tocopherol-transfer protein associated with vitamin E deficiency.[3] Supplementation with 15 000 units of vitamin A daily for up to 12 years was considered to be safe in a study in adults with retinitis pigmentosa; no clinical manifestations of hepatotoxicity were apparent.[4] Addition of lutein to the vitamin A regimen has also been tried.[5] Docosahexaenoic acid has also been investigated, with variable results; some consider that vitamin A and oily fish in the diet could be beneficial in terms of visual preservation.[1] Transplantation of the retina is being investigated as a treatment for retinitis pigmentosa.[1,6] Devices to electrically stimulate the retina, optic nerve, or visual cortex are being developed.[1]

1. Hartong DT, *et al*. Retinitis pigmentosa. *Lancet* 2006; **368:** 1795–1809.
2. Berson EL, *et al*. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol* 1993; **111:** 761–2.
3. Yokota T, *et al*. Retinitis pigmentosa and ataxia caused by a mutation in the gene for the α -tocopherol-transfer protein. *N Engl J Med* 1996; **335:** 1770–1.
4. Sibulesky L, *et al*. Safety of <7500 RE (<25 000 IU) vitamin A daily in adults with retinitis pigmentosa. *Am J Clin Nutr* 1999; **69:** 656–63.
5. Berson EL, *et al*. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol* 2010; **128:** 403–11.
6. Anonymous. Transplantation as a therapy for retinitis pigmentosa? *Br J Ophthalmol* 1997; **81:** 430.

Retinopathy of prematurity. There is some suggestion that vitamin A supplementation may reduce the incidence of retinopathy of prematurity (p. 2120.3).

Adverse Effects and Precautions

The use of excessive amounts of vitamin A substances over long periods can lead to toxicity. Rarely, acute toxicity may also occur with very high doses.

- *Hypervitaminosis A* (chronic toxicity) is characterised by fatigue, irritability, anorexia and loss of weight, vomiting and other gastrointestinal disturbances, low-grade fever, hepatomegaly, skin changes (yellowing, dryness, sensitivity to sunlight), pruritus, alopecia, dry hair, cracking and bleeding lips, anaemia, headache, hypercalcaemia, subcutaneous swelling, nocturia, and pains in bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, and visual disturbances which may be severe. Symptoms usually clear on withdrawal of vitamin A, but in children premature closure of the epiphyses of the long bones may result in arrested bone growth.
- *Acute vitamin A intoxication* is characterised by sedation, dizziness, confusion, diarrhoea and vomiting, sore mouth, bleeding gums, desquamation, and increased intracranial pressure (resulting in bulging fontanelle in infants or severe headache in adults). Hepatomegaly and visual disturbances may occur; irritability may be severe.

Hypervitaminosis A does not appear to be a problem with large doses of carotenoids (see Pharmacokinetics under Betacarotene, p. 2052.1).

Enhanced susceptibility to the effects of vitamin A may be seen in children and in patients with liver disease.

Excessive doses of vitamin A should be avoided in pregnancy because of potential teratogenic effects; for further details see Pregnancy, p. 2102.1.

Gastrointestinal absorption of vitamin A may be impaired in cholestatic jaundice and fat-malabsorption conditions.

Benign intracranial hypertension. High doses of vitamin A cause increased intracranial pressure, and, in infants, this is manifested as bulging of the fontanelle. In one study,[1] 11.5% of infants receiving 3 doses of 50 000 units of vitamin A at monthly intervals had bulging fontanelle, compared with 1% of infants receiving placebo. The bulging lasted between 24 and 72 hours and subsided without treatment,[1] and did not appear to be associated with any physical or developmental abnormalities on long-term follow-up.[2] In another study in neonates, bulging fontanelle occurred in 4.6% of recipients of vitamin A 50 000 units and 2.7% of placebo recipients 24 hours after the dose.[3] In contrast, less than 1% of infants given 3 doses of 25 000 units of vitamin A at monthly intervals had bulging fontanelle in a further study.[4]

1. de Francisco A, *et al*. Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993; **342:** 526–7.
2. van Dillen J, *et al*. Long-term effect of vitamin A with vaccines. *Lancet* 1996; **347:** 1705.
3. Agoestina T, *et al*. Safety of one 52 microgram (50 000 IU) oral dose of vitamin A administered to neonates. *Bull WHO* 1994; **72:** 859–68.
4. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; **352:** 1257–63. Correction. *ibid.* 1999; **353:** 154.

Carcinogenicity. For mention of the *increased* risk of lung cancer in high-risk individuals receiving betacarotene and vitamin A, when compared with placebo, in a study investigating vitamins in lung cancer prevention, see Prophylaxis of Malignant Neoplasms, p. 2047.3.

Effects on the blood. Normochromic macrocytic anaemia developed in a patient who had been receiving oral vitamin A 150 000 units daily for several months.[1] The patient's haemoglobin returned to normal when vitamin A was stopped, and the accompanying symptoms of perioral dermatitis and glossitis also disappeared. Similarly, normochromic normocytic anaemia and thrombocytopenia in an infant given 62 000 units daily for 80 days, resolved on stopping vitamin A.[2] In contrast, vitamin A has been reported to have a beneficial effect on anaemia, see under Deficiency states, p. 2100.1.

1. White JM. Vitamin-A-induced anaemia. *Lancet* 1984; **ii:** 573.
2. Perrotta S, *et al*. Infant hypervitaminosis A causes severe anemia and thrombocytopenia: evidence of a retinol-dependent bone marrow cell growth inhibition. *Blood* 2002; **99:** 2017–22.

Effects on bone. Excessive dietary intake of vitamin A may be associated with osteoporosis. In an epidemiological study,[1] a dietary intake of retinol greater than 1500 micrograms daily (5000 units) doubled the risk of hip fracture compared with an intake of less than 500 micrograms daily (about 1670 units) in women (odds ratio, 2.1; 95% confidence interval 1.1 to 4.0). These data were confirmed by the Nurses' Health Study,[2] which found that postmenopausal women with the highest vitamin A and retinol intakes were at increased risk for hip fracture, irrespective of whether the intakes were from food plus supplements, or food alone. Women with daily retinol intakes of more than 1500 micrograms had a relative risk for hip fracture of 1.64 compared with those consuming less than 500 micrograms daily. Betacarotene intake, however, did not correlate significantly with an increased risk of fracture. A large cohort study[3] of men found that the overall risk of any fracture, including hip fractures, was substantially increased among men with the highest concentrations of serum retinol; there was no association between serum betacarotene levels and the risk of fracture. Subsequently, routine supplementation and the fortification of food with vitamin A in western countries has been questioned.[4] A report[5] from the UK Government's Scientific Advisory Committee on Nutrition cautions against the intake of more than 1.5 mg of vitamin A daily in those at increased risk of osteoporosis, such as postmenopausal women and the elderly. However, results from a cohort study in the elderly[6] suggest a U-shaped dose relationship, in that both high and low intakes of vitamin A were associated with reduced bone mineral density, and another study[7] in women aged between 50 and 74 years, found both high and low serum vitamin A concentrations to be associated with an increased risk of hip fracture. Another large observational epidemiological study from the Women's Health Initiative[8] did not show any association between vitamin A or retinol intake and the risk of fractures in postmenopausal women.

1. Melhus H, *et al*. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med* 1998; **129:** 770–8.
2. Feskanich D, *et al*. Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 2002; **287:** 47–54.
3. Michaëlsson K, *et al*. Serum retinol levels and the risk of fracture. *N Engl J Med* 2003; **348:** 287–94.
4. Lips P. Hypervitaminosis A and fractures. *N Engl J Med* 2003; **348:** 347–9.
5. Scientific Advisory Committee on Nutrition. *Review of dietary advice on vitamin A*. London: The Stationery Office, 2005. Also available at: http://www.sacn.gov.uk/pdfs/sacn_vita_report.pdf (accessed 21/07/08)
6. Promislow JHE, *et al*. Retinol intake and bone mineral density in the elderly: the Rancho Bernardo Study. *J Bone Miner Res* 2002; **17:** 1349–58.
7. Opotowsky AR, Bilezikian JP. Serum vitamin A concentration and the risk of hip fracture among women 50 to 74 years old in the United States: a prospective analysis of the NHANES I Follow-up Study. *Am J Med* 2004; **117:** 169–74.
8. Caire-Juvera G, *et al*. Vitamin A and retinol intakes and the risk of fractures among participants of the Women's Health Initiative Observational Study. *Am J Clin Nutr* 2009; **89:** 323–30.

Effects on the immune system. Vitamin A deficiency is generally associated with impaired immunity, and treatment of deficiency results in reductions in morbidity and mortality from a number of infectious diseases (see under Deficiency States, p. 2099.2). However, a few studies have shown increased prevalence of diarrhoea and/or respiratory-tract infections with high doses of vitamin A. There is a possibility that high single doses of vitamin A may temporarily attenuate the immune response in non-deficient children.[1] For the effect of high-dose vitamin A supplements on the response to measles vaccine in some studies, see p. 2399.3.

1. Anonymous. Childhood morbidity, immunity and micronutrients. *WHO Drug Inf* 1996; **10:** 12–16.

Effects on the liver. Vitamin A is stored in the Dissë space of liver cells and excessive dosage can lead to fibrosis and obstruction of sinusoidal blood flow, causing non-cirrhotic

portal hypertension and hepatocellular dysfunction.[1] Although hepatotoxicity has typically been reported with habitual ingestion of doses of vitamin A greater than 50 000 units daily, a case of severe hepatic fibrosis, with jaundice and hepatomegaly, has been reported in a patient who had been taking 25 000 units daily for at least 6 years in a multivitamin supplement.[2]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Kowalski TE, *etal*. Vitamin A hepatotoxicity: a cautionary note regarding 25,000 IU supplements. *Am J Med* 1994; **97:** 523–8.

Effects on mortality. Vitamin A supplementation has been reported to have beneficial effects on childhood mortality, especially in developing countries, see Deficiency States, p. 2099.2 *et seq*. However, one systematic review[1] of neonatal vitamin A supplementation failed to find evidence of a reduction in mortality or morbidity, and another systematic review of antoxidant supplementation in adults concluded that vitamin A either singly or with other antoxidants increased mortality.[2]

1. Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. *BMJ* 2009; **338:** b919.
2. Bjelakovic G, *et al*. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Hypersensitivity. Local inflammatory reactions and severe anaphylactoid reactions have occurred in patients receiving vitamin A injections, and are usually attributed to solubilisers such as polyoxyl castor oils (p. 2202.3), and, less commonly, polysorbates (p. 2204.1).

A case of cutaneous hypersensitivity to retinol palmitate itself has been described.[1]

1. Shelley WB, *et al*. Hypersensitivity to retinol palmitate injection. *BMJ* 1995; **311:** 232.

Overdosage. Although no clinical manifestations of toxicity were seen in 3 boys who ingested large amounts of vitamin A, their serum retinol concentrations continued to rise over about 3 weeks, and took several months to normalise; the authors cautioned that the use of chewable vitamins resembling confectionery may increase the risk of overdose in children.[1]

1. Lam HS, *et al*. Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. *Pediatrics* 2006; **118:** 820–4.

Pregnancy. The fact that synthetic vitamin A derivatives such as isotretinoin are teratogenic (p. 1709.3) has prompted concern about the potential teratogenicity of high doses of vitamin A.

A prospective cohort study found that a total daily intake of vitamin A from all sources of greater than 15 000 units during early pregnancy was associated with a significantly increased risk of birth defects of structures arising from the cranial neural crest.[1] When vitamin A intake from supplements was analysed separately, an apparent vitamin A threshold dose for the development of birth defects of 10 000 units daily was suggested. However, this study has been criticised[2,3] and some suggest the data allows for a higher threshold dose.[3] A further study found no significant difference in birth defect rates between women consuming greater than 8000 or 10 000 units of vitamin A daily in the period around conception (as supplements and fortified cereals) and those consuming less than 5000 units daily.[4]

After earlier case reports in the USA suggesting that large doses of vitamin A (equivalent to about ten times the daily recommended dietary allowance of 2250 units) taken in early pregnancy may cause birth defects, the UK Chief Medical Officer cautioned women against the use of vitamin A supplements except under medical supervision.[5] Additionally, advice was given that liver or liver products should not be eaten because high concentrations of vitamin A had been detected in some samples of animal liver. However, others thought that the avoidance of liver or liver products might result in inadequate nutrition in some and that a less alarmist view might have been to suggest a limitation on intake rather than total prohibition.[6,7] The Royal College of Obstetricians and Gynaecologists has advised that high-dose vitamin A supplementation (more than about 700 micrograms, or 2300 units daily) is not recommended during pregnancy.[8] The Australian Adverse Drug Reactions Advisory Committee has advised women in this category to avoid vitamin A supplements and not to exceed the recommended daily allowance of 2500 units from all sources.[9]

1. Rothman KJ, *et al*. Teratogenicity of high vitamin A intake. *N Engl J Med* 1995; **333:** 1369–73.
2. Werler MM, *et al*. Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; **334:** 1195–6.
3. Watkins M, *et al*. Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; **334:** 1196.
4. Mills JL, *et al*. Vitamin A and birth defects. *Am J Obstet Gynecol* 1997; **177:** 31–6.
5. DoH. *Women cautioned: watch your vitamin A intake*. London: Department of Health, 1990(18 October).
6. Nelson M. Vitamin A, liver consumption, and risk of birth defects. *BMJ* 1990; **301:** 1176.
7. Sanders TAB. Vitamin A and pregnancy. *Lancet* 1990; **336:** 1375.
8. Royal College of Obstetricians and Gynaecologists. RCOG release: RCOG issues new guidance on vitamin supplementation in pregnancy (issued 19th October, 2009). Available at: http://www.rcog.org.uk/news/rcog-release-rcog-issues-new-guidance-vitamin-supplementation-pregnancy (accessed 15/02/10)
9. Adverse Drug Reactions Advisory Committee (ADRAC). Vitamin A and birth defects. *Aust Adverse Drug React Bull* 1996; **15:** 14–15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 21/07/08)

Interactions

Absorption of vitamin A from the gastrointestinal tract may be reduced by the presence of neomycin, colestyramine, or liquid paraffin.

There is an increased risk of hypervitaminosis A if vitamin A is given with synthetic retinoids such as acitretin, isotretinoin, and tretinoin.

There is conflicting evidence regarding the effect of vitamin A on the response to measles vaccine (see p. 2399.3).

Pharmacokinetics

Vitamin A substances are readily absorbed from the gastrointestinal tract but absorption may be reduced in the presence of fat malabsorption, low protein intake, or impaired liver or pancreatic function. Vitamin A esters are hydrolysed by pancreatic enzymes to retinol, which is then absorbed and re-esterified. Some retinol is stored in the liver. It is released from the liver bound to a specific α_1-globulin (retinol-binding protein) in the blood. The retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid; these and other metabolites are excreted in urine and faeces. Vitamin A does not readily diffuse across the placenta (but see Pregnancy, above), but is present in breast milk.

References.

1. Hartmann D, *et al*. Pharmacokinetic modelling of the plasma concentration-time profile of the vitamin retinyl palmitate following intramuscular administration. *Biopharm Drug Dispos* 1990; **11:** 689–700.
2. Reinersdorff DV, *et al*. Plasma kinetics of vitamin A in humans after a single oral dose of [8,9,19-^{13}] retinyl palmitate. *J Lipid Res* 1996; **37:** 1875–85.
3. Harrison EH, Hussain MM. Mechanisms involved in the intestinal digestion and absorption of dietary vitamin A. *J Nutr* 2001; **131:** 1405–8.

Human Requirements

Dietary vitamin A is derived from 2 sources, *preformed retinoids* from animal sources such as liver, kidney, dairy produce, and eggs (fish-liver oils are the most concentrated natural source), and *provitamin carotenoids* which can be obtained from many plants; the latter are converted to retinol in the body but are less effectively utilised. Carotenes (α, β, and γ) are major sources and of these, β-carotene (betacarotene—see p. 2051.1) has the highest vitamin A activity and is the most plentiful in food. Variable amounts of β-carotenes are found in carrots and dark green or yellow vegetables. Red palm oil is a good source of α- and β-carotenes.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published[1] for vitamin A and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women (but see Pregnancy, above). In the UK the reference nutrient intake (RNI) for adult males and females is 700 and 600 micrograms retinol equivalents (about 2330 and 2000 units) daily, respectively and the estimated average requirement (EAR) is 500 and 400 micrograms retinol equivalents (about 1660 and 1330 units) daily, respectively. This UK report[1] also highlighted the toxicity associated with large doses of vitamin A and recommended that regular intakes should not exceed 9 mg (30 000 units) daily in adult men and 7500 micrograms (25 000 units) daily in adult women. (A later report[3] was unable to establish a safe upper level for vitamin A intake, but considered that total intakes above 1500 micrograms retinol equivalents daily might be inappropriate.) Figures were also given in the earlier report for infants and children who were said to be more sensitive to the effects of vitamin A. These limits did not apply to therapeutic doses of vitamin A used under medical supervision.[1] In pregnancy the RNI is 700 micrograms retinol equivalents (2330 units) daily and in nursing mothers 950 micrograms (3160 units) daily. In the USA the RDA for adults is 900 micrograms daily for men and 700 micrograms daily for women.[2] The tolerable upper intake level is 3 mg daily.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 06/01/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: A-Vitel; Adermicina A Mama; Amenite A; Andrioderma; Arovit; Atomoderma A; Bagovit A; Cazmar; Cutidermin Crema Humect. con Vitamina A†; Domsedan; Fiosen-A; Metabolite-A; Skinderm A; ***Austral.***: Ungvita; ***Belg.***: Vitamuruine; ***Braz.***: Arovit; Lacrigel A; Retinar; ***Canad.***: Arginax†; Arovit†; Theraplex AF; Vitapro A; ***Chile***: Avitana†; Bagovit A; Microret†; ***China***: Oculotect (诺沛); ***Cz.***: Axerophthol; ***Denm.***: A-vitamin; ***Fr.***: A 313; A 313; Avibon; ***Ger.***: Augenschutz NA; Oculotect†; Solan-M†; Vitafluid; Vitagel; ***Gr.***: Avitan; ***Hung.***: Oculotect; ***India***: Arovit; Lipolotion; Mixcarotin; ***Israel***: Avipur†; ***Ital.***: Arovit; Euvitol; Vit-A-N; ***Malaysia***: Fairy ADE; ***Mex.***: A Grin†; Acon; Dermotin A; Microret; Microvita†; Palmyforte; Retigel-A; ***NZ***: Dermalife†; Ungvita; ***Philipp.***: Afaxin; Alici-A; Hypotears; Retimax; ***Pol.***: Aksoderm; Dermosavit; Dermovit A; Masc Ochronna z Witamina A; Masc Witaminowa Ochronna; ***Port.***: A-Vite; Vitaminoftalmina; ***Rus.***: Videstim (Видестим); Vita-POS (Вита-ПОС); ***S.Afr.***: Arovit†; ***Spain***: Auxina A Masiva; Biominol; Rinocusi Vitaminico; Rinovitex; ***Swed.***: Arovit†; ***Switz.***: Oculotect; Vita-POS; ***Thai.***: Cebrin-Fe; ***Turk.***: Avicap; Avigen; Carovigen; ***UK***: Biovit-A; ***USA***: Aquasol A; Palmitate-A†; Pedi-Vit-A; Retinol-A; ***Venez.***: Alfa-Mon; Retiva.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Paediatric Vitamins A, C and D Oral Drops;
BPC 1973: Vitamins A and D Capsules;
USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Oleovitamin A and D Capsules; Oleovitamin A and D; Vitamin A Capsules; Vitamin A Oral Liquid Preparation; Vitamin A Tablets.

Vitamin B Substances

Vitamina B, grupo de la; Витамины Группы В.

The B vitamin group includes the B_1 substances (thiamine and its derivatives), B_2 (riboflavin), B_6 (pyridoxine and derivatives), and B_{12}(the cobalamins). In addition, nicotinic acid and its derivatives (p. 2083.1) and folic acid (p. 2063.1) are held to be part of the group, as is pantothenic acid (p. 2085.2), but these latter substances are not generally referred to by their traditional B nomenclature.

Vitamin B_1 Substances

Vitamina B_1; Витамины Группы B_1.

Acetiamine Hydrochloride *(rINNM)*

Acethiamine Hydrochloride; Acetiamina, hidrocloruro de; Acétiamine, Chlorhydrate d'; Acetiamini Hydrochloridum; Diacethiamine Hydrochloride; Hidrocloruro de acetiamina; Ацетиамина Гидрохлорид.

N-(5-Acetoxy-3-acetylthiopent-2-en-2-yl)-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide hydrochloride monohydrate.

$C_{16}H_{22}N_4O_4S,HCl,H_2O$=420.9

CAS — 299-89-8 (acetiamine).

UNII — W024X5P395.

Benfotiamine *(rINN)*

Benfotiamina; Benfotiaminum; *S*-Benzoylthiamine *O*-Monophosphate; Monofosfato de benzoiltiamina; Бенфотиамин.

N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(2-benzoylthio-4-dihydroxyphosphinyloxy-1-methylbut-1-enyl)formamide.

$C_{19}H_{23}N_4O_6PS$=466.4

CAS — 22457-89-2.

ATC — A11DA03.

ATC Vet — QA11DA03.

UNII — Y92OUS2H9B.

Bisbentiamine *(rINN)*

O-Benzoylthiamine Disulphide; Bisbentiamina; Bisbentiaminum; Бисбентиамин.
NN'-{Dithiobis[2-(2-benzoyloxyethyl)-1-methylvinylene]}bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide].
$C_{38}H_{42}N_8O_6S_2$=770.9
CAS — 2667-89-2.
UNII — MEI78CAM16.

Cocarboxylase *(BAN, rINN)*

Cocarboxilasa; Co-carboxylase; Cocarboxylasum; Diphosphothiamine; Pyruvodehydrase; Thiamine Pyrophosphate; Кокарбоксилаза.
3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-{2-[dihydroxyphosphinyloxy(hydroxy)phosphinyloxy]ethyl}-4-methylthiazolium hydroxide.
$C_{12}H_{20}N_4O_8P_2S$ (hydroxide form)=442.3
CAS — 154-87-0 (cocarboxylase chloride).
UNII — Q57971654Y.

Pharmacopoeias. *Pol.* includes the chloride.

Cycotiamine *(rINN)*

CCT; Cicotiamina; Cyclocarbothiamine; Cycotiaminum; Цикотиамин.
N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl]formamide.
$C_{13}H_{16}N_4O_3S$=308.4
CAS — 6092-18-8.
UNII — FT8753F8R9.

Fursultiamine *(rINN)*

Fursultiamina; Fursultiaminum; Thiamine Tetrahydrofurfuryl Disulphide; TTFD; Фурсультиамин.
N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[4-hydroxy-1-methyl-2-(tetrahydrofurfuryldithio)but-1-enyl]formamide.
$C_{17}H_{26}N_4O_3S_2$=398.5
CAS — 804-30-8.
UNII — 05J61265PX.

Octotiamine *(rINN)*

Octotiamina; Octotiaminum; Oktotiamiini; Oktotiamin; TATD; Thioctothiamine; Октотиамин.
N-[2-(3-Acetylthio-7-methoxycarbonylheptyldithio)-4-hydroxy-1-methylbut-1-enyl]-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide.
$C_{23}H_{36}N_4O_5S_3$=544.7
CAS — 137-86-0.
UNII — UN1Q7096GA.

Prosultiamine *(rINN)*

DTPT; Prosultiamina; Prosultiaminum; Thiamine Propyl Disulphide; Просультиамин.
N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(4-hydroxy-1-methyl-2-propyldithiobut-1-enyl)formamide.
$C_{15}H_{24}N_4O_2S_2$=356.5
CAS — 59-58-5.
UNII — UI32MM3XE3.

Sulbutiamine *(rINN)*

Bisibutamina; Bisibutiamine; *O*-Isobutyrylthiamine Disulphide; Sulbutiamina; Sulbutiaminum; Сульбутиамин.
NN'-{Dithiobis[2-(2-isobutyryloxyethyl)-1-methylvinylene]}bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide].
$C_{32}H_{46}N_8O_6S_2$=702.9
CAS — 3286-46-2.
ATC — A11DA02.
ATC Vet — QA11DA02.
UNII — 42NCM1BW43.

Thiamine Hydrochloride *(BANM, rINNM)*

Aneurine Hydrochloride; Cloruro de tiamina; Hidrocloruro de aneurina; Hidrocloruro de tiamina; Thiamin Hydrochloride; Thiaminchloridhydrochlorid; Thiamine, chlorhydrate de; Thiamine Chloride; Thiamin-hydrochlorid; Thiamini Hydrochloridum; Thiaminii Chloridum; Tiamiinihydrokloridi; Tiamina, hidrocloruro de; Tiamin-hidroklorid; Tiaminhydroklorid; Tiamino hidrochloridas; Tiaminy chlorowodorek; Vitamin B_1; Vitamina B1; Тиамина Гидрохлорид.
3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride.
$C_{12}H_{17}ClN_4OS,HCl$=337.3
CAS — 59-43-8 (thiamine); 67-03-8 (thiamine hydrochloride).
ATC — A11DA01.
ATC Vet — QA11DA01.
UNII — M572600E5P.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Thiamine hydrobromide is included in *Int.*

Ph. Eur. 8: (Thiamine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol; soluble in glycerol. A 2.5% solution in water has a pH of 2.7 to 3.3. Store in nonmetallic containers. Protect from light.

USP 36: (Thiamine Hydrochloride). White crystals or crystalline powder, usually having a slight, characteristic odour. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. Soluble 1 in 1 of water and 1 in 170 of alcohol; insoluble in ether and in benzene; soluble in glycerol. pH of a 1% solution in water is between 2.7 and 3.4. Store in airtight containers. Protect from light.

Stability. Sterile thiamine hydrochloride solutions of pH 4 or less lose activity only very slowly but neutral or alkaline solutions deteriorate rapidly, especially in contact with air.

Thiamine Nitrate *(BANM, rINNM)*

Aneurine Mononitrate; Mononitrato de tiamina; Nitrato de tiamina; Thiamine Mononitrate; Thiamine, Nitrate de; Thiamini Nitras; Thiaminnitrat; Thiamin-nitrát; Tiamiininitraatti; Tiamina, nitrato de; Tiaminnitrat; Tiamin-nitrát; Tiamino nitratas; Tiaminy azotan; Vitamin B_1 Mononitrate; Тиамина Нитрат.
3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium nitrate.
$C_{12}H_{17}N_5O_4S$=327.4
CAS — 532-43-4.
ATC — A11DA01.
ATC Vet — QA11DA01.
UNII — 8K0I04919X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Thiamine Nitrate). A white or almost white, crystalline powder or small, colourless crystals. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in alcohol and in methyl alcohol. A 2% solution in water has a pH of 6.8 to 7.6. Store in nonmetallic containers. Protect from light.

USP 36: (Thiamine Mononitrate). White crystals or crystalline powder, usually having a slight characteristic odour. Soluble 1 in 44 of water; slightly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 6.0 and 7.5. Store in airtight containers. Protect from light.

Uses and Administration

Thiamine is a water-soluble vitamin, although some of its derivatives have greater lipophilicity. It is an essential coenzyme for carbohydrate metabolism in the form of the diphosphate (thiamine pyrophosphate, cocarboxylase). Thiamine deficiency develops when the dietary intake is inadequate; severe deficiency leads to the development of a syndrome known as beri-beri. Chronic 'dry' beri-beri is characterised by peripheral neuropathy, muscle wasting and muscle weakness, and paralysis. Acute 'wet' beri-beri is characterised by cardiac failure and oedema. Wernicke-Korsakoff syndrome (demyelination of the CNS) may develop in severe cases of thiamine deficiency notably in association with chronic alcoholism. Severe thiamine deficiency, characterised by lactic acidosis and neurological deterioration, has been reported within a relatively short time of starting thiamine-free total parenteral nutrition; some deaths have occurred.

Thiamine is used in the treatment and prevention of thiamine deficiency. It is given orally, the preferred route, or if necessary by the intramuscular or intravenous routes (but see Hypersensitivity, p. 2104.1); intravenous injections should be given slowly over 30 minutes. In the treatment of mild chronic thiamine deficiency usual oral doses of 10 to 50 mg daily, in single or divided doses, have been recommended. In severe thiamine deficiency doses of up to 300 mg daily are given, and even higher daily doses may be used in Wernicke-Korsakoff syndrome by the intravenous route. For use in children see below.

Thiamine is usually given as either the hydrochloride or nitrate salts although other salts such as the dicamsylate, disulfide, monophosphate (monophosphothiamine) or pyrophosphate (cocarboxylase) may be used.

Other compounds that possess vitamin B_1 activity and may be given as alternatives to thiamine include benfotiamine, cycotiamine, octotiamine, prosultiamine, and sulbutiamine. Acetiamine, bisbentiamine, and fursultiamine have also been used.

Administration in children. Thiamine is licensed in the UK for oral use in children from 3 years of age in the treatment of **deficiency**; doses are similar to those in adults, above. However, management of vitamin B deficiency in children is usually with compound preparations also containing riboflavin and nicotinamide. The *BNFC* recommends the following oral doses of thiamine hydrochloride by age, as part of such a compound preparation:

- 1 month to 1 year: 5 mg three times daily (treatment) or once daily (prophylaxis)
- 1 to 12 years: 10 mg three times daily (treatment), or 5 mg twice daily (prophylaxis)
- 12 to 18 years: 10 to 15 mg three times daily (treatment) or 5 mg three times daily (prophylaxis)

Thiamine may also be used in the management of certain mitochondrial disorders. The *BNFC* recommends an oral dose of 5 mg/kg daily, adjusted as necessary, in neonates and children up to 18 years of age with **maple syrup urine disease**.

In the treatment of other metabolic disorders including **congenital lactic acidosis** thiamine may be given orally or by intravenous infusion over 30 minutes in the following doses:

- up to 1 month: 50 to 200 mg daily, as a single daily dose or in 2 to 3 divided doses, adjusted as necessary
- 1 month to 18 years: 100 to 300 mg daily, as a single dose or in 2 to 3 divided doses, adjusted as necessary. Up to 2 g daily may be necessary

Diabetes mellitus. Low plasma thiamine concentrations have been found[1] in patients with type 1 and type 2 diabetes mellitus In a small placebo-controlled study, benfotiamine 100 mg given orally four times daily significantly improved neuropathic pain in patients with diabetic polyneuropathy (see p. 8.2).[2]

1. Thornalley PJ, *et al.* High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 2007; **50:** 2164–70.
2. Haupt E, *et al.* Benfotiamine in the treatment of diabetic polyneuropathy—a three-week randomized, controlled pilot study (BEDIP Study). *Int J Clin Pharmacol Ther* 2005; **43:** 71–7.

Wernicke-Korsakoff syndrome. The Wernicke-Korsakoff syndrome is a manifestation of thiamine deficiency seen particularly in alcoholics, but which may accompany other conditions including starvation or prolonged fasting, or persistent vomiting. It was originally classified as two separate disorders, Wernicke's encephalopathy and Korsakoff's syndrome, but these are now thought to represent aspects of a single pathological process.[1,2]

Classical Wernicke's symptoms comprise confusion, ataxia, ophthalmoplegia, and nystagmus. Ophthalmoplegia and ataxia may precede the mental symptoms by some days. Hypothermia may be seen, and collapse and sudden death may occur in some patients. The manifestations of Korsakoff's syndrome are short-term memory loss, learning deficits, and confabulation. The conditions are associated with demyelination and glial proliferation, as well as haemorrhagic lesions, mainly in the periventricular regions of the brain; characteristic biochemical abnormalities include raised serum-pyruvate concentration, which has been postulated as a cause of encephalopathy.[3]

Early recognition and treatment is important, both because of the risk of collapse and sudden death,[4] and to prevent irreversible damage to the CNS.[5] Korsakoff symptoms respond less well to treatment than those associated with Wernicke's encephalopathy,[6] and may indeed only become evident on treatment.

Treatment is with parenteral thiamine, preferably intravenously, to ensure adequate absorption; any risks of parenteral treatment are considered justifiable.[1,2,5,7,8] Low dose parenteral therapy (100 to 250 mg daily) may not restore vitamin status or improve symptoms, and it is generally agreed that higher doses are required.[1,7] Although the optimal treatment regimen for thiamine is not established,[9] typical doses range from 500 to 750 mg given intravenously with other vitamins three times daily for at least 2 days;[5] Up to 1 g thiamine per dose has been used.[8] If there is a response, some recommend continued treatment with 250 mg intravenously or intramuscularly once daily for 5 days or until there is no further improvement.[5,8] Response varies according to the presenting condition, with ocular symptoms responding more rapidly than confusion; however, a noticeable improvement in delirium and acute confusion is said to occur within 1 or 2 days in most cases.[1] Cognitive impairment responds more slowly, if at all.[9] Prophylactic thiamine is considered appropriate in patients at high risk of deficiency such as those undergoing alcohol withdrawal and with signs of malnutrition; an intramuscular or intravenous dose of 250 mg once daily for 3 to 5 days has been used.[1,5,8] In lower risk patients with mild deficiency, an oral dose of thiamine 200 mg daily, given with other B vitamins, is often used.[5] Even several months after the onset of symptoms, treatment with high doses of thiamine has occasionally resulted in recovery.[10] The effects of the syndrome on memory are much harder to reverse.

Some 25% of patients make a full, and 50% a partial, recovery.[6]

1. Cook CCH, *et al*. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol* 1998; **33:** 317–36.
2. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; **35** (suppl): 2–7.
3. Petrie WM, Ban TA. Vitamins in psychiatry: do they have a role? *Drugs* 1985; **30:** 58–65.
4. Reuler JB, *et al*. Wernicke's encephalopathy. *N Engl J Med* 1985; **312:** 1035–9.
5. Thomson AD, *et al*. Royal College of Physicians, London. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department. *Alcohol Alcohol* 2002; **37:** 513–21. Correction. *ibid*. 2003; **38:** 291.
6. Anonymous. Korsakoff's syndrome. *Lancet* 1990; **336:** 912–13.
7. Cook CCH, Thomson AD. B-complex vitamins in the prophylaxis and treatment of Wernicke-Korsakoff syndrome. *Br J Hosp Med* 1997; **57:** 461–5.
8. Cook CCH. Prevention and treatment of Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; **35** (suppl): 19–20.
9. Day E, *et al*. Thiamine for Wernicke-Korsakoff syndrome in people at risk from alcohol abuse. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 16/02/10).
10. Carota A, Schnider A. Dramatic recovery from prolonged Wernicke-Korsakoff disease. *Eur Neurol* 2005; **53:** 45–6.

Adverse Effects and Precautions

Adverse effects with thiamine are rare, but hypersensitivity reactions have occurred, mainly after parenteral doses. These reactions have ranged in severity from very mild to, very rarely, fatal anaphylactic shock (see below).

Breast feeding. Supplementation did not significantly affect thiamine concentration in breast milk of healthy, well-nourished women when compared with those not given thiamine; the authors supposed that absorptive capacity of the mammary gland may be saturable.[1] Based on this, the American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Nail PA, *et al*. The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; **33:** 198–204.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Hypersensitivity. The UK CSM had received, between 1970 and July 1988, 90 reports of adverse reactions associated with the use of an injection containing high doses of vitamins B and C. The most frequent reactions were anaphylaxis (41 cases, including 2 fatalities), dyspnoea or bronchospasm (13 cases), and rash or flushing (22 cases); 78 of the reactions occurred during, or shortly after, intravenous injection and the other 12 after intramuscular injection.[1] They recommended that parenteral treatment be used only when essential, and that, when given, facilities for treating anaphylaxis should be available. They also recommended that, when the intravenous route was used, the injection be given slowly (over 10 minutes). Various authors[2,3] have noted that parenteral treatment is *essential* for the prophylaxis and treatment of Wernicke's encephalopathy (see p. 2103.3). However, further reports of anaphylaxis to parenteral thiamine have since been described,[4-6] including one with a fatal outcome.[4]

1. CSM. Parentrovite & allergic reactions. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 17/04/09)
2. Wrenn KD, Slovis CM. Is intravenous thiamine safe? *Am J Emerg Med* 1992; **10:** 165.
3. Thomson AD, Cook CCH. Parenteral thiamine and Wernicke's encephalopathy: the balance of risks and concerns. *Alcohol Alcohol* 1997; **32:** 207–9.
4. Van Haecke P, *et al*. Thiamine-induced anaphylactic shock. *Am J Emerg Med* 1995; **13:** 371–2.
5. Morinville V, *et al*. Anaphylaxis to parenteral thiamine (vitamin B1). *Schweiz Med Wochenschr* 1998; **128:** 1743–4.
6. Johri S, *et al*. Anaphylaxis from intravenous thiamine—long forgotten? *Am J Emerg Med* 2000; **18:** 642–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Benfotiamine and sulbutiamine are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Small amounts of thiamine are well absorbed from the gastrointestinal tract after oral doses, but the absorption of doses larger than about 5 mg is limited. It is also rapidly absorbed on intramuscular injection. It is widely distributed to most body tissues, and appears in breast milk. Within the cell, thiamine is mostly present as the diphosphate. Thiamine is not stored to any appreciable extent in the body and amounts in excess of the body's requirements are excited in the urine unchanged or as metabolites.

References.

1. Weber W, *et al*. Nonlinear kinetics of the thiamine cation in humans: saturation of nonrenal clearance and tubular reabsorption. *J Pharmacokinet Biopharm* 1990; **18:** 501–23.
2. Tallaksen CME, *et al*. Kinetics of thiamin and thiamin phosphate esters in human blood, plasma and urine after 50 mg intravenously or orally. *Eur J Clin Pharmacol* 1993; **44:** 73–8.
3. Loew D. Pharmacokinetics of thiamine derivatives especially of benfotiamine. *Int J Clin Pharmacol Ther* 1996; **34:** 47–50.
4. Greb A, Bitsch R. Comparative bioavailability of various thiamine derivatives after oral administration. *Int J Clin Pharmacol Ther* 1998; **36:** 216–21.
5. Frank T, *et al*. High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol* 2000; **56:** 251–7.
6. Drewe J, *et al*. Effect of intravenous infusions of thiamine on the disposition kinetics of thiamine and its pyrophosphate. *J Clin Pharm Ther* 2003; **28:** 47–51.

Human Requirements

Thiamine requirements are directly related to the carbohydrate intake and the metabolic rate. A daily dietary intake of about 0.9 to 1.5 mg of thiamine is recommended for healthy men and about 0.8 to 1.1 mg for healthy women. Cereals, nuts, peas, beans, yeast, and pork are rich sources of thiamine. Some other meats especially liver or kidneys, and also fish, contain significant amounts. Flour and bakery products are often enriched with thiamine. Considerable losses of thiamine may result from cooking processes.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for thiamine[1] and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK for adult males and females the reference nutrient intake (RNI) is 400 micrograms per 1000 kcal daily and the estimated average requirement (EAR) is 300 micrograms per 1000 kcal daily. In the USA an RDA of 1.2 mg daily in adult males and 1.1 mg daily in females is recommended.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Megastene; Tiavit; ***Austral.***: Betamin; ***Austria***: Beneuran†; Bevitol; ***Belg.***: Benerva; Betamine; ***Braz.***: Acesyl; Arcalion; Benerva; Beneum; Beum; Fonti; Nervamin; Nerven; Neurivit; Vitaum; ***Canad.***: Betaxin; Thiamiject; ***Chile***: Arcalion; ***China***: Bai Fu Li (百扶力); Qi Cun (齐存); Xin Yuan Da (欣源达); ***Cz.***: Benfogamma; Thiabene; ***Denm.***: BiOrto B1; ***Fin.***: Neuramin; ***Fr.***: Arcalion; Benerva; Bevitine; ***Ger.***: B1-ASmedic; Betabion†; Milgamma mono; Milgamma protekt; Novirell B_1; ***Gr.***: Arcalion; Benerva; ***Hong Kong***: Aneubion†; Arcalion; Bevit†; Neo-Active Vit B-1†; Super B1; ***Hung.***: Benfogamma; Beres B1; ***India***: Arcalion; Benalgis; Benfage; Berin; ***Indon.***: Alinamin; Arcalion; Beston; Licobevit; ***Ital.***: Benerva; Dobetin Vitamina B1; ***Jpn***: Alinamin-F; Neuvita; ***Malaysia***: Arcalion; ***Mex.***: Arcalion; Benal; Benerva; Carzilasa; Fortical; MTX-2 Alf; X-2; ***Philipp.***: Arcalion; Drexabion; Hybutin; Jaga; Lixtress; Meganerv; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Supraneuron; Vineuron; ***Pol.***: Benfogamma; ***Port.***: Arcalion; Trifosfaneurina; Vitanidia†; ***Rus.***: Benfogamma (Бенфогамма); Enerion (Энерион); Vitagamma (Витагамма); ***Singapore***: Arcalion; ***Spain***: Arcalion; Benerva; Surmenalit; ***Swed.***: Benerva†; Betabion†; ***Switz.***: Arcalion; Benerva; ***Thai.***: Alinamin-F; Arcalion†; Beratex; Besasin; Chlorbicap; Menamin; Vitabee-1-10; ***Turk.***: Arcalion; Bevigen; ***UAE***: Thiavit; ***UK***: Benerva; Tyvera; ***Ukr.***: Benfogamma (Бенфогамма); Enerion (Энерион); ***Venez.***: Arcalion; Beplus.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Indon.***: Nufadoxin.

Homoeopathic Preparations. ***Ger.***: Infi-Symphytum.

Pharmacopoeial Preparations

BP 2014: Thiamine Injection; Thiamine Tablets; Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Thiamine Hydrochloride Elixir; Thiamine Hydrochloride Injection; Thiamine Hydrochloride Tablets; Thiamine Mononitrate Elixir; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin B_2 Substances

Vitamina B_2; Витамины Группы B_2.

Riboflavin *(BAN, rINN)*

E101; Lactoflavin; Lactoflavina; Riboflaviini; Riboflavina; Riboflavinas; Riboflavine; Riboflavinum; Ryboflawina; Vitamin B_2; Vitamin G; Vitamina B_2; Рибофлавин.

7,8-Dimethyl-10-(1′-D-ribityl)isoalloxazine; 3,10-Dihydro-7,8-dimethyl-10-(D-*ribo*-2,3,4,5-tetrahydroxypentyl)benzopteridine-2,4-dione.

$C_{17}H_{20}N_4O_6$=376.4

CAS — 83-88-5.

ATC — A11HA04.

ATC Vet — QA11HA04.

UNII — TLM2976OFR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Riboflavin). A yellow or orange-yellow crystalline powder. It exhibits polymorphism. Very slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light. Solutions deteriorate on exposure to light, especially in the presence of alkali.

USP 36: (Riboflavin). A yellow to orange-yellow crystalline powder, having a slight odour. When dry, it is not appreciably affected by diffused light, but in solution light induces quite rapid deterioration, especially in the presence of alkalis. Very slightly soluble in water, in alcohol, and in isotonic sodium chloride solution; insoluble in chloroform and in ether; soluble in dilute solutions of alkalis. Its saturated solution in water is neutral to litmus. Store in airtight containers. Protect from light.

Riboflavin Sodium Phosphate *(BANM, rINNM)*

Fosfato sódico de riboflavina; Natrii Riboflavini Phosphas; Riboflaviininatriumfosfaatti; Riboflavin fosfát sodná sůl; Riboflavin 5′-Phosphate Sodium; Riboflavina, fosfato sódico de; Riboflavine, Phosphate Sodique de; Riboflavine Phosphate (Sodium Salt); Riboflavine Sodium Phosphate; Riboflavin-foszfát-nátrium; Riboflavini natrii phosphas; Riboflavinnatriumfosfat; Riboflavino natrio fosfatas; Riboflavin-phosphat-Natrium; Vitamin B_2 Phosphate; Натрия Рибофлавина Фосфат.

The sodium salt of riboflavin 5′-phosphate.

$C_{17}H_{20}N_4NaO_9P$=478.3

CAS — 130-40-5.

UNII — 20RD1DZH99.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Chin. and *US* specify the dihydrate salt.

Ph. Eur. 8: (Riboflavin Sodium Phosphate). A yellow or orange-yellow, hygroscopic, crystalline powder. Soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Riboflavin 5′-Phosphate Sodium). A fine, orange-yellow, hygroscopic, crystalline powder, having a slight odour. When dry, it is not affected by diffused light, but when in solution light induces rapid deterioration. Sparingly soluble in water. pH of a 1% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Uses and Administration

Riboflavin, a water-soluble vitamin, is essential for the utilisation of energy from food. The active, phosphorylated forms, flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD), are involved as coenzymes in oxidative/reductive metabolic reactions. Riboflavin is also necessary for the functioning of pyridoxine and nicotinic acid.

Riboflavin deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a well-defined syndrome known as ariboflavinosis, characterised by cheilosis, angular stomatitis, glossitis, keratitis, surface lesions of the genitalia, and seborrhoeic dermatitis. There may also be normocytic anaemia and ocular symptoms including itching and burning of the eyes, and corneal vascularisation. Some of these symptoms may, in fact, be due to other vitamins such as pyridoxine or nicotinic acid which do not function correctly in the absence of riboflavin. Riboflavin deficiency may also occur with other vitamin B-complex deficiency states such as pellagra.

Riboflavin is used in the treatment and prevention of riboflavin deficiency. It is usually given in oral doses of 1 or 2 mg for prophylaxis; up to 30 mg daily in divided doses is used for treatment. For administration in children see p. 2105.1. Riboflavin, as the sodium phosphate, is also a component of intramuscular or intravenous vitamins B and

C injections; riboflavin sodium phosphate 1.27 g is equivalent to about 1 g of riboflavin.

Riboflavin tetrabutyrate has also been used.

Riboflavin is also used as a colouring agent for food.

Administration in children. In the UK, management of **vitamin B deficiency** in children is usually with compound preparations also containing thiamine and nicotinamide. The *BNFC* recommends the following oral doses of riboflavin by age, as part of such a compound preparation:

- 1 month to 1 year: 2 mg three times daily (treatment) or once daily (prophylaxis)
- 1 to 12 years: 4 mg three times daily (treatment), or 2 mg twice daily (prophylaxis)
- 12 to 18 years: 4 to 6 mg three times daily (treatment) or 2 mg three times daily (prophylaxis)

Riboflavin may also be used in the management of certain **metabolic disorders**. The *BNFC* recommends the following oral doses:

- up to 1 month: 50 mg once or twice daily, adjusted according to response
- 1 month to 18 years: 50 to 100 mg once or twice daily, adjusted according to response; up to 400 mg daily has been given

See also Glutaric Aciduria, below.

Glutaric aciduria. Milder forms of glutaric aciduria type II (p. 1559.2) may respond to riboflavin.[1] Treatment with riboflavin 50 mg daily resulted in progressive improvement in a 4-year-old boy, with full recovery after 1 year. His brother, who had sustained permanent brain damage after epileptic seizures, showed moderate clinical improvement with riboflavin therapy.[2] In an adult patient with a history of recurrent pancreatitis and exercise intolerance, treatment with riboflavin 120 mg daily and levocarnitine resulted in no further episodes, although abnormal concentrations of amino acids were still apparent in her urine.[3]

1. Gregersen N, *et al.* Riboflavin responsive glutaric aciduria type II. *Prog Clin Biol Res* 1990; **321:** 477–94.
2. Uziel G, *et al.* Riboflavin-responsive glutaric aciduria type II presenting as a leukodystrophy. *Pediatr Neurol* 1995; **13:** 333–5.
3. Liang W-C, *et al.* Riboflavin-responsive glutaric aciduria type II with recurrent pancreatitis. *Pediatr Neurol* 2004; **31:** 218–21.

Migraine. Results from open studies[1,2] and a placebo-controlled trial[3] have suggested that riboflavin in high doses (400 mg daily) might be of some benefit in the prophylaxis of migraine attacks (p. 670.3). However, a controlled study in children found it to be no more effective than placebo.[4]

1. Schoenen J, *et al.* High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia* 1994; **14:** 328–9.
2. Boehnke C, *et al.* High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur J Neurol* 2004; **11:** 475–7.
3. Schoenen J, *et al.* Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. *Neurology* 1998; **50:** 466–70.
4. MacLennan SC, *et al.* High-dose riboflavin for migraine prophylaxis in children: a double-blind, randomized, placebo-controlled trial. *J Child Neurol* 2008; **23:** 1300–4.

Adverse Effects and Precautions

Large doses of riboflavin result in a bright yellow discoloration of the urine that may interfere with certain laboratory tests.

Breast feeding. Supplementation significantly increased riboflavin concentration in the breast milk of women compared with those not given riboflavin. Significant differences between the two groups decreased over the period from 1 to 6 weeks postpartum; both groups of women had breast milk concentrations above previously reported normal values, and the authors concluded that supplementation was not necessary in healthy, well-nourished women.[1] The American Academy of Pediatrics considers the use of riboflavin to be usually compatible with breast feeding.[2]

1. Nail PA, *et al.* The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; **33:** 198–204.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Pharmacokinetics

Riboflavin is readily absorbed from the gastrointestinal tract. Although riboflavin is widely distributed to body tissues little is stored in the body.

Riboflavin is converted in the body to the coenzyme flavine mononucleotide (FMN; riboflavin 5′-phosphate) and then to another coenzyme flavine adenine dinucleotide (FAD). About 60% of FMN and FAD are bound to plasma proteins. Riboflavin is excreted in urine, partly as metabolites. As the dose increases, larger amounts are excreted unchanged. Riboflavin crosses the placenta and is distributed into breast milk.

Human Requirements

The riboflavin requirement is often related to the energy intake but it appears to be more closely related to resting metabolic requirements. A daily dietary intake of about 1.1 to 1.8 mg of riboflavin is recommended. Liver, kidney, fish, eggs, milk, cheese, yeast, and some green vegetables such as broccoli and spinach are the richest sources of riboflavin. In general, little loss of riboflavin occurs during cooking, but considerable losses may occur if foods, especially milk, are exposed to sunlight.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for riboflavin[1] and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females of varying ages, and for pregnant and lactating women; the differences between age groups are intended to reflect the changes in caloric intakes at these ages. In the UK the reference nutrient intake (RNI) is 1.3 mg daily and 1.1 mg daily for adult males and females respectively; the estimated average requirement (EAR) is 1.0 mg daily and 900 micrograms daily respectively. In the USA the RDAs for adult males and females are 1.3 and 1.1 mg daily respectively.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Berivine; Ribon; ***China***: Liluokang (利络康); ***Fr.***: Beflavine; ***Ger.***: B2-ASmedic; ***Hong Kong***: FAD Ophthalmic Soln; Hibon; Ribovit†; Super B2†; ***India***: Lipabol; ***Indon.***: Alinamin; ***Israel***: UV-X-Ribo-Dextran; ***Thai.***: Biovit B2; Boflavin; Flavin; Tebovin; Vitabee-2-25; ***USA***: B_2-400; Cyto B2.

Multi-ingredient Preparations. ***Arg.***: Anemidox; Cistidac; Goteborg; Lociherp Liposomas Vitaminado; ***Austral.***: Antioxidant Forte Tablets†; Antioxidant Tablets†; Bilberry Plus Eye Health†; Extralife Eye-Care†; Methyl Transfer; PM Eye Tonic; PM IQShield; ***Braz.***: Apevinat BC; Frutoplex; Frutovena; Organoneuro Optico; Pre-Mens; ***Chile***: Becomplina Fuerte†; Benutrex 1000†; Rodepan; ***China***: Kai Yu (凯瑜); Norpin A (纳尔平); ***Cz.***: Calcium Pharmavit; ***Fr.***: Lero Pervulane; ***Ger.***: Floradix Eisen-Folsaure; Floradix Krauterblut†; ***Gr.***: Arkadin; Lentamine; ***Hong Kong***: PM Eye Tonic†; ***India***: Aglozyme; Altrazyme; Aminorich; Aneudox-12; Atpro; Carbo Plus; Folnet; Folvina; Ginkoriv Plus; HB-Norm; Hepa-Merz†; Hepawin; Idiglobin; Ipreg; Livosil-B; Lornit; Neurophosphates†; Neurotrat; Oraflora; Ornipan; ***Indon.***: Combiplex; Dansera; Dialac; Matase; My Caps; nutrivision; Oculex; Oculex; Reticopen; Retop; Tonikum Bayer; Vitanox; Vitop; Yeastafort; ***Irl.***: Quiet Life; ***Ital.***: Facovit; Fosforilasi; ***Jpn***: Neurovitan; ***Malaysia***: P-Trovite; ***Mex.***: Pangavit Pediatrico; ***Philipp.***: Fer-Essence; Foramefer; Godex; Hanizyn; Hemovin; Heralink; Mitocore; Mitonerb; Mivex; Nakaron; ***Pol.***: Biovision; ***Rus.***: Corylip (Корилип); Cytoflavin (Цитофлавин); Essliver Forte (Эссливер Форте); Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); ***Singapore***: Alinamin-F; Beafort; Beaplex; Ferbeaplex; Gin-Vita; Nutrivision†; ***Spain***: Aftasone B C†; ***Thai.***: Alinamin-F; B-100 Complex; Neuviplex; Polyvit; Vita-Cal; ***Turk.***: Neuvitan; ***UK***: Pilfood; Quiet Life; Se-Power; ***Ukr.***: B-Complex Multi-Tabs (В-Комплекс Мульти-Табс)†; Cytoflavin (Цитофлавин); Decamevit (Декамевит); Fenules (Фенюльс)†; Fitoval Capsules (Фитовал капсулы); Hepadif (Гепадиф); Hepaforte (Гепафорте); Levasil (Левасил); Neiron (Нейрон); Neurovitan (Нейровитан); Vitrum Foreyes Forte (Вітрум Форайз Форте); Vitrum Memory (Витрум Мемори); ***USA***: L-Methyl-MC; REQ49+.

Pharmacopoeial Preparations

BP 2014: Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Riboflavin Injection; Riboflavin Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin B_6 Substances

Vitamina B_6; Витамины Группы B_6.

Vitamin B_6 is usually available as pyridoxine but the term is also used to refer to the related compounds, pyridoxal and pyridoxamine.

Metadoxine

Metadoxina; Pyridoxine Pidolate.

Pyridoxine *l*-5-oxopyrrolidine-2-carboxylate.

$C_8H_{11}NO_3$, $C_5H_7NO_3$=298.3

CAS — 74536-44-0.

UNII — EJQ7M98H5J.

Pyridoxal Phosphate

Codecarboxylase; MC-I; Piridoxal, fosfato de; Pyridoxal 5-Phosphate; Пиридоксальфосфат.

3-Hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5′-phosphate.

$C_8H_{10}NO_6P$=247.1

CAS — 54-47-7.

ATC — A11HA06.

ATC Vet — QA11HA06.

UNII — 5V5IOJ8338 (pyridoxal phosphate monohydrate); F06SGE49M6 (pyridoxal phosphate).

Pyridoxamine Hydrochloride

Piridoxamina, hidrocloruro de; Pyridoxamine Dihydrochloride; Пиридоксамина Гидрохлорид.

4-Aminomethyl-5-hydroxy-6-methyl-3-pyridinemethanol hydrochloride.

$C_8H_{12}N_2O_2$,2HCl=241.1

CAS — 524-36-7.

UNII — YQ8NCR7V0O.

Pyridoxine Hydrochloride *(BANM, rINNM)*

Adermine Hydrochloride; Hidrocloruro de adermina; Hidrocloruro de piridoxina; Piridoksin Hidroklorür; Piridoksino hidrochloridas; Piridossina Cloridrato; Piridoxina, hidrocloruro de; Piridoxin-hidroklorid; Pirydoksyny chlorowodorek; Pyridoksiinihydrokloridi; Pyridoxine, Chlorhydrate de; Pyridoxinhydrochlorid; Pyridoxin-hydrochlorid; Pyridoxinhydroklorid; Pyridoxini hydrochloridum; Pyridoxinii Chloridum; Pyridoxinium Chloride; Pyridoxol Hydrochloride; Vitamin B_6; Vitamina B_6; Пиридоксина Гидрохлорид.

3-Hydroxy-4,5-bis(hydroxymethyl)-2-picoline hydrochloride.

$C_8H_{11}NO_3$,HCl=205.6

CAS — 65-23-6 (pyridoxine); 58-56-0 (pyridoxine hydrochloride).

ATC — A11HA02.

ATC Vet — QA11HA02.

UNII — 68Y4CF58BV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Pyridoxine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.4 to 3.0. Protect from light.

USP 36: (Pyridoxine Hydrochloride). White or practically white crystals or crystalline powder. Soluble 1 in 5 of water and 1 in 115 of alcohol; insoluble in ether. Its solutions in water have a pH of about 3. Store in airtight containers. Protect from light.

Uses and Administration

Pyridoxine, a water-soluble vitamin, is involved mainly in amino acid metabolism, but is also involved in carbohydrate and fat metabolism. It is also required for the formation of haemoglobin.

Deficiency of pyridoxine is rare in humans because of its widespread distribution in foods. Pyridoxine deficiency may however be drug-induced and can occur, for instance, during isoniazid therapy. Inadequate utilisation of pyridoxine may result from certain inborn errors of metabolism. Pyridoxine deficiency may lead to anaemia, dermatitis, cheilosis, and neurological symptoms such as peripheral neuritis, and convulsions.

Pyridoxine is used in the treatment and prevention of pyridoxine deficiency states. It is usually given orally, the preferred route, but may also be given by the subcutaneous, intramuscular, or intravenous routes. Doses of pyridoxine hydrochloride up to 150 mg daily are used in general deficiency states; higher doses of up to 400 mg daily are used in the treatment of sideroblastic anaemias (see p. 2106.1); and similar high doses have been used to treat certain

metabolic disorders such as homocystinuria (see Amino Acid Metabolic Disorders, below) or primary hyperoxaluria (below). Pyridoxine has also been used to treat seizures due to hereditary syndromes of pyridoxine deficiency or dependency in infants.

Pyridoxine has also been tried in the treatment of many other disorders, including depression and other symptoms associated with the premenstrual syndrome (see below) and the use of oral contraceptives, although its efficacy has been questioned. Pyridoxine hydrochloride is used, as a modified-release combination preparation with doxylamine succinate, in the management of nausea and vomiting of early pregnancy; see under Doxylamine Succinate, p. 627.3, for details of doses.

Pyridoxine is usually given as the hydrochloride although other salts such as the citrate, oxoglurate, phosphate, and phosphoserinate, have also been used. Metadoxine, the pidolate, has been investigated in alcoholism (see below).

For the use of pyridoxine in the prophylaxis of isoniazid-induced peripheral neuritis and for the treatment of acute isoniazid toxicity, see Treatment of Adverse Effects, under Isoniazid, p. 312.3.

Pyridoxal phosphate may be used to treat vitamin B_6 deficiency. Pyridoxamine has also been given.

Reviews.

1. Bender DA. Non-nutritional uses of vitamin B_6. *Br J Nutr* 1999; **81:** 7–20.
2. Lheureux P, *et al.* Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med* 2005; **12:** 78–85.

Administration in children. For doses of pyridoxine in the management of children with **amino acid metabolic disorders** and **pyridoxine-dependent seizures** see below.

Pyridoxine may also be used to treat or prevent **isoniazid-induced neuropathy**. For doses in children see Treatment of Adverse Effects, under Isoniazid, p. 312.3.

Alcoholism and alcohol poisoning. Pyridoxine and its pidolate, known as metadoxine, have been tried in the treatment of alcohol poisoning and alcoholism.[1] One study showed pyridoxine to be ineffective in acute alcohol poisoning[2] but another[3] suggested that the pidolate might be of benefit as an adjunct in the management of alcohol withdrawal (p. 1734.1). In patients treated for alcoholic fatty liver, liver function returned to normal more quickly with metadoxine, even in patients who did not completely abstain from alcohol.[4]

1. Addolorato G, *et al.* Metadoxine in the treatment of acute and chronic alcoholism: a review. *Int J Immunopathol Pharmacol* 2003; **16:** 207–14.
2. Mardel S, *et al.* Intravenous pyridoxine in acute ethanol intoxication. *Hum Exp Toxicol* 1994; **13:** 321–3.
3. Rizzo A, *et al.* Uso terapeutico della metadoxina nell'alcolismo cronico: studio clinico in doppio cieco su pazienti ricoverati in un reparto di medicina generale. *Clin Ter* 1993; **142:** 243–50.
4. Caballería J, *et al.* Metadoxine accelerates fatty liver recovery in alcoholic patients: results of a randomized double-blind, placebo-control trial. *J Hepatol* 1998; **28:** 54–60.

Amino acid metabolic disorders. Pyridoxine has been used in various inborn errors of amino acid metabolism, such as homocystinuria (p. 2042.2), with or without cobalamins and folate. Relatively high doses may need to be given (see Uses and Administration, p. 2105.3). For children with metabolic disorders such as homocystinuria and cystathioninuria, the *BNFC* suggests pyridoxine in an oral dose of 50 to 100 mg once or twice daily for neonates, and 50 to 250 mg once or twice daily in patients aged 1 month to 18 years. For the use of pyridoxine in primary hyperoxaluria, another inherited metabolic disorder, see below.

Anaemias. Some patients with acquired or hereditary sideroblastic anaemia (p. 1123.1) that is severe enough to require treatment will respond to high doses (up to 400 mg daily) of pyridoxine, and a trial is considered worthwhile in all patients.

Cardiovascular disease. For mention of the possible link between vitamin B_6, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid, p. 2063.3. Pyridoxal phosphate is thought to prevent cellular calcium overload in ischaemia-reperfusion injury, but a large multicentre study[1] investigating doses of 250 mg daily orally given 3 to 10 hours before coronary artery bypass graft surgery in intermediate- to high-risk patients, and for a further 30 days after the procedure, found it did not reduce the incidence of cardiovascular death or non-fatal myocardial infarction.

1. Alexander JH, *et al.* MEND-CABG II Investigators. Efficacy and safety of pyridoxal 5′-phosphate (MC-1) in high-risk patients undergoing coronary artery bypass graft surgery: the MEND-CABG II randomized clinical trial. *JAMA* 2008; **299:** 1777–87.

Carpal tunnel syndrome. Pyridoxine has been advocated by some[1] for patients with carpal tunnel syndrome (see Soft-tissue Rheumatism, p. 14.2), but evidence of efficacy is considered to be limited.[2] In most studies reporting improvement with pyridoxine, doses have ranged from 50 to 300 mg daily for 12 weeks; a review concluded that treatment should be stopped if there is no apparent response after this period.[3]

1. Lewis PJ. Pyridoxine supplements may help patients with carpal tunnel syndrome. *BMJ* 1995; **310:** 1534.
2. O'Connor D, *et al.* Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 09/01/06).
3. Aufiero E, *et al.* Pyridoxine hydrochloride treatment of carpal tunnel syndrome; a review. *Nutr Rev* 2004; **62:** 96–104.

Epilepsy. Pyridoxine-dependent epilepsy is an autosomal recessive disorder associated with decreased central γ-aminobutyric acid (GABA) concentrations and elevated cerebral glutamate concentrations. Untreated patients suffer from progressive encephalopathy, mental retardation, and intractable epilepsy; lifelong supplementation with pyridoxine can control epileptic symptoms but mental retardation may still develop. An epidemiological study[1] defined cases as those children with recurrent seizures that ceased within 7 days of oral pyridoxine at a usual dose of 30 mg/kg daily (minimum dose 15 mg/kg daily; maximum dose 1 g/kg daily), or within 30 minutes of intravenous pyridoxine (usual dose 100 mg; minimum dose 50 mg), that recurred when supplementation was withdrawn, and ceased again upon dosage as before. The study found that, despite their rarity, pyridoxine-dependent seizures frequently present atypically, and the author suggested that pyridoxine be given to all children with intractable seizures beginning before 3 years of age, including neonates with suspected hypoxic-ischaemic encephalopathy.

Test doses of pyridoxine intravenously, repeated at intervals of 10 minutes up to a total of 500 mg if necessary, have been suggested in the diagnosis of pyridoxine-dependent epilepsy; if the patient responds then a daily oral dose of 5 mg/kg is suggested although there is no real consensus on the appropriate dosage.[2] The *BNFC* suggests an intravenous test dose of 50 to 100 mg; in those who respond, oral doses of 50 to 100 mg once daily in neonates or 20 to 50 mg once or twice daily in older children (in whom up to 30 mg/kg or 1 g daily has been used), are suggested, adjusted as required. Alternatively, in patients with recurrent seizures refractory to conventional anticonvulsant therapy, oral pyridoxine supplementation of 15 mg/kg daily should lead to resolution of clinical seizures within a week in those with the condition; however, in some patients the daily dose required may be lower.[3]

A study in one patient[4] found that although pyridoxine 5 mg/kg reduced glutamate concentrations in CSF from the untreated value of 200 times normal limits, it did so only to 10 times the normal value, despite remission of symptoms. Doses of 10 mg/kg daily were required to normalise CSF glutamate, and it was suggested that this was a more appropriate target for therapy. In some children, pyridoxal phosphate has been suggested to be more effective than pyridoxine in controlling seizures.[5]

1. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. *Arch Dis Child* 1999; **81:** 431–3.
2. Gospe SM. Current perspectives on pyridoxine-dependent seizures. *J Pediatr* 1998; **132:** 919–23.
3. Gospe SM. Pyridoxine-dependent seizures: findings from recent studies pose new questions. *Pediatr Neurol* 2002; **26:** 181–5.
4. Baumeister FAM, *et al.* Glutamate in pyridoxine-dependent epilepsy: neurotoxic glutamate concentration in the cerebrospinal fluid and its normalization by pyridoxine. *Pediatrics* 1994; **94:** 318–21.
5. Wang H-S, *et al.* Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Arch Dis Child* 2005; **90:** 512–15.

Palmar-plantar erythrodysesthesia syndrome. Pyridoxine, in doses of 100 to 300 mg daily, has been used successfully[1] for treating and preventing palmar-plantar erythrodysesthesia syndrome associated with antineoplastic therapy (see p. 730.1).

1. Nagore E, *et al.* Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. *Am J Clin Dermatol* 2000; **1:** 225–34.

Premenstrual syndrome. Pyridoxine has been widely used in the premenstrual syndrome (p. 2272.3) despite controversy over its effectiveness. Some consider that depressive symptoms may be provoked by pyridoxine deficiency because of its role as a coenzyme in the production of certain neurotransmitters, but it is difficult to attribute any of the other symptoms of the premenstrual syndrome to pyridoxine deficiency and doses of 50 mg are no more effective than a placebo.[1] A systematic review found that although treatment with pyridoxine was more effective than placebo, there was insufficient high-quality evidence to recommend its routine use in premenstrual syndrome.[2] If pyridoxine is used, the dosage should be restricted (see Effects on the Nervous System, below) because of concerns about neurotoxicity.[3] Although unlicensed in the UK, the *BNF* suggests an oral pyridoxine dose of 50 to 100 mg daily for premenstrual syndrome.

1. West CP. The premenstrual syndrome. *Prescribers' J* 1987; **27** (2): 9–15.
2. Wyatt KM, *et al.* Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999; **318:** 1375–81.
3. Severino SK, Moline ML. Premenstrual syndrome: identification and management. *Drugs* 1995; **49:** 71–82.

Primary hyperoxaluria. Primary hyperoxaluria (as distinct from the various forms secondary to other disorders) is a genetic disorder characterised by excessive synthesis and urinary excretion of oxalic acid. Two forms are known, type I (hyperglycolic aciduria) and type II (L-glyceric aciduria), associated with different enzyme defects. They are marked by recurrent calcium oxalate kidney stones, or nephrocalcinosis, leading to renal failure, together with extrarenal deposition of calcium oxalate and frequently severe peripheral vascular insufficiency. Treatment with high doses of pyridoxine may help decrease oxalate excretion particularly in type I disease,[1,2] although response is variable.[3] A few patients may respond to lower (physiological) doses.[4] Such treatment can be used with an oral orthophosphate supplement, which helps reduce renal deposition of calcium oxalate, and the combination appears to preserve renal function.[5] Therapy with magnesium salts, potassium citrate, and thiazide diuretics has also been suggested.[2] In patients in whom renal failure develops, the results of kidney transplantation have been disappointing, due to deposition of calcium oxalate in the new kidney, although transplanting the liver as well can correct the enzyme defect.[1,6] Pre-emptive liver transplantation, performed before renal failure or systemic oxalosis has occurred, may be an option.[2]

1. Cochat P, Basmaison O. Current approaches to the management of primary hyperoxaluria. *Arch Dis Child* 2000; **82:** 470–3.
2. Marangella M, *et al.* The primary hyperoxalurias. *Contrib Nephrol* 2001; **136:** 11–32.
3. Toussaint C. Pyridoxine-responsive PH1: treatment. *J Nephrol* 1998; **11** (suppl 1): 49–50.
4. Yendt ER, Cohanim M. Response to a physiologic dose of pyridoxine in type I primary hyperoxaluria. *N Engl J Med* 1985; **312:** 953–7.
5. Milliner DS, *et al.* Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *N Engl J Med* 1994; **331:** 1553–8.
6. Watts RWE, *et al.* Combined hepatic and renal transplantation in primary hyperoxaluria type I: clinical report of nine cases. *Am J Med* 1991; **90:** 179–88.

Tardive dyskinesia. In a double-blind, controlled, crossover study,[1] daily oral doses of vitamin B_6 1.2 g effectively reduced the symptoms of tardive dyskinesia (see Extrapyramidal Disorders, p. 1049.2).

1. Lerner V, *et al.* Vitamin B_6 treatment for tardive dyskinesia: a randomized, double-blind, placebo-controlled, crossover study. *J Clin Psychiatry* 2007; **68:** 1648–54.

Adverse Effects and Precautions

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies; the dose at which these occur is controversial (see Effects on the Nervous System, below).

Breast feeding. Vitamin B_6 is excreted into breast milk.[1,2] While some have expressed concern over the inhibition of breast milk secretion by pyridoxine,[3] others have cautioned that pyridoxine deficiency may cause seizures in the neonate.[4] The American Academy of Pediatrics considers the use of pyridoxine to be usually compatible with breast feeding.[5]

1. West KD, Kirksey A. Influence of vitamin B_6 intake on the content of the vitamin in human milk. *Am J Clin Nutr* 1976; **29:** 961–9.
2. Roepke JLB, Kirksey A. Vitamin B_6 nutriture during pregnancy and lactation: 1. Vitamin B_6 intake, levels of the vitamin in biological fluids, and condition of the infant at birth. *Am J Clin Nutr* 1979; **32:** 2249–56.
3. Greentree LB. Dangers of vitamin B_6 in nursing mothers. *N Engl J Med* 1979; **300:** 141–2.
4. Lande NI. More on dangers of vitamin B_6 in nursing mothers. *N Engl J Med* 1979; **300:** 926–7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Effects on the nervous system. Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months.[1] There has, however, been debate as to whether smaller doses can produce such effects. Some contend that amounts of pyridoxine below this level are unlikely to produce toxic effects.[2,3] However, there have been some case reports[4,5] with amounts up to about 500 mg daily and prolonged use of even lower doses (about 200 mg daily or less) may also cause sensory peripheral neuropathy.[6,7] After a review of the possible toxicity associated with lower doses of pyridoxine, proposals were put forward in the UK to limit the dose freely available in dietary supplements to 10 mg daily; products supplying up to 50 mg daily would continue to be available from pharmacies and higher doses would only be available on prescription.[8] These proposals were heavily contested.[8,9] An upper level of intake of 50 mg daily is recommended in Australia,[7]

whereas an upper limit of 100 mg daily has been suggested in the USA.[9]

1. Schaumburg H, *et al*. Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 1983; **309:** 445–8.
2. Pauling L. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **310:** 197.
3. Baker H, Frank O. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **310:** 197.
4. Berger A, Schaumburg HH. More on neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **311:** 986.
5. Waterston JA, Gilligan BS. Pyridoxine neuropathy. *Med J Aust* 1987; **146:** 640–2.
6. Dordain G, Deffond D. Neuropathies à la pyridoxine: revue de la littérature. *Therapie* 1994; **49:** 333–7.
7. Adverse Drug Reactions Advisory Committee (ADRAC). High-dose vitamin B6 may cause peripheral neuropathy. *Aust Adverse Drug React Bull* 2008; **27:** 14–15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0808.pdf (accessed 26/01/09)
8. Collier J. Vitamin B-6: food or medicine? *BMJ* 1998; **317:** 92–3.
9. Anonymous. Still time for rational debate about vitamin B_6. *Lancet* 1998; **351:** 1523.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pyridoxine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Pyridoxal phosphate is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Pyridoxine reduces the effects of levodopa (see p. 908.1), but this does not occur if a dopa decarboxylase inhibitor is also given. Pyridoxine reduces the activity of altretamine. It has also been reported to decrease serum concentrations of phenobarbital (p. 538.1) and phenytoin (p. 545.2). Many drugs may increase the requirements for pyridoxine; such drugs include hydralazine, isoniazid, penicillamine, and oral contraceptives.

Pharmacokinetics

Pyridoxine, pyridoxal, and pyridoxamine are readily absorbed from the gastrointestinal tract after oral doses and are converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Pyridoxal crosses the placenta and is distributed into breast milk.

Human Requirements

For adults, the daily requirement of pyridoxine is probably about 1.5 to 2 mg and this amount is present in most normal diets. The requirement tends to increase as protein intake increases due to the role of the vitamin in amino acid metabolism. Meats, especially chicken, kidney, and liver, cereals, eggs, fish, and certain vegetables and fruits are good sources of pyridoxine.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p. 2046.1) have been published for vitamin B_6 and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and during pregnancy and lactation. In the UK the reference nutrient intake (RNI) is 15 micrograms per g of protein daily for adult males and females and the estimated average requirement (EAR) is 13 micrograms per g of protein daily for the same group. In the USA the RDA for adult men ranges from 1.3 to 1.7 mg daily and that for adult women ranges from 1.3 to 1.5 mg daily.[2] The tolerable upper intake level is 100 mg daily.[2] The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for vitamin B_6 of 170 micrograms/kg daily. For recommended limits in dietary supplements see Effects on the Nervous System, p. 2106.3.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Benadon; ***Austral.***: Pyroxin; ***Belg.***: Bedoxine†; ***Braz.***: Fonto-Vit B6†; Metadoxil; Neuri B6; Seis-B; ***Canad.***: B-natal; ***Chile***: Vitabe; ***China***: Fei Li Gu (菲力古); GanXin (甘忻); Hao Qiang (昊强); Jie Ao (洁傲); Shen Kai Neng (申凯能); Xin Li De (欣立得); ***Denm.***: BiOrto B6; Super B6; ***Fin.***: Heksavit†; Vita-B6; ***Fr.***: Becilan; Derrno 6; ***Ger.***: B6-ASmedic; B_6 Vicotrat; Bonasanit†; Novirell B_6; ***Gr.***: Becilan; Benadon; Besix; Bexivit; ***Hong Kong***: Pyribion†; Pyrixin†; Super B6†; ***Hung.***: Beres B6; Feroglobin-B12; Metadoxil; ***India***: Abix; Alcoliv; Benadon; Cobal Forte; Ingavit B6; Metadoxil; Pyricontin; ***Indon.***: Liconam; Stopmun†; ***Irl.***: Compliment†; ***Israel***: Anacrodyne; B-Six; ***Ital.***: Benadon; Metadoxil; Xanturenasi; ***Malaysia***: Upha B6; ***Mex.***: Abrixone; Fortical; Metasin; Valparina†; ***Philipp.***: Drexabion; Hybutin; Jaga; Lixtress; Meganerv; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Pyricar; Supraneuron; Vineuron; ***Port.***: Benadon; ***Rus.***: Metadoxil (Метадоксил); Vitagamma (Витагамма); ***S.Afr.***: Beesix†; Lactosec; ***Spain***: Benadon; Conductasa; ***Swed.***: Benadon†; ***Switz.***: Benadon; ***Thai.***: B Six P; B-6; B6-50; Besix; Biovit B6; Jotexin; Mega-B; Metadoxil; ***Turk.***: B_6 Vigen; Libavit B_6; Postadoxine; ***Venez.***: Beplus; Biprin; Clodoxin; Suprabion.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Canad.***: Isotamine B; ***Ger.***: Isozid comp N; tebesium; ***Hong Kong***: Trisofort†; ***India***: Becox RH; Bicox Kid; Binex; Caviter FD; Cx-3; Cx-4; Cx-5; Gocox Compound; Isokin-300; Mycodot Kit; Mycodot-4; Mycodot-E; Mycodot-Z; Rifa E; Rifa; Wokex-2; Wokex-3; Wokex-4; ***Indon.***: bacbutINH; Erabutol Plus; INH-Ciba; INHA; Inoxin; Kapedoxin; Medinh-OD†; Meditam-6†; Mycothambin-INH†; Niacifort-6; Niazitol; Pehadoxin; Pulmolin†; Pulna; Pyravit; Pyrifort†; Santibi Plus; Suprazid; TB Vit 6; ***Ital.***: Etanicozid B6; ***Philipp.***: CombiKids†; Comprilex; Curazid (Reformulated); Ethamizid; Ethi 400; Eurocoxin; Isodexid; Isoprim; Isoxin; Kidz Kit 2; Kidz Kit 3; Nicetal†; Odinah; Pulmodrin; Refam Duo†; Refam Pedia Kit†; Sthamizide; SVM-Polypac-A†; Techxafort; Terozid; Trisofort†; Vamsoxid†; ***Pol.***: Laktomag B_6; ***Rus.***: Coxerin Plus (Коксерин Плюс); Cyclo Plus (Цикло Плюс); Isocomb (Изокомб); Isozid Comp (Изозид Комп); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Protiocomb (Протиокомб); Protub-2 (Протуб-2); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rezonisate Plus (Резонизат Плюс); Rifacomb (Рифакомб); Tubavit (Тубавит); ***Spain***: Cemidon B6; Tisobrif†; ***Turk.***: Isovit.

Homoeopathic Preparations. ***Ger.***: Infi-Symphytum; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations
BP 2014: Pyridoxine Tablets; Vitamins B and C Injection;
BPC 1973: Strong Compound Vitamin B Tablets;
USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Pyridoxine Hydrochloride Injection; Pyridoxine Hydrochloride Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin B_{12} Substances

Vitamina B_{12}; Витамины Группы B_{12}.

Vitamin B_{12} is the name generally used for a group of related cobalt-containing compounds, also known as cobalamins, of which cyanocobalamin and hydroxocobalamin are the principal forms in clinical use.

Cobamamide *(pINN)*

Adenosylcobalamin; Cobamamida; Cobamamidum; Coenzyme B_{12}; Dibencozide; Dibenzcozamide; Dimebenzcozamide; Kobamamid; Кобамамид.
Inner salt of the *Co*-(5′-deoxyadenosine-5′) derivative of the 3′-ester of cobinamide phosphate with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole.
$C_{72}H_{100}CoN_{18}O_{17}P$=1579.6
CAS — 13870-90-1.
ATC — B03BA04.
ATC Vet — QB03BA04.

Pharmacopoeias. In *Chin.*

Cyanocobalamin *(BAN, rINN)*

Cianocobalamina; Cianokobalamin; Cianokobalaminas; Cobamin; Cyanocobalamine; Cyanocobalaminum; Cyanokobalamin; Cycobemin; Cyjanokobalamina; Kyanokobalamin; Siyanokobalamin; Syanokobalamiini; Цианокобаламин.
*Co*α-[α-(5,6-Dimethylbenzimidazolyl)]-*Co*β-cyanocobamide.
$C_{63}H_{88}CoN_{14}O_{14}P$=1355.4
CAS — 68-19-9.
ATC — B03BA01.
ATC Vet — QB03BA01.
UNII — P6YC3EG204.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cyanocobalamin). A dark red, crystalline powder or dark red crystals. The anhydrous substance is very hygroscopic. Sparingly soluble in water and in alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Cyanocobalamin). Dark red crystals or amorphous or crystalline red powder. In the anhydrous form it is very hygroscopic and when exposed to air it may absorb about 12% of water. Soluble 1 in 80 of water; soluble in alcohol; insoluble in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Hydroxocobalamin *(BAN, USAN, rINN)*

Hidroksokobalamin; Hidroxocobalamina; Hydroksikobalamiini; Hydroxikobalamin; Hydroxocobalamine; Hydroxocobalaminum; Hydroxycobalaminum; Idrossocobalamina; Гидроксокобаламин.
*Co*α-[α-(5,6-Dimethylbenzimidazolyl)]-*Co*β-hydroxocobamide.
$C_{62}H_{89}CoN_{13}O_{15}P$=1346.4
CAS — 13422-51-0.
ATC — B03BA03; V03AB33.
ATC Vet — QB03BA03; QV03AB33.
UNII — Q40X8H422O.

NOTE. The hydrated form of hydroxocobalamin has been referred to as aquocobalamin.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Hydroxocobalamin). Dark red crystals or red crystalline powder. Is odourless or has not more than a slight acetone odour. The anhydrous form is very hygroscopic. Soluble 1 in 50 of water and 1 in 100 of alcohol; practically insoluble in acetone, in chloroform, in ether, and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 8.0 and 10.0. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Hydroxocobalamin Acetate *(BANM, rINNM)*

Acetato de hidroxocobalamina; Acetatocobalamin; Hidroksokobalamino acetatas; Hidroxocobalamina, acetato de; Hidroxokobalamin-acetát; Hydroksokobalamiiniasetaatti; Hydroxocobalaminacetat; Hydroxocobalamine, Acétate d'; Hydroxocobalamini acetas; Hydroxokobalamin acetát; Hydroxokobalaminacetat; Гидроксокобаламина Ацетат.
$C_{64}H_{93}CoN_{13}O_{17}P$=1406.4
CAS — 22465-48-1.
UNII — S535M27N3Q.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.*

Ph. Eur. 8: (Hydroxocobalamin Acetate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2 degrees and 8 degrees in airtight containers. Protect from light.

Hydroxocobalamin Chloride *(BANM, rINNM)*

Cloruro de hidroxocobalamina; Hidroksokobalamino chloridas; Hidroxocobalamina, cloruro de; Hidroxokobalaminklorid; Hydroksokobalamiinikloridi; Hydroxocobalamine, Chlorure d'; Hydroxocobalaminhydrochlorid; Hydroxocobalamini chloridum; Hydroxocobalamini Hydrochloridum; Hydroxokobalamin hydrochlorid; Hydroxokobalaminklorid; Гидроксокобаламина Хлорид.
$C_{62}H_{90}ClCoN_{13}O_{15}P$=1382.8

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Viet.*

Ph. Eur. 8: (Hydroxocobalamin Chloride). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2 degrees and 8 degrees in airtight containers. Protect from light.

Hydroxocobalamin Sulfate *(BANM, rINNM)*

Hidroksokobalamino sulfatas; Hidroxocobalamina, sulfato de; Hidroxokobalamin-szulfát; Hydroksokobalamiinisulfaatti; Hydroxocobalamin Sulphate; Hydroxocobalamine, Sulfate d'; Hydroxocobalamini Sulfas; Hydroxocobalaminsulfat; Hydroxokobalamin sulfát; Hydroxokobalaminsulfat; Sulfato de hidroxocobalamina; Гидроксокобаламина Сульфат.
$C_{124}H_{180}Co_2N_{26}O_{34}P_2S$=2790.8

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Viet.*

Ph. Eur. 8: (Hydroxocobalamin Sulfate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble

in water. Some decomposition may occur on drying. Store at a temperature between 2 degrees and 8 degrees in airtight containers. Protect from light.

Mecobalamin *(BAN, USAN, pINN)*

Mecobalamina; Mécobalamine; Mecobalaminum; Methylcobalamin; Мекобаламин.

Coα-[α-(5,6-Dimethylbenzimidazolyl)]-Coβ-methylcobamide.

$C_{63}H_9{}_1CoN_{13}O_{14}P$=1344.4

CAS — 13422-55-4.

ATC — B03BA05.

ATC Vet — QB03BA05.

UNII — BR1SN1JS2W.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Vitamin B_{12}, a water-soluble vitamin, occurs in the body mainly as methylcobalamin (mecobalamin) and as adenosylcobalamin (cobamamide) and hydroxocobalamin. Mecobalamin and cobamamide act as coenzymes in nucleic acid synthesis. Mecobalamin is also closely involved with folic acid in several important metabolic pathways.

Vitamin B_{12} deficiency can occur in strict vegetarians with an inadequate dietary intake, although it may take many years before a deficiency is produced. Deficiency is more likely in patients with malabsorption syndromes or metabolic disorders, nitrous oxide-induced megaloblastosis, or after gastrectomy or extensive ileal resection. Deficiency leads to the development of megaloblastic anaemias and demyelination and other neurological damage. A specific anaemia known as pernicious anaemia develops in patients with an absence of the intrinsic factor necessary for good absorption of the vitamin from dietary sources.

Vitamin B_{12} preparations are used in the treatment and prevention of vitamin B_{12} deficiency. It is essential to identify the exact cause of deficiency, preferably before starting therapy. Hydroxocobalamin is generally preferred to cyanocobalamin; it binds more firmly to plasma proteins and is retained in the body longer (see under Pharmacokinetics, p. 2110.2). Cyanocobalamin and hydroxocobalamin are generally given by the intramuscular route, although cyanocobalamin may be given orally or subcutaneously, or intranasally (see also under Administration, below). Oral cyanocobalamin may be used in treating or preventing vitamin B_{12} deficiency of dietary origin.

In the UK, recommended doses for **pernicious anaemia** and other megaloblastic anaemias are as follows:

- in patients *without neurological involvement* doses are hydroxocobalamin (or cyanocobalamin) 250 to 1000 micrograms intramuscularly on alternate days for 1 to 2 weeks, then 250 micrograms weekly until the blood count returns to normal. Maintenance doses of 1000 micrograms are given every 2 to 3 months as hydroxocobalamin, or monthly as cyanocobalamin
- if there is *neurological involvement*, hydroxocobalamin or cyanocobalamin may be given intramuscularly in doses of 1000 micrograms on alternate days and continued for as long as improvement occurs. Maintenance doses of 1000 micrograms are given every 2 months as hydroxocobalamin, or monthly as cyanocobalamin
- for the *prophylaxis* of anaemia associated with vitamin B_{12} deficiency resulting from gastrectomy or malabsorption syndromes hydroxocobalamin may be given in doses of 1000 micrograms intramuscularly every 2 or 3 months or cyanocobalamin in doses of 250 to 1000 micrograms intramuscularly each month
- for vitamin B_{12} deficiency of *dietary* origin, oral cyanocobalamin 50 to 150 micrograms may be taken daily between meals. For discussion of oral cyanocobalamin therapy for the treatment of pernicious anaemia, see Administration, below

Lower doses of both cyanocobalamin and hydroxocobalamin are recommended for pernicious anaemia in the USA:

- for *treatment*, the usual intramuscular or subcutaneous dose of cyanocobalamin is 100 micrograms daily for 6 or 7 days; if there is a response, a further 7 doses may be given on alternate days, then every 3 to 4 days for 2 to 3 weeks. For hydroxocobalamin the usual intramuscular dose is 30 micrograms daily for 5 to 10 days
- for *maintenance*, monthly injections of cyanocobalamin 100 micrograms (intramuscularly or subcutaneously), or intramuscular hydroxocobalamin 100 to 200 micrograms are given. Intranasal preparations of cyanocobalamin are also available for maintenance therapy in those without neurological involvement. An initial dose of 500 micrograms (as one 500-microgram spray in one nostril) is given once weekly and then adjusted according to response. Alternatively, an initial dose of 50 micrograms (as one 25-microgram spray in each nostril) is given once daily, and can be increased to twice daily if required
- in patients with normal gastrointestinal absorption, oral cyanocobalamin doses of 1 to 25 micrograms daily are considered sufficient as a *dietary supplement* (see also Administration, below)

Treatment of vitamin B_{12} deficiency usually results in rapid haematological improvement and a striking clinical response. However, neurological symptoms respond more slowly and in some cases remission may not be complete.

Cobamamide and mecobalamin may also be used for vitamin B_{12} deficiency.

Hydroxocobalamin may also be given in the treatment of **tobacco amblyopia** and **Leber's optic atrophy**; initial doses are 1000 micrograms daily for 2 weeks intramuscularly followed by 1000 micrograms twice weekly for as long as improvement is maintained. Thereafter, 1000 micrograms is given every 1 to 3 months.

Hydroxocobalamin is also used for the treatment of known or suspected **cyanide toxicity** (see below). Each 2.5 g vial of hydroxocobalamin is reconstituted with 100 mL of diluent, preferably sodium chloride 0.9%. The starting dose for adults is 5 g intravenously over 15 minutes. Depending on the severity of the toxicity and the clinical response, a second dose of 5 g may be infused over 15 minutes to 2 hours.

For administration in children, see below.

Cyanocobalamin and hydroxocobalamin are also used in the **Schilling test** to investigate vitamin B_{12} absorption and deficiency states. They are given in a non-radioactive form with cyanocobalamin radioactively-labelled with cobalt-57 (p. 2223.3) or cobalt-58 (p. 2223.3) and the amount of radioactivity excreted in the urine can be used to assess absorption status. A differential Schilling test, in which the forms of cyanocobalamin are given under different conditions (such as with intrinsic factor, antibacterials, or pancreatic enzymes) can provide information about the cause of the malabsorption.

Administration. The small amounts of vitamin B_{12} present in the diet are absorbed from the gastrointestinal tract by an active process that involves binding with intrinsic factor. As intrinsic factor is absent in patients who have developed pernicious anaemia it has often been assumed that *oral* vitamin B_{12} preparations will therefore be ineffective. However, about 1% of an oral dose is absorbed by passive diffusion, and with large doses this amount may be sufficient for therapy. Thus attention has been given again to the use of oral cobalamins for the treatment of pernicious anaemia.[1-4] Oral cyanocobalamin 2000 micrograms daily was as effective as intramuscular therapy in patients with vitamin B_{12} deficiency in a comparative study.[5] Some now consider that oral doses of 1000 micrograms daily,[3,6] or every 2 weeks for children,[7] are a suitable alternative to injections given at monthly or so intervals; others still deem oral use to be unjustified on the grounds of negligible oral absorption.[8] A systematic review[9] of 2 studies found some evidence for a satisfactory haematological, biochemical, and clinical short-term response to oral replacement in some patients with conditions associated with malabsorption. Another review[10] concluded that, while there is substantial evidence to support the use of 1000 to 2000 micrograms daily of oral cyanocobalamin as maintenance therapy, parenteral therapy is preferable for initial treatment of those with neurological symptoms. Oral formulations are being developed which use carrier molecules to enhance absorption.

Cyanocobalamin is also effective when given *intranasally*,[11] with peak plasma concentrations greater than those achievable orally, and this may offer another alternative to injection. The intranasal absorption of hydroxocobalamin has been studied.[12,13]

Cyanocobalamin has also been given *sublingually*. Normalisation of serum cobalamin concentration has been reported in 18 patients given sublingual cyanocobalamin 2000 micrograms daily for 7 to 12 days;[14] 500 micrograms sublingually daily was found to be as effective as the same dose given orally in correcting deficiency.[15]

1. Lederle FA. Oral cobalamin for pernicious anemia: medicine's best kept secret? *JAMA* 1991; **265:** 94–5.
2. Hathcock JN, Troendle GJ. Oral cobalamin for treatment of pernicious anemia? *JAMA* 1991; **265:** 96–7.
3. Elia M. Oral or parenteral therapy for B12 deficiency. *Lancet* 1998; **352:** 1721–2.
4. Anonymous. Oral or intramuscular vitamin B_{12}? *Drug Ther Bull* 2009; **47:** 19–21.
5. Kuzminski AM, *et al.* Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; **92:** 1191–8.
6. Andrès E, *et al.* Usefulness of oral cyanocobalamin therapy in severe hematologic manifestations related to vitamin B_{12} deficiency. *Ann Pharmacother* 2004; **38:** 1086–7.
7. Çetin M, Altay C. Efficacy of oral vitamin B_{12} treatment in children. *J Pediatr* 2001; **139:** 754.
8. Van der Kuy P-HM, *et al.* Bioavailability of oral hydroxocobalamin. *Br J Clin Pharmacol* 2000; **49:** 395P–396P.
9. Vidal-Alaball J, *et al.* Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 05/09/06).
10. Lane LA, Rojas-Fernandez C. Treatment of Vitamin B_{12}-deficiency anemia: oral versus parenteral therapy. *Ann Pharmacother* 2002; **36:** 1268–72.
11. Romeo VD, *et al.* Intranasal cyanocobalamin. *JAMA* 1992; **268:** 1268–9.
12. van Asselt DZB, *et al.* Nasal absorption of hydroxocobalamin in healthy elderly adults. *Br J Clin Pharmacol* 1998; **45:** 83–6.
13. Slot WB, *et al.* Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. *Gastroenterology* 1997; **113:** 430–3.
14. Delpre G, *et al.* Sublingual therapy for cobalamin deficiency as an alternative to oral and parenteral cobalamin supplementation. *Lancet* 1999; **354:** 740–1.
15. Sharabi A, *et al.* Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol* 2003; **56:** 635–8.

Administration in children. In neonates and children up to 18 years with congenital transcobalamin II deficiency, the *BNFC* suggests a dose of hydroxocobalamin 1 mg by intramuscular injection given three times weekly. After 1 year this may be reduced to 1 mg once weekly.

In children aged from 1 month with megaloblastic anaemia (p. 2109.1) or children with Leber's optic atrophy, hydroxocobalamin doses are similar to those used in adults in the UK, see Uses and Administration, above.

Hydroxocobalamin is used as an antidote for cyanide poisoning in children. A dose of 70 mg/kg (maximum 5 g) by intravenous infusion is given once or twice according to severity.

Hydroxocobalamin can also be used in children with methylmalonic acidaemia and homocystinuria, see Amino Acid Metabolic Disorders, below.

Amino acid metabolic disorders. References to the use of hydroxocobalamin in the treatment of inborn errors of vitamin B_{12} metabolism.[1-3] Some patients with homocystinuria (p. 2042.2) or methylmalonic acidaemia have responded to cobalamins—the *BNFC* suggests an initial intramuscular dose of hydroxocobalamin 1 mg daily, for 5 to 7 days, in patients from one month of age; this is reduced, according to response, to 1 mg once or twice weekly. Some children respond to maintenance with 5 to 10 mg hydroxocobalamin given orally once or twice weekly.

1. Linnell JC, Bhatt HR. Inherited errors of cobalamin metabolism and their management. *Baillieres Clin Haematol* 1995; **8:** 567–601.
2. Andersson HC, Shapira E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). *J Pediatr* 1998; **132:** 121–4.
3. Smith DL, Bodamer OA. Practical management of combined methylmalonicaciduria and homocystinuria. *J Child Neurol* 2002; **17:** 353–6.

Cardiovascular disease. For mention of the possible link between vitamin B_{12}, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid p. 2063.3.

Cyanide toxicity. Hydroxocobalamin combines with cyanide to form cyanocobalamin, and thus may be used as an antidote to cyanide toxicity (see under Hydrocyanic Acid, p. 2156.2). Hydroxocobalamin is reported to be effective in controlling cyanide toxicity due to nitroprusside infusion,[1] and after exposure to inhaled combustion products in residential fires.[2]

It has been hypothesised that the amount of cyanocobalamin formed is limited by the number of cyanide ions present and the amount of hydroxocobalamin given. For a given dose of hydroxocobalamin a maximum concentration of cyanocobalamin would be reached, allowing measurement of cyanocobalamin as a surrogate emergency marker for cyanide levels, which are difficult and time-consuming to measure. For a 5-g dose of hydroxocobalamin given intravenously over 30 minutes, the authors of one study considered a cyanocobalamin concentration of about 300 micromoles/litre a sign that all the hydroxocobalamin had been used, and more should be given.[2] They cautioned, however, that, unless antidote regimen and blood sampling were similar to that in their study, this concentration should not be extrapolated to other patient populations.

In another patient given hydroxocobalamin 5 g intravenously over 2 hours,[3] plasma concentrations of cyanide rose 1 hour after treatment with hydroxocobalamin. The authors attributed this to hydroxocobalamin extracting cyanide from red blood cells to form cyanocobalamin in plasma, which was then measured as cyanide.

A review[4] of the role of hydroxocobalamin in acute cyanide poisoning found insufficient evidence to routinely recommend empirical use for smoke inhalation, although some advantages over standard therapy were noted. Unlike nitrites, hydroxocobalamin does not cause methaemoglobinaemia, a particular risk after smoke inhalation. Additionally, its low toxicity may be beneficial for cyanide toxicity in children and pregnant women.

For doses of hydroxocobalamin used for cyanide toxicity in adults, see Uses and Administration, above, and in children, see Administration in Children, above.

1. Zerbe NF, Wagner BKJ. Use of vitamin B12 in the treatment and prevention of nitroprusside-induced cyanide toxicity. *Crit Care Med* 1993; **21:** 465–7.

2. Houeto P, *et al*. Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. *Lancet* 1995; **346:** 605–8.
3. Weng T-I, *et al*. Elevated plasma cyanide after hydroxocobalamin infusion for cyanide poisoning. *Am J Emerg Med* 2004; **22:** 492–3.
4. Shepherd G, Velez LI. Role of hydroxocobalamin in acute cyanide poisoning. *Ann Pharmacother* 2008; **42:** 661–9.

Deficiency states. The emergence of newer metabolic assays for homocysteine and methylmalonic acid has led to the identification of subtle vitamin B_{12} deficiency[1-3] without the overt manifestations of megaloblastic anaemia (see below) or neurological disease; this condition appears to be particularly common in the elderly.[1,4-6] At present, there is no clear clinical rationale for treating subtle deficiency,[1,7] although suggestions for management have been made.[8] A study in elderly patients suggested that food-cobalamin malabsorption, a disorder characterised by the inability to release vitamin B_{12} from food or its binding protein, might be to blame for this subtle deficiency; these patients had some neurological or haematological abnormalities, and treatment with oral or parenteral vitamin B_{12} was found to be effective.[6] There have also been suggestions that deficiency may be linked to some immunological impairment, identified as impaired antibody responses to pneumococcal vaccine.[9] Moreover, raised homocysteine concentrations have been identified as a risk factor for atherosclerosis and ischaemic heart disease, and there is increasing interest in the potential of B vitamins, including B_{12}, to reduce homocysteine concentrations and therefore atherosclerotic outcomes (see Cardiovascular Disease, under Uses and Administration of Folic Acid, p. 2063.3). Evidence that hyperhomocysteinaemia may be a risk factor for dementia is limited.[5] A systematic review concluded that evidence for efficacy of vitamin B_{12} in improving cognitive function of people with dementia (and low serum vitamin B_{12} concentrations) was lacking.[10]

Dietary vitamin B_{12} deficiency in infants may lead to developmental abnormalities.[11,12]

The issue of fortification of food with folic acid (see under Folic Acid, p. 2064.2) to reduce the number of infants born with neural tube defects (p. 2064.3) has created debate on the risks of masking vitamin B_{12} deficiency, and fortification with vitamin B_{12} has also been recommended, see under Folic Acid, p. 2066.1. An independent association between low maternal vitamin B_{12} status and an increased risk of neural tube defects has also been reported, see Neural Tube Defects, below.

1. Carmel R. Subtle cobalamin deficiency. *Ann Intern Med* 1996; **124:** 338–40.
2. Green R. Screening for vitamin B_{12} deficiency: caveat emptor. *Ann Intern Med* 1996; **124:** 509–11.
3. Carmel R, *et al*. Update on cobalamin, folate, and homocysteine. *Hematology (Am Soc Hematol Educ Program)* 2003; 62–81.
4. Andrès E, *et al*. Vitamin B_{12}(cobalamin) deficiency in elderly patients. *Can Med Assoc J* 2004; **171:** 251–9.
5. Clarke R. Prevention of vitamin B-12 deficiency in old age. *Am J Clin Nutr* 2001; **73:** 151–2.
6. Andrès E, *et al*. Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. *Am J Med* 2005; **118:** 1154–9.
7. Metz J. What's the use of oral vitamin B_{12}? A neglected but valid treatment route may have new uses in the future. *Med J Aust* 1999; **170:** 407.
8. Carmel R. How I treat cobalamin (vitamin B_{12}) deficiency. *Blood* 2008; **112:** 2214–21.
9. Fata FT, *et al*. Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B_{12} levels. *Ann Intern Med* 1996; **124:** 299–304.
10. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 09/01/06).
11. Emery ES, *et al*. Vitamin B12 deficiency: a cause of abnormal movements in infants. *Pediatrics* 1997; **99:** 255–6.
12. von Schenck U, *et al*. Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. *Arch Dis Child* 1997; **77:** 137–9.

Eczema. A small study found that topical application of a preparation containing vitamin B_{12} was more effective than placebo in patients with atopic eczema.[1]

1. Stücker M, *et al*. Topical vitamin B_{12}—a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol* 2004; **150:** 977–83.

Megaloblastic anaemia. The megaloblastic anaemias are characterised by macrocytosis (an increased mean cell volume) and the production of distinctive morphological changes and abnormal maturation in developing haematopoietic cells in the bone marrow: white cell and platelet lines are affected as well as erythroid precursors, and in severe cases anaemia may be associated with leucopenia and thrombocytopenia. Megaloblastic anaemia is a consequence of impaired DNA biosynthesis in the bone marrow, usually due to a deficiency of vitamin B_{12} (cobalamins) or folate, both of which are essential for this process. Although the haematological symptoms of B_{12} deficiency and folate deficiency are similar it is important to distinguish between them since the use of folate alone in B_{12}-deficient megaloblastic anaemia can improve haematological symptoms without preventing aggravation of accompanying neurological symptoms, and may lead to severe nervous system sequelae such as subacute combined degeneration of the spinal cord. Where it is desirable to start therapy immediately, combined treatment for both deficiencies may be started once suitable samples have been taken to permit diagnosis of the deficiency, and the patient converted to the appropriate treatment once the cause of the anaemia is known.

Vitamin B_{12} deficiency anaemia. Vitamin B_{12} deficiency and its associated symptoms may be due to malabsorption (including following gastrectomy), dietary deficiency (mainly in strict vegetarians), competition with intestinal bacteria or parasites, or to the effect of drugs such as nitrous oxide. In populations of northern European origin, pernicious anaemia, in which atrophy of the gastric mucosa results in a lack of the intrinsic factor essential for B_{12} absorption, is the most frequent cause. As body stores of the vitamin are large, it may take several years for signs of deficiency to manifest once the defect in absorption occurs.

In addition to megaloblastic anaemia, vitamin B_{12} deficiency may result in neurological damage, including peripheral neuropathy and effects on mental function ranging from mild neurosis to dementia.

TREATMENT. The treatment is with vitamin B_{12}, almost always by the intramuscular or sometimes the deep subcutaneous route since in most patients absorption from the gastrointestinal tract is inadequate. Hydroxocobalamin is generally preferred to cyanocobalamin since it need be given less often. Regimens may vary, but hydroxocobalamin 1 mg every few days for 6 doses will restore normal body stores of the vitamin (see also Uses and Administration, p. 2108.1). Dosage has not been well established in children; the *BNFC* recommends similar hydroxocobalamin doses to those licensed in adults. The haematological response to therapy is rapid, with improvement in most parameters and symptoms beginning within 48 hours. Neurological abnormalities may take much longer to respond, and may not do so completely.

PROPHYLAXIS. Where the defect in B_{12} handling is irreversible, as in pernicious anaemia, maintenance therapy must continue for life to prevent a recurrence of the deficiency. Therapy must also be given prophylactically after total gastrectomy or total ileal resection, or where gastrointestinal surgery is shown to have impaired absorption of the vitamin. Typically, injection of hydroxocobalamin 1 mg every 3 months is used. In patients whose diet supplies inadequate B_{12}, deficiency may be prevented, in the absence of other causes, by much lower oral doses given as a supplement; up to 150 micrograms of cyanocobalamin daily has been recommended.

Folate-deficiency anaemia. Deficiency of folate may be due to inadequate diet, or malabsorption syndromes (such as coeliac disease or sprue), to increased need (as in pregnancy, one of the most common causes of megaloblastic anaemia, or the increased haematopoiesis of haemolytic syndromes), to increased urinary loss or loss due to haemodialysis, or to an adverse effect of alcohol, antiepileptics, or other drugs.

The clinical features of folate-deficient megaloblastic anaemia are similar to those of disease due to vitamin-B_{12} deficiency except that the accompanying severe neuropathy does not occur, and deficiency may develop much more rapidly. Deficiency may also be associated with neural tube defects (p. 2064.3) if it occurs in pregnancy.

TREATMENT. Once folate deficiency has been established the usual treatment in the UK is oral folic acid 5 mg daily. Lower doses of up to 1 mg are suggested in the USA. It is customary to continue therapy for at least 4 months, the time necessary for complete red cell replacement. In patients with malabsorption, therapy may require higher doses, up to 15 mg of folic acid daily. As in B_{12}-deficiency anaemia, the response to therapy is rapid.

PROPHYLAXIS. Long-term maintenance is rarely needed, except in a few patients in whom the underlying cause of folate deficiency cannot be treated (for example in some severe haemolytic syndromes). Doses of 5 mg daily or even weekly have been suggested for prophylaxis in patients undergoing dialysis or with chronic haemolytic states, depending on the diet and rate of haemolysis; a dose of 400 micrograms daily is recommended in the USA.

For primary prophylaxis of megaloblastic anaemia in pregnancy, folic acid is given in the UK in a usual dose of 500 micrograms daily, often with a ferrous salt for prophylaxis of iron deficiency.

Drugs that act as inhibitors of dihydrofolate reductase, such as methotrexate, may produce severe megaloblastic anaemia which cannot be reversed by therapy with folic acid. The adverse effects of such drugs may be largely prevented or reversed by therapy with folinic acid, which can be incorporated into folate metabolism without the need for reduction by the inhibited enzyme. For details of such 'folinic acid rescue', see under Folinic Acid, p. 2067.1.

General references.

1. Wickramasinghe SN. Folate and vitamin B_{12} deficiency and supplementation. *Prescribers' J* 1997; **37:** 88–95.
2. Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. *Semin Hematol* 1999; **36:** 3–18.
3. Rasmussen SA, *et al*. Vitamin B_{12} deficiency in children and adolescents. *J Pediatr* 2001; **138:** 10–17.
4. Hoffbrand V, Provan D. Macrocytic anaemias. In: Provan D, ed. *ABC of clinical haematology*. 2nd ed. London: BMJ Publishing Group, 2003.
5. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. *Annu Rev Nutr* 2004; **24:** 299–326.

Neural tube defects. There is abnormality in homocysteine metabolism in many women who give birth to children with neural tube defects (p. 2064.3); the enzyme methionine synthase, which converts homocysteine to methionine, requires both folate and vitamin B_{12} as cofactors, and low maternal vitamin B_{12} concentrations may be an independent risk factor for neural tube defects.[1] A case-control study found elevated mid-trimester methylmalonic acid concentrations in women with pregnancies affected by neural tube defects, suggesting that abnormalities of cobalamin metabolism, and subsequent methylation, may be involved in the aetiology of neural tube defects.[2] Decreased vitamin B_{12} concentrations, but no folate deficiency, were found in 3 women with pregnancies affected by neural tube defects.[3] A review[4] of case-control studies found a moderate association between low maternal vitamin B_{12} status and the risk of fetal neural tube defects, and results from a Canadian population, largely after folic acid supplementation was implemented, suggested a threefold increase in the risk of neural tube defect in offspring of women with vitamin B_{12} status in the lowest quartile.[5] An Irish study[6] produced similar results. If confirmed by controlled prospective studies, this would suggest that additional supplementation with cobalamins may be warranted.[3-5,7]

1. Mills JL, *et al*. Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; **345:** 149–51.
2. Adams MJ, *et al*. Elevated midtrimester serum methylmalonic acid levels as a risk factor for neural tube defects. *Teratology* 1995; **51:** 311–17.
3. Candito M, *et al*. Anomalies du tube neural et vitamine B12: à propos de trois cas. *Ann Biol Clin (Paris)* 2004; **62:** 235–8.
4. Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. *Q J Med* 2003; **96:** 289–95.
5. Thompson MD, *et al*. Vitamin B-12 and neural tube defects: the Canadian experience. *Am J Clin Nutr* 2009; **89:** 697S–701S.
6. Molloy AM, *et al*. Maternal vitamin B_{12} status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic acid fortification. *Pediatrics* 2009; **123:** 917–23.
7. Refsum H. Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *Br J Nutr* 2001; **85** (suppl): S109–S113.

Osteoporosis. An elevated serum homocysteine concentration appears to be a risk factor for osteoporotic fractures in older men and women.[1-3] Treatment with vitamin B_{12} and folate can reduce plasma homocysteine concentrations (see Cardiovascular Disease, under Folic Acid, p. 2063.3). In a placebo-controlled study of patients with hemiplegia following stroke (and at increased risk of hip fracture),[4] those given folate and vitamin B_{12} were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B_{12} status has been associated with bone health in a number of studies,[3,5] and it was suggested that the observed effects on fracture might be due to increased concentrations of vitamin B_{12} rather than the lowering of plasma homocysteine.[3,6]

1. van Meurs JBJ, *et al*. Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; **350:** 2033–41.
2. McLean RR, *et al*. Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 2004; **350:** 2042–9.
3. vanMeurs JBJ, Uitterlinden AG. Homocysteine and fracture prevention. *JAMA* 2005; **293:** 1121–2.
4. Sato Y, *et al*. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005; **293:** 1082–8. Correction. *ibid*. 2006; **296:** 396.
5. Dhonukshe-Rutten RAM, *et al*. Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. *J Nutr* 2003; **133:** 801–7.
6. Sugiyama T, *et al*. Folate and vitamin B_{12} for hip fracture prevention after stroke. *JAMA* 2005; **294:** 792.

Rhinitis. A sublingual formulation of cyanocobalamin (*Pre-Histin; Cobalis, USA*) has been reported to be under investigation in the management of seasonal allergic rhinitis, but published studies are lacking.

Adverse Effects and Precautions

Allergic hypersensitivity reactions have occurred rarely after cyanocobalamin and hydroxocobalamin and include skin reactions such as rash and itching, and anaphylaxis. Patients who are hypersensitive to cyanocobalamin injection may be able to take oral cyanocobalamin. Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy.

Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin. Injection site reactions including pain, erythema, pruritus, induration, swelling, and necrosis can occur.

Intranasal cyanocobalamin may cause arthralgia, dizziness, headache, nasopharyngitis, and rhinitis; epistaxis has also been reported.

Other adverse effects reported with cyanocobalamin and hydroxocobalamin include gastrointestinal disturbances, fever, chills, hot flushing, dizziness, malaise, acneform and bullous eruptions, and tremor. Headaches, paraesthesia, and chromaturia have occurred with hydroxocobalamin.

Cyanocobalamin or hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis. Regular monitoring of the blood is advisable. Use of doses greater than 10 micrograms daily may produce a haematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B_{12} deficiency (see p. 2066.1).

Cyanocobalamin should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further.

Breast feeding. Vitamin B_{12} is distributed into breast milk.[1] The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Samson RR, McClelland DBL. Vitamin B_{12} in human colostrum and milk. *Acta Paediatr Scand* 1980; **69:** 93–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Hypersensitivity. Analysis, by the Boston Collaborative Drug Surveillance Program, of data on 15 438 patients hospitalised between 1975 and 1982 detected 3 allergic skin reactions attributed to cyanocobalamin among 168 recipients of the drug.[1] For the purposes of the study, reactions were defined as being generalised morbilliform exanthems, urticaria, or generalised pruritus only.

In a patient with a generalised pruritic reaction to hydroxocobalamin (with subsequent urticaria, bronchospasm, and oropharyngeal angioedema), cyanocobalamin was relatively well-tolerated, with only one episode of delayed urticaria.[2]

1. Bigby M, *et al*. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.
2. Heyworth-Smith D, Hogan PG. Allergy to hydroxycobalamin, with tolerance of cyanocobalamin. *Med J Aust* 2002; **177:** 162–3.

Local reactions. After 3 years of monthly intramuscular vitamin B_{12} injections, a patient presented with a sclerotic plaque at the injection site, which was successfully treated by excision and local fat transfer. It was unclear as to whether the patient had reacted to the vehicle, the preservative, or to the cyanocobalamin.[1] Fascial haematoma after vitamin B_{12} injection leading to local compression (posterior arm compartment syndrome) has also been reported.[2]

1. Ho J, *et al*. Vitamin B12-associated localized scleroderma and its treatment. *Dermatol Surg* 2004; **30:** 1252–5.
2. Knapke D, Truumees E. Posterior arm and deltoid compartment syndrome after vitamin B12 injection. *Orthopedics* 2004; **27:** 520–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyanocobalamin and hydroxocobalamin as not porphyrinogenic; either drug may be used as a drug of first choice and no precautions are needed. Cobamamide and mecobalamin are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H_2-antagonists, omeprazole, and colchicine. Serum concentrations may be decreased by use of oral contraceptives. Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations. Parenteral chloramphenicol may attenuate the effect of vitamin B_{12} in anaemia.

Pharmacokinetics

Vitamin B_{12} substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

Vitamin B_{12} is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B_{12} is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B_{12} diffuses across the placenta and also appears in breast milk.

Retention in the body. A short review[1] in 1984 noted that after injection of cyanocobalamin a large proportion was excreted in the urine within 24 hours; the body retained only 55% of a 100-microgram dose and 15% of a 1000-microgram dose. Body stores of vitamin B_{12} amounted to 2000 to 3000 micrograms which was believed to be enough for 3 to 4 years. If 1000 micrograms is injected monthly, the 150 micrograms retained lasts for about 1 month. Hydroxocobalamin was better retained than cyanocobalamin; the review stated that 90% of a 100-microgram dose and 30% of a 1000-microgram dose were retained which was believed to be enough for 2 to 10 months. While UK licensed product information supports these figures, it has been pointed out[2] that the latter figure was misquoted by the review from its original source, which claimed that 30% of a 1000 microgram-dose was *excreted* and 70% retained, hence allowing for the longer dosing interval.

1. Anonymous. Time to drop cyanocobalamin? *Drug Ther Bull* 1984; **22:** 43.
2. Raymond P. Cyanocobalamin. *Aust Prescriber* 1988; **11:** 13.

Human Requirements

For adults, the daily requirement of vitamin B_{12} is probably about 1 to 2 micrograms and this amount is present in most normal diets. Vitamin B_{12} occurs only in animal products; it does not occur in vegetables, therefore strict vegetarian (vegan) diets that exclude dairy products may provide an inadequate amount although it has been said that many years of vegetarianism are necessary before a deficiency is produced, if at all. Meats, especially liver and kidney, milk, eggs, and other dairy products, and fish are good sources of vitamin B_{12}.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p. 2046.1) have been published for vitamin B_{12} and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, adults and pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 1.5 micrograms daily for adult males and females and the estimated average requirement (EAR) is 1.25 micrograms daily. In the USA the RDA for adults is 2.4 micrograms daily.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Difenac Forte; Lisoneurin B12†; Reedvit; SL B12; Vitam Doce; ***Austral.***: Cytamen†; Hydroxo-B12; Neo-B12; Neo-Cytamen†; ***Austria***: Cyanokit; Erycytol; Hepavit; ***Belg.***: Cyanokit; ***Braz.***: Bedozil; Cianon B12†; Cronobe; Enzicoba; Rubranova; ***Canad.***: Athlete†; Cyanokit; Formula 1†; Hydro Cobex; Prime†; ***China***: Ai Ke Bao (爱柯保); Ai Xin Bao (爱昕保); Bo Di Tong (博迪同); Bo Ke Bao (博可保); Cheng Qiang (成强); Dai Fang (代芳); Fanminbu (泛敏补); He Bao (禾保); Jia Li Bao (加利保); Le Kang (乐亢); LiWei (力维); Luo Tang (洛唐); Methycobal (弥可保); Mi Er Shen (弥尔神); Mi Nuo (弥诺); Ouwei (欧维); Qi Xin (奇信); Qu Li (曲力); Runjie (润洁); Sancoba (散克巴); Shi Er Xin (实尔新); Tang Xin (唐信); Tuo Pu You (托普优); Wei Ke Da (威可达); Yi Shen Bao (怡神保); Yi Wei Kang (怡维康); Yu Hai Xiang (郁海香); Yue Min Xing (悦敏兴); Zhao Min Xin (兆敏欣); ***Cz.***: Cyanokit; Neurobene; ***Denm.***: Betolvex; Cyanokit; Vibeden; ***Fin.***: Betolvex; Cohemin; ***Fr.***: Cyanokit; Dodecavit; Ecovitamine B12; ***Ger.***: Ambe 12†; B12 Depot-Rotexmedica; B12 Rotexmedica; B12 Steigerwald; B_{12} Ankermann; B_{12} Depot-Hevert†; B_{12}-ASmedic; Cytobion†; Lophakomp-B 12 Depot; Lophakomp-B 12; Novirell B_{12}; Rowo Vitamin B_{12} (Rowo-12); ***Gr.***: Articlox; Bedoc; ***Hong Kong***: Cobalamin†; Cobamin; Cyanokit; Methycobal; Neo-Active Vit B-12†; ***Hung.***: Feroglobin-B12; No Shot; ***India***: Acmic; Acvit; Adee; Adenomin; Alnacob; Alphamix; Ameco; Atnuron; Axineuron; Azed; Balcobal; Basix-OD; Bigvin; Biocobal; Biomic; Cabosoft; Chiny; Citon; Coba; Cobaday; Cobal Forte; Cobal; Cobalom; Cobalvit 1ML; Cobalvit-D; Cobalvit-OD; Cobamet-OD; Cobanerve OD; Cobanerve; Cobaver; Coblona; Cobsa; Compicare; Cubal; Cumee; Diabanerve; Diacobal; E-Cob; Ecobal-OD; Efcoba; Electa; Elmecob; Glomec; Hydrox-12; Ingavit B12; Intacob; Juvinate; Keeneuron; L-Vit-12; Lameco-OD; Logy; Maddox; Malamin; Marinol; Matilda; MB-12; MCB; MCBit; MCBM; Me-12; Mecatin-MD; Mecmin; Mecoba; Mecobal; Mecobest; Mecoflash; Mecofol; Mecolife; Mecomed; Mecona; Meconerv; Meconeuron; Meconovit-OD; Mecophar; Mecoriv; Mecovit; Mecovon; Mecze; Medhamin; Medinerv; Mego; Melife-OD; Mericobal; Metherlin; Methico; Methiloc; Methyco; Methycobal; Methygard; Methyneuron; Mewin; Mezen; Mico-B; Miko; Moblo; Mycobal; Mycol; Myconova; Mycotop; Mycovit-OD; Myelogen; Mynuron; Necob; Nervic-1500; Nervicin; Nervon-M; Nervup; Neucobal; Neuractin; Neuratab-M Forte; Neuroage; Neurolac-MD; Neuromed; Neuromin; Neuroswift; Neurotone; Neurotop-M; Neurovig-M; Neutron; Nifabol; Niscobal; Novomine; Nurobex; Nuroclad; Nuroday; Nurokind; Nuromas; Nuromax; Nurovole; Nuroz-OD; Nuthyal Plus; OB-12; Odicoba; Omybal; ***Indon.***: Arcored; Berthyco; Cobazim; Ethigobal; Interco; Kalmeco; Lanabal; Lapibal; Magerix; Mecolin; Meconeuro; Megabal; Methycobal; Metifer; Mevrabal†; Nerfeco; Neulamin; Nufacobal; Oxicobal; Scanmecob; Sohobal; ***Irl.***: Cyanokit; Cytacon†; Cytamen; Neo-Cytamen; ***Israel***: Bedodeka; Bevitex; ***Ital.***: Cobaforte; Cyanokit; Dobetin; Indusil; Neo-Cytamen; OH B12; ***Jpn***: Methycobal; ***Malaysia***: Methycobal; N-Cobal; Neuromethyn; ***Mex.***: Axofor; Biocobal†; Biotrefon L; Bissel 12; Compensal†; Duradoce; Exorvit†; Fortical; Leo-Doce†; Maxibol; Nebal; Neurofor; Plusvisol; Sanovit; ***Neth.***: Cyanokit; Hydrocobamine; ***Norw.***: Betolvex; Cyanokit; ***NZ***: Neo-B12; Neo-Cytamen; ***Philipp.***: Drexabion; Econvita; Geocobalamin; Heraclene; Hybutin; Jaga; Lixtress; Mecovit; Meganerv; Methycobal; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Rubramin†; Supraneuron; Valcumin; Vineuron; ***Pol.***: Cyanokit; ***Port.***: Co-Vibedoze†; Cobaxid; Cyanokit; Dozefol; Jaba B_{12}; OH B12; Permadoze; ***Rus.***: Cicomin (Цикомин); Vitagamma (Витагамма); ***S.Afr.***: Cobalatec; ***Singapore***: Methycobal; Neuromethyn; ***Spain***: Cromatonbic B12; Cyanokit; Isopto B 12; Megamilbedoce; Optovite B12; Reticulogen Fortificado†; Zimadoce†; ***Swed.***: Behepan; Behepan; Betolvex; Betolvidon; Cyanokit; ***Switz.***: Betolvex; Cyanokit; Vitarubin; ***Thai.***: Ampavit; B Twelve P; Balamine; Hitocobamin M†; Mecoba; Mecobal; Mecobin; Mecze; Merabin; Methycobal; Neuromet; Redisol; ***Turk.***: Aktibol; Betolvex; Dodex; ***UAE***: Cynovit; ***UK***: Cobalin-H; Cyanokit; Cytacon; Cytamen; Neo-Cytamen; ***USA***: B-12 Dots; B-12 SL; B-12; CaloMist†; Crystamine†; Cyanokit; Cyomin†; Nascobal; Rapid B-12 Energy; Twelve Resin-K; ***Venez.***: Bedovit Simple; Beplus; Cristadoce; Dobetin; Hidro-Doce; Ibedox; Maxibol.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Ger.***: Hepar comp; Infi-China; Infi-Symphytum; Infihepan; NeyDil Nr 66†; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Vitalkapsein A; NeyLing Nr 66.

Pharmacopoeial Preparations

BP 2014: Cyanocobalamin Tablets; Hydroxocobalamin Injection; **USP 36:** Cyanocobalamin Injection; Hydroxocobalamin Injection; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Vitamin C Substances

Vitamina C; Витамины Группы С.

Several substances have vitamin C activity, notably ascorbic acid and its calcium and sodium salts. Natural products with a high vitamin C content include black currant (p. 2458.1), lemon (p. 2542.3), sweet orange (p. 2576.2), and rose fruit (p. 2607.1).

Ascorbic Acid *(BAN, rINN)*

Acide ascorbique; Ácido ascórbico; Acidum Ascorbicum; L-Ascorbic Acid; Ascórbico, ácido; Ascorbinsäure; Askorbiinihappo; Askorbik Asit; Askorbinsyra; Askorbo rūgštis; Aszkorbinsav; Cevitamic Acid; E300; Kwas askorbowy; Kyselina askorbová; Vitamin C; Vitamina C; Аскорбиновая кислота.

The enolic form of 3-oxo-L-gulofuranolactone; 2,3-Didehydro-L-*threo*-hexono-1,4-lactone.

$C_6H_8O_6$=176.1

CAS — 50-81-7.

ATC — A11GA01; G01AD03; S01XA15.

ATC Vet — QA11GA01; QG01AD03; QS01XA15.

UNII — PQ6CK8PD0R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ascorbic Acid). A white or almost white crystalline powder or colourless crystals becoming discoloured on exposure to air and moisture. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 2.1 to 2.6. Store in nonmetallic containers. Protect from light.

USP 36: (Ascorbic Acid). White or slightly yellow crystals or powder. On exposure to light, it gradually darkens. In the dry state, is reasonably stable in air, but in solution rapidly oxidises. Soluble 1 in 3 of water and 1 in 40 of alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Calcium Ascorbate *(BANM, rINNM)*

Ascorbate de Calcium; Ascorbato cálcico; Askorban vápenatý dihydrát; Calcii Ascorbas; Calcii Ascorbas Dihydricus; Calcium, ascorbate de; Calciumascorbat; E302; Kalcio askorbatas; Kalciumaskorbat; Kalcium-aszkorbát; Kalsiumaskorbaatti; Кальций Аскорбат.

$(C_6H_7O_6)_2Ca,2H_2O$=426.3

CAS — 5743-27-1.

UNII — 183E4W213W (calcium ascorbate dihydrate); J96U0ZD4Y6 (anhydrous calcium ascorbate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Calcium Ascorbate). A white or slightly yellowish crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH between 6.8 and 7.4. Store in nonmetallic containers. Protect from light.

USP 36: (Calcium Ascorbate). A white to slightly yellow, practically odourless, powder. Freely soluble in water (about 1 in 2); slightly soluble in alcohol; insoluble in ether. pH of a 10% solution in water is between 6.8 and 7.4. Store in airtight containers. Protect from light.

Sodium Ascorbate *(BANM, rINN)*

Ascorbate de sodium; Ascorbate sodique; Ascorbato de sodio; Askorbato sódico; Askorban sodný; E301; Monosodium L-Ascorbate; Natrii Ascorbas; Natrio askorbatas; Natriumascorbat; Natriumaskorbaatti; Natriumaskorbat; Nátrium-aszkorbát; Натрия Аскорбат.

3-Oxo-L-gulofuranolactone sodium enolate.

$C_6H_7NaO_6$=198.1

CAS — 134-03-2.

UNII — S033EH8359.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Sodium Ascorbate). A white or yellowish crystalline powder or crystals. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A freshly prepared 10% solution in water has a pH of 7.0 to 8.0. Store in nonmetallic containers. Protect from light.

USP 36: (Sodium Ascorbate). White or very faintly yellow, odourless or practically odourless, crystals or crystalline powder. On exposure to light it gradually darkens. Soluble 1 in 1.3 of water; very slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.0. Store in airtight containers. Protect from light.

Uses and Administration

Vitamin C, a water-soluble vitamin, is essential for the synthesis of collagen and intercellular material. Vitamin C deficiency develops when the dietary intake is inadequate. It is rare in adults, but may occur in infants, alcoholics, or the elderly. Deficiency leads to the development of a well-defined syndrome known as scurvy. This is characterised by capillary fragility, bleeding (especially from small blood vessels and the gums), normocytic or macrocytic anaemia, cartilage and bone lesions, and slow healing of wounds.

Vitamin C is used in the treatment and prevention of deficiency. It completely reverses symptoms of deficiency. It is usually given orally, the preferred route, as ascorbic acid. Ascorbic acid or sodium ascorbate may be given parenterally, preferably by the intramuscular route, but also by the intravenous or subcutaneous routes. Doses of 25 to 75 mg daily in the prevention of deficiency, and 250 mg or more daily in divided doses for the treatment of deficiency, have been recommended.

Oral ascorbic acid 100 to 200 mg daily may be given with desferrioxamine in the treatment of patients with chronic iron overload, to improve the chelating action of desferrioxamine, thereby increasing the excretion of iron (see p. 1544.1); to reduce toxicity ascorbic acid should not be started until 1 month after starting desferrioxamine. Ascorbic acid should be given separately from food since it can enhance iron absorption. In iron deficiency states ascorbic acid is used to increase gastrointestinal iron absorption and ascorbic acid or ascorbate salts are therefore included in some oral iron preparations. Ascorbic acid or sodium ascorbate have been used in treating methaemoglobinaemia. Ascorbic acid has been used to acidify urine. It has also been tried in the treatment of many other disorders (see below) but there is little evidence of beneficial effect.

For doses in children, see Administration in Children, below.

Eye drops containing potassium ascorbate (ascorbic acid 10%) have been used for the treatment of chemical eye burns (p. 1782.1); they may be used with sodium citrate eye drops (see Uses and Administration of Bicarbonate, p. 1781.2).

Ascorbic acid and calcium and sodium ascorbates are used as antoxidants in pharmaceutical manufacturing and in the food industry.

Administration in children. Vitamin C is used in children to prevent and treat deficiency which can lead to scurvy. It is usually given orally as ascorbic acid (although traditional sources for supplementation have included citrus juices, black currant, and rose hip syrup); when the oral route is not feasible or malabsorption is suspected the vitamin may be given parenterally, preferably by the intramuscular route, but also by the intravenous or subcutaneous routes. Doses used for prevention of deficiency are similar to those used in adults, see Uses and Administration, above. In the treatment of scurvy, oral or parenteral doses range from 100 to 300 mg daily, although higher oral doses have also been suggested; the *BNFC* suggests oral doses according to age:

- 1 month to 4 years: 125 to 250 mg daily in 1 or 2 divided doses
- 4 to 12 years: 250 to 500 mg daily in 1 or 2 divided doses
- 12 to 18 years: 500 to 1000 mg daily in 1 or 2 divided doses

Ascorbic acid may also be given with desferrioxamine to increase the excretion of iron; children from 1 month of age may be given the same dose as adults.

Vitamin C may also be given in the treatment of some inherited metabolic disorders such as tyrosinaemia type III, transient tyrosinaemia of the newborn, glutathione synthase deficiency, and Hawkinsinuria. The *BNFC* suggests the following oral doses for specialist use:

- neonate: 50 to 200 mg daily, adjusted as necessary
- 1 month to 18 years: 200 to 400 mg daily in 1 or 2 divided doses, adjusted as necessary; up to 1 g daily may be required

Non-deficiency disorders. A beneficial effect of vitamin C therapy has been claimed for an extraordinary number of conditions, including age-related macular degeneration (under Betacarotene, p. 2051.2) Alzheimer's disease (see Dementia, under Vitamin E, p. 2120.2), atherosclerosis (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1), cancer (see Prophylaxis of Malignant Neoplasms, p. 2047.3), and the common cold (p. 951.1). Other conditions claimed to benefit include asthma, wound healing, psychiatric disorders, infections due to abnormal leucocyte function, infertility, osteogenesis imperfecta, pain in Paget's disease, tetanus, and opioid withdrawal. Generally there are few properly controlled studies to substantiate these claims. Although preliminary evidence suggested a benefit in prevention of pre-eclampsia, this was not confirmed in later studies (see Hypertension, p. 1251.1). Ascorbic acid is also under investigation for the treatment of Charcot-Marie-Tooth syndrome, a chronic and progressive disorder of the nervous system.

Adverse Effects and Precautions

Ascorbic acid is usually well tolerated. Large doses are reported to cause diarrhoea and other gastrointestinal disturbances. It has also been stated that large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi and ascorbic acid should therefore be given with care to patients with hyperoxaluria (see Effects on the Kidneys, below). Tolerance may be induced with prolonged use of large doses, resulting in symptoms of deficiency when intake is reduced to normal. Prolonged or excessive use of chewable vitamin C preparations may cause erosion of tooth enamel.

Large doses of ascorbic acid have resulted in haemolysis in patients with G6PD deficiency (see Effects on the Blood, below).

Breast feeding. Vitamin C is excreted into breast milk and thus supplied to breast-fed infants. Women in developing countries have significantly lower concentrations of ascorbic acid in their breast milk compared with those in developed countries,[1] and seasonal variation in consumption of foods rich in vitamin C leads to variable amounts of ascorbic acid in breast milk.[2] Supplementation with high-dose ascorbic acid (1 g daily for 10 days) led to significant increases in breast-milk concentrations in both European and African women;[1] however, the overall effect was modest in European women compared with a threefold increase seen in African women. Lower doses of 100 mg daily for 10 days approximately doubled the ascorbic acid breast milk content in the latter, as did supplementation with orange juice 3 or 5 times a week; a significant day-to-day effect was also noted, indicating that the ascorbic acid content of breast milk is regulated. In a small study[2] involving 4 different doses of ascorbic acid supplements, women in West Africa showed that increased intake caused an increase in the ascorbate concentration of breast milk, but concentrations approached a plateau at higher intakes; it was concluded that about 100 to 120 mg of vitamin C daily was needed to achieve acceptable plasma and breast-milk ascorbate concentrations in this population.

1. Daneel-Otterbech S, *et al.* Ascorbic acid supplementation and regular consumption of fresh orange juice increase the ascorbic acid content of human milk: studies in European and African lactating women. *Am J Clin Nutr* 2005; **81:** 1088–93.
2. Bates CJ, *et al.* The effect of vitamin C supplementation on lactating women in Keneba, a West African rural community. *Int J Vitam Nutr Res* 1983; **53:** 68–76.

Effects on the blood. There are reports of haemolysis in patients with G6PD deficiency after large doses of ascorbic acid either intravenously[1,2] or in soft drinks.[3] There has also been a report[4] of a patient with paroxysmal nocturnal haemoglobinuria suffering haemolysis after taking large amounts of ascorbic acid in a soft drink. There is concern that the large quantities of vitamin C in feeds for premature neonates may have a pro-oxidant effect, and lead to haemolysis. However, a double-blind study found no increase in erythrocyte destruction or hyperbilirubinaemia in premature neonates receiving vitamin C.[5]

1. Campbell GD, *et al.* Ascorbic acid-induced hemolysis in G-6-PD deficiency. *Ann Intern Med* 1975; **82:** 810.
2. Rees DC, *et al.* Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *BMJ* 1993; **306:** 841–2.
3. Mehta JB, *et al.* Ascorbic-acid-induced haemolysis in G-6-PD deficiency. *Lancet* 1990; **336:** 944.
4. Iwamoto N, *et al.* Haemolysis induced by ascorbic acid in paroxysmal nocturnal haemoglobinuria. *Lancet* 1994; **343:** 357.
5. Doyle J, *et al.* Does vitamin C cause hemolysis in premature newborn infants? Results of a multicenter double-blind, randomized, controlled trial. *J Pediatr* 1997; **130:** 103–9.

Effects on the kidneys. Although renal impairment associated with excessive oxalate excretion has been reported with large doses of ascorbic acid[1-3] it has been considered that healthy persons can ingest large amounts of ascorbic acid with relatively small increases in oxalate excretion[4-6] and without an increased risk of oxalate stone formation. A study of vitamin C supplementation with 1 or 2 g given daily for 3 days in calcium stone-forming patients, and 1 g given daily for 3 days in healthy subjects, found that urinary oxalate excretion and the risk of calcium oxalate crystallisation increased significantly in all groups.[7] A prospective cohort study found that increased vitamin C intake (over 1 g daily) was positively associated with the risk of stone formation; an increased risk was observed even at lower intakes of about 90 to 250 mg daily. The risk was raised for both dietary and supplemental vitamin C intake. However, the relation between vitamin C intake and stone formation had emerged only after the inclusion of dietary potassium in the analysis, with potassium intake positively associated with dietary vitamin C intake, but inversely associated with stone formation. This led the authors to conclude that, while limiting dietary vitamin C intake in men with calcium oxalate nephrolithiasis was unwarranted (because of the high potassium content of vitamin C-rich foods), supplemental vitamin C should be avoided.[8]

1. Reznik VM, *et al.* Does high-dose ascorbic acid accelerate renal failure? *N Engl J Med* 1980; **302:** 1418–19.
2. Swartz RD, *et al.* Hyperoxaluria and renal insufficiency due to ascorbic acid administration during total parenteral nutrition. *Ann Intern Med* 1984; **100:** 530–1.
3. Balcke P, *et al.* Ascorbic acid aggravates secondary hyperoxalemia in patients on chronic hemodialysis. *Ann Intern Med* 1984; **101:** 344–5.
4. Tsao CS. Ascorbic acid administration and urinary oxalate. *Ann Intern Med* 1984; **101:** 405–6.
5. Wandzilak TR, *et al.* Effect of high dose vitamin C on urinary oxalate levels. *J Urol (Baltimore)* 1994; **151:** 834–7.
6. Curhan GC, *et al.* Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999; **10:** 840–5.
7. Baxmann AC, *et al.* Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int* 2003; **63:** 1066–71.
8. Taylor EN, *et al.* Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol* 2004; **15:** 3225–32.

Effects on mortality. There is some suggestion that serum ascorbic acid concentrations are inversely related to all-cause mortality;[1-4] serum levels were also inversely related to cancer mortality in men but not in women.[1-3] However, a meta-analysis of 3 studies found vitamin C supplementation to have no benefit on mortality in elderly people.[5] A systematic review of antoxidant supplementation in adults also found no significant effect on mortality from studies in which vitamin C was used either singly or with other antoxidants;[6] small beneficial effects or large harmful effects could not be excluded, and since vitamin C can

also act as a pro-oxidant, further studies should monitor closely for any harm.

1. Loria CM, *et al*. Vitamin C status and mortality in US adults. *Am J Clin Nutr* 2000; **72**: 139–45.
2. Simon JA, *et al*. Relation of serum ascorbic acid to mortality among US adults. *J Am Coll Nutr* 2001; **20**: 255–63.
3. Khaw K-T, *et al*. Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. *Lancet* 2001; **357**: 657–63.
4. Fletcher AE, *et al*. Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Am J Clin Nutr* 2003; **78**: 999–1010.
5. Ness A, *et al*. Role of antioxidant vitamins in prevention of cardiovascular diseases. *BMJ* 1999; **319**: 577.
6. Bjelakovic G, *et al*. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Effects on the teeth. A report of dental enamel erosion attributed to the daily ingestion of chewable ascorbic acid tablets over a period of 3 years.[1] The tablets lowered the pH of the saliva to a level at which calcium was lost from the tooth enamel.

1. Giunta JL. Dental erosion resulting from chewable vitamin C tablets. *J Am Dent Assoc* 1983; **107**: 253–6.

Interference with laboratory tests. Ascorbic acid, a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely-elevated or false-negative test results may be obtained from plasma, faeces, or urine samples depending on such factors as the dose of ascorbic acid and specific method used.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ascorbic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

For the effect of ascorbic acid on various drugs see under desferrioxamine (p. 1547.3), hormonal contraceptives (p. 2244.1), HRT (p. 2251.2), fluphenazine (under Chlorpromazine, p. 1053.3), and warfarin (p. 1535.3). Ascorbic acid may increase the absorption of iron in iron-deficiency states. Omeprazole may affect the bioavailability of dietary vitamin C (see Malabsorption, under Omeprazole, p. 1870.2).

Pharmacokinetics

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma.

Ascorbic acid is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate-2-sulfate, which is inactive, and oxalic acid which are excreted in the urine. Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine; this generally occurs with intakes exceeding 100 mg daily. Ascorbic acid crosses the placenta and is distributed into breast milk. It is removed by haemodialysis.

Human Requirements

A daily dietary intake of about 30 to 100 mg of vitamin C has been recommended for adults. There is, however, wide variation in individual requirements. Humans are unable to form their own ascorbic acid and so a dietary source is necessary. Most dietary ascorbic acid is obtained from fruit and vegetable sources; only small amounts are present in milk and animal tissues. Relatively rich sources include rose hips (rose fruit), black currant, citrus fruits, leafy vegetables, tomatoes, potatoes, and green and red peppers.

Ascorbic acid is readily destroyed during cooking processes. Considerable losses may also occur during storage.

General references.

1. Deruelle F, Baron B. Vitamin C: is supplementation necessary for optimal health? *J Altern Complement Med* 2008; **14**: 1291–8.
2. Berger MM. Vitamin C requirements in parenteral nutrition. *Gastroenterology* 2009; **137** (suppl): S70–S78.
3. Lykkesfeldt J, Poulsen HE. Is vitamin C supplementation beneficial? Lessons learned from randomised controlled trials. *Br J Nutr* 2010; **103**: 1251–9.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p. 2046.1) have been published for vitamin C and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 40 mg daily for adult males and females and the estimated average requirement (EAR) is 30 mg daily. In general the amount recommended in the USA for all ages and groups is higher than that set in the UK; the RDA is 90 mg daily for men and 75 mg daily for women.[2] The RDA is increased in smokers by 35 mg daily. The tolerable upper intake level is 2 g daily.[2] The EAR is 75 mg daily for men and 60 mg daily for women.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids*. Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: C-Vitamin; Cellskinlab Serum 15; Cewin; Citrocola; Citrovita†; Gynefix; Redoxon; Urosedac; Vicenrik; Vita Fizz C; ***Austral.***: Cal C; Redoxon†; Sugarless C; VagiCare; ***Austria***: Ascorbin; C-Vit; Ce-Limo; Cebion; Cetebe; Cevitol; Iroviton Vitamin C; Mel-C†; ***Belg.***: C-Will; Cetamine; Cevi-drops†; Megavitin-C; Redoxon†; Redoxon; Upsa C; ***Braz.***: Aceina; Acerogrip C; Active C; Bio-C; Cebion; Ceglen; Cenevit; Cetivit; Cetozone†; Cevita; Ceviton†; Cewin; Citroplex; Citrovit; Coristina Vitamina C; Energil C; Fonto-Vit C†; Hidracid C20; Hydracid; Redoxon; Vagi C; Vi-Ce; Vitacin; Vitamice; Vitaxon C; Vitergyl C; ***Canad.***: Apo-C†; Ascorbplex; Bio-C; C 1000; C 3000†; Ester-C; Formula 1 Bio-C†; Formula 2 Bio-C†; Formula 2†; Inf IC†; Kyolic Formula 103†; Liqui C†; Mega-C; Orti C†; Poly C; Prevegyne; Proflavanol C†; Redoxon; Revitonus C†; Scorbatate†; Super C; Super LSN†; Time Rel Vit C†; UPC†; Vicks Vitamin C Orange; ***Chile***: Cebion; Crevet L; Crevet; Esvit C; Mintavit-C; Necta C; Serum 15; Vitac; Vitaseve; ***China***: Da Wei Xin (达维欣); Gao Xi (高喜); Jia Xin (嘉欣); Redoxon (力度伸); Upsa C (维善希); Wei Ti Yin (维体因); Xin Wei Xi (新维喜); ***Cz.***: Additiva; C-Vitamin; Celaskon; ***Denm.***: Bio-C; C-Tabs†; Mega C; Vita Care C-Long†; ***Fin.***: Ascorbin†; Bio-C-Vitamin†; C-vimin; Cevi-Tabs†; Poremax-C; ***Fr.***: Laroscorbine; Vitascorbol; ***Ger.***: Ascorell; Ascorvit; Cebion†; Cetebe; Forum C†; Hermes Cevitt; Macalvit†; Pascorbin; Vagi-C; ***Gr.***: Ascorbine; Cebion; Pascorbin; Redoxon; Vicef; Viforcit; Vitorange; ***Hong Kong***: Cecap; Celin†; Cetrinets; Cevitt†; Cevizo†; Champs Junior†; Cibion†; Delrosa; Flavettes†; Poten-Cee†; Redoxon†; Vorange; ***Hung.***: Beres C; Cebion; Cetebe; Hermes Cevitt; Vitascor†; ***India***: Acicon; Aquasol C; Aquasol Ceezed; Bex-C; C-Vit; Cecon; Celin; Cell-C; Frutcee; Immunex; Limcee; Lincee; Sukcee; ***Indon.***: Askorbin; Bekamin C; Biferce; Candyvit-C; Cebion†; Ceelin; Champs C; Ever Ce†; Extrace; Fit-C; Flavettes; Sankorbin; Scott's Chewyvit C; Sweeta C; Vicee; Vitacimin; Vitalong C TRC; Vitamex C†; Xon-Ce; Zevit C; ***Irl.***: Haliborange Vitamin C; Redoxon†; Rubex; ***Israel***: C-Tamin; C500†; Moviprep; Redoxon; ***Ital.***: Addivita; Agruvit; Bio-Ci; C Monovit†; C-Tard; Cebion; Cimille; Duo-C†; Dynaphos C; Redoxon; Univit; Vici; ***Jpn***: Hicee; ***Malaysia***: Ascorbin†; Cecap; Ceelin†; Chewette; Citrex Vitamin C; Upha C; Vita C; ***Mex.***: Active C; C-Messel; Ce-Vi-Sol†; Cevalin; Femiprim; Gomas Garde G; Noratoquin; Oxital C; Poly C; Ramy CE; Redoxon; Sinesmin; ***Mon.***: Prevegyne; ***Neth.***: C-Will; Dayvital; ***Norw.***: Bio-C; Nycoplus C-vitamin; ***NZ***: Redoxon; ***Philipp.***: A-Cee; Alka-C; Asconvita; Ascorbin; Ascorcee; Bonalet-Cee; C-4-Kids; Calcebone; Calcimed; CareZee; Ce-Vi-Sol; Cecon; Cee-protect; Ceelin; Ceenergy; Ceetrus; Cetrasol; Cetrinets; Chewette C; Chilcee; Chilvit-Cee; Citrucin; Cixtor; Clusivol Power C; Day-C-Vit; Daycee; EconoCee; Esviceе†; Excel C; EZZ-C; Fern-C; Iconcee; Incee-Vit; Medcee; Myrevit-C; Neo-C; Nutra-Cee; Nutricee; Pedcee; Pediafortan-C; Poten-Cee; Provit-Cee; Supravit-C†; Tropicee; Vamcee; Vi-Cee; Vita-Procee; Zerrucee; ***Pol.***: Ascorgem; Ascorvita; Cebion; Cetebe; Cevikap; Juvit; Monovitan C†; Vicefar; Vita-Gem C; ***Port.***: Anti-rugas C†; C'Nergil; Cebiolon; Cebion; Cecon†; Cecrisina; Redoxon; Vitaminac Retard; Vivin C†; ***Rus.***: Ascovit (Асковит); Celascon (Целаскон); Cetebe (Сетебе); Cevikap (Цевикап); Citravit (Цитравит); Rostvit (Роствит); Upsavit Vitamin C (Упсавит Витамин С); Vaginorm-C (Вагинорм-С); ***S.Afr.***: Scorbex; Vitaforce C†; Vitaforce Massif-C†; ***Singapore***: Active C; Ascorbin; Biferce; Cebion; Ceelin; Champs C†; Dancimin-C; Flavettes†; Gummi King (Vit C); High-C; Redoxon†; Vorange; ***Spain***: Cebion; Citrovit†; Redoxc; Redoxon†; ***Swed.***: C-vimin; Ido-C; ***Switz.***: Cetebe; Demovit C; Redoxon; Vitacen C; ***Thai.***: Ascee 500; Bio-C; C Mon; C-Coated; C-Mic; C-Will; CEE; Cibic; Fa-c†; Hicee; MAG-C; Mancevit†; Med-C; Mita-C; Mymin C; Sweetcee; Teddy-C; V-C†; Vio C; Vit C Frx; Vit C-Mile; Vitacee; Vitacimin; Vitamin Cee; Zee; ***Turk.***: C-plan; Ester Vit; Hermess Cevitt; Monovit-C; Natrol C; Redoxon; Vagi-C; Vitabiol C; ***UK***: Buffered C 500; Buffered C; Haliborange Halibonbons; Redoxon; ***Ukr.***: Celaskon (Целаскон)†; Cyclo 3 Fort (Цикло 3 Форт); Vaginorm C (Вагинорм С); ***USA***: Asco-Caps†; Ascocid; Ascor; Cecon†; Cenolate†; Cevi-Bid†; Chew-C; Dull-C; Halls Defense; N'ice Vitamin C; Sunkist; Vita-C; ***Venez.***: Cebion; Cevax; Cevit; Vitadyn C; Vitrexon.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. ***Arg.***: Anemidox Ultra; Anemidox-Ferrum; Anemidox-Solutab; Ferdromaco; Ferro Folic; Ferrocebrina; Hierro Folico; Hierro Plus†; Iberol; Rubiron; Sideralce; Tardyferon; ***Austral.***: Bio Iron; FAB; Ferrograd C; Iron Max; ***Austria***: Ferretab; Losferron; ***Belg.***: Fero-Grad; Losferron; ***Braz.***: Cobaldoze†; Combiron; Dobiron; Ferrocomplex; Ferroplex; Iberin Folico; Iberol; Iloban; Novofer; Sulfato Ferroso Composto; ***Canad.***: Neo-Fer CF; Palafer CF; ***Chile***: Confer; Ferranem; Ferranim; Ferro Vitaminico†; Folifer; Iberol Folico†; Iberol†; ***Cz.***: Ferro-Folgamma; Losferron†; Sorbifer; Tardyferon-Fol; Tardyferon; ***Fin.***: Duroferon; ***Fr.***: Bio-Fer†; Fero-Grad vitamine C; Tardyferon B_9; Tardyferon; Timoferol; ***Ger.***: Ferro-Folgamma; Kendural C; Kendural-Fol-500†; Losferron; Tardyferon-Fol; Tardyferon; ***Hong Kong***: Iberet-Folic†; Iberet†; ***Hung.***: Ferro-Folgamma; Floradix; Sorbifer; Tardyferon-Fol; ***India***: Alamin-Fez; Anemidox; Autrin; Carnyl-FE; Conviron-TR; Hematrine; Hepasules†; Siderfol; ***Indon.***: Adfer; Bioferron; Bionemi; Biosanbe; Dasabion; Emibion; Emineton; Fercee; Feritrin; Ferofort; Habebion†; Hemafort; Hemarate CE†; Hemobion; Iberet-Folic; Iberet; Inbion; Natabion; Neogobion; Nephrovit-Fe; Nichobion; Nonemi; Nufagrabion-GM; Nufagrabion; Odiron-C†; Opibion; Ovabion; Prenamia; Prenatin-DF; Sangobion; Sangofer; Sangovitin†; Solvitral; Suprabion; Veroscan; Vica-Natal; Viliron; Vitabion; Vitalex; Vitonal; ***Irl.***: Ferrograd C; ***Ital.***: Auxofer†; Bioferal; Bioglufer; Blustark†; Crom; Cromatonferro; Effegyn; Ergon; Eritropiu; Ferro Complex; Ferrograd C; Ferrograd Folic; Ferrogyn; Gloros; Losferron; Megafer; Monoferro†; Niferex; Prontoferro; Sidervim; ***Malaysia***: Iberet-Folic; Opibion; Sangobion; ***Mex.***: Autrin; Ferro Folico; Fumarol†; Iberet†; Iberol†; ***Neth.***: Losferron; ***Norw.***: Duroferon; Niferex; ***NZ***: Ferrograd C; ***Philipp.***: Appetite OB; Iberet-Folic; Iberet; Imefer; Macrobee with Iron; Magniferron; Micron-C; Molvite with Iron; Mulvitron; Odiron-C†; Sangobion; Sorbifer; Terraferron; TriHEMIC; ***Pol.***: Additiva Ferrum†; Ascofer; Sorbifer; Tardyferon-Fol; Tardyferon; ***Rus.***: Fenules (Фенюльс); Ferro-Folgamma (Ферро-Фольгамма); Ferroplex (Ферроплекс); Gyno-Tardyferon (Гино-тардиферон); Hematogen C (Гематоген С); Hematogen C Vita (Гематоген С Вита); Sorbifer (Сорбифер); ***S.Afr.***: Autrin†; Fero-Folic; Fero-Grad†; Foliglobin; ***Singapore***: Iberet-Folic; Iberet; Iron Melts; Neogobion; Odiron-C; Opibion; Sangobion; ***Swed.***: Duroferon; ***Switz.***: Duofer Fol; Duofer; Fero-Folic; Ferrascorbin†; Kendural; Lufer†; ***Thai.***: Glufer-C†; Iberet; Sangobion†; ***Turk.***: Ferro-Vital†; Gyno-Tardyferon; Vi-Fer; ***UK***: Ferrograd C; Floradix; ***Ukr.***: Fenules (Фенюльс)†; Gyno-Tardyferon (Гино-Тардиферон); Sorbifer (Сорбифер); Tardyferon (Тардиферон); ***USA***: Chromagen FA; Chromagen Forte; Chromagen†; Contrin; Feocyte; FeoGen; Fero-Folic; Fero-Grad; Ferotrinsic; Ferralet 90; Ferrex Forte Plus†; Ferrex Plus; Ferrogels Forte; Fetrin; Fumatinic†; Hem Fe; Hematinic Plus; I-L-X; Icar-C Plus; Iron 100 Plus; Irospan; Livitrinsic-f†; Multigen; Niferex Forte; Niferex; Pronemia Hematinic; Tandem Plus; TL Icon; Tolfrinic; TriHEMIC; Trimagen†; Trinsicon†; Vitagen Advance; Vitron-C; ***Venez.***: Fefol; Ferro-Folic; Ferroce B12; Ferroce; Ferronorm; Hepafol con B-12; Iberol C.

Pharmacopoeial Preparations

BP 2014: Ascorbic Acid Injection; Ascorbic Acid Tablets; Chewable Ascorbic Acid Tablets; Paediatric Vitamins A, C and D Oral Drops; Vitamins B and C Injection;

USP 36: Ascorbic Acid Injection; Ascorbic Acid Oral Solution; Ascorbic Acid Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets; Zinc and Vitamin C Lozenges.

Vitamin D Substances

Vitamina D; Витамины Группы D.

The term vitamin D is used for a range of closely related sterol compounds including alfacalcidol, calcifediol, calcitriol, colecalciferol, dihydrotachysterol, and ergocalciferol. Newer vitamin D analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol.

Alfacalcidol *(BAN, rINN)*

Alfacalcidolum; Alfakalcidol; Alfakalcidolis; Alfakalsidol; Alfakalsidoli; EB-644; 1-α-Hidroxivitamina D_3; 1α-Hydroxycholecalciferol; 1α-Hydroxyvitamin D_3; 1α-OHD_3; Альфакальцидол.

(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β-diol.

$C_{27}H_{44}O_2$=400.6

CAS — 41294-56-8.

ATC — A11CC03.

ATC Vet — QA11CC03.
UNII — URQ2517572.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Alfacalcidol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-alfacalcidol takes place in solution, depending on temperature and time. Activity is due to both compounds. Store at 2 degrees to 8 degrees under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

Calcifediol *(BAN, USAN, rINN)*

Calcidiol; Calcifédiol; Calcifediolum; Calcifediolum Monohydricum; 25-Hidroxicolecalciferol; 25-Hidroxivitamina D_3; 25-Hydroxycholecalciferol; 25-Hydroxyvitamin D_3; Kalcifediol; Kalcifediol monohydrát; Kalcifediolis; Kalcyfediol; Kalsifedioli; 25-(OH)D_3; U-32070E; Кальцифедиол.
(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-3β,25-diol monohydrate.
$C_{27}H_{44}O_2,H_2O$=418.7
CAS — 19356-17-3 (anhydrous calcifediol); 63283-36-3 (calcifediol monohydrate).
ATC — A11CC06.
ATC Vet — QA11CC06.
UNII — P6YZ13C99Q (calcifedol); T0WXW8F54E (anhydrous calcifediol).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Calcifediol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-calcifediol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2 degrees to 8 degrees under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

USP 36: (Calcifediol). Store in airtight containers. Protect from light.

Calcitriol *(BAN, USAN, rINN)*

1α,25(OH)$_2$$D_3$; Calcitriolum; 1α,25-Dihidroxivitamina D_3; 1,25-Dihydroxycholecalciferol; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D_3; Kalcitriol; Kalcitriolis; Kalcytriol; Kalsitriol; Kalsitrioli; Ro-21-5535; Кальцитриол.
(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,25-triol.
$C_{27}H_{44}O_3$=416.6
CAS — 32222-06-3 (anhydrous); 77326-95-5 (monohydrate).
ATC — A11CC04; D05AX03.
ATC Vet — QA11CC04; QD05AX03.
UNII — FXC9231JVH.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Calcitriol). White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. It is sensitive to air, heat, and light. A reversible isomerisation to pre-calcitriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2 degrees to 8 degrees under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

USP 36: (Calcitriol). It may be anhydrous or contain one molecule of hydration. White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in ether and in fatty oils. Store in airtight containers. Protect from light.

Colecalciferol *(BAN, rINN)*

Activated 7-Dehydrocholesterol; Cholécalciférol; Cholecalciferol; Cholecalciferolum; Cholekalciferol; Cholekalciferolis; Cholekalcyferol; Colécalciférol; Colecalciferolum; Kolekalciferol; Kolekalsiferol; Kolekalsiferoli; Vitamin D_3; Vitamina D_3; Колекальциферол.
(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-trien-3β-ol.
$C_{27}H_{44}O$=384.6
CAS — 67-97-0.
ATC — A11CC05.
ATC Vet — QA11CC05.
UNII — 1C6V77QF41.

Description. Colecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Eur. also includes monographs for concentrates in an oily form, a powder form, and a water-dispersible form. *US* also includes a solution.

Ph. Eur. 8: (Colecalciferol; Colecalciferol BP 2014). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in trimethylpentane and in fatty oils. Solutions in solvents without an antoxidant are unstable and should be used immediately. A reversible isomerisation to pre-colecalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2 degrees to 8 degrees. The contents of an opened container should be used immediately. Protect from light.

The BP 2014 directs that when calciferol or vitamin D is prescribed or demanded, Colecalciferol or Ergocalciferol shall be dispensed or supplied.

Ph. Eur. 8: (Cholecalciferol Concentrate (Oily Form); Cholecalciferolum Densatum Oleosum; Colecalciferol Concentrate (Oily Form) BP 2014). A solution of colecalciferol in a suitable vegetable oil. It contains not less than 500 000 units/g. It may contain suitable stabilisers such as antoxidants. A clear, yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; miscible with solvents of fats. Partial solidification may occur, depending on the temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.

Ph. Eur. 8: (Cholecalciferol Concentrate (Powder Form); Cholecalciferoli Pulvis; Colecalciferol Concentrate (Powder Form) BP 2014). It is obtained by dispersing an oily solution of colecalciferol in an appropriate matrix which is usually based on a combination of gelatin and carbohydrates of suitable quality. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antoxidants. White or yellowish-white, small particles. Depending on their formulation, it may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.

Ph. Eur. 8: (Cholecalciferol Concentrate (Water-dispersible Form); Cholecalciferolum in Aqua Dispergibile; Colecalciferol Concentrate (Water-dispersible Form) BP 2014). A solution of colecalciferol in a suitable vegetable oil to which suitable solubilisers have been added. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antoxidants. A slightly yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or form a gel at room temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of inert gas.

USP 36: (Cholecalciferol). White, odourless crystals. Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils. M.p. about 85 degrees. It is affected by air and light. Store under nitrogen in hermetically sealed containers at a temperature of 8 degrees to 15 degrees. Protect from light.

USP 36: (Cholecalciferol Solution). A solution of colecalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. Store in airtight containers. Protect from light.

Dihydrotachysterol *(BAN, rINN)*

Dichysterol; Dihidrotakisterol; Dihidrotaquisterol; Dihydrotachystérol; Dihydrotachysterolum; Dihydrotakisterol; Dihydrotakysterol; Dihydrotakysteroli; Дигидротахистерол.
(5*E*,7*E*,22*E*)-10α-9,10-Secoergosta-5,7,22-trien-3β-ol.
$C_{28}H_{46}O$=398.7
CAS — 67-96-9.
ATC — A11CC02.
ATC Vet — QA11CC02.
UNII — R5LM3H112R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dihydrotachysterol). Colourless crystals, or a white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in *n*-hexane. Store under an inert gas in airtight containers at 2 degrees to 8 degrees.

USP 36: (Dihydrotachysterol). Colourless or white, odourless crystals, or white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform and in ether; sparingly soluble in vegetable oils. Store in hermetic glass containers from which the air has been displaced by an inert gas. Protect from light.

Doxercalciferol *(USAN, rINN)*

Doxercalciférol; Doxercalciferolum; 1α-Hidroxivitamina D_2; 1α-Hydroxyergocalciferol; 1α-Hydroxyvitamin D_2; 1α-OH-D_2; Доксэркальциферол.
(5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraene-1α,3β-diol.
$C_{28}H_{44}O_2$=412.7
CAS — 54573-75-0.
ATC — H05BX03.
ATC Vet — QH05BX03.
UNII — 3DIZ9LF5Y9.

Ergocalciferol *(BAN, rINN)*

Calciferol; Ergocalciférol; Ergocalciferolum; Ergokalciferol; Ergokalciferolis; Ergokalsiferol; Ergokalsiferoli; Irradiated Ergosterol; Viosterol; Vitamin D_2; Vitamina D_2; Эрокальциферол.
(5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraen-3β-ol.
$C_{28}H_{44}O$=396.7
CAS — 50-14-6.
ATC — A11CC01.
ATC Vet — QA11CC01.
UNII — VS041H42XC.

Description. Ergocalciferol is an antirachitic substance obtained from ergosterol, a sterol present in fungi and yeasts, by ultraviolet irradiation.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Ergocalciferol). White or almost white, crystals or white or slightly yellowish crystalline powder. It is sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Solutions in volatile solvents are unstable and should be used immediately. A reversible isomerisation to pre-ergocalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2 degrees to 8 degrees. The contents of an opened container should be used immediately. Protect from light.

The BP 2014 directs that when calciferol or vitamin D is prescribed or demanded, Ergocalciferol or Colecalciferol shall be dispensed or supplied.

USP 36: (Ergocalciferol). White, odourless crystals. It is affected by air and light. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils. Store in hermetically sealed containers under nitrogen at a temperature of 8 degrees to 15 degrees. Protect from light.

Falecalcitriol *(rINN)*

Falécalcitriol; Falecalcitriolum; Flocalcitriol; Hexafluorocalcitriol; Ro-23-4194; ST-630; Фалекальцитриол.
(+)-(5*Z*,7*E*)-26,26,26,27,27,27-Hexafluoro-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol.
$C_{27}H_{38}F_6O_3$=524.6
CAS — 83805-11-2.
UNII — G70A8514T8.

Maxacalcitol *(USAN, rINN)*

1α,25-Dihydroxy-22-oxavitamin D_3; Maxacalcitolum; OCT; 22-Oxacalcitriol; Sch-209579; Максакальцитол.
(+)-(5*Z*,7*E*,20*S*)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol.
$C_{26}H_{42}O_4$=418.6
CAS — 103909-75-7.
UNII — N2UJM5NBF6.

Paricalcitol *(USAN, rINN)*

ABT-358; Compound 49510; Paracalcin; Paricalcitolum; Парикальцитол.
(7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol.
$C_{27}H_{44}O_3$=416.6
CAS — 131918-61-1.
ATC — H05BX02.
ATC Vet — QH05BX02.
UNII — 6702D36OG5.

Pharmacopoeias. In *US.*

USP 36: (Paricalcitol). A white to almost white powder. Insoluble in water; soluble in alcohol. Store under argon in airtight containers at a temperature of -25 degrees to -10 degrees.

Units

The Second International Standard Preparation (1949) of vitamin D consisted of bottles containing about 6 g of a solution of colecalciferol in vegetable oil (1000 units/g). This standard has now been discontinued.

NOTE. Pharmacopoeias consider that one unit of vitamin D is contained in 25 nanograms of colecalciferol or ergocalciferol (i.e. 1 mg of colecalciferol or ergocalciferol is equivalent to 40 000 units of vitamin D as determined by bioassay in *rats*), but see below.

Equivalence. It has been proposed that units of vitamin D be defined in moles or molecules rather than weight terms; in which case, 1 unit of colecalciferol and ergocalciferol would be equivalent to 25 nanograms and 25.78 nanograms, respectively. This inequivalence in units might confound optimal vitamin D dosing recommendations.[1] For the view that colecalciferol is more potent than ergocalciferol, and should be preferred for vitamin D supplementation, see Administration, below.

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am J Clin Nutr* 2006; **84:** 694–7.

Uses and Administration

Vitamin D compounds are fat-soluble sterols, sometimes considered to be hormones or hormone precursors, which are essential for the proper regulation of calcium and phosphate homoeostasis and bone mineralisation.

Vitamin D deficiency develops when there is inadequate exposure to sunlight or a lack of the vitamin in the diet. Deficiency generally takes a long time to develop because of slow release of the vitamin from body stores. It may occur in some infants who are breast fed without supplemental vitamin D or exposure to sunlight, in the elderly whose mobility and thus exposure to light may be impaired, and in persons with fat malabsorption syndromes; certain disease states such as renal failure may also affect the metabolism of vitamin D substances to metabolically active forms and thus result in deficiency.

Deficiency leads to the development of a syndrome characterised by hypocalcaemia, hypophosphataemia, undermineralisation or demineralisation of bone, bone pain, bone fractures, and muscle weakness, known in adults as osteomalacia (see p. 2116.2). In children, in whom there may be growth retardation and skeletal deformity, especially of the long bones, it is known as rickets.

Vitamin D compounds are used in the treatment and prevention of vitamin D deficiency states and hypocalcaemia in disorders such as hypoparathyroidism and secondary hyperparathyroidism, p. 2115.3 and p. 2115.2, respectively.

Many forms and analogues of vitamin D are available, and the choice of agent depends on the cause of the condition to be treated and the relative properties of the available agents. Colecalciferol and ergocalciferol are traditionally considered equal in potency (but see Administration, below), and have a slow onset and relatively prolonged duration of action. Dihydrotachysterol has relatively weak antirachitic activity, but its actions are faster in onset and less persistent than those of the calciferols and it does not require renal hydroxylation. Calcifediol, an intermediate metabolite, has some action of its own but is also converted to the more potent 1,25-dihydroxycholecalciferol (calcitriol); calcitriol and its analogue alfacalcidol are the most potent and rapidly acting of the vitamin D substances.

- For the treatment of simple nutritional deficiencies **colecalciferol** or **ergocalciferol** are generally preferred. They are usually given orally, but may also be given by intramuscular injection. A dose of 10 micrograms (400 units) daily is generally sufficient in adults for the prevention of simple deficiency states; in the UK, 20 micrograms (800 units) daily is recommended in those whose exposure to sunlight is limited, in those whose diet is deficient in vitamin D, and in housebound or institutionalised elderly people. Deficiency due to malabsorption states or liver disease often requires higher doses for treatment, of up to 1 mg (40 000 units) daily. Doses of up to 5 mg (200 000 units) daily may be used in the treatment of hypocalcaemia due to hypoparathyroidism.
- Where large doses are required it may be preferable to use one of the more potent derivatives. In particular, when renal function is impaired as in secondary hyperparathyroidism associated with chronic renal failure, with consequent reduction in the conversion of calciferols to their active metabolites, then a drug such as alfacalcidol, calcitriol, doxercalciferol, maxacalcitol, or paricalcitol, which does not require renal hydroxylation, should be given.

  Calcitriol is given orally or by intravenous injection. Usual initial oral doses of 250 nanograms daily or on alternate days are given, increased if necessary, in steps of 250 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 1 microgram daily. Initial doses intravenously are usually 500 nanograms three times a week increased if necessary in steps of 250 to 500 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 3 micrograms three times a week. For moderate to severe secondary hyperparathyroidism in dialysis patients initial doses of 0.5 to 4 micrograms have been given three times a week, increased if necessary in steps of 250 nanograms to 1 microgram at intervals of 2 to 4 weeks to a maximum of 8 micrograms given three times a week.

  Alternatively, **alfacalcidol** is given in initial oral doses of 1 microgram daily, or 500 nanograms for elderly patients. Doses of 0.25 to 1 microgram daily may be given for maintenance. Doses of alfacalcidol may also be given by intravenous injection over 30 seconds.

  Doxercalciferol is given orally or by intravenous injection. The initial oral dose is 10 micrograms three times weekly at dialysis, increased by increments of 2.5 micrograms after 8 weeks if necessary. The maximum recommended oral dose is 20 micrograms three times weekly. The initial intravenous dose is 4 micrograms given three times weekly at dialysis, and increased after 8 weeks in increments of 1 to 2 micrograms if required. Doses are titrated according to parathyroid hormone concentrations.

  Maxacalcitol is given intravenously at a dose of 2.5 to 10 micrograms three times weekly; the dose may be gradually increased if necessary, to a maximum of 20 micrograms three times weekly.

  Paricalcitol is given intravenously in the USA at a dose of 40 to 100 nanograms/kg on alternate days or less frequently; in the UK the initial dose (in micrograms) is calculated by dividing the baseline intact parathyroid hormone concentration (in picograms/mL) by 80. The dose may be increased or decreased if necessary by 2 to 4 micrograms at intervals of 2 to 4 weeks, based on parathyroid hormone concentrations. Paricalcitol is also given orally either as a daily dose or three times weekly (no more frequently than every other day). Again, the initial dose is based on baseline intact parathyroid hormone concentrations. If these are 500 picograms/mL or less, paricalcitol is given at a dose of 1 microgram daily, or 2 micrograms three times weekly; if they are above 500 picograms/mL, paricalcitol 2 micrograms daily, or 4 micrograms three times weekly is suggested. Doses are titrated according to parathyroid hormone concentrations.
- Of the other available forms, **calcifediol**, the 25-hydroxylated metabolite of colecalciferol, may be given in oral doses of up to about 500 micrograms daily for most indications. For hypocalcaemic tetany due to hypoparathyroidism, **dihydrotachysterol** is given in initial oral doses of 750 to 2500 micrograms daily, depending on severity, for about three days. Maintenance doses have ranged from 250 micrograms weekly to 1000 micrograms daily.

When vitamin D substances are given in pharmacological doses, dosage must be individualised for each patient, and should be based on regular monitoring of plasma-calcium concentrations (initially once or twice weekly), to optimise clinical response and avoid hypercalcaemia.

For doses in children, see below and Osteomalacia and Rickets, p. 2116.2.

Vitamin D, usually in the form of calcitriol, may be used in the treatment of osteoporosis (see p. 2116.3). In established postmenopausal osteoporosis, calcitriol 0.25 micrograms twice daily is recommended. Vitamin D and calcium supplements are often given as adjuncts to other therapies in osteoporosis.

Calcitriol has been used in the management of psoriasis (see p. 2117.1); a topical formulation containing maxacalcitol 0.0025% is also available in some countries.

Calciferol derivatives are used as rodenticides.

General references.

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4. Holick MF. Vitamin D: importance in the prevention of cancers, type I diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004; **79:** 362–71.
5. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89:** 552–72.
6. Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. *J Clin Endocrinol Metab* 2003; **88:** 5107–8.
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9. Calvo MS, *et al*. Vitamin D intake: a global perspective of current status. *J Nutr* 2005; **135:** 310–16.
10. Bandeira F, *et al*. Vitamin D deficiency: a global perspective. *Arq Bras Endocrinol Metabol* 2006; **50:** 640–6.
11. Mason P. Vitamin D—function and uses. *Pharm J* 2006; **277:** 227–30.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357:** 266–81.
13. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87:** 1080S–1086S.
14. Kulie T, *et al*. Vitamin D: an evidence-based review. *J Am Board Fam Med* 2009; **22:** 698–706. Correction. *ibid.* 2010; **23:** 138.
15. Borradale D, Kimlin M. Vitamin D in health and disease: an insight into traditional functions and new roles for the 'sunshine vitamin'. *Nutr Res Rev* 2009; **22:** 118–36.
16. Bischoff-Ferrari H. Vitamin D: what is an adequate vitamin D level and how much supplementation is necessary? *Best Pract Res Clin Rheumatol* 2009; **23:** 789–95.
17. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010; **340:** b5664.
18. Chesney RW. Vitamin D and the Magic Mountain: the anti-infectious role of the vitamin. *J Pediatr* 2010; **156:** 698–703.

Administration. Minor differences in the chemistry of the side-chains of ergocalciferol and colecalciferol lead to the production of different metabolites (see Pharmacokinetics, p. 2118.1).[1] Colecalciferol has been reported to raise serum vitamin D concentrations more effectively than ergocalciferol,[2,3] perhaps because of higher affinities of colecalciferol and its metabolites for liver enzymes, plasma vitamin D binding protein, and vitamin D receptors.[1] It has been suggested that 50 000 units of ergocalciferol should be considered equivalent to no more than 15 000 units of colecalciferol, and perhaps closer to 5000 units; the tolerable upper intake level (see UK and US recommended dietary intake, p. 2118.1) ought not to be applied to ergocalciferol.[3] These differences and the inequivalence in units (see Equivalence, under Units, above) may confound optimal vitamin D dosing recommendations.[1,3] The form of vitamin D used in studies should be specified.[2] While ergocalciferol is effective in treating vitamin D deficiency, the differences in potency have led some to suggest that colecalciferol be used as the preferred form of vitamin D.[1,3]

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am J Clin Nutr* 2006; **84:** 694–7.
2. Trang HM, *et al*. Evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D_2. *Am J Clin Nutr* 1998; **68:** 854–8.
3. Armas LAG, *et al*. Vitamin D_2 is much less effective than vitamin D_3 in humans. *J Clin Endocrinol Metab* 2004; **89:** 5387–91.

Administration in children. Vitamin D compounds are used to treat deficiency states in children. The *BNFC* suggests initial doses for various indications which should be adjusted thereafter as necessary.

Colecalciferol or **ergocalciferol** can be used to treat nutritional vitamin D deficiency rickets; oral doses vary according to age:

- 1 to 6 months: 75 micrograms (3000 units) daily
- 6 months to 12 years: 150 micrograms (6000 units) daily
- 12 to 18 years: 250 micrograms (10 000 units) daily

Higher initial doses are required in vitamin D deficiency due to intestinal malabsorption or in chronic liver disease, and may be given orally or by intramuscular injection:

- 1 to 12 years: 250 to 625 micrograms (10 000 to 25 000 units) daily
- 12 to 18 years: 250 to 1000 micrograms (10 000 to 40 000 units) daily

Alfacalcidol is used to treat hypophosphataemic rickets, persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism (see also p. 2115.3) in children. Dose may be given orally or by intravenous injection, according to age:

- 1 month to 12 years: 25 to 50 nanograms/kg (maximum 1 microgram) daily
- 12 to 18 years: 1 microgram daily

For persistent neonatal hypocalcaemia, an initial dose of alfacalcidol 50 to 100 nanograms/kg daily may be given orally or by intravenous injection; up to 2 micrograms/kg daily may be needed in resistant cases.

There is less experience with **calcitriol** and it is unlicensed in the UK for use in children, but it may be given for vitamin D dependent rickets, hypophosphataemic rickets, persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism. Doses are given orally according to age:

- 1 month to 12 years: 15 nanograms/kg (maximum 250 nanograms) daily, increased if necessary in steps of 5 nanograms/kg (maximum 250 nanograms) every 2 to 4 weeks
- 12 to 18 years: 250 nanograms daily, increased if necessary in steps of 5 nanograms/kg (maximum 250 nanograms) every 2 to 4 weeks; the usual dose is 0.5 to 1 microgram daily

Hypocalcaemia in dialysis patients may also be treated with calcitriol; intravenous injection of 250 to 500 nanograms (approximately 10 nanograms/kg) may be given three times weekly to children aged 12 to 18 years. This can be increased if needed in steps of 2 to 5 nanograms/kg every 2 to 4 weeks; the usual dose is 0.5 to 3 micrograms three times weekly.

For discussion on doses of vitamin D considered sufficient for prophylaxis of rickets, see UK and US Recommended Dietary Intake, p. 2118.1 and Osteomalacia and Rickets, p. 2116.2. Further discussion on specific disease

states caused by vitamin D deficiency is contained in the abstracts below.

General references on deficiency in children.

1. Misra M, *et al.* Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 2008; **122:** 398–417.
2. Casey CF, *et al.* Vitamin D supplementation in infants, children, and adolescents. *Am Fam Physician* 2010; **81:** 745–8.

Administration in the elderly. Vitamin D deficiency is common in the elderly,[1-3] especially in housebound patients, and during wintertime.[4] Deficiency is aggravated by a diet low in calcium,[1] lack of sunlight exposure, and decreasing ability of the skin to synthesise vitamin D with advancing age.[3,5] Elderly patients are therefore at risk of secondary hyperparathyroidism, bone loss and osteoporosis, and fractures.[1,6,7] Low serum vitamin D has been associated with increased fracture rates, and there is some evidence from *animal* studies that vitamin D may promote bone healing after fracture, increasing the mechanical strength of bone by promoting mineralisation.[7] Poor muscle strength and weakness may be associated with vitamin D deficiency, and may increase the risk of falling in the elderly.[2,8,9] A meta-analysis[10] of 8 controlled studies found that vitamin D supplementation reduced the risk of falls in the elderly by 19% compared with calcium or placebo. Vitamin D deficiency in the elderly may be less prevalent in the USA, due to fortification of food.[1] Food fortification has therefore been recommended,[1] or supplementation with doses in the region of 10 to 20 micrograms (400 to 800 units) daily;[1,4] in the elderly, doses in the region of 17.5 to 25 micrograms (700 to 1000 units) daily are considered necessary for reduction of falls and fractures.[10] The 2005 Dietary Guidelines for Americans recommend that elderly people should consume 25 micrograms (1000 units) daily; the upper level of 50 micrograms (2000 units) should not be exceeded.[5] See also Osteomalacia and Rickets, p. 2116.2 and Osteoporosis, p. 2116.3.

There are also suggestions that low vitamin D concentrations may be associated with various cardiovascular, metabolic, and malignant disorders; for mention of a reduction in total mortality with vitamin D supplementation in mainly elderly people, see UK and US Recommended Dietary Intake, p. 2118.1.

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; **22:** 477–501.
2. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *BMJ* 2005; **330:** 524–6.
3. Allain TJ, Dhesi J. Hypovitaminosis D in older adults. *Gerontology* 2003; **49:** 273–8.
4. Compston JE. Vitamin D deficiency: time for action. *BMJ* 1998; **317:** 1466–7.
5. Johnson MA, Kimlin MG. Vitamin D, aging, and the 2005 Dietary Guidelines for Americans. *Nutr Rev* 2006; **64:** 410–21.
6. Passeri G, *et al.* Low vitamin D status, high bone turnover, and bone fractures in centenarians. *J Endocrinol Metab* 2003; **88:** 5109–15.
7. Simon J, *et al.* Fractures in the elderly and vitamin D. *J Nutr Health Aging* 2002; **6:** 406–12.
8. Mosekilde L. Vitamin D and the elderly. *Clin Endocrinol (Oxf)* 2005; **62:** 265–81.
9. Janssen HCJP, *et al.* Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002; **75:** 611–15.
10. Bischoff-Ferrari HA, *et al.* Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009; **339:** b3692. Available at: http://www.bmj.com/cgi/reprint/339/oct01_1/b3692 (accessed 04/02/10)

Cardiovascular disease. Myocardial tissue contains a vitamin D-dependent calcium-binding protein, indicating a role for vitamin D in the regulation of myocardial contractility.[1,2] Lack of vitamin D is considered to play a role in the aetiology and pathogenesis of cardiovascular disease such as congestive heart failure;[2] a case series of 16 infants with cardiomyopathy and heart failure associated with vitamin D deficiency and hypocalcaemia has been reported.[3] Case reports have also shown that vitamin D treatment reduced blood pressure and myocardial hypertrophy.[4] However, systematic reviews of the evidence have come to conflicting conclusions about the value of vitamin D supplementation in preventing cardiovascular events,[5,6] and there is currently no rationale to prescribe specific vitamin D analogues for patients with congestive heart failure.[2]

1. Luong KVQ, Nguyen LTH. Vitamin D and cardiovascular disease. *Curr Med Chem* 2006; **13:** 2443–7.
2. Zittermann A, *et al.* Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; **11:** 25–33.
3. Maiya S, *et al.* Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. *Heart* 2008; **94:** 581–4.
4. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006; **92:** 39–48.
5. Pittas AG, *et al.* Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; **152:** 307–14.
6. Wang L, *et al.* Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; **152:** 315–23.

Diabetes mellitus. Vitamin D has a role in glucose homoeostasis and in the mechanism of insulin release.[1] Cohort studies[2,3] have suggested that supplementation with vitamin D may have a beneficial role in reducing the risk for developing both type 1 and type 2 diabetes mellitus. A meta-analysis[4] of 5 observational studies also suggested that vitamin D supplementation in early childhood may offer some protection against the development of type I diabetes mellitus. However, another study[5] found no significant differences in vitamin D status in Finnish or Karelian children, 2 neighbouring geographical areas with vastly differing incidences of type 1 diabetes.

Paricalcitol has also been investigated as an adjunct to reduce residual albuminuria in patients with diabetic nephropathy, see p. 465.1.

1. Reis AF, *et al.* Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease: a review of evidence. *Diabetes Metab* 2005; **31:** 318–25.
2. Hyppönen E, *et al.* Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001; **358:** 1500–1503.
3. Pittas AG, *et al.* Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; **29:** 650–6.
4. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 2008; **93:** 512–17.
5. Viskari H, *et al.* Circulating vitamin D concentrations in two neighboring populations with markedly different incidence of type 1 diabetes. *Diabetes Care* 2006; **29:** 1458–9.

Hyperparathyroidism. Vitamin D has been used for certain forms of hyperparathyroidism (p. 1170.3). The **secondary hyperparathyroidism** of renal osteodystrophy (p. 1170.1) may respond to treatment with calcitriol, or its analogue alfacalcidol,[1,2] which do not require renal hydroxylation for activation. Calcitriol has been used orally,[3] intravenously,[3,4] and intraperitoneally;[5] percutaneous injection directly into the parathyroid gland has also been reported to be safe and effective.[6-8] However, doses capable of suppressing parathyroid hormone secretion may lead to hypercalcaemia,[1-3,5,9,10] hyperphosphataemia,[1,2,5,9,10] and a decline in renal function;[11] the increase in calcium and phosphate may promote soft tissue and vascular calcification,[1,2] see Hypercalcaemia, under Adverse Effects, p. 2117.2.

Newer analogues for this indication include paricalcitol,[12-15] doxercalciferol,[16-18] falecalcitriol,[19] and maxacalcitol.[20-25] These are reported to have less effect on calcium and phosphate concentrations, while retaining the suppressive effect on parathyroid hormone;[1,5,9,10] however, some[2,18] consider clinically relevant benefit to be lacking. Paricalcitol was found to have a faster effect and cause less hypercalcaemia than calcitriol in patients on haemodialysis,[15] as well as offering a significant survival advantage over calcitriol.[13] A review considered paricalcitol to be as effective and as well tolerated as calcitriol.[14] Maxacalcitol and calcitriol were considered equally effective when given intravenously to haemodialysis patients,[25] while oral falecalcitriol was considered better than oral alfacalcidol at reducing parathyroid hormone concentrations.[19] Intravenous doxercalciferol appears to be safer than oral doxercalciferol;[1] comparative data are lacking.[2,18] A meta-analysis found that the use of vitamin D in chronic kidney disease did not consistently reduce parathyroid hormone concentrations.[26]

Some have cautioned against vitamin D supplementation in **primary hyperparathyroidism** because of concerns about exacerbation of hypercalcaemia and hypercalciuria. However, in a small study in patients with mild primary hyperparathyroidism, correction of vitamin D deficiency did not exacerbate hypercalcaemia, and decreased parathyroid hormone concentrations and bone turnover.[27]

1. Brown AJ, Coyne DW. Vitamin D analogs: new therapeutic agents for secondary hyperparathyroidism. *Treat Endocrinol* 2002; **1:** 313–27.
2. Cunningham J. New vitamin D analogues for osteodystrophy in chronic kidney disease. *Pediatr Nephrol* 2004; **19:** 705–8.
3. Quarles LD, *et al.* Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int* 1994; **45:** 1710–21.
4. Morosetti M, *et al.* High doses of intravenous calcitriol in the treatment of severe secondary hyperparathyroidism. *J Nephrol* 2004; **17:** 95–100.
5. Dusso AS, *et al.* Vitamin D receptor and analogs. *Semin Nephrol* 2004; **24:** 10–16.
6. Kitaoka M, *et al.* Percutaneous calcitriol injection therapy (PCIT) for secondary hyperparathyroidism: multicentre trial. *Nephrol Dial Transplant* 2003; **18** (suppl): iii38–iii41.
7. Shiizaki K, *et al.* Effect of percutaneous calcitriol injection therapy on secondary hyperparathyroidism in uraemic patients. *Nephrol Dial Transplant* 2003; **18** (suppl): iii42–iii46.
8. Nakanishi S, *et al.* Efficacy of direct injection of calcitriol into the parathyroid glands in uraemic patients with moderate to severe secondary hyperparathyroidism. *Nephrol Dial Transplant* 2003; **18** (suppl): iii47–iii49.
9. Martín KJ, González EA. Vitamin D analogs: actions and role in the treatment of secondary hyperparathyroidism. *Semin Nephrol* 2004; **24:** 456–9.
10. Hudson JQ. Secondary hyperparathyroidism in chronic kidney disease: focus on clinical consequences and vitamin D therapies. *Ann Pharmacother* 2006; **40:** 1584–93.
11. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; **124:** 520–8.
12. Martín KJ, *et al.* Therapy of secondary hyperparathyroidism with 19-nor-1 α ,25-dihydroxyvitamin D_2. *Am J Kidney Dis* 1998; **32** (suppl 2): S61–6.
13. Teng M, *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; **349:** 446–56.
14. Robinson DM, Scott LJ. Paricalcitol: a review of its use in the management of secondary hyperparathyroidism. *Drugs* 2005; **65:** 559–76.
15. Sprague SM, *et al.* Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; **63:** 1483–90.
16. Frazão JM, *et al.* Intermittent doxercalciferol (1 α -hydroxyvitamin D_2) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 2000; **36:** 550–61.
17. Coburn JW, *et al.* Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. *Am J Kidney Dis* 2004; **43:** 877–90.
18. Dennis VC, Albertson GL. Doxercalciferol treatment of secondary hyperparathyroidism. *Ann Pharmacother* 2006; **40:** 1955–65.
19. Akiba T, *et al.* Controlled trial of falecalcitriol versus alfacalcidol in suppression of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1998; **32:** 238–46.
20. Akizawa T, *et al.* Long-term effect of 1,25-dihydroxy-22-oxavitamin D (3) on secondary hyperparathyroidism in haemodialysis patients: one-year administration study. *Nephrol Dial Transplant* 2002; **17** (suppl 10): 28–36.
21. Yasuda M, *et al.* Multicenter clinical trial of 22-oxa-1,25-dihydroxyvitamin D3 for chronic dialysis patients. *Am J Kidney Dis* 2003; **41** (suppl 1): S108–S111.
22. Doi S, *et al.* Effect of 22-oxacalcitriol on secondary hyperparathyroidism in hemodialysis patients. *Intern Med* 2003; **42:** 955–9.
23. Kubota M, *et al.* The effect of intraperitoneal 22-oxacalcitriol on secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients (IPOX Study). *Adv Perit Dial* 2003; **19:** 227–30.
24. Murakami K, *et al.* Suppression of parathyroid hormone secretion in CAPD patients by intraperitoneal administration of maxacalcitol. *Clin Exp Nephrol* 2004; **8:** 134–8.
25. Hayashi M, *et al.* Comparison of the effects of calcitriol and maxacalcitol on secondary hyperparathyroidism in patients on chronic haemodialysis: a randomized prospective multicentre trial. *Nephrol Dial Transplant* 2004; **19:** 2067–73.
26. Palmer SC, *et al.* Meta-analysis: vitamin D compounds in chronic kidney disease. *Ann Intern Med* 2007; **147:** 840–53.
27. Grey A, *et al.* Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. *J Clin Endocrinol Metab* 2005; **90:** 2122–6.

Hypoparathyroidism. Although parenteral calcium salts may be given acutely for hypocalcaemic tetany, long-term treatment of hypoparathyroidism (p. 1171.2) usually aims at correction of associated hypocalcaemia with oral calcium salts and oral vitamin D compounds, which increase the intestinal absorption of calcium.

Hypoparathyroidism in *pregnancy* poses severe risks of fetal hyperparathyroidism with neonatal hypocalcaemic rickets, which may be fatal. Treatment with calcium and either colecalciferol or ergocalciferol in doses of 1.25 to 2.5 mg daily, or dihydrotachysterol 0.25 to 1.0 mg daily is essential.[1] Calcitriol, in doses of between 0.25 to 3 micrograms daily, with calcium supplementation, has also been suggested; the dosage is adjusted to physiological requirements during pregnancy.[2]

1. Hague WM. Treatment of endocrine diseases. *BMJ* 1987; **294:** 297–300.
2. Callies F, *et al.* Management of hypoparathyroidism during pregnancy - report of twelve cases. *Eur J Endocrinol* 1998; **139:** 284–9.

Inflammatory bowel disease. Some studies have found a high prevalence of vitamin D deficiency in patients with inflammatory bowel disease (IBD). The aetiology of this is not entirely clear and may be multifactorial.[1,2] Patients with IBD may have decreased exposure to sunlight since the incidence and prevalence of IBD are greatest in northern latitudes. Patients might also have inadequate dietary intake of vitamin D, since IBD patients may avoid foods, such as dairy products, that are generally fortified with this vitamin. Deficiency might also be due to malabsorption, especially in IBD patients that have undergone small-bowel resection, although intestinal absorption was normal in many IBD patients with low vitamin D concentrations. The use of drugs such as colestyramine, and disturbed enterohepatic circulation of vitamin D metabolites have also been proposed as mechanisms for hypovitaminosis D in patients with IBD, as has an increased loss of vitamin D through protein-losing enteropathy.[1,2] A study[3] in children and young adults with IBD also found a high prevalence of vitamin D deficiency in this patient population. Predisposing factors included dark-skinned complexion, winter season, lack of vitamin D supplementation, early stage of disease, more severe disease, and upper gastrointestinal tract involvement in patients with Crohn's disease. Vitamin D concentrations were positively correlated with serum albumin concentrations, leading the authors to conclude protein-losing enteropathy was a leading mechanism for deficiency. If this were so, both enteral and parenteral supplementation of vitamin D might prove inadequate at the usual dose, and in patients with active disease.

However, the American Gastroenterological Association concluded, in a review of osteoporosis in gastrointestinal diseases,[4] that osteomalacia and vitamin D deficiency were not common in IBD patients (including Crohn's disease) and were unlikely to be causes of most cases of diminished bone mineral density in patients with IBD.

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2. Pappa HM, *et al.* Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. *Inflamm Bowel Dis* 2006; **12:** 1162–74.

3. Pappa HM, *et al.* Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics* 2006; **118:** 1950–61.
4. Bernstein CN, *et al.* American Gastroenterological Association Clinical Practice Committee. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003; **124:** 795–841.

Malignant neoplasms. The active form of vitamin D, calcitriol (1,25-dihydroxycholecalciferol) has been found to promote tissue differentiation and to inhibit cellular proliferation *in vitro*. These findings have prompted investigation into the potential role and efficacy of vitamin D metabolites or analogues (sometimes referred to as deltanoids) in malignant neoplasms and in other disorders of cell growth such as psoriasis (see p. 2117.1).

There is laboratory evidence that vitamin D compounds can inhibit the growth of cancer cells, including those of the breast,[1,2] colon,[3] and prostate.[4,5] Epidemiological studies have suggested that vitamin D deficiency may be associated with higher risks of cancer.[6-9] Furthermore, increased sun exposure may be associated with improved survival for some cancers.[7,9] Phase I and II studies of calcitriol either alone, or with antineoplastics, have shown promising results.[10,11] A study in humans has been performed with the calcitriol derivative calcipotriol (p. 1697.2); in this trial calcipotriol used topically in advanced or cutaneous metastatic breast cancer was considered to exert some positive effects and further investigation was considered warranted.[12] Regression of T-cell lymphoma of the skin (mycosis fungoides, p. 698.3) has been reported after application of calcipotriol,[13] and after systemic treatment with calcitriol and a retinoid in a patient who failed to respond to topical calcipotriol.[14] However, 3 other patients with cutaneous T-cell lymphoma failed to respond to calcitriol and isotretinoin,[15] which may have been because of the phenotype or stage of the disease.[16] In a 7-year study in 36 282 postmenopausal women, of whom 18 176 received vitamin D_3 (400 units daily) and calcium, supplementation had no effect on the incidence of colorectal cancer.[17] This study has raised debate as to whether the dose of vitamin D used was insufficient.[7] A later analysis[18] of the study results suggested that supplementation had been of benefit in women in the placebo arms of the study but that this had been offset by an increase in risk in women also taking oestrogens. A smaller 4-year study[19] involving 1179 postmenopausal women given calcium with or without vitamin D_3 1100 units daily, or placebo, found that supplementation reduced all-cancer risk, and baseline and treatment-modified serum concentrations of vitamin D were strong predictors of cancer risk.

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2. Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 1427–37.
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10. Trump DL, *et al.* Anti-tumor activity of calcitriol: pre-clinical and clinical studies. *J Steroid Biochem Mol Biol* 2004; **89–90:** 519–26.
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18. Ding EL, *et al.* Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. *Int J Cancer* 2008; **122:** 1690–4.
19. Lappe JM, *et al.* Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; **85:** 1586–91. Correction. *ibid.* 2008; **87:** 794.

Multiple sclerosis. Multiple sclerosis (p. 996.3) is more common in regions further from the equator, and it has been suggested that sunlight exposure and vitamin D exert a protective effect. Studies have also found lower vitamin D concentrations in patients with multiple sclerosis. Results from two large prospective cohorts found an inverse relationship between intake of vitamin D from supplements and risk of the disease; no association was found between vitamin D intake from food and incidence of multiple sclerosis.[1] A prospective, case-control study[2] found that, among whites, the risk of multiple sclerosis significantly decreased with increasing concentrations of vitamin D; no significant association was found among blacks and Hispanics. However, the sample size in the latter groups were smaller and concentrations of vitamin D are lower among blacks. A review[3] found little evidence to support the effectiveness of vitamin D in the treatment of multiple sclerosis; although uncontrolled studies suggest vitamin D may be beneficial, small patient populations and confounding variables have limited the usefulness of the data.

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2. Munger KL, *et al.* Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296:** 2832–8.
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Osteomalacia and rickets. Treatment of osteomalacia and rickets (p. 1168.1) primarily aims at correcting any underlying deficiency states, and vitamin D substances, calcium, or phosphate supplements may be given orally as necessary.

Where **rickets** is due to impaired synthesis of 1,25-dihydroxycholecalciferol (type I pseudodeficiency) or receptor resistance (type II pseudodeficiency) replacement therapy with calcitriol may be indicated (in the latter case with very high dose calcium),[1] while X-linked hypophosphataemic rickets is generally treated with phosphate supplementation and calcitriol.[2] The use of single large doses of a vitamin D substance (Stosstherapie), for the prophylaxis of rickets, is highly controversial because of problems with toxicity, although it may be effective in patients with rickets due to proven[3] or recalcitrant[4] vitamin D deficiency. Factors contributing to reported resurgences in rickets[2,4-8] include increased breast feeding without sufficient vitamin D supplementation, and less exposure to sunlight. A major risk factor for infants is maternal vitamin D deficiency (see Pregnancy and the Neonate, below). In the UK, the Department of Health advises that children aged 5 years and under be supplemented with 7 micrograms (280 units) daily,[8] but renewed public health campaigns have been called for, along with supplementation of infants from high-risk groups with 400 units of vitamin D daily.[6] Similar recommendations have been made in Australia and New Zealand.[4] Others have commented that even 200 units daily may not be enough as a preventive measure,[2,9] and that, in those children with good exposure to sunlight, calcium supplementation may also be necessary.[10] In 2008, the American Academy of Pediatrics revised its previous advice, increasing the recommended vitamin D intake from a minimum of 200 units daily to 400 units daily for all infants, children, and adolescents beginning in the first few days of life.[11]

In adults, vitamin D deficiency may be asymptomatic. Most patients who present clinically do so because of muscle weakness, or muscles aches and pains.[12] Even severe vitamin D deficiency can go unrecognised; patients may present with a syndrome of persistent, non-specific musculoskeletal pain, before the onset or diagnosis of the clinical presentation of **osteomalacia**.[13,14] Although screening for vitamin D deficiency has been suggested in all patients with this type of musculoskeletal pain,[13] the prevalence of vitamin D deficiency in this patient group has been queried.[15]

For discussion on the intake of vitamin D considered sufficient for prophylaxis, see UK and US Recommended Dietary Intake, p. 2118.1; for treatment in adults, see Uses and Administration, p. 2114.1, and in children, see Administration in Children, p. 2114.3. Because the process of ageing decreases the skin's ability to synthesise vitamin D, elderly people may be at risk of deficiency (see Administration in the Elderly, p. 2115.1).

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6. Shaw NJ, Pal BR. Vitamin D deficiency in UK Asian families: activating a new concern. *Arch Dis Child* 2002; **86:** 147–9.
7. Welch TR, *et al.* Vitamin D-deficient rickets: the reemergence of a once-conquered disease. *J Pediatr* 2000; **137:** 143–5.
8. Anonymous. Primary vitamin D deficiency in children. *Drug Ther Bull* 2006; **44:** 12–16.
9. Greer FR. Vitamin D deficiency—it's more than rickets. *J Pediatr* 2003; **143:** 422–3.
10. Bishop N. Rickets today—children still need milk and sunshine. *N Engl J Med* 1999; **341:** 602–4.
11. Wagner CL, Greer FR. American Academy of Pediatrics Section on Breastfeeding. American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008; **122:** 1142–52. Correction. *ibid.* 2009; **123:** 197.
12. Anonymous. Primary vitamin D deficiency in adults. *Drug Ther Bull* 2006; **44:** 25–9.
13. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003; **78:** 1463–70.
14. Sievenpiper JL, *et al.* Unrecognised severe vitamin D deficiency. *BMJ* 2008; **336:** 1371–4.
15. Block SR. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc* 2004; **79:** 1585–6.

PREGNANCY AND THE NEONATE. It has been supposed that most infants receive adequate calcium and vitamin D during pregnancy and during breast feeding or bottle feeding to prevent the development of rickets. However, this has been disputed;[1,2] even infants born to vitamin D replete mothers become vitamin D deficient after 8 weeks if not supplemented, and those born to vitamin D deficient mothers will reach a deficient state more quickly. In many populations where sun exposure is severely limited and there is inadequate corrective vitamin D supplementation, there is also a high prevalence of vitamin D deficiency in nursing mothers.[3] It is accepted that there are certain groups of women whose infants may be at special risk of neonatal rickets; these include those suffering economic deprivation, those living at high latitudes, and Asian immigrants [i.e. from the Indian subcontinent] in northern Europe, especially in winter. It is therefore suggested that pregnant women in such circumstances should receive supplements as the diet and sunshine exposure may not be providing adequate calcium (1 to 1.2 g daily) or vitamin D (400 units daily).[4] Alternatively, 1000 units vitamin D daily during the third trimester, or a single dose of 100 000 to 200 000 units of ergocalciferol during the sixth or seventh month, has been proposed.[5] The Committee on Medical Aspects of Food Policy (COMA) in the UK recommended[6] in 1991 that pregnant women receive supplementary vitamin D to achieve an intake of 10 micrograms daily. A 2008 report[7] commissioned by NICE recommended that women should be informed about the importance, for their own and their baby's health, of maintaining adequate vitamin D stores during pregnancy and while breastfeeding and stated that in order to achieve this, women may choose to take 10 micrograms of vitamin D daily. However, the report also stated that while there is some evidence of benefit from vitamin D supplementation for pregnant women at risk of vitamin D deficiency, there is less evidence in the case of those currently regarded as being at low risk of deficiency. A review[2] of dietary vitamin D requirements during pregnancy and lactation has stated that women who were vitamin D deficient at the beginning of their pregnancy remained deficient despite supplementation with 800 to 1600 units daily. The authors suggested that current recommendations in the UK and the USA were grossly inadequate during pregnancy, especially for ethnic minorities (see UK and US recommended dietary intake, p. 2118.1). Instead, they suggested that doses of about 2000 to 10 000 units daily would be needed in order to achieve normal vitamin D concentrations. Furthermore, routine vitamin D supplementation of infants in high-risk groups has been recommended (see Osteomalacia and Rickets, above).

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6. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
7. National Collaborating Centre for Women's and Children's Health/NICE. Antenatal Care: routine care for the healthy pregnant woman (issued March 2008). Available at: http://www.nice.org.uk/nicemedia/live/11947/40145/40145.pdf (accessed 22/07/10)

Osteopetrosis. For mention of the use of high-dose calcitriol in the management of osteopetrosis, see under Corticosteroids, p. 1609.3.

Osteoporosis. Vitamin D concentrations have been found to correlate positively with bone mineral density (BMD),[1] and supplementation with vitamin D and calcium has led to beneficial increases in BMD in most trials.[2] Sufficient intake of vitamin D and calcium is recommended for prevention of osteoporosis (p. 1168.1), and supplementation is an accepted baseline adjunctive treatment.[2,3] The age-related increase in fracture risk is influenced by BMD changes and an increased propensity to falls, attributable in part to a loss of muscular strength. In addition to its role in calcium homoeostasis, vitamin D status has also been correlated to muscular strength in older people.[3]

Studies using vitamin D (with or without calcium) for the prevention of fractures have produced conflicting results.[4-11] However, in elderly patients, in whom dietary deficiencies are common, calcium and vitamin D supplements are recommended (see Administration in the Elderly, p. 2115.1). Supplementation is also recommended in elderly

institutionalised patients.[12] A meta-analysis[13] of fracture prevention studies found that oral vitamin D supplementation with between 700 to 800 units daily reduced the risk of hip and non-vertebral fractures in elderly patients. However, a systematic review[11] has stated that vitamin D alone is unlikely to prevent fractures.

Calcium may be necessary to optimise the clinical efficacy of vitamin D supplementation in terms of reducing fracture risk.[3] A meta-analysis[14] found that oral vitamin D appeared to reduce the risk of hip fractures only when calcium supplementation was added. However, another meta-analysis[15] found that the difference in relative risk reduction for all fracture types when vitamin D was added to calcium supplementation, was very small and statistically insignificant, although those with low vitamin D serum concentrations tended to have a greater risk reduction than those with normal vitamin D concentrations. A significant difference was seen between the effects of different vitamin D doses. While noting that this could be due to statistical artifact, the authors noted that their analysis had been limited by the scarcity of data for vitamin D doses higher than 800 units, and that it was possible that vitamin D would have a beneficial effect if the dose were greater than 800 units daily.

It has been suggested[16] that the vitamin D analogues alfacalcidol and calcitriol are more effective for osteoporosis than ergocalciferol or colecalciferol. However, a systematic review[11] found no evidence of benefit for analogues compared with vitamin D. Another systematic review[17] found that vitamin D supplementation overall reduced falls and nonvertebral but not vertebral fractures; however, subgroup analysis suggested a reduction in vertebral fractures with alfacalcidol but not with calcitriol.

Vitamin D is also recommended for the prevention of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p. 1616.2).

1. Bischoff-Ferrari HA, *et al*. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004; **116:** 634–9.
2. Rodríguez-Martínez MA, García-Cohen EC. Role of Ca^{2+} and vitamin D in the prevention and treatment of osteoporosis. *Pharmacol Ther* 2002; **93:** 37–49.
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6. Trivedi DP, *et al*. Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; **326:** 469.
7. Porthouse J, *et al*. Randomised controlled trial of supplementation with calcium and cholecalciferol (vitamin D_3) for prevention of fractures in primary care. *BMJ* 2005; **330:** 1003–6.
8. The RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005; **365:** 1621–28.
9. Jackson RD, *et al*. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; **354:** 669–83. Correction. *ibid.*; 1102.
10. Dhesi JK, *et al*. The implications of a growing evidence base for drug use in elderly patients: Part 4: Vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; **61:** 521–8.
11. Avenell A, *et al*. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 22/07/10).
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14. Boonen S, *et al*. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab* 2007; **92:** 1415–23.
15. Tang BMP, *et al*. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; **370:** 657–66.
16. Ringe JD, Schacht E. Prevention and therapy of osteoporosis: the roles of plain vitamin D and alfacalcidol. *Rheumatol Int* 2004; **24:** 189–97.
17. O'Donnell S, *et al*. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. *J Bone Miner Metab* 2008; **26:** 531–42.

Psoriasis. A vitamin D analogue, calcipotriol (p. 1697.2), is often used as an alternative to more traditional topical drugs in the initial management of mild to moderate psoriasis (p. 1688.1). Another vitamin D analogue, tacalcitol (p. 1722.1), is used similarly. Initial studies with topical maxacalcitol,[1] falecalcitriol,[2] and paricalcitol[3] suggest they are safe and effective for psoriasis. Calcitriol itself has been tried, both topically[4-6] and orally.[7] Calcitriol ointment has been found to be as effective as calcipotriol ointment[8] and short-contact dithranol cream; skin irritation was less with calcitriol compared with dithranol.[9] While global improvement and severity scores were found to be better with betamethasone dipropionate ointment, remission times were longer with calcitriol treatment.[10]

1. Barker JNWN, *et al*. Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose-finding study with active comparator. *Br J Dermatol* 1999; **141:** 274–8.
2. Durakovic C, *et al*. Rationale for use and clinical responsiveness of hexafluoro-1,25-dihydroxyvitamin D_3 for the treatment of plaque psoriasis: a pilot study. *Br J Dermatol* 2001; **144:** 500–506.
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5. Langner A, *et al*. A long-term multicentre assessment of the safety and tolerability of calcitriol ointment in the treatment of chronic plaque psoriasis. *Br J Dermatol* 1996; **135:** 385–9.
6. Ring J, *et al*. Calcitriol 3 microgramsg^{-1} ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a comparative study. *Br J Dermatol* 2001; **144:** 495–9.
7. Perez A, *et al*. Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D_3) for the treatment of psoriasis. *Br J Dermatol* 1996; **134:** 1070–8.
8. Lahfa M, *et al*. Calcitriol ointment and clobetasol propionate cream: a new regimen for the treatment of plaque psoriasis. *Eur J Dermatol* 2003; **13:** 261–5.
9. Hutchinson PE, *et al*. The efficacy, safety and tolerance of calcitriol 3 micrograms/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 2000; **201:** 139–45.
10. Camarasa JM, *et al*. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. *J Dermatol Treat* 2003; **14:** 8–13.

Renal osteodystrophy. See under Hyperparathyroidism, p. 2115.2.

Rheumatoid arthritis. A large cohort study[1] found an inverse correlation between vitamin D intake and the risk of developing rheumatoid arthritis. However, a small study[2] of serum vitamin D concentrations in patients with rheumatoid arthritis who had donated blood before the onset of symptoms, found no association between vitamin D deficiency and later development of rheumatoid arthritis, suggesting that vitamin D does not have an important role in the pathogenesis of rheumatoid arthritis.

1. Merlino LA, *et al*. Vitamin D intake is inversely associated with rheumatoid arthritis. *Arthritis Rheum* 2004; **50:** 72–7.
2. Nielen MMJ, *et al*. Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. *Arthritis Rheum* 2006; **54:** 3719–20.

Rickets. See Osteomalacia and Rickets, p. 2116.2.

Adverse Effects and Treatment

Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage (for a discussion of vitamin-D mediated hypercalcaemia and its treatment, see p. 1776.1). Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

The most potent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal.

Hypersensitivity reactions have occurred. Skin irritation or contact dermatitis has been reported with topical preparations.

Hypercalcaemia. Vitamin D is the most likely of all vitamins to cause overt toxicity. Doses of 60 000 units daily can cause hypercalcaemia (p. 1776.1), with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function.[1,2] A number of reports of accidental overdosage, leading to hypercalcaemia or nephrocalcinosis, occurred in the UK after introduction of a concentrated alfacalcidol oral solution that was 10 times stronger than the former presentation.[3]

Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.[4]

A study in children treated for renal osteodystrophy has provided some evidence that hypercalcaemia may occur more frequently with calcitriol than with ergocalciferol.[5] Another such study has suggested that vitamin D has nephrotoxic properties independent of the degree of induced hypercalcaemia, and that the decline in renal function may be more marked with calcitriol.[6]

Topical calcitriol may affect calcium homoeostasis, and hypercalcaemia has been reported in some studies.[7] For reference to the effect of other vitamin D analogues used in psoriasis on calcium homoeostasis, see under Calcipotriol, p. 1698.2.

1. Anonymous. Toxic effects of vitamin overdosage. *Med Lett Drugs Ther* 1984; **26:** 73–4.
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4. Jibani M, Hodges NH. Prolonged hypercalcaemia after industrial exposure to vitamin D_3. *BMJ* 1985; **290:** 748–9.
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6. Chan JCM, *et al*. A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; **124:** 520–8.
7. Bourke JF, *et al*. Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135:** 347–54.

Precautions

Vitamin D should not be given to patients with hypercalcaemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.

It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity (see above). Similar monitoring is recommended in infants if they are breast-fed by mothers receiving pharmacological doses of vitamin D (see below).

Breast feeding. Vitamin D is distributed into breast milk,[1] and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants.[2] The American Academy of Pediatrics considers the use of vitamin D to be usually compatible with breast feeding,[3] although they and others[4] recommend that the infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.

1. Rothberg AD, *et al*. Maternal-infant vitamin D relationships during breast-feeding. *J Pediatr* 1982; **101:** 500–503.
2. Cancela L, *et al*. Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breast-fed infants. *J Endocrinol* 1986; **110:** 43–50.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)
4. Greer FR, *et al*. High concentrations of vitamin D_2 in human milk associated with pharmacologic doses of vitamin D_2. *J Pediatr* 1984; **105:** 61–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alfacalcidol, calcitriol, colecalciferol, and dihydrotachysterol as probably not porphyrinogenic; these may be used as drugs of first choice and no precautions are needed. Calcifediol, ergocalciferol, and paricalcitol are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy. Indeed, one report noted increased requirements for vitamin D preparations during pregnancy for the treatment of hypoparathyroidism;[1] the dose needed tended to increase during the second half of pregnancy. In one woman in whom the dose of calcitriol remained raised after delivery (in an attempt to allow for the calcium loss involved in breast feeding) hypercalcaemia developed; this did not occur in 2 women who did not breast feed and in whom the dose of the vitamin D preparations was reduced soon after delivery.[1] For discussions regarding vitamin D requirements during pregnancy, see UK and US recommended dietary intake, p. 2118.1, and Pregnancy and the Neonate, p. 2116.3.

1. Caplan RH, Beguin EA. Hypercalcemia in a calcitriol-treated hypoparathyroid woman during lactation. *Obstet Gynecol* 1990; **76:** 485–9.

Interactions

There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce

the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D. Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together; care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

Danazol. A report of hypercalcaemia associated with danazol in a patient maintained on alfacalcidol therapy for hypoparathyroidism.[1] Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol.

1. Hepburn NC, *et al.* Danazol-induced hypercalcaemia in alphacalcidol-treated hypoparathyroidism. *Postgrad Med J* 1989; **65:** 849–50.

Levothyroxine. Three patients taking dihydrotachysterol and calcium, for postoperative hypoparathyroidism after thyroidectomy, as well as levothyroxine, developed hypercalcaemia when the latter was stopped before a radio-iodine scan.[1] The dose of dihydrotachysterol should be reduced and serum-calcium concentrations should be monitored when thyroid treatment is interrupted, since elimination of dihydrotachysterol may be delayed in hypothyroidism.

1. Lamberg B-A, Tikkanen MJ. Hypercalcaemia due to dihydrotachysterol treatment in patients with hypothyroidism after thyroidectomy. *BMJ* 1981; **283:** 461–2.

Pharmacokinetics

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Ergocalciferol and colecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives.

Colecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Of the synthetic analogues, alfacalcidol, dihydrotachysterol, and doxercalciferol are converted directly in the liver to their active metabolites (calcitriol, 25-hydroxydihydrotachysterol, and 1,25-dihydroxyergocalciferol respectively).

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

Human Requirements

The daily requirements of vitamin D in adults are small and may be met mainly by exposure to sunlight and/or obtained from the diet. A daily dietary intake of about 200 to 400 units (5 to 10 micrograms of colecalciferol or ergocalciferol) of vitamin D is generally considered adequate for healthy adults. In comparison with older adults (in the age range of 25 years upwards) the requirements per kg bodyweight are greater in infants, children, and young adults and during pregnancy and lactation. Requirements may also be higher in people who are not exposed to adequate sunlight such as the elderly or housebound.

Vitamin D is present in few foods. Fish-liver oils, especially cod-liver oil, are good sources of vitamin D. Other sources, which contain much smaller amounts, include butter, eggs, and liver. Some foods are fortified with vitamin D, and milk and margarine may therefore also supply the vitamin. Cooking processes do not appear to affect the activity of vitamin D.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) for vitamin D have only been published for selected groups of the population.[1] In the USA recommended dietary allowances had been set, and were subsequently replaced by dietary reference intakes[2] (see p. 2046.1). Differing amounts are recommended for infants and children of varying ages, for adults, and for pregnant and lactating women. In the UK a dietary intake was considered unnecessary for adults living a normal lifestyle who were being exposed to solar radiation; for those confined indoors a reference nutrient intake (RNI) of 10 micrograms (400 units) [as colecalciferol or ergocalciferol] daily was set. This RNI of 10 micrograms daily was also considered to be applicable to all persons aged 65 years or more and to pregnant and lactating women. RNIs were set for children up to the age of 3 years; dietary intake was considered unnecessary for older children. Mention was made that in order to achieve the above reference nutrient intakes, supplementation of the diet may actually be required and supplementation was also recommended for Asian [i.e. from the Indian subcontinent] women and children in the UK (see also Pregnancy and the Neonate, p. 2116.3). In the USA,[2] adequate intakes for vitamin D are: 5 micrograms (200 units) daily (as colecalciferol) for all persons from birth through to age 50 years, including pregnant or lactating women; 10 micrograms daily for adults aged 51 to 70 years; and 15 micrograms daily for those aged greater than 70 years. The tolerable upper intake level is 50 micrograms (2000 units) daily. The 2005 Dietary Guidelines for Americans (published jointly by the US Department of Health and Human Services, and the US Department of Agriculture) recommend that high-risk groups including the elderly, those with dark skin, and those exposed to insufficient UV radiation, consume daily intakes of 25 micrograms (1000 units) daily.[3] The definition of vitamin D deficiency and vitamin D insufficiency remains controversial in terms of serum vitamin D concentrations.[4,5] Because vitamin D insufficiency is considered to be common in northern latitudes,[5] and deficiency is increasing worldwide,[4] higher intakes than those mentioned above have been recommended. Some have called for the establishment of an estimated average requirement (EAR) in North America,[4] and estimate a recommended dietary allowance (RDA) of greater than 12.5 micrograms (500 units). Others[5] suggest that the adequate intake be increased to at least 20 to 25 micrograms (800 to 1000 units) daily. A risk assessment analysis concluded that the tolerable upper intake level of vitamin D could be increased to 250 micrograms (10 000 units) daily for the general healthy population.[6] There has been speculation that such supplementation might lead to broader benefits, on the grounds of suggested associations between lack of vitamin D and various cardiovascular, metabolic, and malignant diseases. Interestingly, a meta-analysis[7] of 18 randomised controlled studies in various conditions suggested a reduction in total mortality from any cause with vitamin D supplementation in doses of 7.5 to 50 micrograms (300 to 2000 units) daily. However, most of the studies included were in elderly patients at high risk of fractures, who often have low vitamin D levels.

The consensus of over 300 scientists from 23 countries at a vitamin D workshop was that governmental guidelines, in all countries, with respect to daily vitamin D requirements (to maintain bone health and health in general) were too low and did not reflect advances in vitamin D research over the preceding decade. Eating vitamin D-rich foods does not solve vitamin D deficiency for most adults; fortification of food should be significantly improved and implemented. Recommendations were made that blood concentrations of vitamin D should be at least 20 nanograms/mL, and that the tolerable upper intake level of 50 micrograms (2000 units) be re-evaluated in light of new data.[8]

For the view that colecalciferol is more potent than ergocalciferol, and should be the preferred form of vitamin D supplementation, see Administration, p. 2114.3.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)
3. US Department of Health and Human Services/US Department of Agriculture. Dietary Guidelines for Americans 2005. Available at: http://www.health.gov/DIETARYGUIDELINES/dga2005/document/pdf/DGA2005.pdf (accessed 10/09/07)
4. Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005; **135:** 304–9.
5. Hanley DA, Davison KS. Vitamin D insufficiency in North America. *J Nutr* 2005; **135:** 332–7.
6. Hathcock JN, *et al.* Risk assessment for vitamin D. *Am J Clin Nutr* 2007; **85:** 6–18.
7. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; **167:** 1730–7.
8. Norman AW, *et al.* 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007; **103:** 204–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aderosol; Alpha D3; Dexiven; Findeclin Combi; Lotravel; Oravil; Ostelin; Raquiferol D3; Raquiferol; Raquitriol; Sterogyl; Trevix; Vita D; Zemplar; ***Austral.***: Calcijex; Citrihexal†; Kosteo; Ostelin; OsteVit-D; Rocaltrol; Sical; Sitriol†; Zemplar; ***Austria***: AT 10†; Bocatriol†; Bondiol; Calcijex; Etalpha; Laevovit D_3†; Oleovit D_3; Rocaltrol; Vi-De_3; Zemplar; ***Belg.***: 1-Alpha; D-Cure; Dedrogyl; Rocaltrol; Silkis†; ***Braz.***: Addera D3; Calcijex; Depura; Innosfen; Maxxi D3; Repocal D; Rocaltrol; Sigmacalcidol; Sigmatriol; Silkis†; Zemplar; ***Canad.***: Calciferol; Calcijex; Citracal + D; D-Gel; D-Tabs; D-Vi-Sol; Drisdol†; Erdol; Euro D; One-Alpha; Osto-D2; Riva D+; Rocaltrol; Silkis; Zemplar+; ***Chile***: Acuode; Etalpha; Fosamax Plus; Rocaltrol; Silkis†; Zemplar; ***China***: Alfacan (法能); Alpha-D_3 (阿法迪三); Ao Si Hui (奥司惠); Bon-One (萌格旺); Calcijex (溉纯); De Kai (得凯); Decostriol; Etalpha (依安凡); Faneng (法能)†; Gai Nuo Zhen (盖诺真); Gai San Chun (盖三淳); Hicalol (海卡洛); Liqing (立庆); Lonpryl (龙百利); Rocaltrol (罗盖全); Shuang Ye Hong (霜叶红); Silkis (秀可丝); Yan Di Nuo (延迪诺); Yingkangli (英康利); ***Cz.***: Alpha D3; Calciferol; Calcijex†; Infadin†; OsteoD; Rocaltrol; Silkis; Tachystin†; Vigantol; Zemplar; ***Denm.***: Detremin; Etalpha; Kalciferol†; One-Alpha; Zemplar; ***Fin.***: Deetipat†; Detremin; Devitol; Divisun; Dygratyl; Etalpha; Jekovit; Silkis; Zemplar; ***Fr.***: Adrigyl; Dedrogyl; Rocaltrol; Silkis; Sterogyl; Un-Alfa; Uvedose; Uvesterol D; Zymad; ***Ger.***: AT 10; Bondiol; D_3 Vicotrat; Decostriol; Dedrei; Dedrogyl; Dekristol; Doss; EinsAlpha; Ospur D_3†; Osteotriol; Rocaltrol; Silkis; Tachystin†; Vigantol; Vigantoletten; Zemplar; ***Gr.***: A-Calcid; A-Ostin-D3; Abbocalcijex; Alcidolin; Alestopor; Alfacalcil; Alfadel; Alpha D3; Alpha-Due†; Alpha-Plus; Alphabikal; Alphacal; Alphasidol; Alphazol; Antebe; Axelanol; Baludol; Biovit; Calcidrops; Calcitroject; Calcodol-D3; Calfadol; Calinol; Caltrioject; D-Triol; Decalcit; Dedrogyl†; Didrogyl; Dygratyl; Emarfen; Helposteol; Iasvest; Lifercal; Losefan; Mega-Alpha; One-Alpha; Ossidrol; Ostelin; Osteovile; Ostitriol; Otari; Silkis; Sterogyl; V-D-Bone; Vitocalcit; Votrace; Zemplar; ***Hong Kong***: Alpha D3; Bocatriol†; Bon-One; Calcijex; Decostriol; One-Alpha; Rocaltrol; Silkis; Zemplar; ***Hung.***: Alpha D3; Calcijex; Osteo D+; Rocaltrol; Silkis†; Tachystin†; Vigantol; Zemplar; ***India***: Alfa Caps; Alfabol; Alfacal; Alfacip; Alfarich; Alfaset; Alpha D3†; Alphadol; Arachitol; Architol; Aristrol; Bio-D3; Calci-Best; Calcibest; Calcikind; Calcirol; Calcit SG; Caldikind; Calfa-D; Calosto; Caltrol; CCM; Celol; Cinvit-D; Devita; Dewin; Duracal; Fovit-D3; GR-Alfa; Kalzin; Minroset; One-Alpha; Ostriol; Rolsical; ***Indon.***: Bon-One; Calcijex†; Calcit; Ecatrol; Kolkatriol; One-Alpha; Oscal; Osteofem; Ostovell; Ostriol; Rocaltrol; ***Irl.***: AT 10; One-Alpha; Rocaltrol; Silkis; Zemplar; ***Israel***: Alpha D3; Calcijex†; One-Alpha; Tevalfa; Zemplar; ***Ital.***: Alpha D3; Atiten; Calcijex; Dediol; Deril; Dibase; Didrogyl; Difix; Diseon; Diserinal; Geniad; Ostelin; Ostidil-D3; Rocaltrol; Sefal; Silkis; Tridelta; Trikal†; Zemplar; ***Jpn***: Alfarol; Hornel; Onealfa; Oxarol; Rocaltrol; ***Malaysia***: Alpha D3; Bon-One; Bonky; Calcijex; Fairy ADE; One-Alpha; Osteocap; Rocaltrol; Roical; Zemplar; ***Mex.***: Albrinol; Alfad; Altrical†; Altrol; Calciofem; Felipgel-F; Geldex; Lemytriol†; Nafartol; Rocaltrol†; Silkis; Tirocal; Triolan†; Valmetrol-3; Zemplar; Zygium†; ***Neth.***: Calcijex†; Devaron; Dihydral; Etalpha; Rocaltrol; Silkis; Zemplar; ***Norw.***: AFI-D_2; Detremin; Divisun; Etalpha; Rocaltrol; Silkis; Zemplar; ***NZ***: CalD; One-Alpha; Rocaltrol; ***Philipp.***: Alpha D3; Bon-One†; One-Alpha; Osteomeg†; Rocaltrol; Silkis; ***Pol.***: Alfadiol; Calcijex†; Devikap; Devisol; Juvit D_3; One-Alpha; Rocaltrol†; Silkis†; Vigantol; Vigantoletten; Zemplar; ***Port.***: Calcijex; Dedrogyl; Etalpha; Rocaltrol; Silkis; Vigantol; Zemplar; ***Rus.***: Alpha D3 (Альфа Д3-тев); Aquadetrim (Акводетрим); AT 10 (A T 10); Etalpha (Этальфа); One-Alfa (Ван-Альфа); Osteotriol (Остеотриол); Oxidevit (Оксидевит); Rocaltrol (Рокальтрол); Tachystin (Тахистин)†; Vigantol (Вигантол); Zemplar (Земплар); ***S.Afr.***: AT 10†; One-Alpha; Rocaltrol; ***Singapore***: Alpha D3; Bon-One; Calcijex; One-Alpha†; Osteomed; Rasputin; Rocaltrol; Roical; Silkis; Zemplar; ***Spain***: Calcijex†; Etalpha; Hidroferol; Rocaltrol; Silkis; Zemplar; ***Swed.***: Detremin; Dygratyl; Etalpha; Rocaltrol; Zemplar; ***Switz.***: AT 10†; Natecal D; Renatriol; Rocaltrol; Silkis; Vi-De_3; Zemplar; ***Thai.***: Alpha D3; Alphadol†; Bon-One; Cacare; Calciferol; Calcit; Decostriol; Medi-Alpha; Meditrol; One-Alpha; Osteo D; Rocaltrol; ***Turk.***: Alpha D3; Calcijex; Decostriol; Devit-3; Monovit D3; One-Alpha; Osivit-D3; Osteo-D; Rocaltrol; Vi-D3; Zemplar; ***UAE***: Calciphar; ***UK***: AT 10; Calcijex†; Desunin; Fultium-D_3; One-Alpha; Rocaltrol; Silkis; Vita-D3; Zemplar; ***Ukr.***: Alpha D3 (Альфа Д3); Aquadetrim (Акводетрим); ***USA***: Advanced D; Baby Drops; Calciferol; Calcijex; Calderol; D 400; D-Vita; D1000; D3-50; D_3 Dots; Ddrops; Decara; Delta-D; DHT; Drisdol; Enfamil D-Vi-Sol; Hectorol; High Potency D; Maximum D3; Replesta; Rocaltrol; Thera-D; Ultra Strength D; Vectical; Zemplar; ***Venez.***: Alpha D3; Rocaltrol; Silkis; Zemplar.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Calcitriol Capsules; Calcium and Colecalciferol Tablets; Calcium and Ergocalciferol Tablets; Chewable Calcium and Colecalciferol Tablets; Chewable Calcium and Ergocalciferol Tablets; Colecalciferol Injection; Colecalciferol Tablets; Ergocalciferol Injection; Ergocalciferol Tablets; Paediatric Vitamins A, C and D Oral Drops;

BPC 1973: Calcium with Vitamin D Tablets; Vitamins A and D Capsules;

USP 36: Calcifediol Capsules; Calcitriol Injection; Calcium and Vitamin D with Minerals Tablets; Calcium with Vitamin D Tablets; Cholecalciferol Capsules; Dihydrotachysterol Capsules; Dihydrotachysterol Oral Solution; Dihydrotachysterol Tablets; Ergocalciferol Capsules; Ergocalciferol Oral Solution; Ergocalciferol Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins

with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Oleovitamin A and D Capsules; Oleovitamin A and D; Paricalcitol Injection.

Vitamin E Substances

Vitamina E; Витамины Группы Е.
ATC — A11HA03.
ATC Vet — QA11HA03.

NOTE. The food additive number E306 is used for tocopherols.

Vitamin E is a generic term applied to a large number of natural or synthetic compounds. The most important substances are the **tocopherols** of which **alpha tocopherols** are the most active and widely distributed in nature; other naturally occurring tocopherols include beta, gamma, and delta tocopherols, but these are not used in therapeutics. The other group of compounds with vitamin E activity are the tocotrienols.

Alpha tocopherols occur naturally in the *d* optical isomer form, which is more active than the synthetic racemic *dl* form; for further details concerning the comparative activities of the different forms and isomers of vitamin E compounds, see under Units, below.

d-Alpha Tocopherol

d-Alfa Tokoferol; *RRR*-alpha-Tocophérol; *RRR*-alpha-Tocopherolum; d-Альфа-токоферол; Natural Alpha Tocopherol; Natural α-Tocopherol; D-α-Tocoferol; *d*-α-Tocopherol; *RRR*-α-Tocopherol; *RRR*-α-Tocopherolum; *RRR*-α-Tokoferol; *RRR*-α-Tokoferoli; *RRR*-α-Tokoferolis.
(+)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.
$C_{29}H_{50}O_2$=430.7
CAS — 59-02-9.
UNII — N9PR3490H9.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

Ph. Eur. 8: (*RRR*-α-Tocopherol; *RRR*-Alpha-Tocopherol BP 2014). A clear, colourless, or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas in airtight containers. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

dl-Alpha Tocopherol

Synthetic α-Tocopherol; all-*rac*-α-Tocopherol; all-*rac*-α-Tokoferol; Alpha Tocopherol; *dl*-α-Tocopherol; dl-Альфа-токоферол; E307; int-*rac*-α-Tocopherolum; DL-α-Tocoferol; Synthetic Alpha Tocopherol; Tocoferolum Alfa; α-Tocopherol; α-Tocopherolum; α-Tokoferol; Tokoferol-alfa; tout-*rac*-α-Tocophérol; Visų racematų α-Tokoferolis; (±)-Alpha-Tocopherol.
(±)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.
$C_{29}H_{50}O_2$=430.7
CAS — 10191-41-0.
UNII — H4N855PNZ1 (alpha tocopherol); 7QWA1RIO01 (dl-alpha tocopherol).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn. US* allows it under the title Vitamin E.

Ph. Eur. 8: (all-*rac*-α-Tocopherol; all-*rac*-Alpha Tocopherol BP 2014). A clear, colourless or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

d-Alpha Tocoferil Acetate

(+)-Alpha-Tocopherol Acetate; (+)-Alpha-Tocopheryl Acetate; *d*-Alpha Tocopheryl Acetate; *RRR*-alpha-Tocophéryle, acétate de; *RRR*-alpha-Tocopherylis acetas; d-Альфа-токоферола Ацетат; D-α-Tocoferilo, acetato de; Tocoferoli Alfa *RRR* Acetas; *RRR*-α-Tocopheroli Acetas; *d*-α-Tocopheryl Acetate; *RRR*-α-Tocopheryl Acetate; *RRR*-α-Tocopherylis Acetas; *RRR*-α-Tokoferilio acetatas; *RRR*-α-Tokoferol-acetát; Tokoferol-acetát alfa *RRR*; Tokoferol-alfa-*RRR*-acetát; *RRR*-α-Tokoferylacetat; *RRR*-α-Tokoferylu octan; *RRR*-α-Tokoferyyliasetaatti.
(+)-α-Tocopherol acetate.
$C_{31}H_{52}O_3$=472.8
CAS — 58-95-7.
UNII — A7E6112E4N.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

Ph. Eur. 8: (*RRR*-α-Tocopheryl Acetate; *RRR*-Alpha-Tocopheryl Acetate BP 2014). A clear, colourless or slightly greenish-yellow, viscous oily liquid. Practically insoluble in water; soluble in alcohol; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It may solidify in the cold. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acetate

tout-*rac*-α-Tocophéryle, acétate de; Acetato de *dl*-alfa-tocoferilo; all-*rac*-α-Tocopheryl Acetate; all-*rac*-α-Tokoferylu octan; Alpha Tocopheryl Acetate; *dl*-Alfa Tokoferil Asetat; *dl*-Alpha Tocopheryl Acetate; *dl*-α-Tocopheryl Acetate; dl-Альфа-токоферола Ацетат; int-*rac*-α-Tocopherylis acetas; DL-α-Tocoferilo, acetato de; Tocoferoli Alfa Acetas; α-Tocopherol Acetate; α-Tocopheroli Acetas; Tokoferol alfa-acetát; Tokoferolu octan; Visų racematų α-Tokoferilio acetatas; (±)-Alpha-Tocopherol acetate.
(±)-α-Tocopherol acetate.
$C_{31}H_{52}O_3$=472.8
CAS — 7695-91-2; 52225-20-4.
UNII — 9E8X80D2L0 (alpha tocoferil acetate); WR1WPI7EW8 (dl-alpha tocoferil acetate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Jpn. US* allows it under the title Vitamin E.

Eur. also has a monograph for the concentrated powdered form.

Ph. Eur. 8: (all-*rac*-α-Tocopheryl Acetate; all-*rac*-Alpha Tocopheryl Acetate BP 2014). A clear, colourless or slightly greenish-yellow, viscous, oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

Ph. Eur. 8: (α-Tocopheryl Acetate Concentrate (Powder Form); α-Tocopherylis Acetatis Pulvis; Alpha Tocopheryl Acetate Concentrate (Powder Form) BP 2014). It is prepared either by finely dispersing *dl*-alpha tocoferil acetate in a suitable carrier (e.g. gelatin, acacia, carbohydrates, lactoproteins, or a mixture of these) or by adsorbing *dl*-alpha tocoferil acetate on to silicic acid. The concentrate contains not less than 25% of *dl*-alpha tocoferil acetate. Almost white, yellowish, or light-brown small particles. Depending on the formulation, the powder may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light.

USP 36: (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

d-Alpha Tocoferil Acid Succinate

d-Alpha-Tocopherol acid succinate; *d*-Alpha Tocopheryl Acid Succinate; *RRR*-alpha-Tocophéryle, hydrogénosuccinate de; *RRR*-alpha-Tocopherylis hydrogenosuccinas; d-Альфа Токоферола Сукцинат; D-α-Tocoferilo, succinato ácido; Succinato ácido de *d*-alfa-tocoferilo; Tocoferoli Alfa *RRR* Hydrogenosuccinas; *RRR*-α-Tocopheroli Hydrogenosuccinas; *d*-α-Tocopheryl Acid Succinate; *RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-α-Tocopherylis Hydrogenosuccinas; *RRR*-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa-*RRR*-hydrogen-sukcinát; *RRR*-α-Tokoferol-hidrogén-szukcinát; *RRR*-α-Tokoferylvätesuccinat; *RRR*-α-Tokoferyylivetysuksinaatti.
(+)-α-Tocopherol hydrogen succinate.
$C_{33}H_{54}O_5$=530.8
CAS — 4345-03-3.
UNII — LU4B53JYVE.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

US also includes Vitamin E Polyethylene Glycol Succinate, a mixture formed by the esterification of *d*-alpha tocoferil acid succinate with a macrogol.

Ph. Eur. 8: (*RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-Alpha Tocopheryl Hydrogen Succinate BP 2014). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 36: (Vitamin E). A white, practically odourless, powder. M.p. about 75 degrees; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acid Succinate

Alpha Tocopheryl Hydrogen Succinate; DL-alpha-Tocophéryle, hydrogénosuccinate de; DL-alpha-Tocopherylis hydrogenosuccinas; *dl*-Alpha Tocopheryl Acid Succinate; *dl*-α-Tocopheryl Acid Succinate; dl-Альфа Токоферола Сукцинат; DL-α-Tocoferilo, succinato ácido; Succinato ácido de *dl*-alfa-tocoferilo; Tocoferoli Alfa Hydrogenosuccinas; DL-α-Tocopheroli Hydrogenosuccinas; DL-α-Tocopheryl Hydrogen Succinate; DL-α-tocopherylis Hydrogenosuccinas; DL-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa hydrogen sukcinát; DL-α-tokoferol-hidrogén-szukcinát; DL-α-Tokoferylvätesuccinat; DL-α-Tokoferyylivetysuksinaatti.
(±)-α-Tocopherol hydrogen succinate.
$C_{33}H_{54}O_5$=530.8
CAS — 17407-37-3.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows it under the title Vitamin E.

Ph. Eur. 8: (DL-α-Tocopheryl Hydrogen Succinate; Alpha Tocopheryl Hydrogen Succinate BP 2014). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 36: (Vitamin E). A white, practically odourless, powder. M.p. about 70 degrees; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

Units

Though the potency of preparations of vitamin E is still sometimes expressed in units, the International Standard for vitamin E was discontinued in 1956. The International Unit was the activity contained in 1 mg of a standard preparation of *dl*-alpha-tocoferil acetate. Past editions of the USP have stated that in expressing vitamin E activity of tocopherol products, the following equivalents of 1 mg were to be used:

- *d*-alpha tocopherol, 1.49 units
- *dl*-alpha tocopherol, 1.1 units
- *d*-alpha tocoferil acetate, 1.36 units
- *dl*-alpha tocoferil acetate, 1 unit
- *d*-alpha tocoferil acid succinate, 1.21 units
- *dl*-alpha tocoferil acid succinate, 0.89 unit.

For dietary purposes, vitamin-E activity may now be expressed in terms of alpha tocopherol equivalents (α-TEs). One α-TE is the activity contained in:

- 1 mg of *d*-alpha tocopherol (natural alpha tocopherol; *RRR*-α-tocopherol)
- 1.4 mg *dl*-alpha tocopherol
- 1.1 mg *d*-alpha tocoferil acetate
- 1.5 mg *dl*-alpha tocoferil acetate
- 1.2 mg *d*-alpha tocoferil acid succinate
- 1.7 mg *dl*-alpha tocoferil acid succinate.

Uses and Administration

Vitamin E, a fat-soluble vitamin, prevents the oxidation of polyunsaturated fatty acids. It reacts with free radicals, which are the cause of oxidative damage to cell membranes, without the formation of another free radical in the process.

Vitamin E deficiency is rare but develops when the dietary intake is inadequate. In cystic fibrosis or cholestasis, malabsorption of fat may lead to a vitamin E deficiency; deficiency may also occur in abetalipoproteinaemia where there are abnormalities of lipid transport and malabsorption. In previously healthy adults malabsorption and low intake of vitamin E must continue for several years before signs of deficiency appear. The major signs of vitamin E deficiency are the development of myopathic and neurological disorders.

Vitamin E is used in the treatment and prevention of vitamin E deficiency. It is usually given orally, generally the preferred route, but has also been given by intramuscular or

intravenous routes. It may be given as *d*- or *dl*-alpha tocopherol or as the respective acetates or acid succinates.

Recommended doses vary, in part because of differences in the activity of different preparations; however, a daily dose of several times the recommended dietary allowance (RDA), or around 40 to 50 mg of *d*-alpha tocopherol, has been suggested for deficiency syndromes; somewhat higher daily doses have been given in cystic fibrosis (100 to 200 mg of *dl*-alpha tocoferil acetate, or about 67 to 135 mg of *d*-alpha tocopherol) and much higher daily doses in abetalipoproteinaemia (50 to 100 mg/kg of *dl*-alpha tocoferil acetate, or about 33 to 67 mg/kg *d*-alpha tocopherol).

For doses used in children, see Administration in Children, below.

Vitamin E has also been tried in many other disorders, for which the evidence of value is generally lacking (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1, and Prophylaxis of Malignant Neoplasms, p. 2047.3).

Other substances with vitamin-E activity that have been used include *dl*-alpha tocoferil palmitate and tocofersolan (tocophersolan), a water-soluble substance which is *d*-alpha tocoferil acid succinate combined with a macrogol. Wheatgerm oil (p. 2647.1) is also widely used as a source of vitamin E.

Vitamin E is often used as an antoxidant in pharmaceutical manufacturing.

General reviews.

1. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. *J Physiol Biochem* 2001; **57:** 43–56.
2. Dutta A, Dutta SK. Vitamin E and its role in the prevention of atherosclerosis and carcinogenesis: a review. *J Am Coll Nutr* 2003; **22:** 258–68.
3. Sung L, *et al.* Vitamin E: the evidence for multiple roles in cancer. *Nutr Cancer* 2003; **46:** 1–14.
4. Zingg J-M, Azzi A. Non-antioxidant activities of vitamin E. *Curr Med Chem* 2004; **11:** 1113–33.
5. Schneider C. Chemistry and biology of vitamin E. *Mol Nutr Food Res* 2005; **49:** 7–30.
6. Mustacich DJ, *et al.* Vitamin E. *Vitam Horm* 2007; **76:** 1–21.
7. Sen CK, *et al.* Tocotrienols: the emerging face of natural vitamin E. *Vitam Horm* 2007; **76:** 203–61.
8. Clarke MW, *et al.* Vitamin E in human health and disease. *Crit Rev Clin Lab Sci* 2008; **45:** 417–50.
9. Dotan Y, *et al.* No evidence supports vitamin E indiscriminate supplementation. *Biofactors* 2009; **35:** 469–73.
10. Galli F, Azzi A. Present trends in vitamin E research. *Biofactors* 2010; **36:** 33–42.

Administration in children. Vitamin E supplements are given to children with deficiency, such as that arising from fat malabsorption in cystic fibrosis and cholestatic liver disease; deficiency may also occur in abetalipoproteinaemia where there are abnormalities of lipid transport and malabsorption. The *BNFC* suggests the following doses expressed as *dl*-alpha tocoferil acetate, according to age:

Vitamin E deficiency

orally

- neonate: 10 mg/kg daily
- 1 month to 18 years: 2 to 10 mg/kg daily; up to 20 mg/kg has been used

Malabsorption in cystic fibrosis

orally

- 1 month to 1 year: 50 mg daily adjusted as necessary
- 1 to 12 years: 100 mg daily adjusted as necessary
- 12 to 18 years: as for adults, see Uses and Administration, p. 2119.3.

Cholestasis and severe liver disease

orally

- neonate: 10 mg/kg daily
- 1 month to 12 years: initially 100 mg daily, adjusted according to response; up to 200 mg/kg daily may be required
- 12 to 18 years: initially 200 mg daily, adjusted according to response; up to 200 mg/kg daily may be required

intramuscularly

- neonate: 10 mg/kg once monthly
- 1 month to 18 years: 10 mg/kg (maximum 100 mg) once monthly

For abetalipoproteinaemia in children, the recommended adult dose of 50 to 100 mg/kg *dl*-alpha tocoferil acetate daily is also used, although the higher dose of 100 mg/kg daily is suggested for neonates.

Vitamin E has also been tried in other perinatal disorders (below) such as intraventricular haemorrhage and retinopathy of prematurity (below).

Age-related macular degeneration. Dietary supplementation with antoxidants including vitamin E has been promoted for age-related macular degeneration. For further details, see under Betacarotene, p. 2051.2.

Chemotherapy-induced toxicity. A small pilot study[1] found that oral vitamin E 600 mg daily given during chemotherapy and for 3 months afterwards reduced chemotherapy-induced neuropathy in patients given regimens based on platinum (carboplatin or cisplatin), or paclitaxel, or both. (See also Effects on the Nervous System, under Cisplatin, p. 767.3.) The authors considered that similarities exist between neuropathy induced by cisplatin (and possibly paclitaxel) and that seen in vitamin E deficiency states, (see below). Oral vitamin E 300 mg daily alleviated palmar-plantar erythrodysesthesia in 5 patients given capecitabine and docetaxel.[2] In 4 of these patients, chemotherapy was continued without interruption or dose reduction. Improvement was generally noticed after 7 to 10 days of treatment.

1. Argyriou AA, *et al.* Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology* 2005; **64:** 26–31.
2. Kara IO, *et al.* Palmar-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. *Breast* 2006; **15:** 414–24.

Deficiency states. Vitamin E deficiency may cause neurological damage characterised by sensory loss, ataxia and retinitis pigmentosa. In 2 patients with common variable immunodeficiency and an associated enteropathy, vitamin E deficiency developed. Treatment with intramuscular or oral vitamin E led to objective neurological improvement.[1]

1. Aslam A, *et al.* Vitamin E deficiency induced neurological disease in common variable immunodeficiency: two cases and a review of the literature of vitamin E deficiency. *Clin Immunol* 2004; **112:** 24–9.

Dementia. A hypothesis that free radicals may trigger and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease (p. 388.1) has prompted the investigation of antoxidant therapies.[1] Preliminary studies[1,2] have suggested that alpha tocopherol might possibly slow progression. A prospective cohort study found that self-administration of combined vitamin C and vitamin E was associated with a lower risk of vascular dementia in elderly men,[3] although no significant protective effect was seen against Alzheimer's disease. However, other studies have suggested that high intake of vitamins C and E, whether from diet[4] or supplements,[5] may reduce the risk of Alzheimer's disease. Yet another study suggested that dietary vitamin E, but not vitamin C, intake reduced the risk of Alzheimer's disease;[6] a population-based study found vitamin E intake from food and supplements to be associated with reduced cognitive decline.[7] US guidelines suggested[8] that oral vitamin E 1000 units twice daily be considered in patients with Alzheimer's disease in an attempt to slow progression of the disease. However, a large randomised study in patients with amnestic mild cognitive impairment found that vitamin E 2000 units daily provided no benefit over placebo in terms of probability of progression to Alzheimer's disease.[9] A meta-analysis[10] which included this study also found no evidence of efficacy, and suggested that vitamin E should not be recommended for treatment or prevention of cognitive impairment. Reviewers[11,12] have also recommended against the use of vitamin E for Alzheimer's disease.

1. Berman K, Brodaty H. Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs* 2004; **18:** 807–25.
2. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; **336:** 1216–22.
3. Masaki KH, *et al.* Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology* 2000; **54:** 1265–72.
4. Engelhart MJ, *et al.* Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002; **287:** 3223–9.
5. Zandi PP, *et al.* Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County study. *Arch Neurol* 2004; **61:** 82–8.
6. Morris MC, *et al.* Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002; **287:** 3230–7.
7. Morris MC, *et al.* Vitamin E and cognitive decline in older persons. *Arch Neurol* 2002; **59:** 1125–32.
8. Doody RS, *et al.* Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; **56:** 1154–66. Also available at: http://www.neurology.org/cgi/reprint/56/9/1154.pdf (accessed 09/01/06)
9. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352:** 2379–88.
10. Isaac MGEKN, *et al.* Vitamin E for Alzheimer's disease and mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 30/01/09).
11. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.
12. Boothby LA, Doering PL. Vitamin C and vitamin E for Alzheimer's disease. *Ann Pharmacother* 2005; **39:** 2073–80.

Ischaemic heart disease. For a discussion of studies involving vitamin E in the prophylaxis of ischaemic heart disease, see p. 2047.1.

Malignant neoplasms. For a discussion of studies involving vitamin E in the prophylaxis of malignant neoplasms, see p. 2047.3.

Motor neurone disease. A prospective analysis found that regular use of vitamin E supplements was associated with a decreased risk of amyotrophic lateral sclerosis.[1] However, further studies were considered necessary and significant evidence to support the benefit of antoxidants in motor neurone disease (p. 2605.2) is lacking.[2]

1. Ascherio A, *et al.* Vitamin E intake and risk of amyotrophic lateral sclerosis. *Ann Neurol* 2005; **57:** 104–10.
2. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 20/06/08).

Muscle spasm. Vitamin E is one of several drugs that have been tried in the management of nocturnal cramps (p. 2014.1) but there is little convincing evidence to support its use.[1,2] It has, however, been found to have similar efficacy to quinine for haemodialysis-induced cramp (p. 1779.3).[3] A small study found the combination of vitamins E and C to be more effective than either vitamin alone for reducing haemodialysis-induced cramps; prolonged use was not evaluated.[4]

1. Connolly PS, *et al.* Treatment of nocturnal leg cramps: a crossover trial of quinine vs vitamin E. *Arch Intern Med* 1992; **152:** 1877–80.
2. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
3. Roca AO, *et al.* Dialysis leg cramps: efficacy of quinine versus vitamin E. *ASAIO J* 1992; **38:** M481–M485.
4. Khajehdehi P, *et al.* A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. *Nephrol Dial Transplant* 2001; **16:** 1448–51.

Muscular dystrophies. Vitamin E substances have been used in some countries in the management of muscular dystrophies, but controlled studies[1] have failed to find any benefit.

1. Örndahl G, *et al.* Functional deterioration and selenium-vitamin E treatment in myotonic dystrophy: a placebo-controlled study. *J Intern Med* 1994; **235:** 205–10.

Parkinsonism. Vitamin E has been tried (as *dl*-alpha tocopherol) in an attempt to slow neurodegeneration in patients with Parkinson's disease (p. 889.1) but has proved ineffective.[1]

1. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.

Perinatal disorders. The primary biological action of vitamin E is known to be the protection of polyunsaturated fatty acids, and thus membranes, from oxidation. Two disorders that may particularly affect premature and very low birth-weight infants are *retinopathy of prematurity* (below) and *intraventricular haemorrhage* (p. 1128.3) and as both may have some association with the occurrence of excess oxygen or oxidant stress, there has been interest in the possibility that vitamin E might have a role in their prevention.

Pre-eclampsia. Although preliminary evidence has suggested[1] that women supplemented with vitamin E (with other supplements) may be at decreased risk of developing clinical pre-eclampsia (see Hypertension in Pregnancy, p. 1251.1), large studies[2,3] in women given combined vitamin C and vitamin E supplements failed to show any benefit.

1. Rumbold A, Crowther CA. Vitamin E supplementation in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/01/06).
2. Poston L, *et al.* Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006; **367:** 1145–54.
3. Rumbold AR, *et al.* ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006; **354:** 1796–1806.

Respiratory-tract infections. A randomised study in elderly patients found that supplementation with vitamin E had no effect on the incidence of lower respiratory-tract infections in elderly nursing home residents, although there was some suggestion of benefit from supplementation on upper respiratory-tract infections, particularly the common cold.[1] In contrast, another study found that, among elderly non-institutionalised people with an acute respiratory-tract infection, vitamin E supplementation increased illness duration, number of symptoms, frequency of fever, and restricted activity.[2]

1. Meydani SN, *et al.* Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* 2004; **292:** 828–36. Correction. *ibid.;* 1305.
2. Graat JM, *et al.* Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA* 2002; **288:** 715–21.

Retinitis pigmentosa. Vitamin E has been tried in retinitis pigmentosa (p. 2101.1) with conflicting results.

Retinopathy of prematurity. Retinopathy of prematurity (retrolental fibroplasia) is a disease associated with immature vascularisation of the retina. Formation of retinal lesions may interfere with normal development, resulting in neovascularisation and fibrovascular proliferation. Some cases regress spontaneously but advanced cases can lead to tractional retinal detachment and loss of vision. The pathogenesis of retinopathy of prematurity is not clearly understood, but is likely to be multifactorial;[1,2] greater immaturity, lower birth-weight, and male gender are associated with more severe disease.[3]

After the acknowledgement of a link between retinopathy of prematurity and oxygen therapy, the use of oxygen was reduced and the incidence of this disorder declined. A subsequent rise in incidence probably reflected the increased survival rate of extremely premature infants due to improved neonatal care, and certainly, variations in incidence between countries, or indeed areas, may reflect varying levels of available postnatal care.[2] Despite extensive research (see p. 1801.3), a safe concentration of arterial oxygen has not been defined and antoxidants such as vitamin E have been used prophylactically for several decades. However, this use is controversial. Studies assessing the efficacy of vitamin E prophylaxis have not produced clear results.[4] Some considered that vitamin E prophylaxis had a beneficial effect and recommended[5] routine prophylaxis as soon as possible after birth for infants less than 1.5 kg. However, others feel that there are no data to support prophylaxis with vitamin E[4,6,7] and that antoxidants cannot be recommended for routine use.[1] The various studies have been re-evaluated by meta-analysis, the results of which suggest that vitamin E may reduce the incidence of stage 3+ retinopathy of prematurity,[8] a conclusion supported by a systematic review[9] which noted, however, that supplementation increased the risk of sepsis and could therefore not be recommended. The authors of the meta-analysis recommended that a well-controlled study should be conducted.[8] A systematic review of vitamin A supplementation in very low birth-weight infants concluded that vitamin A may reduce the incidence of retinopathy of prematurity, and that further investigation was warranted.[10]

Other agents tried for prophylaxis include penicillamine and antenatal dexamethasone, with some suggestion of benefit.[11,12] Reduction in ambient-light exposure did not alter the incidence of retinopathy of prematurity.[13,14] Inositol supplementation has also been tried, with conflicting results.[4]

Intravitreal injection of bevacizumab is under investigation for the management of severe retinopathy of prematurity.[15-17]

1. Holmström G. Retinopathy of prematurity. *BMJ* 1993; **307:** 694–5.
2. Wheatley CM, *et al*. Retinopathy of prematurity: recent advances in our understanding. *Arch Dis Child Fetal Neonatal Ed* 2002; **87:** F78–F82.
3. Darlow BA, *et al*. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics* 2005; **115:** 990–6.
4. Reynolds JD. The management of retinopathy of prematurity. *Paediatr Drugs* 2001; **3:** 263–72.
5. Johnson L, *et al*. Effect of sustained pharmacologic vitamin E levels on incidence and severity of retinopathy of prematurity: a controlled clinical trial. *J Pediatr* 1989; **114:** 827–38.
6. Law MR, *et al*. Is routine vitamin E administration justified in very low-birthweight infants? *Dev Med Child Neurol* 1990; **32:** 442–50.
7. Ehrenkranz RA. Vitamin E and retinopathy of prematurity: still controversial. *J Pediatr* 1989; **114:** 801–3.
8. Raju TNK, *et al*. Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. *J Pediatr* 1997; **131:** 844–50.
9. Brion LP, *et al*. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 20/06/08).
10. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 14/03/08).
11. Higgins RD, *et al*. Antenatal dexamethasone and decreased severity of retinopathy of prematurity. *Arch Ophthalmol* 1998; **116:** 601–5.
12. Phelps DL, *et al*. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).
13. Reynolds JD, *et al*. Lack of efficacy of light reduction in preventing retinopathy of prematurity. *N Engl J Med* 1998; **338:** 1572–6.
14. Phelps DL, Watts JL. Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).
15. Mintz-Hittner HA, Kuffel RR. Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. *Retina* 2008; **28:** 831–8.
16. Kusaka S, *et al*. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. *Br J Ophthalmol* 2008; **92:** 1450–5.
17. Quiroz-Mercado H, *et al*. Antiangiogenic therapy with intravitreal bevacizumab for retinopathy of prematurity. *Retina* 2008; **28** (suppl): S19–S25. Correction. *ibid*. 2009; **29:** 127.

Tardive dyskinesia. Reviews[1,2] on the use of vitamin E in the management of antipsychotic-induced tardive dyskinesia (see under Extrapyramidal Disorders, p. 1049.3) concluded that evidence of benefit has generally come from small studies with methodological problems. One review[1] concluded that whereas vitamin E may protect against deterioration of tardive dyskinesia there was no evidence that it produced symptomatic improvement. It was suggested[2] that vitamin E therapy may be most beneficial in those patients with tardive dyskinesia of less than 5-years duration. Some recommend vitamin E as a treatment option in patients with newly diagnosed disease.[3] Further large-scale studies are required to establish its place in treatment.

1. McGrath J, Soares-Weiser K. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/01/06).
2. Boomershine KH, *et al*. Vitamin E in the treatment of tardive dyskinesia. *Ann Pharmacother* 1999; **33:** 1195–1202.
3. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.

Adverse Effects and Precautions

Vitamin E is usually well tolerated. Large doses may cause diarrhoea, abdominal pain, and other gastrointestinal disturbances, and have also been reported to cause blurred vision, dizziness, fatigue and weakness. Contact dermatitis has occurred after topical application.

Large doses of vitamin E have been reported to increase bleeding tendency in vitamin-K deficient patients such as those taking oral anticoagulants. However, it has also been suggested that it may increase the risk of thrombosis in some patients, such as those taking oestrogens. The clinical significance of these effects is not known.

A higher incidence of necrotising enterocolitis has been noted in premature infants weighing less than 1.5 kg treated with vitamin E.

Carcinogenicity. For mention of an *increased* incidence of second primary cancers and reduced cancer-free survival in patients with head and neck cancer receiving vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p. 2047.3.

Effects on mortality. While some studies of antoxidants, including vitamin E, have suggested beneficial effects on the progression of cardiovascular disease and cancer, other studies (including large randomised studies such as the Women's Health Study[1]) have shown little or no effect.[2] Vitamin E may even cause an increased risk of heart failure, or incidence of some cancers (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1, and Prophylaxis of Malignant Neoplasms, p. 2047.3). A meta-analysis[3] and a systematic review[4] of vitamin E supplementation found no benefit in terms of mortality. Another meta-analysis[5] found no effect for vitamin E supplementation on all-cause mortality overall. However, in dose-response analysis, high-dosage vitamin E (greater than 400 units daily) showed a significantly increased risk; there was some suggestion of a decreased risk with low doses (less than 400 units daily); all-cause mortality progressively increased for doses greater than 150 units daily. (Such an effect was not seen in the Women's Health Study, in which participants received 600 units on alternate days.) Some have commented[6] that the meta-analysis may not have isolated the effects of vitamin E, since in many of the trials studied, other nutritional supplements had been given, including betacarotene, itself possibly associated with an increased risk of death; however, the use of high-dose vitamin E was considered unjustified. A systematic review of antoxidant supplementation found that vitamin E, either singly or with other antoxidants, increased mortality.[7] A large cohort study in a population aged 65 years or older, after adjustment for age and sex, found that there was no association between vitamin E use and mortality. However, mortality was increased in vitamin E users who had a history of cardiovascular disease, or who were taking nitrates, warfarin, and diuretics. There was a consistent trend towards reduced mortality in vitamin E users without cardiovascular disease or taking these drugs. The authors concluded that vitamin E should be used with caution in those with cardiovascular disease, and that further investigation of the potential interaction between vitamin E and particular drugs was warranted.[8]

1. Lee I-M, *et al*. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294:** 56–65.
2. Brown BG, Crowley J. Is there any hope for vitamin E? *JAMA* 2005; **293:** 1387–90.
3. Vivekananthan DP, *et al*. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361:** 2017–23.
4. Shekelle PG, *et al*. Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease. *J Gen Intern Med* 2004; **19:** 380–9.
5. Miller ER, *et al*. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142:** 37–46.
6. Greenberg ER. Vitamin E supplements: good in theory, but is the theory good? *Ann Intern Med* 2005; **142:** 75–6.
7. Bjelakovic G, *et al*. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
8. Hayden KM, *et al*. Cache County Investigators. Risk of mortality with vitamin E supplements: the Cache County study. *Am J Med* 2007; **120:** 180–4.

Neonatal toxicity. For a review and discussion of liver and kidney toxicity in premature neonates associated with an intravenous preparation of vitamin E (E-Ferol) and attributed to the inclusion of polysorbates, see Effects in Infants, p. 2204.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vitamin E substances as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Various drugs may interfere with the absorption of vitamin E including colestyramine, colestipol, and orlistat. High doses of vitamin E may increase the effects of oral anticoagulants.

Pharmacokinetics

Absorption of vitamin E from the gastrointestinal tract is dependent on the presence of bile and on normal pancreatic function. The amount of vitamin E absorbed varies widely between about 20% and 80% and appears to decrease as the dose is increased. It enters the blood via the chylomicrons in the lymph and is bound to beta lipoproteins. It is widely distributed to all tissues, and stored in adipose tissue. Some vitamin E is metabolised in the liver to glucuronides of tocopheronic acid and its γ-lactone. Some is excreted in the urine, but most of a dose is slowly excreted in the bile. Vitamin E appears in breast milk but is poorly transferred across the placenta.

Human Requirements

The daily requirement of vitamin E has not been clearly defined but is probably about 3 to 12 mg of *d*-alpha tocopherol or the equivalent of other vitamin E substances. Requirements increase with increased dietary amounts of polyunsaturated fatty acids. There appears to be no evidence that supplements are required in subjects on balanced diets.

Vitamin E is widely distributed in food. The richest sources are vegetable oils especially wheat-germ oil (p. 2647.1), sunflower oil, and cottonseed oil; cereals and nuts are also good sources. Significant losses of vitamin E from food may occur during cooking and storage.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI—see p. 2046.1) nor an estimated average requirement (EAR) has been set for vitamin E although daily intakes of 4 mg and 3 mg α-tocopherol equivalents (see under Units, p. 2119.3) were considered adequate for men and women, respectively.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for vitamin E of 800 units or 540 mg of *d*-alpha tocopherol daily.

In the USA the recommended dietary allowance for adults is 15 mg daily of alpha tocopherol, and the tolerable upper intake level is 1 g daily.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids*. Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antioxidante Natural†; E-devit Protectora†; Ephynal; Etec; Evion; Tonovital E†; ***Austral.***: Chew-E†; Dal-E†; Mega E; Micelle E†; Natural E†; Water Soluble E†; ***Austria***: Avigilen; Etocovit; Evitol; Tocovenos†; ***Belg.***: Ephynal†; Optovit E; ***Braz.***: Bio E; E Plus†; E-Radicaps; E-Tabs; Emama; Ephynal; Fonto-Vit E†; Fort E; Teutovit-E; Vieta; Vita-E; Vitizin E; Zirvit E; ***Canad.***: Aquasol E†; E-Prime†; Kyolic Formula 106†; Novo E†; ***Chile***: Crevet-E; Egogyn; Etec; ***China***: Su Le Kang (苏乐康); ***Cz.***: Erevit; Vedrop; ***Denm.***: E-Vitamin; Vedrop; ***Fin.***: Bio-E-Vitamin; Equiday; Ido-E†; ***Fr.***: Dermorelle; Toco; Tocolion; Tocopa; Vedrop; ***Ger.***: Antioxidans E; Detulin†; Eusovit; Evion†; Flexal Vitamin E†; Malton E; Mowivit; Optovit; Sanavitan S†; Spondyvit†; Tocorell; Uno-Vit†; Vedrop; Vitazell E; ***Gr.***: E-Vicotrat; Ephynal; Eviol; Evion; Evit; ***Hong Kong***: Keri Vit E†; Myra 300-E†; Natopherol†; Super E†; Topher-E†; ***India***: Bio-8888; Bio-E; Covita; E-Cap; Edge; EEE; Ensules; Ephynal; Etoplex; Evion; Evit; Evitam; Evitop; Glyvion; Monovit-EN; Novee; Ocuvit; ***Indon.***: Bio-E; Dalfarol; Edoti; Erpha Vit E; Evion; Evipon; Lanturol; Natopherol; Natur-E; Naturol; Orginal E; Prima-E; Proxidan; Santa-E; Tocopherine†; Vinpo-E; Vitaferol; ***Irl.***: Vedrop; ***Israel***: Evitex; Evitol; ***Ital.***: Armilla; Ephynal; Evasen Crema; Evion; Natovit; Rigentex; Sursum; Vedrop; ***Jpn***: Juvela; ***Malaysia***: Citrex Vitamin E; Enat; Fairy ADE; Natopherol; Toco-E; Vitamin E.F.C.; ***Mex.***: E-Fertoc; Egrin†; EPH; Eugerminol; Ixopolet; Revitare E; Vit-E-

The symbol † denotes a preparation no longer actively marketed

Far; ***Neth.***: Vedrop; ***Norw.***: Bio-E; Ido-E†; Nycoplus E-vitamin; Vedrop; ***NZ***: Micelle E†; ***Philipp.***: Enat; Enervon-E; Evion; Integra-E; Lexivit-E; Myra; Zyme; ***Pol.***: Dermovit E; Tokovit E; Vedrop; Vitole E†; ***Port.***: Ve; Vedrop; ***Rus.***: Evitol (Эвитол); ***S. Afr.***: Ephynal†; Vitaforce E†; ***Singapore***: Enat; Natopherol; Naturee; Rosken Skin Repair Vitamin E; ***Spain***: Auxina E; Ephynal; Vedrop; ***Swed.***: E-vidon†; E-vimin; Ido-E†; Vedrop; ***Switz.***: ecobiosan†; Ephynal; Evit; Optovit†; ***Thai.***: Bio-E; Blackmores Bio E; E-Drops; Nat E; Patar E-400; Tupper-E; ***Turk.***: E-400; Eforol; Ephynal; Evicap; Evigen; Evon; Grandpherol; Natural E†; ***UK***: Ephynal; Prairie Gold; Vedrop; Vita-E; ***Ukr.***: Enat (Энат); ***USA***: Aqua-E; Aquasol E; Aquavit-E; E-Gems; E-Oil; GRX Vitamin E; Natural E; Nutr-E-Sol; Promega; Vita-Plus E; Vitec; ***Venez.***: Best; Egogyn; Epol; Missecap; Nat-E; Vit-E-Nat; Vit-E-Var; Vitae; Viteral.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Ger.***: Infi-Symphytum; NeyChon Nr 68; NeyDil Nr 66†; NeyGero Nr 64; NeyGeront Vitalkapsein A; NeyLing Nr 66.

Pharmacopoeial Preparations
BP 2014: Alpha Tocopheryl Succinate Tablets;
USNF 31: Tocopherols Excipient;
USP 36: Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Vitamin E Capsules; Vitamin E Preparation.

Vitamin K Substances

Vitamina K; Витамины Группы К.

The term vitamin K is used for a range of naphthoquinone compounds that includes: acetomenaphthone, menadiol, menadione, menatetrenone, and phytomenadione.

Acetomenaphthone *(BAN)*

Acetomenadione; Acetomenaftona; Acetomenaph.; Menadiol Diacetate; Vitamin K_4 Diacetate; Ацетоменафтон.
2-Methyl-1,4-naphthylene diacetate.
$C_{15}H_{14}O_4$=258.3
CAS — 573-20-6.
UNII — DWG8UZD9HT.

Pharmacopoeias. In *Chin.*

Menadiol Sodium Phosphate *(BANM)*

Menadiol, fosfato sódico de; Menadiol Sodium Diphosphate; Menadiolum Solubile; Vitamin K_4 Sodium Phosphate.
2-Methylnaphthalene-1,4-diyl bis(disodium phosphate) hexahydrate.
$C_{11}H_8Na_4O_8P_2,6H_2O$=530.2
CAS — 481-85-6 (menadiol); 131-13-5 (anhydrous menadiol sodium phosphate); 6700-42-1 (menadiol sodium phosphate hexahydrate); 84-98-0 (menadiol diphosphate).
UNII — 2OVL75B30W (menadiol sodium phosphate); GRL65FEU3T (menadiol diphosphate).

NOTE. Menadiol Potassium Sulfate (Potassium Menaphthosulfate) is *BAN* and Menadiol Sodium Sulfate is *rINN*.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Menadiol Sodium Phosphate). A white to pink, hygroscopic, crystalline powder with a characteristic odour. Very soluble in water; practically insoluble in alcohol.

USP 36: (Menadiol Sodium Diphosphate). A white to pink, hygroscopic, powder having a characteristic odour. Very soluble in water; insoluble in alcohol. Its solutions in water are neutral or slightly alkaline to litmus having a pH of about 8. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Menadione *(BAN)*

Menadion; Menadiona; Menadionas; Ménadione; Menadioni; Menadionum; Menaftona; Menaph.; Menaphthene; Menaphthone; Methylnaphthochinonum; Vitamin K_3; Vitamina K_3; Менадион.
2-Methyl-1,4-naphthoquinone.
$C_{11}H_8O_2$=172.2
CAS — 58-27-5.
ATC — B02BA02.
ATC Vet — QB02BA02.
UNII — 723JX6CXY5.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Menadione). A pale yellow crystalline powder. It is unstable in light. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in toluene. Protect from light.

USP 36: (Menadione). A bright yellow, practically odourless, crystalline powder. It is affected by sunlight. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 50 of vegetable oils, and 1 in 10 of benzene; sparingly soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Handling. Menadione powder is irritating to the respiratory tract and to the skin. The alcoholic solution has vesicant properties.

Menadione Sodium Bisulfite *(BANM, rINN)*

Bisulfito sódico de menadiona; Kavitanum; Menadiol Sodyum Bisülfit; Menadiona, bisulfito sódico de; Ménadione, Bisulfite Sodique de; Menadione Sodium Bisulphite; Menadioni Natrii Bisulfis; Menadionnatriumbisulfiitti; Menadionnatriumbisulfit; Menadionu wodorosiarczyn sodowy; Menaph. Sod. Bisulphite; Menaphthone Sodium Bisulphite; Methylnaphthochinonumnatrium Bisulfurosum; Vikasolum; Vitamin K_3 Sodium Bisulphite; Менадиона Натрия Бисульфит.
Sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxonaphthalene-2-sulphonate trihydrate.
$C_{11}H_8O_2NaHSO_3,3H_2O$=330.3
CAS — 130-37-0 (anhydrous menadione sodium bisulfite); 6147-37-1 (menadione sodium bisulfite trihydrate).
UNII — 6XF3C2HK77.

Pharmacopoeias. In *Chin.* and *Pol.*

Menatetrenone *(rINN)*

E-3100; Ea-0167; Menaquinone 4; Menaquinone K4; Menaquinone-4; Menatetren; Menatetrenona; Ménatétrénone; Menatetrenonum; MK-4; Vitamin $K_{2(20)}$; Vitamin MK 4; Менатетренон.
2-Methyl-3-(3,7,11,15-tetramethyl-2,6,10,14-hexadeca-tetraenyl)-1,4-naphthoquinone.
$C_{31}H_{40}O_2$=444.7
CAS — 863-61-6.
UNII — 27Y876D139.

Pharmacopoeias. In *Jpn.*

Phytomenadione *(BAN, rINN)*

Filoquinona; Fitomenadion; Fitomenadiona; Fitomenadionas; Fitonadiona; Fytomenadion; Fytomenadioni; Methylphytylnaphthochinonum; Phylloquinone; Phytomenad.; Phytomenadion; Phytoménadione; Phytomenadionum; Phytonadione; Vitamin K_1; Vitamina K_1; Фитоменадион.
2-Methyl-3-[3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione.
$C_{31}H_{46}O_2$=450.7
CAS — 84-80-0.
ATC — B02BA01.
ATC Vet — QB02BA01.
UNII — A034SE7857.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Phytomenadione). A mixture of the *trans* (*E*) and *cis* (*Z*) isomers. It contains not less than 75% of *trans*-phytomenadione, and also allows not more than 4% of *trans*-epoxyphytomenadione.

A clear, intense yellow, viscous, oily liquid, which decomposes on exposure to actinic light. Practically insoluble in water; sparingly soluble in alcohol; miscible with fatty oils. Protect from light.

USP 36: (Phytonadione). A mixture of the *E* and *Z* isomers. It contains not more than 21% of the *Z* isomer. A clear, yellow to amber, very viscous, odourless or practically odourless, liquid. It is stable in air, but decomposes on exposure to sunlight. Insoluble in water; slightly soluble in alcohol; soluble in dehydrated alcohol, in chloroform, in ether, in vegetable oils, and in benzene. Store in airtight containers. Protect from light.

Stability. A polyoxyl castor oil formulation of phytomenadione was stable for at least 30 days at room temperature when repackaged in amber glass dropper bottles.[1] When refrigerated at 4 degrees to 8 degrees, it was stable in both plastic and amber glass bottles.

1. Wong VK, Ho PC. Stability of Konakion repacked in dropper bottles for oral administration. *Aust J Hosp Pharm* 1996; **26:** 641–4.

Uses and Administration

Vitamin K is an essential cofactor in the hepatic synthesis of prothrombin (factor II) and other blood clotting factors (factors VII, IX, and X, and proteins C and S) and in the function of proteins such as osteocalcin important for bone development.

Vitamin K deficiency may develop in neonates (see Vitamin K Deficiency Bleeding, p. 2123.2), but is uncommon in adults, although it may occur in patients with malabsorption syndromes, obstructive jaundice or hepatic disease. Deficiency leads to the development of hypoprothrombinaemia, in which the clotting time of the blood is prolonged and spontaneous bleeding can occur. Coumarin anticoagulants interfere with vitamin K metabolism, and their effects can be antagonised by giving vitamin K.

Vitamin K compounds are used in the treatment and prevention of haemorrhage associated with vitamin K deficiency. The dose of vitamin K should be carefully controlled by prothrombin-time estimations.

Phytomenadione is a naturally occurring vitamin K substance. It is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by anticoagulant therapy. It is not effective as a heparin antidote. For over-anticoagulation, the dose depends on the international normalised ratio (INR) and the degree of haemorrhage. Typical doses of phytomenadione are 0.5 to 10 mg by slow intravenous injection or up to 5 mg orally (see also Over-anticoagulation, p. 2123.1). Depending on the solubilising agents used, some formulations of phytomenadione are more suitable for intravenous use than others, and dosage details vary. Phytomenadione has also been used in hypoprothrombinaemia due to certain cephalosporins (see Cefamandole, Adverse Effects, p. 236.3).

For doses of vitamin K used in children, see Administration in Children, below.

Menadiol sodium phosphate is a water-soluble derivative of menadione, a synthetic lipid-soluble vitamin K analogue. It may be used for the prevention of vitamin K deficiency in patients with malabsorption syndromes in whom oral phytomenadione may be inefficiently absorbed. It is given in usual oral doses equivalent to 10 to 40 mg of menadiol phosphate daily.

Menadiol dibutyrate has also been used; *menatetrenone* is used in the management of osteoporosis. *Acetomenaphthone* has been used in preparations promoted for the relief of chilblains.

General reviews.

1. Shearer MJ. Vitamin K. *Lancet* 1995; **345:** 229–34.
2. Vermeer C, Schurgers LJ. A comprehensive review of vitamin K and vitamin K antagonists. *Hematol Oncol Clin North Am* 2000; **14:** 339–53.
3. Vermeer C, *et al.* Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health. *Eur J Nutr* 2004; **43:** 325–35.
4. Van Winckel M, *et al.* Vitamin K, an update for the paediatrician. *Eur J Pediatr* 2009; **168:** 127–34.

Administration in children. Vitamin K deficiency can occur in children with fat malabsorption, particularly in those with cholestasis or severe liver disease. Neonates are relatively deficient in vitamin K and are at risk of bleeding if not supplemented, see Vitamin K Deficiency Bleeding, p. 2123.2. Vitamin K is also used to reverse over-anticoagulation in children (see p. 2123.1).

Phytomenadione is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by coumarin anticoagulants. For over-anticoagulation in children, specialist advice is recommended; the dose depends on the international normalised ratio (INR), the degree of haemorrhage, and whether continued anticoagulation is required. The *BNFC* suggests the following phytomenadione doses in children aged 1 month to 18 years:

- no significant bleeding or if continued anticoagulation required: intravenous injection of 15 to 30 micrograms/kg (maximum 1 mg) as a single dose, repeated as necessary
- significant bleeding or if continued anticoagulation not required: intravenous injection of 250 to 300 micrograms/kg (maximum 10 mg) as a single dose. UK licensed product information allows this dose to be repeated if response is inadequate after 2 to 6 hours

In less severe cases, an oral dose of phytomenadione 5 or 10 mg has been used in children.

The water-soluble derivative, menadiol sodium phosphate, is given as supplementation in vitamin K malabsorption. The *BNFC* suggests the following oral doses, expressed as menadiol phosphate, according to age:

- 1 to 12 years: 5 to 10 mg daily
- 12 to 18 years: 10 to 20 mg daily

In neonates with biliary atresia and liver disease oral phytomenadione 1 mg daily may be given.

For discussion of the use of vitamin K in the management of neonatal intraventricular haemorrhage, see p. 2123.1.

Action. References to the action of vitamin K and the role of vitamin K-dependent coagulation proteins and carboxyglutamate-containing proteins such as osteocalcin.

1. Friedman PA. Vitamin K-dependent proteins. *N Engl J Med* 1984; **310:** 1458–60.
2. Rick ME. Protein C and protein S: vitamin K-dependent inhibitors of blood coagulation. *JAMA* 1990; **263:** 701–3.
3. Nelsestuen GL, *et al*. Vitamin K-dependent proteins. *Vitam Horm* 2000; **58:** 355–89.
4. Saxena SP, *et al*. Novel vitamin K-dependent pathways regulating cell survival. *Apoptosis* 2001; **6:** 57–68.

Malignant neoplasms. In a small study in women with viral cirrhosis of the liver to establish the effects of vitamin K on bone loss, those given menatetrenone were found to have a lower incidence of hepatocellular carcinoma; larger controlled studies were advocated, with prevention of carcinoma by menatetrenone as a primary end-point.[1] Another study[2] reported reduced recurrence of hepatocellular carcinoma in patients given menatetrenone.

1. Habu D, *et al*. Role of vitamin K_2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004; **292:** 358–61.
2. Mizuta T, Ozaki I. Hepatocellular carcinoma and vitamin K. *Vitam Horm* 2008; **78:** 435–42.

Neonatal intraventricular haemorrhage. Vitamin K crosses the placenta slowly and to a limited extent, but sufficiently to warrant studies to assess whether giving phytomenadione to the mother can reduce the incidence or severity of intraventricular haemorrhage (p. 1128.3) in the preterm neonate. Studies have shown conflicting results. A systematic review concluded that vitamin K given to the mother before birth did not significantly prevent periventricular haemorrhage, and could not be recommended for routine clinical use.[1]

1. Crowther CA, *et al*. Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 27/05/10).

Osteoporosis. The effects of vitamin K on bone, and its role in osteoporosis (p. 1168.1) have been reviewed.[1-5] It is widely prescribed for the management of osteoporosis in Japan.[3] A reduced risk of vertebral[6] and nonvertebral[7] fracture has been reported from 2 studies in postmenopausal women given menatetrenone 45 mg daily by mouth. Vitamin K_2 (menaquinones such as menatetrenone) appears to have more marked effects on bone than vitamin K_1 (phytomenadione).[3] Oral phytomenadione 5 mg daily for 2 to 4 years did not protect against age-related decline in bone mineral density (BMD) in postmenopausal Canadian women with osteopenia, although some protection against fractures (as well as a reduction in the incidence of cancer) was reported.[8] A systematic review[9] to assess whether vitamin K supplementation can reduce bone loss and prevent fractures identified 13 studies with data on bone loss; 7 reported fracture data. Most studies were conducted in Japan among postmenopausal women. Vitamin K supplements increased BMD in all but 1 study. Meta-analyses of the 7 studies with fracture data showed a reduced fracture incidence with menatetrenone supplementation, especially at the hip. The authors advised caution in interpretation of the data, since the studies were not designed to show fracture effects, and quality of many of the trials was poor. In addition, dietary differences in Japan might confound findings. While patients at risk of fracture should be encouraged to consume a diet high in vitamin K, routine supplementation is not justified until these results can be confirmed in a large randomised study with fracture as a primary outcome.

1. Iwamoto J, *et al*. Effects of vitamin K2 on osteoporosis. *Curr Pharm Des* 2004; **10:** 2557–76.
2. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health-Syst Pharm* 2005; **62:** 1574–81.
3. Plaza SM, Lamson DW. Vitamin K2 in bone metabolism and osteoporosis. *Altern Med Rev* 2005; **10:** 24–35.
4. Bügel S. Vitamin K and bone health in adult humans. *Vitam Horm* 2008; **78:** 393–416.
5. Shea MK, Booth SL. Update on the role of vitamin K in skeletal health. *Nutr Rev* 2008; **66:** 549–57.
6. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. *Am J Med* 2004; **117:** 549–55.
7. Sato Y, *et al*. Menatetrenone and vitamin D2 with calcium supplements prevent nonvertebral fracture in elderly women with Alzheimer's disease. *Bone* 2005; **36:** 61–8.
8. Cheung AM, *et al*. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med* 2008; **5:** e196. Available at: http://medicine.plosjournals.org/archive/1549-1676/5/10/pdf/10.1371_journal.pmed.0050196-L.pdf (accessed 13/03/09)
9. Cockayne S, *et al*. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 1256–61.

Over-anticoagulation. Doses of vitamin K for over-anticoagulation with warfarin have traditionally been large, and this continues to be reflected in licensed product information for these products, where recommended oral or parenteral doses range from 2.5 to 25 mg initially, with a maximum dose of 40 to 50 mg. However, large doses of vitamin K may result in overcorrection, and increase the delay before resumed anticoagulant therapy becomes effective. In addition, the time to onset of action is a minimum of 1 to 2 hours, irrespective of dose. There is increasing evidence that lower doses of vitamin K are effective in over-anticoagulation,[1-3] and this is reflected in current guidelines (see Treatment of Adverse Effects of Warfarin, p. 1529.1). The use of vitamin K lowers the elevated INR faster than witholding warfarin alone. However, for patients on phenprocoumon, vitamin K had insufficient effect, and no benefit for those on acenocoumarol; stopping therapy is more effective.[3] The route by which vitamin K is given may also be significant. A meta-analysis[4] of studies of vitamin K for the treatment of over-anticoagulation found that oral or intravenous vitamin K therapy was more effective for warfarin than simply stopping the anticoagulant; however, subcutaneous therapy was not effective. A review[5] noted that over-anticoagulated patients present with a wide range of INR values, and may respond differently to fixed dosing regimens of vitamin K, leaving them outside their target INR 24 hours after treatment and at risk for either haemorrhage or thromboembolism. Patient factors that affect response to vitamin K include age, body-weight, co-morbidity or health status, warfarin daily dose, and genetic polymorphism. The authors called for a more individualised approach to the reversal of over-anticoagulation.

A study has shown that dietary vitamin K intake is an important factor in anticoagulation instability; even brief periods of increased or decreased intake had significant effects on anticoagulation.[6] A high intake of green, leafy vegetables or selected oil-based foods can readily provide a dietary intake of 500 micrograms of vitamin K. Instead of restricting dietary vitamin K, maintenance of a stable intake may result in improved maintenance of therapeutic anticoagulation.[7]

Concern has also been expressed about possible effects on patients taking warfarin if vitamin K is included in their parenteral nutrition.[8]

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2. Fetrow CW, *et al*. Antagonism of warfarin-induced hypoprothrombinemia with use of low-dose subcutaneous vitamin K_1. *J Clin Pharmacol* 1997; **37:** 751–7.
3. Hanslik T, Prinseau J. The use of vitamin K in patients on anticoagulant therapy: a practical guide. *Am J Cardiovasc Drugs* 2004; **4:** 43–55.
4. DeZee KJ, *et al*. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med* 2006; **166:** 391–7.
5. Sconce EA, Kamali F. Appraisal of current vitamin K dosing algorithms for the reversal of over-anticoagulation with warfarin: the need for a more tailored dosing regimen. *Eur J Haematol* 2006; **77:** 457–62.
6. Franco V, *et al*. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med* 2004; **116:** 651–6.
7. Bovill EG, *et al*. Vitamin K and oral anticoagulation: thought for food. *Am J Med* 2004; **116:** 711–13.
8. Bern M. Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy. *J Parenter Enteral Nutr* 2004; **28:** 388–98.

Vitamin K deficiency bleeding. Vitamin K deficiency bleeding (VKDB; haemorrhagic disease of the newborn; HDN), of which 3 types have been recognised, is associated with a clotting defect due to vitamin K deficiency.[1,2]

- In early VKDB bleeding occurs at the time of delivery or during the first 24 hours of life and is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism such as warfarin, some antiepileptics, rifampicin, or isoniazid.
- Classic VKDB, the most common type, usually occurs at 2 to 5 days of age and breast feeding is an important factor as human breast milk has a much lower content of vitamin K than either cow's milk or infant formulas.
- Late VKDB presents frequently as intracranial haemorrhage in infants over one month of age. The vitamin-K deficiency in these cases can be either idiopathic (usually in breast-fed infants who did not receive vitamin K at birth) and/or can be a secondary manifestation of other disorders such as chronic diarrhoea, cystic fibrosis or other malabsorption syndromes, biliary atresia, or α_1-antitrypsin deficiency.

Treatment of VKDB involves use of intravenous phytomenadione, usually 1 mg initially with further doses depending on response. More immediate treatment, in the form of blood transfusion or blood clotting factors, may be needed to compensate for severe blood loss and delayed response to vitamin K. VKDB, particularly the late type, carries a high risk of morbidity or death; therefore, the emphasis has been on prevention.

It has long been known that giving vitamin K to the neonate soon after birth can reduce the incidence of VKDB. Menadiol sodium phosphate was formerly used, but reports in the 1950s of jaundice and kernicterus in infants given this vitamin K analogue caused concern, and led to the preferential use of phytomenadione either intramuscularly or orally. Giving phytomenadione, has been standard practice for neonates considered at high risk of VKDB, such as those who had a complicated delivery, those born prematurely, and those whose mothers were receiving antiepileptic therapy. Since it is not possible to selectively identify all neonates that are at risk for VKDB, the routine use of phytomenadione in all neonates has been advocated. However, such practice has been controversial, particularly as regards the route.[2-4]

Some consider that oral dosage is less invasive and more acceptable to parents.[4] However, there has also been concern about the adequacy of absorption of oral phytomenadione. In addition, there was some evidence[2,5-7] to suggest that a single intramuscular dose was more effective than a single oral dose in preventing late VKDB, and that repeated oral doses might be required, which may be less convenient and carry the risk of poor compliance. More recently, a possible increased risk of childhood cancer in neonates treated with intramuscular, but not oral, phytomenadione has been reported (see Carcinogenicity, p. 2124.2). Although the association remains controversial, it led to recommendations for the preferential use of oral vitamin K in neonates at low-risk of VKDB in some countries, including the UK[8] and Germany,[9] whereas other countries, including the USA,[10,11] still preferred the intramuscular route for all neonates.

There is still no agreement on the most effective route or dosage regimen, and study of this has been complicated by issues concerning the available formulations. A colloidal, micelle formulation (licensed for oral use in some countries) was introduced to replace the original preparation which contained polyoxyl castor oil, propylene glycol, and phenol (unlicensed for oral use but often given in this way). Although replacing the original formulation has eased concerns about the safety of its excipients, it is not known if the new formulation provides sustained protection when given intramuscularly. Oral absorption of the new formulation has also prompted discussion.[12] A report[13] of the failure of prophylaxis in 3 breast-fed babies (2 of whom had unidentified cholestatic liver disease) who received 2 oral doses of the micellar formulation, as recommended in Switzerland, emphasises the importance of the third, and possibly, other, follow-up doses. Plasma vitamin K concentrations in breast-fed infants receiving 3 oral doses of this formulation were at least equal to concentrations in those receiving a single intramuscular dose.[14] A study in Germany, however, found the micellar oral formulation to be no more efficacious than older vitamin K preparations,[15] and a pharmacokinetic study found its absorption to be unreliable in infants with conjugated hyperbilirubinaemia;[16] the authors suggest that even 3 oral doses may not provide sufficient protection against VKDB in infants with latent cholestasis.

Advice issued in 1998 from the UK Department of Health[17] advocates that all newborn infants should receive vitamin K prophylaxis, both oral and intramuscular routes should be available, and that parents should be involved in the decision on which route is used. In healthy neonates of 36 weeks' gestation or over, licensed product information in the UK recommends a dose of 1 mg phytomenadione as a single intramuscular injection soon after birth. Alternatively, 2 mg may be given orally soon after birth, followed by a second dose of 2 mg at 4 to 7 days; a third oral dose of 2 mg should be given to exclusively breast-fed babies one month after birth. In preterm neonates of less than 36 weeks' gestation, an intramuscular or intravenous dose of 400 micrograms/kg (maximum 1 mg) may be given soon after birth. The *BNFC* states that the intramuscular route should be used in those infants considered to be at particular risk for VKDB, and also suggests that infants with cholestatic disease should be given either intramuscular or intravenous phytomenadione as oral absorption is likely to be impaired. Additionally, subsequent oral doses are suggested for neonates given an initial intravenous dose, in order to provide comparable prolonged protection to the intramuscular route.

Other regimens have been investigated or are in use elsewhere. One hospital in the USA has satisfactorily used, for many years, a single 2-mg dose given via nasogastric tube to neonates after birth,[18] although the American Academy of Pediatrics still advocates use of the intramuscular route.[11] In Denmark, a 2-mg oral or intramuscular dose at birth followed by a weekly oral dose of 1 mg during the first 3 months of life has effectively prevented any late VKDB in healthy breast-fed babies.[19] In the Netherlands a lower dose regimen of 1 mg orally or intramuscularly at birth, followed by 25 micrograms daily or 1 mg weekly by mouth from 1 week to 3 months of age has been found satisfactory.[20] However, a retrospective comparison of dose regimens used in Denmark and the Netherlands revealed that the lower doses used in the Netherlands did not provide protection against VKDB in breast-fed infants with unrecognised cholestasis due to biliary atresia.[21] In France, for formula-fed neonates at no risk of haemorrhage, 2 mg is given orally at birth, followed by a second dose between day 2 and 7; infants who are breast-fed are given weekly oral doses of 2 mg until

cessation of exclusive breast feeding. For neonates at high risk of haemorrhage, however, the first dose is given intramuscularly, or even by slow intravenous injection, according to the clinical state of the infant.[2]

Although phytomenadione crosses the placenta slowly and to a limited extent, it is nevertheless recommended that pregnant women receiving drugs that are vitamin K antagonists (particularly antiepileptics) should receive phytomenadione 10 to 20 mg daily from 36 weeks of gestation.[2,22] This is in addition to the requirement that their neonates, who are at high risk of VKDB, receive intramuscular phytomenadione soon after birth. Maternal phytomenadione has been investigated as a means of improving vitamin K status in breast-fed neonates. In 1 study,[23] 5 mg daily for 12 weeks was effective for this purpose.

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4. Brown SG, *et al*. Should intramuscular vitamin K prophylaxis for haemorrhagic disease of the newborn be continued? A decision analysis. *N Z Med J* 1989; **102:** 3–5.
5. Clarkson PM, James AG. Parenteral vitamin K_1: the effective prophylaxis against haemorrhagic disease for all newborn infants. *N Z Med J* 1990; **103:** 95–6.
6. McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. *BMJ* 1991; **303:** 1105–9.
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9. von Kries R, *et al*. Repeated oral vitamin K prophylaxis in West Germany: acceptance and efficacy. *BMJ* 1995; **310:** 1097–8.
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11. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; **112:** 191–2.
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15. von Kries R, *et al*. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F109–F112.
16. Pereira SP, *et al*. Intestinal absorption of mixed micellar phylloquinone (vitamin K_1) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F113–F118.
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19. Nørgaard Hansen K, Ebbesen F. Neonatal vitamin K prophylaxis in Denmark: three years' experience with oral administration during the first three months of life compared with one oral administration at birth. *Acta Paediatr Scand* 1996; **85:** 1137–9.
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21. van Hasselt PM, *et al*. Netherlands Study Group for Biliary Atresia Registry. Prevention of vitamin K deficiency bleeding in breastfed infants: lessons from the Dutch and Danish biliary atresia registries. *Pediatrics* 2008; **121:** e857–e863.
22. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992; **42** (suppl 5): 149–60.
23. Greer FR, *et al*. Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997; **99:** 88–92.

Adverse Effects and Precautions

Intravenous doses of *phytomenadione* have caused severe reactions resembling hypersensitivity or anaphylaxis. Symptoms have included facial flushing, sweating, chest constriction and chest pain, dyspnoea, cyanosis, and cardiovascular collapse; fatalities have been reported. Anaphylactic reactions have generally been associated with an overly rapid rate of infusion but have also been reported even when the solution was diluted and infused slowly. They are generally thought to be due to polyoxyl castor oil which is present as a surfactant in some parenteral formulations; reports of such reactions with formulations that do not contain polyoxyl castor oil are rare (but see Hypersensitivity, below).

Pain, swelling, and phlebitis may occur at the injection site when phytomenadione is given. Localised skin reactions including atrophy or necrosis have been reported after intramuscular or subcutaneous injection of phytomenadione.

Phytomenadione formulations solubilised with lecithin and a bile salt should be given with caution to patients with severely impaired liver function and to premature neonates weighing less than 2.5 kg, since the bile salt may displace bilirubin.

Giving *menadione* and *menadiol sodium phosphate* to neonates, especially premature infants, or to the mother during late pregnancy has been associated with the development in the infant of haemolytic anaemia, hyperbilirubinaemia, and kernicterus, and such use is not recommended. Phytomenadione has a lower risk of haemolysis. Menadione and menadiol sodium phosphate have also been reported to cause haemolysis in patients with G6PD deficiency or vitamin E deficiency.

Breast feeding. Vitamin K is variably distributed into breast milk; a study found phytomenadione concentrations in the first 10 mL of expressed milk ("fore milk") to be lower than those in the last 10 mL ("hind milk"). These changes may be related to the lipid concentration, which is higher in hind milk. Lipid composition also changes over the course of lactation, with pronounced changes in the first week, and the authors proposed that a mechanism exists whereby vitamin K concentration in milk is higher in the first few days of life so as to meet the neonate's nutritional requirements at a time when vitamin K status is precarious.[1] The American Academy of Pediatrics considers[2] that, as no adverse effects have been seen in breast-fed infants whose mothers were receiving phytomenadione, its use is therefore usually compatible with breast feeding.

1. von Kries R, *et al*. Vitamin K_1 content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K_1 supplements given to the mother. *Pediatr Res* 1987; **22:** 513–17.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Carcinogenicity. A case-control study from the UK[1] suggested an increased risk of cancer in children who had received vitamin K at birth for the prevention of vitamin K deficiency bleeding (see p. 2123.2). A further study[2] by the same authors indicated that this risk was associated with intramuscular, but not oral, dosage, and was strongest for childhood leukaemia. In response to these data, the British Paediatric Association recommended that the oral route should be preferred for prophylaxis,[3] whereas the American Academy of Pediatrics continued to advocate the intramuscular route,[4] and still does so, concluding there is no association between this route and childhood leukaemia or other cancers.[5]

Subsequent studies from the USA,[6] Sweden,[7] Denmark,[7,8] Germany,[9] and England[10] did not confirm an increased risk of childhood cancer, including leukaemias, after the use of intramuscular vitamin K. Subsequently 4 further studies were published.[11-14] Two of these, a case-control study in Scotland[11] and an ecological study in Britain,[12] showed no increased risk of any cancers with the use of intramuscular vitamin K. A third case-control study in England and Wales[13] found a borderline association between intramuscular vitamin K and cancers, particularly leukaemia. In the fourth study, a case-control study in northern England,[14] there was an increased risk (odds ratio 1.79) of acute lymphoblastic leukaemia developing 1 to 6 years after birth in children who had received intramuscular vitamin K. In 1998 a review[15] by an expert working group of the UK CSM concluded that there was no increased risk of solid tumours with vitamin K, and that, although an increased risk of leukaemia could not be excluded, observed results were compatible with chance. Moreover, they could not identify a plausible mechanism for a carcinogenic effect of vitamin K. Since then, a pooled analysis of case-control studies in Great Britain and Germany[16] found no convincing evidence that vitamin K given intramuscularly was associated with childhood leukaemia. A national case-control study in the UK[17] concluded there was no evidence that vitamin K, irrespective of the route, influenced the risk of children developing leukaemia or any other cancer. If there is any increased risk, it is likely to manifest only in a very small subpopulation who are at high risk for some as-yet-unidentified biological reason.[18] The UK Department of Health[19] advocates either oral or intramuscular prophylaxis, and recommends that the parents should be involved in the decision on which route is used.

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2. Golding J, *et al*. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.
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4. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; **91:** 1001–3.
5. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; **112:** 191–2. [Re-affirmed May 2006]
6. Klebanoff MA, *et al*. The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993; **329:** 905–8.
7. Ekelund H, *et al*. Administration of vitamin K to newborn infants and childhood cancer. *BMJ* 1993; **307:** 89–91.
8. Olsen JH, *et al*. Vitamin K regimens and incidence of childhood cancer in Denmark. *BMJ* 1994; **308:** 895–6.
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10. Ansell P, *et al*. Childhood leukaemia and intramuscular vitamin K: findings from a case-control study. *BMJ* 1996; **313:** 204–5.
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12. Passmore SJ, *et al*. Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. *BMJ* 1998; **316:** 184–9.
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15. CSM/MCA. Safety of intramuscular vitamin K (Konakion). *Current Problems* 1998; **24:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023232&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)
16. Roman E, *et al*. Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. *Br J Cancer* 2002; **86:** 63–9.
17. Fear NT, *et al*. Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003; **89:** 1228–31.
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Effects on the blood. Cerebral arterial thrombosis developed in 2 patients with malabsorption syndromes due to coeliac disease during treatment with vitamin K for severe deficiency of vitamin-K-dependent coagulation factors. An increased tendency to thrombotic events had previously been reported to be present in patients with intestinal inflammatory disorders. It was suggested that if bleeding did occur in such patients treatment should be with plasma infusions or small doses of vitamin K but that vitamin K deficiency should not be specifically treated since a gluten-free diet or corticosteroids given for the gastrointestinal disorder will result in a gradual correction.[1]

1. Florholmen J, *et al*. Cerebral thrombosis in two patients with malabsorption syndrome treated with vitamin K. *BMJ* 1980; **281:** 541.

Hypersensitivity. Hypersensitivity reactions have been reported after subcutaneous,[1-3] intramuscular,[4] intravenous,[5-7] and oral[7] use of vitamin K, although the incidence is low.[6,7]

Subcutaneous doses are considered to pose less risk of **anaphylaxis** than the intravenous route;[5] fatalities have been reported with intravenous use,[7] even after low doses, given slowly, and by dilute infusion.[5,7] There has also been a fatality associated with oral use.[7] While anaphylactoid reactions have been attributed to the polyoxyl castor oil vehicle,[6,7] a direct immune mechanism has also been proposed.[7]

Vitamin K itself appears to be the antigen causing adverse **cutaneous reactions**.[3] Two types of cutaneous reactions have been described: pruritic, erythematous, eczematous plaques usually occurring up to 2 weeks after a dose, and sclerodermoid morphea-like plaques, with or without eczema, which may be delayed.[1,3,4] In addition, there have been rare reports of diffuse maculopapular eruption, but the relationship of this reaction to vitamin K use has been questioned.[3] Despite reports that the eczematous reactions resolve faster than the sclerodermatous reactions,[1] persistent eczema[4] or pruritus has occurred.[3]

Treatment has been largely symptomatic; topical and systemic corticosteroids and antihistamines have been used.[1,3,4] For patients who have previously reacted to phytomenadione injections, the use of menadione either by injection or by mouth has been suggested;[3] cross-reactivity was not anticipated to be a problem. However, cross-reactions on patch testing have been reported.[4] It has been suggested that reactions to vitamin K in patients might signify underlying hepatic disease,[1] although others believe the condition is seen more frequently in patients with liver disease since they are often those requiring vitamin K.[3]

1. Gettler SL, Fung MA. Indurated plaques on the arms of a 52-year-old man. *Arch Dermatol* 2001; **137:** 957–62.
2. Bui L, *et al*. Skin reaction to subcutaneous phytonadione injections. *Am J Health-Syst Pharm* 2004; **61:** 407.
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7. Fiore LD, *et al*. Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 2001; **11:** 175–83.

Overdosage. UK licensed product information states that, while there is no known clinical syndrome attributable to hypervitaminosis of phytomenadione, adverse effects have been reported after overdose in neonates and infants. These include jaundice, hyperbilirubinaemia, increases in liver enzyme values, abdominal pain, constipation, soft stools, malaise, agitation, and skin eruptions. Most adverse events were not considered to be serious, and resolved without any treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phytomenadione as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Menadione is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Vitamin K decreases the effects of oral anticoagulants (see p. 1535.3), and is used to counteract excessive effects of these drugs, see Uses and Administration, p. 2122.3. Vitamin K may reduce the response to resumed therapy with anticoagulants for a week or more.

Pharmacokinetics

The fat-soluble vitamin K compounds phytomenadione and menadione require the presence of bile for their absorption from the gastrointestinal tract; the water-soluble derivatives can be absorbed in the absence of bile. Vitamin K accumulates mainly in the liver but is stored in the body only for short periods of time. Vitamin K does not appear to cross the placenta readily and it is variably distributed into breast milk. Phytomenadione is rapidly metabolised to more polar metabolites and is excreted in bile and urine as glucuronide and sulfate conjugates.

Absorption. Absorption of phytomenadione from the colloidal (micellar) preparation was more irregular and unpredictable after intramuscular than intravenous dosage in healthy adults;[1] when used as an antidote to anticoagulant, this formulation should be given intravenously. In neonates, plasma phytomenadione concentrations were within or above the adult fasting plasma range 24 days after receiving a single dose of the colloidal preparation either orally (3 mg) or intramuscularly (1.5 mg).[2]

1. Soedirman JR, *et al*. Pharmacokinetics and tolerance of intravenous and intramuscular phylloquinone (vitamin K_1) mixed micelles formulation. *Br J Clin Pharmacol* 1996; **41:** 517–23.
2. Schubiger G, *et al*. Vitamin K_1 concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone. *J Pediatr Gastroenterol Nutr* 1993; **16:** 435–9.

Human Requirements

The minimum daily requirements of vitamin K are not clearly defined but an intake of about 1 microgram/kg daily appears to be adequate. Vitamin K requirements in normal adults can be met from the average diet and from the synthesis of menaquinones (also known as vitamin K_2) by bacterial action in the intestine. Vitamin K occurs naturally as phytomenadione (vitamin K_1), which is present in many foods, especially leafy green vegetables such as cabbage and spinach, and is also present in avocado, meat, cow's milk, egg-yolk, and some cereals.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p. 2046.1) has been set for vitamin K although an intake of 1 microgram/kg daily was considered to be both safe and adequate for adults; a higher intake of 10 micrograms daily (about 2 micrograms/kg daily) was believed to be justified in infants because of the absence of hepatic menaquinones in early life and reliance on dietary vitamin K alone. It was stated that all babies should receive prophylactic vitamin K at birth[1] and for further details concerning neonatal use, see Vitamin K Deficiency Bleeding, p. 2123.2.

In the USA, adequate intake levels have been determined to be 120 micrograms daily for adult men and 90 micrograms daily for adult women.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: K1; Konakion; Mestil-Ka; Rupek; ***Austral.***: Konakion; PM Ausphyllo; ***Austria***: Konakion; ***Belg.***: Konakion; Vitamon K; ***Braz.***: Kanakion; Kavit; Menadion; Vikatron; Vita K; ***Chile***: Auriderm K2†; Konakion; ***China***: Glakay (固力康); Kai Nai Jin (凯乃金); ***Cz.***: Kanavit; ***Denm.***: Konakion; Menadion; ***Fin.***: Konakion; ***Ger.***: Ka-vit; Kanavit†; Konakion; ***Gr.***: Kapavit; Konakion; ***Hong Kong***: Auriderm†; Konakion; Uni-Menadol†; Univitan K1; ***Hung.***: Konakion; ***India***: Injek; K-Nat; Kapilin; Kenadion; KVI; ***Indon.***: Neo-K; ***Irl.***: Konakion; ***Israel***: Konakion; ***Ital.***: Konakion; Vita K Plus; ***Jpn***: Glakay; Kaytwo; Kaywan; ***Malaysia***: Kisan; Konakion; ***Mex.***: Danapril; Dionadion; K-50; Konakion†; Royken; ***Neth.***: Konakion; ***Norw.***: Konakion; ***NZ***: K-Thrombin†; Konakion; ***Phil.ipp.***: Clotigen†; Cycomin; Hema-K; Hemadone; Hemo-K†; Kona-K; Konakion; Vitakay; ***Pol.***: Vitacon; ***Port.***: Kanakion; ***S. Afr.***: Konakion; ***Singapore***: Konakion; ***Spain***: Kaergona Hidrosoluble†; Konakion; ***Swed.***: Konakion; ***Switz.***: Konakion; ***Thai.***: Glakay; Konakion; KP; ***Turk.***: Konakion MM; Libavit K; Vi-Plex K; ***UK***: Konakion; Neokay; ***USA***: Mephyton.

Multi-ingredient Preparations. ***Arg.***: Aderogyl; Estreptocarbocaftiazol; Estreptocarbocaftiazol; Kacerutin; ***Austral.***: Bone Matrix Support; Nutribone; OsteoEze Bone & Joint; PM Kiddiecal; PM NextG Cal; Vitalipid N; ***Austria***: Vitalipid; ***Belg.***: Vitalipid; ***Chile***: Hepabil; K-Gel; Katin; Microret K†; Vitalipid N; ***China***: Vitalipid N (维他利匹特); Zhi Wei Bao (知维保); ***Cz.***: Vitalipid N; ***Denm.***: Vitalipid; ***Fin.***: Vitalipid; ***Fr.***: Vitalipide; ***Ger.***: Vitalipid; ***Gr.***: Vitalipid; ***Hong Kong***: Vitalipid N; ***Hung.***: Vitalipid; ***India***: Cadisper C; CKP†; Gynae-CVP; Gystat; Kalpastic†; Siochrome; Styptocid; Styptocip; ***Indon.***: Biocal-95; Cal-95; Calciviton; Calplex; Calvitos; Hi-Bone; Ossovit Plus; Ossovit; Phoscal; Steopor; Vitalipid N; ***Irl.***: Bio-Calcium + D_3 + K†; Vitlipid N; ***Israel***: Vitalipid N; ***Ital.***: 3Mil; Dicovit DK; Ditrevit K; Nadione; Vitalipid; ***Malaysia***: Vitalipid N†; ***Mex.***: Anadekin†; Hemosin-K; Micro-ka†; Microret K; ***Neth.***: Vitintra; ***Norw.***: Vitalipid; ***NZ***: Vitalipid; ***Pol.***: Vitalipid N; ***Port.***: Vitalipid; ***Rus.***: Vectrum Calcium (Вектрум Кальций); Vitalipid N (Виталипид Н); ***S.Afr.***: Vitalipid; ***Singapore***: Vitalipid N; ***Spain***: Vitalipid; ***Swed.***: Vitalipid; ***Switz.***: Vitalipid N; ***Thai.***: Bio-Calcium + D_3 + K; Siduol; Vitalipid; ***Turk.***: Vitalipid N; ***UK***: Vitlipid N; ***Ukr.***: Osteoartisi Max (Остеоартизи Макс); ***USA***: OstiGen; REQ49+; TheraCal D; Viactiv Calcium†.

Pharmacopoeial Preparations
BP 2014: Menadiol Phosphate Injection; Menadiol Phosphate Tablets; Phytomenadione Injection; Phytomenadione Tablets;
USP 36: Menadiol Sodium Diphosphate Injection; Menadiol Sodium Diphosphate Tablets; Menadione Injection; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Phytonadione Injectable Emulsion; Phytonadione Tablets.

Whey

Milk Plasma; Milk Serum.
CAS — 92129-90-3 (whey protein).
UNII — 8617Z5FMF6.

Profile

Whey is the liquid remaining after milk has curdled or been strained. It contains lactose, proteins, vitamins, and minerals and has been used as a nutritional supplement. It has also been used in skin-care products. Commercially it is used as a source of lactose and lactic acid.

Reviews.
1. Marshall K. Therapeutic applications of whey protein. *Altern Med Rev* 2004; **9:** 136–56.
2. Yalçin AS. Emerging therapeutic potential of whey proteins and peptides. *Curr Pharm Des* 2006; **12:** 1637–43.
3. Krissansen GW. Emerging health properties of whey proteins and their clinical implications. *J Am Coll Nutr* 2007; **26:** 713S–723S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bio-Prot; ***Indon.***: Dermylex; ***Ital.***: Balsamo Primi Denti.

Multi-ingredient Preparations. ***Arg.***: Lactacyd; ***Austral.***: Homme-F; ***Chile***: Lactacyd; ***China***: Lactacyd (乐特喜); ***Hong Kong***: Lactacyd; ***India***: Kiddis; ***Indon.***: Lactacyd; ***Ital.***: Lactacyd Derma; Lactacyd Intimo; ***Malaysia***: Lactacyd; ***Philipp.***: Lactacyd; ***Singapore***: Lactacyd; ***Thai.***: Lactacyd†.

Dried Yeast

Brewers' Yeast; Cerevisiae Fermentum Siccatum; Faex Siccata; Fermento de Cerveja; Levadura desecada; Levedura Sêca; Levure de Bière; Saccharomyces Siccum; Trockenhefe; Сушёные Дрожжи.

Pharmacopoeias. In *Jpn*.

Profile

Dried yeast consists of unicellular fungi belonging to the family Saccharomycetaceae, dried by a process that avoids decomposition of the vitamins present. The chief species are *Saccharomyces cerevisiae*, *S. carlsbergensis*, and *S. monacensis*. Dried yeast contains thiamine, nicotinic acid, riboflavin, pyridoxine, pantothenic acid, biotin, folic acid, cyanocobalamin, aminobenzoic acid, inositol, and chromium.

Dried yeast is a rich source of vitamins of the B group. It has been used for the prevention and treatment of vitamin B deficiency in oral doses of 1 to 8 g daily.

Yeast may be enriched by growing it in the presence of various minerals. Chromium-enriched yeast (chromium yeast), iron-enriched yeast (iron yeast), selenium-enriched yeast (selenium yeast), and zinc-enriched yeast (zinc yeast) have been used as dietary supplements.

Yeast is an ingredient of some preparations for treating haemorrhoids, and some preparations intended to restore normal gastrointestinal flora (see Probiotics, p. 2596.3). Yeast is widely used in brewing.

Antibiotic-associated colitis. Although other organisms, including *Candida* spp., have been implicated in antibiotic-associated diarrhoea, colonisation of the colon with *Clostridium difficile*, a toxin-producing Gram-positive anaerobe, is the most common identifiable cause of antibiotic-associated colitis (p. 183.1) and pseudomembranous colitis. There are reports of benefit with dried yeast in patients with *C. difficile*-associated diarrhoea;[1,2] commercially available brewers' yeast tablets were used, at a dose of 3 tablets three times daily (strength unspecified), in 3 patients refractory to standard treatment,[1] or as adjunctive therapy in 11 patients, using the same dose.[2]

1. Schellenberg D, *et al*. Treatment of Clostridium difficile diarrhoea with brewer's yeast. *Lancet* 1994; **343:** 171–2.
2. Barthram J, *et al*. Further research warranted. *Pharm J* 1997; **259:** 371.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Levedo†; ***Canad.***: Action O G†; ***China***: Ebios (爱表斯); Fu Xi Kang (富希康); Xi Wei Er (西维尔); ***Denm.***: SelenoPrecise; ***Fr.***: Chromasvelt†; ***Ger.***: Eubiol; Hamadin N; Hefekapseln†; Omniflora Akut†; Perocur†; Peromyces†; Santax S†; Yomogi; ***Hung.***: Bio-Strath; ***India***: Laviest†; ***Indon.***: Bio-Strath; ***Ital.***: Zimocel; ***Mex.***: Levifusa; ***Pol.***: Cerosel†; ***Rus.***: Vitanam (Витанам); ***Switz.***: Sanaflor; ***Thai.***: Brewers Yeast; ***UK***: Bio-Strath; ***Ukr.***: Micerol (Мицерол)†.

Multi-ingredient Preparations. ***Arg.***: Bifena; Indian Health - Levadura; Karbonetas†; RNA DNA; Tonovital Plus Antioxidante; Totalflora; Tricomax; ***Austral.***: Cold & Flu Relief; Hair Skin & Nails; ***Austria***: Aktivanad; Levurinetten†; Sperti Preparation H; ***Braz.***: Leveglutan; Pantogar; ***Canad.***: Floradix Kindervital†; Floradix Tab†; Kyolic 101†; Multi Enzyme†; Nervrite; Optibiol†; Preparation H; Right Choice AM†; Ultra-Vit Plus†; ***Chile***: Biogenol; Cellvital†; Sperti Preparation H; ***Cz.***: Merz Spezial†; Preparation H; Revalid; ***Fr.***: Actisoufre; Alpharegul Femme; Calciforte Vitamin D_3; Calciforte†; Calciforte; Carbolevure; Forcical Vitamine D3†; Levure Or†; Notrino†; Phytophanere†; Selenium-ACE†; Solacy; Spasmag; Tranquilimag†; ***Ger.***: Aktivanad-N; Dia-Aktivanad-N; Eulatin NH; Pantovigar; ***Gr.***: Preparation H; ***Hong Kong***: Merz Spezial†; Pantogar; Revicon; ***Hung.***: Epasel; Metabol; Revalid; Sperti Preparation H; Szelen +C; ***India***: Apenic; Cypon; Elferri; Genozyme; Hapeast; Medithane; Miproten; Plastules B-12; ***Indon.***: Bio-Strath; Lycoxy; Maxivit; Oxypen; Pantogar; ProBi; Yeastafort; ***Irl.***: Preparation H†; ***Israel***: Preparation H; ***Ital.***: Biomineral 5-Alfa; Carfosid; Eu-Visus; Eurogel; Florelax; Lactisporin; Lactivis; Lactolife; Lactovit; Lievitosohn; Lievitovit; Preparazione H; Vigogel; Vitreolux; ***Malaysia***: Evelle; Revicon; Seresis; ***Mex.***: Seresis; ***Neth.***: Sperti Preparation H; ***Philipp.***: Lungcaire Plus; Nutricap; Nutrigrow†; Revicon Forte (Improved); Thinber Fiber Complex†; ***Pol.***: Vegevit B_{12}; ***Port.***: Sperti Preparacao H; ***Rus.***: Antioxycaps with Selenium (Антиоксикапс С Селеном); Doppelherz Selevit (Доппельгерц Селевит)†; Pantovigar (Пантовигар); Preparation H (Препарейшн Эйч)†; ***S.Afr.***: Preparation H†; Selenium-ACE; Vitaforce Nutri-B†; ***Singapore***: Bios Life; Evelle; Pantogar; Preparation H; Revicon; Seresis†; Vitaton; ***Spain***: Preparacion H†; ***Switz.***: Carbolevure; Merz Dragees Speciales†; Pantogar; Revalid†; Sperti Preparation H†; Strath Gouttes contre la toux; Strath Gouttes pour l'estomac; Strath Gouttes pour le foie et la bile; Strath Gouttes pour le nerfs et contre l'insomnie; Strath Gouttes pour les muqueuses; Strath Gouttes pour les reins et la vessie; ***Thai.***: Convits; Polybee; Revicon†; ***Turk.***: Pantogar; ***UK***: Bio-Strath Artichoke Formula; Bio-Strath Valerian Formula; Bio-Strath Willow Formula; Brewers Yeast; Preparation H; Se-Power; Tonic Yeast; Travelbac; Yeast Vite; ***Ukr.***: Fitoval Capsules (Фитовал капсулы); OxyLic (ОксиЛик); Pantogar (Пантогар); Revalid (Ревалид); Vitrum Cardio (Вітрум Кардио); ***USA***: Preparation H; Rectagene Medicated Balm; Wyanoids Relief Factor; ***Venez.***: Nutricap; Optibiol; Selene; Uvagen; Vitalux.

Zeaxanthin

Anchovyxanthin; E161(h); Zeaxanthol; Зеаксантин.
(3*R*,3′*R*)-β,β-Carotene-3,3′-diol.
$C_{40}H_{56}O_2$=568.9
CAS — 144-68-3.
UNII — CV0IB81ORO.

Pharmacopoeias. *US* has *meso*-zeaxanthin.

USP 36: (*meso*-Zeaxanthin). *meso*-Zeaxanthin consists chiefly of the 3*R*,3′*S*-isomer of zeaxanthin. It contains not less than 80.0% of total carotenoids calculated as zeaxanthin and not less than 74.0% of zeaxanthin, calculated with reference to the anhydrous drug. Store in airtight containers. Protect from light.

Profile

Zeaxanthin is a naturally occurring carotenoid that is promoted as a dietary supplement for age-related macular degeneration (p. 880.2).

References.

1. Mares-Perlman JA, *et al.* The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; **132** (suppl): 518S–524S.
2. Mozaffarieh M, *et al.* The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: a review based on controversial evidence. *Nutr J* 2003; **2:** 20.
3. Hartmann D, *et al.* Plasma kinetics of zeaxanthin and 3′-dehydro-lutein after multiple oral doses of synthetic zeaxanthin. *Am J Clin Nutr* 2004; **79:** 410–17.
4. Thurnham DI, *et al.* A supplementation study in human subjects with a combination of meso-zeaxanthin, (3R,3′R)-zeaxanthin and (3R,3′R,6′R)-lutein. *Br J Nutr* 2008; **100:** 1307–14.
5. Zeimer M, *et al.* Kurz- und mittelfristige Anderungen der makulären Pigmentdichte infolge der Supplementation mit Lutein und Zeaxanthin sowie Koantioxidanzien: die LUNA-Studie. *Ophthalmologe* 2009; **106:** 29–36.
6. Roberts RL, *et al.* Lutein and zeaxanthin in eye and skin health. *Clin Dermatol* 2009; **27:** 195–201.
7. Stringham JM, *et al.* The influence of dietary lutein and zeaxanthin on visual performance. *J Food Sci* 2010; **75:** R24–R29.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Lutein-Vision Advanced; ***Canad.***: ICaps Lutein and Zeaxanthin; Visionex; ***Chile***: Vision Tabs; ***Fr.***: Difravision; Lero Pervulane; Macula; PreserVision; Sun Vue; Trioptec; Visioprev; ***Hong Kong***: Ocuvite; Visionex†; ***India***: GV-24; I-Lute; I-Site; Lutivit; Lycocare; Lycofact Plus; Ocufree; Ocugold; Oxy-V; ***Indon.***: Ervision; Eyebright; Eyevit; Kapset; Lubire; Lutevit; Matoflam; Matovit AX; Matovit Fifty; nutrivision; Nuvision; Optimax Plus; Proview; Retivit Plus; Retop; ***Irl.***: Ocuvite†; ***Ital.***: Astar; Connivea; Euretin Duo; Macvit; Meralut; Troca Vit; VisuQ10; Zeadema Crono; Zeadema; ***Malaysia***: Eurobio Bio-Vizmax; ***Mex.***: Drusen; Icaps; Optivision; Snelvit; ***Philipp.***: Nutricap; ***Rus.***: Complivit Oftalmo (Компливит Офтальмо); ***Singapore***: i-Vitein; Icaps; Nutrivision†; Ocuvite Adult 50+; Optibiol; Visionex†; ***Thai.***: Ocuvite; ***UK***: Icaps; ***Ukr.***: Ocuvite Complete (Окювайт Комплит); Ocuvite Lutein Forte (Окювайт Лютеин форте); Око-Health (Око-хелс); Optix (Оптикс); Optix Forte (Оптикс Форте); Vitrum Foreyes (Витрум Форайз); Vitrum Foreyes Forte (Вітрум Форайз Форте); ***USA***: Cardio Tone; Clinical Nutrients 50-Plus Men; Fitness Tabs for Men; Fitness Tabs for Women; MacuTrition; Ocuvite Eye + Multi; Preservision Eye Vitamin; REQ49+; ***Venez.***: Vilox; Vitavision.

Zinc

Cynk; Zincum; Zink; Цинк.

Zn=65.38

CAS — 7440-66-6.

UNII — J41CSQ7QDS (zinc); 13S1S8SF37 (zinc ion).

Zinc Acetate

Cink-acetát-dihidrát; Cinko acetatas dihidratas; Cynku octan; E650; Octan zinečnatý dihydrát; Sinkkiasetaatti; Zinc (acétate de) dihydraté; Zinc, acetato de; Zinci Acetas; Zinci Acetas Dihydricus; Zinkacetat; Ацетат Цинка; Уксуснокислый Цинк.

$(CH_3CO_2)_2Zn,2H_2O$=219.5

CAS — 557-34-6 (anhydrous zinc acetate); 5970-45-6 (zinc acetate dihydrate).

ATC — A16AX05.

ATC Vet — QA16AX05.

UNII — FM5526K07A (zinc acetate dihydrate); H2ZEY72PME (anhydrous zinc acetate).

NOTE. Zinc Acetate, Basic is *rINN*.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Zinc Acetate Dihydrate; Zinc Acetate BP 2014). A white or almost white, crystalline powder or leaflets. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 5.8 to 7.0. Store in nonmetallic containers.

USP 36: (Zinc Acetate). White crystals or granules having a slight acetous odour. Is slightly efflorescent. Soluble 1 in 2.5 of water and 1 in 30 of alcohol; freely soluble in boiling alcohol. pH of a 5% solution in water is between 6.0 and 8.0. Store in airtight containers.

Zinc Chloride

Chlorid zinečnatý; Cink-klorid; Cinko chloridas; Cynku chlorek; Sinkkikloridi; Zinc, chlorure de; Zinc, cloruro de; Zinci chloridum; Zincum Chloratum; Zinkchlorid; Zinkklorid; Хлористый Цинк; Цинка Хлорид.

$ZnCl_2$=136.3

CAS — 7646-85-7.

ATC — B05XA12.

ATC Vet — QB05XA12.

UNII — 86Q357L16B.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Zinc Chloride). A white or almost white, deliquescent, crystalline powder or cast in white or almost white sticks. Very soluble in water; freely soluble in alcohol and in glycerol. An approximately 10% solution in water has a pH of 4.6 to 5.5. Store in nonmetallic containers.

USP 36: (Zinc Chloride). A white or practically white, odourless, crystalline powder, or white or practically white crystalline granules. May also be in porcelain-like masses or moulded into cylinders. It is very deliquescent. Soluble 1 in 0.5 of water, 1 in 1.5 of alcohol, and 1 in 2 of glycerol. Its solution in water or in alcohol is usually slightly turbid, but the turbidity disappears when a small quantity of hydrochloric acid is added. A 10% solution in water is acid to litmus. Store in airtight containers.

Turbidity. Zinc chloride almost always contains some oxychloride which produces a slightly turbid aqueous solution. Turbid solutions, except when intended for ophthalmic use, may be cleared by adding gradually a small amount of dilute hydrochloric acid. Solutions of zinc chloride should be filtered through asbestos or sintered glass, since they dissolve paper and cotton wool.

Zinc Citrate

Zinc Citrate Trihydrate; Цитрат Цинка.

2-Hydroxy-1,2,3-propanetricarboxylic acid zinc salt.

$C_{12}H_{10}O_{14}Zn_3,3H_2O$=628.4

CAS — 546-46-3.

UNII — K72I3DEX9B (anhydrous zinc citrate); GNM26GAX7R (zinc citrate trihydrate).

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Zinc Citrate).

Zinc Gluconate

Zinc, gluconate de; Zinc, gluconato de; Zinci gluconas; Zinkgluconat; Цинка Глюконат.

$C_{12}H_{22}O_{14}Zn$=455.7

CAS — 4468-02-4.

ATC — A12CB02.

ATC Vet — QA12CB02.

UNII — U6WSN5SQ1Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Zinc Gluconate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; practically insoluble in absolute alcohol and in dichloromethane. Store in non-metallic, airtight containers.

USP 36: (Zinc Gluconate). White or practically white powder or granules. Soluble in water; very slightly soluble in alcohol. pH of a 1% solution in water is between 5.5 and 7.5.

Zinc Lactate

Zinc Dilactate; Zinc Sarcolactate (*S*-isomer).

$C_6H_{10}O_6Zn$=243.5

CAS — 554-05-2; 16039-53-5.

UNII — 2GXR25858Y.

Zinc Sulfate

Zinc, sulfato de; Çinko Sülfat; Cinko sulfatas; Cink-szulfát; Cynku siarczan; Sinkkisulfaatti; Síran zinečnatý; Zinc, sulfate de; Zinc Sulphate; Zinci sulfas; Zincum Sulfuricum; Zinksulfat; Сернокислый Цинк; Цинка Сульфат.

$ZnSO_4,7H_2O$=287.5

CAS — 7733-02-0 (anhydrous zinc sulfate); 7446-20-0 (zinc sulfate heptahydrate).

ATC — A12CB01.

ATC Vet — QA12CB01.

UNII — 89DS0H96TB (zinc sulfate); 0J6Z13X3WO (anhydrous zinc sulfate); PTX099XSF1 (zinc sulfate monohydrate); N57JI2K7WP (zinc sulfate heptahydrate).

NOTE. 'White vitriol' or 'white copperas' is crude zinc sulfate.

ZSU is a code approved by the BP 2014 for use on single unit doses of eye drops containing zinc sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.*

Eur. also includes the monohydrate and the hexahydrate.

US includes the monohydrate and the heptahydrate in one monograph.

Ph. Eur. 8: (Zinc Sulfate Heptahydrate; Zinci Sulfas Heptahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 8: (Zinc Sulfate Hexahydrate; Zinci Sulfas Hexahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 8: (Zinc Sulfate Monohydrate; Zinci Sulfas Monohydricus). Colourless, transparent, crystals or a white or almost white crystalline powder. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.6. Store in nonmetallic containers.

USP 36: (Zinc Sulfate). It contains one or seven molecules of water of hydration. Colourless, transparent, prisms, or small needles. May occur as a white, granular, crystalline powder. It is odourless and is efflorescent in dry air. Very soluble in water (heptahydrate); freely soluble in water (monohydrate); practically insoluble in alcohol (monohydrate); insoluble in alcohol (heptahydrate); freely soluble in glycerol (heptahydrate). Its solutions are acid to litmus. Store in airtight containers.

Uses and Administration

Zinc is an essential element of nutrition and traces are present in a wide range of foods. It is a constituent of many enzyme systems and is present in all tissues. Features of zinc deficiency include growth retardation and defects of rapidly-dividing tissues such as the skin, the immune system, and the intestinal mucosa. Water-soluble zinc salts are used as supplements to correct zinc deficiency; for example, in malabsorption syndromes, during parenteral feeding, in conditions with increased body losses (trauma, burns, and protein-losing states), and in acrodermatitis enteropathica (a rare genetic disorder characterised by severe zinc deficiency). They have been tried in the treatment of a large number of conditions that may be related to zinc deficiency.

Doses of zinc salts are usually expressed in terms of elemental zinc, and the following salts contain about 50 mg of zinc:

- zinc acetate (dihydrate) 168 mg
- zinc chloride 104 mg
- zinc citrate (trihydrate) 160 mg
- zinc gluconate 348 mg
- zinc lactate 186 mg
- zinc sulfate (heptahydrate) 220 mg

The approximate number of millimoles of zinc contained in these salts are:

- 4.6 mmol in 1 g zinc acetate (dihydrate)
- 7.3 mmol in 1 g zinc chloride
- 4.8 mmol in 1 g zinc citrate (trihydrate)
- 2.2 mmol in 1 g zinc gluconate
- 4.1 mmol in 1 g zinc lactate
- 3.5 mmol in 1 g zinc sulfate (heptahydrate)

In **deficiency states**, zinc is usually given orally as the sulfate, the sulfate monohydrate, or the gluconate, in doses of up to 50 mg of elemental zinc three times daily. When intravenous supplements are required, zinc chloride or zinc sulfate may be given; a suggested dose for parenteral nutrition is 6.5 mg of elemental zinc (100 micromoles) daily.

Oral zinc salts, commonly the acetate, may be used as copper absorption inhibitors in **Wilson's disease** (p. 1567.3). The usual adult dose is 50 mg three times daily up to a maximum of five times daily. An effective dose in pregnant women is usually 25 mg three times daily; however, dosage is adjusted based on copper concentrations.

For doses in children, see Administration in Children, below and Diarrhoea, under Deficiency States, p. 2127.2.

Zinc sulfate is used topically in a variety of skin conditions mainly for its **astringent** properties. The insoluble zinc salts, commonly the oxide (p. 1729.1), are used similarly. A 1.2% solution of zinc acetate is used topically with erythromycin in the treatment of acne vulgaris (p. 1682.2). Zinc sulfate is also used as an astringent in eye drops. Zinc chloride has been used for its powerful caustic and astringent properties, usually in very dilute solution, in, for example, mouthwashes. Zinc citrate and zinc lactate are used in preparations for oral care and as a dietary supplement.

Polaprezinc (p. 1879.1) is also used as a source of zinc.

Homoeopathy

Zinc and its salts have been used in homoeopathic medicines.

Administration in children. Zinc can be given to children to prevent and treat deficiency or as a copper absorption inhibitor in Wilson's disease (p. 1567.3). The following doses are expressed as elemental zinc.

In **deficiency states**, zinc can be given orally according to weight:

- less than 10 kg, 22.5 mg daily
- 10 to 30 kg, 22.5 mg once to three times daily
- over 30 kg, 45 mg once to three times daily

The *BNFC* suggests an oral dose of zinc 1 mg/kg daily for neonates.

When intravenous supplements are required, suggested doses of zinc for children vary between countries. UK licensed product information recommends a dose of 250 micrograms/kg (up to a maximum of 3.75 mg) daily for children weighing 40 kg or less; children weighing more than 40 kg should receive the adult dose (see p. 2126.3). In the USA, licensed product information recommends a dose of 300 micrograms/kg daily for preterm neonates weighing up to 3 kg, and 100 micrograms/kg daily for full term infants and children up to 5 years. Adult doses may be used in older children.

In **Wilson's disease**, zinc is given orally according to age:

- 1 to 6 years, 25 mg twice daily
- 6 to 16 years and body-weight under 57 kg, 25 mg three times daily
- over 16 years or body-weight above 57 kg, 50 mg three times daily

For **acrodermatitis enteropathica**, the *BNFC* suggests an initial oral dose of zinc 0.5 to 1 mg/kg twice daily for all ages (the total daily dose may alternatively be given in 3 divided doses).

For oral zinc doses recommended in the management of acute diarrhoea in children, see below. Zinc sulfate may also be applied topically, see Uses and Administration p. 2126.3.

Age-related macular degeneration. High doses of dietary supplements such as betacarotene, vitamin C, vitamin E, and zinc are being promoted for preservation of vision in the elderly but there are no data to suggest any benefit for patients who do not have age-related macular degeneration or have only mild disease and such treatment is not necessarily harmless.[1] For further details, see under Betacarotene, p. 2051.2.

1. Anonymous. Antioxidant vitamins and zinc for macular degeneration. *Med Lett Drugs Ther* 2003; **45:** 45–46.

Common cold. Zinc salts have been tried (orally or intranasally) in the treatment of the common cold (p. 951.1) with variable results.[1-9] A systematic review of randomised studies (conducted in upper-middle and high-income countries, where zinc deficiency is uncommon) found that oral zinc reduced the duration and severity of common cold symptoms when used therapeutically, and that it reduced the incidence of the common cold in healthy children when used prophylactically. However, no firm recommendations could be made regarding the dose, formulation, and duration that should be used.[10]

1. Mossad SB, *et al*. Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996; **125:** 81–8.
2. Macknin ML, *et al*. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998; **279:** 1962–7.
3. Prasad AS, *et al*. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133:** 245–52.
4. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000; **31:** 1202–8.
5. Eby GA. Zinc lozenges as cure for the common cold—a review and hypothesis. *Med Hypotheses* 2010; **74:** 482–92.
6. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001; **33:** 1865–70.
7. Hirt M, *et al*. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000; **79:** 778–82.
8. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *Q J Med* 2003; **96:** 35–43.
9. Belongia EA, *et al*. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001; **111:** 103–8.
10. Singh M, Das RR. Zinc for the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 20/10/11).

Deficiency states. General references.

1. Hambidge M. Human zinc deficiency. *J Nutr* 2000; **130** (suppl): 1344S–1349S.
2. Prasad AS. Zinc deficiency: has been known of for 40 years but ignored by global health organisations. *BMJ* 2003; **326:** 409–10.
3. Shrimpton R, *et al*. Zinc deficiency: what are the most appropriate interventions? *BMJ* 2005; **330:** 347–9.
4. Mason P. Physiological and medicinal zinc. *Pharm J* 2006; **276:** 271–4.

DIAGNOSIS AND TESTING. A loss of taste acuity is a sign of zinc deficiency (see Taste Disorders, below) and this has been used as a test for the condition: patients who do not immediately perceive a strong flavour on tasting a dilute (typically 0.1 or 0.2%) solution of zinc sulfate are considered likely to benefit from supplementation. However, a study in pregnant women failed to confirm that the ability to taste such a solution was related to zinc deficiency.[1]

Authors of a small study of Japanese children with short stature evaluated body zinc clearance, and considered those patients with high clearance values but normal serum zinc concentrations to have marginal zinc deficiency.[2]

1. Mahomed K, *et al*. Failure to taste zinc sulphate solution does not predict zinc deficiency in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **48:** 169–75.
2. Kaji M, *et al*. Studies to determine the usefulness of the zinc clearance test to diagnose marginal zinc deficiency and the effects of oral zinc supplementation for short children. *J Am Coll Nutr* 1998; **17:** 388–91.

DIARRHOEA. Chronic diarrhoea can be a sign of zinc deficiency, and diarrhoea can lead to excessive zinc losses and zinc deficiency when dietary zinc is inadequate. Zinc supplements have been shown to reduce the incidence, intensity, or duration of acute diarrhoea (p. 1805.2) in children in developing countries.[1-5] Beneficial effects have also been seen with zinc supplementation for persistent diarrhoea.[4,5] A WHO report concluded that zinc supplementation is efficacious in significantly reducing the severity and duration of diarrhoea; the type of zinc salt does not appear to influence efficacy, although the best formulation should be determined to minimise adverse effects such as vomiting.[6] A further report[7] concluded that there was sufficient evidence to recommend the inclusion of zinc as adjunctive therapy to oral rehydration salts in the standard management of both dysenteric and non-dysenteric acute diarrhoea. WHO guidelines on the management of acute diarrhoea recommend 10 to 14 days of oral zinc supplementation at a dose of 10 mg daily for infants under 6 months of age, and 20 mg daily for older children.[8] It has been suggested that HIV-infected children should also receive zinc supplementation for diarrhoea, see HIV infection and AIDS, below.

For a report of increased efficacy in reducing persistent diarrhoea and dysentery when zinc is used with vitamin A, see Diarrhoea, under Deficiency states, p. 2100.1. For suggestions that zinc potentiates the effect of vitamin A, see Vitamin A deficiency, below.

1. Bhutta ZA, *et al*. Zinc Investigators' Collaborative Group. Prevention of diarrhea and pooled analysis of randomized controlled trials. *J Pediatr* 1999; **135:** 689–97.
2. Bhutta ZA, *et al*. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000; **72:** 1516–22.
3. Aggarwal R, *et al*. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics* 2007; **119:** 1120–30.
4. Fischer Walker CL, Black RE. Micronutrients and diarrheal disease. *Clin Infect Dis* 2007; **45** (suppl 1): S73–S77.
5. Lukacik M, *et al*. A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. *Pediatrics* 2008; **121:** 326–36.
6. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *J Health Popul Nutr* 2001; **19:** 338–46.
7. Robberstad B, *et al*. Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. *Bull WHO* 2004; **82:** 523–31.
8. WHO/UNICEF. WHO/UNICEF joint statement: clinical management of acute diarrhoea (issued May 2004). Available at: http://www.afro.who.int/en/tanzania/tanzania-publications/doc_download/617-acute-diarrhoea-joint-statement.html (accessed 22/07/10)

GROWTH RETARDATION. Growth retardation in a group of short Japanese children without endocrine abnormalities was found to be associated with mild to moderate zinc deficiency; supplementation with oral zinc sulfate 5 mg/kg daily over 6 months resulted in an improvement in growth velocity despite unchanged growth hormone production.[1] Similarly, supplementation with 10 mg zinc daily for 6 days of each week, for 6 months, increased the growth rate of stunted Ethiopian infants; weight also increased in both stunted and non-stunted children, and the authors commented that these effects were at least partly due to improvements in appetite, and reduced morbidity from infection.[2] Results from a meta-analysis of these 2 studies and 31 others indicated that zinc supplementation resulted in a highly significant increase in both linear growth and weight gain of prepubertal children; weight-for-height index was not affected. Significant increases in serum zinc concentrations were also noted with supplementation, but additional studies were considered necessary in order to determine whether mean serum zinc concentration could accurately predict response to supplementation.[3]

1. Nakamura T, *et al*. Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. *J Pediatr* 1993; **123:** 65–9.
2. Umeta M, *et al*. Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet* 2000; **355:** 2021–6.
3. Brown KH, *et al*. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002; **75:** 1062–71.

HIV INFECTION AND AIDS. A systematic review[1] found that zinc supplements reduced diarrhoeal morbidity in HIV-infected children in a single study, without causing adverse effects on disease progression; it was considered that children with HIV should receive zinc supplements in the management of diarrhoea (p. 1805.2) or severe malnutrition in the same way as uninfected children.

1. Irlam JH, *et al*. Micronutrient supplementation in children and adults with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 22/12/10).

PNEUMONIA. A pooled analysis[1] of 10 studies performed in developing countries found that zinc supplementation reduced the incidence of pneumonia in children by 41%. A randomised study in Bangladesh, in 270 children aged 2 to 23 months, found that 20 mg daily of elemental zinc, given orally and adjuvant to standard antimicrobial therapy, accelerated recovery from pneumonia when compared with placebo; children aged 12 months or older resolved their respiratory illness earlier than younger infants.[2] Another study in Bangladesh,[3] involving 1621 children 2 to 12 months old, found that prophylaxis with 70 mg of oral zinc acetate [about 20 mg of zinc] given weekly reduced the incidence of pneumonia compared with placebo and also reduced subsequent pneumonia-related mortality; a small reduction in the incidence of diarrhoea was also seen.

However, a later systematic review[4] including 15 randomised controlled studies concluded that on balance the evidence suggested no additional benefit of oral zinc supplementation in children with community-acquired pneumonia who were receiving antimicrobial therapy; there was also no evidence of benefit in preventing pneumonia, and one study had suggested a possible increased incidence and prevalence in children given the supplement.

1. Bhutta ZA, *et al*. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatr* 1999; **135:** 689–97.
2. Brooks WA, *et al*. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet* 2004; **363:** 1683–8.
3. Brooks WA, *et al*. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005; **366:** 999–1004.
4. Mathew JL. Zinc supplementation for prevention or treatment of childhood pneumonia: a systematic review of randomized controlled trials. *Indian Pediatr* 2010; **47:** 61–6.

PREGNANCY. Zinc requirements are increased in pregnancy. Although it is unclear to what extent this has clinical consequences, some have suggested that supplementation with modest doses of zinc (less than 45 mg daily) during pregnancy may have beneficial effects on fetal growth and development, and lead to improved pregnancy outcomes.[1] A controlled study in Peru found that addition of oral zinc (25 mg of zinc daily as zinc sulfate) to iron and folate supplementation improved fetal bone growth, as measured by femur length.[2] A systematic review[3] concluded that, while zinc supplementation during pregnancy appears to reduce preterm delivery, there was no convincing evidence that it resulted in other useful benefits. Since the association with preterm birth might reflect poor nutrition, improvement in the overall nutritional status of impoverished populations would be more beneficial than zinc supplementation in isolation.

1. Favier M, Hininger-Favier I. Zinc et grossesse. *Gynecol Obstet Fertil* 2005; **33:** 253–8.
2. Merialdi M, *et al*. Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *Am J Clin Nutr* 2004; **79:** 826–30.
3. Mahomed K, *et al*. Zinc supplementation for improving pregnancy and infant outcome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 05/03/08).

TASTE DISORDERS. Zinc appears to be effective for the treatment of taste disturbances (p. 1047.2) associated with zinc deficiency but there is insufficient evidence to determine its efficacy for taste dysfunction secondary to conditions that do not involve low serum zinc concentrations.[1] Zinc picolinate was found to significantly improve objective measurement of taste when compared with placebo, both in patients with zinc deficiency and in those with idiopathic taste disorders (and normal serum zinc concentrations); there were no differences in subjective assessment of taste.[2] A later study[3] also found oral zinc gluconate 140 mg daily [about 20 mg of zinc] to be of benefit in idiopathic dysgeusia. In contrast, loss of taste has been reported in some patients using zinc gluconate intranasally, see p. 2128.1.

Polaprezinc (p. 1879.1) is also being investigated as a treatment for taste disorders.

1. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; **30:** 186–7.
2. Sakai F, *et al*. Double-blind, placebo-controlled trial of zinc picolinate for taste disorders. *Acta Otolaryngol* 2002; (suppl 546): 129–33.
3. Heckmann SM, *et al*. Zinc gluconate in the treatment of dysgeusia—a randomized clinical trial. *J Dent Res* 2005; **84:** 35–8. Correction. *ibid.*; 382.

Vitamin A deficiency. It has been proposed[1] that the inconsistent effects on morbidity of vitamin A supplementation (see Diarrhoea, under Deficiency States, p. 2100.1) may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. The authors found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone. There is also some suggestion that zinc may potentiate the effects of vitamin A in the treatment of night blindness,[2] but only in those patients already deficient in zinc. A study in Bangladesh[3] found that the proportional improvement in vitamin A status in vitamin A-deficient children was larger in those given zinc with vitamin A than in those given vitamin A or zinc alone, suggesting a synergistic effect. Similarly, a study in Indonesia[4] of supplementation in pregnant women found that betacarotene with zinc, but not betacarotene or zinc alone, improved vitamin A status in both mothers and infants at 6 months postpartum; the authors suggested that zinc

may have a specific role in the conversion of betacarotene to retinol.

1. Rahman MM, *et al*. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314–18.
2. Christian P, *et al*. Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *Am J Clin Nutr* 2001; **73:** 1045–51.
3. Rahman MM, *et al*. Synergistic effect of zinc and vitamin A on the biochemical indexes of vitamin A nutrition in children. *Am J Clin Nutr* 2002; **75:** 92–8.
4. Dijkhuizen MA, *et al*. Zinc plus β-carotene supplementation of pregnant women is superior to β-carotene supplementation alone in improving vitamin A status in both mothers and infants. *Am J Clin Nutr* 2004; **80:** 1299–1307.

Wilson's disease. References.

1. Anderson LA, *et al*. Zinc acetate treatment in Wilson's disease. *Ann Pharmacother* 1998; **32:** 78–87.
2. Brewer GJ, *et al*. Treatment of Wilson's disease with zinc: XV long-term follow-up studies. *J Lab Clin Med* 1998; **132:** 264–78.
3. Brewer GJ, *et al*. Treatment of Wilson's disease with zinc: XVII: treatment during pregnancy. *Hepatology* 2000; **31:** 364–70.
4. Brewer GJ. Zinc acetate for the treatment of Wilson's disease. *Expert Opin Pharmacother* 2001; **2:** 1473–7.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of zinc salts (the gluconate and sulfate) given orally are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, and gastritis. These are particularly common if zinc salts are taken on an empty stomach, and may be reduced by giving them with meals.

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

Prolonged use of high doses of zinc supplements, orally or parenterally, leads to copper deficiency with associated sideroblastic anaemia and neutropenia; full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. Zinc toxicity has occurred after the use of contaminated water in haemodialysis solutions. High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate (p. 1573.2).

Metal fume fever is an occupational disease associated with inhalation of freshly-oxidised metal fumes, most commonly from zinc, iron or copper. It is characterised by chills, fever, cough, dyspnoea, myalgia, and chest pain, and is generally self-limiting and does not appear to be associated with long-term sequelae.

Effects on the blood. There have been reports[1-3] of anaemia, leucopenia, and neutropenia in patients consuming excessive amounts of zinc supplements for acne. A patient given zinc-containing enteral feeds as well as zinc supplementation was diagnosed with sideroblastic anaemia due to zinc toxicity.[4] All patients were copper-deficient,[1-4] despite supplementation with copper in one case.[4]

1. Porea TJ, *et al*. Zinc-induced anemia and neutropenia in an adolescent. *J Pediatr* 2000; **136:** 688–90.
2. Igic PG, *et al*. Toxic effects associated with consumption of zinc. *Mayo Clin Proc* 2002; **77:** 713–16.
3. Salzman MB, *et al*. Excessive oral zinc supplementation. *J Pediatr Hematol Oncol* 2002; **24:** 582–4.
4. Irving JA, *et al*. Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation. *Can Med Assoc J* 2003; **169:** 129–31.

Effects on the senses. The FDA's adverse event reporting system received 131 reports of anosmia (loss of the sense of smell) associated with the use of intranasal zinc-containing preparations (Zicam).[1] These products contained zinc gluconate, were marketed in the USA from 1999 to June 2008, and were used to prevent and treat cold symptoms, usually for about 3 days. Loss of smell was often associated with an initial burning sensation in the nose, and occurred soon after intranasal use; anosmia was long-lasting or permanent in most cases. Loss of taste was also reported in some patients.

1. FDA. Zinc-containing intranasal cold products (marketed as Zicam) and anosmia. *FDA Drug Safety Newsletter* 2009; **2:** 26–7. Also available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/UCM192395.pdf (accessed 04/02/10)

Hypersensitivity. Report of a patient who developed palmoplantar pustulosis about 1 year after receiving dental fillings containing zinc.[1] Zinc hypersensitivity was confirmed by *in vitro* and patch testing. Complete remission occurred on replacing the dental fillings.

1. Yanagi T, *et al*. Zinc dental fillings and palmoplantar pustulosis. *Lancet* 2005; **366:** 1050.

Parenteral nutrition. Zinc was found to be a common contaminant of various components used for TPN, and rubber stoppers or glass may have been the source.[1] Levels of zinc found may exceed daily requirements even before the addition of supplementary zinc. The authors suggested it may be important to routinely monitor zinc status in patients receiving long-term TPN, particularly infants and children.

1. Hak EB, *et al*. Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55:** 150–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zinc sulfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

The absorption of zinc may be reduced by iron supplements (see also Absorption, under Pharmacokinetics, below), penicillamine, phosphorus-containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones (see Antacids and Metal Ions, under Interactions of Ciprofloxacin, p. 265.1), iron, penicillamine, and tetracyclines (p. 375.3).

Pharmacokinetics

Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the faeces, and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

Absorption. Although zinc deficiency (see Deficiency States, under Uses and Administration, p. 2127.1) in some cases may be due to inadequate dietary intake, inhibitors of zinc absorption may also be causative.[1] *Phytates*, which are present in cereals, corn, legumes, and rice, inhibit zinc absorption. The animal *protein* in beef, eggs, and cheese counteracts the inhibitory effect of phytate, whereas the casein in milk decreases zinc absorption. Proteins also often contain other constituents such as inorganic *phosphate* that can negatively affect zinc absorption. Long-term use of *calcium* supplements has no effect on zinc status, but dietary calcium may form insoluble complexes with phytate and zinc, thus decreasing the absorption of zinc. *Iron* can reduce zinc absorption, although the effect is apparent only at a very high ratio of iron to zinc, and in aqueous solution, which suggests that iron fortification of foods will not affect zinc absorption. Although it is possible that iron supplementation could affect mechanisms of zinc uptake and transport, studies have not found such an effect, and long-term iron supplementation is not considered to impair zinc status.

Zinc can form complexes with ligands or chelators; if the complex is readily absorbed, this can increase zinc absorption. *Edetic acid* has been found to have variable effects on zinc status depending on the ratio of edetic acid to other cations and phytate, which compete for complex formation with zinc. *Histidine* also chelates with zinc and can increase plasma zinc concentrations; however, the ratio of histidine to zinc is important because high doses of histidine may enhance the urinary excretion of zinc. *Methionine* may improve zinc absorption, although evidence is limited. Adding organic acids such as *citrate* to foods can enhance zinc absorption; zinc citrate has been used as a dietary supplement.

1. Lönnerdal B. Dietary factors influencing zinc absorption. *J Nutr* 2000; **130:** 1378S–1383S.

Human Requirements

UK and US recommended dietary intake. In the UK dietary reference values (DRV)[1] and in the USA recommended dietary allowances (RDA)[2] (see Human Requirements, p. 2046.1) have been published for zinc. In the UK the reference nutrient intake (RNI) for adult males and females is 9.5 and 7.0 mg daily respectively; values are also given for infants and children of varying ages and for lactating women. The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for zinc of 25 mg daily. In the USA the RDA for adults is 11 mg daily for men and 8 mg daily for women.[2] The tolerable upper intake level is 40 mg daily.

WHO recommend lower limits of the safe ranges of population mean intakes of dietary zinc for 3 categories of diets based on high, moderate, and low zinc bioavailability: values are 4.0, 6.5, and 13.1 mg dietary zinc daily for women, and 5.6, 9.4, and 18.7 mg dietary zinc daily for men, respectively.[4] They recommend an upper limit of the safe range of population mean intakes of zinc of 35 mg daily for women, and 45 mg daily for men.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 14/11/05)
4. WHO. Zinc. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 72–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Galzin; ***Austral.***: Zincaps; ***Austria***: Wilzin; ***Belg.***: Wilzin; ***Braz.***: Dermezil; Zincopan; ***Canad.***: Anusol; Anuzinc†; Bio Statol; Egozinc; Flavo-Zinc†; Men Formula†; Micro Zn; Rivasol; Shaklee DR; ***Chile***: Altazinc; Cleanance; Num-Zit; ***China***: Likexin (利可欣); Ping An (屏安); Wei Er (威尔); Xing Rui Ling (星瑞灵); ***Cz.***: Wilzin; Zincteral†; Zinkorotat-POS†; ***Denm.***: BiOrto Zink; Wilzin; ***Fr.***: Effizinc; Rubozinc; Suboligo Zinc†; Wilzin†; ***Ger.***: Biolectra Zink; Cefazink; Curazink; Nefro-Zinc†; Ophtal Z†; Ophtopur-Z†; Tussamag Zink†; Unizink; Virudermin; Vitazink; Wilzin; Zink AL; Zink beta; Zink Hexal†; Zink Verla; Zink-D Longoral; Zink-Injekt N; Zink-Ratiopharm; Zink-Sandoz†; Zinkaspart; Zinkbrause; Zinkit; Zinkorot; Zinkotase; ***Gr.***: Solvazinc; Wilzin; ***Hong Kong***: Anuzinc†; Egozinc†; Eye Glo Relief; Zincaps; ***Hung.***: Feroglobin-B12; ***India***: Adrovit-Z; Aquasol Ceezed; Ascazin; Gludel; Infladase Forte; Keeper; ***Indon.***: Interzinc; Orezinc; Zidiar; Zincare; Zincpro; Zn-Diar; ***Irl.***: Solvazinc†; Wilzin; ***Israel***: Avazinc; Micro Zn; Zincol; ***Ital.***: Pontefix; Wilzin; ***Mex.***: Unguento del Bebe; Z-Crim†; ***Neth.***: Wilzin; ***Norw.***: Solvezink; Wilzin; ***NZ***: Zincaps; ***Philipp.***: E-Zinc; Immuzinc; Lipactin; Nutrizinc; Orazinc; Prozinc; Zinbee; ***Pol.***: Wilzin; Zincas; Zincteral; ***Port.***: Wilzin; ***Rus.***: Zincteral (Цинктерал); ***Spain***: Wilzin; ***Swed.***: Solvezink; Wilzin; ***Switz.***: Collazin; Virudermin; Zink Verla; ***Thai.***: Z-G; Zinc Tab; Zincaps; Zincate; Zinctab; ***Turk.***: Medizinc; Nutri-Zinc; Zinco; Zincobest; Zincover; Zinvital; ***UK***: Flavo-Zinc; Solvazinc; Tartar Control Listerine; Wilzin; Zincomed; Zincosol; ***Ukr.***: Zincteral (Цинктерал); Zinkit (Цинкит); ***USA***: Dermadrox; Galzin; Halls Zinc Defense; Ivy Dry; Orazinc; PeleVerus Clear; Verazinc; Zinca-Pak†; Zincate; ***Venez.***: Cicalfate.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus; Snore Eze; ***Austria***: Gracil; ***Canad.***: Cold Tablets with Zinc†; Echinacea Compositum; Formula PC 223†; Weight Loss Kit†; ***Chile***: Ikoplex No 9; ***Cz.***: Vita C-R15 forte†; Vita C-R15†; ***Fr.***: Abbe Chaupitre no 23†; Acidum Phosphoricum Complexe No 5; ***Ger.***: Dormi-cyl L Ho-Len-Complex; Gelsemium Comp; Infi-China; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Phonix Silybum spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Presselin Nervenkomplex; Presselin Nervennahrung N†; Ranocalcin HM; Rufebran regeno†; Zerosorin SN†; Zincum Hevert N; Zinkokehl; Zinkorell; ***Neth.***: Emvita 15; ***Rus.***: Passidorm (Пассидорм).

Pharmacopoeial Preparations

BP 2014: Erythromycin and Zinc Acetate Lotion; Zinc Sulphate Capsules; Zinc Sulphate Eye Drops; Zinc Sulphate Injection; Zinc Sulphate Lotion; Zinc Sulphate Tablets;

USP 36: Calcium and Vitamin D with Minerals Tablets; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Zinc Acetate Oral Solution; Zinc and Vitamin C Lozenges; Zinc Chloride Injection; Zinc Citrate Tablets; Zinc Gluconate Tablets; Zinc Sulfate Injection; Zinc Sulfate Ophthalmic Solution; Zinc Sulfate Oral Solution; Zinc Sulfate Tablets; Zinc Sulfide Topical Suspension.

Obstetric Drugs

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Ergot alkaloids, p. 2129
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This chapter includes drugs used in obstetrics for the management of labour and postpartum haemorrhage, including various prostaglandins, oxytocics, ergot alkaloids, and tocolytics. Some of these drugs have also been used to terminate pregnancy, as has the antiprogestogen mifepristone (p. 2138.1).

Other drugs with important roles in obstetric management to be found elsewhere in *Martindale* include local anaesthetics (p. 1976.1), opioid analgesics (p. 108.1), and medical gases such as oxygen (p. 1799.3) and nitrous oxide (p. 1908.1). For drugs used in the management of perinatal bacterial infection, see Antibacterials (p. 168.1).

Obstetric Drug Groups

Ergot alkaloids

Some ergot alkaloids have a powerful action on the uterus, causing uterine contractions that are utilised in the active management of the third stage of labour, and to prevent or treat postpartum and postabortal haemorrhage.

Described in this chapter are
- Ergometrine, p. 2136.2
- Ergot, p. 2137.1
- Ergotoxine, p. 2137.2
- Methylergometrine, p. 2137.3

Oxytocics

Oxytocics cause contraction of the uterus and may be used for the induction and augmentation of labour, in the management of the third stage of labour, and to prevent and treat postpartum haemorrhage.

Described in this chapter are
- Carbetocin, p. 2132.3
- Demoxytocin, p. 2133.3
- Oxytocin, p. 2143.1

Prostaglandins

Some prostaglandins soften and dilate the cervix and induce contraction of the uterus. They may be used in labour induction, termination of pregnancy, and the treatment of postpartum haemorrhage.

Described in this chapter are
- Carboprost, p. 2133.1
- Dinoprost, p. 2133.3
- Dinoprostone, p. 2134.1
- Gemeprost, p. 2137.2
- Misoprostol, p. 2140.3
- Sulprostone, p. 2145.3

Tocolytics

Tocolytics inhibit uterine contractions and are used in premature labour to delay early delivery. Beta agonists other than ritodrine have also been used, and details on salbutamol (p. 1220.2) and terbutaline (p. 1228.1) can be found in the chapter on Bronchodilators and Anti-asthma Drugs. Other drugs that have been tried for their tocolytic actions include calcium-channel blockers (see Nifedipine, p. 1447.2), glyceryl trinitrate (p. 1391.2), magnesium sulfate (p. 1787.3), and NSAIDs (see Indometacin, p. 71.2).

Described in this chapter are
- Atosiban, p. 2132.2
- Ritodrine, p. 2145.1

Management of Obstetric Conditions

The management of some obstetric conditions is discussed below.

Labour induction and augmentation

The uterus is normally spontaneously contractile but during pregnancy various physiological mechanisms maintain it in a quiescent state; retention of the fetus is also aided by a firm and contracted cervix. During the final 4 to 5 weeks of pregnancy the cervix normally undergoes a 'ripening' process in which it becomes softened and dilated, so that at parturition it is not a barrier to delivery of the fetus. Endogenous prostaglandins play an important role in this process, and also sensitise the uterus in preparation for labour.

- Labour usually begins spontaneously but in some cases it may be necessary to induce labour, for example in pregnancies that go beyond term or where rupture of the membranes occurs without labour. In other cases there may be indications for early delivery such as maternal hypertensive states, antepartum haemorrhage, intra-amniotic infection (chorioamnionitis), or intra-uterine fetal death.[1,2]
- Once labour has started, augmentation of uterine activity may be necessary if contractions fail to progress satisfactorily. A process of active management of labour, including early oxytocin augmentation, has been used in nulliparous women with a single fetus presenting head-first at term and showing no evidence of fetal compromise. Although it may shorten labour without increasing maternal or neonatal harm, it has not been shown to reduce the rate of caesarean section.[3]

Various techniques are available for **induction of labour**, and the choice may be influenced by the ripeness of the cervix and whether the membranes are intact or have ruptured. Mechanical methods are commonly used and may be all that is needed to induce labour. UK guidelines suggest that sweeping of the membranes (manually separating the lower membrane portion from the uterine wall during vaginal examination) should be offered to women at term.[4] It increases the likelihood of spontaneous labour within 48 hours or birth within one week, and reduces the frequency of formal induction of labour.[5] However, it may cause maternal discomfort, irregular contractions, and bleeding. Laminaria tents, hygroscopic cervical dilators, or Foley (balloon) catheters may be used to stimulate cervical ripening.[1] Although some consider the Foley catheter to be an effective alternative to pharmacological induction with prostaglandins,[6,7] others do not recommend these mechanical methods for routine use in labour induction.[4] Such mechanical methods used for cervical ripening might also increase the risk of maternal and neonatal infection, compared with pharmacological induction.[8] Amniotomy (deliberate rupture of the membranes and release of amniotic fluid) may also be used to stimulate labour, once the cervix becomes favourable.[2] When pharmacological induction of labour is required, a prostaglandin or oxytocin is generally used. WHO[6] recommends oxytocin alone if the cervix is favourable but that a prostaglandin or a mechanical method (Foley catheter) should be used to ripen an unfavourable cervix before induction. However, UK guidelines[4] consider vaginal dinoprostone (prostaglandin E_2) to have advantages over both amniotomy and oxytocin in terms of comfort, convenience, and acceptability, and recommend it as the preferred method, regardless of cervical status.

As prostaglandins can both ripen the cervix and initiate uterine activity, they induce labour that is similar to spontaneous labour.[1] The intravenous and oral routes have been associated with frequent adverse, particularly gastrointestinal, effects[9,10] and intravaginal dosage is now preferred. The intracervical route is no more effective than the intravaginal route, and is no longer recommended.[4] Dinoprostone is the most widely used prostaglandin and has been given by various routes, but is usually given intravaginally. A systematic review[11] considered the clinical benefits of vaginal gel, vaginal tablets, and pessaries, to be equivalent. The use of a modified-release vaginal insert was also effective, and associated with a reduction in instrumental vaginal delivery compared with gel or tablets, particularly in women with an unfavourable cervix. Dinoprostone was associated with an increased risk of uterine hyperstimulation with fetal heart rate changes.

Whenever possible, amniotomy should be performed in women with intact membranes before giving oxytocin.[6] If vaginal prostaglandins have already been given, usually to ripen the cervix,[2,6] oxytocin should not be started for at least 6 hours. Oxytocin is given by slow intravenous infusion, adjusted according to response.[2,6] Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/minute, dose increases of 1 to 6 milliunits/minute, and intervals between increases of 15 to 40 minutes.[1] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but cause more uterine hyperstimulation.[1,7] Low-dose regimens are now generally advocated.[1,6] There has been some interest in pulsed administration of oxytocin for induction to mimic the pulsatile secretion of endogenous oxytocin that occurs during spontaneous labour, but such use has not been established.[1]

Misoprostol has also been investigated.[1,12,13] Most studies have used the intravaginal route and have suggested it may be more effective than standard methods of labour induction.[14] Oral misoprostol may have a similar efficacy to intravaginal use.[15] However, the risk of uterine hyperstimulation may be increased with misoprostol, more so with the vaginal route than when given orally, and there is as yet insufficient evidence of its safety to recommend routine use.

The antiprogestogen mifepristone also produces cervical dilatation and stimulates uterine contraction and has been tried for cervical ripening and for induction of labour. A systematic review of studies found that it may be effective, but its place in therapy has yet to be established.[16]

In pregnancies at term, *prelabour rupture of the fetal membranes* may be treated with early induction of labour or expectant management (waiting for labour to occur naturally, which will start within 24 hours in most women[17]). There have been concerns that prolonged rupture of membranes may result in higher rates of maternal and neonatal infection, but that induction may result in more caesarean deliveries.[13] A systematic review[17] of studies in women with prelabour rupture of membranes at 37 weeks or later, comparing induction (oxytocin infusion or intravaginal dinoprostone) with expectant management found no difference in rates of caesarean section or instrumental vaginal births. There were lower rates of chorioamnionitis and endometritis in women treated with induction. In neonates, there was no difference in infection rate, but fewer admissions to the intensive care unit after oxytocin use. Women were also more satisfied with induction than expectant management. Intravaginal dinoprostone has been recommended as a less invasive treatment than intravenous oxytocin.[4] Oral and vaginal misoprostol have also been investigated in this group, and may have a similar efficacy to oxytocin and dinoprostone.[13]

A regimen of oral mifepristone, followed by vaginal dinoprostone or vaginal misoprostol, has been recommended for the management of *intra-uterine fetal death* at 24 weeks of gestation or later.[4] Vaginal misoprostol alone may also be effective for labour induction in the management of fetal anomaly or intra-uterine fetal death; it appears to be as effective as other prostaglandins and more effective than oral use.[18]

Labour augmentation may be started when labour is abnormally slow (dystocia) due to atony. Oxytocin is generally used, in similar doses to those for induction.[6] As for induction, both high- and low-dose regimens have been described, with higher doses reducing the duration of labour and rate of caesarean deliveries, but causing more hyperstimulation.[3] Augmentation using oxytocin results in normal vaginal delivery in about half of all women treated.[19]

Intravaginal dinoprostone has also been used for augmentation of labour. A placebo-controlled study[20] in women with slow cervical dilatation found doses of 1 or 2 mg to be effective for improving cervical dilatation and reducing the time to delivery; women given the higher dose were less likely to require oxytocin augmentation after 6 hours, but were at greater risk of hyperstimulation.

Once delivery has successfully been initiated, management of the third stage of labour may be considered to reduce the risks of postpartum haemorrhage (see p. 2130).

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Lactation inhibition and induction

Lactation is the physiological secretion of milk post partum. Milk production by the breast is induced by prolactin while oxytocin promotes milk ejection into the milk ducts; both prolactin and oxytocin secretion are stimulated by suckling.

Lactation inhibition. The breast engorgement with consequent discomfort and galactorrhoea triggered by prolactin secretion post partum can be problematic in women who choose not to breast feed or are unable to do so. Nonsteroidal or synthetic oestrogens were historically used to suppress lactation in such women, but this use is now considered inappropriate because of an increased risk of thromboembolism. Bromocriptine is a potent inhibitor of prolactin secretion: it has been given post partum in short treatment courses (about 14 days) to suppress lactation. However, it has also been associated with severe adverse effects, and its use for lactation suppression is no longer advocated in some countries. Other dopaminergics with similar actions such as cabergoline, lisuride, metergoline, and quinagolide have also been used to suppress lactation. Although it has been suggested that cabergoline, which is generally better tolerated than bromocriptine, may be a better choice for lactation inhibition,[1] the same general objections as for bromocriptine apply to all these drugs. A study in HIV-infected women requiring lactation suppression (in order to prevent mother-to-child transmission from breast milk) found that a combined oral contraceptive was as effective as bromocriptine.[2] Non-pharmacological methods include warm showers to induce milk leakage and reduce pressure, ice packs to reduce local pain and swelling, and a well fitting supportive brassiere. The removal of just enough milk to reduce the pressure but not enough to empty the breasts may help to reduce milk production gradually. Active treatments including mild analgesics such as ibuprofen or paracetamol are also advocated.[3] However, neither pharmacological nor non-pharmacological methods of lactation inhibition have been well evaluated,[4,5] and one review[4] noted that mild analgesia might not be enough to prevent the considerable pain felt by many women.

Lactation induction. Drug therapy has sometimes been used to help stimulate lactation, although good maternal education and support in techniques that promote physiological lactation remain the most important methods.[6] Dopamine antagonists, of which metoclopramide has been the most widely used, can produce modest increases in breast milk production but carry a risk of adverse effects including dystonias. If used, such therapy should be limited to 1 or 2 weeks;[7] there has also been some concern about the presence of these drugs in breast milk.[6,7] The efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.[8] Domperidone has also been reported to increase milk production,[7,9] and may cause fewer adverse central effects than metoclopramide. Nevertheless, the FDA has warned against the use of domperidone because of the potential risks of adverse effects in both mother and infant.[10] Protirelin has been given intranasally to stimulate lactation by increasing serum prolactin concentrations,[7] but is expensive, and a suitable commercial preparation is unavailable. Although oxytocin nasal spray has been tried to promote milk ejection, a double-blind, placebo-controlled study[11] of women expressing milk for preterm infants found that although milk production increased marginally in the first 2 days with oxytocin, there was no difference overall after 5 days. Most mothers also believed that they were receiving the active spray suggesting a significant placebo effect. Others[12] warn that its use may interfere with the mother's ability to learn to eject milk naturally, resulting in some becoming dependent upon its action. It might, however, facilitate milk let-down in tetraplegic women.[6]

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Postpartum haemorrhage

If the uterus fails to contract adequately after delivery (uterine atony), or if retained placental remnants prevent retraction of the placental bed, postpartum haemorrhage may occur. These two causes account for about 80% of cases of postpartum haemorrhage; in the remainder it is usually due to trauma of the genital tract or coagulopathy.

Primary postpartum haemorrhage has traditionally been defined as vaginal bleeding of more than 500 mL within 24 hours after childbirth. However, the volume of blood loss is often underestimated and the ability of a woman to cope with blood loss may be affected by her previous health, anaemia, and hypovolaemia.[1-3] Postpartum haemorrhage may be fatal to the mother unless promptly dealt with, and **management** generally involves:

- removal of the placenta if it has not been expelled
- the use of oxytocics to contract the uterus
- transfusion if blood loss is severe

Parenteral oxytocin is the oxytocic generally used to control bleeding due to uterine atony,[3,4] and oxytocin infusion may be used to maintain uterine contraction.[2] An ergot alkaloid (ergometrine or methylergometrine),[1,3] or the fixed combination *Syntometrine* (oxytocin and ergometrine),[4] may be used as an alternative or for bleeding that does not respond to oxytocin. Prostaglandins such as carboprost or dinoprostone may also be used,[1,3] usually for haemorrhage that has not been controlled by oxytocin and ergot preparations.[2,4] There is considerable interest in the use of misoprostol, particularly for developing countries,[5,6] because of its better stability and ease of administration.[2] It has been used both rectally and sublingually, but a review[7] found there was insufficient evidence to support the use of rectal misoprostol instead of a combination of oxytocin and ergometrine, and studies of sublingual misoprostol have confirmed that oxytocin is preferred.[8,9] Nevertheless, in women who have not been given prophylactic oxytocics during labour misoprostol could be used for treatment when oxytocin is not available, although the optimum dose remains to be determined.[9] Surgery may be required if medical management does not control bleeding.[1,2]

Oxytocin may be used in the management of retained placenta, given by intramuscular injection[3] or injected into the vein of the umbilical cord[4] (although there is growing evidence that umbilical use may be of no benefit—see p. 2144.1). However, ergometrine is not recommended because it causes tetanic uterine contractions, which may delay expulsion of the placenta.[3,4] Dinoprostone and sulprostone are also not recommended, because of a lack of evidence of efficacy, and concerns about adverse cardiovascular effects.[4]

Secondary postpartum haemorrhage occurs between 24 hours and 12 weeks after delivery and although associated with maternal morbidity rather than death in developed countries, it is a major contributor to maternal death in developing countries. Antibacterials, oxytocics, hormone therapy, and a variety of surgical treatments are used,[1,3,10] but a systematic review[10] concluded that evidence for the best treatment is lacking.

Risk factors for postpartum haemorrhage include prolonged labour, augmented labour, overdistended uterus (for example in multiple pregnancy), and a history of postpartum haemorrhage.[1] However, atonic postpartum haemorrhage occurs in many women without identifiable risk factors, and authorities recommend that **prophylaxis** should be offered to all women during childbirth.[11,12] *Active management of the third stage of labour* involves prophylactic use of an oxytocic, cord clamping before placental delivery, controlled cord traction, and uterine massage after delivery of the placenta.

The routine use of active management, with oxytocics usually given after delivery of the anterior shoulder or immediately after delivery of the baby, reduces blood loss and the risk of postpartum haemorrhage, although this may not be significant for women at low risk of bleeding.[13] However, despite the widespread use of oxytocics there is limited evidence of high quality comparing different drugs. Oxytocin[14] and ergot alkaloids[15] (usually ergometrine) can both reduce postpartum blood loss and appear to be equally effective,[14] while *Syntometrine* may be more effective than oxytocin alone in reducing the risk of moderate postpartum haemorrhage (500 to 1000 mL).[16] However, ergot alkaloids and *Syntometrine* cause more adverse effects than oxytocin, particularly nausea, vomiting, and raised blood pressure.[14,16] Although the quality of evidence is low, WHO recommends that oxytocin is generally preferred for prevention of postpartum haemorrhage; an ergot alkaloid (ergometrine or methylergometrine) or *Syntometrine* may be used if oxytocin is not available.[12]

Prostaglandins, and in particular misoprostol, have also been investigated as an alternative for the routine management of the third stage of labour. Although oral or sublingual misoprostol may reduce the risk of severe postpartum haemorrhage (more than 1000 mL), it is less effective than conventional injectable oxytocics.[17] Data on other prostaglandins are scarce.[17] Based on these findings, a systematic review[17] has suggested that prostaglandins are not preferrable to oxytocin, but that misoprostol may be used where no injectable oxytocic is available. Others have also argued that although misoprostol may be less effective, it would still be useful in developing countries where there are no alternatives,[8,18] and some authorities include misoprostol as an option when other oxytocics are not available or the birth attendant's skills are limited.[6,11,12]

Where a skilled attendant is not available to provide active management, an appropriately trained healthcare worker may give oxytocin or misoprostol alone for the prevention of postpartum haemorrhage.[12]

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All cross-references refer to entries in Volume A

Premature labour

Premature labour (preterm labour) is the onset of labour before the expected date, resulting in delivery of an immature infant. Conventionally the definition includes women giving birth before 37 weeks of gestation but in practice most problems arise with births before 32 to 34 weeks.[1-3] Risk factors for premature labour include infection, premature rupture of the membranes, cervical incompetence, and multiple pregnancy. There are few proven measures to *prevent premature labour*, but cervical cerclage (temporary surgical closure of the cervix) may be used for cervical incompetence,[4] and treatment of infections is being investigated.[5] In women with premature rupture of the membranes who have not gone into spontaneous labour there is some evidence that antibacterial therapy may be effective in delaying delivery and improving outcomes (see Premature Labour, p. 201.3). The value of prophylactic tocolysis, using drugs to prevent the onset of uterine contractions, is unclear[6,7] and such therapy is not recommended.[8] In women who have a history of spontaneous premature delivery, there is some evidence to suggest that a prophylactic progestogen such as hydroxyprogesterone caproate may reduce the risk for premature delivery in subsequent pregnancies.[9,10]

A diagnosis of premature labour is not always easy to make and evidence of cervical change should usually be present in addition to uterine activity.[2,3,11] Once a diagnosis has been established, a decision must be made as to whether to postpone delivery by *acute tocolysis*, using drugs that inhibit uterine contractions. It may not be considered appropriate to stop labour in some women. However, in patients of about 24 to 34 weeks of gestation without complications, attempts to postpone delivery are usually worth trying, if only in the short-term, to allow emergency treatment such as corticosteroids to be given to the mother to enhance the maturation of the fetal respiratory system (see Neonatal Respiratory Distress Syndrome, p. 1608.3) and to enable the patient to be transferred to a specialised unit for preterm delivery.[1-3,11] In the presence of ruptured membranes, tocolysis is rarely considered necessary after this time (some recommend 32 weeks of gestation[2] while others recommend 36 weeks[3]).

- The commonest tocolytics have historically been the beta-adrenoceptor agonists, which relax the smooth muscle of the uterus by stimulation of $beta_2$-adrenoceptors.[12] Nonselective agonists, for example orciprenaline and isoxsuprine, have been replaced by more selective $beta_2$ agonists such as ritodrine, salbutamol, and terbutaline. These can postpone labour for a few days[13,14] and the preferred route for starting treatment is subcutaneous or intravenous infusion.[12] Oral or subcutaneous maintenance therapy with $beta_2$ agonists after successful treatment of an episode of acute premature labour produces no further benefit[15,16] (see also Maintenance Therapy, below). There is little evidence that $beta_2$ agonists significantly reduce perinatal mortality rates.[17] The patient may have adverse cardiovascular and metabolic effects and, in particular, pulmonary oedema has been reported in some women given $beta_2$ agonists intravenously to suppress labour (see p. 1222.3). It is therefore essential that the patient's heart rate and state of hydration are carefully monitored throughout infusion. In the event of caesarean section beta blockers may be needed to combat an increased tendency to uterine bleeding.
- More recently, calcium-channel blockers have been shown to be effective tocolytics, presumably by their action on myometrial calcium.[12] Most experience concerns nifedipine, which has been reported to be at least as effective as, and possibly better than, $beta_2$ agonists or magnesium in delaying labour,[18-20] although a systematic review[21] considered the quality of many of the studies reporting efficacy to be poor. It has the advantage that it can be given orally,[12] and some favour its use as a first-line drug,[1,19] although it is not licensed in the UK for this use. Nicardipine has also produced favourable results.[22] Others have expressed concern about the safety of calcium-channel blockers,[23] and some suggest that they should be used with caution.[2,3] Maintenance nifedipine therapy appears to be of no benefit after preterm labour has been controlled.[24]
- Atosiban is a peptide analogue of oxytocin with oxytocin antagonist properties. A pooled analysis[25] of three controlled studies, and a systematic review,[26] found atosiban to be as effective as beta agonists in the management of premature labour, with fewer maternal cardiovascular adverse effects. These findings were supported by a large open-label study[27] of women treated with atosiban or usual care (usually a beta agonist). A large cohort study also found a lower risk of adverse effects associated with atosiban compared with beta agonists and nifedipine.[28] Some clinicians favour atosiban as a first-line tocolytic in preference to the traditional drugs.[1-3]
- Parenteral magnesium sulfate is thought to act as a tocolytic by calcium antagonism at the neuromuscular junction.[12] Although it has been generally considered to be as effective as the $beta_2$ agonists,[12] a systematic review[29] concluded that it was ineffective at delaying birth or preventing preterm birth, and it has been suggested that tocolytic use of magnesium may be associated with increased paediatric mortality—see p. 1789.1. To decrease the risk of overdose, magnesium sulfate should only be given from a controlled pump.[12] Oral magnesium has been tried but has not been shown to be effective.[12] Although magnesium sulfate is the most widely used tocolytic in the USA, the American College of Obstetricians and Gynecologists does not promote it (or any drug) for first-line tocolysis.[11] It is not recommended in Europe,[3] and some in the USA have called for such use to be stopped.[30,31]
- Prostaglandins have a role in the induction of labour as mediators of uterine contractions and cervical softening and dilatation. Cyclo-oxygenase (prostaglandin synthetase) inhibitors, particularly indometacin, have therefore been given orally or rectally to inhibit premature labour.[12,32] Although this treatment may be as effective as ritodrine,[33,34] adverse effects on the fetus have been reported, such as oligohydramnios, intraventricular haemorrhage, necrotising enterocolitis, and oliguria.[32] The most widely reported complication has been constriction of the fetal ductus arteriosus; pulmonary vascular hypertrophy can develop after prolonged constriction. Sensitivity of the ductus arteriosus appears to increase with gestational age, and indometacin therapy should therefore be limited to gestations of less than 32 weeks. If therapy is to continue for longer than 72 hours, the ductus arteriosus should be monitored for evidence of constriction. An increased incidence of persistent patent ductus arteriosus in the newborn has also been reported after indometacin tocolysis, although an association has been questioned.[32] A systematic review[35] of observational and randomised studies found no significant increase overall in the risk of neonatal complications in infants who had been exposed to indometacin tocolysis compared with infants who had not. However, the data had limited statistical power and the review was unable to exclude the possibility that indometacin may increase the risk of adverse neonatal outcomes. The evidence for efficacy of cyclo-oxygenase inhibitors is based on small studies,[36] and because of the potential for adverse effects, indometacin is generally reserved as a second-line drug or given with other tocolytics for an additive effect.[12] More recently it has been suggested that the enzyme isoform cyclo-oxygenase-2 is associated with labour, while cyclo-oxygenase-1 is responsible for constant prostaglandin synthesis in body tissues. The role of cyclo-oxygenase-2 inhibitors in the treatment or prevention of premature labour remains investigational.
- Other drugs are under investigation. Application of patches of the nitric oxide donor glyceryl trinitrate to the abdomen to produce uterine relaxation was reported to be as effective as ritodrine treatment.[37] However, another study[38] found transdermal glyceryl trinitrate to be less effective than beta agonists, and a systematic review[39] concluded that there was insufficient evidence to support its routine use.

When acute tocolysis has successfully suppressed uterine activity, the use of *maintenance therapy* has been tried to prevent recurrent episodes of premature labour. However, a systematic review[40] found that although there was a small but significant increase in the number of days gained before delivery, maintenance therapy with tocolytics such as selective $beta_2$ agonists, calcium-channel blockers, atosiban, and cyclo-oxygenase inhibitors did not reduce the incidence of premature birth or recurrent premature labour; there was also a non-significant trend towards an increase in adverse perinatal outcomes. Maintenance therapy is not recommended for routine use.[1,3,11]

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Termination of pregnancy

Termination of pregnancy can be achieved medically or surgically. Uterine aspiration is a common method used for *surgical termination*; before 13 weeks of pregnancy it is usually termed suction or vacuum curettage, and after 13 weeks as dilatation and evacuation.[1] Cervical dilatation becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women, and for all women younger than 18 years of age.[2,3] It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators,[1,3] mifepristone, or a prostaglandin such as gemeprost or misoprostol.[1-3] Various drugs, used alone and in combination, have been tried for *medical termination* of pregnancy. Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring

about successful termination when used alone, but the high doses required can cause significant adverse effects.[4-6] The most commonly used prostaglandins are gemeprost and misoprostol;[3,4] others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects.[3] The antiprogestogen mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.[3-5,7,8] The antimetabolite methotrexate has also been used with misoprostol, but it has a delayed effect and the time from induction to abortion can be several days or weeks.[4,5] Other methods that have been used for termination of pregnancy, particularly in the second trimester, include intra-amniotic use of dinoprost, hypertonic sodium chloride, or hyperosmolar urea augmented with oxytocin, carboprost, or dinoprost.[1]

Uterine cramping and bleeding are associated with both surgical and medical termination processes. Surgical termination may be carried out under conscious sedation,[1,2] local anaesthesia using paracervical block,[1-3] or general anaesthesia.[2] Analgesia requirements in medical termination may be higher in younger women, nulliparous women, and those with longer gestations.[3,4] Analgesics such as paracetamol, NSAIDs, and codeine are commonly used.[6] Generally, bleeding lasts longer after medical termination than after vacuum aspiration.[6] With medical termination using mifepristone plus a prostaglandin, bleeding is initially heavy but gradually diminishes over about 2 weeks, although minor bleeding can continue for longer.[1,6]

Factors influencing the choice of method for termination include the stage of gestation, availability of surgical services and abortifacient drugs, and the woman's preference. The most common approaches are outlined below.

- In the early first trimester (up to 49 days) a medical method, using mifepristone followed by a prostaglandin, is preferred because the failure rate is higher with vacuum aspiration.[2,6] Methotrexate followed by a prostaglandin is an alternative at this early stage,[1,5] but expulsion can take several days or weeks.[4] Either a surgical or medical method can be used between 49 and 63 days of gestation. However, oral misoprostol for medical termination becomes less effective as gestation progresses[4,5] so a vaginal prostaglandin is preferred.[2,5,6]
- In the late first trimester (up to 13 weeks) a surgical or medical method may be used. After 9 or 10 weeks of gestation, cervical preparation is used before surgical procedures and multiple doses of prostaglandin may be needed to achieve medical termination.[2]
- In mid-trimester termination (13 to 24 weeks) a surgical or medical method may be used. Cervical preparation is essential before surgical termination and multiple doses of prostaglandin will generally be required for medical termination.[2,3]

Some of the methods used for termination of pregnancy are also used to hasten miscarriage after **early pregnancy loss** (less than 12 weeks of gestation). Surgical evacuation is effective but associated with a higher risk of infection than expectant management.[9,10] Vaginal misoprostol can also hasten miscarriage, but oral use is less effective.[11] The success of medical treatment may also depend on the type of loss;[10] incomplete miscarriage may be managed with a prostaglandin alone, while missed miscarriage may require a higher dose and longer duration of prostaglandin treatment, or the addition of mifepristone.[12] Miscarriage or early fetal death occurring in the second trimester may be managed similarly. For the management of intra-uterine fetal death in later pregnancy, see Labour Induction and Augmentation, p. 2129.1.

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Aglepristone *(rINN)*

Aglepriston; Aglepristona; Aglépristone; Aglepristoni; Aglepristonum; RU-46534; Аглепристон.

11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-[(*Z*)-propenyl]estra-4,9-dien-3-one.

$C_{29}H_{37}NO_2$=431.6

CAS — 124478-60-0.

ATC Vet — QG03XB90.

UNII — 0UT4JLE1CM.

Profile

Aglepristone has antiprogestogenic activity and is used in veterinary medicine as an abortifacient in *dogs*.

Atosiban *(BAN, USAN, rINN)*

Atosibaani; Atosibanum; Atozyban; ORF-22164; RWJ-22164; Атозибан.

1-(3-Mercaptopropionic acid)-2-[3-(*p*-ethoxyphenyl)-D-alanine]-4-L-threonine-8-L-ornithineoxytocin; [1-(3-Sulfanylpropanoyl),2-(4-*O*-ethyltyrosine),4-L-threonine-8-L-ornithine] oxytocin.

$C_{43}H_{67}N_{11}O_{12}S_2$=994.2

CAS — 90779-69-4.

ATC — G02CX01.

ATC Vet — QG02CX01.

UNII — 081D12SI0Z.

Uses and Administration

Atosiban is a peptide analogue of oxytocin (p. 2143.1) but with oxytocin antagonist properties. It is used as a tocolytic in the management of premature labour (p. 2131.1). Atosiban is given intravenously as the acetate, but doses are expressed in terms of the base. An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.

Premature labour. References.

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Adverse Effects and Precautions

Adverse effects reported in women receiving atosiban for premature labour include nausea and vomiting, headache, dizziness, flushes, tachycardia, hypotension, hyperglycaemia, and injection site reactions. Atosiban should not be used where continuation of pregnancy is hazardous to mother or fetus, including where there is uterine haemorrhage requiring immediate delivery, eclampsia or severe pre-eclampsia, intra-uterine growth retardation and abnormal fetal heart rate, suspected intra-uterine infection, placenta praevia, or abruptio placentae. Monitoring of uterine contractions and fetal heart rate is recommended during use, and blood loss should be monitored after delivery.

Although there has been some concern about fetal exposure, licensed product information states that no specific adverse effects on the newborn have been reported.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atosiban as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Pharmacokinetics

In women in premature labour, atosiban reaches steady-state plasma concentrations within one hour of the start of infusion, and has a terminal half-life of 1.7 hours after stopping infusion. Atosiban is 46 to 48% bound to plasma proteins, and crosses the placenta. It is metabolised to an active metabolite, which is excreted in the urine; both atosiban and this metabolite are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tractocile; ***Austria***: Tractocile; ***Belg.***: Tractocile; ***Chile***: Tractocile†; ***China***: Tractocile (托保); ***Cz.***: Tractocile; ***Denm.***: Tractocile; ***Fin.***: Tractocile; ***Fr.***: Tractocile; ***Ger.***: Tractocile; ***Gr.***: Tractocile; ***Hong Kong***: Tractocile; ***Hung.***: Tractocile; ***Irl.***: Tractocile; ***Ital.***: Tractocile; ***Malaysia***: Tractocile; ***Mex.***: Tractocile; ***Neth.***: Tractocile; ***Norw.***: Tractocile; ***NZ***: Tractocile; ***Pol.***: Tractocile; ***Port.***: Tractocile; ***S.Afr.***: Tractocile; ***Spain***: Tractocile; ***Swed.***: Tractocile; ***Switz.***: Tractocile; ***Thai.***: Tractocile; ***Turk.***: Tractocile; ***UK***: Tractocile; ***Ukr.***: Tractocile (Трактоцил).

Carbetocin *(BAN, rINN)*

Carbetocina; Carbétocine; Carbetocinum; Karbetocin; Karbetosiini; Карбетоцин.

2,1-Desamino-4,1-desthio-$O^{4,2}$-methyl[1-homocysteine]oxytocin; 1-Butyric acid-2-[3-(*p*-methoxyphenyl)-L-alanine]oxytocin.

$C_{45}H_{69}N_{11}O_{12}S$=988.2

CAS — 37025-55-1.

ATC — H01BB03.

ATC Vet — QH01BB03.

UNII — 88TWF8015Y.

Uses and Administration

Carbetocin is a synthetic analogue of oxytocin (p. 2143.1) reported to have a longer duration of action. For the prevention of uterine atony and excessive bleeding after caesarean section under epidural or spinal anaesthesia, a single dose of 100 micrograms may be given by slow intravenous injection over 1 minute. Carbetocin must only be given after delivery of the infant, preferably before removal of the placenta.

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3. Leung SW, *et al*. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *BJOG* 2006; **113:** 1459–64.
4. Peters NC, Duvekot JJ. Carbetocin for the prevention of postpartum hemorrhage: a systematic review. *Obstet Gynecol Surv* 2009; **64:** 129–35.
5. Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. *Eur J Obstet Gynecol Reprod Biol* 2009; **147:** 15–20.

Adverse Effects and Precautions

Carbetocin has similar adverse effects and precautions to those associated with oxytocin when it is used after caesarean section (see p. 2144.1 and p. 2144.2, respectively). However, carbetocin should not be used at any stage of labour before delivery of the infant because its effects on the uterus last for several hours.

Breast feeding. In 5 women who were 7 to 14 weeks postpartum, carbetocin was measured in the breast milk within 90 minutes of a single 70-microgram intramuscular dose.[1] The ratio of milk to plasma concentrations was low, suggesting that very little carbetocin was distributed into breast milk. Licensed UK product information states that no significant effects on milk ejection were reported during clinical studies, and that any carbetocin ingested by a breast-fed infant would probably be degraded by enzymes in the gastrointestinal tract. The last available guidance from the American Academy of Pediatrics considered the

use of carbetocin to be usually compatible with breast feeding.[2]

1. Silcox J, *et al.* Transfer of carbetocin into human breast milk. *Obstet Gynecol* 1993; **82:** 456–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/08)

Interactions

Although reports are lacking, carbetocin may be involved in similar interactions to those that can occur with oxytocin (p. 2144.3).

Pharmacokinetics

After intravenous injection of carbetocin, firm uterine contraction occurs within 2 minutes and lasts for several hours. Carbetocin undergoes a biphasic elimination, with a terminal elimination half-life of about 40 minutes. Less than 1% of a dose is excreted unchanged by the kidney. Carbetocin is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duratocin; ***Austral.***: Duratocin; ***Austria***: Pabal; ***Belg.***: Pabal; ***Canad.***: Duratocin; ***Chile***: Duratocin; ***China***: Duratocin (巧特欣); ***Cz.***: Duratocin; ***Denm.***: Pabal; ***Fin.***: Pabal; ***Fr.***: Pabal; ***Ger.***: Pabal; ***Gr.***: Pabal; ***Hong Kong***: Duratocin; ***Hung.***: Pabal; ***Irl.***: Pabal; ***Ital.***: Duratocin; ***Malaysia***: Duratocin; ***Mex.***: Lonactene; ***Neth.***: Pabal; ***Norw.***: Pabal; ***NZ***: Duratocin; ***Philipp.***: Duratocin; ***Pol.***: Pabal; ***Port.***: Pabal; ***Singapore***: Duratocin; ***Spain***: Duratobal; ***Swed.***: Pabal; ***Switz.***: Pabal; ***Thai.***: Duratocin; ***UK***: Pabal; ***Ukr.***: Pabal (Пабал).

Carboprost *(BAN, USAN, rINN)*

Carboprostum; 15-Me-$PGF_{2\alpha}$; Methyldinoprost; (15*S*)-15-Methylprostaglandin $F_{2\alpha}$; U-32921; Карбопрост.

(5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-9,11,15-Trihydroxy-15-methylprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*E*)-(3*S*)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl}hept-5-enoic acid.

$C_{21}H_{36}O_5$=368.5

CAS — 35700-23-3.

ATC — G02AD04.

ATC Vet — QG02AD04.

UNII — 7B5032XT6O.

Carboprost Methyl *(BANM, USAN, rINNM)*

Carboprost Méthyle; Carboprostum Methylis; Methyl Carboprost; Metil carboprost; U-36384; Карбопрост Метил.

The methyl ester of carboprost.

$C_{22}H_{38}O_5$=382.5

CAS — 35700-21-1.

ATC — G02AD04.

ATC Vet — QG02AD04.

Pharmacopoeias. In *Chin.*

Carboprost Trometamol *(BANM, rINNM)*

Carboprost Trométamol; Carboprost-Trometamol; Carboprost Tromethamine (USAN); Carboprostum Trometamoli; Carboprostum Trometamolum; Kaboprosttrometamol; Karboprost z trometamolem; Karboprostas trometamolis; Karboprostitrometamoli; Karboprost-trometamol; U-32921E; Карбопрост Трометамол.

$C_{21}H_{36}O_5.C_4H_{11}NO_3$=489.6

CAS — 58551-69-2.

ATC — G02AD04.

ATC Vet — QG02AD04.

UNII — U4526F86FJ.

Description. Carboprost trometamol is a compound of carboprost with trometamol in a ratio of 1:1.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Carboprost Trometamol). A white or almost white powder. Soluble in water. Store at a temperature below -15 degrees.

USP 36: (Carboprost Tromethamine). A white to off-white powder. Soluble in water. Store at -25 degrees to -10 degrees.

Uses and Administration

Carboprost is a synthetic 15-methyl analogue of dinoprost (prostaglandin $F_{2\alpha}$; below). It is a uterine stimulant with a more prolonged action than dinoprost; the presence of the methyl group delays inactivation by enzymic dehydrogenation.

Carboprost is used for the termination of pregnancy (p. 2131.3) and for the treatment of refractory postpartum haemorrhage due to uterine atony (p. 2130.2) that is not controlled by oxytocin and ergot preparations. It is usually given intramuscularly as the trometamol salt but doses are expressed in terms of carboprost. Carboprost trometamol 1.3 micrograms is equivalent to about 1 microgram of carboprost.

For the **termination** of second trimester pregnancy (between 13 and 20 weeks of gestation) the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection and repeated every 1½ to 3½ hours depending on the uterine response. If necessary the dose may be increased to 500 micrograms, but the total dose given should not exceed 12 mg, and continuous use for more than 2 days is not recommended. If preferred, a test dose of 100 micrograms may be given initially. Carboprost trometamol has also been given intra-amniotically in a dose equivalent to 1 mg of carboprost over five minutes; this dose may be repeated after 24 hours if termination has not occurred and the membranes are intact. A total dose of 5 mg should not be exceeded.

Carboprost methyl given as vaginal pessaries has been tried for termination of pregnancy in the second trimester.

For the treatment of **postpartum haemorrhage** the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection as the trometamol salt. If necessary, the dose may be repeated at intervals of about 90 minutes; the interval may be reduced if necessary, but should not be less than 15 minutes. A total dose of 2 mg should not be exceeded.

Haemorrhagic cystitis. Carboprost trometamol instilled into the bladder successfully controlled cyclophosphamide-induced haemorrhagic cystitis (p. 772.3) in 15 of 24 bone marrow transplant patients.[1] The dose consisted of 50 mL of solutions containing 2 to 10 micrograms/mL instilled four times daily for 7 days.

1. Ippoliti C, *et al.* Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46:** 811–15.

Adverse Effects and Precautions

As for Dinoprostone, p. 2134.3 and p. 2136.1, respectively.

Carboprost may cause bronchospasm and, less frequently, dyspnoea and pulmonary oedema. Patients with cardiopulmonary disorders should be monitored for reductions in arterial-oxygen content.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including carboprost (see under Dinoprostone, p. 2135.2).

Effects on the neonate. For a report of inadvertent intramuscular administration of carboprost to a neonate, see under Dinoprostone, p. 2135.2.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including carboprost, for termination of pregnancy or induction of labour, see Dinoprostone, p. 2135.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carboprost as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Interactions

As for Dinoprostone, p. 2136.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Prostin/15M; ***Canad.***: Hemabate; ***China***: Hemabate (欣母沛); Kayun (卡孕); ***Cz.***: Prostin 15M; ***Denm.***: Prostinfenem; ***India***: Deviprost; Prostodin; ***Malaysia***: Hemabate; ***Neth.***: Prostin/15M†; ***NZ***: Prostin 15M; ***Philipp.***: Prostodin; ***Singapore***: Hemabate; ***Swed.***: Prostinfenem; ***UK***: Hemabate; ***USA***: Hemabate.

Pharmacopoeial Preparations

USP 36: Carboprost Tromethamine Injection.

Demoxytocin *(rINN)*

Deamino-oxytocin; Demoksitosiini; Demoxitocina; Démoxytocine; Demoxytocinum; Desaminocitocina; Desaminooxytocin; ODA-914; Демокситоцин.

1-(3-Mercaptopropionic acid)-oxytocin.

$C_{43}H_{65}N_{11}O_{12}S_2$=992.2

CAS — 113-78-0.

ATC — H01BB01.

ATC Vet — QH01BB01.

UNII — 2N9HM3X95F.

Profile

Demoxytocin is a synthetic analogue of oxytocin (p. 2143.1) and has similar properties. It has been given as buccal tablets for the induction and augmentation of labour. It has also been given before nursing to stimulate milk ejection, although it is generally recommended that oxytocics should not be used for this purpose (see p. 2130.1).

Dinoprost *(BAN, USAN, rINN)*

Dinoprosti; Dinoprostum; $PGF_{2\alpha}$; Prostaglandin $F_{2\alpha}$; U-14583; Динопрост.

(5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-9,11,15-Trihydroxyprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl}hept-5-enoic acid.

$C_{20}H_{34}O_5$=354.5

CAS — 551-11-1.

ATC — G02AD01.

ATC Vet — QG02AD01.

UNII — B7IN85G1HY.

NOTE. In *Martindale* the term dinoprost is used for the exogenous substance and prostaglandin $F_{2\alpha}$ for the endogenous substance.

Pharmacopoeias. In *Jpn.*

Dinoprost Trometamol *(BANM, rINNM)*

Dinoprost Trométamol; Dinoprost Tromethamine (USAN); Dinoprostas trometamolis; Dinoprostitrometamoli; Dinoprosttrometamol; Dinoprost-trometamol; Dinoprostum Trometamoli; Dinoprostum Trometamolum; Dinoproszt-trometamol; $PGF_{2\alpha}$ THAM; Prostaglandin $F_{2\alpha}$ Trometamol; U-14583E; Динопрост Трометамол.

$C_{20}H_{34}O_5.C_4H_{11}NO_3$=475.6

CAS — 38562-01-5.

ATC — G02AD01.

ATC Vet — QG02AD01.

UNII — CT6BBQ5A68.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dinoprost Trometamol). A white or almost white powder. Very soluble in water; freely soluble in alcohol; practically insoluble in acetonitrile.

USP 36: (Dinoprost Tromethamine). A white to off-white crystalline powder. Very soluble in water; slightly soluble in chloroform; freely soluble in dimethylformamide; soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Dinoprost is a prostaglandin of the F series (p. 2598.1) with actions on smooth muscle; the endogenous substance is termed prostaglandin $F_{2\alpha}$ and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasoconstrictor on blood vessels and as a bronchoconstrictor on bronchial muscle.

Dinoprost is used mainly for the termination of pregnancy (p. 2131.3). It may also be used for missed miscarriage, hydatidiform mole, and intra-uterine fetal death. Dinoprost has also been given for the induction of labour but has a higher incidence of adverse effects than dinoprostone, and is no longer routinely recommended; more appropriate treatment is discussed on p. 2129.1.

Dinoprost is usually given intra-amniotically for termination of pregnancy. It has been given intravenously, but with a high incidence of adverse effects. The extra-amniotic route has also been used. Dinoprost is given as the trometamol salt, but doses are described in terms of the base; 1.3 mg of dinoprost trometamol is equivalent to about 1 mg of dinoprost.

For the termination of pregnancy during the second trimester 40 mg of dinoprost is given intra-amniotically by slowly injecting 8 mL of a solution containing 5 mg/mL into the amniotic sac. A further dose of 10 to 40 mg may be given after 24 hours if the termination process has not been established or completed and the membranes are still intact. It should not be given continuously for more than 2 days.

Ileus. Ileus induced by vinca alkaloids in 3 patients with carcinoma of the lung was successfully relieved by the intravenous infusion of dinoprost 300 to 500 nanograms/kg per minute for 2 hours twice daily.[1]

1. Saito H, *et al.* Prostaglandin $F_{2\alpha}$ in the treatment of vinca alkaloid-induced ileus. *Am J Med* 1993; **95:** 549–51.

Adverse Effects and Precautions

As for Dinoprostone, below and p. 2136.1, respectively.

Dinoprost can cause bronchoconstriction, and bronchospasm with wheezing and dyspnoea has occurred, especially in asthmatic patients.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Interactions

As for Dinoprostone, p. 2136.1. Alcohol and beta agonists may reduce the efficacy of dinoprost.

For a report of a severe reaction after the use of oxytocin, methylergometrine, and dinoprost, see under Dinoprostone, p. 2136.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Prostin F2 Alpha; ***Canad.***: Prostin F2 Alpha; ***China***: Enzaprost F (安普诺维); ***Cz.***: Enzaprost F; ***Gr.***: Enzaprost; Prostin F2; ***Hong Kong***: Prostin F2 Alpha; ***Hung.***: Enzaprost F; ***Israel***: Prostin F2 Alpha; ***Jpn***: Prostarmon.F; ***NZ***: Prostin F2 Alpha; ***Pol.***: Enzaprost; ***Rus.***: Enzaprost F (Энзапрост Ф); Prostin F2 Alfa (Простин F2-Альфа); ***S. Afr.***: Prostin F2 Alpha; ***Ukr.***: Enzaprost F (Энзапрост-Ф).

Dinoprostone *(BAN, USAN, rINN)*

Dinoproston; Dinoprostona; Dinoprostonas; Dinoprostoni; Dinoprostonum; Dinoproszton; PGE_2; Prostaglandin E_2; U-12062; Динопростон.

(5*Z*,13*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}hept-5-enoic acid.

$C_{20}H_{32}O_5$=352.5

CAS — 363-24-6.

ATC — G02AD02.

ATC Vet — QG02AD02.

UNII — K7Q1JQR04M.

NOTE. In *Martindale* the term dinoprostone is used for the exogenous substance and prostaglandin E_2 for the endogenous substance.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dinoprostone). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Store at a temperature not exceeding -15 degrees.

USP 36: (Dinoprostone). A white to off-white, crystalline powder. Freely soluble in alcohol, in acetone, in dichloromethane, in ether, in ethyl acetate, in isopropyl alcohol, in methyl alcohol; soluble in diisopropyl ether and in toluene; practically insoluble in hexanes. Protect from light.

Uses and Administration

Dinoprostone is a prostaglandin of the E series (p. 2598.1) with actions on smooth muscle; the endogenous substance is termed prostaglandin E_2 and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasodilator and as a bronchodilator. Dinoprostone is used mainly in the induction of labour (p. 2129.1); it may also be used for the termination of pregnancy (p. 2131.3), missed miscarriage, hydatidiform mole, and intra-uterine fetal death.

Dinoprostone is usually given vaginally. It may also be given intravenously, extra-amniotically, or orally, but the intravenous route has been associated with a high incidence of adverse effects and is generally only used for missed miscarriage or hydatidiform mole.

For the **induction of labour** dinoprostone is used to ripen (soften and dilate) the cervix before the membranes are ruptured and to induce labour at term. The cervical gel used for cervical ripening contains 500 micrograms in 2.5 mL, whereas the vaginal gel used for induction of labour contains 1 or 2 mg in 2.5 mL; the vaginal gel should not be used in the cervical canal. Pessaries and vaginal inserts are also available; these are not bioequivalent to the gels and their dosage is different.

To soften and dilate the cervix before induction of labour dinoprostone 500 micrograms is given as *cervical gel*. This dose may be repeated after 6 hours if there was no response to the initial dose; in some cases a third dose may be used to a maximum cumulative dose of 1.5 mg in 24 hours.

For induction of labour the dose as *vaginal gel* is 1 mg (or 2 mg in primigravid patients with unfavourable induction features) followed, if necessary, by a further 1 or 2 mg after 6 hours; a total dose of 3 mg (or 4 mg in unfavourable primigravid patients) should not be exceeded. Alternatively a *vaginal pessary* containing 3 mg may be used and this may be followed, if necessary, by a further 3 mg after 6 to 8 hours; a total dose of 6 mg should not be exceeded.

Nonbiodegradable vaginal inserts that contain 10 mg of dinoprostone, and deliver about 300 micrograms/hour, are also available for cervical ripening. The insert should be removed when cervical ripening is complete, or after 12 or 24 hours (depending on the product) if there has been insufficient cervical ripening. The insert should also be removed if regular painful uterine contractions have started, irrespective of cervical change, or when there has been spontaneous rupture of the membranes, or before amniotomy.

Dinoprostone may be given *orally* for the induction of labour. An initial dose of 500 micrograms can be repeated after 1 hour. Subsequent doses are then given at hourly intervals, and may be increased by 500 micrograms if necessary, until an adequate response is achieved. Single doses of 1.5 mg should not be exceeded. The induction should be considered to have failed if regular uterine contractions have not started after 8 hours of treatment. Oral use has, however, generally been replaced by intravaginal dosage since the latter is associated with fewer gastrointestinal adverse effects.

Dinoprostone has been given *intravenously* for the induction of labour but is no longer recommended for routine use by most authorities. A suggested intravenous dosage has been 250 nanograms/minute infused as a solution containing 1.5 micrograms/mL for 30 minutes, the dose being subsequently maintained or increased according to the patient's response. In intra-uterine fetal death higher doses may be required and an initial rate of 500 nanograms/minute has been used with increases at intervals of not less than 1 hour.

For the **termination of pregnancy** 1 mL of a solution containing dinoprostone 100 micrograms/mL may be instilled *extra-amniotically* through a suitable Foley catheter, with subsequent doses of 1 or 2 mL given at intervals usually of 2 hours, according to response. Dinoprostone has also been given *intravenously* for the termination of pregnancy and for missed miscarriage or hydatidiform mole. A solution containing 5 micrograms/mL may be infused at a rate of 2.5 micrograms/minute for 30 minutes, the infusion then being maintained or increased to a rate of 5 micrograms/minute; this rate should be maintained for at least 4 hours before making further increases.

In the USA dinoprostone pessaries are licensed for the termination of second trimester pregnancy. A dose of 20 mg is given *intravaginally* and repeated every 3 to 5 hours according to response for up to 2 days. A total maximum dose of 240 mg has been suggested. Pessaries are also licensed in the USA in missed miscarriage, intra-uterine fetal death, and benign hydatidiform mole.

Dinoprostone is used in some centres to maintain the patency of the ductus arteriosus (see below).

Administration in children. Dinoprostone may be used in infants to maintain the patency of the ductus arteriosus (see below).

Haemorrhagic cystitis. Dinoprostone instilled into the bladder for 4 hours and repeated for 4 days successfully improved severe cyclophosphamide-induced haemorrhagic cystitis (p. 772.3) in a bone marrow transplant recipient.[1] Similar results were obtained in another series of 10 patients.[2] A solution containing 750 micrograms of dinoprostone in 200 mL of sodium chloride 0.9% was used.[1,2]

1. Mohiuddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E_2. *Ann Intern Med* 1984; **101:** 142.
2. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; **80:** 421–5.

Hepatic disorders. See under Alprostadil, p. 2352.3, for reference to the use of prostaglandins, including dinoprostone, in the treatment of viral hepatitis.

Patent ductus arteriosus. Prostaglandins, particularly alprostadil (p. 2352.2) and dinoprostone, may be used to maintain the patency of the ductus arteriosus in infants with congenital heart disease until surgery can be performed to correct the malformation. Treatment for a longer period, especially with oral dinoprostone, may facilitate later surgery by allowing growth of the infants and their pulmonary arteries. Beneficial responses to long-term use of dinoprostone have been reported.[1,2] It has been suggested that oral treatment should be continued for up to 4 weeks initially and a decision then made whether to proceed with surgery or to plan a longer course of treatment to encourage further growth. When gastrointestinal absorption is expected to be poor or when oral treatment is ineffective, dinoprostone has been given by intravenous infusion.[1]

Although dinoprostone is not licensed for use in children in the UK, the *BNFC* includes the following doses:

- oral: 20 to 25 micrograms/kg every 1 to 2 hours, doubled if necessary; if treatment continues for more than 1 week then gradually reduce the dose
- intravenous: an initial dose of 5 nanograms/kg per minute increased as necessary, in steps of 5 nanograms/kg per minute, to 20 nanograms/kg per minute; further increases may be needed and doses of up to 100 nanograms/kg per minute have been used, however, these are associated with an increased risk of adverse effects

1. Silove ED, *et al.* Evaluation of oral and low dose intravenous prostaglandin E_2 in management of ductus dependent congenital heart disease. *Arch Dis Child* 1985; **60:** 1025–30.
2. Thanopoulos BD, *et al.* Prostaglandin E_2 administration in infants with ductus-dependent cyanotic congenital heart disease. *Eur J Pediatr* 1987; **146:** 279–82.

Pemphigus. Erosive oral lesions in 3 patients[1] with pemphigus vulgaris (p. 1687.1), that had previously been refractory to standard corticosteroid therapy, resolved on sucking oral dinoprostone tablets 1.5 to 3 mg daily. Symptoms recurred within weeks of ceasing dinoprostone but could be controlled by courses of 0.5 to 1 mg daily for 1 to 2 weeks, when required. In a group of 10 patients,[2] topical dinoprostone produced similar results in 6 patients, but disease was exacerbated in the others; the dinoprostone was applied twice daily, but details of the dosage form and dose were not reported.

1. Morita H, *et al.* Clinical trial of prostaglandin E_2 on the oral lesions of pemphigus vulgaris. *Br J Dermatol* 1995; **132:** 165–6.
2. Kumaran MS, Kanwar AJ. Efficacy of topical PGE2 in recalcitrant oral lesions of pemphigus vulgaris: a clinical trial. *J Eur Acad Dermatol Venereol* 2006; **20:** 898–9.

Peripheral vascular disease. Various prostaglandins have been used in the treatment of peripheral vascular disorders (p. 1272.3), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3), but do not constitute mainline therapy.

Postpartum haemorrhage. Dinoprostone and other prostaglandins have been used to control severe postpartum haemorrhage (p. 2130.2) unresponsive to ergometrine and oxytocin.

Beneficial response to continuous intra-uterine irrigation with dinoprostone solution 1.5 micrograms/mL was seen in 22 patients with postpartum haemorrhage unresponsive to other treatment.[1] Secondary postpartum haemorrhage was controlled in another patient using a dinoprostone 3-mg vaginal pessary held against the uterine wall.[2] A nonbiodegradable dinoprostone vaginal insert has also been tried in the prevention of postpartum blood loss and in one report[3] was as effective as intravenous oxytocin.

1. Peyser MR, Kupfermine MJ. Management of severe postpartum hemorrhage by intrauterine irrigation with prostaglandin E_2. *Am J Obstet Gynecol* 1990; **162:** 694–6.
2. Markos AR. Prostaglandin E_2 intrauterine suppositories in the treatment of secondary postpartum hemorrhage. *J R Soc Med* 1989; **82:** 504–5.
3. Ozalp E, *et al.* Dinoprostone vaginal insert versus intravenous oxytocin to reduce postpartum blood loss following vaginal or cesarean delivery. *Clin Exp Obstet Gynecol* 2010; **37:** 53–5.

Vitiligo. The topical use of dinoprostone has been reported to produce repigmentation in patients with vitiligo (see Pigmentation Disorders, p. 1687.2). In small groups of patients with vitiligo affecting less than 5% of the body-surface, moderate or complete repigmentation occurred in the majority of patients over a treatment period of 6 months.[1,2] The mean onset of effect was seen after 2 months of treatment.[2] In one report a gel containing dinoprostone 166.6 micrograms/g was applied to the affected areas in the evening;[1] in another report a gel containing 250 micrograms/g was applied twice daily.[2] Perilesional hyperpigmentation was seen in many patients, but disappeared after stopping treatment.[1]

1. Parsad D, *et al.* Topical prostaglandin analog (PGE_2) in vitiligo—a preliminary study. *Int J Dermatol* 2002; **41:** 942–5.
2. Kapoor R, *et al.* Evaluation of safety and efficacy of topical prostaglandin E_2 in treatment of vitiligo. *Br J Dermatol* 2009; **160:** 861–3.

Adverse Effects

The incidence and severity of adverse reactions to dinoprostone are dose-related and also depend to some extent on the route; the intravenous route has been associated with a high incidence of adverse effects. Nausea, vomiting, diarrhoea, and abdominal pain are common by all routes. Back pain and rash can occur. Transient cardiovascular (vasovagal) symptoms have included flushing, shivering, headache, dizziness, and hypotension; there have been rare reports of myocardial infarction and cardiac arrest. Hypertension has also been reported. Convulsions and EEG changes have occurred rarely. Local tissue

irritation and erythema, as well as pyrexia and raised white cell count, may follow intravenous doses but generally revert to normal after termination of the infusion. Transient pyrexia and raised white cell count may also occur after intravaginal use. Local infection may follow intra- or extra-amniotic therapy.

Vaginal bleeding and uterine pain, which are expected with prostaglandin use in the medical termination of pregnancy, may also occur when they are used to soften and dilate the cervix before surgical termination. Excessive uterine activity may occur and there have been occasional reports of uterine rupture after the use of prostaglandins to terminate pregnancy or induce labour; fetal distress and, rarely, fetal death have occurred during induction. There have been cases of anaphylactoid syndrome of pregnancy (amniotic fluid embolism) in women given dinoprostone. Disseminated intravascular coagulation has occurred rarely.

Dinoprostone, although generally acting as a bronchodilator, may cause bronchoconstriction in some individuals. Hypersensitivity reactions have occurred.

Incidence of adverse effects. Adverse effects were evaluated in 626 patients[1] undergoing abortion (usually in the second trimester), using extra-amniotic or intra-amniotic dinoprost or dinoprostone, often with oxytocin. Vomiting occurred in 291, diarrhoea in 28, pyrexia in 34, transient hypotension (fall in systolic blood pressure of at least 20 mmHg) in 25, transient bronchospasm in 2 patients given extra-amniotic dinoprost, and blood loss exceeding 250 mL in 68 (38 lost more than 500 mL). No patients had convulsions even though 8 were being treated for epilepsy. Three patients sustained lacerations to the cervix. Five patients complained of breast soreness or lactation; these symptoms may have been under-reported. Overall 14 patients were re-admitted; 13 because of excessive vaginal bleeding and 1 because of pelvic infection.

A later report describes the cumulative experience in 3313 pregnancies[2] in which dinoprostone gel was used for induction of term labour or cervical ripening. Adverse effects were rare. Vomiting, fever, and diarrhoea occurred in about 0.2% of mothers and were difficult to distinguish from the effects of concurrent drug therapy. Detectable myometrial activity was dose-related and more common after intravaginal than after intracervical use. Myometrial activity was reported in 0.6 to 6% of patients following intravaginal application and hyperstimulation was virtually non-existent at an intracervical dose of 500 micrograms. Fetal effects were negligible in the absence of uterine hyperstimulation.

1. MacKenzie IZ, *et al*. Prostaglandin-induced abortion: assessment of operative complications and early morbidity. *BMJ* 1974; **4:** 683–6.
2. Rayburn WF. Prostaglandin E_2 gel for cervical ripening and induction of labor: a critical analysis. *Am J Obstet Gynecol* 1989; **160:** 529–34.

Effects on the bones. Reversible periosteal reactions of the long bones and bone thickening have occurred in infants receiving long-term therapy with prostaglandins of the E series (see Alprostadil, p. 2353.2). In addition, reversible widening of cranial sutures was reported[1] in 2 neonates given dinoprostone intravenously for 95 and 97 days respectively.

1. Hoevels-Guerich H, *et al*. Widening of cranial sutures after long-term prostaglandin E_2 therapy in two newborn infants. *J Pediatr* 1984; **105:** 72–4.

Effects on the cardiovascular system. Cardiovascular adverse effects are most common after intravenous dinoprostone but may also occur with other routes. Severe cardiovascular disorders reported with the intra-amniotic or intravaginal use of dinoprost or dinoprostone have included: cardiac arrhythmias in 3 patients,[1,2] fatal in 2 of them;[2] hypotension, tachypnoea, and tachycardia in 3 patients[3,4] with associated pyrexias in 2 patients;[3] and fatal myocardial infarction in a patient who had several high-risk factors for ischaemic heart disease.[5]

Severe hypertension occurred in a patient[6] who received dinoprostone by direct myometrial injection and by intravenous infusion concomitantly for postpartum haemorrhage.

Adverse cardiovascular effects have also been reported with other prostaglandins used in gynaecological or obstetric indications (see under Gemeprost, p. 2137.2, and Sulprostone, p. 2145.3).

1. Burt RL, *et al*. Hypokalemia and cardiac arrhythmia associated with prostaglandin-induced abortion. *Obstet Gynecol* 1977; **50:** 45S–46S.
2. Cates W, Jordaan HVF. Sudden collapse and death of women obtaining abortions induced with prostaglandin $F_{2\alpha}$. *Am J Obstet Gynecol* 1979; **133:** 398–400.
3. Phelan JP, *et al*. Dramatic pyrexic and cardiovascular response to intravaginal prostaglandin E_2. *Am J Obstet Gynecol* 1978; **132:** 28–32.
4. Cameron IT, Baird DT. Sudden collapse after intra-amniotic prostaglandin E_2 injection. *Lancet* 1984; **ii:** 1046.
5. Patterson SP, *et al*. A maternal death associated with prostaglandin E_2. *Obstet Gynecol* 1979; **54:** 123–4.
6. Veber B, *et al*. Severe hypertension during postpartum haemorrhage after i.v. administration of prostaglandin E2. *Br J Anaesth* 1992; **68:** 623–4.

Effects on the fetus. A woman who failed to abort despite receiving carboprost intravaginally 7 weeks after conception gave birth at 34 weeks of gestation to an infant with hydrocephalus and abnormal digits.[1] There have been reports of 2 infants born, without congenital abnormality, to women who continued with the pregnancy after attempted mid-trimester termination using intravaginal gemeprost.[2,3] However, abnormalities including limb deformities, cleft palate, anencephaly, cerebellar atrophy, and heart malformation were reported in a review[4] of 71 cases of pregnancy that were continued after attempted termination using mifepristone either alone or with a prostaglandin. Of the 8 cases of abnormality that were reported, 7 occurred in the group of 10 women who had been given intravaginal gemeprost. A case of cerebellar agenesis has also been described[5] after a failed medical termination using mifepristone and gemeprost. For abnormalities reported after the failed misuse of misoprostol alone for termination of pregnancy, see p. 2142.2.

For reports of adverse effects on the fetus due to hyperstimulation of the uterus during labour, see under Effects on the Uterus, below.

1. Collins FS, Mahoney MJ. Hydrocephalus and abnormal digits after failed first-trimester prostaglandin abortion attempt. *J Pediatr* 1983; **102:** 620–1.
2. Lakasing L, Spencer JAD. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 1999; **106:** 1319–20.
3. Rolland P, Sinha A. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 2000; **107:** 1184.
4. Sitruk-Ware R, *et al*. Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; **352:** 323.
5. Afadapa FK, Elsapagh K. Isolated one-sided cerebellar agenesis following an attempted medical termination of pregnancy. *J Obstet Gynaecol* 2006; **26:** 581–2.

Effects on the gastrointestinal system. Necrotising enterocolitis has been associated with the use of intravenous[1] or oral[2] dinoprostone, or intravenous alprostadil,[2] in infants with symptomatic congenital heart disease. It has been suggested that induced hypotension and apnoea may be responsible,[1] although others[3] did not support this view, or that pulmonary vasodilatation may produce systemic to pulmonary shunting, rendering the gastrointestinal tract relatively ischaemic.[2]

1. Leung MP, *et al*. Necrotizing enterocolitis in neonates with symptomatic congenital heart disease. *J Pediatr* 1988; **113:** 1044–6.
2. Singh GK, *et al*. Study of low dosage prostaglandin—usages and complications. *Eur Heart J* 1994; **15:** 377–81.
3. Miller MJS, Clark DA. Congenital heart disease and necrotizing enterocolitis. *J Pediatr* 1989; **115:** 335–6.

Effects on the neonate. Aspiration of the undissolved remnants of a dinoprostone vaginal tablet caused neonatal respiratory distress due to mechanical obstruction of the airways; there was no evidence to suggest absorption of dinoprostone from the tablet matrix.[1]

Inadvertent intramuscular injection of carboprost 250 micrograms caused hypertension, bronchospasm, diarrhoea, and hyperthermia in a neonate. There was also an adverse neurological effect that was either a dystonic reaction or seizure activity. The neonate was treated symptomatically and discharged 24 hours later; neurological and developmental examinations were normal at 3 months of age.[2] The authors of this report also learned of 2 other cases that had been reported to the manufacturer, in which neonates given injections of 125 micrograms and 63 micrograms remained asymptomatic.

1. Andersson S, *et al*. Neonatal respiratory distress caused by aspiration of a vaginal tablet containing prostaglandin. *BMJ* 1987; **295:** 25–6.
2. Mrvos R, *et al*. Carboprost exposure in a newborn with recovery. *J Toxicol Clin Toxicol* 1999; **37:** 865–7.

Effects on the nervous system. Convulsions and EEG changes have been occasionally reported during the use of prostaglandins for termination of pregnancy. Convulsions occurred[1] in 5 of 320 women after intra-amniotic dinoprost, but in other large series[2-4] of patients given dinoprost or dinoprostone by various routes no problems occurred despite the inclusion of patients with a history of epilepsy. However, convulsions were reported[5] in 3 of 4 epileptic patients given sulprostone intramuscularly.

1. Lyneham RC, *et al*. Convulsions and electroencephalogram abnormalities after intra-amniotic prostaglandin $F_{2\alpha}$. *Lancet* 1973; **ii:** 1003–5.
2. MacKenzie IZ, *et al*. Convulsions and prostaglandin-induced abortion. *Lancet* 1973; **ii:** 1323.
3. Thiery M, *et al*. Prostaglandins and convulsions. *Lancet* 1974; **i:** 218.
4. Fraser IS, Gray C. Electroencephalogram changes after prostaglandin. *Lancet* 1974; **i:** 360.
5. Brandenburg H, *et al*. Convulsions in epileptic women after administration of prostaglandin E_2 derivative. *Lancet* 1990; **336:** 1138.

Effects on the uterus. Use of prostaglandins to induce labour or to terminate pregnancy is associated with an increased risk of hyperstimulation of the uterus. Uterine rupture has occurred with carboprost,[1] dinoprost or dinoprostone,[2-7] gemeprost,[8-10] misoprostol,[11-14] and sulprostone.[15-17] These effects have been reported with parenteral, local, and oral dosage. The risk of rupture and associated complications is increased in grand multiparae[4] and those with uterine scarring from previous caesarean section.[5,7] Studies have reported relative risks of between 6 and 10 times those of spontaneous labour after labour induction with dinoprostone in the latter group.[5,7] In addition to rupture, with the risk of potentially fatal maternal haemorrhage, hyperstimulation has been associated with fetal distress and death,[18-20] and maternal death due to anaphylactoid syndrome of pregnancy (amniotic fluid embolism).[18,21]

1. Vergote I, *et al*. Uterine rupture due to 15-methyl prostaglandin $F_{2\alpha}$. *Lancet* 1982; **ii:** 1402.
2. Claman P, *et al*. Uterine rupture with the use of vaginal prostaglandin E_2 for induction of labor. *Am J Obstet Gynecol* 1984; **150:** 889–90.
3. Keller F, Joyce TH. Uterine rupture associated with the use of vaginal prostaglandin E_2 suppositories. *Can Anaesth Soc J* 1984; **31:** 80–2.
4. Larsen JV, *et al*. Uterine hyperstimulation and rupture after induction of labour with prostaglandin E_2. *S Afr Med J* 1984; **65:** 615–16.
5. Ravasia DJ, *et al*. Uterine rupture during induced trial of labor among women with previous cesarean delivery. *Am J Obstet Gynecol* 2000; **183:** 1176–9.
6. Rabl M, *et al*. A randomized trial of vaginal prostaglandin E_2 for induction of labor: insert vs tablet. *J Reprod Med* 2002; **47:** 115–19.
7. Taylor DR, *et al*. Uterine rupture with the use of PGE_2 vaginal inserts for labor induction in women with previous cesarean sections. *J Reprod Med* 2002; **47:** 549–54.
8. Thavarasah AS, Achanna KS. Uterine rupture with the use of Cervagem (prostaglandin E1) for induction of labour on account of intrauterine death. *Singapore Med J* 1988; **29:** 351–2.
9. Byrne P, Onyekwuluje T. Uterine rupture after termination of pregnancy with gemeprost. *BMJ* 1991; **302:** 852.
10. Vine SJ, *et al*. Transverse posterior cervicoisthmic rupture after gemeprost pessaries for termination. *BMJ* 1992; **305:** 1332.
11. Blanchette HA, *et al*. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E_1) with those of dinoprostone (prostaglandin E_2) for cervical ripening and induction of labor in a community hospital. *Am J Obstet Gynecol* 1999; **180:** 1551–9.
12. Mathews JE, *et al*. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *Int J Gynaecol Obstet* 2000; **68:** 43–4.
13. Khabbaz AY, *et al*. Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. *J Matern Fetal Med* 2001; **10:** 141–5.
14. Nayki U, *et al*. Uterine rupture during second trimester abortion with misoprostol. *Fetal Diagn Ther* 2005; **20:** 469–71.
15. Larue L, *et al*. Rupture d'un utérus sain lors d'une interruption de grossesse par prostaglandines au deuxième trimestre. *J Gynecol Obstet Biol Reprod (Paris)* 1991; **20:** 269–72.
16. Prasad RNV, Ratnam SS. Uterine rupture after induction of labour for intrauterine death using the prostaglandin E_2 analogue sulprostone. *Aust N Z J Obstet Gynaecol* 1992; **32:** 282–3.
17. de Boer MA, *et al*. Low dose sulprostone for termination of second and third trimester pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2001; **99:** 244–8.
18. Stronge J, *et al*. A neonatal and maternal death following the administration of intravaginal prostaglandin. *J Obstet Gynaecol* 1987; **7:** 271–2.
19. Quinn MA, Murphy AJ. Fetal death following extra-amniotic prostaglandin gel: report of two cases. *Br J Obstet Gynaecol* 1981; **88:** 650–1.
20. Simmons K, Savage W. Neonatal death associated with induction of labour with intravaginal prostaglandin E_2: case report. *Br J Obstet Gynaecol* 1984; **91:** 598–9.
21. Less A, *et al*. Vaginal prostaglandin E_2 and fatal amniotic fluid embolus. *JAMA* 1990; **263:** 3259–60.

Overdosage. Severe adverse effects associated with intra-amniotic prostaglandins have been attributed to absorption into the systemic circulation of doses higher than would normally be given systemically. Rigors, vomiting, severe abdominal pain, and an intense desire to urinate and defaecate occurred[1] in 3 patients given dinoprostone intra-amniotically for mid-trimester abortion; one patient had peripheral vasoconstriction and a rapid low-volume pulse, with hypotension, and another had peripheral cyanosis. It was suggested[2] that this might have been due to displacement of the needle or cannula outside the amniotic sac. In 2 of the patients prior use of urea may have increased the rate of absorption of prostaglandins from the amniotic cavity. In a further report[3] flushing, severe headache, and nausea immediately after a test dose of dinoprost 2.5 mg was also thought to be due to incorrect positioning of the needle and consequent injection into the systemic circulation; at least part of the dose might have been injected into the peritoneal cavity.[4]

Severe reactions have also been reported with prostaglandins given to abort hydatidiform moles. A 20-year-old woman given 20 mg of dinoprostone by injection into the uterine cavity developed profound hypotension, bradycardia, and rigors, followed by nausea, vomiting, suprapubic pain, an increased pulse rate, pyrexia, and generalised flushing.[5] Since there are no fetal membranes in a molar pregnancy, intra-uterine administration is similar to extra-amniotic administration and the dose used was 100 times higher than the usual extra-amniotic dose.[4] However, in a similar patient[6] 'extra-amniotic' instillation of dinoprostone 200 micrograms was followed immediately by nausea, retching, severe abdominal pain, dizziness, difficulty in breathing and the production of frothy blood-stained sputum, an imperceptible pulse, and hypotension; the dinoprostone had probably been injected directly into the maternal circulation.

1. Ross AH, Whitehouse WL. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; **1:** 642.
2. Craft I, Bowen-Simpkins P. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; **2:** 446.
3. Brown R. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **2:** 382.
4. Karim SMM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **3:** 347.

5. Smith AM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **2:** 382–3.
6. McNicol E, Gray H. Adverse reaction to extra-amniotic prostaglandin E_2. *Br J Obstet Gynaecol* 1977; **84:** 229–30.

Precautions

Dinoprostone should not be given to patients in whom oxytocic drugs are generally contra-indicated because spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus (see also Oxytocin, p. 2144.2). This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia, or fetal distress. It should not be used where there is a predisposition to uterine rupture, as in high parity or the presence of a uterine scar from previous caesarean section or major uterine surgery, or in those with a history of pelvic inflammatory disease. Since prostaglandins enhance the effects of oxytocin, use of these drugs together or in sequence should be carefully monitored.

Dinoprostone is contra-indicated in active cardiac, pulmonary, renal, or hepatic disease. It should be used with caution in patients with glaucoma or raised intraocular pressure, a history of asthma or epilepsy, hepatic or renal impairment, or cardiovascular disease.

In the induction of labour cephalopelvic relationships should be carefully evaluated before use. During use uterine activity, fetal status, and the progress of cervical dilatation should be carefully monitored to detect adverse responses, such as hypertonus, sustained uterine contractions, or fetal distress. In patients with a history of hypertonic uterine contractility or tetanic uterine contractions, uterine activity and the state of the fetus should be continuously monitored throughout labour. Where high-tone myometrial contractions are sustained the possibility of uterine rupture should be considered.

Dinoprostone should not be given by the myometrial route, since there is a possible association with cardiac arrest in severely ill patients. The extra-amniotic route should not be used in patients with cervicitis or vaginal infections. Vaginal preparations of dinoprostone are not recommended in the induction of labour once the membranes are ruptured, because information about use in this group is limited. In some countries, intravenous prostaglandins are considered to be contra-indicated in women who smoke.

Dinoprostone should be used with caution in women who have conditions that could further increase the risk of postpartum disseminated intravascular coagulation, which is associated with pharmacologically induced labour. This includes women with gestational diabetes, hypertension, or hypothyroidism. Women over 30 years of age and those past the fortieth week of pregnancy are also at increased risk.

In the therapeutic termination of pregnancy, fetal damage has been seen in cases of incomplete termination and the appropriate treatment for complete evacuation of the uterus should therefore be instituted whenever termination is unsuccessful or incomplete. Dinoprostone should not be used for termination in patients with pelvic infection, unless adequate treatment has already been started.

Administration. For the hazards of unintentional systemic absorption of prostaglandins after intra-uterine use for the termination of pregnancy and abortion of hydatidiform moles, see Overdosage in Adverse Effects, p. 2135.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dinoprostone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Interactions

Dinoprostone enhances the effects of oxytocin on the uterus. There is a theoretical risk that prostaglandin synthetase inhibitors, such as aspirin and NSAIDs, might alter the efficacy of dinoprostone.

Uterine stimulants. Marked hypertension, vomiting, and severe dyspnoea occurred after the sequential use of *oxytocin*, *methylergometrine*, and *dinoprost* within the space of 10 minutes to a woman with postpartum haemorrhage.[1]

1. Cohen S, *et al*. Severe systemic reactions following administration of different ureotonic [uterotonic] drugs. *N Y State J Med* 1983; **83:** 1060–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prolisina E2; Propess; ***Austral.***: Cervidil; Prostin E2; ***Austria***: Prepidil; Propess; Prostin E2; ***Belg.***: Prepidil; Propess; Prostin E2; ***Braz.***: Propess; ***Canad.***: Cervidil; Prepidil; Prostin E2; ***Cz.***: Prepidil; Propess†; Prostin E2; ***Denm.***: Minprostin; Propess; Prostin E2; ***Fin.***: Minprostin†; Propess†; ***Fr.***: Prepidil; Propess; Prostine E_2; ***Ger.***: Minprostin E_2; Prepidil; Propess; ***Gr.***: Minprostin; Prepidil; Propess; Prostin E2; ***Hong Kong***: Prostin E2; ***Hung.***: Prepidil; Prostin E2; ***India***: Cerviprime; Dinoripe; Primiprost; ***Indon.***: Prostin E2†; ***Irl.***: Prostin E2; ***Israel***: Prepidil; Propess; Prostin E2; ***Ital.***: Prepidil; Propess; Prostin E2; ***Malaysia***: Prostin E2; ***Mex.***: Prepidil; Propess; ***Neth.***: Prepidil; Propess; Prostin E2; ***Norw.***: Minprostin; ***NZ***: Cervidil; Prostin E2; ***Philipp.***: Cerviprime; ***Pol.***: Prepidil; Propess; ***Port.***: Propess; Prostin E2; ***Rus.***: Prepidil (Препидил); Prostenongel (Простенонгель); Prostin E2 (Простин E2); ***S.Afr.***: Prandin E_2; Prepidil; Propess; Prostin E2; ***Singapore***: Prostin E2; ***Spain***: Prepidil; Propess; ***Swed.***: Minprostin; Propess; ***Switz.***: Propess; Prostin E2; ***Thai.***: Prostin E2; ***UK***: Propess; Prostin E2; ***Ukr.***: Cervistin (Цервистин); ***USA***: Cervidil; Prepidil; Prostin E2.

Pharmacopoeial Preparations
BP 2014: Dinoprostone Oral Solution.

Ergometrine Maleate *(BANM, rINNM)*

Ergobasine Maleate; Ergometriinimaleaatti; Ergometrina, maleato de; Ergométrine, Maléate d'; Ergometrinhydrogenmaleat; Ergometrini Maleas; Ergometrinmaleat; Ergometrinmaleát; Ergometrin-maleinát; Ergometrino maleatas; Ergonovine Bimaleate; Ergonovine Maleate; Ergostetrine Maleate; Ergotocine Maleate; Maleato de ergobasina; Maleato de ergometrina; Maleato de Ergonovina; Эргометрина Малеат.

N-[(*S*)-2-Hydroxy-1-methylethyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-2-hydroxy-1-methylethyl]-6-methylergoline-8β-carboxamide hydrogen maleate.

$C_{19}H_{23}N_3O_2,C_4H_4O_4$=441.5

CAS — 60-79-7 (ergometrine); 129-51-1 (ergometrine maleate).

ATC — G02AB03.

ATC Vet — QG02AB03.

UNII — YMH3D0ZJWV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ergometrine Maleate). A white or almost white or slightly coloured, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 3.6 to 4.4. Store in airtight glass containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Ergonovine Maleate). A white to greyish-white or faintly yellow, odourless, microcrystalline powder. It darkens with age and on exposure to light. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Stability. Deterioration and degradation of ergometrine-containing injections has been seen when exposed to high temperatures in the tropics.[1-4] The mean loss in one study[3] of ergometrine injection under shipment to the tropics was 5.8%, but in some individual samples the loss was more marked: 18 of 80 test samples contained less than 80% of the stated content, and in 3 cases the content was less than 60%. A similar but much less significant pattern was seen with methylergometrine: the content varied from 98.6 to 99.5% of the labelled amount. Tablets of ergometrine and methylergometrine were also shown to be unstable under simulated tropical conditions, with humidity as the main adverse factor.[5]

1. Walker GJA, *et al*. Potency of ergometrine in tropical countries. *Lancet* 1988; **ii:** 393.
2. Abu-Reid IO, *et al*. Stability of drugs in the tropics. *Int Pharm J* 1990; **4:** 6–10.
3. Hogerzeil HV, *et al*. Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304:** 210–12.
4. Hogerzeil HV, Walker GJ. Instability of (methyl)ergometrine in tropical climates: an overview. *Eur J Obstet Gynecol Reprod Biol* 1996; **69:** 25–9.
5. de Groot ANJA, *et al*. Ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. *J Clin Pharm Ther* 1995; **20:** 109–13.

Uses and Administration

Ergometrine has a much more powerful action on the uterus than most other ergot alkaloids, especially on the puerperal uterus. Its main action is the production of intense contractions, which at higher doses are sustained, in contrast to the more physiological rhythmic uterine contractions induced by oxytocin; its action is more prolonged than that of oxytocin.

Ergometrine maleate is used in the active management of the third stage of labour, and to prevent or treat postpartum or postabortal haemorrhage (p. 2130.2) caused by uterine atony; by maintaining uterine contraction and tone, blood vessels in the uterine wall are compressed, and blood flow reduced.

In the **active management of the third stage of labour**, ergometrine maleate and oxytocin are given together under full obstetric supervision. A dose of ergometrine maleate 500 micrograms and oxytocin 5 units (as the fixed combination *Syntometrine*) is injected intramuscularly after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant; contractions are reported to occur within 2 to 7 minutes. Delivery of the placenta is actively assisted while the uterus is firmly contracted.

In the prevention or treatment of **postpartum haemorrhage**, ergometrine maleate may be used alone, usually in an intramuscular dose of 200 to 500 micrograms. In emergencies such as excessive uterine bleeding, a dose of 250 to 500 micrograms has been given intravenously. Intravenous doses should be given over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. An intramuscular dose of 200 micrograms has also been used for the prevention or treatment of postabortal haemorrhage. Parenteral treatment of haemorrhage may be followed by ergometrine maleate 200 to 400 micrograms orally 2 to 4 times daily until the danger of atony and haemorrhage has passed, which is usually 48 hours. Tablets have also been given sublingually. The combination preparation *Syntometrine* has been used intramuscularly to prevent or treat postpartum haemorrhage; the *BNF* states that it can also be used in the management of incomplete abortion, usually when surgical evacuation of the uterus is delayed.

In the treatment of mild secondary postpartum haemorrhage, ergometrine maleate has been given orally.

Ergometrine tartrate was formerly used.

Diagnosis and testing. Ergometrine maleate[1-8] or methylergometrine maleate[9,10] have been used in a provocation test for the diagnosis of Prinzmetal's angina (variant angina) (p. 1254.3).

1. Waters DD, *et al*. Ergonovine testing in a coronary care unit. *Am J Cardiol* 1980; **46:** 922–30.
2. Health and Public Policy Committee, American College of Physicians. Performance of ergonovine provocative testing for coronary artery spasm. *Ann Intern Med* 1984; **100:** 151–2.
3. Song J-K, *et al*. Safety and clinical impact of ergonovine stress echocardiography for diagnosis of coronary vasospasm. *J Am Coll Cardiol* 2000; **35:** 1850–6.
4. Kashima K, *et al*. Long-term outcome of patients with ergonovine induced coronary constriction not associated with ischemic electrocardiographic changes. *J Cardiol* 2001; **37:** 301–8.
5. Palinkas A, *et al*. Safety of ergot stress echocardiography for non-invasive detection of coronary vasospasm. *Coron Artery Dis* 2001; **12:** 649–54.
6. Song JK, *et al*. Prognostic implication of ergonovine echocardiography in patients with near normal coronary angiogram or negative stress test for significant fixed stenosis. *J Am Soc Echocardiogr* 2002; **15:** 1346–52.
7. Sueda S, *et al*. Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations. *Coron Artery Dis* 2004; **15:** 491–7.
8. Coma-Canella I, *et al*. Ergonovine test in angina with normal coronary arteries: is it worth doing it? *Int J Cardiol* 2006; **107:** 200–6.
9. Bertrand ME, *et al*. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982; **65:** 1299–1306.
10. Lablanche JM, *et al*. Réflexions d'un comité d'experts de la Société française de cardiologie concernant l'usage du maléate de méthylergométrine (Methergin) dans la détection d'une vasomotricité coronaire anormale. *Arch Mal Coeur Vaiss* 1995; **88:** 247–53.

Adverse Effects and Treatment

Nausea and vomiting, abdominal pain, diarrhoea, headache, dizziness, tinnitus, chest pain, palpitations, bradycardia and other cardiac arrhythmias, coronary artery vasospasm, myocardial infarction, dyspnoea, and pulmonary oedema have been reported after use of ergometrine. Hypertension may occur, particularly after rapid intravenous dosage; hypotension has also been reported. Hypersensitivity reactions, including shock, have occurred. Ergometrine shows less tendency to produce gangrene than ergotamine, but ergotism has been reported and symptoms of acute poisoning are similar (see p. 674.2).

Adverse effects should be treated as for ergotamine, p. 674.3.

Effects on the respiratory system. Bronchospasm has been reported after use of ergometrine.[1] Although studies *in vitro* on *canine* bronchi have suggested a direct action on smooth muscle, this could not be confirmed in studies using human bronchi.

1. Hill H, *et al*. Ergometrine and bronchospasm. *Anaesthesia* 1987; **42:** 1115–16.

Overdosage. Ergometrine maleate has been given accidentally in adult doses to neonates,[1-5] sometimes instead of vitamin K. Symptoms have included peripheral vasoconstriction, encephalopathy, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance. When given with oxytocin, water intoxication has also been reported.[1] In all of these cases, recovery occurred after intensive symptomatic treatment including assisted ventilation and anticonvulsants. However, deaths have also been recorded.[5] The long-term outcome of ergometrine overdosage has been reported for 6 infants.[5] Their ages at follow-up ranged from 18 months to 5 years; all had normal physical and behavioural development and neurological outcomes.

1. Whitfield MF, Salfield SAW. Accidental administration of Syntometrine in adult dosage to the newborn. *Arch Dis Child* 1980; **55:** 68–70.
2. Pandey SK, Haines CI. Accidental administration of ergometrine to newborn infant. *BMJ* 1982; **285:** 693.
3. Mitchell AA, *et al*. Accidental administration of ergonovine to a newborn. *JAMA* 1983; **250:** 730–1.

4. Donatini B, *et al.* Inadvertent administration of uterotonics to neonates. *Lancet* 1993; **341:** 839–40.
5. Dargaville PA, Campbell NT. Overdose of ergometrine in the newborn infant: acute symptomatology and long-term outcome. *J Paediatr Child Health* 1998; **34:** 83–9.

Precautions

As for Ergotamine Tartrate, p. 675.1. Ergometrine should also be used with caution in patients with veno-atrial shunts or mitral valve stenosis. Ergometrine is contra-indicated for the induction of labour or for use during the first stage of labour. If used at the end of the second stage of labour, before delivery of the placenta, there must be expert obstetric supervision. Its use should be avoided in patients with pre-eclampsia, eclampsia, or threatened miscarriage.

Interactions

As for Ergotamine Tartrate, p. 675.2. Halothane has been considered to diminish the effects of ergometrine on the uterus.

Sympathomimetics. Use of *dopamine* in a patient treated with ergometrine was associated with subsequent development of gangrene in both hands and feet.[1] In another case,[2] the use of ergometrine with *noradrenaline* resulted in cyanosis of the hands and necrosis in some of the fingers.

1. Buchanan N, *et al.* Symmetrical gangrene of the extremities associated with the use of dopamine subsequent to ergometrine administration. *Intensive Care Med* 1977; **3:** 55–6.
2. Chuang S-S. Finger ischemia secondary to the synergistic agonist effect of norepinephrine and ergonovine and in a burn patient. *Burns* 2003; **29:** 92–4.

Pharmacokinetics

Ergometrine is reported to be rapidly absorbed after oral doses or intramuscular injection, with onset of uterine contractions in about 5 to 15 minutes and 2 to 7 minutes, respectively. Elimination appears to be mainly by hepatic metabolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Evina; Metrergina; ***Gr.***: Mitrotan; Novergo; ***India***: Ergotab; Ergotaur; Erinmet; ***Mex.***: Ergotrate; ***Thai.***: Gynaemine; ***USA***: Ergotrate†.

Multi-ingredient Preparations. ***Austral.***: Syntometrine; ***Hong Kong***: Syntometrine; ***Irl.***: Syntometrine; ***Malaysia***: Syntometrine; ***NZ***: Syntometrine; ***S.Afr.***: Syntometrine; ***Singapore***: Syntometrine; ***UK***: Syntometrine.

Pharmacopoeial Preparations
BP 2014: Ergometrine and Oxytocin Injection; Ergometrine Injection; Ergometrine Tablets;
USP 36: Ergonovine Maleate Injection; Ergonovine Maleate Tablets.

Ergot

Cornezuelo del centeno; Secale Cornutum; Sporysz; Спорынья.
UNII — 01G9XEA93N.

Description. Ergot consists of the sclerotium of the fungus *Claviceps purpurea* (Hypocreaceae) developed in the ovary of the rye, *Secale cereale* (Gramineae). It contains not less than 0.15% of total alkaloids, calculated as ergotoxine, and not less than 0.01% of water-soluble alkaloids, calculated as ergometrine. Some authorities have expressed alkaloidal content in terms of ergotamine and ergometrine.

Uses and Administration

Ergot has the vasoconstricting and oxytocic actions of its constituent alkaloids, especially ergotamine (p. 674.1) and ergometrine (p. 2136.2). A liquid extract or tablets of prepared ergot were formerly used as an oxytocic. Preparations containing ergot extracts have been promoted for use in dyspepsia and nervous disorders.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p. 674.2.

Epidemic ergot poisoning, arising from the ingestion of ergotised rye bread, is now seldom seen. Two forms of epidemic toxicity, which rarely occur together, have been described: a gangrenous form characterised by agonising pain of the extremities of the body followed by dry gangrene of the peripheral parts, and a rarer nervous type giving rise to paroxysmal epileptiform convulsions.

Poisoning. A report of an outbreak of ergotism, attributed to the ingestion of infected wild oats (*Avena abyssinica*), in Ethiopia.[1]

1. King B. Outbreak of ergotism in Wollo, Ethiopia. *Lancet* 1979; **ii:** 1411.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Iris Med Complex; Nux Med Complex; Secale Med Complex; ***Canad.***: Insomnia Passiflora†; PMS; ***Fr.***: Amanita Complexe No 75; Aurum Complexe No 38†; Cimicifuga Complexe No 21†; Hypericum Complexe No 26; Kalium Iodatum Complexe No 84†; L 25; L 28; Passiflora GHL; Sclerocalcine; ***Ger.***: Aderplus spezial Dr Hagedorn†; Aletris Oligoplex†; Arte-cyl Ho-Len-Complex; Cefadybasin SE†; Cefakliman S; Elana†; Flenin; metaginkgo†; Migrane Hevert†; Migrane Hevert; Reproven N; Secale-Gastreu; Secalosan N; Vasa-Gastreu N R63; Vertigo-Hevert; ***Neth.***: Aesculus Comp; Emvita 11; Emvita 6; Homeocare Vasco; ***Rus.***: Ruta-Plus (Рута-Плюс); ***Switz.***: metaginkgo; ***Ukr.***: Arsenik Комп Иов-Диабет (Арсеник Комп Иов-Диабет).

Ergotoxine

Ecboline; Ergotoxina; Эрготоксин.
CAS — 8006-25-5 (ergotoxine); 8047-28-7 (ergotoxine esilate); 8047-29-8 (ergotoxine phosphate); 564-36-3 (ergocornine); 511-08-0 (ergocristine); 511-09-1 (α-ergocryptine); 20315-46-2 (β-ergocryptine).

Profile

Ergotoxine is a mixture of naturally occurring ergot alkaloids. It contains equal proportions of:
- ergocornine ($C_{31}H_{39}N_5O_5 = 561.7$)
- ergocristine ($C_{35}H_{39}N_5O_5 = 609.7$)
- ergocryptine ($C_{32}H_{41}N_5O_5 = 575.7$) as the α- and β-isomers

Ergotoxine esilate was formerly used as an oxytocic and in the treatment of migraine. The phosphate has also been used.

Gemeprost *(BAN, USAN, rINN)*

16,16-Dimethyl-*trans*-Δ^2-prostaglandin E_1 methyl ester; Géméprost; Gemeprosti; Gemeprostum; ONO-802; SC-37681; Гемепрост.
Methyl (2*E*,13*E*)-(8*R*,11*R*,12*R*,15*R*)-11,15-dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-dienoate; Methyl (*E*)-7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyloct-1-enyl]-5-oxocyclopentyl}hept-2-enoate.
$C_{23}H_{38}O_5$=394.6
CAS — 64318-79-2.
ATC — G02AD03.
ATC Vet — QG02AD03.
UNII — 45KZB1FOLS.

Uses and Administration

Gemeprost is a synthetic analogue of alprostadil (prostaglandin E_1; p. 2352.2) that is used in the termination of pregnancy (p. 2131.3). In the first trimester, a pessary containing gemeprost 1 mg is inserted into the vagina 3 hours before surgery to soften and dilate the cervix. Gemeprost may also be used for medical termination of pregnancy in the second trimester when a 1-mg pessary is inserted every 3 hours to a maximum of 5 pessaries. If this is ineffective, one further course may be given starting 24 hours after the beginning of the first course. If termination is not well established after 10 pessaries, alternative treatment should be used to complete uterine evacuation. In the case of intra-uterine fetal death in the second trimester, only one course of up to 5 pessaries should be given. Vaginal gemeprost is also used after oral mifepristone (p. 2138.2) in the termination of pregnancy.

Adverse Effects and Precautions

As for Dinoprostone, p. 2134.3 and p. 2136.1, respectively. Pulse and blood pressure should be monitored in patients given gemeprost.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Incidence of adverse effects. The incidence of vomiting (19% or 35%) and diarrhoea (12% or 19%) in 2 studies of patients treated with gemeprost pessaries was similar to that seen with other prostaglandins, but gemeprost was reported to cause less uterine pain.[1,2]

1. Cameron IT, Baird DT. The use of 16,16-dimethyl-trans-Δ^2 prostaglandin E_1 methyl ester (gemeprost) vaginal pessaries for the termination of pregnancy in the early second trimester: a comparison with extra-amniotic prostaglandin E_2. *Br J Obstet Gynaecol* 1984; **91:** 1136–40.
2. Andersen LF, *et al.* Termination of second trimester pregnancy with gemeprost vaginal pessaries and intra-amniotic $PGF_{2\alpha}$: a comparative study. *Eur J Obstet Gynecol Reprod Biol* 1989; **31:** 1–7.

Effects on the cardiovascular system. Periods of ventricular standstill of up to 6 seconds were seen in a patient during treatment with gemeprost vaginal pessaries.[1] The patient required temporary cardiac pacing, but no persistent cardiac rhythm disturbances were detected on follow-up. Severe cardiogenic shock due to vasospasm, and subsequent stroke, has been reported in a patient who had received gemeprost pessaries some hours earlier; myocardial infarction ensuing from coronary spasm was reported in a second patient.[2]

1. Kalra PA, *et al.* Cardiac standstill induced by prostaglandin pessaries. *Lancet* 1989; **i:** 1460–1.
2. Schulte-Sasse U. Life threatening myocardial ischaemia associated with the use of prostaglandin E_1 to induce abortion. *Br J Obstet Gynaecol* 2000; **107:** 700–2.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including gemeprost (see under Dinoprostone, p. 2135.2).

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including gemeprost, for termination of pregnancy or induction of labour, see under Dinoprostone, p. 2135.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gemeprost as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Interactions

As for Dinoprostone, p. 2136.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cervagem; ***Fr.***: Cervageme; ***Ger.***: Cergem; ***Ital.***: Cervidil; ***Jpn***: Preglandin; ***Malaysia***: Cervagem; ***NZ***: Cervagem†; ***Singapore***: Cervagem; ***Swed.***: Cervagem; ***UK***: Cervagem.

Methylergometrine Maleate *(BANM, rINNM)*

Maleato de metilergometrina; Methylergobasine Maleate; Méthylergométrine, hydrogénomaléate de; Méthylergométrine, Maléate de; Methylergometrini hydrogenomaleas; Methylergometrini Maleas; Methylergometrinmaleat; Methylergonovine Maleate; Metilergobazin Maleat; Metilergometrin Maleat; Metilergometrina, maleato de; Метилэрометрина Малеат.
N-[(*S*)-1-(Hydroxymethyl)propyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-1-(hydroxymethyl)propyl]-6-methylergoline-8β-carboxamide hydrogen maleate.
$C_{20}H_{25}N_3O_2C_4H_4O_4$=455.5
CAS — 113-42-8 (methylergometrine); 57432-61-8 (methylergometrine maleate).
ATC — G02AB01.
ATC Vet — QG02AB01.
UNII — IR84JPZ1RK.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Methylergometrine Maleate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; slightly soluble in anhydrous alcohol. pH of a 0.5% solution is 4.4 to 5.2. Store in airtight containers. Protect from light.

USP 36: (Methylergonovine Maleate). A white to pinkish-tan, odourless, microcrystalline powder. Soluble 1 in 100 of water, 1 in 175 of alcohol, 1 in 1900 of chloroform, and 1 in 8400 of ether. pH of a 0.02% solution in water is between 4.4 and 5.2. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Stability. For mention of slight variations in the methylergometrine content of the injection after transport to a tropical climate, see under Ergometrine Maleate, p. 2136.2.

Uses and Administration

Methylergometrine maleate has an action on the uterus similar to that of ergometrine maleate (p. 2136.2) and is used similarly in the active management of the third stage of labour, and in the prevention and treatment of postpartum or postabortal haemorrhage (p. 2130.2). In the management of the third stage of labour, it may be given in a dose of 200 micrograms intramuscularly after delivery of the anterior shoulder or, at the latest, immediately after delivery of the infant. The same dose may be used for the prevention or treatment of postpartum or postabortal haemorrhage, and may be repeated every 2 to 4 hours as necessary up to a maximum of 5 doses. In emergencies it may be given in similar doses by slow intravenous injection,

over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. During the puerperium, methylergometrine maleate has been given in oral doses of 200 micrograms 3 or 4 times daily for up to a week or 125 to 250 micrograms up to 3 times daily.

Methylergometrine is a metabolite of methysergide (p. 677.1).

Diagnosis and testing. For reference to the use of methylergometrine maleate in the diagnosis of variant angina, see Ergometrine Maleate, p. 2136.3.

Adverse Effects, Treatment, and Precautions

As for Ergometrine Maleate, p. 2136.3 and p. 2137.1.

Overdosage. References.

1. Aeby A, *et al.* Methylergometrine poisoning in children: review of 34 cases. *J Toxicol Clin Toxicol* 2003; **41:** 249–53.
2. Bangh SA, *et al.* Neonatal ergot poisoning: a persistent iatrogenic illness. *Am J Perinatol* 2005; **22:** 239–43.
3. Enweronu-Laryea CC, *et al.* Methylergometrine poisoning in the newborn: report of two cases. *East Afr Med J* 2008; **85:** 463–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methylergometrine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Pharmacokinetics

Methylergometrine maleate is reported to be rapidly absorbed when given orally or intramuscularly, with onset of uterine contractions in about 5 to 15 minutes and 2 to 5 minutes, respectively. Oral bioavailability may show considerable interindividual variation. It undergoes extensive first-pass hepatic metabolism and only small amounts of unchanged drug are excreted in the urine. The elimination half-life is reported to be about 2 to 3 hours.

The pharmacokinetics of methylergometrine maleate have been studied after oral doses in healthy subjects[1,2] and in postpartum women.[3] Small amounts of methylergometrine have been detected in breast milk.[4,5]

1. Mäntylä R, *et al.* Methylergometrine (methylergonovine) concentrations in the human plasma and urine. *Int J Clin Pharmacol Biopharm* 1978; **16:** 254–7.
2. de Groot ANJA, *et al.* Comparison of the bioavailability and pharmacokinetics of oral methylergometrine in men and women. *Int J Clin Pharmacol Ther* 1995; **33:** 328–32.
3. Allonen H, *et al.* Methylergometrine: comparison of plasma concentrations and clinical response of two brands. *Int J Clin Pharmacol Biopharm* 1978; **16:** 340–2.
4. Erkkola R, *et al.* Excretion of methylergometrine (methylergonovine) into the human breast milk. *Int J Clin Pharmacol Biopharm* 1978; **16:** 579–80.
5. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; **191:** 2168–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Basofortina; ***Austria***: Methergin; ***Belg.***: Methergin; ***Braz.***: Ergometrin; Methergin; ***Denm.***: Methergin; ***Fin.***: Methergin; ***Fr.***: Methergin; ***Ger.***: Methergin; ***Gr.***: Demergin; Methergin; ***Hong Kong***: Ergotyl†; Methergin; ***India***: Elmet; Ematrin; Emergin; Ergogin; Ergolin; Ergoriv; G-Metrin; Ingagen-M; Lebergin; Lerin; Mem; Memjet; Mergox; Merzen; Metermin; Methergin; Methging; Methin; Methocin; Methyden; Methygin; Nimeth; Utergin; ***Indon.***: Bledstop; Glomethyl; Methergin; Metherinal; Methovin; Metilat; Metvell; Myomergin; Myotonic†; Pospargin; Utergin; ***Israel***: Methergin; ***Ital.***: Methergin; ***Malaysia***: Methergin; ***Mex.***: Methergin; ***Neth.***: Methergin; ***Philipp.***: Comthergin; Ergomed; Josenta; Lerin; Medisyl; Mem; Mergot; Mergotrex; Methergin; Myometril; Obtrin†; Usamema; ***Port.***: Methergin; ***Rus.***: Methylergobrevin (Метилэргобревин); ***Spain***: Methergin; ***Swed.***: Methergin; ***Switz.***: Methergin; ***Thai.***: Ergotyl†; Expogin; Methergin†; Metrine; ***Turk.***: Methergin; Metiler; Uterjin; ***USA***: Methergine; ***Venez.***: Methergin.

Multi-ingredient Preparations. ***Philipp.***: Uterine.

Pharmacopoeial Preparations

USP 36: Methylergonovine Maleate Injection; Methylergonovine Maleate Tablets.

Mifepristone *(BAN, USAN, rINN)*

C-1073; Mifepriston; Mifepristona; Miféprístone; Mifepristoni; Mifepristonum; R-38486; RU-486-6; RU-486; RU-34486; RU-38486; VGX-410C; Мифепристон.

11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-prop-1-ynylestra-4,9-dien-3-one.

$C_{29}H_{35}NO_2$=429.6

CAS — 84371-65-3.

ATC — G03XB01.

ATC Vet — QG03XB01.

UNII — 320T6RNW1F.

Pharmacopoeias. In *Chin.*

Uses and Administration

Mifepristone is a steroid derived from norethisterone that has potent antiprogestogenic activity and sensitises the myometrium to the effects of prostaglandins. It is used in termination of pregnancy (see p. 2139.2), for either medical termination or for softening and dilatation of the cervix before surgical termination of pregnancy. Mifepristone is also used for labour induction after intra-uterine fetal death (see p. 2139.1). Mifepristone also has antiglucocorticoid activity and is used in the treatment of Cushing's syndrome (see below).

In the **medical termination of pregnancy**, the use of mifepristone with a prostaglandin shortens the duration of the procedure and reduces the dose of prostaglandin required. In the UK the licensed regimen for the termination of pregnancies of up to 49 days is a single oral dose of 600 mg of mifepristone followed by a prostaglandin 36 to 48 hours later; prostaglandin treatment may be with either misoprostol 400 micrograms orally or gemeprost 1 mg vaginally. Alternatively, 200 mg of mifepristone may be given as a single oral dose followed, 36 to 48 hours later, by gemeprost 1 mg vaginally. Regimens containing vaginal gemeprost may also be used for the termination of pregnancies of up to 63 days. In the USA the licensed regimen for the termination of pregnancies up to 49 days of gestation is a single oral dose of 600 mg of mifepristone followed 2 days later by 400 micrograms of misoprostol orally, unless abortion has already been completed. As an adjunct to prostaglandin termination of pregnancy beyond the first trimester, the licensed dose in the UK is a single oral dose of mifepristone 600 mg given 36 to 48 hours before scheduled prostaglandin administration.

For **softening** and **dilatation of the cervix** before surgical termination of pregnancy during the first trimester, a single 200-mg dose of mifepristone orally is given 36 to 48 hours before the procedure.

For labour induction following intra-uterine **fetal death**, oral mifepristone 600 mg is given daily for 2 consecutive days; if labour has not started within 72 hours of the first dose, other methods of induction should be used.

Mifepristone is used to control hyperglycaemia that is secondary to hypercortisolism in endogenous **Cushing's syndrome**; it is given to those patients with secondary type 2 diabetes mellitus or glucose intolerance who are not candidates for surgery or when surgery has failed. The starting dose is 300 mg orally once daily with food. The dose may be increased, according to response, in increments of 300 mg to a maximum of 1.2 g once daily, but to no more than 20 mg/kg daily. The dose should not be increased more frequently than once every 2 to 4 weeks.

When given daily in Cushing's syndrome, a maximum daily dose of 300 mg is recommended when mifepristone must be given with strong inhibitors of the cytochrome P450 isoenzyme CYP3A. Mifepristone may require dose adjustment in patients with hepatic or renal impairment (see below).

Mifepristone has been tried for **other uses** such as postcoital contraception (below), endometriosis (p. 2139.1), uterine fibroids (leiomyomas) (p. 2139.1), and for progestogen-dependent neoplasms such as meningiomas (p. 2139.1). The antiglucocorticoid activity of mifepristone is under investigation in psychotic major depression (below).

General references.

1. Heikinheimo O. Clinical pharmacokinetics of mifepristone. *Clin Pharmacokinet* 1997; **33:** 7–17.
2. Mahajan DK, London SN. Mifepristone (RU486): a review. *Fertil Steril* 1997; **68:** 967–76.
3. Koide SS. Mifepristone: auxiliary therapeutic use in cancer and related disorders. *J Reprod Med* 1998; **43:** 551–60.
4. DeHart RM, Morehead MS. Mifepristone. *Ann Pharmacother* 2001; **35:** 707–19.
5. Weingertner A-S, *et al.* Utilisations actuelles et potentielles de la mifépristone en gynécologie-obstétrique et dans les autres disciplines médicales. *J Gynecol Obstet Biol Reprod (Paris)* 2004; **33:** 692–702.
6. Tang OS, Ho PC. Clinical applications of mifepristone. *Gynecol Endocrinol* 2006; **22:** 655–9.
7. Im A, Appleman LJ. Mifepristone: pharmacology and clinical impact in reproductive medicine, endocrinology and oncology. *Expert Opin Pharmacother* 2010; **11:** 481–8.
8. Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. *Contraception* 2010; **82:** 442–52.

Administration in hepatic and renal impairment. In patients being treated for Cushing's syndrome, a maximum oral daily dose of 600 mg is recommended for those with mild to moderate hepatic impairment. Studies in patients with severe hepatic impairment are lacking and mifepristone should therefore be avoided in these patients. A maximum daily dose of 600 mg is also recommended for patients with Cushing's syndrome and any degree of renal impairment.

Contraception. Mifepristone has been established as an effective emergency contraceptive (p. 2233.2). Initial studies found an oral 600-mg dose given within 72 hours of coitus to be effective.[1,2] Subsequently lower doses, given up to 120 hours after coitus, have been shown to be well tolerated and as effective as standard emergency contraceptive regimens.[3-5] Studies[3,5,6] and meta-analyses[7,8] have confirmed the efficacy of a 10-mg dose. There was some evidence of a slight dose-response effect; it was calculated that there would be 1 extra pregnancy per 146 women treated if the dose were to be reduced from 25 to 10 mg, but the associated increase in availability of the drug might outweigh this.[8]

The development of a mifepristone-based standard contraceptive (p. 2232.3) has been less successful. Regimens based on daily,[9] weekly,[10,11] or monthly[12,13] doses of mifepristone have been investigated.

1. Glasier A, *et al.* Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception. *N Engl J Med* 1992; **327:** 1041–4.
2. Webb AMC, *et al.* Comparison of Yuzpe regimen, danazol, and mifepristone (RU 486) in oral postcoital contraception. *BMJ* 1992; **305:** 927–31.
3. von Hertzen H, *et al.* Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; **360:** 1803–10.
4. Ashok PW, *et al.* Mifepristone versus the Yuzpe regimen (PC4) for emergency contraception. *Int J Gynecol Obstet* 2004; **87:** 188–93.
5. Hamoda H, *et al.* A randomized trial of mifepristone (10 mg) and levonorgestrel for emergency contraception. *Obstet Gynecol* 2004; **104:** 1307–13.
6. Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. *Lancet* 1999; **353:** 697–702.
7. Piaggio G, *et al.* Combined estimates of effectiveness of mifepristone 10 mg in emergency contraception. *Contraception* 2003; **68:** 439–46.
8. Piaggio G, *et al.* Meta-analyses of randomized trials comparing different doses of mifepristone in emergency contraception. *Contraception* 2003; **68:** 447–52.
9. Brown A, *et al.* Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J Clin Endocrinol Metab* 2002; **87:** 63–70.
10. Godfrey EM, *et al.* Low-dose mifepristone for contraception: a weekly versus planned postcoital randomized pilot study. *Contraception* 2004; **70:** 41–6.
11. Pei K, *et al.* Weekly contraception with mifepristone. *Contraception* 2007; **75:** 40–4.
12. Hapangama DK, *et al.* Feasibility of administering mifepristone as a once a month contraceptive pill. *Hum Reprod* 2001; **16:** 1145–50.
13. Narvekar N, *et al.* Toward developing a once-a-month pill: a double-blind, randomized, controlled trial of the effect of three single doses of mifepristone given at midcycle on the pattern of menstrual bleeding. *Fertil Steril* 2006; **86:** 819–24.

Cushing's syndrome. Mifepristone has been used to manage the cardiovascular, metabolic, and psychiatric signs and symptoms of Cushing's syndrome (p. 2559.1) because of its antagonist effects at the glucocorticoid receptor.[1-5] Its use has been reported in a small number of patients who have been given mifepristone in [oral] doses ranging from 5 to 30 mg/kg daily.[4] (See Uses and Administration, above, for licensed doses.) The authors of a retrospective study[5] of 20 patients recommended a starting dose of 200 to 400 mg daily, increasing gradually according to response and tolerance to a usual dose of 400 to 800 mg daily. In general the dose may be adjusted every 2 weeks, but increasing the dose by 200 mg every 3 days might be considered for patients needing rapid treatment, such as those with psychosis. They also suggested that a dose above 1 g daily was probably no more effective but associated with more adverse effects. Patients should be monitored for hypokalaemia, which occurs frequently and may require treatment with potassium supplementation and spironolactone. Adrenal insufficiency can also develop, and has been managed by reducing the dose of mifepristone and giving dexamethasone.[5] Others have suggested that long-term mifepristone therapy may increase the risk of endometrial hyperplasia and thyroid dysfunction, and that patients should be monitored accordingly.[4]

1. Nieman LK, *et al.* Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab* 1985; **61:** 536–40.
2. van der Lely A-J, *et al.* Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med* 1991; **114:** 143–4.
3. Chu JW, *et al.* Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *J Clin Endocrinol Metab* 2001; **86:** 3568–73.
4. Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing's syndrome. *Eur J Endocrinol* 2007; **157:** 561–9.
5. Castinetti F, *et al.* Merits and pitfalls of mifepristone in Cushing's syndrome. *Eur J Endocrinol* 2009; **160:** 1003–10.

Depression. Mifepristone is under investigation in the management of depression (p. 398.1) with psychotic features;[1-4] preliminary results suggest some benefit but its efficacy remains to be proven.

1. Belanoff JK, *et al.* An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* 2002; **52:** 386–92.
2. Simpson GM, *et al.* An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005; **66:** 598–602.
3. Flores BH, *et al.* Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 2006; **31:** 628–36.

4. DeBattista C, *et al.* Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol Psychiatry* 2006; **60:** 1343–9.

Ectopic pregnancy. Methotrexate with mifepristone may be more effective than methotrexate alone[1,2] for the medical treatment of ectopic pregnancy (p. 823.3), although some have not found the combination to produce any benefit over methotrexate alone in the majority of women.[3]

1. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; **13:** 1987–90.
2. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; **179:** 640–3.
3. Rozenberg P, *et al.* Medical treatment of ectopic pregnancies: a randomized clinical trial comparing methotrexate-mifepristone and methotrexate-placebo. *Hum Reprod* 2003; **18:** 1802–8.

Endometriosis. Some results[1,2] have suggested that mifepristone, which is capable of suppressing ovarian function, may be of benefit in patients with endometriosis (p. 2264.1).

1. Kettel LM, *et al.* Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis. *Fertil Steril* 1991; **56:** 402–7.
2. Kettel LM, *et al.* Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; **178:** 1151–6.

Fibroids. Mifepristone has been reported to produce significant decreases in uterine and leiomyoma volumes, and to reduce symptoms such as dysmenorrhoea and menorrhagia, when given to patients with fibroids (p. 2281.2). However, data are from small studies using oral doses ranging from 5 to 50 mg daily. Endometrial changes including hyperplasia and cystic glandular dilatation have also been reported in some studies.[1-5]

1. Steinauer J, *et al.* Systematic review of mifepristone for the treatment of uterine leiomyomata. *Obstet Gynecol* 2004; **103:** 1331–6.
2. Fiscella K, *et al.* Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. *Obstet Gynecol* 2006; **108:** 1381–7.
3. Carbonell Esteve JL, *et al.* Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. *Obstet Gynecol* 2008; **112:** 1029–36.
4. Bagaria M, *et al.* Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. *Aust N Z J Obstet Gynaecol* 2009; **49:** 77–83.
5. Engman M, *et al.* Mifepristone for treatment of uterine leiomyoma: a prospective randomized placebo controlled trial. *Hum Reprod* 2009; **24:** 1870–9.

Labour induction. A few studies[1-5] have reported that mifepristone was effective for cervical ripening and labour induction (p. 2129.1) at term, and sometimes reduced the need for a prostaglandin and oxytocin. However, a dose-finding study[6] found that single oral doses ranging from 50 to 600 mg were no more effective than placebo for inducing labour. The results of a systematic review[7] suggested that mifepristone was better than placebo at ripening the cervix or inducing labour, and might reduce the need for oxytocin. Mifepristone might also reduce the incidence of caesarean section, but increase instrumental delivery. Overall, however, the reviewers concluded that there was insufficient evidence to support its use for labour induction.

Mifepristone is used for cervical ripening and labour induction where **intra-uterine fetal death** has occurred,[8] usually in oral doses of 600 mg given daily for 2 days. The effective use of a single 200 mg dose, followed by misoprostol given orally and/or vaginally, has also been described.[9,10]

1. Frydman R, *et al.* Labor induction in women at term with mifepristone (RU486): a double-blind, randomized, placebo-controlled study. *Obstet Gynecol* 1992; **80:** 972–5.
2. Giacalone PL, *et al.* Cervical ripening with mifepristone before labor induction: a randomized study. *Obstet Gynecol* 1998; **92:** 487–92.
3. Elliott CL, *et al.* The effects of mifepristone on cervical ripening and labor induction in primigravidae. *Obstet Gynecol* 1998; **92:** 804–9.
4. Stenlund PM, *et al.* Induction of labor with mifepristone—a randomized, double-blind study versus placebo. *Acta Obstet Gynecol Scand* 1999; **78:** 793–8.
5. Wing DA, *et al.* Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial. *Obstet Gynecol* 2000; **96:** 543–8.
6. Berkane N, *et al.* Use of mifepristone to ripen the cervix and induce labor in term pregnancies. *Am J Obstet Gynecol* 2005; **192:** 114–20.
7. Hapangama D, Neilson JP. Mifepristone for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 10/09/09).
8. Cabrol D, *et al.* Induction of labor with mifepristone (RU 486) in intrauterine fetal death. *Am J Obstet Gynecol* 1990; **163:** 540–2.
9. Wagaarachchi PT, *et al.* Medical management of late intrauterine death using a combination of mifepristone and misoprostol. *BJOG* 2002; **109:** 443–7.
10. Väyrynen W, *et al.* Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. *Acta Obstet Gynecol Scand* 2007; **86:** 701–5.

Meningioma. Mifepristone has been used successfully in some patients with inoperable meningioma,[1-4] a brain tumour that may be progestogen-receptor positive. It has been given long term in oral doses of 200 mg daily, in some cases for more than 10 years. Adverse effects from long-term therapy have included fatigue, hot flushes, nausea, and depression; gynaecomastia has occurred in men and breast tenderness in women. Cessation of menstruation during mifepristone therapy occurs in premenopausal women, and there have been isolated cases of endometrial hyperplasia in pre- and postmenopausal women.

1. Grunberg SM, *et al.* Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *J Neurosurg* 1991; **74:** 861–6.
2. Lamberts SWJ, *et al.* Mifepristone (RU 486) treatment of meningiomas. *J Neurol Neurosurg Psychiatry* 1992; **55:** 486–90.
3. Spitz IM, *et al.* Management of patients receiving long-term treatment with mifepristone. *Fertil Steril* 2005; **84:** 1719–26.
4. Grunberg SM, *et al.* Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. *Cancer Invest* 2006; **24:** 727–33.

Termination of pregnancy. Mifepristone sensitises the myometrium to prostaglandins, increases uterine contractility, and softens and dilates the cervix.[1] It is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with prostaglandins for the termination of pregnancy (p. 2131.3). Mifepristone has also been tried with methotrexate in the treatment of ectopic pregnancy (see above) and may be used to induce labour where intra-uterine fetal death has occurred (see above).

Mifepristone, followed 36 to 48 hours later by a prostaglandin, is an effective medical alternative to surgical methods for the termination of pregnancy in the *first trimester*.[1] Efficacy decreases with increasing gestational age, and the success rate may be affected by the choice of prostaglandin, its dose, and route of administration. Termination success rates are highest for gestations of up to 49 days; after this the success rate for mifepristone with oral misoprostol tends to decrease compared with other regimens.[2] Vaginal gemeprost may be used with mifepristone for gestations of up to 63 days.[1] The usual dose of oral mifepristone is 600 mg, although lower doses of 200 and 400 mg have been studied in various regimens with prostaglandins and found to be as effective.[1,3] A similar efficacy was also shown in a comparison of 100 and 200 mg doses.[4] However, a further reduction to 50 mg significantly reduced efficacy.[1,3]

Although surgical termination is commonly used for pregnancies of 9 to 13 weeks, there is increasing evidence to support the use of medical termination using mifepristone followed by misoprostol. A regimen using oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, has been described.[5,6] Two further vaginal doses of misoprostol 400 micrograms were given at intervals of 3 hours if the products of conception had not been passed (these doses could be given orally if vaginal bleeding was heavier than a normal period[6]). Surgical evacuation was then used if necessary. In a large case series of 1076 women,[7] medical abortion was successful in 95.8%. A regimen of oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally (or 600 micrograms sublingually), was used, with up to 5 further doses of misoprostol 400 micrograms (vaginally or sublingually) given at intervals of 3 hours if needed. The mean number of misoprostol doses used was 2.31.

Mifepristone is also used to ripen the cervix before vacuum aspiration for surgical termination in the first trimester. Oral doses of 600 mg have been used, but lower doses were also found to be more effective than placebo[8,9] and as effective as prostaglandins;[10-12] consequently, a dose of 200 mg is now often used.

Mifepristone followed by a prostaglandin may also be used for medical termination in the *second trimester* (mid-trimester termination; gestation of 13 to 24 weeks).[13,14] Similarly to early termination, a study found mifepristone 200 mg orally to be as effective as 600 mg when followed by misoprostol.[15] Further retrospective reviews have also reported mifepristone 200 mg followed by misoprostol[16] or gemeprost[17] to be effective.

In the UK the Royal College of Obstetricians and Gynaecologists' guidelines[18] for both early and mid-trimester terminations include the following regimens:

- for gestation up to 63 days (9 weeks), mifepristone 200 mg orally followed 24 to 72 hours later by misoprostol 800 micrograms vaginally; if abortion has not occurred 4 hours after administration of misoprostol in women at 49 to 63 days of gestation, a further dose of misoprostol 400 micrograms may be given orally or vaginally
- for gestation between 9 and 13 weeks, mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally; a maximum of 4 further doses of misoprostol 400 micrograms may be given every 3 hours, orally or vaginally, if necessary
- for mid-trimester termination (13 to 24 weeks), mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, then up to 4 further doses of misoprostol 400 micrograms given every 3 hours orally

Mifepristone followed by a prostaglandin has also been used in **early pregnancy loss**, particularly missed miscarriage, and has been reported to be an effective alternative to surgical evacuation.[19,20] As for termination, mifepristone doses of 200 and 600 mg orally, followed by misoprostol, appear to be equally effective,[21] although some studies[22,23] suggest that pretreatment with mifepristone does not improve the expulsion rate compared with vaginal or oral misoprostol alone.

1. Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with a prostaglandin analogue. *Contraception* 2006; **74:** 66–86.
2. Kahn JG, *et al.* The efficacy of medical abortion: a meta analysis. *Contraception* 2000; **61:** 29–40.
3. Marions L. Mifepristone dose in the regimen with misoprostol for medical abortion. *Contraception* 2006; **74:** 21–5.
4. von Hertzen H, *et al.* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. *BJOG* 2009; **116:** 381–9.
5. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; **352:** 542–3.
6. Ashok PW, *et al.* A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. *Hum Reprod* 2002; **17:** 92–8.
7. Hamoda H, *et al.* Medical abortion at 9–13 weeks' gestation: a review of 1076 consecutive cases. *Contraception* 2005; **71:** 327–32.
8. WHO. The use of mifepristone (RU 486) for cervical preparation in first trimester pregnancy termination by vacuum aspiration. *Br J Obstet Gynaecol* 1990: **97:** 260–6.
9. WHO Task Force on Postovulatory Methods of Fertility Regulation. Cervical ripening with mifepristone (RU 486) in late first trimester abortion. *Contraception* 1994; **50:** 461–75.
10. Henshaw RC, Templeton AA. Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486). *Br J Obstet Gynaecol* 1991; **98:** 1025–30.
11. Ngai SW, *et al.* Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study. *Br J Obstet Gynaecol* 1996; **103:** 1120–3.
12. Ashok PW, *et al.* Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study. *Am J Obstet Gynecol* 2000; **183:** 998–1002.
13. Rodger M, Baird D. Pretreatment with mifepristone (RU486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. *Br J Obstet Gynaecol* 1990; **97:** 41–5.
14. Thong KJ, Baird DT. Induction of second trimester abortion with mifepristone and gemeprost. *Br J Obstet Gynaecol* 1993; **100:** 758–61.
15. Webster D, *et al.* A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. *Br J Obstet Gynaecol* 1996; **103:** 706–9.
16. Ashok PW, *et al.* Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. *Contraception* 2004; **69:** 51–8.
17. Tang OS, *et al.* Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. *Contraception* 2001; **64:** 29–32.
18. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/NEBInducedAbortionfull.pdf (accessed 22/08/10)
19. Chia KV, Ogbo VI. Medical termination of missed abortion. *J Obstet Gynaecol* 2002; **22:** 184–6.
20. Niinimäki M, *et al.* A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. *Fertil Steril* 2006; **86:** 367–72.
21. Coughlin LB, *et al.* Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? *J Obstet Gynaecol* 2004; **24:** 69–71.
22. Grønlund A, *et al.* Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation: a multi-center trial in Copenhagen county, Denmark. *Acta Obstet Gynecol Scand* 2002; **81:** 1060–5.
23. Stockheim D, *et al.* A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. *Fertil Steril* 2006; **86:** 956–60.

Adverse Effects and Treatment

Uterine bleeding and cramps often occur after the use of mifepristone in procedures for the termination of pregnancy, and will occur in almost all patients after the addition of a prostaglandin. Bleeding typically continues for about 9 to 16 days, and may be severe enough to warrant curettage and transfusion in a small proportion of patients. However, prolonged heavy bleeding may also be a sign of incomplete abortion or other complications that require medical or surgical intervention. Other adverse effects of mifepristone include malaise, dizziness, chills, fever, headache, diarrhoea, nausea, vomiting, rashes, and urticaria; although some of these effects may be caused by the prostaglandin given after mifepristone.

Serious, sometimes fatal, infections have occurred in women undergoing abortion, although no causal relationship has been established between these events and the use of mifepristone.

When given in the management of Cushing's syndrome, the most frequent adverse effects of mifepristone are gastrointestinal disturbances, decreased appetite, fatigue, drowsiness, dizziness, headache, anxiety, dyspnoea, peripheral oedema, and hypertension. Arthralgia, myalgia, and back pain can also occur. Hypokalaemia is a common adverse effect, and serum-potassium should be measured before and 1 to 2 weeks after starting mifepristone, during any dose adjustment, and periodically throughout therapy. A mineralocorticoid antagonist, such as spironolactone, may be needed if potassium supplementation does not

control hypokalaemia. Abnormal thyroid function tests have been reported. Endometrial thickening, cystic dilatation of endometrial glands, and vaginal bleeding have been found in women treated with continuous mifepristone. Mifepristone prolongs the QTc interval in a dose-dependent way.

Symptoms of adrenal insufficiency may develop in patients being treated with mifepristone for Cushing's syndrome. However, serum-cortisol concentrations stay raised during mifepristone therapy and do not provide an accurate assessment of hypoadrenalism. In such cases, mifepristone should be stopped and glucocorticoid therapy given; high doses may be needed to overcome the receptor blockade of mifepristone. Treatment may be restarted at a lower mifepristone dose after symptoms resolve.

Effects on the cardiovascular system. For a report of a woman who died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone, see p. 2145.3.

Effects on the fetus. Studies in *rabbits*, but not *rats* or *mice*, suggest mifepristone causes fetal malformation. There have been reports of normal fetal development after the use of a single dose of mifepristone alone in mothers who subsequently decided to continue their pregnancy.[1,2] However, in two reports, use of mifepristone was possibly related to malformations of the fetus including sirenomelia.[2,3] Cerebellar agenesis has been reported after a failed medical termination using mifepristone and gemeprost (see under Dinoprostone, p. 2135.2).

1. Lim BH, *et al.* Normal development after exposure to mifepristone in early pregnancy. *Lancet* 1990; **336:** 257–8.
2. Pons J-C, *et al.* Development after exposure to mifepristone in early pregnancy. *Lancet* 1991; **338:** 763.
3. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; **352:** 323.

Infection. Patients with endogenous Cushing's syndrome are at risk of opportunistic infection. The development of *Pneumocystis jirovecii* pneumonia shortly after starting mifepristone has been described. The authors suggested that the antiglucocorticoid effect of mifepristone could allow a restoration of the immune response to pre-existing subclinical *P. jirovecii* infection, resulting in the precipitation of clinical symptoms of pneumonia.[1]

1. Oosterhuis JK, *et al.* Life-threatening Pneumocystis jiroveci pneumonia following treatment of severe Cushing's syndrome. *Neth J Med* 2007; **65:** 215–17.

TOXIC SHOCK SYNDROME. Fatal toxic shock syndrome occurred in 5 women who underwent medical termination of pregnancy using mifepristone and misoprostol.[1,2] In 4 cases it was specified that mifepristone 200 mg had been given orally, followed by misoprostol 800 micrograms vaginally.[2] Within a week of termination, these patients presented with signs and symptoms that included abdominal pain, nausea and vomiting, tachycardia, hypotension, oedema, haemoconcentration, profound leucocytosis, and absence of fever. Postmortem examination found evidence of endometritis and toxic shock syndrome that was attributed to *Clostridium sordellii* infection. This is an infrequent human pathogen, but the authors of one report[2] noted that *C. sordellii* infection of the genital tract had also been reported in 8 women after delivery, suggesting that pregnancy, childbirth, or termination of pregnancy may predispose a small number of women to acquire this organism, and that associated dilatation of the cervix may allow for ascending infection.

Although there has also been some speculation about the possible mechanisms, both pharmacological[3] and physical,[4] by which oral mifepristone or vaginal misoprostol might potentiate *C. sordellii* infection, a causal relationship between these drugs and the 5 reported deaths has not been established.[5] A review[6] of further cases found that infection can also occur after miscarriage, that it can occur with regimens other than oral mifepristone followed by vaginal misoprostol, and that *C. perfringens* infection may also cause toxic shock after termination. A retrospective analysis[7] of data from 227 823 women who underwent medical termination of pregnancy found a significant reduction in the rate of serious infection after the route of misoprostol delivery was changed from vaginal to buccal. However, the relative effect of this change was difficult to estimate because routine infection reduction measures (screening for sexually transmitted infection or prophylactic doxycycline) had been introduced at the same time.

1. Sinave C, *et al.* Toxic shock syndrome due to Clostridium sordellii: a dramatic postpartum and postabortion disease. *Clin Infect Dis* 2002; **35:** 1441–3.
2. Fischer M, *et al.* Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. *N Engl J Med* 2005; **353:** 2352–60.
3. Miech RP. Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; **39:** 1483–8.
4. Sicard D, Chauvelot-Moachon L. Comment: pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; **39:** 2142–3.
5. FDA. Questions and answers on Mifeprex (mifepristone) (issued 4th November, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111341.htm (accessed 29/03/11)
6. Cohen AL, *et al.* Toxic shock associated with Clostridium sordellii and Clostridium perfringens after medical and spontaneous abortion. *Obstet Gynecol* 2007; **110:** 1027–33.
7. Fjerstad M, *et al.* Rates of serious infection after changes in regimens for medical abortion. *N Engl J Med* 2009; **361:** 145–51.

Precautions

The use of mifepristone for termination of pregnancy is contra-indicated in women with a confirmed or suspected ectopic pregnancy, because medical termination using mifepristone and a prostaglandin will not be effective (for use with methotrexate, see p. 2139.1). The expected symptoms of a medical termination may also be similar to those of a ruptured ectopic pregnancy. In women being treated for Cushing's syndrome, pregnancy must be excluded before starting mifepristone or if treatment is interrupted for more than 14 days, and non-hormonal contraception should be used during treatment and for 1 month after stopping mifepristone. Women who develop abnormal vaginal bleeding should be investigated for endometrial changes. Mifepristone should be given with care to patients with haemostatic disorders or anaemia.

During treatment for Cushing's syndrome, patients with heart failure or cardiovascular disease should be monitored because raised serum-cortisol concentrations, which may activate mineralocorticoid receptors, are not reduced by mifepristone.

Mifepristone is contra-indicated in patients with chronic adrenal failure. It should be avoided in patients with serious conditions being treated with systemic corticosteroids, such as immunosuppression after transplantation. Mifepristone should be given with care in other chronic conditions requiring corticosteroid therapy, including inhaled therapy in asthma; it should be avoided in severe uncontrolled asthma. Mifepristone should be used with caution in hepatic or renal impairment, and is not recommended for termination of pregnancy in women with renal or hepatic failure.

Breast feeding. Mifepristone was detected in the breast milk of 10 lactating women who underwent medical termination of pregnancy using mifepristone (600 mg orally) and misoprostol. Concentrations of mifepristone were found to be the highest in the first 12 hours after the dose, and then declined over the next 7 days. However, the measured concentrations were low and the authors estimated that an exclusively breast-fed infant aged 6 to 12 months might ingest a relative dose of up to 1.5% of that given to the mother. Mifepristone was below the detection limit in 2 other women given a 200-mg dose of mifepristone. It was suggested that breast feeding could continue during medical termination using mifepristone, especially if a dose of 200 mg was used.[1] Licensed product information advises against breast feeding by women given mifepristone.

1. Sääv I, *et al.* Medical abortion in lactating women—low levels of mifepristone in breast milk. *Acta Obstet Gynecol Scand* 2010; **89:** 618–22.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mifepristone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Interactions

The metabolism of mifepristone is mediated by the cytochrome P450 isoenzyme CYP3A4. Theoretically, use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of mifepristone. The impact of this on the efficacy of mifepristone for the termination of pregnancy is unknown. During treatment for Cushing's syndrome, mifepristone and strong inhibitors of CYP3A4 should only be used together with extreme caution and the dose of mifepristone limited (see Uses and Administration, p. 2138.2); moderate inhibitors may be used with caution. The use of mifepristone with CYP3A4 inducers should be avoided.

Mifepristone is an inhibitor of CYP3A4. Continuous concomitant use is contra-indicated with simvastatin and lovastatin, and with CYP3A4 substrates that have a narrow therapeutic index. Other substrates should be used with caution. Mifepristone is also an inhibitor of CYP2C8, CYP2C9, and CYP2B6, and could increase the exposure to drugs metabolised by these enzymes.

Mifepristone should be used with caution in women also receiving anticoagulant therapy. Through its antagonist effects, mifepristone reduces the efficacy of corticosteroids and hormonal contraceptives.

NSAIDs. The effects of mifepristone on the uterus and cervix may be mediated by increased prostanoid synthesis resulting from its inhibitory effect on progesterone. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of mifepristone. However, a placebo-controlled study[1] in 28 women found that in the 13 given *naproxen* 500 mg orally 60, 48, 36, 24, and 12 hours before surgical termination of pregnancy the efficacy of mifepristone 100 mg given orally to soften the cervix was not reduced. Also, NSAIDs did not affect medical termination using mifepristone followed by misoprostol (see p. 2142.3).

1. Rådestad A, Bygdeman M. Cervical softening with mifepristone (RU 486) after pretreatment with naproxen: a double-blind randomized study. *Contraception* 1992; **45:** 221–7.

Pharmacokinetics

Peak plasma concentrations of mifepristone occur about 1 to 2 hours after a single oral dose, and between 1 and 4 hours after multiple doses; bioavailability is about 70%. Mifepristone is about 98% bound to plasma proteins, mainly α_1-acid glycoprotein. Elimination is biphasic; a slow phase is followed by a more rapid terminal phase, with an elimination half-life of about 18 hours. At steady state, the half-life is about 85 hours. Mifepristone undergoes hepatic oxidative metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and metabolites are excreted in the bile and eliminated in the faeces. Only a small fraction is detected in the urine. Mifepristone is distributed into breast milk.

Reviews.

1. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. *Eur J Obstet Gynecol Reprod Biol* 2002; **101:** 113–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Mifegyne; ***Belg.***: Mifegyne; ***China***: Bi Yun (碧韵); Han Zhu Ting (含珠停); Hou Ding Nuo (后定诺); Mi Fu (米福); Mifolian (弗乃尔); Nuo Lv Ting (诺虑婷); Si Mi An (司米安); Xiyin (息隐); ***Denm.***: Mifegyne; ***Fin.***: Mifegyne; ***Fr.***: Mifegyne; ***Ger.***: Mifegyne; ***Gr.***: Mifegyne; ***India***: Abo Pill; Abortom; Cedate; Elmif; Mefipil; MF-Kare; Mifebort; Mifegest; Mifeprin; Miferiv; Mistone; MT Pill; ***Israel***: Mifegyne; ***Neth.***: Mifegyne; ***Norw.***: Mifegyne; ***NZ***: Mifegyne; ***Port.***: Mifegyne; ***Rus.***: Gynepriston (Гинепристон); Gynestril (Гинестрил); Mifegyn (Мифегин); Mifeprex (Мифепрекс); Mifolian (Мифолиан); Pencroftonum (Пенкрофтон); ***S.Afr.***: Mifegyne; ***Spain***: Mifegyne; ***Swed.***: Mifegyne; ***Switz.***: Mifegyne; ***UK***: Mifegyne; ***Ukr.***: Ginepriston (Гинепристон); Miropriston (Миропристон); ***USA***: Korlym; Mifeprex.

Multi-ingredient Preparations. ***China***: Zi Yun (紫韵); ***Neth.***: Medabon.

Misoprostol *(BAN, USAN, rINN)*

Misoprostoli; Misoprostolo; Misoprostolum; Mizoprostol; SC-29333; Мизопростол.

(±)-Methyl 7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl}heptanoate; (±)-Methyl (13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate.

$C_{22}H_{38}O_5$=382.5

CAS — 59122-46-2.

ATC — A02BB01; G02AD06.

ATC Vet — QA02BB01; QG02AD06.

UNII — 0E43V0BB57.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Misoprostol). A clear, colourless or yellowish, hygroscopic, oily liquid. Practically insoluble in water; soluble in alcohol; sparingly soluble in acetonitrile. Store in airtight containers at -20 degrees.

USP 36: (Misoprostol). A clear, colourless or light yellow viscous liquid. Very slightly soluble in water. Store in airtight containers at a temperature of -10 degrees to -25 degrees.

Uses and Administration

Misoprostol is a synthetic analogue of alprostadil (prostaglandin E_1; p. 2352.2).

It is used in the treatment of benign gastric and duodenal **ulceration** (p. 2141.2) including that associated with NSAIDs. The usual oral dose is 800 micrograms daily in two to four divided doses, taken with food and at bedtime. Treatment is initially given for at least 4 weeks, even if symptoms are relieved sooner, and may continue for up to 8 weeks if necessary. Further courses may be used to treat relapse.

Misoprostol is also used prophylactically with NSAIDs to prevent NSAID-induced ulcers. The usual oral dose is 200 micrograms two to four times daily. A dose of 100 micrograms four times daily may be used in patients not tolerating the higher dose. Some preparations of

NSAIDs contain misoprostol in an attempt to limit their adverse effects on the gastrointestinal mucosa.

Misoprostol may be used to ripen the cervix before surgical **termination of pregnancy** (below) in the first trimester. A single oral dose of misoprostol 400 micrograms is given 3 to 4 hours before surgery. It may also be used for medical termination of pregnancy at up to 49 days of amenorrhoea, in a single oral dose of 400 micrograms given 36 to 48 hours after mifepristone. Misoprostol has also been used for induction of labour (see below) and in the management of postpartum haemorrhage (see below).

General reviews.

1. Goldberg AB, *et al.* Misoprostol and pregnancy. *N Engl J Med* 2000; **344:** 38–47.
2. Blanchard K, *et al.* Misoprostol for women's health: a review. *Obstet Gynecol* 2002; **99:** 316–32.
3. Lokugamage AU, *et al.* Misoprostol and pregnancy: ever-increasing indications of effective usage. *Curr Opin Obstet Gynecol* 2003; **15:** 513–18.
4. Chong YS, *et al.* Misoprostol: a quarter century of use, abuse, and creative misuse. *Obstet Gynecol Surv* 2004; **59:** 128–40.
5. Weeks A, Faúndes A. Misoprostol in obstetrics and gynecology. *Int J Gynaecol Obstet* 2007; **99** suppl: S156–S159.
6. Elati A, Weeks AD. The use of misoprostol in obstetrics and gynaecology. *BJOG* 2009; **116** (suppl 1): 61–9.
7. Choksuchat C. Clinical use of misoprostol in nonpregnant women: review article. *J Minim Invasive Gynecol* 2010; **17:** 449–55.

Labour induction and augmentation. Prostaglandins are well established for the induction of labour (p. 2129.1) at term and misoprostol has been widely investigated for this indication. A systematic review[1] of studies of misoprostol given *vaginally* found that it increased cervical ripening and induced labour. It was more effective than vaginal or intracervical dinoprostone, reducing the need for oxytocin augmentation and improving the rate of vaginal delivery achieved within 24 hours. It was also found to be more effective than intravenous oxytocin. Most studies used misoprostol tablets in a dose of 50 micrograms vaginally every 4 hours, but reported doses have varied from 25 micrograms every 2 to 3 hours, to 100 micrograms every 6 to 12 hours. Low doses of misoprostol resulted in more use of oxytocin, but caused less uterine hyperstimulation. Although unlicensed, misoprostol is reported to be used outside clinical studies particularly in the USA, and the American College of Obstetricians and Gynecologists has recommended a dose of 25 micrograms intravaginally every 3 to 6 hours.[2]

Misoprostol has also been given *orally* but this route is less well established. Reported doses have varied widely but most studies have used 50 micrograms every 4 hours. Some reviews have found oral to be less effective than vaginal misoprostol.[2,3] However, others[4] have concluded that oral use produces similar outcomes to vaginal misoprostol, but that comparison is complicated by the wide variation in doses. Overall, oral misoprostol appears to be at least as effective as vaginal dinoprostone, but because of limited data it should be used with caution.[4] The risk of uterine hyperstimulation may be increased with misoprostol by either route, particularly when given vaginally[4] or at higher doses,[1,4] and it should not be used in women with scarred uteri from previous caesarean delivery or uterine surgery[2] (see also Effects on the Uterus, under Adverse Effects of Dinoprostone, p. 2135.2). There has also been some limited investigation of misoprostol given *sublingually*.[3,5,6]

Misoprostol has been used for labour induction for terminations in the second and third trimesters for fetal anomaly or after **intra-uterine fetal death**. Vaginal misoprostol appears to be as effective as other prostaglandins, and more effective than oral use. Studied dosage regimens have varied considerably, including cumulative doses ranging from 400 to 3200 micrograms over 24 hours, and dosage intervals of 3 to 12 hours.[7] Misoprostol has also been used with mifepristone for intra-uterine fetal death (see Labour Induction, p. 2139.1).

Misoprostol may also be used for active management of the third stage of labour (see Postpartum Haemorrhage, below).

1. Hofmeyr GJ, *et al.* Vaginal misoprostol for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 09/02/11).
2. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. *Drug Safety* 2002; **25:** 665–76.
3. Bartusevicius A, *et al.* Oral, vaginal and sublingual misoprostol for induction of labor. *Int J Gynecol Obstet* 2005; **91:** 2–9.
4. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
5. Shetty A, *et al.* Sublingual misoprostol for the induction of labor at term. *Am J Obstet Gynecol* 2002; **186:** 72–6.
6. Shetty A, *et al.* Sublingual compared with oral misoprostol in term labour induction: a randomised controlled trial. *Br J Obstet Gynaecol* 2002; **109:** 645–50.
7. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 09/02/11).

Organ and tissue transplantation. Misoprostol 200 micrograms orally four times daily improved renal function in ciclosporin-treated recipients of renal transplants.[1] The number of patients who had acute graft rejection was lower in the misoprostol group than in the placebo group. However, another study[2] did not indicate any difference in the incidence of rejection episodes or in renal function when misoprostol was added to immunosuppressant regimens for kidney transplantation, and misoprostol does not appear to have gained a role in the usual management of renal transplantation (p. 1935.2).

1. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E_1 analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; **322:** 1183–8.
2. Pouteil-Noble C, *et al.* Misoprostol in renal transplant recipients: a prospective, randomized, controlled study on the prevention of acute rejection episodes and cyclosporin A nephrotoxicity. *Nephrol Dial Transplant* 1994; **9:** 552–5.

Peptic ulcer disease. Misoprostol is used in the prophylaxis and treatment of peptic ulceration (p. 1813.2) in patients taking NSAIDs. There is good evidence that misoprostol can reduce the risk of gastric and duodenal ulcer formation in patients on long-term NSAID treatment,[1-4] and it appears more effective in this respect than histamine H_2-antagonists,[1] for which evidence of benefit against gastric injury is less persuasive. However, misoprostol's abdominal adverse effects, particularly diarrhoea and abdominal cramps, may limit its usefulness and patient acceptability. Omeprazole, which is equally effective in preventing NSAID-induced ulceration, is better tolerated.[3] Improved formulations, in which the active isomer of misoprostol is bound to a polymer, may reduce adverse effects.[5]

1. Koch M, *et al.* Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury: a meta-analysis of randomized controlled clinical trials. *Arch Intern Med* 1996; **156:** 2321–32.
2. Champion GD, *et al.* NSAID-induced gastrointestinal damage: epidemiology, risk and prevention, with an evaluation of the role of misoprostol: an Asia-Pacific perspective and consensus. *Drugs* 1997; **53:** 6–19.
3. Hawkey CJ, *et al.* Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1998; **338:** 727–34.
4. Rostom A, *et al.* Prevention of NSAID-induced gastroduodenal ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/06/08).
5. Chen D, *et al.* Stabilization and sustained-release effect of misoprostol with methacrylate copolymer. *Int J Pharmaceutics* 2000; **203:** 141–8.

Postpartum haemorrhage. Prostaglandins, usually given parenterally, have an accepted role in the management of established *postpartum haemorrhage* (p. 2130.2) not controlled by oxytocin and ergot preparations. There have been reports[1-3] of the successful use of rectal misoprostol to control postpartum haemorrhage, using single doses of 800 or 1000 micrograms. A review[4] found that there was some evidence for reduced blood loss with lower doses of misoprostol, and suggested that oral, sublingual, rectal, or a combination of these, might be the most effective routes; possible regimens were 200 to 400 micrograms sublingually or rectally, or similar doses plus 200 micrograms orally. It also suggested that the oral dose of misoprostol should not exceed 600 micrograms because of the risk of hyperpyrexia. WHO has suggested that in settings where other uterotonics are not available or if all other measures fail, misoprostol may be used as a last resort in a dose of 200 to 800 micrograms orally or sublingually.[5] Subsequently, a large study provided evidence of sublingual misoprostol 800 micrograms being less effective than intravenous oxytocin for control of postpartum bleeding in women who had not received prophylactic oxytocin during labour.[6] In women who had already received prophylactic oxytocin, studies have provided variable results: one study found that sublingual misoprostol 600 micrograms was no better than placebo for treatment,[7] while another found misoprostol 800 micrograms to be clinically equivalent to oxytocin.[8] All 3 studies noted the increased incidence of shivering and fever associated with misoprostol. There have also been a few cases in which intra-uterine misoprostol 800 micrograms has controlled refractory secondary postpartum haemorrhage.[9,10]

Misoprostol has also been given immediately after delivery in the *active management of third-stage labour*. In a study[11] of more than 18 500 women treated in hospital, which compared oral misoprostol 600 micrograms with intramuscular or intravenous oxytocin, a higher proportion of women who received misoprostol had blood loss of at least 1000 mL and required additional oxytocics. Misoprostol was also associated with significantly more shivering and pyrexia. The results of this large study suggest that parenteral oxytocin is preferred for active management, but it has been argued that misoprostol may be particularly useful in preventing postpartum haemorrhage in developing countries where there is limited access to healthcare facilities and parenteral oxytocics.[12-14] Two placebo-controlled studies have addressed this argument, reporting that oral[15] or sublingual[16] misoprostol used in rural primary healthcare settings reduced postpartum haemorrhage, particularly severe haemorrhage (1000 mL or more). A systematic review[17] concluded that oral misoprostol was less effective than injectable oxytocics in reducing blood loss and the use of additional oxytocics, but that it may be used where no injectable uterotonic is available. WHO has recommended that in the absence of personnel trained to offer active management of the third stage of labour, a trained health worker should offer misoprostol 600 micrograms orally immediately after the birth of the baby, without active intervention to deliver the placenta.[5]

1. O'Brien P, *et al.* Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstet Gynecol* 1998; **92:** 212–4.
2. Lokugamage AU, *et al.* A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 2001; **80:** 835–9.
3. Shojai R, *et al.* Le misoprostol par voie rectale dans l'hémorragie de la délivrance: rectal misoprostol for postpartum hemorrhage. *Gynecol Obstet Fertil* 2004; **32:** 703–7.
4. Hofmeyr GJ, *et al.* Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; **112:** 547–53.
5. WHO, Department of Reproductive Health and Research. WHO statement regarding the use of misoprostol for postpartum haemorrhage prevention and treatment (issued 2009). Available at: http://whqlibdoc.who.int/hq/2009/WHO_RHR_09.22_eng.pdf (accessed 18/09/09)
6. Winikoff B, *et al.* Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; **375:** 210–16.
7. Widmer M, *et al.* Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. *Lancet* 2010; **375:** 1808–13.
8. Blum J, *et al.* Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; **375:** 217–23.
9. Adekanmi OA, *et al.* Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum haemorrhage. *BJOG* 2001; **108:** 541–2.
10. Oboro VO, *et al.* Intrauterine misoprostol for refractory postpartum hemorrhage. *Int J Gynecol Obstet* 2003; **80:** 67–8.
11. Gülmezoglu AM, *et al.* WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet* 2001; **358:** 689–95.
12. Darney PD. Misoprostol: a boon to safe motherhood...or not? *Lancet* 2001; **358:** 682–3.
13. Shannon C, Winikoff B. Use of misoprostol in third stage of labour. *Lancet* 2002; **359:** 709.
14. Langenbach C. Misoprostol in preventing postpartum hemorrhage: a meta-analysis. *Int J Gynecol Obstet* 2006; **92:** 10–18.
15. Derman RJ, *et al.* Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *Lancet* 2006; **368:** 1248–53.
16. Høj L, *et al.* Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. Abridged version: *BMJ* 2005; **331:** 723–7. Full version: http://www.bmj.com/cgi/content/full/331/7519/723 (accessed 30/06/08)
17. Gülmezoglu AM, *et al.* Prostaglandins for preventing postpartum haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).

Termination of pregnancy. Prostaglandins are widely used for the termination of pregnancy (p. 2131.3) and misoprostol has been studied both for cervical preparation and for inducing uterine contractions.

In the *first trimester*, misoprostol is used for cervical ripening before surgical termination; it has been reported to be effective when given orally, sublingually, or vaginally,[1-4] usually in a dose of 400 micrograms. Oral misoprostol (400 micrograms) given after mifepristone is effective in medical termination of early pregnancy of up to 63 days, and especially so at up to 49 days.[5,6] Misoprostol 800 micrograms has also been given vaginally after mifepristone,[7-10] and a regimen of 2 or 3 doses of sublingual misoprostol after oral mifepristone has been reported to be effective.[11] When given as a single dose of misoprostol, vaginal and sublingual routes are equally effective after mifepristone, but there is a greater risk of failure when the dose of misoprostol is 400 micrograms compared with 800 micrograms, and adverse effects are more frequent with sublingual use.[12] The interval between doses of mifepristone and misoprostol is usually 36 to 48 hours, but the use of vaginal misoprostol 24 hours after mifepristone is also effective.[9,12,13] Successful use of vaginal misoprostol with intramuscular or oral methotrexate has also been described.[14-17]

Misoprostol on its own is only a weak abortifacient, particularly when given orally, and congenital malformations have been reported after failed abortion attempts using misoprostol alone (see Effects on the Fetus, p. 2142.2). However, there is interest in finding a regimen that is effective, particularly in countries where mifepristone is unavailable. A dose of 800 micrograms vaginally, repeated after 24 hours, has been suggested for pregnancy of up to 63 days.[18,19] A large study[20] has also reported that 800 micrograms given every 12 hours for 3 doses was less effective when given sublingually than vaginally; the routes were equally effective when misoprostol was given every 3 hours, but sublingual administration caused more adverse effects such as fever, chills, shivering, and diarrhoea.

Misoprostol has also been studied for termination of pregnancy during the *second trimester*. It has been used in various regimens to induce medical termination, given either alone[21-23] or after oral mifepristone,[24,25] and reported to be effective when given vaginally, sublingually, or orally. The time to complete abortion may depend on the dose,

dosage interval, and route of administration. Compared with other prostaglandins, intravaginal misoprostol alone (generally as a single dose of 200 micrograms or repeated after 12 hours if necessary) has been reported to be as effective as dinoprostone for medical termination.[26] Another study[27] found 400 micrograms intravaginally every 3 hours, up to 5 doses, to be at least as effective as intra-amniotic carboprost. The use of buccal misoprostol to prepare the cervix before surgical termination has also been described.[28]

In the management of **early pregnancy loss**, intravaginal misoprostol has been proposed as an alternative to surgery for evacuation of the uterus.[29] Doses have ranged from 400 to 800 micrograms, but the lower doses tend to be less effective.[30] The American College of Obstetricians and Gynecologists has suggested that for women with a uterine size of less than 12 weeks of gestation, an oral dose of misoprostol 600 micrograms may be given for incomplete abortion or miscarriage. For missed miscarriage a dose of 800 micrograms may be given vaginally, or 600 micrograms sublingually, which may be repeated every 3 hours for 2 additional doses.[31] Misoprostol has also been used with mifepristone for uterine evacuation after early pregnancy loss (see Termination of Pregnancy, p. 2139.2).

1. Ngai SW, *et al.* The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. *Hum Reprod* 1999; **14:** 2139–42.
2. Saxena P, *et al.* Comparison between the sublingual and oral route of misoprostol for pre-abortion cervical priming in first trimester abortions. *Hum Reprod* 2004; **19:** 77–80.
3. Vimala N, *et al.* Cervical priming with sublingual misoprostol vs. 15-methyl-prostaglandin F2 α prior to surgical abortion. *Int J Gynecol Obstet* 2005; **88:** 134–7.
4. Carbonell Esteve JL, *et al.* Sublingual versus vaginal misoprostol (400 micrograms) for cervical priming in first-trimester abortion: a randomized trial. *Contraception* 2006; **74:** 328–33.
5. Peyron R, *et al.* Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993; **328:** 1509–13.
6. Spitz IM, *et al.* Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998; **338:** 1241–7.
7. El-Refaey H, *et al.* Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995; **332:** 983–7.
8. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; **52:** 542–3.
9. Schaff EA, *et al.* Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. *JAMA* 2000; **284:** 1948–53.
10. Shannon C, *et al.* Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. *BJOG* 2006; **113:** 621–8.
11. Hamoda H, *et al.* A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG* 2005; **112:** 1102–8.
12. von Hertzen H, *et al.* WHO Research Group on Postovulatory Methods of Fertility Regulation. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. *BJOG* 2010; **117:** 1186–96.
13. von Hertzen H, *et al.* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. *BJOG* 2009; **116:** 381–9.
14. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90:** 611–16.
15. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; **57:** 83–8.
16. Borgatta L, *et al.* Early medical abortion with methotrexate and misoprostol. *Obstet Gynecol* 2001; **97:** 11–16.
17. Aldrich T, Winikoff B. Does methotrexate confer a significant advantage over misoprostol alone for early medical abortion? A retrospective analysis of 8678 abortions. *BJOG* 2007; **114:** 555–62.
18. Philip NM, *et al.* A consensus regimen for early abortion with misoprostol. *Int J Gynecol Obstet* 2004; **87:** 281–3.
19. Blanchard K, *et al.* Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception* 2005; **72:** 91–7.
20. von Hertzen H, *et al.* WHO Research Group on Postovulatory Methods of Fertility Regulation. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial. *Lancet* 2007; **369:** 1938–46.
21. Tang OS, *et al.* A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG* 2004; **111:** 1001–5.
22. Caliskan E, *et al.* Randomized comparison of 3 misoprostol protocols for abortion induction at 13–20 weeks of gestation. *J Reprod Med* 2005; **50:** 173–80. Correction. *ibid.;* 732. [dose]
23. von Hertzen H, *et al.* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Comparison of vaginal and sublingual misoprostol for second trimester abortion: randomized controlled equivalence trial. *Hum Reprod* 2009; **24:** 106–12.
24. Hamoda H, *et al.* A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. *Hum Reprod* 2005; **20:** 2348–54.
25. Tang OS, *et al.* A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005; **20:** 3062–6.
26. Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E_2 for termination of second-trimester pregnancy. *N Engl J Med* 1994; **331:** 290–3.
27. Su L-L, *et al.* A prospective, randomized comparison of vaginal misoprostol versus intra-amniotic prostaglandins for midtrimester termination of pregnancy. *Am J Obstet Gynecol* 2005; **193:** 1410–14.
28. Patel A, *et al.* Planned Parenthood Federation of America Buccal Misoprostol Waiver Group. Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. *Contraception* 2006; **73:** 420–30.
29. Zhang J, *et al.* A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005; **353:** 761–9.
30. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).
31. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 427: misoprostol for postabortion care. *Obstet Gynecol* 2009; **113:** 465–8. Also available at: http://www.who.int/selection_medicines/committees/expert/17/application/ACOG_ref.pdf (accessed 11/09/09)

Adverse Effects

The commonest adverse effect of misoprostol is diarrhoea. Other gastrointestinal effects include abdominal pain, dyspepsia, flatulence, and nausea and vomiting. Increased uterine contractility and abnormal vaginal bleeding (including menorrhagia and intermenstrual bleeding) have been reported. Other adverse effects include rashes, headache, and dizziness. Hypotension is rarely seen at doses recommended for peptic ulcer disease.

For adverse effects associated with the obstetric and gynaecological use of prostaglandins see under Dinoprostone, p. 2134.3.

Incidence of adverse effects. Data on misoprostol presented to the FDA have been summarised.[1] During controlled studies the most common adverse effect was diarrhoea (8.2% compared with 3.1% for placebo); it was dose-related but usually mild, only 8 of 2003 subjects receiving misoprostol having withdrawn because of incapacitating diarrhoea. Headaches and abdominal discomfort were also reported. The effects of misoprostol on the uterus and the potential risks of uterine bleeding or abortion in pregnant women were of more concern. In non-pregnant women taking part in the controlled studies there were menstrual complaints in 15 of 410 (3.7%) receiving misoprostol compared with 2 of 115 (1.7%) given placebo. In a study in pregnant women who had elected to undergo first trimester abortion, all 6 who had a spontaneous expulsion of the uterine contents had received 1 or 2 doses of misoprostol 400 micrograms the previous evening, while none of those given placebo aborted spontaneously; overall 25 of the 56 women given misoprostol had uterine bleeding compared with only 2 of 55 on placebo.

1. Lewis JH. Summary of the 29th meeting of the Gastrointestinal Drugs Advisory Committee, Food and Drug Administration—June 10, 1985. *Am J Gastroenterol* 1985; **80:** 743–5.

Effects on the fetus. Misoprostol on its own is only a weak abortifacient and is often ineffective when used alone for the termination of pregnancy (see p. 2141.3). However, it has been widely misused for this purpose in some countries, notably Brazil,[1,2] and anecdotal reports have associated congenital malformations with such misuse during the first trimester of pregnancy. A systematic review[3] of 4 case-control studies confirmed that misoprostol was associated with an increased risk of congenital abnormality, particularly Möbius syndrome and terminal transverse limb defects.

A case of Möbius syndrome has also been reported after a failed termination using the approved regimen of mifepristone followed by misoprostol.[4]

1. Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. *Lancet* 1993; **341:** 1258–61.
2. Coêlho HLL, *et al.* Misoprostol and illegal abortion in Fortaleza, Brazil. *Lancet* 1993; **341:** 1261–3. Correction. *ibid.;* 1486.
3. da Silva Dal Pizzol T, *et al.* Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. *Reprod Toxicol* 2006; **22:** 666–71.
4. Bos-Thompson M-A, *et al.* Möbius syndrome in a neonate after mifepristone and misoprostol elective abortion failure. *Ann Pharmacother* 2008; **42:** 888–92.

Effects on the uterus. For reference to uterine rupture in women given misoprostol to induce labour or terminate pregnancy, see under Dinoprostone, p. 2135.2.

Toxic shock syndrome. Fatal toxic shock syndrome has occurred in a few women who underwent medical termination of pregnancy using oral mifepristone and vaginal misoprostol, although a causal relationship between these drugs and the deaths has not been established (see under Mifepristone, p. 2140.1).

Precautions

Misoprostol should not be used to treat peptic ulcer disease in patients who are pregnant or who may become pregnant because it can cause uterine contraction. It should be used with caution in patients in whom hypotension might cause severe complications. Patients with conditions such as inflammatory bowel disease, for whom profound diarrhoea could be dangerous, should be monitored carefully if misoprostol is given.

Like other prostaglandins used in the termination of pregnancy (see Dinoprostone, p. 2136.1), misoprostol should not be used in women at increased risk of uterine rupture, such as those with multiple pregnancy or a uterus scarred by previous caesarean section. Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Breast feeding. Misoprostol acid was detected in the breast milk of 10 women given a single oral dose of misoprostol for postpartum uterine atony.[1] The concentration rose rapidly, peaked at about 1 hour, and had fallen towards the detection limit by about 5 hours after the dose. Product information for misoprostol licensed for use in gastric ulceration advises that it should not be given to breast-feeding women because misoprostol acid could potentially cause diarrhoea in the infant.

1. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; **191:** 2168–73.

Inflammatory bowel disease. Life-threatening diarrhoea was reported in a patient with unrecognised Crohn's disease after 6 doses of misoprostol.[1] Abdominal cramps, pain, and profuse watery diarrhoea also occurred after 3 doses of misoprostol in a woman with Crohn's disease.[2] In a cohort study of misoprostol taken with NSAIDs for arthritis there were 13 patients with a history of inflammatory bowel disease; 7 did not develop diarrhoea, 3 developed mild diarrhoea, 1 developed severe diarrhoea that stopped when misoprostol was withdrawn, and 2 developed bloody diarrhoea.[3]

1. Kornbluth A, *et al.* Life-threatening diarrhea after short-term misoprostol use in a patient with Crohn ileocolitis. *Ann Intern Med* 1990; **113:** 474–5.
2. Johnson JS, *et al.* Profuse diarrhea after misoprostol use in a patient with a history of Crohn's disease. *Ann Pharmacother* 1992; **26:** 1092–3.
3. Faich GA, *et al.* Diarrhea after misoprostol in Crohn disease. *Ann Intern Med* 1991; **114:** 342.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies misoprostol as probably not porphyrinogenic when used in the treatment of peptic ulcer disease; it may be used as a drug of first choice and no precautions are needed. A classification is not offered for its use in obstetrics.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/08/11)

Interactions

NSAIDs. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of misoprostol used for termination of pregnancy by inhibiting uterine cramping and cervical ripening. However, studies in women undergoing medical[1] or surgical[2] termination found that NSAIDs did not reduce the efficacy of misoprostol. In another study,[3] *diclofenac* did not reduce the efficacy of medical termination using mifepristone followed by misoprostol.

1. Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. *Contraception* 1997; **56:** 165–8.
2. Li CFI, *et al.* A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. *Contraception* 2003; **67:** 101–5. Correction. *ibid.;* 339.
3. Fiala C, *et al.* The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation. *Hum Reprod* 2005; **20:** 3072–7.

Pharmacokinetics

Misoprostol is reported to be rapidly absorbed and metabolised to its active form (misoprostol acid; SC-30695) after oral doses; peak plasma concentrations of misoprostol acid occur after about 15 to 30 minutes. Food reduces the rate but not the extent of absorption. Misoprostol acid is further metabolised by oxidation in several body organs and is excreted mainly in the urine. The plasma elimination half-life is reported to be between 20 and 40 minutes. Misoprostol acid is distributed into breast milk.

References.

1. Schoenhard G, *et al.* Metabolism and pharmacokinetic studies of misoprostol. *Dig Dis Sci* 1985; **30** (suppl): 126S–128S.
2. Karim A, *et al.* Effects of food and antacid on oral absorption of misoprostol, a synthetic prostaglandin E_1 analog. *J Clin Pharmacol* 1989; **29:** 439–43.
3. Foote EF, *et al.* Disposition of misoprostol and its active metabolite in patients with normal and impaired renal function. *J Clin Pharmacol* 1995; **35:** 384–9.
4. Zieman M, *et al.* Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; **90:** 88–92.
5. Khan R-U, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. *Obstet Gynecol* 2003; **101:** 968–74.
6. Khan R-U, *et al.* Oral, rectal, and vaginal pharmacokinetics of misoprostol. *Obstet Gynecol* 2004; **103:** 866–70.
7. Schaff EA, *et al.* Comparison of misoprostol plasma concentrations following buccal and sublingual administration. *Contraception* 2005; **71:** 22–5.
8. Aronsson A, *et al.* Pharmacokinetic profiles up to 12 h after administration of vaginal, sublingual and slow-release oral misoprostol. *Hum Reprod* 2007; **22:** 1912–18.
9. Tang OS, *et al.* Pharmacokinetics of repeated doses of misoprostol. *Hum Reprod* 2009; **24:** 1862–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cytotec; ***Austria***: Cyprostol; ***Belg.***: Cytotec; ***Braz.***: Cytotec†; ***Chile***: Alumbra; Misotrol; ***China***: Cytotec (喜克馈); ***Denm.***: Cytotec; ***Fin.***: Cytotec; ***Fr.***: Cytotec; Gymiso; ***Gr.***: Cytotec; ***Hong Kong***: Cytotec; ***India***: Aboprost; Cedate-F; Cytolog; Kontrac; Mesopil; Misobort; Misogest; Misolast; Misolup; Misoprost; Misotol; Mizolast; MS-Kare; ***Indon.***: Chromalux; Citrosol; Cytotec; Gastrul; Noprostol; ***Irl.***: Cytotec; ***Israel***: Cytotec; ***Ital.***: Cytotec; Misodex; ***Malaysia***: Cytotec; ***Mex.***: Cyrux; Cytotec; ***Neth.***: Cytotec; MisoOne; ***Norw.***: Cytotec; ***NZ***: Cytotec; ***Pol.***: Cytotec; ***Port.***: Cytotec; ***Rus.***: Cytotec (Сайтотек); Mirolut (Миролют); ***S.Afr.***: Cytotec; ***Singapore***: Cytotec; Misel; ***Spain***: Cytotec; Misofar; ***Swed.***: Cytotec; ***Switz.***: Cytotec; ***Thai.***: Cytotec; ***Turk.***: Cytotec; ***UK***: Cytotec; Topogyne; ***Ukr.***: Mirolut (Миролют); ***USA***: Cytotec; ***Venez.***: Cytotec.

Multi-ingredient Preparations. ***Neth.***: Medabon.

Used as an adjunct in:. ***Arg.***: Blokium Prost†; Oxaprost; ***Austral.***: Arthrotec; ***Austria***: Arthrotec; ***Belg.***: Arthrotec; ***Canad.***: Arthrotec; ***China***: Arthrotec (奥斯克); ***Denm.***: Arthrotec; ***Fin.***: Arthrotec; ***Fr.***: Artotec; ***Ger.***: Arthotec; ***Gr.***: Arthrotec; ***Hong Kong***: Arthrotec; ***India***: Mifenac; Misonac; ***Irl.***: Arthrotec; ***Israel***: Arthrotec; ***Ital.***: Artrotec; Misofenac; ***Mex.***: Artrenac Pro; Artrene; Artrotec; ***Neth.***: Arthrotec; Misofenac†; Normulen†; ***Norw.***: Arthrotec; ***Pol.***: Arthrotec; ***Port.***: Arthrotec; Diclotec†; ***Rus.***: Arthrotec (Артротек); ***S.Afr.***: Arthrotec; ***Spain***: Artrotec; Normulen†; ***Swed.***: Arthrotec; ***Switz.***: Arthrotec; ***Turk.***: Arthrotec; ***UK***: Arthrotec; Misofen; Napratec; ***USA***: Arthrotec; ***Venez.***: Arthrotec.

Oxytocin *(BAN, rINN)*

Alpha-hypophamine; Hipofamina; Ocitocina; Ocytocine; Oksitocinas; Oksitosiini; Oksitosin; Oksytocyna; Ossitocina; Oxitocin; Oxitocina; Oxytocine; Oxytocinum; Oxytósin; Окситоцин.

Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 cyclic (1→6) disulphide; [2-Leucine,7-isoleucine]vasopressin.

$C_{43}H_{66}N_{12}O_{12}S_2$=1007.2

CAS — 50-56-6.

ATC — H01BB02.

ATC Vet — QH01BB02.

UNII — 1JQS135EYN.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Oxytocin). A cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary that stimulates contraction of the uterus and milk ejection in receptive mammals. It is obtained by chemical synthesis and is available in the freeze-dried form as an acetate. A white or almost white, hygroscopic powder. Very soluble in water and in dilute solutions of dehydrated alcohol and of acetic acid. A 2% solution in water has a pH of 3.0 to 6.0. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Ph. Eur. 8: (Oxytocin Concentrated Solution). A solution of oxytocin with a concentration of not less than 250 micrograms of oxytocin per mL. It may contain a suitable antimicrobial preservative. A clear colourless liquid with a pH of 3.0 to 5.0. Store at 2 degrees to 8 degrees. Protect from light.

USP 36: (Oxytocin). A nonapeptide hormone having the property of causing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary glands. It is prepared by synthesis. Its oxytocic activity is not less than 400 units/mg. Store in airtight containers at 2 degrees to 8 degrees.

Units

12.5 units of oxytocin for bioassay are contained in about 21.4 micrograms of synthetic peptide (with human albumin 5 mg and citric acid) in one ampoule of the fourth International Standard (1978).

Uses and Administration

Oxytocin is a cyclic nonapeptide secreted by the hypothalamus and stored in the posterior lobe of the pituitary gland. It may be prepared from the gland of mammals or by synthesis.

Oxytocin causes contraction of the uterus, the effect increasing with the duration of pregnancy due to proliferation of oxytocin receptors. Small doses increase the tone and amplitude of the uterine contractions; large or repeated doses result in tetany. Oxytocin also stimulates the smooth muscle associated with the secretory epithelium of the lactating breast causing the ejection of milk but having no direct effect on milk secretion. It has a weak antidiuretic action.

Oxytocin is used for the induction and augmentation of labour, to control postpartum bleeding and uterine hypotonicity in the third stage of labour, and to promote lactation in cases of faulty milk ejection. It is also used as an adjunctive therapy in some types of miscarriage or abortion, but other measures may be preferred.

When given for the **induction** or **augmentation of labour**, oxytocin should not be started for 6 hours after vaginal prostaglandins have been given. Oxytocin is given by slow intravenous infusion, preferably by means of an infusion pump, but licensed doses vary between countries and guidelines may also suggest regimens that differ again (see also below). Licensed product information generally recommends using a solution containing 5 units in 500 mL of a physiological electrolyte solution such as sodium chloride 0.9%, but more concentrated solutions may be given via infusion pump. In the UK the infusion may be started at a rate of 1 to 4 milliunits/min, and then gradually increased at intervals of at least 20 minutes until a maximum of 3 or 4 contractions are occurring every 10 minutes. In the USA, licensed dosage recommendations are lower, starting at 0.5 to 1 milliunit/min, and gradually increasing the dose in increments of 1 to 2 milliunits/min at intervals of 30 to 60 minutes. A rate of up to 6 milliunits/min is reported to produce plasma oxytocin concentrations comparable to those in natural labour. About 10 milliunits/min is usually the most that is needed at term, but doses of up to 20 milliunits/min or more may be required in situations such as labour induction at an earlier stage of pregnancy or for intra-uterine fetal death. UK information also suggests that if regular contractions are not established after a total of 5 units then the attempt to induce labour should be stopped. However, it may be repeated on the following day, starting again with a rate of 1 to 4 milliunits/min. Fetal heart rate and uterine contractions should be monitored continuously. Once labour is progressing, oxytocin infusion may be gradually withdrawn.

Oxytocin may be used for the prevention and treatment of **postpartum haemorrhage** (p. 2144.1). In the active management of the third stage of labour, to prevent postpartum haemorrhage, the fixed combination of *Syntometrine* (oxytocin 5 units with ergometrine maleate 500 micrograms) may be given by intramuscular injection after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant. The *BNF* suggests a single intramuscular dose of oxytocin 10 units may be used alone, causing less nausea, vomiting, and hypertension than the combination. An alternative for the prevention of postpartum haemorrhage is the administration of oxytocin 5 units by slow intravenous injection, or intramuscular *Syntometrine*, after delivery of the placenta. In women given oxytocin for induction or augmentation of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter. A single dose of oxytocin 5 units by slow intravenous injection may be given during caesarean section, immediately after delivery of the child.

In the treatment of haemorrhage, oxytocin may be given in a dose of 5 units by slow intravenous injection. This may be followed in severe cases by intravenous infusion of a solution containing 5 to 20 units in 500 mL of a suitable non-hydrating diluent, at a rate that controls uterine atony. The *BNF* suggests that the initial dose of 5 units by slow intravenous injection may be repeated, then followed if necessary in severe cases by an infusion containing 40 units in 500 mL, the rate being adjusted to control atony. A dose of intramuscular *Syntometrine* is another option. In the USA a dose of up to 10 units of oxytocin, by intravenous infusion at a rate of 20 to 40 milliunits/min after delivery of the infant, or as an intramuscular injection after delivery of the placenta, has been used for control of postpartum haemorrhage.

For adjunctive therapy in **incomplete, inevitable, or missed miscarriage** (see Termination of Pregnancy, p. 2131.3) a suggested dose in the UK is 5 units by slow intravenous injection, followed if necessary by intravenous infusion at a rate of 20 to 40 milliunits/min or higher.

Oxytocin nasal spray is used to facilitate **lactation**; a dose of one spray, delivering 4 units, into one nostril 5 minutes before suckling has been used. However, evidence for its efficacy is limited and there is a danger that the mother may become dependent upon its action; such usage is not generally recommended (see p. 2130.1).

An **oxytocin challenge test** (below) has been used to evaluate fetal distress in pregnant patients at high risk.

Synthetic derivatives of oxytocin such as demoxytocin (p. 2133.3) have been used similarly.

Labour induction and augmentation. Oxytocin infusions are used for induction and augmentation of labour, as discussed on p. 2129.1. They are usually used to induce labour in women with ruptured membranes and will reduce the number of women who are undelivered 24 hours after starting therapy. However, oxytocin is less effective than dinoprostone, and caesarean section and epidural analgesia use are more likely with oxytocin than with expectant management.[1]

There have been many studies on the dosage of oxytocin required to induce or augment labour. Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/min, dose increases of 1 to 6 milliunits/min, and intervals between increases of 15 to 40 minutes.[2] However, it has been pointed out that no one regimen has been clearly proved superior.[2-4] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but result in more uterine hyperstimulation and emergency caesarean deliveries for fetal distress.[2] The American College of Obstetricians and Gynecologists has suggested that both low- and high-dose regimens within this range are appropriate for labour induction.[5] WHO[6] suggests a starting dose of 2.5 milliunits/min, increased at intervals of 30 minutes, and titrated against contractions to a maximum of 30 milliunits/min in multigravida and women with previous caesarean scars, or 60 milliunits/min in primigravida. WHO also includes a more rapid dose escalation regimen that may be considered for use in primigravida.

1. Alfirevic Z, *et al.* Intravenous oxytocin alone for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 10/02/11).
2. Stubbs TM. Oxytocin for labor induction. *Clin Obstet Gynecol* 2000; **43:** 489–94.
3. Patka JH, *et al.* High- versus low-dose oxytocin for augmentation or induction of labor. *Ann Pharmacother* 2005; **39:** 95–101.
4. Smith JG, Merrill DC. Oxytocin for induction of labor. *Clin Obstet Gynecol* 2006; **49:** 594–608.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Induction of labour (practice bulletin number 107, August 2009). *Obstet Gynecol* 2009; **114:** 386–97.
6. WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors*. Geneva: WHO, 2000. Also available at: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf (accessed 23/08/10)

Lactation induction. Oxytocin has been used to promote milk ejection, but good maternal education and support in techniques that promote physiological lactation remain the most important methods for successful breast feeding (see p. 2130.1). However, intranasal oxytocin might be useful in tetraplegic women, where the suckling-induced stimulation that normally triggers the release of oxytocin from the hypothalamus is impaired, as described in a case report.[1]

1. Cowley KC. Psychogenic and pharmacologic induction of the let-down reflex can facilitate breastfeeding by tetraplegic women: a report of 3 cases. *Arch Phys Med Rehabil* 2005; **86:** 1261–4.

Oxytocin challenge test. The oxytocin challenge test (OCT) is designed to detect placental insufficiency, and identify fetuses at risk of still-birth or complications during labour. Its use has declined with the development of other surveillance methods based on ultrasonography.[1] In a study, it was performed on 399 occasions in 305 women with pregnancies at risk and a gestational age of 36 weeks or more.[2] Oxytocin 1 milliunit/minute was given by infusion pump and increased every 5 to 10 minutes until a contraction rate of 3 per 10 minutes was achieved. Less than 10% of late or variable decelerations of fetal heart rate (FHR) was judged negative; 10 to 29% was judged equivocal; and 30% or more was judged positive. The finding of a positive or equivocal response to the OCT was considered a prediction of decelerations of the FHR during parturition, though the type of risk might vary. After 100 OCTs in 90 pregnant women considered at risk[3] it was concluded that a negative result is a reliable test of fetal well-being which should encourage obstetricians to await spontaneous onset of labour in preference to intervention. However, there have been reports of fetal death occurring despite a negative response to the OCT.[4-6] Another study[7] found that in 239 women with an unequivocal OCT result, a negative response was a reliable test for a good outcome, but that a positive result was not a reliable predictor of poor outcome.

Adverse effects associated with the OCT have included haemorrhage occurring in a patient after the second of two tests (the patient was found to have a major placenta praevia)[8] and neonatal hyperbilirubinaemia.[9] The latter effect led to the suggestion that the OCT should be used with caution in women whose babies might be at risk from hyperbilirubinaemia.

1. Devoe LD. Antenatal fetal assessment: contraction stress test, nonstress test, vibroacoustic stimulation, amniotic fluid volume, biophysical profile, and modified biophysical profile—an overview. *Semin Perinatol* 2008; **32:** 247–52.
2. Schulman H, *et al.* Quantitative analysis in the oxytocin challenge test. *Am J Obstet Gynecol* 1977; **129:** 239–44.
3. Sellappah S, Wagman H. Oxytocin challenge test as an out patient procedure. *Br J Clin Pract* 1984; **38:** 255–8.
4. Marcum RG. False negative oxytocin challenge test. *Am J Obstet Gynecol* 1977; **127:** 894.
5. Lorenz RP, Pagano JS. A case of intrauterine fetal death after a negative oxytocin challenge test. *Am J Obstet Gynecol* 1978; **130:** 232.
6. Dittman R, Belcher J. False-negative oxytocin challenge test. *N Engl J Med* 1978; **298:** 56.
7. Ocak V, *et al.* The predictive value of fetal heart rate monitoring: a retrospective analysis of 2165 high-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1992; **44:** 53–8.

8. Ng KH, Wong WP. Risk of haemorrhage in oxytocin stress test. *BMJ* 1976; **2:** 698–9.
9. Peleg D, Goldman JA. Oxytocin challenge test and neonatal hyperbilirubinaemia. *Lancet* 1976; **ii:** 1026.

Postpartum haemorrhage. Oxytocin is used for the prophylaxis and treatment of postpartum haemorrhage (p. 2130.2). In the active management of the third stage of labour, the combination of oxytocin and ergometrine may be associated with a small reduction in the risk of postpartum haemorrhage compared with oxytocin alone, but a higher incidence of nausea, vomiting, and hypertension.

Oxytocin injected into the vein of the umbilical cord has been used to assist the removal of retained placenta. A meta-analysis[1] of 12 studies found evidence that oxytocin reduced the incidence of manual removal of the retained placenta, although there was no apparent benefit in terms of other measures including blood loss, curettage, and infection. Most studies had used a dose of oxytocin 10 units in 20 mL of sodium chloride 0.9%. In the UK, a dose of 20 units in 20 mL, followed by proximal clamping of the cord, has been recommended.[2] However, a large controlled study (Release study)[3] subsequently found that umbilical injection of oxytocin 50 units in 30 mL was no better than placebo in reducing the need for manual removal of placenta. The authors also updated the previous meta-analysis[1] with this new data and found that there was no statistically significant benefit associated with oxytocin use.

1. Carroli G, Bergel E. Umbilical vein injection for management of retained placenta. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 21/09/09).
2. National Collaborating Centre for Women's and Children's Health/NICE. Intrapartum care: care of healthy women and their babies during childbirth (issued September 2007; corrected June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG55FullGuideline.pdf (accessed 21/09/09)
3. Weeks AD, *et al*. Umbilical vein oxytocin for the treatment of retained placenta (Release Study): a double-blind, randomised controlled trial. *Lancet* 2010; **375:** 141–7.

Adverse Effects

Oxytocin given in high doses, or to women who are hypersensitive to it, may cause uterine hyperstimulation with hypertonic or tetanic contractions, leading to uterine rupture and soft tissue damage. Effects in the fetus include bradycardia, arrhythmias, asphyxiation, and perhaps death.

Maternal deaths from severe hypertension and subarachnoid haemorrhage have occurred. Rapid intravenous injection of oxytocin has produced acute transient hypotension with flushing and reflex tachycardia. Postpartum haemorrhage, fatal afibrinogenaemia, and disseminated intravascular coagulation have been reported, but may be due to complications of labour induction rather than oxytocin itself.

High doses of oxytocin infused over prolonged periods can also cause water retention leading to hyponatraemia and intoxication, which may progress to convulsions, coma, and even death. Vasopressin-like activity (see p. 2643.3) is more likely with oxytocin of natural origin but may occur even with the synthetic peptide.

Other adverse effects include headache, nausea and vomiting, rashes, cardiac arrhythmias, pelvic haematoma, and anaphylactic and other hypersensitivity reactions.

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

Adverse effects after intranasal use of oxytocin have included nasal irritation, rhinorrhoea, lachrymation, uterine bleeding, and violent uterine contractions.

Inappropriate use. In a 1988 comment on the misuse of oxytocin in labour,[1] it was noted that statements on the management of labour were often misinterpreted as meaning that all women who failed to make adequate progress in terms of cervical dilatation should be given oxytocin. This was only true if poor progress was due to poor uterine action, and would be dangerous where there was disproportion; the decision to use oxytocin required careful assessment by an experienced obstetrician. In the previous 2 years the authors had seen one case of fractured pelvis, 2 of ruptured uterus, and 7 of cerebral palsy from fetal hypoxia, all of which were thought to be due to the ill-advised use of oxytocin to augment labour. More than a decade later the injudicious use of oxytocin during labour, with adverse outcomes including neonatal brain damage and death, continues to be reported. A review[2] of obstetric malpractice claims in Sweden found that the incorrect use of oxytocin was obvious in 37 of 54 cases; often, the oxytocin infusion had been increased despite a non-reassuring fetal heart rate pattern with or without overly frequent uterine contractions, or fetal monitoring was inadequate and hence fetal distress not recognised.

1. Taylor RW, Taylor M. Misuse of oxytocin in labour. *Lancet* 1988; **i:** 352.
2. Jonsson M, *et al*. Analysis of malpractice claims with a focus on oxytocin use in labour. *Acta Obstet Gynecol Scand* 2007; **86:** 315–19.

For reference to haemorrhage and to neonatal hyperbilirubinaemia occurring after an oxytocin challenge test, see under Uses and Administration, p. 2143.3.

Neonatal jaundice. Analysis of neonatal jaundice in 12 461 single births confirmed a higher incidence of jaundice in offspring of mothers given oxytocin, independent of gestational age at birth, male sex, Afro-Caribbean, Chinese, or Japanese race, epidural analgesia, ventouse delivery, and birth-weight, which were also associated with jaundice.[1] A later review[2] of 12 023 single births also found some of these factors to be associated with neonatal hyperbilirubinaemia, but not Afro-Caribbean race, epidural analgesia, or the use of oxytocin. Another smaller population study[3] also concluded that oxytocin was not significantly related to neonatal jaundice. In a total of 90 infants born to mothers after oxytocin-induced labour in 2 studies,[4,5] haematological disturbances were noted. These included erythrocyte fragility or reduction in erythrocyte deformability, hyponatraemia, hypo-osmolality, and an increase in serum-bilirubin concentration. Glucose injection, used as a vehicle for oxytocin may have further aggravated these changes.[5] A comparison[6] of women who received oxytocin infusion in either glucose 5% or sodium chloride 0.9% found the use of glucose to be associated with more cases of hyponatraemia in cord plasma, and neonatal hyperbilirubinaemia. In contrast, another study[7] found no difference between these diluents, but did report that neonatal bilirubin concentrations were higher when oxytocin had been used for augmentation of labour, compared with labour induction.

See also under Oxytocin Challenge Test in Uses and Administration, p. 2143.3.

1. Friedman L, *et al*. Factors influencing the incidence of neonatal jaundice. *BMJ* 1978; **1:** 1235–7.
2. Linn S, *et al*. Epidemiology of neonatal hyperbilirubinemia. *Pediatrics* 1985; **75:** 770–4.
3. Seidman DS, *et al*. Predicting the risk of jaundice in fullterm healthy newborns: a prospective population-based study. *J Perinatol* 1999; **19:** 564–7.
4. Buchan PC. Pathogenesis of neonatal hyperbilirubinaemia after induction of labour with oxytocin. *BMJ* 1979; **2:** 1255–7.
5. Singhi S, Singh M. Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia. *Arch Dis Child* 1979; **54:** 400–2.
6. Omigbodun AO, *et al*. Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. *Int J Gynecol Obstet* 1993; **40:** 235–9.
7. Oral E, *et al*. Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. *Arch Gynecol Obstet* 2003; **267:** 117–20.

Water intoxication. Oxytocin-induced water intoxication is most likely to arise as a result of prolonged attempts to empty the uterus in missed abortion or mid-trimester termination of pregnancy, but it has also been described after oxytocin infusion in other conditions including induction of labour.[1] Irrespective of the oxytocin concentration, patients in virtually all the reported cases have received more than 3.5 litres of infused fluid. Convulsions and somnolence associated with hyponatraemia have also been reported in a patient who was drinking more than 5 litres of herbal tea daily while using intranasal oxytocin 8 times or more daily.[2]

Another factor contributing to hyponatraemia is the antidiuretic effect of the pethidine and morphine commonly used for analgesia with oxytocin infusions. Water intoxication usually presents with fits and loss of consciousness but in some cases there may be preceding signs such as raised venous pressure, bounding pulse, and tachycardia. Diagnosis is confirmed by profound hyponatraemia; the mechanism appears to be more complex than simply haemodilution by the infused water. Treatment consists of controlling convulsions and maintaining an airway; oxytocin infusion must be stopped and isotonic, or even hypertonic, saline may be infused. Diuresis may then be assisted with furosemide. The prime objective, however, should be prevention; no patient should receive more than 3 litres of fluid containing oxytocin, and a careful fluid balance record is essential.

1. Feeney JG. Water intoxication and oxytocin. *BMJ* 1982; **285:** 243.
2. Mayer-Hubner B. Pseudotumour cerebri from intranasal oxytocin and excessive fluid intake. *Lancet* 1996; **347:** 623.

Precautions

Oxytocin should not be given where spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus. This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia or vasa praevia, placental abruption, cord presentation or prolapse, mechanical obstruction to delivery, fetal distress or hypertonic uterine contractions. It should not be used where there is a predisposition to uterine rupture, as in multiple pregnancy or high parity, polyhydramnios, or the presence of a uterine scar from previous caesarean section. Oxytocin should not be used for prolonged periods in resistant uterine inertia, severe pre-eclampsia, or severe cardiovascular disorders.

When given for induction or enhancement of labour particular care is needed in borderline cephalopelvic disproportion, less severe degrees of cardiovascular disease, and in patients over 35 years of age or with other risk factors. Careful monitoring of fetal heart rate and uterine motility is essential so that dosage of oxytocin can be adjusted to individual response; the drug should be given by intravenous infusion, preferably by means of an infusion pump. Infusion should be stopped immediately if fetal distress or uterine hyperactivity occur.

Over-vigorous labour should be avoided in cases of intrauterine fetal death, or where there is meconium-stained amniotic fluid, because there is a risk of amniotic fluid embolism.

The risk of water intoxication should be borne in mind, particularly when high doses of oxytocin are given over a long time. Infusion volumes should be kept low, and in such circumstances an electrolyte-based infusion fluid should be used rather than glucose solution. Oral fluid intake should be restricted and a fluid balance chart maintained; serum electrolytes should be measured if electrolyte imbalance is suspected.

Oxytocin challenge test. For the suggestion that oxytocin challenge testing should be used with caution in women whose offspring might be at risk of hyperbilirubinaemia, see under Uses and Administration, p. 2143.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxytocin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/07/11)

Interactions

Oxytocin may enhance the vasopressor effects of sympathomimetics. Some inhalational anaesthetics, such as cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic effect; cardiac arrhythmias may occur. Prostaglandins and oxytocin may potentiate the effects of each other on the uterus; the UK licensed product information for oxytocin states that it should not be started for 6 hours after use of vaginal prostaglandins.

Pharmacokinetics

Oxytocin undergoes enzymatic destruction in the gastrointestinal tract but it is rapidly absorbed from the mucous membranes when given intranasally. It is metabolised by the liver and kidneys with a plasma half-life of only a few minutes. Only small amounts are excreted unchanged in the urine.

References.

1. Seitchik J, *et al*. Oxytocin augmentation of dysfunctional labor IV: oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; **150:** 225–8.
2. Perry RL, *et al*. The pharmacokinetics of oxytocin as they apply to labor induction. *Am J Obstet Gynecol* 1996; **174:** 1590–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hipofisina; Syntocinon; Veracuril; ***Austral.***: Syntocinon; ***Austria***: Syntocinon; ***Belg.***: Syntocinon; ***Braz.***: Naox; Ocitoc; Orastina; Oxiton; Syntocinon; ***Chile***: Syntocinon; ***China***: Ao Sai Tuo Xing (奥赛托星); ***Denm.***: Syntocinon; ***Fin.***: Syntocinon; ***Fr.***: Syntocinon; ***Ger.***: Syntocinon; ***Hong Kong***: Syntocinon; ***India***: Evatocin; Foetocin; Genox; Gynotocin; Indox; Labtocin; Nitocin; Oxybro; Oxystar; Oxyton; Pitocin; Syntocinon; ***Indon.***: Induxin; Oxyla; Pitogin; Piton-S; Santocyn; Syntocinon; ***Irl.***: Syntocinon; ***Ital.***: Syntocinon; ***Malaysia***: Syntocinon; Udoxan; ***Mex.***: Oxitopisa; Syntocinon; Xitocin; ***Neth.***: Syntocinon; ***Norw.***: Syntocinon; ***NZ***: Syntocinon; ***Philipp.***: Comxytocin; Estima; Evatocin; Fetusin†; Lavoxin; NeOxyn; Obcin; Otoxin; Oxitone; Oxtimon; Oxymed; Oxyten; Roxipan; Solvoxine; Syntocinon; Syntox; Tocinox; Tranoxy; ***Port.***: Syntocinon; ***S.Afr.***: Syntocinon; ***Singapore***: Syntocinon; ***Spain***: Syntocinon; ***Swed.***: Syntocinon; ***Switz.***: Syntocinon; ***Thai.***: Octocin; ***Turk.***: Postuitrin; Synpitan; ***UK***: Syntocinon; ***USA***: Pitocin; ***Venez.***: Syntocinon.

Multi-ingredient Preparations. ***Austral.***: Syntometrine; ***Hong Kong***: Syntometrine; ***Irl.***: Syntometrine; ***Malaysia***: Syntometrine; ***NZ***: Syntometrine; ***S.Afr.***: Syntometrine; ***Singapore***: Syntometrine; ***UK***: Syntometrine.

Pharmacopoeial Preparations

BP 2014: Ergometrine and Oxytocin Injection; Oxytocin Injection;

USP 36: Oxytocin Injection; Oxytocin Nasal Solution.

Prolactin

Galactin; Galactina; Hormona lactogénica; Hormona luteotrópica; Lactoestimulina; Lactogen; Lactogenic Hormone; Lactógeno; Lactotropin; LMTH; LTH; Luteomammotropic Hormone; Luteotrophic Hormone; Luteotropin; Luteotropina; Mammotropin; Mamotropina; Prolactina; Prolactine; Prolaktiini; Prólaktín; Prolaktin; Prolaktinas; Prolaktyna; Prolattina; Пролактин.

CAS — 9002-62-4; 12585-34-1 (sheep); 56832-36-1 (ox); 9046-05-3 (pig).

UNII — 2558538ZG2.

Profile

Prolactin is a water-soluble protein from the anterior pituitary; it is structurally related to growth hormone (p. 1919.3). In *animals*, prolactin has many actions and is involved in reproduction, parental care, feeding of the young, electrolyte balance, and growth and development. In humans it has a definite role in inducing milk production; oxytocin (p. 2143.1) stimulates milk ejection. Relatively high concentrations of prolactin have been found in amniotic fluid. Placental lactogen has been shown to have prolactin-like activity. Prolactin secretion is stimulated by suckling and, for a few months after delivery, it has an inhibitory effect on the ovaries, acting as a natural contraceptive.

The hypothalamus can both stimulate and inhibit prolactin secretion by the anterior pituitary; the inhibitory influence is predominant and is mediated through a dopaminergic system. Dopamine binds to the lactotrope D_2 receptor to inhibit prolactin synthesis and release. Noradrenaline and gamma-aminobutyric acid are also inhibitory as are dopaminergic drugs such as bromocriptine. Although protirelin (p. 2344.2) has prolactin-releasing activity, there is evidence for the existence of a separate hypothalamic releasing factor (PRF). Prolactin secretion may also be stimulated by methyldopa, metoclopramide, reserpine, opioid analgesics, and phenothiazine or butyrophenone antipsychotics.

Hyperprolactinaemia, which is associated with a variety of other endocrine disorders, is discussed on p. 2252.2.

Prolactin has been given by intramuscular injection in the management of lactation disorders and some forms of menstrual disturbance.

Ritodrine Hydrochloride

(BANM, USAN, rINNM) ⊗

DU-21220 (ritodrine); Hidrocloruro de ritodrina; Ritodrin Hidroklorür; Ritodrina, hidrocloruro de; Ritodrine, Chlorhydrate de; Ritodrini Hydrochloridum; Ритодрина Гидрохлорид.

erythro-2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl) propan-1-ol hydrochloride.

$C_{17}H_{21}NO_3$,HCl=323.8

CAS — 26652-09-5 (ritodrine); 23239-51-2 (ritodrine hydrochloride).

ATC — G02CA01.

ATC Vet — QG02CA01.

UNII — ESJ56Q60GC.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Ritodrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in acetone and in ether. A 2% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

USP 36: (Ritodrine Hydrochloride). A white to nearly white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in ether; soluble in propyl alcohol. pH of a 2% solution in water is between 4.5 and 6.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Ritodrine hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has general properties similar to those of salbutamol (see p. 1220.2). It decreases uterine contractility and is used to arrest premature labour (p. 2131.1).

Ritodrine hydrochloride is usually given by intravenous infusion. Where possible this should be with the aid of a **syringe pump**, when the concentration should be 3 mg/mL, using glucose 5% as the diluent. A recommended initial rate of infusion is 50 to 100 micrograms/min, increased at intervals of 10 to 20 minutes by increments of 50 micrograms/min until there is evidence of patient response. The lowest effective dose should be used for maintenance, which is usually around 50 to 100 micrograms/min. If no syringe pump is available then the infusion may be made using a **controlled infusion device** to deliver a more dilute solution of 300 micrograms/mL, with glucose 5% being used once again as the diluent. The same dose is used as with the syringe pump.

The maternal pulse should be monitored throughout the infusion and the rate adjusted to avoid a maternal heart rate of more than 120 beats/min. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3).

Oral or **rectal** $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, ritodrine hydrochloride could be given orally in a dose of 10 to 20 mg every 4 to 6 hours, to a maximum daily dose of 120 mg, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

Reviews.

1. Yaju Y, Nakayama T. Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review. *Pharmacoepidemiol Drug Safety* 2006; **15**: 813–22.

Adverse Effects and Precautions

As for Salbutamol Sulfate, p. 1221.3. Leucopenia or agranulocytosis has been reported occasionally with prolonged intravenous use.

In women given ritodrine for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p. 1222.3, apply.

Effects on the eyes. Ritodrine and to a lesser extent salbutamol have been implicated in retinopathy in the premature infant when used for premature labour.[1]

1. Michie CA, *et al*. Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; **71**: F149.

Effects on the heart. Myocardial ischaemia or signs of myocardial ischaemia have been reported in patients given ritodrine.[1-3] Sinus tachycardia and ST-segment depression commonly occur in patients given ritodrine, but the relationship between these changes and ischaemia remains unclear.[3]

1. Brosset P, *et al*. Cardiac complications of ritodrine in mother and baby. *Lancet* 1982; **i**: 1468.
2. Ben-Shlomo I, *et al*. Myocardial ischaemia during intravenous ritodrine treatment: is it so rare? *Lancet* 1986; **ii**: 917–18.
3. Verhaert D, Van Acker R. Acute myocardial infarction during pregnancy. *Acta Cardiol* 2004; **59**: 331–9.

Effects on skeletal muscle. Elevated serum-creatine kinase concentrations have been found in women given ritodrine tocolysis,[1] and there have been rare reports of rhabdomyolysis.[1,2]

1. Matsuda Y, *et al*. Evaluation of creatine kinase level during long-term tocolysis. *J Perinat Med* 2002; **30**: 476–9.
2. Nasu K, *et al*. Rhabdomyolysis caused by tocolysis with oral ritodrine hydrochloride in a pregnant patient with myotonic dystrophy. *Gynecol Obstet Invest* 2006; **61**: 53–5.

Pulmonary oedema. Several cases of pulmonary oedema have been reported in patients given a $beta_2$ agonist, including ritodrine, for premature labour.[1-4] In 1995 the UK CSM[4] commented that it had received 10 reports of pulmonary oedema, fatal in 2 patients. The CSM considered that fluid overload was the most important predisposing factor. Other risk factors included multiple pregnancies, a history of cardiac disease, and maternal infection. For further discussion of the precautions necessary in the use of $beta_2$ agonists to treat premature labour, and the risk factors involved, see Salbutamol, p. 1222.3.

1. Hawker F. Pulmonary oedema associated with β_2-sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12**: 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; **110**: 714–18.
3. Clesham GJ, *et al*. β Adrenergic agonists and pulmonary oedema in preterm labour. *BMJ* 1994; **308**: 260–2.
4. CSM/MCA Reminder: ritodrine and pulmonary oedema. *Current Problems* 1995; **21**: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)

Interactions

As for Salbutamol Sulfate, p. 1223.1.

Pharmacokinetics

Ritodrine is rapidly absorbed from the gastrointestinal tract but is subject to fairly extensive first-pass metabolism; about 30% of an oral dose is bioavailable. It is metabolised in the liver mainly by conjugation with glucuronic acid or sulfate and excreted in urine as unchanged drug and metabolites. About 70 to 90% of a dose is reported to be excreted in the urine within 10 to 12 hours. It crosses the placenta.

References.

1. Gandar R, *et al*. Serum level of ritodrine in man. *Eur J Clin Pharmacol* 1980; **17**: 117–22.
2. Gross AS, Brown KF. Plasma protein binding of ritodrine at parturition and in nonpregnant women. *Eur J Clin Pharmacol* 1985; **28**: 479–81.
3. Kuhnert BR, *et al*. Ritodrine pharmacokinetics. *Clin Pharmacol Ther* 1986; **40**: 656–64.
4. Caritis SN, *et al*. Pharmacokinetics of orally administered ritodrine. *Am J Obstet Gynecol* 1989; **161**: 32–5.
5. Caritis SN, *et al*. Pharmacokinetics of ritodrine administered intravenously: recommendations for changes in the current regimen. *Am J Obstet Gynecol* 1990; **162**: 429–37.
6. Caritis SN, *et al*. Pharmacokinetics and pharmacodynamics of ritodrine after intramuscular administration to pregnant women. *Am J Obstet Gynecol* 1990; **162**: 1215–19.
7. Pacifici GM, *et al*. Sulphation and glucuronidation of ritodrine in human foetal and adult tissues. *Eur J Clin Pharmacol* 1993; **44**: 259–64.
8. Pacifici GM, *et al*. Ritodrine sulphation in the human liver and duodenal mucosa: interindividual variability. *Eur J Drug Metab Pharmacokinet* 1998; **23**: 67–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ritopar; ***Belg.***: Pre-Par; ***Braz.***: Miodrina; ***China***: Anpo (安宝); ***Gr.***: Miolene; Pre-Par; Yutopar; ***India***: Miolene; Yutopar; ***Indon.***: Yutopar; ***Ital.***: Miolene; ***Spain***: Pre-Par; ***Turk.***: Pre-Par; ***UK***: Yutopar†.

Pharmacopoeial Preparations

BP 2014: Ritodrine Injection; Ritodrine Tablets;

USP 36: Ritodrine Hydrochloride Injection; Ritodrine Hydrochloride Tablets.

Sulprostone *(USAN, rINN)*

CP-34089; 16-Phenoxy-ω-17,18,19,20-tetranor-prostaglandin E_2-methylsulfonylamide; SHB-286; Sulproston; Sulprostona; Sulprostoni; Sulprostonum; ZK-57671; Сульпростон.

(*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4-phenoxy-but-1-enyl]-5-oxocyclopentyl}-*N*-(methylsulphonyl)hept-5-enamide.

$C_{23}H_{31}NO_7S$=465.6

CAS — 60325-46-4.

ATC — G02AD05.

ATC Vet — QG02AD05.

UNII — 501Q5EQ1GM.

Uses and Administration

Sulprostone is a synthetic derivative of dinoprostone (prostaglandin E_2; p. 2134.1) that has uterine stimulant effects. It is used for dilatation of the cervix before surgical termination of pregnancy in the first trimester, for medical termination of pregnancy in the first or second trimester (p. 2131.3), and to empty the uterus in missed miscarriage, hydatidiform mole, and intra-uterine fetal death. It is also used to control postpartum haemorrhage (p. 2130.2) that has not responded to oxytocin.

Sulprostone is given by intravenous infusion. A dose of 500 micrograms over 3 to 6 hours is used for cervical dilatation in the first trimester. For medical termination of pregnancy in the first or second trimester, or to empty the uterus, sulprostone is infused at a rate of 100 micrograms/hour for up to 10 hours; if necessary the infusion rate may be increased to up to 500 micrograms/hour, to a maximum total dose of 1.5 mg in 24 hours. If termination is unsuccessful the course may be repeated once, 12 to 24 hours after the end of the first infusion.

To control postpartum haemorrhage, an initial infusion of 100 micrograms/hour is given. This may be increased to 500 micrograms/hour if necessary to control bleeding, then reduced to a maintenance dose of 100 micrograms/hour. A total dose of 1.5 mg in 24 hours should not be exceeded.

Sulprostone has also been given extra-amniotically and locally into the cervix. It has also been given by the intramuscular route, but this is no longer recommended.

Adverse Effects and Precautions

As for Dinoprostone, p. 2134.3 and p. 2136.1, respectively. In some countries, such as France, the licensed product information for sulprostone contra-indicates its use for dilatation of the cervix before first trimester surgical termination of pregnancy in smokers or those who have smoked in the last 2 years, and in women over 35 years of age. In these women, methods with a lower risk of cardiovascular adverse effects should be used.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the cardiovascular system. A 31-year-old woman died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone. She had

12 children, one previous abortion, and was a heavy cigarette smoker.[1] Four other deaths with sulprostone had not been associated with abortion. Other reported cases that did not result in death have included myocardial infarction in a 32-year-old woman given sulprostone for intrauterine fetal death,[2] and cardiac arrest in a 38-year-old woman, with no history of smoking, after sulprostone was given by both intramyometrial and intravenous bolus injection for postpartum haemorrhage;[3] in both cases the authors suggested that sulprostone had caused coronary artery spasm.

Inadvertent subcutaneous infusion of sulprostone was thought to have caused arterial spasm with pain and oedema in the arm of a woman being treated for postpartum haemorrhage; she recovered after treatment with iloprost infusion.[4]

1. Anonymous. A death associated with mifepristone/sulprostone. *Lancet* 1991; **337:** 969–70.
2. Fliers E, *et al.* A prostaglandin analogue as a probable cause of myocardial infarction in a young woman. *BMJ* 1991; **302:** 416.
3. Chen FG, *et al.* Cardiac arrest associated with sulprostone use during caesarean section. *Anaesth Intensive Care* 1998; **26:** 298–301.
4. de Koning YWCM, *et al.* Critical limb ischemia after accidental subcutaneous infusion of sulprostone. *Eur J Obstet Gynecol Reprod Biol* 1995; **61:** 171–3.

Effects on the nervous system. For a report of convulsions in epileptic patients given sulprostone, see under Dinoprostone, p. 2135.2.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including sulprostone, for termination of pregnancy or induction of labour, see under Dinoprostone, p. 2135.2.

Pulmonary oedema. A 35-year-old woman was given a sulprostone infusion, at a rate varying from 126 to 492 micrograms/hour, as part of the emergency management of postpartum haemorrhage;[1] her religious beliefs prohibited the use of blood products but she was given fluid replacement with lactated Ringer's solution and etherified starches and underwent procedures to control blood loss. However, during recovery, the patient developed pulmonary oedema that the authors suspected to be due to the infusion rate of sulprostone as well as the total dose given (about 600 micrograms).

1. Hagenaars M, *et al.* Pulmonary oedema after high infusion rate of sulprostone. *Br J Anaesth* 2009; **102:** 281–2.

Interactions

As for Dinoprostone, p. 2136.1. Sulprostone should not be given with oxytocin or methylergometrine because of the increased risk of tachycardia and coronary vasoconstriction; fatalities have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nalador; ***Fr.***: Nalador; ***Ger.***: Nalador; ***Hong Kong***: Nalador†; ***Hung.***: Nalador; ***Ital.***: Nalador; ***Neth.***: Nalador; ***Port.***: Nalador; ***Switz.***: Nalador; ***Thai.***: Nalador.

Pesticides and Repellents

Pediculosis, p. 2147
Scabies, p. 2148
Vector control, p. 2148

This chapter describes compounds used as pesticides and as insect repellents. The term pesticide covers fungicides, herbicides, insecticides (including acaricides), molluscicides, and rodenticides, among others. Most of the pesticides included here are used in clinical or veterinary practice or in vector control against human or animal disease. Some are used mainly in an agricultural or horticultural setting and are included because of their potential toxicity.

Pesticides can be absorbed during application, by consumption of treated or contaminated products or by accidental contamination, and they may be stored or retained in the tissues. International regulations and controls operate to reduce the risk to both public and user. Values for acceptable daily intakes of pesticides have been published by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) through the WHO Technical Report series of publications or through *Pesticides Residues in Food: yearly evaluations*, FAO Plant Production and Protection Papers, Rome.

Classification of the main pesticides included in this chapter is given in Table 1, below.

The **fungicides** included in this chapter are some of those used in the management of plant disease.

Herbicides are used for weed control both in the domestic setting and professionally in agriculture and horticulture. Those included here may be toxic and have been associated with cases of poisoning.

Insect repellents can help to avoid insect bites and the unpleasant reactions they may produce. Perhaps more importantly, the correct use of insect repellents plays a major role in personal protection against some communicable diseases transmitted by insect vectors. Examples are babesiosis (ticks), Lyme disease (ticks), malaria (mosquitoes), relapsing fevers (lice and ticks), spotted fevers (ticks), and typhus fever (fleas, lice, and mites). Some compounds, such as diethyltoluamide, dimethyl phthalate, and icaridin, are effective as repellents while others, such as benzyl benzoate and some of the pyrethroids, are effective both as repellents and as insecticides.

Insecticides have many applications. They are used in the treatment of ectoparasitic infections such as pediculosis (lice infections) (below) and in the vector control (p. 2148.1) of some communicable diseases that are spread by insects. Acaricides are used to treat scabies (mite infections) (see, p. 2148.1) and are included within the broad classification of insecticides, although acari (mites) are not, technically, insects. Insecticides are also widely used in veterinary practice and in agriculture and horticulture.

The insecticides used in veterinary practice are often classified as topical or systemic ectoparasiticides. Topical ectoparasiticides are applied topically to the host animal (such as dogs or cats) to kill its ectoparasites (such as fleas). In the case of systemic ectoparasiticides the term 'systemic' refers to the ingestion of the insecticide by the ectoparasite from the host's blood; the insecticide may be present in the host's blood either as a result of absorption through the skin after topical application or after systemic dosage.

Molluscicides are used in agriculture or horticulture or in the domestic garden to control snail and slug pests. Additionally, molluscicides such as niclosamide (described in the Anthelmintics chapter on p. 161.2) are used against the freshwater snail vector *Bulinus* in the control of schistosomiasis.

Rodenticides may be used to exterminate rats and mice, which may be vectors for diseases such as leptospirosis, plague, rat-bite fever, and some haemorrhagic fevers. Many rodenticides are anticoagulants. Warfarin (p. 1526.3) is a commonly used rodenticide.

Table 1. Classification of pesticides.

Fungicides	Benomyl, cicloheximide, copper naphthenate, hexachlorobenzene, pentachlorophenol, pyraclostrobin
Herbicides	Dichlorophenoxyacetic acid, dinitro-*o*-cresol, dinitrophenol, diquat, glyphosate, paraquat, pentachlorophenol, trichlorophenoxyacetic acid
Insect repellents	Butopyronoxyl, dibutyl phthalate, diethyltoluamide, dimethyl phthalate, dioctyl adipate, ethohexadiol, piperonal
Insecticides	
Carbamate	Bendiocarb, carbaryl, carbosulfan, methomyl, propoxur
Chlorinated	Chlordane, clofenotane, dieldrin, endosulfan, endrin, heptachlor, lindane, methoxychlor
Organophosphorus	Azamethiphos, bromophos, chlorpyrifos, clofenvinfos, coumafos, cythioate, dichlorvos, dimethoate, dimpylate, dioxation, ethion, famphur, fenitrothion, fenthion, heptenophos, iodofenphos, malathion, naled, parathion, phosmet, phoxim, pirimiphos-methyl, propetamphos, pyraclofos, temefos
Pyrethroid	Alpha-cypermethrin, bioallethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esdepallethrine, etofenprox, fenvalerate, flumethrin, permethrin, phenothrin, pyrethrum flower, resmethrin, tetramethrin
Miscellaneous	Amitraz, benzyl benzoate, chloropicrin, copper oleate, cymiazole, cyromazine, diflubenzuron, emamectin, ethylene dibromide, ethylene dichloride, fipronil, fluazuron, fluvalinate, lufenuron, methoprene, methyl bromide, pyriproxyfen, rotenone, sulfiram, triflumuron
Molluscicides	Endod, metaldehyde, pentachlorophenol
Rodenticides	Aluminium phosphide, antu, brodifacoum, bromadiolone, chloralose, chlorophacinone, coumatetralyl, difenacoum, diphenadione, flocoumafen, fluoroacetamide, norbormide, red squill, sodium fluoroacetate

The symbol † denotes a preparation no longer actively marketed

Clinical Uses of Pesticides and Repellents

Pediculosis

Two species of louse cause pediculosis[1-3] in man; these are *Pediculus humanus* with its two varieties, *Pediculus humanus capitis* (the head louse) and *Pediculus humanus humanus* (the body louse), and *Pthirus pubis* (*Phthirus pubis*) (the pubic or crab louse). Unlike the head louse, the body louse is an important vector for infections such as epidemic typhus (p. 212.3), trench fever (p. 210.2), and relapsing fever (p. 202.2).

Insecticides used in the treatment of head lice include the organophosphate malathion, and some pyrethroids such as bioallethrin, permethrin, phenothrin, and tetramethrin. The carbamate, carbaryl, is also effective, although there has been some concern over a theoretical risk of carcinogenicity. Lindane has been used but is no longer recommended as a first-line treatment due to its neurotoxicity and resistance. To be effective, insecticide products need to be applied correctly; a quantity of 50 to 100 mL should be applied thoroughly to the hair from hair root to the tip and left on for 8 to 12 hours. Insecticide products (with the exception of spinosad, see below) kill only adult lice and not the ova (nits), therefore treatment is usually repeated 7 days later. Close contacts should be screened and if infected with living lice should also receive treatment. The insecticide spinosad, derived from the fermentation of *Saccharopolyspora spinosa*, is also used and has been effective in treating permethrin-resistant head lice.[4] Unlike other insecticides, it only needs to be left on the hair for 10 minutes; it is also ovicidal and a second application is only needed if live lice are seen after 7 days.

Resistance has been reported to many of the currently used insecticides. Resistance is considered to be most likely to pyrethroids, intermediate to malathion, and least likely to carbaryl. In the UK the policy of rotating insecticides on a district-wide basis in order to overcome the development of resistance is considered outdated. The current recommendation in the case of suspected resistance and treatment failure is to use an insecticide from a different class for the next course. Lotions are preferred to shampoos for head lice since contact time with the insecticide is longer and treatment is thus more effective. A head louse repellent containing piperonal is available. *Non-insecticide* treatments include a 4% dimeticone lotion[5,6] (see p. 2209.3), 5% benzyl alcohol lotion (see p. 1739.3), 0.5% ivermectin lotion (see p. 155.1), and wet-combing (also called 'bug-busting') with conditioner.[6] Dimeticone is thought to act by disrupting the ability of the lice to manage their water balance. Dimeticone and benzyl alcohol are applied similarly to the insecticide products, although some products have a shorter application time; 2 treatments are also required to kill any newly hatched nymphs. Repeat treatment is not needed with ivermectin lotion. A dry-on, suffocation-based pediculicide has also been claimed to be effective,[7,8] although some have questioned the claims.[9] (Benzyl alcohol is also thought to act by asphyxiation.[10]) Oral ivermectin has been used for refractory infestations.[11] Six methods of delivering hot air at a minimum mean temperature of 55 degrees, for 30 minutes, have been tried and all of them resulted in a high egg mortality rate (greater than or equal to 88%), but showed more variable success in killing the hatched head lice.[12] Guidelines for the management of head lice are available in the UK[13] and in the USA a clinical report on head lice provides guidance and recommendations.[14]

Infestations of crab lice and body lice respond to the same insecticides as head lice. Guidelines for the management of pubic lice are available in the UK.[15] Aqueous solutions are generally preferred to alcoholic for crab louse infestations, since the latter may irritate excoriated skin and genitalia.

Malathion or permethrin have also been suggested for treatment of infestation of the eyelashes and brows with pubic lice (pthiriasis or phthiriasis palpebrarum). Other treatments have included the application of a thick layer of yellow soft paraffin or application of yellow mercuric oxide 1% eye ointment twice daily for about 7 or 8 days or a single application of fluorescein eye drops.

Body louse infestations in the developed world are mainly seen in homeless individuals, and often respond to the provision of opportunities for simple hygiene. Clothing and bed linen of persons with body lice should be washed at high temperature or dry cleaned or treated with insecticides.

There is some evidence that oral ivermectin may be effective in killing body lice.

Topical or systemic antimicrobials should be given as necessary for secondary infections.

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12. Goates BM, *et al.* An effective nonchemical treatment for head lice: a lot of hot air. *Pediatrics* 2006; **118:** 1962–70.
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15. Clinical Effectiveness Group, British Association of Sexual Health and HIV. United Kingdom national guideline on the management of *Phthirus pubis* infestation (2007). Available at: http://www.bashh.org/documents/28/28.pdf (accessed 28/05/10)

Scabies

Scabies is a parasitic infection of the skin by the mite *Sarcoptes scabiei*. The main symptom is pruritus, which is caused by an allergic reaction to the parasite and may not occur until several weeks after infection for the first time. Subsequent infections usually result in pruritus after a few days. Pruritus may persist for some months after effective treatment with an acaricide, but is not necessarily an indication for further acaricidal treatment; rather, antipruritics should be used. A severe crusted form (Norwegian scabies) may occur rarely, particularly in immunocompromised or incapacitated patients.

Treatment is with the acaricides permethrin or malathion applied, preferably as aqueous lotions, to clean, cool, dry skin over the entire body and left on for 8 to 24 hours, depending upon the preparation. The preparation should be reapplied to the hands whenever they are washed during this period. In adults, it is not usually necessary to treat the face and scalp, but these areas should be treated in young children or patients with atypical or crusted scabies. A single treatment may be effective, but treatment is usually repeated after 7 to 10 days if necessary. Other drugs used topically in the treatment of scabies include benzyl benzoate, crotamiton, lindane, and sulfur; sulfiram is used with benzyl benzoate. Oral ivermectin is an effective alternative. Close family and personal contacts should be treated at the same time and all clothes, towels, and bedding used by the infected person 2 days before treatment should be washed in hot water and dried in a hot dryer.

In addition to treatment with an acaricide, symptomatic treatment of the itching with crotamiton, calamine lotion, or systemic antihistamines or corticosteroids may be required.

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Vector control

Many pests are involved in the transmission of communicable diseases, and vector control[1,2] is an important part of the fight against such diseases. Insecticides are used in the control of:

- filariasis (p. 146.3) (*Aedes*, *Anopheles*, *Culex*, and *Mansonia* mosquitoes)[3]
- leishmaniasis (p. 922.1) (*Phlebotomus* or *Lutzomyia* sandflies)[4]
- malaria (p. 644.1) (*Anopheles* mosquitoes)[5-8]
- dengue fever (see Haemorrhagic Fevers, p. 952.1) (*Aedes* mosquitoes)[9,10]
- onchocerciasis (p. 147.2) (*Simulium* blackflies)[11]
- African trypanosomiasis (p. 925.2) (*Glossina* tsetse flies)[12]
- American trypanosomiasis (p. 925.3) (*Triatoma* bugs)[13]

The insecticide temefos is useful in dracunculiasis (p. 145.1) (crustacean host to the guinea worm larvae). In some cases, as in filariasis or onchocerciasis, the insecticides used act mainly against the larval stage of the insect vector, whereas in other situations, as in malaria, activity is against the adult insect; in trypanosomiasis, activity is directed against both adult and immature stages. The majority of the experience gained in insecticidal vector control has probably been in malaria, and, for instance, a positive effect seen in the control of leishmaniasis has been considered to be mainly a byproduct of the concomitant malaria control programmes.

Insect repellents can provide personal protection against many insect vectors. For example, in malaria, insect repellents as well as the use of insecticides are important in preventing mosquito bites.

Molluscicides are used in the control of schistosomiasis (p. 148.1) (*Bulinus* snails).[14]

Rodenticides are also extremely valuable in the vector control of some diseases such as leptospirosis (p. 189.3), plague (p. 199.3), rat-bite fever (p. 174.2), and some haemorrhagic fevers (p. 952.1).

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Aluminium Phosphide

Aluminum Phosphide; Fosfuro de aluminio; Фосфористый Алюминий; Фосфид Алюминия.
AlP=57.96
CAS — 20859-73-8 (aluminium phosphide); 7803-51-2 (phosphine); 1314-84-7 (zinc phosphide).
UNII — E23DR6L595.

Profile

Aluminium phosphide is used for the fumigation of grain and as a rodenticide. It releases phosphine (PH_3) in the presence of moisture and this accounts for its pesticidal activity. Phosphine gas has a garlic-like odour repulsive to man and domestic animals but apparently not to *rats*. Zinc phosphide is used similarly.

References[1-9] to poisoning associated with aluminium phosphide.

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Amitraz *(BAN, USAN, pINN)*

Amitratsi; Amitrazum; U-36059; Амитраз.
N,N'-[(Methylimino)dimethylidyne]di-2,4-xylidine.
$C_{19}H_{23}N_3$=293.4
CAS — 33089-61-1.
ATC Vet — QP53AD01.
UNII — 33IAH5017S.

Pharmacopoeias. In *BP(Vet)*. Also in *US* for veterinary use only.

BP(Vet) 2014: (Amitraz). A white to buff powder. Practically insoluble in water; decomposes slowly in alcohol; freely soluble in acetone.

Profile

Amitraz is used as a topical ectoparasiticide in veterinary practice. It is effective against various lice, mites, and ticks.

References[1-12] to poisoning with amitraz.

1. Jorens PG, *et al.* An unusual poisoning with the unusual pesticide amitraz. *Hum Exp Toxicol* 1997; **16:** 600–1.
2. Aydin K, *et al.* Amitraz poisoning in children: clinical and laboratory findings of eight cases. *Hum Exp Toxicol* 1997; **16:** 680–2.
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9. Avsarogullari L, *et al.* Acute amitraz poisoning in adults: clinical features, laboratory findings, and management. *Clin Toxicol* 2006; **44:** 19–23.
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Azamethiphos *(BAN)*

Azametifós; CGA-18809; OMS-1825; Азаметифос.
S-[(6-Chloro-2,3-dihydro-2-oxo-1,3-oxazolo[4,5-*b*]pyridin-3-yl)methyl] *O,O*-dimethyl phosphorothioate.
$C_9H_{10}ClN_2O_5PS$=324.7
CAS — 35575-96-3.
ATC Vet — QP53AF17.
UNII — 9440R8149U.

Profile

Azamethiphos is an organophosphorus insecticide (p. 2158.3) used in veterinary practice for the control of sea-lice infestation in salmon and for the control of ectoparasites in the environment.

Bendiocarb

Бендиокарб.
2,3-Isopropylidenedioxyphenyl methylcarbamate.
$C_{11}H_{13}NO_4$=223.2
CAS — 22781-23-3.
ATC Vet — QP53AE03.
UNII — QFH0ZU0A5U.

Profile

Bendiocarb is a carbamate insecticide (p. 2149.3) used in veterinary practice for the control of ectoparasites and for agricultural and household use.

Benomyl

Benomilo; Беномил.
Methyl 1-(butylcarbamoyl)benzimidazol-2-ylcarbamate.
$C_{14}H_{18}N_4O_3$=290.3
CAS — 17804-35-2.
UNII — TLW21058F5.

Profile

Benomyl is a fungicide used for the treatment and control of fungal plant diseases.

References.

1. WHO. Benomyl. *Environmental Health Criteria 148*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc148.htm (accessed 23/04/04)
2. WHO. Benomyl health and safety guide. *IPCS Health and Safety Guide 81.* Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/hsg/hsg/hsg81_e.htm (accessed 23/04/04)

Toxicity. Although experimental evidence in *animals* has suggested a possible link between benomyl and congenital eye defects (anophthalmia) the association could not be confirmed in humans.[1-4]

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Benzyl Benzoate

Bencilo, benzoato de; Bensylbensoat; Bentsyylibentsoaatti; Benzil Benzoat; Benzil-benzoát; Benzilbenzoatas; Benzoato de bencilo; Benzoato de Benzilo; Benzoesäurebenzylester; Benzyl Benz.; Benzylbenzoat; Benzyl-benzoát; Benzyle, benzoate de; Benzylis Benzoas; Benzylu benzoesan; Бензилбензоат.

$C_6H_5.CO.O.CH_2.C_6H_5$=212.2

CAS — 120-51-4.

ATC — P03AX01.

ATC Vet — QP53AX11.

UNII — N863NB338G.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Benzyl Benzoate). Colourless or almost colourless crystals, or a colourless or almost colourless oily liquid. F.p. is not below 17 degrees. Practically insoluble in water; miscible with alcohol, with dichloromethane, and with fatty and essential oils. Store in well-filled airtight containers. Protect from light.

USP 36: (Benzyl Benzoate). A clear, colourless, oily liquid with a slight aromatic odour. Practically insoluble in water and in glycerol; miscible with alcohol, with chloroform, and with ether. Store at a temperature not exceeding 40 degrees in well-filled airtight containers. Protect from light.

Uses and Administration

Benzyl benzoate is an acaricide used in the treatment of scabies (p. 2148.1) although other treatments are generally preferred. A 25% emulsion is applied to the whole body, usually from the neck down (although the *BNF* considers that application should be extended to the scalp, neck, face, and ears). If the application is thorough, one treatment may suffice, although the possibility of failure is lessened by a second application within 5 days. Alternatively, three applications at 12-hour intervals, without bathing, may be made, followed by bathing 12 hours after the last application. The *BNF* recommends one application to the whole body, repeated, without bathing, on the next day, and washed off 24 hours later; a third application may sometimes be necessary. Benzyl benzoate is not generally recommended for infants and children, but if used the application should be diluted to minimise the risk of irritation, although this also reduces efficacy.

Benzyl benzoate has also been used as a pediculicide.

Benzyl benzoate is also used as a solubilising agent.

Adverse Effects and Treatment

Benzyl benzoate is irritant to the eyes and mucous membranes and it may be irritant to the skin. Hypersensitivity reactions have been reported. If ingested, benzyl benzoate may cause stimulation of the CNS and convulsions. Systemic symptoms have been reported on excessive topical use. For poisoning associated with topical use the skin should be washed. Appropriate symptomatic measures should also be instituted.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ascabiol; Benzemul; ***Braz.***: Acarsan; Bencocan; Benzoax; Benzotisan; Miticocan; Parasimed; Pruridol; Sanasar; Sarnerico; Sarnilab†; Sarnodex; Scabenzil; Scabioid; Zilaben; ***Ger.***: Antiscabiosum; ***Gr.***: Benzogal; ***Hong Kong***: Academ†; Antiscab†; Antiscabio†; Benz Application†; Wail Treatment†; ***India***: Dermin; ***Israel***: Scabiex; ***Ital.***: Mom Lozione Preventiva; ***Mex.***: Ansar†; Hastilan; ***Pol.***: Novoscabin; ***Port.***: Acarilbial; Piozil†; ***S.Afr.***: Ascabiol; ***Turk.***: Neoskabi; Scabin; ***UK***: Ascabiol†; ***Venez.***: Benzalcor; Benzo-Bencil; Niostal.

Multi-ingredient Preparations. ***Arg.***: Anusol Duo S; Anusol-A; Bencil Scab; Detebencil; Detebencil; Hexabencil; Kinderval Max; Perbel; Permecil; Scabioderm; ***Austral.***: Anusol; ***Belg.***: Pulmex Baby; Pulmex†; ***Braz.***: Anusol-HC; ***Fr.***: Ascabiol; ***Hung.***: Novascabin; ***Irl.***: Anugesic-HC; Anugesic-HC; Anusol-HC; Sudocrem; ***Ital.***: Antiscabbia CM; Dekar 2†; Mom Zanzara; Prurex; Skab 2†; ***Malaysia***: Anucare; Anusol†; ***NZ***: Anusol; ***Pol.***: Cetriscabin†; ***S.Afr.***: Anugesic†; ***Singapore***: Anusol; Anusol; Jacutin; ***Spain***: Tulgrasum Cicatrizante; ***Swed.***: Tenutex; ***Thai.***: Anusol†; ***UK***: Anugesic-HC†; Anugesic-HC; Anusol-HC, Plus HC; Sudocrem; ***Ukr.***: Sudocrem (Судокрем); ***USA***: Anumed HC; Anumed; Hemril; ***Venez.***: Kertyol.

Pharmacopoeial Preparations
BP 2014: Benzyl Benzoate Application;
USP 36: Benzyl Benzoate Lotion.

Bioallethrin *(BAN)*

Allethrin I; Bioaletrina; Depallethrin; Биоаллетрин.

(*RS*)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{19}H_{26}O_3$=302.4

CAS — 584-79-2.

ATC — P03AC02.

ATC Vet — QP53AC02.

UNII — G79DM7O471.

Profile

Bioallethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used topically, with the synergist piperonyl butoxide (p. 2160.2), in the treatment of pediculosis (p. 2147.3). It is also used in anti-mosquito devices and for the control of household insect pests.

References.
1. WHO. Allethrins. *Environmental Health Criteria 87*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc87.htm (accessed 23/04/04)
2. WHO. Allethrins health and safety guide. *IPCS Health and Safety Guide 24*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg024.htm (accessed 23/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cinq sur Cinq; Mousticologne†; ***UK***: Actomite.

Multi-ingredient Preparations. ***Arg.***: Limpacid; Para Piojicida; Scabioderm; ***Austral.***: Paralice; ***Belg.***: Para; ***Fr.***: Para Special Poux; ***Ger.***: Jacutin; Spregal†; ***Israel***: Monocide†; ***Ital.***: Cruzzy; ***Neth.***: Para-Speciaal†.

Brodifacoum

Brodifacum; WBA-8119; Бродифакум.

3-[3-(4′-Bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin.

$C_{31}H_{23}BrO_3$=523.4

CAS — 56073-10-0.

UNII — A25P3CP5S7.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides, including brodifacoum, bromadiolone (below), chlorophacinone (p. 2150.3), and difenacoum (p. 2153.2).

Profile

Brodifacoum is an anticoagulant rodenticide. It is reported to be effective in warfarin-resistant strains of rodents.

References.
1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 23/04/04)
2. WHO. Brodifacoum health and safety guide. *IPCS Health and Safety Guide 93*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg093.htm (accessed 23/04/04)

Toxicity. Brodifacoum, a second-generation anticoagulant rodenticide, inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with brodifacoum.[2-10]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Watts RG, *et al.* Accidental poisoning with a superwarfarin compound (brodifacoum) in a child. *Pediatrics* 1990; **86:** 883–7.
3. Ross GS, *et al.* An acquired hemorrhagic disorder from long-acting rodenticide ingestion. *Arch Intern Med* 1992; **152:** 410–12.
4. Kruse JA, Carlson RW. Fatal rodenticide poisoning with brodifacoum. *Ann Emerg Med* 1992; **21:** 331–6.
5. Tecimer C, Yam LT. Surreptitious superwarfarin poisoning with brodifacoum. *South Med J* 1997; **90:** 1053–5.
6. Corke PJ. Superwarfarin (brodifacoum) poisoning. *Anaesth Intensive Care* 1997; **25:** 707–9.
7. La Rosa FG, *et al.* Brodifacoum intoxication with marijuana smoking. *Arch Pathol Lab Med* 1997; **121:** 67–9.
8. Miller MA, *et al.* Rapid identification of surreptitious brodifacoum poisoning by analysis of vitamin K-dependent factor activity. *Am J Emerg Med* 2006; **24:** 383.
9. Olmos V, López CM. Brodifacoum poisoning with toxicokinetic data. *Clin Toxicol* 2007; **45:** 487–9.
10. Kapadia P, Bona R. Acquired deficiency of vitamin K-dependent clotting factors due to brodifacoum ingestion. *Conn Med* 2008; **72:** 207–9.

Bromadiolone

Bromadiolona; Бромадиолон.

3-[3-(4′-Bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin.

$C_{30}H_{23}BrO_4$=527.4

CAS — 28772-56-7.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides including brodifacoum (above), bromadiolone, chlorophacinone (p. 2150.3), and difenacoum (p. 2153.2).

Profile

Bromadiolone is an anticoagulant rodenticide.

References.
1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 23/04/04)
2. WHO. Bromadiolone health and safety guide. *IPCS Health and Safety Guide 94*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg094.htm (accessed 23/04/04)

Toxicity. Bromadiolone, a second-generation anticoagulant rodenticide, inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with bromadiolone.[2-5]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Greeff MC, *et al.* "Superwarfarin" (bromodialone) poisoning in two children resulting in prolonged anticoagulation. *Lancet* 1987; **ii:** 1269.
3. Chow EY, *et al.* A case of bromadiolone (superwarfarin) ingestion. *CMAJ* 1992; **147:** 60–2.
4. Grobosch T, *et al.* Acute bromadiolone intoxication. *J Anal Toxicol* 2006; **30:** 281–6.
5. Lo VM, *et al.* Bromadiolone toxicokinetics: diagnosis and treatment implications. *Clin Toxicol* 2008; 1–8.

Bromophos

Bromofos; Bromofós; OMS-658; Бромофос.

O-4-Bromo-2,5-dichlorophenyl *O,O*-dimethyl phosphorothioate.

$C_8H_8BrCl_2O_3PS$=366.0

CAS — 2104-96-3.

ATC Vet — QP53AF11.

Profile

Bromophos is an organophosphorus insecticide (p. 2158.3) used in veterinary practice for the control of ectoparasites in the environment. It has also been used as an agricultural insecticide.

Butopyronoxyl

Butopiroxinilo; Indalona; Indalone; Бутопироноксил.

Butyl 3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-pyran-6-carboxylate.

$C_{12}H_{18}O_4$=226.3

CAS — 532-34-3.

UNII — 415PG5VZ0V.

Profile

Butopyronoxyl has been used as an insect repellent.

Carbamate Insecticides

Insecticidas del grupo de los carbamatos.

Description. The carbamate insecticides are *N*-substituted esters of carbamic acid.

References.
1. WHO. Carbamate pesticides: a general introduction. *Environmental Health Criteria 64*. Geneva: WHO,1986. Available at: http://www.inchem.org/documents/ehc/ehc/ehc64.htm (accessed 24/07/08)

Adverse Effects

As for Organophosphorus Insecticides, p. 2158.3.

The carbamates are cholinesterase inhibitors, differing from the organophosphorus insecticides in that the inhibition they produce is generally less intense and more rapidly reversible. In addition, they do not appear to enter the CNS as readily and severe central effects are therefore uncommon.

Treatment of Adverse Effects

If substantial amounts of carbamate insecticides have been ingested the use of gastric lavage should be considered if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Treatment is largely symptomatic and supportive and includes atropine for muscarine effects, although this may not always be necessary due to the rapidly reversible nature of the cholinesterase inhibition produced. The use of pralidoxime is controversial, see Carbamate Poisoning, under Pralidoxime, p. 1571.3.

References.
1. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 21/07/08)
2. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.
3. Rosman Y, *et al.* Carbamate poisoning: treatment recommendations in the setting of a mass casualties event. *Am J Emerg Med* 2009; **27:** 1117–24.

Carbaryl *(BAN)*

Caprolin; Carbaril (pINN); Carbarilo; Carbarilum; Karbaril; OMS-29; Карбарил.
1-Naphthyl methylcarbamate.
$C_{12}H_{11}NO_2$=201.2
CAS — 63-25-2.
ATC Vet — QP53AE01.
UNII — R890C8J3N1.

Pharmacopoeias. In *Br.*

BP 2014: (Carbaryl). A white to off-white or light grey powder which darkens on exposure to light. Very slightly soluble in water; soluble in alcohol and in acetone. Store at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Carbaryl is a carbamate insecticide (p. 2149.3). It is used as a 0.5 or 1.0% lotion or shampoo in the treatment of head and pubic pediculosis (p. 2147.3). Lotions are generally preferred to shampoos as the contact time is longer. Aqueous lotions are preferred to treat pubic lice because alcoholic lotions are irritant to excoriated skin and the genitalia; aqueous lotions may also be preferable in asthmatic subjects or children to avoid alcoholic fumes. Skin or hair treated with an alcohol-based preparation should be allowed to dry naturally.

Carbaryl is also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide.

References.
1. WHO. Carbaryl health and safety guide. *IPCS Health and Safety Guide 78.* Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/hsg/hsg/hsg78_e.htm (accessed 23/04/04)
2. WHO. Carbaryl. *Environmental Health Criteria 153.* Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/ehc/ehc/ehc153.htm (accessed 23/04/04)

Adverse Effects and Treatment

As for Carbamate Insecticides, p. 2149.3. Carbaryl may be absorbed after ingestion, inhalation, or skin contamination.

Carbaryl has been reported to produce neoplasms in *mice* and *rats* and in late 1995 the UK DoH advised that it would be prudent to consider carbaryl as a potential human carcinogen; its medicinal use was limited to prescription only. However, the DoH emphasised that the risk was a theoretical one and that any risk from the intermittent use of head lice preparations was likely to be very small.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Lysatox; ***Irl.***: Suleo-C†; ***Israel***: Hafif; ***UK***: Carylderm.

Pharmacopoeial Preparations
BP 2014: Carbaryl Lotion.

Carbosulfan

Carbosulfán; Карбосульфан.
2,3-Dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio) methylcarbamate.
$C_{20}H_{32}N_2O_3S$=380.5
CAS — 55285-14-8.
UNII — V1DGN4AK6G.

Profile

Carbosulfan is a carbamate insecticide (p. 2149.3) used in agriculture and for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2).

Chloralose *(rINN)*

Alphachloralose; Chloralosane; α-Chloralose; Chloralosum; Cloralosa; α-Cloralosa; Glucochloral; Хлоралоза.
(*R*)-1,2-*O*-(2,2,2-Trichloroethylidene)-α-D-glucofuranose.
$C_8H_{11}Cl_3O_6$=309.5
CAS — 15879-93-3.
UNII — 238BZ29MUE.

Profile

Chloralose has general properties similar to those of cloral hydrate (p. 1055.2), of which it is a derivative. It is used as a rodenticide. It was formerly used for its hypnotic properties.

Chlordane

Chlordan; Clordán; Clordano; Хлордан.
1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene.
$C_{10}H_6Cl_8$=409.8
CAS — 57-74-9.
UNII — A9RLM212CY.

Profile

Chlordane is a chlorinated insecticide (below). Its use is limited, or even prohibited, in some countries because of toxicity due to its persistent nature.

References.
1. Kutz FW, *et al.* A fatal chlordane poisoning. *J Toxicol Clin Toxicol* 1983; **20:** 167–74.
2. Olanoff LS, *et al.* Acute chlordane intoxication. *J Toxicol Clin Toxicol* 1983; **20:** 291–306.
3. WHO. Chlordane. *Environmental Health Criteria 34.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc34.htm (accessed 23/04/04)
4. WHO. Chlordane health and safety guide. *IPCS Health and Safety Guide 13.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg013.htm (accessed 23/04/04)

Chlorinated Insecticides

Insecticidas clorados.

Uses

The chlorinated or organochlorine insecticides were widely used but, because of persistence in man, many have been banned or restricted.

References.
1. WHO. Polychlorinated biphenyls and terphenyls. *Environmental Health Criteria 140.* Geneva: WHO,1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc140.htm (accessed 28/05/04)
2. WHO. Polychlorinated biphenyls (PCBs) and polychlorinated terphenyls (PCTs) health and safety guide. *IPCS Health and Safety Guide 68.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg68.htm (accessed 28/05/04)

Adverse Effects

Chlorinated or organochlorine insecticides form a very wide group and the toxicity of individual members varies considerably. In general these insecticides produce symptoms consistent with CNS stimulation. They may be absorbed through the respiratory and gastrointestinal tracts and through the skin.

Symptoms of acute poisoning include nausea and vomiting, paraesthesia, giddiness, tremors, convulsions, coma, and respiratory failure. Liver, kidney, and myocardial toxicity have been reported. Effects on the blood include agranulocytosis and aplastic anaemia. Symptoms may be complicated by the effects of the solvent.

Chlorinated insecticides have been reported to enhance microsomal hepatic enzyme activity. Skin reactions can occur after contact.

Polychlorinated biphenyl (PCB) and terphenyl compounds were formerly used as insecticides in many countries. They accumulate in body fat and are not readily excreted, although they are distributed into breast milk and possibly cross the placenta; because of this and because of accidental contamination they remain a cause for concern. The related polybrominated biphenyl compounds (PBB), which have no insecticidal uses, have also been absorbed by humans after accidental contamination of the food chain.

Some chlorinated insecticides have weak oestrogenic effects; it has been proposed that exposure may increase the risk of breast cancer.

Treatment of Adverse Effects

If chlorinated insecticides have been ingested, gastric lavage or activated charcoal may be considered if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Treatment is largely symptomatic and supportive with treatment of CNS stimulation such as hyperactivity and convulsions.

References.
1. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 24/07/08)
2. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.

Chlorophacinone

Clorofacinona; LM-91; Хлорфацинон.
2-[2-(4-Chlorophenyl)-2-phenylacetyl]indane-1,3-dione.
$C_{23}H_{15}ClO_3$=374.8
CAS — 3691-35-8.
UNII — 34Y6E0063Y.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides, including brodifacoum, (p. 2149.2), bromadiolone, (p. 2149.3) chlorophacinone, and difenacoum (p. 2153.2).

Profile

Chlorophacinone is an indanedione derivative used as an anticoagulant rodenticide. It is also reported to uncouple oxidative phosphorylation with consequent stimulation of cellular metabolism which may contribute to its toxicity.

References.
1. Burucoa C, *et al.* Chlorophacinone intoxication: biological and toxicological study. *J Toxicol Clin Toxicol* 1989; **27:** 79–89.
2. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 28/05/04)
3. Lagrange F, *et al.* Toxicological management of chlorophacinone poisoning. *Acta Clin Belg Suppl* 1999; **1:** 13–16.
4. Papin F, *et al.* Lethal paradoxical cerebral vein thrombosis due to suspicious anticoagulant rodenticide intoxication with chlorophacinone. *Forensic Sci Int* 2007; **166:** 85–90.

Chloropicrin

Cloropicrina; Nitrochloroform; Nitrocloroformo; Nitrotriclorometano; Хлорпикрин.
Trichloronitromethane.
CCl_3NO_2=164.4
CAS — 76-06-2.
UNII — I4JTX7Z7U2.

Profile

Chloropicrin is a lachrymatory agent with an intense odour. It is intensely irritating to the skin and mucous membranes. It is an insecticide and is used for fumigating stored grain and soil. Chloropicrin is also added to other fumigants as a warning gas.

Chlorpyrifos *(BAN)*

Clorpirifós; Хлорпирифос.
O,O-Diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate.
$C_9H_{11}Cl_3NO_3PS$=350.6
CAS — 2921-88-2.
UNII — JCS581644W.

Profile

Chlorpyrifos is an organophosphorus insecticide (p. 2158.3) used in agriculture.

Cycloheximide *(rINN)*

Cicloheximida; Cycloheximidum; Cycloheximide (USAN); Cycloheximide; U-4527; Циклогексимид.
3-[(2*R*)-2-[(1*S*,3*S*,5*S*)-3,5-Dimethyl-2-oxocyclohexyl]-2-hydroxyethyl]glutarimide.
$C_{15}H_{23}NO_4$=281.4
CAS — 66-81-9.
UNII — 98600C0908.

Profile

Cycloheximide is an antimicrobial substance produced by strains of *Streptomyces griseus.* It has antifungal properties and has been used for the treatment and control of certain mycotic plant diseases.

Clofenotane *(rINN)*

Chlorofenotano; Chlorophenothane; Chlorphenothanum; Cloténotane; Clofenotano; Clofenotanum; Clorofenotano; DDT; Dichlorodiphenyltrichloroethane; Dichophanum; Dicophane; Klofenotaani; Klofenotan; Клофенотан.
1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane.
$C_{14}H_9Cl_5$=354.5
CAS — 50-29-3.
ATC — P03AB01.
ATC Vet — QP53AB01.
UNII — CIW5S16655.

Pharmacopoeias. In *It.*

Uses

Clofenotane is a chlorinated insecticide (p. 2150.2). It is a stomach and contact poison and retains its activity for long periods under a variety of conditions. It is effective against disease vectors such as fleas, lice, and mosquitoes and has been applied topically for pediculosis (p. 2147.3) and scabies (p. 2148.1), although more suitable alternatives exist.

Because of the extreme persistence of clofenotane, concern over its effect in the environment, and the problem of resistance, the widespread use of clofenotane is now generally discouraged. It is no longer used in some countries while in others its use is limited.

Despite reservations regarding the use of clofenotane for vector control, many countries have relied on it for the control of both malaria and visceral leishmaniasis. WHO has concluded[1,2] that clofenotane might be used provided:

- that it was used only for indoor spraying
- that it was known to be effective
- that it was manufactured to WHO's specifications
- that the necessary safety precautions were taken in its use and disposal

However, they recommended further investigation of the effects of clofenotane in breast milk and of suspected carcinogenicity, as well as clarification of the significance of the reduced density of muscarinic receptors caused by clofenotane.

1. WHO. WHO expert committee on malaria: twentieth report. *WHO Tech Rep Ser 892* 2000. Available at: http://libdoc.who.int/trs/WHO_TRS_892.pdf (accessed 21/07/08)
2. WHO Global Malaria Programme. Indoor residual spraying: use of indoor residual spraying for scaling up global malaria control and elimination 2006. Available at: http://malaria.who.int/docs/IRSposition.pdf (accessed 21/04/08)

Adverse Effects and Treatment

As for Chlorinated Insecticides, p. 2150.2.

References.

1. WHO. DDT and its derivatives. *Environmental Health Criteria 9*. Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc009.htm (accessed 28/05/04)
2. WHO. DDT and its derivatives—environmental aspects. *Environmental Health Criteria 83*. Geneva: WHO,1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc83.htm (accessed 28/05/04)

Carcinogenicity. Some small epidemiological studies have suggested that certain organochlorines, namely 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), a metabolite of clofenotane, and polychlorinated biphenyls (PCBs), might increase the risk of breast cancer in women. However, re-analysis[1,2] of the available data indicated that an association with breast cancer was unlikely for clofenotane; there was no evidence for an association with the PCBs. Any link between exposure to clofenotane and the development of testicular cancer in men was also refuted[3] after long-term monitoring of populations in Scandinavia.

1. Key T, Reeves G. Organochlorines in the environment and breast cancer. *BMJ* 1994; **308:** 1520–1.
2. van't Veer P, *et al.* DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. *BMJ* 1997; **315:** 81–5.
3. Ekbom A, *et al.* DDT and testicular cancer. *Lancet* 1996; **347:** 553–4.

Effects on fertility. A metabolite of clofenotane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), was reported[1] to have anti-androgenic properties in *rats* and exposure to clofenotane might account for a previously reported decline in male fertility and an increase in male reproductive abnormalities.

1. Keke WR, *et al.* Persistent DDT metabolite p,p′-DDE is a potent androgen receptor antagonist. *Nature* 1995; **375:** 581–5.

Effects on the nervous system. A retrospective study[1] found that retired malaria workers exposed long-term to clofenotane did less well in neurobehavioural tests than a control group, and had an increase in neuropsychological and psychiatric symptoms.

1. van Wendel de Joode B, *et al.* Chronic nervous-system effects of long-term occupational exposure to DDT. *Lancet* 2001; **357:** 1014–16.

Pregnancy. In a large prospective study[1] of children born between 1959 and 1966, an association was found between preterm births and small-for-gestational-age babies, and maternal concentrations of a metabolite of clofenotane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) measured in serum samples which had been stored during pregnancy.

1. Longnecker MP, *et al.* Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet* 2001; **358:** 110–14.

Pharmacokinetics

Clofenotane may be absorbed after ingestion or inhalation or through the skin. Clofenotane is stored in the body, particularly in body fat, and is very slowly eliminated. It crosses the placenta and appears in breast milk. It is metabolised in the body to the ethylene derivative, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE); the acetic acid derivative (DDA) also appears in the urine.

Clofenvinfos *(BAN, rINN)*

Chlorfenvinphos; Chlorofenwinfos; Clofenvinfós; Clofenvinfosum; Клофенвинфос.
2-Chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate.
$C_{12}H_{14}Cl_3O_4P$=359.6
CAS — 470-90-6.
UNII — F2G9XS1W91.

Profile

Clofenvinfos is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice and in agriculture.

Copper Naphthenate

Cobre, naftenato de; Нафтенат Меди.
CAS — 1338-02-9.

Profile

Copper naphthenate is the copper salt of naphthenic acid and is classified as a general use pesticide. It is used to preserve wood against a broad spectrum of fungi, termites, and other wood-destroying insects. Copper naphthenate has also been used as a topical antifungal in veterinary medicine.

Copper Oleate

Cobre, oleato de; Oléate de Cuivre; Олеат Меди.
$Cu(C_{18}H_{33}O_2)_2$=626.5
CAS — 1120-44-1.
UNII — KT1O45G674.

Profile

Copper oleate has been used topically as an insecticide for the treatment of pediculosis (p. 2147.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.:*** Plus & Plus.

Coumafos *(BAN, rINN)*

Bayer-21199; Coumafosum; Coumaphos; Cumafós; Kumafoosi; Kumafos; Кумафос.
O-3-Chloro-4-methyl-7-coumarinyl *O,O*-diethyl phosphorothioate.
$C_{14}H_{16}ClO_5PS$=362.8
CAS — 56-72-4.
ATC Vet — QP53AF08.
UNII — L08SZ5Z5JC.

Profile

Coumafos is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice.

Coumatetralyl

Cumatetralilo; Кумателралил.
4-Hydroxy-3-(1,2,3,4-tetrahydro-1-naphthyl)coumarin.
$C_{19}H_{16}O_3$=292.3
CAS — 5836-29-3.

Profile

Coumatetralyl is an anticoagulant rodenticide.

References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 28/05/04)

Cyfluthrin *(BAN)*

Bay-VI-1704; Ciflutrina; Cyfluthin; Цифлутрин.
(*RS*)-α-Cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{18}Cl_2FNO_3$=434.3
CAS — 68359-37-5.
ATC — P03BA01.
ATC Vet — QP53AC12.
UNII — SCM2QLZ6S0.

Profile

Cyfluthrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in agriculture and veterinary practice, and in the vector control of malaria (p. 644.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.:*** Solfac.

Cyhalothrin *(BAN)*

Cihalotrina; Cyhalotryna; PP-563; Цигалотрин.
(*RS*)-α-Cyano-3-phenoxybenzyl (*Z*)-(1*RS*,3*RS*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{23}H_{19}ClF_3NO_3$=449.9
CAS — 68085-85-8.
ATC Vet — QP53AC06.
UNII — V0V73PEB8M.

Profile

Cyhalothrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) that is used, particularly as a mixture of the (*Z*)-(1*R*,3*R*) *S* ester and the (*Z*)-(1*S*,3*S*) *R* ester (known as lambda-cyhalothrin), for the control of insect pests in public health. It has also been used in agriculture and in veterinary practice.

References.

1. WHO. Cyhalothrin. *Environmental Health Criteria 99*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc99.htm (accessed 23/04/04)
2. WHO. Cyhalothrin and lambda-cyhalothrin health and safety guide. *IPCS Health and Safety Guide 38*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/hsg/hsg/hsg038.htm (accessed 23/04/04)

Cymiazole

CGA-50439; CGA-192357 (cymiazole hydrochloride); Cimiazol; Cymiazol; Cymiazolum; Symiatsoli; Xymiazole; Цимиазол.
2,4-Dimethyl-*N*-(3-methyl-2(3*H*)-thiazolylidene)benzenamine.
$C_{12}H_{14}N_2S$=218.3
CAS — 61676-87-7 (cymiazole); 121034-85-3 (cymiazole hydrochloride).
ATC Vet — QP53AA02.
UNII — 7XR6MQQ6BK.

Profile

Cymiazole is a pesticide used in beekeeping.

Cypermethrin *(BAN)*

Cipermetrina; Cypermetryna; NRDC-149; Циперметрин.
(*RS*)-α-Cyano-3-phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{19}Cl_2NO_3$=416.3
CAS — 52315-07-8.
ATC — P03BA02.
ATC Vet — QP53AC08.
UNII — 1TR49121NP.

Alpha-cypermethrin *(BAN)*

Alfacipermetrina; Альфа-циперметрин.
(*SR*)-α-Cyano-3-phenoxybenzyl (1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{19}Cl_2NO_3$=416.3
CAS — 67375-30-8.
UNII — 99W8X078CA.

Profile

Cypermethrin, an isomeric mixture containing alpha-cypermethrin, is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in veterinary practice as a topical ectoparasiticide and to control sea-lice infestation in salmon. It is also used in agriculture. Zeta-cypermethrin is also used. Alpha-cypermethrin is used in agriculture and for vector control in the management of malaria (p. 644.1).

References.

1. WHO. Cypermethrin. *Environmental Health Criteria 82*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc82.htm (accessed 23/04/04)
2. WHO. Cypermethrin health and safety guide. *IPCS Health and Safety Guide 22*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg022.htm (accessed 23/04/04)
3. WHO. Alpha-cypermethrin. *Environmental Health Criteria 142*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc142.htm (accessed 23/04/04)

Cyromazine *(BAN, rINN)*

CGA-72662; Ciromazina; Cyromazinum; Циромазин.
N-Cyclopropyl-1,3,5-triazine-2,4,6-triamine.
$C_6H_{10}N_6$=166.2
CAS — 66215-27-8.
UNII — CA49Y29RA9.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Cyromazine). A white or off-white, odourless, crystalline powder. Slightly soluble in water and in methyl alcohol.

Profile

Cyromazine is used as a topical ectoparasiticide in veterinary practice.

Cythioate *(BAN)*

Citioato; Цитиоат.
O,O-Dimethyl *O*-(4-sulphamoylphenyl) phosphorothioate.
$C_8H_{13}NO_5PS_2$=297.3
CAS — 115-93-5.
ATC Vet — QP53AF10; QP53BB01.
UNII — 3OOH7Q4333.

Profile

Cythioate is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is given orally to the host animal.

Daminozide

Daminozida; Даминозид.
N-Dimethylaminosuccinamic acid.
$C_6H_{12}N_2O_3$=160.2
CAS — 1596-84-5.

Profile

Daminozide is a plant growth regulator that has been used in pesticides to improve fruit crops. There have been concerns about residues of the chemical in the fruit.

Deltamethrin *(BAN)*

Decamethrin; Decametrina; Deltamethrinum; Deltametriini; Deltametrin; Deltametrina; Deltametryna; NRDC-161; Дельтаметрин.
(*S*)-α-Cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{19}Br_2NO_3$=505.2
CAS — 52918-63-5.
ATC — P03BA03.
ATC Vet — QP53AC11.
UNII — 2JTS8R821G.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Deltamethrin). A white to buff-coloured crystalline powder. Insoluble in water; soluble in alcohol and in acetone.

Profile

Deltamethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in the vector control of malaria (p. 644.1). It is also used as a topical ectoparasiticide in veterinary practice and as an agricultural and household insecticide.

References.

1. WHO. Deltamethrin health and safety guide. *IPCS Health and Safety Guide 30*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg030.htm (accessed 26/04/04)
2. WHO. Deltamethrin. *Environmental Health Criteria 97*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc97.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Deltacid; Deltalab; Deltapil; Deotrin; Pediderm; ***Fr.***: Cinq sur Cinq; Pharmavoyage Moustiquaires; ***Venez.***: Nopucid.

Multi-ingredient Preparations. ***Arg.***: Deca-Scab; Hexa-Defital NF; Nopucid Compuesto; Nopucid Rapida; ***Braz.***: Deltacid Plus; ***Chile***: Launol.

Dibromochloropropane

DBCP; Dibromocloropropano; Дибромохлоропропан.
1,2-Dibromo-3-chloropropane.
$C_3H_5Br_2Cl$=236.3
CAS — 96-12-8.
UNII — 96K0FD4803.

Profile

Dibromochloropropane has been used as a pesticide. Low sperm counts and evidence of testicular damage have occurred in workers exposed to dibromochloropropane.

Dibutyl Phthalate

Butyl Phthalate; DBP; Dibutil-ftalát; Dibutilo ftalatas; Dibutilo, ftalato de; Dibutyle, phtalate de; Dibutylftalat; Dibutyl-ftalát; Dibutylis Phthalas; Dibutylphthalat; Dibutylu ftalan; Dibutyyliftalaatti; Дибутилфталат.
Dibutyl benzene-1,2-dicarboxylate.
$C_{16}H_{22}O_4$=278.3
CAS — 84-74-2.
ATC — P03BX03.
UNII — 2286E5R2KE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8 (Dibutyl Phthalate). A clear, oily, colourless or very slightly yellow liquid. Practically insoluble in water; miscible with alcohol. Store in airtight containers.

USNF 31: (Dibutyl Phthalate). A clear, oily, colourless or very slightly yellow liquid. Practically insoluble in water; miscible with alcohol and with ether. Store in airtight containers.

Uses and Administration

Dibutyl phthalate has been used as an insect repellent although it is slightly less effective than dimethyl phthalate (p. 2153.3). It is less volatile and less easily removed by washing than dimethyl phthalate, and its chief use therefore has been for the impregnation of clothing.

Dibutyl phthalate has also been used in latex adhesives, as a solvent in dyes, in coatings of medications, in cosmetics, and as a plasticiser.

References.

1. WHO. Di-*n*-butyl phthalate. *Environmental Health Criteria 189*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc189.htm (accessed 26/04/04)
2. Kamrin MA. Phthalate risks, phthalate regulation, and public health: a review. *J Toxicol Environ Health B* 2009; **12:** 157–74.

Adverse Effects and Precautions

Dibutyl phthalate has occasionally caused hypersensitivity reactions. As with other phthalates contact with plastics should be avoided.

Dichlorophenoxyacetic Acid

2,4-D; Diclorofenoxiacético, ácido; Дихлорфеноксиуксусная Кислота.
2,4-Dichlorophenoxyacetic acid.
$C_8H_6Cl_2O_3$=221.0
CAS — 94-75-7.
UNII — 2577AQ9262.

Uses

Dichlorophenoxyacetic acid is a herbicide widely used for weed control in cereals and other crops. It is usually used as its salts or esters with other herbicides.

Adverse Effects, Treatment, and Precautions

Most cases of poisoning with dichlorophenoxyacetic acid have involved its ingestion with other herbicides; the solvent may also play a part in any toxicity. There is little pattern to the range of adverse effects that may occur after ingestion, inhalation, or topical exposure.

Adverse effects have involved the CNS and peripheral nervous system, muscles, and the cardiovascular system. Gastrointestinal effects are common with poisoning. Hepatotoxicity, nephrotoxicity, and pulmonary disorders have occurred but it is not clear that dichlorophenoxyacetic acid contributed to the toxicity. The role of phenoxyacetic acids in cancer is discussed under trichlorophenoxyacetic acid (p. 2162.3).

Activated charcoal or possibly gastric lavage should be considered after ingestion of substantial amounts if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Forced alkaline diuresis or haemodialysis have been reported to be effective in removing dichlorophenoxyacetic acid; the latter is considered more effective. Further treatment is symptomatic.

References.

1. WHO. 2,4-Dichlorophenoxyacetic acid (2,4-D). *Environmental Health Criteria 29*. Geneva: WHO,1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc29.htm (accessed 26/04/04)
2. WHO. 2,4-Dichlorophenoxyacetic (2,4-D) health and safety guide. *IPCS Health and Safety Guide 5*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg005.htm (accessed 26/04/04)
3. WHO. 2,4-Dichlorophenoxyacetic acid (2,4-D)—environmentalaspects. *Environmental Health Criteria 84*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc84.htm (accessed 26/04/04)
4. Bradberry SM, *et al*. Mechanisms of toxicology, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. *J Toxicol Clin Toxicol* 2000; **38:** 111–22.
5. Garabrant DH, Philbert MA. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) epidemiology and toxicology. *Crit Rev Toxicol* 2002; **32:** 233–57.
6. Bradberry SM, *et al*. Poisoning due to chlorophenoxy herbicides. *Toxicol Rev* 2004; **23:** 65–73.

Dichlorvos *(BAN, USAN, rINN)*

DDVP; Dichlorfos; Dichlorvosum; Diclorvós; NSC-6738; OMS-14; SD-1750; Дихлорвос.
2,2-Dichlorovinyl dimethyl phosphate.
$C_4H_7Cl_2O_4P$=221.0
CAS — 62-73-7.
ATC Vet — QP52AB03; QP53AF04.
UNII — 7U370BPS14.

Pharmacopoeias. In *Fr.* for veterinary use.

Profile

Dichlorvos is an organophosphorus insecticide (p. 2158.3) of short persistence, effective against a wide range of insects. It is sometimes used as a fumigant. It has been used for the extermination of insects in aircraft (disinsection). It is also used as a topical ectoparasiticide and as an anthelmintic in veterinary practice. Concern has been expressed over its possible carcinogenicity.

References.

1. WHO. Dichlorvos health and safety guide. *IPCS Health and Safety Guide 18*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg018.htm (accessed 26/04/04)
2. WHO. Dichlorvos. *Environmental Health Criteria 79*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc79.htm (accessed 26/04/04)
3. Van Maele-Fabry G, *et al*. Dichlorvos and carcinogenicity: a systematic approach to a regulatory decision. *Regul Toxicol Pharmacol* 2000; **31:** 13–21.
4. Ishmael J, *et al*. Dichlorvos—a comprehensive review of 11 rodent carcinogenicity studies. *Regul Toxicol Pharmacol* 2006; **44:** 238–48.
5. Booth ED, *et al*. Review of the in vitro and in vivo genotoxicity of dichlorvos. *Regul Toxicol Pharmacol* 2007; **49:** 316–26.

Dieldrin *(BAN, pINN)*

Dieldrina; Dieldrine; Dieldrinum; Dieldryna; Диэлдрин.
CAS — 60-57-1 (HEOD).
UNII — I0246D2ZS0.

Description. Dieldrin contains about 85% of (1*R*,4*S*,5*S*,8*R*)-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4:5,8-dimethanonaphthalene (HEOD), $C_{12}H_8Cl_6O$ = 380.9. The remaining 15% is mainly chlorinated organic compounds related to HEOD.

Uses

Dieldrin is a chlorinated insecticide (p. 2150.2) formerly used as a sheepdip. Its use is now limited to a few specified purposes such as termite control.

Adverse Effects and Treatment

As for Chlorinated Insecticides, p. 2150.2.

Dieldrin is more toxic than clofenotane (p. 2151.1) and is readily absorbed through the skin.

References.

1. WHO. Aldrin and dieldrin. *Environmental Health Criteria 91*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc91.htm (accessed 26/04/04)

2. WHO. Aldrin and dieldrin health and safety guide. *IPCS Health and Safety Guide 21*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg021.htm (accessed 26/04/04)
3. Høyer AP, *et al*. Organochlorine exposure and risk of breast cancer. *Lancet* 1998; **352:** 1816–20.
4. Jorgenson JL. Aldrin and dieldrin: a review of research on their production, environmental deposition and fate, bioaccumulation, toxicology, and epidemiology in the United States. *Environ Health Perspect* 2001; **109** (suppl 1): 113–39.

Di-(2-ethylhexyl)adipate

DEHA; Dioctilo, adipato de; Dioctyl Adipate; DOA; Диоктиладипинат.
$C_{22}H_{42}O_4$=370.6
CAS — 103-23-1.
UNII — MBY1SL921L.

NOTE. Do not confuse with the plasticiser di-*n*-octyl adipate (*CAS*—123-79-5), which is also referred to as dioctyl adipate.

Profile

Di-(2-ethylhexyl)adipate is used as an insect repellent. It is also used as a plasticiser by the plastics industry; concern about the migration of this and other plasticisers into foodstuffs from polythene films used to wrap them ('cling film') have led to its use at lower concentrations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Protec.

Diethyltoluamide *(BAN, rINN)*

DEET; *N,N*-Diethyl-3-methylbenzamide; Diéthyltoluamide; Diethyltoluamidum; Dietiltoluamida; Диэтилтолуамид.
NN-Diethyl-*m*-toluamide.
$C_{12}H_{17}NO$=191.3
CAS — 134-62-3.
ATC — P03BX01.
ATC Vet — QP53GX01.
UNII — FB0C1XZV4Y.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Diethyltoluamide). A colourless liquid with a faint pleasant odour. Practically insoluble in water and in glycerol; miscible with alcohol, with carbon disulfide, with chloroform, with ether, and with isopropyl alcohol. Store in airtight containers.

Uses

Diethyltoluamide is an insect repellent that is effective against mosquitoes as well as blackflies, harvest-bugs or chiggers, midges, ticks, and fleas. It is considered to be of value for personal protection against malaria (p. 644.1). It has also been used as a repellent against leeches. It may be applied to skin and clothing. It is also used in veterinary practice as a fly repellent.

Adverse Effects and Precautions

Occasional hypersensitivity to diethyltoluamide has been reported. Diethyltoluamide should not be applied near the eyes, to mucous membranes, to broken skin, or to areas of skin flexion, as irritation or blistering may occur. Systemic toxicity has been reported after application of large topical doses, particularly in children.

Hypersensitivity and anaphylaxis has been described in a patient after exposure to diethyltoluamide.[1] Toxic encephalopathy has been noted in children given liberal applications of this compound;[2] seizures have also been reported,[3] and there have been cases of manic psychosis[4] and cardiovascular toxicity (sinus bradycardia and orthostatic hypotension)[5] associated with topical application. An assessment[6] of both published and unpublished data concluded that there had been remarkably few problems considering the widespread use of diethyltoluamide and that the encephalopathy in children had not been substantiated by detailed surveillance; however, another case analysis[7] did find an association with encephalopathy in children.

Toxic reactions, including death, have been reported after the ingestion of large amounts of diethyltoluamide-containing insect repellents.[8]

1. Miller JD. Anaphylaxis associated with insect repellent. *N Engl J Med* 1982; **307:** 1341–2.
2. Roland EH, *et al*. Toxic encephalopathy in a child after brief exposure to insect repellents. *Can Med Assoc J* 1985; **132:** 155–6.
3. Anonymous. Seizures temporally associated with use of DEET insect repellent—New York and Connecticut. *Arch Dermatol* 1989; **125:** 1619–20.
4. Snyder JW, *et al*. Acute manic psychosis following the dermal application of N,N-diethyl-m-toluamide (DEET) in an adult. *J Toxicol Clin Toxicol* 1986; **24:** 429–39.
5. Clem JR, *et al*. Insect repellent (N,N-diethyl-m-toluamide) cardiovascular toxicity in an adult. *Ann Pharmacother* 1993; **27:** 289–93.
6. Goodyer L, Behrens RH. Short report: the safety and toxicity of insect repellents. *Am J Trop Med Hyg* 1998; **59:** 323–4.
7. Briassoulis G, *et al*. Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children. *Hum Exp Toxicol* 2001; **20:** 8–14.
8. Tenenbein M. Severe toxic reactions and death following the ingestion of diethyltoluamide-containing insect repellents. *JAMA* 1987; **258:** 1509–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kinderval RI; ***Austral.***: Apex Repel; ***Belg.***: Mouskito Tropical; ***Canad.***: Muskol; Off Skintastic†; Off; Ungava; ***Chile***: Repelex; ***Fr.***: Biovectrol Tropique; Insect Ecran; ***NZ***: Apex Repel Junior; Apex Repel Super with Sunscreen; Apex Repel Super; Repel Tropical Strength; ***Swed.***: MyggA; ***UK***: Bens; Jungle Formula Insect Repellent; Mijex; Mijex; Ultrathon.

Multi-ingredient Preparations. ***Arg.***: Standard XXI; ***Austral.***: Apex Repel Super†; Apex Repel Ultra; Apex Repel with Sunscreen; Apex Repel; ***Belg.***: Mouskito Sun†; Mouskito Travel Milk†; Mouskito Travel Stick; ***Ital.***: Sinezan; ***Jpn***: Una Repellent†; ***NZ***: Active Duty with Sunscreen; Active Duty; Apex Repel Super†; Apex Repel Ultra; ***UK***: Autan.

Pharmacopoeial Preparations
USP 36: Diethyltoluamide Topical Solution.

Difenacoum

Difenacum; Дифенакум.
3-(3-Biphenyl-4-yl-1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxycoumarin.
$C_{31}H_{24}O_3$=444.5
CAS — 56073-07-5.

NOTE. The name "superwarfarin" has been used to describe several anticoagulant rodenticides, including brodifacoum (p. 2149.2), bromadiolone (p. 2149.3), chlorophacinone (p. 2150.3), and difenacoum.

Profile

Difenacoum is an anticoagulant rodenticide.

References.
1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 26/04/04)
2. WHO. Difenacoum health and safety guide. *IPCS Health and Safety Guide 95*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg095.htm (accessed 26/04/04)

Toxicity. Difenacoum, a second-generation anticoagulant rodenticide inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with difenacoum.[2-4]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Barlow AM, *et al*. Difenacoum (Neosorexa) poisoning. *BMJ* 1982; **285:** 541.
3. Butcher GP, *et al*. Difenacoum poisoning as a cause of haematuria. *Hum Exp Toxicol* 1992; **11:** 553–4.
4. McCarthy PT, *et al*. Covert poisoning with difenacoum: clinical and toxicological observations. *Hum Exp Toxicol* 1997; **16:** 166–70.

Diflubenzuron

Дифлубензурон.
1-(4-Chlorophenyl)-3-(2,6-difluorobenzoyl)urea.
$C_{14}H_9ClF_2N_2O_2$=310.7
CAS — 35367-38-5.
ATC Vet — QP53BC02.
UNII — J76U6ZSI8D.

Profile

Diflubenzuron is an insecticide and larvicide that acts as a growth regulator by interfering with the formation of cuticle. It is used in agriculture and for the control of disease vectors. It is also used in veterinary practice for its activity against flies and lice.

Diflubenzuron possesses residual activity against mosquito larvae.

References.
1. WHO. Diflubenzuron. health and safety guide. *IPCS Health and Safety Guide 99*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg099.htm (accessed 26/04/04)
2. WHO. Diflubenzuron. *Environmental Health Criteria 184*. Geneva: WHO, 1996. Available at: http://www.inchem.org/documents/ehc/ehc/ehc184.htm (accessed 26/04/04)

Dimethoate

Dimetoato; Fosfamid; Диметоат; Фосфамид.
O,O-Dimethyl *S*-methylcarbamoylmethyl phosphorodithioate.
$C_5H_{12}NO_3PS_2$=229.2
CAS — 60-51-5.
UNII — W6U08B045O.

Profile

Dimethoate is an organophosphorus insecticide (p. 2158.3) used in agriculture.

References.
1. WHO. Dimethoate health and safety guide. *IPCS Health and Safety Guide 20*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg020.htm (accessed 28/05/04)
2. WHO. Dimethoate. *Environmental Health Criteria 90*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc90.htm (accessed 28/05/04)
3. Jovanović D, *et al*. A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; **9:** 49–51.
4. Hoffmann U, Papendorf T. Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med* 2006; **32:** 464–8.
5. Eddleston M, *et al*. Relationship between blood alcohol concentration on admission and outcome in dimethoate organophosphorus self-poisoning. *Br J Clin Pharmacol* 2009; **68:** 916–19.

Dimethyl Phthalate

Dimetilo, ftalato de; DMP; Methyl Phthalate; Диметилфталат.
Dimethyl benzene-1,2-dicarboxylate.
$C_{10}H_{10}O_4$=194.2
CAS — 131-11-3.
ATC — P03BX02.
ATC Vet — QP53GX02.
UNII — 08X7F5UDJM.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Dimethyl Phthalate). A colourless or faintly coloured liquid, odourless or almost odourless. Slightly soluble in water; miscible with alcohol, with ether, and with most organic solvents.

Uses

Dimethyl phthalate is an insect repellent.

References.
1. Kamrin MA. Phthalate risks, phthalate regulation, and public health: a review. *J Toxicol Environ Health B* 2009; **12:** 157–74.

Adverse Effects and Precautions

Dimethyl phthalate may cause temporary smarting and should not be applied near the eyes or to mucous membranes. As with other phthalates contact with plastics should be avoided.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Novascabin.

Dimpylate *(BAN, rINN)*

Diazinon; Diazynon; Dimpilato; Dimpylaatti; Dimpylat; Dimpylatum; Димпилат.
O,O-Diethyl *O*-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate.
$C_{12}H_{21}N_2O_3PS$=304.3
CAS — 333-41-5.
ATC Vet — QP53AF03.
UNII — YUS1M1Q929.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Dimpylate). A clear, yellowish-brown, slightly viscous liquid. Practically insoluble in water; miscible with alcohol, with ether, and with most organic solvents.

Profile

Dimpylate is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. It is also used as an insecticide in agriculture and horticulture.

References.
1. Wagner SL, Orwick DL. Chronic organophosphate exposure associated with transient hypertonia in an infant. *Pediatrics* 1994; **94:** 94–7.

Dinitro-o-cresol

DNOC; Динитро-о-крезол.
4,6-Dinitro-*o*-cresol.
$C_7H_6N_2O_5$=198.1
CAS — 534-52-1.
UNII — 1604ZJR09T.

Profile

Dinitro-*o*-cresol is a dinitrophenol formerly used as an insecticide and herbicide. It increases metabolism by uncoupling oxidative phosphorylation and was also formerly used in obesity. Fatal poisoning has occurred.

References.
1. WHO. Dinitro-ortho-cresol. *Environmental Health Criteria 220.* Geneva: WHO, 2000. Available at: http://www.inchem.org/documents/ehc/ehc/ehc220.htm (accessed 26/04/04)

Dinitrophenol

Dinitrofenol; DNP; Динитрофенол.
2,4-Dinitrophenol.
$C_6H_4N_2O_5$=184.1
CAS — 51-28-5.
UNII — Q13SKS21MN.

Profile

Dinitrophenol has been used as a herbicide. Since dinitrophenol increases metabolism by uncoupling oxidative phosphorylation it was formerly used in the treatment of obesity. Fatal poisoning has occurred.

Dioxation *(BAN, rINN)*

Dioxathion; Dioxatión; Dioxationum; Диоксатион.
It consists mainly of *cis* and *trans* isomers of *S,S'*-1,4-dioxan-2,3-diyl bis(*O,O*-diethyl phosphorodithioate).
$C_{12}H_{26}O_6P_2S_4$=456.5
CAS — 78-34-2.
UNII — J2DF82JA7N.

Profile

Dioxation is an organophosphorus insecticide (p. 2158.3) that has been used in agriculture and as a topical ectoparasiticide in veterinary practice.

Diphenadione *(BAN, pINN)*

Difenadiona; Diphacinone; Diphénadione; Diphenadionum; Дифенадион.
2-(Diphenylacetyl)indan-1,3-dione.
$C_{23}H_{16}O_3$=340.4
CAS — 82-66-6.
ATC — B01AA10.
ATC Vet — QB01AA10.
UNII — 54CA01C6JX.

Profile

Diphenadione is used as an anticoagulant rodenticide.

Diquat Dibromide

Diquat, dibromuro de; Дикват Дибромид.
9,10-Dihydro-8a,10a-diazoniaphenanthrene dibromide; 1,1'-Ethylene-2,2'-bipyridyldiylium dibromide.
$C_{12}H_{12}Br_2N_2$=344.0
CAS — 2764-72-9 (diquat); 85-00-7 (diquat dibromide).
UNII — 6BDV3T272W.

Profile

Diquat dibromide is a contact herbicide used in agriculture and horticulture. It has similar adverse effects to those of paraquat (p. 2159.1).

References.
1. WHO. Paraquat and diquat. *Environmental Health Criteria 39.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc39.htm (accessed 26/04/04)
2. WHO. Diquat health and safety guide. *IPCS Health and Safety Guide 52.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg052.htm (accessed 26/04/04)
3. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.
4. Jones GM, Vale JA. Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. *J Toxicol Clin Toxicol* 2000; **38:** 123–8.

Emamectin

Emamectina; Эмамектин.
A mixture of (4″-*R*)-5-*O*-Demethyl-4″-deoxy-4″-(methylamino)avermectin A_{1a} and (4″-*R*)-5-*O*-Demethyl-25-de(1-methylpropyl)-4″-deoxy-4″-(methylamino)-25-(1-methylethyl)avermectin A_{1a} in the ratio of 9:1.
CAS — 121124-29-6 (major component); 121424-52-0 (minor component); 137335-79-6.
ATC Vet — QP54AA06.
UNII — 8C43B81H4W.

Profile

Emamectin is an avermectin insecticide used for the control of sea-lice infestation in salmon.

Endod

CAS — 39278-85-8.

Profile

Endod is obtained from the dried fruits of *Phytolacca dodecandra* (Phytolaccaceae) and has molluscicidal properties. It has been investigated for the control of the snail vector of schistosomiasis.

Endosulfan

Endosulfán; Эндосульфан.
1,4,5,6,7,7-Hexachloro-8,9,10-trinorborn-5-en-2,3-ylenebismethylene sulphite.
$C_9H_6Cl_6O_3S$=406.9
CAS — 115-29-7.
UNII — QY5Y9R7G0E.

Profile

Endosulfan is a chlorinated insecticide (p. 2150.2) used in agriculture.

References.
1. WHO. Endosulfan. *Environmental Health Criteria 40.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc40.htm (accessed 26/04/04)
2. WHO. Endosulfan health and safety guide. *IPCS Health and Safety Guide 17.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg017.htm (accessed 26/04/04)
3. Blanco-Coronado JL, *et al.* Acute intoxication by endosulfan. *J Toxicol Clin Toxicol* 1992; **30:** 575–83.
4. Boereboom FT, *et al.* Nonaccidental endosulfan intoxication: a case report with toxicokinetic calculations and tissue concentrations. *J Toxicol Clin Toxicol* 1998; **36:** 345–52.
5. Chugh SN, *et al.* Endosulfan poisoning in Northern India: a report of 18 cases. *Int J Clin Pharmacol Ther* 1998; **36:** 474–7.
6. Venkateswarlu K, *et al.* Endosulfan poisoning—a clinical profile. *J Assoc Physicians India* 2000; **48:** 323–5.
7. Karatas AD, *et al.* Characteristics of endosulfan poisoning: a study of 23 cases. *Singapore Med J* 2006; **47:** 1030–2.
8. Bektas M, *et al.* Management of acute endosulfan poisoning in an organophosphate poisoning clinic. *Clin Toxicol* 2007; **45:** 563–4.
9. Durukan P, *et al.* Experiences with endosulfan mass poisoning in rural areas. *Eur J Emerg Med* 2009; **16:** 53–6.
10. Moon JM, Chun BJ. Acute endosulfan poisoning: a retrospective study. *Hum Exp Toxicol* 2009; **28:** 309–16.

Endrin

Endrín; Endryna; Эндрин.
(1*R*,4*S*,4a*S*,5*S*,6*S*,7*R*,8*R*,8a*R*)-1,2,3,4,10,10-Hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene.
$C_{12}H_8Cl_6O$=380.9
CAS — 72-20-8.
UNII — OB9NVE7YCL.

Profile

Endrin is a chlorinated insecticide (p. 2150.2), but its use was prohibited, at least in some countries, because of toxicity and persistence in the environment.

General references to endrin,[1-4] including reports of poisoning.[2,3]

1. Anonymous. Acute convulsions associated with endrin poisoning—Pakistan. *JAMA* 1985; **253:** 334–5.
2. Runhaar EA, *et al.* A case of fatal endrin poisoning. *Hum Toxicol* 1985; **4:** 241–7.
3. WHO. Endrin health and safety guide. *IPCS Health and Safety Guide 60.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg060.htm (accessed 26/04/04)
4. WHO. Endrin. *Environmental Health Criteria 130.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc130.htm (accessed 26/04/04)

Esdepallethrine

Esdepaletrina; Эсденалетрин.
(*S*)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)-cyclopropanecarboxylate.
$C_{19}H_{26}O_3$=302.4
CAS — 28434-00-6.

Profile

Esdepallethrine is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used as an acaricide with piperonyl butoxide (p. 2160.2) in the topical treatment of scabies (p. 2148.1).

Esdepallethrine is also used in devices and sprays to control insects, including mosquitoes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Spregal; ***Gr.***: Spregal; ***Israel***: Acardust; ***Neth.***: Spregal; ***Rus.***: Spregal (Спрегаль); ***S.Afr.***: Spregal; ***Ukr.***: Spregal (Спрегаль).

Ethion

Diethion; Etión; Etion; Этион.
O,O,O',O'-Tetraethyl *S,S'*-methylenediphosphorodithioate.
$C_9H_{22}O_4P_2S_4$=384.5
CAS — 563-12-2.
UNII — 2TI07NO12Y.

Profile

Ethion is an organophosphorus insecticide used as a topical ectoparasiticide in veterinary practice.

Ethohexadiol

Ethylhexanediol; Etohexadiol; Rutgers-612; Этогексадиол.
2-Ethylhexane-1,3-diol.
$C_8H_{18}O_2$=146.2
CAS — 94-96-2.
ATC — P03BX06.
ATC Vet — QP53GX04.
UNII — M9JGK7U88V.

Profile

Ethohexadiol is an insect repellent. It may be applied topically to the skin and to clothing. It has been used with dimethyl phthalate.

Ethyl Butylacetylaminopropionate

EBAAP; IR-3535; Merck-3535; Repellent 3535.
(*N*-Butyl-*N*-acetyl)-3-ethylaminopropionate; *N*-Acetyl-*N*-butyl-beta-alanine ethyl ester.
$C_{11}H_{21}NO_3$=215.3
CAS — 52304-36-6.
UNII — 65GQA237EH.

Profile

Ethyl butylacetylaminopropionate is used as an insect repellent; it may be applied to the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hyalpur Moustique; ***Belg.***: Mouskito; Shampoux Repel; ***Braz.***: Johnson's Baby Locao Anti-Mosquito; ***Fr.***: Biovectrol Famille; Cinq sur Cinq; Para Repulsif†; Prebutix; ***Thai.***: Johnson's Baby Clear; ***UK***: Mijex Extra.

Multi-ingredient Preparations. ***Arg.***: Standard XXI; ***Austral.***: Apex Repel Ultra; Apex Repel with Sunscreen; Apex Repel; ***Belg.***: Mouskito Sun†; ***Fr.***: Mousticologne†; ***Mon.***: Akipic; ***NZ***: Active Duty with Sunscreen; Apex Repel Super†; Apex Repel Ultra.

Ethylene Dibromide

Dibromoetano; EDB; Etileno, dibromuro de; Этилен Дибромид.
1,2-Dibromoethane.
$C_2H_4Br_2$=187.9
CAS — 106-93-4.
UNII — 1N41638RNO.

Profile

Ethylene dibromide is an insecticidal fumigant and a lead scavenger used in the petroleum industry. Its use has been restricted in certain areas because of carcinogenicity in *animals* and because of evidence of persistence in fruit and cereals that have undergone fumigation.

Ethylene dibromide is more toxic than carbon tetrachloride or ethylene dichloride. It is irritant to the eyes, skin, and mucous membranes. Inhalation leads to drowsiness, CNS depression, and possibly pulmonary oedema. Contact with the skin causes blistering and it is readily absorbed. Kidney and liver damage may occur.

Reports[1-4] of poisoning due to ethylene dibromide.

1. Letz GA, *et al*. Two fatalities after acute occupational exposure to ethylene dibromide. *JAMA* 1984; **252:** 2428–31.
2. Singh S, *et al*. Non-fatal ethylene dibromide ingestion. *Hum Exp Toxicol* 2000; **19:** 152–3.
3. Mehrotra P, *et al*. Two cases of ethylene dibromide poisoning. *Vet Hum Toxicol* 2001; **43:** 91–2.
4. Singh N, *et al*. Outcome of sixty four cases of ethylene dibromide ingestion treated in tertiary care hospital. *J Assoc Physicians India* 2007; **55:** 842–5.

Ethylene Dichloride

Brocide; Dicloroetano; Dutch Liquid; Etileno, dicloruro de; Этилен Дихлорид.
1,2-Dichloroethane.
$C_2H_4Cl_2$=98.95
CAS — 107-06-2.
UNII — 55163IJI47.

Profile

Ethylene dichloride is an insecticidal fumigant. It is also used in the petroleum industry and as an industrial solvent. Exposure to the vapour may cause lachrymation and corneal clouding, nasal irritation, and vertigo due to the depressant effect on the CNS. Contact with the skin may cause dermatitis. Kidney and liver damage, hypotension and cardiac impairment, gastrointestinal disturbances, haemorrhage, coma, and pulmonary oedema may follow absorption after inhalation, topical application, or ingestion.

Ethylene dichloride has been reported to be carcinogenic in *animals*.

References.

1. WHO. 1,2-Dichloroethane health and safety guide. *IPCS Health and Safety Guide 55*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg055.htm (accessed 26/04/04)
2. WHO. 1,2 Dichloroethane. *Environmental Health Criteria 176*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc176.htm (accessed 06/06/06)
3. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.

Etofenprox *(rINN)*

Ethofenprox; Étofenprox; Etofenproxum; Этофенпрокс.
α-[(*p*-Ethoxy-β,β-dimethylphenethyl)oxy]-*m*-phenoxytoluene.
$C_{25}H_{28}O_3$=376.5
CAS — 80844-07-1.
UNII — 0LD7P9153C.

Profile

Etofenprox is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in the vector control of malaria (p. 644.1).

Famphur

Famfur; Famophos; Фамфур.
$C_{10}H_{16}NO_5PS_2$=325.3
CAS — 52-85-7.
UNII — 02UOP4Z0O0.

Profile

Famphur is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal.

Fenitrothion *(BAN)*

Fenitrotión; Фенитротион.
O,O-Dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate.
$C_9H_{12}NO_5PS$=277.2
CAS — 122-14-5.
UNII — W8M4X3Y7ZY.

Profile

Fenitrothion is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice. It is also used as an agricultural insecticide.

References.

1. WHO. Fenitrothion health and safety guide. *IPCS Health and Safety Guide 65*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg065.htm (accessed 26/04/04)
2. WHO. Fenitrothion. *Environmental Health Criteria 133*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc133.htm (accessed 26/04/04)
3. Bouma MJ, Nesbit R. Fenitrothion intoxication during spraying operations in the malaria programme for Afghan refugees in North West Frontier Province of Pakistan. *Trop Geogr Med* 1995; **47:** 12–14.
4. Inoue S, *et al*. Prognostic factors and toxicokinetics in acute fenitrothion self-poisoning requiring intensive care. *Clin Toxicol* 2008; **46:** 528–33.

Fenthion *(BAN)*

Bayer-29493; Fentión; S-752; Фентион.
O,O-Dimethyl *O*-4-methylthio-*m*-tolyl phosphorothioate.
$C_{10}H_{15}O_3PS_2$=278.3
CAS — 55-38-9.
ATC Vet — QP53BB02.
UNII — BL0L45OVKT.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Fenthion). A yellowish-brown oily substance. Immiscible with water; miscible with alcohol and with chloroform.

Profile

Fenthion is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. Fenthion has also been used in agriculture.

Toxicity. Macular changes have been detected in the eyes of workers regularly exposed to fenthion.[1] It was considered that there was a need for long-term studies on subjects exposed to different organophosphorus compounds to assess their role in producing macular changes.

1. Misra UK, *et al*. Some observations on the macula of pesticide workers. *Hum Toxicol* 1985; **4:** 135–45.

Fenvalerate *(BAN)*

Fenvalerato; Fenwalerianian; OMS-2000; Pydrin; S-5602; SD-43775; WL-43775; Фенвалерат.
(*RS*)-α-Cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl)-3-methylbutyrate.
$C_{25}H_{22}ClNO_3$=419.9
CAS — 51630-58-1.
ATC Vet — QP53AC14; QP53AX02.
UNII — Z6MXZ39302.

Profile

Fenvalerate is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used as a topical ectoparasiticide in veterinary practice. It has also been used as an insecticide in agriculture and horticulture.

Esfenvalerate, one of the stereoisomers of fenvalerate, is also used as an agricultural insecticide.

References.

1. WHO. Fenvalerate health and safety guide. *IPCS Health and Safety Guide 34*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg034.htm (accessed 26/04/04)
2. WHO. Fenvalerate. *Environmental Health Criteria 95*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc95.htm (accessed 26/04/04)

Fipronil *(BAN)*

Fiproniili; Fipronilo; MB-46030; RM-1601; Фипронил.
(*RS*)-5-Amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(trifluoromethylsulfinyl)pyrazole-3-carbonitrile.
$C_{12}H_4Cl_2F_6N_4OS$=437.1
CAS — 120068-37-3.
ATC Vet — QP53AX15.
UNII — QGH063955F.

Profile

Fipronil is used as a topical ectoparasiticide in veterinary practice. It has also been investigated for the treatment of head lice.

Flocoumafen

Flocoumafene; Flocumafeno; OMS-3047; Флокумафен.
4-Hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin.
$C_{33}H_{25}F_3O_4$=542.6
CAS — 90035-08-8.

Profile

Flocoumafen is a coumarin derivative used as an anticoagulant rodenticide. It is said to be effective in rodents resistant to other anticoagulant rodenticides.

References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 26/04/04)

Fluazuron *(rINN)*

CGA-157419; Fluazurón; Fluazuronum; Флуазурон.
1-(4-Chloro-3-[[3-chloro-5-(trifluoromethyl)-2-pyridyl]oxy}phenyl)-3-(2,6-difluorobenzoyl)urea.
$C_{20}H_{10}Cl_2F_5N_3O_3$=506.2
CAS — 86811-58-7.
UNII — VB0PV6I7L6.

Profile

Fluazuron is used as a topical ectoparasiticide in veterinary practice.

Flumethrin *(BAN)*

Flumethrinum; Flumetriini; Flumetrin; Flumetrina; Флуметрин.
α-Cyano-4-fluoro-3-phenoxybenzyl 3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate.
$C_{28}H_{22}Cl_2FNO_3$=510.4
CAS — 69770-45-2.
ATC Vet — QP53AC05.

Profile

Flumethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used as a topical ectoparasiticide in veterinary practice.

A report[1] of poisoning with flumethrin.

1. Box SA, Lee MR. A systemic reaction following exposure to a pyrethroid insecticide. *Hum Exp Toxicol* 1996; **15:** 389–90.

Fluoroacetamide

Compound 1081; Fluoroacetamida; Фторацетамид.
FCH_2CONH_2=77.06
CAS — 640-19-7.
UNII — B18R611M38.

Profile

Fluoroacetamide is a rodenticide and produces adverse effects similar to those of sodium fluoroacetate (p. 2161.3).

Fluvalinate

Fluvalinato; ZR-3210; Флювалинат.
Cyano(3-phenoxyphenyl)methyl ester of *N*-[2-chloro-4-(trifluoromethyl)phenyl]-DL-valine.
$C_{26}H_{22}ClF_3N_2O_3$=502.9
CAS — 69409-94-5.
ATC Vet — QP53AC10.
UNII — 364G5G03VC.

Profile

Fluvalinate is a pesticide used in beekeeping.

Glyphosate

Glifosato; Glyfosato; Глифосат.
N-(Phosphonomethyl)glycine.
$C_3H_8NO_5P$=169.1
CAS — 1071-83-6.
UNII — 4632WW1X5A.

Profile

Glyphosate is used as a herbicide.

References.

1. WHO. Glyphosate. *Environmental Health Criteria 159*. Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/ehc/ehc/ehc159.htm (accessed 26/04/04)

Toxicity. Reports[1-5] and reviews[6] of poisoning with glyphosate products, prognostic factors,[7] guidelines for treatment[8] have been published. The toxicity has been believed to be largely due to the inclusion of surfactants, particularly polyoxyethyleneamine, in the herbicide (Roundup) formulation but products vary considerably as to the surfactant contained and the concentration and salt of glypho-

sate used, and the evidence that surfactants potentiate glyphosate toxicity is unclear.[8]

1. Sawada Y, *et al*. Probable toxicity of surface-active agent in commercial herbicide containing glyphosate. *Lancet* 1988; **i:** 299.
2. Talbot AR, *et al*. Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. *Hum Exp Toxicol* 1991; **10:** 1–8.
3. Menkes DB, *et al*. Intentional self-poisoning with glyphosate-containing herbicides. *Hum Exp Toxicol* 1991; **10:** 103–7.
4. Chen YJ, *et al*. The epidemiology of glyphosate-surfactant herbicide poisoning in Taiwan, 1986-2007: a poison center study. *Clin Toxicol* 2009; **47:** 670–7.
5. Roberts DM, *et al*. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning. *Clin Toxicol* 2010; **48:** 129–36.
6. Bradberry SM, *et al*. Glyphosate poisoning. *Toxicol Rev* 2004; **23:** 159–67.
7. Lee CH, *et al*. The early prognostic factors of glyphosate-surfactant intoxication. *Am J Emerg Med* 2008; **26:** 275–81.
8. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.

Heptachlor

Heptacloro; Гептахлор.

1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene.

$C_{10}H_5Cl_7$=373.3

CAS — 76-44-8.

UNII — 7GLS9ACN3L.

Profile

Heptachlor is a chlorinated insecticide (p. 2150.2), but its use was prohibited, at least in some countries, because of its persistent nature.

References.

1. WHO. Heptachlor. *Environmental Health Criteria 38*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc38.htm (accessed 26/04/04)
2. WHO. Heptachlor health and safety guide. *IPCS Health and Safety Guide 14*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg014.htm (accessed 26/04/04)

Heptenophos

Heptenofós; Hoe-02982; Хептенофос.

7-Chlorobicyclo[3.2.0]hepta-2,6-dien-6-yl dimethyl phosphate.

$C_9H_{12}ClO_4P$=250.6

CAS — 23560-59-0.

Profile

Heptenophos is an organophosphorus insecticide (p. 2158.3) that has been used in veterinary practice for the control of ectoparasites. It is also used in agriculture.

Hexachlorobenzene

HCB; Heksachlorobenzen; Hexaclorobenceno; Гексахлорбензол.

C_6Cl_6=284.8

CAS — 118-74-1.

UNII — 4Z87H0LKUY.

NOTE. Hexachlorobenzene should not be confused with gamma benzene hexachloride (lindane).

Profile

Hexachlorobenzene has been used as an agricultural fungicide. It is not biodegradable to any significant extent and hexachlorobenzene residues in food have arisen as a result of its occurrence in industrial wastes as well as its use as a fungicide; its use is banned in some countries.

Hexachlorobenzene is reported to be distributed into breast milk.

References.

1. WHO. Hexachlorobenzene. *Environmental Health Criteria 195*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc195.htm (accessed 26/04/04)
2. WHO. Hexachlorobenzene health and safety guide. *IPCS Health and Safety Guide 107*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg107.htm (accessed 26/04/04)
3. Reed L, *et al*. Environmental toxicology and health effects associated with hexachlorobenzene exposure. *Rev Environ Health* 2007; **22:** 213–43.

Toxicity. Porphyria cutanea tarda[1] and parkinsonism[2] have both been reported in subjects who had ingested seed crops treated with hexachlorobenzene. In a further report the symptoms of porphyria in some patients have been said to persist for many years.[3]

1. Cam C, Nigogosyan G. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. *JAMA* 1963; **183:** 88–91.
2. Chapman LJ, *et al*. Parkinsonism and industrial chemicals. *Lancet* 1987; **i:** 332–3.
3. Cripps DJ, *et al*. Porphyria turcica due to hexachlorobenzene: a 20 to 30 year follow-up study on 204 patients. *Br J Dermatol* 1984; **111:** 413–22.

Hydrocyanic Acid

Ácido hidrociánico; Ácido prúsico; Cianhídrico, ácido; Prussic Acid; Синильная Кислота; Цианисто-водородная Кислота.

CAS — 74-90-8.

Description. Hydrocyanic acid is an aqueous solution containing hydrogen cyanide, HCN = 27.03. A colourless liquid with a characteristic almond odour.

Uses

Cyanides have various industrial applications. Hydrocyanic acid and cyanide salts produce hydrogen cyanide, which has been used as a gas for the eradication of rabbits, rodents, and some other pests. Cyanide salts that might be encountered include calcium cyanide, mercuric cyanide, potassium cyanide, potassium ferricyanide, potassium sodium cyanide, and sodium cyanide.

Adverse Effects and Precautions

Hydrocyanic acid and its vapour are intensely poisonous. Cyanides interfere with the oxygen uptake of cells by inhibition of cytochrome oxidase, an enzyme necessary for cellular oxygen transport.

Poisoning by cyanides may occur from inhalation of the vapour, ingestion, or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure, or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits.

When large doses of hydrocyanic acid are taken, unconsciousness occurs within a few seconds and death within a few minutes. With smaller toxic doses the symptoms, which occur within a few minutes, may include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hyperpnoea then dyspnoea, bradycardia (although initially there may be tachycardia), unconsciousness, and violent convulsions, followed by death. The characteristic smell of bitter almonds may not be obvious and not all individuals can detect it. Cyanosis is not prominent. Similar but usually slower effects occur with cyanide salts.

The fatal dose of hydrocyanic acid for man is considered to be about 50 mg and of the cyanides about 250 mg.

Treatment of Adverse Effects

Cyanide is highly toxic. It is absorbed very rapidly on inhalation and the poisoned patient should be removed from the area and given oxygen. Steps should be taken to ensure that the airway is adequate. In cases of dermal exposure, contaminated clothing should be removed and the skin washed thoroughly with soap and water. When cyanide has been ingested, gastric lavage or activated charcoal may be considered if the patient presents within 1 hour. Appropriate measures should be instituted to correct hypotension and acidosis. The choice of an antidote depends on the severity of the poisoning, certainty of diagnosis, and the cause.

In some countries cyanide antidote kits containing amyl nitrite, sodium nitrite, and sodium thiosulfate are available. In conscious patients, amyl nitrite (p. 1540.2) may be inhaled until intravenous access is established. Intravenous injection of sodium nitrite (p. 1574.3) is then followed immediately by intravenous sodium thiosulfate (p. 1576.2). The nitrite components from amyl nitrite and sodium nitrite convert haemoglobin to methaemoglobin which competes with cytochrome oxidase for cyanide, with the formation of cyanmethaemoglobin; sodium thiosulfate acts as a sulfur donor and aids the conversion or inactivation of cyanide from cyanmethaemoglobin to thiocyanate. The methaemoglobinaemia induced by the nitrites in the antidote kits can be dangerous and fatalities have been reported.

The UK *National Poisons Information Service* recommends that intravenous sodium thiosulfate be used alone in mild poisoning. The preferred treatment for those with moderate to severe poisoning is intravenous dicobalt edetate (p. 1548.3) since it forms a stable complex with the cyanide ion. However, cyanide poisoning should be confirmed, as absence of cyanide puts the patient at risk from the adverse effects of dicobalt edetate. Each dose of dicobalt edetate may be followed immediately by intravenous injection of glucose 50% to reduce cobalt toxicity; in cases of proven cyanide toxicity glucose is unnecessary but is generally given as a precaution. Sodium thiosulfate alone (in cases of moderate poisoning) or sodium nitrite followed by sodium thiosulfate (in cases of severe poisoning) are alternative treatment options if dicobalt edetate is not available.

Hydroxocobalamin (p. 2108.1) may be used intravenously for the management of cyanide toxicity, particularly for victims of smoke inhalation, and an antidote kit is available in some countries for this purpose.

Some references concerning the management of cyanide poisoning.[1-7] The use of solutions A and B (15.8% ferrous sulfate in 0.3% citric acid, and 6% sodium carbonate respectively) as so called oral antidotes in persons exposed to cyanide has been condemned as ineffective and lacking scientific evidence.[2]

1. Langford RM, Armstrong RF. Algorithm for managing injury from smoke inhalation. *BMJ* 1989; **299:** 902–5.
2. Koizumi A. Fighting myths. *Lancet* 1994; **344:** 559–60.
3. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
4. Geller RJ, *et al*. Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. *Pediatrics* 2006; **118:** 2146–58.
5. Baud FJ. Cyanide: critical issues in diagnosis and treatment. *Hum Exp Toxicol* 2007; **26:** 191–201.
6. Shepherd G, Velez LI. Role of hydroxocobalamin in acute cyanide poisoning. *Ann Pharmacother* 2008; **42:** 661–9.
7. Hall AH, *et al*. Which cyanide antidote? *Crit Rev Toxicol* 2009; **39:** 541–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Rus.***: Tonginal (Тонгинал); ***Ukr.***: Tonginal (Тонгинал).

Icaridin *(rINN)*

Hepidanin; Icaridina; Icaridine; Icaridinum; KBR-3023; Picaridan; Picaridin; Икаридин.

1-Methylpropyl 2-(2-hydroxyethyl)piperidine-1-carboxylate.

$C_{12}H_{23}NO_3$=229.3

CAS — 119515-38-7.

UNII — N51GQX0837.

NOTE. Bayrepel and Saltidin are trade names that have been used for icaridin.

Profile

Icaridin is an insect repellent that is reported to be effective against mosquitoes, flies, and ticks.

References.

1. Scheinfeld N. Picaridin: a new insect repellent. *J Drugs Dermatol* 2004; **3:** 59–60.
2. Anonymous. Picardin—a new insect repellent. *Med Lett Drugs Ther* 2005; **47:** 46–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Apex Repel New Era; ***Fr.***: Insect Ecran; ***Malaysia***: Moz Away Junior; Moz Away Long Hour Protection; ***NZ***: Apex Repel New Era; ***Singapore***: Moz Away; ***USA***: Cutter Advanced.

Multi-ingredient Preparations. ***Fr.***: Mousticologne†; ***UK***: Autan.

Imidacloprid

Bay-NTN-33893; Имидаклоприд.

1-[(6-Chloro-3-pyridinyl)methyl]-4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine.

$C_9H_{10}ClN_5O_2$=255.7

CAS — 105827-78-9; 138261-41-3.

ATC Vet — QP53AX17.

UNII — 3BN7M937V8.

Profile

Imidacloprid is used as a topical ectoparasiticide in veterinary practice, and as an insecticide in agriculture. It has also been investigated for use in the treatment of head lice.

Iodofenphos *(BAN)*

Iodofenfós; Jodfenphos; Иодофенфос.

O-2,5-Dichloro-4-iodophenyl *O,O*-dimethyl phosphorothioate.

$C_8H_8Cl_2IO_3PS$=413.0

CAS — 18181-70-9.

UNII — SME6G1846X.

Profile

Iodofenphos is an organophosphorus insecticide (p. 2158.3) used in veterinary practice for the control of ectoparasites in the environment. It has also been used as an agricultural insecticide. It is an effective mosquito larvicide.

Iodopropynyl Butyl Carbamate

Iodocarb; IPBC; Йодопропинил Бутилкарбамат.

3-Iodo-2-propynyl-*N*-butyl carbamate.

$C_8H_{12}INO_2$=281.1

CAS — 55406-53-6.

UNII — 603P14DHEB.

Profile

Iodopropynyl butyl carbamate is a carbamate pesticide (p. 2149.3). It is used as a preservative in cosmetic preparations; contact sensitisation has been reported. It is also used as a wood preservative.

References.

1. Bryld LE, *et al*. Iodopropynyl butylcarbamate: a new contact allergen. *Contact Dermatitis* 1997; **36:** 156–8.
2. Badreshia S, Marks JG. Iodopropynyl butylcarbamate. *Am J Contact Dermat* 2002; **13:** 77–9.
3. Davis RF, Johnston GA. Iodopropynyl butylcarbamate contact allergy from wood preservative. *Contact Dermatitis* 2007; **56:** 112.
4. Natkunarajah J, *et al*. Allergic contact dermatitis to iodopropynyl butylcarbamate found in a cosmetic cleansing wipe. *Contact Dermatitis* 2008; **58:** 316–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Effaclar Gel Moussant Purifiant.

Multi-ingredient Preparations. ***Braz.***: Effaclar; Pityval; Saliker; ***Chile***: Effaclar Agua Desmaquillante Purificante; Effaclar AI; Effaclar K; Normaderm Exfoliante; Normaderm Gel de Limpieza; Normaderm Tonico Astringente; Podexine Anti-Transpirante; ***Fr.***: Effaclar K; Pityval†; ***Irl.***: Effaclar AI; Effaclar K; Effaclar.

Lindane *(BAN, USAN, rINN)*

666; Benhexachlor; Gamma Benzene Hexachloride; Gamma-BHC; Gamma-HCH; HCH; Hexicide; Lindaani; Lindan; Lindán; Lindanas; Lindano; Lindanum; Линдан.

1α,2α,3β,4α,5α,6β-Hexachlorocyclohexane.

$C_6H_6Cl_6$=290.8

CAS — 58-89-9.

ATC — P03AB02.

ATC Vet — QP53AB02; QS02QA01.

UNII — 59NEE7PCAB.

Pharmacopoeias. In *Chin.*, *Int.*, and *US*.

USP 36: (Lindane). A white, crystalline powder with a slight musty odour. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in chloroform; sparingly soluble in ether; slightly soluble in ethylene glycol.

Uses and Administration

Lindane is a chlorinated insecticide (p. 2150.2). It has been used topically in a concentration of 1% for scabies (p. 2148.1) in selected patients and has also been used in pediculosis (p. 2147.3), but use for head lice is restricted by resistance.

Lindane has been used for the control of disease vectors including mosquitoes, lice, and fleas, but resistance has developed. It has also been used as an agricultural and a horticultural insecticide, but its use is prohibited or restricted in many countries.

References.

1. WHO. Lindane. *Environmental Health Criteria 124*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc124.htm (accessed 26/04/04)
2. WHO. Lindane health and safety guide. *IPCS Health and Safety Guide 54*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg054.htm (accessed 26/04/04)

Adverse Effects, Treatment, and Precautions

As for Chlorinated Insecticides, p. 2150.2.

Serious adverse effects, including seizures and deaths, have been reported in patients who have used higher than recommended concentrations of lindane, or after a second application of lindane to the skin in the treatment of scabies and pediculosis: lindane should not be used as a first-line treatment in the management of the latter conditions. Babies, children, the elderly and people weighing less than 50 kg are considered to be particularly at risk. Lindane should not be used in patients who have a body-weight less than 50 kg, a history of epilepsy, have open or crusted sores on the skin around the head and neck or broken skin around the treatment areas, or skin conditions such as psoriasis or atopic dermatitis. Lindane is excreted into the breast milk but the amount excreted is not considered to be clinically significant; breastfeeding should, however, be avoided for at least 4 days after stopping treatment. There are limited human data on the use of lindane in pregnancy and *animal* data indicate a low risk for congenital defects, but because of its serious toxic potential safer alternative products are recommended.

Seizures have been reported after the topical use of lindane.[1] In reply, one of the manufacturers stated that up to the end of 1983 they were aware of 21 cases of convulsive disorders apparently associated with the use of their product; it had been used by over 40 million people. Of the 21 cases, the seizures were definitely or probably caused by the product in 11, but in 9 the seizures were associated with ingestion or excessive use.[2] From 1998 to 2003, 870 cases of unintentional lindane ingestion were reported in the USA.[3] Signs and symptoms of illness after ingestion included abdominal cramps, confusion, cough, headache, nausea, oral irritation, seizures, and vomiting.

Isolated reports of adverse effects associated with lindane include disseminated intravascular coagulation and subsequent death after oral ingestion[4] and aplastic anaemia after prolonged topical exposure (twice daily application for 3 weeks).[5]

1. Etherington JD. Major epileptic seizures and topical gammabenzene hexachloride. *BMJ* 1984; **289:** 228.
2. Kelly VT. Major epileptic seizures and topical gammabenzene hexachloride. *BMJ* 1984; **289:** 837.
3. CDC. Unintentional topical lindane ingestions—United States, 1998–2003. *MMWR* 2005; **54:** 533–5. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5421a2.htm (accessed 22/04/08)
4. Rao CVSR, *et al*. Disseminated intravascular coagulation in a case of fatal lindane poisoning. *Vet Hum Toxicol* 1988; **30:** 132–4.
5. Rauch AE, *et al*. Lindane (Kwell)-induced aplastic anemia. *Arch Intern Med* 1990; **150:** 2393–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gamma-Scab; Hexa-Defital†; ***Austria***: Jacutin†; ***Braz.***: Pedileten; Pilensar†; ***Canad.***: Hexit; ***Chile***: Plomurol; ***Hung.***: Jacutin†; ***India***: Ascabiol; Bexarid; Gab; Gamaric; Gamascab; GBHC; Labscab; Nit-N-Mite†; Scaboma; ***Indon.***: Obat Kutu Rambut Cap Dua Jempol†; ***Israel***: Bicide†; ***Malaysia***: Jacutin†; Scaboma; ***Mex.***: Herklin; ***NZ***: Benhex; ***Pol.***: Jacutin†; ***S.Afr.***: Gambex; ***Singapore***: Jacutin; ***Switz.***: Jacutin†; ***Thai.***: Jacutin†; ***Venez.***: Somergan.

Multi-ingredient Preparations. ***Arg.***: Gamma-Scab; Hexa-Defital†; Lyndan; ***Fr.***: Elenol†; ***India***: Agloscab; Antiscab; Emscab†; Escab Plus; Freescab; Gamaley; Gamazex; GBTop; Novascab; NT-Scab; Scabine; Scaboma; Scarab; ***Indon.***: Scabicid; Topicide†; ***Mex.***: Herklin; ***Singapore***: Jacutin.

Pharmacopoeial Preparations
USP 36: Lindane Cream; Lindane Lotion; Lindane Shampoo.

Lufenuron *(BAN, rINN)*

CGA-184699; Lufenurón; Lufénurone; Lufenuronum; Луфенурон.

1-[2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea; (*RS*)-*N*-[2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenylcarbamoyl]-2,6-difluorobenzamide.

$C_{17}H_8Cl_2F_8N_2O_3$=511.1

CAS — 103055-07-8.

ATC Vet — QP53BC01.

UNII — 1R754M4918.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Lufenuron (Anhydrous) for Veterinary Use). A white or pale yellow powder. It exhibits polymorphism. Practically insoluble in water; soluble in anhydrous ethanol; freely soluble in acetonitrile.

Profile

Lufenuron is used as a systemic ectoparasiticide in veterinary practice; it is given orally (by adding to the feed) or by injection to the host animal.

Malathion *(BAN)*

Carbofos; Carbophos; Compound 4047; Malathionum; Malatión; Malation; Malationas; Malationi; OMS-1; Карбофос; Малатион.

Diethyl 2-(dimethoxyphosphinothioylthio)succinate.

$C_{10}H_{19}O_6PS_2$=330.3

CAS — 121-75-5.

ATC — P03AX03.

ATC Vet — QP53AF12.

UNII — U5N7SU872W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Malathion). A clear, colourless or slightly yellowish liquid. It freezes at about 3 degrees. Slightly soluble in water; miscible with alcohol, with acetone, with cyclohexane, and with vegetable oils. Store in airtight containers. Protect from light.

USP 36: (Malathion). A clear, colourless, or slightly yellowish liquid with a characteristic odour. Congeals at about 2.9 degrees. Slightly soluble in water; miscible with alcohols, with ethers, with esters, with ketones, with aromatic and alkylated aromatic hydrocarbons, and with vegetable oils. Store in airtight containers. Protect from light.

Stability. The manufacturers have reported that malathion is sensitive to heat and is degraded at temperatures above 30 degrees.

Uses and Administration

Malathion is an organophosphorus insecticide (p. 2158.3). It is used in the treatment of head and pubic pediculosis (p. 2147.3) and in scabies (p. 2148.1); lotions of 0.5% and shampoos of 1% are commonly available. Lotions are generally preferred to shampoos as the contact time is longer. Aqueous lotions are preferred to treat pubic lice and scabies because alcoholic lotions are irritant to excoriated skin and the genitalia; aqueous lotions may also be preferable in asthmatic subjects or children to avoid alcoholic fumes. Skin or hair treated with an alcohol-based preparation should be allowed to dry naturally.

Malathion is also used in veterinary practice, agriculture, and horticulture. It is widely used for adult and larval mosquito control although resistance occurs.

Adverse Effects, Treatment, and Precautions

As for Organophosphorus Insecticides, p. 2158.3.

Malathion is one of the safer organophosphorus insecticides but its toxicity may be increased by the presence of impurities.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies malathion as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Toxicity. Acute renal insufficiency has been described in a patient associated with excessive exposure to a malathion spray.[1] The condition resolved without specific treatment. Renal toxicity had not previously been associated with organophosphorus pesticides. In a second case of acute poisoning,[2] due to ingestion of malathion, mild transient renal insufficiency and proteinuria with several other late complications including cardiac arrhythmias, pulmonary oedema, diffuse interstitial fibrosis, and muscle weakness due to peripheral neuropathy, were seen subsequent to recovery from the initial cholinergic toxicity.

1. Albright RK, *et al*. Malathion exposure associated with acute renal failure. *JAMA* 1983; **250:** 2469.
2. Dive A, *et al*. Unusual manifestations after malathion poisoning. *Hum Exp Toxicol* 1994; **13:** 271–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Prioderm; Radikal; ***Denm.***: Prioderm; ***Fin.***: Prioderm; ***Fr.***: Prioderm; ***Gr.***: Sicaril; Specifthir; Zitotox; ***Hong Kong***: A-Lices; ***Irl.***: Derbac-M; Prioderm†; Quellada M†; Suleo-M†; ***Israel***: Prioderm; ***Ital.***: Aftir Gel; ***Malaysia***: A-Lices; ***Neth.***: Prioderm; ***Norw.***: Prioderm; ***NZ***: A-Lices; Derbac-M; Prioderm†; ***Philipp.***: A-Lices; ***Rus.***: Pedilin (Педилин)†; ***Singapore***: A-Lices; Derbac-M; Lice Care; ***Swed.***: Prioderm; ***Switz.***: Prioderm; ***Thai.***: A-Lices; ***UK***: Derbac-M; Prioderm†; Quellada M†; ***Ukr.***: Pedilin (Педилин); ***USA***: Ovide.

Multi-ingredient Preparations. ***Arg.***: Para Plus; ***Belg.***: Para Plus; ***Fr.***: Para Plus; ***Gr.***: Para-plus; ***Israel***: Monocide†; Para Plus; ***NZ***: Para Plus; ***Rus.***: Para Plus (Пара Плюс); ***Turk.***: Sac-Bi-Toks; ***Ukr.***: Para Plus (Пара Плюс).

Pharmacopoeial Preparations
BP 2014: Malathion Lotion; Malathion Shampoo;
USP 36: Malathion Lotion.

Metaldehyde

Metaldehído; Метальдегид.

$(C_2H_4O)_x$

CAS — 9002-91-9.

Description. Metaldehyde is a cyclic polymer of acetaldehyde.

Uses

Metaldehyde is a molluscicide used in pellets against slugs and snails. It is an ingredient of some firelighters.

'Meta' is compressed metaldehyde which has been used as a solid fuel burning with a non-luminous carbon-free flame.

Adverse Effects and Treatment

Symptoms of poisoning by metaldehyde, which may be delayed, include vomiting and diarrhoea, fever, drowsiness, convulsions, and coma. Death from respiratory failure may occur within 48 hours. Kidney and liver damage may occur.

Treatment is symptomatic, although activated charcoal may be considered if more than 50 mg/kg has been ingested within the preceding hour.

References.
1. Longstreth WT, Pierson DJ. Metaldehyde poisoning from slug bait ingestion. *West J Med* 1982; **137:** 134–7.
2. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.
3. Bleakley C, *et al.* Self-poisoning with metaldehyde. *Emerg Med J* 2008; **25:** 381–2.

Methomyl

Metomilo; Метомил.
S-Methyl *N*-(methylcarbamoyloxy)thioacetimidate.
$C_5H_{10}N_2O_2S$=162.2
CAS — 16752-77-5.
UNII — 1NQ08HN02S.

Profile

Methomyl is a carbamate insecticide (p. 2149.3) that has been used in agriculture.

References.
1. WHO. Methomyl health and safety guide. *IPCS Health and Safety Guide 97.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg097.htm (accessed 26/04/04)
2. WHO. Methomyl. *Environmental Health Criteria 178.* Geneva: WHO, 1996. Available at: http://www.inchem.org/documents/ehc/ehc/ehc178.htm (accessed 26/04/04)

Reports[1,2] of poisoning with methomyl and its management.

1. Martinez-Chuecos J, *et al.* Management of methomyl poisoning. *Hum Exp Toxicol* 1990; **9:** 251–4.
2. Buchholz U, *et al.* An outbreak of food-borne illness associated with methomyl-contaminated salt. *JAMA* 2002; **288:** 604–10.

Methoprene *(rINN)*

Méthoprène; Methoprenum; Metopreno; ZR-515; Метопрен.
Isopropyl 11-methoxy-3,7,11-trimethyldodeca-2(*E*),4(*E*)-dienoate.
$C_{19}H_{34}O_3$=310.5
CAS — 40596-69-8.
ATC Vet — QP53AX28.
UNII — 8B830OJ2UX.

Profile

Methoprene is an insect growth regulator which mimics the action of insect juvenile hormones and, if it is applied at the appropriate period of sensitivity, it causes death by preventing the transformation of larva to pupa. It is used against a variety of insects including fleas and mosquitoes. It is used in veterinary practice for the control of ectoparasites in the environment, rather than being applied to the animals themselves. It is also used in agriculture.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Altopou†.

Methoxychlor

Methoxy-DDT; Metoksychlor; Metoxicloro; Метоксихлор.
1,1,1-Trichloro-2-2-bis(*p*-methoxyphenyl)-ethane.
$C_{16}H_{15}Cl_3O_2$=345.6
CAS — 72-43-5.
UNII — RIA79UD69L.

Profile

Methoxychlor is a chlorinated insecticide (p. 2150.2) used in agriculture, horticulture, and veterinary practice.

Methyl Bromide

Bromometano; Metilo, bromuro de; Monobromometano; Метилбромид.
Bromomethane; Monobromomethane.
CH_3Br=94.94
CAS — 74-83-9.
UNII — 9V42E1Z7B6.

Uses

Methyl bromide has been used as an insecticidal fumigant for soil and some foodstuffs.

When supplied for fumigation it usually contains chloropicrin as a lachrymatory warning agent.

Methyl bromide has been used as a gaseous disinfectant; it has low antimicrobial activity but good penetrating power.

Methyl bromide was formerly used with carbon tetrachloride in some fire extinguishers. It has also been used as a refrigerant.

General references.
1. WHO. Methyl bromide (bromomethane) health and safety guide. *IPCS Health and Safety Guide 86.* Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/hsg/hsg/hsg86_e.htm (accessed 26/04/04)
2. WHO. Methyl bromide. *Environmental Health Criteria 166.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc166.htm (accessed 26/04/04)

Adverse Effects, Treatment, and Precautions

Methyl bromide is a vesicant. Toxic effects after inhalation or percutaneous absorption are mainly due to neurotoxicity and include dizziness, headache, vomiting, blurred vision, weakness, ataxia, confusion, mania, hallucinations, mental depression, convulsions, pulmonary oedema, and coma. Renal and hepatic toxicity may also occur and death may be due to circulatory collapse or respiratory failure. Onset of symptoms may be preceded by a latent period. Concentrations of 1% or more are irritant to the eyes. Treatment is symptomatic although dimercaprol or acetylcysteine therapy has been tried.

Rubber absorbs and retains methyl bromide and should not therefore be used in protective clothing.

References[1-10] to toxicity of methyl bromide including reports of poisoning.

1. Chavez CT, *et al.* Methyl bromide optic atrophy. *Am J Ophthalmol* 1985; **99:** 715–19.
2. Langard S, *et al.* Fatal accident resulting from methyl bromide poisoning after fumigation of a neighbouring house: leakage through sewage pipes. *J Appl Toxicol* 1996; **16:** 445–8.
3. De Haro L, *et al.* Central and peripheral neurotoxic effects of chronic methyl bromide intoxication. *J Toxicol Clin Toxicol* 1997; **35:** 29–34.
4. Michalodimitrakis MN, *et al.* Death following intentional methyl bromide poisoning: toxicological data and literature review. *Vet Hum Toxicol* 1997; **39:** 30–4.
5. Horowitz BZ, *et al.* An unusual exposure to methyl bromide leading to fatality. *J Toxicol Clin Toxicol* 1998; **36:** 353–7.
6. Lifshitz M, Gavrilov V. Central nervous system toxicity and early peripheral neuropathy following dermal exposure to methyl bromide. *J Toxicol Clin Toxicol* 2000; **38:** 799–801.
7. Yamano Y, *et al.* Three cases of acute methyl bromide poisoning in a seedling farm family. *Ind Health* 2001; **39:** 353–8.
8. Hoizey G, *et al.* An unusual case of methyl bromide poisoning. *J Toxicol Clin Toxicol* 2002; **40:** 817–21.
9. Geyer HL, *et al.* Methyl bromide intoxication causes reversible symmetric brainstem and cerebellar MRI lesions. *Neurology* 2005; **64:** 1279–81.
10. Breeman W. Methylbromide intoxication: a clinical case study. *Adv Emerg Nurs J* 2009; **31:** 153–60.

Naled

Bromchlophos; Налед.
Dimethyl 1,2-dibromo-2,2-dichloroethyl phosphate.
$C_4H_7Br_2Cl_2O_4P$=380.8
CAS — 300-76-5.
UNII — PAM1AI9KU1.

Profile

Naled is an organophosphorus insecticide used as a topical ectoparasiticide in veterinary practice.

Naphthalene

Naftalen; Naftaleno; Naphthalin; Нафталин.
$C_{10}H_8$=128.2
CAS — 91-20-3.
UNII — 2166IN72UN.

Uses

Naphthalene has been used in lavatory deodorant discs and in mothballs. It has also been used as a soil fumigant.

Adverse Effects, Treatment, and Precautions

Ingestion of naphthalene can produce headache, nausea and vomiting, diarrhoea, profuse sweating, dysuria, coma, and convulsions. Less than one naphthalene mothball (200 to 500 mg) may cause haemolysis. Ingestion of 5 to 15 g is considered lethal for adults and a dose as low as 74 mg/kg has proved fatal. In children ingestion of 100 mg/kg is lethal. Doses as low as 2 g and 80 mg/kg ingested over 2 days have proved fatal in young children. Treatment is symptomatic; lavage may be considered if the patient presents within 1 hour of ingestion. The vapour is irritating to the eyes; chronic exposure has led to cataract formation. Haemolytic anaemia and haematuria leading to acute renal failure may occur particularly in persons with G6PD deficiency. Blood transfusions may be required.

Pregnancy. Haemolytic anaemia in a neonate has been attributed to inhalation of naphthalene by the mother during the twenty-eighth week of pregnancy.[1]

1. Athanasion M, *et al.* Hemolytic anemia in a female newborn infant whose mother inhaled naphthalene before delivery. *J Pediatr* 1997; **130:** 680–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Tartephedreel; ***Ger.***: Pulmo Bronchialcomplex.

Norbormide

McN-1025; Norbormida; Норбормид.
5-[α-Hydroxy-α-(2-pyridyl)benzyl]-7-[α-(2-pyridyl)benzylidene]-8,9,10-trinorborn-5-ene-2,3-dicarboximide.
$C_{33}H_{25}N_3O_3$=511.6
CAS — 991-42-4.

Profile

Norbormide is a selective rodenticide effective against most species of *rats*, in which it produces extreme irreversible peripheral vasoconstriction. It is not very toxic to other rodents.

Organophosphorus Insecticides

Insecticidas organofosforados; Organofosforlu İnsektisitler.

Description. The organophosphorus or organophosphate insecticides may be esters, amides, or thiol derivatives of phosphoric, phosphonic, phosphorothioic, or phosphonothioic acids.

References.
1. WHO. Organophosphorus insecticides: a general introduction. *Environmental Health Criteria 63.* Geneva: WHO, 1986. Available at: http://www.inchem.org/documents/ehc/ehc/ehc63.htm (accessed 19/07/04)

Adverse Effects

Organophosphorus insecticides are potent cholinesterase inhibitors and can be very toxic. This inhibition results in both muscarinic and nicotinic effects with some central involvement.

Toxic effects may include abdominal cramps, nausea, vomiting, diarrhoea, pancreatitis, urinary incontinence, miosis or mydriasis, weakness, respiratory disturbances, lachrymation, increased salivation and sweating, bradycardia or tachycardia, hypotension or hypertension, cyanosis, muscular twitching, and convulsions. Some organophosphorus compounds cause delayed neuropathy. CNS symptoms include restlessness, anxiety, dizziness, confusion, coma, and depression of the respiratory or cardiovascular system. Patients may experience mental disturbances. Inhalation or external contact can cause local as well as systemic effects.

Repeated exposure may have a cumulative effect though the organophosphorus insecticides are, in contrast to the chlorinated insecticides, rapidly metabolised and excreted and are not appreciably stored in body tissues.

References[1-12] to the adverse effects and poisoning encountered with organophosphorus compounds such as insecticides (including sheepdips).

1. Minton NA, Murray VSG. A review of organophosphate poisoning. *Med Toxicol* 1988; **3:** 350–75.
2. Karalliedde L, Senanayake N. Organophosphorus insecticide poisoning. *Br J Anaesth* 1989; **63:** 736–50.
3. Öztürk MA, *et al.* Anticholinesterase poisoning in Turkey—clinical, laboratory and radiologic evaluation of 269 cases. *Hum Exp Toxicol* 1990; **9:** 273–9.
4. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 24/07/08)
5. Casey P, Vale JA. Deaths from pesticide poisoning in England and Wales: 1945–1989. *Hum Exp Toxicol* 1994; **13:** 95–101.
6. Eyer P. Neuropsychopathological changes by organophosphorus compounds—a review. *Hum Exp Toxicol* 1995; **14:** 857–64.
7. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.
8. Steenland K. Chronic neurological effects of organophosphate pesticides. *BMJ* 1996; **312:** 1312–13.
9. Brown AA, Brix KA. Review of health consequences from high-, intermediate- and low-level exposure to organophosphorus nerve agents. *J Appl Toxicol* 1998; **18:** 393–408.
10. Koksal N, *et al.* Organophosphate intoxication as a consequence of mouth-to-mouth breathing from an affected case. *Chest* 2002; **122:** 740–1.
11. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ* 2007; **334:** 629–34.
12. Aardema H, *et al.* Organophosphorus pesticide poisoning: cases and developments. *Neth J Med* 2008; **66:** 149–53.

Treatment of Adverse Effects

Rapid treatment for poisoning with organophosphorus insecticides is essential. Use of gastric lavage may be considered if a substantial amount has been ingested within 1 to 2 hours of presentation, unless the product is

formulated in a hydrocarbon solvent (as there is a high risk of fatal aspiration pneumonia). Contaminated clothing should be removed and the skin, including any areas contaminated by vomiting or hypersecretion, should receive copious and prolonged washing with soap and water. Contamination of the eye is treated by washing of the conjunctiva. The patient should be treated with atropine (see Poisoning, p. 1311.3) and either pralidoxime (p. 1571.2) or obidoxime (p. 1566.3) and symptomatic treatment should be instituted. Diazepam is sometimes given; it may be necessary to give it parenterally in moderate to severe poisoning to control muscle fasciculations and convulsions; oral dosage in mild poisoning may be helpful in relieving anxiety. The patient should be observed for signs of deterioration due to delayed absorption.

Paraquat

Parakuat; Паракват.
1,1′-Dimethyl-4,4′-bipyridyldiylium ion.
$C_{12}H_{14}N_2$=186.3
CAS — 4685-14-7.
UNII — PLG39H7695.

Paraquat Dichloride

Paraquat, dicloruro de; Паракват Дихлорид.
$C_{12}H_{14}Cl_2N_2$=257.2
CAS — 1910-42-5.
UNII — 2KZ83GSS73.

Uses

Paraquat is a contact herbicide widely used as the dichloride in agriculture and horticulture. Liquid concentrates are supplied in the UK only to approved users.

Adverse Effects

Concentrated solutions of paraquat may cause irritation, inflammation, and possibly blistering of the skin, cracking and shedding of the nails, and delayed healing of cuts and wounds. It is not significantly absorbed from undamaged skin. A few fatalities have occurred after skin contact, but these appear to have been associated with prolonged contact and concentrated solutions.

Splashes in the eye cause severe inflammation, which may be delayed for 12 to 24 hours, corneal oedema, reduced visual acuity, and extensive superficial stripping of the corneal and conjunctival epithelium, which usually slowly heals. Inhalation of dust or spray may cause nasal bleeding.

Paraquat weedkillers available for use in domestic gardens contain 2.5% w/v paraquat, sometimes with other herbicides such as diquat. While this strength of paraquat can cause nausea and vomiting as well as some respiratory changes when ingested, it is not considered to be a lethal form.

Most of the cases of severe poisoning follow the ingestion or sometimes injection of the concentrated forms of paraquat herbicide (20% w/v), the distribution of which is restricted to agriculturalists and horticulturalists. Ingestion of, or dermal exposure to small amounts of concentrated paraquat may result in severe pulmonary fibrosis and death within 24 hours. A dose of 10 to 15 mL of the concentrate (20% w/v) is considered to be lethal. Most, but not all patients who ingest 20 to 40 mg of paraquat ion/kg (7.5 to 15 mL of the concentrate) die within 2 or 3 weeks after ingestion. Ingestion of doses of more than 40 mg of paraquat ion/kg (more than 15 mL of concentrate) usually results in death within 1 to 7 days after ingestion. The irritant effects of paraquat are reflected in oesophageal ulceration and gastrointestinal effects. There is widespread organ damage, most notably involving the kidneys and lungs. In such poisoning death is virtually certain and occurs rapidly.

Preparations of paraquat may contain an emetic or a laxative and some contain a malodorous agent to deter ingestion.

General references[1-9] concerning paraquat toxicity and its treatment.

1. WHO. Paraquat and diquat. *Environmental Health Criteria 39*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc39.htm (accessed 26/04/04)
2. Bismuth C, *et al*. Paraquat poisoning. *Drug Safety* 1990; **5:** 243–51.
3. Pond SM. Manifestations and management of paraquat poisoning. *Med J Aust* 1990; **152:** 256–9.
4. Paraquat health and safety guide. *Health and Safety Guide 51*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg051.htm (accessed 26/04/04)
5. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 21/07/08)
6. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
7. Eddleston M, *et al*. Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review. *Q J Med* 2003; **96:** 809–24.
8. Dinis-Oliveira RJ, *et al*. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. *Crit Rev Toxicol* 2008; **38:** 13–71.
9. Chen HW, *et al*. Intravenous paraquat poisoning. *J Chin Med Assoc* 2009; **72:** 547–50.

Treatment of Adverse Effects

After contact with paraquat, contaminated clothing should be removed and the skin washed with soap and water. The eyes, if splashed, should be irrigated; later topical therapy may involve the symptomatic use of antibacterials or corticosteroids.

There is no specific treatment for paraquat poisoning and the immediate aim is to remove or inactivate the paraquat. Although the benefit of gastric decontamination is uncertain, if the patient presents less than 6 hours after ingestion the initial management involves giving an oral adsorbent, preferably activated charcoal in a dose of 100 g and followed by 50 g every 2 hours for up to 6 hours post ingestion. Fuller's earth and bentonite have been used as alternative oral adsorbents. When none of these adsorbents is available, a suspension of clay or of uncontaminated soil should be considered if medical attention is likely to be delayed. An osmotic laxative may be used with the first dose of the adsorbent in order to hasten bowel evacuation and prevent obstruction due to the adsorbent. Patients may require intensive supportive therapy, but oxygen should not be given initially as it appears to enhance the pulmonary toxicity of paraquat; however, it may be needed in later stages as part of palliative care.

Methods aimed at hastening elimination such as forced diuresis, peritoneal dialysis, haemodialysis, and haemoperfusion have been tried but the first three appear to be ineffective and results with the last method have varied; no method is of proven value.

For some general references concerning the treatment of paraquat toxicity, see under Adverse Effects, above.

Once paraquat has been absorbed, moderate to severe poisoning may result in acute renal failure, hepatitis, and pulmonary fibrosis; death may occur after 2 to 3 weeks. Pulse therapy with cyclophosphamide and methylprednisolone might be of benefit in such patients but not in those with fulminant poisoning.[1,2] Delayed management with such immunosuppressive regimens has been described;[3] however, use of sirolimus has proved unsuccessful in another case.[4]

1. Lin J-L, *et al*. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. *Thorax* 1996; **51:** 661–3.
2. Lin J-L, *et al*. A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat poisoned patients. *Am J Respir Crit Care Med* 1999; **159:** 357–60. Correction to the dose of cyclophosphamide. *ibid*. 2001; **163:** 292.
3. Descatha A, *et al*. Delayed immunosuppressive treatment in life-threatening paraquat ingestion: a case report. *J Med Toxicol* 2009; **5:** 76–9.
4. Lorenzen JM, *et al*. Failed rescue therapy with rapamycin after paraquat intoxication. *Clin Toxicol* 2010; **48:** 84–6.

Parathion

Paratión; Паратион.
O,O-Diethyl *O*-4-nitrophenyl phosphorothioate.
$C_{10}H_{14}NO_5PS$=291.3
CAS — 56-38-2.
UNII — 61G466064D.

Profile

Parathion is an organophosphorus insecticide (p. 2158.3) that has been used in agriculture and horticulture. Its metabolite diethyl nitrophenyl phosphate (paraoxon) contributes to its toxicity.

References.

1. WHO. Parathion health and safety guide. *IPCS Health and Safety Guide 74*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg74.htm (accessed 26/04/04)

Reports[1-7] of poisoning with parathion.

1. Anastassiades CJ, Ioannides M. Organophosphate poisoning and auricular fibrillation. *BMJ* 1984; **289:** 290.
2. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; **4:** 339–40.
3. Clifford NJ, Nies AS. Organophosphate poisoning from wearing a laundered uniform previously contaminated with parathion. *JAMA* 1989; **262:** 3035–6.
4. Wang M-H, *et al*. Q-T interval prolongation and pleomorphic ventricular tachyarrhythmia ('Torsade de pointes') in organophosphate poisoning: report of a case. *Hum Exp Toxicol* 1998; **17:** 587–90.
5. Eyer F, *et al*. Human parathion poisoning: a toxicokinetic analysis. *Toxicol Rev* 2003; **22:** 143–63.
6. Lund CM, Iversen G. Bladanforgiftning forekommer endnu. *Ugeskr Laeger* 2005; **167:** 3195–6.
7. Hoffmann U, Papendorf T. Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med* 2006; **32:** 464–8.

Pentachlorophenol

PCP; Penta; Pentaclorofenol; Пентахлорфенол.
C_6HCl_5O=266.3
CAS — 87-86-5.
UNII — D9BSU0SE4T.

NOTE. The name PCP has also been used as a synonym for phencyclidine hydrochloride (p. 2587.3).

Uses

Pentachlorophenol has been used mainly as the sodium salt (C_6Cl_5NaO = 288.3), as a preservative for a wide range of industrial and agricultural products, including wood and other building materials, textiles, glues, and starch. It has also been used for the control of slime and algae, and as a molluscicide, fungicide, and herbicide.

Adverse Effects, Treatment, and Precautions

Pentachlorophenol may be absorbed in toxic amounts through the skin or by inhalation, as well as by ingestion. Pentachlorophenol and its aqueous solutions are irritant to the eyes, mucous membranes, and to the skin, and may produce caustic burns. The systemic effects are due to uncoupling of oxidative phosphorylation with consequent stimulation of cellular metabolism. Acute poisoning with pentachlorophenol increases metabolic rate, leading to raised temperature with copious sweating and thirst, restlessness, fatigue, increased rate and depth of respiration, and tachycardia. There may be abdominal pain and nausea, and death has occurred from respiratory failure. Symptoms of subacute or chronic poisoning include hyperpyrexia and CNS, haematological, renal, reproductive, respiratory, and skin disorders.

Treatment is symptomatic. Raised body temperature should be treated by physical means; the use of antipyretics is not recommended since they can increase toxicity.

Reviews[1-5] of the toxicity of pentachlorophenol.

1. Health and Safety Executive. Pentachlorophenol. *Toxicity Review 5*. London: HMSO, 1982.
2. WHO. Pentachlorophenol. *Environmental Health Criteria 71*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc71.htm (accessed 26/04/04)
3. Pentachlorophenol health and safety guide. *Health and Safety Guide 19*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg019.htm (accessed 26/04/04)
4. Jorens PG, Schepens PJC. Human pentachlorophenol poisoning. *Hum Exp Toxicol* 1993; **12:** 479–95.
5. Proudfoot AT. Pentachlorophenol poisoning. *Toxicol Rev* 2003; **22:** 3–11.

There have been reports of malignant neoplasms,[1,2] aplastic anaemia,[3] pancreatitis,[4] intravascular haemolysis,[5] and urticaria[6] associated with exposure to pentachlorophenol.

1. Greene MH, *et al*. Familial and sporadic Hodgkin's disease associated with occupational wood exposure. *Lancet* 1978; **ii:** 626–7.
2. Hardell L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. *Lancet* 1979; **i:** 55–6.
3. Roberts HJ. Aplastic anemia due to pentachlorophenol. *N Engl J Med* 1981; **305:** 1650–1.
4. Cooper RG, Macaulay MB. Pentachlorophenol pancreatitis. *Lancet* 1982; **i:** 517.
5. Hassan AB, *et al*. Intravascular haemolysis induced by pentachlorophenol. *BMJ* 1985; **291:** 21–2.
6. Kentor PM. Urticaria from contact with pentachlorophenate. *JAMA* 1986; **256:** 3350.

Pharmacokinetics

Pentachlorophenol may be absorbed after ingestion or inhalation or through the skin. After ingestion, the majority of a dose is eliminated in the urine as unchanged pentachlorophenol and its glucuronide, with small amounts appearing in the faeces.

Permethrin *(BAN, USAN, rINN)*

Perméthrine; Permethrinum; Permetriini; Permetrin; Permetrina; Permetryna; Перметрин.
3-Phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{21}H_{20}Cl_2O_3$=391.3
CAS — 52645-53-1.
ATC — P03AC04.
ATC Vet — QP53AC04.
UNII — 509F88P9SZ.

Profile

Permethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used in the treatment of head pediculosis (p. 2147.3) as a 1% application; there have been signs of resistance. It is also used as a 5% cream for pubic pediculosis (p. 2147.3) and as an acaricide in the treatment of scabies (p. 2148.1).

Permethrin is also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide.

Permethrin is active against mosquitoes and is widely used for the impregnation of bednets and curtains in the control of malaria (p. 644.1). It is also active against blackflies in the adult and larval stages and is used for the

larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2). It is also active against tsetse flies.

Permethrin is suitable for aircraft disinsection.

References.
1. WHO. Permethrin health and safety guide. *IPCS Health and Safety Guide 33*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg033.htm (accessed 26/04/04)
2. WHO. Permethrin. *Environmental Health Criteria 94*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc94.htm (accessed 26/04/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies permethrin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Assy Crema de Enjuague; Assy Espuma; Assy Tratamiento Integral; B-Jen; Blum; Capitis; Dermoper; Fripi; Hairclin; Helpp; Kinderval; Kwell; Nopucid; Pedicrem; Pelo Libre; Quitoso NF; Witty; ***Austral.***: Lyclear; Pyrifoam; Quellada; ***Austria***: Infectoscab; ***Belg.***: Mouskito Textile†; Nix; Zalvor; ***Braz.***: Clean Hair; Keltrina; Kwell; Nedax Plus; Nedax; Pediletan Permetrina; Piodrex; Pioletal; Piosan; ***Canad.***: Kwellada-P; Nix; ***Chile***: Kilnits; Nolais; ***Cz.***: Infectoscab; ***Denm.***: Nix; ***Fin.***: Nix; ***Fr.***: Biovectrol Tissu; Cinq sur Cinq; Insect Ecran; Mousticologne†; Parapoux†; Pharmavoyage Moustiquaires; ***Ger.***: InfectoPedicul; Infectoscab; ***Gr.***: Nix; ***Hong Kong***: A-Scabs; Quellada; ***Hung.***: Infectoscab; ***India***: Clearkin; Endlic; Jolice; Medilice; Merisoft; Metper; Mityscab; Monoscab; Perlice; Permite; ***Indon.***: Scabimite; ***Irl.***: Lyclear; ***Israel***: Lyclear; Mite-X†; New-Nok; Zehu-Ze†; ***Ital.***: Nix; Pre Clean Mom; Scabiacid; Scabianil; ***Malaysia***: A-Scabs; ***Mex.***: Novo-Herklin 2000; Scabisan Plus; Scabisan; ***Neth.***: Loxazol; ***Norw.***: Nix; ***NZ***: Lyderm; Pyrifoam; ***Philipp.***: Kwell Reformulated; Lindell; Pyrifoam; ***Pol.***: Infectoscab; ***Port.***: Nix; Quitoso; ***Rus.***: Nittyfor (Ниттифор); Nix (Никс); ***S.Afr.***: Lyclear; Skabi-Rid; ***Spain***: Perme-Cure; Sarcop; ***Swed.***: Nix; ***Switz.***: Loxazol; ***Turk.***: Anti-Scab; Kwellada; Niksen†; Zalvor; ***UK***: Lyclear Creme Rinse; Residex P55; ***Ukr.***: Nittyfor (Ниттифор); Permin (Пермин); ***USA***: Acticin; Elimite; Nix; ***Venez.***: Piokil Plus.

Multi-ingredient Preparations. ***Arg.***: Bencil Scab; Detebencil Nit; Detebencil; Detebencil; Hexa-Defital Plus; Hexabencil; Kinderval Max; Para Plus; Perbel; Permecil; ***Belg.***: Para Plus; Shampoux†; ***Fr.***: Altopou†; Charlieu Anti-Poux†; Para Plus; Pyreflor†; Pyreflor; ***Gr.***: Para-plus; ***India***: Escab Plus; ***Israel***: Para Plus; ***Ital.***: Antiscabbia CM; ***NZ***: Active Duty with Sunscreen; Active Duty; Para Plus; ***Rus.***: Para Plus (Пара Плюс); ***S.Afr.***: Nitagon; ***Ukr.***: Para Plus (Пара Плюс).

Phenothrin *(BAN, rINN)*

Fenotrin; Fenotrina; Phénothrine; Phenothrinum; S-2539; Фенотрин.

3-Phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{23}H_{26}O_3$=350.5

CAS — 26002-80-2.

ATC — P03AC03.

ATC Vet — QP53AC03.

UNII — 707484X33X.

Profile

Phenothrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1). It is used for the treatment of head and pubic pediculosis (p. 2147.3) as a 0.2% alcoholic or 0.5% aqueous lotion, or as a 0.5% alcoholic foam; as with permethrin there have been signs of resistance.

Phenothrin is also used in veterinary practice as a topical ectoparasiticide, as a household insecticide, and for the disinsection of public areas and aircraft.

References.
1. WHO. d-Phenothrin health and safety guide. *IPCS Health and Safety Guide 32*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg032.htm (accessed 26/04/04)
2. WHO. d-Phenothrin. *Environmental Health Criteria 96*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc96.htm (accessed 26/04/04)

Aircraft disinsection. References.
1. Russell RC, Paton R. In-flight disinsection as an efficacious procedure for preventing international transport of insects of public health importance. *Bull WHO* 1989; **67**: 543–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nopucid MC; Sumo; ***Cz.***: Parasidose; ***Fr.***: Itax Antipoux; Item Antipoux; Parasidose; ***Gr.***: Ivaliten; Pubex; Sitem; Venatren; ***Irl.***: Full Marks†; Headmaster†; ***Israel***: Sof-Sof†; ***Ital.***: Cruzzy Shampoo Potenziato alla Sumitrina; Mediker; Mom Gel; Mom Shampoo Schiuma; Neo Mom; Ottocid; ***Mex.***: Herklin NF; ***Mon.***: Hegor; ***NZ***: Full Marks; Parasidose; ***Port.***: Parasidose; ***Rus.***: Anti-Bit (Анти-Вит)†; Itax (Итакс); Parasidose (Парази́Д(О3); ***Turk.***: Anti-Bit; ***UK***: Full Marks†; ***USA***: Pronto.

Multi-ingredient Preparations. ***Fr.***: A-Par; ***Gr.***: Cif Candioli; ***Ital.***: Neo Mom; ***Mex.***: Herklin NF.

Phosmet *(BAN)*

Fosmet; Фталофос; Фосмет.

O,O-Dimethyl phthalimidomethyl phosphorodithioate.

$C_{11}H_{12}NO_4PS_2$=317.3

CAS — 732-11-6.

ATC Vet — QP53AF06; QP53BB03.

UNII — VN04LI540Y.

Profile

Phosmet is an organophosphorus insecticide (p. 2158.3) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. It has also been used in agriculture and horticulture.

Phoxim *(BAN, pINN)*

Bayer-9053; Foksiimi; Foxim; Foxima; Phoxime; Phoximum; Фоксим.

2-(Diethoxyphosphinothioyloxyimino)-2-phenylacetonitrile.

$C_{12}H_{15}N_2O_3PS$=298.3

CAS — 14816-18-3.

ATC Vet — QP53AF01.

UNII — 6F5V775VPO.

Profile

Phoxim is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice. It is also used for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2).

Piperonal

Heliotropin; Heliotropina; Piperonylaldehyde; Пиперонал.

1,3-Benzodioxole-5-carboxaldehyde.

$C_8H_6O_3$=150.1

CAS — 120-57-0.

UNII — KE109YAK00.

Profile

Piperonal is used as an insect repellent against head lice (see Pediculosis, p. 2147.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Rappell.

Piperonyl Butoxide *(BAN)*

Piperonil Butoksit; Piperonilo, butóxido de; Пиперонилбутоксил.

5-[2-(2-Butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole.

$C_{19}H_{30}O_5$=338.4

CAS — 51-03-6.

UNII — LWK91TU9AH.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Piperonyl Butoxide). A yellow or pale brown oily liquid. Very slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with petroleum oils.

Profile

Piperonyl butoxide is used as a synergist for pyrethrin and pyrethroid insecticides. Mixtures of piperonyl butoxide and pyrethrins or pyrethroids are used in the treatment of pediculosis (p. 2147.3).

Piperonyl butoxide is considered to cause a variety of gastrointestinal effects as well as mild CNS depression.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Deca-Scab; Hexa-Defital NF; Limpacid; Nopucid Compuesto; Nopucid Rapida; Para Piojicida; Para Plus; Scabioderm; ***Austral.***: Banlice; Paralice; ***Belg.***: Para Plus; Para; Shampoux†; ***Braz.***: Deltacid Plus; ***Canad.***: Lice Killing; Pronto; R & C†; R & C; ***Chile***: Launol; ***Fr.***: Altopou†; Charlieu Anti-Poux†; Para Plus; Para Special Poux; Pyreflor†; Pyreflor; Spray-Pax; Spregal; ***Ger.***: Goldgeist; Jacutin; Spregal†; ***Gr.***: Lice-Enz; Mom; Para-plus; Runde; Spregal; ***Israel***: Acardust; Kin Soff†; Para Plus; ***Ital.***: Baygon; Cruzzy; Milice; Sinezan; ***Neth.***: Para-Speciaal†; Spregal; ***NZ***: Para Plus; ***Rus.***: Para Plus (Пара Плюс); Pedilin Ko (Педилин Ко)†; Spray-Pax (Спрей-пакс); Spregal (Спрегаль); ***S.Afr.***: Nitagon; Spregal; ***Turk.***: Kwell-P; ***UK***: Fortefog; Prevent; ***Ukr.***: Para Plus (Пара Плюс); Pedilin Ko (Педилин Ко)†; Spray-Pax (Спрей-Пакс)†; Spregal (Спрегаль); ***USA***: Blue; Licide; Pronto; Pyrinyl II; Pyrinyl Plus; RID; Tisit.

Pirimiphos-Methyl

Metilpirimifós; Pyrimiphos Methyl; Пиримифос-метил.

O-2-Diethylamino-6-methylpyrimidin-4-yl *O,O*-dimethyl phosphorothioate.

$C_{11}H_{20}N_3O_3PS$=305.3

CAS — 29232-93-7.

UNII — 2VQZ4PK548.

Profile

Pirimiphos-methyl is an organophosphorus insecticide (p. 2158.3). It is used in agriculture and domestically.

Propetamphos *(BAN)*

Propetamfos; Propetamfós; Пропетамфос.

Isopropyl (*E*)-3-[(ethylamino)(methoxy)phosphinothio-oxy]but-2-enoate.

$C_{10}H_{20}NO_4PS$=281.3

CAS — 31218-83-4.

ATC Vet — QP53AF09.

UNII — G4A07F635U.

Profile

Propetamphos is an organophosphorus insecticide (p. 2158.3) used as a topical ectoparasiticide in veterinary practice.

Propoxur *(BAN)*

Пропоксур.

2-Isopropoxyphenyl methylcarbamate.

$C_{11}H_{15}NO_3$=209.2

CAS — 114-26-1.

ATC Vet — QP53AE02.

UNII — BFH029TL73.

Profile

Propoxur is a carbamate insecticide (p. 2149.3) used as a topical ectoparasiticide in veterinary practice. It is also used as a fumigant in agriculture.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Baygon.

Pyraclofos

Piraclofós; Пираклофос.

(*RS*)-[*O*-1-(4-Chlorophenyl)pyrazol-4-yl *O*-ethyl *S*-propyl phosphorothioate].

$C_{14}H_{18}ClN_2O_3PS$=360.8

CAS — 77458-01-6.

Profile

Pyraclofos is an organophosphorus insecticide (p. 2158.3) used for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2).

Pyraclostrobin

Пираклостробин.

Methyl 2-[1-(4-chlorophenyl)pyrazol-3-yloxymethyl]-*N*-methoxycarbanilate.

$C_{19}H_{18}ClN_3O_4$=387.8

CAS — 175013-18-0.

UNII — DJW8M9OX1H.

Profile

Pyraclostrobin is a fungicide used for the treatment and control of fungal plant disease.

Pyrethrum Flower

Chrysanthème Insecticide; Dalmatian Insect Flowers; Flor del pelitre; Flor del Piretro; Insect Flowers; Insektenblüten; Piretro; Pyrethri Flos; Цветки Ромашки Далматской.
CAS — 8003-34-7 (pyrethrum); 121-21-1 (pyrethrin I); 121-29-9 (pyrethrin II); 25402-06-6 (cinerin I); 121-20-0 (cinerin II).
ATC — P03AC01.
ATC Vet — QP53AC01.
ATC Herb — HP03AC5001 (Tanacetum cinerariifolium: flower); HP03BA5001 (Tanacetum cinerariifolium: flower).
UNII — CGF76TP7X6 (Tanacetum cinerariifolium); ZUM06L90GV (pyrethrum extract).

Pharmacopoeias. In *BP(Vet)*, which also includes the extract.

US includes only the extract.

BP(Vet) 2014: (Pyrethrum Flower). The dried flowerheads of *Chrysanthemum cinerariaefolium* containing not less than 1% of pyrethrins of which not less than one-half consists of pyrethrin I. It has a faint but characteristic odour.

BP(Vet) 2014: (Pyrethrum Extract). An extract prepared from Pyrethrum Flower. It contains 24.5 to 25.5% of pyrethrins, of which not less than half consists of pyrethrin I. A dark olive green or brown viscous liquid or, if decolourised, a pale amber liquid. Store in a well-filled container. Protect from light. It should be thoroughly stirred before use.

USP 36: (Pyrethrum Extract). A mixture of three naturally occurring, closely related insecticidal esters of chrysanthemic acid (pyrethrins I: jasmolin I, cinerin I, and pyrethrin I) and three closely related esters of pyrethric acid (pyrethrins II: jasmolin II, cinerin II, and pyrethrin II). The ratio of pyrethrins I to pyrethrins II is not less than 0.8 and not more than 2.8. It may contain pigments characteristic of chrysanthemum species, triglyceride oils, terpenoids, and carotenoid. It may also contain suitable solvents and antoxidants. It contains no other added substances. It is a pale yellow liquid having a bland, flowery odour. Insoluble in water; soluble in liquid paraffin and in most organic solvents. Store in airtight containers. Protect from light.

Uses

Pyrethrum flower is mainly used for the preparation of pyrethrum extracts containing a mixture of chrysanthemic acid and pyrethric acid esters (pyrethrins I and II).

Pyrethrins in the form of pyrethrum extract have a long history of use as insecticides. Pyrethrum is rapidly toxic to many insects. It has a much quicker knock-down effect than clofenotane or lindane, but it is less persistent and less stable. Its action can be enhanced by certain substances such as piperonyl butoxide (p. 2160.2), and pyrethrins with piperonyl butoxide are used clinically in the treatment of pediculosis (p. 2147.3).

Pyrethroid insecticides (synthetic analogues of pyrethrins), such as permethrin and phenothrin, are also used clinically; deltamethrin and permethrin are among those used for the vector control of malaria.

Pyrethrum, pyrethrins, and pyrethroids are used as topical ectoparasiticides in veterinary practice and as agricultural, horticultural, and household insecticides. They are also used in total release foggers (or "bug bombs"); pesticide products that release their contents at once to fumigate an area.

Adverse Effects and Precautions

Pyrethrum is irritant to the eyes and mucosa. Hypersensitivity reactions have been reported.

References[1-6] to the potential for toxicity of pyrethrin and pyrethroid insecticides.

1. Ray DE, Forshaw PJ. Pyrethroid insecticides: poisoning syndromes, synergies, and therapy. *J Toxicol Clin Toxicol* 2000; **38:** 95–101.
2. Bateman DN. Management of pyrethroid exposure. *J Toxicol Clin Toxicol* 2000; **38:** 107–9.
3. Bradberry SM, *et al.* Poisoning due to pyrethroids. *Toxicol Rev* 2005; **24:** 93–106.
4. Proudfoot AT. Poisoning due to pyrethrins. *Toxicol Rev* 2005; **24:** 107–13.
5. Ray DE, Fry JR. A reassessment of the neurotoxicity of pyrethroid insecticides. *Pharmacol Ther* 2006; **111:** 174–93.
6. CDC. Illnesses and injuries related to total release foggers—eight states, 2001-2006. *MMWR* 2008; **57:** 1125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Pearsol; SH3; ***Philipp.***: Licealiz.

Multi-ingredient Preparations. ***Austral.***: Banlice; ***Canad.***: Lice Killing; Pronto; R & C†; R & C; ***Fr.***: Spray-Pax; ***Ger.***: Goldgeist; ***Gr.***: Lice-Enz; ***Israel***: Kin Soff†; ***Ital.***: Milice; Sinezan; ***Rus.***: Bubil (Бубил)†; Spray-Pax (Спрей-пакс); ***Turk.***: Kwell-P; ***UK***: Fortefog; Prevent; ***Ukr.***: Spray-Pax (Спрей-Пакс)†; ***USA***: Blue; Licide; Pronto; Pyrinyl II; Pyrinyl Plus; RID; Tisit.

Pyriproxyfen

Piriproxifeno; Pyriproksifeeni; Pyriproxifen; Pyriproxifène; Pyriproxifenum; Pyriproxyfeno; Pyriproxyfenum; S-9318; S-31183; Пирипроксифен.
2-[1-Methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine.
$C_{20}H_{19}NO_3$=321.4
CAS — 95737-68-1.
ATC Vet — QP53AX23.

Profile

Pyriproxyfen is used as a topical ectoparasiticide in veterinary practice.

Red Squill

Escila; Esquila; Морской Лук.
CAS — 507-60-8 (scilliroside).

Profile

Red squill is a red variety of *Urginea maritima*, which contains, in addition to cardiac glycosides, an active principle, scilliroside. It is very toxic to *rats* and has been incorporated in rat poisons; it has neurotoxic and cardiotoxic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Ger.***: Asthmakhell N; Cardioject; ***Neth.***: Asakell.

Resmethrin

Resmetrina; Ресметрин.
5-Benzyl-3-furylmethyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.
$C_{22}H_{26}O_3$=338.4
CAS — 10453-86-8.

Profile

Resmethrin is a pyrethroid insecticide (see Pyrethrum Flower, above) used in veterinary practice for the control of ectoparasites in the environment. Resmethrin is also used as an agricultural, horticultural, and household insecticide, but is not synergised by pyrethrum synergists such as piperonyl butoxide (p. 2160.2).

References.

1. WHO. Resmethrins. *Environmental Health Criteria 92.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc092.htm (accessed 26/04/04)
2. WHO. Resmethrins health and safety guide. *IPCS Health and Safety Guide 25.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg025.htm (accessed 26/04/04)

Rotenone

Rotenona; Rotenonum; Ротенон.
(2*R*,6a*S*,12a*S*)-1,2,6,6a,12,12a-Hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-*b*]furo[2,3-*h*]chromen-6-one.
$C_{23}H_{22}O_6$=394.4
CAS — 83-79-4.
UNII — 03L9OT429T.

Profile

Rotenone is a non-systemic insecticide used in agriculture and in horticulture.

Rotenone is the active ingredient of derris (the dried rhizome and roots of *Derris elliptica*; also known as tuba root or aker-tuba) and of lonchocarpus (the dried root of *Lonchocarpus utilis*; also known as cube root, timbo, or barbusco). Powdered forms of derris and of lonchocarpus have been used as insecticides and fish poisons.

References.

1. WHO. Rotenone health and safety guide. *IPCS Health and Safety Guide 73.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg073.htm (accessed 26/04/04)

Sodium Fluoroacetate

Compound 1080; Fluoroacetato sódico; Sodium Monofluoroacetate; Фторацетат Натрия.
$FCH_2.CO_2Na$=100.0
CAS — 62-74-8.
UNII — 166WTM3843.

Uses

Sodium fluoroacetate is a highly effective rodenticide but must be used with great caution because of its toxicity to other animals and to man.

Adverse Effects, Treatment, and Precautions

Sodium fluoroacetate is highly toxic, the lethal dose if ingested being about 1 to 5 mg/kg. Toxic effects may be delayed for several hours after oral absorption or inhalation, and include nausea and vomiting, apprehension, muscle twitching, cardiac irregularities, convulsions, respiratory failure, coma, and death usually due to ventricular fibrillation.

Treatment is generally supportive and symptomatic.

References[1-4] to sodium fluoroacetate toxicity.

1. Chi CH, *et al.* Clinical presentation and prognostic factors in sodium monofluoroacetate intoxication. *J Toxicol Clin Toxicol* 1996; **34:** 707–12.
2. Chi CH, *et al.* Hemodynamic abnormalities in sodium monofluoroacetate intoxication. *Hum Exp Toxicol* 1999; **18:** 351–3.
3. Goncharov NV, *et al.* Toxicology of fluoroacetate: a review, with possible directions for therapy research. *J Appl Toxicol* 2006; **26:** 148–61.
4. Proudfoot AT, *et al.* Sodium fluoroacetate poisoning. *Toxicol Rev* 2006; **25:** 213–19.

Spinosad *(USAN)*

LY-232105; PP-105; XDE-105.
CAS — 168316-95-8.
UNII — XPA88EAP6V.

Description. Spinosad is derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. It is a mixture of spinosad factor A (below) and spinosad factor D (below), in a ratio of about 5 to 1, respectively.

Spinosad Factor A

A-83543A; Lepicidin A; Spinosyn A.
(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-13-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy}-9-ethyl-14-methyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione.
$C_{41}H_{65}NO_{10}$=732.0
CAS — 131929-60-7.
UNII — OY0L59V61N.

Spinosad Factor D

Spinosyn D.
(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-13-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy}-9-ethyl-4,14-dimethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione.
$C_{42}H_{67}NO_{10}$=746.0
CAS — 131929-63-0.
UNII — 78G4631RTT.

Profile

Spinosad is an insecticide available as a 0.9% topical solution for the treatment of head pediculosis (p. 2147.3) in adults and children from 4 years of age. It should be applied to dry hair and left on for 10 minutes before rinsing out. Spinosad has ovicidal activity and therefore nit combing is not necessary; a second application is only required if live lice are seen 7 days after the first treatment. The solution contains benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p. 1740.1).

It is also used as an agricultural and horticultural insecticide.

References.

1. Cole SW, Lundquist LM. Spinosad for treatment of head lice infestation. *Ann Pharmacother* 2011; **45:** 954–9.
2. McCormack PL. Spinosad: in pediculosis capitis. *Am J Clin Dermatol* 2011; **12:** 349–53.
3. Villegas SC, Breitzka RL. Head lice and the use of spinosad. *Clin Ther* 2012; **34:** 14–23.
4. Villegas SC. Spinosad for the treatment of head lice infestations. *Drugs Today* 2012; **48:** 595–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Natroba.

Sulfiram *(BAN, rINN)*

Monosulfiram; Sulfiramum; Сульфирам.
Tetraethylthiuram monosulphide.
$C_{10}H_{20}N_2S_3$=264.5
CAS — 95-05-6.
ATC Vet — QS02QA02.
UNII — 1XHL4Q8P7Y.

Uses and Administration

Sulfiram is a pesticide that has been used as an acaricide, either alone or with benzyl benzoate, in the treatment of scabies (p. 2148.1), although other treatments are now preferred.

Sulfiram has also been used as a pesticide in veterinary practice.

Adverse Effects and Precautions

An erythematous rash has occasionally been reported. Sulfiram produces effects similar to those of disulfiram (p. 2496.1) if ingested with alcohol. As there may be a risk of absorption after application of sulfiram to the whole body, patients are advised to abstain from alcohol for at least 48 hours.

The reactions to alcohol occasionally reported in patients who have applied sulfiram solution[1,2] resemble those seen with disulfiram. Analysis has shown that sulfiram solutions exposed to room light undergo photochemical conversion to disulfiram, and that the concentration of disulfiram, and the ability of the solution to inhibit aldehyde dehydrogenase and hence the metabolism of alcohol, increases with the duration of such storage.[3,4] Whether patients who have applied sulfiram solution should avoid direct light immediately afterwards has not been elucidated.[4]

1. Blanc D, Deprez P. Unusual adverse reaction to an acaricide. *Lancet* 1990; **335:** 1291–2.
2. Burgess I. Adverse reactions to monosulfiram. *Lancet* 1990; **336:** 873.
3. Mays DC, *et al.* Photolysis of monosulfiram: a mechanism for its disulfiram-like reaction. *Clin Pharmacol Ther* 1994; **55:** 191.
4. Lipsky JJ, *et al.* Monosulfiram, disulfiram, and light. *Lancet* 1994; **343:** 304.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Sarfiram; Sulfitrat; Tetmosol; Valfiran; ***India***: Cure Scab; Tetmosol; ***S.Afr.***: Tetmosol.

Multi-ingredient Preparations. ***Fr.***: Ascabiol.

Temefos *(USAN, rINN)*

27165; Temefós; Téméfos; Temefosum; Temephos; Темефос.

O,O'-(Thiodi-*p*-phenylene) *O,O,O',O'*-tetramethyl bis(phosphorothioate).

$C_{16}H_{20}O_6P_2S_3$=466.5

CAS — 3383-96-8.

UNII — ONP3ME32DL.

Profile

Temefos is an organophosphorus insecticide (p. 2158.3). It is effective against the larvae of mosquitoes, blackflies, and other insects, and is used for the larvicidal treatment of rivers in the control of onchocerciasis (p. 147.2). It is also effective against the crustacean host to the larvae of the guinea worm and is used in the control of dracunculiasis (p. 145.1); treatment of drinking water is both effective and acceptable. It is also used as a topical ectoparasiticide in veterinary practice.

Tetrachlorvinphos

ENT-25841; SD-8447; Tetrachlorowinfos; Tetraclorvinfós; Тетрахлорвинфос.

2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate.

$C_{10}H_9Cl_4O_4P$=366.0

CAS — 961-11-5; 22248-79-9 (Z-tetrachlorvinphos); 22350-76-1 (E-tetrachlorvinphos).

ATC Vet — QP53AF14.

Profile

Tetrachlorvinphos is an organophosphorus insecticide (p. 2158.3) used as an ectoparasiticide in veterinary practice.

Tetramethrin *(rINN)*

Tétraméthrine; Tetramethrinum; Tetrametrina; Тетраметрин.

Cyclohex-1-ene-1,2-dicarboximidomethyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{19}H_{25}NO_4$=331.4

CAS — 7696-12-0.

ATC — P03BA04.

ATC Vet — QP53AC13.

UNII — Z72930Q46K.

Profile

Tetramethrin is a pyrethroid insecticide (see Pyrethrum Flower, p. 2161.1) used in the treatment of pediculosis (p. 2147.3). It is also used in veterinary practice for the control of ectoparasites in the environment and as a household insecticide.

References.

1. WHO. Tetramethrin health and safety guide. *IPCS Health and Safety Guide 31.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg031.htm (accessed 26/04/04)
2. WHO. Tetramethrin. *Environmental Health Criteria 98.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc98.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: A-Par; ***Gr.***: Cif Candioli; Mom; Runde; ***Ital.***: Baygon; Neo Mom; ***Rus.***: Pedilin Ko (Педилин Ко)†; ***Ukr.***: Pedilin Ko (Педилин Ко)†.

Trichlorophenoxyacetic Acid

2,4,5-T; Triclorofenoxiacético, ácido; Трихлорфеноксиуксусная Кислота.

2,4,5-Trichlorophenoxyacetic acid.

$C_8H_5Cl_3O_3$=255.5

CAS — 35915-18-5.

UNII — 9Q963S4YMX.

Profile

Trichlorophenoxyacetic acid is a selective herbicide with similar actions to dichlorophenoxyacetic acid (p. 2152.2). It is usually used in ester formulations. It was used with dichlorophenoxyacetic acid as a defoliating agent in the Vietnam war.

Toxicity. The phenoxy herbicides were used for defoliation in Vietnam as Agent Orange, which consisted of a mixture of dichlorophenoxyacetic acid, trichlorophenoxyacetic acid, and the impurity TCDD (dioxin), and concern has been expressed that they may have contributed to an increased incidence of cancer among exposed subjects as well as an adverse effect on the offspring of those subjects. This has been a matter of considerable debate,[1] prompting a series of biennial reassessments of the health effects of Agent Orange by the US National Academy of Sciences' Institute of Medicine.[2] To date the Institute has concluded[3] that there is evidence of increased incidence of chronic lymphocytic leukaemia, soft tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, and chloracne, with phenoxy herbicides.

1. McCarthy M. Agent Orange. *Lancet* 1993; **342:** 362.
2. Stephenson J. New IOM report links Agent Orange exposure to risk of birth defect in Vietnam vets' children. *JAMA* 1996; **275:** 1066–7.
3. Institute of Medicine. *Veterans and Agent Orange: update 2002 (2003).* Washington: The National Academies Press. Also available at: http://www.nap.edu/openbook.php?isbn=0309086167 (accessed 24/07/08)

Triflumuron

Triflumurón; Trifluron; Трифлумурон.

2-Chloro-*N*-{[4-(trifluoromethoxy)phenyl]amino}carbonyl) benzamide.

$C_{15}H_{10}ClF_3N_2O_3$=358.7

CAS — 64628-44-0.

UNII — 3FT64DYG8K.

Profile

Triflumuron is an insecticide used in agriculture and as a topical ectoparasiticide in veterinary practice.

Pharmaceutical Excipients

Binders and compression aids, p. 2163
Coatings and films, p. 2163
Colouring agents, p. 2163
Diluents and vehicles, p. 2163
Disintegrants, p. 2163
Emulsifying and solubilising agents, p. 2164
Flavours and sweeteners, p. 2164
Glidants and lubricants, p. 2165
Plasticisers, p. 2165
Preservatives, p. 2165
Propellants, p. 2165
Solvents, p. 2165
Stabilisers, p. 2166
Suspending agents and viscosity enhancers, p. 2166

Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form not for their direct therapeutic action but to aid the manufacturing process; to protect, support, or enhance stability, bioavailability, or patient acceptability; to assist in product identification; or to enhance in another way the overall safety or function of the product during storage or use.

Although very diverse, excipients can be broadly classified according to their function or uses, and their chemical characteristics. Many excipients have more than one use (multifunctional excipients) and this can be an advantage since it reduces the number of excipients needed and minimises the risk of interactions between them.

Ideally, an excipient has no pharmacological action of its own, is non-toxic, and does not interact chemically or physically with the active ingredients or other excipients; however, few excipients meet these criteria in practice. Toxicity may relate to compounds used as excipients in the final dosage form, or to residues of compounds (such as solvents) used during the manufacturing process.

Basic details of the major groups of pharmaceutical excipients follow, together with lists of the substances described in this chapter.

General references.
1. Kalász H, Antal I. Drug excipients. *Curr Med Chem* 2006; **13:** 2535–63.
2. Anonymous. What are excipients doing in medicinal products? *Drug Ther Bull* 2009; **47:** 81–4.

Binders and compression aids

Binders, compression aids, and granulating agents are used in tablet and granule manufacture to hold the ingredients together and give the finished product mechanical strength. They are mainly natural or synthetic polymers, such as starches, sugars, and sugar alcohols (all of which are described in the chapter on Nutritional Agents, p. 2042.1), or cellulose derivatives. Gelatin (p. 1154.1), guar gum (p. 475.1), magnesium carbonate (p. 1856.2), and derivatives and polymers of methylmethacrylate (p. 2558.2) are also used.

Described in this chapter are

- Acacia, p. 2166.1
- Alginic Acid, p. 2167.2
- Aluminium Magnesium Silicate, p. 2168.2
- Carbomers, p. 2173.3
- Carmellose, p. 2175.1
- Cellulose, p. 2177.1
- Dextrates, p. 2181.1
- Ethylcellulose, p. 2185.2
- Glyceryl Behenate, p. 2186.2
- Hyetellose, p. 2188.3
- Hyprolose, p. 2189.1
- Hypromellose, p. 2189.2
- Methylcellulose, p. 2197.3
- Palm Oil, p. 2200.2
- Poloxamers, p. 2201.3
- Polydextrose, p. 2202.2
- Polyethylene Oxide, p. 2202.2
- Povidone, p. 2204.3
- Zein, p. 2221.2

Coatings and films

Tablets are usually coated to provide protection from the environment (air, light, and moisture), to increase mechanical strength, to mask taste and smell, to aid swallowing, and for product identification; coatings may also be used to modify the release of the active ingredient. Traditionally, sugar (sucrose, p. 2096.3) has been the most widely used coating; sealants such as cellulose or shellac, and subcoatings of acacia or gelatin (p. 1154.1) may be applied first, and waxes and paraffins may be used as a final polishing layer. However, this process has now mainly been replaced by film coating using natural or synthetic polymers such as cellulose derivatives, derivatives of methylmethacrylate (p. 2558.2), polyvinyl acetates, and shellac. Polymers that are insoluble in acid, such as phthalate derivatives, are used for enteric coatings. Other excipients used as coatings include glycerides of fatty acids, such as glyceryl behenate and glyceryl palmitostearate.

Described in this chapter are

- Beeswax, p. 2170.2
- Carmellose, p. 2175.1
- Carnauba Wax, p. 2176.2
- Cellaburate, p. 2177.2
- Cellacefate, p. 2177.3
- Cellulose Acetate, p. 2177.3
- Cetyl Alcohol, p. 2178.2
- Cetyl Esters, p. 2178.2
- Ethylcellulose, p. 2185.2
- Glyceryl Behenate, p. 2186.2
- Glyceryl Palmitostearate, p. 2187.2
- Hard Paraffin, p. 2188.1
- Hyetellose, p. 2188.3
- Hyprolose, p. 2189.1
- Hypromellose, p. 2189.2
- Macrogol Poly(vinyl Alcohol) Grafted Copolymer, p. 2194.3
- Methylcellulose, p. 2197.3
- Microcrystalline Wax, p. 2198.1
- Palm Oil, p. 2200.2
- Poloxamers, p. 2201.3
- Polyvinyl Acetate, p. 2204.1
- Povidone, p. 2204.3
- Pullulan, p. 2206.3
- Shellac, p. 2208.3
- Zein, p. 2221.2

Colouring agents

Colouring agents are used in foods and cosmetics. They are also used in medicinal preparations to improve acceptability to patients, to aid identification and prevent counterfeiting, and to increase the stability of light-sensitive drugs. Most countries restrict the nature and extent of colouring agents used for such purposes. Matters of concern that have received considerable publicity include sensitivity reactions (see Tartrazine, p. 2215.2) and hyperactive behaviour in children (see below).

The colouring agents described in this chapter can be broadly categorised into synthetic dyes and natural colours (see below). Lakes are insoluble forms of water-soluble dyes. Synthetic and natural substances elsewhere in *Martindale* that may be used as colouring agents include aluminium (p. 2439.2), (betacarotene p. 2051.1), gold (p. 2521.1), indigo carmine (p. 2532.2), lutein (p. 2079.2), lycopene (p. 2546.2), patent blue V (p. 2584.2), riboflavin (p. 2104.3), silver (p. 2615.1), and titanium dioxide (p. 1725.1).

Synthetic or artificial dyes include a wide range of organic compounds and have many industrial and domestic applications. Some are also used for colouring medicines, foods, and cosmetics.

Described in this chapter are

- Allura Red AC, p. 2168.2
- Amaranth, p. 2168.3
- Black PN, p. 2171.2
- Bordeaux B, p. 2171.3
- Brilliant Blue FCF, p. 2171.3
- Brown FK, p. 2172.1
- Brown HT, p. 2172.1
- Carbazole Violet, p. 2173.3
- Carmoisine, p. 2176.2
- CI Solvent Yellow 18, p. 2179.2
- CI Vat Orange 1, p. 2179.2
- Citrus Red 2, p. 2179.2
- Eosin, p. 2184.2
- Erythrosine, p. 2184.3
- Green S, p. 2187.3
- Orange B, p. 2200.2
- Pigment Rubine, p. 2201.3
- Ponceau 4R, p. 2204.3
- Quinoline Yellow, p. 2207.1
- Red 2G, p. 2207.2
- Sunset Yellow FCF, p. 2215.1
- Tartrazine, p. 2215.2
- Yellow 2G, p. 2221.1

Natural colours include minerals and colours from plants and animals. Compounds that are themselves natural pigments of foodstuffs, such as anthocyanins (E163; see Flavonoid Compounds, p. 2505.2) and carotenoids, may also be used. Some natural colours are also used for their flavouring or nutritional properties.

Described in this chapter are

- Annatto, p. 2169.1
- Apocarotenal, p. 2169.2
- Astaxanthin, p. 2170.1
- Beetroot Red, p. 2170.3
- Bixin, p. 2169.2
- Canthaxanthin, p. 2173.2
- Caramel, p. 2173.3
- Carmine, p. 2176.1
- Carotenoids, p. 2176.2
- Chlorophyll, p. 2178.3
- Chlorophyllin Copper Complex Sodium, p. 2178.3
- Citranaxanthin, p. 2179.2
- Cochineal, p. 2179.2
- Curcumin, p. 2180.1
- Ethyl Apocarotenoate, p. 2169.2
- Ferric Oxide, p. 2186.1
- Logwood, p. 2192.1
- Norbixin, p. 2169.2
- Raspberry, p. 2207.2
- Red Cherry, p. 2207.2
- Red-Poppy Petal, p. 2207.3
- Red-Rose Petal, p. 2207.3
- Saffron, p. 2208.2
- Turmeric, p. 2218.1
- Vegetable Carbon, p. 2219.1

Hyperactivity. The role of foods and food additives in hyperactive behaviour (p. 2314.1) has been debated for many years.

A meta-analysis[1] sought to evaluate whether artificial food colours (including carmoisine, sunset yellow, and tartrazine) contribute to the symptomatology of childhood hyperactivity in children already diagnosed with hyperactive syndromes. For the primary analysis only double-blind placebo-controlled studies were evaluated. Overall, the results supported the hypothesis that such food colours promote hyperactivity in hyperactive children as measured on behavioural ratings. However, caution was advised about making any clinical recommendations. The restrictions needed for a colour-free diet may be too much of a burden on the children and their families. Also, there is a need to find out more about the biology of artificial food colours and to ascertain whether responses depend on an allergic or pharmacological mechanism. A further study[2] in a more general population of children also found that mixtures of food additives including food colourings were associated with an increase in hyperactivity, although the European Food Safety Authority considered[3] that the results of the study were not conclusive enough to necessitate a change in the approved daily intakes for the additives involved.

1. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr* 2004; **25:** 423–34.
2. McCann D, *et al.* Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007; **370:** 1560–7. Correction. *ibid.*; 1542.
3. European Food Safety Authority. Assessment of the results of the study by McCann et al. (2007) on the effect of some colours and sodium benzoate on children's behaviour: scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). Available at: http://www.efsa.europa.eu/en/efsajournal/doc/660.pdf (accessed 17/10/11)

Diluents and vehicles

Diluents and vehicles are used to aid handling and dosing of potent active ingredients and delivery of the active ingredient to the appropriate area of the body. Many types of excipient may be used, depending upon the required function.

In *oral solid dosage forms* such as capsules and tablets, diluents are used to provide bulk and enable accurate dosing of potent ingredients. Lactose is often used, and other sugar compounds, such as dextrin, glucose, sucrose, and sorbitol, may also be used. Inorganic compounds such as silicates, calcium salts, magnesium salts, and sodium or potassium chloride are also used, although the effect of the electrolyte content needs to be considered.

Diluents used for *oral or parenteral liquid formulations* include water and aqueous solutions, alcoholic solutions, and oils and other nonaqueous liquids. The active ingredient may be dissolved or suspended in the vehicle.

Vehicles used as *cream and ointment bases* include petroleum hydrocarbons, animal fats and waxes, vegetable oils, and silicones. They may act as inert carriers, or may have emulsifying, emollient, or humectant properties. Macrogols (p. 2547.3) and other glycols may also be used.

For *suppositories*, glyceride fatty bases or macrogols are mainly used.

Vehicles used as *bulking agents for freeze-drying* include creatinine, mannitol (p. 1427.3), and polydextrose.

Described in this chapter are

- Alkyl Benzoate, p. 2168.1
- Beeswax, p. 2170.2
- Calcium Sulfate, p. 2173.1
- Candelilla Wax, p. 2173.2
- Cellulose, p. 2177.1
- Cetostearyl Alcohol, p. 2178.1
- Cetyl Alcohol, p. 2178.2
- Cetyl Esters, p. 2178.2
- Cholesterol, p. 2179.1
- Coconut Oil, p. 2179.3
- Cottonseed Oil, p. 2180.1
- Creatinine, p. 2180.1
- Dextrates, p. 2181.1
- Dimethyl Sulfoxide, p. 2182.2
- Emulsifying Wax, p. 2184.1
- Erythritol, p. 2184.3
- Ethyl Oleate, p. 2185.1
- Glyceryl Palmitostearate, p. 2187.2
- Hard Fat, p. 2188.1
- Hard Paraffin, p. 2188.1
- Isopropyl Myristate, p. 2190.3
- Isopropyl Palmitate, p. 2191.1
- Macrogol Monomethyl Ethers, p. 2194.2
- Liquid Paraffin, p. 2191.2
- Microcrystalline Wax, p. 2198.1
- Myristyl Alcohol, p. 2198.3
- Oleic Acid, p. 2200.1
- Oleyl Alcohol, p. 2200.1
- Palm Oil, p. 2200.2
- Polydextrose, p. 2202.2
- Shea Butter, p. 2208.2
- Silicones, p. 2209.2
- Soft Paraffin, p. 2211.3
- Squalane, p. 2213.3
- Stearyl Alcohol, p. 2214.2
- Theobroma, p. 2216.1
- Theobroma Oil, p. 2216.1
- Wool Alcohols, p. 2219.2
- Wool Fat, p. 2219.3
- Vegetable Fatty Oils, p. 2219.1

Disintegrants

Disintegrants are used to aid the break up of tablets and other oral dosage forms in the gastrointestinal tract, releasing the active ingredient and increasing the surface area available for dissolution. They are usually hydrophilic compounds such as starch (p. 2095.1), cellulose derivatives, and alginates, that swell or dissolve in water; crospovidone takes up water by a capillary action, causing the tablet to expand and disintegrate.

Described in this chapter are

- Alginic Acid, p. 2167.2
- Aluminium Magnesium Silicate, p. 2168.2
- Carmellose, p. 2175.1
- Cellulose, p. 2177.1
- Crospovidone, p. 2205.1

Hypromellose, p. 2189.2
Methylcellulose, p. 2197.3
Polacrilin, p. 2201.3
Sodium Starch Glycolate, p. 2211.2

Emulsifying and solubilising agents

Many therapeutically active ingredients are insoluble or immiscible in the vehicles most suitable for the required dosage form and excipients are needed to allow incorporation of the active ingredient and to improve the stability of the final product. Surface-active agents or surfactants are widely used as emulsifying, solubilising, suspending, or wetting agents in pharmaceutical products and in other industrial processes, as well as in cleaning and detergent preparations. Other suspending agents (see p. 2166.1) based on natural polymers or finely-divided particles also have emulsifying properties.

Surfactants are compounds that contain both a hydrophilic and a hydrophobic region within the same molecule, enabling them to reduce the interfacial tension between aqueous and non-aqueous phases so that mixing can occur; they also form a barrier to prevent droplets coalescing. Their exact properties depend upon the degree of hydrophilicity or hydrophobicity of the different regions, and they are often classified according to their *hydrophilic-lipophilic balance* (HLB). This is an arbitrary scale of values denoting the relative affinity of the surfactant for oil and water, and depends on the ratio of hydrophilic groups to hydrophobic groups in the molecule. Lipophilic surfactants have low HLB values (less than 10) and are generally used as antifoaming agents, water-in-oil emulsifying agents, and as wetting agents; hydrophilic surfactants have higher HLB values (greater than 10) and are generally used as oil-in-water emulsifying agents and solubilising agents.

The hydrophobic portion of most surfactants consists of a long chain hydrocarbon or fatty acid and the degree of hydrophobicity increases with the number of alkyl groups in the chain. Hydrophilic groups vary between the different types of surfactant and are usually responsible for the presence and nature of any charge on the molecule:

- *Anionic surfactants* dissociate in water into an amphiphilic anion and a cation (usually an alkali metal or ammonia). The amphiphilic portion generally contains an acid, sulfate, or sulfonate group, which bears the negative charge
- *Cationic surfactants* dissociate into an amphiphilic cation and an anion (usually a halogen). The amphiphilic portion generally contains an amine or quaternary ammonium group, which bears the positive charge
- *Ampholytic surfactants* contain both cationic and anionic groups and their properties are dependent on the pH
- *Nonionic surfactants* do not ionise in water and bear no charge. Hydrophilicity is provided by a non-dissociable group such as an alcohol, ether, or ester; polyethylene-oxide groups also provide hydrophilicity

Because of the way they are manufactured, many surfactants are mixtures of related compounds; the properties of a particular material may vary from one manufacturer to another and there may be variation in batches from an individual source.

Ampholytic (amphoteric) surfactants have the detergent properties of anionic surfactants and the disinfectant properties of cationic surfactants. Their activity depends on the pH of the media in which they are used. Compounds used include aminocarboxylic acids, aminopropionic acid derivatives, imidazoline derivatives, and dodicin. Long-chain betaines are sometimes classed as ampholytic surfactants.

When the strength of the cationic portion of the molecule is equivalent to that of the anionic portion the isoelectric point occurs at pH 7 and the molecule is said to be balanced. Balanced ampholytic surfactants are reputed to be non-irritant to the eyes and skin and have therefore been used in baby shampoos.

Anionic surfactants have both emulsifying and cleansing properties and are mainly used as detergents, although some are used as emulsifiers in pharmaceuticals and in the cosmetic and food industries. Many of the anionic surfactants used are *soaps* (salts of fatty acids) and have traditionally been produced by the alkaline hydrolysis of fatty acid esters in natural fats and oils (saponification). Anionic surfactants used in pharmaceutical preparations include:

- *Alkali-metal soaps* (monovalent alkyl carboxylates) which are the sodium and potassium salts of the higher fatty acids. They are often produced from vegetable oils (see Soft Soap, p. 2212.3) or from specific fatty acids such as stearic acid, lauric acid, or oleic acid; animal fats such as tallow may also be used. They are generally water-soluble but produce insoluble deposits with hard water; they may also irritate the skin. *Ammonium soaps* have similar properties and have also been used
- *Metallic soaps* (polyvalent alkyl carboxylates), the calcium, zinc, magnesium, and aluminium salts of the higher fatty acids. They are oil-soluble and their main pharmaceutical application is as lubricants for tablet and capsule manufacturing. They produce water-in-oil emulsions and are often formed by chemical reaction during the preparation of the emulsion
- *Amine soaps*, which are the amine salts of fatty acids and include trolamine (triethanolamine) stearate and diolamine (diethanolamine) stearate. They are mainly used in cosmetic and personal care products
- *Ester carboxylates*, which are salts of fatty acids esterified with hydroxyacids or dicarboxylic acids; they include sodium stearoyl-lactylate and sodium stearyl fumarate
- *Alkyl sulfates* (sulfated fatty alcohols; alkyl ester sulfates), such as sodium laurilsulfate (p. 2210.3), which are the salts of sulfuric acid esters of fatty alcohols. They are widely used as detergents, wetting agents, and lubricants. *Alkyl ether sulfates* (ethoxylated alkyl sulfates) are similar compounds but the fatty alcohols are ethoxylated; examples include sodium laureth sulfate
- *Sulfated oils*, which are vegetable and animal oils and fats that have been treated with sulfuric acid and then neutralised. Sulfated castor oil (neutralised with sodium hydroxide; see p. 2215.1) has been widely used.
- *Sulfonated compounds*, including alkyl sulfonates such as sodium caprylyl sulfonate and sodium cocoyl isetionate, and alkyl aryl sulfonates such as sodium dodecylbenzenesulfonate. Salts of sulfonated carboxylic acids such as sodium lauril sulfoacetate and disodium lauril sulfosuccinate are also used; docusate sodium (sodium dioctyl sulfosuccinate; p. 1836.2) has both medicinal and pharmaceutical uses
- *Alkyl phosphates*, including alkyl ester phosphates such as sodium lauryl phosphate and alkyl ether phosphates such as sodium laureth phosphate, have been used in cosmetic and personal care products
- *Alkyl sarcosides* or *sarcosinates* are fatty acid amides produced from acylation of the synthetic amino acid sarcosine (*N*-methylglycine) with fatty acids. Salts such as sodium cocoyl sarcosinate and sodium lauroyl sarcosinate have anionic surfactant properties and are used for a range of applications.

Described in this chapter are
Aluminium Monostearate, p. 2168.3
Calcium Stearoyl-lactylate, p. 2173.1
Sodium Cetostearyl Sulfate, p. 2210.2
Sodium Cocoyl Isetionate, p. 2210.3
Sodium Cocoyl Sarcosinate, p. 2210.3
Sodium Laurilsulfate, p. 2210.3
Sodium Lauroyl Isetionate, p. 2210.3
Sodium Lauroyl Sarcosinate, p. 2210.3
Sodium Oleate, p. 2211.2
Sodium Stearate, p. 2211.3
Sodium Stearoyl-lactylate, p. 2173.1
Sulfated Castor Oil, p. 2215.1

Cationic surfactants are mainly used for their disinfectant properties and are described in the chapter on Disinfectants and Preservatives (p. 1730.1), but some are used pharmaceutically for their surfactant effects.

Described in this chapter are
Tonzonium Bromide, p. 2217.1

Nonionic surfactants are widely used as pharmaceutical excipients; they also have applications in the food, cosmetic, paint, pesticide, and textile industries as well as being used as oil slick dispersants. Some nonionic surfactants are used as spermicides. Nonionic surfactants tend to be less irritant than anionic or cationic surfactants, and are generally compatible with both anionic and cationic substances; however, they reduce the antimicrobial action of many preservatives.

The range of nonionic surfactants used is large and classification is not always easy, particularly as they are often used as mixtures. Many of them are complex molecules and nomenclature may be confusing; various systems are used and there are many inconsistencies, making precise identification difficult. Most of the compounds used are esters of glycols (diols), glycerol (a triol), or other polyalcohols with fatty acids, or ethers of glycols with fatty alcohols. The main groups used are described below; examples are given in Table 1 (p. 2165). *Higher fatty acid acids and alcohols* also have nonionic surfactant properties, but are mainly used for other purposes.

- *Glycol and glycerol (glyceryl) esters.* Simple esters of fatty alcohols and fatty acids have some surfactant properties but this can be improved by further hydroxyl or ester groups. Glycol and glycerol esters (mono-esters of ethylene glycol, diethylene glycol, and propylene glycol, and mono- or di-esters of glycerol) contain both ester and hydroxyl groups and are widely used as nonionic surfactants. They have relatively few hydroxyl groups and hydrophobic properties therefore predominate. They are poor emulsifying agents if used alone, though they are useful stabilisers for both oil-in-water and water-in-oil emulsions. 'Self-emulsifying' products may be formed by addition of a small amount of soap or a similar surfactant and these are capable of producing satisfactory oil-in-water emulsions. Compounds used may be based on a single fatty acid or a mixture of fatty acids; mixed glycerol esters in which the glycerol is esterified partly with a fatty acid and partly with acetic acid (*acetoglycerides*) are also used.
- *Macrogol esters.* Polyethoxylation of glycols provides additional hydrophilicity, which increases with the degree of ethoxylation, and fatty acid esters with a wide range of macrogols (polyethylene glycols) are used. Increased ethoxylation produces efficient oil-in-water emulsifying agents, which may also be used as wetting and solubilising agents. Mixtures of macrogol and glycerol esters *(macrogolglycerides)* and *polyethoxylated glycerol esters* (esters of macrogol glycerol ethers) are also used.
- *Glycol ethers.* Ethers of glycols with fatty alcohols are generally included in the same class as macrogol ethers and are used similarly. Glycol ethers with short-chain alcohols such as methyl alcohol and ethyl alcohol are used as solvents and solubilising agents.
- *Macrogol ethers.* Ethers of macrogols with fatty alcohols (*macrogol alkyl ethers*) or alkylphenols (*macrogol aryl ethers*) have similar properties to macrogol esters but the ether linkage is more stable to hydrolysis making macrogol ethers more resistant to acids and alkalis. Macrogol ethers with short-chain alcohols are also used, particularly as solvents. Macrogol aryl ethers such as octoxinols and nonoxinols are used as spermicides.
- *Polyalcohol esters.* Fatty acid esters of polyalcohols such as glycerol polymers (polyglycerols), sorbitol, and sucrose also have nonionic surfactant properties. *Sorbitan esters* (esters of the cyclic mono- or di-anhydrides of sorbitol with fatty acids) are oil-soluble, water-dispersible, nonionic surfactants and are effective water-in-oil emulsifiers. *Polysorbates* (polyethoxylated sorbitan esters) are more hydrophilic, water-soluble compounds and are used as oil-in-water emulsifying agents.
- *Poloxamers* are copolymers of polyoxyethylene and polyoxypropylene. They are used as oil-in-water emulsifiers and as solubilising and wetting agents in pharmaceutical preparations intended for internal use.

Described in this chapter are
Acetoglycerides, p. 2166.3
Diethylene Glycol Esters, p. 2182.1
Diethylene Glycol Ethers, p. 2182.2
Ethylene Glycol Esters, p. 2185.2
Glyceryl Behenate, p. 2186.2
Glyceryl Mono- and Di-esters, p. 2186.3
Glyceryl Monocaprylocaprate, p. 2186.3
Glyceryl Monolinoleate, p. 2186.3
Glyceryl Mono-oleate, p. 2187.1
Glyceryl Stearates, p. 2187.1
Macrogol Cetostearyl Ethers, p. 2192.2
Macrogol/glycerol Esters, p. 2192.3
Macrogol 6 Glyceryl Caprylocaprate, p. 2193.2
Macrogol 20 Glyceryl Monostearate, p. 2193.2
Macrogol 15 Hydroxystearate, p. 2193.3
Macrogol Laurates, p. 2193.3
Macrogol Lauril Ethers, p. 2193.3
Macrogol Monomethyl Ethers, p. 2194.2
Macrogol Oleates, p. 2194.2
Macrogol Oleyl Ethers, p. 2194.3
Macrogol 40 Sorbitol Heptaoleate, p. 2195.1
Macrogol Stearates, p. 2195.1
Macrogolglycerol Cocoates, p. 2195.2
Nonoxinols, p. 2199.1
Octoxinols, p. 2199.3
Oleyl Oleate, p. 2200.2
Palmitic Acid, p. 2200.3
Poloxamers, p. 2201.3
Polyoxyl Castor Oils, p. 2202.3
Polyoxyl Hydrogenated Castor Oils, p. 2203.1
Polysorbates, p. 2203.1
Polyvinyl Alcohol, p. 2204.2
Propylene Glycol Caprylates, p. 2206.1
Propylene Glycol Diacetate, p. 2206.2
Propylene Glycol Laurates, p. 2206.2
Propylene Glycol Monopalmitostearate, p. 2206.2
Quillaia, p. 2207.1
Sorbitan Esters, p. 2213.1
Sucrose Esters, p. 2214.3
Triglycerol Diisostearate, p. 2218.1
Tyloxapol, p. 2218.2

Flavours and sweeteners

Flavours, flavour enhancers, and sweeteners are used in oral pharmaceutical preparations to improve the palatability of the preparation and mask the taste of the active ingredient. In addition to those listed below, many natural, synthetic, and semisynthetic compounds are used, of which a great number are components of herbs, spices, and other foodstuffs; aromatic oils are also used, as is chloroform (p. 1898.1). Sugars have been widely used as sweetening agents and are described in the chapter on Nutritional Agents (p. 2042.1). Compounds with strongly aversive tastes may be used as denaturing agents, that is, unpalatable agents that are added to other substances to deter their consumption.

Described in this chapter are
Acesulfame Potassium, p. 2166.2
Alitame, p. 2168.1
Aspartame, p. 2169.2
Aspartame Acesulfame, p. 2170.1
Benzaldehyde, p. 2171.1
Caramel, p. 2173.3
Cyclamates, p. 2180.2
Denatonium Benzoate, p. 2181.1
Dibutyl Sebacate, p. 2181.2
Erythritol, p. 2184.3
Ethyl Acetate, p. 2184.3
Ethyl Cinnamate, p. 2185.1
Ethyl Maltol, p. 2196.1
Ethyl Vanillin, p. 2185.2
Maltol, p. 2196.1
Monosodium Glutamate, p. 2198.2
Neohesperidin Dihydrochalcone, p. 2198.3

Table 1. Examples of main groups of nonionic surfactants.

Glycol and Glycerol Esters	Glycerol Esters	Glyceryl Behenate Glyceryl Mono- and Di-esters Glyceryl Monocaprylocaprate Glyceryl Monolinoleate Glyceryl Mono-oleate Glyceryl Distearate Glyceryl Monostearate Glyceryl Palmitostearate
	Diethylene Glycol Esters	Diethylene Glycol Monolauarate Diethylene Glycol Mono-oleate Diethylene Glycol Monostearate Diethylene Glycol Palmitostearate
	Ethylene Glycol Esters	Ethylene Glycol Distearate Ethylene Glycol Monopalmitostearate
	Propylene Glycol Esters	Propylene Glycol Dicaprylocaprate Propylene Glycol Monocaprylate Propylene Glycol Diacetate Propylene Glycol Dilaurate Propylene Glycol Monolaurate Propylene Glycol Monopalmitostearate
Glycol Ethers	Diethylene Glycol Ethers	Diethylene Glycol Monoethyl Ether
Macrogol Derivatives	Ethoxylated Glycerol Esters	Macrogol 6 Glyceryl Caprylocaprate Macrogol 20 Glyceryl Monostearate Macrogolglycerol Cocoates Polyoxyl 35 Castor Oil Polyoxyl 40 Hydrogenated Castor Oil
	Macrogol Esters	Macrogol 15 Hydroxystearate Macrogol Laurates Macrogol Oleates Macrogol Stearates
	Macrogol/glycerol Esters	Behenoyl Macrogolglycerides Caprylocaproyl Macrogolglycerides Lauroyl Macrogolglycerides Linoleoyl Macrogolglycerides Oleoyl Macrogolglycerides Stearoyl Macrogolglycerides
	Macrogol Alkyl Ethers	Macrogol Lauril Ethers Macrogol Monomethyl Ethers Macrogol Oleyl Ethers
	Macrogol Aryl Ethers	Nonoxinol 9 Nonoxinol 10 Nonoxinol 11 Octoxinol 9 Octoxinol 10 Tyloxapol
Polyalcohol Esters	Polyglycerol Esters	Triglycerol Diisostearate
	Sorbitan Esters	Sorbitan Laurate Sorbitan Oleate Sorbitan Palmitate Sorbitan Sesquioleate Sorbitan Stearate Sorbitan Trioleate Sorbitan Tristearate
	Sorbitan Macrogol Esters	Macrogol 40 Sorbitol Heptaoleate Polysorbate 20 Polysorbate 40 Polysorbate 60 Polysorbate 80 Polysorbate 85
	Sucrose Esters	Sucrose Esters
Poloxamers		Poloxalene Poloxamer 188 Poloxamer 407

Neotame, p. 2199.1
Raspberry, p. 2207.2
Red Cherry, p. 2207.2
Saccharin, p. 2207.3
Saffron, p. 2208.2
Stevioside, p. 2214.2
Sucrose Octa-acetate, p. 2215.1
Thaumatin, p. 2216.1
Theobroma, p. 2216.1
Tributyl Acetylcitrate, p. 2217.2
Vanilla, p. 2218.3
Vanillin, p. 2218.3
Xylitol, p. 2220.3

Glidants and lubricants

Glidants are used to improve the flow of powders during tablet and capsule manufacturing by reducing friction and adhesion between particles; they may also be used as anticaking agents. Colloidal anhydrous silicon and other silica compounds, including calcium silicate (p. 1784.3) and magnesium silicate, are often used. Lubricants reduce friction between powders and metal surfaces and also have an important role in preventing adherence during the manufacturing process. Most lubricants are hydrophobic compounds, and long-chain fatty acids, particularly stearic acid and its salts, are most widely used; their main disadvantage is that they may slow disintegration and dissolution of the dosage form in the body. The properties of glidants and lubricants differ, although some compounds, such as starch (p. 2095.1) and talc (p. 1722.2), have both actions.

Described in this chapter are
Calcium Stearate, p. 2172.3
Glyceryl Behenate, p. 2186.2
Glyceryl Monostearate, p. 2187.2
Glyceryl Palmitostearate, p. 2187.2
Hydrogenated Vegetable Oil, p. 2219.1
Magnesium Silicate, p. 2195.3
Magnesium Stearate, p. 2195.3
Palmitic Acid, p. 2200.3
Silicon Dioxide, Colloidal, p. 2209.1
Sodium Stearyl Fumarate, p. 2211.3
Sodium Laurilsulfate, p. 2210.3
Stearic Acid, p. 2214.1
Zinc Stearate, p. 2221.2

Plasticisers

Plasticisers or softeners are relatively low-molecular-weight compounds that are used to improve the physical and mechanical properties of films by increasing the mobility of the polymer chains. They may reduce the temperature at which a polymer changes from a hard to a soft substance. Plasticisers are also used in soft gelatin capsules. Compounds used include glycerol (p. 2517.2), glycols and macrogols (p. 2547.3), and sorbitol (p. 2092.1); organic esters such as citrates, phthalates, and sebacates; and oils and glycerides. Triacetin (p. 596.2), which has antifungal properties, has also been used.

Described in this chapter are
Acetyltriethyl Citrate, p. 2167.1
Coconut Oil, p. 2179.3
Diacetylated Monoglycerides, p. 2166.3
Dibutyl Sebacate, p. 2181.2
Diethyl Phthalate, p. 2181.3
Macrogol Monomethyl Ethers, p. 2194.2
Propylene Glycol, p. 2205.2
Triethyl Citrate, p. 2218.1
Tributyl Acetylcitrate, p. 2217.2
Tributyl Citrate, p. 2217.2
Tri-*n*-butyl Phosphate, p. 2217.2

Preservatives

Preservatives are used in pharmaceutical preparations to prevent chemical or microbial degradation. They include antoxidants and antimicrobial preservatives, and are described in the chapter on Disinfectants and Preservatives, p. 1730.1.

Propellants

Propellants are used to aid delivery of the active ingredient in aerosol preparations. Some are described in the chapter on Gases, p. 1797.1.

Solvents

Solvents may be used both in the manufacturing process for solid pharmaceutical preparations and to enable active ingredients to be given in liquid form. Water (p. 2646.2) and aqueous electrolytes (p. 1775.1) are widely used, but many active ingredients are not soluble in aqueous solutions and organic solvents are therefore also used. These include alcohols, chlorinated hydrocarbons such as chloroform, fixed oils, glycols, and paraffins, some of which are described elsewhere in *Martindale*. Cosolvents are water-miscible organic solvents used to increase the solubility of poorly soluble ingredients and include alcohol, glycerin, macrogols, and propylene glycol.

Described in this chapter are
Acetone, p. 2166.3
Amyl Acetate, p. 2168.3
Amylene Hydrate, p. 2169.1
Butyl Alcohol, p. 2172.2
Butylene Glycol, p. 2172.2
Dichloromethane, p. 2181.2
Dimethyl Sulfoxide, p. 2182.2
Dimethylacetamide, p. 2183.2
Ethyl Acetate, p. 2184.3
Glycerol Formal, p. 2186.2
Glycofurol, p. 2187.3
Hexylene Glycol, p. 2188.3
Methyl Alcohol, p. 2196.2
Methyl Iso-butyl Ketone, p. 2197.1
N-Methylpyrrolidone, p. 2206.3
Octyldodecanol, p. 2199.3
Petroleum Spirit, p. 2201.2
Polyoxyl 35 Castor Oil, p. 2202.3
Propylene Carbonate, p. 2205.2
Propylene Glycol, p. 2205.2
Propylene Glycol Diacetate, p. 2206.2
Pyrrolidone, p. 2206.3
Solvent Ether, p. 2212.3
Xylene, p. 2220.2

Toxicity is a problem with organic solvents and may be associated with residual solvent in the pharmaceutical preparation, or with acute or chronic exposure during industrial and manufacturing processes, and some **industrial solvents** are described in this chapter mainly because of this. Toxicity may follow inhalation, ingestion, or absorption through the skin. Organic solvents may be irritant to the skin and mucous membranes, and often affect the CNS. They may sensitise the myocardium to catecholamines and cardiac arrhythmias may occur. Chronic exposure may lead to central and peripheral neurotoxicity, as well as to renal toxicity and hepatotoxicity. Toxicity may also occur due to deliberate abuse of solvents. For further details of general toxicity and abuse of solvents, see under Toluene, p. 2216.2.

Described in this chapter are
Acetonitrile, p. 2167.1
Aniline, p. 2169.1
Benzene, p. 2171.1
1-Bromopropane, p. 2172.1
Butyl Acetate, p. 2172.1
Carbon Disulfide, p. 2174.2
Carbon Tetrachloride, p. 2174.3
Cyclohexane, p. 2181.1
Dichloropropane, p. 2181.3
Diethyl Phthalate, p. 2181.3
Dimethylformamide, p. 2183.2
Dioxan, p. 2183.3

Epichlorohydrin, p. 2184.2
Formamide, p. 2186.1
Hexachloroethane, p. 2188.2
n-Hexane, p. 2188.2
Isobutyl Alcohol, p. 2190.3
Kerosene, p. 2191.1
2-Methoxyethanol, p. 2196.1
Methyl Butyl Ketone, p. 2197.1
Methyl Chloride, p. 2197.2
Methyl Ethyl Ketone, p. 2197.2
Pentane, p. 2201.1
Tetrachloroethane, p. 2215.3
Tetrachloroethylene, p. 2215.3
Toluene, p. 2216.2
Trichloroethane, p. 2217.3
White Spirit, p. 2219.2

Stabilisers

Physical, chemical, and microbial stability is important for pharmaceutical preparations. Preservatives (above) and chelators (p. 1537.1) are the main excipients used to prevent chemical and microbial degradation; complexing agents such as cyclodextrins may be used to improve stability and solubility, and to aid drug delivery. Buffering agents such as citric acid (p. 2480.3), tartaric acid (p. 2626.1), and ethanolamine derivates such as trolamine (p. 2634.3) may be used to control pH; this increases stability and also may improve the tolerability of parenteral preparations. Physical stability may be provided by suspending agents and viscosity enhancers (below). Colouring agents or UV absorbers (see Dermatological Drugs and Sunscreens, p. 1681.1) may be used to improve photostability, while humectants, which are compounds with water-retaining properties, are used to reduce the evaporation of water from topical preparations.

Described in this chapter are

Calcium Saccharate, p. 2172.3
Calcium Stearoyl-lactylate, p. 2173.1
Ceratonia, p. 2178.1
Cetostearoyl Alcohol, p. 2178.1
Diethylene Glycol Monopalmitostearate, p. 2182.1
Cyclodextrins, p. 2180.3
Ethylenediamine, p. 2185.3
Ethylene Glycol Monopalmitostearate, p. 2185.2
Gentisic Acid Ethanolamide, p. 2186.2
Glyceryl Monostearate, p. 2187.2
Hexylene Glycol, p. 2188.3
Maleic Acid, p. 2195.3
Monoglyceride Citrate, p. 2198.1
Potassium Metaphosphate, p. 2204.3
Propylene Glycol, p. 2205.2
Sodium Stearoyl-lactylate, p. 2173.1
Sucrose Esters, p. 2214.3
Trehalose, p. 2217.1

Suspending agents and viscosity enhancers

Compounds used as suspending agents, gelling agents, and viscosity enhancers are usually hydrophilic polymers that have the property of increasing the viscosity of water when dissolved or dispersed. The rheological properties of the dispersions can vary widely from thin liquids to thick gels.

They have wide applications both in pharmaceutical manufacturing and in the food industry. As well as being used as thickening and suspending agents many are used in emulsions as stabilisers and in some cases as emulsifying agents; some are also used in the manufacture of tablets as disintegrants, binding and granulating agents, and for film or enteric coating.

Viscosity enhancers are also used in artificial tear and artificial saliva preparations for the management of dry eye and dry mouth respectively. Those most commonly used are carbomers, cellulose ethers such as carmellose and hypromellose, polyvinyl alcohol, and povidone. Some, such as the alginates and methylcellulose, are also used in gastrointestinal disorders. Gelatin (p. 1154.1), a blood-volume expander, is also used.

Described in this chapter are

Acacia, below
Agar, p. 2167.2
Alginic Acid, p. 2167.2
Aluminium Magnesium Silicate, p. 2168.2
Aluminium Monostearate, p. 2168.3
Bentonite, p. 2170.3
Carbomers, p. 2173.3
Carmellose, p. 2175.1
Carrageenan, p. 2176.3
Cellulose, p. 2177.1
Ceratonia, p. 2178.1
Cetostearyl Alcohol, p. 2178.1
Cetyl Alcohol, p. 2178.2
Ethylcellulose, p. 2185.2
Gellan Gum, p. 2186.1
Guaraprolose, p. 2187.3
Hyetellose, p. 2188.3
Hymetellose, p. 2189.1
Hyprolose, p. 2189.1
Hypromellose, p. 2189.2
Methylcellulose, p. 2197.3
Polyethylene Oxide, p. 2202.2
Polyvinyl Acetate, p. 2204.1
Polyvinyl Alcohol, p. 2204.2
Povidone, p. 2204.3
Silicas, p. 2208.3
Stearyl Alcohol, p. 2214.2
Tragacanth, p. 2217.1
Xanthan Gum, p. 2220.1

Acacia

Acac.; Acaciae Gummi; Akaasiakumi; Akaciagummi; Arabmézga; Arabská klovatina; E414; Goma arábiga; Gomme arabique; Gomme de Sénégal; Gum Acacia; Gum Arabic; Guma arabska; Gumiarabikas; Gummi Africanum; Gummi Arabicum; Gummi, Arabisches; Gummi Mimosae; Акация; Гума арабика; Гуммиарабик.

CAS — 9000-01-5.
UNII — 5C5403N26O.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Acacia). The air-hardened gummy exudate from the trunk and branches of *Acacia senegal*, other species of *Acacia* of African origin, and *Acacia seyal*. Yellowish-white, yellow, or pale amber tears, sometimes with a pinkish tint. It is friable, opaque, frequently with a cracked surface, easily broken into irregular, whitish or slightly yellowish angular fragments with conchoidal fracture and a glassy and transparent appearance. Very slowly but almost completely soluble, after about 2 hours, in twice its mass of water leaving only a very small residue of vegetable particles; the liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent, and weakly acid to blue litmus paper. Practically insoluble in alcohol. Protect from light.

Ph. Eur. 8: (Acacia, Spray-dried; Acaciae Gummi Dispersione Desiccatum). It is obtained from a solution of acacia. Dissolves, rapidly and completely, after about 20 minutes, in twice its mass of water. The liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent, and weakly acid to blue litmus paper. Practically insoluble in alcohol. Protect from light.

USNF 31: (Acacia). The dried gummy exudate from the stems and branches of *Acacia senegal* (Leguminosae) or of other related African species of *Acacia*. Spheroidal tears or angular fragments of white to yellowish-white colour. It is translucent or somewhat opaque from the presence of numerous minute fissures. It is very brittle, the fractured surface is glassy and occasionally iridescent. It is also available as flakes, powder, granules, or as a spray-dried form. It is practically odourless. Insoluble in alcohol. Store in airtight containers.

Incompatibility. Incompatibilities of acacia have been reported with several substances including alcohol, aminophenazone, apomorphine, cresol, ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin. Acacia contains an oxidising enzyme that may affect preparations containing easily oxidised substances; the enzyme may be inactivated by heating at 100 degrees for a short time.

Uses

Acacia is used in pharmaceutical manufacturing as a suspending and emulsifying agent, as a tablet binder, and in pastilles. It is often used with tragacanth.

It is used as an emulsifier and stabiliser in the food industry.

Chronic renal failure. Oral supplementation with acacia gum has been investigated[1-4] for its potential benefit in patients with end-stage kidney disease.

1. Al-Mosawi AJ. Acacia gum supplementation of a low-protein diet in children with end-stage renal disease. *Pediatr Nephrol* 2004; **19:** 1156–9.
2. Al Mosawi AJ. The use of acacia gum in end stage renal failure. *J Trop Pediatr* 2007; **53:** 362–5.
3. Ali AA, *et al.* The effects of gum arabic oral treatment on the metabolic profile of chronic renal failure patients under regular haemodialysis in Central Sudan. *Nat Prod Res* 2008; **22:** 12–21.
4. Al Mosawi AJ. Six-year dialysis freedom i n end-stage renal disease. *Clin Exp Nephrol* 2009; 494–500.

Dental care. An acacia gel[1] has been used for the management of gingivitis and dental plaque in Ayurvedic medicine.

1. Pradeep AR, *et al.* Short-term clinical effects of commercially available gel containing *Acacia arabica*: a randomized controlled clinical trial. *Aust Dent J* 2010; **55:** 65–9.

Adverse Effects

Hypersensitivity reactions have occurred rarely after inhalation or ingestion of acacia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: GR[2] Control Appetite Reducer; ***Chile***: Vaselina Emulsionada; ***Indon.***: Norflam; ***Ital.***: Duofibra; Plurilac; ***Singapore***: Bios Life.

Pharmacopoeial Preparations
USNF 31: Acacia Syrup.

Acesulfame Potassium *(BANM, rINNM)*

Acesulfaam-K; Acesulfam draselná sůl; Acesulfam K; Acesulfam-K; Acesulfam-Kalium; Acesulfam potasowy; Acesulfame K; Acésulfame potassique; Acesulfamkalium; Acesulfamo kalio druska; Acesulfamo potásico; Acesulfamum Kalicum; Aceszulfám-kálium; Asesulfaamikalium; E950; H73-3293; H-733293; Hoe-095K; Kalii Acesulfamum; Калия Ацесульфам.

6-Methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide potassium.

$C_4H_4KNO_4S$=201.2

CAS — 55589-62-3.
UNII — 23OV73Q5G9.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Acesulfame Potassium). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone.

USNF 31: (Acesulfame Potassium). A white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

Profile

Acesulfame potassium is an intense sweetener about 200 times as sweet as sucrose. It is used in beverages, cosmetics, pharmaceuticals, and foods and does not appear to be affected by cooking.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Genser Sweet†; Rondo Sweet; ***Chile***: Marco Sweet Light; ***UK***: Sweet 'n Low; ***USA***: Mucotrol; ***Venez.***: Hermesetas Gold.

Acetoglycerides

Acetylated Glycerides; E472a (acetic acid esters of mono- and diglycerides of fatty acids).

CAS — 68990-54-5 (C14-22 monoglyceride acetates).

Diacetylated Monoglycerides

Monoglicéridos diacetilados; Моноглицериды Диацетилированные.

UNII — 5Z17386USF.

Pharmacopoeias. In *USNF*.

USNF 31: (Diacetylated Monoglycerides). Consists of glycerol esterified with edible fat-forming fatty acids and acetic acid. A clear liquid. Very soluble in alcohol 80%, in vegetable oils, and in mineral oils; sparingly soluble in alcohol 70%. Store in airtight containers. Protect from light.

Profile

Acetoglycerides are glycerol ester nonionic surfactants (p. 2164.2) and consist of esters of fatty acids and acetic acid with glycerol in which at least one of the hydroxyl groups is esterified with a fatty acid and at least one is esterified with acetic acid. They have been used as plasticisers, pharmaceutical excipients, and food additives.

Acetone

Aceton; Acetonă; Acetona; Acetonas; Acétone; Acetons; Acetonum; Aicéatón; Aseton; Asetoni; Atsetoon; Dimethyl Ketone; Dimetilcetona; 2-Propanona; 2-Propanone; Propanone; Ацетон.

C_3H_6O=58.08

CAS — 67-64-1.
UNII — 1364PS73AF.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Acetone). A volatile, clear, colourless liquid; the vapour is flammable. Miscible with water and with alcohol. Protect from light.

USNF 31: (Acetone). A transparent, colourless, mobile, volatile, very flammable liquid, having a characteristic odour. Sp. gr. not more than 0.789. Miscible with water, with alcohol, with chloroform, with ether, and with most volatile oils. A 50% solution in water is neutral to litmus. Store in airtight containers remote from fire.

Uses

Acetone is widely used as an industrial, pharmaceutical, and domestic solvent; it is also used as an extraction solvent in food processing.

Adverse Effects and Treatment

Inhalation of acetone vapour causes excitement followed by CNS depression with headache, restlessness, fatigue, and possibly convulsions, leading to coma and respiratory depression in severe cases. Vomiting and haematemesis may occur. There may be a latent period before the onset of symptoms of acetone poisoning. Similar symptoms may be seen after ingestion of acetone although hyperglycaemia has also been reported. Systemic toxicity may occur after extensive or prolonged skin exposure. The vapour is irritant to mucous membranes in high concentrations.

Acetone is commonly implicated in volatile substance abuse (see under Toluene, p. 2216.3).

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures. Acetone is rapidly absorbed, so gastric aspiration has little benefit unless ingestion was large and recent. Activated charcoal is also of limited value. Haemodialysis may be considered in those who do not respond to supportive therapy. Acetone has a long half-life, and observation of symptomatic patients for up to 30 hours post-ingestion has been recommended.

For the possible effect of acetone on the metabolism of acetonitrile, see under Acetonitrile, below.

Pharmacokinetics

Acetone is absorbed through the lungs and from the gastrointestinal tract, and poorly through the skin. Small amounts are oxidised to acetate and formate, but larger doses are mainly excreted unchanged in the breath, and to a much lesser extent the urine. Acetone has an elimination half-life of 17 to 27 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Sekumatic†.

Acetonitrile

Acetonitril; Acetonitrila; Acétonitrile; Acetonitrilo; Acetonitryl; Asetonitriili; Asetonitril; Cianometano; Cianuro de metilo; Cyanure de Méthyle; Etanonitrilo; Ethanenitrile; Methyl Cyanide; Metil cianuro; Ацетонитрил.

C_2H_3N=41.05

CAS — 75-05-8.

UNII — Z072SB282N.

Description. Acetonitrile is a colourless liquid with an aromatic odour. Wt per mL about 0.79 g. B.p. about 81 degrees. It emits highly toxic fumes of hydrogen cyanide when heated to decomposition or when reacted with acids or oxidising agents. Store in airtight containers.

Uses

Acetonitrile is used as an industrial solvent. It may also be present in artificial nail removers.

Adverse Effects and Treatment

As for cyanides (see Hydrocyanic Acid, p. 2156.2).

Cyanide poisoning, including a fatality, has been reported[1,2] in several infants after ingestion of artificial nail removers containing acetonitrile. As acetonitrile is slowly metabolised to cyanide, serious toxic effects may not occur until several hours after ingestion and there is the danger that these products may be confused with acetone-based nail polish removers which are less toxic. In a report[3] of an adult who died after ingestion of acetonitrile, the onset of symptoms was delayed for 24 hours. It was considered that concomitant ingestion of acetone had slowed the metabolism of acetonitrile. In another case[4] vomiting, diarrhoea, convulsions, and reduced consciousness developed in a 35-year-old man 15 hours after occupational exposure to acetonitrile. Despite treatment for cyanide poisoning, acute renal failure and rhabdomyolysis subsequently developed.

1. Caravati EM, Litovitz TL. Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. *JAMA* 1988; **260:** 3470–3.
2. Losek JD, *et al.* Cyanide poisoning from a cosmetic nail remover. *Pediatrics* 1991; **88:** 337–40.
3. Boggild MD, *et al.* Acetonitrile ingestion: delayed onset of cyanide poisoning due to concurrent ingestion of acetone. *Postgrad Med J* 1990; **66:** 40–1.
4. Muraki K, *et al.* Massive rhabdomyolysis and acute renal failure after acetonitrile exposure. *Intern Med* 2001; **40:** 936–9.

Pharmacokinetics

Acetonitrile is absorbed by inhalation, ingestion, and through the skin. It undergoes metabolism to cyanide, which is responsible for the toxicity of acetonitrile.

Acetyltriethyl Citrate

Triethyl Acetylcitrate; Ацетилированный Триэтилцитрат.

Triethyl 2-acetoxy-1,2,3-propanetricarboxylate.

$C_{14}H_{22}O_8$=318.3

CAS — 77-89-4.

UNII — 5WBR36T90E.

Pharmacopoeias. In *USNF.*

USNF 31: (Acetyltriethyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Acetyltriethyl citrate is a citric acid ester used as a plasticiser in tablet and other pharmaceutical coatings.

Agar

Agar-agar; Agaras; Colle du Japon; E406; Gelosa; Gélose; Hán Tiân; Japanese Isinglass; Layor Carang; Arap; Arap-arap.

CAS — 9002-18-0.

UNII — 89T13OHQ2B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Agar). Polysaccharides extracted from various species of Rhodophyceae algae, mainly those belonging to the genus *Gelidium.* It is prepared by treating the algae with boiling water; the extract is filtered while hot, concentrated, and dried. Colourless to pale yellow translucent strips, flakes, or powder; tough when damp but becoming more brittle on drying.

USNF 31: (Agar). The dried, hydrophilic, colloidal substance consisting of the polysaccharides extracted from *Gelidium cartilagineum* (Gelidiaceae), *Gracilaria confervoides* (Sphaerococcaceae), and related red algae (Class Rhodophyceae). It usually occurs in bundles consisting of thin, membranous, agglutinated strips, or in cut, flaked, or granulated forms. It may be coloured weak yellowish-orange, yellowish-grey to pale yellow, or colourless. It is tough when damp, brittle when dry. Odourless or has a slight odour. Insoluble in cold water; soluble in boiling water.

Profile

Agar is used as a suspending or thickening agent in pharmaceutical manufacturing and as an emulsifying and stabilising agent in the food industry.

It was formerly used similarly to methylcellulose (p. 2197.3) as a bulk laxative. Preparations containing agar with liquid paraffin and phenolphthalein are available to treat constipation, but the relatively small amount of agar in these probably acts solely as an emulsion stabiliser.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Agarol; ***Austral.***: Colon Care; Detox Program; ***Braz.***: Agarol; ***Chile***: Agarol†; Vaselina Emulsionada; ***Fr.***: Pseudophage; ***Switz.***: Paragar; ***USA***: Agoral.

Alginic Acid

Acide alginique; Ácido polimanúrico; Acidum alginicum; Algiinhapped; Algiinihappo; Alginezuur; Algínico, ácido; Algino rūgštis; Alginsäure; Alginsav; Alginsyra; Algínsýra; Alginsyre; Aljinik Asit; E400; Kwas alginowy; Kyselina alginová; Polymannuronic Acid; Альгиновая Кислота.

CAS — 9005-32-7.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — 8C3Z4148WZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Alginic Acid). A mixture of polyuronic acids composed of residues of D-mannuronic and L-guluronic acids extracted from algae belonging to the Phaeophyceae. A white or pale yellowish-brown, crystalline or amorphous powder. It swells in water. Very slightly soluble or practically insoluble in alcohol; practically insoluble in organic solvents; dissolves in solutions of alkali hydroxides.

USNF 31: (Alginic Acid). A hydrophilic colloidal carbohydrate extracted with dilute alkali from various species of brown seaweeds (Phaeophyceae). A white to yellowish-white, odourless or practically odourless, fibrous powder. Insoluble in water and in organic solvents; soluble in alkaline solutions. pH of a 3% dispersion in water is between 1.5 and 3.5.

Potassium Alginate

E402; Альгинат Калия.

CAS — 9005-36-1.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — 44ZPJ5W2J1.

Pharmacopoeias. In *USNF.*

USNF 31: (Potassium Alginate). A purified carbohydrate product extracted from various species of brown seaweeds by the use of dilute alkali. It consists chiefly of the potassium salt of alginic acid.

A white to yellow, fibrous or granular powder. It dissolves in water to form a viscous, colloidal solution; insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight; insoluble in chloroform, in ether, and in acids having a pH lower than about 3.

Propylene Glycol Alginate

E405; Propilenglicol, alginato de; Альгинат Пропиленгликоля.

Propane-1,2-diol Alginate.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — 26CD3J2R0C.

Pharmacopoeias. In *USNF.*

USNF 31: (Propylene Glycol Alginate). A white to yellowish, practically odourless, fibrous or granular powder. Soluble in water, in solutions of dilute organic acids, and, depending on the degree of esterification, in hydroalcoholic mixtures containing up to 60% by weight of alcohol, to form stable, viscous colloidal solutions at a pH of 3.

Sodium Alginate

Algin; Alginato sódico; E401; Natrii alginas; Natrio alginatas; Natriumalginaatti; Natriumalginat; Natrium-alginát; Nátrium-alginát; Sodium, alginate de; Sodium Polymannuronate; Sodyum Aljinat; Альгинат Натрия.

CAS — 9005-38-3.

ATC — A02BX13.

ATC Vet — QA02BX13.

UNII — C269C4G2ZQ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Alginate). It consists chiefly of the sodium salt of alginic acid. A white or pale yellowish-brown powder. Slowly soluble in water, forming a viscous, colloidal solution; practically insoluble in alcohol.

USNF 31: (Sodium Alginate). A yellowish-white, practically odourless, coarse or fine powder. Soluble in water, forming a viscous, colloidal solution; insoluble in alcohol, in chloroform, and in ether, in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight, and in acids when the pH of the resulting solution becomes lower than about 3. Store in airtight containers.

Incompatibility. Incompatibilities of sodium alginate have been seen with acridine derivatives, methylrosanilinium chloride, phenylmercuric acetate and nitrate, calcium salts, alcohol in concentrations greater than 5%, and heavy metals. High concentrations of electrolytes cause an increase in viscosity until salting-out of sodium alginate occurs; salting-out occurs if more than 4% of sodium chloride is present.

Profile

Alginic acid and alginates such as propylene glycol alginate and sodium alginate are used in pharmaceutical manufacturing as suspending and thickening agents. They may be used as stabilisers for oil-in-water emulsions and as binding and disintegrating agents in tablets. Various grades are usually available commercially for different applications and yield solutions of varying viscosity. A reduction in viscosity has been said to occur if sodium alginate solutions are autoclaved for sterilisation.

Alginic acid and alginates such as ammonium alginate (E403), calcium alginate (p. 1136.3), potassium alginate, propylene glycol alginate, and sodium alginate are also used as emulsifiers and stabilisers in the food industry.

Alginic acid or the alginates, magnesium alginate and sodium alginate, are given, usually formulated with an antacid, in the management of gastro-oesophageal reflux disease (p. 1807.2). Alginic acid or the alginate reacts with gastric acid to form a viscous gel (often termed a raft) that floats on top of the gastric contents. This raft then acts as a mechanical barrier to reduce reflux.

Alginates such as calcium alginate and a mixed calcium-sodium salt are used as haemostatics and wound dressings (see p. 1136.3).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alginic acid used for gastrointestinal disorders as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nu-Gel Hidrogel con Alginato†; ***Canad.***: Kaltostat; Restore CalciCare; Tegaderm Alginate; ***China***: Bo Lai Tong (伯来通); Wei Yi (唯易); Xin Bai Chang (欣百昌); ***Irl.***: Kaltostat†; ***Israel***: Nu-Gel; ***Ital.***: Kaltostat; Melgisorb; Nu-Gel; ***NZ***: Gaviscon; ***Rus.***: Alginatol (Альгинатол); Natalsid (Натальсидум); ***S.Afr.***: Gaviscon Advance†; Kaltostat; ***UK***: Comfeel SeaSorb.

Multi-ingredient Preparations. ***Arg.***: Comfeel SeaSorb; Hyalogran; Mylanta Reflux; Redudiet; Rennie; SeaSorb†; ***Austral.***: Flaminal; Gaviscon Double Strength; Gaviscon; Gaviscon; Infant Gaviscon; Mylanta Heartburn Relief; Mylanta Heartburn Relief; ***Belg.***: Gastriphar; Gaviscon Advance; Gaviscon; Gaviscon; Gaviscon; Rennie†; ***Braz.***: Gaviscon; ***Canad.***: Carboflex; Gastrifom; Gaviscon Heartburn & Acid Reflux Relief; Gaviscon Heartburn & Acid Reflux Relief; Gaviscon Maxrelief; Maalox HRF†; Stomach Comfort; ***Chile***: Algicote†; Gaviscon†; Gaviscon; Reflumox; ***Cz.***: Gaviscon; Gaviscon; Rennie Duo†; ***Denm.***: Galieve; Gaviscon; Gaviscon; ***Fin.***: Galieve; Gaviscon; Gaviscon; ***Fr.***: Cicactive; Gaviscon; Gavisconell; Gavisconell; Pseudophage; Release Ag†; Topaal; Topalkan†; ***Ger.***: Gaviscon Advance; Gaviscon Kautabletten; Recatol Algin; ***Gr.***: Dyspagone; Gaviscon-L; Gaviscon; ***Hong Kong***: Gaviscon Advance; Gaviscon Extra Strength; Gaviscon; Gaviscon; ***Hung.***: Gaviscon; ***India***: Acifix; Acigon; Acihit; Arfagel; Gastromax-O; Gaviscon; Raftace; Raftace; Visco; ***Irl.***: Acidex; Gaviscon Advance; Gaviscon Infant; Gaviscon†; Gaviscon; Pyrogastrone†; Rennie Dual Action; Topaal; ***Israel***: Algical Kalzarevet; Gaviscon Forte; Gaviscon; Kaltocarb; Kaltostat; ***Ital.***: Gastrotuss; Gaviscon Advance; Gaviscon†; Gaviscon; Hyalogran; Noremifa; Silvercel; ***Malaysia***: Gaviscon Advance; Gaviscon Extra Strength; Gaviscon†; Gaviscon; ***Neth.***: Algicon; Algicon; Gaviscon Extra Sterk; Gaviscon Forte†; Gaviscon; Rennie Duo; ***Norw.***: Galieve; Gaviscon; Gaviscon; ***NZ***: Gaviscon; Gaviscon; Mylanta Heartburn Relief; ***Philipp.***: Algycon; Gaviscon; ***Pol.***: Gaviscon Advance; Gaviscon; Gealcid; ***Port.***: Gavigard; Gaviscon; Kaltostat; ***Rus.***: Gaviscon (Гевискон); Gaviscon Forte (Гевискон форте); ***S.Afr.***: Gaviscon; Gaviscon; Gelacid; Gelacid; Infant Gaviscon; ***Singapore***: Acticoat Absorbent; Gaviscon Advance; Gaviscon Extra Strength; Gaviscon†; Gaviscon; ***Spain***: Dolcopin; Gaviscon; ***Swed.***: Galieve; Gaviscon; Gaviscon; ***Thai.***: Algycon; Gaviscon Dual Action; Gaviscon; Gaviscon; ***Turk.***: Gaviscon Advance; Gaviscon Infant; Gaviscon; Gaviscon; Rennie Duo; ***UK***: Acidex; Bisodol Extra; Bisodol Heartburn Relief; Flaminal; Gastrocote; Gaviscon Advance; Gaviscon Cool; Gaviscon Double Action; Gaviscon Infant; Gaviscon Instants; Peptac; Raft-Eze; Rennie Duo†; Setlers Heartburn & Indigestion Liquid; Topal; ***Ukr.***: Gaviscon (Гавискон); Gaviscon Forte (Гавискон Форте); ***USA***: Gaviscon; Genaton; Pretts Diet Aid.

Pharmacopoeial Preparations

BP 2014: Alginate Raft-forming Oral Suspension; Compound Alginate Antacid Oral Suspension.

Alitame *(USAN)*

Alitam; Alitamas; CP-54802; Алитам.

(3*S*)-Amino-*N*-{(1*R*)-1-[(2,2,4,4-tetramethyl-3-thietanyl)carbamoyl]ethyl}succinamic acid hydrate.

$C_{14}H_{25}N_3O_4S.2½H_2O$=376.5

CAS — 80863-62-3 (anhydrous alitame); 99016-42-9 (alitame hydrate).

UNII — 6KI9M51JOG (alitame); PCE8DAE750 (anhydrous alitame).

Profile

Alitame is an intense sweetener used in foods. It is about 2000 times sweeter than sucrose.

Alkyl Benzoate

Alkyl (C12-15) Benzoate; Benzoato de alquilo; C12-15 Alkyl Benzoate; Алкил Бензоат.

CAS — 68411-27-8 (C_{12}-C_{15} alkyl ester).

UNII — A9EJ3J61HQ.

Pharmacopoeias. In *USNF*.

USNF 31: (Alkyl (C12-15) Benzoate). It consists of esters of a mixture of C_{12} to C_{15} primary and branched alcohols and benzoic acid (average molecular formula $C_{20}H_{32}O_2$ = 304.5). It is a clear, practically colourless, oily liquid. Insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in acetone, in ethyl acetate, in isopropyl alcohol, in isopropyl myristate, in isopropyl palmitate, in liquid paraffin, in vegetable oils, in volatile silicones, and in wool fat. Store in airtight containers. Protect from light.

Profile

Alkyl benzoate has emollient properties. It may be used as an oily vehicle.

Allura Red AC

Allura Rood AC; Alluranpunainen; Aliurarot AC; Aliurarött AC; CI Food Red 17; Colour Index No. 16035; Czerwień Allura AC; E129; FD & C Red No. 40; Rojo allura AC; Rouge Allura AC; Красный Очаровательный АС.

Disodium 6-hydroxy-5-(6-methoxy-4-sulphonato-*m*-tolylazo)naphthalene-2-sulphonate.

$C_{18}H_{14}N_2Na_2O_8S_2$=496.4

CAS — 25956-17-6.

UNII — WZB9127XOA.

Profile

Allura red AC is a synthetic azo dye used as a colouring agent in medicines, cosmetics, and foodstuffs.

Aluminium Magnesium Silicate

Aliuminio-magnio silikatas; Alumiinimagnesiumsilikaatti; Aluminii magnesii silicas; Aluminium-Magnesium-Silicat; Aluminium (silicate d') et de magnésium; Aluminiummagnesiumsilikat; Alumínium-magnézium-szilikát; Aluminosilicato magnésico; Aluminum Magnesium Silicate; Křemičitan hořečnato-hlinitý; Magnesium Aluminium Silicate; Magnesium Aluminum Silicate; Saponite; Магний-алюминий Кремнекислый; Алюминиевый Силикат Магния.

CAS — 1327-43-1; 12511-31-8.

UNII — 6M3P64V0NC (aluminium magnesium silicate); SUS08ZOA9S (aluminium magnesium silicate type IA); 4J2YH8VV13 (aluminium magnesium silicate type IB); XLI9KNX1FT (aluminium magnesium silicate type IC); 7LVU907546 (magnesium aluminometasilicate type I-A); 8XK1039013 (magnesium aluminometasilicate type I-B); II0CAA4909 (aluminium magnesium silicate type II-A).

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF*. *USNF* also includes Magnesium Aluminosilicate and Magnesium Aluminometasilicate.

Ph. Eur. 8: (Aluminium Magnesium Silicate). A mixture of colloidal-size particles of montmorillonite and saponite, free from grit and nonswellable ore. Almost white powder, granules, or plates. Practically insoluble in water and in organic solvents; swells in water to form a colloidal dispersion. A 5% dispersion in water has a pH of 9.0 to 10.0.

USNF 31: (Magnesium Aluminum Silicate). A blend of colloidal montmorillonite and saponite that has been processed to remove grit and nonswellable ore components. There are several types, differing in viscosity and in ratio of aluminium content to magnesium content. It is an odourless, fine (micronised) powder, small cream to tan granules, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol; swells when added to water or glycerol. pH of a 5% suspension in water is between 9.0 and 10.0. Store in airtight containers.

USNF 31: (Magnesium Aluminosilicate). A synthetic material that contains 20.5 to 27.7% of magnesium oxide, 27.0 to 34.3% of aluminium oxide, and 14.4 to 21.7% of silicon dioxide, calculated on the dried basis. A white powder or granules having an amorphous structure. Practically insoluble in water and in alcohol; partially soluble in acids and alkalis. A 4% suspension in water has a pH of 8.5 to 10.5. Store at a temperature not exceeding 40 degrees in airtight containers.

USNF 31: (Magnesium Aluminometasilicate). A synthetic material that contains 29.1 to 35.5% of aluminium oxide, 11.4 to 14.0% of magnesium oxide, and 29.2 to 35.6% of silicon dioxide, calculated on the dried basis. It exists in two forms, Type I-A and Type I-B. A white powder or granules having an amorphous structure. Practically insoluble in water and in alcohol; partially soluble in acids and alkalis. A 4% suspension in water has a pH of 6.5 to 8.5 (Type I-A) and 8.5 to 10.5 (Type I-B). Store at a temperature not exceeding 40 degrees in airtight containers.

Profile

Aluminium magnesium silicates are mineral clays belonging to the smectite group (see p. 1887.1). They occur naturally in various forms, depending on the mineral composition and the physical structure, and may contain varying amounts of other minerals, such as calcium, sodium, and iron. Synthetic aluminium magnesium silicates are also available.

Aluminium magnesium silicates have a variety of pharmaceutical uses, including use as suspending and thickening agents, as emulsion stabilisers, and as binders and disintegrating agents in tablets.

Other smectites with similar uses include bentonite (p. 2170.3) and Fullers earth (p. 1553.2); almasilate (p. 1815.3) and attapulgite (p. 1820.1) also have uses in gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Neusilin†.

Multi-ingredient Preparations. ***India***: Aglocid; Alupectin; Digene; Gelusil MPS; Gelusil Plus; ***Indon.***: Flatucid†; Stomadon†; ***Jpn***: Cabe 2†; ***Thai.***: Diasgest; ***UAE***: Alkasid.

Aluminium Monostearate

Aluminii monostearas; Aluminium, monostéarate d'; Aluminum Monostearate; Glinu monostearynian; Monoestearato de aluminio; Monostearato de aluminio; Алюминия Моностеарат.

Dihydroxy(octadecanoato-*O*-)aluminium; Dihydroxy(stearato)aluminium.

$C_{18}H_{37}AlO_4$=344.5

CAS — 7047-84-9 (aluminium monostearate); 300-92-5 (aluminium distearate); 637-12-7 (aluminium tristearate).

UNII — P9BC99461E.

Pharmacopoeias. In *Jpn* and *Pol.* Also in *USNF*.

USNF 31: (Aluminum Monostearate). A compound of aluminium with a mixture of solid organic acids obtained from fats and consisting mainly of variable proportions of aluminium monostearate and aluminium monopalmitate. A fine, white to yellowish-white, bulky powder with a faint characteristic odour. Insoluble in water, in alcohol, and in ether.

Profile

Aluminium monostearate is a metal soap anionic surfactant (p. 2164.1) used as a gelling agent in oil-based cosmetic and pharmaceutical formulations. It may also be used as a stabiliser in cosmetic emulsions. The distearate and tristearate are also used.

Amaranth

Amarant; Amarante; Amaranto; Bordeaux S; CI Acid Red 27; CI Food Red 9; Colour Index No. 16185; E123; formerly FD & C Red No. 2; Naphtol Rot S; Амарант.

It consists mainly of trisodium 3-hydroxy-4-(4-sulphonato-1-naphthylazo)naphthalene-2,7-disulphonate.

$C_{20}H_{11}N_2Na_3O_{10}S_3$=604.5

CAS — 915-67-3.

UNII — 37RBV3X49K.

NOTE. The name amaranth is also used to refer to some species of plant in the genus *Amaranthus*, some of which have been used as a source of dyes.

Uses

Amaranth is a synthetic azo dye used as a colouring agent in medicines, foodstuffs, and cosmetics.

Adverse Effects

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies, subsequent work failed to confirm these findings and in the UK amaranth is considered suitable for use as a food colour.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.

Amyl Acetate

Acétate de Pentyle; Acetato de amilo; Acetato di Amile; Amil Asetat; Amylacetaat; Amyyliasetaatti; Essigsäurepentylester; Pentyl Acetate (*n*-amyl acetate); Pentylacetat; Амилацетат.

$C_7H_{14}O_2$=130.2

CAS — 123-92-2 (iso-amyl acetate); 53496-15-4 (sec-amyl acetate); 628-63-7 (n-amyl acetate).

UNII — 92Q24NH7AS.

Description. Amyl acetate is a mixture of isomers, principally *iso*-, *sec*-, and *n*-amyl acetate. *iso*-Amyl acetate is a clear colourless liquid with a sharp, fruity odour. Wt per mL about 0.87 g. B.p. about 140 degrees. Slightly soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Uses

Amyl acetate is used as a pharmaceutical and industrial solvent. Isoamyl acetate is used as a flavouring in foods.

Adverse Effects and Treatment

Prolonged exposure to amyl acetate may produce headache, fatigue, and depression of the CNS. Irritation of mucous membranes may also occur.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures; activated charcoal may be given if the patient presents within 1 hour of ingestion.

Effects on the heart. A 27-year-old man developed headache, nausea, and vomiting after using a paint containing amyl acetate as the solvent in an unventilated room.[1] Some days later chest pain and dyspnoea developed; he was admitted to hospital 2 weeks after exposure with heart failure which slowly responded to treatment.

1. Weissberg PL, Green ID. Methyl-cellulose paint possibly causing heart failure. *BMJ* 1979; **ii:** 1113–14.

Amylene Hydrate

Aethyldimethylmethanolum; Dimethylethyl Carbinol; Hidrato de amileno; Tertiary Amyl Alcohol; *tert*-Pentyl Alcohol; Амилгидрат.

2-Methylbutan-2-ol.

$C_5H_{12}O$=88.15

CAS — 75-85-4.

UNII — 69C393R11Z.

Pharmacopoeias. In *USNF*.

USNF 31: (Amylene Hydrate). A clear, colourless liquid having a camphoraceous odour. Sp. gr. 0.803 to 0.807. Distilling range 97 degrees to 103 degrees. Freely soluble in water; miscible with alcohol, with chloroform, with ether, and with glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Uses

Amylene hydrate is used as a pharmaceutical solvent. It was formerly used as a hypnotic.

Adverse Effects

Amylene hydrate is irritant and has a depressant effect on the CNS.

Aniline

Aminobenceno; Aminobenzeen; Aminobenzene; Aniliin; Aniliini; Anilin; Anilină; Anilina; Anilīns; Bencenamina; Benzenamine; Fenilamina; Fenüülamiin; Fenylamin; Phenylamine; Анилин.

C_6H_7N=93.13

CAS — 62-53-3.

UNII — SIR7XX2F1K.

Description. Aniline is a colourless or pale yellow oily liquid with a characteristic odour, readily darkening to brown on exposure to air and light. Wt per mL about 1.02 g. B.p. about 183 degrees. Store in airtight containers. Protect from light.

Uses

Aniline is a solvent with wide industrial applications.

Adverse Effects, Treatment, and Precautions

Inhalation, ingestion, or cutaneous absorption of aniline results in methaemoglobinaemia, with cyanosis, headache, weakness, stupor, convulsions, and coma. Irritation of the skin or mucous membranes, nausea and vomiting, and cardiac arrhythmias may occur. Haemolysis has been reported and may give rise to renal damage or jaundice. Death is usually a result of cardiovascular collapse.

Treatment may involve oxygen, methylthioninium chloride (p. 1559.1), transfusions, or possibly haemodialysis. Gastric aspiration or activated charcoal may be considered in patients who present within 1 hour of ingestion.

Bladder papillomas have been reported in workers previously exposed to aniline. Commercial aniline may be contaminated with β-naphthylamine, a potential carcinogen.

Handling. Suitable precautions should be taken to avoid skin contact with aniline as it can penetrate skin and produce systemic toxicity.

Annatto

Achiote; Anatas; Annotta; Arnotta; CI Natural Orange 4; Colour Index No. 75120; E160(b); Rocou; Roucou; Аннато.

CAS — 1393-63-1.

UNII — 6PQP1V1B6O.

Bixin

β-Bixin (*all-trans*-bixin); α-Bixin (*cis*-bixin); E160(b); Биксин.

Methyl (9-*cis*)-hydrogen-6,6′-diapo-ψ,ψ-carotenedioate (*cis*-bixin).

$C_{25}H_{30}O_4$=394.5

CAS — 6983-79-5 (cis-bixin); 39937-23-0 (all-trans-bixin).

UNII — 9L7T4VB66G.

Norbixin

E160(b); β-Norbixin (*all-trans*-norbixin); α-Norbixin (*cis*-norbixin); Норбиксин.

6,6′-Diapo-ψ,ψ-carotenedioic acid.

$C_{24}H_{28}O_4$=380.5

CAS — 626-76-6 (cis-norbixin); 542-40-5 (all-trans-norbixin).

UNII — E8MS9E17AI.

Uses

Annatto is a colouring agent extracted from the seeds of *Bixa orellana*. It and its derivatives, the carotenoids bixin and norbixin, are used to colour foods, drugs, and cosmetics.

Bixin and norbixin exist in both *cis*- and *trans*- forms, with the *cis*- forms being the major colouring components.

Adverse Effects

Hypersensitivity. Hypersensitivity reactions to annatto have been reported rarely, including 2 cases of anaphylaxis associated with use of annatto as a food colouring.[1,2] In both cases, sensitivity was confirmed by skin testing. A literature review also found some evidence that annatto might worsen the symptoms of recurrent urticaria, although the design of several oral challenge studies with annatto was criticised.[3]

1. Nish WA, *et al.* Anaphylaxis to annatto dye: a case report. *Ann Allergy* 1991; **66:** 129–31.
2. Ebo DG, *et al.* Allergy for cheese: evidence for an IgE-mediated reaction from the natural dye annatto. *Allergy* 2009; **64:** 1558–60.
3. Lucas CD, *et al.* The role of natural color additives in food allergy. *Adv Food Nutr Res* 2001; **43:** 195–216.

Apocarotenal

β-Apo-8′-carotenal; Apocaroténal; β-Apo-8′-karotenal; Beta Apocarotenal; Beta Apo-8′-karotenalis; Beta-apo-8′-karotenal; Béta-apo-8′-karotenal; CI Food Orange 6; Colour Index No. 40820; E160(e); 8′-Apo-β-caroten-8′-al.

all trans-2,6,11,15-Tetramethyl-17-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8,10,12,14,16-heptadecaoctenal.

$C_{30}H_{40}O$=416.6

CAS — 1107-26-2.

UNII — V22N3E2U32.

Ethyl Apocarotenoate

CI Food Orange 7; Colour Index No. 40825; E160(f); Ethyl-8′-apo-β-caroten-8′-oate.

The ethyl ester of β-apo-8′-carotenoic acid.

$C_{32}H_{44}O_2$=460.7

CAS — 1109-11-1.

Profile

Apocarotenal and ethyl apocarotenoate are carotenoids that are used as colouring agents in foods, drugs, and cosmetics.

Aspartame *(BAN, USAN, rINN)*

APM; Aspartaami; Aspartam; Aspartamas; Aspartamo; Aspartamum; Aszpartám; E951; SC-18862; Аспартам.

Methyl *N*-L-α-aspartyl-L-phenylalaninate; 3-Amino-*N*-(α-methoxycarbonylphenethyl)succinamic acid; *N*-L-α-aspartyl-L-phenylalanine, 1-methyl ester.

$C_{14}H_{18}N_2O_5$=294.3

CAS — 22839-47-0.

UNII — Z0H242BBR1.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Aspartame). A white or almost white, slightly hygroscopic, crystalline powder. Sparingly or slightly soluble in water and in alcohol; practically insoluble in dichloromethane and in *n*-hexane. Store in airtight containers.

USNF 31: (Aspartame). White, odourless, crystalline powder having a sweet taste. Sparingly soluble in water; slightly soluble in alcohol. pH of a 0.8% solution in water is about 5.

Stability. In the presence of moisture aspartame hydrolyses to form aspartylphenylalanine and a diketopiperazine derivative, with a resulting loss of sweetness.

Uses

Aspartame is an intense sweetening agent about 180 to 200 times as sweet as sucrose. It is used in foods, beverages, and pharmaceuticals. Each g provides about 17 kJ (4 kcal).

Sickle-cell disease. It has been suggested that aspartame might have beneficial effects in sickle-cell disease.[1]

1. Manion CV, *et al.* Aspartame effect in sickle cell anemia. *Clin Pharmacol Ther* 2001; **69:** 346–55.

Adverse Effects and Precautions

Excessive use of aspartame should be avoided by patients with phenylketonuria since one of its metabolic products is phenylalanine. Aspartame's sweetness is lost during prolonged cooking.

Adverse effects. The safety and adverse effects of aspartame as a pharmaceutical excipient[1,2] and in general use[3] have been reviewed.

Aspartame is hydrolysed in the gastrointestinal tract to methyl alcohol, aspartic acid, and phenylalanine. However, even with extraordinary consumption, methyl alcohol toxicity stemming from aspartame use is extremely unlikely. Aspartate concentrations in blood do not rise significantly after a very large dose (50 to 100 mg/kg) and therefore toxicity related to aspartate is also not expected to occur. Despite the similarity of aspartate to glutamate, studies in glutamate-sensitive persons have shown that they are not affected by aspartame consumption. Plasma concentrations of phenylalanine are also unlikely to be markedly elevated after modest consumption of aspartame by healthy persons but persons with phenylketonuria should avoid or limit their use of aspartame.

Adverse effects have been reported[1,2] after the use of aspartame, either as spontaneously recorded complaints from consumers or as published case reports in the medical literature. Most frequently reported problems have been headache, neuropsychiatric or behavioural symptoms, seizures, gastrointestinal symptoms, and hypersensitivity or dermatological symptoms. Available data do not provide evidence for serious widespread health consequences attendant upon the use of aspartame but it would appear that certain individuals may have an unusual sensitivity to the product. A safety review[4] by the European Commission Scientific Committee on Food (ECSCF) concluded that no causal link could be established between the consumption of aspartame and the occurrence of epilepsy or seizures, or cognition, mood and behaviour; this included individuals considered sensitive to aspartame.

Studies have confirmed aspartame's lack of effect on children's behaviour or cognitive function.[5,6]

An increased incidence of brain cancer was postulated to be related to aspartame use in one report;[7] however, the FDA[8] and the ECSCF[4] maintained that the available evidence did not support an association. Multiple malignancies have been reported[9] in *rats* given doses lower than the current acceptable daily intake of 40 or 50 mg/kg. The European Food Safety Authority assessed this study and concluded,[10] on the basis of all the available evidence, that the increased incidence of cancers in the *rats* was unrelated to aspartame treatment, and that there was no need to further review the safety of aspartame, nor to revise the established acceptable daily intake for aspartame of 40 mg/kg.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). *Med Toxicol* 1988; **3:** 209–40.
2. American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; **99:** 268–78.
3. Magnuson BA, *et al.* Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. *Crit Rev Toxicol* 2007; **37:** 629–727.
4. European Commission Health and Consumer Protection Directorate-General. Opinion of the Scientific Committee on Food: update on the safety of aspartame (expressed on 4 December 2002). Available at: http://ec.europa.eu/food/fs/sc/scf/out155_en.pdf (accessed 23/08/10)
5. Shaywitz BA, *et al.* Aspartame, behavior, and cognitive function in children with attention deficit disorder. *Pediatrics* 1994; **93:** 70–5.
6. Wolraich ML, *et al.* Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; **330:** 301–7.
7. Olney JW, *et al.* Increasing brain tumor rates: is there a link to aspartame? *J Neuropathol Exp Neurol* 1996; **55:** 1115–23.
8. Anonymous. Aspartame: no apparent link with brain tumours. *WHO Drug Inf* 1997; **11:** 18–19.
9. Soffritti M, *et al.* First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006; **114:** 379–85.
10. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a new long-term carcinogenicity study on aspartame. *EFSA J* 2006; **356** 1–44. Available

at: http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_op_ej356_aspartame_en1,2.pdf (accessed 03/03/08)

Breast feeding. Aspartame 50mg/kg given orally to healthy women resulted in small but significant increases in breast milk aspartate, phenylalanine, and tyrosine concentrations.[1] However, it was noted that these levels were similar to postprandial milk samples and were unlikely to impact upon total amounts of amino acids ingested by the infant. Furthermore, the dose of aspartame given in the study was considerably higher than the projected intake of about 7.5 to 8.5 mg/kg daily, assuming all sucrose intake were replaced by aspartame, and no aspartame abuse. Nonetheless, the last available guidance from the American Academy of Pediatrics[2] considered that caution was required when aspartame was ingested by mothers where either the mother or breast-fed infant had phenylketonuria.

1. Stegink LD, *et al.* Plasma, erythrocyte and human milk levels of free amino acids in lactating women administered aspartame or lactose. *J Nutr* 1979; **109:** 2173–81.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/11/04)

Pharmacokinetics

Aspartame is hydrolysed in the gastrointestinal tract to its 3 primary constituents, methyl alcohol, aspartic acid, and phenylalanine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Equalsweet; Slap; ***Braz.***: Dietacil†; Finn; ***Canad.***: Equal; ***Chile***: Naturalist; Originalsweet; Valsweet†; ***India***: Aspasweet; Equal; Lo-Kal; ***Ital.***: Aspartina; Futura†; Suaviter; ***NZ***: Equal†; ***Rus.***: Sugarfree (Шугафри); ***Thai.***: Espar; ***Turk.***: Aspartil; Canderel; Demi Canderel; Diyet Tat; Hermesetas Gold†; Nutra-Tat; Sanpa; ***Venez.***: Dulcosil; Edul; Hermesetas Gold.

Multi-ingredient Preparations. ***Arg.***: Genser Sweet†; Rondo Sweet; ***Chile***: Marco Sweet Light; ***India***: Glutammune; ***Ital.***: Floridral; ***UK***: Sweet 'n Low; ***Venez.***: Hermesetas Gold.

Aspartame Acesulfame

Аспартама Ацесульфам.

L-Phenylalanine, L-α-aspartyl-2-methyl ester, compound with 6-methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide (1:1).

$C_{18}H_{23}O_9N_3S$=457.5

CAS — 106372-55-8.

UNII — IFE6C6BS24.

Pharmacopoeias. In *USNF*.

USNF 31: (Aspartame Acesulfame). White, odourless, crystalline powder. Slightly soluble in water and in alcohol. It contains not less than 63.0% and not more than 66.0% of aspartame, calculated on the dried basis, and not less than 34.0% and not more than 37.0% of acesulfame, calculated as the acid form on the dried basis.

Profile

Aspartame acesulfame is a compound of aspartame (see p. 2169.2) and acesulfame (see p. 2166.2), and is used similarly in foods. It is an intense sweetener about 350 times as sweet as sucrose.

Astaxanthin

Astaksantiini; Astaksantin; Astaxanthine; Astaxantina; E161(j); Ovoester; Астаксантин.

(3*S*,3′*S*)-3,3′-Dihydroxy-β,β-carotene-4,4′-dione.

$C_{40}H_{52}O_4$=596.9

CAS — 472-61-7.

UNII — 8XPW32PR7I.

Profile

Astaxanthin is a carotenoid pigment used in fish feeds to colour the flesh of salmon and similar fish. It may be obtained synthetically or from natural sources.

Astaxanthin has also been used in dietary supplements for its antoxidant effects.

Reviews.

1. Higuera-Ciapara I, *et al.* Astaxanthin: a review of its chemistry and applications. *Crit Rev Food Sci Nutr* 2006; **46:** 185–96.
2. Pashkow FJ, *et al.* Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. *Am J Cardiol* 2008; **101:** 58D–68D.
3. Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. *Mar Drugs* 2011; **9:** 447–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Astacor; Asthin; Axanthin; Axtan; ***Ital.***: Sincorten-A.

Multi-ingredient Preparations. ***India***: Lycocare; Lycofact Plus; ***Indon.***: Astadiab; Asthin B-OND; Matoflam; Matovit AX; nutrivision; ***Ital.***: Caresel; Euretin; Pentaker; ***Mex.***: Drusen; ***Singapore***: Nutrivision†.

Beeswax

Balmumu; Bienenwachs; Bijenwas; Bišu vasks; Bivax; Bivoks; Cera d'abella; Cera d'api; Cire d'abeille; E901; Mehiläisvaha; Méhviasz; Mesilasvaha; Pčelinji vosak; Včelí vosk; Wosk pszczeli; Čebelji vosek; Пчелиный Воск.

CAS — 8012-89-3.

White Beeswax

Baltasis vaškas; Bleached Wax; Cera alba; Cera Blanca; Cêra Branca; Cera de abejas; Cire Blanche; Cire d'abeille blanche; E901; Fehér viasz; Gebleichtes Wachs; Valkovaha; Vax, vitt; Vosk bílý; White Wax; Wosk biały; Осветлённый Пчелиный Воск.

CAS — 8012-89-3.

UNII — 7G1J5DA97F.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Beeswax, White). It is bleached yellow beeswax. It occurs as white or yellowish-white pieces or plates, translucent when thin, with an odour similar to that of yellow beeswax, though fainter and never rancid, and with a fine-grained, matt and non-crystalline fracture, becoming soft and malleable when warmed in the hand. Drop point 61 degrees to 66 degrees. Practically insoluble in water; partially soluble in hot alcohol; completely soluble in fatty and essential oils.

USNF 31: (White Wax). It is bleached and purified yellow beeswax. A yellowish-white solid, somewhat translucent in thin layers. It has a faint characteristic odour and is free from rancidity. M.p. 62 degrees to 65 degrees. Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin that are constituents of the wax; completely soluble in chloroform, in ether, in fixed oils, and in volatile oils; partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30 degrees.

Yellow Beeswax

Cêra Amarela; Cera Amarilla; Cera de abejas amarilla; Cera Flava; Cire d'abeille jaune; Cire Jaune; E901; Gelbes Wachs; Geltonasis vaškas; Keltavaha; Refined Wax; Sárga viasz; Vax, gult; Vosk žlutý; Wosk żółty; Yellow Wax; Жёлтый Пчелиный Воск.

CAS — 8012-89-3.

UNII — 2ZA36H0S2V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Beeswax, Yellow). The wax obtained by melting with hot water the walls of the honeycomb of the bee, *Apis mellifera*, and removing the foreign matter. It occurs as yellow or light brown pieces or plates with a faint and characteristic odour of honey, and with a fine-grained, matt and non-crystalline fracture, becoming soft and malleable when warmed in the hand. Drop point 61 degrees to 66 degrees. Practically insoluble in water; partially soluble in hot alcohol; completely soluble in fatty and essential oils.

USNF 31: (Yellow Wax). The purified wax from the honeycomb of the bee, *Apis mellifera* (Apidae). It is a solid, varying in colour from yellow to greyish-brown with an agreeable honey-like odour, somewhat brittle when cold, pliable when warmed in the hand, and presenting a dull, granular, noncrystalline fracture when broken. M.p. 62 degrees to 65 degrees. Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin that are constituents of the wax; completely soluble in chloroform, in ether, in fixed oils, and in volatile oils; partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30 degrees.

Uses

Beeswax is used as a stiffening agent in ointments and creams, and enables water to be incorporated to produce water-in-oil emulsions. It is also used as a coating in the manufacture of modified-release oral preparations. White beeswax is occasionally used to adjust the melting-point of suppositories.

A sterile preparation of white beeswax, hard paraffin, and isopropyl palmitate (Sterile Surgical Bone Wax) is used to control bleeding from damaged bone during surgery. It should not be confused with Aseptic Surgical Wax (BPC 1949), also known as Horsley's Wax, which contained yellow beeswax, olive oil, and phenol in a mercuric chloride solution and was used to control haemorrhage in bone or cranial surgery.

Beeswaxes are also used in foods and cosmetics.

Adverse Effects

Granuloma formation. Use of surgical bone wax has been associated with an inflammatory response in some patients. Formation of granuloma tissue at the site of application to the orbit,[1] foot,[2] hip,[3] and sternum[4] has been reported. Seven patients developed local pain and tenderness after use of bone wax in foot surgery; further surgery to remove granulomatous tissue 4 to 52 months later resolved pain in 5 patients.[2] In another patient,[5] a large, granulomatous, retroperitoneal tumour associated with a foreign-body reaction developed 19 years after the use of bone wax on the iliac crest. In an autopsy study of 18 cadavers with evidence of sternotomy, 17 of which had macroscopic evidence of bone wax use, signs of inflammation or granuloma formation were found in all but one. The authors concluded that bone wax is non-resorbable and can cause chronic inflammation up to 10 years after application.[4] However, in a prospective randomised study[6] in 400 patients undergoing coronary bypass surgery, the application of bone wax to the sternal edges appeared to be neither unsafe nor of benefit.

1. Katz SE, Rootman J. Adverse effects of bone wax in surgery of the orbit. *Ophthal Plast Reconstr Surg* 1996; **12:** 121–6.
2. Anfinsen O-G, *et al.* Complications secondary to the use of standard bone wax in seven patients. *J Foot Ankle Surg* 1993; **32:** 505–8.
3. Lavigne M, *et al.* Bone-wax granuloma after femoral neck osteoplasty. *Can J Surg* 2008; **51:** E58–E60.
4. Sudmann B, *et al.* Histologically verified bone wax (beeswax) granuloma after median sternotomy in 17 of 18 autopsy cases. *Pathology* 2006; **38:** 138–41.
5. Verborgt O, *et al.* A retroperitoneal tumor as a late complication of the use of bone wax. *Acta Orthop Belg* 2000; **66:** 389–91.
6. Przborowski J, *et al.* Is bonewax safe and does it help? *Ann Thorac Surg* 2008; **85:** 1002–6.

Hypersensitivity. For reference to hypersensitivity reactions with bee products, including beeswax, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aqualane; Zoodermina Crema; ***Austria***: Tiroler Steinol; ***Braz.***: Balmex; ***Canad.***: Pure Gardens; ***Chile***: Cold Cream Avene; ***Fr.***: Cerat Inalterable†; Cold Cream Naturel; Jouvence; Menolistica; ***Ital.***: Eavit; Vitalux; ***Philipp.***: BSI Medicated Plaster; Livermin; ***USA***: Boudreaux's All Natural Butt Paste; Paladin; Palomar E; ***Venez.***: Nutricap.

Pharmacopoeial Preparations

BP 2014: Paraffin Ointment;

USP 36: Rose Water Ointment; White Ointment; Yellow Ointment.

Beetroot Red

Beet Red; E162 (beetroot red or betanin); Rojo de remolacha; Rouge de betterave; Свекольный Красный.

CAS — 89957-89-1 (beetroot extract); 89957-90-4 (beetroot extract); 7659-95-2 (betanin).

NOTE. The name beetroot red has been used for an extract of *Beta vulgaris* and for betanin (betanine), its main constituent.

Profile

Beetroot red is obtained from the roots of red beets, *Beta vulgaris* var. *rubra* (Chenopodiaceae). The main colouring principle consists of betacyanins of which the glycoside betanin is the main constituent. Beetroot red is used as a colouring agent for medicines, foodstuffs, and cosmetics.

Bentonite

Bentoniet; Bentoniit; Bentoniitti; Bentonit; Bentonita; Bentonitas; Bentonitum; E558; Mineral Soap; Soap Clay; Wilkinite; Бентонит.

CAS — 1302-78-9.

UNII — A3N5ZCN45C.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn*. Also in *USNF*, which also includes a purified form.

Ph. Eur. 8: (Bentonite). A natural clay containing a high proportion of montmorillonite, a native hydrated aluminium silicate in which some aluminium and silicon atoms

may be replaced by other atoms such as magnesium and iron. A very fine, homogeneous, greyish-white powder with a more or less yellowish or pinkish tint. Practically insoluble in water and in aqueous solutions, but swells with a little water forming a malleable mass.

USNF 31: (Bentonite). A native, colloidal, hydrated aluminium silicate. A very fine, odourless, hygroscopic, pale buff or cream-coloured to greyish powder, free from grit. Insoluble in water, but swells to about 12 times its volume when added to water; insoluble in, and does not swell in, organic solvents. pH of a 2% suspension in water, mixed vigorously to facilitate wetting, is between 9.5 and 10.5. Store in airtight containers.

USNF 31: (Purified Bentonite). A colloidal montmorillonite that has been processed to remove grit and nonswellable ore components. An odourless, fine, micronised powder, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerol. pH of a 5% suspension in water is between 9.0 and 10.0. Store in airtight containers.

Profile

Bentonite is a mineral clay belonging to the smectite group (see p. 1887.1). It absorbs water readily to form sols or gels, depending on its concentration, and is used in pharmaceutical manufacturing as a suspending and stabilising agent and as an adsorbent or clarifying agent. It is also used as an anticaking agent in the food industry.

Bentonite may be used as an oral adsorbent in paraquat poisoning (p. 2159.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Stomagel; ***Malaysia***: Clearasil Pimple Treatment; ***S.Afr.***: Clearasil T†; ***Singapore***: Clearasil Pimple Treatment; ***Switz.***: Prevalin.

Pharmacopoeial Preparations
USNF 31: Bentonite Magma.

Benzaldehyde

Aldehído benzoico; Aldehyd benzoesowy; Bensaldehyd; Bentsaldehydi; Benzaldehīds; Benzaldehid; Benzaldehído; Benzaldehit; Benzaldehyd; Benzaldéhyde; Benzaldeide; Benzaldeído; Бензальдегид.

C_7H_6O=106.1

CAS — 100-52-7.

UNII — TA269SD04T.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Benzaldehyde). A clear colourless liquid with a characteristic odour of bitter almonds. Slightly soluble in water; miscible with alcohol and with ether. Store at a temperature not exceeding 15 degrees in well-filled containers. Protect from light.

USNF 31: (Benzaldehyde). A colourless strongly refractive liquid. Slightly soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils. Store in well-filled, airtight containers. Protect from light. Avoid excessive heat.

Profile

Benzaldehyde is used as a flavour as an alternative to volatile bitter almond oil. It may cause contact dermatitis.

Preparations

Pharmacopoeial Preparations
USNF 31: Compound Benzaldehyde Elixir.

Benzene

Beinséin; Benceno; Benseen; Bensen; Bentseeni; Benzè; Benzeen; Benzen; Benzenas; Benzène; Benzeno; Benzol; Benzolas; Benzols; Cyclohexatriene; Hidruro de fenilo; Phenyl Hydride; Бензол; Бензен.

C_6H_6=78.11

CAS — 71-43-2.

UNII — J64922108F.

NOTE. Benzene may be known by names such as 'benzina', 'benzol', 'benzole', or 'benzolum'. However, 'benzol' is also used to describe a mixture of hydrocarbons and 'benzin' or 'benzine' is used as a name for a petroleum distillate (see also Petroleum Spirit, p. 2201.2).

Description. Benzene is a clear colourless flammable liquid with a characteristic aromatic odour. Wt per mL about 0.88 g. B.p. about 80 degrees. Store in airtight containers.

Uses

Benzene was formerly applied as a pediculicide. Its use as an industrial solvent is decreasing.

Adverse Effects, Treatment, and Precautions

Symptoms of acute poisoning after inhalation or ingestion of benzene include initial excitement or euphoria followed by CNS depression with headache, dizziness, blurred vision, and ataxia, which in severe cases may progress to coma (accompanied by hyperactive reflexes), convulsions, and death from respiratory failure. Other symptoms include nausea and irritation of the mucous membranes; ventricular arrhythmias may occur. Direct skin contact with liquid benzene may result in marked irritation, and dermatitis may develop on prolonged or repeated exposure.

Prolonged industrial exposure to benzene vapour has been associated with adverse effects on the gastrointestinal tract and the CNS but in particular with marked effects on the bone marrow and blood. Decreases in the numbers of red or white blood cells or of platelets may occur, producing symptoms of headache, fatigue, anorexia, pallor, and petechiae. In severe cases pancytopenia or aplastic anaemia may develop. Leukaemia, particularly acute myeloid leukaemia, has also developed, often many years after exposure to benzene has ceased. These effects have been reported in workers exposed to relatively high concentrations of the vapour (around 200 ppm or more) but reduced red blood cell counts and anaemia have also been reported at lower concentrations. Chromosome abnormalities have been seen after prolonged exposure to benzene, particularly at the higher concentrations associated with blood dyscrasias; however, the significance of these abnormalities in the development of leukaemia is unclear.

Treatment of poisoning consists of symptomatic and supportive measures. The UK National Poisons Information Service considers that gut decontamination (gastric lavage) is contra-indicated because it may increase the risk of aspiration. In chronic poisoning, repeated blood transfusions may be necessary. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

Reviews.
1. Health and Safety Executive. Benzene. *Toxicity Review 4.* London: HMSO, 1982.
2. WHO. Benzene. *Environmental Health Criteria 150.* Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc150.htm (accessed 29/06/04)
3. Khan HA. Benzene's toxicity: a consolidated short review of human and animal studies. *Hum Exp Toxicol* 2007; **26:** 677–85.

Malignant neoplasms. Epidemiological data support an association between benzene exposure and acute myeloid leukaemia, but the risk after low levels of exposure (1 to 10 ppm) is less clear.[1] However, a large cohort study[2] suggested that there is an increased risk of acute myeloid leukaemia and of non-Hodgkin's lymphoma with benzene exposure at levels below 10 ppm. The general association between benzene exposure and non-Hodgkin's lymphoma was also supported by a review of case-control and cohort studies.[3]

1. Austin H, *et al.* Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol* 1988; **127:** 419–39.
2. Hayes RB, *et al.* Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997; **89:** 1065–71.
3. Smith MT, *et al.* Benzene exposure and risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007; **16:** 385–91.

Pregnancy. An evaluation of the USA National Natality and Fetal Mortality Survey noted that maternal or paternal occupational exposure to agents such as benzene was associated with an increased risk of still-birth and that paternal exposure to benzene increased the risk of low-birth-weight infants.[1]

1. Savitz DA, *et al.* Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol* 1989; **129:** 1201–18.

Pharmacokinetics

Benzene is absorbed after inhalation and ingestion, but is not significantly absorbed through the skin. Some is excreted unchanged from the lungs. Oxidation to phenol and related quinol compounds occurs in the liver, the metabolites being excreted in the urine as conjugates of sulfuric or glucuronic acid.

Black PN

Briliantinis Juodasis BN; Briljantsvart BN; Briljanttimusta BN; Briljantzwart BN; Brillantschwarz BN; Brilliant Black BN; Brilliant Black PN; CI Food Black 1; Colour Index No. 28440; Czerń Brylantowa PN; E151; Fekete PN; Negro Brilhante; Negro brillante BN; Negro PN; Nero Brillante BN; Noir Brillant BN; Бриллиантовый Чёрный PN; Чёрный Блестящий PN.

It consists mainly of tetrasodium 4-acetamido-5-hydroxy-6-[7-sulphonato-4-(4-sulphonatophenylazo)-1-naphthylazo] naphthalene-1,7-disulphonate.

$C_{28}H_{17}N_5Na_4O_{14}S_4$=867.7

CAS — 2519-30-4.

UNII — 2WPR32U0CP.

Profile

Black PN is a synthetic diazo dye used as a colouring agent in medicines, cosmetics, and foods.

Bordeaux B

Azorubrum; Bordeaux R; Burdeos B; CI Acid Red 17; Colour Index No. 16180; Кислотный Бордо.

It consists mainly of disodium 3-hydroxy-4-(1-naphthylazo) naphthalene-2,7-disulphonate.

$C_{20}H_{12}N_2Na_2O_7S_2$=502.4

CAS — 5858-33-3.

Profile

Bordeaux B is a synthetic azo dye formerly used as a colouring agent for medicines and foods that has been generally replaced by other colours.

Brilliant Blue

Azul brillante; Bleu brillant; Błękit brylantowy; Blu Brillante; Briliantinis mėlynasis; Briljantblått; Briljantblauw; Brillantblau; Brillantkék.

Brilliant Blue FCF

Azul brillante FCF; Bleu brilliant FCF; Blue EGS; CI Acid Blue 9; CI Food Blue 2; Colour Index No. 42090; E133; FD & C Blue No. 1; Patent Blue AC; Бриллиантовый Голубой FCF; Синий Блестящий FCF.

Disodium 4′,4″-bis(*N*-ethyl-3-sulphonatobenzylamino)triphenylmethylium-2-sulphonate.

$C_{37}H_{34}N_2Na_2O_9S_3$=792.8

CAS — 3844-45-9.

UNII — H3R47K3TBD.

Brilliant Blue G

Acid Blue 90.

$C_{47}H_{48}N_3NaO_7S_2$=854.0

CAS — 6104-58-1.

Profile

The name brilliant blue has been used for various synthetic triarylmethane (triphenylmethane) dyes. Brilliant blue FCF is used as a colouring agent in medicines, cosmetics, and foodstuffs. The related compound, brilliant blue G, is used as an ophthalmological stain. Other related dyes include sulfan blue (p. 2624.1) and patent blue V (p. 2584.2).

References.
1. Enaida H, Ishibashi T. Brilliant blue in vitreoretinal surgery. *Dev Ophthalmol* 2008; **42:** 115–25.
2. Gerding H, *et al.* Intravital staining of the internal limiting membrane with a novel heavy solution of brilliant blue G. *Klin Monbl Augenheilkd* 2011; **228:** 298–301.

Enteral feeds. Blue colourings such as brilliant blue FCF have been added to enteral feeds to aid the detection of pulmonary aspiration but such use has been associated with toxic effects. Blue discoloration of the skin, initially attributed to cyanosis, has been reported[1] in a child who received a large quantity of brilliant blue FCF as a colouring in an enteral feed. Abnormal systemic absorption of the dye has also been reported[2] in 2 critically ill patients, both of whom subsequently died. As of September 2003 the FDA was aware of 20 cases of blue discoloration of body fluids and skin associated with the use of blue dyes, including 12 fatalities.[3] Most cases occurred in patients with a history of sepsis, suggesting that altered intestinal permeability could be a factor.

1. Zillich AJ, *et al.* Skin discoloration with blue food colouring. *Ann Pharmacother* 2000; **34:** 868–70.
2. Lucarelli MR, *et al.* Toxicity of Food Drug and Cosmetic Blue No. 1 dye in critically ill patients. *Chest* 2004; **125:** 793–5.
3. Anonymous. Blue discoloration and death from FD&C Blue No. 1. *WHO Drug Inf* 2003; **17:** 239–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Brilliant Peel.

Multi-ingredient Preparations. ***Fr.***: Viticolor.

1-Bromopropane

n-Propyl Bromide; Propyl Bromide.
C_3H_7Br=123.0
CAS — 106-94-5.
UNII — Y9746DNE68.

Uses

1-Bromopropane is used as an industrial solvent.

Adverse Effects

1-Bromopropane is irritant. Neurotoxicity has been reported after occupational exposure. Studies in *animals* have shown reproductive toxicity.

References.

1. Ichihara G, *et al.* A survey on exposure level, health status, and biomarkers in workers exposed to 1-bromopropane. *Am J Ind Med* 2004; **45:** 63–75.
2. Ichihara G, *et al.* Neurologic abnormalities in workers of a 1-bromopropane factory. *Environ Health Perspect* 2004; **112:** 1319–25.
3. Majersik JJ, *et al.* Severe neurotoxicity associated with exposure to the solvent 1-bromopropane (n-propyl bromide). *Clin Toxicol* 2007; **45:** 270–6.
4. Raymond LW, Ford MD. Severe illness in furniture makers using a new glue: 1-bromopropane toxicity confounded by arsenic. *J Occup Environ Med* 2007; **49:** 1009–19.
5. Centers for Disease Control and Prevention (CDC). Neurologic illness associated with occupational exposure to the solvent 1-bromopropane—New Jersey and Pennsylvania, 2007-2008. *MMWR* 2008; **57:** 1300–2.
6. Li W, *et al.* Dose-dependent neurologic abnormalities in workers exposed to 1-bromopropane. *J Occup Environ Med* 2010; **52:** 769–77.

Brown FK

Braun FK; Brun FK; Brąz FK; Chocolate Brown FK; CI Food Brown 1; E154; Marrón FK; Rudasis FK; Ruskea FK; Коричневый FK.
A mixture of: sodium 2′,4′-diaminoazobenzene-4-sulphonate; sodium 2′,4′-diamino-5′-methylazobenzene-4-sulphonate; disodium 4,4′-(4,6-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4′-(2,4-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4′-(2,4-diamino-5-methyl-1,3-phenylenebisazo) dibenzenesulphonate; trisodium 4,4′,4″-(2,4-diaminobenzene-1,3,5-triazo)tribenzenesulphonate.
CAS — 8062-14-4.

Profile

Brown FK, a mixture of 6 synthetic azo dyes, is used as a colouring agent for foodstuffs.

Brown HT

Braun HT; Brun chocolat HT; Brun HT; Brąz HT; Chocolate Brown HT; CI Food Brown 3; Colour Index No. 20285; Csokoládébarna HT; E155; Marrón HT; Marrone HT; Rudasis HT; Ruskea HT; Коричневый HT.
Disodium 4,4′-(2,4-dihydroxy-5-hydroxymethyl-1,3-phenylenebisazo)di(naphthalene-1-sulphonate).
$C_{27}H_{18}N_4Na_2O_9S_2$=652.6
CAS — 4553-89-3.

Profile

Brown HT, a synthetic diazo dye, is used as a colouring agent for medicines and foodstuffs.

2-Butoxyethanol

Butyl Glycol; Butyl Oxitol; EGBE; Ethyleenglycol(mono) butylether; Ethylene Glycol Butyl Ether; Ethylene Glycol Monobutyl Ether; Ethylenglycolmonobutylether.
2-Butoxy-1-ethanol.
$C_6H_{14}O_2$=118.2
CAS — 111-76-2.
UNII — I0P9XEZ9WV.

NOTE. The name Butyl Cellosolve has been used as a trade mark for 2-butoxyethanol.

Profile

2-Butoxyethanol is a glycol ether solvent with similar properties to 2-methoxyethanol (p. 2196.1).

Butyl Acetate

Acétate de Butyle; Acetato de butilo; Acetato di n-butile; AcOnBu; Butil-acetát; Butylacetaat; Butylacetat; Butylethanoat; Butylu octan; *N*-butyyliasetaatti; Essigsäure-*n*-butylester; Éster butílico; Etanoato de butila; Etanoato de butilo; Бутилацетат.
n-Butyl acetate.
$C_6H_{12}O_2$=116.2
CAS — 123-86-4.
UNII — 464P5N1905.

Description. Butyl acetate is a clear, colourless flammable liquid with a strong fruity odour. Wt per mL about 0.88 g. B. p. 123 degrees to 126 degrees. Slightly soluble in water; miscible with alcohol. Store in airtight containers.

Uses

Butyl acetate is used as an industrial solvent and as an extraction solvent in food processing.

Adverse Effects

Butyl acetate is irritant. High concentrations may cause CNS depression.

Butyl Alcohol

Alcohol butílico; 1-Butanol; *n*-Butanol; Butanole; Butanoli; Butanolo; 1-Butyl alcohol; *n*-Butyl Alcohol; Бутиловый Спирт.
Butan-1-ol.
$C_4H_{10}O$=74.12
CAS — 71-36-3.
UNII — 8PJ61P6TS3.

Pharmacopoeias. In *USNF.*

USNF 31: (Butyl Alcohol). A clear, colourless, mobile liquid having a characteristic, penetrating vinous odour. Soluble in water; miscible with alcohol, with ether, and with many other organic solvents. Store in airtight containers at a temperature not exceeding 40 degrees.

Uses

Butyl alcohol is used as an industrial and pharmaceutical solvent and as an extraction solvent in food processing.

Adverse Effects and Precautions

Butyl alcohol may be irritant and may cause mild CNS depression with headache, dizziness, and drowsiness.

References to the toxicity of butyl alcohol.

1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 29/06/04)
2. WHO. 1-Butanol health and safety guide. *IPCS Health and Safety Guide 3.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg003.htm (accessed 29/06/04)
3. Bunc M, *et al.* Butanol ingestion in an airport hangar. *Hum Exp Toxicol* 2006; **25:** 195–7.
4. McLain VC. Final report of the addendum to the safety assessment of *n*-butyl alcohol as used in cosmetics. *Int J Toxicol* 2008; **27** (suppl 2): 53–69.

Handling. Suitable precautions should be taken to avoid skin contact with butyl alcohol as it can penetrate skin and produce systemic toxicity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India:*** Ableed.

Butylamine

Butilamina; Butylamina; *n*-Butylamine; Butyloamina; Бутиламин.
$C_4H_{11}N$=73.14
CAS — 109-73-9.
UNII — N2QV60B4WR.

Description. Butylamine is a colourless to pale yellow flammable liquid with an ammoniacal odour. Wt per mL about 0.744 g. B.p. about 78 degrees. Miscible with water, with alcohol, and with ether. Store in airtight containers.

Uses

Butylamine is used as a solvent.

Adverse Effects and Precautions

Butylamine is irritant. Symptoms of CNS depression may occur after exposure to high concentrations of the vapour.

Handling. Suitable precautions should be taken to avoid skin contact with butylamine as it can penetrate skin and produce systemic toxicity.

Butylene Glycol

1,3-Butanediol; Butanediol; 1,3-Butylene Glycol; β-Butylene Glycol; 1,3-Dihydroxybutane; Methyltrimethylene Glycol.
Butane-1,3-diol.
$C_4H_{10}O_2$=90.12
CAS — 107-88-0.
UNII — 3XUS85K0RA.

NOTE. Do not confuse with butyl glycol, which is ethylene glycol monobutyl ether.

Profile

Butylene glycol has similar properties to propylene glycol (p. 2205.2) and is used as a solvent in pharmaceutical manufacturing. It is also used in foods and cosmetics, including preparations for hand disinfection, as a solvent and humectant and for its antimicrobial preservative properties. Hypersensitivity reactions have been reported.

The related isomer, 1,4-butylene glycol (1,4-butanediol) is used as an industrial solvent and chemical intermediate but has also been the subject of abuse (see Abuse under Adverse Effects of Sodium Oxybate, p. 1914.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.:*** Manorapid Synergy; ***Ger.:*** GeloBacin; Poly-Alkohol†; ***Israel:*** Monorapid†; Skin Des†; ***Singapore:*** Bio-Taches Masque†; Bio-Taches†.

Calcium Saccharate *(rINN)*

Calcii Saccharas; Calcium D-Saccharate; Sacarato cálcico; Sacarato de calcio; Saccharate de Calcium; Sucrate de Calcium; Кальция Сахарат.
Calcium D-glucarate tetrahydrate.
$C_6H_8CaO_8.4H_2O$=320.3
CAS — 5793-88-4 (anhydrous calcium saccharate); 5793-89-5 (calcium saccharate tetrahydrate).
UNII — SST07NLK7J (anhydrous calcium saccharate); 6AP9J91K4V (calcium saccharate tetrahydrate).

NOTE. Do not confuse with Saccharin Calcium (p. 2208.1). The names calcium saccharate and calcium sucrate have also been used to describe saccharated lime.

Pharmacopoeias. In *US.*

USP 36: (Calcium Saccharate). A white, odourless, crystalline powder. Very slightly soluble in cold water and in alcohol; slightly soluble in boiling water; practically insoluble in chloroform and in ether; soluble in dilute mineral acids and in solutions of calcium gluconate.

Profile

Calcium saccharate is used as a stabilising agent in solutions of calcium gluconate for injection. Each g of calcium saccharate contains about 3.1 mmol of calcium. Calcium saccharate 8 g is equivalent to about 1 g of calcium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria:*** Calcium Fresenius; ***Cz.:*** Calcium Biotika; ***Spain:*** Suplecal.

Multi-ingredient Preparations. ***Ger.:*** Calcium Braun†; ***Mex.:*** Prevefem Complex.

Calcium Stearate

Calcii stearas; Calcium, stéarate de; Calciumstearat; E470a (sodium, potassium and calcium salts of fatty acids); Estearato de calcio; Kalcio stearatas; Kalciumstearat; Kalciumsztearát; Kalsiumstearaatti; Stearan vápenatý; Stearato di calcio; Кальция Стеарат.
Calcium octadecanoate.
CAS — 542-42-7 (calcium palmitate); 1592-23-0 (calcium stearate).
UNII — 776XM7047L.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8 (Calcium Stearate). A mixture of calcium salts of different fatty acids consisting mainly of stearic acid ($C_{36}H_{70}CaO_4$ = 607.0) and palmitic acid ($C_{32}H_{62}CaO_4$ = 550.9) with minor proportions of other fatty acids. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acids is not less than 90.0%. A fine, white or almost white, crystalline powder. Practically insoluble in water and in alcohol.

USNF 31: (Calcium Stearate). A compound of calcium with a mixture of solid organic acids obtained from fats, consisting mainly of variable proportions of calcium stearate ($C_{36}H_{70}CaO_4$ = 607.0) and calcium palmitate ($C_{32}H_{62}CaO_4$ = 550.9). A fine, white to yellowish-white bulky, unctuous powder, free from grittiness with a slight

characteristic odour. Insoluble in water, in alcohol, and in ether.

Uses

Calcium stearate is a metal soap anionic surfactant (p. 2164.1). It is used as a lubricant and anticaking agent in the manufacture of tablets and capsules and is also used in foods, cosmetics, and other industrial applications.

Adverse Effects

Acute eosinophilic pneumonia in 1 patient has been attributed to the presence of calcium stearate used as an additive in an antihistamine tablet formulation.[1]

1. Kurai J, *et al.* Acute eosinophilic pneumonia caused by calcium stearate, an additive agent for an oral antihistaminic medication. *Intern Med* 2006; **45:** 1011–16.

Calcium Stearoyl-lactylate

Calcium Stearoyl-2-lactylate; Calcium Stearyl Lactylate; Calcium Verate; E482; Стеароиллактилат Кальция.
Calcium 2-(1-Carboxyethoxy)-1-methyl-2-oxoethyloctadecanoate.
CAS — 5793-94-2.

Sodium Stearoyl-lactylate

E481; Natriumstearoyl-2-lactylaat; Natriumstearoyl-2-lactylat; Natriumstearoyyli-2-laktylaatti; Nátrium-sztearoil-2-laktilát; Sodium Stearoyl Lactate; Sodium Stearoyl-2-lactylate; Sodium Stearyl Lactylate; Стеароиллактилат Натрия.
Sodium 2-(1-Carboxyethoxy)-1-methyl-2-oxoethyloctadecanoate sodium salt.
CAS — 25383-99-7.
UNII — IN99IT31LN.

Profile

Calcium and sodium stearoyl lactylate are ester carboxylate anionic surfactants (p. 2164.1) consisting mainly of salts of stearic acid esterified with lactic acid lactate. They are used as emulsifiers and stabilisers in the food industry, including in foods for special diets; they also have pharmaceutical and cosmetic applications.

Calcium Sulfate

Calcii sulfas; Calcium, sulfate de; Calcium Sulphate; Calciumsulfat; E516; Gypsum (calcium sulfate dihydrate); Kalcija sulfāts; Kalcio sulfatas; Kalciumsulfat; Kalcium-szulfát; Kalsiumsulfaatti; Kalsiumsulfat; Kalsiyum Sülfat; Shí Gāo (calcium sulfate dihydrate); Síran vápenatý; Solfato di calcio; Sulfat de calci; Sulfato cálcico; Sulfato de Cálcio; Wapnia siarczan; Сульфат Кальция; Сернокислый Кальций.
$CaSO_4$=136.1
CAS — 7778-18-9 (anhydrous calcium sulfate); 10101-41-4 (calcium sulfate dihydrate).
UNII — WAT0DDB505 (calcium sulfate); E934B3V59H (anhydrous calcium sulfate); 4846Q921YM (calcium sulfate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn* which specify the dihydrate. Also in *USNF* which specifies the dihydrate or the anhydrous material.

Ph. Eur. 8: (Calcium Sulfate Dihydrate). A white or almost white fine powder. Very slightly soluble in water; practically insoluble in alcohol.

USNF 31: (Calcium Sulfate). It is anhydrous or contains two molecules of water of hydration. A white to slightly yellow-white odourless fine powder. Soluble 1 in 375 of water and 1 in 485 of boiling water; soluble in 3N hydrochloric acid.

Profile

Calcium sulfate dihydrate is used as an excipient for the preparation of tablets or capsules.

Homoeopathy

Calcium sulfate has been used in homoeopathic medicines under the following names: Calcium sulfuricum; Calcarea sulphurica; Cal. sul.; Calc sulph.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Celloids CS 36†.

Multi-ingredient Preparations. ***Jpn***: Eppikajutsuto; Makyokansekito; Mokuboito; Shin'iseihaito; Shofusan; Shosaikotokakikyosekko; ***Pol.***: Padma 28; ***Switz.***: Arteria-vita; Padma 28; Padmed Circosan; ***UK***: Padma 28; Padma Circosan; ***Ukr.***: Pregnalac (Прегналак)†.

Homoeopathic Preparations. ***Austria***: Asinis; ***Canad.***: Combinaison†; Diamite; Hylands Bioplasma; Melange†; Nuage Bioplasma†; ***Ger.***: Drufusan N†; Drufusan; Sinuselect N; ***Rus.***: Asinis (Асинис); ***Ukr.***: Asinis (Асинис).

Candelilla Wax

Candelillawachs; Cire de Candelilla; E902; Kandelilla viasz; Канделильский Воск.
CAS — 8006-44-8.
UNII — WL0328HX19.

Pharmacopoeias. In *USNF.*

USNF 31: (Candelilla Wax). The purified wax from the leaves of the plant *Euphorbia antisyphilitica.* It is a hard, yellowish-brown, opaque to translucent wax. M.p. between 68.5 degrees and 72.5 degrees. Insoluble in water; soluble in chloroform and in toluene.

Profile

Candelilla wax is used as a pharmaceutical excipient and in the food industry.

Canthaxanthin

Cantaxantina; Canthaxanthine; Canthaxantinum; CI Food Orange 8; Colour Index No. 40850; E161(g); Kantaksantiini; Kantaksantin; Kantaksantinas; Kantaxantin; Кантаксантин.
β,β-Carotene-4,4′-dione.
$C_{40}H_{52}O_2$=564.9
CAS — 514-78-3.
UNII — 4C3C6403MU.

Uses

Canthaxanthin is a carotenoid but unlike betacarotene or apocarotenal it has no vitamin A activity. It has selected uses as a food colouring and may be given to salmon, trout, and poultry to colour their flesh, and to laying hens to colour the yolks of their eggs. It is also used to colour medicines and cosmetics.

Canthaxanthin has also been given orally to produce an artificial suntan, and as an adjunct to betacarotene in the management of erythropoietic protoporphyria (see Porphyrias under Haem Derivatives, p. 1556.1).

Adverse Effects

Use of canthaxanthin as a food colouring is generally regarded as safe, although there have been concerns about hepatotoxicity and urticaria has been reported. Oral doses of canthaxanthin have been associated with retinal toxicity. For further details, see below.

Canthaxanthin has been associated with retinal changes involving accumulation of bright yellow particles around the macula ('gold speck' maculopathy), and alterations in eye function and visual deterioration have occurred.[1-3] Although these reports have related to oral use either for the production of an artificial tan by means of pigment deposition in the skin or for the medical treatment of erythropoietic protoporphyria, there has been concern about the use of canthaxanthin as a food colouring, and it was suggested that it should be restricted to use as a feed additive for farmed salmon and trout in order to produce a coloration of the fish flesh.[1] The results of long-term toxicity studies in *animals* also led to concern[2] about the potential for hepatotoxicity. However, subsequent studies failed to confirm hepatotoxicity in humans and it is now allowed as a food colouring,[4] although its uses are restricted in some countries. Canthaxanthin is one of several food colourings that have been reported to provoke chronic urticaria.[5]

There has also been a report of fatal aplastic anaemia in a patient who took canthaxanthin in order to produce an artificial tan.[6]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 25/05/07)
3. Hueber A, *et al.* Canthaxanthin retinopathy: long-term observations. *Ophthalmic Res* 2011; **46:** 103–106.
4. FAO/WHO. Evaluation of certain food additives and contaminants: forty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 859* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_859.pdf (accessed 25/05/07)
5. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104:** 369–81.
6. Bluhm R, *et al.* Aplastic anemia associated with canthaxanthin ingested for 'tanning' purposes. *JAMA* 1990; **264:** 1141–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bronsual; Bronzearte.

Multi-ingredient Preparations. ***Arg.***: Sol Bronce Vital.

Capryloyl Glycine

Capriloyl Glycine; Caprylylglycine.
N-(1-Oxo-octyl)glycine.
$C_{10}H_{19}NO_3$=201.3
CAS — 14246-53-8.
UNII — 8TY5YO42NJ.

Profile

Capryloyl glycine is an amino acid fatty acid ester (lipoamino acid) derived from the amino acid glycine and caprylic acid. It is used as a moisturiser in cosmetic products and may also have antibacterial properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Saliker; ***Chile***: Kerium Anticaspa -Caspa Grasa; Kerium Anticaspa -Caspa Seca; Kerium Anticaspa Intensivo.

Caramel

Burnt Sugar; Caramelo; Karamell; Sacch. Ust.; Saccharum Ustum; Sockerkulör; Sokerikulööri; Sukkerkulør; Zuckercouleur; Жжёный Сахар; Сахарный Колер.
CAS — 8028-89-5.
UNII — T9D99G2B1R.

Pharmacopoeias. In *USNF.*

USNF 31: (Caramel). A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali or of alkaline carbonate or a trace of mineral acid being added while heating. It is a thick, dark brown liquid, having the characteristic odour of burnt sugar, and a pleasant bitter taste. One part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish-orange colour. The colour of this solution is not changed and no precipitate is formed after exposure to sunlight for 6 hours. When spread as a thin layer on a glass plate, it appears homogeneous, reddish-brown, and transparent. Miscible with water; immiscible with ether, with chloroform, with acetone, with petroleum spirit, and with benzene; soluble in dilute alcohol up to 55%. Store in airtight containers.

Profile

Caramels are used in foods, medicines, and cosmetics to produce pale yellow to dark brown colours. They have no calorific value. They are complex mixtures of compounds prepared by heating carbohydrates (food-grade sweeteners consisting of glucose, fructose, or polymers of these) either alone or in the presence of acids or alkalis (food-grade citric or sulfuric acids or calcium, potassium, or sodium hydroxides, or mixtures of these). The caramels can be classified according to the reactants used in the manufacturing process:

Class I (E150a, plain caramel, spirit caramel, or caustic caramel); no ammonium or sulfite compounds are used.

Class II (E150b or caustic sulfite caramel); sulfite compounds used but not ammonium compounds.

Class III (E150c, ammonia caramel, or beer caramel); ammonium compounds used but not sulfite compounds

Class IV (E150d, sulfite ammonia caramel, or soft-drink caramel); both ammonium and sulfite compounds used.

Some caramels also have flavouring properties.

Carbazole Violet

Colour Index No. 51319; Permanent Violet RL; Pigment Violet 23; Фиолетовый Карбазол.
8,18-Dichloro-5,15-diethyl-5,15-dihydrodiindolo(3,2-*b*:3′,2′-*m*)triphenodioxazine.
$C_{34}H_{22}Cl_2N_4O_2$=589.5
CAS — 6358-30-1.
UNII — 8U8Z6628KF.

Profile

Carbazole violet is a synthetic dye used as a colouring agent in cosmetics and contact lenses.

Carbomers

Acrylic Acid Polymers; Carbomera; Carbomere; Carbomères; Carbómeros; Carbopols; Carboxipolimetilenos; Carboxypolymethylene; Carboxyvinyl Polymers; Carpolenos; Karbo-

meerit; Karbomerai; Karbomerek; Karbomerer; Karbomerler; Karbomery; Poliakrilic Asit; Polímeros de carboxivinilo; Polyacrylic Acid; Карбомеры.
CAS — 9003-01-4; 54182-57-9.
UNII — 4Q93RCW27E (carbomer 940).

NOTE. Carbomer is *BAN*, *USAN*, and *rINN*.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Int. USNF* has separate monographs for a range of carbomers.

USNF also includes Carbomer Copolymer and Carbomer Interpolymer.

Ph. Eur. 8: (Carbomers). High-molecular-weight polymers of acrylic acid cross-linked with polyalkenyl ethers of sugars or polyalcohols. They are produced in several grades characterised by the viscosity of a defined solution. White or almost white, fluffy, hygroscopic powders. They swell in water and in other polar solvents after dispersion and neutralisation with sodium hydroxide solution. Store in airtight containers.

USNF 31: (Carbomer 934; Carbomer 934P; Carbomer 940; Carbomer 941; Carbomer 1342). Carbomers are high-molecular-weight polymers of acrylic acid cross-linked with allyl ethers of pentaerythritol. The viscosity of a neutralised aqueous dispersion for each carbomer is:

- Carbomer 934 (0.5%), 30 500 to 39 400 cP
- Carbomer 934P (0.5%), 29 400 to 39 400 cP
- Carbomer 940 (0.5%), 40 000 to 60 000 cP
- Carbomer 941 (0.5%), 4000 to 11 000 cP
- Carbomer 1342 (1.0%), 9500 to 26 500 cP

They are white, fluffy, hygroscopic powders having a slight characteristic odour. pH of a 1% dispersion in water is about 3. When neutralised with alkali hydroxides or with amines, they dissolve in water, in alcohol, and in glycerol. Store in airtight containers.

USNF 31: (Carbomer Copolymer). A high-molecular-weight copolymer of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of polyalcohols. Different types of Carbomer Copolymer are characterised by the viscosity of a defined solution. Carbomer Copolymer does not constitute the official title when benzene is used in the manufacturing process, in which case the name will be Carbomer 1342 if it complies with the requirements of that monograph. Store in airtight containers at a temperature not exceeding 45 degrees.

USNF 31: (Carbomer Interpolymer). A carbomer homopolymer or copolymer that contains a block copolymer of macrogol and a long chain alkyl acid ester. Different types of Carbomer Interpolymer are characterised by the viscosity of a defined solution. Store in airtight containers at a temperature not exceeding 45 degrees.

Profile

Carbomers are used in pharmaceutical manufacturing as suspending agents, gel bases, emulsifiers, and binding agents in tablets.

Carbomers, in liquid gel formulations containing typically 0.2 or 0.3%, are used topically as tear substitutes in the management of dry eye (p. 2190.1).

Carbomers have also been investigated as vaginal spermicides and microbicides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acrylarm; Alivialux; Gimonte XXI; Liposic; Phoenix Lagrimas; Refresh Gel; Siccafluid; Viscotears; ***Austral.***: Poly Gel; Viscotears; ***Austria***: Aqua-Tears; Vidisic; ***Belg.***: Alcon Eye Gel; Lacrinorm; Liposic; Ocugel; Thilo Tears; Vidisic; ***Braz.***: Refresh Gel; Vidisic; Viscotears; ***Canad.***: Tear-Gel†; ***Chile***: Feels; Lacryvisc; Nicotears; Viscotears; ***China***: Liposic (立宝舒); Vidisic (唯地息); ***Cz.***: Oftagel; Vidisic; ***Denm.***: Oftagel; Viscotears; ***Fin.***: Oftagel; Viscotears; ***Fr.***: Aquarest; Civigel; Gel-Larmes; Lacrinorm; Lacryvisc; Liposic; Siccafluid; ***Ger.***: Arufil C†; Lacrigel C†; Liposic; Liquigel; MuGard; Siccapos; Thilo-Tears; Vidisic; Visc-Ophtal; Visco-Vision; ***Gr.***: Dacrio Gel; Liposic; Siccafluid; Tear drops; Thilogel; Viscoter; ***Hong Kong***: Lacryvisc; Liposic; Viscotears†; ***Hung.***: Oftagel; Vidisic; ***Irl.***: GelTears; Liposic; Liquivisc; Vidisic; ***Israel***: Liposic; Viscotears; ***Ital.***: Dacriogel; Dropgel; Lacrigel; Lacrinorm; Lipovisc; Siccafluid; Viscotirs; ***Malaysia***: Siccapos; ***Mex.***: Acrylarm; Conforgel; Lacryvisc; Lipolac; Refresh; Viscotears; ***Mon.***: Lacrifluid; Lacrigel; ***Neth.***: Dry Eye Gel; Lacrinorm; Liposic; Siccafluid; Siccafree; Siccamed; Thilo-Tears; Vidisic; ***Norw.***: Oftagel; Viscotears; ***NZ***: Viscotears; ***Philipp.***: Lacryvisc; Lipolin; Siccafluid; Vidisic; ***Pol.***: Oftagel; Oftipan; Vidisic; ***Port.***: Lacryvisc; Liposic; Siccafluid; Vidisic; ***Rus.***: Oftagel (Офтагель); Vidisic (Видисик); ***S.Afr.***: Teargel; ***Singapore***: Lacryvisc; Vidisic; ***Spain***: Lacryvisc; Lipolac; Ofarsin; Siccafluid; Viscotears; ***Swed.***: Oftagel; Viscotears; ***Switz.***: Fluidose; Lacrifluid; Lacrinorm; Lacryvisc; Liposic; Siccafluid; Viscotears; ***Thai.***: Lacryvisc; Liposic; Vidisic; ***Turk.***: Lacryvisc; Lipotears; Siccafluid; Siccapos; Thilo-Tears; Viscotears; ***UK***: Artelac Nighttime; Clinitas Gel; GelTears; Liposic†; Liquivisc; Lumecare Long Lasting; Viscotears; ***Ukr.***: Vidisic (Видисик); ***Venez.***: Acrylarm; Lacryvisc; Siccafluid; Viscotears.

Multi-ingredient Preparations. ***Arg.***: Caien†; Latlas Fresh; Latlas; ***Austral.***: Genteal; Visine Professional†; ***Braz.***: Liposic; ***Chile***: Gelsolets; ***Cz.***: Hypotears; ***Fin.***: Lakrimont; ***Ger.***: Repithel; Visine Trockene Augen; Visine zur Nacht; ***Hong Kong***: Clinac OC; ***Indon.***: Genteal; Oculotect; Sodermix; ***Ital.***: Dropyal; Recugel; Visine Dry Eyes†; ***Malaysia***: Genteal; ***Pol.***: Oculotect; ***Port.***: Hidratante VG; ***Switz.***: Lacrycon; ***Thai.***: Genteal; ***USA***: Maxilube; Mimyx†; ***Venez.***: Genteal.

Pharmacopoeial Preparations
BP 2014: Carbomer Eye Drops.

Carbon Disulfide

Bisulfuro de carbono; Carbon Bisulphide; Carbon Disulphide; Carbonei Sulfidum; Carboneum Bisulfuratum; Carboneum Sulfuratum; Dissulfeto de carbono; Disulfuro de carbono; Dwusiarczek węgla; Hiilidisulfidi; Karbondisulfid; Karbondisülfür; Kohlenstoffdisulfid; Koldisulfid; Koolstofdisulfide; Ogljikov Diosulfid; Schwefelkohlenstoff; Sērogleklis; Sirouhlík; Solfuro di carbonio; Sulfură de carbon; Sulfure de carbone; Szén-diszulfid; Węgla disiarczek; Въглероден Дисулфид; Сероуглерод.
CS_2=76.13
CAS — 75-15-0.
UNII — S54S8B99E8.

Description. Carbon disulfide is a clear, colourless, volatile, flammable liquid with a chloroform-like odour. Commercial grades have an unpleasant odour described by some as being reminiscent of decaying radishes. Wt per mL about 1.26 g. B.p. about 46 degrees. Store in airtight containers.

Stability. The vapour of carbon disulfide when mixed with air in the proportions of 1 to 50% is highly explosive.

Uses

Carbon disulfide is used as an industrial solvent and has been used, in the vapour form, as an insecticide.

Adverse Effects, Treatment, and Precautions

Carbon disulfide is irritant. Toxic effects may occur as a result of inhalation, ingestion, or absorption through the skin.

Acute poisoning may result in gastrointestinal disturbances and euphoria, followed by CNS depression. Symptoms include headache, dizziness, mood changes, and in severe cases, manic psychoses, delirium, hallucinations, coma, convulsions, and death due to respiratory failure.

Chronic poisoning has been associated with occupational exposure to carbon disulfide vapour for prolonged periods. It is characterised by peripheral neuropathies; CNS effects such as headache, fatigue, insomnia, tremor, emotional lability, extrapyramidal disorders, bipolar disorder, and encephalopathy; gastrointestinal effects including anorexia, dyspepsia, and ulcerative changes; and effects on the eye. Hearing loss due to noise exposure may be exacerbated. Occupational exposure to carbon disulfide has been shown to be associated with an increased incidence of mortality from coronary heart disease. The action of carbon disulfide on endocrine function has resulted in menstrual irregularities, an increased incidence of spontaneous abortions and premature births, loss of libido, sperm abnormalities, and decreased serum-thyroxine concentrations; there is limited evidence of impaired glucose tolerance.

Treatment consists of removal from exposure and general supportive and symptomatic measures. Gastric lavage should be avoided. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias. Peripheral neuropathies may be only slowly reversible.

Reviews of the toxicity of carbon disulfide.

1. WHO. Carbon Disulfide. *Environmental Health Criteria 10*. Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc010.htm (accessed 29/06/04)
2. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
3. Health and Safety Executive. Carbon disulphide. *Toxicity Review 3*. London: HMSO,1981.
4. Beauchamp RO, *et al*. A critical review of the literature on carbon disulfide toxicity. *Crit Rev Toxicol* 1983; **11:** 169–278.
5. Huang CC. Carbon disulfide neurotoxicity: Taiwan experience. *Acta Neurol Taiwan* 2004; **13:** 3–9.

Effects on endocrine function. The effects of exposure to carbon disulfide were studied retrospectively in 265 female workers in the rayon industry exposed for at least 1 year, and 291 non-exposed female workers.[1] Levels of exposure varied over the study period from 0.7 to 30.6 mg/m^3. Women exposed to carbon disulfide had a higher risk of menstrual disturbances than non-exposed women. However, there was no difference between the 2 groups in incidence of toxaemia, emesis gravidarum, spontaneous abortion, premature or overdue delivery, or congenital malformation.

1. Zhou SY, *et al*. Effects of occupational exposure to low-level carbon disulfide (CS_2) on menstruation and pregnancy. *Ind Health* 1988; **26:** 203–14.

Effects on the heart. An increased incidence of mortality from cardiovascular disease has been found in workers occupationally exposed to carbon disulfide.[1-3] The evidence suggested that the risk decreases after cessation of exposure. However, a critical review[4] found that evidence for an association was mixed and that any effect was likely to be small.

1. Nurminen M, Hernberg S. Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. *Br J Ind Med* 1985; **42:** 32–5.
2. Sweetnam PM, *et al*. Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. *Br J Ind Med* 1987; **44:** 220–7.
3. MacMahon B, Monson RR. Mortality in the US rayon industry. *J Occup Med* 1988; **30:** 698–705.
4. Sulsky SI, *et al*. Critical review of the epidemiological literature on the potential cardiovascular effects of occupational carbon disulfide exposure. *Int Arch Occup Environ Health* 2002; **75:** 365–80.

Handling. Suitable precautions should be taken to avoid skin contact with carbon disulfide as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Carbon disulfide is rapidly absorbed after inhalation and ingestion, and is also absorbed through intact skin. It is excreted unchanged through the lungs and in the urine mainly as metabolites.

Carbon Tetrachloride

Anglies Tetrachloridas; Czterochlorek węgla; Hiilitetrakloridi; Koltetraklorid; Koolstoftetrachloride; Szén-tetraklorid; Tetra; Tetrachloormethaan; Tetrachlormethan; Tétrachlorométhane; Tétrachlorure de carbone; Tetracloreto de carbono; Tetraclorur de carboni; Tetracloruro de carbono; Tetracloruro di carbonio; Tetrahlorogleklis; Tetraklorkulstof; Węgla tetrachlorek; Четырёххлористый Углерод.
Tetrachloromethane.
CCl_4=153.8
CAS — 56-23-5.
UNII — CL2T97X0V0.

Description. Carbon tetrachloride is a clear, colourless, mobile, liquid with a chloroform-like odour. Sp. gr. 1.588 to 1.590. B.p. 76 degrees to 78 degrees. Practically insoluble in water; miscible with alcohol, chloroform, ether, petroleum spirit, and fixed and volatile oils. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Handling. Avoid contact with carbon tetrachloride; the vapour and liquid are poisonous. Care should be taken not to vaporise carbon tetrachloride in the presence of a flame because of the production of harmful gases, mainly phosgene.

Uses

Carbon tetrachloride is used in industry as a solvent and degreaser. It was formerly used in certain types of fire extinguisher and as an industrial and domestic dry cleaner but has been largely replaced for this purpose by less toxic substances. Carbon tetrachloride has also been used for the fumigation of cereals.

Carbon tetrachloride was formerly given orally as an anthelmintic but it has been superseded by equally effective and less toxic drugs.

Adverse Effects

Individual response to carbon tetrachloride varies widely; inhalation or ingestion of a few mL of carbon tetrachloride has proved fatal and its toxicity appears to be increased by alcohol. Poisoning may follow inhalation, ingestion, or topical application but develops more rapidly after inhalation.

Carbon tetrachloride is irritant; repeated application to the skin may result in dermatitis. Aspiration may result in pulmonary oedema.

Adverse effects after acute exposure from any route include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and CNS disturbances such as headache, dizziness, and drowsiness, with progression to convulsions, coma, and death from respiratory depression or circulatory collapse. Death may also occur as a result of ventricular arrhythmia. Hepatic and renal cellular necrosis can occur and are associated with free radical production; symptoms usually begin a few days or up to 2 weeks after acute exposure to carbon tetrachloride. Renal damage may present as oliguria, progressing to proteinuria, anuria, weight gain, and oedema. Symptoms of hepatic damage

include anorexia, jaundice, and hepatomegaly. If hepatorenal necrosis is not fatal recovery is eventually complete.

Symptoms of chronic poisoning are similar to those of acute poisoning; in addition, paraesthesias, visual disturbances, anaemia, and aplastic anaemia have occurred. Carcinogenicity has been found in *animals*.

References.

1. Melamed E, Lavy S. Parkinsonism associated with chronic inhalation of carbon tetrachloride. *Lancet* 1977; **i:** 1015.
2. Johnson BP, *et al.* Cerebellar dysfunction after acute carbon tetrachloride poisoning. *Lancet* 1983; **ii:** 968.
3. Perez AJ, *et al.* Acute renal failure after topical application of carbon tetrachloride. *Lancet* 1987; **i:** 515–6.
4. Health and Safety Executive. Carbon tetrachloride, chloroform. *Toxicity Review 23*. London: HMSO,1992.
5. Manno M, Rezzadore M. Critical role of ethanol abuse in carbon tetrachloride poisoning. *Lancet* 1994; **343:** 232.
6. WHO. Carbon tetrachloride health and safety guide. *IPCS Health and Safety Guide 108*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg108.htm (accessed 29/06/04)
7. IARC/WHO. Carbon tetrachloride. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 401–32. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Treatment of Adverse Effects

If carbon tetrachloride vapour has been inhaled the patient should be removed to the fresh air. Clothing contaminated by liquid should be removed and the skin washed. If carbon tetrachloride has been ingested activated charcoal may be given.

The usual symptomatic and supportive measures should be instituted. Hepatic and renal function should be monitored closely. Haemodialysis or peritoneal dialysis may be needed if renal function is impaired. Dopamine or noradrenaline may be used cautiously for severe hypotension unresponsive to fluid replacement, but adrenaline may be best avoided because of the risk of precipitating cardiac arrhythmias.

Acetylcysteine (p. 1653.2) may be given to patients recently exposed to carbon tetrachloride in an attempt to prevent or modify hepatic and renal damage.

Pharmacokinetics

Carbon tetrachloride is readily absorbed after inhalation and ingestion. It is also absorbed through the skin. Metabolism to reactive free radicals is thought to account for the hepatorenal toxicity of carbon tetrachloride.

Carbon tetrachloride is slowly excreted from the body via the lungs and the urine.

Carmellose *(rINN)*

Carbossimetilcellulosa; Carboximetilcelulosa; Carboximetilcelulose; Carboximetilcelulozã; Carboxymethylcellulose; Carboxyméthylcellulose; Carmellosum; Carmelosa; CMC; E466; Karboksimetyyliselluloosa; Karboksymetyloceluloza; Karboximetil-cellulóz; Karboxymethylcelulóza; Кармеллоза.

CAS — 9000-11-7.

UNII — 05JZI7B19X.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Carmellose). A white or almost white, hygroscopic powder. It swells in water to form a suspension; becomes viscid in sodium hydroxide; practically insoluble in dehydrated alcohol. A 1% solution in water has a pH of 3.5 to 5.0. Store in airtight containers.

USNF 31: (Carmellose). A white, hygroscopic powder. Swells with water to form a suspension. Practically insoluble in ethanol 99.5%. Becomes viscous in a 4% solution of sodium hydroxide. Store in airtight containers.

Carmellose Calcium *(rINNM)*

Calcii Carmellosum; Calcium Carboxymethylcellulose; Carboximetilcelulosa cálcica; Carboxymethylcellulose Calcium; Carmellose Calcique; Carmellose-Calcium; Carmellosum Calcicum; Carmellosum Calcium; Carmelosa cálcica; Karmeliozės kalcio druska; Karmelloosikalsium; Karmelloskalcium; Karmellóz-kalcium; Karmelosa vápenatá sůl; Кальций Кармеллоза.

CAS — 9050-04-8.

UNII — UTY7PDF93L.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Carmellose Calcium). A white or yellowish-white, hygroscopic powder. It swells in water to form a suspension; practically insoluble in alcohol, in acetone, and in toluene. Store in airtight containers.

USNF 31: (Carboxymethylcellulose Calcium). A white to yellowish-white, hygroscopic powder. It swells in water to form a suspension; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 1% suspension in water is between 4.5 and 6.0. Store in airtight containers.

Carmellose Sodium *(BAN, rINNM)*

Carboximetilcelulosa sódica; Carboxymethylcellulose Sodium; Carboxymethylcellulosum Natricum; Carmellose-Natrium; Carmellose sodique; Carmellosum natricum; Carmelosa sódica; Cellulose Gum; E466; Karmeliozės natrio druska; Karmelloosinatrium; Karmellosnatrium; Karmellóznátrium; Karmelosa sodná sůl; Karmeloza sodowa; Natrii Carmellosum; SCMC; Sodium Carboxymethylcellulose; Sodium Cellulose Glycollate; Натрий Кармеллоза.

CAS — 9004-32-4.

UNII — K679OBS311.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Eur. and *USNF* also include low-substituted carmellose sodium and *USNF* includes enzymatically-hydrolysed carmellose sodium.

USNF also includes Carboxymethylcellulose Sodium 12.

Ph. Eur. 8: (Carmellose Sodium). A white or almost white, hygroscopic granular powder. It has a sodium content of 6.5 to 10.8% calculated on the dry substance. Easily dispersed in water forming colloidal solutions; practically insoluble in dehydrated alcohol, in acetone, in ether, and in toluene. A 1% colloidal solution in water has a pH of 6.0 to 8.0.

Ph. Eur. 8: (Carmellose Sodium, Low-substituted; Carmellosum Natricum, Substitutum Humile). It contains not less than 2.0% and not more than 4.5% of sodium, calculated with reference to the dried substance. A white or almost white powder or short fibres. It swells in water to form a gel; practically insoluble in dehydrated alcohol, in acetone, and in toluene. A 1% suspension in water has a pH of 6.0 to 8.5.

USP 36: (Carboxymethylcellulose Sodium). A white to cream-coloured, hygroscopic powder or granules. It contains not less than 6.5% and not more than 9.5% of sodium, calculated on the dried basis. Easily dispersed in water to form colloidal solutions; insoluble in alcohol, in ether, and in most other organic solvents. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

USNF 31: (Low-Substituted Carboxymethylcellulose Sodium). It has a sodium content of 2.0 to 4.5%, calculated on the dried basis. A white or almost white powder or short fibres. Practically insoluble in alcohol, in acetone, and in toluene. It swells in water to form a gel. pH of a 1% suspension in water is between 6.0 and 8.5. Store in airtight containers.

USNF 31: (Enzymatically-Hydrolyzed Carboxymethylcellulose Sodium). The sodium salt of a polycarboxymethyl ether of cellulose, which has been partially hydrolysed by enzymatic treatment with food grade cellulase from *Trichoderma reesei*. White or slightly yellowish or greyish, odourless, slightly hygroscopic granular or fibrous powder. Soluble in water; insoluble in alcohol. pH of a 1% solution in carbon dioxide-free water is 6.0 to 8.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

USNF 31: (Carboxymethylcellulose Sodium 12). A colourless or white to off-white, odourless, powder or granules. Water solubility depends on degree of substitution (easily dispersed in water at all temperatures, forming a clear, colloidal solution). Insoluble in alcohol, in acetone, in ether, and in toluene. It has a sodium content of 10.4 to 12.0%, calculated on the dry substance. Store in airtight containers.

Incompatibility. Incompatibilities of carmellose sodium have been reported with strongly acidic solutions, with soluble salts of iron and some other metals, and with xanthan gum.

Croscarmellose Sodium *(USAN)*

Carboximetilcelulosa sódica reticulada; Carmellosum Natricum Conexum; Croscarmellose-Natrium; Croscarmellose sodique; Croscarmelosa sódica; Crosslinked Carboxymethylcellulose Sodium; E468; Kroskarmeliozės natrio druska; Kroskarmelloosi natrium; Kroskarmellosnatrium; Kroskarmelosa sodná sůl; Kroskarmeloza sodowa; Kroszkarmellóznátrium; Modified Cellulose Gum; Кроскармеллоза Натрия.

UNII — M28OL1HH48.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Croscarmellose Sodium). A cross-linked polymer of carmellose sodium. A white or greyish-white powder. Practically insoluble in dehydrated alcohol, in acetone, and in toluene. A 1% suspension in water has a pH of 5.0 to 7.0.

USNF 31: (Croscarmellose Sodium). The sodium salt of a cross-linked partly *O*-(carboxymethylated) cellulose. A white, free-flowing powder. Partially soluble in water; insoluble in alcohol, in ether, and in other organic solvents. pH of a dispersion containing 1 g mixed with 100 mL of water for 5 minutes is between 5.0 and 7.0.

Profile

Pharmaceutical uses of carmellose calcium and carmellose sodium include suspending, thickening, and emulsifying agents, disintegrants, binders, and coating agents in tablets. Carmellose sodium is also used as an emulsifier or stabiliser in the food industry. Croscarmellose sodium is used as a tablet disintegrant.

Carmellose sodium is used topically as an ingredient of protective preparations for stoma care, in the management of wounds, and for the mechanical protection of oral and perioral lesions, such as mouth ulceration (p. 1811.2). It is also used, in concentrations of up to 1%, in artificial saliva preparations for the treatment of dry mouth (below), and in eye drops for the management of dry eye (p. 2190.1).

Carmellose sodium given orally absorbs water and acts as a bulk-forming agent; the volume of faeces is increased and peristalsis promoted. It is used in the treatment of constipation (p. 1804.3). Carmellose sodium has been included in preparations to control appetite in the management of obesity (p. 2315.1) but there is little evidence of efficacy. For precautions to be observed with bulk-forming agents, see under Methylcellulose, p. 2198.1.

Dry mouth. Dryness of the mouth (xerostomia) resulting from decreased salivary secretion is often an adverse effect of therapy with drugs such as antimuscarinics, antihistamines, tricyclic antidepressants, and diuretics. Other causes include dehydration, anxiety, Sjögren's syndrome (see Dry Eye, under Uses of Hypromellose, p. 2190.1), and radiotherapy of the head and neck. Dry mouth can cause eating difficulties and lead to oral disease such as candidiasis, dental caries, and bacterial infections.[1-7]

Treatment of dry mouth is mainly symptomatic. Where possible any underlying disorder should be treated first. Frequent sips of fluids may help to relieve dryness. Artificial saliva products may also be beneficial, although again they may need to be used frequently, seldom relieving symptoms for more than 1 to 2 hours. They aim to mimic normal saliva and generally contain viscosity-increasing agents, such as mucins or cellulose derivatives such as carmellose,[8,9] as well as electrolytes, including fluoride. Preparations containing lactoperoxidase and lactoferrin have also been used.[10] Sialogogues may be used in an attempt to stimulate salivation and may be more effective than saliva substitutes where some salivary function remains. Mechanical stimulants such as sugar-free chewing gum may be effective, and citrus or citric acid preparations are also used, although these may damage the teeth due to their low pH. Malic acid has been used similarly.

Systemic therapies may have a role in some patients. These are mainly based on drugs with cholinergic effects, which stimulate the salivary glands. Pilocarpine is used for dry mouth after radiotherapy and may also be effective in Sjögren's syndrome or other causes of dry mouth; benefit has been reported[11] in patients with dry mouth associated with psychoactive medications. Adverse effects, particularly increased sweating, may, however, limit its use.[12] Cevimeline, which is reported to be more specific for the M_1-muscarinic receptor, may be an alternative in patients with Sjögren's syndrome. Other cholinergics that have been used include carbachol and anethole trithione. Acupuncture has also been tried.[13]

For patients at risk of dry mouth due to radiotherapy, preventative measures are important.[14] Salivary gland-sparing radiation techniques have been developed and cytoprotectants, such as amifostine, have also been used.

1. Silvestre-Donat FJ, *et al.* Protocol for the clinical management of dry mouth. *Med Oral* 2004; **9:** 276–9.
2. Al-Hashimi I. Xerostomia secondary to Sjögren's syndrome in the elderly: recognition and management. *Drugs Aging* 2005; **22:** 887–99.
3. Chambers MS, *et al.* Radiation-induced xerostomia. *Head Neck* 2007; **29:** 58–63.
4. Taubert M, *et al.* Dry mouth. *BMJ* 2007; **334:** 534.
5. Turner MD, Ship JA. Dry mouth and its effects on the oral health of elderly people. *J Am Dent Assoc* 2007; **138** (suppl): 15S–20S.
6. Fox PC. Xerostomia: recognition and management. *Dent Assist* 2008; **77:** 18, 20, 44–8.
7. Visvanathan V, Nix P. Managing the patient presenting with xerostomia: a review. *Int J Clin Pract* 2010; **64:** 404–7.
8. Vissink A, *et al.* A clinical comparison between commercially available mucin- and CMC-containing saliva substitutes. *Int J Oral Surg* 1983; **12:** 232–8.
9. Duxbury AJ, *et al.* A double-blind cross-over trial of a mucin-containing artificial saliva. *Br Dent J* 1989; **166:** 115–20.
10. Gil-Montoya JA, *et al.* Evaluation of the clinical efficacy of a mouthwash and oral gel containing the antimicrobial proteins lactoperoxidase, lysozyme and lactoferrin in elderly patients with dry mouth—a pilot study. *Gerodontology* 2008; **25:** 3–9.
11. Masters KJ. Pilocarpine treatment of xerostomia induced by psychoactive medications. *Am J Psychiatry* 2005; **162:** 1023.
12. Davies AN, Shorthose K. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 23/06/08).
13. Meidell L, Holritz Rasmussen B. Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study. *Int J Palliat Nurs* 2009; **15:** 12–20.
14. Dirix P, *et al.* Radiation-induced xerostomia in patients with head and neck cancer: a literature review. *Cancer* 2006; **107:** 2525–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aqua Lent Lubricante; Aquacel; Aucic; Comfeel Plus; Comfeel; Natura Fresh; Nu-Derm Hidrocoloide; Refresh Liquigel; Refresh Tears; ***Austral.***: Cellufresh; Celluvisc; Refresh Contacts; Refresh Liquigel; Refresh Plus; Refresh Tears Plus; TheraTears; ***Belg.***: Aquacel; Comfeel; Gelilact†; ***Braz.***: Cellufresh; Ecofilm; Fresh Tears; Lacrifilm; Plenigell; Salivan; ***Canad.***: Aquacel; Refresh Celluvisc; Refresh Contacts; Refresh Liquigel; Refresh Plus; Refresh Tears; TheraTears; ***Chile***: Refresh Liquigel; Refresh Tears; ***China***: Celluvisc (潇莱威); Kai Shi (开仕); Refresh Plus (瑞新); ***Cz.***: Cellufluid; ***Denm.***: Cellufluid; Celluvisc; ***Fin.***: Cellufluid; Celluvisc; ***Fr.***: Aquacel; Biatain; Celluvisc; Clip Ampoules†; Clip Brulures†; Comfeel; Hydrocoll; Physiotulle; Urgomed; Urgotul; ***Ger.***: Algoplaque; Alione; Cellufresh; Cellumed; Celluvisc; Comfeel Plus Transparenter; DracoHydro; Physiotulle; UrgoCell Adhesive; UrgoCell Contact; UrgoCell Heel Contact; Urgocell Lite; UrgoCell Non Adhesive; Urgotul comfort; Urgotul Duo; Urgotul Lite Border; Urgotul Soft; Urgotul; ***Gr.***: Cellufluid; Celluvisc; Refresh Plus; ***Hong Kong***: Refresh; ***India***: Add Tears; Aftee DPS; Celluvisc; E-Moist; Eco Tears; Flogel; I-Lax; Irivisc; Lacrimos; Lubrex; Max-Moist; MCM-Tear; Mep-Con; Moitz; Nistear; Oass; Optive; ***Irl.***: Celluvisc; ***Israel***: Celluvisc†; Refresh Tears; TheraTears; ***Ital.***: Cellufresh; Celluvisc; Lacrilens; ***Malaysia***: Celluvisc; Clarastill; Refresh Liquigel; Refresh Plus; Refresh Tears; ***Mex.***: Acutears; Novafix Ultra Fuerte; Refresh Liquigel; Refresh Tears; ***Neth.***: Cellufluid; Celluvisc; ***Norw.***: Celluvisc; ***NZ***: Refresh Tears Plus; ***Philipp.***: Cellufresh; Celluvisc; ***Port.***: Cellufluid; Celluvisc; ***S.Afr.***: Aquacel†; Cellufresh; Celluvisc; Comfeel; Intrasite; Refresh Liquigel; Refresh Tears; ***Singapore***: Celluvisc; Optive; Refresh Contacts; Refresh Liquigel; Refresh Plus; Refresh Tears; ***Spain***: Cellufresh; Celluvisc†; Viscofresh; ***Swed.***: Cellufluid; Celluvisc; ***Switz.***: Cellufluid; Celluvisc; ***Thai.***: Cellufresh; Celluvisc; ***Turk.***: Cellufresh; Refresh Liquigel; Refresh Tears Lubricant; ***UK***: Aquacel; Carmize; Celluvisc; Comfeel; Intrasite; Murine Contacts; Physiotulle; ***USA***: Celluvisc; Clear Eyes for Dry Eyes; Optive; Refresh Liquigel; Refresh Plus; Refresh Tears; Tears Again; TheraTears; ***Venez.***: Refresh Liquigel; Refresh Tears.

Multi-ingredient Preparations. ***Arg.***: Comfeel Purilon; Comfeel SeaSorb; Humectante Bucal; Mucobase; Optive; Purilon†; SeaSorb†; ***Austral.***: Aquae; Optive; Orabase; SoloSite; Stomahesive; ***Austria***: Glandosane; Sialin; ***Belg.***: Aquacel-Ag; ***Braz.***: Chofranina†; Optive; Seprafilm; ***Canad.***: Carboflex; Clear Eyes for Dry Eyes; Genteal Geldrops; Moi-Stir; Orabase; Orahesive; Tegasorb†; ***Chile***: Delgadol Fibra; K.C.M.C; Novafix Extra Fuerte; Novafix Ultra Fuerte; Optive; Reducform-F; ***Cz.***: Spofax; ***Fr.***: Altreet Ag; Aquacel Ag; Artisial; Biatain Ag; Cellosorb†; Clip Hemo†; Intrasite; Melgisorb; Purilon; Release Ag†; SeaSorb; Sorbalgon Plus; Urgosorb; Urgotul S.Ag; ***Ger.***: Comfeel Plus; DracoAlgin; Glandosane; GoTa-Derm; Lary-Phary; Melgisorb Ag; Optive; Physiotulle-Ag; Purilon; Recatol Algin; SeaSorb Soft; SeaSorb-Ag; UrgoCell Silver; UrgoCell Start; Urgoclean Kompresse; UrgoSTART; Urgotul S.Ag; Urgotul Silver; Xerotin; ***Hong Kong***: Glandosane; Optive; Salivart†; ***India***: Alupectin DGL; Alupectin; Aqwet; Bioffin; Coolpep; Digene; Entagene; Fittydent; Laxit; Novagel; ***Irl.***: Orabase†; ***Israel***: Optive; ***Ital.***: Aquacel Ag; ***Malaysia***: Seprafilm; ***Mex.***: Optive; ***NZ***: Orabase; Stomahesive; ***Philipp.***: Optive; ***Port.***: Glandosane†; ***S. Afr.***: Granuflex; Granugel; Orabase†; ***Singapore***: Seprafilm; ***Spain***: Laxvital†; ***Switz.***: Glandosane; Optive; ***Thai.***: Bisolax; Emulax; Glandosane; Optive; ***UK***: Aquacel Ag; Comfeel Plus; Glandosane; Luborant†; Murine Dry & Tired Eyes; Optive; Orabase; Orahesive; Physiotulle-Ag; SeaSorb Soft; Seprafilm; Stomahesive; Xerotin; ***Ukr.***: Optive (Оптиве); ***USA***: Entertainer's Secret; Moi-Stir; Pretts Diet Aid; Salivart; Seprafilm; Surgel; ***Venez.***: Klincosal; Novafix; Polantac.

Pharmacopoeial Preparations

BP 2014: Carmellose Sodium Eye Drops;
USP 36: Carboxymethylcellulose Sodium Paste; Carboxymethylcellulose Sodium Tablets.

Carmine

Carmim; Carmín; Carminio; CI Natural Red 4; Cochineal Carmine; Colour Index No. 75470; E120; Karmijn; Karmin; Karmín; Karminas; Kárminvörös; Rouge cochenille; Кармин.

CAS — 1390-65-4.

Uses

Carmine is an aluminium lake of the colouring matter of cochineal (p. 2179.2). It contains carminic acid, an anthraquinone glycoside. Unless precautions are taken during manufacture and transport to prevent contamination, carmine may be infected with salmonella microorganisms.

Carmine and some of its salts are used as colouring agents in medicines, foodstuffs, and cosmetics.

Carmine passes through the gastrointestinal tract unchanged and has been used as a faecal 'marker'.

Adverse Effects

Hypersensitivity. By February 2004 the FDA was aware of 35 cases of hypersensitivity to carmine, carminic acid, or cochineal extract published in the scientific and medical literature and/or reported directly to the FDA. Hypersensitivity reactions to carmine, carminic acid, or cochineal extract included contact dermatitis (4 cases), urticaria/angioedema (9), occupational asthma (10), and systemic anaphylaxis (12). In more than half of these reports, there was evidence of an IgE-mediated diagnostic response. The adverse effects included allergic reactions to foods containing carmine and cochineal extract, occupational asthma from exposure to carmine, and allergic reactions to topically applied cosmetics containing carmine.

The FDA concluded that carmine and cochineal extract may cause potentially severe allergic responses and proposed that food and cosmetic labelling be enhanced; a declaration of inactive ingredients in drugs was already in force.[1] From January 2011, the FDA will require that the presence of cochineal extract or carmine must be declared on the product label of foods and cosmetics.[2]

1. FDA. Food, drug, and cosmetic labelling: cochineal extract and carmine declaration. Proposed risk. *Fed Regist* 2006; **71:** 4839–51. Available at: http://edocket.access.gpo.gov/2006/pdf/E6-1104.pdf (accessed 23/08/10)
2. FDA. Food, drug, and cosmetic labelling: cochineal extract and carmine declaration. Final rule. *Fed Regist* 2009; **74:** 207–17. Available at: http://edocket.access.gpo.gov/2009/pdf/E8-31253.pdf (accessed 23/08/10)

Carmoisine

Atsorubiini; Azorrubina; Azorubin; Azorubine; Carmoisina; CI Food Red 3; Colour Index No. 14720; E122; Кармуазин.

It consists mainly of disodium 4-hydroxy-3-(4-sulphonato-1-naphthylazo)naphthalene-1-sulphonate.

$C_{20}H_{12}N_2Na_2O_7S_2$=502.4

CAS — 3567-69-9.

UNII — DR4641L47F.

Profile

Carmoisine is a synthetic azo dye used as a colouring agent in foods, medicines, and cosmetics. It has also been investigated clinically as a stain, to aid visualisation of malignant neoplasms of the skin during surgery.

Carnauba Wax

Brazil Wax; Caranda Wax; Carnauba, cire de; Carnaubawachs; Carnaubawas; Cera carnauba; Cera Coperniciae; Cera de carnauba; E903; Karnauba pálmaviasz; Karnaubavaha; Karnaubavax; Karnaubo vaškas; Vosk karnaubský; Карнаубский Воск.

CAS — 8015-86-9.

UNII — R12CBM0EIZ.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Carnauba Wax). It is obtained from the leaves of *Copernicia cerifera.* Pale yellow or yellow powder, flakes, or hard masses. It has a relative density of about 0.97. M.p. 80 degrees to 88 degrees. Practically insoluble in water and in alcohol; soluble on heating in ethyl acetate and in xylene. Protect from light.

USNF 31: (Carnauba Wax). It is obtained from the leaves of *Copernicia cerifera* (Palmae). A light brown to pale yellow, moderately coarse powder or flakes, possessing a characteristic bland odour, and free from rancidity. Sp. gr. about 0.99. M.p. 80 degrees to 86 degrees. Insoluble in water; slightly soluble in boiling alcohol; soluble in warm chloroform and in warm toluene; freely soluble in warm benzene.

Profile

Carnauba wax is used in pharmacy as a coating agent. Its use is also permitted in certain foods. Various types and grades are used industrially in the manufacture of polishes.

Carotenoids

Carotenoïden; Carotenoides; Caroténoïdes; Carotenoidi; Carotinoide; Karatenoidler; Karotenoider; Karotenoidit; Karotenoidy; Karotinoidid; Каротиноиды.

CAS — 36-88-4.

Profile

Carotenoids are tetraterpenoid compounds that occur naturally as pigments in plants and algae. They can be divided into carotenes and xanthophylls (which also contain oxygen). Some are used as colouring agents in foods, drugs, and cosmetics, while others are also used for their nutritional properties. Some carotenoids are metabolised in the body to retinoids and have vitamin A activity. Carotenoids used as colourings include bixin and norbixin (derivatives of annatto, p. 2169.1), capsanthin and capsorubin (derivatives of paprika, E160c), apocarotenal (p. 2169.2), astaxanthin (p. 2170.1), canthaxanthin (p. 2173.2), and citranaxanthin (p. 2179.2); those that have been used therapeutically include carotene (see Betacarotene, p. 2051.1), lutein (p. 2079.2), lycopene (p. 2546.2), and zeaxanthin (p. 2125.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Betarene†; Eyegold†.

Multi-ingredient Preparations. ***India***: GB-Lex; Kefive Plus; Lycogold; Macuchek; Macugold; Menofit; Multivite Gold; Multivite Vision; Multivite Woman; Multivite-FM Omega; Ocufree; ***Mex.***: Optima IFX; ***Thai.***: Diavit; ***Ukr.***: Perfectil Plus (Перфектил Плюс); Wellman (Велмен).

Carrageenan

Carrageen; Carrageenanum; Carrageenin; Carragenano; Carragenatos; Carragenina; Carragenos; Carraghénanes; Carraghénates; Carraghenina; Chondrus Extract; E407; Irish Moss Extract; Karagenan; Karragén; Karrageenan; Каррагинан.

CAS — 9000-07-1 (carrageenan); 11114-20-8 (κ-carrageenan); 9064-57-7 (λ-carrageenan).

UNII — 5C69YCD2YJ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Fr.* Also in *USNF* which also includes the related substance Galageenan.

Ph. Eur. 8: (Carrageenan). Polysaccharides obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweeds). It consists chiefly of a mixture of the calcium, magnesium, potassium, and sodium salts of the sulfate esters of D-galactose and 3,6-anhydro-D-galactose copolymers. The prevalent copolymers are κ-carrageenan, ι-carrageenan, and λ-carrageenan.

A yellowish, brownish, or white or almost white powder. Soluble in water giving a viscous or colloidal solution; insoluble in organic solvents.

USNF 31: (Carrageenan). The hydrocolloid obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweeds). It consists chiefly of a mixture of the ammonium, calcium, magnesium, potassium, and sodium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. The prevalent copolymers in the hydrocolloids are κ-carrageenan, ι-carrageenan, and λ-carrageenan.

A yellowish or tan to white, coarse to fine, practically odourless, powder. Soluble in water at 80 degrees forming a viscous, clear or slightly opalescent solution that flows readily. It disperses more readily in water if first moistened with alcohol, with glycerol, or with a saturated solution of glucose in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

USNF 31: (Galageenan). The hydrocolloid obtained by extraction with water or aqueous alkali from the red seaweed *Eucheuma gelatinae* (Rhodophyceae). Galageenan consists chiefly of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. These hexoses are alternately linked in α-1,3 and β-1,4 in the polymer. The ester sulfate content ranges from 8 to 18%. In addition, it contains inorganic salts that originate from the seaweed and from the process of recovery from the extract. Galageenan is recovered by alcohol precipitation or by freezing and pressing. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Carrageenans are a family of polysaccharides containing different copolymers of D-galactose and 3,6-anhydro-D-galactose. They are obtained from various red seaweeds. Carrageenans are used in pharmaceutical manufacturing and the food industry as suspending and gelling agents. Galageenan, a carrageenan also obtained from a red seaweed (*Eucheuma gelatinae*) is used similarly.

Carrageenan has been used as a bulk-forming laxative to treat constipation; for precautions to be observed with bulk-forming laxatives, see under Methylcellulose, p. 2198.1. Carrageenan is also included in topical preparations for the symptomatic relief of anorectal disorders. A gel containing carrageenan has been investigated as a topical microbicide.

A degraded form of carrageenan was formerly used in gastrointestinal disorders but it was associated with lesions in *animals* and is no longer used.

Irish moss (*Chondrus crispus*), a source of carrageenan, is used in herbal medicine.

Refined non-degraded carrageenan and furcellaran, a similar extract from Rhodophyceae that is included in the

specifications for food-grade carrageenan, have generally been considered safe for use as food additives, although this may not be the case with degraded and 'semi-refined' forms.[1,2] However, in the UK the Food Advisory Committee has recommended that carrageenan should not be permitted as an additive for infant formulas because of the possibility of immunological consequences after absorption from the immature gut.[3] Carrageenans affect the immune system of experimental *animals* after parenteral or oral use, and small amounts of food-grade carrageenan cross the intestinal epithelium in *rats* and are taken up by gut-associated lymphoid tissue.[4]

1. FAO/WHO. Evaluation of certain food additives and contaminants: twenty-eighth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 710* 1984.
2. Cohen SM, Ito N. A critical review of the toxicological effects of carrageenan and processed eucheuma seaweed on the gastrointestinal tract. *Crit Rev Toxicol* 2002; **32:** 413–44.
3. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. FdAC/REP/12. London: HMSO, 1992.
4. MAFF. Food Advisory Committee: report on the review of the emulsifiers and stabilisers in food regulations. FdAC/REP/11. London: HMSO, 1992.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Bonningtons Irish Moss; Calporo†; ***China***: Titanoreine (太宁); Titanoreine (太宁); ***Fr.***: Elgydium Blancheur; Herpclair; Titanoreine Lidocaine; Titanoreine; ***Ger.***: Saseem; Silence; ***Ital.***: Emoform Alifresh; Resource Gelificata†; ***NZ***: Bonningtons Irish Moss; ***Singapore***: Silence; ***Spain***: Titanorein; ***Switz.***: Silence†; Silence; ***UK***: Fam-Lax Senna; ***USA***: Numoisyn.

Cellulose

Celiuliozė; Cellulosa; Cellulóz; Celulosa; Celulose; Celuloză; Celuloza; Celulóza; Selluloosa; Sellulósi; Selulosa; Selüloz; Tselluloos; Zellulose; Целулоза; Целлюлоза.

UNII — SMD1X3XO9M.

Description. Cellulose is an unbranched polysaccharide polymer consisting of 1,4-β-linked glucopyranose units. It is the chief constituent of fibrous plant material.

Dispersible Cellulose *(BAN)*

Cellulose microcristalline et carmellose sodique; Cellulose, Mikrokristalline und Carmellose-Natrium; Cellulosum microcristallinum et carmellosum natricum; Celulosa dispersable; Microcrystalline Cellulose and Carboxymethylcellulose Sodium; Microcrystalline Cellulose and Carmellose Sodium; Диспергируемая Целлюлоза.

Pharmacopoeias. In *Br.* and *Eur.* (see p. vii). Also in *USNF.*

BP 2014: (Dispersible Cellulose). An odourless or almost odourless, white or off-white, coarse or fine powder consisting of a colloid-forming attrited mixture of microcrystalline cellulose and carmellose sodium. Disperses in water to produce a white, opaque dispersion or gel; practically insoluble in organic solvents and in dilute acids. Store at a temperature between 8 degrees and 15 degrees.

Ph. Eur. 8: (Microcrystalline Cellulose and Carmellose Sodium). A colloid-forming, powdered mixture of microcrystalline cellulose with 5 to 22% of carmellose sodium. It contains 75 to 125% of the nominal amount of carmellose sodium, calculated with reference to the dried substance. A white or off-white, coarse or fine powder. Dispersible in water producing a white, opaque colloidal dispersion; practically insoluble in organic solvents and in dilute acids. pH of a 2% dispersion in water is 6 to 8.

USNF 31: (Microcrystalline Cellulose and Carboxymethylcellulose Sodium). A colloid-forming, attrited mixture of microcrystalline cellulose and carmellose sodium. A white to off-white, odourless, coarse to fine, powder. It swells in water, producing, when dispersed, a white, opaque dispersion or gel; insoluble in organic solvents and in dilute acids. Store in airtight containers in a dry place, and at a temperature not exceeding 40 degrees.

Microcrystalline Cellulose

Celiuliozė, mikrokristalinė; Cellulosa Microgranulare; Cellulosa, mikrokristallin; Cellulose Gel; Cellulose microcristalline; Cellulosum Microcristallinum; Cellulosum Microcristallinum; Cellulosum Microristallinum; Celulosa microcristalina; Celulosa mikrokrystalická; Celuloza mikrokrystaliczna; Crystalline Cellulose; E460; Gel de celulosa; Mikrokristályos cellulóz; Selluloosa, mikrokiteinen; Целлюлоза Микрокристаллическая.

CAS — 9004-34-6.

UNII — OP1R32D61U.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

USNF also includes silicified microcrystalline cellulose.

Ph. Eur. 8: (Cellulose, Microcrystalline). A purified, partly depolymerised cellulose, prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant materials, with mineral acids. It is a white or almost white, fine or granular powder. Practically insoluble in water, in dehydrated alcohol, in acetone, in toluene, in dilute acids, and in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid obtained from a 12.5% mixture in water after 20 minutes of shaking is 5.0 to 7.5.

USNF 31: (Microcrystalline Cellulose). A purified, partially depolymerised cellulose, prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material, with mineral acids. It is a fine, white or almost white powder consisting of free-flowing, nonfibrous particles. Insoluble in water, in dilute acids, and in most organic solvents; practically insoluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid obtained from a 12.5% mixture in water after 20 minutes of shaking is between 5.0 and 7.5. Store in airtight containers.

USNF 31: (Silicified Microcrystalline Cellulose). A white or almost white, fine powder. Practically insoluble in water, in alcohol, in acetone, in diluted acid, and in toluene; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant obtained from a 12.5% mixture in water after 20 minutes of shaking is between 5.0 and 7.5. Store in airtight containers.

Powdered Cellulose

Celiuliozės milteliai; Cellulosapulver; Cellulose en poudre; Cellulose Powder; Cellulosi Pulvis; Cellulózpor; Celulosa en polvo; Celulosový prášek; E460; Selluloosajauhe; Целлюлоза В Порошке.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Cellulose, Powdered). A purified mechanically disintegrated cellulose prepared from alpha-cellulose obtained as a pulp from fibrous plant materials. It is a white or almost white, fine or granular powder. Practically insoluble in water, in dehydrated alcohol, in acetone, in toluene, in most organic solvents, and in dilute acids; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid of an 11.1% mixture in water is between 5.0 and 7.5 one hour after preparation.

USNF 31: (Powdered Cellulose). A purified, mechanically disintegrated cellulose prepared by processing alpha-cellulose obtained as a pulp from fibrous plant materials. It is a white or almost white powder. Exhibits degrees of fineness ranging from a free-flowing, dense powder to a coarse, fluffy, nonflowing material. Insoluble in water, in nearly all organic solvents, and in dilute acids; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid of an 11.1% mixture in water is between 5.0 and 7.5 one hour after preparation. Store in airtight containers.

Profile

Powdered cellulose and microcrystalline cellulose are used in pharmaceutical manufacturing as tablet binders and disintegrants and as capsule and tablet diluents. These two forms of cellulose are also used in the food industry. Dispersible cellulose (which also contains some carmellose sodium) forms a thixotropic gel with water and is used pharmaceutically as a suspending and thickening agent.

Various forms of cellulose have been included in preparations used in the management of constipation and obesity. Cellulose is also used in adsorbent powder preparations used for skin disorders including hyperhidrosis.

Derivatives of cellulose, including cellulose esters (below) and cellulose ethers (see Methylcellulose, p. 2197.3), are also widely used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Nasaleze; ***Ital.***: Fibrasan†; ***UK***: Allergy Defence; Sterigel; ***USA***: Unifiber.

Multi-ingredient Preparations. ***Arg.***: ZeaSorb; ***Austral.***: ZeaSorb†; ***Canad.***: ZeaSorb; ***Fr.***: Gelopectose; Hydroclean; ZeaSorb; ***India***: Mezol; ***Irl.***: ZeaSorb; ***Thai.***: ZeaSorb†; ***UK***: ZeaSorb.

Cellulose Esters

Cellaburate *(rINN)*

Celaburát; Celaburato; Celiuliozės acetatas-butiratas; Cellaburatum; Cellulosaacetatbutyrat; Cellulose Acetate Butanoate; Cellulose Acetate Butyrate; Cellulose, acétate butyrate de; Celluloseacetatbutyrat; Celulosi acetas butyras; Celulóz-acetát-butirát; Selluloosa-asetaattibutyraatti; Целлабурат.

CAS — 9004-36-8.

NOTE. Cabufocon A and Cabufocon B are both USAN for cellulose acetate butyrate.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Cellulose Acetate Butyrate). A partly or completely *O*-acetylated and *O*-butyrated cellulose containing not less than 2.0% and not more than 30.0% of acetyl groups and not less than 16.0% and not more than 53.0% of butyryl groups, calculated with reference to the dried substance. A white, yellowish-white, or greyish-white, slightly hygroscopic, powder or granules. Practically insoluble in water and in alcohol; soluble in acetone, in formic acid, and in a mixture of equal volumes of methyl alcohol and dichloromethane. Store in airtight containers.

Cellacefate *(BAN, rINN)*

Acetato ftalato de celulosa; CAP; Celacefat; Celacefát; Celacefato; Celiuliozės acetatas-ftalatas; Cellacéfate; Cellacefatum; Cellacephate; Cellulosaacetatftalat; Cellulose, acétate phtalate de; Cellulose Acetate Phthalate; Celluloseacetatphthalat; Cellulosi acetas phthalas; Cellulosum Acetylphthalicum; Cellulóz-acetát-ftalát; Celophthalum; Selluloosa-asetaattiftalaatti; Целлацефат.

CAS — 9004-38-0.

UNII — F2O5O2OI9F.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Cellulose Acetate Phthalate; Cellacefate BP 2014). Cellulose in which some of the hydroxyl groups are acetylated (21.5 to 26.0%) and some are phthalylated (30.0 to 36.0%), both calculated with reference to the anhydrous, acid-free substance.

A hygroscopic, white or almost white, free-flowing powder or colourless flakes. Practically insoluble in water, in dehydrated alcohol, and in dichloromethane; freely soluble in acetone; soluble in diethylene glycol; it dissolves in dilute solutions of alkalis. Store in airtight containers.

USNF 31: (Cellacefate). A reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains 21.5 to 26.0% of acetyl groups, and 30.0 to 36.0% of phthalyl (*o*-carboxy-benzoyl) groups, calculated on the anhydrous, acid-free basis. A white, free-flowing powder that may have a slight odour of acetic acid. Insoluble in water and in alcohol; soluble in acetone and in dioxan. Store in airtight containers.

Cellulose Acetate

Acetát celulosy; Acetyl cellulose; Acetylcellulose; Celiuliozės acetatas; Cellulosaacetat; Cellulose, acétate de; Celluloseacetat; Cellulosi Acetas; Celulóz-acetát; Celulozy octan; Selluloosa-asetaatti; Ацетилцеллюлоза.

CAS — 9004-35-7 (cellulose acetate); 9035-69-2 (cellulose diacetate); 9012-09-3 (Cellulose triacetate).

UNII — 3J2P07GVB6.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Cellulose Acetate). Partly or completely *O*-acetylated cellulose. A white, yellowish-white, or greyish-white, hygroscopic powder or granules. Practically insoluble in water and in alcohol; soluble in acetone, in formic acid, and in a mixture of equal volumes of methyl alcohol and dichloromethane.

USNF 31: (Cellulose Acetate). A partially or completely acetylated cellulose. It contains not less than 29.0% and not more than 44.8%, by weight, of acetyl groups, calculated on the dried basis. A fine, white powder or free-flowing pellets. Available in a range of viscosities and acetyl contents. High viscosity, which reflects high molecular weight, decreases solubility slightly. High acetyl content cellulose acetates generally have more limited solubility in commonly used organic solvents than low acetyl content cellulose acetates, but are more soluble in dichloromethane. All acetyl content cellulose acetates are insoluble in water and in alcohol; soluble in dioxane and in dimethylformamide. Store in airtight containers.

Profile

Cellulose esters are derivatives of cellulose (above) in which some or all of the hydroxyl groups are esterified. Organic cellulose esters such as cellulose acetate and the mixed esters cellaburate and cellacefate are used as tablet and capsule coatings and in the formulation of modified-release and transdermal drug delivery systems. Cellacefate is unaffected by immersion in acid media in the stomach but softens and swells in intestinal fluid. It is used as an enteric-coating material for tablets and capsules, usually with a plasticiser. Films of cellacefate are reported to be permeable to some ionic substances such as ammonium chloride and potassium iodide, and such substances require a sealing coat.

Cellulose esters have many industrial applications, particularly in plastics. Cellulose acetate film has been used in the photographic and cinematographic industries, and cellulose acetate fibre is used in the textiles industry.

Cellulose esters including cellacefate and cellulose sulfate, an inorganic cellulose ester, have been tried as vaginal microbicides but results have been disappointing (see HIV Infection and AIDS, below).

HIV infection and AIDS. Both cellulose sulfate and cellacefate have shown activity against HIV *in vitro* and in *animal* models but studies in humans have been less promising. A study[1] using a cellulose sulfate vaginal microbicidal gel for the prevention of HIV infection (p. 959.1) was terminated early because of evidence that suggested that it might in fact increase the risk of acquiring the virus.

1. Van Damme L, *et al.* CS Study Group. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *N Engl J Med* 2008; **359:** 463–72.

Ceratonia

Carob Bean Gum; Carob Gum; Cerat.; Ceratonia Gum; E410; Farine de Caroube; Fruktkärnmjöl; Goma de garrofín; Goma de semillas de algarrobo; Gomme de Caroube; Guma z nasion Carobe; Locust Bean Gum; Saldžiosios ceratonijos lipai; Szentjánoskenyér-liszt; Камедь Рожкового Дерева; Цератония.

CAS — 9000-40-2.
ATC — A07XA02.
ATC Vet — QA07XA02.
ATC Herb — HA04WB5002 (Ceratonia siliqua: fruit); HA07BW5001 (Ceratonia siliqua: fruit); HA04WB5001 (Ceratonia siliqua: endosperm).
UNII — V4716MY704.

Profile

Ceratonia consists of the endosperms separated from the seeds of the locust bean tree, *Ceratonia siliqua* (Leguminosae). It is used as a thickening agent and stabiliser in the food industry.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Carobel; ***Switz.***: Nestargel†; ***UK***: Carobel; Nestargel.

Multi-ingredient Preparations. ***Austria***: China-Eisenwein†; ***Fr.***: Gumilk; ***Indon.***: Polysilane; ***Singapore***: Bios Life.

Cetostearyl Alcohol

Alcohol cetoestearílico; Alcohol cetylicus et stearylicus; Alcohol Cetylstearylicus; Alcool Cetostearilico; Alkohol cetostearylowy; Cetearyl Alcohol; Cetil-sztearil-alkohol; Cetostearilo alkoholis; Cetostearyl Alc.; Cetostearylalkohol; Cétostéarylique, alcool; Cetylstearylalkohol; Setostearyylialkoholi; Цетостеариловый Спирт.

CAS — 8005-44-5; 67762-27-0.
UNII — 2DMT128M1S.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF*.

Eur. also includes Cetostearyl Alcohol, Emulsifying, but this is described under Emulsifying Waxes (p. 2184.1).

Ph. Eur. 8: (Cetostearyl Alcohol). A mixture of solid aliphatic alcohols, mainly stearyl alcohol and cetyl alcohol. It contains not less than 90% of stearyl plus cetyl alcohols and not less than 40% of stearyl alcohol. A white or pale yellow wax-like mass, plates, flakes, or granules. M.p. 49 degrees to 56 degrees. Practically insoluble in water; soluble in alcohol and in petroleum spirit. When melted, it is miscible with fatty oils, with liquid paraffin, and with melted wool fat.

USNF 31: (Cetostearyl Alcohol). It contains not less than 40% of stearyl alcohol ($C_{18}H_{38}O$ = 270.5) and the sum of the stearyl alcohol content and the cetyl alcohol ($C_{16}H_{34}O$ = 242.4) content is not less than 90%. Unctuous, white flakes or granules, having a faint, characteristic odour. M.p. 48 degrees to 55 degrees. Insoluble in water; soluble in alcohol and in ether.

Uses

Cetostearyl alcohol is used in creams, ointments, and other topical preparations as a stiffening agent and emulsion stabiliser. It is also used to improve the emollient properties of paraffin ointments. Emulsifying forms are prepared by adding a suitable surfactant and are described under Emulsifying Waxes (p. 2184.1). Cetostearyl alcohol is also used in the formulation of modified-release oral preparations.

Adverse Effects

Cetostearyl alcohol can cause hypersensitivity.

Hypersensitivity. Sensitivity reactions to cetostearyl alcohol in topical preparations have been reported rarely.[1-3]

1. Pecegueiro M, *et al.* Contact dermatitis to Hirudoid cream. *Contact Dermatitis* 1987; **17:** 290–3.
2. Marston S. Contact dermatitis from cetostearyl alcohol in hydrocortisone butyrate lipocream, and from lanolin. *Contact Dermatitis* 1991; **24:** 372.
3. Rademaker M, *et al.* Contact dermatitis from cetostearyl alcohol. *Australas J Dermatol* 1997; **38:** 220–1.

Preparations

Pharmacopoeial Preparations
BP 2014: Cetomacrogol Emulsifying Wax; Cetrimide Emulsifying Ointment; Emulsifying Wax;
USNF 31: Emulsifying Wax.

Cetyl Alcohol

Alcohol cetílico; Alcohol cetylicus; Alcohol Hexadecílico; Álcool Cetílico; Alkohol cetylowy; Cetanol; Cetil-alkohol; Cetilo alkoholis; Cetylalkohol; Cétylique, alcool; Ethal; Ethol; 1-Hexadecanol; Hexadecan-1-ol; Hexadecyl Alcohol; *n*-Hexadecyl Alcohol; Palmityl Alcohol; Setyylialkoholi; Цетиловый Спирт.

$C_{16}H_{34}O$=242.4
CAS — 36653-82-4; 124-29-8.
UNII — 936JST6JCN.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Cetyl Alcohol). A mixture of solid alcohols, mainly cetyl alcohol, of animal or vegetable origin. It occurs as a white or almost white, unctuous mass, powder, flakes, or granules. M.p. 46 degrees to 52 degrees. Practically insoluble in water; freely to sparingly soluble in alcohol; miscible when melted with animal and vegetable oils, with liquid paraffin, and with melted wool fat.

USNF 31: (Cetyl Alcohol). A mixture containing not less than 90% of cetyl alcohol the remainder consisting chiefly of related alcohols. White unctuous flakes, cubes, granules, or castings, with a faint characteristic odour. M.p. 45 degrees to 50 degrees. Insoluble in water; soluble in alcohol and in ether, the solubility increasing with increasing temperature.

Uses

Cetyl alcohol is used in topical preparations for its emollient, water absorptive, stiffening, and weak emulsifying properties. It may be incorporated into suppositories to raise the melting-point and may be used in the coating of modified-release solid dose forms. It is also used in cosmetics.

Adverse Effects

Cetyl alcohol can cause hypersensitivity.

Hypersensitivity. Hypersensitivity reactions have occasionally been attributed to the presence of cetyl alcohol in topical preparations.[1-4] One report suggested that minor impurities in the cetyl alcohol may be responsible.[1]

1. Komamura H, *et al.* A case of contact dermatitis due to impurities of cetyl alcohol. *Contact Dermatitis* 1997; **36:** 44–6.
2. Oiso N, *et al.* Concomitant allergic reaction to cetyl alcohol and crotamiton. *Contact Dermatitis* 2003; **49:** 261.
3. Soga F, *et al.* Contact dermatitis due to lanoconazole, cetyl alcohol and diethyl sebacate in lanoconazole cream. *Contact Dermatitis* 2004; **50:** 49–50.
4. Kiec-Swierczynska M, *et al.* Photoallergic and allergic reaction to 2-hydroxy-4-methoxybenzophenone (sunscreen) and allergy to cetyl alcohol in cosmetic cream. *Contact Dermatitis* 2005; **53:** 170–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lactopan; ***India***: Nosoap.

Multi-ingredient Preparations. ***Arg.***: Caien†; ***Hong Kong***: Ego Skin Cream; ***Malaysia***: Ego Skin Cream; ***NZ***: Ego Skin Cream; ***Philipp.***: Dermalin†; Sebo Fluid†; ***Singapore***: Ego Skin Cream.

Cetyl Esters

Cetylated Fatty Acids.
UNII — D072FFP9GU.

Cetyl Esters Wax

Cera Cetyla; Cera de ésteres cetílicos; Cera de ésteres del alcohol cetílico; Esperma de ballena sintético; Spermaceti Wax Replacement; Synthetic Spermaceti; Воск Сложных Цетиловых Эфиров.

CAS — 85566-24-1.

Pharmacopoeias. In *Int.* Also in *USNF*.

USNF 31: (Cetyl Esters Wax). A mixture consisting primarily of esters of saturated fatty alcohols (C_{14} to C_{18}) and saturated fatty acids (C_{14} to C_{18}). White to off-white somewhat translucent flakes with a crystalline structure and a pearly lustre when caked; it has a faint odour and is free from rancidity. M.p. 43 degrees to 47 degrees. Insoluble in water; practically insoluble in cold alcohol; soluble in boiling alcohol, in chloroform, in ether, and in fixed and volatile oils; slightly soluble in cold petroleum spirit. Store in a dry place at a temperature not exceeding 40 degrees.

Cetyl Palmitate

Cetilo palmitatas; Cetil-palmität; Cetyl Cetylate; Cetyle, palmitate de; Cetylis Palmitas; Cetylpalmitat; Cetyl-palmität; Hexadecyl Palmitate; Setyylipalmitaatti; Цетилпальмитат.

Hexadecyl hexadecanoate.
$C_{32}H_{64}O_2$=480.9
CAS — 540-10-3.
UNII — 5ZA2S6B08X.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Cetyl Palmitate). A mixture of C_{14} to C_{18} esters of lauric (dodecanoic), myristic (tetradecanoic), palmitic (hexadecanoic) and stearic (octadecanoic) acids ('cetyl esters wax'). It contains (expressed as hexadecyl hexadecanoate): 10 to 20% for Cetyl Palmitate 15, 60 to 70% for Cetyl Palmitate 65, and not less than 90% for Cetyl Palmitate 95. White or almost white, waxy plates, flakes or powder. Practically insoluble in water and in anhydrous alcohol; soluble in boiling anhydrous alcohol and in dichloromethane; slightly soluble in light petroleum. M.p. about 45 degrees for Cetyl Palmitate 15 and Cetyl Palmitate 65, and about 52 degrees for Cetyl Palmitate 95. Store at a temperature not exceeding 25 degrees.

USNF 31: (Cetyl Palmitate). It consists of esters of cetyl alcohol and saturated high molecular weight fatty acids, principally palmitic acid. White crystals or flakes. Practically insoluble in water; freely soluble in alcohol and in ether. M. p. 46 degrees to 53 degrees. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees; avoid exposure to excessive heat above 40 degrees.

Profile

Mixtures of cetyl esters such as cetyl palmitate or cetyl esters wax are used as emollients and stiffening agents in creams and ointments. Cetyl esters wax is also used in the coating of some oral dosage forms. It is a synthetic replacement for natural spermaceti, a waxy substance obtained from the sperm whale and the bottle-nosed whale that is composed mainly of cetyl palmitate and has been used similarly.

Mixtures of cetyl esters containing mainly cetyl myristoleate have been used as nutritional supplements (see p. 2473.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Zoodermina Crema; ***Fr.***: Cold Cream Naturel; ***Thai.***: Hemorhin†.

Pharmacopoeial Preparations
USP 36: Rose Water Ointment.

Chlorophyll

Bladgroen; Chlorofilas; Chlorofile; Chlorofyl; Chlorophylle; Chlorophyllum; CI Natural Green 3; Clóraifill; Cloroffyl; Clorofilă; Clorofila; Clorofilla; Colour Index No. 75810; E140 (chlorophylls or chlorophyllins); Hlorofil; Hlorofils; Klorofil; Klorofill; Klorofüll; Klorofyl; Klorofyll; Lehtivihreä; Хлорофил; Хлорофилл.

CAS — 479-61-8 (chlorophyll a); 519-62-0 (chlorophyll b).

Chlorophyllin Copper Complex Sodium

Clorofilina cúprica, complejo sódico de; Медного Комплекса Хлорофиллина Натриевая Соль.

Pharmacopoeias. In *US.*

USP 36: (Chlorophyllin Copper Complex Sodium). It contains sodium salts of copper-chelated chlorophyll derivatives, but no artificial colouring. Store in airtight containers. Protect from light.

Profile

Chlorophyll is a green photosynthetic pigment found in plants, algae, and cyanobacteria (blue-green algae).

There are four closely related forms of chlorophyll. Chlorophyll a ($C_{55}H_{72}MgN_4O_5$ = 893.5) and chlorophyll b ($C_{55}H_{70}MgN_4O_6$ = 907.5) are found in plants and some types of algae; chlorophyll c, further subdivided into chlorophyll c1 ($C_{35}H_{30}MgN_4O_5$ = 611.0) and chlorophyll c2 ($C_{35}H_{28}MgN_4O_5$ = 608.9), is found in some types of algae; and chlorophyll d ($C_{54}H_{70}MgN_4O_6$ = 895.5) is found in some types of algae and in cyanobacteria.

*Oil-soluble chlorophyll derivatives.*Replacement of the magnesium atom in the chlorophylls by 2 hydrogen atoms using dilute mineral acids produces olive-green water-insoluble phaeophytins. Copper phaeophytins (sometimes called copper chlorophyll complex; E141) can be formed; these are more stable to acids and to light than the chlorophylls.

Water-soluble chlorophyll derivatives. When the chlorophylls are hydrolysed with alkali, phytyl alcohol and methyl alcohol are split off and green water-soluble chlorophyllins are formed as the potassium or sodium salts. Similar water-soluble compounds can be prepared in which the magnesium is replaced by copper to give copper chlorophyllin complex (E141).

Chlorophylls and chlorophyllins, as well as the copper complexes of these compounds, are used mainly as colouring agents, in foods, medicines, and cosmetics.

Chlorophyll is used clinically, as an external application in the treatment of wounds and ulcers, and as a mouthwash. There is no clear evidence that it accelerates healing but it is considered to have a deodorant action. Chlorophyllin and copper chlorophyllin complex are used similarly. Chlorophyll is also used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ganxuebao (肝血宝); ***Ger.***: Stozzon; ***Ukr.***: Chlorophyllipt (Хлорофиллипт); ***USA***: Chloresium†; Derifil; Ennds; Nullo; Pals.

Multi-ingredient Preparations. ***Arg.***: Fanaletas; Gineseptina; Minamint; Notoxin; ***Braz.***: Anapyon; Emoform Clorofila; ***China***: Qianbao (乾宝); ***Hong Kong***: Epilon; ***Indon.***: Methaphyllin†; ***Spain***: Vitavox†; ***UK***: Chlorophyll; ***USA***: AllanEnzyme†; AllanfillEnzyme†; Fresh-N-Free; Gladase-C†; Iron Complex; Panafil†; Papfyll; Prophyllin; Wound Cleanser; Ziox†.

Cholesterol

Cholesterin; Cholestérol; Cholesterolis; Cholesterolum; Colesterina; Colesterol; Colesterolo; Holesterîns; Holesterol; Kolesterol; Kolesteroli; Kolesterool; Koleszterin; Холестерол; Холестерин.

Cholest-5-en-3β-ol.

$C_{27}H_{46}O$=386.7

CAS — 57-88-5.

UNII — 97C5T2UQ7J.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Eur. also includes a form for parenteral use.

Ph. Eur. 8: (Cholesterol). A white or almost white, crystalline powder. It is sensitive to light. M.p. 147 degrees to 150 degrees. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

Ph. Eur. 8: (Cholesterol for Parenteral Use). A white or almost white, crystalline powder. It is sensitive to light. M.p. 147 degrees to 150 degrees. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

USNF 31: (Cholesterol). White or faintly yellow, practically odourless, pearly leaflets, needles, powder, or granules. It acquires a yellow to pale tan colour on prolonged exposure to light. M.p. 147 degrees to 150 degrees. Insoluble in water; slowly soluble 1 in 100 of alcohol; soluble 1 in 50 of dehydrated alcohol; soluble in acetone, in chloroform, in dioxan, in ether, in ethyl acetate, in petroleum spirit, and in vegetable oils. Protect from light.

Profile

Cholesterol imparts water-absorbing power to pharmaceutical preparations and is used as an emulsifying agent. It has emollient activity and is used mainly in topical preparations. It is also used in ophthalmic and vaginal formulations, and in liposomal preparations for parenteral use.

Cholesteryl benzoate (cholesterol benzoate, below) has been used as an ingredient in dermatological preparations.

Physiologically, cholesterol is an important component of cell membranes and lipoproteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Liposomas; ***Chile***: Perfungol†; ***Fr.***: Totephan†; ***Singapore***: Ceradan.

Homoeopathic Preparations. ***Canad.***: Carduus Plex†; Formula Homeo QR 209†; Hepar Compositum; ***Fr.***: Bilinum Complexe No 113; Cholesterolum Complexe No 112†; Strontium Compose; ***Ger.***: Chol-Do; Chole-cyl L Ho-Len-Complex; NeyArthrosome (Revitorgan-Dilution)†.

Cholesteryl Benzoate

Cholesterol Benzoate.

Cholest-5-en-3β-yl benzoate.

$C_{34}H_{50}O_2$=490.8

CAS — 604-32-0.

UNII — N09H13SHLB.

Profile

Cholesteryl benzoate is an ingredient in dermatological preparations; it acts as a humectant and emulsifier.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Senophile; ***Fr.***: Senophile.

CI Solvent Yellow 18

CI Food Yellow 12; Colour Index No. 12740.

4-[(2,4-Dimethylphenyl)azo]-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one.

$C_{18}H_{18}N_4O$=306.4

CAS — 6407-78-9.

Profile

CI Solvent Yellow 18 is a synthetic azo dye used as a colouring agent in contact lenses.

CI Vat Orange 1

CI Кубовый Оранжевый 1; Colour Index No. 59105.

Dibromodibenzo(b,def)chrysene-7,14-dione.

$C_{24}H_{10}Br_2O_2$=490.2

CAS — 1324-11-4.

Profile

CI Vat Orange 1 is a synthetic dye used as a colouring agent in contact lenses.

Citranaxanthin

Citranaksantinas; Citranaxanthine; Citranaxantina; Cytranaksantyna; E161(i); Цитранаксантин.

6′-Methyl-6′-apo-β-caroten-6′-one.

$C_{33}H_{44}O$=456.7

CAS — 3604-90-8.

Profile

Citranaxanthin is a carotenoid pigment. It occurs naturally but is usually made synthetically and is used as a colouring agent in animal feeds, to colour the fat of poultry and the egg-yolks of laying hens. It has vitamin A activity.

Citrus Red 2

CI Solvent Red 80; Colour Index No. 12156; Цитрусовый Красный 2.

1-(2,5-Dimethoxyphenylazo)-2-naphthol.

$C_{18}H_{16}N_2O_3$=308.3

CAS — 6358-53-8.

UNII — 2QE5Y68984.

Profile

Citrus Red 2 is a synthetic azo dye used as a colouring agent in foods.

Cochineal

Bíbortetű; CI Natural Red 4; Cocciniglia del Carminio; Coccionella; Coccus; Coccus Cacti; Cochenille; Cochenilleluis; Cochenillelus; Cochinilla; Cochonilha; Colour Index No. 75470; Czerwiec kaktusowy; E120; Kokenillikirva; Koschenille; Koszenila; Кошениль.

CAS — 1343-78-8.

UNII — TZ8Z31B35M.

Pharmacopoeias. In *Br.*

BP 2014: (Cochineal). The dried female insect, *Dactylopius coccus* containing eggs and larvae. It has a characteristic odour. It complies with a test for contamination with *Escherichia coli*and salmonellae.

Profile

Cochineal, which is a source of carmine, is used as a red colouring agent in food, medicines, and cosmetics.

There have been reports of sensitivity reactions including anaphylaxis, after use of products containing cochineal (see Hypersensitivity under Adverse Effects of Carmine, p. 2176.2).

Homoeopathy

Cochineal has been used in homoeopathic medicines under the following names: Coccus; Coccus cacti; Dactylopius coccus; Coc. c.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Port.***: Stodal.

Homoeopathic Preparations. ***Austria***: Pertudoron†; ***Canad.***: Drosera Complex; Drosera Plex†; Kids Cough & Cold Phytux; Male +; Pertudoron 1†; Phytotux H; Renelix; Stodal; ***Cz.***: Drosetux; Stodal; ***Fr.***: Baudry; Boripharm No 11†; Drosera Complexe No 64; Drosera Compose; Drosetux; L 8; Pertudoron; Stodal; Stodal; Uva Ursi Complexe No 9; ***Ger.***: Bomapect N; Monapax; Pertudoron 1; Roth's RKT Tropfen; ***Hung.***: Drosetux; Stodal; ***Neth.***: Drosinula; Stodal; ***Rus.***: Stodal (Стодаль); ***S.Afr.***: Pertudoron Drops†; ***Switz.***: Drosetux; Stodal; ***Ukr.***: Stodal (Стодаль).

Coconut Oil

Coco (huile de) raffinée; Aceite de Coco; Cocois Oleum Raffinatum; Coconut Butter; Copra Oil; Finomított kókuszolaj; Hindistancevizi Yağı; Klapperolie; Kokosų aliejus, rafinuotas; Kokosfett; Kokosnussöl; Kokosöl; Kokosolie; Kokosolja, raffinerad; Kokosolje; Kokosový olej čištěný; Kokosvet; Kookosöljy, puhdistettu; Masło Kokosowe; Minyak Kelapa; Olej Kokosowy; Óleo de Coco; Oleum Cocois; Oleum Cocos Raffinatum; Oleum Cocosis; Olio di cocco; Tłuszcz Kokosowy; Кокосово Масло; Кокосовое Масло.

CAS — 8001-31-8.

UNII — Q9L0O73W7L.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn.*, and *USNF.*

USNF includes hydrogenated coconut oil.

Ph. Eur. 8: (Coconut Oil, Refined). The refined fatty oil obtained from the dried, solid part of the endosperm of *Cocos nucifera.* A white or almost white, unctuous mass. M.p. 23 degrees to 26 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65 degrees to 70 degrees). Store in well-filled containers. Protect from light.

USNF 31: (Coconut oil). The refined fixed oil obtained from the seeds of *Cocos nucifera.* A clear, white to light yellow-tan, viscous liquid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in light petroleum. M.p. 23 degrees to 26 degrees. Store in airtight, well-filled containers. Protect from light.

USNF 31: (Hydrogenated Coconut Oil). Obtained by refining and hydrogenating the oil obtained from the seeds of *Cocos nucifera.* A white to yellowish, fatty solid to semi-solid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in ether. Store in airtight containers at a temperature not exceeding 55 degrees. Protect from light.

Uses

Coconut oil contains a mixture of mainly saturated C_6 to C_{20} fatty acids, with lauric acid and myristic acid being the most abundant. It is used as a basis for topical creams and ointments, in rectal and vaginal suppositories, in solid dosage forms, and as a plasticiser. Hydrogenated coconut oil is used similarly; it contains an even higher proportion of saturated fatty acids and melts at a higher temperature. Coconut oil is also used in food manufacturing, including infant formulas, food for special diets, and parenteral nutrition. Topical preparations have been used for pediculosis.

Fractionated coconut oil (thin vegetable oil) is used as a source of medium-chain triglycerides (p. 2082.2).

Adverse Effects

Hypersensitivity. Sensitivity reactions to coconut products, including coconut oil,[1] have been reported rarely. Cases of anaphylaxis have been reported.[2,3]

1. Couturier P, *et al.* Un cas d'allergie à l'huile de noix de coco chez un nourrisson: responsabilité des laits maternisés. *Allerg Immunol (Paris)* 1994; **26:** 386–7.
2. Rosado A, *et al.* Anaphylaxis to coconut. *Allergy* 2002; **57:** 182–3.
3. Nguyen SA, *et al.* Cross-reactivity between coconut and hazelnut proteins in a patient with coconut anaphylaxis. *Ann Allergy Asthma Immunol* 2004; **92:** 281–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Maternity Sapolan Bronceador; ***Ger.***: Aesculo Gel L; ***UK***: Nitlotion.

Multi-ingredient Preparations. ***Arg.***: Paranix; ***Ger.***: Paranix; ***India***: N-Rich Baby; ***Indon.***: Minyak Telon Cap Tiga Anak†; Minyak Telon†; Telon 3 Anak; Yanthi Baby Oil†; ***NZ***: Mr Nits; ***Philipp.***: Enfacare; ***Singapore***: Bio-Taches†; ***Switz.***: Paranix; ***Turk.***: Kataljin.

Cottonseed Oil

Algodón, Aceite de; Baumwollsaatöl; Baumwollsamenöl; Bomullsfröolja; Coton, huile de; Cotton Oil; Cottonöl; Gossypii Oleum; Gyapotmagolaj; Ol. Gossyp. Sem.; Oléo de Algodoeiro; Oleum Gossypii Seminis; Oli de llavors de cotó; Puuvillansiemenöljy; Vilnamedžių aliejus; Хлопковое Масло.
CAS — 8001-29-4.
UNII — H3E878020N (cottonseed oil); Z82Y2C65EA (hydrogenated cottonseed oil).

Pharmacopoeias. In *USNF*, which also includes hydrogenated cottonseed oil.

Eur. (see p. vii) includes only the hydrogenated oil.

Ph. Eur. 8: (Cottonseed Oil, Hydrogenated; Gossypii Oleum Hydrogenatum). Obtained by refining and hydrogenation of oil obtained from seeds of cultivated plants of various varieties of *Gossypium hirsutum* or of other species of *Gossypium*. It consists mainly of triglycerides of palmitic and stearic acids. It is a white or almost white mass or powder which melts to a clear pale yellow liquid when heated. M.p. 57 degrees to 70 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in toluene. Protect from light.

USNF 31: (Cottonseed Oil). The refined fixed oil obtained from the seed of plants of various varieties of *Gossypium hirsutum* or of other species of *Gossypium* (Malvaceae). It may contain suitable antoxidants. It is a pale yellow, oily liquid, odourless or nearly so. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, with ether, and with petroleum spirit. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light. At temperatures below 10 degrees particles of solid fat may separate from the oil and at about 0 degrees to -5 degrees the oil becomes a solid or nearly so.

USNF 31: (Hydrogenated Cottonseed Oil). It is obtained by hydrogenating Cottonseed Oil and consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. 57 degrees to 70 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in toluene. Store in airtight containers. Protect from light.

Profile

Cottonseed oil is used as an oily vehicle.

An extract of cottonseed oil, gossypol (p. 2521.2), has been tried as a contraceptive in males.

Creatinine

Creatinină; Creatinina; Créatinine; Kreatiniini; Kreatinin; Kreatynina; Креатинин.
2-Amino-1-methyl-4-imidazolidinone.
$C_4H_7N_3O$=113.1
CAS — 60-27-5.
UNII — AYI8EX34EU.

Pharmacopoeias. In *Ger.* Also in *USNF*.

USNF 31: (Creatinine). White, odourless, crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether.

Profile

Creatinine is used as a bulking agent for freeze-drying.

Plasma concentrations or clearance of endogenous creatinine are used as an index of renal function.

Curcumin

Colour Index No. 75300; Curcumina; Curcumine; E100; Kurkum; Kurkumin; Kurkumina; Kurkuminas; Turmeric Yellow; Куркумин.
1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione.
$C_{21}H_{20}O_6$=368.4
CAS — 458-37-7.
UNII — IT942ZTH98.

Profile

Curcumin is the main colouring component of turmeric (p. 2218.1). It is used as a colouring agent for medicines, foodstuffs, and cosmetics. Curcumin and related curcuminoids (p. 2489.3) are also used as dietary supplements. Like turmeric, they have been tried in various disorders, as they are thought to be responsible for its pharmacological activity (see p. 2218.2 for further details).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Curmunos; Curviplex; Dhavit; Letrosil; ***Ital.***: Depatox; ***UK***: Potenzia; ***USA***: Immunicare; NicAzel Forte.

Cyclamic Acid *(BAN, USAN)*

Ciclámico, ácido; Cyclam. Acid; E952; Hexamic Acid; Цикламовая Кислота.
N-Cyclohexylsulphamic acid.
$C_6H_{13}NO_3S$=179.2
CAS — 100-88-9.
UNII — HN3OFO5036.

Calcium Cyclamate

Calc. Cyclam.; Calcium Cyclohexanesulfamate; Ciclamato de calcio; Ciclohexanosulfamato de calcio; Cyclamate Calcium; E952; Кальция Цикламат.
Calcium *N*-cyclohexylsulphamate dihydrate.
$C_{12}H_{24}CaN_2O_6S_2.2H_2O$=432.6
CAS — 139-06-0 (anhydrous calcium cyclamate); 5897-16-5 (calcium cyclamate dihydrate).
UNII — OK71859Z12 (calcium cyclamate); X12LMJ1WYL (anhydrous calcium cyclamate).

Potassium Cyclamate

Cyclamate Potassium; HSDB 1239; Monopotassium Cyclohexanesulfamate; Potassium Cyclohexanesulfamate; Калия Цикламат.
Potassium *N*-cyclohexysulphamate.
$C_6H_{12}NO_3SK$=217.3
CAS — 7758-04-5.
UNII — 0DS7R9NQB0.

Sodium Cyclamate *(BAN, rINN)*

Ciclamato de sodio; Ciclohexanosulfamato de sodio; Cyclamate de Sodium; Cyclamate Sodium; E952; Natrii Cyclamas; Natrio ciklamatas; Nátrium-ciklamát; Natriumcyclamat; Natriumcyklamat; Natrium-cyklamát; Natriumsyklamaatti; Siklamat Sodyum; Sod. Cyclam.; Sodium, cyclamate de; Sodium Cyclohexanesulphamate; Натрия Цикламат.
Sodium *N*-cyclohexylsulphamate.
$C_6H_{12}NNaO_3S$=201.2
CAS — 139-05-9.
UNII — 116F42RME1.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Cyclamate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 5.5 to 7.5.

Profile

Cyclamic acid and its salts are intense sweetening agents. In dilute solutions (up to about 0.17%) sodium cyclamate is about 30 times as sweet as sucrose but this factor decreases at higher concentrations. When the concentration approaches 0.5%, a bitter taste becomes noticeable. It is stable to heat.

The use of cyclamates as artificial sweeteners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in Great Britain and some other countries because of concern about the metabolite cyclohexylamine. However, after reappraisal their use is now allowed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Sucaryl†.

Multi-ingredient Preparations. ***Arg.***: Chuker; Chuker; Dulsiluet; Kaldil Diet; Rondo; Sucaryl; Suimel; ***Austral.***: Sucaryl; ***Braz.***: Finn Cristal; ***Chile***: Endulzante; Sukar-Sin; ***Fr.***: Sucaryl; ***Israel***: Sucrin; ***Ital.***: Diet Sucaryl†; ***NZ***: Sucaryl; ***Rus.***: Zuckli (Цюкли)†; ***Turk.***: Dolce†; Dulcaryl; Tadalin.

Cyclodextrins

Ciclodextrinas; Циклодекстрины.

Alfadex *(BAN, rINN)*

Alfadeksas; Alfadeksi; Alfadexum; Alpha Cyclodextrin; Alphacyclodextrin; α-Cyclodextrin; Cyclohexaamylose; Cyclomaltohexose; Альфадекс.
Cyclomaltohexaose.
$C_{36}H_{60}O_{30}$=972.8
CAS — 10016-20-3.
UNII — Z1LH97KTRM.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Alfadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; practically insoluble in dehydrated alcohol and in dichloromethane. Store in airtight containers.

USNF 31: (Alfadex). A white or almost white, amorphous or crystalline, powder. Freely soluble in water and in propylene glycol; practically insoluble in dehydrated alcohol and in dichloromethane. Store in airtight containers.

Betadex *(BAN, USAN, rINN)*

Beetadeksi; Betadeksas; Bétadex; Betadexum; β-Cyclodextrin; Cycloheptaamylose; E459; Бетадекс.
Cyclo-α-(1→4)-D-heptaglucopyranoside.
$C_{42}H_{70}O_{35}$=1135
CAS — 7585-39-9.
UNII — JV039JZZ3A.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Betadex). A white or almost white, amorphous or crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane; freely soluble in propylene glycol. Store in airtight containers.

USNF 31: (Betadex). A nonreducing cyclic compound composed of 7 α-(1→4) linked D-glucopyranosyl units. It is a white, practically odourless, fine crystalline powder. Soluble 1 in 54 of water. Store in airtight containers.

Gamma Cyclodextrin

Cyclomaltooctaose; Cyclooctaamylose.
$C_{48}H_{80}O_{40}$=1297.1
CAS — 17465-86-0.
UNII — KZJ0BYZ5VA.

Pharmacopoeias. In *USNF*.

USNF 31: (Gamma Cyclodextrin). A cyclic compound composed of 8 α-(1→4) linked D-glycopyranosyl units. A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; very slightly soluble in alcohol.

Hydroxypropylbetadex

Hidroksipropilbetadeksas; Hydoxipropylbetadex; Hydroksipropyylibetadeksi; Hydroxypropylbétadex; Hydroxypropylbetadexum; 2-Hydroxypropyl-β-cyclodextrin.
UNII — 1196OHX6EK (hydroxypropylbetadex (0.58-0.68 ms)).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Hydroxypropylbetadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol.

USNF 31: (Hydroxypropyl Betadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol.

Profile

Cyclodextrins, such as alfadex, betadex, and gamma cyclodextrin, are cyclic oligosaccharides obtained by enzymatic degradation of starch. They form inclusion compounds with a wide range of molecules and are used as carriers for oral, parenteral, and topical drug delivery systems. They improve dissolution and solubility, increase stability, and may also be used for taste-masking. Substituted cyclodextrins such as hydroxypropylbetadex, sulfobutylether-β-cyclodextrin, and dimethyl-β-cyclodextrin are also used.

Cyclodextrins are also used in the food industry.

References.

1. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. *Pharm Res* 1997; **14:** 556–67.
2. Loftsson T, Olafsson JH. Cyclodextrins: new drug delivery systems in dermatology. *Int J Dermatol* 1998; **37:** 241–6.
3. Redenti E, *et al.* Drug/cyclodextrin/hydroxy acid multicomponent systems: properties and pharmaceutical applications. *J Pharm Sci* 2000; **89:** 1–8.

4. Loftsson T, Masson M. Cyclodextrins in topical drug formulations: theory and practice. *Int J Pharm* 2001; **225:** 15–30.
5. Loftsson T, Stefansson E. Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye. *Acta Ophthalmol Scand* 2002; **80:** 144–50.
6. Dass CR. Cyclodextrins and oligonucleotide delivery to solid tumours. *J Drug Target* 2004; **12:** 1–9.
7. Kaur IP, *et al.* Role of cyclodextrins in ophthalmics. *Curr Drug Deliv* 2004; **1:** 351–60.
8. Challa R, *et al.* Cyclodextrins in drug delivery: an updated review. *AAPS PharmSciTech* 2005; **6:** E329–E357.
9. Loftsson T, Duchêne D. Cyclodextrins and their pharmaceutical applications. *Int J Pharm* 2007; **329:** 1–11.
10. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. *Adv Drug Deliv Rev* 2007; **59:** 645–66.
11. Carrier RL, *et al.* The utility of cyclodextrins for enhancing oral bioavailability. *J Control Release* 2007; **123:** 78–99.
12. Cal K, Centkowska K. Use of cyclodextrins in topical formulations: practical aspects. *Eur J Pharm Biopharm* 2008; **68:** 467–78.
13. Stella VJ, He Q. Cyclodextrins. *Toxicol Pathol* 2008; **36:** 30–42.
14. Otero-Espinar FJ, *et al.* Cyclodextrins: more than pharmaceutical excipients. *Mini Rev Med Chem* 2010; **10:** 715–25.

Cyclohexane

Cicloexano; Ciclohexà; Ciclohexano; Cikloheksán; Cyclohexaan; Cyclohexan; Cyclohexano; Cykloheksan; Cyklohexan; Hexahidroxibenzeno; Hexahydrobenzene; Hexamethylene; Hexametileno; Hexanafteno; Sykloheksaani; Sykloheksan; Циклогексан; Циклохексан.

C_6H_{12}=84.16

CAS — 110-82-7.

UNII — 48K5MKG32S.

Description. Cyclohexane is a colourless, flammable liquid. Wt per mL about 0.78 g. B.p. about 81 degrees. Store in airtight containers.

Uses

Cyclohexane is used as an industrial solvent.

Adverse Effects

Cyclohexane is irritant, and may also have effects on the CNS.

Reviews of the toxicity of cyclohexane.

1. Health and Safety Executive. Cyclohexane, cumene, para-dichlorobenzene (p-DCB), chlorodifluoromethane (CFC 22). *Toxicity Review 25.* London: HMSO, 1991.

Denatonium Benzoate *(BAN, USAN, rINN)*

Benzoate de dénatonium; Benzoato de denatonio; Benzoesan Denatonium; Denatonii Benzoas; Denatonio, benzoato de; Dénatonium, Benzoate de; Denatoniumbensoat; Denatonium-bentsoaatti; Denatoniumbenzoaat; Denatoniumbenzoat; Denatoniumbenzoát; NSC-157658; Денатония бензоат.

Benzyldiethyl(2,6-xylylcarbamoylmethyl)ammonium benzoate monohydrate.

$C_{28}H_{34}N_2O_3.H_2O$=464.6

CAS — 3734-33-6 (anhydrous denatonium benzoate); 86398-53-0 (denatonium benzoate monohydrate).

UNII — 4YK5Z54AT2.

Pharmacopoeias. In *USNF.*

USNF 31: (Denatonium Benzoate). When dried at 105 degrees for 2 hours, it contains one molecule of water of hydration or is anhydrous. Soluble 1 in 20 of water, 1 in 2.4 of alcohol, 1 in 2.9 of chloroform, and 1 in 5000 of ether; very soluble in methyl alcohol. pH of a 3% solution in water is between 6.5 and 7.5. Store in airtight containers.

Profile

Denatonium benzoate is used where an intensely bitter taste is required for medicinal or industrial purposes and as a partial denaturant for alcohol in toiletries. It is known commercially as Bitrex.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.:* Skin Nail.

Dextrates *(USAN)*

Dextratos.

CAS — 39404-33-6.

UNII — G263MI44RU.

Pharmacopoeias. In *USNF.*

USNF 31: (Dextrates). A purified, anhydrous or hydrated, mixture of saccharides obtained by the controlled enzymatic hydrolysis of starch. Free-flowing, porous, white, odourless, spherical granules consisting of aggregates of microcrystals. Freely soluble in water (heating increases its solubility in water); soluble in dilute acids and alkalis and in basic organic solvents such as pyridine; insoluble in the common organic solvents. pH of a 20% solution in water is between 3.8 and 5.8. Store in a dry place at a temperature of 8 degrees to 15 degrees.

Profile

Dextrates are used as a capsule and tablet diluent and as a tablet binding agent.

Dibutyl Sebacate

Dibutylsebacaat; Sebacato de dibutilo; Sebacinsäuredibutylester; Дибутилсебацинат.

Dibutyl decanedioate.

$C_{18}H_{34}O_4$=314.5

CAS — 109-43-3.

UNII — 4W5IH7FLNY.

Pharmacopoeias. In *USNF.*

USNF 31: (Dibutyl Sebacate). It consists of esters of *n*-butyl alcohol and saturated dibasic acids, principally sebacic acid. A colourless, oily liquid of very mild odour. Practically insoluble in water and in glycerol; soluble in alcohol, in isopropyl alcohol, and in liquid paraffin; very slightly soluble in propylene glycol. Store in airtight containers. Protect from moisture.

Profile

Dibutyl sebacate is a plasticiser used in pharmaceutical formulation of tablets (including modified release), beads, and granules, and microcapsule preparations. It is also used as a food flavouring.

Dichloromethane

Cloruro de metileno; Dichloormethaan; Dichlormethan; Diclorometano; Dikloorimetaani; Diklormetan; Diklórmetán; Methylene Chloride; Méthylène, chlorure de; Methyleni Chloridum; Metilēnhlorīds; Metileno cloridas; Metüleenkloriid; Metyleenikloridi; Metylenklorid; Metylenu chlorek; Дихлорметан.

CH_2Cl_2=84.93

CAS — 75-09-2.

UNII — 588X2YUY0A.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Methylene Chloride; Dichloromethane BP 2014). A clear, colourless, volatile liquid. Relative density 1.320 to 1.332. It may contain not more than 2% of alcohol and/or not more than 0.03% of 2-methylbut-2-ene as stabiliser. Sparingly soluble in water; miscible with alcohol. Store in airtight containers. Protect from light.

USNF 31: (Methylene Chloride). A clear, colourless, mobile liquid having an odour resembling chloroform. Sp. gr. 1.318 to 1.322. Miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers.

Stability. Phosgene is produced on heating of dichloromethane.

Uses

Dichloromethane is used as a pharmaceutical and industrial solvent, and as an extraction solvent in food processing.

Dichloromethane is widely used in paint strippers.

Adverse Effects and Treatment

Acute exposure to dichloromethane vapour may depress the CNS; symptoms progress from headache and dizziness to coma and death in severe cases. Pulmonary oedema has been reported. Significant exposure may result in raised blood concentrations of carboxyhaemoglobin and symptoms of carbon monoxide poisoning. Cardiovascular effects have been attributed to hypoxia secondary to carboxyhaemoglobinaemia. There has been a report of haemolysis after acute ingestion of dichloromethane.

Chronic occupational exposure to dichloromethane vapour has produced gastrointestinal disturbances in addition to symptoms seen after acute poisoning. Dichloromethane is a common constituent of paint strippers and may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

The liquid is irritant and high concentrations of the vapour are irritant to the eyes.

Treatment of acute poisoning consists of removal from exposure and supportive and symptomatic measures. Carboxyhaemoglobinaemia should be managed as for carbon monoxide poisoning (p. 1798.1) by giving 100% oxygen. After ingestion gastric lavage or activated charcoal are generally contra-indicated.

References.

1. WHO. Methylene Chloride. *Environmental Health Criteria 32.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc32.htm (accessed 29/06/04)
2. Health and Safety Executive. Dichloromethane (methylene chloride). *Toxicity Review 12.* London: HMSO,1985.
3. WHO. Methylene chloride health and safety guide. *IPCS Health and Safety Guide 6.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg006.htm (accessed 29/06/04)
4. Rioux JP, Myers RAM. Methylene chloride poisoning: a paradigmatic review. *J Emerg Med* 1988; **6:** 227–38.
5. Manno M, *et al.* Double fatal inhalation of dichloromethane. *Hum Exp Toxicol* 1992; **11:** 540–5.
6. Dhillon S, Von Burg R. Methylene chloride. *J Appl Toxicol* 1995; **15:** 329–35.
7. IARC/WHO. Dichloromethane. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 251–315. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
8. Chang YL, *et al.* Diverse manifestations of oral methylene chloride poisoning: report of 6 cases. *J Toxicol Clin Toxicol* 1999; **37:** 497–504.
9. Jacubovich RM, *et al.* Facial nerve palsy after acute exposure to dichloromethane. *Am J Ind Med* 2005; **48:** 389–92.

Pharmacokinetics

Dichloromethane is rapidly absorbed after inhalation and is also absorbed after ingestion and slowly through intact skin. It appears to be partially metabolised to carbon dioxide and carbon monoxide which are exhaled, although significant blood-carboxyhaemoglobin concentrations may be attained. Some unchanged dichloromethane is exhaled and small amounts are excreted in the urine.

Dichloropropane

Dicloropropano; Dicloruro de propileno; Propylene Dichloride; Дихлорпропан.

1,2-Dichloropropane.

$C_3H_6Cl_2$=113.0

CAS — 78-87-5.

UNII — RRZ023OFWL.

Description. Dichloropropane is a colourless, mobile, flammable liquid. Wt per mL about 1.16 g. B.p. about 96 degrees. Store in airtight containers.

Uses

Dichloropropane is used as an industrial solvent, dry cleaning agent, and agricultural defumigant.

Adverse Effects and Treatment

Dichloropropane is an irritant to the respiratory tract, eyes, and skin. Both acute and chronic exposure to dichloropropane may cause liver and kidney damage. Ingestion causes nausea, vomiting, diarrhoea, abdominal pain, headache, CNS depression, disseminated intravascular coagulation, and haemolytic anaemia. Inhalation produces similar effects to ingestion.

Acute exposure to dichloropropane should be treated with supportive and symptomatic therapy. Activated charcoal may be given to those who present within 1 hour of ingestion.

References.

1. Locatelli F, Pozzi C. Relapsing haemolytic-uraemic syndrome after organic solvent sniffing. *Lancet* 1983; **ii:** 220.
2. IARC/WHO. 1,2-Dichloropropane. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 1393–1400. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
3. Lazo-Torres AM, *et al.* Intoxicación por dicloropropano: comunicación de 2 casos. *Med Clin (Barc)* 2005; **124:** 318.

Diethyl Phthalate

DEP; Diéthyle, phtalate de; Diethylftalaat; Diethyl-ftalát; Diethylis Phthalas; Diethylphthalat; Dietil-ftalát; Dietilo ftalatas; Dietylftalat; Dietyyliftalaatti; Ethyl Phthalate; Ftalato de dietilo; Диэтилфталат.

Benzene-1,2-dicarboxylic acid diethyl ester.

$C_{12}H_{14}O_4$=222.2

CAS — 84-66-2.

UNII — UF064M00AF.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.* Also in *USNF.*

Ph. Eur. 8: (Diethyl Phthalate). A clear, colourless or very slightly yellow, oily liquid. Relative density 1.117 to 1.121. Practically insoluble in water; miscible with alcohol. Store in airtight containers.

USNF 31: (Diethyl Phthalate). A colourless, practically odourless, oily liquid. Sp. gr. 1.118 to 1.122 at 20 degrees. Insoluble in water; miscible with alcohol, with ether, and with other usual organic solvents. Store in airtight containers.

Uses

Diethyl phthalate is used as a denaturant of alcohol, for example in surgical spirit, and as a solvent and plasticiser.

Adverse Effects

Diethyl phthalate is irritant and, in high concentrations, causes CNS depression. There has been concern about potential toxicity resulting from exposure to phthalates used as plasticisers.

References.
1. Health and Safety Executive. Review of the toxicity of the esters of o-phthalic acid (phthalate esters). *Toxicity Review 14*. London: HMSO,1986.
2. Kamrin MA, Mayor GH. Diethyl phthalate: a perspective. *J Clin Pharmacol* 1991; **31:** 484–9.
3. Shea KM, *et al*. American Academy of Pediatrics Technical Report. Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics* 2003; **111:** 1467–74. [Re-affirmed May 2009, Retired January 2011]
4. Kamrin MA. Phthalate risks, phthalate regulation, and public health: a review. *J Toxicol Environ Health B* 2009; **12:** 157–74.

Preparations

Pharmacopoeial Preparations
BP 2014: Surgical Spirit.

Diethylene Glycol Esters

Diglycol Esters; PEG-2 Esters; Polyethylene Glycol 100 Esters.

NOTE. The nomenclature used for these esters is potentially confusing. Diethylene glycol is an ethylene oxide polymer and has thus sometimes been referred to as a polyethylene glycol (macrogol) although this term is more usually applied to oligomers containing larger numbers of ethylene glycol units. The molecular weight of diethylene glycol is slightly over 100, and esters of diethylene glycol have therefore sometimes been termed polyethylene glycol 100 esters.

Diethylene Glycol Monolaurate

Diethylene Glycol Laurate; Diglycol Laurate; PEG-2 Laurate; Polyethylene Glycol 100 Laurate.
2-(2-Hydroxyethoxy)ethyl dodecanoate.
$C_{16}H_{32}O_4$=288.4
CAS — 141-20-8.

Diethylene Glycol Mono-oleate

Diethylene Glycol Oleate; Diglycol Oleate; PEG-2 Oleate; Polyethylene Glycol 100 Oleate.
2-(2-Hydroxyethoxy)ethyl octadecenoate.
$C_{22}H_{42}O_4$=370.6
CAS — 106-12-7.

Diethylene Glycol Monostearate

Diethylene Glycol Stearate; Diglycol Stearate; PEG-2 Stearate; Polyethylene Glycol 100 Stearate.
2-(2-Hydroxyethoxy)ethyl octadecanoate.
$C_{22}H_{44}O_4$=372.6
CAS — 106-11-6.

NOTE. The name Diethylene Glycol Stearate has also been used for the palmitostearate (below).

Diethylene Glycol Palmitostearate

Diethylene Glycol Monopalmitostearate; Diéthylèneglycol, palmitostéarate de; Diethylenglycoli Monopalmitostearas; Diethylenglycoli Palmitostearas; Diethylenglykol monopalmitostearát; Diethylenglykol palmito stearát; Dietilenglicol, monopalmitoestearato de; Dietilenglikolio palmitostearatas; Dietilénglikol-monopalmitát és monosztearát; Dietyleenieglykolipalmitostearaatti; Dietylenglykolpalmitostearat; Диэтиленгликоля Монопальмитостеарат.
CAS — 106-11-6 (diethylene glycol monostearate); 36381-62-1 (diethylene glycol monopalmitate); 109-30-8 (diethylene glycol distearate).
UNII — 5A70WD5W3Z (diethylene glycol palmitostearate); 94YQ11Y95F (diethylene glycol stearate).

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* includes Diethylene Glycol Stearates.

Ph. Eur. 8: (Diethylene Glycol Palmitostearate). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids produced by esterification of diethylene glycol and stearic acid of vegetable or animal origin. It contains 45.0 to 60.0% of monoesters and 35.0 to 55.0% of diesters, and a maximum of 2.5% of free diethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43 degrees to 50 degrees. Protect from light.

USNF 31: (Diethylene Glycol Stearates). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 45.0% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43 degrees to 50 degrees. Store in airtight containers.

Profile

Diethylene glycol esters are esters of fatty acids with diethylene glycol. They are glycol ester nonionic surfactants (p. 2164.2) and have similar properties to glycerol esters (see under Glyceryl Palmitostearate, p. 2187.2). Diethylene glycol palmitostearate is used as an emulsifier and emollient in topical cosmetic and pharmaceutical preparations. The monolaurate and mono-oleate are used in cosmetic and personal care products.

Diethylene Glycol Ethers

PEG-2 Ethers; Polyethylene Glycol 100 Ethers; Polyoxyl 2 Ethers.

Diethylene Glycol Monoethyl Ether

Carbitol; DEGMEE; Diéthylèneglycol, éther monoéthylique de; Diethylenglycoli monoethylicum aetherum; Diethylenglycoli Monoethylicum Etherum; Diethylenglycolmonoethylether; Diethylenglykolmonoethyl ether; Dietilenglikolio monoetilo eteris; Dietiléngликol-monoetiléter; Dietyleeniglykolimonoetyylieetteri; Dietylenglykolmonoetyleter; Ethoxydiglycol.
3,6-Dioxaoctan-1-ol; 2-(2-Ethoxyethoxy)ethanol.
$C_6H_{14}O_3$=134.2
CAS — 111-90-0.
UNII — A1A1I8X02B.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Diethylene Glycol Monoethyl Ether). 2-(2-Ethoxyethoxy)ethanol, produced by condensation of ethylene oxide and alcohol, followed by distillation. A clear, colourless, hygroscopic liquid. Miscible with water, with acetone and with alcohol; miscible in certain proportions with vegetable oils; not miscible with mineral oils. Relative density about 0.991. Store in an airtight container under an inert gas.

USNF 31: (Diethylene Glycol Monoethyl Ether). Produced by condensation of ethylene oxide and alcohol, followed by distillation. A clear, colourless, hygroscopic liquid. Miscible with water, with acetone, and with alcohol; partially miscible with vegetable oils; immiscible with mineral oils. Specific gravity about 0.991. Store in airtight containers under an atmosphere of an inert gas, at a temperature not exceeding 35 degrees.

Profile

Diethylene glycol monoethyl ether is a glycol ether nonionic surfactant (p. 2164.2) used as a solubiliser and solvent. The monomethyl ether is also used.

Diethylene glycol ethers with fatty alcohols are also used but are included under the corresponding macrogol ethers.

Diisopropanolamine

Diisopropanolamina; Диизопропаноламин.
1,1′-Iminobis(propan-2-ol).
$C_6H_{15}NO_2$=133.2
CAS — 110-97-4.
UNII — 0W44HYL8T5.

Pharmacopoeias. In *USNF.*

USNF 31: (Diisopropanolamine). A mixture of isopropanolamines, consisting largely of diisopropanolamine. Store in airtight containers. Protect from light.

Profile

Diisopropanolamine is an organic base that is used as a neutralising agent in cosmetics and toiletries.

Dimethyl Sulfoxide *(BAN, USAN, rINN)*

Dimethyl Sulphoxide; Dimethyli Sulfoxidum; Dimethylis Sulfoxidum; Dimethylsulfoxid; Diméthylsulfoxyde; Dimetil Sülfoksit; Dimetil sulfóxido; Dimetilsolfossido; Dimetilsulfoksidas; Dimetilsulfóxido; Dimetil-szulfoxid; Dimetylosulfotlenek; Dimetylsulfoxid; Dimetyylisulfoksidi; DMSO; Methyl Sulphoxide; NSC-763; SQ-9453; Sulfóxido de dimetilo; Sulphinylbismethane; Диметилсульфоксид.
C_2H_6OS=78.13
CAS — 67-68-5.
ATC — G04BX13; M02AX03.
ATC Vet — QG04BX13; QM02AX03.
UNII — YOW8V9698H.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dimethyl Sulfoxide). A colourless hygroscopic liquid or crystals. F.p. not lower than 18.3 degrees. Relative density 1.100 to 1.104. Miscible with water and with alcohol. Store in airtight glass containers. Protect from light.

USP 36: (Dimethyl Sulfoxide). A clear, colourless, odourless, hygroscopic liquid. M.p. about 18.4 degrees. Sp. gr. 1.095 to 1.097. Soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Dimethyl sulfoxide is a highly polar substance with exceptional solvent properties for both organic and inorganic chemicals, and is widely used as an industrial solvent.

It has been reported to have a wide spectrum of pharmacological activity including membrane penetration, anti-inflammatory effects, local analgesia, weak bacteriostasis, diuresis, vasodilatation, dissolution of collagen, and free-radical scavenging.

The principal use of dimethyl sulfoxide is as a vehicle for drugs such as idoxuridine (p. 985.1); it aids penetration of the drug into the skin, and so may enhance the drug's effect. It is also used as a 50% aqueous solution for bladder instillation for the symptomatic relief of interstitial cystitis; doses of 50 mL are instilled and allowed to remain for 15 minutes. Treatment is repeated every 2 weeks initially.

Dimethyl sulfoxide has been given orally, intravenously, or topically for a wide range of indications including cutaneous and musculoskeletal disorders, but evidence of beneficial effects is limited.

Dimethyl sulfoxide is used as a cryoprotectant for various human tissues.

Amyloidosis. Oral or local dimethyl sulfoxide has been tried[1-3] as part of the management of some forms of amyloidosis (p. 819.3).

1. Ichida M, *et al*. Successful treatment of multiple myeloma-associated amyloidosis by interferon-alpha, dimethyl sulfoxide, and VAD (vincristine, adriamycin, and dexamethasone). *Int J Hematol* 2000; **72:** 491–3.
2. Malek RS, *et al*. Primary localized amyloidosis of the bladder: experience with dimethyl sulfoxide therapy. *J Urol (Baltimore)* 2002; **168:** 1018–20.
3. Amemori S, *et al*. Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. *J Gastroenterol* 2006; **41:** 444–9.

Cryopreservation. Dimethyl sulfoxide is used as a cryoprotectant in various assisted conception techniques.[1] Adverse effects have been reported in patients receiving haematopoietic stem cells cryopreserved in dimethyl sulfoxide (see under Adverse Effects, p. 2183.1).

1. Trounson AO. Cryopreservation. *Br Med Bull* 1990; **46:** 695–708.

Extravasation of antineoplastics. Several reports have suggested a role for topical dimethyl sulfoxide in the treatment of anthracycline extravasation.[1-4] The problem of antineoplastic extravasation and its management is discussed further on p. 731.3.

1. Lawrence HJ, Goodnight SH. Dimethyl sulfoxide and extravasation of anthracycline agents. *Ann Intern Med* 1983; **98:** 1025.
2. Olver IN, *et al*. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *J Clin Oncol* 1988; **6:** 1732–5.
3. Rospond RM, Engel LM. Dimethyl sulfoxide for treating anthracycline extravasation. *Clin Pharm* 1993; **12:** 560–1.
4. Bertelli G, *et al*. Dimethylsulphoxide and cooling after extravasation of antitumour agents. *Lancet* 1993; **341:** 1098.

Interstitial cystitis. Bladder instillation of dimethyl sulfoxide is used[1,2] in the symptomatic management of interstitial cystitis (p. 2348.1). Treatment usually consists of 50 mL of a 50% aqueous solution that is retained in the bladder for 15 minutes. This may be repeated every 1 to 2 weeks for 4 to 8 treatments, and overall response rates of 50 to 90% have been reported. Although relapse rates after a 4- to 8-week course of treatment are high (35 to 40%), about half of these patients will respond to additional dimethyl sulfoxide treatment. Maintenance therapy on either a regular or intermittent basis may be used.[1]

1. Parkin J, *et al*. Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis—a practical approach. *Urology* 1997; **49** (suppl 5A): 105–7.
2. Rössberger J, *et al*. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol* 2005; **39:** 73–7.

Osteoarthritis. Dimethyl sulfoxide has been applied topically in the treatment of osteoarthritis (p. 12.3) but a systematic review, which noted that empirical reports had suggested concentrations of 60 to 90% dimethyl sulfoxide were needed topically for therapeutic effect, found that it was not possible to draw any conclusions as to benefit;[1] many studies used suboptimal concentrations or were over inadequate time periods.

1. Brien S, *et al*. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2008; **16:** 1277–88.

Adverse Effects and Treatment

High concentrations of dimethyl sulfoxide applied to the skin may cause burning discomfort, itching, erythema, vesiculation, and urticaria. Continued use may result in scaling.

Systemic effects, including gastrointestinal disturbances, drowsiness, headache, and hypersensitivity reactions, may occur after use by any route. A garlic-like odour on the breath and skin is attributed to the formation of dimethyl sulfide (see Pharmacokinetics, below). Intravascular haemolysis has followed intravenous use. Local discomfort and spasm may occur when given by bladder instillation.

Treatment of adverse effects consists of symptomatic and supportive measures.

Reviews.

1. Brobyn RD. The human toxicology of dimethyl sulfoxide. *Ann N Y Acad Sci* 1975; **243:** 497–506.
2. Willhite CC, Katz PI. Toxicology updates: dimethyl sulfoxide. *J Appl Toxicol* 1984; **4:** 155–60.

Dimethyl sulfoxide given by intravenous infusion for spinal cord injury to 14 patients caused transient haemolysis and haemoglobinuria.[1] Infusion strengths greater than 10% were associated with grossly discoloured urine but there was no evidence of renal damage. In 2 patients, raised liver and muscle enzyme concentrations, mild jaundice, and evidence of haemolysis developed when given dimethyl sulfoxide intravenously for arthritis.[2] One also developed acute renal tubular necrosis, deterioration in level of consciousness, and evidence of cerebral infarction. Acute, reversible neurological deterioration in a patient has been associated with intravenous dimethyl sulfoxide.[3]

Adverse effects have also been reported in patients given haematopoietic stem cells cryopreserved in dimethyl sulfoxide. A patient with pre-existing diabetes insipidus[4] developed serum hyperosmolality when given stem cells after chemotherapy for a malignant germ-cell tumour; symptoms included severe headache, confusion, and abdominal pain. Acute neurotoxicity has also been reported,[5,6] although it appears to be rare;[5] 2 patients also had myocardial damage.[6]

1. Muther RS, Bennett WM. Effects of dimethyl sulfoxide on renal function in man. *JAMA* 1980; **244:** 2081–3.
2. Yellowlees P, *et al*. Dimethylsulphoxide-induced toxicity. *Lancet* 1980; **ii:** 1004–6.
3. Bond GR, *et al*. Dimethylsulphoxide-induced encephalopathy. *Lancet* 1989; **i:** 1134–5.
4. Thomé S, *et al*. Dimethylsulphoxide-induced serum hyperosmolality after cryopreserved stem-cell graft. *Lancet* 1994; **344:** 1431–2.
5. Mueller LP, *et al*. Neurotoxicity upon infusion of dimethylsulfoxide-cryopreserved peripheral blood stem cells in patients with and without pre-existing cerebral disease. *Eur J Haematol* 2007; **78:** 527–31.
6. Chen-Plotkin AS, *et al*. Encephalopathy, stroke, and myocardial infarction with DMSO use in stem cell transplantation. *Neurology* 2007; **68:** 859–61.

Precautions

When used as a penetrating basis for other drugs applied topically, dimethyl sulfoxide may enhance their toxic effects.

Since dimethyl sulfoxide has been associated with lens changes in *animals*, licensed product information recommends assessment of ophthalmic function every 6 months during long-term treatment of cystitis with intravesical instillation of dimethyl sulfoxide. Hepatic and renal function should also be assessed at intervals of 6 months. Bladder instillation may be harmful in patients with urinary-tract malignancy because of vasodilatation.

Interactions

Increased psychomotor impairment has been reported in patients who drank alcohol after topical exposure to dimethyl sulfoxide, including inadvertent occupational exposure.

For mention of an interaction between dimethyl sulfoxide and *sulindac*, see p. 135.2.

Pharmacokinetics

Dimethyl sulfoxide is readily absorbed by all routes. It is metabolised by oxidation to dimethyl sulfone (p. 2493.3) and by reduction to dimethyl sulfide. Dimethyl sulfoxide and the sulfone metabolite are excreted in the urine and faeces. Dimethyl sulfide is excreted through the lungs and skin and is responsible for the characteristic odour from patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Kemsol†; Rimso; ***Rus.***: Prostatilen (Простатилен); Silocast (Силокаст); ***UK***: Rimso; ***USA***: Rimso.

Multi-ingredient Preparations. ***Arg.***: Verrugard; ***Austria***: Dolobene; Verrumal; ***Braz.***: Dolobene†; ***China***: Dolobene (瑞乐平); ***Cz.***: Dolobene; Verrumal; ***Ger.***: Dolobene†; GeloBacin; Verrumal; ***Hong Kong***: Dolobene†; Verrumal; ***Hung.***: Dolobene; Verra-med; Verrumal; ***Israel***: Verrumal; ***Malaysia***: Verrumal; ***Pol.***: Brodacid; Dolobene†; ***Rus.***: Capsicam (Капсикам); Chondroitine-Akos (Хондроитин-Акос); Chondroxide (Хондроксид); Dolobene (Долобене); Espol (Эспол); Hondrofen (Хондрофен); ***Singapore***: Verrumal; ***Spain***: Artrodesmol Extra; ***Switz.***: Assan rem; Dolo Demotherm†; Dolobene; Histalgane mite; Histalgane; Sportusal Spray sine heparino; Sportusal; Venucreme; Venugel; Verra-med; Verrumal; ***Thai.***: Verrumal; ***Ukr.***: Capsicam (Капсикам); Chondrasil (Хондрасил)†; Chondroxide (Хондроксид); Dolobene (Долобене); Phytobene (Фитобене).

Pharmacopoeial Preparations

USP 36: Dimethyl Sulfoxide Irrigation.

Dimethylacetamide

Acetyldimethylamine; Ácido acético dimetilamida; Dimethylaceetamide; Dimethylacetamid; Diméthylacétamide; Dimethylacetamidum; Dimetilacetamida; Dimetilacetamidas; Dimetilacetammide; Dimetylacetamid; Dimetyletanamid; Dimetyloacetamid; Dimetyyliasetamidi; DMAC; Диметилацетамид.

NN-Dimethylacetamide.

C_4H_9NO=87.12

CAS — 127-19-5.

UNII — JCV5VDB3HY.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dimethylacetamide). A clear, colourless, slightly hygroscopic liquid. Relative density 0.941 to 0.944. B.p. about 165 degrees. Miscible with water, with alcohol, and with most common organic solvents. Store in airtight containers. Protect from light.

Uses

Dimethylacetamide is used as an industrial and pharmaceutical solvent.

Adverse Effects and Precautions

As for Dimethylformamide (below), although a disulfiram-like reaction with alcohol has not been reported.

A review[1] of the toxicology of dimethylacetamide with reference to its use as a vehicle for antineoplastics. A pharmacokinetic study[2] of the use of dimethylacetamide in children found no safety concerns. However, reversible hepatotoxicity has been reported[3] after occupational exposure.

1. Kim S-N. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metab Rev* 1988; **19:** 345–68.
2. Hempel G, *et al*. Cytotoxicity of dimethylacetamide and pharmacokinetics in children receiving intravenous busulfan. *J Clin Oncol* 2007; **25:** 1772–8.
3. Jung S-J, *et al*. Dimethylacetamide-induced hepatic injuries among spandex fibre workers. *Clin Toxicol* 2007; **45:** 435–9.

Handling. Suitable precautions should be taken to avoid skin contact with dimethylacetamide as it can penetrate skin and produce systemic toxicity.

Dimethylformamide

Dimethylformamid; Diméthylformamide; Dimetilamida del ácido fórmico; Dimetilformamid; Dimetilformamida; Dimetilformammide; Dimetylformamid; Dimetyloformamid; DMF; Диметилформамид.

NN-Dimethylformamide.

C_3H_7NO=73.10

CAS — 68-12-2.

UNII — 8696NH0Y2X.

Description. Dimethylformamide is a colourless liquid. Wt per mL about 0.95 g. B.p. about 153 degrees.

Uses

Dimethylformamide is used as an industrial solvent.

Adverse Effects and Precautions

Dimethylformamide is irritant. Gastrointestinal effects including nausea, vomiting, loss of appetite, and abdominal pain, CNS effects such as headache, dizziness, and weakness, and liver damage have been reported in workers occupationally exposed to the liquid or vapour. Some workers exposed to dimethylformamide have had a disulfiram-like effect after consumption of alcohol.

Reviews of the adverse effects of dimethylformamide.

1. WHO. Dimethylformamide. *Environmental Health Criteria 114*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc114.htm (accessed 30/06/04)
2. IARC/WHO. Dimethylformamide. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 545–74. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Effects on the liver. Exposure to dimethylformamide was considered to be the most likely cause of elevated liver enzyme values in 36 of 58 (62%) workers in a fabric coating factory.[1] Symptoms reported were generally mild and included anorexia, abdominal pain, nausea, headache, dizziness, and a disulfiram-type reaction to alcohol. In another report,[2] 3 of 4 workers with probable dimethylformamide liver toxicity presented with skin eruptions.

Hepatotoxicity has occurred after acute poisoning with a veterinary drug formulated in dimethylformamide. There were only minor increases in liver enzyme values in a patient who was treated early with acetylcysteine.[3]

1. Redlich CA, *et al*. Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 1988; **108:** 680–6.
2. Hamada M, *et al*. Occupational liver injury due to N,N-dimethylformamide in the synthetics industry. *Intern Med* 2009; **48:** 1647–50.
3. Buylaert W, *et al*. Hepatotoxicity of N,N-dimethylformamide (DMF) in acute poisoning with the veterinary euthanasia drug T-61. *Hum Exp Toxicol* 1996; **15:** 607–11.

Handling. Suitable precautions should be taken to avoid skin contact with dimethylformamide as it can penetrate skin and produce systemic toxicity.

Malignant neoplasms. There have been reports of testicular cancer in men occupationally exposed to dimethylformamide.[1] Such an association could not, however, be substantiated by epidemiological data[2] on 3859 male employees exposed to dimethylformamide between 1950 and 1970 and followed up to 1984. It has been suggested that although dimethylformamide may not itself be carcinogenic, it may increase absorption through the skin of heavy metal carcinogens, possibly including chromates.[3]

1. Levin SM, *et al*. Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet* 1987; **ii:** 1153.
2. Chen JL, Kennedy GL. Dimethylformamide and testicular cancer. *Lancet* 1988; **i:** 55.
3. Ducatman AM. Dimethylformamide, metal dyes, and testicular cancer. *Lancet* 1989; **i:** 911.

Pharmacokinetics

Dimethylformamide is absorbed after inhalation and through intact skin. It is excreted mainly in the urine as metabolites.

Diolamine *(plNN)*

Diaethanolamin; Dietanolamina; Dietanolammina; Dietanoloamina; Diethanolamin; Diethanolamine; Diolamina; Diolaminum; Диоламин.

Bis(2-hydroxyethyl)amine; 2,2′-Iminobisethanol.

$C_4H_{11}NO_2$=105.1

CAS — 111-42-2.

UNII — AZE0STDV2V.

Pharmacopoeias. In *USNF*.

USNF 31: (Diethanolamine). It is a mixture of olamines, consisting largely of diolamine. White or clear, colourless crystals, deliquescing in moist air, or a colourless liquid. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerol; slightly soluble to insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers. Protect from light.

Profile

Diolamine is an organic base that is used as an emulsifier and dispersant.

It is used to solubilise fusidic acid and sulfafurazole by the formation of the diolamine salt. It has been used for the preparation of salts of iodinated organic acids used as contrast media. It may be irritating to the skin and mucous membranes.

Dioxan

Diethylene Dioxide; Diethylene Ether; Dioksaan; Dioksaani; Dioksan; Dioxane; 1,4-Dioxano; Dioxano; 1,4-Dióxido de dietileno; Éter de dietileno; Диоксан.

1,4-Dioxane.

$C_4H_8O_2$=88.11

CAS — 123-91-1.

UNII — J8A3S10O7S.

NOTE. Do not confuse dioxan and dioxin (p. 2494.2).

Description. Dioxan is a colourless flammable liquid with an ethereal odour. Wt per mL about 1.03 g. B.p. about 101 degrees. Store in airtight containers.

Stability. It is dangerous to distil or evaporate dioxan unless precautions have been taken to remove explosive peroxides.

Uses

Dioxan is used as an industrial solvent.

Adverse Effects, Treatment, and Precautions

Dioxan vapour is irritant to mucous membranes. High concentrations may cause nausea and vomiting, and CNS depression with headache, dizziness, drowsiness, and in severe cases unconsciousness. On repeated exposure, severe hepatic and renal damage, including necrotic changes, can occur and may be fatal. Direct contact with liquid dioxan can result in dermatitis. Dioxan has been shown to be carcinogenic in *animals*.

Treatment consists of removal from exposure and general supportive and symptomatic measures.

Handling. Suitable precautions should be taken to avoid skin contact with dioxan as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Dioxan is absorbed after inhalation and through the skin. It is metabolised by oxidation to β-hydroxyethoxy-acetic acid.

Emulsifying Waxes

Cera emulgente; Cera Emulsificans; Cera emulsionante; Cetylanum; Emulsif. Wax; Эмульгирующий Воск.
CAS — 8014-38-8.

Pharmacopoeias. *Br., Eur.* (see p. vii), and *USNF* all have monographs for different emulsifying waxes.

Ph. Eur. 8: (Cetostearyl Alcohol (Type A), Emulsifying; Alcohol Cetylicus et Stearylicus Emulsificans A). A mixture containing not less than 80% cetostearyl alcohol and not less than 7% sodium cetostearyl sulfate, both calculated with reference to the anhydrous substance. A suitable buffer may be added. White or pale yellow, waxy mass, plates, flakes, or granules. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; slightly soluble in alcohol.

Ph. Eur. 8: (Cetostearyl Alcohol (Type B), Emulsifying; Alcohol Cetylicus et Stearylicus Emulsificans B). A mixture containing not less than 80% cetostearyl alcohol and not less than 7% sodium laurilsulfate, both calculated with reference to the anhydrous substance. A suitable buffer may be added. White or pale yellow, waxy mass, plates, flakes, or granules. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; slightly soluble in alcohol.

BP 2014: (Emulsifying Wax; Anionic Emulsifying Wax). It is prepared from 9 parts of cetostearyl alcohol and 1 part of sodium laurilsulfate or sodium salts of similar sulfated higher primary aliphatic alcohols. An almost white or pale yellow, waxy solid or flakes, becoming plastic when warmed. Practically insoluble in water, forming an emulsion; partly soluble in alcohol.

BP 2014: (Cetomacrogol Emulsifying Wax; Non-ionic Emulsifying Wax). It is prepared from 4 parts of cetostearyl alcohol and 1 part of macrogol cetostearyl ether (22). A white or almost white, waxy solid or flakes melting when heated to a clear almost colourless liquid. Practically insoluble in water, producing an emulsion; moderately soluble in alcohol; partly soluble in ether.

USNF 31: (Emulsifying Wax). It is prepared from cetostearyl alcohol containing a polyoxyethylene derivative of a fatty acid ester of sorbitan. M.p. 50 degrees to 54 degrees. It is a creamy-white, wax-like solid, with a mild characteristic odour. Insoluble in water; soluble in alcohol; freely soluble in chloroform, in ether, in most hydrocarbon solvents, and in aerosol propellants.

Profile

Emulsifying waxes are mixtures of fatty alcohols with surfactants. They are mainly based on cetostearyl alcohol (p. 2178.1) and can be classified as anionic, cationic, or nonionic depending on the surfactant used (see Emulsifying and Solubilising Agents, p. 2164.1). Pharmacopoeias may use the name Emulsifying Wax for either anionic or nonionic forms, and nomenclature may therefore be confusing.

Emulsifying waxes are used to produce oil-in-water emulsions that are stable over a wide pH range; their compatibilities depend on the surfactant used. Added to fatty or paraffin bases they produce preparations that are absorbed and nongreasy when rubbed into the skin. They are a constituent of hydrophilic ointment bases for so called washable ointments, and are also used in rectal preparations, and in cosmetics.

Sunscreen activity. Emulsifying ointment, which contains emulsifying wax with white soft paraffin and liquid paraffin, was found to have major sunscreen activity in clinically normal skin.[1] It should not be used before phototherapy or in phototesting procedures.

1. Cox NH, Sharpe G. Emollients, salicylic acid, and ultraviolet erythema. *Lancet* 1990; **335:** 53–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Epaderm; Epaderm; ***Irl.***: Silcocks Base; ***Malaysia***: Aqua Cream; ***UK***: Epaderm; Hydromol.

Pharmacopoeial Preparations
BP 2014: Aqueous Cream; Emulsifying Ointment.

Eosin

CI Acid Red 87; Colour Index No. 45380; D & C Red No. 22; Eosin Y; Eosina; Éosine Disodique; Eozin; Eozyna; Эозин.
The disodium salt of 2′,4′,5′,7′-tetrabromofluorescein .
$C_{20}H_6Br_4Na_2O_5$=691.9
CAS — 548-26-5; 17372-87-1.
ATC — D08AX02.
ATC Vet — QD08AX02.
UNII — TDQ283MPCW.

Pharmacopoeias. In *Fr.*

Uses

The name eosin is used for a range of red synthetic dyes that are derivatives of bromofluorescein. It is most commonly used for Eosin Y, the tetrabromo derivative, but Eosin B, the dibromodinitro derivative, has also been widely used.

Eosin has been incorporated in solution-tablets to give a distinctive colour to solutions prepared from them. It is also used in cosmetics.

Eosin has been used as a topical antiseptic in nappy rash, burns and other skin conditions, although other drugs are usually preferred.

Adverse Effects

Hypersensitivity. Contact dermatitis associated with the use of eosin in cosmetics such as lipsticks was once relatively common but the incidence decreased with reduced use of eosin and the availability of purer forms. There have also been cases reported with topical application of antiseptic preparations containing eosin, which one report[1] suggested might be due to an impurity. However, another[2] implicated eosin itself after patch tests were performed with various products and pure tetrabromofluorescein.

1. Tomb RR. Allergic contact dermatitis from eosin. *Contact Dermatitis* 1991; **24:** 27–9.
2. Koch P, *et al.* Allergic contact dermatitis from purified eosin. *Contact Dermatitis* 1995; **32:** 92–5.

Epichlorohydrin

Epichloorhydrine; Epichlorhydrin; Epichlorohydryna; Epiclorhidrina; Эпихлоргидрин.
1-Chloro-2,3-epoxypropane.
C_3H_5ClO=92.52
CAS — 106-89-8.
UNII — 08OOR508C0.

Description. Epichlorohydrin is a colourless, flammable liquid. Wt per mL about 1.18g. B.p. 115 degrees to 118 degrees. Store in airtight containers.

Stability. The vapour of epichlorohydrin forms explosive mixtures with air. Harmful gases including phosgene are liberated on heating of epichlorohydrin.

Uses

Epichlorohydrin is used as an industrial solvent.

Adverse Effects and Precautions

Epichlorohydrin is irritant. It has been shown to be carcinogenic in *animals*.

References to the toxicity of epichlorohydrin.

1. WHO. Epichlorohydrin. *Environmental Health Criteria 33.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc33.htm (accessed 30/06/04)
2. WHO. Epichlorohydrin health and safety guide. *IPCS Health and Safety Guide 8.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg008.htm (accessed 30/06/04)
3. Health and Safety Executive. Ammonia, 1-chloro-2,3-epoxypropane (epichlorohydrin), carcinogenicity of cadmium and its compounds. *Toxicity Review 24.* London: HMSO, 1991.
4. IARC/WHO. Epichlorohydrin. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 603–28. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
5. Kolman A, *et al.* Genotoxic effects of ethylene oxide, propylene oxide and epichlorohydrin in humans: update review (1990–2001). *Mutat Res* 2002; **512:** 173–94.

Handling. Suitable precautions should be taken to avoid skin contact with epichlorohydrin as it can penetrate skin and produce systemic toxicity.

Erythritol

Eritrit; Eritritolis; Érythritol; Erythritolum; Erytritol; Erytritoli; Erytrytol; *meso*-Erythritol; Tetrahydroxybutane; Эритрит.
(2*R*,3*S*)-Butane 1,2,3,4-tetrol.
$C_4H_{10}O_4$=122.1
CAS — 149-32-6.
UNII — RA96B954X6.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Erythritol). A white or almost white, crystalline powder or free-flowing granules. Freely soluble in water; very slightly soluble in alcohol.

USNF 31: (Erythritol). A white or almost white crystalline powder or free-flowing granules. Freely soluble in water; very slightly soluble in alcohol,

Profile

Erythritol is a sugar alcohol used as a sweetener and tablet diluent.

Erythrosine

CI Food Red 14; Colour Index No. 45430; E127; Eritrosin BS; Eritrosina; Eritrozin; Eritrozinas; Erythrosin; Érythrosine; Erythrosine BS; Erythrosine Sodium; Erytrosin; Erytrozyna; FD & C Red No. 3; Эритрозин.
The monohydrate of the disodium salt of 2′,4′,5′,7′-tetraiodofluorescein .
$C_{20}H_8I_4Na_2O_5.H_2O$=897.9
CAS — 568-63-8 (anhydrous erythrosine sodium); 16423-68-0 (anhydrous erythrosine sodium); 49746-10-3 (erythrosine sodium monohydrate).
UNII — PN2ZH5LOQY.

Profile

Erythrosine is a synthetic dye used as a colouring agent for medicines, foods, and cosmetics. It is also used as a disclosing agent for plaque on teeth.

Although early *animal* studies had indicated that erythrosine might have an adverse effect on the thyroid gland, a review[1] of the evidence and later studies, suggested that erythrosine was not genotoxic or mutagenic and was suitable for use as a food colour. Similarly, no evidence was found to support restricting its use in pharmaceutical products.[2]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. European Commission. Opinion on toxicological data on colouring agents for medicinal products: erythrosin, adopted by the Scientific Committee on Medicinal Products and Medical Devices on 21 October 1998. Available at: http://ec.europa.eu/health/scientific_committees/emerging/opinions/scmpmd/scmp_out08_en.htm (accessed 23/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Revelplac; ***Austral.***: DiscloGel; DiscloTabs; ***Canad.***: Chrom-O-Red; ***UK***: Ceplac.

Multi-ingredient Preparations. ***Arg.***: Revelplac 2001.

Ethyl Acetate

Acetat d'etil; Acetato de etila; Acetato de etilo; Acetato di etile; Acetic Ether; Acetoxietano; Aethylis Acetas; Aethylium Aceticum; Essigester; Essigsäureethylester; Éster etil acético; Éster etílico del ácido acético; Etanoato de etilo; Éter acético; Éthanoate d'éthyle; Ethyl Ethanoate; Ethylacetaat; Ethylacetat; Ethyl-acetát; Éthyle, acétate d'; Ethylis acetas; Etil asetat; Etil-acetát; Etilacetatas; Etilacetāts; Etylacetat; Etylu octan; Etyyliasetaatti; Octan ethylnatý; Vinagre de nafta; Этилацетат.
$C_4H_8O_2$=88.11
CAS — 141-78-6.
UNII — 76845O8NMZ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Ethyl Acetate). A colourless, clear, volatile liquid. Relative density 0.898 to 0.902. B.p. 76 degrees to 78 degrees. Soluble in water; miscible with alcohol, with acetone, and with dichloromethane. Store at a temperature not exceeding 30 degrees. Protect from light.

USNF 31: (Ethyl Acetate). A transparent, colourless, flammable liquid having a fragrant, refreshing, slightly acetous odour. Sp. gr. 0.894 to 0.898. Soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers at a temperature not exceeding 40 degrees.

Uses

Ethyl acetate is used as a flavour and solvent in pharmaceutical preparations. It is also used in industry as a solvent and as an extraction solvent in food processing.

Adverse Effects

Ethyl acetate is irritant to mucous membranes. High concentrations may cause CNS depression. Ethyl acetate may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

For discussion of neurotoxicity after occupational exposure to solvents and the absence of such an effect with ethyl acetate, see under Toluene, p. 2216.2.

Ethyl Cinnamate

Cinamato de etilo; Cinnamate d'éthyle; Ethylcinnamaat; Ethylcinnamát; Zimtsäureethylester; Этилциннамат.
Ethyl (*E*)-3-phenylprop-2-enoate.
$C_{11}H_{12}O_2$=176.2
CAS — 103-36-6.
UNII — C023P3M5JJ.

Pharmacopoeias. In *Br.*

BP 2014: (Ethyl Cinnamate). A clear, colourless or almost colourless liquid with a fruity, balsamic odour. Practically insoluble in water; miscible with most organic solvents.

Profile

Ethyl cinnamate is used as a flavour and perfume; it is an ingredient of Tolu-flavour Solution (BP 2014).

Preparations

Pharmacopoeial Preparations
BP 2014: Tolu-flavour Solution.

Ethyl Lactate

Ethyllactat; Etilo, lactato de; Milchsäureethylester; Mleczan etylu; Этиллактат.
$C_5H_{10}O_3$=118.1
CAS — 97-64-3.
UNII — F3P750VW8I.

Profile

Ethyl lactate is used in the flavouring of pharmaceutical preparations and foods. It is also used as a solvent.

Ethyl lactate has been applied topically in the treatment of acne vulgaris. It is reported to lower the pH within the skin thereby exerting a bactericidal effect.

Ethyl Oleate

Aethylis Oleas; Éthyle, oléate d'; Ethylis Oleas; Ethyloleat; Ethyl-oleát; Etil-oleát; Étiloleatas; Etyloleat; Etyylioleaatti; Oleato de etilo; Этилолеат.
$C_{20}H_{38}O_2$=310.5
CAS — 111-62-6.
UNII — Z2Z439864Y.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Ethyl Oleate). A clear, pale yellow or colourless liquid. It consists of the ethyl esters of fatty acids, mainly oleic acid. It may contain a suitable antoxidant. Practically insoluble in water; miscible with alcohol, with dichloromethane, and with petroleum spirit (40 degrees to 60 degrees). Protect from light.

USNF 31: (Ethyl Oleate). It consists of esters of ethyl alcohol and high-molecular-weight fatty acids, principally oleic acid. A mobile, practically colourless liquid. Insoluble in water; miscible with alcohol, with vegetable oils, with liquid paraffin, and with most organic solvents. Store in airtight containers. Protect from light.

Incompatibility. Ethyl oleate dissolves some types of rubber and causes others to swell.

Profile

Ethyl oleate is used as an oily vehicle.

Ethyl Vanillin

Etilvanilina; Этилванилин.
3-Ethoxy-4-hydroxybenzaldehyde.
$C_9H_{10}O_3$=166.2
CAS — 121-32-4.
UNII — YC9ST449YJ.

Pharmacopoeias. In *USNF.*

USNF 31: (Ethyl Vanillin). Fine, white or slightly yellowish crystals with a vanilla-like odour. M.p. is between 76 degrees and 78 degrees. Soluble 1 in 100 of water at 50 degrees and 1 in 2 of alcohol; freely soluble in chloroform, in ether, and in solutions of alkali hydroxides. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Profile

Ethyl vanillin is used as a flavour and in perfumery to impart the odour and taste of vanilla.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.:* Granugen†.

Ethylcellulose *(rINN)*

Cellulose Ethyl Ether; E462; Éthylcellulose; Ethylcellulosum; Ethylcelulosa; Etilceliuliozė; Etilcelulóz; Etilcelulosa; Etylcellulosa; Etyyliselluloosa; Этилцеллюлоза.
CAS — 9004-57-3.
UNII — 7Z8S9VYZ4B (ethylcellulose); H3UP11403C (ethylcellulose (7 cps)); 6I475159RA (ethylcellulose (50 cps)); 47MLB0F1MV (ethylcellulose (100 cps)).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Int.* Also in *USNF.*

Ph. Eur. 8: (Ethylcellulose). A partly *O*-ethylated cellulose. It contains 44 to 51% of ethoxy ($-OC_2H_5$) groups, calculated on the dried basis. A white to yellowish-white, odourless or almost odourless, powder or granular powder. Solutions of ethylcellulose may show a slight opalescence. Practically insoluble in water, in glycerol (85%), and in propylene glycol; soluble in dichloromethane and in a mixture of 20 parts alcohol and 80 parts toluene (w/w); slightly soluble in ethyl acetate and methyl alcohol.

USNF 31: (Ethylcellulose). A partly *O*-ethylated cellulose. It contains 44.0 to 51.0% of ethoxy groups, calculated with reference to the dried substance. A free-flowing white to light tan powder. Its aqueous suspensions are neutral to litmus. Insoluble in water, in glycerol, and in propylene glycol. Ethylcellulose containing less than 46.5% of ethoxy groups is freely soluble in chloroform, in methyl acetate, in tetrahydrofuran, and in mixtures of aromatic hydrocarbons with alcohol; ethylcellulose containing 46.5% or more of ethoxy groups is freely soluble in alcohol, in chloroform, in ethyl acetate, in methyl alcohol, and in toluene.

Profile

Ethylcellulose is used as a binder in tablets and as a coating material for tablets, granules, and microcapsules. It is also used as a thickening agent.

Preparations

Pharmacopoeial Preparations
USNF 31: Ethylcellulose Aqueous Dispersion; Ethylcellulose Dispersion Type B.

Ethylene Glycol Esters

Ethylene Glycol Distearate

Glycol Distearate (USAN).
1,2-Ethanediyl Octadecanoate.
$C_{38}H_{74}O_4$=595.0
CAS — 627-83-8.
UNII — 13W7MDN21W.

NOTE. The name Glycol Stearate has been used for various esters of ethylene glycol with stearic acid, including ethylene glycol distearate.

Ethylene Glycol Monopalmitostearate

Estearato de etilenglicol; Ethylene Glycol Monostearate; Ethylene Glycol Stearate; Éthylène Glycol (Stéarate d'); Éthylèneglycol, monopalmitostéarate d'; Ethyleneglycoli Monopalmitostearas; Ethylenglycoli Monopalmitostearas; Ethylenglycoli Monostearas; Ethylenglycolmonopalmitostearat; Ethylenglykol-monopalmitostearát; Ethyleni Glycoli Stearas; Etilenglicol, monopalmitoestearato de; Etilenglikolio monopalmitostearatas; Etilénglikol-monopalmitát és monosztearát; Etyleeniglykolimonopalmitostearaatti; Etylenglykol-monopalmitostearat; Monoestearato de etilenglicol; Этиленгликоля Монопальмитостеарат.
CAS — 111-60-4 (ethylene glycol monostearate); 4219-49-2 (ethylene glycol monopalmitate); 91031-31-1 (ethylene glycol C16-C18 fatty acid esters).
UNII — 0324G66D0E.

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* includes Ethylene Glycol Stearates.

Ph. Eur. 8: (Ethylene Glycol Monopalmitostearate). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid and not more than 5% of free ethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54 degrees to 60 degrees. Protect from light.

USNF 31: (Ethylene Glycol Stearates). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54 degrees to 60 degrees. Store in airtight containers.

Profile

Ethylene glycol distearate and monopalmitostearate are glycol ester nonionic surfactants (p. 2164.2) used as emulsion stabilisers, emollients, and opacifying agents; they have similar properties to glyceryl stearates (p. 2187.1). Ethylene glycol monolaurate and mono-oleate have also been used.

Ethylenediamine

Edamina; Édamine; Edamine (USAN); Edamine (pINN); Edaminum; Ethyleendiamine; Ethylendiamin; Ethylendiaminum; Éthylènediamine; Ethylenediaminum; Etilén-diamin; Etilendiamina; Etilendiaminas; Etilendiammina; Etilenodiamina; Etyleenidiamiini; Etylendiamin; Etylenodiamina; Эдамин.
$C_2H_8N_2$=60.10
CAS — 107-15-3 (anhydrous ethylenediamine); 6780-13-8 (ethylenediamine monohydrate).
UNII — 60V9STC53F.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Ethylenediamine). A clear, colourless or slightly yellow, hygroscopic liquid. On exposure to air, white fumes are evolved. On heating it evaporates completely. Miscible with water and with alcohol. Store in airtight containers. Protect from light.

USP 36: (Ethylenediamine). A clear, colourless or only slightly yellow liquid having an ammonia-like odour. It is strongly alkaline and may readily absorb carbon dioxide from the air to form a non-volatile carbonate. Miscible with water and with alcohol. Store in well-filled, airtight, glass containers.

Uses and Administration

Ethylenediamine or ethylenediamine hydrate forms a stable mixture with theophylline to produce aminophylline or aminophylline hydrate. Ethylenediamine is widely used in the chemical and pharmaceutical industries and as an ingredient of some topical creams.

Adverse Effects

Ethylenediamine is irritant to the skin and to mucous membranes. Severe exfoliative dermatitis has been reported after systemic use of preparations containing ethylenediamine. Hypersensitivity reactions are common. Concentrated solutions cause skin burns. Headache, dizziness, shortness of breath, nausea, and vomiting have also been reported after exposure to fumes. Ethylenediamine splashed onto the skin or eyes should be removed by flooding with water for a prolonged period.

Precautions

Skin reactions may occur in patients given aminophylline after they have become sensitised to ethylenediamine. Cross-sensitivity with edetic acid and with some antihistamines has been reported.

Cross-sensitivity. It was reported that some topical corticosteroid creams, including *Tri-Adcortyl* in the UK,[1] and

Kenacomb, *Halcicomb*, and *Viaderm* in Canada,[2] contained ethylenediamine and could cause unexpected cross-sensitivity reactions with piperazine[1] or aminophylline.[2]

1. Wright S, Harman RRM. Ethylenediamine and piperazine sensitivity. *BMJ* 1983; **287**: 463–4.
2. Hogan DJ. Excipients in topical corticosteroid preparations in Canada. *Can Med Assoc J* 1989; **141**: 1032.

Ferric Oxide

Demir Oksitler; E172 (iron oxides or hydroxides); Eisen(III)-oxid; Ferri Oxidum Flavum (yellow ferric oxide); Ferri Oxidum Fuscum (brown ferric oxide); Ferri Oxidum Nigrum (black ferric oxide); Ferri Oxidum Rubrum (red ferric oxide); Ferrum Oxydatum Flavum (yellow ferric oxide); Ferrum Oxydatum Fuscum (brown ferric oxide); Ferrum Oxydatum Nigrum (black ferric oxide); Ferrum Oxydatum Rubrum (red ferric oxide); Hierro, óxido de; IJzer(III)oxide; Järn(III)oxid; Ossido Ferrico; Oxid Železitý; Óxido de Ferro (III); Óxido Férrico; Oxyde Ferrique; Rauta(III)oksidi; Tlenek Żelaza(III); Vas(III)-oxid; Оксид Железа.

CAS — 51274-00-1; 1309-37-1.

UNII — 1K09F3G675 (ferric oxide red); EX438O2MRT (ferric oxide yellow).

Pharmacopoeias. *Chin.* includes red, black, brown, purple, and yellow ferric oxide. *It.* includes both red and yellow ferric oxide. *USNF* allows the basic colours of red or yellow ferric oxide or mixtures of these.

USNF 31: (Ferric Oxide). A powder exhibiting two basic colours (red and yellow), or other shades produced on blending the basic colours. Insoluble in water and in organic solvents; dissolves in hydrochloric acid upon warming, a small amount of insoluble residue usually remaining.

Profile

Ferric oxide is used for colouring medicines, contact lenses, cosmetics, and foodstuffs.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Herbadict; ***Rus.***: Liv 52 (Лив 52); ***Ukr.***: Liv 52 (Лив 52).

Formamide

Carbamaldehído; Carbamaldehyde; Formamid; Formamida; Metanamida; Methanamide; Формамид.

CH_3NO=45.04

CAS — 75-12-7.

UNII — 4781T907ZS.

Description. Formamide is a colourless, oily liquid. B.p. 210 degrees. Wt per mL, about 1.13 g.

Profile

Formamide is used as an industrial solvent. It is reported to be irritant.

Gastric Mucin *(BAN)*

Mucina gástrica; Муцин; Желудочная Слизь.

Profile

Gastric mucin is a high-molecular-weight glycoprotein precipitated by alcohol (60%) after digestion of the stomach linings of hogs by pepsin and hydrochloric acid. It is used in artificial saliva formulations for dry mouth (p. 2175.3) as an oral spray containing 3.5% or as lozenges.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Neth.***: Saliva Orthana; ***UK***: AS Saliva Orthana; AS Saliva Orthana.

Gellan Gum

E418; Gellángumi; Goma gellan; Gomme gellane; Геллановая Камедь.

CAS — 71010-52-1.

UNII — 7593U09I4D.

Pharmacopoeias. In *USNF.*

USNF 31: (Gellan Gum). A high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Pseudomonas elodea*, purified by recovery with isopropyl alcohol, and then dried and milled. It is a heteropolysaccharide comprising a tetrasaccharide repeating unit of one rhamnose, one glucuronic acid, and two glucose units. The glucuronic acid is neutralised to mixed potassium, sodium, calcium, and magnesium salts. It may contain acyl (glyceryl and acetyl) groups as the *O*-glycosidically linked esters. An off-white powder. Soluble in hot or in cold deionised water.

Profile

Gellan gum is a sphingan polysaccharide produced by the bacterium *Pseudomonas elodea* (*Sphingomonas elodea*). It is used to produce gels and as a stabilising and suspending agent in pharmaceutical preparations. It is also used in the food and cosmetics industries.

References.

1. Fialho AM, *et al.* Occurrence, production, and applications of gellan: current state and perspectives. *Appl Microbiol Biotechnol* 2008; **79:** 889–900.

Gentisic Acid Ethanolamide

Etanolamida del ácido gentísico.

2,5-Dihydroxybenzoic acid ethanolamide.

$C_9H_{11}NO_4$=197.2

CAS — 61969-53-7.

UNII — H4E039OIGX.

Profile

Gentisic acid ethanolamide has been used as a complexing agent in the manufacture of pharmaceutical preparations.

Glycerol Formal

Formaldehyde Glycerol; Glycérol formal; Glycerol-formalum; Methylene Glycerin; Глицерол Формаль.

A mixture of the two isomers 4-hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane present in a constant ratio of 40:60 respectively.

$C_4H_8O_3$=104.1

CAS — 4740-78-7 (5-hydroxy-1,3-dioxane); 5464-28-8 (4-hydroxymethyl-1,3-dioxolane).

UNII — 3L7GR2604E (glycerol formal); F6UP32GBII (5-hydroxy-1,3-dioxane); Q45U46I791 (4-hydroxymethyl-1,3-dioxolane).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Glycerol Formal). A clear, colourless liquid. Miscible with water and with alcohol. Store under nitrogen, in airtight containers.

Profile

Glycerol formal is used as a pharmaceutical solvent.

Glyceryl Behenate

Behenin; Behenoylglycerol; Docosanoin; Glicerol, behenato de; Глицерил Бегенат.

1,2,3-Propanetriol docosanoate.

CAS — 77538-19-3 (glyceryl behenate); 30233-64-8 (glyceryl monobehenate); 99880-64-5 (glyceryl dibehenate); 18641-57-1 (glyceryl tribehenate).

UNII — R8WTH25YS2.

NOTE. The name docosanoin has been used for glyceryl behenate; distinguish from docosanol (p. 974.3), which is behenyl alcohol.

Pharmacopoeias. In *USNF. Eur.* (see p. vii) includes Glycerol Dibehenate.

Ph. Eur. 8: (Glycerol Dibehenate; Glyceroli Dibehenas). A mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 15 to 23% of monoacylglycerols, 40 to 60% of diacylglycerols, and 21 to 35% of triacylglycerols, obtained by esterification of glycerol and behenic acid. A hard, waxy mass or powder or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 65 degrees to 77 degrees.

USNF 31: (Glyceryl Behenate). A mixture of glycerides of fatty acids, mainly behenic acid. A fine powder with a faint odour. M.p. about 70 degrees. Practically insoluble in water and in alcohol; soluble in chloroform. Store in airtight containers at a temperature not exceeding 35 degrees.

Profile

Glyceryl behenates are glycerol ester nonionic surfactants (p. 2164.2). They are used as lubricants, binders, and coatings in tablet-making, including modified-release oral preparations, and as emollients and emulsifiers in creams and lotions. They are also used in foods and cosmetics.

Glyceryl Mono- and Di-esters

E471 (mono- and di-glycerides of fatty acids); Glycerol Mono- and Di-esters; Mono- and Di-glycerides; Mono y diglicéridos; Моно- и Диглицериды.

Pharmacopoeias. In *USNF.*

USNF 31: (Mono- and Di-glycerides). A mixture of glycerol mono- and di-esters, with minor amounts of tri-esters, of fatty acids from edible oils. It contains not less than 40% of monoglycerides. It may contain suitable stabilisers. Store in airtight containers. Protect from light.

Profile

Glyceryl mono- and di-esters are mixtures of the glycerol esters of edible fatty acids. They are glycerol ester nonionic surfactants (p. 2164.2) and are used as emulsifying agents and food additives. Mixtures containing varying proportions of mono-, di-, and tri-esters are available and have differing properties; specific mixtures containing mainly esters of a single fatty acid are also used. Self-emulsifying forms (self-emulsifying mono- and diglycerides of food fatty acids) containing a small amount of soap or another surfactant are available for some of these mixtures; self-emulsifying glyceryl stearate is a commonly used example (see Glyceryl Stearates, p. 2187.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Grassolind Neutral.

Glyceryl Monocaprylocaprate

Glycerol Monocaprylocaprate; Glyceroli Monocaprylocapras; Glycerolmonocaprylocaprat.

CAS — 91744-32-0 (C8-10 mono-, di- and triglycerides); 26402-22-2 (glyceryl monocaprate); 26402-26-6 (glyceryl monocaprylate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Glycerol Monocaprylocaprate). A mixture of monoacylglycerols, mainly mono-*O*-octanoylglycerol and mono-*O*-decanoylglycerol, containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with octanoic and decanoic acids, followed by a distillation step in the case of glycerol monocaprylocaprate (type II). Content of glycerol monocaprylocaprate (type I): monoacylglycerols: 45 to 75%; diacylglycerols: 20 to 50%; triacylglycerols: maximum 10%. Content of glycerol monocaprylocaprate (type II): monoacylglycerols: minimum 80%; diacylglycerols: maximum 20%; triacylglycerols: maximum 5%. A colourless or slightly yellow, oily liquid or soft mass. Practically insoluble in water; very soluble in alcohol; freely soluble in dichloromethane.

Profile

Glyceryl monocaprylocaprate, a mixture of glyceryl caprate and glyceryl caprylate (p. 2562.3), is a glycerol ester nonionic surfactant (p. 2164.2). It is used as a solubiliser and emulsifier in pharmaceutical preparations.

Glyceryl Monolinoleate

Glicerin-monolinoleát; Glicerol, monolinoleato de; Glicerolio monolinoleatas; Glycerol Monolinoleate; Glycérol, monolinoléate de; Glyceroli monolinoleas; Glycerol-monolinolát; Glycerolmonolinoleat; Glyceryl Octadecadienoate; Glyserolimonolinoleaatti; Linoleoylglycerol; Monolinolein; Глицерилмонолинолеат.

CAS — 26545-74-4.

UNII — 4763AXI84L.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Glycerol Monolinoleate). A mixture of monoacylglycerols, mainly mono-oleoylglycerol and monolinoleoylglycerol, with variable quantities of di- and triacylglycerols. It contains 32 to 52% of monoacylglycerols, 40 to 55% of diacylglycerols, and 5 to 20% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of linoleic acid. A suitable antoxidant may be added.

Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Glyceryl Monolinoleate). A mixture of monoglycerides, mainly glyceryl mono-oleate and glyceryl monolinoleate, with variable quantities of diglycerides and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of linoleic acid. It contains 32 to 52% of monoglycerides, 40 to 55% of

diglycerides, and 5 to 20% of triglycerides. A suitable antoxidant may be added.

Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile

Glyceryl monolinoleate is a glycerol ester nonionic surfactant (p. 2164.2). It is used as an emulsifying and/or solubilising agent.

Glyceryl Mono-oleate

Glicerol, monooleato de; Glycerol Monooleate; Glycérol, mono-oléate de; Glyceroli mono-oleas; Glyceryl Monooleate; Glyceryl Octadecenoate; Monolein; Oleoylglycerol; Глицерилмоноолеат.

CAS — 25496-72-4.
UNII — 4PC054V79P.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Glycerol Mono-oleates). Mixtures of monoacylglycerols, mainly mono-oleoylglycerol, with variable quantities of di- and triacylglycerols. They are defined by the nominal content of monoacylglycerols and obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of oleic acid, or by esterification of glycerol by oleic acid. A suitable antoxidant may be added.

Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Glyceryl Monooleate). A mixture of monoglycerides, mainly glyceryl mono-oleate, with variable quantities of di- and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of oleic acid, or by esterification of glycerol with oleic acid of vegetable or animal origin. It is defined by the nominal content of monoglycerides. A suitable antoxidant may be added.

Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile

Glyceryl mono-oleate is a glycerol ester nonionic surfactant (p. 2164.2). It has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (below).

Glyceryl Stearates

Glycerol Octadecanoates; Glycerol Stearates; Stearoylglycerols.

Glyceryl Distearate

Distearoylglycerol; Glicerin-disztearát; Glicerol, diestearato de; Glicerolio distearatas; Glycerol Distearate; Glycérol, distéarate de; Glyceroldistearat; Glycerol-distearát; Glyceroli distearas; Glyserolidistearaatti; Глицерилдистеарат.

CAS — 1323-83-7.
UNII — 73071MW2KM.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Glycerol Distearate). A mixture of diacylglycerols, mainly distearoylglycerol, with variable quantities of mono- and triacylglycerols. It contains 8 to 22% of monoacylglycerols, 40 to 60% of diacylglycerols, and 25 to 35% of triacylglycerols, obtained by partial glycerolysis of vegetable oils containing triacylglycerols of palmitic and stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A hard, waxy mass or powder, or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 50 degrees to 60 degrees (types I and II) or 50 degrees to 70 degrees (type III).

USNF 31: (Glyceryl Distearate). A mixture of diglycerides, mainly glyceryl distearate, with variable quantities of monoglycerides and triglycerides. It contains 8 to 22% of monoglycerides, 40 to 60% of diglycerides, and 25 to 35% of triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

Hard, waxy mass or powder, or white or almost white flakes. Insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane and in tetrahydrofuran. Store in airtight containers.

Glyceryl Monostearate

Gliceril, monoestearato de; Glicerin-monosztearát; Glicerolio monostearatas; Glicerolu monostearynian; Glycérol, monostéarate de; Glyceroli monostearas; Glycerolmonostearat; Glycerol-monostearát; Glyserolimonostearaatti; GMS; Monoestearato de glicerilo autoemulsionable (Self-emulsifying Glyceryl Monostearate); Monostearin; Monostearin Emulsificans (Self-emulsifying Glyceryl Monostearate); Monostearoylglycerol; Глицерилмоностеарат.

CAS — 31566-31-1 (glyceryl monostearate); 26657-96-5 (glyceryl monopalmitate).
UNII — 230OU9XXE4 (glyceryl monostearate); 6Y2XJ05B35 (glyceryl monopalmitate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF. Br.* also includes Self-emulsifying Glyceryl Monostearate.

Ph. Eur. 8: (Glycerol Monostearate 40-55). A mixture of monoacylglycerols, mainly monostearoylglycerol, with variable quantities of di- and triacylglycerols. It contains 40 to 55% of monoacylglycerols, 30 to 45% of diacylglycerols, and 5 to 15% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of palmitic or stearic acid, or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A white or almost white, hard, waxy mass or unctuous powder or flakes. Practically insoluble in water; soluble in alcohol at 60 degrees. M.p. 54 degrees to 66 degrees.

USNF 31: (Glyceryl Monostearate). It contains not less than 90% of monoglycerides of saturated fatty acids, chiefly glyceryl monostearate ($C_{21}H_{42}O_4 = 358.6$) and glyceryl monopalmitate ($C_{19}H_{38}O_4 = 330.5$). It may contain a suitable antoxidant.

A white to yellowish wax-like solid, beads, flakes, or powder with a slight, agreeable, fatty odour. M.p. not below 55 degrees. Insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble 1 in 10 of chloroform, 1 in 100 of ether and of methyl alcohol, 1 in 33 of isopropyl alcohol; dissolves in hot organic solvents such as alcohol, acetone, mineral or fixed oils, and benzene. Store in airtight containers. Protect from light.

BP 2014: (Self-emulsifying Glyceryl Monostearate). A mixture consisting principally of mono-, di-, and triglycerides of stearic and palmitic acids, and of minor proportions of other fatty acids; it may also contain free fatty acids, free glycerol, and soap. It contains not less than 30% of monoglycerides, not more than 7% of free glycerol, and not more than 6% of soap, calculated as sodium oleate, all calculated with reference to the anhydrous substance.

A white to cream-coloured, hard, waxy solid with a faint fatty odour. Dispersible in hot water; soluble in hot dehydrated alcohol and in hot liquid paraffin; soluble in hot vegetable oils, but may give turbid solutions at concentrations below 20%.

Incompatibility. Because of the presence of soap, self-emulsifying glyceryl monostearate is incompatible with acids and high concentrations of ionisable salts, hard water, calcium compounds, zinc oxide, and oxides of heavy metals.

Glyceryl Palmitostearate

Glicerol, palmitoestearato de.

A mixture of mono-, di-, and triglycerides of C_{16} and C_{18} fatty acids.

CAS — 8067-32-1; 68002-71-1 (C16-18 glycerides).
UNII — GSY51O183C.

Profile

Glyceryl stearates are glycerol ester nonionic surfactants (p. 2164.2). They include a range of mixtures of glycerol mono-, di-, and tri-esters with palmitic and stearic acids and are used as emulsifiers and stabilisers in pharmaceuticals, foods, and cosmetics. They also have emollient properties.

Glyceryl monostearate is used as an emulsifying agent, emollient, and tablet and capsule lubricant. It is a poor water-in-oil emulsifier but is a useful stabiliser of water-in-oil and oil-in-water emulsions and can be included in preparations for internal or external use. A self-emulsifying form, which contains a small amount of soap or other surfactant, is also available. This can produce satisfactory oil-in-water emulsions and is used as an emulsifier for oils, fats, solvents, and waxes in the preparation of bases of the non-emulsified, emulsified, and vanishing-cream types. It is not intended for internal use and aqueous preparations containing it should also contain a preservative to prevent fungal or bacterial growth.

Glyceryl distearate and glyceryl tristearate (tristearin; tristearoylglycerol) have similar properties and uses to the monostearate. Glyceryl palmitostearate is used mainly as a diluent, lubricant, and modified-release agent for tablets and capsules.

Glycofurol

Glicofurol; Glycofural; Glycofurol 75; Tetrahydrofurfuryl Alcohol Polyethylene Glycol Ether; Гликофурфурол.

α-(Tetrahydrofuranyl)-ω-hydroxypoly(oxyethylene).

$C_5H_9O.(C_2H_4O)_nOH$

CAS — 9004-76-6; 31692-85-0.
UNII — YZC5LZ8BUB.

Description. Glycofurol is a clear, colourless, almost odourless liquid. Wt per mL about 1.08 g. B.p. 80 degrees to 100 degrees. Incompatible with oxidising agents. Store under nitrogen in airtight containers. Protect from light.

Profile

Glycofurol is used as a pharmaceutical solvent for injections.

Green S

Acid Brilliant Green BS; Acid Green S; Briljantzuurgroen BS; Brillantsäuregrün BS; CI Food Green 4; Colour Index No. 44090; E142; Grön S; Grün S; Lissamine Green; Verde Brillante BS; Verde Lisamina; Verde S; Vert acide brillant BS; Vert lissamine; Wool Green B; Žaliasis S; Yeşil S; Zieleń Brylantowa BS; Zieleń S; Zöld S; Зелёный S.

Sodium 1-[4-dimethylamino-α-(4-dimethyliminiocyclohexa-2,5-dienylidene)benzyl]-2-hydroxynaphthalene-3,6-disulphonate.

$C_{27}H_{25}N_2NaO_7S_2$=576.6

CAS — 3087-16-9.
UNII — 9B7E8Y9D0X.

Uses

Green S is a synthetic triarylmethane dye used as a colouring agent in medicines, cosmetics, and foodstuffs. Strips impregnated with green S are used to stain the cornea to detect abnormalities.

References.

1. Berntsen DA, *et al.* Reliability of grading lissamine green conjunctival staining. *Cornea* 2006; **25:** 695–700.
2. Korb DR, *et al.* An evaluation of the efficacy of fluorescein, rose bengal, lissamine green, and a new dye mixture for ocular surface staining. *Eye Contact Lens* 2008; **34:** 61–4.
3. Machado LM, *et al.* Staining patterns in dry eye syndrome: rose bengal versus lissamine green. *Cornea* 2009; **28:** 732–4.

Adverse Effects

Studies in *animals* indicated that there is some absorption of green S and caecal enlargement but it was considered that there is a very large margin of safety between the highest estimated human intake of green S of 130 micrograms daily and the level at which changes were seen in *animal* studies (500 mg/kg daily). It was recommended that the use of green S in food is acceptable.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Green Glo.

Guaraprolose *(rINN)*

Guar Gum Hydroxypropyl Ether; Guaraprolosa; Guaraprolosum; HP-Guar; Hydroxypropyl Guar; 2-Hydroxypropyl Guar Gum; Hydroxypropyl Guar Gum; Гидроксипропил Гуар; Гуараполоза.

(1→6)-α-D-Galactopyrano-(1→4)-β-D-mannopyranan 2-hydroxypropyl ether.

$[C_{18}H_{30}O_{15}(C_3H_6O)_x]_n$

CAS — 39421-75-5.

Profile

Guaraprolose is a nonionic thickening agent derived from guar gum (p. 475.1) that is used in eye drops for the management of dry eye conditions. It also used in skin and hair care products and has many industrial applications.

References.
1. Petricek I, *et al*. Hydroxypropyl-guar gellable lubricant eye drops for dry eye treatment. *Expert Opin Pharmacother* 2008; **9:** 1431–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Systane; ***Irl.***: Systane; ***UK***: Systane.

Multi-ingredient Preparations. ***Braz.***: Mirugell; ***Chile***: Systane; ***Fr.***: Lubri-Mucal; Systane; ***Ital.***: Systane; ***Singapore***: Systane; ***Thai.***: Systane.

Hard Fat

Adeps Neutralis; Adeps Solidus; Glicéridos semisintéticos sólidos; Glycérides hémi-synthétiques solides; Glycérides Semi-synthétiques Solides; Grasa sólida; Hårdfett; Hartfett; Kietieji riebalai; Kovarasva; Massa Esterarínica; Neutralfett; Szilárd zsír; Tłuszcz obojętny; Tuk ztužený; Твёрдый Жир.
UNII — 8334LX7S21.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8 (Hard Fat). A mixture of triglycerides, diglycerides, and monoglycerides obtained either by esterification of fatty acids of natural origin with glycerol or by transesterification of natural fats. A white or almost white, waxy, brittle mass. M.p. 30 degrees to 45 degrees; it does not differ by more than 2 degrees from the nominal value. Practically insoluble in water; slightly soluble in dehydrated alcohol. When heated to 50 degrees, it melts giving a colourless or slightly yellowish liquid. Protect from light and heat.

USNF 31: (Hard Fat). A mixture of glycerides of saturated fatty acids. A white mass, almost odourless and free from rancid odour, and greasy to the touch. M.p. is between 27 degrees and 44 degrees and does not differ by more than 2 degrees from the nominal value. The melted substance is colourless or slightly yellowish and forms a white emulsion when shaken with an equal amount of hot water. Practically insoluble in water; slightly soluble in alcohol; freely soluble in ether. Store in airtight containers at a temperature 5 degrees or more below the melting-point.

Profile

Hard fat is a name applied to a range of bases with varying degrees of hardness and differing melting ranges used for the preparation of suppositories and vaginal pessaries. Hard fat is also used in some topical preparations.

Hard Paraffin

Cera de parafina; Cera de petróleo; Hard Wax; Hartparaffin; Kietasis parafinas; Paraff. Dur.; Paraffin; Paraffin, fast; Paraffin Wax; Paraffine solide; Paraffinum Durum; Paraffinum solidum; Parafiini, kiinteä; Parafin tvrdý; Parafina sólida; Parafina stała; Szilárd paraffin; Твёрдый Парафин.
CAS — 8002-74-2.
UNII — I9O0E3H2ZE.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

USNF also includes Synthetic Paraffin.

Ph. Eur. 8: (Paraffin, Hard). A purified mixture of solid saturated hydrocarbons, generally obtained from petroleum. M.p. 50 degrees to 61 degrees. It is a colourless or white mass. The melted substance is free from fluorescence in daylight. Practically insoluble in water and in alcohol; freely soluble in dichloromethane. Protect from light.

USNF 31: (Paraffin). A purified mixture of solid saturated hydrocarbons obtained from petroleum. It may contain suitable antoxidants. It is a colourless or white, odourless, more or less translucent mass showing a crystalline structure, and is slightly greasy to the touch. It has a congealing range of 47 degrees to 65 degrees. Insoluble in water and in alcohol; slightly soluble in dehydrated alcohol; freely soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. An alcoholic extract is neutral to litmus. Store at a temperature not exceeding 40 degrees. Protect from light.

USNF 31: (Synthetic Paraffin). A very hard odourless white wax containing mostly long-chain, unbranched, saturated hydrocarbons, with a small amount of branched hydrocarbons. The average molecular weight may range from 400 to 1400. Insoluble in water; very slightly soluble in aliphatic, oxygenated, and halogenated hydrocarbon solvents; slightly soluble in aromatic and normal paraffinic solvents.

Profile

Hard paraffin is used mainly as a stiffening agent in ointment bases. It is also used in creams, and as a coating for capsules and tablets.

Hard paraffin is used in physiotherapy in the form of paraffin-wax baths for the relief of pain in inflamed joints and sprains.

The injection of paraffins may produce granulomatous reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Melrose; ***USA***: DermaPhor.

Pharmacopoeial Preparations
BP 2014: Paraffin Ointment; Simple Ointment; Wool Alcohols Ointment.

Hexachloroethane

Carbon Hexachloride; Heksakloorietaani; Hexachloorethaan; Hexachlorethan; Hexachloroéthane; Hexacloroetano; Hexacloruro de carbono; Hexacloruro de etano; Hiiliheksakloridi; Perchloorethaan; Perchloroethane; Percloroetano; Perkloorietaani; Гексахлорэтан.
C_2Cl_6=236.7
CAS — 67-72-1.
UNII — G30K3QQT4J.

Profile

Hexachloroethane is a chlorinated hydrocarbon used in industry as a solvent. Eye irritation and photophobia have resulted from industrial exposure to the vapour. It was formerly used in veterinary medicine as an anthelmintic, but has been superseded by less toxic drugs.

n-Hexane

n-Esano; *n*-Heksaani; *n*-Heksan; *n*-Heksâns; *n*-Hekzan; *n*-Hexà; *n*-Hexaan; *n*-Hexan; *n*-Hexán; *n*-Hexano; Hexano normal; Hidruro de hexilo; н-Гексан.
C_6H_{14}=86.18
CAS — 110-54-3.
UNII — 2DDG612ED8.

Description. *n*-Hexane is a colourless, flammable, volatile liquid with a faint odour. Wt per mL about 0.66 g. B.p. about 69 degrees. Store in airtight containers.

Uses

n-Hexane is widely used as an industrial solvent, as a solvent in glues, and as an extraction solvent in food processing.

Adverse Effects

n-Hexane is irritant. Acute exposure to the vapour may result in CNS depression with headache, drowsiness, dizziness, and in severe cases unconsciousness. Chronic occupational exposure and abuse of *n*-hexane have been associated with the development of peripheral neuropathies. *n*-Hexane is a constituent of some adhesives and may be implicated in volatile substance abuse (see under Toluene, p. 2216.3). Some adverse effects of petrol have been attributed to its content of *n*-hexane.

References.
1. Health and Safety Executive. *n*-Hexane. *Toxicity Review 18*. London: HMSO,1987.
2. WHO. *n*-Hexane. *Environmental Health Criteria 122*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc122.htm (accessed 30/06/04)
3. WHO. *n*-Hexane health and safety guide. *IPCS Health and Safety Guide 59*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg059.htm (accessed 30/06/04)

Effects on the nervous system. There have been many reports of peripheral neuropathy attributed to the abuse of, and occupational exposure to, *n*-hexane, although symptoms tend to be milder in the latter.[1] Tetraplegia has occurred in severe cases. There is typically a clinical deterioration several weeks after exposure followed by a slow recovery which, in severe cases, may not be complete. It has been suggested that methyl ethyl ketone potentiates the peripheral neuropathy induced by *n*-hexane. Occupational exposure to *n*-hexane has also been associated with cranial nerve neuropathy.

Parkinsonism in a leather worker, possibly associated with exposure to solvents, mainly *n*-hexane, has been noted.[2]

For further discussion of neurotoxicity after occupational exposure to solvents including *n*-hexane, see under Toluene, p. 2216.2.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.
2. Pezzoli G, *et al*. Parkinsonism due to n-hexane exposure. *Lancet* 1989; **ii:** 874.

Pharmacokinetics

n-Hexane is absorbed after inhalation and to a limited extent through the skin. Oxidative metabolites, including 2,5-hexanedione are excreted in the urine largely as conjugates. Some unchanged *n*-hexane is excreted via the lungs.

Hexylene Glycol

Hexilenglicol; Гексиленгликоль.
2-Methyl-2,4-pentanediol.
$C_6H_{14}O_2$=118.2
CAS — 107-41-5.
UNII — KEH0A3F75J.

Pharmacopoeias. In *USNF.*

USNF 31: (Hexylene Glycol). A clear, colourless, viscous liquid. Absorbs moisture when exposed to moist air. Miscible with water and with many organic solvents including alcohol, acetone, chloroform, ether, and hexanes. Store in airtight containers.

Profile

Hexylene glycol has properties similar to those of propylene glycol (p. 2205.2). It is used as a solvent and humectant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Bodi Kleen.

Hydrogenated Polydecene

E907; Hydrogenated Polydec-1-ene; Hydrogenated Poly-α-olefin; INS No. 907; Гидрогенизированный Полидецен.
CAS — 68037-01-4.
UNII — U333RI6EB7.

Pharmacopoeias. In *USNF.*

USNF 31: (Hydrogenated Polydecene). A mixture of saturated, synthetic hydrocarbons in the range $C_{30}H_{62}$ to $C_{70}H_{142}$, made from direct oligomerisation of 1-decene (C_{10} alpha olefin). The oligomer mixture may be distilled to fractions of a suitable calculated viscosity and hydrogenated to reach saturation, or it may be hydrogenated to reach saturation and then distilled to the desired viscosity. It may contain a stabiliser. A clear, colourless, odourless, tasteless liquid. Very slightly soluble in water. Store in airtight containers.

Profile

Hydrogenated polydecene is used as an emollient, mainly in cosmetic preparations. It is also used as a coating agent in the food industry.

Hyetellose *(rINN)*

Hidroksietilceliuliozė; Hidroxietilcellulóz; Hidroxietilcelulosa; Hydroksietyyliselluloosa; Hydroksyetyloceluloza; Hydroxietylcellulosa; Hydroxyethyl Cellulose; Hydroxyethylcellulose; Hydroxyéthylcellulose; Hydroxyethylcellulosum; Hyétellose; Hyetellosum; Hyetelosa; Idrossietilcellulosa; Гиетэллоза.
CAS — 9004-62-0.
UNII — 8136Y38GY5 (hyetellose (140 cps at 5%)).

NOTE. HECL is a code approved by the BP 2014 for use on single unit doses of eye drops containing hyetellose and sodium chloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8 (Hydroxyethylcellulose). A partially substituted 2-hydroxyethyl ether of cellulose. Various grades are available and are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% solution measured at 25 degrees. A white, yellowish-white, or greyish-white, powder or granules. Soluble in cold or hot water, forming colloidal solutions; practically insoluble in alcohol, in acetone, and in toluene. A 1% solution in water has a pH of 5.5 to 8.5.

USNF 31: (Hydroxyethyl Cellulose). A partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades, varying in viscosity and degree of substitution, and some grades are modified to improve

their dispersion in water. It may contain suitable anticaking agents. A white to light tan, practically odourless, hygroscopic, powder. Soluble in cold or hot water, giving a colloidal solution; practically insoluble in alcohol and in most organic solvents. pH of a 1% solution in water is between 6.0 and 8.5.

Profile

Hyetellose is used in pharmaceutical manufacturing as a thickener and stabiliser and as a tablet coating and binding agent. It is present in lubricant preparations for dry eye (p. 2190.1), contact lens care (p. 1730.2), and dry mouth (p. 2175.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Goniosol†; ***Israel***: Celluspan; Lyteers; V-Tears; ***USA***: Comfort Tears; TearGard†.

Multi-ingredient Preparations. ***Arg.***: Hidratagel†; ***China***: Le Dun Qing (乐敦清); ***Ger.***: Lubricano; ***Irl.***: Minims Artificial Tears; ***Israel***: Lacrimol; V-Crima; ***Turk.***: Gleitgelen; ***UK***: Minims Artificial Tears; ***USA***: Biotene with Calcium; Mimyx†; Optimoist.

Hymetellose *(rINN)*

HEMC; Hidroxietilmetilcelulosa; Hydroxyethyl Methylcellulose; Hydroxyethylmethylcellulose; Hymétellose; Hymetellosum; Methylhydroxyethylcellulose; Méthylhydroxyéthylcellulose; Methylhydroxyethylcellulosum; Metilhidroksietilceliuliozė; Metilhidroxietilcelulóz; Metylhydroxietylcellulosa; Metyylihydroksietyyliselluloosa; Гимэтеллоза.

CAS — 9032-42-2.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Methylhydroxyethylcellulose; Hydroxyethylmethylcellulose BP 2014). A partially substituted ether of cellulose containing methoxyl and 2-hydroxyethyl groups. Various grades are available and are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20 degrees. A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene; dissolves in cold water forming a colloidal solution. A 1% w/w solution in water has a pH of 5.5 to 8.0.

USNF 31: (Hymetellose). A partly *O*-(methylated) and *O*-(2-hydroxyethylated) cellulose. Various grades are available, labelled with the viscosity of a 2% w/w solution measured at 20 degrees. A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Insoluble in hot water, in alcohol, in acetone, in ether, and in toluene; dissolves in cold water forming a colloidal solution. pH of a 1% w/w solution in water is between 5.5 and 8.0.

Profile

Hymetellose is used similarly to other cellulose ethers, such as methylcellulose (p. 2197.3), as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Cellobexon.

Hyprolose *(rINN)*

E463; Hidroksipropilceliuliozė; Hidroxipropilcelulóz; Hidroxipropilcelulosa; Hydroksipropyyliselluloosa; Hydroxipropylcellulosa; Hydroxypropyl Cellulose; Hydroxypropylcellulose; Hydroxypropylcellulosum; Hydroxypropylcelulosa; Hyprolosum; Гипролоза.

CAS — 9004-64-2.

UNII — RFW2ET671P (hyprolose); 2165RE0K14 (hydroxypropyl cellulose, low-substituted).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn*. Also in *USNF* which has two separate monographs, for Hydroxypropyl Cellulose and for Low-substituted Hydroxypropyl Cellulose.

Ph. Eur. 8: (Hydroxypropylcellulose). A partially substituted 2-hydroxypropyl ether of cellulose. Various grades are available and may be distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20 degrees. White or yellowish-white, granules or powder; hygroscopic after drying. Soluble in cold water, in dehydrated alcohol, in glacial acetic acid, in methyl alcohol, in propylene glycol, and in a mixture of 10 parts methyl alcohol and 90 parts dichloromethane, forming colloidal solutions; practically insoluble in hot water, in ethylene glycol, and in toluene; sparingly soluble or slightly soluble in acetone. A 1% w/w solution in water has a pH of 5.0 to 8.5.

USNF 31: (Hydroxypropyl Cellulose). A partially substituted poly(hydroxypropyl) ether of cellulose. When dried at 105 degrees for 1 hour, it contains not more than 80.5% of hydroxypropoxy groups. It may contain not more than 0.60% of silica or other suitable anticaking agent. A white to cream-coloured, practically odourless, granular solid or powder, hygroscopic after drying. Soluble in cold water, in alcohol, in chloroform, and in propylene glycol, giving a colloidal solution; insoluble in hot water. pH of a 1% solution in water is between 5.0 and 8.0.

USNF 31: (Low-Substituted Hydroxypropyl Cellulose). It contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups. A white to yellowish-white, practically odourless, hygroscopic, fibrous or granular powder. Practically insoluble in dehydrated alcohol and in ether; dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution; swells in water, in sodium carbonate, and in 2N hydrochloric acid. pH of the suspension obtained by shaking 1.0 g with 100 mL of water is between 5.0 and 7.5. Store in airtight containers.

Uses and Administration

Hyprolose is used in pharmaceutical manufacturing in the film coating of tablets, as a tablet excipient, as a thickener, and in microencapsulation. It is used as an emulsifier and stabiliser in the food industry.

Hyprolose is also used as a modified-release solid ophthalmic insert in the management of dry eye (p. 2190.1).

Adverse Effects

Hyprolose used as a solid ocular insert may result in blurred vision and ocular discomfort or irritation, including hypersensitivity and oedema of the eyelids.

Hypersensitivity. Allergic contact dermatitis was reported in a patient, associated with the hyprolose present in the reservoir layer of a transdermal estradiol patch.[1]

1. Schwartz BK, Clendenning WE. Allergic contact dermatitis from hydroxypropyl cellulose in a transdermal estradiol patch. *Contact Dermatitis* 1988; **18**: 106–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Lacrisert; ***Fin.***: Lacrisert†; ***Fr.***: Lacrisert; ***India***: Homex; ***Neth.***: Lacrisert†; ***Swed.***: Lacrisert†; ***USA***: Lacrisert.

Pharmacopoeial Preparations

USP 36: Hydroxypropyl Cellulose Ocular System.

Hypromellose *(BAN, rINN)*

E464; Hidroxipropilmetilcelulosa; Hipromeliozė; Hipromellóz; Hipromelosa; Hipromeloz; HPMC; Hydroxypropyl Methylcellulose; Hydroxypropylmethylcellulose; Hypromelloosi; Hypromellos; Hypromellosum; Hypromelosa; Hypromeloza; Methyl Hydroxypropyl Cellulose; Methylcellulose Propylene Glycol Ether; Methylhydroxypropylcellulose; Methylhydroxypropylcellulosum; Гипромеллоза.

CAS — 8063-82-9; 9004-65-3.

ATC — S01KA02.

ATC Vet — QS01KA02.

UNII — 3NXW29V3WO.

NOTE. HPRM is a code approved by the BP 2014 for use on single unit doses of eye drops containing hypromellose where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Hypromellose). A methyl and hydroxypropyl mixed ether of cellulose It contains methoxy and hydroxypropoxy groups conforming to the limits for the types 1828, 2208, 2906, and 2910, calculated on the dried basis (see Labelling, below). A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Dissolves in cold water, forming a colloidal solution; practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene. A 1% w/w solution in water has a pH of 5.0 to 8.0.

USP 36: (Hypromellose). A methyl and hydroxypropyl mixed ether of cellulose It contains methoxy and hydroxypropoxy groups conforming to the limits for the types 1828, 2208, 2906, and 2910, calculated on the dried basis (see Labelling, below). A white to slightly off-white fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture; insoluble in dehydrated alcohol, in chloroform, and in ether.

Labelling. In Europe, grades of hypromellose are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20 degrees (e.g. hypromellose 4500). In the USA, they are distinguished by appending a number in which the first 2 digits represent the approximate percentage content of methoxy groups, and the third and fourth digits the approximate percentage content of hydroxypropoxy groups.

Hypromellose Acetate Succinate

HPMCAS; Hydroxypropylmethylcellulose Acetate Succinate; Shin-etsu AQOAT (AS-HF) (06081224); Shin-etsu AQOAT (AS-HG) (06081224).

CAS — 71138-97-1.

UNII — 24P2YXD2PW (16070722); 36BGF0E889 (12070923); 6N003M473W (06081224).

Pharmacopoeias. In *USNF*.

USNF 31: (Hypromellose Acetate Succinate). A mixture of acetic acid and monosuccinic acid esters of hypromellose. White to yellowish-white, slightly hygroscopic, powder or pills. It is odourless or has a faint, acetic acid-like odour. Practically insoluble in water, in dehydrated alcohol, in xylene, and in *n*-hexane. Dissolves in 1N sodium hydroxide. Addition of a mixture of dehydrated alcohol and dichloromethane (1:1) or of acetone, produces a clear or turbid viscous liquid. Store in tight containers.

Hypromellose Phthalate *(BANM, rINNM)*

Ftalát hypromelosy; Ftalato de hidroxipropilmetilcelulosa; Ftalato de hipromelosa; Hipromeliozės ftalatas; Hipromellóz-ftalát; Hipromelosa, ftalato de; HPMCP; Hydroxypropyl Methylcellulose Phthalate; Hypromelloosiftalaatti; Hypromellose, Phtalate d'; Hypromellosephthalat; Hypromellosftalat; Hypromellosi phthalas; Methylhydroxypropylcellulose Phthalate; Methylhydroxypropylcellulosi Phthalas; Гипромеллозы Фталат.

CAS — 9050-31-1.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Hypromellose Phthalate). A monophthalic acid ester of hypromellose containing methoxy, 2-hydroxypropoxy, and phthalyl groups. It contains 21.0 to 35.0% of phthalyl groups calculated with reference to the anhydrous substance. White or slightly off-white, free-flowing flakes or a granular powder. Practically insoluble in water and in dehydrated alcohol; very slightly soluble in acetone and in toluene; soluble in a mixture of equal volumes of acetone and methyl alcohol, and of dichloromethane and methyl alcohol. Store in airtight containers.

USNF 31: (Hypromellose Phthalate). A monophthalic acid ester of hypromellose. It contains methoxy, hydroxypropoxy, and phthalyl groups. It contains 21.0 to 35.0% of phthalyl groups, calculated on the anhydrous basis. Store in airtight containers. A white, odourless, powder or granules. Practically insoluble in water, in dehydrated alcohol, and in hexane; produces a viscous solution in a mixture of dehydrated alcohol and acetone (1:1), or in a mixture of methyl alcohol and dichloromethane (1:1); dissolves in 1N sodium hydroxide. Store in airtight containers.

Labelling. Different grades of hypromellose phthalate in the USA are distinguished by appending a number in which the first 2 digits represent the approximate percentage content of the methoxy groups, the next 2 digits the approximate percentage content of hydroxypropoxy groups, and the last 2 digits the approximate percentage content of the phthalyl groups. Another system of nomenclature involves appending a number which indicates the pH value (X 10) at which the polymer dissolves in aqueous buffer solutions; letters such as S or F may also be used to indicate grades of high molecular-weight or small particle size respectively.

Profile

Hypromellose has properties similar to those of methylcellulose (p. 2197.3). It is used in pharmaceutical manufacturing for film-coating tablets, as a tablet binder, as a modified-release matrix, and as an emulsifier, suspending agent, and stabiliser in topical gels and ointments. Hypromellose may also be used as an emulsifier and stabiliser in the food industry.

Hypromellose acetate succinate and hypromellose phthalate are used as coating agents, particularly for enteric-coating of tablets and granules and for the preparation of modified-release granules. They may also be used in film coating and as a coating to mask the unpleasant taste of some tablets.

Hypromellose is widely used clinically in ophthalmic solutions; it is preferred to methylcellulose since mucilages of hypromellose have greater clarity and usually contain

fewer undispersed fibres. Hypromellose is used to prolong the action of medicated eye drops and, either alone or with other viscosity-increasing agents, in artificial tears preparations for the management of dry eye (below); solutions containing 0.3 to 1% of hypromellose are commonly used. Solutions for contact lens care (p. 1730.2) and for lubricating artificial eyes contain similar concentrations. Hypromellose is also used intra-ocularly, usually as a 2% solution, as an adjunct in ophthalmic surgery (below) and concentrations of up to 2.5% may be used topically to protect the cornea during gonioscopy procedures.

Hypromellose has been included in artificial saliva preparations used in the management of dry mouth (p. 2175.3), but other drugs are usually preferred.

Dry eye. Dry eye is a chronic condition caused by a disturbance in tear function. It is associated with instability of the tear film covering the eye, which breaks up to leave dry spots rather than being maintained between blinks, and also with tear hyperosmolarity.

Tears consist of a slightly alkaline fluid that is spread across the eye by blinking and is lost via the lachrymal ducts or by evaporation. Mucus secreted by the conjunctiva is also required to maintain tear film stability and dry eye can result from reduced production of either tears or conjunctival mucus. Reduced tear secretion is common in the elderly, but also occurs in some systemic disorders or as an adverse effect of drugs such as those, like tricyclic antidepressants, that have antimuscarinic effects.

Tear film instability may also result from increased tear evaporation, for example due to corneal exposure in thyroid disease, or from lid, corneal, or other eye disorders.

The main symptoms of dry eye are discomfort, typically with a chronic gritty sensation, visual disturbances, and sometimes photophobia. Inflammation of the ocular surface develops and, if left untreated, corneal ulceration and eventual loss of sight may occur. Keratoconjunctivitis sicca is sometimes used as a synonym for dry eye[1] but may also refer to the corneal inflammation that results from severe dry eye in Sjögren's syndrome (see below).

Treatment of dry eye is mainly symptomatic. 'Artificial tears' preparations are the mainstay of therapy[2-5] and are generally based on lubricating or viscosity-increasing agents, although some also contain electrolytes similar to those found in natural tears. Eye drops containing hypromellose or other cellulose ethers (carmellose, hyetellose, methylcellulose), guaraprolose, polyvinyl alcohol, or povidone are widely used. Carbomer, in liquid gel formulations, and ointments containing soft or liquid paraffins are also used. A systematic review[6] found no evidence that any type of artificial tear or ocular lubricant was markedly better than others. Ointments have a longer duration of action than drops, but tend to blur the vision and are most suitable for use at night. Drops should be used as frequently as required, up to hourly or more often if necessary. Frequent use of eye drops may cause sensitivity to the preservative, in which case preservative-free preparations should be considered. An alternative in patients needing very frequent instillation of drops is a slow-release ophthalmic insert of hyprolose.

Another approach to treatment is to reduce tear loss, for example using moisture-retaining glasses or contact lenses. Punctal occlusion with gelatin rods or collagen implants blocks tear outflow and may be used diagnostically or for treatment. Drugs that stimulate tear production or alter tear composition have also been tried; these include diquafosol, ecabet, icomucret (15-HETE), and rebamipide. Mucus build-up due to reduced tear production may respond to topical mucolytics such as acetylcysteine or bromhexine. In severe dry eye use of autologous serum eye drops may be effective; surgical procedures may be necessary in some patients.

Dry eye is increasingly being recognised as an inflammatory disorder and topical immunosuppressants and anti-inflammatory drugs have been investigated. Topical ciclosporin may be of benefit in some patients with keratoconjunctivitis sicca,[7,8] and short-term topical corticosteroids have also been used. Tetracyclines may be effective where there is inflammation of the lipid-secreting meibomian glands in the lid margin.

Sjögren's syndrome is an auto-immune inflammatory disease mainly affecting the lachrymal and salivary glands; it is often secondary to an auto-immune disorder such as rheumatoid arthritis.[9] Patients typically present with dry eye and dry mouth, but extra-glandular symptoms such as arthritis, vasculitis, nephritis, and neuropathies may also occur. Treatment is mainly symptomatic,[10-12] using artificial tears and other topical therapies for dry eye and artificial saliva for dry mouth (see under Carmellose, p. 2175.3). Oral pilocarpine or cevimeline may be of benefit for both dry eye and dry mouth, but adverse effects may limit their use. Systemic treatment with corticosteroids and immunosuppressants may be required for patients with extra-glandular symptoms;[10-12] other approaches such as B-cell depletion using the anti-CD20 antibody rituximab are under investigation.[10-12]

1. Lemp MA, *et al*. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; **5:** 75–92.
2. Lemp MA. Management of dry eye disease. *Am J Manag Care* 2008; **14** (suppl): S88–S101.
3. Pflugfelder SC, *et al*. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; **5:** 163–78.
4. Jackson WB. Management of dysfunctional tear syndrome: a Canadian consensus. *Can J Ophthalmol* 2009; **44:** 385–94.
5. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol* 2009; **3:** 405–12.
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11. Ramos-Casals M, *et al*. Treatment of primary Sjögren syndrome: a systematic review. *JAMA* 2010; **304:** 452–60.
12. Becker H, *et al*. Emerging treatment strategies and potential therapeutic targets in primary Sjögren's syndrome. *Inflamm Allergy Drug Targets* 2010; **9:** 10–9.

Ophthalmic surgery. Intra-ocular hypromellose may be used as a visco-elastic agent to protect the eye during surgery. In cataract extraction it is used to maintain the anterior chamber and to coat the intra-ocular lens to facilitate its implantation. Although intra-ocular hypromellose is generally considered to be well tolerated, some[1] have reported an increased incidence of pupil abnormalities (non-reactive semi-dilated pupils) after such use; others[2] did not confirm this. There has also been a report[3] of corneal opacities in several patients after use of intra-ocular hypromellose.

1. Tan AKK, Humphry RC. The fixed dilated pupil after cataract surgery—is it related to intraocular use of hypromellose? *Br J Ophthalmol* 1993; **77:** 639–41.
2. Eason J, Seward HC. Pupil size and reactivity following hydroxypropyl methylcellulose and sodium hyaluronate. *Br J Ophthalmol* 1995; **79:** 541–3.
3. Newton JN, *et al*. Corneal opacities after cataract surgery with hypromellose. *Lancet* 2000; **355:** 290.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Artelac; Cool Tears; Genteal; Lacrigest; Lagrima Dorf; Latlas Tears; Lubrilag; Natura Lagrimas; Ocutears; Oftalook Plus; ***Austral.***: Genteal; In A Wink Moisturising; ***Austria***: Artelac; Okuzell†; Prosicca; ***Belg.***: Artelac; Isopto Tears; ***Braz.***: Artelac; Filmcel; Genteal; ***Canad.***: Eyelube; Genteal; Isopto Tears; Lacril†; Visine Advance True Tears; Visine Contact Lens; ***Chile***: Genteal; Luvis; Meticel; ***Denm.***: Artelac; Viskose ojendraber; ***Fin.***: Artelac; Isopto Alkaline; Isopto Plain; ***Fr.***: Artelac; Ocucoat†; ***Ger.***: Artelac; Berberil Dry Eye; Cellugel; Celoftal; Genteal; Lacri-Vision; Methocel; Pan-Vision; Sic-Ophtal; Sicca-Stulln; ***Gr.***: Hymecel; Lubrilac; Vidilac; ***Hong Kong***: Artears†; Blueye; Eye Glo Moist; Eye Mo Moist†; Genteal; Isopto Tears; Lac-Oph; Methopt†; ***Hung.***: Humalac B; ***India***: Aquaplus; Caresol; Erisol; Eyefil; Eyemist; Eysol; Genteal; Gonosol; Hymelose; Hyprosol†; Ikleen; Intavisc; Lacrigel; Lub-Gel; Lubiziab; Moisol-Z; Moisol; Nova Vizol†; Optear; Sanvisc; ***Indon.***: Genteal; ***Irl.***: Artelac; Isopto Alkaline†; Isopto Plain†; ***Israel***: Artelac; Genteal; Ocucoat†; ***Ital.***: Gel 4000; Genteal; Lacrisifi; Lacrisol; Methocel; ***Malaysia***: Cellugel†; Eye Glo Moist; Genteal; ***Mex.***: Artelac; Celulose; Genteal; Lub Alvar; Luvistar; Meticel; ***Neth.***: Artelac; ***Norw.***: Artelac; ***NZ***: Genteal; Methopt; ***Philipp.***: Artears; Artelac; Genteal; Hypromax; Ilube; Itearz; Methopt; Opticul; Vistatears; ***Pol.***: Artelac; ***Port.***: Artelac; Davilose; ***Rus.***: Defislez (Дефислёз); Lacrisifi (Лакрисифи); Lacrisyn (Лакрисин); ***S.Afr.***: Cellugel†; Methocel†; Spersatear; Viscotraan; ***Singapore***: Artelac; Eye Mo Moist; Genteal; Methocel; Optovisc; ***Spain***: Acuolens; Artific; ***Swed.***: Artelac; Isopto Plain; ***Switz.***: Isopto Tears; Methocel; ***Thai.***: Genteal; Isopto Tears†; Lac-Oph; Natear; Opsil Tears; Optal-Tears; ***Turk.***: Lacrisifi; ***UK***: Artelac; Brolene Cool Eyes; Hydromoor; Isopto Alkaline; Isopto Plain; Lumecare Tear Drops; ***Ukr.***: Artelac (Артелак); ***USA***: Artificial Tears; Entrocel†; Genteal; Gonak; Goniosoft; Goniosol; Isopto Plain; Isopto Tears; Lacril; Natural Balance Tears; Ocucoat; Tearisol; Tears Again MC; Ultra Tears†; ***Venez.***: Genteal.

Multi-ingredient Preparations. ***Arg.***: Alcon Lagrimas; Irix Lagrimas; Kalopsis Lagrimas; Phoenix Lagrimas; Prednifarma; Punto G†; Solucion Oral; Tears Naturale Forte; Tears Naturale†; Visine Lagrimas; ***Austral.***: Bion Tears; Blink-N-Clean; Genteal; Poly-Tears; Tears Naturale; ***Belg.***: Alcon Adequad; Lacrystat; Tears Naturale; ***Braz.***: Lacribell; Lacrima Plus; Opti-Tears; Trisorb; ***Canad.***: Artificial Tears†; Bion Tears; Clear Eyes for Dry Eyes Plus Redness Relief; Genteal Geldrops; Tears Naturale Forte; Tears Naturale; ***Chile***: Kliner; Lagrimas Artificiales; Nico Drops; Nicotears; Novo-Tears; Tears Naturale; Tears Visine†; ***China***: Bion Tears (倍然); Tears Naturale Forte (新泪然); Tears Naturale II (泪然II); ***Cz.***: Tears Naturale; ***Denm.***: Dacriosol; ***Ger.***: Herba-Vision Augenbad; Herba-Vision Augentrost; Herba-Vision Blaubeere; Herba-Vision Kamille; Lacrisic; Oculotect; ***Gr.***: Gastrovison; Tearprol; Tears Naturale; ***Hong Kong***: Bion Tears; Tears Naturale Forte; Tears Naturale; Visine for Contacts†; ***Hung.***: Dacrolux; Tears Naturale; ***India***: Binea; Decomic; Fixiflox-H; Flubip; Flurbiren; Irimist; Moisol; Naflin; O-Dex; Oculear; ***Indon.***: Genteal; Isotic Tearin; Tears Naturale II; Tears; ***Irl.***: Ilube†; Physiotears†; Tears Naturale; ***Israel***: Tears Natural; ***Ital.***: Dacriosol; Pupilla Light; Tirs; ***Malaysia***: Bion Tears; Dacrolux; Genteal; Tears Naturale; ***Mex.***: Lacrima Plus; Naphacel; Naphtears; Naturalag; Splash Tears; Tears Naturale; ***Neth.***: Duratears; Tears Naturale; ***Norw.***: Tears Naturale; ***NZ***: Poly-Tears; Tears Naturale; ***Philipp.***: Gentle Tears; Tears Naturale; Visine Refresh; ***Pol.***: Tears Naturale; ***Rus.***: Tears Naturale (Слеза Натуральная); ***S.Afr.***: Tears Naturale; ***Singapore***: Bion Tears; Hair and Nails; Tears Naturale; ***Spain***: Dacrolux; Humectante; Tears Humectante; ***Swed.***: Bion Tears; ***Switz.***: Herba-Vision Euphrasia; Herba-Vision Myrtillus; Tears Naturale; ***Thai.***: Bion Tears†; Genteal; Opsar Tears; Tears Naturale; ***Turk.***: Dacrolux; Tears Naturale; ***UK***: Ilube; Murine Bright & Moist Eyes; Tears Naturale; Uvistat Eye Drops; ***Ukr.***: Tears Naturale (Штучні Сльози)†; ***USA***: Bion Tears; Clear Eyes CLR; Lacri-Tears; Lubri-Tears; Maximum Strength Allergy Drops; Moisture Drops; Nature's Tears; Ocucoat†; Tears Naturale; Tears Renewed†; Visine Maximum Redness Relief; Visine Pure Tears; Visine Tears; Visine Tired Eye Relief; Visine Totality Multi-Symptom Relief; ***Venez.***: Genteal; OptiFresh.

Pharmacopoeial Preparations
BP 2014: Hypromellose Eye Drops;
USP 36: Hypromellose Ophthalmic Solution.

Isobutyl Alcohol

Alcohol isobutílico; 1-Hydroxymethylpropane; 1-Isobutanol; Isobutanol; Isopropylcarbinol; 2-Methylpropyl alcohol; Изобутиловый Спирт.
2-Methyl-1-propanol.
$C_4H_{10}O$=74.12
CAS — 78-83-1.
UNII — 56F9Z98TEM.

Pharmacopoeias. In *USNF*.

USNF 31: (Isobutyl Alcohol). A clear, colourless, mobile liquid. Soluble in water; miscible with alcohol, with ether, and with many other organic solvents. Store in airtight containers; avoid exposure to excessive heat above 40 degrees.

Profile

Isobutyl alcohol is used as an industrial solvent. It is also used as an anaesthetic in the American lobster, *Homarus americanus*.

References.
1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 30/06/04)
2. WHO. Isobutanol health and safety guide. *IPCS Health and Safety Guide 9*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg009.htm (accessed 30/06/04)

Isopropyl Myristate *(USAN)*

Isopropyl myristát; Isopropyle, myristate d'; Isopropylis myristas; Isopropylmyristat; Isopropyylimyristaatti; Izopropilmirisztát; Izopropilo miristatas; Izopropylu mirystynian; Miristato de isopropilo; Изопропилмиристат.
Tetradecanoic acid 1-methylethyl ester; Isopropyl tetradecanoate.
$C_{17}H_{34}O_2$=270.5
CAS — 110-27-0.
UNII — 0RE8K4LNJS.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Isopropyl Myristate). A clear, colourless, oily liquid. Relative density about 0.853. Immiscible with water; miscible with alcohol, with dichloromethane, with fatty oils, and with liquid paraffin. Protect from light.

USNF 31: (Isopropyl Myristate). A clear practically colourless, almost odourless, oily liquid; congeals at about 5 degrees. Insoluble in water, in glycerol and in propylene glycol; freely soluble in alcohol. Miscible with most organic solvents and with fixed oils. Store in airtight containers. Protect from light.

Incompatibility. Isopropyl myristate is incompatible with hard paraffin.

Uses

Isopropyl myristate is resistant to oxidation and hydrolysis and does not become rancid. It is absorbed fairly readily by the skin and is used as a basis for relatively nongreasy emollient ointments and creams. It is also used as a penetration enhancer for many substances applied externally as creams, sprays, or transdermal patches. A 50% application of isopropyl myristate has been used as a pediculicide.

Other isopropyl fatty acid esters, including di-isopropyl adipate, isopropyl laurate, isopropyl linoleate, and isopropyl palmitate (below) have similar pharmaceutical properties and are used in formulation for similar purposes to those of isopropyl myristate.

References.
1. Kaul N, *et al.* North American efficacy and safety of a novel pediculicide rinse, isopropyl myristate 50% (Resultz). *J Cutan Med Surg* 2007; **11:** 161–7.

Adverse Effects

Hypersensitivity. A 64-year-old woman developed a rash[1] after using a sunscreen containing isopropyl myristate for 3 days, and patch testing confirmed a sensitivity both to this substance and to isohexadecane (a mixture of C_{16} paraffins).

1. Bharati A, King CM. Allergic contact dermatitis from isohexadecane and isopropyl myristate. *Contact Dermatitis* 2004; **50:** 256–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Resultz; ***Indon.***: Blue Cap; ***Spain***: Nucoa†.

Multi-ingredient Preparations. ***Canad.***: Secol; ***Fr.***: Neuriplege Sport; ***Gr.***: Hydromol; ***India***: Aquasoft; Calyx; ***Indon.***: Sodermix; ***Irl.***: Diprobath; Emulsiderm; Hydromol; Hydromol; ***Israel***: Emulsiderm; ***UK***: Dermol; Diprobath†; Doublebase; Emulsiderm; Full Marks Solution; Hydromol; Hydromol; Soleve.

Isopropyl Palmitate

Isopropyl palmität; Isopropyle, palmitate d'; Isopropylis Palmitas; Isopropylpalmitat; Isopropyylipalmitaatti; Izopropilo palmitatas; Izopropil-palmität; Palmitato de isopropilo; Изопропилпальмитат.

Hexadecanoic acid 1-methylethyl ester; Isopropyl hexadecanoate.

$C_{19}H_{38}O_2$=298.5

CAS — 142-91-6.

UNII — 8CRQ2TH63M.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Isopropyl Palmitate). A clear, colourless, oily liquid. Relative density about 0.854. Immiscible with water; miscible with alcohol, with dichloromethane, with fatty oils, and with liquid paraffin. Protect from light.

USNF 31: (Isopropyl Palmitate). A colourless, mobile, liquid with a very slight odour. Insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in acetone, in castor oil, in chloroform, in cottonseed oil, in ethyl acetate, and in mineral oil. Store in airtight containers. Protect from light.

Profile

Isopropyl palmitate has properties and pharmaceutical uses similar to those of isopropyl myristate (p. 2190.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Fotoprotector Isdin Extrem; ***USA***: SaltStable Lo.

Kerosene

Cherosene; Fotogen; Keroseno; Kerosin; Kerosine; 'Paraffin'; Petrolej; Querosè; Querosene; Queroseno; Querosina; Žibalas; Керосин.

CAS — 8008-20-6.

UNII — 1C89KKC04E.

NOTE. The nomenclature for kerosene and petroleum spirit (p. 2201.2) is confusing and not always clearly distinguishable; in many languages similar terms are used for both.

Description. Kerosene is a mixture of hydrocarbons, chiefly members of the alkane series, distilled from petroleum. It is a clear, colourless liquid with a characteristic odour. Sp. gr. about 0.8 g. B.p. 180 degrees to 300 degrees. An odourless grade is available. Store in airtight containers.

Uses

Kerosene is used as a degreaser and cleaner and as an illuminating and fuel oil in kerosene ('paraffin') lamps and stoves. The odourless grade has been used as a solvent in the preparation of some insecticide sprays.

Adverse Effects

The chief danger from ingestion of kerosene is pneumonitis and pulmonary complications resulting from aspiration. Spontaneous or induced vomiting increases the risk of aspiration. Ingestion of kerosene results in a burning sensation in the mouth and throat, gastrointestinal disturbances, and possibly cough, dyspnoea, and transient cyanosis. There may be excitation followed by CNS depression, with weakness, dizziness, drowsiness, confusion, incoordination, and restlessness progressing to convulsions, coma, and respiratory depression in severe cases. Cardiac arrhythmias have been reported.

The course of poisoning from inhalation is similar to that after ingestion although CNS and cardiac effects are more likely. Kerosene is irritant.

Abuse. Volatile substance abuse (p. 2216.3) involving inhalation and ingestion of kerosene has been reported.[1]

1. Das PS, *et al.* Kerosene abuse by inhalation and ingestion. *Am J Psychiatry* 1992; **149:** 710.

Treatment of Adverse Effects

Treatment of kerosene poisoning is supportive and symptomatic. Every precaution should be taken to avoid aspiration of kerosene into the lungs. The UK National Poisons Information Service considers that gastric lavage should not be used. Adrenaline and other sympathomimetics may also be best avoided because of the risk of precipitating cardiac arrhythmias.

Laurocapram *(USAN, rINN)*

Azone; Laurocapramum; N-0252; Лаурокапрам.

1-Dodecylazacycloheptan-2-one; 1-Dodecylhexahydro-2*H*-azepin-2-one.

$C_{18}H_{35}NO$=281.5

CAS — 59227-89-3.

UNII — 1F3X9DRV9X.

Pharmacopoeias. In *Chin.*

Profile

Laurocapram has been investigated for enhancing the penetration of drugs through the skin.

References.
1. López-Cervantes M, *et al.* Chemical enhancers for the absorption of substances through the skin: Laurocapram and its derivatives. *Drug Dev Ind Pharm* 2006; **32:** 267–86.

Liquid Paraffin

Aceite de parafina; Aceite de petróleo; Aceite de vaselina; Aceite mineral; Aceite mineral blanco; Dickflüssiges Paraffin; Folyékony paraffin; Heavy Liquid Petrolatum; Heavy Mineral Oil; Huile de Vaseline Épaisse; INS No. 905a; Liquid Petrolatum; Mineral Oil; Oleum Petrolei; Oleum Vaselini; Paraffin, flytande; Paraffin Oil; Paraffine liquide; Paraffinum Liquidum; Paraffinum Subliquidum; Parafiini, nestemäinen; Parafin tekutý; Parafina ciekła; Parafina líquida; Skystasis parafinas; Sivi Parafin; Vaselinöl; Vaselinum Liquidum; White Mineral Oil; Медицинское Парафиновое Масло; Парафин Жидкий; Вазелиновое Масло; Жидкий Вазелин.

CAS — 8012-95-1.

ATC — A06AA01.

ATC Vet — QA06AA01.

UNII — T5L8T28FGP.

NOTE. The code 905 has been used for mineral hydrocarbons including liquid paraffin but E905 is now used specifically for microcrystalline wax (p. 2198.1).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Paraffin, Liquid). A purified mixture of liquid saturated hydrocarbons obtained from petroleum. It is a transparent, colourless, oily liquid, free from fluorescence in daylight. Relative density 0.827 to 0.890. Viscosity 110 to 230 mPa s. Practically insoluble in water; slightly soluble in alcohol; miscible with hydrocarbons. Protect from light.

USP 36: (Mineral Oil). A purified mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It is a transparent, colourless, odourless or almost odourless, oily liquid, free, or practically free, from fluorescence. Insoluble in water and in alcohol; soluble in volatile oils; miscible with fixed oils (except castor oil). Store in airtight containers. Protect from light.

Light Liquid Paraffin

Dünnflüssiges Paraffin; Hígan folyó paraffin; Huile de Vaseline Fluide; Light Liquid Petrolatum; Light Mineral Oil; Light White Mineral Oil; Paraff. Liq. Lev.; Paraffin, lättflytande; Paraffine liquide légère; Paraffinum Liquidum Leve; Paraffinum Liquidum Tenue; Paraffinum Perliquidum; Parafiini, kevyt nestemäinen; Parafin tekutý lehký; Skystasis lengvas parafinas; Spray Paraffin; Vaselina líquida.

ATC — A06AA01.

ATC Vet — QA06AA01.

UNII — N6K5787QVP.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF. US* also includes Topical Light Mineral Oil .

Ph. Eur. 8: (Paraffin, Light Liquid). A purified mixture of liquid saturated hydrocarbons obtained from petroleum. It is a transparent, colourless, oily liquid, free from fluorescence in daylight. Relative density 0.810 to 0.875. Viscosity 25 to 80 mPa s. Practically insoluble in water; slightly soluble in alcohol; miscible with hydrocarbons. Protect from light.

USNF 31: (Light Mineral Oil). A purified mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It has similar characteristics to Mineral Oil but a lower kinematic viscosity. Store in airtight containers. Protect from light.

Uses and Administration

Taken orally, liquid paraffin acts as a lubricant and, since it keeps the stools soft, it has been used in the symptomatic treatment of constipation (p. 1804.3), although it should be used with caution because of its adverse effects. The recommended daily oral dose is 10 to 30 mL in divided doses, preferably before breakfast and at night. An emulsion of liquid paraffin may also be used in a dose of 10 to 30 mL at night. Liquid paraffin and its preparations should not, however, be taken immediately before going to bed. Liquid paraffin is an ingredient of several preparations that contain other laxatives such as cascara, magnesium hydroxide, or phenolphthalein. It has also been given as an enema in a usual dose of 120 mL.

Externally, liquid paraffin may be used as an ingredient of ointment bases, as an emollient and cleanser in certain skin conditions, and as an ophthalmic lubricant in the management of dry eye (p. 2190.1).

Light liquid paraffin has similar uses to liquid paraffin.

Administration in children. UK licensed product information gives the following oral doses of liquid paraffin for constipation in children, to be taken at night:

- under 3 years: not recommended
- 3 to 5 years: 2.5 to 5 mL
- 5 to 12 years: 5 to 10 mL
- over 12 years: as for adults

The Paediatric Formulary Committee considered doses of liquid paraffin preparations unsuitable for inclusion in the *BNFC2009* and subsequent editions.

Adverse Effects and Precautions

Excessive oral or rectal dosage with liquid paraffin may result in anal seepage and irritation, excessive purgation, and watery diarrhoea. Liquid paraffin is absorbed to a slight extent and may give rise to foreign-body granulomatous reactions. Similar reactions have followed the injection of liquid paraffin and may be considerably delayed in onset. Injection may also cause vasospasm and prompt surgical removal may be required to prevent severe damage. Lipoid pneumonia has been reported after aspiration of liquid paraffin. Because of the risk of aspiration, oral liquid paraffin should not be given to patients who have difficulty swallowing, or to those with impaired neurodevelopment.

Some licensed product information warns that chronic ingestion of liquid paraffin may rarely be associated with impaired absorption of fat-soluble vitamins and possibly other compounds. There is little published evidence to support this. Prolonged use should, however, be avoided. Liquid paraffin should not be used when abdominal pain, nausea, or vomiting is present. The UK CSM considers that it should not be used in children under 3 years of age.

Granuloma. References.

1. Di Benedetto G, *et al.* Paraffin oil injection in the body: an obsolete and destructive procedure. *Ann Plast Surg* 2002; **49:** 391–6.

Lipoid pneumonia. References.

1. Becton DL, *et al.* Lipoidpneumonia in an adolescent girl secondary to use of lip gloss. *J Pediatr* 1984; **105:** 421–3.
2. Ohwada A, *et al.* Exogenous lipoid pneumonia following ingestion of liquid paraffin. *Intern Med* 2002; **41:** 483–6.
3. Karacan O, *et al.* Fire-eater's pneumonia after aspiration of liquid paraffin. *Turk J Pediatr* 2006; **48:** 85–8.
4. Meltzer E, *et al.* Lipoid pneumonia: a preventable complication. *Isr Med Assoc J* 2006; **8:** 33–5.
5. Cottin V, *et al.* Exogenous lipid pneumonia. *Respiration* 2008; **76:** 442–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Babix; Lansoyl; Lax Ewe Jalea†; Laxante Arceli; Laxuave Enteral; Laxuave Jalea; Lexavite; Lubritina Franklin†; Modaton NI; Oilatum; ***Austral.***: Agarol; Hamilton Dry Skin; Hamilton Skin Active Urederm Cleanser; Oilatum Bar†; Oilatum Emollient†; Oilatum Shower Gel†; Parachoc; ***Belg.***: Lansoyl; ***Braz.***: Nujol; ***Canad.***: Fleet Enema Mineral Oil; Lansoyl; Oilatum; ***Chile***: Laxonarol; ***Cz.***:

Oilatum Emollient; Oilatum Gel; ***Fr.***: Lansoyl; Lubentyl; Oilatum Emollient; Restrical; ***Ger.***: Obstinol M; ***Gr.***: Agarol Plain; Nujol; Paragel; ***Hong Kong***: Hamilton Body Wash†; Keri†; Oilatum Bar; Oilatum Emollient; Oilatum Gel; Vigarol†; ***India***: Moyzen; Oilatum; ***Indon.***: Oilatum Bar†; Oilatum Gel†; ***Irl.***: Oilatum Gel; Oilatum Junior; Oilatum Soap; ***Malaysia***: Balneum†; Egozite Protective Baby Lotion†; Oilatum; ***Mon.***: Parlax; ***NZ***: Fleet Mineral Enema†; Oilatum†; ***Philipp.***: Oilatum; ***Pol.***: Mentholaxin; Oilatum; ***S.Afr.***: Oilatum Bar†; Oilatum Emollient†; ***Singapore***: Balneum†; Laxarol; Oilatum Bar; Oilatum Emollient; Oilatum Gel; ***Spain***: Emuliquen Simple; Hodernal; ***Switz.***: Lansoyl; Laxamalt; Paragol N; ***Thai.***: Agarol†; Oilatum Bar†; Oilatum Emollient†; Oilatum Gel†; ***Turk.***: Duratears; Sokol; ***UK***: Cetraben Emollient; Dermamist; Keri; LPL; Lyclear Treatment Shampoo; Oilatum Bath Formula; Oilatum Fragrance Free; Oilatum Gel; Oilatum Junior; Oilatum Soap; Zerobase; Zerolatum; ***USA***: Kondremul; Liqui-Doss†; Min-O-Ear.

Multi-ingredient Preparations. ***Arg.***: Agarol; Alcon Lagrimas; Aqualane; Mil-Par; Percutalfa; ***Austral.***: Alpha Keri; Dermeze; Duratears; E45; Egozite Baby Cream; Epaderm; Granugen†; Hamilton Dry Skin; Hamilton Skin Active Urederm Cream; Ircal; Lacri-Lube; Oilatum Plus; Pinetarsol; QV Flare Up; QV Flare Up; Soov Prickly Heat; ***Austria***: Balneum F; Neda Fruchtewurfel; ***Belg.***: Duratears; Lacrytube; Transitol; ***Braz.***: Agarol; Balmex; Parapsyl; ***Canad.***: Agarol Plain; Akwa Tears; Duolube; Episec; Huile de Bain Therapeutique; Hypotears; Lotion Lubrifiante Calmante Hydratante†; Magnolax; Optilube; Refresh Lacri-Lube; Sebamed; Secol; Tears Naturale PM; ***Chile***: Acnaid; Agarol†; Agarol; Cold Cream Avene; Durasolets; Duratears; Lacri-Lube; Vaselina Emulsionada; ***Cz.***: Balmandol; Balneum Hermal F; Oilatum Plus; ***Denm.***: Ojensalve Neutral; ***Fin.***: Lacri-Lube; ***Fr.***: Cerat Inalterable†; Cold Cream Naturel; Dexeryl; Lubentyl a la Magnesie; Melaxose; Parapsyllium; Transitol; Transulose; ***Ger.***: Balneum F; Coliquifilm; Gleitgelen; Neuroderm; Oleobal; Vita-POS; ***Gr.***: Duratears; Hydromol; ***Hong Kong***: Duratears; Ego Skin Cream; Egozite Baby Cream; Oilatum Cream; Oilatum Plus; Polytar Emollient; Soov Prickly Heat; ***Hung.***: Balneum Hermal F; ***India***: Adlube; Agarol; Aquasoft; Asilax; Bajoffin; Bioffin; Calkem; Calosoft; Calvera; Calyx; Cetraben; Cimfi; Coslax; Creamee; Cremaffin Plus; Cremaffin; Daffolac-P; Dermoys; Dershine; Dewee; Diafoot; Duolaxin; Easylax; Elsoft; Elure; Emoderm; Foot Care; Gowet; Hidrate; Himost; Laxicare; Laxifin; Laxit Plus; Laxit; Leoben; Moisturex; Moitz; Momplus; Moyzen; Novalax; Oilatum Plus; Oilatum; ***Indon.***: Laxadine; Oilatum Plus†; Yanthi Baby Oil†; ***Irl.***: Diprobath; Emulsiderm; Hydromol; Hydromol; Lacri-Lube; Milpar; Oilatum Cream; Oilatum Emollient; Oilatum Junior Flare-Up; Oilatum Plus; Polytar Emollient; ***Israel***: Balneum F; CleanEars; Duratears; Emulsiderm; Lacrimol†; Vita-POS; ***Ital.***: Balneum Hermal Forte; Duolaxan; Lacrilube; Transitol; Transulose; ***Malaysia***: Aqua Cream; Balneum†; Duratears Naturale; Ego Skin Cream; Egozite Baby Cream; Lacrilube; Oilatum Plus Antibacterial; Oilatum; QV Flare Up†; ***Mex.***: Acuafil Ungena; Milpar; Transilax; ***Mon.***: Dermagor Betacade; ***Neth.***: Duratears Z; Transulose; ***Norw.***: Simplex; ***NZ***: Alpha Keri; BK; DP Lotion - HC; DP; Ego Skin Cream; Egozite Baby; Hydroderm; Lacrilube; Oilatum Plus; Poly-Visc; Polytar Emollient†; ***Philipp.***: CleanEars; Oilatum Plus; Oilatum; ***Pol.***: Amfobase†; Balneum Hermal F†; Diprobase; E45; Mentho-Paraffinol; Oilatum Plus; Unibasis; ***Port.***: Banholeum Gele; Betacade; Melaxose; ***S.Afr.***: Oilatum Plus; ***Singapore***: Balneum; Beagarol; Duratears; Ego Skin Cream; Egozite Baby Cream; Lacrilube†; Metanium Everyday Barrier; Oilatum Cream; Oilatum Plus; QV Flare Up; ***Spain***: Aceite Acalorico; Emuliquen Laxante; Lubrifilm†; Vaselatum; ***Switz.***: Antidry; Antidry; Balmandol; Balmed Hermal F; Coliquifilm; Dexeryl; Paragar; ***Thai.***: Duratears; Emulax; Oilatum Cream†; Oilatum Plus†; ***Turk.***: Balmandol; ***UK***: 50:50; Alpha Keri; Cetraben Emollient; Dermalo; Dermol; Diprobase; Diprobath†; Doublebase; Emollin; Emulsiderm; Epaderm; Feminesse; Hydromol; Hydromol; Imuderm†; Infaderm; Lacri-Lube; Lubri-Tears†; Lyclear Mousse; Lyclear Spray; Mil-Par; Oilatum Cream; Oilatum Emollient; Oilatum Junior; Oilatum Plus; Polytar Emollient; VitA-POS; Zerocream; Zeroguent; ***Ukr.***: Transuloza (Трансулоза); ***USA***: Agoral; Akwa Tears†; Albolene; Alpha Keri; Aquaphor Healing Ointment; Aquaphor†; Bodi Care Lotion; Bodi Oil; Boudreaux's Butt Paste; DermaPhor; Desitin Creamy; Dry Eyes; Duratears Naturale; Geri-Silk; Haley's M-O; Hemorid For Women; Hemorid For Women; Hydrocerin; Hydrocerin; Hypotears; Lacri-Gel; Lacri-Lube; Lacticare; LubriFresh PM; LubriTears; Paladin; Palomar E; Puralube; Refresh Lacri-Lube; Refresh PM; Soothe Night Time; Soothe XP; Stye; Systane Nighttime; Tears Again; Tears Renewed†; Throat Discs; Vagisil; ***Venez.***: Mil-Par; Oleoderm.

Pharmacopoeial Preparations
BP 2014: Cetomacrogol Emulsifying Ointment; Cetrimide Emulsifying Ointment; Emulsifying Ointment; Light Liquid Paraffin Eye Drops; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion; Liquid Paraffin Oral Emulsion; Simple Eye Ointment; Wool Alcohols Ointment;
USP 36: Bland Lubricating Ophthalmic Ointment; Mineral Oil Emulsion; Mineral Oil, Rectal; Topical Light Mineral Oil.

Logwood

CI Natural Black 1; Colour Index No. 75290; Кампешевое Дерево (*Haematoxylon campechianum*).
CAS — 8005-33-2 (CI natural black); 517-28-2 (haematoxylin).

Profile

Logwood extract is a colouring agent derived from the logwood tree, *Haematoxylum (Haematoxylon) campechianum*. The logwood extract haematoxylin is used mainly as a histological stain. It is also used for colouring non-absorbable sutures.

References.

1. Titford M. The long history of hematoxylin. *Biotech Histochem* 2005; **80:** 73–8.
2. Smith C. Our debt to the logwood tree: the history of hematoxylin. *MLO Med Lab Obs* 2006; **38:** 18, 20–2.

Macrogol Cetostearyl Ethers

Ceteareth Compounds; Ceteth Compounds (Macrogol Cetyl Ethers); Macrogol, éteres cetoestearílicos de; Macrogol, ether cétostéarylique de; Macrogoli Aether Cetostearylicus; Makrogol-cetil-sztearil-éter; Makrogolcetostearyleter; Makrogolio cetostearilo eteris; Makrogolisetostearyylieetteri; Полиэтиленгликоля и Цетостеарилового Спирта Эфиры.
CAS — 68439-49-6.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogol Cetostearyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly cetostearyl alcohol. It may contain some free macrogols and it contains various amounts of free cetostearyl alcohol. The amount of ethylene oxide reacted with cetostearyl alcohol is from 2 to 33 units per molecule (nominal value). White or yellowish-white waxy, unctuous mass, pellets, microbeads, or flakes. Macrogol cetostearyl ether with low numbers of ethylene oxide units per molecule is practically insoluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether with higher numbers of ethylene oxide units per molecule is dispersible or soluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether solidifies at 32 degrees to 52 degrees. Store in airtight containers. The labelling states the amount of ethylene oxide reacted with cetostearyl alcohol (nominal value).

Cetomacrogol 1000 *(BAN, rINN)*

Cétomacrogol 1000; Cetomacrogolum 1000; Éter monocetílico de polietilenglicol 1000; Polyethylene Glycol 1000 Monocetyl Ether; Polyoxyethylene Glycol 1000 Monocetyl Ether; Кетомакрогол 1000; Цетомакрогол 1000.
CAS — 9004-95-9 (macrogol cetyl ethers); 68439-49-6 (macrogol cetostearyl ethers).
UNII — I835H2IHHX.

NOTE. The name Cetomacrogol 1000 (*BAN*, *INN*) refers to a macrogol 20 ether with cetyl (hexadecyl) alcohol. The name has also been used for macrogol ethers with either cetyl or cetostearyl alcohol, such as Cetomacrogol 1000 BP, a macrogol ether containing 20 to 24 oxyethylene groups in the polyoxyethylene chain prepared from either cetyl alcohol or cetostearyl alcohol. However, the more specific term macrogol cetostearyl ether (22) has replaced cetomacrogol 1000 in BP formulations.

Pharmacopoeias. In *Int.*

Incompatibility. Cetomacrogol has been reported to be incompatible with phenols and to reduce the antibacterial activity of quaternary ammonium compounds. Cetomacrogol may separate from solutions in the presence of a high concentration of electrolytes.

Polyoxyl 20 Cetostearyl Ether

Polioxil 20, éter cetoestearílico de; Полиоксиэтилендиола 20 и Цетостеариловой Кислоты Эфир.
CAS — 68439-49-6.
UNII — YRC528SWUY.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 20 Cetostearyl Ether). A mixture of the monocetostearyl (mixed hexadecyl and octadecyl) ethers of mixed macrogols, the average polymer length being equivalent to 17.2 to 25.0 oxyethylene units. A cream-coloured waxy unctuous mass, melting, when heated, to a clear brownish-yellow liquid. Soluble in water, in alcohol, and in acetone; insoluble in petroleum spirit. A 10% solution in water has a pH of 4.5 to 7.5. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

Profile

Macrogol cetostearyl ethers are mixtures of macrogol ethers with mainly cetyl (palmitic) and stearyl alcohol. They are macrogol alkyl ether nonionic surfactants (p. 2164.2) and are used as surfactants and emulsifiers. Macrogol cetostearyl ether (22) is used with cetostearyl alcohol (for example, in the form of Cetomacrogol Emulsifying Wax BP 2014) as an emulsifying agent for making oil-in-water emulsions that are unaffected by moderate concentrations of electrolytes and that are stable over a wide pH range. It is also used to disperse volatile oils in water to form transparent sols.

Preparations

Pharmacopoeial Preparations
BP 2014: Cetomacrogol Emulsifying Wax.

Macrogol/glycerol Esters

Macrogolglycerides; Polyoxylglycerides.

Behenoyl Macrogolglycerides

Behenoyl Polyoxylglycerides.

Pharmacopoeias. In *USNF.*

USNF 31: (Behenoyl Polyoxylglycerides). A mixture of mono-esters, di-esters, and tri-esters of glycerol and mono-esters and di-esters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight of 400. It is produced by esterification of glycerol and polyethylene glycols with behenic acid. A waxy solid or fine powder. Dispersible in water; insoluble in alcohol; soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 35 degrees. Protect from light, heat, and moisture.

Caprylocaproyl Macrogolglycerides

Glyceromacrogoli Octanodecanoates; Glyceromakrogol-oktanodekanoáty; Kaprylokaproylmakrogolglycerider; Kaprylokaproyylimakrogoliglyseridit; Macrogolglycérides caprylocapriques; Macrogolglyceridorum Caprylocaprates; Macrogolglycerolcaprylocaprate; Macrogolglyceroli Caprylocapras; Makrogol-és glicerin-kaprilátok és kaprátok; Makrogolgliceridų kaprilokaproilatai.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Caprylocaproyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols with a mean relative molecular mass between 200 and 400. They are obtained by partial alcoholysis of medium-chain triglycerides using macrogol or by esterification of glycerol and macrogol with caprylic (octanoic) acid and capric (decanoic) acid or a mixture of glycerol esters and condensates of ethylene oxide with caprylic acid and capric acid. They may contain free macrogols. A pale-yellow, oily liquid. Dispersible in hot water, freely soluble in dichloromethane.

USNF 31: (Caprylocaproyl Polyoxylglycerides). A mixture of mono-esters, di-esters, and tri-esters of glycerol and mono-esters and di-esters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight between 200 and 400. It is produced by partial alcoholysis of medium-chain triglycerides with polyethylene glycol, by esterification of glycerol and polyethylene glycol with caprylic acid and capric acid, or as a mixture of glycerol esters and ethylene oxide condensate with caprylic acid and capric acid. It may contain free polyethylene glycols. Pale yellow, oily liquids. Dispersible in hot water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees to 30 degrees. Protect from light and moisture.

Lauroyl Macrogolglycerides

Glyceromacrogoli Laurates; Glyceromakrogol-lauráty; Lauroyl Polyoxyglycerides; Lauroylmakrogolglycerider; Lauroyylimakrogoliglyseridit; Macrogolglycérides lauriques; Macrogolglyceridorum laurates; Macrogolglyceroli Lauras; Macrogolglycerollaurate; Macrogolgyceridorum Laurates; Makrogol-és glicerin-laurátok; Makrogolgliceridų lauratai; Makrogologlicerydów lauryniany.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Lauroyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols with a mean relative molecular mass between 300 and 1500. They are obtained by partial alcoholysis of saturated oils mainly containing triglycerides of lauric (dodecanoic) acid, using macrogol, or by esterification of glycerol and macrogol with saturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of these hydrogenated oils. A pale yellow waxy solid. Dispersible in hot water, freely soluble in dichloromethane.

USNF 31: (Lauroyl Polyoxylglycerides). A mixture of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight between 300 and 1500. It is produced by partial alcoholysis of saturated oils, mainly containing triglycerides of lauric

acid with polyethylene glycols, by esterification of glycerol and polyethylene glycols with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. It may contain free polyethylene glycols. Pale yellow, waxy liquids. Dispersible in hot water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Linoleoyl Macrogolglycerides

Glyceromacrogoli Linoleates; Glyceromakrogol-linoleáty; Linoleoylmakrogolglycerider; Linoleoyylimakrogoliglyseridit; Macrogolglycérides linoléiques; Macrogolglyceridorum Linoleates; Macrogolglyceroli Linoleas; Macrogolglycerollinoleate; Makrogol-és glicerin-linolátok; Makrogolgliceridų linoleatai; Makrogologlicerydów linoleiniany.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Linoleoyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols. They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of linoleic (*cis,cis*-9,12-octadecadienoic) acid, using macrogol with a mean relative molecular mass between 300 and 400, or by esterification of glycerol and macrogol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil. An amber, oily liquid which may give rise to a deposit after prolonged periods at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Protect from light.

USNF 31: (Linoleoyl Polyoxylglycerides). A mixture of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. The polyethylene glycols have a mean molecular weight between 300 and 400. It is produced by partial alcoholysis of unsaturated oils, mainly containing triglycerides of linoleic acid, with polyethylene glycol, by esterification of glycerol and polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the unsaturated oils. It may contain free polyethylene glycols. Amber, oily liquids. May develop deposit after prolonged storage periods at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Oleoyl Macrogolglycerides

Macrogolglycérides oléiques; Macrogolglyceridorum oleates; Macrogolglyceroli Oleas; Macrogolglycerololeate; Oleoyl Polyoxylglycerides.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Oleoyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols. They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of oleic (*cis*-9-octadecenoic) acid, using macrogol with a mean relative molecular mass between 300 and 400, or by esterification of glycerol and macrogol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil. An amber oily liquid, which may give rise to a deposit after prolonged periods at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Protect from light.

USNF 31: (Oleoyl Polyoxylglycerides). A mixture of monoesters, di-esters, and tri-esters of glycerol and mono-esters and di-esters of polyethylene glycols. Polyethylene glycols used have a mean molecular weight between 300 and 400. It is produced by partial alcoholysis of unsaturated oils, mainly containing triglycerides of oleic acid, with polyethylene glycol, by esterification of glycerol and polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with fatty acids of the unsaturated oils. It may contain free polyethylene glycols. Amber, oily liquids. May develop deposit after prolonged storage at 20 degrees. Practically insoluble but dispersible in water; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Stearoyl Macrogolglycerides

Glyceromacrogoli Stearates; Glyceromakrogol-stearáty; Macroglyceridorum Stearas; Macrogolglycérides stéariques; Macrogolglyceridorum Stearates; Macrogolglyceroli Stearas; Macrogolglycerolstearate; Makrogol-és glicerin-sztearátok; Stearoilmakrogolgliceridai; Stearoylmakrogolglycerider; Stearoyylimakrogoliglyseridit.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Stearoyl Macrogolglycerides). Mixtures of mono-esters, di-esters and tri-esters of glycerol and mono-esters and di-esters of macrogols with a mean relative molecular mass between 300 and 4000. They are obtained by partial alcoholysis of saturated oils containing mainly triglycerides of stearic (octadecanoic) acid, using macrogol, or by esterification of glycerol and macrogol with saturated fatty acids, or by mixture of glycerol esters and condensates of ethylene oxide with the fatty acids of these hydrogenated oils. A pale yellow waxy solid. Dispersible in warm water and in warm liquid paraffin; freely soluble in dichloromethane; soluble in warm anhydrous ethanol.

USNF 31: (Stearoyl Polyoxylglycerides). A mixture of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols. The polyethylene glycols used have a mean molecular weight between 300 and 4000. It is produced by partial alcoholysis of saturated oils, mainly containing triglycerides of stearic acid, with polyethylene glycol, by esterification of glycerol and polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. It may contain free polyethylene glycols. Pale yellow, waxy solids. Dispersible in warm water and in warm paraffin; soluble in warm methyl alcohol; freely soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Profile

Macrogol/glycerol esters are mixtures of glycerol ester and macrogol ester nonionic surfactants (p. 2164.2) and consist of macrogol esters and glycerol esters of the same fatty acid. They are used as self-emulsifying and solubilising agents in oral and topical formulations. They are also used in foods and cosmetics.

Macrogol 6 Glyceryl Caprylocaprate

Glyceromacrogoli 6 Octanodecanoas; Glyceromakrogol-6-oktanodekanoát; Macrogol 6 Glycerol Caprylocaprate; Macrogol 6 glycérol, caprylocaprate de; Macrogol 6 glyceroli caprylocapras; Macrogol-6-glycerolcaprylocaprat; Makrogol 6-glicerin éterek kaprilátjai és kaprátjai; Makrogol-6-glycerolkaprylokaprat; Makrogoli-6-glyserolikaprylokapraatti; Makrogolio 6 glicerolio kaprilokapratas; PEG-6 Caprylic/capric Glycerides; Polyoxyethylene 6 Caprylic/capric Glycerides.

CAS — 361459-38-3; 68954-97-2.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogol 6 Glycerol Caprylocaprate). A mixture of mainly mono- and di-esters of polyoxyethylene glycerol ethers mainly with caprylic (octanoic) and capric (decanoic) acids. The average number of moles of ethylene oxide reacted per mole of substance is 6. Macrogol 6 glycerol caprylocaprate may be obtained by ethoxylation of glycerol and esterification with distilled coconut or palm kernel fatty acids, or by ethoxylation of mono- and diglycerides of caprylic and capric acids. A pale yellow liquid. Partly soluble in water, freely soluble in castor oil, in glycerol, in isopropanol and in propylene glycol. Viscosity about 145 mPa s.

Profile

Macrogol 6 glyceryl caprylocaprate is an ethoxylated glycerol ester nonionic surfactant (p. 2164.2). It is used as a solubiliser and emulsifier and as an emollient in topical preparations.

Macrogol 20 Glyceryl Monostearate

Glyceromacrogoli 20 Monostearas; Glyceromakrogol-20-monostearát; Macrogol 20 Glycerol Monostearate; Macrogol 20 glycérol, monostéarate de; Macrogol 20 glyceroli monostearas; Macrogol-20-glycerolmonostearat; Macrogoli 20 Glycerol Monostearate; Macrogoli 20 Glyceroli Monostearas; Makrogol-20-glicerin-monosztearát; Makrogol-20-glycerolmonostearat; Makrogoli-20-glyserolimonostearaatti; Makrogolio 20 glicerolio monostearatas; Makrogolo-20-glicerolu monostearynian; PEG-20 Glyceryl Stearate.

CAS — 68153-76-4.

UNII — MJV0165YY8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogol 20 Glycerol Monostearate). Macrogol 20 glycerol monostearate is obtained by ethoxylation with ethylene oxide of different types of glycerol stearates, mainly Glycerol Monostearate 40–55. The number of moles of ethylene oxide reacted per mole of glycerol stearate is 20 (nominal value). A pale yellow, oily liquid or gel. Soluble in water at 40 degrees and above and in alcohol; practically insoluble in light liquid paraffin and in fatty oils. Relative density about 1.07. Protect from light.

Profile

Macrogol 20 glyceryl monostearate is an ethoxylated glycerol ester nonionic surfactant (p. 2164.2). It is used as an emulsifier and solubiliser in pharmaceuticals, foods, and cosmetics.

Macrogol 15 Hydroxystearate

Macrogol 15, hydroxystéarate de; Macrogol-15-hydroxystearat; Macrogoli 15 Hydroxystearas; Makrogol hydroxystearát; Makrogol-15-hydroxistearat; Makrogoli-15-hydroksistearaatti; Makrogolio 15 hidroksistearatas; Polyethylene Glycol (15)-Hydroxystearate; Polyoxyethylated 12-Hydroxystearic Acid; Полиэтиленгликоля 15 Гидроксистеарат.

CAS — 70142-34-6.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Macrogol 15 Hydroxystearate). A mixture of mainly mono- and di-esters of 12-hydroxystearic acid and macrogols obtained by ethoxylation of 12-hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-hydroxystearic acid is 15 (nominal value). It contains free macrogols. A yellowish, waxy mass. It solidifies at about 25 degrees. Very soluble in water; soluble in alcohol; insoluble in liquid paraffin. Store in airtight containers.

USNF 31: (Polyoxyl 15 Hydroxystearate). A product resulting from the reaction of about 15 moles of ethylene oxide with 1 mole of 12-hydroxystearic acid. It consists mainly of 12-hydroxystearic acid polyethoxylated at both the carboxyl and the hydroxyl groups with macrogol. It contains free macrogols. A yellowish to white waxy mass. Very soluble in water; soluble in alcohol and in isopropyl alcohol; insoluble in liquid paraffin. Store in airtight containers at a temperature below 25 degrees, the point at which it solidifies.

Profile

Macrogol 15 hydroxystearate is a macrogol ester nonionic surfactant (p. 2164.2). It is used as a solubilising agent.

Macrogol Laurates

PEG Laurates; Polyethylene Glycol Laurates; Polyoxyl Laurates.

CAS — 9004-81-3.

Profile

Macrogol laurates are macrogol ester nonionic surfactants (p. 2164.2) used as emulsifiers.

Macrogol Lauril Ethers

α-Dodecyl-ω-hydroxypoly(oxyethylene); Éteres laurílicos de macrogol; Laureth Compounds; Lauromacrogols; Macrogol, éteres láuricos de; Macrogol, éther laurique de; Macrogol Lauryl Ethers; Macrogoli aether laurilicum; Makrogolilauryylieetteri; Makrogolio laurilo eteris; Makrogollauryleter; Oxypolyethoxydodecanes; Polyoxyl Lauryl Ethers; Полиэтиленгликоля и Лаурилового Спирта Эфиры.

CAS — 9002-92-0.

Description. Macrogol lauril ethers have the general formula $C_{12}H_{25}(OCH_2CH_2)_nOH$.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Macrogol Lauryl Ether). A mixture of ethers of mixed macrogols with fatty alcohols, mainly $C_{12}H_{26}O$. It contains a variable amount of free $C_{12}H_{26}O$ and it may contain free macrogols. The number of moles of ethylene oxide reacted per mole of $C_{12}H_{26}O$ is 3 to 23 (nominal value). Macrogol lauril ether with 3 to 5 units of ethylene oxide per molecule is a colourless liquid. Practically insoluble in water and in petroleum spirit; soluble or dispersible in alcohol. Macrogol lauril ether with 9 to 23 units of ethylene oxide per molecule is a white or almost white, waxy mass. Soluble or dispersible in water; soluble in alcohol; practically insoluble in petroleum spirit. Macrogol lauril ether should be stored in airtight containers.

USNF 31: (Polyoxyl Lauryl Ether). A mixture of the monolauril ethers of mixed polyethylene glycols, the average polymer length being equivalent to not less than 3 and not more than 23 oxyethylene units (nominal value). It

contains various amounts of free lauril alcohol, and it may contain some free polyethylene glycols. Store in airtight containers in a dry place at a temperature of 8 degrees to 15 degrees.

Laureth 4 *(USAN)*

Лаурет 4.
CAS — 9002-92-0.
UNII — 6HQ855798J.

Description. A mixture of monolauril ethers of macrogols where the average value of *n* in the formula given on p. 2193.3 is 4.

Lauromacrogol 400 *(rINN)*

Laureth 9 (USAN); Lauromacrogolum 400; Polidocanol; Polidocanol 600; Polidocanolum; Polidocanolum 600; Polidokanol; Polidokanoli; Лауромакрогол 400.
CAS — 9002-92-0; 3055-99-0.
ATC — C05BB02.
ATC Vet — QC05BB02.
UNII — 0AWH8BFG9A.

Description. Lauromacrogol 400 is a mixture of monolauril ethers of macrogols where the average value of *n* in the formula given on p. 2193.3 is 9. It has sometimes, however, been erroneously described as containing 8, rather than 9, oxyethylene groups. However, note that Lauromacrogol *(BAN)* is described as containing an average of 8 ethylene oxide groups per molecule.

The number 400 in the name Lauromacrogol 400 corresponds approximately to the average molecular mass of the macrogol portion whereas the number 600 in the name Polidocanol 600 corresponds approximately to the average molecular mass of the whole molecule.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lauromacrogol 400). A mixture of lauril alcohol (dodecanol) monoethers of mixed macrogols. It may contain some free macrogols and it contains various amounts of free lauril alcohol. The number of moles of ethylene oxide reacted per mole of lauril alcohol is 9. The number (400) following the name approximately corresponds to the average molecular mass of the macrogol portion. A white or almost white, unctuous, and hygroscopic mass, which melts at 24 degrees into a colourless or yellowish, viscous liquid. Freely soluble in water; very soluble in alcohol and in acetone.

Uses and Administration

Macrogol lauril ethers are mixtures of macrogol ethers of mainly lauril alcohol. They are macrogol alkyl ether nonionic surfactants (p. 2164.2) and are used as solubilisers and dispersants; they have also been used as spermicides. Lauromacrogol 400 is used as a sclerosant in the treatment of oesophageal and gastric varices (p. 2563.1) and varicose veins (p. 2564.1), and has been tried in endoscopic injection therapy for bleeding peptic ulcer (p. 1813.2); it has also been used as a local anaesthetic and antipruritic (see p. 1687.3) in combination topical preparations.

Adverse Effects

There have been occasional reports of allergic skin reactions after topical application of preparations containing macrogol lauril ethers.

A 63-year-old man developed pulmonary oedema, a dramatic fall in heart rate, transient left pyramidal syndrome and died after sclerotherapy with lauromacrogol 400 to control gastric variceal bleeding;[1] the fatality was attributed to the action of the drug that had passed into the systemic circulation. Another patient[2] suffered a reversible ischaemic neurological deficit after sclerotherapy with lauromacrogol 400 for varicose veins of the leg, and ischaemic stroke[3] and other neurological symptoms,[4] probably due to embolism after passage of foam through a patent foramen ovale, have been reported after foam injection sclerotherapy using the compound. Allergic respiratory symptoms have reported[5] in a patient on the sixth occasion of her receiving lauromacrogol 400 as sclerotherapy for varicose veins; no adverse events had occurred during five previous treatment sessions.

A study[6] involving 1605 patients that covered 3357 patient years revealed 5 adverse events with liquid, and 46 with foam, preparations of lauromacrogol 400. Visual disturbances were the most frequent event (14) and muscular vein thrombosis the most serious (8). Overall, it was considered that lauromacrogol 400 was a safe sclerosing agent for varicose veins.

1. Paterlini A, *et al.* Heart failure and endoscopic sclerotherapy of variceal bleeding. *Lancet* 1984; **i:** 1241.
2. Van der Plas JPL, *et al.* Reversible ischaemic neurological deficit after sclerotherapy of varicose veins. *Lancet* 1994; **343:** 428.
3. Forlee MV, *et al.* Stroke after varicose vein foam injection sclerotherapy. *J Vasc Surg* 2006; **43:** 162–4.
4. Ceulen RPM, *et al.* Microembolism during foam sclerotherapy of varicose veins. *N Engl J Med* 2008; **358:** 1525–6.
5. Geslin JM, *et al.* Manifestations respiratoires allergiques lors de sclérose de varices par le lauromacrogol 400. *Therapie* 2004; **59:** 651–2.
6. Guex JJ, *et al.* The French polidocanol study on long-term side effects: a survey covering 3,357 patient years. *Dermatol Surg* 2010; **36** (suppl 2): 993–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aet; Aetoxysklerol; ***Austral.***: Aethoxysklerol; ***Austria***: Aethoxysklerol; ***Belg.***: Aethoxysklerol; ***Cz.***: Aethoxysklerol; ***Denm.***: Aethoxysklerol; ***Fin.***: Aethoxysklerol; ***Fr.***: Aetoxisclerol; ***Ger.***: Aethoxysklerol; Anaesthesulf; Pruriderm; Recessan; ***Gr.***: Aethoxysklerol; Atossisclerol; Etoxisklerol; ***Hung.***: Aethoxysklerol; ***India***: Asklerol; ***Israel***: Polidoc†; ***Ital.***: Atossisclerol; ***Mex.***: Farmaflebon; ***Neth.***: Aethoxysklerol; ***Pol.***: Aethoxysklerol; ***Spain***: Etoxisclerol; ***Swed.***: Aethoxysklerol; ***Switz.***: Aethoxysklerol; Balmed Hermal Plus; Sclerovein; ***Thai.***: Aethoxysklerol; ***Turk.***: Aethoxysklerol; ***Ukr.***: Sclerovein (Склеровейн); ***USA***: Asclera; Varithena; ***Venez.***: Etoxisclerol.

Multi-ingredient Preparations. ***Arg.***: Nene Dent NF; ***Austria***: Balneum Plus; Dentinox†; Dentinox; Optiderm; Prurimix; Solcoseryl Dental; Vonum; ***Belg.***: Cose-Anal; ***Braz.***: Nene Dent N; ***Chile***: Mentobalsam†; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; Vatanal; ***Cz.***: Balneum Hermal Plus; ***Ger.***: Balneum Plus; Brand- u. Wundgel-Medice; Dentinox N; Optiderm; Solcoseryl akut†; Solcoseryl Dental†; ***Hong Kong***: Collomack†; Haemoral†; Solcoseryl Dental; ***Hung.***: Balneum Hermal Plus; Dentinox N; Dentinox; ***Indon.***: Solcoseryl Dental†; ***Irl.***: Balneum Plus†; Itch Relief; ***Israel***: Balneum Plus; Derma-Care†; ***Ital.***: Optiderm; Pitiren; ***Malaysia***: Balneum Intensiv Plus; Solcoseryl Dental; ***Mex.***: Nene Dent; ***Neth.***: Epianal; ***Norw.***: Alcos-Anal; ***Philipp.***: Solcoseryl Dental; ***Pol.***: Balneum Hermal Plus†; Dentinox N; Optiderm†; ***Port.***: Anacal; Hidratante VV; ***Rus.***: Collomac (Колломак); Dentinox (Дентинокс); Hepatrombin H (Гепатромбин Г); Solcoseryl Dental (Солкосерил Дентальная); ***Singapore***: Balneum Intensiv Plus; Solcoseryl Dental; ***Switz.***: Assan rem; Decasept N†; Dentinox; Optiderm; Oxydermine; Parapic; Pruri-med Lipolotion; Pruri-med; Solcoseryl Dentaire; Sportusal Spray sine heparino; Sportusal; Venucreme; Venugel; ***Thai.***: Collomak; Solcoseryl Dental; ***Turk.***: Dentinox; Kortos; Solcoseryl; ***UK***: Anacal; Balneum Plus; Balneum Plus; Diprobath†; E45 Itch Relief; ***Ukr.***: Collomak (Колломак); Dentinox N (Дентинокс Н); Hepathrombin H (Гепатромбин Г); Solcoseryl Dental (Солкосерил Дентальная); ***Venez.***: Collomack.

Macrogol Monomethyl Ethers

Éteres monometílicos de polietilenglicol; Macrogol, éteres monometílicos de; Methoxy-PEGs; Methoxypolyethylene Glycols; MPEGs; Polyethylene Glycol Monomethyl Ethers; Polyoxyethylene Monomethyl Ethers; Полиэтиленгликоля и Метилового Спирта Эфиры.
α-Methyl-ω-hydroxypoly(oxyethylene).
CAS — 9004-74-4.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyethylene Glycol Monomethyl Ether). Addition polymers of ethylene oxide and methyl alcohol, represented by the formula $CH_3(OCH_2CH_2)_nOH$, where *n* represents the average number of oxyethylene groups. The name is usually designated by a number that corresponds approximately to its average molecular weight.

As the average molecular weight increases, the water solubility, vapour pressure, hygroscopicity, and solubility in organic solvents decrease while congealing temperature, specific gravity, flash-point, and viscosity increase. Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids with a slight characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material with a consistency similar to beeswax, or as creamy white flakes, beads, or powders. Liquid grades are miscible with water; solid grades are freely soluble in water; all grades are soluble in alcohol, in acetone, in chloroform, in ethyl acetate, in ethylene glycol monoethyl ether, and in toluene; all grades are insoluble in ether and in hexane. Store in airtight containers.

Profile

Macrogol monomethyl ethers are macrogol ether nonionic surfactants (p. 2164.2). They may be used as ointment bases, solvents, and plasticisers.

Macrogol Oleates

Macrogol Mono-oleates; Macrogol, oléate de; Macrogoli Oleas; Makrogolio oleatas; Makrogolioleaatti; Makrogololeat; Makrogol-oleát; Polyethylene Glycol Monooleates; Polyoxyl Oleates.
CAS — 9004-96-0.

Pharmacopoeias. *Eur.* (see p. vii) includes a monograph for Macrogol Oleate. *USNF* includes Polyoxyl Oleate.

Ph. Eur. 8: (Macrogol Oleate). A mixture of mono- and di-esters of mainly oleic (cis-9-octadecenoic) acid and macrogols. It may be obtained by ethoxylation of oleic acid or by esterification of macrogols with oleic acid of animal or vegetable origin. It may contain free macrogols. The average polymer length is equivalent to 5 to 6 or 10 moles of ethylene oxide per mole (nominal value). A suitable antoxidant may be added. A slightly yellowish, viscous liquid. Dispersible in water and in oils; soluble in alcohol and in isopropyl alcohol; miscible with fatty oils and with waxes. It has a refractive index of about 1.466. Store in airtight containers.

USNF 31: (Polyoxyl Oleate). A mixture of the mono- and di-esters of oleic acid and mixed polyethylene glycols. It may be obtained by ethoxylation of oleic acid or by esterification of polyethylene glycols with oleic acid of animal or vegetable origin. It may contain free polyethylene glycol. The average polymer length is equivalent to either 5 to 6 or 10 oxyethylene units (nominal values). A suitable antoxidant may be added. A slightly yellowish, viscous liquid. Dispersible in water and in oils; soluble in alcohol and in isopropyl alcohol; miscible with fatty oils and with waxes. Its refractive index is about 1.466. Store in airtight containers. Protect from moisture.

Profile

Macrogol oleates are macrogol ester nonionic surfactants (p. 2164.2) used as emulsifiers.

Macrogol Oleyl Ethers

Ethoxylated Oleyl Alcohol; Macrogol, éteres oleílicos de; Macrogol, éther oléique de; Macrogoli aether oleicum; Macrogoli Aetherum Oleicum; Makrogolio oleilo eteris; Makrogolioleyylieetteri; Makrogol-oleil-éter; Makrogololeyl-eter; Oleth Compounds; Polyethylene Glycol Mono-oleyl Ethers; Полиэтиленгликоля и Олеилового Спирта Эфиры.
CAS — 9004-98-2.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogol Oleyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly oleyl alcohol. It may contain some free macrogols and it contains various amounts of free oleyl alcohol. Macrogol oleyl ether with 2 to 5 units of ethylene oxide per molecule is a yellow liquid. Practically insoluble in water and in petroleum spirit; soluble in alcohol. Macrogol oleyl ether with 10 to 20 units of ethylene oxide per molecule is a yellowish-white, waxy mass. Dispersible or soluble in water; soluble in alcohol; practically insoluble in petroleum spirit. Macrogol oleyl ethers should be stored in airtight containers. Protect from light.

Polyoxyl 10 Oleyl Ether

Polioxil 10, éter oleílico de; Полиоксиэтиленгликоля и Олеиновой Кислоты Эфир.
UNII — JD797EF70J.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 10 Oleyl Ether). A mixture of the mono-oleyl ethers of mixed macrogols, the average polymer length being equivalent to not less than 9.1 and not more than 10.9 oxyethylene units. It may contain suitable stabilisers.

A soft white semisolid or pale yellow liquid with a bland odour. Soluble in water and in alcohol; dispersible in liquid paraffin and in propylene glycol with possible separation on standing. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

Profile

Macrogol oleyl ethers are mixtures of macrogol ethers of mainly oleyl alcohol. They are macrogol ether nonionic surfactants (p. 2164.2) and are used as emulsifying and solubilising agents.

Macrogol Poly(vinyl Alcohol) Grafted Copolymer

Ethenol Graft Polymer with Oxirane; Ethylene Glycol and Vinyl Alcohol Graft Copolymer; Macrogol-Poly(vinylalkohol)-

Pfropfcopolymer; Polyvinyl Alcohol-Polyethylene Glycol Graft Copolymer; PVA-PEG Graft Copolymer.
CAS — 96734-39-3; 121786-16-1.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Macrogol Poly(vinyl Alcohol) Grafted Copolymer); Copolymerum Macrogolo et Alcoholi Poly (vinylico) Constatum. A grafted copolymer of macrogol and poly(vinyl alcohol), having a mean relative molecular mass of about 45 000. It consists of about 75% of poly(vinyl alcohol) units and 25% of macrogol units. It may contain anhydrous colloidal silica to improve flowability. A white or slightly yellowish powder; opalescent solutions may be obtained during testing due to the presence of anhydrous colloidal silica. Very soluble in water; practically insoluble in dehydrated alcohol and in acetone. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 20% solution in water has a pH of 5.0 to 8.0.

USNF 31: (Ethylene Glycol and Vinyl Alcohol Graft Copolymer). A graft copolymer of ethylene glycol and vinyl alcohol. It consists of about 75% of vinyl alcohol units and 25% of ethylene glycol units. The copolymer is produced by using macrogol and vinyl acetate as starting materials. The macrogol forms the polymer backbone onto which polyvinyl acetate is grafted. Hydrolysis of polyvinyl acetate side-chains leads to formation of polyvinyl alcohol grafted chains. It may contain a glidant to improve flowability. A white or slightly yellowish powder. Very soluble in water; practically insoluble in anhydrous alcohol and in acetone. It dissolves in dilute acids and dilute solutions of alkali hydroxides. A 20% solution in carbon dioxide-free water has a pH of 5.0 to 8.0. Store at a temperature below 25 degrees.

Profile

Macrogol poly(vinyl alcohol) grafted copolymer is used in film coatings for immediate-release tablets and pellets.

Macrogol 40 Sorbitol Heptaoleate

Macrogol 40 Sorbitoli Heptaoleas; Macrogol-40-sorbitolheptaoleat.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogol 40 Sorbitol Heptaoleate). A mixture of esters of fatty acids, mainly oleic acid, and sorbitol ethoxylated with approximately 40 moles of ethylene oxide for each mole of sorbitol. 7 moles of oleic acid are used for each mole of sorbitol. It also contains macrogol fatty acid esters. A clear or slightly opalescent, yellowish, viscous, hygroscopic liquid. Dispersible in water; soluble in isopropyl myristate, in isopropyl palmitate, in mineral oils, and in vegetable fatty oils. Store in airtight containers. Protect from light.

Profile

Macrogol 40 sorbitol heptaoleate is a macrogol sorbitol ester, similar to the polysorbates but containing about 40 moles of ethylene oxide per mole of sorbitol rather than 20. It is a sorbitan ester nonionic surfactant (p. 2164.2) and is used as an emulsifier in topical preparations.

Macrogol Stearates

Ésteres de polietilenglicol; Ésteres de polioxietileno; Macrogol, ésteres del; Macrogol, stéarate de; Macrogoli Stearas; Makrogolio stearatas; Makrogolistearaatti; Makrogolstearat; Makrogol-stearát; Makrogol-sztearát; Polyoxyethylene Glycol Stearates; Polyoxyethylene Stearates; Polyoxyl Stearates; Макрогола Стеараты; Полиэтиленгликоля Стеараты.
CAS — 9004-99-3.

Nomenclature. There are two systems of nomenclature used for these compounds; these substances have the general formula $C_{17}H_{35}COO.[O.CH_2CH_2]_n.H$. In the systems used by *BAN* and *USAN* the numbers in the names refer to the approximate polymer length in oxyethylene units whereas in the system used by *INN* the number refers to the average molecular weight of the polymer chain. Thus, the names Macrogol 8 Stearate (*BAN*), Polyoxyl 8 Stearate (*USAN*), and Macrogol Stearate 400 (*rINNM*) all describe the same compound.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Macrogol Stearate). A mixture of the mono- and di-esters of mainly stearic acid and/or palmitic acid and macrogols. It may be obtained by ethoxylation or by esterification of macrogols with stearic acid 50 (type I) or stearic acid 95 (type II). The average polymer length is equivalent to 6 to 100 ethylene oxide units per molecule (nominal value). It may contain free macrogols. White or slightly yellowish waxy mass. Soluble in alcohol and in isopropyl alcohol. Compounds containing 6 to 9 units of ethylene oxide per molecule are practically insoluble but freely dispersible in water; miscible with fatty oils and with waxes. Compounds containing 20 to 100 units of ethylene oxide per molecule are soluble in water; practically insoluble in fatty oils and in waxes. Store in airtight containers.

USNF 31: (Polyoxyl Stearate). A mixture of the mono- and di-esters of mainly stearic (octadecanoic) acid and/or palmitic (hexadecanoic) acid and polyethylene glycols. The fatty acids may be of vegetable, animal, or synthetic origin. Polyoxyl Stearate Type I or Type II differs in its content of stearic acid. It may contain free polyethylene glycols. The average polymer length is equivalent to 6 to 100 ethylene oxide units per molecule (nominal value). A white or slightly yellowish waxy mass. Soluble in alcohol and in isopropyl alcohol. Polyoxyl stearate corresponding to a product with 6 to 8 units of ethylene oxide per molecule is practically insoluble in water; soluble in fatty oils and in waxes. Polyoxyl stearate corresponding to a product with 20 to 100 units of ethylene oxide per molecule is soluble in water; practically insoluble in fatty oils and in waxes.

Store in airtight containers. Protect from light and moisture.

Polyoxyl 40 Stearate *(USAN)*

E431; Estearato de macrogol 2000; Estearato de Polioxila 40; Macrogol 2000, Stéarate de; Macrogol 40 Stearate (BAN); Macrogol Ester 2000; Macrogol Stearate 2000 (rINNM); Macrogol Stearate 2000; Macrogoli Stearas 2000; Polyoxyethylene 40 Stearate; Stearethate 40; Макрогола 2000 Стеарат.
UNII — 13A4J4NH9I (polyoxyl stearate); ECU18C66Q7 (polyoxyl 40 monostearate); 1PC44PS35Z (polyoxyl 40 distearate).

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 31: (Polyoxyl 40 Stearate). A mixture of the mono- and di-esters of stearic acid and mixed macrogols, the average polymer length being about 40 oxyethylene units. It contains not less than 17% and not more than 27% of free macrogols. It is a waxy, white to light tan solid, odourless or with a faint fat-like odour. Congealing range 37 degrees to 47 degrees. Soluble in water, in alcohol, in acetone, and in ether; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Incompatibility. Macrogol stearates have been reported to be generally stable with electrolytes and weak acids or bases although strong acids or bases may cause hydrolysis and saponification. Discoloration or precipitation may occur with phenolic substances and complexation with preservatives. Decrease in the antimicrobial activity of bacitracin, chloramphenicol, phenoxymethylpenicillin, and tetracycline has been stated to occur with concentrations of macrogol stearates exceeding 5%.

Profile

Macrogol stearates are macrogol ester nonionic surfactants (p. 2164.2) that are used as emulsifying and solubilising agents.

Macrogolglycerol Cocoates

Macrogol Glycerol Cocoates; Macrogol Glyceryl Cocoates; Macrogolglycerolcocoate; Macrogolglyceroli Cocoates; PEG Glyceryl Cocoates; Polyethylene Glycol Glyceryl Cocoates.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogolglycerol Cocoates). Mixtures of mono-, di-, and triesters of ethoxylated glycerol with fatty acids of vegetable origin having a composition corresponding to the fatty acid composition of the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera.* The average number of moles of ethylene oxide reacted per mole of substance (nominal value) is either 7 (macrogol 7 glycerol cocoate) or 23 (macrogol 23 glycerol cocoate). Relative density about 1.05 for macrogol 7 glycerol cocoate and about 1.09 for macrogol 23 glycerol cocoate A clear, yellowish, oily liquid. Soluble in water and in alcohol; practically insoluble in petroleum spirit at 50 degrees to 70 degrees for macrogol 7 glycerol cocoate and macrogol 23 glycerol cocoate.

Profile

Macrogolglycerol cocoates are ethoxylated glycerol ester nonionic surfactants (p. 2164.2). They are used as nonionic surfactants cleansers, emulsifiers and solubilisers in topical preparations.

Magnesium Silicate

E553(a); Silicato de magnesio; Магний Кремнекислый; Силикат Магния.
CAS — 1343-88-0.
ATC — A02AA05.
ATC Vet — QA02AA05.
UNII — 9B9691B2N9.

NOTE. The code E553(a) has also been applied to magnesium trisilicate.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 31: (Magnesium Silicate). A compound of magnesium oxide and silicon dioxide. It contains not less than 15.0% of magnesium oxide and not less than 67.0% of silicon dioxide, calculated on the ignited basis. It is a fine, white, odourless powder, free from grittiness. Insoluble in water and in alcohol. It is readily decomposed by mineral acids. pH of a well-mixed 10% suspension in water is between 7.0 and 10.8.

Profile

Magnesium silicate is used in the food industry and in pharmaceutical manufacturing as an anticaking agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Acnoil Free†.

Multi-ingredient Preparations. ***Braz.***: Cutisanol; ***Fr.***: ZeaSorb.

Magnesium Stearate

572; E470b (magnesium salts of fatty acids); Estearato de magnesio; Estearato de Magnésio; Magnesii Stearas; Magnésium, stéarate de; Magnesiumstearaat; Magnesiumstearaatti; Magnesiumstearat; Magnézium-sztearát; Magnezu stearynian; Magnio stearatas; Stearan hořečnatý; Stéarate de magnésium; Stearato di magnesio; Stearynian magnezu; Стеарат Магния.
Magnesium octadecanoate.
CAS — 1555-53-9 (magnesium oleate); 2601-98-1 (magnesium palmitate); 557-04-0 (magnesium stearate).
UNII — 70097M6I30.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *Viet.* Also in *USNF.*

Ph. Eur. 8: (Magnesium Stearate). A compound of magnesium with a mixture of solid organic acids and consisting mainly of variable proportions of magnesium stearate ($C_{36}H_{70}MgO_4 = 591.3$) and magnesium palmitate ($C_{32}H_{62}MgO_4 = 535.1$) obtained from sources of vegetable or animal origin. It contains 4.0 to 5.0% of magnesium calculated on the dried substance. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90.0%. A white or almost white, very fine, light powder, greasy to the touch. Practically insoluble in water and in dehydrated alcohol.

USNF 31: (Magnesium Stearate). A compound of magnesium with a mixture of solid organic acids, and consisting mainly of variable proportions of magnesium stearate ($C_{36}H_{70}MgO_4 = 591.3$) and magnesium palmitate ($C_{32}H_{62}MgO_4 = 535.1$). It is a very fine, light, white powder, slippery to touch. Insoluble in water, in alcohol, and in ether.

Profile

Magnesium stearate is a metal soap anionic surfactant (p. 2164.1). It is used as a lubricant in the manufacture of tablets and capsules, and has been used as a dusting powder and in barrier creams. It is also used in foods, cosmetics, and other industrial applications.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Holomagnesio Vital; ***Israel***: Acti Talc; ***Ital.***: Ferromina; ***Philipp.***: Exofat; Johnson's Baby Double Protection Powder; Thinber Fiber Complex†; ***UK***: Calci-Plus.

Homoeopathic Preparations. ***Canad.***: Biomag†.

Maleic Acid

Acide maléique; Ácido *cis*-buteno dioico; Acido Maleico; Ácido maleínico; Acidum Maleicum; (*Z*)-Butenedioic Acid; Kwas maleinowy; Kyselina maleinová; Maleico, ácido; Maleiinihappo; Maleïnezuur; Maleino rūgštis; Maleinsäure; Maleinsav; Maleinsyra; Maleïnskåbe; Toxilic Acid; Малеиновая Кислота.

cis-Butenedioic acid.
$C_2H_2(CO_2H)_2$=116.1
CAS — 110-16-7.
UNII — 91XW058U2C.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Maleic Acid). A white or almost white, crystalline powder. Freely soluble in water and in alcohol. A 5% solution in water has a pH of less than 2. Store in glass containers. Protect from light.

USNF 31: (Maleic Acid). A white crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in ether. Store in airtight glass containers. Protect from light.

Profile

Maleic acid is a dicarboxylic acid used to adjust the acidity of pharmaceutical preparations and as an acidulant in foods.

Maltol

636; Мальтол.
3-Hydroxy-2-methyl-4-pyrone.
$C_6H_6O_3$=126.1
CAS — 118-71-8.
UNII — 3A9RD92BS4.

Pharmacopoeias. In *USNF.*

USNF 31: (Maltol). A white, crystalline powder having a characteristic caramel-butterscotch odour, suggestive of a fruity-strawberry aroma in dilute solution. 1 g dissolves in about 82 mL of water, in 21 mL of alcohol, in 80 mL of glycerol, and in 28 mL of propylene glycol. Store in airtight container. Protect from light.

Ethyl Maltol

637; Этил Мальтол.
2-Ethyl-3-hydroxy-4-pyrone.
$C_7H_8O_3$=140.1
CAS — 4940-11-8.
UNII — L6Q8K29L05.

Pharmacopoeias. In *USNF.*

USNF 31: (Ethyl Maltol). A white, crystalline powder having a cotton-candy odour and a sweet, fruitlike flavour in dilute solution. One g dissolves in about 55 mL of water, 10 mL of alcohol, 17 mL of propylene glycol, and 5 mL of chloroform. Store in airtight containers.

Profile

Maltol is used as a flavouring in pharmaceutical formulations and as a food additive. Ethyl maltol is used similarly.

2-Methoxyethanol

Éter monometílico de etilenglicol; Eter monometylowy glikolu etylenowego; Ethylene Glycol Monomethyl Ether; Metilglicol; 2-Metoxietanol; 2-Метоксиэтанол.
$C_3H_8O_2$=76.10
CAS — 109-86-4.
UNII — EK1L6XWI56.

Description. 2-Methoxyethanol is a clear, colourless to slightly yellow liquid. Wt per mL about 0.96 g. B.p. about 125 degrees. Miscible with water, with alcohol, with acetone, with dimethylformamide, with ether, and with glycerol. Store in airtight containers.

Uses

2-Methoxyethanol is used as an industrial solvent. Other glycol ethers, such as 2-butoxyethanol (p. 2172.1) and 1-*tert*-butoxy-2-propanol are also used.

Adverse Effects and Precautions

2-Methoxyethanol is irritant to mucous membranes. Ingestion may result in CNS depression with confusion, weakness, and in severe cases coma and death from respiratory depression. Nausea, metabolic acidosis, and renal damage may also occur. Prolonged industrial exposure to the vapour has been associated with severe effects on the CNS characterised by headache, dizziness, lethargy, weakness, ataxia, tremor, disorientation, mental changes, weight loss, and visual disturbances. Anaemia has also been reported. There has been concern about the potential for reproductive toxicity.

References to the toxicity of 2-methoxyethanol and other glycol ethers.

1. Health and Safety Executive. Glycol ethers. *Toxicity Review 10.* London: HMSO,1985.
2. WHO. 2-Methoxyethanol, 2-ethoxyethanol, and their acetates. *Environmental Health Criteria 115.* Geneva: WHO,1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc115.htm (accessed 30/06/04)
3. Browning RG, Curry SC. Clinical toxicology of ethylene glycol monoalkyl ethers. *Hum Exp Toxicol* 1994; **13:** 325–35.
4. Johanson G. Toxicity review of ethylene glycol monomethyl ether and its acetate ester. *Crit Rev Toxicol* 2000; **30:** 307–45.
5. Bagchi G, Waxman DJ. Toxicity of ethylene glycol monomethyl ether: impact on testicular gene expression. *Int J Androl* 2008; **31:** 269–74.

Handling. Suitable precautions should be taken to avoid skin contact with 2-methoxyethanol as it can penetrate skin and produce systemic toxicity.

Methyl Alcohol

Alcohol de la madera; Alcohol de quemar; Alcohol metílico; Alkohol metylowy; Brandalcohol; Carbinol; Metanol; Metanoli; Metanolis; Metanolo; Metanols; Metanool; Methanol; Méthanol; Methanolum; Monohidroximetano; Метиловый Спирт; Метанол.
CH_3OH=32.04
CAS — 67-56-1.
UNII — Y4S76JWI15.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Methanol). A colourless, clear, volatile, hygroscopic liquid. It is flammable. B.p. about 64 degrees. Relative density 0.791 to 0.793. Miscible with water and with dichloromethane. Store in airtight containers.

The BP 2014 gives Methyl Alcohol as an approved synonym.

USNF 31: (Methyl Alcohol). A clear, colourless, flammable liquid having a characteristic odour. Miscible with water, with alcohol, with ether, with benzene, and with most other organic solvents. Store in airtight containers remote from heat, sparks, and open flames.

Uses

Methyl alcohol is used as a pharmaceutical and industrial solvent. It is also used as 'wood naphtha' to denature ethanol in the preparation of industrial methylated spirits. Methyl alcohol is also used as an extraction solvent in food processing.

Adverse Effects

Immediate signs of acute poisoning after ingestion of methyl alcohol resemble those of ethanol (alcohol; ethyl alcohol) intoxication (see p. 1733.3), but are milder. Characteristic symptoms of methyl alcohol poisoning are caused by toxic metabolites and develop after a latent period of about 12 to 24 hours, or longer if taken with ethanol. The outstanding features of poisoning are metabolic acidosis with rapid, shallow breathing, visual disturbances which often proceed to irreversible blindness, and severe abdominal pain. Other symptoms include headache, gastrointestinal disturbances, pain in the back and extremities, and coma which in severe cases may result in death due to respiratory failure or, rarely, to circulatory collapse. Mania and convulsions occasionally occur. Individual response to methyl alcohol varies widely. Ingestion of 30 mL is considered to be potentially fatal.

Absorption of methyl alcohol through the skin or inhalation of the vapour may also lead to toxic systemic effects.

References to the adverse effects of methyl alcohol.

1. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings: mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986; **1:** 309–34.
2. Anderson TJ, *et al.* Neurologic sequelae of methanol poisoning. *Can Med Assoc J* 1987; **136:** 1177–9.
3. Cavalli A, *et al.* Severe reversible cardiac failure associated with methanol intoxication. *Postgrad Med J* 1987; **63:** 867–8.
4. Shapiro L, *et al.* Unusual case of methanol poisoning. *Lancet* 1993; **341:** 112.
5. Medinsky MA, Dorman DC. Recent developments in methanol toxicity. *Toxicol Lett* 1995; **82–83:** 707–11.
6. McKellar MJ, *et al.* Acute ocular methanol toxicity: clinical and electrophysiological features. *Aust N Z J Ophthalmol* 1997; **25:** 225–30.
7. Williams GF, *et al.* Methanol poisoning: a review and case study of four patients from central Australia. *Aust Crit Care* 1997; **10:** 113–18.
8. Shelby M, *et al.* NTP-CERHR expert panel report on the reproductive and developmental toxicity of methanol. *Reprod Toxicol* 2004; **18:** 303–90.
9. Hantson PE. Intoxication aiguë par le méthanol: physiopathologie, pronostic et traitement. *Bull Mem Acad R Med Belg* 2006; **161:** 425–34.
10. Paasma R, *et al.* Methanol poisoning and long term sequelae—a six years follow-up after a large methanol outbreak. *BMC Clin Pharmacol* 2009; **9:** 5. Available at: http://www.biomedcentral.com/content/pdf/1472-6904-9-5.pdf (accessed 16/06/10)
11. Jammalamadaka D, Raissi S. Ethylene glycol, methanol and isopropyl alcohol intoxication. *Am J Med Sci* 2010; **339:** 276–81.
12. Epker JL, Bakker J. Accidental methanol ingestion: case report. *BMC Emerg Med* 2010; **10:** 3. Available at: http://www.biomedcentral.com/content/pdf/1471-227X-10-3.pdf (accessed 27/06/11)
13. Singh A, *et al.* Portrait of a methanol-intoxicated brain. *Am J Med* 2011; **124:** 125–7.

Handling. Suitable precautions should be taken to avoid skin contact with methyl alcohol as it can penetrate skin and produce systemic toxicity.

Treatment of Adverse Effects

Gastric aspiration may be considered if the patient presents within 1 hour of ingesting methyl alcohol. Activated charcoal is probably of little use as it does not absorb significant amounts of methyl alcohol. Metabolic acidosis (p. 1775.2) should be corrected immediately with intravenous sodium bicarbonate. If significant amounts of methyl alcohol have been ingested, early treatment with an antidote (ethanol or fomepizole) is recommended. Ethanol delays the oxidation of methyl alcohol to its toxic metabolites formaldehyde and formic acid; dosage is adjusted to achieve and maintain a blood-ethanol concentration of 1 to 1.5 mg/mL. In the UK, the National Poisons Information Service recommends that it be given as follows. An *oral* **loading** dose should be given equivalent to 800 mg/kg of absolute (100% v/v) C_2H_5OH. This may be given in the form of alcoholic spirits such as whisky, gin, or vodka (about 40% v/v C_2H_5OH) in a dose of 2.5 mL/kg. Alternatively, an *intravenous* loading dose of 10 mL/kg of C_2H_5OH 10% v/v may be given over 30 minutes via a central line. Loading doses may be followed by oral or intravenous **maintenance** doses as follows:

orally (as a 40% v/v solution of C_2H_5OH):
- for an average adult, 0.375 mL/kg per hour
- for a non-drinker or child, 0.25 mL/kg per hour
- for a chronic drinker, 0.58 mL/kg per hour

by *intravenous infusion* (as a 10% v/v solution of C_2H_5OH):
- for an average adult, 1.5 mL/kg per hour
- for a non-drinker or child, 1 mL/kg per hour
- for a chronic drinker, 2.3 mL/kg per hour

A 5% v/v solution of C_2H_5OH may be given either *orally* or *intravenously* at twice the maintenance doses described above for the 10% solution.

Maintenance doses should be continued until methyl alcohol concentrations are undetectable, or have fallen below 50 micrograms/mL with resolution of systemic toxicity.

Fomepizole (p. 1553.1), an inhibitor of alcohol dehydrogenase, is also used; it inhibits the metabolism of methyl alcohol to its toxic metabolites.

Haemodialysis may be indicated to increase the removal of methyl alcohol and its toxic metabolites. Peritoneal dialysis has been used but is less efficient. Haemodialysis may be considered if the blood-methyl alcohol concentration is greater than 500 micrograms/mL, if there is severe metabolic acidosis unresponsive to sodium bicarbonate, or there is visual disturbance, CNS toxicity, renal failure, or severe electrolyte disturbance. If haemodialysis is used, a constant blood-ethanol concentration may be ensured either by increasing the ethanol infusion rate or by addition of ethanol to the dialysate fluid.

Treatment should not be stopped prematurely since oxidation and excretion of methyl alcohol may continue for several days; patients should, therefore, be closely observed and monitored. Suitable supportive treatment should be carried out as required.

Folinic acid and folic acid have been given in the treatment of methyl alcohol toxicity because they may enhance the metabolism of formic acid.

References.

1. Barceloux DG, *et al.* American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; **40:** 415–46.

Pharmacokinetics

Methyl alcohol is readily absorbed from the gastrointestinal tract and distributed throughout the body fluids. It may also be absorbed after inhalation or through large areas of skin. Oxidation by alcohol dehydrogenase with formation of formaldehyde and formic acid takes place mainly in the liver and also in the kidneys. These metabolites are thought to be largely responsible for the characteristic symptoms of methyl alcohol poisoning. Metabolism is much slower than for ethanol, which competitively inhibits the metabolism of methyl alcohol. Oxidation and excretion may continue for several days after ingestion. Elimination of unchanged methyl alcohol via the lungs and in the urine is a minor route of excretion.

References.

1. Coulter CV, *et al.* The pharmacokinetics of methanol in the presence of ethanol: a case study. *Clin Pharmacokinet* 2011; **50:** 245–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Methazil†.

Methyl *tert*-Butyl Ether

Éter metil *terc*-butílico; Éter metilterbutílico; Eter *tert*-butylowo-metylowy; Methyl Terbutyl Ether; Méthyl tert-butyl éther; Methyl Tertiary Butyl Ether; Metil-*t*-butil etere;

Metüültert-butüüleeter; Metyylitertiääributyylieetteri; MTBE; *tert*-Butylmethylether; Метил-трет-бутиловый Эфир.
2-Methoxy-2-methylpropane.
$C_5H_{12}O$=88.15
CAS — 1634-04-4.
UNII — 29I4YB3589.

Description. Methyl *tert*-butyl ether is a volatile, flammable liquid. Wt per mL about 0.74g. B.p. about 55 degrees. Store in airtight containers.

Stability. Explosive peroxides may be generated by the atmospheric oxidation of methyl *tert*-butyl ether, but the risk is lower than with solvent ether.

Uses and Administration

Methyl *tert*-butyl ether is used as an industrial solvent. It has also been used for the dissolution of cholesterol gallstones, but is no longer generally recommended (see below).

Gallstones. Gallstones (p. 2639.1) are usually treated surgically, but therapy with oral bile acids to dissolve the stones may have a role in some patients. Direct instillation of solvents into the gallbladder has also been tried, and positive results have been reported[1-4] with use of methyl *tert*-butyl ether. However, the technique is not generally recommended due to the frequency and severity of complications. Nausea has been reported in about one-third of patients, sometimes with vomiting, and sedation may also occur. Severe complications that have been reported include ulcerative duodenitis and intravascular haemolysis,[1] and coma and acute renal failure.[5]

1. Thistle JL, *et al.* Dissolution of cholesterol gallbladder stones by methyl *tert*-butyl ether administered by percutaneous transhepatic catheter. *N Engl J Med* 1989; **320:** 633–9.
2. Foerster E-Ch, *et al.* Direct dissolution of gallbladder stones. *Lancet* 1989; **i:** 954.
3. Hellstern A, *et al.* Gall stone dissolution with methyl tert-butyl ether: how to avoid complications. *Gut* 1990; **31:** 922–5.
4. McNulty J, *et al.* Dissolution of cholesterol gall stones using methyltertbutyl ether: a safe effective treatment. *Gut* 1991; **32:** 1550–3.
5. Ponchon T, *et al.* Renal failure during dissolution of gallstones by methyl-*tert*-butyl ether. *Lancet* 1988; **ii:** 276–7.

Adverse Effects

Methyl *tert*-butyl ether is irritant and may cause CNS depression. Adverse effects that have been reported after use as a gallstone solvent are described under Uses and Administration, above.

Methyl Butyl Ketone

Butilmetilcetona; 2-Hexanone; MBK; Methyl *n*-Butyl Ketone; Metil *n*-butilcetona; Metilbutilcetona; Propylacetone; Метилбутилкетон.
Hexan-2-one.
$C_6H_{12}O$=100.2
CAS — 591-78-6.
UNII — 6QDY60NH6N.

Description. Methyl butyl ketone is a colourless, volatile liquid. Wt per mL about 0.82 g. B.p. about 127 degrees. Store in airtight containers.

Methyl Isobutyl Ketone

Hexone; Isobutilmetilcetona; Isopropylacetone; Méthylisobutylcétone; Methylisobutylketon; Metilisobutilchetone; Metyyli-isobutyyliketoni; MIBK; Метилизобутилкетон.
4-Methylpentan-2-one.
$C_6H_{12}O$=100.2
CAS — 108-10-1.
UNII — U5T7B88CNP.

Pharmacopoeias. In *USNF.*

USNF 31: (Methyl Isobutyl Ketone). A transparent, colourless, mobile, volatile liquid having a faint ketonic and camphoraceous odour. Sp. gr. not more than 0.799. Distilling range 114 degrees to 117 degrees. Slightly soluble in water; miscible with alcohol, with ether, and with benzene. Store in airtight containers.

Uses

Methyl isobutyl ketone is used as an industrial and pharmaceutical solvent and also as an alcohol denaturant. Methyl butyl ketone is used as an industrial solvent.

Adverse Effects and Precautions

Methyl butyl ketone and methyl isobutyl ketone may depress the CNS in high concentrations. Their vapours are irritating to mucous membranes. Methyl isobutyl ketone may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

References.
1. WHO. Methyl isobutyl ketone. *Environmental Health Criteria 117.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc117.htm (accessed 30/06/04)
2. WHO. Methyl isobutyl ketone health and safety guide. *IPCS Health and Safety Guide 58.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg058.htm (accessed 30/06/04)

Effects on the nervous system. Peripheral neuropathy[1] has occurred after occupational exposure to methyl butyl ketone, particularly an outbreak of neuropathy in a printing plant after the replacement of methyl isobutyl ketone by methyl butyl ketone in a solvent mixture with methyl ethyl ketone. Methyl ethyl ketone may have potentiated the neurotoxicity induced by methyl butyl ketone.

For further discussion of neurotoxicity after occupational exposure to solvents including methyl butyl ketone, see under Toluene, p. 2216.2.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.

Handling. Suitable precautions should be taken to avoid skin contact with methyl butyl ketone or methyl isobutyl ketone as they can penetrate skin and produce systemic toxicity.

Methyl Chloride

Chloormethaan; Chlormethan; Chlorometan; Chlorométhane; Cloreto de metila; Clorometano; Cloruro de metilo; Hlormetāns; Klormetan; Klórmetán; Methylchlorid; Metylklorid; Monochloromethane; Метилхлорид.
Chloromethane.
CH_3Cl=50.48
CAS — 74-87-3.
UNII — A6R43525YO.

Description. Methyl chloride is a colourless gas compressed to a colourless liquid with an ethereal odour. B.p. about -24 degrees. Store in airtight containers.

Uses

Methyl chloride is used as an industrial solvent. It has been used as an aerosol propellant and refrigerant and was formerly used as a local anaesthetic.

Adverse Effects and Treatment

Symptoms of methyl chloride intoxication often appear after a latent period of several hours and are similar after acute or chronic exposure to the vapour. Symptoms include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and signs of CNS depression including headache, weakness, drowsiness, confusion, visual disturbances, and incoordination progressing to convulsions, coma, and death from respiratory depression in severe cases. There have been a few reports of hepatic and renal damage.

Treatment consists of removal from exposure and supportive and symptomatic measures. Neurological effects may persist for many months.

References to the toxicity of methyl chloride.

1. Repko JD, Lasley SM. Behavioral, neurological, and toxic effects of methyl chloride: a review of the literature. *CRC Crit Rev Toxicol* 1979; **6:** 283–302.
2. IARC/WHO. Methyl chloride. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 737–47. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Methyl Ethyl Ketone

Ethyl Methyl Ketone; Etilmetilcetona; Etylometyloketon; MEK; Metiletilcetona; Metyloetyloketon; Метилэтилкетон.
Butan-2-one.
C_4H_8O=72.11
CAS — 78-93-3.
UNII — 6PT9KLV9IO.

Description. Methyl ethyl ketone is a colourless flammable liquid with an acetone-like odour. Wt per mL about 0.81 g. B.p. 79 degrees to 81 degrees. Soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Uses

Methyl ethyl ketone is used as an industrial solvent and as an extraction solvent in food processing.

Adverse Effects

Methyl ethyl ketone is irritant. Inhalation may result in mild CNS effects including headache and dizziness; nausea and vomiting may also occur.

Methyl ethyl ketone may be implicated in volatile substance abuse (see under Toluene, p. 2216.3).

References.
1. WHO. Methyl ethyl ketone. *Environmental Health Criteria 143.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc143.htm (accessed 30/06/04)

Effects on the nervous system. There are isolated reports of neurotoxicity produced by methyl ethyl ketone alone.[1] These include 1 of retrobulbar neuritis and 1 of peripheral neuropathy. It has been suggested, however, that methyl ethyl ketone potentiates the peripheral neuropathy induced by methyl butyl ketone and *n*-hexane.

For further discussion of neurotoxicity after occupational exposure to solvents including methyl ethyl ketone, see under Toluene, p. 2216.2.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.

Methylcellulose *(rINN)*

E461; Méthylcellulose; Methylcellulosum; Metilcelulosa; Metilceliuliozė; Metilcelulóz; Metilcelulosa; Metylcelulosa; Metyloceluloza; Metyyliselluloosa; Метилцеллюлоза.
CAS — 9004-67-5.
ATC — A06AC06.
ATC Vet — QA06AC06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Methylcellulose). A cellulose having some of the hydroxyl groups in the form of the methyl ether. Various grades of methylcellulose are available and are distinguished by appending a number indicating the apparent viscosity in millipascal seconds of a 2% w/w solution at 20 degrees. It contains 26.0 to 33.0% of methoxy groups, calculated on the dried basis. It is a white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene; dissolves in cold water, forming a colloidal solution. A 2% w/w solution in water has a pH of 5.0 to 8.0.

USP 36: (Methylcellulose). A methyl ether of cellulose. When dried at 105 degrees for 2 hours, it contains 27.5 to 31.5% of methoxy groups. It is a white, fibrous powder or granules. It swells in water and produces a clear to opalescent, viscous, colloidal suspension; insoluble in alcohol, in chloroform, and in ether; soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform. Its aqueous suspensions are neutral to litmus.

Incompatibility. Incompatibilities of methylcellulose have been reported with several compounds including chlorocresol, hydroxybenzoates, and phenol. Large amounts of electrolytes increase the viscosity of methylcellulose mucilages owing to salting-out of the methylcellulose; in very high concentrations of electrolytes, the methylcellulose may be completely precipitated.

Uses and Administration

The various grades of methylcellulose are widely used in pharmaceutical manufacturing as emulsifying, suspending, and thickening agents and as binding, disintegrating, and coating agents in tablet manufacturing. Low-viscosity grades are preferred for use as emulsifying agents as the surface tension produced is lower than with the higher-viscosity grades. Low-viscosity grades may also be used as suspending or thickening agents for liquid oral dosage forms and solutions of methylcellulose may be used as replacements for sugar-based syrups or other suspension bases. For thickening topically applied products such as gels and creams a high-viscosity grade is usually used. In tablet technology low- or medium-viscosity grades are used as binding agents while high-viscosity grades act as tablet disintegrants by swelling on contact with the disintegration medium. For tablet coating, highly substituted low-viscosity grades are usually used. Methylcellulose may also be included in modified-release tablet formulations.

Methylcellulose is also used as an emulsifier and stabiliser in the food industry.

Methylcellulose is used clinically as a bulk-forming agent. Medium- or high-viscosity grades are used as bulk laxatives in the treatment of constipation (p. 1804.3); by taking up moisture they increase the volume of the faeces and promote peristalsis. Methylcellulose is usually given in an oral dosage of up to 6 g daily in divided doses, taken with plenty of fluid. In the UK, the *BNFC* recommends a dose of 1 g twice daily for children aged from 7 to 12 years. Methylcellulose is also given in similar doses but with a minimum amount of water for the control of diarrhoea (p. 1805.2) and for the control of faecal consistency in ostomies. It is also used in the management of diverticular disease (p. 1806.2). Methylcellulose has also been used as an aid to appetite control in the management of obesity (p. 2315.1) but there is little evidence of efficacy.

Solutions of high-viscosity grade methylcellulose (usually 0.5 to 1%) have been used as a vehicle for eye

drops, as artificial tears, and in contact lens care, but hypromellose (p. 2189.3) is now generally preferred for this purpose.

Adverse Effects

Large quantities of oral methylcellulose may temporarily increase flatulence and distension and there is a risk of intestinal obstruction. Oesophageal obstruction may occur if compounds such as methylcellulose are swallowed dry.

Precautions

Methylcellulose and other bulk-forming agents should not be given orally to patients with intestinal obstruction or conditions likely to lead to intestinal obstruction. They should be taken with sufficient fluid to prevent faecal impaction or oesophageal obstruction, and should not be taken immediately before going to bed. Methylcellulose should not be used in infective bowel disease.

Interactions

Bulk laxatives such as oral methylcellulose lower the transit time through the gut and could affect the absorption of other drugs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bulk†; ***Canad.***: Entrocel†; ***Irl.***: Celevac; ***Ital.***: Lacrimart; ***Spain***: Muciplazma; ***UK***: Celevac; ***USA***: Citrucel; Murocel†.

Multi-ingredient Preparations. ***Austral.***: 3B Beer Belly Buster†; Citri Slim+Trim†; ***Braz.***: Kolantyl DMP; Kolantyl; Kolantyl; ***Chile***: Vaselina Emulsionada; ***Fr.***: Lubri-Mucal; ***India***: Exxon; Fibropil; N-Zolin; NCZ; Nefacool; Ofet-H; ***Ital.***: Merankol Pastiglie; ***S.Afr.***: Kolantyl†; Merasyn†.

Pharmacopoeial Preparations
BP 2014: Methylcellulose Granules; Methylcellulose Tablets;
USP 36: Methylcellulose Ophthalmic Solution; Methylcellulose Oral Solution; Methylcellulose Tablets.

Microcrystalline Wax

Amorphous Wax; Cera microcristalina; Cerum microcrystallinum; Cire microcristalline; E905; INS No. 905c; Mikrokristályos Viasz; Petroleum Ceresin; Petroleum Wax (microcrystalline); Микрокристаллический Воск.
CAS — 63231-60-7.
UNII — XOF597Q3KY.

NOTE. The code E907 has been used for refined microcrystalline wax but is now used for hydrogenated polydecene (p. 2188.3).

Pharmacopoeias. In *USNF*.

USNF 31: (Microcrystalline Wax). A mixture of straight-chain, branched-chain, and cyclic hydrocarbons, obtained by solvent fractionation of the still bottom fraction of petroleum by suitable dewaxing or de-oiling means. A white or cream-coloured odourless waxy solid. Melting range 54 degrees to 102 degrees. Insoluble in water; sparingly soluble in dehydrated alcohol; soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. Store in airtight containers.

Profile

Microcrystalline wax is used as a stiffening agent in creams and ointments and as a coating agent for solid dosage forms, including modified-release preparations. Microcrystalline wax is also used in foods and cosmetics.

Monoglyceride Citrate

E472c (citric acid esters of mono- and diglycerides of fatty acids).
CAS — 36291-32-4.

Pharmacopoeias. In *USNF*.

USNF 31: (Monoglyceride Citrate). A mixture of glyceryl mono-oleate and its citric acid monoester. It contains not less than 14.0% and not more than 17.0% total citric acid, calculated on the anhydrous basis. A soft white to ivory-coloured, waxy solid with a lard-like consistency and bland odour. Insoluble in water; dispersible in alcohol and in most common fat solvents.

Profile

Monoglyceride citrate is used as an emulsifier and as a stabiliser for antoxidants in the food industry.

Monophosphoryl Lipid A

Adeps A 3-*O*-Desacyl-4′-monophosphorylatus; 3-*O*-Desacyl-4′-monophosphoryl Lipid A; MPL.
UNII — MWC0ET1L2P.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (3-*O*-Desacyl-4′-monophosphoryl lipid A). A detoxified derivative of the lipopolysaccharide (LPS) of *Salmonella minnesota*, strain R595, which retains the immunostimulatory activities of the parent LPS. It consists of a mixture of congeners, all containing a backbone of β1′→6-linked disaccharide of 2-deoxy-2-aminoglucose phosphorylated at the 4′-position, but differing in the fatty acid substitutions at the 2, 2′, and 3′ positions. It is a lyophilised powder or a sterile liquid.

Profile

Lipopolysaccharides are important components of bacterial cell membranes and act as endotoxins, stimulating an immune response. Detoxified derivatives such as monophosphoryl lipid A are used as vaccine adjuvants, often combined with aluminium hydroxide. The immunostimulatory activities of monophosphoryl lipid A when combined with a vaccine include up-regulation of co-stimulatory molecules on antigen-presenting cells and secretion of pro-inflammatory cytokines, resulting in an enhanced immune response of the Th1-type against the antigens.

References.
1. Casella CR, Mitchell TC. Putting endotoxin to work for us: monophosphoryl lipid A as a safe and effective vaccine adjuvant. *Cell Mol Life Sci* 2008; **65**: 3231–40.

Monosodium Glutamate

Chinese Seasoning; E621; Glutaman sodný; Glutamat monosòdic; Glutamate monosodique; Glutamato monosódico; Glutamato monossódico; Glutaminian sodu; Glutammato monosodico; Mononatrio glutamatas; Mononatriumglutamaat; Mononatriumglutamat; Monosodyum glutamat; MSG; Naatriumvesinikglutamaat; Natrii Glutamas; Natriumglutamaatti; Natriumglutamat; Nátrium-glutamát; Sodium Glutamate; Мононатриев глутамат; Глутамат Натрия; Глутамат-мононатрий.
Sodium hydrogen L-(+)-2-aminoglutarate monohydrate.
$C_5H_8NNaO_4,H_2O$=187.1
CAS — 142-47-2 (anhydrous monosodium glutamate).
UNII — W81N5U6R6U (monosodium glutamate); C3C196L9FG (anhydrous monosodium glutamate).

Pharmacopoeias. In *Chin.* Also in *USNF*.

USNF 31: (Monosodium Glutamate). White, practically odourless, free-flowing crystals or crystalline powder. It may have either a slightly sweet or slightly salty taste. Freely soluble in water; sparingly soluble in alcohol. pH of a 5% solution in water is between 6.7 and 7.2. Store in airtight containers.

Profile

Monosodium glutamate is widely used as a flavour enhancer and imparts a meaty flavour.

In susceptible individuals, ingestion of foods containing monosodium glutamate may cause MSG symptom complex, a condition characterised by burning sensations, or numbness, in the back of the neck and arms, tingling or warmth or weakness in the face, back and neck, facial pressure, chest pain, headache, nausea, drowsiness or weakness. In patients with asthma, who may be predisposed to develop this condition, bronchospasm may occur. The symptoms tend to occur within an hour of eating 3 g or more of monosodium glutamate on an empty stomach.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Wei Mei (味美).

Multi-ingredient Preparations. ***Chile***: Glutacyl Vitaminado; ***Ital.***: Dermitina; ***Thai.***: Hemo-Cyto-Serum†.

Musk

Almíscar; Almizcle; Deer Musk; Mesc; Misk; Mosc.; Moschus; Musc; Muschio; Muskus; Muskusas; Mysk; Myski; Piżmo; Piżmo; Мускус.
CAS — 123-69-3 (musk); 541-91-3 (muskone).
UNII — 0951377U8F (musk); 8KFK4W7KP7 (musk sac resin); 5JO79R7S9R (muskone).

Pharmacopoeias. In *Chin.*

Profile

Musk is the dried secretions from the preputial follicles of the musk deer, *Moschus moschiferus* or some other spp. of *Moschus* (Cervidae). It is used as a fragrance and fixative in perfumery. The main source of musk's fragrance is muskone (muscone).

A series of nitrated tertiary butyl toluenes or xylenes, or related compounds, are used as artificial musks. Musk ambrette, a synthetic nitromusk compound used in perfumery and as a food flavour, has been reported to cause contact dermatitis and photosensitivity.

Homoeopathy

Musk has been used in homoeopathic medicines under the following names: Moschus; Mosc.

References.
1. Schmeiser HH, *et al.* Evaluation of health risks caused by musk ketone. *Int J Hyg Environ Health* 2001; **203**: 293–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ukr.***: Bezornil (Безорнил).

Homoeopathic Preparations. ***Austria***: Ignatia-Homaccord; ***Cz.***: Hormeel S; Ypsiloheel; ***Hung.***: Hormeel S; ***Switz.***: Ignatia-Homaccord.

Myristic Acid

Kwas mirystynowy; 1-Tetradecanoic Acid; 1-Tridecanecarboxylic Acid; Миристиновая Кислота.
Tetradecanoic acid.
$C_{14}H_{28}O_2$=228.4
CAS — 544-63-8.
UNII — 0I3V7S25AW.

Pharmacopoeias. In *USNF*.

USNF 31: (Myristic Acid). It is obtained from coconut oil and other fats. A hard, white or faintly yellow, somewhat glossy, crystalline solid or a white or yellow-white powder. Congealing temperature between 48 degrees and 55.5 degrees. Practically insoluble in water; soluble in alcohol, in chloroform, and in ether.

Profile

Myristic acid is a saturated fatty acid with similar properties to palmitic acid (p. 2200.3). It is used in oral and topical pharmaceutical formulations.

Myristyl Alcohol

Alcohol miristilo; Alkohol mirystyłowy; NSC-8549; 1-Tetradecanol; Миристиловый Спирт.
$C_{14}H_{30}O$=214.4
CAS — 112-72-1.
UNII — V42034O9PU.

Pharmacopoeias. In *USNF*.

USNF 31: (Myristyl Alcohol). M.p. 36 degrees to 42 degrees.

Profile

Myristyl alcohol is used as an oleaginous vehicle. Contact dermatitis has been associated with its use.

Neohesperidin Dihydrochalcone

E959; NCI-C60764; Neohesperidiinidihydrokalkoni; Neohesperidin DC; Neohesperidin-dihidrochalkonas; Neohesperidin-dihydrochalconum; Neohesperidin-dihydrochalkon; Neohesperidindivätekalkon; Neohesperidine DC; Neohesperidine dihydrochalcone; Néohespéridine-dihydrochalcone; Neoheszperidin-dihidro-kalkon; NHDC; Неорецнеридин Дигидрохалкон.
3,5-Dihydroxy-4-[3-(3-hydroxy-4-methoxyphenyl)propionyl] phenyl 2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside.
$C_{28}H_{36}O_{15}$=612.6
CAS — 13241-33-3 (neohesperidin); 20702-77-6 (neohesperidin dihydrochalcone); 18916-17-1 (naringin dihydrochalcone); 65520-51-6 (neoeriocitrin dihydrochalcone).
UNII — OA5C88H3L0 (neohesperidin); 3X476D83QV (neohesperidin dihydrochalcone); 7233QDO0QW (naringin dihydrochalcone).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Neohesperidin-dihydrochalcone). A white or yellowish-white powder. Practically insoluble in water and in dichloromethane; freely soluble in dimethyl sulfoxide; soluble in methyl alcohol. Protect from light.

Profile

Neohesperidin dihydrochalcone is an intense sweetener derived from naringin, a flavonoid present in citrus peel. It is about 1000 to 1800 times as sweet as sucrose and is used in foods, beverages, and pharmaceuticals. It has a synergistic sweetening effect when used with other sweeteners.

Neotame

Neotaam; Neotam; Néotame; Neotamo; Неотам.

N-[*N*-(3,3-Dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

$C_{20}H_{30}N_2O_5$=378.5

CAS — 165450-17-9.

UNII — VJ597D52EX.

Pharmacopoeias. In *USNF.*

USNF 31: (Neotame). Store in a dry place at a temperature not exceeding 40 degrees.

Profile

Neotame is an intense sweetener used in foods and beverages. It has between 7000 and 13 000 times the sweetening power of sucrose and is stable to heat.

References.

1. Anonymous. Neotame—a new artificial sweetener. *Med Lett Drugs Ther* 2002; **44:** 73–4.

Nonoxinols

Macrogol Nonylphenyl Ethers; Nonoxinoles; Nonoxynols; Нонокснолы.

α-(4-Nonylphenyl)-ω-hydroxypoly(oxyethylene).

CAS — 26027-38-3.

Nomenclature. Nonoxinols are a series of nonylphenyl ethers of macrogols of differing chain lengths, represented by the formula $C_{15}H_{23}.[O.CH_2.CH_2]_n.OH$.

Nonoxinol is *BAN* and *rINN*. The name may be followed by a figure indicating the approximate number of oxyethylene groups in the polyoxyethylene chain. *USAN* specifies Nonoxynol 4, Nonoxynol 9, Nonoxynol 15, and Nonoxynol 30.

Nonoxinol 9 *(BAN, rINN)*

Nonoksinoli-9; Nonoksynol-9; Nonoxinol-9; Nonoxinolum 9; Nonoxynol 9 (USAN); Нонокснол 9.

α-(4-Nonylphenyl)-ω-hydroxynona(oxyethylene).

$C_{33}H_{60}O_{10}$ (nominal)=616.8

UNII — 48Q180SH9T.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Nonoxinol 9). A mixture consisting mainly of monononylphenyl ethers of macrogols corresponding to the formula: $C_{15}H_{23}.(O.CH_2.CH_2)_n.OH$ where the average value of *n* is 9. A clear, colourless to light yellow, viscous liquid. Miscible with water, with alcohol, and with vegetable oils. Store in airtight containers.

USP 36: (Nonoxynol 9). An anhydrous liquid mixture consisting chiefly of monononylphenyl ethers of macrogols corresponding to the formula $C_{15}H_{23}.[O.CH_2.CH_2]n.OH$, in which the average value of *n* is about 9. A clear, colourless to light yellow, viscous liquid. Soluble in water, in alcohol, and in maize oil. Store in airtight containers.

Nonoxinol 10 *(BAN, rINN)*

Nonoxinolum 10; Nonoxynol 10; Нонокснол 10.

α-(4-Nonylphenyl)-ω-hydroxydeca(oxyethylene).

$C_{35}H_{64}O_{11}$ (nominal)=660.9

UNII — K7O76887AP.

Nonoxinol 11 *(BAN, rINN)*

Nonoxinolum 11; Nonoxynol 11; Нонокснол 11.

α-(4-Nonylphenyl)-ω-hydroxyundeca(oxyethylene).

$C_{37}H_{68}O_{12}$ (nominal)=704.9

Uses

Nonoxinols are macrogol aryl ether nonionic surfactants (p. 2164.2) used as solubilising agents. Nonoxinol 9 is used as a spermicide (see Contraception, p. 2232.3).

Antimicrobial activity. Nonoxinol 9 has activity *in vitro* against some bacteria and viruses and it was hoped[1,2] that use of spermicidal contraceptives containing nonoxinol 9 might provide some protection against sexually transmitted diseases, including chlamydial, gonococcal, and HIV infection. However, controlled studies involving HIV-negative female sex workers or other high-risk women have found that use of nonoxinol 9 does not reduce the rate of new HIV,[3,4] or gonorrhoea or chlamydia infection;[3,5] meta-analyses[6,7] including these and other studies have come to similar conclusions. Furthermore, nonoxinol 9 has an irritant action and may increase the risk of genital ulceration, leading to an increased risk of infection by HIV. The United Nations,[8] WHO,[9] and FDA[10] have therefore advised against its use by women at high risk.

1. North BB. Vaginal contraceptives: effective protection from sexually transmitted diseases for women? *J Reprod Med* 1988; **33:** 307–311.
2. Anonymous. Multipurpose spermicides. *Lancet* 1992; **340:** 211–13.
3. Roddy RE, *et al.* A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. *N Engl J Med* 1998; **339:** 504–10.
4. Van Damme L, *et al.* Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360:** 971–7. Correction. *ibid.*; 1892.
5. Roddy RE, *et al.* Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydial infection: a randomized controlled trial. *JAMA* 2002; **287:** 1117–22.
6. Wilkinson D, *et al.* Nonoxynol-9 for preventing vaginal acquisition of HIV infection by women from men. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/04/08).
7. Wilkinson D, *et al.* Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/04/08).
8. Anonymous. UN warns against use of spermicide. *BMJ* 2000; **321:** 194.
9. Anonymous. Nonoxinol 9 ineffective in preventing HIV infection. *WHO Drug Inf* 2002; **16:** 120–1.
10. FDA. FDA mandates new warning for nonoxynol 9 OTC contraceptive products (issued 18/12/07). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109043.htm (accessed 23/08/10)

Contraception. A review[1] of the contraceptive use of nonoxinol 9. The antimotility and spermicidal properties of nonoxinols vary with their chain length: oligomers containing between 6 and 8 oxyethylene groups have the strongest effects on motility, while those with 8 to 10 units are the most spermicidal. The spermicidal action depends on lysis of sperm membranes resulting in detachment of the acrosome, midpiece, and neck, leading to immobilisation and cell death. Nonoxinol 9 is an effective spermicide at threshold concentrations of 100 micrograms/mL or above, and has been used for this purpose for more than 30 years in the form of over-the-counter creams, gels, foams, and condom lubricants. Studies have suggested that it is effective in preventing pregnancy in about 75% of cases. Factors contributing to failure may include inadequate concentration within cervical mucus (due to low partitioning from the aqueous phase and possibly micelle formation), and inadequate distribution in the vagina.

1. Iyer V, Poddar SS. Update on nonoxynol-9 as vaginal spermicide. *Eur J Contracept Reprod Health Care* 2008; **13:** 339–50.

Adverse Effects and Precautions

Nonoxinols used as vaginal spermicides may cause local irritation.

Genito-urinary infections. Use of spermicidal foam or jelly containing nonoxinol 9 may disturb the normal vaginal flora and predispose to colonisation with *Escherichia coli* and the development of bacteriuria.[1] An increased risk of acute *E. coli* urinary-tract infection has been reported[2] associated with the use of condoms coated with nonoxinol 9. However, another study[3] of women using nonoxinol-9 spermicidal contraceptives showed that most users had minimal disruption to the vaginal microbial ecosystem.

For reference to an increased risk of some sexually transmitted diseases in women using nonoxinol 9, see Antimicrobial Activity, above.

1. Hooton TM, *et al.* Escherichia coli bacteriuria and contraceptive method. *JAMA* 1991; **265:** 64–9.
2. Fihn SD, *et al.* Association between use of spermicide-coated condoms and Escherichia coli urinary tract infection in young women. *Am J Epidemiol* 1996; **144:** 512–20.
3. Schreiber CA, *et al.* Effects of long-term use of nonoxynol-9 on vaginal flora. *Obstet Gynecol* 2006; **107:** 136–43.

Pregnancy. Maternal use of spermicidal contraceptives has been linked to an increased frequency of congenital abnormalities, including trisomy, but it has been suggested that such studies may be flawed by recall bias.[1] Meta-analysis of 9 studies also supported the view that peri- and postconceptual maternal use of spermicides was not associated with adverse fetal outcome.[2]

1. Mishell DR. Contraception. *N Engl J Med* 1989; **320:** 777–87.
2. Einarson TR, *et al.* Maternal spermicide use and adverse reproductive outcome: a meta-analysis. *Am J Obstet Gynecol* 1990; **162:** 655–60.

Toxic shock syndrome. Toxic shock syndrome has been associated with the use of a vaginal contraceptive sponge impregnated with nonoxinol 9. A review[1] of 13 cases reported in the USA up to November 1984 found that in 4 of the cases there were other predisposing conditions: postpartum use, use during menstruation, and prolonged retention.

1. Faich G, *et al.* Toxic shock syndrome and the vaginal contraceptive sponge. *JAMA* 1986; **255:** 216–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lorophyn; ***Austral.***: Lubarol†; ***Austria***: Patentex; ***Braz.***: Preserv Nonoxinol-9; ***Canad.***: Delfen†; Lifestyles†; Ortho-Gynol†; Ramses†; Trojan†; VCF†; ***Chile***: Impidol; Supoviol; ***China***: Ai Lv Shuang (爱侣栓); Lelemi (乐乐迷); ***Cz.***: Patentex Oval N†; ***Fin.***: Patentex; ***Ger.***: Patentex Oval; ***Gr.***: Patentex; ***Hong Kong***: Patentex†; VCF; ***Hung.***: Patentex; ***India***: Delfen†; ***Irl.***: Ortho-Creme†; ***Mex.***: Lorophyn†; ***NZ***: Lifestyles; ***Pol.***: Patentex Oval; Secural; ***Port.***: Rendells; ***Rus.***: Patentex Oval N (Патентекс Овал Н); Sterilin (Стерилин); ***S. Afr.***: Delfen†; Gynol II†; ***Turk.***: Lorophyn; ***UK***: Gygel; Prelude; ***USA***: Advantage 24; Delfen; Encare; Gynol II; Semicid; Sheik Elite; Shur-Seal; Today; VCF.

Multi-ingredient Preparations. ***Arg.***: Merthiolate Iodopovidona; ***Ger.***: A-gen 53†; ***Hong Kong***: Protectaid; ***Israel***: Glovan; Protectaid; ***Mex.***: Sin-A-Gen; ***Spain***: Lavolen†; ***Turk.***: Agen; ***UK***: Protectaid.

Octoxinols

Macrogol Tetramethylbutylphenyl Ethers; Octoxinoles; Octoxynols; Octylphenoxy Polyethoxyethanol; Октоксинолы.

α-[4-(1,1,3,3-Tetramethylbutyl)phenyl]-ω-hydroxypoly(oxyethylene).

CAS — 9002-93-1.

Nomenclature. Octoxinols are a series of tetramethylbutylphenyl ethers of macrogols of differing chain lengths, represented by the formula $C_{14}H_{21}.[O.CH_2.CH_2]_n.OH$.

Octoxinol is *BAN* and *rINN*. The name may be followed by a figure indicating the approximate number of oxyethylene groups in the polyoxyethylene chain. *USAN* specifies Octoxynol 9.

The name *p*-di-isobutyl-phenoxypolyethoxyethanol has been used to describe octoxinol 9 but may have also been applied to other octoxinols.

Octoxinol 9 *(BAN, rINN)*

Octoxinolum 9; Octoxynol 9 (USAN); Октоксинол 9.

$C_{32}H_{58}O_{10}$ (nominal)=602.8

Pharmacopoeias. In *USNF.*

USNF 31: (Octoxynol 9). An anhydrous liquid mixture consisting chiefly of mono[*p*-(1,1,3,3-tetramethylbutyl)] phenyl ethers of macrogols, corresponding to the formula $C_{14}H_{21}.[O.CH_2.CH_2]n.OH$, in which the average value of *n* is about 9. A clear, pale yellow, viscous liquid with a faint odour. Miscible with water, with alcohol, and with acetone; soluble in toluene and in benzene; practically insoluble in petroleum spirit. Store in airtight containers.

Octoxinol 10 *(BAN, rINN)*

Octoxinolum 10; Oktoksinoli-10; Oktoksinolis 10; Oktoksynol 10; Oktoxinol 10; Oktoxinol-10; Октоксинол 10.

$C_{34}H_{62}O_{11}$(nominal)=646.9

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Octoxinol 10). A mixture consisting mainly of mono-octylphenyl ethers of macrogols corresponding to the formula: $C_{14}H_{21}.(O.CH_2.CH_2)_n.OH$ where the average value of *n* is 10. A clear, colourless or light yellow, viscous liquid. Miscible with water, with alcohol, and with vegetable oils. Store in airtight containers.

Profile

Octoxinols are macrogol aryl ether nonionic surfactants (p. 2164.2) used as solubilising agents. They have also been used as spermicides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ortho-Gynol†; Summer's Eve Feminine; ***NZ***: Ortho-Gynol†.

Multi-ingredient Preparations. ***Austral.***: Summer's Eve Feminine; ***Canad.***: Aseptone Quat.

Octyldodecanol

Octildodecanol; Octyldodécanol; Octyldodecanolum; Oktildodekanol; Oktildodekanolis; Oktyldodekanol; Oktylododekanol; Oktyylidodekanoli; Октилдодеканол.

$C_{20}H_{42}O$=298.6

UNII — 461N1O614Y.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Octyldodecanol). A condensation product of saturated liquid fatty alcohols. It contains not less than 90% of (*RS*)-2-octyldodecan-1-ol, the remainder consisting

mainly of related alcohols. A clear, colourless to yellowish, oily liquid. Relative density 0.830 to 0.850. Practically insoluble in water; miscible with alcohol. Protect from light.

USNF 31: (Octyldodecanol). It contains not less than 90% of 2-octyldodecanol, the remainder consisting chiefly of related alcohols. A clear, water-white, free-flowing liquid. Insoluble in water; soluble in alcohol and in ether. Store in airtight containers.

Uses

Octyldodecanol is used as a pharmaceutical solvent.

Adverse Effects

Octyldodecanol can cause hypersensitivity reactions.

References.

1. Dharmagunawardena B, Charles-Holmes R. Contact dermatitis due to octyldodecanol in clotrimazole cream. *Contact Dermatitis* 1997; **36:** 231.
2. Dawn G, Forsyth A. Genital swelling caused by octyldodecanol contact dermatitis. *Clin Exp Dermatol* 2003; **28:** 228–9.
3. Singh M, *et al*. Contact sensitivity to octyldodecanol and trometamol in an anti-itch cream. *Contact Dermatitis* 2007; **56:** 289–90.

Oleic Acid

Acide oléique; Acido oleico; Acidum Oleicum; Elaic Acid; Kwas oleinowy; Kyselina olejová; Olajsav; Oleico, ácido; Oleinic Acid; Oleino rūgštis; Oleïnskābe; Oliezuur; Oljesyra; Oljesyre; Öljyhappo; Ölsäure; Масляная Кислота; Олеинова Киселина; Олеиновая Кислота.

(*Z*)-9-Octadecenoic acid.

$C_{18}H_{34}O_2$=282.5

CAS — 112-80-1.

UNII — 2UMI9U37CP.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Oleic Acid). It contains 65 to 88% of oleic acid together with varying amounts of saturated and other unsaturated fatty acids. It may contain a suitable antoxidant. It is a clear, yellowish or brownish, oily liquid. Practically insoluble in water; miscible with alcohol and with dichloromethane. Store in well-filled airtight containers. Protect from light.

USNF 31: (Oleic Acid). It is manufactured from fats and oils derived from edible sources, animal or vegetable, and consists chiefly of oleic acid. It may contain suitable stabilisers. Oleic acid solely for external use is exempt from the requirement that it be prepared from edible sources. It is a colourless to pale yellow oily liquid when freshly prepared with a characteristic lard-like odour. On exposure to air it gradually absorbs oxygen and darkens in colour. When strongly heated in air, it is decomposed with the production of acid vapours. Congealing point between 3 degrees and 10 degrees for oleic acid from animal sources and between 10 degrees and 16 degrees for oleic acid from vegetable sources. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene and with fixed and volatile oils. Protect from light. Avoid excessive heat.

Profile

Oleic acid forms soaps with alkaline substances and is used as an emulsifying or solubilising agent. It occurs in edible fats and oils which are used as foods or food components. Oleic acid is used in topical preparations, including transdermal films and patches, and in oral and inhalation preparations. It has also been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Glavit†; ***Fr.***: Totephan†; ***Ital.***: Esterol; ***Singapore***: Natal Care.

Pharmacopoeial Preparations

BP 2014: Chloroxylenol Solution; White Liniment.

Oleyl Alcohol

Alcohol oleico; Alcohol oleicus; *cis*-9-Octadecen-1-ol; Oleic Alcohol; Oleilo alkoholis; Oléique (alcool); Oleo Alcohol; Oleol; Oleylalkohol; Oleyylialkoholi; Олеиловый Спирт.

(*Z*)-Octadec-9-en-1-ol.

$C_{18}H_{36}O$=268.5

CAS — 143-28-2.

UNII — 172F2WN8DV.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Oleyl Alcohol). A mixture of unsaturated and saturated long-chain fatty alcohols consisting mainly of oleyl alcohol and elaidyl alcohol; (*E*-octadec-9-en-1-ol; *trans*-9-octadecenol) It may be of vegetable or animal origin. A colourless or light yellow liquid.

USNF 31: (Oleyl Alcohol). A mixture of unsaturated and saturated high molecular weight fatty alcohols consisting chiefly of oleyl alcohol. A clear, colourless to light yellow, oily liquid with a faint characteristic odour. Insoluble in water; soluble in alcohol, in ether, in isopropyl alcohol, and in light liquid paraffin. Store in well-filled airtight containers at a temperature not exceeding 25 degrees.

Profile

Oleyl alcohol is used as an emollient, as an emulsifying and solubilising agent, and as a penetration enhancer in substances applied externally, including some delivered via transdermal patches. Oleyl alcohol has also been used in aerosol preparations for rectal use. The acetate has also been used.

Oleyl Oleate

Олеилолеат.

The oleyl ester of (*Z*)-9-octadecenoic acid.

$C_{36}H_{68}O_2$=532.9

CAS — 3687-45-4.

UNII — 3X3L452Y85.

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 31: (Oleyl Oleate). It consists of esters of oleyl alcohol and high molecular weight fatty acids, principally oleic acid. A clear, colourless to light yellow liquid with a faint characteristic odour. Slightly soluble in alcohol; miscible with chloroform and with ether. Store in airtight containers.

Profile

Oleyl oleate is used as an emollient and emulsifying or solubilising agent in preparations for topical use.

Orange B

CI Acid Orange 137; Colour Index No. 19235; Naranja B; Оранжевый В.

The disodium salt of 1-(4-Sulfophenyl)-3-ethylcarboxyl-4-(4-sulfonaphthylazo)-5-hydroxypyrazole.

$C_{22}H_{16}N_4Na_2O_9S_2$=590.5

CAS — 15139-76-1.

UNII — RGU455OS50.

Profile

Orange B is a synthetic azo dye used as a colouring agent in foods.

Palm Oil

Aceite de palma; Azeite de dendê; Huile de palme; Mawese; Minyak kelapa sawit; Olej palmowy; Oli de Palma; Olio di palma; Palmių aliejus; Palmöl; Palmolie; Palmolja; Palmový olej; Palmuõljy; Пальмовое Масло; Палмово Масло.

UNII — 5QUO05548Z (palm oil); 257THB963H (hydrogenated palm oil).

Description. The crude oil is deep orange with a characteristic odour; it is semi-solid at 21 to 27 degrees.

Pharmacopoeias. In *USNF*, which also includes the hydrogenated oil.

USNF 31: (Palm Oil). It is obtained by refining the oil obtained from the pulp of the fruit of the oil palm *Elaeis guineensis*. A white to yellowish, fatty solid. Insoluble in water. Do not store above 55 degrees.

USNF 31: (Hydrogenated Palm Oil). It is obtained by refining and hydrogenating the oil obtained from the pulp of the fruit of the oil palm *Elaeis guineensis* and consists mainly of triglycerides of palmitic and stearic acids. A white to yellowish, fatty solid to semi-solid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in ether. Store in airtight containers. Protect from light.

Palm Kernel Oil

Oleum Palmae Nuclei; Palm-nut Oil; Масло Пальмовое Косточковое; Пальмоядровое Масло.

CAS — 8023-79-8.

UNII — B0S90M0233.

Pharmacopoeias. In *USNF. Br.* includes the fractionated oil.

USNF 31: (Palm Kernel Oil). The refined fixed oil obtained from the kernels of the fruit of *Elaeis guineensis*. A white to yellowish, fatty solid. M.p. 27 degrees to 29 degrees. Insoluble in water. Store at a temperature not exceeding 45 degrees.

BP 2014: (Fractionated Palm Kernel Oil). It is obtained by expression of the natural oil from the kernels of *Elaeis guineensis* followed by selective solvent fractionation and hydrogenation. A white, odourless or almost odourless, solid, brittle fat. M.p. 31 degrees to 36 degrees. Practically insoluble in water and in alcohol; miscible with chloroform, with ether, and with petroleum spirit (boiling range, 40 degrees to 60 degrees). Store at a temperature not exceeding 25 degrees.

Profile

Palm oil is obtained from the fruit of the oil palm (*Elaeis guineensis*). Palm kernel oil is obtained from the kernels of the same species. The two substances have different characteristics and properties, although many of their uses are similar. Unrefined palm oil is rich in carotenoids, which are largely or wholly removed during standard refinement and processing.

Palm oil and palm kernel oil are produced and used worldwide on a large scale. Pharmaceutical applications of the oils or their derivatives include the compounding of creams and ointments, as a base for suppositories, and as a lubricant and binder in tablet and capsule formulation. They are also used in cooking and food processing and in the manufacture of a wide range of industrial and domestic products including soaps and cosmetics.

References.

1. Edem DO. Palm oil: biochemical, physiological, nutritional, hematological, and toxicological aspects: a review. *Plant Foods Hum Nutr* 2002; **57:** 319–41.
2. Sundram K, *et al*. Palm fruit chemistry and nutrition. *Asia Pac J Clin Nutr* 2003; **12:** 355–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Androlistica; Oxelio; Phytosolaire†; ***Philipp.***: Livermin; ***Singapore***: Androlistica.

Palmitic Acid *(USAN)*

Acide Palmitique; Acido palmitico; Acidum Palmiticum; Cetylic Acid; Hexadecansäure; Kwas palmitynowy; Kyselina palmitová; Palmitiinhape; Palmitiinihappo; Palmitik asit; Palmitinezuur; Palmitino rūgštis; Palmitinsäure; Palmitinsav; Palmitinsyra; Palmitinsyre; Palmitinskābe; Пальмитиновая Кислота; Палмитинова киселина.

Hexadecanoic Acid.

$C_{16}H_{32}O_2$=256.4

CAS — 57-10-3.

UNII — 2V16EO95H1.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Palmitic Acid). A hexadecanoic acid ($C_{16}H_{32}O_2$ = 256.4), obtained from fats or oils of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in alcohol.

USNF 31: (Palmitic Acid). A mixture of solid organic acids obtained from fats or oils of animal or vegetable origin. It contains not less than 92% of $C_{16}H_{32}O_2$ and not more than 6% of stearic acid ($C_{18}H_{36}O_2$). A hard, white or faintly yellow, somewhat glossy crystalline solid, or white or yellowish-white powder. It has a slight characteristic odour and taste. Practically insoluble in water; soluble in alcohol, in chloroform, and in ether.

Profile

Palmitic acid is used as an emulsifying agent, skin penetration enhancer, and tablet and capsule lubricant.

Pectin

E440 (amidated pectin or pectin); Pectina; Pectine; Pektiin; Pektiini; Pektin; Pektyn; Пектин.

CAS — 9000-69-5.

ATC — A07BC01.

ATC Vet — QA078C01.

UNII — 89NA02M4RX (pectin); O2ZUP321U8 (apple pectin); 47EQO8LE7H (citrus pectin).

Pharmacopoeias. In *US.*

USP 36: (Pectin). A purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace; it consists mainly of partially methoxylated polygalacturonic acids. A yellowish-white, almost odourless, coarse or fine powder. Almost completely soluble in 1 in 20 of water, forming a viscous, opalescent, colloidal solution which flows readily and is acid to litmus; practically insoluble in alcohol or in diluted alcohol and in other organic solvents. It dissolves more readily in water if first moistened with alcohol, glycerol, or simple syrup, or if mixed with 3 or more parts of sucrose. Store in airtight containers.

Uses and Administration

Pectin is a complex polysaccharide consisting mainly of partially methylated polygalacturonic acids and their salts. Pectins are important constituents of plant cell walls and contribute to dietary fibre (see under Dietary Role in Bran, p. 1823.3). They have a long history of use as emulsifiers, stabilisers, and gelling agents in the food industry.

Pectin is an adsorbent and bulk-forming agent and is present in multi-ingredient preparations for the management of diarrhoea, constipation, and obesity. Pectin has also been tried for reducing or slowing carbohydrate absorption in the dumping syndrome (p. 1806.2). Related compounds such as aluminium and magnesium polygalacturonate have also been used.

Interactions

Bulk-forming agents such as dietary fibre lower the transit time through the gut and may affect the absorption of other drugs.

Lipid regulating drugs. Pectin, used as a source of fibre, with a lipid-lowering diet and *lovastatin,* has resulted in a paradoxical increase in low-density lipoprotein (LDL)-cholesterol in patients with hypercholesterolaemia. It was believed the pectin reduced the absorption of lovastatin from the gut.[1]

1. Richter WO, *et al.* Interaction between fibre and lovastatin. *Lancet* 1991; **338:** 706.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Arhemapectine Antihemorragique†.

Multi-ingredient Preparations. ***Arg.***: Crema De Bismuto; Mucobase; ***Austral.***: 3B Beer Belly Buster†; Betaine Digestive Aid; Citri Slim+Trim†; Diarcalm†; Diareze†; Donnagel; Orabase; Psylli-Mucil Plus†; Stomahesive; Zellulean with Escin†; ***Austria***: Diarrhoesan; ***Belg.***: Tanalone; ***Braz.***: Kaomagma; Parenterin; ***Canad.***: Orabase; Orahesive; Tegasorb†; Watkins Settelz†; ***Chile***: Enterol†; Furazolidona; ***Fr.***: Filigel†; Gelopectose; Transifine; ***Ger.***: Diarrhoesan; GoTa-Derm; ***Gr.***: Kaopectate; Polypictine; ***Hong Kong***: Diapectin†; Enterocin Compound†; Kaopectin; Pectolin†; Uni-Kaotin; ***Indon.***: Andikap†; Arcapec; Diaend; Diagit; Entrogard; Envios; Kaopectate†; Licopec; Molagit; Neo Diaform; Neo Diastop; Neo Entrostop; Neo Kaocitin; Neo Kaolana; Neo Kaominal; Neo Koniform†; Opidiar; ***Irl.***: Orabase†; ***Israel***: Kaopectin; ***Ital.***: Cruscasohn; Fibrovit; Nuleron; Streptomagma; ***Mex.***: Ameban; Caopecfar†; Colfur†; Colistin Magma†; Coralzul; Depofin; Dia-Par Compuesto; Dibapec Compuesto†; Estibal; Exofur; Facetin-D; Farpectol; Furoxona CP; Isocar; K-Omistron; Kaomycin†; Kaopectate†; Kapecfuran; Kediar; Lactopectin†; Neokap; Neoxil; Nineka; Olam†; Optazol; Quimefuran; Suyodil; Treda; Yodozona; ***NZ***: Orabase; Stomahesive; ***S.Afr.***: Adco-Biskapect†; Betapect; Bipectinol†; Chloropect; Collodene†; Enterolyte; Gastropect; Granuflex; Granugel; Kantrexil; Kaostatex; Orabase†; Pectin-K†; Pectrolyte; ***Singapore***: Apple Cider Vinegar Diet; Axcel Kaopec; Beakopectin; Bios Life; Diapectin; Pectolin; ***Spain***: Dextricea†; Lupidon; ***Switz.***: HEC†; ***Thai.***: Biodan; Carbonpectate; Cenopec†; Diaropect; Difuran; Diocin; Disento PF; Furamed; Furasian; Furopectal; Furopectin; Kaolin Mixture w/ Pectin; Kaolin Mixture; Kaopectal; Kaptate; Patarlin; Profura; Suratin; ***Turk.***: Streptomagma; ***UAE***: Kaptin; ***UK***: Goodypops; KLN; Orabase; Orahesive; Stomahesive; ***USA***: Acidophilus with Citrus Pectin; Cepacol Sore Throat + Coating Relief Maximum Numbing; K-C; Kao-Paverin; Kao-Spen; Kaodene Non-Narcotic; Sucrets Herbal; ***Venez.***: Klincosal; Micyn-2; Streptomagma.

Pentane

Amyl Hydride; Pentà; *n*-Pentaan; Pentaani; Pentan; Pentán; *n*-Pentane; Pentano; Pentāns; Пентан.

C_5H_{12}=72.15

CAS — 109-66-0.

UNII — 4FEX897A91.

Profile

Pentane is used as a solvent and as a fuel. It is highly volatile and has also been used topically for its cooling effects.

References.

1. McKee R, *et al.* Toxicology of n-pentane (CAS no. 109-66-0). *J Appl Toxicol* 1998; **18:** 431–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Frionex; ***Hung.***: Deep Freeze; ***UK***: Deep Freeze.

Petroleum Spirit

Bencina; Bencina de petróleo; Benzyna; Éter de petróleo; Light Petroleum; Ligroína; Nafta; Nafta de petróleo; Nafta de petróleo alifática; Petroleum Benzin; Petroleum Ether; Solvent Hexane; Петролейный Эфир; Бензин.

NOTE. The nomenclature for kerosene (p. 2191.1) and petroleum spirit is confusing and not always clearly distinguishable; in many languages similar terms are used for both.

Description. Petroleum spirit is a purified distillate of petroleum, consisting of a mixture of the lower members of the paraffin series of hydrocarbons. It is a colourless, transparent, very volatile, highly flammable liquid with a characteristic odour. It is available in a variety of boiling ranges.

Pharmacopoeias. In *Ger., Jpn.,* and *Pol.* Various boiling ranges are specified.

Swiss describes Benzinum Medicinale, consisting mainly of hexane and heptane.

NOTE. The motor fuel termed 'petrol' in the UK and 'gasoline' in the USA is a mixture of volatile hydrocarbons of variable composition containing paraffins (alkanes), olefins (alkenes), cycloparaffins, and aromatic compounds.

Uses

Petroleum spirit and other petroleum distillates are used as pharmaceutical solvents.

Adverse Effects and Treatment

As for Kerosene, p. 2191.1. Petroleum spirit and petrol, being more volatile and of lower viscosity than kerosene, are more likely to be inhaled and to cause aspiration pneumonitis. The toxicity of petrol varies with its composition; some adverse effects have been attributed to lead additives or to the content of *n*-hexane or benzene. Petrol may be implicated in volatile solvent abuse (see under Toluene, p. 2216.3).

References to the toxicity of petroleum spirit.[1-5]

For discussion of neurotoxicity after occupational exposure to solvents including petrol, see under Toluene, p. 2216.2.

1. WHO. Selected petroleum products. *Environmental Health Criteria 20.* Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc020.htm (accessed 30/06/04)
2. Reese E, Kimbrough RD. Acute toxicity of gasoline and some additives. *Environ Health Perspect* 1993; **101** (suppl 6): 115–31.
3. Skalko RG. Reproductive and developmental toxicity of the components of gasoline. *Environ Health Perspect* 1993; **101** (suppl 6): 143–9.
4. Tenenbein M. Leaded gasoline abuse: the role of tetraethyl lead. *Hum Exp Toxicol* 1997; **16:** 217–22.
5. Cairney S, *et al.* The neurobehavioural consequences of petrol (gasoline) sniffing. *Neurosci Biobehav Rev* 2002; **26:** 81–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Travelex; Vertigopas; ***Ger.***: Capillaron Vertigo; Kinolymphat†; Procordal vertigo; Steiroderm; Vertigopas; ***Switz.***: Regenaplex Nr. 21e.

Phospholipids

Fosfolipidai; Fosfolipiden; Fosfolipidi; Fosfolípidos; Fosfolipidy; Fosfolipiidid; Fosfolipitler; Phosphatides; Phosphoacylglycérols; Phospholipide; Фосфолипиды; Фосфолипиди.

Pharmacopoeias. *USNF* includes egg phospholipids.

USNF 31: (Egg Phospholipids). It is a mixture of naturally occurring phospholipids obtained from the yolk of hens' eggs. Store at a temperature of -10 degrees or below under an atmosphere of nitrogen in airtight containers.

Profile

Phospholipids are naturally occurring lipids. They are amphiphilic molecules and are important components of cell membranes, partly due to their ability to form lipid bilayers; they also have emulsifying properties.

Most phospholipids are glycerophospholipids (phosphoglycerides) and consist of a glycerol backbone esterified with fatty acids and a phosphate group. Another group of phospholipids, phosphosphingolipids, have sphingosine, an amino-alcohol, as their backbone.

Phospholipids are generally obtained from sources such as egg yolk (egg phospholipids; egg phosphatides) or soya bean (soy phospholipids; soy phosphatides). They are used as emulsifying agents in pharmaceuticals and the food industry, and are also used to produce liposomal formulations. They are important constituents of pulmonary surfactants (p. 2599.2) used in neonatal respiratory distress syndrome. Lecithin (p. 2542.2), a mixture of phospholipids, and specific phospholipids such as phosphatidyl choline (p. 2588.3) and phosphatidyl serine (p. 2589.1), have been used as dietary supplements in many disorders. Highly purified phospholipid preparations, also known as essential phospholipids, are also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Essliver (Эсслив); ***Thai.***: Essentiale Forte.

Multi-ingredient Preparations. ***Arg.***: Fosfamina; Fosfotonic; Lipiforce; ***Austria***: Essentiale; ***Cz.***: Essentiale Forte N; ***Fr.***: Lecitone; Optibiol; ***Ger.***: Essentiale; ***Hong Kong***: Essentiale; Physiogel; ***India***: Mixo-EPL; ***Indon.***: Hepabion†; Heparviton NF; Heparviton; Lecur; Lipimix; Nessiol; Procur Plus; Prolivit; Sensikol; Tripid; Vionin NF; ***Ital.***: Leciplus; Memovigor; Nolder†; Vasobrain; ***Malaysia***: Essentiale; Livolin; ***Philipp.***: Essentiale Forte P; ***Rus.***: Essentiale N (Эссенциале Н); Essliver Forte (Эсслив Форте); Phosphogliv (Фосфоглив); Phosphonciale (Фосфонциале); ***S. Afr.***: Essentiale; ***Singapore***: Essentiale; Livipids; Livolin; Manhae; Optibiol; ***Spain***: Essavenon†; ***Thai.***: Essaven; Essentiale; Essiver; Hepacap; ***UK***: Emustil; ***Ukr.***: Essentiale N (Эссенциале Н); Essliver Forte (Эсслив Форте); Farcovit B12 (Фарковит В12)†; Hepaforte (Гепафорте); Livolin Forte (Ліволін Форте); Phosphogliv (Фосфоглив); Venosan (Веносан).

Pigment Rubine

Brilliant Carmine 6B; Carmine 6B; CI Pigment Red 57; Colour Index No. 15850; Czerwień litolowa BK; E180; FD & C Red No. 7; Lithol Rubine BK; Litholrubin BK; Litholrubine BK; Litholrubintoner BKL; Litolrubin BK; Litolrubina BK; Permanent Rubin L6B; Pigmento rubí; Rubinpigment; Рубиновый Литол ВК.

Calcium 3-hydroxy-4-(4-methyl-2-sulfonatophenylazo)-2-naphthalene carboxylate.

$C_{18}H_{12}CaN_2O_6S$=424.4

CAS — 5281-04-9.

UNII — ECW0LZ41X8.

Profile

Pigment rubine is a synthetic azo dye used as a colouring agent for foodstuffs and cosmetics.

Polacrilin Potassium *(USAN, rINNM)*

Kalii Polacrilinum; Polacrilina potásica; Polacriline Potassique; Polacrilinum Kalii; Калия Полакрилин.

CAS — 54182-62-6 (polacrilin); 50602-21-6 (polacrilin).

UNII — 0BZ5A00FQU.

Pharmacopoeias. In *USNF.*

USNF 31: (Polacrilin Potassium). The potassium salt of a unifunctional low-cross-linked carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene. A white to off-white, free-flowing powder. Has a faint odour or is odourless. Insoluble in water and in most liquids.

Profile

Polacrilin potassium is used as a tablet and capsule disintegrant.

Poloxamers

Polioxietilen-propilenglicol; Poloksameerit; Poloksamerai; Poloxamera; Poloxamere; Poloxamerek; Poloxamerer; Poloxamères; Poloxámeros; Poloxamery; Polyethylene-polypropylene glycol; Полоксамеры.

α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer.

CAS — 9003-11-6.

Nomenclature. Poloxamer is *BAN* and *rINN.* The name is followed by a figure, the first 2 digits of which, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene portion and the third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene portion. *USAN* specifies Poloxamer 182D, Poloxamer 182LF, Poloxamer 188, Poloxamer 188LF, and Poloxamer 331.

Poloxalene (*BAN, USAN, rINN*) is also a poloxamer.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 5 (Poloxamers). A synthetic block copolymer of ethylene oxide and propylene oxide represented by the general formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. It may contain a suitable antioxidant. Poloxamer 124 is a colourless or almost colourless liquid. Poloxamer 237 and poloxamer 338 are white or almost white, waxy powders, microbeads or flakes; m.p. about 50 degrees. Poloxamers 124, 237, and 338 are very soluble in water and in alcohol; practically insoluble in petroleum spirit (50 degrees to 70 degrees). pH of a 10% solution in water is 5.0 to 7.5. Store in airtight containers.

USNF 31: (Poloxamer). A synthetic block copolymer of ethylene oxide and propylene oxide with the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. It may contain a suitable antoxidant. Poloxamer 124 is a colourless liquid with a mild odour. Poloxamers 237 and 338 are white, prilled or cast solids, odourless or with a mild odour. All poloxamers are freely soluble in water and in alcohol. Poloxamer 124 is freely soluble in isopropyl alcohol and in propylene glycol; poloxamer 237 is sparingly soluble in isopropyl alcohol and in xylene; poloxamer 338 is sparingly soluble in propylene glycol; poloxamer 124 is freely soluble in xylene. A 2.5% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Incompatibility. Poloxamers have been reported to be incompatible with hydroxybenzoates and phenols.

Poloxalene *(BAN, USAN, rINN)*

Poloxalène; Poloxaleno; Poloxalenum; SKF-18667; Полоксален.
CAS — 9003-11-6.
UNII — V8B3K56SW0.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Poloxalene). A synthetic block copolymer of ethylene oxide and propylene oxide. A colourless or pale yellow liquid. Soluble in water, in chloroform, and in ethylene dichloride. A 2.5% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Poloxamer 188 *(BAN, USAN, rINN)*

Poloxalkol; Poloxamère 188; Poloxámero 188; Poloxamerum 188; Полоксамер 188.
UNII — LQA7B6G8JG.

NOTE. Compounded preparations of poloxamer 188 may be represented by the following names:

- Co-danthramer *x*/*y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Poloxamers). Poloxamer 188 is a poloxamer in which *a* in the general formula given on p. 2201.3 is 75 to 85 and *b* is 25 to 30; it has an average molecular weight of 7680 to 9510. It is a white or almost white, waxy powder, microbeads, or flakes. M.p. about 50 degrees. Very soluble in water and in alcohol; practically insoluble in petroleum spirit (50 degrees to 70 degrees). pH of a 10% solution is 5.0 to 7.5. Store in airtight containers.

USNF 31: (Poloxamer). Poloxamer 188 is a poloxamer in which *a* in the general formula averages 80 and *b* averages 27; it has an average molecular weight of 7680 to 9510. A white prilled or cast solid, odourless or with a very mild odour. M.p. about 52 degrees. Freely soluble in water and in alcohol. Store in airtight containers.

Poloxamer 407 *(BAN, rINN)*

Poloxamère 407; Poloxámero 407; Poloxamerum 407; Полоксамер 407.
UNII — TUF2IVW3M2.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Poloxamers). Poloxamer 407 is a poloxamer in which *a* in the general formula given on p. 2201.3 is 95 to 105 and *b* is 54 to 60; it has an average molecular weight of 9840 to 14 600. It is a white or almost white, waxy powder, microbeads, or flakes. M.p. about 50 degrees. Very soluble in water and in alcohol; practically insoluble in petroleum spirit (50 degrees to 70 degrees). pH of a 10% solution in water is 5.0 to 7.5. Store in airtight containers.

USNF 31: (Poloxamer). Poloxamer 407 is a poloxamer in which *a* in the general formula averages 101 and *b* averages 56; it has an average molecular weight of 9840 to 14 600. A white, prilled or cast solid, odourless or with a very mild odour. M.p. about 56 degrees. Freely soluble in water, in alcohol, and in isopropyl alcohol. Store in airtight containers.

Uses and Administration

Poloxamers are copolymer nonionic surfactants (p. 2164.2). They are used as emulsifying agents for intravenous fat emulsions, as solubilising agents to maintain clarity in elixirs and syrups, and as wetting agents for antibacterials. They may also be used in ointment or suppository bases and as tablet binders or coaters.

Poloxamer 188 is used as a wetting agent in the treatment of constipation, usually with a laxative such as dantron. It has also been used as an emulsifying agent in fluorocarbon blood substitutes. It is thought to have effects on blood flow and cellular repair and has been investigated in sickle-cell crisis, myocardial infarction, and burns.

Poloxamer 407 is used in solutions for contact lens care, as is poloxamer 338.

Poloxalene is used as a defoaming agent in the treatment of bloat in ruminants.

References.

1. Orringer EP, *et al.* Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA* 2001; **286:** 2099–2106.
2. Gibbs WJ, Hagemann TM. Purified poloxamer 188 for sickle cell vaso-occlusive crisis. *Ann Pharmacother* 2004; **38:** 320–4.
3. Dumortier G, *et al.* A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 2006; **23:** 2709–28.

Precautions

Poloxamers may increase the absorption of liquid paraffin and other fat-soluble substances.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Coloxyl; ***NZ***: Coloxyl; ***S.Afr.***: Pliagel†.

Multi-ingredient Preparations. ***Arg.***: Natura Confort; ***Ger.***: Linola Wundgel; ***Irl.***: Ailax†; Codalax; Cotron; ***Malaysia***: Cationorm; ***NZ***: Pinorax; ***Rus.***: Perftoran (Перфторан); ***Singapore***: Listerine Bright & Clean; Listerine Cool Citrus; ***Thai.***: Siduol; ***UK***: Codalax; Danlax; ***USA***: Baby Orajel Tooth and Gum Cleanser; ControlRx.

Polydextrose *(USAN)*

CP-31081; E1200; Polidextrosa; Polydekstroosi.
CAS — 68424-04-4.
UNII — VH2XOU12IE.

Pharmacopoeias. *USNF* includes Polydextrose and Hydrogenated Polydextrose

USNF 31: (Polydextrose). A randomly branched polymer prepared by melting and subsequent condensation of the ingredients, which consist of approximately 90 parts glucose, 10 parts sorbitol, and up to 1 part citric acid or 0.1 part phosphoric acid. The 1,6-glycosidic linkage predominates in the polymer but other linkages are present. It contains small quantities of free glucose, sorbitol, and 1,6-anhydro-D-glucose (levoglucosan), with traces of citric acid or phosphoric acid. An off-white to light tan-coloured solid. Very soluble in water; insoluble in alcohol; slightly soluble in glycerol and in propylene glycol. A 10% solution has a pH of 2.5 to 5.0. Store in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light and moisture.

USNF 31: (Hydrogenated Polydextrose). Hydrogenated Polydextrose is obtained by transition metal catalytic hydrogenation of Polydextrose in aqueous solution. It contains not less than 90.0% of glucose polymer units, calculated on the anhydrous and ash-free basis. The polymer chain end groups are mainly sorbitol-terminated. An off-white to light tan-coloured solid. Very soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycol. A 10% solution has a pH of 5.0 to 7.0. Store in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light and moisture.

Profile

Polydextrose is a random polymer of glucose used as a bulking agent, binder, and coating agent in pharmaceutical preparations. It is also used as a low-calorie carbohydrate bulking agent in the food industry.

Polyethylene Oxide

Polietileno, óxido de; Полиэтилен Оксид.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyethylene Oxide). A nonionic homopolymer of ethylene oxide, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups (about 2000 to 200 000). It is obtainable in several grades, varying in viscosity profile in an aqueous isopropyl alcohol solution. It may contain not more than 3% of silicon dioxide. A white to off-white powder. Miscible with water; freely soluble in acetonitrile, in dichloromethane, in ethylene dichloride, and in trichloroethylene; insoluble in aliphatic hydrocarbons, in ethylene glycol, in diethylene glycol, and in glycerol. Store in airtight containers. Protect from light.

Profile

Polyethylene oxide is a high-molecular-weight macrogol (p. 2547.3) used as a tablet binder and as a suspending and thickening agent in pharmaceutical preparations. Polyethylene oxide has been used in hydrogel wound dressings.

Polyisobutylene

Polyisobutene; Полиизобутилен.
2-Methyl-1-propene homopolymer.
$(C_4H_8)_x$
CAS — 9003-27-4.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyisobutylene). A synthetic polymer produced by the low-temperature polymerisation of isobutylene in liquid ethylene, dichloromethane, or hexane, using an aluminium chloride or boron trifluoride catalyst. It may contain a suitable stabiliser. Grades are characterised by the range of intrinsic viscosity or the range for the Staudinger Index.

Low molecular-weight grades are soft and gummy; high molecular-weight grades are tough and elastic. All grades are light in colour, odourless, and tasteless. Insoluble in water; soluble in chloroform, in di-isobutylene, and in toluene.

Profile

Polyisobutylene is a synthetic polymer available in a range of molecular weights. It is used as an adhesive in transdermal patches, and has many other industrial applications.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Stomahesive; ***UK***: Stomahesive.

Polyoxyl Castor Oils

Aceites de ricino polioxietilenados; Glycerol Polyethylene Glycol Ricinoleate; Macrogol Glycerol Ricinoleates; Macrogolglycerol Ricinoleate; Macrogolglycérol, ricinoléate de; Macrogolglyceroli ricinoleas; Macrogolglycerolricinoleat; Makrogol-glicerin-éter -ricinoleát; Makrogolglicerolio ricinoleatas; Makrogolglycerolricinoleat; Makrogoliglyserolirisiinioleaatti; Makrogologlicerolu rycynooleinian; PEG Glyceryl Ricinoleates; Polyethoxylated Castor Oils; Polyethylene Glycol Glyceryl Ricinoleates; Polyoxyethylene Castor Oils; Polyoxyethylene Glyceryl Ricinoleates; Полиэтиленгликоля Касторовые Масла.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogolglycerol Ricinoleate; Polyoxyl Castor Oil BP 2014). It contains mainly ricinoleyl glycerol ethoxylated with 30 to 50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate and of the corresponding free glycols. It results from the reaction of castor oil with ethylene oxide. A clear, yellow, viscous liquid or semi-solid. Relative density about 1.05; viscosity, at 25 degrees, 500 to 800 mPa s. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Polyoxyl 35 Castor Oil

Aceite de ricino polioxil 35; Полиэтиленгликоля 35 Касторовое Масло.
UNII — 6D4M1DAL6O.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 35 Castor Oil). A mixture of the triricinoleate ester of ethoxylated glycerol with smaller amounts of macrogol ricinoleate and the corresponding free glycols. It is produced by reacting 1 mole of glycerol ricinoleate with about 35 moles of ethylene oxide.

A yellow oily liquid with a faint characteristic odour. Sp. gr. 1.05 to 1.06; viscosity, at 25 degrees, 650 to 850 mPa s. Very soluble in water, producing a practically odourless and colourless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. Store in airtight containers.

Incompatibility. Polyoxyl castor oils are reported to affect PVC containers and apparatus adversely.

Uses

Polyoxyl castor oils are ethoxylated glycerol ester nonionic surfactants (p. 2164.2) used as emulsifying and solubilising agents. Polyoxyl 35 castor oil has been used as a solvent in vehicles for various intravenous injections.

Adverse Effects

Polyoxyl castor oils (such as *Cremophor EL*) used as vehicles in intravenous injections have been associated with severe anaphylactoid reactions, hyperlipidaemias, alterations in blood viscosity, and erythrocyte aggregation. They may also

lead to adverse effects due to alterations in the pharmacokinetics of the formulated drug.

References.
1. Bagnarello AG, *et al.* Unusual serum lipoprotein abnormality induced by the vehicle of miconazole. *N Engl J Med* 1977; **296:** 497–9.
2. Forrest ARW, *et al.* Long-term Althesin infusion and hyperlipidaemia. *BMJ* 1977; **2:** 1357–8.
3. Dye D, Watkins J. Suspected anaphylactic reaction to Cremophor EL. *BMJ* 1980; **280:** 1353.
4. Howrie DL, *et al.* Anaphylactoid reactions associated with parenteral cyclosporine use: possible role of Cremophor EL. *Drug Intell Clin Pharm* 1985; **19:** 425–7.
5. Chapuis B, *et al.* Anaphylactic reaction to intravenous cyclosporine. *N Engl J Med* 1985; **312:** 1259.
6. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; **i:** 394.
7. ten Tije AJ, *et al.* Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003; **42:** 665–85.
8. Hennenfent KL, Govindan R. Novel formulations of taxanes: a review. Old wine in a new bottle? *Ann Oncol* 2006; **17:** 735–49.

Polyoxyl Hydrogenated Castor Oils

Aceites de ricino hidrogenados y polioxietilenados; Ethoxylated Hydrogenated Castor Oils; Glycerol Polyethylene Glycol Hydroxystearates; Macrogolglycerol Hydroxystearate; Macrogolglycérol, hydroxystéarate de; Macrogolglycerolhydroxystearat; Macrogolglyceroli hydroxystearas; Macrogrol Glycerol Hydroxystearates; Makrogol-glicerin-éter-hidroxisztearát; Makrogolglicerolio hidroksisteratas; Makrogolglycerolhydroxistearat; Makrogoliglyserolihydroksistearaatti; PEG Hydrogenated Castor Oils; Polyethylene Glycol Hydrogenated Castor Oils; Polyoxyethylene Hydrogenated Castor Oils; Полиэтиленгликоля Касторовые Масла Гидрогенизированные.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Macrogolglycerol Hydroxystearate; Hydrogenated Polyoxyl Castor Oil BP 2014). It contains mainly trihydroxystearyl glycerol ethoxylated with 7 to 60 molecules of ethylene oxide (nominal value), with small amounts of macrogol hydroxystearate and of the corresponding free glycols. It results from the reaction of hydrogenated castor oil with ethylene oxide. Polyoxyl hydrogenated castor oil with less than 10 units of ethylene oxide per molecule is a yellowish, turbid, viscous liquid. Practically insoluble in water; dispersible in alcohol; soluble in acetone. Polyoxyl hydrogenated castor oil with more than 20 units of ethylene oxide per molecule is a white or yellowish, semi-liquid or pasty mass. Freely soluble in water, in alcohol, and in acetone; practically insoluble in petroleum spirit.

Polyoxyl 40 Hydrogenated Castor Oil

Aceite de ricino hidrogenado polioxil 40; Полиэтиленгликоля 40 Касторовое Масло Гидрогенизированное.
UNII — 7YC686GQ8F.

Pharmacopoeias. In *USNF.*

USNF 31: (Polyoxyl 40 Hydrogenated Castor Oil). A mixture of mainly the trihydroxystearate ester of ethoxylated glycerol, with smaller amounts of macrogol trihydroxystearate and the corresponding free glycols. It is produced by reacting 1 mole of glycerol trihydroxystearate with about 40 to 45 moles of ethylene oxide.

A white to yellowish paste or pasty liquid with a faint odour. Congealing range 20 degrees to 30 degrees. Very soluble in water, producing an odourless, colourless solution; soluble in alcohol and in ethyl acetate; insoluble in liquid paraffin. Store in airtight containers.

Profile

Polyoxyl hydrogenated castor oils are ethoxylated glycerol ester nonionic surfactants (p. 2164.2). They are used as solubilisers and emulsifiers in oral and topical pharmaceutical preparations; they are also used in cosmetics.

Polysorbates

Macrogol Sorbitan Esters; Polisorbatos; Polyethylene Glycol Sorbitan Esters; Polyoxyethylene Sorbitan Esters; Sorbimacrogols; Полисорбаты.

Description. Polysorbates are polyoxyethylene derivatives of cyclic sorbitol anhydrides partially esterified with a fatty acid. The numbered polysorbates listed as *BAN, INN,* and *USAN* are polyoxyethylene 20 sorbitan esters, in which each mole of sorbitan is ethoxylated with about 20 moles of ethylene oxide.

Incompatibility. Polysorbates have been reported to be stable with electrolytes and weak acids and bases although saponification may occur in the presence of strong acids and bases. Discoloration or precipitation may occur with phenolic substances. The oleic acid esters are sensitive to oxidation. For reference to the possible incompatibility of polysorbate 80 with hydroxybenzoates, see p. 1757.3.

Polysorbate 20 *(BAN, USAN, rINN)*

E432; Monolaurato de polietileno 20 sorbitano; Monolaurato de polioxietileno 20 sorbitano; Polisorbat 20; Polisorbatas 20; Polisorbato 20; Poliszorbát 20; Polyoxyethylene 20 Sorbitan Monolaurate; Polysorbaatti 20; Polysorbat 20; Polysorbát 20; Polysorbatum 20; Sorbimacrogol Laurate 300; Sorboxaethenum Laurinicum; Полисорбат 20.
$C_{58}H_{114}O_{26}$(approximate)
CAS — 9005-64-5.
UNII — 7T1F30V5YH.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Polysorbate 20). A mixture of partial esters of fatty acids, mainly lauric acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A clear or slightly opalescent yellowish to brownish-yellow oily liquid. Relative density about 1.10. Soluble in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polysorbate 20). A laurate ester of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to amber liquid with a faint characteristic odour. Soluble in water, in alcohol, in dioxan, in ethyl acetate, and in methyl alcohol; insoluble in liquid paraffin. Store in airtight containers.

Polysorbate 40 *(BAN, USAN, rINN)*

E434; Monopalmitato de polietileno 20 sorbitano; Monopalmitato de polioxietileno 20 sorbitano; Polisorbatas 40; Polisorbato 40; Poliszorbát 40; Polyoxyethylene 20 Sorbitan Monopalmitate; Polysorbaatti 40; Polysorbat 40; Polysorbát 40; Polysorbatum 40; Sorbimacrogol Palmitate 300; Полисорбат 40.
$C_{62}H_{122}O_{26}$(approximate)
CAS — 9005-66-7.
UNII — STI11B5A2X.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Polysorbate 40). Mixture of partial esters of fatty acids, mainly palmitic acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. An oily, viscous, yellowish or brownish-yellow liquid. Relative density about 1.10. Miscible with water, with dehydrated alcohol, with ethyl acetate, and with methyl alcohol; practically insoluble in fatty oils and in liquid paraffin. Store in airtight containers. Protect from light.

The BP 2014 gives Polyoxyethylene 20 Sorbitan Monopalmitate as an approved synonym.

USNF 31: (Polysorbate 40). A palmitate ester of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A yellow liquid with a faint characteristic odour. Soluble in water and in alcohol; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Polysorbate 60 *(BAN, USAN, rINN)*

E435; Monoestearato de polietileno 20 sorbitano; Monoestearato de polioxietileno 20 sorbitano; Polisorbat 60; Polisorbatas 60; Polisorbato 60; Poliszorbát 60; Polyoxyethylene 20 Sorbitan Monostearate; Polysorbaatti 60; Polysorbat 60; Polysorbát 60; Polysorbatum 60; Sorbimacrogol Stearate 300; Sorboxaethenum Stearinicum; Полисорбат 60.
$C_{64}H_{126}O_{26}$(approximate)
CAS — 9005-67-8.
UNII — CAL22UVI4M.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Polysorbate 60). A mixture of partial esters of fatty acids, mainly stearic acid 50, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A yellowish-brown gelatinous mass which becomes a clear liquid at temperatures above 25 degrees. Relative density about 1.10. Soluble in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polysorbate 60). A mixture of stearate and palmitate esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to orange-coloured oily liquid or semi-gel with a faint characteristic odour. Soluble in water, in ethyl acetate, and in toluene; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Polysorbate 80 *(BAN, USAN, rINN)*

E433; Monooleato de polietileno 20 sorbitano; Monooleato de polioxietileno 20 sorbitano; Olethytan 20; Polisorbat 80; Polisorbatas 80; Polisorbato 80; Poliszorbát 80; Polyäthylenglykol-Sorbitanoleat; Polyoxyethylene 20 Sorbitan Monooleate; Polysorbaatti 80; Polysorbat 80; Polysorbát 80; Polysorbatum 80; Polysorbitanum 80 Oleinatum; Sorbimacrogol Oleate 300; Sorboxaethenum Oleinicum; Sorethytan 20 Mono-oleate; Полисорбат 80.
$C_{64}H_{124}O_{26}$(approximate)
CAS — 9005-65-6.
UNII — 6OZP39ZG8H.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.,* and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Polysorbate 80). A mixture of partial esters of fatty acids, mainly oleic acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. An oily, colourless or brownish-yellow, clear or slightly opalescent liquid. Relative density about 1.10. Dispersible in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polysorbate 80). An oleate ester of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to amber-coloured oily liquid with a faint characteristic odour. Sp. gr. between 1.06 and 1.09; viscosity, at 25 degrees, between 300 and 500 mPa s. Very soluble in water, producing an odourless and practically colourless solution; soluble in alcohol and in ethyl acetate; insoluble in liquid paraffin. Store in airtight containers.

Polysorbate 85 *(BAN, USAN, rINN)*

Polisorbatas 85; Polisorbato 85; Poliszorbát 85; Polyoxyethylene 20 Sorbitan Trioleate; Polysorbaatti 85; Polysorbat 85; Polysorbát 85; Polysorbatum 85; Sorbimacrogol Trioleate 300; Trioleato de polietileno 20 sorbitano; Trioleato de polioxietileno 20 sorbitano; Полисорбат 85.
$C_{100}H_{188}O_{28}$(approximate)
CAS — 9005-70-3.
UNII — A7F3N56197.

Description. A mixture of mainly trioleate esters of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

Uses

Polysorbates are ethoxylated sorbitan ester nonionic surfactants (p. 2164.2). They usually correspond to polyoxyethylene 20 sorbitan esters, in which each mole of sorbitan is ethoxylated with about 20 moles of ethylene oxide, although polysorbates with different ethoxylation ratios may also be used. The number following polysorbate in the name relates to both the ethoxylation ratio and the fatty acid component of the sorbitan ester.

Polysorbates are hydrophilic and are used as emulsifying agents for the preparation of stable oil-in-water emulsions in pharmaceutical products; they are frequently used with a sorbitan ester in varying proportions to produce products with a range of texture and consistency. Polysorbates have also been used in the formulation of insecticide and herbicide sprays, industrial detergents, and cosmetic products. They are also used as emulsifiers in the food industry.

Polysorbates are used as solubilising agents for a variety of substances including essential oils and oil-soluble vitamins such as vitamins A, D, and E, and as wetting agents in the formulation of oral and parenteral suspensions. However, hypersensitivity reactions have been attributed to the presence of polysorbates, see Hypersensitivity, p. 2204.1.

Polysorbates may also be used for their surfactant properties in preparations for the removal of ear wax, and for the management of dry eyes and upper respiratory-tract disorders.

Adverse Effects and Precautions

Polysorbates may increase the absorption of fat-soluble substances.

There have been occasional reports of hypersensitivity after topical application of preparations containing polysorbates.

For discussion of fatalities in low-birth-weight infants associated with the injection of a polysorbate-containing preparation, see p. 2204.1.

Polysorbates used as excipients may also lead to adverse effects due to alterations in the pharmacokinetics of the formulated drug.

References.

1. ten Tije AJ, *et al*. Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003; **42:** 665–85.

Effects in infants. After the introduction in the USA of an intravenous preparation of vitamin E (*E-Ferol*) there were a number of reports of unusual liver and kidney disorders, with 38 deaths being reported among treated low-birthweight infants. Affected infants had unexplained hypotension, thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, and metabolic acidosis;[1-3] the preparation was subsequently withdrawn from the market in April 1984 about 5 months after it was introduced. *In-vitro* evidence was produced showing that *E-Ferol* suppressed the response of human lymphocytes to phytohaemagglutinin. However, it was the mixture of polysorbates, polysorbate 20 and in particular polysorbate 80, that was shown to be responsible for this suppression rather than the α-tocopherol acetate component. Despite this *in-vitro* data, overwhelming infection was not a feature in the affected infants.[2] Large doses of polysorbates were unavoidably injected when *E-Ferol* was used and it was suggested that polysorbates may accumulate as a result of an alteration in the metabolism by low-birth-weight infants; polysorbate-induced alteration of membrane fluidity in cells of vessel walls may have led to changes in structure and function.[2]

Polysorbate 80 was also suggested as part of the cause of a severe hypotensive episode in an infant given an intravenous overdose of amiodarone; benzyl alcohol in the formulation may also have contributed.[4]

1. Alade SL, *et al*. Polysorbate 80 and E-Ferol toxicity. *Pediatrics* 1986; **77:** 593–7.
2. Balistreri WF, *et al*. Lessons from the E-Ferol tragedy. *Pediatrics* 1986; **78:** 503–6.
3. Golightly LK, *et al*. Pharmaceutical excipients: adverse effects associated with inactive ingredients in drug products. *Med Toxicol* 1988; **3:** 128–65 and 209–240.
4. Masi S, *et al*. Acute amiodarone toxicity due to an administration error: could excipient be responsible? *Br J Clin Pharmacol* 2009; **67:** 691–3.

Hypersensitivity. Local inflammatory reactions after intramuscular injection of a vitamin A preparation were considered[1] to be due to a hypersensitivity reaction to polysorbate 80, included as an excipient. Anaphylactoid reactions which occurred in 2 patients after treatment with omalizumab for 27 and 13 months respectively, were likely to be due to the polysorbate excipient and not to the monoclonal antibody itself.[2] The presence of polysorbate 80 in the injection may also contribute to hypersensitivity reactions to docetaxel (see Adverse Effects of Docetaxel, p. 781.3).

1. Shelley WB, *et al*. Polysorbate 80 hypersensitivity. *Lancet* 1995; **345:** 1312–13.
2. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; **28:** 313–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sinroncar; ***Belg.***: Oleosorbate†; ***Canad.***: Dioptears; ***Fr.***: Cerumenol†; ***USA***: OptiZen; Viva-Drops.

Multi-ingredient Preparations. ***Arg.***: Endura; Otoclean Gotas Oticas; ***Fin.***: Expigen; ***Fr.***: Fluisedal sans promethazine; Fluisedal; Paroplak†; Prorhinel; ***Hong Kong***: Asonor; ***S.Afr.***: Expigen; ***Singapore***: Endura; ***Switz.***: Prorhinel; Rhinocure simplex; Rhinocure; ***Thai.***: Endura; ***Turk.***: Kansilak; Libalaks; ***UK***: Asonor; Episil; ***USA***: Episil; Refresh Dry Eye Therapy; Soothe XP; Soothe.

Polyvinyl Acetate

Acetato de polivinilo; Poli(octan winylu); Poli(vinil-acetát); Polivinilacetatas; Polüvinüülatsetaat; Poly(acétate de vinyle); Polyvinylacetaat; Polyvinylacetat; Poly(vinylacetat); Polyvinylacetát; Poly(vinylis Acetas); Polyvinylis Acetas; Poly(vinyyliasetaatti); Поливинилацетат.
CAS — 9003-20-7.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF* Eur. also includes a 30% dispersion and *USNF* a 25 to 30% dispersion.

Ph. Eur. 8: (Poly(vinyl acetate)). A white or almost white powder or colourless granules or beads. Practically insoluble in water; soluble in alcohol; freely soluble in ethyl acetate. It is hygroscopic and swells in water. It softens at temperatures above 40 degrees to 50 degrees. Store in airtight containers.

Ph. Eur. 8: (Poly(Vinyl Acetate) Dispersion 30 per cent). A dispersion in water of polyvinyl acetate having a mean relative molecular mass of about 450 000. It may contain povidone and a suitable surface-active agent, such as sodium laurilsulfate, as stabilisers.

An opaque, white or almost white, slightly viscous liquid. Miscible with water and with alcohol. It is sensitive to spoilage by microbial contaminants. Store at a temperature of 5 degrees to 30 degrees.

USNF 31: (Polyvinyl Acetate). A white or off-white powder or colorless granules or beads. It is hygroscopic and swells in water. Practically insoluble in water; soluble in alcohol, in acetone, and in chloroform; freely soluble in ethyl acetate.

USNF 31: (Polyvinyl Acetate Dispersion). It contains 25 to 30% of polyvinyl acetate. It may contain suitable surface active agents and stabilisers. An opaque, white or off-white, slightly viscous liquid. Miscible with water and with alcohol. pH 3.0 to 5.5. Store in airtight containers at a temperature below 25 degrees. Protect from freezing.

Polyvinyl Acetate Phthalate

Polivinilo, acetato ftalato de; Поливинилацетата Фталат.
UNII — 58QVG85GW3.

Pharmacopoeias. In *USNF*.

USNF 31: (Polyvinyl Acetate Phthalate). A reaction product of phthalic anhydride and a partially hydrolysed polyvinyl acetate. It contains 55.0 to 62.0% of phthalyl groups, calculated on an anhydrous acid-free basis. It is a free-flowing white powder that may have a slight odour of acetic acid. Insoluble in water, in chloroform, and in dichloromethane; soluble in alcohol and in methyl alcohol. Store in airtight containers.

Profile

Polyvinyl acetate phthalate is a viscosity-modifying agent that is used in the manufacture of enteric coatings for tablets. Polyvinyl acetate is used in tablet coating; it is also widely used as a glue.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Fittydent.

Polyvinyl Alcohol

Alcohol polivinílico; Alcohol Polyvinylicus; Alcool polivinilico; Alcool polyvinylique; Alkohol poliwinylowy; Polivinil Alkol; Poli(vinil-alkohol); Polivinilo alkoholis; Poly(alcohol Vinylicus); Poly(alcool vinylique); Polyvinylalcohol; Poly(vinylalkohol); Polyvinylalkohol; Poly(vinyylialkoholi); Поливиниловы Спирт.
CAS — 9002-89-5.
UNII — 532B59J990.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Poly(Vinyl Alcohol)). It is obtained by polymerisation of vinyl acetate followed by partial or complete hydrolysis of polyvinyl acetate in the presence of catalytic amounts of alkali or mineral acids. Various grades are available and they differ in their degree of polymerisation and their degree of hydrolysis, which determine the physical properties of the different grades. They are characterised by the viscosity and the ester value of the substance. The mean relative molecular mass lies between 20 000 and 150 000. The viscosity is 3 to 70 millipascal seconds. The ester value, which characterises the degree of hydrolysis, is not greater than 280.

Polyvinyl alcohol occurs as a yellowish-white powder or translucent granules. Soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 4% solution in water has a pH of 4.5 to 6.5.

USP 36: (Polyvinyl Alcohol). A synthetic resin represented by the formula $(CH_2CHOH)_n$, where the average value of n is 500 to 5000. It is prepared by 85 to 89% hydrolysis of polyvinyl acetate. White to cream-coloured, odourless, granules or powder. Freely soluble in water at room temperature; solution may be effected more rapidly at somewhat higher temperatures. pH of a 4% solution in water is between 5.0 and 8.0. Store in a dry place.

Profile

Polyvinyl alcohol is a nonionic surfactant (p. 2164.2) that is used in pharmaceutical manufacturing as a stabilising agent and as a viscosity-increasing agent and lubricant.

Polyvinyl alcohol has also been used in the preparation of jellies that dry rapidly when applied to the skin to form a soluble plastic film.

Polyvinyl alcohols of various grades are used for a wide variety of industrial applications.

Polyvinyl alcohol has been used to increase the viscosity of ophthalmic preparations thus prolonging contact of the active ingredient with the eye. It is included in artificial tears preparations used for dry eye (p. 2190.1) and in contact lens solutions (p. 1730.2). For dry eye it is often used in a concentration of 1.4% with or without povidone.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bio Tears; Lagrima Artificial; Lentisol†; Lersan Lagrimas; Liquifilm Lagrimas; Natura Wet; Total Solucion†; ***Austral.***: Liquifilm; PVA; ***Belg.***: Liquifilm; ***Braz.***: Lacril; ***Canad.***: Artificial Tears; Hypotears; Liquifilm†; Optilube PVA; ***Chile***: Lagrimas Artificiales; Visidic; ***Denm.***: Lacril; ***Fin.***: Liquifilm; Oftan†; ***Ger.***: Liquifilm; Vistil; ***Gr.***: Liquifilm Tears; ***Hong Kong***: Liquifilm; PMS-Artificial Tears†; ***Hung.***: Humalac A and C; ***India***: Alphagan; Liquifilm Tears; ***Indon.***: Optifresh†; ***Irl.***: Liquifilm; Sno Tears†; ***Israel***: Liquifilm Tears; ***Ital.***: Lacrilux; Vistil; ***Malaysia***: Liquifilm; ***Mex.***: Acuafil Ofteno; Lubrik; ***Norw.***: Kunstig Tarevaeske†; Ocufri†; ***NZ***: Liquifilm; ***Pol.***: Lacrimal; ***Port.***: Liquifilm; ***S.Afr.***: Liquifilm Tears†; ***Singapore***: Hypotears; Liquifilm Tears; ***Spain***: Liquifilm Lagrimas; ***Swed.***: Sincon; ***Switz.***: Liquitears; ***Thai.***: Liquifilm Tears; ***Turk.***: Liquifilm; ***UK***: Liquifilm Tears; Refresh; Sno Tears; ***USA***: Akwa Tears; Dry Eyes; Liquifilm†; Nu-Tears; Ocu-Tears; Puralube; Tears Again; ***Venez.***: Acuafil Ofteno; Lacril.

Multi-ingredient Preparations. ***Arg.***: Consil†; Latlas Fresh; Latlas; Panoptic Lagrimas; Soquette†; ***Austral.***: Murine Revital Eyes; Murine Tears†; Refresh; ***Austria***: Siccaprotect; ***Braz.***: Fresh Clear; Refresh; ***Canad.***: Artificial Tears Extra; Artificial Tears Plus; Clear Eyes Triple; Murine; Refresh; Tears Plus; ***Chile***: Red Off Aqua; ***Cz.***: Siccaprotect; ***Fr.***: Refresh; ***Ger.***: Dispatenol; Lacrimal OK; Liquifilm OK; Siccaprotect; ***Gr.***: Onufrid; Refresh; ***Hong Kong***: Hypotears; Murine Natural Tears†; Murine Plus Natural†; ***India***: Aansoo; Adle; Aquatears; Dudrop; Eyedrip; Flotears; I-Lube; Irisol Plus; Lacrisan; Lacrisol; Mist; Moss Eye; Ocuwet; Optilube; ***Irl.***: Refresh; ***Israel***: Refresh; ***Ital.***: Hypotears; ***Malaysia***: Hypotears; ***Mex.***: Lagrifilm Plus; Soltrictor con Lagrifilm; ***Neth.***: Tears Plus†; ***NZ***: Refresh; ***Rus.***: Ophtholique (Офтолик); ***S.Afr.***: Refresh; Tears Plus†; ***Singapore***: Bio-Taches Masque†; Murine Plus; Refresh; ***Spain***: Liquifresh; ***Switz.***: Hypotears; Siccaprotect; ***Thai.***: Refresh; ***Turk.***: Refresh; Siccaprotect; ***UK***: Blink; ***Ukr.***: Ophtholique (Офтолик); ***USA***: Freshkote; Hypotears; Murine Plus; Murine†; Nu-Tears II; Refresh Classic; Refresh Redness Relief; Tears Plus.

Ponceau 4R

Brilliant Ponceau 4RC; Brilliant Scarlet; CI Food Red 7; Coccine Nouvelle; Cochenillerot A; Cochineal Red A; Colour Index No. 16255; Czerwień Koszenilowa A; E124; Nykockin; Punzó 4R; Rojo de Cochinilla A; Rouge Cochenille A; Uuskokkiini; Понсо 4R; Пунцовый 4R.
Trisodium 7-hydroxy-8-(4-sulphonato-1-naphthylazo) naphthalene-1,3-disulphonate.
$C_{20}H_{11}N_2Na_3O_{10}S_3$=604.5
CAS — 2611-82-7.
UNII — Z525CBK9PG.

Profile

Ponceau 4R is a synthetic azo dye used as a colouring agent in medicines, cosmetics, and foods. Sensitivity reactions have been reported.

Potassium Metaphosphate

E452 (potassium polyphosphates); Polifosfato potásico; Potassium Kurrol's Salt; Potassium Polymetaphosphate; Метафосфорнокислый Калий; Метафосфат Калия.
$(KPO_3)_x$
CAS — 7790-53-6.
UNII — 01DMT14Z63.

Pharmacopoeias. In *USNF*.

USNF 31: (Potassium Metaphosphate). A straight-chain polyphosphate, having a high degree of polymerisation. It contains the equivalent of 59 to 61% of P_2O_5. A white, odourless powder. Insoluble in water; soluble in dilute solutions of sodium salts.

Profile

Potassium metaphosphate is used as a buffer.

Povidone *(BAN, USAN, rINN)*

E1201; Polivinilpirolidon; Polivinilpirolidons; Polivinilpirrolidona; Polivinilpirrolidone; Poliwinylopirolidon; Polyvidone; Polyvidonum; Polyvinylpyrrolidon; Polyvinylpyrrolidone; Povidon; Povidona; Povidonas; Povidoni; Povidonum; Powidon; PVP; Vinylpyrrolidinone Polymer; Повидон.
Poly (2-oxopyrrolidin-1-ylethylene).
$(C_6H_9NO)_n$
CAS — 9003-39-8.
UNII — FZ989GH94E.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US*.

Ph. Eur. 8: (Povidone). Linear polymers of 1-ethenylpyrrolidin-2-one. The different types of povidone are char-

acterised by their viscosity in solution. A white or yellowish-white, hygroscopic powder or flakes. Freely soluble in water, in alcohol, and in methyl alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 3.0 to 7.0 depending on the viscosity. Store in airtight containers.

USP 36: (Povidone). A synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerisation of which results in polymers of various molecular weights. The different types of povidone are characterised by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. A white to slightly creamy-white, hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in acetone; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 7.0 (depending on K-values). Store in airtight containers.

Copovidone

Copolyvidone; Copolyvidonum; Copovidon; Copovidona; Copovidonum; Kopovidon; Kopovidonas; Kopovidoni; Коповидон.

CAS — 25086-89-9.
UNII — D9C330MD8B.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. & (Copovidone). A copolymer of 1-vinylpyrrolidin-2-one and vinyl acetate in the mass proportion 3:2. A white or yellowish-white, hygroscopic powder or flakes. Freely soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USNF 31: (Copovidone). A copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a mass proportion of 3:2. A white to yellowish-white, hygroscopic, powder or flakes. Freely soluble in water, in alcohol, and in dichloromethane; practically insoluble in ether. Store in airtight containers.

Crospovidone *(BAN, rINN)*

Crospovidon; Crospovidona; Crospovidonum; Krospovidon; Krospovidonas; Krospovidoni; Kroszpovidon; Polyplasdone XL; Кросповидон.

CAS — 9003-39-8.
ATC — A07BC03.
ATC Vet — QA07BC03.
UNII — 68401960MK.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. & (Crospovidone). A cross-linked homopolymer of 1-ethenylpyrrolidin-2-one. Two types of crospovidone are available, depending on the particle size: type A and type B. A white or yellowish-white, hygroscopic powder or flakes. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from moisture.

USNF 31: (Crospovidone). A synthetic cross-linked homopolymer of *N*-vinyl-2-pyrrolidinone. A white to creamy-white, hygroscopic powder having a faint odour. Insoluble in water and in ordinary organic solvents. pH of a 1% suspension in water is between 5.0 and 8.0. Store in airtight containers.

Uses and Administration

Povidone is used in pharmaceutical manufacturing as a suspending and dispersing agent and as a tablet binding, granulating, and coating agent. It is used as a carrier for iodine (see Povidone-Iodine, p. 1767.1). An insoluble cross-linked form of povidone known as crospovidone is used as a tablet disintegrant. Copovidone, a copolymer with vinyl acetate, is used as a tablet binding and coating agent.

Povidone is included in artificial tears preparations used in the management of dry eye (p. 2190.1) and in solutions for contact lens care (p. 1730.2). For dry eye it is often used in a concentration of 0.6% with other viscosity-increasing agents (such as polyvinyl alcohol); it may also be used alone in solutions containing 1.5 to 5%.

Povidone has also been used as an adsorbent in gastrointestinal disorders.

Povidone was formerly used as a plasma expander but other compounds are now preferred.

Adverse Effects

Some products intended for parenteral use contain povidone as an excipient and injection has led to deposition of povidone in the tissues with consequent lesions and pain. There have been occasional reports of liver involvement.

Reviews of adverse effects associated with pharmaceutical excipients including povidone.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive ingredients' in drug products (part II). *Med Toxicol* 1988; **3:** 209–40.

Hypersensitivity. For reference to anaphylaxis caused by the povidone component of povidone-iodine, see p. 1767.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hypotears Plus; Renu Plus Gotas; Sol-O-Flex†; ***Austria***: Oculotect; Protagent; ***Belg.***: Oculotect; Siccagent; Telebrix Hystero; ***Braz.***: Hypotears Plus; ***Chile***: Lepex; Oculotec†; ***Cz.***: Arufil; Hypotears Plus; ***Denm.***: Oculac; ***Fin.***: Oculac; ***Fr.***: Dulcilarmes; Fluidabak; Larmecran†; Nutrivisc; Unifluid; ***Ger.***: Aloclair†; Arufil†; Lacophtal; Lacri-Stulln; Oculotect Fluid; Protagent; Vidisept; Wet-COMOD; ***Gr.***: Oculotect; Protagent; ***Hong Kong***: Hypotears Plus; Protagent; ***Hung.***: Arufil†; Oculotect; ***India***: Hypotears Plus; ***Irl.***: Oculotect†; ***Israel***: Hypotears E; ***Ital.***: Clarover; Nu-Gel; Wet-COMOD; ***Malaysia***: Oculotect†; ***Mex.***: Hypotears Plus; Logical†; Renu Plus†; ***Mon.***: Bolinan; ***Neth.***: Duratears Free; Oculotect; Protagens; Vidisic PVP; ***Norw.***: Oculac; ***Philipp.***: Oculotect; Vidisept N; ***Pol.***: Oculotect; Vidisept; ***Port.***: Oculotect; ***Rus.***: Enterodes (Энтеродез); Vid-COMOD (Вид-КОМОД); ***S.Afr.***: Hypotears†; ***Singapore***: Oculotect; Vidisept N†; ***Spain***: Oculotect; ***Swed.***: Oculac; ***Switz.***: Lacri-Stulln; Oculac; Protagent; ***Thai.***: Hypotears Plus†; ***Turk.***: Oculotect; Protagent; ***UK***: Aloclair; Oculotect†; ***USA***: Soothe Hydration; ***Venez.***: Hypotears Plus.

Multi-ingredient Preparations. ***Arg.***: Maxilac†; Panoptic Lagrimas; Visine Plus; ***Austral.***: Murine Revital Eyes; Murine Tears†; QV Flare Up; Refresh; Visine Advanced Relief; Visine Professional†; ***Braz.***: Refresh; ***Canad.***: Artificial Tears Extra; Artificial Tears Plus; Clear Eyes Triple; Murine; Refresh; Tears Plus; Visine Advance Triple Action; ***Chile***: Gelclair; ***Fr.***: Poly-Karaya; Refresh; ***Ger.***: Gelclair; Lacrimal OK; Lacrisic; Liquifilm OK; Visine Trockene Augen; Visine zur Nacht; ***Gr.***: Onufrid; Refresh; ***Hong Kong***: Murine Natural Tears†; Murine Plus Natural†; ***India***: Aansoo; Adle; Aquatears; Dudrop; Eyedrip; I-Lube; Irisol Plus; Lacrisan; Mist; Moss Eye; Ocuwet; Optilube; ***Indon.***: Aloclair; ***Irl.***: Refresh; ***Israel***: Aphtagone†; Aptha-X†; Lacrimol; Refresh; V-Crima; ***Ital.***: Filmabak; Visine Dry Eyes†; ***Malaysia***: Aloclair; ***Mex.***: Lagrifilm Plus; Soyaloid; Soydex; Visine Extra; ***Neth.***: Tears Plus†; ***NZ***: Refresh; Visine Advanced Relief; ***Rus.***: Gluconeodesum (Глюконеодез); Haemodez-N (Гемодез-Н); Krashaemodes (Красгемодез); Neohemodes (Неогемодез); Ophtholique (Офтолик); ***S.Afr.***: Refresh; Tears Plus†; ***Singapore***: Murine Plus; Refresh; ***Spain***: Liquifresh; ***Thai.***: Refresh; ***Turk.***: Refresh; ***UK***: Gelclair; ***Ukr.***: Ophtholique (Офтолик); ***USA***: Advanced Relief Visine; Freshkote; Gelclair; Murine Plus; Murine†; Refresh Classic; Tears Plus.

Propylene Carbonate

Carbonato de propileno; Пропиленкарбонат.

4-Methyl-1,3-dioxolan-2-one.

$C_4H_6O_3$=102.1

CAS — 108-32-7.
UNII — 8D08K3551E.

Description. Propylene carbonate is a clear colourless mobile liquid. Freely soluble in water; miscible with alcohol and with chloroform; practically insoluble in petroleum spirit.

Pharmacopoeias. In *USNF.*

USNF 31: (Propylene Carbonate). Sp. gr. 1.203 to 1.210 at 20 degrees. Store in airtight containers.

Profile

Propylene carbonate is used as a solvent in oral and topical pharmaceuticals and for cellulose-based polymers and plasticisers. It has been used as a nonvolatile, stabilising liquid carrier in hard gelatin capsules.

Propylene Glycol

E1520; Glicol Propilênico; Glicole propilenico; Glikol propylenowy; Propilenglicol; Propiléngликol; Propilenglikolis; Propilėnglikols; Propilenoglicol; Propüleenglükool; Propyleenglycol; Propyleeniglykoli; Propylèneglycol; Propylenglycol; Propylenglycolum; Propylenglykol; Пропиленгликоль.

(±)-Propane-1,2-diol.

$C_3H_8O_2$=76.10

CAS — 57-55-6 ((±)-propylene glycol); 4254-16-4 ((±)-propylene glycol); 4254-14-2 ((-)-propylene glycol); 4254-15-3 ((+)-propylene glycol).
ATC Vet — QA16QA01.
UNII — 6DC9Q167V3.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. & (Propylene Glycol). A clear, colourless, viscous, hygroscopic liquid. Miscible with water and with alcohol. Store in airtight containers.

USP 36: (Propylene Glycol). A clear, colourless, practically odourless, viscous liquid. It absorbs moisture when exposed to moist air. Miscible with water, with acetone, and with chloroform; soluble in ether; will dissolve in many essential oils but is immiscible with fixed oils. Store in airtight containers.

Uses and Administration

Propylene glycol is widely used in pharmaceutical manufacturing as a solvent and vehicle, especially for drugs unstable or insoluble in water. It may also be used as a stabiliser in vitamin preparations, as a plasticiser, and as a preservative. Propylene glycol is used extensively in foods and cosmetics.

Propylene glycol has humectant properties and is used similarly to glycerol in topical moisturising preparations.

Propylene glycol is used in veterinary medicine as a glucose precursor.

Adverse Effects, Treatment, and Precautions

Systemic toxicity of propylene glycol is considered to be low after oral doses unless large quantities have been ingested, or when preparations containing propylene glycol are given to neonates or to patients in renal failure. Systemic toxicity is manifested most commonly by CNS depression, especially in neonates and children. Other reported adverse effects include hepatic or renal impairment, intravascular haemolysis, seizures, hypoglycaemia, coma, arrhythmias, and cardiorespiratory arrest. Hyperosmolality has occurred, particularly in small infants and in patients with renal impairment; lactic acidosis may also be a greater problem in the latter group. Management of toxicity is symptomatic, with appropriate supportive care (see p. 1537.1). In severely poisoned patients who do not respond to supportive management, treatment with alcohol or fomepizole, to inhibit propylene glycol metabolism, may be considered; haemodialysis may also be of use.

After topical use, propylene glycol may produce some local irritation, particularly if applied under occlusive dressings or to mucous membranes; toxicity may occur on application to burns. Hypersensitivity reactions have also been reported. Local sensitivity has been reported after use of ear drops with a propylene glycol vehicle. Injections of preparations containing high concentrations of propylene glycol may produce pain or irritation.

Toxicity. Use of propylene glycol as a solubiliser in parenteral preparations has been suggested as the cause of toxicity in some patients. Hyperosmolality, metabolic acidosis, and nephrotoxicity seen in patients after prolonged or excessive doses of *lorazepam* injection have been attributed to propylene glycol in the formulation;[1-4] the injection also contains macrogol (polyethylene glycol) 400 and this has also been suggested as the cause.[5,6] Most of the reported patients recovered with supportive therapy and haemodialysis,[1,3,5,6] but fatalities also occurred.[2,4] An observational study[7] found that metabolic disturbances were common in patients receiving intravenous *benzodiazepines* formulated with propylene glycol but not in those receiving alternative benzodiazepines; Lactic acidosis has also been reported[8] in a patient who received a high-dose continuous intravenous infusion of a *pentobarbital* formulation containing 40% v/v of propylene glycol; symptoms resolved on stopping therapy.

Propylene glycol and macrogol 400 in enteral solutions of lorazepam and diazepam have also been suggested[9] as the cause of diarrhoea in an infant given large oral doses, possibly due to their combined osmotic effect.

1. Seay RE, *et al.* Possible toxicity from propylene glycol in lorazepam infusion. *Ann Pharmacother* 1997; **31:** 647–8. Woycik CL, Walker PC. Correction and comment: possible toxicity from propylene glycol in injectable drug preparations. *ibid.*; 1413.
2. Neale BW, *et al.* Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. *Ann Pharmacother* 2005; **39:** 1732–6.
3. Zar T, *et al.* Acute kidney injury, hyperosmolality and metabolic acidosis associated with lorazepam. *Nat Clin Pract Nephrol* 2007; **3:** 515–20.
4. Zosel A, *et al.* Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy* 2010; **30:** 219.
5. Laine GA, *et al.* Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. *Ann Pharmacother* 1995; **29:** 1110–14.
6. Tayar J *et al.* Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med* 2002; **346:** 1253–4.
7. Wilson KC, *et al.* Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. *Chest* 2005; **128:** 1674–81.
8. Miller MA, *et al.* Propylene glycol-induced lactic acidosis in a patient receiving continuous infusion pentobarbital. *Ann Pharmacother* 2008; **42:** 1502–6.
9. Marshall JD, *et al.* Diarrhea associated with enteral benzodiazepine solutions. *J Pediatr* 1995; **126:** 657–9.

Interactions

Anticoagulants. Propylene glycol has been reported to decrease the effect of *heparin.*[1]

1. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; **110:** 171–3.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal tract. There is evidence of topical absorption when applied to damaged skin.

It is extensively metabolised in the liver mainly by oxidation to lactic and pyruvic acid and is also excreted in the urine unchanged.

References.
1. Yu DK, *et al.* Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. *J Pharm Sci* 1985; **74:** 876–9.
2. Speth PAJ, *et al.* Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. *Ther Drug Monit* 1987; **9:** 255–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Advanced Eye Relief; Systane Balance.

Multi-ingredient Preparations. ***Arg.***: Punto G†; Systane; ***Austral.***: Dermatech Liquid†; Systane; ***Braz.***: Mirugell; ***Canad.***: Bausch & Lomb Moisture Eyes; Episec; Lubricating Nasal Gel; Lubricating Nasal Mist; Manorapid Synergy; Rhinaris; Salinex Nasal Lubricant; Secaris; Systane; ***Chile***: Systane; ***China***: Systane (思然); ***Fr.***: Intrasite; Propy-Lacticare†; Systane; ***Hong Kong***: Moisture Eyes; Systane; ***India***: Dew Derm; Diafoot; Emolene; Foot Care; Fungidrops; Gowet; Moisturex-AF; Moisturex; ***Indon.***: Sodermix; Systane; ***Israel***: Systan UL; Systane; ***Ital.***: Cue Soluzione Otologica; Dopo Pik; Sekudrill†; Systane; ***Malaysia***: Systane; ***Mex.***: Moisture Eyes; Systane; ***Philipp.***: Moisture Eyes; Systane; ***S.Afr.***: Aserbine; ***Singapore***: Effaclar K; Octenisept Wound Gel; Systane; ***Spain***: Acerbiol†; ***Thai.***: Systane; ***Turk.***: Systane; ***UK***: Episil; ***USA***: Astroglide; Biotene with Calcium; Episil; Sonafine; Surgel; Systane; Zonite; ***Venez.***: Systane.

Pharmacopoeial Preparations
BP 2014: Propylene Glycol Solution.

Propylene Glycol Caprylates

Propylene Glycol Dicaprylocaprate

Propilenglikolio dikaprilokapratas; Propyleeniglykolidikaprylokapraatti; Propylene Glycol Octanoatedecanoate; Propylèneglycol, dicaprylocaprate de; Propylenglycoi Octanoas et Decanoas; Propylenglycoldicaprylocaprat; Propylenglycoli Dicaprylocapras; Propylenglycoli Dioctanodidecanoas; Propylenglykoldikaprylokaprat; Propylenglykol-dioktanodidekanoát.
CAS — 68583-51-7 (propylene glycol dicaprylocaprate); 53824-77-4 (propylene glycol dicaprate); 7384-98-7 (propylene glycol dicaprylate).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Dicaprylocaprate). Propylene glycol diesters of saturated fatty acids of vegetable origin, mainly octanoic acid and decanoic acid ($C_{10}H_{20}O_2$). An almost colourless to light yellow, oily liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in fatty oils and in petroleum spirit. Protect from light.

USNF 31: (Propylene Glycol Dicaprylate/Dicaprate). A mixture of the propylene glycol mono-and diesters of octanoic acid and decanoic acid, the diesters fraction being predominant. Clear, colourless or slightly yellow oily liquid at 20 degrees. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in fatty oils and in petroleum spirit. Protect from moisture.

Propylene Glycol Monocaprylate

Propylene glycol mono-octanoate.
CAS — 31565-12-5.

Pharmacopoeias. In *USNF.*

USNF 31: (Propylene Glycol Monocaprylate). A mixture of the propylene glycol monoesters and diesters of fatty acids composed mainly of octanoic acid. Propylene Glycol Monocaprylate Type I contains 55 to 80% of the monoesters and 20 to 45% of the diesters. Propylene Glycol Monocaprylate Type II contains not less than 90% of the monoesters and not more than 10% of the diesters. A clear, colourless, or slightly yellow, oily liquid at 20 degrees. Practically insoluble in water; very soluble in alcohol, in chloroform, and in dichloromethane. Protect from moisture.

Profile

Propylene glycol caprylates are propylene glycol ester nonionic surfactants (p. 2164.2). They are used as oily vehicles and emulsifying and solubilising agents in oral and topical preparations. Both the monocaprylate and mixtures of the dicaprylate and dicaprate (dicaprylocaprate) are used. Propylene glycol dicaprate (propylene glycol didecanoate) has been used similarly.

Propylene Glycol Diacetate

1,2-Diacetoxypropane; Propilenglicol, diacetato de; 1,2-Propylene Diacetate; Диацетат Пропиленгликоля.
1,2-Propanediol diacetate.
$C_7H_{12}O_4$=160.2
CAS — 623-84-7 (1,2-isomer); 628-66-0 (1,3-isomer).
UNII — 5Z492UNF9O.

Profile

Propylene glycol diacetate is a propylene glycol ester nonionic surfactant (p. 2164.2). It is used as an emulsifying and/or solubilising agent, and a solvent. It is included in some external preparations for ear infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***NZ***: VoSoL; ***USA***: Acetasol HC; Acetasol.

Propylene Glycol Laurates

E477 (propylene glycol esters of fatty acids); Propilenglicol, laurato de; Пропиленгликоля Лаураты.
UNII — 40KT317HGP.

Propylene Glycol Dilaurate

E477 (propylene glycol esters of fatty acids); Propilenglicol, dilaurato de; Propilenglikolio dilauratas; Propyleeniglykolidilauraatti; Propylene Dilaurate; Propylèneglycol, dilaurate de; Propylenglycoldilaurat; Propylenglycoli dilauras; Propylenglykoldilaurat; Propylenglykol-dilaurát; Пропиленгликоля Дилаурат.
CAS — 22788-19-8.
UNII — RMY7XGC3LV.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Dilaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains a minimum of 70% of di-esters and a maximum of 30% of mono-esters. The content of free propylene glycol is not more than 2%. A colourless or slightly yellow, clear oily liquid at 20 degrees. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Protect from moisture.

USNF 31: (Propylene Glycol Dilaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains not less than 70.0% of di-esters and not more than 30.0% of mono-esters. Protect from moisture.

Propylene Glycol Monolaurate

E477 (propylene glycol esters of fatty acids); Propilenglicol, monolaurate de; Propilenglikolio monolauratas; Propyleeniglykolimonolauraatti; Propylèneglycol, monolaurate de; Propylenglycoli monolauras; Propylenglycolmonolaurat; Propylenglykol monolaurát; Propylenglykolmonolaurat; Пропиленгликоля Монолаурат.
CAS — 27194-74-7.
UNII — 668Z5835Z3.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Monolaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains 45 to 70% of mono-esters and 30 to 55% of di-esters (type I) or a minimum of 90% of mono-esters and a maximum of 10% of di-esters (type II). The content of free propylene glycol is not more than 5% (type I) or not more than 1% (type II). A colourless or slightly yellow, clear oily liquid at 20 degrees. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Protect from moisture.

USNF 31: (Propylene Glycol Monolaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains 45 to 70% of mono-esters and 30 to 55% of di-esters (type I) or a minimum of 90% of mono-esters and a maximum of 10% of di-esters (type II). The content of free propylene glycol is not more than 5.0% (type I) or not more than 1.0% (type II). Protect from moisture.

Profile

Propylene glycol mono- and dilaurate are propylene glycol ester nonionic surfactants (p. 2164.2). They are used as emulsifying and solubilising agents, including in food.

Propylene Glycol Monopalmitostearate

E477 (propylene glycol esters of fatty acids); Propilenglicol, monopalmitoestearato de; Propilenglikolio monopalmitostearatas; Propilénglikol-monopalmitil-sztearát; Propyleeniglykolimonopalmitostearaatti; Propyleeniglykolimonostearaatti; Propylene Glycol Monostearate; Propylene Glycol Stearate; Propylèneglycol, monopalmitostéarate de; Propylèneglycol (Stéarate de); Propylenglycoli monopalmitostearas; Propylenglycoli Monostearas; Propylenglycolmonopalmitostearat; Propylenglykolmonopalmitostearat; Propylenglykol-monopalmitostearát; Propylenglykolmonostearat; Prostearin; Пропиленгликоля Монопальмитостеарат.
CAS — 1323-39-3 (propylene glycol monostearate); 29013-28-3 (propylene glycol monopalmitate).
UNII — F76354LMGR (propylene glycol monopalmitostearate); MZM1I680W0 (propylene glycol monostearate).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propylene Glycol Monopalmitostearate). A mixture of the propylene glycol mono- and di-esters of stearic and palmitic acids. It contains a minimum of 50% of mono-esters produced from the condensation of propylene glycol and stearic acid 50. A white or almost white, waxy solid. M.p. 33 degrees to 40 degrees. Practically insoluble in water; soluble in hot alcohol and in acetone. Protect from light.

USNF 31: (Propylene Glycol Monostearate). A mixture of the propylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 90% of mono-esters of saturated fatty acids, chiefly propylene glycol monostearate and propylene glycol monopalmitate. A white, wax-like solid, beads, or flakes, with a slight agreeable fatty odour. Congealing temperature not less than 45 degrees. Insoluble in water but it may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble in organic solvents such as alcohol, acetone, ether, benzene, and fixed or mineral oils.

Profile

Propylene glycol monopalmitostearate is a propylene glycol ester nonionic surfactant (p. 2164.2). It is used as a stabiliser or emulsifier similarly to glyceryl monostearate (p. 2187.2). Self-emulsifying forms are also used.

Pullulan

E1204; Pullulane; Pululano; Пуллулан.
$(C_{36}H_{60}O_{30})_n$
CAS — 9057-02-7.
UNII — 8ZQ0AYU1TT.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 31: (Pullulan). A neutral, simple polysaccharide produced by the growth of *Aureobasidium pullulans.* It has a chain structure of repeated α-1,6-bonds of maltotriose composed of three glucoses in α-1,4-bonds. It may contain some maltotetraosyl units. It contains not less than 90% of glucan, calculated with reference to the dried substance. A white powder. Freely soluble in water; practically insoluble in dehydrated alcohol.

Profile

Pullulan is a naturally-occurring polysaccharide with adhesive, film-forming, and fibre-forming properties. It is used for tablet coating, as an excipient to aid tabletting processes, in the production of edible films, and as an alternative to gelatin in capsule production. It is also used in the food and cosmetics industries.

References.
1. Leathers TD. Biotechnological production and applications of pullulan. *Appl Microbiol Biotechnol* 2003; **62:** 468–73.

Pyrrolidone

2-Pirolidon; Pyrrolidon; 2-Pyrrolidone; Пирролидон.
2-Pyrrolidinone.
C_4H_7NO=85.11
CAS — 616-45-5.
UNII — KKL5D39EOL.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pyrrolidone). A clear, colourless or slightly greyish liquid, or white or almost white crystals, or colourless crystal needles. Miscible with water, with alcohol, and with most common organic solvents. Protect from light.

N-Methylpyrrolidone

Methylpyrrolidon; *N*-Methyl-2-pyrrolidone; *N*-Méthylpyrrolidone; Methylpyrrolidonum; *N*-Methylpyrrolidonum; *N*-Metilpirolidonas; *N*-Metylpyrrolidon; *N*-Metyylipyrrolidoni; N-Метилпирролидон.

1-Methylpyrrolidin-2-one.
C_5H_9NO=99.13
CAS — 872-50-4.
UNII — JR9CE63FPM.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (*N*-Methylpyrrolidone). A clear, colourless liquid. Miscible with water and with alcohol. Protect from light.

USP 36: (Methylpyrrolidone). A clear, colourless liquid. Miscible with water and with most organic solvents including alcohol, ketones, and aromatic and chlorinated hydrocarbons. Protect from light.

Profile

Pyrrolidones such as pyrrolidone and *N*-methylpyrrolidone are used as solvents in veterinary formulations and as skin penetration enhancers.

Quillaia

Corteza de Panamá; Corteza de quillay; Corteza palo de jabón; E999 (quillaia extract); Panama Wood; Quilaya; Quillaia Bark; Quillaiae Cortex; Quillay; Quillaya, écorce de; Seifenrinde; Soap Bark; Кора Мыльного Дерева.
CAS — 631-01-6 (quillaic acid).
*ATC Herb — HR05WA5050 (*Quillaja saponaria*: bark).*
*UNII — 8N0K3807ZW (*Quillaja saponaria *bark).*

Pharmacopoeias. In *Br.*, *Fr.*, and *Swiss. Eur.* (see p. vii) includes Quillaia Bark.

Ph. Eur. 8: (Quillaia Bark; Quillajae Cortex). The whole or fragmented, dried bark, with the cork and underlying parenchyma removed, of *Quillaja saponaria.* It contains not less than 6.5% of triterpene glycosides, expressed as quillaia saponin III, ($C_{104}H_{168}O_{55}$ = 2298), calculated with reference to the dried drug.

BP 2014: (Quillaia). The dried inner part of the bark of *Quillaja saponaria* and other species of *Quillaja* containing not less than 22% of alcohol (45%)-soluble extractive. It is odourless or almost odourless, but the dust or powder is strongly sternutatory.

Uses

Quillaia contains 2 amorphous saponin glycosides, quillaic acid and quillaiasapotoxin. It is used as an emulsifying agent and frothing agent, including in foodstuffs; it is often used with tragacanth mucilage or another thickening agent. Quillaia is also used for its surfactant properties in preparations for skin and respiratory-tract disorders.

Adverse Effects

Quillaia taken orally has been reported to produce gastrointestinal irritation. It has been suggested that the ingestion of large amounts may produce liver damage, respiratory failure, convulsions, and coma.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile:*** Fitotos; ***Fin.:*** Kvilla; ***Rus.:*** Solutan (Солутан)†; ***Spain:*** Novogumil; ***Swed.:*** Quilla simplex.

Pharmacopoeial Preparations
BP 2014: Quillaia Liquid Extract; Quillaia Tincture.

Quinoline Yellow

Amarillo de quinoleína; Canary Yellow; Chinolinegeel; Chinolingelb; Chinolino geltonasis; CI Acid Yellow 3; CI Food Yellow 13; Colour Index No. 47005; E104; Jaune de Quinoléine; Kinolin Sarisi; Kinolingult; Kinolinsárga; Żółcień chinolinowa; Жёлтый Хинолиновый.
It consists of sodium salts of a mixture of disulfonates (mainly), monosulfonates, and trisulfonates of 2-(2-quinolyl)-1,3-indandione or a mixture containing about two-thirds of 2-(2-quinolyl)-1,3-indandione and one-third of 2-[2-(6-methyl-quinolyl)]1,3-indandione.
CAS — 8004-92-0 (unmethylated disulfonic acids).
UNII — 35SW5USQ3G.

NOTE. D & C yellow No. 10 has been used as a synonym for quinoline yellow, but describes a mixture consisting mainly of a monosulfonate.

Uses

Quinoline yellow is a synthetic dye used as a colouring agent in medicines, cosmetics, and foodstuffs.

Adverse Effects

Hypersensitivity. Hypersensitivity reactions, including a case of severe urticaria,[1] have been attributed to quinoline yellow. Urticarial reactions have also been reported with D & C yellow No.10, a closely related compound.[2]

1. Bell T. Colourants and drug reactions. *Lancet* 1991; **338:** 55–6.
2. Gidseg G. Methyldopa-induced skin rash. *South Med J* 1986; **79:** 389.

Raspberry

Ahududu; Avietė; Bringebær; Framboesa; Framboise; Framboos; Frambuesa; Fructus Rubi Idaei; Gerd; Hallon; Himbeere; Hindbær; Lampone; Malina; Málna; Vaarikas; Vadelma; Zmeur; Малина.
CAS — 8027-46-1.
UNII — 4N14V5R27W.

Profile

Raspberry, the fresh ripe fruit of *Rubus idaeus* (Rosaceae), is used as a colouring and flavouring agent in medicines and foodstuffs.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.:*** IgeE†; Pruriced; ***Indon.:*** Proview; ***USA:*** Immunicare.

Red Cherry

Amareno; Cerasus; Cerise Rouge; Guinda; Hapankirsikka; Kirsebær; Meggy; Paprastoji Vyšnia; Rojo cereza; Sauerkirsche; Sour Cherry; Sur-Kirsebær; Surkörsbär; Tart Cherry; Višin; Višne; Višeň; Wiśnia Pospolita; Zure Kers; Вина; Вишня Кислая.
*UNII — 9PLM3OM8VL (*Prunus avium*); 3GH35I9L1L (*Prunus cerasus*); 1L29G6428X (*Prunus cerasus *fruit); 4XTQ10247Y (*Prunus cerasus *fruit juice).*

Pharmacopoeias. *USNF* includes cherry juice.

Fr. includes, under the title Griottier, cherry stalks from either the red (sour) cherry, *Prunus cerasus*, or from the sweet cherry, *P. avium.*

USNF 31: (Cherry Juice). The liquid expressed from the fresh ripe fruit of *Prunus cerasus* (Rosaceae). It contains not less than 1.0% of malic acid. pH 3.0 to 4.0. Store in airtight containers. Protect from light.

Profile

Red cherry is used as a colouring and flavouring agent. Cherry stalks (cherry tails) from either red cherry or sweet cherry have been used in herbal medicines. Red cherry juice is under investigation for its antoxidant and anti-inflammatory effects (see below).

Inflammation. Red cherry juice contains anthocyanins and flavonoids and it has been suggested that these may provide antoxidant and anti-inflammatory effects. Small placebo-controlled crossover studies[1,2] have indicated that prior consumption of red cherry juice reduced some symptoms of muscle damage (pain and strength loss) induced by exercise, while another study[3] found that red cherry juice reduced markers of damage after experimentally-induced oxidative stress.

1. Connolly DAJ, *et al.* Efficacy of a tart cherry juice blend in preventing the symptoms of muscle damage. *Br J Sports Med* 2006; **40:** 679–83.
2. Kuehl KS, *et al.* Efficacy of tart cherry juice in reducing muscle pain during running: a randomized controlled trial. *J Int Soc Sports Nutr* 2010; **7:** 17.
3. Traustadóttir T, *et al.* Tart cherry juice decreases oxidative stress in healthy older men and women. *J Nutr* 2009; **139:** 1896–1900.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.:*** Vitamina C-Complex; ***Fr.:*** Evacrine; Hydracur; ***Switz.:*** Resiston.

Pharmacopoeial Preparations
USNF 31: Cherry Syrup.

Red 2G

Acid Red 1; Azogeranina; Azogeranine; CI Food Red 10; Colour Index No. 18050; E128; Ext. D & C Red No. 11; Geranine 2G; Rojo 2G; Rouge 2G; Красный 2G.
Disodium 5-acetamido-4-hydroxy-3-phenylazonaphthalene-2,7-disulphonate.
$C_{18}H_{13}N_3Na_2O_8S_2$=509.4
CAS — 3734-67-6.

Profile

Red 2G is a synthetic azo dye that may be used as a colouring agent in cosmetics. Its use as a food colour was suspended in the EU in 2007 on the basis that its main metabolite, aniline, has both genotoxic and carcinogenic effects in *rodents.*

Red-Poppy Petal

Rhoead. Pet.; Aguonų birulių žiedai; Coquelicot; Coquelicot, pétales de; Corn Poppy Petal; Klatschrose; Kornvallmo, kronblad; Květ máku vlčího; Papaveris Rhoeados Flos; Pétalos de Amapola; Rhoeados Petalum; Unikonkukan terälehdet; Мака Самосейки Лепестки.
*ATC Herb — HN05CM5018 (*Papaver rhoeas*: flower); HR05DB5009 (*Papaver rhoeas*: flower); HN02BG5011 (*Papaver rhoeas*: flower).*
*UNII — 9UBF401EYA (*Papaver rhoeas*); Y1MLS7E68X (*Papaver rhoeas *flower); BYL35G8DGJ (*Papaver rhoeas *petal); 7I7P659L0Q (*Papaver rhoeas *seed).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Red Poppy Petals). The dried, whole or fragmented petals of *Papaver rhoeas.*

Profile

Red-poppy petal has been used as a colouring agent. It is also included in several herbal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.:*** Formula T13 Tea†; ***Fr.:*** Calmotisan†; Dystolise; Nocvalene†; ***Ital.:*** Altuss; Gastrotuss; ***Switz.:*** Baume Zeller; Pommade au Baume; Tisane pectorale et antitussive.

Red-Rose Petal

Fleur de Rose; Flos Rosae; Pétalos de rosa; Red Rose Petals; Ros. Pet.; Rosae Gallicae Petala; Rosae Petalum; Rose Rouge; Rosenblüte; Лепестки Розы.
*ATC Herb — HA01WX5002 (*Rosa gallica*: flower).*
*UNII — X8W61WUV70 (*Rosa gallica *flower).*

Pharmacopoeias. In *Fr.*

Profile

Red-rose petal, the petals of the red or Provins rose, *Rosa gallica* (Rosaceae), has been used as a colouring agent and for its mild astringent properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.:*** Expectosan Hierbas y Miel.

Homoeopathic Preparations. ***Fr.:*** Poconeol no 18.

Saccharin

Benzoic Acid Sulphimide; Benzoic Sulfimide; Benzosulphimide; E954; Gluside; Sacarina; Saccarina; Saccharine; Saccharinum; Sacharin; Sacharinas; Sacharine; Sacharyna; Sackarin; Saharin; Sakkariini; Sakkarin; o-Sulfobenzimide; Szacharin; Zaharină; Захарин; Сахарин.
1,2-Benzisothiazolin-3-one 1,1-dioxide.
$C_7H_5NO_3S$=183.2
CAS — 81-07-2.
UNII — FST467XS7D.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Saccharin). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in cold water; sparingly soluble in boiling water and in alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. A saturated solution, prepared without heating, is acid to litmus.

USNF 31: (Saccharin). White crystals or white, crystalline powder. Is odourless or has a faint, aromatic odour. In dilute solutions, it is intensely sweet. Soluble 1 in 290 of water, 1 in 25 of boiling water, and 1 in 31 of alcohol; slightly soluble in chloroform and in ether; is readily dissolved by dilute solutions of ammonia, by solutions of alkali hydroxides, and by solutions of alkali carbonates with the evolution of carbon dioxide. Its solutions are acid to litmus.

Saccharin Calcium

Benzosulfimida cálcica; Calcium Benzosulphimide; Calcium Saccharin; E954; Sacarina cálcica; Saccharine calcique; Saccharinum calcicum; Кальция Сахарат.

$C_{14}H_8CaN_2O_6S_2,3½H_2O$=467.5

CAS — 6485-34-3 (anhydrous saccharin calcium); 6381-91-5 (hydrated saccharin calcium).

UNII — 09AW1ODN7B (anhydrous saccharin calcium); 5101OP7P2I (hydrated saccharin calcium).

Pharmacopoeias. In *US*.

USP 36: (Saccharin Calcium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. Soluble 1 in 2.6 of water and 1 in 4.7 of alcohol.

Saccharin Potassium

E954; Potassium Benzosulphimide; Potassium Saccharate; Potassium Saccharin; Калия Сахарат.

$C_7H_5NO_3SK$=222.3

CAS — 10332-51-1.

UNII — K2BEG3J28N.

NOTE. Although the name Potassium Saccharate has been applied to saccharin potassium do not confuse with Potassium Glucarate, the potassium salt of saccharic acid, which may also be named potassium saccharate.

Saccharin Sodium

Benzosulfimida sódica; E954; Sacarina sódica; Saccharin-Natrium; Saccharin Sod.; Saccharine sodique; Saccharinnatrium; Saccharinum Natricum; Saccharoidum Natricum; Sacharin sodná sůl; Sacharino natrio druska; Sacharyna sodowa; Sackarinnatrium; Sakkariininatrium; Sodium Benzosulphimide; Sodium Saccharin; Soluble Gluside; Soluble Saccharin; Szacharin-nátrium; Натрия Сахарат.

$C_7H_4NNaO_3S$=205.2

CAS — 128-44-9 (anhydrous saccharin sodium); 6155-57-3 (saccharin sodium dihydrate).

UNII — SB8ZUX40TY (saccharin sodium); I4807BK602 (anhydrous saccharin sodium).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*. Some pharmacopoeias specify the dihydrate but it may contain a variable quantity of water as a result of efflorescence.

Ph. Eur. 8: (Saccharin Sodium). A white or almost white, crystalline powder or colourless crystals. It may contain a variable quantity of water. Efflorescent in dry air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

USP 36: (Saccharin Sodium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. When in powdered form, it usually contains about one-third the theoretical amount of water of hydration as a result of efflorescence. Soluble 1 in 1.5 of water and 1 in 50 of alcohol.

Uses and Administration

Saccharin and its salts are intense sweeteners, dilute solutions having about 300 times the sweetening power of sucrose. They are used in pharmaceuticals and in foods and beverages and are heat stable. They have no food value. The salts are more often used than saccharin itself as they are considered to be more palatable.

Adverse Effects

There have been rare reports of hypersensitivity and photosensitivity reactions with saccharin.

Saccharin-associated bladder tumours in *rats* given high doses have been the cause of much concern and investigation. However, it is now generally accepted that these findings are not relevant to the use of saccharin as a sweetener in man.

Effects on the liver. Elevated liver enzyme values in an elderly woman followed use of two different medications sweetened with saccharin sodium.[1] Findings resolved on stopping all preparations containing saccharin, and recurred on rechallenge with a small amount of saccharin sodium.

1. Negro F, *et al.* Hepatotoxicity of saccharin. *N Engl J Med* 1994; **331:** 134–5.

Pharmacokinetics

Saccharin is readily absorbed from the gastrointestinal tract. It is almost all excreted unchanged in the urine within 24 to 48 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Dul-Suc; Endulza; Sukar-Sin; ***NZ***: Sactabs; ***Turk.***: Hermesetas; ***Venez.***: Hermesetas.

Multi-ingredient Preparations. ***Arg.***: Chuker; Chuker; Dulsiluet; Kaldil Diet; Rondo; Semble; Sucaryl; Suimel; ***Austral.***: Sucaryl; ***Braz.***: Finn Cristal; ***Chile***: Endulzante; Sukar-Sin; ***Fr.***: Sucaryl; ***Israel***: Sucrin; ***Ital.***: Diet Sucaryl†; ***NZ***: Sucaryl; ***Rus.***: Zuckli (Цюкли)†; ***Thai.***: Corinap; ***Turk.***: Dolce†; Tadalin.

Pharmacopoeial Preparations

USP 36: Saccharin Sodium Oral Solution; Saccharin Sodium Tablets.

Saffron

Açafrão; Azafrán; CI Natural Yellow 6; Colour Index No. 75100; Croci Stigma; Crocus; Estigmas de Azafrán; French Saffron; Keshar; Saffran; Safraan; Safran; Sahrami; Spanish Saffron; Xī Hóng Hhuā; Шафран.

*UNII — E849G4X5YJ (*Crocus sativus *stigma); 00IF91KFKQ (*Crocus sativus *flower).*

NOTE. Do not confuse with the meadow saffron (*Colchicum autumnale*), the source of colchicum (p. 607.1) and colchicine (p. 604.1), or Indian saffron, which is a name sometimes used for Turmeric (p. 2218.1).

Pharmacopoeias. In *Chin.* and *Jpn*.

Eur. (see p. vii) includes Saffron for Homoeopathic Preparations.

Ph. Eur. 8: (Saffron for Homoeopathic Preparations). The dried stigmas of *Crocus sativus* usually joined by the base to a short style. It has a characteristic, aromatic odour. Protect from light.

Profile

Saffron consists of the dried stigmas and tops of the styles of *Crocus sativus* (Iridaceae), containing crocines, crocetins, and picrocrocine. Saffron is used to colour medicines, foods, and cosmetics. It is also used as a flavouring agent. Saffron has been used in herbal and traditional medicines and has been included in preparations for teething pain. It has also been investigated in disorders such as depression and cancer. There have been reports of poisoning with saffron, but in some cases these may have been due to meadow saffron, *Colchicum autumnale*.

Homoeopathy

Saffron has been used in homoeopathic medicines under the following names: Croci stigma; Crocus sativus; Crocus; Croc. s.

References.

1. Schmidt M, *et al.* Saffron in phytotherapy: pharmacology and clinical uses. *Wien Med Wochenschr* 2007; **157:** 315–19.
2. Bathaie SZ, Mousavi SZ. New applications and mechanisms of action of saffron and its important ingredients. *Crit Rev Food Sci Nutr* 2010; **50:** 761–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pansoral Primeros Dientes; ***Cz.***: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; ***Fr.***: Safralite; ***Ger.***: Infi-tract V; ***Hung.***: Bano Svedkeseru; ***India***: Abana; Geriforte; Geriforte; ***Rus.***: Pansoral Teething (Пансорал Первые Зубы); Tentex (Тентекс); ***Singapore***: Tentex Royal; ***Spain***: Dentomicin†; ***Switz.***: Eau pour les yeux†; ***Ukr.***: Imunin (Иммунин)†; Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Homoeopathic Preparations. ***Austria***: Orgafem; ***Fr.***: Abbe Chaupitre no 6; Dolirelax†; Sclerocalcine; ***Ger.***: Aderplus spezial Dr Hagedorn†; Cefakliman S; Cimicifuga N Oligoplex; Flenin; Secale-Gastreu.

Shea Butter

Manteca de Karité; Карите; Масло Ши.

UNII — K49155WL9Y (shea butter); O88E196QRF (shea butter extract).

Profile

Shea butter is a natural fat obtained from the kernel of the fruit of *Vitellaria paradoxa* (*Butyrospermum parkii*) (Sapotaceae) indigenous to West Africa. It is used as an ointment and cream basis. Shea butter is widely used in cosmetics. It is also used in cooking oil, and as a substitute for theobroma oil in chocolate manufacturing.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Sigestrial; ***Fr.***: Ictyane HD; Node K; ***Philipp.***: Enfacare; ***Singapore***: Rosken Skin Repair High Potency.

Shellac

E904; Goma laca; Gommalacca; Gomme Laque; Gommes laques; Lacca; Lacca in Tabulis; Schellack; Schellak; Šelak; Šelakas; Sellak; Shellack; Shellak; Shellakka; Skjellakk; Szelak; Шеллак.

CAS — 9000-59-3.

UNII — 46N107B71O.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Jpn includes Purified Shellac and White Shellac (Bleached).

Ph. Eur. 8: (Shellac). It is obtained by purification of the resinous secretion of the female insect *Kerria lacca* (Kerr) Lindinger (*Laccifer lacca* Kerr). There are 4 types of shellac depending on the nature of the treatment of crude secretion (seedlac): Wax-containing Shellac; Bleached Shellac; Dewaxed Shellac; and Bleached, Dewaxed Shellac.

Brownish-orange or yellow, shining, translucent, hard or brittle more or less thin flakes (Wax-containing Shellac; Dewaxed Shellac), or a creamy-white or brownish-yellow powder (Bleached Shellac; Bleached, Dewaxed Shellac).

Practically insoluble in water. With dehydrated alcohol it gives a more or less opalescent solution (Wax-containing Shellac; Bleached Shellac) or a clear solution (Dewaxed Shellac; Bleached, Dewaxed Shellac). When warmed, it is sparingly soluble or soluble in alkaline solutions. Protect from light. Store Bleached Shellac and Bleached, Dewaxed Shellac at a temperature not exceeding 15 degrees.

USNF 31: (Shellac). It is obtained by purification of lac, the resinous secretion of the insect *Laccifer lacca kerr* (Coccidae). There are 4 varieties: Orange Shellac, Dewaxed Orange Shellac, Regular Bleached (White) Shellac, and Refined Bleached Shellac. Orange Shellac occurs as thin, hard, brittle, transparent, pale lemon-yellow to brownish-orange flakes, having little or no odour. Bleached Shellac occurs as opaque, amorphous, cream to yellow granules or coarse powder, having little or no odour.

Insoluble in water; very slowly soluble in alcohol, 85 to 95% (w/w); soluble in ether, 13 to 15%, in petroleum spirit, 2 to 6%, in benzene, 10 to 20%, and in aqueous solutions of ethanolamines, alkalis, and borax; sparingly soluble in turpentine oil. Store preferably at a temperature not exceeding 8 degrees.

Profile

Shellac is used as an enteric coating for pills and tablets, but disintegration time has been reported to increase markedly on storage.

Preparations

Pharmacopoeial Preparations

USNF 31: Pharmaceutical Glaze.

Silicas

Sílice.

Purified Siliceous Earth

Diatomaceous Earth; Diatomeeënaarde; Diatomiit; Diatomita; Diatomitas; Diatomite; Diatomito; Farina fossile; Křemelina; Kieselgur; Kísilgúr; Piimaa; Purified Infusorial Earth; Purified Kieselguhr; Terra Silicea Purificada; Tierra de diatomeas; Ziemia okrzemkowa; Очищенный Кремнезём.

CAS — 7631-86-9.

UNII — 2RF6EJ0M85.

Pharmacopoeias. In *USNF*.

USNF 31: (Purified Siliceous Earth). A form of silicon dioxide consisting of frustules and fragments of diatoms purified by calcining. A very fine, white, light grey, or pale buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite. It is gritty and readily absorbs moisture, and retains about four times its weight of water before becoming fluid. Insoluble in water, in acids, and in dilute solutions of alkali hydroxides.

Silicon Dioxide

Colloidal Hydrated Silica; Ditlenek krzemu; E551; Kiseldioxid, kolloidal, hydratiserad; Koloidinis silicio dioksidas, hidratuotas; Oxid křemičitý koloidní hydratovaný; Piidioksidi, kolloidinen, hydratoitu; Precipitated Silica; Ränidioksiid; Silicija dioksīds; Silica Colloidalis Hydrica; Silica Gel; Silice

colloïdale hydratée; Silice precipitada; Silicio, dióxido de; Siliciumdioxid; Siliciumdioxide; Víztartalmú, kolloid szilíciumdioxid; Диоксид Кремния; Двуокись Кремния; Силициев диоксид.
SiO_2xH_2O=60.08 (anhydrous)
CAS — 63231-67-4; 7631-86-9.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*. *Eur.* and *USNF* also include dental-type silica.

Ph. Eur. 8: (Silica, Colloidal Hydrated). A light, fine, white or almost white, amorphous powder. Practically insoluble in water, and in mineral acids except hydrofluoric acid; dissolves in hot solutions of alkali hydroxides.

Ph. Eur. 8: (Silica, Dental Type). An amorphous silica (precipitated, gel, or obtained by flame hydrolysis). A white or almost white, light, fine amorphous powder. Practically insoluble in water and in mineral acids; dissolves in hydrofluoric acid and in hot solutions of alkali hydroxides.

USNF 31: (Silicon Dioxide). It is obtained by insolubilising the dissolved silica in sodium silicate solution. Where obtained by the addition of sodium silicate to a mineral acid, the product is termed silica gel; where obtained by the destabilisation of a solution of sodium silicate in such a manner as to yield very fine particles, the product is termed precipitated silica. A fine, white, odourless, hygroscopic, amorphous powder in which the diameter of the average particles ranges from 2 to 10 micrometres. Insoluble in water, in alcohol, and in other organic solvents; soluble in hot solutions of alkali hydroxides. pH of 5% slurry in water is between 4.0 and 8.0. Store in airtight containers. Protect from moisture.

USNF 31: (Dental-Type Silica). It is obtained from sodium silicate solution by destabilising with acid in such a way as to yield very fine particles. A fine, white, odourless, hygroscopic, amorphous powder in which the diameter of the average particles ranges from 0.5 to 40 micrometres. Insoluble in water, in alcohol, and in acid (except hydrofluoric acid); soluble in hot solutions of alkali hydroxides. pH of 5% slurry in water is between 4.0 and 8.5. Store in airtight containers.

Colloidal Silicon Dioxide

Acidum Silicicum Colloidale; Colloidal Anhydrous Silica; Colloidal Silica; Hochdisperses Silicumdioxid; Kiseldioxid, kolloidal, vattenfri; Koloidinis silicio dioksidas, bevandenis; Krzemu dwutlenek koloidalny; Oxid křemičitý koloidní bezvodý; Piidioksidi, kolloidinen, vedetön; Silica Colloidalis Anhydrica; Silice colloïdale anhydre; Sílice coloidal; Sílice coloidal anhidra; Silicii Dioxidum Colloidalle; Silicio coloidal, dióxido de; Vízmentes, kolloid, szilícium-dioxid; Коллоидный Диоксид Кремния.
SiO_2=60.08
CAS — 7631-86-9.
UNII — ETJ7Z6XBU4.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Eur. and *USNF* also include hydrophobic colloidal silica.

Ph. Eur. 8: (Silica, Colloidal Anhydrous). A light, fine, white or almost white, amorphous powder. It has a particle size of about 15 nm. Practically insoluble in water and in mineral acids except hydrofluoric acid; dissolves in hot solutions of alkali hydroxides. A 3.3% suspension in water has a pH of 3.5 to 5.5.

Ph. Eur. 8: (Silica, Hydrophobic Colloidal; Silica Hydrophobica Colloidalis). Colloidal silicon dioxide partly alkylated for hydrophobation. A light, fine, white or almost white, amorphous powder, not wettable by water. Practically insoluble in water and mineral acids except hydrofluoric acid. It dissolves slowly in hot solutions of alkali hydroxides.

USNF 31: (Colloidal Silicon Dioxide). A submicroscopic fumed silicon dioxide, prepared by the vapour-phase hydrolysis of a silicon compound. A light, white, non-gritty powder of extremely fine particle size (about 15 nm). Insoluble in water and in acid (except hydrofluoric acid); soluble in hot solutions of alkali hydroxides. pH of a 4% dispersion in water is between 3.5 and 5.5.

USNF 31: (Hydrophobic Colloidal Silica). Prepared by partial alkylation for hydrophobation. A light, fine, white or almost white, amorphous powder, not wettable by water. Practically insoluble in water and in mineral acids, except hydrofluoric acid; dissolves slowly in hot solutions of alkali hydroxides.

Uses

Silica is a general name used for the different forms of silicon dioxide. These different forms have various pharmaceutical uses. Purified siliceous earth is used as a filtering medium and adsorbent. Silicon dioxide is used as a suspending and thickening agent and, in the form of silica gel, as a desiccant. Colloidal silicon dioxide is used as a suspending agent and thickener, as a stabiliser in emulsions, and as an anticaking agent and desiccant. Silicon dioxide is also used as an anticaking agent in the food industry.

Silicas and silicic acids have also been used as a source of silicon (p. 2088.3) in dietary supplements.

Homoeopathy

Silicon dioxide has been used in homoeopathic medicines under the following names: Acidum silicicum; Silicea; Sil.

Adverse Effects

Prolonged inhalation of some forms of silica dust may be associated with the development of fibrosis of the lung (silicosis). The forms of silica described here and used as pharmaceutical excipients may cause irritation of the respiratory tract if inhaled but do not appear to be associated with silicosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Celloids S 79†; ***Ger.***: Entero-Teknosal; ***Mon.***: Dissolvurol; ***Rus.***: Polisorb (Полисорб); ***UK***: Aerosil; ***Ukr.***: Gastrogel (Гастрогель)†; Silics (Силикс).

Multi-ingredient Preparations. ***Arg.***: Kelo-Cote; ***Austral.***: Bio-Disc†; Duo Celloids SCF†; Duo Celloids SPS†; Duo Celloids SSS†; Hair Skin & Nails; Nails Hair and Skin; Silica Compound; ***Austria***: Kephalodoron; ***Canad.***: Osteogen; ***Chile***: Cartilago T-500†; Fittig Desodorante; Normaderm Concentrado Activo; Xeragel; ***Fr.***: Gelopectose; Kelo-Cote; Kinesamine; Naturophta Macula; Silibiol; Topaal; Topalkan†; ***Ger.***: anabol-loges†; Aplona; Equisil N†; Kelo-Cote; ***Gr.***: Dyspagone; Gastrovison; ***Hong Kong***: Disflatyl; ***India***: One-Up; Orbone Forte; Orbone; ***Indon.***: Kelo-Cote; ***Irl.***: Topaal; ***Israel***: Adinol†; Kelo-Cote; ***Ital.***: Lacalut; ***Malaysia***: Rowarolan; ***NZ***: Lamisil Odor Eze†; ***Philipp.***: BioSil†; ***S.Afr.***: Lotio Pruni Comp cum Cupro†; Zeel; ***Singapore***: Disflatyl†; Glow; Hair and Nails; ***Switz.***: Acne Creme; Kelo-cote†; ***USA***: NeutraSal.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; Hangover Relief; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; Teething Relief; ***Austria***: Nebenhohlen-Tropfen Nr 26†; Osteoplex; Otodolor; Spigelon; Steiroplex; Sulfur Med Complex; Tonsiotren; Zom; ***Canad.***: Calnor†; Combinaison†; Cruroheel S†; Diamite; Earache; Endoteel†; Ervopax†; Formula CA 205†; Homeo-Form P†; Homeo-S-Asp; Hylands Bioplasma; Ikoplex 21†; Ikoplex 5†; Melange†; Minerals+; Nuage Bioplasma†; Optalia†; Phyto-Cal; Rexorubia†; Sinus Ease; Sinuspax†; Spigelon†; Ubicoenzyme; Urticalcin; ***Chile***: Bioactiv D; Bioactiv P; Ikoplex No 15; Ikoplex No 17; Ikoplex No 19; Ikoplex No 1; Ikoplex No 20; Ikoplex No 21; Ikoplex No 23; Ikoplex No 24; Ikoplex No 3; Ikoplex No 4; Ikoplex No 5; Ikoplex No 7; Ikoplex No 8; Ikoplex No 9; Silik; ***Cz.***: Zeel Salbe†; ***Fr.***: Abbe Chaupitre no 23†; Abbe Chaupitre no 48†; Abbe Chaupitre no 79†; Boripharm No 22†; Dermo-Drainol†; Dolirelax†; Jenoverine†; Kreosotum Complexe No 62; Nervopax; Pulmo-Drainol†; Rexorubia; Sclerocalcine; Silicea Complexe No 11; Sinuspax; Veino-Drainol†; ***Ger.***: Araniforce rheuma†; Arthrorell N; Broncho-Injektopas; Derma-Plantin†; Dermarell; Dermi-cyl L Ho-Len-Complex; Disci Bamb; Discocyl Ho-Len-Complex; Drufusan N†; Drufusan; Girheulit HM†; Girheulit HOM; Hevertotox; Hevertotox; Hewelymphon N†; Humoval; Infi-Symphytum; Lymphaden Lymphdrusentabletten; Naranotox comp; Osteoplex; Pascoe-Agil HOM; Pflugerplex Lemna; Ranocalcin HM; Roth's Rotacard; Rufebran rheumo†; Sinuselect N; Sinusitis Hevert SL; Steirocall; Steiroplex†; Tamechol; Tonsillosyx; Tonsiotren H; ***Hung.***: Spigelon; Zeel; ***Neth.***: Chavita 1; Geovita; Jenoverine†; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Lymphomyosot; Nisyspray; Oteel H; Tonsiotreen; ***Rus.***: Pharyngomed (Фарингомед); Tonsilotren (Тонзилотрен); ***Switz.***: Exsepta; Regenaplex Nr. 21c; Regenaplex Nr. 21e; Regenaplex Nr. 24c; Regenaplex Nr. 88b; Sinusin; Sinuspax†; Spigelon; Urticalcin; ***Ukr.***: Tonsilotren (Тонзилотрен).

Silicones

Siliconas; Силиконы.
ATC — A03AX13.
ATC Vet — QA03AX13.

Description. Silicones are polymers with a structure consisting of alternate atoms of silicon and oxygen, with organic groups attached to the silicon atoms. As the degree of polymerisation increases, the products become more viscous and the various grades are distinguished by a number, approximately corresponding to the viscosity of the particular grade. Silicones may be fluids, greases, waxes, resins, or rubbers depending on the degree of polymerisation.

Cyclomethicone

Cyclic Polydimethylsiloxane; Cyclodimethicone; Cyclohexasiloxane (cyclomethicone 6); Cyclopentasiloxane (cyclomethicone 5); Cyclopolydimethylsiloxane; Cyclotetrasiloxane (cyclomethicone 4); Decamethylcyclopentasiloxane (cyclomethicone 5); Dimethlycyclopolysiloxane; Dodecamethylcyclohexasiloxane (cyclomethicone 6); Octamethylcyclotetrasiloxane (cyclomethicone 4); Polydimethylcyclosiloxane; Циклометикон.
$(C_2H_6OSi)_n$
CAS — 69430-24-6; (cyclomethicone); 556-67-2 (cyclomethicone 4); 541-02-6 (cyclomethicone 5); 540-97-6 (cyclomethicone 6).
UNII — NMQ347994Z (cyclomethicone); CZ227117JE (cyclomethicone 4); 0THT5PCI0R (cyclomethicone 5); XHK3U310BA (cyclomethicone 6).

Pharmacopoeias. In *USNF*.

USNF 31: (Cyclomethicone). A fully methylated cyclic siloxane containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, in which n is 4, 5, or 6, or a mixture of them. Store in airtight containers and avoid exposure to excessive heat.

Dimeticone *(BAN, rINN)*

Dimethicone (USAN); Dimethyl Silicone Fluid; Dimethylpolysiloxane; Dimethylsiloxane; Dimeticon; Dimeticona; Dimeticonas; Diméticone; Dimeticonum; Dimetikon; Dimetikonas; Dimetikoni; Dimetilpolisiloxano; Dimetykon; E900; Huile de Silicone; Methyl Polysiloxane; Metilpolisiloksan; Metilpolisiloxano; Permethylpolysiloxane; Polidimetilsiloxano; Silicone Oil; Siliconum Liquidum; Диметикон.
Poly(dimethylsiloxane).
$CH_3.[Si(CH_3)_2.O]_n.Si(CH_3)_3$
CAS — 9006-65-9.
ATC — A03AX13.
ATC Vet — QA03AX13.
UNII — 92RU3N3Y1O (dimethicone); 2Y53S6ATLU (dimethicone 350); TYU5GP6XGE (dimethicone 410).

Description. Dimeticones are fluid silicones in which the organic group is a methyl radical.

Simeticone (activated dimeticone), a mixture of liquid dimeticones with silicon dioxide, is described on p. 1886.2.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Dimeticone). The degree of polymerisation is such that the kinematic viscosities are nominally between 20 and 1300 mm^2/second; dimeticones with a nominal viscosity of 50 mm^2/second or lower are intended for external use only. Dimeticones are clear, colourless, liquids of various viscosities. Practically insoluble in water; very slightly soluble to practically insoluble in dehydrated alcohol; miscible with ethyl acetate, with methyl ethyl ketone, and with toluene.

USNF 31: (Dimethicone). A mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilised with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, wherein n has an average value such that the corresponding nominal viscosity is in a discrete range between 20 and 30 000 centistokes. It is a clear colourless, odourless liquid. Insoluble in water, in alcohol, in acetone, and in methyl alcohol; very slightly soluble in isopropyl alcohol; soluble in amyl acetate, in chlorinated hydrocarbons, in ether, in *n*-hexane, in petroleum spirit, in benzene, in toluene, and in xylene. Store in airtight containers.

Uses and Administration

Dimeticones and other silicones are water-repellent and have a low surface tension. They are used in topical barrier preparations for protecting the skin against water-soluble irritants. Creams, lotions, and ointments containing a dimeticone are used for the prevention of bedsores and napkin rash and to protect the skin against trauma due to incontinence or stoma discharge. Silicone preparations should not be applied where free drainage is necessary or to inflamed or abraded skin. Silicones, usually a dimeticone, are also used topically as wound dressings, and to reduce scar elevation and pigmentation. They are also used in oral solid dosage forms, including modified-release preparations.

Dimeticones and cyclomethicones are used in the treatment of head pediculosis (p. 2147.3). Solutions containing 4 to 95% dimeticone have been used and act by physically coating the lice and disrupting their water management; cyclomethicones are usually included for their volatility as solvents.

Silicones have also been used for arthroplasty in rheumatic disorders, by intravitreal injection for retinal detachment, and by subcutaneous injection or implantation in reconstructive or cosmetic surgery.

Dimeticones, in particular simeticone (activated dimeticone) (p. 1886.2), are used in the treatment of flatulence.

Pediculosis. References.

1. Burgess IF, *et al.* Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; **330:** 1423.

2. Burgess IF, *et al.* Randomised, controlled, assessor blind trial comparing 4% dimeticone lotion with 0.5% malathion liquid for head louse infestation. *PLoS One* 2007; **2:** e1127.
3. Heukelbach J, *et al.* A highly efficacious pediculicide based on dimeticone: randomized observer blinded comparative trial. *BMC Infect Dis* 2008; **8**: 115.
4. Burgess IF. The mode of action of dimeticone 4% lotion against head lice, *Pediculus capitis*. *BMC Pharmacol* 2009; **9:** 3.

Retinal detachment. Retinal detachment is separation of the retina from the underlying retinal pigmentary epithelium and usually requires surgical repair. Intravitreal injection of liquid silicone, either alone or with a perfluorocarbon,[1,2] is used for retinal tamponade with or after surgery in complicated or persistent detachment of the retina.[3] In most cases, the silicone fluid is later removed from the eye.[4] High-density silicone fluids are increasingly being used.[5] Use of silicone fluid is reported to trigger a local inflammatory response, which may persist after the fluid is removed.[6] Other late complications after its use may include cataract, glaucoma, and keratopathy.

1. Rizzo S, *et al.* Long-term vitreous replacement with perfluorohexyloctane and silicone oil: preliminary reports of a multicentric study. *Ophthalmologica* 2005; **219:** 147–53.
2. Schwartz SG, *et al.* Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 16/06/10).
3. Quiram PA, *et al.* Outcomes of vitrectomy with inferior retinectomy in patients with recurrent rhegmatogenous retinal detachments and proliferative vitreoretinopathy. *Ophthalmology* 2006; **113:** 2041–7.
4. Szurman P, *et al.* Primary silicone oil tamponade in the management of severe intraocular foreign body injuries: an 8-year follow-up. *Retina* 2007; **27:** 304–11.
5. Herbrig E, *et al.* Anatomical and functional results of endotamponade with heavy silicone oil – Densiron 68 – in complicated retinal detachment. *Ophthalmic Res* 2007; **39:** 198–206.
6. Wickham LJ, *et al.* Immunopathology of intraocular silicone oil: retina and epiretinal membranes. *Br J Ophthalmol* 2007; **91:** 258–62.

Adverse Effects and Precautions

Adverse effects from the clinical use of silicones appear to be rare. Foreign-body reactions have been reported after their use as joint implants. Other implants, notably breast implants used for reconstruction after mastectomy or for cosmetic purposes, carry the risk of migration of silicone with cyst formation and other complications; accidental intravascular injection has been fatal. Late adverse ocular effects can follow the intravitreal injection of liquid silicone in the management of retinal detachment (see above).

Breast feeding. Concern has been raised regarding the possible effects on infants of mothers with silicone breast implants who breast feed. Oesophageal dysfunction has been reported in several such children,[1] although this finding has not been confirmed by subsequent reports. The last available guidance from the American Academy of Pediatrics therefore stated[2] that the current evidence did not justify classifying silicone implants as a contra-indication to breast feeding.

1. Levine JJ, Ilowite NT. Sclerodermalike esophageal disease in children breast-fed by mothers with silicone breast implants. *JAMA* 1994; **271:** 213–6. Correction. *ibid.*; **272:** 770.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 20/11/07)

Connective tissue disorders. Since the introduction of silicone breast implants in the early 1960s there have been many anecdotal reports of connective tissue disorders in women who have undergone breast reconstruction or augmentation with these implants. Scleroderma has been the most frequently reported disorder; others have included SLE, rheumatoid arthritis, and inflammatory myopathies. A syndrome of vague musculoskeletal symptoms, fever, and fatigue has also been reported. These cases led the FDA to call for a moratorium in the USA on the use of silicone breast implants in January 1992. However, with the exception of one study of self-reported symptoms which showed only a small increase in risk,[1] large epidemiological studies,[2-5] meta-analyses,[6-8] and a review by the Medical Devices Agency in the UK have so far failed to show any association between silicone breast implants and connective tissue disorders. After conducting a review of the evidence, the FDA in 2006 re-approved the sale of silicone breast implants, for use in women of all ages for breast reconstruction, and for cosmetic use in women aged 22 years or more;[9] the approval obliges the manufacturers to conduct a 10-year post-approval safety study.

1. Hennekens CH, *etal.* Self-reported breast implants and connective-tissue diseases in female health professionals: a retrospective cohort study. *JAMA* 1996; **275:** 616–21.
2. Gabriel SE, *et al.* Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994; **330:** 1697–1702.
3. Sánchez-Guerrero J, *et al.* Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med* 1995; **332:** 1666–70.
4. Silverman BG, *et al.* Reported complications of silicone gel breast implants: an epidemiologic review. *Ann Intern Med* 1996; **124:** 744–56.
5. Nyrén O, *et al.* Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. *BMJ* 1998; **316:** 417–22.
6. Janowsky EC, *et al.* Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. *N Engl J Med* 2000; **342:** 781–90.
7. Lipworth L, *et al.* Silicone breast implants and connective tissue disease: an updated review of the epidemiologic evidence. *Ann Plast Surg* 2004; **52:** 598–601.
8. Lipworth L, *et al.* Breast implants and fibromyalgia: a review of the epidemiological evidence. *Ann Plast Surg* 2004; **52:** 284–7.
9. FDA. FDA approves silicone gel-filled breast implants after in-depth evaluation (issued 17/11/06). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108790.htm (accessed 23/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerogal; Darin-KA; EpiDerm; Europiel; Finescar; Kurapel; Skinderm SIL; Xeragel; ***Austral.***: Cica-Care; Dermatix; Egozite Protective Baby Lotion†; Hospital Skin Care Lotion; Kelo-cote; Mepiform; NYDA; Rosken Skin Repair; Silic 15; ***Belg.***: Mepitel; ***Braz.***: Skimatix; ***Canad.***: Barriere; Clinique Comfort†; Comfort Shield; Dermatix Si†; Dermatix Ultra; Proshield Plus; Readybath; Readycleanse; Sween 24; ***Chile***: Epi-Derm; Lomprax; Neogasol; Para†; Sensei; ***Fr.***: Cica-Care; Dermatix; Ophtasiloxane; ***Ger.***: Dermatix; Jacutin; Mepiform; Mepilex; Mepitel; Nyda L; Siluron; Symadal M; ***Hong Kong***: Dermatix; Egozite Protective Baby Lotion†; Silic 15; Skin Repair†; Uni-Methicone†; ***Hung.***: Dermatix; ***Indon.***: Dermatix; ***Irl.***: Dermatix; ***Israel***: Hedrin; ***Ital.***: Cica-Care; Mepiform; Mepitel; ***Malaysia***: Dermatix; Egozite Protective Baby Lotion†; Silic 15; ***Mex.***: Dermatix Ultra; ***Neth.***: SIL-1000, -5000; XT Luis; ***NZ***: DP Barrier Cream†; Egozite Protective Baby Lotion; ***Philipp.***: Cica-Care; Dermatix; ***Pol.***: Silol†; ***Port.***: Piky; ***Singapore***: Dermatix; Rosken Skin Repair; Silic 15; Strataderm; ***UK***: Cica-Care; Dermatix; Hedrin; Linicin; Mepiform; NYDA; Pro-Sil; Silgel; ***Ukr.***: Headring (Хедринг); ***USA***: 4-N-1; Mentholatum Softlips; Pro-Q.

Multi-ingredient Preparations. ***Arg.***: Assy Max; Basta; Hyalomatrix-PA; Kelo-Cote; Nopucid Bio Citrus; Nopucid Bio II; Sumo Full Contact; Talquisedan; ***Austral.***: Dermalife Plus†; Dimethicream; Eczema Cream; Egozite Baby Cream; Hamilton Pine Tar with Menthol; ***Austria***: Ceolat Compositum; ***Braz.***: Balmex; Cicaplast; ***Canad.***: Blistex Lip Balm; Blistex Ultra Protection Lip Balm; Gold Bond Anti-Itch; Gold Bond Extra Strength Medicated; Gold Bond Medicated; Moisturel; ***Chile***: Aero Itan; Balsamo Analgesico con Fenilbutazona; Blisprotex; Exomega Barrera; Neopankreoflat; Talquisedan; Ureadin 30; Xeragel; ***Denm.***: Silan; ***Fr.***: Cicatridine; Flex-Tonic; Kelo-Cote; ***Ger.***: Densiron 68; Dimet; EtoPril; Itax†; Kelo-Cote; ***Gr.***: Rikospray Silicone; ***Hong Kong***: 2nd Skin ScarGel; Dermatix Ultra; DS Emulsion†; Egozite Baby Cream; Hamilton Skin Repair†; Natamin C†; Vasogen†; ***India***: Biolite; Calyx; Diafoot; Dibi; KC-Lite; Nestosule-MV; Silodern; Tinidafyl Plus; ***Indon.***: Kelo-Cote; Sodermix; ***Irl.***: Cymex; Sprilon; Vasogen†; ***Israel***: Kamil Blue; Kamil Blue; Kelo-Cote; ***Ital.***: Angstrom Viso; Plurilac; Rikospray; ***Malaysia***: Egozite Baby Cream; Norash; Palmer's Cocoa Butter Formula Scar Serum; QV Lip Balm; ***Mon.***: Dermo Silanols; ***NZ***: Egoderm; Egozite Baby; Rosken Skin Repair; Silic; ***Philipp.***: Dermatix Ultra; ***S.Afr.***: Arola Rosebalm†; Siopel; ***Singapore***: Dermatix Ultra; Egozite Baby Cream; Metanium Everyday Barrier; Norash; Scar Esthetique; ***Spain***: Dermo H Infantil†; Proskin; Silidermil; ***Swed.***: Silon; ***Switz.***: Kelo-cote†; ***UK***: Conotrane; Cymex; Full Marks Solution; Lyclear Mousse; Lyclear Spray; Siopel; Sprilon; Vasogen; ***USA***: A+D Zinc Oxide Cream; Blistex Lip Balm; ControlRx; Diaper Guard; Dyprotex; Gold Bond Intensive Healing; Gold Bond Medicated Triple Action Relief; Herpecin-L; Lansinoh Diaper Rash; Maxilube; Mentholatum Cherry Ice; Mentholatum Natural Ice; Mentholatum Softlips Lipbalm (UV); Mentholatum Softlips Lipbalm; Neosalus; Soothe & Cool; ***Venez.***: Hidribet.

Sodium Cetostearyl Sulfate

Cetoestearilsulfato de sodio; Cétostéaryle (sulfate de) sodique; Cetylstearylschwefelsaures Natrium; Natrii Cetyloet Stearylosulfas; Natrio cetostearilo sulfatas; Natrium Cetylosulphuricum; Natrium Cetylstearylosulphuricum; Nátrium-cetil-sztearil-szulfát; Natriumcetostearylsulfat; Natriumcetylstearylsulfat; Natrium-cetylstearyl-sulfát; Natriumsetostearyylisulfaatti; Sodium Cetearyl Sulfate; Sodium Cetostearyl Sulphate; Sodu cetostearylosiarczan; Натрия Цетостеарилсульфат.

CAS — 59186-41-3 (sodium cetostearyl sulfate); 68955-20-4 (sodium mono-C16-18-alkyl sulfates); 1120-01-0 (sodium cetyl sulfate); 1120-04-3 (sodium stearyl sulfate).
UNII — 7ZBS06BH4B.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. & (Sodium Cetostearyl Sulfate). A mixture of sodium cetyl sulfate ($C_{16}H_{33}NaO_4S = 344.5$) and sodium stearyl sulfate ($C_{18}H_{37}NaO_4S = 372.5$). A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; partly soluble in alcohol.

USNF 31: (Sodium Cetostearyl Sulfate). A mixture of sodium cetyl sulfate ($C_{16}H_{33}NaSO_4 = 344.5$) and sodium stearyl sulfate ($C_{18}H_{37}NaSO_4 = 372.5$). It contains not less than 40% of sodium cetyl sulfate and the sum of the sodium cetyl sulfate content and sodium stearyl sulfate content is not less than 90%, both contents calculated on the anhydrous basis. A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; partly soluble in alcohol.

Profile

Sodium cetostearyl sulfate is an alkyl sulfate anionic surfactant (p. 2164.1). It is used as an oil-in-water emulsifier and as a detergent and wetting agent.

Sodium Cocoyl Isetionate

Sodium Cocoyl Isethionate; Кокоил Изетионат Натрия.

CAS — 61789-32-0.
UNII — 518XTE8493.

Sodium Lauroyl Isetionate

Sodium Lauroyl Isethionate; Sodium Lauroylisethionate; Sodium Lauryl Isethionate; Sodium 2-Sulfoethyl Laurate. Sodium 2-sulfoethyldodecanoate.

$C_{14}H_{27}NaO_5S = 330.4$
CAS — 7381-01-3.
UNII — M590021Z02.

Profile

Sodium cocoyl isetionate is the sodium salt of sulfoethyl esters of coconut oil fatty acids. It is an alkyl sulfonate anionic surfactant (p. 2164.1) and is used as a soap substitute. Sodium lauroyl isetionate, which is derived from lauric acid, and ammonium cocoyl isetionate have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Physiogel; ***Indon.***: Physiogel†; ***Ital.***: Physiogel; ***Philipp.***: Physiogel; ***Thai.***: Physiogel†.

Multi-ingredient Preparations. ***Mex.***: Bonaven.

Sodium Cocoyl Sarcosinate

CAS — 61791-59-1.
UNII — 1R9DUY89CZ.

Sodium Lauroyl Sarcosinate

Sodium Lauroylsarcosinate; Лаурилсаркозинат Натрия. Sodium *N*-dodecanoyl-*N*-methylglycine.

$C_{15}H_{29}NNaO_3 = 294.4$
CAS — 137-16-6.
UNII — 632GS99618.

Profile

Sodium cocoyl sarcosinate is an alkyl sarcosinate anionic surfactant (p. 2164.1) and is used as a soap substitute. Sodium lauroyl sarcosinate has been used similarly.

Sodium Laurilsulfate *(pINNM)*

Laurilsulfate de Sodium; Laurilsulfato de Sódio; Laurilsulfato de sodio; Natrii Laurilsulfas; Natrio laurilsulfatas; Natrium Lauryl Sulphuricum; Natriumdodecylsulfat; Natriumlaurilsulfat; Nátrium-lauril-szulfát; Natrium-lauryl-sulfát; Natriumlauryylisulfaatti; Sodium Dodecyl Sulphate; Sodium, laurilsulfate de; Sodium Lauryl Sulfate; Sodium Lauryl Sulphate; Sodu dodecylosiarczan; Sodu laurylosiarczan; Натрий Лаурилсульфат.

CAS — 151-21-3.
UNII — 368GB5141J.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF.*

Ph. Eur. & (Sodium Laurilsulfate; Sodium Lauryl Sulfate BP 2014). A mixture of sodium alkyl sulfates, consisting mainly of sodium dodecyl sulfate ($C_{12}H_{25}NaO_4S = 288.4$). It contains not less than 85% of sodium alkyl sulfates and not more than a total of 8% of sodium chloride and sodium sulfate. A white or pale yellow powder or crystals. Freely soluble in water giving an opalescent solution; partly soluble in alcohol.

USNF 31: (Sodium Lauryl Sulfate). A mixture of sodium alkyl sulfates, consisting mainly of sodium laurilsulfate ($C_{12}H_{25}NaO_4S = 288.4$). The combined content of sodium

chloride and sodium sulfate is not more than 8%. Small, white or light yellow crystals with a slight, characteristic odour. Soluble 1 in 10 of water giving an opalescent solution.

Incompatibility. Sodium laurilsulfate interacts with cationic surfactants such as cetrimide, resulting in a loss of activity. It is also incompatible with salts of polyvalent metal ions (e.g. aluminium, lead, tin, or zinc) and with acids of pH below 2.5. It is not affected by hard water because of the solubility of the corresponding calcium and magnesium salts.

Uses

Sodium laurilsulfate is an alkyl sulfate anionic surfactant (p. 2164.1). It is a detergent and wetting agent, effective in both acid and alkaline solution and in hard water. It is used in medicated shampoos, as a skin cleanser, and in toothpastes, and in the preparation of Emulsifying Wax (p. 2184.1). It is also used as a tablet lubricant.

Other salts of laurilsulfate have been used for their surfactant properties. These include monoethanolamine, diolamine, and trolamine laurilsulfates, and magnesium and ammonium laurilsulfates.

Alkyl ether sulfates such as sodium lauril ether sulfate (sodium laureth sulfate) and ammonium lauril ether sulfate (ammonium laureth sulfate), are ethoxylated derivatives and are used similarly. Sodium lauril sulfoacetate, which contains a sulfonate rather than a sulfate group, and sodium lauril ether sulfosuccinate (disodium laureth sulfosuccinate), an ethoxylated sulfonate, are also used.

Sodium laurilsulfate and related surfactants are also included in some combination preparations used rectally for the management of constipation.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies laurilsulfate used as a laxative as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Adverse Effects

Prolonged exposure to sodium laurilsulfate may irritate the skin or mucous membranes. Hypersensitivity reactions have been reported.

Skin thinning and increased transepidermal water loss were seen in a study in 6 healthy subjects after application of Aqueous Cream BP twice daily for 4 weeks.[1] The effect was attributed to the preparation's content of sodium laurilsulfate; it was suggested that use of the cream as an emollient in patients with eczema should be reconsidered.

1. Tsang M, Guy RH. Effect of Aqueous Cream BP on human stratum corneum in vivo. *Br J Dermatol* 2010; **163:** 954–8.

Hypersensitivity. Hypersensitivity reactions have been reported[1,2] after use of toothpastes containing sodium laurilsulfate. There has also been a report[3] of hypersensitivity associated with ingestion of sodium laurilsulfate as an excipient in an oral preparation.

1. Lee A-Y, *et al.* Two cases of allergic contact cheilitis from sodium lauryl sulfate in toothpaste. *Contact Dermatitis* 2000; **42:** 111.
2. Ersoy M, *et al.* The allergy of toothpaste: a case report. *Allergol Immunopathol (Madr)* 2008; **36:** 368–70.
3. Sugiura K, *et al.* Delayed-type hypersensitivity reactions due to sodium lauryl sulphate in omeprazole. *J Eur Acad Dermatol Venereol* 2009; **23:** 610–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Euroclear; Lactofilm; Limectant; ***Chile***: Solucion Detergente; ***Fr.***: Saforelle†; ***Hong Kong***: Lowila Cake†; ***Mex.***: Aquanil; ***Spain***: Anticerumen.

Multi-ingredient Preparations. ***Arg.***: Caien†; Micronema; Nigalax; Ninderm; Plus & Plus; Xicanil Control NF; ***Austral.***: Fleet Micro-Enema†; Micolette; Microlax; Pinetarsol; ***Austria***: Microklist; ***Belg.***: Microlax; Neo-Sabenyl; ***Canad.***: Aseptone 2; Microlax; Plax†; ***Cz.***: Dermofug†; ***Denm.***: Microlax; ***Fin.***: Microlax; ***Fr.***: Bactident†; Microlax; Ysol 206†; ***Ger.***: Dermowas; Microklist; ***Gr.***: Dermacide; Sabenyl; ***Hong Kong***: Microlax†; ***Indon.***: Laxarec; Microlax; Sodermix; ***Irl.***: Dentinox Cradle Cap; Micolette; Microlax; ***Israel***: Microlet; ***Ital.***: Eso Zim; Merankol Pastiglie; Novilax; ***Malaysia***: Dentinox Cradle Cap; pH Care; ***Mex.***: Microlax; ***Neth.***: Casen Mikroklysma†; Microlax; ***Norw.***: Microlax; ***NZ***: Microlax; ***Pol.***: Rektiolax; ***Port.***: Microlax; ***Rus.***: Microlax (Микролакс); ***Singapore***: Dentinox Cradle Cap; Microlax; ***Spain***: Clisteran; Micralax; ***Swed.***: Microlax; ***Switz.***: Microklist; Microlax; ***Turk.***: SH-206; ***UK***: Dentinox Cradle Cap; Micolette; Micralax; Relaxit; ***USA***: Bodi Kleen; Cetaklenz; Geri-Lav Free; Klout; Maxilube; Summer's Eve Post-Menstrual; Trichotine; Trimo-San; ***Venez.***: Novafix.

Pharmacopoeial Preparations
BP 2014: Emulsifying Wax.

Sodium Oleate

E470a (sodium, potassium, and calcium salts of fatty acids); Oleato de sodio; Олеиновокислый Натрий.
Sodium 9(*Z*)-octadecenoate.
$C_{18}H_{34}NaO_2$=305.5
CAS — 143-19-1 (sodium oleate); 143-18-0 (potassium oleate); 142-17-6 (calcium oleate); 557-07-3 (zinc oleate).
UNII — 399SL044HN.

Profile

Sodium oleate is an alkali-metal soap anionic surfactant (p. 2164.1). It is used as an emulsifier and has also been used as an ingredient in preparations for the symptomatic relief of haemorrhoids and pruritus ani. It is one of the main components of soaps made from olive oil.

Other salts of oleic acid that have been used in skin preparations include zinc oleate and potassium oleate. Sodium, potassium, and calcium oleate are used as emulsifiers and anticaking agents in food, and the calcium salt has also been used in nutritional supplements. Monoethanolamine oleate is used as a sclerosant (see p. 2562.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Cose-Anal; ***Canad.***: Artecho†; ***Neth.***: Epianal; ***Norw.***: Alcos-Anal; ***Swed.***: Alcos-Anal.

Sodium Starch Glycolate

Carboximetilalmidón sódico; Carboxyméthylamidon sodique; Carboxymethylamylum natricum; Glicolato sódico de almidón; Karboksymetyloskrobia sodowa; Karboximetilkeményítő-nátrium; Karboxymethylškrob sodná sůl; Natriumstärkelseglykolat; Natriumtärkkelysglykolaatti; Sodium Carboxymethyl Starch; Sodium Starch Glycollate; Starch Sodium Glycolate; Натрия Гликолят Крахмала.
CAS — 9063-38-1.
UNII — 5856J3G2A2 (sodium starch glycolate type A potato).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Sodium Starch Glycolate (Type A); Carboxymethylamylum Natricum A). The sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.8 to 4.2% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent suspension in water; practically insoluble in dichloromethane. pH of a 3.33% dispersion in water is 5.5 to 7.5. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Sodium Starch Glycolate (Type B); Carboxymethylamylum Natricum B). The sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.0 to 3.4% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent suspension in water; practically insoluble in dichloromethane. pH of a 3.33% dispersion in water is 3.0 to 5.0. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Sodium Starch Glycolate (Type C); Carboxymethylamylum Natricum C). The sodium salt of a cross-linked by physical dehydration, partly *O*-carboxymethylated starch. It contains 2.8 to 5.0% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent gel-like product in water; practically insoluble in dichloromethane. pH of a 3.33% gel in water is 5.5 to 7.5. Store in airtight containers. Protect from light.

USNF 31: (Sodium Starch Glycolate). The sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain not more than 7.0% of sodium chloride. The sodium content is 2.8 to 4.2% (Type A) or 2.0 to 3.4% (Type B). pH of a 1 g in 30 mL suspension in water is between 5.5 and 7.5 (Type A) or between 3.0 and 5.0 (Type B).

A white, odourless, relatively free-flowing powder available in several different viscosity grades. A 2% dispersion in cold water settles, on standing, in the form of a highly hydrated layer. Protect from wide variations in temperature and humidity which may cause caking.

Profile

Sodium starch glycolate is used as a disintegrating agent in tablet manufacture.

Sodium Stearate

E470a (sodium, potassium, and calcium salts of fatty acids); Estearato de Sodio; Natrii Stearas; Natrio stearatas; Natriumstearaatti; Natriumstearat; Sodium, stéarate de; Sodu stearynian; Stearan sodný; Stearato di Sodio; Стеарат Натрия.
Sodium Octadecanoate.
CAS — 408-35-5 (sodium palmitate); 822-16-2 (sodium stearate).
UNII — QU7E2XA9TG.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sodium Stearate). A mixture of sodium salts of different fatty acids consisting mainly of stearic acid ($C_{18}H_{35}O_2Na$ = 306.5) and palmitic acid ($C_{16}H_{31}O_2Na$ = 278.4). It contains 7.4 to 8.5% of sodium, calculated with reference to the dried substance. The fatty acid fraction contains not less than 40% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90%. A white or yellowish, fine powder, with a greasy touch. Slightly soluble in water and in alcohol. Store in airtight containers. Protect from light.

USNF 31: (Sodium Stearate). A mixture containing not less than 90% of sodium stearate ($C_{18}H_{35}NaO_2$ = 306.5) and sodium palmitate ($C_{16}H_{31}NaO_2$ = 278.4); the content of sodium stearate is not less than 40% of the total. It contains small amounts of the sodium salts of other fatty acids. A fine, white powder, soapy to the touch, usually with a slight tallow-like odour. Slowly soluble in cold water and in cold alcohol; readily soluble in hot water and in hot alcohol. Protect from light.

Profile

Sodium stearate is an alkali-metal soap anionic surfactant (p. 2164.1) used as an emulsifying and stiffening agent in a variety of topical and rectal preparations. It is also used as an emulsifier in foods and is one of the main components of soaps produced from animal fats. Potassium stearate has been used similarly.

Preparations

Pharmacopoeial Preparations
USP 36: Glycerin Suppositories.

Sodium Stearyl Fumarate

Fumarato de estearilo y sodio; Natrii Stearylis Fumaras; Natrio stearilfumaratas; Natriumstearylfumarat; Natrium-stearylfumarát; Natriumstearyylifumaraatti; Nátrium-sztearil-fumarát; Stéaryle (fumarate de) sodique; Натрия Стеарилфумарат.
Sodium monooctadecyl 2-butenedioate.
$C_{22}H_{39}NaO_4$=390.5
CAS — 4070-80-8.
UNII — 7CV7WJK4UI.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sodium Stearyl Fumarate). A fine, white or almost white powder with agglomerates of flat, circular shaped particles. Practically insoluble in water, in alcohol, and in acetone; slightly soluble in methyl alcohol.

USNF 31: (Sodium Stearyl Fumarate). A fine white powder. Practically insoluble in water; slightly soluble in methyl alcohol.

Profile

Sodium stearyl fumarate, the sodium salt of the stearate ester of fumaric acid, is an ester carboxylate anionic surfactant (p. 2164.1). It is used as a lubricant in the manufacture of tablets and capsules, and is also used in foods and cosmetics.

Soft Paraffin

INS No. 905b (petroleum jelly).

NOTE. The code 905 has been used for mineral hydrocarbons including soft paraffin but E905 is now used specifically for microcrystalline wax (p. 2198.1).

White Soft Paraffin

905 (mineral hydrocarbons); Minkštasis baltas parafinas; Paraff. Moll. Alb.; Paraffinum Molle Album; Parafina blanda blanca; Valkovaseliini; Vaselin, vitt; Vaselina blanca; Vaselina Branca; Vaselina filante; Vaseline blanche; Vaseline Officinale; Vaselinum album; Vazelína bílá; Wazelina biała; White Petrolatum; White Petroleum Jelly; Белый Вазелин.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Many pharmacopoeias use the title Vaselinum Album; in some countries the name 'Vaseline' is a trade-mark.

Ph. Eur. 8: (Paraffin, White Soft). Purified and wholly or nearly decolorised mixture of semi-solid hydrocarbons, obtained from petroleum. It may contain a suitable antoxidant. It is not suitable for oral use. A white or almost white, translucent, soft unctuous mass, slightly fluorescent in daylight when melted. Drop point 35 degrees to 70 degrees. Practically insoluble in water, in alcohol, and in glycerol; slightly soluble in dichloromethane. Protect from light.

The BP 2014 gives White Petroleum Jelly as an approved synonym.

USP 36: (White Petrolatum). A purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or nearly decolorised. It may contain a suitable stabiliser. A white or faintly yellowish unctuous mass, transparent in thin layers even after cooling to 0 degrees. Insoluble in water; slightly soluble in cold or hot alcohol and in cold dehydrated alcohol; freely soluble in chloroform, in benzene, and in carbon disulfide; soluble in ether, in petroleum spirit, and in most fixed and volatile oils.

Yellow Soft Paraffin

Keltavaseliini; Minkštasis geltonas parafinas; Paraff. Moll. Flav.; Paraffinum Molle Flavum; Petrolatum; Petroleum Jelly; Sárga vazelin; Vaselin, gult; Vaselina Amarela; Vaselina amarilla; Vaselina filante amarilla; Vaseline jaune; Vaselinum Flavum; Vazelína žlutá; Wazelina żółta; Yellow Petrolatum; Yellow Petroleum Jelly; Жёлтый Вазелин.

CAS — 8009-03-8.

UNII — 4T6H12BN9U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Many pharmacopoeias use the title Vaselinum Flavum; in some countries the name 'Vaseline' is a trade-mark.

Ph. Eur. 8: (Paraffin, Yellow Soft). A purified mixture of semi-solid hydrocarbons obtained from petroleum. A yellow, translucent, unctuous mass, slightly fluorescent in daylight when melted. It has a drop point of 40 degrees to 60 degrees. Practically insoluble in water, in alcohol, and in glycerol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Petrolatum). A purified mixture of semi-solid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It is an unctuous yellowish to light amber mass, having not more than a slight fluorescence even after being melted. It is transparent in thin layers. It is free or practically free from odour. M.p. 38 degrees to 60 degrees. Insoluble in water; practically insoluble in cold or hot alcohol and in cold dehydrated alcohol; freely soluble in benzene, in carbon disulfide, in chloroform, and in turpentine oil; soluble in ether, in petroleum spirit, and in most fixed and volatile oils.

Uses and Administration

Soft paraffin is used as an ointment basis and as an emollient in the management of skin disorders. It is not readily absorbed by the skin. Sterile dressings containing soft paraffin are used for wound dressing and as a packing material. Soft paraffin is also included in ointments used as ophthalmic lubricants in the management of dry eye (p. 2190.1). Application of soft paraffin has been used for the eradication of pubic lice from the eyelashes (see Pediculosis, p. 2147.3). It has been used as a contact medium to reduce pain during extracorporeal shock wave lithotripsy. Soft paraffin is also used in food manufacturing.

Adverse Effects

Adverse effects of soft paraffin are rare when used in topical preparations, but sensitivity reactions and acne have been reported after topical use. Granulomatous reactions after absorption or injection and lipoid pneumonia after aspiration have occurred.

Fire risk. Burns to the scalp, face, and hands have been reported[1] in 5 patients who accidentally ignited their hair after the application of paraffin-based hair grease. Four patients suffered inhalation injury, 2 of whom required intubation. The death of a patient who, while smoking, ignited bandages covering a paraffin-based ointment for psoriasis,[2] prompted the *BNF* to recommend that patients should be told not to smoke and to keep away from flames when using paraffin-based emollients.

1. Bascom R, *et al.* Inhalation injury related to use of petrolatum-based hair grease. *J Burn Care Rehabil* 1984; **5:** 327–30.
2. National Patient Safety Agency. Managing the fire hazard with paraffin based skin products on dressings and clothing (issued on 26 November 2007). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60266&type=full&servicetype=Attachment (accessed 23/08/10)

Hypersensitivity. The allergenicity of soft paraffin products has been investigated.[1-4] Considering their widespread use there are very few reports of sensitivity;[4] of nearly 80 000 patients patch tested with white soft paraffin, only 29 showed a positive reaction. White soft paraffin is generally less sensitising than yellow soft paraffin, although allergenicity differs from product to product. The allergenic components are probably polycyclic aromatic hydrocarbons present as impurities and quantities found in a particular paraffin depend on the source and purification method. Only the purest forms should be used in pharmaceuticals, cosmetics, and for patch testing, and highly purified white soft paraffin is preferred to yellow soft paraffin.

1. Dooms-Goossens A, Degreef H. Contact allergy to petrolatums (I). Sensitising capacity of different brands of yellow and white petrolatums. *Contact Dermatitis* 1983; **9:** 175–85.
2. Dooms-Goossens A, Degreef H. Contact allergy to petrolatums (II). Attempts to identify the nature of the allergens. *Contact Dermatitis* 1983; **9:** 247–56.
3. Dooms-Goossens A, Dooms M. Contact allergy to petrolatums (III). Allergenicity prediction and pharmacopoeial requirements. *Contact Dermatitis* 1983; **9:** 352–9.
4. Schnuch A, *et al.* White petrolatum (Ph. Eur.) is virtually non-sensitizing: analysis of IVDK data on 80 000 patients tested between 1992 and 2004 and short discussion of identification and designation of allergens. *Contact Dermatitis* 2006; **54:** 338–43.

Lipoid pneumonia. Various uses of soft paraffin have been associated with lipoid pneumonia, including topical facial use to treat psoriasis,[1] long-term intranasal application for a dry nose,[2] and use as a lubricant during nasogastric intubation.[3]

1. Cohen MA, *et al.* Exogenous lipoid pneumonia caused by facial application of petrolatum. *J Am Acad Dermatol* 2003; **49:** 1128–30.
2. Brown AC, *et al.* Exogenous lipoid pneumonia due to nasal application of petroleum jelly. *Chest* 1994; **105:** 968–9.
3. Bernabeu Mora R, *et al.* Neumonía lipoidea aguda debiba a la aspiratión accidental de vaselina utilizada en un sondaje nasogástrico. *Arch Bronconeumol* 2000; **36:** 485–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Jelonet; ***Braz.***: Vaselina; ***Canad.***: Cetraben†; Critic-Aid Clear; Prevex; Protective Ointment; Summerberry Skin Cream; Vaseline; ***Fr.***: Jelonet; Tulle Gras; Vaselitulle; ***Ger.***: Oleo Tull; ***Gr.***: Vaseline Pure; ***Irl.***: Dermamist; ***Ital.***: Adaptic; Jelonet; Lomatuell H; ***Mex.***: Formula Dermica; Lubrilin†; ***Philipp.***: Apollo; ***Rus.***: Kliotex (Клиотекс); ***S.Afr.***: Jelonet; ***Spain***: Lacrilube; Vasfilm; ***Turk.***: Duratears; ***UK***: Dermamist; Jelonet; Vaseline; ***USA***: Ocu-Lube.

Multi-ingredient Preparations. ***Arg.***: Alcon Lagrimas; Aqualane; Benzalcrem; Macoderm; Milorix†; ***Austral.***: Dermeze; E45; Epaderm; Epaderm; Granugen†; Ircal; Lacri-Lube; Poly Visc; QV Flare Up; Triple Care Cream; ***Austria***: Tiroler Steinol; ***Belg.***: Duratears; Lacrytube; Transitol; ***Canad.***: A & D Ointment; Akwa Tears; Bum-Butt-R; Duolube; Everything Butt; Flexitol Heel Balm†; Hydrophil; Hypotears; Moisturel; Optilube; Refresh Lacri-Lube; Sebamed; Tears Naturale PM; ***Chile***: Chapstick Medicated; Durasolets; Duratears; Ictyane; Lacri-Lube; Pasta Lassar; ***Denm.***: Ojensalve Neutral; ***Fin.***: Lacri-Lube; ***Fr.***: Cellosorb†; Codexial Zinc†; Dexeryl; Grassolind Neutral; Ictyane HD; Ictyane; Transitol; Transulose; Vaseline Gomenolee; ***Ger.***: Coliquifilm; Dexeryl; Sofra-Tull sine; Vita-POS; ***Gr.***: Duratears; Vaseline Borique; Vaseline Oxyde Zinc; ***Hong Kong***: Duratears; Oilatum Cream; ***India***: Adlube; Cetraben; Dermoys; Dershine; Dewee; Elsoft; Emoderm; Himost; Leoben; Microgard Tulle; Moitz; Moyzen; Oilatum; ***Irl.***: Lacri-Lube; Oilatum Cream; Silcocks Base; ***Israel***: Duratears; Kamil Blue; Lacrimol†; Vita-POS; ***Ital.***: Lacrilube; Transitol; Transulose; ***Malaysia***: Aqua Cream; Balneum†; Duratears Naturale; Lacrilube; Oilatum; Palmer's Cocoa Butter Formula Nappy Rash Ointment; Palmer's Cocoa Butter Formula Nursing Cream; QV Lip Balm; ***Mex.***: Transilax; ***Neth.***: Duratears Z; Transulose; ***Norw.***: Simplex; ***NZ***: Lacrilube; Poly-Visc; ***Philipp.***: Oilatum; ***Pol.***: Amfobase†; Diprobase; E45; Unibasis; ***Singapore***: Balneum; Duratears; Lacrilube†; Metanium Everyday Barrier; Oilatum Cream; ***Spain***: Lubrifilm†; Vaselina Boricada†; ***Switz.***: Coliquifilm; Dexeryl; ***Thai.***: Duratears; Oilatum Cream†; ***Turk.***: Cinkos; ***UK***: 50:50; Cetraben Emollient; Diprobase; Emollin; Epaderm; Hewletts†; Hydromol; Imuderm†; Lacri-Lube; Lubri-Tears†; Melrose; Oilatum Cream; Oilatum Junior; VitA-POS; Zerocream; Zeroguent; ***Ukr.***: Transuloza (Трансулоза); ***USA***: Akwa Tears†; Albolene; Aquaphor Healing Ointment; Aquaphor†; ARC; Bodi Care Lotion; Bottom Better†; Boudreaux's Butt Paste; Chapstick Medicated Lip Balm; DermaPhor; Desitin Creamy; Diaper Guard; Dry Eyes; Duratears Naturale; Formulation R; Hemorid For Women; Hemorid For Women; Hydrocerin; Hypotears; Lacri-Gel; Lacri-Lube; LubriFresh PM; LubriTears; Paladin; Palomar E; Puralube; Refresh Lacri-Lube; Refresh PM; Soothe Night Time; Stye; Systane Nighttime; Tears Again; Tears Renewed†; Venelex.

Pharmacopoeial Preparations

BP 2014: Cetomacrogol Emulsifying Ointment; Cetrimide Emulsifying Ointment; Emulsifying Ointment; Paraffin Ointment; Simple Eye Ointment; Simple Ointment; Wool Alcohols Ointment;

USP 36: Bland Lubricating Ophthalmic Ointment; Hydrophilic Ointment; Hydrophilic Petrolatum; Petrolatum Gauze; White Ointment; Yellow Ointment.

Soft Soap

Green Soap; Jabón blando; Jabón verde; Medicinal Soft Soap; Sabão Mole; Sapo Mollis; Калиевое Мыло; Зелёное Мыло.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Soft Soap). It is made by the interaction of potassium hydroxide or sodium hydroxide with a suitable vegetable oil or oils or their fatty acids. It may be coloured with chlorophyll or not more than 0.015% of a suitable green soap dye. A yellowish-white to green or brown, unctuous substance. Soluble in water and in alcohol.

USP 36: (Green Soap). It is made by the saponification of suitable vegetable oils, excluding coconut oil and palm kernel oil, without the removal of glycerol. The method given in the USP 36 involves mixing the oil with oleic acid and to the heated mixture adding potassium hydroxide dissolved in glycerol and water. The homogeneous emulsion is then adjusted to weight with hot water. A yellowish-white to brownish- or greenish-yellow, transparent to translucent, soft unctuous mass with a slight, characteristic odour.

Uses

The name soap may be applied to a range of anionic surfactants (p. 2164.1) used for their detergent properties. The characteristics of soaps differ depending on the fatty acids they are derived from, the alkali used in their preparation, and whether they contain glycerol (a byproduct of their manufacture). Soaps defined in pharmacopoeias vary in the fatty acids allowed and whether they are sodium salts, potassium salts (potassium soap), or either.

Soft soaps contain glycerol and have been used to remove incrustations in chronic scaly skin diseases such as psoriasis (p. 1688.1) and to cleanse the scalp before the application of lotions. A solution of soft soap in warm water has been used as an enema to soften impacted faeces but should be avoided as it may inflame the colonic mucosa; other measures are now preferred (see Constipation, p. 1804.3). Alcoholic solutions of soft soap, such as Soap Spirit (BP 2014) and Green Soap Tincture (USP 36), are used as skin cleansers and detergents. A similar product was formerly used as a liniment (Soap Liniment; Opodeldoc).

Other soaps with pharmaceutical applications include: potash soap (linseed oil soap) made from linseed oil and potassium hydroxide, which has been used in the preparation of liquid soaps; hard soap (castile soap), made from olive oil and sodium hydroxide with glycerol removed, which has been used as a tablet excipient and in the preparation of plasters; and curd soap, made from animal fat and sodium hydroxide with glycerol removed, which has been used as a tablet excipient.

Adverse Effects and Treatment

Soaps, and anionic detergents in general, may be irritant to the skin by removing natural oils and may produce redness, soreness, cracking and scaling, and papular dermatitis. There may be some irritation of the mucous membranes and because of this soap enemas are no longer recommended; marked irritation may occur if soaps or detergents enter the eye. Ingestion of anionic detergents may cause gastrointestinal irritation with nausea, diarrhoea, intestinal distension, and occasionally vomiting. Treatment is symptomatic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Waldheim Abfuhrdragees forte†; ***Spain***: Linimento Naion; ***USA***: Therevac Plus; Therevac SB.

Pharmacopoeial Preparations

BP 2014: Soap Spirit;

USP 36: Green Soap Tincture; Green Soap.

Solvent Ether

Aether; Aether Aethylicus; Aether Solvens; Diethyl Ether; Eetteri; Eter; Éter; Éter dietílico; Éter disolvente; Éter etílico; Éter ordinario; Eteris; Ether; Éther; Éther rectifié; Ethyl Ether; Ethyl Oxide; Etoxietano; Óxido dietílico; Этиловый Эфир; Диэтиловый Эфир.

$(C_2H_5)_2O$=74.12

CAS — 60-29-7.

UNII — 0F5N573A2Y.

NOTE. Solvent ether is not intended for anaesthesia; only ether of a suitable quality (see p. 1900.3) should be so used.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ether). A colourless, clear, volatile, highly flammable liquid. It may contain a suitable non-volatile antoxidant at a suitable concentration. Relative density 0.714 to 0.716. Distillation range 34 degrees to 35 degrees. Soluble in water; miscible with alcohol, with dichloromethane, and with fatty oils. Store at 8 degrees to 15 degrees in airtight containers. Protect from light.

USP 36: (Ether). A colourless, mobile, volatile, flammable liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. B.p. about 35 degrees. Sp. gr. 0.713 to 0.716. Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly filled airtight containers at a temperature not exceeding 30 degrees and remote from fire. Protect from light.

Stability. Though ether is one of the lightest of liquids, its vapour is very heavy, being 2½ times heavier than air.

Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark; precautions should be taken against the production of static electrical discharge. Explosive peroxides are generated by the atmospheric oxidation of solvent ether and it is dangerous to distil a sample that contains peroxides.

Uses

Solvent ether is widely used as a pharmaceutical and industrial solvent, and is used as an extraction solvent in food processing.

Adverse Effects

As for Anaesthetic Ether, p. 1901.1. Ingestion of 30 to 60 mL may be fatal.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Proseptine†.

Multi-ingredient Preparations. ***Ger.***: Hoffmannstropfen; ***S.Afr.***: Chamberlains Traditional Colic Remedy†; Krampdruppels; Moultons Pain Paint†.

Sorbitan Esters

Sorbitán, ésteres del; Эфиры Сорбитана.

Description. A series of mixtures of the partial esters of sorbitol and its mono- and di-anhydrides with fatty acids.

Sorbitan Laurate *(BAN, rINN)*

E493; Laurato de sorbitán; Monolaurato de sorbitán; Sorbitaanilauraatti; Sorbitan, laurate de; Sorbitán, laurato de; Sorbitan Monododecanoate; Sorbitan Monolaurate (USAN); Sorbitani Lauras; Sorbitanlaurat; Sorbitan-laurát; Sorbitanmonolaurat; Sorbitano lauratas; Szorbitán-laurát; Сорбитана Лаурат.

$C_{18}H_{34}O_6$ (approximate)

CAS — 1338-39-2.

UNII — 6W9PS8B71J.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Laurate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with lauric acid. A brownish-yellow viscous liquid. Relative density about 0.98. Practically insoluble but dispersible in water; miscible with alcohol; slightly soluble in cottonseed oil. Protect from light.

USNF 31: (Sorbitan Monolaurate). A partial ester of sorbitol and its mono-and di-anhydrides with lauric acid. A yellow to amber oily liquid with a bland characteristic odour. Insoluble in water; soluble in liquid paraffin; slightly soluble in cottonseed oil and in ethyl acetate. Store in airtight containers.

Sorbitan Oleate *(BAN, rINN)*

E494; Monooleato de sorbitán; NSC-406239; Oleato de sorbitán; Sorbitaanioleaatti; Sorbitan Mono-9-octadecenoate; Sorbitan Mono-oleate; Sorbitan Monooleate (USAN); Sorbitan, Oléate de; Sorbitán, oleato de; Sorbitani oleas; Sorbitanmonooleat; Sorbitano oleatas; Sorbitanoleat; Sorbitan-oleát; Szorbitán-oleát; Сорбитана Олеат.

$C_{24}H_{44}O_6$ (approximate)

CAS — 1338-43-8.

UNII — 06XEA2VD56.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Oleate). A mixture usually obtained by esterification of 1 mole of sorbitol and its mono- and di-anhydrides per mole of oleic acid. A suitable antoxidant may be added. A brownish-yellow viscous liquid. Relative density about 0.99. Practically insoluble but dispersible in water; miscible with alcohol; soluble in fatty oils producing a hazy solution. Protect from light.

USNF 31: (Sorbitan Monooleate). A partial oleate ester of sorbitol and its mono- and di-anhydrides. A yellow to amber-coloured, viscous, oily liquid with a bland characteristic odour. Insoluble in water and in propylene glycol; miscible with mineral and vegetable oils. Store in airtight containers.

Sorbitan Palmitate *(BAN, rINN)*

E495; Monopalmitato de sorbitán; Palmitato de sorbitán; Sorbitaanipalmitaatti; Sorbitan Monohexadecanoate; Sorbitan Monopalmitate (USAN); Sorbitan, Palmitate de; Sorbitán, palmitato de; Sorbitani Palmitas; Sorbitanmonopalmitat; Sorbitano palmitatas; Sorbitanpalmitat; Sorbitan-palmitát; Szorbitán-palmitát; Сорбитана Пальмитат.

$C_{22}H_{42}O_6$ (approximate)

CAS — 26266-57-9.

UNII — 77K6Z421KU.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Palmitate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with palmitic acid. A yellowish or yellow powder, waxy flakes, or hard masses. M.p. 44 degrees to 51 degrees. Practically insoluble in water; slightly soluble in alcohol; soluble in fatty oils. Protect from light.

USNF 31: (Sorbitan Monopalmitate). A partial ester of sorbitol and its mono- and di-anhydrides with palmitic acid. A cream-coloured, waxy solid with a faint fatty odour. Insoluble in water; soluble in warm dehydrated alcohol; soluble with haze in warm liquid paraffin and in warm arachis oil.

Sorbitan Sesquioleate *(BAN, USAN, rINN)*

A mixture of sorbitan mono-9-octadecenoate and sorbitan di-9-octadecenoate; Sesquioleato de sorbitán; Sorbitaanisekvioleaatti; Sorbitan, sesquioléate de; Sorbitán, sesquioleato de; Sorbitani Sesquioleas; Sorbitano seskvioleatas; Sorbitanseskvioleat; Sorbitan-seskvioleát; Sorbitansesquioleat; Szorbitán-szeszkvioleát; Сорбитана Сесквиолеат.

$C_{33}H_{60}O_{6.5}$(approximate)

CAS — 8007-43-0.

UNII — 0W8RRI5W5A.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Sorbitan Sesquioleate). A mixture usually obtained by esterification of 2 moles of sorbitol and its mono-and di-anhydrides per 3 moles of oleic acid. A suitable antoxidant may be added. Relative density about 0.99. A pale yellow or slightly brownish-yellow paste, which becomes a viscous, oily, brownish-yellow liquid at about 25 degrees. Dispersible in water; slightly soluble in dehydrated alcohol; soluble in fatty oils. Protect from light.

USNF 31: (Sorbitan Sesquioleate). A partial oleate ester of sorbitol and its mono- and di-anhydrides. A yellow to amber-coloured, oily viscous liquid. Insoluble in water and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in cottonseed oil, and in liquid paraffin. Store in airtight containers.

Sorbitan Stearate *(BAN, rINN)*

E491; Estearato de sorbitán; Monoestearato de sorbitán; Sorbitaanisteraatti; Sorbitán, estearato de; Sorbitan Mono-octadecanoate; Sorbitan Monostearate (USAN); Sorbitan, stéarate de; Sorbitani Stearas; Sorbitanmonostearat; Sorbitano stearatas; Sorbitanstearat; Sorbitan-stearát; Szorbitán-sztearát; Сорбитана Стеарат.

$C_{24}H_{46}O_6$ (approximate)

CAS — 1338-41-6.

UNII — NVZ4I0H58X.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Stearate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with stearic acid. A pale yellow, waxy solid. M.p. 50 degrees to 55 degrees. Practically insoluble but dispersible in water; slightly soluble in alcohol. Protect from light.

USNF 31: (Sorbitan Monostearate). A partial ester of sorbitol and its mono- and di-anhydrides with stearic acid. A cream-coloured to tan, hard, waxy solid with a bland odour. Insoluble in cold water and in acetone; dispersible in warm water; soluble, with haze, above 50 degrees in ethyl acetate and in liquid paraffin.

Sorbitan Trioleate *(BAN, USAN, rINN)*

Sorbitaanitrioleaatti; Sorbitan Tri-9-octadecenoate; Sorbitan, trioléate de; Sorbitán, trioleato de; Sorbitani Trioleas; Sorbitano trioleatas; Sorbitantrioleat; Sorbitan-trioleát; Szorbitán-trioleát; Trioleato de sorbitán; Сорбитана Триолеат.

$C_{60}H_{108}O_8$ (approximate)

CAS — 26266-58-0.

UNII — QE6F49RPJ1.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbitan Trioleate). A mixture usually obtained by esterification of 1 mole of sorbitol and its mono- and di-anhydrides per 3 moles of oleic acid. A suitable antoxidant may be added. A pale yellow, light yellowish or brown solid which becomes a brownish-yellow, viscous, oily liquid at about 25 degrees. Relative density about 0.98. Practically insoluble but dispersible in water; slightly soluble in alcohol; soluble in fatty oils. Protect from light.

USNF 31: (Sorbitan Trioleate). A tri-ester of sorbitol and its mono- and di-anhydrides with oleic acid. A yellow to amber-coloured, oily liquid. Insoluble in water, in ethylene glycol, and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in methyl alcohol, in maize oil, in cottonseed oil, and in liquid paraffin. Store in airtight containers.

Sorbitan Tristearate *(BAN, USAN, rINN)*

E492; Sorbitán, triestearato de; Sorbitan Tri-octadecanoate; Sorbitan, Tristéarate de; Sorbitani Tristearas; Triestearato de sorbitán; Сорбитана Тристеарат.

$C_{60}H_{114}O_8$ (approximate)

CAS — 26658-19-5.

UNII — 6LUM696811.

Description. A mixture of the partial tri-esters of sorbitol and its mono- and di-anhydrides with stearic acid.

Uses

Sorbitan esters are polyalcohol ester nonionic surfactants (p. 2164.2). They are lipophilic and are used as emulsifying agents in the preparation of emulsions, creams, and ointments for pharmaceutical and cosmetic use. When used alone they produce stable water-in-oil emulsions but they are frequently used with a polysorbate in varying proportions to produce water-in-oil or oil-in-water emulsions or creams with a variety of different textures and consistencies. Sorbitan esters are also used as emulsifiers and stabilisers in food.

Adverse Effects

There have been occasional reports of hypersensitive skin reactions after the topical application of creams containing sorbitan esters.

Hypersensitivity. References.

1. Finn OA, Forsyth A. Contact dermatitis due to sorbitan monolaurate. *Contact Dermatitis* 1975; **1:** 318.
2. Hannuksela M, *et al.* Allergy to ingredients of vehicles. *Contact Dermatitis* 1976; **2:** 105–10.
3. Austad J. Allergic contact dermatitis to sorbitan monooleate (Span 80). *Contact Dermatitis* 1982; **8:** 426–7.
4. Boyle J, Kennedy CTC. Contact urticaria and dermatitis to Alphaderm. *Contact Dermatitis* 1984; **10:** 178.
5. Hardy MP, Maibach HI. Contact urticaria syndrome from sorbitan sesquioleate in a corticosteroid ointment. *Contact Dermatitis* 1995; **32:** 114.
6. Wakelin SH, *et al.* Sorbitan mono-oleate: a potential allergen in paste bandages. *Contact Dermatitis* 1996; **35:** 377.
7. de Waard-van der Spek FB, *et al.* Allergic contact dermatitis to sorbitan sesquioleate in Adaptic wound dressing. *Contact Dermatitis* 2007; **57:** 54–6.
8. Asarch A, Scheinman PL. Sorbitan sesquioleate, a common emulsifier in topical corticosteroids, is an important contact allergen. *Dermatitis* 2008; **19:** 323–7.
9. Asarch A, Scheinman PL. Sorbitan sesquioleate: an emerging contact allergen. *Dermatitis* 2008; **19:** 339–41.
10. Castanedo-Tardan MP, Jacob SE. Allergic contact dermatitis to sorbitan sesquioleate in children. *Contact Dermatitis* 2008; **58:** 171–2.

Squalane

Cosbiol; Dodecahydrosqualene; Escualano; Perhidroescualeno; Perhydrosqualène; Skvalaani; Skvalan; Skvalanas; Skwalan; Spinacane; Squalan; Squalanum; Szkvalán; Сквалан.

2,6,10,15,19,23-Hexamethyltetracosane.

$C_{30}H_{62}$=422.8

CAS — 111-01-3 (squalane); 111-02-4 (squalene).

UNII — GW89575KF9.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Squalane). A clear, colourless, oily liquid. Relative density about 0.815. It may be of vegetable (unsaponifiable matter of olive oil) or animal (shark liver oil) origin. Practically insoluble in water and in alcohol;

freely soluble in acetone and in cyclohexane; miscible with most fats and oils.

USNF 31: (Squalane). A saturated hydrocarbon obtained by hydrogenation of squalene, an aliphatic triterpene occurring in some fish oils. It is a colourless, almost odourless, transparent oil. Insoluble in water; very slightly soluble in dehydrated alcohol; miscible with chloroform and with ether; slightly soluble in acetone. Store in airtight containers.

Profile

Squalane is a saturated derivative of squalene, a constituent of human sebum. It is miscible with human sebum and is included in topical preparations to increase skin permeability. It is also used as an emollient. Squalene is used similarly and has also been included in nutritional supplements for its supposed antoxidant effect. It is also used as an adjuvant in vaccines.

Adverse effects of squalene. There has been concern[1] about the potential adverse effects of squalene used as an adjuvant in vaccines, which some have attempted to link to the development of Gulf War syndrome after the detection of anti-squalene antibodies in vaccinees with this condition. However, it has been pointed out that in fact these patients had not been given squalene-containing vaccines, that squalene is a normal product of hepatic metabolism, and that antibodies to squalene develop in most adults regardless of whether they receive such vaccines.

1. WHO Global Advisory Committee on Vaccine Safety. Squalene-based adjuvants in vaccines (reviewed 03/12/08). Available at: http://www.who.int/vaccine_safety/topics/adjuvants/squalene/questions_and_answers/en/ (accessed 12/04/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Effaclar H; ***Fr.***: Trioptec; ***Hong Kong***: Physiogel; Tocovid; ***India***: Arjet; Elure; Hidrate; Humidus; ***Israel***: CleanEars; ***Ital.***: Babygella; ***Malaysia***: O'Yes; Tocovid Suprabio with DHA; Tocovid Suprabio; ***Philipp.***: CleanEars; Tocovid Suprabio; ***Port.***: Creme Laser Hidrante†; ***Singapore***: Tocovid; ***USA***: Mimyx†.

Stearic Acid

Acide stéarique; Acido Esteárico; Acido stearico; Acidum stearicum; Esteárico, ácido; Kwas stearowy; Kwas stearynowy; Kyselina stearová; Octadecanoic Acid; Steariinihappo; Stearik asit; Stearinezuur; Stearino rūgštis; Stearinsäure; Stearinsyra; Stearinskābe; Sztearinsav; Стеариновa кислина; Стеариновая Кислота.

CAS — 57-11-4 (stearic acid); 57-10-3 (palmitic acid).
UNII — 4ELV7Z65AP.

NOTE. Stearic acid is sometimes incorrectly called 'stearine' in commerce.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

USNF also includes a purified form.

Ph. Eur. 8: (Stearic Acid). It is obtained from fat or oils from a vegetable or animal source and is a mixture consisting mainly of stearic acid ($C_{18}H_{36}O_2$ = 284.5) and palmitic acid. Stearic Acid 50 contains 40 to 60% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 90%. Stearic Acid 70 contains 60 to 80% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 90%. Stearic Acid 95 contains a minimum of 90% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 96%. White or almost white, waxy, flaky crystals, white or almost white, hard masses, or a white or yellowish-white powder. Practically insoluble in water; soluble in alcohol and in petroleum spirit (50 degrees to 70 degrees).

USNF 31: (Stearic Acid). A mixture of stearic acid and palmitic acid, the content of stearic acid being not less than 40%, and the sum of the two not less than 90%. Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or white or yellowish-white powder, with a slight odour, suggesting tallow. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform and in ether.

USNF 31: (Purified Stearic Acid). It contains not less than 90% stearic acid and not less than 96% of stearic and palmitic acids. Congealing point 66 degrees to 69 degrees.

Profile

Stearic acid is used as a lubricant in making tablets and capsules. It is also used as an emulsifying and solubilising agent.

Stearyl Alcohol

Alcohol estearílico; Alcohol octadecílico; Alcohol Stearylicus; Alcool Stéarylique; Alkohol stearylowy; 1-Octadecanol; Octadecan-1-ol; Octadecyl Alcohol; Stearilo alkoholis; Stearilspirts; Stearylalkohol; Stéarylique, alcool; Stearyylialkoholi; Sztearil-alkohol; Стеариловый Спирт.

$C_{18}H_{38}O$=270.5
CAS — 112-92-5.
UNII — 2KR89I4H1Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Stearyl Alcohol). A mixture of solid alcohols; it contains not less than 95.0% of stearyl alcohol. White or almost white, unctuous flakes, granules, or mass. M.p. 57 degrees to 60 degrees. Practically insoluble in water; soluble in alcohol. When melted, it is miscible with fatty oils, with liquid paraffin, and with melted wool fat.

USNF 31: (Stearyl Alcohol). It contains not less than 90% of stearyl alcohol the remainder consisting chiefly of related alcohols. White unctuous flakes or granules with a faint characteristic odour. M.p. 55 degrees to 60 degrees. Insoluble in water; soluble in alcohol and in ether.

Uses

Stearyl alcohol is used to thicken topical and vaginal ointments and creams, and to increase their water-holding capacity; it has emollient and weak emulsifying properties. Stearyl alcohol is also used in oral solid dosage forms, including modified-release preparations.

Adverse Effects

Stearyl alcohol has been reported to cause hypersensitivity.

Hypersensitivity. Stearyl alcohol is usually considered to have a low potential for sensitisation although there have been isolated case reports of contact dermatitis from its use in topical products.[1-3]

1. Black H. Contact dermatitis from stearyl alcohol in Metosyn (fluocinonide) cream. *Contact Dermatitis* 1975; **1:** 125.
2. de Berker D, *et al*. Contact sensitivity to the stearyl alcohol in Efudix™ cream (5-fluorouracil). *Contact Dermatitis* 1992; **26:** 138.
3. Yesudian PD, King CM. Allergic contact dermatitis from stearyl alcohol in Efudix™ cream. *Contact Dermatitis* 2001; **45:** 313–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: SFC Lotion†.

Multi-ingredient Preparations. ***Arg.***: Caien†.

Stevioside

Esteviósido; Eupatorin; Rebaudin; Stevin; Steviosid; Stévioside; Steviosin; Steviozid; Steviozidas; Szteviozid; Стевиозид.

(4α)-β-D-Glucopyranosyl 13-[(2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]kaur-16-en-18-oate.
$C_{38}H_{60}O_{18}$=804.9
CAS — 57817-89-7.
UNII — 0YON5MXJ9P.

Pharmacopoeias. In *Chin.*

Profile

Stevioside is a glycoside extracted from the leaves of yerba dulce, *Stevia rebaudiana* (Compositae). It has about 300 times the sweetness of sucrose and has been used as a sweetening agent in foods. Both the related glycoside rebaudioside A (rebiana), and an extract of the leaves of *Stevia rebaudiana*, which contains these and other glycosides, have been used similarly. The use of stevioside or stevia leaves as a sweetener has been banned in some countries due to concerns about genotoxicity and possible effects on fertility.

References.

1. Geuns JM. Stevioside. *Phytochemistry* 2003; **64:** 913–21.
2. Wheeler A, *et al*. Pharmacokinetics of rebaudioside A and stevioside after single oral doses in healthy men. *Food Chem Toxicol* 2008; **46** (suppl 7): S54–S60.
3. Brusick DJ. A critical review of the genetic toxicity of steviol and steviol glycosides. *Food Chem Toxicol* 2008; **46** (suppl 7): S83–S91.
4. Chatsudthipong V, Muanprasat C. Stevioside and related compounds: therapeutic benefits beyond sweetness. *Pharmacol Ther* 2009; **121:** 41–54.

Hypertension. The antihypertensive action of stevioside has been investigated. An oral dose of 250 mg three times daily was found to lower blood pressure in patients with mild to moderate hypertension,[1] and 500 mg three times daily decreased blood pressure and the incidence of left ventricular hypertrophy in patients with mild hypertension.[2] There appeared to be no clinically significant effects on blood pressure in a study in normotensive patients given rebaudioside A 1 g daily in divided doses.[3]

1. Chan P, *et al*. A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. *Br J Clin Pharmacol* 2000; **50:** 215–20.
2. Hsieh M-H, *et al*. Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. *Clin Ther* 2003; **25:** 2797–2808.
3. Maki KC, *et al*. The hemodynamic effects of rebaudioside A in healthy adults with normal and low-normal blood pressure. *Food Chem Toxicol* 2008; **46** (suppl 7): S40–S46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Eco-Swett; Edulsan; Natural Sweet; Stevia Dulri.

Multi-ingredient Preparations. ***Austral.***: Fe-Max; ***Chile***: Nature Complex Reduct-Te; ***Ukr.***: Sadifit (Садифит).

Succinic Acid

Acide succinique; Acido succinico; Ácido succínico; Amber Acid; Barnsteenzuur; Bärnstenssyra; Bernsteinsäure; Borostyánkősav; Dihydrofumaric Acid; Dzintarskābe; E363; Ethylenesuccinic Acid; Kwas bursztynowy; Kyselina jantarová; Meripihkahappo; Ravsyre; Янтарная Кислота; Янтарна киселина.

Butanedioic acid.
$C_4H_6O_4$=118.1
CAS — 110-15-6.
UNII — AB6MNQ6J6L.

Pharmacopoeias. In *USNF*.

USNF 31: (Succinic Acid). White, odourless crystals. Soluble in water, in alcohol, and in glycerol; freely soluble in boiling water.

Profile

Succinic acid is a naturally occurring organic acid used as a food additive (as is its sodium salt, p. 2620.1) and as a buffering agent in pharmaceuticals. It is also used as an intermediate in many industrial processes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: XLS; ***Rus.***: Cytoflavin (Цитофлавин); Limontar (ЛИМОНТАР); Remaxol (Ремаксол); ***Ukr.***: Cytoflavin (Цитофлавин); ***USA***: VitaMed MD Iron 21/7.

Used as an adjunct in:. ***Arg.***: Ferdromaco; ***Fr.***: Inofer; ***India***: Hematrine; ***USA***: Chromagen FA; Chromagen Forte; Chromagen†; Multigen; Niferex; Repliva†; Trimagen†; Vitagen Advance.

Homoeopathic Preparations. ***Canad.***: Ubicoenzyme; ***Ger.***: Zitronensaurezyklus-Heel.

Sucrose Esters

E473 (sucrose esters of fatty acids); Sacarosa, ésteres de; Sacchari monopalmitas (sucrose monopalmitate); Sacchari monostearas (sucrose monostearate); Saccharose, monopalmitate de (sucrose monopalmitate); Saccharose, monostéarate de (sucrose monostearate); Sucroésteres; Эфиры Сахарозы.

Pharmacopoeias. *Eur.* (p. vii) and *USNF* include the palmitate and stearate esters.

Ph. Eur. 8: (Sucrose Monopalmitate). A mixture of sucrose monoesters, mainly sucrose monopalmitate, obtained by transesterification of palmitic acid methyl esters of vegetable origin with sucrose. It contains 55.0% monoesters, a maximum 40.0% diesters, and a maximum of 20.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

Ph. Eur. 8: (Sucrose Stearate). A mixture of sucrose esters, mainly sucrose stearate, obtained by transesterification of stearic acid methyl esters of vegetable origin with sucrose. Sucrose stearate type I contains a minimum 50.0% monoesters, a maximum 40.0% diesters, and a maximum of 25.0% for the sum of triesters and polyesters. Sucrose stearate type II contains 20.0 to 45.0% monoesters, 30.0 to 40.0% diesters, and a maximum of 30.0% for the sum of triesters and polyesters. Sucrose stearate type III contains 15.0 to 25.0% monoesters, 30.0 to 45.0% diesters, and 35.0 to 50.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

USNF 31: (Sucrose Palmitate). A mixture of sucrose monoesters, mainly sucrose monopalmitate, obtained by transesterification of palmitic acid methyl esters of vegetable origin with sucrose. It contains a minimum of 55.0%

monoesters, a maximum 40.0% diesters, and a maximum 20.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

USNF 31: (Sucrose Stearate). A mixture of sucrose esters, mainly sucrose stearate, obtained by transesterification of stearic acid methyl esters of vegetable origin with sucrose. Sucrose stearate type I contains a minimum 50.0% monoesters, a maximum 40.0% diesters, and a maximum of 25.0% for the sum of triesters and polyesters. Sucrose stearate type II contains 20.0 to 45.0% monoesters, 30.0 to 40.0% diesters, and a maximum of 30.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

Profile

Sucrose esters are polyalcohol ester nonionic surfactants (p. 2164.2) produced by esterification of 1 or more hydroxyl groups in sucrose with a fatty acid such as stearic or palmitic acid. Commercial sucrose esters are mixtures of the mono-, di-, and tri-esters of palmitic and stearic acids with sucrose; various grades are available. Sucrose esters are used as dispersing, emulsifying, and stabilising agents in food and cosmetic preparations.

Sucrose Octa-acetate

Octaacétate de saccharose; Octaacetylsucrose; Sacarosa, octaacetato de; Sucrose Octaacetate; Sucroseoctaacetat; Сахароза Октаацетат.

$C_{28}H_{38}O_{19}$=678.6

CAS — 126-14-7.

UNII — 07V591057T.

Pharmacopoeias. In *USNF.*

USNF 31: (Sucrose Octaacetate). A white, practically odourless, hygroscopic powder. M.p. not lower than 78 degrees. Soluble 1 in 1100 of water, 1 in 11 of alcohol, 1 in 0.3 of acetone, 1 in 0.5 of toluene, and 1 in 0.6 of benzene; very soluble in chloroform and in methyl alcohol; soluble in ether. Store in airtight containers.

Profile

Sucrose octa-acetate is an intensely bitter substance that has been used as an alcohol denaturant. It is also incorporated into preparations intended to deter nail biting.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Morde X†; ***Switz.***: Bite-X.

Sulfated Castor Oil

Aceite de ricino sulfatado; Ol. Ricin. Sulphat.; Oleum Ricini Sulphatum; Red Oil; Sulfonated Castor Oil; Sulphated Castor Oil; Turkey-red Oil; Ализариновое Масло; Сульфированное Касторовое Масло.

CAS — 8002-33-3.

Profile

Sulfated castor oil is a sulfated oil anionic surfactant (p. 2164.1) made by treating castor oil (p. 2472.1) with sulfuric acid then neutralising with sodium hydroxide. One of its main constituents is the sodium salt of sulfated ricinoleic acid. It is a detergent and wetting agent and has been used as a skin cleanser and emulsifier; it also has industrial and cosmetic applications.

Sulfated hydrogenated castor oil (hydroxystearin sulfate) has been used in the manufacture of hydrophilic ointment bases and other emulsions.

Other castor oil derivatives that have been used as anionic surfactants include sodium ricinoleate and potassium ricinoleate, which are alkali-metal soaps, and zinc ricinoleate (p. 2650.2), a metal soap.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Dermac.

Multi-ingredient Preparations. ***Fr.***: Pyorex.

Sunset Yellow FCF

Amarillo anaranjado S; Amarillo ocaso FCF; CI Food Yellow 3; Colour Index No. 15985; Crelborange S; E110; FD & C Yellow No. 6; Günbatimi Sarisi FCF; Jaune Orangé S; Jaune Soleil; Orange Yellow S; Para-orange; Paraoranssi; Żółcień Pomarańczowa FCF; Zonnegeel FCF; Жёлтый Солнечный Закат.

Disodium 6-hydroxy-5-(4-sulphonatophenylazo)naphthalene-2-sulphonate.

$C_{16}H_{10}N_2Na_2O_7S_2$=452.4

CAS — 2783-94-0.

UNII — H77VEI93A8.

Uses

Sunset yellow FCF is a synthetic azo dye used as a colouring agent in foods, medicines, and cosmetics. Sensitivity reactions have been reported.

Adverse Effects

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies subsequent work failed to confirm these findings and in the UK sunset yellow FCF is considered suitable for use as a food colour.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London. HMSO, 1987.

Hypersensitivity. Hypersensitivity reactions including severe abdominal cramps,[1] Quincke's oedema,[2] and a severe skin reaction[3] have been recorded in individual patients receiving medication that was coloured with sunset yellow FCF.

1. Gross PA, *et al.* Additive allergy: allergic gastroenteritis due to yellow dye #6. *Ann Intern Med* 1989; **111:** 87–8.
2. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; **338:** 393.
3. Rogkakou A, *et al.* Severe skin reaction due to excipients of an oral iron treatment. *Allergy* 2007; **62:** 334–5.

Tamarind Polyose

E411; Tamarind Gum; Tamarind Gum Xyloglucan; Tamarind Kernel Gum; Tamarind Seed Polysaccharide; TSP.

CAS — 39386-78-2.

NOTE. The code E411 has been used for both tamarind seed flour and oat gum. The name Glyloid has been used as a trade mark for tamarind polyose.

Profile

Tamarind polyose is a polysaccharide extracted from the seed kernel of the tamarind tree, *Tamarindus indica* (see p. 1892.2). It is used as a gelling and thickening agent in foods and cosmetics, and industrially in the manufacture of textiles, paper, and gums. Pharmaceutically it has also been used as a tablet binder and as a component of modified-release tablets and mucoadhesive preparations. Tamarind polyose is also used in ophthalmic solutions for dry eye, and has been tried in formulations for prolonged ocular drug release.

References.

1. Rolando M, Valente C. Establishing the tolerability and performance of tamarind seed polysaccharide (TSP) in treating dry eye syndrome: results of a clinical study. *BMC Ophthalmol* 2007; **7:** 5.
2. Kumar CS, Bhattacharya S. Tamarind seed: properties, processing and utilization. *Crit Rev Food Sci Nutr* 2008; **48:** 1–20.
3. Gupta V, *et al.* Tamarind kernel gum: an upcoming natural polysaccharide. *Syst Rev Pharm* 2010; **1:** 50–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Visine Professional†; Visine Tired Eyes†; ***Ger.***: Visine Intensiv; Visine Mude; ***Ital.***: Visine Intensive†; Visine Tired Eyes†.

Multi-ingredient Preparations. ***UK***: Rohto Dry Eye Relief.

Tartrazine

CI Food Yellow 4; Colour Index No. 19140; E102; FD & C Yellow No. 5; Jaune Tartrique; Tartracina; Tartrasiin; Tartratsiini; Tartrazin.; Tartrazina; Tartrazinas; Tartrazol Yellow; Tartrazyna; Тартразин.

It consists mainly of trisodium 5-hydroxy-1-(4-sulphonatophenyl)-4-(4-sulphonatophenylazo)pyrazole-3-carboxylate.

$C_{16}H_9N_4Na_3O_9S_2$=534.4

CAS — 1934-21-0.

UNII — I753WB2F1M.

Uses

Tartrazine is a synthetic azo dye used as a colouring agent in foods, cosmetics, and medicines.

Adverse Effects

In addition to classical hypersensitivity reactions (see below), tartrazine has been considered to be implicated in the aggravation of hyperactive behaviour in children, as discussed under Colouring Agents, p. 2163.2.

Hypersensitivity. There have been many reports of reactions to tartrazine including angioedema, asthma, urticaria, and anaphylactic shock. Some of the reports have dealt with cross-sensitivity, especially with aspirin, although the connection with aspirin has been questioned.[1] A suggested incidence[2] of tartrazine sensitivity is 1 in 10 000. The mechanism of the reactions may not necessarily be immunological.[3]

In considering the reports of tartrazine sensitivity or intolerance the Food Advisory Committee in the UK[1] reported that similar evidence of intolerance might well be obtained for a variety of natural food ingredients if as many studies were conducted on them as on tartrazine. The Committee considered that tartrazine posed no more problems than other colours or food ingredients and recommended that the continued use of tartrazine in food was acceptable. However, use of tartrazine in medicines appears to be diminishing.

A systematic review[4] noted that there was no evidence that tartrazine makes asthma worse, nor did avoiding it make asthma any better.

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. Anonymous. Tartrazine: a yellow hazard. *Drug Ther Bull* 1980; **18:** 53–5.
3. Murdoch RD, *et al.* Tartrazine induced histamine release in vivo in normal subjects. *J R Coll Physicians Lond* 1987; **21:** 257–61.
4. Ardern K, Ram FSF. Tartrazine exclusion for allergic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 18/04/07).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Viticolor.

Tetrachloroethane

Acetylene Tetrachloride; Tetrachloroetan; Tetracloroetano; Tetracloroetano simétrico; Tetracloruro de acetileno; Тетрахлорэтан.

1,1,2,2-Tetrachloroethane.

$C_2H_2Cl_4$=167.8

CAS — 79-34-5.

Description. Tetrachloroethane is a colourless liquid with a chloroform-like odour. B.p. about 146 degrees. Wt per mL about 1.59 g. Store in airtight containers.

Uses

Tetrachloroethane is used as an industrial solvent.

Adverse Effects and Treatment

As for Carbon Tetrachloride, p. 2174.3. Tetrachloroethane is probably the most toxic of the chlorinated hydrocarbons. Poisoning can occur through percutaneous absorption as well as after ingestion or inhalation.

Handling. Suitable precautions should be taken to avoid skin contact with tetrachloroethane as it can penetrate skin and produce systemic toxicity.

Tetrachloroethylene

Czterochlorek etylenu; PERC; Perchloroethylene; Perchloroéthylène; Percloroetileno; Perkloretylen; Tetrachlooretheen; Tetrachlorethen; Tetrachlorethylen; Tetrachloroeten; Tetrachloroethene; Tétrachloroéthylène; Tetrachloroethylenum; Tetracloroetene; Tetracloroetilè; Tetracloroetileno; Тетрахлороетен; Тетрахлорэтилен.

C_2Cl_4=165.8

CAS — 127-18-4.

UNII — TJ904HH8SN.

Uses and Administration

Tetrachloroethylene is a chlorinated hydrocarbon widely used as a solvent in industry. It was formerly given orally as an anthelmintic, but has been superseded by equally effective and less toxic drugs.

Adverse Effects and Treatment

As for Carbon Tetrachloride, p. 2174.3. Symptoms, especially after ingestion, are less severe with tetrachloroethylene than with carbon tetrachloride.

The vapour or liquid may be irritating to skin or mucous membranes.

Tetrachloroethylene may be implicated in volatile substance abuse (see under Toluene, p. 2216.3). Depend-

ence may follow habitual inhalation of small quantities of tetrachloroethylene vapour.

References to adverse effects of tetrachloroethylene.

1. Bagnell PC, Ellenberger HA. Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. *Can Med Assoc J* 1977; **117:** 1047–8.
2. WHO. Tetrachloroethylene. *Environmental Health Criteria 31.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc31.htm (accessed 30/06/04)
3. WHO. Tetrachloroethylene health and safety guide. *IPCS Health and Safety Guide 10.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg010.htm (accessed 30/06/04)
4. Health and Safety Executive. Tetrachloroethylene (tetrachloroethene, perchloroethylene). *Toxicity Review 17.* London: HMSO, 1987.
5. Mutti A, *et al*. Nephropathies and exposure to perchloroethylene in dry-cleaners. *Lancet* 1992; **340:** 189–93.

Pharmacokinetics

Tetrachloroethylene is slightly absorbed from the gastrointestinal tract; absorption is increased in the presence of alcohol and fats or oils. It is absorbed after inhalation and after direct contact with the skin. It is excreted unchanged in expired air; initial elimination is rapid but a proportion may be retained and excreted slowly.

Metabolites of tetrachloroethylene, mainly trichloroacetic acid, have been found in the urine.

Thaumatin *(BANJ)*

E957; Katemfe; Taumatin; Taumatina; Taumatyna; Thaumatine; Тауматин.

CAS — 53850-34-3.

UNII — KNC9Q0EE6G.

Profile

Thaumatin is a protein extracted from the fruit of *Thaumatococcus daniellii* (Marantaceae). It is a mixture of polypeptides, mainly thaumatin I and thaumatin II, each consisting of 207 amino acid residues and having a molecular weight of about 22 000. The amino-acid range excludes histidine. Thaumatin is an odourless, cream-coloured powder with an intensely sweet taste. The sweetness builds up gradually but persists for up to an hour, and has 2000 to 3000 times the sweetness of sucrose. It is approved as a sweetener and flavour modifier in foods, beverages, and pharmaceuticals.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Talin.

Theobroma

Cacao en polvo; Cacao or Cocoa Powder; Chocolate; Teobroma; Theobrom.; Какао.

*ATC Herb — HA05BA5004 (*Theobroma cacao*: seed).*

UNII — D9108TZ9KG.

Pharmacopoeias. In *USNF*.

USNF 31: (Chocolate). A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao* (Sterculiaceae).

Theobroma Oil

Beurre de cacao; Burro di cacao; Butyrum Cacao; Cacao Butter; Cacao Oleum; Cacaoboter; Cocoa Butter; Kaakaovoi; Kakaobutter; Kakaofett; Kakaosmör; Kakaosmør; Kakaóvaj; Kakaové máslo; Kakaový olej; Manteca de cacao; Manteiga de Cacau; Masło kakaowe; Ol. Theobrom.; Olej kakaowy; Oleum Cacao; Oleum Theobromatis; Tłuszcz kakaowy; Какао-Масло; Масло Какао.

CAS — 8002-31-1.

UNII — 512OYT1CRR.

Pharmacopoeias. In *Br., Fr., Ger., Jpn*, and *Pol*. Also in *USNF*.

BP 2014: (Theobroma Oil). The solid fat obtained from the roasted seeds of *Theobroma cacao*. A yellowish-white, somewhat brittle, solid fat, with a slight odour of cocoa. M.p. 31 degrees to 34 degrees. Slightly soluble in alcohol; freely soluble in chloroform, in ether, and in petroleum spirit (boiling range, 40 degrees to 60 degrees). Store at a temperature not exceeding 25 degrees.

USNF 31: (Cocoa Butter). A fat obtained from the seeds of *Theobroma cacao* (Sterculiaceae). It is a yellowish-white, usually brittle solid with a faint agreeable odour. M.p. 31 degrees to 35 degrees. Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in chloroform and in ether.

Uses

Theobroma is used as a flavoured basis for tablets and lozenges. Theobroma oil is used as a basis for suppositories. If it is heated to more than 36 degrees during preparation the solidification point will be appreciably lowered due to the formation of metastable states; this leads to subsequent difficulty in setting. Theobroma oil is a major ingredient of chocolate.

Precautions

Breast feeding. The latest available guidance from the American Academy of Pediatrics[1] stated that irritability or increased bowel activity have been reported in infants whose mothers ate excessive amounts of chocolate (16 ounces (about 450 g) or more daily).

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Asthmatee EF-EM-ES; ***Braz.***: Pomaderme; ***Chile***: Cellenergy; ***Fr.***: Amana Cellium; ***India***: Aloat NC; ***Malaysia***: Palmer's Cocoa Butter Formula Nappy Rash Ointment; Palmer's Cocoa Butter Formula Nursing Cream; Palmer's Cocoa Butter Formula Scar Serum; Palmer's Cocoa Butter Formula; ***Singapore***: Rosken Skin Repair High Potency.

Pharmacopoeial Preparations

USNF 31: Chocolate Syrup.

Toluene

Fenilmetano; Metacida; Methylbenzene; Metilbenceno; Phenylmethane; Toluè; Tolueen; Tolueeni; Toluen; Toluenas; Toluène; Tolueno; Toluol; Toluole; Toluols; Толуол; Толуен.

C_7H_8=92.14

CAS — 108-88-3.

UNII — 3FPU23BG52.

Description. Toluene is a colourless, volatile, flammable liquid with a characteristic odour. Wt per mL about 0.87 g. B.p. about 111 degrees. Store in airtight containers.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of toluene:

Tolley; Tolly; Tooly.

Uses

Toluene is widely used as an industrial solvent.

Adverse Effects, Treatment, and Precautions

Toluene has similar acute toxicity to benzene (p. 2171.2) but is a less serious industrial hazard. Adverse effects are treated similarly to benzene. It is a common constituent of adhesives and is frequently implicated in volatile substance abuse (below). Commercial toluene may contain benzene, and this may perhaps influence the pattern of adverse effects. In addition to acute toxic effects, toluene abuse has been associated with damage to the nervous system, kidneys, liver, heart, and lungs (see below). Chronic poisoning caused by occupational exposure to toluene has resulted mainly in nervous system disorders.

Reviews.

1. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
2. WHO. Toluene. *Environmental Health Criteria 52.* Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc52.htm (accessed 30/06/04)
3. Health and Safety Executive. Toluene. *Toxicity Review 20.* London: HMSO, 1989.
4. IARC/WHO. Toluene. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 829–64. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

The non-neurological toxicity after volatile substance abuse has been reviewed.[1] Chronic toluene abuse may result in damage to the *kidneys*; renal tubular acidosis and glomerulonephritis have been described, although evidence for the latter is only circumstantial. Renal tubular acidosis has been regarded as reversible; however, there are reports suggesting that damage to renal tubules is permanent.

The few reports linking chronic toluene abuse with *liver* damage cover hepatomegaly and hepatorenal failure. Effects on the *heart* are usually acute; sudden death has resulted from ventricular arrhythmias. Chronic myocarditis with fibrosis has been reported. Chronic toluene inhalation can cause damage to the *lungs*. Autopsies in a few patients have shown changes indicative of emphysema.

Nervous system toxicity has also been reviewed.[2-5] Cerebellar dysfunction has occurred after toluene abuse; an acute intoxication phase, which usually subsides within weeks of abstinence, is followed by a chronic phase which may be permanent. Diffuse CNS disease such as encephalopathy, dementia, and multifocal brain injury may also develop. An association between toluene abuse and peripheral neuropathy has not been confirmed; muscle weakness may be a result of electrolyte and fluid disturbances. Choreoathetosis, epilepsy, and optic atrophy with anosmia and deafness have been reported after toluene abuse. Some of these neurological effects, particularly cerebellar effects and diffuse CNS disease have also occurred after occupational exposure to toluene.

Some studies have noted an excess mortality from motor neurone diseases among leather workers,[6] although this has not been confirmed by others.[7] Occupational exposure to solvents has been postulated as the cause.[6] Of the many agents currently used in leather work, those with known or probable neurotoxic effects are *n*-hexane, methyl butyl ketone, toluene, and methyl ethyl ketone. Ethyl acetate is commonly used but has no recognised neurological adverse effects.[6] A Swedish study of workers in a range of occupations has found some support for an increased risk of amyotrophic lateral sclerosis after occupational exposure to solvents, probably toluene and petrol.[8] Another Swedish study found an association between multiple sclerosis and occupational exposure to solvents, especially white spirit and petrol.[8]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.
3. White RF, Proctor SP. Solvents and neurotoxicity. *Lancet* 1997; **349:** 1239–43.
4. Filley CM, *et al*. The effects of toluene on the central nervous system. *J Neuropathol Exp Neurol* 2004; **63:** 1–12.
5. Yücel M, *et al*. Toluene misuse and long-term harms: a systematic review of the neuropsychological and neuroimaging literature. *Neurosci Biobehav Rev* 2008; **32:** 910–26.
6. Hawkes CH, *et al*. Motoneuron disease: a disorder secondary to solvent exposure? *Lancet* 1989; **i:** 73–6.
7. Martyn CN. Motoneuron disease and exposure to solvents. *Lancet* 1989; **i:** 394.
8. Gunnarsson L-G, Lindberg G. Amyotrophic lateral sclerosis in Sweden 1970-83 and solvent exposure. *Lancet* 1989; **i:** 958.

Abuse. Since they are volatile liquids and have CNS effects many organic solvents, including toluene, are implicated in volatile substance abuse. Clinical features of intoxication are similar to those of alcohol intoxication, with initial CNS stimulation followed by CNS depression, which may progress to delirium, convulsions, coma, and death. Sudden death due to cardiac arrhythmias has also been reported.

References.

1. Proceedings of a meeting on substance abuse. *Hum Toxicol* 1989; **8:** 253–334.
2. Ashton CH. Solvent abuse. *BMJ* 1990; **300:** 135–6.
3. Brouette T, Anton R. Clinical review of inhalants. *Am J Addict* 2001; **10:** 79–94.

Handling. Suitable precautions should be taken to avoid skin contact with toluene as it can penetrate skin and produce systemic toxicity.

Pregnancy. Retrospective surveys of pregnancies in mothers with a history of solvent abuse suggested that toluene abuse during pregnancy can cause preterm delivery and perinatal death. It was suggested that toluene may be teratogenic as intra-uterine exposure was associated with prenatal and postnatal growth retardation, microcephaly, impairment of mental development, and facial dysmorphia.[1-4] It is uncertain if these results can be extrapolated to cover occupational exposure. Although some studies of occupational exposure to solvents during pregnancy have suggested an association,[5,6] exposure is usually to several solvents[6] and there is little consistent evidence to link exposure to any particular one with spontaneous abortion, retarded fetal development, still-birth, or congenital malformation.[7]

1. Wilkins-Haug L, Gabow PA. Toluene abuse during pregnancy: obstetric complications and perinatal outcomes. *Obstet Gynecol* 1991; **77:** 504–9.
2. Pearson MA, *et al*. Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 1994; **93:** 211–15.
3. Arnold GL, *et al*. Toluene embryopathy: clinical delineation and developmental follow-up. *Pediatrics* 1994; **93:** 216–20.
4. Bowen SE, Hannigan JH. Developmental toxicity of prenatal exposure to toluene. *AAPS J* 2006; **8:** E419–E424.
5. McDonald JC, *et al*. Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. *Br J Ind Med* 1987; **44:** 527–33.
6. Khattak S, *et al*. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA* 1999; **281:** 1106–9.
7. Scott A. *BMJ* 1992; **304:** 369.

Pharmacokinetics

Toluene is absorbed after inhalation and ingestion, and to some extent through the skin. It is rapidly metabolised mainly by oxidation to benzoic acid which is excreted in the urine largely as the glycine conjugate hippuric acid; *o*-, *m*-, and *p*-cresol are minor urinary metabolites. Some unchanged toluene is excreted through the lungs.

Tonzonium Bromide *(rINN)*

Bromuro de tonzonio; NC-1264; NSC-5648; Thonzonium Bromide (USAN); Tonzonii Bromidum; Tonzonio, bromuro de; Tonzonium, Bromure de; Тонзония Бромид.
Hexadecyl[2-(*N*-*p*-methoxybenzyl-*N*-pyrimidin-2-ylamino) ethyl]dimethylammonium bromide.
$C_{32}H_{55}BrN_4O$=591.7
CAS — 553-08-2.
UNII — JI2B19CR0R.

Profile

Tonzonium bromide is a cationic surfactant. As an additive in ear drops and aerosol sprays it has been claimed to promote tissue contact by dispersion and penetration of cellular debris and exudate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Coly-Mycin S Otic; Cortisporin-TC.

Tragacanth

Dragant; E413; Goma adragante; Goma Alcatira; Goma de tragacanto; Gomma adragante; Gomme Adragante; Gum Dragon; Gum Tragacanth; Kitre; Trag.; Tragacanta; Tragacantha; Tragacanto; Tragakanta; Tragakantas; Tragant; Traganth; Tragantmézga; Tragantti; Трагакантовая Камедь.
CAS — 9000-65-1.
*ATC Herb — HA06AC5001 (*Astragalus gummifer*: mucilage).*
UNII — 2944357O2O.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8 (Tragacanth). The air-hardened gummy exudation flowing naturally or obtained by incision from the trunk and branches of *Astragalus gummifer* and some other species of *Astragalus* (Leguminosae) from western Asia. It occurs as thin, flattened, ribbon-like, white or pale yellow, translucent, horny strips. When reduced to a powder it forms a mucilaginous gel with about ten times its weight of water. Protect from light.

USNF 31: (Tragacanth). The dried gummy exudation from *Astragalus gummifer* or other Asiatic species of *Astragalus* (Leguminosae). It occurs as odourless, flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces. It is white to weak yellow, translucent, and horny in texture. Powdered tragacanth is white to yellowish-white.

Uses

Tragacanth forms viscous solutions or gels with water, depending on the concentration. It is used in pharmaceutical manufacturing as a suspending agent and as an emulsifying agent. In dispensing aqueous preparations of tragacanth, the powdered tragacanth is first dispersed in a wetting agent, such as alcohol, to prevent agglomeration on the addition of water.

Tragacanth is also used for similar purposes in the food industry.

Adverse Effects

Hypersensitivity reactions, sometimes severe, have occurred rarely after the ingestion of products containing tragacanth. Contact dermatitis has been reported after the external use of tragacanth.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Vaselina Emulsionada.

Trehalose *(BAN)*

Mycose; Trealosio; Trehaloosi; Trehalosa; α,α-Trehalose; Tréhalose; Trehalosum; Trehalóz; Trehaloza; Trehalóza; Tremalose; Треналоза.
α-D-Glucopyranosyl-α-D-glucopyranoside.
$C_{12}H_{22}O_{11}$=342.3
CAS — 99-20-7 (anhydrous trehalose); 6138-23-4 (trehalose dihydrate).
UNII — B8WCK70T7I (trehalose); 7YIN7J07X4 (trehalose dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *USNF.*

Ph. Eur. 8 (Trehalose Dihydrate). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. pH of a 10% solution in water is 4.5 to 6.5.

USNF 31: (Trehalose). A white, odourless, non-hygroscopic crystalline powder. Soluble in water, the solubility increasing with increasing temperature; practically insoluble in dehydrated alcohol. pH of a 10% solution is 4.5 to 6.5. Store in airtight containers.

Profile

Trehalose is a naturally-occurring disaccharide used by various organisms as an energy source and to protect against the effects of freezing or drying. It is used as a filler and taste-masking agent in pharmaceutical formulations, and as a stabiliser for freeze-drying and lyophilisation. It is also used in cell cryopreservation and in the food and cosmetic industries.

References.

1. Richards AB, *et al.* Trehalose: a review of properties, history of use and human tolerance, and results of multiple safety studies. *Food Chem Toxicol* 2002; **40:** 871–98.

Tributyl Acetylcitrate

Acetyltributyl Citrate; Tributilo acetilcitratas; Tributylacetylcitrat; Tributyl-acetylcitrát; Tributyle, acétylcitrate de; Tributylis acetylcitras; Tributyyliasetyylisitraatti; Трибутилацетилцитрат.
Tributyl 2-(acetyloxy)propane-1,2,3-tricarboxylate.
$C_{20}H_{34}O_8$=402.5
CAS — 77-90-7.
UNII — 0ZBX0N59RZ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Tributyl Acetylcitrate). A clear oily liquid. Immiscible with water; miscible with alcohol and with dichloromethane.

USNF 31: (Acetyltributyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Tributyl acetylcitrate is a plasticiser and flavour used in pharmaceutical manufacturing and in the food industry.

Tributyl Citrate

Butyl Citrate; Tributylu cytrynian; Трибутилцитрат.
Tributyl 2-hydroxy-1,2,3-propanetricarboxylate.
$C_{18}H_{32}O_7$=360.4
CAS — 77-94-1.
UNII — 827D5B1B6S.

Pharmacopoeias. In *USNF.*

USNF 31: (Tributyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Tributyl citrate is a citric acid ester used as a plasticiser in tablet and other pharmaceutical coatings.

Tri-*n*-butyl Phosphate

Fosfato de tributilo; Tributyl Phosphate; Tributyl-fosfát; Tributylis Phosphas; Tri-*n*-butylis Phosphas; Tri(*n*-butyl) phosphate; Tri-n-butilo fosfatas; Tri-n-butyle, phosphate de; Tri-n-butylfosfat; Tri-n-butylis Phosphas; Tri-n-butyylifosfaatti; Три-н-бутилфосфат.
Phosphoric acid tributyl ester.
$C_{12}H_{27}O_4P$=266.3
CAS — 126-73-8.
UNII — 95UAS8YAF5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tri-*n*-butyl Phosphate; Tributyl Phosphate BP 2014). A clear, colourless to pale yellow liquid. Slightly soluble in water; miscible with alcohol. Protect from light.

Profile

Tri-*n*-butyl phosphate is an organophosphate that is used as a solvent and plasticiser.

References.

1. WHO. Tri-*n*-butyl phosphate. *Environmental Health Criteria 112.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc112.htm (accessed 29/06/04)

Trichloroethane

Methylchloroform; Metilcloroformo; α-Trichloroethane; Tricloroetano; α-Tricloroetano; Triclorometilmetano; Трихлорэтан.
1,1,1-Trichloroethane.
$C_2H_3Cl_3$=133.4
CAS — 71-55-6.
UNII — 113C650IR1.

Description. Trichloroethane is a colourless, slightly hygroscopic liquid. Sp. gr. about 1.31. B.p. about 74 degrees. Practically insoluble in water; miscible with alcohol, with chloroform, and with ether. Non-flammable. Store in airtight containers.

Uses

Trichloroethane has wide applications as an industrial solvent. It is commonly used in dry cleaning, typewriter correction fluids, and as a solvent for plaster removal.

Adverse Effects and Treatment

Acute intoxication with trichloroethane may result in initial excitement followed by CNS depression with dizziness, drowsiness, headache, lightheadedness, and ataxia, progressing to coma and death from respiratory depression in severe cases. Death may also occur from ventricular arrhythmias. Fatalities have occurred after accidental exposure to high concentrations of trichloroethane in confined spaces. Trichloroethane is commonly used in dry cleaning, type correction fluids, and as a solvent for plaster removal and is frequently implicated in volatile substance abuse (see under Toluene, p. 2216.3).

Nausea, vomiting, and diarrhoea have been reported after ingestion. Trichloroethane is a mild irritant.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures. Activated charcoal is unlikely to be of benefit after ingestion and gastric lavage is contra-indicated. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

Reviews.

1. Health and Safety Executive. 1,1,1-Trichloroethane. *Toxicity Review 9.* London: HMSO, 1984.
2. WHO. 1,1,1-Trichloroethane. *Environmental Health Criteria 136.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc136.htm (accessed 30/06/04)
3. IARC/WHO. 1,1,1,-Trichloroethane. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 881–903. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)
4. The Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of trichloroethane. *Int J Toxicol* 2008; **27** (suppl 4): 107–38.

Effects on the heart. Effects on the heart of trichloroethane abuse were considered usually to be acute, and sudden death from ventricular arrhythmias had occurred in abusers. There have, however, been a few cases of chronic cardiotoxicity after both abuse and occupational exposure.[1]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.

Effects on the liver. According to a brief review of non-neurological toxicity from volatile substance abuse,[1] there were no reports of damage to the liver after the abuse of trichloroethane. There was a report of hepatotoxicity after acute occupational exposure, but this might have been a hypersensitivity reaction. There was another report[2] of fatty liver disease in 4 patients with a history of occupational exposure to trichloroethane although there has been some debate over the validity of the association for 2 of these cases.[3,4] Chronic active hepatitis associated with trichloroethane exposure has since been reported.[5]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Hodgson MJ, *et al.* Liver disease associated with exposure to 1,1,1-trichloroethane. *Arch Intern Med* 1989; **149:** 1793–8.
3. Guzelian PS. 1,1,1-Trichloroethane and the liver. *Arch Intern Med* 1991; **151:** 2321–2.
4. Hodgson MJ, Vanthiel DH. 1,1,1-Trichloroethane and the liver. *Arch Intern Med* 1991; **151:** 2322 and 2325–6.
5. Croquet V, *et al.* Hépatite chronique active probablement induite par le 1,1,1-trichloroéthane. *Gastroenterol Clin Biol* 2003; **27:** 120–2.

Effects on the skin. Scleroderma has been reported[1] in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Pharmacokinetics

Trichloroethane is absorbed after inhalation and ingestion, and through intact skin. Small amounts are metabolised to trichloroethanol and trichloroacetic acid and excreted in the urine, but it is largely excreted unchanged through the lungs over a period of days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Zoff.

Triethyl Citrate

Citronensäuretriethylester; E1505; Triethyl citrát; Triëthylcitraat; Triethylcitrat; Triéthyle, citrate de; Triethyli Citras; Triethylis Citras; Trietil-citrát; Trietilo citratas; Trietilo, citrato de; Trietylcitrat; Trietyylisitraatti; Триэтилцитрат.

Triethyl 2-hydroxy-1,2,3-propanetricarboxylate.

$C_{12}H_{20}O_7$=276.3

CAS — 77-93-0.

UNII — 8Z96QXD6UM.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8 (Triethyl Citrate). A clear, viscous, colourless or almost colourless, hygroscopic liquid. Soluble in water; miscible with alcohol; slightly soluble in fatty oils. Store in airtight containers.

USNF 31: (Triethyl Citrate). A practically colourless oily liquid. Soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Profile

Triethyl citrate is a plasticiser used in pharmaceutical manufacturing and in the food and cosmetics industries.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Uriage Desodorante Tri-Actif; ***Fr.***: Spirial.

Triglycerol Diisostearate

Polyglyceryl-3 Diisostearate; Triglyceroldiisostearat; Triglyceroli Diisostearas; Triglyceryl Diisostearate.

CAS — 66082-42-6.

UNII — 46P231IQV8.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8 (Triglycerol Diisostearate). A mixture of polyglycerol diesters of mainly isostearic acid, obtained by esterification of polyglycerol and isostearic acid. The polyglycerol consists mainly of triglycerol. A clear, yellowish, viscous liquid. Practically insoluble in water; miscible with alcohol and with fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Polyglyceryl 3 Diisostearate). A mixture of polyglycerol diesters of mainly isostearic acid, obtained by esterification of polyglycerol and isostearic acid. The polyglycerol consists mainly of triglycerol. A viscous liquid. Insoluble in water; soluble in alcohol, in dichloromethane, in liquid paraffin, and in vegetable oils. Store in airtight containers. Protect from heat, light, and moisture.

Profile

Triglycerol diisostearate is a polyalcohol (polyglycerol) ester nonionic surfactant (p. 2164.2) used as an emulsifier in topical preparations. Other polyglycerol esters are used similarly; polyglycerol polyricinoleate (E476) is used as an emulsifier in foods.

Turmeric

Açafrão-da-terra; CI Natural Yellow 3; Cúrcuma; Curcumae Rhizoma; Dažinė ciberžolė; Gurkemeie; Gurkemeje; Gurkmeja; Haldi; Indian Saffron; Kunir; Kunyit; Kurkuma; Maustekurkuma; Ostryż Długi; Termeric; Zerdeçal; Куркума; Турмерик.

CAS — 458-37-7.

*ATC Herb — HA05AW5005 (*Curcuma longa*: rhizome); HA03AW5020 (*Curcuma longa*: rhizome).*

UNII — 856YO1Z64F.

Pharmacopoeias. In *Chin*, *Eur.* (see p. vii), and *Jpn*. Also in *US* which also includes a powdered form and a powdered extract.

Ph. Eur. 8: (Turmeric Rhizome; Curcumae Longae Rhizoma). The whole, cured (by boiling or steaming), dried rhizome of *Curcuma longa* (*Curcuma domestica*) with roots and outer surface removed. It contains not less than 25 mL/kg of essential oil and not less than 2.0% of dicinnamoyl methane derivatives expressed as curcumin, ($C_{21}H_{20}O_6$ = 368.4), both calculated with reference to the anhydrous drug. It has a spicy odour.

USP 36: (Turmeric). The dried rhizome of *Curcuma longa* (*C. domestica*) (Zingiberaceae). It is commonly known as Curcuma, Curcum, Haridra, and Indian Saffron. It contains not less than 3.0% of curcuminoids, calculated on the dried basis. Protect from light and moisture.

Uses

Turmeric is the dried rhizome of *Curcuma longa* (Zingiberaceae). Its main use is as a constituent of curry powders and other condiments, but it is also used as a yellow colouring agent in foods, either as the dried powder or as the oleoresin extract. It contains curcumin (p. 2180.1), which is the main colouring component, and other curcuminoids (p. 2489.3).

Turmeric and related Curcuma species, such as Javanese turmeric (*Curcuma xanthorrhiza*, p. 2636.2) and zedoary (*Curcuma zedoaria*) have been used in preparations indicated for biliary and gastrointestinal disorders and have also been promoted as anti-inflammatories. Turmeric oil has also been used.

Turmeric has been investigated for a wide range of pharmacological actions thought to be due to its curcuminoid content; curcumin and curcuminoid extracts have also been studied (see below).

Turmeric is a commonly used Ayurvedic medicine.

Reviews of the properties of turmeric and curcumin. See also reference to the properties of curcuminoids (p. 2489.3).

1. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. *Planta Med* 1991; **57:** 1–7.
2. Grant KL, Schneider CD. Turmeric. *Am J Health-Syst Pharm* 2000; **57:** 1121–2.
3. Ringman JM, *et al.* A potential role of the curry spice curcumin in Alzheimer's disease. *Curr Alzheimer Res* 2005; **2:** 131–6.
4. Singh S, Khar A. Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anticancer Agents Med Chem* 2006; **6:** 259–70.
5. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. *Adv Exp Med Biol* 2007; **595:** 105–25.
6. Sharma RA, *et al.* Pharmacokinetics and pharmacodynamics of curcumin. *Adv Exp Med Biol* 2007; **595:** 453–70.
7. Strimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid Redox Signal* 2008; **10:** 511–45.
8. Hatcher H, *et al.* Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci* 2008; **65:** 1631–52.
9. Wongcharoen W, Phrommintikul A. The protective role of curcumin in cardiovascular diseases. *Int J Cardiol* 2009; **133:** 145–51.
10. Bengmark S, *et al.* Plant-derived health: the effects of turmeric and curcuminoids. *Nutr Hosp* 2009; **24:** 273–81.
11. Epstein J, *et al.* Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. *Br J Nutr* 2010; **103:** 1545–57.

Adverse Effects

Effects on the thyroid. There has been some concern about the safety of turmeric oleoresin after reports of adverse thyroid changes in *pigs*.[1,2]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 30/05/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Turmerik; ***China***: Du Di (杜迪); ***Indon.***: Rheumakur†; ***Pol.***: Solaren; ***Spain***: Encimenal.

Multi-ingredient Preparations. ***Austral.***: Arthriforte†; Boswellia Complex; Extralife Arthri-Care†; Extralife Liva-Care†; Joint Mobility†; PulmaCo; Vitanox; ***Austria***: Apozema†; Spasmo Claim†; ***Canad.***: Milk Thistle†; Optomega; Painease; ***Cz.***: Cholagol; ***Fr.***: Aromavital†; Cledist; Expuryl; Hepatoum; Silibiol; ***Ger.***: Chol-Arbuz NF; Ventracid N†; ***Hong Kong***: Procosa II†; ***Hung.***: Antifront; Antifront; Cholagol; Munipyrin; ***India***: Aglotus; Baknil; FN-T-Tus†; Healing Dust; ***Indon.***: Aptivium Liver Support†; Cursil; Diapet; Entrodiar†; Fitodiar; Heparviton NF; Hepasil; Lanagogum; Lecur; Nutrijoint; Osimax; Ositin; Procur Plus; Proliva; Tripid; Vidoran Emulsion Rasa; Vidoran Plus; ***Israel***: Coltect†; ***Ital.***: Cinarepa; Cistefi; Clebolider†; Reumafort; ***Jpn***: Cabe 2 New; Eki Cabe U; ***Mex.***: Ifuchol; Procosa II; Rodan; ***Philipp.***: Cogent db+; ***Pol.***: Chelicur; Cholitol; ***Rus.***: Cholagol (Холагол); Doktor Mom (Доктор Мом); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); ***S.Afr.***: Lewensessens; ***Singapore***: Artrex; Essentials†; Hepasil DTX†; Procosa II†; ***Switz.***: Kernosan 24; ***UK***: Arheumacare; BackOsamine; ***Ukr.***: Antifront (Антифронт); Antifront (Антифронт); Artritosamin (Артритозамин); Bon-Apetit (Бон-Аппетит); Cholagol (Холагол); Choliver (Холивер)†; Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Hepahealth (Гепахелс); Memory Booster (Мемори Бустер); Olesan (Олесан)†; Vitrum Beauty Elite (Витрум Бьюти Элит).

Homoeopathic Preparations. ***Fr.***: Billerol.

Tyloxapol *(BAN, USAN, rINN)*

Superinone; Tiloxapol; Tyloksapoli; Tyloxapolum; Тилоксапол.

CAS — 25301-02-4.

ATC — R05CA01.

ATC Vet — QR05CA01.

UNII — Y27PUL9H56.

Pharmacopoeias. In *US*.

USP 36: (Tyloxapol). A polymer of 4-(1,1,3,3-tetramethylbutyl)phenol with ethylene oxide and formaldehyde. A viscous amber liquid, sometimes slightly turbid, with a slight aromatic odour. Slowly but freely miscible with water; soluble in chloroform, in glacial acetic acid, in carbon disulfide, in carbon tetrachloride, in toluene, and in benzene. A 5% solution has a pH of 4.0 to 7.0. Tyloxapol should not be allowed to come into contact with metals. Store in airtight containers.

Uses and Administration

Tyloxapol is an alkyl aryl polyether alcohol nonionic surfactant (polymerised macrogol aryl ether; see p. 2164.2). It is used in solutions for cleansing contact lenses and artificial eyes. Aqueous solutions have been used for inhalation as a mucolytic for tenacious bronchopulmonary secretions. Tyloxapol has also been used as a vehicle for aerosol medication and for antibacterials given in irrigation solutions for pyogenic bone or joint infections.

Adverse Effects

Slight inflammation of the eyelids has been reported after prolonged use of aqueous inhalations of tyloxapol. It has been reported that occasional febrile reactions may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Enuclene; ***Ger.***: Tacholiquin; ***NZ***: Enuclene; ***USA***: Enuclene.

Multi-ingredient Preparations. ***Austral.***: Blink-N-Clean; ***Malaysia***: Cationorm.

Vanilla

Baunilha; Semilla de vainilla; Vaina de vainilla; Vainilla; Vanilė; Vanilj; Vanilja; Vanilje; Vanilka; Vanilla Beans; Vanilla Pods; Vanille; Vanilya; Wanilia; Ваниль; Ванилия.

UNII — Q74T35078H.

Pharmacopoeias. In *USNF*.

USNF 31: (Vanilla). The cured, full-grown, unripe fruit of *Vanilla planifolia*, often known in commerce as Mexican, Bourbon, or Madagascar vanilla, or of *V. tahitensis*, known in commerce as Tahitian vanilla (Orchidaceae). Vanilla that has become brittle should not be used. Store in airtight containers at a temperature not exceeding 8 degrees.

Profile

Vanilla is used as a flavour and in perfumery. However, the odour and flavour of vanilla are not entirely due to vanillin (see below) but depend on the presence of other aromatic substances. Preparations of vanilla have been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Cyclotelia.

Pharmacopoeial Preparations

USNF 31: Vanilla Tincture.

Vanillin

Vainillina; Vaniliini; Vanilin; Vanilinas; Vanillic Aldehyde; Vanilline; Vanillinum; Wanilina; Ванилин.

4-Hydroxy-3-methoxybenzaldehyde.

$C_8H_8O_3$=152.1

CAS — 121-33-5.

UNII — CHI530446X.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet*. Also in *USNF*.

Ph. Eur. 8 (Vanillin). White or slightly yellowish crystalline needles or powder. M.p. 81 degrees to 84 degrees. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Vanillin). Fine, white to slightly yellow crystals, usually needle-like, having an odour and taste suggestive of vanilla. M.p. 81 degrees to 83 degrees. Soluble 1 in 100 of water at 25 degrees, 1 in 20 of water at 80 degrees, 1 in 20 of glycerol; freely soluble in alcohol, in chloroform, in ether, and in solutions of fixed alkali hydroxides. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Profile

Vanillin is used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Pulmex Baby; Pulmex†; ***Turk.***: Musilaks.

Pharmacopoeial Preparations
BP 2014: Tolu-flavour Solution.

Vegetable Carbon

Bitkisel Kömür; Carbon Black; Carbón vegetal; Cendres végétales; Charbon végétal; Colour Index No. 77268:1; E153; Negro vegetal; Vegetable Black; Уголь Растительный.
UNII — 4XYU5U00C4.

NOTE. The name Carbon Black has also been used as a synonym for Channel Black, a colouring agent not used in food; care should be taken to avoid confusion between the two compounds.

Profile

Vegetable carbon, which consists essentially of finely divided carbon, is produced by the carbonisation of vegetable material such as peat or wood. It is used as a colouring agent for medicines, foodstuffs, and cosmetics.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Rus.***: Iris-Plus (Ирис-Плюс).

Vegetable Fatty Oils

Kasvirasvaöljyt; Olea Herbaria; Oljor, feta, vegetabiliska; Растительные Масла Жирные.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Vegetable Fatty Oils). Vegetable fatty oils are mainly solid or liquid triglycerides of fatty acids that may contain small amounts of other lipids such as waxes, free fatty acids, partial glycerides, or unsaponifiable matters. They are obtained from the seeds or fruits of plants by expression and/or solvent extraction, and may then be refined or hydrogenated with the addition of a suitable antoxidant if necessary. The following are defined:

- *virginoil*: the oil obtained from raw materials of special quality by mechanical procedures such as cold expression or centrifugation
- *refinedoil*: the oil obtained by expression and/or solvent extraction, and subsequently, either alkali refining (followed by bleaching and deodorisation) or physical refining
- *hydrogenatedoil*: an oil obtained by expression and/or solvent extraction, and subsequently, either alkali refining or physical refining, then possible bleaching, followed by drying, hydrogenation, and subsequently bleaching and deodorisation.

Only phosphoric acid and alkali refined oils may be used in the preparation of parenteral dosage forms.

Hydrogenated Vegetable Oil

Aceite vegetal hidrogenado.

Pharmacopoeias. In *Br.* *Jpn* allows under the title Hydrogenated Oil a product from fish, other animals or vegetables. Also in *USNF*.

BP 2014: (Hydrogenated Vegetable Oil). A mixture of triglycerides of fatty acids of vegetable origin. An almost white, fine powder at room temperature and a pale yellow, oily liquid above its m.p. of 57 degrees to 70 degrees. Practically insoluble in water; soluble in chloroform, in hot isopropyl alcohol, and in petroleum spirit. Store at a temperature of 8 degrees to 25 degrees.

USNF 31: (Hydrogenated Vegetable Oil). A mixture of triglycerides of fatty acids. Type 1 Hydrogenated Vegetable Oil occurs as a fine, white powder, beads, or small flakes; m. p. 57 degrees to 85 degrees. Type 2 Hydrogenated Vegetable Oil occurs as a plastic (semi-solid) or flakes, having a softer consistency than Type 1; m.p. 20 degrees to 50 degrees.

Insoluble in water; soluble in chloroform, in hot isopropyl alcohol, and in petroleum spirit. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Vegetable fatty oils are generally solid or liquid triglycerides of fatty acids that may contain small amounts of other lipids. They are obtained from the seeds or fruits of plants by expression and/or solvent extraction, and may then be refined or hydrogenated with the addition of a suitable antoxidant if necessary. They are fixed oils (expressed oils) and do not evaporate on warming as opposed to essential oils (ethereal oils, volatile oils), which evaporate readily and are usually obtained from their aromatic plant source by distillation. Some fixed vegetable oils are used to modify the consistency of ointments and for their emollient properties. They have also been used as vehicles for fat-soluble substances such as vitamins.

Hydrogenated vegetable oil is refined, bleached, hydrogenated, and deodorised vegetable oil stearins consisting mainly of the triglycerides of stearic and palmitic acids. It is used as a tablet lubricant and as an ointment or suppository basis.

White Spirit

Acquaragia; Lakibensiin; Lakkasprii; Siedegrenzbenzin; Stoddard Solvent; Terpentinersatz; Testbenzin; Trementina; Waschbenzin; Уайтспирит.
CAS — 64742-82-1 (white spirit type 1); 64741-92-0 (white spirit type 2); 64742-48-9 (white spirit type 3); 64742-88-7 (white spirit type 0); 8052-41-3 (Stoddard solvent).
UNII — 37LNJ1116R (Stoddard solvent).

Description. White spirit is a mixture of hydrocarbons available as a colourless liquid. Store in airtight containers.

Uses

White spirit is used as an industrial solvent. It is available in various grades. One grade available in the USA is known as Stoddard solvent.

Adverse Effects and Treatment

As for Kerosene, p. 2191.1.

References to the toxicity of white spirit.[1]

For discussion of neurotoxicity after occupational exposure to solvents including white spirit, see under Toluene, p. 2216.2.

1. WHO. Selected petroleum products. *Environmental Health Criteria 20.* Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc020.htm (accessed 30/06/04)

Wool Alcohols

Alcoholes Adipis Lanae; Alcoholes de lana; Alcoholes de lanolina; Alcoholia Lanae; Alcolanum; Alcools de graisse de laine; Alkoholy tuku z ovčí vlny; Gyapjúviaszalkoholok; Lanalcolum; Lanolin Alcohols; Ullfettalkoholer; Villa-alkoholit; Vilnų riebalų alkoholiai; Wollwachsalkohole; Wool Wax Alcohols; Спирты Шерстяного Жира.
CAS — 8027-33-6.
UNII — 884C3FA9HE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Wool Alcohols). A mixture of sterols and higher aliphatic alcohols obtained from wool fat and containing not less than 30.0% of cholesterol. A suitable antoxidant may be added. A pale yellow to brownish-yellow, brittle mass becoming plastic on heating. M.p. not lower than 56 degrees. Practically insoluble in water; slightly soluble in alcohol (90%); soluble in boiling dehydrated alcohol, and in dichloromethane. Store in well-filled containers. Protect from light.

USNF 31: (Lanolin Alcohols). A mixture of sterols, aliphatic alcohols, and triterpenoid alcohols obtained by the hydrolysis of wool fat. It may contain not more than 0.1% of a suitable antoxidant. It is a hard, waxy amber solid with a characteristic odour. M.p. not below 56 degrees. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform, in ether, and in petroleum spirit. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Wool alcohols is incompatible with coal tar, ichthammol, resorcinol, and phenol.

Profile

Wool alcohols is an emulsifying agent and emulsion stabiliser used in the preparation of water-in-oil creams and ointments. It increases the water absorbing capacity of hydrocarbon mixtures; the addition of 5% of wool alcohols permits a threefold increase in the amount of water that can be incorporated in soft paraffin and such emulsions are not 'cracked' by the addition of weak acids.

It has an emollient action on the skin and is used in preparations for dry skin and dry eyes.

Derivatives of wool alcohols with similar uses include acetylated wool alcohols and ethoxylated wool alcohols.

Wool alcohols may cause hypersensitivity (but see also under Wool Fat, below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Refresh Lacri-Lube; ***Fin.***: Lacri-Lube; ***Ger.***: Coliquifilm; ***Irl.***: Lacri-Lube; Oilatum Emollient; ***Israel***: Adinol†; ***Ital.***: Lacrilube; ***NZ***: Lacrilube; ***Switz.***: Coliquifilm; ***UK***: Dermalo; Lacri-Lube; Oilatum Emollient; ***USA***: Aquaphor Healing Ointment; DermaPhor; Hydrocerin; Hydrocerin; Refresh Lacri-Lube; Refresh PM.

Pharmacopoeial Preparations
BP 2014: Wool Alcohols Ointment.

Wool Fat

Adeps lanae; Adeps lanae hydrogenatus (wool fat, hydrogenated); Anhydrous Lanolin; Cera Lanae; Graisse de laine; Graisse de laine hydrogénée (wool fat, hydrogenated); Graisse de Suint Purifiée; Gyapjúviasz; Lanoléine; Lanolin; Lanolina; Lanolina anhidra; Lanolinum; Purified Lanolin; Refined Wool Fat; Suarda; Tuk z ovčí vlny; Tuk z ovčí vlny hydrogenovaný (wool fat, hydrogenated); Ullfett; Villarasva; Vilnų riebalai; Wollfett; Wollwachs; Ланолин; Шерстяной Жир.
CAS — 8006-54-0.
UNII — 7EV65EAW6H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include Hydrous Wool Fat which is prepared by the addition of water to wool fat.

Eur. also includes Hydrogenated Wool Fat.

US also includes Modified Lanolin.

Ph. Eur. 8: (Wool Fat). A purified, anhydrous, waxy material obtained from the wool of the sheep (*Ovis aries*). A suitable antoxidant may be added. A yellow, unctuous substance. When melted, it is a clear or almost clear, yellow liquid. Drop point 38 degrees to 44 degrees. 10 g absorbs not less than 20 mL of water. Practically insoluble in water; slightly soluble in boiling dehydrated alcohol; it forms an opalescent solution in petroleum spirit. Store at a temperature not exceeding 25 degrees.

Ph. Eur. 8: (Wool Fat, Hydrogenated; Adeps Lanae Hydrogenatus). A mixture of higher aliphatic alcohols and sterols obtained from the direct, high-pressure, high-temperature hydrogenation of anhydrous wool fat during which the esters and acids present are reduced to corresponding alcohols. A suitable antoxidant may be added. A white or pale yellow, unctuous substance. M.p. 45 degrees to 55 degrees. Practically insoluble in water; soluble in boiling dehydrated alcohol and in petroleum spirit. Store in well-filled containers. Protect from light.

Ph. Eur. 8: (Wool Fat, Hydrous; Adeps Lanae Cum Aqua). A mixture of 75% of wool fat and 25% of water. A suitable antoxidant may be added. A pale yellow, unctuous substance. Drop point 38 degrees to 44 degrees. Store at a temperature not exceeding 25 degrees.

USP 36: (Lanolin). A purified wax-like substance obtained from the wool of the sheep, *Ovis aries* (Bovidae). It is a yellow tenacious unctuous mass with a slight characteristic odour. Melting range 38 degrees to 44 degrees. It contains not more than 0.25% of water. It may contain not more than 0.02% of a suitable antoxidant. Insoluble in water, but mixes without separation with about twice its weight of water; sparingly soluble in cold alcohol; more soluble in hot alcohol; freely soluble in chloroform and in ether. Store at a temperature preferably between 15 degrees and 30 degrees.

USP 36: (Modified Lanolin). It is Lanolin that has been processed to reduce the contents of free lanolin alcohols and detergent and pesticide residues. It contains not more than 0.25% of water. It may contain not more than 0.02% of a suitable antoxidant. Store in airtight, preferably rust-proof, containers and preferably at a temperature of 15 degrees to 30 degrees.

Uses

Wool fat is used in the formulation of water-in-oil creams and ointments. When mixed with a suitable vegetable oil or with soft paraffin it gives emollient creams that penetrate the skin. It can absorb about 30% of water. Wool fat is also used in other topical, vaginal, rectal, and ophthalmic preparations.

Derivatives and modifications of wool fat include hydrogenated wool fat (hydrogenated lanolin), hydrous wool fat (hydrous lanolin), poloxyl lanolin (ethoxylated lanolin), isopropyl lanolate, lanolin oil, and lanolin wax.

Adverse Effects and Precautions

Wool fat can cause hypersensitivity reactions.

Hypersensitivity. Wool fat is widely regarded as a common sensitising agent, but the true extent of allergy to it is controversial.[1] Suspected sensitivity reactions have proved dif-

ficult to reproduce in skin patch testing.[2] The allergens are unknown but are thought to be in the alcoholic fraction. A retrospective study[3] of more than 24 000 patients with eczema who received skin patch testing found that sensitivity reactions to a standard patch reagent of wool alcohols 30% in soft paraffin were rare; an average of 1.7% of patients per year showed sensitivity.

1. Lee B, Warshaw E. Lanolin allergy: history, epidemiology, responsible allergens, and management. *Dermatitis* 2008; **19:** 63–72.
2. Wolf R. The lanolin paradox. *Dermatology* 1996; **192:** 198–202.
3. Wakelin SH, *et al.* A retrospective analysis of contact allergy to lanolin. *Br J Dermatol* 2001; **145:** 28–31.

Pesticide residues. Concerns have been raised in the past about pesticide residues in wool fat,[1-3] because of the possible risk to breast-fed infants whose mothers were using wool fat-based nipple ointments. Official published standards such as Ph. Eur. and USP now include limits for pesticide levels in wool fat.

1. Copeland CA, *et al.* Pesticide residue in lanolin. *JAMA* 1989; **261:** 242.
2. Cade PH. Pesticide in lanolin. *JAMA* 1989; **262:** 613.
3. Copeland CA, Wagner SL. Pesticide in lanolin. *JAMA* 1989; **262:** 613.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Lansinoh; ***Canad.***: PureLan; ***Ger.***: Oleo Tull; ***India***: Nipcare; ***S.Afr.***: Duratears; ***Turk.***: Duratears; ***UK***: Evolve Plus; ***USA***: Lan-O-Smooth; Lansinoh.

Multi-ingredient Preparations. ***Arg.***: Alcon Lagrimas; Crema Para Paspaduras†; Dr Selby; Ninderm; ***Austral.***: Alpha Keri; Duratears; E45; Poly Visc; Soothe'n Heal†; ***Austria***: Tiroler Steinol; ***Belg.***: Duratears; Lacrytube; ***Canad.***: A & D Ointment; Akwa Tears; Flexitol Heel Balm†; Huile de Bain Therapeutique; Lotion Lubrifiante Calmante Hydratante†; Optilube; Secol; Tears Naturale PM; ***Chile***: Duratears; Lacri-Lube; Pasta Lassar; ***Fr.***: Jouvence; ***Ger.***: Sofra-Tull sine; Vita-POS; ***Gr.***: Duratears; Fissan-Pate; ***Hong Kong***: Duratears; ***India***: Elure; ***Indon.***: Yanthi Baby Oil†; ***Israel***: Duratears; Kamil Blue; Lacrimol†; Pedisol†; Vita-POS; ***Malaysia***: Balneum†; Duratears Naturale; Lacrilube; ***Mex.***: Acuafil Ungena; ***Neth.***: Duratears Z; ***NZ***: Alpha Keri; BK; DP Lotion - HC; DP; Hydroderm; Oralife Peppermint; ***Pol.***: E45; ***Singapore***: Balneum; Duratears; Lacrilube†; ***Spain***: Lubrifilm†; Pasta Lassar Imba; ***Switz.***: Nasomed; ***Thai.***: Duratears; ***UK***: Alpha Keri; Hewletts†; Lubri-Tears†; Melrose; VitA-POS; ***USA***: Akwa Tears†; Alpha Keri; Bodi Oil; Bottom Better†; Dermadrox; Dry Eyes; Duratears Naturale; Geri-Silk; Lacri-Gel; Lacri-Lube; Lansinoh Diaper Rash; Lantiseptic; LubriFresh PM; LubriTears; Paladin; Palomar E; Systane Nighttime; ***Venez.***: Oleoderm.

Pharmacopoeial Preparations
BP 2014: Simple Eye Ointment; Simple Ointment.

Xanthan Gum

Corn Sugar Gum; E415; Goma de xantána; Gomma di xantano; Gomme xanthane; Guma ksantanowa; Ksantaanikumi; Ksantano lipai; Polysaccharide B 1459; Xantán gumi; Xantangummi; Xanthaangom; Xantham Gum; Xanthangummi; Xanthani gummi; Xanthanová klovatina; Ксантановa Гума; Ксантановая Камедь.

CAS — 11138-66-2.
UNII — TTV12P4NEE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. & (Xanthan Gum). A gum produced by fermentation of a carbohydrate with *Xanthomonas campestris* and purified. It is the sodium, potassium, or calcium salt of a high-molecular-weight polysaccharide containing D-glucose, mannose, and glucuronic acid. It also contains not less than 1.5% of pyruvic acid, calculated with reference to the dried substance. A white or yellowish-white, free-flowing powder. Soluble in water giving a highly viscous solution; practically insoluble in organic solvents. A 1% solution in water has a pH of 6.0 to 8.0.

USNF 31: (Xanthan Gum). A high-molecular-weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris* and purified. It contains D-glucose, D-mannose, and D-glucuronic acid. It is prepared as the sodium, potassium, or calcium salt. A cream-coloured powder. Soluble in hot or cold water. Its solutions are neutral to litmus.

Profile

Xanthan gum is used in pharmaceutical manufacturing as a suspending, stabilising, thickening, and emulsifying agent. It is also used similarly in the food industry.

Suspensions of crushed tablets or insoluble powders made with xanthan gum were reported to be preferable to those made with tragacanth.[1]

The stability was generally good and only a small number of drugs had been found to be incompatible (amitriptyline, tamoxifen, and verapamil).[1] For extemporaneous dispensing, a 1% solution of xanthan gum with hydroxybenzoate, prepared in advance, was diluted to 0.5% with water when preparing the suspension.

Xanthan gum was found to be a suitable suspending vehicle for delivering antispasmodics topically along the length of the oesophagus in patients with oesophageal spasm.[2] Coagulation of the gum had occurred when it was used for suspensions of certain film-coated tablets.

1. Anonymous. "Extremely useful" new suspending agent. *Pharm J* 1986; **237:** 665.
2. Evans BK, Fenton-May V. Keltrol. *Pharm J* 1986; **237:** 736–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Ronfnyl.

Multi-ingredient Preparations. ***Fr.***: Cyamox; Cyamox; Herpclair; ***Ital.***: Noremifa; Panamir; Resource Gelificata†; Xanternet; ***Switz.***: Prevalin; ***Turk.***: Xialine; ***USA***: Mimyx†.

Pharmacopoeial Preparations
USNF 31: Xanthan Gum Solution.

Xylene

Dimethylbenzene; Dimetilbenceno; Ksilenas; Ksilols; Ksylen; Xilè; Xilene; Xileno; Xyleen; Xylen; Xylène; Xylol; Xylole; Ксилол.

C_8H_{10}=106.2

CAS — 1330-20-7; 108-38-3 (m-xylene); 95-47-6 (o-xylene); 106-42-3 (p-xylene).
UNII — D856J1047R (xylene mixed); O9XS864HTE (m-xylene); Z2474E14QP (o-xylene); 6WAC1O477V (p-xylene).

Description. Xylene is a mixture of the *o-*, *m-*, and *p-*isomers in which the *m*-isomer predominates. It is a colourless, volatile, flammable liquid. Wt per mL about 0.86 g. B.p. about 138 degrees to 142 degrees. Store in airtight containers.

Uses

Xylene is used as an industrial and pharmaceutical solvent and in preparations to dissolve ear wax.

Adverse Effects, Treatment, and Precautions

The acute toxicity of xylene is similar to that of benzene (p. 2171.2) but is less marked. Adverse effects are treated similarly to benzene.

Xylene has been implicated in volatile substance abuse (see under Toluene, p. 2216.3). Commercial xylene may contain benzene, and this may perhaps influence the pattern of adverse effects.

Xylene should not be used to dissolve ear wax if the tympanic membrane is perforated.

References.

1. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
2. Health and Safety Executive. Xylenes. *Toxicity Review 26*. London: HMSO, 1992.
3. WHO. Xylenes. *Environmental Health Criteria 190*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc190.htm (accessed 30/06/04)
4. IARC/WHO. Xylenes. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans* 1999; **71:** 1189–1208. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 10/06/09)

Effects on the eyes. Eye injuries due to accidental contact with paints containing xylene have been reported.[1] The injuries resembled alkali burns and were treated in a similar manner. Xylene-induced keratopathy has been reviewed.[2]

1. Ansari EA. Ocular injury with xylene - a report of two cases. *Hum Exp Toxicol* 1997; **16:** 273–5.
2. Trujillo F, *et al.* Xylene keratopathy: a case report and review of the literature. *Cornea* 2003; **22:** 88–90.

Effects on the nervous system. References.

1. Arthur LJH, Curnock DA. Xylene-induced epilepsy following innocent glue sniffing. *BMJ* 1982; **284:** 1787.
2. Roberts FP, *et al.* Near-pure xylene causing reversible neuropsychiatric disturbance. *Lancet* 1988; **ii:** 273.
3. Draper TH, Bamiou DE. Auditory neuropathy in a patient exposed to xylene: case report. *J Laryngol Otol* 2009; **123:** 462–5.

Handling. Suitable precautions should be taken to avoid skin contact with xylene as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Xylene is absorbed after inhalation, ingestion, and to some extent through the skin. It is rapidly metabolised by oxidation to the corresponding *o-*, *m-*, or *p*-methylbenzoic (toluic) acids and excreted in the urine largely as the glycine conjugate, methylhippuric acid (toluric acid). Xylenols are minor metabolites and are excreted in the urine as the glucuronide and sulfate conjugates. Some unchanged xylene is excreted through the lungs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Cerulyx; ***Fr.***: Cerulyse; ***Ital.***: Cerulisina.

Xylitol *(BAN)*

E967; Ksilitolis; Ksylitol; Ksylitoli; *meso*-Xylitol; Xilit; Xilitol; Xylit; Xylitolum; Ксилит.

$C_5H_{12}O_5$=152.1

CAS — 87-99-0 (xylitol); 16277-71-7 (D-xylitol).
UNII — VCQ006KQ1E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. & (Xylitol). A white or almost white crystalline powder or crystals. M.p. 92 degrees to 96 degrees. Very soluble in water; sparingly soluble in alcohol.

USNF 31: (Xylitol). White crystals or crystalline powder. Crystalline xylitol has a melting range between 92 degrees and 96 degrees. It has a sweet taste and produces a cooling sensation in the mouth. Soluble 1 in about 0.65 of water; sparingly soluble in alcohol.

Uses and Administration

Xylitol is a polyhydric alcohol (polyol) related to the pentose sugar, xylose (p. 2649.2). It is similar in sweetness to sucrose and is used as a bulk sweetener in foods and as a sweetener or excipient in pharmaceuticals. Xylitol is also used as a sweetening agent in sugar-free preparations as it is noncariogenic and is less likely to cause dental caries than sucrose. It may also have a role in the prevention of dental caries (see below). It was formerly considered as a substitute for glucose in intravenous nutrition but such use has generally been abandoned due to adverse effects.

Dental caries. Preparations containing xylitol appear to have a useful role in the prevention of dental caries (p. 192.3),[1-6] both by stimulating salivation and by direct effects. They may also aid dental remineralisation.[7]

1. Edgar WM. Sugar substitutes, chewing gum and dental caries—a review. *Br Dent J* 1998; **184:** 29–32.
2. Gales MA, Nguyen T-M. Sorbitol compared with xylitol in prevention of dental caries. *Ann Pharmacother* 2000; **34:** 98–100.
3. Maguire A, Rugg-Gunn AJ. Xylitol and caries prevention—is it a magic bullet? *Br Dent J* 2003; **194:** 429–36.
4. van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? *Caries Res* 2004; **38:** 286–93.
5. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. *J Am Dent Assoc* 2006; **137:** 190–6. Correction. *ibid.*; 447.
6. Milgrom P, *et al.* Xylitol pediatric topical oral syrup to prevent dental caries: a double-blind randomized clinical trial of efficacy. *Arch Pediatr Adolesc Med* 2009; **163:** 601–7.
7. Mäkinen KK. Sugar alcohols, caries incidence, and remineralization of caries lesions: a literature review. *Int J Dent* 2010; **2010:** 981072.

Otitis media. There is some evidence that xylitol chewing gum[1,2] or syrup,[2,3] used 5 times daily, has a preventative effect against acute otitis media (p. 195.2) in children. However, another study[4] found that xylitol had no effect when given only during acute respiratory-tract infections, and use of a higher dose 3 times daily also proved ineffective.[5] A systematic review[6] concluded that use of xylitol was of benefit but that further study was needed to establish more convenient dosage regimens.

1. Uhari M, *et al.* Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ* 1996; **313:** 1180–4.
2. Uhari M, *et al.* A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics* 1998; **102:** 879–84.
3. Uhari M, *et al.* Xylitol in preventing acute otitis media. *Vaccine* 2001; **19:** S144–S147.
4. Tapiainen T, *et al.* Xylitol administered only during respiratory infections failed to prevent acute otitis media. Abstract: *Pediatrics* 2002; **109:** 302. Full version: http://pediatrics.aappublications.org/cgi/reprint/109/2/e19 (accessed 23/08/10)
5. Hautalahti O, *et al.* Failure of xylitol given three times a day for preventing acute otitis media. *Pediatr Infect Dis J* 2007; **26:** 423–7.
6. Danhauer JL, *et al.* Xylitol as a prophylaxis for acute otitis media: systematic review. *Int J Audiol* 2010; **49:** 754–61.

Adverse Effects

Large amounts of xylitol taken orally may cause diarrhoea and flatulence. Hyperoxaluria, which can occur with intravenous infusion, is unlikely after oral use. Hyperuricaemia, changes in liver-function tests, and acidosis (including lactic acidosis) have occurred after intravenous infusion.

Hypersensitivity. A report of oral erosions caused by contact hypersensitivity to xylitol-containing chewing gum.[1]

1. Hanakawa Y, *et al.* Xylitol as a causative agent of oral erosive eczema. *Br J Dermatol* 2005; **152:** 821–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Trident; ***China***: De Li Er Xin (得力尔欣); Ya Qing Ning (雅清宁); ***Ger.***: Xylit†; ***Philipp.***: Xylogel; ***USA***: XyliMelts.

Multi-ingredient Preparations. ***Arg.***: Bucal Hyper Sensitive; Bucal Tac Whitening Gel; Emoform Total; Esmedent; Fluorogel 2001 para Dientes Sensibles; Fluorogel 2001; Minamint; Periobacter; Periodent; Solucion Oral; Tac Fluor; ***Chile***: Oralgene; ***Ger.***: GX; InfectoGripp; Infesol XE; Parentamin X-E†; Periplasmal XE; Saliva natura; Saseem; ***India***: Hermin; Kidodent; ***Indon.***: Aminofusin L; Comafusin Hepar; Intrafusin SX-E; Precopar; Trifluid; ***Jpn***: Amizet XB; Proteamin; Trifluid; Triparen; ***Mex.***: Dentsiblen†; Fluoxytil†; Periodentyl; Perioxidin†; ***Neth.***: Saliva Orthana; ***Philipp.***: Xylorinse; ***UK***: AS Saliva Orthana; AS Saliva Orthana; Biotene Oralbalance; Saliva Natura; ***Ukr.***: Glauxyl (Глюксил)†; Gluxyl (Глюксил); Infesol 40 (Инфезол 40); Xylat (Ксилат); ***USA***: Optimoist; SalivaSure.

Yellow 2G

107; Acid Light Yellow 2G; Acid Yellow 17; Amarillo 2G; CI Food Yellow 5; Colour Index No. 18965; Geel 2G; Geltonasis 2G; Gul 2G; Jaune 2G; Żółcień 2G; Жёлтый 2G.

Disodium 2,5-dichloro-4-[5-hydroxy-3-methyl-4-(4-sulphonatophenylazo)pyrazol-1-yl]benzenesulphonate.

$C_{16}H_{10}Cl_2N_4Na_2O_7S_2$=551.3

CAS — 6359-98-4.

Profile

Yellow 2G is a synthetic azo dye used as a colouring agent in cosmetics.

Zein

Zeína; Зеин.

CAS — 9010-66-6 (zeins).

UNII — 80N308T1NN.

Pharmacopoeias. In *Chin.* Also in *USNF.*

USNF 31: (Zein). A prolamine derived from corn, *Zea mays* (Gramineae). A white to yellow powder. Insoluble in water and in acetone; readily soluble in acetone-water mixtures between the limits of 60% and 80% of acetone by volume; soluble in aqueous alcohols, in ethoxyethanol, in glycols, in furfuryl alcohol, in tetrahydrofurfuryl alcohol, and in aqueous alkaline solutions of pH 11.5 and above; insoluble in all anhydrous alcohols except methyl alcohol.

Profile

Zein is used as a tablet binder and coating agent for pharmaceutical preparations and foodstuffs. It has been used as a substitute for shellac.

Zinc Stearate

Cinko stearatas; Cink-sztearát; Cynku stearynian; Estearato de Zinc; Sinkkistearaatti; Stearan zinečnatý; Zinc, stéarate de; Zinci stearas; Zinkstearat; Стеарат Цинка.

Zinc octadecanoate.

CAS — 4991-47-3 (zinc palmitate); 557-05-1 (zinc stearate).

UNII — H92E6QA4FV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Zinc Stearate). Zinc stearate $[(C_{17}H_{35}CO_2)_2Zn = 632.3]$ may contain varying proportions of zinc palmitate $[(C_{15}H_{31}CO_2)_2Zn = 576.2]$ and zinc oleate $[(C_{17}H_{33}CO_2)_2Zn = 628.3]$. A light, white or almost white, amorphous powder, free from gritty particles. Practically insoluble in water and in dehydrated alcohol.

USP 36: (Zinc Stearate). A compound of zinc with a mixture of solid organic acids obtained from fats and consisting mainly of variable proportions of zinc stearate $[(C_{17}H_{35}CO_2)_2Zn = 632.3]$ and zinc palmitate $[(C_{15}H_{31}CO_2)_2Zn = 576.2]$. A fine, white, bulky powder, free from grittiness, with a faint characteristic odour. Insoluble in water, in alcohol, and in ether.

Uses

Zinc stearate is a metal soap anionic surfactant (p. 2164.1). It is used as a lubricant for granules in the manufacture of tablets and capsules and also has industrial and cosmetic applications. It has been used as a soothing and protective application in the treatment of skin inflammation and may be used as a powder or as a cream.

Adverse Effects

Zinc stearate inhalation has caused fatal pneumonitis, particularly in infants.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Prurisedan; ***Israel***: Acti Talc; ***Ital.***: Steril Zeta; ***Switz.***: Hydrocortisone compositum†; ***Thai.***: Banocin; ***UK***: Simpsons; ***Venez.***: Borocanfor.

Pharmacopoeial Preparations

USP 36: Compound Clioquinol Topical Powder.

Radiopharmaceuticals

Radioactive compounds are used in nuclear medicine as sources of radiation for radiotherapy and for diagnostic purposes. They have many uses in research and industry.

Radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose. Usually they consist of a cold kit, a non-radioactive chemical component or drug, coupled with a radionuclide. The chemical component or drug localises in the target area and the radionuclide emits radiation. Some radiopharmaceuticals are designed to act as a signal generator, providing relatively harmless emissions to provide physiological imaging for diagnosis (tracer procedures or studies), whereas others are therapeutic in nature and intentionally harmful to targeted tissue, in order to destroy aberrant or cancerous cells. Radiopharmaceuticals are prepared in many forms, including intravenous injections, gases, aerosols, oral solutions, and capsules.

The aim of this chapter is to provide background information on the radionuclides that are used as radiopharmaceuticals. Care is required in the preparation, handling, use, and disposal of these compounds; they are thus best dealt with by those with suitable experience and training.

Atomic Structure

The classical model of the atom represents it as a central positively charged nucleus around which negatively charged electrons revolve in orbits. The electrons are arranged round the atomic nucleus in a series of 'shells' in each of which is a limited number of orbits. Although now superseded in physics, this model remains useful as a convenient simplification in chemistry and radiochemistry.

The nucleus consists of 2 main kinds of particles: protons, each of unit positive charge, and neutrons, which are uncharged; the total number of these particles in the nucleus is known as the *mass number* (A).

The number of protons in the nucleus is known as the *atomic number* (Z). All the atoms of a particular chemical element have the same atomic number, but while the number of protons is constant, the number of neutrons (N) in the atoms, and thus their masses (mass numbers), may vary. These different forms of the same element are known as *isotopes* of the element and these isotopes differ in some of their physical properties.

Each electron carries a negative charge which is of the same magnitude as the positive charge of the proton, so that in the neutral atom the number of electrons is equal to the number of protons in the nucleus.

Some isotopes may be stable, the differences between them arising solely from their difference in mass; others may be radioactive (*radioisotopes*), their unstable nuclei changing spontaneously and emitting particles or electromagnetic waves, or both, in an attempt to move towards a more stable nuclear arrangement (see also Radioactive Decay, below).

Most of the naturally occurring isotopes are stable, though there are some that are unstable and therefore radioactive, for example, uranium-235. In addition, artificial radionuclides are prepared by converting stable nuclei into unstable forms or naturally occurring radionuclides may be prepared by artificial means.

Nomenclature. The symbol used for a nuclide is a development of the chemical symbol for the atom, with the mass number (A) as a left or preceding superscript and the atomic number (Z) as a left subscript; the neutron number (N) has occasionally been given as a right subscript. Thus, element X may be depicted as: ${}^{A}_{Z}X_{N}$. However, the neutron number may be inferred so it is almost always omitted. Thus the symbols for the 3 hydrogen isotopes—common hydrogen, deuterium, and tritium—would be ${}^{1}_{1}H$, ${}^{2}_{1}H$, and ${}^{3}_{1}H$, and the symbols for the 3 naturally occurring uranium isotopes ${}^{234}_{92}U$, ${}^{235}_{92}U$, and ${}^{238}_{92}U$. As the atomic number can also be inferred from the chemical symbol it is usual to omit the subscript and refer to, for example, ${}^{3}H$ or ${}^{235}U$. It is also common practice to write out the full name of the element followed by the mass number, e.g. chromium-51 for ${}^{51}Cr$.

Radioactive Decay

Radionuclides decay (transform to more stable nuclides) in various ways that depend upon their initial structure. Each radionuclide has a distinct half-life, which is the time taken for a given quantity to decay to one half of its initial value or original activity. The activity of radionuclides is measured in terms of the rate of transformation or disintegration. The SI unit for radioactivity is the becquerel (Bq), which equals 1 disintegration/second (or 1 transformation/second). The SI units are metric and technically are the preferred method of quantifying radioactivity. However, the older system using curies (Ci) may still be used in practice; $1\ Ci = 3.7 \times 10^{10}\ Bq$.

Radioactive decay or transformation may involve the emission of charged particles, electron capture, or isomeric transition. The type of emission from a radionuclide largely determines its usefulness in medicine. The products of decay may themselves be radioactive and undergo further transformation, e.g. the decay of molybdenum-99 to technetium-99m, which undergoes further decay to technetium-99. Most sources emit more than one type of radiation.

Alpha decay emits alpha particles from the nucleus; these are positively charged particles (identical to a helium nucleus) consisting of 2 protons and 2 neutrons. Alpha decay occurs in elements with high atomic mass. These radionuclides are rarely used in nuclear medicine because elements of high atomic mass are uncommon in biological systems such as the human body. In addition, alpha particles have limited penetrative power, but the dense ionisation they produce results in high tissue damage. They are also difficult to detect so are of little use in imaging.

Beta decay emits beta particles from the nucleus at high velocity; each particle carries a charge and has a mass equal to that of an electron. A negatively charged beta particle (or negatron) (β^-) is therefore identical to an electron. Negative beta decay occurs in atoms with an excess of neutrons and results in the conversion of neutrons to protons. A positively charged beta particle is also called a positron (β^+). *Positron decay* usually occurs in atoms with an excess of protons, and these are effectively converted into neutrons. A positron has only a transient existence and after losing its energy, it interacts with an electron and is annihilated, producing gamma rays (see below) in the process. Radiopharmaceuticals that contain β^--emitting radionuclides such as iodine-131 (${}^{131}I$) are common in radiotherapy, whereas positron-emitters such as carbon-11 (${}^{11}C$), fluorine-18 (${}^{18}F$), nitrogen-13 (${}^{13}N$), and oxygen-15 (${}^{15}O$) are used mainly in positron emission tomography (PET) imaging. Single photon emission computed tomography (SPECT) is a similar technique to PET, using gamma-ray emitting radionuclides.

Gamma radiation is electromagnetic radiation that occurs when the nucleus eliminates excess energy by means of *photon* emission. Photons are uncharged and highly penetrative.

In the process of *electron capture* (EC; or K-capture), an electron from an inner shell is drawn into the nucleus, and electromagnetic radiation in the form of *X-rays* is produced. (The distinction between X-rays and gamma radiation is now considered to be that the latter arises from the nucleus while the former are produced by electron events.)

The decay from an excited nuclear state to a lower energy state is called *isomeric transition* (IT), which can accompany beta- or positron-decay or EC, and may emit gamma rays. If the excited state occurs for long enough to be measurable, it is called a metastable state and denoted by the suffix m attached to the mass number e.g. technetium-99m or ${}^{99m}Tc$. Another form of IT occurs when a gamma photon from the nucleus strikes an orbital electron, dislodging the electron; this is termed *internal conversion*, and X-rays are emitted. If the originally displaced electron energy is transferred to another electron, an *Auger electron* is produced. X-rays produced from internal conversion or electron capture are of little use in nuclear medicine.

Supply, Preparation, and Control

Radiopharmaceuticals can be classified by half-life into those with long half-lives (over 12 hours), which can be manufactured commercially and supplied to the user as a finished product, and those with short half-lives (less than 12 hours) which need to be prepared in hospital radiopharmacies as commercial supply is impractical. Most countries have regulations concerning the preparation, use, transport, storage, and disposal of such compounds.

Radionuclides may be produced in nuclear reactors, particle accelerators, or generators. Medically useful isotopes produced in a nuclear reactor include molybdenum-99 (${}^{99}Mo$), iodine-131 (${}^{131}I$), phosphorus-32 (${}^{32}P$), and xenon-133 (${}^{133}Xe$). Many radionuclides used in nuclear medicine are produced in an accelerator such as a cyclotron; these include iodine-123 (${}^{123}I$), indium-111 (${}^{111}In$), gallium-67 (${}^{67}Ga$), and thallium-201 (${}^{201}Tl$). Generators are systems that contain both a parent and daughter radionuclide in equilibrium; ideally the parent radioisotope will have a significantly longer half-life than the daughter radioisotope. However, the daughter half-life should be sufficiently long enough for it to be obtained from the generator, prepared in the desired dose, and delivered to the patient, but still short enough to minimise radiation exposure to the patient by decaying to a non-radioactive component in a timely fashion. Generator-produced radionuclides include technetium-99m (${}^{99m}Tc$), gallium-68 (${}^{68}Ga$), and krypton-81m (${}^{81m}Kr$).

Radiopharmaceutical kits allow pharmacists to radiolabel a desired ligand (the properties of which are mainly responsible for dictating how the product will behave in the body); most pharmaceutical kits use technetium-99m (${}^{99m}Tc$) as the radioisotope.

Most radiopharmaceuticals require storage in an airtight container that is sufficiently shielded to protect from primary and secondary emissions, and that complies with national and international regulations. During storage, containers may darken due to irradiation, although this does not necessarily involve deterioration of the preparations.

General Uses

Radiopharmaceuticals are used in the diagnosis of many clinical conditions and as a source of radiation for the treatment of disease. These include:

- static imaging procedures to provide structural or functional information; some radiopharmaceuticals concentrate in the normal tissue, and the diseased tissue appears as an area of reduced activity (a 'cold' area), whereas others concentrate in diseased tissue which appears as an area of increased activity (a 'hot' area)
- dynamic imaging procedures which provide functional information about an organ, showing how the radiopharmaceutical is handled by the organ over a period of time
- uptake and retention measurements using counting equipment to measure the ability of an organ or the body to concentrate and retain a radiopharmaceutical
- clearance measurements which measure the rate at which a radiopharmaceutical clears from the blood
- dilution techniques in which the total volume of a body fluid is determined by measuring the dilution of a radiopharmaceutical
- therapeutic procedures in which the radiation emitted by the radiopharmaceutical is used to destroy diseased tissue

Specific procedures include the following:

- bone scans to detect and stage bone disease, or assess bone viability
- cardiology: myocardial perfusion; myocardial viability; cardiac blood pool studies (to assess cardiac function such as left ventricular ejection fraction)
- CNS: CSF physiological imaging; blood flow assessment; brain metabolism
- endocrine procedures: thyroid, parathyroid, and adrenal scans; thyroid uptake assessment
- gastrointestinal procedures: gastrointestinal motility; gastrointestinal bleeding localisation
- liver and spleen imaging
- genito-urinary imaging including renal function assessment
- infection imaging using gallium scans or leucocyte scans
- lymphatic procedures to assess lymphatic flow using sentinel node imaging or lymphangiography
- non-imaging procedures: *Helicobacter pylori* breath test; red cell mass; plasma volume
- in oncology to localise and assess suspected and proven cancers: somatostatin receptor imaging; prostate cancer imaging; scintimammography; glucose metabolism imaging
- radionuclide therapy: thyroid ablation; bone pain palliation; polycythaemia vera treatment; non-Hodgkin's lymphoma treatment
- respiratory function: ventilation and perfusion lung imaging for the detection of pulmonary emboli

Adverse Effects and Precautions

Ionising radiation can be delivered using external sources (such as external beam radiation therapy) or internally via radioactive implants, seeds, wires, or plaques placed within or near the target tumour, (brachytherapy) or via the use of systemic radioisotopes. Radiation therapy damages DNA, and is most effective against rapidly dividing cells. Hypoxic, poorly vascularised tissues are less sensitive to the effects of radiation, and some large bulky tumours are relatively radioresistant because of tumour hypoxia.

All cross-references refer to entries in Volume A

Adverse effects of radiation may be acute or delayed, and depend on the organ most affected. Rapidly proliferating tissues such as the skin, mucosa, and bone marrow often suffer acute effects such as desquamation, erythema, and cytopenias. Long term sequelae are tissue specific and usually occur if normal tissue tolerance is exceeded; careful dosimetry and radiation planning are important to ensure treatment does not exceed a maximum tolerated dose. Secondary tumours can occur.

Penetration potential of radionuclides is also a factor. Alpha particles have only a short range and skin is thick enough to protect from alpha radiation. However, if ingested, extensive damage can occur. Exposure is not usually an issue since alpha-emitters are rarely used in nuclear pharmacy. However, since monitoring is difficult, insidious exposure can occur. Ingestion of beta-emitting isotopes, especially radioisotopes of carbon, hydrogen, sulfur, and phosphorus, can have severe consequences, as these can be deposited into tissues causing extensive damage; their prolonged half-lives also mean they can cause genetic problems. However, since beta emission is easily monitored, workers can be aware of shielding needs. Gamma photons penetrate skin and tissue easily, although of the typical emissions used in nuclear pharmacy, it is least worrisome in terms of tissue damage.

Many of the adverse effects of radiopharmaceuticals have been attributed to carriers or contaminants. Reported adverse reactions include rash, gastrointestinal disturbances, headache, light-headedness, chest discomfort, and hypersensitivity reactions including anaphylaxis.

Many radiopharmaceuticals are excreted in breast milk, and temporary cessation of breast feeding is recommended for some, such as iodine-131 (^{131}I) and technetium-99m (^{99m}Tc).

References.
1. Silberstein EB, Ryan J. Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions in nuclear medicine. *J Nucl Med* 1996; **37:** 185–92.
2. Silberstein EB. Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. *J Nucl Med* 1998; **39:** 2190–2.
3. Stabin MG, Breitz HB. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. *J Nucl Med* 2000; **41:** 863–73.
4. Mazrani W, *et al*. The radiation burden of radiological investigations. *Arch Dis Child* 2007; **92:** 1127–31.
5. Santos-Oliveira R. Undesirable events with radiopharmaceuticals. *Tohoku J Exp Med* 2009; **217:** 251–7.

Carbon-11

Carbone 11; Carbonio-11; Carbono 11; Carbono-11; Hiili-11; Karbon-11; Kohlenstoff-11; Kol-11; Koolstof-11; Szén-11; Węgiel-11; Углерод-11.

CAS — 14333-33-6 (carbon-11); 10456-04-9 (carbon monoxide (^{11}C)); 94153-50-1 (mespiperone (^{11}C)); 58576-49-1 (methionine (^{11}C)); 97849-54-2 (raclopride (^{11}C)).

UNII — 07BH0IKF2I (carbon monoxide (^{11}C)); GE077RPG04 (raclopride (^{11}C)); Y1WPQ66L9G (sodium acetate (^{11}C)).

NOTE. Carbon Monoxide C 11 is *USAN*.
Mespiperone (^{11}C) is *rINN* and Mespiperone C 11 is *USAN*.
Raclopride C 11 is *USAN*.
HALF-LIFE. 20.4 minutes.

Profile

Carbon-11 (^{11}C) is a radioactive isotope of carbon that emits positrons and gamma rays. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). In theory almost any organic molecule can be labelled with carbon-11, although its short half-life may limit the useful yield in prolonged syntheses. Labelled compounds for which official standards exist include L-methionine for the detection of malignant neoplasms, acetate for the study of myocardial metabolism and imaging of malignant neoplasms, raclopride and mespiperone for the study of CNS dopaminergic D_2 and D_3 receptors, and flumazenil for the study of GABA receptors. Labelled carbon monoxide has been used to assess blood volume.

Other substances that have been labelled with carbon-11 include *meta*-hydroxyephedrine and beta blockers to study sympathetic innervation, carfentanil and diprenorphine to image opiate receptors, and palmitate for myocardial metabolic studies. Pittsburgh Compound B (PIB; N-methyl-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole) labelled with carbon-11 has been investigated for the imaging of beta amyloid and possible diagnosis of Alzheimer's disease.

References.
1. Klein LJ, *et al*. Carbon-11 acetate as a tracer of myocardial oxygen consumption. *Eur J Nucl Med* 2001; **28:** 651–68.
2. Halldin C, *et al*. PET studies with carbon-11 radioligands in neuropsychopharmacological drug development. *Curr Pharm Des* 2001; **7:** 1907–29.
3. Dence CS, *et al*. Imaging myocardium enzymatic pathways with carbon-11 radiotracers. *Methods Enzymol* 2004; **385:** 286–315.
4. Song WS, *et al*. Normal organ standard uptake values in carbon-11 acetate PET imaging. *Nucl Med Commun* 2009; **30:** 462–5.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: L-Methionine ((^{11}C)Methyl) Injection; Flumazenil (N-(^{11}C)Methyl) Injection; Raclopride ((^{11}C)Methoxy) Injection; Sodium Acetate ((1-^{11}C)) Injection;
USP 36: Carbon Monoxide C 11; Flumazenil C 11 Injection; Mespiperone C 11 Injection; Methionine C 11 Injection; Raclopride C 11 Injection; Sodium Acetate C 11 Injection.

Carbon-14

Carbone 14; Carbonio-14; Carbono 14; Carbono-14; Hiili-14; Karbon-14; Kohlenstoff-14; Kol-14; Koolstof-14; Szén-14; Węgiel-14; Углерод-14.

CAS — 14762-75-5.

UNII — 7V68J5677O (carbon-14); WBZ6M63TEE (urea (^{14}C)).

HALF-LIFE. 5730 years.

Profile

Carbon-14 (^{14}C) is a radioactive isotope of carbon; it is a pure beta particle emitter (see Radioactive Decay, p. 2222.1). It has been used to label various organic compounds; these are then used in breath tests.

Urea (p. 1727.3) labelled with carbon-14 is used in a breath test to detect *Helicobacter pylori* as an aid in the diagnosis of peptic ulcer disease (p. 1813.2).

Carbon-13 (^{13}C) (see p. 2470.3) is a stable (non-radioactive) isotope of carbon that is used similarly.

References.
1. Warwick T. Carbon-14-urea breath test: a cautionary note. *J Nucl Med* 1996; **37:** 1916.
2. Balon H, *et al*. Society of Nuclear Medicine. Procedure guideline for carbon-14-urea breath test. *J Nucl Med* 1998; **39:** 2012–14.
3. Leide-Svegborn S, *et al*. Biokinetics and radiation doses for carbon-14 urea in adults and children undergoing the Helicobacter pylori breath test. *Eur J Nucl Med* 1999; **26:** 573–80.
4. Abrams DN, *et al*. Pharmaceutical interference with the ^{14}C carbon urea breath test for the detection of Helicobacter pylori infection. *J Pharm Pharm Sci* 2000; **3:** 228–33.
5. McCarthy KE. Recent advances in the design and synthesis of carbon-14 labelled pharmaceuticals from small molecule precursors. *Curr Pharm Des* 2000; **6:** 1057–83.
6. Higazy E, *et al*. The impact of brushing teeth on carbon-14 urea breath test results. *J Nucl Med Technol* 2000; **28:** 162–4.
7. Öztürk E, *et al*. A new, practical, low-dose ^{14}C-urea breath test for the diagnosis of Helicobacter pylori infection: clinical validation and comparison with the standard method. *Eur J Nucl Med Mol Imaging* 2003; **30:** 1457–62.
8. Özdemir E, *et al*. Could the simplified ^{14}C urea breath test be a new standard in noninvasive diagnosis of Helicobacter pylori infection? *Ann Nucl Med* 2008; **22:** 611–16.
9. Bentur Y, *et al*. Safety of ^{14}C-UBT for diagnosis of Helicobacter pylori infection in pregnancy. *Can Fam Physician* 2009; **55:** 479–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: HeliCap†; ***Neth.***: HeliCap; ***Port.***: HeliCap; ***Swed.***: Heliprobe; ***USA***: Pytest.

Pharmacopoeial Preparations
USP 36: Urea C 14 Capsules.

Chromium-51

Chrom-51; Chrome-51; Chroom-51; Cromo 51; Króm-51; Krom-51; Kromi-51; Хром-51.

CAS — 14392-02-0 (chromium-51); 16284-59-6 (chromic chloride (^{51}Cr)); 27849-89-4 (chromium edetate (^{51}Cr)); 7775-11-3 (sodium chromate (^{51}Cr)).

ATC — V09CX04 (chromium edetate ($_{51}$Cr)).

ATC Vet — QV09CX04 (chromium edetate ($_{51}$Cr)); QV09GX03 (chromate labelled cells ($_{51}$Cr)).

UNII — 9QAU17N705 (chromium-51); N3Y22O955Z (chromium edetate (^{51}Cr)).

NOTE. Chromic Chloride Cr 51 is *USAN*.
Chromic Phosphate Cr 51 is *USAN*.
Sodium Chromate (^{51}Cr) is *rINN* and Sodium Chromate Cr 51 is *USAN*.
HALF-LIFE. 27.7 days.

Profile

Chromium-51 (^{51}Cr) is a radioactive isotope of chromium (p. 2055.3) that emits X-rays, gamma rays, and Auger electrons (see Radioactive Decay, p. 2222.1). As sodium chromate (^{51}Cr), it is used to label red blood cells so that red cell survival and red cell volume can be measured. Chromium-51 activity in the faeces can be used to estimate gastrointestinal blood losses. Red blood cells labelled with chromium-51 and damaged by heat before re-injection have been used for spleen scanning.

As chromium edetate (^{51}Cr), chromium-51 has been used in the determination of the GFR.

As chromic chloride (^{51}Cr), chromium-51 has been given for the determination of loss of serum protein into the gastrointestinal tract. It has also been used to label albumin for the determination of protein-losing enteropathy.

References.
1. Godfrey T, *et al*. Chromium-51 ethylenediamine tetraacetic acid glomerular filtration rate: a better predictor than glomerular filtration rate calculated by the Cockcroft-Gault formula for renal involvement in systemic lupus erythematosus patients. *Rheumatology (Oxford)* 2001; **40:** 324–8.
2. Bird NJ, *et al*. Extracellular distribution volumes of hydrophilic solutes used to measure the glomerular filtration rate: comparison between chromium-51-EDTA and iohexol. *Physiol Meas* 2007; **28:** 223–34.
3. Dworkin HJ, *et al*. Comparison of red cell and whole blood volume as performed using both chromium-51-tagged red cells and iodine-125-tagged albumin and using I-131-tagged albumin and extrapolated red cell volume. *Am J Med Sci* 2007; **334:** 37–40.
4. Bird NJ, *et al*. Reproducibilities and responses to food intake of GFR measured with chromium-51-EDTA and iohexol simultaneously and independently in normal subjects. *Nephrol Dial Transplant* 2008; **23:** 1902–9.
5. Kumar P, *et al*. Estimation of blood volume in burns patients using radioisotope chromium-51: a pilot study. *Burns* 2007; **33:** 1072–3.
6. Descazeaud A, *et al*. Committee for Lower Urinary Tract Symptoms of the French Association of Urology. Blood loss during transurethral resection of the prostate as measured by the chromium-51 method. *J Endourol* 2010; **24:** 1813–16.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Chromium(^{51}Cr) Edetate Injection; Sodium Chromate (^{51}Cr) Sterile Solution;
USP 36: Chromium Cr 51 Edetate Injection; Sodium Chromate Cr 51 Injection.

Cobalt-57

Cobalto 57; Kobalt-57; Kobolt-57; Koboltti-57; Кобальт-57.

CAS — 13981-50-5 (cobalt-57); 16413-89-1 (cobaltous (^{57}Co) chloride); 13115-03-2 (cyanocobalamin (^{57}Co)); 41559-38-0 (cyanocobalamin (^{57}Co)).

ATC — V09XX01 (cobalt cyanocobalamin ($_{57}$Co)).

ATC Vet — QV09XX01 (cobalt cyanocobalamin ($_{57}$Co)).

UNII — 72GWV0852V (cobalt-57); ZL40NE83QQ (cobaltous (^{57}Co) chloride); 025P9I542Y (cyanocobalamin (^{57}Co)).

NOTE. Cobaltous Chloride Co 57 is *USAN*.
Cyanocobalamin (^{57}Co) is *rINN* and Cyanocobalamin Co 57 is *USAN*.
HALF-LIFE. 271.8 days.

Profile

Cobalt-57 (^{57}Co) is a radioactive isotope of cobalt (p. 2482.2) that emits X-rays and gamma rays and decays by electron capture (see Radioactive Decay, p. 2222.1). An aqueous solution or capsules of cyanocobalamin (^{57}Co) have been given orally in the Schilling test for the measurement of absorption of vitamin B_{12} in the diagnosis of pernicious anaemia and other malabsorption syndromes (see under Vitamin B_{12} Substances, p. 2108.1). It is also used with cyanocobalamin (^{58}Co), see below.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Dicopac†.

Pharmacopoeial Preparations
Ph. Eur.: Cyanocobalamin(^{57}Co) Capsules; Cyanocobalamin (^{57}Co) Solution;
USP 36: Cyanocobalamin Co 57 Capsules; Cyanocobalamin Co 57 Oral Solution.

Cobalt-58

Cobalto 58; Kobalt-58; Kobolt-58; Koboltti-58; Кобальт-58.

CAS — 13981-38-9 (cobalt-58); 18195-32-9 (cyanocobalamin (^{58}Co)).

ATC — V09XX02 (cobalt cyanocobalamin ($_{58}$Co)).

ATC Vet — QV09XX02 (cobalt cyanocobalamin ($_{58}$Co)).

UNII — U0E93N6V2A (cyanocobalamin (^{58}Co)).

HALF-LIFE. 70.9 days.

Profile

Cobalt-58 (^{58}Co) is a radioactive isotope of cobalt (p. 2482.2) that emits Auger electrons, X-rays, gamma rays, and decays by positron emission (see Radioactive Decay, p. 2222.1). An aqueous solution or capsules of cyanocobalamin (^{58}Co) have been given orally in the Schilling test for the measurement of absorption of vitamin B_{12} in the diagnosis of pernicious anaemia and other malabsorption syndromes (see under Vitamin B_{12} Substances, p. 2108.1).

The different emissions of cobalt-57 and cobalt-58 allow the isotopes to be distinguished. This can be used to differentiate between failure of absorption due to lack of intrinsic factor (pernicious anaemia) and that due to ileal malabsorption, by giving both free cyanocobalamin (^{58}Co)

and cyanocobalamin (^{57}Co) bound to intrinsic factor. A dual isotope kit has been used for this purpose.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Dicopac†.

Pharmacopoeial Preparations
Ph. Eur.: Cyanocobalamin(^{58}Co) Capsules; Cyanocobalamin (^{58}Co) Solution;
USP 36: Cyanocobalamin Co 58 Capsules.

Erbium-169

Erb-169; Erbio 169; Érbio-169; Эрбий-169.
CAS — 15840-13-8.
ATC — V10AX04 (erbium citrate colloid ($_{169}$Er)).
ATC Vet — QV10AX04 (erbium citrate colloid ($_{169}$Er)).

HALF-LIFE. 9.4 days.

Profile

Erbium-169 (^{169}Er) is a radioactive isotope of erbium. A colloidal suspension of erbium citrate (^{169}Er), is used by local injection for the treatment of arthritic conditions particularly of the small joints after failure of intra-articular corticosteroid therapy or when corticosteroids are contra-indicated.

References.

1. Manil L, *et al.* Physical and biological dosimetry in patients undergoing radiosynoviorthesis with erbium-169 and rhenium-186. *Nucl Med Commun* 2001; **22:** 405–16.
2. van der Zant FM, *et al.* Radiation synovectomy with ^{90}yttrium, ^{186}rhenium and ^{169}erbium: a systematic literature review with meta-analyses. *Clin Exp Rheumatol* 2009; **27:** 130–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Ermm-1.

Fluorine-18

Flúor 18; Fluor-18; Fluori-18; Fluoro-18; Фтор-18.
CAS — 13981-56-1 (fluorine-18); 902143-01-5 (florbetaben (^{18}F)); 956103-76-7 (florbetapir (^{18}F)); 879894-01-6 (fluciclatide (^{18}F)); 222727-39-1 (fluciclovine (^{18}F)); 105851-17-0 (fludeoxyglucose (^{18}F)); 92812-82-3 (fluorodopa (^{18}F)); 863887-89-2 (flurpiridaz (^{18}F)); 765922-62-1 (flutemetamol (^{18}F)); 22554-99-0 (sodium fluoride (^{18}F)).
ATC — V09AX05 (florbetapir ($_{18}$F)); V09IX04 (fludeoxyglucose ($_{18}$F)); V09IX05 (fluorodopa ($_{18}$F)); V09IX06 (sodium fluoride ($_{18}$F)).
ATC Vet — QV09AX05 (florbetapir ($_{18}$F)); QV09IX04 (fludeoxyglucose ($_{18}$F)) QV09IX05 (fluorodopa ($_{18}$F)); QV09IX06 (sodium fluoride ($_{18}$F)).
UNII — 0Z5B2CJX4D (fludeoxyglucose (^{18}F)); 2C598205QX (fluorodopa (^{18}F)); TLA7312TOI (florbetaben (^{18}F)); 6W15Z5R0RU (florbetapir (^{18}F)); 9L75099X6R (sodium fluoride (^{18}F)).

NOTE. Florbetaben (^{18}F) is *rINN*.
Florbetapir (^{18}F) is *rINN* and Florbetapir F 18 is *USAN*.
Fluciclatide (^{18}F) is *rINN* and Fluciclatide F 18 is *USAN*.
Fluciclovine (^{18}F) is *rINN*.
Fludeoxyglucose (^{18}F) is *rINN* and Fludeoxyglucose F 18 is *USAN*.
Fluorodopa (^{18}F) is *rINN* and Fluorodopa F 18 is *USAN*.
Flurpiridaz (^{18}F) is *rINN* and Flurpiridaz F 18 is *USAN*.
Flutemetamol (^{18}F) is *rINN*.
HALF-LIFE. 110 minutes.

Profile

Fluorine-18 (^{18}F) is a radioactive isotope of fluorine that emits positrons. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1).

Various substances have been labelled with fluorine-18 for diagnostic purposes; among those for which official standards exist, fludeoxyglucose (^{18}F) (2-deoxy-2-fluoro-^{18}F-α-D-glucopyranose; ^{18}F-fluorodeoxyglucose; ^{18}F-FDG) is given by intravenous injection for the assessment of cerebral and myocardial glucose metabolism in various physiological or pathological states. It is also used for the evaluation and detection of malignant tumours including those of the brain, head and neck, lung, colon and rectum, and thyroid gland, as well as for lymphoma and malignant melanoma. It has also been occasionally used for renal imaging. Florbetapir (^{18}F) (4-[(1*E*)-2-(6-{2-[2-(2-[^{18}F]Fluoroethoxy)ethoxy]ethoxy}pyridin-3-yl)ethenyl]-*N*-methylbenzenamine; 18F-AV-45) is given intravenously for the imaging of beta-amyloid neuritic plaque density in the brain of patients being evaluated for Alzheimer's disease and other causes of cognitive impairment. Fluorodopa (^{18}F) (^{18}F-FD) is also used in cerebral imaging and assessment of dopaminergic neurons. Sodium fluoride (^{18}F) is used in bone scanning.

Other carrier substances that have been labelled with fluorine-18 for imaging procedures include choline (Fluorocholine (^{18}F) or Fluoroethylcholine (^{18}F)), thymidine (^{18}F-FLT), opiate receptor antagonists, and beta blockers. Florbetaben (^{18}F) (Bay-94-9172) is also being investigated for imaging of beta-amyloid plaques in the study of Alzheimer's disease. Fluciclatide (^{18}F) ([^{18}F]AH-111585) is being studied as an imaging agent in the evaluation of anti-angiogenic therapy.

References.

1. Giorgetti A, *et al.* Clinical oncological applications of positron emission tomography (PET) using fluorine-18-fluoro-2-deoxy-D-glucose. *Radiol Med* 2002; **103:** 293–318.
2. Liu S-H, *et al.* False positive fluorine-18 fluorodeoxy-D-glucose positron emission tomography finding caused by osteoradionecrosis in a nasopharyngeal carcinoma patient. *Br J Radiol* 2004; **77:** 257–60.
3. Dollé F. Fluorine-18-labelled fluoropyridines: advances in radiopharmaceutical design. *Curr Pharm Des* 2005; **11:** 3221–35.
4. Khan N, *et al.* Review of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the follow-up of medullary and anaplastic thyroid carcinomas. *Cancer Control* 2005; **12:** 254–60.
5. Wester HJ, Schottelius M. Fluorine-18 labeling of peptides and proteins. *Ernst Schering Res Found Workshop* 2007; 79–111.
6. Kwee SA, *et al.* Cancer imaging with fluorine-18-labeled choline derivatives. *Semin Nucl Med* 2007; **37:** 420–8.
7. de Beco V, *et al.* Le fluor 18 en radiopharmacie. *Ann Pharm Fr* 2008; **66:** 60–5.
8. Terasawa T, *et al.* Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. *J Clin Oncol* 2009; **27:** 1906–14.
9. Kasper B, *et al.* The use of fluorine-18 fluorodesoxyglycose-positron emission tomography for treatment monitoring in patients with soft tissue sarcomas. *Hell J Nucl Med* 2010; **13:** 40–4.
10. Clark CM, *et al.* AV45-A07 Study Group. Use of florbetapir-PET for imaging β-amyloid pathology. *JAMA* 2011; **305:** 275–83. Correction. *ibid.*; 1096.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: 18F-FDG; ***Belg.***: Glucotrace; ***China***: Fu Tang Pai Te (弗唐派特); ***Cz.***: Efdege; FDG Scan†; GlucoRos; ***Denm.***: PCA (18F); ***Fin.***: Steripet; ***Fr.***: Cisnaf; Dopacis; Flucis; Glucotep; Gluscan; ***Hung.***: Pozitron-Scan-FDG; ***Irl.***: Dopacis; Ertracer; ***Ital.***: Efdege; Glucompet; Steripet†; ***Neth.***: Dopacis; Efdege; FDG Scan F18†; Flucis; Glucotrace; SteriPet; ***Port.***: Contracer; Efdege; Flucis; Steripet; ***Spain***: Barnascan; Dopacis; Farna FDG; FDG Scan†; FDGCadpet; Flucis; Fluodos; Fluorscan; Fluotracer; Metabolimax; MetaTrace; Steripet†; ***UK***: Amyvid; ***USA***: Amyvid; Vizamyl.

Multi-ingredient Preparations. ***Spain***: Gluscan.

Pharmacopoeial Preparations
Ph. Eur.: Fludeoxyglucose (^{18}F) Injection; Fluoride (^{18}F) Solution for Radiolabelling; Sodium Fluoride (^{18}F) Injection;
USP 36: Fludeoxyglucose F 18 Injection; Fluorodopa F 18 Injection; Sodium Fluoride F 18 Injection.

Gallium-67

Gal 67; Galio 67; Gàlio-67; Gallio-67; Галлий-67.
CAS — 14119-09-6 (gallium-67); 41183-64-6 (gallium citrate (^{67}Ga)); 52260-70-5 (gallium citrate (^{67}Ga)).
ATC — V09HX01 (gallium citrate ($_{67}$Ga)).
ATC Vet — QV09HX01 (gallium citrate ($_{67}$Ga)).
UNII — 99T03J52W0 (gallium-67); 4LJK511Z86 (gallium citrate (^{67}Ga)).

NOTE. Gallium (^{67}Ga) Citrate is *rINN* and Gallium Citrate Ga 67 is *USAN*.
HALF-LIFE. 3.26 days.

Profile

Gallium-67 (^{67}Ga) is a radioactive isotope of gallium that decays by electron capture with emission of X-rays (see Radioactive Decay, p. 2222.1). It is used in the form of an intravenous injection of gallium citrate (^{67}Ga).

Gallium in the form of gallium citrate (^{67}Ga) is taken up by iron-binding proteins (transferrin and lactoferrin) and is thus concentrated in some malignant tumours of the lymphatic system, as well as in some other tissues, and may be used for tumour visualisation. It may also be used to determine the response to chemotherapy and detect recurrence of suitable tumours. Concentration of lactoferrin also occurs in inflammatory lesions and gallium-67 is therefore used for the localisation of focal inflammatory sites, such as may occur in abscesses, or sarcoidosis. Gallium scans have proved useful for the detection of various infections such as pneumonia encountered in patients with AIDS.

References.

1. Kostakoglu L, Goldsmith SJ. Positron emission tomography in lymphoma: comparison with computed tomography and Gallium-67 single photon emission computed tomography. *Clin Lymphoma* 2000; **1:** 67–74.
2. Even-Sapir E, Israel O. Gallium-67 scintigraphy: a cornerstone in functional imaging of lymphoma. *Eur J Nucl Med Mol Imaging* 2003; **30** (suppl 1): S65–S81.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to gallium-67 since radioactivity has been reported to be present in breast milk for 2 weeks.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Gallium(^{67}Ga) Citrate Injection;
USP 36: Gallium Citrate Ga 67 Injection.

Gallium-68

Gal 68; Gàlio-68; Gallio-68.
CAS — 15757-14-9.

HALF-LIFE. 67.6 minutes.

Profile

Gallium-68 (^{68}Ga) is a radioactive isotope of gallium that emits positrons, Auger electrons, X-rays and gamma rays (see Radioactive Decay, p. 2222.1). It is used in positron-emission tomography to radiolabel a somatostatin analogue in order to image neuroendocrine and other tumours.

References.

1. Win Z, *et al.* Somatostatin receptor PET imaging with gallium-68 labeled peptides. *Q J Nucl Med Mol Imaging* 2007; **51:** 244–50.
2. Al-Nahhas A, *et al.* Gallium-68 PET: a new frontier in receptor cancer imaging. *Anticancer Res* 2007; **27:** 4087–94.
3. Khan MU, *et al.* Clinical indications for gallium-68 positron emission tomography imaging. *Eur J Surg Oncol* 2009; **35:** 561–7.
4. Pagou M, *et al.* Can gallium-68 compounds partly replace ^{18}F-FDG in PET molecular imaging? *Hell J Nucl Med* 2009; **12:** 102–5.

Indium-111

Ind-111; Indio 111; Índio-111; Индий-111.
CAS — 15750-15-9 (indium-111); 139039-70-6 (indium (^{111}In) altumomab pentetate); 10025-82-8 (indium (^{111}In) chloride); 65389-08-4 (indium (^{111}In) hydroxyquinoline); 139096-04-1 (indium (^{111}In) pentetreotide); 138955-27-8 (indium (^{111}In) satumomab pendetide).
ATC — V09AX01 (indium pentetate ($_{111}$In)); V09GX02 (indium imciromab ($_{111}$In)); V09HB01 (indium oxinate labelled cells ($_{111}$In)); V09HB02 (indium tropolonate labelled cells ($_{111}$In)); V09IB01 (indium pentetreotide ($_{111}$In)); V09IB02 (indium satumomab pendetide ($_{111}$In)); V09IB03 (indium antiovarium-carcinoma antibody ($_{111}$In)); V09IB04 (indium capromab pendetide ($_{111}$In)).
ATC Vet — QV09AX01 (indium pentetate ($_{111}$In)); QV09GX02 (indium imciromab ($_{111}$In)); QV09HB01 (indium oxinate labelled cells ($_{111}$In)); QV09HB02 (indium tropolonate labelled cells ($_{111}$In)); QV09I801 (indium pentetreotide ($_{111}$In)); QV09IB02 (indium satumomab pendetide ($_{111}$In)); QV09IB03 (indium antiovariumcarcinoma antibody ($_{111}$In)); QV09IB04 (indium capromab pendetide ($_{111}$In)).
UNII — E9NGC49E0T (indium-111); WJZ06C0H8L (indium-111 ion); 58TD96H03I (indium (^{111}In) chloride); S9U4ZR2W8V (indium (^{111}In) ibritumomab tiuxetan); LGX9OL562T (indium (^{111}In) oxyquinoline); 5K3UP561AX (indium (^{111}In) pentetate); 7UIT3ZGC8E (indium (^{111}In) pentetate disodium); M312JJ6Z32 (indium (^{111}In) pentetreotide).

NOTE. Indium In 111 Altumomab Pentetate, Indium In 111 Oxyquinoline, and Indium In 111 Pentetreotide are *USAN*. Indium[^{111}In] Satumomab Pendetide is *BAN* and Indium In 111 Satumomab Pendetide is *USAN*.
HALF-LIFE. 67 hours (2.8 days).

Profile

Indium-111 (^{111}In) is a radioactive isotope of indium that decays by electron capture with emission of X-rays (see Radioactive Decay, p. 2222.1). It is complexed with pentetic acid (pentetate) and used intrathecally in diagnostic CSF studies.

Leucocytes labelled with indium (^{111}In) hydroxyquinoline (indium (^{111}In) oxyquinoline or indium (^{111}In) oxine) are used for the location of inflammatory lesions; applications have been the detection or localisation of abscesses or infections and the evaluation of inflammatory bowel disease. Platelets have been similarly labelled.

Indium (^{111}In) bleomycin has been given by intravenous injection for the detection of tumours. Indium (^{111}In) pentetreotide is used for the detection and localisation of tumours originating from neuroendocrine cells.

Monoclonal antibodies such as capromab pendetide and ibritumomab tiuxetan have been labelled with indium-111 in the form of indium (^{111}In) chloride. These are used for the

detection and imaging of malignant neoplasms. Other monoclonal antibodies that have been labelled with indium-111 include altumomab pentetate, imciromab pentetate, and satumomab pendetide. Uses include the detection, diagnosis, and evaluation of malignant neoplasms as well as the detection and localisation of myocardial infarction.

References.

1. Medina M, *et al.* Indium-111 labelled white blood cell scintigraphy in cranial and spinal septic lesions. *Eur J Nucl Med* 2000; **27:** 1473–80.
2. Nathan J, *et al.* Fused SPECT/CT imaging of peri-iliopsoas infection using indium-111-labeled leukocytes. *Clin Nucl Med* 2006; **31:** 801–2.
3. Manyak MJ. Indium-111 capromab pendetide in the management of recurrent prostate cancer. *Expert Rev Anticancer Ther* 2008; **8:** 175–81.
4. Fisher DR, *et al.* MIRD dose estimate report No. 20: radiation absorbed-dose estimates for ^{111}In- and ^{90}Y-ibritumomab tiuxetan. *J Nucl Med* 2009; **50:** 644–52.
5. Bal CS, *et al.* Radiolabeled somatostatin analogs for radionuclide imaging and therapy in patients with gastroenteropancreatic neuroendocrine tumors. *Trop Gastroenterol* 2010; **31:** 87–95.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to indium-111 since a very small amount of radioactivity has been reported to be present in breast milk for 20 hours.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: OctreoScan; ***Belg.***: OctreoScan; ***Cz.***: OctreoScan; ***Denm.***: OctreoScan; ***Fin.***: OctreoScan; ***Israel***: Prostascint Kit; ***Ital.***: OctreoScan; ***Neth.***: OctreoScan; ***Port.***: OctreoScan; ***Spain***: OctreoScan; ***USA***: OctreoScan.

Multi-ingredient Preparations. ***Irl.***: OctreoScan.

Pharmacopoeial Preparations

Ph. Eur.: Indium(^{111}In) Chloride Solution; Indium(^{111}In) Oxine Solution; Indium(^{111}In) Pentetate Injection;

USP 36: Indium In 111 Capromab Pentetide Injection; Indium In 111 Chloride Solution; Indium In 111 Ibritumomab Tiuxetan Injection; Indium In 111 Oxyquinoline Solution; Indium In 111 Pentetate Injection; Indium In 111 Pentetreotide Injection; Indium In 111 Satumomab Pendetide Injection.

Iodine-123

Iod-123; Iode-123; Iodio-123; Iodo 123; Jód-123; Jod-123; Jodi-123; Jodium-123; Yodo 123; Иод-123.

CAS — 15715-08-9 (iodine-123); 76924-93-1 (iobenguane (^{123}I)); 139755-80-9 (iobenguane (^{123}I) sulfate); 74855-17-7 (iocanlidic acid (^{123}I)); 54510-20-2 (iodocetylic acid (^{123}I)); 75917-92-9 (iofetamine (^{123}I)); 85068-76-4 (iofetamine (^{123}I) hydrochloride); 123748-56-1 (iodofiltic acid (^{123}I)); 155798-07-5 (ioflupane (^{123}I)); 113716-48-6 (iolopride (^{123}I)); 127396-36-5 (iomazenil (^{123}I)); 136794-86-0 (iometopane (^{123}I)); 41927-88-2 (sodium iodide (^{123}I)); 56254-07-0 (sodium iodohippurate (^{123}I)).

ATC — V09AB01 (iofetamine ($_{123}$I)); V09AB02 (iodine iolopride ($_{123}$I)); V09AB03 (iodine ioflupane ($_{123}$I)); V09CX01 (sodium iodohippurate ($_{123}$I)); V09FX02 (sodium iodide ($_{123}$I)); V09IX01 (iobenguane ($_{123}$I)).

ATC Vet — QV09AB01 (iofetamine ($_{123}$I)); QV09AB02 (iodine iolopride ($_{123}$I)); QV09AB03 (iodine ioflupane ($_{123}$I)); QV09CX01 (sodium iodohippurate ($_{123}$I)); QV09FX02 (sodium iodide ($_{123}$I)); QV09IX01 (iobenguane ($_{123}$I)).

UNII — 8YWR746RPQ (iodine-123); P2TH1XYZ84 (iobenguane (^{123}I)); 23X1185WBO (iobenguane (^{123}I) sulfate); LV23B78IJC (iofetamine (^{123}I)); R5O1XB5L3M (iofetamine (^{123}I) hydrochloride); 0J7USQ749M (iodofiltic acid (^{123}I)); 3MM99T8R5Q (ioflupane (^{123}I)); 5E76SOQ99K (iolopride (^{123}I)); B851121553 (iomazenil (^{123}I)); 719Y64M4R6 (iometopane (^{123}I)); 29UKX3A616 (sodium iodide (^{123}I)); 4NW20GFQ7H (sodium iodohippurate (^{123}I)).

NOTE. Iobenguane Sulfate I 123 is *USAN*.

Iocanlidic Acid (^{123}I) is *rINN* and Iocanlidic Acid I 123 is *USAN*.

Iodocetylic Acid (^{123}I) is *rINN* and Iodocetylic Acid I 123 is *USAN*.

Iodofiltic Acid (^{123}I) is *rINN* and Iodofiltic Acid I 123 is *USAN*.

Iodohippurate Sodium I 123 is *USAN*.

Iofetamine (^{123}I) is *rINN* and Iofetamine Hydrochloride I 123 is *USAN*.

Ioflupane (^{123}I) is *rINN*, Ioflupane[^{123}I] is *BAN*, and Ioflupane I 123 is *USAN*.

Iolopride (^{123}I) is *rINN*.

Iomazenil (^{123}I) is *rINN*.

Iometopane (^{123}I) is *rINN* and Iometopane I 123 is *USAN*.

HALF-LIFE. 13.3 hours.

Profile

Iodine-123 (^{123}I) is a radioactive isotope of iodine (p. 2336.3) that decays by electron capture with emission of X-rays (see Radioactive Decay, p. 2222.1). It has similar adverse effects and precautions to those of iodine-131 (see p. 2226.2).

Its principal use is in thyroid uptake tests and thyroid imaging when it is given orally or by intravenous injection as sodium iodide (^{123}I).

Sodium iodohippurate (^{123}I) is given intravenously in tests of renal function and in renal imaging.

Iobenguane (^{123}I) (*m*-iodobenzylguanidine (^{123}I)) is given intravenously for the localisation of certain tumours, for example phaeochromocytomas, and for the evaluation of neuroblastoma.

Ioflupane (^{123}I) is given intravenously to detect loss of functioning dopaminergic neurones in the differential diagnosis of tremor and parkinsonism. Iometopane (^{123}I) has been studied for the early diagnosis of parkinsonism.

Iomazenil (^{123}I), an analogue of flumazenil reported to have high affinity for central benzodiazepine receptors, has been used to study cerebrovascular diseases.

Iodofiltic acid (^{123}I) (BMIPP; *Zemiva*™) is being studied in the prognosis of coronary artery disease.

Various monoclonal antibodies have been labelled with iodine-123; potential applications include the detection of malignant neoplasms.

References.

1. Biswas SK, *et al.* 123I-BMIPP fatty acid analogue imaging is a novel diagnostic and prognostic approach following acute myocardial infarction. *Singapore Med J* 2009; **50:** 943–8.
2. Inaba Y, Bergmann SR. Prognostic value of myocardial metabolic imaging with BMIPP in the spectrum of coronary artery disease: a systematic review. *J Nucl Cardiol* 2010; **17:** 61–70.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to iodine-123 since radioactivity has been reported to be present in breast milk for up to 36 hours.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: AdreView†; DaTSCAN†; MIBG; ***Cz.***: DaTSCAN; Hippuran; MIBG; ***Fin.***: MIBG; ***Fr.***: AdreView; DaTSCAN; ***Irl.***: DaTSCAN; ***Israel***: DaTSCAN; ***Ital.***: DaTSCAN; ***Neth.***: AdreView; DaTSCAN; Hippuran; MIBG; ***Pol.***: DaTSCAN; ***Port.***: DaTSCAN; ***Spain***: AdreView; DaTSCAN; MIBG; ***Switz.***: AdreView; DaTSCAN; ***UK***: AdreView; DaTSCAN; ***USA***: AdreView; DaTSCAN.

Multi-ingredient Preparations. ***Irl.***: MIBG.

Pharmacopoeial Preparations

Ph. Eur.: Sodium Iodide(^{123}I) Injection; Sodium Iodide(^{123}I) Solution for Radiolabelling; Sodium Iodohippurate(^{123}I) Injection;

USP 36: Iobenguane I 123 Injection; Iodohippurate Sodium I 123 Injection; Sodium Iodide I 123 Capsules; Sodium Iodide I 123 Solution.

Iodine-124

Iod-124; Iode-124; Iodio-124; Iodo-124; Jód-124; Jod-124; Jodi-124; Jodium-124; Yodo-124.

CAS — 14158-30-6 (iodine-124); 1011710-99-8 (iodine (^{124}I) girentuximab).

UNII — P0I0FT82VK (iodine (^{124}I) girentuximab).

NOTE. Iodine (^{124}I) Girentuximab is *rINN* and Iodine I 124 Girentuximab is *USAN*.

HALF-LIFE. 4.2 days.

Profile

Iodine-124 (^{124}I) is a radioactive isotope of iodine (p. 2336.3) that decays by electron capture and positron emission (see Radioactive Decay, p. 2222.1). It is used in positron-emission tomography for the imaging of thyroid tissue and is under investigation for the radiolabelling of various compounds, including the monoclonal antibody girentuximab (p. 802.3). Iodine (^{124}I) girentuximab (*Redectane*™) is being studied for imaging of renal tumours.

Iodine-125

Iod-125; Iode-125; Iodio-125; Iodo 125; Jód-125; Jod-125; Jodi-125; Jodium-125; Yodo 125.

CAS — 14158-31-7 (iodine-125); 17033-82-8 (iometin (^{125}I)); 24359-64-6 (sodium iodide (^{125}I)); 7230-65-1 (sodium iodohippurate (^{125}I)); 17692-74-9 (sodium iotalamate (^{125}I)).

ATC — V09CX03 (sodium iotalamate ($_{125}$I)); V09GB01 (fibrinogen ($_{125}$I)); V09GB02 (iodinated human albumin ($_{125}$I)); V09IX03 (iodine CC49 monoclonal antibody ($_{125}$I)).

ATC Vet — QV09CX03 (sodium iotalamate ($_{125}$I)); QV09GB01 (fibrinogen ($_{125}$I)); QV09GB02 (iodinated human albumin ($_{125}$I)); QV09IX03 (iodine CC49 monoclonal antibody ($_{125}$I)).

UNII — GVO776611R (iodine-125); 6BWQQ3N9TI (iodinated (^{125}I) human serum albumin); HXP39D7UB1 (iometin (^{125}I)); HII3IK0W0I (sodium iodide (^{125}I)); T5536Q4O60 (sodium iodohippurate (^{125}I)); 31J5U3Q9ZN (sodium iotalamate (^{125}I)).

NOTE. Diohippuric Acid I 125 is *USAN*. Diotyrosine I 125 is *USAN*.

Fibrinogen (^{125}I) is *rINN* and Fibrinogen I 125 is *USAN*.

Iodinated (^{125}I) Human Serum Albumin is *rINN*.

Iodohippurate Sodium I 125 is *USAN*.

Iodopyracet I 125 is *USAN*.

Iometin (^{125}I) is *rINN* and Iomethin I 125 is *USAN*.

Rose Bengal Sodium I 125 is *USAN*.

Sodium Iodide (^{125}I) is *rINN* and Sodium Iodide I 125 is *USAN*.

Sodium Iotalamate (^{125}I) is *rINN* and Iothalamate Sodium I 125 is *USAN*.

HALF-LIFE. 59.4 days.

Profile

Iodine-125 (^{125}I) is a radioactive isotope of iodine (p. 2336.3) that decays by electron capture (see Radioactive Decay, p. 2222.1). It has similar adverse effects and precautions to those of iodine-131 (see p. 2226.2).

Iodine-125 is not very suitable for external detection after thyroid uptake because its gamma-energy is weak, and it is best reserved for *in vitro* applications. Sodium iodide (^{125}I) is used for radio-immunoassay kits and for iodination of compounds such as proteins.

Sodium iotalamate (^{125}I) is used intravenously in the determination of GFR in patients with renal disease.

Human albumin iodinated with iodine-125 is used for the determination of blood or plasma volume.

Iodine-125, as iodinated (^{125}I) human fibrinogen, has been used intravenously to demonstrate and locate deep-vein thrombosis of the leg. Iodinated (^{125}I) fibrinogen has also been used in the measurement of fibrinogen metabolism.

Iodine-125 implants are used for the local treatment of cancers (brachytherapy). Titanium capsules containing iodine-125 adsorbed onto a silver rod are used in the treatment of prostate cancer and other selected, localised tumours. It has also been used for intracavitary brachytherapy of malignant gliomas, where it is instilled into an inflatable balloon catheter.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to iodine-125 since radioactivity has been reported to be present in breast milk for 12 days.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: OncoSeeds†; Rapid Strand†; ***Switz.***: Seralb-I-125; ***USA***: Glofil.

Pharmacopoeial Preparations

Ph. Eur.: Human Albumin Injection, Iodinated (^{125}I);

USP 36: Iodinated I 125 Albumin Injection; Iothalamate Sodium I 125 Injection.

Iodine-131

Iod-131; Iode-131; Iodio-131; Iodo 131; Jód-131; Jod-131; Jodi-131; Jodium-131; Yodo 131.

CAS — 10043-66-0 (iodine-131); 14679-68-6 (diotyrosine (^{131}I)); 77679-27-7 (iobenguane (^{131}I)); 149210-33-3 (iobenguane (^{131}I) sulfate); 24360-85-8 (iodipamide (^{131}I)); 3791-63-7 (iodoantipyrine (^{131}I)); 42220-21-3 (iodocholesterol (^{131}I)); 1214283-52-9 (ioflubenzamide (^{131}I)); 17033-83-9 (iometin (^{131}I)); 16624-40-1 (iotyrosine (^{131}I)); 54182-63-7 (macrosalb (^{131}I)); 24916-55-0 (rose bengal (^{131}I) sodium closed form); 50291-21-9 (rose bengal (^{131}I) sodium open form); 7790-26-3 (sodium iodide (^{131}I)); 881-17-4 (sodium iodohippurate (^{131}I)); 15845-98-4 (sodium iotalamate (^{131}I)); 9015-62-7 (tolpovidone (^{131}I)).

ATC — V09CX02 (sodium iodohippurate ($_{131}$I)); V09FX03 (sodium iodide ($_{131}$I)); V09IX02 (iobenguane ($_{131}$I)); V09XA01 (iodine norcholesterol ($_{131}$I)); V09XA02 (iodocholesterol ($_{131}$I)); V09XA03 (iodinated human albumin ($_{131}$I)); V10XA01 (sodium iodide ($_{131}$I)); V10XA02 (iobenguane ($_{131}$I)); V10XA53 (iodine tositumomab ($_{131}$I)).

ATC Vet — QV09CX02 (sodium iodohippurate (^{131}I)); QV09FX03 (sodium iodide (^{131}I)); QV09IX02 (iobenguane (^{131}I)); QV09XA01 (iodine norcholesterol (^{131}I)); QV09XA02 (iodocholesterol (^{131}I)); QV09XA03 (iodinated human albumin (^{131}I)); QV10XA01 (sodium iodide (^{131}I)); QV10XA02 (iobenguane (^{131}I)); QV10XA53 (iodine tositumomab (^{131}I)).

UNII — I5X6L61HUT (iodine-131); 4GC1FOQ22U (iodine-131 ion); Q461L7AK4R (iobenguane (^{131}I)); M575VKV19N (iobenguane (^{131}I) sulfate); ACH35131L1 (iodinated (^{131}I) human serum albumin); K1KT5M40JC (iodine (^{131}I) tositumomab); QR6HQ1U73Z (iodoantipyrine (^{131}I)); C5F4248GPJ (iodocholesterol (^{131}I)); POY4SKT67X (iometin (^{131}I)); Q1M94GA18P (iotyrosine (^{131}I)); 24I7KUI7MK (rose bengal (^{131}I) sodium); 29VCO8ACHH (sodium iodide (^{131}I)); 9BRV734R3E (sodium iodohippurate (^{131}I)).

NOTE. Diohippuric Acid I 131 is *USAN*.

Diotyrosine I 131 is *USAN*.

Ethiodized Oil (^{131}I) is *rINN* and Ethiodized Oil I 131 is *USAN*.

Iobenguane (^{131}I) is *rINN* and Iobenguane I 131 is *USAN*.

Iobenguane Sulfate I 131 is *USAN*.

Iodinated (^{131}I) Human Serum Albumin is *rINN*.

Iodipamide Sodium I 131 is *USAN*.

Iodoantipyrine I 131 is *USAN*.

Iodocholesterol (^{131}I) is *rINN* and Iodocholesterol I 131 is *USAN*.

Iodopyracet I 131 is *USAN*.

Ioflubenzamide (^{131}I) is *rINN*.

Iometin (^{131}I) is *rINN* and Iomethin I 131 is *USAN*.

Iotyrosine I 131 is *USAN*.

Macrosalb (^{131}I) is *rINN* and *BAN*.

Rose Bengal (^{131}I) Sodium is *rINN* and Rose Bengal Sodium I 131 is *USAN*.

Sodium Iodide (^{131}I) is *rINN* and Sodium Iodide I 131 is *USAN*.

Sodium Iodohippurate (^{131}I) is *rINN* and Iodohippurate Sodium I 131 is *USAN*.

Sodium Iotalamate (^{131}I) is *rINN* and Iothalamate Sodium I 131 is *USAN*.

Tolpovidone (^{131}I) is *rINN* and Tolpovidone I 131 is *USAN*.

HALF-LIFE. 8.02 days.

Uses and Administration

Iodine-131 (^{131}I) is a radioactive isotope of iodine (p. 2336.3) that decays by beta and gamma emission (see Radioactive Decay, p. 2222.1). It is mainly used in studies of thyroid function and in the treatment of hyperthyroidism (p. 2332.2) and some forms of thyroid carcinoma (p. 716.1). It is common practice to saturate the thyroid with non-radioactive iodine when uptake of radiation by the gland is not desired (see Radiation Protection, p. 2338.1).

Sodium iodide (^{131}I) is given orally and by intravenous injection in studies of thyroid function, particularly in measurements of the uptake of iodine by the thyroid, and in thyroid scanning. It is also used in the treatment of hyperthyroidism and in the treatment of malignant neoplasms of the thyroid.

Iodine radioisotopes can be incorporated into many other compounds, for various diagnostic and therapeutic purposes.

Injections containing iobenguane (^{131}I) (*m*-iodobenzylguanidine (^{131}I)) may be used for the localisation and treatment of phaeochromocytoma (p. 1278.1), neuroblastoma (p. 716.2), and thyroid gland carcinoma.

Iodinated (^{131}I) norcholesterol (6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (^{131}I)) has been used for adrenal scintigraphy by slow intravenous injection.

Various monoclonal antibodies labelled with iodine-131 are used for the detection of malignant neoplasms and some are used for therapeutic purposes, such as iodine (^{131}I) tositumomab (p. 874.2) for non-Hodgkin's lymphoma. Fatty acids may be iodinated with radioactive iodine and used for the treatment of unresectable malignant neoplasms of the liver.

Human albumin iodinated with iodine-131 was used in the determination of CSF dynamics, protein losing enteropathy, and for liver imaging but its use has been superseded by other radiopharmaceuticals.

Sodium iodohippurate (^{131}I) was used intravenously for renal-function tests and for renal imaging.

Rose bengal sodium (^{131}I) has been given intravenously in tests of liver function.

References.

1. Van Nostrand D. The benefits and risks of I-131 therapy in patients with well-differentiated thyroid cancer. *Thyroid* 2009; **19:** 1381–91.
2. Araujo F, *et al.* Optimization of (131)I doses for the treatment of hyperthyroidism. *Cell Mol Biol (Noisy-le-grand)* 2009; **55:** 1–6.
3. Lassmann M, *et al.* Dosimetry and thyroid cancer: the individual dosage of radioiodine. *Endocr Relat Cancer* 2010; **17:** R161–R172.

Adverse Effects and Treatment

Therapy with iodine-131 may temporarily exacerbate existing hyperthyroidism, and can precipitate thyroid storm (see Hyperthyroidism, p. 2332.2). Dose-dependent hypothyroidism may occur as a late consequence, occurring weeks or years after treatment, and requiring thyroid replacement therapy. However, this hypothyroidism may also be transient, and replacement therapy should not be started too early. Both hyperparathyroidism and hypoparathyroidism have been reported. High doses, such as those used to treat thyroid cancer, can cause radiation thyroiditis resulting in swelling and localised pain; this may cause tracheal constriction and rarely, respiratory distress. This can subside spontaneously or may need corticosteroid treatment. Sialadenitis (inflammation of the salivary glands) can occur, causing loss of taste and dry mouth. While it usually subsides spontaneously, anti-inflammatory treatment may be required, and there are reports of persistent symptoms leading to tooth loss. Gastrointestinal disturbances are common with radio-iodine, especially after oral use, and usually occur within the first hours or days after ingestion. Bone marrow depression, with isolated thrombocytopenia or erythrocytopenia, may occur after a high dose. Although this is usually reversible, it may sometimes be irreversible or fatal.

Although the use of radio-iodine for hyperthyroidism is not generally considered to increase the risk of malignancy, there have been some reports of an increased incidence of cancers including those of bladder, breast, and stomach, after radio-iodine therapy, and high-dose treatment may increase the risk of leukaemia.

Hypersensitivity reactions can occur with iodine (see also under Iodine, p. 2338.2).

References.

1. Ron E, *et al.* Cancer mortality following treatment for adult hyperthyroidism. *JAMA* 1998; **280:** 347–55.
2. Franklyn JA, *et al.* Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 1999; **353:** 2111–15.
3. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. *Pediatrics* 2003; **111:** 745–9.

Precautions

The use of sodium iodide (^{131}I) is contra-indicated, even in diagnostic doses, during pregnancy. It should also not be used for diagnostic purposes in children younger than 10 years of age. Sodium iodide (^{131}I) is not recommended for thyroid scanning except in the follow-up of malignant disease, or where iodine-123 or technetium-99m are not available. There is some controversy as to whether radioiodine therapy exacerbates Graves' ophthalmopathy (see Hyperthyroidism, p. 2332.2). Sodium iodide (^{131}I) is contra-indicated in patients with dysphagia, oesophageal stricture, active gastritis, gastric erosions, peptic ulceration, or reduced gastrointestinal motility. Caution is advised in patients with renal impairment.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to iodine-131 since radioactivity has been reported to be present in breast milk for 2 to 14 days; high doses used for the treatment of thyroid cancer may prolong exposure to the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Interactions

Many drugs interact with radio-iodine; mechanisms vary but can affect protein binding, pharmacokinetics, or the uptake of iodine-131. Licensed product information recommends that the following drugs be withdrawn before use of sodium iodide (^{131}I):

- antithyroid drugs e.g. carbimazole, thiamazole, propylthiouracil, or perchlorates: withdrawn 2 to 7 days before use and withheld until several days after use
- salicylates, corticosteroids, sodium nitroprusside, sulfobromophthalein sodium, anticoagulants, antihistamines, antibacterials such as penicillins or sulfonamides or rifampicin, amphotericin B, tiabendazole, tolbutamide, thiopental: withdrawn 1 week before use
- iodine-containing preparations for systemic use such as vitamins or expectorants: withdrawn 2 weeks before use
- iodine-containing preparations for topical use: withdrawn 1 to 9 months before use
- iodine-containing contrast media: withdrawn up to 1 year before use
- thyroid hormone preparations: withdrawn 2 to 6 weeks before use
- amiodarone, benzodiazepines, lithium: withdrawn about 4 weeks before use

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Curicap; Theracap†; ***Canad.***: Bexxar; ***China***: Li Ka Ting (利卡汀); Wei Mei Sheng (唯美生); ***Cz.***: Capsion; Curicap; Theracap; ***Denm.***: Theracap; ***Fin.***: Theracap; ***Fr.***: Capsion; Lipiocis†; Theracap; ***Israel***: Theracap; ***Neth.***: Capsion; Curicap†; Jobenguaan†; Theracap; ***Port.***: Capsion; Curicap; Theracap; ***Spain***: Capsion; Curicap; Theracap; ***Switz.***: Theracap; ***UK***: Capsion; Theracap; ***USA***: Bexxar; Hicon; Iodotope†.

Pharmacopoeial Preparations

Ph. Eur.: Iobenguane(^{131}I) Injection for Diagnostic Use; Iobenguane(^{131}I) Injection for Therapeutic Use; Iodinated(^{131}I) Norcholesterol Injection; Sodium Iodide(^{131}I) Capsules for Diagnostic Use; Sodium Iodide(^{131}I) Capsules for Therapeutic Use; Sodium Iodide(^{131}I) Solution for Radiolabelling; Sodium Iodide(^{131}I) Solution; Sodium Iodohippurate(^{131}I) Injection;

USP 36: Iobenguane I 131 Injection; Iodinated I 131 Albumin Aggregated Injection; Iodinated I 131 Albumin Injection; Iodohippurate Sodium I 131 Injection; Rose Bengal Sodium I 131 Injection; Sodium Iodide I 131 Capsules; Sodium Iodide I 131 Solution.

Krypton-81m

Criptón 81m; Crípton-81m; Kripton-81m; Krypton Kr 81m (USAN); Криптон-81м.

CAS — 15678-91-8.

ATC — V09EX01 (krypton gas (^{81m}Kr)).

ATC Vet — QV09EX01 (krypton gas (^{81m}Kr)).

UNII — 68QN45K12N.

HALF-LIFE. 13.1 seconds.

Profile

Krypton-81m (^{81m}Kr) decays by isomeric transition and emits gamma rays (see Radioactive Decay, p. 2222.1). It is a daughter of rubidium-81 (^{81}Rb, half-life 4.58 hours), and is prepared immediately before use by elution from a generator containing rubidium-81 adsorbed on a suitable ion-exchange column using air or oxygen as the eluent. Krypton-81m is used as a gas in lung ventilation studies. Such ventilation studies can be combined with lung perfusion studies to diagnose pulmonary embolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: KryptoScan; ***Irl.***: KryptoScan; ***Neth.***: KryptoScan.

Pharmacopoeial Preparations

Ph. Eur.: Krypton(^{81m}Kr) Inhalation Gas;

USP 36: Krypton Kr 81m.

Nitrogen-13

Azot-13; Azote-13; Azoto-13; Dusík-13; Köfnunarefni-13; Kväve-13; Kvælstof-13; Nitrogén-13; Nitrógeno 13; Stickstoff-13; Stikstof-13; Tyrpi-13; Азот-13.

CAS — 13981-22-1.

HALF-LIFE. 9.96 minutes.

Profile

Nitrogen-13 (^{13}N) is a radioactive isotope of nitrogen (p. 1799.3) that emits positrons. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). In the form of ammonia (^{13}N) it is given intravenously for imaging blood flow in organs such as the heart. Nitrogen gas (^{13}N) may be used for pulmonary ventilation and perfusion studies.

References.

1. Hove JD, *et al.* Simultaneous cardiac output and regional myocardial perfusion determination with PET and nitrogen 13 ammonia. *J Nucl Cardiol* 2003; **10:** 28–33.
2. Hove JD, *et al.* Left atrial versus left ventricular input function for quantification of the myocardial blood flow with nitrogen-13 ammonia and positron emission tomography. *Eur J Nucl Med Mol Imaging* 2004; **31:** 71–6.
3. Kumar R, *et al.* Production of nitrogen-13-labeled ammonia by using 11MeV medical cyclotron: our experience. *Hell J Nucl Med* 2009; **12:** 248–50.

Preparations

Pharmacopoeial Preparations

Ph. Eur.: Ammonia(^{13}N) Injection;

USP 36: Ammonia N 13 Injection.

Oxygen-15

Happi-15; Ilt-15; Kyslík-15; Oksygen-15; Ossigeno-15; Oxigén-15; Oxigénio-15; Oxígeno 15; Oxygène-15; Sauerstoff-15; Súrefni-15; Syre-15; Tlen-15; Zuurstof-15; Кислород-15.

CAS — 13982-43-9 (oxygen-15); 24286-21-3 (water (^{15}O)).
UNII — 63M8RYN44N (water (^{15}O)).

NOTE. Water O 15 is *USAN*.
HALF-LIFE. 122.2 seconds.

Profile

Oxygen-15 (^{15}O) is a radioactive isotope of oxygen (p. 1799.3) that emits positrons. It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). It is used in the form of water (^{15}O) and is given intravenously to study cerebral and myocardial perfusion.

Oxygen gas, carbon dioxide, and carbon monoxide have also been labelled with oxygen-15.

References.
1. Koh T, *et al.* Oxygen-15 positron-emission tomography for predicting selective delivery of a chemotherapeutic agent to hepatic cancers during angiotensin II-induced hypertension. *Cancer Chemother Pharmacol* 2003; **51:** 349–58.
2. van den Heuvel OA, *et al.* Amygdala activity in obsessive-compulsive disorder with contamination fear: a study with oxygen-15 water positron emission tomography. *Psychiatry Res* 2004; **132:** 225–37.
3. Iwanishi K, *et al.* Influence of residual oxygen-15-labeled carbon monoxide radioactivity on cerebral blood flow and oxygen extraction fraction in a dual-tracer autoradiographic method. *Ann Nucl Med* 2009; **23:** 363–71.
4. Luurtsema G, *et al.* Pharmaceutical preparation of oxygen-15 labelled molecular oxygen and carbon monoxide gasses in a hospital setting. *J Clin Pharm Ther* 2010; **35:** 63–9.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Carbon Monoxide(^{15}O); Oxygen(^{15}O); Water(^{15}O) Injection;
USP 36: Water O 15 Injection.

Phosphorus-32

Fosfor-32; Fosfór-32; Fosfori-32; Fósforo 32; Fosforo-32; Foszfor-32; Phosphor-32; Phosphore-32; Фосфор-32.
CAS — 14596-37-3 (phosphorus-32); 24381-60-0 (chromic phosphate (^{32}P)); 7635-46-3 (sodium phosphate (^{32}P)).
ATC — V10AX01 (phosphorus chromic phosphate colloid ($_{32}$P)); V10XX01 (sodium phosphate ($_{32}$P)).
ATC Vet — QV10AX01 (phosphorus chromic phosphate colloid ($_{32}$P)); QV10XX01 (sodium phosphate ($_{32}$P)).
UNII — 690284A407 (phosphorus-32); QHO02LZ4H2 (chromic phosphate (^{32}P)); O181101B5G (sodium phosphate (^{32}P)).

NOTE. Chromic Phosphate P 32 is *USAN*.
Sodium Phosphate (^{32}P) is *rINN* and Sodium Phosphate P 32 is *USAN*.
HALF-LIFE. 14.3 days.

Profile

Phosphorus-32 (^{32}P) is a radioactive isotope of phosphorus (p. 2589.2) that decays by beta emission (see Radioactive Decay, p. 2222.1). Given as sodium phosphate (^{32}P), it is used intravenously in the treatment of polycythaemia vera (p. 695.2). Phosphorus-32 is taken up by the rapidly proliferating haematopoietic cells sufficiently to reduce their reproduction. Sodium phosphate (^{32}P) has also been used intravenously in the treatment of chronic myeloid (p. 694.2) and chronic lymphocytic leukaemia (p. 693.3) and in the palliative treatment of bone metastases (p. 700.3).

Chromic phosphate (^{32}P) has been given intraperitoneally or intrapleurally in the treatment of malignant effusions (p. 700.1); it has also been given by interstitial injection for the treatment of ovarian (p. 711.2) or prostatic carcinoma (p. 712.3). Intra-articular injection into the synovial joint space has been used for the treatment of diseases such as rheumatoid arthritis and arthropathies (radiation synovectomy).

References.
1. Parmentier C. Use and risks of phosphorus-32 in the treatment of polycythaemia vera. *Eur J Nucl Med Mol Imaging* 2003; **30:** 1413–17.
2. Hasegawa T, *et al.* Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. *Neurosurgery* 2004; **54:** 813–20.
3. Vinjamuri S, Ray S. Phosphorus-32: the forgotten radiopharmaceutical? *Nucl Med Commun* 2008; **29:** 95–7.
4. Zhao R, *et al.* Treatment of cystic craniopharyngioma with phosphorus-32 intracavitary irradiation. *Childs Nerv Syst* 2010; **26:** 669–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Phosphocol†.

Pharmacopoeial Preparations
Ph. Eur.: Sodium Phosphate(^{32}P) Injection;
USP 36: Chromic Phosphate P 32 Suspension; Sodium Phosphate P 32 Solution.

Radium-223

BAY-88-8223 (radium (^{223}Ra) chloride); Raadium-223; Rad-223; Radi-223; Radij-223; Rādijs-223; Radijum-223; Radín-223; Radio-223; Rádio-223; Radis-223; Rádium-223; Radiwm-223; Radyum-223; Raidiam-223; Радий-223.
CAS — 15623-45-7(radium-223); 444811-40-9 (radium (^{223}Ra) chloride).

NOTE. Radium Ra 223 Dichloride is *USAN*.
The name Alpharadin has been used as a trade mark for radium-223 chloride.
HALF-LIFE. 11.4 days.

Profile

Radium-223 (^{223}Ra) is a radioactive isotope of radium that emits alpha particles (see Radioactive Decay, p. 2222.1). Radium (^{223}Ra) chloride is given intravenously for the treatment of bone metastases in patients with castration-resistant prostate cancer (p. 712.3).

References.
1. Harrison MR, *et al.* Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease. *Cancer Manag Res* 2013; **5:** 1–14.
2. Joung JY, *et al.* Radium Ra 223 dichloride in castration-resistant prostate cancer. *Drugs Today* 2013; **49:** 483–90.
3. Parker C, *et al.* ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; **369:** 213–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Xofigo; ***USA***: Xofigo.

Rhenium-186

Ren-186; Renín-186; Renio 186; Renio-186; Rênio-186; Renium-186; Rénium-186; Rhénium-186; Рений-186.
CAS — 14998-63-1.
ATC — V10AX05 (rhenium sulfide colloid ($_{186}$Re)); V10BX03 (rhenium etidronate ($_{186}$Re)).
ATC Vet — QV10AX05 (rhenium sulfide colloid ($_{186}$Re)); QV10BX03 (rhenium etidronate ($_{186}$Re)).

HALF-LIFE. 89.2 hours.

Profile

Rhenium-186 (^{186}Re) is a radioactive isotope of rhenium that decays by beta and gamma emission (see Radioactive Decay, p. 2222.1). It has been used in the form of a colloidal sulfide, as an imaging agent and for the treatment of arthritic joint conditions. Rhenium (^{186}Re) etidronate is used for the palliation of painful bone metastases (p. 700.3) of prostate cancer. Monoclonal antibodies labelled with rhenium-186 have been investigated for the treatment of various malignant neoplasms.

References.
1. Han SH, *et al.* 186Re-etidronate: efficacy of palliative radionuclide therapy for painful bone metastases. *Q J Nucl Med* 2001; **45:** 84–90.
2. Liu G, Hnatowich DJ. Labeling biomolecules with radiorhenium: a review of the bifunctional chelators. *Anticancer Agents Med Chem* 2007; **7:** 367–77.
3. Klett R, *et al.* Radiosynoviorthesis of medium-sized joints with rhenium-186-sulphide colloid: a review of the literature. *Rheumatology (Oxford)* 2007; **46:** 1531–7.
4. van der Zant FM, *et al.* Radiation synovectomy with (90)Yttrium, (186) Rhenium and (169)Erbium: a systematic literature review with meta-analyses. *Clin Exp Rheumatol* 2009; **27:** 130–9.
5. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; **40:** 89–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: RE-186-MM-1; Re-Bone†; ***Fr.***: Nanocis; ***Irl.***: Nanocis.

Rhenium-188

Ren-188; Renín-188; Renio-188; Rênio-188; Renium-188; Rénium-188; Rhénium-188; Рений-188.
CAS — 14378-26-8.

HALF-LIFE. 16.98 hours.

Profile

Rhenium-188 (^{188}Re) is a radioactive isotope of rhenium that decays by beta and gamma emission (see Radioactive Decay, p. 2222.1). It has been used to label antibody fragments. Rhenium (^{188}Re) etidronate is used for the palliation of painful bone metastases (p. 700.3). Iodised oil labelled with rhenium-188 is used intra-arterially for the treatment of liver tumours. A rhenium-188-filled balloon catheter has also been used for recurrent restenosis.

References.
1. Klein SA, *et al.* Transplantation-related toxicity and acute intestinal graft-versus-host disease after conditioning regimens intensified with rhenium 188-labeled anti-CD66 monoclonal antibodies. *Blood* 2002; **99:** 2270–1.
2. Scheffler J, *et al.* Application of rhenium-188 HEDP in bone metastases therapy. *Nucl Med Rev Cent East Eur* 2003; **6:** 55–7.
3. Wöhrle J, *et al.* Intracoronary β-brachytherapy using a rhenium-188 filled balloon catheter in restenotic lesions of native coronary arteries and venous bypass grafts. *Eur J Nucl Med Mol Imaging* 2006; **33:** 1314–20.
4. Zanzonico PB, Divgi C. Patient-specific radiation dosimetry for radionuclide therapy of liver tumors with intrahepatic artery rhenium-188 lipiodol. *Semin Nucl Med* 2008; **38:** S30–S39.
5. Bernal P, *et al.* International Atomic Energy Agency-sponsored multination study of intra-arterial rhenium-188-labeled lipiodol in the treatment of inoperable hepatocellular carcinoma: results with special emphasis on prognostic value of dosimetric study. *Semin Nucl Med* 2008; **38:** S40–S45.
6. Lambert B, *et al.* Rhenium-188 based radiopharmaceuticals for treatment of liver tumours. *Q J Nucl Med Mol Imaging* 2009; **53:** 305–10.
7. Shamim SA, *et al.* Role of rhenium-188 tin colloid radiosynovectomy in patients with inflammatory knee joint conditions refractory to conventional therapy. *Nucl Med Commun* 2010; **31:** 814–20.

Rubidium-82

Rubid-82; Rúbidín-82; Rubídio; Rubidio 82; Rubídium-82; Рубидий-82.
CAS — 14391-63-0 (rubidium-82); 132486-03-4 (rubidium (^{82}Rb) chloride).
UNII — 9K730EL8KU (rubidium-82); F0Z746KRKQ (rubidium (^{82}Rb) chloride).

NOTE. Rubidium Chloride Rb 82 is *USAN*.
HALF-LIFE. 75 seconds.

Profile

Rubidium-82 (^{82}Rb) is a radioactive isotope of rubidium that emits positrons. It is a daughter nuclide of strontium-82 (^{82}Sr). It is used in positron-emission tomography (see Radioactive Decay, p. 2222.1). Rubidium chloride (^{82}Rb) is given intravenously for cardiac imaging to assess myocardial perfusion and heart function.

Preparations

Pharmacopoeial Preparations
USP 36: Rubidium Chloride Rb 82 Injection.

Samarium-153

Samario 153; Samario-153; Samário-153; Szamárium-153; Самарий-153.
CAS — 15766-00-4 (samarium-153); 154427-83-5 (samarium (^{153}Sm) lexidronam); 160369-78-8 (samarium (^{153}Sm) lexidronam pentasodium).
ATC — V10AX02 (samarium hydroxyapatite colloid ($_{153}$Sm)); V10BX02 (samarium lexidronam ($_{153}$Sm)).
ATC Vet — QV10AX02 (samarium hydroxyapatite colloid ($_{153}$Sm)); QV10BX02 (samarium lexidronam ($_{153}$Sm)).
UNII — 6Q1KA41UWM (samarium-153); 7389YR3OOV (samarium (^{153}Sm) lexidronam pentasodium).

NOTE. Samarium (^{153}Sm) Lexidronam is *rINN* and Samarium Sm 153 Lexidronam is *USAN*.
Samarium (^{153}Sm) Lexidronam Pentasodium is *rINNM* and Samarium Sm 153 Lexidronam Pentasodium is *USAN*.
HALF-LIFE. 46.3 hours.

Profile

Samarium-153 (^{153}Sm) is a radioactive isotope of samarium that emits beta and gamma radiation (see Radioactive Decay, p. 2222.1). Samarium (^{153}Sm) lexidronam (samarium (^{153}Sm) EDTMP) is given intravenously as the pentasodium for the palliative treatment of painful bone metastases (p. 700.3).

References.
1. Sartor O, *et al.* Samarium-153-lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004; **63:** 940–5.
2. Finlay IG, *et al.* Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005; **6:** 392–400.
3. Anderson P. Samarium for osteoblastic bone metastases and osteosarcoma. *Expert Opin Pharmacother* 2006; **7:** 1475–86.
4. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; **40:** 89–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Quadramet; ***Fr.***: Quadramet; ***Irl.***: Quadramet; ***Ital.***: Quadramet; ***Neth.***: Quadramet; ***Pol.***: Quadramet; ***Port.***: Quadramet; ***Spain***: Quadramet; ***Switz.***: Quadramet; ***UK***: Quadramet; ***USA***: Quadramet.

Pharmacopoeial Preparations
USP 36: Samarium Sm 153 Lexidronam Injection.

Selenium-75

Seleen-75; Seleeni-75; Selen-75; Selenio 75; Selênio-75; Sélénium-75; Szelén-75; Селен-75.

CAS — 14265-71-5 (selenium-75); 1187-56-0 (selenomethionine (^{75}Se)).

ATC — V09DX01 (selenium tauroselcholic acid ($_{75}$Se)); V09XX03 (selenium norcholesterol ($_{75}$Se)).

ATC Vet — QV09DX01 (selenium tauroselcholic acid ($_{75}$Se)); QV09XX03 (selenium norcholesterol ($_{75}$Se)).

UNII — 0X5608YSTZ (dl-selenomethionine (^{75}Se)); P6708E7555 (l-selenomethionine (^{75}Se)).

NOTE. Selenomethionine (^{75}Se) is *rINN* and Selenomethionine Se 75 is *USAN*.

HALF-LIFE. 119.8 days.

Profile

Selenium-75 (^{75}Se) is a radioactive isotope of selenium (p. 2086.3) that emits gamma radiation (see Radioactive Decay, p. 2222.1). Tauroselcholic acid (^{75}Se) (^{75}SeHCAT) is used orally in the measurement of bile acid absorption for the assessment of ileal function.

Selenium-75 in the form of 6β-[(methyl[^{75}Se]seleno) methyl]-19-norcholest-5(10)-en-3β-ol (selenonorcholesterol (^{75}Se)) has been used intravenously in adrenal scintigraphy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: SeHCAT†; ***Denm.***: SeHCAT; ***Fin.***: SeHCAT; ***Irl.***: SeHCAT; ***Neth.***: SeHCAT; ***Spain***: SeHCAT; ***UK***: Scintadren; SeHCAT.

Strontium-89

Estroncio 89; Estrôncio-89; Stroncium-89; Stront-89; Strontín-89; Stronzio-89; Стронций-89.

CAS — 14158-27-1 (strontium-89); 38270-90-5 (strontium (^{89}Sr) chloride).

ATC — V10BX01 (strontium chloride ($_{89}$Sr)).

ATC Vet — QV10BX01 (strontium chloride ($_{89}$Sr)).

UNII — 06A33308KH (strontium-89 ion); 5R78837D4A (strontium chloride (^{89}Sr)).

NOTE. Strontium Chloride Sr 89 is *USAN*.

HALF-LIFE. 50.5 days.

Profile

Strontium-89 (^{89}Sr) is a radioactive isotope of strontium that decays by beta emission (see Radioactive Decay, p. 2222.1). Strontium chloride (^{89}Sr) is given intravenously for the palliation of pain in patients with bone metastases (p. 700.3).

References.

1. Robinson RG, *et al.* Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995; **274:** 420–4.
2. Giammarile F, *et al.* Bone pain palliation with strontium-89 in cancer patients with bone metastases. *Q J Nucl Med* 2001; **45:** 78–83.
3. Finlay IG, *et al.* Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005; **6:** 392–400.
4. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; **40:** 89–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Metastron; ***Belg.***: Metastron†; ***Cz.***: Metastron; ***Denm.***: Metastron; ***Fin.***: Metastron; ***Fr.***: Metastron; ***Irl.***: Metastron; ***Israel***: Metastron; ***Ital.***: Metastron; ***Neth.***: Metastron; ***Port.***: Metastron; ***Spain***: Metastron; ***Switz.***: Metastron; ***UK***: Metastron; ***USA***: Metastron.

Pharmacopoeial Preparations

Ph. Eur.: Strontium(^{89}Sr) Chloride Injection;
USP 36: Strontium Chloride Sr 89 Injection.

Technetium-99m

Technécium-99m; Technecium-99m; Technet-99m; Technétium-99m; Tecnecio 99m; Tecnécio-99m; Tecnezio-99m; Teknetín-99m; Teknetium-99m; Технеций-99m.

CAS — 14133-76-7 (technetium-99); 154361-49-6 (arcitumomab (^{99m}Tc)); 54277-47-3 (macrosalb (^{99m}Tc)); 178959-14-3 (technetium (^{99m}Tc) apcitide); 121281-41-2 (technetium (^{99m}Tc) bicisate); 479410-20-3 (technetium (^{99m}Tc) etarfolatide); 105613-48-7 (technetium (^{99m}Tc) exametazime); 225239-31-6 (technetium (^{99m}Tc) fanolesomab); 142481-95-6 (technetium (^{99m}Tc) furifosmin); 125224-05-7 (technetium (^{99m}Tc) mertiatide); 131608-78-1 (technetium (^{99m}Tc) nitridocade); 165942-79-0 (technetium (^{99m}Tc) nofetumomab merpentan); 65454-61-7 (technetium (^{99m}Tc) pentetate); 157476-76-1 (technetium (^{99m}Tc) pintumomab); 109581-73-9 (technetium (^{99m}Tc) sestamibi); 106417-28-1 (technetium (^{99m}Tc) siboroxime); 7704-34-9 (technetium (^{99m}Tc) sulfur colloid); 104716-22-5 (technetium (^{99m}Tc) teboroxime); 104348-91-6 (technetium (^{99m}Tc) tiatide anion); 1262984-82-6 (technetium (^{99m}Tc) tilmanocept).

ATC — V09AA01 (technetium exametazime ($_{99m}$Tc)); V09AA02 (technetium bicisate ($_{99m}$Tc)); V09BA01 (technetium oxidronate ($_{99m}$Tc)); V09BA02 (technetium medronate ($_{99m}$Tc)); V09BA03 (technetium pyrophosphate ($_{99m}$Tc)); V09BA04 (technetium butedronate ($_{99m}$Tc)); V09CA01 (technetium pentetate ($_{99m}$Tc)); V09CA02 (technetium succimer ($_{99m}$Tc)); V09CA03 (technetium mertiatide ($_{99m}$Tc)); V09CA04 (technetium gluceptate ($_{99m}$Tc)); V09CA05 (technetium gluconate ($_{99m}$Tc)); V09CA06 (technetium ethylenedicysteine ($_{99m}$Tc)); V09DA01 (technetium disofenin ($_{99m}$Tc)); V09DA02 (technetium etifenin ($_{99m}$Tc)); V09DA03 (technetium lidofenin ($_{99m}$Tc)); V09DA04 (technetium mebrofenin ($_{99m}$Tc)); V09DA05 (technetium galtifenin ($_{99m}$Tc)); V09DB01 (technetium nanocolloid ($_{99m}$Tc)); V09DB02 (technetium microcolloid ($_{99m}$Tc)); V09DB03 (technetium millimicrospheres ($_{99m}$Tc)); V09DB04 (technetium tin colloid ($_{99m}$Tc)); V09DB05 (technetium sulfur colloid ($_{99m}$Tc)); V09DB06 (technetium rhenium sulfide colloid ($_{99m}$Tc)); V09DB07 (technetium phytate ($_{99m}$Tc)); V09EA01 (technetium pentetate ($_{99m}$Tc)); V09EA02 (technetium technegas ($_{99m}$Tc)); V09EA03 (technetium nanocolloid ($_{99m}$Tc)); V09EB01 (technetium macrosalb ($_{99m}$Tc)); V09EB02 (technetium microspheres ($_{99m}$Tc)); V09FX01 (technetium pertechnetate ($_{99m}$Tc)); V09GA01 (technetium sestamibi ($_{99m}$Tc)); V09GA02 (technetium tetrofosmin ($_{99m}$Tc)); V09GA03 (technetium teboroxime ($_{99m}$Tc)); V09GA04 (technetium human albumin ($_{99m}$Tc)); V09GA05 (technetium furifosmin ($_{99m}$Tc)); V09GA06 (technetium stannous agent labelled cells ($_{99m}$Tc)); V09GA07 (technetium apcitide ($_{99m}$Tc)); V09HA01 (technetium human immunoglobulin ($_{99m}$Tc)); V09HA02 (technetium exametazime labelled cells ($_{99m}$Tc)); V09HA03 (technetium antigranulocyte antibody ($_{99m}$Tc)); V09HA04 (technetium sulesomab ($_{99m}$Tc)); V09IA01 (technetium antiCEA antibody ($_{99m}$Tc)); V09IA02 (technetium antimelanoma antibody ($_{99m}$Tc)); V09IA03 (technetium pentavalent succimer ($_{99m}$Tc)); V09IA04 (technetium votumumab ($_{99m}$Tc)); V09IA05 (technetium depreotide ($_{99m}$Tc)); V09IA06 (technetium arcitumomab ($_{99m}$Tc)).

ATC Vet — QV09AA01 (technetium exametazime ($_{99m}$Tc)); QV09AA02 (technetium bicisate ($_{99m}$Tc)); QV09BA01 (technetium oxidronate ($_{99m}$Tc)); QV09BA02 (technetium medronate ($_{99m}$Tc)); QV09BA03 (technetium pyrophosphate ($_{99m}$Tc)); QV09BA04 (technetium butedronate ($_{99m}$Tc)); QV09CA01 (technetium pentetate ($_{99m}$Tc)); QV09CA02 (technetium succimer ($_{99m}$Tc)); QV09CA03 (technetium mertiatide ($_{99m}$Tc)); QV09CA04 (technetium gluceptate ($_{99m}$Tc)); QV09CA05 (technetium gluconate ($_{99m}$Tc)); QV09CA06 (technetium ethylenedicysteine ($_{99m}$Tc)); QV09DA01 (technetium disofenin ($_{99m}$Tc)); QV09DA02 (technetium etifenin ($_{99m}$Tc)); QV09DA03 (technetium lidofenin ($_{99m}$Tc)); QV09DA04 (technetium mebrofenin ($_{99m}$Tc)); QV09DA05 (technetium galtifenin ($_{99m}$Tc)); QV09DB01 (technetium nanocolloid ($_{99m}$Tc)); QV09DB02 (technetium microcolloid ($_{99m}$Tc)); QV09DB03 (technetium millimicrospheres ($_{99m}$Tc)); QV09DB04 (technetium tin colloid ($_{99m}$Tc)); QV09DB05 (technetium sulfur colloid ($_{99m}$Tc)); QV09DB06 (technetium rhenium sulfide colloid ($_{99m}$Tc)); QV09DB07 (technetium phytate ($_{99m}$Tc)); QV09EA01 (technetium pentetate ($_{99m}$Tc)); QV09EA02 (technetium technegas ($_{99m}$Tc)); QV09EA03 (technetium nanocolloid ($_{99m}$Tc)); QV09EB01 (technetium macrosalb ($_{99m}$Tc)); QV09EB02 (technetium microspheres ($_{99m}$Tc)); QV09FX01 (technetium pertechnetate ($_{99m}$Tc)); QV09GA01 (technetium sestamibi ($_{99m}$Tc)); QV09GA02 (technetium tetrofosmin ($_{99m}$Tc)); QV09GA03 (technetium teboroxime ($_{99m}$Tc)); QV09GA04 (technetium human albumin ($_{99m}$Tc)); QV09GA05 (technetium furifosmin ($_{99m}$Tc)); QV09GA06 (technetium stannous agent labelled cells ($_{99m}$Tc)); QV09GA07 (technetium apcitide ($_{99m}$Tc)); QV09HA01 (technetium human immunoglobulin ($_{99m}$Tc)); QV09HA02 (technetium exametazime labelled cells ($_{99m}$Tc)); QV09HA03 (technetium antigranulocyte antibody ($_{99m}$Tc)); QV09HA04 (technetium sulesomab ($_{99m}$Tc)); QV09IA01 (technetium antiCEA antibody ($_{99m}$Tc)); QV09IA02 (technetium antimelanoma antibody ($_{99m}$Tc)); QV09IA03 (technetium pentavalent succimer ($_{99m}$Tc)); QV09IA04 (technetium votumumab ($_{99m}$Tc)); QV09IA05 (technetium depreotide ($_{99m}$Tc)); QV09IA06 (technetium arcitumomab ($_{99m}$Tc)); QV09IA07 (technetium hynic-octreotide ($_{99m}$Tc)).

UNII — Z8E46IA45W (technetium (^{99m}Tc) albumin aggregated); IV7T84QA4T (technetium (^{99m}Tc) apcitide); H25WJA31XE (technetium (^{99m}Tc) bicisate); 9M48M2SF02 (technetium (^{99m}Tc) depreotide); QTJ2VIW97T (technetium (^{99m}Tc) disofenin); 13W7DMI45X (technetium (^{99m}Tc) etidronate); 3B744AG22N (technetium (^{99m}Tc) exametazime); I853LE095B (technetium (^{99m}Tc) gluceptate); 36ITO9SKQJ (technetium (^{99m}Tc) mertiatide); F2NQ468L52 (technetium (^{99m}Tc) mebrofenin); X89XV46R07 (technetium (^{99m}Tc) medronate); 36ITO9SKQJ (technetium (^{99m}Tc) mertiatide); UQ9G2F6I3H (technetium (^{99m}Tc) nitridocade); MG4KI49HHJ (technetium (^{99m}Tc) oxidronate); VW78417PU1 (technetium (^{99m}Tc) pentetate); 971Z4W1S09 (technetium (^{99m}Tc) sestamibi); A0730CX801 (technetium (^{99m}Tc) sodium pertechnetate); 494JNQ8L28 (technetium (^{99m}Tc) succimer); 556Q0P6PB1 (technetium (^{99m}Tc) sulfur colloid); UT0WHJ4951 (technetium (^{99m}Tc) teboroxime); 42FOP1YX93 (technetium (^{99m}Tc) tetrofosmin).

NOTE. Macrosalb (^{99m}Tc) is *rINN* and *BAN*.

Technetium Tc 99m Albumin Aggregated, Technetium Tc 99m Albumin Colloid, and Technetium Tc 99m Albumin Microaggregated are *USAN*.

Technetium Tc 99m Antimony Trisulfide Colloid is *USAN*.

Technetium (^{99m}Tc) Apcitide is *rINN* and Technetium Tc 99m Apcitide is *USAN*.

Technetium (^{99m}Tc) Bicisate is *rINN*, Technetium[^{99m}Tc] Bicisate is *BAN*, and Technetium Tc 99m Bicisate is *USAN*.

Technetium (^{99m}Tc) Depreotide is *rINNM*.

Technetium (^{99m}Tc) Etarfolatide is *pINN* and Technetium Tc 99m Etarfolatide is *USAN*.

Technetium Tc 99m Exametazime is *USAN*.

Technetium (^{99m}Tc) Fanolesomab is *rINN* and Technetium Tc 99m Fanolesomab is *USAN*.

Technetium (^{99m}Tc) Furifosmin is *rINN* and Technetium Tc 99m Furifosmin is *USAN*.

Technetium Tc 99m Lidofenin is *USAN*.

Technetium Tc 99m Mebrofenin is *USAN*.

Technetium Tc 99m Medronate Disodium is *USAN*.

Technetium Tc 99m Mertiatide is *USAN*.

Technetium (^{99m}Tc) Nitridocade is *rINN* and Technetium Tc 99m is Nitridocade is *USAN*.

Technetium (^{99m}Tc) Nofetumomab Merpentan is *rINN*.

Technetium Tc 99m Pentetate Calcium Trisodium is *USAN*.

Technetium (^{99m}Tc) Pintumomab is *rINN*.

Technetium Tc 99m Red Blood Cells is *USAN*.

Technetium (^{99m}Tc) Sestamibi is *rINN*, Technetium[^{99m}Tc] Sestamibi is *BAN*, and Technetium Tc 99m Sestamibi is *USAN*.

Technetium (^{99m}Tc) Siboroxime is *rINN* and Technetium Tc 99m Siboroxime is *USAN*.

Technetium Tc 99m Sulfur Colloid is *USAN*.

Technetium (^{99m}Tc) Teboroxime is *rINN*, Technetium[^{99m}Tc] Teboroxime is *BAN*, and Technetium Tc 99m Teboroxime is *USAN*.

Technetium[^{99m}Tc] Tiatide is *BAN*.

Technetium Tc 99m Tilmanocept is *USAN*.

HALF-LIFE. 6.01 hours.

Uses and Administration

Technetium-99m (^{99m}Tc) decays by isomeric transition and emits gamma rays (see Radioactive Decay, p. 2222.1). It is a daughter of molybdenum-99 (^{99}Mo, half-life 65.9 hours) and because of its short half-life is normally prepared just before use by elution from a sterile generator consisting of molybdenum-99 adsorbed onto alumina in a glass column. Technetium-99m as pertechnetate ($^{99m}TcO_4^-$) is obtained by elution with a sterile solution of sodium chloride 0.9%. Radiopharmaceuticals of technetium-99m are prepared shortly after elution to reduce loss by decay.

Because it has a short half-life and can be given in relatively large doses, and because the energy of its gamma-emission is readily detected, technetium-99m is very widely used, either as the pertechnetate or in the form of various labelled compounds, particles, and colloids for scanning bone and organs such as the brain, heart, kidney, liver, lung, spleen, and thyroid.

Sodium pertechnetate (^{99m}Tc) is used orally or intravenously for angiography and for imaging blood pools, brain, salivary glands, and the thyroid gland. Topical application to the eye is used for studying nasolachrymal drainage and the intraurethral route for imaging the urinary tract. Potassium perchlorate may be given before the pertechnetate to prevent uptake in the thyroid or choroid plexus.

Macroaggregates of human albumin labelled with technetium-99m (macrosalb (^{99m}Tc)) are used in lung scanning for the detection of abnormal lung perfusion patterns. Labelled macroaggregates of albumin have also been used in venography for the detection of deep-vein thrombosis of the legs. Technetium (^{99m}Tc) apcitide is a labelled peptide that binds to the glycoprotein IIb/IIIa receptor of activated platelets, and is also used for imaging of deep-vein thrombosis.

When technetium-99m bound to human serum albumin is given intravenously it becomes evenly distributed in the circulation and highly vascular organs or pools of blood may be readily located. Such a preparation is used in the examination of the heart.

Technetium-99m in the form of a colloid, such as albumin, sulfur, antimony sulfide, calciumphytate, or tin, is used intravenously for the examination of the liver, spleen, and bone marrow. Sulfur colloid (^{99m}Tc) may be given orally

for oesophageal and gastrointestinal imaging, and subcutaneously for scanning of the lymphatic system. Colloidal rhenium sulfide (^{99m}Tc) has been used for sentinel lymph node detection in patients with malignancies.

Technetium-99m complexes of iminodiacetic acid derivatives, such as disofenin, etifenin, lidofenin, and mebrofenin are used intravenously in the investigation of hepatic function and in the imaging of the hepatobiliary system.

Agents used intravenously in both brain and renal imaging are technetium-99m-labelled gluceptate and pentetate. Technetium (^{99m}Tc) gluconate and technetium (^{99m}Tc) glucoheptonate were used for renal studies; they are used for labelling red blood cells. Other technetium-99m-labelled compounds are used in brain or kidney scanning; for instance, labelled bicisate and exametazime have been used in brain imaging and betiatide, mertiatide, and succimer have been used in kidney studies. The pentetate is also given by inhalation for lung ventilation imaging.

For bone scanning various labelled phosphate compounds may be used and include medronate, oxidronate, and pyrophosphate, all given intravenously. Technetium-99m as the pyrophosphate was also used in cardiac scintigraphy; it is also used to label red blood cells for use in blood pool scintigraphy and for the detection of gastrointestinal bleeding.

Compounds used intravenously in cardiac imaging include technetium-99m-labelled sestamibi, teboroxime, and tetrofosmin. Technetium (^{99m}Tc) sestamibi is also used for breast imaging.

Technetium-99m-labelled leucocytes (prepared using exametazime) are used for localisation of sites of inflammation or infection. Red blood cells are labelled with technetium-99m and used for blood pool imaging, and detection of gastrointestinal bleeding.

Monoclonal antibodies labelled with technetium-99m, such as arcitumomab and nofetumomab merpentan, are used for the detection and localisation of malignant neoplasms. Labelled sulesomab is used in the detection of osteomyelitis. Labelled fanolesomab was used in the diagnosis of appendicitis but was withdrawn from the market due to severe adverse effects. Technetium (^{99m}Tc) depreotide is a labelled peptide used intravenously for imaging of pulmonary malignancy.

Many other technetium-99m-labelled compounds have been prepared and used in different clinical studies for the examination of different organs or systems. Use with other radionuclides includes subtraction scanning with thallium-201 to detect parathyroid tumours.

Reviews.

1. Banerjee S, *et al.* Evolution of Tc-99m in diagnostic radiopharmaceuticals. *Semin Nucl Med* 2001; **31:** 260–77.
2. Mease RC, Lambert C. Newer methods of labeling diagnostic agents with Tc-99m. *Semin Nucl Med* 2001; **31:** 278–85.
3. Arano Y. Recent advances in 99mTc radiopharmaceuticals. *Ann Nucl Med* 2002; **16:** 79–93.
4. Decristoforo C, Mather SJ. The influence of chelator on the pharmacokinetics of 99mTc-labelled peptides. *Q J Nucl Med* 2002; **46:** 195–205.
5. Ballinger JR. The influence of carrier on 99mTc radiopharmaceuticals. *Q J Nucl Med* 2002; **46:** 224–32.
6. Eckelman WC. Unparalleled contribution of technetium-99m to medicine over 5 decades. *JACC Cardiovasc Imaging* 2009; **2:** 364–8.

Adverse Effects and Precautions

Hypersensitivity reactions have been reported with technetium-99m preparations.

Breast feeding. The last available guidance from the American Academy of Pediatrics stated[1] that temporary cessation of breast feeding was required after exposure to technetium-99m since radioactivity has been reported to be present in breast milk for 15 to 72 hours.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cardiolite; Ceretec; Myoview; Neurolite; ***Austria***: TechneScan MAG3; Ultra Technekow FM; ***Belg.***: Amerscan Medronate†; Maasol†; Myoview†; Nanocoll†; Stabilised Ceretec†; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan PYP; Ultra TechneKow FM; Venticoll†; ***Cz.***: 6-MDP, 8-MDP; Amerscan Hepatate†; Amerscan Medronate; Amerscan Stannous†; Brain-Spect; Cardio-Spect; Cardiolite†; Ceretec; Drytec; DTPA; Elumatic III; Hibida; HM-PAO Kit†; Leuco-Scint; LeukoScan; Macro-Albumon; Macrotec; Mag 3; Myoview; Nano-Albumon; Nanocis; Nanocoll; NeoSpect†; Neurolite; Neuroscan; Pulmocis; Scintimun; Senti-Scint; Stamicis; TechneScan DMSA; TechneScan DTPA; TechneScan Has†; TechneScan HDP; TechneScan HIG; TechneScan LyoMAA; TechneScan MAG3; TechneScan PYP; TechneScan Sestamibi; Trimetyl-HIDA; Ultra Technekow FM; UltraTag RBC; ***Denm.***: Drytec; Neurolite; Pulmotec; ***Fin.***: Amerscan Hepatate†; Amerscan Medronate†; Amerscan Stannous; Angiocis; Bridatec; Cardiolite; Ceretec; Drytec; Maasol; Myoview; Nanocoll; Neurolite; Osteocis; Osteosol†; Pentacis; Pulmocis; Pulmotec; Renocis; Sammibi; Stamicis; Teceos; TechneScan LyoMAA; TechneScan Sestamibi; Vasculocis; Venticoll; ***Fr.***: Amerscan Etain Stanneux†; Amerscan Hepatate†; Amerscan Medronate†; Amerscan Pentetate†; Angiocis; Cardiolite; Cerestab; Ceretec; Elumatic; Myoview; Nanocoll; NeoSpect†; Neurolite; Osteocis; Pentacis; Phytacis; Pulmocis; Pulmotec; Renocis; Scintimun; Stamicis; Teceos; TechneScan DMSA; TechneScan HDP; TechneScan LyoMAA; Vasculocis; ***Ger.***: Draxmibi†; Macrosalb Draximage; ***Gr.***: Humaspect†; ***Irl.***: Amerscan Medronate; Amerscan Stannous†; Ceretec; Choledíam; Drytec; Elumatic; LeukoScan; Myoview; NeoSpect†; Osteocis; Pentacis; Pulmocis; Pulmotec; Renocis; Scintimun; Stamicis; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; TechneScan MIBI; TechneScan PYP; Ultra TechneKow FM; ***Israel***: Ceretec; Myoview; Neurolite; RBC-Kit; Technelite†; ***Ital.***: Cardiolite; Ceretec; LeukoScan; Myoview; NeoSpect†; Neurolite; TechneScan MAG3; ***Neth.***: Amerscan Hepatate†; Amerscan Stannous†; Bridatec; Cardiolite; Ceretec; Choledíam†; DraxMibi; Drytec; Elumatic; Hepatate; LeukoScan; Maasol; Macrosalb Draximage†; Macrosalb†; Medronaat Draximage; Myoview; Nanocoll; NeoSpect†; Neurolite†; Osteocis; Penetaat DraxImage†; Phytacis; Pulmocis; Pulmotec; Scintimun; Stamicis; Stannous Agent; Teceos; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; TechneScan PYP; TechneScan Sestamibi; Tekcis; Ultra TechneKow; UltraTag; ***Pol.***: LeukoScan; Scintimun; ***Port.***: Angiocis; Bridatec†; Cardiolite†; Ceretec; Elumatic; LeukoScan; Macrotec; Mertioscan; Myoview; Nanocis; Nanocoll; NeoSpect†; Neurolite; Osteocis; Pentacis; Phytacis; Pulmotec; Renocis; Scintimun; Stamicis; TechneScan DTPA; TechneScan HDP; TechneScan MAG3; TechneScan Sestamibi; Ultra TechneKow FM; ***Rus.***: Myoview (Миовью); NeoSpect (Неоспект); ***Spain***: Angiocis; Bridatec; Cardiolite; Ceretec; Drytec; Elumatic; LeukoScan; Macrotec; Myoview; Nanocoll; NeoSpect†; Neurolite†; Osteocis; Pentacis; Pulmotec; Scintimun; Stamicis; TechneScan DTPA; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; Ultra Technekow; ***Switz.***: Maasol; Myoview; Nanocoll; Teceos; TechneScan HDP; Tekcis; UltratechneKow; ***UK***: Amerscan DMSA; Amerscan Hepatate; Amerscan Medronate; Amerscan Pentetate; Amerscan Pulmonate; Amerscan Stannous; Amertec; Angiocis; Cardiolite; CEA-Scan; Ceretec; Cholecis; Drytec; Myoview; Nanocoll; Osteocis; Pentacis; Pulmocis; Renocis; ***USA***: AcuTect; Cardiolite; CEA-Scan; Choletec; Lymphoseek; Miraluma; NeoTect; TechneScan HDP.

Multi-ingredient Preparations. ***Fin.***: Tekcis; ***Spain***: Teceos.

Pharmacopoeial Preparations

Ph. Eur.: Sodium Pertechnetate(^{99m}Tc) Injection (Fission); Sodium Pertechnetate(^{99m}Tc) Injection (Non-fission); Technetium (^{99m}Tc) Mebrofenin Injection; Technetium(^{99m}Tc) Bicisate Injection; Technetium(^{99m}Tc) Colloidal Rhenium Sulphide Injection; Technetium(^{99m}Tc) Colloidal Sulphur Injection; Technetium(^{99m}Tc) Colloidal Tin Injection; Technetium(^{99m}Tc) Etifenin Injection; Technetium(^{99m}Tc) Exametazime Injection; Technetium(^{99m}Tc) Gluconate Injection; Technetium(^{99m}Tc) Human Albumin Injection; Technetium(^{99m}Tc) Macrosalb Injection; Technetium(^{99m}Tc) Medronate Injection; Technetium (^{99m}Tc) Mertiatide Injection; Technetium(^{99m}Tc) Microspheres Injection; Technetium(^{99m}Tc) Pentetate Injection; Technetium (^{99m}Tc) Sestamibi Injection; Technetium(^{99m}Tc) Succimer Injection; Technetium(^{99m}Tc) Tin Pyrophosphate Injection;

USP 36: Sodium Pertechnetate Tc 99m Injection; Technetium ^{99m}Tc Fanolesomab Injection; Technetium Tc 99m (Pyro- and trimeta-) Phosphates Injection; Technetium Tc 99m Albumin Aggregated Injection; Technetium Tc 99m Albumin Colloid Injection; Technetium Tc 99m Albumin Injection; Technetium Tc 99m Apcitide Injection; Technetium Tc 99m Arcitumomab Injection; Technetium Tc 99m Bicisate Injection; Technetium Tc 99m Depreotide Injection; Technetium Tc 99m Disofenin Injection; Technetium Tc 99m Etidronate Injection; Technetium Tc 99m Exametazime Injection; Technetium Tc 99m Gluceptate Injection; Technetium Tc 99m Lidofenin Injection; Technetium Tc 99m Mebrofenin Injection; Technetium Tc 99m Medronate Injection; Technetium Tc 99m Mertiatide Injection; Technetium Tc 99m Nofetumomab Merpentan Injection; Technetium Tc 99m Oxidronate Injection; Technetium Tc 99m Pentetate Injection; Technetium Tc 99m Pyrophosphate Injection; Technetium Tc 99m Red Blood Cells Injection; Technetium Tc 99m Sestamibi Injection; Technetium Tc 99m Succimer Injection; Technetium Tc 99m Sulfur Colloid Injection; Technetium Tc 99m Tetrofosmin Injection.

Thallium-201

Tal-201; Talio 201; Tálio-201; Tallio-201; Tallium-201; Таллий-201; Pallín-201.

CAS — 15064-65-0 (thallium-201); 55172-29-7 (thallous (^{201}Tl) chloride).

ATC — V09GX01 (thallium chloride ($_{201}$Tl)).

ATC Vet — QV09GX01 (thallium chloride ($_{201}$Tl)).

UNII — H91Z8HBK1B (thallium-201).

NOTE. Thallous Chloride Tl 201 is *USAN*.

HALF-LIFE. 72.9 hours.

Profile

Thallium-201 (^{201}Tl) is a radioactive isotope of thallium that decays by electron capture and emits X-rays and gamma rays (see Radioactive Decay, p. 2222.1). It is given intravenously in the form of thallous chloride (^{201}Tl) for scanning the myocardium in the investigation of acute myocardial infarction. It is also used with exercise stress testing as an adjunct in the diagnosis of ischaemic heart disease. Adenosine (see Ischaemic Heart Disease, p. 1291.2), dipyridamole (see Myocardial Imaging, p. 1362.3), or dobutamine (see Diagnosis and Testing, p. 1366.2) may be used to induce pharmacological stress in those patients unable to tolerate exercise.

A dual isotope method has been developed to aid the diagnosis of coronary artery disease, using thallous chloride (^{201}Tl) and technetium-99m-labelled sestamibi.

Other uses include localisation of sites of parathyroid hyperactivity and tumour imaging.

References.

1. Steien S, Aaseth J. Thallium-201 as an agent for myocardial imaging studies. *Analyst* 1995; **120:** 779–81.
2. Sumiya H, *et al.* Nuclear imaging of bone tumors: thallium-201 scintigraphy. *Semin Musculoskelet Radiol* 2001; **5:** 177–82.
3. Berk F, *et al.* Thallium-201 imaging in the assessment of tumor response to anti-tumor treatments. *Q J Nucl Med* 2003; **47:** 63–74.
4. Okudan B, Smitherman TC. The value and throughput of rest Thallium-201/stress Technetium -99m sestamibi dual-isotope myocardial SPECT. *Anadolu Kardiyol Derg* 2004; **4:** 161–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: DRN 8103.

Pharmacopoeial Preparations

Ph. Eur.: Thallous(^{201}Tl) Chloride Injection;

USP 36: Thallous Chloride Tl 201 Injection.

Tritium

Hidrógeno 3; Hydrogen-3; Trícium; Tritio; Trítio; Trizio; Tryt; Тритий.

CAS — 10028-17-8.

NOTE. Water, Tritiated is *USAN*.

HALF-LIFE. 12.3 years.

Profile

Tritium is a radioactive isotope of hydrogen that emits beta particles (see Radioactive Decay, p. 2222.1). It has been used in the form of tritiated water to determine the total body water by a dilution technique.

Preparations

Pharmacopoeial Preparations

Ph. Eur.: Tritiated(^{3}H) Water Injection.

Xenon-127

Ksenon-127; Xenón 127; Xénon-127; Xenonum-127; Ксенон-127.

CAS — 13994-19-9.

ATC — V09EX02 (xenon gas ($_{127}$Xe)).

ATC Vet — QV09EX02 (xenon gas ($_{127}$Xe)).

UNII — H95KBR1GDB.

HALF-LIFE. 36.4 days.

Profile

Xenon-127 (^{127}Xe) is a radioactive isotope of xenon (p. 1917.3) that emits gamma radiation (see Radioactive Decay, p. 2222.1). It was used by inhalation for pulmonary function studies and lung imaging.

Preparations

Pharmacopoeial Preparations

USP 36: Xenon Xe 127.

Xenon-133

Ksenon-133; Xenón 133; Xénon (^{133}Xe); Xenon (^{133}Xe) (rINN); Xenón (^{133}Xe); Xenon Xe 133 (USAN); Xenonum (^{133}Xe); Ксенон (^{133}Xe).

CAS — 14932-42-4.

ATC — V09EX03 (xenon gas ($_{133}$Xe)).

ATC Vet — QV09EX03 (xenon gas ($_{133}$Xe)).

UNII — X3P9A5HNYF.

HALF-LIFE. 5.24 days.

Profile

Xenon-133 (^{133}Xe) is a radioactive isotope of xenon (p. 1917.3) that emits beta and gamma radiation (see

Radioactive Decay, p. 2222.1). In the gaseous form, it is mixed with air or oxygen in a bag or in a closed respirator system or spirometer. When the gas is stopped, xenon-133 is excreted promptly and completely through the lungs. It is used by inhalation in pulmonary function studies and lung imaging. It has also been used in cerebral blood flow studies.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Xenon(^{133}Xe) Injection;
USP 36: Xenon Xe 133 Injection; Xenon Xe 133.

Yttrium-90

Itr-90; Itrio 90; Ítrio-90; Ittrio-90; Ittrium-90; Yttrí-90; Иттрий-90.

CAS — 10098-91-6 (yttrium-90); 943976-23-6 (yttrium (^{90}Y) clivatuzumab tetraxetan); 501423-23-0 (yttrium (^{90}Y) epratuzumab); 501423-25-2 (yttrium (^{90}Y) epratuzumab tetraxetan); 501423-27-4 (yttrium (^{90}Y) labetuzumab); 501423-30-9 (yttrium (^{90}Y) labetuzumab tetraxetan); 500784-58-7 (yttrium (^{90}Y) tacatuzumab); 476413-07-7 (yttrium (^{90}Y) tacatuzumab tetraxetan).

ATC — V10AA01 (yttrium citrate colloid ($_{90}$Y)); V10AA02 (yttrium ferrihydroxide colloid ($_{90}$Y)); V10AA03 (yttrium silicate colloid ($_{90}$Y)); V10XX02 (ibritumomab tiuxetan ($_{90}$Y)).

ATC Vet — QV10AA01 (yttrium citrate colloid ($_{90}$Y)); QV10AA02 (yttrium ferrihydroxide colloid ($_{90}$Y)); QV10AA03 (yttrium silicate colloid ($_{90}$Y)); QV10XX02 (ibritumomab tiuxetan ($_{90}$Y)).

UNII — 1K8M7UR6O1 (yttrium-90); 433ME2ATHW (yttrium-90 ion); 2L271110ED (yttrium clivatuzumab tetraxetan (^{90}Y)); J36232195E (ytrrium epratuzumab tetraxetan (^{90}Y)); QA846JAV5B (yttrium ibritumomab tiuxetan (^{90}Y)); GJ2416WK6Y (ytrrium tacatuzumab tetraxetan (^{90}Y)).

NOTE. Yttrium (^{90}Y) Clivatuzumab Tetraxetan is *rINN* and Yttrium Y 90 Clivatuzumab Tetraxetan is *USAN*.
Yttrium Y 90 Epratuzumab is *USAN*.
Yttrium Y 90 Epratuzumab Tetraxetan is *USAN*.
Yttrium Y 90 Labetuzumab is *USAN*.
Yttrium Y 90 Labetuzumab Tetraxetan is *USAN*.
Yttrium Y 90 Tacatuzumab is *USAN*.
Yttrium (^{90}Y) Tacatuzumab Tetraxetan is *rINN* and *BAN* and Yttrium Y 90 Tacatuzumab Tetraxetan is *USAN*.
HALF-LIFE. 64.1 hours.

Profile

Yttrium-90 (^{90}Y) is a radioactive isotope of yttrium that decays by beta emission (see Radioactive Decay, p. 2222.1). It is the daughter nuclide of strontium-90 (^{90}Sr). Yttrium (^{90}Y) chloride conjugated to ibritumomab tiuxetan (p. 804.3) is used in the treatment of non-Hodgkin's lymphoma (p. 696.3). Conjugates with various other monoclonal antibodies and compounds are also under investigation for malignant neoplasms.

Yttrium-90, in the form of a colloidal suspension of yttrium silicate (^{90}Y) has been used for instillation into pleural or peritoneal cavities in the treatment of malignant pleural effusion or malignant ascites.

Yttrium-90, as either yttrium citrate (^{90}Y) or yttrium silicate (^{90}Y), has also been used in the treatment of arthritic conditions of the knee joint.

Yttrium-90 enclosed in glass or resin microspheres has been used for the local treatment of malignant neoplasms of the liver.

References.

1. Heuft-Dorenbosch LL, *et al*. Yttrium radiosynoviorthesis in the treatment of knee arthritis in rheumatoid arthritis: a systematic review. *Ann Rheum Dis* 2000; **59:** 583–6.
2. Gordon LI. Practical considerations and radiation safety in radioimmunotherapy with yttrium 90 ibritumomab tiuxetan (Zevalin). *Semin Oncol* 2003; **30** (6 suppl 17): 23–8.
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7. Gisselbrecht C, *et al*. Current status and future perspectives for yttrium-90 (^{90}Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40:** 1007–17.
8. Zinzani PL, *et al*. Consensus conference: implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice—report of a European workshop. *Eur J Cancer* 2008; **44:** 366–73.
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11. Riaz A, *et al*. Yttrium-90 radioembolization using TheraSphere in the management of primary and secondary liver tumors. *Q J Nucl Med Mol Imaging* 2009; **53:** 311–16.
12. Van De Wiele C, *et al*. Yttrium-90 labelled resin microspheres for treatment of primary and secondary malignant liver tumors. *Q J Nucl Med Mol Imaging* 2009; **53:** 317–24.
13. Riaz A, *et al*. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol* 2009; **20:** 1121–30.
14. Kennedy AS, Salem R. Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies. *Cancer J* 2010; **16:** 163–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Ytracis; Yttriga; ***Fr.***: Ytracis; ***Hung.***: Ytracis; ***Irl.***: Ytracis; Yttriga; ***Israel***: Ytracis; ***Ital.***: Ytracis; ***Neth.***: Ytracis; Yttriga; ***Pol.***: Ytracis; Yttriga; ***Port.***: Ytracis; Yttriga; ***Spain***: Ytracis; Yttriga; ***Switz.***: Ytracis; ***UK***: Ytracis.

Pharmacopoeial Preparations
USP 36: Yttrium Y 90 Ibritumomab Tiuxetan Injection.

Zirconium-89

Cyrkon-89; Sirkon-89; Tsirkoonium-89; Zircônio-89; Zircónio-89; Zirconio-89; Zirconiu; Zirkónium-89; Zirkonium-89; Цирконий-89.

CAS — 13981-27-6.

HALF-LIFE. 78 hours.

Profile

Zirconium-89 (^{89}Zr) is a radioactive isotope of zirconium (p. 2650.3) that emits positrons and gamma rays and decays by electron capture. It is used in positron-emission tomography (PET; see Radioactive Decay, p. 2222.1) to confirm and quantify tumour uptake of monoclonal antibodies ('immuno-PET').

References.

1. Perk LR, *et al*. *p*-Isothiocyanatobenzyl-desferrioxamine: a new bifunctional chelate for facile radiolabeling of monoclonal antibodies with zirconium-89 for immuno-PET imaging. *Eur J Nucl Med Mol Imaging* 2010; **37:** 250–9.
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Sex Hormones and their Modulators

The male and female sex organs, the adrenal cortex, and the placenta produce steroidal hormones that influence the development and maintenance of structures directly and indirectly associated with reproduction. The secretion of these sex hormones is controlled by gonadotrophic hormones of the anterior lobe of the pituitary gland (and in pregnancy, from the placenta); the secretion of pituitary gonadotrophic hormones is in turn influenced by the hypothalamus and also by the concentration of circulating sex hormones. There are 3 groups of endogenous sex hormones, androgens, oestrogens, and progestogens, all of which are derived from the same steroidal precursors. The progestogenic hormone, progesterone, is formed from pregnenolone, and both of these compounds may be converted to androgen precursors such as androstenedione. Androstenedione is converted to the androgenic hormone testosterone by hydroxysteroid dehydrogenases. Oestrogenic hormones are synthesised from androstenedione (and also from testosterone) by the action of aromatase.

Figure 1 (below) shows the basic steroidal skeleton structure.

Figure 1. Steroidal skeleton.

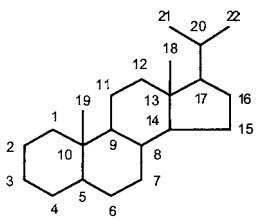

Testosterone is the main androgenic hormone formed in the interstitial (Leydig) cells of the testes. A small proportion of circulating testosterone is also derived from the metabolism of less potent androgens secreted by the adrenal cortex and ovaries. In many target tissues testosterone is then converted to the more active dihydrotestosterone by 5α-reductase. Some testosterone also undergoes peripheral conversion to oestradiol.

Testosterone controls the development and maintenance of the male sex organs and the male secondary sex characteristics. It also produces systemic anabolic effects, such as increased retention of nitrogen, calcium, sodium, potassium, chloride, and phosphate. This leads to an increase in water retention and bone growth. The skin becomes more vascular and less fatty and erythropoiesis is increased.

Numerous derivatives of testosterone have been developed. Alkylation at the 17α position results in derivatives that are orally active, but associated with a risk of hepatotoxicity (see Table 1, below). Esterification of the 17β-hydroxyl group increases lipid solubility and is used to prepare long-acting intramuscular preparations (e.g. testosterone enantate). Removal of the 19-methyl group is reported to improve the anabolic to androgenic ratio (e.g. nandrolone). The derivatives also vary in their plasma protein binding affinity, and degree of conversion to dihydrotestosterone and aromatic conversion to oestrogen. Numerous other structural modifications have been made.

Oestradiol is the most active of the naturally occurring oestrogens formed from androgen precursors in the ovarian follicles of premenopausal women. In men and postmenopausal women (and to an insignificant extent in premenopausal women) oestrogens are also formed in adipose tissue from adrenal androgens.

Oestrogens control the development and maintenance of the female sex organs, secondary sex characteristics, and mammary glands as well as certain functions of the uterus and its accessory organs (particularly the proliferation of the endometrium, the development of the decidua, and the cyclic changes in the cervix and vagina). Large amounts of oestradiol are also formed in the placenta; in late pregnancy, this increases the spontaneous activity of the uterine muscle and its response to oxytocic drugs. The additional activity of progesterone is essential for the complete biological function of the female sex organs. Oestrogens also have some direct effects on metabolic processes, including those affecting bone mass, lipids, carbohydrates, and proteins.

Table 1. 17α-Alkylated testosterone derivatives

Danazol	Norethandrolone
Ethylestrenol	Oxandrolone
Fluoxymesterone	Oxymetholone
Methandienone	Stanozolol
Methyltestosterone	

Many oestrogens are used therapeutically. Ethinyl substitution at the C17 position has led to the development of synthetic oestrogens such as ethinylestradiol and mestranol, which have greatly improved potency and oral activity. Oral activity of natural oestrogens is improved by esterification (e.g. estradiol valerate) or by conjugation (e.g. estrone sulfate). Esterification also increases solubility in lipid vehicles and is used to prepare long-acting intramuscular preparations.

Several nonsteroidal oestrogens, including chlorotrianisene, dienestrol, and diethylstilbestrol, have also been used.

Progesterone is the main hormone secreted by the corpus luteum. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase thereby preparing the uterus to receive the fertilised ovum. Progesterone has a catabolic action and causes a slight rise in basal body temperature during the secretory phase of menstruation. During pregnancy the placenta produces large quantities of progesterone, which suppresses uterine motility and is responsible for the further development of the breasts.

Progestogens (gestagens, progestagens, progestins) are synthetic compounds with actions similar to those of progesterone. They are either progesterone derivatives or 19-nortestosterone analogues. The 19-nortestosterone analogues (such as norethisterone and norgestrel) possess some androgenic activity, but some newer norgestrel derivatives (desogestrel, gestodene, and norgestimate) have little androgenic activity. The progesterone derivatives dydrogesterone, hydroxyprogesterone, and medroxyprogesterone are less androgenic than the 19-nortestosterone analogues. The progesterone derivatives chlormadinone, and particularly cyproterone, have anti-androgenic activity.

The principal natural and synthetic sex hormones covered in this chapter are thus:

- **androgens and anabolic steroids**, typified by testosterone (p. 2305.1)
- **oestrogens**, typified by estradiol (p. 2271.1)
- **progestogens**, typified by progesterone (p. 2300.2)

Other related substances also described in this chapter are:

- drugs with mainly **weak androgenic** properties such as danazol and gestrinone
- drugs that combine **oestrogenic and progestogenic** properties such as tibolone
- drugs with mainly **anti-androgenic** properties including the progesterone derivative cyproterone acetate. Those anti-androgens used principally in the hormonal treatment of prostate cancer are covered in the Antineoplastics chapter; they include the nonsteroidal drugs bicalutamide (p. 749.1), flutamide (p. 798.2), and nilutamide (p. 836.2). The nonsteroidal 5α-reductase inhibitors finasteride (p. 2358.3) and dutasteride (p. 2357.2) and the plant extract saw palmetto (p. 2363.3), used in the treatment of benign prostatic hyperplasia, are covered in the Urological Drugs chapter
- drugs with mainly **anti-oestrogenic** properties. These include the nonsteroidal anti-oestrogens clomifene and cyclofenil. Those anti-oestrogens used principally in the hormonal treatment of breast cancer are covered in the Antineoplastics chapter; they include the oestrogen receptor antagonists tamoxifen (p. 860.2) and toremifene (p. 873.3), and various aromatase inhibitors such as formestane (p. 799.2) and anastrozole (p. 742.1)
- **selective oestrogen receptor modulators**, such as ormeloxifene and raloxifene, that have agonist and antagonist effects in different tissues
- **gonad-regulating hormones** (see p. 2251.2 for more detail) include endogenous and recombinant forms of luteinising and follicle-stimulating hormones, and their releasing hormone gonadorelin and its analogues.

The therapeutic applications of sex hormones and related substances are broad and cover many circumstances where hormonal manipulation is desirable. Major applications are the use of oestrogens and progestogens for **contraception** (p. 2232.3) and for the alleviation of **menopausal symptoms** (p. 2245.1). A physiological application is the use of sex hormones or gonad-regulating hormones in the management of **delayed puberty** (p. 2252.1) and **hypogonadism** (p. 2252.3). Other clinical applications include the management of **benign prostatic hyperplasia** (p. 2347.1), **endometriosis** (p. 2264.1), **gynaecomastia** (p. 2264.3), **hirsutism** (p. 2262.1), **infertility** (p. 2253.1), **mastalgia** (p. 2265.1), **menorrhagia** (p. 2300.3), and **premenstrual syndrome** (p. 2272.3). Hormonal manipulation also has an important role in the treatment of **malignant neoplasms** of the breast (p. 702.1), prostate (p. 712.3), and endometrium (p. 704.3).

Hormonal Contraceptives

Anticonceptivos hormonales; Contraceptifs Hormonaux; Hormonale Kontrazeptiva; Гормональный Контрацептивы.

Types of Contraceptive

Hormonal contraceptives are currently only available for women although preparations for men are being evaluated. Oral hormonal contraceptives for women are divided into 2 main types: 'combined' (containing an oestrogen and a progestogen) and 'progestogen-only'. Parenteral preparations have also been developed and include subcutaneous implants and depot intramuscular injections. Progestogen-releasing intra-uterine devices and a combined hormonal contraceptive vaginal ring are available. A combined hormonal transdermal patch has also been developed.

Parenteral progestogen-only contraceptives provide reliable suppression of ovulation by suppressing the necessary mid-cycle surge of luteinising hormone. However, the low doses in progestogen-only oral contraceptives do not suppress it reliably in all cycles. Contraceptive efficacy is instead achieved by thickening the cervical mucus so that it is not readily penetrated by sperm, and by preventing proliferation of the endometrium so that it remains unfavourable for implantation of any fertilised ova. Intra-uterine progestogen-only devices act similarly; the physical presence of the system in the uterus may also contribute to overall contraceptive efficacy.

Oestrogens inhibit ovulation by suppressing the mid-cycle release of follicle-stimulating hormone. They act synergistically with progestogens in combined oral contraceptives to provide regular and consistent suppression of ovulation.

Oral preparations are also available for *emergency contraception* after unprotected coitus; they prevent implantation of any fertilised ova.

Uses and Administration

The main use of hormonal contraceptives is for contraception, but combined oral contraceptives are also commonly used in menstrual disorders such as dysmenorrhoea (p. 8.2), premenstrual syndrome (p. 2272.3), and menorrhagia (p. 2300.3), particularly where contraception is also required. Combined oral contraceptives are also used in polycystic ovary syndrome (p. 2253.3) and Turner's syndrome (p. 2254.3), and may be used in endometriosis (p. 2264.1); those containing non-androgenic progestogens may be used in acne (p. 2232.3) and hirsutism (p. 2262.1).

Combined oral contraceptives containing both an oestrogen and a progestogen are the most effective type of oral contraceptive for general use. The synthetic ethinyl derivative ethinylestradiol is the oestrogen typically used, although mestranol or estradiol valerate may be found in some preparations. The progestogenic component is usually a 19-nortestosterone derivative such as desogestrel, etynodiol diacetate, gestodene, levonorgestrel, lynestrenol, norethisterone, norethisterone acetate, norgestimate, or norgestrel. Other progestogenic compounds in use include chlormadinone acetate, dienogest, drospirenone, and nomegestrol acetate. Preparations may be *monophasic* (containing a fixed dose of oestrogen and progestogen), or *multiphasic* (when the dose of progestogen, or both the progestogen and oestrogen, are varied through the cycle). Multiphasic preparations are designed to mimic more closely the pattern of endogenous hormone secretion and may provide better cycle control than monophasic preparations. More rarely, *sequential* preparations are used, which contain an oestrogen alone for part of the cycle. Most combined oral contraceptives are taken for 21 days followed by an interval of 7 days when menstrual bleeding will occur. Some preparations include 21 active tablets plus 7 inert tablets to remove the need for counting days ('every day' preparations). Variations on this 28-day cycle include 22 days of active tablets followed by a 6-day interval for bleeding, and 24 days of active tablets followed by a 4-day interval. Long- or extended-cycle preparations are also available: some preparations may be taken continuously for 84 days, followed by 7 days of inert tablets or a lower dose of oestrogen alone (such as ethinylestradiol 10 micrograms).

More recently, a preparation containing active tablets to be taken every day without any tablet-free interval has been introduced. The oestrogen content of most preparations is currently ethinylestradiol 20 to 40 micrograms daily; in some preparations a lower dose of 15 micrograms is used and in others up to 50 micrograms is available (even higher doses were often formerly used). A formulation containing the lowest dose of oestrogen compatible with good cycle control should be chosen, considering the following:

- *low-strength* preparations (ethinylestradiol 20 micrograms) are most appropriate for women with risk factors for cardiovascular disease (see under Precautions, p. 2241.2), provided a combined oral contraceptive is considered otherwise suitable
- *standard-strength* preparations (ethinylestradiol 30 or 35 micrograms or mestranol 50 micrograms if monophasic, or ethinylestradiol 30 to 40 micrograms if phased) are appropriate for most other women
- *high-strength* preparations (ethinylestradiol 50 micrograms) are generally used only in circumstances where bioavailability of the oestrogen is reduced, such as concomitant use of some enzyme-inducing drugs (see Interactions, p. 2242.3)

Of the progestogens used in combined oral contraceptives, desogestrel, drospirenone, and gestodene may be useful for women who have adverse effects, such as acne, headache, depression, weight gain, breast symptoms, or breakthrough bleeding, with other progestogens. However, desogestrel and gestodene have been associated with an increased risk of venous thromboembolism (see p. 2238.1), and drospirenone should not be used in women at risk of hyperkalaemia.

When first **starting** combined oral contraceptives, if the first tablet is taken on the first day of the menstrual cycle (the first day of bleeding) additional contraceptive precautions are unnecessary. If the first tablet is taken on the fourth day of the cycle or later, additional contraceptive precautions should be undertaken for 7 days (or 14 days for 'every day' preparations in case the inert tablets are inadvertently taken first). If amenorrhoea is present and pregnancy has been excluded, combined oral contraceptives may be started on any day, but additional precautions should be used for the first 7 days. In the case of abortion or miscarriage combined oral contraceptives should be started on the same day. In women not breast feeding, they may be started 3 weeks postpartum, but additional contraceptive precautions should be taken for the first 7 days if the combined oral contraceptive is started later than 3 weeks postpartum; progestogen-only contraceptives are preferred in breast-feeding women (see under Precautions, p. 2241.1).

When **changing** to a combined preparation containing a different progestogen, the new preparation should be started on the day after the last active tablet of the old preparation. If a tablet-free interval is taken then extra contraceptive precautions are necessary for the first 7 days of the new preparation. In the case of 'every day' preparations, to allow for the fact that the inert tablets may inadvertently be taken first, extra contraceptive precautions are necessary during the first 14 days. Meticulous regularity of dosage is essential and contraceptive protection may be lost if a dose is not taken at the proper time or is missed, especially if the missed dose is at the beginning or end of a cycle.

If a tablet is **missed** the risk of pregnancy is greatest when this happens at the beginning or at the end of a cycle, which lengthens the tablet-free interval. Over time, advice for dealing with missed tablets has changed and varies between countries and preparations. In 2004, WHO issued recommendations based on how many combined oral contraceptive tablets have been missed and when.

- If 1 or 2 tablets containing 30 or 35 micrograms of ethinylestradiol (or 1 tablet of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; no additional contraceptive protection or emergency contraception is needed. This advice also applies if a new course of tablets has been started 1 or 2 days late for 30- or 35-microgram tablets, or 1 day late for 20-microgram tablets.
- If 3 or more tablets containing 30 or 35 micrograms of ethinylestradiol (or 2 or more tablets of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; the woman should also use condoms or abstain from intercourse until she has taken active tablets for 7 days in a row. This advice also applies if a new course of tablets has been started 3 or more days late for 30- or 35-microgram tablets, or 2 or more days late for 20-microgram tablets. In addition, emergency contraception should be considered if the tablets were missed in the first week of the course and she had unprotected intercourse during the tablet-free interval or in the first week. If the tablets were missed in the third week of the course, then the tablet-free interval (or the 7 inert tablets) should be omitted and the next course of tablets started immediately after the last.

If the woman has missed more than 1 tablet, she can take the first missed tablet and then either continue taking the rest of the missed tablets or discard them to stay on schedule. Depending on when she realises that she has missed a tablet, she may take 2 tablets on the same day or even at the same time.

For extended-cycle preparations, licensed product information gives similar advice regarding missed tablets (or starting a course late), in that the course should be resumed as soon as possible. If 1 tablet has been missed, additional contraception is not needed, but if 2 or more tablets have been missed, additional contraception should be used until 7 days of active tablets have been taken.

Similarly, extra contraceptive measures may be needed during, and after recovery from, vomiting or diarrhoea. WHO recommends that if the woman vomits within 2 hours after taking a tablet, she should take another tablet. If there is severe vomiting or diarrhoea for more than 24 hours she should continue taking the course if she can, and if it continues for 2 or more days she should follow the advice for missed tablets.

Licensed product information for some multiphasic sequential preparations may offer advice regarding additional contraceptive precautions that differs from these general recommendations.

Progestogen-only oral contraceptives are suitable for women when an oestrogen component is contra-indicated. They are taken continuously, usually **starting** on day one of the menstrual cycle, with no interval during menstrual bleeding. They are associated with a higher failure rate than the combined preparations. Regularity in taking the doses is even more important with this type of preparation; contraceptive efficacy is reduced if a dose is delayed by more than 3 hours (a delay of up to 12 hours is acceptable for desogestrel). Commonly used progestogens include the 19-nortestosterone derivatives etynodiol diacetate, levonorgestrel or norgestrel, and norethisterone.

When **changing** from a combined oral contraceptive preparation to an oral progestogen-only contraceptive, the new tablets should be started immediately with no tablet-free interval (or, in the case of 'every day' preparations, omitting the inert tablets).

If a **missed tablet** is delayed by more than 3 hours (or 12 hours for desogestrel), it should be taken as soon as possible and the next tablet taken at the correct time. Although some UK licensed product information suggests that additional contraceptive methods should be used for the next 7 or 14 days, depending on the product, WHO suggests that extra contraception is only required for the next 2 days. Emergency contraception should be considered if unprotected intercourse has occurred before 2 further tablets have been taken correctly. Additional contraceptive methods may also be needed during, and after recovery from, vomiting or diarrhoea, and WHO gives the same advice as that for combined oral contraceptives described above.

Progestogens are also used alone as **parenteral contraceptives** and provide a very high level of contraceptive efficacy. They are usually given within the first 5 days of the menstrual cycle. Injectable contraceptives are usually used to provide short-term protection for several months or are used in women unable to use other methods. Medroxyprogesterone acetate is given by intramuscular or subcutaneous injection as a long-acting depot preparation to provide contraception for at least 12 weeks. Norethisterone enantate is used similarly by intramuscular injection to provide protection for up to 8 weeks. Levonorgestrel is used in the form of a subcutaneous implant providing contraception for up to 5 years. A contraceptive implant containing etonogestrel, effective for 3 years, is also available. A combined parenteral contraceptive containing the oestrogen estradiol cipionate with medroxyprogesterone acetate, and given monthly by intramuscular injection, has been developed.

Intra-uterine contraceptive devices that release levonorgestrel can provide contraception for 3 or 5 years, depending on the device. They are usually inserted within 7 days of the onset of menstruation, or immediately after first trimester termination of pregnancy. To reduce the risk of uterine perforation, insertion postpartum or after second trimester termination should be delayed for at least 6 weeks, and until the uterus is fully involuted. A contraceptive **vaginal ring**, which releases ethinylestradiol and etonogestrel, is retained in the vagina for 3 weeks; it is then removed for a one-week interval after which a new ring is inserted.

A contraceptive **transdermal patch**, which releases ethinylestradiol and norelgestromin, has been developed. A new patch is applied each week for 3 weeks, followed by a one-week patch-free interval. If the patch becomes partly or completely detached, or there is a delay in its application, contraceptive efficacy can be reduced or lost.

- If the patch has been detached for less than 24 hours, it should be re-applied if it is still sufficiently adhesive, or replaced with a new patch; no additional contraceptive method is needed and the following patch should be applied on the usual day. If it has been detached for 24 hours or more, a new 4-week cycle should be started and a new patch applied; additional contraceptive precautions should be taken for the first 7 days.
- If application of the first patch of a new cycle is delayed after the patch-free interval, it should be applied as soon as remembered and this day used as the first day of the new cycle; additional contraceptive precautions should be used for 7 days, and if unprotected intercourse has occurred during the patch-free interval then the possibility of fertilisation should be considered.
- When the patch is changed in the middle of the cycle (week 2 and 3), if there is a delay of up to 48 hours the new patch should be applied immediately, with the next patch applied on the usual day; no additional contraceptive precaution is needed. If the delay is more than 48 hours, the new patch should be applied and a new 4-week cycle started; additional contraceptive precautions should be taken for 7 days.
- If there is a delay in removing the third patch, before the patch-free interval, it should be removed as soon as possible and the next cycle started on the usual day; no additional contraception is required.

Postcoital hormonal contraceptives (emergency contraception) should be taken within 72 hours after unprotected intercourse to be most effective (for details see Emergency Contraception, p. 2233.2). A single oral dose of levonorgestrel 1.5 mg may be given within 72 hours of intercourse, or it may be given as a dose of 750 micrograms within 72 hours of intercourse followed by a second dose 12 hours later. An alternative preparation available for such use consists of tablets each containing ethinylestradiol 50 micrograms and levonorgestrel 250 micrograms. Two tablets should be taken within 72 hours and a further 2 tablets 12 hours later. UK licensed product information for levonorgestrel-only preparations suggests that if vomiting occurs within 3 hours of any dose it can be repeated. However, WHO considers that 2 hours is probably sufficient for hormone absorption and that no action is needed if vomiting occurs after this time. WHO also considers that combined hormonal preparations are more likely to cause nausea and vomiting, and that the use of an antiemetic may be considered before repeating a dose. The efficacy of postcoital emergency contraception may be reduced in women who are being treated with enzyme-inducing drugs, and a higher dose of levonorgestrel has been suggested (see Interactions, p. 2242.3).

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6. Spencer AL, *et al.* Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications. *Am J Med* 2009; **122:** 497–506.

Acne. Oral contraceptives have been shown to be effective[1,2] in reducing inflammatory and non-inflammatory lesions in women with acne (p. 1682.2) who require contraception, probably by a multifactorial action on circulating androgens. Studies have used combinations of ethinylestradiol with various progestogens; a systematic review[2] considered that combinations with chlormadinone acetate or cyproterone acetate were more effective than those with levonorgestrel, but noted that this was based on limited evidence. Combination preparations based on cyproterone acetate, that also have a contraceptive effect, are generally reserved for the management of moderate to severe acne in women with signs of hyperandrogenism (see also p. 2261.3).

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Contraception. Contraception is used for fertility control, and some methods have additional non-contraceptive health benefits. There are many regular methods including periodic abstinence (natural family planning), male and female barrier methods, intra-uterine devices (IUDs), female hormonal contraceptives, and female or male steri-

lisation. In addition, female hormonal contraceptives and copper IUDs are available for emergency (postcoital) contraception. The methods used for contraceptive purposes can be grouped into three categories: those that prevent ovulation, those that prevent fertilisation of the ovum, and those that prevent implantation of the fertilised ovum. None of the available contraceptive methods are effective once implantation of a fertilised ovum has occurred, i.e. they are not abortifacients.

A large number of factors will influence the choice of contraceptive method. Those relating to the woman include age (and therefore likely fertility), parity, medical disorders, risk of sexually transmitted diseases, smoking status, breast feeding, and cultural and religious considerations. Those relating to the method include its failure rate, reversibility, ease of use, mechanism of action, adverse effects, and non-contraceptive benefits.

The most reliable reversible methods for contraception are those for which there can be no 'user' failure such as *progestogen injections* and *implants*, and progestogen or copper *intra-uterine devices* (IUDs). When used perfectly, these methods have reported failure rates of between 0.05 and 0.6% during the first year of use; higher rates had been reported with older IUDs. The duration of action of the various progestogen injections is up to 2 or 3 months, whereas progestogen implants and progestogen IUDs can be effective for 1 to 5 years, depending on the preparation. These long-acting progestogen preparations thicken cervical mucus, so preventing sperm penetration, and suppress the endometrium, so preventing implantation. In addition, they suppress ovulation; the degree of suppression is complete for injectable preparations, about 50% for implants, and low for the progestogen IUDs. Copper IUDs were traditionally thought to act by preventing implantation, but it is now thought that the biochemical changes which they produce in the uterus also prevent fertilisation. They are effective and have a prolonged action (up to 5 or 10 years). There is an increased risk of pelvic infection in the 20 days after insertion of an IUD, but the risk is the same as non-IUD users thereafter. An IUD must not be used in women with a current sexually transmitted infection or pelvic inflammatory disease, but it may be considered in those who are no longer at risk after an infection has been treated. For women at increased risk of infection, prophylactic antibacterial therapy may be given before IUD insertion if screening test results are not yet available. In the past, it was recommended that IUDs were not suitable for nulliparous women because of a risk of impaired fertility after removal. However, this may have been biased by other factors such as the increased risk of sexually transmitted infection associated with sexual behaviour in younger women. Nulliparity alone is therefore no longer considered a contra-indication to IUD use, and indeed some IUDs have been designed specifically for this group of women. Although IUDs are effective at preventing pregnancy, in the uncommon event of IUD failure, the risk of ectopic pregnancy is increased and can occur in 6 to 8% of these pregnancies.

Of methods subject to 'user' failure, *combined oral contraceptives* are the most effective. They have a reported failure rate during the first year of 0.3% if used perfectly, but 8% in typical practice. Their principal mechanism of action is to prevent ovulation, and they also decrease the chances of fertilisation and implantation. Combined oral contraceptives offer the non-contraceptive advantages of avoidance of dysmenorrhoea, premenstrual tension, and iron-deficiency anaemia, and in the long-term they protect against endometrial and ovarian cancer. However, they do not protect against sexually transmitted diseases, they are unsuitable for older women who smoke, and long-term use carries a slight increased risk of breast cancer. Other forms of combined contraceptive which have been developed recently include *monthly injection*, *vaginal ring*, and *transdermal patch*.

Progestogen-only oral contraceptives are considered to have a slightly higher failure rate than that for combined preparations because of the need for more accurate dosage timing. A 0.9% failure rate has been given for the first year of use if taken correctly, but in practice failure rates of up to 10% have been reported. Failure rates are lower in women taking these contraceptives during breast feeding, as breast feeding itself provides additional contraception (see also Natural Family Planning Methods, below). Regularity in taking them is essential; a dose should not be delayed for more than 3 hours (up to 12 hours for desogestrel). They act mainly to decrease the chance of fertilisation and implantation since they prevent ovulation in only 14 to 50% of cycles, although desogestrel is said to reliably inhibit ovulation. They are useful for women who are breast feeding, for those who smoke and are more than 35 years of age, and if medical conditions contra-indicate the use of oestrogens.

Barrier methods, including both male and female condoms, vaginal sponges containing spermicide, and diaphragms and cervical caps used with spermicide, act as a mechanical barrier to prevent fertilisation, and inactivate sperm. Barrier methods decrease the risk of sexually transmitted diseases and a shift towards their use has occurred since the emergence of HIV infection in particular. However, barrier methods are not as effective in preventing conception as hormonal contraception and IUDs. Even when used correctly, failure rates in the first year of use vary from 2% for the male condom, to 6% for the diaphragm with spermicide, to 20% for the vaginal sponge in parous women. Spermicides, such as nonoxinol 9, may be used as foam, cream, jelly, dissolvable vaginal tablets or pessaries, or as a spermicide-containing polyvinyl alcohol film placed over the cervix. However, they are generally considered relatively ineffective when used as the sole method of contraception, and such use is not recommended.

Natural family planning methods such as periodic abstinence using the calendar, temperature, cervical mucus ('Billings') or sympto-thermal methods require high motivation to learn and practice effectively. However, they may be the only acceptable method to some people. More recently, daily measurement of urine hormone concentrations has been used as a predictor of the timing of ovulation and hence the risk of becoming pregnant; on 'unsafe' days abstinence or barrier methods are required. Traditional methods such as withdrawal (coitus interruptus) are widely used in some areas, but are considered relatively ineffective. The lactational amenorrhoea method of contraception can be used during breast feeding for up to 6 months after childbirth. For it to be an effective contraceptive method, breast feeding must start immediately after birth, the infant must be fully or nearly fully breast-fed, feedings must be no more than 4 to 6 hours apart, and menstruation must not have restarted. When carried out consistently and correctly, this method has a failure rate of 0.9% in the first 6 months.

Various other methods of contraception are under investigation including the use of the antiprogestogen mifepristone, selective sex-hormone receptor modulators, and contraceptive vaccines. There has also been some investigation of **male contraception**. Weekly intramuscular injection of high-dose testosterone or nandrolone to produce azoospermia has been investigated with some success, but development of an oral contraceptive dosage form for males has been slow. Use of a progestogen with testosterone is being studied, as is the use of implants of synthetic androgens such as trestolone (7-α-methyl-19-nortestosterone; MENT).

The available irreversible methods of contraception are surgical male or female *sterilisation*. The use of mepacrine for non-surgical female sterilisation has been attempted but has proved extremely controversial.

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Emergency contraception. Emergency contraception (postcoital contraception) can be used after unprotected intercourse but before a fertilised ovum has been implanted. Methods that act after implantation are considered abortifacients. The two most commonly used emergency contraceptives are *oral contraceptives* and *copper IUDs*.

Oral hormonal contraceptive regimens (the so-called 'morning after pill') have historically used a preparation containing high-dose oestrogen with a progestogen, taken within 72 hours of intercourse, and repeated 12 hours later (the Yuzpe regimen). This preparation is thought to act by a variety of mechanisms, which may depend on when in the menstrual cycle it is used. It may prevent implantation, prevent or delay ovulation, disrupt ovum transport, and alter corpus luteum function. However, levonorgestrel alone (without an oestrogen) is now widely recommended as an emergency contraceptive. A large WHO multicentre study found that levonorgestrel 750 micrograms alone within 72 hours of intercourse and repeated after 12 hours was more effective than the Yuzpe regimen and better tolerated.[1] Both regimens were most effective when given within 24 hours of intercourse.[1,2] A small observational study[3] of the Yuzpe method used between 72 and 120 hours after unprotected intercourse reported a trend towards decrease in efficacy. A further large study[4] by WHO found that for up to 120 hours after intercourse, a single dose of levonorgestrel 1.5 mg was as effective as two doses of 750 micrograms given 12 hours apart, with a pregnancy rate of about 1.5%.

Efficacy rates vary between studies, but the Yuzpe method has been shown to reduce the risk of pregnancy by about 75% and levonorgestrel by about 89%.[5] Based on its greater efficacy and better tolerability, levonorgestrel is now generally recommended as the hormonal emergency contraceptive of choice that can be offered up to 120 hours after intercourse.[5-9]

Copper, but not progestogen, IUDs can be inserted up to 120 hours after unprotected intercourse for postcoital contraception. They have a failure rate of no more than 1% when used for emergency contraception.[9] Thus, when efficacy is a priority the IUD is the emergency contraceptive method of choice.

The *antiprogestogen* mifepristone is under investigation as an emergency contraceptive. Its action appears to depend on inhibiting ovulation or, if ovulation has occurred, preventing implantation. Mifepristone also appears to be at least as effective as levonorgestrel but it can delay the onset of subsequent menstruation, which might cause anxiety in some women.[10,11] Another drug with antiprogestogen effects, the progesterone receptor modulator ulipristal acetate, may be at least as effective as levonorgestrel.[12,13] It can be used up to 120 hours after intercourse, but it is yet to become established for emergency contraception.

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Malignant neoplasms. The prophylactic use of oral contraceptives may protect against ovarian cancer in women with mutations of the BRCA1 or BRCA2 genes, but must be balanced against the risk of breast cancer in these women (see Ovary, under Carcinogenicity, p. 2236.1).

Adverse Effects

Many reports have been published of adverse effects associated with the use of **combined oral contraceptives**. The data have mostly been gained retrospectively and often involve older preparations containing higher doses of oestrogen and progestogen than are used currently. A similar spectrum of adverse effects has also been reported for

combined hormonal contraceptives administered transdermally and vaginally.

There may be gastrointestinal adverse effects such as nausea or vomiting, chloasma (melasma) and other skin or hair changes, headache, water retention, weight gain, breast tenderness, and changes in libido.

Menstrual irregularities such as spotting, breakthrough bleeding, or amenorrhoea can occur during treatment. These effects may result from the relative balance of oestrogenic and progestogenic effects of particular products and their incidence may be reduced by changing to a different product. For example, early or mid-cycle spotting or absence of withdrawal bleeding may require a preparation with a greater oestrogen to progestogen ratio or less progestogen as in multiphasic preparations.

Intolerance to contact lenses has been reported and vision may deteriorate in myopic patients. Some patients may develop depression and other mental changes. Preparations containing a progestogen with androgenic properties such as levonorgestrel or norgestrel may be associated with increased oiliness of the skin and acne. Conversely, acne may be improved with progestogens such as norgestimate or desogestrel.

There is an increased risk of cardiovascular disease and associated mortality related, at least in part, to the oestrogen content of combined oral contraceptives. The incidence of cardiovascular adverse effects is probably less with the newer lower-dose preparations than with the older higher-dose preparations. Increased mortality from myocardial infarction is much greater with increased age and in cigarette smokers, although some evidence suggests that healthy women aged over 35 years who do not smoke are not at increased risk. Other risk factors include a family history of arterial disease, diabetes mellitus, hypertension, obesity, and migraine. Thrombosis may be more common when factor V Leiden is present or in patients with blood groups A, B, or AB. Specific risk factors for venous thromboembolism include varicose veins, long-term immobilisation, obesity, and a family history of venous thromboembolism. Recent evidence has also indicated that the risk of venous thromboembolism varies according to the progestogen component of combined oral contraceptives; a higher incidence has been associated with desogestrel and gestodene than with levonorgestrel, norethisterone, and etynodiol. For further discussion see Venous Thromboembolism, p. 2238.1.

Combined oral contraceptives may cause hypertension and there may be reduced glucose tolerance and changes in lipid metabolism. Liver function can be impaired, although jaundice is rare. There appears to be a marked increase (though the incidence is still very low) in the relative risk of benign liver tumours. Malignant liver tumours have also been reported.

Combined oral contraceptives are reported to slightly increase the risk of cervical cancer (although other factors may be involved) and breast cancer, but to protect against ovarian cancer and endometrial cancer. For further discussion, see Carcinogenicity, below.

As with combined oral contraceptives, **progestogen-only contraceptives** may cause nausea, vomiting, headache, breast discomfort, depression, skin disorders, and weight gain. Menstrual irregularities such as amenorrhoea, breakthrough bleeding, spotting, and menorrhagia are more common with progestogen-only contraceptives, and are particularly common with parenteral preparations. Ovarian cysts are also common in women using progestogen-only contraceptives, since they do not prevent ovulation in all cycles and may delay follicular atresia. These enlarged follicles usually disappear spontaneously, but are sometimes associated with pelvic pain or dyspareunia. Available progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives.

Carcinogenicity. Concern has often been expressed as to whether the use of hormonal contraceptives by normally healthy women may either cause or increase the risk of developing malignant neoplasms. To investigate any possible link between such use and cancer, two main types of study have been used by epidemiologists, namely the prospective study and the case-control study. Many factors have made direct comparison of results difficult and such factors include the type and composition of oral contraceptive used (which has changed over the years), the age of the patient, the age at which use first began, and the sexual and obstetric history of the patient. Overall the evidence indicates that combined oral contraceptives in fact exert a protective effect against the development of endometrial and ovarian carcinoma. However, there is a small increase in risk of breast cancer during use and for 10 years after discontinuation. In addition, there does appear to be a slight risk of cervical cancer with the prolonged use of combined oral contraceptives and a negligible risk of liver cancer. For further details concerning the effects on individual organs, see the following sections. It should be noted that even where the relative risk has been shown to be substantially increased this will not translate into many new cases of a rare cancer, and this contributes to the difficulties of assessing clinical relevance.

In the long-term Oxford Family Planning Association contraceptive study, the beneficial effects of oral contraceptives on the uterus and ovary were calculated to outweigh the adverse effect on the cervix.[1] This large cohort study also found no increased risk of breast cancer although the data could not exclude a small increase in risk with current use that declined after stopping. Long-term follow-up of the prospective Royal College of General Practitioners' study has found no overall increased risk of cancer.[2] It is also worthy of note that two large prospective cohort studies (the Nurses' Health Study and the Royal College of General Practitioners' study) found no evidence of a difference in overall mortality between women who had used oral contraceptives and those who had not.[3,4] Some general reviews on hormonal contraceptives and cancer are cited below.[5-9]

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BREAST. Many epidemiological studies have been published on the potential link between hormonal contraceptives and breast cancer. Most of these data relate to **combined oral contraceptives**, which are the most widely used form. The breast cancer risk from use of these contraceptives will require monitoring for some time to come as the first users of oral contraceptives continue to age, and because of the changing patterns of use.

Early studies from the 1980s variously failed to show any significant increase in risk of breast cancer in women who had ever used hormonal contraceptives compared with those who had never done so,[1-4] or showed an increase in risk,[5] or identified a risk in specific sub-groups of users.[6-12] Potential identified risk factors, for which much of the evidence was conflicting, included current use,[10] duration of use,[7,11] age at first use,[6] duration of use before a first full-term pregnancy,[7,8] nulliparity,[9] high-dose preparations,[11] and family history of breast cancer.[12] It was also reported that use of oral contraceptives might lead to an accelerated presentation of breast cancer,[13] or an increased risk of invasive cancer.[4]

In response to these studies, the UK CSM,[14] the FDA in the USA,[15] and the International Committee for Research in Reproduction[16] issued advice that the available evidence did not require a change in prescribing practice. This advice has not been subsequently changed, although patients should be informed of the possible small increase in risk of breast cancer, which has to be weighed against established benefits of therapy.[17]

A Collaborative Group on Hormonal Factors in Breast Cancer was set up to re-analyse all the worldwide epidemiological evidence on breast cancer risk and hormonal contraceptives. The group identified individual data on 53 297 women with breast cancer, and 100 239 controls (women without breast cancer) from 54 studies, and published a summary of their findings,[18] and a further detailed review.[19] They reported that women currently using oral contraceptives have a slight increase in the relative risk of breast cancer (1.24; 95% confidence intervals 1.15 to 1.33), and that this risk decreases after stopping use, and is no longer significant after 10 or more years. There was a weak trend towards an increase in risk with increasing duration of use. Thus, it appears that the risk of breast cancer

- increases soon after first exposure
- does not increase with duration of exposure
- returns to normal 10 years after cessation of exposure.[18]

Reviews[20,21] of major studies published between 1990 and 2000, including that of the Collaborative Group, have also indicated that, in general, there is some excess breast cancer risk in current or recent users of oral contraceptives, but that excess risk does not persist in the long term after cessation of oral contraceptive use, regardless of duration of use.

The Collaborative Group found that cancers diagnosed in those who had ever used hormonal contraceptives were clinically less advanced than in those who had never done so.[18] Further information is required on whether this is related to earlier diagnosis or a biological effect of the hormones. In addition, data on breast cancer mortality are required.

When analysed by *age at first use*, the risk was largest in those women who started use as teenagers. Because of the trend towards earlier use, further review of long-term data is required.[18] The most important risk factor is, however, the *age at which women discontinue* the contraceptive; the greater the age at stopping, the more breast cancers are diagnosed.[17]

Data from the collaborative group suggested that there was no difference in risk with *parity* when comparing nulliparous women, parous women who began use of oral contraceptives before their first child, and parous women who began use of oral contraceptives after the birth of their first child.[18] However, a later meta-analysis[22] reported higher risks in parous women, particularly those who used oral contraceptives for 4 or more years before first full-term pregnancy.

Low-dose oral contraceptives were not associated with a decreased risk of breast cancer.[18] When preparations were grouped according to oestrogen dose (< 50 micrograms, 50 micrograms, and >50 micrograms), there was, if anything, a decrease in breast cancer risk with increasing dose among women who had stopped use 10 or more years before, largely due to a reduction in breast cancer risk in those who had used the highest dose preparations.

The Collaborative Group's analysis did not note any difference in risk according to *family history*.[18] However, a subsequent cohort study found an increased risk of breast cancer among women with a strong family history of the disease who used earlier formulations of oral contraceptives.[23] Another cohort study[24] provided support for the Collaborative Group's findings, reporting no statistical difference in the risk with oral contraceptive use in women with a family history of breast cancer; there was actually a trend towards a reduction in risk of breast cancer with long-term use. Women carrying mutations in the BRCA1 or BRCA2 genes are at increased risk of developing breast cancer; any additional risk from oral contraceptives is of particular concern because these women may be encouraged to take them to reduce their risk of ovarian cancer (see Ovary, p. 2236.1). However, results from studies in known carriers of these mutations have been mixed. A modest increase in the risk of breast cancer in BRCA1 carriers has been reported with ever use of oral contraceptives,[25] but another study[26] found a reduced risk in carriers who used current preparations containing lower oestrogen doses than those available before 1975. Further study is needed in these women.

There are far fewer data on risk of breast cancer with **progestogen-only contraceptives**, which are less frequently used than combined preparations.

A WHO study published in 1991 indicated that, overall, depot medroxyprogesterone acetate did not increase the risk of breast cancer (relative risk compared with never users 1.21; 95% confidence intervals 0.96 to 1.53) and that risk did not increase with duration of use.[27] However, there appeared to be a slight increase in risk within the first 4 years of use, especially in women under 35 years of age. These findings agreed with those of a smaller study[28] in which women who had used depot medroxyprogesterone acetate for 2 years or longer before the age of 25 had a relative risk of 4.6. Pooled analysis of these 2 studies indicated that current or recent use was the key factor.[29] The relative risk of breast cancer in women who had used medroxyprogesterone acetate in the last 5 years was 2.0, and there was no increased risk in women who had ceased use more than 5 years previously, regardless of their duration of use. Another small study[30] reported no increase in risk overall in women who had ever used medroxyprogesterone acetate; there was an increase for current use in the subgroup of women aged 35 to 44 (relative risk 2.3), but this was no longer the case 4 years after stopping.

The Collaborative Group on Hormonal Factors in Breast Cancer reported that there was some evidence of an increased risk of breast cancer for use of oral or injectable progestogens in the previous 5 years (relative risk 1.17), and no risk 10 or more years after stopping use.[18] These findings were broadly similar to those for combined preparations. As for combined preparations, the most important factor is the *age at discontinuation*. For women who stop by age 30 after 5 years use of a progestogen-only preparation there would be an estimated increase from 44 to 46 or 47 cases per 10 000 compared with those who have never used a hormonal contraceptive. For 5 years use stopping by age 40 there would be an estimated increase from 160 to 170 cases diagnosed in the following 10 years.[17]

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CERVIX. It is often considered difficult to carry out satisfactory epidemiological studies on the relationship between hormonal contraceptives and cervical cancer because of the many known variables that can influence the development of this type of neoplasm. For example, sexual activity *per se*, and multiple sexual partners (both of the woman and her partner) increase the risk, while the use of other non-hormonal barrier methods of contraception may offer some protection against cervical neoplasia. Nevertheless, there have been some suggestions that the use of oral contraceptives may be associated with an increased risk.

Two UK cohort studies from the 1980s revealed an increased risk of cervical cancer in women receiving oral contraceptives that was shown to increase with increasing duration of use.[1,2]

In 1992, WHO reviewed[3] these cohort data, and data from 18 case-controlled studies carried out up to 1990. They concluded that use of oral contraceptives for more than 5 years was associated with a modest increase in the relative risk of cervical squamous cell carcinoma (in the order of 1.3 to 1.8). Additional potential risk factors included recent or current use and high oestrogen dose. Of known risk factors for cervical cancer, women with multiple sexual partners, genital infection, or high parity had enhanced risks associated with oral contraceptives.[3] A later analysis[4] of 24 studies came to similar conclusions, finding a relative risk of 1.90 (95% confidence interval 1.69 to 2.13) for current use of 5 or more years. Also, the risk had returned to normal by 10 or more years after stopping hormonal contraceptive use.

Most cervical cancers are squamous cell carcinomas, but it has been proposed that oral contraceptive use might be a particular risk factor for the rarer adenocarcinoma of the cervix, the incidence of which has risen in younger women. Reviewing studies up to 1990, WHO concluded that data were insufficient to draw firm conclusions on links between oral contraceptives and the risk of cervical adenocarcinoma.[3] A case-controlled study from 1994 found an increased risk of adenocarcinoma of the cervix in users of oral contraceptives.[5] Any use of oral contraceptives was associated with an approximate doubling of risk, and use for more than 12 years was associated with a relative risk 4.4 times greater than that in women who never used an oral contraceptive. In 1996, a WHO study reported that the strength of the relationship seen for cervical adenocarcinomas and adenosquamous carcinomas and oral contraceptives was about the same as that for invasive squamous cell cervical carcinomas.[6]

Human papillomavirus (HPV) has a role in the aetiology of cervical cancer; women who are HPV positive and using oral contraceptives may be at increased risk of cervical neoplasm.[7,8] A pooled analysis of 8 case-control studies in women who tested positive for HPV DNA suggested risk of invasive squamous cervical cancer or carcinoma *in situ* was increased about threefold in those who used oral contraceptives for 5 years or more.[9] A larger systematic review,[10] which also included these 8 studies, found the increased risk for HPV positive women to be broadly similar to that for all women.

Data on the risk of cervical cancer with **progestogen-only contraceptives** are limited. WHO have investigated any possible link between the use of medroxyprogesterone acetate as a long-acting injectable contraceptive and cervical neoplasia. Analysis showed a small non-significant elevated risk (1.11; 95% confidence interval 0.9 to 1.29), and no clear association with duration of use.[11] A later case-control study[12] found no significant association between injectable progestogen contraceptives and invasive cervical cancer risk. A subsequent analysis[4] of data from 10 studies found a slightly raised risk of 1.22 (95% confidence interval 1.01 to 1.46) for women using a progestogen-only injectable contraceptive for 5 or more years, with no clear effect of time since last use.

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ENDOMETRIUM. It has been shown that **combined oral contraceptives** decrease the risk of endometrial cancer. WHO analysed data from case-control and cohort studies published up to 1990,[1] including data from the large Cancer and Steroid Hormone Study (CASH) in the USA,[2] and reported that there was a highly significant trend of decreasing risk of endometrial cancer with increasing duration of use of combined oral contraceptives. The reduction in risk was estimated to be 20% after 1 year and 50% after 4 years of use.[1] The protective effect was seen for endometrial cancer with and without squamous elements,[1,2] and was found to persist for at least 15 years after cessation of use.[2] More recent studies with longer term follow-up have indicated that the protection persists for at least 20 years.[3,4] Further follow-up is required to determine the true duration of protection; data from one study[5] suggested that the reduction in risk was more pronounced in women who had stopped contraceptive use more than 25 years before, but another study[4] suggested that any protective effect may no longer be present 30 years after stopping combined oral contraceptive use.

The results of the WHO Collaborative Study on Neoplasia and Steroid Contraceptives suggested that protection may be greater with preparations containing high-dose progestogen.[6] However, another study found that risk of endometrial cancer was unrelated to progestogen potency of the oral contraceptive, although this study also reported no protective effect for less than 5 years of use.[7] Further analysis of the CASH study data[8] found that although preparations containing high and low doses of progestogen had a similar protective effect overall, it was greatest for high-dose progestogen preparations in women with a higher BMI.

Unopposed menopausal oestrogen replacement therapy is known to increase the risk of endometrial cancer (see p. 2247.3), and there is some evidence[3,7] that it reduces the protective effect of previous oral contraception.

There are limited data on the effect of **progestogen-only contraceptives** on the risk of endometrial cancer, although they would be expected to be protective. Results from the WHO Collaborative Study[9] suggest that depot medroxyprogesterone acetate reduced the risk of endometrial cancer; the estimated relative risk in users was 0.21. However, many of the women in this study received supplemental oestrogen to control menstrual irregularity, and were therefore technically taking a form of combined therapy.[10] There was some evidence that the protective effect of medroxyprogesterone acetate was greater in women who had not received oestrogen,[10] although this remains to be proven.

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GASTROINTESTINAL TRACT. A link between female sex hormones and the risk of colorectal cancer has been postulated. Epidemiological studies have variously shown a possible increased risk of rectal cancer,[1] a possible decreased risk of colorectal cancer[2] in women ever having used oral contraceptives, and no association between past oral contraceptive use and colorectal cancer.[3] A meta-analysis,[4] which included these 3 studies, found a reduction in the risk of colorectal cancer for women who had ever used oral contraceptives. Duration of use was not related to risk reduction, but the effect was apparently stronger for recent contraceptive use although this was based on limited data. Subsequent studies have produced similar results. A reduction in risk has been associated with ever use of oral contraceptives in one report,[5] while others have found no effect statistically but a trend towards protection with current or recent use.[6,7] (See also under Hormone Replacement Therapy, p. 2248.1.)

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LIVER. The use of **combined oral contraceptives** has been rarely associated with liver tumours, both benign (hepatic adenomas and focal nodular hyperplasia)[1] and malignant (hepatocellular carcinoma).[1,2]

Early studies of *hepatic adenoma* found that risk increased with the duration of use of oral contraceptives, and appeared to be higher in women who had used preparations with a high oestrogen content.[1] There are also case reports of adenoma that has regressed after stopping oral contraceptive use.[3] However, a study[4] in the 1990s found no increase in risk associated with contraceptive use, and the authors considered that lower doses of oestrogens might explain the different findings. The association between oral contraceptive use and *focal nodular hyperplasia* has also been

studied. One case-control study[4] found a slight increase in risk associated with use for 10 years or more. Another study[5] that followed a series of patients for about 2 years after diagnosis found no correlation between oral contraceptive use and lesion size or number, and no increase in lesion size in those patients who continued to use hormonal contraception.

Hepatocellular carcinomas are associated with hepatitis B, and are relatively common in countries where this is endemic but rare elsewhere. Case-control studies in populations at high risk for hepatocellular carcinoma suggest that the use of oral contraceptives does not significantly affect the risk, although long-term data are scanty.[6,7] However, survival after curative treatment is better in women than men, and a retrospective study from Hong Kong has suggested that this may be associated with a history of oral contraceptive use.[8] In contrast, case-control studies in countries where the prevalence of hepatitis B is low have shown an increased risk of hepatocellular carcinoma among users of oral contraceptives, particularly after long-term use (reviewed by WHO[1] and La Vecchia[2,9]). However, because the malignancy is so rare, this increased risk may be negligible.[2] For example, there has been no increase in mortality from liver cancer in young women in the UK since the introduction and use of oral contraceptives.[10] Similar findings have been reported for the USA and Sweden.[11]

There are limited data specifically on **progestogen-only contraceptives**. Results from a WHO study[12] provided no evidence that use of medroxyprogesterone acetate as a long-acting injectable contraceptive altered the risk of developing liver cancer but the power of the study to detect small alterations in risk was low.

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OVARY. There is convincing evidence that **combined oral contraceptives** reduce the risk of ovarian cancer,[1,2] possibly as a function of their inhibition of ovulation. Relative risks for ovarian cancer have variously been reported as 0.4 to 0.8 in those who have ever used oral contraceptives, and decrease with increasing duration of use. There is evidence that there may be a delay of several years before the protective effect becomes apparent,[3] but that it persists for as long as 20 or 30 years after cessation of use.[3-5] The protective effect has been noted for both malignant and borderline malignant tumours[6] and for each of the major histological subtypes of epithelial ovarian cancer, although there have been conflicting data for mucinous tumours.[5]

It has been suggested that newer lower-dose oestrogen preparations may be slightly less protective than higher-dose preparations.[7] The relative risk for use of high-dose preparations was 0.68, and for low-dose preparations was 0.81, but it was noted that this difference could have occurred by chance. A later study[4] reported that risk reduction was not affected by oral contraceptive formulation. In contrast, another study[8] found a greater risk reduction associated with low-dose contraceptives than older high-dose preparations (odds ratio of 0.24 versus 0.70). The authors speculated that the accompanying changes in progestogen content might have played a role. This was examined using the data from the Cancer and Steroid Hormone (CASH) study, which suggested that higher progestogen potency provided greater risk reduction than lower progestogen potency, regardless of oestrogen dose.[9] Androgenicity of the progestogen does not appear to influence the protective effect of combined oral contraceptives.[10]

A systematic review[11] of 45 studies confirmed many of these findings, showing an overall relative risk of ovarian cancer of 0.73 (95% confidence interval 0.70 to 0.76) associated with ever use of oral contraceptives. Risk declined with increasing duration of use, and although the benefits were attenuated over time after stopping use, the risk of ovarian cancer was still significantly reduced 30 or more years after contraceptive use had finished. Results also suggested that changes in formulation over time had not significantly affected risk reduction.

The protective effect against ovarian cancer may have significant implications for public health. There have been substantial declines in ovarian cancer incidence and mortality in younger women in countries where oral contraceptives have become widely used; it is estimated that 3000 to 5000 cases (and consequently 2000 to 3000 deaths) are avoided each year in Europe; similar numbers are quoted in North America.[12] The number of cancers prevented each year is also likely to increase as past users age and oral contraceptive use by new users worldwide grows.[11]

There are few data on the effects of **progestogen-only contraceptives** on the risk of ovarian cancer. WHO have investigated the effect of depot medroxyprogesterone acetate on ovarian cancer, and found that it was not associated with either a decrease or increase in risk (relative risk 1.07; 95% confidence interval 0.6 to 1.8).[13] This is perhaps surprising since the preparation, like combined oral contraceptives, inhibits ovulation.

Women carrying mutations in either the BRCA1 or BRCA2 gene are at increased risk of ovarian cancer, and the effect of oral contraceptives in these women has been evaluated. Although there was no protective effect in one study,[14] others have found a risk reduction with contraceptive use similar to that reported for non-carriers.[15-18] It has been suggested that oral contraceptives might be used prophylactically to protect against ovarian cancer in women with these mutations, but this must be considered in the context of their increased risk of breast cancer (see Breast, p. 2234.2). Women with endometriosis may also be at increased risk of ovarian cancer, and an analysis[19] of the pooled data from 4 studies suggested that long-term use of oral contraceptives may also be protective in this group.

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8. Royar J, *et al*. Low-dose oral contraceptives: protective effect on ovarian cancer risk. *Int J Cancer* 2001; **95:** 370–4.
9. Schildkraut JM, *et al*. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst* 2002; **94:** 32–8.
10. Greer JB, *et al*. Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. *Obstet Gynecol* 2005; **105:** 731–40.
11. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls. *Lancet* 2008; **371:** 303–14.
12. La Vecchia C. Oral contraceptives and ovarian cancer: an update, 1998–2004. *Eur J Cancer Prev* 2006; **15:** 117–24.
13. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. *Int J Cancer* 1991; **49:** 191–5.
14. Modan B, *et al*. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001; **345:** 235–40.
15. Narod SA, *et al*. Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med* 1998; **339:** 424–8.
16. McGuire V, *et al*. Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. *Am J Epidemiol* 2004; **160:** 613–18.
17. Whittemore AS, *et al*. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer* 2004; **91:** 1911–15.
18. McLaughlin JR, *et al*. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *Lancet Oncol* 2007; **8:** 26–34.
19. Modugno F, *et al*. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004; **191:** 733–40.

SKIN. Although there have been some suggestions of a possible association between the use of oral contraceptives and the development of malignant melanoma[1-4] most studies, including analyses of relatively large numbers of women suffering from malignant melanoma, found no such association with either current or prior use of oral contraceptive preparations.[5-12] A meta-analysis of 18 case-control studies confirmed the lack of association.[13]

1. Beral V, *et al*. Malignant melanoma and oral contraceptive use among women in California. *Br J Cancer* 1977; **36:** 804–9.
2. Lerner AB, *et al*. Effects of oral contraceptives and pregnancy on melanomas. *N Engl J Med* 1979; **301:** 47.
3. Beral V, *et al*. Oral contraceptive use and malignant melanoma in Australia. *Br J Cancer* 1984; **50:** 681–5.
4. Feskanich D, *et al*. Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer* 1999; **81:** 918–23.
5. Bain C, *et al*. Oral contraceptive use and malignant melanoma. *J Natl Cancer Inst* 1982; **68:** 537–9.
6. Helmrich SP, *et al*. Lack of an elevated risk of malignant melanoma in relation to oral contraceptive use. *J Natl Cancer Inst* 1984; **72:** 617–20.
7. Green A, Bain C. Hormonal factors and melanoma in women. *Med J Aust* 1985; **142:** 446–8.
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9. Palmer JR, *et al*. Oral contraceptive use and risk of cutaneous malignant melanoma. *Cancer Causes Control* 1992; **3:** 547–54.
10. Holly EA, *et al*. Cutaneous melanoma in women III: reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; **141:** 943–50.
11. Smith MA, *et al*. Hormonal and reproductive influences and risk of melanoma in women. *Int J Epidemiol* 1998; **27:** 751–7.
12. Naldi L, *et al*. Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol* 2005; **15:** 545–50.
13. Gefeller O, *et al*. Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol* 1998; **138:** 122–4.

Ectopic pregnancy. All methods of contraception effectively reduce the risk of ectopic pregnancy overall by reducing the rate of pregnancy. However, when contraception fails the proportion of pregnancies that are ectopic is higher for users of oral and intra-uterine **progestogen-only contraceptives** and levonorgestrel implants than in the general population.[1] There is no increase in the proportion of ectopic pregnancies for methods that inhibit ovulation more reliably, such as combined oral contraceptives[1] and medroxyprogesterone acetate depot injection.[2]

A small number of cases of ectopic pregnancy after failure of **emergency contraception**, with both the Yuzpe regimen (oestrogen plus progestogen)[3] and progestogen-only contraception,[4] have been reported. However, data from clinical studies[5] and postmarketing surveillance[6] have shown that when levonorgestrel emergency contraception does rarely fail, there is no increase in the chance of ectopic pregnancy occurring.

1. Furlong L-A. Ectopic pregnancy risk when contraception fails: a review. *J Reprod Med* 2002; **47:** 881–5.
2. Borgatta L, *et al*. Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
3. Nielsen CL, Miller L. Ectopic gestation following emergency contraceptive pill administration. *Contraception* 2000; **62:** 275–6.
4. Harrison-Woolrych M, Woolley J. Progestogen-only emergency contraception and ectopic pregnancy. *J Fam Plann Reprod Health Care* 2003; **29**(1): 5–6.
5. Trussell J, *et al*. Ectopic pregnancy following use of progestin-only ECPs. *J Fam Plann Reprod Health Care* 2003; **29:** 249.
6. Gainer E, *et al*. Progestogen-only emergency contraception. *J Fam Plann Reprod Health Care* 2003; **29**(2): 60. Correction. *ibid.*; 159.

Effects on body-weight. Weight gain has been reported as an adverse effect of combined oral contraceptives, but there is no strong evidence from clinical studies to confirm that they have a significant effect on weight.[1,2] However, there is some evidence that weight gain might be associated with medroxyprogesterone acetate when given as a long-acting injectable contraceptive. There have been reports of both weight gain[3] over 5 years, and no change in weight[4] over 10 years, in women using medroxyprogesterone compared with those using a copper IUD. Studies[5,6] in adolescents using medroxyprogesterone or an oral contraceptive for 12 or 18 months have reported more weight gain in those using medroxyprogesterone, and that significant weight gain was more likely in those who were overweight when contraception was started. The risk of weight gain, however, may be confounded by several factors including age, race, diet, exercise, and prior pregnancy.

For discussion of a possible association between obesity and oral contraceptive failure, see Obesity, under Precautions, p. 2241.3.

1. Gupta S. Weight gain on the combined pill—is it real? *Hum Reprod Update* 2000; **6:** 427–31.
2. Gallo MF, *et al*. Combination contraceptives: effects on weight. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 25/09/09).
3. Bahamondes L, *et al*. Comparison of weight increase in users of depot medroxyprogesterone acetate and copper IUD up to 5 years. *Contraception* 2001; **64:** 223–5.
4. Taneepanichskul S, *et al*. Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; **59:** 301–3.
5. Mangan SA, *et al*. Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. *J Pediatr Adolesc Gynecol* 2002; **15:** 79–82.
6. Bonny AE, *et al*. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. *Arch Pediatr Adolesc Med* 2006; **160:** 40–5.

Effects on carbohydrate metabolism. The potential effects of oral contraceptives on carbohydrate metabolism are of concern because impaired glucose tolerance, hyperinsulinism, and insulin resistance contribute to atherogenesis and cardiovascular disease.[1] Early studies suggested that the prevalence of abnormal glucose tolerance in oral contraceptive users was increased from about 4 to 35%.[2] This decreased glucose tolerance was found to be related to oestrogen dose, particularly those greater than 75 micrograms daily, and to the type of progestogen. Marked

hyperglycaemia has been associated with contraceptives containing high doses of oestrogen but is not seen with combined oral contraceptives used currently, which contain lower doses of oestrogen.[1] Progestogens have little effect on glucose tolerance, but are associated with hyperinsulinaemia. This effect is dose-dependent, and levonorgestrel has the most potent effect, with desogestrel, gestodene, and norethisterone reported to have less effect.[1] Combined oral contraceptives can also induce insulin resistance;[1] it is believed that the oestrogen is responsible and that the progestogen modifies this effect.[3]

Despite evidence of these effects, more recent studies of lower-dose preparations containing desogestrel, levonorgestrel, or norethisterone have found little or no effect on various measurements of carbohydrate metabolism;[4-6] this lack of effect has also been confirmed in a meta-analysis[7] of studies of hormonal contraceptive use in non-diabetic women although it was noted that no strong statement could be made since few studies compared the same types of contraceptives and some had large drop out rates. Also, data from the Nurses' Health Study indicate that oral contraceptive use does not appear to increase the risk of developing type 2 diabetes mellitus.[8,9] However, a study in the USA of breast-feeding women of Hispanic origin who had recently had gestational diabetes, suggested that the use of progestogen-only, but not combined, contraceptives was associated with an increased risk of developing type 2 diabetes mellitus in this group.[10]

Injectable progestogen-only contraceptives have been reported in epidemiological studies to be associated with an increase in the incidence of type 2 diabetes mellitus. However, metabolic studies in lean, non-diabetic women have generally found no effect on glucose concentrations, suggesting that obesity or weight gain associated with injectable progestogen-only contraceptive use may play a role.[11]

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; **57:** 189–201.
2. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; (Oct.): 659–62.
3. Godsland IF, *et al*. Insulin resistance, secretion, and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 1992; **74:** 64–70.
4. Kim C, *et al*. Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA study. *Diabetes Care* 2002; **25:** 1027–32.
5. Troisi RJ, *et al*. Oral contraceptive use and glucose metabolism in a national sample of women in the United States. *Am J Obstet Gynecol* 2000; **183:** 389–95.
6. Knopp RH, *et al*. Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; **63:** 1–11.
7. Lopez LM, *et al*. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 21/07/10).
8. Rimm EB, *et al*. Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. *Diabetologia* 1992; **35:** 967–72.
9. Chasan-Taber L, *et al*. A prospective study of oral contraceptives and NIDDM among US women. *Diabetes Care* 1997; **20:** 330–5.
10. Kjos SL, *et al*. Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. *JAMA* 1998; **280:** 533–8.
11. Kahn HS, *et al*. Effects of injectable or implantable progestin-only contraceptives on insulin-glucose metabolism and diabetes risk. *Diabetes Care* 2003; **26:** 216–25.

Effects on the cardiovascular system. Soon after their introduction in the 1960s it became apparent that **combined oral contraceptives** were associated with an increased risk of cardiovascular effects including *hypertension, venous thromboembolism, myocardial infarction,* and *stroke*. Consequently, there are contra-indications and precautions relating to their use in women with risk factors for cardiovascular disease (see under Precautions, p. 2241.2).

Changing patterns of use, and a progressive reduction in doses, have meant a continued need to evaluate the risks associated with oral contraceptives.

Current use of lower-dose combined oral contraceptives (less than 50 micrograms oestrogen) increases blood pressure in many women, and also results in a small but significant increased risk of venous thromboembolism. Any increased risk of myocardial infarction and stroke is low in women aged less than 35 years who do not smoke and who do not have pre-existing hypertension. Further details of these adverse effects are covered in the sections below.

The effect of progestogens on the cardiovascular risk profile of oral contraceptives has not been established. Some of the newer progestogens have been reported to have more favourable effects on plasma lipids (see Effects on Lipids, p. 2239.2) and there is some suggestion that they may have a lower risk of myocardial infarction, but there are insufficient data to confirm or refute this. However, it has been reported that desogestrel and gestodene are associated with a higher risk of venous thromboembolism than older progestogens.

The Nurses' Health Study found no association between ever having used oral contraceptives and death from cardiovascular disease.[1] The Royal College of General Practitioners' study reported an increase in death from cerebrovascular disease with current or recent (within 10 years) use of oral contraceptives, but not for past use (greater than 10 years).[2]

Some general reviews are cited below.[3-7]

1. Colditz GA, *et al*. Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med* 1994; **120:** 821–6.
2. Beral V, *et al*. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 1999; **318:** 96–100.
3. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptive: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
4. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. *Ann Intern Med* 1998; **128:** 467–77.
5. WHO. Cardiovascular disease and steroid hormone contraception. *WHO Tech Rep Ser 877* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_877.pdf (accessed 14/01/08)
6. Hannaford P. Cardiovascular events associated with different combined oral contraceptives: a review of current data. *Drug Safety* 2000; **22:** 361–71.
7. Godsland IF, *et al*. Occlusive vascular diseases in oral contraceptive users: epidemiology, pathology and mechanisms. *Drugs* 2000; **60:** 721–869.

HYPERTENSION. In a one-year prospective multicentre study[1] involving 704 women under the age of 35 using a **combined oral contraceptive** containing levonorgestrel 250 micrograms and ethinylestradiol 50 micrograms and 703 women using a non-hormonal intra-uterine contraceptive device, those using the oral contraceptive developed higher systolic and diastolic blood pressures (systolic pressures were 3.6 to 5.0 mmHg higher, diastolic pressures were 1.9 to 2.7 mmHg higher). Only 4 women receiving oral contraceptives developed hypertension. A similar increase in blood pressure was noted in a study[2] involving 222 users of combined oral contraceptives containing 30 micrograms ethinylestradiol. There was a greater increase in blood pressure for those preparations containing 250 micrograms levonorgestrel than those containing 150 micrograms levonorgestrel.

More recently, data from the Nurses' Health Study[3] showed an increased risk (relative risk 1.8) for the development of hypertension in women taking lower-dose combined oral contraceptives. Increasing doses of progestogen were positively associated with hypertension, and the lowest risk occurred in women receiving triphasic preparations, which have the lowest total dose of progestogen. A UK study[4] found a small increase in blood pressure of 2.3/1.6 mmHg associated with the use of combined oral contraceptives. In this study, oral **progestogen-only contraceptives** were not associated with an increase in blood pressure. A more recent review[5] also found no evidence that use of progestogen-only contraception for up to 2 to 3 years was associated with high blood pressure. Similarly, depot medroxyprogesterone acetate does not raise blood pressure.[6]

1. WHO Task Force on Oral Contraceptives. The WHO multicentre trial of the vasopressor effects of combined oral contraceptives I: comparisons with IUD. *Contraception* 1989; **40:** 129–45.
2. Khaw K-T, Peart WS. Blood pressure and contraceptive use. *BMJ* 1982; **285:** 403–7.
3. Chasan-Taber L, *et al*. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 1996; **94:** 483–9.
4. Dong W, *et al*. Blood pressure in women using oral contraceptives: results from the Health Survey for England 1994. *J Hypertens* 1997; **15:** 1063–8.
5. Hussain SF. Progestogen-only pills and high blood pressure: is there an association? A literature review. *Contraception* 2004; **69:** 89–97.
6. Taneepanichskul S, *et al*. Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; **59:** 301–3.

MYOCARDIAL INFARCTION. Case-control studies from the 1970s and early 1980s revealed an increased risk of acute myocardial infarction in users of oral contraceptives (generally of the high-dose type) relative to those never having used them.[1,2] Several large cohort studies have provided similar findings.[3-6] Among current users the reported[1-3,5,6] relative risk of myocardial infarction has varied between about 1.8 and 6.4, whereas in women having used oral contraceptives in the past the reported[2-5] relative risk has varied between about 0.8 and 2.5. Women who *smoke* while using oral contraceptives are at a greatly increased risk,[1,5,7] those smoking more than 15 to 25 cigarettes daily having at least a twentyfold increased risk of myocardial infarction compared with non-smoking non-oral contraceptive users.[1,5]

These studies have principally been from the USA or the UK. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception has reported the findings of an international multicentre case-control study.[8] The overall odds ratio for acute myocardial infarction in current users of combined oral contraceptives was 5.01 in Europe and 4.78 in Africa, Asia, and Latin America. This increase in risk reflected use in women who had coexistent risk factors such as smoking, and who had not had their blood pressure checked before use. Thus, when the background incidence of acute myocardial infarction is taken into account, use of combined oral contraceptives in non-smoking women aged less than 35 years is associated with an excess of 3 per million women-years, and this is likely to be lower in those women who have their blood pressure screened before and during use. However, in older women who smoke, the excess risk associated with the use of combined oral contraceptives is substantial (400 per million women-years). There was no increase in risk associated with past use of oral contraceptives irrespective of duration of use.

There has been interest in the effect of different progestogen components on the risk of myocardial infarction. Limited data from the WHO study[8] and from the USA[9] and the UK[10] suggested no difference in risk between desogestrel or gestodene compared with levonorgestrel. Analysis of European data[11] suggested a reduction in risk with gestodene- and desogestrel-containing products compared with other progestogens (0.28; 95% confidence intervals 0.09 to 0.86). A WHO Scientific Group meeting concluded that available data did not allow the conclusion that risk of myocardial infarction was related to progestogen type.[12]

More recently, data on combined oral contraceptives that have lower oestrogen doses have revealed at most small and non-significant increases in risk of acute myocardial infarction associated with oral contraceptive use,[10,13-15] although case-control studies have suggested that again, there may be a greatly increased risk in women who smoke more than 20 to 25 cigarettes daily.[10,16] However, subsequent meta-analyses including these and other studies have concluded that, overall, there was an increased risk of myocardial infarction with current use of lower-dose combined oral contraceptives (oestrogen less than 50 micrograms). Subgroup analyses of progestogen type found that there was an increased risk in users of second generation contraceptives (generally containing levonorgestrel) compared with non-users; calculated odds ratios were 2.18 (1.62 to 2.94),[17] 2.17 (1.76 to 2.69),[18] and 1.85 (1.03 to 3.32).[19] However, the risk was not increased in users of third generation contraceptives (generally containing desogestrel or gestodene) compared with non-users.[17-19] Clinically, although the risk of myocardial infarction may be increased, the absolute risk is very low in healthy young women who do not smoke and do not have cardiovascular risk factors. Despite reassuring data for these newer progestogens regarding the risk of myocardial infarction, there is probably an increased risk of venous thromboembolism associated with desogestrel or gestodene (see p. 2238.1).

1. Shapiro S, *et al*. Oral-contraceptive use in relation to myocardial infarction. *Lancet* 1979; **i:** 743–7.
2. Slone D, *et al*. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N Engl J Med* 1981; **305:** 420–4.
3. Royal College of General Practitioners' Oral Contraception Study. Further analyses of mortality in oral contraceptive users. *Lancet* 1981; **i:** 541–6.
4. Stampfer MJ, *et al*. A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. *N Engl J Med* 1988; **319:** 1313–17.
5. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. *BMJ* 1989; **298:** 165–8.
6. Vessey MP, *et al*. Mortality among oral contraceptive users: 20 year follow up of women in a cohort study. *BMJ* 1989; **299:** 1487–91.
7. Goldbaum GM, *et al*. The relative impact of smoking and oral contraceptive use on women in the United States. *JAMA* 1987; **258:** 1339–42.
8. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet* 1997; **349:** 1202–9.
9. Jick H, *et al*. Risk of acute myocardial infarction and low-dose combined oral contraceptives. *Lancet* 1996; **347:** 627–8.
10. Dunn N, *et al*. Oral contraceptives and myocardial infarction: results of the MICA case-control study. *BMJ* 1999; **318:** 1579–83.
11. Lewis MA, *et al*. The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: results from the transnational study on oral contraceptives and the health of young women. *Contraception* 1997; **56:** 129–40.
12. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
13. Thorogood M, *et al*. Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study. *Br J Obstet Gynaecol* 1991; **98:** 1245–53.
14. Sidney S, *et al*. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. *Circulation* 1998; **98:** 1058–63.
15. Tanis BC, *et al*. Oral contraceptives and the risk of myocardial infarction. *N Engl J Med* 2001; **345:** 1787–93.
16. Rosenberg L, *et al*. Low-dose oral contraceptive use and the risk of myocardial infarction. *Arch Intern Med* 2001; **161:** 1065–70.
17. Spitzer WO, *et al*. Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. *Hum Reprod* 2002; **17:** 2307–14.
18. Khader YS, *et al*. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception* 2003; **68:** 11–17.
19. Baillargeon J-P, *et al*. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

STROKE. Current use of **combined oral contraceptives** has been associated with an increased risk of stroke, with most data relating to older high-dose oestrogen preparations. In general this association has been strongest for ischaemic stroke, and relatively weak for haemorrhagic stroke.[1] A Danish study found that lower-dose oral contraceptives (30 to 40 micrograms of oestrogen) were associated with a lower risk of cerebral thromboembolism than preparations containing 50 micrograms oestrogen.[2]

Data on 2198 cases of stroke (haemorrhagic, ischaemic, and unclassified) and 6086 controls have been reported from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.[3,4] For all strokes combined, odds ratios for the current use of lower-dose (less than 50 micrograms oestrogen) and higher-dose preparations were, respectively, 1.41 (95% confidence intervals 0.90 to 2.20) and 2.71 (1.70 to 4.32) in Europe, and 1.86 (1.49 to 2.33) and 1.92 (1.48 to 2.50) in Africa, Asia, and Latin America. In Europe, it was estimated that the incidence rate of stroke in women aged 20 to 44 years was 4.8 per 100 000 women-years, and that this was increased to 6.7 per 100 000 in users of lower-dose preparations and 12.9 per 100 000 in users of higher-dose preparations.[3]

The risk of haemorrhagic stroke was significant only in women aged greater than 35 years, those who had a history of hypertension, and those who were current smokers.[3]

The overall odds ratio for ischaemic stroke was 2.99 (1.65 to 5.40) in Europe and 2.93 (2.15 to 4.00) in Africa, Asia, and Latin America.[4] Odds ratios were lower in women aged less than 35 years, those who did not smoke, those with no history of hypertension, and those who reported that their blood pressure had been checked before use. Duration of current use and past use were unrelated to risk.[4] A similar overall odds ratio of 2.3 (1.15 to 4.59) has been reported from the UK.[5] Similar findings have also been published from the USA.[6] Lower-dose preparations (less than 50 micrograms oestrogen) were associated with a non-significant increase in ischaemic stroke; the odds ratio was 1.18 (0.54 to 2.59); a later meta-analysis considered the association between lower-dose combined oral contraceptives and stroke to be tenuous at best, and possibly non-existent.[7]

A meta-analysis[8] of studies of ischaemic stroke found that there was an overall increased risk associated with the current use of oral contraceptives. However, the risk was less elevated with lower oestrogen doses, and in studies that controlled for smoking and hypertension.

As regards the effect of the type of progestogen on risk of stroke, one case-control study[9] reported that there was no significant difference in risk of ischaemic stroke between lower-dose oral contraceptives containing second generation progestogens and those containing desogestrel, gestodene, or norgestimate. However, another study[10,11] found that levonorgestrel- or norgestimate-containing preparations were associated with a higher risk of cerebral thrombosis than preparations containing desogestrel or gestodene. A re-analysis of the WHO data led to the cautious conclusion that the risk for stroke between second and third generation progestogens was similar,[12] and this was also supported by analysis of the General Practice Research Database[13] and a Dutch case-control study.[14] Meta-analyses[8,15] also found no significant difference between progestogen generations in the risk of ischaemic stroke.

Data for **progestogen-only contraceptives** are limited. The Danish study reported no increase in cerebral thromboembolic attacks in users of oral progestogen-only contraceptives; the odds ratio was 0.9 (0.4 to 2.4).[2]

1. Vessey MP, *et al*. Oral contraceptives and stroke: findings in a large prospective study. *BMJ* 1984; **289:** 530–1.
2. Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993; **306:** 956–63.
3. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 505–10.
4. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 498–505.
5. Nightingale AL, Farmer RDT. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke* 2004; **35:** 1574–8.
6. Petitti DB, *et al*. Stroke in users of low-dose oral contraceptives. *N Engl J Med* 1996; **335:** 8–15.
7. Chan W-S, *et al*. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med* 2004; **164:** 741–7.
8. Gillum LA, *et al*. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000; **284:** 72–8.
9. Heinemann LAJ, *et al*. Case-control study of oral contraceptives and risk of thromboembolic stroke: results from international study on oral contraceptives and health of young women. *BMJ* 1997; **315:** 1502–4.
10. Lidegaard Ø, Kreiner S. Cerebral thrombosis and oral contraceptives: a case-control study. *Contraception* 1998; **57:** 303–14.
11. Lidegaard Ø, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception* 2002; **65:** 197–205.
12. Poulter NR, *et al*. Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. *Lancet* 1999; **354:** 301–2.
13. Jick SS, *et al*. Risk of idiopathic cerebral haemorrhage in women on oral contraceptives with differing progestagen components. *Lancet* 1999; **354:** 302–3.
14. Kemmeren JM, *et al*. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke* 2002; **33:** 1202–8.
15. Baillargeon J-P, *et al*. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

VENOUS THROMBOEMBOLISM. Use of **combined oral contraceptives** has long been known to be associated with an increased risk of venous thromboembolic events, particularly deep-vein thrombosis and pulmonary embolism. This increased risk applies both to idiopathic events and events associated with surgery or trauma, is limited to current users and is probably highest in the first year of use. Most early data relate to high-dose combined preparations, and it has been suggested by some studies,[1] but not others,[2,3] that preparations containing lower doses of oestrogen may be associated with a lower risk. More recently, reports have identified an increased risk of cerebral-vein thrombosis with oral contraceptives.[4]

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception reported data from over 10 times more cases than any previous study.[5] The increased risk of idiopathic deep-vein thrombosis and/or pulmonary embolism associated with current use of combined oral contraceptives was 4.15 (95% confidence intervals 3.09 to 5.57) in Europe and 3.25 (2.59 to 4.08) in Africa, Asia, and Latin America. The increased risk was apparent within 4 months of starting use, was unaffected by duration of use, and had disappeared within 3 months of stopping use. Risk was unaffected by age, hypertension, or smoking (in contrast to myocardial infarction, see p. 2237.2), but was increased in those with a body-mass index greater than 25 kg/m^2 and in those with a history of hypertension of pregnancy. Of preparations containing progestogens of the norethisterone or norgestrel type, risk was non-significantly less with lower-dose oestrogen than with high-dose oestrogen.

The progestogen component has generally been considered to be unrelated to thromboembolic events; therefore, it came as a surprise when WHO found a higher risk in combined oral contraceptives containing *desogestrel* or *gestodene* than in those containing older progestogens.[5] These risk data were the subject of a separate report,[6] and were subsequently confirmed by 3 further case-control studies.[7-9] The increased risk varied from 4.8 to 9.1 compared with non-users, and was found to be 1.5 to 2.6 times higher than for preparations containing levonorgestrel or other progestogens. The incidence of venous thromboembolic disease has been estimated to be 25 per 100 000 users per year for desogestrel- and gestodene-containing products and 15 per 100 000 users per year for products containing low-dose oestrogen with other progestogens, compared with 5 per 100 000 per year for non-users. The risk was especially high in women with the factor V Leiden mutation,[8] who are at increased risk of thrombosis, but screening to exclude these women from using oral contraceptives was not considered necessary.[10,11] Despite much debate about possible bias and confounding in these results,[12,13] and the ambiguous or contradictory results of subsequent studies,[14-16] many sources seem now to agree with the 1997 conclusion of a WHO scientific group meeting[17] that there is a modestly increased risk of venous thromboembolism associated with the use of products containing desogestrel or gestodene, compared with levonorgestrel. The extent of any risk associated with combined products containing *drospirenone* has also been questioned. Data from a prescription event monitoring study suggested that it was associated with a high incidence of deep-vein thrombosis and pulmonary embolism,[18] but the authors acknowledged potential bias that may have affected the result. Subsequent large cohort studies[19,20] reported that the risk of venous thromboembolism was similar to that for users of other combined oral contraceptives, including levonorgestrel-containing preparations. Products containing *cyproterone* are also associated with increased risk (see Effects on the Cardiovascular System, under Cyproterone Acetate, p. 2262.3).

Regulatory agencies have reacted in different ways to these data. The UK CSM has advised caution in prescribing of these products (see Cardiovascular Disease under Precautions, p. 2241.2), as have some other European authorities.

The mechanism behind differences in thrombotic potential is unknown, but there is evidence that oral contraceptives may increase concentrations of prothrombin and factor VIII, and induce a resistance to the blood's natural anticoagulation system.[11] These effects may be greater with products containing desogestrel and gestodene compared with older progestogens.[11] Thrombophilias, including factor V Leiden, further increase the risk of thromboembolism from hormonal contraceptives.[21]

There has also been some concern about a possible increase in cardiovascular risk with a **transdermal patch** that releases ethinylestradiol and norelgestromin, because users are exposed to about 60% more total oestrogen than users of an oral contraceptive containing ethinylestradiol 35 micrograms (peak serum concentrations are lower but steady-state concentrations are higher). However, 2 studies comparing the patch with a combined oral contraceptive (ethinylestradiol plus norgestimate) came to different conclusions; one found the risk of venous thromboembolism to be similar,[22] while the other found a twofold increase in risk with the patch.[23] Further study is needed to explain this discrepancy, and to determine whether there is any effect on the risks of myocardial infarction and stroke.

1. Vessey M, *et al*. Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
2. Kierkegaard A. Deep vein thrombosis and the oestrogen content in oral contraceptives—an epidemiological analysis. *Contraception* 1985; **31:** 29–41.
3. Helmrich SP, *et al*. Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol* 1987; **69:** 91–5.
4. Dentali F, *et al*. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. *Blood* 2006; **107:** 2766–73.
5. WHO Collaborative Study Group. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995; **346:** 1575–82.
6. WHO Collaborative Study Group. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995; **346:** 1582–8.
7. Jick H, *et al*. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; **346:** 1589–93.
8. Bloemenkamp KWM, *et al*. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995; **346:** 1593–6.
9. Spitzer WO, *et al*. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996; **312:** 83–8.
10. Vandenbroucke JP, *et al*. Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1996; **313:** 1127–30.
11. Vandenbroucke JP, *et al*. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344:** 1527–35.
12. Lewis MA, *et al*. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. *Contraception* 1996; **54:** 5–13.
13. Farley TMM, *et al*. Oral contraceptives and thrombotic diseases: impact of new epidemiologic studies. *Contraception* 1996; **54:** 193–5.
14. Farmer RDT, *et al*. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997; **349:** 83–8.
15. Farmer RDT, *et al*. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. *BMJ* 2000; **321:** 477–9.
16. Jick H, *et al*. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000; **321:** 1190–5. Correction. *ibid*. 2001; **322:** 28.
17. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
18. Pearce HM, *et al*. Deep vein thrombosis and pulmonary embolism reported in the Prescription Event Monitoring Study of Yasmin. *Br J Clin Pharmacol* 2005; **60:** 98–102.
19. Dinger JC, *et al*. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contraception* 2007; **75:** 344–54.
20. Seeger JD, *et al*. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007; **110:** 587–93.
21. Wu O, *et al*. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.
22. Jick SS, *et al*. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. *Contraception* 2006; **73:** 223–8.
23. Cole JA, *et al*. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007; **109:** 339–46.

Effects on the ears. In the Royal College of General Practitioners' study of oral contraception in the UK,[1] by 1981 there had been 13 cases of newly occurring otosclerosis in each of the groups of oral contraceptive users (101 985 woman-years) and controls (146 534 woman-years); this showed a non-significant relative risk of 1.29. Although, by analogy with pregnancy, it may be prudent to suppose that oral contraceptives could exacerbate pre-existing otosclerosis, the data do not support the view that the condition is associated with their use. Similarly, the Oxford Family Planning Association contraceptive study[2] of 17 032 women followed for up to 26 years found no association between oral contraceptive use and the development of a range of ear diseases, including otosclerosis.

1. Kay CR, Wingrave SJ. Oral contraceptives and otosclerosis. *BMJ* 1984; **288:** 1164.
2. Vessey M, Painter R. Oral contraception and ear disease: findings in a large cohort study. *Contraception* 2001; **63:** 61–3.

Effects on the eyes. Analysis of data from 2 large UK cohort studies suggested that oral contraceptive use does not increase the risk of eye disease, with the possible exception of retinal vascular lesions.[1] Retinal vein thrombosis has also been reported after the use of emergency contraception.[2] The patient presented with a 10-day history of blurred vision that started the day after taking a regimen of ethinylestradiol with norgestrel; the condition resolved after 2 months of treatment with low-dose aspirin.

1. Vessey MP, *et al*. Oral contraception and eye disease: findings in two large cohort studies. *Br J Ophthalmol* 1998; **82:** 538–42.
2. Lake SR, Vernon SA. Emergency contraception and retinal vein thrombosis. *Br J Ophthalmol* 1999; **83:** 630–1.

Effects on fertility. After stopping hormonal contraceptives some patients may develop amenorrhoea, anovulation, and infertility. This infertility, however, has been shown by most studies to be only temporary.

Data from the Oxford Family Planning Association study[1] have indicated that impairment of fertility after oral contraceptives was only very slight and short-lived in women who had previously had a baby. In nulliparous women aged 25 to 29 years impairment of fertility was more pronounced but the effect had almost entirely disappeared after 48 months. In nulliparous women aged 30 to 34 years the duration of impairment was longer but, again, this was not permanent as by 72 months after stopping oral contraceptive use the numbers of women who had not conceived were similar to a group who had previously used non-hormonal methods of contraception. In contrast to women using intra-uterine devices, in whom long-term use was associated with greater impairment of fertility than short-term (less than 42 months) use, there appears to be no association between fertility and duration of oral contraceptive use.[2] However, a later survey,[3] although concurring that the effects were transient, did find a relationship between duration of use of combined oral contraceptives and subsequent time to pregnancy.

Oral progestogen-only preparations do not appear to have a significant effect on fertility.[3] Smaller studies have also indicated that injectable progestogen-only contraceptives have no long-lasting effects on fertility;[3,4] but it has been suggested that a return to ovulation occurs significantly earlier in prior norethisterone enantate users than in medroxyprogesterone users.[5]

Infertility may also be related to the presence of pelvic inflammatory disease; for further details concerning the role of oral contraceptives in this disorder, see Pelvic Inflammatory Disease, p. 2240.3.

1. Anonymous. "Pill" use appears to impair fertility in a certain group of women. *Pharm J* 1986; **236:** 227.
2. Doll H, *et al.* Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception. *Br J Obstet Gynaecol* 2001; **108:** 304–14.
3. Hassan MAM, Killick SR. Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity? *Hum Reprod* 2004; **19:** 344–51.
4. Fotherby K, *et al.* Return of ovulation and fertility in women using norethisterone enanthate. *Contraception* 1984; **29:** 447–55.
5. Garza-Flores J, *et al.* Return to ovulation following the use of long-acting injectable contraceptives: a comparative study. *Contraception* 1985; **31:** 361–6.

Effects on the gallbladder. Data from the Royal College of General Practitioners' (RCGP) oral contraception study accumulated up to December 1979 revealed no overall increased risk of gallbladder disease in the long-term, despite the indications of earlier data and other studies relating to short-term use.[1] Further studies[2,3] have identified an increased risk of gallbladder disease in oral contraceptive users under the age of 30 or 20, respectively. A systematic review[4] also found that oral contraceptives were associated with a slightly and transiently increased risk of gallbladder disease. However, the results of separate studies varied considerably and the reviewers highlighted several possible confounding factors and biases, nonetheless, it was concluded that newer lower-dose contraceptives (less than 50 micrograms of oestrogen) were less likely to cause problems than older formulations. Later data from the RCGP study showed an increase in risk of mild hepatitis during the first 4 years of oral contraceptive use, possibly reflecting gallstone-associated cholestasis.[5] This risk then decreased to less than that seen in women who had never used oral contraceptives.

1. Wingrave SJ, Kay CR. Oral contraceptives and gallbladder disease: Royal College of General Practitioners' oral contraception study. *Lancet* 1982; **ii:** 957–9.
2. Scragg RKR, *et al.* Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease—a case-control study. *BMJ* 1984; **288:** 1795–9.
3. Strom BL, *et al.* Oral contraceptives and other risk factors for gallbladder disease. *Clin Pharmacol Ther* 1986; **39:** 335–41.
4. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health* 1993; **83:** 1113–20.
5. Hannaford PC, *et al.* Combined oral contraceptives and liver disease. *Contraception* 1997; **55:** 145–51.

Effects on the gastrointestinal tract. Several studies,[1-3] epidemiological data,[4] and a meta-analysis,[5] have shown a weak association between oral contraceptive use and the onset of Crohn's disease or ulcerative colitis. However, the suggestion that oral contraceptives have an aetiological role in chronic inflammatory bowel disease cannot be regarded as established.

The rate of relapse of Crohn's disease in women taking oral contraceptives has also been studied. Although one study[6] reported an increased risk of relapse in women who had taken oral contraceptives in the past, both this study and another prospective cohort study[7] found no increase in risk in current users. These results may have been influenced by smoking, or changes in oestrogen dose and progestogen content.

Women with inflammatory bowel disease may be offered the same contraceptive choices as other women, although oral contraceptive absorption, and hence efficacy, may be reduced when there is small bowel involvement or malabsorption.[8]

1. Corrao G, *et al.* Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. *Int J Epidemiol* 1998; **27:** 397–404.
2. Sicilia B, *et al.* Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Dig Liver Dis* 2001; **33:** 762–7.
3. García Rodríguez LA, *et al.* Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* 2005; **22:** 309–15.
4. Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease. *Gut* 2000; **46:** 140.
5. Godet PG, *et al.* Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 1995; **37:** 668–73.
6. Timmer A, *et al.* Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. *Gastroenterology* 1998; **114:** 1143–50.
7. Cosnes J, *et al.* Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. *Gut* 1999; **45:** 218–22.
8. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Clinical guidance: sexual and reproductive health for individuals with inflammatory bowel disease (issued June 2009). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceIBD09.pdf (accessed 25/09/09)

Effects on lipids. Combined oral contraceptives have been reported to be associated with an excess risk of various adverse cardiovascular events (see p. 2237.1). Because other epidemiological evidence suggests that the composition of blood lipids may be one of several factors involved in the aetiology of some of these disorders, many workers have investigated the biochemical profiles of women taking various formulations of oral contraceptives. Results have often been conflicting as the net effect is the result of opposing actions of the oestrogen and the progestogen components, and depends on the ratio between these. In general, the oestrogen component increases triglycerides, but decreases low-density lipoproteins, whereas the progestogen component tends to decrease high-density lipoproteins and increase low-density lipoproteins, particularly if it is androgenic (19-nortestosterone-derived progestogens). Newer non-androgenic progestogens such as desogestrel and gestodene appear to have a less detrimental effect on serum lipids. However, the contribution of these lipid changes to the incidence of cardiovascular disease in oral contraceptive users is uncertain. In particular, contrary to expectations, desogestrel and gestodene appear to be associated with a higher risk of venous thromboembolism than older progestogens (see p. 2238.1).

Some references to the effects of various oral contraceptives on serum lipid profiles are given below.[1-4]

For further details concerning the proposed role of the various serum lipids and subfractions in the aetiology of cardiovascular disease, see Hyperlipidaemias, p. 1248.1.

For reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives, see p. 2240.2.

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; **57:** 189–201. Correction. *ibid.*: 420.
2. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; **63:** 1–11.
3. Graff-Iversen S, Tonstad S. Use of progestogen-only contraceptives/medications and lipid parameters in women age 40 to 42 years: results of a population-based cross-sectional Norwegian Survey. *Contraception* 2002; **66:** 7–13.
4. Gaspard U, *et al.* A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. *Contraception* 2004; **69:** 271–8.

Effects on the liver. The use of combined oral contraceptives has been rarely associated with the benign liver tumours, hepatic adenoma and focal nodular hyperplasia (see under Carcinogenicity, p. 2235.3).

Hepatitis possibly associated with gallstones has also been reported (see Effects on the Gallbladder, above).

Effects on mental state. Changes in mood and affect have been reported with oral contraceptives, and the onset of depression is a common reason given for stopping use. Nonetheless, a review[1] concluded that most women taking oral contraceptives actually feel beneficial effects, with less variability in affect across the menstrual cycle and less negative affect during the menstrual phase compared with non-users. However, there may be a subgroup of women predisposed to negative changes in mood and affect because of factors such as a history of depression, premenstrual mood symptoms before oral contraceptive use, a history of mood symptoms related to pregnancy, or a family history of mood complaints related to oral contraceptives. A lower ratio of progestogen to oestrogen was associated with more negative mood changes in women with a history of premenstrual emotional symptoms, while a higher ratio was associated with negative changes in women without such a history. In addition, monophasic regimens appeared to have a greater stabilising effect than triphasic preparations. Some possible mechanisms have been suggested to explain how combined hormonal contraceptives might influence mood.[2]

Cohort studies of injectable[3] and implantable[4] progestogen-only contraceptives found no overall change in depressive symptom score. A small increase in depressive score noted at the 2-year follow-up of implant users was found to occur in women who also had a decrease in relationship satisfaction, which the authors concluded was independent of contraceptive use. Another study[5] found an association between injectable medroxyprogesterone acetate and depressive symptoms, but other factors that might have influenced this result were also identified and another explanation could not be ruled out.

1. Oinonen KA. Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord* 2002; **70:** 229–40.
2. Kurshan N, Epperson CN. Oral contraceptives and mood in women with and without premenstrual dysphoria: a theoretical model. *Arch Womens Ment Health* 2006; **9:** 1–14.
3. Westhoff C, *et al.* Depressive symptoms and Depo-Provera. *Contraception* 1998; **57:** 237–40.
4. Westhoff C, *et al.* Depressive symptoms and Norplant contraceptive implants. *Contraception* 1998; **57:** 241–5.
5. Civic D, *et al.* Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. *Contraception* 2000; **61:** 385–90.

Effects on the musculoskeletal system. *BONE DENSITY.* Combined oral contraceptives are generally considered not to have a detrimental effect on bone mineral density but study results have been inconsistent and any clinical significance unclear. However, overall, combined oral contraceptives appear not to affect bone mineral density or biochemical markers of bone turnover.[1]

Reviews of studies in different age groups have found that bone mineral density in healthy premenopausal women does not appear to be significantly affected.[2,3] However, there is limited evidence that adolescents and young women (less than 23 years of age) using oral combined contraceptives have a lower bone mineral density than non-users; it is unclear whether contraceptives might prevent young women from reaching their peak bone mass and put them at increased risk of osteoporosis later in life.[3] There is some evidence of a positive effect on bone mineral density in perimenopausal[2,3] and postmenopausal women[3] taking combined oral contraceptives, but past use in postmenopausal women appeared to have no effect. Although bone mineral density is used as an indicator of fracture risk, the true effects of combined oral contraceptives on this clinical outcome are unclear;[1] there is a particular lack of data in older women, in whom osteoporotic fractures are most common.[3]

There is stronger evidence that bone mineral density is reduced in current users of the depot progestogen-only contraceptive, **medroxyprogesterone acetate**. Recovery occurs after stopping treatment,[4,5] but it is still unclear whether adult women can regain baseline bone mineral density levels, and whether adolescents can reach peak bone mass.[4] There is also a lack of data on fracture risk in both current and former users of all ages.[1,4]

As adolescence is an age at which bone mineral density is normally increasing there is some concern about the possible long-term effects of depot medroxyprogesterone. The UK CSM has advised that in adolescents it should only be used if other methods of contraception are unsuitable or unacceptable, and that there should be a re-evaluation of risks and benefits for women of all ages who wish to continue use beyond 2 years.[6] The FDA has also advised[7] that, for all women, medroxyprogesterone should only be used as a long-term contraceptive, giving an example of more than 2 years, if other contraceptive methods are inadequate. In contrast, however, WHO[8] advises that there should be no restriction, including duration of use, on the use of medroxyprogesterone in women aged 18 to 45 who are otherwise eligible to use it. For adolescents and women over 45, WHO advises that they may use it if the patient and her healthcare provider decide that it is the best method of contraception for her, even if it may decrease her bone density. Others[9] offer similar recommendations in support, pointing out that further research is needed.

There is some evidence that oestrogen supplementation may reduce or prevent the reduction in bone mineral density caused by medroxyprogesterone acetate.[10,11] Although such supplementation could be considered in medroxyprogesterone users who have osteopenia or are at high risk, the optimal dose, route, and extent of benefit has not been established.[9]

1. Lopez LM, *et al.* Steroidal contraceptives: effect on bone fractures in women. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 25/09/09).
2. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. *Br J Sports Med* 2006; **40:** 11–24.
3. Martins SL, *et al.* Combined hormonal contraception and bone health: a systematic review. *Contraception* 2006; **73:** 445–69.
4. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density: a systematic review. *Contraception* 2006; **73:** 470–87.
5. Kaunitz AM, *et al.* Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. *Contraception* 2006; **74:** 90–9.
6. MHRA. Updated prescribing advice on the effect of Depo-Provera contraception on bones. Message from Professor G Duff, Chairman of CSM (issued 16th November, 2004). Available at: http://www.mhra.

gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con019478&RevisionSelectionMethod=Latest (accessed 14/01/08)
7. FDA. Depo-Provera (medroxyprogesterone acetate injectable suspension) (issued November 18, 2004). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154784.htm (accessed 21/07/10)
8. WHO. Hormonal contraception and bone health (issued 2007). Available at: http://www.who.int/reproductivehealth/topics/family_planning/pbrief_bonehealth.pdf (accessed 21/07/10)
9. Cromer BA, *et al*. Depot medroxyprogesterone acetate and bone mineral density in adolescents—the Black Box Warning: a Position Paper of the Society for Adolescent Medicine. *J Adolesc Health* 2006; **39:** 296–301.
10. Cundy T, *et al*. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *J Clin Endocrinol Metab* 2003; **88:** 78–81.
11. Cromer BA, *et al*. Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception. *Am J Obstet Gynecol* 2005; **192:** 42–7.

RHEUMATOID ARTHRITIS. There have been rare reports of arthritis or arthropathies attributed to oral contraceptives, and some large studies have investigated the incidence of rheumatoid arthritis in oral contraceptive users. A negative association between the use of oral contraceptives and the development of rheumatoid arthritis has been reported in some studies thus giving rise to the suggestion that oral contraceptive use may, in fact, have some sort of protective role. These findings were not, however, substantiated by a recent, large, long-term cohort study[1] which found no association, either beneficial or detrimental, between the use of oral contraceptives and the later development of rheumatoid arthritis. An earlier meta-analysis also found no conclusive evidence of a protective effect of oral contraceptives on rheumatoid arthritis risk.[2] There is limited information about the effect of oral contraceptives on pre-existing rheumatoid arthritis. One study[3] found that there was no significant influence on the progression of the disease, but there was a trend towards less radiographic joint damage and disability with long-term oral contraceptive use.

1. Karlson EW, *et al*. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004; **50:** 3458–67.
2. Pladevall-Vila M, *et al*. Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. *Am J Epidemiol* 1996; **144:** 1–14.
3. Drossaers-Bakker KW, *et al*. Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis. *Ann Rheum Dis* 2002; **61:** 405–8.

Effects on the nervous system. *Headache* is reported as a common adverse effect and frequent reason for stopping combined oral contraceptives. However, a systematic review[1] found that although study results could not be pooled, there was no strong evidence associating combined oral contraceptive use with headache. There may have been an increase in headache in the early cycles, but this tended to improve with continued use; for most women there was no effect on headache activity and some actually reported improvement. Headache also appeared to be associated with oestrogen withdrawal during the tablet-free week of the cycle, but there was no evidence that headache was improved by changing to a preparation with a lower dose of oestrogen. However, some women appeared to be at higher risk, such as those with a strong personal or family history of troublesome headaches, particularly migraine. Combined oral contraceptives are not contra-indicated in women with non-migrainous headache, but they should be used with caution or avoided in women with migraine because of the increased risk of stroke (see Migraine, under Precautions, p. 2241.3).

Chorea has been reported in women using combined oral contraceptives. Reviews of the literature have reported the onset of chorea to range from 1 week to 11 months,[2] with an average of 3 months,[3] and resolution of symptoms after stopping the contraceptive to occur after 1 week to 5 months[2] or an average of 5 weeks.[3] The mechanism of this effect is unclear. Some cases occurred in patients with no history of neurological disease,[2,3] but others had a history of rheumatic fever, often with Sydenham chorea, or chorea gravidarum, chorea secondary to other conditions, or congenital heart disease.[3] There is some evidence that chorea could be mediated by the production of antiphospholipid antibodies, as either a primary antiphospholipid syndrome or secondary to SLE.[4,5] It has been suggested that the production of these antibodies could be aggravated by the oestrogen component of combined oral contraceptives.[4] In another case report[6] it was suggested that the presence of anti-basal ganglia antibodies might have played a role in the development of chorea by making the basal ganglia more susceptible to the effects of the oestrogen component of an oral contraceptive.

It is generally advised that combined oral contraceptives should be used with caution or avoided in women with antiphospholipid antibodies because they are at increased risk of venous thromboembolism, see Cardiovascular Disease, under Precautions, p. 2241.2.

1. Loder EW, *et al*. Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol* 2005; **193:** 636–49.
2. Wadlington WB, *et al*. Chorea associated with the use of oral contraceptives: report of a case and review of the literature. *Clin Pediatr (Phila)* 1981; **20:** 804–6.
3. Galimberti D. Chorea induced by the use of oral contraceptives: report of a case and review of the literature. *Ital J Neurol Sci* 1987; **8:** 383–6.
4. Omdal R, Roalsø S. Chorea gravidarum and chorea associated with oral contraceptives—diseases due to antiphospholipid antibodies? *Acta Neurol Scand* 1992; **86:** 219–20.
5. Cervera R, *et al*. Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine (Baltimore)* 1997; **76:** 203–12.
6. Miranda M, *et al*. Oral contraceptive induced chorea: another condition associated with anti-basal ganglia antibodies. *J Neurol Neurosurg Psychiatry* 2004; **75:** 327–8.

Effects on the pancreas. There have been reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives.[1,2]

1. Parker WA. Estrogen-induced pancreatitis. *Clin Pharm* 1983; **2:** 75–9.
2. Stuyt PMJ, *et al*. Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinaemia. *BMJ* 1986; **293:** 734.

Effects on the skin. Oral contraceptives may cause chloasma, and those containing androgenic progestogens may cause or aggravate acne and hirsutism. More rarely, oral contraceptives have been implicated in photosensitivity reactions[1] and photosensitivity associated with drug-induced lupus erythematosus.[2] A survey of people using UVA sunbeds at commercial premises in the UK revealed that the prevalence of pruritus, nausea, and skin rashes as adverse reactions to sunbed use was higher in women taking oral contraceptives than in women receiving no medication.[3] There has been a report of hidradenitis suppurativa, a condition resulting in the recurrence of boils at the axillary apocrine sweat glands, anogenital region, and breasts, occurring in 7 women using oral contraceptives.[4] Sweet's syndrome (acute febrile neutrophilic dermatosis) has been described very rarely with hormonal contraceptives. In one case,[5] the reaction started 10 days after beginning a combined oral contraceptive and resolved after stopping the contraceptive and treating with oral and topical corticosteroids. The woman reported that a similar reaction had occurred 6 months earlier with a different combined oral contraceptive. Sweet's syndrome has also occurred 1 month after insertion of a levonorgestrel IUD; the condition was controlled with corticosteroids, but only resolved completely after removal of the IUD.[6]

For mention of the refuted association between oral contraceptives and malignant melanoma, see Skin under Carcinogenicity p. 2236.2. Auto-immune progesterone dermatitis has been reported in women with a history of oral contraceptive use (see p. 2301.3).

1. Cooper SM, George S. Photosensitivity reaction associated with use of the combined oral contraceptive. *Br J Dermatol* 2001; **144:** 641–2.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; (Jun.): 508–11.
3. Diffey BL. Use of UV-A sunbeds for cosmetic tanning. *Br J Dermatol* 1986; **115:** 67–76.
4. Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptives. *BMJ* 1989; **298:** 28–9.
5. Sáez M, *et al*. Sweet's syndrome induced by oral contraceptive. *Dermatology* 2002; **204:** 84.
6. Hamill M, *et al*. Sweet's syndrome and a Mirena intrauterine system. *J Fam Plann Reprod Health Care* 2004; **30:** 115–16.

Effects on the uterus. The Oxford Family Planning Association study found that the risk of developing uterine leiomyomas (uterine fibroids) was reduced by the use of oral contraceptives[1] by about 17% with each 5 years of oral contraceptive use. This was not thought to be due to selective prescribing.[2,3] The authors hypothesised that unopposed oestrogen may be a risk factor for uterine fibroids, and that the reduced risk with oral contraceptives might be analogous to the reduction in endometrial carcinoma seen with these drugs (see p. 2235.2).[1] Other studies[4,5] have also reported a reduced risk of uterine leiomyomas in current users of oral contraceptives, while past users have a risk similar to that in women who have never used oral contraceptives. However, one study[4] did suggest that in women who had first used oral contraceptives at an early age (13 to 16 years) there was a modestly elevated risk. Another case-control study involving 390 women with leiomyomas failed to find a protective (or detrimental) effect with oral contraceptive use.[6] A further cohort study[7] also found no association between oral contraceptive use and leiomyoma formation, but did report a reduced risk with current use of medroxyprogesterone acetate depot injection.

1. Ross RK, *et al*. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 359–62. Correction. *ibid*.; 1027.
2. Ratner H. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 1027.
3. Ross RK, *et al*. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 1027.
4. Marshall LM, *et al*. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. *Fertil Steril* 1998; **70:** 432–9.
5. Chiaffarino F, *et al*. Use of oral contraceptives and uterine fibroids: results from a case-control study. *Br J Obstet Gynaecol* 1999; **106:** 857–60.
6. Parazzini F, *et al*. Oral contraceptive use and risk of uterine fibroids. *Obstet Gynecol* 1992; **79:** 430–3.
7. Wise LA, *et al*. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. *Am J Epidemiol* 2004; **159:** 113–23.

Pelvic inflammatory disease. It has been suggested that oral contraceptives protect against pelvic inflammatory disease. However, although oral contraceptives are thought to reduce the risk of developing acute pelvic inflammatory disease, higher rates of infection of the lower genital tract by *Chlamydia trachomatis*,[1] and, more tentatively, *Neisseria gonorrhoeae*,[2] have been reported. Other studies[3,4] have suggested that oral contraceptive use is associated with reduced symptom severity, but absence of symptoms is not the same as absence of disease: oral contraceptives might reduce the inflammatory reaction to infection, resulting in unrecognised disease and subsequent complications such as tubal infertility and ectopic pregnancy.[5] There is evidence that users of older oral contraceptives containing more than 50 micrograms of oestrogen may have been at increased risk of tubal infertility, particularly if first used before 20 years of age.[6] No increased risk, or an active decrease in risk (depending on age at first use) was reported for formulations containing 50 micrograms or less of oestrogen, which are now favoured.

The possible effects of depot medroxyprogesterone acetate have also been examined and one study[7] suggested that it was associated with an increase in cervical chlamydial and gonococcal infections. However, confounding factors in this study such as sexual practices, a history of infection, and the background pool of infectivity in sexual partners, have been highlighted[8,9] and cast doubt on a true causal relationship between medroxyprogesterone acetate and risk of infection.

1. Washington AE, *et al*. Oral contraceptives, Chlamydia trachomatis infection, and pelvic inflammatory disease: a word of caution about protection. *JAMA* 1985; **253:** 2246–50.
2. Louv WC, *et al*. Oral contraceptive use and the risk of chlamydial and gonococcal infections. *Am J Obstet Gynecol* 1989; **160:** 396–402.
3. Wølner-Hanssen P, *et al*. Decreased risk of symptomatic chlamydial pelvic inflammatory disease associated with oral contraceptive use. *JAMA* 1990; **263:** 54–9.
4. Ness RB, *et al*. Hormonal and barrier contraception and risk of upper genital tract disease in the PID Evaluation and Clinical Health (PEACH) study. *Am J Obstet Gynecol* 2001; **185:** 121–7.
5. Henry-Suchet J. Hormonal contraception and pelvic inflammatory disease. *Eur J Contracept Reprod Health Care* 1997; **2:** 263–7.
6. Cramer DW, *et al*. The relationship of tubal infertility to barrier method and oral contraceptive use. *JAMA* 1987; **257:** 2446–50.
7. Morrison CS, *et al*. Hormonal contraceptive use, cervical ectopy, and the acquisition of cervical infections. *Sex Transm Dis* 2004; **31:** 561–7.
8. Dayan L, Donovan B. Chlamydia, gonorrhoea, and injectable progesterone. *Lancet* 2004; **364:** 1387–8.
9. Warner P. Concerns regarding design, analysis, and interpretation of the Morrison study on hormonal contraceptive use and acquisition of cervical infections. *Sex Transm Dis* 2005; **32:** 644.

Precautions

Before hormonal contraceptives are given, the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use. The contraceptive efficacy of combined and progestogen-only preparations may be reduced during episodes of vomiting or diarrhoea and extra contraceptive measures may be necessary during and for 7 days after recovery. For precautions to be taken if doses are missed, see Uses and Administration, p. 2231.3.

Combined hormonal contraceptives are *contra-indicated* in women with markedly impaired liver function or cholestasis, the Dubin-Johnson or Rotor syndromes, hepatic tumour, oestrogen-dependent neoplasms such as breast or endometrial cancer, cardiovascular disease (see also p. 2241.2) including previous or current thromboembolic disorders or high risk of them, and arterial disease or multiple risk factors for it, disorders of lipid metabolism, undiagnosed vaginal bleeding, possible pregnancy, or a history during pregnancy of pruritus or cholestatic jaundice, chorea, herpes gestationis, pemphigoid gestationis, or deteriorating otosclerosis. They are also contra-indicated in severe or focal migraine (or where there are other risk factors for cardiovascular disease) and should be used with caution in other forms of migraine (for further details, see p. 2241.3). Combined hormonal contraceptives should not be used during active trophoblastic disease, or until urine and plasma gonadotrophin concentrations have returned to normal after treatment. They should be *given with caution* to women with a history of clinical depression, gallbladder disease, sickle-cell disease, or conditions influenced by fluid retention. Oral contraceptive absorption, and hence efficacy, may be reduced in women with inflammatory bowel disease when there is small bowel involvement or malabsorption. They should also be used with caution in those with varicose veins, and should be avoided during sclerosing treatment. Where not actually contra-indicated, they should also be used with caution in those with a risk factor for cardiovascular disease such as diabetes mellitus, smoking, obesity, hypertension, or a family history of cardiovascular disorders (see also p. 2241.2). A low-strength combined oral contraceptive (containing 20 micrograms of

ethinylestradiol) may be suitable for women with risk factors for cardiovascular disease, provided a combined oral contraceptive is otherwise suitable. A standard-strength combined hormonal contraceptive (such as a monophasic oral preparation containing 30 or 35 micrograms of ethinylestradiol) may be used in women over the age of 35 years provided they do not smoke and have no other risk factors for cardiovascular disease. Once women are aged over 40 years, the first choice of oral combined hormonal contraceptive should contain the lowest dose of ethinylestradiol that provides adequate cycle control, such that a preparation containing less than 30 micrograms of ethinylestradiol may be suitable. After 50 years of age, women taking a combined hormonal contraceptive should switch to a non-hormonal method or a progestogen-only method (such as a progestogen-only oral contraceptive, progestogen implant, or levonorgestrel intra-uterine device). Use by those undergoing surgery or prolonged bed rest may increase the risk of thromboembolic episodes and it is generally recommended that combined hormonal contraceptives should be stopped 4 weeks before major elective surgery (but see also p. 2242.2). Contact lenses may irritate. The use of combined oral contraceptives may influence the results of certain laboratory tests including liver, thyroid, adrenal, and renal-function tests, plasma concentrations of binding proteins and lipid/lipoprotein fractions, and fibrinolysis and coagulation parameters.

Combined hormonal contraceptives should be *stopped immediately*, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 95 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during oral contraception or pregnancy.

Progestogen-only contraceptives, whether oral or injectable, may be used when oestrogen-containing preparations are contra-indicated but certain contra-indications and precautions must still be observed. They are contra-indicated in women with undiagnosed vaginal bleeding, possible pregnancy, severe arterial disease, hormone-dependent neoplasms, and severe liver disease such as hepatic tumour.

Like combined hormonal contraceptives they should not be used during active trophoblastic disease. Progestogen-only contraceptives should be used with caution in women with arterial disease, malabsorption syndromes, liver dysfunction including recurrent cholestatic jaundice, or a history of jaundice in pregnancy. Oral progestogen-only contraceptives should also be used with caution in past ectopic pregnancy (see p. 2236.3) or functional ovarian cysts. Despite unsatisfactory evidence of hazard, other suggested cautions for progestogen-only contraceptives include diabetes mellitus, hypertension, migraine, and thromboembolic disorders.

Breast feeding. Progestogen-only contraceptives are the hormonal contraceptives of choice for breast-feeding women because they do not affect lactation,[1] but recommendations vary about when they can or should be started, and may not match licensed product information. Some guidelines[2] recommend that all progestogen-only methods can be started 6 weeks after birth. Others[3] suggest that oral preparations can be started any time in breast-feeding women, although they are not needed before 3 weeks postpartum. Progestogen-only parenteral contraceptives, such as medroxyprogesterone acetate, are usually not given until 6 weeks postpartum;[1-3] troublesome bleeding can occur before this time.[3] The etonogestrel subdermal implant may be inserted at 3 weeks postpartum. The levonorgestrel IUD may also be used during lactation, although insertion should be delayed because of an increased risk of perforation of the uterine wall or cervix. Licensed product information advises waiting until 6 weeks after delivery, but others[3] suggest that it may be inserted from 4 weeks postpartum (with additional contraceptive cover for the first 7 days if necessary).

Combined hormonal contraceptives may reduce the volume of breast milk and are therefore avoided in breast-feeding women for the first 6 weeks after birth.[1,3] In general, they are not recommended for 6 months or until weaning.[2,3] Between 6 weeks and 6 months postpartum, some[3] suggest that they may be considered for women who are fully breast feeding if other contraceptive methods are unacceptable. It is also consider that for women who are partially or token breast feeding during this time, the benefits of combined hormonal contraception may outweigh the risks.

Very small amounts of oestrogens and progestogens from hormonal contraceptives are distributed into breast milk, but there is no indication that this adversely affects development of the breast-fed infant.[3,4] The American Academy of Pediatrics[5] has also reviewed the use of hormonal contraceptives during lactation, commenting that early information was based on the use of high-dose contraceptives. It was noted that there might be a decrease in milk production, but that there was insufficient information to confirm that there was any alteration in the composition of breast milk, and that although there had been rare cases of gynaecomastia in breast-fed infants of mothers who received high-dose contraceptives, there was no consistent evidence of long-term adverse effects on the infant. A later study[6] of 48 children whose mothers had received high-dose combined oral contraceptives during breast feeding found no effect on these children compared with controls, up to 8 years of age. The Academy therefore considers[7] that combined oral contraceptives are usually compatible with breast feeding.

Breast feeding itself suppresses ovulation and can be used, if started immediately postpartum, as the lactational amenorrhoea method of contraception; for further details, see Contraception, p. 2232.3.

1. Queenan JT. Contraception and breastfeeding. *Clin Obstet Gynecol* 2004; **47:** 734–9.
2. Hatcher RA, *et al*. *The essentials of contraceptive technology: a handbook for clinical staff*. Baltimore: John Hopkins Bloomberg School of Public Health, Population Information Program, 2003. Also available at: http://www.infoforhealth.org/pubs/ect/ (accessed 14/01/08)
3. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Clinical guidance: postnatal sexual and reproductive health (issued September 2009). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidancePostnatal09.pdf (accessed 09/10/09)
4. Fraser IS. A review of the use of progestogen-only minipills for contraception during lactation. *Reprod Fertil Dev* 1991; **3:** 245–54.
5. American Academy of Pediatrics Committee on Drugs. Breast-feeding and contraception. *Pediatrics* 1981; **68:** 138–40. Also available at: http://pediatrics.aappublications.org/cgi/reprint/68/1/138.pdf (accessed 14/01/08)
6. Nilsson S, *et al*. Long-term follow-up of children breast-fed by mothers using oral contraceptives. *Contraception* 1986; **34:** 443–57.
7. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 14/01/08)

Cardiovascular disease. Combined hormonal contraceptives are associated with several arterial and venous risks. Progestogen-only contraceptives are associated with fewer risks, although they still need to be avoided when arterial disease is severe.

Arterial disease. In the UK the *BNF* has recommended that combined hormonal contraceptives may be used with **caution** if any **one** of the following factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of arterial disease* in first-degree relative aged under 45 years (avoid if there is also an atherogenic lipid profile)
- *diabetes mellitus* (avoid if diabetic complications are present)
- *hypertension* (avoid if blood pressure is above systolic 160 mmHg or diastolic 95 mmHg)
- *smoking* (avoid if 40 or more cigarettes are smoked daily)
- *age over 35 years* (avoid if over 50 years)
- *obesity* (avoid if BMI $\geqslant$ 35 kg/m^2, unless no suitable alternative)
- *migraine*, see under Migraine, below

Venous thromboembolism. Combined hormonal contraceptives increase the risk of venous thromboembolism and should not be used in women with a personal history of venous or arterial thrombosis. In addition they should be used with **caution** if any **one** of the following risk factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of venous thromboembolism* in first-degree relative aged under 45 years (avoid if there is a known prothrombotic coagulation abnormality such as antiphospholipid antibodies, which may occur in patients with SLE, or factor V Leiden)
- *long-term immobilisation* such as wheelchair use (avoid if confined to bed or with a leg in plaster)
- *history of superficial thrombophlebitis*
- *smoking*
- *age over 35 years* (avoid if over 50 years)
- *obesity*—BMI $\geqslant$ 30 kg/m^2 (avoid if BMI $\geqslant$ 35 kg/m^2, unless no suitable alternative)

The *BNF* also advises that women taking combined hormonal contraceptives may be at an increased risk of deep-vein thrombosis during *travel* involving prolonged periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey, and possibly by wearing graduated compression hosiery.

In the light of evidence indicating an increased risk of venous thromboembolism with combined oral contraceptives containing *desogestrel* or *gestodene* (see Venous Thromboembolism, under Effects on the Cardiovascular System, p. 2238.1), the UK CSM advised additional precautions for these products. As well as the usual precautions, it was initially advised they should not be used by obese women (BMI greater than 30 kg/m^2), those with varicose veins, or those with a history of thrombosis of any cause. Moreover, it was also recommended that they should be used only by women who were intolerant of other combined oral contraceptives and who were prepared to accept an increased risk of venous thromboembolism. Subsequently the CSM[1] modified its advice as follows: they recommended that these products should be avoided in women with known risk factors for venous thromboembolism. However, in women without contra-indications, the type of combined contraceptive was considered a matter of clinical judgement and personal choice, as long as the woman was fully informed of the small excess risk associated with desogestrel- and gestodene-containing products.

1. CSM/MCA. Combined oral contraceptives containing desogestrel or gestodene and the risk of venous thromboembolism. *Current Problems* 1999; **25:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)

Lupus erythematosus. SLE is an auto-immune disease that is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that oral contraceptive use may be associated with a slightly increased risk in the onset of SLE.[1-3] There are also reports and studies of the effect of contraceptives on disease exacerbation, although there has been an apparent reduction in reports which has coincided with the lowering of oestrogen content in contraceptive preparations.[2] More recently, controlled studies[4,5] have found that disease activity and flares over 12 months in women with stable SLE were similar whether they were given a combined oral contraceptive (containing ethinylestradiol 30 or 35 micrograms), a progestogen-only oral preparation, placebo, or copper IUD. However, patients with major disease, such as lupus nephritis, could be at greater risk of exacerbation. It is also generally advised that combined oral contraceptives should be avoided in women with antiphospholipid antibodies (which includes about a third of all patients with SLE) because they are at increased risk of venous thromboembolism.[1,2]

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10:** 222–6.
2. Mok CC, *et al*. Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30:** 426–35.
3. Costenbader KH, *et al*. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56:** 1251–62.
4. Sánchez-Guerrero J, *et al*. A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2539–49.
5. Petri M, *et al*. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2550–8.

Migraine. Both migraine and the use of combined oral contraceptives have been identified as risk factors for ischaemic stroke. A systematic review[1] concluded that in women with a history of migraine, users of combined oral contraceptives were 2 to 4 times more likely to have an ischaemic stroke than non-users. It was unclear, however, whether this increase in relative risk was due to independent effects of contraceptives and migraine, or whether contraceptive use had a greater effect in women with a history of migraine than in those without.

In the UK the *BNF* has recommended that combined hormonal contraceptives be **contra-indicated** in:

- migraine with typical focal aura
- severe migraine frequently lasting longer than 72 hours despite treatment
- migraine treated with an ergot derivative

It also recommends **caution** in migraine without focal aura. A woman receiving a combined hormonal contraceptive should report any increase in headache frequency or the onset of focal symptoms. If focal neurological symptoms not typical of aura persist for longer than 1 hour the contraceptive should be discontinued and the woman referred urgently to a neurologist.

Other risk factors for arterial disease should also be considered in women with a history of migraine (see Cardiovascular Disease, above).

1. Curtis KM, *et al*. Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception* 2006; **73:** 189–94.

Obesity. It has been suggested that higher body-weight or BMI might be associated with a greater risk of oral contraceptive failure. Several cohort and case-control studies have evaluated this association, with mixed results that may have been confounded by recall bias, inaccuracy

of reported body-weight, noncompliance, and change in oestrogen dose over time. Some studies have suggested that there is an increased risk of contraceptive failure,[1,2] while others have found no association.[3] In addition, some have found a weak association that was no longer statistically significant when results were adjusted for confounders such as education, income, and ethnicity.[4,5] It is therefore unclear whether an association exists, but obesity is a risk factor for cardiovascular disease and combined oral contraceptives should be used with caution, or avoided, in these women (see Cardiovascular Disease, p. 2241.2).

1. Holt VL, *et al.* Body weight and risk of oral contraceptive failure. *Obstet Gynecol* 2002; **99:** 820–7.
2. Holt VL, *et al.* Body mass index, weight, and oral contraceptive failure risk. *Obstet Gynecol* 2005; **105:** 46–52.
3. Vessey M, Painter R. Oral contraceptive failures and body weight: findings in a large cohort study. *J Fam Plann Reprod Health Care* 2001; **27:** 90–1.
4. Brunner LR, Hogue CJ. The role of body weight in oral contraceptive failure: results from the 1995 national survey of family growth. *Ann Epidemiol* 2005; **15:** 492–9.
5. Brunner Huber LR, *et al.* Body mass index and risk for oral contraceptive failure: a case-cohort study in South Carolina. *Ann Epidemiol* 2006; **16:** 637–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies many progestogen-only and combined hormonal contraceptives as porphyrinogenic or as probably porphyrinogenic; they should be prescribed only for compelling reasons and precautions should be taken or considered in all patients.[1]

The *BNF* suggests that progestogens are more hazardous than oestrogens, and that they should be avoided whenever possible. However, progestogens may be used with extreme caution if non-hormonal contraception is inappropriate and potential benefit outweighs the risk. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. In contrast to the numerous cases of congenital malformations reported after the use of high doses of sex hormones formerly used for hormonal pregnancy tests, there have been only a few suggestions that continued use of oral contraceptives during early pregnancy may result in congenital limb reduction deformities,[1-3] and one case of neonatal choreoathetosis after prenatal exposure to oral contraceptives.[4]

Many studies, conversely, have shown no evidence that the use of oral contraceptives is associated with congenital malformations or teratogenic effects, whether past use (stopped before conception), use after the last menstrual period, or known use in early pregnancy. A meta-analysis[5] confirmed this; the relative risk for all malformations with use of oral contraceptives was estimated to be 0.99 (95% confidence intervals 0.83 to 1.19). The use of oral contraceptives in early pregnancy also appears unlikely to increase the risk of hypospadia in male fetuses[6,7] (see also under Precautions of Estradiol, p. 2273.3).

Depot intramuscular medroxyprogesterone acetate is a highly effective contraceptive, but failures do occur rarely. A review[8] of such failures had limited data on birth outcome in 100 women who continued the pregnancy, but no abnormalities or fetal anomalies were reported.

In 25 pregnancies that were continued after the failure of levonorgestrel-based emergency contraception,[9] there was 1 case of gastro-oesophageal reflux requiring medical treatment and 1 case of nasolachrymal duct obstruction that was surgically drained, but compared with a control group and expected baseline risk there was no increased risk of congenital or genital abnormalities.

For a discussion of the ectopic pregnancy risk in users of hormonal contraceptives, see p. 2236.3.

1. Janerich DT, *et al.* Oral contraceptives and congenital limb reduction defects. *N Engl J Med* 1974; **291:** 697–700.
2. McCredie J, *et al.* Congenital limb defects and the pill. *Lancet* 1983; **ii:** 623.
3. Kricker A, *et al.* Congenital limb reduction deformities and use of oral contraceptives. *Am J Obstet Gynecol* 1986; **155:** 1072–8.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86:** 648–9.
5. Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990; **76:** 552–7.
6. Raman-Wilms L, *et al.* Fetal genital effects of first trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995; **85:** 141–9.
7. Wogelius P, *et al.* Maternal use of oral contraceptives and risk of hypospadias—a population-based case-control study. *Eur J Epidemiol* 2006; **21:** 777–81.
8. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
9. De Santis M, *et al.* Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. *Fertil Steril* 2005; **84:** 296–9.

Sickle-cell disease. *Sickle-cell disease* and oral contraceptive use are both associated with an increased risk of thrombosis but it is by no means certain that the two risks are additive. Study of a small number of women with sickle-cell disease found that combined and progestogen-only contraceptives had no effect on red cell deformability.[1] Licensed product information for some preparations has specifically warned against the use of combined oral contraceptives in sickle-cell disease. However, there is a lack of strong clinical evidence to support such a contra-indication,[2,3] and there is some suggestion that progestogen-only contraception may be associated with improvements in clinical symptoms and sickle-cell crises.[4] WHO considers[5] that in women with sickle-cell disease the benefits generally outweigh the risks for low-dose combined oral contraceptives (35 micrograms or less of ethinylestradiol) and other forms of combined hormonal contraceptives (injectable, transdermal patch, and vaginal ring), and that there is no restriction for the use of progestogen-only contraceptives (oral, depot injection, implant, and intra-uterine device).

For *sickle-cell trait* there is no increased risk of thrombosis and no contra-indication to the use of a combined or progestogen-only preparation. Many women with sickle-cell trait have, unnecessarily, been denied the use of oral contraceptives in the mistaken belief that advice for sickle-cell disease applies to the trait.[6]

1. Yoong WC, *et al.* Red cell deformability in oral contraceptive pill users with sickle cell anaemia. *Br J Haematol* 1999; **104:** 868–70.
2. Freie HMP. Sickle cell diseases and hormonal contraception. *Acta Obstet Gynecol Scand* 1983; **62:** 211–17.
3. Howard RJ, *et al.* Contraceptives, counselling, and pregnancy in women with sickle cell disease. *BMJ* 1993; **306:** 1735–7.
4. Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception* 2006; **73:** 195–204.
5. WHO. *Medical eligibility criteria for contraceptive use.* Fourth ed. Geneva: WHO, 2009. Available at: http://whqlibdoc.who.int/publications/2009/9789241563888_eng.pdf (accessed 21/07/10)
6. Evans DIK. Should patients who say that they have "sickle cells" be prescribed the contraceptive pill? *BMJ* 1984; **289:** 425.

Surgery. Case reports and epidemiological studies showing an increased risk of idiopathic deep-vein thrombosis and pulmonary embolism in young women taking **combined oral contraceptives** (see Venous Thromboembolism, p. 2238.1) led to the widespread belief that oral contraceptives may predispose to deep-vein thrombosis postoperatively. In consequence, the advice commonly given in the UK has been that, if possible, combined oral contraceptives should be stopped 4 weeks before major elective surgery and all surgery of the legs, and that prophylactic heparin should be considered where this was not possible.[1] They can normally be started again at the first menses occurring at least 2 weeks after full mobilisation. However, estimates of the size of the risk are variable;[2-5] one report[2] found that the incidence of deep-vein thrombosis postoperatively in young women taking combined oral contraceptives was about twice that of women not taking contraceptives but the difference was not statistically significant. Some have considered[6] that the risk to young women of becoming pregnant after stopping oral contraceptives, or of developing adverse effects from heparin prophylaxis, may be greater than the risk of developing postoperative deep-vein thrombosis. This is in line with the views of the Thromboembolic Risk Factors (THRIFT) Consensus Group.[7] They suggested that unless there were other risk factors there was insufficient evidence to support a policy of routinely stopping combined oral contraceptives before major surgery. Additionally, there was insufficient evidence to support routine specific thromboembolic prophylaxis in women without additional risk factors. A review[8] has subsequently recommended that women for whom major elective surgery was planned should continue taking the combined oral contraceptive but should receive thromboprophylaxis in the perioperative period. It has also been pointed out[9,10] that for patients awaiting surgery who require contraception, a progestogen-only oral contraceptive or an injection of medroxyprogesterone acetate may be suitable since neither preparation increases the risk of thrombosis.

1. Guillebaud J. Surgery and the pill. *BMJ* 1985; **291:** 498–9.
2. Vessey M, *et al.* Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
3. Tso SC, *et al.* Deep vein thrombosis and changes in coagulation and fibrinolysis after gynaecological operations in Chinese: the effect of oral contraceptives and malignant disease. *Br J Haematol* 1980; **46:** 603–12.
4. Gallus AS, *et al.* Oral contraceptives and surgery: reduced antithrombin and antifactor XA levels without postoperative venous thrombosis in low-risk patients. *Thromb Res* 1984; **35:** 513–26.
5. Sagar S, *et al.* Oral contraceptives, antithrombin III activity, and postoperative deep-vein thrombosis. *Lancet* 1976; **i:** 509–11.
6. Sue-Ling H, Hughes LE. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 447–8.
7. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; **305:** 567–74.
8. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.
9. Guillebaud J. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 786–7.
10. Guillebaud J, Robinson GE. Stopping the pill. *BMJ* 1991; **302:** 789.

Travel. For a warning that women taking oral contraceptives may be at increased risk of deep-vein thrombosis from travel involving prolonged immobility see Cardiovascular Disease, p. 2241.2.

Interactions

Enzyme-inducing drugs have the potential to cause combined hormonal contraceptives to fail by increasing their metabolism and clearance. This effect is well established for several *antiepileptics* and *rifamycin antibacterials*, and is likely for some *antivirals*. Although less well documented, these interactions would also be expected to apply to most progestogen-only contraceptives.

The *Faculty of Sexual and Reproductive Healthcare (FSRH)* in the UK has provided recommendations for contraception in women taking enzyme-inducing drugs.

- All women should be advised to use a reliable contraceptive method that is unaffected by enzyme-inducing drugs; these include the progestogen-only injectables (medroxyprogesterone and norethisterone enantate), the levonorgestrel-releasing IUD, copper IUDs, and barrier methods. They should be used to cover the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.
- For women taking a combined hormonal contraceptive (oral, transdermal patch, or vaginal ring) who require a short course (no more than 2 months) of an enzyme-inducing drug and do not want to change to a different method of contraception, the hormonal contraceptive may be continued with additional non-hormonal contraceptive methods (e.g. condoms). The hormonal contraceptive should be used in a tricycling or extended regimen: a tricycling regimen consists of taking three 21-day cycles continuously without a break followed by a shortened break of 4 days; in an extended regimen the hormonal contraceptive is taken continuously (for not less than 3 weeks) until breakthrough bleeding occurs, at which time a shortened break of 3 to 4 days may be taken. If the contraceptive is being given orally it must be a monophasic preparation and should provide at least 30 micrograms of ethinylestradiol daily. The efficacy of these regimens is uncertain however.
- For women taking a combined hormonal contraceptive who require long-term treatment (more than 2 months) with an enzyme-inducing drug and do not want to change to a different method of contraception, or when there are difficulties in using additional contraceptive precautions during short courses, an alternative is to use a combined oral contraceptive in a regimen that provides ethinylestradiol 50 micrograms or more daily (maximum 70 micrograms daily) in a tricycling or extended regimen. The use of two patches or two vaginal rings simultaneously is not recommended. However, these measures are **not** sufficient for long-term use of rifamycins, and an alternative method such as an IUD is always recommended.
- For women taking a progestogen-only oral contraceptive or using an implant, an additional non-hormonal or alternative method of contraception is recommended to cover short courses of enzyme-inducing drugs. An alternative method of contraception should be used if long-term treatment with an enzyme-inducing drug is required.
- For women requiring postcoital (emergency) contraception during or in the 4 weeks after stopping enzyme-inducing drugs, a single oral dose of levonorgestrel 3 mg given within 120 hours of intercourse has been suggested. Alternatively, a copper IUD may be used.

Combined oral contraceptive failure has been attributed to an interaction with *broad-spectrum antibacterials*, purportedly through a reduction in the enterohepatic recycling of the oestrogen component. However, the evidence does not generally support such an interaction and the FSRH advises that additional contraceptive precautions are not necessary during or after courses of antibacterials that do not induce liver enzymes. Nevertheless, if the antibacterial causes vomiting or diarrhoea then the advice for missed doses should be considered (see Uses, p. 2231.3).

Further details of drugs affecting hormonal contraceptives are given below under specific headings.

Oral contraceptives may also *affect other drugs*. Compounds undergoing oxidative metabolism can have their plasma concentration raised by oral contraceptives through an inhibitory action. Conversely, oral contraceptives appear to induce glucuronidation of some drugs thus reducing their plasma concentration. Oral contraceptives can also antagonise the actions of several drugs. Drugs affected include:

- some analgesics (increased clearance of paracetamol and morphine)
- anticoagulants (increased and decreased effects reported; see p. 1535.1)
- some antidepressants (reduced efficacy, but also increased toxicity; see p. 407.2)

- antidiabetics (antagonism of effect)
- the antiepileptic lamotrigine (decreased plasma concentrations; see p. 530.2)
- antihypertensives (antagonism of effect)
- benzodiazepines (increased or decreased clearance; see p. 1070.2)
- ciclosporin (increased toxicity; see p. 1955.1)
- clofibrate (increased clearance and antagonism of effect)
- corticosteroids (enhanced effect; see p. 1620.3)
- levothyroxine (reduced free fraction due to increased binding globulin concentration; see p. 2342.2)
- lidocaine (increased free fraction due to altered protein binding; see Protein Binding, under Pharmacokinetics, p. 1991.3)
- melatonin (increased concentrations; see p. 2552.2)
- selegiline (decreased clearance; see p. 916.2)
- tizanidine (reduced clearance; see p. 2027.2)
- xanthines (decreased clearance; see p. 1236.2)

Reviews.

1. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; **18:** 472–84.
2. Shenfield GM. Oral contraceptives: are drug interactions of clinical significance? *Drug Safety* 1993; **9:** 21–37.
3. Quereux C, Bory JP. Interaction médicamenteuse et contraception orale. *Contracept Fertil Sex* 1998; **26:** 129–31.
4. Schwartz JB. Oral contraceptive therapy in women: drug interactions and unwanted outcomes. *J Gend Specif Med* 1999; **2:** 26–9.
5. Elliman A. Interactions with hormonal contraception. *Br J Fam Plann* 2000; **26:** 109–11. Correction. *ibid.*; 151.
6. Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. Drug interactions with hormonal contraception (issued January 2011). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceDrugInteractionsHormonal.pdf (accessed 18/04/11)

Antibacterials. An interaction between the *rifamycins (rifampicin* and *rifabutin)* and hormonal contraceptives is well established and alternative contraceptive measures are necessary (see Rifamycins, below).

A variety of *broad-spectrum antibacterials* have also been reported to decrease oral contraceptive efficacy. Some studies have pointed to interference with intestinal flora involved in enterohepatic circulation of oestrogens as being a likely mechanism for this interaction. Although up until 1985 there had been 32 reports[1] of unintended pregnancies in women receiving *penicillins* (25 of them with *ampicillin*) the ability of antibacterials to inhibit oral contraceptive efficacy remains unproven. The data are consistent, however, with the supposition that efficacy is occasionally impaired.[2] Several cases of unintended pregnancies have been reported after the use of *tetracyclines*. With regard to other antibacterials, in theory any one with significant effects on intestinal flora could affect contraceptive efficacy. Isolated cases of pregnancy have been reported following the use of *cephalosporins, chloramphenicol, dapsone, isoniazid, nitrofurantoin, sulfonamides,* and *co-trimoxazole* but it is impossible to determine which, if any, of these interactions is real.

Advice on the use of broad-spectrum antibacterials with combined hormonal contraceptives has traditionally been cautious, despite the lack of strong evidence of an interaction. It was usually recommended that additional contraceptive precautions should be used while taking, and for 7 days after stopping, a short course of any broad-spectrum antibacterial. It was also suggested that if the course of antibacterial exceeded 3 weeks the intestinal flora would develop resistance making additional precautions unnecessary, unless a new antibacterial was started. However, a review[3] of the evidence by the Faculty of Sexual Health and Reproduction (UK) concluded that overall the evidence did not generally support an interaction, and advised that additional contraceptive precautions are not necessary during or after courses of antibacterials that do not induce liver enzymes. This advice was in agreement with contemporaneous advice issued by WHO and CDC. Nevertheless, if the antibacterial causes vomiting or diarrhoea then the advice for missed doses should be considered (see Uses, p. 2231.3).

1. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
2. Dickinson BD, *et al.* Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; **98:** 853–60.
3. Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. Drug interactions with hormonal contraception (issued January 2011). Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceDrugInteractionsHormonal.pdf (accessed 18/04/11)

RIFAMYCINS. Rifampicin regularly results in menstrual irregularities and occasionally in unintended pregnancies in women receiving oral contraceptives. It is a potent enzyme inducer and considerably enhances the metabolism of hormonal contraceptives. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, including rifamycins, see Interactions, p. 2242.3.

Similar precautions are recommended during *rifabutin* therapy.

Contraceptive failure, resulting in an ectopic pregnancy, has also been reported in a woman who started rifampicin therapy 3 months after placement of an etonogestrel implant.[1]

1. Patni S, *et al.* Ectopic pregnancy with Implanon. *J Fam Plann Reprod Health Care* 2006; **32:** 115.

TROLEANDOMYCIN. Severe pruritus and jaundice may occur if oral contraceptives and troleandomycin are given together.[1] It has been suggested that their hepatic effects may be additive or synergistic, and that concurrent use should be avoided.

1. Miguet J-P, *et al.* Jaundice from troleandomycin and oral contraceptives. *Ann Intern Med* 1980; **92:** 434.

Antidepressants. *St John's wort* may decrease blood concentrations of oral contraceptives by enzyme induction.[1-3] There have been reports of intermenstrual bleeding and altered menstrual bleeding in women on long-term oral contraceptives who started taking St John's wort.[4] Several pregnancies have also been reported.[5,6]

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

1. Hall SD, *et al.* The interaction between St John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003; **74:** 525–35.
2. Pfrunder A, *et al.* Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br J Clin Pharmacol* 2003; **56:** 683–90.
3. Murphy PA, *et al.* Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005; **71:** 402–8.
4. Yue Q-Y, *et al.* Safety of St. John's wort (Hypericum perforatum). *Lancet* 2000; **355:** 576–7.
5. Läkemedelsverket (Medical Products Agency—Sweden). Minskad effekt av p-piller vid samtidig användning av johannesört har lett till oönskad graviditet (issued 4th February, 2002). Available at: http://www.lakemedelsverket.se/Tpl/NewsPage%5F%5F%5F%5F580.aspx (accessed 20/08/10)
6. Schwarz UI, *et al.* Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. *Br J Clin Pharmacol* 2003; **55:** 112–13.

Antiepileptics. Oral contraceptive failure and breakthrough bleeding have been reported in numerous cases during antiepileptic therapy.[1,2] *Phenytoin,* barbiturates such as *phenobarbital* and *primidone,* and *carbamazepine* have been most frequently implicated, and *oxcarbazepine, felbamate,* and *topiramate* may interact similarly.[3] These drugs increase the clearance of both oestrogens and progestogens by enzyme induction, so diminishing their effects. Contraceptive methods that are not affected by enzyme induction include a copper or levonorgestrel IUD, or intramuscular depot medroxyprogesterone acetate.[4,5] If these are unsuitable, a combined oral contraceptive with an increased oestrogen content equivalent to ethinylestradiol 50 micrograms or more, and a corresponding increase in progestogen, is generally recommended. In addition, the use of a monophasic preparation given for 3 cycles without a break followed by a tablet-free interval of 4 days (tricycling) has also been suggested.[4] The importance of the progestogen in suppressing ovulation has also been discussed, with the suggestion that ethinylestradiol doses of less than 50 micrograms could be used provided the dose of progestogen is at least 1 mg of norethisterone, 150 micrograms of levonorgestrel, or 300 micrograms of norgestrel.[5] Biphasic, triphasic, and progestogen-only oral contraceptives are not recommended.[5]

Lamotrigine may also reduce contraceptive efficacy, and is markedly affected in turn by the contraceptive (see p. 530.2). Contraceptive efficacy may also be reduced, in a dose-dependent manner, by *perampanel* (see p. 535.2).

For the effects of oral contraceptives on *valproate,* see p. 558.1.

The efficacy of postcoital hormonal contraception (emergency contraception) is also reduced by enzyme-inducing antiepileptic drugs,[4] and an increased dose has been suggested (see Interactions, p. 2242.3).

Antiepileptics that are reported not to affect hormonal contraceptives include *ethosuximide, gabapentin, levetiracetam, tiagabine, valproate,* and *vigabatrin.*[4,5]

1. Mattson RH, Cramer JA. Epilepsy, sex hormones, and antiepileptic drugs. *Epilepsia* 1985; **26** (suppl 1): S40–S51.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
3. Wilbur K, Ensom MHH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. *Clin Pharmacokinet* 2000; **38:** 355–65.
4. O'Brien MD, Guillebaud J. Contraception for women with epilepsy. *Epilepsia* 2006; **47:** 1419–22.
5. Thorneycroft I, *et al.* The impact of antiepileptic drug therapy on steroidal contraceptive efficacy. *Epilepsy Behav* 2006; **9:** 31–9.

Antifungals. Menstrual irregularities and pregnancies have been reported in women receiving oral contraceptives and *griseofulvin.*[1,2] It has been described as an inducer of hepatic enzymes that may increase the metabolism of hormonal contraceptives, but clinical evidence for this mechanism of interaction is lacking. Nevertheless, additional contraceptive measures should be considered during concomitant use and after stopping griseofulvin; for general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3. There have also been anecdotal reports[3-5] of menstrual irregularities and contraceptive failure with *fluconazole, itraconazole,* and *ketoconazole,* and similar advice applies to these if pregnancy is to be avoided with certainty.

1. van Dijke CPH, Weber JCP. Interaction between oral contraceptives and griseofulvin. *BMJ* 1984; **288:** 1125–6.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
3. Pillans PI, Sparrow MJ. Pregnancy associated with a combined oral contraceptive and itraconazole. *N Z Med J* 1993; **106:** 436.
4. Meyboom RHB, *et al.* Disturbance of withdrawal bleeding during concomitant use of itraconazole and oral contraceptives. *N Z Med J* 1997; **110:** 300.
5. van Puijenbroek EP, *et al.* Verstoring van de pilcyclus tijdens het gelijktijdig gebruik van itraconazol en orale anticonceptiva. *Ned Tijdschr Geneeskd* 1998; **142:** 146–9.

Antivirals. Some antivirals are likely to accelerate the metabolism of oestrogens and progestogens; theoretically therefore, they may decrease the efficacy of hormonal contraceptives. This has been suggested for HIV-protease inhibitors such as *nelfinavir,*[1] *ritonavir,*[2] and ritonavir-boosted HIV-protease inhibitors, and for the NNRTI *nevirapine.*[3] An alternative form of contraception should be considered. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

Conversely, the area under the plasma-concentration-time curve for ethinylestradiol is reported to be increased by HIV-protease inhibitors such as *amprenavir, atazanavir,* and *indinavir,* and the NNRTIs *delavirdine* and *efavirenz.* Although the clinical implications are unknown, the licensed product information recommends alternative or additional contraception.

The use of condoms with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of infection.

1. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr* 2004; **37:** 1219–20.
2. Ouellet D, *et al.* Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998; **46:** 111–16.
3. Mildvan D, *et al.* Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr* 2002; **29:** 471–7.

Endothelin receptor antagonists. In a pharmacokinetic study of healthy women[1] the area under the concentration-time curve (AUC) of both ethinylestradiol and norethisterone were reduced by *bosentan,* probably by enzyme induction. The possibility of contraceptive failure should be considered, and licensed product information for bosentan suggests that an additional or alternative method of contraception should be used during bosentan therapy. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

In contrast, *sitaxentan* is an inhibitor of some cytochrome P450 isoenzymes, and it has increased exposure to ethinylestradiol and norethisterone in women taking a combined oral contraceptive. An increase in oestrogen exposure may possibly increase the risk of thromboembolism.

1. van Giersbergen PLM, *et al.* Pharmacokinetic interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. *Int J Clin Pharmacol Ther* 2006; **44:** 113–18.

Mifepristone. The antiprogestogen effect of mifepristone will interfere with the effectiveness of hormonal contraceptives. A non-hormonal method of contraception should be used by women given continuous mifepristone for conditions such as Cushing's syndrome.

Retinoids. One woman taking an oral progestogen-only contraceptive (levonorgestrel 30 micrograms daily) showed a significant increase in plasma-progestogen while receiving *acitretin,* which indicated ovulation had occurred.[1] However, progestogen-only contraceptives do not suppress ovulation in all cycles, and this is not thought to be their primary mechanism of contraceptive efficacy (see Types of Contraceptive, p. 2231.3). Nevertheless, because it is imperative that women receiving retinoids do not conceive, some have concluded that oral progestogen-only contraceptives are not suitable for use with retinoids.[2]

The anti-ovulatory efficacy of combined oral contraceptives was not affected by acitretin in 8 women in the study above,[1] or by *etretinate* in a study[3] in 12 women. Other studies have reported that *isotretinoin* did not significantly change plasma concentrations or adversely affect contraceptive efficacy of ethinylestradiol and levonorgestrel in 9 women,[4] or ethinylestradiol and norethisterone in 26 women.[5] It has been concluded that, unless otherwise contra-indicated, oral combined contraceptives are the contraceptive method of choice for women undergoing retinoid treatment.[2] Licensed product informa-

tion for retinoids, including isotretinoin, reminds prescribers that two effective forms of contraception such as a combined oral contraceptive with a barrier method should be used during and after retinoid treatment (see also Pregnancy, under Isotretinoin, p. 1709.3).

Both isotretinoin and combined oral contraceptives can have adverse effects on plasma lipids;[6] it has therefore been recommended that plasma lipids should be monitored during concurrent retinoid and oral contraceptive therapy, and that an oral contraceptive containing a non-androgenic progestogen is preferred,[2] since these have less detrimental effects on lipids (p. 2239.2).

1. Berbis P, *et al.* Acitretin (RO10-1670) and oral contraceptives: interaction study. *Arch Dermatol Res* 1988; **280:** 388–9.
2. Lehucher Ceyrac D, *et al.* Retinoids and contraception. *Dermatology* 1992; **184:** 161–70.
3. Berbis P, *et al.* Study on the influence of etretinate on biologic activity of oral contraceptives. *J Am Acad Dermatol* 1987; **17:** 302–3.
4. Orme M, *et al.* Isotretinoin and contraception. *Lancet* 1984; **ii:** 752–3.
5. Hendrix CW, *et al.* The effect of isotretinoin on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 2004; **75:** 464–75.
6. Chen Y, *et al.* Elevation of serum triglyceride and cholesterol levels from isotretinoin therapy with concomitant oral contraceptives. *Pharmacoepidemiol Drug Safety* 1995; **4:** 91–6.

Stimulants. *Modafinil* induces hepatic enzymes and may reduce the efficacy of oral contraceptives.[1] Licensed product information for modafinil suggests that alternative or additional methods of contraception are needed; US information recommends that this is also continued for 1 month after stopping modafinil, but in the UK it is recommended for 2 months.

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, p. 2242.3.

1. Robertson P, *et al.* Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* 2002; **71:** 46–56.

Sugammadex. The neuromuscular blockade reverser sugammadex may bind to oestrogens and progestogens, which could decrease the efficacy of hormonal contraceptives. If a bolus dose of sugammadex is given on the same day as an oral hormonal contraceptive, the appropriate action for a missed dose of contraceptive should be taken (see Uses and Administration, p. 2231.3). If a bolus of sugammadex is given to a patient using a non-oral hormonal contraceptive, an additional non-hormonal contraceptive method should be used for the next 7 days, and the product information for the contraceptive consulted.

Vitamins. Large supplements of *vitamin C* have been reported to increase serum ethinylestradiol concentrations in women taking oral contraceptives,[1] but a further study showed no effect on either ethinylestradiol[2] or levonorgestrel.[3]

1. Back DJ, *et al.* Interaction of ethinyloestradiol with ascorbic acid in man. *BMJ* 1981; **282:** 1516.
2. Zamah NM, *et al.* Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception* 1993; **48:** 377–91.
3. Kuhnz W, *et al.* Influence of high doses of vitamin C on the bioavailability and the serum protein binding of levonorgestrel in women using a combination oral contraceptive. *Contraception* 1995; **51:** 111–16.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p. 2273.3 and Progesterone, p. 2302.2, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

Reference to the effects of hormonal contraceptives on binding proteins.[1]

1. Fotherby K. Interactions of contraceptive steroids with binding proteins and the clinical implications. *Ann N Y Acad Sci* 1988; **538:** 313–20.

Hormone Replacement Therapy

Hormonersatztherapie; HRT; THS; Traitement Hormonal Substitutif; Tratamiento hormonal restitutivo; Гормонозаместительная Терапия.

The Menopause

The menopause is defined as the permanent cessation of cyclical menstruation due to loss of ovarian follicular activity. It is therefore determined in retrospect, conventionally after 1 year without menstruation. In the few years before the menopause (the menopausal transition), ovarian oestradiol secretion declines, sometimes in a fluctuating manner, and there is a resultant increase in pituitary follicle-stimulating hormone (FSH) secretion. The menopausal transition may be characterised by irregular menstrual cycles and dysfunctional uterine bleeding, and fertility is much reduced compared with the early reproductive years. The term perimenopause is used to cover the menopausal transition and the first year after the menopause, and may last 6 years or more. It has sometimes been referred to as the climacteric. Oestrogen concentrations reach their minimum and FSH concentrations their maximum about 4 years after the menopause. After the menopause the ovaries may continue to produce some androgens; adrenal and ovarian androgens are aromatised to oestrogens (mainly oestrone) in the periphery, but oestrogen concentrations are much lower than in premenopausal women. The median age for the natural menopause is about 51 years. If the menopause occurs in women aged 40 years or less, it is considered premature. The menopause may be induced by surgical removal of both ovaries, or sometimes by antineoplastic drugs or radiotherapy.

The decline in oestrogen concentrations during the perimenopause may be associated with both acute and long-term effects. However, some of these may be difficult to differentiate from the effects of ageing, and the incidence varies geographically. Established *acute symptoms* can include vasomotor instability, manifesting as hot flushes and night sweats, and vaginal atrophy and dyspareunia. Non-specific symptoms include palpitations, headache, backache, and psychological symptoms such as tiredness, lack of concentration, loss of libido, irritability, insomnia, and depression. Insomnia may occur secondary to night sweats. There is little evidence that depressive illness is disproportionately increased at the menopause. Urinary problems are common in ageing women, and may occur in the perimenopause, but the extent that these are due to lack of oestrogens has not been determined. An established *long-term consequence* of the decline in oestrogen concentrations is an increased risk of bone fractures resulting from an increase in the rate of bone resorption. In addition, decline in oestrogen concentrations is associated with adverse effects on blood lipoproteins, and this may be a risk factor for cardiovascular disease.

Acute and longer-term effects of the menopause may be managed by using hormone replacement therapy (HRT) with oestrogens, with or without progestogens, and non-hormonal therapies (see Menopausal Disorders, p. 2245.1).

Uses and Administration

The term *hormone replacement therapy* (HRT) is often used to represent the use of an oestrogen, with or without a progestogen, in peri- and postmenopausal women. HRT is used for the management of acute menopausal symptoms (see p. 2245.1) such as vasomotor symptoms and atrophic vaginitis, and can be used long-term in women with premature or surgically-induced menopause until the normal age of menopause. HRT may also be used for postmenopausal osteoporosis (see p. 2246.1) in selected women, when other preferred drugs cannot be used or have been ineffective. The most commonly used oestrogens in menopausal HRT are natural oestrogens such as estradiol, and conjugated oestrogens. Dosages of oestrogens used in HRT are generally lower than those used in combined oral contraceptives, and do not therefore provide contraception.

Oestrogens for HRT are available as oral tablets, intranasal sprays, subcutaneous implants, topical applications for vulvovaginal use, intravaginal rings, and transdermal patches and gels. Generally, if prolonged therapy (for more than 2 to 4 weeks) with an oestrogen by any route is envisaged in a woman with an intact uterus, a progestogen is required to prevent endometrial proliferation. This may be given cyclically or continuously, depending on the woman's menopausal status. Cyclical regimens usually include a progestogen for 10 to 14 days of each 28-day cycle, although an extended regimen that includes a progestogen for 14 days of a 91-day cycle is also in use. Progestogens may be given orally or transdermally. Both progesterone derivatives such as medroxyprogesterone and dydrogesterone, and 19-nortestosterone analogues such as norethisterone, norgestrel, and levonorgestrel are used. Doses of progestogens for HRT are similar to those used in combined oral contraceptives.

Administration. In a discussion of the relative merits of oral and transdermal oestrogen therapy[1] it was suggested that there was circumstantial and theoretical evidence to suppose that transdermal therapy might be preferable in women who smoke, who suffer from migraine, hepatobiliary disease, or hypertriglyceridaemia, or who have a history of thromboembolism. In contrast, oral HRT might be preferable in patients with hypercholesterolaemia. However, studies to examine these suppositions were needed. Although there have been further studies comparing cardiovascular risk markers in women given oral or transdermal HRT, data on clinical outcome are scarce[2] (see also Venous Thromboembolism, under Adverse Effects, p. 2249.3). Various alternatives to oral oestrogen therapy have been reviewed.[3-5] For references and reviews about estradiol given buccally or sublingually, as implants, intranasally, or transdermally, see p. 2271.3 and p. 2272.1.

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Cardiovascular disorders. Observational studies have shown a decreased risk of ischaemic heart disease and consequent mortality in women receiving menopausal HRT and oestrogens are known to have some beneficial effects on the plasma lipid profile (see Effects on Lipids, p. 2250.1). However, results from randomised placebo-controlled studies of combined HRT for primary or secondary prevention of ischaemic heart disease have shown no overall benefit from HRT, and possibly an increased risk of coronary events (see Ischaemic Heart Disease, under Adverse Effects, p. 2248.3). It has therefore been recommended that HRT should not be used for prevention of cardiovascular disease.[1] Cardiovascular risk reduction, including management of blood lipids, is discussed on p. 1246.1.

1. Mosca L, *et al.* Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004; **109:** 672–93.

Dementia. Several observational studies[1-3] have suggested that oestrogens can reduce the risk and delay the onset of Alzheimer's disease (p. 388.1) in postmenopausal women receiving HRT. However, subsequent meta-analyses[4,5] concluded that studies conducted so far had substantial methodological problems and that results were conflicting. A further observational study[6] has also reported improved global cognition, and a slower rate of decline over 3 years in women receiving HRT. This study also found[7] that previous HRT use reduced the risk of developing dementia, but that current HRT use had no effect unless it was taken for more than 10 years. In contrast, another observational study (a substudy of the Nurse's Health Study[8] including 13 807 women) found no association between HRT use and cognitive performance over 2 years, and a suggestion that long-term use or initiation at older ages may increase the risk of cognitive decline. Any apparent benefits of HRT have also been thrown into question by the results of two large controlled studies of women who received conjugated oestrogens with medroxyprogesterone, or placebo, for about 4 years. At the end of the Heart and Estrogen/Progestin Replacement Study of women with coronary disease, there was no difference in cognitive function tests between those receiving HRT or placebo.[9] In the Women's Health Initiative Memory Study of over 4000 women aged 65 years and older, HRT had no clinically significant effect on global cognitive function, but the risk of suffering a substantial decline was higher for the HRT group.[10] Also, HRT did not prevent the development of mild cognitive impairment, and actually doubled the risk of dementia.[11] The absolute risk of dementia is small, however, and this increase is equivalent to 45 cases of dementia per year for every 10 000 women taking HRT compared with 22 cases for placebo. Similar effects were found for conjugated oestrogens alone in women with a prior hysterectomy who were studied in a separate arm of the Women's Health Initiative.[12,13] Pooling of data from both the oestrogen alone and combined HRT arms of this study suggested that HRT had an adverse effect on cognition,[13] increased the risk for both dementia and mild cognitive impairment, and should not be used to prevent dementia or cognitive decline.[12] A substudy of the Women's Health Initiative examined changes in specific cognitive domains, particularly memory and affect, in 1416 women given combined HRT or placebo.[14] After an average of 4 to 5 years, combined HRT had a negative effect on verbal memory, but a trend to a positive effect on figural memory; there was no significant influence on other cognitive domains and affect.

It has been suggested that age might provide an explanation for the conflict between results of observational and controlled studies. A review that compared results from controlled studies in younger women (less than 65 years old) and older women (65 or older) found that younger women may not be at risk from oestrogen alone and may benefit in verbal memory and attention.[15] However, the reviewer noted that there were limited data available on oestrogen alone in younger women and a lack of studies of combined HRT. A case-control study[16] has also reported a

reduced risk of Alzheimer's disease in younger women (50 to 63 years old), but not older women, given HRT.

Some reports[17-19] suggest that treatment with oestrogens may be of benefit in women who already have Alzheimer's disease. However, in a controlled study in women with mild to moderate Alzheimer's disease, oestrogen replacement therapy for one year did not slow the progression of disease or improve global, cognitive, or functional outcomes.[20] Further analysis of the range of hormone concentrations measured in this study[21] found no association between plasma concentrations of estradiol and estrone, and cognitive function.

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Hyperparathyroidism. The effects of HRT have been studied in postmenopausal women with mild primary hyperparathyroidism (p. 1170.3). Oestrogens have been reported to reduce the rate of bone turnover and plasma concentrations of calcium in these patients, as well as increase bone mineral density.[1-4]

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Menopausal disorders. The menopause (p. 2244.1) is a natural process that occurs in women with normal ageing. For some, the only noticeable change during the perimenopause is irregular menstrual periods that eventually stop, but for others vasomotor symptoms and atrophic vaginitis can cause significant discomfort; effects vary not only between women, but also for the individual woman as she progresses through the menopausal transition. Menopausal effects can be more sudden and intense in women who have the abrupt loss of oestrogen associated with menopause induced by surgery, chemotherapy, or radiotherapy. Many reviews and guidelines have been published on management of the menopause including the use of HRT.

Acute menopausal symptoms. There are several strategies that may be tried for the management of acute menopausal symptoms.

- In postmenopausal women with only *vaginal symptoms*, non-hormonal vaginal lubricants and moisturisers can be tried first.[1] If these are inadequate, locally-acting vaginal oestrogen therapy may be effective;[1,2] improvement typically occurs within a few weeks, but may take 4 to 6 weeks. Oestrogen therapy may continue for as long as required for symptomatic relief, but data on the effects of long-term use are lacking.[1] Systemic exposure from vaginal preparations is believed to be limited, and the addition of a progestogen to protect against endometrial hyperplasia in women with a uterus is generally not indicated when low-dose local oestrogen therapy is used.[1] Nevertheless, studies have reported cases of endometrial hyperplasia and overstimulation; a systematic review found that there were insufficient data to confirm whether a progestogen should be given when vaginal oestrogens are used for more than 6 months.[2] Women using a cream may be at higher risk of systemic absorption since dosing relies on the amount of cream measured by the woman, which may be variable compared with vaginal tablets. (Some vaginal preparations are designed to deliver sufficient systemic oestrogen to treat vasomotor symptoms—see below.)
- Mild *vasomotor symptoms* may be adequately managed with lifestyle changes such as maintaining a lower core body temperature, physical activity, and relaxation techniques.[3] Moderate to severe symptoms can be controlled with HRT,[3-9] usually given orally or transdermally; some vaginal rings also deliver sufficient oestrogen to the circulation to treat vasomotor symptoms. The lowest dose that controls symptoms is given short term, generally for no more than 5 years. Women without a uterus, and who have not had endometriosis, can be given continuous oestrogen alone.[6,7,9] Women with a uterus should also receive a progestogen to reduce the risk of endometrial hyperplasia and cancer associated with unopposed oestrogen therapy[3,4,6,9] (for a discussion of the risks of endometrial cancer with HRT, see under Adverse Effects, p. 2247.3). In women who are postmenopausal (more than 12 months) continuous combined HRT may be used.[7] However, continuous combined HRT can cause irregular bleeding in perimenopausal women, so they are usually given a cyclical progestogen orally or transdermally, which will cause regular withdrawal bleeding; an alternative is the levonorgestrel intra-uterine device. Vaginal progesterone or oral long-cycle regimens (progestogen for 12 to 14 days every 3 to 6 months) have been used to reduce adverse effects, but it is not clear that these provide adequate endometrial protection.[9]
  Perimenopausal women are still potentially fertile and HRT does not provide contraception. It is now considered that women free of all risk factors for venous and arterial disease may use a low-dose combined oral contraceptive (p. 2231.3) to provide both relief of menopausal symptoms and contraception.[3] However, it is recommended that they should stop the oral contraceptive at the age of 50, so that the menstrual cycle and menopausal status can be assessed. Non-hormonal contraceptives or a progestogen-only contraceptive (see p. 2232.3) may be used if contraception is required in perimenopausal women using HRT, and continued to the age of 55 when natural sterility can be assumed.[10]
  Alternative hormonal therapies for vasomotor symptoms include the progestogens megestrol and medroxyprogesterone.[3,6,11] Tibolone, which has oestrogenic, progestogenic, and androgenic properties, is another option for postmenopausal women.[4,7,12,13]
  Non-hormonal therapies have also been tried although evidence for the efficacy of these is less conclusive than that for HRT.[3,6,11,14] The antidepressants fluoxetine, paroxetine, and venlafaxine have shown some benefit in small studies, and low doses of gabapentin have been reported to be effective. Indeed, low-dose paroxetine is used in some countries for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Clonidine or veralipride may be considered when HRT is not suitable, but the use of these can be limited by adverse effects. Other therapies have been used to manage vasomotor symptoms based on anecdotal reports of benefit, but they have generally not been effective in placebo-controlled studies. These include isoflavones from soya or red clover, evening primrose oil, cimicifuga (black cohosh), *Angelica sinensis* (dong quai), and vitamin E.
- *Non-specific symptoms* may also improve in women given HRT, but good evidence is somewhat scanty and HRT should not be used solely for these indications. Oestrogens might reduce recurrent urinary-tract infections in susceptible women,[7] but incontinence can worsen (see p. 2246.2). Many women report improved mood and well-being when given oestrogens, although it is unclear to what extent this is due to relief of other symptoms. Two large controlled studies[15,16] have found that combined HRT improved some quality of life measures in postmenopausal women with vasomotor symptoms, but that asymptomatic women in general received no benefit. There is insufficient evidence to support the use of oestrogen, alone or in combined HRT, for the treatment of depression.[9] Moreover, the addition of progestogens carries some risk of adverse effects on mood such as depression, anxiety, and irritability. Androgens such as testosterone are sometimes used as adjuncts to HRT to improve psychological well-being and libido. However, despite some evidence for efficacy in selected populations, such as surgically menopausal women, testosterone cannot be recommended for generalised use because of poorly-defined indications and a lack of evidence on long-term safety.[17]

Initiation of HRT. There is increasing discussion about when to start HRT, as the timing of treatment after menopause seems to relate to long-term health outcomes. There has been interest particularly in how the effect of HRT on ischaemic heart disease might be affected by age, considering that many women who took part in studies of HRT were older than those who generally take HRT for vasomotor symptoms in their 50s (see Ischaemic Heart Disease under Effects on the Cardiovascular System, p. 2248.3). The benefit-risk ratio is more likely to be acceptable for short-term symptomatic management in younger women around the age of typical natural menopause (about 51 years). It is also now generally advised that, unless there is a compelling indication, HRT should not be started in women older than 60 who have had a natural menopause at the typical age because they will usually have higher baseline risks of cardiovascular disease and breast cancer.[9] It is also generally agreed that all women who have had a *premature natural or induced menopause* should be offered HRT or a combined oral contraceptive until about 52 years of age, unless there are specific contra-indications to therapy. These women may need higher doses of HRT than those normally used to control vasomotor symptoms. Adjunctive androgen therapy may also be considered, particularly in oophorectomised women.[18] Considerations as to how long they need to continue HRT after the usual age for the menopause are probably the same as for other women.

Long-term use of HRT. There are extensive data from observational studies on the beneficial effects on fracture rates and cardiovascular disease, on the risks for development of breast cancer and endometrial cancer, and on the possible effects on overall mortality. However, the women receiving HRT in these studies may differ from women not receiving HRT, and the extent of any bias resulting from this is unclear.[19] Randomised prospective studies have confirmed the increased risk of breast cancer, venous thromboembolism, stroke, and dementia associated with combined HRT (see under Adverse Effects, p. 2246.3). Contrary to the anticipated benefits for preventing ischaemic heart disease, these studies also found an increase in coronary events, and such use is now not recommended (see Cardiovascular Disorders, p. 2244.3). These results have led to recommendations that HRT should not be used long term solely for the prevention of chronic disease in generally healthy postmenopausal women.[6,20,21] However, although other treatments are now preferred for the prevention and treatment of osteoporosis (p. 1168.1), long-term HRT may be suitable for some women (see also p. 2246.1).

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Osteoporosis. Oestrogens may be used in selected patients for the treatment and prevention of postmenopausal osteoporosis (p. 1168.1). They have a direct antiresorptive effect on bone, and will increase bone mass density (BMD). However, data from the Heart and Estrogen/Progestin Replacement Study (HERS) have called into question the benefit of HRT in reducing the incidence of fractures.[1,2] A meta-analysis[3] including the initial HERS data,[1] most of which were from women without osteoporosis, consequently found only non-significant reduction in fracture risk in older women although overall the risk of fracture was reduced by between 20 and 30%. Subsequent results from the Women's Health Initiative[4] showed that, contrary to the results of this meta-analysis, combined HRT did reduce the risk of fracture in healthy postmenopausal women. Similarly, cohort data from 138 737 women in the Million Women Study[5] showed that current use of HRT reduced fracture risk, but that this protection wore off rapidly after stopping HRT. Other studies have also reported that protection against loss of bone mineral density[6] and fracture[7] is not retained after stopping HRT.

Despite the probable benefits, there is substantial evidence to show that HRT is associated with an increased risk of cancer, particularly breast cancer (see Breast under Carcinogenicity, below), and some cardiovascular diseases such as stroke and venous thromboembolism (see Effects on the Cardiovascular System, p. 2248.2). It is now generally recommended by authorities, such as the UK CSM,[8] that the risk to benefit ratio of HRT is unfavourable for the prevention of osteoporosis as first-line therapy, and that it should not be used in this way for women over 50 years of age. HRT does, however, remain an option when other osteoporosis prevention therapies are unsuitable. Younger women who have undergone premature menopause may be given HRT for menopausal symptoms and to prevent osteoporosis until the age of 50, after which its use should be reviewed and considered a second-line choice.

Suggested minimum daily doses are 625 micrograms of oral conjugated oestrogens, 2 mg of oral estradiol or 50 micrograms transdermally, and 15 micrograms of oral ethinylestradiol; lower doses may also be effective,[9-15] and a transdermal patch supplying 14 micrograms of estradiol daily is licensed for the prevention of osteoporosis in the USA. Addition of a progestogen (required to prevent endometrial hyperplasia in women with a uterus) does not impair the beneficial effect of oestrogens on BMD, whether given cyclically or continuously,[16,17] and may provide a further reduction in risk of fractures.[18] Although current, long-term use of HRT can increase BMD and reduce fracture risk, unresolved issues are the duration of therapy required to prevent fractures in old age, and the ideal age to start therapy to obtain the maximum benefits to the bone with the minimum risk of breast cancer.[18-20]

Oestrogens may also be used in women to reduce the risk of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p. 1616.2).

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Urinary incontinence. Urinary incontinence (p. 2349.2) may be one of several acute symptoms associated with a decline in oestrogen levels at the menopause (see Menopausal Disorders, p. 2245.1). Studies[1,2] suggest that oestrogens used with alpha-adrenoceptor agonists are effective in the management of female stress incontinence and this combination has been advocated for use in postmenopausal patients with mild symptoms. Unfortunately addition of a progestogen to treatment to reduce the risk of endometrial carcinoma in women with an intact uterus might exacerbate the incontinence.[3] The value of oestrogens used without an alpha-adrenoceptor agonist in urinary incontinence is less clear. One study[4] reported that oestrogen therapy and pelvic floor exercises for 18 months was more effective than exercises alone in women with mild stress incontinence. However, a placebo-controlled study[5] found no improvement after 6 months of oestrogen therapy.

Some consider that oestrogens may be of use for symptoms of urgency, frequency, and nocturia in postmenopausal patients with urge incontinence, particularly if given locally;[6] it has been suggested that hypoestrogenism may reduce the sensory threshold of the bladder.[7] A meta-analysis of 23 studies concluded that oestrogen therapy subjectively improved urinary incontinence in postmenopausal women but many of the studies examined were considered to be deficient in some respect.[8] Later well-designed studies[9,10] of women with stress, urge, or mixed incontinence found that HRT did not improve, or even worsened, measures of incontinence, although there was the possibility that concomitant progestogen therapy might have affected efficacy. Furthermore, the placebo-controlled Women's Health Initiative[11] found that both oestrogen alone and combination HRT increased the overall risk of developing stress, urge, or mixed incontinence, and worsened incontinence in women who were symptomatic before starting HRT. Another placebo-controlled study[12] also found that combination HRT increased the risk of developing stress or urge incontinence, and the large Nurses' Health Study cohort reported[13] that the current use of HRT increased the risk of developing urinary incontinence.

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Adverse Effects of HRT

When oestrogens are used for menopausal HRT, adverse effects include nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, altered blood lipids, cholestatic jaundice, glucose intolerance, rashes and chloasma (melasma), changes in libido, migraine, dizziness, depression, mood changes, headache, leg cramps, vaginal candidiasis, and decreased tolerance of contact lenses. Transdermal delivery systems may cause contact sensitisation (possibly severe hypersensitivity reactions on continued exposure), and nasal sprays may cause local irritation, rhinorrhoea, and epistaxis. Headache has been reported on vigorous exercise. Use of oestrogen without a progestogen results in endometrial hyperplasia and an increased risk of endometrial carcinoma (see p. 2247.3). The addition of a progestogen for 10 to 14 days of a 28-day cycle reduces this risk but results in regular withdrawal bleeding towards the end of the progestogen. Use of continuous progestogen and oestrogen avoids withdrawal bleeding, but may result in irregular breakthrough bleeding, particularly in the early stages of therapy, or if used within 12 months of the last menstrual period. Current use of menopausal HRT is associated with an increased risk of venous thromboembolism and breast cancer (see p. 2249.3 and below).

Reviews.

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Carcinogenicity. Use of unopposed oestrogen as menopausal HRT in women with a uterus increases the risk of endometrial cancer, irrespective of the route of administration. This risk is reduced, although possibly not eliminated completely, by the concomitant use of a progestogen. There is also evidence that use of HRT, as oestrogen alone or with a progestogen, increases the risk of breast cancer.

Because of continuing modifications in regimens for HRT there is a continuing need to monitor the incidence of various cancers in users of this therapy.

The carcinogenicity of combined menopausal HRT has been reviewed.[1]

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BREAST. Early age at menarche and late age at menopause increase the risk of breast cancer, and surgical oophorectomy at an early age decreases the risk of breast cancer. In addition, higher concentrations of unbound endogenous oestrogens in postmenopausal women appear to increase the risk of developing breast cancer.[1] Such risk factors have prompted concerns that menopausal HRT might be associated with an increased risk of breast cancer.

Reviews and analyses[2-4] of studies published during the 1970s and/or 1980s on the use of **unopposed oestrogen** replacement therapy in postmenopausal women have generally shown that there is an associated moderate increase in the risk of breast cancer; figures for overall relative risk compared with non-oestrogen users ranged from under 1 to up to 2. One of these,[3] a meta-analysis of studies from 1976 to 1989, further showed that although the relative risk of breast cancer rose to 1.3 after 15 years of oestrogen use, it did not appear to rise at all until after 5 years of use. A similar meta-analysis[4] differentiated between low-dose oestrogens and high-dose oestrogens; those taking

625 micrograms daily of conjugated oestrogens had a risk of breast cancer 1.08 times higher than non-oestrogen users, whereas the relative risk in those taking 1.25 mg daily or more was up to 2.0. A subsequent meta-analysis[5] differentiated between current use of HRT, duration of use, and use at any time. The highest relative risk of breast cancer was associated with current use (1.4); use for 10 years or more was associated with a relative risk of about 1.2, and having ever used HRT was not associated with an increased risk. In 1997 the Collaborative Group on Hormonal Factors in Breast Cancer reanalysed about 90% of the worldwide evidence on breast cancer and the use of HRT.[6] They reported that the relative risk of having breast cancer diagnosed was increased by a factor of 1.023 for each year of use, being 1.35 for 5 or more years of use. However, this effect was reduced on cessation of use, and had largely disappeared after about 5 years. In women who started therapy at age 50, the cumulative excess number of breast cancers diagnosed per 1000 women between age 50 and 70 were estimated to be 2, 6, and 12 for 5, 10, and 15 years of use, respectively, from a baseline of 45 per 1000 in never-users.[6] In contrast, the arm of the Women's Health Initiative[7] that compared conjugated oestrogens with placebo over an average of about 7 years found a trend towards a reduction in breast cancer risk with HRT. A Finnish cohort study[8] also found no increase in risk with less than 5 years of oral estradiol or estriol therapy. For women taking unopposed oestrogen in the Nurses' Health Study[9] cohort the linear increase in risk with increasing duration of use did not become statistically significant until current use exceeded 20 years.

Most data relate to the use of unopposed oestrogen. There has been speculation both that the concomitant use of progestogen in HRT could reduce the risk of breast cancer and that it might increase it. Bergkvist *et al.*[10] suggested an increased relative risk of 4.4 in the small subgroup using long-term **combined therapy**, but because of the large confidence intervals they considered these results inconclusive. Analysis of the Nurses' Health Study cohort has provided evidence that current use of oestrogen and progestogen is associated with a similar increased relative risk of breast cancer to that of unopposed oestrogen (1.4 versus 1.3).[11] The Collaborative Group on Hormonal Factors in Breast Cancer[6] found no evidence of marked differences between preparations containing oestrogens alone and those containing oestrogens and progestogens. However, in a randomised study, oestrogen plus progestogen was associated with greater increases in radiographic breast density than unopposed oestrogen.[12] The results of further cohort studies[13,14] and case-control studies[15,16] also suggest that the risk of breast cancer may be higher for current or recent use of combined HRT compared with oestrogen alone, and a cohort study[17] of over 1 million women (the Million Women Study) found relative risks of 1.3 for users of oestrogen alone, and 2.0 for combined HRT, compared with never-users. After an average follow-up of about 5 years the Women's Health Initiative,[18] comparing combined HRT with placebo in more than 16 000 women, was stopped early because of an increased rate of invasive breast cancer in women given HRT.

The public health perspective on the **implications** of any increased risk of breast cancer will depend on the background risk. This is high in western countries, so a small increased relative risk would equate to a large absolute increase in number of cases.[19]

If menopausal oestrogen therapy increases the risk of breast cancer, there is a need to ascertain whether these cancers can be detected early, how aggressive they are, and what the mortality rate from them is. Currently, there are limited data on these points.

- There is evidence[20,21] that the use of HRT decreases the sensitivity and specificity of screening mammography (resulting in more false positives and more false negatives), apparently because it increases radiographic breast density[22,23] or slows the natural change from dense patterns to fatty patterns,[24] so decreasing the ability to interpret the mammogram. This is of concern for the success of screening programmes, and has been suggested as a factor in the increased detection of interval cancers (those detected between screening appointments).[25] In addition, HRT-associated increases in radiographic breast density could actually be a marker for risk of breast cancer.[12,26]
- Some data suggest that breast cancers in women on HRT may be of better prognostic grade.[27,28] The Collaborative Group on Hormonal Factors in Breast Cancer reported that breast cancers were more likely to be localised in current or recent users of HRT, but that there was evidence of an increased risk of metastasis with increasing duration of use.[6] However, the Women's Health Initiative[26] did not confirm previous findings of favourable prognosis, and found breast cancers in combined HRT users to be larger, more likely to be node positive, and at a more advanced stage at diagnosis. The likelihood of good prognostic grade in women on HRT may depend on the histological type of any lesion that develops: invasive lobular and tubular cancers are more strongly associated with current use of HRT than invasive ductal cancer.[29]
- Follow-up of most studies is currently insufficient to give a clear indication of mortality risk with long-term use. Early data from a UK cohort study[30] suggested a decreased risk of breast cancer mortality, but after further follow-up the risk was no longer reduced.[31] Similarly, a study in 2614 women with breast cancer followed up for up to 22 years found that the use of HRT at the time of diagnosis was associated with a reduction in mortality, but the effect waned over time.[32] In contrast, data[11] from the Nurses' Health Study cohort suggest an increase in risk of death from breast cancer in women who have currently used HRT for 5 years or more (1.45). Similarly, although mortality was lower overall, a trend towards an increased risk of death from breast cancer (1.9; 95% confidence interval 0.4 to 8.4) was seen in a study of long-term use (mean of 17 years).[33]

The risk of breast cancer may be increased further by the use of HRT in women who are already at an increased risk. Although a study found a modest increase in risk in these women, it was not significantly higher, and there was a reduced total mortality rate.[34] It is unclear whether use of HRT in breast cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, p. 2250.2).

1. Toniolo PG, *et al.* A prospective study of endogenous estrogens and breast cancer in postmenopausal women. *J Natl Cancer Inst* 1995; **87:** 190–7.
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5. Colditz GA, *et al.* Hormone replacement therapy and risk of breast cancer: results from epidemiologic studies. *Am J Obstet Gynecol* 1993; **168:** 1473–80.
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28. Gapstur SM, *et al.* Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA* 1999; **281:** 2091–7.
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CERVIX. Studies of the effect of HRT on cervical cancer risk are likely to be subject to the potential confounding of other risk factors such as sexual activity. There are few data on this risk; one study[1] suggested oestrogens do not increase, and may decrease, the risk of cervical cancer, but another[2] suggested that unopposed oestrogen might increase the risk of adenocarcinoma. Therapy with combined HRT did not significantly affect the incidence of cytological abnormalities found in annual cervical smears in women in the Heart and Estrogen/progestin Replacement Study (HERS).[3] In the Women's Health Initiative study,[4] however, there was an overall increase in the incidence of new abnormalities in women given combined HRT, compared with placebo, although the incidence of high-grade squamous intra-epithelial lesion and cervical cancer was not affected.

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ENDOMETRIUM. The increased incidence of endometrial hyperplasia and risk of cancer in women receiving unopposed oestrogen replacement therapy is well established. An analysis of case control studies published during the 1970s and 1980s revealed a relative risk of developing endometrial cancer of 1.4 to 7.6 in women who had ever used oestrogen, and a relative risk of 3.1 to 15 in long-term users, compared with nonusers.[1] Risk was also increased with higher doses of oestrogens. In general, endometrial cancer in oestrogen users was of a better prognostic stage, and survival rates were better, than in nonusers.[1] An elevated risk of endometrial cancer persists for several years after stopping unopposed oestrogen therapy.[2]

Addition of a progestogen to oestrogen replacement therapy reduces the incidence of endometrial hyperplasia[3] and cancer. However, the extent to which this alters the risks and benefits of oestrogen replacement therapy, and the optimum progestogen type, and dose and duration, have not been fully elucidated.

As regards risk of endometrial cancer, preliminary data from a cohort study revealed that the addition of cyclical progestogen to oestrogen therapy reduced this risk compared with oestrogen therapy alone.[4] A further case-control study confirmed that progestogens decreased the relative risk, and that the reduction in risk was greater when progestogens were used for 10 or more days per month than when they were used for less than 10 days per month.[5] Two much larger case-control studies have confirmed these findings.[6,7] However, 1 of these studies[6] reported that in long-term users the addition of a progestogen did not reduce the risk of endometrial cancer to that seen in nonusers—after 5 years of use, the relative risk of endometrial cancer with HRT containing 10 or more days of progestogen per month was 2.5 (95% confidence intervals 1.1 to 5.5). This finding remains to be confirmed.

Use of progestogens for 10 days of an 84-day cycle (long cycle) has been suggested to improve acceptability of combined HRT. However, one study of a long-cycle regimen was stopped because of an increased risk of endometrial hyperplasia and atypia compared with a conventional monthly cycle regimen.[8]

Some newer regimens of HRT use continuous low doses of progestogen with oestrogen, which avoid withdrawal bleeding. Data on the incidence of endometrial hyperplasia from randomised studies of these regimens have been reassuring.[3,9,10] Continuous norethisterone plus ethinylestradiol,[9] and continuous medroxyprogesterone plus conjugated oestrogens,[10] protected the endometrium against the hyperplasia seen with the oestrogen alone. In comparing continuous and sequential regimens of combined oral HRT, a meta-analysis[3] suggested that they were associated with similar risks of endometrial hyperplasia, but the sequential regimens that had been studied were quite varied and there were insufficient data available to adequately compare different regimens. The first data on endometrial cancer risk from continuous combined HRT suggest that it is as protective as sequential therapy with the progestogen given

for 10 or more days per month (odds ratio 1.07 per 5 years of use for both regimens).[7] The Women's Health Initiative reported[11] that although the rate of endometrial cancer for continuous combined HRT was reduced, it was not significantly different to placebo over 5 years. However, in the analysis of endometrial cancer in the Million Women cohort study,[12] in which 55% of the 716 738 women had not used HRT, there was a lower risk of endometrial cancer with continuous combined HRT, whereas it was not altered for cyclic combined HRT, and was higher for oestrogen-only HRT and tibolone. The beneficial effects of combined HRT were also found to be greatest in obese women.

It is unclear whether use of HRT in endometrial cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, p. 2250.2).

1. Henderson BE. The cancer question: an overview of recent epidemiologic and retrospective data. *Am J Obstet Gynecol* 1989; **161:** 1859–64.
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GASTROINTESTINAL TRACT. Evidence of an effect of oestrogen replacement therapy on colorectal cancer is ambiguous, since studies have reported both an increased and a decreased incidence; a meta-analysis in 1995 suggested no overall effect.[1] However, subsequent cohort studies did suggest a lower incidence of colon cancer in those who had received oestrogens.[2,3] This was most pronounced in current users in whom the relative risk was about one-third to one-half of that for women who had never taken oestrogen. Similarly, a large case-control study also reported a significant reduction in colon cancer, but not rectal cancer.[4] A later meta-analysis[5] concluded that the risk of colon cancer might be decreased among women who have recently used HRT, and that the risk of death from colon cancer might also be reduced. The Women's Health Initiative,[6] a placebo-controlled study of combined HRT in more than 16 000 women, found that those taking HRT had a decreased risk of developing colorectal cancer, but that at diagnosis there was greater lymph node involvement and it was at a more advanced stage.

There is less information on the effect of HRT on death from colorectal cancer. In the Nurses' Health Study cohort[7] there were decreased risks of death from colorectal cancer and death overall for women taking HRT when cancer was diagnosed, compared with those who had never taken HRT. However, this benefit was limited to women who had been taking HRT for no more than 5 years before diagnosis; longer duration of use and past use had no effect on survival.

1. MacLennan SC, *et al.* Colorectal cancer and oestrogen replacement therapy: a meta-analysis of epidemiological studies. *Med J Aust* 1995; **162:** 491–3.
2. Calle EE, *et al.* Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995; **87:** 517–23.
3. Grodstein F, *et al.* Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med* 1998; **128:** 705–12.
4. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* 1995; **87:** 1067–71.
5. Nanda K, *et al.* Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999; **93:** 880–8.
6. Chlebowski RT, *et al.* Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004; **350:** 991–1004.
7. Chan JA, *et al.* Hormone replacement therapy and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006; **24:** 5680–6.

OVARY. There was no clear evidence that the use of oestrogen replacement therapy altered the risk of invasive ovarian cancer in various case-control studies reviewed by the Collaborative Ovarian Cancer Group.[1] However, subsequent study of a large cohort has suggested that long-term oestrogen replacement therapy may increase the risk of fatal ovarian cancer.[2,3] Similarly, a meta-analysis indicated an increased risk for invasive epithelial ovarian cancer, especially after long-term use of HRT.[4] Another, later, cohort study[5] also reported that there was an increased risk of ovarian cancer with oestrogen replacement therapy, particularly when given for 10 years or more, but found no increase for combined HRT. A Swedish case-control study[6] looked at different types of HRT and also found that the risk was increased with oestrogen replacement therapy. For combined HRT, however, the risk was increased for women who had used sequential combined HRT (continuous oestrogen plus cyclical progestogen), but not for those who had used continuous combined HRT. Similarly, in the Women's Health Initiative,[7] a placebo-controlled study of continuous combined HRT in more than 16 000 women, the increased incidence of ovarian cancer was not significant during 5.6 years of follow-up. Further cohort data support an association with long-term current use of unopposed oestrogen replacement therapy,[8-10] but the role of progestogen remains less clear; the Million Women Study[10] also found increased risks with combined HRT, but the Nurses' Health Study[9] found no association. In the cohort NIH-AARP Diet and Health Study[8] the risk of ovarian cancer was also increased overall for 5 or more years of combined HRT use, and found to be higher for users of sequential compared with continuous combined HRT.

1. Whittemore AS, *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. *Am J Epidemiol* 1992; **136:** 1184–1203.
2. Rodriguez C, *et al.* Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995; **141:** 828–35.
3. Rodriguez C, *et al.* Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001; **285:** 1460–5.
4. Garg PP, *et al.* Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 1998; **92:** 472–9.
5. Lacey JV, *et al.* Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002; **288:** 334–41. Correction. *ibid.;* 2544.
6. Riman T, *et al.* Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst* 2002; **94:** 497–504.
7. Anderson GL, *et al.* Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003; **290:** 1739–48.
8. Lacey JV, *et al.* Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst* 2006; **98:** 1397–1405.
9. Danforth KN, *et al.* A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer* 2007; **96:** 151–6.
10. Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2007; **369:** 1703–10.

Effects on carbohydrate metabolism. Data from a survey of postmenopausal women showed that diabetic women who were currently taking HRT had better glycaemic control than those who had never taken HRT or were previous users.[1] In the Heart and Estrogen/Progestin Replacement study[2] in postmenopausal women with ischaemic heart disease, there was no significant change in fasting glucose concentrations after 4 years of combined HRT in women with or without diabetes compared with a rise in women given placebo. There was also a lower risk of developing diabetes in those given HRT (cumulative incidence 6.2%) compared with placebo (9.5%). The Women's Health Initiative study[3] reported changes in fasting glucose and insulin concentrations, indicating a fall in insulin resistance, in women treated with combined HRT. During an average 5.6 years of follow-up there was a lower incidence of diabetes in women given HRT (3.5%) compared with placebo (4.2%). This represented an absolute reduction of 15 cases of treated diabetes per 10 000 women per year of HRT treatment.

Although HRT may improve glycaemic control in diabetic postmenopausal women, it is generally used with caution in this group. Diabetic patients are already at increased risk of cardiovascular disease, and HRT may be associated with an increased risk of ischaemic heart disease (see below).

1. Crespo CJ, *et al.* Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2002; **25:** 1675–80.
2. Kanaya AM, *et al.* Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003; **138:** 1–9.
3. Margolis KL, *et al.* Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004; **47:** 1175–87.

Effects on the cardiovascular system. Various facts support the theory that endogenous oestrogens may be cardioprotective. For example, mortality rates for cardiovascular disease in women are lower than those in men at all ages. In addition, women who have a surgically induced menopause at a young age are at increased risk of ischaemic heart disease compared with women who have a natural menopause.

Conversely, use of high doses of oestrogens for malignant disease is associated with an increased risk of cardiovascular events. Similarly, use of oestrogens in combined oral contraceptives carries a small increased risk of cardiovascular disease (see p. 2237.1). Moreover, an early study in men surviving a myocardial infarction found that high doses of conjugated oestrogens (5 mg daily) were associated with a higher incidence of subsequent coronary events than placebo (see Effects on the Cardiovascular System, in Conjugated Oestrogens, p. 2260.3).

In practice, some large observational studies found a decreased risk of ischaemic heart disease and mortality in women receiving menopausal HRT compared with those who have never received this therapy (see below). The reduction in risk was estimated as 30 to 50%, but biases such as the healthy user effect seem to play a part in this estimate; unfortunately, results from controlled studies have cast doubt on the extent of any reduction in risk. There is also evidence to show that HRT *increases* the risk of stroke (see p. 2249.2) and venous thromboembolism (see p. 2249.3).

The mechanisms by which oestrogen exerts its cardiovascular effects are not fully understood.[1] Oestrogen has beneficial effects on lipoproteins, but adverse effects on triglycerides (see p. 2250.1). Similarly, it has beneficial effects on some, and adverse effects on other, mediators of thrombosis. Oestrogen may also have a direct beneficial effect on the coronary vasculature. Progestogens may reduce the beneficial effects of oestrogens on some lipids, although observational data has suggested that this is not sufficient to reverse potential benefit.

1. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; **340:** 1801–11.

HYPERTENSION. Although high doses of oestrogens have been associated with increased blood pressure, use of menopausal HRT in normotensive and hypertensive women has little effect on blood pressure or may be associated with a small decrease.[1-4] An observational study[5] of normotensive postmenopausal women also found that, over time, the average increase in systolic blood pressure was significantly less in women who were taking HRT.

1. Affinito P, *et al.* Effects of hormonal replacement therapy in postmenopausal hypertensive patients. *Maturitas* 2001; **40:** 75–83.
2. Mueck AO, Seeger H. Effect of hormone therapy on BP in normotensive and hypertensive postmenopausal women. *Maturitas* 2004; **49:** 189–203.
3. Steiner AZ, *et al.* Postmenopausal oral estrogen therapy and blood pressure in normotensive and hypertensive subjects: the Estrogen in the Prevention of Atherosclerosis Trial. *Menopause* 2005; **12:** 728–33.
4. Karalis I, *et al.* Hormone replacement therapy and arterial blood pressure in postmenopausal women with hypertension. *Blood Pressure* 2005; **14:** 38–44.
5. Scuteri A, *et al.* Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. *Ann Intern Med* 2001; **135:** 229–38.

ISCHAEMIC HEART DISEASE. In 1991, Stampfer and Colditz reviewed 31 case-control and cohort studies on the risk of ischaemic heart disease in women using menopausal HRT.[1] Four studies showed an adverse trend, 2 showed no effect on risk, and 25 showed a trend to **reduction in risk** or a significant reduction in risk. The summary relative risk was 0.56, with estimated 95% confidence intervals of 0.50 to 0.61. Other reviews have reported similar reductions in risk.[2,3] Much of the data relate to the use of unopposed oestrogen, which is no longer recommended in women with a uterus because of the risk of endometrial cancer (see p. 2247.3).

There was concern that the **addition of progestogen** might negate or reduce the cardiovascular benefits of oestrogens by reducing the oestrogen-induced rise in serum high-density-lipoprotein cholesterol concentrations. It was postulated that this might be particularly true for progestogens derived from nortestosterone rather than progesterone. Results from the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) indicated that the beneficial effects on blood lipoproteins and fibrinogen, although greatest with unopposed oestrogen, were still present when combined with medroxyprogesterone or micronised progesterone (micronised progesterone was preferable to medroxyprogesterone).[4] Moreover, the UK Medical Research Council Study reported a fairly even balance between possibly beneficial and adverse effects on lipid concentrations and coagulability when conjugated oestrogens alone were compared with conjugated oestrogens plus norgestrel (a nortestosterone derivative).[5] Similar results were reported in the CHART study for ethinylestradiol with or without norethisterone.[6] Although reassuring, these 3 studies provided information only on surrogate endpoints.

Data from the Nurses' Health Study cohort[7] showed a greater reduction in the risk of major ischaemic heart disease among women receiving an oestrogen plus a progestogen (relative risk 0.4) than those receiving an oestrogen alone (0.6), as compared with the risk in women not using hormones. *In-vitro* data suggest that progestogens may actually protect against atherosclerosis via inhibition of smooth muscle cell proliferation.[8]

As regards **duration of HRT use**, current use appeared to be the most important factor for cardiovascular risk reduction. Users with coronary risk factors appeared to derive greater benefit from HRT than those at low risk of coronary artery disease.[9] Of concern, the Nurses' Health Study reported that the apparent benefit from HRT

decreased with increasing duration of use beyond 10 years because of an increase in mortality from breast cancer.[9]

However, a number of studies have now found **no beneficial effect** on risk of heart disease. In contrast to previous findings, a retrospective case-control study[10] did not find a decreased risk of myocardial infarction in women currently using combined HRT or oestrogens alone. The authors of this study suggested that the benefit of HRT may not be as large as has been estimated in some qualitative overviews, and emphasised the need for data from randomised studies.[10] This has been confirmed by results[11] of the Heart and Estrogen/Progestin Replacement Study, a randomised placebo-controlled study in women with established ischaemic heart disease. Combined HRT with conjugated oestrogens plus medroxyprogesterone produced no overall reduction in the occurrence of myocardial infarction or death due to ischaemic heart disease in these women. This overall lack of effect was due to an initial increase in cardiac events during the first year, with a later beneficial effect in years 3 to 5. During unblinded follow-up[12] of 2.7 years, these late beneficial effects did not persist and the risk of cardiovascular events was not reduced. Observational data from the Nurses' Health Study cohort[13] also noted a trend towards an initial increase in cardiac events followed by a decrease in risk with long-term use of HRT, in women with a history of ischaemic heart disease. Other studies found that HRT did not affect the progression of existing coronary atherosclerosis as measured by angiography.[14,15] Oestrogen therapy for 2 years also had no effect on the risk of further cardiac events in postmenopausal women who had survived a myocardial infarction.[16] There is also some evidence that the risks and benefits of HRT may vary according to the presence or absence of particular prothrombotic mutations.[17]

These worrying results have suggested that HRT should **not** be used for secondary prevention in women with heart disease, in contrast to some earlier suggestions (see also Cardiovascular Disorders under Uses and Administration, p. 2244.3).

In women without pre-existing heart disease, observational data from the Nurses' Health Study[18] showed a reduced risk of major coronary events in users of HRT, compared with never-users. However, there were increased rates of coronary events at an average follow-up of about 5 years in the Women's Health Initiative,[19] a primary prevention study comparing combined HRT with placebo in over 16 000 women. The risk was highest in the first year of HRT but decreased to a smaller non-significant excess risk in the following years.[20] The arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy found that over an average of 7 years there was no difference in the risk of ischaemic heart disease.[21,22] These results suggest that HRT should also **not** be used for primary prevention of ischaemic heart disease.

There is continuing debate about the effect of HRT on ischaemic heart disease, and how it might be influenced by age. The generalisability of some study results, such as in the Women's Health Initiative, has been questioned because the mean age of the study group has been much older than women who generally take HRT for vasomotor symptoms in their 50s. A meta-analysis[23] has compared data from younger and older women, and found that for younger women (less than 10 years since menopause or under 60 years of age) there was a reduced risk of myocardial infarction or cardiac death with HRT. In older women, however, events increased in the first year then decreased after 2 years, resulting in a neutral effect over time. Secondary analysis[24] of the Women's Health Initiative data found that for women who started HRT closer to menopause (aged 50 to 59 years or less than 10 years since menopause) there was a trend towards reduced risks of ischaemic heart disease and death, while risk increased with age and time since menopause. One factor might be the reduction by HRT of atherosclerotic calcification in the coronary arteries.[25] Further studies are underway to examine the effect of HRT, started soon after menopause, in the prevention of atherosclerosis.

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; **20:** 47–63.
2. Grady D, *et al*. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; **117:** 1016–37.
3. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. *JAMA* 1991; **265:** 1861–7.
4. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; **273:** 199–208. Correction. *ibid.;* **274:** 1676.
5. Medical Research Council's General Practice Research Framework. Randomised comparison of oestrogen versus oestrogen plus progestogen hormone replacement therapy in women with hysterectomy. *BMJ* 1996; **312:** 473–8.
6. Speroff L, *et al*. The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA* 1996; **276:** 1397–1403.
7. Grodstein F, *et al*. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61. Correction. *ibid.;* 1046.
8. Lee W-S, *et al*. Progesterone inhibits arterial smooth muscle cell proliferation. *Nature Med* 1997; **3:** 1005–1008.
9. Grodstein F, *et al*. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997; **336:** 1769–75.
10. Sidney S, *et al*. Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med* 1997; **127:** 501–8.
11. Hulley S, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280:** 605–13.
12. Grady D, *et al*. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 49–57. Correction. *ibid.;* 1064.
13. Grodstein F, *et al*. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: a prospective, observational study. *Ann Intern Med* 2001; **135:** 1–8.
14. Herrington DM, *et al*. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000; **343:** 522–9.
15. Hodis HN, *et al*. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003; **349:** 535–45.
16. The ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002; **360:** 2001–8.
17. Psaty BM, *et al*. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001; **285:** 906–13.
18. Grodstein F, *et al*. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; **133:** 933–41.
19. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
20. Manson JE, *et al*. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; **349:** 523–34.
21. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291:** 1701–12.
22. Hsia J, *et al*. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006; **166:** 357–65.
23. Salpeter SR, *et al*. Coronary heart disease events associated with hormone therapy in younger and older women. *J Gen Intern Med* 2006; **21:** 363–6.
24. Rossouw JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77. Correction. *ibid.* 2008; **299:** 1426.
25. Manson JE, *et al*. WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007; **356:** 2591–2602.

STROKE. The Framingham Study suggested a more than twofold increased risk of stroke in women using menopausal HRT.[1] However, subsequent studies reporting risk of stroke separately from other cardiovascular events showed either no effect on risk[2] or a decreased risk in the order of 30 to 50%.[3,4]

Data from the Nurses' Health Study cohort[5] revealed little association between the risk of stroke of any type and current use of unopposed oestrogens or oestrogen plus progestogen. However, they reported a trend towards an increased risk of stroke in current users of high-dose oestrogen therapy (1.25 mg or higher). Similarly, a large Danish case-control study found that unopposed oestrogens or oestrogen plus progestogen had no effect on the risk of non-fatal haemorrhagic or thromboembolic stroke,[6] and data from the Heart and Estrogen/Progestin Replacement Study indicated that combined HRT in women with pre-existing ischaemic heart disease had no effect on risk of stroke.[7,8] In contrast to these results, the Women's Health Initiative, a placebo-controlled study of over 16 000 healthy women, found that combined HRT increased the risk of ischaemic stroke, and that the increase in risk became apparent after about 1 year of starting HRT.[9] Furthermore, the arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy also found an increased risk of stroke;[10] additional data and analysis also confirmed that the increased risk was for ischaemic stroke, and appeared after about 4 years.[11] Although the numbers of haemorrhagic strokes were small in both Women's Health Initiative studies, the combined data showed no significant effect of hormone therapy.[11] A systematic review,[12] which was dominated by the results of the Women's Health Initiative, found that HRT was associated with an increase in stroke. This was attributed largely to ischaemic stroke, whereas there was no significant change in the risks of haemorrhagic stroke, fatal stroke, or transient ischaemic attack. A poor outcome (death or dependency) was also found to be more likely with HRT. Secondary analysis[13] of the Women's Health Initiative data also found that the risk of stroke was increased regardless of years since menopause.

In a controlled study in postmenopausal women who had recently had a stroke or transient ischaemic attack, the use of unopposed oestrogen had no significant effect on mortality or the recurrence of stroke.[14]

1. Wilson PWF, *et al*. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham study. *N Engl J Med* 1985; **313:** 1038–43.
2. Stampfer MJ, *et al*. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991; **325:** 756–62.
3. Paganini-Hill A, *et al*. Postmenopausal oestrogen treatment and stroke: a prospective study. *BMJ* 1988; **297:** 519–22.
4. Finucane FF, *et al*. Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. *Arch Intern Med* 1993; **153:** 73–9.
5. Grodstein F, *et al*. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61. Correction. *ibid.;* 1406.
6. Tønnes Pedersen A, *et al*. Hormone replacement therapy and risk of non-fatal stroke. *Lancet* 1997; **350:** 1277–83.
7. Simon JA, *et al*. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001; **103:** 638–42.
8. Grady D, *et al*. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 49–57. Correction. *ibid.;* 1064.
9. Wassertheil-Smoller S, *et al*. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; **289:** 2673–84.
10. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291:** 1701–12.
11. Hendrix SL, *et al*. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006; **113:** 2425–34.
12. Bath PMW, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005; **330:** 342–4.
13. Rossouw JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77. Correction. *ibid.* 2008; **299:** 1426.
14. Viscoli CM, *et al*. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; **345:** 1243–9.

VENOUS THROMBOEMBOLISM. Traditionally it has been assumed that, unlike combined oral contraceptives, menopausal HRT is not associated with an increased risk of venous thromboembolism.

However, observational studies have provided substantial evidence that there is an increased risk of deep-vein thrombosis and/or pulmonary embolism in women receiving HRT.[1-4] The relative risk of venous thromboembolism was found to be 2.1 to 3.6 in current users compared with past-users or those who had never received HRT. This equates to an excess of 16 to 23 cases per 100 000 women per year. One study found that the increase in risk was restricted to the first year of use.[4] Another reported an increased risk with increasing oestrogen dose.[2]

Evidence from later randomised placebo-controlled studies[5-8] supports the findings of the observational studies above. Results from the Women's Health Initiative also suggest that the risk is higher with combined HRT than oestrogen alone.[9] It has been suggested that transdermal HRT might be preferable in women with a history of thromboembolism (see Administration, p. 2244.2) and a case-control study[10] reported that unlike oral preparations, transdermal oestrogen was not associated with an increased risk of venous thromboembolism.

The UK CSM considers that the absolute risk of venous thromboembolism in all women using HRT is higher than was originally suggested, and that the risks are higher particularly in older women and in women with predisposing factors, such as a history of venous thromboembolism.[11] Women with the factor V Leiden thrombophilia are at high risk of developing venous thromboembolism when taking HRT. The pooled results of 2 studies showed[12] that in the presence of this thrombophilia alone the odds ratio of developing venous thromboembolism was 3.58, and for HRT alone was 3.16, but women who had both these risk factors had a much higher risk of 13.16.

1. Daly E, *et al*. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996; **348:** 977–80.
2. Jick H, *et al*. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; **348:** 981–83.
3. Grodstein F, *et al*. Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996; **348:** 983–7.
4. Pérez Gutthann S, *et al*. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997; **314:** 796–800.
5. Grady D, *et al*. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000; **132:** 689–96. Correction. *ibid.* 2001; **134:** 81.
6. Hulley S, *et al*. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
7. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
8. Cushman M, *et al*. Women's Health Initiative Investigation. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; **292:** 1573–80.
9. Curb JD, *et al*. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006; **166:** 772–80.
10. Canonico M, *et al*. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; **115:** 840–5.
11. CSM/MCA. New product information for hormone replacement therapy. *Current Problems* 2002; **28:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=-CON007454&RevisionSelectionMethod=LatestReleased (accessed 23/01/08)
12. Wu O, *et al*. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.

Effects on the eyes. The risk of dry eye increases with age, when tear production normally decreases. The incidence is

higher in women, but it is unclear whether sex hormone changes in perimenopausal and postmenopausal women play a role in ocular surface dysfunction.[1] The effects of HRT on the incidence and management of dry eye have been debated. Relief of symptoms has occurred in some women given HRT[1] and improvements in tests of tear function and conjunctival epithelium have been reported.[2] However, a large cohort study[3] found a higher prevalence of dry eye syndrome in women taking HRT, particularly oestrogen alone, than in those not taking HRT.

1. Versura P, Campos EC. Menopause and dry eye: a possible relationship. *Gynecol Endocrinol* 2005; **20:** 289–98.
2. Pelit A, *et al*. Tear function tests and conjunctival impression cytology before and after hormone replacement therapy in postmenopausal women. *Eur J Ophthalmol* 2003; **13:** 337–42.
3. Schaumberg DA, *et al*. Hormone replacement therapy and dry eye syndrome. *JAMA* 2001; **286:** 2114–19.

Effects on the gallbladder. The use of HRT is reported to increase the risk of gallstone formation and cholecystectomy in postmenopausal women.[1-4]

1. Uhler ML, *et al*. Estrogen replacement therapy and gallbladder disease in postmenopausal women. *Menopause* 2000; **7:** 162–7.
2. Simon JA, *et al*. Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2001; **135:** 493–501.
3. Hulley S, *et al*. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
4. Cirillo DJ, *et al*. Effect of estrogen therapy on gallbladder disease. *JAMA* 2005; **293:** 330–9.

Effects on lipids. Oestrogens increase serum high-density-lipoprotein cholesterol and decrease low-density-lipoprotein cholesterol concentrations, effects that are considered favourable and may be a mechanism behind their apparent reduction in ischaemic heart disease in postmenopausal women, although controlled studies have not found combined HRT to reduce coronary events (see Effects on the Cardiovascular System, p. 2248.2). Oestrogens may also increase serum triglyceride concentrations, which is undesirable. Severe hypertriglyceridaemia and pancreatitis have occurred in women with hypertriglyceridaemia treated with oestrogens.[1,2] Use of concomitant progestogen reduces oestrogen-induced hypertriglyceridaemia.[2]

1. Glueck CJ, *et al*. Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. *J Lab Clin Med* 1994; **123:** 59–64.
2. Isley WL, Oki J. Estrogen-induced pancreatitis after discontinuation of concomitant medroxyprogesterone therapy. *Am J Med* 1997; **102:** 416–17.

Effects on mental function. For results suggesting that HRT may increase the risk of developing dementia see under Uses and Administration, p. 2244.3.

Effects on the pancreas. Unopposed oestrogen has been associated with pancreatitis in women with hypertriglyceridaemia (see Effects on Lipids, above). There have also been a few cases of pancreatitis, attributed to HRT, in which triglyceride concentrations were within the normal range.[1,2]

1. Blake WED, Pitcher ME. Estrogen-related pancreatitis in the setting of normal plasma lipids: case report. *Menopause* 2003; **10:** 99–101.
2. Trenque-Tessereau M-GB, *et al*. Combined estradiol/gestodene and acute pancreatitis. *Ann Pharmacother* 2005; **39:** 1953–4.

Precautions

Before menopausal HRT is given the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use.

HRT should be avoided in women with active thrombophlebitis or thromboembolic disease; it should not be given to those with a history of recurrent thromboembolism unless they are already receiving anticoagulant treatment.

HRT should not be given to those with undiagnosed abnormal vaginal bleeding, and abnormal vaginal bleeding during therapy should be investigated (see p. 2251.1). HRT is also contra-indicated in women with oestrogen-dependent neoplasms such as those of the breast or endometrium, and is usually considered contra-indicated in women with a history of these conditions although this has been debated (see below). Active liver disease and Dubin-Johnson or Rotor syndromes are also generally considered to be contra-indications.

Prolonged exposure to unopposed oestrogens increases the risk of endometrial cancer whatever the route of administration (see p. 2247.3); they must not be given to women with untreated endometrial hyperplasia. HRT should be used with caution in women with antiphospholipid antibodies or predisposing factors to thromboembolism (see also Venous Thromboembolism, p. 2249.3), and in gallbladder disease, migraine, a history of breast nodules or fibrocystic disease, uterine fibroids, or a history of endometriosis. HRT should also be used with caution in women with diabetes because of the increased risk of heart disease. Consideration should be given to temporarily stopping HRT 4 to 6 weeks before elective surgery (but see also below).

HRT should be stopped immediately, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 95 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during HRT or pregnancy.

Although evidence is in many cases less well established, HRT should perhaps also be used with caution in diseases that may be exacerbated during pregnancy or oestrogen therapy including asthma, epilepsy, hypertension, renal disease, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and SLE.

Doses of oestrogen in HRT are insufficient to provide contraception. HRT is contra-indicated in known or suspected pregnancy, and in women who are breast feeding.

Endometriosis. Women with endometriosis who are treated with hysterectomy and bilateral oophorectomy undergo a surgically-induced menopause and can have acute menopausal symptoms; they are also at risk of conditions such as osteoporosis from long-term oestrogen deficiency. HRT until about 50 years of age has been recommended for women who undergo premature menopause, but disease reactivation and malignant transformation to adenocarcinoma in residual foci have been reported in women with a history of endometriosis, particularly with unopposed oestrogen. Although there are limited data to quantify the risks from HRT, they appear to be small. Nevertheless, recurrent disease may be more severe, with a greater chance of causing ureteric obstruction and consequent renal damage. To minimise the risks of reactivation and malignancy, women with a history of endometriosis should probably be given continuous combined HRT at the lowest effective dose. Although witholding HRT for a few months to wait for endometriosis to regress after surgery has been recommended, there is limited supporting evidence and others suggest that HRT may be started soon after surgery.[1]

1. Soliman NF, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. *Climacteric* 2006; **9:** 325–35.

Lupus erythematosus. SLE is an auto-immune disease which is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that menopausal HRT use may be associated with a slightly increased risk in the onset of SLE in older women.[1-3] In women with pre-existing SLE, small studies found no apparent effect of HRT on disease flares.[2] In a larger study of 351 women, who were given either combined HRT or placebo for 12 months, severe flares were rare in both groups but mild to moderate flares were increased in the HRT group.[4]

Women with SLE are at increased risk of thromboembolic disease, and it has been suggested that transdermal oestrogen HRT may have less of a thrombogenic effect than oral HRT.[5] Women with antiphospholipid antibodies (which includes about a third of all patients with SLE) are at the highest risk and some[5] suggest that HRT should be avoided altogether in patients with persistent antibodies.

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10:** 222–6.
2. Mok CC, *et al*. Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30:** 426–35.
3. Costenbader KH, *et al*. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56:** 1251–62.
4. Buyon JP, *et al*. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005; **142:** 953–62.
5. Gompel A, Piette JC. Systemic lupus erythematosus and hormone replacement therapy. *Menopause Int* 2007; **13:** 65–70.

Malignant neoplasms. HRT is usually avoided in women who have been treated for *breast cancer* because of the concern that oestrogen will stimulate cancer recurrence. A retrospective observational study[1] and a retrospective case-control study[2] among women diagnosed with breast cancer did not find any evidence of an adverse effect in those who began HRT after diagnosis. A systematic review[3] of studies of HRT in breast cancer survivors reached a similar conclusion, but also noted that these studies were small, not randomised, and many were uncontrolled. More recently, an open randomised study[4] was stopped early when it was found that 2 years of HRT increased the risk of breast cancer (local recurrence, contralateral cancer, or distant metastases); this has cast doubt on the safety of HRT in these patients. A similar study, however, found that about 4 years of HRT did not increase the risk of cancer recurrence.[5] Comparing these two results, the authors suggested that the increased risk may have been due to the use of combined HRT that included continuous progestogen, rather than cyclic or long-cycle regimens. A systematic review[6] of 20 studies, including these two, highlighted the many differences in design such as HRT regimens used, and concluded that in the absence of sufficient evidence of safety HRT should not be used in women with a history of breast cancer. Other reviewers[7] have also recommended a cautious approach, suggesting that HRT should not be used for first-line management of menopausal symptoms in these women, but may be justified when other treatments have failed. The safety of different HRT regimens requires further study.[6,7]

Similarly, HRT is usually avoided in patients who have been treated for *endometrial cancer*, because of the theoretical risk of stimulating tumour recurrence.[8] There is a lack of well-designed studies on this subject, but some data suggest that HRT might not increase the rate of recurrence or death.[9,10]

Women who carry *mutations of the BRCA1 and BRCA2 genes* are at greatly increased risk of breast and ovarian cancers, and prophylactic oophorectomy after child-bearing may be considered as a means of reducing this risk. The use of HRT to manage the subsequent menopausal symptoms has been controversial because of concerns that it may adversely affect the risk of breast cancer. One study[11] that used a decision analytical model concluded that HRT did not negate the benefits of oophorectomy; the degree of life expectancy loss or gain was relatively small and influenced by length of HRT use, age at oophorectomy, and presence or absence of concurrent mastectomy. The authors suggested that the decision to use short-term HRT should be based on quality of life issues rather than life expectancy, and that HRT should be stopped at or before the expected age of natural menopause. A subsequent cohort study[12] also found that the use of HRT did not negate the protective effect of prophylactic oophorectomy against breast cancer in BRCA1/2 mutation carriers. Despite these reassuring results, data are limited and further studies are needed to determine appropriate formulations and the optimal timing and duration of HRT for these women.[13]

1. Durna EM, *et al*. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust* 2002; **177:** 347–51.
2. O'Meara ES, *et al*. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001; **93:** 754–62.
3. Col NF, *et al*. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001; **19:** 2357–63.
4. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* 2004; **363:** 453–5.
5. von Schoultz E, *et al*. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* 2005; **97:** 533–5.
6. Antoine C, *et al*. Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007; **22:** 616–22.
7. Hickey M, *et al*. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncol* 2005; **6:** 687–95.
8. Committee on Gynecologic Practice. ACOG committee opinion: hormone replacement therapy in women treated for endometrial cancer (number 235, May 2000). *Int J Gynecol Obstet* 2001; **73:** 283–4.
9. Suriano KA, *et al*. Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet Gynecol* 2001; **97:** 555–60.
10. Barakat RR, *et al*. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2006; **24:** 587–92.
11. Armstrong K, *et al*. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol* 2004; **22:** 1045–54.
12. Rebbeck TR, *et al*. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005; **23:** 7804–10.
13. Rubinstein WS. Surgical management of BRCA1 and BRCA2 carriers: bitter choices slightly sweetened. *J Clin Oncol* 2005; **23:** 7772–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies several HRT combinations as probably porphyrinogenic; they should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

The *BNF* suggests that progestogens should be avoided whenever possible, but that oestrogens may be safe in replacement doses. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/10/13)

Surgery. A review[1] recommended that women receiving HRT and due to have major elective surgery or leg surgery should continue taking the HRT and should routinely

receive thromboprophylaxis (e.g. subcutaneous low-molecular-weight heparins and the use of graduated elastic compression stockings) in the perioperative period. Similar management was proposed when undergoing emergency surgery but prophylaxis was considered unnecessary with minor surgery. These conclusions were based on the advice of specialist groups but it was noted that there was some conflict with recommendations in licensed product information and those of the *BNF* at that time.

The *BNF* currently states that it may be prudent to stop HRT 4 to 6 weeks before major surgery; failing that, prophylaxis as above is recommended. HRT should only be restarted after full mobilisation.

1. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.

Vaginal bleeding. Menopausal HRT is contra-indicated in patients with undiagnosed abnormal vaginal bleeding, which may be a symptom of endometrial carcinoma. The causes of abnormal vaginal bleeding in women receiving HRT and guidelines on their investigation and treatment have been reviewed.[1-3]

1. Good AE. Diagnostic options for assessment of postmenopausal bleeding. *Mayo Clin Proc* 1997; **72:** 345–9.
2. Spencer CP, *et al.* Management of abnormal bleeding in women receiving hormone replacement therapy. *BMJ* 1997; **315:** 37–42.
3. Oehler MK, *et al.* Assessment of abnormal bleeding in menopausal women: an update. *J Br Menopause Soc* 2003; **9:** 117–21.

Withdrawal. Although it is now generally recommended that menopausal HRT used to relieve vasomotor and vaginal symptoms should be given at the lowest effective dose for no longer than necessary (see Menopausal Disorders, p. 2245.1), there has been little study of how to effectively withdraw HRT without a recurrence of menopausal symptoms. When the Women's Health Initiative (WHI) study was stopped prematurely, the effect of HRT withdrawal was assessed in 8405 of the women in this study who were receiving either combined HRT or placebo at the time.[1] A range of menopausal symptoms were reported in both groups. Moderate to severe vasomotor symptoms (hot flushes and night sweats) occurred in 21.2% of women who stopped HRT, compared with 4.8% stopping placebo; younger women were more likely to develop symptoms. Pain and stiffness was reported by about 37% who stopped HRT, with a similar incidence across age groups. Having these symptoms at study entry was the strongest factor for recurrence when treatment ended.

Once the WHI study was stopped, many other women were also advised, or independently chose, to stop HRT; retrospective studies in smaller groups have reported the recurrence of troublesome menopausal symptoms in 30% or more.[2-4] There also appeared to be no advantage to tapering the withdrawal of HRT, compared with stopping abruptly.[2,3] Women reported using various measures to manage recurrent menopausal symptoms,[1,3,4] including lifestyle management such as exercise and drinking more fluids, vaginal oestrogen therapy, antidepressants, and preparations such as cimicifuga (black cohosh), soya, or red clover; in some cases women restarted HRT.

1. Ockene JK, *et al.* Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005; **294:** 183–93.
2. Grady D, *et al.* Predictors of difficulty when discontinuing postmenopausal hormone therapy. *Obstet Gynecol* 2003; **102:** 1233–9.
3. Haskell SG. After the Women's Health Initiative: postmenopausal women's experiences with discontinuing estrogen replacement therapy. *J Womens Health (Larchmt)* 2004; **13:** 438–42.
4. Ness J, *et al.* Menopausal symptoms after cessation of hormone replacement therapy. *Maturitas* 2006; **53:** 356–61.

Interactions

Drugs that increase the hepatic metabolism of oestrogens and progestogens have been associated with failure of the combined oral contraceptive (see p. 2242.3). Important examples include rifamycins and some antiepileptics. It is not unreasonable to assume that these drugs would also be associated with decreased efficacy of HRT, but there appears to be little information on this (for one report, see Antiepileptics, below).

Although oral contraceptives alter the effects of many drugs (see p. 2242.3), the lower doses of oestrogens used in HRT are considered less likely to induce interactions, although the possibility remains.

A study[1] in 12 healthy women aged 20 to 25 years, using bupropion as a probe reaction, found that HRT (estradiol valerate with levonorgestrel) was an inhibitor of the cytochrome P450 isoenzyme CYP2B6.

1. Palovaara S, *et al.* Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2003; **74:** 326–33.

Alcohol. Acute ingestion of an alcoholic beverage led to a threefold increase in circulating estradiol in a study of women on menopausal HRT.[1] Another study[2] that included 309 women taking HRT found that about half had low serum-estradiol concentrations, and that moderate alcohol consumption was one of the factors associated with achieving therapeutic concentrations.

Both alcohol consumption and HRT are risk factors for breast cancer, and cohort studies[3,4] have suggested that the risk from the combination may be higher than the individual risks alone.

1. Ginsburg ES, *et al.* Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA* 1996; **276:** 1747–51.
2. Gavaler JS. Oral hormone replacement therapy: factors that influence the estradiol concentrations achieved in a multiracial study population. *J Clin Pharmacol* 2002; **42:** 137–44.
3. Chen WY, *et al.* Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* 2002; **137:** 798–804.
4. Zhang SM, *et al.* Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol* 2007; **165:** 667–76.

Antiepileptics. *Phenytoin* was reported to reduce the effect of conjugated oestrogens in a menopausal woman.[1]

1. Notelovitz M, *et al.* Interaction between estrogen and Dilantin in a menopausal woman. *N Engl J Med* 1981; **304:** 788–9.

Levothyroxine. Increased doses of levothyroxine may be needed in hypothyroid women who receive oestrogens for postmenopausal HRT—see p. 2342.2.

Melatonin. For the effect of oestrogens on melatonin, see p. 2552.2.

Vitamins. The effect of oral *ascorbic acid* (500 mg twice daily) on plasma concentrations of estradiol was studied in 25 postmenopausal women stabilised on transdermal estradiol gel.[1] After 1 month, estradiol concentrations had risen for the group overall by about 21%. The greatest responses were in those who initially had low plasma concentrations of ascorbic acid or estradiol. The authors suggested that the antioxidant effect of ascorbic acid might reverse the oxidation of oestrogens, but that these results did not support the general use of ascorbic acid as an adjuvant to HRT.

1. Vihtamäki T, *et al.* Oral ascorbic acid increases plasma oestradiol during postmenopausal hormone replacement therapy. *Maturitas* 2002; **42:** 129–35.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p. 2273.3 and Progesterone, p. 2302.2, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

Gonad-regulating Hormones

The Hypothalamic-Pituitary-Gonadal Axis

The regulation of sexual function involves the so-called hypothalamic-pituitary-gonadal axis.

The pituitary gland or hypophysis is composed in humans of 2 parts, the anterior lobe or adenohypophysis, and the posterior lobe (neurohypophysis) and neural stalk, above which lies the hypothalamus. Both parts of the pituitary secrete hormones: posterior pituitary hormones are synthesised in the hypothalamus and transported down nerve fibres to the pituitary where they are stored until required, whereas anterior pituitary hormones are synthesised *in situ* by specialised cells, but are subject to complex hormonal control by hypothalamic regulatory hormones and target organ hormones, as well as excitatory and inhibitory impulses from the brain. These interacting systems are collectively known as the hypothalamic-pituitary-endocrine axes.

The anterior pituitary hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) are collectively known as **gonadotrophic hormones** or gonadotrophins. They are glycoproteins secreted by specialised pituitary cells (gonadotropes) that stimulate gonadal function and sex hormone production. In men, LH stimulates the synthesis of testosterone and other androgens, while in women, FSH and LH regulate production of oestradiol and synthesis of progesterone in a complex and interacting manner. A third substance with gonadotrophic (mainly luteinising) actions, chorionic gonadotrophin, is secreted by the placenta.

The synthesis and secretion of pituitary gonadotrophic hormones is in turn stimulated by a hypothalamic releasing hormone, **gonadotrophin-releasing hormone** (GnRH). In post-pubertal subjects, GnRH is secreted from the hypothalamus at regular intervals determined by an internal 'clock' or neuronal pulse generator in the arcuate nucleus, and enters the blood of the portal vascular system that links the hypothalamus to the anterior pituitary. This results in pulsatile release of the gonadotrophic hormones, which is essential for normal gonadal function. More prolonged and continuous exposure to GnRH leads to desensitisation and downregulation of its receptors on pituitary gonadotropes, and hence, after an initial surge, to suppression of gonadotrophic hormone secretion.

The sex hormones themselves produce negative feedback effects at both hypothalamic and pituitary levels. In general, both oestrogen and progesterone reduce the amplitude (i.e. the amount) of gonadotrophic hormone released; progesterone also reduces the frequency of the pulses. Testosterone is thought to act by conversion to oestrogen via aromatase, although it also has some direct action. The gonads also produce a hormone, inhibin, that selectively inhibits FSH secretion from the pituitary without affecting LH, and its biological opposite, activin, which stimulates pituitary FSH secretion.

Types of Gonad-regulating Hormone

Gonad-regulating hormones in clinical use may be divided into 3 major groups.

- Endogenous follicle-stimulating and luteinising hormones are available from urinary sources as human menopausal gonadotrophins (p. 2284.1) or menotrophin (p. 2284.1) and as urofollitropin (p. 2312.2), and in recombinant forms such as follitropins alfa (p. 2278.2) and beta (p. 2278.2) and lutropin alfa (p. 2287.1). Chorionic gonadotrophin (p. 2258.1) and its recombinant form choriogonadotropin alfa (p. 2258.1) are also used.
- The hypothalamic releasing hormone gonadorelin (p. 2280.2), and its longer-acting analogues such as buserelin (p. 2256.2), deslorelin (p. 2266.3), goserelin (p. 2282.3), histrelin (p. 2283.3), leuprorelin (p. 2285.3), nafarelin (p. 2292.2), and triptorelin (p. 2310.3) are widely used to stimulate or inhibit the hypothalamic-pituitary-gonadal axis.
- More recently, direct gonadotrophin-releasing hormone antagonists have become available, such as abarelix (p. 2255.1), cetrorelix (p. 2257.2), and ganirelix (p. 2279.2).

Use of Gonad-regulating Hormones

The gonad-regulating hormones play an important role in the management of particular endocrine disorders, as discussed in the reviews below and elsewhere in this chapter. They also play an important role in the management of endocrine-sensitive malignant neoplasms (see p. 691.2).

Amenorrhoea

Amenorrhoea is the absence or abnormal cessation of menstruation whereas oligomenorrhoea is infrequent and erratic periods. Amenorrhoea occurring from the time of puberty is known as primary, while amenorrhoea developing later in life is referred to as secondary. Primary amenorrhoea is generally investigated when menstruation has not started by 15 years of age in the presence of normal secondary sexual development, or within 5 years after breast development if that occurred before age 10. Secondary amenorrhoea lasting 3 months, and oligomenorrhoea involving less than 9 cycles a year, should be investigated in women who have had regular menstrual cycles and are not pregnant, lactating, or menopausal. Pathological amenorrhoea is usually associated with infertility (see also p. 2253.1). Hirsutism (p. 2262.1) may also be present.

The causes of amenorrhoea or oligomenorrhoea are most often ovarian or hypothalamic/pituitary in origin. Ovarian causes include failure of normal gonadal development, as in Turner's syndrome (p. 2254.3); premature ovarian failure including that due to trauma, drugs, radiotherapy, or autoimmunity; and conditions such as the polycystic ovary syndrome (p. 2253.3). Hypothalamic or pituitary causes include reduced production of gonadotrophins due to inadequate nutrition, excessive exercise, or pituitary trauma (see also Hypogonadism, p. 2252.3); or excess prolactin production (see Hyperprolactinaemia, p. 2252.2). Other causes, including adrenal disorders, thyroid disorders, abnormalities of the vagina or uterus, or testicular feminisation, may be found rarely.

The management of amenorrhoea essentially involves the identification of any underlying disorder and its correction, if possible. When the cause cannot be corrected, oestrogen replacement therapy, usually in the form of an oral contraceptive, is appropriate to minimise the consequences of long-term oestrogen deficiency.

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1. McIver B, *et al.* Evaluation and management of amenorrhea. *Mayo Clin Proc* 1997; **72:** 1161–9.
2. Baird DT. Amenorrhoea. *Lancet* 1997; **350:** 275–9.
3. Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril* 2008; **90** (suppl 3): S219–S225.

Cryptorchidism

The testes are formed within the abdomen and subsequently descend the inguinal canal to the scrotum. Failure of the testes to descend (cryptorchidism) occurs in about 3 to 6% of newborn males but in many the testes descend during the first year of life decreasing the prevalence to about 1%. In children with cryptorchidism, pathological testicular damage has been noted by the age of 1 year, and may result in subsequent infertility; cryptorchidism also significantly increases the risk of testicular cancer. Abnormalities of the testes and anatomical abnormalities such as inguinal hernia may contribute to maldescent, and both primary testicular disease and gonadotrophin deficiency may be associated with cryptorchidism. For discussions of Hypogonadism and Infertility, see below and p. 2253.1, respectively. Cryptorchidism should be distinguished from retractile testes in which the testes develop normally and for which treatment is usually not required.

Although cryptorchidism is common, there is no consensus on the best treatment: surgery is commonly used in the USA whereas primary hormonal treatment is more popular in Europe.[1,2]

Surgery is successful in almost all cases, and is usually undertaken at around 1 year of age.[1,2] Primary hormonal therapy generally uses chorionic gonadotrophin or gonadorelin to stimulate androgen production. Success rates vary but reports are difficult to compare because of differences in patient age and treatment regimens, and the possible inclusion of retractile testes. Systematic reviews[3,4] suggest that gonadorelin and chorionic gonadotrophin are more effective than placebo with a success rate of about 20% overall, although this may be considerably lower if care is taken to exclude retractile testes. The lower the position of the undescended testis, the more likely benefit from hormonal therapy appears to be.[3,5] Treatment may also be less successful as boys grow older, and treatment before 12 to 18 months[6] or 2 years of age[4] has been recommended. Some reports suggest that results may be improved by combined therapy with gonadorelin and chorionic gonadotrophin,[7] but others have found no advantage over single drug therapy.[8,9] Surgery is used second-line when hormonal treatment is unsuccessful. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, which may be a predictor of future fertility.[6] Chorionic gonadotrophin may also be useful as an adjuvant before surgery, in order to cause a non-palpable testis to become palpable;[10] however, changes suggestive of inflammation in the testis have been reported after such treatment.[5]

Even after successful treatment, however, there may still be impaired fertility.[1,2,6] Similarly, the risk of testicular cancer is not necessarily reduced to that found in the general population, although there is some evidence that prepubertal surgery may decrease the risk of testicular cancer more than postpubertal treatment.[6] Also, orchidopexy does facilitate testicular examination to enable early detection,[2] and all patients should be monitored.

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5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19:** 293–8.
6. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (update March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf (accessed 20/10/09)
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8. Bertelloni S, *et al.* Hormonal treatment for unilateral inguinal testis: comparison of four different treatments. *Horm Res* 2001; **55:** 236–9.
9. Esposito C, *et al.* Comparison of five different hormonal treatment protocols for children with cryptorchidism. *Scand J Urol Nephrol* 2003; **37:** 246–9.
10. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10 year-old experience. *J Urol (Baltimore)* 1996; **156:** 804–6.

Delayed puberty

The onset of puberty is associated with an increase in the secretion of luteinising hormone. There is a subsequent increase in concentrations of sex hormones, the development of secondary sexual characteristics, and an associated growth spurt. Delayed puberty is diagnosed when there is no breast development by 13.4 years of age in girls, and no testicular enlargement by 14 in boys. In addition to the various causes of hypogonadism (see below), some of which may be difficult to diagnose, severe systemic illness such as asthma or diabetes, or hypothyroidism, may cause delay in sexual maturation. Where no apparent cause can be found a family history of delayed maturation may suggest constitutional delayed puberty, in which normal pubertal development can eventually be expected.

Where pubertal delay is secondary to some other condition appropriate management of the precipitating cause is required. In constitutional delayed puberty small doses of oestrogens in girls, or androgens (such as oxandrolone or a testosterone ester) in boys, may be given to promote growth and sexual development if psychological problems are apparent. Care is required as overly aggressive therapy with sex hormones may lead to premature closure of the epiphyses and compromise final adult height. Treatment should be interrupted periodically to see if spontaneous pubertal development has begun. Sex hormone replacement is also used in children with hypogonadism, which may be difficult to distinguish from constitutional delay. In boys with hypogonadotrophic hypogonadism, testosterone will induce virilisation but gonadotrophins are needed to stimulate testicular development. Treatment with chorionic gonadotrophin, plus either human menopausal gonadotrophins or follicle-stimulating hormone, provides the required luteinising and follicle-stimulating hormone effects. Alternatively, pulsatile gonadorelin may be given to stimulate endogenous production of these hormones in patients who have hypothalamic dysfunction but are still able to secrete gonadotrophins.

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Endometriosis

Gonadorelin analogues are used in the management of endometriosis (see p. 2264.1) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy, with concomitant hormone replacement, can be used to prevent this.

Hyperprolactinaemia

Hyperprolactinaemia is a condition of elevated circulating prolactin concentrations. It occurs for physiological reasons in pregnancy or after mechanical stimulation of the nipple, as in suckling. However, hyperprolactinaemia may also be an adverse effect of drugs that inhibit dopaminergic function, such as antipsychotics and metoclopramide; other drugs causing hyperprolactinaemia include opioid analgesics, methyldopa, reserpine, oestrogens, SSRIs, and verapamil. Furthermore, pathological hyperprolactinaemia may be associated with prolactin-secreting pituitary adenomas (prolactinomas), damage to the pituitary stalk or hypothalamus (including that caused by non-secreting tumours), or trauma to the chest wall; it may also be associated with disorders such as Cushing's syndrome or hypothyroidism. Prolactinomas are amongst the commonest pathological causes, and so-called idiopathic hyperprolactinaemia, in which no apparent cause is found, may in fact represent undetected microadenoma.

The consequences of hyperprolactinaemia include suppression of ovarian function in women, leading to erratic cycles or amenorrhoea, and infertility (see also p. 2251.3 and p. 2253.1 respectively); in men, in whom the condition is less common, reduced gonadotrophin production leads to testosterone deficiency, diminished libido, and impotence. Both sexes may develop unwanted milk flow (galactorrhoea), although this also requires the presence of oestrogens; men may rarely develop gynaecomastia (p. 2264.3) due to the change in oestrogen/androgen balance.

Management of hyperprolactinaemia depends on its cause. Pathological hyperprolactinaemia must be distinguished from physiological, and where it is secondary to another disease this should be managed appropriately; any drug thought likely to be causative should be withdrawn if possible. Some patients are asymptomatic, or are untroubled by their symptoms; whether such patients should be treated has been a matter of some controversy, although the risk of osteoporosis in women with prolonged suppression of ovarian function has been cited as a reason for such treatment.[1]

In many cases hyperprolactinaemia will be secondary to a prolactinoma. These are generally classified as microadenomas (less than 10 mm in size) or macroadenomas (over 10 mm in size); macroadenomas are often associated with prolactin concentrations more than 10 times the normal upper limit and their rapid expansion may result in visual defects and headache. Initially a course of treatment with a dopamine agonist such as bromocriptine, while rarely curative, is extremely effective in controlling hyperprolactinaemia and restoring gonadal function.[2,3] Surgical removal is now rarely indicated, although transsphenoidal decompression may be necessary for macroadenomas despite bromocriptine therapy, and ultimately radiotherapy may also be required.

The most extensively used dopamine agonist is bromocriptine; it decreases prolactin secretion and reduces tumour size in the majority of patients.[2] There are reports of maintained normoprolactinaemia and reduced tumour size when bromocriptine has been withdrawn after about 2 to 4 years of treatment.[4] However, this occurs in only a minority of patients, and macroadenomas in particular can re-expand, sometimes rapidly, when treatment is stopped.[2] It has been suggested[3] that when the prolactin concentration has been normal for 2 years and the tumour has decreased by at least 50%, the dose of bromocriptine can be gradually reduced, with close follow-up to detect tumour enlargement. The short half-life and the adverse effects of bromocriptine may pose problems, although depot formulations can minimise these. Giving oral prednisolone with intramuscular depot bromocriptine has been reported to reduce the incidence of adverse effects.[5]

Treatment of hyperprolactinaemia restores ovulation in the majority of female patients. In those who become pregnant it is generally advised that fetal exposure to the dopamine agonist should be as short as possible, and therefore stopped when pregnancy is confirmed. Bromocriptine is the drug of choice for patients who are planning pregnancy, because most experience exists with its use compared with other dopamine agonists. The hyperoestrogenic state of pregnancy itself can stimulate prolactinoma growth and patients must be carefully monitored throughout gestation. If symptomatic tumour growth occurs, bromocriptine may be restarted, which is probably less harmful to the mother and fetus than surgery. Surgical debulking before pregnancy has been advocated by some, but may not prevent symptomatic tumour enlargement during pregnancy.[2,6]

Alternative dopaminergic treatments include cabergoline and quinagolide.[2,7] Cabergoline appears to be more effective, and better tolerated, than bromocriptine, and can also be effective in patients who do not respond to bromocriptine. It is considered by some to be a first-line alternative, although bromocriptine is favoured in women who wish to become pregnant. Quinagolide appears to be of similar efficacy to bromocriptine, and may be useful in patients intolerant of or unresponsive to other drugs. Pergolide has also been tried, with similar efficacy to bromocriptine, but it is not licensed for such use.

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Hypogonadism

Hypogonadism (decreased or absent gonadal function) may occur in both men and women, and may be either primary, due to some dysfunction of the gonads themselves, or secondary, due to hypopituitarism or some other cause of decreased gonadotrophic stimulation.

Primary ovarian dysfunction may be due to failure of the ovaries to form normally, as in Turner's syndrome (see p. 2254.3), or their degeneration before puberty; there may be premature failure, effectively an early menopause, due to low initial follicle numbers or to destruction of follicles by autoantibodies, chemotherapy, radiotherapy, infection, or trauma. Primary testicular dysfunction may be due to congenital disorders such as Klinefelter's syndrome (associated with an XXY chromosome constitution); the effects of chemotherapy, radiotherapy, infections (particularly mumps), or trauma; and a few other conditions such as testicular degeneration.

Secondary hypogonadism may be due to general hypopituitarism, or to a specific deficiency of gonadotrophin production, or gonadorelin production. Kallmann's syndrome is a congenital disorder of hypogonadotrophic hypogonadism due to gonadorelin deficiency associated with anosmia or hyposmia. The causes of pituitary or hypothalamic failure include neoplasms, radiotherapy to the head and neck, trauma, or infiltrative granulomatous diseases such as tuberculosis. Gonadotrophin production may also be suppressed by various drugs (notably exogenous sex steroids and continuous, rather than pulsatile, use of gonadorelin analogues), by weight loss or inadequate nutrition, by excessive exercise, by severe systemic illness, and by hyperprolactinaemia (see above).

The fundamental treatment for primary hypogonadism is replacement therapy with sex hormones to produce appropriate sexual development and activity and counteract effects such as osteoporosis, but fertility cannot usually be restored. In prepubertal children, the induction of secondary sexual characteristics must be balanced against a possible reduction in final height due to premature closure of the bone epiphyses (see also Delayed Puberty, p. 2252.1). Women are generally given an oestrogen with a progestogen, and men are treated with androgens, often in the form of a long-acting testosterone ester such as the cipionate or enantate given intramuscularly. Transdermal testosterone is also effective.

The cause of secondary hypogonadism should be determined and managed appropriately if possible. In some cases this may be adequate to restore gonadal function but in other cases sex hormone replacement therapy as in primary hypogonadism will be required. Where there is no fundamental defect in gonadal function the possibility of using a gonadotrophic hormone or stimulating the release of gonadotrophins also exists. In general, however, such therapy is often reserved for attempts to restore fertility (see under Infertility, below), since it is inconvenient and expensive.

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Infertility

Although about one couple in 6 may have sufficient difficulty in conceiving children that they seek medical help, most are subfertile rather than infertile, and may eventually conceive, with or without treatment. Several possible treatments are available, but which is used depends upon the cause of the problem. Reduced fertility can have its origins in the male or the female partner or may be due to a combination of factors from both.

The most obvious cause of infertility is a failure of either ovulation in the female or spermatogenesis in the male. Such failures may be due to damage or abnormal formation of the gonads, a failure of hypothalamic/pituitary stimulation, abnormal feedback as in the polycystic ovary syndrome, or suppression of gonadal function as in hyperprolactinaemia. These conditions and their management are briefly discussed under Hypogonadism (p. 2252.3), Polycystic Ovary Syndrome (PCOS; below), and Hyperprolactinaemia (p. 2252.2).

Female factors. The primary problem in about 20% of infertile women is ovulatory dysfunction, and most of these women will have PCOS. *Clomifene* is often used first-line to stimulate ovulation in women with hypothalamic dysfunction, as in PCOS,[1-4] and has been reported to produce ovulation in about 70% of anovulatory women. Alternatively, *metformin* or a combination of clomifene and metformin may be used.[4] Women with PCOS who do not respond to clomifene may be treated with ovarian drilling (laparoscopic diathermy),[2,4] or metformin may be added to clomifene if the combination has not already been tried.[4] The addition of a mid-cycle injection of chorionic gonadotrophin has also been tried for women who fail to ovulate with clomifene,[1] and to define the optimal time for intra-uterine insemination,[2] but such a regimen has not been proven to be better. Some women with clomifene-resistant anovulation may benefit from the sequential use of clomifene and a gonadotrophin that has follicle-stimulating activity.[2] In women with elevated dehydroepiandrosterone concentrations, the addition of a corticosteroid to clomifene may improve the ovulation rate.[1,2] Because of concerns about a possibly increased risk of ovarian cancer, opinion varies as to the maximum number of cycles for which clomifene should be used, but is usually a maximum of 6 cycles (see Carcinogenicity, p. 2259.2). *Tamoxifen* has been used as an alternative in those who cannot tolerate clomifene.[3] Aromatase inhibitors such as *letrozole* have also been tried, and seem to be at least as effective as clomifene in inducing ovulation,[5,6] although concerns about the potential for maternal or fetal toxicity remain to be assuaged.

Gonadotrophins with follicle-stimulating activity can be given directly to women with PCOS who have not ovulated with clomifene.[4] Women with hypothalamic anovulation or hypogonadotrophic hypogonadism generally require gonadotrophins that also have luteinising hormone activity, because of low endogenous levels.[4,7] There is growing interest in the use of recombinant luteinising hormone in these patients.[7] Various regimens have been used but in general, follicle-stimulating hormone is given until a dominant follicle is suitably mature, and then chorionic gonadotrophin is given to trigger ovulation and provide luteal support.[7] The risks of ovarian hyperstimulation syndrome and multiple pregnancies are considerable however, particularly in PCOS, and close monitoring is mandatory using ovarian ultrasound to assess follicle development.[3,4]

Another method used for anovulation is pulsatile *gonadorelin*[4] (gonadotrophin-releasing hormone). It is mainly indicated in women with hypothalamic causes of anovulation; it is less effective in women with PCOS than in hypogonadotrophic patients.

Where anovulation is secondary to hyperprolactinaemia, treatment with dopamine agonists such as bromocriptine can restore fertility (see Hyperprolactinaemia, p. 2252.2).

Where infertility is due to obstruction of the fallopian tubes or intra-uterine adhesions, surgery may be effective for some women.[4] If infection is the cause, appropriate anti-infective agents may be useful. (See also under Pelvic Inflammatory Disease, p. 196.3.)

Endometriosis (p. 2264.1) is another important cause of infertility in women, although the reason for the association is not fully understood. Medical treatment of endometriosis does not enhance fertility, although conservative surgery may do so.[4]

Various other drugs have been used, on a more or less empirical basis. Growth hormone or one of its analogues has been used as an adjunct to ovarian stimulation with gonadotrophins but is not considered to improve pregnancy rates.[4]

Assisted reproduction may be considered when other methods fail. IVF is the most commonly used technique, in which oocytes are retrieved from the ovaries, fertilised *in vitro*, and resulting embryos are selected for transfer to the uterus. Less common techniques include transfer into a fallopian tube of gametes (an unfertilised egg and sperm) or a zygote (fertilised egg). Unlike ovulation induction described above, assisted reproduction techniques intentionally use ovarian hyperstimulation regimens to produce multiple oocytes for retrieval; women are therefore at risk of the ovarian hyperstimulation syndrome and should be monitored appropriately.[4] The most commonly used regimens are the 'long protocols' in which a *gonadorelin agonist* is started in the midluteal phase of the menstrual cycle to desensitise the pituitary and prevent a premature surge of luteinising hormone. When pituitary and ovulation suppression has been achieved, gonadotrophins (human menopausal gonadotrophins or follicle-stimulating hormone) are given to stimulate follicle production. At the appropriate stage of follicular development, a single dose of chorionic gonadotrophin is given to trigger ovulation. These 'long protocols' appear to give better results than short ('flare-up') or ultrashort regimens, in which gonadorelin agonists are given for less time, although short regimens may be useful in poor responders.[7] Guidelines advise that gonadorelin agonists should only be given to women with a low risk of ovarian hyperstimulation syndrome, and that either urinary or recombinant gonadotrophins may be used for ovarian stimulation and triggering ovulation.[4] *Gonadorelin antagonists*, such as cetrorelix and ganirelix, are used as an alternative to gonadorelin agonists. Pituitary desensitisation occurs more rapidly and shorter treatment regimens are used, live birth rates are similar, and the incidence of severe ovarian hyperstimulation syndrome is significantly lower with antagonists.[8] *Progesterone* is the preferred drug for luteal support for IVF procedures because of the increased likelihood of ovarian hyperstimulation syndrome with chorionic gonadotrophin.[4]

Male factors. Impaired male fertility may result from urogenital abnormalities, infections of the genital tract, increased scrotal temperature associated with varicocele, endocrine disturbances, genetic abnormalities, and immunological factors, but 30 to 40% of cases may be idiopathic, where no causal factor is found.[9] Some forms of obstructive azoospermia can be corrected surgically. Varicocele repair with surgery, percutaneous embolisation, or sclerotherapy may be considered in some men but the effects on fertility outcome are unclear.[9-11]

In men with hypogonadotrophic hypogonadism, replacement therapy with a gonadotrophin that has luteinising hormone activity, such as chorionic gonadotrophin or recombinant luteinising hormone, is given to stimulate testosterone production. Menopausal gonadotrophins, or the more specific follicle-stimulating hormone, are then added to stimulate spermatogenesis.[9,10,12] Spermatozoa may appear in the ejaculate after about 6 to 9 months of treatment, but may take considerably longer in some men.[10] Pulsatile gonadorelin may restore gonadotrophin secretion and correct infertility in men with hypogonadotrophic hypogonadism of hypothalamic origin, such as those with Kallmann's syndrome;[9,10,12] therapy for 1 to 2 years may be necessary to achieve adequate sperm production in patients who developed hypogonadism before puberty and have not previously received gonadotrophins or gonadorelin.[9]

In idiopathic oligospermia, results of drug therapy have been disappointing. Corticosteroids have been used in men with autoantibodies to spermatozoa, but efficacy is unproven and corticosteroids are generally not recommended[4,9,10] although they might be considered in men with autoantibodies who have failed assisted reproduction techniques.[10] However, corticosteroids may have a beneficial effect on infertility associated with auto-immune orchitis.[10] Various other drugs have been used on an empirical basis for idiopathic male infertility but evidence for their efficacy is either limited or lacking.[9,10]

When other methods fail, assisted reproduction may be considered. Techniques for male infertility include intra-uterine insemination and intracytoplasmic sperm injection.[4,10,11]

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Polycystic ovary syndrome

The polycystic ovary syndrome comprises enlargement of the ovaries with multiple follicular cysts and a thickened, whitish, capsule; there is persistent elevation of serum luteinising hormone concentrations, with a tendency to increased androgen concentrations. Women typically present with erratic menstruation, hirsutism, and obesity, although not all these features may be present; fertility is often impaired. Associated metabolic changes include hyperinsulinaemia with insulin resistance, and increased risk of developing hyperlipidaemia, hypertension, and ischaemic heart disease. The risk of endometrial cancer is also increased.

Management is essentially symptomatic. Patients should be encouraged to modify their lifestyle, to correct lipid abnormalities, and to lose weight if obese;[1,2] weight loss alone may be sufficient to improve menstrual regularity, hirsutism, and fertility. Symptoms of hyperandrogenism can be treated with an anti-androgen, such as cyproterone acetate or spironolactone, with an oestrogen or a combined contraceptive pill.[1-5] Flutamide and finasteride have also been used in these patients (see also the discussion of the management of hirsutism, p. 2262.1).[5] In women who do not desire pregnancy, an oral contraceptive is also the recommended treatment for amenorrhoea or oligomenorrhoea.[2,5-7] Alternatively a progestogen that lacks androgenic properties may be given cyclically, in order to induce withdrawal bleeding (anovular women who do not receive hormonal treatment may be at increased risk of endometrial cancer).[3,6,7] Metformin may also improve metabolic abnormalities and menstrual regularity (see also below), and endocrinologists in the USA have suggested that it may be considered particularly for women who are overweight or obese.[1] Long-term effects of metformin in polycystic ovary syndrome have not been studied, however, and any reduction in cardiovascular risks is yet to be established.[8] Other practitioners have argued that weight reduction is more effective and should be the initial management for obese women with polycystic ovary syndrome.[2]

In patients who wish to conceive, clomifene citrate is used to induce ovulation. In patients who do not respond, gonadotrophins or laparoscopic ovarian diathermy may be tried. When these have not been successful, IVF may be considered. The effects of metformin on ovulation induction are also under investigation (see below).[2,3,6,7,9] Patients must be monitored carefully during any therapy to induce ovulation, as women with polycystic ovaries are more prone to multiple follicle development and ovarian hyperstimulation. For further details on ovulation induction and assisted reproduction, see Infertility, above.

Insulin resistance is a feature of polycystic ovary syndrome, particularly in obese women. Small non-randomised studies of metformin have reported

improvements in insulin metabolism, a reduction in circulating androgen concentrations, small reductions in body-mass index or waist/hip ratio, and improvements in menstrual cycles.[10,11] Early controlled studies found that metformin alone improved ovulation rates and menstrual cycles, and that rates could be improved further when it was given with clomifene citrate.[10] However, 2 large, placebo-controlled studies later found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[2] A subsequent meta-analysis[12] concluded that although there was some evidence for improvements in pregnancy and ovulation rates with metformin, this did not lead to increases in live birth rates (whether it was used alone or with clomifene). Another meta-analysis[13] concluded that metformin did not improve live birth rates in clomifene therapy-naive women, but there was evidence of better rates when metformin was added to clomifene therapy in clomifene-resistant women. Based on limited data, it also appeared that there was no benefit from the addition of metformin to laparoscopic ovarian drilling or follicle-stimulating hormone. Consensus opinion is that metformin should not be used first-line for management of infertility in PCOS, and should be restricted to women with glucose intolerance.[9] There has also been some interest in the use of thiazolidinediones, such as rosiglitazone, but these drugs can increase body-mass, which is undesirable in women who are already overweight.[5,10,11] Their use is considered investigational.[1]

Bromocriptine[4] may be useful in women with polycystic ovary syndrome and associated hyperprolactinaemia (see p. 2252.2).

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Precocious puberty

Precocious puberty is commonly understood to mean the development of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys; it is four to five times more common in girls. However, the age limit used to define precocious puberty in girls has been questioned.[1] Recent data from the United States suggest that puberty is occurring earlier in girls, at age 7 years for white girls, and 6 years for African-American girls. Precocious puberty is either central, due to premature activation of the hypothalamic-pituitary-gonadal axis, or peripheral, due to secretion of extrapituitary gonadotrophins or gonadal steroids independent of gonadorelin secretion from the hypothalamus or pituitary gonadotrophins. In many cases the cause is not apparent, and they are classified as idiopathic. A small proportion of cases are due to tumours. Central precocious puberty may be caused by CNS lesions secondary to diseases such as encephalitis, meningitis, or granuloma, or due to head trauma. Peripheral precocious puberty can be associated with congenital or familial syndromes such as McCune-Albright syndrome or familial testotoxicosis (familial male precocious puberty). Congenital adrenal hyperplasia (see p. 1603.2) can also produce premature sexual development in boys and virilisation in girls.

Apart from early sexual maturation and the associated emotional distress, the chief clinical consequence of precocious puberty is short stature as an adult, due to premature closure of the epiphyses under the influence of sex steroids.[2,3] Age, emotional impact and final height potential should be considered in deciding when to begin and end treatment.[2]

Gonadorelin analogues are the treatment of choice in central precocious puberty.[2,3] The use of continuous rather than pulsatile gonadorelin can paradoxically suppress gonadotrophin secretion by desensitisation and down regulation of pituitary receptors. Cyproterone acetate has been given at the beginning of treatment to prevent the initial stimulatory effect of the gonadorelin analogue.[2] Although originally given daily, by subcutaneous injection or nasal insufflation, intramuscular and subcutaneous depot preparations of gonadorelin analogues are more convenient, and are now more widely used.[2,3] Treatment suppresses sexual development and skeletal maturation, and most studies have reported an improvement in final height.[3,4] However, the treatment of girls with borderline early puberty (between 6 and 8 years of age) has been questioned, as studies suggest that most will reach adult height within the normal range without treatment.[1] Such girls with idiopathic slowly progressing puberty, and no evidence of advanced bone age, may not require gonadorelin therapy, but should be monitored for an onset of rapid pubertal development.[1,5] Children with concomitant growth hormone deficiency (for example after cranial irradiation) may need additional therapy with somatropin or its analogues for maximum benefit.[6] Somatropin has also been used in children who do not have growth hormone deficiency but who have a poor response to gonadorelin analogue therapy; evidence for a beneficial effect is limited.[7]

In the peripheral forms of precocious puberty the gonadorelin analogues are ineffective. Any underlying condition such as a gonadal or adrenal neoplasm should be sought and treated appropriately. Otherwise, therapy is aimed at suppressing premature sexual maturation, and drugs such as cyproterone and medroxyprogesterone have been used.[8] In girls with precocious puberty associated with the McCune-Albright syndrome, the aromatase inhibitor testolactone has been used with some success to block oestrogen biosynthesis,[9,10] ketoconazole has been used in 2 cases,[11] and tamoxifen has been reported to be beneficial.[12] Although ineffective when given alone, testolactone was reported to be of benefit when used with the anti-androgen, spironolactone, in boys with testotoxicosis;[13] a reduction in the rate of bone maturation was reported. Response diminished with long-term treatment, but could be restored by the addition of a gonadorelin analogue, deslorelin, to therapy.[14] This regimen has also been reported[15] to improve predicted adult height. Ketoconazole, which has anti-androgenic properties, has also been tried in boys with familial male precocious puberty; it had beneficial effects on testosterone concentrations and adult height reported in a series of 5 patients.[16]

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7. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* 1999; **104** (suppl): 1010–14.
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9. Feuillan PP, *et al*. Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; **77:** 647–51.
10. Albers N, *et al*. McCune-Albright syndrome - the German experience. *J Pediatr Endocrinol Metab* 2002; **15** (suppl): 897–901.
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12. Eugster EA, *et al*. Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. *J Pediatr* 2003; **143:** 60–6.
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14. Laue L, *et al*. Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
15. Leschek EW, *et al*. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.
16. Soriano-Guillén L, *et al*. Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90:** 147–51.

Premenstrual syndrome

Gonadorelin analogues have been used to treat patients with severe symptoms attributable to the premenstrual syndrome (p. 2272.3), with 'add-back' therapy with oestrogen plus progestogen to prevent the symptoms of oestrogen deficiency.

Turner's syndrome

Turner's syndrome is a congenital disorder associated with the absence of an X or Y chromosome, resulting in an individual with only a single X chromosome who is female in phenotype but in whom the ovaries do not develop. In addition to this gonadal dysgenesis, which results in infertility and primary amenorrhoea, various physical abnormalities may be present including short stature, a short webbed neck and characteristic facial appearance, shield-like chest, multiple naevi, eye and ear disorders, and certain renal and cardiovascular abnormalities. Hypothyroidism and glucose intolerance may occur.

As with other forms of ovarian failure, hormonal therapy is indicated in patients with Turner's syndrome in order to produce sexual maturation and the development of secondary sexual characteristics, as well as to avoid complications such as osteoporosis. Low-dose oestrogen therapy may be started if spontaneous puberty has not begun by 12 to 13 years of age and the follicle-stimulating hormone value is elevated. The dose is gradually increased over 2 to 4 years to promote a normal pace of pubertal development, and a cyclic progestogen is usually added about 2 years after starting oestrogen therapy or when breakthrough bleeding occurs. There is no consensus on which oestrogen is preferred for these patients. Conjugated oestrogens, ethinylestradiol, and estradiol have all been used, but transdermal or injectable depot estradiol may be the most physiological options. An oral contraceptive may be used in adults for maintenance therapy. The duration of oestrogen therapy should be individualised, and adjusted or stopped at the age of normal menopause based on the same considerations used for other postmenopausal women.[1]

A minority of patients with Turner's syndrome have some residual ovarian function, and there are reports of pregnancy in such patients. In women without ovaries it may be possible to maintain pregnancy by appropriate hormone replacement and implantation of a fertilised donor egg.[1]

Short stature is the most common clinical manifestation of Turner's syndrome and growth hormone therapy has been widely used. Results from 622 girls enrolled in the National Cooperative Growth Study[2] suggested a mean height gain of 6.4 ± 4.9 cm, and another cohort database[3] of 485 girls found that when treatment was started before puberty a mean increase in final height of 5 cm or more would be expected. A systematic review[4] of 4 controlled studies found that growth hormone increased short-term growth, and the one study that reported final height found that treated patients were 7 cm taller than untreated ones. Nevertheless, final height in treated patients was about 148 cm, which is still below the normal range for adult women. Growth hormone therapy during childhood and adolescence may also be important in maximising bone mass and reducing the risk of osteoporosis.[5] The optimal age for starting growth hormone therapy has not been established, although studies have found beneficial effects in children as young as 9 months of age. In general, therapy should be considered as soon as growth failure is detected. For girls below about 9 years of age, treatment usually starts with growth hormone alone. For older girls, or those with extremely short stature, higher doses of growth hormone with a non-aromatisable anabolic steroid (such as oxandrolone) may be considered.[1]

There has been some concern that oestrogen therapy might interfere with the effects of growth hormone therapy, and that the timing of pubertal induction would be important in maximising final height. Studies have found that patients who receive growth hormone for a longer period before starting oestrogen therapy attain greater adult height,[6,7] and it has been suggested that optimal height can be achieved by the early use of growth hormone and induction of puberty at an appropriate physiological age.[8] Guidelines now consider that oestrogens can be started at 12 years of age to achieve age-appropriate pubertal maturation without interfering with the positive effects of growth hormone treatment, which should be considered as soon as growth failure is found.[1] However, the use of low-dose oestrogen from an even earlier age (as young as 8 years) to stimulate linear growth does not add to the effect of growth hormone therapy and may even reduce final height.[9]

Patients with Turner's syndrome require multidisciplinary management throughout life, including cardiovascular monitoring, psychological support, and a programme of prevention for diabetes, dyslipidaemia, osteoporosis, and hypertension.[1]

1. Bondy CA. The Turner Syndrome Consensus Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; **92:** 10–25.
2. Plotnick L, *et al*. Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study experience. *Pediatrics* 1998; **102:** 479–81.

3. Betts PR, *et al*. A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999; **80:** 221–5.
4. Baxter L, *et al*. Recombinant growth hormone for children and adolescents with Turner syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 30/12/08).
5. Rubin K. Turner syndrome and osteoporosis: mechanisms and prognosis. *Pediatrics* 1998; **102** (suppl): 481–5.
6. Chernausek SD, *et al*. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. *J Clin Endocrinol Metab* 2000; **85:** 2439–45.
7. Reiter EO, *et al*. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001; **86:** 1936–41.
8. Soriano-Guillen L, *et al*. Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. *J Clin Endocrinol Metab* 2005; **90:** 5197–5204.
9. Quigley CA, *et al*. Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 2002; **87:** 2033–41.

Abarelix *(USAN, rINN)*

Abarélix; Abarelixum; PPI-149; R-3827; Абареликс.
N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide.
$C_{72}H_{95}ClN_{14}O_{14}$=1416.1
CAS — 183552-38-7.
ATC — L02BX01.
ATC Vet — QL02BX01.
UNII — W486SJ5824.

Uses and Administration

Like cetrorelix (p. 2257.2), abarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used to reduce testosterone concentrations in the palliative hormonal therapy of prostate cancer (p. 712.3). A dose of abarelix 100 mg is given intramuscularly on days 1, 15, and 29, and then every 4 weeks thereafter.

Abarelix has been investigated for the treatment of endometriosis.

Malignant neoplasms. References.

1. Tomera K, *et al*. The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer. *J Urol (Baltimore)* 2001; **165:** 1585–9.
2. McLeod D, *et al*. A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. *Urology* 2001; **58:** 756–61.
3. Trachtenberg J, *et al*. A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol (Baltimore)* 2002; **167:** 1670–4.
4. Koch M, *et al*. An open-label study of abarelix in men with symptomatic prostate cancer at risk of treatment with LHRH agonists. *Urology* 2003; **62:** 877–82.
5. Kirby RS, *et al*. Abarelix and other gonadotrophin-releasing hormone antagonists in prostate cancer. *BJU Int* 2009; **104:** 1580–4.

Adverse Effects and Precautions

Immediate hypersensitivity reactions, including urticaria, pruritus, hypotension, and syncope, can occur with abarelix, and the cumulative risk of such a reaction increases with repeated doses. Patients should be monitored for at least 30 minutes after each injection. Hot flushes, sleep disturbance, breast enlargement and tenderness may result from testosterone reduction. Prolongation of the QT interval has occurred in patients receiving abarelix.

Elevations in transaminase concentrations have occurred, and liver function should be monitored before starting treatment, and periodically during treatment. The efficacy of abarelix in the management of prostate cancer decreases with duration of therapy, and may be further reduced in patients weighing more than about 100 kg (225 pounds). Serum-testosterone should therefore be measured on day 29 of therapy and then every 8 weeks, to monitor for treatment failure.

Pharmacokinetics

Abarelix is absorbed slowly after intramuscular injection; peak serum concentrations occur after about 3 days. It is metabolised by hydrolysis and has an elimination half-life of about 13 days with intramuscular use.

References.

1. Wong SL, *et al*. Pharmacokinetics and pharmacodynamics of a novel depot formulation of abarelix, a gonadotropin-releasing hormone (GnRH) antagonist, in healthy men ages 50 to 75. *J Clin Pharmacol* 2004; **44:** 495–502.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Plenaxis; ***Ger.***: Plenaxis; ***Neth.***: Plenaxis.

Alfatradiol *(rINN)*

Alfatradiolum; Alpha-estradiol; Epiestradiol; 17α-Estradiol; NSC-20293; Альфатрадиол.
Estra-1,3,5(10)-triene-3,17α-diol.
$C_{18}H_{24}O_2$=272.4
CAS — 57-91-0.
UNII — 3VQ38D63M7.

Profile

Alfatradiol is the 17-α isomer of estradiol (p. 2271.1) but has much weaker oestrogenic actions. It is a 5α-reductase inhibitor and is used topically as a 0.025% solution for alopecia androgenetica (p. 1682.3).

References.

1. Blume-Peytavi U, *et al*. Comparison of the efficacy and safety of topical minoxidil and topical alfatradiol in the treatment of androgenetic alopecia in women. *J Dtsch Dermatol Ges* 2007; **5:** 391–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avixis; ***Ger.***: Ell-Cranell alpha; Pantostin; ***Mex.***: Avixis.

Algestone Acetophenide *(USAN, rINNM)*

Acetofenido de alfasona; Acetofenido de algestona; Acetofenido de dihidroxiprogesterona; Algestona, acetofenido de; Algestone, Acétophenide d'; Algestoni Acetophenidum; Alphasone Acetophenide; Dihydroxyprogesterone Acetophenide; SQ-15101; Альгестона Ацетофенид.
16α,17α-(1-Phenylethylidenedioxy)pregn-4-ene-3,20-dione; 16α,17α-Isopropylidenedioxypregn-4-ene-3,20-dione.
$C_{29}H_{36}O_4$=448.6
CAS — 595-77-7 (algestone); 24356-94-3 (algestone acetophenide).
UNII — OL7KC2O3OT.

Profile

Algestone acetophenide is a progestogen (see Progesterone, p. 2300.2) that is given by intramuscular injection in monthly doses of 150 mg, with estradiol enantate, as a hormonal contraceptive (see p. 2231.3). It has also been applied topically in the treatment of acne.

References.

1. Martínez GH, *et al*. Vaginal bleeding patterns in users of Perlutal, a once-a-month injectable contraceptive consisting of 10 mg estradiol enanthate combined with 150 mg dihydroxyprogesterone acetophenide: a trial of 5462 woman-months. *Contraception* 1998; **58:** 21–7.
2. Coutinho EM, *et al*. Efficacy, acceptability, and clinical effects of a low-dose injectable contraceptive combination of dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2000; **61:** 277–80.
3. Coutinho EM, *et al*. Comparison of two regimens of a monthly injectable contraceptive containing dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2006; **73:** 249–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Atrimon; Patector; Perlutal; ***Braz.***: Daiva; Perlutan; Preg-Less; Pregnolan; Uno Ciclo; ***Chile***: Unalmes; ***Mex.***: Anafertin; Patector; Perludil; Perlutal; Yectames; ***Singapore***: Unijab.

Allylestrenol *(BAN, rINN)*

Alilestrenol; Allylestrénol; Allylestrenolum; Allyloestrenol; Allylöstrenol; Allyyliestrenoli; Аллилэстренол.
17α-Allylestr-4-en-17β-ol.
$C_{21}H_{32}O$=300.5
CAS — 432-60-0.
ATC — G03DC01.
ATC Vet — QG03DC01.
UNII — I47VB5DZ8O.

Profile

Allylestrenol is a progestogen (see Progesterone, p. 2300.2) structurally related to progesterone that has been given in threatened and recurrent miscarriage, and to prevent premature labour. However, with the exception of proven progesterone deficiency, such use is no longer recommended. In threatened miscarriage in progesterone-deficient women a suggested oral dose is 5 mg three times daily for 5 to 7 days.

Pregnancy. A case-control study of allylestrenol use in pregnancy during 1980 to 1984 in Hungary indicated that it was not teratogenic.[1]

1. Czeizel A, Huiskes N. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. *Clin Ther* 1988; **10:** 725–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Gestanon; ***Hong Kong***: Turinal†; ***India***: Alese; Allynol; Allytry; Anin; Fetugard; Foegard; Fulterm; Gestin; Gravida; Gravidin; Gravinol; Gravion; Gynerol; Gynonys; Iugr; Loestrol; Maintane; Nidagest; Profar; ***Indon.***: Alynol; Gravynon; Lestron; Preabor; Pregnolin; Pregtenol; Premaston; Prenolin†; Prestrenol; Progeston; ***Malaysia***: Gestrenol; ***Philipp.***: Turinal; ***Rus.***: Turinal (Туринал)†; ***Singapore***: Gestrenol; ***Ukr.***: Turinal (Туринал)†.

Altrenogest *(BAN, USAN, rINN)*

A-35957; A-41300; Altrénogest; Altrenogesti; Altrenogestum; RH-2267; RU-2267; Альтреногест.
17α-Allyl-17β-hydroxy-19-norandrosta-4,9,11-trien-3-one; 17β-Hydroxy-19,21,24-trinorchola-4,9,11,22-tetraen-3-one.
$C_{21}H_{26}O_2$=310.4
CAS — 850-52-2.
ATC Vet — QG03DX90.
UNII — 2U0X0JA2NB.

Profile

Altrenogest is a progestogen (see Progesterone, p. 2300.2) used in veterinary medicine.

Androstanolone *(BAN, rINN)* ⊗

Androstanolo; Androstanolon; Androstanolona; Androstanoloni; Androstanolonum; Dihidrotestosterona; Dihydrotestosterone; Estanolona; Stanolon; Stanolone; Андростанолон.
17β-Hydroxy-5α-androstan-3-one.
$C_{19}H_{30}O_2$=290.4
CAS — 521-18-6.
ATC — A14AA01; G03BB02.
ATC Vet — QA14AA01; QG03BB02.
UNII — 08J2K08A3Y.

Profile

Androstanolone is formed naturally in the body from testosterone (p. 2305.1) by the action of 5α-reductase, and is more active than the parent compound. It has anabolic and androgenic properties and is applied topically in the form of a 2.5% gel for male hypogonadism and gynaecomastia, and for lichen sclerosus in both men and women.

References.

1. Wang C, Swerdloff RS. Should the nonaromatizable androgen dihydrotestosterone be considered as an alternative to testosterone in the treatment of the andropause? *J Clin Endocrinol Metab* 2002; **87:** 1462–6.
2. Kunelius P, *et al*. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab* 2002; **87:** 1467–72.
3. Sakhri S, Gooren LJ. Safety aspects of androgen treatment with 5 α -dihydrotestosterone. *Andrologia* 2007; **39:** 216–22.
4. Kaya C, *et al*. The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: a prospective, controlled, randomized study. *J Urol (Baltimore)* 2008; **179:** 684–8.

Lichen sclerosus. For references to the use of androgens such as androstanolone in lichen sclerosus, see under Testosterone, p. 2307.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Andractim; ***Fr.***: Andractim; ***Singapore***: Andractim.

Androstenedione ⊗

Androstenodiona; Андростендион.
Androst-4-ene-3,17-dione.
$C_{19}H_{26}O_2$=286.4
CAS — 63-05-8.
UNII — 409J2J96VR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of androstenedione:
Andro.

Profile

Androstenedione is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens (see p. 2231.1). It has been used in an attempt to enhance athletic performance and as hormone replacement for men. In March 2004 the FDA banned the distribution of dietary supplements containing androstenedione, considering them to be adulterated and warning that they did not meet safety requirements.

Action. The effects of androstenedione have been studied in groups of young (under 40 years of age) and older (up to 65 years) men with normal serum testosterone concentrations.[1-4] Testosterone concentrations were reported to remain unchanged[1,4] as well as increase,[2,3] although they returned to baseline in the longer study of 12 weeks.[3] In 3 of the studies, oestrogens (oestradiol and oestrone) increased.[1-3] Changes in lipid profiles were also noted, particularly a decrease in high-density lipoprotein (HDL) cholesterol.[1,3] Androstenedione did not enhance the effects of resistance training.[1,3]

There has been a report of impotence and severe oligospermia associated with ingestion of androstenedione by a bodybuilder.[5] Priapism has also been reported.[6]

1. King DS, *et al.* Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. *JAMA* 1999; **281:** 2020–8.
2. Leder BZ, *et al.* Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 2000; **283:** 779–82.
3. Broeder CE, *et al.* The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. *Arch Intern Med* 2000; **160:** 3093–3104.
4. Beckham SG, Earnest CP. Four weeks of androstenedione supplementation diminishes the treatment response in middle aged men. *Br J Sports Med* 2003; **37:** 212–8.
5. Ritter RH, *et al.* Oral androstenedione-induced impotence and severe oligospermia. *Fertil Steril* 2005; **84:** 217.e7–e8.
6. Kachhi PN, Henderson SO. Priapism after androstenedione intake for athletic performance enhancement. *Ann Emerg Med* 2000; **35:** 391–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Thai.***: Metharmon-F†.

Bazedoxifene Acetate *(USAN, rINNM)* ⊗

Acetato de bazedoxifeno; Bazédoxifène, Acétate de; Bazedoxifeni Acetas; TSE-424; WAY-140424; WAY-TSE-424; Базедоксифена Ацетат.

1-{*p*-[2-(Hexahydro-1*H*-azepin-1-yl)ethoxy]benzyl}-2-(*p*-hydroxyphenyl)-3-methylindol-5-ol monoacetate.

$C_{30}H_{34}N_2O_3,C_2H_4O_2$=530.7

CAS — 198481-32-2 (bazedoxifene); 198481-33-3 (bazedoxifene acetate).

ATC — G03XC02.

ATC Vet — QG03XC02.

UNII — J70472UD3D.

Uses and Administration

Bazedoxifene acetate is a selective oestrogen receptor modulator that has oestrogen-receptor agonist effects on bone, and antagonist effects on uterine and breast tissue. It is used in the prevention and treatment of postmenopausal osteoporosis (p. 1168.1) in women at increased risk of fracture. It is also given to reduce the risk of endometrial hyperplasia associated with oestrogen therapy; a combination of conjugated oestrogens with bazedoxifene may be used in the management of moderate to severe menopausal vasomotor symptoms (p. 2245.1), and in the prevention of postmenopausal osteoporosis. Bazedoxifene is given as the acetate, but doses are expressed in terms of the base; 11.3 mg of bazedoxifene acetate is equivalent to about 10 mg of bazedoxifene. For the above indications, an oral dose equivalent to bazedoxifene 20 mg is given once daily.

References.

1. Stovall DW, *et al.* Tissue-selective estrogen complex bazedoxifene and conjugated estrogens for the treatment of menopausal vasomotor symptoms. *Drugs* 2011; **71:** 1649–57.
2. Duggan ST, McKeage K. Bazedoxifene: a review of its use in the treatment of postmenopausal osteoporosis. *Drugs* 2011; **71:** 2193–2212.
3. Taylor HS, Ohleth K. Using bazedoxifene plus conjugated estrogens for treating postmenopausal women: a comprehensive review. *Menopause* 2012; **19:** 479–85.
4. Pinkerton JV, *et al.* Bazedoxifene/conjugated estrogens for menopausal symptom treatment and osteoporosis prevention. *Climacteric* 2012; **15:** 411–18.
5. Mirkin S, Pickar JH. Management of osteoporosis and menopausal symptoms: focus on bazedoxifene/conjugated estrogen combination. *Int J Womens Health* 2013; **5:** 465–75.

Adverse Effects and Precautions

As for Raloxifene Hydrochloride, p. 2303.3 and p. 2304.1. Other effects reported for bazedoxifene include somnolence and dry mouth. Increases in blood triglycerides and liver enzymes values may also occur commonly.

Pharmacokinetics

Bazedoxifene is absorbed from the gastrointestinal tract, with peak plasma concentrations occurring after about 2 hours. It has an absolute bioavailability of about 6% and is highly bound to plasma proteins. Bazedoxifene is extensively metabolised, mainly by glucuronidation, and eliminated in the faeces via biliary excretion with a half-life of about 30 hours. It is expected to undergo enterohepatic recycling.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Conbriza; ***Gr.***: Conbriza; ***Irl.***: Conbriza; ***Jpn***: Viviant; ***Neth.***: Conbriza; ***Pol.***: Conbriza; ***Port.***: Conbriza; ***Spain***: Conbriza; ***Switz.***: Conbriza.

Multi-ingredient Preparations. ***USA***: Duavee.

Boldenone Undecenoate *(BANM, rINNM)* ⊗

Ba-29038; Boldenone Undecylenate (USAN); Boldénone, Undécylénate de; Boldenoni Undecylenas; 1-Dehydrotestosterone (boldenone); Undecilenato de boldenona; Болденона Ундециленат.

17β-Hydroxyandrosta-1,4-dien-3-one 17-(undec-10-enoate).

$C_{30}H_{44}O_3$=452.7

CAS — 846-48-0 (boldenone); 13103-34-9 (boldenone undecenoate).

UNII — ZS6D2ITA30.

Profile

Boldenone undecenoate is an anabolic steroid (see Testosterone, p. 2305.1) that has been used in veterinary practice. It has been subject to abuse in sport.

Buserelin *(BAN, rINN)* ⊗

Busereliini; Buserelina; Buserelinas; Busséréline; Buserelinum; Buszerelin; S74-6766; Бусерелин.

(6-*O*-*tert*-Butyl-D-serine)-des-10-glycinamidegonadorelin ethylamide; 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

$C_{60}H_{86}N_{16}O_{13}$=1239.4

CAS — 57982-77-1.

ATC — L02AE01.

ATC Vet — QH01CA90; QL02AE01.

UNII — PXW8U3YXDV.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Buserelin). A white or slightly yellowish hygroscopic powder. Sparingly soluble in water and in dilute acids. Store at 2 degrees to 8 degrees. Protect from light and moisture.

Buserelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de buserelina; Buserelin Asetat; Buserelina, acetato de; Busséréline, Acétate de; Buserelini Acetas; Hoe-766; D-Ser(Bu^t)^6 Pro^9 NEt LHRH acetate; Бусерелина Ацетат.

$C_{60}H_{86}N_{16}O_{13},C_2H_4O_2$=1299.5

CAS — 68630-75-1.

ATC — L02AE01.

ATC Vet — QL02AE01.

UNII — 13U86G7YSP.

Uses and Administration

Buserelin is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used for the suppression of testosterone in the treatment of malignant neoplasms of the prostate; it is also used in the treatment of endometriosis and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. It has been used in central precocious puberty and tried in the treatment of uterine fibroids (see p. 2257.1 and below respectively). Buserelin is usually given as the acetate but doses are expressed in terms of the base; 105 micrograms of buserelin acetate is equivalent to about 100 micrograms of buserelin.

In advanced **prostatic carcinoma** doses of 500 micrograms are injected subcutaneously every 8 hours for 7 days. On the eighth day treatment is changed to the nasal route; 100 micrograms is sprayed into each nostril 6 times daily (usually before and after meals). An acceptable response should be achieved within 4 to 6 weeks. Since there is an initial increase in circulating testosterone, an anti-androgen such as cyproterone acetate may be given for at least 3 days before beginning buserelin therapy, and continued for at least 3 weeks, to avoid the risk of a disease flare. Long-acting subcutaneous depot preparations that release buserelin over a 2- or 3-month period are also available.

In **endometriosis** a dose of 150 micrograms is sprayed into each nostril three times daily. The usual duration of a course of therapy is 6 months, which should not be exceeded.

In **infertility**, pituitary desensitisation before ovulation induction with gonadotrophins is achieved by giving 150 micrograms intranasally four times daily, beginning either in the early follicular phase (day 1) or midluteal phase (day 21) of the menstrual cycle. Alternatively, 200 to 500 micrograms may be given daily as a subcutaneous injection. Therapy should be continued until pituitary downregulation occurs, which normally takes 1 to 3 weeks; if necessary 300 micrograms four times daily intranasally, or 500 micrograms twice daily subcutaneously may be given. Gonadotrophin treatment is then added to buserelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

General reviews.

1. Brogden RN, *et al.* Buserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical profile. *Drugs* 1990; **39:** 399–437.

Administration in children. Buserelin may be used in the management of central precocious puberty—see p. 2257.1.

Endometriosis. Gonadorelin analogues such as buserelin have a role in the management of endometriosis (p. 2264.1), but the need for long-term therapy limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

1. Lemay A, *et al.* Efficacy of intranasal or subcutaneous luteinizing hormone-releasing hormone agonist inhibition of ovarian function in the treatment of endometriosis. *Am J Obstet Gynecol* 1988; **158:** 233–6.
2. Donnez J, *et al.* Administration of nasal buserelin as compared with subcutaneous buserelin implant for endometriosis. *Fertil Steril* 1989; **52:** 27–30.
3. Nieto A, *et al.* Long term follow-up of endometriosis after two different therapies (gestrinone and buserelin). *Clin Exp Obstet Gynecol* 1996; **23:** 198–204.
4. Regidor P-A, *et al.* Long-term follow-up on the treatment of endometriosis with the GnRH-agonist buserelin acetate. *Eur J Obstet Gynecol Reprod Biol* 1997; **73:** 153–60.
5. Takeuchi H, *et al.* A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26:** 325–31.

Fibroids. Like other gonadorelin analogues (see also p. 2281.2) buserelin has been used to reduce the volume of uterine fibroids.

References.

1. Maheux R, *et al.* Use of intranasal luteinizing hormone-releasing hormone agonist in uterine leiomyomas. *Fertil Steril* 1987; **47:** 229–33.
2. Matta WHM, *et al.* Long-term follow-up of patients with uterine fibroids after treatment with the LHRH agonist buserelin. *Br J Obstet Gynaecol* 1989; **96:** 200–6.
3. Fedele L, *et al.* Intranasal buserelin versus surgery in the treatment of uterine leiomyomata: long-term follow-up. *Eur J Obstet Gynecol Reprod Biol* 1991; **38:** 53–7.
4. Ueki M, *et al.* Endocrinological and histological changes after treatment of uterine leiomyomas with danazol or buserelin. *J Obstet Gynaecol* 1995; **21:** 1–7.

Infertility. Buserelin is given with gonadotrophic hormone therapy for induction of ovulation and as an aid to improving IVF procedures. Buserelin with gonadotrophic hormones has been found to result in pregnancies in women previously unresponsive to clomifene citrate,[1,2] although there may be a greater risk of multiple births.[3]

The regimens used in IVF may be characterised according to how long the gonadorelin analogue is given for:

- long, 2 weeks or more
- short, 8 to 10 days
- ultrashort, 3 days

A comparative study of such regimens found that the best results in all age groups were consistently associated with the long buserelin protocol.[4] The timing of buserelin dosage may also be important. Starting buserelin in the midluteal phase of the cycle has been reported to produce more rapid pituitary down regulation and higher pregnancy rates from IVF than when buserelin was begun in the early follicular phase.[5]

For a general discussion of the management of infertility, see p. 2253.1.

1. Armitage M, *et al.* Successful treatment of infertility due to polycystic ovary disease using a combination of luteinising hormone releasing hormone agonist and low dosage menotrophin. *BMJ* 1987; **295:** 96.
2. Owen EJ, *et al.* The use of a short regimen of buserelin, a gonadotrophin-releasing hormone agonist, and human menopausal gonadotrophin in assisted conception cycles. *Hum Reprod* 1989; **4:** 749–53.
3. Rutherford AJ, *et al.* Improvement of in vitro fertilisation after treatment with buserelin, an agonist of luteinising hormone releasing hormone. *BMJ* 1988; **296:** 1765–8.
4. Tan S-L, *et al.* Cumulative conception and live-birth rates after in vitro fertilization with and without the use of long, short, and ultrashort regimens of the gonadotrophin-releasing hormone agonist buserelin. *Am J Obstet Gynecol* 1994; **171:** 513–20.
5. Urbancsek J, Witthaus E. Midluteal buserelin is superior to early follicular phase buserelin in combined gonadotropin-releasing hormone analog and gonadotropin stimulation in in vitro fertilization. *Fertil Steril* 1996; **65:** 966–71.

Malignant neoplasms. The long-term use of buserelin in men decreases the testicular concentration of testosterone. For this reason it is used in the treatment of prostatic cancer (p. 712.3), which is androgen-dependent.[1] Gonadorelin analogues are an effective alternative to orchidectomy, sometimes combined with an anti-androgen for enhanced effect, and play a major role in the management of advanced, incurable disease.

Other reports of malignant neoplasms treated with buserelin include its use in metastatic breast cancer[2,3] (p. 702.1).

1. de Voogt HJ, *et al.* The use of the LHRH-analogue buserelin in the treatment of prostatic cancer: a 10-year review on 1522 patients treated in 119 centers on 4 continents. *Scand J Urol Nephrol Suppl* 1991; **138:** 131–6.
2. Falkson CI, *et al.* Cyclophosphamide, doxorubicin and fluorouracil (CAF) plus depo-buserelin in the treatment of premenopausal women with metastatic breast cancer. *Ann Oncol* 1992; **3:** 849–53.
3. Klijn JG, *et al.* Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. *J Natl Cancer Inst* 2000; **92:** 903–11.

Porphyria. Buserelin given with medroxyprogesterone acetate suppressed cyclic and premenstrual exacerbations of porphyria (p. 1556.1) in 2 patients. Doses used were 300 micrograms buserelin intranasally in the evenings of days 1 to 21 of the menstrual cycle and 10 mg of oral medroxyprogesterone acetate daily from day 12 to 21. Both patients were free from porphyric attacks during the reported 11 months of treatment.[1] Intranasal buserelin has also been used in 1 patient to prevent premenstrual exacerbation of coproporphyria.[2] The initial dose of 900 micrograms daily could be tapered to 150 micrograms daily, with only 1 minor attack in 5 years of treatment. The authors of this report also noted several case reports of buserelin used in acute intermittent porphyria.

1. Bargetzi MJ, *et al.* Premenstrual exacerbations in hepatic porphyria: prevention by intermittent administration of an LH-RH agonist in combination with a gestagen. *JAMA* 1989; **261:** 864.
2. Yamamori I, *et al.* Prevention of premenstrual exacerbation of hereditary coproporphyria by gonadotropin-releasing hormone analogue. *Intern Med* 1999; **38:** 365–8.

Precocious puberty. The gonadorelin analogues have largely replaced other treatments in the management of central precocious puberty (p. 2254.1).

References to the use of buserelin.

1. Drop SLS, *et al.* The effect of treatment with an LH-RH agonist (buserelin) on gonadal activity growth and bone maturation in children with central precocious puberty. *Eur J Pediatr* 1987; **146:** 272–8.
2. Cacciari E, *et al.* Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. *Arch Pediatr Adolesc Med* 1994; **148:** 1194–9.
3. Juul A, *et al.* Serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 levels are increased in central precocious puberty: effects of two different treatment regimens with gonadotropin-releasing hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). *J Clin Endocrinol Metab* 1995; **80:** 3059–67.
4. Bertelloni S, *et al.* Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr* 1998; **157:** 363–7.
5. Tuvemo T, *et al.* Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. *Horm Res* 2002; **57:** 27–31.

Premenstrual syndrome. For reference to the use of buserelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug treatment, see under Gonadorelin, p. 2281.3.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies buserelin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] For the use of buserelin in the prevention of premenstrual exacerbations of acute porphyria, see above.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Buserelin is completely absorbed after subcutaneous injection and peak plasma concentrations occur about 1 hour after a dose. It accumulates in liver and kidneys as well as in the anterior pituitary. It is metabolised by tissue peptidases and is excreted in urine and bile as unchanged drug and metabolites. The half-life after injection is stated to be about 80 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Suprefact; ***Austria***: Suprecur; Suprefact; ***Belg.***: Suprefact; ***Braz.***: Suprefact; ***Canad.***: Suprefact; ***Denm.***: Suprecur; Suprefact; ***Fin.***: Suprecur; Suprefact; ***Fr.***: Bigonist; Suprefact; ***Ger.***: Metrelef; Profact; ***Gr.***: Suprefact; ***Hong Kong***: Suprecur; ***Hung.***: Suprefact; ***Irl.***: Suprecur; Suprefact; ***Israel***: Suprefact; ***Ital.***: Suprefact; ***Jpn***: Suprecur; ***Malaysia***: Suprefact; ***Mex.***: Suprefact; ***Neth.***: Suprefact; ***Norw.***: Suprecur; Suprefact†; ***NZ***: Suprefact; ***Port.***: Suprefact; ***S.Afr.***: Suprefact; ***Singapore***: Suprefact; ***Spain***: Suprefact; ***Swed.***: Suprecur; Suprefact; ***Switz.***: Suprefact†; ***Thai.***: Suprefact; ***Turk.***: Suprecur; Suprefact; ***UK***: Suprecur; Suprefact; ***Ukr.***: Buserin (Бусерин); Suprefakt Depo (Супрефакт Депо)†.

Cetrorelix Acetate *(BANM, USAN, rINNM)*

Acetato de cetrorelix; Cétrorélix, Acétate de; Cetrorelix, acetato de; Cetrorelixi Acetas; D-20761; NS-75A; SB-075 (cetrorelix); SB-75 (cetrorelix); Цетрореликса Ацетат.

N-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^5-carbamoyl-D-ornithyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide acetate.

$C_{70}H_{92}ClN_{17}O_{14}xC_2H_4O_2$=1431.1 (cetrorelix)

CAS — 120287-85-6 (cetrorelix); 145672-81-7 (cetrorelix acetate).

ATC — H01CC02.

ATC Vet — QH01CC02.

UNII — W9Y8L7GP4C.

Uses and Administration

Cetrorelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist used as a component of ovarian stimulation regimens for assisted reproduction in infertility (p. 2253.1); it is used to prevent luteinising hormone surges and premature ovulation. It has also been tried in benign prostatic hyperplasia, malignant neoplasms of the prostate, endometriosis, and for uterine fibroids.

Cetrorelix is given by subcutaneous injection as the acetate; an intramuscular depot formulation containing cetrorelix embonate is in development.

For assisted reproduction, doses of cetrorelix acetate equivalent to cetrorelix 250 micrograms daily may be given either in the morning beginning on day 5 or 6 of ovarian stimulation or in the evening beginning on day 5, and continued until ovulation induction. Alternatively a single dose equivalent to 3 mg of cetrorelix may be given on day 7; if follicle growth does not allow ovulation induction within 4 days, additional doses of cetrorelix 250 micrograms once daily may be given until the day of ovulation induction.

References.

1. Gonzalez-Barcena D, *et al.* Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist cetrorelix. *Hum Reprod* 1997; **12:** 2028–35.
2. Comaru-Schally AM, *et al.* Efficacy and safety of luteinizing hormone-releasing hormone antagonist cetrorelix in the treatment of symptomatic benign prostatic hyperplasia. *J Clin Endocrinol Metab* 1998; **83:** 3826–31.
3. Felberbaum RE, *et al.* Treatment of uterine fibroids with a slow-release formulation of the gonadotrophin releasing hormone antagonist cetrorelix. *Hum Reprod* 1998; **13:** 1660–8.
4. Huirne JAF, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* 2001; **358:** 1793–1803.
5. Ludwig M, *et al.* Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol: meta-analysis. *Arch Gynecol Obstet* 2001; **265:** 175–82.
6. Roulier R, *et al.* Depot GnRH agonist versus the single dose GnRH antagonist regimen (cetrorelix, 3 mg) in patients undergoing assisted reproduction treatment. *Reprod Biomed Online* 2003; **7:** 185–9.
7. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
8. Al-Inany HG, *et al.* Gonadotrophin-releasing hormone antagonists for assisted conception. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/07/08).
9. Finas D, *et al.* Cetrorelix in the treatment of female infertility and endometriosis. *Expert Opin Pharmacother* 2006; **7:** 2155–68.
10. Tur-Kaspa I, Ezcurra D. GnRH antagonist, cetrorelix, for pituitary suppression in modern, patient-friendly assisted reproductive technology. *Expert Opin Drug Metab Toxicol* 2009; **5:** 1323–36.

Adverse Effects and Precautions

Transient reactions at the injection site, including erythema, pruritus, and swelling, may occur. Nausea and headache have been reported occasionally. Systemic hypersensitivity reactions have been reported rarely.

Cetrorelix should not be used in patients with moderate to severe renal or hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cetrorelix as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

The bioavailability of cetrorelix after subcutaneous injection is about 85%. The mean terminal half-life after a subcutaneous injection of 3 mg is about 60 hours; it is less with lower doses (about 5 and 20 hours respectively after single and multiple doses of 250 micrograms).

References.

1. Pechstein B, *et al.* Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 266–74.
2. Nagaraja NV, *et al.* Pharmacokinetic and pharmacodynamic modeling of cetrorelix, an LH-RH antagonist, after subcutaneous administration in healthy premenopausal women. *Clin Pharmacol Ther* 2000; **68:** 617–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cetrotide; ***Austral.***: Cetrotide; ***Austria***: Cetrotide; ***Belg.***: Cetrotide; ***Braz.***: Cetrotide; ***Canad.***: Cetrotide; ***Chile***: Cetrotide†; ***China***: Cetrotide (思则凯); ***Cz.***: Cetrotide; ***Denm.***: Cetrotide; ***Fin.***: Cetrotide; ***Fr.***: Cetrotide; ***Ger.***: Cetrotide†; ***Gr.***: Cetrotide; ***Hong Kong***: Cetrotide; ***Hung.***: Cetrotide; ***India***: Cetrotide; Ovurelix; ***Indon.***: Cetrotide; ***Irl.***: Cetrotide; ***Israel***: Cetrotide; ***Ital.***: Cetrotide; ***Malaysia***: Cetrotide; ***Mex.***: Cetrotide; ***Neth.***: Cetrotide; ***Norw.***: Cetrotide; ***NZ***: Cetrotide; ***Philipp.***: Cetrotide; ***Pol.***: Cetrotide; ***Port.***: Cetrotide; ***Rus.***: Cetrotide (Цетротид); ***S.Afr.***: Cetrotide; ***Singapore***: Cetrotide; ***Spain***: Cetrotide; ***Swed.***: Cetrotide; ***Switz.***: Cetrotide; ***Thai.***: Cetrotide; ***Turk.***: Cetrotide; ***UK***: Cetrotide; ***USA***: Cetrotide; ***Venez.***: Cetrotide.

Chlormadinone Acetate *(BANM, USAN, rINNM)*

Acetato de clormadinona; Chlormadinone, Acétate de; Chlormadinoni Acetas; Clormadinona, acetato de; NSC-92338; Хлормадинона Ацетат.

6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate.

$C_{23}H_{29}ClO_4$=404.9

CAS — 1961-77-9 (chlormadinone); 302-22-7 (chlormadinone acetate).

ATC — G03DB06.

ATC Vet — QG03DB06.

UNII — 0SY050L61N.

Pharmacopoeias. In *Chin.*, *Fr.*, and *Jpn.*

Uses and Administration

Chlormadinone acetate is a progestogen structurally related to progesterone (p. 2300.2) that has anti-androgenic activity. It is given either alone or with an oestrogen in the treatment of menstrual disorders such as menorrhagia (p. 2300.3) and endometriosis (p. 2264.1) in oral doses of 2 to 10 mg daily either cyclically or continuously. It may also be used as the progestogen component of combined oral contraceptives (see p. 2231.3) at a dose of 1 to 2 mg daily, particularly in women with androgen-dependent conditions such as acne and hirsutism. Chlormadinone acetate has been used in some countries in the management of prostatic hyperplasia and prostate cancer; oral doses of 25 or 50 mg, respectively have been given twice daily.

Reviews.

1. Curran MP, Wagstaff AJ. Ethinylestradiol/chlormadinone acetate. *Drugs* 2004; **64:** 751–60.
2. Bouchard P. Chlormadinone acetate (CMA) in oral contraception—a new opportunity. *Eur J Contracept Reprod Health Care* 2005; **10** (suppl 1): 7–11.
3. Schramm G, Heckes B. Switching hormonal contraceptives to a chlormadinone acetate-containing oral contraceptive: the Contraceptive Switch Study. *Contraception* 2007; **76:** 84–90.
4. Druckmann R. Profile of the progesterone derivative chlormadinone acetate - pharmocodynamic [sic] properties and therapeutic applications. *Contraception* 2009; **79:** 272–81.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Effects on the skin. A report of auto-immune dermatitis in a patient associated with chlormadinone acetate.[1]

1. Katayama I, Nishioka K. Autoimmune progesterone dermatitis with persistent amenorrhoea. *Br J Dermatol* 1985; **112:** 487–91.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Luteran; ***Jpn***: Prostal; ***Mex.***: Lutoral.

Multi-ingredient Preparations. ***Austria***: Balanca; Belara; Madinette; ***Braz.***: Belara; ***Chile***: Belara; Gynorelle; Lovinda; ***Cz.***: Belara; Clormetin; Egretta; Esete; Larabel†; Madinelle; ***Fr.***: Belara; ***Ger.***: Balanca†; Belara; Bellissima; Chariva; Enriqa; Esticia†; Madinette; Minette; Neo-Eunomin; Pink Luna; Verana; ***Hung.***: Belara; ***Israel***: Belara; ***Ital.***: Belara; Lybella; ***Mex.***: Belara; Lutoral-E; Secuentex-21; ***Pol.***: Madinette; ***Port.***: Belara; Libeli; ***Rus.***: Belara (Белара); ***Spain***: Balianca; Belara; Elynor; ***Switz.***: Belara; Belarina; Ladonna; Madinette; Tyarena; ***Thai.***: Belara; ***Turk.***: Belara; ***Ukr.***: Belara (Белара); ***Venez.***: Belara.

Chlorotrianisene *(BAN, rINN)*

Chlorotrianisène; Chlorotrianisenum; Clorotrianiseno; Kloortitraniseeni; Klortrianisen; NSC-10108; Tri-*p*-anisylchloroethylene; Хлоротрианизен.

Chlorotris(4-methoxyphenyl)ethylene.

$C_{23}H_{21}ClO_3$=380.9

CAS — 569-57-3.

ATC — G03CA06.

ATC Vet — QG03CA06.

UNII — 6V5034L121.

Pharmacopoeias. In *Chin.*

Profile

Chlorotrianisene is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (p. 2267.3). It has a prolonged action, and has been given orally for the treatment of menopausal symptoms, female hypogonadism, and prostatic carcinoma.

Chorionic Gonadotrophin

(BAN, rINN) ⊗

CG; Choriogonadotrophin; Chorionic Gonadotropin; Chorioninis gonadotropinas; Coriogonadotrofina; Coriogonadotropina; Gonadotrofina coriónica; Gonadotrofina coriónica humana; Gonadotrophine Chorionique; Gonadotrophinum Chorionicum; Gonadotropin choriový; Gonadotropina coriónica; Gonadotropina coriónica humana; Gonadotropine chorionique; Gonadotropinum Chorionicum; HCG; Human Chorionic Gonadotrophin; Koriongonadotropiini; Korion-gonadotropin; Koriongonadotropin; Koriyonik Gonadotrofin; Pregnancy-urine Hormone; PU; Гонадотропин Хорионический.

CAS — 9002-61-3.

ATC — G03GA01.

ATC Vet — QG03GA01.

UNII — 20ED16GHEB (human chorionic gonadotrophin).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Gonadotrophin, Chorionic). A dry preparation of placental glycoproteins extracted from the urine of pregnant women. The potency is not less than 2500 units/mg. A white to yellowish-white, amorphous powder. Soluble in water. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Chorionic Gonadotropin). A gonad-stimulating polypeptide hormone obtained from the urine of pregnant women. It has a potency of not less than 1500 USP units/mg. A white or practically white, amorphous powder. Freely soluble in water. Store in airtight containers at 2 degrees to 8 degrees.

Choriogonadotropin Alfa *(BAN, USAN, rINN)* ⊗

Choriogonadotropine Alfa; Choriogonadotropinum Alfa; Coriogonadotropina alfa; Хориогонадотропин Альфа.

CAS — 177073-44-8 (choriogonadotropin alfa); 56832-30-5 (α subunit); 56832-34-9 (β subunit).

ATC — G03GA08.

ATC Vet — QG03GA08.

UNII — 6413W06WR3.

Uses and Administration

Chorionic gonadotrophin is a hormone produced by the placenta and obtained from the urine of pregnant women. Its effects are mainly those of the gonadotrophin, luteinising hormone (p. 2287.1), which is responsible for triggering ovulation and formation of the corpus luteum in women, and stimulates the production of testosterone by the testes in men. It is usually given by intramuscular injection although the subcutaneous route has also been used. Choriogonadotropin alfa is a recombinant form of chorionic gonadotrophin.

In *women* with **anovulatory infertility** due to absent or low concentrations of gonadotrophins, chorionic gonadotrophin is given to induce ovulation after follicular development has been stimulated with follicle-stimulating hormone or human menopausal gonadotrophins. A single dose of 5000 to 10 000 units of chorionic gonadotrophin is given by intramuscular injection to mimic the midcycle peak of luteinising hormone which normally stimulates ovulation. Chorionic gonadotrophin is also used with follicle stimulation as an adjunct to IVF procedures and other assisted conception techniques involving superovulation and oocyte collection. A further 2 or 3 injections of 1000 to 3000 units may be given for luteal support in the 9 days after ovulation or embryo transfer.

Choriogonadotropin alfa is used similarly to induce ovulation in the treatment of anovulatory infertility, or as an adjunct to IVF procedures and other assisted conception techniques. A single dose of 250 micrograms is given, by subcutaneous injection, when optimal stimulation of follicular growth is achieved.

Chorionic gonadotrophin is also given for *male* infertility associated with hypogonadotrophic **hypogonadism**. There is considerable variation between dosage regimens, and doses have ranged from 500 to 4000 units two or three times weekly by intramuscular injection. A drug with follicle-stimulating activity such as menotrophin is often added to enable normal spermatogenesis.

For the use of chorionic gonadotrophin in children, see below.

Administration in children. Chorionic gonadotrophin may be used in various conditions in boys, including cryptorchidism and delayed puberty, and in tests of testicular function (see below).

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with chorionic gonadotrophin is widely used for cryptorchidism (p. 2252.1). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, which may act as a predictor of future fertility.[3] Chorionic gonadotrophin may also be used as an adjuvant before surgery, to render the testes palpable,[4] but changes suggestive of inflammation in the testis have been reported after such treatment.[5]

Treatment should be given before puberty. The dose of chorionic gonadotrophin will depend on weight and age, and recommended regimens vary widely between different licensed products as well as clinical guidelines. In general, doses may range from 500 to 4000 units three times weekly by intramuscular injection, and may be given for 3 to 6 weeks or possibly longer.

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (update March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf (accessed 23/10/09)
4. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10-year experience. *J Urol (Baltimore)* 1996; **156:** 804–6.
5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19:** 293–8.

Delayed puberty. Use of chorionic gonadotrophin may be appropriate in boys with delayed puberty due to hypogonadotrophic hypogonadism (p. 2252.1). An initial dose of 500 units may be given twice weekly by intramuscular injection, and the dose should be titrated against the plasma-testosterone concentration. Doses up to 1500 units twice weekly for at least 6 months may be used.

Infertility. In women with anovulatory infertility chorionic gonadotrophin and choriogonadotropin alfa can be used to provoke ovulation and provide luteal support once maturation of a suitable number of follicles has been stimulated by other means. They are used similarly in the various protocols for assisted reproduction. However, use is not recommended for assisted reproduction in patients at risk of ovarian hyperstimulation, such as those with polycystic ovary syndrome. In men with hypogonadotrophic hypogonadism chorionic gonadotrophin is used to stimulate and maintain spermatogenesis. The management of male and female infertility, including the role of chorionic gonadotrophin, is discussed on p. 2253.1.

Malignant neoplasms. Control of Kaposi's sarcoma (p. 718.1) has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but regrowth occurred when dosage was reduced or withdrawn.[1] Another study, using lower doses, was stopped due to toxicity and lack of benefit,[2] but others have confirmed benefit after intralesional injection.[3] There is some suggestion that preparations vary in their activity against the tumour and that it is not chorionic gonadotrophin itself, but some impurity (perhaps a ribonuclease[4] or the degradation product of the β-subunit[5]), that is the active principle.[3,6,7] Some contaminants may have a stimulant effect on the neoplasm, which might also contribute to the variable results.[5]

1. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. *Lancet* 1995; **346:** 118–19.
2. Bower M, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346:** 642.
3. Gill PS, *et al.* The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. *N Engl J Med* 1996; **335:** 1261–9. Correction. *ibid.* 1997; **336:** 1115.
4. Griffiths SJ, *et al.* Ribonuclease inhibits Kaposi's sarcoma. *Nature* 1997; **390:** 568.
5. Simonart T, *et al.* Treatment of Kaposi's sarcoma with human chorionic gonadotropin. *Dermatology* 2002; **204:** 330–3.
6. Gill PS, *et al.* Intralesional human chorionic gonadotropin for Kaposi's sarcoma. *N Engl J Med* 1997; **336:** 1188.
7. von Overbeck J, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346:** 642–3.

Obesity. A meta-analysis[1] involving 24 studies concluded that there was no evidence that chorionic gonadotrophin was effective in the treatment of obesity (p. 2315.1).

1. Lijesen GKS, *et al.* The effect of human chorionic gonadotropin (HCG) in the treatment of obesity by means of the Simeons therapy: a criteria-based meta-analysis. *Br J Clin Pharmacol* 1995; **40:** 237–43.

Testicular function. Chorionic gonadotrophin is used in the assessment of testicular function in suspected primary hypogonadism and incomplete masculinisation. Although unlicensed for this use in the UK, the *BNFC* states that for children aged 1 month to 18 years a dose of 1500 to 2000 units may be given intramuscularly once daily for 3 days (short stimulation test) or twice weekly for 3 weeks (prolonged test).

Adverse Effects and Precautions

Adverse effects that have been reported with chorionic gonadotrophin include headache, tiredness, changes in mood, depression, restlessness, oedema (especially in males), and pain on injection. Treatment for cryptorchidism may produce premature epiphyseal closure or precocious puberty. Gynaecomastia has been reported. Ovarian hyperstimulation may occur, with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock, and thromboembolic disorders in severe cases.

Chorionic gonadotrophin should be given with care to patients in whom androgen-induced fluid retention might be a hazard as in asthma, epilepsy, migraine, or cardiovascular disorders, including hypertension, or renal disorders. Hypersensitivity reactions may occur and it is recommended that patients suspected to be susceptible should be given skin tests before treatment. It should not be given to patients with disorders that might be exacerbated by androgen release such as carcinoma of the prostate or precocious puberty. Use should also be avoided in the presence of breast, uterine, ovarian, and testicular tumours, as well as tumours of the hypothalamus, pituitary, thyroid, and adrenal glands.

Pharmacokinetics

Peak concentrations of chorionic gonadotrophin occur about 6 hours after an intramuscular dose and 16 to 20 hours after a subcutaneous injection. It is distributed mainly to the gonads. Blood concentrations decline in a biphasic manner, with half-lives of about 6 to 11 hours and 23 to 38 hours, respectively. Chorionic gonadotrophin is metabolised mainly in the kidneys. About 10 to 12% of an intramuscular dose is excreted in urine within 24 hours.

After subcutaneous doses, choriogonadotropin alfa has a bioavailability of about 40%. It is metabolised and excreted similarly to chorionic gonadotrophin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dinaron; Endocorion; Gonacor; Ovidrel; Pregnyl; ***Austral.***: Ovidrel; Pregnyl; Profasi†; ***Austria***: Ovitrelle; Pregnyl; ***Belg.***: Choragon; Ovitrelle; Pregnyl; ***Braz.***: Choriomon; Ovidrel; Pregnyl; Profasi HP†; ***Canad.***: Ovidrel; Pregnyl; Profasi HP†; ***Chile***: Gonacor; Ovidrel; Pregnyl; ***China***: Ovidrel (艾泽); Pregnyl (波热尼乐); ***Cz.***: Ovitrelle; Pregnyl; ***Denm.***: Ovitrelle; Pregnyl; ***Fin.***: Ovitrelle; Pregnyl; ***Fr.***: Ovitrelle; ***Ger.***: Brevactid; Choragon†; Ovitrelle; Predalon; ***Gr.***: Ovitrelle; Pregnyl; Profasi; ***Hong Kong***: Choragon; Ovidrel; Pregnyl; Profasi†; ***Hung.***: Choragon; Ovitrelle; Pregnyl; ***India***: Choragon; Choriolife; Choriomon; Corion; Corlova; Fergonad-C; Fertigyn; Huchogon; Hucog; Humunis; LG IVF-C; Materna HCG; Origin; Ovidac; Ovidrel; Ovulate-C; Ovumax-HP; Ovutrig-HP; Profasi; Proligon; Provigil; Pubergen; ***Indon.***: Ovidrel; Pregnyl; ***Irl.***: Ovitrelle; Pregnyl; Profasi†; ***Israel***: Ovitrelle; Pregnyl; ***Ital.***: Gonasi HP; Ovitrelle; Pregnyl; ***Malaysia***: Choragon†; Ovidrel; Pregnyl; ***Mex.***: Choragon; Choriomon; Ovidrel; Pregnyl; ***Neth.***: Choragon; Ovitrelle; Pregnyl; ***Norw.***: Ovitrelle; Pregnyl; ***NZ***: Ovidrel; Pregnyl; Profasi; ***Philipp.***: Ovidrel; Pregnyl; ***Pol.***: Choragon; Ovitrelle; Pregnyl; ***Port.***: Ovitrelle; Pregnyl; ***Rus.***: Choragon (Хорагон); Ecostimulin (Экостимулин); Ovitrelle (Овитрель); Pregnyl (Прегнил); ***S.Afr.***: APL†; Ovidrel; Pregnyl; Profasi; ***Singapore***: Ovidrel; Pregnyl; Profasi; ***Spain***: Ovitrelle; ***Swed.***: Ovitrelle; Pregnyl; ***Switz.***: Choriomon; Ovitrelle; Pregnyl; ***Thai.***: IVF-C; Ovidrel; Pregnyl; ***Turk.***: Choragon; Ovitrelle; Pregnyl; Profasi; ***UK***: Choragon; Ovitrelle; Pregnyl; ***Ukr.***: Choragon (Хорагон); Pregnyl (Прегнил); ***USA***: Choron†; Gonic†; Novarel; Ovidrel; Pregnyl; Profasi†; ***Venez.***: Ovidrel; Pregnyl.

Multi-ingredient Preparations. ***Mex.***: Gonakor.

Pharmacopoeial Preparations

BP 2014: Chorionic Gonadotrophin Injection;
USP 36: Chorionic Gonadotropin for Injection.

Clomifene Citrate (BANM, rINNM) ⊗

Chloramiphene Citrate; Citrato de clomifeno; Citrato de cloramifeno; Clomifencitrat; Clomifène, citrate de; Clomifeni Citras; Clomifeno, citrato de; Clomiphene Citrate (USAN); Clomiphene Citrate; Klomifeenisitraatti; Klomifen Sitrat; Klomifencitrat; Klomifen-citrát; Klomifén-citrát; Klomifeno citratas; MER-41; MRL-41; NSC-35770; Кломифена Цитрат.

A mixture of the *E* and *Z* isomers of 2-[4-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate.

$C_{26}H_{28}ClNO,C_6H_8O_7$=598.1

CAS — 911-45-5 (clomifene); 15690-57-0 ((E)-clomifene); 15690-55-8 ((Z)-clomifene); 50-41-9 (clomifene citrate); 7599-79-3 ((E)-clomifene citrate); 7619-53-6 ((Z)-clomifene citrate).

ATC — G03GB02.

ATC Vet — QG03GB02.

UNII — 1B8447E7YI (clomifene citrate); UY5X264QZV ((Z)-clomifene citrate).

NOTE. Clomifene may be separated into its *Z*-and *E*-isomers, zuclomifene and enclomifene.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Clomifene Citrate). A white or pale yellow, crystalline powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Clomiphene Citrate). A white to pale yellow, essentially odourless powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water and in chloroform; sparingly soluble in alcohol; insoluble in ether; freely soluble in methyl alcohol.

Uses and Administration

Clomifene is a nonsteroidal compound that has both oestrogenic and anti-oestrogenic properties, the latter residing mainly in the *E*-isomer. Its action in stimulating ovulation is believed to be related to its anti-oestrogenic properties. It stimulates the secretion of pituitary gonadotrophic hormones, probably by blocking the negative feedback effect of oestrogens at receptor sites in the hypothalamus and pituitary.

Clomifene is used in the treatment of anovulatory infertility (p. 2253.1). Therapy with clomifene will not be successful unless the woman, though anovulatory, is capable of ovulation and her partner is fertile. It is ineffective in primary pituitary or primary ovarian failure. The usual oral dose is 50 mg of clomifene citrate daily for 5 days, starting on or about the fifth day of the menstrual cycle or at any time if there is amenorrhoea. Ovulation is expected to occur about 5 to 10 days after a course of clomifene, and coitus should be timed to coincide with this. If ovulation does not occur, a course of 100 mg daily for 5 days may be given starting as early as 30 days after the previous one. Women should be examined for pregnancy and ovarian enlargement or cysts between treatment cycles. In general, 3 courses of therapy are adequate to assess whether ovulation is obtainable. If ovulation has not occurred, the diagnosis should be re-evaluated. Once ovulation is established, each treatment cycle of clomifene should be started on or about the fifth day of the menstrual cycle. If pregnancy has not occurred within 3 ovulatory cycles, further treatment is not recommended. A maximum of 6 cycles in total is generally advised (see also Carcinogenicity, below).

Clomifene has been used in the treatment of male infertility due to oligospermia to stimulate gonadotrophin release and enhance spermatogenesis, but there is limited convincing evidence of benefit.

Infertility. Reviews.

1. Homburg R. Clomiphene citrate—end of an era? a mini-review. *Hum Reprod* 2005; **20:** 2043–51.
2. Cèdrin-Durnerin I. Contre l'utilisation d u citrate de clomifène dans les infertilités inexpliquées. *Gynecol Obstet Fertil* 2006; **34:** 61–5.
3. Merviel P. Pour une utilisation raisonnable du citrate de clomifène dans les infertilitiés inexpliquées. *Gynecol Obstet Fertil* 2006; **34:** 66–9.
4. The Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril* 2006; **86** (5 suppl): S187–S193.

Adverse Effects

The incidence and severity of adverse effects of clomifene citrate tend to be related to the dose used. The most commonly reported adverse effects are reversible ovarian enlargement and cyst formation, vasomotor flushes resembling menopausal symptoms, and abdominal or pelvic discomfort or pain, sometimes with nausea or vomiting. Ovarian hyperstimulation syndrome has occurred. Breast tenderness, abnormal uterine bleeding, weight gain, headache, and endometriosis have also been reported. Transient visual disturbances such as spots or flashes, after-images, and blurring of vision may occur, and there have been rare reports of cataracts and optic neuritis. Skin reactions such as allergic rashes and urticaria have occasionally been reported and reversible hair loss has been reported rarely. CNS disturbances have included convulsions, dizziness, lightheadedness, nervous tension, fatigue, vertigo, insomnia, and depression. Abnormalities in liver function tests and jaundice have sometimes been reported.

There is an increased risk of multiple births with clomifene therapy, but rarely more than twins. There is also an increased risk of ectopic pregnancy. Although there have been reports of congenital disorders such as neural tube defects or Down's syndrome in infants born to women treated with clomifene, the role of the drug in the causation of these defects has not been established and the incidence is reported to be similar to that for the general population.

Carcinogenicity. There have been several reports suggesting an association between drug therapy to treat infertility by stimulating ovulation and the subsequent development of ovarian cancer.[1-5] Concern has focused in particular on the use of clomifene citrate and gonadotrophins, and a study has reported an increased risk of ovarian cancer in women who had prolonged clomifene therapy (for one year or more) although not in those who received the drug for a shorter period.[6] No association between gonadotrophin therapy and ovarian cancer was noted in this study. The conclusions of this study were only tentative, since the numbers who developed ovarian cancer were small; it has been pointed out that a successfully achieved pregnancy may reduce the risk of some other cancers, and that the risks and benefits of the procedure are not easy to balance.[7] A review[8] of epidemiological and cohort studies concluded that clomifene was not associated with any increase in the risk of ovarian cancer when used for less than 12 cycles, but noted conflicting results, limitations of the data, and the need to control for infertility and nulliparity as risk factors for ovarian cancer. Further cohort[9,10] and case-control[11] studies, and pooled analyses,[12,13] have also found no association between use of clomifene and ovarian cancer.

As a matter of prudence the UK CSM has recommended that clomifene should not normally be used for more than 6 cycles.[14] UK guidelines on the management of infertility[15] also recommend that clomifene should be used for a maximum of 6 months.

1. Fishel S, Jackson P. Follicular stimulation for high tech pregnancies: are we playing it safe? *BMJ* 1989; **299:** 309–11.
2. Kulkarni R, McGarry JM. Follicular stimulation and ovarian cancer. *BMJ* 1989; **299:** 740.
3. Dietl J. Ovulation and ovarian cancer. *Lancet* 1991; **338:** 445.
4. Willemsen W, *et al.* Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993; **341:** 986–8.
5. Tewari K, *et al.* Fertility drugs and malignant germ-cell tumour of ovary in pregnancy. *Lancet* 1998; **351:** 957–8.
6. Rossing MA, *et al.* Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994; **331:** 77–6.
7. Whittemore AS. The risk of ovarian cancer after treatment for infertility. *N Engl J Med* 1994; **331:** 805–6.
8. Duckitt K, Templeton AA. Cancer in women with infertility. *Curr Opin Obstet Gynecol* 1998; **10:** 199–203.
9. Potashnik G, *et al.* Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertil Steril* 1999; **71:** 853–9.
10. Brinton LA, *et al.* Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 2004; **103:** 1194–1203.
11. Rossing MA, *et al.* A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; **160:** 1070–8.
12. Ness RB, *et al.* Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002; **155:** 217–24.
13. Kashyap S, *et al.* Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol* 2004; **103:** 785–94.
14. CSM/MCA. Clomiphene (Clomid, Serophene): possible association with ovarian cancer. *Current Problems* 1995; **21:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)
15. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)

Effects on the CNS. An infertile woman had convulsions when given clomifene citrate;[1] only 5 other cases had been reported since 1963.

1. Rimmington MR, *et al.* Convulsions after clomiphene citrate. *BMJ* 1994; **309:** 512.

Effects on the eyes. As mentioned above, clomifene may cause visual disturbances, which resolve on stopping treatment. However, visual symptoms have persisted in a few cases.[1]

1. Purvin VA. Visual disturbance secondary to clomiphene citrate. *Arch Ophthalmol* 1995; **113:** 482–4.

Effects on the fetus. After reports of neural tube defects in fetuses conceived after ovulation induction, analyses of congenital defect registers and follow-up studies of clomifene use suggested that the drug might possibly be associated with an increase in risk.[1-5] However, subsequent studies reported no increased risk,[6-8] and a pooled analysis[9] of 10 epidemiological studies found no strong evidence to confirm an association. Further studies have also reported no increased risk of neural tube defects[10] or hypospadias in male offspring[11] after exposure to fertility treatment. However, another case-control study[12] did find a potential association between clomifene and neural tube defects, but noted that because of the low baseline prevalence of the malformation, the absolute risk difference would be small. It is not clear whether the underlying infertility itself affects the risk of congenital defects and whether it may confound the calculated risk associated with clomifene.[9]

1. Cornel MC, *et al.* Ovulation induction and neural tube defects. *Lancet* 1989; **i:** 1386.
2. Czeizel A. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 167.
3. Cuckle H, Wald N. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 1281.
4. Cornel MC, *et al.* Ovulation induction, in-vitro fertilisation, and neural tube defects. *Lancet* 1989; **ii:** 1530.
5. Vollset SE. Ovulation induction and neural tube defects. *Lancet* 1990; **337:** 178.
6. Mills JL, *et al.* Risk of neural tube defects in relation to maternal fertility and fertility drug use. *Lancet* 1990; **336:** 103–4.
7. Rosa F. Ovulation induction and neural tube defects. *Lancet* 1990; **336:** 1327.
8. Werler MM, *et al.* Ovulation induction and risk of neural tube defects. *Lancet* 1994; **344:** 445–6.
9. Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 1995; **64:** 936–41.
10. Whiteman D, *et al.* Reproductive factors, subfertility, and risk of neural tube defects: a case-control study based on the Oxford Record Linkage Study Register. *Am J Epidemiol* 2000; **152:** 823–8.
11. Sørensen HT, *et al.* Use of clomifene during early pregnancy and risk of hypospadias: population based case-control study. *BMJ* 2005; **330:** 126–7.
12. Wu YW, *et al.* Potential association between infertility and spinal neural tube defects in offspring. *Birth Defects Res A Clin Mol Teratol* 2006; **76:** 718–22.

Effects on mental function. Acute psychotic reactions with paranoid tendencies have occurred rarely during clomifene use.[1,2]

1. Siedentopf F, *et al.* Clomiphene citrate as a possible cause of a psychotic reaction during infertility treatment. *Hum Reprod* 1997; **12:** 706–7.
2. Oyffe I, *et al.* Clomiphene-induced psychosis. *Am J Psychiatry* 1997; **154:** 1169–70.

Precautions

Clomifene is contra-indicated in patients with liver disease or a history of liver dysfunction. It should not be used in pregnancy. Clomifene should not be used in women with uterine bleeding that is undiagnosed or caused by hormone-dependent tumours, or in patients with pre-existing mental depression or thrombophlebitis because of the risk of exacerbation. Patients should be warned of the possibility of multiple births.

Clomifene should not be given to women with ovarian cysts, except those with polycystic ovary syndrome, and the lowest doses possible should be used to minimise ovarian enlargement or cyst formation; some patients with polycystic ovary syndrome may have an exaggerated response to usual doses of clomifene. Patients should be instructed to report any abdominal or pelvic pain, distension, or weight gain, as this may indicate the presence or enlargement of ovarian cysts. They should also be evaluated for the presence of ovarian cysts before each cycle of treatment. If abnormal enlargement occurs, clomifene should not be given until the ovaries have returned to pre-treatment size, and subsequent doses should be reduced. Clomifene should be used with caution in patients with uterine fibroids, due to the potential for enlargement of the fibroids.

Treatment should be stopped if visual disturbances develop and the patient warned that this might affect their ability to drive or operate machinery. Long-term cyclic therapy is not recommended, because of the uncertainty regarding increased risk of ovarian cancer, and a maximum of 6 cycles of treatment is generally advised (see also Carcinogenicity, above).

Pharmacokinetics

Clomifene citrate is absorbed from the gastrointestinal tract. It is metabolised in the liver and slowly excreted via the bile. Unchanged drug and metabolites are excreted in the faeces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Enterohepatic recirculation takes place. The *E*-isomer is reported to be less well absorbed and more rapidly eliminated than the *Z*-isomer.

References.

1. Szutu M, *et al.* Pharmacokinetics of intravenous clomiphene isomers. *Br J Clin Pharmacol* 1989; **27:** 639–40.
2. Ghobadi C, *et al.* Single-dose pharmacokinetic study of clomiphene citrate isomers in anovular patients with polycystic ovary disease. *J Clin Pharmacol* 2009; **49:** 147–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Genozym; Serofene; Tocofeno; ***Austral.***: Clomhexal†; Clomid; Fermil†; Serophene; ***Belg.***:

Clomid; Pergotime; ***Braz.***: Clomid; Indux; Serophene; ***Canad.***: Clomid; Serophene; ***Chile***: Serophene; Zimaquin; ***China***: Fertilan (法地兰); ***Cz.***: Clomhexal†; Clostilbegyt; ***Denm.***: Pergotime; ***Fin.***: Clomifen; ***Fr.***: Clomid; Pergotime; ***Ger.***: Clomhexal†; ***Gr.***: Serpafar; ***Hong Kong***: Clostilbegyt; Fertilan; Ova-Mit†; Serophene; ***Hung.***: Clostilbegyt; ***India***: Clofert; Clomidac; Clomiriv; Clomit; Clopreg; Clowin; Fertifact; Fertik; Fertomid; Ferton; Fertova; Fetrop; Folistim; Fulfyn; Mephy; Omicite; Ovipreg; Ovitec; Ovobel; Ovofar; Ovuclom; Siphene; ***Indon.***: Blesifen; Clomifil†; Clovertil†; Dipthen; Fensipros; Fertilphen; Fertin; Genoclom; Mestrolin†; Ofertil; Pinfetil; Profertil; Provula; ***Irl.***: Clomid; ***Israel***: Ikaclomin; ***Ital.***: Clomid; Prolifen; Serofene; ***Malaysia***: Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate; ***Mex.***: Omifin; ***Neth.***: Clomid; Serophene†; ***Norw.***: Pergotime; ***NZ***: Phenate†; Serophene; ***Philipp.***: Clomene; Clomid; Clostil; Ferticlo; Fertyl; I-Clom; Ova-Mit; Ovulet; Ovulin; ***Pol.***: Clostilbegyt; ***Port.***: Dufine; ***Rus.***: Clostilbegyt (Клостилбегит); ***S.Afr.***: Clomid; Clomihexal; Fertomid; ***Singapore***: Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate; Profertil; Serophene; Sunophene; ***Spain***: Omifin; ***Swed.***: Pergotime; ***Switz.***: Clomid†; Serophene; ***Thai.***: Clomid; Duinum; Ova-Mit; Ovinum; Serophene; ***Turk.***: Fertilin; Gonaphene; Klomen; Serophene; ***UK***: Clomid; ***Ukr.***: Clostilbegyt (Клостилбегит); ***USA***: Clomid; Serophene; ***Venez.***: Serophene.

Multi-ingredient Preparations. ***India***: Ovipro-MF.

Pharmacopoeial Preparations
BP 2014: Clomifene Tablets;
USP 36: Clomiphene Citrate Tablets.

Clostebol Acetate *(BAN, rINNM)* ⊗

Acetato de clostebol; 4-Chlorotestosterone Acetate; Chlortestosterone Acetate; Clostébol, Acétate de; Clostebol, acetato de; Closteboli Acetas; Клостебола Ацетат.
4-Chloro-3-oxoandrost-4-en-17β-yl acetate; 4-Chloro-17β-hydroxyandrost-4-en-3-one acetate.
$C_{21}H_{29}ClO_3$=364.9
CAS — 1093-58-9 (clostebol); 855-19-6 (clostebol acetate).
UNII — 780ZZX4P14.

Profile

Clostebol acetate has anabolic properties (see Testosterone, p. 2305.1) and has been given by intramuscular injection and orally. It has also been applied topically to wounds and ulcers, and has been used as an ophthalmological preparation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Trofodermin†.

Multi-ingredient Preparations. ***Braz.***: Clostemin; Novaderm; Trofodermin; ***Chile***: Trofodermin Neomicina†; ***Ital.***: Trofodermin; ***Mex.***: Neobol.

Conjugated Oestrogens

Conjugated Estrogens; Estrogeenit, konjugoidut; Estrogena Coniugata; Estrogenai, konjuguoti; Estrogener, konjugerade; Estrogènes conjugués; Estrogeni Coniunct; Estrogeni Coniuncti; Estrógenos conjugados; Estrogeny konjugované; Konjugált ösztrogének; Konjüge Östrojen; Эстрогены Конъюгированные.
ATC — G03CA57.
ATC Vet — QG03CA57.
UNII — 1U5QR144QX (conjugated oestrogens); 8CC9ET5H86 (sodium 17β-dihydroequilin sulfate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Estrogens, Conjugated). A mixture of various conjugated forms of oestrogens obtained from the urine of pregnant mares or by synthesis, dispersed in a suitable powdered diluent. It contains two principal components, 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the combined two is 79.5 to 88.0%. It also contains 2.5 to 9.5% of sodium 17α-estradiol sulfate, 13.5 to 19.5% of sodium 17α-dihydroequilin sulfate, and 0.5 to 4.0% of sodium 17β-dihydroequilin sulfate. All percentages are related to the labelled content.

An almost white brownish amorphous powder.

USP 36: (Conjugated Estrogens). A mixture of sodium estrone sulfate and sodium equilin sulfate, derived wholly or in part from equine urine or synthetically from estrone and equilin. It contains other conjugated oestrogenic substances of the type excreted by pregnant mares. It contains 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the two combined should comprise 79.5 to 88.0% of the labelled content of conjugated oestrogens. It should contain, as sulfate conjugates, 13.5 to 19.5% of 17α-dihydroequilin, 2.5 to 9.5% of 17α-estradiol, and 0.5 to 4.0% of 17β-dihydroequilin, relative to the labelled content of conjugated oestrogens.

If it is obtained from natural sources it is a buff-coloured amorphous powder which is odourless or has a slight characteristic odour; the synthetic form is a white to light buff-coloured crystalline or amorphous powder, odourless or with a slight odour. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Synthetic Conjugated Estrogens, A

Synthetic Conjugated Oestrogens, A; Синтетические Конъюгированные Эстрогены, А.
UNII — JM2621P2LS.

Synthetic Conjugated Estrogens, B *(USAN)*

CE-10; Synthetic Conjugated Oestrogens, B; Синтетические Конъюгированные Эстрогены, В.
CAS — 746658-13-9.
UNII — 8L6LAK9BTR.

Uses and Administration

Conjugated oestrogens have actions and uses similar to those described for estradiol (see p. 2271.2).

When used as menopausal HRT (p. 2244.2) doses of 0.3 to 1.25 mg daily are given orally either cyclically or continuously; in women with a uterus a progestogen is also given either cyclically or continuously. Doses of 0.3 to 1.25 mg may also be used for the prevention of postmenopausal osteoporosis, but oestrogen therapy is generally reserved for women who are at significant risk and who cannot be given non-hormonal treatment. Topical vaginal therapy may be used specifically for menopausal atrophic vaginitis, atrophic urethritis, and kraurosis vulvae; 0.5 to 2 g of a 0.0625% cream may be used daily for 3 weeks of a 4-week cycle. For moderate to severe dyspareunia associated with menopausal vulvar and vaginal atrophy, a topical vaginal dose of 0.5 g may be used twice weekly in a continuous regimen, or daily for 3 weeks of a 4-week cycle. In women with an intact uterus, the endometrial safety of topical oestrogen therapy is uncertain. The addition of a progestogen should be considered, although it might not be required during low-dose, short-term topical oestrogen treatment. During long-term therapy, these women should be monitored for evidence of endometrial hyperplasia, whether or not a progestogen is also used.

When given as replacement therapy on a cyclical basis, oral doses of 1.25 mg daily are used for primary ovarian failure, adjusted according to response. Doses of 300 to 625 micrograms daily are usually given for female hypogonadism, although higher doses were formerly used.

For the palliative treatment of prostatic carcinoma (p. 712.3), an oral dose of 1.25 to 2.5 mg three times daily has been used. A dose of 10 mg three times daily for at least 3 months has been used for palliative treatment of breast carcinoma in men (p. 704.1) and postmenopausal women (p. 702.1).

Abnormal uterine bleeding has been treated acutely by giving 25 mg of conjugated oestrogens by slow intravenous injection, repeated if required after 6 to 12 hours; the intramuscular route has also been used.

Synthetic conjugated oestrogens are derived from plant material, and are not a generic equivalent of Conjugated Estrogens described in USP 36 (see above). Synthetic conjugated estrogens, A, contains a mixture of nine derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.45 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. An oral dose of 300 micrograms daily may be used for menopausal vulvar and vaginal atrophy, but an alternative, topical therapy should be considered if this is the only symptom being treated. For local management of moderate to severe vaginal dryness or dyspareunia associated with menopausal vulvar and vaginal atrophy, 1 g of a 0.0625% vaginal cream may be used daily for 1 week followed by 1 g twice weekly. As for vaginal conjugated oestrogens, above, the addition of a progestogen should be considered for women with a uterus. Synthetic conjugated estrogens, B, contains a mixture of ten derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.3 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. An oral dose of 300 micrograms daily may be used for relief of symptoms associated with menopausal vulvar and vaginal atrophy, but an alternative, topical therapy should be considered if this is the only symptom being treated.

Administration in children. Conjugated oestrogens have been used to reduce final height in girls with constitutional tall stature (see Growth Disorders, under Estradiol, p. 2272.2). They have also been used in children for some haemorrhagic disorders (below).

Haemorrhagic disorders. Case reports and small studies have described the use of high-dose conjugated oestrogens in the management of haemorrhagic disorders associated with renal failure,[1-5] although it is unclear how oestrogens might reduce prolonged bleeding times in these patients.[6] Treatment has been given orally, but an intravenous dose of 600 micrograms/kg given over 30 to 40 minutes, once daily for 5 days, has been reported most often.[6]

Conjugated oestrogens have also been used in various doses in the management of haemorrhagic cystitis (p. 2347.3), particularly that caused by high-dose cyclophosphamide therapy (p. 772.3). The successful use of 25 mg intravenously for 2 consecutive days has been reported,[7] as has a regimen consisting of a 1 mg/kg intravenous dose followed by 5 mg orally for 3 weeks.[8] A report[9] of treatment in 10 patients described the use of oral conjugated oestrogens in doses of 6 to 12 mg daily, usually in three divided doses, for durations of 5 days to 16 weeks.[9] Another report[10] of therapy in 10 children aged between 8 and 19 years described intravenous doses of 12.5 to 50 mg twice daily, often for 2 or 3 days, followed by oral doses ranging from 2.5 mg twice daily to 5 mg four times daily for durations of a few days to about 3 weeks.

Oestrogens have also been used in the treatment of other bleeding disorders (see Estradiol, p. 2272.2).

1. Liu YK, *et al.* Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 1984; **ii:** 887–90.
2. Livio M, *et al.* Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986; **315:** 731–5.
3. Seth S, Geier TM. Use of conjugated estrogens to control gastrointestinal tract bleeding in two patients with chronic renal failure. *Clin Pharm* 1988; **7:** 906–9.
4. Shemin D, *et al.* Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med* 1990; **89:** 436–40.
5. Heunisch C, *et al.* Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998; **18:** 210–7.
6. Hedges SJ, *et al.* Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007; **3:** 138–53.
7. Kopterides P, *et al.* Cyclophosphamide-induced hemorrhagic cystitis successfully treated with conjugated estrogens. *Am J Hematol* 2005; **80:** 166–7.
8. Rodriguez Luna JM, *et al.* Control of massive hematuria in idiopathic hemorrhagic cystitis after administration of conjugated estrogen. *J Urol (Baltimore)* 1992; **148:** 1524–5.
9. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen–report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25:** 981–5.
10. Heath JA, *et al.* Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. *Bone Marrow Transplant* 2006; **37:** 523–6.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormone Replacement Therapy, p. 2246.3 and p. 2250.1.

Effects on the cardiovascular system. In an early study of *men* with a previous myocardial infarction, treatment with conjugated oestrogens 5 mg daily was stopped because of a higher incidence of subsequent coronary events.[1] Moreover, treatment with the lower 2.5 mg dose was later also stopped because of suggestions of adverse trends including a greater incidence of venous thromboembolism.[2]

For the cardiovascular effects of HRT, including conjugated oestrogens, in women, see p. 2248.2.

1. Coronary Drug Project Research Group. The Coronary Drug Project: initial findings leading to modifications of its research protocol. *JAMA* 1970; **214:** 1303–13.
2. Coronary Drug Project Research Group. The Coronary Drug Project: findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 1973; **226:** 652–7.

Effects on the nervous system. Reversible chorea has been described in 2 women given conjugated oestrogens with a progestogen as postmenopausal HRT;[1,2] in 1 case the patient had a history of migraine and Sydenham's chorea.[1] Chorea also recurred in a postmenopausal woman with a history of chorea gravidarum when she was given vaginal conjugated oestrogens.[3]

1. Steiger MJ, Quinn NP. Hormone replacement therapy induced chorea. *BMJ* 1991; **302:** 762.
2. Suchowersky O, Muthipeedika J. A case of late-onset chorea. *Nat Clin Pract Neurol* 2005; **1:** 113–16.
3. Caviness JN, Muenter MD. An unusual cause of recurrent chorea. *Mov Disord* 1991; **6:** 355–7.

Hypersensitivity. An anaphylactic reaction after intravenous conjugated oestrogens has been reported.[1]

1. Searcy CJ, *et al.* Anaphylactic reaction to intravenous conjugated estrogens. *Clin Pharm* 1987; **6:** 74–6.

Interactions

See under Hormone Replacement Therapy, p. 2251.1.

Pharmacokinetics

Conjugated oestrogens taken orally are hydrolysed by enzymes present in the intestine that remove the sulfate group and allow absorption of the unconjugated oestrogen.

Metabolism occurs mainly in the liver; there is some enterohepatic recycling (see also under Estradiol, p. 2273.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Belestar; Livomarin; Premarin; ***Austral.***: Premarin; ***Braz.***: Estrinolon; Estrogenon; Estroplus; Gestrocon; Menoprin; Prem; Premarin; Repogen; ***Canad.***: Apo-Conest†; CES; Congest; Premarin; ***Chile***: Climatrol E; Conpremin; Estrarona; Profemina†; ***China***: Premarin (倍美力); ***Ger.***: Climopax mono; Presomen; ***Gr.***: Premarin; ***Hong Kong***: Equin; Premarin; ***India***: Espauz; Estrin; Premarin; ***Irl.***: Premarin; ***Israel***: Estrogenus; ***Malaysia***: Premarin; ***Mex.***: DNA-EC; Equifan; Esonovag; Fahifem; Neradin; Premarin; Six Din; Sultrona; Terapova; ***Neth.***: Dagynil; ***NZ***: Premarin; ***Philipp.***: Menpoz†; Premarin; Primax; ***S.Afr.***: Premarin; ***Singapore***: Equin; Premarin; ***Spain***: Equin†; ***Thai.***: Estromon; Premarin; ***Turk.***: Premarin; ***UK***: Premarin; ***USA***: Cenestin; Enjuvia; Premarin; ***Venez.***: Biostrogen; Climatrol E; Menostat; Premarin.

Multi-ingredient Preparations. ***Austral.***: Premia Continuous; Premia†; ***Braz.***: Menotensil; Premelle Ciclo; Premelle; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Conti; Selecta; ***Canad.***: Premplus; ***Chile***: Climatrol Continuo†; Climatrol HT Continuo; Climatrol HT†; Conpremin Pak Plus†; Conpremin Pak†; Novafac 30; Novafac CC; Novafac†; Profemina MP†; ***China***: Premelle (倍美罗); ***Ger.***: Climopax Cyclo; Climopax; Presomen Compositum; Presomen conti; ***Gr.***: Premelle Cycle; Premelle; ***Hong Kong***: Premelle Cycle†; Premelle; ***India***: Conjugase; ***Irl.***: Premique Cycle; Premique; Prempak-C; ***Ital.***: Premelle Combinato†; Premia; ***Malaysia***: Premelle; ***Mex.***: Premelle; ***NZ***: Premia Continuous; ***Philipp.***: Premelle Cycle; Premelle; ***S.Afr.***: Premelle Cycle; Premelle; Prempak N†; ***Singapore***: Premelle Cycle; Premelle; Prempak-C†; ***Turk.***: Premelle Cycle; Premelle†; ***UK***: Premique Cycle†; Premique; Prempak-C; ***USA***: Duavee; Premphase; Prempro; ***Venez.***: Climatrol HT Ciclico; Climatrol HT Continuo; Premelle Continuo.

Pharmacopoeial Preparations
USP 36: Conjugated Estrogens Tablets.

Corifollitropin Alfa *(BAN, USAN, rINN)*

Corifolitropina alfa; Corifollitropine Alfa; Corifollitropinum Alfa; FSH-CTP; Org-36286; Корифоллитропин Альфа.

Follicle-stimulating hormone (human α-subunit reduced), complex with follicle-stimulating hormone (human β-subunit reduced) fusion protein with 118-145-chorionic gonadotropin (human β-subunit).

CAS — 195962-23-3.
ATC — G03GA09.
ATC Vet — QG03GA09.
UNII — T7K20Y2GWY.

Uses and Administration

Corifollitropin alfa is a recombinant DNA product that has a prolonged duration of follicle-stimulating activity. It is used with a gonadorelin (gonadotrophin releasing hormone) antagonist for controlled ovarian stimulation, to be used in assisted reproduction techniques in women with anovulatory infertility (see Infertility, p. 2253.1).

Treatment should be started during the early follicular phase of the menstrual cycle.

- On day 1 of a treatment cycle corifollitropin alfa is given as a single subcutaneous injection into the abdominal wall. A dose of 100 micrograms is used for women weighing 60 kg or lighter and 150 micrograms for those heavier than 60 kg.
- Treatment with a gonadorelin antagonist may then be given on day 5 or 6 depending on ovarian response.
- On day 8, usual daily injections of 150 units of a recombinant follicle-stimulating hormone may be started. Adequate follicular development is usually achieved by the ninth day (range 6 to 18 days).
- When adequate follicular development is seen, a single injection of 5000 to 10 000 units of chorionic gonadotrophin is given on the same or next day to induce ovulation.

References.

1. Devroey P, *et al.* Induction of multiple follicular development by a single dose of long-acting recombinant follicle-stimulating hormone (FSH-CTP, corifollitropin alfa) for controlled ovarian stimulation before in vitro fertilization. *J Clin Endocrinol Metab* 2004; **89:** 2062–70.
2. Balen AH, *et al.* Pharmacodynamics of a single low dose of long-acting recombinant follicle-stimulating hormone (FSH-carboxy terminal peptide, corifollitropin alfa) in women with World Health Organization group II anovulatory infertility. *J Clin Endocrinol Metab* 2004; **89:** 6297–6304.
3. Corifollitropin Alfa Dose-finding Study Group. A randomized dose-response trial of a single injection of corifollitropin alfa to sustain multifollicular growth during controlled ovarian stimulation. *Hum Reprod* 2008; **23:** 2484–92.
4. Fauser BCJM, *et al.* Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. *Hum Reprod Update* 2009; **15:** 309–21.
5. Devroey P, *et al.* ENGAGE Investigators. A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. *Hum Reprod* 2009; **24:** 3063–72.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3.

Ovarian response may be greater after corifollitropin alfa than after follicle-stimulating hormone and careful monotoring for signs of ovarian hyperstimulation syndrome is recommended for patients receiving their first cycle of treatment. Use in women with impaired renal function is not recommended.

Pharmacokinetics

Corifollitropin alfa is absorbed after subcutaneous injection with an absolute bioavailability of 58% and peak serum concentrations occur after 44 hours. It is eliminated mainly through the kidneys and has an elimination half-life of 69 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Elonva; ***Austria***: Elonva; ***Belg.***: Elonva; ***Cz.***: Elonva; ***Denm.***: Elonva; ***Ger.***: Elonva; ***Gr.***: Elonva; ***Israel***: Elonva; ***Neth.***: Elonva; ***Norw.***: Elonva; ***Pol.***: Elonva; ***Port.***: Elonva; ***Singapore***: Elonva; ***Spain***: Elonva; ***Swed.***: Elonva; ***UK***: Elonva.

Cyclofenil *(BAN, rINN)* ⊗

Ciclofenilo; Cyclofénil; Cyclofenilum; Cyklofenil; F-6066; H-3452; ICI-48213; Siklofenil; Syklofeniili; Циклофенил.

4,4′-(Cyclohexylidenemethylene)bis(phenyl acetate).

$C_{23}H_{24}O_4$=364.4

CAS — 2624-43-3.
ATC — G03GB01.
ATC Vet — QG03GB01.
UNII — J468V64WZ1.

Profile

Cyclofenil is a nonsteroidal anti-oestrogen that has been used in the treatment of menstrual disturbances and anovulatory infertility due to hypothalamic-pituitary dysfunction.

It has been given orally in doses of 200 mg three times daily for 5 days, in a cyclical regimen for 3 or 4 cycles. It has also been given for menopausal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Menopax; ***Ital.***: Neoclym; ***Turk.***: Fertodur†.

Cyproterone Acetate *(BANM, USAN, rINNM)*

Acetato de ciproterona; Ciproterona, acetato de; Cyproteron-acetát; Ciproterono acetatas; Cyproteronacetat; Cyproteron-acetát; Cyprotérone, Acétate de; Cyproteroni Acetas; NSC-81430; SH-714; SH-881 (cyproterone); Siproteron Asetat; Syproteroniasetaatti; Ципротерона Ацетат.

6-Chloro-1β,2β-dihydro-17α-hydroxy-3′*H*-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione acetate.

$C_{24}H_{29}ClO_4$=416.9

CAS — 2098-66-0 (cyproterone); 427-51-0 (cyproterone acetate).
ATC — G03HA01.
ATC Vet — QG03HA01.
UNII — 4KM2BN5JHF.

NOTE. Compounded preparations of cyproterone acetate may be represented by the following names:

- Co-cyprindiol (*BAN*)—cyproterone acetate 2000 parts and ethinylestradiol 35 parts (w/w).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Cyproterone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone; very soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Uses and Administration

Cyproterone acetate is a progestogen (see Progesterone, p. 2300.2) with anti-androgenic properties.

It is used for the **control of libido** in severe hypersexuality or sexual deviation in men (see Disturbed Behaviour, p. 1030.2). The usual oral dose is 50 mg twice daily after meals. Given by depot intramuscular injection, a dose of 300 mg once every 10 to 14 days has been used to control libido. When a satisfactory effect has been obtained, the dose may be reduced by gradually increasing the interval between injections until a stable maintenance dose is reached.

It is also used for the palliative treatment of **prostatic carcinoma** (p. 712.3), to control the initial disease flare associated with gonadorelin analogue therapy, and to control hot flushes associated with gonadorelin analogues or orchidectomy. In palliative treatment where gonadorelin analogues or surgery are contra-indicated, not tolerated, or where oral therapy is preferred, oral doses of 200 to 300 mg daily are given in 2 or 3 divided doses after meals. For the suppression of disease flare, cyproterone acetate is given orally in a dose of 100 mg twice daily; it is used alone for 5 to 7 days, then with the gonadorelin analogue for 3 to 4 weeks. For the treatment of hot flushes, an oral dose of 50 mg daily is used; this may be increased up to 150 mg daily in 3 divided doses if necessary. In palliative therapy of prostatic carcinoma, 300 mg may be given intramuscularly once every 2 weeks after orchidectomy, or once weekly without orchidectomy.

Cyproterone acetate may be used with ethinylestradiol in women for the control of moderate to severe androgen-dependent **acne**, when topical treatment or systemic antibacterials have failed, and in **hirsutism**. The usual oral doses are 2 mg of cyproterone acetate with 35 micrograms of ethinylestradiol given daily for 21 days of each menstrual cycle; the first treatment course is started on the first day of the menstrual cycle and each subsequent course is started after 7 tablet-free days have followed the preceding course. This regimen also provides contraception, and patients relying on this effect should be given the same advice regarding missed doses and reduced efficacy due to vomiting and diarrhoea as that given for combined oral contraceptives (see p. 2231.3); additional hormonal contraception is not necessary and should not be used. At least 3 months of treatment is generally needed, and the need for continuing therapy should be regularly assessed. Regimens using higher doses may be given in more severe cases of hyperandrogenism. Doses of 50 or 100 mg daily for the first 10 days of the menstrual cycle may be used, with a combined hormonal contraceptive given to stabilise the cycle and avoid pregnancy. The dose should be reduced once there has been a satisfactory response. For other high-dose regimens that have been used, see Acne, below, and Hirsutism, p. 2262.1.

Dose-related hepatotoxicity has occurred with cyproterone, particularly in men treated for prostate cancer (see Effects on the Liver, p. 2262.3, and Precautions, p. 2263.1).

For the use of cyproterone acetate for precocious puberty in children, see p. 2262.2.

Administration in children. Cyproterone acetate may be used in the management of precocious puberty (see p. 2262.2).

Acne. Cyproterone acetate may be used in the management of acne (p. 1682.2) in women with signs of hyperandrogenism. An oral combination of cyproterone acetate 2 mg with ethinylestradiol 35 micrograms, which also provides contraception, is used when the condition is moderate to severe. A systematic review[1] considered that combinations such as this were more effective in the treatment of acne than combined oral contraceptives containing levonorgestrel, but noted that this was based on limited evidence. In more severe disease, higher doses of cyproterone have been added to this low-dose regimen; examples include giving cyproterone acetate 50 mg daily for 10 or 21 days of each cycle.[2]

1. Arowojolu AO, *et al.* Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2012 (accessed 19/12/13).
2. Beylot C, *et al.* Oral contraceptives and cyproterone acetate in female acne treatment. *Dermatology* 1998; **196:** 148–52.

Alopecia. Cyproterone acetate has been tried in the treatment of female-pattern alopecia (p. 1682.3). In premenopausal women, oral doses of 50 or 100 mg daily have usually been given in sequential regimens with an oestrogen or combined oral contraceptive; continuous treatment using 50 mg daily has been given to postmenopausal women. It has generally been considered that women with other signs of hyperandrogenism, such as acne and seborrhoea, as well as hair loss are most likely to benefit from cyproterone but results from small studies have been mixed.[1-3]

1. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; **146:** 992–9.
2. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril* 2003; **79:** 91–5.
3. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; **152:** 466–73.

Gender reassignment. Cyproterone acetate is used for its anti-androgenic effects in male-to-female transsexuals.[1,2]

An oral dose of 50 mg twice daily is usually given with an oestrogen (see Estradiol, p. 2272.2).

1. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
2. Gooren LJ, *et al*. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Hidradenitis suppurativa. Beneficial responses to cyproterone acetate with ethinylestradiol have been seen[1-3] in women with hidradenitis suppurativa, an androgen-dependent disorder of the skin and hair in the pubic and axillary regions.

1. Mortimer PS, *et al*. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986; **115:** 263–8.
2. Sawers RS, *et al*. Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1986; **115:** 269–74.
3. Mortimer PS, *et al*. Mediation of hidradenitis suppurativa by androgens. *BMJ* 1986; **292:** 961.

Hirsutism. Hirsutism is an abnormal growth in females of coarse pigmented terminal hair in an adult male pattern, and is one of the clinical expressions of hyperandrogenism. Most women with hirsutism have increased concentrations of circulating androgens from the ovaries associated with polycystic ovary syndrome (p. 2253.3). However, many women with mild hirsutism have idiopathic hirsutism; they have regular menses and normal serum-androgen concentrations but the hair follicles are more sensitive to the effects of androgens. In rare cases, the adrenal gland is the primary source of increased androgens, for example, in congenital adrenal hyperplasia (p. 1603.2). In a few cases, severe hirsutism is associated with frank virilisation due to massively increased circulating androgen concentrations from an androgen-secreting tumour. Hirsutism is an adverse effect of androgenic progestogens, such as norgestrel, used in hormonal contraceptives and HRT. Androgens and anabolic steroids may also cause hirsutism in females.

Treatment for hirsutism includes cosmetic treatments such as bleaching, shaving, plucking, electrolysis, and laser hair removal, and in the mildest cases this may be all that is required. However, such mechanical means of treatment are more usually combined with drug therapy to prevent further conversion of vellus to terminal hair, and to slow the regrowth of terminal hair, which may become lighter and softer. Because the growth cycle of hair is long, a response to therapy may not be seen for 6 to 12 months.[1-4]

Combined *hormonal contraceptives* containing non-androgenic progestogens are widely used for hirsutism but their effects are generally limited.[1-3] *Drospirenone*, a progestogen used in combined oral contraceptives, has a very weak anti-androgenic effect.[4] The mainstay of oral drug therapy for hirsutism is an anti-androgen, the most commonly used being the steroidal anti-androgens *cyproterone acetate* and *spironolactone*. To increase efficacy (by suppressing ovarian androgen production) and minimise the chance of conception (because of the risk of feminisation of a male fetus), cyclical ethinylestradiol is commonly used with cyproterone acetate. Combined non-androgenic hormonal contraceptives are commonly used with spironolactone, which has no progestogenic activity. Cyproterone acetate may be used in a low-dose combined preparation containing cyproterone acetate 2 mg with ethinylestradiol 35 micrograms.[2-5] In more severe hirsutism, the two drugs may be prescribed separately in a 'reversed sequential regimen'. High-dose regimens[2] have used cyproterone acetate 100 mg daily given on days 5 to 14 of the menstrual cycle with ethinylestradiol 50 micrograms on days 5 to 24. However, lower doses are also effective, with fewer adverse effects; such regimens include[5] cyproterone acetate 50 mg (days 5 to 15) with ethinylestradiol 20 micrograms (days 5 to 25), or cyproterone acetate 12.5 mg (days 5 to 15) with ethinylestradiol 10 to 20 micrograms (days 5 to 25). Alternatively,[2] cyproterone acetate 25 to 50 mg daily may be added to the first 10 days of any low-dose combined oral contraceptive. When a satisfactory response has been achieved, the cyproterone dosage is gradually reduced, and eventually the low-dose combination preparation may be sufficient. In some countries spironolactone is the drug of choice for the treatment of hirsutism, particularly if there is associated obesity and hypertension; doses of 100 to 200 mg daily are generally used.[1,2,5] Despite its wide use, however, evidence of benefit is considered scanty.[6]

Flutamide, *finasteride*, and *leuprorelin* have also been shown to be effective, although some consider finasteride to be less active.[5] These are not recommended for routine management of hirsutism;[4] flutamide can cause hepatotoxicity, and long-term use of gonadorelin analogues reduces bone mineral density. Finasteride has significant teratogenic potential.[2] The condition has also been reported to respond to *ketoconazole*. *Eflornithine* is used topically for the reduction of facial hair.[1,3,5] It is thought to slow hair growth by the inhibition of ornithine decarboxylase in hair follicles. Eflornithine may be used alone or with other therapies, including laser hair removal.[4]

Corticosteroids can suppress adrenal androgen production, but results with *dexamethasone* have been disappointing and the addition of an anti-androgen is usually needed.[5] Corticosteroids may have a limited role in managing hirsutism associated with nonclassic congenital adrenal hyperplasia.[1,4]

1. Rosenfield RL. Hirsutism. *N Engl J Med* 2005; **353:** 2578–88.
2. Claman P, *et al*. Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines no. 110, January 2002: Hirsutism: evaluation and treatment. *J Obstet Gynaecol Can* 2002; **24:** 62–7. Also available at: http://www.sogc.org/guidelines/public/110E-CPG-January2002.pdf (accessed 27/06/08)
3. Moghetti P, Toscano V. Treatment of hirsutism and acne in hyperandrogenism. *Best Pract Res Clin Endocrinol Metab* 2006; **20:** 221–34.
4. Martin KA, *et al*. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; **93:** 1105–20. Also available at: http://www.endo-society.org/guidelines/final/upload/Hirsutism_Guideline.pdf (accessed 20/11/09)
5. Carmina E. A risk-benefit assessment of pharmacological therapies for hirsutism. *Drug Safety* 2001; **24:** 267–76.
6. Brown J, *et al*. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 20/11/09).

Precocious puberty. Although cyproterone acetate has been used for the treatment of central precocious puberty (p. 2254.1), it has generally been superseded and is now given in a short course to prevent the initial stimulatory effect of gonadorelin analogue therapy. The use of an oral dose of cyproterone acetate 50 mg twice daily, given from 3 weeks before to 2 weeks after starting the gonadorelin analogue, has been reported.[1] Menstrual-like bleeding may occur in girls after stopping cyproterone, depending on the degree of precocity. Gonadorelin analogue therapy does not control adrenal production of sex hormones, which, if overactive, can stimulate adrenarche and advancement of bone age; cyproterone acetate in usual doses of 10 to 20 mg twice daily has been used to treat this.[1]

Cyproterone acetate may sometimes be used to suppress sexual maturation in the management of peripheral forms of precocious puberty. Although it is not licensed for this, the *BNFC* includes an initial oral dose of 25 mg twice daily, adjusted according to response.

1. Laron Z, Kauli R. Experience with cyproterone acetate in the treatment of precocious puberty. *J Pediatr Endocrinol Metab* 2000; **13** (suppl): 805–10.

Adverse Effects

When given to men cyproterone reduces libido, inhibits spermatogenesis, reduces the volume of ejaculate, and causes infertility. There may be azoospermia after 8 weeks and slight atrophy of the seminiferous tubules, but these changes are slowly reversible and spermatogenesis usually recovers to pre-treatment levels about 3 to 5 months after stopping cyproterone. Abnormal spermatozoa may be produced. Gynaecomastia is common and permanent enlargement of the mammary glands may occur; galactorrhoea and benign nodules have been reported rarely. Fatigue and weakness are common and depressive mood changes can occur occasionally. Patients may have weight changes, alterations in hair pattern, dry skin, and rarely rashes or hypersensitivity. Shortness of breath may occur, and anaemia and osteoporosis have been reported rarely. Liver function tests may be altered; there have also been reports of hepatitis, jaundice, and hepatic failure, sometimes fatal, developing usually after several months of high-dose cyproterone therapy, but an association with liver cancer is uncertain. High doses of cyproterone have also been associated with reports of meningioma.

When low-dose cyproterone is given with ethinylestradiol to women, adverse effects associated with combined oral contraceptives (see p. 2233.3) may occur.

Carcinogenicity. See Effects on the Brain and Effects on the Liver, below.

Effects on the brain. Meningiomas, including multiple meningiomas, have been reported in patients given high doses of cyproterone acetate. Up to September 2009, the MHRA was aware of 36 cases worldwide, 19 of which were multiple meningiomas. Women accounted for 32 cases, and most were in France where there is extensive use of high-dose cyproterone for the treatment of hyperandrogenism. The dose was higher than 25 mg daily in all but 1 case, and the duration of treatment had ranged from 4 to 27 years.[1] The MHRA advised that patients with existing meningioma, or a history of meningioma, must not be given high doses of cyproterone acetate (25 mg or more daily). However, this advice did not apply to low-dose products, such as those containing co-cyprindiol (2 mg daily of cyproterone acetate orally with ethinylestradiol).

1. MHRA/CHM. High-dose cyproterone acetate: potential risk of (multiple) meningiomas. *Drug Safety Update* 2009; **3** (3): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON059813&RevisionSelectionMethod=LatestReleased (accessed 13/11/09)

Effects on the cardiovascular system. Combined oral contraceptives are associated with a small increased risk of cardiovascular disease (see p. 2237.1), which also applies to the combination of cyproterone acetate and an oestrogen. In 2002, the UK CSM[1] warned that preparations containing cyproterone and ethinylestradiol should not be used solely for contraception, but for treatment of severe acne that had not responded to oral antibacterials, or for moderately severe hirsutism, and that they should be withdrawn 3 or 4 cycles after the treated condition has completely resolved. However, others[2,3] questioned some study results, concluding that preparations containing cyproterone were not associated with a risk in excess of that associated with conventional combined oral contraceptives including those containing levonorgestrel. Some[4] also called for the removal of the CSM recommendation to limit the duration of therapy, particularly as acne and hirsutism frequently recur after stopping cyproterone therapy. In 2008, the CHM (formerly the CSM) reconfirmed its 2002 advice on the use of cyproterone with ethinylestradiol.[5] However, it added that for women with severe hyperandrogenism, in whom symptoms usually recur when treatment is stopped, therapy could be continued with regular specialist review until the symptoms were judged unlikely to recur. It was also recommended that, for all women, treatment can be restarted at any time if acne or hirsutism recurs after stopping therapy.

In 2013, the EMA concluded from an updated review of data that the risk of venous thromboembolism associated with co-cyprindiol (cyproterone acetate 2 mg with ethinylestradiol 35 micrograms) was 1.5 to 2 times higher than for combined oral contraceptives containing levonorgestrel, and may be similar to that associated with contraceptives containing desogestrel, drospirenone, or gestodene. However, it suggested that the balance of benefits and risks of co-cyprindiol remained positive in moderate to severe androgen-sensitive acne and hirsutism, and reminded prescribers that it should not be used solely for contraception or with an additional hormonal contraceptive.[6]

The study of any association may be confounded by the adverse cardiovascular risk associated with polycystic ovary disease, an underlying condition in many women given cyproterone with ethinylestradiol to manage acne and hirsutism.[3]

1. CSM/MCA. Cyproterone acetate (Dianette): risk of venous thromboembolism (VTE). *Current Problems* 2002; **28:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
2. Spitzer WO. Cyproterone acetate with ethinylestradiol as a risk factor for venous thromboembolism: an epidemiological evaluation. *J Obstet Gynaecol Can* 2003; **25:** 1011–18.
3. Seaman HE, *et al*. Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol (Dianette): observational studies using the UK General Practice Research Database. *Pharmacoepidemiol Drug Safety* 2004; **13:** 427–36.
4. Franks S, *et al*. Cyproterone acetate/ethinyl estradiol for acne and hirsutism: time to revise prescribing policy. *Hum Reprod* 2008; **23:** 231–2.
5. MHRA/CHM. Cyproterone acetate with ethinylestradiol (co-cyprindiol): recommended duration of use. *Drug Safety Update* 2008; **1** (9): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)
6. EMA. Benefits of Diane 35 and its generics outweight risks in certain patient groups (issued 25th July, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/cyproterone_ethinylestradiol_107i/European_Commission_final_decision/WC500147176.pdf (accessed 11/12/13)

Effects on the eyes. Bilateral optic atrophy in an elderly male patient was thought to be associated with cyproterone.[1] The authors could find no other cases from the published literature or the manufacturers' records. Central retinal vein occlusion occurred in a 28-year-old woman given cyproterone for the treatment of hair loss.[2]

1. Markus H, *et al*. Visual loss and optic atrophy associated with cyproterone acetate. *BMJ* 1992; **305:** 159.
2. Zaoui M, *et al*. Occlusion de la veine centrale de la rétine sous anti-androgènes. *J Fr Ophtalmol* 2000; **23:** 42–4.

Effects on the liver. There have been many reports of hepatic reactions associated with cyproterone acetate. In February 1995, the UK CSM noted that it had received 96 reports (33 fatal) of reactions including hepatitis, cholestatic jaundice, and hepatic failure, after cyproterone treatment;[1] 91 of these were in elderly men typically given high doses (300 mg daily) for prostatic cancer, and toxicity usually developed after several months of treatment. In view of this it was recommended that the use of cyproterone acetate in prostatic cancer be restricted to short courses for the testosterone flare associated with the commencement of gonadorelin analogue therapy, or for hot flushes after surgical or chemical castration, or for patients unresponsive to, or intolerant of, other treatments. A retrospective analysis[2] of data from 105 patients with advanced prostate cancer, who had received cyproterone

acetate 150 mg daily, found mild to moderate hepatotoxicity in 6 patients and severe toxicity in 4. There was a higher occurrence of hepatotoxicity (19 cases out of 124 patients) in a similar group that had been given flutamide. Fourteen published case reports have also been briefly reviewed.[3] Patients with chronic viral hepatitis might be at higher risk of developing hepatotoxicity from cyproterone therapy.[4]

Although there is little doubt of the risk of hepatotoxicity, suggestions of an association between cyproterone therapy and the development of liver cancer remain contentious. There are individual reports of hepatocellular carcinoma developing in patients receiving cyproterone,[5,6] and some evidence *in vitro* of the formation of DNA adducts in exposed hepatocytes,[7] but there does not seem to be clinical evidence to support any association between use of cyproterone acetate and the development of liver tumours.[7,8]

1. CSM/MCA. Hepatic reactions with cyproterone acetate (Cyprostat, Androcur). *Current Problems* 1995; **21:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
2. Lin ADY, *et al*. Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66:** 735–40.
3. Savidou I, *et al*. Hepatotoxicity induced by cyproterone acetate: a report of three cases. *World J Gastroenterol* 2006; **12:** 7551–5.
4. Pu Y-S, *et al*. Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36:** 293–7.
5. Watanabe S, *et al*. Three cases of hepatocellular carcinoma among cyproterone users. *Lancet* 1994; **344:** 1567–8.
6. Rüdiger T, *et al*. Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinyloestradiol. *Lancet* 1995; **345:** 452–3.
7. Lewis S. Warning on cyproterone. *Lancet* 1995; **345:** 247.
8. Rabe T, *et al*. Liver tumours in women on oral contraceptives. *Lancet* 1994; **344:** 1568–9.

Precautions

When used for hypersexuality, cyproterone is contra-indicated in men with liver diseases or malignant or wasting diseases. In addition, it should not be given to patients with severe chronic depression, severe diabetes with vascular changes, or sickle-cell anaemia. It should also be avoided in those with existing, or a history of, thromboembolic disorders or meningioma (see also Effects on the Brain, p. 2262.2). It may delay bone maturation and testicular development and so should not be given to immature youths. When used for prostate cancer, there are no absolute contra-indications to the use of cyproterone (except perhaps meningioma), but the above conditions should prompt cautious consideration of the risks and benefits.

In men treated with cyproterone, liver function should be monitored before starting, and regularly during, treatment, and whenever any symptoms or signs suggestive of hepatotoxicity occur. If cyproterone-induced hepatotoxicity occurs, treatment should be withdrawn. In men with prostate cancer, it may be advisable to limit the duration of treatment (see Effects on the Liver, p. 2262.3). Men with diabetes require careful monitoring of diabetic control. Since anaemia has been seen, regular blood counts are recommended before and during treatment. Adrenocortical suppression has been reported and function should be monitored regularly during treatment. Patients should be advised that fatigue and weakness are common and may interfere with driving and the operation of machinery.

Similar precautions apply to women treated with high doses of cyproterone for hyperandrogenism. When low doses are used with ethinylestradiol (co-cyprindiol), the precautions for combined oral contraceptives (see p. 2240.3) should be observed.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyproterone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Use of cyproterone during pregnancy might carry a risk of feminisation of a male fetus. However, there are a few case reports of healthy male infants born to mothers who had inadvertently taken a combination of cyproterone acetate and ethinylestradiol during the early stages of pregnancy,[1,2] and of a male fetus that was found to have no malformations after abortion was induced.[3] For further information on oral contraceptive use in pregnancy, see p. 2242.1.

1. Statham BN, *et al*. Conception during 'Diane' therapy—a successful outcome. *Br J Dermatol* 1985; **113:** 374.
2. Bye P. Comments on 'conception during "Diane" therapy—a successful outcome'. *Br J Dermatol* 1986; **114:** 516.
3. Bergh T, Bakos O. Exposure to antiandrogen during pregnancy: case report. *BMJ* 1987; **294:** 677–8.

Interactions

UK licensed product information states that alcohol may reduce the efficacy of cyproterone acetate as it is ineffective in chronic alcoholics. Dosage requirements of oral antidiabetics and insulin may be altered because of cyproterone's effects on carbohydrate metabolism.

When given with ethinylestradiol to women, interactions similar to those for combined oral contraceptives (see p. 2242.3) might be anticipated.

Pharmacokinetics

Cyproterone acetate is slowly absorbed from the gastrointestinal tract; peak plasma concentrations occur in about 3 hours. It is about 96% bound to plasma proteins, mainly albumin. The terminal elimination half-life is about 43 hours. Cyproterone is metabolised by various pathways including hydroxylation and conjugation; about 35% of a dose is excreted in urine, the remainder being excreted in the bile. The principal metabolite, 15β-hydroxycyproterone, has anti-androgenic activity.

The elderly. In a study[1] of healthy men, a decrease in hepatic clearance of cyproterone acetate was found in elderly men and thought to be due to an age-related reduction in liver volume.

1. Kuhnz W, *et al*. Investigation into the age-dependence of the pharmacokinetics of cyproterone acetate in healthy male volunteers. *Eur J Clin Pharmacol* 1997; **53:** 75–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Androcur; Androstat; Asoteron; Ceprater; Ciclamil; Ciprofarma; Ciproplex; Kebirterona; Omnigeriat; Purfilx; ***Austral.***: Androcur; Cyprohexal; Cyprone; Cyprostat; Procur; ***Austria***: Andro-Diane; Androcur; ***Belg.***: Androcur; Cyproplex; ***Braz.***: Andelux; Androcur; Androneo; Androsteron; Cetoteron; Ciprostat; Prostman; ***Canad.***: Androcur; ***China***: Androcur (色普龙); ***Cz.***: Androcur; Cyproplex; Cysaxal; ***Denm.***: Androcur; ***Fin.***: Androcur; ***Fr.***: Androcur; Kaliale†; ***Ger.***: Androcur; Virilit†; ***Gr.***: Androcur; ***Hong Kong***: Androcur; ***Hung.***: Androcur; Cysaxal; ***Indon.***: Androcur; ***Irl.***: Androcur; ***Israel***: Androcur; Cypron; ***Ital.***: Androcur; ***Malaysia***: Androcur; Cyproplex†; ***Mex.***: Androcur; Bagopront†; Neoproxil†; ***Neth.***: Androcur; Curandron†; Cysaxal; ***Norw.***: Androcur; ***NZ***: Androcur†; Procur; Siterone; ***Philipp.***: Androcur; ***Pol.***: Androcur; ***Port.***: Androcur; ***Rus.***: Androcur (Андрокур); ***S.Afr.***: Androcur; Cyproplex; ***Singapore***: Androcur; Procur; ***Spain***: Androcur; ***Swed.***: Androcur; ***Switz.***: Androbas†; Androcur; Elleacnelle; ***Thai.***: Androcur; ***Turk.***: Androcur; ***UK***: Androcur; Cyprostat; ***Ukr.***: Androfarm (Андрофарм); ***Venez.***: Androcur; Asoteron.

Multi-ingredient Preparations. ***Arg.***: Avancel; Biofem 35†; Climene; Diane; Mileva; Tess 35; Zinnia; ***Austral.***: Brenda-35 ED; Climen†; Diane; Estelle; Juliet; Laila-35 ED; ***Austria***: Bellgyn; Climen; Diane; Midane; Minerva; Xylia; ***Belg.***: Claudia; Climen; Cyprodiol†; Daphne; Diane; Doccyproestra†; Docdonna†; Elisamylan; Gratiella; Ratiopharmeva†; ***Braz.***: Artemidis; Ciprane; Climene; Diane; Diclin; Elamax; Ferane 35; Repopil; Selene; Tess; ***Canad.***: CyEstra; Diane; ***Chile***: Anuar; Climene; Diane; Dixi-35; Drina; Evilin; Lady-Ten 35; ***China***: Climen (克龄蒙); Diane (达英); ***Cz.***: Bellune; Chloe; Climen; Diane; Minerva; Vreya; ***Denm.***: Diane; Dianova; Feminil; Vreya; Zafira†; Zyrona; ***Fin.***: Cypretyl; Diane; Femilar; Feminil; Vreya; ***Fr.***: Climene; Diane; Evepar; Holgyeme; Lumalia; Minerva; ***Ger.***: Attempta; Bella†; Clevia†; Climen; Cyproderm; Cypronette†; Diane; Ergalea†; Morea; ***Gr.***: Gynofen; ***Hong Kong***: Climen 28†; Daphne; Diane; ***Hung.***: Climen†; Cypromix; Diane; Minerva; ***India***: Diane; Dinac; Frauline; Ginette; Krimson; ***Indon.***: Climen 28; Diane; ***Irl.***: Dianette; ***Israel***: Diane; Estelle; ***Ital.***: Climen; Diane; Pausene; Visofid; ***Malaysia***: Climen; Diane; Estelle; Sucee; ***Mex.***: Angie; Climene; Diane; Eunice 35-ED; Mileva; ***Neth.***: Climene†; Diane; Minerva; Zypina†; ***Norw.***: Diane; Feminil; Zyrona; ***NZ***: Diane; Estelle; Ginet; ***Philipp.***: Althea; Ancea; Climen 28; Crimson; Diane; ***Pol.***: Chloe; Climen; Cyprest; Cyprodiol; CyproGen; Diane; OC-35; Syndi-35; ***Port.***: Climen; Diane; ***Rus.***: Bellune (Беллуне); Chloe (Хлое); Climen (Климен); Diane (Диане); ***S.Afr.***: Adco-Fem; Claro; Climen; Diane; Diva; Ginette; Minerva; ***Singapore***: Climen; Diane; Estelle; ***Spain***: Climen; Diacare†; Dialider; Diane; Gyneplen; ***Swed.***: Diane; Zyrona; ***Switz.***: Climen; Cypestra; Cyprelle; Diane; Feminac; Holgyeme; Minerva; ***Thai.***: Annie; B-Lady; Climen; Cypress; Dafne; Diane; Helen; Lady-35; Manoane; OC-35; Preme; Sucee; ***Turk.***: Climen; Diane; Gynelle; ***UK***: Acnocin; Cicafem; Clairette; Dianette; Diva; ***Ukr.***: Climen (Климен); Diane-35 (Диане-35); ***Venez.***: Climene; Diane; Dixi.

Pharmacopoeial Preparations

BP 2014: Cyproterone Tablets.

Danazol *(BAN, USAN, pINN)* ⊗

Danatsoli; Danazolum; Win-17757; Даназол.

17α-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17β-ol.

$C_{22}H_{27}NO_2$=337.5

CAS — 17230-88-5.

ATC — G03XA01.

ATC Vet — QG03XA01.

UNII — N29QWW3BUO.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Danazol). A white to pale yellow crystalline powder. Practically insoluble or insoluble in water and in petroleum spirit; sparingly soluble in alcohol and in benzene; soluble in acetone; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers. Protect from light.

Uses and Administration

Danazol suppresses the pituitary-ovarian axis by inhibiting pituitary output of gonadotrophins. It has weak androgenic activity, and is described as an attenuated androgen.

Danazol has been given orally in the treatment of various conditions including endometriosis (p. 2264.1), some benign breast disorders such as mastalgia and fibrocystic breast disease (p. 2265.1), gynaecomastia (p. 2264.3), menorrhagia associated with dysfunctional uterine bleeding (p. 2265.2), and the prevention of hereditary angioedema (see p. 2265.1). It may also be used for the pre-operative thinning of the endometrium before hysteroscopic endometrial ablation. Danazol has been tried in other conditions including various blood and skin disorders (see below and p. 2265.2).

When given to women, treatment with danazol should be started on day 1 of the menstrual cycle or after pregnancy has been otherwise excluded.

In **endometriosis** the usual dose is 200 to 800 mg daily in 2 to 4 divided doses, adjusted according to the response. Therapy is given for 3 to 6 months or continued for up to 9 months if necessary.

In the treatment of **benign breast disorders** the usual initial dose is 100 to 400 mg daily in 2 divided doses, adjusted according to response, and continued for 3 to 6 months. For **gynaecomastia** 200 mg daily has been given to male adolescents, increased after 2 months to 400 mg daily if no response occurs; adult men have been given 400 mg daily initially, in up to 4 divided doses. Daily doses of up to 800 mg have been used, and therapy is usually tried for 6 months.

In dysfunctional uterine bleeding manifesting as **menorrhagia** doses of 200 mg daily have been given and treatment is reviewed after 3 months.

In the management of **hereditary angioedema** initial doses of 200 mg two or three times daily are given, and then reduced according to the patient's response. For doses used in children with hereditary angioedema, see p. 2265.1.

For **pre-operative thinning** of the endometrium danazol has been given in a dose of 400 to 800 mg daily in up to 4 divided doses, for 3 to 6 weeks.

Administration in children. Although the use of danazol is generally avoided in children, it has been given in the management of hereditary angioedema (see p. 2265.1) and to treat gynaecomastia in male adolescents (see above).

Blood disorders. Although danazol may produce thrombocytopenia and leucopenia its use has also been investigated in some blood disorders. Increased platelet counts have been reported in patients with *immune thrombocytopenia* (p. 1606.1). Small cohort studies have reported response rates of about 60 to 70%, including both partial and complete responses,[1-3] with a mean or median time to response of about 3 months.[1,2] Analysis of data from 96 patients suggested that age, sex, and spleen status may affect the response to danazol.[2] The response in men was not affected by age, but was better in splenectomised patients. However, in women there was a better response rate with advancing age in unsplenectomised patients, and the benefit of splenectomy on rates of response to danazol was only seen in younger women (45 years or younger). A better overall response rate in older patients (60 years and older) was also reported in another group.[4] However, others have found only a trend to less frequent response in younger patients, and no apparent relationship between response and sex or prior splenectomy.[1] *Thrombocytopenia associated with rheumatic disorders,* such as SLE, the antiphospholipid antibody syndrome, and rheumatoid arthritis has also been reported to respond to treatment with danazol.[5-7] For mention of the use of danazol in *Henoch-Schönlein purpura* see Hypersensitivity Vasculitis, p. 1606.1.

Additionally there have been reports of response to danazol therapy in patients with *auto-immune haemolytic anaemia*[8,9] (p. 1122.2), anaemia of *myelofibrosis with myeloid metaplasia,*[10] *paroxysmal nocturnal haemoglobinuria,*[11] *hereditary haemorrhagic telangiectasia,*[12] and *Evan's syndrome*

due to SLE.[13] There have been conflicting reports in patients with *myelodysplastic syndromes*.[14-18]

1. Maloisel F, *et al*. Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. *Am J Med* 2004; **116:** 590–4.
2. Ahn YS, *et al*. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. *Ann Intern Med* 1989; **111:** 723–9.
3. Zimmer J, *et al*. Current management of adult idiopathic thrombocytopenic purpura in practice: a cohort study of 201 patients from a single center. *Clin Lab Haematol* 2004; **26:** 137–42.
4. Andrès E, *et al*. Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of the influence of age on the response to corticosteroids, splenectomy and danazol. *Drugs Aging* 2003; **20:** 841–6.
5. Blanco R, *et al*. Successful therapy with danazol in refractory autoimmune thrombocytopenia associated with rheumatic diseases. *Br J Rheumatol* 1997; **36:** 1095–9.
6. Arnal C, *et al*. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol* 2002; **29:** 75–83.
7. Aviña-Zubieta JA, *et al*. Long-term effectiveness of danazol corticosteroids and cytotoxic drugs in the treatment of hematologic manifestations of systemic lupus erythematosus. *Lupus* 2003; **12:** 52–7.
8. Ahn YS, *et al*. Danazol therapy for autoimmune hemolytic anemia. *Ann Intern Med* 1985; **102:** 298–301.
9. Tan AM, *et al*. Danazol for treatment of refractory autoimmune hemolytic anaemia. *Ann Acad Med Singapore* 1989; **18:** 707–9.
10. Cervantes F, *et al*. Efficacy and tolerability of danazol as a treatment for the anaemia of myelofibrosis with myeloid metaplasia: long-term results in 30 patients. *Br J Haematol* 2005; **129:** 771–5.
11. Harrington WJ, *et al*. Danazol for paroxysmal nocturnal hemoglobinuria. *Am J Hematol* 1997; **54:** 149–54.
12. Haq AU, *et al*. Hereditary hemorrhagic telangiectasia and danazol. *Ann Intern Med* 1988; **109:** 171.
13. Aranegui P, *et al*. Danazol for Evan's syndrome due to SLE. *DICP Ann Pharmacother* 1990; **24:** 641–2.
14. Wattel E, *et al*. Androgen therapy in myelodysplastic syndromes with thrombocytopenia: a report on 20 cases. *Br J Haematol* 1994; **87:** 205–8.
15. Chabannon C, *et al*. A review of 76 patients with myelodysplastic syndromes treated with danazol. *Cancer* 1994; **73:** 3073–80.
16. Letendre L, *et al*. Myelodysplastic syndrome treatment with danazol and cis-retinoic acid. *Am J Hematol* 1995; **48:** 233–6.
17. Viniou N, *et al*. Danazol therapy for thrombocytopenia in patients with myelodysplastic syndromes. *Acta Haematol (Basel)* 2002; **107:** 234–6.
18. Chan G, *et al*. Danazol for the treatment of thrombocytopenia in patients with myelodysplastic syndrome. *Am J Hematol* 2002; **71:** 166–71.

Endometriosis. Endometriosis is a condition affecting women mainly in their reproductive years, and caused by endometrial tissue developing outside the uterine cavity. It occurs most often in the pelvic peritoneal cavity and occasionally elsewhere such as the thoracic cavity. The aetiology is uncertain, although it is widely believed that retrograde flow of menstrual tissue introduces endometrial cells into the pelvic cavity, and that the implantation and growth of these cells may be influenced by genetic, immunologic, hormonal, and environmental factors.[1,2]

The presentation of endometriosis is variable, and while symptoms can range from mild to severe, many affected women are asymptomatic.[3] There is considerable overlap of symptoms with other conditions such as irritable bowel syndrome and pelvic inflammatory disease, but a definitive diagnosis of endometriosis can be made by visualisation at laparoscopy. The most common symptom is pain, usually manifesting as secondary dysmenorrhoea, dyspareunia, or cyclical back or pelvic pain. Pain may occur on micturition or defaecation if endometriosis affects the bladder or bowel; fibrosis and adhesions can develop. Endometriosis is also strongly associated with infertility. Severe endometriosis can distort the pelvic anatomy and thereby reduce fecundity, but how minimal and mild disease might affect fertility is unclear.[1,4] Management will depend in part on the presenting complaint, the extent of disease, and whether fertility is an issue. Conservative laparoscopic surgery or drug therapy may be used, but disease recurrence is common and long-term management is usually needed.[1,5] Nevertheless, spontaneous regression may occur in about a third of patients.[4,5]

Where **infertility** is the presenting symptom, surgery is generally performed in more severe disease, based on the assumption that correction of anatomical defects should improve fecundity although there is a lack of controlled studies to confirm this.[2,3,6,7] There is also limited evidence to suggest that surgery may improve fertility in mild disease,[3] but it is likely that the effect is small.[7] Assisted reproductive techniques such as IVF (see Infertility, p. 2253.1) offer the best chance of conception in more severe disease.[6,7] The extent of benefit in mild or moderate endometriosis is less clear.[6] Superovulation with intra-uterine insemination may be considered in such cases, with IVF an alternative for women aged 35 or more, and postoperative expectant management another option in younger women.[7]

Drug therapy has not been shown to be of direct value for infertility.[7,8] Also, because the drugs used for endometriosis tend to suppress ovulation and are potentially contraceptive, they will delay the opportunity for conception during treatment.[3,6,9] Pre- and postoperative drug therapy have also been tried, but there is insufficient evidence to show that these are any more effective than surgery alone.[10]

For patients whose primary symptom is **pain**, drug treatments that cause anovulatory hypoestrogenism (to induce atrophy and shrinkage of the hormonally sensitive ectopic endometrial deposits) are effective and are the mainstay of treatment.[4]

One of the most widely used treatments has been *danazol*, which produces subjective improvement in symptoms of pain and reduction of some pelvic abnormalities and tissue implants.[1,11] Its androgenic effects can be a problem and there is concern about its effect on blood lipids, therefore therapy is restricted to 6 months, or rarely up to 9 months. *Gestrinone* has been shown to be equally effective and may be a useful alternative.[3,8,12] *Progestogens* such as medroxyprogesterone acetate, dydrogesterone, or norethisterone acetate are also commonly used. They appear to be as effective as danazol in relieving pain symptoms[12] and tend to be better tolerated.[1,4] The use of local levonorgestrel from an intra-uterine device is also under investigation.[2,13]

Combined oral contraceptives are often used to relieve endometriosis pain, although the evidence for their benefit is largely observational[1] and data from controlled studies remain scanty.[14] They have been used in a continuous fashion to induce amenorrhoea, as well as the usual cyclical regimens, but it is unclear which is most effective.[3,8]

The other major group of drugs that are used in endometriosis are *gonadorelin analogues* such as buserelin, goserelin, leuprorelin, nafarelin, and triptorelin, which are as effective as danazol.[1,6,15] Long-term use is limited by the risk of osteoporosis, but concomitant 'add-back' therapy such as low-dose oestrogen and progestogen HRT,[1,3,6,8] or tibolone,[1,3] can be used to prevent this. Adverse effects resembling menopausal symptoms can also be relieved by 'add-back' therapy, which may make gonadorelin analogues more tolerable than danazol.[4] Parathyroid hormone[16,17] may also be effective for 'add-back' therapy to prevent bone loss.

Investigational drugs include the *antiprogestogens* such as mifepristone,[18] and *aromatase inhibitors* such as anastrozole and letrozole.[19]

There is some evidence that laparoscopic ablation can also reduce pain but controlled studies are limited.[4,6] Ideally, endometrial deposits found during diagnostic laparoscopy should be removed during the procedure.[3,8,20] There is a lack of comparison between surgery and drug treatment. Although there are reports of improved pain control using postoperative medical therapy,[20] study results have been mixed and there is insufficient evidence to confirm whether a combination of surgery and drug therapy has any additional benefit.[6,10]

There is a relatively high recurrence rate of endometriosis after conservative surgery and drug therapy. In women who can accept loss of child-bearing potential, definitive therapy is surgical oophorectomy and hysterectomy with complete excision or ablation of endometrial deposits.[3,8,20] Oestrogen replacement therapy is given, but carries a risk of recurrence of the disease; some have suggested that combined HRT may be preferable (see p. 2250.2).

1. Crosignani P, *et al*. Advances in the management of endometriosis: an update for clinicians. *Hum Reprod Update* 2006; **12:** 179–89.
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3. Royal College of Obstetricians and Gynaecologists. The investigation and management of endometriosis (green-top guideline no. 24, issued October 2006). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT24InvestigationEndometriosis2006.pdf (accessed 19/07/10)
4. Child TJ, Tan SL. Endometriosis: aetiology, pathogenesis and treatment. *Drugs* 2001; **61:** 1735–50.
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6. Olive DL, Pritts EA. The treatment of endometriosis: a review of the evidence. *Ann N Y Acad Sci* 2002; **955:** 360–72.
7. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. *Fertil Steril* 2006; **86** (suppl 4): S156–S160.
8. European Society for Human Reproduction and Embryology. ESHRE guideline for the diagnosis and treatment of endometriosis (last updated 30th June, 2007). Available at: http://guidelines.endometriosis.org/index.html (accessed 30/06/08)
9. Hughes E, *et al*. Ovulation suppression for endometriosis for women with subfertility. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 10/11/09).
10. Yap C, *et al*. Pre and post operative medical therapy for endometriosis surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 30/06/08).
11. Selak V, *et al*. Danazol for pelvic pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/06/08).
12. Prentice A, *et al*. Progestagens and anti-progestagens for pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 30/06/08).
13. Vercellini P, *et al*. Endometriosis: current therapies and new pharmacological developments. *Drugs* 2009; **69:** 649–75.
14. Davis L, *et al*. Modern combined oral contraceptives for pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
15. Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. *N Engl J Med* 2008; **359:** 1136–42.
16. Finkelstein JS, *et al*. Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; **331:** 1618–23.
17. Finkelstein JS, *et al*. Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; **280:** 1067–73.
18. Kettel LM, *et al*. Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; **178:** 1151–6.
19. Ferrero S, *et al*. Pharmacological treatment of endometriosis: experience with aromatase inhibitors. *Drugs* 2009; **69:** 943–52.
20. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril* 2008; **90** (suppl 3): S260–S269.

Gynaecomastia. Gynaecomastia is a common benign glandular enlargement of the male breast, caused either by increased oestrogenic activity or decreased androgenic activity. Examples of gynaecomastia caused by increased oestrogenic activity include oestrogen-secreting malignancies, increased aromatisation of androgens into oestrogens (associated with an increase in adipose tissue), and exposure to drugs with oestrogenic activity such as digitoxin. Neonatal and pubertal gynaecomastia also come into this category, the former due to exposure to maternal oestrogens and the latter because oestrogen levels increase before androgens do. Gynaecomastia caused by decreased androgenic activity may be associated with the natural decline of testosterone concentrations in ageing men, various forms of hypogonadism, increased metabolism of androgens (for example in alcoholism), and exposure to drugs with anti-androgenic properties such as spironolactone, cimetidine, ketoconazole, cyproterone acetate, or flutamide. Some systemic disorders may also be associated with gynaecomastia, including cirrhosis of the liver, hyperthyroidism, and renal failure; it may also occur on refeeding after starvation.

Gynaecomastia has a high rate of spontaneous regression, and specific therapy (other than the removal of any cause) need only be considered if the enlarged breast tissue causes sufficient pain, embarrassment, or emotional discomfort to interfere with the patient's daily life.[1-3] Drug therapy is only likely to be of benefit while tissue is still proliferating; once glandular tissue has become inactive and fibrotic (usually after more than 12 months) a complete response is unlikely.[2,3]

Except in primary hypogonadism,[3] testosterone itself is unlikely to be of benefit (and may be aromatised to oestradiol, exacerbating the situation),[2] but a non-aromatisable androgen such as *androstanolone* (dihydrotestosterone) may produce some benefit.[2,4] *Danazol* has produced marked responses in some patients,[4] but adverse effects may limit its usefulness.[2] Quite good responses have also been reported with *tamoxifen*,[4-6] and this has been recommended as a drug of choice.[2,3] A retrospective review[7] of men treated for idiopathic gynaecomastia found that a complete response occurred in 18 of 23 men treated with tamoxifen, but in only 8 of 20 who received danazol. The decrease in pain was similar for both groups, but relapse occurred in 5 of the men treated with tamoxifen. The use of other drugs with anti-oestrogen effects, such as *clomifene*[8,9] and *raloxifene*,[6] has also been described in small numbers of boys with pubertal gynaecomastia. Aromatase inhibitors have been investigated for their potential to prevent the peripheral aromatisation of androgens to oestrogens. Improvement in pubertal gynaecomastia has been reported with *testolactone*,[10] but a controlled study[11] in 80 boys found 6 months of treatment with *anastrozole* to be no better than placebo. Studies in men being treated for prostate cancer also found anastrozole to be ineffective for the prevention[12,13] and treatment[12] of gynaecomastia associated with bicalutamide therapy; in comparison, tamoxifen was effective in both studies.

Where drug therapy is unsuccessful, or the breast enlargement is long-standing, surgical removal of breast tissue is advocated.[2,3] Prophylactic low-dose radiotherapy to the breast can significantly reduce the risk of gynaecomastia and breast pain in men undergoing anti-androgen treatment for prostate cancer,[2] although comparative studies suggest that it may be less effective than tamoxifen.[14,15]

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2. Gikas P, Mokbel K. Management of gynaecomastia: an update. *Int J Clin Pract* 2007; **61:** 1209–15.
3. Braunstein GD. Gynecomastia. *N Engl J Med* 2007; **357:** 1229–37.
4. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; **2:** 643–9.
5. McDermott MT, *et al*. Tamoxifen therapy for painful idiopathic gynecomastia. *South Med J* 1990; **83:** 1283–5.
6. Lawrence SE, *et al*. Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; **145:** 71–6.
7. Ting ACW, *et al*. Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. *Am Surg* 2000; **66:** 38–40.
8. LeRoith D, *et al*. The effect of clomiphene citrate on pubertal gynaecomastia. *Acta Endocrinol (Copenh)* 1980; **95;** 177–80.
9. Plourde PV, *et al*. Clomiphene in the treatment of adolescent gynecomastia: clinical and endocrine studies. *Am J Dis Child* 1983; **137:** 1080–2.
10. Zachmann M, *et al*. Treatment of pubertal gynaecomastia with testolactone. *Acta Endocrinol (Copenh)* 1986; **279** (suppl): 218–26.
11. Plourde PV, *et al*. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 4428–33.
12. Saltzstein D, *et al*. Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; **8:** 75–83.
13. Boccardo F, *et al*. Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; **23:** 808–15.

14. Perdonà S, *et al*. Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; **6:** 295–300.
15. Di Lorenzo G, *et al*. Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; **174:** 2197–2203.

Hereditary angioedema. Danazol may be given to prevent attacks of hereditary angioedema (p. 2485.2). Oral doses of 200 mg once or twice daily are typically used, but may range from 100 mg three times each week up to 400 mg twice daily.[1] The lowest effective prophylactic dose should be used to minimise adverse effects from long-term use.[2] Different regimens have been described, starting with either high (400 to 600 mg daily) or low (200 mg daily) induction doses that are gradually adjusted according to response, with the aim of reaching a maintenance dose of about 50 mg daily.[3] Short-term prophylaxis may be given in situations expected to provoke an attack, such as surgery or dental procedures, when complement C1 esterase inhibitor is not available. Danazol 100 to 600 mg daily may be given, starting 5 days before the procedure and continuing for 48 hours after.[1,3] Attenuated androgens are not usually given in the acute management of hereditary angioedema. However, the early use of up to 1 g daily of danazol may shorten the duration of an attack of peripheral swelling.[1]

Attenuated androgens are also generally avoided in children because of adverse effects. They may be considered when other treatments are ineffective,[4] and may be helpful in children with frequent abdominal attacks occurring more than once a month.[1] The use of the lowest effective dose, an intermittent regimen, and careful monitoring have been advocated.[1,4] Long-term prophylactic doses of danazol 50 to 200 mg daily (or 2.5 mg/kg daily) have been used, and should be given even less frequently in alternate-day or twice-weekly regimens if possible. Short-term prophylaxis before surgery or dental procedures has been given in doses of 300 mg daily (or 5 mg/kg daily), from 5 days before until 48 hours after the procedure. Similarly,[4] doses of 5 mg/kg daily for 2 or 3 days may be used as short-term prophylaxis in the presence of other precipitating factors, such as infection. As for adults, attenuated androgens are not usually given in the acute management of hereditary angioedema, but early doubling of the long-term prophylactic dose in use may be considered in mild attacks, and continued until the patient has been asymptomatic for 48 hours.

Patients with lupus erythematosus-like syndromes associated with hereditary angioedema have also benefited from danazol therapy.[5-7]

1. Gompels MM, *et al*. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid;* **141:** 189–90. [dose]
2. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proc* 2008; **29:** 225–31.
3. Bowen T, *et al*. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008; **100** (suppl 2): S30–S40.
4. Farkas H, *et al*. Management of hereditary angioedema in pediatric patients. Abstract: *Pediatrics* 2007; **120:** 635. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/3/e713 (accessed 10/12/09)
5. Masse R, *et al*. Reversal of lupus-erythematosus-like disease with danazol. *Lancet* 1980; **ii:** 651.
6. Donaldson VH, Hess EV. Effect of danazol on lupus-erythematosus-like disease in hereditary angioneurotic oedema. *Lancet* 1980; **ii:** 1145.
7. Duhra P, *et al*. Discoid lupus erythematosus associated with hereditary angioneurotic oedema. *Br J Dermatol* 1990; **123:** 241–4.

Mastalgia. Mastalgia may occur alone or be associated with nodularity or other fibrocystic changes in the female breast. It is usually divided into cyclical mastalgia, which accounts for about two-thirds of all cases, non-cyclical mastalgia, and chest-wall or costochondral pain (Tietze's syndrome). Cyclical mastalgia has a temporal association with the menstrual cycle and is most common in the third decade of life, with a chronic relapsing course thereafter; it usually resolves at the menopause. Non-cyclical mastalgia tends to present later in life as constant or intermittent pain that is not associated with the menstrual cycle.

Once clear pathological causes of pain have been excluded most patients can be managed by simple reassurance.[1-3] In the management of mild mastalgia, simple measures such as wearing a properly fitting brassiere and the use of relaxation techniques are widely recommended.[1-3] Warm compresses or ice packs and gentle massage may provide relief, particularly when the pain is cyclic or intermittent and of short duration.[1] There is some evidence that a low-fat diet may reduce symptoms of mastalgia, but the evidence to support a restriction of dietary caffeine intake is inconsistent and such a measure is not generally recommended.[1,3] Although few studies have been done to confirm a beneficial effect, many women are likely to self-medicate as required with simple analgesics such as paracetamol and oral or topical NSAIDs.[1] Patients who take an oral contraceptive or HRT may find that symptoms improve on reducing the estrogen dose or stopping treatment.[1,3]

Women with moderate to severe mastalgia that has lasted for more than 6 months may require specific drug treatment. *Danazol* is probably the most effective drug for mastalgia, and studies suggest that it is of benefit in about 70% or more of patients with cyclical mastalgia,[1-3] and somewhat fewer with the non-cyclical form.[2] However, adverse effects may force the dose to be reduced or stopped. Danazol given only during the luteal phase (days 14 to 28) has been reported to be effective in cyclical mastalgia, and to cause few adverse effects.[4] *Gestrinone* has also been reported to be effective in cyclical mastalgia.[1] Although effective in cyclical mastalgia,[3,5] *bromocriptine* is not as effective as danazol, and its use is similarly limited by adverse effects.[1,2] A small study[6] has reported that *lisuride* was effective in cyclical mastalgia.

Gamolenic acid (usually as evening primrose oil) has been widely used in cyclical mastalgia because of early studies suggesting that it was an effective treatment with few adverse effects. Although further studies have produced conflicting results and there is now doubt about its efficacy,[2,3,5] some still suggest that it can be tried as there may be a beneficial effect with minimal risk.[1]

In refractory cyclical or non-cyclical mastalgia *tamoxifen*[3,5] has been shown to be effective; controlled studies have reported efficacy rates of up to 96% in cyclical mastalgia and 56% in non-cyclical mastalgia.[1] However, the concept of using tamoxifen in otherwise healthy premenopausal women has produced some concern.[7-9] *Toremifene* has been reported to be of benefit.[10,11] *Goserelin* has also been shown to be effective,[12,13] but there is limited experience with the use of gonadorelin analogues and severe adverse effects are likely to limit their use.[1] Injection of a *local anaesthetic* with a *corticosteroid* has proved effective for the pain of non-cyclical mastalgia.[14]

Other drugs that have been used for cyclical mastalgia include antibacterials, diuretics, and various vitamins but there is no evidence that they are any better than placebo.[1]

1. Smith RL, *et al*. Evaluation and management of breast pain. *Mayo Clin Proc* 2004; **79:** 353–72.
2. Gumm R, *et al*. Evidence for the management of mastalgia. *Curr Med Res Opin* 2004; **20:** 681–4.
3. Rosolowich V, *et al*. Society of Obstetricians and Gynecologists of Canada. Mastalgia. *J Obstet Gynaecol Can* 2006; **28:** 49–57. Also available at: http://www.sogc.org/guidelines/public/170E-CPG-January2006.pdf (accessed 30/06/08)
4. O'Brien PMS, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol* 1999; **180:** 18–23.
5. Srivastava A, *et al*. Evidence-based management of mastalgia: a meta-analysis of randomised trials. *Breast* 2007; **16:** 503–12.
6. Kaleli S, *et al*. Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; **75:** 718–23.
7. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; **i:** 305.
8. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; **i:** 680–1.
9. Fentiman IS, *et al*. Tamoxifen for mastalgia. *Lancet* 1986; **i:** 681.
10. Gong C, *et al*. A double-blind randomized controlled trial of toremifen therapy for mastalgia. *Arch Surg* 2006; **141:** 43–7.
11. Oksa S, *et al*. Toremifene for premenstrual mastalgia: a randomised, placebo-controlled crossover study. *BJOG* 2006; **113:** 713–18.
12. Hamed H, *et al*. LHRH analogue for treatment of recurrent and refractory mastalgia. *Ann R Coll Surg Engl* 1990; **72:** 221–4.
13. Mansel RE, *et al*. European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. *Am J Obstet Gynecol* 2004; **191:** 1942–9.
14. Khan HN, *et al*. Local anaesthetic and steroid combined injection therapy in the management of non-cyclical mastalgia. *Breast* 2004; **13:** 129–32.

Menorrhagia. Danazol is effective in the treatment of menorrhagia (p. 2300.3) but it is only used short term because of its adverse effects.[1] It may also be used for pre-operative endometrial thinning.[2]

1. Beaumont H, *et al*. Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
2. Sowter MC, *et al*. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 30/06/08).

Premenstrual syndrome. Danazol may be useful[1-3] in the management of the premenstrual syndrome (p. 2272.3), but some have found it to be of value only for cyclical mastalgia rather than for general symptoms,[4] and in any case adverse effects limit its long-term use.

1. Halbreich U, *et al*. Elimination of ovulation and menstrual cyclicity (with danazol) improves dysphoric premenstrual syndromes. *Fertil Steril* 1991; **56:** 1066–9.
2. Deeny M, *et al*. Low dose danazol in the treatment of the premenstrual syndrome. *Postgrad Med J* 1991; **67:** 450–4.
3. Hahn PM, *et al*. A randomized, placebo-controlled, crossover trial of danazol for the treatment of premenstrual syndrome. *Psychoneuroendocrinology* 1995; **20:** 193–209.
4. O'Brien PMS, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol* 1999; **180:** 18–23.

Skin disorders. Danazol has been reported to relieve pruritus (p. 1687.3) refractory to usual treatment with antihistamines; underlying conditions have included cholinergic urticaria,[1,2] chronic actinic dermatitis,[3] myeloproliferative disorders,[4] and auto-immune disorders.[4] In 2 reports, the skin disorder had been associated with low plasma concentrations of antiprotease.[1,3] Danazol has generally been given in oral doses of 200 to 800 mg daily.[4] Maintenance treatment may be needed, and relapse can occur when the dose is reduced or treatment is withdrawn.

Danazol was also reported to reduce induration and pain in a man with lipodermatosclerosis.[5]

1. Berth-Jones J, Graham-Brown RAC. Cholinergic pruritus, erythema and urticaria: a disease spectrum responding to danazol. *Br J Dermatol* 1989; **121:** 235–7.
2. La Shell MS, England RW. Severe refractory cholinergic urticaria treated with danazol. *J Drugs Dermatol* 2006; **5:** 664–7.
3. Humbert P, *et al*. Chronic actinic dermatitis responding to danazol. *Br J Dermatol* 1991; **124:** 195–7.
4. Kolodny L, *et al*. Danazol relieves refractory pruritus associated with myeloproliferative disorders and other diseases. *Am J Hematol* 1996; **51:** 112–16.
5. Hafner C, *et al*. Lipodermatosclerosis: successful treatment with danazol. *Acta Derm Venereol* 2005; **85:** 365–6.

Adverse Effects

Adverse effects of danazol that reflect inhibition of the pituitary-ovarian axis include menstrual disturbances and amenorrhoea (occasionally persistent), hot flushes, sweating, reduction in breast size, changes in libido, vaginal dryness and irritation, emotional lability, and nervousness.

Adverse effects attributable to androgenic activity include acne, oily skin or hair, mild hirsutism, oedema, weight gain, deepening of the voice, androgenic alopecia, and rarely clitoral hypertrophy. Testicular atrophy and a reduction in spermatogenesis may occur.

Other adverse effects include gastrointestinal disturbances, increased or decreased blood cell counts, thrombotic events, headache, backache, dizziness, tremor, depression, fatigue, sleep disorders, muscle spasm or cramp, rash, hyperglucagonaemia, abnormal glucose tolerance, decreased serum high-density-lipoprotein cholesterol, increased serum low-density-lipoprotein cholesterol, and elevation of liver-function test values and rarely cholestatic jaundice. Some patients may have palpitations, tachycardia, and hypertension. Benign intracranial hypertension and visual disturbances have occurred.

Effects on carbohydrate metabolism. Diabetes mellitus developed in a patient 8 weeks after starting danazol 400 mg twice daily for endometriosis[1] and resolved completely after the drug was stopped.

1. Seifer DB, *et al*. Insulin-dependent diabetes mellitus associated with danazol. *Am J Obstet Gynecol* 1990; **162:** 474–5.

Effects on the liver. As with other 17α-alkylated steroids (see p. 2308.1), hepatic adverse effects have been associated with danazol, including hepatitis[1] and cholestasis.[2,3] Hepatic adenoma has occurred after long-term danazol use.[4-7] Adenomas are often removed surgically because of the risks of haemorrhage and malignant transformation, but regression over 18 months and 2 years after stopping danazol has been described in 2 patients.[6] There have also been rare reports of focal nodular hyperplasia,[7,8] hepatocellular carcinoma,[9] and peliosis hepatis.[10]

A case of acute hepatic failure has been attributed to danazol in a patient already taking ciclosporin (see p. 2266.1).

1. Ohsawa T, Iwashita S. Hepatitis associated with danazol. *Drug Intell Clin Pharm* 1986; **20:** 889.
2. Boue F, *et al*. Danazol and cholestatic hepatitis. *Ann Intern Med* 1986; **105:** 139–40.
3. Bray GP, *et al*. Resolution of danazol-induced cholestasis with S-adenosylmethionine. *Postgrad Med J* 1993; **69:** 237–9.
4. Fermand JP, *et al*. Danazol-induced hepatocellular adenoma. *Am J Med* 1990; **88:** 529–30.
5. Bork K, *et al*. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet* 1999; **353:** 1066–7.
6. Bork K, Schneiders V. Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. *J Hepatol* 2002; **36:** 707–9.
7. Bartley J, *et al*. Hepatocellular adenoma and focal nodular hyperplasia after long-term use of danazol for endometriosis: a case report. *Arch Gynecol Obstet* 2004; **269:** 290–3.
8. Helsing P, Nielsen EW. Hepatocellular focal nodular hyperplasia after danazol treatment for hereditary angio-oedema. *Acta Derm Venereol* 2006; **86:** 272–3.
9. Confavreux C, *et al*. Danazol-induced hepatocellular carcinoma. *Q J Med* 2003; **96:** 317–18.
10. Makdisi WJ, *et al*. Fatal peliosis of the liver and spleen in a patient with agnogenic myeloid metaplasia treated with danazol. *Am J Gastroenterol* 1995; **90:** 317–8.

Effects on the pancreas. There have been reports of pancreatitis in patients receiving danazol.[1,2]

1. Chevalier X, *et al*. Danazol induced pancreatitis and hepatitis. *Clin Rheumatol* 1990; **9:** 239–41.
2. Balasch J, *et al*. Acute pancreatitis associated with danazol treatment for endometriosis. *Hum Reprod* 1994; **9:** 1163–5.

Effects on the skin and hair. There have been isolated reports of erythema multiforme occurring in patients given danazol. In 3 cases the reaction developed about 2 weeks after starting danazol, and was effectively managed by stopping danazol and treating with corticosteroids.[1,2]

Hirsutism is a recognised adverse effect of danazol, but is usually mild. Excessive facial hair growth of sudden onset,

sufficient to cause distress, has been described in a woman given danazol for mastalgia. The hirsutism improved after stopping the danazol.[3]

1. Gately LE, Andes WA. Danazol and erythema multiforme. *Ann Intern Med* 1988; **109:** 85.
2. Reynolds NJ, Sansom JE. Erythema multiforme during danazol therapy. *Clin Exp Dermatol* 1992; **17:** 140.
3. Zawar V, Sankalecha C. Facial hirsutism following danazol therapy. *Cutis* 2004; **74:** 301–3.

Precautions

Danazol should be used with caution in conditions that may be adversely affected by fluid retention, such as in cardiovascular, hepatic, and renal disorders; it should be avoided in marked dysfunction. It should also be used with care in patients with diabetes mellitus, polycythaemia, abnormal blood lipids, migraine, or epilepsy. Danazol should not be given to patients with undiagnosed genital bleeding or androgen-dependent tumours. As with other 17α-alkylated compounds, there is an increased risk of liver disorders and liver function should be monitored during therapy. It should not be used in patients with a thromboembolic disorder or a history of thrombosis.

Danazol should not be given during pregnancy because of a possible androgenic effect on the female fetus (see below), and non-hormonal contraception is recommended during treatment. Caution is required in children and adolescents since precocious sexual development may occur in boys and virilisation in girls, and premature epiphyseal closure may occur in both sexes.

In the event of androgenic effects, danazol should be withdrawn, as they may prove irreversible on continued use.

Breast feeding. Licensed product information warns that danazol should be avoided in breast-feeding women because of the theoretical potential for androgenic effects in the infant.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies danazol as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Reports of masculinisation of female infants born to mothers who had received danazol during pregnancy.[1-3]

1. Shaw RW, Farquhar JW. Female pseudohermaphroditism associated with danazol exposure in utero: case report. *Br J Obstet Gynaecol* 1984; **91:** 386–9.
2. Kingsbury AC. Danazol and fetal masculinization: a warning. *Med J Aust* 1985; **143:** 410–11.
3. Brunskill PJ. The effects of fetal exposure to danazol. *Br J Obstet Gynaecol* 1992; **99:** 212–15.

Interactions

Therapy with danazol may inhibit the hepatic metabolism of several drugs including carbamazepine (see p. 517.3), ciclosporin (see below), and possibly tacrolimus (see p. 1973.2). Danazol may also enhance the effects of warfarin (see Sex Hormones under Warfarin, p. 1535.1). Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol (see p. 2118.1). Rhabdomyolysis has been attributed to use of danazol with statins (see p. 1495.2).

Ciclosporin. Danazol may raise ciclosporin concentrations (see p. 1955.1), possibly by inhibiting its metabolism.

A case of fatal acute hepatic failure due to centrilobular massive hepatic necrosis was attributed to danazol in a patient already taking ciclosporin.[1] Danazol may have raised the ciclosporin concentrations in this case, but the authors speculated that an alternative interaction between the two drugs might have played a role in this reaction to danazol.

1. Hayashi T, *et al.* Fatal acute hepatic failure induced by danazol in a patient with endometriosis and aplastic anemia. *J Gastroenterol* 2001; **36:** 783–6.

Pharmacokinetics

Danazol is absorbed from the gastrointestinal tract and metabolised in the liver; absorption is markedly increased if it is taken with food. A plasma elimination half-life of 3 to 6 hours has been reported after a single dose, but is increased to about 26 hours with repeated dosing. Ethisterone, 2-hydroxymethylethisterone, and 17-hydroxymethylethisterone are the major metabolites, though none have pituitary inhibiting activity. Danazol and its metabolites may undergo enterohepatic circulation. Metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ladogal; ***Austral.***: Azol; Danocrine†; ***Austria***: Danokrin; ***Belg.***: Danatrol; ***Braz.***: Ladogal; ***Canad.***: Cyclomen; ***China***: Gong Fu Yi Kang (宫福伊康); ***Cz.***: Danoval; ***Fr.***: Danatrol; ***Gr.***: Danatrol; ***Hong Kong***: Anargil; Azol†; Danocrine; ***Hung.***: Danoval; ***India***: Benzol; Danogen; Endozol; Gonablok; Gynadom; Gynazol; Gynodan; Ladogal; Zendol; ***Indon.***: Azol; Danocrine; ***Irl.***: Danol†; ***Israel***: Danol; ***Ital.***: Danatrol; ***Jpn***: Bonzol; ***Malaysia***: Anargil; Azol†; Ladogal; Nazol; ***Mex.***: Danalem; Ladogal; Novaprin; ***Neth.***: Danatrol; ***NZ***: Azol; D-Zol†; ***Philipp.***: Ladogal; ***Port.***: Danatrol; ***Rus.***: Danol (Данол); Danoval (Дановал); ***S.Afr.***: Danogen; Ladazol; ***Singapore***: Azol†; Ladogal; Nazol; ***Spain***: Danatrol; ***Switz.***: Danatrol†; ***Thai.***: Anargil; Ectopal; Ladogal; Vabon; ***Turk.***: Danasin; ***UK***: Danol; ***Venez.***: Danogen; Ladogal.

Pharmacopoeial Preparations
USP 36: Danazol Capsules.

Degarelix *(BAN, USAN, rINN)*

Dégarélix; Degarelixum; FE-200486 (degarelix or degarelix acetate); Дегареликс.

N-Acetyl-3-(naphthalen-2-yl)-D-alanyl-4-chloro-D-phenylalanyl-3-(pyridin-3-yl)-D-alanyl-L-seryl-4-({[(4*S*)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl}amino)-L-phenylalanyl-4-(carbamoylamino)-Dphenylalanyl-L-leucyl-N^6-(1-methylethyl)-L-lysyl-Lprolyl-D-alaninamide.

$C_{82}H_{103}ClN_{18}O_{16}$=1632.3

CAS — 214766-78-6.

ATC — L02BX02.

ATC Vet — QL02BX02.

UNII — SX0XJI3A11.

Degarelix Acetate *(USAN, rINNM)*

Acetato de degarelix; Dégarélix, Acétate de; Degarelixi Acetas; FE-200486 (degarelix or degarelix acetate); Дегареликс Ацетат.

$C_{82}H_{103}ClN_{18}O_{16}.xC_2H_4O_2.nH_2O$

CAS — 934246-14-7.

ATC — L02BX02.

ATC Vet — QL02BX02.

UNII — I18589P20R.

Uses and Administration

Like cetrorelix (p. 2257.2), degarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used to reduce testosterone concentrations in the hormonal therapy of advanced prostate cancer (p. 712.3). Degarelix is given as the acetate, but doses are expressed in terms of the base. It is given as a subcutaneous depot injection in the abdominal area. An initial dose of degarelix 240 mg is given in two separate injections of 120 mg, as a solution of 40 mg/mL. Maintenance doses of 80 mg are then given once every 28 days, as a solution of 20 mg/mL.

References.

1. Van Poppel H, *et al.* Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker—results from a 1-yr, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. *Eur Urol* 2008; **54:** 805–13.
2. Gittelman M, *et al.* Degarelix Study Group. A 1-year, open label, randomized phase II dose finding study of degarelix for the treatment of prostate cancer in North America. *J Urol (Baltimore)* 2008; **180:** 1986–92.
3. Klotz L, *et al.* The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008; **102:** 1531–8.
4. Frampton JE, Lyseng-Williamson KA. Degarelix. *Drugs* 2009; **69:** 1967–76.
5. Steinberg M. Degarelix: a gonadotropin-releasing hormone antagonist for the management of prostate cancer. *Clin Ther* 2009; **31:** 2312–31.

Adverse Effects and Precautions

Injection site reactions of pain and erythema are very common with degarelix, while swelling, induration, and nodules occur less often but may still be common. Transient chills, fever, and flu-like symptoms may occur hours after dosing. Other effects commonly reported for degarelix have included increases in liver enzyme values, insomnia, dizziness, headache, and gastrointestinal disturbances.

Hot flushes are a very common consequence of androgen suppression by degarelix, while night sweats, fatigue, and weight gain are common complaints. Degarelix can also contribute to loss of libido, erectile dysfunction, testicular atrophy, and gynaecomastia. Long-term androgen deprivation therapy in general has also been associated with prolongation of the QT interval and decreases in bone density.

Pharmacokinetics

Degarelix is about 90% bound to plasma proteins. It undergoes peptide hydrolysis in the hepato-biliary system, and is mainly excreted as peptide fragments in the faeces. About 20 to 30% of a dose is renally excreted. Degarelix is injected to form a subcutaneous depot, and the pharmacokinetics of the drug is strongly influenced by the concentration of the injected solution. After subcutaneous injection of 240 mg at a concentration of 40 mg/mL, degarelix has a terminal half-life of about 43 to 53 days; after maintenance doses of 80 mg as 20 mg/mL the half-life is about 28 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Firmagon; ***Austria***: Firmagon; ***Belg.***: Firmagon; ***Canad.***: Firmagon; ***Cz.***: Firmagon; ***Denm.***: Firmagon; ***Fr.***: Firmagon; ***Ger.***: Firmagon; ***Gr.***: Firmagon; ***Irl.***: Firmagon; ***Israel***: Firmagon; ***Jpn***: Gonax; ***Neth.***: Firmagon; ***Norw.***: Firmagon; ***Pol.***: Firmagon; ***Port.***: Firmagon; ***Swed.***: Firmagon; ***Switz.***: Firmagon; ***UK***: Firmagon; ***USA***: Firmagon.

Delmadinone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de delmadinona; Delmadinona, acetato de; Delmadinonacetat; Delmadinone, Acétate de; Delmadinoni Acetas; Delmadinoniasetaatti; RS-1301; Дельмадинона Ацетат.

6-Chloro-17α-hydroxypregna-1,4,6-triene-3,20-dione acetate.

$C_{23}H_{27}ClO_4$=402.9

CAS — 15262-77-8 (delmadinone); 13698-49-2 (delmadinone acetate).

ATC Vet — QG03DX91.

UNII — 92833M0LD9.

Profile

Delmadinone acetate is a progestogen with anti-androgenic and anti-oestrogenic activity. It is used as an anti-androgen in veterinary practice.

Deslorelin *(BAN, USAN, rINN)* ⊗

Deslorelina; Desloréline; Deslorelinum; D-Trp LHRH-PEA; Дезлорелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

$C_{64}H_{83}N_{17}O_{12}$=1282.5

CAS — 57773-65-6.

ATC Vet — QH01CA93.

UNII — TKG3I66TVE.

Profile

Deslorelin is an analogue of gonadorelin (p. 2280.2) that has been investigated in the treatment of precocious puberty, short stature, prostate cancer, and endometriosis.

References.

1. Anonymous. Deslorelin: D-Trp-LHRH-PEA, LHRH agonist analogue, Somagard. *Drugs R D* 1999; **2:** 420–2.
2. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
3. Yanovski JA, *et al.* Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 2003; **348:** 908–17.
4. Weise M, *et al.* Determinants of growth during gonadotropin-releasing hormone analog therapy for precocious puberty. *J Clin Endocrinol Metab* 2004; **89:** 103–7.

Desogestrel *(BAN, USAN, rINN)*

Desogestreeli; Désogestrel; Desogestrelum; Dezogestrel; Org-2969; Дезогестрел.

13β-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17β-ol.

$C_{22}H_{30}O$=310.5

CAS — 54024-22-5.

ATC — G03AC09.

ATC Vet — QG03AC09.

UNII — 81K9V7M3A3.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Desogestrel). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane; very soluble in methyl alcohol.

Uses and Administration

Desogestrel is a progestogen (see Progesterone, p. 2300.2) structurally related to levonorgestrel that is used as a hormonal contraceptive (see p. 2231.3). A typical daily dose of 150 micrograms is used as the progestogenic component

of monophasic combined oral contraceptive preparations. Doses of 50 to 150 micrograms daily may be used in triphasic combined preparations. A dose of 75 micrograms daily is used as an oral progestogen-only contraceptive; unlike traditional progestogen-only contraceptives, desogestrel is said to reliably inhibit ovulation. Progestogen-only contraceptive efficacy is reduced if a dose of desogestrel is delayed by more than 12 hours.

Contraception. The effects of a progestogen-only contraceptive containing desogestrel have been reported.[1-3] Oral desogestrel has also been investigated as a male contraceptive, combined with testosterone given by intramuscular injection,[4] subcutaneous implant,[5,6] or transdermal patch.[7]

1. Collaborative study group on the desogestrel-containing progestogen-only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. *Eur J Contracept Reprod Health Care* 1998; **3:** 169–78.
2. Rice CF, *et al.* A comparison of the inhibition of ovulation achieved by desogestrel 75 micrograms and levonorgestrel 30 micrograms daily. *Hum Reprod* 1999; **14:** 982–5.
3. Korver T, *et al.* Maintenance of ovulation inhibition with the 75-microgram desogestrel-only contraceptive pill (Cerazette) after scheduled 12-h delays in tablet intake. *Contraception* 2005; **71:** 8–13.
4. Wu FCW, *et al.* Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis, and lipid metabolism. *J Clin Endocrinol Metab* 1999; **84:** 112–22.
5. Kinniburgh D, *et al.* Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. *Hum Reprod* 2002; **17:** 1490–1501.
6. Anderson RA, *et al.* Investigation of hormonal male contraception in African men: suppression of spermatogenesis by oral desogestrel with depot testosterone. *Hum Reprod* 2002; **17:** 2869–77.
7. Hair WM, *et al.* A novel male contraceptive pill-patch combination: oral desogestrel and transdermal testosterone in the suppression of spermatogenesis in normal men. *J Clin Endocrinol Metab* 2001; **86:** 5201–9.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. When used as a progestogen-only contraceptive, irregular bleeding is more common with desogestrel than with other progestogen-only preparations. Desogestrel is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that desogestrel-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p. 2238.1, and for precautions, see p. 2241.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desogestrel in combined hormonal contraceptives as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

After oral doses, desogestrel undergoes oxidative transformation in the intestinal mucosa and liver to its active metabolite 3-keto-desogestrel (etonogestrel—see p. 2277.3).

References.

1. Madden S, *et al.* Metabolism of the contraceptive steroid desogestrel by the intestinal mucosa. *Br J Clin Pharmacol* 1989; **27:** 295–9.
2. Madden S, *et al.* Metabolism of the contraceptive steroid desogestrel by human liver in vitro. *J Steroid Biochem* 1990; **35:** 281–8.
3. Kuhnz W, *et al.* Protein binding of the contraceptive steroids gestodene, 3-keto-desogestrel and ethinyloestradiol in human serum. *J Steroid Biochem* 1990; **35:** 313–18.
4. Kuhnz W, *et al.* Pharmacokinetics and serum protein binding of 3-keto-desogestrel in women during three cycles of treatment with a low-dose combination oral contraceptive. *Arzneimittelforschung* 1992; **42:** 1142–6.
5. Timmer CJ, *et al.* Bioavailability and bioequivalence of etonogestrel from two oral formulations of desogestrel: Cerazette and Liseta. *Eur J Drug Metab Pharmacokinet* 1999; **24:** 335–43.
6. Verhoeven CH, *et al.* Excretion and metabolism of desogestrel in healthy postmenopausal women. *J Steroid Biochem Mol Biol* 2001; **78:** 471–80.
7. Korhonen T, *et al.* The role of CYP2C and CYP3A in the disposition of 3-keto-desogestrel after administration of desogestrel. *Br J Clin Pharmacol* 2005; **60:** 69–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Camelia; Carmin; Cerazette; Lumilac; ***Austria***: Cerazette; ***Belg.***: Cerazette; Lueva; ***Braz.***: Cerazette; Kelly; ***Chile***: Arlette; Cerazette; Lactafem; Nogesta; Vanish; ***Cz.***: Azalia; Cerazette; Fleur; ***Denm.***: Cerazet; Cerazette; Nacrez; ***Fin.***: Cerazette; ***Fr.***: Cerazette; ***Ger.***: Cerazette; ***Gr.***: Cerazette; ***Hong Kong***: Cerazette; ***Hung.***: Azalia; Cerazette; ***India***: Cerazette; ***Indon.***: Cerazette; ***Irl.***: Cerazette; ***Israel***: Cerazette; ***Ital.***: Cerazet; Cerazette; ***Mex.***: Cerazette; ***Neth.***: Cerazette; ***Norw.***: Cerazette; ***NZ***: Cerazette; ***Philipp.***: Cerazette; ***Pol.***: Azalia; Cerazette; ***Port.***: Cerazette; ***Rus.***: Cerazette (Чарозетта); Lactinette (Лактинет); ***Spain***: Azalia; Cerazet; ***Swed.***: Cerazette; ***Switz.***: Cerazette; ***Thai.***: Cerazette; ***UK***: Aizea; Cerazette; Cerelle; Zelleta; ***Ukr.***: Cerazette (Чарозетта); Lactinette (Лактинет); ***Venez.***: Arlette; Cerazette.

Multi-ingredient Preparations. ***Arg.***: Marvelon; Mercilon; ***Austral.***: Marvelon; ***Austria***: Gracial; Liberel; Marvelon; Mercilon; ***Belg.***: Desorelle†; Gracial; Marvelon; Mercilon; Ovidol; ***Braz.***: Femina; Gestradiol; Gracial; Malu; Mercilon Conti; Mercilon; Microdiol; Minian; Novial; Primera; Primeravinte†; ***Canad.***: Apri; Linessa; Marvelon; Ortho-Cept; ***Chile***: Ciclidon; Conti-Marvelon; Dal; Desoren; Gracial; Gynostat; Marvelon; Midalet; Miniestrel; Neolette; ***China***: Mercilon (美欣乐); ***Cz.***: Adele; Gracial; Laurina; Marvelon; Mercilon; Natalya; Novynette; Regulon; Tricia; ***Denm.***: Daisynelle; Desorelle; Femelle; Femigen; Femistad; Gracial; Marvelon; Mercilon; Novynette; ***Fin.***: Gracial; Laurina; Marvelon; Mercilon; ***Fr.***: Cycleane†; Desobel; Mercilon; Varnoline; ***Ger.***: Biviol; Cyclosa†; Desmin; Lamuna†; Lovelle; Marvelon; Novial; Oviala; Oviol†; ***Gr.***: Gracial; Laurina; Marvelon; Mercilon; ***Hong Kong***: Gracial; Marvelon; Mercilon; Novynette; ***Hung.***: Gracial; Laurina; Marvelon; Mercilon; Novynette; Regulon; Samba; ***India***: Femilon; Locipil; Novelon; ***Indon.***: Marvelon; Mercilon; ***Irl.***: Gracial; Leticia; Marviol; Mercilon; Vivides; ***Israel***: Feminet; Mercilon; Microdiol; ***Ital.***: Dueva; Gracial; Lucille; Mercilon; Novynette; Planum; Practil; Securgin; ***Malaysia***: Marvelon; Mercilon; Novynette; Regulon; ***Mex.***: Desmin; Detegen; Marvelon; Mercilon; Novial; ***Neth.***: Gracial; Juliane; Laurina; Lonicera; Marvelon; Mercilon; Ovidol†; ***Norw.***: Marvelon; Mercilon; ***NZ***: Marvelon; Mercilon; ***Philipp.***: Gracial; Marvelon; Mercilon; ***Pol.***: Marvelon; Mercilon; Novynette; Regulon; ***Port.***: Gracial; Laurina; Marvelon; Mercilon; Novynette; Regulon; ***Rus.***: Marvelon (Марвелон); Mercilon (Мерсилон); Novynette (Новинет); Regulon (Регулон); Tri-Merci (Три-Мерси); ***S.Afr.***: Marvelon; Mercilon; ***Singapore***: Marvelon; Mercilon; ***Spain***: Bemasive; Gracial; Microdiol; Regulon; Suavuret; ***Swed.***: Desolett; Mercilon; Trimiron†; ***Switz.***: Desoren; Gracial; Marvelon; Mercilon; ***Thai.***: Daisy; Marvelon; Mercilon; Minny; Novynette; Oilezz; ***Turk.***: Desolett; Myralon; ***UK***: Cimizt; Gedarel; Marvelon; Mercilon; ***Ukr.***: Marvelon (Марвелон); Mercilon (Мерсилон); Novynette (Новинет); Regulon (Регулон); Tri-Merci (Три-Мерси); ***USA***: Apri; Azurette; Caziant; Cesia; Cyclessa; Desogen; Kariva; Mircette; Ortho-Cept; Reclipsen; Solia; Velivet; Viorele; ***Venez.***: Ciclidon; Marvelon; Mercilon; Mipil; Novial.

Pharmacopoeial Preparations
BP 2014: Desogestrel Tablets;
USP 36: Desogestrel and Ethinyl Estradiol Tablets.

Dienestrol *(BAN, rINN)*

Dehydrostilbestrol; Dièn estrol; Dienestroli; Dienestrolis; Dienestrolum; Dienoestrol; Dienoestrolum; Dienösztrol; Oestrodienolum; Диенэстрол.

(E,E)-4,4′-[Di(ethylidene)ethylene]diphenol; 4,4′-(1,2-Diethylidene-1,2-ethanediyl)bisphenol.

$C_{18}H_{18}O_2$=266.3

CAS — 84-17-3 (dienestrol); 13029-44-2 ((E,E)-dienestrol).

ATC — G03CB01.

ATC Vet — QG03CB01; QG03CC02.

UNII — RRW32X4U1F.

Pharmacopoeias. In *US*.

USP 36: (Dienestrol). Colourless, white, or practically white needle-like crystals, or white or practically white crystalline powder. It is odourless. Practically insoluble in water; soluble in alcohol, in acetone, in ether, in methyl alcohol, in propylene glycol, and in solutions of alkali hydroxides; slightly soluble in chloroform and in fatty oils.

Profile

Dienestrol is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (below). It has been used as a vaginal cream in the treatment of menopausal atrophic vaginitis. If used on a long-term basis in women with a uterus a progestogen is required.

Dienestrol diacetate has been used as an ingredient of topical preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Ortho-Dienestrol†.

Pharmacopoeial Preparations
USP 36: Dienestrol Cream.

Dienogest *(BAN, USAN, rINN)*

Diénogest; Dienogesti; Dienogestum; STS-557; Диеногест.

17-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile.

$C_{20}H_{25}NO_2$=311.4

CAS — 65928-58-7.

UNII — 46M3EV8HHE.

Profile

Dienogest is a nonethinylated progestogen (see Progesterone, p. 2300.2) structurally related to nortestosterone. It is reported to have anti-androgenic properties. Dienogest is used as the progestogen component of some combined oral contraceptives (see p. 2231.3). A dose of 2 mg daily is typically used in monophasic preparations, and doses of 2 or 3 mg daily may be found in multiphasic sequential preparations. It is also used as the progestogen component in menopausal HRT (see p. 2244.1) in a daily dose of 2 mg. In the management of endometriosis (p. 2264.1) an oral dose of dienogest 2 mg daily is used; it is given in a continuous regimen regardless of menstrual bleeding.

Reviews.

1. Foster RH, Wilde MI. Dienogest. *Drugs* 1998; **56:** 825–33.
2. Wellington K, Perry CM. Estradiol valerate/dienogest. *Drugs* 2002; **62:** 491–504.
3. Hoy SM, Scott LJ. Estradiol valerate/dienogest: in oral contraception. *Drugs* 2009; **69:** 1635–46.
4. Pérez-Campos EF. Ethinylestradiol/dienogest in oral contraception. *Drugs* 2010; **70:** 681–9.
5. McCormack PL. Dienogest: a review of its use in the treatment of endometriosis. *Drugs* 2010; **70:** 2073–88.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dienogest and oestrogen combinations as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Visanne; ***Austria***: Visanne; ***Canad.***: Visanne; ***Cz.***: Visanne; ***Denm.***: Visanne; ***Fin.***: Visanne; ***Ger.***: Visanne; ***Gr.***: Visannette; ***Hung.***: Visanne; ***Israel***: Visabelle; ***Jpn***: Dinagest; ***Neth.***: Visanne; ***Norw.***: Visanne; ***Port.***: Visanne; ***Singapore***: Visanne; ***Spain***: Visannette; ***Swed.***: Visanne; ***Switz.***: Visanne.

Multi-ingredient Preparations. ***Arg.***: Dienopil; Florence; Rubi; ***Austral.***: Qlaira; Valette; ***Austria***: Motion; Qlaira; Valette; ***Belg.***: Climodien; Qlaira; ***Chile***: Gianda; Tinelle; ***Cz.***: Dienille; Dienorette; Jeanine; Klimodien; Qlaira; ***Denm.***: Climodien†; Qlaira; ***Fin.***: Qlaira; ***Fr.***: Climodiene; Qlaira; ***Ger.***: Climodien; Lafamme; Maxim; Qlaira; Valette; ***Gr.***: Climodien; Qlaira; ***Hung.***: Dienille; Qlaira; ***Irl.***: Qlaira; ***Israel***: Qlair; ***Ital.***: Klaira; ***Neth.***: Climodien; Lafamme; Qlaira; ***Norw.***: Climodien†; Qlaira; ***Pol.***: Atywia; Jeanine; Qlaira; ***Port.***: Climodien; Lafamme; Qlaira; Valette; ***Rus.***: Climodien (Климодиен); Jeanine (Жанин); ***Singapore***: Qlaira; ***Spain***: Ailyn; Climodien; Danielle; Donabel; Mevaren; Qlaira; ***Swed.***: Climodien†; Qlaira; ***Turk.***: Climodien; ***UK***: Qlaira; ***Ukr.***: Jeanine (Жанин); Klimodien (Климодиен)†; Silhouette (Силует); ***USA***: Natazia.

Diethylstilbestrol *(BAN, rINN)*

DES; Diéthylstilbestrol; Diethylstilbestrolum; Diethylstilboestrol; Dietilestilbestrol; Dietilstilbestrolis; Dietilstilbösztrol; Dietylstilbestrol; Dietyylistilbestroli; Estilbestrol; NSC-3070; Stilbestrol; Stilboestrol; Диэтилстильбэстрол.

(*E*)-α,β-Diethylstilbene-4-4′-diol.

$C_{18}H_{20}O_2$=268.4

CAS — 56-53-1.

ATC — G03CB02; L02AA01.

ATC Vet — QG03CB02; QG03CC05; QL02AA01.

UNII — 731DCA35BT.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Diethylstilbestrol). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 36: (Diethylstilbestrol). A white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, in fatty oils, and in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Diethylstilbestrol Dipropionate *(BANM, rINNM)*

Diéthylstilbestrol, Dipropionate de; Diethylstilbestroli Dipropionas; Dietilestilbestrol, dipropionato de; Dipropionato de dietilestilbestrol; Stilboestrol Dipropionate; Диэтилстильбэстрола Дипропионат.

(*E*)-α,β-Diethylstilbene-4,4′-diol dipropionate.

$C_{24}H_{28}O_4$=380.5

CAS — 130-80-3.

ATC — G03CB02; L02AA01.

ATC Vet — QG03CB02; QL02AA01.
UNII — Y98CK3J0OL.

Uses and Administration

Diethylstilbestrol is a synthetic nonsteroidal oestrogen that has been used in the palliation of breast and prostate cancer.

Daily oral doses of 10 to 20 mg are occasionally used in the palliative treatment of malignant neoplasms of the breast (p. 702.1) in postmenopausal women. The usual oral dose in carcinoma of the prostate (p. 712.3) is 1 to 3 mg daily; higher doses were formerly given. Diethylstilbestrol has also been used in the treatment of prostatic carcinoma in the form of its diphosphate salts (see Fosfestrol, p. 2279.1).

Diethylstilbestrol has been used as pessaries in the short-term management of menopausal atrophic vaginitis.

Adverse Effects and Precautions

Dose-related adverse effects of diethylstilbestrol include nausea, fluid retention, and arterial and venous thrombosis, and these effects are common at the doses used for palliation of cancer. Impotence and gynaecomastia occur in men, and withdrawal bleeding may occur in women, as may hypercalcaemia and bone pain in women treated for breast cancer. Diethylstilbestrol should be used with caution in those with cardiovascular disease or renal or hepatic impairment. Use of diethylstilbestrol is contra-indicated if pregnancy is suspected.

Adverse effects and precautions of oestrogens in general (steroidal compounds) are covered under Estradiol, on p. 2273.2.

Historically, high doses of diethylstilbestrol and related substances were used for 'hormonal support' in pregnant women to try to prevent miscarriages and preterm births, most commonly in the USA. This practice was later shown to be ineffective. Adverse effects on the genito-urinary tract of offspring of these women have been noted. In particular, an increased incidence of changes in the cervix and vagina including adenosis and rarely clear-cell adenocarcinoma has been seen in postpubertal daughters of women who received diethylstilbestrol or related substances during pregnancy (see below). A possible increased incidence of abnormalities of the genital tract and of abnormal spermatozoa has been reported in male offspring similarly exposed (see below). The recipients themselves appear to be at a small increased risk of breast cancer (see below).

Carcinogenicity. *BREAST.* No statistically significant difference in the incidence of breast cancer was found among a group of 693 women given diethylstilbestrol during pregnancy 25 years earlier compared with a control group of 668 who were not.[1] This finding was, however, criticised[2] on the basis that the study lacked the statistical power to reject the null hypothesis. In another study[3] the incidence of breast cancer in 3033 women who had taken diethylstilbestrol in pregnancy during the period 1940 to 1960 was compared with the incidence in a comparable group of unexposed women. This study involved over 85 000 women-years of follow-up in each group and it was found that the incidence of breast cancer per 100 000 women-years was 134 in the exposed group and 93 in the unexposed group (a relative risk of 1.4). The authors concluded that in those women given diethylstilbestrol there was a moderately increased incidence of breast cancer but that some unrecognised concomitant of exposure could not be excluded as a possibility for the increase. Although this study suggested that the risk increased over time, subsequent follow-up,[4] while confirming a modest increase in risk overall, did not confirm a higher risk in these women as time went on. Further follow-up and analysis[5] of the combined data from these cohort studies[1,3,4] confirmed a modest increase in risk of breast cancer associated with diethylstilbestrol (relative risk 1.27, 95% confidence interval 1.07 to 1.52). Another large population cohort study[6] suggested that the risk of fatal breast cancer might also be increased in women who had been given diethylstilbestrol.

Two cases of breast cancer[7] in premenopausal women exposed to diethylstilbestrol *in utero* have raised the possibility that the risk of breast cancer may be increased in these women, in addition to the known genito-urinary risk (see below under Pregnancy, Effects on Female Offspring). However, a cohort study[8] involving 4536 women exposed *in utero* found no increased risk of other cancers overall, and did not show an increased risk of breast cancer (relative risk 1.18; 95% confidence intervals 0.56 to 2.49). A later study[9] of further follow-up of this cohort, plus additional data from another group, found that although the risk overall and for younger women was not increased, from the age of 40 years the risk increased to 1.91 (95% confidence interval 1.09 to 3.33). The risk appeared to increase further with greater age, but the relatively small number of cases in women aged 50 years and over made this harder to establish.

1. Bibbo M, *et al.* A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. *N Engl J Med* 1978; **298:** 763–7.
2. Clark LC, Portier KM. Diethylstilbestrol and the risk of cancer. *N Engl J Med* 1979; **300:** 263–4.
3. Greenberg ER, *et al.* Breast cancer in mothers given diethylstilbestrol in pregnancy. *N Engl J Med* 1984; **311:** 1393–8.
4. Colton T, *et al.* Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. *JAMA* 1993; **269:** 2096–2100.
5. Titus-Ernstoff L, *et al.* Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001; **84:** 126–33.
6. Calle EE, *et al.* Diethylstilbestrol and risk of fatal breast cancer in a prospective cohort of US women. *Am J Epidemiol* 1996; **144:** 645–52.
7. Huckell C, *et al.* Premenopausal breast cancer after in-utero exposure to stilboestrol. *Lancet* 1996; **348:** 331.
8. Hatch EE, *et al.* Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 1998; **280:** 630–4.
9. Palmer JR, *et al.* Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 1509–14.

GENITO-URINARY TRACT. See below under Pregnancy, Effects on Female Offspring.

KIDNEY. Renal carcinoma was associated with the long-term use of diethylstilbestrol for prostate cancer in 2 men.[1]

1. Nissenkorn I, *et al.* Oestrogen-induced renal carcinoma. *Br J Urol* 1979; **51:** 6–9.

LIVER. Hepatic angiosarcoma developed in a 76-year-old man who had received diethylstilbestrol 3 mg daily for 12 years.[1] Hepatoma developed in another elderly man who had received a similar dose for 4.5 years.[2]

1. Hoch-Ligeti C. Angiosarcoma of the liver associated with diethylstilbestrol. *JAMA* 1978; **240:** 1510–11.
2. Brooks JJ. Hepatoma associated with diethylstilbestrol therapy for prostate carcinoma. *J Urol (Baltimore)* 1982; **128:** 1044–5.

Effects on the blood. Adverse haematological effects reported with diethylstilbestrol have included severe bone-marrow changes in a 71-year-old man given diethylstilbestrol in a massive dose of 150 mg daily for 7 years[1] and fatal immune haemolytic anaemia in a 69-year-old man given weekly infusions of diethylstilbestrol 1 g for 9 weeks.[2] The latter reaction was due to an IgG antibody specific for diethylstilbestrol.

1. Anderson AL, Lynch EC. Myelodyspoietic syndrome associated with diethylstilbestrol therapy. *Arch Intern Med* 1980; **140:** 976–7.
2. Rosenfeld CS, *et al.* Diethylstilbestrol-associated hemolytic anemia with a positive direct antiglobulin test result. *Am J Med* 1989; **86:** 617–18.

Pregnancy. *EFFECTS ON FEMALE OFFSPRING.* The DESAD (Diethylstilbestrol and Adenosis) Project carried out by the National Cancer Institute in the USA led to several reports linking exposure to diethylstilbestrol *in utero* to adverse genital-tract effects.[1-3] It was reported that of nearly 300 young females with clear-cell adenocarcinoma of the genital tract, more than 80% had been exposed *in utero* to diethylstilbestrol-type hormones.[1] Patients had been aged 7 to 28 years at the time of diagnosis. Doses and duration of treatment varied widely; the association existed for both 1.5 mg of diethylstilbestrol daily throughout pregnancy and variable amounts for a week or more during the first trimester. Vaginal adenosis, rare in unexposed young women, was present in about a third of those exposed in the first 4 months of pregnancy, and cervical ectropion in more than two-thirds. Vaginal epithelial changes were most closely associated with early exposure to diethylstilbestrol, with the total dose, and with the duration of exposure; their incidence decreased with age. The risk of cancer in the first 25 years after exposure was small.[2] Fertility did not appear to be impaired in women who had been exposed *in utero* to diethylstilbestrol but the relative risk of an unfavourable outcome of pregnancy in such a group was 1.69. However, of the women who became pregnant, 81% of those exposed to diethylstilbestrol and 95% of control subjects had at least one full-term live birth.[3] In a review of vaginal adenosis and its association with maternal diethylstilbestrol ingestion during pregnancy[4] it was noted that the link between diethylstilbestrol and particularly the benign changes in the vagina and cervix (adenosis) seemed well established. The association between this drug and the development of genital malignancies was less clear, and the very low incidence in the prospective studies in the USA supported this concept. The problem was rare in the UK, but clinicians should be aware that it existed. Cases of vaginal adenosis in young women should be investigated and screened appropriately, and preferably referred to centres where colposcopic expertise was available. Treatment of simple vaginal adenosis should be avoided.

Later reviews[5,6] have highlighted the fact that adverse effects were still emerging in women who had been exposed to diethylstilbestrol *in utero* several decades before. The need for thorough medical screening of such women was emphasised; genital-tract examination was particularly important. It was pointed out[6] that many women exposed to diethylstilbestrol *in utero* were in the reproductive stage of their lives and warranted special observation since a diethylstilbestrol-damaged genital tract posed a potential problem during pregnancy.[5,6] It has also been suggested, for example, that such women are at increased risk of developing pre-eclampsia.[7,8]

There has been concern about the possibility of transgenerational effects on the grandchildren of women given diethylstilbestrol during pregnancy. There has been very little reported on *female offspring of exposed women*, but there were no breast or gynaecological abnormalities found on examination of 28 daughters (over 15 years of age) of women who had been exposed *in utero* and had in many cases cervical and/or vaginal changes characteristic of diethylstilbestrol exposure.[9] Limited data from a Dutch cohort[10] of 16 284 mothers and 8934 sons suggested that the *male offspring of exposed women* may in turn be at greatly increased risk of hypospadias, although the absolute risk was small. A case-control study[11] also found an increased risk, but of a much smaller magnitude, and another cohort study[12] (including DESAD data) found no support for a greatly increased risk of hypospadias. The earlier cohort study that reported the greatly increased risk may have been affected by factors related to infertility, as the study was done in a cohort of subfertile women, about half of whom had undergone IVF.

Further information on the adverse effects of diethylstilbestrol in females exposed to the drug *in utero* can be obtained from the references listed below.[13-23] For mention of the possible increased risk of breast cancer in these women, see Carcinogenicity, above.

1. Professional and Public Relations Committee of the DESAD (Diethylstilbestrol and Adenosis) Project of the Division of Cancer Control and Rehabilitation. Exposure in utero to diethylstilbestrol and related synthetic hormones: association with vaginal and cervical cancers and other abnormalities. *JAMA* 1976; **236:** 1107–9.
2. O'Brien PC, *et al.* Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. *Obstet Gynecol* 1979; **53:** 300–8.
3. Barnes AB, *et al.* Fertility and outcome of pregnancy in women exposed in utero to diethylstilbestrol. *N Engl J Med* 1980; **302:** 609–13.
4. Emens M. Vaginal adenosis and diethylstilboestrol. *Br J Hosp Med* 1984; **31:** 42–8.
5. Anonymous. Diethylstilboestrol—effects of exposure in utero. *Drug Ther Bull* 1991; **29:** 49–50.
6. Wingfield M. The daughters of stilboestrol. *BMJ* 1991; **302:** 1414–15.
7. Mittendorf R, Williams MA. Stilboestrol exposure in utero and risk of pre-eclampsia. *Lancet* 1995; **345:** 265–6.
8. Troisi R, *et al.* Preeclampsia risk in women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2007; **110:** 113–20.
9. Kaufman RH, Adam E. Findings in female offspring of women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2002; **99:** 197–200.
10. Klip H, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. *Lancet* 2002; **359:** 1102–7.
11. Brouwers MM, *et al.* Hypospadias: a transgenerational effect of diethylstilbestrol? *Hum Reprod* 2006; **21:** 666–9.
12. Palmer JR, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology* 2005; **16:** 583–6.
13. Herbst AL, *et al.* Prenatal exposure to stilbestrol: a prospective comparison of exposed female offspring with unexposed controls. *N Engl J Med* 1975; **292:** 334–9.
14. Herbst AL, *et al.* Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. *Am J Obstet Gynecol* 1977; **128:** 43–50.
15. Kaufman RH, *et al.* Upper genital tract changes associated with in-utero exposure to diethylstilbestrol. *Am J Obstet Gynecol* 1977; **128:** 51–9.
16. Fowler WC, Edelman DA. In utero exposure to DES: evaluation and followup of 199 women. *Obstet Gynecol* 1978; **51:** 459–63.
17. Anderson B, *et al.* Development of DES-associated clear-cell carcinoma: the importance of regular screening. *Obstet Gynecol* 1979; **53:** 293–9.
18. Noller KL, *et al.* Maturation of vaginal and cervical epithelium in women exposed in utero to diethylstilbestrol (DESAD project). *Am J Obstet Gynecol* 1983; **146:** 279–85.
19. Robboy SJ, *et al.* Increased incidence of cervical and vaginal dysplasia in 3980 diethylstilbestrol-exposed young women: experience of the National Collaborative Diethylstilbestrol Adenosis Project. *JAMA* 1984; **252:** 2979–83.
20. Kaufman RH, *et al.* Upper genital tract changes and infertility in diethylstilbestrol-exposed women. *Am J Obstet Gynecol* 1986; **154:** 1312–18.
21. Melnick S, *et al.* Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix—an update. *N Engl J Med* 1987; **316:** 514–16.
22. Helmerhorst TJM, *et al.* Colposcopic findings and intraepithelial neoplasia in diethylstilbestrol-exposed offspring: the Dutch experience. *Am J Obstet Gynecol* 1989; **161:** 1191–4.
23. Giusti RM, *et al.* Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995; **122:** 778–88.

EFFECTS ON MALE OFFSPRING. The effects of exposure to diethylstilbestrol *in utero* have been studied in male offspring.[1-4] Problems in passing urine and abnormalities of the penile urethra were found to be more common in young males exposed to diethylstilbestrol *in utero* than in controls in one study.[1] In another,[2] genital tract abnormalities such as epididymal cysts, capsular induration, and defective testicles occurred in 41 of 163 diethylstilbestrol-exposed men compared with 11 of 168 controls; sperm counts and motility were also reduced in exposed males. In contrast, comparison of 828 men exposed to diethylstilbestrol *in utero* with 676 unexposed men suggested that, overall, diethylstilbestrol exposure did not result in an increased risk of genito-urinary abnormalities, infertility, or testicular cancer.[3] It was suggested that previously reported increased frequencies of such abnormalities may have resulted from a selection bias and/or from a difference in diethylstilbestrol usage. Another study[4] in 253 exposed men found that although there was an increased incidence of congenital malformations of the genitalia (18 cases compared with 5 of 241 controls), this was not associated with any decrease in fertility or impairment of sex-

ual function. An analysis[5] of the combined data from 4 cohorts suggested that there was a small increase in the risk of infertility (relative risk 1.3, 95% confidence interval 1.0 to 1.6) in men who had been exposed to diethylstilbestrol, but that overall this was not associated with an increased likelihood of never fathering a pregnancy or live birth, and did not affect the number of pregnancies or live births. Data from these 4 cohorts were also analysed[6] for the development of cancer. The overall rates of cancer were similar to those in unexposed men and to national rates. The rate of testicular cancer was increased in men who had been exposed to diethylstilbestrol *in utero*, but this finding did not reach statistical significance and was limited to only one of the cohorts. Further follow-up will be needed as these men approach the age at which most cancers are diagnosed.

For reference to possible effects on the male *grandchildren* of women who took diethylstilbestrol (the offspring of women exposed *in utero*) see Effects on Female Offspring, p. 2268.2.

1. Henderson BE, *et al*. Urogenital tract abnormalities in sons of women treated with diethylstilbestrol. *Pediatrics* 1976; **58:** 505–7.
2. Anonymous. Offspring of women given DES remains under study. *JAMA* 1977; **238:** 932.
3. Leary FJ, *et al*. Males exposed in utero to diethylstilbestrol. *JAMA* 1984; **252:** 2984–9.
4. Wilcox AJ, *et al*. Fertility in men exposed prenatally to diethylstilbestrol. *N Engl J Med* 1995; **332:** 1411–16.
5. Perez KM, *et al*. National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril* 2005; **84:** 1649–56.
6. Strohsnitter WC, *et al*. Cancer risk in men exposed in utero to diethylstilbestrol. *J Natl Cancer Inst* 2001; **93:** 545–51.

Veterinary use. In the EU, the use of diethylstilbestrol or other stilbenes in veterinary medicine is banned unless prior steps are taken to ensure the treated animal and its products are not available for human or animal consumption.

Pharmacokinetics

Diethylstilbestrol is readily absorbed from the gastrointestinal tract. It is slowly metabolised in the liver and excreted in the urine and faeces, mainly as the glucuronide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gobbibestrol; Novo Fosfostilben†; ***Braz.***: Destilbenol; ***Fr.***: Distilbene; ***Gr.***: Distilbene; ***Irl.***: Boestrol†; ***Mex.***: Dimeprost.

Multi-ingredient Preparations. ***China***: Fukexin (复可欣).

Pharmacopoeial Preparations
BP 2014: Diethylstilbestrol Pessaries; Diethylstilbestrol Tablets;
USP 36: Diethylstilbestrol Injection; Diethylstilbestrol Tablets.

Drospirenone *(BAN, USAN, rINN)*

Dihydrospirenone; Drospirenon; Drospirenona; Drospirénone; Drospirenoni; Drospirenonum; SH-470; ZK-30595; Дроспиренон.

(6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione.

$C_{24}H_{30}O_3$=366.5

CAS — 67392-87-4.

UNII — N295J34A25.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Drospirenone). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in dichloromethane.

USP 36: (Drospirenone). A white to off-white powder. Practically insoluble in water and in hexane; sparingly soluble in alcohol and in ethyl acetate; soluble in methyl alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Drospirenone is a structural analogue of spironolactone (p. 1499.3); it has the effects of a progestogen (see Progesterone, p. 2300.2) with antimineralocorticoid and anti-androgenic activity. It is used as the progestogenic component of combined oral contraceptives (see p. 2231.3), usually in a dose of 3 mg daily with ethinylestradiol 30 micrograms, for 21 days of each 28-day cycle. A combination of drospirenone 3 mg with ethinylestradiol 20 micrograms, given daily for 24 days of each 28-day cycle, may also be used for contraception and for the management of premenstrual dysphoric disorder (see Premenstrual Syndrome, below) or moderate acne (p. 1682.2) in women who also require an oral contraceptive. Drospirenone is also used as the progestogenic component of menopausal HRT (see below) in a continuous dosage regimen of 0.5 or 2 mg daily.

Reviews.
1. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception* 2000; **62:** 29–38.
2. Sitruk-Ware R. Pharmacology of different progestogens: the special case of drospirenone. *Climacteric* 2005; **8** (suppl 3): 4–12.
3. Oelkers WH. Drospirenone in combination with estrogens: for contraception and hormone replacement therapy. *Climacteric* 2005; **8** (suppl 3): 19–27.
4. Fenton C, *et al*. Drospirenone/ethinylestradiol 3mg/20 µg (24/4 day regimen): a review of its use in contraception, premenstrual dysphoric disorder and moderate acne vulgaris. *Drugs* 2007; **67:** 1749–65.
5. Bitzer J, Paoletti AM. Added benefits and user satisfaction with a low-dose oral contraceptive containing drospirenone: results of three multicentre trials. *Clin Drug Investig* 2009; **29:** 73–8.

Contraception. References.
1. Huber J, *et al*. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. *Eur J Contracept Reprod Health Care* 2000; **5:** 25–34.
2. Foidart JM, *et al*. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care* 2000; **5:** 124–34. Correction. *ibid*. 2001; **6:** 63.
3. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. *Contraception* 2000; **61:** 105–11.
4. Oelkers W, *et al*. Effect of an oral contraceptive containing drospirenone on the renin-angiotensin-aldosterone system in healthy female volunteers. *Gynecol Endocrinol* 2000; **14:** 204–13.
5. Bachmann G, *et al*. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. *Contraception* 2004; **70:** 191–8.
6. Gruber DM, *et al*. A comparison of the cycle control, safety, and efficacy profile of a 21-day regimen of ethinylestradiol 20 µg and drospirenone 3mg with a 21-day regimen of ethinylestradiol 20 µg and desogestrel 150 µg. *Treat Endocrinol* 2006; **5:** 115–21.
7. Cibula D, *et al*. Efficacy and safety of a low-dose 21-day combined oral contraceptive containing ethinylestradiol 20 µg and drospirenone 3mg. *Clin Drug Investig* 2006; **26:** 143–50.

Menopausal disorders. Drospirenone is used as the progestogenic component of menopausal HRT[1-4] (p. 2244.2). The antimineralocorticoid effect of drospirenone has also been investigated and found to lower blood pressure in postmenopausal women with treated and untreated hypertension.[5]

1. Schürmann R, *et al*. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 2004; **7:** 189–96.
2. Whitehead M. Hormone replacement therapy with estradiol and drospirenone: an overview of the clinical data. *J Br Menopause Soc* 2006; **12** (suppl 1): 4–7.
3. Archer DF, *et al*. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. *Menopause* 2005; **12:** 716–27.
4. Anonymous. Drospirenone in HRT? *Drug Ther Bull* 2009; **47:** 41–4.
5. Mallareddy M, *et al*. Drospirenone, a new progestogen, for postmenopausal women with hypertension. *Drugs Aging* 2007; **24:** 453–66.

Premenstrual syndrome. The use of drospirenone with ethinylestradiol has been studied in the management of premenstrual syndrome (p. 2272.3). A systematic review[1] of 5 studies found some evidence that the combination may be useful in the treatment of premenstrual dysphoric disorder. However, it was unknown whether the effect lasted beyond 3 cycles of treatment, whether the combination was effective for less severe symptoms, or whether combinations using drospirenone were any better than combined contraceptives containing other progestogens.

1. Lopez LM, *et al*. Oral contraceptives containing drospirenone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 16/11/09).

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. Drospirenone has antimineralocorticoid activity and therefore should not be used in patients at risk of hyperkalaemia, such as those with renal or hepatic impairment or adrenal insufficiency.

Reviews.
1. Heinemann LAJ, Dinger J. Safety of a new oral contraceptive containing drospirenone. *Drug Safety* 2004; **27:** 1001–18.
2. Simoncini T, Genazzani AR. A review of the cardiovascular and breast actions of drospirenone in preclinical studies. *Climacteric* 2010; **13:** 22–33.

Effects on the cardiovascular system. As with combined oral contraceptives containing other progestogens, there are reports[1-4] of thrombotic and ischaemic events in patients taking a preparation of ethinylestradiol and drospirenone. The extent of risk associated with hormonal contraceptives that contain drospirenone is mentioned under Venous Thromboembolism, p. 2238.1.

1. Vayá A, *et al*. Transient ischaemic attack associated with the new contraceptive Yasmin. *Thromb Res* 2003; **112:** 121.
2. van Grootheest K, Vrieling T. Thromboembolism associated with the new contraceptive Yasmin. *BMJ* 2003; **326:** 257.
3. Ortí G, *et al*. Acute myocardial infarction associated with Yasmin oral contraceptive. *Clin Appl Thromb Hemost* 2007; **13:** 336–7.
4. Girolami A, *et al*. Retinal central artery occlusion in a young woman after ten days of a drospirenone-containing oral contraceptive (Yasmin). *Thromb Haemost* 2007; **98:** 473–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies drospirenone in combined hormonal contraceptives as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Renal impairment. US licensed product information for preparations containing drospirenone contra-indicates its use in renal impairment, and in the UK it is contra-indicated in severe impairment. A study[1] of women with renal impairment that was mild (creatinine clearance 50 to 80 mL/minute) or moderate (30 to 50 mL/min) found a trend toward increasing drospirenone exposure with decreasing creatinine clearance. Serum-potassium concentrations were not significantly altered by drospirenone, despite the concomitant use of other drugs that can also potentially increase potassium concentrations including beta blockers and ACE inhibitors.

1. Schürmann R, *et al*. Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. *J Clin Pharmacol* 2006; **46:** 867–75.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3, and Hormone Replacement Therapy, p. 2251.1. Because drospirenone has antimineralocorticoid activity, it may potentially exacerbate the effects of drugs that can increase serum-potassium, such as ACE inhibitors, angiotensin II receptor antagonists, aldosterone antagonists, potassium-sparing diuretics, or NSAIDs. Drospirenone may also reduce blood pressure, such that antihypertensive treatment may require adjustment.

Diuretics. The pharmacokinetics of hydrochlorothiazide were not affected by the addition of drospirenone and estradiol in a placebo-controlled study of 36 hypertensive postmenopausal women.[1] However, those given the combination in this study developed lower blood pressure and higher serum-potassium concentrations, which was attributed to the antimineralocorticoid effect of drospirenone.[2] Nontheless, there were no cases of hyperkalaemia. It has been suggested that these potential antihypertensive and potassium-sparing effects might be beneficial in women requiring treatment for both menopausal symptoms and hypertension (see also Menopausal Disorders, above).

1. Karara AH, *et al*. Pharmacokinetics and pharmacodynamics of drospirenone-estradiol combination hormone therapy product coadministered with hydrochlorothiazide in hypertensive postmenopausal women. *J Clin Pharmacol* 2007; **47:** 1292–1302.
2. Preston RA, *et al*. Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on blood pressure and potassium balance in hypertensive postmenopausal women receiving hydrochlorothiazide. *Menopause* 2007; **14:** 408–14.

NSAIDs. Drospirenone has the potential to exacerbate the effects of other drugs, such as NSAIDs, that can increase serum potassium. Licensed product information suggests that a clinical effect is unlikely in practice, although the use of several such drugs together or the presence of renal impairment may increase the risk. In a small study[1] of healthy postmenopausal women, there was no evidence that potassium concentrations were any higher when *indometacin* was used with a combination of drospirenone plus estradiol compared with indometacin alone.

1. Schütt B, *et al*. Coadministration of estradiol/drospirenone and indomethacin does not cause hyperkalemia in healthy postmenopausal women: a randomized open-label crossover study. *J Clin Pharmacol* 2007; **47:** 774–81.

Pharmacokinetics

After oral doses, drospirenone is rapidly absorbed with a bioavailability of about 76%. It is about 97% bound to plasma proteins, though it does not bind to sex hormone binding globulin or corticosteroid binding globulin. It is extensively metabolised with a terminal half-life of about 30 to 40 hours. The metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diva Total.

Multi-ingredient Preparations. ***Arg.***: Angeliq; Damsel; Damsella; Diva; Divina; Eos; Equifem; Gadofem; Isis Fe; Isis; Jade; Kala; Kir; Kirum; Kirumelle; Maxima MD 24; Maxima; Umma; Yasmin; Yasminelle; YAZ; ***Austral.***: Angeliq; Yasmin; YAZ; ***Austria***: Aliane; Angeliq; Yasmin; Yasminelle; YAZ; Yirala; ***Belg.***: Angel-

iq; Rimendia; Yasmin; Yasminelle; YAZ; ***Braz.***: Angeliq; Elani; Yasmin; YAZ; ***Canad.***: Angeliq; Yasmin; YAZ; ***Chile***: Altesse; Angeliq; Clinomat; Dahlia; Femelle; Femiplus; Miafem; Vexa; Yasmin; YAZ; ***China***: Angeliq (安今益); Yasmin (优思明); ***Cz.***: Angeliq; Belanette; Belusha; Daylette; Drosetil; Eloine; Jangee; Kirga; Maitalon; Softinelle; Sylviane; Yadine; Yasminelle; YAZ; ***Denm.***: Angemin; Dretine; Eloine; Finminette; Movinella; Palandra; Rubira; Yasmin; Yasminelle; YAZ; ***Fin.***: Angeliq; Linatera; Liofora; Palandra; Stefaminelle; Tasminetta; Yasmin; Yasminelle; YAZ; ***Fr.***: Angeliq; Belanette; Convuline; Drospibel; Jasmine; Jasminelle; Jasminellecontinu; Rimendia; YAZ; ***Ger.***: Aida; Angeliq; Petibelle; Yasmin; Yasminelle; YAZ; ***Gr.***: Angeliq; Liofora; Yasmin; Yasminelle; YAZ; ***Hong Kong***: Angeliq; Yasmin; YAZ; ***Hung.***: Angeliq; Jangee; Symicia; Volina; Yadine; Yasminelle; ***India***: Crisanta; Dronis; ***Indon.***: Angeliq; Yasmin; YAZ; ***Irl.***: Allurene†; Angeliq; Dretine; Dretinelle; Enador; Liofora; Palandra; Yasmin; Yasminelle; YAZ; ***Israel***: Angeliq; Yasmin; Yasminelle†; YAZ; ***Ital.***: Angeliq; Credigyne; Credigynette; Midiana; Yarina; Yasmin; Yasminelle; YAZ; ***Malaysia***: Angeliq; Yasmin; YAZ; ***Mex.***: Angeliq; Radiance; Yasmin; ***Neth.***: Allurene†; Angeliq; Armarrok; Armunia; Belanette; Liofora; Palandra; Rosal; Vallclara; Volina; Yasmin; Yasminelle; YAZ; Yira†; Yvidually; ***Norw.***: Finminette; Rubira; Yasmin; Yasminelle; YAZ; ***NZ***: Yasmin; YAZ; ***Philipp.***: Angeliq; Yasmin; YAZ; ***Pol.***: Aliane; Angeliq; Asubtela; Dronin; Linatera; Midiana; Naraya; Yasmin; Yasminelle; YAZ; ***Port.***: Aliane; Allurene; Angeliq; Petibelle; Yasmin; Yasminelle; YAZ; ***Rus.***: Angeliq (Анжелик); Yarina (Ярина); YAZ (Джес); ***S.Afr.***: Angeliq; Yasmin; YAZ; ***Singapore***: Yasmin; YAZ; ***Spain***: Angeliq; Antin; Antinelle; Aranka; Arankelle; Daylette; Drelle; Dretine; Dretinelle; Drosiane Diario; Drosianelle; Drospil; Drosure; Drosurelle; Eloine; Liofora; Yasmin; Yasminelle; YAZ; Yira; ***Swed.***: Angemin; Eloine; Liofora; Yasmin; Yasminelle; YAZ; ***Switz.***: Angeliq; Eloine; Yasmin; Yasminelle; YAZ; ***Thai.***: Angeliq; Melodia; Yasmin; YAZ; ***Turk.***: Angeliq; Yasmin; Yazz; ***UK***: Angeliq; Yasmin; YAZ; ***Ukr.***: Angeliq (Анжелик); Darilia (Дарилия); Midiana (Мидиана); Yarina (Ярина); ***USA***: Angeliq; Beyaz; Gianvi; Loryna; Ocella; Safyral; Syeda; Vestura; Yasmin; YAZ; Zarah; ***Venez.***: Yasmin.

Pharmacopoeial Preparations
USP 36: Drospirenone and Ethinyl Estradiol Tablets.

Drostanolone Propionate *(BANM, rINNM)* ⊗

Compound 32379; Dromostanolone Propionate (USAN); Drostanolone, propionate de; Drostanoloni Propionas; 2α-Methyldihydrotestosterone Propionate; NSC-12198; Propionato de drostanolona; Дростанолона Пропионат.
17β-Hydroxy-2α-methyl-5α-androstan-3-one propionate.
$C_{23}H_{36}O_3$=360.5
CAS — 58-19-5 (drostanolone); 521-12-0 (drostanolone propionate).
UNII — X20UZ57G4O.

Profile

Drostanolone propionate has anabolic and androgenic properties (see Testosterone, p. 2305.1) and has been used in the treatment of advanced malignant neoplasms of the breast in postmenopausal women. It has been subject to abuse in sport.

Dydrogesterone *(BAN, USAN, rINN)*

6-Dehydro-9β,10α-progesterone; 6-Dehydro-*retro*-progesterone; Didrogesteron; Didrogesterona; Dydrogesteron; Dydrogestérone; Dydrogesteroni; Dydrogesteronum; Isopregnenone; NSC-92336; Дидрогестерон.
9β,10α-Pregna-4,6-diene-3,20-dione.
$C_{21}H_{28}O_2$=312.5
CAS — 152-62-5.
ATC — G03DB01.
ATC Vet — QG03DB01.
UNII — 90I02KLE8K.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dydrogesterone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone.

USP 36: (Dydrogesterone). A white to pale yellow crystalline powder. Practically insoluble in water; soluble 1 in 40 of alcohol, 1 in 2 of chloroform, and 1 in 200 of ether.

Uses and Administration

Dydrogesterone is a progestogen structurally related to progesterone (p. 2300.2). It does not have oestrogenic or androgenic properties.

Dydrogesterone has been given orally in the treatment of menstrual disorders such as menorrhagia (p. 2300.3), usually in a dose of 10 mg twice daily in a cyclical regimen, and for the treatment of endometriosis (p. 2264.1) in a dose of 10 mg two or three times daily cyclically or continuously. It has also been given cyclically in doses of 10 mg once or twice daily, or continuously in doses of 5 mg daily, for endometrial protection during menopausal HRT (p. 2244.2).

In threatened miscarriage suggested doses have been 40 mg initially followed by 10 mg or more every 8 hours, continued for a week after symptoms cease then gradually reduced unless symptoms return. In recurrent miscarriage suggested doses have been 10 mg twice daily given cyclically until conception then continuously until week 20 of pregnancy, the dose may then be gradually reduced. However, such use is not recommended unless there is proven progesterone deficiency. Cyclical dydrogesterone has also been used in infertility (p. 2253.1) in doses of 10 mg twice daily.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormone Replacement Therapy, p. 2246.3 and p. 2250.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dydrogesterone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Anomalies (non-virilising) of the genitourinary tract were found in a 4-month-old baby whose mother had taken dydrogesterone 20 mg daily from the eighth to twentieth week of pregnancy and 10 mg daily from then until term.[1] She had also been given hydroxyprogesterone caproate 250 mg by intramuscular injection weekly from the eighth to the twentieth week.

1. Roberts IF, West RJ. Teratogenesis and maternal progesterone. *Lancet* 1977; **ii:** 982.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Duphaston†; ***Austria***: Duphaston; ***Belg.***: Duphaston; ***Braz.***: Duphaston; ***Chile***: Duphaston; ***China***: Duphaston (达芙通); ***Cz.***: Duphaston; ***Fin.***: Terolut; ***Fr.***: Duphaston; ***Ger.***: Duphaston; ***Gr.***: Duphaston; Medichrol; ***Hong Kong***: Duphaston; ***Hung.***: Duphaston; ***India***: Duphaston; ***Indon.***: Duphaston; ***Irl.***: Duphaston; ***Israel***: Duphaston; ***Ital.***: Dufaston; ***Malaysia***: Duphaston; ***Mex.***: Duphaston; ***Neth.***: Duphaston; ***NZ***: Duphaston†; ***Philipp.***: Duphaston; ***Pol.***: Duphaston; ***Port.***: Duphaston; ***Rus.***: Duphaston (Дюфастон); ***S.Afr.***: Duphaston; ***Singapore***: Duphaston; ***Swed.***: Duphaston†; ***Switz.***: Duphaston; ***Thai.***: Duphaston; ***Turk.***: Duphaston; ***Ukr.***: Duphaston (Дуфастон); ***Venez.***: Duphaston.

Multi-ingredient Preparations. ***Austral.***: Femoston; ***Austria***: Femoston Conti; Femoston; ***Belg.***: Femoston Conti; Femoston; ***Braz.***: Femoston Conti; Femoston; ***Chile***: Femoston Conti; Femoston; ***China***: Femoston (芬鸣通); ***Cz.***: Femoston Conti; Femoston Mini; Femoston; ***Fin.***: Femoston Conti; Femoston; ***Fr.***: Climaston; Climaston; ***Ger.***: Femoston Conti; Femoston; ***Gr.***: Femaston; ***Hong Kong***: Femoston Conti†; Femoston; ***Hung.***: Femoston; ***Indon.***: Femoston; ***Irl.***: Femoston Conti; Femoston; Femurest-Conti; ***Ital.***: Femoston Conti; Femoston; ***Malaysia***: Femoston Conti; Femoston; ***Mex.***: Lutalmin; ***Neth.***: Climaston Continu; Femoston Continu; Femoston; Femphascyl Continu; Femphascyl; ***NZ***: Femoston; ***Philipp.***: Femoston†; ***Pol.***: Femoston Conti; Femoston Mini; Femoston; ***Port.***: Femoston 1/5; Femoston; ***Rus.***: Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); ***S.Afr.***: Femoston Conti; Femoston; ***Singapore***: Femoston Conti; Femoston; ***Switz.***: Femoston Conti; Femoston; ***Thai.***: Femoston 1/10; Femoston Conti; ***Turk.***: Femoston; ***UK***: Femapak†; Femoston Conti; Femoston; ***Ukr.***: Femoston (Фемостон); ***Venez.***: Femoston Conti; Femoston.

Pharmacopoeial Preparations
BP 2014: Dydrogesterone Tablets;
USP 36: Dydrogesterone Tablets.

Elcometrine

Elcometrina; 16-Methylene-17-alpha-acetoxy-19 Norprogesterone; ST-1435.
$C_{23}H_{30}O_4$=370.5
CAS — 7759-35-5.

NOTE. The name Nestorone has been used as a trade mark for elcometrine.

Profile

Elcometrine is a synthetic progestogen that is being developed for use in contraception and menopausal HRT, and in the management of endometriosis.

References.
1. Ylänen K, *et al.* Subdermal progestin implant (Nestorone) in the treatment of endometriosis: clinical response to various doses. *Acta Obstet Gynecol Scand* 2003; **82:** 167–72.
2. Sitruk-Ware R, *et al.* Nestorone: clinical applications for contraception and HRT. *Steroids* 2003; **68:** 907–13.
3. Sivin I, *et al.* Two-year performance of a Nestorone-releasing contraceptive implant: a three-center study of 300 women. *Contraception* 2004; **69:** 137–44.
4. Sivin I, *et al.* Contraceptive vaginal rings releasing Nestorone and ethinylestradiol: a 1-year dose-finding trial. *Contraception* 2005; **71:** 122–9.
5. Fraser IS, *et al.* Serum Nestorone and ethinyl estradiol levels, and ovulation inhibition in women using three different dosage combinations of a Nestorone progestogen-ethinyl estradiol contraceptive vaginal ring on a bleeding-signaled regimen. *Contraception* 2005; **72:** 40–5.
6. Weisberg E, *et al.* Clinical performance and menstrual bleeding patterns with three dosage combinations of a Nestorone progestogen/ethinyl estradiol contraceptive vaginal ring used on a bleeding-signaled regimen. *Contraception* 2005; **72:** 46–52.
7. Croxatto HB, *et al.* Feasibility study of Nestorone-ethinylestradiol vaginal contraceptive ring for emergency contraception. *Contraception* 2006; **73:** 46–52.
8. Mahabadi V, *et al.* Combined transdermal testosterone gel and the progestin nestorone suppresses serum gonadotropins in men. *J Clin Endocrinol Metab* 2009; **94:** 2313–20.

Epimestrol *(BAN, USAN, rINN)*

Épimestrol; Epimestroli; Epimestrolum; NSC-55975; Org-817; Эпиместрол.
3-Methoxyestra-1,3,5(10)-triene-16α,17α-diol.
$C_{19}H_{26}O_3$=302.4
CAS — 7004-98-0.
ATC — G03GB03.
ATC Vet — QG03GB03.
UNII — 7IVE3SDZ38.

Profile

Epimestrol is the 3-methyl ether of the naturally occurring hormone 17-epioestriol. It has been used in the treatment of female infertility due to anovulation and amenorrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Menest; ***Canad.***: Estragyn; ***Chile***: Femibel†; ***USA***: Estratab; Menest.

Equilin

Equilina.
3-Hydroxyestra-1,3,5(10),7-tetraen-17-one.
$C_{18}H_{20}O_2$=268.4
CAS — 474-86-2.
UNII — 08O86EX0J4.

Pharmacopoeias. In *US*.

USP 36: (Equilin). Store in airtight containers. Protect from light.

Profile

Equilin is a natural oestrogenic hormone found in horses. Sodium equilin sulfate is one of the components of both conjugated oestrogens (p. 2260.1) and esterified oestrogens (see below) used for menopausal HRT.

Esterified Oestrogens

Esterified Estrogens; Estrógenos esterificados; Эстрогены Этерифицированные.

Pharmacopoeias. In *US*.

USP 36: (Esterified Estrogens). A mixture of the sodium salts of the sulfate esters of the oestrogenic substances, mainly estrone. It contains 75 to 85% of sodium estrone sulfate and 6 to 15% of sodium equilin sulfate, in such a proportion that the total of these two components is not less than 90%, of the labelled amount of esterified oestrogens. A white or buff-coloured amorphous powder; odourless or having a slight characteristic odour. Store in airtight containers.

Profile

Esterified oestrogens have actions and uses similar to those described for estradiol (see p. 2271.1). They are used for the same purposes (mainly menopausal HRT), and in a similar oral dosage, as conjugated oestrogens (see p. 2260.2), although higher cyclical doses of 2.5 to 7.5 mg daily are still licensed for use in female hypogonadism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Menest; ***Canad.***: Estragyn; ***Chile***: Femibel†; ***USA***: Estratab; Menest.

Multi-ingredient Preparations. *Chile*: Delitan; Feminova-T†; *USA*: Covaryx; Estratest†; Syntest.

Pharmacopoeial Preparations
USP 36: Esterified Estrogens Tablets.

Estradiol *(BAN, rINN)*

Beta-oestradiol; Dihidrofoliculina; Dihidroxiestratrieno; Dihidroxiestrina; Dihydrofolliculin; Dihydrotheelin; Dihydroxyoestrin; Estradioli; Estradiolis; Estradiolum; NSC-9895; Oestradiol; Östradiol; Ösztradiol; Эстрадиол.

Estra-1,3,5(10)-triene-3,17β-diol.

$C_{18}H_{24}O_2$=272.4

CAS — 50-28-2 (anhydrous estradiol); 35380-71-3 (estradiol hemihydrate).

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — 4TI98Z838E (estradiol); CXY7B3Q98Z (estradiol hemihydrate).

NOTE. In *Martindale* the term oestradiol is used for the endogenous substance.

Pharmacopoeias. In *Chin.* and *US*.

Eur. (see p. vii) includes the hemihydrate.

Ph. Eur. 8: (Estradiol Hemihydrate). A white or almost white crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.

USP 36: (Estradiol). White or creamy-white, odourless, hygroscopic small crystals or crystalline powder. Practically insoluble in water; soluble 1 in 28 of alcohol, 1 in 435 of chloroform, and 1 in 150 of ether; soluble in acetone, in dioxan, and in solutions of fixed alkali hydroxides; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Estradiol Acetate *(BANM, USAN, rINNM)*

Acetato de estradiol; E-3A; Estradiol, Acétate d'; Estradiol-3-acetate; Estradioli Acetas; Oestradiol Acetate; Эстрадиола Ацетат.

Estra-1,3,5(10)-triene-3,17β-diol 3-acetate.

$C_{20}H_{26}O_3$=314.4

CAS — 4245-41-4.

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — 5R97F5H93P.

Estradiol Benzoate *(BANM, rINN)*

Benzoato de estradiol; Beta-oestradiol Benzoate; Dihydroxyoestrin Monobenzoate; Estradiol, Benzoate d'; Estradiol, benzoato de; Estradiolbensoat; Estradiolbenzoat; Estradiolbenzoát; Estradioli Benzoas; Estradiolibentsoaatti; Estradiolio benzoatas; Estradiolu benzoesan; NSC-9566; Oestradiol Benzoate; Östradiol Benzoat; Ösztradiol-benzoát; Эстрадиола Бензоат.

Estra-1,3,5(10)-triene-3,17β-diol 3-benzoate.

$C_{25}H_{28}O_3$=376.5

CAS — 50-50-0.

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — 1S4CJB5ZGN.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Estradiol Benzoate). An almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in acetone; freely soluble in dichloromethane; slightly soluble in methyl alcohol.

USP 36: (Estradiol Benzoate). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in acetone; slightly soluble in ether. Store in airtight containers. Protect from light.

Estradiol Cipionate *(BANM, rINNM)*

Cipionato de estradiol; Estradiol, Cipionate d'; Estradiol, cipionato de; Estradiol Cypionate; Estradioli Cipionas; Oestradiol Cyclopentylpropionate; Oestradiol Cypionate; Эстрадиола Ципионат.

Estra-1,3,5(10)-triene-3,17β-diol 17-(3-cyclopentylpropionate).

$C_{26}H_{36}O_3$=396.6

CAS — 313-06-4.

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — 7E1DV054LO.

Pharmacopoeias. In *US*.

USP 36: (Estradiol Cypionate). A white to practically white crystalline powder, odourless or has a slight odour. Insoluble in water; soluble 1 in 40 of alcohol, 1 in 7 of chloroform, and 1 in 2800 of ether; soluble in acetone and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers. Protect from light.

Estradiol Dipropionate *(BANM, rINNM)*

Dihydroxyoestrin Dipropionate; Dipropionato de estradiol; Estradiol, Dipropionate d'; Estradiol, dipropionato de; Estradioli Dipropionas; Oestradiol Dipropionate; Эстрадиола Дипропионат.

Estra-1,3,5(10)-triene-3,17β-diol dipropionate.

$C_{24}H_{32}O_4$=384.5

CAS — 113-38-2.

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — NIG5418BXB.

Estradiol Enantate *(BANM, rINNM)*

Enantato de estradiol; Estradiol, Enantate d'; Estradiol, enantato de; Estradiol Enanthate (USAN); Estradioli Enantas; Oestradiol Enanthate; Oestradiol 17-Heptanoate; SQ-16150; Эстрадиола Энантат.

Estra-1,3,5(10)-triene-3,17β-diol 17-heptanoate.

$C_{25}H_{36}O_3$=384.6

CAS — 4956-37-0.

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — PAP315WZIA.

Estradiol Hexahydrobenzoate *(BANM, rINNM)*

Estradiol, hexahidrobenzoato de; Estradiol, Hexahydrobenzoate d'; Estradioli Hexahydrobenzoas; Hexahidrobenzoato de estradiol; Oestradiol Hexahydrobenzoate; Эстрадиола Гексагидробензоат.

Estra-1,3,5(10)-triene-3,17β-diol 17-cyclohexanecarboxylate.

$C_{25}H_{34}O_3$=382.5

CAS — 15140-27-9.

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Phenylpropionate *(BANM, rINNM)*

Estradiol, fenilpropionato de; Estradiol, Phénylpropionate de; Estradioli Phenylpropionas; Fenilpropionato de estradiol; Oestradiol Phenylpropionate; Östradiol Fenilpropiyonat; Эстрадиола Фенилпропионат.

Estra-1,3,5(10)-triene-3,17β-diol 17-(3-phenylpropionate).

$C_{27}H_{32}O_3$=404.6

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Valerate *(BANM, rINN)*

Estradiol, valérate d'; Estradiol, valerato de; Estradioli Valeras; Estradiolio valeratas; Estradiolivaleraatti; Estradiolvalerat; Estradiol-valerát; NSC-17590; Oestradiol Valerate; Östradiol-17-Valerat; Ösztradiol-valerát; Valerato de estradiol; Эстрадиола Валерат.

Estra-1,3,5(10)-triene-3,17β-diol 17-valerate.

$C_{23}H_{32}O_3$=356.5

CAS — 979-32-8.

ATC — G03CA03.

ATC Vet — QG03CA03.

UNII — OKG364O896.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Estradiol Valerate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 36: (Estradiol Valerate). A white crystalline powder which is usually odourless or may have a faint fatty odour. Practically insoluble in water; soluble in benzyl benzoate, in dioxan, in methyl alcohol, and in castor oil; sparingly soluble in arachis oil and in sesame oil. Store in airtight containers. Protect from light.

Uses and Administration

Estradiol is the most active of the naturally occurring oestrogens (for further details, see p. 2231.1). Estradiol and its semisynthetic esters and other natural oestrogens are mainly used as menopausal HRT (see p. 2244.2) whereas synthetic derivatives such as ethinylestradiol have a major role as components of combined hormonal contraceptives (see p. 2231.3). Estradiol may also be used as replacement therapy for female hypogonadism or primary ovarian failure (p. 2252.3). Replacement therapy ('add-back' therapy) may also be given to women in whom the pituitary-ovarian axis is suppressed by therapy with gonadorelin or its analogues.

Estradiol hemihydrate 1.03 mg is equivalent to about 1 mg of the anhydrous substance.

For **menopausal HRT** oral preparations or transdermal patches of estradiol are commonly used. Other transdermal formulations, subcutaneous implants, and a nasal spray are also available. Intramuscular injections were formerly used. In women with a uterus, a progestogen is also required, given cyclically or continuously, usually orally although some combined transdermal preparations are available. Local vaginal estradiol preparations are used specifically for the treatment of menopausal atrophic vaginitis; these are generally recommended for short-term use only, if given without a progestogen in women with a uterus, although specific recommendations vary between products.

For *oral* use estradiol or estradiol valerate is normally given in doses of 1 or 2 mg daily cyclically, or more often continuously. Estradiol acetate may be given in an initial dose of 450 micrograms daily, increasing if necessary to 0.9 or 1.8 mg once daily.

Estradiol may be used topically as *transdermal skin patches* to provide a systemic effect; a variety of patches are available which release between 25 and 100 micrograms of estradiol every 24 hours. A low-dose patch supplying 14 micrograms daily is also available specifically for the prevention of postmenopausal osteoporosis in women at significant risk; with this low dose, the addition of a 14-day course of progestogen in women with a uterus is only required once every 6 to 12 months. Depending on the preparation, patches are replaced once or twice weekly. Each new patch is applied to a different area of skin in rotation, usually below the waistline; patches should not be applied on or near the breasts. *Topical gel* preparations are also used for systemic effect. The usual applied dose is 0.25 to 1.5 mg of estradiol daily, depending on the preparation, but up to 3 mg daily may be required for control of menopausal symptoms in some women. The gel should not be applied on the face or on or near the breasts, vagina, or vulval region. A *topical emulsion* is also available; estradiol hemihydrate 8.7 mg is applied daily to provide a systemic estradiol dose of about 50 micrograms. A *transdermal spray* has also been developed, delivering a single dose of estradiol 1.53 mg onto the skin. It should be applied to the skin of the inner surface of the forearm, and the dose may be increased up to 3 sprays once daily in the morning, at separate sites on the forearm, according to response.

A *nasal spray* is available, delivering 150 micrograms of estradiol hemihydrate per spray. The usual initial dose is 150 micrograms daily (1 spray in 1 nostril). After 2 or 3 cycles the dose may be adjusted according to response; the usual maintenance dose is 300 micrograms daily (1 spray in each nostril once daily) but may range from 150 micrograms once daily up to 450 to 600 micrograms daily in 2 divided doses.

In order to prolong the duration of action *subcutaneous implants* of estradiol may be used. The dose of estradiol is generally 25 to 100 mg with a new implant being given after about 4 to 8 months according to oestrogen concentrations.

Estradiol may be used locally:

- a 10-microgram *vaginal tablet* is inserted in an initial dose of one tablet daily for 2 weeks, followed by a maintenance dose of one tablet twice a week
- alternatively, a 0.01% *vaginal cream* is inserted in initial amounts of 2 to 4 g of cream daily for 1 to 2 weeks then gradually reduced to half the initial dose for a similar period, followed by a maintenance dose of 1 g up to 3 times weekly
- a local delivery system using a 3-month *vaginal ring* contains 2 mg of estradiol hemihydrate, and delivers about 7.5 micrograms of estradiol per 24 hours. Another 3-month vaginal ring system, which contains estradiol acetate, releases either 50 or 100 micrograms of estradiol daily, and is used for the relief of both local and systemic postmenopausal symptoms.

Intramuscular injections of estradiol benzoate or valerate esters have been used as oily depot solutions, usually given once every 3 to 4 weeks. The cipionate, dipropionate, enantate, hexahydrobenzoate, phenylpropionate, and undecylate esters have been used similarly.

Estradiol valerate is used as the oestrogenic component in some combined oral **contraceptives**. Doses ranging from 1 to 3 mg daily are used in multiphasic preparations. The enantate, cipionate, benzoate butyrate, and valerate esters are used in combined injectable contraceptives.

Estradiol and other oestrogens have sometimes been used in higher doses for palliative treatment in **prostate cancer** (p. 712.3) and **breast cancer** in men and postmenopausal women (p. 702.1).

Administration. *BUCCAL AND SUBLINGUAL ADMINISTRATION.* Estradiol is absorbed through the *buccal* route, and has been reported to improve postmenopausal vasomotor symptoms.[1] A pharmacokinetic study[2] of micronised estradiol found the *sublingual* route resulted in more rapid

absorption, a higher peak concentration, and more rapid elimination, than oral dosage. Sublingual micronised estradiol has been studied for the management of postpartum depression.[3]

1. Gass MS, *et al.* A short study in the treatment of hot flashes with buccal administration of 17-β estradiol. *Maturitas* 2004; **49:** 140–7.
2. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β-estradiol. *Obstet Gynecol* 1997; **89:** 340–5.
3. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17 β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62:** 332–6.

IMPLANTS. There may be a striking interpatient variation in blood-estradiol concentrations in women receiving estradiol implants,[1] and symptoms of oestrogen deficiency have re-appeared in some patients even though serum-estradiol concentrations were within or above the physiological range.[2] After debate on the appropriateness of using serum concentrations of estradiol as a guide to implant use, rather than symptoms,[3-7] it is now recommended that estradiol concentration should be monitored during therapy.

Cyclical progestogen may be required for a prolonged period after removal of estradiol implants in women with a uterus.[7]

1. Guirgis RR. Oestradiol implants: what dose, how often? *Lancet* 1987; **ii:** 856.
2. Gangar K, *et al.* Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *BMJ* 1989; **299:** 601–2.
3. Ginsburg J, Hardiman P. Oestrogen deficiency and oestradiol implants. *BMJ* 1989; **299:** 1031.
4. Studd J, *et al.* Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 1400–1.
5. Swyer GIM. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 854.
6. Tobias JH, Chambers TJ. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 854.
7. Wardle P, Fox R. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 1102.

INTRANASAL ADMINISTRATION. The intranasal route for estradiol HRT has been reviewed.[1] It appears to be comparable in efficacy to oral[2] or transdermal use[3,4] in the treatment of menopausal symptoms. As with transdermal application, the intranasal route avoids intestinal and hepatic first-pass metabolism.

1. Dooley M, *et al.* Estradiol-intranasal: a review of its use in the management of menopause. *Drugs* 2001; **61:** 2243–62.
2. Studd J, *et al.* Efficacy and acceptability of intranasal 17 β-oestradiol for menopausal symptoms: randomised dose-response study. *Lancet* 1999; **353:** 1574–8. Correction. *ibid.*; **354:** 780.
3. Lopes P, *et al.* Randomized comparison of intranasal and transdermal estradiol. *Obstet Gynecol* 2000; **96:** 906–12.
4. Davis SR, *et al.* Intranasal versus transdermal matrix oestrogen replacement in Australasian women. *Maturitas* 2005; **51:** 163–71.

TRANSDERMAL ADMINISTRATION. Transdermal estradiol given via *patches* applied to the skin has been reviewed.[1-3] This method of delivery has certain advantages over the oral route in that gastrointestinal and hepatic first-pass metabolism is avoided, liver enzymes are not stimulated (although this may also mean that beneficial effects on serum lipids are absent), and the prolonged drug release from the patch means less frequent application is necessary and hence patient compliance may be improved. For oestrogen replacement in menopausal and postmenopausal women estradiol patches are used continuously or in a cyclical manner, with added progestogen for part of the cycle in those women with an intact uterus. This does not lead to drug accumulation and produces blood-estradiol concentrations and estradiol to estrone ratios similar to those normally seen in premenopausal women. The patch is well tolerated with skin irritation being the main problem. Patches are as effective as oral oestrogens in treating menopausal and postmenopausal symptoms such as flushing and vaginal atrophy and in preventing osteoporosis. Combined HRT patches, providing both estradiol and a progestogen, have also been developed.[4]

Estradiol is also effective when applied topically to the skin as a *gel*[5] or *emulsion*.[6]

1. Balfour JA, Heel RC. Transdermal estradiol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints. *Drugs* 1990; **40:** 561–82.
2. Cheang A, *et al.* A risk-benefit appraisal of transdermal estradiol therapy. *Drug Safety* 1993; **9:** 365–79.
3. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; **67:** 1–12.
4. Dando TM, Perry CM. 17 β-Estradiol/levonorgestrel transdermal system. *Treat Endocrinol* 2004; **3:** 319–24.
5. Naunton M, *et al.* Estradiol gel: review of the pharmacology, pharmacokinetics, efficacy, and safety in menopausal women. *Menopause* 2006; **13:** 517–27.
6. Simon JA. ESTRASORB Study Group. Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms. *Menopause* 2006; **13:** 222–31.

Depression. The use of oestrogen therapy in the treatment of premenopausal women with **postnatal** depression was reported to be effective in a few studies.[1,2] However, although such therapy might be a useful adjunct to conventional treatment (see Depression, p. 398.1), the risk of serious adverse effects including thrombosis may limit its value.

Whether oestrogens are of benefit in older women, typically with depression associated with the **menopause** (p. 2245.1), is less clear. Some studies of transdermal estradiol have reported benefit,[3-5] whereas other studies of transdermal[6] or oral[7] dosage have not found it to be effective. Whether the presence of a progestogen in combination HRT would reduce any purported benefit is also unclear. Antidepressants remain the standard of care in perimenopausal or postmenopausal women with clinical depression.

1. Gregoire AJP, *et al.* Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; **347:** 930–3.
2. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17 β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62:** 332–6.
3. Soares C de N, *et al.* Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry* 2001; **58:** 529–34.
4. Cohen LS, *et al.* Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003; **160:** 1519–22.
5. Schiff R, *et al.* Short-term transdermal estradiol therapy, cognition and depressive symptoms in healthy older women: a randomised placebo controlled pilot cross-over study. *Psychoneuroendocrinology* 2005; **30:** 309–15.
6. Morrison MF, *et al.* Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004; **55:** 406–12.
7. Almeida OP, *et al.* A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. *Neurobiol Aging* 2006; **27:** 141–9.

Gender reassignment. Oestrogens are used in male-to-female transsexuals to develop and maintain secondary sexual characteristics. Although ethinylestradiol and conjugated oestrogens have been used for this purpose, and there is some evidence that such use can improve vascular function,[1] others consider ethinylestradiol too thrombogenic at the doses required [typically 50 to 100 micrograms daily or more] and suggest that estradiol, as the valerate in oral doses of 2 to 4 mg daily, or transdermally as a patch supplying 100 micrograms daily, is the oestrogen of choice.[2,3] Cyproterone acetate is usually also given for its anti-androgenic effect (see p. 2261.3).

1. New G, *et al.* Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol* 1997; **29:** 1437–44.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Growth disorders. Supraphysiological doses of oestrogens inhibit somatic growth and have been used, with a cyclical progestogen, to reduce final height in girls with constitutional tall stature, although such treatment has declined markedly with changing social norms.[1] In early reports, diethylstilbestrol was used, but this is an unsuitable choice because of the increased risk of cancer. Ethinylestradiol has been given in the past in doses of up to 500 micrograms daily, but doses of 50 to 100 micrograms daily came to be preferred, although lower doses may be equally effective.[2,3] Conjugated oestrogens have also been used, and a study[4] reported that doses of 7.5 to 11.25 mg daily resulted in an average decrease of about 5 cm from final predicted height. In practice, doses as low as 625 micrograms daily have been used.[3] Reported height reductions have ranged from 2 to 10 cm but studies are difficult to compare. Treatment has generally been continued until closure of the epiphyses, but the effects of oestrogen therapy may be influenced by both chronological and bone age at the onset of treatment, duration of treatment, the oestrogen used and its dose, and the point of final height assessment.[2] High-dose oestrogen therapy is also associated with adverse effects such as weight gain, headache, nausea, and pigmentation of the areolae or nipples,[2,3] and there can be adverse changes to haemostatic and lipid measures.[2] A retrospective cohort review[5] has also reported that girls who had been treated with high-dose oestrogens were more likely to report fertility problems in later life than similar girls who had not been treated.

Oestrogen therapy has occasionally been used to help promote growth in girls with constitutional delayed puberty (see p. 2252.1).

1. Lee JM, Howell JD. Tall girls: the social shaping of a medical therapy. *Arch Pediatr Adolesc Med* 2006; **160:** 1035–9.
2. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.
3. Barnard ND, *et al.* The current use of estrogens for growth-suppressant therapy in adolescent girls. *J Pediatr Adolesc Gynecol* 2002; **15:** 23–6.
4. Weimann E, *et al.* Oestrogen treatment of constitutional tall stature: a risk-benefit ratio. *Arch Dis Child* 1998; **78:** 148–51.
5. Venn A, *et al.* Oestrogen treatment to reduce the adult height of tall girls: long-term effects on fertility. *Lancet* 2004; **364:** 1513–18.

Haemorrhagic disorders. Limited evidence supports the use of oestrogens in various bleeding disorders. There have been mixed results from small studies of oestrogens, given alone or with a progestogen, in patients with hereditary haemorrhagic telangiectasia;[1,2] the use of a combined oral contraceptive has been suggested as a suitable option for fertile women with symptomatic epistaxis.[3] There are also some reports[2,4,5] of bleeding being reduced in patients with gastrointestinal vascular malformations from other causes. Conjugated oestrogens have been used in haemorrhagic disorders associated with chronic renal failure and haemorrhagic cystitis (see p. 2260.3).

1. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia. *Acta Med Scand* 1981; **209:** 393–6.
2. van Cutsem E, *et al.* Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. *Lancet* 1990; **335:** 953–5.
3. Jameson JJ, Cave DR. Hormonal and antihormonal therapy for epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2004; **114:** 705–9.
4. Bronner MH, *et al.* Estrogen-progesterone therapy for bleeding gastrointestinal telangiectasias in chronic renal failure: an uncontrolled trial. *Ann Intern Med* 1986; **105:** 371–4.
5. Siple JF, *et al.* Use of estrogen therapy in a patient with gastrointestinal bleeding secondary to arteriovenous malformations. *Ann Pharmacother* 1997; **31:** 1311–14.

Lactation inhibition. Synthetic oestrogens (e.g. quinestrol) and nonsteroidal oestrogens (e.g. diethylstilbestrol) were historically used to suppress lactation (p. 2130.1). However, this use is now considered inappropriate because of an increased risk of puerperal thromboembolism.

Premenstrual syndrome. Premenstrual syndrome (PMS) presents as a variable combination of psychological and somatic symptoms occurring during the luteal phase of the menstrual cycle, which resolve during, and immediately after, menstruation. Another term, premenstrual dysphoric disorder, has been proposed to cover severe cyclical mood disorder that is functionally incapacitating.[1,2] Whereas about 20 to 40% of women have complaints that may be classified as PMS, only 3 to 8% meet criteria for premenstrual dysphoric disorder.[2] The term premenstrual tension (PMT) has sometimes been applied to the psychological symptoms. Many symptoms of PMS are the same as normal premenstrual symptoms, but are more severe. The aetiology of PMS is not fully understood, although it is thought that affected women may be more sensitive to the effects of normal hormonal fluctuations on CNS neurotransmitter function.[2]

Initial management includes non-medical interventions[3] such as education and support, counselling, stress management, relaxation techniques, and exercise; caffeine and salt restriction are of unproven benefit. The herbal remedy agnus castus has been found to be of benefit.[4] For patients with moderate to severe symptoms, several drugs have been tried with varying degrees of success; objective assessment of efficacy has been hampered by varying diagnostic criteria, a marked placebo response, and difficulties in obtaining reproducible responses. Treatment may be aimed at modifying the menstrual cycle or treating specific symptoms.

SSRIs, particularly fluoxetine and sertraline, have been shown in controlled studies to alleviate both psychological and somatic symptoms in women with PMS.[3,5,6] They may be given intermittently (only in the luteal phase) or continuously for severe PMS,[1,3] and some suggest that they are particularly useful when mood symptoms predominate.[1,7] If treatment with one SSRI is ineffective or not tolerated, another SSRI or *venlafaxine* may be substituted.[1,3,5] There is limited information on the use of SSRIs for PMS in adolescents, and precautions regarding suicidal ideation in young adults should be considered.[2] *Clomipramine*, a nonselective serotonin reuptake inhibitor, has been tried for PMS with some success. The anxiolytic *alprazolam* has also been used, and may be useful when insomnia or overwhelming anxiety are significant.[7] However, use of this and other benzodiazepines should be restricted to the luteal phase of the cycle in selected patients to minimise the risk of dependence and tolerance.[8]

Abdominal bloating and swelling associated with PMS has traditionally been thought to be due to sodium and water retention. However, in most women with these symptoms there is no evidence of an increase in bodyweight or in body sodium or total water, and use of *diuretics* is therefore not justified.[9] Nevertheless, in women with appreciable weight gain and abdominal bloating in the luteal phase, the aldosterone antagonist spironolactone may be useful.[1,5,10] Another symptom of PMS, cyclical mastalgia, is discussed on p. 2265.1.

Pyridoxine has been tried on the basis that it is a cofactor in neurotransmitter (specifically serotonin) synthesis, and has been found to relieve depression induced by oral contraceptives in selected patients. However, its efficacy in PMS is equivocal, and high daily doses have been associated with neurotoxicity.[11] *Calcium* supplementation may relieve symptoms of PMS.[5,12]

Treatments that modify the menstrual cycle have often been used in women with PMS. In general, drugs with proven efficacy such as danazol, oestrogen implants, and gonadorelin analogues are reserved for women with severe PMS unresponsive to other treatments, because of their adverse effects. *Progestogen* therapy was once popular, but

beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground. In addition, a systematic review[13] of clinical studies found no evidence to support the use of progesterone or progestogens for PMS. *Combined oral contraceptives* have met with limited success.[2] They may be useful in some women for the control of somatic symptoms, but in others, PMS is caused or exacerbated by them. There is some suggestion that combined contraceptives containing drospirenone may be more effective in managing PMS than those containing progestogens such as levonorgestrel or norethisterone.[3] Regimens that have a shorter tablet-free interval (less than 7 days) may be useful for some women,[7] and consideration should be given to continuous rather than cyclical use.[3] Perimenopausal women may benefit from *oestrogen* delivered from transdermal patches. In women with a uterus, use with a cyclical progestogen is required to avoid endometrial hyperplasia; unfortunately, the progestogen may be associated with the return of symptoms. Possible strategies to minimise this include the use of a less androgenic progestogen, reducing the frequency with which it is given, or using an intra-uterine device to deliver the progestogen locally.[14] *Danazol* can be useful,[1,3] but there is concern over its adverse effects on lipids during long-term use and over the risk of masculinisation of a female fetus should pregnancy occur. For patients with severe symptoms not amenable to other treatments, gonadorelin analogues such as *goserelin* can be used to eliminate ovarian function, 'add-back' treatment with oestrogen plus progestogen being given to protect against the adverse effects of oestrogen deficiency including osteoporosis.[3] This treatment is very effective for both physical and psychological symptoms.[15] Short-term use (3 months) of a gonadorelin analogue alone has been used to confirm the diagnosis of PMS, or to predict the response to bilateral oophorectomy.[1,3]

1. Johnson SR. Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: a clinical primer for practitioners. *Obstet Gynecol* 2004; **104:** 845–59.
2. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol* 2007; **20:** 3–12.
3. Royal College of Obstetricians and Gynaecologists. Management of premenstrual syndrome (Green-top guideline 48, issued December 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT48ManagementPremensturalSyndrome.pdf (accessed 24/11/09)
4. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; **322:** 134–7.
5. Halbreich U. Algorithm for treatment of premenstrual syndromes (PMS): experts' recommendations and limitations. *Gynecol Endocrinol* 2005; **20:** 48–56.
6. Brown J, *et al*. Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 24/11/09).
7. Yonkers KA, *et al*. Premenstrual syndrome. *Lancet* 2008; **371:** 1200–10.
8. Severino SK, Moline ML. Premenstrual syndrome: identification and management. *Drugs* 1995; **49:** 71–82.
9. O'Brien PMS. Helping women with premenstrual syndrome. *BMJ* 1993; **307:** 1471–5.
10. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. *Drug Safety* 1994; **10:** 160–9.
11. Wyatt KM, *et al*. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999; **318:** 1375–81.
12. Thys-Jacobs S, *et al*. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998; **179:** 444–52.
13. Wyatt K, *et al*. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323:** 776–80.
14. Hassan I, *et al*. PMS in the perimenopause. *J Br Menopause Soc* 2004; **10:** 151–6.
15. Wyatt KM, *et al*. The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *BJOG* 2004; **111:** 585–93.

Turner's syndrome. Oestrogen therapy is used in Turner's syndrome (p. 2254.3) to produce sexual maturation and the development of secondary sexual characteristics, as well as to avoid complications such as osteoporosis. Low-dose oestrogen therapy may be started at about one-tenth to one-eighth of the adult replacement dose if spontaneous puberty has not begun by 12 to 13 years of age. Estradiol has been given in initial doses of 200 to 400 micrograms each month as an intramuscular depot injection, or 250 micrograms orally daily. Transdermal estradiol patches have also been tried, with the intention of giving an initial dose of 6.25 micrograms daily. However, because commercially available patches deliver 14 or 25 micrograms daily, methods of dose fractionation have included using a quarter of a patch overnight or daily, or using a whole patch for 7 to 10 days per month. It is unknown whether such methods deliver equivalent doses.[1] The use of transdermal estradiol gel has also been studied, starting with a dose of 100 micrograms daily.[2]

The oestrogen dose is gradually increased to adult doses over 2 to 4 years, to promote a normal pace of pubertal development. A cyclic progestogen is usually added about 2 years after starting oestrogen therapy or when breakthrough bleeding occurs. There is no consensus on which oestrogen is preferred, but transdermal or injectable depot estradiol may be the most physiological options. Adult daily doses of estradiol are generally 100 to 200 micrograms transdermally or 2 to 4 mg orally, or a monthly dose of injectable estradiol cipionate 2.5 mg may be used. Alternative oestrogens include oral ethinylestradiol 20 micrograms, or conjugated oestrogens 1.25 to 2.5 mg, daily. Progesterone may be given in oral doses of 200 mg daily on days 20 to 30 of a monthly cycle, or days 100 to 120 of a 3-month cycle. A combined oral contraceptive is another option for maintenance.[1]

1. Bondy CA. The Turner Syndrome Consensus Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; **92:** 10–25.
2. Piippo S, *et al*. Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome. *J Clin Endocrinol Metab* 2004; **89:** 3241–7.

Adverse Effects

The adverse effects of estradiol and other oestrogens are related, in part, to dose and duration of therapy, and to the gender and age of the recipient. In addition, adverse effects may be modified by a progestogen in combined oral contraceptives or menopausal HRT. Whether adverse effects of natural and synthetic oestrogens differ, and whether the dosage route has an effect, is less clear.

The adverse effects of oestrogens used in hormonal contraceptives are considered in detail starting on p. 2233.3. Those of oestrogens used in HRT are considered in detail starting on p. 2246.3.

The use of oestrogens in children may cause premature closure of the epiphyses resulting in decreased final adult height.

Large doses of oestrogens used in palliation of cancers have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, they cause impotence and feminising effects such as gynaecomastia. In women, they may cause withdrawal bleeding, and, when used for breast cancer, they have caused hypercalcaemia and bone pain.

Effects on the skin. Transdermal patches in which estradiol is dissolved in the adhesive matrix may cause fewer skin reactions than those releasing estradiol from an alcoholic reservoir.

1. Ross D. Randomised crossover comparison of skin irritation with two transdermal oestradiol patches. *BMJ* 1997; **315:** 288.

Precautions

The precautions for the use of estradiol and other oestrogens used as menopausal HRT are considered in detail starting on p. 2250.1. Those for oestrogens used in hormonal contraceptives are considered in detail starting on p. 2240.3.

High doses of oestrogen used in treating malignant disease should be used cautiously in patients with cerebrovascular disorders, coronary artery disease, or venous thromboembolism. They may exacerbate hypercalcaemia of malignancy.

Oestrogens should be used with caution in children because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature.

Women using topical formulations of estradiol should take care to avoid skin-to-skin contact with others for an appropriate time after application, according to advice in the licensed product information. Premature puberty in girls and gynaecomastia in boys have occurred in young children who have been inadvertently exposed to estradiol, by contact with the treated area of skin of women using a transdermal spray.

Oestrogens have been reported to interfere with some diagnostic tests such as those for thyroid function and glucose tolerance.

Breast feeding. Estradiol has been detected in breast milk after the use of pessaries containing 50 or 100 mg of estradiol.[1] The American Academy of Pediatrics considers that estradiol is usually compatible with breast feeding.[2]

1. Nilsson S, *et al*. Transfer of estradiol to human milk. *Am J Obstet Gynecol* 1978; **132:** 653–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Cosmetic use. Use of cosmetic products containing oestrogens has led to adverse effects such as precocious puberty in children[1,2] and gynaecomastia or postmenopausal bleeding in adults.[1] Such products have been used by a greater proportion of African Americans than any other ethnic group in the USA, and it has been hypothesised that this may have contributed to the observations of earlier onset of puberty in girls[3,4] and increased risk of breast cancer in young women.[4]

1. Anonymous. Estrogens in cosmetics. *Med Lett Drugs Ther* 1985; **27:** 54–5.
2. Tiwary CM. Premature sexual development in children following the use of estrogen- or placenta-containing hair products. *Clin Pediatr (Phila)* 1998; **37:** 733–9.
3. Li S-T, *et al*. Hormone-containing hair product use in prepubertal children. *Arch Pediatr Adolesc Med* 2002; **156:** 85–6.
4. Donovan M, *et al*. Personal care products that contain estrogens or xenoestrogens may increase breast cancer risk. *Med Hypotheses* 2007; **68:** 756–66.

Pregnancy. Although gross abnormalities of the genitourinary tract have been reported in the male offspring of women who took diethylstilbestrol during pregnancy there is conflicting evidence as to whether the oestrogen produced an increased risk of abnormalities, infertility, or testicular cancer in such offspring (see p. 2268.3). The male fetus is normally protected from the feminising effects of the natural oestrogens in the uterine environment by the early development of the testes and the secretion of male hormones.[1] However, there has been considerable concern about a rising incidence of disorders of the male reproductive tract, and a reduction in sperm counts, which has been noted in the last 20 to 30 years. It has been hypothesised that overexposure of male fetuses to environmental oestrogens derived from pollutants such as pesticides and plastics may be responsible for this decline,[2,3] although some dispute this.[4] A systematic review[5] of epidemiological data found no strong evidence to link fetal exposure to oestrogens (as pharmaceuticals or pollutants) with reduced sperm count, cryptorchidism, or hypospadias, although there was some evidence to support a possible link with testicular cancer.

For discussion of the lack of effects of hormonal contraceptives on the fetus, including evidence that they are unlikely to increase the risk of hypospadia in the male fetus, see Pregnancy, under Precautions of Hormonal Contraceptives, p. 2242.1.

1. Mittwoch U, *et al*. Male sexual development in "a sea of oestrogen". *Lancet* 1993; **342:** 123–4.
2. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993; **341:** 1392–5.
3. de Kretser DM. Declining sperm counts. *BMJ* 1996; **312:** 457–8.
4. Thomas JA. Falling sperm counts. *Lancet* 1995; **346:** 635.
5. Storgaard L, *et al*. Male reproductive disorders in humans and prenatal indicators of estrogen exposure: a review of published epidemiological studies. *Reprod Toxicol* 2006; **21:** 4–15.

Veterinary use. An FAO/WHO expert committee examining the risks from residues of veterinary drugs in foodstuffs established an acceptable daily intake for estradiol, but concluded that there would be no need to specify a numerical maximum residue limit for estradiol in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as oestrogens in veterinary practice is restricted, and their use as growth promotors is banned.

There is concern about the effect of environmental oestrogens on male fertility and development, see Pregnancy, above.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Interactions involving estradiol and other oestrogens used in menopausal HRT are covered on p. 2251.1. Interactions for oestrogens used in hormonal contraceptives are covered on p. 2242.3.

Pharmacokinetics

In general, estradiol and other oestrogens are readily absorbed from the gastrointestinal tract and through the skin or mucous membranes. However, the natural unconjugated oestrogens such as estradiol undergo extensive first-pass metabolism in the gastrointestinal tract and liver after oral doses. They are, therefore, generally not orally active, although a micronised preparation of estradiol has sufficient bioavailability (3 to 5%) to be orally active. Estradiol is metabolised in part to less active oestrogens such as estriol and estrone. Synthetic oestrogens produced by alkylation of the C17 position, such as ethinylestradiol, are more slowly metabolised and are therefore orally active. Conjugated oestrogens, which are essentially oestrogen metabolites, are also orally active because they are hydrolysed by enzymes in the lower gastrointestinal tract allowing absorption of the active oestrogen. Vaginal, transdermal, intranasal, or parenteral use of oestrogens also avoids first-pass hepatic metabolism. Plasma-estradiol concentrations are reported to reach a peak 1.5 to 2 hours after an oral dose, and again at about 8 hours due to enterohepatic recycling. Estradiol esters are rapidly hydrolysed to free estradiol when given orally. After intramuscular injection of the esters, absorption is prolonged.

Oestrogens are extensively bound to plasma proteins. Naturally occurring oestrogens such as estradiol are mainly bound to sex-hormone binding globulin. Conversely, ethinylestradiol is mostly bound to albumin.

Oestrogens are metabolised in the liver. A variety of sulfate and glucuronide conjugates are formed, and these are excreted in the urine and the bile. Those excreted in the bile undergo enterohepatic recycling or are excreted in the faeces.

References to the pharmacokinetics of estradiol[1-4] and other oestrogens.[5,6]

1. Kuhnz W, *et al*. Pharmacokinetics of estradiol, free and total estrone, in young women following single intravenous and oral administration of 17 β -estradiol. *Arzneimittelforschung* 1993; **43:** 966–73.
2. Schubert W, *et al*. Pharmacokinetic evaluation of oral 17 β -oestradiol and two different fat soluble analogues in ovariectomized women. *Eur J Clin Pharmacol* 1993; **44:** 563–8.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, other methods of delivery. *Obstet Gynecol Clin North Am* 1994; **21:** 271–9.
4. Price TM, *et al*. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β -estradiol. *Obstet Gynecol* 1997; **89:** 340–5.
5. Stumpf PG. Pharmacokinetics of estrogen. *Obstet Gynecol* 1990; **75** (suppl): 9S–14S.
6. O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol* 1995; **35** (suppl): 18S–24S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerodiol; Estraderm†; Estradot†; Estrofem; Etrosteron; Eutocol; Evorel; Ginatex; Ginediol; Hormodiol; Lindisc; Oestro Gel; Progynon; Progynova; Ronfase; Rontagel; Trial Gel; Trial SAT; ***Austral.***: Aerodiol†; Climara; Estraderm; Estradot; Estrofem; Femtran; Menorest†; Primogyn Depot†; Progynova; Sandrena; Vagifem; Zumenon; ***Austria***: Climara; Dermestril; Estradot; Estramon; Estrofem; Estrogel; FemSeven; Klimapur; Linoladiol; Menorest†; Progynon†; Progynova; Systen; Vagifem; ***Belg.***: Aerodiol†; Climara; Dermestril; Estraderm; Estreva; Estrofem; Feminova; Meno-Implant; Oestrogel; Progynova; Systen; Vagifem; Vivelle; Zumenon; ***Braz.***: Aerodiol; Avicis; Benzo-Ginoestril; Climaderm; Estradelle†; Estradot; Estreva; Estrofem; Fem 7; Hormodose; Lindisc; Merimono; Natifa; Oestrogel; Primogyna; Riselle; Sandrena; Systen; Tegan; ***Canad.***: Climara; Divigel; Estrace; Estraderm; Estradot; Estring; Estrogel; Oesclim; Vagifem; ***Chile***: Climaderm†; Dermatrans†; Enadiol†; Epiestrol†; Estranova E†; Estreva; Farlutes†; Fem 7; Femalon; Femiderm; Femidot†; Ginoderm; Hormogel; Mirion; Primaquin; Progynova; Sandrena; Transvital; Vagifem; ***China***: Climara (康美华); Dermestril (得美素)†; Estrofem (诺坤复); Fem 7 (松奇); Happier (更乐); Oestrogel (爱斯妥); Progynova (补佳乐); Xie Kun (协坤); Yi Er (伊尔); Yi Tai Li (意泰丽); ***Cz.***: Agofollin; Climara; Dermestril; Divigel; Estraderm†; Estradot†; Estrahexal; Estrapatch; Estrimax; Estrofem; Linoladiol N; Neofollin; Octodiol†; Oestrogel; Riselle; Systen; Vagifem; ***Denm.***: Climara†; Divigel; Estreva†; Estring; Estrofem; Estrogel; Evorel; Femanest; Progynon; Systen Conti; Vagifem; Vivelle Dot; ***Fin.***: Climara; Dermestril†; Divigel; Estradot; Estrena; Estring; Estrofem; Estrogel; Evorel; FemSeven; Merimono†; Progynova; Vagifem; Zumenon; ***Fr.***: Climara; Delidose; Dermestril; Estraderm†; Estrapatch; Estrofem; Oesclim; Oestrodose; Oestrogel; Oromone; Progynova; Provames; Thais; Vivelledot; ***Ger.***: Cutanum†; Dermestril; Estrabeta†; Estraderm†; Estradot; Estramon†; Estreva; Estrifam; Estring; Estronorm†; Fem 7; Femoston mono; Gynokadin; Gyn-Polar; Linoladiol N; Merimono; Progynova; Sisare mono†; Tradelia; Vagifem; ***Gr.***: Aerodiol; Climara; Dermestril; Estraderm TTS; Estradot; Estramon; Estring; Estrofem; Estrogel†; Menorest; Oesclim; Oestrogel; Progynon; Systen; Vagifem; ***Hong Kong***: Dermestril†; Estraderm†; Estreva; Estrofem; Oestrogel; Progynova†; Vagifem; ***Hung.***: Calidiol†; Dermestril; Divigel; Estraderm†; Estramon†; Estrapatch†; Estrimax; Estrofem; FemSeven†; Linoladiol N; Oestrogel†; Vagifem; ***India***: Divigel; E2; Estraderm; Estrofem; ETS; Evalon; Oestrogel; ***Indon.***: Estreva†; Fem 7†; Progynova; ***Irl.***: Aerodiol†; Climara; Dermestril; Divigel; Epiestrol†; Estraderm†; Estradot; Estreva†; Estrofem; Evorel; Fematab; Oestrogel; Vagifem; ***Israel***: Estraderm†; Estrofem; Evorel; Oestrodose†; Oestrogel; Progynova; Vagifem; ***Ital.***: Armonil; Climara; Dermestril; Ephelia†; Epiestrol; Esclima†; Estraderm; Estrodose; Estrofem; FemSeven; Gelestra; Ginaikos; Progynova; Sandrena; Systen; Vagifem; Zerella; ***Malaysia***: Divigel; Oestrogel; Progynova; ***Mex.***: Armistor†; Benzo-Ginestryl; Climaderm; Essventia; Estraderm†; Estramon; Estreva; Evorel; Fem 7; Ginedisc; Oestrogel; Primogyn; Sandrena; Systen; ***Mon.***: Estreva; Femsept; ***Neth.***: Aerodiol; Cetura; Climara†; Dermestril†; Estraderm†; Estradot; Estreva†; Estrofem; Fem 7†; Meno-Implant; Ovestal†; Progynova; Systen; Vagifem; Zumenon; ***Norw.***: Climara†; Estradot; Estring; Evorel; Progynova; Vagifem; ***NZ***: Aerodiol†; Climara; Estraderm; Estradot; Estrofem; Femtran; Progynova; Vagifem; ***Philipp.***: Climara; Estrofem; Progynova; Vagifem; ***Pol.***: Calidiol; Climara; Divigel; Estraderm; Estradot; Estrapatch†; Estreva; Estrofem; Estroplast†; Fem 7; Oesclim; Progynova; Systen; Vagifem; ***Port.***: Climara; Dermestril; Epiestrol; Estraderm; Estradot; Estrapatch; Estreva; Estrofem; Femring†; Femsete; Oestrodose†; Vagifem; Zumenon; ***Rus.***: Climara (Климара); Divigel (Дивигель); Estrimax (Эстримакс); Estrofem (Эстрофем); Oestrogel (Эстрожель); Progynova (Прогинова); ***S.Afr.***: Climara; Estraderm; Estradot; Estring; Estro-Pause; Estrofem; Evorel; Femigel; Primogyn Depot†; Progynova; Vagifem; ***Singapore***: Divigel; Estraderm; Estring; Estrofem; Menostar; Oestrogel; Progynova; Vagifem; ***Spain***: Absorlent†; Alcis; Dermestril†; Endomina†; Esprasone†; Estraderm; Estradot; Estrapatch†; Estroffik†; Evopad; Meriestra; Oestraclin; Progynova; Vagifem; ***Swed.***: Climara†; Divigel; Estradot; Evorel; Femanest; Oesclim†; Oestring; Progynon; Vagifem; ***Switz.***: Climara; Divigel; Estradot; Estramon†; Estreva†; Estring; Estrofem N; Femoston mono; Oestrogel; Progynova; Sandrena†; Systen; Vagifem; Zumenon†; ***Thai.***: Climara; Divigel; Ediol; Estrofem; Oestrogel; Postmenop; Progynon†; Progynova; Vagifem†; ***Turk.***: Aerodiol; Akrofolline; Climara; Estraderm; Estramon; Estrava; Estrofem; Fem 7; Femijel; Vagifem; ***UK***: Bedol; Climaval; Elleste-Solo; Estraderm; Estradot; Estring; Evorel; Fematrix†; FemSeven; Oestrogel; Progynova; Sandrena; Vagifem; Zumenon; ***Ukr.***: Divigel (Дивигель); Estramon (Эстрамон); Oestrogel (Эстрожель); Progynova (Прогинова); ***USA***: Alora; Climara; Delestrogen; depGynogen; Depogen; Divigel; Elestrin; Esclim†; Estrace; Estraderm; Estrasorb; Estring; Estrogel; Evamist; FemPatch; Femring; Femtrace; Gynodiol; Menostar; Minivelle; Vagifem; Valergen; Vivelle; ***Venez.***: Aerodiol; Climaderm; Estradot; Estrogel; FemSeven; Progynova.

Multi-ingredient Preparations. ***Arg.***: Activelle; Angeliq; Atrimon; Ciclocur; Climene; Cristerona; Cyclofem; Disequens; Dos Dias N; Eos; Equifem; Estalis Sequi†; Estalis†; Estracomb†; Estragest; Evorel Conti; Evorel Sequi; Farludiol Ciclo; Farludiol; Fempack; Gadofem; Gynodian Depot; Hosterona; Kliogest; Lubriderm; Menstrogen†; Mesigyna; Patector; Perlutal; Prefest; Primosiston; Rubi; Supligol NF; Totelle Ciclico; Totelle Continuo; Trial Combi; Trial Gest; Trisequens; ***Austral.***: Angeliq; Climen†; Estalis Continuous; Estalis Sequi; Estracombi; Femoston; Kliogest; Kliovance; Qlaira; Trisequens; Zoely; ***Austria***: Activelle; Angeliq; Climen; Duokliman; Estalis Sequens†; Estalis; Estracomb†; Femoston Conti; Femoston; FemSeven Combi; Gynodian Depot; Kliogest; Mericomb; Merigest; Perikliman; Qlaira; Sequidot 2-Phasen; Trisequens; ***Belg.***: Activelle; Angeliq; Climen; Climodien; Cyclocur; Diviplus; Diviva; Duogestan; Estalis; Estracombi; Feminova Plus; Femoston Conti; Femoston; Kliogest; Naemis; Novofem; Qlaira; Trisequens; ***Braz.***: Activelle; Angeliq; Avaden; Ciclioprimogyna; Cliane; Climene; Cyclofemina; Daiva; Dilena; Elamax; Estalis SQ; Estalis; Estandron P; Estragest; Femoston Conti; Femoston; Gestadinona; Gineane; Kliogest; Lindisc Duo; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Perlutan; Prefest; Preg-Less; Pregnolan; Suprelle; Suprema; System Conti; Systen Sequi; Totelle Ciclo; Totelle; Trinestril; Trisequens; Uno Ciclo; ***Canad.***: Activelle; Angeliq; Climara Pro; Estalis; Estracomb†; ***Chile***: Activelle; Altesse; Angeliq; Avaden†; Cliane; Climene; Clinomat; Enadiol CC†; Enadiol MP†; Enadiol Neta†; Estandron Prolongado†; Estracomb†; Estragest; Estranova 30 Simple†; Estranova CC†; Farluposf†; Fem 7 Combi; Femoston Conti; Femoston; Ginefolin; Ginotex; Gynodian Depot; Kilios; Kliogest; Lovelle Ciclico; Lovelle Continuo; Mesigyna; Novafem; Primaquin MP Continuo†; Primaquin MP†; Progyluton; Totelle Ciclico; Totelle Continuo; Trisequens; Unalmes; ***China***: Activelle (诺更宁); Angeliq (安今益); Climen (克龄蒙); Femoston (芬吗通); Lunella (月纳); Novofem; Trisequens (诺康律); Yi Wei Xian (逸维仙); ***Cz.***: Activelle; Alpicort F; Angeliq; Climen; Divina; Diviseq; Estalis Sequi†; Estalis†; Femoston Conti; Femoston Mini; Femoston; Folivirin; Gynodian Depot; Gynovel; Indivina; Kliane; Klimodien; Klimonorm; Kliogest; Noviana; Novofem; Pausogest†; Qlaira; Sequidot†; Systen Conti; Systen Sequi; Trisequens; ***Denm.***: Activelle; Angemin; Climodien†; Cliovelle; Divina Plus; Divina; Estracomb†; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Indivina; Kliogest; Novofem; Nuvelle†; Qlaira; Trevina; Trisekvens; Trisequens; Zoely; ***Fin.***: Activelle; Angeliq; Cliovelle; Cyclabil†; Divina; Divitren; Estalis Sekvens†; Estalis; Evorel Conti; Evorel Sequi; Femilar; Femoston Conti; Femoston; FemSeven Combi†; Indivina; Kliogest; Mericomb†; Merigest†; Novofem; Qlaira; Sequidot; Trisekvens; ***Fr.***: Activelle; Angeliq; Avadene; Climaston; Climaston; Climene; Climodiene; Divina; Duova; Kliogest; Novofemme; Qlaira; Trisequens; ***Ger.***: Activelle; Alpicort F; Angeliq; Climen; Climodien; Clionara; Cliovelle; Crinohermal fem; Cyclo-Progynova N; CycloOstrogynal; Estalis Sequi†; Estragest; Fem 7 Combi; Fem 7 Conti; Femoston Conti; Femoston; Gianda†; Gynamon†; Gynodian Depot; Indivina; Klimonorm; Kliogest N; Lafamme; Linoladiol-H N; Mericomb; Merigest; Novofem; Osmil†; Ostronara; Qlaira; Sequidot; Sisare 28†; Sisare†; Trisequens; Wellnara; ***Gr.***: Activelle; Angeliq; Climodien; Cyclacur; Divina; Estalis Sequi; Estalis Sequidot; Estalis; Estopause; Estracomb TTS; Femaston; Kliogest; Nuvelle; Qlaira; Systen Conti; Systen Sequi; Trisequens; ***Hong Kong***: Activelle; Angeliq; Climen 28†; Cyclofem; Dilena†; Estracomb†; Femoston Conti†; Femoston; Hormonin†; Kliogest; Novofem; Trisequens; ***Hung.***: Activelle; Alpicort F; Angeliq; Climen†; Divina; Estracomb†; Estragest; Femoston; FemSeven Combi†; Indivina; Klimonorm; Kliogest; Novofem; Pausogest; Qlaira; Triaklim; Trisequens; Tulita; ***India***: Kemicetine Antiozena; Mixogen; ***Indon.***: Angeliq; Climen 28; Cyclo-Progynova; Cyclofem†; Femoston; Mediol†; Renodiol; ***Irl.***: Activelle; Allurene†; Angeliq; Estalis Sequi†; Estalis†; Estracombi†; Evorel Conti; Femoston Conti; Femoston; FemSeven Conti; FemSeven Sequi†; Femurest-Conti; Indivina; IOA; Kliogest; Naemis†; Novofem; Qlaira; Trisequens; Zoely; ***Israel***: Activelle; Angeliq; Eviana; Evorel Conti; Evorel Sequi; Kliogest; Novofem; Progyluton; Qlair; Trisequens; ***Ital.***: Activelle; Angeliq; Climen; Combiseven; Estalis Sequi; Estracomb†; Femity; Femoston Conti; Femoston; Filena; Gynodian Depot; Klaira; Kliogest; Menovis; Naemis; Pausene; Trisequens; ***Malaysia***: Activelle; Angeliq; Climen; Duogynon; Femoston Conti; Femoston; Progyluton; ***Mex.***: Anafertin; Angeliq; Avaden; Binodian; Cliane; Climene; Cyclofemina; Damax; Despamen; Dilena; Estalis†; Estracomb; Evorel Conti; Genofort; Gravidinona; Lutalmin; Lutoginestryl F; Mesigyna; Metrigen Fuerte; Nostidyn; Patector; Perludil; Perlutal; Prefest; Primoson-F; Proger-F; Progyluton; Totelle Continuo; Totelle Secuencial; Xofemina; Yectames; ***Mon.***: FemseptCombi; Femseptevo; Naemis; Zoely; ***Neth.***: Activelle; Allurenet; Angeliq; Climaston Continu; Climene†; Climodien; Cyclocur†; Estalis Sequi†; Estalis†; Estandron Prolongatum†; Estracomb†; Eviana; Fem 7 Sequi†; Femoston Continu; Femoston; Femphascyl Continu; Femphascyl; Ioa; Kliogest; Lafamme; Naemis†; Novofem; Qlaira; Trisequens; Zoely; ***Norw.***: Activelle; Climodien†; Cliovelle; Estalis Sekvens†; Estalis; Eviana; Indivina; Kliogest†; Novofem; Qlaira; Sequidot; Trisekvens; Zoely; ***NZ***: Cliane†; Femoston; Kliogest; Kliovance; Nuvelle; Trisequens; ***Philipp.***: Angeliq; Climen 28; Femoston†; Kliogest; ***Pol.***: Activelle; Alpicort E; Angeliq; Climen; Cliovelle; Cyclo-Progynova; Divina; Diviseq; Estalis Sequi†; Estalis; Estracomb; Fem 7 Combi; Femoston Conti; Femoston Mini; Femoston; Gynodian Depot†; Indivina; Klimonorm; Kliogest; Novofem; Qlaira; Systen Conti; Systen Sequi; Trisequens; ***Port.***: Activelle; Allurene; Angeliq; Avadene; Climen; Climodien; Dilena; Estalis Sequi; Estalis; Estracomb†; Femoston 1/5; Femoston; Femsete Combi; Femsete Evo; Kliogest; Lafamme; Naemis; Novofem; Nuvelle; Progyluton; Qlaira; Trisequens; ***Rus.***: Angeliq (Анжелик); Climen (Климен); Climodien (Климодиен); Cyclo-Progynova (Цикло-прогинова); Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен)†; Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); Gynodian Depot (Гинодиан Депо)†; Indivina (Индивина); Klimonorm (Климонорм); Kliogest (Клиогест); Pausogest (Паузогест); Triaklim (Триаклим); Trisequens (Трисеквенс); ***S.Afr.***: Activelle; Angeliq; Climen; Divina†; Estalis; Estracombi†; Estro-Pause N; Evorel Conti; Evorel Sequi; Femoston Conti; Femoston; Kliogest; Mixogen†; Novofem; Postoval; Prefesta†; Primodian Depot†; Trisequens; Trivina†; ***Singapore***: Activelle; Climen; Estracomb; Femoston Conti; Femoston; Kliogest†; Progyluton; Qlaira; Trisequens; Unijab; ***Spain***: Absorlent Plus†; Activelle; Angeliq; Climen; Climodien; Duofemme; Endomina Plus†; Estalis Sequi; Estalis; Estracomb†; Eviana; Merigest Sequi†; Merigest†; Mevaren; Nuvelle†; Perifem; Progyluton; Qlaira; Trisequens; Zoely; ***Swed.***: Activelle; Angemin; Climodien†; Cliovelle; Divina Plus; Estalis; Eviana; Femanor; Femasekvens; Indivina; Kliogest†; Novofem; Qlaira; Sequidot; Trisekvens†; Trivina; Zoely; ***Switz.***: Activelle; Alpicort F; Angeliq; Climen; Cyclacur; Diviseq†; Estalis Sequi†; Estalis; Estracomb†; Estragest; Estranor; Femoston Conti; Femoston; Gynodian Depot; Indivina; Kliogest N; Mericomb†; Merigest†; Novofem; Sequidot; Systen Conti; Systen Sequi; Triaval†; Trisequens; Zoely; ***Thai.***: Activelle; Angeliq; Climen; Cyclo-Progynova; Diviseq†; Duoton; Femoston 1/10; Femoston Conti; Havina†; Indivina†; Klimonorm†; Phenokinon-F; Primodian Depot†; ***Turk.***: Activelle; Angeliq; Climen; Climodien; Cyclo-Progynova; Di-Pro; Divina; Estandron Prolan; Estracombi; Femoston; Kliogest; Mesigyna; Trisequens; ***UK***: Angeliq; Climagest; Climesse; Clinorette; Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; Elleste Duet Conti; Elleste-Duet; Estracombi†; Evorel Conti; Evorel Sequi; Femapak†; Femoston Conti; Femoston; FemSeven Conti; FemSeven Sequi; Hormonin; Indivina; Kliofem; Kliovance; Novofem; Nuvelle Continuous; Nuvelle†; Qlaira; Tridestra; Trisequens; Zoely; ***Ukr.***: Angeliq (Анжелик); Climen (Климен); Divina (Дивина)†; Femoston (Фемостон); Indivina (Индивина)†; Klimodien (Климодиен)†; Klimonorm (Климонорм); Pausogest (Паузогест)†; Revmelid (Ревмелид)†; ***USA***: Activella; Angeliq; ClimaraPro; CombiPatch; Depo-Testadiol†; Depotestogen†; Mimvey; Natazia; Prefest; ***Venez.***: Avaden; Cliane; Climene; Estragest; Femoston Conti; Femoston; Ginecosid; Ginecosid; Gynodian Depot; Mesigyna; Progyluton; Totelle Ciclico; Totelle Continuo.

Pharmacopoeial Preparations

BP 2014: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Estradiol Injection; Estradiol Transdermal Patches;

USP 36: Estradiol and Norethindrone Acetate Tablets; Estradiol Cypionate Injection; Estradiol Tablets; Estradiol Transdermal System; Estradiol Vaginal Cream; Estradiol Vaginal Inserts; Estradiol Valerate Injection.

Estrapronicate *(rINN)*

Estrapronicato; Estrapronicatum; Эстрапроникат.

Oestradiol 17-nicotinate 3-propionate.

$C_{27}H_{31}NO_4$=433.5

CAS — 4140-20-9.

UNII — BC621AC03L.

Profile

Estrapronicate is a derivative of estradiol (p. 2271.1) with nicotinic acid. It has been used as an ingredient of a combined preparation with an anabolic steroid and a progestogen for osteoporosis.

Estriol *(BAN, rINNM)*

Estrioli; Estriolis; Estriolum; Follicular Hormone Hydrate; Oestriol; Östriol; Ösztriol; Theelol; Эстриол.

Estra-1,3,5(10)-triene-3,16α,17β-triol.

$C_{18}H_{24}O_3$=288.4

CAS — 50-27-1.

ATC — G03CA04.

ATC Vet — QG03CA04; QG03CC06.

UNII — FB33469R8E.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Estriol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol.

USP 36: (Estriol). A white or practically white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, in dioxan, in ether, and in vegetable oils. Store in airtight containers.

Estriol Sodium Succinate *(BAN, rINNM)*

Estriol, Succinate Sodique d'; Estriol, succinato sódico de; Estrioli Natrii Succinas; Oestriol Sodium Succinate; Succinato sódico de estriol; Эстриола Натрия Сукцинат.

Disodium 3-hydroxyestra-1,3,5(10)-triene-16α,17β-diyl disuccinate.

$C_{26}H_{30}Na_2O_9$=532.5

CAS — 113-22-4.

ATC — G03CA04.

ATC Vet — QG03CA04.

UNII — 64I100CU65.

Estriol Succinate *(BAN, rINN)*

Estriol, Succinate d'; Estriol, succinato de; Estrioli Succinas; Estriolisuksinaatti; Estriolsuccinat; Oestriol Succinate; Succinato de estriol; Эстриола Сукцинат.

3-Hydroxyestra-1,3,5(10)-triene-16α,17β-diyl di(hydrogen succinate).

$C_{26}H_{32}O_9$=488.5

CAS — 514-68-1.

ATC — G03CA04.

ATC Vet — QG03CA04.

UNII — AS13K2DY03.

Profile

Estriol is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (p. 2271.1).

It is used for menopausal HRT (p. 2244.1). When oestrogens are given to women with a uterus, a progestogen is required, particularly if used long term. Oral doses of estriol 4 to 8 mg daily may be used initially, followed by a gradual reduction to the lowest effective dose. Estriol has also been given with other natural oestrogens such as estradiol and estrone (see below); usual doses of estriol have ranged from about 0.25 to 2 mg daily. Estriol may be used intravaginally for the short-term treatment of menopausal atrophic vaginitis and kraurosis vulvae. A dose of 500 micrograms may be given as a 0.01% or 0.1% cream or as a pessary; initial treatment may be given once daily, then reduced to twice each week.

Estriol has also been given orally for infertility (p. 2253.1) caused by poor cervical penetration, in a dose of 1 to 2 mg daily on days 6 to 15 of the menstrual cycle. The dose may be increased if necessary each month, until an optimal effect on the cervical mucous is obtained. Doses of up to 8 mg daily on treatment days may be needed.

Estriol succinate has also been given orally in the treatment of menopausal disorders. The sodium succinate salt has been used parenterally in the treatment of haemorrhage and thrombocytopenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Colpoestriol; Menoclim; Orgestriol; ***Austral.***: Ovestin; ***Austria***: Ortho-Gynest; Ovestin; ***Belg.***: Aacifemine; Ortho-Gynest; ***Braz.***: Estriopax; Hormocervix; Hormoniol; Ovestrion; Styptanon†; ***Chile***: Ovestin; Sinapause; Vacidox; ***China***: Ovestin (欧维婷); Yi Te Le (伊特乐); ***Cz.***: Ortho-Gynest; Ovestin; ***Denm.***: Ovestin; ***Fin.***: Ovestin; Pausanol; ***Fr.***: Gydrelle; Physiogine; Trophicreme; ***Ger.***: Cordes Estriol; OeKolp; Oestro-Gynaedron M; Ortho-Gynest; Ovestin; Synapause E†; Xapro; ***Gr.***: Ovestin; ***Hung.***: Estrokad; Ortho-Gynest; Ovestin; ***Indon.***: Ovestin; ***Irl.***: Ortho-Gynest†; Ovestin; ***Israel***: Ortho-Gynest; Ovestin; ***Ital.***: Colpogyn; Ortho Gynest Depot; Ovestin†; Trofogin; ***Jpn***: Estriel; ***Mex.***: Ortho-Gynest; Ovestin; Sinapause; ***Neth.***: Synapause-E_3; ***Norw.***: Ovesterin; ***NZ***: Ovestin; ***Philipp.***: Ovestin; ***Pol.***: Oekolp; Ortho-Gynest; Ovestin; ***Port.***: Ovestin; Pausigin; ***Rus.***: Estrokad (Эстрокад); Ovestin (Овестин); ***S.Afr.***: Synapause; ***Spain***: Ovestinon; ***Swed.***: Ovesterin; ***Switz.***: Oestro-Gynaedron; Ortho-Gynest; Ovestin; ***Thai.***: Ovestin; ***Turk.***: Ovestin; ***UK***: Gynest; Ortho-Gynest†; Ovestin; ***Ukr.***: Ovestin (Овестин); ***Venez.***: Ortho-Gynest; Ovestin.

Multi-ingredient Preparations. ***Arg.***: Tropivag Plus; ***Austria***: Gynoflor; ***Belg.***: Gynoflor; ***Cz.***: Gynoflor; ***Fr.***: Florgynal; Trophigil; ***Ger.***: CycloOstrogynal; Gynoflor; ***Hong Kong***: Gynoflor; Hormonin†; ***Hung.***: Gynoflor; ***Ital.***: Donaflor; ***Malaysia***: Gynoflor; ***Pol.***: Gynoflor; ***Port.***: Gynoflor; ***Rus.***: Gynoflor E (Гинофлор Э); ***Switz.***: Gynoflor; ***Thai.***: Gynoflor; ***Turk.***: Gynoflor; ***UK***: Hormonin; ***Ukr.***: Gynoflor (Гінофлор).

Pharmacopoeial Preparations

BP 2014: Estriol Cream.

Estrone *(BAN, rINN)*

Estron; Estrona; Estroni; Estronum; Foliculina; Follicular Hormone; Folliculin; Ketohydroxyoestrin; Oestrone; Östron; Эстрон.

3-Hydroxyestra-1,3,5(10)-trien-17-one.

$C_{18}H_{22}O_2$=270.4

CAS — 53-16-7.

ATC — G03CA07.

ATC Vet — QG03CA07; QG03CC04.

UNII — 2DI9HA706A.

Pharmacopoeias. In *US.*

USP 36: (Estrone). Odourless, small white crystals or white to creamy-white crystalline powder. Practically insoluble in water; soluble 1 in 250 of alcohol and 1 in 110 of chloroform at 15 degrees; soluble 1 in 50 of boiling alcohol, 1 in 33 of boiling acetone, 1 in 145 of boiling benzene, and 1 in 80 of boiling chloroform; soluble 1 in 50 of acetone at 50 degrees; soluble in dioxan and in vegetable oils; slightly soluble in solutions of fixed alkali hydroxides. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Estrone is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (see p. 2271.1).

For menopausal HRT (see p. 2244.1) estrone has been given orally at a dose of 1.4 to 2.8 mg daily in a cyclical or continuous regimen, as a combination product with estradiol and estriol (see p. 2274.3). Estrone has also been given by intramuscular injection in oily solutions and aqueous suspensions. When used specifically for menopausal atrophic vaginitis, estrone has been given vaginally. If used in women with a uterus, estrone by any route should be given with a progestogen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Estragyn; ***USA***: Kestrone.

Multi-ingredient Preparations. ***Hong Kong***: Hormonin†; ***Mon.***: Synergon; ***Port.***: Gretalvite; ***Spain***: Cicatral; Grietalgen; ***Thai.***: Metharmon-F†; ***Turk.***: Synergon; ***UK***: Hormonin.

Pharmacopoeial Preparations

USP 36: Estrone Injectable Suspension.

Estropipate *(BAN)*

Estropipato; Piperazine Estrone Sulfate; Piperazine Oestrone Sulphate; Эстропипат.

Piperazine 17-oxoestra-1,3,5-(10)-trien-3-yl hydrogen sulphate.

$C_{18}H_{22}O_5S.C_4H_{10}N_2$=436.6

CAS — 7280-37-7.

UNII — SVI38UY019.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Estropipate). A white or almost white crystalline powder. Very slightly soluble in water, in alcohol, in chloroform, and in ether.

USP 36: (Estropipate). A white to yellowish-white fine crystalline powder, odourless or may have a slight odour. Very slightly soluble in water, in alcohol, in chloroform, and in ether; soluble 1 in 500 of warm alcohol; soluble in warm water. Store in airtight containers.

Uses and Administration

Estropipate is a semisynthetic conjugate of estrone with piperazine that is used for menopausal HRT (see p. 2244.2). Its action is due to estrone (see above) to which it is hydrolysed in the body.

Estropipate is given orally for the short-term treatment of menopausal symptoms in doses ranging from 0.75 to 3 mg daily, given cyclically or continuously; doses up to 6 mg daily have also been given cyclically. Daily doses such as 0.75 mg cyclically or 1.5 mg continuously may be given for the prevention of postmenopausal osteoporosis, but oestrogen therapy is generally reserved for women who are at significant risk and who cannot be given non-hormonal treatment. In women with a uterus estropipate should be used with a progestogen. Estropipate has also been used short term for menopausal atrophic vaginitis as a vaginal cream containing 0.15%; 2 to 4g of cream is applied daily. In the treatment of female hypogonadism, castration, and primary ovarian failure, estropipate is given orally in doses of 1.5 to 3 mg daily, in a cyclical regimen; higher doses of up to 9 mg daily given cyclically have also been used.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormone Replacement Therapy, p. 2246.3.

Interactions

See under Hormone Replacement Therapy, p. 2251.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Genoral; Ogen†; ***Canad.***: Ogen; ***Indon.***: Ogen†; ***S.Afr.***: Ortho-Est; ***UK***: Harmogen†; ***USA***: Ogen.

Pharmacopoeial Preparations

BP 2014: Estropipate Tablets;

USP 36: Estropipate Tablets; Estropipate Vaginal Cream.

Ethinylestradiol *(BAN, rINN)*

Aethinyloestradiolum; Ethinyl Estradiol; Éthinylestradiol; Ethinylestradiolum; Ethinyloestradiol; Etinilestradiol; Etinilestradiolis; Etinilöstradiol; Etinilösztradiol; Etinylestradiol; Etinyyliestradioli; Etynyloestradiol; NSC-10973; Этинилэстрадиол.

17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol; 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol.

$C_{20}H_{24}O_2$=296.4

CAS — 57-63-6.

ATC — G03CA01; L02AA03.

ATC Vet — QG03CA01; QL02AA03.

UNII — 423D2T571U.

NOTE. Compounded preparations of ethinylestradiol may be represented by the following names:

- Co-cyprindiol (*BAN*)—ethinylestradiol 35 parts and cyproterone acetate 2000 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Ethinylestradiol). A white to slightly yellowish-white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol; dissolves in dilute alkaline solutions. Protect from light.

USP 36: (Ethinyl Estradiol). A white to creamy white, odourless, crystalline powder. Insoluble in water; soluble in alcohol, in chloroform, in ether, in vegetable oils, and in solutions of fixed alkali hydroxides. Store in nonmetallic airtight containers. Protect from light.

Uses and Administration

Ethinylestradiol is a synthetic oestrogen with actions similar to those of estradiol (see p. 2271.2).

It is frequently used as the oestrogenic component of combined oral **contraceptive** preparations; a typical daily dose is 20 to 40 micrograms (for guidance on appropriate dose, see p. 2231.3). Ethinylestradiol betadex clathrate has been used similarly in combined oral contraceptives. Ethinylestradiol is also used in a combined contraceptive transdermal patch that releases 33.9 micrograms of ethinylestradiol daily with norelgestromin. A new patch is applied each week for 3 weeks of a 4-week cycle. Oestrogen exposure from such a patch may be higher than with a comparable oral contraceptive, and may be associated with a higher risk of venous thromboembolism (see p. 2238.1). A combined contraceptive vaginal ring device delivering an average of 15 micrograms ethinylestradiol daily with etonogestrel is also available; it remains in the vagina for 3 weeks and is then removed for a one-week break, after which a new ring is inserted. Ethinylestradiol has also been used orally as an emergency contraceptive (p. 2233.2) combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne (p. 1682.2) and hirsutism (p. 2262.1), particularly when contraception is also required (see Uses and Administration, under Cyproterone Acetate, p. 2261.2).

Ethinylestradiol has also been used for **menopausal HRT** (p. 2244.2), although natural oestrogens are usually preferred. Oral doses of 10 to 50 micrograms daily have been given cyclically (with a progestogen in women with a uterus), but preparations providing lower doses of 2.5 or 5 micrograms daily are also available.

For the treatment of female **hypogonadism**, doses of 10 to 50 micrograms daily on a cyclical basis have been used.

For the palliative treatment of **prostate cancer** (p. 712.3) doses of 150 micrograms to 1.5 mg have been given daily. Ethinylestradiol has also been used for palliation of malignant neoplasms of the **breast** (p. 702.1) in postmenopausal women.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include doses of ethinylestradiol. An initial oral dose of 2 micrograms daily

may be used in the management of **delayed puberty** (p. 2252.1) in girls. This may be increased every 6 months to 5 micrograms, then to 10 micrograms, then to 20 micrograms daily, according to response. After 12 to 18 months of treatment, a progestogen should be added for 7 days of each 28-day cycle. A daily dose of ethinylestradiol 20 micrograms with cyclical progestogen may then be used to maintain sexual maturation. For the prevention of constitutional **tall stature**, oral ethinylestradiol may be given to girls aged 2 to 12 years old in a dose of 20 to 50 micrograms daily (see also Growth Disorders in Estradiol, p. 2272.2).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p. 1918.3). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using ethinylestradiol has been tried in both boys and girls in order to increase responsiveness to the test,[1,2] although there appears to be no consensus on such use.[3] The *BNFC* includes an oral dose of 100 micrograms daily for 3 days before the test, for girls with a bone age above 10 years.

1. Loche S, *et al*. The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82:** 861–4.
2. Coutant R, *et al*. Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86:** 5805–12.
3. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 22/08/08)

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Effects on calcium homoeostasis. Two patients with metastatic breast cancer given ethinylestradiol developed rapidly progressive irreversible and fatal hypercalcaemia, considered to be due to stimulation of osteolysis by the oestrogen.[1]

1. Cornbleet M, *et al*. Fatal irreversible hypercalcaemia in breast cancer. *BMJ* 1977; **1:** 145.

Effects on the liver. Cholestasis and pruritus developed in a liver transplant recipient receiving ethinylestradiol at a dose of 50 micrograms daily for the treatment of menorrhagia.[1] Symptoms subsided on withdrawal of ethinylestradiol but returned on its re-introduction.

1. Fedorkow DM, *et al*. Cholestasis induced by oestrogen after liver transplantation. *BMJ* 1989; **299:** 1080–1.

Interactions

See under Hormonal Contraceptives, p. 2242.3, and Hormone Replacement Therapy, p. 2251.1.

Reviews.

1. Zhang H, *et al*. Pharmacokinetic drug interactions involving 17 α-ethinylestradiol: a new look at an old drug. *Clin Pharmacokinet* 2007; **46:** 133–57.

Pharmacokinetics

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active by mouth, but there is some initial conjugation by the gut wall, and the systemic bioavailability is only about 40%. Ethinylestradiol is highly protein bound, but unlike naturally occurring oestrogens, which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. It is metabolised in the liver, initially by aromatic hydroxylation catalysed by the cytochrome P450 isoenzyme CYP3A4, to form 2-hydroxyethinylestradiol and various conjugated metabolites. These are excreted in urine and faeces. Metabolites undergo enterohepatic recycling.

References.

1. Back DJ, *et al*. The gut wall metabolism of ethinyloestradiol and its contribution to the pre-systemic metabolism of ethinyloestradiol in humans. *Br J Clin Pharmacol* 1982; **13:** 325–30.
2. Guengerich FP. Metabolism of 17 α-ethynylestradiol in humans. *Life Sci* 1990; **47:** 1981–8.
3. van den Heuvel MW, *et al*. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005; **72:** 168–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diva Total; ***India***: Ethinorm-E; Lynoral; ***Indon.***: Lynoral; ***Neth.***: Lynoral; ***Rus.***: Microfollin (Микрофоллин); ***Switz.***: Elleacnelle; ***Thai.***: NuvaRing; ***USA***: Estinyl†.

Multi-ingredient Preparations. ***Arg.***: Afrodita; Aleli; Anubis; April; Avancel; Biofem 35†; Biofem; Cilest; Cuarcic†; Cuidafem; Damsel; Damsella; Diane; Dienopil; Diva; Divina; Dos Dias N; Elektra; Evelea; Evra; Femexin; Femiane; Florence; Ginelea T; Ginelea; Gynovin; Harmonet; Isis Fe; Isis; Jade; Kala; Kir; Kirum; Kirumelle; Livianne; Loette; Lutogynestryl; Marvelon; Maxima MD 24; Maxima; Mercilon; Mesconcept†; Microfem; Microgynon; Microvlar; Mileva; Minesse; Minulet; Miranova; Mirelle; Neogynon; Nordette; Norfen; Norgestrel Cex; Norgestrel Minor; Norgestrel Plus; Primosiston; Secret 28; Tess 35; Tridestan N; Tridette; Trinordiol; Triquilar; Umma; Venisse; Yasmin; Yasminelle; YAZ; Zinnia; ***Austral.***: Brenda-35 ED; Brevinor; Diane; Estelle; Femoden ED†; Improvil; Juliet; Laila-35 ED; Levlen ED; Loette; Logynon ED; Marvelon; Microgynon; Microlevlen ED; Minulet; Monofeme; Nordette; Norimin; NuvaRing; Sequilar ED†; Synphasic; Trifeme; Trioden†; Triphasil; Triquilar; Valette; Yasmin; YAZ; ***Austria***: Aliane; Balanca; Belara; Bellgyn; Cileste; Diane; Evra; Gracial; Gynovin; Harmonette; Lenea; Leonore; Liberel; Loette; Madinette; Madonella; Marvelon; Meliane; Mercilon; Microgynon; Midane; Minerva; Minesse; Minulet; Mirelle; Motion; NuvaRing; Ovranette; Ovysmen; Primosiston; Sequilar†; Sylgestrel; TriCilest; Trigynon†; Trinordiol; Trinovum; Triodena; Valette; Vivelle; Wave; Xylia; Xyliette; Yasmin; Yasminelle; YAZ; Yirala; Yris; ***Belg.***: Cilest; Claudia; Cyprodiol†; Daphne; Desorelle†; Diane; Doccyproestra†; Docdonna†; Eleonor; Elisamylan; Evra; Femodene; Gestodelle; Gestofeme; Gracial; Gratiella; Harmonet; Lowette; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Mirelle; Mylenamylan†; Nora-30; NuvaRing; Ovidol; Ovysmen; Ratiopharmeva†; Rimendia; Stediril 30; Tri-Minulet; Trigynon; Trinordiol; Trinovum; Triodene; Yasmin; Yasminelle; YAZ; ***Braz.***: Adoless; Alexa; Allestra; Anfertil; Artemidis; Belara; Ciclo; Ciclofemme; Ciclogyn; Ciclovulon; Ciprane; Concepnor; Diane; Diclin; Diminut; Elani; Evanor; Evra; Femiane; Femina; Ferane 35; Fertnon; Gestinol; Gestradiol; Gestrelan; Ginesse; Gracial; Gynera; Harmonet; Level; Levordiol; Lizzy; Lovelle; Malu; Mercilon Conti; Mercilon; Microdiol; Micropil; Microvlar; Minesse; Minian; Minima; Minulet; Miranova; Mirelle; Neovlar; Nociclin; Nordette; Normamor; Novial; NuvaRing; Ovoresta†; Previane; Primera; Primeravinte†; Primosiston; Repopil; Selene; Siblima; Tamisa; Tantin; Tess; Trinordiol; Triquilar; Yasmin; YAZ; ***Canad.***: Alesse; Apri; Aviane; Brevicon; Cyclen; CyEstra; Demulen; Diane; Evra; FemHRT; Linessa; Loestrin 1.5/30; Marvelon; Min-Ovral; Minestrin; NuvaRing; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Ortho-Cept; Ovral; Portia; Seasonale; Seasonique; Select 1/35; Synphasic; Tri-Cyclen; Triquilar; Yasmin; YAZ; ***Chile***: Alesse†; Anovulatorio Micro-Dosis; Anuar; Anulette; Belara; Careza; Ciclidon; Ciclomex; Conti-Marvelon; Dahlia; Dal; Desoren; Diane; Dixi-35; Drina; Evilin; Evra; Femelle; Feminol; Femiplus; Femitres; Gianda; Gracial; Gynera; Gynorelle; Gynostat; Harmonet; Innova Cd; Lady-Ten 35; Lovinda; Mactex; Marvelon; Miafem; Microgen; Microgynon; Midalet; Minesse; Miniestrel; Minigest; Minulet; Miranova; Mirelle; Modutrol†; Neofam†; Neolette; Nordette; Nordiol; Norvetal; NuvaRing; Orlon; Primosiston; Tinelle; Tri-Ciclomex†; Tri-Mactex†; Trinordiol; Triquilar; Trolit; Vexa; Yasmin; YAZ; ***China***: Compound Norethisterone (复方炔诺酮); Diane (达英); Duorina (多日纳); Mercilon (美欣乐); Minulet (敏定偶); Triquilar (特居乐); Yasmin (优思明); Yiketing (谊可婷); ***Cz.***: Adele; Artizia; Belanette; Belara; Bellune; Belusha; Chloe; Cilest; Circlet; Clormetin; Daylette; Diane; Dienille; Dienorette; Drosetil; Egretta; Eloine; Esete; Evra; Femoden; Gracial; Gravistat; Harmonet; Jangee; Jeanine; Katya; Kirga; Larabel†; Laurina; Lindynette; Loette; Logest; Lunafem; Madinelle; Maitalon; Marvelon; Mercilon; Microgynon; Milligest; Minerva; Minesse; Minisiston; Minulet; Mirelle; Natalya; Nelya; Novynette; NuvaRing; Pramino; Regulon; Softinelle; Stodette; Sunya; Sylviane; Tri-Minulet; Tri-Regol; Tricia; Trinordiol†; Trinovum; Triquilar; Vreya; Yadine; Yasminelle; YAZ; ***Denm.***: Cilest; Daisynelle; Desorelle; Diane; Dianova; Dretine; Eloine; Estinette; Evra; Femelle; Femicept; Femigen; Feminil; Femistad; Finminette; Gestinyl; Gestodilat; Gestonette; Gracial; Harmonet; Lindynette; Loette; Malonetta; Marvelon; Mercilon; Microgyn; Milligest; Milna; Milvane; Minero; Minulet; Modina; Movinella; Neogynon†; Novynette; NuvaRing; Palandra; Rigevidon; Rubira; Tercette; Triafem; Triminetta; Trinordiol†; Trinovum†; Triquilar; Triregol; Vellena; Vreya; Yasmin; Yasminelle; YAZ; Zafira†; Zyrona; ***Fin.***: Cilest; Cypretyl; Diane; Evra; Feminil; Femoden; Gestinyl; Gestodilat; Gracial; Harmonet; Laurette; Laurina; Linatera; Liofora; Marvelon; Meliane; Mercilon; Microgynon; Minero; Minulet; Miranova; Mirelle; Modina; NuvaRing; Palandra; Stefaminelle; Tasminetta; Tri-Femoden; Trikvilar; Vreya; Yasmin; Yasminelle; YAZ; ***Fr.***: Adepal; Amarance; Belanette; Belara; Carlin; Cilest; Convuline; Cycleane†; Daily; Desobel; Diane; Drospibel; Edenelle; Efezial; Effiprev; Evanecia; Evepar; Evra; Harmonet; Holgyeme; Jasmine; Jasminelle; Jasminellecontinu; Lovavulo; Ludeal; Lumalia; Meliane; Melodia; Mercilon; Minerva; Minesse; Minidril; Miniphase†; Minulet; Moneva; NuvaRing; Optinesse; Ortho-Novum 1/35†; Pacilia; Perleane; Phaeva; Rimendia; Stediril; Sylviane; Tri-Minulet; Triafemi; TriCilest; Triella; Trinordiol; Varnoline; YAZ; ***Ger.***: Aida; Asumate; Attempta; Balanca†; Belara; Bella†; Bellissima; Biviol; Chariva; Cilest; Clevia†; Conceplan M; Cyclosa†; Cyproderm; Cypronette†; Desmin; Diane; Enriqa; Ergalea†; Evaluna; Eve; Evra; Femigoa; Femigyne; Femovan; Femranette mikro†; Gravistat; illina†; Lamuna†; Leios; Leona; Liana; Lovelle; Madinette; Marvelon; Maxim; Microgynon; Minette; Ministon; Minulet; Miranova; MonoStep; Morea; Neo-Eunomin; NovaStep; Novial; NuvaRing; Oviala; Oviol†; Ovoresta M†; Petibelle; Pink Luna; Pramino; Synphasec; Triette†; Trigoa; Trinovum; Triquilar; Trisiston; Valette; Verana; Yasmin; Yasminelle; YAZ; ***Gr.***: Evra; Gracial; Gynera; Gynofen; Harmonette; Laurina; Liofora; Loette; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Neogynon; Nordette; Nordiol; NuvaRing; Ovral; Tri-Minulet; Trigynera; Trinordiol; Triquilar; Yasmin; Yasminelle; YAZ; ***Hong Kong***: Daphne; Diane; Eugynon†; Evra; Gracial; Gynera; Harmonet; Loette; Marvelon; Meliane; Mercilon; Microgynon; Nordette; Novynette; Rigevidon; Tri-Regol; Yasmin; YAZ; ***Hung.***: Anteovin†; Belara; Cilest; Cypromix; Diane; Dienille; Evra; Femoden; Gestomix; Gracial; Harmonet; Jangee; Laurina; Lindynette; Loette†; Marvelon; Meliane; Mercilon; Milligest; Minerva; Minesse†; Minulet; Novynette; NuvaRing; Ovidon†; Regulon; Rigevidon; Samba; Sensonette; Symicia; Tri-Regol; Trinordiol†; Triodena; Triquilar†; Volina; Yadine; Yasminelle; ***India***: Choice; Combee; Crisanta; Dear-21; Diane; Dinac; Divacon; Dronis; Duoluton-L; Ergest; Femilon; Frauline; Ginette; Krimson; Locipil; Loette; Mixogen; Novelon; Ovilow; Ovimed; Ovipauz-L; Ovral; Triquilar; ***Indon.***: Diane; Gynera; Marvelon; Mercilon; Microdiol; Microgynon; Pil Keluarga Berencana†; Planak; Trinordiol†; Triquilar; Yasmin; YAZ; ***Irl.***: Brevinor†; Cilest; Dianette; Dretine; Dretinelle; Enador; Estelle; Evra; Gracial; Leonore; Leticia; Liofora; Logynon; Marviol; Mercilon; Microlite; Minesse; Minulet; NuvaRing; Ovogrel†; Ovran; Ovranette; Palandra; Rigevidon; Tri-Minulet; Trinordiol; Vivides; Vonodiol; Yasmin; Yasminelle; YAZ; ***Israel***: Belara; Circlet; Diane; Emily; Estelle; Evra; Feminet; Flame; Floret; Gynera; Harmonet; Lodene; Meliane; Mercilon; Microdiol; Microgynon; Minesse; Minulet; Nordette; NuvaRing; Ortho Cyclen; Seasonique; Shelly; Yael; Yasmin; Yasminelle†; YAZ; ***Ital.***: Arianna; Belara; Circlet; Credigyne; Credigynette; Diane; Dueva; Egogyn; Estinette; Evra; Fedra; Femodette; Gestodiol; Ginoden; Gracial; Harmonet; Kipling; Loette; Lucille; Lybella; Mercilon; Microgynon; Midiana; Milvane; Minesse; Minigeste; Minulet; Miranova; Novogyn; Novynette; NuvaRing; Planum; Practil; Securgin; Tri-Minulet; Visofid; Yarina; Yasmin; Yasminelle; YAZ; ***Jpn***: Ange; Lunabell; Ortho 777; ***Malaysia***: Diane; Estelle; Evra; Gynera; Lindynette; Loette; Marvelon; Meliane; Mercilon; Microgynon 30; Minulet; Nordette; Novynette; NuvaRing; Oralcon; Regulon; Rigevidon; Sucee; Trigestrel; Trinordiol; Yasmin; YAZ; ***Mex.***: Alesse; Angie; Belara; Cilest; Desmin; Detegen; Diane; Esdegen; Eunice 35-ED; Evra; Femexin; Ginelea; Gynovin; Letinnov; Marvelon; Mercilon; Microgynon; Mileva; Minesse; Minulet; Neogynon; Nordet; Nordiol†; Novial; NuvaRing; Ortho-Novum 1/35; Ovral; Radiance; Secret 28; Trinordiol; Triquilar; Yasmin; ***Mon.***: Felixita; Leeloo; ***Neth.***: Alesse†; Annantah; Armarrok; Armunia; Belanette; Cilest; Circlet; Diane; Evra; Femodeen; Gracial; Jamyle; Juliane; Laurina; Logynon†; Lonicera; Lovette; Marvelon; Mercilon; Microgynon; Minerva; Ministat; Minulet; Miranova; Modicon; Neocon; NuvaRing; Oralcon; Ovidol†; Palandra; Rosal; Stediril; Trigynon; Trinordiol; Trinovum; Vallclara; Volina; Yasmin; Yasminelle; YAZ; Yira†; Yvidually; Zypina†; ***Norw.***: Diane; Evra; Feminil; Finminette; Loette; Marvelon; Mercilon; Microgynon; NuvaRing; Oralcon; Rubira; Synfase; Yasmin; Yasminelle; YAZ; Zyrona; ***NZ***: Brevinor; Diane; Estelle; Femodene; Ginet; Levlen ED; Loette; Marvelon; Melodene†; Mercilon; Microgynon; Minulet; Monofeme; Nordette; Norimin; Roxanne; Synphasic; Trifeme; Triphasil; Triquilar; Yasmin; YAZ; ***Philipp.***: Althea; Ancea; Azul; Blush; Charlize; Crimson; Diane; Evra; Femenal†; Femme; Gracial; Gynera; Lady; Logynon; Marvelon; Meliane; Mercilon; Microgynon†; Micropil Plus; Micropil; Minulet†; Nordette; Nordiol; Norfem; Rigevidon; Safe Pill; Seif; Trinordiol; Trust Pill; Yasmin; YAZ; ***Pol.***: Aliane; Anteovin†; Artizia; Asubtela; Atywia; Chloe; Cilest; Circlet; Cyprest; Cyprodiol; Cyprogen; Diane; Dronin; Evra; Femipol; Femoden; Gravistat†; Harmonet; Jeanine; Kontracept; Linatera; Logest; Madinette; Marvelon; Mercilon; Microgynon; Midiana; Milvane; Minisiston†; Minulet†; Mirelle; Naraya; Novynette; NuvaRing; OC-35; Regulon; Rigevidon; Stediril; Sylvie; Syndi-35; Tri-Minulet†; Tri-Regol; Trinordiol; Trinovum†; Triquilar; Trisiston; Yasmin; Yasminelle; YAZ; ***Port.***: Aliane; Belara; Diane; Effiplen; Estinette; Evra; Gracial; Gynera; Harmonet; Laurina; Libeli; Marvelon; Mercilon; Microgeste; Microginon; Minesse; Minigeste; Minulet; Miranova; Novynette; NuvaRing; Petibelle; Regulon; Tetragynon; Tri-Gynera; Tri-Minulet; Trinordiol; Triquilar†; Valette; Yasmin; Yasminelle; YAZ; ***Rus.***: Anteovin (Антеовин)†; Belara (Белара); Bellune (Беллуне); Chloe (Хлое); Cilest (Силест); Diane (Диане); Evra (Евра); Femoden (Фемоден); Jeanine (Жанин); Lindynette (Линдинет); Logest (Логест); Marvelon (Марвелон); Mercilon (Мерсилон); Microgynon (Микрогинон); Minisiston (Минизистон); Non-Ovlon (Нон-овлон)†; Novynette (Новинет); NuvaRing (НоваРинг); Ovidon (Овидон)†; Regulon (Регулон); Rigevidon (Ригевидон); Tri-Merci (Три-Мерси); Tri-Regol (Три-Регол); Triquilar (Триквилар); Trisiston (Тризистон); Yarina (Ярина); YAZ (Джес); ***S.Afr.***: Adco-Fem; Biphasil; Cilest; Claro; Diane; Diva; E-Gen-C; Evra; Femodene ED; Ginette; Harmonet†; Loette†; Logynon ED; Marvelon; Melodene; Menoflush; Mercilon; Minerva; Minesse; Minulette; Miranova†; Mirelle; Nordette; Nordiol; Ovral; Tri-Minulet†; TriCilest; Trinovum; Triodene; Triphasil; Yasmin; YAZ; ***Singapore***: Diane; Estelle; Evra; Gynera; Loette†; Marvelon; Meliane; Mercilon; Microgynon; Minulet†; Nordette†; NuvaRing; Trinordiol†; Yasmin; YAZ; ***Spain***: Ailyn; Antin; Antinelle; Aranka; Arankelle; Balianca; Belara; Bemasive; Danielle; Daylette; Diacare†; Dialider; Diane; Donabel; Drelle; Dretine; Dretinelle; Drosiane Diario; Drosianelle; Drospil; Drosure; Drosurelle; Edelsin; Eloine; Elynor; Evra; Gestinyl; Gracial; Gyneplen; Gynovin; Harmonet; Levobel; Liofora; Loette; Meliane; Melodene 15; Melteva; Microdiol; Microgynon; Minesse; Minulet; Neogynona; NuvaRing; Ovoplex; Regulon; Suavuret; Tevalet; Tri-Minulet; Triagynon; Triciclor; Trigynovin; Yasmin; Yasminelle; YAZ; Yira; ***Swed.***: Abelonelle;

Cilest; Desolett; Diane; Eloine; Evra; Liofora; Mercilon; Neovletta; NuvaRing; Orthonett Novum; Prionelle; Restovar; Synfase; Trimiron†; Trinordiol; Trinovum; Trionetta; Triregol; Yasmin; Yasminelle; YAZ; Zyrona; ***Switz.***: Belara; Belarina; Cilest; Cypestra; Cyprelle; Desoren; Diane; Eloine; Elyfem; Estinette; Evra; Femadiol; Feminac; Gestoden Plus; Gracial; Gynera; Gyselle; Harmonet; Holgyeme; Ladonna; Levomin; Liosanne; Madinette; Marvelon; Meliane; Meloden; Mercilon; Microgynon; Milvane; Minerva; Minesse; Minulet; Miranova; Mirelle; Myvlar; NuvaRing; Ologyn; Primosiston†; Trinovum; Tyarena; Yasmin; Yasminelle; YAZ; ***Thai.***: Anna; Annie; Annylyn; B-Lady; Belara; Ciclomex; Cilest; Cypress; Dafne; Daisy; Diane; Dior; Evra; Gynera; Helen; Jeny-FMP; Lady-35; Lindynette; Manoane; Manodiol; Marvelon; Meliane; Melodia; Mercilon; Microgest†; Microgynon; Microlenyn; Minidoz; Minny; Nordette; Novynette; OC-35; Oilezz; Oralcon-F; Preme; R-Den; Riget†; Rigevidon; Sucee; TriCilest; Trigestrel; Triquilar; Yasmin; YAZ; ***Turk.***: Belara; Desolett; Diane; Ginera; Gynelle; Lo-Ovral; Lyndiol; Microgynon; Minulet; Miranova; Myralon; NuvaRing; Preven; Reginon; Triquilar†; Yasmin; Yazz; ***UK***: Acnocin; Binovum; Brevinor; Cicafem; Cilest; Cimizt; Clairette; Dianette; Diva; Evra; Femodene; Femodette; Gedarel; Katya; Levest; Lizinna; Loestrin; Logynon; Marvelon; Mercilon; Microgynon 30; Millinette; Norimin; NuvaRing; Ovran 30; Ovranette; Ovysmen; Rigevidon; Sunya; Synphase; Triadene; Trinovum; Triregol; Yasmin; YAZ; ***Ukr.***: Belara (Белара); Darilia (Дарилия); Diane-35 (Диане-35); Femoden (Фемоден); Jeanine (Жанин); Lindynette (Линдинет); Logest (Логест); Marvelon (Марвелон); Mercilon (Мерсилон); Microgynon (Микрогинон)†; Midiana (Мидиана); Novynette (Новинет); NuvaRing (НоваРинг); Ovidon (Овидон)†; Regulon (Регулон); Rigevidon (Ригевидон); Silhouette (Силует); Tri-Merci (Три-Мерси); Tri-Regol (Три-Регол); Triquilar (Триквилар); Tristin (Тристин)†; Yarina (Ярина); ***USA***: Alesse†; Altavera; Alyacen 1/35; Alyacen 7/7/7; Amethia; Apri; Aranelle; Aviane; Azurette; Balziva; Beyaz; Brevicon; Briellyn; Camrese; Caziant; Cesia; Chateal; Cryselle; Cyclessa; Daysee; Desogen; Enpresse; Estarylla; Estrostep Fe; Falmina; Femcon Fe; FemHRT; Gianvi; Jinteli; Jolessa; Junel Fe; Kariva; Kelnor; Kurvelo; Leena; Lessina; Levora; Lo Loestrin Fe; Lo Minastrin Fe; Lo/Ovral; Loestrin Fe; Loestrin; Loryna; LoSeasonique; Lutera; Lybrel; Marlissa; Minastrin 24 FE; Mircette; Modicon; Myzilra; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Nordette; Norinyl 1 + 35; Nortrel; NuvaRing; Ocella; Ortho Cyclen; Ortho Evra; Ortho Tri-Cyclen; Ortho-Cept; Ortho-Novum 1/35; Ortho-Novum 10/11†; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Ovral†; Pirmella 1/35; Pirmella 7/7/7; Portia; Previfem; Quartette; Quasense; Reclipsen; Safyral; Seasonale; Seasonique; Solia; Sprintec; Sronyx; Syeda; Tilia Fe; Tri-Estarylla; Tri-Legest; Tri-Linyah; Tri-Lo-Sprintec; Tri-Norinyl; Tri-Previfem; Tri-Sprintec; TriNessa; Triphasil†; Trivora; Velivet; Vestura; Viorele; Wymzya Fe; Yasmin; YAZ; Zarah; Zenchent Fe; Zenchent; Zovia; ***Venez.***: Alesse; Belara; Ciclidon; Diane; Dixi; Evra; Femiane; Gynera; Harmonet; Marvelon; Mercilon; Minesse; Minigynon; Minulet; Mipil; Mirelle; Neogynon; Nordette; Nordiol; Novial; Ortrel; Ovral; Rigevidon; Tri-Regol; Trinordiol; Triquilar; Yasmin.

Pharmacopoeial Preparations

BP 2014: Ethinylestradiol Tablets; Levonorgestrel and Ethinylestradiol Tablets;

USP 36: Desogestrel and Ethinyl Estradiol Tablets; Drospirenone and Ethinyl Estradiol Tablets; Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Levonorgestrel and Ethinyl Estradiol Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norgestimate and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets.

Ethisterone *(BAN, rINN)*

Anhydrohydroxyprogesterone; Ethinyltestosterone; Ethistérone; Ethisteronum; Etisteron; Etisterona; Etisteroni; Etysteronum; NSC-9565; Praeginum; Pregneninolone; Pregnin; Этистерон.

17β-Hydroxy-17α-pregn-4-en-20-yn-3-one.

$C_{21}H_{28}O_2$=312.5

CAS — 434-03-7.

ATC — G03DC04.

ATC Vet — QG03DC04.

UNII — P2018VY1MJ.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Ethisterone is a progestogen that is structurally related to testosterone (p. 2305.1); it also has oestrogenic and androgenic properties. It is given orally with an oestrogen for the treatment of amenorrhoea (p. 2251.3). A dose of ethisterone 40 mg with ethinylestradiol 40 micrograms may be given twice daily for 3 days, and withdrawal bleeding occurs about 3 to 7 days later.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Lutogynestryl.

Ethylestrenol *(BAN, USAN, rINN)* ⊗

Éthylestrénol; Ethylestrenolum; Ethyloestrenol; Etilestrenol; Etylestrenol; Etyyliestrenoli; Этилэстренол.

17α-Ethylestr-4-en-17β-ol; 19-Nor-17α-pregn-4-en-17β-ol.

$C_{20}H_{32}O$=288.5

CAS — 965-90-2.

ATC — A14AB02.

ATC Vet — QA14AB02.

UNII — ADC79EK5Q8.

Profile

Ethylestrenol is a 17α-alkylated anabolic steroid (see Testosterone, p. 2305.1) with little androgenic effect and slight progestogenic activity. It has been used for the promotion of growth in boys with short stature or delayed bone growth. It is used in veterinary medicine.

Etonogestrel *(BAN, USAN, rINN)*

Etonogestreeli; Étonogestrel; Etonogestrelum; 3-keto-Desogestrel; Org-3236; Этоногестрел.

13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one; 17β-Hydroxy-11-methylene-18-homo-19-nor-17α-pregn-4-en-20-yn-3-one.

$C_{22}H_{28}O_2$=324.5

CAS — 54048-10-1.

ATC — G03AC08.

ATC Vet — QG03AC08.

UNII — 304GTH6RNH.

Uses and Administration

Etonogestrel, the active metabolite of desogestrel (p. 2266.3), is used as a hormonal contraceptive (see p. 2231.3). A subdermal implant containing 68 mg of etonogestrel is used as a progestogen-only contraceptive that is effective for 3 years. Etonogestrel is also used as the progestogen component of a combined contraceptive delivered via a vaginal ring device. The ring releases an average of 120 micrograms daily of etonogestrel and 15 micrograms daily of ethinylestradiol and remains in the vagina for 3 weeks; it is then removed for a one-week break after which a new ring is inserted.

Etonogestrel is under investigation as a male contraceptive, given orally or by implant, with testosterone implants or injections.

References.

1. Edwards JE, Moore A. Implanon: a review of clinical studies. *Br J Fam Plann* 1999; **24:** 3–16.
2. Le J, Tsourounis C. Implanon: a critical review. *Ann Pharmacother* 2001; **35:** 329–36.
3. Roumen F. Contraceptive efficacy and tolerability with a novel combined contraceptive vaginal ring, NuvaRing. *Eur J Contracept Reprod Health Care* 2002; **7** (suppl 2): 19–24.
4. Meirik O, *et al.* WHO Consultation on Implantable Contraceptives for Women. Implantable contraceptives for women. *Hum Reprod Update* 2003; **9:** 49–59.
5. Sarkar NN. The combined contraceptive vaginal device (NuvaRing): a comprehensive review. *Eur J Contracept Reprod Health Care* 2005; **10:** 73–8.
6. Roumen FJ. The contraceptive vaginal ring compared with the combined oral contraceptive pill: a comprehensive review of randomized controlled trials. *Contraception* 2007; **75:** 420–9.
7. Mommers E, *et al.* Male hormonal contraception: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2008; **93:** 2572–80.
8. Adams K, Beal MW. Implanon: a review of the literature with recommendations for clinical management. *J Midwifery Womens Health* 2009; **54:** 142–9.
9. Barreiros FA, *et al.* Extended regimens of the contraceptive vaginal ring: evaluation of clinical aspects. *Contraception* 2010; **81:** 223–5.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Breast feeding. Etonogestrel was found in the breast milk of 42 women given a contraceptive etonogestrel implant. Over the 4-month study, compared with a group who used an intra-uterine non-hormonal device, etonogestrel did not affect the volume or composition of breast milk, or the growth of the breast-fed infants.[1] At 3 years of age there was no difference in growth between these 2 groups of children.[2]

1. Reinprayoon D, *et al.* Effects of the etonogestrel-releasing contraceptive implant (Implanon) on parameters of breastfeeding compared to those of an intrauterine device. *Contraception* 2000; **62:** 239–46.
2. Taneepanichskul S, *et al.* Effects of the etonogestrel-releasing implant Implanon and a nonmedicated intrauterine device on the growth of breast-fed infants. *Contraception* 2006; **73:** 368–71.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etonogestrel as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Vaginal bleeding. Prolonged vaginal bleeding, lasting from 2 to 26 weeks, has been reported with the use of etonogestrel subdermal implants. Blood transfusion was needed in the management of one patient.[1] Mifepristone, combined with either ethinylestradiol or doxycycline has also proved effective in terminating bleeding episodes caused by etonogestrel.[2] Heavy bleeding has been described in 2 women after the implant had broken while in place.[3,4]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Implanon and vaginal bleeding. *Aust Adverse Drug React Bull* 2003; **22:** 11–12. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0306.pdf (accessed 27/06/08)
2. Weisberg E, *et al.* A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. *Hum Reprod* 2009; **24:** 1852–61.
3. Pickard S, Bacon L. Persistent vaginal bleeding in a patient with a broken Implanon. *J Fam Plann Reprod Health Care* 2002; **28:** 207–8.
4. Agrawal A, Robinson C. Spontaneous snapping of an Implanon in two halves in situ. *J Fam Plann Reprod Health Care* 2003; **29:** 238.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Etonogestrel is highly bound to plasma proteins; about 32% is bound to sex hormone binding globulin and 66% to albumin. It is metabolised by the cytochrome P450 isoenzyme CYP3A4, and both metabolites and unchanged drug are excreted in the urine and faeces. The elimination half-life is about 25 to 30 hours. Etonogestrel is distributed into breast milk.

References.

1. Timmer CJ, Mulders TMT. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clin Pharmacokinet* 2000; **39:** 233–42.
2. Bennink HJ. The pharmacokinetics and pharmacodynamics of Implanon, a single-rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care* 2000; **5** (suppl 2): 12–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Implanon; ***Austria***: Implanon; ***Belg.***: Implanon; ***Braz.***: Implanon; ***Chile***: Implanon; ***China***: Implanon (依伴依); ***Cz.***: Implanon; ***Denm.***: Implanon; Nexplanon; ***Fin.***: Implanon†; Nexplanon; ***Fr.***: Implanon†; Nexplanon; ***Ger.***: Implanon; ***Gr.***: Implanon; ***Hung.***: Implanon; ***Indon.***: Implanon; ***Irl.***: Implanon; ***Malaysia***: Implanon; ***Mex.***: Implanon; ***Neth.***: Implanon; ***Norw.***: Implanon†; Nexplanon; ***NZ***: Implanon; ***Port.***: Implanon; ***Singapore***: Implanon; ***Spain***: Implanon; ***Swed.***: Implanon†; Nexplanon; ***Switz.***: Implanon; ***Thai.***: Implanon; NuvaRing; ***Turk.***: Implanon; ***UK***: Implanon†; Nexplanon; ***USA***: Implanon; Nexplanon; ***Venez.***: Implanon.

Multi-ingredient Preparations. ***Austral.***: NuvaRing; ***Austria***: NuvaRing; ***Belg.***: NuvaRing; ***Braz.***: NuvaRing; ***Canad.***: NuvaRing; ***Chile***: NuvaRing; ***Cz.***: Circlet; NuvaRing; ***Denm.***: NuvaRing; ***Fin.***: NuvaRing; ***Fr.***: NuvaRing; ***Ger.***: NuvaRing; ***Gr.***: NuvaRing; ***Hung.***: NuvaRing; ***Irl.***: NuvaRing; ***Israel***: Circlet; NuvaRing; ***Ital.***: Circlet; NuvaRing; ***Malaysia***: NuvaRing; ***Mex.***: NuvaRing; ***Neth.***: Circlet; NuvaRing; ***Norw.***: NuvaRing; ***Pol.***: Circlet; NuvaRing; ***Port.***: NuvaRing; ***Rus.***: NuvaRing (НоваРинг); ***Singapore***: NuvaRing; ***Spain***: NuvaRing; ***Swed.***: NuvaRing; ***Switz.***: NuvaRing; ***Turk.***: NuvaRing; ***UK***: NuvaRing; ***Ukr.***: NuvaRing (НоваРинг); ***USA***: NuvaRing.

Etynodiol Diacetate *(BANM, pINNM)*

Aethynodiolum Diaceticum; Diacetato de etinodiol; Ethynodiol Diacetate (USAN); Etinodiol, diacetato de; Étynodiol, Diacetate d'; Etynodioli Diacetas; SC-11800; Этинодиола Диацетат.

19-Nor-17α-pregn-4-en-20-yne-3β,17β-diol diacetate.

$C_{24}H_{32}O_4$=384.5

CAS — 1231-93-2 (etynodiol); 297-76-7 (etynodiol diacetate).

ATC — G03DC06.

ATC Vet — QG03DC06.

UNII — 62H10A1236.

Pharmacopoeias. In *Br.*, *Pol.*, and *US.*

BP 2014: (Etynodiol Diacetate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Protect from light.

USP 36: (Ethynodiol Diacetate). A white, odourless, crystalline powder. Insoluble in water; soluble in alcohol; very soluble in chloroform; freely soluble in ether; sparingly soluble in fixed oils. Protect from light.

Uses and Administration

Etynodiol diacetate is a progestogen (see Progesterone, p. 2300.2) that is used as the progestogenic component of combined oral contraceptives and also alone as an oral progestogen-only contraceptive (see p. 2231.3); typical daily doses are 1 or 2 mg in combination products and 500 micrograms for progestogen-only contraceptives.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Pregnancy. Fetal adrenal cytomegaly in a 17-week-old fetus was associated with the maternal ingestion of an oral contraceptive containing etynodiol diacetate 2 mg and mestranol 100 micrograms from the sixth to the fourteenth week of pregnancy.[1]

1. Gau GS, Bennett MJ. Fetal adrenal cytomegaly. *J Clin Pathol* 1979; **32:** 305–6.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Etynodiol diacetate is readily absorbed from the gastrointestinal tract and rapidly metabolised, largely to norethisterone (p. 2294.2). About 60% of a dose is stated to be excreted in urine and about 30% in faeces; the half-life in plasma is about 25 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***NZ***: Femulen†; ***UK***: Femulen†.

Multi-ingredient Preparations. ***Arg.***: Soluna; ***Canad.***: Demulen; ***USA***: Kelnor; Zovia.

Pharmacopoeial Preparations
USP 36: Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Mestranol Tablets.

Flugestone Acetate *(BANM, rINNM)*

Acetato de flugestona; Flugestona, acetato de; Flugestone, Acétate de; Flugestoni Acetas; Flurogestone Acetate (USAN); NSC-65411; SC-9880; Флугестона Ацетат.

9α-Fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione 17-acetate.

$C_{23}H_{31}FO_5$=406.5

CAS — 337-03-1 (flugestone); 2529-45-5 (flugestone acetate).

UNII — X60881643X.

Profile

Flugestone acetate is a progestogen (see Progesterone, p. 2300.2) used in veterinary medicine.

Fluoxymesterone *(BAN, rINN)* ⊗

Fluoksimesteroni; Fluoximesteron; Fluoximesterona; Fluoxymestérone; Fluoxymesteronum; Fluximesterona; NSC-12165; Флуоксиместерон.

9α-Fluoro-11β,17β-dihydroxy-17α-methylandrost-4-en-3-one.

$C_{20}H_{29}FO_3$=336.4

CAS — 76-43-7.

ATC — G03BA01.

ATC Vet — QG03BA01.

UNII — 9JU12S4YFY.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Fluoxymesterone). A white or practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Protect from light.

Uses and Administration

Fluoxymesterone has androgenic properties (see Testosterone, p. 2305.2). It is effective when given orally and is more potent than methyltestosterone.

In the treatment of male hypogonadism (p. 2252.3), fluoxymesterone has been given in a dosage of 5 to 20 mg daily. For the use of fluoxymesterone in boys with delayed puberty, see Administration in Children, below. In the palliation of inoperable neoplasms of the breast in postmenopausal women (p. 702.1) it has been given in doses of 10 to 40 mg daily, in divided doses. Fluoxymesterone has also been used in the treatment of aplastic anaemia.

Administration in children. In the treatment of delayed puberty (p. 2252.1) in boys, fluoxymesterone has been given orally in usual daily doses of 2.5 to 10 mg, adjusted according to response (doses up to 20 mg daily have been used). Care is necessary because of the risk of epiphyseal closure and treatment is generally only given for 4 to 6 months.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

As with other 17α-alkylated compounds fluoxymesterone may cause hepatotoxicity, and is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Halotestin; ***Mex.***: Stenox; ***USA***: Androxy.

Multi-ingredient Preparations. ***Arg.***: Ferona†.

Pharmacopoeial Preparations
USP 36: Fluoxymesterone Tablets.

Follicle-stimulating Hormone

Folitrofina; Folitropina; FSH; Gonadotrofina foliculoestimulante; Hormona estimulante del folículo.

ATC Vet — QG03GA90.

UNII — 8W9AS43IDH (follicle stimulating hormone beta polypeptide).

Pharmacopoeias. *Eur.* (see p. vii) includes Follitropin and Follitropin Concentrated Solution.

Follitropin Alfa *(BAN, rINN)*

Folitrofina alfa; Folitropin Alfa; Folitropina alfa; Follitropine Alfa; Follitropinum Alfa; Фоллитропин Альфа.

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10 206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12 485 (β-subunit)

CAS — 9002-68-0 (follitropin alfa); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit); 146479-72-3 (follitropin alfa).

ATC — G03GA05.

ATC Vet — QG03GA05.

UNII — 076WHW89TW.

Follitropin Beta *(BAN, rINN)*

Folitrofina beta; Folitropin Beta; Folitropina beta; Follitropine Bêta; Follitropinum Beta; Org-32489; Фоллитропин Бета.

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10 206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12 485 (β-subunit)

CAS — 169108-34-3 (follitropin beta); 150490-84-9 (follitropin beta); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit).

ATC — G03GA06.

ATC Vet — QG03GA06.

Units

80 units of human pituitary follicle-stimulating hormone are contained in about 4.17 micrograms (with 5 mg of mannitol and 1 mg human serum albumin) in one ampoule of the first International Standard (1986).

138 units of recombinant human follicle-stimulating hormone for bioassay are contained in one ampoule of the first International Standard (1995).

Uses and Administration

Follicle-stimulating hormone is secreted by the anterior lobe of the pituitary gland, with another gonadotrophin, luteinising hormone (p. 2287.1).

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova; in men it has a role in spermatogenesis.

Recombinant human follicle-stimulating hormones (follitropins alfa or beta) are used in the treatment of female infertility due to anovulation, in women who have not responded to clomifene therapy. Follitropins are also used for the stimulation of spermatogenesis in the management of male infertility caused by hypogonadotrophic hypogonadism (see Infertility, p. 2253.1).

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. In menstruating patients treatment should be started within the first 7 days of the menstrual cycle.

- Treatment is usually begun with 75 to 150 units daily by subcutaneous or intramuscular injection for 7 or 14 days; if there is no response, dosage is increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation.

It has been suggested in UK licensed product information for follitropin alfa that a daily dose of 225 units is the usual maximum, and that if a patient fails to respond adequately after 4 weeks of treatment that cycle should be abandoned and the patient should subsequently begin the next cycle at a higher starting dose.

Follitropins are also used as part of IVF or other assisted reproductive technologies.

- For this purpose doses of 150 to 225 units daily are generally given, for at least 4 days, starting on the second or third day of the menstrual cycle. Thereafter the dose may be adjusted individually based on ovarian response to a usual maximum of about 450 units; adequate follicular development generally occurs within about 5 to 10 days of treatment.
- Pituitary downregulation with a gonadorelin analogue may be used with follitropin therapy, in which case the gonadorelin analogue is generally begun about 2 weeks before follitropin, and the 2 are then continued together until follicular development is adequate.
- A single dose of up to 10 000 units of chorionic gonadotrophin is then given to induce final follicular maturation and oocyte retrieval performed about 35 hours later.

Follitropins are used for the stimulation of spermatogenesis in the management of **male infertility** caused by hypogonadotrophic hypogonadism. Before starting follitropin therapy, chorionic gonadotrophin is given to raise serum testosterone concentrations to the normal range, which may take 3 to 6 months. A dose of follitropin alfa or beta of 150 units subcutaneously three times weekly is then used, with continued chorionic gonadotrophin; doses of follitropin alfa up to 300 units three times weekly may be required. Treatment is continued for at least 4 months, and more than 18 months of treatment may be needed. A dose of follitropin beta 75 units daily or two or three times weekly, by subcutaneous or intramuscular injection, has been used similarly.

Other substances with follicle-stimulating activity are used similarly: these include human menopausal gonadotrophins (p. 2284.1), which have both luteinising and follicle-stimulating activity, and urofollitropin (p. 2312.2).

Infertility. For a suggestion that human menopausal gonadotrophins may be associated with higher live-birth rates than recombinant follicle-stimulating hormone when used in current IVF protocols, see p. 2284.2.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3. Varicocele has occurred in men treated with follitropin alfa.

Spongiform encephalopathies. In a few countries, gonadotrophins derived from cadaver pituitary glands have been used in the treatment of infertility, and a small number of patients are reported to have acquired Creutzfeldt-Jakob disease from such preparations.[1] However, most countries have preferred to use gonadotrophins derived from urine,[1] and these in their turn are being replaced with recombinant products;[2] such preparations appear to carry negligible risk of transmitting prion disease.[3-5]

1. Healy DL, Evans J. Creutzfeldt-Jakob disease after pituitary gonadotrophins. *BMJ* 1993; **307:** 517–18.
2. Eshkol A, Page ML. Human gonadotrophin preparations. *BMJ* 1994; **308:** 789.
3. Matorras R, Rodríguez-Escudero FJ. Bye-bye urinary gonadotrophins? The use of urinary gonadotrophins should be discouraged. *Hum Reprod* 2002; **17:** 1675.
4. Balen A. Is there a risk of prion disease after the administration of urinary-derived gonadotrophins? *Hum Reprod* 2002; **17:** 1676–80.
5. Jansen C. Bye-bye urinary gonadotrophins? Reply to debate. *Hum Reprod* 2003; **18:** 895–6.

Pharmacokinetics

Follitropins alfa and beta are slowly absorbed after subcutaneous or intramuscular injection, with an absolute bioavailability of about 70 to 80%. Peak plasma concentrations of follitropin beta have occurred about 12 hours after subcutaneous or intramuscular injection. Accumulation occurs with repeated doses, reaching a steady state within 3 to 5 days. Follitropins are slowly eliminated from the body, with a terminal half-life ranging from 12 to 70 hours. About one-eighth of a dose of follitropin alfa is reported to be excreted in the urine.

References.

1. Karlsson MO, *et al.* The population pharmacokinetics of recombinant- and urinary-human follicle stimulating hormone in women. *Br J Clin Pharmacol* 1998; **45:** 13–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gonal-F; Puregon; ***Austral.***: Gonal-F; Puregon; ***Austria***: Gonal-F; Puregon; ***Belg.***: Gonal-F; Puregon; ***Braz.***: Gonal-F; Puregon; ***Canad.***: Gonal-F; Puregon; ***Chile***: Gonal-F; Puregon; ***China***: Gonal-F (果纳芬); Puregon (普丽康); ***Cz.***: Fertavid; Gonal-F; Puregon; ***Denm.***: Gonal-F; Puregon; ***Fin.***: Gonal-F; Puregon; ***Fr.***: Gonal-F; Puregon; ***Ger.***: Gonal-F; Puregon; ***Gr.***: Gonal-F; Puregon; ***Hong Kong***: Gonal-F; Puregon; ***Hung.***: Gonal-F; Puregon; ***India***: Foligraf; Gonal-F; Nisfollic; ***Indon.***: Gonal-F; Puregon; ***Irl.***: Fertavid; Gonal-F; Puregon; ***Israel***: Gonal-F; Puregon; ***Ital.***: Gonal-F; Puregon; ***Malaysia***: Gonal-F; Puregon; ***Mex.***: Gonal-F†; Puregon; ***Neth.***: Fertavid; Gonal-F; Puregon; ***Norw.***: Gonal-F; Puregon; ***NZ***: Gonal-F; Puregon; ***Philipp.***: Gonal-F; Puregon; ***Pol.***: Fertavid; Gonal-F; Puregon; ***Port.***: Fertavid; Gonal-F; Puregon; ***Rus.***: Follitrop (ФОЛЛИТРОП); Gonal-F (Гонал-Ф); Puregon (Пурегон); ***S.Afr.***: Gonal-F; ***Singapore***: Gonal-F; Puregon; ***Spain***: Gonal-F; Puregon; ***Swed.***: Gonal-F; Puregon; ***Switz.***: Forielle; Gonal-F; Puregon; ***Thai.***: Gonal-F; Puregon; ***Turk.***: Gonal-F; Puregon; ***UK***: Gonal-F; Puregon; ***Ukr.***: Puregon (Пурегон); ***USA***: Follistim; Gonal-F; ***Venez.***: Gonal-F; Puregon.

Multi-ingredient Preparations. ***Arg.***: Pergoveris; ***Austria***: Pergoveris; ***Belg.***: Pergoveris; ***Braz.***: Pergoveris; ***Cz.***: Pergoveris; ***Denm.***: Pergoveris; ***Fr.***: Pergoveris; ***Ger.***: Pergoveris; ***Gr.***: Pergoveris; ***Hung.***: Pergoveris; ***Irl.***: Pergoveris; ***Israel***: Pergoveris; ***Ital.***: Pergoveris; ***Neth.***: Pergoveris; ***Norw.***: Pergoveris; ***Pol.***: Pergoveris; ***Port.***: Pergoveris; ***Rus.***: НыМоG (ХуМоГ); ***Singapore***: Pergoveris; ***Spain***: Pergoveris; ***Swed.***: Pergoveris†; ***Switz.***: Pergoveris; ***UK***: Pergoveris.

Formebolone *(BAN, rINN)* ⊗

Formebolona; Formébolone; Formebolonum; Formyldienolone; Формеболон.

11α,17β-Dihydroxy-17β-methyl-3-oxoandrosta-1,4-diene-2-carbaldehyde.

$C_{21}H_{28}O_4$=344.5

CAS — 2454-11-7.

UNII — Z2MMV08KUQ.

Profile

Formebolone has been used for its anabolic properties (see Testosterone, p. 2305.1). It appears to be widely abused by body-builders.

Fosfestrol *(BAN, rINN)*

Diethylstilbestrol Diphosphate; Fosfestroli; Fosfestrolum; Phosphoestrolum; Stilboestrol Diphosphate; Фосфэстрол.

(*E*)-α,α′-Diethylstilbene-4,4′-diol bis(dihydrogen phosphate); (*E*)-4,4′-(1,2-Diethylvinylene)bis(phenyl dihydrogen orthophosphate).

$C_{18}H_{22}O_8P_2$=428.3

CAS — 522-40-7.

ATC — L02AA04.

ATC Vet — QL02AA04.

UNII — A0E0NMA80F.

Pharmacopoeias. In *Jpn*.

Fosfestrol Sodium *(BANM, rINNM)*

Fosfestrol sódico; Fosfestrol Sodique; Natrii Fosfestrolum; Натрий Фосфэстрол.

$C_{18}H_{18}Na_4O_8P_2$=516.2

CAS — 23519-26-8 (fosfestrol tetrasodium xH_2O); 4719-75-9 (anhydrous fosfestrol tetrasodium).

ATC — L02AA04.

ATC Vet — QL02AA04.

UNII — G9I1882VSD.

Pharmacopoeias. In *Br.*, which specifies xH_2O.

BP 2014: (Fosfestrol Sodium). A white or almost white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. A 5% solution in water has a pH of 7.0 to 9.0. Protect from light.

Uses and Administration

Fosfestrol is a synthetic nonsteroidal oestrogen that requires dephosphorylation to diethylstilbestrol (p. 2267.3) before it is active. It is used in the treatment of malignant neoplasms of the prostate (p. 712.3).

Fosfestrol and its sodium salt have both been used, and doses of fosfestrol sodium may be expressed in terms of either the base or the salt; anhydrous fosfestrol sodium 300 mg is equivalent to about 250 mg of fosfestrol. Expressed in terms of fosfestrol sodium, initial doses of 600 to 1200 mg daily by slow intravenous injection over about 1 hour may be given for 5 to 10 days, followed by 300 mg daily for 10 to 20 days. Injections should be given preferably with the patient lying down. Maintenance intravenous doses of fosfestrol sodium 300 to 600 mg may be given, reduced gradually over several months from dosing 4 times a week to once weekly. Fosfestrol sodium may also be given orally. If initial doses cannot be given intravenously, doses of 360 to 480 mg three times daily have been given orally. For maintenance therapy, doses of 120 to 240 mg three times daily may be used, and gradually reduced to 240 mg daily.

Adverse Effects and Precautions

As for Diethylstilbestrol, see p. 2268.1.

After intravenous injection of fosfestrol sodium there may be a temporary burning sensation in the perineal region and pain at the site of bony metastases. Slow infusion is not recommended as cytotoxic concentrations of the drug may not be achieved.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Honvol†; ***Gr.***: Honvan; ***India***: Honvan.

Pharmacopoeial Preparations

BP 2014: Fosfestrol Injection; Fosfestrol Tablets.

Ganirelix Acetate *(BANM, USAN, rINNM)*

Acetato de ganirelix; Ganirélix, Acétate de; Ganirelix, acetato de; Ganirelixi Acetas; Org-37462; RS-26306; Ганиреликса Ацетат.

N-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-(*N*,*N*′-diethylamidino)-D-lysyl-L-leucyl-N^6-(*N*,*N*′-diethylamidino)-L-lysyl-L-prolyl-D-alaninamide acetate.

$C_{80}H_{113}ClN_{18}O_{13}.2C_2H_4O_2$=1690.5

CAS — 124904-93-4 (ganirelix); 129311-55-3 (ganirelix acetate).

ATC — H01CC01.

ATC Vet — QH01CC01.

UNII — 56U7906FQW.

Uses and Administration

Like cetrorelix (p. 2257.2), ganirelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is given to prevent premature luteinising hormone surges that can occur during controlled ovarian stimulation, which is a component of assisted reproduction used in infertility (p. 2253.1). Doses are expressed in terms of the acetate or the equivalent amount of base. Ganirelix acetate 108 mg is equivalent to about 100 mg of ganirelix. In the UK a dose equivalent to ganirelix 250 micrograms is given by subcutaneous injection once daily, starting on day 5 or 6 of ovarian stimulation and continued until ovulation induction. In the USA a dose of ganirelix acetate 250 micrograms is used similarly.

References.

1. Gillies PS, *et al.* Ganirelix. *Drugs* 2000; **59:** 107–11.
2. The European Orgalutran Study Group, *et al.* Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. *Hum Reprod* 2000; **15:** 1490–8. Correction. *ibid.*; 1877.
3. The North American Ganirelix Study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. *Fertil Steril* 2001; **75:** 38–45.
4. European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. *Hum Reprod* 2001; **16:** 644–51.
5. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
6. Out HJ, *et al.* A randomized, double-blind, multicentre clinical trial comparing starting doses of 150 and 200 IU of recombinant FSH in women treated with the GnRH antagonist ganirelix for assisted reproduction. *Hum Reprod* 2004; **19:** 90–5.
7. Wilcox J, *et al.* CAP IV Investigator Group. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertil Steril* 2005; **84:** 108–17.
8. Lambalk CB, *et al.* Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. *Hum Reprod* 2006; **21:** 632–9.

Adverse Effects and Precautions

As for Cetrorelix, p. 2257.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ganirelix as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Ganirelix is rapidly absorbed after subcutaneous injection, with a bioavailability of about 91%. It is metabolised by enzymatic hydrolysis and about 75% of a dose is excreted as metabolites in the faeces. Unchanged drug is found in the urine. The elimination half-life of ganirelix is about 13 hours.

References.

1. Oberyé JJL, *et al.* Pharmacokinetic and pharmacodynamic characteristics of ganirelix (Antagon/Orgalutron) part I: absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. *Fertil Steril* 1999; **72:** 1001–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Orgalutran; ***Austral.***: Orgalutran; ***Austria***: Orgalutran; ***Belg.***: Orgalutran; ***Braz.***: Orgalutran; ***Canad.***: Orgalutran; ***Chile***: Orgalutran; ***Cz.***: Orgalutran; ***Denm.***: Orgalutran; ***Fin.***: Orgalutran; ***Fr.***: Orgalutran; ***Ger.***: Orgalutran; ***Gr.***: Orgalutran; ***Hong Kong***: Orgalutran; ***Hung.***: Orgalutran; ***India***: Orgalutran; ***Indon.***: Orgalutran; ***Irl.***: Orgalutran; ***Israel***: Orgalutran; ***Ital.***: Orgalutran; ***Malaysia***: Orgalutran; ***Mex.***: Orgalutran; ***Neth.***: Orgalutran; ***Norw.***: Orgalutran; ***NZ***: Orgalutran; ***Philipp.***: Orgalutran†; ***Pol.***: Orgalutran; ***Port.***: Orgalutran; ***Rus.***: Orgalutran (Оргалутран); ***Singapore***: Orgalutran; ***Spain***: Orgalutran; ***Swed.***: Orgalutran; ***Switz.***: Orgalutran; ***Thai.***: Orgalutran; ***Turk.***: Orgalutran; ***UK***: Orgalutran; ***Ukr.***: Orgalutran (Оргалутран); ***Venez.***: Orgalutran.

Gestodene *(BAN, USAN, rINN)*

Gestodeeni; Gestoden; Gestodène; Gestodeno; Gestodenum; SH-B-331; Гестоден.

13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one.

$C_{21}H_{26}O_2$=310.4

CAS — 60282-87-3.

UNII — 1664P6E6MI.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Gestodene). A white or yellowish, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in dichloromethane.

Uses and Administration

Gestodene is a progestogen (see Progesterone, p. 2300.2) structurally related to levonorgestrel. It is used as the progestogenic component of combined oral contraceptives (see p. 2231.3); a typical daily dose is 75 micrograms in monophasic preparations, and 50 to 100 micrograms in triphasic preparations. Gestodene is also used orally as the progestogenic component of menopausal HRT (see p. 2244.2) in a regimen of 25 or 50 micrograms daily for 12 days of a 28-day cycle.

Reviews.

1. Anonymous. Femodene/Minulet—how different is gestodene? *Drug Ther Bull* 1990; **28:** 41–2.
2. Wilde MI, Balfour JA. Gestodene: a review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. *Drugs* 1995; **50:** 364–95.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. Gestodene is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that gestodene-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p. 2238.1, and for precautions, see under Cardiovascular Disease, p. 2241.2).

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Antiepileptics. *Felbamate* significantly increased gestodene clearance from a low-dose combined oral contraceptive, and might decrease contraceptive efficacy.[1] See also p. 2243.2.

1. Saano V, *et al.* Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. *Clin Pharmacol Ther* 1995; **58:** 523–31.

Pharmacokinetics

Gestodene is well absorbed with a high bioavailability when given orally. It is extensively bound to plasma proteins; 75 to 87% to sex hormone binding globulin, and 13 to 24% to albumin. Gestodene is metabolised in the liver, less than 1% of a dose being excreted in the urine unchanged. After

multiple doses with ethinylestradiol, gestodene has an elimination half-life of about 20 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aleli; Biofem; Cuidafem; Femiane; Ginelea T; Ginelea; Gynovin; Harmonet; Livianne; Mesconcept†; Minesse; Minulet; Mirelle; Secret 28; Venisse; ***Austral.***: Femoden ED†; Minulet; Trioden†; ***Austria***: Gynovin; Harmonette; Lenea; Meliane; Minesse; Minulet; Mirelle; Sylgestrel; Triodena; Wave; Yris; ***Belg.***: Femodene; Gestodelle; Gestofeme; Harmonet; Meliane; Minulet; Mirelle; Mylenamylan†; Tri-Minulet; Triodene; ***Braz.***: Adoless; Alexa; Allestra; Avaden; Ciclogyn; Diminut; Femiane; Fertnon; Gestinol; Ginesse; Gynera; Harmonet; Lizzy; Micropil; Minesse; Minima; Minulet; Mirelle; Previane; Siblima; Tamisa; Tantin; ***Chile***: Avaden†; Careza; Ciclomex; Feminol; Gynera; Harmonet; Microgen; Minesse; Minigest; Minulet; Mirelle; Tri-Ciclomex†; ***China***: Minulet (敏定偶); ***Cz.***: Artizia; Femoden; Harmonet; Katya; Lindynette; Logest; Lunafem; Milligest; Minesse; Minulet; Mirelle; Nelya; Stodette; Sunya; Tri-Minulet; ***Denm.***: Estinette; Gestinyl; Gestodilat; Gestonette; Harmonet; Lindynette; Milligest; Milna; Milvane; Minero; Minulet; Modina; Vellena; ***Fin.***: Femoden; Gestinyl; Gestodilat; Harmonet; Meliane; Minero; Minulet; Mirelle; Modina; Tri-Femoden; ***Fr.***: Avadene; Carlin; Edenelle; Efezial; Harmonet; Meliane; Melodia; Minesse; Minulet; Moneva; Optinesse; Perleane; Phaeva; Sylviane; Tri-Minulet; ***Ger.***: Femovan; Minulet; ***Gr.***: Gynera; Harmonette; Meliane; Minulet; Tri-Minulet; Trigynera; ***Hong Kong***: Gynera; Harmonet; Meliane; ***Hung.***: Femoden; Gestomix; Harmonet; Lindynette; Meliane; Milligest; Minesse†; Minulet; Sensonette; Triodena; ***Indon.***: Gynera; ***Irl.***: Estelle; Minesse; Minulet; Tri-Minulet; ***Israel***: Emily; Flame; Floret; Gynera; Harmonet; Lodene; Meliane; Minesse; Minulet; Shelly; Yael; ***Ital.***: Arianna; Estinette; Fedra; Femodette; Gestodiol; Ginoden; Harmonet; Kipling; Milvane; Minesse; Minigeste; Minulet; Tri-Minulet; ***Malaysia***: Gynera; Lindynette; Meliane; Minulet; ***Mex.***: Avaden; Ginelea; Gynovin; Minesse; Minulet; Secret 28; ***Mon.***: Felixita; ***Neth.***: Annantah; Femodeen; Jamyle; Minulet; ***NZ***: Femodene; Melodene†; Minulet; ***Philipp.***: Gynera; Meliane; Minulet†; ***Pol.***: Artizia; Femipol; Femoden; Harmonet; Kontracept; Logest; Milvane; Minulet†; Mirelle; Sylvie; Tri-Minulet†; ***Port.***: Avadene; Effiplen; Estinette; Gynera; Harmonet; Microgeste; Minesse; Minigeste; Minulet; Tri-Gynera; Tri-Minulet; ***Rus.***: Femoden (Фемоден); Lindynette (Линдинет); Logest (Логест); ***S.Afr.***: Femodene ED; Harmonet†; Melodene; Minesse; Minulette; Mirelle; Tri-Minulet†; Triodene; ***Singapore***: Gynera; Meliane; Minulet†; ***Spain***: Gestinyl; Gynovin; Harmonet; Meliane; Melodene 15; Melteva; Minesse; Minulet; Tevalet; Tri-Minulet; Trigynovin; ***Switz.***: Estinette; Femadiol; Gestoden Plus; Gynera; Gyselle; Harmonet; Liosanne; Meliane; Meloden; Milvane; Minesse; Minulet; Mirelle; Myvlar; ***Thai.***: Annylyn; Ciclomex; Gynera; Lindynette; Meliane; Minidoz; ***Turk.***: Ginera; Minulet; Reginon; ***UK***: Femodene; Femodette; Katya; Millinette; Sunya; Triadene; ***Ukr.***: Femoden (Фемоден); Lindynette (Линдинет); Logest (Логест); Tristin (Тристин)†; ***Venez.***: Avaden; Femiane; Gynera; Harmonet; Minesse; Minulet; Mirelle.

Gestonorone Caproate *(BANM, USAN, rINN)*

Caproato de gestonorona; Caproato de gestronol; Gestonorona, caproato de; Gestonorone, caproate de; Gestonoroni Caproas; Gestronol Hexanoate; Hexanoato de gestonorona; Hexanoato de gestronol; NSC-84054; SH-582; Гестонорона Капроат.

17α-Hydroxy-19-norpregn-4-ene-3,20-dione hexanoate.

$C_{26}H_{38}O_4$=414.6

CAS — 1253-28-7.

ATC — G03DA01; L02AB03.

ATC Vet — QG03DA01; QL02AB03.

UNII — U38E620NS6.

Uses and Administration

Gestonorone caproate is a long-acting potent progestogen structurally related to progesterone (p. 2300.2). It has been given in an oily solution by intramuscular injection in doses of 200 to 400 mg every 5 to 7 days for the adjunctive treatment of endometrial carcinoma (p. 704.3). It has also been used in the management of benign prostatic hyperplasia (p. 2347.1) in doses of 200 mg weekly, increased to 300 to 400 mg weekly if necessary.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3).

Local reactions have occurred at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may develop during or immediately after injection but can be avoided by injecting gestonorone very slowly. In males, spermatogenesis is temporarily inhibited.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Depostat; ***Gr.***: Depostat; ***Mex.***: Primostat; ***Rus.***: Depostat (Депостат).

Gestrinone *(BAN, USAN, rINN)* ⊗

A-46745; Ethylnorgestrienone; Gestrinon; Gestrinona; Gestrinoni; Gestrinonum; R-2323; RU-2323; Гестринон.

13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,9,11-trien-20-yn-3-one.

$C_{21}H_{24}O_2$=308.4

CAS — 16320-04-0; 40542-65-2.

ATC — G03XA02.

ATC Vet — QG03XA02.

UNII — 1421533RCM.

Uses and Administration

Gestrinone is a synthetic steroidal hormone reported to have antiprogestogenic properties, with some androgenic and anti-oestrogenic activity; it inhibits pituitary gonadotrophin release. It is used in the treatment of endometriosis (p. 2264.1) in oral doses of 2.5 mg twice weekly; the first dose is taken on the first day of the menstrual cycle with the second dose taken three days later; thereafter the doses should be taken on the same two days of each week, usually for a period of 6 months. If a dose is missed it should be given as soon as possible and the original dose sequence maintained thereafter; if 2 or more doses are missed gestrinone should be stopped and restarted on the first day of a new cycle after a negative pregnancy test.

Gestrinone has been studied in the management of cyclical mastalgia (p. 2265.1) and uterine fibroids (p. 2281.2).

References.

1. Thomas EJ, Cooke ID. Impact of gestrinone on the course of asymptomatic endometriosis. *BMJ* 1987; **294:** 272–4.
2. Brosens IA, *et al.* The morphologic effect of short-term medical therapy of endometriosis. *Am J Obstet Gynecol* 1987; **157:** 1215–21.
3. Coutinho EM, Azadian-Boulanger G. Treatment of endometriosis by vaginal administration of gestrinone. *Fertil Steril* 1988; **49:** 418–22.
4. Hornstein MD, *et al.* A randomized double-blind prospective trial of two doses of gestrinone in the treatment of endometriosis. *Fertil Steril* 1990; **53:** 237–41.
5. Peters F. Multicentre study of gestrinone in cyclical breast pain. *Lancet* 1992; **339:** 205–8.
6. Worthington M, *et al.* A randomized comparative study of the metabolic effects of two regimens of gestrinone in the treatment of endometriosis. *Fertil Steril* 1993; **59:** 522–6.
7. Gestrinone Italian Study Group. Gestrinone versus a gonadotropin-releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomized, double-blind study. *Fertil Steril* 1996; **66:** 911–19.
8. Dawood MY, *et al.* Clinical, endocrine, and metabolic effects of two doses of gestrinone in treatment of pelvic endometriosis. *Am J Obstet Gynecol* 1997; **176:** 387–94.
9. La Marca A, *et al.* Gestrinone in the treatment of uterine leiomyomata: effects on uterine blood supply. *Fertil Steril* 2004; **82:** 1694–6.

Adverse Effects and Precautions

As for Danazol, p. 2265.3.

Interactions

Antiepileptic drugs and rifampicin may accelerate the metabolism of gestrinone.

Pharmacokinetics

Gestrinone is well absorbed after oral doses with negligible first-pass hepatic metabolism. Peak plasma concentrations occur about 3 hours after a dose. The plasma half-life is about 24 hours. Gestrinone is metabolised in the liver to form conjugated metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nemestran; ***Austral.***: Dimetriose; ***Braz.***: Dimetrose; ***China***: Nemestran (内美通); Yanchang (言昌); ***Ital.***: Dimetrose; ***Malaysia***: Dimetriose; ***Mex.***: Nemestran; ***Neth.***: Nemestran†; ***NZ***: Dimetriose; ***Port.***: Dimetriose; ***Rus.***: Nemestran (Неместран); ***S.Afr.***: Tridomose†; ***Singapore***: Dimetriose; ***Switz.***: Nemestran†; ***Thai.***: Dimetriose†; ***UK***: Dimetriose†.

Gonadorelin *(BAN, rINN)* ⊗

Follicle Stimulating Hormone-releasing Factor; GnRH; Gonadoliberin; Gonadoreliini; Gonadorelina; Gonadoréline; Gonadorelinum; Gonadotrophin-releasing Hormone; Hoe-471; LH/FSH-RF; LH/FSH-RH; LH-RF; LH-RH; Luliberin; Luteinising Hormone-releasing Factor; Гонадорелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosylglycyl-L-leucyl-L-arginyl-L-prolylglycinamide.

$C_{55}H_{75}N_{17}O_{13}$=1182.3

CAS — 33515-09-2.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

UNII — 9O7312W37G.

Gonadorelin Acetate *(BANM, USAN, rINNM)* ⊗

Abbott-41070; Acetato de gonadorelina; Gonadolrelin-acetát; Gonadoreliiniasetaatti; Gonadorelina, acetato de; Gonadorelinacetat; Gonadorelin-acetát; Gonadoréline, acétate de; Gonadorelini acetas; Gonadorelino acetatas; Гонадорелина Ацетат.

$C_{55}H_{75}N_{17}O_{13}.xC_2H_4O_2.yH_2O$

CAS — 34973-08-5 (anhydrous gonadorelin diacetate); 52699-48-6 (gonadorelin diacetate tetrahydrate).

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

UNII — 2RG1XQ1NYJ (gonadorelin acetate as mixture of monoacetate and diacetate hydrates); L8CRY8PWF2 (gonadorelin diacetate tetrahydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US* for veterinary use only.

USP 36: (Gonadorelin Acetate). A white to slightly yellowish powder. Soluble in water; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of not more than 8 degrees.

Ph. Eur. 8: (Gonadorelin Acetate). The acetate form of a hypothalamic peptide that stimulates the release of follicle-stimulating hormone and luteinising hormone from the pituitary gland. It is obtained by chemical synthesis. A white or slightly yellowish powder; soluble in water and in 1% v/v glacial acetic acid; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Gonadorelin Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-24031; Gonadorelina, hidrocloruro de; Gonadoréline, Chlorhydrate de; Gonadorelini Hydrochloridum; Hidrocloruro de gonadorelina; Гонадорелина Гидрохлорид.

$C_{55}H_{75}N_{17}O_{13}.2HCl$=1255.2

CAS — 51952-41-1.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

UNII — 3PFC574ITA.

Pharmacopoeias. In *US.*

USP 36: (Gonadorelin Hydrochloride). A synthetic polypeptide hormone having the property of stimulating the release of the luteinising hormone from the hypothalamus. It is extremely hygroscopic. Protect from exposure to moisture and store in airtight well-sealed containers, in a desiccator.

Uses and Administration

Gonadorelin is a synthetic form of hypothalamic gonadotrophin-releasing hormone. It stimulates the synthesis and release of follicle-stimulating hormone and, in particular, luteinising hormone in the anterior lobe of the pituitary. The secretion of endogenous gonadotrophin-releasing hormone is pulsatile and is controlled by several factors including circulating sex hormones. Gonadotrophic hormones (gonadotrophins), released from the pituitary gland in response to gonadorelin, stimulate secretion of sex hormones from the gonads. A single dose of gonadorelin or one of its analogues has the effect of increasing circulating sex hormones; continued use leads to down-regulation of gonadorelin-receptor synthesis in the pituitary and results in a paradoxical reduction in sex-hormone secretion.

Gonadorelin may be given as the base, acetate, or hydrochloride, and the dose may be expressed in terms of any of these.

Gonadorelin is used in the **diagnosis of hypothalamic-pituitary-gonadal dysfunction** (see p. 2281.1). Assessment is usually based on the response to a dose of gonadorelin of 100 micrograms by intravenous or subcutaneous injection. In females, where possible, it should be given early in the follicular stage of the menstrual cycle. For diagnostic doses used in children, see p. 2281.1.

Gonadorelin is also used in the treatment of **amenorrhoea** (p. 2251.3) and **infertility** (see p. 2281.2) associated with hypogonadotrophic hypogonadism. Weight-related amenorrhoea should have been corrected by diet. Treatment in such conditions is based on an intermittent pulse pump providing 5 to 20 micrograms over one minute every 90 minutes, either subcutaneously or intravenously, for up to 6 months or until conception.

Gonadorelin may be used in the management of cryptorchidism (p. 2281.1) and delayed puberty (p. 2281.1). Its analogues, such as buserelin, goserelin, leuprorelin,

nafarelin, and triptorelin (which are more potent and have a longer duration of action) can be used in central precocious puberty, endometriosis, uterine fibroids, and malignant neoplasms, especially of the prostate. They may also be used in the management of infertility (see below for further details).

Administration in children. Gonadorelin may be used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction in children (see also below). The *BNFC* includes gonadorelin for children aged from 1 year to 18 years. A single dose of 2.5 micrograms/kg, to a maximum of 100 micrograms, is given subcutaneously or intravenously.

Conditions in which gonadorelin may be used for treatment include cryptorchidism and delayed puberty. Gonadorelin analogues are used in precocious puberty (see below).

Benign prostatic hyperplasia. The gonadorelin analogues have been tried in the management of benign prostatic hyperplasia (p. 2347.1) but are considered unsatisfactory for indefinite use. See also under Leuprorelin, p. 2286.1, and Nafarelin Acetate, p. 2292.2.

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with gonadorelin may be used for cryptorchidism (p. 2252.1). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, which may be a predictor of future fertility.[3]

Gonadorelin is usually given intranasally, in a dose of 1.2 mg daily, in 3 divided doses, for 4 weeks.[3]

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (update March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Paediatric_Urology.pdf (accessed 28/10/09)

Delayed puberty. Gonadorelin may be used in the management of delayed puberty (p. 2252.1) that is secondary to hypogonadotrophic hypogonadism. It is given to boys to stimulate the release of endogenous gonadotrophins that are needed for testicular development.[1] In order to mimic the pulsatile release of endogenous gonadotrophin-releasing hormone, gonadorelin acetate or hydrochloride is given subcutaneously or intravenously, in pulses of about 5 to 20 micrograms at intervals of 90 to 120 minutes. Treatment may be given for 30 to 50 weeks.

1. Delemarre EM, *et al.* Inducing puberty. *Eur J Endocrinol* 2008; **159** (suppl): S9–S15.

Diagnosis of hypothalamic and pituitary dysfunction. Gonadorelin may be used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction such as in hypogonadism, delayed puberty, and precocious puberty.[1,2] Gonadorelin analogues, such as triptorelin (p. 2311.1), have also been used in the diagnosis of delayed puberty.

1. Eckert KL, *et al.* A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics* 1996; **97:** 517–19.
2. De Martino MU, *et al.* Dynamic testing in the evaluation of male gonadal function. *J Endocrinol Invest* 2003; **26** (suppl): 107–13.

Disturbed behaviour. Gonadorelin analogues such as leuprorelin (p. 2286.1) or triptorelin (p. 2311.2) may be tried in men with paraphilias.

Reviews.

1. Briken P, *et al.* Pharmacotherapy of paraphilias with long-acting agonists of luteinizing hormone-releasing hormone: a systematic review. *J Clin Psychiatry* 2003; **64:** 890–7.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value, because of the risk of osteoporosis. 'Add-back' therapy (hormone replacement) may be given in an attempt to reduce bone mineral density loss and vasomotor symptoms.

Some references to gonadorelin analogues in endometriosis are listed below. For further references, see Buserelin, p. 2256.3, Goserelin, p. 2283.1, Leuprorelin, p. 2286.1, Nafarelin Acetate, p. 2292.2, and Triptorelin, p. 2311.2.

1. Gargiulo AR, Hornstein MD. The role of GnRH agonists plus add-back therapy in the treatment of endometriosis. *Semin Reprod Endocrinol* 1997; **15:** 273–84.
2. Hemmings R. Combined treatment of endometriosis: GnRH agonists and laparoscopic surgery. *J Reprod Med* 1998; **43** (suppl 3): 316–20.
3. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
4. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.
5. Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. *N Engl J Med* 2008; **359:** 1136–42.

Fibroids. Uterine fibroids (leiomyomas) are benign tumours of uterine smooth muscle.[1-3] They are found in about 25% of women, most of whom are aged in their 30s or 40s when the condition becomes symptomatic. Fibroids may give rise to menstrual problems, particularly menorrhagia, pelvic discomfort, infertility, and miscarriage. Although small fibroids may not require treatment, the management of symptomatic fibroids has traditionally been surgical. However, because fibroids are oestrogen responsive, gonadorelin analogues have also been tried as medical treatment for their ability to induce a hypogonadotrophic hypogonadal state. These drugs produce a significant reduction in uterine and fibroid volume, and amenorrhoea, but when treatment stops uterine and fibroid volume tend to return to pretreatment values. The hypoestrogenism produced during treatment also causes menopausal symptoms such as hot flushes and vaginal dryness, and bone loss may occur. Giving oestrogens or progestogens, once the uterine fibroid size has significantly reduced, has been tried as 'add-back' therapy to counteract these adverse effects.[4,5] Tibolone has also been reported to reduce bone loss and vasomotor symptoms.[2,3] Subcutaneous injection of long-acting depot preparations of gonadorelin or its analogues appears to be the preferred method and is considered a valuable pre-operative adjunct to surgery, simplifying the procedure by reducing uterine and fibroid volume and intra-operative blood loss, as well as correcting pre-operative iron-deficiency anaemia.[6,7] However, not all centres favour general pre-operative use,[3] and concern has been expressed that the use of gonadorelin analogues for treating fibroids may complicate the differentiation of benign and malignant growths,[8] or cause smaller fibroids to be missed at excision.[3]

For further references to use of gonadorelin analogues in the treatment of fibroids, see Buserelin, p. 2256.3, Goserelin, p. 2283.1, Leuprorelin, p. 2286.1, Nafarelin Acetate, p. 2292.3, and Triptorelin, p. 2311.2.

Ulipristal acetate, a progesterone receptor modulator, may be used pre-operatively to control excessive bleeding and reduce fibroid size.[9] It may control bleeding more quickly than leuprorelin, but be less effective in reducing uterine volume.[10] Other drugs that are under investigation for fibroids include gonadorelin antagonists such as cetrorelix and ganirelix, and mifepristone. Danazol and gestrinone have also been tried in a small number of patients.[2,3]

1. Stewart EA. Uterine fibroids. *Lancet* 2001; **357:** 293–8.
2. De Leo V, *et al.* A benefit-risk assessment of medical treatment for uterine leiomyomas. *Drug Safety* 2002; **25:** 759–79.
3. Sankaran S, Manyonda IT. Medical management of fibroids. *Best Pract Res Clin Obstet Gynaecol* 2008; **22:** 655–76.
4. Friedman AJ, *et al.* Efficacy and safety considerations in women with uterine leiomyomas treated with gonadotropin-releasing hormone agonists: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1990; **163:** 1114–19.
5. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
6. Lethaby A, *et al.* Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 15/09/05).
7. Agence Française de Sécurité Sanitaire des Produits de Santé. Les traitements médicamenteux du fibrome utérin - octobre 2004. Available at: http://www.afssaps.sante.fr/content/download/3971/39226/version/4/file/fibrorec.pdf (accessed 19/07/10)
8. Mesia AF, *et al.* Aborted leiomyosarcoma after treatment with leuprolide acetate. *Obstet Gynecol* 1998; **92:** 664–6.
9. Donnez J, *et al.* PEARL I Study Group. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med* 2012; **366:** 409–20.
10. Donnez J, *et al.* PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med* 2012; **366:** 421–32.

Growth retardation. The use of a gonadorelin analogue to delay precocious puberty may improve the final height of children with the disorder. However, the use of a gonadorelin analogue with growth hormone in short but otherwise normal children is controversial—see under Triptorelin, p. 2311.2.

Hirsutism. For reference to the use of gonadorelin analogues such as leuprorelin in the treatment of hirsutism, see p. 2286.1.

Infertility. Gonadorelin and its analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both women and men (p. 2253.1). Some further references are given below. See also under Buserelin, p. 2256.3, Leuprorelin, p. 2286.2, and Nafarelin Acetate, p. 2292.3.

For mention of the use of gonadorelin and its analogues in the management of infertility in polycystic ovary syndrome, see below.

1. Lingle L, Hart LL. Gonadotropin-releasing hormone in infertility. *DICP Ann Pharmacother* 1989; **23:** 246–8.
2. Thomas AK, *et al.* Induction of ovulation with subcutaneous pulsatile gonadotropin-releasing hormone: correlation with body weight and other parameters. *Fertil Steril* 1989; **51:** 786–90.
3. Homburg R, *et al.* One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation. *BMJ* 1989; **298:** 809–12.
4. Kovacs GT, *et al.* Induction of ovulation with gonadotrophin-releasing hormone—life-table analysis of 50 courses of treatment. *Med J Aust* 1989; **151:** 21–6.
5. Santoro N. Efficacy and safety of intravenous pulsatile gonadotropin-releasing hormone: Lutrepulse for injection. *Am J Obstet Gynecol* 1990; **163:** 1759–64.
6. Nachtigall LB, *et al.* Adult-onset idiopathic hypogonadotropic hypogonadism–a treatable form of male infertility. *N Engl J Med* 1997; **336:** 410–15.

Malignant neoplasms. Gonadorelin analogues are used in the treatment of prostatic cancer (p. 712.3) where they provide an alternative to orchidectomy in the management of advanced disease. They may also be used for ovarian ablation in premenopausal women with breast cancer (p. 702.1). Gonadorelin analogues have been tried in neoplasms of the endometrium and ovary, but their use is much less well established.

Analogues used include buserelin (p. 2256.3), goserelin (p. 2283.1), leuprorelin (p. 2286.2), and triptorelin (p. 2311.2).

Mastalgia. Gonadorelin analogues such as goserelin may be effective in severe refractory mastalgia (p. 2265.1).

Polycystic ovary syndrome. Gonadorelin and its analogues have been used in the management of infertility associated with polycystic ovary syndrome (see Infertility, p. 2253.1), even though some product information contra-indicates their use in this syndrome.

Pulsatile gonadorelin has been tried for ovulation induction but rates of ovulation and pregnancy are poor when it is used alone in women with polycystic ovary syndrome. Pretreatment with a gonadorelin analogue for pituitary desensitisation before starting pulsatile gonadorelin has shown some benefit in patients with polycystic ovary syndrome who have high levels of luteinising hormone.[1] However, there are only limited clinical data from small short-term studies and case series on the use of pulsatile gonadorelin in these women.[2]

Gonadorelin analogues may be used for pituitary desensitisation before the use of gonadotrophins for ovulation induction, and there is a suggestion that this strategy may improve pregnancy rates compared with gonadotrophins alone in women with polycystic ovary syndrome.[3] Gonadorelin analogues are used also in ovarian stimulation protocols for assisted reproduction techniques.[1]

Women with polycystic ovary syndrome are at increased risk of ovarian hyperstimulation syndrome and must be carefully monitored throughout the use of ovulation induction regimens.[1]

1. Buckett WM, Tan SL. Use of luteinizing hormone releasing hormone agonists in polycystic ovary syndrome. *Baillieres Clin Obstet Gynaecol* 1998; **12:** 593–606.
2. Bayram N, *et al.* Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 15/09/05).
3. Nugent D, *et al.* Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 15/09/05).

Porphyria. For mention of the use of gonadorelin analogues to suppress cyclic premenstrual exacerbations of acute porphyria, see Buserelin, p. 2257.1, Nafarelin Acetate, p. 2292.3, and Triptorelin, p. 2311.3.

Precocious puberty. Gonadorelin analogues are the treatment of choice in central precocious puberty (p. 2254.1).[1] Analogues used include buserelin (p. 2257.1), goserelin (p. 2283.2), histrelin (p. 2284.1), leuprorelin (p. 2286.2), nafarelin (p. 2292.3), and triptorelin (p. 2311.3).

1. Carel J-C, *et al.* ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Abstract: *Pediatrics* 2009; **123:** 1242. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/4/e752 (accessed 28/10/09)

Premenstrual syndrome. In women in whom other drug treatments for premenstrual syndrome (p. 2272.3) are ineffective, use of a gonadorelin analogue, usually with HRT as 'add-back' therapy to prevent menopausal symptoms, may be considered.[1] Short-term therapy (3 months) has been used to confirm the diagnosis of premenstrual syndrome, or to predict the response to bilateral oophorectomy when this is being considered. Some references to the use of gonadorelin analogues in premenstrual syndrome are given below.[2-7]

1. Wyatt KM, *et al.* The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *Br J Obstet Gynaecol* 2004; **111:** 585–93.
2. Hussain SY, *et al.* Buserelin in premenstrual syndrome. *Gynecol Endocrinol* 1992; **6:** 57–64.
3. Mezrow G, *et al.* Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. *Fertil Steril* 1994; **62:** 932–7.

4. Brown CS, *et al*. Efficacy of depot leuprolide in premenstrual syndrome: effect of symptom severity and type in a controlled trial. *Obstet Gynecol* 1994; **84:** 779–86.
5. West CP, Hillier H. Ovarian suppression with the gonadotrophin-releasing hormone agonist goserelin (Zoladex) in management of the premenstrual tension syndrome. *Hum Reprod* 1994; **9:** 1058–63.
6. Leather AT, *et al*. The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. *Gynecol Endocrinol* 1999; **13:** 48–55.
7. Di Carlo C, *et al*. Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; **75:** 380–4.

Adverse Effects

Gonadorelin and its analogues are generally well tolerated but may cause gastrointestinal adverse effects, usually nausea and abdominal pain or discomfort. There may be headache or lightheadedness, and an increase in menstrual bleeding. Continued therapy with gonadorelin analogues results in paradoxical suppression of the pituitary gonadal axis; in premenopausal women this may produce menopausal symptoms, including vaginal dryness, hot flushes, and loss of libido. If sufficiently prolonged the suppression of circulating oestrogens may lead to osteoporosis. In men, hot flushes and sexual dysfunction can occur, and breast swelling and tenderness have been reported infrequently with gonadorelin analogues. Long-term treatment can also cause a loss of bone mineral density in men. Other adverse effects reportedly associated with gonadorelin analogue therapy, and presumably related to changes in the hormonal milieu, include mood changes, nervousness, palpitations, acne and dry skin, changes in scalp and body hair, alterations in liver function tests and blood lipids, and decreased glucose tolerance. Arthralgia and paraesthesias have been reported. Ovarian hyperstimulation (as seen with chorionic gonadotrophin, p. 2258.3), although rare, has occurred in women given gonadorelin.

Reactions or pain may occur at the site of injection with rash (local or generalised), thrombophlebitis, swelling, or pruritus. Hypersensitivity reactions, including bronchospasm and anaphylaxis, have been reported. Convulsions have occurred in patients given gonadorelin analogues.

Other effects may be a consequence of the particular use of gonadorelin or its analogues. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment for cancer of the prostate and prophylactic anti-androgen therapy may be added. Flare may manifest as an increase in bone pain; occasionally there has been spinal cord compression, or a worsening of urinary-tract symptoms with haematuria and urinary obstruction. Acute degeneration of submucous fibroids with severe bleeding has been reported following use of leuprorelin. An initial increase in signs and symptoms has also been reported in women with breast cancer receiving gonadorelin analogues; hypercalcaemia has occurred in those with metastatic disease. In girls being treated for precocious puberty, vaginal bleeding may occur in the first month of treatment because of initial ovarian stimulation followed by treatment-induced oestrogen withdrawal.

Effects on the cardiovascular system. Gonadorelin analogues are widely used as a component of androgen deprivation therapy in the treatment of prostate cancer. However, the hypogonadism associated with this therapy may contribute to the development of metabolic complications such as insulin resistance, hyperglycaemia, dyslipidaemia, and the metabolic syndrome. There is some evidence that long-term use of androgen deprivation therapy may increase the risk of diabetes, atherosclerosis, and cardiovascular disease.

References.
1. Keating NL, *et al*. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006; **24:** 4448–56.
2. Saigal CS, *et al*. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007; **110:** 1493–1500.
3. Tsai HK, *et al*. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 2007; **99:** 1516–24.
4. Shahani S, *et al*. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* 2008; **93:** 2042–9.

Hypersensitivity. Acquired hypersensitivity led to an anaphylactic reaction after an intravenous dose of gonadorelin in a man who had been receiving pulsatile subcutaneous gonadorelin therapy for 10 weeks.[1]

1. Potashnik G, *et al*. Anaphylactic reaction to gonadotropin-releasing hormone. *N Engl J Med* 1993; **328:** 815.

Osteoporosis. Long-term use of a gonadorelin analogue results in oestrogen deficiency-associated osteoporosis and various drugs have been investigated for their ability to reduce this effect. Parathyroid hormone has been reported to prevent bone loss in small studies of young women receiving nafarelin.[1,2] 'Add-back' therapy with tibolone[3,4] or oestrogen plus progestogen[5,6] has also had beneficial effects on bone mineral density in women receiving gonadorelin analogues. However, studies have used various combination regimens and it is not possible to determine which is most effective.[6,7] There is less information available about the management of osteoporosis in men receiving gonadorelin analogues as androgen deprivation therapy, but measures have included supplemental calcium and vitamin D, and the use of bisphosphonates.[8] Raloxifene is also under investigation in both women[9] and men.[10]

1. Finkelstein JS, *et al*. Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; **331:** 1618–23.
2. Finkelstein JS, *et al*. Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; **280:** 1067–73.
3. Lindsay PC, *et al*. The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
4. Palomba S, *et al*. A clinical trial of the effects of tibolone administered with gonadorelin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; **70:** 111–18.
5. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
6. Sagsveen M, *et al*. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Surrey ES, the Add-back Consensus Working Group. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.
8. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. *Cancer* 2003; **97** (suppl): 789–95.
9. Palomba S, *et al*. Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; **87:** 4476–81.
10. Smith MR, *et al*. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3841–6.

Pituitary apoplexy. Pituitary apoplexy has been reported after endocrine stimulation testing using gonadorelin. A review[1] of 14 cases found that 2 patients had received gonadorelin alone but most had also received protirelin (thyrotropin-releasing hormone). The onset of initial symptoms was within 2 hours and pituitary tumour haemorrhage was much more common than infarction alone.

1. Matsuura I, *et al*. Infarction followed by hemorrhage in pituitary adenoma due to endocrine stimulation test. *Endocr J* 2001; **48:** 493–8.

Precautions

Gonadorelin or its analogues should not generally be used in patients with pituitary adenoma as haemorrhagic infarction (pituitary apoplexy) has sometimes occurred. It has also been recommended that patients with weight-related amenorrhoea should not receive these drugs until their weight is corrected. Although at least one manufacturer recommends that gonadorelin should not be used in women with polycystic ovary disease or with endometriotic cysts, gonadorelin and its analogues have been used for ovulation induction in polycystic disease and produced improvement in uterine fibroids; gonadorelin analogues have also been used with benefit in endometriosis. Gonadorelin analogues may increase cervical resistance, making it difficult to dilate the cervix for intra-uterine surgical procedures. Gonadorelin or its analogues should be stopped if the patient becomes pregnant. Contraceptive measures should be taken to protect against unwanted ovulation. Men at risk from tumour flare should be carefully monitored in the first month of therapy. Patients with diabetes should be monitored for effects on glucose control.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gonadorelin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1] NAPOS classifies several gonadorelin analogues as porphyrinogenic: buserelin (p. 2257.1), goserelin (p. 2283.2), leuprorelin (p. 2287.1), and triptorelin (p. 2311.3); or as possibly porphyrinogenic: nafarelin (p. 2292.3).

For reference to the use of gonadorelin analogues to prevent premenstrual exacerbations of acute porphyria, see p. 2281.3.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Drugs affecting pituitary secretion of gonadotrophins may alter the response to gonadorelin or its analogues; other hormonal therapy and corticosteroids can affect the response. Spironolactone and levodopa can stimulate gonadotrophins while phenothiazines, dopamine antagonists, digoxin, and sex hormones can inhibit gonadotrophin secretion.

Pharmacokinetics

Gonadorelin is poorly absorbed from the gastrointestinal tract. It has a terminal plasma half-life of only 10 to 40 minutes after intravenous injection. It is hydrolysed in the plasma and excreted in the urine as inactive metabolites.

Gonadorelin analogues are absorbed after oral, intramuscular, intranasal, or rectal doses and have a longer half-life.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Luteoliberina; ***Austria***: Kryptocur; Lutrelef; Relefact LH-RH†; ***Belg.***: HRF; ***Canad.***: Lutrepulse; Relisorm; ***Fr.***: Lutrelef; Stimu-LH†; ***Ger.***: Kryptocur; Lutrelef; Relefact LH-RH; ***Gr.***: Cryptocur; Relefact LH-RH; Relisorm; ***Irl.***: HRF; ***Ital.***: Kryptocur; Lutrelef; ***Neth.***: HRF†; Lutrelef; Relefact LH-RH; ***S.Afr.***: HRF†; ***Swed.***: Lutreleft; ***Switz.***: Kryptocur†; Lutrelef; ***UK***: HRF; ***USA***: Factrel†.

Pharmacopoeial Preparations

USP 36: Gonadorelin for Injection.

Goserelin *(BAN, USAN, rINN)* ⊗

Gosereliini; Goserelina; Goserelinas; Goséréline; Goserelinum; Goszerelin; ICI-118630; Гозерелин.

3-[5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-(3-*O*-*tert*-butyl)-D-seryl-L-leucyl-L-arginyl-L-prolyl]carbazamide.

$C_{59}H_{84}N_{18}O_{14}$=1269.4

CAS — 65807-02-5.

ATC — L02AE03.

ATC Vet — QL02AE03.

UNII — 0F65R8P09N.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Goserelin). A nonapeptide analogue of the hypothalamic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white powder. Soluble in water; freely soluble in glacial acetic acid. It dissolves in dilute solutions of mineral acids and alkali hydroxides. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Goserelin Acetate *(BANM, rINNM)* ⊗

Acetato de goserelina; Goserelina, acetato de; Goséréline, Acétate de; Goserelini Acetas; D-Ser (Bu^t)^6 Azgly^{10}-LHRH Acetate; Гозерелина Ацетат.

$C_{59}H_{84}N_{18}O_{14}.C_2H_4O_2$=1329.5

CAS — 145781-92-6.

ATC — L02AE03.

ATC Vet — QL02AE03.

UNII — 6YUU2PV0U8.

Pharmacopoeias. In *US.*

USP 36: (Goserelin Acetate). Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Goserelin is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in breast cancer in pre-and perimenopausal women, and in the management of endometriosis. Limited courses of treatment are given for endometrial thinning before surgery for dysfunctional uterine bleeding, and with iron supplementation to improve anaemia before surgery in women being treated for fibroids. It is also used as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. Goserelin is usually given as the acetate but doses are expressed in terms of the base; 10.5 mg of goserelin acetate is equivalent to about 10 mg of goserelin.

Goserelin acetate is generally given in biodegradable implants, which are injected subcutaneously into the anterior abdominal wall. The continuous release of drug gradually suppresses serum concentrations of oestradiol and testosterone over about 3 weeks after the first injection, and low hormone concentrations are maintained with repeated doses. One such preparation containing the equivalent of 3.6 mg of goserelin is given once every 28 days in the treatment of **prostate** and **breast cancers**. Preparations containing the equivalent of 10.8 mg of goserelin, given every 12 weeks, are also available for the treatment of prostate cancer. In the treatment of prostate cancer an anti-androgen such as cyproterone acetate may be given for several days before starting goserelin therapy and continued for at least 3 weeks, to avoid the risk of a disease flare.

Preparations containing the equivalent of 3.6 mg of goserelin given once every 28 days are also used to treat **endometriosis** for up to 6 months. For **endometrial thinning** before surgery in dysfunctional uterine bleeding,

a single dose is given 4 weeks before surgery. Some women may require a second dose to provide 8 weeks of treatment—for example, those with a large uterus or to allow flexible timing of surgery. In women with anaemia as a result of **uterine fibroids**, goserelin 3.6 mg is given with iron supplementation for up to 3 months before surgery.

In **infertility**, regimens for oocyte collection for IVF use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins. The equivalent of 3.6 mg of goserelin is given as a subcutaneous implant and serum-oestradiol concentrations monitored until they decline to levels similar to those in the early follicular phase, a process which usually takes 7 to 21 days. Once downregulation occurs gonadotrophin (follicle stimulating) therapy is begun until an appropriate stage of follicular development, when it is withdrawn and chorionic gonadotrophin is given to induce ovulation.

Goserelin has also been given in other sex-hormone-related conditions. For the use of goserelin in children, see below.

Reviews of goserelin.

1. Chrisp P, Goa KL. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical use in sex hormone-related conditions. *Drugs* 1991; **41:** 254–88.
2. Perry CM, Brogden RN. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in benign gynaecological disorders. *Drugs* 1996; **51:** 319–46.

Administration in children. Goserelin may be used in the management of central precocious puberty—see below.

Endometriosis. Gonadorelin analogues such as goserelin are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis. Hormone replacement (add-back therapy) may also be given in an attempt to reduce bone mineral density loss and vasomotor symptoms in women receiving goserelin.

References.

1. Shaw RW, *et al.* An open randomized comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. *Fertil Steril* 1992; **58:** 265–72.
2. Schlaff WD. Extending the treatment boundaries: Zoladex and add-back. *Int J Gynaecol Obstet* 1999; **64** (suppl 1): S25–S31.
3. Franke HR, *et al.* Gonadotropin-releasing hormone agonist plus "add-back" hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. *Fertil Steril* 2000; **74:** 534–9.
4. Pierce SJ, *et al.* Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. *Fertil Steril* 2000; **74:** 964–8.

Fibroids. Gonadorelin analogues such as goserelin have been tried as an adjunct or an alternative to surgery in the treatment of uterine fibroids (p. 2281.2) although there has been some concern that this might complicate the diagnosis of malignancy. Some further references are listed below.

1. Lumsden MA, *et al.* Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *Br J Obstet Gynaecol* 1994; **101:** 438–42.
2. Benagiano G, *et al.* Zoladex (goserelin acetate) and the anemic patient: results of a multicenter fibroid study. *Fertil Steril* 1996; **66:** 223–9.
3. Parazzini F, *et al.* Goserelin acetate to avoid hysterectomy in premenopausal women with fibroids requiring surgery. *Eur J Obstet Gynecol Reprod Biol* 1999; **87:** 31–3.
4. Bozzini N, *et al.* Comparative study of different dosages of goserelin in size reduction of myomatous uteri. *J Am Assoc Gynecol Laparosc* 2004; **11:** 462–3.
5. Muneyyirci-Delale O, *et al.* Goserelin acetate 10.8 mg plus iron versus iron monotherapy prior to surgery in premenopausal women with iron-deficiency anemia due to uterine leiomyomas: results from a phase III, randomized, multicenter, double-blind, controlled trial. *Clin Ther* 2007; **29:** 1682–91.
6. Lim SS, *et al.* Goserelin versus leuprolide before hysterectomy for uterine fibroids. *Int J Gynaecol Obstet* 2008; **101:** 178–83.

Malignant neoplasms. Goserelin is effective in the treatment of prostate cancer (p. 712.3). It has produced a response similar to that of orchidectomy (surgical removal of the testes) in patients with metastatic prostate cancer.[1] Goserelin has been combined with an anti-androgen such as flutamide to provide maximum androgen blockade, but this appears to produce modest additional benefits at most. There is some evidence[2,3] that adjuvant therapy with goserelin may improve survival in patients with localised or locally advanced prostate cancer when combined with radiotherapy or radical prostatectomy, and adjuvant use of goserelin appears to be more beneficial than neoadjuvant use.[2]

Goserelin may also be used as hormonal therapy in premenopausal women with advanced breast cancer (p. 702.1); it seems to be as effective as oophorectomy,[4] and use with tamoxifen is more effective than goserelin alone.[5] It is also used as an alternative or addition to adjuvant chemotherapy in pre- or peri-menopausal women with oestrogen-receptor positive early breast cancer,[6-12] and has been investigated for its potential to preserve ovarian function in this group.[12]

1. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566–77. Correction. *ibid.* 2005; **143:** 764–5.
2. Akaza H. Adjuvant goserelin improves clinical disease-free survival and reduces disease-related mortality in patients with locally advanced or localized prostate cancer. *BJU Int* 2004; **93:** 42–6.
3. Roach M, Izaguirre A. Goserelin acetate in combination with radiotherapy for prostate cancer. *Expert Opin Pharmacother* 2007; **8:** 257–64.
4. Taylor CW, *et al.* Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998; **16:** 994–9.
5. Klijn JGM, *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; **19:** 343–53.
6. Jakesz R, *et al.* Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002; **20:** 4621–7.
7. Jonat W, *et al.* Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002; **20:** 4628–35.
8. International Breast Cancer Study Group (IBCSG). Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1833–46.
9. Cheer SM, *et al.* Goserelin: a review of its use in the treatment of early breast cancer in premenopausal and perimenopausal women. *Drugs* 2005; **65:** 2639–55.
10. Baum M, *et al.* ZIPP International Collaborators' Group. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. *Eur J Cancer* 2006; **42:** 895–904.
11. Hackshaw A, *et al.* Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. *J Natl Cancer Inst* 2009; **101:** 341–9.
12. Sverrisdottir A, *et al.* Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. *Breast Cancer Res Treat* 2009; **117:** 561–7.

Mastalgia. For reference to the use of goserelin in mastalgia, see under Danazol, p. 2265.1.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). Although not licensed for use in children in the UK, the *BNFC* includes doses of goserelin for central precocious puberty. Implants are given by subcutaneous injection into the anterior abdominal wall; preparations that contain a dose of 3.6 mg are given once every 28 days, another containing 10.8 mg is given once every 12 weeks. Injections may be needed more frequently in some patients.

References to the use of goserelin.

1. Trueman JA, *et al.* Suppression of puberty with long-acting goserelin (Zoladex-LA): effect on gonadotrophin response to GnRH in the first treatment cycle. *Clin Endocrinol (Oxf)* 2002; **57:** 223–30.
2. Paterson WF, *et al.* Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. *Clin Endocrinol (Oxf)* 2004; **61:** 626–34.
3. Isaac H, *et al.* Efficacy of a monthly compared to 3-monthly depot GnRH analogue (goserelin) in the treatment of children with central precocious puberty. *Horm Res* 2007; **68:** 157–63.
4. Mouat F, *et al.* Initial growth deceleration during GnRH analogue therapy for precocious puberty. *Clin Endocrinol (Oxf)* 2009; **70:** 751–6.

Premenstrual syndrome. For reference to the use of goserelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug treatment, see under Gonadorelin, p. 2281.3.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1. Some women may have vaginal bleeding during initial therapy, which normally resolves spontaneously.

Pituitary apoplexy. Pituitary apoplexy (a clinical syndrome caused by haemorrhage and infarction of a pituitary adenoma) occurred in a few elderly patients with a symptomless pituitary adenoma who were given goserelin for advanced prostate cancer.[1,2] Symptoms included headache, vomiting, visual disturbances, gradual impairment of consciousness, intermittent fever, and progressive hyponatraemia. Symptoms were treated with corticosteroid replacement therapy.

1. Ando S, *et al.* Pituitary apoplexy after goserelin. *Lancet* 1995; **345:** 458.
2. Eaton HJ, *et al.* Rapid onset of pituitary apoplexy after goserelin implant for prostate cancer: need for heightened awareness. *Intern Med J* 2001; **31:** 313–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies goserelin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Goserelin is almost completely absorbed after subcutaneous injection, and has a serum elimination half-life of 2 to 4 hours, which may be increased in renal impairment. More than 90% of a dose is excreted in urine, as unchanged drug and metabolites.

Reviews.

1. Cockshott ID. Clinical pharmacokinetics of goserelin. *Clin Pharmacokinet* 2000; **39:** 27–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Goselin; Larmadex; Zoladex; ***Austral.***: Zoladex; ***Austria***: Zoladex; ***Belg.***: Zoladex; ***Braz.***: Zoladex; ***Canad.***: Zoladex; ***Chile***: Vacromil†; Vicromil†; Zoladex; ***China***: Zoladex (诺雷得); ***Cz.***: Zoladex; ***Denm.***: Zoladex; ***Fin.***: Zoladex; ***Fr.***: Zoladex; ***Ger.***: Zoladex; ***Gr.***: Zoladex; ***Hong Kong***: Zoladex; ***Hung.***: Zoladex; ***Indon.***: Zoladex; ***Irl.***: Zoladex; ***Israel***: Zoladex; ***Ital.***: Zoladex; ***Malaysia***: Zoladex; ***Mex.***: Zoladex; ***Neth.***: Zoladex; ***Norw.***: Zoladex; ***NZ***: Zoladex; ***Philipp.***: Zoladex; ***Pol.***: Zoladex; ***Port.***: Zoladex; ***Rus.***: Zoladex (Золадекс); ***S.Afr.***: Zoladex; ***Singapore***: Zoladex; ***Spain***: Zoladex; ***Swed.***: Zoladex; ***Switz.***: Zoladex; ***Thai.***: Zoladex; ***Turk.***: Zoladex; ***UK***: Novgos†; Zoladex; ***Ukr.***: Zoladex (Золадекс); ***USA***: Zoladex; ***Venez.***: Zoladex.

Multi-ingredient Preparations. ***Arg.***: Zolapack; ***Austral.***: ZolaCos CP; ***NZ***: ZolaCos CP.

Pharmacopoeial Preparations
BP 2014: Goserelin Implants.

Hexestrol *(rINN)*

Dihydrodiethylstilboestrol; Dihydrostilboestrol; Hexanoestrol; Hexestrolum; Hexoestrol; NSC-9894; Synestrol; Synoestrol; Гексэстрол.

4,4′-(1,2-Diethylethylene)diphenol.

$C_{18}H_{22}O_2$=270.4

CAS — 5635-50-7 (hexestrol); 84-16-2 (meso-hexestrol).

UNII — 10BI795R7D.

Profile

Hexestrol is a synthetic nonsteroidal oestrogen that is used for oestrogen replacement therapy and in the treatment of malignant neoplasms and gynaecological disorders.

Histrelin *(USAN, rINN)* ⊗

Histrelina; Histréline; Histrelinum; ORF-17070; RWJ-17070; Гистрелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*N*^{τ}-benzyl-D-histidyl-L-leucyl-L-argininyl-*N*-ethyl-L-prolinamide.

$C_{66}H_{86}N_{18}O_{12}$=1323.5

CAS — 76712-82-8.

ATC — L02AE05.

ATC Vet — QL02AE05.

UNII — H50H353W74.

Histrelin Acetate *(rINNM)* ⊗

Acetato de histrelina; Histrelina, acetato de; Histréline, Acétate d'; Histrelini Acetas; Гистрелина Ацетат.

$C_{66}H_{86}N_{18}O_{12}.xC_2H_4O_2.yH_2O$

CAS — 220810-26-4.

ATC — L02AE05.

ATC Vet — QL02AE05.

UNII — QMG7HLD1ZE.

Uses and Administration

Histrelin is an analogue of gonadorelin (p. 2280.3) with similar properties. A subcutaneous implant containing histrelin acetate 50 mg, and designed to release about 50 micrograms daily for 12 months, is used in the palliative treatment of advanced prostate cancer (p. 712.3).

Histrelin is used in the treatment of precocious puberty in children (see p. 2284.1). It has also been investigated in disorders related to the menstrual cycle, and in the treatment of acute porphyrias.

References.

1. Anderson KE, *et al.* A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. *Arch Intern Med* 1990; **150:** 1469–74.
2. Mortola JF, *et al.* Successful treatment of severe premenstrual syndrome by combined use of gonadotropin-releasing hormone agonist and estrogen/progestin. *J Clin Endocrinol Metab* 1991; **72:** 252A–F.
3. Cheung AP, Chang RJ. Pituitary responsiveness to gonadotrophin-releasing hormone agonist stimulation: a dose-response comparison of luteinizing hormone/follicle-stimulating hormone secretion in women with polycystic ovary syndrome and normal women. *Hum Reprod* 1995; **10:** 1054–9.
4. Chertin B, *et al.* An implant releasing the gonadotropin hormone-releasing hormone agonist histrelin maintains medical castration for up

to 30 months in metastatic prostate cancer. *J Urol (Baltimore)* 2000; **163:** 838–44.
5. Schlegel PN, *et al*. Effective long-term androgen suppression in men with prostate cancer using a hydrogel implant with the GnRH agonist histrelin. *Urology* 2001; **58:** 578–82.
6. Dineen MK, *et al*. An evaluation of the pharmacokinetics and pharmacodynamics of the histrelin implant for the palliative treatment of prostate cancer. *J Clin Pharmacol* 2005; **45:** 1245–9.
7. Schlegel PN. Histrelin Study Group. Efficacy and safety of histrelin subdermal implant in patients with advanced prostate cancer. *J Urol (Baltimore)* 2006; **175:** 1353–8.
8. Schlegel P. A review of the pharmacokinetic and pharmacological properties of a once-yearly administered histrelin acetate implant in the treatment of prostate cancer. *BJU Int* 2009; **103** (suppl 2): 7–13.
9. Crawford ED. A review of the use of histrelin acetate in the treatment of prostate cancer. *BJU Int* 2009; **103** (suppl 2): 14–22.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). Histrelin acetate has been given by subcutaneous injection in usual doses equivalent to histrelin 10 micrograms/kg daily. Alternatively, a subcutaneous implant containing histrelin acetate 50 mg and designed to release histrelin acetate 65 micrograms daily for 12 months may be used. The implant is not recommended for children under 2 years of age.

References to the use of histrelin.

1. Barradell LB, McTavish D. Histrelin: a review of its pharmacological properties and therapeutic role in central precocious puberty. *Drugs* 1993; **45:** 570–88.
2. Feuillan PP, *et al*. Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab* 1999; **84:** 44–9.
3. Klein KO, *et al*. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
4. Hirsch HJ, *et al*. The histrelin implant: a novel treatment for central precocious puberty. Abstract: *Pediatrics* 2005; **116:** 1534–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/116/6/e798 (accessed 04/12/07)
5. Eugster EA, *et al*. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab* 2007; **92:** 1697–1704.
6. Lewis KA, Eugster EA. Experience with the once-yearly histrelin (GnRHa) subcutaneous implant in the treatment of central precocious puberty. *Drug Des Devel Ther* 2009; **3:** 1–5.
7. Rahhal S, *et al*. Results of a second year of therapy with the 12-month histrelin implant for the treatment of central precocious puberty. *Int J Pediatr Endocrinol* 2009; **2009:** 812517.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Effects on the liver. A report of hepatotoxicity associated with a subcutaneous implant of histrelin acetate.[1]

1. Ricker JM, *et al*. Drug-induced liver injury caused by the histrelin (Vantus) subcutaneous implant. *South Med J* 2010; **103:** 84–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vantas; ***Belg.***: Vantasse; ***Canad.***: Vantas; ***Cz.***: Vantas; ***Denm.***: Vantas; ***Fin.***: Vantas; ***Ger.***: Vantas; ***Irl.***: Vantas; ***Malaysia***: Vantas†; ***Neth.***: Vantasse; ***Norw.***: Vantas; ***Pol.***: Vantas; ***Singapore***: Vantas; ***Spain***: Vantas; ***Swed.***: Vantas; ***Switz.***: Vantas; ***Thai.***: Vantas†; ***UK***: Vantas; ***Ukr.***: Vantas (Вантас); ***USA***: Supprelin; Vantas.

Human Menopausal Gonadotrophins *(BAN)* ⊗

Gonadotrofina menopáusica humana; Gonadotropina menopáusica humana; HMG; Org-31338; Urogonadotrophin.

ATC — G03GA02.
ATC Vet — QG03GA02.

Description. A purified extract of human postmenopausal urine containing follicle-stimulating hormone (FSH) and luteinising hormone (LH); the relative *in-vivo* activity is expressed as a ratio. Human menopausal gonadotrophins with a ratio of FSH:LH of 1:1 are known as menotrophin (see below).

Menotrophin *(BAN)* ⊗

Menotrofina; Menotropiini; Menotropin; Menotropina; Menotropins (USAN); Menotropinum.

CAS — 9002-68-0.
UNII — 5Y9QQM372Q.

Pharmacopoeias. In *Br.*, *Chin.*, and *Jpn*.

BP 2014: (Menotrophin). A dry preparation containing glycoprotein gonadotrophins possessing follicle-stimulating and luteinising activities. It contains not less than 40 units of follicle-stimulating hormone activity per mg. The ratio of units of luteinising hormone activity to units of follicle-stimulating hormone activity is about 1. The preparation is exclusively or mainly of pituitary origin and obtained from the urine of postmenopausal women but, when necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the above ratio. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers. Protect from light.

Uses and Administration

Human menopausal gonadotrophins possess both follicle-stimulating hormone (FSH) activity (see p. 2278.2) and luteinising hormone (LH) activity (see p. 2287.1).

Human menopausal gonadotrophins are used in the treatment of male and female infertility due to hypogonadism. In anovulatory infertility unresponsive to clomifene, human menopausal gonadotrophins are given to induce follicular maturation and are followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation, a topic discussed further on p. 2253.1.

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or plasma-oestradiol or by ultrasonic visualisation of follicles, or a combination of these. Human menopausal gonadotrophins may be given daily by intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and gradually adjusted if necessary until an adequate response is achieved. Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units (see p. 2258.1). In menstruating patients treatment should be started within the first 7 days of the menstrual cycle. In the UK it has been suggested that the treatment course should be abandoned if no response is seen in 3 weeks. The course may be repeated at least twice more if necessary. In the USA, licensed product information recommends a maximum daily dose of 450 units and that a course should not exceed 12 days.

An alternative schedule is to give three equal doses by intramuscular or subcutaneous injection, each providing 225 to 375 units of FSH on alternate days followed by chorionic gonadotrophin one week after the first dose.

In IVF and other assisted conception techniques, human menopausal gonadotrophins are used with chorionic gonadotrophin and sometimes also clomifene citrate or a gonadorelin analogue. Stimulation of follicular growth is produced by human menopausal gonadotrophins given by intramuscular or subcutaneous injection, in a dose providing 75 to 300 units of FSH daily, usually beginning on the 2nd or 3rd day of the menstrual cycle. Treatment is continued until an adequate response is obtained and the final injection of human menopausal gonadotrophins is followed 1 to 2 days later with up to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is carried out about 32 to 36 hours later. US licensed product information recommends a starting dose of 225 units daily in women who have undergone pituitary suppression, and a maximum daily dose of 450 units.

In **men with infertility** due to hypogonadotrophic hypogonadism (see Infertility, p. 2253.1), spermatogenesis is stimulated with chorionic gonadotrophin and then human menopausal gonadotrophins are added in a dose of 75 or 150 units of FSH two or three times weekly by intramuscular or subcutaneous injection. Treatment should be continued for at least 3 or 4 months.

Infertility. Systematic reviews initially found no evidence of a significant difference in efficacy for human menopausal gonadotrophins compared with urinary-derived gonadotrophins in women with anovulatory infertility[1] (p. 2253.1), or compared with recombinant follicle-stimulating hormone in assisted reproduction cycles.[2] However, it has since been suggested that there is evidence of an improved live-birth rate when human menopausal gonadotrophins are used in current IVF protocols rather than follicle-stimulating hormone.[3,4] UK guidelines suggest that either urinary or recombinant gonadotrophins may be used during controlled ovarian stimulation in IVF treatment.[5]

1. Nugent D, *et al*. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 16/09/05).
2. Van Wely M, *et al*. Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. Coomarasamy A, *et al*. Urinary hMG versus recombinant FSH for controlled ovarian hyperstimulation following an agonist long down-regulation protocol in IVF or ICSI treatment: a systematic review and meta-analysis. *Hum Reprod* 2008; **23:** 310–15.
4. Afnan M. Identifying real differences in live birth rates between HMG and rFSH in IVF. *Reprod Biomed Online* 2009; **18** (suppl 2): 25–30.
5. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)

Adverse Effects

Human menopausal gonadotrophins may cause dose-related ovarian hyperstimulation varying from mild ovarian enlargement and abdominal discomfort to severe hyperstimulation with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. Rupture of ovarian cysts and intraperitoneal haemorrhage has occurred, usually after pelvic examination. Fatalities have been reported.

Hypersensitivity reactions and local reactions at the injection site may occur. Nausea and vomiting, joint pains and fever have been reported; gynaecomastia, acne, and weight gain have occurred in men.

Carcinogenicity. In a case-control study of 4575 women with primary invasive breast cancer, an evaluation of risk factors found that, overall, the use of infertility drugs was not associated with an increased risk of breast cancer.[1] However, subgroup analysis of individual drugs found that the use of human menopausal gonadotrophins for at least 6 months or 6 treatment cycles was associated with a risk of breast cancer that was 2 to 3 times greater than for women who had never received any fertility treatment. The authors of this study noted that these results were based on small numbers and that other studies had failed to show an association between fertility treatment and breast cancer.

1. Burkman RT, *et al*. Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 2003; **79:** 844–51.

Effects on the ovary. Ovarian hyperstimulation syndrome after use of human menopausal gonadotrophins in 4 women progressed to acute adnexal torsion.[1] Deep-vein thrombosis has also been a rare complication of ovarian hyperstimulation syndrome associated with the use of human menopausal gonadotrophins plus chorionic gonadotrophin.[2,3] In another case in which thrombosis followed the use of human menopausal gonadotrophins alone, hereditary activated protein C resistance and smoking may have been contributing factors.[4]

1. Kemmann E, *et al*. Adnexal torsion in menotropin-induced pregnancies. *Obstet Gynecol* 1990; **76:** 403–6.
2. Kaaja R, *et al*. Severe ovarian hyperstimulation syndrome and deep venous thrombosis. *Lancet* 1989; **ii:** 1043.
3. Sobande AA, *et al*. Ovarian hyperstimulation syndrome and deep vein thrombosis. *Saudi Med J* 2000; **21:** 783–4.
4. Ludwig M, *et al*. Deep vein thrombosis during administration of HMG for ovarian stimulation. *Arch Gynecol Obstet* 2000; **263:** 139–41.

Precautions

Human menopausal gonadotrophins should not be given to pregnant patients. Use should be avoided in patients with abnormal genital bleeding, hormone sensitive malignancies such as those of the breast, uterus, prostate, ovaries or testes, or ovarian cysts or enlargement not caused by the polycystic ovary syndrome. Pituitary or hypothalamic lesions, adrenal or thyroid disorders, and hyperprolactinaemia should be treated appropriately to exclude them as causes of infertility before attempting therapy with human menopausal gonadotrophins. Patients who have ovarian enlargement are at risk of rupture; pelvic examinations should be avoided or carried out with care and the recommendation has been made that sexual intercourse should be avoided while there is such a risk.

There is a risk of multiple births.

Interactions

In women who show evidence of excessive ovarian stimulation while receiving human menopausal gonadotrophins the use of drugs with luteinising-hormone (LH) activity increases the risk of ovarian hyperstimulation syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: HMG Ferring; Lifecell; Menopur; ***Austral.***: Humegon†; Menopur; ***Austria***: Menopur; ***Belg.***: Menopur; ***Braz.***: Merional-HMG; Pergonal†; ***Canad.***: Menopur; Repronex; ***Chile***: Menopur; ***China***: Lebaode (乐宝得); Menopur (贺美奇); ***Cz.***: Menogon; Menopur; Merional; ***Denm.***: Menopur; ***Fin.***: Menopur; ***Fr.***: Menopur; ***Ger.***: Menogon; ***Gr.***: Altermon; Humegon; Menogon; Menopur; Merional; Pergogreen; Pergonal; ***Hong Kong***: Menogon; Menopur; Merional†; Pergonal†; ***Hung.***: Menopur; Merional; ***India***: Eventin; Fergonad-M; Follilutin; Follinis; GMH; Gynogen; Humegon; Humog; IVF-M; Materna HMG; Menodac; Menogon; Menolife; Menonys; Menopur; Menotec; Menovul; Ovugraf-HP; Ovulate-M; Pergonal; Pregnorm; ***Irl.***: Humegon†; Menopur; ***Israel***: Menogon; Menopur; ***Ital.***: Menogon; Meropur; ***Jpn***: Gonador-yl†; ***Malaysia***: Menopur; ***Mex.***: Merapur HP; Merional; ***Neth.***: Menogon†; Menopur; ***Norw.***: Menopur; ***Philipp.***: Menogon; ***Pol.***: Menopur; Merional; ***Port.***: Menopur; ***Rus.***: Menogon

All cross-references refer to entries in Volume A

(Меногон)†; Menopur (Менопур); Pergonal (Пергонал); ***S.Afr.***: Menopur; ***Singapore***: Menogon; Menopur; ***Spain***: HMG; Menopur; ***Swed.***: Menopur; ***Switz.***: Menopur; Merional; ***Thai.***: IVF-M; Menogon; Menopur; ***Turk.***: Humegon; Menogon; Menopur; Merional; Pergonal; ***UK***: Menopur; Merional; ***Ukr.***: Menogon (Меногон); Menopur (Менопур); Merional (Мерионал); ***USA***: Humegon†; Menopur; Repronex.

Pharmacopoeial Preparations
BP 2014: Menotrophin Injection.

Hydroxyestrone Diacetate

Hidroxiestrona, diacetato de; 16α-Hydroxyoestrone Diacetate.
3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.
$C_{22}H_{26}O_5$=370.4
CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (hydroxyestrone diacetate).

Profile

Hydroxyestrone diacetate is an oestrogen (see Estradiol, p. 2271.1). It has been given in vulvovaginal disorders and for female infertility.

Hydroxyprogesterone Caproate

(BANM, rINN)

17-AHPC; Caproate d'Hydroxyprogestérone; Caproato de hidroxiprogesterona; Hidroksiprogesteron Heksanoat; Hidroksiprogesteron Kaproat; Hidroxiprogesterona, caproato de; Hydroxyprogesterone Hexanoate; Hydroxyprogesteroni Caproas; NSC-17592; Гидроксипрогестерона Капроат.
3,20-Dioxopregn-4-en-17α-yl hexanoate; 17α-Hydroxypregn-4-ene-3,20-dione hexanoate.
$C_{27}H_{40}O_4$=428.6
CAS — 68-96-2 (hydroxyprogesterone); 630-56-8 (hydroxyprogesterone caproate).
ATC — G03DA03.
ATC Vet — QG03DA03.
UNII — 276F2O42F5.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Hydroxyprogesterone Caproate). A white or creamy-white, crystalline powder. Odourless or having a slight odour. Insoluble in water; soluble in ether; slightly soluble in benzene. Protect from light. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Hydroxyprogesterone caproate is a progestogen structurally related to progesterone (p. 2300.2) that may be given to reduce the risk of recurrent miscarriage and of premature birth (see Premature Labour, below). It has also been used, often with an oestrogen, in the management of various menstrual disorders such as oligomenorrhoea or amenorrhoea (p. 2251.3), and dysmenorrhoea (p. 8.2).

In the prevention of recurrent miscarriage associated with proven progesterone deficiency, doses of 250 to 500 mg weekly by intramuscular injection have been given during the first half of pregnancy.

Hydroxyprogesterone caproate may also be used to reduce the risk of premature birth in women with a singleton pregnancy who have a history of singleton spontaneous premature delivery. A dose of 250 mg is given by deep intramuscular injection once weekly, starting between 16 weeks 0 days, and 20 weeks 6 days, of gestation. Treatment is continued until the start of week 37 or delivery, whichever occurs first.

In the management of menstrual disorders, a single intramuscular dose of hydroxyprogesterone caproate 250 mg has been given sometime between days 16 and 20 of the menstrual cycle.

The acetate and the enantate have also been used.

Premature labour. In women who have a history of spontaneous premature delivery (p. 2131.1), there is some evidence to suggest that prophylactic progesterone may reduce the risk for premature delivery in subsequent pregnancies.[1,2] Most studies have used vaginal progesterone formulations or intramuscular hydroxyprogesterone caproate, generally starting around week 16 to 20 of gestation and continuing through to week 36 or delivery. In women with a singleton pregnancy, who have a history of spontaneous premature delivery, prophylactic therapy can reduce the risk of perinatal death and of preterm delivery (before 34 weeks of gestation). Neonatal benefits include a reduction in the risks of low birth-weight (less than 2.5 kg), morbidity including necrotising enterocolitis, the need for assisted ventilation, and neonatal death. Preterm birth has also been reduced in women at risk because of a short cervix, although less information is available about other maternal and neonatal outcomes in this group. The effects of prophylactic therapy in women with other risk factors for premature delivery, and those presenting with threatened premature labour, are uncertain, although there is limited evidence to suggest that the risk of infant birth-weight less than 2.5 kg may be reduced. However, prophylactic therapy does not appear to be of benefit in multiple gestations. Overall, further study is required, particularly to identify the optimal timing, route, and dose of treatment, and long-term effects on infant health.[2]

An expert committee in the USA has recommended[3] that progesterone or hydroxyprogesterone caproate should be offered to women with a singleton pregnancy and a history of spontaneous preterm singleton delivery, starting at 16 to 24 weeks of gestation. It also recommended the use of vaginal progesterone as an option for women with a singleton pregnancy, without a history of preterm birth, who have a short cervix (20 mm or less) before or at 24 weeks of gestation. In Canada,[4] a history of preterm labour is considered an indication for intramuscular hydroxyprogesterone caproate 250 mg weekly, or vaginal progesterone 100 mg daily, given from 20 weeks of gestation until the risk of prematurity is low. For women with a short cervix (less than 15 mm at 22 to 26 weeks of gestation), vaginal progesterone 200 mg daily may be used.

1. Schmouder VM, *et al.* The rebirth of progesterone in the prevention of preterm labor. *Ann Pharmacother* 2013; **47:** 527–36.
2. Dodd JM, *et al.* Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2013 (accessed 26/11/13).
3. American College of Obstetricians and Gynecologists. Practice bulletin 130: prediction and prevention of preterm birth. *Obstet Gynecol* 2012; **120:** 964–73.
4. Farine D, *et al.* Society of Obstetricians and Gynaecologists of Canada. The use of progesterone for prevention of preterm birth. *J Obstet Gynaecol Can* 2008; **30:** 67–71. Also available at: http://www.sogc.org/guidelines/documents/guiJOGC202TU080l.pdf (accessed 03/12/13)

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3).

There may be local reactions at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may occur during or immediately after injection of hydroxyprogesterone caproate but can be avoided by injecting the drug very slowly.

Pregnancy. Abnormalities reported in infants born to mothers who had received hydroxyprogesterone during pregnancy have included tetralogy of Fallot in one infant,[1] genito-urinary abnormalities in 2 infants,[2] and adrenocortical carcinoma in one infant.[3]

1. Heinonen OP, *et al.* Cardiovascular birth defects and antenatal exposure to female sex hormones. *N Engl J Med* 1977; **296:** 67–70.
2. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.
3. Mann JR, *et al.* Transplacental carcinogenesis (adrenocortical carcinoma) associated with hydroxyprogesterone hexanoate. *Lancet* 1983; **ii:** 580.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Pharmacokinetics

After a single intramuscular dose of 1 g, peak serum concentrations of hydroxyprogesterone caproate occur in 3 to 7 days, and the elimination half-life is about 7.8 days. Hydroxyprogesterone caproate is highly bound to plasma proteins. It is extensively metabolised, mainly via the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Both conjugated metabolites and free steroids are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gestageno; Proluton Depot; ***Austria***: Proluton Depot; ***Cz.***: Neolutin Forte; ***Fr.***: Progesterone-retard Pharlon; ***Ger.***: Progesteron-Depot†; Proluton Depot†; ***Gr.***: Proluton Depot; ***India***: Anin; Arisafe; Darvon; Depovig; Fetugest; Gestaur; Gestimax; Gynonys; Hiprogress; HPC Depot; Hylex; Hyprogres; Hyprosafe; LGP-H; Maintane; Maloxy; Novadepot; NT-Natal; Nunest; Proluton Depot; ***Ital.***: Lentogest; Proluton; ***Malaysia***: Hiprogin; Proluton Depot; ***Mex.***: Capostent†; Primolut Depot; ***Philipp.***: Proluton Depot†; ***Pol.***: Kaprogest†; ***Thai.***: Proluton Depot; ***Turk.***: Proluton Depot; ***USA***: Makena.

Multi-ingredient Preparations. ***Arg.***: Dos Dias N; Primosiston; ***Braz.***: Gestadinona; Trinestril; ***Mex.***: Gravidinona.

Pharmacopoeial Preparations
USP 36: Hydroxyprogesterone Caproate Injection.

Leuprorelin *(BAN, rINN)* ⊗

Leuprolide; Leuproreliini; Leuprorelina; Leuprorelinas; Leuproréline; Leuprorelinum; Лейпрорелин.
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.
$C_{59}H_{84}N_{16}O_{12}$=1209.4
CAS — 53714-56-0.
ATC — L02AE02.
ATC Vet — QL02AE02.
UNII — EFY6W0M8TG.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Leuprorelin). A synthetic nonapeptide analogue of the hypothalamic peptide gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white, hygroscopic, powder. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Leuprorelin Acetate *(BANM, rINNM)* ⊗

Abbott-43818; Acetato de leuprorelina; Leuprolide Acetate (USAN); Leuproreliniasetaatti; Leuprorelina, acetato de; Leuprorelinacetat; Leuproréline, Acétate de; Leuprorelini Acetas; Löprorelin Asetat; TAP-144; Лейпрорелина Ацетат.
$C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$=1269.5
CAS — 74381-53-6.
ATC — L02AE02.
ATC Vet — QL02AE02.
UNII — 37JNS02E7V.

Pharmacopoeias. In *US.*

USP 36: (Leuprolide Acetate). Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Leuprorelin is an analogue of gonadorelin (p. 2280.3) with similar properties. Continuous administration is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate; it may also be used in the treatment of breast cancer in premenopausal women. In the management of endometriosis, leuprorelin may be used for pain relief and endometrial reduction, and for preparation before endometrial ablation or resection. It may also be used preoperatively to reduce the size of uterine fibroids and associated bleeding. For its use in precocious puberty, see p. 2286.2. Leuprorelin has also been given in other sex-hormone-related disorders. It is used as the acetate.

In the palliative treatment of **advanced prostate cancer**, leuprorelin acetate may be given by subcutaneous injection in a usual single daily dose of 1 mg. It is also given subcutaneously or intramuscularly as depot preparations but the dosage and route of these may differ between countries. In the USA, the dose is 7.5 mg monthly, 22.5 mg every 3 months, 30 mg every 4 months, or 45 mg every 6 months, given subcutaneously or intramuscularly, depending on the preparation. In the UK, leuprorelin acetate may also be used in advanced prostate cancer, as well as medical treatment of locally advanced cancer, as an adjuvant to surgery in locally advanced cancer at high risk of progression, or as an adjuvant to radiotherapy in high-risk localised or locally advanced disease. A dose of 3.75 mg may be given once a month, by subcutaneous or intramuscular injection, or 11.25 mg may be given subcutaneously every 3 months. A nonbiodegradable titanium alloy implant, which was inserted subcutaneously into the inner part of the upper arm, was also available in the USA for advanced disease. It contained 72 mg of leuprorelin acetate and delivered the drug at a controlled rate of 120 micrograms daily for 12 months. An anti-androgen such as cyproterone acetate may be given for several days before beginning leuprorelin therapy and continued for about 3 weeks, to avoid the risk of a disease flare.

Depot injections of leuprorelin acetate may also be used for hormonal therapy in the management of **breast cancer**; for example, subcutaneous doses of 3.75 mg monthly, or 11.25 mg once every 3 months, may be given.

For the management of **endometriosis**, leuprorelin acetate 3.75 mg may be given as a monthly depot injection intramuscularly or subcutaneously, depending on the preparation. Alternatively, 11.25 mg may be given as an intramuscular depot every 3 months. Treatment is started during the first 5 days of the menstrual cycle, and may be continued for up to 6 months. To prepare for uterine surgery such as endometrial ablation or resection, a single 3.75 mg depot injection may be given 5 to 6 weeks before the procedure.

When used for pre-operative management of **uterine fibroids**, leuprorelin is usually given for about 3 months, but may be continued for up to 6 months. Leuprorelin acetate 3.75 mg may be given as a monthly depot injection

intramuscularly or subcutaneously, depending on the preparation. Alternatively, a single intramuscular 3-month depot dose of 11.25 mg may be used.

General references.

1. Plosker GL, Brogden RN. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. *Drugs* 1994; **48:** 930–67.
2. Wilson AC, *et al*. Leuprolide acetate: a drug of diverse clinical applications. *Expert Opin Invest Drugs* 2007; **16:** 1851–63.

Administration in children. Leuprorelin may be used in the management of central precocious puberty—see below.

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p. 2347.1.

References to the use of leuprorelin.

1. Gabrilove JL, *et al*. Effect of long-acting gonadotropin-releasing hormone analog (leuprolide) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. *J Clin Endocrinol Metab* 1989; **69:** 629–32.
2. Eri LM, Tveter KJ. A prospective, placebo-controlled study of the luteinizing hormone-releasing hormone agonist leuprolide as treatment for patients with benign prostatic hyperplasia. *J Urol (Baltimore)* 1993; **150:** 359–64.
3. Eri LM, Tveter KJ. Safety, side effects and patient acceptance of the luteinizing hormone releasing hormone agonist leuprolide in treatment of benign prostatic hyperplasia. *J Urol (Baltimore)* 1994; **152:** 448–52.
4. Eri LM, *et al*. Effects on the endocrine system of long-term treatment with the luteinizing hormone-releasing hormone agonist leuprolide in patients with benign prostatic hyperplasia. *Scand J Clin Lab Invest* 1996; **56:** 319–25.

Disturbed behaviour. Leuprorelin has been used in the treatment of men with paraphilias (p. 1030.2). Case series have reported reductions in abnormal sexual thoughts and behaviours.[1-3]

1. Briken P, *et al*. Treatment of paraphilia with luteinizing hormone-releasing hormone agonists. *J Sex Marital Ther* 2001; **27:** 45–55.
2. Krueger RB, Kaplan MS. Depot-leuprolide acetate for treatment of paraphilias: a report of twelve cases. *Arch Sex Behav* 2001; **30:** 409–22.
3. Saleh FM, *et al*. Treatment of paraphilia in young adults with leuprolide acetate: a preliminary case report series. *J Forensic Sci* 2004; **49:** 1343–8.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' hormone replacement therapy can be used to prevent this.

References to the use of leuprorelin.

1. Hornstein MD, *et al*. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol* 1998; **91:** 16–24.
2. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol* 1999; **93:** 51–8.
3. Takeuchi H, *et al*. A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26:** 325–31.
4. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 2002; **99:** 709–19.
5. Rotondi M, *et al*. Depot leuprorelin acetate versus danazol in the treatment of infertile women with symptomatic endometriosis. *Eur J Gynaecol Oncol* 2002; **23:** 523–6.
6. Schlaff WD, *et al*. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. *Fertil Steril* 2006; **85:** 314–25.
7. Bedaiwy MA, Casper RF. Treatment with leuprolide acetate and hormonal add-back for up to 10 years in stage IV endometriosis patients with chronic pelvic pain. *Fertil Steril* 2006; **86:** 220–2.

Fibroids. Gonadorelin analogues may be of some benefit as an adjunct or alternative to surgery in women with uterine fibroids (p. 2281.2), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of leuprorelin.

1. Friedman AJ, *et al*. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. *Obstet Gynecol* 1991; **77:** 720–5.
2. Friedman AJ, *et al*. Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin 'add-back' for 2 years. *Hum Reprod* 1994; **9:** 1618–25.
3. Zullo F, *et al*. A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: efficacy and ultrasonographic predictors. *Am J Obstet Gynecol* 1998; **178:** 108–112.
4. Scialli AR, Levi AJ. Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. *Fertil Steril* 2000; **74:** 540–6.
5. Jasonni VM, *et al*. Randomized double-blind study evaluating the efficacy on uterine fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate depot treatment before myomectomy. *Acta Obstet Gynecol Scand* 2001; **80:** 956–8.

Hirsutism. The mainstay of drug treatment for hirsutism (p. 2262.1) has been an anti-androgen, usually cyproterone acetate or spironolactone. Although gonadorelin analogues have been used, and are effective, they must be given parenterally or nasally and may produce menopausal effects, notably osteoporosis.

References to the use of leuprorelin.

1. Elkind-Hirsch KE, *et al*. Combination gonadotropin-releasing hormone agonist and oral contraceptive therapy improves treatment of hirsute women with ovarian hyperandrogenism. *Fertil Steril* 1995; **63:** 970–8.
2. Azziz R, *et al*. Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *J Clin Endocrinol Metab* 1995; **80:** 3406–11.
3. Ciotta L, *et al*. Clinical and hormonal effects of gonadotropin-releasing hormone agonist plus an oral contraceptive in severely hirsute patients with polycystic ovary disease. *Fertil Steril* 1996; **65:** 61–7.
4. Bayhan G, *et al*. A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. *Clin Exp Obstet Gynecol* 2000; **27:** 203–6.

Infertility. Gonadorelin analogues are used in the treatment of infertility—see p. 2253.1.

References to the use of leuprorelin.

1. Stone BA, *et al*. Gonadotrophin and estradiol levels during ovarian stimulation in women treated with leuprolide acetate. *Obstet Gynecol* 1989; **73:** 990–5.
2. Sathanandan M, *et al*. Adjuvant leuprolide in normal, abnormal, and poor responders to controlled ovarian hyperstimulation for in vitro fertilization/gamete intrafallopian transfer. *Fertil Steril* 1989; **51:** 998–1006.
3. Filicori M, *et al*. Different gonadotropin and leuprorelin ovulation induction regimens markedly affect follicular fluid hormone levels and folliculogenesis. *Fertil Steril* 1996; **65:** 387–93.
4. Surrey ES, *et al*. Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002; **78:** 699–704.

Malignant neoplasms. Gonadorelin analogues are used as an alternative to orchidectomy in the management of advanced malignant neoplasms of the prostate (p. 712.3). Such therapy is as effective as orchidectomy in prolonging survival;[1] combination of leuprorelin or other gonadorelin analogues with nonsteroidal anti-androgens to produce maximal androgen blockade produces only modest additional benefit.[2] Intermittent maximal androgen blockade is being studied in an attempt to improve results, and leuprorelin is also under investigation as neoadjuvant therapy in localised disease.[3] Leuprorelin is also used for ovarian ablation[4] in premenopausal women with breast cancer (p. 702.1).

There are isolated reports of endometrial cancer[5] and ovarian cancer[6] responding to leuprorelin, but the role of the gonadorelin analogues in these conditions is much less well established.

1. Seidenfeld J, *et al*. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566–77.
2. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000; **355:** 1491–8.
3. Persad R. Leuprorelin acetate in prostate cancer: a European update. *Int J Clin Pract* 2002; **56:** 389–96.
4. Schmid P, *et al*. Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). *Anticancer Res* 2002; **22:** 2325–32.
5. Noci I, *et al*. Longstanding survival without cancer progression in a patient affected by endometrial carcinoma treated primarily with leuprolide. *Br J Cancer* 2001; **85:** 333–6.
6. Paskeviciute L, *et al*. No rules without exception: long-term complete remission observed in a study using a LH-RH agonist in platinum-refractory ovarian cancer. *Gynecol Oncol* 2002; **86:** 297–301.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). Leuprorelin may be used, although the dosages and routes of administration can vary between products in different countries. In the USA, leuprorelin acetate may be given by intramuscular depot injection once every month in the following initial doses according to weight:

- up to 25 kg: 7.5 mg
- 25 to 37.5 kg: 11.25 mg
- more than 37.5 kg: 15 mg

The dose should be adjusted according to response, and may be titrated upwards in steps of 3.75 mg at the next monthly dose. Depot injections containing 11.25 mg or 30 mg for intramuscular use once every 3 months are also available.

Leuprorelin acetate has also been given in a dose of 50 micrograms/kg daily by subcutaneous injection. This should be adjusted according to response, and may be titrated upwards in steps of 10 micrograms/kg daily.

Although leuprorelin is not licensed for use in children in the UK, the *BNFC* includes a dose of 3.75 mg, given once every 4 weeks as a subcutaneous or intramuscular depot injection; this dose may be halved for children weighing less than 20 kg. Alternatively, a dose of 11.25 mg may be given once every 12 weeks.

References to the use of leuprorelin.

1. Carel J-C, *et al*. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). *J Clin Endocrinol Metab* 2002; **87:** 4111–16.
2. Tanaka T, *et al*. Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function: the TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab* 2005; **90:** 1371–6.
3. Neely EK, *et al*. Leuprolide acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. *Int J Pediatr Endocrinol* 2010; **2010:** 398639.
4. Lee PA, *et al*. Efficacy of leuprolide acetate 1-month depot for central precocious puberty (CPP): growth outcomes during a prospective, longitudinal study. *Int J Pediatr Endocrinol* 2011; **2011:** 7.
5. Jaruratanasirikul S, Thaiwong M. Outcome of gonadotropin-releasing analog treatment for children with central precocious puberty: 15-year experience in southern Thailand. *J Pediatr Endocrinol Metab* 2011; **24:** 519–23.
6. Lee PA, *et al*. Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty. *J Clin Endocrinol Metab* 2012; **97:** 1572–80.

Premenstrual syndrome. For reference to the use of leuprorelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug therapy, see under Gonadorelin, p. 2281.3.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1. Thrombocytopenia and leucopenia have been reported rarely.

Benign intracranial hypertension. Increased intracranial pressure associated with leuprorelin treatment has been reported in a few isolated cases.[1,2]

1. Arber N, *et al*. Pseudotumor cerebri associated with leuprorelin acetate. *Lancet* 1990; **335:** 668.
2. Boot JH. Pseudotumour cerebri as a side effect of leuprorelin acetate. *Ir J Med Sci* 1996; **165:** 60.

Effects on the eyes. Leuprorelin may be associated with blurred vision, usually lasting 1 to 2 hours after injection, but in rare instances longer.[1] Haemorrhage or occlusion of intra-ocular blood vessels, ocular pain, and lid oedema have also been reported but the association is less well established.

1. Fraunfelder FT, Edwards R. Possible ocular adverse effects associated with leuprolide injections. *JAMA* 1995; **273:** 773–4.

Effects on the liver. A report of hepatotoxicity associated with the use of leuprorelin.[1]

1. Gabbi C, *et al*. Nonalcoholic fatty liver disease induced by leuprorelin acetate. *J Clin Gastroenterol* 2008; **42:** 107–10.

Hypersensitivity. An anaphylactic reaction started within 5 minutes of the injection of a leuprorelin depot formulation in a patient with prostate cancer.[1] Recurrent anaphylaxis developed in another patient given a depot injection of leuprorelin acetate for endometriosis, requiring both acute and chronic management.[2]

1. Taylor JD. Anaphylactic reaction to LHRH analogue, leuprorelin. *Med J Aust* 1994; **161:** 455.
2. Letterie GS, *et al*. Recurrent anaphylaxis to a depot form of GnRH analogue. *Obstet Gynecol* 1991; **78:** 943–6.

Local reactions. Local reactions, including erythema, pain, induration, granulomas, and sterile abscess are particularly associated with depot injections of gonadorelin analogues such as leuprorelin and triptorelin;[1-9] they may also occur with subcutaneous daily injection.[1] It has been suggested that the depot vehicle, a lactic acid-glycolic acid copolymer, may be responsible for many, although not all, such reactions.[1-5] Reactions are claimed to be more prevalent in children than in adults:[4] an incidence of about 5% of patients has been suggested. Reactions are apparently idiosyncratic and may occur at any time during therapy, may be intermittent, or may never recur.[4]

1. Manasco PK, *et al*. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123:** 334–5.
2. Neely EK, *et al*. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123:** 335.
3. Tonini G, *et al*. Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126:** 159.
4. Neely EK, *et al*. Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126:** 159–60.
5. Yasukawa K, *et al*. Leuprorelin acetate granulomas: case reports and review of the literature. *Br J Dermatol* 2005; **152:** 1045–7.
6. Dangle P, *et al*. Noninfective cutaneous granuloma with leuprorelin acetate—reality or myth. *Urology* 2007; **69:** 779.e5–6.
7. Shiota M, *et al*. Injection-site granulomas resulting from the administration of both leuprorelin acetate and goserelin acetate for the treatment of prostatic cancer. *J Nippon Med Sch* 2007; **74:** 306–8.
8. Vieu C, *et al*. Granulome sur le site d'injection de leuproréline retard: réaction à corps étranger à l'excipient? *Ann Dermatol Venereol* 2007; **134:** 771–3.
9. Watanabe T, *et al*. A morphological study of granulomas induced by subcutaneous injection of leuprorelin acetate. *J Cutan Pathol* 2009; **36:** 1299–1302.

Pituitary apoplexy. Pituitary apoplexy occurred shortly after the injection of a depot formulation of leuprorelin for the treatment of prostate cancer in 2 patients with occult pituitary adenomas.[1,2] In a woman receiving leuprorelin daily in preparation for oocyte donation, symptoms began after the third dose.[3] Signs and symptoms in these cases included headache, visual disturbances, generalised weakness, nausea and vomiting, and haemorrhagic necrosis of the macroadenoma.

1. Morsi A, *et al*. Pituitary apoplexy after leuprolide administration for carcinoma of the prostate. *Clin Endocrinol (Oxf)* 1996; **44:** 121–4.
2. Reznik Y, *et al*. Pituitary apoplexy of a gonadotroph adenoma following gonadotrophin releasing hormone agonist therapy for prostatic cancer. *J Endocrinol Invest* 1997; **20:** 566–8.
3. Engel G, *et al*. Pituitary apoplexy after leuprolide injection for ovum donation. *J Adolesc Health* 2003; **32:** 89–93.

All cross-references refer to entries in Volume A

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies leuprorelin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Leuprorelin acetate is not active when given orally but is well absorbed on subcutaneous or intramuscular injection. After a parenteral dose it has an elimination half-life of about 3 hours.

References.

1. Sennello LT, *et al*. Single-dose pharmacokinetics ofleuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci* 1986; **75:** 158–60.
2. Periti P, *et al*. Clinical pharmacokinetics of depot leuprorelin. *Clin Pharmacokinet* 2002; **41:** 485–504.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Eligard; Lectrum; Leprid; Lupron; ***Austral.***: Eligard; Lucrin; ***Austria***: Eligard; Enantone; Sixantone; Trenantone; ***Belg.***: Depo-Eligard; Lucrin; ***Braz.***: Eligard; Lectrum; Lorelin; Lupron; Relisert; ***Canad.***: Eligard; Lupron; ***Chile***: Eligard; Lupron; ***China***: Enantone (抑那通); ***Cz.***: Eligard; Lucrin; ***Denm.***: Eligard; Procren; Prostap†; ***Fin.***: Eligard; Enanton; Procren; ***Fr.***: Eligard; Enantone; ***Ger.***: Eligard; Enantone-Gyn; Enantone; Leupro-Sandoz†; Leuprone†; Sixantone; Trenantone; ***Gr.***: Daronda; Elityran; Leuprol; ***Hong Kong***: Enantone; Lorelin; ***Hung.***: Eligard; Lucrin; ***India***: Eligard; Leuprofact; Lucrin; Lupride; ***Indon.***: Endrolin; Lectrum; Tapros; ***Irl.***: Eligard; Prostap; ***Israel***: Eligard†; Lucrin; ***Ital.***: Eligard; Enantone; ***Jpn***: Leuplin; Lupron†; ***Malaysia***: Lucrin; ***Mex.***: Lectrum; Lorelin; Lucrin; Prelar; Prostide; ***Neth.***: Daronda†; Eligard; Lucrin; ***Norw.***: Eligard; Enanton; Procren; ***NZ***: Eligard; Lucrin; ***Philipp.***: Luphere; Luprolex; ***Pol.***: Eligard; Lucrin Depot; ***Port.***: Eligard; Lucrin; ***Rus.***: Eligard (Элигард); Lucrin (Люкрин); ***S.Afr.***: Lucrin†; ***Singapore***: Lucrin; ***Spain***: Eligard; Ginecrin; Lutrate; Procrin; ***Swed.***: Eligard; Enanton; Procren; ***Switz.***: Eligard; Lucrin; ***Thai.***: Enantone; ***Turk.***: Lucrin; ***UK***: Prostap; ***Ukr.***: Eligard (Элигард); ***USA***: Eligard; Lupron; ***Venez.***: Lupron.

Multi-ingredient Preparations. ***USA***: Lupaneta Pack.

Pharmacopoeial Preparations
BP 2014: Leuprorelin Injection.

Luteinising Hormone ⊗

Gonadotropina luteinizante; Hormona luteinizante; Human Interstitial-cell-stimulating Hormone; ICSH; LH; Lutropin; Lutropina.

CAS — 9002-67-9; 39341-83-8 (human).

Lutropin Alfa *(BAN, USAN, rINN)* ⊗

Lutropina alfa; Lutropine Alfa; Lutropinum Alfa; Лутропин Альфа.

CAS — 152923-57-4 (lutropin alfa); 56832-30-5 (α subunit); 53664-53-2 (β subunit).
ATC — G03GA07.
ATC Vet — QG03GA07.
UNII — 3JGY52XJNA.

Units

35 units of human pituitary luteinising hormone are contained in about 5.8 micrograms (with 1 mg of human albumin, 5 mg of mannitol, and 1 mg of sodium chloride) in one ampoule of the second International Standard (1988).

10 units of the alpha subunit of human pituitary luteinising hormone are contained in about 10 micrograms (with 500 micrograms of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

10 units of the beta subunit of human pituitary luteinising hormone are contained in 10 micrograms (with 500 micrograms of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

189 units of recombinant human luteinising hormone are contained in about 8.8 micrograms (with 2 mg of human albumin, 10 mg of lactose, and 8.9 mg of sodium chloride) in one ampoule of the first International Standard (2003).

Uses and Administration

Luteinising hormone (LH) is secreted with follicle-stimulating hormone (FSH) (p. 2278.2), another gonadotrophin, by the anterior pituitary lobe.

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova. As the follicle develops it produces oestrogen in increasing amounts which at mid-cycle stimulates the release of LH. This causes rupture of the follicle with ovulation and converts the follicle into the corpus luteum which secretes progesterone. In men, luteinising hormone stimulates the interstitial cells of the testis to secrete testosterone, which in turn has a direct effect on the seminiferous tubules.

Gonadotrophic substances with luteinising or follicle-stimulating activity or both are used in the treatment of infertility (p. 2253.1), chiefly in females but also in males. Such substances include chorionic gonadotrophin (p. 2258.1) which possesses LH activity and human menopausal gonadotrophins (p. 2284.2) which possess both LH and FSH activity.

Lutropin alfa is a recombinant human luteinising hormone used to induce ovulation in women with severe deficiency of luteinising and follicle-stimulating hormones. It is used at the same time as a preparation with follicle-stimulating activity, usually follitropin alfa. The dosage and schedule of treatment must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. Treatment is usually begun with 75 units of lutropin alfa daily by subcutaneous injection for 7 to 14 days, accompanied by FSH. If there is no response, the FSH dosage may be increased at 7- or 14-day intervals until an adequate but not excessive response is achieved. A treatment cycle of up to 5 weeks may be needed. Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation. These patients are generally amenorrhoeic and treatment may be started at any time.

References.

1. The European Recombinant Human LH Study Group. Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: a dose-finding study. *J Clin Endocrinol Metab* 1998; **83:** 1507–14.
2. Burgués S, The Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: evidence from a multicentre study in Spain. *Hum Reprod* 2001; **16:** 2525–32.
3. The European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. *J Clin Endocrinol Metab* 2001; **86:** 2607–18.
4. Dhillon S, Keating GM. Lutropin alfa. *Drugs* 2008; **68:** 1529–40.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lutropin alfa as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

The absolute bioavailability of lutropin alfa after subcutaneous doses is about 60%, and the terminal half-life is at least 10 to 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Luveris; ***Austral.***: Luveris; ***Austria***: Luveris; ***Belg.***: Luveris; ***Braz.***: Luveris; ***Canad.***: Luveris; ***Chile***: Luveris; ***China***: Luveris (乐芮); ***Cz.***: Luveris; ***Denm.***: Luveris; ***Fin.***: Luveris; ***Fr.***: Luveris; ***Ger.***: Luveris; ***Gr.***: Luveris; ***Hong Kong***: Luveris; ***Hung.***: Luveris; ***India***: Luveris; ***Indon.***: Luveris; ***Irl.***: Luveris; ***Israel***: Luveris; ***Ital.***: Luveris; ***Malaysia***: Luveris; ***Mex.***: Luveris†; ***Neth.***: Luveris; ***Norw.***: Luveris; ***NZ***: Luveris; ***Philipp.***: Luveris; ***Pol.***: Luveris; ***Port.***: Luveris; ***Rus.***: Luveris (Луверис); ***S.Afr.***: Luveris; ***Singapore***: Luveris; ***Spain***: Luveris; ***Swed.***: Luveris; ***Switz.***: Luveris; ***Thai.***: Luveris; ***Turk.***: Luveris; ***UK***: Luveris; ***USA***: Luveris†; ***Venez.***: Luveris.

Multi-ingredient Preparations. ***Arg.***: Pergoveris; ***Austria***: Pergoveris; ***Belg.***: Pergoveris; ***Braz.***: Pergoveris; ***Cz.***: Pergoveris; ***Denm.***: Pergoveris; ***Fr.***: Pergoveris; ***Ger.***: Pergoveris; ***Gr.***: Pergoveris; ***Hung.***: Pergoveris; ***Irl.***: Pergoveris; ***Israel***: Pergoveris; ***Ital.***: Pergoveris; ***Neth.***: Pergoveris; ***Norw.***: Pergoveris; ***Pol.***: Pergoveris; ***Port.***: Pergoveris; ***Rus.***: HuMoG (ХуМоГ); ***Singapore***: Pergoveris; ***Spain***: Pergoveris; ***Swed.***: Pergoveris†; ***Switz.***: Pergoveris; ***UK***: Pergoveris.

Lynestrenol *(BAN, USAN, rINN)*

Ethinylestrenol; Etinilestrenol; Linestrenol; Linestrenolis; Linesztrenol; Linoestrenol; Lynenol; Lynestrénol; Lynestrenoli; Lynestrenolum; Lynoestrenol; NSC-37725; Линэстренол.

19-Nor-17α-pregn-4-en-20-yn-17β-ol.
$C_{20}H_{28}O$=284.4
CAS — 52-76-6.
ATC — G03AC02; G03DC03.
ATC Vet — QG03AC02; QG03DC03.
UNII — N2Z8ALG4U5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lynestrenol). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. Protect from light.

Profile

Lynestrenol is a progestogen (see Progesterone, p. 2300.2) structurally related to norethisterone that is used alone or as the progestogenic component of oral contraceptives (see p. 2231.3). Typical oral daily doses for contraception are 500 micrograms when used as a progestogen-only preparation, and 0.75 or 2.5 mg when combined with an oestrogen. When used alone for menstrual disorders, doses of 5 to 10 mg daily are given, often as cyclical regimens.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lynestrenol as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Exluton; ***Austria***: Orgametril; ***Belg.***: Orgametril; ***Braz.***: Exluton; ***Chile***: Exluton; Linosun; Normalac; ***Cz.***: Orgametril; ***Denm.***: Orgametril†; ***Fin.***: Orgametril; ***Fr.***: Orgametril†; ***Gr.***: Orgametril; ***Hung.***: Orgametril†; ***Indon.***: Endometril; Exluton; ***Mex.***: Exluton; ***Neth.***: Exluton; Orgametril; ***Philipp.***: Amber; Daphne; Exluton; ***Pol.***: Orgametril; ***Rus.***: Exluton (Экслютон); Orgametril (Органетрил); ***Spain***: Orgametril; ***Swed.***: Exlutena; Orgametril; ***Thai.***: Dailyton; Exluton; ***Turk.***: Orgametril; ***Ukr.***: Exluton (Экслютон); Orgametril (Органетрил); ***Venez.***: Exluton; Normalac.

Multi-ingredient Preparations. ***Braz.***: Ovoresta†; ***Chile***: Anovulatorios; ***Ger.***: Ovoresta M†; ***Neth.***: Ministat; ***Swed.***: Restovar; ***Turk.***: Lyndiol.

Medrogestone *(BAN, USAN, rINN)*

AY-62022; Medrogeston; Medrogestona; Médrogestone; Medrogestoni; Medrogestonum; Metrogestone; NSC-123018; R-13-615; Медрогестон.

6,17α-Dimethylpregna-4,6-diene-3,20-dione.
$C_{23}H_{32}O_2$=340.5
CAS — 977-79-7.
ATC — G03DB03.
ATC Vet — QG03DB03.
UNII — 077DN93G5B.

Profile

Medrogestone is a progestogen structurally related to progesterone (p. 2300.2) that is used in the treatment of menstrual disorders, and as the progestogen in menopausal HRT (see p. 2244.1). It is usually given orally in daily doses of 5 to 10 mg, generally in a cyclical regimen. Higher doses were used in the treatment of endometrial carcinoma, prostatic hyperplasia, and breast disorders including carcinoma. It has also been used for threatened or recurrent miscarriage, but such use is not recommended unless there is proven progesterone deficiency.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Colprone.

Multi-ingredient Preparations. ***Ger.***: Presomen Compositum; Presomen conti; ***S.Afr.***: Prempak N†.

Medroxyprogesterone Acetate

(BANM, rINNM)

Acetato de medroxiprogesterona; Medroksiprogesteron Asetat; Medroksiprogesteroniasetaatti; Medroksiprogesterono acetatas; Medroksyprogesteronu octan; Medroxiprogesterona, acetato de; Medroxiprogesteronacetat; Medroxiprogeszteron-acetát; Medroxyprogesteronacetat; Medroxyprogesteron-acetát; Médroxyprogestérone, Acétate de; Medroxyprogesteroni Acetas; Methylacetoxyprogesterone; Metipregnone; NSC-26386; Медроксипрогестерона Ацетат.

6α-Methyl-3,20-dioxopregn-4-en-17α-yl acetate; 17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate.

$C_{24}H_{34}O_4$=386.5

CAS — 520-85-4 (medroxyprogesterone); 71-58-9 (medroxyprogesterone acetate).

ATC — G03AC06; G03DA02; L02AB02.

ATC Vet — QG03AC06; QG03DA02; QL02AB02.

UNII — C2QI4IOI2G.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Medroxyprogesterone Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Medroxyprogesterone Acetate). A white to off-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in dioxan; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Medroxyprogesterone acetate is a progestogen structurally related to progesterone, with actions and uses similar to those of the progestogens in general (see Progesterone, p. 2300.2). It is given orally or, for prolonged action, as an aqueous suspension by intramuscular or subcutaneous injection, depending on the product.

It is used for the treatment of **menorrhagia** (p. 2300.3) and **secondary amenorrhoea** in oral doses of 2.5 to 10 mg daily for 5 to 10 days starting on the assumed or calculated 16th to 21st day of the menstrual cycle, although treatment may begin on any day in secondary amenorrhoea.

In the treatment of mild to moderate **endometriosis** (p. 2264.1) usual oral doses are 10 mg three times daily for 90 consecutive days, or 50 mg weekly or 100 mg every 2 weeks by intramuscular injection for at least 6 months. An alternative formulation used for the treatment of pain associated with endometriosis is given in a dose of 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

Medroxyprogesterone acetate is also given by injection as a **contraceptive** (see under Hormonal Contraceptives, p. 2231.3). As a progestogen-only contraceptive an intramuscular dose of 150 mg is given every 12 or 13 weeks. A combined contraceptive injection containing medroxyprogesterone acetate 25 mg with estradiol cipionate 5 mg is given monthly as an intramuscular injection. An alternative formulation used as a progestogen-only contraceptive is given as a dose of medroxyprogesterone acetate 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

When used as the progestogen component of **menopausal HRT** (see p. 2244.2), medroxyprogesterone acetate is given orally in a variety of regimens including 1.5, 2.5, or 5 mg daily continuously, 5 or 10 mg daily for 12 to 14 days of a 28-day cycle, and 20 mg daily for 14 days of a 91-day cycle.

Medroxyprogesterone acetate may also be used in the palliative treatment of some hormone-dependent malignant neoplasms. In **breast carcinoma** (see below) oral doses of 0.4 to 1.5 g daily may be given, although doses up to 2 g daily have been used in the past. Intramuscular medroxyprogesterone acetate has been given in initial doses of 500 mg daily for 4 weeks, then in maintenance doses twice weekly. In **endometrial** (below) and **renal carcinoma** (p. 708.3) oral doses have ranged from 200 to 600 mg daily. Initial doses of 0.6 to 1.2 g weekly have been given by intramuscular injection, reducing to a maintenance schedule of as little as 450 mg monthly. In **prostatic carcinoma** (p. 712.3) oral doses have been 100 to 600 mg daily; 500 mg has also been given by intramuscular injection, initially twice weekly for 3 months then once weekly for maintenance.

Cachexia. Medroxyprogesterone may improve appetite and food intake, and prevent loss of body-weight in cachexia (p. 2289.3) associated with severe chronic disorders,[1-3] although information is limited.

1. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996; **14:** 1077–84.
2. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial. *Cancer* 1998; **82:** 553–60.
3. Madeddu C, *et al.* Medroxyprogesterone acetate in the management of cancer cachexia. *Expert Opin Pharmacother* 2009; **10:** 1359–66.

Contraception. Medroxyprogesterone acetate has an established use as a parenteral progestogen-only contraceptive (p. 2232.3). It has also been developed as the progestogenic component of a combined injectable contraceptive and has been investigated as a component of hormonal contraceptives for men.

References.

1. Garza-Flores J, *et al.* Introduction of Cyclofem once-a-month injectable contraceptive in Mexico. *Contraception* 1998; **58:** 7–12.
2. Kaunitz AM, *et al.* Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). *Contraception* 1999; **60:** 179–87.
3. Kaunitz AM. Current concepts regarding use of DMPA. *J Reprod Med* 2002; **47** (suppl): 785–9.
4. Turner L, *et al.* Contraceptive efficacy of a depot progestin and androgen combination in men. *J Clin Endocrinol Metab* 2003; **88:** 4659–67.
5. Gu YQ, *et al.* Male hormonal contraception: effects of injections of testosterone undecanoate and depot medroxyprogesterone acetate at eight-week intervals in Chinese men. *J Clin Endocrinol Metab* 2004; **89:** 2254–62.
6. Page ST, *et al.* Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. *J Clin Endocrinol Metab* 2006; **91:** 4374–80.

Epilepsy. Early findings[1] suggested that medroxyprogesterone acetate might be of value in the management of catamenial epilepsy (p. 506.1). In a later review[2] it was suggested that hormonal manipulation with drugs such as medroxyprogesterone should be reserved for highly selected groups under close supervision.

1. Mattson RH, *et al.* Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology* 1984; **34:** 1255–8.
2. Herkes GK. Drug treatment of catamenial epilepsy. *CNS Drugs* 1995; **3:** 260–6.

Male hypersexuality. The anti-androgenic action of medroxyprogesterone has been used for suppression of libido in the control of men with deviant or disinhibited sexual behaviour[1-8] (see Disturbed Behaviour, p. 1030.2). Most have received intramuscular medroxyprogesterone acetate; doses of about 300 mg weekly have been used,[3] but ranged from 100 mg each month to 500 mg each week in one report of 5 cases,[8] and up to 750 mg each week in another case.[6] Oral treatment with 30 mg daily was also successful in 1 case.[5]

1. Kiersch TA. Treatment of sex offenders with Depo-Provera. *Bull Am Acad Psychiatry Law* 1990; **18:** 179–87.
2. Weiner MF, *et al.* Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. *Lancet* 1992; **339:** 1121–2.
3. Kravitz HM, *et al.* Medroxyprogesterone treatment for paraphiliacs. *Bull Am Acad Psychiatry Law* 1995; **23:** 19–33.
4. Britton KR. Medroxyprogesterone in the treatment of aggressive hypersexual behaviour in traumatic brain injury. *Brain Inj* 1998; **12:** 703–7.
5. Brooks JO, Waikar MV. Inappropriate masturbation and schizophrenia. *J Clin Psychiatry* 2000; **61:** 451.
6. Stewart JT. Optimizing antilibidinal treatment with medroxyprogesterone acetate. *J Am Geriatr Soc* 2005; **53:** 359–60.
7. Maletzky BM, *et al.* The Oregon depo-Provera program: a five-year follow-up. *Sex Abuse* 2006; **18:** 303–16.
8. Light SA, Holroyd S. The use of medroxyprogesterone acetate for the treatment of sexually inappropriate behaviour in patients with dementia. *J Psychiatry Neurosci* 2006; **31:** 132–4.

Malignant neoplasms. *BREAST.* Progestogens are used as second- or third-choice drugs in the hormonal therapy of advanced breast cancer (p. 702.1). Some references to the use of medroxyprogesterone acetate in advanced breast cancer are cited below.[1-8] Comparative studies have shown that patients respond equally well to medroxyprogesterone and either mepitiostane,[1] aminoglutethimide,[2] or oophorectomy.[3]

1. Izuo M, *et al.* A phase III trial of oral high-dose medroxyprogesterone acetate (MPA) versus mepitiostane in advanced postmenopausal breast cancer. *Cancer* 1985; **56:** 2576–9.
2. Canney PA, *et al.* Randomized trial comparing aminoglutethimide with high-dose medroxyprogesterone acetate in therapy for advanced breast carcinoma. *J Natl Cancer Inst* 1988; **80:** 1147–51.
3. Martoni A, *et al.* High-dose medroxyprogesterone acetate versus oophorectomy as first-line therapy of advanced breast cancer in premenopausal patients. *Oncology* 1991; **48:** 1–6.
4. Muss HB, *et al.* Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. *J Clin Oncol* 1994; **12:** 1630–8.
5. Clinton OP, *et al.* A prospective randomized trial to evaluate different oral dose regimens of medroxyprogesterone acetate in women with advanced breast cancer. *Clin Oncol* 1995; **7:** 251–6.
6. Byrne MJ, *et al.* Medroxyprogesterone acetate addition or substitution for tamoxifen in advanced tamoxifen-resistant breast cancer: a phase III randomized trial. *J Clin Oncol* 1997; **15:** 3141–8.
7. Koyama H, *et al.* A randomized controlled comparative study of oral medroxyprogesterone acetate 1,200 and 600 mg in patients with advanced or recurrent breast cancer. *Oncology* 1999; **56:** 283–90.
8. Kloke O, *et al.* Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. *Breast Cancer Res Treat* 1999; **55:** 51–9.

ENDOMETRIUM. Progestogens are used in the treatment of advanced endometrial carcinoma (p. 704.3) but there are doubts about their value in the earlier stages of disease.[1] Medroxyprogesterone acetate was effective in a rare case of low-grade endometrial stromal sarcoma.[2] It has also been used in a few patients as adjuvant therapy after surgery[3] and for the treatment of metastatic disease.[4]

1. Martin-Hirsch PL, *et al.* Progestagens for endometrial cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/06/08).
2. Rand RJ, Lowe JW. Low-grade endometrial stromal sarcoma treated with a progestogen. *Br J Hosp Med* 1990; **43:** 154–6.
3. Amant F, *et al.* Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. *Br J Cancer* 2007; **97:** 1194–9.
4. Pink D, *et al.* Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol* 2006; **101:** 464–9.

Respiratory disorders. Reviews of the use of medroxyprogesterone acetate in obstructive sleep apnoea have concluded that it has a limited role.[1,2]

Progesterone and, more commonly, medroxyprogesterone acetate are used in the treatment of pulmonary lymphangioleiomyomatosis, a rare disease affecting only women.[3-7] Anecdotal evidence suggests some patients improve or stabilise on treatment, possibly those with chylous effusions or chylous ascites.[8] However, a more rapid decline in lung function has also been seen with progestogen therapy in some groups.[5,6]

Medroxyprogesterone acetate was reported to be effective in treating congenital central hypoventilation syndrome in 2 children.[9] It has also been used in adults with central hypoventilation resulting from brainstem stroke[10] and other causes.[11] Medroxyprogesterone has also been investigated for its effects on respiration in chronic obstructive pulmonary disease, sometimes with acetazolamide.[12-14]

1. Millman RP. Medroxyprogesterone and obstructive sleep apnea. *Chest* 1989; **96:** 225–6.
2. Terra SG, Oberg KC. Medroxyprogesterone acetate in the treatment of obstructive sleep apnea. *Ann Pharmacother* 1997; **31:** 776–8.
3. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
4. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.
5. Johnson SR, *et al.* Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004; **59:** 800–3.
6. Taveira-DaSilva AM, *et al.* Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004; **126:** 1867–74.
7. Schiavina M, *et al.* Efficacy of hormonal manipulation in lymphangioleiomyomatosis: a 20-year-experience in 36 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2007; **24:** 39–50.
8. Taylor JR, *et al.* Lymphangioleiomyomatosis: clinical course in 32 patients. *N Engl J Med* 1990; **323:** 1254–60.
9. Milerad J, *et al.* Alveolar hypoventilation treated with medroxyprogesterone. *Arch Dis Child* 1985; **60:** 150–5.
10. Smyth A, Riley M. Chronic respiratory failure: an unusual cause and treatment. *Thorax* 2002; **57:** 835–6.
11. Bootsma GP, *et al.* Chronic respiratory failure. *Thorax* 2003; **58:** 281.
12. Wagenaar M, *et al.* Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; **20:** 1130–7.
13. Wagenaar M, *et al.* Comparison of acetazolamide and medroxyprogesterone as respiratory stimulants in hypercapnic patients with COPD. *Chest* 2003; **123:** 1450–9.
14. Saaresranta T, *et al.* Medroxyprogesterone improves nocturnal breathing in postmenopausal women with chronic obstructive pulmonary disease. *Respir Res* 2005; **6:** 28.

Sickle-cell disease. The frequency of painful crises has been reduced in women with homozygous sickle-cell disease (p. 1123.2) given intramuscular depot medroxyprogesterone acetate,[1,2] and it is now considered to be a suitable contraceptive for this group (see also Sickle-cell Disease, under Precautions of Hormonal Contraceptives, p. 2242.1).

1. de Ceulaer K, *et al.* Medroxyprogesterone acetate and homozygous sickle-cell disease. *Lancet* 1982; **ii:** 229–31.
2. de Abood M, *et al.* Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. *Contraception* 1997; **56:** 313–16.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3. Medroxyprogesterone acetate may have glucocorticoid effects when given long term at high doses.

Breast feeding. Medroxyprogesterone is reported to be distributed into breast milk when given as a depot progestogen-only contraceptive.[1] No adverse effects have been seen in breast-fed infants of mothers given medroxyprogesterone, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding. It is recommended that progestogen-only parenteral contraceptives should not be used until 6 weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p. 2241.1) but the evidence for delaying postpartum use

of medroxyprogesterone in this group has been questioned.[3]

1. Schwallie PC. The effect of depot-medroxyprogesterone acetate on the fetus and nursing infant: a review. *Contraception* 1981; **23:** 375–86.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)
3. Rodriguez MI, Kaunitz AM. An evidence-based approach to postpartum use of depot medroxyprogesterone acetate in breastfeeding women. *Contraception* 2009; **80:** 4–6.

Carcinogenicity. The risk of various cancers associated with the use of depot medroxyprogesterone acetate as a contraceptive has been evaluated by WHO.[1] Overall, there was no increase in risk of breast cancer, although there is some evidence that current or recent use may be associated with a slight increase in risk (see also p. 2234.2). There was no significant increased risk of cervical cancer (see also p. 2235.1), and a protective effect against endometrial cancer (see p. 2235.2). In contrast to combined oral contraceptives, there was no evidence of a protective effect against ovarian cancer (p. 2236.1).

1. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1993; **71:** 669–76.

Effects on bone density. Use of medroxyprogesterone acetate as a parenteral progestogen-only contraceptive has been associated with reductions in bone density (see under Effects on the Musculoskeletal System, p. 2239.3). This effect has also been reported after oral doses for menstrual disorders,[1] and is thought to be due to medroxyprogesterone-induced oestrogen deficiency.

1. Cundy T, *et al.* Short-term effects of high dose oral medroxyprogesterone acetate on bone density in premenopausal women. *J Clin Endocrinol Metab* 1996; **81:** 1014–17.

Effects on the skin. Acute local skin necrosis has been reported[1] after the intramuscular injection of medroxyprogesterone acetate as a depot contraceptive. A case of pigmented purpura on the lower legs, occurring about 4 months after starting medroxyprogesterone acetate injections, has been described.[2]

1. Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera. *Br J Dermatol* 2000; **143:** 1356–7.
2. Tsao H, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000; **43:** 308–10.

Glucocorticoid effects. There have been reports of Cushing's syndrome induced by medroxyprogesterone acetate in patients receiving long-term therapy with high doses for the treatment of malignant neoplasms[1-5] or paraphilia.[6] Cushingoid symptoms regressed when treatment was stopped. Medroxyprogesterone possesses glucocorticoid activity and there is a risk of adrenal insufficiency during periods of stress or after sudden withdrawal of treatment. Some[4] consider that patients should be monitored for glucose intolerance and adrenal insufficiency during treatment.

1. Siminoski K, *et al.* The Cushing syndrome induced by medroxyprogesterone acetate. *Ann Intern Med* 1989; **111:** 758–60.
2. Donckier JE, *et al.* Cushing syndrome and medroxyprogesterone acetate. *Lancet* 1990; **335:** 1094.
3. Grenfell A, *et al.* Cushing's syndrome and medroxyprogesterone acetate. *Lancet* 1990; **336:** 256.
4. Merrin PK, Alexander WD. Cushing's syndrome induced by medroxyprogesterone. *BMJ* 1990; **301:** 345.
5. Shotliff K, Nussey SS. Medroxyprogesterone acetate induced Cushing's syndrome. *Br J Clin Pharmacol* 1997; **44:** 304.
6. Krueger RB, *et al.* Prescription of medroxyprogesterone acetate to a patient with pedophilia, resulting in Cushing's syndrome and adrenal insufficiency. *Sex Abuse* 2006; **18:** 227–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies medroxyprogesterone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] However, for a reference to the use of medroxyprogesterone acetate with buserelin acetate in the prevention of premenstrual exacerbations of porphyria in 2 women, see p. 2257.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). Aminoglutethimide markedly reduces plasma concentrations of medroxyprogesterone so that an increase in medroxyprogesterone dosage is likely to be required.

Pharmacokinetics

Medroxyprogesterone is absorbed from the gastrointestinal tract. In the blood, it is highly protein bound, principally to albumin. It is metabolised in the liver and excreted mainly as glucuronide conjugates in the urine and faeces. It has a half-life of about 16 to 30 hours after oral doses; the half-life may be as long as 50 days after intramuscular injection. Medroxyprogesterone is reported to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Depo-Provera; Farlutale; Livomedrox; Map An†; Medrosterona; Veraplex; ***Austral.***: Depo-Provera; Depo-Ralovera; Medroxyhexal†; Provera; Ralovera; ***Austria***: Depocon; Farlutal; Prodafem; Sayana; ***Belg.***: Depo-Provera; Farlutal; Provera; Sayana; Veraplex; ***Braz.***: Acemedrox; Acetoflux; Contracep; Cycrin; Demedrox; Depo-Provera; Farlutal; Medroxitest; Medroxon; Provera; ***Canad.***: Apo-Medroxy; Depo-Provera; Gen-Medroxy†; Medroxy; Novo-Medrone†; Provera; ***Chile***: Depo-Prodasone; Farlutal†; Farlutes†; Prodasone; Provera†; ***China***: Bei En (倍恩); Depo Geston (迪波盖斯通); Depo-Provera (狄波-普维拉); Farlutal (法禄达); Mei Qu Luo (美曲罗); Provera (普维拉); ***Cz.***: Depo-Provera; Femihexal†; Medroplex; Provera; Sayana; ***Denm.***: Depo-Provera; Perlutex†; Provera; ***Fin.***: Depo-Provera; Farlutal; Mepastat†; Provera; ***Fr.***: Depo-Prodasone; Depo-Provera; Farlutal; ***Ger.***: Depo-Clinovir; MPA Gyn†; MPA-beta; MPA†; Sayana; ***Gr.***: Depo-Provera; Farlutal; Neolut; Progevera; Provera; ***Hong Kong***: Apo-Medroxy; Depo-Provera; Farlutal†; Provera; ***Hung.***: Depo-Provera; Provera; ***India***: Depo Progestin; Depo-Provera; Depro; Deviry; Dubloc; Empeea; Farlutal; Geeva; Maxogest; Medrigest; Medronorm; Medtet; Megest; Meprate; Modus; Orgamed; ***Indon.***: Planibu; Prothyra†; Provera; Triclofem†; Veraplex; ***Irl.***: Depo-Provera; Provera; Sayana; ***Israel***: Depo-Provera; Provera; Sayana; ***Ital.***: Depo-Provera; Farlutal; Provera; ***Jpn***: Hysron; ***Malaysia***: Condep; Depo-Provera; Non-Preg; Provera; Ravimed; Veraplex; ***Mex.***: Ciclotal†; Megestron; Provera; ***Neth.***: Depo-Provera; Megestron; Provera; Sayana; ***Norw.***: Depo-Provera; Farlutal†; Perlutex†; Provera; ***NZ***: Depo-Provera; Provera; ***Philipp.***: Depo-Provera; Deporeva; Depotrust; Lyndavel; Provera; Provestin; ***Pol.***: Depo-Provera; Gestomikron; Provera; Sayana; ***Port.***: Depo-Provera; Provera; ***Rus.***: Ciclotal (Циклотал); Depo-Provera (Депо-провера); Provera (Провера); Veraplex (Вераплекс); ***S.Afr.***: Depo-Provera; Hexal-MPA; Petogen; Provera; ***Singapore***: Depo-Provera; Provera; ***Spain***: Depo-Progevera; Farlutal; Progevera 250; Progevera; ***Swed.***: Depo-Provera; Gestapuran†; Provera; ***Switz.***: Depo-Provera; Farlutal; Prodafem; Sayana; ***Thai.***: Contracep; Depo-Gestin; Depo-M; Depo-Progesno; Depo-Progesta; Enaf; Farlutal; Manodepo; Medeton; Pheno-M†; Provera; Veraplex; ***Turk.***: Depo-Provera; Farlutal; ***UK***: Climanor; Depo-Provera; Provera; Sayana; ***Ukr.***: Depo-Provera (Депо-Провера); ***USA***: Depo-Provera; Depo-subQ Provera; Provera; ***Venez.***: Depo-Provera; Provera.

Multi-ingredient Preparations. ***Arg.***: Cyclofem; Farludiol Ciclo; Farludiol; ***Austral.***: Premia Continuous; Premia†; ***Belg.***: Diviplus; Diviva; ***Braz.***: Ciclofemina; Dilena; Premelle Ciclo; Premelle; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Conti; Selecta; ***Canad.***: Premplus; ***Chile***: Climatrol Continuo†; Climatrol HT Continuo; Climatrol HT†; Conpremin Pak Plus†; Conpremin Pak†; Enadiol CC†; Enadiol MP†; Estranova 30 Simple†; Estranova CC†; Farlupost†; Kilios; Novafac 30; Novafac CC; Novafac†; Novafem; Primaquin MP Continuo†; Primaquin MP†; Profemina MP†; ***China***: Lunella (月纳); Premelle (倍美罗); ***Cz.***: Divina; Diviseq; Indivina; ***Denm.***: Divina Plus; Divina; Indivina; Trevina; ***Fin.***: Divina; Divitren; Indivina; ***Fr.***: Divina; Duova; Precyclan†; ***Ger.***: Climopax Cyclo; Climopax; Gianda†; Indivina; Osmil†; Sisare 28†; Sisare†; ***Gr.***: Divina; Estopause; Premelle Cycle; Premelle; ***Hong Kong***: Cyclofem; Dilena†; Premelle Cycle†; Premelle; ***Hung.***: Divina; Indivina; ***Indon.***: Cyclofem†; ***Irl.***: Indivina; Premique Cycle; Premique; ***Ital.***: Filena; Premelle Combinato†; Premia; ***Malaysia***: Premelle; ***Mex.***: Cyclofemina; Dilena; Premelle; Xofemina; ***Norw.***: Indivina; ***NZ***: Premia Continuous; ***Philipp.***: Premelle Cycle; Premelle; ***Pol.***: Divina; Diviseq; Indivina; ***Port.***: Dilena; ***Rus.***: Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен)†; Indivina (Индивина); ***S.Afr.***: Divina†; Premelle Cycle; Premelle; Trivina†; ***Singapore***: Premelle Cycle; Premelle; ***Spain***: Medrivas Antib; Medrivas; Perifem; ***Swed.***: Divina Plus; Indivina; Trivina; ***Switz.***: Diviseq†; Indivina; Triaval†; ***Thai.***: Diviseq†; Indivina†; ***Turk.***: Divina; Premelle Cycle; Premelle†; ***UK***: Indivina; Premique Cycle†; Premique; Tridestra; ***Ukr.***: Divina (Дивина)†; Indivina (Индивина)†; ***USA***: Premphase; Prempro; ***Venez.***: Climatrol HT Ciclico; Climatrol HT Continuo; Premelle Continuo.

Pharmacopoeial Preparations

BP 2014: Medroxyprogesterone Injection; Medroxyprogesterone Tablets;

USP 36: Medroxyprogesterone Acetate Injectable Suspension; Medroxyprogesterone Acetate Tablets.

Megestrol Acetate *(BANM, USAN, rINNM)*

Acetato de megestrol; BDH-1298; Compound 5071; Megestol Asetat; Mégestrol, Acétate de; Megestrol, acetato de; Megestrolacetat; Megestrol-acetát; Megestroli Acetas; Megestroliasetaatti; Megestrolio acetatas; Megesztrol-acetát; NSC-71423; SC-10363; Мегестрола Ацетат.

6-Methyl-3,20-dioxopregna-4,6-dien-17α-yl acetate; 17α-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate.

$C_{24}H_{32}O_4$=384.5

CAS — 3562-63-8 (megestrol); 595-33-5 (megestrol acetate).

ATC — G03AC05; G03DB02; L02AB01.

ATC Vet — QG03AC05; QG03DB02; QL02AB01.

UNII — TJ2M0FR8ES.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Megestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. Protect from light.

USP 36: (Megestrol Acetate). A white to creamy-white, essentially odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone; very soluble in chloroform; slightly soluble in ether and in fixed oils. Protect from light.

Uses and Administration

Megestrol acetate is a progestogen structurally related to progesterone (p. 2300.2).

It is used for the palliative treatment of some hormone-dependent malignant neoplasms (see p. 2290.1). Oral doses of 40 to 320 mg daily in divided doses may be given in **endometrial carcinoma**, and doses of 40 mg four times daily or 160 mg once daily may be used in **breast cancer**.

Megestrol acetate is also used in the treatment of **anorexia** and **cachexia** (see below) in patients with cancer or AIDS. The usual dose is 400 to 800 mg daily, as tablets or oral suspension. A suspension of megestrol acetate that has an increased bioavailability is also available (*Megace ES; Par Pharmaceutical, USA*) and is given in a dose of 625 mg in 5 mL daily for anorexia, cachexia, or unexplained significant weight loss in patients with AIDS.

Cachexia. In some patients with severe chronic disorders or malignant neoplasms, anorexia (loss of appetite) forms part of a syndrome of metabolic abnormalities and progressive physical wasting known as cachexia. Improved nutrition and dietary counselling are usually insufficient to reverse cachexia, and drug therapy has been tried to stimulate appetite and promote weight gain.

In **cancer-related cachexia**, corticosteroids are frequently used for appetite stimulation in patients with advanced malignancies, although they do not appear to promote weight gain. However, because their effect is usually temporary, and adverse effects occur with prolonged use,[1-3] they tend to be reserved for short-term treatment in patients with a limited life expectancy of weeks.[4] Megestrol has produced weight gain in some randomised controlled studies,[5] although some of this may result from increase in fat mass rather than increase in lean body-mass.[2,3] It is generally used in patients with a longer life expectancy of months.[4] Similar properties have been reported with medroxyprogesterone.[1] A systematic review[6] concluded that only corticosteroids and the progestogens megestrol and medroxyprogesterone had sufficient evidence to support their use in cancer-related anorexia. Anabolic steroids have also been tried, but further evaluation is necessary:[1,7] a comparison of megestrol or dexamethasone with fluoxymesterone found the latter to be less effective than the progestogen or the corticosteroid.[8] Prokinetic drugs such as metoclopramide may be useful in patients whose symptoms are secondary to decreased gastrointestinal motility,[1,2] although relief of nausea may not necessarily lead to improved caloric intake or appetite.[6] It has been suggested that NSAIDs might inhibit the effects of pro-inflammatory cytokines associated with weight loss in cancer patients. The addition of ibuprofen improved the response to megestrol in one small study,[9] but more work is needed. There has also been interest in the effects of eicosapentaenoic acid, which may inhibit muscle protein degradation, but study results have been mixed[3] and a systematic review[10] concluded that there was insufficient evidence to recommend the use of eicosapentaenoic acid. Further investigation is needed to confirm its clinical effects, possibly using higher doses or treating for longer periods than have been so far reported.[6] Thalidomide was found to attenuate weight loss in a study[11] of patients with advanced pancreatic cancer, but quality of life and duration of survival were not significantly improved. Combination anticachectic therapy has also been investigated. A study comparing an oral progestogen (medroxyprogesterone or megestrol), eicosapentaenoic acid, carnitine, thalidomide, or a combination of all 4, in patients with cancer cachexia, found that the individual treatments were ineffective or at best mildly effective, but that the combined treatment produced significant benefit.[12] Other drugs studied but with little, if any, benefit include cannabinoids, cyproheptadine and hydrazine.[1,2,6]

High-dose megestrol[13-15] or oxandrolone[16-19] are effective in **HIV-related cachexia**, a topic discussed under HIV-associated Wasting, p. 959.1.

Management of cachexia associated with **other chronic conditions**, including in dialysis patients[20] and the elderly,[21] is less well studied. There have been controversies about the relative risks and benefits, particularly in the latter group: increased mortality was reported in one study of the

use of megestrol to treat significant weight loss in the elderly,[22] although others have reported benefit.[23]

Other compounds under investigation in cachectic states include growth hormone[19] and the endogenous hormones ghrelin[24] and melatonin,[7] and selective androgen receptor modulators.

1. Mantovani G, *et al*. Managing cancer-related anorexia/cachexia. *Drugs* 2001; **61:** 499–514.
2. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin* 2002; **52:** 72–91.
3. Tisdale MJ. Clinical anticachexia treatments. *Nutr Clin Pract* 2006; **21:** 168–74.
4. Jatoi A. Pharmacologic therapy for the cancer anorexia/weight loss syndrome: a data-driven, practical approach. *J Support Oncol* 2006; **4:** 499–502.
5. Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 27/06/08).
6. Yavuzsen T, *et al*. Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol* 2005; **23:** 8500–11.
7. Bossola M, *et al*. Cancer cachexia: it's time for more clinical trials. *Ann Surg Oncol* 2007; **14:** 276–85.
8. Loprinzi CL, *et al*. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999; **17:** 3299–3306.
9. McMillan DC, *et al*. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *Br J Cancer* 1999; **79:** 495–500.
10. Dewey A, *et al*. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Gordon JN, *et al*. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54:** 540–5.
12. Mantovani G, *et al*. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist* 2010; **15:** 200–11.
13. Von Roenn JH, *et al*. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 1994; **121:** 393–9.
14. Oster MH, *et al*. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med* 1994; **121:** 400–408.
15. Clarick RH, *et al*. Megestrol acetate treatment of growth failure in children infected with human immunodeficiency virus. *Pediatrics* 1997; **99:** 354–7.
16. Strawford A, *et al*. Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. *JAMA* 1999; **281:** 1282–90.
17. Mwamburi DM, *et al*. Comparing megestrol acetate therapy with oxandrolone therapy for HIV-related weight loss: similar results in 2 months. *Clin Infect Dis* 2004; **38:** 895–902.
18. Grunfeld C, *et al*. Oxandrolone in the treatment of HIV-associated weight loss in men: a randomized, double-blind, placebo-controlled study. *J Acquir Immune Defic Syndr* 2006; **41:** 304–14.
19. Gullett NP, *et al*. Update on clinical trials of growth factors and anabolic steroids in cachexia and wasting. *Am J Clin Nutr* 2010; **91** (suppl): 1143S–1147S.
20. Bossola M, *et al*. Mechanisms and treatment of anorexia in end-stage renal disease patients on hemodialysis. *J Ren Nutr* 2009; **19:** 2–9.
21. Yeh S-S, *et al*. Pharmacological treatment of geriatric cachexia: evidence and safety in perspective. *J Am Med Dir Assoc* 2007; **8:** 363–77.
22. Bodenner D, *et al*. A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss. *Am J Geriatr Pharmacother* 2007; **5:** 137–46.
23. Yeh S-S, *et al*. Usage of megestrol acetate in the treatment of anorexia-cachexia syndrome in the elderly. *J Nutr Health Aging* 2009; **13:** 448–54.
24. Ashitani J, *et al*. Ghrelin and its therapeutic potential for cachectic patients. *Peptides* 2009; **30:** 1951–6.

Hot flushes. Megestrol has been used to treat hot flushes in women with breast cancer (to avoid the potentially tumour-stimulating effects of an oestrogen—see Malignant Neoplasms, under Precautions of HRT, p. 2250.2), as well as in men with hot flushes after orchidectomy or anti-androgen therapy for prostate cancer.[1] Therapy, which involved low oral doses of 20 mg twice daily, was associated with a decrease in frequency of flushes of 50% or more in about three-quarters of all patients. About 3 years after the study had finished, these patients were asked about any ongoing use of megestrol and the occurrence of hot flushes.[2] Although symptoms still occurred in many of the patients taking megestrol, they were less common and less severe than in those who had stopped therapy, which included some who had stopped because of no perceived benefit. In patients taking megestrol, most were on doses of 20 mg or less daily. Information collected about adverse effects of megestrol revealed unexpected reports of chills, but these were described as being not as disabling as the hot flushes had been. A later study[3] in women with breast cancer found that a lower dose of 20 mg of megestrol acetate daily was as effective as 40 mg daily.

1. Loprinzi CL, *et al*. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994; **331:** 347–52.
2. Quella SK, *et al*. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer* 1998; **82:** 1784–8.
3. Goodwin JW, *et al*. Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. *J Clin Oncol* 2008; **26:** 1650–6.

Malignant neoplasms. Like some other progestogens megestrol acetate is used in endometrial cancer (p. 704.3), and it has been reported to have similar efficacy to anastrozole[1] and tamoxifen[2] in postmenopausal women with advanced breast cancer (p. 702.1). There was no advantage in terms of response or survival in escalating the standard dose of megestrol (160 mg daily) to 800 or 1600 mg daily in a randomised study in women with breast cancer.[3]

1. Buzdar A, *et al*. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncol* 1996; **14:** 2000–11.
2. Stuart NSA, *et al*. A randomised phase III cross-over study of tamoxifen versus megestrol acetate in advanced and recurrent breast cancer. *Eur J Cancer* 1996; **32A:** 1888–92.
3. Abrams J, *et al*. Dose-response trial of megestrol acetate in advanced breast cancer: cancer and Leukemia Group B phase III study 8741. *J Clin Oncol* 1999; **17:** 64–73.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). The weight gain that may occur with megestrol acetate appears to be associated with an increased appetite and food intake rather than with fluid retention. Megestrol acetate may have glucocorticoid effects when given long term.

Effects on carbohydrate metabolism. Megestrol therapy has been associated with hyperglycaemia[1-3] or diabetes mellitus[4] in AIDS patients being treated for cachexia. It has been suggested that megestrol produces peripheral insulin resistance due to a glucocorticoid action.[5]

1. Panwalker AP. Hyperglycemia induced by megestrol acetate. *Ann Intern Med* 1992; **116:** 878.
2. BornemannM, Johnson AC. Endocrine effects of HIV infection. *N Engl J Med* 1993; **328:** 890.
3. Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clinic: preexisting versus drug-associated diabetes mellitus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 46–50.
4. Henry K, *et al*. Diabetes mellitus induced by megestrol acetate in a patient with AIDS and cachexia. *Ann Intern Med* 1992; **116:** 53–4.
5. Leinung MC, *et al*. Induction of adrenal suppression by megestrol acetate in patients with AIDS. *Ann Intern Med* 1995; **122:** 843–5.

Effects on the musculoskeletal system. Severe pain of the hands similar to carpal tunnel syndrome occurred in 4 women while taking megestrol acetate and melphalan;[1] megestrol appeared to be responsible.

Osteoporosis and vertebral compression fractures occurred in 2 postmenopausal women taking megestrol for anorexia.[2] In both cases there was evidence of adrenocortical insufficiency that recovered after megestrol therapy was stopped, suggesting that the glucocorticoid effect of megestrol may have contributed to the development of osteoporosis.

1. DiSaia PJ, Morrow CP. Unusual side effect of megestrol acetate. *Am J Obstet Gynecol* 1977; **129:** 460–1.
2. Wermers RA, *et al*. Osteoporosis associated with megestrol acetate. *Mayo Clin Proc* 2004; **79:** 1557–61.

Effects on the respiratory system. Hyperpnoea occurred in 2 patients given megestrol acetate 80 mg three times daily.[1]

1. Fessel WJ. Megestrol acetate and hyperpnea. *Ann Intern Med* 1989; **110:** 1034–5.

Glucocorticoid effects. Megestrol has glucocorticoid-like properties that can cause adrenocortical suppression in a significant number of patients.[1-5] There are also reports of adrenal insufficiency severe enough to require corticosteroid replacement therapy, usually with hydrocortisone.[3,6-9]

1. Naing KK, *et al*. Megestrol acetate therapy and secondary adrenal suppression. *Cancer* 1999; **86:** 1044–9.
2. Ron IG, *et al*. A low-dose adrenocorticotropin test reveals impaired adrenal function in cancer patients receiving megestrol acetate therapy. *Eur J Cancer* 2002; **38:** 1490–4.
3. Orme LM, *et al*. Megestrol acetate in pediatric oncology patients may lead to severe, symptomatic adrenal suppression. *Cancer* 2003; **98:** 397–405.
4. Chidakel AR, *et al*. High prevalence of adrenal suppression during acute illness in hospitalized patients receiving megestrol acetate. *J Endocrinol Invest* 2006; **29:** 136–40.
5. Dev R, *et al*. Association between megestrol acetate treatment and symptomatic adrenal insufficiency with hypogonadism in male patients with cancer. *Cancer* 2007; **110:** 1173–7.
6. Mann M, *et al*. Glucocorticoidlike activity of megestrol: a summary of Food and Drug Administration experience and a review of the literature. *Arch Intern Med* 1997; **157:** 1651–6.
7. Stockheim JA, *et al*. Adrenal suppression in children with the human immunodeficiency virus treated with megestrol acetate. *J Pediatr* 1999; **134:** 368–70.
8. Bulchandani D, *et al*. Megestrol acetate-associated adrenal insufficiency. *Am J Geriatr Pharmacother* 2008; **6:** 167–72.
9. Ibarra Barrueta O, *et al*. Insuficiencia suprarrenal asociada a acetato de megestrol en un paciente con el virus de la inmunodeficiencia humana. *Farm Hosp* 2009; **33:** 115–16.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies megestrol as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for progestogens in general (see Progesterone, p. 2302.2).

Pharmacokinetics

Megestrol acetate is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. Megestrol acetate is highly protein bound in plasma. It undergoes hepatic metabolism, with 57 to 78% of a dose being excreted in the urine and 8 to 30% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Megacorp; Meltonar†; Varigestrol; ***Austral.***: Megace; ***Belg.***: Megace; ***Braz.***: Femigestrol; Gynodal; Megestat; ***Canad.***: Megace; ***Chile***: Megace; ***China***: Ai Nuo Ke (艾诺克); AiKe (爱克); Jiadi (佳迪); Megace (梅格施); Mi Tuo Suo (米托索); Yi Li Zhi (宜利治); ***Cz.***: Megace; Megaplex; ***Denm.***: Megace; ***Fin.***: Megace†; ***Fr.***: Megace; ***Ger.***: Megestat; ***Gr.***: Megace; ***Hong Kong***: Megace; ***Hung.***: Megace; Megesin; Megyrina; ***India***: Endace; ***Indon.***: Megace†; Megaplex; ***Irl.***: Megace; ***Ital.***: Megace; Megestil; ***Malaysia***: Megace; ***Mex.***: Megace; Mestrel; ***Neth.***: Megace†; ***Norw.***: Megace; ***NZ***: Megace; ***Philipp.***: Megace†; Megaplex; ***Pol.***: Cachexan†; Gestar†; Megace; Megalia; Megesin†; ***Port.***: Acestrol; Megace; ***Rus.***: Megace (Мегейс); Megaplex (Мегаплекс); ***Spain***: Borea; Maygace; Megefren; ***Swed.***: Megace; ***Switz.***: Megestat†; ***Thai.***: Megace; Megaplex; Mestrel; ***Turk.***: Borea; Megace; ***UK***: Megace; ***USA***: Megace; ***Venez.***: Megase.

Pharmacopoeial Preparations
BP 2014: Megestrol Tablets;
USP 36: Megestrol Acetate Oral Suspension; Megestrol Acetate Tablets.

Melengestrol Acetate *(BANM, USAN, rINNM)*

5373; Acetato de melengestrol; BDH-1921; Mélengestrol, Acétate de; Melengestroli Acetas; NSC-70968; Меленгестрола Ацетат.

17-Hydroxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione acetate.

$C_{25}H_{32}O_4$=396.5

CAS — 5633-18-1 (melengestrol); 2919-66-6 (melengestrol acetate).

UNII — 4W5HDS3936.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Melengestrol Acetate). A white to light yellow, crystalline powder. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform and in ethyl acetate. Store in airtight containers. Protect from light.

Profile

Melengestrol acetate is a progestogen that is used as an animal feed in beef heifers to improve feed efficiency, increase the rate of body-weight gain, and suppress oestrus.

WHO specifies an acceptable daily intake of melengestrol acetate as a residue in foods, and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of melengestrol acetate and other steroidal hormones as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: sixty-sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 939* 2006. Also available at: http://libdoc.who.int/publications/2006/9241209399_eng.pdf (accessed 24/06/08)

Mepitiostane *(rINN)* ⊗

Mépitiostane; Mepitiostano; Mepitiostanum; S-10364; Мепитиостан.

17β-(1-Methoxycyclopentyloxy)-2α,3α-epithio-5α-androstane; Cyclopentanone 2α,3α-epithio-5α-androstan-17β-yl methyl acetal.

$C_{25}H_{40}O_2S$=404.7

CAS — 21362-69-6.

UNII — O00404969K.

Pharmacopoeias. In *Jpn*.

Profile

Mepitiostane has androgenic and anabolic properties (see Testosterone, p. 2305.1) and is given in usual oral doses of 10 mg twice daily for the management of neoplasms of the breast and anaemia associated with renal failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Thioderon.

Mesterolone (BAN, USAN, rINN) ⊗

Mesterolon; Mesterolona; Mesterolonas; Mestérolone; Mesteroloni; Mesterolonum; Meszterolon; NSC-75054; SH-723; Местеролон.

17β-Hydroxy-1α-methyl-5α-androstan-3-one.

$C_{20}H_{32}O_2$=304.5

CAS — 1424-00-6.

ATC — G03BB01.

ATC Vet — QG03BB01.

UNII — 0SRQ75X9I9.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Mesterolone). A white or yellowish crystalline powder. Practically insoluble in water; sparingly soluble in acetone, in ethyl acetate, and in methyl alcohol.

Uses and Administration

Mesterolone has androgenic properties (see Testosterone, p. 2305.2) but is reported to have less inhibitory effect on intrinsic testicular function than testosterone.

Mesterolone is given orally in the treatment of androgen deficiency or male infertility associated with hypogonadism (p. 2252.3). Initial treatment with 75 to 100 mg daily, in 3 or 4 divided doses, is given for several months, followed by 50 to 75 mg daily for maintenance.

Adverse Effects and Precautions

As for androgens in general (see Testosterone, p. 2307.3).

Mesterolone is reported not to inhibit gonadotrophin secretion or spermatogenesis.

Pharmacokinetics

Mesterolone is rapidly and almost completely absorbed after an oral dose and peak serum concentrations occur after about 1.6 hours. It is rapidly metabolised, with an absolute bioavailability of about 3% of the oral dose, and a terminal half-life of 12 to 13 hours. Unlike other androgens (see Testosterone, p. 2308.3), mesterolone is not metabolised to oestrogenic compounds. Mesterolone is bound to serum proteins; about 40% to albumin and 58% to sex-hormone binding globulin. About 77% of the metabolites are excreted in the urine, and about 13% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Proviron; ***Austria***: Proviron; ***Belg.***: Proviron; ***Braz.***: Proviron; ***Chile***: Proviron; ***Cz.***: Proviron; ***Gr.***: Proviron; ***Hung.***: Proviron; ***India***: Mestilon; Provironum; ***Indon.***: Androlon†; Infelon; Proviron; ***Israel***: Provir-on; ***Ital.***: Proviron; ***Malaysia***: Malvinum; Provironum; ***Mex.***: Proviron; ***Philipp.***: Proviron; Restore; ***Pol.***: Proviron; ***Port.***: Proviron; ***S.Afr.***: Proviron; ***Singapore***: Provironum; Restore; ***Spain***: Proviron; ***Thai.***: Mesviron; Provironum; ***Turk.***: Proviron; ***UK***: Proviron; ***Ukr.***: Proviron (Провирон); ***Venez.***: Proviron.

Multi-ingredient Preparations. ***Rus.***: Proviron (Провирон).

Mestranol (BAN, USAN, rINN)

Compound 33355; EE_3ME; Ethinyloestradiol-3-methyl Ether; Mestranoli; Mestranolis; Mestranolum; Mesztranol; Местранол.

3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol.

$C_{21}H_{26}O_2$=310.4

CAS — 72-33-3.

UNII — B2V233XGE7.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Mestranol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Mestranol). A white to creamy-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in chloroform; soluble in dioxan; slightly soluble in methyl alcohol. Protect from light.

Uses and Administration

Mestranol is a synthetic oestrogen prodrug that is rapidly metabolised to ethinylestradiol; it therefore has actions similar to those of estradiol (see p. 2271.2). It is used as the oestrogen component of combined oral contraceptive preparations (see p. 2231.3) in a usual dose of 50 micrograms daily. The progestogen component is often norethisterone. Mestranol has also been used as the oestrogen component of some preparations for menopausal HRT (see p. 2244.2), although natural oestrogens are often preferred. It has been given in a sequential regimen in a dose of 50 micrograms daily, with a cyclical progestogen.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Interactions

See under Hormonal Contraceptives, p. 2242.3, and Hormone Replacement Therapy, p. 2251.1.

Pharmacokinetics

Mestranol is readily absorbed from the gastrointestinal tract, and about 70% is rapidly metabolised in the liver to ethinylestradiol (p. 2276.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Norinyl-1; ***Chile***: Anovulatorios; ***Ger.***: Esticia†; ***Hong Kong***: Norinyl-1†; ***Mex.***: Lutoral-E; Norace; Norinyl; Secuentex-21; ***NZ***: Norinyl-1; ***S.Afr.***: Norinyl-1/28; ***Thai.***: Anamai; ***UK***: Norinyl-1; ***USA***: Necon 1/50; Norinyl 1 + 50; Ortho-Novum 1/50†.

Pharmacopoeial Preparations

USP 36: Ethynodiol Diacetate and Mestranol Tablets; Norethindrone and Mestranol Tablets.

Metenolone (BAN, rINN) ⊗

Metenolon; Metenolona; Méténolone; Metenoloni; Metenolonum; Methenolone; Метенолон.

17β-Hydroxy-1-methyl-5α-androst-1-en-3-one.

$C_{20}H_{30}O_2$=302.5

CAS — 153-00-4.

ATC — A14AA04.

ATC Vet — QA14AA04.

UNII — 9062ZT8Q5C.

Metenolone Acetate (BANM, rINNM) ⊗

Acetato de metenolona; Acetato de metilandrostenolona; Metenolona, acetato de; Méténolone, Acétate de; Metenoloni Acetas; Methenolone Acetate (USAN); Methenolone Acetate; NSC-74226; SH-567; SQ-16496; Метенолона Ацетат.

17β-Hydroxy-1-methyl-5α-androst-1-en-3-one acetate.

$C_{22}H_{32}O_3$=344.5

CAS — 434-05-9.

ATC — A14AA04.

ATC Vet — QA14AA04.

UNII — W75590VPKQ.

Pharmacopoeias. In *Jpn.*

Metenolone Enantate (BANM, rINNM) ⊗

Enantato de metenolona; Enantato de metilandrostenolona; Metenolona, enantato de; Méténolone, Enantate de; Metenoloni Enantas; Methenolone Enanthate (USAN); Methenolone Oenanthate; NSC-64967; SH-601; SQ-16374; Метенолона Энантат.

17β-Hydroxy-1-methyl-5α-androst-1-en-3-one heptanoate.

$C_{27}H_{42}O_3$=414.6

CAS — 303-42-4.

ATC — A14AA04.

ATC Vet — QA14AA04.

UNII — 0SPD480WFH.

Pharmacopoeias. In *Jpn.*

Profile

Metenolone is an anabolic steroid (see Testosterone, p. 2305.1) that has been used in treating aplastic anaemia, breast cancer, and postmenopausal osteoporosis. Metenolone acetate has been given in oral doses of 2 to 3 mg/kg daily for aplastic anaemia. Intramuscular depot injections of metenolone enantate have been given for osteoporosis in doses of 100 mg every 2 weeks, reducing to once every 3 to 4 weeks after an initial response. The acetate was also used orally in the past for osteoporosis. Intramuscular injections of 100 mg of the enantate every 1 to 2 weeks, or 200 mg every 2 to 3 weeks, have been used in progressive breast cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Primobolan†; ***Gr.***: Primobolan; ***Mex.***: Primobolan; ***S.Afr.***: Primobolan; ***Spain***: Primobolan Depot; ***Turk.***: Primobolan.

Homoeopathic Preparations. ***Ger.***: NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†.

Methandienone (BAN) ⊗

Metandienon; Metandienona; Metandienone (pINN); Métandiénone; Metandienoni; Metandienonum; Methandrostenolone; NSC-42722; Метандиенон.

17β-Hydroxy-17α-methylandrosta-1,4-dien-3-one.

$C_{20}H_{28}O_2$=300.4

CAS — 72-63-9.

ATC — A14AA03; D11AE01.

ATC Vet — QA14AA03; QD11AE01.

UNII — COZ1R7EOCC.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methandienone:

Iron Brew.

Pharmacopoeias. In *Pol.*

Uses and Administration

Methandienone has anabolic and some androgenic properties (see Testosterone, p. 2305.2). It has little progestogenic activity. Methandienone has been given orally as an anabolic drug. It has been subject to abuse in sport.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

As with other 17α-alkylated compounds, methandienone is associated with hepatotoxicity and hepatic function should be monitored during therapy. It should probably be avoided in patients with hepatic impairment, and certainly if this is severe.

Virilisation was reported[1] in 2 children, one of whom also developed adrenal suppression, after being given an 'appetite stimulant' containing methandienone and cyproheptadine.

1. Poomthavorn P, *et al.* Childhood virilization and adrenal suppression after ingestion of methandienone and cyproheptadine. *J Pediatr Endocrinol Metab* 2009; **22:** 459–62.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Metanabol; ***Thai.***: Anabol; Dronabol; Melic†; Methandon.

Methyl-1-testosterone ⊗

17β-Hydroxy-17α-methyl-5α-androst-1-en-3-one; M1T; Метил-1-тестостерон.

$C_{20}H_{30}O_2$=302.5

CAS — 65-04-3.

Profile

Methyl-1-testosterone is an anabolic steroid (see Testosterone, p. 2305.1) that appears to be widely abused by body-builders.

References.

1. Health Canada. Health Canada warns consumers not to use supplements containing methyl-1-testosterone due to potential serious health risks (issued February 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_06-eng.php (accessed 19/07/10)

Methyltestosterone (BAN, rINN) ⊗

Methyltestosteron; Méthyltestostérone; Methyltestosteronum; Metiltestosterona; Metiltestosteronas; Metiltesztoszteron; Metylotestosteron; Metyltestosteron; Metyylitestosteroni; NSC-9701; Метилтестостерон.

17β-Hydroxy-17α-methylandrost-4-en-3-one.

$C_{20}H_{30}O_2$=302.5

CAS — 58-18-4.

ATC — G03BA02.

ATC Vet — QG03BA02; QG03EK01.

UNII — V9EFU16ZIF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Methyltestosterone). A white or slightly yellowish-white, crystalline powder. Practically insoluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Methyltestosterone). White or creamy-white, odourless, slightly hygroscopic, crystals or crystalline powder. Practically insoluble in water; soluble in alcohol,

in ether, in methyl alcohol, and in other organic solvents; sparingly soluble in vegetable oils. Protect from light.

Uses and Administration

As for androgens and anabolic steroids in general (see Testosterone, p. 2305.2).

Methyltestosterone is effective when given orally; its effect is increased about twofold when given buccally, as this avoids first-pass hepatic metabolism.

Suggested doses of methyltestosterone for androgen replacement therapy in male hypogonadism (p. 2252.3) have been 10 to 50 mg daily orally or 5 to 25 mg daily buccally. Doses of 50 to 200 mg daily orally or 25 to 100 mg daily buccally have been given for metastatic breast carcinoma (p. 702.1) in postmenopausal women. Oral doses of 1.25 to 2.5 mg daily, for 21 days of a 28-day cycle, have been given with oestrogens for the short-term treatment of menopausal vasomotor symptoms (p. 2245.1) unresponsive to oestrogens alone.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

As with other 17α-alkylated compounds, methyltestosterone can produce a cholestatic hepatitis with jaundice, and has caused peliosis hepatis and hepatic neoplasms (see below). Methyltestosterone should be used with caution in patients with liver impairment, and is probably best avoided if this is severe. Liver function should be monitored during therapy.

Effects on the liver. Reports of peliosis hepatis[1] and liver damage[2-4] associated with methyltestosterone.

See also under Malignant Neoplasms, below.

1. Bagheri SA, *et al*. Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann InternMed* 1974; **81:** 610–18.
2. Westaby D, *et al*. Liver damage from long-term methyltestosterone. *Lancet* 1977; **ii:** 261–3.
3. Lowdell CP, Murray-Lyon IM. Reversal of liver damage due to long term methyltestosterone and safety of non-17 α -alkylated androgens. *BMJ* 1985; **291:** 637.
4. Borhan-Manesh F, Farnum JB. Methyltestosterone-induced cholestasis: the importance of disproportionately low serum alkaline phosphatase level. *Arch Intern Med* 1989; **124:** 2127–9.

MALIGNANT NEOPLASMS. Hepatocellular carcinoma[1-7] and hepatic adenoma[5,8] have been associated with methyltestosterone. A review[9] of reports of liver tumours associated with anabolic androgens found that methyltestosterone was an androgen that had been commonly implicated, and that the majority of tumours were hepatocellular carcinomas.

1. Johnson FL, *et al*. Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; **ii:** 1273–6.
2. Henderson JT, *et al*. Androgenic-anabolic steroid therapy and hepatocellular carcinoma. *Lancet* 1973; **i:** 934.
3. Farrell GC, *et al*. Androgen-induced hepatoma. *Lancet* 1975; **i:** 430–2.
4. Goodman MA, Laden AMJ. Hepatocellular carcinoma in association with androgen therapy. *Med J Aust* 1977; **1:** 220–1.
5. Boyd PR, Mark GJ. Multiple hepatic adenomas and a hepatocellular carcinoma in a man on oral methyl testosterone for eleven years. *Cancer* 1977; **40:** 1765–70.
6. Cocks JR. Methyltestosterone-induced liver-cell tumours. *Med J Aust* 1981; **2:** 617–19.
7. Gleeson D, *et al*. Androgen associated hepatocellular carcinoma with an aggressive course. *Gut* 1991; **32:** 1084–6.
8. Coombes GB, *et al*. An androgen-associated hepatic adenoma in a transsexual. *Br J Surg* 1978; **65:** 869–70.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.

Pregnancy. For reference to virilisation of a female fetus whose mother received methyltestosterone during pregnancy, see p. 2308.3.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Pharmacokinetics

Methyltestosterone is absorbed from the gastrointestinal tract and from the oral mucosa. It undergoes less extensive first-pass hepatic metabolism than testosterone after oral doses, and has a longer half-life.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Teston; ***Thai.***: Metesto; ***Turk.***: Afro; ***USA***: Android; Testred; Virilon.

Multi-ingredient Preparations. ***Chile***: Delitan; Feminova-T†; ***Hong Kong***: Sessoforte†; Wari-Procomil†; ***India***: Mixogen; ***Mex.***: Bigenol†; ***Thai.***: Men Hormone Compound; ***UK***: Prowess; ***USA***: Covaryx; Estratest†; Syntest.

Pharmacopoeial Preparations
USP 36: Methyltestosterone Capsules; Methyltestosterone Tablets.

Mibolerone *(BAN, USAN, rINN)* ⊗

Mibolerona; Mibolérone; Miboleronum; NSC-72260; U-10997; Миболерон.

17β-Hydroxy-7α,17-dimethylestr-4-en-3-one.

$C_{20}H_{30}O_2$=302.5

CAS — 3704-09-4.

UNII — 9OGY4BOR8D.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Mibolerone). A white to off-white powder. Practically insoluble in water; slightly soluble in chloroform, in dioxan, and in dichloromethane.

Profile

Mibolerone is an androgen that is used in veterinary practice as a contraceptive for female dogs. It also has anabolic properties.

Nafarelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de nafarelina; Nafareliinasetaatti; Nafarelin Asetat; Nafarelina, acetato de; Nafarelinacetat; Nafaréline, Acétate de; Nafarelini Acetas; D-Nal(2)^6-LHRH acetate hydrate; RS-94991298; Нафарелина Ацетат.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolylglycinamide acetate hydrate.

$C_{66}H_{83}N_{17}O_{13}xC_2H_4O_2yH_2O$=1322.5 (nafarelin)

CAS — 76932-56-4 (nafarelin); 86220-42-0 (nafarelin acetate).

ATC — H01CA02.

ATC Vet — QH01CA02.

UNII — 8ENZ0QJW4H.

Uses and Administration

Nafarelin acetate is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used in the treatment of endometriosis and central precocious puberty, and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility.

For **endometriosis** it is given in usual doses equivalent to 200 micrograms of nafarelin twice daily intranasally, doubled after 2 months if amenorrhoea has not occurred. Treatment should begin on days 2 to 4 of the menstrual cycle, and may be continued for up to 6 months.

Regimens for **oocyte collection for IVF** use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins; the equivalent of 400 micrograms of nafarelin is given intranasally twice daily, beginning either in the early follicular phase (day 2) or midluteal phase (day 21) of the menstrual cycle. Therapy should be continued until downregulation is achieved; if this does not occur within 12 weeks therapy should be withdrawn. Once downregulation occurs gonadotrophin treatment is added to nafarelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

Nafarelin has also been given in other sex hormone-related conditions.

The derivative azagly-nafarelin is used in veterinary medicine.

Administration in children. Nafarelin may be used in the management of central precocious puberty—see below.

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p. 2347.1.

Prostate size decreased by a mean of 24.2% in 9 men treated for benign prostatic hyperplasia for 6 months with nafarelin acetate 400 micrograms daily subcutaneously.[1] Six months after the end of treatment, prostate size approached that of pretreatment values.

1. Peters CA, Walsh PC. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. *N Engl J Med* 1987; **317:** 599–604.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References to the use of nafarelin.

1. Henzl MR, *et al*. Administration of nasal nafarelin as compared with oral danazol for endometriosis: a multicenter double-blind comparative clinical trial. *N Engl J Med* 1988; **318:** 485–9.
2. Burry KA. Nafarelin in the management of endometriosis: quality of life assessment. *Am J Obstet Gynecol* 1992; **166:** 735–9.
3. Hornstein MD, *et al*. Retreatment with nafarelin for recurrent endometriosis symptoms: efficacy, safety, and bone mineral density. *Fertil Steril* 1997; **67:** 1013–18.
4. Adamson GD, *et al*. Therapeutic efficacy and bone mineral density response during and following a three-month re-treatment of endometriosis with nafarelin (Synarel). *Am J Obstet Gynecol* 1997; **177:** 1413–18.
5. Agarwal SK, *et al*. Nafarelin vs. leuprolide acetate depot for endometriosis: changes in bone mineral density and vasomotor symptoms. *J Reprod Med* 1997; **42:** 413–23.
6. Zhao SZ, *et al*. Impact of nafarelin and leuprolide for endometriosis on quality of life and subjective clinical measures. *J Reprod Med* 1999; **44:** 1000–1006.
7. Bergqvist A, *et al*. A comparative study of the acceptability and effect of goserelin and nafarelin on endometriosis. *Gynecol Endocrinol* 2000; **14:** 425–32.
8. Cheng MH, *et al*. A randomized, parallel, comparative study of the efficacy and safety of nafarelin versus danazol in the treatment of endometriosis in Taiwan. *J Chin Med Assoc* 2005; **68:** 307–14.

Fibroids. Gonadorelin analogues have been tried as an adjunct or alternative to surgery in the treatment of uterine fibroids (see p. 2281.2), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of nafarelin.

1. Minaguchi H, *et al*. Clinical use of nafarelin in the treatment of leiomyomas: a review of the literature. *J Reprod Med* 2000; **45:** 481–9.

Infertility. Gonadorelin analogues are used in the treatment of infertility (p. 2253.1). As well as being used directly they are employed in regimens to induce superovulation to enable ova collection and IVF. A meta-analysis[1] found that the outcome of IVF treatment using nafarelin was equivalent to that using other gonadorelin analogues, but that nafarelin was associated with a shorter time needed for ovarian stimulation and a reduced gonadotrophin requirement.

1. Wong JM, *et al*. Efficacy of nafarelin in assisted reproductive technology: a meta-analysis. *Hum Reprod Update* 2001; **7:** 92–101.

Porphyria. Nafarelin nasal spray was used to prevent premenstrual exacerbations of acute intermittent porphyria (p. 1556.1) in 2 sisters.[1]

1. McNulty SJ, Hardy KJ. Two patients with acute intermittent porphyria treated with nafarelin to prevent menstrual exacerbations. *J R Soc Med* 2000; **93:** 429–30.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p. 2254.1). The usual dose of nafarelin acetate is the equivalent of nafarelin 800 micrograms intranasally (400 micrograms in each nostril) twice daily. If adequate suppression is not achieved at this dose it may be increased to 600 micrograms three times daily in alternate nostrils (1800 micrograms daily).

References to the use of nafarelin.

1. Kreiter M, *et al*. Preserving adult height potential in girls with idiopathic true precocious puberty. *J Pediatr* 1990; **117:** 364–70.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Effects on electrolytes. Severe hyperkalaemia occurred in a woman receiving nafarelin therapy for uterine fibroids.[1] Despite serum-potassium greater than 10 mmol/litre she had no symptoms and the electrocardiogram was normal. Hyperkalaemia resolved without treatment on stopping nafarelin.

1. Hata T, *et al*. Severe hyperkalaemia with nafarelin. *Lancet* 1996; **347:** 333.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nafarelin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1] For the use of nafarelin in the prevention of premenstrual exacerbations of acute porphyria, see above.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Nafarelin is rapidly absorbed on intranasal use and peak plasma concentrations occur within 20 minutes of a dose, although bioavailability is only about 3%. The plasma half-life is about 3 to 4 hours. Nafarelin is metabolised by peptidases in the body; after subcutaneous dosage it is excreted in urine, as metabolites and a small amount of unchanged drug, and in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Synrelin; ***Austral.***: Synarel; ***Braz.***: Synarel; ***Canad.***: Synarel; ***Cz.***: Synarel; ***Denm.***: Synarel; Synarela; ***Fin.***: Synarela; ***Fr.***: Synarel; ***Ger.***: Synarela; ***Gr.***: Synarel; ***India***: Nasarel; ***Irl.***: Synarel; ***Israel***: Synarel; ***Neth.***: Synarel; ***Norw.***: Synarela; ***Pol.***: Synarel†; ***S.Afr.***: Synarel†; ***Spain***: Synarel; ***Swed.***: Synarela; ***Switz.***: Synrelina; ***Turk.***: Synarel; ***UK***: Synarel; ***USA***: Synarel.

Nandrolone *(BAN, rINN)* ⊗

Estrenolona; Hidroxiestrenona; Nandrolon; Nandrolona; Nandroloni; Nandrolonum; Norandrostenolona; 19-Nortestosterone; Nortestrionato; Нандролон.

17β-Hydroxyestr-4-en-3-one; 3-Oxoestr-4-en-17β-yl.

$C_{18}H_{26}O_2$=274.4

CAS — 434-22-0.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

UNII — 6PG9VR430D.

Nandrolone Cyclohexylpropionate *(BANM, rINNM)* ⊗

Ciclohexilpropionato de nandrolona; Nandrolona, ciclohexilpropionato de; Nandrolone Cyclohexanepropionate; Nandrolone, Cyclohexylpropionate de; Nandroloni Cyclohexylpropionas; Nortestosterone Cyclohexylpropionate; Нандролона Циклогексилпропионат.

3-Oxoestr-4-en-17β-yl 3-cyclohexylpropionate; 17β-Hydroxyestr-4-en-3-one cyclohexylpropionate.

$C_{27}H_{40}O_3$=412.6

CAS — 912-57-2.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

UNII — K4NE48GG1Y.

Nandrolone Decanoate *(BANM, USAN, rINNM)* ⊗

Decanoato de nandrolona; Nandrolona, decanoato de; Nandrolondecanoat; Nandrolon-dekanoát; Nandrolone, décanoate de; Nandroloni Decanoas; Nandrolonu dekanonian; Nortestosterone Decanoate; Nortestosterone Decylate; Нандролона Деканоат.

3-Oxoestr-4-en-17β-yl decanoate; 17β-Hydroxyestr-4-en-3-one decanoate.

$C_{28}H_{44}O_3$=428.7

CAS — 360-70-3.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

UNII — H45187T098.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Nandrolone Decanoate). A white or almost white, crystalline powder. M.p. 34 degrees to 38 degrees. Practically insoluble in water; very soluble in alcohol and in dichloromethane. Store under nitrogen at 2 degrees to 8 degrees. Protect from light.

USP 36: (Nandrolone Decanoate). A white to creamy-white fine crystalline powder, odourless or may have a slight odour. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, and in vegetable oils. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Nandrolone Laurate *(BANM, rINNM)* ⊗

Dodecanoato de nandrolona; Laurato de nandrolona; Nandrolona, laurato de; Nandrolone Dodecanoate; Nandrolone, Laurate de; Nandroloni Lauras; Nortestosterone Laurate; Нандролона Лаурат.

3-Oxoestr-4-en-17β-yl dodecanoate; 17β-Hydroxyestr-4-en-3-one dodecanoate.

$C_{30}H_{48}O_3$=456.7

CAS — 26490-31-3.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Nandrolone Laurate). A white to creamy-white crystalline powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, in ether, in fixed oils, and in esters of fatty acids. Store at 2 degrees to 8 degrees. Protect from light.

Nandrolone Phenylpropionate *(BANM, rINNM)* ⊗

Fenilpropionato de nandrolona; Nandrolona, fenilpropionato de; Nandrolone Hydrocinnamate; Nandrolone Phenpropionate; Nandrolone, Phénylpropionate de; Nandroloni Phenylpropionas; Nandrolonu fenylopropionian; 19-Norandrostenolone Phenylpropionate; Nortestosterone Phenylpropionate; NSC-23162; Нандролона Фенилпропионат.

3-Oxoestr-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyestr-4-en-3-one 3-phenylpropionate.

$C_{27}H_{34}O_3$=406.6

CAS — 62-90-8.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

UNII — KF7Z9K2T3W.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nandrolone phenylpropionate:

Iron Brew.

Pharmacopoeias. In *Br., Chin., Pol.*, and *US.*

BP 2014: (Nandrolone Phenylpropionate). A white to creamy-white crystalline powder with a characteristic odour. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 36: (Nandrolone Phenpropionate). Store in airtight containers. Protect from light.

Nandrolone Sodium Sulfate *(BANM, rINNM)* ⊗

Nandrolona, sulfato sódico de; Nandrolone Sodium Sulphate; Nandrolone, Sulfate Sodique de; Nandroloni Natrii Sulfas; Nortestosterone Sodium Sulphate; Sulfato sódico de nandrolona; Нандролона Натрия Сульфат.

3-Oxoestr-4-en-17β-yl sodium sulphate; 17β-Hydroxyestr-4-en-3-one sodium sulphate.

$C_{18}H_{25}O_5SNa$=376.4

CAS — 60672-82-4.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

UNII — W945A5Q7XN.

Nandrolone Undecylate *(rINNM)* ⊗

Nandrolona, undecilato de; Nandrolone Undecanoate (BANM); Nandrolone, Undécylate de; Nandroloni Undecylas; Nortestosterone Undecanoate; Undecilato de nandrolona; Нандролона Ундесилат.

3-Oxoestr-4-en-17β-yl undecanoate; 17β-Hydroxyestr-4-en-3-one undecanoate.

$C_{29}H_{46}O_3$=442.7

CAS — 862-89-5.

ATC — A14AB01; S01XA11.

ATC Vet — QA14AB01; QS01XA11.

UNII — K64MCF119Z.

Uses and Administration

Nandrolone is an anabolic steroid with some androgenic properties (see Testosterone, p. 2305.2). It is usually given as the decanoate ester in the form of oily intramuscular injections. The hexyloxyphenylpropionate, propionate, phenylpropionate, and undecylate esters have also been used.

Doses of nandrolone decanoate 25 to 100 mg once every 3 to 4 weeks have been used as an anabolic after debilitating illness, for postmenopausal osteoporosis, and for postmenopausal metastatic breast carcinoma. Doses of between 50 and 200 mg weekly have been suggested for the treatment of anaemia of chronic renal failure, and doses of 50 to 150 mg weekly for aplastic anaemia.

Nandrolone sodium sulfate has been used topically in the treatment of corneal damage.

Nandrolone cyclohexylpropionate, laurate, and phenylpropionate are used in veterinary medicine.

Cachexia. Nandrolone increased lean body-mass in patients with HIV-associated wasting[1-4] (p. 959.1) and in one study[5] was found to have greater effect than testosterone on body-weight and BMI but a similar effect on lean body-mass. Nandrolone has also increased lean body-mass in patients with end-stage renal failure undergoing dialysis.[6,7] Although caution is generally advised with the use of androgenic and anabolic steroids in patients with renal impairment (see Testosterone, p. 2308.2), a study[8] of nandrolone given for 3 months to patients with predialysis chronic renal impairment found that lean body-mass increased without fluid retention or adverse effect on renal function or serum-lipids. In these reports, intramuscular doses of nandrolone decanoate have ranged from 100 mg once every 2 weeks[4] up to 600 mg weekly,[2] and treatment has generally been given for 12 to 24 weeks.

1. Gold J, *et al.* Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. *AIDS* 1996 **10:** 745–52.
2. Sattler FR, *et al.* Effects of pharmacological doses of nandrolone decanoate and progressive resistance training in immunodeficient patients infected with human immunodeficiency virus. *J Clin Endocrinol Metab* 1999; **84:** 1268–76.
3. Storer TW, *et al.* A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. *J Clin Endocrinol Metab* 2005; **90:** 4474–82.
4. Mulligan K, *et al.* Effect of nandrolone decanoate therapy on weight and lean body mass in HIV-infected women with weight loss: a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* 2005; **165:** 578–85.
5. Gold J, *et al.* Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. *HIV Med* 2006; **7:** 146–55.
6. Johansen KL, *et al.* Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. *JAMA* 1999; **281:** 1275–81.
7. Johansen KL, *et al.* Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. *J Am Soc Nephrol* 2006; **17:** 2307–14.
8. Eiam-Ong S, *et al.* Nutritional effect of nandrolone decanoate in predialysis patients with chronic kidney disease. *J Ren Nutr* 2007; **17:** 173–8.

Male contraception. Preliminary findings showed that nandrolone suppressed spermatogenesis,[1-3] suggesting potential as a male contraceptive (p. 2232.3), but later studies seem to have favoured other androgens.

1. Schürmeyer T, *et al.* Reversible azoospermia induced by the anabolic steroid 19-nortestosterone. *Lancet* 1984; **i:** 417–20.
2. Knuth UA, *et al.* Combination of 19-nortestosterone-hexyloxyphenylpropionate (Anadur) and depot-medroxyprogesterone-acetate (Clinovir) for male contraception. *Fertil Steril* 1989; **51:** 1011–18.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Comparison of two androgens plus depot-medroxyprogesterone acetate for suppression to azoospermia in Indonesian men. *Fertil Steril* 1993; **60:** 1062–8.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

Abuse. Nandrolone, like other anabolic compounds, has been abused by athletes and bodybuilders. However, controversy has arisen over the methods used to detect abuse, and there is some evidence that metabolites of nandrolone may be produced endogenously (see under Precautions of Testosterone, p. 2308.2).

References.

1. Hemmersbach P, Grosse J. Nandrolone: a multi-faceted doping agent. *Handb Exp Pharmacol* 2010; **195:** 127–54.

Effects on the liver. Intrahepatic cholestasis occurred in a patient receiving nandrolone cyclohexylpropionate.[1]

1. Gil VG, *et al.* A non-C17-alkylated steroid and long-term cholestasis. *Ann Intern Med* 1986; **104:** 135–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nandrolone for systemic use as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] It has not yet classified nandrolone for ophthalmic use.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Deca-Durabolin; ***Austral.***: Deca-Durabolin; ***Austria***: Deca-Durabolin; ***Belg.***: Deca-Durabolin; ***Braz.***: Deca-Durabolin; ***Canad.***: Deca-Durabolin†; ***Chile***: Anaprolina; Deca-Durabolin; Nandrosande†; ***Cz.***: Deca-Durabolin; Superanabolon†; ***Fin.***: Deca-Durabolin; ***Fr.***: Keratyl†; ***Gr.***: Anaboline Depot; Anadurin; Deca-Durabolin; Elphihormo; Extraboline; Nurezan; Ziremilon; ***Hong Kong***: Deca-Durabolin; ***Hung.***: Retabolil; ***India***: Abonic; Afdec; Alidec; Amdrec; Andysan; Aridron; Avillin; Beedec; Betabolin; Betadecabolin; Betalobin; Bonobol; Bonodec; Cadec; Cadesol; Canon; CNP; Conbol; Cudec; Curebol; DDLon; Dec-Ombolin; Deca Nandrobol; Deca-Arodec; Deca-Durabolin; Deca-Intabolin; Decamax; Decameribol; Decaneurabol; Decaneurophen; Decaras; Decarise; Decasoz; Decasun; Decatop; Decatrolin; Decaven; Decavillin; Decodeca; Decolane; Decolone; Deconbol; Decozoom; Decwell; Dekot; Dena-N; Destar; Drocan; Drona; Durabolin; Duras; Dynamax; Eldec; Esnadec; Foetacare; Fordec; HND; Idec; Indac; Indobol; Indodec; Indolone; Intradec; ITN; Kandrodec; Labdec; Megabol; Mendro; Metabol; Metadec; Metup; Mitydec; Multi-ND; Myobolin; N-Zol; Nabolin Dec; Nadrone; Nandodel; Nandro; Nandrobol; Nandrodec; Nandy; Nankair; Nanzon; NDMas; NDN; Neodec; Neurabol; Neurophen; Newbolin; Nikidac; Ninza; Nisdrol; NMX; Nubolin; Octobolin; Octodec; Osidec; ***Indon.***: Deca-Durabolin; ***Irl.***: Deca-Durabolin; ***Ital.***: Deca-Durabolin; ***Malaysia***: Deca-Durabolin; ***Mex.***: Deca-Durabolin; ***Neth.***: Deca-Durabolin; Durabolin†; ***Norw.***: Deca-Durabolin†; ***NZ***: Deca-Durabolin; ***Pol.***: Deca-Durabolin; ***Port.***: Deca-Durabolin; ***Rus.***: Retabolil (Ретаболил); ***S.Afr.***: Deca-Durabolin; ***Singapore***: Deca-Durabolin; ***Spain***: Deca-Durabolin; ***Swed.***: Deca-Durabol†; ***Switz.***: Deca-Durabolin; ***Thai.***: Deca-Durabolin; Keratyl†; Nandro; ***UK***:

Deca-Durabolin; ***Ukr.***: Retabolil (Ретаболил); ***USA***: Androlone-D; Deca-Durabolin; Durabolin; Hybolin; Neo-Durabolic; ***Venez.***: Deca-Durabolin.

Multi-ingredient Preparations. ***Gr.***: Docabolin†; ***Indon.***: Dexatopic.

Pharmacopoeial Preparations
BP 2014: Nandrolone Decanoate Injection; Nandrolone Phenylpropionate Injection;
USP 36: Nandrolone Decanoate Injection; Nandrolone Phenpropionate Injection.

Nomegestrol Acetate *(BANM, USAN, rINNM)*

Acetato de nomegestrol; Nomegestrol acetát; Noménestrol, acétate de; Nomegestrol, acetato de; Nomegestrol Asetat; Nomegestrolacetat; Nomegestroli Acetas; Nomegestroliasetaatti; Nomegestrolio acetatas; Nomegesztrol-acetát; Org-10486-0; TX-066; Номегестрола Ацетат.

17-Hydroxy-6-methyl-19-norpregna-4,6-diene-3,20-dione acetate.

$C_{23}H_{30}O_4$=370.5

CAS — 58691-88-6 (nomegestrol); 58652-20-3 (nomegestrol acetate).

ATC — G03DB04.

ATC Vet — QG03DB04.

UNII — 83J78V5W05.

NOTE. The name Uniplant has been used as a trade mark for nomegestrol acetate.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nomegestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Protect from light.

Profile

Nomegestrol acetate is a progestogen structurally related to progesterone (p. 2300.2) that has been used in the treatment of menstrual disorders and as the progestogen component of menopausal HRT (p. 2244.1) and combined oral hormonal contraceptives (see p. 2231.3). An oral dose of nomegestrol acetate for menstrual disorders is 5 mg daily for 10 days (from day 16 to day 25 of the cycle). For HRT, typical daily doses are 3.5 to 5 mg given for 12 to 14 days of a 28-day cycle. When used in monophasic combined oral contraceptive preparations, a dose of 2.5 mg may be given daily for 24 days of each 28-day cycle. A subdermal implant is under investigation as a long-acting progestogen-only contraceptive.

References.
1. Coutinho EM, *et al.* Multicenter clinical trial on the efficacy and acceptability of a single contraceptive implant of nomegestrol acetate, Uniplant. *Contraception* 1996; **53:** 121–5.
2. Devoto L, *et al.* Hormonal profile, endometrial histology and ovarian ultrasound assessment during 1 year of nomegestrol acetate implant (Uniplant). *Hum Reprod* 1997; **12:** 708–13.
3. Barbosa IC, *et al.* Carbohydrate metabolism in sickle cell patients using a subdermal implant containing nomegestrol acetate (Uniplant). *Contraception* 2001; **63:** 263–5.
4. Arowojolu AO, Ladipo OA. Nonmenstrual adverse events associated with subdermal contraceptive implants containing normegestrel [sic] and levonorgestrel. *Afr J Med Med Sci* 2003; **32:** 27–31.
5. Barbosa IC, *et al.* Effects of a single Silastic contraceptive implant containing nomegestrol acetate (Uniplant) on endometrial morphology and ovarian function for 1 year. *Contraception* 2006; **74:** 492–7.
6. Lello S. Nomegestrol acetate: pharmacology, safety profile and therapeutic efficacy. *Drugs* 2010; **70:** 541–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lutenyl; ***Belg.***: Lutenyl; Nogest; ***Braz.***: Lutenil; ***Chile***: Lutenyl; ***Hong Kong***: Lutenyl; ***Indon.***: Lutenyl; ***Ital.***: Lutenyl; ***Mex.***: Luvenyl; ***Mon.***: Lutenyl; ***Pol.***: Lutenyl; ***Port.***: Lutenyl; ***Turk.***: Lutenyl; ***Ukr.***: Lutenyl (Лютенил).

Multi-ingredient Preparations. ***Austral.***: Zoely; ***Belg.***: Naemis; ***Denm.***: Zoely; ***Irl.***: IOA; Naemis†; Zoely; ***Ital.***: Naemis; ***Mon.***: Naemis; Zoely; ***Neth.***: Ioa; Naemis†; Zoely; ***Norw.***: Zoely; ***Port.***: Naemis; ***Spain***: Zoely; ***Swed.***: Zoely; ***Switz.***: Zoely; ***UK***: Zoely.

Norelgestromin *(BAN, USAN, rINN)*

17-Deacylnorgestimate; Norelgestromiini; Norelgestromina; Norelgestromine; Norelgestrominum; RWJ-10553; Норэльгестромин.

13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime.

$C_{21}H_{29}NO_2$=327.5

CAS — 53016-31-2.

UNII — R0TAY3X631.

Profile

Norelgestromin is a progestogen (see Progesterone, p. 2300.2); it is the primary active metabolite of norgestimate (p. 2295.3). Norelgestromin is used as the progestogenic component of a combined contraceptive transdermal patch. About 203 micrograms of norelgestromin is released daily with ethinylestradiol. A new patch is applied each week for 3 weeks of a 4-week cycle. Norelgestromin exposure from such a patch may be greater than that resulting from a comparable oral contraceptive.

References.
1. Audet M-C, *et al.* Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. *JAMA* 2001; **285:** 2347–54.
2. Abrams LS, *et al.* Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches. *J Clin Pharmacol* 2001; **41:** 1232–7.
3. Abrams LS, *et al.* Pharmacokinetics of norelgestromin and ethinyl estradiol delivered by a contraceptive patch (Ortho Evra™/Evra™) under conditions of heat, humidity, and exercise. *J Clin Pharmacol* 2001; **41:** 1301–9.
4. Abrams LS, *et al.* Pharmacokinetics of a contraceptive patch (Evra™/Ortho Evra™) containing norelgestromin and ethinyloestradiol at four application sites. *Br J Clin Pharmacol* 2002; **53:** 141–6.
5. Burkman RT. The transdermal contraceptive system. *Am J Obstet Gynecol* 2004; **190** (suppl): S49–S53.
6. Devineni D, *et al.* Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. *J Clin Pharmacol* 2007; **47:** 497–509.
7. Jick S, *et al.* Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. *Contraception* 2007; **76:** 4–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Evra; ***Austria***: Evra; ***Belg.***: Evra; ***Braz.***: Evra; ***Canad.***: Evra; ***Chile***: Evra; ***Cz.***: Evra; ***Denm.***: Evra; ***Fin.***: Evra; ***Fr.***: Evra; ***Ger.***: Evra; ***Gr.***: Evra; ***Hong Kong***: Evra; ***Hung.***: Evra; ***Irl.***: Evra; ***Israel***: Evra; ***Ital.***: Evra; ***Malaysia***: Evra; ***Mex.***: Evra; ***Neth.***: Evra; ***Norw.***: Evra; ***Philipp.***: Evra; ***Pol.***: Evra; ***Port.***: Evra; ***Rus.***: Evra (Евра); ***S.Afr.***: Evra; ***Singapore***: Evra; ***Spain***: Evra; ***Swed.***: Evra; ***Switz.***: Evra; ***Thai.***: Evra; ***UK***: Evra; ***USA***: Ortho Evra; ***Venez.***: Evra.

Norethandrolone *(BAN, rINN)* ⊗

17α-Ethyl-17β-hydroxyestr-4-en-3-one; 17β-Hydroxy-19-nor-17α-pregn-4-en-3-one; Noretandrolona; Noréthandrolone; Norethandrolonum; Норэтандролон.

$C_{20}H_{30}O_2$=302.5

CAS — 52-78-8.

ATC — A14AA09.

ATC Vet — QA14AA09.

UNII — P7W01638W6.

Uses and Administration

Norethandrolone is an anabolic steroid with some androgenic properties (see Testosterone, p. 2305.2). It is given in the treatment of aplastic anaemia in an oral dose of 0.25 to 2 mg/kg daily.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3). As with other 17α-alkylated compounds, norethandrolone may produce hepatotoxicity and liver function should be monitored. It should probably be avoided in patients with impaired liver function, and certainly if this is severe.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Nilevar.

Norethisterone *(BAN, pINN)*

Ethinylnortestosterone; Etinil hidroxiestrona; Etinilnortestosterona; Norethindrone; Norethisteron; Noréthistérone; Norethisteronum; Noretindrona; Noretisteron; Noretisterona; Noretisteronas; Noretisterone; Noretisteroni; Noretiszteron; Noretysteron; Norpregneninolona; Norpregneninolone; NSC-9564; Норэтистерон.

17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one.

$C_{20}H_{26}O_2$=298.4

CAS — 68-22-4.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

UNII — T18F433X4S.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Norethisterone). A white or yellowish-white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in acetone; soluble in dichloromethane.

USP 36: (Norethindrone). A white to creamy-white odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in chloroform and in dioxan; slightly soluble in ether.

Norethisterone Acetate *(BANM, pINNM)*

Acetato de noretisterona; Norethindrone Acetate; Norethisteronacetat; Norethisteron-acetát; Noréthistérone, Acétate de; Norethisteroni Acetas; Noretisteron Asetat; Noretisterona, acetato de; Noretisteronacetat; Noretisteroniasetaatti; Noretisterono acetatas; Noretiszteron-acetát; Норэтистерона Ацетат.

17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate; 3-Oxo-19-nor-17α-pregn-4-en-20-yn-17β-yl acetate.

$C_{22}H_{28}O_3$=340.5

CAS — 51-98-9.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

UNII — 9S44LIC7OJ.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Norethisterone Acetate). A white or yellowish-white crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Norethindrone Acetate). A white to creamy-white odourless crystalline powder. Practically insoluble in water; soluble 1 in 10 of alcohol, 1 in less than 1 of chloroform, 1 in 2 of dioxan, and 1 in 18 of ether.

Norethisterone Enantate *(BANM, pINNM)*

Enantato de noretisterona; Norestisteron Enantat; Norethindrone Enanthate; Noréthistérone, Enantate de; Norethisterone Enanthate; Norethisterone Heptanoate; Norethisteroni Enantas; Noretisterona, enantato de; Норэтистерона Энантат.

17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate.

$C_{27}H_{38}O_3$=410.6

CAS — 3836-23-5.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

UNII — HY3S2K0J0F.

Pharmacopoeias. In *Int.*

Uses and Administration

Norethisterone and its acetate and enantate esters are progestogens (see Progesterone, p. 2300.2) derived from nortestosterone that have weak oestrogenic and androgenic properties. They are commonly used as **hormonal contraceptives** (see p. 2231.3). Norethisterone and norethisterone acetate are both given orally. Typical daily doses are 350 micrograms for norethisterone and 600 micrograms for norethisterone acetate when used alone, or 0.5 to 1 mg for norethisterone and 1 to 1.5 mg for norethisterone acetate when used with an oestrogen. Norethisterone enantate is given by intramuscular injection; a dose of 200 mg provides contraception for 8 weeks. An intramuscular injection containing norethisterone enantate 50 mg with estradiol valerate 5 mg is given once each month.

Norethisterone and norethisterone acetate are used as the progestogen component of **menopausal HRT** (see p. 2244.2). Typical regimens have included either continuous daily doses of norethisterone 700 micrograms or norethisterone acetate 0.5 to 1 mg, or cyclical regimens of norethisterone or norethisterone acetate 1 mg daily for 10 to 12 days of a 28-day cycle. Norethisterone acetate is also available as transdermal patches supplying 140, 170, or 250 micrograms in 24 hours, that are applied twice weekly for 2 weeks of a 4-week cycle; the lower strengths may also be applied twice weekly on a continuous basis.

Norethisterone and norethisterone acetate may be given orally, usually in divided doses, for the treatment of conditions such as **menorrhagia** (p. 2295.1) and **endometriosis** (p. 2264.1). In menorrhagia (dysfunctional uterine bleeding), norethisterone is given in usual doses of 10 to 15 mg daily and norethisterone acetate in doses of 2.5 to 10 mg daily, in a cyclical regimen. In endometriosis the dosage of norethisterone is 10 to 25 mg daily and of norethisterone acetate 5 to 15 mg daily. Treatment of endometriosis is usually continuous for 4 to 9 months.

Norethisterone has been used in daily doses of up to 15 mg orally in a cyclical regimen in the treatment of **premenstrual syndrome** (p. 2272.3).

In **breast cancer** (p. 702.1) oral doses of up to 60 mg daily of norethisterone have been used.

For the use of norethisterone in children, see below.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include norethisterone for the management of delayed puberty (p. 2252.1) in girls. It is added after 12 to 24 months of

oestrogen therapy to establish a menstrual cycle and maintain sexual maturation, in an oral dose of 5 mg once daily for the last 7 days of a 28-day cycle.

Menorrhagia. Although cyclical norethisterone has been widely used for menorrhagia (p. 2300.3), it is of limited efficacy during ovulatory cycles[1] being most effective for anovulatory bleeding, which occurs in a minority of women with menorrhagia.

1. Lethaby A, *et al.* Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Effects on the liver. There were 6 cases of jaundice among 107 patients with breast cancer treated with high-dose norethisterone acetate;[1] the jaundice was reversible and of an obstructive type. A retrospective analysis[2] found that the use of norethisterone to prevent menstrual haemorrhage during the thrombocytopenic phase of allogeneic bone marrow transplantation was a significant risk factor for hepatic veno-occlusive disease.

1. Langlands AO, Martin WMC. Jaundice associated with norethisterone-acetate treatment of breast cancer. *Lancet* 1975; **i:** 584–5.
2. Hägglund H, *et al.* Norethisterone treatment, a major risk-factor for veno-occlusive disease in the liver after allogeneic bone marrow transplantation. *Blood* 1998; **92:** 4568–72.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies norethisterone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Abnormalities seen in the offspring of women given norethisterone during pregnancy (either alone or with ethinylestradiol) included: hypospadias,[1] masculinisation of female infants,[2] meningomyelocele or hydrocephalus,[3] and neonatal choreoathetosis associated with oral contraceptive use.[4] For reference to the fact that oral contraceptives have not generally been associated with teratogenicity, even when used inadvertently in pregnancy, see p. 2242.1.

1. Aarskog D. Clinical and cytogenetic studies in hypospadias. *Acta Paediatr Scand* 1970; (suppl 203): 1–62.
2. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172:** 1028–32.
3. Gal I, *et al.* Hormonal pregnancy tests and congenital malformation. *Nature* 1967; **216:** 83.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86:** 648–9.

Venous thromboembolism. For mention that combined oral contraceptives containing older progestogens such as norethisterone appear to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p. 2238.1.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Norethisterone is absorbed from the gastrointestinal tract, undergoing first-pass hepatic metabolism and peak plasma concentrations occur 1 to 2 hours after an oral dose. It has biphasic pharmacokinetics; an initial distribution phase is followed by a prolonged elimination phase with a half-life of about 8 hours or more. Norethisterone is highly protein bound; about 60% to albumin and 35% to sex hormone binding globulin. Use with an oestrogen increases the proportion bound to sex hormone binding globulin. It is metabolised in the liver with 50 to 80% of a dose being excreted in the urine and up to 40% appearing in the faeces.

Norethisterone acetate is rapidly hydrolysed to norethisterone, mainly by intestinal tissue.

After intramuscular injection of norethisterone enantate peak concentrations of norethisterone in plasma are not attained for several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ginediol; Primolut-Nor; Selectan; ***Austral.***: Locilan; Micronor; Noriday; Primolut N; ***Austria***: Micronovum; ***Belg.***: Primolut-Nor; ***Braz.***: Linatis; Micronor; Norestin; Primolut-Nor; ***Canad.***: Micronor; Norlutate; ***Chile***: Primolut-Nor†; ***Denm.***: Mini-Pe; Noriday; Systen Conti; ***Fin.***: Mini-Pill; Primolut N; Primolut-Nor; ***Fr.***: Milligynon†; ***Ger.***: Gestakadin†; Noristerat; Primolut-Nor†; ***Gr.***: Fortilut; Primolut-Nor; Santalut; Vilcolut; ***Hong Kong***: Norcolut; Norelut†; Primolut N†; ***Hung.***: Norcolut; ***India***: Amenova; Corolut-N; Cycloreg; Dub; Dubact; Ethisone; Gynut-N; Menor-N; Mensil-N; Norate; Noreta HRT; Norfast; Norgest; Norglen; Noristerat; Noritis; Norlut N; Nostra; Noteron; Primolut N; Styptin; ***Indon.***: Anore; Norelut; Primolut N; Regumen; ***Irl.***: Noriday; Primolut N; ***Israel***: Primolut-Nor; ***Ital.***: Primolut-Nor; ***Malaysia***: Depocon; Norcolut; Norcutin; Noriday; Noristerat; Primolut N†; Sunolut; ***Mex.***: Noristerat; Primolut-Nor; ***Neth.***: Primolut N; ***Norw.***: Conludag; Primolut N; ***NZ***: Noriday; Primolut N; ***Philipp.***: Noristerat†; Oretes; Primolut N; ***Pol.***: Primolut-Nor; ***Port.***: Primolut-Nor; ***Rus.***: Norcolut (Норколут); Primolut-Nor (Примолют-нор)†; ***S.Afr.***: Micro-Novum; Nur-Isterate; Primolut N; ***Singapore***: Depocon; Micronor†; Norcolut; Norcutin; Primolut N; SP-Norvulin; Sunolut; ***Spain***: Primolut-Nor; ***Swed.***: Mini-Pe; Primolut-Nor; ***Switz.***: Micronovum; Primolut N; ***Thai.***: Norterone; Primolut N; Steron; Sunolut; ***Turk.***: Primolut N; ***UK***: Micronor; Noriday; Noristerat; Primolut N; Utovlan; ***Ukr.***: Norcolut (Норколут); Primolut-Nor (Примолют-Нор); ***USA***: Aygestin; Heather; Jencycla; Jolivette; Nor-QD; Ortho Micronor.

Multi-ingredient Preparations. ***Arg.***: Activelle; Disequens; Estalis Sequi†; Estalis†; Estracomb†; Estragest; Evorel Conti; Evorel Sequi; Kliogest; Mesigyna; Primosiston; Trial Combi; Trial Gest; Trisequens; ***Austral.***: Brevinor; Estalis Continuous; Estalis Sequi; Estracombi; Improvil; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; ***Austria***: Activelle; Duokliman; Estalis Sequens†; Estalis; Estracomb†; Kliogest; Mericomb; Merigest; Ovysmen; Perikliman; Primosiston; Sequidot 2-Phasen; Trinovum; Trisequens; ***Belg.***: Activelle; Estalis; Estracombi; Kliogest; Novofem; Ovysmen; Trinovum; Trisequens; ***Braz.***: Activelle; Ciclovulon; Cliane; Estalis SQ; Estalis; Estragest; Gineane; Kliogest; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Primosiston; Suprelle; Suprema; Systen Conti; Systen Sequi; Trisequens; ***Canad.***: Activelle; Brevicon; Estalis; Estracomb†; FemHRT; Loestrin 1.5/30; Minestrin; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Select 1/35; Synphasic; ***Chile***: Activelle; Cliane; Enadiol Neta†; Estracomb†; Estragest; Ginefolin; Kliogest; Mesigyna; Primosiston; Trisequens; ***China***: Activelle (诺更宁); Compound Norethisterone (复方炔诺酮); Novofem; Trisequens (诺康律); Yi Wei Xian (逸维仙); Yiketing (谊可婷); ***Cz.***: Activelle; Estalis Sequi†; Estalis†; Gynovel; Kliane; Kliogest; Noviana; Novofem; Pausogest†; Sequidot†; Systen Conti; Systen Sequi; Trinovum; Trisequens; ***Denm.***: Activelle; Cliovelle; Estracomb†; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Kliogest; Novofem; Trinovum†; Trisekvens; Trisequens; ***Fin.***: Activelle; Cliovelle; Estalis Sekvens†; Estalis; Evorel Conti; Evorel Sequi; Kliogest; Mericomb†; Merigest†; Novofem; Sequidot; Trisekvens; ***Fr.***: Activelle; Kliogest; Minephase†; Novofemme; Ortho-Novum 1/35†; Triella; Trisequens; ***Ger.***: Activelle; Clionara; Cliovelle; Conceplan M; Estalis Sequi†; Estragest; Eve; Gynamon†; Kliogest N; Mericomb; Merigest; Novofem; Sequidot; Synphasec; Trinovum; Trisequens; ***Gr.***: Activelle; Estalis Sequi; Estalis Sequidot; Estalis; Estracomb TTS; Kliogest; Systen Conti; Systen Sequi; Trisequens; ***Hong Kong***: Activelle; Estracomb†; Kliogest; Norinyl-1†; Novofem; Trisequens; ***Hung.***: Activelle; Estracomb†; Estragest; Kliogest; Novofem; Pausogest; Triaklim; Trisequens; Tulita; ***Irl.***: Activelle; Brevinor†; Estalis Sequi†; Estalis†; Estracombi†; Evorel Conti; Kliogest; Novofem; Trisequens; ***Israel***: Activelle; Eviana; Evorel Conti; Evorel Sequi; Kliogest; Novofem; Trisequens; ***Ital.***: Activelle; Estalis Sequi; Estracomb†; Kliogest; Trisequens; ***Jpn***: Lunabell; Ortho 777; ***Malaysia***: Activelle; ***Mex.***: Cliane; Estalis†; Estracomb; Evorel Conti; Mesigyna; Norace; Norinyl; Nostidyn; Ortho-Novum 1/35; ***Neth.***: Activelle; Estalis Sequi†; Estalis†; Estracomb†; Eviana; Kliogest; Modicon; Neocon; Novofem; Trinovum; Trisequens; ***Norw.***: Activelle; Cliovelle; Estalis Sekvens†; Estalis; Eviana; Kliogest†; Novofem; Sequidot; Synfase; Trisekvens; ***NZ***: Brevinor; Cliane†; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; ***Philipp.***: Kliogest; Micropil Plus; Micropil; ***Pol.***: Activelle; Cliovelle; Estalis Sequi†; Estalis; Estracomb; Kliogest; Novofem; Systen Conti; Systen Sequi; Trinovum†; Trisequens; ***Port.***: Activelle; Estalis Sequi; Estalis; Estracomb†; Kliogest; Novofem; Trisequens; ***Rus.***: Kliogest (Клиогест); Non-Ovlon (Нон-овлон)†; Pausogest (Паузогест); Triaklim (Триаклим); Trisequens (Трисеквенс); ***S.Afr.***: Activelle; Estalis; Estracombi†; Estro-Pause N; Evorel Conti; Evorel Sequi; Kliogest; Norinyl-1/28; Novofem; Trinovum; Trisequens; ***Singapore***: Activelle; Estracomb; Kliogest†; Trisequens; ***Spain***: Absorlent Plus†; Activelle; Duofemme; Endomina Plus†; Estalis Sequi; Estalis; Estracomb†; Eviana; Merigest Sequi†; Merigest†; Trisequens; ***Swed.***: Activelle; Cliovelle; Estalis; Eviana; Femanor; Femasekvens; Kliogest†; Novofem; Orthonett Novum; Sequidot; Synfase; Trinovum; Trisekvens†; ***Switz.***: Activelle; Estalis Sequi†; Estalis; Estracomb†; Estragest; Estranor; Kliogest N; Mericomb†; Merigest†; Novofem; Primosiston†; Sequidot; Systen Conti; Systen Sequi; Trinovum; Trisequens; ***Thai.***: Activelle; Anamai; Havina†; ***Turk.***: Activelle; Estracombi; Kliogest; Mesigyna; Trisequens; ***UK***: Binovum; Brevinor; Climagest; Climesse; Clinorette; Elleste Duet Conti; Elleste-Duet; Estracombi†; Evorel Conti; Evorel Sequi; Kliofem; Kliovance; Loestrin; Norimin; Norinyl-1; Novofem; Nuvelle Continuous; Ovysmen; Synphase; Trinovum; Trisequens; ***Ukr.***: Pausogest (Паузогест)†; Revmelid (Ревмелид)†; ***USA***: Activella; Alyacen 1/35; Alyacen 7/7/7; Aranelle; Balziva; Brevicon; Briellyn; CombiPatch; Estrostep Fe; Femcon Fe; FemHRT; Jinteli; Junel Fe; Leena; Lo Loestrin Fe; Lo Minastrin Fe; Loestrin Fe; Loestrin; Lupaneta Pack; Mimvey; Minastrin 24 FE; Modicon; Necon 1/50; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Norinyl 1 + 35; Norinyl 1 + 50; Nortrel; Ortho-Novum 1/35; Ortho-Novum 1/50†; Ortho-Novum 10/11†; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Pirmella 1/35; Pirmella 7/7/7; Tilia Fe; Tri-Legest; Tri-Norinyl; Wymzya Fe; Zenchent Fe; Zenchent; ***Venez.***: Cliane; Estragest; Mesigyna.

Pharmacopoeial Preparations

BP 2014: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Norethisterone Tablets;

USP 36: Estradiol and Norethindrone Acetate Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone Acetate Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norethindrone and Mestranol Tablets; Norethindrone Tablets.

Noretynodrel *(BAN, rINN)*

Norethynodrel (USAN); Norethynodrel; Noretinodrel; Noretynodreeli; Norétynodrel; Noretynodrelum; NSC-15432; SC-4642; Норэтинодрел.

17β-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

$C_{20}H_{26}O_2$=298.4

CAS — 68-23-5.

UNII — 88181ACA0M.

Profile

Noretynodrel is a progestogen (see Progesterone, p. 2300.2) structurally related to norethisterone that has been given orally with an oestrogen such as mestranol for the treatment of various menstrual disorders and endometriosis.

Breast feeding. About 1% of an oral dose of radiolabelled noretynodrel was detected in breast milk in a study of 4 women.[1] No adverse effects have been seen in breast-fed infants of mothers given noretynodrel, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Laumas KR, *et al.* Radioactivity in the breast milk of lactating women after oral administration of ^{3}H-norethynodrel. *Am J Obstet Gynecol* 1967; **98:** 411–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Pregnancy. A woman given noretynodrel during pregnancy to prevent threatened miscarriage gave birth to a female infant showing signs of masculinisation.[1]

1. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172:** 1028–32.

Norgestimate *(BAN, USAN, rINN)*

D-138; Dexnorgestrel Acetime; Norgestimaatti; Norgestimat; Norgestimato; Norgestimatum; ORF-10131; RWJ-10131; Норгестимат.

13β-Ethyl-3-hydroxyimino-18,19-dinor-17α-pregn-4-en-20-yn-17β-yl acetate.

$C_{23}H_{31}NO_3$=369.5

CAS — 35189-28-7.

UNII — C291HFX4DY.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Norgestimate). A white or almost white powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in acetone.

USP 36: (Norgestimate). A mixture of (*E*)- and (*Z*)-isomers having a ratio of (*E*)- to (*Z*)-isomer between 1.27 and 1.78. A white to pale yellow powder. Insoluble in water; sparingly soluble in acetonitrile; freely to very soluble in dichloromethane.

Profile

Norgestimate is a progestogen (see Progesterone, p. 2300.2) structurally related to levonorgestrel (to which it is partly metabolised) that is used as the progestogenic component of combined oral contraceptives (see p. 2231.3) and in menopausal HRT (see p. 2244.1). A typical daily dose is 250 micrograms in monophasic contraceptive preparations, and 180 to 250 micrograms in triphasic preparations. For HRT, a regimen of estradiol daily for 3 days followed by estradiol with norgestimate 90 micrograms daily for 3 days is used; this 6-day cycle is repeated continuously without interruption.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies norgestimate in combined hormonal contraceptives as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cilest; Prefest; Tridette; ***Austria***: Cileste; TriCilest; Vivelle; ***Belg.***: Cilest; ***Braz.***: Prefest; ***Canad.***: Cyclen; Tri-Cyclen; ***Chile***: Mactex; Neofam†; Orlon; Tri-Mactex†; ***Cz.***: Cilest; Pramino; ***Denm.***: Cilest; ***Fin.***: Cilest; ***Fr.***: Cilest; Effiprev; Triafemi; TriCilest; ***Ger.***: Cilest; Pramino; ***Hung.***: Cilest; ***Irl.***: Cilest; ***Israel***: Ortho Cyclen; ***Mex.***: Cilest; Prefest; ***Neth.***: Cilest; ***Pol.***: Cilest; ***Rus.***: Cilest (Силест); ***S.Afr.***: Cilest; Prefesta†; TriCilest; ***Spain***: Edelsin; ***Swed.***: Cilest; ***Switz.***: Cilest; ***Thai.***: Cilest; TriCilest; ***UK***: Cilest; Lizinna; ***USA***: Estarylla; Ortho Cyclen; Ortho Tri-Cyclen; Prefest; Previfem; Sprintec; Tri-Estarylla; Tri-Linyah; Tri-Lo-Sprintec; Tri-Previfem; Tri-Sprintec; TriNessa; ***Venez.***: Ortrel.

Pharmacopoeial Preparations
USP 36: Norgestimate and Ethinyl Estradiol Tablets.

Norgestomet *(BAN, USAN, rINN)*

Norgestometum; SC-21009; Норгестомет.
11β-Methyl-3,20-dioxo-19-norpregn-4-en-17α-yl acetate.
$C_{23}H_{32}O_4$=372.5
CAS — 25092-41-5.
UNII — 3L33UD42X4.

Profile

Norgestomet is a progestogen (see Progesterone, p. 2300.2) used in veterinary medicine with estradiol.

Norgestrel *(BAN, USAN, rINN)*

dl-Norgestrel; Norgestreeli; DL-Norgestrel; Norgestrelis; Norgestrelum; Norgesztrel; Wy-3707; Норгестрел.
(±)-13-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.
$C_{21}H_{28}O_2$=312.5
CAS — 6533-00-2.
UNII — 3J8Q1747Z2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Norgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Norgestrel). A white or practically white, practically odourless crystalline powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform.

Levonorgestrel *(BAN, USAN, rINN)*

Levonorgestreeli; Lévonorgestrel; Levonorgestrelis; Levonorgestrelum; Levonorgesztrel; D-Norgestrel; Wy-5104; Левоноргестрел.
(-)-13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.
CAS — 797-63-7.
ATC — G03AD01.
ATC Vet — QG03AC03.
UNII — 5W7SIA7YZW.

NOTE. The name Dexnorgestrel has also been used.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Levonorgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Levonorgestrel). A white or practically white, odourless powder. Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform. Protect from light.

Uses and Administration

Norgestrel and its active (-)-isomer levonorgestrel are progestogens (see Progesterone, p. 2300.2) derived from nortestosterone. They are more potent inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is more commonly used than norgestrel and is twice as potent. For example, levonorgestrel 10 micrograms is equivalent to norgestrel 20 micrograms.

They are both used as **hormonal contraceptives** (see p. 2231.3). The typical daily dose is the equivalent of:

- 30 micrograms of levonorgestrel as an oral progestogen-only contraceptive
- 150 micrograms of levonorgestrel in monophasic combined oral contraceptives (doses may range from a low dose of 100 micrograms of levonorgestrel in some preparations up to 250 micrograms in others; a preparation containing 90 micrograms of levonorgestrel for continuous use without a tablet-free interval is also available)
- 50 to 125 micrograms of levonorgestrel in triphasic preparations

Subcutaneous implants containing levonorgestrel may be used for long-acting progestogen-only contraception. Insertion and removal must be carried out by personnel fully trained in the technique. One available product consists of 2 implants, each containing 75 mg of levonorgestrel. It should be inserted under the skin within the first 7 days of the menstrual cycle, and is effective for up to 5 years. Another product consisting of 6 implants, which also provided up to 5 years of contraception, is no longer widely marketed. Each implant contained 36 mg of levonorgestrel. Uterine, cervical, and vaginal devices containing levonorgestrel have also been investigated. One intra-uterine device (*Mirena, Bayer*) available for contraception contains a total of 52 mg of levonorgestrel, which is released at an initial rate of about 20 micrograms per 24 hours; the device is effective for 5 years. Another intra-uterine device (*Skyla, Bayer*) contains 13.5 mg of levonorgestrel, and releases an average of about 6 micrograms daily to provide contraception for 3 years.

For **emergency contraception** (p. 2233.2), levonorgestrel may be given alone in a single oral dose of 1.5 mg within 72 hours of coitus (preferably as soon as possible). Alternatively, a dose of 750 micrograms is given within 72 hours of coitus (preferably as soon as possible), and repeated after 12 hours. Another regimen uses levonorgestrel 500 micrograms plus ethinylestradiol 100 micrograms, given within 72 hours of coitus and repeated after 12 hours.

An intra-uterine device (*Mirena, Bayer*) is available for **menorrhagia** (below). It contains a total of 52 mg of levonorgestrel, which is released at an initial rate of 20 micrograms per 24 hours, and is effective for 5 years. Another treatment should be considered if bleeding does not improve within 3 to 6 months after insertion.

Both levonorgestrel and norgestrel are used as the progestogenic component of **menopausal HRT** (see p. 2244.2). Typical regimens are the equivalent of 75 to 250 micrograms of levonorgestrel orally for 10 to 12 days of a 28-day cycle. Levonorgestrel may also be given via a combined transdermal patch, releasing 10 micrograms per 24 hours, which is applied once weekly for 2 weeks of a 4-week cycle. Alternatively, a patch releasing 7 or 15 micrograms per 24 hours with an oestrogen is applied once weekly for continuous HRT. The intra-uterine device *Mirena*, as described above, may be used for up to 4 years with oestrogen replacement therapy.

Administration. *IMPLANTS.* Some references to the use of levonorgestrel by subcutaneous implant for hormonal contraception.[1-3]

1. Coukell AJ, Balfour JA. Levonorgestrel subdermal implants: a review of contraceptive efficacy and acceptability. *Drugs* 1998; **55:** 861–87.
2. Sivin I. Risks and benefits, advantages and disadvantages of levonorgestrel-releasing contraceptive implants. *Drug Safety* 2003; **26:** 303–35.
3. Power J, *et al.* Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).

INTRA-UTERINE DEVICES. Some references to the use of levonorgestrel-releasing intra-uterine devices for contraception[1-8] and menopausal HRT.[9,10]

1. Backman T, *et al.* Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nationwide study of 17,360 users. *Br J Obstet Gynaecol* 2000; **107:** 335–9.
2. French RS, *et al.* Levonorgestrel-releasing (20 microgram/day) intrauterine systems (Mirena) compared with other methods of reversible contraceptives. *Br J Obstet Gynaecol* 2000; **107:** 1218–25.
3. Backman T. Benefit-risk assessment of the levonorgestrel intrauterine system in contraception. *Drug Safety* 2004; **27:** 1185–1204.
4. Guillebaud J. The levonorgestrel intrauterine system: a clinical perspective from the UK. *Ann N Y Acad Sci* 2003; **997:** 185–93.
5. Jensen JT. Contraceptive and therapeutic effects of the levonorgestrel intrauterine system: an overview. *Obstet Gynecol Surv* 2005; **60:** 604–12.
6. Peled Y, *et al.* Levonorgestrel-releasing intrauterine system as an adjunct to estrogen for the treatment of menopausal symptoms—a review. *Menopause* 2007; **14:** 550–4.
7. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. FSRH guidance (November 2007): intrauterine contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceIntrauterineContraceptionNov07.pdf (accessed 18/07/08)
8. Rose S, *et al.* Mirena (levonorgestrel intrauterine system): a successful novel drug delivery option in contraception. *Adv Drug Deliv Rev* 2009; **61:** 808–12.
9. Sitruk-Ware R. The levonorgestrel intrauterine system for use in peri- and postmenopausal women. *Contraception* 2007; **75** (suppl): S155–S160.
10. Chrisman C, *et al.* The levonorgestrel-releasing intrauterine system: an updated review of the contraceptive and noncontraceptive uses. *Clin Obstet Gynecol* 2007; **50:** 886–97.

Menorrhagia. Although oral cyclical progestogens have limited efficacy in the treatment of menorrhagia (p. 2300.3), a levonorgestrel-containing intra-uterine device appears to be particularly useful in reducing menstrual blood loss.[1-5]

1. Lethaby AE, *et al.* Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 06/09/13).
2. Kaunitz AM, *et al.* Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. *Obstet Gynecol* 2009; **113:** 1104–16.
3. Kaunitz AM, Inki P. The levonorgestrel-releasing intrauterine system in heavy menstrual bleeding: a benefit-risk review. *Drugs* 2012; **72:** 193–215.
4. Jensen J, *et al.* Bleeding patterns with the levonorgestrel-releasing intrauterine system when used for heavy menstrual bleeding in women without structural pelvic pathology: a pooled analysis of randomized controlled studies. *Contraception* 2013; **87:** 107–12.
5. Gupta J, *et al.* ECLIPSE Trial Collaborative Group. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *N Engl J Med* 2013; **368:** 128–37.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p. 2301.2 and p. 2301.3). See also under Hormonal Contraceptives, p. 2233.3 and p. 2240.3.

Incidence of adverse effects. After the introduction of levonorgestrel in a subdermal implant formulation in February 1991, the US FDA had received about 5800 reports of adverse effects as of December 1993 (out of an estimated 891 000 implants distributed).[1] Serious adverse effects associated with the implant included 24 cases of infection related to insertion of the implant, 15 cases of stroke and 39 of benign intracranial hypertension, 3 cases of thrombocytopenic purpura and 6 of thrombocytopenia (1 fatal). None of the reporting rates for these disorders exceeded the expected rate in this population. In a 5-year cohort study[2] of more than 16 000 women who received either a levonorgestrel implant or an IUD (not progestogen-releasing), or underwent sterilisation, there was no significant risk of major morbidity associated with the implant, although there were moderately elevated risks of gallbladder disease and raised blood pressure in current users.

1. Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol* 1995; **85:** 538–42.
2. Meirik O, *et al.* Safety and efficacy of levonorgestrel implant, intrauterine device, and sterilization. *Obstet Gynecol* 2001; **97:** 539–47.

Benign intracranial hypertension. Intracranial hypertension, presenting as headaches, vomiting, and visual obscuration associated with florid bilateral papilloedema developed in 2 patients 4 to 5 months after subdermal implantation of levonorgestrel.[1] Despite a further 56 cases reported to various drug monitoring centres, and 70 cases known to the manufacturers,[2] it remained unclear whether the drug actually caused intracranial hypertension, but removal of implants was recommended in patients in whom intracranial pressure increased.

1. Alder JB, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; **332:** 1720–1.
2. Weber ME, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; **332:** 1721.

Breast feeding. Levonorgestrel was detected in breast milk and the circulation of breast-fed infants during the use of either a levonorgestrel IUD, subcutaneous implant, or progestogen-only oral contraceptive.[1] A review[2] of studies of a levonorgestrel implant used during lactation concluded that it did not adversely affect the duration of lactation, infant growth or development. Further studies of a levonorgestrel IUD[3] and implant[4] also found no adverse effect on lactation or infant growth. The implant study[4] did find an increased incidence of mild respiratory, skin, and eye diseases in infants in the first year of life, but the possibility of bias or chance could not be excluded. The American Academy of Pediatrics considers that levonorgestrel is usually compatible with breast feeding.[5] Progestogen-only contraceptives should not be started until several weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p. 2241.1).

In a pharmacokinetic study[6] using a single oral dose of levonorgestrel 1.5 mg, the drug concentration peaked between 2 and 4 hours in breast milk and then fell rapidly. The authors suggested that breast-feeding women who are given this dose of levonorgestrel for emergency contraception should be advised to breast feed immediately before the dose, then discard milk for at least 8 hours but not more than 24 hours.

1. Shikary ZK, *et al.* Transfer of levonorgestrel (LNG) administered through different drug delivery systems from the maternal circulation into the newborn infant's circulation via breast milk. *Contraception* 1987; **35:** 477–86.
2. Díaz S. Contraceptive implants and lactation. *Contraception* 2002; **65:** 39–46.
3. Shaamash AH, *et al.* A comparative study of the levonorgestrel-releasing intrauterine system Mirena versus the copper T380A intrauterine device during lactation: breast-feeding performance, infant growth and infant development. *Contraception* 2005; **72:** 346–51.
4. Schiappacasse V, *et al.* Health and growth of infants breastfed by Norplant contraceptive implants users: a six-year follow-up study. *Contraception* 2002; **66:** 57–65.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

6. Gainer E, *et al*. Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception. *Hum Reprod* 2007; **22:** 1578–84.

Effects on the blood. Studies[1-3] of women who had been given different levonorgestrel subcutaneous implants found that over 5 years there were various changes in blood clotting factors, fibrinolytic activity, and platelet number and aggregation, some of which persisted even 6 months after removal of the implants. However, these haemostatic changes did not result in activation of the coagulation system or a state of hypercoagulation.

1. Singh K, *et al*. Evaluation of hemostatic function following Norplant implant removal. *Adv Contracept* 1993; **9:** 49–58.
2. Singh K, *et al*. Evaluation of hemostatic function following Norplant-2 rods removal. *Adv Contracept* 1993; **9:** 241–50.
3. Koh SCL, *et al*. A prospective study on the effects of reformulated 2-rod Norplant implant on haemostasis after five years of use. *J Obstet Gynaecol Res* 1999; **25:** 177–83.

Effects on carbohydrate metabolism. For a mention that levonorgestrel has been reported to be the most potent progestogen associated with hyperinsulinaemia when used as a combined oral contraceptive, see p. 2236.3.

Glucocorticoid effects. Reference to the minimal suppressive effect of subdermal levonorgestrel on adrenal function.[1]

1. Toppozada MK, *et al*. Effect of Norplant implants on the pituitary-adrenal axis function and reserve capacity. *Contraception* 1997; **55:** 7–10.

Myasthenia gravis. Myasthenia gravis occurring after insertion of a levonorgestrel implant improved on removal of the implant.[1]

1. Brittain J, Lange LS. Myasthenia gravis and levonorgestrel implant. *Lancet* 1995; **346:** 1556.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levonorgestrel and oestrogen combinations as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Adverse effects in infants whose mothers had received oral contraceptives containing norgestrel during early pregnancy have included tracheo-oesophageal fistula in one infant[1] and inoperable hepatoblastoma in another.[2] However, many epidemiological studies have failed to show any association between fetal malformations and oral contraceptives, even when used inadvertently during pregnancy, see p. 2242.1.

1. Frost O. Tracheo-oesophageal fistula associated with hormonal contraception during pregnancy. *BMJ* 1976; **2:** 978.
2. Otten J, *et al*. Hepatoblastoma in an infant after contraceptive intake during pregnancy. *N Engl J Med* 1977; **297:** 222.

Venous thromboembolism. For mention that levonorgestrel-containing combined oral contraceptives appeared to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p. 2238.1. See also Effects on the Blood, above.

Interactions

As for progestogens in general (see Progesterone, p. 2302.2). See also under Hormonal Contraceptives, p. 2242.3.

Pharmacokinetics

Levonorgestrel is rapidly and almost completely absorbed after an oral dose, and undergoes little first-pass hepatic metabolism. It is highly bound to plasma proteins; 42 to 68% to sex hormone binding globulin and 30 to 56% to albumin. The proportion bound to sex hormone binding globulin is higher when it is given with an oestrogen. Levonorgestrel and norgestrel are metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine and to a lesser extent in the faeces. Levonorgestrel is distributed into breast milk.

References.

1. Fotherby K. Levonorgestrel: clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **28:** 203–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Marplan; Microlut; Mirena; Norgestrel Continuo; Norgestrel Max; Ovulol; Postinor-2; Preventor; Secufem; Segurite; ***Austral.***: Levonelle; Microlut; Microval†; Mirena; Norlevo; Postinor; ***Austria***: Mirena; Postinor; Vikela; ***Belg.***: Microlut; Mirena; Norlevo; Postinor; ***Braz.***: Dia D; Minipil-2 Post; Minipil; Mirena; Neodia; Nortrel†; Pilem; Poslov; Postinor Uno; Postinor-2; Pozato; Previdez-2; Prevyol; ***Canad.***: Mirena; Norlevo; Plan B; ***Chile***: Microval; Mirena; Tace; ***China***: An Ting (安婷); Escapelle (爱乐保)†; Hui Ting (惠婷); Mirena (曼月乐); Postinor (保仕婷); Yu Ting (毓婷); ***Cz.***: Escapelle; Mirena; Postinor; ***Denm.***: Mirena; NorLevo; ***Fin.***: Jadelle; Microluton; Mirena; Norlevo; ***Fr.***: Microval; Mirena; Norlevo; ***Ger.***: 28 mini; Duofem†; Levogynon†; Microlut; Mirena; PiDaNa; unofem†; ***Gr.***: Mirena; Norlevo; Postinor; ***Hong Kong***: Escapelle; Mirena; Pill 72; Postinor-2; ***Hung.***: Escapelle; Mirena; Rigesoft; ***India***: Ecee; G-Pill; I-Pill; MPill; Nofear-72; Norlevo; Oh God; Pill 72; ***Indon.***: Microlut; Mirena; Norplant†; Postinor-2; ***Irl.***: Levonelle; Microval; Mirena; Norlevo; ***Israel***: Afterday; Microlut; Mirena; Norlevo; Postinor; ***Ital.***: Levonelle; Mirena; Norlevo; ***Jpn***: NorLevo; ***Malaysia***: Escapelle; Madonna; Me; Mirena; Postinor; ***Mex.***: Alterna; Ceciora T; Dreams; Glanique; Hispatrel†; Ladiades; Microlut; Mirena; Post-Day; Postinor-2; Silogin; ***Neth.***: Jadelle†; Mirena; Norlevo; Postinor; Vikela; ***Norw.***: Jadelle†; Mirena; Norlevo; Postinor; ***NZ***: Jadelle; Levonelle; Microlut; Mirena; Postinor; ***Philipp.***: Mirena; ***Pol.***: Escapelle; Mirena; Postinor-Duo†; ***Port.***: Jadelle; Levonelle†; Mirena; Norlevo; Postinor; ***Rus.***: Escapelle (Эскапел); Microlut (Микролют); Mirena (Мирена); Postinor (Постинор); ***S.Afr.***: Escapelle; Microval; Mirena; Norlevo; ***Singapore***: Estinor; Mirena; Postinor; ***Spain***: Jadelle†; Mirena; Norlevo; Postinor; ***Swed.***: Jadelle†; Levonova†; Mirena; NorLevo; Postinor; ***Switz.***: Mirena; NorLevo; ***Thai.***: Hyan; Jadelle; Madonna; Mirena; Norplant; Postinor; ***Turk.***: Mirena; Norlevo; ***UK***: Levonelle; Mirena; Norgeston; Postinor-2; Upostelle; ***Ukr.***: Escapelle (Эскапел); Mirena (Мирена); Postinor (Постинор); ***USA***: Mirena; My Way; Next Choice; Plan B; Skyla; ***Venez.***: Jadelle; Microval; Mirena; Norlevo; Postinor-2.

Multi-ingredient Preparations. ***Arg.***: Afrodita; Anubis; April; Ciclocur; Cuarcic†; Dos Dias N; Elektra; Evelea; Femexin; Loette; Microfem; Microgynon; Microvlar; Miranova; Neogynon; Nordette; Norfen; Norgestrel Cex; Norgestrel Minor; Norgestrel Plus; Tridestan N; Trinordiol; Triquilar; ***Austral.***: Levlen ED; Loette; Logynon ED; Microgynon; Microlevlen ED; Monofeme; Nordette; Sequilar ED†; Trifeme; Triphasil; Triquilar; ***Austria***: FemSeven Combi; Leonore; Loette; Madonella; Microgynon; Ovranette; Sequilar†; Trigynon†; Trinordiol; Xyliette; ***Belg.***: Cyclocur; Eleonor; Feminova Plus; Lowette; Microgynon; Nora-30; Stediril 30; Trigynon; Trinordiol; ***Braz.***: Anfertil; Ciclo; Ciclofemme; Ciloprimogyna; Concepnor; Evanor; Gestrelan; Level; Levordiol; Lindisc Duo; Lovelle; Microvlar; Miranova; Neovlar; Nociclin; Nordette; Normamor; Trinordiol; Triquilar; ***Canad.***: Alesse; Aviane; Climara Pro; Min-Ovral; Ovral; Portia; Seasonale; Seasonique; Triquilar; ***Chile***: Alesse†; Anovulatorio Micro-Dosis; Anulette; Fem 7 Combi; Femitres; Innova Cd; Microgynon; Miranova; Modutrol†; Nordette; Nordiol; Norvetal; Progyluton; Trinordiol; Triquilar; Trolit; ***China***: Compound Norgestrel (复方炔诺孕酮); Duorina (多日纳); Triquilar (特居乐); Yueketing (悦可婷); ***Cz.***: Gravistat; Klimonorm; Loette; Microgynon; Minisiston; Tri-Regol; Trinordiol†; Triquilar; ***Denm.***: Femicept; Loette; Malonetta; Microgyn; Neogynon†; Nuvelle†; Rigevidon; Tercette; Triafem; Triminetta; Trinordiol†; Triquilar; Triregol; ***Fin.***: Cyclabil†; FemSeven Combi†; Laurette; Microgynon; Miranova; Trikvilar; ***Fr.***: Adepal; Amarance; Daily; Evanecia; Lovavulo; Ludeal; Minidril; Pacilia; Stediril; Trinordiol; ***Ger.***: Asumate; Cyclo-Progynova N; CycloOstrogynal; Evaluna; Fem 7 Combi; Fem 7 Conti; Femigoa; Femigyne; Femranette mikro†; Gravistat; illina†; Klimonorm; Leios; Leona; Liana; Microgynon; Minisiston; Miranova; MonoStep; NovaStep; Ostronara; Triette†; Trigoa; Triquilar; Trisiston; Wellnara; ***Gr.***: Cyclacur; Loette; Microgynon; Neogynon; Nordette; Nordiol; Nuvelle; Ovral; Trinordiol; Triquilar; ***Hong Kong***: Eugynon†; Loette; Microgynon; Nordette; Rigevidon; Tri-Regol; ***Hung.***: Anteovin†; FemSeven Combi†; Klimonorm; Loette†; Ovidon†; Rigevidon; Tri-Regol; Trinordiol†; Triquilar†; ***India***: Choice; Combee; Dear-21; Divacon; Duoluton-L; Ergest; Loette; Ovilow; Ovimed; Ovipauz-L; Ovral; Triquilar; ***Indon.***: Cyclo-Progynova; Microdiol; Microgynon; Pil Keluarga Berencana†; Planak; Trinordiol†; Triquilar; ***Irl.***: FemSeven Conti; FemSeven Sequi†; Leonore; Logynon; Microlite; Ovogrel†; Ovran; Ovranette; Prempak-C; Rigevidon; Trinordiol; Vonodiol; ***Israel***: Microgynon; Nordette; Progluton; Seasonique; ***Ital.***: Combiseven; Egogyn; Femity; Loette; Microgynon; Miranova; Novogyn; ***Jpn***: Ange; ***Malaysia***: Loette; Microgynon 30; Nordette; Oralcon; Progyluton; Rigevidon; Trigestrel; Trinordiol; ***Mex.***: Alesse; Esdegen; Femexin; Letinnov; Microgynon; Neogynon; Nordet; Nordiol†; Ovral; Progyluton; Trinordiol; Triquilar; ***Mon.***: FemseptCombi; Femseptevo; Leeloo; ***Neth.***: Alesse†; Cyclocur†; Fem 7 Sequi†; Logynon†; Lovette; Microgynon; Miranova; Oralcon; Stediril; Trigynon; Trinordiol; ***Norw.***: Loette; Microgynon; Oralcon; ***NZ***: Levlen ED; Loette; Microgynon; Monofeme; Nordette; Nuvelle; Roxanne; Trifeme; Triphasil; Triquilar; ***Philipp.***: Azul; Blush; Charlize; Femenal†; Femme; Lady; Logynon; Microgynon†; Nordette; Nordiol; Norfem; Rigevidon; Safe Pill; Seif; Trinordiol; Trust Pill; ***Pol.***: Anteovin†; Cyclo-Progynova; Fem 7 Combi; Gravistat†; Klimonorm; Microgynon; Minisiston†; Rigevidon; Stediril; Tri-Regol; Trinordiol; Triquilar; Trisiston; ***Port.***: Femsete Combi; Femsete Evo; Microginon; Miranova; Nuvelle; Progyluton; Tetragynon; Trinordiol; Triquilar†; ***Rus.***: Anteovin (Антеовин)†; Cyclo-Progynova (Цикло-прогинова); Klimonorm (Климонорм); Microgynon (Микрогинон); Minisiston (Минизистон); Ovidon (Овидон)†; Rigevidon (Ригевидон); Tri-Regol (Три-Регол); Triquilar (Триквилар); Trisiston (Тризистон); ***S.Afr.***: Biphasil; E-Gen-C; Loette†; Logynon ED; Miranova†; Nordette; Nordiol; Ovral; Postoval; Triphasil; ***Singapore***: Loette†; Microgynon; Nordette†; Prempak-C†; Progyluton; Trinordiol†; ***Spain***: Levobel; Loette; Microgynon; Neogynona; Nuvelle†; Ovoplex; Progyluton; Triagynon; Triciclor; ***Swed.***: Abelonelle; Neovletta; Prionelle; Trinordiol; Trionetta; Triregol; ***Switz.***: Cyclacur; Elyfem; Levomin; Microgynon; Miranova; Ologyn; ***Thai.***: Anna; Cyclo-Progynova; Dior; Jeny-FMP; Klimonorm†; Manodiol; Microgest†; Microgynon; Microlenyn; Nordette; Oralcon-F; R-Den; Riget†; Rigevidon; Trigestrel; Triquilar; ***Turk.***: Cyclo-Progynova; Lo-Ovral; Microgynon; Miranova; Preven; Triquilar†; ***UK***: Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; FemSeven Conti; FemSeven Sequi; Levest; Logynon; Microgynon 30; Nuvelle†; Ovran 30; Ovranette; Prempak-C; Rigevidon; Triregol; ***Ukr.***: Klimonorm (Климонорм); Microgynon (Микрогинон)†; Ovidon (Овидон)†; Rigevidon (Ригевидон); Tri-Regol (Три-Регол); Triquilar (Триквилар); ***USA***: Alesse†; Altavera; Amethia; Aviane; Camrese; Chateal; ClimaraPro; Cryselle; Daysee; Enpresse; Falmina; Jolessa; Kurvelo; Lessina; Levora; Lo/Ovral; LoSeasonique; Lutera; Lybrel; Marlissa; Myzilra; Nordette; Ovral†; Portia; Quartette; Quasense; Seasonale; Seasonique; Sronyx; Triphasil†; Trivora; ***Venez.***: Alesse; Minigynon; Neogynon; Nordette; Nordiol; Ovral; Progyluton; Rigevidon; Tri-Regol; Trinordiol; Triquilar.

Pharmacopoeial Preparations

BP 2014: Levonorgestrel and Ethinylestradiol Tablets; Levonorgestrel Tablets; Norgestrel Tablets;

USP 36: Levonorgestrel and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets; Norgestrel Tablets.

Norgestrienone *(rINN)*

Norgestrienona; Norgestriénone; Norgestrienonum; Норгестриенон.

17β-Hydroxy-19-nor-17α-pregna-4,9,11-trien-20-yn-3-one.

$C_{20}H_{22}O_2$=294.4

CAS — 848-21-5.

ATC — G03AC07.

ATC Vet — QG03AC07.

UNII — 89386PYU9O.

Profile

Norgestrienone is a progestogen (see Progesterone, p. 2300.2) structurally related to norethisterone. It is used as a progestogen-only oral contraceptive (see p. 2231.3) in a dose of 350 micrograms daily. Norgestrienone has also been used with an oestrogen in combined oral contraceptives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ogyline†.

Normethandrone ⊗

Methylestrenolone; Methylestrenolonum; 17α-Methyl-19-nortestosterone; Methylnortestosterone; Metylöstrenolon; Metyyliestrenoloni; Normethandrolone; NSC-10039; Норметандрон.

17β-Hydroxy-17α-methylestr-4-en-3-one.

$C_{19}H_{28}O_2$=288.4

CAS — 514-61-4.

ATC — G03DC31.

ATC Vet — QG03DC31.

UNII — 743F1Z557A.

Profile

Normethandrone is a progestogen that also has androgenic and anabolic properties. It has been given orally with an oestrogen for the treatment of amenorrhoea and menopausal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Mediol†; Renodiol; ***Venez.***: Ginecosid.

Ormeloxifene *(rINN)* ⊗

Centchroman; Orméloxifène; Ormeloxifeno; Ormeloxifenum; Ормелоксифен.

trans-1-{2-[4-(3,4-Dihydro-7-methoxy-2,2-dimethyl-3-phenyl-2*H*-1-benzopyran-4-yl)phenoxy]ethyl}pyrrolidine.

$C_{30}H_{35}NO_3$=457.6

CAS — 31477-60-8.

ATC — G03XC04.

ATC Vet — QG03XC04.

UNII — 44AXY5VE90.

Profile

Ormeloxifene is a selective oestrogen receptor modulator with anti-oestrogenic actions and weak oestrogenic activity. It is used as an oral contraceptive (p. 2232.3), at a starting dose of 30 mg twice each week for 12 weeks, and followed by 30 mg once weekly thereafter. In the management of dysfunctional uterine bleeding (see Menorrhagia, p. 2300.3), 60 mg is given twice each week for 12 weeks,

then once weekly for up to 12 weeks. Ormeloxifene has been investigated in the management of benign breast diseases such as mastalgia. The *l*-isomer, levormeloxifene, which has oestrogenic effects, has been investigated in the management of postmenopausal osteoporosis, but development appears to have been discontinued because of adverse effects.

References.
1. Kamboj VP, *et al.* New products: centchroman. *Drugs Today* 1992; **28:** 227–32.
2. Gupta RC, *et al.* Centchroman: a new non-steroidal oral contraceptive in human milk. *Contraception* 1995; **52:** 301–5.
3. Lal J, *et al.* Pharmacokinetics of centchroman in healthy female subjects after oral administration. *Contraception* 1995; **52:** 297–300.
4. Lal J, *et al.* Optimization of contraceptive dosage regimen of centchroman. *Contraception* 2001; **63:** 47–51.
5. Alexandersen P, *et al.* Efficacy of levormeloxifene in the prevention of postmenopausal bone loss and on the lipid profile compared to low dose hormone replacement therapy. *J Clin Endocrinol Metab* 2001; **86:** 755–60.
6. Skrumsager BK, *et al.* Levormeloxifene: safety, pharmacodynamics and pharmacokinetics in healthy postmenopausal women following single and multiple doses of a new selective oestrogen receptor modulator. *Br J Clin Pharmacol* 2002; **53:** 284–95.
7. Ravn P, *et al.* What can be learned from the levormeloxifene experience? *Acta Obstet Gynecol Scand* 2006; **85:** 135–42.
8. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. *World J Surg* 2007; **31:** 1178–84.
9. Kriplani A, *et al.* Efficacy and safety of ormeloxifene in management of menorrhagia: a pilot study. *J Obstet Gynaecol Res* 2009; **35:** 746–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Centron†.

Ospemifene *(BAN, USAN, rINN)* ⊗

Fc-1271; FC-1271a; Ospémifène; Ospemifeno; Ospemifenum; Оспемифен.

2-{*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy}ethanol.

$C_{24}H_{23}ClO_2$=378.9

CAS — 128607-22-7.

UNII — B0P231ILBK.

NOTE. The name Ophena has been used as a trade mark for ospemifene.

Uses and Administration

Ospemifene is a selective oestrogen receptor modulator that appears to have oestrogen agonist or antagonist effects depending on tissue type. It is used in the treatment of dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The usual oral dose is 60 mg daily with food. It is also under investigation in the management of postmenopausal osteoporosis.

References.
1. Gennari L, *et al.* Ospemifene use in postmenopausal women. *Expert Opin Invest Drugs* 2009; **18:** 839–49.
2. McCall JL, DeGregorio MW. Pharmacologic evaluation of ospemifene. *Expert Opin Drug Metab Toxicol* 2010; **6:** 773–9.

Adverse Effects

The most common adverse effects of ospemifene are hot flushes, muscle spasm, hyperhidrosis, and vaginal discharge. Arterial and venous thromboembolic events, including thromboembolic stroke and deep-vein thrombosis, and haemorrhagic stroke have also been reported.

Precautions

Ospemifene should be avoided in women with active venous or arterial thromboembolism, or a history of thromboembolic disorders. It should be stopped at least 4 to 6 weeks before surgery that is associated with increased risk of thromboembolism. Ospemifene should be used with caution in women with risk factors for venous thromboembolism or for stroke. Ospemifene should not be used in patients with known or suspected oestrogen-dependent malignancy or undiagnosed uterine bleeding. It has not been studied in patients with severe hepatic impairment.

Ospemifene had adverse effects in *animal* teratogenicity studies and should not be used in women who are or may become pregnant.

Interactions

Ospemifene is mainly metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9; CYP2C19 and other pathways may also contribute. Interactions may occur with other drugs that inhibit or induce these enzymes. Plasma concentrations of ospemifene were reduced by the hepatic enzyme inducer rifampicin; increased plasma concentrations occurred with the enzyme inhibitor fluconazole.

Pharmacokinetics

Following oral dosing the peak median serum concentration of ospemifene is reached at about 2 hours. Steady-state concentrations are reached after about 9 days. Ospemifene is highly bound to serum proteins (more than 99%). It undergoes metabolism mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19 and has an apparent terminal half-life of about 26 hours. About 75% of a dose of ospemifene is excreted in the faeces and 7% in the urine. Less than 0.2% is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Osphena.

Ovary Extracts

Extractos de ovario; Ovarian Extracts.

Profile

Ovary extracts of animal origin (usually porcine or bovine) have been used for a variety of disorders including gynaecological and menopausal disorders. They have often been used in preparations containing other mammalian tissue extracts or herbal medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Fr.***: Amphosca Ovarine; ***Ger.***: Glandulae-F-Gastreu R20; Neydin-F†; NeyGeront Vitalkapsein A; ***Neth.***: Chavita 1; Emvita 2; Emvita 3; Emvita 4.

Oxandrolone *(BAN, USAN, rINN)* ⊗

NSC-67068; Oxandrolona; Oxandrolonum; SC-11585; Оксандролон.

17β-Hydroxy-17α-methyl-2-oxa-5α-androstan-3-one.

$C_{19}H_{30}O_3$=306.4

CAS — 53-39-4.

ATC — A14AA08.

ATC Vet — QA14AA08.

UNII — 7H6TM3CT4L.

Pharmacopoeias. In *US*.

USP 36: (Oxandrolone). A white odourless crystalline powder. Soluble 1 in 5200 of water, 1 in 57 of alcohol, 1 in 69 of acetone, 1 in less than 5 of chloroform, and 1 in 860 of ether. Protect from light.

Uses and Administration

Oxandrolone has anabolic and androgenic properties (see Testosterone, p. 2305.2) and is given as adjunctive therapy to promote weight gain in oral doses of 2.5 to 20 mg daily in 2 to 4 divided doses. Treatment is usually given as a course of 2 to 4 weeks, which may be repeated intermittently as required. Elderly patients may be more susceptible to the adverse effects of oxandrolone, and a dose of up to 5 mg twice daily is recommended. See below for doses of oxandrolone used in children.

Administration in children. Oxandrolone has been given to children as adjunctive therapy to promote weight gain in oral doses of up to 100 micrograms/kg daily in 2 to 4 divided doses. Treatment is usually given as a course of 2 to 4 weeks, which may be repeated intermittently as required.

For the promotion of growth in boys with constitutional delay of growth and puberty, and in girls with Turner's syndrome, usual oral daily doses of 100 micrograms/kg have been used. Treatment may be given for up to a year, but bone age must be assessed during therapy to avoid the risk of premature epiphyseal closure (see also Growth Retardation, below).

Burns. For references to the use of oxandrolone in burn injuries see Cachexia, below.

Cachexia. Oxandrolone has been used for its protein anabolic effect in conditions associated with cachexia (p. 2289.3) or wasting,[1] including alcoholic hepatitis, burn injury,[2,3] HIV-infection, and muscular dystrophy (p. 1608.1).

1. Orr R, Singh MF. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. *Drugs* 2004; **64:** 725–50.
2. Miller JT, Btaiche IF. Oxandrolone in pediatric patients with severe thermal burn injury. *Ann Pharmacother* 2008; **42:** 1310–15.
3. Miller JT, Btaiche IF. Oxandrolone treatment in adults with severe thermal injury. *Pharmacotherapy* 2009; **29:** 213–26.

Growth retardation. A beneficial effect of oxandrolone on growth rate in *boys* with constitutional delay of growth and puberty (p. 2252.1) has been shown in various studies,[1-6] two of which[2,5] were placebo-controlled. Doses used have included 1.25 or 2.5 mg daily[1-3] and 50 or 100 micrograms/kg daily,[4-6] generally for 3 to 12 months. Although a slight advance in bone age has been noted,[1,4,5] final predicted height[5] and actual adult height[3] was not compromised by oxandrolone therapy. Oxandrolone did not affect the rate of pubertal progression and as the aim of such therapy is mainly to relieve psychosocial difficulties associated with short stature and sexual immaturity, it is not clear that it achieves this.[5]

Oxandrolone is also used for the promotion of growth in *girls* with Turner's syndrome (p. 2254.3), usually added to growth hormone therapy.[7-10]

1. Stanhope R, Brook CGD. Oxandrolone in low dose for constitutional delay of growth and puberty in boys. *Arch Dis Child* 1985; **60:** 379–81.
2. Stanhope R, *et al.* Double blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch Dis Child* 1988; **63:** 501–5.
3. Tse W-Y, *et al.* Long-term outcome of oxandrolone treatment in boys with constitutional delay of growth and puberty. *J Pediatr* 1990; **117:** 588–91.
4. Papadimitriou A, *et al.* Treatment of constitutional growth delay in prepubertal boys with a prolonged course of low dose oxandrolone. *Arch Dis Child* 1991; **66:** 841–3.
5. Wilson DM, *et al.* Oxandrolone therapy in constitutionally delayed growth and puberty. *Pediatrics* 1995; **96:** 1095–1100.
6. Lampit M, Hochberg Z. Androgen therapy in constitutional delay of growth. *Horm Res* 2003; **59:** 270–5.
7. Nilsson KO, *et al.* Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 1996; **81:** 635–40.
8. Ranke MB, *et al.* KIGS International Board. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. *J Clin Endocrinol Metab* 2000; **85:** 4212–18.
9. Stahnke N, *et al.* Favorable final height outcome in girls with Ullrich-Turner syndrome treated with low-dose growth hormone together with oxandrolone despite starting treatment after 10 years of age. *J Pediatr Endocrinol Metab* 2002; **15:** 129–38.
10. Menke LA, *et al.* Efficacy and safety of oxandrolone in growth hormone-treated girls with Turner syndrome. *J Clin Endocrinol Metab* 2010; **95:** 1151–60.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3). As with other 17α-alkylated compounds, oxandrolone may cause hepatotoxicity, and liver function should be monitored. It should be avoided if hepatic impairment is severe.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p. 2308.3).

Pharmacokinetics

Oxandrolone is rapidly absorbed from the gastrointestinal tract, and extensively bound to plasma proteins. It is excreted mainly in the urine as unchanged oxandrolone and some metabolites, with an elimination half-life of about 9 to 10 hours. A small amount is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Oxandrin†; ***Mex.***: Xtendrol; ***USA***: Oxandrin.

Pharmacopoeial Preparations

USP 36: Oxandrolone Tablets.

Oxymetholone *(BAN, USAN, rINN)* ⊗

Cl-406; HMD; Oksimetolon; Oksimetoloni; Oximetolon; Oximetolona; Oxymétholone; Oxymetholonum; Оксиметолон.

17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one.

$C_{21}H_{32}O_3$=332.5

CAS — 434-07-1.

ATC — A14AA05.

ATC Vet — QA14AA05.

UNII — L76T0ZCA8K.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Oxymetholone). A white to creamy-white, odourless or almost odourless, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light. Avoid contact with ferrous metals.

USP 36: (Oxymetholone). A white to creamy-white, odourless crystalline powder. Practically insoluble in water; soluble 1 in 40 of alcohol, 1 in 5 of chloroform, 1 in 82 of ether, and 1 in 14 of dioxan.

Uses and Administration

Oxymetholone has anabolic and androgenic properties (see Testosterone, p. 2305.2). It has been used mainly in the treatment of anaemias such as aplastic anaemia at a usual oral dose of 1 to 5 mg/kg daily. Treatment for 3 to 6 months has been suggested, with the drug either withdrawn

gradually on remission or reduced to an appropriate maintenance dose.

Reviews.
1. Pavlatos AM, *et al*. Review of oxymetholone: a 17 α -alkylated anabolic-androgenic steroid. *Clin Ther* 2001; **23:** 789–801.

Aplastic anaemia. There have been mixed results[1-5] with oxymetholone in the treatment of aplastic anaemia (p. 1121.3); generally, the response and survival rates have been disappointing. Although it was used extensively in the past, oxymetholone is now generally reserved for patients who have failed, or cannot tolerate, immunosuppressant therapy.
1. Davis S, Rubin AD. Treatment and prognosis in aplastic anaemia. *Lancet* 1972; **i:** 871–3.
2. Mir MA, Delamore IW. Oxymetholone in aplastic anaemia. *Postgrad Med J* 1974; **50:** 166–71.
3. Camitta BM, *et al*. A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood* 1979; **53:** 504–14.
4. Mir MA, Geary CG. Aplastic anaemia: an analysis of 174 patients. *Postgrad Med J* 1980; **56:** 322–9.
5. Webb DKH, *et al*. Acquired aplastic anaemia: still a serious disease. *Arch Dis Child* 1991; **66:** 858–61.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3).

Liver disturbances and jaundice are common with normal doses and hepatic neoplasms have also been reported (see below). Liver function should be monitored during therapy. As with other 17α-alkylated compounds, oxymetholone should probably be avoided in patients with liver impairment, and certainly if this is severe.

Effects on carbohydrate metabolism. Pronounced hyperglucagonaemia developed in 6 patients receiving oxymetholone.[1]
1. Williams G, *et al*. Severe hyperglucagonaemia during treatment with oxymetholone. *BMJ* 1986; **292:** 1637–8.

Effects on the liver. Peliosis hepatis[1-4] and various liver tumours[4-8] has been associated with oxymetholone use. A review[9] of reports of liver tumours associated with anabolic androgens found that oxymetholone was the androgen most often implicated, and that the majority of tumours were hepatocellular carcinomas.
1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann Intern Med* 1974; **81:** 610–18.
2. McDonald EC, Speicher CE. Peliosis hepatis associated with administration of oxymetholone. *JAMA* 1978; **240:** 243–4.
3. Hirose H, *et al*. Fatal splenic rupture in anabolic steroid-induced peliosis in a patient with myelodysplastic syndrome. *Br J Haematol* 1991; **78:** 128–9.
4. Linares M, *et al*. Hepatocellular carcinoma and squamous cell carcinoma in a patent with Fanconi's anemia. *Ann Hematol* 1991; **63:** 54–5.
5. Lesna M, *et al*. Liver nodules and androgens. *Lancet* 1976; **i:** 1124.
6. Mokrohisky ST, *et al*. Fulminant hepatic neoplasia after androgen therapy. *N Engl J Med* 1977; **296:** 1411–12.
7. Kosaka A, *et al*. Hepatocellular carcinoma associated with anabolic steroid therapy: report of a case and review of the Japanese literature. *J Gastroenterol* 1996; **31:** 450–4.
8. Nakao A, *et al*. Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. *J Gastroenterol* 2000; **35:** 557–62.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.

Effects on the nervous system. Toxic confusional state and choreiform movements developed in an elderly man given oxymetholone 200 to 300 mg daily.[1]
1. Tilzey A, *et al*. Toxic confusional state and choreiform movements after treatment with anabolic steroids. *BMJ* 1981; **283:** 349–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Hemogenin; ***India***: Adroyd; ***Malaysia***: Oxylone; ***Singapore***: Oxylone; ***Thai.***: Androlic; ***Turk.***: Anapolon; ***USA***: Anadrol.

Pharmacopoeial Preparations
BP 2014: Oxymetholone Tablets;
USP 36: Oxymetholone Tablets.

Polyestradiol Phosphate *(BAN, rINN)*

Fosfato de poliestradiol; Leo-114; Poliestradiol, fosfato de; Polyestradiol, Phosphate de; Polyestradiolfosfat; Polyestradioli Phosphas; Polyestradiolifosfaatti; Polyoestradiol Phosphate; Полиэстрадиола Фосфат.

A water-soluble polymeric ester of estradiol and phosphoric acid with a molecular weight of about 26 000..

CAS — 28014-46-2.
ATC — L02AA02.
ATC Vet — QL02AA02.
UNII — P14877CDX2.

Uses and Administration

Polyestradiol phosphate is a polymer of estradiol (see p. 2271.1) that has a prolonged duration of action, and is used in the treatment of metastatic prostatic carcinoma (p. 712.3). It has been given by deep intramuscular injection in initial doses of 80 to 160 mg every 4 weeks for 2 to 3 months, reduced to 40 to 80 mg every 4 weeks for maintenance. Higher initial doses of up to 320 mg and maintenance doses of up to 240 mg have also been used.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p. 2273.2). Pain may occur at the site of injection, and mepivacaine is included in some preparations to minimise this.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies polyestradiol phosphate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]
1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pharmacokinetics

After intramuscular injection polyestradiol phosphate is released slowly into the bloodstream where it is slowly metabolised to estradiol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Estradurin; ***Belg.***: Estradurine†; ***Denm.***: Estradurin; ***Fin.***: Estradurin; ***Norw.***: Estradurin†; ***Rus.***: Estradurin (Эстрадурин); ***Swed.***: Estradurin; ***Switz.***: Estradurin; ***Ukr.***: Estradurin (Эстрадурин)†.

Prasterone *(rINN)* ⊗

Dehydroandrosterone; Dehydroepiandrosteron; Dehydroepiandrosterone; Dehydroepiandrosteroni; Dehydroepiandrosteronum; Dehydroisoandrosterone; DHEA; GL-701; Prasterona; Prastérone; Prasteronum; Прастерон.

3β-Hydroxyandrost-5-en-17-one.

$C_{19}H_{28}O_2$=288.4

CAS — 53-43-0.
ATC — A14AA07.
ATC Vet — QA14AA07.
UNII — 459AG36T1B.

NOTE. The names Anastar, Aslera, Fidelin T, and Prestara have been used as trade marks for prasterone. The name Anastar has also been used for a proprietary preparation of anastrozole (p. 742.1). The name Aslera has also been used for proprietary preparations of serrapeptase (p. 2613.3).

Pharmacopoeias. In *Fr.*

Prasterone Enantate *(rINNM)* ⊗

Dehydroepiandrosterone Enanthate; EDHEA; Enantato de prasterona; Prasterona, enantato de; Prastérone, Enantate de; Prasterone Enanthate; Prasteroni Enantas; Прастерона Энантат.

3β-Hydroxyandrost-5-en-17-one heptanoate.

$C_{26}H_{40}O_3$=400.6

CAS — 23983-43-9.
ATC — A14AA07.
ATC Vet — QA14AA07.
UNII — 2W8I1S6T5L.

Prasterone Sodium Sulfate *(rINNM)* ⊗

Dehydroepiandrosterone Sulphate Sodium; DHA-S (prasterone sulfate); DHEAS (prasterone sulfate); PB-005; Prasterona, sulfato sódico de; Prasterone Sodium Sulphate; Prastérone, Sulfate Sodique de; Prasteroni Natrii Sulfas; Sulfato sódico de prasterona; Прастерона Натрия Сульфат.

3β-Hydroxyandrost-5-en-17-one hydrogen sulphate sodium.

$C_{19}H_{27}NaO_5S$=390.5

CAS — 651-48-9 (prasterone sulfate); 1099-87-2 (prasterone sodium sulfate).
ATC — A14AA07.
ATC Vet — QA14AA07.
UNII — E1CR8487EN.

NOTE. The names Aylistormer, Levospa, and Mylis have been used as trade marks for prasterone sodium sulfate.

Pharmacopoeias. *Chin.* includes the dihydrate.

Profile

Prasterone is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens. Prasterone enantate, in a dose of 200 mg every 4 weeks, is given by intramuscular depot injection with estradiol valerate as menopausal HRT (p. 2244.2). The sodium sulfate has been given for cervical ripening. Prasterone is also being investigated in adrenal insufficiency and in SLE, and the sodium sulfate has been investigated for the treatment of burns and acute asthma.

General reviews.
1. Kroboth PD, *et al*. DHEA and DHEA-S: a review. *J Clin Pharmacol* 1999; **39:** 327–48.
2. Pepping J. DHEA: dehydroepiandrosterone. *Am J Health-Syst Pharm* 2000; **57:** 2048–56.
3. Cameron DR, Braunstein GD. The use of dehydroepiandrosterone therapy in clinical practice. *Treat Endocrinol* 2005; **4:** 95–114.

HIV infection and AIDS. Plasma concentrations of endogenous prasterone are reported to be abnormally low in patients with AIDS, and it has been suggested that use of prasterone might be of benefit; however, large controlled studies are lacking.[1] Small controlled studies have confirmed that oral use increases circulating concentrations of prasterone and its sulfated form, and have reported improvements in quality of life measures[2] and reductions in symptoms of mild depression,[3] but no beneficial antiviral or immunomodulatory effects.[4] Also, there were no significant changes in measures of serum lipids, insulin, growth hormone, or the overall function of the gonadal or hypothalamic-pituitary-adrenal axes.[5]
1. Centurelli MA, *et al*. The role of dehydroepiandrosterone in AIDS. *Ann Pharmacother* 1997; **31:** 639–42.
2. Piketty C, *et al*. Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease. *Clin Endocrinol (Oxf)* 2001; **55:** 325–30.
3. Rabkin JG, *et al*. Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *Am J Psychiatry* 2006; **163:** 59–66.
4. Abrams DI, *et al*. Dehydroepiandrosterone (DHEA) effects on HIV replication and host immunity: a randomized placebo-controlled study. *AIDS Res Hum Retroviruses* 2007; **23:** 77–85.
5. Poretsky L, *et al*. Endocrine effects of oral dehydroepiandrosterone in men with HIV infection: a prospective, randomized, double-blind, placebo-controlled trial. *Metabolism* 2006; **55:** 858–70.

Replacement therapy. There has been much speculation about the physiological role and importance of prasterone, which is the most abundant steroid hormone in the circulation. It is produced by the adrenal gland and is a precursor of androgens and oestrogens. Serum concentrations peak at about 20 years then gradually decline with age. Epidemiological and *animal* studies suggest that certain age-related diseases may be linked to this decline, including reduced immunocompetence, obesity, diabetes, and cancers.[1] It has been suggested, therefore, that replacement therapy with prasterone might alleviate some of the problems of **ageing**. Prasterone has been studied for its effect on cognition and memory, sexual function, insulin sensitivity, cardiovascular risk factors, muscle strength and body composition, bone loss, and immune function, but results have generally been conflicting,[1,2] and there is insufficient evidence of safety and efficacy to recommend such use. A systematic review[3] of studies in healthy adults taking prasterone supplementation found no support for an improvement in cognitive function. A review[4] of the use of prasterone as a 'food supplement' noted that although it was being taken in the belief that it could reverse some of the effects of ageing there was no good evidence of this. Various androgenic effects, including hirsutism and voice changes, have been reported in women taking prasterone and there is a theoretical possibility that it might promote growth of hormone-sensitive tumours in both sexes.[1,4]

Prasterone has also been studied as replacement therapy for patients with **adrenal insufficiency**, who have subnormal levels of prasterone. Such therapy, usually in oral doses of 50 mg daily, has been reported to raise serum levels of prasterone to normal, and improve measures of well-being, mood, and fatigue.[1,5-7] Others[8] have found no significant improvement in fatigue, cognitive function, or sexual function after 12 months of treatment, but did detect beneficial effects on bone mineral density in the femoral neck, lean body-mass, and some measures of psychological well-being. A systematic review[9] of its effects on quality of life in women with adrenal insufficiency concluded that there was insufficient evidence of benefit to recommend its use. There have been mixed results from studies of the effects of prasterone on carbohydrate metabolism with reports of either no effect[10,11] or increased insulin sensitivity.[12] Prasterone may have an unfavourable effect on the lipoprotein profile of hypoadrenal women.[13]
1. Dhatariya KK, Nair KS. Dehydroepiandrosterone: is there a role for replacement? *Mayo Clin Proc* 2003; **78:** 1257–73.
2. GISEG (Italian Study Group on Geriatric Endocrinology). Consensus document on substitution therapy with DHEA in the elderly. *Aging Clin Exp Res* 2006; **18:** 277–300. Also available at: http://www.kurtis.it/abs/index.cfm?id_articolo_numero=2297 (accessed 13/11/07)

3. Grimley Evans J, *et al.* Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 13/11/07).
4. Anonymous. Dehydroepiandrosterone (DHEA). *Med Lett Drugs Ther* 1996; **38:** 91–2.
5. Arlt W, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; **341:** 1013–20.
6. Hunt PJ, *et al.* Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 2000; **85:** 4650–6.
7. Brooke AM, *et al.* Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 2006; **91:** 3773–9.
8. Gurnell EM, *et al.* Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab* 2008; **93:** 400–409.
9. Alkatib AA, *et al.* A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab* 2009; **94:** 3676–81.
10. Callies F, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. *J Clin Endocrinol Metab* 2001; **86:** 1968–72.
11. Libè R, *et al.* Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. *J Endocrinol Invest* 2004; **27:** 736–41.
12. Dhatariya K, *et al.* Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. *Diabetes* 2005; **54:** 765–9.
13. Srinivasan M, *et al.* Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. *J Clin Endocrinol Metab* 2009; **94:** 761–4.

Systemic lupus erythematosus. In several small studies carried out by one group,[1-5] there was symptomatic improvement in SLE (p. 1613.3), and a reduction in corticosteroid dosage, in women who received oral prasterone 200 mg daily for several months. Although they considered that there was clear evidence of benefit,[6] larger studies[7-9] have produced more statistically ambiguous results. They suggested that prasterone might stabilise or improve disease, and reduce corticosteroid requirements and time to disease flare, but only in patients with active disease. Nested data from one of these studies[10] also showed that prasterone treatment for up to a year improved bone mineral density of the lumbar spine and hip. A larger study[11] of 155 women receiving chronic corticosteroid therapy was designed to confirm this effect on bone. The results were not statistically significant in favour of prasterone in the first 6 placebo-controlled months. However, an open-label 1-year extension found a small increase in bone mineral density of the lumbar spine, and maintenance in density of the hip, in patients given prasterone 200 mg daily for 18 months; a lower dose of 100 mg daily was not protective. In a study[12] of lumbar spine bone mineral density in women with quiescent SLE, prasterone may have had a protective effect in postmenopausal women who were not otherwise treated with oestrogens or bisphosphonates, but there was no change in premenopausal women.

1. van Vollenhoven RF, *et al.* An open study of dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1994; **37:** 1305–10.
2. van Vollenhoven RF, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1995; **38:** 1826–31.
3. van Vollenhoven RF, *et al.* Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. *J Rheumatol* 1998; **25:** 285–9.
4. Barry NN, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus: relationship between dosage, serum levels, and clinical response. *J Rheumatol* 1998; **25:** 2352–6.
5. van Vollenhoven RF, *et al.* A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 1999; **8:** 181–7.
6. van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; **26:** 349–62.
7. Petri MA, *et al.* Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1820–9.
8. Chang D-M, *et al.* Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus. *Arthritis Rheum* 2002; **46:** 2924–7.
9. Petri MA. *et al.* Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus: results of a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; **50:** 2858–68.
10. Mease PJ, *et al.* Effects of prasterone on bone mineral density in women with systemic lupus erythematosus receiving chronic glucocorticoid therapy. *J Rheumatol* 2005; **32:** 616–21.
11. Sánchez-Guerrero J, *et al.* Effects of prasterone on bone mineral density in women with active systemic lupus erythematosus receiving chronic glucocorticoid therapy. *J Rheumatol* 2008; **35:** 1567–75.
12. Hartkamp A, *et al.* The effect of dehydroepiandrosterone on lumbar spine bone mineral density in patients with quiescent systemic lupus erythematosus. *Arthritis Rheum* 2004; **50:** 3591–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Di Luo An (蒂洛安); ***Mex.***: Biolaif; ***Pol.***: Biosteron; BioStym Balance.

Multi-ingredient Preparations. ***Arg.***: Dastonil; Gynodian Depot; Longevital; Supligol NF; ***Austria***: Gynodian Depot; ***Chile***: Gynodian Depot; ***Cz.***: Gynodian Depot; ***Ger.***: Gynodian Depot; ***Ital.***: Gynodian Depot; ***Mex.***: Binodian; Sten; ***Pol.***: Gynodian Depot†; ***Rus.***: Gynodian Depot (Гинодиан Депо)†; ***Switz.***: Gynodian Depot; ***Venez.***: Gynodian Depot.

Progesterone *(BAN, rINN)*

Corpus Luteum Hormone; Luteal Hormone; Luteine; Luteohormone; NSC-9704; Pregnenedione; Pregnenodiona; Progesteron; Progesterona; Progesteronas; Progestérone; Progesteroni; Progesteronum; Progestina; Progeszteron; Прогестерон.

Pregn-4-ene-3,20-dione.

$C_{21}H_{30}O_2$=314.5

CAS — 57-83-0.

ATC — G03DA04.

ATC Vet — QG03DA04.

UNII — 4G7DS2Q64Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Progesterone). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol; sparingly soluble in acetone and in fatty oils. Protect from light.

USP 36: (Progesterone). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Progesterone is a natural hormone whereas progestogens are synthetic compounds, derived from progesterone or 19-nortestosterone, with actions similar to those of progesterone (for further details, see p. 2231.1).

Progestogens derived from 19-nortestosterone are used as **hormonal contraceptives** (see p. 2231.3), either alone or combined with an oestrogen. The progesterone derivative medroxyprogesterone acetate is also used, and progesterone itself has been used.

Progestogens, and sometimes progesterone, are used with oestrogens for **menopausal HRT** (p. 2244.2) to reduce the increased risk of endometrial hyperplasia and carcinoma that occurs when long-term oestrogen therapy is unopposed.

Similarly, drugs with progestogenic actions may be used in **menstrual disorders** such as dysmenorrhoea (p. 8.2) and menorrhagia associated with dysfunctional uterine bleeding (below). Progestogens may also be used in the management of endometriosis (p. 2264.1). Although progestogens and progesterone have been used for the management of the premenstrual syndrome (p. 2301.2), such a practice is of debatable value.

Progestogens may be valuable in advanced **endometrial cancer** (p. 704.3) and have been tried in some other malignancies. The progestogens typically used for malignant disease include medroxyprogesterone acetate, megestrol, and norethisterone. Some progestogens such as megestrol and medroxyprogesterone are used for the **cachexia** or wasting associated with severe illness including cancer and AIDS (p. 2289.3).

Progestogens have been widely advocated for either the prevention of **recurrent miscarriage** or the treatment of threatened miscarriage (p. 2301.2). However, there is little evidence of any benefit from such a practice and the use of progestogens in early pregnancy is not now generally advised, with the exception of the use of progesterone or a progesterone derivative in women who are progesterone deficient (see also Precautions, p. 2301.3). Progesterone is, however, the preferred drug for luteal support in women undergoing **assisted reproductive techniques** such as IVF (see Infertility, p. 2253.1).

USES AND ADMINISTRATION OF PROGESTERONE. Progesterone is usually given as an oily intramuscular injection, a vaginal gel or pessaries, or as suppositories. Preparations containing micronised progesterone are also available for oral and vaginal use.

In dysfunctional uterine bleeding or amenorrhoea 5 to 10 mg daily of progesterone may be given by intramuscular injection for about 5 to 10 days until 2 days before the anticipated onset of menstruation. Alternatively, progesterone may be given for amenorrhoea as a vaginal gel at a usual dose of 45 mg on alternate days for up to 6 doses; the dose may be increased to 90 mg in those who do not respond to the lower dose. An oral dose of 400 mg given daily at bedtime for 10 days may also be used for amenorrhoea.

In women with a history of recurrent miscarriage and proven progesterone deficiency, twice weekly intramuscular injection (increased to daily if necessary) of 25 to 100 mg of progesterone, from about day 15 of the pregnancy until 8 to 16 weeks, has been used. The dose may be increased to 200 mg daily if necessary. Vaginal doses of micronised progesterone 200 to 400 mg daily, in 2 divided doses, have also been given until week 12 of pregnancy. A similar intramuscular schedule has been used for luteal support in IVF or gamete intra-fallopian transfer techniques with treatment beginning on the day of transfer of embryo or gametes. Alternatively, progesterone may be given vaginally in assisted reproduction, but doses can vary widely depending on the preparation. A vaginal gel may be given at a dose of 90 mg daily; it is given for 30 days if pregnancy occurs, and may be continued until there is placental autonomy (up to 10 to 12 weeks). A dose of 90 mg twice daily has been used in women with ovarian failure. A vaginal tablet containing micronised progesterone 100 mg may be given 2 or 3 times daily; treatment is started at oocyte retrieval and continued for up to 10 weeks. Some soft capsules containing micronised progesterone may also be suitable for intravaginal use in a dose of 400 to 600 mg daily, in 2 or 3 divided doses, from the day of gonadotrophin administration until week 12 of pregnancy.

Progesterone may be given vaginally or rectally in doses of 200 mg daily to 400 mg twice daily for the management of the premenstrual syndrome. Treatment usually starts on day 12 to 14 of the menstrual cycle and continues until the onset of menstruation. Similar vaginal or rectal doses have also been used in the treatment of puerperal (post-natal) depression.

Progesterone has been given as the progestogen component of menopausal HRT. Soft capsules containing micronised progesterone are available in some countries for oral use, given in a dose of 200 mg daily at bedtime for 12 to 14 days of each month. Alternatively, a dose of 100 mg daily may be given from day 1 to 25 of each cycle, resulting in less withdrawal bleeding.

A progesterone-releasing intra-uterine device has been used as a hormonal contraceptive; the device contained 38 mg of progesterone and was effective for up to 12 months. A vaginal ring device that releases 10 mg of progesterone daily is used in some countries for contraception in lactating women. The first ring is inserted 6 weeks after delivery, then replaced every 90 days.

Administration. Progesterone creams for *topical* application to the skin are promoted in some countries for the management of menopausal symptoms and conditions associated with progesterone deficiency. These are sometimes described as containing 'natural' progesterone or phyto-progesterone from plant sources. However, many of these products are available without prescription or medical consultation and there has been some concern about their safety and efficacy. Reviews[1,2] have found early studies reporting that absorption of progesterone from these creams was minimal. However, a later study[3] using liquid chromatography-tandem spectrometry of whole blood reported that steady-state progesterone exposure was similar for women given either oral micronised progesterone or topical cream.[3] The authors suggested that the differences between their results and previous studies were likely to have been caused by the use of different analytical techniques, and that women using these creams may in fact be exposed to higher systemic concentrations of progesterone than previously thought. Some proponents of topical progesterone therapy have questioned the importance of using serum concentrations as a marker for absorption. A review[4] concluded that available serum-progesterone concentrations probably remain low after topical use and that further studies on the pharmacokinetics of topical progesterone are needed. In terms of efficacy, several small controlled studies have not shown progesterone cream to be any better than placebo for the management of menopausal vasomotor symptoms or the prevention of bone loss, and mixed results have been reported regarding the prevention of endometrial proliferation associated with oestrogen therapy.[1,2,4]

1. Anonymous. Natural' progesterone creams for postmenopausal women. *Drug Ther Bull* 2001; **39:** 10–11.
2. Wren BG. Transdermal progesterone creams for postmenopausal women: more hype than hope? *Med J Aust* 2005; **182:** 237–9.
3. Hermann AC, *et al.* Over-the-counter progesterone cream produces significant drug exposure compared to a Food and Drug Administration-approved oral progesterone product. *J Clin Pharmacol* 2005; **45:** 614–19.
4. Elshafie MAA, Ewies AAA. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynaecol* 2007; **27:** 655–9.

Menorrhagia. Menorrhagia, or excessive menstrual bleeding, is usually defined as a blood loss exceeding 80 mL per menstrual period,[1,2] compared with a normal loss of about 30 mL. However, many women consider losses below 80 mL to be excessive particularly if 'flooding' occurs. Although not life-threatening, menorrhagia can lead to iron deficiency anaemia and considerably impair quality of life. Menorrhagia may be associated with pelvic disorders such as fibroids or endometriosis, the use of copper IUDs, or some systemic disorders.[1-3] However, most commonly it is associated with dysfunctional uterine bleeding;[1] a term used to denote frequent, prolonged or heavy uterine

bleeding for which no specific cause is found (essential, idiopathic, or primary menorrhagia). Both ovulatory (regular) and anovulatory cycles may give rise to dysfunctional uterine bleeding.[2] In general, medical treatment is used initially in women with no underlying uterine abnormalities.[3] The most commonly used drugs are NSAIDs, tranexamic acid, combined oral contraceptives, and progestogens, and choice of therapy may be influenced by the contraceptive needs of the patient.[1-3] Surgery can be used if medical management is ineffective, and may be considered for first-line treatment in selected patients.[3]

NSAIDs such as mefenamic acid, ibuprofen, and naproxen have been widely used. They reduce menstrual blood loss by about 20 to 50%, and there does not seem to be evidence to suggest that one NSAID is more effective than another.[1] They are taken only during the menstrual phase, which reduces adverse effects, and probably improves patient compliance; they also have the benefit of relieving dysmenorrhoea (p. 8.2).[1] Systematic review[4] suggests that NSAIDs are less effective than tranexamic acid, danazol, and intra-uterine levonorgestrel in reducing bleeding. NSAIDs are considered a suitable option when hormonal therapy is not acceptable. They should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds them to be beneficial.[3]

Given during menstruation *tranexamic acid* reduces menstrual blood loss by about half;[1] the benefits of tranexamic therapy have been confirmed by systematic review.[5] Like NSAIDs, tranexamic acid is considered a suitable option when hormonal therapy is not acceptable. It should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds it to be beneficial.[3] *Etamsylate* has been used for menorrhagia, but it is less effective than NSAIDs and tranexamic acid, and is no longer recommended.[1,3]

In women who require contraception, a *combined oral contraceptive* appears to be effective,[1,3] although good evidence of this is actually lacking.[6] It has been suggested that extended-cycle regimens should be considered for women with menorrhagia, as there are fewer bleeding episodes per year of treatment.[2] Traditional therapy with *progestogens* such as norethisterone or medroxyprogesterone given during the luteal phase appears to be ineffective in women with normal ovulatory cycles,[1,3,7] although cyclical therapy may be of benefit in anovulatory patients as it imposes a cycle.[2] Progestogen therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss,[1,3,7] but is associated with adverse effects that may limit its acceptability. Long-acting injectable progestogens, such as medroxyprogesterone acetate, reduce menstrual blood loss or induce amenorrhoea when they are used as contraceptives. They have therefore been used for menorrhagia, although specific studies for this indication are lacking.[1,3]

More recently, a contraceptive *levonorgestrel-containing IUD* has been shown to be very effective in reducing menstrual blood loss in menorrhagia.[1,2] UK guidelines[3] suggest that it should be considered first when either hormonal or non-hormonal treatment is acceptable and long-term use is anticipated, although comparative data are scanty.[8] There is also some evidence that it may be an effective alternative to surgery, but data from long-term follow-up are needed.[9] As there can be changes in bleeding pattern associated with this device, particularly in the first few cycles, use for at least 6 months is advised to enable full assessment of benefit.[3]

Danazol is also effective,[10] producing about a 50% reduction in menstrual blood loss,[1] but has significant adverse effects and treatment is usually limited to 3 to 6 months. *Gonadorelin analogues* are effective for menorrhagia associated with fibroids (p. 2281.2).[1] When used preoperatively for endometrial thinning, they produce more consistent results than danazol.[11] Gonadorelin analogues may therefore be considered before surgery or when other options for fibroids are contra-indicated, but 'add-back' hormone replacement is recommended for the management of adverse effects from oestrogen deficiency or if they are used for more than 6 months.[3]

In patients who fail to respond to drug treatment, or in whom such therapy is inappropriate, various *surgical options* exist. Conservative surgical techniques, where the endometrium is ablated or resected, are increasingly being used, and are an effective alternative to hysterectomy.[3,12] Hysterectomy is the ultimate therapy, but is associated with significant morbidity.

1. Roy SN, Bhattacharya S. Benefits and risks of pharmacological agents used for the treatment of menorrhagia. *Drug Safety* 2004; **27:** 75–90.
2. Nelson AL, Teal SB. Medical therapies for chronic menorrhagia. *Obstet Gynecol Surv* 2007; **62:** 272–81.
3. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 27/06/08)
4. Lethaby A, *et al.* Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
5. Lethaby A, *et al.* Antifibrinolytics for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 27/06/08).
6. Farquhar C, Brown J. Oral contraceptive pill for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/11/09).
7. Lethaby A, *et al.* Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).
8. Lethaby AE, *et al.* Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/06/08).
9. Marjoribanks J, *et al.* Surgery versus medical therapy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 27/06/08).
10. Beaumont H, *et al.* Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Sowter MC, *et al.* Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 27/06/08).
12. Lethaby A, *et al.* Endometrial resection/ablation techniques for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/11/09).

Miscarriage. Threatened miscarriage is a common complication of pregnancy that presents before 20 weeks of gestation as vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable. Endogenous progesterone is normally produced by the corpus luteum to maintain pregnancy, and low concentrations have been associated with pregnancy loss. Progestogen therapy has therefore been widely used in the treatment of threatened miscarriage,[1] but there is a paucity of clinical study data to support routine use.[2] Similarly, progestogens have been used prophylactically to prevent miscarriage, but studies have suffered from various limitations.[3] A systematic review[4] found no evidence to support routine use, but there was limited evidence to suggest that women with a history of recurrent miscarriage (3 or more consecutive miscarriages) might gain some benefit. The *BNF* advises that progestogen prophylaxis in women with a history of recurrent miscarriage is not recommended. (See also Pregnancy, p. 2302.1, for reports of hypospadias in the offspring of women given hormonal support therapy.)

1. Sotiriadis A, *et al.* Threatened miscarriage: evaluation and management. *BMJ* 2004; **329:** 152–5.
2. Wahabi HA, *et al.* Progestogen for treating threatened miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
3. Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. *Best Pract Res Clin Obstet Gynaecol* 2008; **22:** 375–89.
4. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 27/06/08).

Premature labour. Recommendations have been made regarding progesterone therapy for the prevention of premature birth in women at risk of preterm delivery (see under Hydroxyprogesterone Caproate, p. 2285.1).

Premenstrual syndrome. Progestogen therapy was once popular for premenstrual syndrome, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground (see p. 2272.3). Progesterone has been given orally, vaginally, and rectally, in continuous and luteal phase regimens. However, systematic reviews[1,2] have found no convincing evidence to support its use.

1. Wyatt K, *et al.* Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323:** 776–80.
2. Ford O, *et al.* Progesterone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 20/11/09).

Spinal cord and head injury. Progesterone is under investigation as a neuroprotectant in the treatment of traumatic brain injury.[1-3]

1. Wright DW, *et al.* Steady-state serum concentrations of progesterone following continuous intravenous infusion in patients with acute moderate to severe traumatic brain injury. *J Clin Pharmacol* 2005; **45:** 640–8.
2. Wright DW, *et al.* ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann Emerg Med* 2007; **49:** 391–402.
3. Xiao G, *et al.* Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit Care* 2008; **12:** R61.

Adverse Effects

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely. Alterations in the serum lipid profile may occur, and rarely alterations in liver-function tests and jaundice. Pain, diarrhoea, and flatulence have followed rectal use. Injection-site reactions have followed parenteral use.

Adverse effects vary depending on the dose and type of progestogen. For example, androgenic effects such as acne and hirsutism are more likely to occur with nortestosterone derivatives such as norethisterone and norgestrel. These derivatives may also be more likely to adversely affect serum lipids. Conversely, adverse effects on serum lipids appear less likely with gestodene and desogestrel, but these 2 drugs have been associated with a higher incidence of thromboembolism than norethisterone and norgestrel when used in combined oral contraceptives (see p. 2238.1). High doses of progestogens such as those used in treating cancer have also been associated with thromboembolism. For a discussion of the effect of progestogens on the cardiovascular risk profile of menopausal HRT see p. 2248.2. Breakthrough uterine bleeding is more common with oral progestogen-only contraceptives than when progestogens are used for menstrual irregularities or as part of menopausal HRT.

Some progestogens when given during pregnancy have been reported to cause virilisation of a female fetus. This appears to have been associated with those progestogens with more pronounced androgenic activity such as norethisterone; the natural progestogenic hormone progesterone and its derivatives such as dydrogesterone and medroxyprogesterone do not appear to have been associated with such effects.

For the adverse effects of progestogens when administered either alone or with oestrogens as contraceptives, see p. 2233.3. For those of menopausal HRT, see p. 2246.3.

Carcinogenicity. In a cohort study[1] of women aged 40 to 64 years, the premenopausal use of oral progestogens alone, mainly for benign breast, uterine, and ovarian conditions, and irregular menstruation, was not associated with an increased risk of breast cancer. However, the data did suggest that there was an increased risk for current users of progestogens for longer than 4.5 years (relative risk 1.44, 95% confidence interval 1.03 to 2.00) compared with women who had never used progestogens. Limitations of this study included the lack of analysis of different progestogens or a record of the reasons for progestogen treatment.

1. Fabre A, *et al.* Oral progestagens before menopause and breast cancer risk. *Br J Cancer* 2007; **96:** 841–4.

Effects on the skin. Auto-immune progesterone dermatitis includes reactions such as eczema, urticaria, and angioedema that usually begin 3 to 10 days before the onset of menstrual flow and end 1 to 2 days into menses, which correlates with raised endogenous progesterone concentrations during the luteal phase of the menstrual cycle. The onset of the condition can be as early as menarche, and many women have never been exposed to exogenous progesterone, but it has also occurred in women with a history of oral contraceptive use. Management has been based on the suppression of endogenous progesterone secretion and oral contraceptives are usually tried first, although they appear to have limited success possibly because of the progestogen component. Other drugs that have been used include corticosteroids, conjugated oestrogens, gonadorelin analogues, androgens, and tamoxifen, but all have significant adverse effects associated with long-term use. Bilateral oophorectomy has been used in severe cases, when drug therapy has been unsuccessful.[1]

A woman with a history of auto-immune progesterone dermatitis developed pruritic, pink, oedematous plaques and macules on the upper thighs, axillae, and buttocks after the use of vaginal progestogen gel during infertility treatment.[2] The reaction was managed with topical corticosteroids. In another woman, with a history of chronic urticaria exacerbated by progesterone, the use of progesterone and various other progestogens as a component of HRT after oophorectomy caused urticaria and angioedema.[3] Desensitisation using micronised progesterone was successful in this case.

1. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy* 2004; **2:** 10.
2. Jenkins J, *et al.* Autoimmune progesterone dermatitis associated with infertility treatment. *J Am Acad Dermatol* 2008; **58:** 353–5.
3. Poole JA, Rosenwasser LJ. Chronic idiopathic urticaria exacerbated with progesterone therapy treated with a novel desensitization protocol. *J Allergy Clin Immunol* 2004; **114:** 456–7.

Precautions

Progesterone and the progestogens should be used with caution in patients with hypertension, cardiac or renal impairment, asthma, epilepsy, and migraine, or other conditions which may be aggravated by fluid retention. Progestogens can decrease glucose tolerance and diabetic

patients should be carefully monitored. They should also be used with care in persons with a history of depression. High doses should be used with caution in patients susceptible to thromboembolism.

Progesterone and the progestogens should not be given to patients with undiagnosed vaginal bleeding, nor to those with a history or current high risk of arterial disease and should generally be avoided in hepatic impairment, especially if severe. Unless progestogens are being used as part of the management of breast or genital-tract carcinoma they should not be given to patients with these conditions.

Although progestogens have been given as hormonal support during early pregnancy such use is not now generally advised. However, the use of a progesterone-type progestogen might still be considered for women who are progesterone-deficient. Such use may prevent spontaneous evacuation of a dead fetus, therefore careful monitoring of pregnancy is required. Progestogens should not be used diagnostically for pregnancy testing and should not be given in missed or incomplete abortion.

For precautions to be observed when progestogens are used as contraceptives, see p. 2240.3. For those to be observed when progestogens are used in preparations for menopausal HRT, see p. 2250.1.

Abuse. A case report of abuse of and dependency on progesterone.[1]

1. Keefe DL, Sarrel P. Dependency on progesterone in woman with self-diagnosed premenstrual syndrome. *Lancet* 1996; **347:** 1182.

Breast feeding. A large study[1] compared a contraceptive progesterone-releasing vaginal ring and a copper IUD for 1 year in breast-feeding women. There was little difference in infant weight gain during the study, although at 12 months the infants of mothers using the IUD were breast-fed less frequently, receiving more supplementary feeding, and were heavier. There was no adverse effect of progesterone on lactation or infant growth. Further smaller studies[2,3] have also found no adverse effect on lactation or infant growth. The American Academy of Pediatrics has found no reports of adverse effects in breast-fed infants of mothers given progesterone, and therefore considers it to be usually compatible with breast feeding.[4]

1. Sivin I, *et al.* Contraceptives for lactating women: a comparative trial of a progesterone-releasing vaginal ring and the copper T 380A IUD. *Contraception* 1997; **55:** 225–32.
2. Díaz S, *et al*. Fertility regulation in nursing women: IX contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant implants, and copper T 380-A intrauterine devices. *Contraception* 1997; **56:** 223–32.
3. Massai R, *et al*. Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception* 1999; **60:** 9–14.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies progesterone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1] NAPOS also provides classification for some progestogens—see individual drug monographs, as well as Porphyria under Hormonal Contraceptives (p. 2242.1) and Hormone Replacement Therapy (p. 2250.3).

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. In Hungary, where 30% of all pregnant women were given hormonal support therapy with progestogens during the early 1980s, a case-control study suggested that there was a causal relationship between such treatment and hypospadias in their offspring.[1] Mixed results have been reported in other studies of the association between maternal progestogen use and the risk of hypospadias, but the indications and types of progestogens used in early pregnancy have also changed over time (for example, withdrawal bleeding induced by progestogens as a form of pregnancy testing is no longer used, and progestogen luteal support in early pregnancy is no longer recommended for routine use; see also Miscarriage, p. 2301.2). Nevertheless, results from a more recent case-control study[2] of deliveries between October 1997 and December 2000 suggested an increase in risk of at least twofold.

There have also been reports of nongenital malformations, including limb reduction defects, neural tube defects, and congenital heart malformations, after intra-uterine exposure to progestogens in early pregnancy. However, many analyses of accumulated data have found no evidence of a recognisable malformation syndrome.[3]

For details of individual case reports, see Pregnancy under Dydrogesterone (p. 2270.2), Hydroxyprogesterone (p. 2285.2), Norethisterone (p. 2295.1), and Noretynodrel (p. 2295.3). For the effects of hormonal contraceptive use during early pregnancy, see p. 2242.1. For the risk of ectopic pregnancy with progestogen-only contraceptives, see p. 2236.3.

1. Czeizel A. Increasing trends in congenital malformations of male external genitalia. *Lancet* 1985; **i:** 462–3.
2. Carmichael SL, *et al*. Maternal progestin intake and risk of hypospadias. *Arch Pediatr Adolesc Med* 2005; **159:** 957–62.
3. Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. *Birth Defects Res A Clin Mol Teratol* 2005; **73:** 906–18.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for progesterone, but concluded that there would be no need to specify a numerical maximum residue limit for progesterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as progestogens in veterinary practice is restricted, and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, and rifampicin may enhance the clearance of progesterone and the progestogens. These interactions are likely to reduce the efficacy of progestogen-only contraceptives (see p. 2242.3), and additional or alternative contraceptive measures are recommended.

Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect; an increase in progestogen dose is likely to be required.

Since progesterone and other progestogens can influence diabetic control an adjustment in antidiabetic dosage could be required. Progestogens may inhibit ciclosporin metabolism leading to increased plasma-ciclosporin concentrations and a risk of toxicity (see p. 1955.1).

Pharmacokinetics

Progesterone has a short elimination half-life and undergoes extensive first-pass hepatic metabolism when given orally; oral bioavailability is very low although it may be increased somewhat by an oily vehicle and by micronisation. Progesterone is absorbed when given buccally, rectally, or vaginally, and rapidly absorbed from the site of an oily intramuscular injection.

Various derivatives have been produced to extend the duration of action and to improve oral activity. Esters of progesterone derivatives such as hydroxyprogesterone caproate are used intramuscularly, and megestrol acetate is orally active. The ester medroxyprogesterone acetate is used orally and parenterally. 19-Nortestosterone progestogens have good oral activity because the 17-ethinyl substituent slows hepatic metabolism.

Progesterone and the progestogens are highly protein bound; progesterone is bound to albumin and corticosteroid binding globulin; esters such as medroxyprogesterone acetate are mainly bound to albumin; and 19-nortestosterone analogues are bound to sex-steroid binding globulin and albumin. Progesterone is metabolised in the liver to various metabolites including pregnanediol, which are excreted in the urine as sulfate and glucuronide conjugates. Similarly, progestogens undergo hepatic metabolism to various conjugates, which are excreted in the urine. Progesterone is distributed into breast milk.

Reviews.

1. Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996; **51:** 188–215.
2. Stanczyk FZ. Structure-function relationships, metabolism, pharmacokinetics and potency of progestins. *Drugs Today* 1996; **32** (suppl H): 1–14.
3. Schindler AE, *et al*. Classification and pharmacology of progestins. *Maturitas* 2003; **46** (suppl 1): S7–S16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crinone; Gester; Mafel; Progest; Proluton; Utrogestan; ***Austral.***: Crinone; Proluton†; ***Austria***: Utrogestan; ***Belg.***: Crinone; Progestogel; Utrogestan; ***Braz.***: Crinone; Evocanil; Utrogestan; ***Canad.***: Crinone; Endometrin; Prometrium; ***Chile***: Crinone; Fertiring; Hormoral; Progendo; Progering; ***China***: Crinone (雪诺同); Lai Ting (来婷); Qi Ning (累宁); Utrogestan (安累坦); Yi Ma Xin (益玛欣); ***Cz.***: Agolutin; Crinone; Lutinus; Utrogestan; ***Denm.***: Crinone; Lutinus; ***Fin.***: Crinone; Lugesteron; Lutinus; ***Fr.***: Estima; Evapause†; Progestan; Progestogel; Utrogestan; ***Ger.***: Crinone; Progestogel; Utrogest; ***Gr.***: Crinone; Gestone; Lutorm; Promenorea; Tithogel; Utrogestan; Vasclor; ***Hong Kong***: Crinone; Cyclogest; Endometrin; Progestogel; Utrogestan; ***Hung.***: Crinone; Utrogestan; ***India***: Algest; Alpreg; Arigest; Belgest; Cap Voranin; Conest; Corion NP; Crinone; Cygest; Deltron; Dubagest; Durogest; E-Gest; Endogest; ETS; Evagest; Femicare; Femigest; Firm Up; Forgest; Fulgest; Fydogest; Ges-One; Gesry; Gester-NP; Gestmate; Gestofit; Gestone; Gestorin; Hema; Horpeg; LGP; LPD; Lupigestrone; Lutacare; Manogest; Medpro; Menoxy-N; Micpro; Microgest; Micronat; Miprogen; N-Sanigest; Namgem; Natpreg; Natron; Naturogest; Neogest; Nidagen; NT-Natal MP; Ogest; Onastrone; Remens; Uterone; Voranin; ***Indon.***: Crinone; Cygest; ***Irl.***: Crinone; Utrogestan; ***Israel***: Crinone; Endometrin; Gestone; Utrogestan; ***Ital.***: Crinone; Esolut; Lutogin; Progeffik; Prometrium; Prontogest; ***Malaysia***: Crinone; Cyclogest; Utrogestan; ***Mex.***: Crinone†; Cuerpo Amarillo Fuerte; Gepromi†; Geslutin; Gestageno; Premastan; Prosphere; Utrogestan; ***Mon.***: Menaelle; ***Neth.***: Lutinus; Utrogestan; ***Norw.***: Crinone; Lutinus; ***NZ***: Crinone; Gestone; Utrogestan; ***Philipp.***: Crinone; ***Pol.***: Luteina; ***Port.***: Crinone; Progestogel; Utrogestan; ***Rus.***: Crinone (Крайнон); Progestogel (Прожестожель); Utrogestan (Утрожестан); ***S.Afr.***: Crinone; Cyclogest; Utrogestan; ***Singapore***: Crinone; Cyclogest; Utrogestan; ***Spain***: Crinone; Darstin; Progeffik; Progestosol†; Utrogestan; ***Swed.***: Crinone; Lutinus; ***Switz.***: Crinone; Progestogel; Utrogestan; ***Thai.***: Crinone; Cyclogest; Progestogel†; Utrogestan; ***Turk.***: Crinone; Cyclogest; Progestan; Progynex; ***UK***: Crinone; Cyclogest; Gestone; Utrogestan; ***Ukr.***: Endometrin (Эндометрин); Luteina (Лютеина); Progestogel (Прожестожель); Utrogestan (Утрожестан); ***USA***: Crinone; Endometrin; Prochieve†; Prometrium; ***Venez.***: Crinone; Progendo; Progestogel; Utrogestan.

Multi-ingredient Preparations. ***Arg.***: Cristerona; Fempack; Hosterona; Lubriderm; Menstrogen†; Tropivag Plus; ***Belg.***: Duogestan; ***Fr.***: Florgynal; Trophigil; ***Ital.***: Menovis; ***Malaysia***: Duogynon; ***Mex.***: Damax; Genofort; Lutoginestryl F; Metrigen Fuerte; Primoson-F; Proger-F; ***Mon.***: Synergon; ***Thai.***: Duoton; Phenokinon-F; ***Turk.***: Di-Pro; Synergon; ***Venez.***: Ginecosid.

Pharmacopoeial Preparations

BP 2014: Progesterone Injection;
USP 36: Progesterone Injectable Suspension; Progesterone Injection; Progesterone Intrauterine Contraceptive System; Progesterone Vaginal Suppositories.

Proligestone *(BAN, rINN)*

Proligeston; Proligestona; Proligestoni; Proligestonum; Пролигестон.

14a,17a-Propylidene dioxypregn-4-ene-3,20-dione.

$C_{24}H_{34}O_4$=386.5

CAS — 23873-85-0.

ATC Vet — QG03DA90.

UNII — 55772LJ01V.

Profile

Proligestone is a progestogen used in veterinary medicine.

Promegestone *(rINN)*

Promegestona; Promégestone; Promegestonum; R-5020; Промегестон.

17α-Methyl-17-propionylestra-4,9-dien-3-one.

$C_{22}H_{30}O_2$=326.5

CAS — 34184-77-5.

ATC — G03DB07.

ATC Vet — QG03DB07.

UNII — 9XE0V2SQYX.

Profile

Promegestone is a progestogen structurally related to progesterone (p. 2300.2). It has been given orally on a cyclical basis, in doses of 125 to 500 micrograms daily, in the treatment of menstrual disorders and mastalgia, and as the progestogen component of menopausal HRT.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Surgestone; ***Port.***: Surgestone.

Promestriene *(rINN)*

Promestrien; Promestriène; Promestrieno; Promestrienum; Проместруен.

17β-Methoxy-3-propoxyestra-1,3,5(10)-triene.

$C_{22}H_{32}O_2$=328.5

CAS — 39219-28-8.

ATC — G03CA09.

ATC Vet — QG03CA09.

UNII — GXM4PER6WZ.

Profile

Promestriene is a derivative of estradiol (p. 2271.1) that has been used topically in menopausal atrophic vaginitis, and in seborrhoea and acne.

References.
1. Santos I, Clissold S. Urogenital disorders associated with oestrogen deficiency: the role of promestriene as topical oestrogen therapy. *Gynecol Endocrinol* 2010; **26:** 644–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Colpotrophine; ***Braz.***: Colpotrofine; ***China***: Colpotrophine (更宝芬); ***Hong Kong***: Colpotrophine; ***Ital.***: Colpotrophine; ***Mex.***: Colpotrophine; ***Mon.***: Colpotrophine; ***Port.***: Colpotrophine; ***Singapore***: Colpotrophine†; ***Spain***: Colpotrofin; Delipoderm†; ***Switz.***: Colpotrophine; ***Turk.***: Colpotrophine; ***Ukr.***: Colpotrophine (Колпотрофин).

Multi-ingredient Preparations. ***China***: Colposeptine (可宝净); ***Hong Kong***: Colposeptine; ***Mon.***: Colposeptine; ***Port.***: Trophoseptine; ***Turk.***: Colposeptine; ***Ukr.***: Colposeptine (Колпосептин).

Quinestradol *(BAN, rINN)*

Oestriol 3-Cyclopentyl Ether; Quinestradiol; Quinestradolum; Хинэстрадол.

3-Cyclopentyloxyestra-1,3,5(10)-triene-16α,17β-diol.

$C_{23}H_{32}O_3$=356.5

CAS — 1169-79-5.

UNII — 422L8173W8.

Profile

Quinestradol is a synthetic oestrogen that has been given orally for the treatment of menopausal vaginal symptoms.

Quinestrol *(BAN, USAN, rINN)*

17α-Ethinyloestradiol 3-cyclopentyl Ether; Quinestrolum; W-3566; Хинэстрол.

3-Cyclopentyloxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol.

$C_{25}H_{32}O_2$=364.5

CAS — 152-43-2.

UNII — JR0N7XD5GZ.

Pharmacopoeias. In *Chin.*

Profile

Quinestrol is a synthetic oestrogen that has a prolonged duration of action and is metabolised to ethinylestradiol (p. 2275.3). Quinestrol has been given orally for the treatment of menopausal symptoms and other conditions arising from oestrogen deficiency. It has also been used as the oestrogen component of combined oral contraceptive preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Qui-Lea.

Multi-ingredient Preparations. ***Arg.***: Soluna; ***China***: Compound Norgestrel (复方炔诺孕酮); Yueketing (悦可婷).

Raloxifene Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de keoxifeno; Hidrocloruro de raloxifeno; Keoxifene Hydrochloride; LY-139481 (raloxifene); LY-156758; Raloksifen Hidroklorür; Raloxifène, Chlorhydrate de; Raloxifenhydrochlorid; Raloxifeni Hydrochloridum; Raloxifeno, hidrocloruro de; Ралоксифена Гидрохлорид.

6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-*p*-(2-piperidinoethoxy)phenyl ketone hydrochloride.

$C_{28}H_{27}NO_4S$,HCl=510.0

CAS — 84449-90-1 (raloxifene); 82640-04-8 (raloxifene hydrochloride).

ATC — G03XC01.

ATC Vet — QG03XC01.

UNII — 4F86W47BR6.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Raloxifene Hydrochloride). An almost white or pale-yellow powder. Very slightly soluble or practically insoluble in water and in acetone; slightly soluble in alcohol.

USP 36: (Raloxifene Hydrochloride). An almost white to pale yellow powder. Very slightly soluble in water, in isopropyl alcohol, and in octanol; slightly soluble in alcohol; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; practically insoluble in ether and in ethyl acetate.

Uses and Administration

Raloxifene hydrochloride is a selective oestrogen receptor modulator; it is a benzothiophene that appears to have oestrogen agonist effects on bone and antagonist effects in uterine and breast tissue. It is used, in oral doses of 60 mg daily, for the prevention and treatment of postmenopausal osteoporosis (below). The same dose is also used to reduce the risk of invasive breast cancer in postmenopausal women who have osteoporosis or are at high risk of invasive breast cancer (below).

Reviews.
1. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999; **130:** 431–9.
2. Snyder KR, *et al.* Raloxifene hydrochloride. *Am J Health-Syst Pharm* 2000; **57:** 1669–75.
3. Barrett-Connor E. Raloxifene: risks and benefits. *Ann N Y Acad Sci* 2001; **949:** 295–303.
4. Heringa M. Review on raloxifene: profile of a selective estrogen receptor modulator. *Int J Clin Pharmacol Ther* 2003; **41:** 331–45.
5. Trémollières F, Ribot C. Indications du raloxifène chez la femme ménopausée. *Gynecol Obstet Fertil* 2006; **34:** 147–53.

Administration in renal impairment. Although unexpected, renal impairment reduced raloxifene clearance in a pharmacokinetic study (see p. 2304.1). Licensed product information in the UK contra-indicates the use of raloxifene in severe renal impairment, and in the USA it advises caution in moderate and severe impairment. Nevertheless, raloxifene has been studied in postmenopausal women with renal impairment and severe osteopenia or osteoporosis. An oral dose of 60 mg daily for 1 year was given to 25 women on haemodialysis and found to improve bone mineral density of the lumbar spine, compared with 25 women given placebo; there were no reported adverse effects.[1]

1. Hernández E, *et al.* Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 2003; **63:** 2269–74.

Hyperparathyroidism. The effects of raloxifene have been reported in postmenopausal women with mild primary hyperparathyroidism (p. 1170.3). Reductions in markers of bone turnover and plasma concentrations of calcium have been described in an observational report[1] and a small, short-term, placebo-controlled study.[2] An increase in bone mineral density was also detected after 12 months of treatment with raloxifene.[1]

1. Zanchetta JR, Bogado CE. Raloxifene reverses bone loss in postmenopausal women with mild asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 189–90.
2. Rubin MR, *et al.* Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 1174–8.

Malignant neoplasms of the breast. Studies have found raloxifene to be effective for the prophylaxis of breast cancer (p. 703.2).[1] In a placebo-controlled study[2] of postmenopausal women with osteoporosis and no history of breast cancer (MORE), the use of raloxifene for about 3 years reduced the risk of developing breast cancer. This was seen as a reduction in the risk of invasive oestrogen-receptor positive breast cancer, as there was no effect on the risk of oestrogen-receptor negative disease. The reduction in risk was maintained in an extension[3] of this study (CORE) to a total of 8 years of treatment. Similar results were reported in a large placebo-controlled study (RUTH)[4] of postmenopausal women who were treated for about 5 years. Both MORE/CORE[5] and RUTH[4] reported risk reduction in women at either high or low risk, but the MORE study[5] found the effect to be greater in women with a family history of breast cancer.

In a study[6] of postmenopausal women with a predicted increased risk of breast cancer (STAR), prophylactic raloxifene for up to 5 years was found to be as effective as tamoxifen in reducing the risk of invasive breast cancer.

1. Moen MD, Keating GM. Raloxifene: a review of its use in the prevention of invasive breast cancer. *Drugs* 2008; **68:** 2059–83.
2. Cummings SR, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; **281:** 2189–97. Correction. *ibid.*; **282:** 2124.
3. Martino S, *et al.* Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004; **96:** 1751–61.
4. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; **355:** 125–37.
5. Lippman ME, *et al.* Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. *Clin Cancer Res* 2006; **12:** 5242–7.
6. Vogel VG, *et al.* Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006; **295:** 2727–41. Corrections. *ibid.*; **296:** 2926 and *ibid.* 2007; **298:** 973.

Osteoporosis. Raloxifene partially mimics the effects of oestrogens in bone to increase bone mineral density in postmenopausal women.[1,2] The MORE study in 7705 postmenopausal women with osteoporosis (p. 1168.1) found that up to 4 years of raloxifene treatment reduced the risk of vertebral fracture,[3-6] but the risk of nonvertebral fracture did not differ significantly from that in women given placebo.[3,5] A meta-analysis[7] of data from this and other smaller studies concluded that raloxifene reduced the risk of vertebral fracture by between 40 and 49% in postmenopausal women with osteoporosis. NICE recommends raloxifene as an alternative treatment option for the secondary[8] prevention of osteoporotic fragility fractures in high-risk postmenopausal women who are unable to take bisphosphonates. It is not recommended for primary prevention in postmenopausal women.[9]

Small studies suggest that raloxifene may be effective as 'add-back' therapy to prevent the loss of bone mineral density associated with gonadorelin analogue therapy in women[10,11] and men.[12]

1. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs* 2000; **60:** 379–411.
2. Cranney A, Adachi JD. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. *Drug Safety* 2005; **28:** 721–30.
3. Ettinger B, *et al.* Multiple Outcomes of Raloxifene Evaluation Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999; **282:** 637–45.
4. Maricic M, *et al.* Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med* 2002; **162:** 1140–3.
5. Delmas PD, *et al.* Multiple Outcomes of Raloxifene Evaluation Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002; **87:** 3609–17.
6. Qu Y, *et al.* The effect of raloxifene therapy on the risk of new clinical vertebral fractures at three and six months: a secondary analysis of the MORE trial. *Curr Med Res Opin* 2005; **21:** 1955–9.
7. Seeman E, *et al.* Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporos Int* 2006; **17:** 313–16.
8. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended): Technology Appraisal 161 (issued October 2008, amended January 2010). Available at: http://www.nice.org.uk/nicemedia/live/11748/47177/47177.pdf (accessed 19/07/10)
9. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 160 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA160guidance.pdf (accessed 12/01/09)
10. Palomba S, *et al.* Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; **87:** 4476–81.
11. Palomba S, *et al.* Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. *Hum Reprod* 2004; **19:** 1308–14.
12. Smith MR, *et al.* Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3841–6.

Adverse Effects

The most common adverse effects of selective oestrogen receptor modulators such as raloxifene are hot flushes, leg cramps, and a flu-like syndrome. Raloxifene is associated with an increased risk of venous thromboembolic events including deep-vein thrombosis, pulmonary embolism, and retinal vein thrombosis, particularly during the first 4 months of treatment. Peripheral oedema has also been reported. Rashes, gastrointestinal disturbances, thrombocytopenia, increased blood pressure, headache including migraine, and mild breast symptoms such as pain, enlargement, and tenderness have occurred very rarely.

Incidence of adverse effects. An observational cohort study[1] examined postmarketing adverse events that occurred during raloxifene use in primary care in England. The cohort of 13 987 patients consisted largely of women aged about 62 years, who were receiving raloxifene for the prevention or treatment of osteoporosis. Of the 461 events reported, the most common included flushing, headache or migraine, malaise or lassitude, cramp, oedema, sweating, depression, weight gain, and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, and diarrhoea. Other less common effects included mastalgia and other breast symptoms, vaginal bleeding, thrombophlebitis, and visual disturbances. Rare events included cerebrovascular attack, transient ischaemic attack, pulmonary embolus, deep-vein thrombosis, bullous eruption, leucopenia, thrombocytopenia, upper gastrointestinal haemorrhage, and perforated duodenal ulcer.

See also Effects on the Cardiovascular System, below.

1. Layton D, *et al.* Safety profile of raloxifene as used in general practice in England: results of a prescription-event monitoring study. *Osteoporosis Int* 2005; **16:** 490–500.

Effects on the cardiovascular system. The incidence of cardiovascular effects associated with raloxifene treatment was examined in the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE), which studied its effects in postmenopausal women with osteoporosis, and in a subsequent 4-year follow-up (Continuing Outcomes Relevant to Evista; CORE).[1] There were 7705 women in the MORE study, of whom 4011 were enrolled in CORE. Overall no significant differences were seen between active treatment and placebo for any cardiovascular event over the 8 years; the calculated incidence was 72 per 10 000 woman-years in those taking raloxifene and 62 per 10 000 in the placebo

group. Another large placebo-controlled study[2] (Raloxifene Use for The Heart: RUTH) investigated the cardiovascular effects of raloxifene in postmenopausal women with, or at increased risk of, ischaemic heart disease. After treatment for about 5 years there was no significant difference between the groups for overall cardiovascular events and related deaths. However, in those given raloxifene there was an increased risk of fatal stroke (absolute risk increase, 0.7 per 1000 women-years) and venous thromboembolism (1.2 per 1000 women-years).

1. Ensrud K, *et al.* Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol* 2006; **97:** 520–7.
2. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; **355:** 125–37.

Effects on the liver. Hepatitis, probably associated with the drug, occurred in a woman a month after starting raloxifene.[1] Non-alcoholic steatohepatitis was associated with raloxifene in a woman with minor liver dysfunction, a fatty liver, and a family history of cryptogenic liver cirrhosis.[2] Her liver function worsened during the 3 months after starting the drug, and had returned to baseline 3 months after stopping.

1. Vilches AR, *et al.* Raloxifene-associated hepatitis. *Lancet* 1998; **352:** 1524–5.
2. Takamura T, *et al.* Selective estrogen receptor modulator raloxifene-associated aggravation of nonalcoholic steatohepatitis. *Intern Med* 2007; **46:** 579–81.

Precautions

Raloxifene should be avoided in women with active venous thromboembolism, or a history of thromboembolic disorders. It should be stopped at least 72 hours before periods of prolonged immobilisation, such as post-surgical recovery. Raloxifene should be used with caution in women with risk factors for venous thromboembolism including congestive heart failure or active malignancy, or risk factors for stroke such as transient ischaemic attack or atrial fibrillation. It should be avoided in hepatic and severe renal impairment, and used with caution in moderate renal impairment (but see also Administration in Renal Impairment, p. 2303.2).

Raloxifene had adverse effects in *animal* teratogenicity studies and should not be used in women who are or may become pregnant. It should not be given to women with undiagnosed uterine bleeding. An increase in triglycerides has been reported in some women with a history of hypertriglyceridaemia caused by oestrogen therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies raloxifene as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Colestyramine reduces the absorption and enterohepatic recycling of raloxifene, and they should not be given together. Raloxifene may decrease the efficacy of warfarin. Levothyroxine requirements may also be increased with raloxifene use (see Sex Hormones under the interactions of Levothyroxine Sodium, p. 2342.2).

Fibrates. Cholestasis developed when *fenofibrate* was given to a woman who had been on raloxifene therapy for about 3 years.[1] The authors reviewed other rare reports of liver reactions to either raloxifene or fibrates and suggested that the reaction was likely to be due to an interaction, although the mechanism was not clear.

1. Lucena MI, *et al.* Prolonged cholestasis after raloxifene and fenofibrate interaction: a case report. *World J Gastroenterol* 2006; **12:** 5244–6.

Pharmacokinetics

Raloxifene is absorbed from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism to the glucuronide conjugates. It is highly bound to plasma proteins, mainly albumin and α_1-acid glycoprotein. Raloxifene undergoes enterohepatic recycling, and has a half-life of about 27 hours. It is excreted almost entirely in the faeces.

Renal impairment. The pharmacokinetics of raloxifene are not expected to be affected by renal impairment because the renally excreted fraction is only about 6% in healthy subjects. However, a study[1] in male subjects found the clearance of a single 120-mg oral dose to be significantly reduced in 10 men with renal impairment (creatinine clearance 24 to 51 mL/minute) compared with a group of 10 with normal renal function. It was calculated that steady-state concentrations could be about 2.3 times higher in patients with renal impairment. The authors suggested that this unexpected result might be due to reduced metabolic clearance in the renal tubules or by impairment of biliary excretion of raloxifene glucuronides by uraemic toxins.

1. Czock D, *et al.* Raloxifene pharmacokinetics in males with normal and impaired renal function. *Br J Clin Pharmacol* 2005; **59:** 479–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Evista; Ketidin; Oseofem†; Raxeto; ***Austral.***: Evista; ***Austria***: Evista; ***Belg.***: Evista; ***Braz.***: Evista; ***Canad.***: Evista; ***Chile***: Evista; ***China***: Bei Bang (贝邦); Evista (易维特); ***Cz.***: Evista; Optruma; Ralfeen; ***Denm.***: Evista; ***Fin.***: Evista; ***Fr.***: Evista; Optruma; ***Ger.***: Evista; Optruma; ***Gr.***: Evista; ***Hong Kong***: Evista; ***Hung.***: Evista; ***India***: Bonmax; Bontact; Esserm; Estroact; Evomate; Fiona; Gynista; Osral; Ralista; ***Indon.***: Evista; ***Irl.***: Evista; Optruma; Raloxiep; ***Israel***: Evista; ***Ital.***: Evista; Optruma; ***Jpn***: Evista; ***Malaysia***: Evista; ***Mex.***: Evista; ***Neth.***: Evista; Optruma; RaloMeer; Ralover; Raloxa; Raloxiep; RaloxStar; Raloxten; ***Norw.***: Evista; ***NZ***: Evista; ***Philipp.***: Evista; ***Pol.***: Evista; Optruma; ***Port.***: Evista; Optruma; ***Rus.***: Evista (Эвиста); ***S.Afr.***: Evista; ***Singapore***: Evista; ***Spain***: Evista; Optruma; ***Swed.***: Evista; ***Switz.***: Evista; ***Thai.***: Celvista; ***Turk.***: Evista; ***UK***: Evista; ***USA***: Evista; ***Venez.***: Evista.

Pharmacopoeial Preparations
USP 36: Raloxifene Hydrochloride Tablets.

Stanozolol *(BAN, USAN, rINN)* ⊗

Androstanazol; Androstanazole; Estanazol; Estanozolol; Methylstanazole; Metistanazol; NSC-43193; Stanotsololi; Stanozololis; Stanozololum; Stanozolum; Sztanozolol; Win-14833; Станозолол.

17α-Methyl-2′*H*-5α-androst-2-eno[3,2-*c*]pyrazol-17β-ol.

$C_{21}H_{32}N_2O$=328.5

CAS — 10418-03-8.

ATC — A14AA02.

ATC Vet — QA14AA02.

UNII — 4R1VB9P8V3.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of stanozolol:

Iron Brew.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Stanozolol). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dimethylformamide; very slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Stanozolol). An odourless crystalline powder occurring in 2 forms; needles melt at about 155 degrees and prisms at about 235 degrees. Insoluble in water; soluble 1 in 41 of alcohol, 1 in 74 of chloroform, and 1 in 370 of ether; slightly soluble in acetone and in ethyl acetate; soluble in dimethylformamide; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Stanozolol has anabolic and androgenic properties (see Testosterone, p. 2305.2). As with other anabolic steroids, stanozolol has been used for breast cancer in postmenopausal women, and for anaemias, osteoporosis, and catabolic disorders. It has been given in oral doses of 2 mg every 8 to 12 hours, or 50 mg by intramuscular injection every 2 or 3 weeks.

Stanozolol may be used in the management of hereditary angioedema (see below).

Hereditary angioedema. Stanozolol raises serum concentrations of C1 esterase inhibitor and has been used to prevent attacks of hereditary angioedema (p. 2485.2). Initial doses are titrated down to the lowest effective prophylactic dose, to minimise adverse effects from long-term use. Stanozolol is typically given orally in doses of 1 to 2 mg daily or on alternate days,[1,2] and possibly less frequently,[3] although doses of up to 5 mg once or twice daily may be necessary.[4] Additional short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental procedures. Stanozolol 2 mg three times daily may be used for this, but should be started about 5 to 7 days before the procedure,[1] and continued for 48 hours after.[4] A higher dose of 4 mg every 6 hours, for 5 days before the procedure, has also been reported.[3]

Attenuated androgens are not usually given in the acute management of hereditary angioedema. However, the early use of up to 16 mg daily of stanozolol may shorten the duration of an attack of peripheral swelling.[4] A dose of stanozolol 4 mg every 6 to 8 hours, with fresh frozen plasma, has also been used in the early management of severe acute attacks.[3]

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.
2. Banerji A, *et al.* Hereditary angioedema: a current state-of-the-art review, V: attenuated androgens for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008; **100** (suppl 2): S19–S22.
3. Sloane DE, *et al.* Hereditary angioedema: safety of long-term stanozolol therapy. *J Allergy Clin Immunol* 2007; **120:** 654–8.
4. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]

Vascular disorders. Stanozolol has been used in the treatment of vascular manifestations of Behçet's syndrome. It has also been reported to promote fibrinolysis in vascular disorders, and has been tried in various conditions. However, most studies have been noncomparative and in small numbers of patients, and results have been variable.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p. 2307.3). As with other 17α-alkylated compounds stanozolol may produce hepatotoxicity, and liver function should be monitored. It is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Haematocrit and haemoglobin concentrations should also be monitored.

Because of its androgenic effects it has been recommended that stanozolol should not be used to treat hereditary angioedema in premenopausal women except in life-threatening situations.

Effects on the kidneys. Renal failure with cholestatic jaundice has been reported with stanozolol (see below).

Effects on the liver. Cholestatic jaundice has been reported with stanozolol,[1-3] in some cases with acute tubular necrosis and renal failure.[4]

1. Slater SD, *et al.* Jaundice induced by stanozolol hypersensitivity. *Postgrad Med J* 1976; **52:** 229–32.
2. Evely RS, *et al.* Severe cholestasis associated with stanozolol. *BMJ* 1987; **294:** 612–13.
3. Martínez B, *et al.* Colestasis inducida por consumo de estanozolol. *Rev Esp Enferm Dig* 2006; **98:** 219–20.
4. Yoshida EM, *et al.* At what price, glory? Severe cholestasis and acute renal failure in an athlete abusing stanozolol. *Can Med Assoc J* 1994; **151:** 791–3.

Effects on the nervous system. Benign intracranial hypertension developed in an elderly woman receiving stanozolol; CSF pressure returned to normal after stanozolol was stopped.[1]

1. Tully MP, *et al.* Intracranial hypertension associated with stanozolol. *DICP Ann Pharmacother* 1990; **24:** 1234.

Interactions

As mentioned under Testosterone, p. 2308.3, anabolic steroids may enhance the activity of various drugs. For the effect of stanozolol on some anticoagulants, see p. 1535.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Stromba†; ***India***: Menabol; Neurabol; ***Spain***: Winstrol; ***Thai.***: Stanztab.

Multi-ingredient Preparations. ***Thai.***: Cetabon†.

Pharmacopoeial Preparations
USP 36: Stanozolol Tablets.

Testis Extracts ⊗

Extractos testiculares; Testicular Extracts; Тестикулярный Экстракт.

Profile

Testis extracts are usually of bovine origin and have been used in a variety of disorders. They have been given to elderly men as androgenic supplements. They have also been used topically, often in preparations containing other mammalian tissue extracts, in the treatment of peripheral circulatory or musculoskeletal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: FegaCoren; ***Hong Kong***: Sessoforte†; Wari-Procomil†.

Homoeopathic Preparations. ***Fr.***: Amphosca Orchitine; ***Ger.***: NeyChon Nr 68; NeyChondrin Nr 68-Sol†; NeyDil Nr 66†; Neydin-M†; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A; NeyLing Nr 66; NeySol L 66†; ***Neth.***: Chavita 1; Emvita 3; ***USA***: Estrex.

Testosterone *(BAN, rINN)* ⊗

Testosteron; Testosterona; Testosteronas; Testostérone; Testosteroni; Testosteronum; Tesztoszteron; Тестостерон.

17β-Hydroxyandrost-4-en-3-one.

$C_{19}H_{28}O_2$=288.4

CAS — 58-22-0.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — 3XMK78S47O.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of testosterone:

T-Stoff.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Testosterone). A white or almost white, crystalline powder, or colourless or yellowish-white crystals. Practically insoluble in water and in fatty oils; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Testosterone). White or slightly creamy-white, odourless, crystals or crystalline powder. Practically insoluble in water; soluble 1 in 6 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 100 of ether; soluble in dioxan and in vegetable oils. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Testosterone Cipionate *(BANM, rINNM)* ⊗

Cipionato de testosterona; Testosterona, cipionato de; Testostérone, Cipionate de; Testosterone Cyclopentylpropionate; Testosterone Cypionate; Testosteroni Cipionas; Тестостерона Ципионат.

3-Oxoandrost-4-en-17β-yl 3-cyclopentylpropionate; 17β-Hydroxyandrost-4-en-3-one cyclopentanepropionate; 17β-(3-Cyclopentyl-1-oxopropoxy)androst-4-en-3-one.

$C_{27}H_{40}O_3$=412.6

CAS — 58-20-8.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — M0XW1UBI14.

Pharmacopoeias. In *US.*

USP 36: (Testosterone Cypionate). A white or creamy-white, crystalline powder, odourless or has a slight odour. Insoluble in water; freely soluble in alcohol, in chloroform, in dioxan, and in ether; soluble in vegetable oils. Protect from light.

Testosterone Decanoate *(BANM, rINNM)* ⊗

Decanoato de testosterona; Testosteron Dekanoat; Testosterona, decanoato de; Testosterondecanoat; Testostérone, décanoate de; Testosteroni decanoas; Тестостерона Деканоат.

3-Oxoandrost-4-en-17β-yl decanoate; 17β-Hydroxyandrost-4-en-3-one decanoate.

$C_{29}H_{46}O_3$=442.7

CAS — 5721-91-5.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — IJW60LAO6S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Testosterone Decanoate). A white or almost white powder. Practically insoluble in water; very soluble in anhydrous alcohol, in acetone, and in dichloromethane; freely soluble in fatty oils. Store at a temperature of 2 degrees to 8 degrees.

Testosterone Enantate *(BANM, rINNM)* ⊗

Enantato de testosterona; NSC-17591; Testosteron enantát; Testosterona, enantato de; Testostérone, Enantate de; Testosterone Enanthate; Testosterone Heptanoate; Testosterone Heptylate; Testosteronenantat; Testosteroni Enantas; Testosteronienantaatti; Testosterono enantatas; Testosteronu enantan; Tesztoszteronönantát; Тестостерона Энантат.

3-Oxoandrost-4-en-17β-yl heptanoate; 17β-Hydroxyandrost-4-en-3-one heptanoate.

$C_{26}H_{40}O_3$=400.6

CAS — 315-37-7.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — 7Z6522T8N9.

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Testosterone Enantate). A white or yellowish-white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in fatty oils. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Testosterone Enanthate). A white or creamy-white crystalline powder. It is odourless or has a faint odour characteristic of heptanoic acid. Insoluble in water; very soluble in ether; soluble in vegetable oils. Store in a cool place.

Testosterone Isocaproate *(BANM, rINNM)* ⊗

Isocaproato de testosterona; Testosteron Isokaproat; Testosterona, isocaproato de; Testostérone, isocaproate de; Testosterone Isohexanoate; Testosteroni isocaproas; Testosteronisocaproat; Тестостерона Изокапронат.

3-Oxoandrost-4-en-17β-yl 4-methylpentanoate; 17β-Hydroxyandrost-4-en-3-one 4-methylpentanoate.

$C_{25}H_{38}O_3$=386.6

CAS — 15262-86-9.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — X8ST05GYDM.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Testosterone Isocaproate). A white or almost white powder. Practically insoluble in water; very soluble in acetone and in dichloromethane; freely soluble in fatty oils.

Testosterone Phenylpropionate *(BANM, rINNM)* ⊗

Fenilpropionato de testosterona; Testosteron Fenilpropiyonat; Testosterona, fenilpropionato de; Téstosterone, Phénylpropionate de; Testosteroni Phenylpropionas; Тестостерона Фенилпропионат.

3-Oxoandrost-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyandrost-4-en-3-one 3-phenylpropionate.

$C_{28}H_{36}O_3$=420.6

CAS — 1255-49-8.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — BGN84GWX51.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Testosterone Phenylpropionate). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

Testosterone Propionate *(BANM, rINNM)* ⊗

NSC-9166; Propionato de testosterona; Testosteron Propiyonat; Testosterona, propionato de; Testostérone, Propionate de; Testosteroni Propionas; Testosteronipropionaatti; Testosterono propionatas; Testosteronpropionat; Testosteronpropionát; Testosteronu propionian; Tesztoszteronpropionát; Тестостерона Пропионат.

3-Oxoandrost-4-en-17β-yl propionate; 17β-Hydroxyandrost-4-en-3-one propionate.

$C_{22}H_{32}O_3$=344.5

CAS — 57-85-2.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — WI93Z913BA.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Testosterone Propionate). A white or almost white powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in fatty oils.

USP 36: (Testosterone Propionate). White or creamy-white, odourless, crystals or crystalline powder. Insoluble in water; freely soluble in alcohol, in dioxan, in ether, and in other organic solvents; soluble in vegetable oils. Protect from light.

Testosterone Undecylate *(rINNM)* ⊗

Org-538; Testosteron Undekanoat; Testosterona, undecilato de; Testosterone Undecanoate (USAN); Testosterone Undecanoate (BANM); Testostérone, Undécylate de; Testosteroni Undecylas; Undecilato de testosterona; Тестостерона Ундесилат.

3-Oxoandrost-4-en-17β-yl undecanoate; 17β-Hydroxyandrost-4-en-3-one undecanoate.

$C_{30}H_{48}O_3$=456.7

CAS — 5949-44-0.

ATC — G03BA03.

ATC Vet — QG03BA03.

UNII — H16A5VCT9C.

Pharmacopoeias. In *Chin.*

Uses and Administration

The natural hormone testosterone and its derivatives have anabolic and androgenic properties (for further details, see p. 2231.1).

The primary indication for androgens, such as testosterone or its esters, is as replacement therapy in **male hypogonadal disorders** (p. 2306.3) caused by either pituitary or testicular disorders or in hypogonadism following orchidectomy. Testosterone may be used as a subcutaneous implant in a dose of 100 to 600 mg; plasma concentrations of testosterone are usually maintained within the physiological range for 4 to 5 months with a dose of 600 mg. It may also be given by transdermal delivery systems. Patches are applied to the back, abdomen, thighs or upper arms to supply 2 to 7.5 mg daily. A scrotal patch has been used, but is no longer widely available. Hydroalcoholic gels containing 1 or 2% testosterone are also used; they are applied daily to the shoulders and upper arms, abdomen, or thighs, depending on the preparation. About 10% of the applied dose is absorbed across the skin to provide a systemic dose of testosterone 5 to 10 mg. An alcoholic solution containing 30 mg testosterone per 1.5 mL for application to the axillae is also used. The recommended starting dose is 60 mg applied once daily, as 30 mg to each axilla. The dose may be adjusted within a range of 30 to 120 mg daily. A sustained-release adhesive buccal system that contains testosterone 30 mg is applied twice daily; by this route the systemic dose is about 3 mg. Testosterone has also been given by intramuscular injection in a dose of up to 50 mg two or three times weekly, but testosterone esters are generally preferred by this route.

The testosterone esters are usually formulated as oily solutions for intramuscular use to give a prolonged duration of action. Doses that have been used for the various esters are:

- testosterone cipionate 50 to 400 mg every 2 to 4 weeks
- testosterone enantate 50 to 400 mg every 2 to 4 weeks, or an initial dose of 250 mg every 2 to 3 weeks followed by maintenance dosing every 3 to 6 weeks
- testosterone propionate up to 50 mg two or three times weekly
- testosterone undecylate 1 g every 10 to 14 weeks

The isocaproate, phenylpropionate, and propionate esters may be given as a combined intramuscular preparation, sometimes also containing testosterone decanoate. Testosterone hexahydrobenzoate, testosterone hexahydrobenzylcarbonate, and testosterone isobutyrate have also been used. The undecylate ester is also given orally in an initial dose of 120 to 160 mg daily, in 2 divided doses, for 2 to 3 weeks, followed by a maintenance dose of 40 to 120 mg daily. See p. 2306.1 for some doses of testosterone used in children.

Androgens and anabolic steroids have sometimes been used with oestrogens in the management of menopausal symptoms in **women**. Intramuscular injections containing an androgen and an oestrogen have been used for the treatment of menopausal vasomotor symptoms, and testosterone implants have been given as an adjunct to menopausal HRT for symptoms such as decreased libido. A transdermal patch was also available for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause (bilateral oophorectomy and hysterectomy) who were receiving oestrogen therapy. However, there are concerns about the use of these preparations and conflicting opinion as to their usefulness (see p. 2307.1). The use of androgens and anabolic steroids in women with osteoporosis is no longer advocated because their adverse effects essentially outweigh any benefit they may produce. In postmenopausal women androgens, and sometimes anabolic steroids are occasionally used in the hormonal therapy of disseminated breast carcinoma but care should be taken to choose a compound with a lower masculinising effect; the short-acting synthetic compounds are usually preferred for such purposes. Testosterone enantate has been used in doses of 200 to 400 mg every 2 to 4 weeks by intramuscular injection.

Anabolic steroids, and sometimes androgens, have been used in the treatment of refractory anaemias characterised by deficient red cell production, such as aplastic anaemia (p. 1121.3). Anabolic steroids and synthetic androgens with an attenuated action (sometimes known as 'attenuated androgens') such as danazol are also used in the management of hereditary angioedema (p. 2485.2).

Topical androgens may be used in the treatment of lichen sclerosus (p. 2307.1).

Androgens and anabolic steroids have been used for their anabolic properties in various catabolic states (see Anabolic Effects, p. 2306.1).

Testosterone hemisuccinate is an ingredient of preparations that have been promoted for the management of cataracts.

General reviews of androgens and anabolic steroids.

1. Hickson RC, *et al.* Adverse effects of anabolic steroids. *Med Toxicol Adverse Drug Exp* 1989; **4:** 254–71.
2. Bagatell CJ, Bremner WJ. Androgens in men—uses and abuses. *N Engl J Med* 1996; **334:** 707–14.
3. Conway AJ, *et al.* Use, misuse and abuse of androgens: the Endocrine Society of Australia consensus guidelines for androgen prescribing. *Med J Aust* 2000; **172:** 220–4. Correction. *ibid.;* 334. Also available at: http://www.mja.com.au/public/issues/172_05_060300/conway/conway.html (accessed 13/11/07)
4. Handelsman DJ. Testosterone: use, misuse and abuse. *Med J Aust* 2006; **185:** 436–9.

Administration in children. Testosterone is used in adolescent males with hypogonadism, and has been used in constitutionally delayed puberty. It has also been used to reduce final height in boys with constitutional tall stature (see below).

Although not licensed in the UK for the induction and maintenance of **sexual maturation** in boys over 12 years of age, the *BNFC* recommends a dose of testosterone undecylate 40 mg orally on alternate days; this may be increased up to 120 mg daily according to response. Alternatively, testosterone enantate may be given by deep intramuscular injection in doses of 25 to 50 mg/m^2 every month, increasing every 6 to 12 months according to response. Testosterone propionate 50 mg may be given once weekly by intramuscular injection. Although no longer marketed in the UK, an injection containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg) has been given intramuscularly, once each month for 3 doses, for delayed puberty. The *BNFC* also suggests that an implant may be used in children over 16 years of age for maintenance of sexual maturation. See p. 2305.2 for doses. However, great care is necessary when using androgens for such conditions as bone growth and final height may be inhibited by the early fusion of the epiphyses. Extemporaneously prepared testosterone 5% cream has been applied topically, 3 times daily for 3 weeks, in the management of microphallus (the alcohol in proprietary gels can cause irritation).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p. 1918.3). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using testosterone has been tried in boys in order to increase responsiveness to the test,[1-3] although there appears to be no consensus on such use.[4] One regimen that has been used is a single intramuscular dose of a product containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg), given 3 to 5 days before the test.

1. Loche S, *et al.* The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82:** 861–4.
2. Coutant R, *et al.* Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86:** 5805–12.
3. Gönç EN, *et al.* Comparison of stimulated growth hormone levels in primed versus unprimed provocative tests: effect of various testosterone doses on growth hormone levels. *Horm Res* 2001; **56:** 32–7.
4. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 22/08/08)

Anabolic effects. The androgens generally possess anabolic activity and were formerly used to increase weight in patients suffering from emaciation or debilitating diseases but efficacy was doubtful. The anabolic steroids were developed in order to enhance the ability to build proteins and diminish the virilising and masculinising effects of the natural androgens, but all anabolics retain some androgenic activity. The anabolic steroids have again, like the androgens, been used in an attempt to produce weight gain in cachexia and wasting diseases (p. 2289.3).

The anabolic steroids and androgens have been the subject of much misuse and abuse by athletes, sports persons, and body builders (see under Precautions, p. 2308.2) in an attempt to increase muscle mass and body-weight but such use cannot be justified.

References to the anabolic effects of testosterone.

1. Bhasin S, *et al.* The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996; **335:** 1–7.
2. Basaria S, *et al.* Anabolic-androgenic steroid therapy in the treatment of chronic diseases. *J Clin Endocrinol Metab* 2001; **86:** 5108–17.
3. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. *Lancet Infect Dis* 2002; **2:** 692–9.
4. Johns K, *et al.* Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).

Antineoplastic-induced infertility. For reference to the use of testosterone to preserve gonadal function during cyclophosphamide therapy, see Effects on Reproductive Potential, p. 773.1.

Constitutionally delayed puberty. Testosterone enantate given by intramuscular injection every 1 to 2 months for periods ranging from 3 months to several years, produced beneficial effects in boys with constitutionally delayed puberty and growth;[1,2] growth rate increased, sexual and skeletal maturation were stimulated, and full height potential did not appear to be compromised. However, it has been pointed out that repeated intramuscular injections are painful and are disliked by adolescents;[3] oral testosterone undecylate or oxandrolone have been shown to be effective in the treatment of delayed puberty and growth in boys,[4,5] and may be preferred.[3] It should be noted that giving androgens to boys with constitutional delay of growth and puberty is controversial (see p. 2252.1). For reference to the use of testosterone in boys with delayed puberty due to hypogonadism see below.

1. Donaldson MDC, Savage DCL. Testosterone therapy in boys with delayed puberty. *Arch Dis Child* 1987; **62:** 647–8.
2. Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. *N Engl J Med* 1988; **319:** 1563–7.
3. Kelnar CJH. Treatment of the short, sexually immature adolescent boy. *Arch Dis Child* 1994; **71:** 285–7.
4. Albanese A, *et al.* Oral treatment for constitutional delay of growth and puberty in boys: a randomised trial of an anabolic steroid or testosterone undecanoate. *Arch Dis Child* 1994; **71:** 315–17.
5. Brown DC, *et al.* A double blind, placebo controlled study of the effects of low dose testosterone undecanoate on the growth of small for age, prepubertal boys. *Arch Dis Child* 1995; **73:** 131–5.

Constitutionally tall stature. Supraphysiological doses of androgens have been used to *reduce* final height in tall adolescent boys. Testosterone esters in monthly doses of up to 1 g by intramuscular injection have been used.[1] Preliminary evidence after a mean of 10 years follow-up suggests that there was no long-term effect on reproductive function.[2] For reference to the use of testosterone to *increase* growth rate, see Constitutionally Delayed Puberty, above.

1. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.
2. de Waal WJ, *et al.* Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child* 1995; **73:** 311–15.

Dementia. There has been some suggestion that age-related reduction in endogenous testosterone may have a role in cognitive decline in men (see Dementia, p. 388.1). In a longitudinal study[1] of 574 men who were followed for about 19 years, a lower calculated concentration of free testosterone was found to be one of several risk factors associated with the development of Alzheimer's disease. A possible role for testosterone treatment has therefore been proposed and some preliminary studies have been undertaken. A small short-term study[2] of older men with Alzheimer's disease or mild cognitive impairment reported improvements in some measures of cognitive function in patients given intramuscular testosterone. In another study,[3] however, testosterone applied as a topical gel was reported to improve quality of life as scored by the caregivers of men with mild Alzheimer's disease, but to have no significant effect on quality of life in healthy elderly men or on cognitive function in either group. The possible role of androgens has been reviewed.[4,5]

1. Moffat SD, *et al.* Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004; **62:** 188–93.
2. Cherrier MM, *et al.* Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 2005; **64:** 2063–8.
3. Lu PH, *et al.* Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch Neurol* 2006; **63:** 177–85.
4. Fuller SJ, *et al.* Androgens in the etiology of Alzheimer's disease in aging men and possible therapeutic interventions. *J Alzheimers Dis* 2007; **12:** 129–42.
5. Drummond ES, *et al.* Androgens and Alzheimer's disease. *Curr Opin Endocrinol Diabetes Obes* 2009; **16:** 254–9.

Erectile dysfunction. Although testosterone is known to enhance libido its physiological role in erection is still not fully understood. Studies have produced mixed results, but suggest that men with sexual or erectile dysfunction (p. 2348.2) and low baseline concentrations of testosterone may derive some benefit from testosterone monotherapy;[1,2] the use of testosterone may also have some benefit in those who have responded poorly to phosphodiesterase type-5 inhibitors.[1,3] However, because of limited evidence and the potential for adverse effects, therapy should probably be limited to men with severe hypogonadism[1,2] (see also Hypogonadism, below).

For reference to the use of a cream containing testosterone, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p. 1392.2.

1. Mikhail N. Does testosterone have a role in erectile function? *Am J Med* 2006; **119:** 373–82.
2. Boloña ER, *et al.* Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82:** 20–8.
3. Shabsigh R, *et al.* The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Pract* 2006; **60:** 1087–92.

Gender reassignment. Testosterone is used in female-to-male transsexuals to develop and maintain secondary sexual characteristics.[1,2] A testosterone ester, or a combination of esters, is usually given by intramuscular injection in doses of 200 to 250 mg every 2 weeks, adjusted according to response.[2,3] Alternatively, testosterone undecylate 1 g may be given once every 10 to 12 weeks.[3] Oral or transdermal testosterone is less commonly used, and the addition of a progestogen may be needed to fully suppress menstruation in non-oophorectomised patients.[2]

1. Moore E, *et al.* Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 2003; **88:** 3467–73.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Heart failure. Low serum-testosterone concentrations have been reported in men with chronic heart failure (p. 1262.3). A study in men with moderate heart failure and low or low-normal testosterone concentrations found that 12 months of transdermal testosterone therapy improved symptoms of heart failure and exercise capacity.[1] The mechanism of benefit was unclear. A subsequent study reported similar benefits,[2] which were considered to be due to metabolic and peripheral effects.

1. Malkin CJ, *et al.* Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006; **27:** 57–64.
2. Caminiti G, *et al.* Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009; **54:** 919–27.

Hypogonadism. Replacement therapy with testosterone or a testosterone ester is the standard treatment for *primary hypogonadism* in men (see p. 2252.3). The androgen is often given as an intramuscular depot injection of one of the esters, although subcutaneous implants, oral formulations, transdermal systems, topical gels and solutions and a buccal preparation are also used (for doses see Uses and Administration, p. 2305.2).[1-3] Testosterone is also used to promote masculinisation in hypogonadal adolescent boys,[4,5] and is of value in the prevention of osteoporosis in hypogonadal men.[6,7] Testosterone has a negative feedback effect on gonadotrophin secretion, therefore any remaining spermatogenesis is generally suppressed; androgens are thus rarely useful in reversing male infertility (p. 2253.1). Recommendations for monitoring therapy have been made.[3,8]

Transdermal testosterone may possibly be of benefit as an adjunct to oestrogen replacement in *women* who have undergone hysterectomy and oophorectomy (see Menopausal Hormone Replacement Therapy, p. 2307.1).

There has also been growing interest in the use of testosterone therapy in *healthy older men*, although there is limited evidence to prove a direct association between clinical changes and the natural decline of endogenous hormone concentrations with age.[9] This aspect of ageing is increasingly being described as the andropause, but the fall in testosterone concentrations is gradual, and not a rapid and significant decline of hormones with loss of fertility like that which occurs in the female menopause[9,10] (p. 2244.1); other terms such as partial androgen deficiency or late-onset hypogonadism have also been proposed.[9] Testosterone therapy has been studied in healthy older men with normal or low-normal serum-testosterone concentrations. Modest beneficial changes in body composition (increased lean body-mass and decreased fat-mass) have been reported, but many studies have found no associated improvement in muscle strength, mobility, or functional autonomy, or a reduced risk of falls. Results are also inconsistent or negative from studies measuring skeletal effects, sexual function, cognitive function, mood, and quality of life.[9] A meta-analysis[11] of 8 studies suggested that intramuscular testosterone might be more effective than transdermal administration for increasing lumbar bone mineral density. There are concerns about potential adverse effects of testosterone on the prostate (see Carcinogenicity, p. 2307.3) and the cardiovascular system, and high doses have been reported to cause or exacerbate sleep apnoea.[9,12] Although recommendations have been made for the use and monitoring of testosterone therapy in healthy older men with androgen deficiency,[12-14] many caution that until further clinical studies have been done it should only be used in those with confirmed hypogonadism.[9,10]

1. Gooren LJG, Bunck MCM. Androgen replacement therapy: present and future. *Drugs* 2004; **64:** 1861–91.
2. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clin Endocrinol (Oxf)* 2006; **65:** 275–81.
3. Bhasin S, *et al.* Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; **95:** 2536–59. Also available at: http://www.endo-society.org/guidelines/final/upload/FINAL-Androgens-in-Men-Standalone.pdf (accessed 14/07/10)
4. Moorthy B, *et al.* Depot testosterone in boys with anorchia or gonadotrophin deficiency: effect on growth rate and adult height. *Arch Dis Child* 1991; **66:** 197–9.
5. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. *Arch Dis Child* 1997; **76:** 495–9.
6. Wang C, *et al.* Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)* 2001; **54:** 739–50.
7. Zacharin MR, *et al.* Bone mineral density outcomes following long-term treatment with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol (Oxf)* 2003; **58:** 691–5.
8. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; **350:** 482–92.
9. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005; **26:** 833–76.

All cross-references refer to entries in Volume A

10. Juul A, Skakkebæk NE. Androgens and the ageing male. *Hum Reprod Update* 2002; **8:** 423–33.
11. Tracz MJ, *et al*. Testosterone use in men and its effects on bone health: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab* 2006; **91:** 2011–16.
12. Liu PY, *et al*. The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J Clin Endocrinol Metab* 2004; **89:** 4789–96.
13. Wald M, *et al*. Testosterone replacement therapy for older men. *J Androl* 2006; **27:** 126–32.
14. Wang C, *et al*. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Int J Impot Res* 2009; **21:** 1–8. Also available at: http://www.nature.com/ijir/journal/v21/n1/abs/ijir200841a.html (accessed 11/11/09)

Lichen sclerosus. Topical androgens such as androstanolone and testosterone have been used to treat vulvar lichen sclerosus (p. 1685.2) in postmenopausal women.[1-4] However, virilisation can occur and a topical corticosteroid is generally preferred.[5]

1. Paslin D. Treatment of lichen sclerosus with topical dihydrotestosterone. *Obstet Gynecol* 1991; **78:** 1046–9.
2. Bracco GL, *et al*. Clinical and histologic effects of topical treatments of vulval lichen sclerosus: a critical evaluation. *J Reprod Med* 1993; **38:** 37–40.
3. Paslin D. Androgens in the topical treatment of lichen sclerosus. *Int J Dermatol* 1996; **35:** 298–301.
4. Joura EA, *et al*. Short-term effects of topical testosterone in vulvar lichen sclerosus. *Obstet Gynecol* 1997; **89:** 297–9.
5. Neill SM, *et al*. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol* 2010; **163:** 672–82. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Lichen%20Sclerosus%20Guidelines%202010.pdf (accessed 31/01/11)

Male contraception. In male contraceptive studies it was found that high-dose testosterone severely reduced sperm production.[1] In those in whom azoospermia was not induced there was oligozoospermia with remaining sperm having a markedly reduced fertilising capacity. In a multicentre study carried out by WHO[2] involving 271 healthy fertile men, weekly intramuscular injection of testosterone enantate 200 mg produced azoospermia in 157 men within 6 months. In a subsequent 12-month study of these azoospermic men, during which time testosterone enantate was the only contraceptive measure used, there was only 1 pregnancy. Spermatogenesis was re-established on withdrawal of testosterone. These findings have been confirmed in a larger study of the same regimen, which additionally assessed contraceptive efficacy in men who achieved oligozoospermia (less than 3×10^6/mL).[3] No pregnancies occurred in couples where the man was azoospermic. However, the pregnancy rate was 8.1 per 100-person-years in the subgroup of couples where the man was oligozoospermic. This rate is sixfold higher than is generally seen with hormonal contraceptives in women.[4] Both studies found that consistent azoospermia was achieved in a higher percentage of Asian men (95%) than Western men (70%).[4] Testosterone undecylate has also been studied as a longer-acting intramuscular injection. In a study[5] involving Chinese men, a loading dose of 1 g followed by monthly maintenance doses of 500 mg effectively and persistently suppressed spermatogenesis in about 95% of 296 men who had initially responded; pregnancy occurred in the partner of 1 of the 6 men with sperm rebound.

An alternative approach being investigated is the use of testosterone with a progestogen, which enhances the suppression of spermatogenesis and may allow lower doses of androgen to be used with fewer adverse effects. Progestogens under investigation include cyproterone, desogestrel, etonogestrel, levonorgestrel, medroxyprogesterone, and norethisterone.[6,7]

For a general discussion on choice of contraceptive method, including mention of male contraception, see p. 2232.3.

1. Matsumoto AM. Is high dosage testosterone an effective male contraceptive agent? *Fertil Steril* 1988; **50:** 324–8.
2. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet* 1990; **336:** 955–9.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril* 1996; **65:** 821–9.
4. Anonymous. An androgen contraceptive for men: preliminary findings. *WHO Drug Inf* 1996; **10:** 50–3.
5. Gu Y-Q, *et al*. A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab* 2003; **88:** 562–8.
6. Amory JK, *et al*. Drug insight: Recent advances in male hormonal contraception. *Nat Clin Pract Endocrinol Metab* 2006; **2:** 32–41.
7. Grimes DA, *et al*. Steroid hormones for contraception in men. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 13/11/07).

Menopausal hormone replacement therapy. Menopause does not necessarily result in androgen deficiency in women, and androgen replacement is therefore not routinely required (see Menopausal Disorders, p. 2245.1). In the UK menopausal women may nonetheless sometimes be given implants of testosterone as an adjunct to menopausal HRT. In the USA, injectable preparations containing an androgen and an oestrogen have been available for the treatment of menopausal vasomotor symptoms, but there is conflicting opinion as to their usefulness, and further data are needed.[1] In Canada, a preparation containing estradiol and testosterone esters for intramuscular injection (*Climacteron; Sabex, Canad.*) was discontinued in 2005 because of concerns that testosterone is partially metabolised to oestrogen, which should be opposed by a progestogen in women with a uterus, and that there was no established dose of progestogen that could be recommended in this situation.[2] A study[3] in healthy postmenopausal women found that oral testosterone alone did not stimulate endometrial proliferation as estradiol did, and that it appeared to reduce the effect of estradiol when they were used together. However, therapy was given for only 3 months and long-term effects need further study.

Improvements in mood and libido have been reported when androgens were given to postmenopausal women with an established cause of androgen deficiency such as surgically induced menopause.[4] A systematic review of the addition of testosterone to postmenopausal HRT considered that there was some evidence of benefit on sexual function, but that studies varied too much to estimate the effect of any particular combination.[5] More recently, several placebo-controlled studies in women with surgically induced[6-9] or natural[10] menopause have reported improvements in sexual activity and desire with HRT plus transdermal testosterone. A product (*Intrinsa; Proctor and Gamble, UK*) was licensed for use in the UK for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause who were also receiving oestrogen replacement therapy, but the FDA did not license it in the USA and expressed concern about the lack of data on long-term safety.[11] Subsequently, a 1-year study[12] found that transdermal testosterone, without an oestrogen, improved sexual function in postmenopausal women. The most commonly reported androgenic adverse effect was increased hair growth, but there were also a few cases of mild clitoral enlargement. Breast cancer was diagnosed in a few women; a causal relationship could not be established and further study is needed. The role of testosterone for sexual function in postmenopausal women continues to be evaluated.[13]

The Endocrine Society[14] has evaluated data on the use of testosterone in various groups of women, including those with menopausal symptoms, and advises that although there is some evidence for efficacy in selected populations, such as surgically menopausal women, it cannot be recommended for generalised use because of poorly-defined indications and a lack of evidence on long-term safety.

The use of transdermal testosterone, with oestrogen and progestogen replacement therapy, is also being investigated in young women with spontaneous premature ovarian failure.[15]

1. Abraham D, Carpenter PC. Issues concerning androgen replacement therapy in postmenopausal women. *Mayo Clin Proc* 1997; **72:** 1051–5.
2. Sandoz Canada. Discontinuation of Climacteron Injection (estradiol dienanthate/estradiol benzoate and testosterone enanthate benzilic acid hydrazone injection in corn oil) (issued 23rd November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/climacteron_hpc-cps-eng.pdf (accessed 22/08/08)
3. Zang H, *et al*. Effects of testosterone treatment on endometrial proliferation in postmenopausal women. *J Clin Endocrinol Metab* 2007; **92:** 2169–75.
4. Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; **154:** 1–11.
5. Somboonporn W, *et al*. Testosterone for peri- and postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).
6. Shifren JL, *et al*. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000; **343:** 682–8.
7. Simon J, *et al*. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005; **90:** 5226–33.
8. Braunstein GD, *et al*. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005; **165:** 1582–9.
9. Buster JE, *et al*. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005; **105:** 944–52.
10. Shifren JL, *et al*. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause* 2006; **13:** 770–9.
11. Moynihan R. FDA panel rejects testosterone patch for women on safety grounds. *BMJ* 2004; **329:** 1363.
12. Davis SR, *et al*. APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008; **359:** 2005–17.
13. Krapf JM, Simon JA. The role of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *Maturitas* 2009; **63:** 213–19.
14. Wierman ME, *et al*. Androgen therapy in women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 3697–3710. Also available at: http://www.endo-society.org/guidelines/final/upload/Androgens_in_Women_CG.pdf (accessed 22/08/08)
15. Kalantaridou SN, *et al*. A pilot study of an investigational testosterone transdermal patch system in young women with spontaneous premature ovarian failure. *J Clin Endocrinol Metab* 2005; **90:** 6549–52.

Rheumatoid arthritis. A hypogonadal condition characterised by low serum-testosterone concentrations appears to be associated with at least the active stages of rheumatoid arthritis (p. 13.2) in men.[1] Clinical improvement and reductions in IgM rheumatoid factor concentration, tender joint count, and the daily dosage of NSAIDs required, were seen in a small study[1] of men with rheumatoid arthritis and low serum-testosterone concentrations given oral testosterone undecylate 40 mg three times daily for 6 months. Improvements in rheumatoid arthritis were also seen in 12 of 36 postmenopausal women treated with intramuscular testosterone propionate 50 mg plus a low dose of progesterone (2.5 mg) once every 2 weeks compared with 2 of 32 women given placebo.[2] However, a placebo-controlled study[3] in 30 men with normal serum-testosterone concentrations found no beneficial effect from intramuscular testosterone enantate on measures of disease activity.

1. Cutolo M, *et al*. Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum* 1991; **34:** 1–5.
2. Booij A, *et al*. Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. *Ann Rheum Dis* 1996; **55:** 811–15.
3. Hall GM, *et al*. A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol* 1996; **35:** 568–73.

Adverse Effects

Testosterone and other **androgens** may give rise to adverse effects related to their androgenic or anabolic activities. These include increased retention of sodium and water, oedema, hypercalcaemia, and impaired glucose tolerance. Other effects include increased low-density-lipoprotein cholesterol, decreased high-density-lipoprotein cholesterol, increased haematocrit, and suppression of clotting factors. Androgens may cause headache, depression, irritability, aggression, and gastrointestinal disturbances including bleeding. It has been suggested that androgens may induce sleep apnoea in susceptible patients.

Abnormal liver function tests may occur and there have been reports of liver toxicity including jaundice and cholestatic hepatitis. There have also been reports of peliosis hepatis and hepatic tumours in patients given high doses over prolonged periods. These adverse hepatic effects have occurred mainly with the 17α-alkylated derivatives (e.g. methyltestosterone, stanozolol).

In men, large doses suppress spermatogenesis and cause testicular atrophy. Epididymitis and bladder irritability can occur. Priapism is a sign of excessive dosage and may occur especially in elderly males. Gynaecomastia may occur. Androgens may cause prostatic hyperplasia and accelerate the growth of malignant neoplasms of the prostate. Prostate specific antigen values can increase during testosterone therapy.

In women, the inhibitory action of androgens on the activity of the anterior pituitary results in the suppression of ovarian activity and menstruation. Continued use produces symptoms of virilism, such as hirsutism or male-pattern baldness, deepening of the voice, atrophy of the breasts and endometrial tissue, oily skin, acne, and hypertrophy of the clitoris. Virilisation may not be reversible, even after stopping therapy.

Large and repeated doses in early puberty may cause closure of the epiphyses and stop linear growth. Children may show virilisation: in boys there may be precocious sexual development with phallic enlargement and increased frequency of erection, and in girls, clitoral enlargement. Gynaecomastia may also occur in boys.

Masculinisation of the external genitalia of the female fetus may occur if androgens are given during pregnancy.

After transdermal application of testosterone, skin reactions may include irritation, erythema, allergic contact dermatitis, and sometimes burn-like lesions. Skin reactions are more common with patches that contain permeation enhancers.

The **anabolic steroids**, because they generally retain some androgenic activity, share the adverse effects of the androgens described above, but their virilising effects, especially in women, are usually less. There have been reports of adverse psychiatric effects in athletes taking large doses to try and improve performance. For adverse effects after misuse of anabolic steroids, see Abuse under Precautions, p. 2308.2.

Carcinogenicity. Testosterone therapy is used in healthy older men with low or low-normal serum-testosterone concentrations (see Hypogonadism, under Uses and Administration, p. 2306.3), but there is some concern about a possible associated increase in prostate cancer risk. This concern is based on the fact that, regardless of any treatment, the incidence of prostate cancer increases with age, that normal prostate growth is dependent on androgens, and that androgen deprivation causes regression of advanced prostate cancer.[1] However, the relationship between androgens and the onset of prostate cancer is far from clear. Some data show that low serum-testosterone can predict more aggressive high-grade tumours, with a higher likelihood of metastatic disease and poorer outcome.[1-3] Although there have been reports of prostate cancer developing in men who have been treated with testosterone,[4] considerable evidence, but from mostly small

clinical studies has, overall, not shown an increase in the risk of prostate cancer.[3,5] The effect of 6 months of testosterone enantate therapy on the prostate has been studied in 21 men (44 to 78 years old).[6] Although low serum-testosterone concentrations were normalised, there were no significant changes in androgen concentrations in prostate tissue, prostate volume, prostate specific antigen, or prostate cancer incidence. Further study of longer duration in larger numbers of men is needed to confirm the safety of this therapy.

In men with a history of prostate cancer, testosterone therapy for hypogonadism is generally contra-indicated because of the presumed risk of tumour recurrence. However, there are a small number of reports of testosterone being used safely after curative surgery, suggesting that testosterone therapy with close monitoring may be considered in such men with symptomatic hypogonadism.[3,7] There is even less data on the use of testosterone for hypogonadism in men who have been treated with radiotherapy with curative intent,[3] or with androgen ablation by gonadorelin analogue therapy. Testosterone has also been used for hypogonadism in a small number of men with high-grade intra-epithelial neoplasia, a precancerous lesion, without increasing the risk of cancer development.[7]

For reference to hepatic malignancies associated with androgens and anabolic steroids, see Effects on the Liver, below. Renal cell carcinoma has also been reported after their abuse (see under Precautions, below).

1. Raynaud J-P. Prostate cancer risk in testosterone-treated men. *J Steroid Biochem Mol Biol* 2006; **102:** 261–6.
2. Barqawi A, Crawford ED. Testosterone replacement therapy and the risk of prostate cancer: is there a link? *Int J Impot Res* 2006; **18:** 323–8.
3. Raynaud J-P. Testosterone deficiency syndrome: treatment and cancer risk. *J Steroid Biochem Mol Biol* 2009; **114:** 96–105.
4. Brand TC, *et al*. Testosterone replacement therapy and prostate cancer: a word of caution. *Curr Urol Rep* 2007; **8:** 185–9.
5. Gould DC, Kirby RS. Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer? *Prostate Cancer Prostatic Dis* 2006; **9:** 14–18.
6. Marks LS, *et al*. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; **296:** 2351–61.
7. Kaufman J. A rational approach to androgen therapy for hypogonadal men with prostate cancer. *Int J Impot Res* 2006; **18:** 26–31.

Effects on the cardiovascular system. A cerebrovascular accident has been reported in a young man after the over-zealous self-administration of testosterone enantate intramuscularly for hypogonadism.[1] It was noted that thromboembolic complications are not generally recognised as adverse effects of androgen therapy although there is some experimental evidence that testosterone stimulates thrombus formation. A systematic review[2] found evidence concerning cardiovascular events in studies of testosterone given to men with low or normal testosterone concentrations to be of poor quality, but some data to suggest that alterations in plasma lipid concentrations and blood pressure were not significant.

1. Nagelberg SB, *et al*. Cerebrovascular accident associated with testosterone therapy in a 21-year-old hypogonadal man. *N Engl J Med* 1986; **314:** 649–50.
2. Haddad RM, *et al*. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82:** 29–39.

Effects on the liver. Hepatotoxicity, including elevations in liver enzymes, hepatic cholestasis and jaundice, and rarely peliosis hepatis and hepatic tumours, has occurred with androgens and anabolic steroids, particularly the 17α-alkylated derivatives. Prolonged treatment and high doses may be significant contributory factors. Tumours have included hepatocellular carcinomas, benign adenomas, and less commonly angiosarcomas and cholangiocarcinomas. Tumours and peliosis may regress on stopping therapy, but they can also progress to liver failure and death. Some reviews of the hepatic effects of androgens and anabolic steroids are cited below.[1-5] There has been a specific report of benign hepatic adenoma in a patient treated with testosterone enantate for 11 years,[6] and of hepatocellular carcinoma in a patient given testosterone enantate and methyltestosterone.[7] Further specific references may be found under individual drug monographs.

1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy. *Ann Intern Med* 1974; **81:** 610–18.
2. Ishak KG, Zimmerman HJ. Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis* 1987; **7:** 230–6.
3. Søe KL, *et al*. Liver pathology associated with the use of anabolic-androgenic steroids. *Liver* 1992; **12:** 73–9.
4. Touraine RL, *et al*. Hepatic tumours during androgen therapy in Fanconi anaemia. *Eur J Pediatr* 1993; **152:** 691–3.
5. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.
6. Carrasco D, *et al*. Hepatic adenomata and androgen treatment. *Ann Intern Med* 1984; **100:** 316.
7. Johnson FL, *et al*. Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; **ii:** 1273–6.

Effects on sexual function. Priapism has occurred after the use of testosterone for the management of delayed puberty[1-4] or hypogonadism.[5-7]

1. Zelissen PMJ, Stricker BHC. Severe priapism as a complication of testosterone substitution therapy. *Am J Med* 1988; **85:** 273–4.
2. Ruch W, Jenny P. Priapism following testosterone administration for delayed male puberty. *Am J Med* 1989; **86:** 256.
3. Madrid Garcia FJ, *et al*. Priapismo secundario a la administración de testosterona en el tratamiento del retraso puberal. *Arch Esp Urol* 2001; **54:** 703–5.
4. Arrigo T, *et al*. High-flow priapism in testosterone-treated boys with constitutional delay of growth and puberty may occur even when very low doses are used. *J Endocrinol Invest* 2005; **28:** 390–1.
5. Zargooshi J. Priapism as a complication of high dose testosterone therapy in a man with hypogonadism. *J Urol (Baltimore)* 2000; **163:** 907.
6. Shergill IS, *et al*. Testosterone induced priapism in Kallmann's syndrome. *J Urol (Baltimore)* 2003; **169:** 1089.
7. Ichioka K, *et al*. Testosterone-induced priapism in Klinefelter syndrome. *Urology* 2006; **67:** e17–e18.

Precautions

Testosterone and other androgens and anabolic steroids should be used cautiously in patients with cardiovascular disorders, renal or hepatic impairment, epilepsy, migraine, diabetes mellitus or other conditions that may be aggravated by the possible fluid retention or oedema caused. They should not be given to patients with hypercalcaemia or hypercalciuria, and should be used cautiously in conditions in which there is a risk of these developing such as skeletal metastases. The use of the 17α-alkylated derivatives, which are associated with an increased risk of hepatotoxicity, is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

In men, androgens and anabolic steroids should not be given to those with carcinoma of the breast or prostate (although in women they have been used in the treatment of certain breast carcinomas; see also Carcinogenicity, p. 2307.3, regarding the use of testosterone in men with a history of prostate cancer). The prostate should be examined regularly during treatment.

Androgens and anabolic steroids should not be given during pregnancy because of the risk of virilisation of the female fetus.

Androgens and anabolic steroids should be used with extreme care in children because of the masculinising effects and also because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature. Skeletal maturation should be monitored during therapy.

Patients using testosterone gels or topical solutions should take care to wash their hands after every application, and to cover the site with clothing once the preparation has dried. The area should also be washed thoroughly before skin-to-skin contact with another person. Inappropriate virilisation, advanced bone age, increased libido, and aggressive behaviour have been reported in children who have been inadvertently exposed to testosterone in this way.

Androgens and anabolic steroids may interfere with some clinical laboratory tests such as those for glucose tolerance and thyroid function.

Abuse. The adverse effects arising from the illicit use of androgens and anabolic steroids by athletes, often taken together at doses well in excess of those used therapeutically, have been discussed.[1-5] Such misuse is associated with potentially serious health risks. Effects have included abnormal liver function and hepatic neoplasms (see also Effects on the Liver, above), an atherogenic blood lipid profile and increased risk of cardiovascular disease, and reduced glucose tolerance. Hypogonadal states are commonly induced (azoospermia or oligospermia and testicular atrophy in men, and amenorrhoea or oligomenorrhoea in women). Gynaecomastia is relatively common in men, and virilisation in women. Psychiatric disturbances such as mania, hypomania, depression, aggression, and emotional lability, have been described. There is also some evidence that dependence associated with an acute withdrawal syndrome can occur. Rare reports include alterations in immune response, tendon damage, renal cell carcinoma, and peliosis hepatis.

There has been some dispute about the methods used to detect abuse of certain anabolic steroids in athletes. A study in healthy subjects has apparently confirmed endogenous production of small amounts of nandrolone metabolites;[6] several different factors might have an influence including genetics, intense exercise, trauma, and hypoglycaemic stress.[7]

1. Pärssinen M, Seppälä T. Steroid use and long-term health risks in former athletes. *Sports Med* 2002; **32:** 83–94.
2. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004; **34:** 513–54.
3. Maravelias C, *et al*. Adverse effects of anabolic steroids in athletes: a constant threat. *Toxicol Lett* 2005; **158:** 167–75.
4. Trenton AJ, Currier GW. Behavioural manifestations of anabolic steroid use. *CNS Drugs* 2005; **19:** 571–95.
5. Sjöqvist F, *et al*. Use of doping agents, particularly anabolic steroids, in sports and society. *Lancet* 2008; **371:** 1872–82.
6. Reznik Y, *et al*. Urinary nandrolone metabolites of endogenous origin in man: a confirmation by output regulation under human chorionic gonadotropin stimulation. *J Clin Endocrinol Metab* 2001; **86:** 146–50.
7. Kohler RMN, Lambert MI. Urine nandrolone metabolites: false positive doping test? *Br J Sports Med* 2002; **36:** 325–9.

Breast feeding. It is unknown whether testosterone is distributed into breast milk, but it should be avoided in women who are breast feeding because of the theoretical potential androgenic effect on the infant. High doses of testosterone can suppress lactation.

Inadvertent transfer. A brief review[1] of the risks of inadvertent secondary exposure to testosterone gel used for male hormone replacement in women or children, with consequent virilisation or hyperandrogenism.

1. de Ronde W. Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. *Hum Reprod* 2009; **24:** 425–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies testosterone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

A female patient with acute intermittent porphyria (p. 1556.1) who suffered from severe attacks premenstrually was successfully managed with subcutaneous implants of testosterone when suppression of the menstrual cycle with buserelin met with limited success.[2]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)
2. Savage MW, *et al*. Acute intermittent porphyria treated by testosterone implant. *Postgrad Med J* 1992; **68:** 479–81.

Pregnancy. Reports of female fetal virilisation after maternal use of testosterone[1] or methyltestosterone[2] during pregnancy.

1. Reschini E, *et al*. Female pseudohermaphroditism due to maternal androgen administration: 25-year follow-up. *Lancet* 1985; **i:** 1226.
2. Dewhurst J, Gordon RR. Fertility following change of sex. *Lancet* 1984; **ii:** 1461.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for testosterone, but concluded that there would be no need to specify a numerical maximum residue limit for testosterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that, in the EU, the use of androgens in veterinary practice is restricted and their use as growth promotors is banned. In addition, the use of anabolic steroids is banned in animals intended for human consumption.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 09/07/08)

Interactions

Testosterone and other androgens and anabolic steroids have been reported to enhance the activity of various drugs, with resulting increases in toxicity. Drugs affected include ciclosporin (see p. 1955.1), levothyroxine (see p. 2342.2), and anticoagulants such as warfarin (see p. 1535.1). Resistance to the effects of neuromuscular blockers (p. 2033.2) has also been reported. As androgens and anabolic steroids can alter glucose metabolism, doses of insulin or oral antidiabetics may need adjustment.

Pharmacokinetics

Testosterone is absorbed from the gastrointestinal tract, the skin, and the oral mucosa. However, it undergoes extensive first-pass hepatic metabolism when given orally and is therefore usually given intramuscularly, subcutaneously, or transdermally. The basic molecule of testosterone has also been modified to produce orally active compounds and to extend the duration of action. Alkylation of the 17α position produces compounds that are more slowly metabolised by the liver, and hence may be given orally. Esterification of the 17β hydroxyl group increases lipid solubility and results in slower systemic absorption after intramuscular injection. The rate of absorption of the esters is related to the size of the ester group. The undecylate ester undergoes less complete inactivation after oral doses because of distribution into the lymphatic system. Testosterone esters are hydrolysed to testosterone after absorption.

Testosterone is about 80% bound to sex-hormone binding globulin. Derivatives of 19-nortestosterone and 17-α-methylated compounds have reduced binding to this globulin. The plasma half-life of testosterone is reported to range from about 10 to 100 minutes. It is largely metabolised in the liver via oxidation at the 17-OH group with the formation of androstenedione, which is further metabolised to the weakly androgenic androsterone and inactive etiocholanolone which are excreted in the urine mainly as glucuronides and sulfates. About 6% is excreted

unchanged in the faeces after undergoing enterohepatic recirculation. Testosterone is converted to the more active dihydrotestosterone in some target organs by 5α-reductase. 19-Nortestosterone derivatives appear to be less susceptible to this enzyme. Small amounts of testosterone are aromatised to form oestrogenic derivatives, particularly oestradiol. Compounds with a saturated A-ring, such as mesterolone, appear to be less likely to be aromatised to oestrogen.

References to the pharmacokinetics of subcutaneous testosterone pellets,[1] intramuscular depot injection,[2] scrotal[3,4] and non-scrotal[5-8] transdermal patches, gel,[9,10] and a buccal preparation,[11,12] are given below.

1. Handelsman DJ, *et al*. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab* 1990; **71:** 216–22.
2. Yassin AA, Haffejee M. Testosterone depot injection in male hypogonadism: a critical appraisal. *Clin Interv Aging* 2007; **2:** 577–90.
3. Findlay JC, *et al*. Transdermal delivery of testosterone. *J Clin Endocrinol Metab* 1987; **64:** 266–8.
4. Cunningham GR, *et al*. Testosterone replacement with transdermal therapeutic systems: physiological serum testosterone and elevated dihydrotestosterone levels. *J AMA* 1989; **261:** 2525–30.
5. Meikle AW, *et al*. Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site. *J Clin Endocrinol Metab* 1996; **81:** 1832–40.
6. Yu Z, *et al*. Transdermal testosterone administration in hypogonadal men: comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. *J Clin Pharmacol* 1997; **37:** 1129–38.
7. Dobs AS, *et al*. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999; **84:** 3469–78.
8. Singh AB, *et al*. Pharmacokinetics of a transdermal testosterone system in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. *J Clin Endocrinol Metab* 2001; **86:** 2437–45.
9. Swerdloff RS, *et al*. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 2000; **85:** 4500–10.
10. Marbury T, *et al*. Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim™, compared to AndroGel. *Biopharm Drug Dispos* 2003; **24:** 115–20.
11. Korbonits M, *et al*. A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. *J Clin Endocrinol Metab* 2004; **89:** 2039–43.
12. Wang C, *et al*. New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. *J Clin Endocrinol Metab* 2004; **89:** 3821–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Androlone; Androtag; Nebido; Sustanon 250; Testex; Testoviron Depot 100; Testoviron Depot 250; Undestor; ***Austral.***: Andriol; Andro-Feme; Androderm; Primoteston Depot; Reandron; Sustanon 100†; Sustanon 250; Testogel; ***Austria***: Andriol; Nebido; Testogel; ***Belg.***: AndroGel; Itnogen; Nebido; Sustanon 250; Testim; Testocaps; ***Braz.***: Androxon; Deposteron; Nebido; ***Canad.***: Andriol; Androderm; AndroGel; Delatestryl; Testim; ***Chile***: Actiser-T; Nebido; Primoniat Depot; Sustenan 250; Sustenan†; Testocaps; Testovital; ***China***: Andriol (安特尔); Nuo Shi (诺仕); Si Te Long (思特珑); ***Cz.***: Agovirin; AndroGel; Intrinsa†; Livensa†; Nebido; Sustanon; Testopatch†; Tostran†; Undestor; ***Denm.***: Andriol; Nebido; Testim; Testogel; Testoviron Depot 250†; Tostran; ***Fin.***: Nebido; Panteston; Sustanon 250; Testim; Testogel; Tostran; ***Fr.***: AndroGel; Androtardyl; Fortigel; Intrinsa†; Nebido; Pantestone; Testopatch; ***Ger.***: Andriol; Androtop; Intrinsa†; Nebido; Striant†; Testim; Testogel; Testopatch; Testotop; Testoviron Depot 250; Tostran; ***Gr.***: Androderm; Andropatch; Nebido; Restandol; Testim; Testogel; Testopatch; Testoviron; Tostran; ***Hong Kong***: Andriol; AndroGel; Nebido; Sustanon; Testoviron Depot; ***Hung.***: Andriol; AndroGel; Nebido; Tostran; ***India***: Andriol; Androfil; Aquaviron; Cernos; Nuvir; Sustanon 100; Sustanon 250; Testanon 25†; Testanon 50†; Testoviron Depot; ***Indon.***: Andriol; Nebido; Sustanon 250; ***Irl.***: AndroGel; Andropatch†; Intrinsa†; Livensa†; Nebido; Restandol; Striant†; Sustanon 100†; Sustanon 250†; Testim; Testogel; Tostran; ***Israel***: AndroGel; Androxon; Nebido; Sustanon 250; Testomax; Testoviron Depot; ***Ital.***: Andriol; AndroGel; Intrinsa†; Nebid; Striant; Sustanon; Testim; Testo-Enant; Testogel; Testopatch; Testovis; Tostrex; ***Malaysia***: Andriol; Nebido; ***Mex.***: Andriol; Lowtiyel; Nebido; Primoteston Depot; Sostenon; Testoprim-D; ***Neth.***: Andriol; AndroGel; Intrinsa†; Livensa†; Nebido; Striant†; Sustanon 100; Sustanon 250; Testim; Testogel; Tostran; ***Norw.***: Andriol; Atmos†; Nebido; Testim; Testogel; Tostran; ***NZ***: Andriol; Androderm; Panteston; Primoteston Depot†; Reandron; Sustanon; ***Philipp.***: Andriol; Nebido; ***Pol.***: Androtop; Intrinsa†; Livensa†; Nebido; Omnadren; Testosteronum Prolongatum; Tostran; Undestor; ***Port.***: Andriol; AndroGel; Intrinsa†; Livensa†; Nebido; Striant†; Testim; Testogel; Testopatch; Testoviron Depot; Tostran; ***Rus.***: Andriol (Андриол); AndroGel (Андрогель); Nebido (Небидо); Omnadren (Омнадрен); Sustanon 250 (Сустанон 250); ***S.Afr.***: Androxon; Depotrone; Nebido; Sustanon 250; ***Singapore***: Andriol; AndroGel; Nebido; Sustanon 250; ***Spain***: Intrinsa†; Itnogen; Numanis†; Reandron; Testex; Testim; Testogel; Testopatch; ***Swed.***: Atmos†; Intrinsa†; Nebido; Testim; Testogel; Tostrex; Undestor; ***Switz.***: Andriol; Nebido; Testogel; Testoviron Depot; Tostran; ***Thai.***: Andriol; Cypionax; Depo-Test; Nebido; Test-Comp; Testolic; Testoviron Depot; ***Turk.***: Nebido; Sustanon 250; Testogel; Virigen; ***UK***: Andropatch†; Intrinsa†; Nebido; Restandol; Striant; Sustanon 100†; Sustanon 250; Testim; Testogel; Testosterone Implants; Tostran; Virormone; ***Ukr.***: Andriol (Андриол ТК); AndroGel (Андрожель); Nebido (Небідо); Omnadren (Омнадрен); ***USA***: Androderm; AndroGel; Axiron; Delatestryl; Fortesta; Striant; Testim; Testopel; ***Venez.***: Andriol; AndroGel; Polysteron 250; Proviron Depot.

Multi-ingredient Preparations. ***Braz.***: Durateston; Estandron P; Trinestril; ***Chile***: Estandron Prolongado†; ***Cz.***: Folivirin; ***India***: Mixogen; ***Ital.***: Facovit; Testoviron; ***Malaysia***: Sustanon 250; ***Mex.***: Despamen; Sten; ***Neth.***: Estandron Prolongatum†; ***Port.***: Sustenon 250; ***S.Afr.***: Mixogen†; Primodian Depot†; ***Thai.***: Metharınon-F†; Primodian Depot†; ***Turk.***: Estandron Prolan; ***USA***: Depo-Testadiol†; Depotestogen†.

Pharmacopoeial Preparations

BP 2014: Testosterone Enantate Injection; Testosterone Implants; Testosterone Propionate Injection;

USP 36: Testosterone Cypionate Injection; Testosterone Enanthate Injection; Testosterone Injectable Suspension; Testosterone Propionate Injection.

Tetrahydrogestrinone ⊗

THG.

18a-Homo-pregna-4,9,11-trien-17β-ol-3-one.

$C_{21}H_{28}O_2$=312.5

CAS — 618903-56-3.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of tetrahydrogestrinone:

The Clear.

Profile

Tetrahydrogestrinone is a synthetic anabolic steroid that is structurally related to gestrinone (p. 2280.2) and trenbolone (p. 2310.2). It has been subject to abuse in sport.

Action. Tetrahydrogestrinone had androgenic and progestogenic activity in a yeast-based *in-vitro* bioassay study.[1] The anabolic and androgenic properties of tetrahydrogestrinone have also been studied in *animals*.[2-4]

1. Death AK, *et al*. Tetrahydrogestrinone is a potent androgen and progestin. *J Clin Endocrinol Metab* 2004; **89:** 2498–2500.
2. Labrie F, *et al*. Tetrahydrogestrinone induces a genomic signature typical of a potent anabolic steroid. *J Endocrinol* 2005; **184:** 427–33.
3. Jasuja R, *et al*. Tetrahydrogestrinone is an androgenic steroid that stimulates androgen receptor-mediated, myogenic differentiation in C3H10T1/2 multipotent mesenchymal cells and promotes muscle accretion in orchidectomized male rats. *Endocrinology* 2005; **146:** 4472–8.
4. Friedel A, *et al*. Tetrahydrogestrinone is a potent but unselective binding steroid and affects glucocorticoid signalling in the liver. *Toxicol Lett* 2006; **164:** 16–23.

Tibolone *(BAN, USAN, rINN)* ⊗

7α-Methylnorethynodrel; Org-OD-14; Tibolon; Tibolona; Tiboloni; Tibolonum; Тиболон.

17β-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

$C_{21}H_{28}O_2$=312.5

CAS — 5630-53-5.

ATC — G03CX01.

ATC Vet — QG03CX01.

UNII — FF9X0205V2.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tibolone). A white or almost white, crystalline powder or crystals. It exhibits polymorphism. Practically insoluble in water; soluble in acetone and in methyl alcohol. Store at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Tibolone is a steroid derived from noretynodrel that has oestrogenic, progestogenic, and weak androgenic properties. It is used as menopausal HRT (below) for oestrogen deficiency symptoms, including vasomotor symptoms, in postmenopausal women. Tibolone may also be used in the prevention of postmenopausal osteoporosis in women at high risk of fracture who cannot be treated with other therapy. The usual oral dose is 2.5 mg daily in a continuous regimen. Tibolone should not be started for at least 12 months after the last menstrual period of a natural menopause, but may be started immediately in women who have undergone a surgical menopause or who are being treated with a gonadorelin analogue. Unlike oestrogen-based HRT, a progestogen is not added to tibolone therapy for women with an intact uterus.

In women with a uterus who are transferring from an oestrogen-only form of HRT to tibolone, it is suggested that a withdrawal bleed be induced with a progestogen before starting tibolone, and in those transferring from a cyclical combined HRT, tibolone should be started the day after finishing a full cycle. Women taking continuous combined HRT can be transferred to tibolone at any time.

'Add-back' therapy. Tibolone reduces the vasomotor symptoms and bone loss caused by gonadorelin analogues, without impairing their efficacy in the treatment of endometriosis[1,2] (p. 2264.1) and fibroids[3] (p. 2281.2). Tibolone also reduced vasomotor symptoms in a short-term study of women being treated with leuprorelin for premenstrual syndrome[4] (p. 2272.3).

1. Lindsay PC, *et al*. The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapetyl). *Fertil Steril* 1996; **65:** 342–8.
2. Taskin O, *et al*. Effectiveness of tibolone on hypoestrogenic symptoms induced by goserelin treatment in patients with endometriosis. *Fertil Steril* 1997; **67:** 40–5.
3. Palomba S, *et al*. A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; **70:** 111–18.
4. Di Carlo C, *et al*. Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; **75:** 380–4.

Menopausal disorders. The oestrogenic effects of tibolone make it effective in the management of menopausal disorders (p. 2245.1) such as vasomotor symptoms and vaginal atrophy. It may also be used for the prevention of postmenopausal bone loss, and there is some evidence that it may be useful for treating postmenopausal osteoporosis and reducing fracture risk. The progestogenic effects of tibolone are thought to be sufficient to prevent endometrial proliferation, so that, unlike the oestrogens that are generally used for menopausal HRT (p. 2244.2), a progestogen is not added to tibolone therapy for women with an intact uterus.

Reviews.

1. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. *J Clin Endocrinol Metab* 2002; **87:** 16–23.
2. Swegle JM, Kelly MW. Tibolone: a unique version of hormone replacement therapy. *Ann Pharmacother* 2004; **38:** 874–81.
3. Kenemans P, Speroff L. Tibolone: clinical recommendations and practical guidelines: a report of the International Tibolone Consensus Group. *Maturitas* 2005; **51:** 21–8.
4. Ettinger B. Tibolone for prevention and treatment of postmenopausal osteoporosis. *Maturitas* 2007; **57:** 35–8.

Adverse Effects

Irregular vaginal bleeding or spotting may occur with tibolone, mainly during the first few months of treatment; unlike cyclical, but similar to continuous, combination HRT (p. 2246.3), tibolone does not produce regular withdrawal bleeding. Other effects on the genital tract may include leucorrhoea, pruritus, candidiasis, and vaginitis. Other adverse effects have included breast pain, weight gain, oedema, dizziness, skin reactions, headache, migraine, visual disturbances, gastrointestinal disturbances, hypertrichosis, altered liver function, depression, and arthralgia or myalgia.

Incidence of adverse effects. In 1994, the UK CSM had received reports of 2796 suspected adverse reactions with tibolone over 3 years, out of about 666 000 prescriptions.[1] The commonest reported effects were headache, dizziness, nausea, rash, itching, and weight gain. Vaginal bleeding appeared to occur in about 8 to 9% of recipients. There had also been 52 reports of migraine, 4 of exacerbation of migraine, and 49 reports of visual disturbances, some suggestive of migraine.

1. CSM/MCA. Tibolone (Livial). *Current Problems* 1994; **20:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 18/08/08)

Carcinogenicity. *BREAST.* The large cohort Million Women study[1] examined breast cancer incidence and mortality in relation to HRT use. After an average follow-up of 2.6 years for incidence, and 4.1 years for mortality, data were available for a group of 18 186 women who had used tibolone. There were 184 cases of invasive breast cancer equating to an overall risk of 1.45 (95% confidence interval 1.25 to 1.68) relative to women who had never used HRT. This was between the relative risks calculated for oestrogen-only HRT (1.30) and combined HRT (2.00). The risk was raised for current but not past use of tibolone, and increased with total duration of use.

For comment on the risk of recurrence in women with a history of breast cancer see Malignant Neoplasms under Precautions, p. 2310.1.

1. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362:** 419–27. Correction. *ibid.*; 1160.

ENDOMETRIUM. Endometrial hyperplasia and endometrial carcinoma have been rarely reported after investigation of uterine bleeding in women receiving tibolone therapy,[1-3] as has exacerbation of adenomyosis.[4] Some of these women had previously received oestrogens.

A cohort and nested case-control study[5] found that tibolone might have been associated with an increased risk of endometrial cancer compared with conventional forms of combined HRT, but the data were weak and might have been affected by bias and uncontrolled confounding factors. The large cohort Million Women Study[6] of HRT included a

group of 28 028 who had used tibolone for an average of about 3 years. The risk of endometrial cancer was increased to 1.79 (95% confidence interval 1.43 to 2.25) in those who had used tibolone, compared with women who had never used HRT, and the risk was higher with more than 3 years of use compared with shorter durations. In contrast, a smaller randomised study[7] comparing tibolone with combined HRT recorded no cases of endometrial hyperplasia or carcinoma in 1317 women given tibolone for up to 2 years.

1. von Dadelszen P, *et al.* Endometrial hyperplasia and adenocarcinoma during tibolone (Livial) therapy. *Br J Obstet Gynaecol* 1994; **101:** 158–61.
2. Ginsburg J, Prelevic GM. Cause of vaginal bleeding in postmenopausal women taking tibolone. *Maturitas* 1996; **24:** 107–10.
3. Yazigi R, *et al.* Carcinoma of the endometrium in patients treated with tibolone. *Gynecol Oncol* 2004; **93:** 568–70.
4. Prys Davies A, Oram D. Exacerbation of adenomyosis in a postmenopausal woman taking tibolone associated with an elevation in serum CA 125. *Br J Obstet Gynaecol* 1994; **101:** 632–3.
5. de Vries CS, *et al.* Tibolone and endometrial cancer: a cohort and nested case-control study in the UK. *Drug Safety* 2005; **28:** 241–9.
6. Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; **365:** 1543–51.
7. Archer DF, *et al.* Endometrial effects of tibolone. *J Clin Endocrinol Metab* 2007; **92:** 911–18.

Effects on the cardiovascular system. A study[1] of tibolone in the treatment of osteoporosis in postmenopausal women aged between 60 and 85 years found that although it reduced the risk of fracture, breast cancer, and possibly colon cancer, there was an increased risk of stroke. The authors therefore concluded that tibolone should not be used in elderly women and women with risk factors for stroke.

1. Cummings SR, *et al.* LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008; **359:** 697–708.

Precautions

Tibolone is contra-indicated in women with breast cancer or oestrogen-dependent tumours, cardiovascular or cerebrovascular disorders including arterial or venous thromboembolism, or a history of these conditions, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, and acute liver disorders. It should not be given to pregnant or breast-feeding women and is not intended for use in premenopausal women, except those being treated with a gonadorelin analogue.

Use of tibolone within 12 months of a natural menopause is not recommended because irregular vaginal bleeding is likely. Breakthrough bleeding and spotting may occur in the first few months of therapy, but should be investigated if it persists beyond 6 months, starts after that time, or continues after tibolone has been stopped. Missing a dose may increase the likelihood of bleeding and spotting.

Care should be taken when giving tibolone to patients with uterine fibroids, endometriosis, liver disease, gallstones, disorders that may be exacerbated by fluid retention such as cardiac or renal dysfunction, hypertension, epilepsy, or migraine, or with a history of these conditions. It should also be given with caution to patients with dyslipidaemia or diabetes mellitus. Patients with risk factors for thromboembolic disorders or oestrogen-dependent tumours, or a history of endometrial hyperplasia, should be closely monitored. Tibolone should be stopped if there are signs of thromboembolism, a significant increase in blood pressure, new onset of migraine-type headache, or if abnormal liver function tests or cholestatic jaundice occur. Consideration should be given to stopping tibolone 4 to 6 weeks before elective surgery when prolonged immobilisation after surgery is likely.

Malignant neoplasms. Licensed product information contra-indicates the use of tibolone in women with oestrogen-dependent tumours, as well as those with a history of breast cancer. Previously it had been suggested that, because of a less oestrogenic effect on breast tissue, tibolone might be a suitable alternative to oestrogen-based HRT for women with a history of breast cancer and there have been a few reports of its use for menopausal symptoms in such patients. An observational study[1] and a case-control study[2] of women who had been treated for breast cancer found no evidence that tumour recurrence was higher in those subsequently given tibolone than in those who were not. Case-control studies also suggested that tibolone did not increase the risk of recurrence of treated endometrial[3] or ovarian[4] cancers. Although promising, these data were limited and further studies were needed to confirm the safety of tibolone in these groups of patients, particularly as there was some evidence[5] that in UK general practice it may have been prescribed preferentially to women at increased risk of breast and endometrial cancers, including women with a history of breast cancer. The LIBERATE study[6] was aimed at testing whether tibolone did not increase the risk of breast cancer recurrence in postmenopausal women who had been treated surgically, many of whom were receiving adjuvant therapy. The study was stopped early, based on an interim safety assessment. Final results showed that after a median follow-up of about 3 years, there was an increased risk of cancer recurrence in those given tibolone, compared with placebo.

For reports of the incidence of breast and endometrial cancers in women given tibolone, see Carcinogenicity, p. 2309.3.

1. Dimitrakakis C, *et al.* Clinical effects of tibolone in postmenopausal women after 5 years of tamoxifen therapy for breast cancer. *Climacteric* 2005; **8:** 342–51.
2. Goutzioulis M, *et al.* Tibolone therapy in breast cancer survivors: a retrospective study. *J Obstet Gynaecol Res* 2007; **33:** 68–73.
3. Lee K-B, *et al.* Endometrial cancer patients and tibolone: a matched case-control study. *Maturitas* 2006; **55:** 264–9.
4. Lee K-B, *et al.* The safety of tibolone in epithelial ovarian cancer patients. *Maturitas* 2006; **55:** 156–61.
5. Velthuis-te Wierik EJM, *et al.* Preferential prescribing of tibolone and combined estrogen plus progestogen therapy in postmenopausal women. *Menopause* 2007; **14:** 518–27.
6. Kenemans P, *et al.* LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009; **10:** 135–46.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tibolone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Compounds that induce liver enzymes, such as phenytoin, carbamazepine, and rifampicin, might theoretically enhance the metabolism of tibolone and thus reduce its activity.

For reference to the effect of tibolone on the activity of oral anticoagulants, see Sex Hormones under Warfarin, p. 1535.1.

Pharmacokinetics

Tibolone is rapidly and extensively absorbed after oral doses and quickly metabolised into three active metabolites, two of which have mainly oestrogenic activity while the third, like the parent compound, has progestogenic and androgenic activity. Peak concentrations of tibolone and its metabolites occur after about 1 to 1.5 hours, and the two main metabolites have an elimination half-life of about 7 hours. Metabolites are excreted in the bile and eliminated in the faeces. About 30% of a dose is excreted in the urine.

References.
1. Timmer CJ, Doorstam DP. Effect of renal impairment on the pharmacokinetics of a single oral dose of tibolone 2.5 mg in early postmenopausal women. *Pharmacotherapy* 2002; **22:** 148–53.
2. Timmer CJ, Huisman JA. Effect of a standardized meal on the bioavailability of a single oral dose of tibolone 2.5 mg in healthy postmenopausal women. *Pharmacotherapy* 2002; **22:** 310–15.
3. Timmer CJ, *et al.* Pharmacokinetics of tibolone in early and late postmenopausal women. *Br J Clin Pharmacol* 2002; **54:** 101–6.
4. Verheul HAM, *et al.* Pharmacokinetic parameters of sulfated tibolone metabolites in postmenopausal women after single and multiple doses of tibolone. *Clin Pharmacol Ther* 2007; **81:** 573–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cervictal; Climalona†; Climatix; Discretal; Paraclim; Senalina; Tiboclim; Tibofem; Tirovarina; Tocline; ***Austral.***: Livial; Xyvion; ***Austria***: Liviel; ***Belg.***: Heria; Livial; ***Braz.***: Klimater; Libiam; Livial; Livolon; Reduclim; Tibial; ***Chile***: Climafen; Lirex; Livial; Plenovid†; Tinox; Tobe; ***China***: Livial (利维爱); Qi Luo Shu (绮罗淑); ***Cz.***: Ladybon; Livial; Tibolvivax; ***Denm.***: Livial; ***Fin.***: Livial; ***Fr.***: Livial; ***Ger.***: Liviella; ***Gr.***: Livial; ***Hong Kong***: Livial; ***Hung.***: Livial; ***India***: Livial; Maxtib; Tibofem; Tibomax; ***Indon.***: Livial; ***Irl.***: Livial; ***Israel***: Livial; ***Ital.***: Livial; ***Malaysia***: Livial; ***Mex.***: Bontil; Lisertil; Livial; Sintemel; ***Neth.***: Livial; ***Norw.***: Livial; ***NZ***: Livial; ***Philipp.***: Livial; Menorest; ***Pol.***: Ladybon; Livial; ***Port.***: Clitax; Goldar; Livial; Ulcinil; ***Rus.***: Ladybon (Ледибон); Livial (Ливиал); ***S. Afr.***: Livifem; ***Singapore***: Livial; ***Spain***: Boltin; ***Swed.***: Livial; ***Switz.***: Livial; ***Thai.***: Livial; ***Turk.***: Livial; ***UK***: Livial; ***Ukr.***: Livial (Ливиал); ***Venez.***: Femsel; Fomene; Livial; Tinox.

Pharmacopoeial Preparations
BP 2014: Tibolone Tablets.

Trenbolone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de trenbolona; RU-1697; Trenbolona, acetato de; Trenbolone, Acétate de; Trenboloni Acetas; Trienbolone Acetate; Тренболона Ацетат.

17β-Hydroxyestra-4,9,11-trien-3-one acetate.

$C_{20}H_{24}O_3$=312.4

CAS — 10161-33-8 (trenbolone); 10161-34-9 (trenbolone acetate).

UNII — RUD5Y4SV0S.

Pharmacopoeias. In *US*, for veterinary use only.

USP 36: (Trenbolone Acetate). Store in airtight containers at a temperature of 2 degrees to 8 degrees.

Profile

Trenbolone acetate has been used as an anabolic agent in veterinary practice. The hexahydrobenzylcarbonate has also been used for its anabolic properties.

WHO specifies an acceptable daily intake of trenbolone acetate as a residue in foods, and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of trenbolone acetate and other anabolic steroids is restricted to certain therapeutic indications in non-food producing animals and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: thirty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 788* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_788.pdf (accessed 13/11/07)

Trimegestone *(BAN, USAN, rINN)*

RU-27987; Trimegeston; Trimegestona; Trimégestone; Trimegestoni; Trimegestonum; Тримегестон.

17β-(*S*)-Lactoyl-17-methylestra-4,9-dien-3-one; 17β-[(*S*)-2-Hydroxypropionyl]-17α-methylestra-4,9-dien-3-one.

$C_{22}H_{30}O_3$=342.5

CAS — 74513-62-5.

UNII — 4658K0H08W.

Profile

Trimegestone is a progestogen (see Progesterone, p. 2300.2) used as the progestogenic component of menopausal HRT (see p. 2244.1). It is given orally in daily doses of 250 or 500 micrograms in a cyclical regimen, or 125 micrograms in a continuous regimen. Trimegestone is also under investigation as a component of a combined oral contraceptive.

Reviews.
1. Grubb G, *et al.* Clinical experience with trimegestone as a new progestin in HRT. *Steroids* 2003; **68:** 921–6.
2. Sitruk-Ware R, *et al.* Preclinical and clinical properties of trimegestone: a potent and selective progestin. *Gynecol Endocrinol* 2007; **23:** 310–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trimegestone and oestrogen combinations as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Totelle Ciclico; Totelle Continuo; ***Braz.***: Totelle Ciclo; Totelle; ***Chile***: Ginotex; Lovelle Ciclico; Lovelle Continuo; Totelle Ciclico; Totelle Continuo; ***Mex.***: Totelle Continuo; Totelle Secuencial; ***Venez.***: Totelle Ciclico; Totelle Continuo.

Triptorelin *(BAN, USAN, rINN)* ⊗

AY-25650; BIM-21003; BN-52014; CL-118532; [6-D-Tryptophan] luteinising hormone-releasing factor; Triptorelina; Triptoreline; Triptoréline; Triptorelinum; D-Trp^6-LHRH; Трипторелин.

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide.

$C_{64}H_{82}N_{18}O_{13}$=1311.5

CAS — 57773-63-4.

ATC — L02AE04.

ATC Vet — QL02AE04.

UNII — 9081Y98W2V.

Triptorelin Acetate *(BANM, rINNM)* ⊗

Acetato de triptorelina; Triptoreliiniasetaatti; Triptorelin Asetat; Triptorelina, acetato de; Triptorelinacetat; Triptoréline, Acétate de; Triptorelini Acetas; Трипторелина Ацетат.

$C_{64}H_{82}N_{18}O_{13}$,$C_2H_4O_2$=1371.5

CAS — 140194-24-7.

ATC — L02AE04.

ATC Vet — QL02AE04.

UNII — 43OFW291R9.

Triptorelin Diacetate *(BANM, rINNM)* ⊗

Diacetato de triptorelina; Triptoréline, Diacetate de; Triptorelini Diacetas; Трипторелина Диацетат.

$C_{64}H_{82}N_{18}O_{13}$,$2C_2H_4O_2$=1431.6

CAS — 105581-02-0.

ATC — L02AE04.
ATC Vet — QL02AE04.

Triptorelin Embonate *(BANM, rINNM)* ⊗

Embonato de triptorelina; Triptorelin Pamoate (USAN); Triptorelina, embonato de; Triptoréline, Embonate de; Triptorelini Embonas; Трипторелина Эмбонат.

$C_{64}H_{82}N_{18}O_{13},C_{23}H_{16}O_6$=1699.8

CAS — 124508-66-3.
ATC — L02AE04.
ATC Vet — QL02AE04.
UNII — 08AN7WA2G0.

Uses and Administration

Triptorelin is an analogue of gonadorelin (p. 2280.3) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, deviant sexual behaviour in men, central precocious puberty, and in the management of endometriosis, female infertility, and uterine fibroids. Triptorelin may be given as the base, acetate, diacetate, or embonate, although for some preparations stated to contain the acetate or diacetate it is not always clear which has actually been used. Doses are usually given in terms of the base, and the following are each equivalent to about 1 mg of triptorelin:

- triptorelin acetate, 1.05 mg
- triptorelin diacetate, 1.09 mg
- triptorelin embonate, 1.30 mg

Triptorelin is given as a daily subcutaneous injection, or as an intramuscular or subcutaneous depot preparation lasting a month or longer.

In the palliative treatment of advanced **prostate cancer**, a dose equivalent to triptorelin 3 or 3.75 mg is given intramuscularly as a depot preparation every 4 weeks; the first dose may be preceded by 100 micrograms daily for 7 days by subcutaneous injection. In some countries, depot preparations containing 3.75 mg may be given subcutaneously instead. A longer-acting depot preparation that contains the equivalent of triptorelin 11.25 mg is given once every 12 to 13 weeks; a depot supplying the equivalent of 22.5 mg every 24 weeks is also available in some countries. Some countries also allow use of depot doses of 3 mg once every 4 weeks or 11.25 mg once every 12 to 13 weeks for medical therapy in locally advanced disease. An anti-androgen such as cyproterone acetate may be given for several days before beginning therapy with triptorelin and continued for about 3 weeks to avoid the risk of a disease flare.

An 11.25-mg intramuscular depot preparation, given every 12 weeks, may be used in the management of **deviant sexual behaviour** in men. The addition of an anti-androgen should be considered when starting therapy, to counteract the initial rise in serum-testosterone concentrations. Similarly, the addition of an anti-androgen should be considered before stopping triptorelin because of a risk of increased sensitivity to restored testosterone.

Similar doses of the 3- or 3.75-mg depot preparations may be given for up to 6 months in the management of **endometriosis** or **uterine fibroids**, with treatment begun during the first 5 days of the menstrual cycle. The 11.25-mg depot may be used as an alternative for endometriosis. In the management of female infertility doses of 100 micrograms subcutaneously daily, with gonadotrophins, have been recommended from the second day of the menstrual cycle for about 10 to 12 days.

Administration in children. Triptorelin may be used in the management of central precocious puberty and has been used in the diagnosis of delayed puberty. It has also been tried in the treatment of growth retardation (see below).

Diagnosis of hypothalamic and pituitary dysfunction. Gonadorelin analogues have been used in the diagnosis of delayed puberty (p. 2252.1). Triptorelin has been used in boys to differentiate gonadotrophin deficiency from constitutional delayed puberty,[1,2] although one study[3] found it to be less accurate than a test using human chorionic gonadotrophin.

1. Zamboni G, *et al.* Use of the gonadotropin-releasing hormone agonist triptorelin in the diagnosis of delayed puberty in boys. *J Pediatr* 1995; **126:** 756–8.
2. Kauschansky A, *et al.* Use of GnRH agonist and human chorionic gonadotrophin tests for differentiating constitutional delayed puberty from gonadotrophin deficiency in boys. *Clin Endocrinol (Oxf)* 2002; **56:** 603–7.
3. Degros V, *et al.* The human chorionic gonadotropin test is more powerful than the gonadotropin-releasing hormone agonist test to discriminate male isolated hypogonadotropic hypogonadism from constitutional delayed puberty. *Eur J Endocrinol* 2003; **149:** 23–9.

Disturbed behaviour. Combined therapy with triptorelin, which suppressed testosterone secretion by inhibiting the pituitary-gonadal axis, and supportive psychotherapy, has been tried in the treatment of men with paraphilias (see p. 1030.2): a reduction in abnormal sexual thoughts and behaviours has been reported, although the study was uncontrolled.[1]

1. Rösler A, Witztum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. *N Engl J Med* 1998; **338:** 416–22.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p. 2264.1), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

1. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
2. Bergqvist A, *et al.* Effects of triptorelin versus placebo on the symptoms of endometriosis. *Fertil Steril* 1998; **69:** 702–8.
3. Donnez J, *et al.* Equivalence of the 3-month and 28-day formulations of triptorelin with regard to achievement and maintenance of medical castration in women with endometriosis. *Fertil Steril* 2004; **81:** 297–304.
4. Wong AY, Tang L. An open and randomized study comparing the efficacy of standard danazol and modified triptorelin regimens for postoperative disease management of moderate to severe endometriosis. *Fertil Steril* 2004; **81:** 1522–7.
5. Loverro G, *et al.* A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2008; **136:** 194–8.

Fibroids. Gonadorelin analogues have been used as an alternative to surgery in the treatment of uterine fibroids (see p. 2281.2), despite some concern that this may complicate the diagnosis of malignancy.

References to the use of triptorelin.

1. van Leusden HA. Symptom-free interval after triptorelin treatment of uterine fibroids: long-term results. *Gynecol Endocrinol* 1992; **6:** 189–98.
2. Golan A, *et al.* Pre-operative gonadotrophin-releasing hormone agonist treatment in surgery for uterine leiomyomata. *Hum Reprod* 1993; **8:** 450–2.
3. Broekmans FJ, *et al.* Two-step gonadotropin-releasing hormone agonist treatment of uterine leiomyomas: standard-dose therapy followed by reduced-dose therapy. *Am J Obstet Gynecol* 1996; **175:** 1208–16.
4. Vercellini P, *et al.* Treatment with a gonadotrophin releasing hormone agonist before hysterectomy for leiomyomas: results of a multicentre, randomised controlled trial. *Br J Obstet Gynaecol* 1998; **105:** 1148–54.
5. Seracchioli R, *et al.* GnRH agonist treatment before total laparoscopic hysterectomy for large uteri. *J Am Assoc Gynecol Laparosc* 2003; **10:** 316–19.

Growth retardation. As discussed on p. 1918.3 gonadorelin analogues have been given with growth hormone to short girls without growth hormone deficiency, in an attempt to delay puberty and bone maturation and thus maximise the final height achieved. Use in growth hormone-deficient children has also been investigated. However, there is some doubt about the extent of benefit, and in any case the concept of such treatment in children who are not clinically deficient in growth hormone is controversial, and some authorities do not consider it appropriate.

References to the use of triptorelin.

1. Saggese G, *et al.* Combination treatment with growth hormone and gonadotropin-releasing hormone analogs in short normal girls. *J Pediatr* 1995; **126:** 468–73.
2. Saggese G, *et al.* The effect of administering gonadotropin-releasing hormone agonist with recombinant-human growth hormone (GH) on the final height of girls with isolated GH deficiency: results from a controlled study. *J Clin Endocrinol Metab* 2001; **86:** 1900–4.
3. Kamp GA, *et al.* A randomized controlled trial of three years growth hormone and gonadotropin-releasing hormone agonist treatment in children with idiopathic short stature and intrauterine growth retardation. *J Clin Endocrinol Metab* 2001; **86:** 2969–75.
4. Tauber M, *et al.* Can some growth hormone (GH)-deficient children benefit from combined therapy with gonadotropin-releasing hormone analogs and GH? Results of a retrospective study. *J Clin Endocrinol Metab* 2003; **88:** 1179–83.

Infertility. Gonadorelin analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both men and women. For a discussion of infertility and its management, including the role of gonadorelin analogues, see p. 2253.1.

Malignant neoplasms. Triptorelin, like other gonadorelin analogues, may be used in the production of androgen blockade in patients with prostate cancer (p. 712.3).

References.

1. Klippel KF, *et al.* Wirksamkeit und Vertraglichkeit von 2 Applikationsformen (s.c. und i.m.) von Decapeptyl Depot bei Patienten mit fortgeschrittenem Prostatakarzinom. *Urologe* 1999; **38:** 270–5.
2. Heyns CF, *et al.* Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. *BJU Int* 2003; **92:** 226–31.
3. Botto H, *et al.* Etude randomisée multicentrique comparant la castration médicale par triptoréline à la castration chirurgicale dans le traitement du cancer de la prostate localement avancé ou métastatique. *Prog Urol* 2007; **17:** 235–9.
4. Lundström EA, *et al.* Triptorelin 6-month formulation in the management of patients with locally advanced and metastatic prostate cancer: an open-label, non-comparative, multicentre, phase III study. *Clin Drug Investig* 2009; **29:** 757–65.
5. Keating GM. Triptorelin embonate (6-month formulation). *Drugs* 2010; **70:** 347–53.

Porphyria. Triptorelin has been used successfully to suppress premenstrual exacerbations of acute intermittent porphyria (p. 1556.1), in doses of 3.75 mg by intramuscular depot injection given monthly.[1,2] To reduce the risk of osteoporosis, 'add-back' therapy with topical oestrogen and oral calcium was used in one case,[1] and tibolone in another.[2]

1. De Block CEM, *et al.* Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects – a case report. *Eur J Endocrinol* 1999; **141:** 50–4.
2. Castelo-Branco C, *et al.* Use of gonadotropin-releasing hormone analog with tibolone to prevent cyclic attacks of acute intermittent porphyria. *Metabolism* 2001; **50:** 995–6.

Precocious puberty. The gonadorelin analogues have largely replaced other treatments in the management of central precocious puberty (p. 2254.1). A dose equivalent to triptorelin 50 micrograms/kg, from a 3-mg depot preparation, may be given intramuscularly every 4 weeks. Alternatively, using a 3.75-mg preparation, doses of 1.875 mg for children weighing less than 20 kg, 2.5 mg for children of 20 to 30 kg, or 3.75 mg for children of more than 30 kg, may be given intramuscularly or subcutaneously. The first 3 doses should be given at 14-day intervals, with further doses given every 4 weeks; this may be increased to once every 3 weeks if necessary. A longer acting 11.25-mg depot preparation, given intramuscularly once every 3 months, is another alternative.

References to the use of triptorelin.

1. Oostdijk W, *et al.* Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Arch Dis Child* 1996; **75:** 292–7.
2. Cassio A, *et al.* Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5—8.5 years. *Arch Dis Child* 1999; **81:** 329–32.
3. Heger S, *et al.* Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab* 1999; **84:** 4583–90.
4. Carel J-C, *et al.* Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. *J Clin Endocrinol Metab* 1999; **84:** 1973–8.
5. Mul D, *et al.* Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. *Horm Res* 2002; **58:** 1–7.
6. Carel JC, *et al.* Triptorelin 3-month CPP Study Group. Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty. *Eur J Endocrinol* 2006; **154:** 119–24.

Adverse Effects and Precautions

As for Gonadorelin, p. 2282.1.

Local reactions. For reference to local reactions occurring following injection of gonadorelin analogues, including triptorelin, see Leuprorelin Acetate, p. 2286.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies triptorelin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1] For the use of triptorelin in the prevention of premenstrual exacerbations of acute porphyria, see above.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Sepsis. A report of 2 patients in whom triptorelin therapy led to sepsis caused by expulsion of necrotic fibroids through the cervix.[1]

1. Ellenbogen A, *et al.* Complication of triptorelin treatment for uterine myomas. *Lancet* 1989; **ii:** 167–8.

Interactions

As for Gonadorelin, p. 2282.2.

Pharmacokinetics

Triptorelin is rapidly absorbed after subcutaneous injection and peak plasma concentrations occur about 40 minutes after a dose. The biological half-life is about 7.5 hours, although longer half-lives have been reported in patients with prostate cancer, and shorter half-lives in some groups of healthy subjects.

References.

1. Müller FO, *et al.* Pharmacokinetics of triptorelin after intravenous bolus administration in healthy males and in males with renal or hepatic insufficiency. *Br J Clin Pharmacol* 1997; **44:** 335–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Decapeptyl; Gonapeptyl; ***Austral.***: Diphereline; ***Austria***: Decapeptyl; Pamorelin; ***Belg.***: Decapeptyl; Gonapeptyl; Salvacyl; ***Braz.***: Gonapeptyl; Neo Decapeptyl; ***Canad.***: Trelstar; ***Chile***: Decapeptyl; ***China***: Decapeptyl (达必佳); Diphereline (达菲林); ***Cz.***: Decapeptyl; Diphereline;

Denm.: Decapeptyl; Gonapeptyl; Pamorelin; Salvacyl; ***Fin.***: Decapeptyl; Gonapeptyl; Pamorelin; Salvacyl; ***Fr.***: Decapeptyl; Gonapeptyl; Salvacyl; ***Ger.***: Decapeptyl; Pamorelin; Salvacyl; ***Gr.***: Arvekap; Gonapeptyl; ***Hong Kong***: Decapeptyl; Diphereline; ***Hung.***: Decapeptyl; Diphereline; ***India***: Decapeptyl; ***Irl.***: Decapeptyl; Gonapeptyl; ***Israel***: Decapeptyl; Diphereline; ***Ital.***: Decapeptyl; Gonapeptyl; ***Malaysia***: Decapeptyl; ***Mex.***: Pamorelin; ***Neth.***: Decapeptyl; Gonapeptyl; Pamorelin; Salvacyl; Triptofem; ***Norw.***: Pamorelin; Salvapar; ***Philipp.***: Decapeptyl; ***Pol.***: Decapeptyl; Diphereline; ***Port.***: Decapeptyl; Fertipeptil; Gonapeptyl; ***Rus.***: Decapeptyl (Декапептил); Diphereline (Диферелин); ***S.Afr.***: Decapeptyl†; Gonapeptyl; ***Singapore***: Decapeptyl; ***Spain***: Decapeptyl; Gonapeptyl; ***Swed.***: Decapeptyl†; Gonapeptyl; Moapar†; Pamorelin; ***Switz.***: Decapeptyl; Pamorelin; Salvacyl; ***Thai.***: Decapeptyl; Diphereline; ***Turk.***: Decapeptyl; ***UK***: Decapeptyl; Gonapeptyl; Salvacyl; ***Ukr.***: Decapeptyl (Декапептил); Diphereline (Диферелин); ***USA***: Trelstar; ***Venez.***: Decapeptyl.

Ulipristal Acetate *(BANM, USAN, rINNM)*

Acetato de ulipristal; CDB-2914; RTI-3021-012; Uliprisnil Acetate; Ulipristal, Acétate d'; Ulipristali Acetas; VA-2914; Улипристала Ацетат.

(11β)-17-(Acetyloxy)-11-[4-(dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione.

$C_{30}H_{37}NO_4$=475.6

CAS — 159811-51-5 (ulipristal); 126784-99-4 (ulipristal acetate).

ATC — G03AD02.

ATC Vet — QG03AD02.

UNII — YF7V70N02B.

Uses and Administration

Ulipristal is a progesterone receptor modulator with antagonist and partial agonist effects. It inhibits or delays ovulation, alters the endometrial epithelium, and can reduce fibroid size.

A single oral dose of ulipristal acetate 30 mg may be given for emergency contraception (p. 2233.2). It should be taken as soon as possible, and no later than 120 hours (5 days), after unprotected sexual intercourse. If vomiting occurs within 3 hours, another dose should be taken. Ulipristal is also under investigation as a continuous form of contraception.

Ulipristal acetate may be used for pre-operative management in women with symptoms of uterine fibroids (p. 2281.2). An oral dose of 5 mg once daily is used, usually for up to 3 months before surgery. Treatment should be started during the first week of a menstrual cycle. A significant reduction in menstrual blood loss or amenorrhoea is expected within the first 10 days of treatment; menstrual periods generally return within 4 weeks after stopping treatment.

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Adverse Effects and Precautions

Adverse effects reported for ulipristal acetate include abdominal pain and gastrointestinal disturbances, such as nausea and vomiting. Other effects include headache, dizziness, mood disorders, breast tenderness, myalgia, back pain, and fatigue. Less commonly reported effects have included blurred vision, vertigo, and skin reactions such as acne, rash, pruritus, and urticaria. Other adverse effects reported with continuous use include hot flushes, functional ovarian cysts that usually disappear spontaneously within a few weeks, and a few cases of uterine haemorrhage in women at risk of excessive bleeding associated with uterine fibroids. Increases in blood cholesterol and triglycerides have also been recorded.

Dysmenorrhoea is common after a dose of ulipristal acetate for emergency contraception. Menstrual disturbances can also occur and the next menstrual period may start several days earlier or later than expected after a single dose. Endometrial changes and thickening may occur in patients being treated for uterine fibroids. However, these changes are different from endometrial hyperplasia and reversible after stopping treatment. Endometrial thickening that persists 3 months after ulipristal is stopped and menstruation has returned should be investigated.

Pregnancy should be excluded before the use of ulipristal acetate for emergency contraception. In women being treated for fibroids, ulipristal acetate should be started in the first week of a menstrual cycle. Although continuous treatment causes anovulation in most patients, a non-hormonal method of contraception is recommended.

The elimination of ulipristal acetate is expected to be reduced in patients with hepatic impairment and its use in moderate or severe impairment is not recommended without close monitoring. Ulipristal acetate has a high affinity for glucocorticoid receptors, and antiglucocorticoid effects have been seen in *animal* studies. The use of ulipristal acetate is not recommended in patients who have asthma that is inadequately controlled by oral corticosteroid therapy.

Interactions

Drugs that increase gastric pH (such as antacids, H_2-receptor antagonists, and proton pump inhibitors) may reduce the absorption of ulipristal acetate. This may reduce its efficacy for emergency contraception and concomitant use is therefore not recommended. However, during continuous use the systemic exposure to ulipristal increases (with a delayed and decreased peak plasma concentration) and the effect is not expected to be clinically significant for patients being treated for uterine fibroids. Drugs that alter the activity of the cytochrome P450 isoenzyme CYP3A4 have the potential to affect the plasma concentrations of ulipristal acetate. CYP3A4 inducers may decrease its efficacy as an emergency contraceptive, and an interaction should be considered possible for at least 2 to 3 weeks after such inducers have been stopped. Concomitant use with potent inducers is not recommended with ulipristal acetate given continuously for fibroid treatment. Moderate and potent inhibitors of CYP3A4 are also not recommended with continuous therapy.

Ulipristal acetate may interfere with the action of progestogens, such as those found in combined and progestogen-only hormonal contraceptives. Regular hormonal contraception may be continued when ulipristal acetate is used for emergency contraception, but a reliable barrier method of contraception should also be used until the next menstrual period starts. The concomitant use of ulipristal acetate and levonorgestrel for emergency contraception is not recommended. A non-hormonal contraceptive method is recommended during continuous ulipristal acetate treatment of fibroids.

In-vitro studies suggest that ulipristal acetate may be an inhibitor of P-glycoprotein. Co-administration of ulipristal with substrates of this transporter protein is therefore not recommended, although clinical evidence of an interaction is lacking.

Pharmacokinetics

Ulipristal acetate is rapidly absorbed from the gastrointestinal tract; its absorption is pH-dependent and may be reduced when gastric pH is raised. The drug is highly bound to plasma proteins. It is extensively metabolised to demethylated and hydroxylated metabolites, mainly by the cytochrome P450 isoenzyme CYP3A4 and to a small extent by CYP1A2 and CYP2D6. The terminal plasma half-life of ulipristal acetate is about 32 to 38 hours after a single dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: ellaOne; ***Belg.***: ellaOne; ***Cz.***: ellaOne; ***Denm.***: ellaOne; Esmya; ***Fr.***: ellaOne; Esmya; ***Ger.***: ellaOne; ***Gr.***: ellaOne; ***Hung.***: ellaOne; ***Irl.***: ellaOne; ***Israel***: ella; ***Ital.***: ellaOne; ***Neth.***: ellaOne; Esmya; ***Norw.***: ellaOne; Esmya; ***Pol.***: ellaOne; ***Port.***: ellaOne; ***Singapore***: ella; ***Spain***: ellaOne; ***Swed.***: ellaOne; ***UK***: ellaOne; Esmya; ***Ukr.***: Dvella (Двелла); ***USA***: ella.

Urofollitropin *(BAN, USAN, rINN)*

Ürofolitropin; Urofolitropin; Urofolitropina; Urofolitropinas; Urofollitrophin; Urofollitropiini; Urofollitropine; Urofollitropinum; Урофоллитропин.

CAS — 97048-13-0.

ATC — G03GA04.

ATC Vet — QG03GA04.

UNII — W9BB98U6HP.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Urofollitropin). A dry preparation containing menopausal gonadotrophin obtained from the urine of postmenopausal women. It has follicle-stimulating activity and no or virtually no luteinising activity. The potency is not less than 90 units of follicle-stimulating hormone per mg; the ratio of units of luteinising hormone to units of follicle-stimulating hormone is not more than 1:60. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Urofollitropin is a gonadotrophin, obtained from the urine of postmenopausal women, possessing follicle-stimulating hormone (FSH) activity but virtually no luteinising activity. For details of the actions of FSH, see p. 2278.2.

Urofollitropin is used similarly to human menopausal gonadotrophins (p. 2284.2) in the treatment of **female infertility** with the exception that, being without luteinising hormone activity, it can be used in patients where any increase in luteinising hormone activity is not required, as in polycystic ovarian disease. Urofollitropin is given subcutaneously or intramuscularly in a dosage adjusted according to the patient's response. Usually a dose providing 75 to 150 units of FSH daily is given initially. When an adequate response is achieved, as determined by oestrogen monitoring or ultrasonic visualisation of follicles, treatment is stopped and after 1 or 2 days a single dose of chorionic gonadotrophin 5000 to 10 000 units is given to induce ovulation. Treatment with urofollitropin should be stopped if there is no response after 4 weeks although treatment may be attempted again in future cycles. US product information has recommended that a maximum daily dose of 450 units should not be exceeded, and that courses of treatment should be no longer than 12 days.

Urofollitropin is also used with other drugs as part of IVF procedures. It is typically given in a dose providing 150 to 225 units of FSH daily, usually beginning from day 2 or 3 of the menstrual cycle. Alternatively, therapy has been begun with clomifene citrate and continued with urofollitropin, or urofollitropin may be given after suppression of gonadotrophin release with a gonadorelin analogue. Treatment is continued until an adequate response is obtained and the final injection of urofollitropin is followed 1 to 2 days later by 5000 to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is performed 34 to 35 hours later.

Urofollitropin is also used with chorionic gonadotrophin to stimulate spermatogenesis in the treatment of **male infertility**, although a preparation with combined luteinising activity, such as human menopausal gonadotrophins, may be preferred. The usual dose of urofollitropin provides 150 units of FSH three times a week. Treatment with urofollitropin and chorionic gonadotrophin should be continued for at least 4 months. For a brief discussion of hypogonadism see p. 2252.3.

Infertility. For reference to the use of preparations with follicle-stimulating hormone activity in infertility, see p. 2253.1.

References to the use of urofollitropin including contradictory results as to its relative efficacy versus recombinant follicle-stimulating hormone.

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Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p. 2284.3.

Pharmacokinetics

After multiple intramuscular or subcutaneous dosing of urofollitropin, peak plasma concentrations of follicle-stimulating hormone occur about 10 hours after a dose and the elimination half-life is about 15 or 20 hours respectively.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Follitrin; Fostimon; ***Austral.***: Metrodin†; ***Austria***: Bravelle; Fostimon; ***Belg.***: Fostimon; ***Braz.***: Bravelle; Fostimon; Metrodin†; ***Canad.***: Bravelle; ***Chile***: Follitrin; ***China***: Lishenbao (丽申宝); ***Cz.***: Bravelle; Fostimon;

Denm.: Bravelle; Fostimon; ***Fin.***: Fostimon; ***Fr.***: Fostimon; ***Ger.***: Bravelle; ***Gr.***: Bravelle; Metrodin; ***Hong Kong***: Bravelle; Fostimon†; ***Hung.***: Fostimon; ***India***: Endogen; Fergonad-F; Folliculin; Foligem; Foligest; Folliova; Follitec; Follokon; Fostine; Gonotrop F; LG Follimon; Materna FSH; Metrodin; Neogentin; Ovitrop; Ovufol-HP; ***Irl.***: Bravelle; Fostimon; ***Israel***: Bravelle; Fostimon; ***Ital.***: Fostimon; ***Mex.***: Fostimon; ***Neth.***: Bravelle; Fostimon; ***Norw.***: Bravelle; Fostimon; ***Pol.***: Bravelle; Fostimon; ***Port.***: Bravelle; Fostimon; Metrodin†; ***Rus.***: Metrodin (Метродин); ***Spain***: Bravelle; Fostipur; ***Swed.***: Bravelle; Fostimon; ***Switz.***: Fostimon; ***Thai.***: Follimon; ***Turk.***: Follegon; Fostimon; Metrodin; ***UK***: Fostimon; ***Ukr.***: Bravelle (Бравель); Fostimon (Фостимон); ***USA***: Bravelle; Fertinex†; Metrodin†.

Pharmacopoeial Preparations
BP 2014: Urofollitropin Injection.

Zeranol *(BAN, USAN, rINN)* ⊗

MK-188; P-1496; THFES (HM); Zearalanol; Zéranol; Zeranolum; Зеранол.

(3*S*,7*R*)-3,4,5,6,7,8,9,10,11,12-Decahydro-7,14,16-trihydroxy-3-methyl-1*H*-2-benzoxacyclotetradecin-1-one.

$C_{18}H_{26}O_5$=322.4

CAS — 26538-44-3.

UNII — 76LO2L2V39.

Profile

Zeranol is a nonsteroidal oestrogen that has been used for the management of menopausal and menstrual disorders. It has also been used as a growth promotor in veterinary practice. Its anabolic properties may be subject to abuse in sport.

WHO specifies an acceptable daily intake of zeranol as a residue in foods and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of zeranol in veterinary medicine is prohibited. Certain other steroidal hormones are permitted for restricted use but their use as growth promotors is banned.

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Stimulants and Anorectics

Hyperactivity, p. 2314
Narcoleptic syndrome, p. 2314
Obesity, p. 2315
Prader-Willi syndrome, p. 2315

This chapter includes compounds used, generally under specialist supervision, for their central stimulant or their anorectic effects. Many are sympathomimetics and are subject to extensive abuse, which has led to strict limitations on their availability.

Hyperactivity

Attention deficit hyperactivity disorder (ADHD) is a syndrome of developmentally inappropriate and socially disruptive behaviour beginning in childhood and characterised by varying degrees of hyperactivity, inattention, and impulsiveness. Children with ADHD are easily distracted and have difficulty in completing tasks. Associated features may include low frustration tolerance, mood lability, and defiance. Some children continue to have symptoms throughout adolescence and into adulthood. The terms hyperkinesis, hyperkinetic syndrome, minimal brain dysfunction, attention deficit disorder, and attention deficit disorder with hyperactivity have sometimes been used synonymously for ADHD, but patients described as having these disorders do not necessarily satisfy the diagnostic criteria for ADHD.

Both drug and behaviour therapy may be used for the management of ADHD. Drug therapy is useful for the control of symptoms but is not curative and should take into account co-existing disorders such as tics, Tourette's syndrome, and epilepsy. In the USA drug treatment for ADHD is quite common even in mild forms, and in the hands of specialists appears superior to behavioural therapy, but in the UK drugs are generally reserved for severely affected children and those who fail to respond to counselling and behaviour therapy.

The central stimulant methylphenidate or the selective noradrenaline reuptake inhibitor atomoxetine are usually the drugs of first choice; dexamfetamine is an alternative in children who do not respond to these drugs. There are multiple formulations of stimulants available to allow treatment to be individualised and to improve compliance. Other stimulants that have been used include pemoline but its use was associated with hepatotoxicity which led to its withdrawal in many countries. Modafinil is under investigation for the treatment of hyperactivity disorders. Many authorities consider that young, particularly pre-school, children should not receive stimulants, although they do appear to be of use when the disorder persists into adulthood.

The use of central stimulants has been associated with sudden death and some authorities recommend screening for cardiovascular disorders before starting treatment and to monitor heart rate and blood pressure during treatment (for further details, see Effects on the Cardiovascular System, under Dexamfetamine, p. 2319.3). Children who benefit from drug therapy may require several years of treatment. Growth is not generally affected by treatment with stimulants but monitoring during treatment is advised. If growth is noted to be significantly reduced, a planned treatment break may be considered to allow growth to catch up. Treatment should be reviewed periodically to determine whether continued therapy is necessary.

Tricyclic antidepressants such as imipramine and desipramine are also used for ADHD in both children and adults and their effect appears to be independent of their antidepressant action. However, they tend to be reserved for patients who fail to respond to, or are intolerant of, central stimulants. Tricyclic antidepressants may be useful in patients with co-existing Tourette's syndrome or in those with a family history of the disorder, as some stimulants may precipitate or exacerbate associated tics (p. 1030.1). Tricyclic antidepressants might also be preferred in patients with co-existing anxiety, depression, or enuresis, or in those with a history of drug abuse. Use with central stimulants has been studied but careful monitoring is advised (see also Interactions under Dexamfetamine, p. 2320.2). MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use. SSRIs such as fluoxetine have produced beneficial results as an adjunct to central stimulants in a small number of patients with associated depression or obsessive-compulsive disorder, but their value in ADHD alone is unclear. Bupropion has shown promising results in controlled studies in children but may exacerbate tics and increase the risk of seizures in predisposed patients. Venlafaxine has been effective in open studies in a small number of adult patients.

There is some evidence that carbamazepine may be an effective alternative to central stimulants. Clonidine, an alpha$_2$ agonist, has been used successfully as monotherapy, or with stimulants in children with an inadequate response to stimulants alone. However, there have been reports of adverse cardiac events associated with such combinations; some recommend performing a cardiovascular examination and an ECG before starting treatment with clonidine. Guanfacine, another alpha$_{2A}$ agonist, has also been tried successfully, and may be better tolerated. Antipsychotics can produce severe adverse effects and are probably only warranted as adjunctive therapy to central stimulants in severe cases or when there is also extremely violent or destructive behaviour. Dopaminergics such as levodopa or pergolide have been tried with beneficial results for the treatment of restless legs syndrome and periodic limb movements in sleep associated with ADHD; some improvements in ADHD symptoms were also noted on resolution of the parasomnias.

Much controversy has surrounded the hypothesis that certain synthetic food additives including preservatives and artificial flavours and colours are aetiological agents in ADHD. Controlled studies have not proved the efficacy of dietary manipulation.

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Narcoleptic syndrome

Narcolepsy is characterised by excessive daytime sleepiness and irresistible sleep attacks that last from a few minutes to hours. The narcoleptic syndrome often includes **cataplexy**, a sudden short-lived loss of muscle tone and paralysis of voluntary muscles induced by strong emotions. The severity of the attack can vary and some patients have complete collapse but there is no loss of consciousness. **Sleep paralysis** consists of transient episodes of complete paralysis while falling asleep or during waking; respiration is unaffected. Some patients also have vivid auditory or visual hallucinations while falling asleep (**hypnagogic hallucinations**) or disturbed sleep.

For the management of narcoleptic syndrome the patient is initially encouraged to take planned regular short periods of sleep during the day and to avoid stressful events that may provoke attacks. If drug treatment is required then central stimulants are the main drugs used for the sleep attacks of narcolepsy. However, most are ineffective against cataplexy. The selection, dose, and timing of these drugs need to be titrated for each patient, and drug holidays have been suggested to reduce the risk of developing tolerance. Amfetamines were the first drugs used. However, methylphenidate is often preferred to dexamfetamine as it has a rapid action and is considered to have fewer adverse effects. Alternative non-amfetamine stimulants used in the treatment of narcolepsy include mazindol, which also appears to be effective in cataplexy, and modafinil and its *R*-enantiomer, armodafinil. Selegiline has been reported to improve excessive daytime sleepiness and cataplexy. There is anecdotal or other limited evidence of efficacy in narcolepsy for many other drugs but there appears to be no evidence that they are superior to the central stimulants.

Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis. However, a recent systematic review concluded that evidence supporting the use of antidepressants in cataplexy is scarce. Imipramine and clomipramine appear to have been widely used (some consider that clomipramine is the most effective of the tricyclics for this indication); desipramine and protriptyline have also been given. The onset of action is quicker, and the effective doses seem to be lower, than when tricyclics are used for depression, although tolerance to the effect may develop after 6 to 8 months, requiring an increase in dose. The daily dose should be titrated to provide maximal protection for the time of day when symptoms usually occur.

The use of sodium oxybate at night with stimulants during the day has been reported to improve the symptoms of patients with narcoleptic syndrome.

Patients requiring treatment for both narcolepsy and cataplexy may be given central stimulants and tricyclic antidepressants but require careful monitoring as the combination may produce serious adverse effects such as cardiac arrhythmias or hypertension; see also Interactions of Dexamfetamine, p. 2320.2.

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Obesity

Obesity results from an imbalance between energy intake and energy expenditure and increases the risk of cardiovascular disease, diabetes mellitus, gallstones, respiratory disease, osteoarthritis, and some forms of cancer. The prevalence of obesity is increasing especially in developed countries and is a particular concern in children. Obesity may be defined in terms of the body-mass index (BMI), which is the weight (kg) divided by the square of the height (m^2):

- BMI 25.0 to 29.9: overweight
- BMI 30.0 to 34.9: obese, moderate risk of comorbidity
- BMI 35.0 to 39.9: obese, severe risk of comorbidity
- BMI 40.0 or more: obese, very severe risk of comorbidity

Weight loss appears to improve control of diabetes mellitus and hypertension, and to reduce cardiovascular risk factors but long-term benefits are difficult to assess as weight is often regained.

Initial management involves dietary modification and includes calorie restriction and changes in the dietary proportions of fat, protein, and carbohydrates. Physical activity should also be increased and excess alcohol avoided. These measures should be followed for at least 3 months. If there has then been less than 10% reduction in weight and the BMI is still above 30, drug treatment may be considered. For patients with associated risk factors such as diabetes mellitus, ischaemic heart disease, hyperlipidaemias, hypertension, or sleep apnoea, drugs may be considered when the BMI is 27 or 28. Combination drug therapy is not recommended. Drugs should be given initially for 12 weeks. If weight loss is less than 5% then they should be considered a failure and stopped. If weight loss is more than 5% they may be continued and the patient monitored at monthly intervals. Treatment should be stopped once the BMI falls below 30 (or 27/28 as appropriate, see above), or if weight is regained, or there is any suspicion of toxicity. Drug treatment should only be considered for obese children after lifestyle interventions have been initiated, and who have associated conditions such as orthopaedic problems or sleep apnoea.

Many drugs are capable of reducing appetite and have been used as such in the treatment of obesity. Both centrally acting (appetite suppressant, anorectic) drugs and those with a local action on the gastrointestinal tract have been used. However, toxicity has been a major problem with centrally acting drugs and very few are still in current use.

Appetite suppressants can be divided into two main groups: central stimulants that act on central catecholamine pathways and drugs acting on central serotonin pathways. Stimulants such as the amfetamines and phenmetrazine are no longer recommended because of their addictive potential. Other stimulants that have been used include diethylpropion, phentermine, mazindol, and phenylpropanolamine but they are also no longer recommended. The serotonergic drugs dexfenfluramine and fenfluramine were formerly used in long-term therapy (up to 1 year) but have both been associated with valvular heart defects and have generally been withdrawn worldwide. There have also been reports of valvular heart defects in patients receiving combinations of anorectics. Rimonabant, a cannabinoid type-1 receptor antagonist, has been used as an adjunct in the treatment of obesity but was withdrawn from most markets after concern about psychiatric reactions. Guidelines have recommended the centrally acting serotonin and noradrenaline reuptake inhibitor sibutramine, and the gastric lipase inhibitor orlistat, as appropriate choices for the drug treatment of obesity, along with diet and exercise. A systematic review of long-term studies (1 year or more) found orlistat and sibutramine to be modestly effective in reducing weight. However, the marketing authorisation for sibutramine was suspended in the EU and withdrawn in the USA after a safety review found that the cardiovascular risks outweighed the benefits (for further details see Effects on the Cardiovascular System, under Sibutramine Hydrochloride, p. 2330.2). It remained available in some other countries. The selective serotonin 5-HT_{2C} agonist lorcaserin is now licensed for the management of obesity.

Many other drugs have been tried, including fluoxetine, which has met with some success, and ephedrine with caffeine. The antiepileptics topiramate and zonisamide have also been investigated and topiramate is available as a modified-release combination preparation with phentermine for the management of obesity. The biguanide antidiabetic metformin, liraglutide, an analogue of the incretin hormone, glucagon-like peptide 1 (GLP-1), and the serotonin, noradrenaline and dopamine re-uptake inhibitor tesofensine are other areas of interest. Bulk-forming drugs such as methylcellulose and sterculia have been used in an attempt to control appetite by the local effect they might exert when they swell in the gastrointestinal tract, but there is little evidence of efficacy. Nondigestible fat substitutes such as sucrose polyesters have been promoted by the food industry, as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

Bariatric surgery may be considered in severely obese patients including children with comorbidities when other measures have failed.

The control of appetite and the mechanisms of obesity are under investigation. A gene, called the ob-gene, and its protein product, leptin, have been identified and appear to be involved in regulation of food intake.

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Prader-Willi syndrome

Compulsive eating and a voracious appetite are two of the many clinical features of Prader-Willi syndrome, a congenital disorder characterised by infantile hypotonia, hypogonadism, and facial dysmorphism, with subsequent development of abnormalities of behaviour and intellect.[1-3] Supervision and restricted access to food are the mainstay in preventing obesity, but are commonly not sufficient. Fluoxetine may decrease food intake in some patients. It has also been tried for associated self-mutilatory behaviour (skin picking) with variable results.[4,5] Growth hormone may be of benefit in increasing associated short stature and decreasing percentage body fat,[6-12] but close surveillance of glucose homoeostasis is advisable and there have been reports of fatalities in patients with severe obesity or risk factors for respiratory impairment or obstruction.[13] Anorectics have been ineffective.[2]

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7. Myers SE, *et al.* Physical effects of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr Suppl* 1999; **433:** 112–14.
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9. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; **88:** 283–5.
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Adrafinil (rINN) ⊗

Adrafinilo; Adrafinilum; CRL-40028; Адрафинил.

2-[(Diphenylmethyl)sulfinyl]acetohydroxamic acid.

$C_{15}H_{15}NO_3S$=289.3

CAS — 63547-13-7.

ATC — N06BX17.

ATC Vet — QN06BX17.

UNII — BI81Z4542G.

Profile

Adrafinil is a central stimulant and alpha$_1$-adrenergic agonist chemically related to modafinil (p. 2327.2). It is given orally for mental function impairment in the elderly in doses of 600 mg to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Olmifon†.

Almitrine Dimesilate (BANM, rINNM)

Almitrina, dimesilato de; Almitrine Bismesylate; Almitrine, Dimésilate d'; Almitrine Dimesylate; Almitrine Mesylate (USAN); Almitrini Dimesilas; Dimesilato de almitrina; S-2620 (almitrine or almitrine dimesilate); Альмитрина Димезилат.

NN'-Diallyl-6-[4-(4,4'-difluorobenzhydryl)piperazin-1-yl]-1,3,5-triazine-2,4-diyldiamine bis(methanesulphonate).

$C_{26}H_{29}F_2N_7.2CH_4SO_3$=669.8

CAS — 27469-53-0 (almitrine); 29608-49-9 (almitrine dimesilate).

ATC — R07AB07.

ATC Vet — QR07AB07.

UNII — 6RY6V6XM8T.

Pharmacopoeias. In *Chin.*

Profile

Almitrine dimesilate has been used as a respiratory stimulant in acute respiratory failure associated with conditions such as chronic obstructive pulmonary disease (see Respiratory System Disorders, below). Usual oral doses range from 50 to 100 mg daily and treatment may be intermittent. Up to 3 mg/kg has been given daily by intravenous infusion in 2 or 3 divided doses, each dose being infused over 2 hours. It is also available in a compound preparation with raubasine for mental function impairment in the elderly.

Mental impairment. References.

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Respiratory system disorders. Respiratory stimulants (such as almitrine) have a limited and short-term role in acute respiratory failure in chronic obstructive pulmonary disease (p. 1199.1). Almitrine has been reported[1-4] to

improve ventilation and blood oxygenation, and to decrease the number of episodes of dyspnoea and hospital admissions, although others[5] have failed to note benefit. There are also reports[6,7] of beneficial effects when used with inhaled nitric oxide in patients with severe hypoxaemic acute respiratory distress syndrome (p. 1599.3) as well as in patients with hypoxia caused by focal lung lesions.[8] However, any modest benefits may be outweighed by the adverse effects, which have included peripheral paraesthesia and weight loss,[1] and headache, urticaria, breathlessness, diarrhoea, chest pain, nausea, and vomiting.[3] The peripheral neuropathy that sometimes occurs during long-term use of almitrine[9,10] may be due to an underlying feature of the pulmonary disease being treated,[11-13] although some disagree with this.[14]

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Vectarion; ***Fr.***: Vectarion†; ***Irl.***: Vectarion†; ***Pol.***: Armanor†; ***Port.***: Vectarion†; ***Rus.***: Armanor (Арманор); ***Spain***: Vectarion†.

Multi-ingredient Preparations. ***China***: Duxil (都可喜); ***Hong Kong***: Duxaril; ***Philipp.***: Duxaril; ***Singapore***: Duxaril; ***Thai.***: Duxaril†.

Amfetamine *(BAN, rINN)* ⊗

Amfetamiini; Amfetamin; Amfétamine; Amfetaminum; Amphetamine; Amphetaminum; Anfetamina; Racemic Desoxynorephedrine; Амфетамин.

(*R,S*)-α-Methylphenethylamine.

$C_9H_{13}N$=135.2

CAS — 300-62-9 (amfetamine); 139-10-6 (amfetamine phosphate).

ATC — N06BA01.

ATC Vet — QN06BA01.

UNII — CK833KGX7E.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of amfetamine:

A; Affe; Aimies; Amf; Amfa; Amfis; Amp; Amph; Amphes; Amphet; Anfes; Anfetas; A-Plus; Back dex; Bam; Bambinos; Bass; B-bombs; Beans; Bennie; Bennies; Benny and the Jets; Bens; Benz; Benzedrine; Benzidrine; Berick; Billy; Billy Whizz; Biphetamine; Bippies; Black beauties; Black birds; Black bombers; Black cadillacs; Black hollies; Black mollies; Black and white; Blacks; Blue belly; Blue boy; Blue mollies; Bolt; Bombido; Bombita; Bombitas; Boostant; Bottles; Brain pills; Brain ticklers; Brownies; Browns; Bumblebees; Candy; Cartwheels; Chalk; Chicken powder; Chocolate; Christina; Christmas tree; Clear rocks; Coast to coast; Coasts to coasts; Colorado Rockies; Co-pilot; Crank; Crisscross; Croke; Cross tops; Cross-tops; Crossroads; Crystal; Crystal methadrine; Debs; Dex; Dexadrine; Dexedrine; Dexies; Diamonds; Diet Coke; Diet pills; Dolls; Dominoes; Double cross; Drivers; Eve; Eye opener; Eye openers; Fast; Fast balls; Fastin; Fives; Fly Boys; Football; Footballs; Forwards; French blue; French blues; Gaggler; Gas; GB's; Glass; Go; Go-ee; Goey; Greenies; Halloo-Wach; Hanyak; Head drugs; Head fruit; Hearts; Hi speeds; High speed; Höökipulveri; Horse heads; Hydro; Iboga; Ice; Inbetweens; Jam; Jam cecil; Jelly baby; Jelly bean; Jelly beans; Johnny go fast; Jolly bean; Jolly beans; Jugs; Khat; L. A.; La Glass; LA ice; LA turnarounds; Leapers; Lid poppers; Lid proppers; Lightning; Lip poppers; Little bomb; Little Guys; Louee; Louie; Macka; 357 Magnum; 357 Magnums; MAO; Marathons; Marching Powder; Meth; Methedrine; Methlies Quik; Mini beans; Mini berries; Minibennie; Mollies; Monoamine oxidase; Morning shoot; Morning shot; Nineteen; Nitro; Nugget; Oranges; Peaches; Pep; Pep pills; Pervitiini; Pink hearts; Pixies; Pollutants; Powder; Proszek; Pulver; Purple hearts; Rhythm; Rippers; Road dope; Rosa; Roses; Shight; Shighty; Slammin'; Slamming; Slipvins; Snap; Snow; Snow pallets; Sparkle plenty; Sparklers; Speckled birds; Speckled eggs; Speed; Speed ball; Speed balls; Speed cristal; Speedball; Spivias; Splash; Splivins; Sprinkles; Star; Strawberry shortcake; Sulph; Sulphate; Sulphates; Sweeties; Sweets; Tens; The C; Thrusters; Toffee whizz; Topette; TR-6s; Truck drivers; Turkey; Turnabout; Turnarounds; Tweak; Tweek; Up; Uppers; Uppies; U.S.P.; Wake amine; Wake ups; Water; West Coast turnarounds; Wheels; Whiffle dust; Whiffledust; White; White Cross; White Crunch; Whites; Whiz; Whizz; Wire; X; X-mas tree; Zoomers.

Amfetamine Sulfate *(BANM, rINNM)* ⊗

Amfetamiinisulfaatti; Amfétamine, sulfate d'; Amfetamine Sulphate; Amfetamini Sulfas; Amfetamino sulfatas; Amfetaminsulfat; Amfetamin-sulfát; Amfetamin-szulfát; Amphetamine Sulfate; Amphetamine Sulphate; Amphetamini Sulfas; Anfetamina, sulfato de; Phenaminum; Phenylaminopropanum Racemicum Sulfuricum; Sulfato de anfetamina; Амфетамина Сульфат.

(*R,S*)-α-Methylphenethylamine sulphate.

$(C_9H_{13}N)_2H_2SO_4$=368.5

CAS — 60-13-9.

ATC — N06BA01.

ATC Vet — QN06BA01.

UNII — 6DPV8NK46S.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Amfetamine Sulfate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Amphetamine Sulfate). A white odourless crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. Its solutions are acid to litmus, having a pH of 5 to 6.

Incompatibility. Amfetamine sulfate is incompatible with alkalis and calcium salts.

Profile

Amfetamine is an indirect-acting sympathomimetic with actions and uses similar to those of its isomer dexamfetamine (p. 2319.1). Amfetamine sulfate and amfetamine aspartate are usually given as oral combination preparations also containing dexamfetamine salts. The laevo-isomer, levamfetamine was formerly used. Amfetamine, being volatile, was formerly given by inhalation; it has also been given orally.

Breast feeding. Amfetamine is concentrated in breast milk and the American Academy of Pediatrics has stated[1] that it has caused irritability and poor sleep pattern in breast-fed infants when used as a drug of abuse by mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Adderall; ***USA***: Adderall; MAS-ER.

Pharmacopoeial Preparations

USP 36: Amphetamine Sulfate Tablets.

Ammonium Camphocarbonate

Canfocarbonato de amonio.

$C_{11}H_{19}NO_3$=213.3

CAS — 5972-75-8.

Profile

Ammonium camphocarbonate has been used in preparations for the treatment of respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Pulmofasa.

Armodafinil *(USAN, rINN)* ⊗

Armodafinilo; Armodafinilum; CEP-10953; CRL-40982; Армодафинил.

2-[(*R*)-(Diphenylmethyl)sulfinyl]acetamide.

$C_{15}H_{15}NO_2S$=273.4

CAS — 112111-43-0.

UNII — V63XWA605I.

Profile

Armodafinil is the *R*-enantiomer of modafinil (p. 2327.2) and is used similarly in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p. 2314.3), obstructive sleep apnoea, and shift-work sleep disorder. In the treatment of the narcoleptic syndrome or obstructive sleep apnoea, armodafinil is given orally in a single dose of 150 or 250 mg in the morning. For the management of shift-work sleep disorder, the daily dose is 150 mg taken as a single dose 1 hour before starting work. Reduced doses are recommended in the elderly and in patients with severe hepatic impairment.

References.

1. Harsh JR, *et al*. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin* 2006; **22:** 761–74.
2. Roth T, *et al*. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther* 2006; **28:** 689–706.
3. Hirshkowitz M, *et al*. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med* 2007; **101:** 616–27.
4. Czeisler CA, *et al*. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc* 2009; **84:** 958–72.
5. Krystal AD, *et al*. A double-blind, placebo-controlled study of armodafinil for excessive sleepiness in patients with treated obstructive sleep apnea and comorbid depression. *J Clin Psychiatry* 2010; **71:** 32–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Nuvigil.

Atomoxetine Hydrochloride

(BANM, USAN, rINNM)

Atomoxétine, Chlorhydrate d'; Atomoxetini Hydrochloridum; Hidrocloruro de tomoxetina; LY-135252; LY-139602; LY-139603; Tomoxetina, hidrocloruro de; Tomoxetine Hydrochloride; Томоксетина Гидрохлорид.

(-)-*N*-Methyl-γ-(2-methylphenoxy)-benzenepropanamine hydrochloride.

$C_{17}H_{21}NO,HCl$=291.8

CAS — 83015-26-3 (atomoxetine); 82248-59-7 (atomoxetine hydrochloride).

ATC — N06BA09.

ATC Vet — QN06BA09.

UNII — 57WVB6I2W0.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Atomoxetine Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in anhydrous alcohol; practically insoluble in heptane. It shows polymorphism.

USP 36: (Atomoxetine Hydrochloride). A white to practically white solid. Sparingly soluble in water.

Uses and Administration

Atomoxetine hydrochloride is a selective noradrenaline reuptake inhibitor used in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1) in adults and children aged 6 years and over. It is given orally as the hydrochloride although doses are expressed in terms of the base; atomoxetine hydrochloride 11.4 mg is equivalent to about 10 mg of atomoxetine.

- In *children and adolescents weighing 70 kg and under*, the initial dose is the equivalent of about 500 micrograms/kg daily; this may be gradually increased to about 1.2 mg/kg daily. Licensed product information states that the total daily dose in this group should not exceed 1.4 mg/kg or 100 mg, whichever is less; however, the *BNFC* suggests that up to 1.8 mg/kg daily (maximum of 120 mg daily) may be given under specialist supervision
- In *adults and adolescents and children weighing over 70 kg*, the initial dose is the equivalent of 40 mg daily, gradually increased to 80 mg daily. Licensed product information permits a further increase, after 2 to 4 weeks, to a maximum of 100 mg daily; however, the *BNFC* suggests

that up to 120 mg daily may be given under specialist supervision

Doses may be given as either a single dose in the morning or as equally divided doses in the morning and late afternoon or early evening. US licensed product information recommends that an increase in dose can be made after a minimum of 3 days although, in the UK, at least 7 days of treatment is suggested before any increases.

In patients taking atomoxetine for extended periods, the need for continued treatment beyond 1 year should be assessed periodically.

Reduced doses are recommended in patients with hepatic impairment, see below. A lower initial dose and slower titration of atomoxetine may be required in patients who are poor CYP2D6 metabolisers (see Adverse Effects and Precautions, and Pharmacokinetics, below) and in those also taking CYP2D6 inhibitors (see Interactions, below). US licensed product information recommends increasing to the usual target dose only if symptoms fail to improve after 4 weeks and the initial dose is well tolerated in these patients.

References.

1. Michelson D, *et al.* Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Abstract: *Pediatrics* 2001; **108:** 1197. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/5/e83 (accessed 15/04/04)
2. Simpson D, Plosker GL. Atomoxetine: a review of its use in adults with attention deficit hyperactivity disorder. *Drugs* 2004; **64:** 205–22.
3. Kelsey DK, *et al.* Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. Abstract: *Pediatrics* 2004; **114:** 240. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/1/e1 (accessed 14/05/08)
4. Corman SL, *et al.* Atomoxetine: the first nonstimulant for the management of attention-deficit/hyperactivity disorder. *Am J Health-Syst Pharm* 2004; **61:** 2391–9.
5. Gibson AP, *et al.* Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; **40:** 1134–41.
6. Wilens TE, *et al.* Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *J Pediatr* 2006; **149:** 112–19.
7. Newcorn JH, *et al.* Low-dose atomoxetine for maintenance treatment of attention-deficit/hyperactivity disorder. Abstract: *Pediatrics* 2006; **118:** 2527. Full version: http://pediatrics.aappublications.org/cgi/reprint/118/6/e1701 (accessed 14/05/08)
8. Bangs ME, *et al.* Atomoxetine ADHD/ODD Study Group. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder and oppositional defiant disorder. Abstract: *Pediatrics* 2008; **121:** 383–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/121/2/e314 (accessed 22/01/10)

Administration in children. For doses of atomoxetine in children and adolescents, see Uses and Administration, p. 2316.3.

Administration in hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh class B) the dose of atomoxetine (see Uses and Administration, p. 2316.3) should be reduced by 50%, while in those with severe impairment (Child-Pugh class C) it should be reduced by 75%.

References.

1. Chalon SA, *et al.* Effect of hepatic impairment on the pharmacokinetics of atomoxetine and its metabolites. *Clin Pharmacol Ther* 2003; **73:** 178–91.

Adverse Effects and Precautions

Adverse effects of atomoxetine include dyspepsia and other gastrointestinal disturbances, anorexia and weight loss, fatigue, sleep disturbances, dizziness, cough, sinusitis or rhinorrhoea, urinary hesitancy or retention, decreased libido and sexual dysfunction, priapism, rashes, increased sweating, and hot flushes. Psychotic or manic symptoms (such as hallucinations, delusional thinking, mania, or agitation) and aggressive behaviour, hostility, or emotional lability have occurred; suicidal behaviour has also been reported (see Effects on Mental State, below). Hypersensitivity reactions have occurred rarely. There have also been rare reports of severe hepatotoxicity (see Effects on the Liver, below).

There may be increases in blood pressure and heart rate, and atomoxetine should be given with caution to patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease (see also Effects on the Cardiovascular System, under Dexamfetamine Sulfate, p. 2319.3). Orthostatic hypotension and syncope have also been reported. QT prolongation has been associated with atomoxetine therapy and it should be used with caution in patients with known or suspected prolonged QT interval. Use with drugs liable to inhibit the cytochrome P450 isoenzyme CYP2D6, other drugs that may prolong the QT interval, or drugs likely to cause electrolyte imbalance may also increase the risk (see Interactions, below). Sudden death, stroke, and myocardial infarction have also been reported in patients given atomoxetine. All patients should be assessed for cardiovascular disease before treatment is started. Atomoxetine should generally not be used in those with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems.

Seizures are a potential risk with atomoxetine therapy and it should be used with caution in patients with a history of seizures; treatment may need to be stopped in those who develop seizures or have an increase in seizure frequency.

Atomoxetine is contra-indicated in patients with angle-closure glaucoma as it may increase the risk of mydriasis.

The weight and height gain of children receiving atomoxetine has been reported to lag behind that of the predicted norm for about the first 9 to 12 months of treatment and generally normalises within about the first 3 years of treatment; licensed product information recommends that growth be monitored and consideration given to dose reduction or interrupting treatment in patients who are not growing or gaining weight satisfactorily.

Poor metabolisers of atomoxetine (see Pharmacokinetics, below) may have an increased risk of adverse reactions.

Effects on the liver. In December 2004, the US manufacturer stated that 2 cases of severe hepatotoxicity had been reported with atomoxetine treatment since the drug was launched in 2002.[1] In both cases the patients recovered; however, because of the risk of acute hepatic failure resulting in death or the need for transplantation, it was recommended that atomoxetine should be permanently discontinued in patients with jaundice or markedly increased liver enzyme values.

Similar advice was also issued in the UK by the CSM.[2] Up to February 2005, the CSM were aware of 3 reports of hepatic disorders (one each of hepatitis, jaundice, and increased bilirubin) with atomoxetine treatment in the UK; a total of 41 reports of hepatic disorders had been received worldwide.

A further report by the US manufacturer covered clinical study data in 7961 patients as well as 4 years postmarketing experience (since 2002) in about 4.3 million patients. Of the 7961 patients who received atomoxetine in studies, 41 had hepatobiliary events; most were mild increases in ALT and AST levels. None progressed to liver failure. Postmarketing experience indicated that there were only 3 spontaneously reported cases of reversible drug-induced liver injury probably related to atomoxetine use.[3]

1. Eisenberg P. Lilly. Safety data on Strattera (atomoxetine hydrochloride)–hepatic effects (issued 21st December, 2004).
2. MHRA. Strattera (atomoxetine)–risk of hepatic disorders. Message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 2nd February 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019459&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
3. Bangs ME, *et al.* Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. *Drug Safety* 2008; **31:** 345–54.

Effects on mental state. In an observational study of 153 children, irritability, aggression, mania, or hypomania were associated with atomoxetine in 51 cases. Of these, 31 had a family history, and 41 a personal history, of mood disorders; 27 had both and 6 had neither. The authors therefore recommended that all patients receiving atomoxetine should be monitored closely.[1]

Subsequently, the FDA[2] requested the US manufacturer (*Eli Lilly*) to conduct an analysis of adverse events from 12 clinical studies involving 2208 patients. The risk of suicidal behaviour during the first few months of treatment was found to be 0.4% in children receiving atomoxetine compared with no risk in those on placebo; no suicides were reported although there was one unsuccessful suicide attempt in the atomoxetine-treated group. This finding resulted in the inclusion of a warning in US labelling about the increased risk of suicidal ideation in children and adolescents being treated with atomoxetine; it was also recommended that changes in behaviour must be closely monitored, particularly during the initial months of therapy or when the dose is changed. Similar warnings were issued by the UK CSM[3] and regulatory authorities in other countries.[4]

In light of these concerns a review of available data in Europe was conducted in 2006; it was considered that the overall risk to benefit ratio of atomoxetine in children remained favourable.[5]

An update published by Health Canada[6] noted 189 reports of adverse reactions associated with atomoxetine by December 2007; of these, 55 were reported as suicide attempts of which one was successful. A reminder to monitor moods, behaviours, thoughts, and feelings during treatment was given.

1. Henderson TA, Hartman K. Aggression, mania, and hypomania induction associated with atomoxetine. *Pediatrics* 2004; **114:** 895–6.
2. FDA. FDA alert for healthcare professionals: atomoxetine (marketed as Strattera)–suicidal thinking in children and adolescents (issued 29th September, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124391.htm (accessed 22/01/10)
3. MHRA. Strattera (atomoxetine): risk of suicidal thoughts/behaviour. Message from Professor G Duff, Chairman of Committee on Safety of Medicine (issued 29th September, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2018039.pdf (accessed 11/08/08)
4. Lilly, Canada. WARNING for atomoxetine regarding the potential for behavioural and emotional changes, including risk of self-harm (issued 28th September, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/strattera_hpc-cps-eng.pdf (accessed 08/08/08)
5. MHRA. Updated warnings on the attention deficit hyperactivity disorder drug Strattera: information for healthcare professionals. Message from Professor G Duff, Chairman of Commission on Human Medicines (issued 16th February, 2006). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2018039.pdf (accessed 22/01/10)
6. Health Canada. Atomoxetine and suicidal behaviour: update. *Can Adverse React News* 2008; **18** (3): 2–3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v18n3-eng.php (accessed 22/01/10)

Handling. Atomoxetine is an ocular irritant and atomoxetine capsules should not therefore be opened. If the capsule contents do accidentally come into contact with the eye, the affected eye must be flushed immediately with water; hands and other potentially contaminated surfaces should be washed as soon as possible.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atomoxetine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Tourette's syndrome. There is, at best, weak evidence that central stimulants such as dexamfetamine may cause or exacerbate tics or Tourette's syndrome (see under Dexamfetamine, p. 2320.2, for further details). Data for the selective noradrenaline reuptake inhibitor atomoxetine, suggests that it does not worsen tics, and may be used in patients with attention deficit hyperactivity disorder (ADHD) and comorbid motor tics or Tourette's disorder.[1] Nonetheless, there have been individual cases reported.

Health Canada[2] had received a report of tics and another of exacerbation of tics suspected of being associated with atomoxetine. In the first case, a 7-year-old girl receiving atomoxetine for ADHD had new-onset motor tics after the dose was increased to 40 mg daily; the tics persisted, but were less severe, when the dose was reduced to 25 mg daily. After risperidone was added to the regimen, the tics disappeared. The second case described exacerbation of vocal tics in an 11-year-old boy given atomoxetine 60 mg daily for ADHD; he also had Tourette's syndrome. The dose was reduced to 40 mg daily, but he continued to have tics.

1. Allen AJ, *et al.* Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology* 2005; **65:** 1941–9.
2. Health Canada. Atomoxetine (Strattera): suspected association with tics. *Can Adverse React News* 2006; **16** (4): 3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n4-eng.php (accessed 22/01/10)

Interactions

Atomoxetine should not be taken with an MAOI, or within 2 weeks of stopping MAOI therapy, nor should MAOI therapy be started for 2 weeks after stopping atomoxetine. Care should be taken if given with other drugs that raise blood pressure, because of a possible additive affect; the actions of salbutamol on the cardiovascular system may be potentiated. In addition, there is a risk of cardiac events in patients receiving atomoxetine who are also taking drugs that affect cardiac conduction or electrolyte balance, or that inhibit the cytochrome P450 isoenzyme CYP2D6 (see below).

Seizures have been noted with atomoxetine and caution is advised when used with drugs known to lower the seizure threshold.

Atomoxetine is metabolised via the isoenzyme CYP2D6 and inhibitors of this enzyme such as paroxetine, fluoxetine, and quinidine may increase plasma concentrations of atomoxetine in extensive, but not poor, metabolisers.

Antidepressants. *Paroxetine* was found to inhibit atomoxetine's metabolism by cytochrome P450 isoenzyme CYP2D6 in extensive metabolisers resulting in pharmacokinetics for atomoxetine similar to those in poor metabolisers.[1]

1. Belle DJ, *et al.* Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. *J Clin Pharmacol* 2002; **42:** 1219–27.

Pharmacokinetics

Atomoxetine is well absorbed after oral doses and peak plasma concentrations occur 1 to 2 hours later. Bioavailability is about 94% in poor metabolisers but only 63% in extensive metabolisers. Atomoxetine is about 98% bound to plasma proteins. Atomoxetine is metabolised mainly via the cytochrome P450 isoenzyme CYP2D6 to the active metabolite 4-hydroxyatomoxetine; a minority of the population are poor metabolisers and have plasma concentrations about 5 times those in extensive metabolisers. It is excreted in the urine as glucuronide metabolites and a small amount of unchanged drug; less than 17% of a dose appears in the faeces. The half-life of atomoxetine is

about 5.2 hours in extensive and 21.6 hours in poor metabolisers.

References.
1. Sauer J-M, *et al*. Clinical pharmacokinetics of atomoxetine. *Clin Pharmacokinet* 2005; **44:** 571–90.
2. Cui YM, *et al*. Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele. *Br J Clin Pharmacol* 2007; **64:** 445–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Recit; Strattera; ***Austral.***: Strattera; ***Austria***: Strattera; ***Belg.***: Strattera; ***Canad.***: Strattera; ***Chile***: Abretia; Deaten; Strattera; ***China***: Strattera (择思达); ***Cz.***: Strattera; ***Denm.***: Strattera; ***Fin.***: Strattera; ***Fr.***: Strattera†; ***Ger.***: Strattera; ***Gr.***: Strattera; ***Hong Kong***: Strattera; ***Hung.***: Strattera; ***India***: Attentrol; Axepta; ***Irl.***: Strattera; ***Ital.***: Strattera; ***Jpn***: Strattera; ***Malaysia***: Strattera; ***Mex.***: Strattera; ***Neth.***: Strattera; ***Norw.***: Strattera; ***NZ***: Strattera; ***Philipp.***: Strattera; ***Pol.***: Strattera; ***Port.***: Strattera; ***Rus.***: Strattera (Страттера); ***S.Afr.***: Strattera; ***Singapore***: Strattera; ***Spain***: Strattera; ***Swed.***: Strattera; ***Switz.***: Strattera; ***Thai.***: Strattera; ***Turk.***: Strattera; ***UK***: Strattera; ***Ukr.***: Strattera (Страттера); ***USA***: Strattera.

Pharmacopoeial Preparations
USP 36: Atomoxetine Capsules.

Bemegride *(BAN, rINN)*

Bemegrida; Bémégride; Bemegridum; Methetharimide; Бемегрид.
3-Ethyl-3-methylglutarimide; 4-Ethyl-4-methylpiperidine-2,6-dione.
$C_8H_{13}NO_2$=155.2
CAS — 64-65-3.
ATC — R07AB05.
ATC Vet — QR07AB05.
UNII — 57DQA39DO2.

Profile

Bemegride has properties similar to those of doxapram (p. 2321.2). It has been given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Megibal.

Benzfetamine Hydrochloride *(BANM, rINNM)* ⊗

Benzfetamina, hidrocloruro de; Benzfétamine, Chlorhydrate de; Benzfetamini Hydrochloridum; Benzphetamine Hydrochloride; Hidrocloruro de benzfetamina; Бензфетамина Гидрохлорид.
(+)-*N*-Benzyl-*N*,α-dimethylphenethylamine hydrochloride.
$C_{17}H_{21}N,HCl$=275.8
CAS — 156-08-1 (benzfetamine); 5411-22-3 (benzfetamine hydrochloride).
UNII — 43DWT87QT7.

Profile

Benzfetamine hydrochloride is a central stimulant and sympathomimetic with properties similar to those of dexamfetamine (p. 2319.1). It has been used as an anorectic in the treatment of obesity (p. 2315.1), although amfetamines are no longer recommended for this indication. The usual initial oral dose is 25 to 50 mg given once daily, subsequently adjusted according to response, to a dose of 25 to 50 mg up to three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Didrex; Regimex.

Benzylpiperazine ⊗

1-Benzylpiperazine; *N*-Benzylpiperazine; Бензилпиперазин.
1-(Phenylmethyl)piperazine.
$C_{11}H_{16}N_2$=176.3
CAS — 2759-28-6.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of benzylpiperazine:

A2; Blast; BZP; Charge; Charlie; Cosmic Kelly; ESP; Euphoria; Exodus; Frenzy; Herbal ecstasy; Legal E; Legal X; Nemesis; Pep; Pep Love; Pep Stoned; Pep Twisted; Rapture; Red Eye; The Good Stuff.

Profile

Benzylpiperazine is reported to produce CNS stimulant effects similar to those of the amfetamines (see Dexamfetamine, p. 2319.1) and is subject to abuse.

Other piperazine derivatives subject to abuse include:
- 1-(3,4-methylenedioxybenzyl)piperazine (MDBP)
- 1-(3-trifluoromethylphenyl)piperazine (TFMPP)
- 1-(3-chlorophenyl)piperazine (mCPP)—NOTE: Do not confuse with MCPP, which has been used as an abbreviation for the pesticide Mecoprop
- 1-(4-methoxyphenyl)piperazine (MeOPP)

References.
1. Gee P, *et al*. Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand. *N Z Med J* 2005; **118:** U1784.
2. Staack RF. Piperazine designer drugs of abuse. *Lancet* 2007; **369:** 1411–13.
3. Johnstone AC, *et al*. Benzylpiperazine: a drug of abuse? *J Psychopharmacol* 2007; **21:** 888–94.
4. Wood DM, *et al*. Collapse, reported seizure—and an unexpected pill. *Lancet* 2007; **369:** 1490.

Bromantan ⊗

N-(2-Adamantyl)-4-bromoaniline; Bromantane.
N-(4-Bromophenyl)tricyclo[3.3.1.1^{3,7}]decan-2-amine.
$C_{16}H_{20}BrN$=306.2
CAS — 87913-26-6.

Profile

Bromantan is reported to be a stimulant that may be subject to abuse in sport. It is also reported to have immunostimulant properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Ladasten (Ладастен).

Catha ⊗

Abyssinian, African, or Arabian Tea; Kat; Kath; Khat; Miraa; Qat; Somali Tea; Té abisinio; Té de Arabia; Кат.
*UNII — 57O5451KGF (*Catha edulis*); E14P64525U (*Catha edulis *leaf).*

Description. Catha consists of the leaves of *Catha edulis* (Celastraceae), and contains cathine, cathinone, celastrin, choline, tannins, and inorganic salts.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of catha:

Cat; Chat; Feline; Kat; Miraa; Pootie; Qat; Quaadka.

Cathine *(pINN)* ⊗

Cathinum; Catina; (+)-Norpseudoephedrine; Катин.
threo-2-Amino-1-phenylpropan-1-ol.
$C_9H_{13}NO$=151.2
CAS — 492-39-7; 36393-56-3.
ATC — A08AA07.
ATC Vet — QA08AA07.
UNII — E1L4ZW2F8O.

Cathinone *(pINN)* ⊗

Cathinonum; Catinona; Катинон.
(*S*)-2-Aminopropiophenone.
$C_9H_{11}NO$=149.2
CAS — 71031-15-7.
UNII — 540El4406J.

Profile

Catha, the leaves of *Catha edulis* (Celastraceae), is used for its stimulant properties among some cultures of Africa and the Middle East, usually by chewing the leaves. Its effects are reported to resemble those of the amfetamines (see Dexamfetamine Sulfate, p. 2319.1), and are thought to be largely due to the content of cathinone. Dependence, cardiovascular complications, hepatotoxicity, and psychotic reactions have been reported. Derivatives of cathinone are also subject to abuse for their stimulant effects. Cathine, another constituent of catha, has been used as the hydrochloride as an anorectic.

References to the pharmacology and pharmacokinetics of catha and its constituents[1-8] and reports of adverse effects.[9-21]

1. Brenneisen R, *et al*. Metabolism of cathinone to (-)-norephedrine and (-)-norpseudoephedrine. *J Pharm Pharmacol* 1986; **38:** 298–300.
2. Brenneisen R, *et al*. Amphetamine-like effects in humans of the khat alkaloid cathinone. *Br J Clin Pharmacol* 1990; **30:** 825–8.
3. Kalix P. Pharmacological properties of the stimulant khat. *Pharmacol Ther* 1990; **48:** 397–416.
4. Kalix P. Chewing khat, an old drug habit that is new in Europe. *Int J Risk Safety Med* 1992; **3:** 143–56.
5. Kalix P. Cathinone, a natural amphetamine. *Pharmacol Toxicol* 1992; **70:** 77–86.
6. Widler P, *et al*. Pharmacodynamics and pharmacokinetics of khat: a controlled study. *Clin Pharmacol Ther* 1994; **55:** 556–62.
7. Kalix P. Catha edulis, a plant that has amphetamine effects. *Pharm World Sci* 1996; **18:** 69–73.
8. Toennes SW, *et al*. Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. *Br J Clin Pharmacol* 2003; **56:** 125–30.
9. Rumpf KW, *et al*. Rhabdomyolysis after ingestion of an appetite suppressant. *JAMA* 1983; **250:** 2112.
10. Gough SP, Cookson IB. Khat-induced schizophreniform psychosis in UK. *Lancet* 1984; **i:** 455.
11. Roper JP. The presumed neurotoxic effects of Catha edulis—an exotic plant now available in the United Kingdom. *Br J Ophthalmol* 1986; **70:** 779–81.
12. Zureikat N, *et al*. Chewing khat slows the orocaecal transit time. *Gut* 1992; **33** (suppl): S23.
13. Yousef G, *et al*. Khat chewing as a cause of psychosis. *Br J Hosp Med* 1995; **54:** 322–6.
14. Al-Motarreb A, *et al*. Khat chewing and acute myocardial infarction. *Heart* 2002; **87:** 279–280.
15. Al-Motarreb A, *et al*. Khat chewing is a risk factor for acute myocardial infarction: a case-control study. *Br J Clin Pharmacol* 2005; **59:** 574–81.
16. Chapman MH, *et al*. Severe, acute liver injury and khat leaves. *N Engl J Med* 2010; **362:** 1642–4.
17. Al-Motarreb A, *et al*. Khat chewing, cardiovascular diseases and other internal medical problems: the current situation and directions for future research. *J Ethnopharmacol* 2010; **132:** 540–8.
18. Ali WM, *et al*. Association of khat chewing with increased risk of stroke and death in patients presenting with acute coronary syndrome. *Mayo Clin Proc* 2010; **85:** 974–80.
19. Colzato LS, *et al*. Khat use is associated with impaired working memory and cognitive flexibility. *PLoS One* 2011; **6:** e20602.
20. Roelandt P, *et al*. Acute liver failure secondary to khat (Catha edulis)-induced necrotic hepatitis requiring liver transplantation: case report. *Transplant Proc* 2011; **43:** 3493–5.
21. Ali WM, *et al*. Acute coronary syndrome and khat herbal amphetamine use: an observational report. *Circulation* 2011; **124:** 2681–9.

Abuse. Several cathinone derivatives have been synthesised and are subject to abuse for their CNS stimulant effects;[1-4] compounds include:
- butylone
- dimethylcathinone (see Metamfepramone, p. 2557.2)
- ethcathinone
- ethylone
- 3-fluoromethcathinone
- 4-fluoromethcathinone (flephedrone)
- methcathinone (ephedrone, see p. 2325.1)
- 4-methoxymethcathinone (methedrone)
- 4-methylmethcathinone (see Mephedrone, p. 2325.2)
- 3,4-methylenedioxymethcathinone (methylone)
- 3,4-methylenedioxypyrovalerone (MDPV)
- naphyrone (see p. 2328.2)
- pyrovalerone

Synthetic cathinones are often described as bath salts or plant food in order to disguise their intended use. In large doses the adverse effects of cathinone and related compounds resemble those of the amfetamines (see Dexamfetamine, p. 2319.2).

1. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol* 2012; **8:** 33–42.
2. Mas-Morey P, *et al*. Clinical toxicology and management of intoxications with synthetic cathinones ("Bath Salts"). *J Pharm Pract* 2012; **26:** 353–7.
3. Ross EA, *et al*. Psychoactive "bath salts" intoxication with methylenedioxypyrovalerone. *Am J Med* 2012; **125:** 854–8.
4. Baumann MH, *et al*. Psychoactive "bath salts": not so soothing. *Eur J Pharmacol* 2013; **698:** 1–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Alvalin; Antiadipositum X-112 T†; ***S.Afr.***: Dietene; Eetless; Leanor; Nobese No. 1; Reli Slim; Slim 'n Trim; Thinz; ***Thai.***: Mirapront N.

Multi-ingredient Preparations. ***Mex.***: Redotex NF; Redotex.

Clobenzorex Hydrochloride *(rINNM)* ⊗

Clobenzorex, Chlorhydrate de; Clobenzorex, hidrocloruro de; Clobenzorexi Hydrochloridum; Hidrocloruro de clobenzorex; SD-271-12; Клобензорекса Гидрохлорид.
(+)-*N*-(2-Chlorobenzyl)-α-methylphenethylamine hydrochloride.
$C_{16}H_{18}ClN,HCl$=296.2
CAS — 13364-32-4 (clobenzorex); 5843-53-8 (clobenzorex hydrochloride).
ATC — A08AA08.
ATC Vet — QA08AA08.
UNII — BC6X5MB664.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of clobenzorex:

Dinintels.

Profile

Clobenzorex hydrochloride is a central stimulant and sympathomimetic with properties similar to those of dexamfetamine (p. 2319.1). It has been used as an anorectic

in the treatment of obesity but regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Asenlix; Itravil†; Obeclox; Redicres.

Deanol (BAN) ⊗

Démanol; Динол.

2-Dimethylaminoethanol.

$C_4H_{11}NO$=89.14

CAS — 108-01-0 (deanol); 3342-61-8 (deanol aceglumate); 3635-74-3 (deanol acetamidobenzoate); 968-46-7 (deanol benzilate); 71-79-4 (deanol benzilate hydrochloride); 15585-86-1 (deanol cyclohexylpropionate); 5988-51-2 (deanol tartrate).

ATC — N06BX04.

ATC Vet — QN06BX04.

UNII — 2N6K9DRA24.

NOTE. Deanol Aceglumate is *pINN*.

Profile

Deanol, a precursor of choline, may enhance central acetylcholine formation. It has been used as a central stimulant in the treatment of hyperactivity in children but its efficacy is not proven. It has been included in preparations used as tonics and for the management of impaired mental function.

It has been used as a variety of salts and esters including deanol aceglumate, deanol acetamidobenzoate, deanol bisorcate, deanol cyclohexylpropionate (cyprodenate; cyprodemanol), deanol glutamate, deanol hemisuccinate, deanol orotate, deanol pidolate, and deanol tartrate. Deanol benzilate (deanol diphenylglycolate; benzacine) has been used as the hydrochloride in antispasmodic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: DM Active; ***Fr.***: Cleregil†; ***Ger.***: Risataran†; ***Pol.***: Bimanol†; ***Rus.***: Nooclerin (Нооклерин).

Multi-ingredient Preparations. ***Arg.***: Pharmaton Complex; ***Austria***: Vita-Gerin; ***Chile***: Bedovit Pharmaton; Fortavil; Tonopron Ginseng; Ultrac E; Ultrac; ***Cz.***: Geriavit; ***Fr.***: Acti 5; Debrumyl; ***Ger.***: Vita-Gerin N; ***Gr.***: Doprene; Pharmaton Geriatric; ***Hung.***: Pharmaton Vital; ***Indon.***: Pharmaton Formula; ***Mex.***: Pharmaton Complex; ***Philipp.***: K-A Plus; Pharmaton; Rogin-E; ***Pol.***: Geriavit†; Geronpol†; ***Port.***: Actilam; Debrumyl; Forticol; Tonice; Tonice; ***Rus.***: Geriavit (Гериавит)†; Vitamax (Витамакс)†; ***S.Afr.***: Gericomplex†; ***Spain***: Anti-Anorex Triple; Denubil; Pharmaton Complex†; ***Switz.***: Pharmaton Vital Geriavit; Vita-Gerin; ***Thai.***: Pharmaton; ***Ukr.***: Energin (Энергин); ***Venez.***: Energyvit.

Dexamfetamine Sulfate (BANM, pINNM) ⊗

Deksamfetamin Sülfat; Dexamfétamine, Sulfate de; Dexamfetamine Sulphate; Dexamfetamini Sulfas; Dexamphetamine Sulphate; Dexamphetamini Sulfas; Dexanfetamina, sulfato de; Dextro Amphetamine Sulphate; Dextroamphetamine Sulfate; NSC-73713 (dexamfetamine); Sulfato de dexanfetamina; Дексамфетамина Сульфат.

(*S*)-α-Methylphenethylammonium sulphate; (+)-α-Methylphenethylamine sulphate.

$(C_9H_{13}N)_2H_2SO_4$=368.5

CAS — 51-64-9 (dexamfetamine); 7528-00-9 (dexamfetamine phosphate); 51-63-8 (dexamfetamine sulfate).

ATC — N06BA02.

ATC Vet — QN06BA02.

UNII — JJ768O327N.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dexamfetamine:

Dex; Dexies; Dexy; Oranges; Panama; Peaches.

Pharmacopoeias. In *Br.*, *Swiss*, and *US*.

BP 2014: (Dexamfetamine Sulfate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether.

USP 36: (Dextroamphetamine Sulfate). A white, odourless, crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in ether. pH of a 5% solution in water is between 5.0 and 6.0.

Uses and Administration

Dexamfetamine, the dextrorotatory isomer of amfetamine, is an indirect-acting sympathomimetic with alpha- and beta-adrenergic agonist activity. It has a marked stimulant effect on the CNS, particularly the cerebral cortex.

Dexamfetamine is used in the treatment of narcolepsy (p. 2314.3). It is also used in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1); the UK licensed product information limits its use to children with refractory hyperactivity disorders. Dexamfetamine has been given in the treatment of obesity, although amfetamines are no longer recommended for this indication. Amfetamines have also been used to overcome fatigue but, again, such use is considered undesirable. In some countries dexamfetamine has been tried for motion sickness, but safer drugs are available.

Dexamfetamine is generally used as the sulfate and is given orally.

In the treatment of **narcolepsy**, the usual initial dose is 5 to 10 mg daily in divided doses, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily. The lower initial dose of 5 mg daily is recommended for children aged 6 to 12 years and the elderly; any weekly increments should also be restricted to 5 mg in these patients.

In children with **hyperactivity** individualisation of treatment is especially important. Children aged 6 years and over usually start with a dose of 5 mg once or twice daily; the dose may be increased if necessary by 5 mg at weekly intervals to an upper limit of 20 mg daily, although older children might require up to 40 mg or more daily. Dexamfetamine is licensed for the treatment of children younger than 6 years of age in some countries, including the UK and the USA; however, many authorities consider that stimulants should not be used in young children. In the UK NICE suggests that adults may be given initial doses of 5 mg twice daily, increased according to response to a maximum of 60 mg daily.

A modified-release, combination preparation containing dexamfetamine sulfate and saccharate, with amfetamine sulfate and amfetamine aspartate monohydrate (*Adderall XR, Shire*) is also available for the treatment of attention deficit hyperactivity disorder in adults and children. In children aged 6 years and older, it is given orally as for dexamfetamine in initial doses of 10 mg of total amfetamine salts once daily increased gradually, at weekly intervals, to a maximum of 30 mg daily; in older children aged 13 to 17 years the dose may be increased to 20 mg once daily after 1 week if necessary. The initial dose in adults is 20 mg of total amfetamine salts once daily.

Administration in children. For doses of dexamfetamine in children and adolescents, see Uses and Administration, above.

Adverse Effects

The adverse effects of dexamfetamine are commonly symptoms of overstimulation of the CNS and include insomnia, night terrors, nervousness, restlessness, irritability, and euphoria that may be followed by fatigue and depression. There may be dryness of the mouth, anorexia, abdominal cramps and other gastrointestinal disturbances, headache, dizziness, tremor, sweating, tachycardia, palpitations, myocardial infarction, increased or sometimes decreased blood pressure, altered libido, and impotence. Psychotic reactions, such as hallucinations and delusional thinking, mania, seizures, and stroke have occurred, as has muscle damage with associated rhabdomyolysis and renal complications. Rarely, cardiomyopathy has occurred with chronic use. Sudden death has been reported in patients with structural cardiac abnormalities (see also Effects on the Cardiovascular System, below). In addition in children, growth retardation may occur during prolonged treatment.

In *acute overdosage*, the adverse effects are accentuated and may be accompanied by hyperpyrexia, mydriasis, hyperreflexia, chest pain, cardiac arrhythmias, confusion, panic states, aggressive behaviour, hallucinations, delirium, convulsions, respiratory depression, coma, circulatory collapse, and death. Individual patient response may vary widely and toxic manifestations may occur with quite small overdoses.

Tolerance can develop to some of dexamfetamine's central effects leading to increased doses and habituation. Abrupt cessation after prolonged treatment or abuse of amfetamines has been associated with extreme fatigue, hyperphagia, and depression. However, it is generally accepted that the amfetamines, although widely abused, are not associated with substantial physical dependence.

Abuse of amfetamines for their euphoriant effects has resulted in personality changes, compulsive and stereotyped behaviour, and may induce a toxic psychosis with auditory and visual hallucinations and paranoid delusions.

Abuse. Abuse of amfetamines can lead to toxicity affecting many organs or body systems. There have been reports of *intracerebral haemorrhage*[1-3] and of *cardiomyopathy*.[4-6] *Acute myocardial infarction* has also occurred.[7]

A syndrome characterised by *circulatory collapse, fever, leukaemoid reaction, disseminated intravascular coagulation,* and *rhabdomyolysis* with *diffuse myalgias* and *muscle tenderness* has been described[8] in 5 drug abusers who had used amfetamines or phenmetrazine intravenously. In an earlier study,[9] *necrotising angiitis* was associated with intravenous metamfetamine abuse. A 30-year-old man who had ingested 50 amfetamine sulfate tablets developed *rhabdomyolysis* and *myoglobinuric renal failure*, possibly secondary to a crush syndrome, but in the absence of prolonged coma or other major myotoxic factors.[10] However, *acute interstitial nephritis* and *acute renal failure* have followed oral amfetamine abuse without the associated factors of rhabdomyolysis, hyperpyrexia, or necrotising angiitis.[11] *Hyperglycaemia* has also been noted after the recreational abuse of dexamfetamine tablets.[12]

Chronic use may result in adverse effects such as *hallucinations*, a *delusional disorder* resembling *paranoid schizophrenia, stereotyped behaviour*, and *movement disorders*.[13] Although chronic intoxication is the most common precondition for psychosis, individual sensitivities are an important aspect of the drug reaction.

Increased serum concentrations of *levothyroxine* have been associated with heavy amfetamine abuse in 4 psychiatric patients.[14]

Abrupt cessation after prolonged treatment or abuse of amfetamines may cause *extreme fatigue, hyperphagia,* and *depression. Depressive stupor* has been reported in 3 long-term abusers of amfetamine after sudden withdrawal.[15]

1. Delaney P, Estes M. Intracranial hemorrhage with amphetamine abuse. *Neurology* 1980; **30:** 1125–8.
2. Harrington H, *et al.* Intracerebral hemorrhage and oral amphetamine. *Arch Neurol* 1983; **40:** 503–7.
3. Salanova V, Taubner R. Intracerebral haemorrhage and vasculitis secondary to amphetamine use. *Postgrad Med J* 1984; **60:** 429–30.
4. Smith HJ, *et al.* Cardiomyopathy associated with amphetamine administration. *Am Heart J* 1976; **91:** 792–7.
5. Call TD, *et al.* Acute cardiomyopathy secondary to intravenous amphetamine abuse. *Ann Intern Med* 1982; **97:** 559–60.
6. Hong R, *et al.* Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; **265:** 1152–4.
7. Waksman J, *et al.* Acute myocardial infarction associated with amphetamine use. *Mayo Clin Proc* 2001; **76:** 323–6.
8. Kendrick WC, *et al.* Rhabdomyolysis and shock after intravenous amphetamine administration. *Ann Intern Med* 1977; **86:** 381–7.
9. Citron BP, *et al.* Necrotizing angiitis associated with drug abuse. *N Engl J Med* 1970; **283:** 1003–11.
10. Scandling J, Spital A. Amphetamine-associated myoglobinuric renal failure. *South Med J* 1982; **75:** 237–40.
11. Foley RJ, *et al.* Amphetamine-induced acute renal failure. *South Med J* 1984; **77:** 258–60.
12. Henley DE, Glatthaar C. ADHD: a diabetic hyperglycemic dilemma. *Diabetes Care* 2004; **27:** 3020–1.
13. Ellinwood EH, Kilbey MM. Fundamental mechanisms underlying altered behavior following chronic administration of psychomotor stimulants. *Biol Psychiatry* 1980; **15:** 749–57.
14. Morley JE, *et al.* Amphetamine-induced hyperthyroxinemia. *Ann Intern Med* 1980; **93:** 707–9.
15. Tuma TA. Depressive stupor following amphetamine withdrawal. *Br J Hosp Med* 1993; **49:** 361–3.

Effects on the cardiovascular system. There have been very rare reports of sudden death in children and adults taking *Adderall* (*Shire*), a combination preparation of amfetamine salts. In February 2005 Health Canada[1] reported that, worldwide, there have been 20 cases of sudden death in patients taking the product at usual recommended doses; 14 of these deaths occurred in children. In some cases there was no history of cardiac disorders nor any structural abnormalities. Health Canada considered the incidence of fatal adverse effects to be greater with this combination preparation than with other stimulants and consequently withdrew the product from the Canadian market. However, a subsequent independent review committee recommended[2] that *Adderall* be allowed back onto the Canadian market although they did warn that it should not be used in patients with structural cardiac abnormalities.[3]

The committee also recommended that all stimulants used in ADHD undergo enhanced postmarketing surveillance and consequently, in May 2006, Health Canada[4] revised the labelling of amfetamine, atomoxetine, dexamfetamine, dexmethylphenidate, and methylphenidate to include warnings about their effects on the cardiovascular system. However, it was also noted that the incidence or reporting rates of serious cardiovascular adverse effects with these drugs, including fatal cases, were no greater than background rates. (Similar changes have since been made in the labelling of these products in other countries.)

In June 2009, the FDA[5] commented on a case-control study[6] that had found an association between the use of stimulants and sudden death in healthy children and adolescents. The FDA[5] was unable to conclude that the data from this study had affected the overall risk to benefit ratio of stimulants because of the study's limitations in methodology; they advised that stimulant medication should not be stopped on the basis of this study. Prescribers

were reminded to screen children for cardiovascular disease, including family history, and to consider obtaining further tests if there is an underlying risk for, or presence of, heart disease. A review of the use of stimulants for ADHD in children is ongoing.

1. Health Canada. Health Canada has suspended market authorization of ADDERALL XR® (amphetamine salts), a drug approved for Attention Deficit Hyperactivity Disorder (ADHD) in children (issued 9th February, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adderall_xr_hpc-cps-eng.pdf (accessed 11/08/08)
2. Health Canada. Report of the "Adderall XR New Drug Committee" (issued 26th August, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ndca_rep_cnma_rap_2005-08-25-eng.pdf (accessed 11/08/08)
3. Shire, Canada. ADDERALL XR and serious adverse events (issued 31st August, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adderall_xr2_hpc-cps-eng.pdf (accessed 11/08/08)
4. Health Canada. Attention deficit hyperactivity disorder (ADHD) drugs: updated and standardized labelling regarding very rare cardiac-related adverse events (issued May 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adhd-tdah_medic_hpc-cps_e.pdf (accessed 21/09/06)
5. FDA. Communication about an ongoing safety review of stimulant medications used in children with attention-deficit/hyperactivity disorder (ADHD) (issued 23rd June, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165858.htm (accessed 25/06/09)
6. Gould MS, *et al.* Sudden death and use of stimulant medications in youths. *Am J Psychiatry* 2009; **166:** 922–1001.

Effects on growth. The Pediatric Subcommittee of the FDA Psychopharmacologic Drugs Advisory Committee reviewed the growth-suppressing effects of stimulant medication (dextroamfetamine, methylphenidate, and pemoline) in hyperkinetic children.[1] There was reasonable evidence that stimulant drugs, particularly in higher doses, moderately suppressed growth in weight and might have a minor suppressing effect on growth in stature. There were indications that some growth caught up during drug holidays, and that early growth suppression was not evident in adulthood. Careful monitoring during treatment was recommended.

See also under Methylphenidate Hydrochloride, p. 2327.1.

1. Roche AF, *et al.* The effects of stimulant medication on the growth of hyperkinetic children. *Pediatrics* 1979; **63:** 847–50.

Treatment of Adverse Effects

Activated charcoal may be given to delay absorption if the patient presents within 1 hour of ingesting any amount of an amfetamine; however, the benefit of gastric decontamination is uncertain. In general the management of overdosage with amfetamines involves supportive and symptomatic therapy. Sedation is usually sufficient. Forced acid diuresis has been used to increase amfetamine excretion in severely poisoned patients but is seldom necessary; it requires close supervision and monitoring.

Precautions

Dexamfetamine is contra-indicated in patients with cardiovascular disease including moderate to severe hypertension and those with structural cardiac abnormalities, cardiomyopathy, or advanced arteriosclerosis. It should also not be used in patients with hyperthyroidism, glaucoma, hyperexcitability, or agitated states. Dexamfetamine should not be given to those with a history of drug or alcohol abuse and it should be avoided in pregnant or breast-feeding women.

It should be given with caution to patients with mild hypertension, renal impairment, bipolar disorder, or unstable personality. Behavioural disturbances and thought disorders may be exacerbated in psychotic patients.

Height and weight in children should be monitored as growth retardation may occur.

Care may be needed in certain patients predisposed to tics or Tourette's syndrome as symptoms may be provoked. Dexamfetamine is likely to reduce the convulsive threshold; caution is therefore advised in patients with epilepsy. However, it appears that in some countries amfetamines have been included in antiepileptic preparations containing phenytoin or phenobarbital in an attempt to increase their antiepileptic action. Amfetamines may impair patients' ability to drive or to operate machinery.

It was recommended that diabetic control should be monitored when central stimulants were used for the control of obesity, but dexamfetamine is no longer licensed for this indication.

Prolonged high doses may need gradual withdrawal as abrupt cessation may produce fatigue and mental depression.

Abuse. Dexamfetamine is subject to extensive abuse and for this reason its availability is severely curtailed. For adverse effects associated with abuse, see p. 2319.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexamfetamine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Pregnancy. No difference was found in the incidence of severe congenital anomalies between 1824 children of mothers prescribed amfetamines or phenmetrazine during pregnancy and 8989 children of mothers not given these drugs.[1] Though an excess of oral clefts was noted in the offspring of mothers prescribed amfetamines, there was no excess of congenital heart disease.[1] This was contrary to a previous suggestion[2] in which congenital heart disease in 184 infants had been studied and a link to maternal dexamfetamine exposure postulated. There has been a report of a bradycardia followed by death in a fetus due to maternal intravenous self-administration of 500 mg of amfetamine.[3]

1. Milkovich L, van den Berg BJ. Effects of antenatal exposure to anorectic drugs. *Am J Obstet Gynecol* 1977; **129:** 637–42.
2. Nora JJ, *et al.* Dexamphetamine: a possible environmental trigger in cardiovascular malformations. *Lancet* 1970; **i:** 1290–1.
3. Dearlove JC, Betteridge TJ. Stillbirth due to intravenous amphetamine. *BMJ* 1992; **304:** 548.

Tourette's syndrome. A review[1] of clinical reports concluded that there was virtually no evidence that central stimulants caused or provoked Tourette's syndrome and weak or inadequate evidence that clinically appropriate doses of central stimulants caused tics in previously asymptomatic patients or exacerbated pre-existing symptoms. However, the authors suggested that there was evidence that high or toxic doses might exacerbate or provoke tics in predisposed patients. Long-term methylphenidate therapy did not appear to exacerbate motor or vocal tics in a study[2] of 34 children with ADHD and chronic multiple tic disorder who were followed up for 2 years. However, the authors did point out that careful clinical monitoring is essential to eliminate the possibility of drug-induced exacerbation in individual patients. In contrast, a report[3] on 15 children who developed Tourette's syndrome while receiving stimulant medication for hyperactivity considered that such therapy was contra-indicated in children with motor tics or diagnosed Tourette's syndrome; it should also be used with caution in children with a family history of these symptoms. In addition, it suggested that the development of motor tic symptoms in any child given stimulants should be a clear indication for stopping immediately to minimise the possibility of eliciting a full-blown Tourette's syndrome.

1. Shapiro AK, Shapiro E. Do stimulants provoke, cause, or exacerbate tics and Tourette syndrome? *Compr Psychiatry* 1981; **22:** 265–73.
2. Gadow KD, *et al.* Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry* 1999; **56:** 330–6.
3. Lowe TL, *et al.* Stimulant medications precipitate Tourette's syndrome. *JAMA* 1982; **247:** 1729–31.

Interactions

Dexamfetamine is an indirect-acting sympathomimetic and may interact with many other drugs. To avoid precipitating a hypertensive crisis, it should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment. Use of beta blockers with amfetamines may produce severe hypertension. Dexamfetamine may also diminish the effects of other antihypertensives, including guanethidine and similar drugs, and concurrent use should be avoided. Patients receiving amfetamines and tricyclic antidepressants require careful monitoring as the risk of cardiovascular effects including arrhythmias may be increased. The urinary excretion of amfetamines is reduced by urinary alkalinisers, which may enhance or prolong their effects; excretion is increased by urinary acidifiers.

Amfetamines may delay the absorption of ethosuximide, phenobarbital, and phenytoin. The stimulant effects of amfetamines are inhibited by chlorpromazine, haloperidol, and lithium. Disulfiram may inhibit the metabolism and excretion of amfetamines.

Use of sympathomimetics with volatile liquid anaesthetics such as halothane is associated with an increased risk of cardiac arrhythmias.

Pharmacokinetics

Amfetamines are readily absorbed from the gastrointestinal tract and are distributed into most body tissues with high concentrations in the brain and CSF. They are partially metabolised in the liver but a considerable fraction may be excreted in the urine unchanged. Urinary elimination is pH-dependent and enhanced in acid urine. Amfetamines are distributed into breast milk.

References.

1. Steiner E, *et al.* Amphetamine secretion in breast milk. *Eur J Clin Pharmacol* 1984; **27:** 123–4.
2. de la Torre R, *et al.* Clinical pharmacokinetics of amfetamine and related substances: monitoring in conventional and non-conventional matrices. *Clin Pharmacokinet* 2004; **43:** 157–85.
3. Ilett KF, *et al.* Transfer of dexamphetamine into breast milk during treatment for attention deficit hyperactivity disorder. *Br J Clin Pharmacol* 2007; **63:** 371–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Dexedrine; ***UK***: Dexedrine†; ***USA***: Dexedrine; Dextrostat; Liquadd†; ProCentra; Zenzedi.

Multi-ingredient Preparations. ***Canad.***: Adderall; ***USA***: Adderall; MAS-ER.

Pharmacopoeial Preparations

BP 2014: Dexamfetamine Tablets.

Dexfenfluramine Hydrochloride

(BANM, USAN, rINNM) ⊗

Deksfenfluramiinihydrokloridi; Dexfenfluramina, hidrocloruro de; Dexfenfluramine, Chlorhydrate de; Dexfenfluraminhydroklorid; Dexfenfluramini Hydrochloridum; Hidrocloruro de dexfenfluramina; S-5614 (dexfenfluramine); Дексфенфлурамина Гидрохлорид.

(*S*)-*N*-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

$C_{12}H_{16}F_3N$,HCl=267.7

CAS — 3239-44-9 (dexfenfluramine); 3239-45-0 (dexfenfluramine hydrochloride).

ATC — A08AA04.

ATC Vet — QA08AA04.

UNII — PM28L0FHNP.

Profile

Dexfenfluramine is the *S*-isomer of fenfluramine (p. 2322.3). It stimulates the release of serotonin and selectively inhibits its reuptake, but differs from fenfluramine in not possessing any catecholamine agonist activity.

Dexfenfluramine was formerly given orally as the hydrochloride in the treatment of obesity but, like fenfluramine, was withdrawn worldwide after reports of valvular heart defects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Isomeran.

Dexmethylphenidate Hydrochloride

(USAN, rINNM) ⊗

d-MPH; Dexméthylphénidate, Chlorhydrate de; Dexmethylphenidati Hydrochloridum; Dexmetilfenidato, hidrocloruro de; *d-threo*-Methylphenidate; Hidrocloruro de dexmetilfenidato; *d*-Methylphenidate Hydrochloride; Дексметилфенидата Гидрохлорид.

Methyl (2*R*)-phenyl[(2*R*)-piperidin-2-yl]acetate hydrochloride.

$C_{14}H_{19}NO_2$,HCl=269.8

CAS — 40431-64-9 (dexmethylphenidate); 19262-68-1 (dexmethylphenidate hydrochloride).

ATC — N06BA11.

ATC Vet — QN06BA11.

UNII — 1678OK0E08.

NOTE. The name Attenade has been used as a trade mark for dexmethylphenidate.

Profile

Dexmethylphenidate hydrochloride is the *d-threo*-enantiomer of racemic methylphenidate hydrochloride (p. 2326.1). It is given orally as a central stimulant in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1).

Dexmethylphenidate hydrochloride is licensed for use in children aged 6 years and older. For patients new to methylphenidate the starting dose of dexmethylphenidate hydrochloride is 2.5 mg twice daily. Each dose should be given at least four hours apart. Dosage may be adjusted in 2.5 to 5 mg increments weekly to a maximum of 10 mg twice daily.

For patients currently using methylphenidate the starting dose of dexmethylphenidate hydrochloride is half the dose of the racemic substance. The maximum recommended dose is 10 mg twice daily.

A modified-release formulation is also available for once-daily dosing.

Dexmethylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond to assess the patient's condition.

References.
1. Robinson DM, Keating GM. Dexmethylphenidate extended release: in attention-deficit hyperactivity disorder. *Drugs* 2006; **66:** 661–8.
2. Coury D. Dexmethylphenidate for attention deficit hyperactivity disorder. *Expert Opin Pharmacother* 2009; **10:** 2679–85.
3. Moen MD, Keam SJ. Dexmethylphenidate extended release: a review of its use in the treatment of attention-deficit hyperactivity disorder. *CNS Drugs* 2009; **23:** 1057–83.

Administration in children. For doses of dexmethylphenidate hydrochloride in children and adolescents, see p. 2320.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Focalin; ***USA***: Focalin.

Diethylaminoethanol ⊗

Dietilaminoetanol; Диэтиламиноэтанол.
2-Diethylaminoethanol.
$C_6H_{15}NO$=117.2
CAS — 100-37-8.
UNII — S6DL4M053U.

Profile

Diethylaminoethanol is an analogue of deanol (p. 2319.1) and has been used similarly as the malate. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Durobion.

Diethylpropion Hydrochloride *(BANM)* ⊗

Amfépramone, Chlorhydrate d'; Amfepramone Hydrochloride (pINNM); Amfepramoni Hydrochloridum; Anfepramona, hidrocloruro de; Hidrocloruro de anfepramona; Hidrocloruro de dietilpropión; Амфепрамона Гидрохлорид.
N-(1-Benzoylethyl)-*NN*-diethylammonium chloride; 2-Diethylaminopropiophenone hydrochloride; (*RS*)-α-Diethylaminopropiophenone hydrochloride.
$C_{13}H_{19}NO,HCl$=241.8
CAS — 90-84-6 (diethylpropion); 134-80-5 (diethylpropion hydrochloride).
ATC — A08AA03.
ATC Vet — QA08AA03.
UNII — 19V2PL39NG.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of diethylpropion:
Blue; Blues.

Pharmacopoeias. In *US*.

USP 36: (Diethylpropion Hydrochloride). A white to off-white, fine crystalline powder. Is odourless or has a slight characteristic odour. It may contain tartaric acid as a stabilising agent. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, and 1 in 3 of chloroform; practically insoluble in ether. Protect from light.

Uses and Administration

Diethylpropion hydrochloride is a central stimulant and indirect-acting sympathomimetic with the actions of dexamfetamine (p. 2319.2). It is used as an oral anorectic in the short-term treatment of obesity (p. 2315.1), although stimulants are not generally recommended for this indication.

Doses of 25 mg three times daily 1 hour before meals or 75 mg once daily in mid-morning as a modified-release preparation, are given. To reduce the risk of dependence, diethylpropion should not be given for more than a few weeks at a time.

Regulatory authorities in the EU have called for the withdrawal of diethylpropion from the market (see under Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2. In addition gynaecomastia has been reported rarely. The incidence of central adverse effects may be lower with diethylpropion than with dexamfetamine. Diethylpropion should not be given to patients with emotional instability or a history of psychiatric illness. It should be avoided in children and the elderly. Diethylpropion hydrochloride is subject to abuse.

Interactions

Diethylpropion is an indirect-acting sympathomimetic; interactions are similar to those seen with dexamfetamine (p. 2320.2).

Pharmacokinetics

Diethylpropion is readily absorbed from the gastrointestinal tract. It is extensively metabolised in the liver and possibly the gastrointestinal tract and is excreted in the urine. Diethylpropion crosses the blood-brain barrier and the placenta. Diethylpropion and its metabolites are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tenuate†; ***Braz.***: Dualid S; Hipofagin S; Inibex S; ***Canad.***: Tenuate†; ***Chile***: Sacin†; ***Denm.***: Regenon; ***Ger.***: Regenon; Tenuate Retard; ***Gr.***: Linea; ***Hong Kong***: Atractil; Prothin; ***Mex.***: Ifa Norex†; Neobes; ***NZ***: Tenuate Dospan†; ***S.Afr.***: Tenuate Dospan; ***Thai.***: Atractil†; Dietil†; Prefamone; ***USA***: Tenuate.

Multi-ingredient Preparations. ***Arg.***: Tratobes; ***Indon.***: Apisate†.

Pharmacopoeial Preparations
USP 36: Diethylpropion Hydrochloride Tablets.

Dimefline Hydrochloride *(BANM, USAN, rINNM)*

Dimeflina, hidrocloruro de; Diméfline, Chlorhydrate de; Dimeflini Hydrochloridum; DW-62; Hidrocloruro de dimeflina; NSC-114650; Rec-7/0267; Димефлина Гидрохлорид.
8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenylchromen-4-one hydrochloride.
$C_{20}H_{21}NO_3,HCl$=359.8
CAS — 1165-48-6 (dimefline); 2740-04-7 (dimefline hydrochloride).
ATC — R07AB08.
ATC Vet — QR07AB08.
UNII — H0XB4R74ID.

Profile

Dimefline has actions similar to those of doxapram (below). The hydrochloride has been given orally or parenterally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fei Er (菲而); Lin Mai Xin (林迈欣); ***Ital.***: Remeflin.

Doxapram Hydrochloride *(BANM, USAN, rINNM)*

AHR-619; Doksapraamihydrokloridi; Doksapram Hidroklorür; Doksapramo hidrochloridas; Doxapram, Chlorhydrate de; Doxapram, hidrocloruro de; Doxaprám-hidroklorid; Doxapramhydrochlorid; Doxapram-hydrochlorid monohydrát; Doxapramhydroklorid; Doxaprami hydrochloridum; Doxaprami Hydrochloridum Monohydricum; Hidrocloruro de doxapram; Доксапрама Гидрохлорид.
1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate.
$C_{24}H_{30}N_2O_2,HCl,H_2O$=433.0
CAS — 309-29-5 (doxapram); 113-07-5 (anhydrous doxapram hydrochloride); 7081-53-0 (doxapram hydrochloride monohydrate).
ATC — R07AB01.
ATC Vet — QR07AB01.
UNII — P5RU6UOQ5Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Doxapram Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. A 0.4% solution in water has a pH of 3.5 to 5.0.

USP 36: (Doxapram Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 50 of water; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 5.0. Store in airtight containers.

Incompatibility. The commercial injection of doxapram hydrochloride is reported to be incompatible with alkaline solutions such as aminophylline, furosemide, or thiopental sodium.

Uses and Administration

Doxapram hydrochloride is a central and respiratory stimulant with a brief duration of action. It acts by stimulation of peripheral chemoreceptors and central respiratory centres; at higher doses, it stimulates other parts of the brain and spinal cord. Doxapram has a pressor action and may also increase catecholamine release.

Doxapram has limited uses in the treatment of acute respiratory failure (for example where this is superimposed on chronic obstructive pulmonary disease— below), and of postoperative respiratory depression (below).

Doxapram hydrochloride may be infused at a rate of 1.5 to 4 mg/minute in the treatment of acute respiratory failure.

For postoperative respiratory depression it has been given in a dose of 0.5 to 1.5 mg/kg by intravenous injection over a period of at least 30 seconds. This dose may be repeated at hourly intervals. It may also be given by intravenous infusion, initially at a rate of 2 to 5 mg/minute and then reduced, according to response, to 1 to 3 mg/minute; a recommended maximum total dosage is 4 mg/kg.

Doxapram hydrochloride has also been used to treat respiratory and CNS depression following drug overdose but its use for this indication is no longer recommended.

Chronic obstructive pulmonary disease. Respiratory stimulants such as doxapram have a limited and short-term role in hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (p. 1199.1). Benefit has been reported in such patients in whom doxapram was used as an alternative to intubation.[1,2] However, a systematic review suggested that despite short-term improvements in blood-gas exchange with doxapram, techniques such as non-invasive ventilation might be more effective.[3]

1. Hirshberg AJ, *et al.* Use of doxapram hydrochloride injection as an alternative to intubation to treat chronic obstructive pulmonary disease patients with hypercapnia. *Ann Emerg Med* 1994; **24:** 701–3.
2. Kerr HD. Doxapram in hypercapnic chronic obstructive pulmonary disease with respiratory failure. *J Emerg Med* 1997; **15:** 513–15.
3. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).

Neonatal apnoea. Doxapram is effective in neonatal apnoea (p. 1204.3) and may be considered as an alternative, or in addition, to xanthines in infants with apnoea that does not respond to xanthine therapy alone. However, it is less convenient to use as it must be given by continuous intravenous infusion and blood pressure must be monitored (although it has also been suggested that the oral route may be used after the initial intravenous dose). Additionally, some preparations may contain benzyl alcohol as a preservative making them unsuitable for use in neonates (see p. 1740.1). It has been used in intravenous doses of 2.5 mg/kg per hour.[1-3] Adverse CNS effects have been reported.[3] Lower doses of 0.25 or 1.5 mg/kg per hour have been shown to be effective.[4,5] However, use of low doses of 500 micrograms/kg per hour in very low birth-weight premature infants produced higher than expected plasma-doxapram concentrations and a greater increase in systolic blood pressure compared with controls.[6] A systematic review[7] concluded that the place of doxapram in the management of neonatal apnoea had not yet been properly established.

1. Sagi E, *et al.* Idiopathic apnoea of prematurity treated with doxapram and aminophylline. *Arch Dis Child* 1984; **59:** 281–3.
2. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
3. Dear PRF, Wheeler D. Doxapram and neonatal apnoea. *Arch Dis Child* 1984; **59:** 903–4.
4. Bairam A, Vert P. Low-dose doxapram for apnoea of prematurity. *Lancet* 1986; **i:** 793–4.
5. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
6. Huon C, *et al.* Low-dose doxapram for treatment of apnoea following early weaning in very low birthweight infants: a randomized, double-blind study. *Acta Paediatr* 1998; **87:** 1180–4.
7. Henderson-Smart DJ, Steer PA. Doxapram treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/10/07).

Respiratory depression. References to the use of doxapram in postoperative respiratory depression (see Respiratory Failure, under Oxygen, p. 1801.1).

1. Jansen JE, *et al.* Effect of doxapram on postoperative pulmonary complications after upper abdominal surgery in high-risk patients. *Lancet* 1990; **335:** 936–8.
2. Thangathurai D, *et al.* Doxapram for respiratory depression after epidural morphine. *Anaesthesia* 1990; **45:** 64–5.
3. Sajjad T. Comparison of the effects of doxapram or carbon dioxide on ventilatory frequency and tidal volume during induction of anaesthesia with propofol. *Br J Anaesth* 1994; **73:** 266P.
4. Alexander-Williams M, *et al.* Doxapram and the prevention of postoperative hypoxaemia. *Br J Anaesth* 1995; **75:** 233P.

Shivering. Doxapram is one of several drugs that have been used in postoperative shivering (p. 1897.2).

References.
1. Sarma V, Fry ENS. Doxapram after general anaesthesia: its role in stopping shivering during recovery. *Anaesthesia* 1991; **46:** 460–1.

2. Singh P, *et al.* Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71:** 685–8.
3. Wrench IJ, *et al.* The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; **52:** 32–6.

Adverse Effects

As with other respiratory stimulants, there is a risk that doxapram will produce adverse effects due to general stimulation of the CNS.

Doxapram may produce dyspnoea and other respiratory problems such as coughing, bronchospasm, laryngospasm, hiccup, hyperventilation, and rebound hypoventilation. Muscle involvement may range from fasciculations to spasticity. Convulsions, headache, dizziness, hyperactivity, and confusion can occur as can sweating, flushing, fever or a sensation of warmth, particularly in the genital or perineal regions. Hallucinations may occur rarely. There may be nausea, vomiting, diarrhoea, and problems with urination. Cardiovascular effects include hypertension and various arrhythmias although sudden hypotension may also occur.

Thrombophlebitis may follow extravasation of doxapram during injection.

Effects on the heart. Second-degree AV block caused by prolongation of the QT interval has been associated with doxapram use in 3 neonates.[1] Although the preparation used contained benzyl alcohol this was not considered to play a role in the adverse effect. A prospective study[2] involving 40 premature infants given doxapram for apnoea of prematurity also found QT interval lengthening at 48 and 72 hours of treatment, even when the drug plasma concentrations were kept within therapeutic ranges. In 6 infants, the QT interval lengthened to a degree considered to be life-threatening. There was also a trend towards moderate increases in blood pressure. The authors recommended heart monitoring when doxapram was given to premature infants.

1. De Villiers GS, *et al.* Second-degree atrioventricular heart block after doxapram administration. *J Pediatr* 1998; **133:** 149–50.
2. Maillard C, *et al.* QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther* 2001; **70:** 540–5.

Effects on the liver. Acute hepatic necrosis in a patient was attributed to a 24-hour infusion of doxapram.[1] Liver function tests returned to normal over 3 weeks.

1. Fancourt GJ, *et al.* Hepatic necrosis with doxapram hydrochloride. *Postgrad Med J* 1985; **61:** 833–5.

Precautions

Doxapram should not be given to patients with epilepsy or other convulsive disorders, cerebral oedema, cerebrovascular accident, head injury, acute severe asthma, physical obstruction of the airway, severe hypertension, ischaemic heart disease, hyperthyroidism, or phaeochromocytoma. Caution is also advisable if doxapram is used in patients with less severe degrees of hypertension or impaired cardiac reserve. It should be given with care to patients with significant hepatic or renal impairment.

Patients should be carefully supervised during use of doxapram; special attention should be paid to changes in blood gas measurements. Doxapram should be given with oxygen in severe irreversible airways obstruction or severely decreased lung compliance because of the increased work of breathing. A beta$_2$ agonist should also be given to patients with bronchoconstriction.

Interactions

Additive pressor effects may occur when doxapram is used with sympathomimetics or MAOIs. Cardiac arrhythmias may occur when doxapram is given with anaesthetics known to sensitise the myocardium, such as halothane, enflurane, and isoflurane; it has been recommended that doxapram should not be given for at least 10 minutes after stopping these anaesthetics. Doxapram may temporarily mask the residual effects of neuromuscular blockers. The manufacturers have reported that there may be an interaction between doxapram and aminophylline manifested by agitation and increased skeletal muscle activity.

Pharmacokinetics

After intravenous doses doxapram is rapidly distributed into the tissues. Onset of respiratory stimulation usually occurs in 20 to 40 seconds, with a peak effect achieved in 1 to 2 minutes. Duration of effect following a single dose varies from 5 to 12 minutes. Doxapram is extensively metabolised in the liver. The major route of excretion of metabolites and a small amount of unchanged drug is thought to be via bile to the faeces. It is also excreted in the urine.

Some absorption occurs when doxapram is given orally.

References.

1. Robson RH, Prescott LF. A pharmacokinetic study of doxapram in patients and volunteers. *Br J Clin Pharmacol* 1978; **7:** 81–7.
2. Baker JR, *et al.* Normal pharmacokinetics of doxapram in a patient with renal failure and hypothyroidism. *Br J Clin Pharmacol* 1981; **11:** 305–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Dopram; ***China***: Boda (波达); Dai Er Song (代尔松); Jia Su Lun (佳苏仑); Ze Lun (泽仑); ***Denm.***: Dopram; ***Fin.***: Dopram; ***Fr.***: Dopram; ***Ger.***: Dopram; ***Gr.***: Dopram; ***India***: Caropram; ***Irl.***: Dopram†; ***Neth.***: Dopram; ***Norw.***: Dopram†; ***S.Afr.***: Dopram†; ***UK***: Dopram; ***USA***: Dopram.

Pharmacopoeial Preparations
BP 2014: Doxapram Injection;
USP 36: Doxapram Hydrochloride Injection.

Etamivan *(BAN, rINN)* ⊗

Etamivaani; Etamiván; Étamivan; Etamivanum; Ethamivan (USAN); Ethamivan; NSC-406087; Vanillic Acid Diethylamide; Vanillic Diethylamide; Этамиван.

N,N-Diethylvanillamide.

$C_{12}H_{17}NO_3$=223.3

CAS — 304-84-7.

ATC — R07AB04.

ATC Vet — QR07A804.

UNII — M44O63YPV9.

Profile

Etamivan has actions similar to those of doxapram (p. 2321.2). It was formerly used as a respiratory stimulant, but the risk of toxicity associated with effective doses is now considered to be unacceptable.

Etamivan is available in oral compound preparations for cerebrovascular and circulatory disorders and hypotension, but such use is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Dosulfin Bronquial; ***Hong Kong***: Instenon; ***Rus.***: Instenon (Инстенон); ***Ukr.***: Instenon (Инстенон).

Fencamfamin Hydrochloride *(BANM, rINNM)* ⊗

Fencamfamine, Chlorhydrate de; Fencamfamini Hydrochloridum; Fencanfamina, hidrocloruro de; H-610; Hidrocloruro de fencanfamina; Фенкамфамина Гидрохлорид.

N-Ethyl-3-phenylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

$C_{15}H_{21}N$,HCl=251.8

CAS — 1209-98-9 (fencamfamin); 2240-14-4 (fencamfamin hydrochloride).

ATC — N06BA06.

ATC Vet — QN06BA06.

UNII — 0M1J60BWEX.

Profile

Fencamfamin hydrochloride has been given orally as a central stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Reactivan†.

Fenetylline Hydrochloride *(BANM, rINNM)* ⊗

Amfetyline Hydrochloride; 7-Ethyltheophylline Amphetamine Hydrochloride; Fenethylline Hydrochloride (USAN); Fenethylline Hydrochloride; Fenetilina, hidrocloruro de; Fénétylline, Chlorhydrate de; Fenetyllini Hydrochloridum; H-814; Hidrocloruro de fenetilina; R-720-11; Фенетиллина Гидрохлорид.

7-[2-(α-Methylphenethylamino)ethyl]theophylline hydrochloride.

$C_{18}H_{23}N_5O_2$,HCl=377.9

CAS — 3736-08-1 (fenetylline); 1892-80-4 (fenetylline hydrochloride).

ATC — N06BA10.

ATC Vet — QN06BA10.

UNII — YA7K8ADZ2V.

Profile

Fenetylline is a theophylline derivative of amfetamine with properties similar to those of dexamfetamine (p. 2319.1). It is given orally in the management of narcolepsy (p. 2314.3) in an initial dose of 25 mg daily, increased to usual maintenance doses of 50 to 100 mg daily in 2 divided doses; no more than 150 mg daily should be used. It has also been used in the management of hyperactivity disorders. Fenetylline is subject to abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Captagon†.

Fenfluramine Hydrochloride

(BANM, USAN, rINNM) ⊗

AHR-3002; Fenfluramina, hidrocloruro de; Fenfluramine, Chlorhydrate de; Fenfluramini Hydrochloridum; Hidrocloruro de fenfluramina; S-768; Фенфлюрамина Гидрохлорид.

N-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

$C_{12}H_{16}F_3N$,HCl=267.7

CAS — 458-24-2 (fenfluramine); 404-82-0 (fenfluramine hydrochloride).

ATC — A08AA02.

ATC Vet — QA08AA02.

UNII — 3KC089243P.

Uses and Administration

Fenfluramine is an indirect-acting sympathomimetic related to amfetamine, but at standard doses it usually depresses rather than stimulates the CNS. It appears to stimulate the release of serotonin and selectively inhibits its reuptake resulting in increased CNS serotonin concentrations. It may also increase glucose utilisation and lower blood-glucose concentrations.

Fenfluramine was formerly given orally as the hydrochloride in the treatment of obesity but was generally withdrawn worldwide after reports of valvular heart defects.

Adverse Effects and Precautions

As for Dexamfetamine, p. 2319.2, but fenfluramine usually depresses rather than stimulates the CNS. Fenfluramine has been associated with serious cardiovascular toxicity. Pulmonary hypertension led to certain precautions being imposed upon its use and subsequent reports of valvular heart defects led to its general withdrawal worldwide.

Effects on the cardiovascular system. The association of primary *pulmonary hypertension* with the use of anorectics including fenfluramine, dexfenfluramine, and phentermine is well recognised.[1-3] Both reversible and irreversible cases have been reported and in some cases it has proved fatal.[1,4-9] The condition appears to be linked to prolonged or repeated therapy.[1,10] In 1992 the UK CSM advised that treatment should not exceed 3 months[1] but later in 1997 it revised its recommendations for fenfluramine and dexfenfluramine allowing treatment for up to 12 months under certain conditions.[2] The CSM stated that treatment could be continued beyond 3 months only if there had been a satisfactory response (more than 10% weight loss) and that this loss was maintained. Patients should also be monitored for symptoms of pulmonary hypertension. For other anorectics such as phentermine the maximum duration of treatment remained 3 months.

However, shortly after this, a report was published[11] that outlined an association between the use of a fenfluramine-phentermine combination and the development of *valvular heart disease* in 24 patients. Initially, the response by the CSM was to advise against the use of combinations of anorectics[12] although subsequently fenfluramine, along with dexfenfluramine, was withdrawn from the world market after more cases became known.[13,14] By September 1997 the FDA in the USA[14] had received 144 reports of valvulopathy, including the original 24, associated with fenfluramine or dexfenfluramine, with or without phentermine; none were associated with phentermine treatment alone. As a consequence the US authorities made recommendations[14] for the screening of all patients who had previously received fenfluramine or dexfenfluramine in order to detect heart valve lesions and to provide optimal care. Further studies[15-21] have supported the association with valvular abnormalities, and suggested that prolonged exposure or exposure to high doses of dexfenfluramine or fenfluramine increased the risk; clinically important disease would probably not develop in most patients with only short-term exposure.[22]

In 2000, the European Commission called for the withdrawal of all anorectics from the European market. Those anorectics involved in the decision included clobenzorex, diethylpropion, fenproporex, mazindol, mefenorex, phendimetrazine, phenmetrazine, and phentermine. However in 2002, after an appeal by some manufacturers, the European Court ruled that the Commission did not have the authority to withdraw marketing authorisations.

Subsequently, some anorectics have been allowed back onto the European market.

1. CSM. Fenfluramine (Ponderax Pacaps), dexfenfluramine (Adifax) and pulmonary hypertension. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. CSM/MCA. Anorectic agents: risks and benefits. *Current Problems* 1997; **23:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
3. Abenhaim L, *et al*. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996; **335:** 609–16.
4. Douglas JG, *et al*. Pulmonary hypertension and fenfluramine. *BMJ* 1981; **283:** 881–3.
5. McMurray J, *et al*. Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986; **292:** 239–40.
6. Fotiadis I, *et al*. Fenfluramine-induced irreversible pulmonary hypertension. *Postgrad Med J* 1991; **67:** 776–7.
7. Atanassoff PG, *et al*. Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; **339:** 436.
8. Cacoub P, *et al*. Pulmonary hypertension and dexfenfluramine. *Eur J Clin Pharmacol* 1995; **48:** 81–3.
9. Roche N, *et al*. Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; **339:** 436–7.
10. Thomas SHL, *et al*. Appetite suppressants and primary pulmonary hypertension in the United Kingdom. *Br Heart J* 1995; **74:** 600–63.
11. Connolly HM, *et al*. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; **337:** 581–8. Correction. *ibid.*; 1783.
12. CSM/MCA. Anorectic agents and valvular heart disease. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
13. CSM/MCA. Fenfluramine and dexfenfluramine withdrawn. *Current Problems* 1997; **23:** 13–14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
14. Anonymous. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *MMWR* 1997; **46:** 1061–6.
15. Khan MA, *et al*. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998; **339:** 713–18.
16. Jick H, *et al*. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med* 1998; **339:** 719–24.
17. Weissman NJ, *et al*. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med* 1998; **339:** 725–32.
18. Gardin JM, *et al*. Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA* 2000; **283:** 1703–9.
19. Lepor NE, *et al*. Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. *Am J Cardiol* 2000; **86:** 107–10.
20. Jollis JG, *et al*. Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000; **101:** 2071–7.
21. Dahl CF, *et al*. Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. *BMC Med* 2008; **6:** 34. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-6-34.pdf (accessed 23/06/09)
22. Devereux RB. Appetite suppressants and valvular heart disease. *N Engl J Med* 1998; **339:** 765–6.

Effects on the liver. The UK MHRA had warned[1] that there had been cases of hepatotoxicity associated with adulteration of traditional Chinese slimming medicines with fenfluramine and/or nitrosofenfluramine. Nitrosofenfluramine was known to be hepatotoxic.

1. MHRA. Shubao slimming capsules containing fenfluramine and nitrosofenfluramine (issued 28th April, 2004). Available at: http://www.mhra.gov.uk/home/groups/es-herbal/documents/websiteresources/con009291.pdf (accessed 11/08/08)

Fenproporex Hydrochloride *(rINNM)* ⊗

N-2-Cyanoethylamphetamine Hydrochloride; Fenproporex, Chlorhydrate de; Fenproporex, hidrocloruro de; Fenproporexi Hydrochloridum; Hidrocloruro de fenproporex; Фенпропорекса Гидрохлорид.

(±)-3-(α-Methylphenethylamino)propionitrile hydrochloride.

$C_{12}H_{16}N_2$,HCl=224.7

CAS — 15686-61-0 (fenproporex); 18305-29-8 (fenproporex hydrochloride).

UNII — 09PE91J6V6.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of fenproporex:

Pasexes.

Profile

Fenproporex is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.1). After oral doses it is reported to be metabolised to amfetamine. Fenproporex has been given as the hydrochloride, the diphenylacetate, and as a resinate.

Fenproporex hydrochloride has been used as an anorectic in the treatment of obesity although the use of stimulants in this way is no longer recommended. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Desobesi-M; ***Chile***: Salcal; ***Mex.***: Feprorex; Ifa-Diety.

Multi-ingredient Preparations. ***Arg.***: Tratobes; ***Mex.***: Esbelcaps.

Lisdexamfetamine Mesilate *(rINNM)* ⊗

Lisdexamfetamine Dimesylate (USAN); Lisdexamfétamine, Mésilate de; Lisdexamfetamini Mesilas; Mesilato de lisdexanfetamina; NRP-104; Лисдексамфетамина Мезилат.

(2*S*)-2,6-Diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate.

$C_{15}H_{25}N_3O$,$(CH_4O_3S)_2$=455.6

CAS — 608137-32-2 (lisdexamfetamine); 608137-33-3 (lisdexamfetamine mesilate).

ATC — N06BA12.

ATC Vet — QN06BA12.

UNII — SJT761GEGS.

Profile

Lisdexamfetamine is a prodrug of dexamfetamine (p. 2319.1). It is used as a central stimulant in the treatment of attention deficit hyperactivity disorders (see Hyperactivity, p. 2314.1).

Lisdexamfetamine is given orally as the mesilate and doses are expressed in terms of this salt. For adults and children aged 6 years and over, the starting dose is 30 mg once daily in the morning, increased if necessary in increments of 10 or 20 mg daily at about weekly intervals, up to a total maximum dose of 70 mg daily. It may also be used for maintenance treatment in adults. In patients taking lisdexamfetamine for extended periods, the need for continued treatment should be assessed periodically and, where possible, interrupted occasionally.

References.

1. Blick SK, Keating GM. Lisdexamfetamine. *Paediatr Drugs* 2007; **9:** 129–35.
2. Cowles BJ. Lisdexamfetamine for treatment of attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2009; **43:** 669–76.
3. Weber J, Siddiqui MAA. Lisdexamfetamine dimesylate: in attention-deficit hyperactivity disorder in adults. *CNS Drugs* 2009; **23:** 419–25.
4. Popovic B, *et al*. Lisdexamfetamine: a prodrug for the treatment of attention-deficit/hyperactivity disorder. *Am J Health-Syst Pharm* 2009; **66:** 2005–12.
5. Findling RL, *et al*. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2011; **50:** 395–405.
6. Childress AC, Sallee FR. The use of lisdexamfetamine dimesylate for the treatment of ADHD. *Expert Rev Neurother* 2012; **12:** 13–26.

Administration in children. For doses of lisdexamfetamine mesilate in children and adolescents, see above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Venvanse; ***Canad.***: Vyvanse; ***UK***: Elvanse; ***USA***: Vyvanse.

Lobelia ⊗

Indian Tobacco; Tabaco indio; Лобелия Одутлая (*Lobelia inflata*).

ATC Herb — HR03WA5002 (Lobelia inflata: *herb*).

UNII — 1G4GK01F67.

Description. Lobelia consists of the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent.

Lobeline Hydrochloride *(BANM, rINNM)* ⊗

Alpha-lobeline Hydrochloride; Hidrocloruro de lobelina; Lobeliinihydrokloridi; Lobelina, hidrocloruro de; Lobéline, chlorhydrate de; Lobelin-hidroklorid; Lobelinhydrochlorid; Lobelin-hydrochlorid; Lobelinhydroklorid; Lobelini Hydrochloridum; Lobelino hidrocloridas; Лобелина Гидрохлорид.

2-[6-(β-Hydroxyphenethyl)-1-methyl-2-piperidyl]acetophenone hydrochloride.

$C_{22}H_{27}NO_2$,HCl=373.9

CAS — 90-69-7 (lobeline); 134-63-4 (lobeline hydrochloride).

UNII — 96J834CB88.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Lobeline Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water; freely soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.6 to 6.4. Protect from light.

Lobeline Sulfate *(BANM, rINNM)* ⊗

Lobelina, sulfato de; Lobéline, Sulfate de; Lobeline Sulphate; Lobelini Sulfas; Sulfato de lobelina; Лобелина Сульфат.

$(C_{22}H_{27}NO_2)_2H_2SO_4$=773.0

CAS — 134-64-5.

UNII — 4CJ480V2HP.

Uses and Administration

Lobelia is the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent and has peripheral and central effects similar to those of nicotine (p. 2569.3).

Lobelia has been used mainly in preparations aimed at relieving respiratory-tract disorders. Lobeline has been given orally as the hydrochloride or sulfate as a smoking deterrent. Lobelia has been used similarly given either orally or incorporated into herbal cigarettes.

Smoking cessation. Reviews of smoking cessation therapy (p. 2570.2) generally consider lobeline to have little benefit compared with placebo.[1-3]

1. Nunn-Thompson CL, Simon PA. Pharmacotherapy for smoking cessation. *Clin Pharm* 1989; **8:** 710–20.
2. Gourlay SG, McNeil JJ. Antismoking products. *Med J Aust* 1990; **153:** 699–707.
3. Stead LF, Hughes JR. Lobeline for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 16/05/05).

Adverse Effects

Adverse effects of lobelia and lobeline include nausea and vomiting, coughing, tremor, and dizziness. Symptoms of overdosage include profuse diaphoresis, paresis, tachycardia, hypothermia, hypotension, and coma; fatalities have occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Butt it Out; ***Spain***: Smokeless†; ***UK***: Lobelina.

Multi-ingredient Preparations. ***Braz.***: Bronquidex; Brontoss; MM Expectorante; ***Canad.***: Calmane; ***Chile***: Paltomiel Plus; Pulmagol; Ramistos; ***Spain***: Pazbronquial; ***UK***: Antibron; Asthma & Catarrh Relief; Balm of Gilead†; Chest Mixture; Herbelix; Horehound and Aniseed Cough Mixture; Modern Herbals Cold & Congestion; Quitacoff; Vegetable Cough Remover; ***Venez.***: Novacodin.

Homoeopathic Preparations. ***Austria***: Bronchalis-Heel; Lobelia Med Complex; Luffa compositum-Heel; Tartephedreel; ***Canad.***: Breathe More; Bronkeel†; Homeo-Form T†; Nixotinex; ***Chile***: Drosemiel; Similibus; TBR/X; ***Cz.***: Bronchalis-Heel; Luffeel; ***Fr.***: Boripharm No 12†; Boripharm No 3; Drosera Complexe No 64; Gentiana Complexe No 33†; Lobelia Complexe No 74†; Santaherba; ***Ger.***: Angioton H; Angioton S†; Antinicoticum mono†; Aralis; Asthmavowen-N†; Broncho-Injektopas; Bronchopas; Corselect N; HanoTussan; Lobelia comp; Luffeel Comp; Neolin-Entoxin; Presselin All; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Roth's RKT Tropfen; Tabarell; ***Hung.***: Bronchalis-Heel; Luffeel; ***Neth.***: Bronchalis; Lergilite; Luffeel H; ***Rus.***: Sambucus-Plus (Самбукус-Плюс); Tabacum-Plus (Табакум-Плюс); ***Switz.***: Bronchalis-Heel; Regenaplex Nr. 24b.

Lorcaserin *(rINN)*

Lorcaserina; Lorcasérine; Lorcaserinum; Лоркасерин.

(1*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

$C_{11}H_{14}ClN$=195.7

CAS — 616202-92-7.

UNII — 637E494O0Z.

Lorcaserin Hydrochloride *(USAN, rINNM)*

APD-356; Hidrocloruro de lorcaserina; Lorcasérine, Chlorhydrate de; Lorcaserini Hydrochloridum; Лоркасерин а Гидрохлорид.

$C_{11}H_{14}ClN$,HCl=232.1

CAS — 846589-98-8.

UNII — 0QJF08GDPE.

Uses and Administration

Lorcaserin, a selective serotonin agonist that acts at 5-HT_{2C} receptors, is used in the management of obesity (p. 2315.1). It may also be used in overweight patients (BMI of 27 kg/m^2 or more) if other risk factors such as hypertension, diabetes mellitus, or hyperlipidaemias are present.

Lorcaserin hydrochloride is given orally in a usual dose of 10 mg twice daily. Treatment should be stopped if the patient has not lost at least 5% of initial body-weight by week 12 of starting therapy; continued treatment is unlikely to be of benefit.

References.
1. Smith SR, *et al.* APD356-004 Study Group. Lorcaserin (APD356), a selective 5-HT_{2C} agonist, reduces body weight in obese men and women. *Obesity (Silver Spring)* 2009; **17:** 494 503.
2. Smith SR, *et al.* Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; **363:** 245–56.
3. Bai B, Wang Y. The use of lorcaserin in the management of obesity: a critical appraisal. *Drug Des Devel Ther* 2010; **5:** 1 7.
4. Redman LM, Ravussin E. Lorcaserin for the treatment of obesity. *Drugs Today* 2010; **46:** 901–10.
5. Fidler MC, *et al.* BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011; **96:** 3067 77.
6. Hurren KM, Berlie HD. Lorcaserin: an investigational serotonin 2C agonist for weight loss. *Am J Health-Syst Pharm* 2011; **68:** 2029–37.
7. O'Neil PM, *et al.* Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; **20:** 1426–36.

Adverse Effects and Precautions

The most common adverse effects reported with the use of lorcaserin in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation; hypoglycaemia, headache, back pain, cough, and fatigue occur commonly in diabetic patients. Other adverse effects in all patients include euphoria, depression and suicidal ideation, and eye disorders. Patients should be monitored for emergence or worsening of depression and/or suicidal ideation, and changes in mood or behaviour; lorcaserin should be stopped in those who develop suicidal thoughts or behaviours. Laboratory abnormalities such as lowered haemoglobin, lymphocyte, and neutrophil count, and hyperprolactinaemia have been reported; periodic monitoring of complete blood count should be considered during lorcaserin therapy. Bradycardia and symptoms suggestive of a serotonin syndrome have also occurred. Lorcaserin should be used with caution in patients with bradycardia or a history of heart block greater than first degree. Valvular heart disease has been associated with some serotonergic drugs (see Effects on the Cardiovascular System under Fenfluramine, p. 2322.3); lorcaserin may need to be stopped in those who develop signs and symptoms of cardiac valvulopathy or a new murmur. Because priapism is a potential effect of 5-HT_{2C} receptor agonism, lorcaserin should be used with caution in men with conditions predisposing to such an event.

Lorcaserin should be used with caution in patients with moderate renal or severe hepatic impairment; use is not recommended in those with severe renal impairment or end-stage renal disease.

Lorcaserin may impair cognitive function; if affected, patients should not drive or operate machinery.

Interactions

Lorcaserin should not be used with serotonergic or dopaminergic drugs that are potent 5-HT_{2B} agonists and known to increase the risk of cardiac valvulopathy, such as cabergoline. It should be used with extreme caution with other drugs known to act on the serotonergic neurotransmitter system, such as bupropion, dextromethorphan, lithium, MAOIs, SSRIs, tramadol, tricyclic antidepressants, triptans, and St John's wort, because of the increased risk of serotonin syndrome. Lorcaserin inhibits cytochrome P450 isoenzyme CYP2D6-mediated metabolism and should be used with caution with drugs that are substrates of this isoenzyme.

Weight loss may increase the risk of hypoglycaemia in patients with type 2 diabetes mellitus who are using insulin and/or oral antidiabetics; the dosage of antidiabetics may need to be decreased.

Pharmacokinetics

Lorcaserin is absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1.5 to 2 hours. It has a plasma half-life of about 11 hours and is distributed into the CSF and CNS. It is moderately (about 70%) bound to plasma proteins. Lorcaserin is extensively metabolised in the liver by multiple enzymatic pathways to principally inactive metabolites. Excretion is mainly in the urine with about 2% recovered in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Belviq.

Mazindol *(BAN, USAN, rINN)* ⊗

42-548; AN-448; Matsindoli; Mazindolum; SaH-42548; Мазиндол.

5-(4-Chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol.

$C_{16}H_{13}ClN_2O$=284.7

CAS — 22232-71-9.

ATC — A08AA05.

ATC Vet — QA08AA05.

UNII — C56709M5NH.

Pharmacopoeias. In *US.*

USP 36: (Mazindol). A white to off-white crystalline powder, having not more than a faint odour. Insoluble in water; slightly soluble in chloroform and in methyl alcohol. Store in airtight containers.

Profile

Mazindol is a central stimulant with actions similar to those of dexamfetamine (p. 2319.1), although structurally the two compounds are unrelated. It appears to inhibit reuptake of dopamine and noradrenaline. It has been used as an anorectic, given orally in the treatment of obesity, although stimulants are no longer recommended for this indication. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Mazindol has been investigated in the treatment of Duchenne muscular dystrophy.

Adverse effects. Testicular pain developed in 8 men after taking mazindol.[1]

1. McEwen J, Meyboom RHB. Testicular pain caused by mazindol. *BMJ* 1983; **287:** 1763–4.

Interactions. For a report of mazindol interacting with *lithium* to cause lithium toxicity, see Central Stimulants, p. 432.1.

Narcolepsy. Mazindol has been reported[1-4] to be beneficial in patients with narcolepsy and associated cataplexy (p. 2314.3). A wide range of doses has been used: 3 to 8 mg daily in one study,[1] 1 mg weekly to 16 mg daily in another;[3] children have been given 1 to 2 mg daily.[4]

1. Parkes JD, Schachter M. Mazindol in the treatment of narcolepsy. *Acta Neurol Scand* 1979; **60:** 250–4.
2. Shindler J, *et al.* Amphetamine, mazindol, and fencamfamin in narcolepsy. *BMJ* 1985; **290:** 1167–70.
3. Alvarez B, *et al.* Mazindol in long-term treatment of narcolepsy. *Lancet* 1991; **337:** 1293–4.
4. Allsopp MR, Zaiwalla Z. Narcolepsy. *Arch Dis Child* 1992; **67:** 302–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Afilan; Dimagrir; Fagolip Plus; Samonter†; ***Braz.***: Absten S†; Fagolipo; Moderine; ***China***: Mei Xin Da (美新达); ***Gr.***: Teronac; ***Hong Kong***: Qualizindol; ***Indon.***: Teronac; ***Jpn***: Sanorex; ***Mex.***: Diestet; Ifa Lose†; Ilezol; MZ1; Obendol; Rezin; Solucaps; ***Philipp.***: Mazzol; ***Singapore***: Teronac†.

Multi-ingredient Preparations. ***Arg.***: Maxitratobes†.

Pharmacopoeial Preparations

USP 36: Mazindol Tablets.

Metamfetamine Hydrochloride *(rINNM)* ⊗

d-Deoxyephedrine Hydrochloride; *d*-Desoxyephedrine Hydrochloride; Hidrocloruro de metanfetamina; Métamfétamine, Chlorhydrate de; Metamfetamini Hydrochloridum; Metanfetamina, hidrocloruro de; Methamphetamine Hydrochloride; Methamphetamini Hydrochloridum; Methylamphetamine Hydrochloride; Phenylmethylaminopropane Hydrochloride; Метамфетамина Гидрохлорид.

(+)-*N*,α-Dimethylphenethylamine hydrochloride.

$C_{10}H_{15}N$,HCl=185.7

CAS — 537-46-2 (metamfetamine); 51-57-0 (metamfetamine hydrochloride).

ATC — N06BA03.

ATC Vet — QN06BA03.

UNII — 997F43Z9CV.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of metamfetamine:

20/20; 222; 417; Agua; Albino Poo; Alffy; All tweakend long; Amp; Anny; Anything going on; Artie; Bache knock; Bache rock; Bag chasers; Baggers; Barney dope; Batak; Bathtub crank; Bato; Batu; Batu kilat; Batunas; Batuwhore; Beannies; Beegokes; Bianca; Bikerdope; Billy; Bitch; Biznack; Black; Black beauty; Blade; Blanco; Bling; Blizzard; Blue acid; Blue belly; Blue devils; Blue funk; Blue meth; Bomb; Bombita; Bombitas; Boo; Booger; Boorit-Cebuano; Bottles; Boo-Yah!; Brian Ed; Brown; Buff stick; Bugger sugar; Buggs; Bump; Bumps; Buzzard dust; Caca; Cale Gerst; California white cross; Candy; Cankinstien; Cartwheels; CC; ChaChaCha; Chach; Chalk; Chalk dust; Champagne; Chank; Cheebah; Cheese; Chicken; Chicken feed; Chicken flippin; Chikin; Chimichanga; Chingadera; Chittle; Chizel; Chiznad; Choad; Chris; Chrissy; Christal; Christina; Christine; Christmas tree; Christy; Chunkylove; Cinnamon; Clavo; Clean out the chimney; Clear; Coco; Coffee; Colorado Rockies; Cookies; Cotton Candy; CR; Crack Whore; Crank; Cranster Gansters; Creek Rock; Cri, cri; Criddle; Criddy; Cringe; Crink; Crip; Cris; Crisco; Crissie; Crissy; Cristina; Cristy; Critty; Crizzy; Croak; Crossles; Crothch dope; Crow; Crunk; Crypto; Crysnax; Crystal; Crystal glass; Crystal meth; Crystal methadrine; Crystalight; Crystals; Cube; D; Debbie; Desocsins; Desogtion; Devil dust; Devils dandruff; Devils drug; Dingles; Dirt; Dirty; Dizzle; Dizzo; Dizzy D; D-Monic; Do da; Doe; Doody; Doo-my-lau; Dope; Drano; Dummy dust; Dunk; Dyno; El Gato Diablo; Epimethrine; Epod; Eraser dust; Ethyl-M; Evil yellow; Fast; Fatch; Fedrin; Fil-layed; Fire; Fizz whizz; Fizz Wizz; Flash; Fluff; Future; G; G-unit; Gackle-a Fackle-a; Gab; Gagger; Gak; Gas; Gear; Geek; Geep; Geeter; Gemini; George; Get geared up; Getgo; Gina; Glass; Go; Go-ey; Go Fast; Go-fast; Go-go; Go-go juice; Gonzales; Goop; Go Pills; Goose-Egg; Got anything; Grads; Granulated orange; Grit; Gumption; Gyp; Haiwaiian salt; Hank; Hanyak; Hard Crystal; Hawaiis finest; Hidi; High Riders; High speed chicken feed; Highthen; Hillbilly crack; Hippy crack; Hironpon; Hiropon; Holy Smoke; Homework; Honk the BoBo; Hoo; Horse mumpy; Hot Ice; Hydro; Hypes; "I want to talk to Gina tonight"; Ibski; Ice; Ice cream; Icee; Ink; Ish; Izice; Jab; Jasmine; Jenny Crank; Jenny Crank Program; Jet fuel; Jetfuel; Jib; Jib nugget; Jibb Tech Warrier; Jibber jabbin; Jinga; Juddha; Juice; Junk; Kaksonjae; Kibble; Killer; KooLAID; Kryptonite; L.A.; LA Glass; L.A. glass; la glass; L.A. ice; LA Ice; Lamer; Laundry detergent; Leapers; Lemon drop; Life; Lily; Linda; Linga; Livin the Dream; Load of Laundry; Lost weekend; Love; Low; Lucille; M man; Magic; Maui-wowie; Met; Meth; Meth amps; Meth monsters; Methaine; Methandfriend; Methandfriendsofmine; Methanfelony; Methatrim; Methedrine; Methlies Quik; Methmood; Method; Mexican crack; Minibennies; Monster; Moon Juice; Motivation; Motivation in a bag; Motorcycle crack; Moving on G; Nazi crank; Nazi dope; Nazi vitamens; Nazimeth; Ned; Newday; Night Train; No doze; Nose candy; On a good one; Orange; OZs; P; Patsie; Peaking; Peanut butter; Peel dope; Pervatine; Pervitin; Phazers; Phets; Philopon; Pieta; Piko; Pink; Pink elephants; Pink hearts; Poison; Poof; Pookie; Poop; Poop'd out; Poor man's coccaine; Poor man's coke; Poot; Pootananny; Poppers; Powder; Powder monkeys; Powder point; Project propellant; Puddle; Pump; Pure; Q'd; Quarter Tee Bag; Quartz; Quick; Quill; Rachet jaw; Rails; Rank; Red; Red devils; Red phosphorus; Redneck cocaine; Redneck heroin; Richie Rich; Rip; Rippers; Robin eggs; Rock; Rock crank; Rocket fuel; Rocky mountain high; Rosebud; Rudy; Rudy's; Rumdumb; Running Pizo; Sack; Sam's sniff; Sarahs; Satan dust; Scante; Scap; Schlep rock; Schmiz; Sciznac; Scooby snax; Scootie; Scud; Scwadge; Sean; Sha-bang; Shab; Shabs; Shabu; Shamers; Shards; Shia; Shit; Shiznac; Shiznack; Shiznastica; Shiznit; Shiznittlebang; Shiznitty; Shizzo; Shnizzie snort; Shwack; Skeech; Sketch; Ski; Skitz; Sky rocks; Sliggers; Smiley smile; Smurf dope; Smzl; Snaps; Sniff; Snow; Soap; Soap dope; Space food; Spaceman; Spackle; Spagack; Sparacked; Sparked; Sparkle; Speckled birds; Speed; Speed racer; Spin, spin, spin; Spinack; Spindarella; Spinney Boo; Spinning; Spishak; Splash; Spook; Spoosh; Sprack; Sprizzlefracked; Sprung; Spun Ducky Woo; Squawk; Stallar; Sto-Pid; Stove top; Styels; Sugar; Suger; Super ice; Sweetness; Swerve; Syabu; Ta'doww; Talkie; Tanner; Tasmanian Devil; T.D.; Teena; Tenner; Terry; Texas Tea; The attenborough; The New Prozac; The White House; Tic; Tical; Tick tick; Tik; Time; Tina; Tink Dust; Tish; Tobats; Tootie; Toots; Torqued; Trash; Trippin Trip; Truck Stop Special; Tubbytoast; Tuk; Tuk-tuk; Tutu; Twack; Twacked out; Tweak; Tweedle Doo; Tweek; Tweezwasabi; Twistaflexin; Twiz; Twizacked; Ugly Dust; Upside-down b; Uppers; Vanilla Pheromones; Wake; Wash; Water; Way; We We We; Wet; Whacked; Whip; White; White bitch; White Cross; White Crosses; White Crunch; White ink; White junk; White lady; White pony; Whiz; Whizz; Who-Ha; Wigg; Work; Working man's cocaine; Xaing; YAMA; Ya Ba; Yaaba; Yaba; Yammer Bammer; Yank; Yankee; Yay; Yead Out; Yellow bam; Yellow barn; Yellow jackets; Yellow powder; Zingin; Zip; Zoiks; Zoom.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Methamphetamine Hydrochloride). White, odourless or practically odourless, crystals or crystalline powder. Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Its solutions in water have a pH of about 6. Store in airtight containers. Protect from light.

Uses and Administration

Metamfetamine hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p. 2319.2).

It has been given orally in the treatment of attention deficit hyperactivity disorder (see Hyperactivity, p. 2314.1) in children aged 6 years and over, although it is not one of

the main stimulants used. Initial doses are 5 mg once or twice daily, increased if necessary by 5 mg at weekly intervals to the optimum effective dose, usually 20 to 25 mg daily given in 2 divided doses.

Metamfetamine hydrochloride has also been used as an anorectic in the management of obesity (p. 2315.1), although amfetamines are no longer recommended for this indication. A dose of 5 mg before each meal has been given orally. Treatment should be for no longer than a few weeks.

Metamfetamine hydrochloride has also been used parenterally as a pressor agent.

The laevorotatory form, levmetamfetamine (p. 1668.3) is used as a nasal decongestant.

Administration in children. For doses of metamfetamine hydrochloride in children and adolescents, see Uses and Administration, p. 2324.3.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2.

Metamfetamine is subject to extensive abuse.

Abuse. Pulmonary oedema,[1,2] cardiomyopathy,[2,3] and choreoathetosis and rhabdomyolysis[4] have occurred after smoking of metamfetamine crystals. It is also abused orally and intravenously, and has been associated with fatalities;[5] rectal abuse has been reported.[6,7] Dental problems such as rampant caries and tooth wear and fracture, colloquially termed "meth mouth", may occur with long-term abuse.[8,9] A marked increase in prevalence of abuse in recent years, particularly in the USA, has led to increased research into the consequences of such abuse and methods for management.[10-13]

A study of former users suggests that metamfetamine abuse may cause long-term neuronal damage.[14]

There has been concern about metamfetamine abuse during pregnancy, suggesting its use has been associated with fetal growth restriction.[15]

1. Nestor TA, *et al.* Acute pulmonary oedema caused by crystalline methamphetamine. *Lancet* 1989; **ii:** 1277–8.
2. Hong R, *et al.* Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; **265:** 1152–4.
3. Yeo K-K, *et al.* The association of methamphetamine use and cardiomyopathy in young patients. *Am J Med* 2007; **120:** 165–71.
4. Sperling LS, Horowitz JL. Methamphetamine-induced choreoathetosis and rhabdomyolysis. *Ann Intern Med* 1994; **121:** 986.
5. Albertson TE, *et al.* Methamphetamine and the expanding complications of amphetamines. *West J Med* 1999; **170:** 214–19.
6. Cantrell FL, *et al.* Transrectal methamphetamine use: a novel route of exposure. *Ann Intern Med* 2006; **145:** 78–9.
7. Gupta M, *et al.* Bottoms up: methamphetamine toxicity from an unusual route. *Western J Emerg Med* 2009; **10:** 58–60.
8. Curtis EK. Meth mouth: a review of methamphetamine abuse and its oral manifestations. *Gen Dent* 2006; **54:** 125–9.
9. Donaldson M, Goodchild JH. Oral health of the methamphetamine abuser. *Am J Health-Syst Pharm* 2006; **63:** 2078–82. Correction. *ibid.*; 2180.
10. Cho AK, Melega WP. Patterns of methamphetamine abuse and their consequences. *J Addict Dis* 2002; **21:** 21–34.
11. Rawson RA, *et al.* Treatment of methamphetamine use disorders: an update. *J Subst Abuse Treat* 2002; **23:** 145–50.
12. Cretzmeyer M, *et al.* Treatment of methamphetamine abuse: research findings and clinical directions. *J Subst Abuse Treat* 2003; **24:** 267–77.
13. Lineberry TW, Bostwick JM. Methamphetamine abuse: a perfect storm of complications. *Mayo Clin Proc* 2006; **81:** 77–84.
14. Ernst T, *et al.* Evidence for long-term neurotoxicity associated with methamphetamine abuse: a ^{1}H MRS study. *Neurology* 2000; **54:** 1344–9.
15. Smith LM, *et al.* The infant development, environment, and lifestyle study: effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. *Pediatrics* 2006; **118:** 1149–56.

Interactions

As for Dexamfetamine Sulfate, p. 2320.2.

Pharmacokinetics

Like most amfetamines (see Dexamfetamine Sulfate, p. 2320.2) metamfetamine is readily absorbed from the gastrointestinal tract and is distributed into most body tissues. It is partially metabolised in the liver and excreted in the urine.

References.

1. Shappell SA, *et al.* Chronopharmacokinetics and chronopharmacodynamics of dextromethamphetamine in man. *J Clin Pharmacol* 1996; **36:** 1051–63.
2. Harris DS, *et al.* The bioavailability of intranasal and smoked methamphetamine. *Clin Pharmacol Ther* 2003; **74:** 475–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Cidrin†; ***USA***: Desoxyn.

Pharmacopoeial Preparations

USP 36: Methamphetamine Hydrochloride Tablets.

Methcathinone ⊗

Ephedrone; Methylcathinone; Monomethylpropion; Меткатинон.

2-(Methylamino)-1-phenyl-1-propan-1-one.

$C_{10}H_{13}NO$=163.2

CAS — 5650-44-2.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methcathinone:

Bathtub speed; Cadillac express; Cat; Catt; Cosmos; Crank; Gagers; Gaggers; Go fast; Go-fast; Goob; Jee cocktail; Jeff; Khat; Mulk; Mulka; Qat; Slick superspeed; Sniff; Somali; Somali tea; Speed; Star; Stat; The C; Tweak; Tweek; Tweeker; Wild cat; Wonder star.

4-Methylmethcathinone ⊗

Mephedrone; 4-MMC.

$C_{11}H_{15}NO$=177.2

CAS — 1189805-46-6.

UNII — 8BA8T27317.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of 4-Methylmethcathinone:

Bubble; Bubbleluv; Bubbles; Drone; M kat; MCAT; M-Cat; MD3; Meow; Meow-meow; Meph; Methadrone; Miaow; Miaow miaow; MMCAT; Moonshine; Neo drones; Plant feeder; Roxy; Rush; SC spirit; Sub coca I; Top cat; White magic.

Profile

Methcathinone, a methyl derivative of cathinone (p. 2318.2), produces CNS stimulant effects similar to those of the amfetamines (see Dexamfetamine, p. 2319.1) and is subject to abuse. The methyl derivative 4-methylmethcathinone (mephedrone; 4-MMC) is also subject to abuse. (See also Abuse, under Catha, p. 2318.3).

References.

1. Belhadj-Tahar H, Sadeg N. Methcathinone: a new postindustrial drug. *Forensic Sci Int* 2005; **153:** 99–101.

Methylenedioxymethamfetamine ⊗

MDMA; 3,4-Methylenedioxymethamphetamine; Methylenedioxymethamphetamine; Metilendioximetanfetamina.

N,α-Dimethyl-1,3-benzodioxole-5-ethanamine.

$C_{11}H_{15}NO_2$=193.2

CAS — 42542-10-9.

UNII — KE1SEN21RM.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methylenedioxymethamfetamine:

007s; 69s; Acid; Adam; Adam MTX; AKA; Anastasia; Apples; Baby slits; Bacalao; Bart Simpson; Batmans; B-bombs; Bean; Beans; Bens; Benzedrine; Bermuda triangles; Bibs; Bicho; Bickies; Bikkies; Biphetamine; Biscuits; Blue kisses; Blue lips; Blue nile; Booty juice; Bomber; Brownies; Burgers; Candies; Candy; Care bears; Cat in the hats; Charity; Chocolate chips; Chrystal methadrine; Clarity; Cloud nine; Clovers; Cowies; Cristal; Crowns; Crystal; Dancing Shoes; Dead road; Debs; Decadence; Deccadence; Denis the Menace; Dennis the Menaces; Dex; Dexedrine; Diamonds; Diamond Whites; Disco biscuit; Disco biscuits; Doctor; Dollars; Dolls; Dolphins; Doobies; Dove; Doves; Drivers; E; EA1475; Eazy; Eazy E; E-ball; Ebeneezer; E-bomb; E-bombs; Eccies; Ecsta; Ecstacy; Ecstasy; Ecstasy Tablets; Eddie Bo; Egg Rolls; Egyptians; Ekies; Elaine; Elephants; Em; Empathy; Essence; Eve; Ex; Exiticity; Extasy; Fantasia; Fantasy; Fastin; Fizzle; Flipper; Flipping; Four leaf clover; Fuckstasy; Gaggler; Gary Abletts; Garys; Go; Googs; Green triangles; Greenies; Grey biscuits; Gum; Gurners; Gurns; GWM; Hamburger; Hamburgers; Happy drug; Happy pill; Herbal bliss; Hug drug; Hug-Drug; Huggers; Hydro; Hype; Iboga; Ice; Igloo; Illies; Jack and jills; Jellies; Jerry Garcias; Jiggas; Jills; Junnov; Khat; Kiks; Kleenex; Letter biscuits; Light meth; Lollies; Long lasting lollies; Louie Vuitton; Love-Bug; Love doctor; Love Doves; Love drug; Love drug of the '80s; Love drug of the '90s; Love heart; Love Medicine; Love pill; Love potion #9; Lovers' special; Lover's speed; Lucky charmz; "M"; M and m's; M25; Madman; Malcolm; Mandy; MAO; MDM; MDMA; Mercedes; Meth amps; Methedrine; Mini beans; Mitsibushis; Mitsies; Mitsu's; Mitsubishi; Mitsubishis; M&M; M&Ms; Mellow drug of America; Molly; Mollys; Monoamine oxidase; Morning shot; New yorker; New Yorkers; Nineteen; Number 9; Orange bandits; Orbit; Pasti; Pillage; Pills; Pilules d'Amour; Pingers; Pink Calis; Pink panthers; Pink studs; Play Station; Playboy bunnies; Playboys; Pollutants; Pressies; Rave energy; Red and Black; Red devils; Rhubarb and custard; Rhubarb & Custards; Rib; Ritual spirit; Road Runner; Roca; Roker's Barnet; Rolexes; Roll; Rolling; Rolls Royce; Running; Scooby snacks; Scum; Shabu; Shaking head pill; Skates; Slammin'; Slamming; Slits; Slows; Smartees; Smurfs; Speed for lovers; Spivias; Stars; Strawberry shortcake; Supermans; Swadger; Swans; Sweeties; Sweets; Tablets; Tabs; Tacha; Tachas; Tangos; Tens; The love drug; The yuppie drug; Thizz; Tom and Jerries; Triple crowns; Triple rolexes; Triple stacks; Tutus; Tweety Birds; Ultimate Xphoria; U.S.P.; Vitamin E; Vitamin X; Vowels; Wafers; Wee Boys; West Coast turnarounds; Wheels; Whiffledust; White Burger; White diamonds; White dove; White doves; Whiz bombs; Wigits; Wingers; X; X-ing; X-Men; X-Men 2; X-Pills; XTC; Yao tou wan; Yáo tóu wán; Yellow Burger; Yips; Yokes; Yuppie drug; Yuppie psychedelic; Zen.

Profile

Methylenedioxymethamfetamine is a phenylethylamine compound structurally related to amfetamine and mescaline and is an analogue of tenamfetamine (p. 2330.3). It is subject to abuse. Its toxicity is similar to that of dexamfetamine (see Abuse, below and under Dexamfetamine, p. 2319.2) and may be treated similarly.

Abuse. Methylenedioxymethamfetamine may be ingested as tablets or capsules, or inhaled as a powder. It is often mixed with adulterants such as other amfetamines, caffeine, ephedrine, and pseudoephedrine.[1]

The toxicity associated with abuse of methylenedioxymethamfetamine has been discussed.[2-7] Acute effects can be severe and symptoms have included cardiac arrhythmias, fulminant hyperthermia, convulsions, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure; fatalities may occur. Repeated use may cause hepatic damage. Psychiatric effects reported include psychosis[8-10] and depression.[9-11] Damage to central serotonergic nerves has been implicated[8-12] and hence there is some concern about the long-term effects of methylenedioxymethamfetamine abuse.[13,14] Hyponatraemia, inappropriate antidiuretic hormone secretion, and cerebral oedema have also been reported;[15-20] the severity may be increased by excessive fluid intake that is frequently advocated to prevent dehydration and hyperthermia.[18-22] Urinary retention has also been reported.[23]

There has been concern about abuse during *pregnancy*. Twelve congenital malformations, including 2 cases of congenital heart disease, have been noted among 78 liveborn infants whose mothers had taken methylenedioxymethamfetamine, often with other drugs of abuse, during their pregnancies.[24]

For reviews of the properties of other phenylethylamine compounds, see under Tenamfetamine, p. 2331.1.

1. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
2. Henry JA. Ecstasy and the dance of death. *BMJ* 1992; **305:** 5–6.
3. Henry JA, *et al.* Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992; **340:** 384–7.
4. O'Connor B. Hazards associated with the recreational drug 'ecstasy'. *Br J Hosp Med* 1994; **52:** 507–14.
5. McCann UD, *et al.* Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'). *Drug Safety* 1996; **15:** 107–115.
6. Hall AP. Ecstasy and the anaesthetist. *Br J Anaesth* 1997; **79:** 697–8.
7. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. *Pediatrics* 1997; **100:** 705–8.
8. McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). *BMJ* 1991; **302:** 697.
9. Winstock AR. Chronic paranoid psychosis after misuse of MDMA. *BMJ* 1991; **302:** 1150–1.
10. Schifano F. Chronic atypical psychosis associated with MDMA ("ecstasy") abuse. *Lancet* 1991; **338:** 1335.
11. Benazzi F, Mazzoli M. Psychiatric illness associated with "ecstasy". *Lancet* 1991; **338:** 1520.
12. McCann UD, *et al.* Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; **352:** 1433–7.
13. Green AR, Goodwin GM. Ecstasy and neurodegeneration. *BMJ* 1996; **312:** 1493–4.
14. Bolla KI, *et al.* Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 1998; **51:** 1532–7.
15. Maxwell DL, *et al.* Hyponatraemia and catatonic stupor after taking "ecstasy". *BMJ* 1993; **307:** 1399.
16. Kessel B. Hyponatraemia after ingestion of "ecstasy". *BMJ* 1994; **308:** 414.
17. Satchell SC, Connaughton M. Inappropriate antidiuretic hormone secretion and extreme rises in serum creatinine kinase following MDMA ingestion. *Br J Hosp Med* 1994; **51:** 495.
18. Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after ecstasy (3,4-MDMA). *Lancet* 1996; **347:** 1052.
19. Matthai SM, *et al.* Cerebral oedema after ingestion of MDMA (ecstasy) and unrestricted intake of water. *BMJ* 1996; **312:** 1359.
20. Parr MJA, *et al.* Hyponatraemia and death after ecstasy ingestion. *Med J Aust* 1997; **166:** 136–7.
21. Cook TM. Cerebral oedema after MDMA ('ecstasy') and unrestricted water intake. *BMJ* 1996; **313:** 689.
22. Henry JA, *et al.* Low-dose MDMA ("ecstasy") induces vasopressin secretion. *Lancet* 1998; **351:** 1784.
23. Bryden AA, *et al.* Urinary retention with misuse of 'ecstasy'. *BMJ* 1995; **310:** 504.
24. McElhatton PR, *et al.* Congenital anomalies after prenatal ecstasy exposure. *Lancet* 1999; **354:** 1441–2.

Interactions. A psychotic reaction has been reported in a patient who took methylenedioxymethamfetamine while receiving therapy with *citalopram*.[1]

A patient receiving *phenelzine* and lithium therapy experienced a serotonin syndrome (p. 443.2) after ingesting methylenedioxymethamfetamine.[2] Symptoms included

markedly increased muscle tension, tremulousness, abnormal posturing, limited pain response, tachycardia, hypertension, hyperthermia, increased white blood cell count, increased creatine phosphokinase concentration, respiratory acidosis, metabolic acidosis, delirium, and agitation. Within 15 minutes of methylenedioxymethamfetamine ingestion the patient was comatose; within 5 hours the patient was alert with a normal muscle tone. An interaction between phenelzine and methylenedioxymethamfetamine was suggested as the cause of the serotonin syndrome.

A fatal serotonergic reaction to methylenedioxymethamfetamine possibly due to an interaction with *ritonavir* has been described.[3] A prolonged and exaggerated effect from a small dose of methylenedioxymethamfetamine has been reported[4] in another patient also receiving ritonavir. Although this patient was also receiving saquinavir, the authors postulated that the mechanism may be ritonavir-induced inhibition of the cytochrome P450 isoenzyme CYP2D6.

1. Lauerma H, *et al*. Interaction of serotonin reuptake inhibitor and 3,4-methylenedioxymethamphetamine? *Biol Psychiatry* 1998; **43:** 923–8.
2. Kaskey GB. Possible interaction between an MAOI and "ecstasy". *Am J Psychiatry* 1992; **149:** 411–12.
3. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; **352:** 1751–2.
4. Harrington RD, *et al*. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and γ-hydroxybutyrate. *Arch Intern Med* 1999; **159:** 2221–4.

Methylphenidate *(BAN, USAN, rINN)* ⊗

Méthylphénidate; Methylphenidatum; Metilfenidato; Metylfenidat; Metyylifenidaatti; Метилфенидат.

Methyl α-phenyl-2-piperidylacetate.

$C_{14}H_{19}NO_2$=233.3

CAS — 113-45-1.

ATC — N06BA04.

ATC Vet — QN06BA04.

UNII — 207ZZ9QZ49.

Methylphenidate Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metilfenidato; Methyl Phenidate Hydrochloride; Méthylphénidate, chlorhydrate de; Methylphenidathydrochlorid; Methylphenidati hydrochloridum; Metilfenidat Hidroklorür; Metilfenidato, hidrocloruro de; Метилфенидата Гидрохлорид.

$C_{14}H_{19}NO_2$,HCl=269.8

CAS — 298-59-9; 23655-65-4.

ATC — N06BA04.

ATC Vet — QN06BA04.

UNII — 4B35C438HI.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methylphenidate:

Kiddie cocaine; R ball; Rities; Skippy; Vitamin R; West coast.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Methylphenidate Hydrochloride). A white or almost white, fine crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Methylphenidate Hydrochloride). A white, odourless, fine crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Solutions are acid to litmus.

Uses and Administration

Methylphenidate hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p. 2319.2). It is used in the treatment of narcolepsy (p. 2314.3) and as an adjunct to psychological, educational, and social measures in the treatment of hyperactivity disorders (below). Methylphenidate is given orally as the hydrochloride, but the transdermal patches supply methylphenidate as the base.

In the treatment of **narcolepsy** the usual oral dose of methylphenidate hydrochloride is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In **hyperactivity disorders** in children aged 6 years and over, the usual initial oral dose of methylphenidate hydrochloride is 5 mg once or twice daily (as an immediate-release preparation), increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses; the *BNFC* suggests that up to 2.1 mg/kg daily (maximum of 90 mg daily) may be given under specialist supervision. Methylphenidate may be given before breakfast and lunch. A later dose can be considered if the effect wears off in the evening causing rebound hyperactivity. Treatment is not usually continued beyond puberty, however, in some patients drug therapy may be required into adulthood. In the UK NICE suggests that adults may be given the usual initial oral dose of 5 mg three times daily, increased according to response to a maximum of 100 mg daily.

Methylphenidate hydrochloride is also available as modified-release preparations for the treatment of hyperactivity disorders. Some modified-release preparations also contain immediate-release methylphenidate within the formulation. Doses of modified-release preparations may vary according to the brand chosen. Licensed doses for one brand of modified-release tablets (*Concerta: Janssen-Cilag, UK; McNeil, USA*) are as follows:

- children and adolescents aged 6 to 17 years and not currently taking conventional methylphenidate should be started on 18 mg once daily in the morning
- in the USA it is also licensed for use in adults: those not currently taking conventional methylphenidate should be started on 18 or 36 mg once daily in the morning
- the dose may then be increased by 18 mg at weekly intervals to a maximum of 54 mg once daily in children and adolescents in the UK; US product information permits a maximum of 72 mg once daily in those aged 13 years and over. The *BNFC* suggests that *Concerta* may be increased to 2.1 mg/kg daily (maximum 108 mg daily)
- the dose in patients already taking conventional methylphenidate should be based on their current dose although the initial dose should not exceed 72 mg once daily

Transdermal patches delivering amounts of methylphenidate ranging from 1.1 to 3.3 mg/hour are available for once-daily application in the treatment of hyperactivity disorders in children and adolescents aged 6 to 17 years. Patients should be started on the lowest strength patch regardless of any previous methylphenidate use; thereafter, doses should be individually titrated for each patient according to response and increased at weekly intervals if necessary to a maximum of 3.3 mg/hour (at week 4). Patches should be applied to the hip area 2 hours before an effect is needed and removed after a maximum of 9 hours later.

Methylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond, to assess the patient's condition.

A single isomer form of methylphenidate, dexmethylphenidate (p. 2320.3) is also used for hyperactivity disorders.

References.

1. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc* 2000; **75:** 711–21.

Administration in children. For doses of methylphenidate hydrochloride in children and adolescents, see Uses and Administration, above.

Depression. Stimulants are no longer recommended as sole treatment for depression (p. 398.1), although they have been tried in augmenting the effect of standard antidepressants such as the SSRIs[1] in patients with refractory depressive disorders.

1. Stoll AL, *et al*. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 1996; **57:** 72–6.

Disturbed behaviour. Disturbed behaviour can have several causes and is usually treated with an antipsychotic or benzodiazepine (see p. 1030.2). A review[1] of the published clinical studies between 1966 and June 2004 found that although methylphenidate was likely to improve memory, attention, concentration, and mental processing in patients with traumatic brain injury, its effect on behaviour remains to be determined; the most commonly used dosage was 300 micrograms/kg twice daily.

1. Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann Pharmacother* 2005; **39:** 1309–13.

Hyperactivity. Methylphenidate is one of the main drugs used in hyperactivity, including ADHD (p. 2314.1).

Small studies have indicated that different aspects of attention deficit disorders in children might respond to different doses of methylphenidate.[1-4] In addition to the morning and noon doses commonly used in hyperactivity disorders, studies[5,6] have shown improved clinical outcome with little adverse effect on sleep patterns if a third late afternoon dose is given.

Modified-release preparations with a slow onset of action have been developed to overcome the short duration of action of methylphenidate although they may be less effective than immediate-release preparations. A study,[7] using a regimen to simulate the prolonged steady plasma concentration profile obtained with the slow-onset, modified-release preparations, has suggested that unlike twice-daily treatment acute tolerance might develop with the use of modified-release preparations. However, some modified-release preparations that also consist of an immediate-release component, have been reported to be as effective as an immediate-release preparation in short-term studies.[8-11] Transdermal patches containing methylphenidate released over 9 hours are available in the USA.[12-14]

UK guidelines for the use of methylphenidate in children and adolescents with ADHD are available.[15]

1. Sprague RL, Sleator EK. Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science* 1977; **198:** 1274–6.
2. Tannock R, *et al*. Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. *Pediatrics* 1989; **84:** 648–57.
3. Sebrechts MM, *et al*. Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. *Pediatrics* 1986; **77:** 222–8.
4. Barkley RA, *et al*. Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991; **87:** 519–31.
5. Kent JD, *et al*. Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorders. *Pediatrics* 1995; **96:** 320–5.
6. Stein MA, *et al*. Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 1996; **98:** 748–56.
7. Swanson J, *et al*. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999; **66:** 295–305.
8. Pelham WE, *et al*. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Abstract: *Pediatrics* 2001; **107:** 1417. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/6/e105 (accessed 15/04/04)
9. Wolraich ML, *et al*. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001; **108:** 883–92.
10. Reimherr FW, *et al*. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *J Clin Psychiatry* 2007; **68:** 93–101.
11. Jain U, *et al*. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2007; **68:** 268–77.
12. Anderson VR, Scott LJ. Methylphenidate transdermal system: in attention-deficit hyperactivity disorder in children. *Drugs* 2006; **66:** 1117–26.
13. Arnold LE, *et al*. Treating attention-deficit/hyperactivity disorder with a stimulant transdermal patch: the clinical art. *Pediatrics* 2007; **120:** 1100–6.
14. Findling RL, *et al*. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2008; **69:** 149–59. Correction. *ibid.*; 329.
15. NICE. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: review of Technology Appraisal 13 (Technology Appraisal 98, issued March 2006, reviewed March 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/TA098guidance.pdf (accessed 11/08/08)

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2. Hypersensitivity reactions have been reported. Skin reactions have included exfoliative dermatitis and erythema multiforme. Purpura, thrombocytopenia, and leucopenia have occurred. Blood counts should be monitored periodically during prolonged therapy.

Local reactions such as rash, skin irritation, redness, and itching have been reported with transdermal use.

References.

1. Ahmann PA, *et al*. Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* 1993; **91:** 1101–6.
2. Efron D, *et al*. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997; **100:** 662–6.
3. Rappley MD. Safety issues in the use of methylphenidate: an American perspective. *Drug Safety* 1997; **17:** 143–8.
4. Klein-Schwartz W. Abuse and toxicity of methylphenidate. *Curr Opin Pediatr* 2002; **14:** 219–23.
5. Leonard BE, *et al*. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol* 2004; **19:** 151–80.

Abuse. Reports of adverse effects after the abuse of methylphenidate by injecting solutions of crushed tablets.[1-3] Intravenous abuse of methylphenidate with pentazocine has also been reported.[4,5] In addition, there are also reports of intranasal methylphenidate abuse,[6-8] including fatalities.[8]

See also Effects on the Liver, p. 2327.1.

1. Wolf J, *et al*. Eosinophilic syndrome with methylphenidate abuse. *Ann Intern Med* 1978; **89:** 224–5.
2. Gunby P. Methylphenidate abuse produces retinopathy. *JAMA* 1979; **241:** 546.
3. Parran TV, Jasinski DR. Intravenous methylphenidate abuse: prototype for prescription drug abuse. *Arch Intern Med* 1991; **151:** 781–3.
4. Debooy VD, *et al*. Intravenous pentazocine and methylphenidate abuse during pregnancy: maternal lifestyle and infant outcome. *Am J Dis Child* 1993; **147:** 1062–5.
5. Carter HS, Watson WA. IV pentazocine/methylphenidate abuse—the clinical toxicity of another Ts and blues combination. *J Toxicol Clin Toxicol* 1994; **32:** 541–7.
6. Jaffe SL. Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991; **30:** 773–5.
7. Garland EJ. Intranasal abuse of prescribed methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1998; **37:** 573–4.
8. Massello W, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). *J Forensic Sci* 1999; **44:** 220–1.

Breast feeding. No adverse effects were noted[1] in a 6-month-old breast-fed infant whose 26-year-old mother had been taking methylphenidate 40 mg twice daily for

about 5 weeks. Despite the relatively high milk-to-plasma ratio of 2.7 the relative infant dose was low, at 0.2% of the maternal dose. Nonetheless the authors recommended caution when giving methylphenidate to breast-feeding mothers. Licensed product information also recommends that methylphenidate should be used with caution or avoided during breast feeding.

1. Hackett LP, *et al.* Methylphenidate and breast-feeding. *Ann Pharmacother* 2006; **40:** 1890–1.

Effects on the cardiovascular system. For mention of the adverse cardiovascular effects of stimulants, see under Dexamfetamine Sulfate, p. 2319.3.

Effects on growth. Concern has been expressed about the effects of central stimulants such as methylphenidate on growth rate when used to treat hyperactivity in children. One study showed that methylphenidate produced decreases in weight percentiles after 1 year of therapy and progressive decrement in height percentiles that became significant after 2 years of use.[1] However, another suggested that moderate doses might have a lower risk for long-term height suppression than dexamfetamine.[2] There has also been a study which showed that, even when methylphenidate had an adverse effect on growth rate during active treatment, final height was not compromised and that a compensatory rebound of growth appeared to occur on stopping stimulant treatment.[3] Height and weight should be monitored during treatment with methylphenidate.

See also under Dexamfetamine Sulfate, p. 2320.1.

1. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry* 1983; **40:** 317–21.
2. Greenhill LL, *et al.* Prolactin, growth hormone and growth responses in boys with attention deficit disorder and hyperactivity treated with methylphenidate. *J Am Acad Child Psychiatry* 1984; **23:** 58–67.
3. Klein RG, Mannuzza S. Hyperactive boys almost grown up III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 1988; **45:** 1131–4.

Effects on the liver. Hepatotoxicity with raised liver enzyme values in a 67-year-old woman was associated with the oral use of methylphenidate hydrochloride 30 mg daily.[1] Methylphenidate-induced hepatocellular injury was reported in a 19-year-old woman who developed jaundice, fever, and malaise after intravenous abuse of methylphenidate hydrochloride tablets.[2]

1. Goodman CR. Hepatotoxicity due to methylphenidate hydrochloride. *N Y State J Med* 1972; **72:** 2339–40.
2. Mehta H, *et al.* Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. *J Clin Gastroenterol* 1984; **6:** 149–51.

Effects on mental state. Hallucinations (visual and haptic) occurred in 3 patients treated with methylphenidate.[1] All cases resolved promptly after treatment with methylphenidate was stopped.

1. Gross-Tsur V, *et al.* Hallucinations during methylphenidate therapy. *Neurology* 2004; **63:** 753–4.

Effects on sexual function. Withdrawal of modified-release preparations of methylphenidate has been associated with priapism. A 15-year-old boy[1] had priapism during his weekly scheduled 24-hour withdrawal of methylphenidate; he also sometimes had erections during the school week that were relieved when he took his morning dose of methylphenidate. In another case, a 16-year-old boy[2] had priapism whenever he forgot to take his medication, which would resolve when he took his next dose.

1. Schwartz RH, Rushton HG. Stuttering priapism associated with withdrawal from sustained-release methylphenidate. *J Pediatr* 2004; **144:** 675–6.
2. Health Canada. Extended-release methylphenidate (Concerta) withdrawal: suspected association with priapism. *Can Adverse React News* 2006; **16:** 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n3-eng.php (accessed 04/02/10)

Effects on the skin. A fixed drug eruption of the scrotum has been reported in 2 children treated with methylphenidate for attention deficit disorder.[1]

1. Cohen HA, *et al.* Fixed drug eruption of the scrotum due to methylphenidate. *Ann Pharmacother* 1992; **26:** 1378–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methylphenidate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Tourette's syndrome. For a discussion on whether central stimulants provoke Tourette's syndrome, see Dexamfetamine Sulfate, p. 2320.2.

Interactions

As for Dexamfetamine Sulfate, p. 2320.2.

Anticoagulants. For the effect of methylphenidate on *ethyl biscoumacetate*, see Central Stimulants under the Interactions of Warfarin, p. 1533.2.

Antidepressants. For the effect of methylphenidate on *tricyclic antidepressants*, see under Amitriptyline, p. 406.1.

Antiepileptics. Methylphenidate blood concentrations decreased, and symptoms of attention deficit hyperactivity disorder worsened, in a 13-year-old girl after starting therapy with *carbamazepine*.[1]

For the effect of stimulants, such as methylphenidate on antiepileptics, see under Phenytoin, p. 545.1.

1. Schaller JL, *et al.* Carbamazepine and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 112–13.

Pharmacokinetics

Methylphenidate is readily absorbed from the gastrointestinal tract. The presence of food in the stomach accelerates the rate of absorption but not the total amount absorbed. Methylphenidate undergoes extensive first-pass metabolism and peak plasma concentrations occur about 2 hours after oral doses of immediate-release preparations. The first-pass effect is less with transdermal patches, which are designed to release a stated amount of drug over 9 hours. Protein binding is low. It is excreted as metabolites mainly in the urine with small amounts appearing in the faeces; less than 1% appears in the urine as unchanged methylphenidate. The major metabolite is ritalinic acid (2-phenyl-2-piperidyl acetic acid). The plasma elimination half-life is about 2 hours after oral doses, and about 3 to 4 hours after removal of the patch. Methylphenidate is distributed into breast milk.

References.

1. Aoyama T, *et al.* Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44;** 79–84.
2. Aoyama T, *et al.* Pharmacokinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia. *Clin Pharmacol Ther* 1994; **55:** 270–6.
3. Shader RI, *et al.* Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999; **39:** 775–785.
4. Kimko HC, *et al.* Pharmacokinetics and clinical effectiveness of methylphenidate. *Clin Pharmacokinet* 1999; **37:** 457–70.
5. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *J Clin Pharmacol* 2000; **40:** 379–88.
6. Teo SK, *et al.* A single-dose, two-way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects. *J Clin Pharmacol* 2004; **44:** 173–8.
7. Quinn D, *et al.* Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007; **47:** 760–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Concerta; Methylin; Ritalina; Rubifen; ***Austral.***: Attenta; Concerta; Ritalin; ***Austria***: Concerta; Medikinet; Ritalin; ***Belg.***: Concerta; Rilatine; ***Braz.***: Concerta; Ritalina; ***Canad.***: Biphentin; Concerta; Ritalin; ***Chile***: Aradix; Concerta; Nebapul; Ritalin; Ritrocel†; ***China***: Concerta (专注达); ***Cz.***: Concerta; Medikinet; Ritalin; ***Denm.***: Concerta; Equasym; Medikinet; Motiron; Ritalin; ***Fin.***: Concerta; Equasym; Medikinet; Ritalin; ***Fr.***: Concerta; Ritaline; ***Ger.***: Concerta; Equasym; Medikinet; Methylpheni; Ritalin; ***Gr.***: Concerta; Equasym†; Ritalin; ***Hong Kong***: Concerta; Ritalin; ***Hung.***: Ritalin; ***India***: Addwize; Inspiral; ***Indon.***: Concerta; Prohiper; Ritalin; ***Irl.***: Concerta; Equasym; Medikinet; Ritalin; ***Israel***: Concerta; Medikinet; Ritalin; ***Ital.***: Ritalin; ***Malaysia***: Concerta; Ritalin; Rubifen; ***Mex.***: Concerta; Metadate; Ritalin; Tradea; ***Neth.***: Concerta; Equasym; Medikinet; Ritalin; Tifinidat†; ***Norw.***: Concerta; Equasym; Medikinet; Ritalin; ***NZ***: Concerta; Ritalin; Rubifen; ***Philipp.***: Concerta; Ritalin; ***Pol.***: Concerta; Medikinet; ***Port.***: Concerta; Ritalina; Rubifen; ***S.Afr.***: Adaphen†; Concerta; Ritalin; ***Singapore***: Concerta; Ritalin; Rubifen; ***Spain***: Concerta; Equasym; Medicebran; Medikinet; Omozin†; Rubifen; ***Swed.***: Concerta; Equasym; Medikinet; Ritalin; ***Switz.***: Concerta; Medikinet; Ritaline; ***Thai.***: Concerta; Ritalin; ***Turk.***: Concerta; Ritaline; ***UK***: Concerta; Equasym; Medikinet; Ritalin; ***USA***: Concerta; Daytrana; Metadate; Methylin; Quillivant; Ritalin; ***Venez.***: Concerta; Ritalin.

Pharmacopoeial Preparations

USP 36: Methylphenidate Hydrochloride Extended-Release Tablets; Methylphenidate Hydrochloride Tablets.

Modafinil *(BAN, USAN, rINN)* ⊗

CEP-1538; CRL-40476; Modafinilo; Modafinilum; Модафинил.

2-[(Diphenylmethyl)sulfinyl]acetamide.

$C_{15}H_{15}NO_2S$=273.4

CAS — 68693-11-8.

ATC — N06BA07.

ATC Vet — QN06BA07.

UNII — R3UK8X3U3D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Modafinil). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble or practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in alcohol.

USP 36: (Modafinil). A white, odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Modafinil is a central stimulant chemically related to adrafinil (p. 2315.3). It is used in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p. 2314.3). The usual oral dose is 200 to 400 mg daily, in two divided doses, in the morning and at midday, or as a single dose in the morning. An initial dose of 100 mg daily should be used in the elderly and adjusted as necessary. For doses in hepatic impairment, see below.

Modafinil has also been used in oral doses of 200 mg daily for the treatment of obstructive sleep apnoea/hypopnoea syndrome and shift-work sleep disorder although in 2010 the EMEA recommended that such indications be removed from marketing authorisations (see p. 2328.1). For the treatment of obstructive sleep apnoea/hypopnoea syndrome, the daily dose should be taken in the morning and for shift-work sleep disorder, the daily dose should be taken as a single dose 1 hour before starting work.

Modafinil is usually given as a racemic mixture but preparations containing only the *R*-isomer, armodafinil, are also available, see Armodafinil, p. 2316.3.

Modafinil has also been investigated for the treatment of fatigue associated with various disorders including multiple sclerosis and for the treatment of hyperactivity disorders.

References.

1. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000; **54:** 1166–75.
2. Kingshott RN, *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2001; **163:** 918–23.
3. Czeisler CA, *et al.* The US Modafinil in Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005; **353:** 476–86. Correction. *ibid.*; 1078.
4. Gill M, *et al.* Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. *Acad Emerg Med* 2006; **13:** 158–65. Correction. *ibid.*; 477.
5. Turner D. A review of the use of modafinil for attention-deficit hyperactivity disorder. *Expert Rev Neurother* 2006; **6:** 455–68.
6. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006; **67:** 554–66.
7. Lindsay SE, *et al.* Use of modafinil for the treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; **40:** 1829–33.
8. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs* 2008; **68:** 1803–39.

Administration in hepatic impairment. UK licensed product information states that the total oral dose of modafinil (see Uses and Administration, above) should be reduced by half in patients with severe hepatic impairment.

Adverse Effects, Treatment, and Precautions

The most commonly reported adverse effect of modafinil, affecting about 21% of patients, is headache, which is usually mild or moderate, dose-dependent, and disappears within a few days. Other adverse effects may be a result of CNS stimulation and effects such as nervousness, insomnia, agitation, confusion, personality disorder, tremor, and anxiety have been noted. There may also be gastrointestinal disturbances, including nausea and abdominal pain, dry mouth, diarrhoea, dyspepsia, and constipation, dizziness, and anorexia. Abnormal liver function tests including dose-related increases in alkaline phosphatase, and dyskinesia have been seen.

Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis, have been reported (see also Effects on the Skin, p. 2328.1). Benign pruritic rashes have also occurred and since it is not possible to predict which rashes will become serious, modafinil should be stopped at the first sign of rash unless it is clearly not drug-related. Other hypersensitivity reactions such as angioedema have also been reported rarely.

Psychiatric symptoms including psychosis, depression, hallucinations, suicidal ideation, and mania have been reported. Modafinil should be given with caution to those with a history of psychosis, depression, or mania.

Cardiovascular effects such as hypertension, palpitations, and tachycardia have been reported. Modafinil is contra-indicated in patients with uncontrolled, moderate to severe hypertension or cardiac arrhythmias. It is not recommended in patients with a history of left ventricular hypertrophy or ischaemic ECG changes, chest pain, or other signs of mitral valve prolapse.

As with other stimulants, there is the possibility of dependence with long-term use. Modafinil has been misused as a so-called 'lifestyle drug' to promote alertness and wakefulness in otherwise healthy subjects.

In July 2010, the EMEA's Committee for Medicinal Products for Human Use (CHMP) reported on its safety review of modafinil.[1] The committee concluded that the benefits of modafinil only outweighed the risks in narcolepsy. For all other indications the risk of developing skin or hypersensitivity reactions and neuropsychiatric disorders outweighed efficacy. Therefore, the CHMP concluded that all indications except narcolepsy should be withdrawn from the marketing authorisations for modafinil.

1. EMEA. European Medicines Agency recommends restricting the use of modafinil (issued 22 July, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/07/WC500094976.pdf (accessed 09/08/10)

Effects on mental state. The Australian Adverse Drug Reactions Advisory Committee[1] reported that it had been notified of 5 cases of serious psychiatric reactions associated with modafinil since 2003. All patients had a history of paranoid personality, depression, or post-natal depression. The presenting symptoms were anxiety, abnormal behaviour, guilt feelings, rapid relapse/onset of depression, suicidal ideation, suicidal behaviour, psychotic disorder, and delusion. In 3 cases, the reaction occurred after only a few doses but in the other 2 cases onset was over 1 year after the drug was started. All cases resolved when modafinil was stopped; re-challenge was positive in one case of depression. See also above.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Modafinil: adverse skin and psychiatric reactions. *Aust Adverse Drug React Bull* 2008; **27:** 22–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0812.pdf (accessed 20/01/10)

Effects on the skin. The FDA[1] reported that it had received 6 cases of severe cutaneous adverse effects associated with modafinil from its initial marketing in December 1998 to January 2007; of these, 5 required hospitalisation. The cutaneous effects, which included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, were reported in adults and children although use in patients under 16 years of age is unlicensed. The median time to onset was 17.5 days with a range of 5 days to 5 weeks. See also above.

1. Modafinil (marketed as Provigil): serious skin reactions. *FDA Drug Safety Newsletter* 2007; **1:** 5–7. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109158.pdf (accessed 26/01/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies modafinil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Modafinil is partially metabolised by cytochrome P450 isoenzymes. In addition, it also has enzyme-inducing and -inhibiting activity. Use with other drugs that inhibit, induce, or act as a substrate to these isoenzymes such as oral contraceptives and antiepileptics may result in changes in plasma concentration of modafinil and/or the other drug.

Pharmacokinetics

Modafinil is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral doses. Plasma protein binding is about 60%, mainly to albumin. Modafinil is metabolised in the liver, partially by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5; two major metabolites have been identified: acid modafinil and modafinil sulfone, both of which are inactive. Excretion is mainly through the kidneys with less than 10% of the dose being eliminated unchanged. The elimination half-life after multiple doses is 15 hours.

References.

1. Wong YN, *et al.* A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 1999; **39:** 30–40.
2. Wong YN, *et al.* Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. *J Clin Pharmacol* 1999; **39:** 281–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Forcilin; Intensit; Nopral; Vigicer; ***Austral.***: Modavigil; ***Austria***: Modasomil; ***Belg.***: Provigil; ***Braz.***: Stavigile; ***Canad.***: Alertec; ***Chile***: Alertex; Mentix; Movigil; Naxelan; Resotyl; Zalux; ***Cz.***: Vigil; ***Denm.***: Modiodal; Provigil†; ***Fr.***: Modiodal; ***Ger.***: Vigil; ***Gr.***: Modiodal; ***Hung.***: Vigil; ***India***: Modalert; Modfil; ***Irl.***: Provigil; ***Israel***: Provigil; ***Ital.***: Provigil; ***Jpn***: Modiodal; ***Mex.***: Modiodal; ***Neth.***: Aspendos; Modiodal; ***Norw.***: Modiodal; ***NZ***: Modavigil; ***Pol.***: Vigil†; ***Port.***: Modiodal; ***S.Afr.***: Provigil; ***Spain***: Modiodal; ***Swed.***: Modiodal; ***Switz.***: Modasomil; ***Turk.***: Modiodal; ***UK***: Provigil; ***USA***: Provigil.

Pharmacopoeial Preparations
USP 36: Modafinil Tablets.

Naphyrone ⊗

Naphthylpyrovalerone; NRG-1; O-2482.
1-(2-Napthalenyl)-2-(1-pyrrolidinyl)-1-pentanone.
$C_{19}H_{23}NO$=281.4
CAS — 850352-53-3 (naphyrone); 850352-11-3 (naphyrone hydrochloride).

NOTE. The term NRG-1 has also been applied to the protein Neuroregulin 1.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of naphyrone:
Energy-1; Rave.

Profile

Naphyrone, a derivative of pyrovalerone, is reported to have stimulant properties and is subject to abuse (see also Abuse, under Catha, p. 2318.3).

Nikethamide *(BAN, rINN)* ⊗

Cordiaminum; Nicetamid; Nicethamid; Nicéthamide; Nicethamidum; Nicotinic Acid Diethylamide; Nicotinoyldiaethylamidum; Niketamid; Niketamidas; Niketamidi; Nikethamid; Nikethylamide; Niquetamida; Никетамид.
N,N-Diethylnicotinamide; *N,N*-Diethylpyridine-3-carboxamide.
$C_{10}H_{14}N_2O$=178.2
CAS — 59-26-7.
ATC — R07AB02.
ATC Vet — QR07AB02.
UNII — 368IVD6M32.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Viet.*

Ph. Eur. 8: (Nikethamide). A colourless or slightly yellow oily liquid or crystalline mass. Miscible with water and with alcohol. A 25% solution in water has a pH of 6.0 to 7.8.

Profile

Nikethamide has actions similar to those of doxapram (p. 2321.2). It was formerly used as a respiratory stimulant but has largely been abandoned because of toxicity. Nikethamide and its calcium thiocyanate salt have also been used in some countries as central stimulants and for hypotensive disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Cardiamidum.

Multi-ingredient Preparations. ***Fr.***: Coramine Glucose; ***Pol.***: Cardiamid-Coffein†; Glucardiamid; ***Switz.***: Gly-Coramin.

Pharmacopoeial Preparations
BP 2014: Nikethamide Injection.

Pemoline *(BAN, USAN, rINN)* ⊗

Fenoxazol; LA-956; NSC-25159; Pemoliini; Pemolin; Pemolina; Pémoline; Pemolinum; Phenoxazole; Phenylisohydantoin; Phenylpseudohydantoin; Пемолин.
2-Imino-5-phenyl-4-oxazolidinone.
$C_9H_8N_2O_2$=176.2
CAS — 2152-34-3 (pemoline); 68942-31-4 (pemoline hydrochloride); 18968-99-5 (magnesium pemoline).
ATC — N06BA05.
ATC Vet — QN06BA05.
UNII — 7GAQ2332NK.

Profile

Pemoline is a central stimulant with actions similar to those of dexamfetamine (p. 2319.1).

It has been used in the management of hyperactivity disorders in children; however, in many countries it was withdrawn from such use after reports of serious hepatotoxicity. Hypertensive crisis may possibly occur if pemoline is given with MAOIs.

Pemoline has been included in preparations also containing yohimbine hydrochloride and methyltestosterone that are claimed to combat failure of sexual desire and functioning in males and females; such preparations are not recommended.

Pemoline has been given with magnesium hydroxide (magnesium pemoline) in an attempt to increase its absorption.

Abuse. Paranoid psychosis occurred in a 38-year-old man taking pemoline 75 to 225 mg daily.[1] His compulsive use of the drug, development of tolerance, depressive withdrawal syndrome, and inability to abstain indicated dependence and it was evident that the patient was addicted to pemoline.

Choreoathetosis and rhabdomyolysis developed in a patient after a marked increase in intake of pemoline.[2] Abnormal movements responded to diazepam.

1. Polchert SE, Morse RM. Pemoline abuse. *JAMA* 1985; **254:** 946–7.
2. Briscoe JG, *et al.* Pemoline-induced choreoathetosis and rhabdomyolysis. *Med Toxicol* 1988; **3:** 72–6.

Effects on the liver. Pemoline has been associated with hepatotoxicity.

Elevated concentrations of serum aspartate aminotransferase and serum alanine aminotransferase have been noted in 2% of children taking pemoline for hyperactivity; the effect was stated to be transient and reversible.[1]

However, more serious reactions have also occurred. Acute hepatitis[2] was associated with pemoline in a 10-year-old boy and the drug was believed to be the cause of fatal fulminant liver failure[3] in a 14-year-old boy and in 2 previously published cases. The UK CSM[4] subsequently became aware of 33 reports of serious hepatic reactions in the USA, including a total of 6 fatalities and the need for liver transplantation in 2 cases; this prompted the withdrawal of pemoline for the treatment of hyperactivity in the UK. Following further reports of liver failure resulting in transplantation or death, the FDA[5] similarly withdrew pemoline in the USA.

1. Anonymous. Hyperkinesis' can have many causes, symptoms. *JAMA* 1975; **232:** 1204–16.
2. Patterson JF. Hepatitis associated with pemoline. *South Med J* 1984; **77:** 938.
3. Berkovitch M, *et al.* Pemoline-associated fulminant liver failure: testing the evidence for causation. *Clin Pharmacol Ther* 1995; **57:** 696–8.
4. CSM/MCA. Volital (pemoline) has been withdrawn. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
5. FDA. Alert for healthcare professionals: pemoline tablets and chewable tablets (marketed as Cylert) (issued October, 2005). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126462.pdf (accessed 09/04/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Ceractiv; Cylert†; ***Israel***: Nitan†.

Multi-ingredient Preparations. ***UK***: Prowess.

Pentetrazol *(BAN, rINN)* ⊗

Corazol; Leptazol; Pentamethazol; 1,5-Pentamethylenetetrazole; Pentazol; Pentetratsoli; Pentétrazol; Pentetrazolum; Pentylenetetrazol; Пентетразол.
6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine.
$C_6H_{10}N_4$=138.2
CAS — 54-95-5.
ATC — R07AB03.
ATC Vet — QR07AB03.
UNII — WM5Z385K7T.

Pharmacopoeias. In *It.*

Profile

Pentetrazol is a central and respiratory stimulant similar to doxapram (p. 2321.2). It has been used in respiratory depression and in multi-ingredient preparations intended for the treatment of respiratory-tract disorders including cough, cardiovascular disorders including hypotension, and for the treatment of pruritus. It has been given orally and by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Cardiazol-Paracodina; ***Port.***: Broncodiazina†.

Phendimetrazine Tartrate *(BANM, rINNM)* ⊗

Fendimetrazina, tartrato de; Phendimetrazine Acid Tartrate; Phendimetrazine Bitartrate; Phendimétrazine, Tartrate de; Phendimetrazini Tartras; Tartrato de fendimetrazina; Фендиметразина Тартрат.
(+)-3,4-Dimethyl-2-phenylmorpholine hydrogen tartrate.

$C_{12}H_{17}NO,C_4H_6O_6$=341.4
CAS — 634-03-7 (phendimetrazine); 7635-51-0 (phendimetrazine hydrochloride); 50-58-8 (phendimetrazine tartrate).
UNII — 6985IP0T80.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phendimetrazine:
Fringas; Prelo.

Pharmacopoeias. In *US.*

USP 36: (Phendimetrazine Tartrate). A white odourless crystalline powder. Freely soluble in water; sparingly soluble in warm alcohol; insoluble in acetone, in chloroform, in ether, and in benzene. pH of a 2.5% solution in water is between 3.0 and 4.0. Store in airtight containers.

Uses and Administration

Phendimetrazine tartrate is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.2). It has been used as an anorectic in the short-term treatment of obesity (p. 2315.1), although stimulants are no longer recommended for this indication. The usual oral dose is 35 mg two or three times daily before food. An alternative dose is 105 mg once daily in the morning as a modified-release preparation.

Phendimetrazine hydrochloride has been used similarly.

Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2.

Pulmonary hypertension and valvular heart defects have been reported in patients receiving phendimetrazine with other anorectics; these adverse effects, with the relevant precautions to be observed, are discussed under Fenfluramine Hydrochloride (see Effects on the Cardiovascular System, p. 2322.3). Phendimetrazine should not be used with other anorectics nor within a year of their use.

Interactions

Phendimetrazine is an indirect-acting sympathomimetic and may interact with other drugs similarly to dexamfetamine (p. 2320.2).

Pharmacokinetics

Phendimetrazine tartrate is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as phenmetrazine and other metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Obesan-X; Obex-LA; ***USA***: Bontril; Melfiat; Prelu-2.

Pharmacopoeial Preparations
USP 36: Phendimetrazine Tartrate Capsules; Phendimetrazine Tartrate Tablets.

Phenmetrazine Hydrochloride

(BANM, rINNM) ⊗

Fenmetrazina, hidrocloruro de; Hidrocloruro de fenmetrazina; Oxazimédrine; Phenmétrazine, Chlorhydrate de; Phenmetrazini Hydrochloridum; Фенметразина Гидрохлорид.
(±)-*trans*-3-Methyl-2-phenylmorpholine hydrochloride.
$C_{11}H_{15}NO,HCl$=213.7
CAS — 134-49-6 (phenmetrazine); 1707-14-8 (phenmetrazine hydrochloride); 13931-75-4 (phenmetrazine teoclate).
UNII — 6U85YRT588.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of Phenmetrazine:
Preludes.

Pharmacopoeias. In *US.*

USP 36: (Phenmetrazine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 0.4 of water, 1 in 2 of alcohol, and 1 in 2 of chloroform. pH of a 2.5% solution in water is between 4.5 and 5.5. Store in airtight containers.

Profile

Phenmetrazine hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.1). It has been used as an anorectic in the treatment of obesity. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3). It has been subject to extensive abuse.

Abuse. For reference to a serious syndrome involving rhabdomyolysis after intravenous abuse of phenmetrazine, see Dexamfetamine Sulfate, p. 2319.3.

Preparations

Pharmacopoeial Preparations
USP 36: Phenmetrazine Hydrochloride Tablets.

Phentermine *(BAN, USAN, rINN)* ⊗

Fentermiini; Fentermin; Fentermina; Phenterminum; Фентермин.
α,α-Dimethylphenethylamine.
$C_{10}H_{15}N$=149.2
CAS — 122-09-8.
ATC — A08AA01.
ATC Vet — QA08AA01.
UNII — C045TQL4WP.

Phentermine Hydrochloride *(BANM, rINNM)* ⊗

Fentermina, hidrocloruro de; Hidrocloruro de fentermina; Phentermine, Chlorhydrate de; Phentermini Hydrochloridum; Фентермина Гидрохлорид.
$C_{10}H_{15}N,HCl$=185.7
CAS — 1197-21-3.
ATC — A08AA01.
ATC Vet — QA08AA01.
UNII — 0K2I505OTV.

Pharmacopoeias. In *US.*

USP 36: (Phentermine Hydrochloride). A white, odourless, hygroscopic, crystalline powder. Soluble in water and in the lower alcohols; slightly soluble in chloroform; insoluble in ether. pH of a 2% solution in water is between 5.0 and 6.0. Store in airtight containers.

Uses and Administration

Phentermine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.2). It has been used as an anorectic in the short-term treatment of moderate to severe obesity (p. 2315.1), although stimulants are no longer recommended for this indication; it may also be used in overweight patients (BMI of 27 kg/m^2 or more) if other risk factors such as hypertension, diabetes mellitus, or dyslipidaemia are present. Phentermine is given orally as the hydrochloride or the base; phentermine hydrochloride 15 mg is equivalent to about 12 mg of phentermine.

The usual dose of phentermine hydrochloride ranges from 15 to 37.5 mg daily given as a single dose before or after breakfast; alternatively, the higher dose of 37.5 mg daily may be given in 2 divided doses. Phentermine base is given as a modified-release, ion-exchange resin complex in a usual dose of 15 or 30 mg once daily before breakfast or 10 to 14 hours before bedtime.

A once-daily modified-release combination preparation containing phentermine hydrochloride and topiramate (p. 551.1) is also available. The recommended initial dose is the equivalent of phentermine 3.75 mg with topiramate 23 mg daily in the morning; after 14 days, this may be increased to phentermine 7.5 mg/topiramate 46 mg daily. If the patient has not lost at least 3% of initial body-weight after 12 weeks at this dose, treatment should be stopped or the dose further increased to phentermine 11.25 mg/topiramate 69 mg daily for 14 days, followed by phentermine 15 mg/topiramate 92 mg daily.

Treatment should be stopped if the patient has not lost at least 5% of initial body-weight after 12 weeks at the highest dose, as continued treatment is unlikely to be of benefit; withdrawal of therapy should be made gradually by taking a dose every other day for at least 1 week before stopping altogether to avoid precipitating a seizure.

Reduced doses are recommended in patients with hepatic or renal impairment, see below.

Regulatory authorities in the EU have called for the withdrawal of phentermine from the market (see Effects on the Cardiovascular System in Fenfluramine, p. 2322.3).

References.
1. Cameron F, *et al.* Phentermine and topiramate extended release (Qsymia®): first global approval. *Drugs* 2012; **72:** 2033–42.
2. Smith SM, *et al.* Phentermine/topiramate for the treatment of obesity. *Ann Pharmacother* 2013; **47:** 340–9.
3. Cosentino G, *et al.* Phentermine and topiramate for the management of obesity: a review. *Drug Des Devel Ther* 2013; **7:** 267–78.
4. Shin JH, Gadde KM. Clinical utility of phentermine/topiramate (Qsymia®) combination for the treatment of obesity. *Diabetes Metab Syndr Obes* 2013; **6:** 131–9.

Administration in hepatic or renal impairment. Phentermine is excreted in the urine and increased exposure may occur in patients with renal impairment. Licensed product information recommends that the dose of the oral modified-release combination preparation should not exceed phentermine 7.5 mg/topiramate 46 mg once daily in patients with moderate hepatic (Child-Pugh score 7 to 9) or moderate to severe renal (creatinine clearance below 50 mL/min) impairment; its use is not recommended in those with severe hepatic impairment or end-stage renal impairment requiring dialysis due to a lack of data.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p. 2319.2. Urticaria may occur with use of phentermine.

Pulmonary hypertension has been reported in patients receiving phentermine and valvular heart defects in patients receiving the drug with other anorectics such as fenfluramine or dexfenfluramine; these adverse effects, with the relevant precautions to be observed, are discussed under Fenfluramine Hydrochloride (see Effects on the Cardiovascular System, p. 2322.3).

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; however, activated charcoal may be given orally to adults or children who present within 1 hour of ingesting 1 mg/kg or more of phentermine. Lavage may be considered in adults who present within 1 hour of a potentially life-threatening overdose.

Interactions

Phentermine is an indirect-acting sympathomimetic and may interact with other drugs, similarly to dexamfetamine (p. 2320.2).

Pharmacokinetics

Phentermine is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Duromine; Metermine; ***Cz.***: Adipex; ***Hong Kong***: Duromine; Panbesy; Redusa; ***Israel***: Razin; ***Malaysia***: Adipex; Duromine; ***Mex.***: Acxion; Ifa Acxion; Ifa Reduccing†; Raamcap; Sinpet†; Terfamex; ***NZ***: Duromine; ***Philipp.***: Duromine; Supremin; ***S.Afr.***: Duromine; ***Singapore***: Duromine; Panbesy; Umine†; ***Thai.***: Duromine; Panbesy; ***USA***: Adipex-P; Ionamin†; Suprenza; ***Venez.***: Mirubal.

Multi-ingredient Preparations. ***USA***: Qsymia.

Pharmacopoeial Preparations
USP 36: Phentermine Hydrochloride Capsules; Phentermine Hydrochloride Tablets.

Pipradrol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipradrol; Pipradol Hydrochloride; Pipradrol, Chlorhydrate de; Pipradrol, hidrocloruro de; Pipradroli Hydrochloridum; Пипрадрола Гидрохлорид.
α-2-Piperidylbenzhydrol hydrochloride; α,o-Diphenyl-2-piperidinemethanol hydrochloride.
$C_{18}H_{21}NO,HCl$=303.8
CAS — 467-60-7 (pipradrol); 71-78-3 (pipradrol hydrochloride).
ATC — N06BX15.
ATC Vet — QN06BX15.
UNII — F6E46VR9Y2.

Profile

Pipradrol hydrochloride has been given orally in tonic preparations as a CNS stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Alertonic; ***S.Afr.***: Alertonic†.

Prethcamide ⊗

G-5668; Pretcamida; Преткамид.
CAS — 8015-51-8.
ATC — R07AB06.
ATC Vet — QR07AB06.
UNII — 41A1FCW148.

Description. Prethcamide is a mixture of equal parts by weight of cropropamide and crotetamide.

Cropropamide *(BAN, pINN)* ⊗

Cropropamida; Cropropamidum; Kropropamid; Kropropamidi; Кропропамид.

N,N-Dimethyl-2-(*N*-propylcrotonamido)butyramide.

$C_{13}H_{24}N_2O_2$=240.3

CAS — 633-47-6.

UNII — W8TYE9V9BX.

Crotetamide *(BAN, rINN)* ⊗

Crotetamida; Crotétamide; Crotetamidum; Crotethamide; Кротетамид.

2-(*N*-Ethylcrotonamido)-*N,N*-dimethylbutyramide.

$C_{12}H_{22}N_2O_2$=226.3

CAS — 6168-76-9.

UNII — 642I97LB5B.

Profile

Prethcamide, a mixture of equal parts by weight of cropropamide and crotetamide, has actions similar to those of doxapram (p. 2321.2) and has been used orally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Micoren†.

Propylhexedrine *(BAN, rINN)* ⊗

Hexahydrodesoxyephedrine; Propilhexedrina; Propylhexed; Propylhexédrine; Propylhexedrinum; Пропилгекседрин.

2-Cyclohexyl-1-methylethyl-(methyl)amine; (±)-*N*-α-Dimethylcyclo-hexaneethylamine.

$C_{10}H_{21}N$=155.3

CAS — 101-40-6; 3595-11-7 ((±)-propylhexedrine).

UNII — LQU92IU8LL.

Pharmacopoeias. In *US*.

USP 36: (Propylhexedrine). A clear colourless liquid having a characteristic amine-like odour. It slowly volatilises at room temperature and absorbs carbon dioxide from the air. Very slightly soluble in water; soluble 1 in 0.4 of alcohol, 1 in 0.2 of chloroform, and 1 in 0.1 of ether. Its solutions are alkaline to litmus. Store in airtight containers.

Propylhexedrine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de propilhexedrina; Propilhexedrina, hidrocloruro de; Propylhexédrine, Chlorhydrate de; Propylhexedrini Hydrochloridum; Пропилгекседрина Гидрохлорид.

$C_{10}H_{21}N,HCl$=191.7

CAS — 1007-33-6; 6192-95-6 ((±)-propylhexedrine hydrochloride).

UNII — 064LUN7NZ5.

Uses and Administration

Propylhexedrine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p. 2319.2). It has been used as an inhalant for nasal decongestion.

Propylhexedrine hydrochloride has been given orally as an anorectic in the treatment of obesity but stimulants are no longer recommended for this indication. The (-)-isomer, levopropylhexedrine hydrochloride, has been used similarly.

Adverse Effects, Treatment and Precautions

As for Dexamfetamine Sulfate, p. 2319.2.

Nasal inhalation may cause transient burning, stinging, mucosal dryness, and sneezing. Prolonged use can cause rebound congestion, redness, swelling, and rhinitis. Systemic effects such as headache, hypertension, nervousness, and increased heart rate may occur.

Propylhexedrine is subject to oral and intravenous abuse; fatalities due to myocardial infarction, heart failure, or pulmonary hypertension have been reported. Psychosis may occur.

Abuse. References.

1. White L, DiMaio VJM. Intravenous propylhexedrine and sudden death. *N Engl J Med* 1977; **297:** 1071.
2. Anderson RJ, *et al*. Intravenous propylhexedrine (Benzedrex) abuse and sudden death. *Am J Med* 1979; **67:** 15–20.
3. Cameron J, *et al*. Possible association of pulmonary hypertension with an anorectic drug. *Med J Aust* 1984; **140:** 595–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Benzedrex.

Pharmacopoeial Preparations

USP 36: Propylhexedrine Inhalant.

Sibutramine Hydrochloride

(BANM, USAN, rINNM) ⊗

BTS-54524; Hidrocloruro de sibutramina; Sibutramin Hidroklorür; Sibutramina, hidrocloruro de; Sibutramine, Chlorhydrate de; Sibutramini Hydrochloridum; Сибутрамина Гидрохлорид.

(±)-1-(*p*-Chlorophenyl)-α-isobutyl-*N,N*-dimethylcyclobutanemethylamine hydrochloride monohydrate.

$C_{17}H_{26}ClN,HCl,H_2O$=334.3

CAS — 106650-56-0 (sibutramine); 84485-00-7 (anhydrous sibutramine hydrochloride); 125494-59-9 (sibutramine hydrochloride monohydrate).

ATC — A08AA10.

ATC Vet — QA08AA10.

UNII — OGM0YHD1WF.

Pharmacopoeias. In *US*.

USP 36: (Sibutramine Hydrochloride). White to cream, crystalline powder. Slightly soluble in water at pH 5.2. Store in airtight containers.

Profile

Sibutramine, which is structurally related to amfetamine (p. 2316.1), is a serotonin and noradrenaline reuptake inhibitor; it also inhibits dopamine reuptake but to a lesser extent. Sibutramine has been used in the management of obesity. However, cardiovascular and cerebrovascular adverse effects, sometimes serious, including vasodilatation, cardiac arrhythmias, hypertension, myocardial infarction, and stroke, have been noted and this has led to the suspension of sibutramine in many countries (see below for further details).

References.

1. Nisoli E, Carruba MO. A benefit-risk assessment of sibutramine in the management of obesity. *Drug Safety* 2003; **26:** 1027–48.
2. Vettor R, *et al*. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* 2005; **28:** 942–9.

Adverse effects and precautions. *EFFECTS ON THE CARDIOVASCULAR SYSTEM.* In January 2010, the EMEA's Committee for Medicinal Products for Human Use (CHMP) reported on its safety review of sibutramine.[1] Data from a large study, the Sibutramine Cardiovascular OUTcomes (SCOUT) study showed an increased risk of non-fatal, but serious, cardiovascular events such as myocardial infarction and stroke in patients taking sibutramine. It was also noted that the average weight loss achieved with sibutramine in all studies was modest. Consequently, the CHMP considered that the cardiovascular risks of sibutramine outweighed its benefits and recommended that sibutramine be suspended across the EU.

The SCOUT study was a randomised, double-blind, placebo-controlled study in about 10 000 obese and overweight patients, with cardiovascular disease and/or type 2 diabetes treated over a 6-year period.[1,2] Patients treated with sibutramine had a 16% increased risk of non-fatal cardiovascular events compared with those taking placebo. Although most of the patients enrolled within the SCOUT study had contra-indications for sibutramine under normal conditions of use, the CHMP considered the cardiovascular risk to be relevant to normal clinical use because it is not always possible to identify underlying cardiovascular disease in patients who are obese or overweight. Therefore, it considered that further restrictions on the use of sibutramine would be unlikely to reduce the risk to an acceptable level.

Based on the SCOUT data, the FDA did not initially withdraw sibutramine from the US market in January 2010, but stated that it was now contra-indicated in patients with a history of cardiovascular disease. However, after further analysis[3] of the data, sibutramine was subsequently withdrawn from the US market in October 2010.

1. EMEA. The European Medicines Agency recommends suspension of marketing authorisations for sibutramine: weight-loss medicine associated with increased risk of cardiovascular events to be removed from all markets in the European Union (issued 21st January, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/01/WC500069995.pdf (accessed 21/07/10)
2. MHRA. Sibutramine: suspension of marketing authorisation as risks outweigh benefits (issued 21st January, 2010). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON068475 (accessed 27/01/10)
3. FDA. Drug safety communication: FDA recommends against the continued use of Meridia (sibutramine) (issued 8th October, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm228746.htm#Safety_Announcement (accessed 11/10/10)

PORPHYRIA. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sibutramine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

PREGNANCY. Between May 2001 and September 2004,[1] the prospective outcomes of 52 pregnant women who were exposed to sibutramine in the first trimester of pregnancy were recorded. Hypertensive complications were seen in 7 cases but there were no cases of congenital anomalies. The authors suggest that, based on a small number of exposures, sibutramine may not be teratogenic in pregnancy.

1. De Santis M, *et al*. Early first-trimester sibutramine exposure: pregnancy outcome and neonatal follow-up. *Drug Safety* 2006; **29:** 255–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aderan; Downtrat; Ipomex; Restrical; Saciety†; Sertinal†; Sibu-Estirol†; Sibu-Tratobes†; ***Austral.***: Reductil†; ***Austria***: Reductil†; ***Belg.***: Reductil†; ***Braz.***: Biomag; Nolipo; Plenty; Reductil†; Saciette; Sibuctil; Sibus; Sibutran; Sigran (C1); Slenfig; Vazy; ***Canad.***: Meridia†; ***Chile***: Adisar; Atenix; Ipogras; Medixil; Mesura; Milical; Mintagras; Noducil†; Reductil†; Reduten; Saton; ***Cz.***: Lindaxa†; Meridia†; ***Denm.***: Reductil†; ***Fin.***: Reductil†; ***Fr.***: Subutral†; ***Ger.***: Reductil†; ***Gr.***: Reductil†; ***Hong Kong***: Reductil†; ***Hung.***: Lindaxa†; Reductil†; ***India***: Fetrasil; Leptos; Obestat; ***Indon.***: Maxislim; Reductil†; ***Irl.***: Reductil†; ***Israel***: Reductil†; ***Ital.***: Ectiva†; Reductil†; ***Malaysia***: Reductil†; ***Mex.***: Adelseril; Adelvag; Ectiva; Gea; Ifa-Certez; Kifenip; Obectiv; Raductil; Randism†; Segusiv; Serotramin; Siruton; Tramentel; Vivelisi; ***Neth.***: Reductil†; ***Norw.***: Reductil†; ***NZ***: Reductil†; ***Philipp.***: Lesfat; Nobese; Reductil†; Sibutrim†; Slenfig; Zytrim†; ***Pol.***: Lindaxa†; Meridia†; Zelixa†; ***Port.***: Egostar†; Reductil†; Zelium†; ***Rus.***: Goldline (Голдлайн); Lindaxa (Линдакса); Meridia (Меридиа); Reduksin (Редуксин); Slimia (Слимия); ***S.Afr.***: Ciplatrim; Ectiva; Reductil†; ***Singapore***: Ectiva†; Reductil†; Slenfig†; ***Spain***: Reductil†; ***Swed.***: Reductil†; ***Switz.***: Reductil†; ***Thai.***: Reductil†; ***Turk.***: Burna; Nadyak; Reductil†; Zelium; ***UK***: Reductil†; ***Ukr.***: Lindaxa (Линдакса)†; Meridia (Меридиа)†; ***USA***: Meridia†; ***Venez.***: Milical; Reductil†; Repentil; Vintix.

Multi-ingredient Preparations. ***Mex.***: Ifa-Certez Duo; Redumed.

Tenamfetamine *(rINN)* ⊗

MDA; 3,4-Methylenedioxyamphetamine; Methylenedioxyamphetamine; SKF-5; Ténamfétamine; Tenamfetaminum; Tenanfetamina; Тенамфетамин.

α-Methyl-3,4-methylenedioxyphenethylamine.

$C_{10}H_{13}NO_2$=179.2

CAS — 4764-17-4; 51497-09-7.

UNII — XJZ28FJ27W.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of tenamfetamine:

EA1299; Eve; Love Drug; Love Pill; MDMA; Mellow Drug of America.

Profile

Tenamfetamine is a phenylethylamine compound, structurally related to amfetamine and mescaline, with hallucinogenic effects. It has been subject to abuse and dependence. Several similar compounds are known because of their abuse and include:

- brolamfetamine (4-bromo-2,5-dimethoxyamfetamine; bromo-DMA; bromo-DOM; 2,5-dimethoxy-4-bromoamfetamine; DOB)
- 4-bromo-2,5-dimethoxyphenylethylamine (2's; Afterburner; BDMPEA; Bees; Bromo; Bromo Mescaline; 2-CB; MFT; Nexus; Spectrum; Toonies; Venus)
- 2,5-dimethoxy-4-metamfetamine (DOM; 4-methyl-2,5-dimethoxyamfetamine; Serenity, Tranquillity and Peace; STP)
- 3,4-methylenedioxyethylamfetamine (Adam and eve; *N*-ethyltenamfetamine; Eve; MDE; MDEA; 3,4-methylenedioxyethamfetamine)
- *N*-hydroxy methylenedioxyamfetamine (*N*-hydroxytenamfetamine *N*-hydroxy MDA; 3,4-methylenedioxy-*N*-hydroxyamfetamine)
- methoxyamfetamine (Death; 4-methoxyamfetamine; *p*-methoxyamfetamine; PMA)
- methylenedioxymethamfetamine (Ecstasy) (see p. 2325.2)
- 2,4,5-trimethoxyamfetamine (2,4,5-TMA; TMA; TMA-2)

In large doses the adverse effects of tenamfetamine and related compounds are similar to those of dexamfetamine and may be treated similarly (see p. 2319.2). Fatalities have been associated with the abuse of some of these compounds.

Reviews of the properties of some designer drugs, including phenylethylamine compounds.

1. Buchanan JF, Brown CR. Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. Chesher G. Designer drugs—the "whats" and the "whys". *Med J Aust* 1990; **153:** 157–61.
3. Christophersen AS. Amphetamine designer drugs—an overview and epidemiology. *Toxicol Lett* 2000; **112-113:** 127–31.
4. Kraemer T, *et al.* Toxicokinetics of amphetamines: metabolism and toxicokinetic data of designer drugs, amphetamine, methamphetamine, and their N-alkyl derivatives. *Ther Drug Monit* 2002; **24:** 277–89.
5. Reneman L. Designer drugs: how dangerous are they? *J Neural Transm* 2003; **66** (suppl): 61–83.

Tesofensine *(rINN)*

NS-2330; Tesofensina; Tésofensine; Tesofensinum; Тезофенсин.

(1*R*,2*R*,3*S*,5*S*)-3-(3,4-Dichlorophenyl)-2-(ethoxymethyl)-8-methyl-8-azabicyclo[3.2.1]octane.

$C_{17}H_{23}Cl_2NO$=328.3

CAS — 195875-84-4.

UNII — BLH9UKX9V1.

Profile

Tesofensine is a dopamine, noradrenaline and serotonin reuptake inhibitor that is being investigated for its use in the management of obesity.

References.

1. Astrup A, *et al.* Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372:** 1906–13.

Thyroid and Antithyroid Drugs

The main role of the thyroid gland is to regulate tissue metabolism through production of the **thyroid hormones** 3,5,3′,5′-tetra-iodo-L-thyronine (levothyroxine, L-thyroxine, thyroxine; T_4) and, in smaller amounts, 3,5,3′-tri-iodo-L-thyronine (liothyronine, L-tri-iodothyronine, tri-iodothyronine; T_3). Most of the T_3 in the body is derived from peripheral conversion of T_4.

The production of thyroid hormones is dependent on an adequate supply of dietary iodine. Iodine is reduced to iodide in the gastrointestinal tract and is then readily absorbed and actively transported into the thyroid, where it undergoes oxidation, catalysed by thyroid peroxidase. Oxidised iodide is incorporated into the glycoprotein thyroglobulin to form inactive iodotyrosines. A coupling reaction, also catalysed by thyroid peroxidase, yields the hormonally active iodothyronines, T_3 and T_4, joined by a peptide bond to thyroglobulin for storage in the follicular colloid. The release of proteolytic enzymes from lysosomes degrades the thyroglobulin into its constituent amino acids to release T_3 and T_4 into the circulation; iodide resulting from this reaction is recycled.

Thyroid hormone homoeostasis is maintained by autoregulatory mechanisms within the gland, and by the hypothalamic-pituitary-thyroid axis. In response to falling plasma concentrations of unbound T_3 and T_4, the hypothalamus secretes thyrotropin releasing hormone (protirelin; TRH—see p. 2344.2), which in turn stimulates the synthesis and release of thyroid stimulating hormone (thyrotropin; TSH—see p. 2346.1) by the anterior pituitary gland. TSH acts on its receptor in the thyroid gland to increase production of T_3 and T_4, and also to release hormone stored in the gland. As thyroid hormone concentrations in blood increase, the secretion of TSH, and possibly TRH, will be suppressed. The term euthyroidism is used when the thyroid gland is functioning normally and there are normal amounts of thyroid hormone in the blood.

Goitre and thyroid nodules

Goitre is the enlargement of the thyroid gland. The swelling may be focal (caused by a solitary thyroid nodule, adenoma, or cyst) or generalised, in which case it is usually diffuse at first, later becoming multinodular. The management of toxic (hormone oversecreting) goitres is discussed under Hyperthyroidism, below.

Non-toxic goitres may be associated with intrinsic defects in hormone production, or extrinsic factors such as dietary-iodine deficiency in endemic goitre (see Iodine Deficiency Disorders, p. 2337.3). Decreased secretion of thyroid hormone results in an excessive output of thyroid-stimulating hormone (TSH) from the pituitary. This stimulates thyroid-hormone production but also leads to hypertrophy and hyperplasia of the thyroid gland. If the response to TSH overcomes the deficiency in thyroid-hormone synthesis then the patient is goitrous and euthyroid but if the compensatory response to TSH is inadequate then goitre with hypothyroidism (see p. 2333.3) occurs. Other factors can also contribute, such as autoantibody-stimulated thyroid growth, and thyroid autonomy, in which the gland functions independently of TSH control.

The general aims in the management of thyroid masses are:

- the detection and treatment of malignancy
- the reduction of goitre or prevention of further enlargement, and the relief of obstructive symptoms
- the maintenance of a euthyroid state

In established **malignancy**, surgery, followed by levothyroxine replacement therapy, is the usual course (for further discussion of the treatment of thyroid cancer, see p. 716.1).

There is controversy as to whether a **benign solitary nodule** should be treated and, if so, how.[1] Surgery is sometimes indicated for symptomatic patients or for cosmetic reasons.[1-3] Laser ablation therapy is an alternative in those patients in whom surgery is not an option.[2] Alternatively suppressive therapy with doses of levothyroxine sufficient to suppress TSH production and reduce the size of the nodule has been widely practised.[1,3] However, treatment seems beneficial mostly in a subgroup of patients with small, solid nodules,[4] and guidelines[2,5] state that routine levothyroxine is not recommended; it may be considered for small nodules in young patients from areas of iodine deficiency, and in nodular goitres with no evidence of autonomous thyroid hormone production.[2] Sclerotherapy by percutaneous alcohol injection can produce substantial reductions, but the procedure is painful and requires considerable skill;[1,2] repeat injections are necessary to achieve complete cure.[3] Guidelines[2] consider it an option for cysts and complex nodules with a lot of fluid, but not for solid solitary nodules, whether hyperfunctioning or not. Radio-iodine (^{131}I) is an option for treatment of a functioning nodule.[1-3]

There is no ideal treatment for **benign multinodular goitre**.[6] Surgery is recommended for large goitres.[3,6] Non-surgical options include levothyroxine therapy and radio-iodine (^{131}I) therapy. Levothyroxine suppression therapy is effective in patients with **diffuse** non-toxic goitre, and may be of benefit in some patients with multinodular disease. However, many patients with large multinodular goitres have autonomous thyroid hormone production, and in such patients levothyroxine is of no benefit and may cause overt hyperthyroidism.[3] Radio-iodine (^{131}I) treatment appears to be more effective and better tolerated than levothyroxine,[7] and is the routine choice for non-toxic multinodular goitre in a few European countries.[3] However, in other countries with high dietary iodine intake, the uptake of iodine by the thyroid is low, and higher doses are necessary.[3] Thyrotropin alfa can increase the absorbed radio-iodine (^{131}I) dose, and this strategy is under investigation.[6]

1. Hegedüs L. The thyroid nodule. *N Engl J Med* 2004; **351:** 1764–71.
2. Gharib H, *et al.* AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *Endocr Pract* 2010; **16:** 468–75. Full version: http://www.aace.com/sites/default/files/ThyroidGuidelines.pdf (accessed 18/05/11)
3. Hegedüs L, *et al.* Management of simple nodular goiter: current status and future perspectives. *Endocr Rev* 2003; **24:** 102–32.
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Hyperthyroidism

Hyperthyroidism is overactivity of the thyroid gland, with consequent excess secretion of hormones. The terms thyrotoxicosis and hyperthyroidism are used interchangeably, although some apply 'thyrotoxicosis' to the *effects* of excessive thyroid hormone. The most common causes of hyperthyroidism are Graves' disease (diffuse toxic goitre) and hyperactivity arising from single or multiple thyroid nodules (toxic nodular goitre or Plummer's disease). Graves' disease (or Basedow's disease) is an auto-immune condition in which thyroid-stimulating antibodies bind to thyroid-stimulating hormone (TSH) receptors, mimicking the effect of prolonged TSH stimulation. Graves' disease, frequently occurs with other diseases such as Addison's disease, type 1 diabetes mellitus, and pernicious anaemia, and there may be a genetic predisposition. Iodine and its salts, or iodine-containing drugs such as amiodarone, can also be a cause of both hyperthyroidism and hypothyroidism (see Effects on Thyroid Function, under Amiodarone, p. 1302.3). Thyroiditis (an inflammation of the thyroid gland) may cause transient hyperthyroidism, followed by progression to hypothyroidism.

A **diagnosis** of primary hyperthyroidism may be confirmed by finding a low TSH value and a high concentration of free T_4 or T_3 in the circulation. Determination of TSH, which is low in hyperthyroidism due to negative feedback, allows differential diagnosis of hyperthyroidism from a TSH-secreting pituitary tumour.

Subclinical hyperthyroidism is characterised by normal thyroid hormone concentrations, decreased TSH concentrations, but no clinical symptoms. It has been reported to occur less frequently than subclinical hypothyroidism. Consensus on management has been lacking.[1-3] Treatment decisions are based on age, TSH concentrations, risk of progression to overt disease, symptoms, and cardiac and skeletal manifestations.[4] Generally, evidence supports treatment in patients with a TSH less than 0.1 milli-units/litre, in those with multinodular goitre, those with osteoporosis or at risk of atrial fibrillation.[1,3-6] Treatment options include antithyroid drugs and radio-active iodine (see below for discussions of both therapies);[3,4] partial thyroidectomy is reserved for those patients with multi-nodular goitre causing compression.[4]

There are three main forms of **treatment** for hyperthyroidism: drug therapy, use of radio-iodine, or surgery.

Drug therapy. The main **antithyroid drugs** are carbimazole (in the UK), thiamazole (in the USA), and propylthiouracil.[3,6-8] These are all thiourea drugs that inhibit thyroid hormone production; propylthiouracil also blocks peripheral conversion of thyroxine to tri-iodothyronine.[6,8] Carbimazole or thiamazole are preferred in most situations, particularly because of concerns about the hepatotoxicity of propylthiouracil (see Hyperthyroidism, under Propylthiouracil, p. 2344.1).

Many patients begin treatment with an antithyroid drug in the hope of achieving remission (defined as euthyroidism for 1 year after stopping drug therapy);[7-10] they receive higher doses initially until they become euthyroid, generally within 1 to 2 months. Once a response to the antithyroid drug has been obtained, patients with more severe or recurrent disease may require ablative treatment with either radio-iodine or surgery (see below), while those with mild to moderate disease may be best managed with lower maintenance doses of antithyroid drugs (*'titration regimen'*). Treatment is typically given for 12 to 18 months.[3,6,7,9,11-13] Relapse at some stage after stopping therapy occurs in about 50 to 60% of cases,[7,10,11] usually within 3 to 6 months after stopping the drugs,[7] but may also occur years later.[8] Use of levothyroxine during and after antithyroid therapy was reported to reduce relapse rates, but subsequent studies failed to corroborate this,[7] and concomitant[8,11] or continued[13] thyroxine replacement therapy is considered to provide no benefit in terms of recurrence.

The *'block-replace regimen'* has also been used, in which thyroxine replacement therapy is added, while maintaining the high initial dose of antithyroid drug.[9] This has been suggested to help prevent hypothyroidism induced by the antithyroid drug,[8] and some consider it useful for patients with unstable hyperthyroidism.[11] Therapy is usually given for 6 to 12 months,[8] although 6 months was found to be as effective as 12 months in one study.[13] However, the titration regimen was found to be no less effective than the block-replace regimen, with fewer adverse effects and fewer patient withdrawals,[13] and US guidelines recommend against using the block-replace regimen.[3]

Beta blockers are used to relieve symptoms of hyperthyroidism such as tachycardia, tremor, anxiety, and sweating.[6,8,10] They are used as short-term adjuncts to therapy.[3,6,8,10] Their use in heart failure associated with thyrotoxicosis is controversial due to the risk of cardiac deterioration.[14] In general, all beta blockers are considered equally effective, although those with a longer duration of action such as atenolol, metoprolol, or nadolol are preferred.[8] Those who cannot tolerate beta blockers may be treated with calcium-channel blockers.[3]

Potassium and sodium perchlorate have also been used; they increase responsiveness to conventional antithyroid drugs and may be useful in patients with iodine-induced hyperthyroidism, possibly including that associated with amiodarone therapy, as well as for prophylaxis against hyperthyroidism from the use of iodinated contrast agents.[15]

In those patients in whom drug therapy fails to achieve long-term remission, ablative therapy may be considered in the form of radio-iodine therapy or surgery.

Radio-iodine therapy with ^{131}I as oral sodium iodide (^{131}I) treats hyperthyroidism by destroying the functioning cells of the thyroid gland to produce a state of mild hypothyroidism.[3] It is often used as initial therapy in the USA.[3,8] It is also used in patients who have not responded to antithyroid drug therapy or who have relapsed after it.[3,7,8,11]

Pretreatment of patients with an antithyroid drug for 4 to 8 weeks before radio-iodine therapy has been advocated, to deplete the thyroid gland of stored hormone and reduce the risk of precipitating thyroid storm due to ^{131}I-induced thyroiditis. However, this is not considered necessary for all patients, although it is generally agreed that the elderly or those with severe disease or increased risk of cardiac symptoms should receive some form of pretreatment.[3,8,16] Meta-analysis has shown that use of antithyroid drugs in the week before or after radio-iodine therapy decreases its effectiveness, increasing the risk of treatment failure.[17] The efficacy of radio-iodine treatment is not diminished after treatment with carbimazole or thiamazole as long as the drug is stopped 3 to 5 days before radio-iodine is given;[6] US guidelines[3] recommend that if thiamazole pretreatment is used, the drug should be stopped 3 to 5 days before radio-

iodine is given and restarted 3 to 7 days later before being tapered off over 4 to 6 weeks as thyroid function normalises. Although it has been considered that a poor response to radio-iodine was more likely with propylthiouracil than thiamazole,[6-8] this was not supported by meta-analysis.[17] Pretreatment with a beta blocker for symptomatic relief may be given to patients receiving radio-iodine,[18] and US guidelines[3] recommend this in patients with severe disease or at increased risk from worsening symptoms.

The dose of radio-iodine needed to achieve control is difficult to predict and there has been disagreement on the most appropriate dosage schedule.[18] A radioactive iodine uptake test can be used to help estimate the thyroid's ability to trap iodine, but giving a fixed dose (typically 10 to 15 millicuries) may be just as effective.[3] Radio-iodine therapy may take several months to achieve a clinical response, and cover with an antithyroid drug may be required during this period.[11] Radio-iodine is not generally considered to increase the risk of malignancy,[3,8,11] teratogenicity,[11,16] or infertility,[3,8] but it is contra-indicated in pregnancy and while breast feeding.[3,6] Adequate radio-iodine therapy generally results in hypothyroidism and all patients require long-term follow-up and possible levothyroxine replacement therapy.[3] Cohort studies have found increased mortality in those patients with hyperthyroidism treated with radio-iodine.[19,20] However, this risk was no longer evident once patients with overt hypothyroidism (induced by radio-iodine therapy) were given thyroxine replacement therapy. The authors considered these findings to strongly support a definitive treatment of hyperthyroidism with doses of radio-iodine sufficient to cause overt hypothyroidism, and the prompt treatment of subclinical hypothyroidism after radio-iodine therapy.[20]

Surgery. Thyroidectomy is usually used only in specific situations. These include patient preference, pregnancy, patients who are intolerant of or unresponsive to antithyroid drugs, the presence of a very large goitre, or suspicious nodules.[3,8,10] Total thyroidectomy is the procedure of choice, to prevent recurrent hyperthyroidism.[3,8,11] Complications may include hypoparathyroidism and laryngeal nerve injury.[3,6,8] Euthyroidism is established before surgery with antithyroid drugs if possible,[3,6,11] and iodide is given for 7 to 10 days before surgery to reduce the vasculature of the gland.[3,6,10] Alternatively, a combination of iodine and a beta blocker,[3] and possibly glucocorticoids,[8] has been suggested if surgery is urgent. Iopanoic acid has been used short-term for rapid preparation for surgery, but is ineffective as long-term therapy.[6] However, some[21] have stated that pre-operative iodine probably has no beneficial effect. Surgery results in permanent hypothyroidism in most patients,[6] necessitating thyroxine replacement therapy.[3,11]

Arterial embolisation. There are some patients who cannot, or choose not to, receive any of the three main forms of treatment for hyperthyroidism. Thyroid arterial embolisation has been used as an alternative with an outcome similar to that of subtotal thyroidectomy.[22]

If untreated or inadequately controlled, hyperthyroidism can complicate **pregnancy** and have adverse perinatal effects.[23-25] While there is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome,[23] and treatment is therefore considered unnecessary,[24] overt hyperthyroidism is generally treated throughout pregnancy with an antithyroid drug at the minimum dose needed to maintain a borderline euthyroid state.[3,7,8] Propylthiouracil has usually been considered the treatment of choice, mainly because of reports of congenital defects with alternatives.[7,10,23-25] If propylthiouracil is unavailable or unsuitable for use carbimazole and thiamazole are recommended;[7,23] the potential maternal and fetal risk of not treating active hyperthyroidism is considered to outweigh the risk of rare congenital abnormalities.[25] Propylthiouracil is itself associated with a risk of maternal and neonatal hepatotoxicity, and US guidelines recommend that its use should be limited to the first trimester, and that an alternative antithyroid drug, such as thiamazole, should be considered for treatment later in pregnancy.[3] Occasionally, the antithyroid drug can be withdrawn in the third trimester.[7,8] Drug therapy during pregnancy may cause fetal or neonatal hypothyroidism, with or without goitre. This risk appears unrelated to the dose of the drug,[25,26] and the condition may mask neonatal hyperthyroidism[26] (see below). While a beta blocker such as propranolol may be used short-term as adjunctive therapy during pregnancy,[24,25] the use of radio-iodine is contra-indicated during pregnancy and breast feeding.[3,8,23-25] The block-replace regimen is also contra-indicated during pregnancy, because the dose of antithyroid drug that crosses the placenta may be excessive in proportion to the amount of levothyroxine, which increases the risk of fetal goitre and hypothyroidism.[24,25]

For pregnant women who have severe refractory hyperthyroidism, or who cannot take drug therapy for any reason, surgery may be needed. If it cannot be delayed till after birth, it is best done during the second trimester.[3,23,24]

Fetal or **neonatal hyperthyroidism** may occur rarely due to transfer of thyroid-stimulating immunoglobulins across the placenta.[26-28] These immunoglobulins may be present even in women who have been receiving levothyroxine for some years after thyroidectomy or radio-iodine treatment. Fetal disease can also be caused by insufficient treatment for maternal hyperthyroidism.[28] Fetal hyperthyroidism may be treated by giving antithyroid drugs to the mother (which can lead to maternal hypothyroidism);[28] neonatal disease is treated with antithyroid drugs, iodide, and appropriate therapy for cardiovascular complications.[27]

Treatment options for **children** with hyperthyroidism are the same as for adults, namely antithyroid drugs, surgery, or radio-iodine;[3,29-31] the initial choice of therapy varies between countries.[30] Because a minority of children will go into remission with antithyroid drug therapy, treatment with thiamazole for 1 to 2 years is noted as a potential first-line treatment for most children by US guidelines.[3] However, short- and long-term effects of drug therapy can be a cause for concern,[29,31] and some consider definitive therapy in the form of surgery or radio-iodine to be unavoidable.[29] There is some controversy as to the optimal dose of radio-iodine; limited data suggest that a gland-specific low dose is potentially effective for paediatric disease,[30] while others consider a low dose to be associated with an increased risk of malignancy, and advocate higher doses.[31] Radio-iodine is usually considered best avoided in children under 5 years of age.[3,31]

Thyroid storm (also known as thyroid crisis or thyrotoxic crisis) is an extreme accentuation of the hyperthyroid state and should be treated as a medical emergency. It usually occurs in patients with Graves' disease, but can also occur in other types of hyperthyroidism. It is usually abrupt in onset and is often related to some precipitating factor such as inadequate preparation for thyroidectomy or radio-iodine therapy, or infection in previously unrecognised hyperthyroid subjects. Treatment consists of supportive measures, treatment of the precipitating cause, and drug therapy to halt the synthesis, release, and peripheral effects of thyroid hormone.[3,32] The order of therapy is important; inhibition of thyroid gland synthesis with an antithyroid drug should be started before iodine is given to inhibit release of stored thyroid hormone from the gland, to avoid the stimulation of synthesis that could occur if iodine were given first. However, there is some controversy as to the appropriate delay; 30 to 60 minutes is advocated, depending on the clinical urgency.[32] Therapy to decrease peripheral effects includes beta blockers and corticosteroids. Lithium may be used when antithyroid drugs are contra-indicated; it can also be used with antithyroid drugs.[32]

The clinical manifestations of **Graves' ophthalmopathy** may not always occur with those of systemic hyperthyroidism, and may also occur in patients who are euthyroid or even hypothyroid;[33-35] immunoreactivity against the thyrotropin receptor may underlie the disease.[35] Severity is classified as mild, moderate, or severe based on the degree of proptosis, constancy of diplopia, and the effect of optic neuropathy on visual acuity.[36] Treatment aims to protect vision, relieve discomfort, correct dysfunction, and improve cosmetic deformity.[33] Factors such as cigarette smoking that are associated with an increased risk of progression should be eliminated or controlled; thyroid dysfunction should be corrected.[3,34,36] Most patients with mild ocular involvement in hyperthyroidism require no specific therapy;[34,36] dry eye should be managed appropriately (see p. 2190.1). Corticosteroids are often used for moderate to severe disease;[34,36] intravenous pulse therapy has been shown to have a small but statistically significant advantage over oral therapy.[37] However, the optimal glucocorticoid regimen remains uncertain.[34] Orbital corticosteroid injections have been used with varying levels of success.[36] Orbital radiotherapy remains a standard treatment option, despite disputes as to its efficacy,[36,37] and the combination of this and oral glucocorticoids has been shown to be synergistic.[34,37] The appropriate use of radio-iodine therapy for managing hyperthyroidism in patients with Graves' ophthalmopathy remains uncertain[34] as it has been reported to exacerbate ophthalmopathy in some patients. US guidelines[3] suggest that in patients with moderate to severe disease thiamazole or surgery should be preferred; in milder disease radio-iodine is an option but concurrent corticosteroid treatment should be considered unless ophthalmopathy is inactive. Corticosteroids were definitely recommended when radio-iodine was given to those with risk factors such as smoking. Other drugs that have been investigated include immunosuppressive agents and somatostatin analogues.[34,36,37] Ciclosporin plus prednisone has been reported to be of benefit,[33,36] and methotrexate may be an option for refractory disease.[36] Somatostatin analogues such as long-acting octreotide and lanreotide have marginal clinical efficacy.[37]

Surgical orbital decompression may be required if patients do not respond to such therapy or cannot tolerate its adverse effects, or if vision is threatened by severe optic nerve compression.[34,36]

Beta blockers may be used as primary treatment in patients with thyrotoxicosis due to **thyroiditis**, in whom thiourea antithyroid drugs are inappropriate.[3,6] NSAIDs, or in those with more severe symptoms or who fail to respond, corticosteroids, are also recommended in patients with symptomatic subacute thyroiditis.[3]

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Hypothyroidism

Hypothyroidism is the clinical syndrome resulting from deficiency of thyroid hormones. The term **myxoedema** is often reserved for severe or advanced hypothyroidism. Hypothyroidism is usually primary, resulting from malfunction of the thyroid gland. In areas where iodine intake is sufficient the commonest cause of hypothyroidism is auto-immune lymphocytic thyroiditis of which there are two major variants. In **Hashimoto's thyroiditis** there is also goitre whereas in **idiopathic** or **primary myxoedema** (**atrophic thyroiditis**) there is no thyroid enlargement. High-dose radiotherapy to the head and neck, radio-iodine thyroid ablation, or thyroidectomy can also cause hypothyroidism. Hypothyroidism can also be caused by a deficiency of iodine. Endemic cretinism is a result of

maternal, and hence fetal, iodine deficiency and consequent lack of thyroid hormone production (see Iodine Deficiency Disorders, p. 2337.3). Iodine and its salts, or iodine-containing drugs such as amiodarone, can also be a cause of both hypothyroidism or hyperthyroidism (see Effects on Thyroid Function, under Amiodarone, p. 1302.3). Drugs that decrease thyroid hormone synthesis, such as lithium, can also be a cause of hypothyroidism. Central hypothyroidism occurs secondary to disorders of the hypothalamus or pituitary gland.

The **diagnosis** of hypothyroidism may be confirmed by a raised thyroid stimulating hormone (TSH) value and a low free T_4 or T_3 concentration in the circulation. Protirelin and thyrotrophin have also been used for the differential diagnosis of hypothyroidism.

Subclinical hypothyroidism is a condition in which there are normal concentrations of thyroid hormones, raised concentrations of TSH, but no clinical symptoms. Patients with subclinical hypothyroidism are at a greater risk of developing clinical hypothyroidism if they have higher TSH concentrations, or if antibodies against thyroid peroxidase are present.[1-3] Controversy has surrounded the issue of whether the consequences of undiagnosed, and therefore untreated, subclinical disease justifies widespread routine screening; screening has been proposed in those with several risk factors, and for pregnant women.[4,5] Management differs depending on TSH concentrations. While levothyroxine therapy is generally recommended if TSH concentrations are greater than 10 milliunits/litre,[1-9] treatment in those with concentrations below this remains a subject of much debate. Arguments for treatment include avoiding progression to overt disease, improvement in symptoms and quality of life, improvement in lipid profiles, and the possible reduction in cardiovascular risk factors.[4,9,10] Arguments against include the danger of overtreatment, leading to hyperthyroidism,[5] and the fact that, while studies have shown an association between subclinical hypothyroidism and cardiovascular morbidity and mortality,[3] evidence is strongest in those with TSH greater than 10 milliunits/litre.[7,11] Furthermore, while some studies have shown improvement in cardiovascular risk factors with levothyroxine therapy,[12] and there is some evidence that it improved lipid profiles and left ventricular function,[13] others have failed to show conclusive benefit of thyroxine replacement in reducing adverse cardiovascular outcomes,[3,13] especially in those with TSH concentrations between 5 to 10 milliunits/litre.[7] It has been recommended that therapy be individualised in these patients, taking into account patient preference, presence of symptoms, age, and associated comorbidities.[9] Levothyroxine treatment has also been recommended if TSH levels are between 5 and 10 milliunits/litre and the patient has symptoms of hypothyroidism,[3,5-7] or goitre,[1,7,8] or dyslipidaemia,[2,7,8] or if thyroid antibodies are present.[1,2,7,8,14] Treatment is also generally recommended for pregnant women,[3,6,8,9,13,15] infants,[16] and children with subclinical hypothyroidism.[9]

Hypothyroidism is readily **treated** by lifelong replacement therapy with levothyroxine.[1-3,7,10,14,17] Initial and periodic checks should be made to ensure that thyroid replacement treatment is restoring deficiencies in thyroid hormone but not providing an excess. This is best done by monitoring hormone concentrations and the goal of replacement therapy is a normal TSH value.[1,7,14,17,18] The dose of levothyroxine needed to normalise TSH may be supraphysiological, resulting in a slightly elevated T_4 value.[18] Although the thyroid gland produces both T_3 (liothyronine) and T_4 (thyroxine), T_3 is mainly produced by peripheral monodeiodination of circulating T_4 and it is therefore sufficient to give levothyroxine alone. There is no rationale for the use of combined preparations containing liothyronine and levothyroxine,[2,3,7,14,17,18] or of dried thyroid hormone extracts,[3] which may lead to elevated serum concentrations of T_3 and thyrotoxic symptoms.[7,10,14] Nonetheless, some patients prefer a combination and some clinicians recommend combination therapy when a patient remains lethargic or has memory impairment despite a normalised TSH with levothyroxine therapy.[18] Liothyronine itself may be used initially for its rapid onset of action in severe hypothyroid states such as myxoedema coma (see below).

Untreated or inadequately controlled hypothyroidism during **pregnancy** increases the risk of early and late obstetric complications and can have potentially serious adverse effects on the mother and the fetus, including impaired cognitive development in the latter.[1,15,17,19-21] Levothyroxine therapy of clinical hypothyroidism during pregnancy is standard practice.[1,15] During the first trimester there is an estimated 30 to 50% increase in the patient's levothyroxine requirement,[21,22] and some have suggested that hypothyroid women should increase their dose by 30% as soon as they discover they are pregnant.[17,19-21] A prospective study of dosage increases, started at confirmation of pregnancy in hypothyroid women, provided evidence that a roughly 30% increase in maternal levothyroxine (accomplished by the addition of 2 tablets weekly) significantly reduced the risk of maternal hypothyroidism throughout the first trimester.[23] Thyroid function tests should be performed as soon as pregnancy is confirmed,[17] and every 2 to 6 weeks thereafter;[1,17,20,22] the TSH concentration is used to guide further levothyroxine dose adjustment.[14,17,20] Some suggest that once the patient is stable, TSH can be checked every 8 weeks.[21]

Congenital or neonatal hypothyroidism is defined as thyroid hormone deficiency at birth.[16] Unrecognised, it can lead to mental retardation, and newborn screening programmes are standard in many countries.[16,24,25] The timing of therapy and the severity of hypothyroidism are important factors in determining the neurocognitive outcome.[16] All infants should be rendered euthyroid as promptly as possible, and rapid replacement therapy with adequate doses of levothyroxine is the treatment of choice;[16,24,25] clinical evaluation should be performed every few months during the first 3 years of life.[16,24] In those with more severe hypothyroidism at diagnosis, some small degree of deficit and incoordination may remain;[16,24,26] tailoring the initial levothyroxine dose to the severity of hypothyroidism and giving higher doses of levothyroxine has been advocated.[16] However, a systematic review[27] failed to confirm the benefits of a high initial dose over a low dose, due to paucity of data, and further studies are required.

Childhood (acquired) hypothyroidism occurs after 6 months of age; if the onset is after 2 to 3 years of age, no permanent intellectual damage or neurological deficit is considered likely. Treatment is with levothyroxine, and doses are individualised according to serum TSH and free T_4 concentrations. Overall, the prognosis is good if it is diagnosed early and the hypothyroidism is not of long-standing duration.[28]

Myxoedema coma (or hypothyroid coma) is an extreme accentuation of the hypothyroid state and should be treated as a medical emergency. It typically presents in older women in the winter months, and is often related to some precipitating factor such as drug therapy, systemic illness, or other causes. It has a poor prognosis, and despite treatment, is associated with substantial mortality.[7,10,17,29,30] Treatment consists of supportive measures aimed at cardiovascular, respiratory, and neurological symptoms, the management of any precipitating factor or coexisting problems, and thyroid hormone replacement therapy.[7,17,29,30] Treatment should include intravenous hydrocortisone because of the likelihood of adrenocortical insufficiency;[17,29,30] the first dose of this should be given before thyroid hormone therapy,[17] and then tapered and stopped on the basis of clinical response.[29] Controversy exists as to which preparation of thyroid hormone should be used, and the optimal dose and regimen. Proponents variously advocate the use of levothyroxine alone, or liothyronine alone, or a combination of both.[7,14,17,29,30] Advantages of liothyronine include its rapid onset of action, the fact that it crosses the blood-brain barrier more readily than levothyroxine, and lack of any need for peripheral conversion of T_4 to T_3, which may be compromised in sick hypothyroid patients.[17,29] However, results with liothyronine monotherapy have been mixed, with some fatalities. There may be an increased risk of cardiac complications,[30] and serum concentrations fluctuate.[29] Patient selection and the choice of dose regimen may be as important as which drug is used.[30] Intravenous therapy should be used initially until oral therapy is possible.[17,29,30] Alternatively, the nasogastric route may be used.[29]

1. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002; **8:** 457–69. Amended 2006 version available at: http://www.aace.com/sites/default/files/hypo_hyper.pdf (accessed 19/05/11)
2. Topliss DJ, Eastman CJ. Diagnosis and management of hyperthyroidism and hypothyroidism. *Med J Aust* 2004; **180:** 186–93.
3. Vaidya B, Pearce SHS. Management of hypothyroidism in adults. *BMJ* 2008; **337:** a801.
4. Gharib H, *et al.* Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab* 2005; **90:** 581–5. Also available at: http://jcem.endojournals.org/cgi/reprint/90/1/581.pdf (accessed 19/05/11)
5. Arrigo T, *et al.* Subclinical hypothyroidism: the state of the art. *J Endocrinol Invest* 2008; **31:** 79–84.
6. Surks MI, *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; **291:** 228–38.
7. McDermott MT. Hypothyroidism. *Ann Intern Med* 2009; **151:** ITC6-1–ITC6-14.
8. Jones DD, *et al.* Subclinical thyroid disease. *Am J Med* 2010; **123:** 502–4.
9. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. *Mayo Clin Proc* 2009; **84:** 65–71.
10. Roberts CGP, Ladenson PW. Hypothyroidism. *Lancet* 2004; **363:** 793–803.
11. Rodondi N, *et al.* Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; **304:** 1365–74.
12. Razvi S, *et al.* The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 2007; **92:** 1715–23.
13. Villar HCCE, *et al.* Thyroid hormone replacement for subclinical hypothyroidism. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/05/11).
14. Singer PA, *et al.* American Thyroid Association. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Available at: http://thyroidguidelines.net/hypothyroidism_1995/guidelines (accessed 29/06/11)
15. Reid SM, *et al.* Interventions for clinical and subclinical hypothyroidism in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2010 (accessed 27/05/11).
16. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis* 2010; **5:** 17.
17. Devdhar M, *et al.* Hypothyroidism. *Endocrinol Metab Clin North Am* 2007; **36:** 595–615.
18. Joffe RT, *et al.* Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: a literature review and metaanalysis. *Psychosomatics* 2007; **48:** 379–84.
19. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; **351:** 241–9.
20. Glinoer D, Abalovich M. Unresolved questions in managing hypothyroidism during pregnancy. *BMJ* 2007; **335:** 300–302.
21. Fitzpatrick DL, Russell MA. Diagnosis and management of thyroid disease in pregnancy. *Obstet Gynecol Clin North Am* 2010; **37:** 173–93.
22. Abalovich M, *et al.* Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007; **92** (suppl): S1–S47. Also published in: *Thyroid* 2007; **17:** 1159–67. Also available at: http://www.endo-society.org/guidelines/final/upload/Clinical-Guideline-Management-of-Thyroid-Dysfunction-during-Pregnancy-Postpartum.pdf (accessed 29/12/08)
23. Yassa L, *et al.* Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab* 2010; **95:** 3234–41.
24. Rose SR, *et al.* American Academy of Pediatrics. American Thyroid Association. Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics* 2006; **117:** 2290–2303. [Re-affirmed December 2011] Available at: http://pediatrics.aappublications.org/cgi/reprint/117/6/2290 (accessed 11/05/12)
25. Hopwood NJ. Treatment of the infant with congenital hypothyroidism. *J Pediatr* 2002; **141:** 752–4.
26. Rovet JF. Congenital hypothyroidism: long term outcome. *Thyroid* 1999; **9:** 741–8.
27. Ng SM, *et al.* High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 26/05/11).
28. Counts D, Varma SK. Hypothyroidism in children. *Pediatr Rev* 2009; **30:** 251–8.
29. Wartofsky L. Myxedema coma. *Endocrinol Metab Clin North Am* 2006; **35:** 687–98.
30. Kwaku MP, Burman KD. Myxedema coma. *J Intensive Care Med* 2007; **22:** 224–31.

Benzylthiouracil

Benciltiouracilo; Бензилтиоурацил.

6-Benzyl-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one; 6-Benzyl-2-mercaptopyrimidin-4-ol; 6-Benzyl-2-thiouracil.

$C_{11}H_{10}N_2OS$=218.3

CAS — 33086-27-0; 6336-50-1.

ATC — H03BA03.

ATC Vet — QH03BA03.

UNII — PZ35LUM333.

Profile

Benzylthiouracil is a thiourea antithyroid drug similar to carbimazole (below). It is given in the treatment of hyperthyroidism (p. 2332.2) in an initial oral dose of 150 to 200 mg daily, reducing gradually to a maintenance dose of 100 mg daily; it is given in divided doses, preferably with food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Basdene.

Carbimazole *(BAN, rINN)*

Carbimazol; Carbimazolum; Karbimatsoli; Karbimazol; Karbimazolas; Карбимазол.

Ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate.

$C_7H_{10}N_2O_2S$=186.2

CAS — 22232-54-8.

ATC — H03BB01.

ATC Vet — QH03BB01.

UNII — 8KQ660G60G.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Carbimazole). A white or yellowish-white crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone.

Uses and Administration

Carbimazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p. 2332.1). It is used in the management of hyperthyroidism (p. 2332.2), including the treatment of Graves' disease, the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Carbimazole is completely metabolised to thiamazole and it is this metabolite that is responsible for the antithyroid activity of carbimazole.

Carbimazole is given orally in a typical initial dosage of 15 to 40 mg daily, in divided doses; occasionally up to 60 mg daily may be required. Control of symptoms is usually achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to the smallest amount that will maintain the euthyroid state. Typical maintenance doses are 5 to 15 mg daily, which may be given as a single daily dose. Higher initial doses may be needed in thyroid storm.

Carbimazole is also given orally in a dose of 20 to 60 mg daily, with supplemental levothyroxine, as a *blocking-replacement regimen*.

Either form of maintenance treatment is usually continued for at least a year, and often for 18 months; up to 2 years of treatment may be required.

For the use of carbimazole in children and adolescents, see below.

Administration in children. For the treatment of hyperthyroidism (including Graves' disease) in neonates and children up to 12 years of age, the *BNFC* recommends an initial oral dose of carbimazole 750 micrograms/kg (up to a maximum of 30 mg) daily, in divided doses or as a single dose. Children aged 12 to 18 years may be given 30 mg daily initially, in single or divided doses. Doses are adjusted according to response; higher initial doses may be needed in thyroid storm.

Adverse Effects, Treatment, and Precautions

Adverse effects from carbimazole and other thiourea antithyroid drugs occur most frequently during the first 8 weeks of treatment. An immune mechanism has been implicated in many of these reactions and cross-sensitivity between the thiourea antithyroid drugs may occur.

The most common minor adverse effects are nausea and vomiting, gastric discomfort, headache, arthralgia, rashes, and pruritus. These effects are usually self-limiting and may not require therapy to be stopped. However, propylthiouracil should be stopped if arthralgia occurs, as severe transient migratory polyarthritis may develop. Similarly, urticaria with propylthiouracil may herald a serious hypersensitivity reaction and the drug should be stopped; cross-sensitivity for this adverse effect is uncommon and an alternative thiourea drug may be tried.

Bone marrow depression including neutropenia, leucopenia, eosinophilia, and agranulocytosis has been reported. Agranulocytosis is the most serious adverse effect associated with this class of drugs, and fatalities have occurred. Patients or their carers should be told how to recognise such toxicity and should be advised to seek immediate medical attention if mouth ulcers or sore throat, fever, bruising, malaise, or non-specific illness develop. Full blood counts should be performed, and treatment should be stopped immediately if there is any clinical or laboratory evidence of neutropenia. Aplastic anaemia or isolated thrombocytopenia have been reported rarely, as have haemolytic anaemia and hypoprothrombinaemia.

Hepatotoxicity can occur with the thiourea drugs, and can be serious. Jaundice is the most common presentation with carbimazole; there have been rare reports of fulminant hepatitis, hepatic necrosis, encephalopathy, and death with propylthiouracil and thiamazole. Therapy should be withdrawn if hepatic disorders occur.

Other adverse effects sometimes seen with the thiourea antithyroid compounds include hair loss, a lupus-like syndrome, myopathy, vasculitis, nephritis, and taste disturbances. Drowsiness, paraesthesia, neuritis, oedema, skin pigmentation changes, sialadenopathy, and lymphadenopathy can also occur. Creatine phosphokinase values should be measured if patients develop myalgia.

Excessive doses of antithyroid drugs may cause hypothyroidism and goitre; the dose should be reduced, or therapy interrupted. High doses in pregnancy may result in fetal hypothyroidism and goitre (see Pregnancy, p. 2336.1).

Breast feeding. The safety of breast feeding during maternal treatment depends partly on how much drug is distributed into the breast milk. Thiourea antithyroid drugs may be used with care in breast-feeding mothers; neonatal development and thyroid function of the infant should be closely monitored and the lowest effective dose used.

Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily.[1-3] In a small study[4] of breast-feeding mothers taking doses of propylthiouracil as high as 750 mg daily for Graves' disease, no adverse effects were seen on the thyroid status of their infants.

Thiamazole enters breast milk freely, with plasma to milk ratios of almost one.[3-5] The infant's intake of thiamazole after maternal use of carbimazole (or thiamazole) might be greatly reduced by discarding the breast milk produced 2 to 4 hours after a dose,[6] since the highest concentration was found at this time. Two studies found no adverse effects on thyroid function,[7,8] thyroid hormone levels,[7] or physical and intellectual development, in breast-fed infants during up to 6 months[7] to 1 year[8] of maternal treatment with thiamazole. Maximum maternal daily doses of 10 mg of thiamazole,[3] 15 mg of carbimazole, and 150 mg of propylthiouracil[9] have been recommended, although thiamazole 20 to 30 mg has been given to thyrotoxic lactating women for the first month of a year of therapy with no observable adverse effects on the thyroid function of their breast-fed infants.[10] Despite stating that goitre has been associated with the use of carbimazole, the last available guidance from the American Academy of Pediatrics considered the use of all three drugs to be compatible with breast feeding.[11]

1. Kampmann JP, *et al.* Propylthiouracil in human milk: revision of a dogma. *Lancet* 1980; **i:** 736–8.
2. Johansen K, *et al.* Excretion of methimazole in human milk. *Eur J Clin Pharmacol* 1982; **23:** 339–41.
3. Cooper DS. Antithyroid drugs: to breast-feed or not to breast-feed. *Am J Obstet Gynecol* 1987; **157:** 234–5.
4. Momotani N, *et al.* Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol (Oxf)* 2000; **53:** 177–81.
5. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
6. Rylance GW, *et al.* Carbimazole and breastfeeding. *Lancet* 1987; **i:** 928.
7. Azizi F. Effect of methimazole treatment of maternal thyrotoxicosis on thyroid function in breast-feeding infants. *J Pediatr* 1996; **128:** 855–8.
8. Azizi F, *et al.* Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab* 2000; **85:** 3233–8.
9. Lamberg B-A, *et al.* Antithyroid treatment of maternal hyperthyroidism during lactation. *Clin Endocrinol (Oxf)* 1984; **21:** 81–7.
10. Azizi F, Hedayati M. Thyroid function in breast-fed infants whose mothers take high doses of methimazole. *J Endocrinol Invest* 2002; **25:** 493–6.
11. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)

Effects on the blood. While **leucopenia** is considered to be a common adverse effect of the thiourea antithyroid drugs, occurring in up to a quarter of patients, it is usually mild and improves as treatment continues.[1]

Agranulocytosis, a more serious hazard, is usually reported to affect 0.03% of patients in Europe,[2] who are mostly treated with carbimazole. However, the incidence has been reported to be higher (0.4%) in areas where thiamazole is used.[3,4] Fatalities have been reported.[1,2,4,5] Although a direct toxic effect had been suggested, the agranulocytosis associated with the thiourea drugs is generally considered to be immunologically mediated.[1,6] The onset of agranulocytosis is usually rapid and monitoring of the blood count is not always of predictive value;[3] routine monitoring is not indicated.[2] Agranulocytosis has occurred in patients receiving propylthiouracil for a second time who had no such complications in their first course of therapy.[7] There is limited evidence that agranulocytosis is more common at higher doses, and in older patients. However, this has not been proven conclusively.[1] In fact, life-threatening agranulocytosis and hepatotoxicity during initiation of a standard dose of carbimazole has been described.[8]

There have been some case reports of **aplastic anaemia** being produced by antithyroid drugs, but the excess risk associated with their use is considered to be very low[6,9] and complete recovery has been reported after withdrawal of the antithyroid drug. An immune mechanism has been implicated.

Carbimazole has produced **haemolytic anaemia**.[10] In this case the immune reaction was specific to carbimazole and could not be shown with thiamazole.

On very rare occasions patients taking propylthiouracil have had a reduction in prothrombin values and bleeding.[11-13] In one patient bleeding was linked to propylthiouracil-induced **thrombocytopenia**.[14]

1. Bartalena L *et al.* Adverse effects of thyroid hormone preparations and antithyroid drugs. *Drug Safety* 1996; **15:** 53–63.
2. CSM/MCA. Reminder: agranulocytosis with antithyroid drugs. *Current Problems* 1999; **25:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
3. Tajiri J, *et al.* Antithyroid drug-induced agranulocytosis: the usefulness of routine white blood cell count monitoring. *Arch Intern Med* 1990; **150:** 621–4.
4. Anonymous. Elaboration: drug-induced agranulocytosis–monitoring antithyroid treatment. *Drug Ther Bull* 1997; **35:** 88.
5. Anonymous. Drug-induced agranulocytosis. *Drug Ther Bull* 1997; **35:** 49–52.
6. International Agranulocytosis and Aplastic Anaemia Study. Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. *BMJ* 1988; **297:** 262–5.
7. Shiran A, *et al.* Propylthiouracil-induced agranulocytosis in four patients previously treated with the drug. *JAMA* 1991; **266:** 3129–30.
8. Vilchez FJ, *et al.* Concomitant agranulocytosis and hepatotoxicity after treatment with carbimazole. *Ann Pharmacother* 2006; **40:** 2059–63.
9. Bishara J. Methimazole-induced aplastic anemia. *Ann Pharmacother* 1996; **30:** 684.
10. Salama A, *et al.* Carbimazole-induced immune haemolytic anaemia: role of drug-red blood cell complexes for immunization. *Br J Haematol* 1988; **68:** 479–82.
11. D'Angelo G, Le Gresley LP. Severe hypoprothrombinaemia after propylthiouracil therapy. *Can Med Assoc J* 1959; **81:** 479–81.
12. Naeye RL, Terrien CM. Hemorrhagic state after therapy with propylthiouracil. *Am J Clin Pathol* 1960; **34:** 254–7.
13. Gotta AW, *et al.* Prolonged intraoperative bleeding caused by propylthiouracil-induced hypoprothrombinemia. *Anesthesiology* 1972; **37:** 562–3.
14. Ikeda S, Schweiss JF. Excessive blood loss during operation in the patient treated with propylthiouracil. *Can Anaesth Soc J* 1982; **29:** 477–80.

Effects on the cardiovascular system. A study found that the use of antithyroid drugs was associated with a three-fold increased risk of sudden cardiac death. The authors stated that, while this effect might be caused directly by the drugs, this was unlikely since different drugs were involved and a plausible biological mechanism was lacking. Underlying poorly controlled hyperthyroidism was suggested as a more likely cause, since some treated patients were found to have had low thyroid-stimulating hormone concentrations shortly before death.[1]

1. van Noord C, *et al.* Population-based studies of antithyroid drugs and sudden cardiac death. *Br J Clin Pharmacol* 2009; **68:** 447–54.

Effects on the ears. Earache, high-frequency hearing loss, and tinnitus in a patient with Graves' disease were attributed to hypersensitivity to carbimazole;[1] hearing loss, but not the tinnitus, resolved when carbimazole was replaced with propylthiouracil. However, in another case,[2] propylthiouracil was associated with bilateral sensorineural hearing loss, which was thought to be caused by cochlear dysfunction from small-vessel vasculitis that locally compromised inner ear blood flow. Antineutrophil cytoplasmic antibodies (ANCA) were seen in the serum. ANCA concentrations returned to within normal limits and hearing loss was greatly improved after propylthiouracil was stopped and high-dose methylprednisolone was given,

1. Hill D, *et al.* Hearing loss and tinnitus with carbimazole. *BMJ* 1994; **309:** 929.
2. Sano M, *et al.* Progressive bilateral sensorineural hearing loss induced by an antithyroid drug. *ORL J Otorhinolaryngol Relat Spec* 2004; **66:** 281–5.

Effects on the kidneys. Glomerulonephritis associated with the development of antineutrophil cytoplasmic antibodies has been reported in patients receiving thiourea antithyroid drugs.[1-6]

1. Vogt BA, *et al.* Antineutrophil cytoplasmic autoantibody-positive crescentic glomerulonephritis as a complication of treatment with propylthiouracil in children. *J Pediatr* 1994; **124:** 986–8.
2. D'Cruz D, *et al.* Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with anti-thyroid drug treatment. *Br J Rheumatol* 1995; **34:** 1090–1.
3. Yuasa S, *et al.* Antineutrophil cytoplasmic antibodies (ANCA)-associated crescentic glomerulonephritis and propylthiouracil therapy. *Nephron* 1996; **73:** 701–3.
4. Kudoh Y, *et al.* Propylthiouracil-induced rapidly progressive glomerulonephritis associated with antineutrophil cytoplasmic autoantibodies. *Clin Nephrol* 1997; **48:** 41–3.
5. Prasad GVR, *et al.* Propylthiouracil-induced diffuse proliferative lupus nephritis: review of immunological complications. *J Am Soc Nephrol* 1997; **8:** 1205–10.
6. Trimeche Ajmi S, *et al.* Benzylthiouracil-induced glomerulonephritis. *Case Report Med* 2009; **2009:** 687285.

Effects on the liver. Jaundice, usually cholestatic, has been reported with thiamazole and carbimazole.[1-5] An immune-mediated mechanism rather than a toxic reaction has been proposed. Hepatotoxicity with agranulocytosis has been reported with carbimazole (see Effects on the Blood above). Hepatitis (sometimes progressing to cirrhosis[6]) and hepatic necrosis have been associated with propylthiouracil,[6-9] sometimes with fatal consequences.[7,8] The FDA has evaluated postmarketing adverse events from 1969 to 2009 and identified 34 cases of severe liver injury associated with propylthiouracil.[10] These included 23 adult cases where 13 resulted in death and 5 patients needed a liver transplant. There were also 11 paediatric reports, including 2 deaths and 7 children needing a transplant. In one study[11] almost 30% of patients being treated with propylthiouracil developed asymptomatic liver changes (increased alanine aminotransferase values). Dose reduction resulted in a return to normal values in 13 of the 15 patients affected.

Despite reports of liver damage, propylthiouracil has been investigated in the treatment of patients with alcoholic liver disease (see p. 2344.1).

1. Becker CE, *et al.* Hepatitis from methimazole during adrenal steroid therapy for malignant exophthalmos. *JAMA* 1968; **206:** 1787–9.
2. Fischer MG, *et al.* Methimazole-induced jaundice. *JAMA* 1973; **223:** 1028–9.
3. Blom H, *et al.* A case of carbimazole-induced intrahepatic cholestasis. *Arch Intern Med* 1985; **145:** 1513–15.
4. Schmidt G, *et al.* Methimazole-associated cholestatic liver injury: case report and brief literature review. *Hepatogastroenterology* 1986; **33:** 244–6.
5. Arab DM, *et al.* Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 1995; **80:** 1083–5.
6. Özenirler S, *et al.* Propylthiouracil-induced hepatic damage. *Ann Pharmacother* 1996; **30:** 960–3.
7. Hanson JS. Propylthiouracil and hepatitis. Two cases and a review of the literature. *Arch Intern Med* 1984; **144:** 994–6.
8. Limaye A, Ruffolo PR. Propylthiouracil-induced fatal hepatic necrosis. *Am J Gastroenterol* 1987; **82:** 152–4.
9. Ichiki Y, *et al.* Propylthiouracil-induced severe hepatitis: a case report and review of the literature. *J Gastroenterol* 1998; **33:** 747–50.
10. FDA. Drug Safety Communication: new boxed warning on severe liver injury with propylthiouracil (issued 21st April, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm (accessed 29/06/10)

11. Liaw Y-F, *et al.* Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. *Ann Intern Med* 1993; **118:** 424–8.

Effects on the lungs. Diffuse interstitial pneumonitis occurred in 2 patients given propylthiouracil[1] and a hypersensitivity reaction was suggested. Propylthiouracil and benzylthiouracil have also been implicated in cases of pulmonary haemorrhage associated with antineutrophil cytoplasmic antibody (ANCA) vasculitis.[2-5]

1. Miyazono K, *et al.* Propylthiouracil-induced diffuse interstitial pneumonitis. *Arch Intern Med* 1984; **144:** 1764–5.
2. Ohtsuka M, *et al.* Propylthiouracil-induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. *Eur Respir J* 1997; **10:** 1405–7.
3. Dhillon SS, *et al.* Diffuse alveolar hemorrhage and pulmonary capillaritis due to propylthiouracil. *Chest* 1999; **116:** 1485–8.
4. Thabet F, *et al.* ANCA-associated diffuse alveolar hemorrhage due to benzylthiouracil. *Eur J Pediatr* 2006; **165:** 435–6.
5. Tu Y-L, *et al.* Occult pulmonary hemorrhage as a rare presentation of propylthiouracil-induced vasculitis. *Pediatrics* 2011; **127:** e245–e249.

Effects on the muscles. Myositis with pain, weakness, and increased creatine kinase concentrations has been reported with carbimazole.[1,2] This effect might be explained by 'tissue hypothyroidism', and might respond to dosage reduction.[3]

1. Page SR, Nussey SS. Myositis in association with carbimazole therapy. *Lancet* 1989; **i:** 964.
2. Pasquier E, *et al.* Biopsy-proven myositis with microvasculitis in association with carbimazole. *Lancet* 1991; **338:** 1082–3.
3. O'Malley B. Carbimazole-induced cramps. *Lancet* 1989; **i:** 1456.

Hypersensitivity. Many of the adverse effects associated with the thiourea antithyroid drugs appear to have an immune basis. These effects may be associated with polyarthritis[1] or hypersensitivity vasculitis.[2-7] The latter is sometimes severe and multisystemic, and fatalities have occurred.

Hypersensitivity reactions may also be associated with the development of antineutrophil cytoplasmic antibodies (ANCA), or sometimes with a lupus-like syndrome with or without the presence of antinuclear antibodies.[2,5]

Serum sickness with arthralgias and raised immunoglobulin M (IgM) concentrations has been reported with thiamazole,[8] and the production of antibodies to insulin, resulting in episodes of hypoglycaemia, has been associated with thiamazole[9] and carbimazole.[10]

The thiourea antithyroid drugs all contain a thioamide group and cross-sensitivity between them might be expected. In particular, complete cross-reactivity may be expected between thiamazole and carbimazole since the latter is converted *in vivo* to thiamazole, although one report[11] suggests this is not necessarily the case. Cross-sensitivity between propylthiouracil and carbimazole[12] or thiamazole[13] has been reported but the incidence and clinical importance is not clear. Although it has been suggested that carbimazole or thiamazole may be substituted for propylthiouracil in hypersensitive patients, it is safer to stop antithyroid drugs in such patients.[12]

1. Bajaj S, *et al.* Antithyroid arthritis syndrome. *J Rheumatol* 1998; **25:** 1235–9.
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5. Mathieu E, *et al.* Systemic adverse effect of antithyroid drugs. *Clin Rheumatol* 1999; **18:** 66–8.
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7. ten Holder SM, *et al.* Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; **36:** 130–47.
8. Van Kuyk M, *et al.* Methimazole-induced serum sickness. *Acta Clin Belg* 1983; **38:** 68–9.
9. Hakamata M, *et al.* Insulin autoimmune syndrome after the third therapy with methimazole. *Intern Med* 1995; **34:** 410–12.
10. Burden AC, Rosenthal FD. Methimazole and insulin autoimmune syndrome. *Lancet* 1983; **ii:** 1311.
11. Kroll H, *et al.* Drug-dependent antibodies against the prodrug carbimazole do not react with the metabolite thiamazole. *Blood* 2001; **97:** 2186–7.
12. Smith A, *et al.* Cross sensitivity to antithyroid drugs. *BMJ* 1989; **298:** 1253.
13. De Weweire A, *et al.* Failure to control hyperthyroidism with a thionamide after potassium perchlorate withdrawal in a patient with amiodarone associated thyrotoxicosis. *J Endocrinol Invest* 1987; **10:** 529.

Pregnancy. Thiourea antithyroid drugs have been used successfully in pregnancy, although there are risks associated with their use (see Hyperthyroidism, p. 2332.2).

Thiamazole (the metabolite of carbimazole) has been the drug most frequently involved in the few reports of congenital defects following maternal use of such compounds. Several infants exposed to thiamazole *in utero* have been born with scalp defects (aplasia cutis congenita—a localised absence of skin at birth)[1,2] although hyperthyroidism itself may give rise to such defects.[3] Individual cases of other congenital defects associated with thiamazole have included choanal atresia (an upper respiratory-tract defect), oesophageal atresia, and tracheo-oesophageal fistula[3] but the incidence of congenital abnormalities is not increased compared with the general population.[4]

Aplasia cutis congenita and choanal atresia (the latter with coarctation of the aorta) have also been reported after maternal exposure to carbimazole in the first trimester.[5] Other reported major malformations have included abdominal wall defects such as gastroschisis (or laparoschisis)[5,6] and omphalocele; digestive malformation has occurred, manifesting as a patent omphalomesenteric duct.[5] Other reported malformations include facial dysmorphisms, a high-arched palate, and an anomalous ear helix.[5]

A controlled cohort study concluded that propylthiouracil did not appear to be a major human teratogen.[7] However, the risk is unclear, due to a lack of data,[8] and US licensed product information states that cases of maternal and neonatal liver failure sometimes fatal, have been associated with the use of propylthiouracil. As with carbimazole and thiamazole, aplasia cutis congenita has also been reported after maternal use of propylthiouracil.[9] A case-control analysis[8] found maternal propylthiouracil exposure in the first trimester to be associated with situs inversus with or without dextrocardia, unilateral kidney agenesis or dysgenesis, and cardiac outflow defects. However, further studies were considered necessary to evaluate these associations because of the low number of affected subjects. The use of carbimazole or thiamazole was found to be significantly associated with omphalocele and choanal atresia, which was consistent with previous reports.

There have been some reports of neonates exposed to thiourea antithyroid drugs *in utero* displaying signs of hypothyroidism including goitre.[7,10,11]

1. Milham S. Scalp defects in infants of mothers treated for hyperthyroidism with methimazole or carbimazole during pregnancy. *Teratology* 1985; **32:** 321.
2. Vogt T, *et al.* Aplasia cutis congenita after exposure to methimazole: a causal relationship? *Br J Dermatol* 1995; **133:** 994–6.
3. Johnsson E, *et al.* Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* 1997; **350:** 1520.
4. Wing DA, *et al.* A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol* 1994; **170:** 90–5.
5. Koenig D, *et al.* Birth defects observed with maternal carbimazole treatment: six cases reported to Nice's Pharmacovigilance Center. *Ann Endocrinol (Paris)* 2010; **71:** 535–42.
6. Guignon A-M, *et al.* Carbimazole-related gastroschisis. *Ann Pharmacother* 2003; **37:** 829–31.
7. Rosenfeld H, *et al.* Pregnancy outcome, thyroid dysfunction and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. *Br J Clin Pharmacol* 2009; **68:** 609–17.
8. Clementi M, *et al.* SAFE-Med Study Group. Treatment of hyperthyroidism in pregnancy and birth defects. *J Clin Endocrinol Metab* 2010; **95:** E337–E341.
9. Löllgen RM, *et al.* Aplasia cutis congenita in surviving co-twin after propylthiouracil exposure in utero. *J Pediatr Endocrinol Metab* 2011; **24:** 215–18.
10. O'Doherty MJ, *et al.* Treating thyrotoxicosis in pregnant or potentially pregnant women. *BMJ* 1999; **318:** 5–6.
11. Masiukiewicz US, Barrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid* 1999; **9:** 647–52.

Pharmacokinetics

The pharmacokinetics of carbimazole and thiamazole can be considered together since carbimazole is rapidly and completely metabolised to thiamazole in the body. The antithyroid activity of carbimazole is dependent upon this conversion to thiamazole.

Carbimazole and thiamazole are rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 to 2 hours after oral doses.

Thiamazole is concentrated in the thyroid gland; since duration of action is more closely related to the intrathyroidal drug concentration than plasma half-life, prolonged antithyroid activity results from single daily doses. Thiamazole is moderately bound to plasma proteins.

Thiamazole has an elimination half-life from plasma of about 3 to 6 hours and is metabolised, probably by the liver, and excreted in the urine. Less than 12% of a dose of thiamazole may be excreted as unchanged drug. 3-Methyl-2-thiohydantoin has been identified as a metabolite of thiamazole. The elimination half-life may be increased in hepatic and renal impairment.

Thiamazole crosses the placenta and is distributed into breast milk.

References to the pharmacokinetics of carbimazole and thiamazole.

1. Skellern GG, *et al.* The pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. *Br J Clin Pharmacol* 1980; **9:** 137–43.
2. Kampmann JP, Hansen JM. Clinical pharmacokinetics of antithyroid drugs. *Clin Pharmacokinet* 1981; **6:** 401–28.
3. Jansson R, *et al.* Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J Clin Endocrinol Metab* 1983; **57:** 129–32.
4. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
5. Jansson R, *et al.* Pharmacokinetic properties and bioavailability of methimazole. *Clin Pharmacokinet* 1985; **10:** 443–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Neo-Mercazole; ***Austria***: Carbistad†; ***Denm.***: Neo-Mercazole; ***Fin.***: Tyrazol; ***Fr.***: Neo-Mercazole; ***Gr.***: Thyrostat; ***Hong Kong***: Cazole; Neo-Mercazole; ***India***: Anti-Thyrox; Neo-Mercazole; ***Indon.***: Neo-Mercazole; ***Irl.***: Neo-Mercazole; ***Malaysia***: Thymazole; ***Norw.***: Neo-Mercazole; ***NZ***: Neo-Mercazole; ***Philipp.***: Anti-Thyrox; Carbinom; Neomercazole; Neomerdin; ***S.Afr.***: Neo-Mercazole; ***Singapore***: Camazol; ***Spain***: Neo Tomizol; ***Switz.***: Neo-Mercazole; ***UK***: Neo-Mercazole†; ***Ukr.***: Espa-Carb (Эспа-карб).

Pharmacopoeial Preparations

BP 2014: Carbimazole Tablets.

Dibromotyrosine

Dibromotirosina; Дибромотирозин.

3,5-Dibromo-L-tyrosine.

$C_9H_9Br_2NO_3$=339.0

CAS — 300-38-9.

ATC — H03BX02.

ATC Vet — QH03BX02.

UNII — QD49LEP46E.

Profile

Dibromotyrosine is an antithyroid drug used in the treatment of hyperthyroidism (p. 2332.2) in oral doses of 300 to 900 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Bromotiren.

Multi-ingredient Preparations. ***Ital.***: Bromazolo.

Iodine

Iaidín; Iod; Iode; Ïodin; Iodio; Iodiu; Iodium; Iodo; Iodum; Jód; Jod; Joð; Jodas; Jodi; Jodium; Jods; Jodum; Jood; Įyot; Yodo; Йод.

I_2=253.80894

CAS — 7553-56-2.

ATC — D08AG03.

ATC Vet — QD08AG03.

UNII — 9679TC07X4 (iodine); 09G4I6V86Q (iodine ion).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Iodine). Greyish-violet, brittle plates or fine crystals, with a metallic sheen. It is slowly volatile at room temperature. Very slightly soluble in water; soluble in alcohol; slightly soluble in glycerol; very soluble in concentrated solutions of iodides.

USP 36: (Iodine). Heavy, greyish-black plates or granules with a metallic sheen and a characteristic odour. Soluble 1 in 3000 of water, 1 in 13 of alcohol, 1 in 4 of carbon disulfide, and 1 in 80 of glycerol; freely soluble in chloroform, in ether, and in carbon tetrachloride; soluble in solutions of iodides. Store in airtight containers.

Incompatibility. With acetone, iodine forms a pungent irritating compound.

Potassium Iodate

Iodate de Potassium; Iodato de Potássio; Iodato di Potassio; Iodato potásico; Kaliumiodat; Kaliumjodaat; Kaliumjodaatti; Potasu jodan; Yodato potásico; Йодат Калия.

KIO_3=214.0

CAS — 7758-05-6.

UNII — I139E44NHL.

Pharmacopoeias. In *Br.*, *Chin.*, and *It.*

BP 2014: (Potassium Iodate). A white crystalline powder with a slight odour. Slowly soluble in water; insoluble in alcohol. A 5% solution in water has a pH of 5.0 to 8.0.

Potassium Iodide

Iodeto de Potássio; Iodur de Potassi; Ioduro di Potassio; Ioduro potásico; Jodid draselný; Kalii iodetum; Kalii Iodidum; Kalii Jodidum; Kālija Jodīds; Kalijum Jodid; Kalio jodidas; Kalium Iodatum; Kalium Jodatum; Kaliumiodid; Kaliumjodid; Kálium-jodid; Kaliumjodide; Kaliumjodidi; Pot. Iod.; Potassii Iodidum; Potassium, iodure de; Potasu jodek; Potasyum Iyodür; Yoduro de Potasio; Yoduro potásico; Калиев йодид; Йодид Калия.

KI=166.0

CAS — 7681-11-0.

ATC — R05CA02; S01XA04; V03AB21.

ATC Vet — QR05CA02; QS01XA04; QV03AB21.
UNII — 1C4QK22F9J.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Potassium Iodide). A white or almost white powder or colourless crystals. Very soluble in water; soluble in alcohol; freely soluble in glycerol. Protect from light.

USP 36: (Potassium Iodide). Hexahedral crystals, either transparent and colourless or somewhat opaque and white, or a white, granular powder. It is slightly hygroscopic. Soluble 1 in 0.7 of water and 1 in 0.5 of boiling water, 1 in 22 of alcohol, and 1 in 2 of glycerol. Its solutions are neutral or alkaline to litmus.

Sodium Iodide

Iodeto de Sódio; Iodur de Sodi; Ioduro di Sodio; Ioduro sódico; Jodid sodný; Natrii Iodetum; Natrii Iodidum; Natrii Jodidum; Natrijum Jodid; Natrio jodidas; Natrium Iodatum; Natriumiodid; Natriumjodid; Nátrium-jodid; Natriumjodide; Natriumjodidi; Sod. Iod.; Sodii Iodidum; Sodium (Iodure de); Sodium, iodure de; Sodu jodek; Sodyum Iyodür; Yoduro de Sodio; Yoduro sódico; Йодид Натрия.

NaI=149.9
CAS — 7681-82-5.
UNII — F5WR8N145C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Sodium Iodide). Colourless crystals or white or almost white, crystalline powder. It is hygroscopic. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Sodium Iodide). Colourless, odourless crystals, or white crystalline powder. It is deliquescent in moist air and develops a brown tint upon decomposition. Soluble 1 in 0.6 of water, 1 in 2 of alcohol, and 1 in 1 of glycerol. Store in airtight containers.

Uses and Administration

Iodine is an essential trace element in the human diet, necessary for the formation of thyroid hormones (see p. 2332.1), and consequently it is used in iodine deficiency and thyroid disorders. It also has antimicrobial activity.

For the prophylaxis and treatment of **iodine deficiency disorders** (below) it may be given as potassium iodide, potassium iodate, or as iodised oil. Sodium iodide has also been used. Each g of potassium iodide represents about 6 mmol of potassium and of iodine. Each g of sodium iodide represents about 6.7 mmol of sodium and of iodine. Each g of potassium iodate represents about 4.7 mmol of potassium and of iodine.

In the pre-operative management of **hyperthyroidism** (p. 2332.2) iodine and iodides are used with antithyroid drugs such as carbimazole, thiamazole, or propylthiouracil. Such use has been thought to render the thyroid firm and avoid the increased vascularity and friability (with increased risk of haemorrhage) that may result from the use of an antithyroid drug alone. However, there is little evidence of a beneficial effect.

Iodine may be given as a solution with potassium iodide (Aqueous Iodine Oral Solution BP 2014; Lugol's Solution or Strong Iodine Solution USP 36) which contains in each mL 130 mg of free and combined iodine; a dose of 0.1 to 0.3 mL in milk or water is given three times daily for 10 to 14 days. Alternatively, potassium iodide has been given in doses of up to 250 mg three times daily with food. Solutions of potassium iodide intended for oral use should be given well diluted to avoid gastric irritation. Potassium iodide may also be given 1 hour after an antithyroid drug as part of the management of thyroid storm; doses as high as 500 mg every 4 hours have been suggested.

Radioactive sodium iodide (see Iodine-131, p. 2225.3) is also used for the treatment of hyperthyroidism, especially when medical treatment or compliance is problematic, in patients with cardiac disease, or in patients who relapse after thyroidectomy.

Potassium iodide or potassium iodate are taken orally for **radiation protection** (p. 2338.1) to saturate the thyroid when uptake of radio-iodine by the gland is not desired.

Iodine has a powerful bactericidal action. It is also active against fungi, viruses, protozoa, cysts, and spores. Potassium iodide has been used in the treatment of fungal infections such as sporotrichosis (below). Iodine is used as an **antiseptic** and **disinfectant** generally as a 2% or 2.5% solution. Its activity is reduced in the presence of organic matter, though not to the same extent as with the other halogen disinfectants. If industrial methylated spirit is used for the solution, it should be free from acetone, with which iodine forms an irritant and lachrymatory compound. Iodine solutions may be applied to small wounds or abrasions as well as to unbroken skin, but an iodophore such as povidone-iodine (p. 1767.1) may be preferred.

Iodine may also be used to sterilise drinking water; see below. Tablets containing tetraglycine hydroperiodide (p. 1771.3) may be preferred.

When iodine combines chemically it is decolorised and so-called colourless iodine preparations do not have the disinfectant properties of iodine.

Iodine stains the skin a deep reddish-brown; the stain can be readily removed by dilute solutions of alkalis or sodium thiosulfate. A dilute solution of iodine (Schiller's Iodine) may also be used as a **diagnostic** stain in colposcopy.

There have been many other uses of iodine and iodides. Iodides have long been used as ingredients of expectorant mixtures (see Cough, p. 1651.2) but there has been concern over their safety because of their potential for thyroid suppression. A diatomic iodine formulation has been investigated for the treatment of fibrocystic breast disease. Iodinated organic compounds including iodised oil are used as X-ray contrast media (see Radiographic Contrast Media, p. 1580.1). Potassium iodide has been given in the treatment of Sweet's syndrome (acute febrile neutrophilic dermatosis). A mixture of iodine and sodium iodide is used as sclerotherapy for varicose veins (p. 2564.1).

Administration in children. For dosage of iodine or iodide in children, see Iodine Deficiency Disorders (below) and Radiation Protection (p. 2338.1), respectively.

Disinfection of water. Iodine may be used to sterilise drinking water although WHO recommends its use only short-term or as an emergency measure (see p. 1731.3). It may be useful for individual water treatment where surface water is ingested or water quality is questionable. Iodine for this purpose is available in many forms including alcoholic solutions (tinctures), tablets, and iodine resins. Iodine resins may be incorporated into filters.[1] Five drops of a 2% alcoholic solution added to about one litre (one US quart) of water is reported to kill most pathogens; the water must stand for a minimum of 30 minutes before use; however, longer contact is required to kill *Giardia* cysts, especially if the water is cold, and it is ineffective against *Cryptosporidium*.[2] Some have commented that since the volume of a drop may differ between delivery devices, this may not yield a concentration of about 8 mg/litre, which is required for inactivation of *Giardia* cysts.[3]

Iodine-based water treatments are not recommended for patients who have or are at increased risk of iodine-induced thyroid disorders. Where iodine water disinfection is used, its use should be limited in euthyroid patients to 3 months if high concentrations of iodine (5 to 32 mg/litre) are produced. However, coupled with periodic monitoring of thyroid function, lower concentrations of iodine in water (1 to 2 mg/litre) can be safely used for long periods of time.[1]

1. Backer H, Hollowell J. Use of iodine for water disinfection: iodine toxicity and maximum recommended dose. *Environ Health Perspect* 2000; **108:** 679–84.
2. WHO. Preventing traveller's diarrhoea: how to make drinking water safe (issued 2005). Available at: http://www.who.int/water_sanitation_health/hygiene/envsan/sdwtravel.pdf (accessed 24/06/11)
3. Goodyer L. Food and water hygiene for the traveller. *Pharm J* 2000; **264:** 134–9.

Fungal infections. Potassium iodide is used in the treatment of cutaneous sporotrichosis (p. 568.3), although how it acts is unclear since antifungal activity was not found *in vitro* against *Sporothrix schenkii*. It has also been shown to be effective in the treatment of phycomycosis caused by *Basidiobolus haptosporus*[1,2] but again the mode of action is unclear.[3] Mycetomas due to *Pseudallescheria boydii* are usually treated with azole antifungals such as itraconazole (p. 567.1) but there is a report of response to oral potassium iodide.[4] The authors suggested that its action might be due to proteolysis or activation of myeloperoxidase. Potassium iodide is usually given orally in a gradually increasing dosage up to the limit of tolerance. The WHO[5] recommended initial dose is 1 mL [1 g] of a saturated solution of potassium iodide (1 g/mL) given three times daily; this may be increased by 1 mL daily, to a maximum daily dose of 10 mL. Treatment should be continued for at least 4 weeks after the disappearance or stabilisation of the lesions.

Potassium iodide and sodium iodide have been tried by local intracavitary instillation for the treatment of life-threatening haemoptysis from pulmonary aspergillomas.[6] Mechanical factors may have accounted for a beneficial effect rather than any antifungal action. Aspergillomas are usually managed conservatively or, in more severe disease, with antifungals or surgery (see p. 563.1).

1. Kelly S, *et al.* Subcutaneous phycomycosis in Sierra Leone. *Trans R Soc Trop Med Hyg* 1980; **74:** 396–7.
2. Kamalam A, Thambiah AS. Muscle invasion by Basidiobolus haptosporus. *Sabouraudia* 1984; **22:** 273–7.
3. Yangco BG, *et al.* In vitro susceptibilities of human and wild-type isolates of Basidiobolus and Conidiobolus species. *Antimicrob Agents Chemother* 1984; **25:** 413–16.
4. Khan FA, *et al.* Multiple subcutaneous mycetomas caused by *Pseudallescheria boydii*: response to therapy with oral potassium iodide solution. *J Infect* 2010; **60:** 178–81.
5. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 28/04/10)
6. Rumbak M, *et al.* Topical treatment of life threatening haemoptysis from aspergillomas. *Thorax* 1996; **51:** 253–5.

Iodine deficiency disorders. Iodine is an essential trace element required for thyroid hormone production. In the UK the reference nutrient intake (RNI) for adults is 140 micrograms (1.1 micromoles) of iodine daily[1] and in the USA the recommended dietary allowance (RDA) is 150 micrograms daily.[2] A full explanation of the terms RNI and RDA can be found under Human Requirements of Vitamins, p. 2046.1.

The International Council for Control of Iodine Deficiency Disorders, UNICEF, and WHO recommend[3,4] the following daily iodine intakes:

- 90 micrograms for infants and children up to 59 months of age
- 120 micrograms for children in their 6th to 12th year
- 150 micrograms for adolescents and adults
- 200 to 250 micrograms for pregnant and lactating women

When iodine requirements are not met, a range of disorders can develop. These iodine deficiency disorders include endemic goitre (enlargement of the thyroid), endemic cretinism (a syndrome characterised by deaf-mutism, intellectual deficit, spasticity, and sometimes hypothyroidism), impaired mental function in children and adults, and an increased incidence of still-births as well as perinatal and infant mortality.[4-6]

Iodine deficiency disorders can be prevented by iodine supplementation. The incidence of endemic goitre, endemic cretinism, mental retardation, pregnancy loss, and infant mortality can be reduced and some of the effects of established iodine deficiency ameliorated, with only modest risks.[6,7]

Although various methods of iodine supplementation, including iodination of water and bread, as well as giving potassium iodide or iodate, have been investigated, the two methods generally used are iodination of culinary salt and the use of iodised oil.[4,6,8]

Salt may be iodinated by the addition of potassium iodide or potassium iodate.[6,9] The concentration used in different countries varies over a wide range from 10 to about 100 ppm of elemental iodine; 20 to 40 ppm has been suggested as being a more appropriate concentration.[6]

The chief alternative to supplementation with iodinated salt is *iodised oil*, usually by intramuscular injection; it is useful where salt consumption is unreliable or inadequate or where immediate action is necessary to correct severe iodine deficiency.[4,6,9] A commonly used type of iodised oil has been a poppyseed oil containing about 38% w/w or 480 mg/mL of iodine (see Iodised Oil, p. 1589.1). Some countries have produced iodised oil based on alternatives such as peanut or rapeseed oil.[10,11] Single intramuscular doses can provide adequate protection from iodine deficiency for up to 3 years. WHO has recommended[9] the following intramuscular doses of iodised oil (480 mg/mL iodine):

- 190 mg for infants up to 1 year
- 380 mg for children and adults up to age 45

Subjects over the age of 45 years and those with nodular goitre are susceptible to hyperthyroidism when given iodine, and iodised oil may not be a suitable means of supplementation. If it is used, doses of 76 mg are given.[9]

Iodised oil may also be given orally. The evidence suggests that oral iodised oil is as effective as intramuscular for preventing iodine deficiency disorders in children.[8] WHO recommends[9] the following oral doses:

- a single dose of 100 mg in infants up to 1 year
- 200 mg once yearly in children from 1 to 5 years
- 400 mg once yearly for children over 6 years
- 400 mg once yearly for adults, except during pregnancy, when
- a single dose of 200 mg is given to pregnant women

Iodine or iodides may suppress neonatal thyroid function and it is generally recommended that iodine compounds should be avoided during **pregnancy**. However, where it is essential to prevent neonatal goitre and cretinism, iodine supplementation should not be withheld from pregnant women.[12,13] Iodine supplementation has been found to be effective in preventing brain-damage in the fetus provided it is given to the mother in the first or second trimester;[12] treatment later in pregnancy was not effective in improving neurological status, although some developmental improvement was seen and hypothyroidism will be corrected. WHO has stated that in areas where iodine deficiency disorders are moderate to severe, iodised oil given either before or at any stage of gestation is beneficial.[9,13] The following doses are recommended[9] during pregnancy and for one year postpartum:

- 480 mg intramuscularly once yearly, *or*
- 300 to 480 mg orally once yearly, *or*
- 100 to 300 mg orally every 6 months

Non-pregnant fertile women may be given:

- 480 mg intramuscularly once yearly, *or*
- 400 to 960 mg orally once yearly, *or*
- 200 to 480 mg orally every 6 months

Indirect iodine supplementation, by addition of potassium iodate to the water used to irrigate crops, has been tried in areas of iodine deficiency where other methods had proved difficult to implement.[14] Iodine-fortified animal fodder has also increased the iodine content of foods derived from animal sources.[6]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the Committee on Medical Aspects of Food Policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 23/06/11)
3. WHO. Iodine. In *Vitamin and mineral requirements in human nutrition*. 2nd ed. Geneva: WHO, 2004: 303–17. Also available at: http://libdoc.who.int/publications/2004/9241546123_chap16.pdf (accessed 23/06/11)
4. ICCIDD/UNICEF/WHO. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination: a guide for programme managers*. 3rd ed. Geneva: WHO, 2007. Also available at: http://whqlibdoc.who.int/publications/2007/9789241595827_eng.pdf (accessed 23/06/11)
5. WHO. Iodine status worldwide: WHO Global Database on Iodine Deficiency. Geneva: WHO, 2004. Also available at: http://whqlibdoc.who.int/publications/2004/9241592001.pdf (accessed 23/06/11)
6. Zimmermann MB. Iodine deficiency. *Endocr Rev* 2009; **30:** 376–408.
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8. Angermayr L, Clar C. Iodine supplementation for preventing iodine deficiency disorders in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/06/11).
9. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 23/06/11)
10. Ingenbleek Y, *et al*. Iodised rapeseed oil for eradication of severe endemic goitre. *Lancet* 1997; **350:** 1542–5.
11. Untoro J, *et al*. Efficacy of different types of iodised oil. *Lancet* 1998; **351:** 752–3.
12. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
13. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
14. Cao X-Y, *et al*. Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in Xinjiang, China. *Lancet* 1994; **344:** 107–10.

Radiation protection. Giving a radiologically stable form of iodine to saturate the thyroid gland confers thyroid protection from iodine radionuclides.[1,2]

Potassium iodide or iodate may be used when thyroid protection from a *medical procedure* involving radio-iodine is needed. Oral doses of potassium iodide 130 mg or potassium iodate 170 mg (to provide about 100 mg of iodine) are given daily, starting 24 to 48 hours before the procedure. Treatment is continued until the estimated activity of radioiodine in the body has fallen to acceptable levels, which may be up to 15 days after the procedure depending on the radiopharmaceutical formulation used.

In the event of a *nuclear accident* authorities in the USA recommend[1,3] an oral dose of 130 mg of potassium iodide daily in adults (including pregnant and lactating women). Daily doses should be given until risk of exposure has passed and adjunctive measures have been implemented. Recommended daily doses of potassium iodide for children are:

- up to 1 month of age, 16 mg
- 1 month to 3 years, 32 mg
- 3 to 12 years (up to 18 years if body-weight is less than 70 kg), 65 mg

In the UK the oral dose recommended[4] is a single dose of 100 mg of stable iodine (as 170 mg of potassium iodate) for adults (including pregnant women and women who are breast feeding) as soon as possible after exposure and before evacuation. Dosages for children are:

- 3 to 12 years, 50 mg of stable iodine (85 mg of potassium iodate)
- 1 month to 3 years, 25 mg of stable iodine (42.5 mg of potassium iodate)
- neonates, 12.5 mg of stable iodine (21.25 mg of potassium iodate)

In the event of prolonged exposure, repeated daily doses may become necessary. However, UK authorities advise that repeated doses should be avoided in neonates and pregnant and breast-feeding women because of the sensitivity of the thyroid in the neonate and fetus to large doses of iodine. They also advise that all neonates should be monitored for a few weeks after treatment with potassium iodate.

1. Halperin JA. Potassium iodide as a thyroid blocker—Three Mile Island today. *Drug Intell Clin Pharm* 1989; **23:** 422–7.
2. Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. *Am J Med* 1993; **94:** 524–32.
3. FDA Center for Drug Evaluation and Research. Guidance: potassium iodide as a thyroid blocking agent in radiation emergencies (issued December 2001). Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080542.pdf (accessed 23/06/11)
4. National Radiological Protection Board. Stable iodine prophylaxis: recommendations of the 2nd UK Working Group on Stable Iodine Prophylaxis. *Doc NRPB* 2001; **12** (3): 1–30. Also available at: http://www.hpa.org.uk/web/HPAwebfile/HPAweb_C/1194947336017 (accessed 23/06/11)

Adverse Effects and Treatment

Iodine and iodides have variable effects on the thyroid (see below) and can produce hyperthyroidism (the Iod-Basedow or Jod-Basedow phenomenon) as well as goitre and hypothyroidism; the latter have also occurred in infants born to mothers who had taken iodides during pregnancy.

Hypersensitivity reactions to iodides may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia. Large doses or prolonged use of iodides may lead to a range of adverse effects, often called 'iodism', some of which resemble hypersensitivity reactions. Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be coryza-like symptoms, and swelling and inflammation of the throat and salivary glands. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchospasm may develop. Skin reactions include mild acneform eruptions or, more rarely, severe eruptions (iododerma). Other reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances.

Retinal toxicity has been seen with overdose of potassium iodate.

Ingestion of iodine can also cause a metallic taste, thirst, and corrosive effects on the gastrointestinal tract; vomiting, abdominal pain, and bloody diarrhoea can occur. Systemic toxicity may lead to hypotension, tachycardia, fever, headache, delirium, metabolic acidosis, and renal impairment. Circulatory failure due to shock, pulmonary oedema, aspiration pneumonia, or asphyxiation can occur; fatalities have been reported. Oesophageal stricture is a possible complication if the patient survives the acute stage.

Victims of acute iodine poisoning have been given copious draughts of milk or starch mucilage; however, the UK National Poisons Information Service contra-indicates the use of gastric lavage, due to the corrosive nature of iodine. Sodium thiosulfate (usually as a 1% solution) will reduce iodine to the less toxic iodide. Activated charcoal may be considered in both iodine and iodide poisoning if the patient presents within 1 hour of ingestion.

Inhalation of iodine vapour is very irritating to mucous membranes, causing conjunctivitis and rhinitis; corrosive effects can lead to pulmonary oedema.

Effects on the thyroid. Iodide may be isolated by the body from a variety of sources, including an iodine-rich diet, or some disinfectants and drugs containing iodine (see also under Amiodarone, p. 1302.3). Although iodine is required for the production of thyroid hormones, excessive quantities can cause hyperthyroidism, or even paradoxical goitre and hypothyroidism.

The normal daily requirement ranges from 100 to 300 micrograms.[1,2] Quantities of 500 micrograms to 1 mg daily probably have no untoward effects on thyroid function in most cases.[2] When progressively larger doses are given there is an initial rise in thyroid hormone production, but at still higher doses, production decreases (the Wolff-Chaikoff effect). This effect is usually seen with doses of more than about 2 mg daily, but is normally transient, adaptation occurring on repeated dosage. In certain individuals a lack of adaptation produces a chronic inhibition of thyroid hormone synthesis leading to goitre and **hypothyroidism**.[1,2] Population studies looking at iodine intake have discovered an increased incidence of hypothyroidism, especially in those with previous iodine deficiency.[3,4]

Excess iodine may also induce **hyperthyroidism** (the Iod-Basedow or Jod-Basedow phenomenon). Iodine-induced hyperthyroidism has been associated with iodine prophylaxis programmes in developing countries.[5] The highest incidence of hyperthyroidism has been reported to occur 1 to 3 years after supplementation begins, with the incidence returning to normal within 3 to 10 years despite continued iodine exposure.[6] Elderly subjects and those with nodular goitres have been found to be at greatest risk.

To overcome any adverse effects on thyroid function as a result of iodine prophylaxis during **pregnancy**, WHO has issued guidelines on the safe use of iodised oil during gestation.[7,8] There is some evidence that the use of iodine-containing antiseptics on pregnant women and neonates may cause disturbances in thyroid function.[9,10]

1. Arthur JR, Beckett GJ. Thyroid function. *Br Med Bull* 1999; **55:** 658–68.
2. WHO. Iodine. In *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 49–71.
3. Teng W, *et al*. Effect of iodine intake on thyroid diseases in China. *N Engl J Med* 2006; **354:** 2783–93.
4. Pedersen IB, *et al*. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J Clin Endocrinol Metab* 2007; **92:** 3122–7.
5. Delange F, *et al*. Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 1999; **9:** 545–56.
6. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine (Baltimore)* 1983; **62:** 1–20.
7. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
8. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
9. Linder N *et al*. Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; **131:** 434–9.
10. Weber G *et al*. Neonatal transient hypothyroidism: aetiological study. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F70–2.

Precautions

Caution is necessary if preparations containing iodine or iodides are taken for long periods, and such preparations should not be taken regularly during pregnancy except when iodine supplementation is required. Caution is also required when giving iodine or iodides to children. Patients over the age of 45 years or with nodular goitres are especially susceptible to hyperthyroidism when given iodine supplementation. Reduced doses should therefore be used and supplementation with iodised oil may not be appropriate.

Solutions of iodine applied to the skin should not be covered with occlusive dressings. The disinfectant activity of iodine is reduced by alkalis as well as by protein.

As iodine and iodides can affect the thyroid gland, their use may interfere with tests of thyroid function.

Breast feeding. Iodine is concentrated by the mammary gland into breast milk to ensure an adequate supply to the breast-fed infant. Since this is dependent on the maternal dietary intake,[1] WHO recommends a daily iodine intake of 200 micrograms for lactating women, see Iodine Deficiency Disorders, p. 2337.3.

The *BNFC* considers treatment with iodine or iodides to be a contra-indication to breast feeding. However, the last available guidance from the American Academy of Pediatrics[2] considered that such treatment was usually compatible with breast feeding although it was noted that goitre or effects on thyroid function had been reported. Any risk is not confined to oral treatment: transient neonatal hypothyroidism has been reported in a breast-fed infant whose mother was treated with iodine tampons,[3] and for a report of increased milk-iodine concentrations associated with vaginal povidone-iodine see p. 1767.2.

1. Semba RD, Delange F. Iodine in human milk: perspectives for infant health. *Nutr Rev* 2001; **59:** 269–78.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)
3. Casteels K, *et al*. Transient neonatal hypothyroidism during breastfeeding after post-natal maternal topical iodine treatment. *Eur J Pediatr* 2000; **159:** 716–17.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium iodide as not porphyrinogenic when used as an antidote; it may be used as a drug of first choice and no precautions are needed.[1] No classification is offered when used in cough or cold preparations or in ophthalmological preparations.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/09/11)

Interactions

The effects of iodine and iodides on the thyroid may be altered by other compounds including amiodarone and lithium.

Pharmacokinetics

Iodine is slightly absorbed when applied to the skin. When taken orally, iodine preparations (which are converted to iodide) and iodides are transported to, and concentrated in, the thyroid gland (see p. 2332.1). Iodides not taken up by the thyroid are excreted mainly in the urine, with smaller amounts appearing in the faeces, saliva, and sweat. They cross the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Jodid; ***Braz.***: Fluidelan; Glitosslab†; Iodeton; Iodetoss; Iodex; Xarope Neo; ***Canad.***: Micro I; Radblock; Sclerodine; ***China***: Jindian (金典); ***Cz.***: Kalijev†; ***Fin.***: Jodix; ***Ger.***: Jod beta; Jodetten†; Jodgamma; Jodid; Mono-Jod; Thyprotect†; ***Gr.***: Jodosan; ***Hung.***: Jod plus†; Jodid; Jodomax†; ***India***: Collosol; ***Indon.***: Yodsaben†; ***Israel***: Iosat; ***Ital.***: Chitodine†; Goccemed; ***Mex.***: Yodolactina; ***Neth.***: Kajodan; ***Norw.***: Jodosan†; ***Philipp.***: Ilens; Jodid; Vistalens; Vitreolent; ***Pol.***: Jodid; Vitreolent; ***Rus.***: Iodomarin (Йодомарин); Jodbalance (Йодбаланс); Jodid (Йодид); Microiodid (Микройодид); ***Spain***: Yodafar; Yodiquer; Yoduk; ***Thai.***: Pose-Iodophore†; ***Turk.***: Tenturdiyot; ***UK***: Bioiodine; ThySat; ***Ukr.***: Antistrumin (Антиструмин); Iodomarin (Йодомарин); Lugs (Люгс); ***USA***: Curity; Geri-Dyne; Iodoflex; Iodopen; Iosat; Pima; SSKI; Thyro-Block; ThyroSafe; ThyroShield.

Multi-ingredient Preparations. ***Arg.***: Antikatarata Plus; ***Austral.***: Asa Tones†; Gartech†; Haemo-Red; I-Folic; PM IQShield; ***Austria***: Jodthyrox; ***Braz.***: Bronquidex; Brontoss; Dermicon; Endo-

tussin†; Expec; Fungolab†; Glicodin; Glycon; Glyteol Balsamico†; Hebrin; Ikaflux; Iodesin; Iodetal; Iodex com Salicilato de Metila; KI-Expectorante; Micotiazol; MM Expectorante; ***Canad.***: Herba Tone†; Iode†; ratio-Theo-Bronc; Theraplex F†; ***Chile***: Paralymphine; ***Cz.***: Jodthyrox; ***Fr.***: Femibion Grossesse; Folio; Nitrol†; Sel D; ***Ger.***: Adelheid-Jodquelle, Tolzer; Jodthyrox; L-Thyrox Jod†; Lento Nit K; Thyronajod; ***Gr.***: Iodocollyre; Tentil; Vitreolent; ***Hong Kong***: Duraprep†; Vitreolent†; ***India***: Anofer; Arofil; Calodin; Caracsol; Carbosyl; Carbosyl; Catarest; Cato-Bell†; Contrastin; Cureg; Dordent; Elferri Plus; Elixir Efelin; Ethnorub; Fejet-OD; Fejet; Icee; Ioprep; Me-Fresh Gum Paint; Multimix; Oxi-Red; ***Indon.***: Calmin-AF; Feritrin; Vitachol; ***Israel***: Iodax†; Iodine Tincture; ***Ital.***: Antiadiposo; Facovit; Fertomcidina-U; Jodo Calcio Vitaminico; Linfoiodine†; Natalben; Olimag; Polijodurato; Rubjovit; ***Malaysia***: Bio-Cal; Hyiodine; ***Mex.***: Calciyodina; Iodex Clasico; Jarabe de Rabano Yodado; ***Pol.***: Jodthyrox; ***Rus.***: Antioxycaps with Iodine (Антиоксикапс с Йодом); Iodocomb (Йодокомб); Jodthyrox (Йодтирокс); Neo-Anusol (Нео-анузол); Solutan (Солутан)†; Thyreocomb (Тиреокомб); ***S.Afr.***: SB Blood Purifying Mixture†; ***Singapore***: Chitosano; Shine Bio-Cal; Vitreolent; ***Spain***: Adiod; Audione†; Callicida Rojo†; Depurativo Richelet†; Natifar; Natimed; Nitroina; Yodocefol; Yoduk Complex; Yofolvit; ***Switz.***: Radix†; Vitreolent; ***Thai.***: Cenamin; Tincture Sahakarn; Tr Iodine Sahakarn; ***Turk.***: Broksin; Eupnase; Fenasthma; Fenastma; Neo Sedeks; ***UK***: Estroven; Nasciodine; TCP; ***Ukr.***: Femibion 400 (Фемибион 400); Femibion 800 (Фемибион 800); Folio (Фолио); Prostalin (Просталин); Stifimol (Стифимол); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Yodofol (Йодофол); ***USA***: Elixophyllin-KI; Iodex with Methyl Salicylate; KIE; One A Day Vitacraves; ORA5; Pediacof; Pedituss Cough; Phylorinol; Quadrinal; REQ49 +; ***Venez.***: Iodex con Salicilato de Metilo.

Homoeopathic Preparations. ***Austral.***: Childrens Runny Nose Relief; Hay Fever; Respatona Nasal Spray Decongestant; ***Austria***: Erbiode Haarvital; Famulan; Gentos; Globuli gegen Husten Nr 2; Otovowen; ***Canad.***: C-Plus; Calnor†; Complete Flu Care 4 Kids†; Homeo-Form S†; Hylands Flu; Hylands Formula F; Itires; Osteel†; Rhinar†; Sore Throat L39†; Urarthone†; Weight Control; ***Chile***: Formula II Especial; Fucus Especial; ***Fr.***: Abbe Chaupitre no 48†; Abbe Chaupitre no 91†; Arthro-Drainol; Badiaga Complexe No 47; Boripharm No 31; Dolistamine†; Iodum Complexe No 118; Kalium Iodatum Complexe No 84†; Mercurius Solubilis Complexe No 39; Urarthone; Urtica Complexe No 82†; Zincum Cyanidum Complexe No 101†; ***Ger.***: Arte-cyl Ho-Len-Complex; Asthmavowen-N†; Bronchosyx comp; Drufusan N†; Febro-cyl L Ho-Len-Complex; Girheulit HM†; Girheulit HOM; Hewethyreon N; Infekt-Komplex L Ho-Fu-Complex; Lymphaden Lymphdrusentabletten; Neuri-cyl N Ho-Len-Complex; Otovowen; Phonix Thuja-Lachesis spag; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Rufebran allergo†; Thuja N Oligoplex†; Thuja WA Oligoplex; ***Hung.***: Gentos; Osteoheel; ***Neth.***: Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Nisyspray; ***Rus.***: Berberis Comp (Барбарис Комп); Famulan (Фамулан); Gentos (Гентос); ***Switz.***: Osteoheel; Regenaplex Nr. 21e; Regenaplex Nr. 24c; ***Ukr.***: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); Gentos (Гентос).

Pharmacopoeial Preparations

BP 2014: Alcoholic Iodine Solution; Aqueous Iodine Oral Solution; Potassium Iodate Tablets; Sodium Iodide Injection;

BPC 1968: Compound Iodine Paint;

USP 36: Iodine Tincture; Iodine Topical Solution; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Potassium Iodide Delayed-release Tablets; Potassium Iodide Oral Solution; Potassium Iodide Tablets; Strong Iodine Solution; Strong Iodine Tincture; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Levothyroxine Sodium *(BANM, rINN)*

Levothyroxin-Natrium; Levothyroxin sodná sůl hydrát; Lévothyroxine sodique; Levothyroxinnatrium; Levothyroxinum Natricum; Levothyroxinum Natricum Hydricum; Levotiroksin Sodyum; Levotiroksino natrio druska; Levotiroxina sódica; Levotiroxin-nátrium; Levotyroksiininatrium; Levotyroxinnatrium; Lewotyroksyna sodowa; L-Thyroxine Sodium; Thyroxine Sodium; Thyroxinum Natricum; Tirossina; Tiroxina Sodica; Левотироксин Натрий; 3,5,3′,5′-Tetra-iodo-L-thyronine Sodium.

Sodium 4-*O*-(4-hydroxy-3,5-di-iodophenyl)-3,5-di-iodo-L-tyrosine hydrate.

$C_{15}H_{10}I_4NNaO_4.xH_2O$=798.9 (anhydrous)

CAS — 51-48-9 (levothyroxine); 55-03-8 (anhydrous levothyroxine sodium); 25416-65-3 (levothyroxine sodium, hydrate); 8065-29-0 (liotrix).

ATC — H03AA01.

ATC Vet — QH03AA01.

UNII — 054I36CPMN (anhydrous levothyroxine sodium); 9J765S329G (levothyroxine sodium); YW8HJ0N26X (liotrix).

NOTE. The abbreviation T_4 is often used for endogenous thyroxine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Int. includes the anhydrous form.

Ph. Eur. 8: (Levothyroxine Sodium). An almost white or slightly brownish-yellow, fine, slightly hygroscopic, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Levothyroxine Sodium). The sodium salt of L-3,3′,5,5′-tetraiodothyronine. A light yellow to buff-coloured, odourless, hygroscopic, powder. It may assume a slight pink colour on exposure to light. Soluble 1 in 700 of water and 1 in 300 of alcohol; insoluble in acetone, in chloroform, and in ether; soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates. pH of a saturated solution in water is about 8.9. Store in airtight containers. Protect from light.

Uses and Administration

Levothyroxine is a thyroid hormone (see p. 2332.1 for a description of the endogenous hormones) used as replacement therapy in the treatment of hypothyroidism (p. 2333.3). It is given in conditions such as diffuse non-toxic goitre (see Goitre and Thyroid Nodules, p. 2332.1) and Hashimoto's thyroiditis (see Hypothyroidism, p. 2333.3) to suppress the secretion of thyroid-stimulating hormone (TSH) and hence prevent or reverse enlargement of the thyroid gland. Levothyroxine is also used to suppress TSH production in the treatment of thyroid carcinoma (p. 716.1) and as a diagnostic agent for the differential diagnosis of hyperthyroidism. It is given with antithyroid drugs in the blocking-replacement regimen for the management of hyperthyroidism (p. 2332.2).

The peak therapeutic effect of regular oral levothyroxine may not be achieved for several weeks and there is a slow response to changes in dosage. Similarly, effects may persist for several weeks after withdrawal. Levothyroxine is given as the sodium salt in a single daily dose. Its absorption can be irregular and it is probably best taken on an empty stomach, usually before breakfast.

The dose of levothyroxine sodium for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

In hypothyroidism an initial oral dose of 50 to 100 micrograms of levothyroxine sodium daily may be increased by 25 to 50 micrograms at intervals of about 3 to 4 weeks until the thyroid deficiency is corrected and a maintenance dose is established. The maintenance dose is usually between 100 and 200 micrograms daily.

In patients over 50 years, in those with cardiac disease, or in those with severe hypothyroidism of long standing, treatment should be introduced more gradually: an initial dose of 12.5 to 50 micrograms daily increased by increments of 12.5 to 25 micrograms at intervals ranging from about 2 to 8 weeks may be appropriate, to usual maintenance doses between 50 and 200 micrograms daily.

For the use of levothyroxine in children, see below.

Levothyroxine sodium may be given by intravenous injection. It has also been given intramuscularly. In myxoedema (hypothyroid) coma a dose of 300 to 500 micrograms by intravenous injection may be given initially. Further doses of 50 to 100 micrograms may be given daily until the patient is clinically stable and can tolerate oral doses.

Dextrothyroxine, the D-isomer of levothyroxine, has lipid regulating properties and has been used in the management of hypercholesterolaemia, but its use is severely limited by cardiotoxicity; it has only weak thyroid hormone activity.

General references.

1. Mandel SJ, *et al.* Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med* 1993; **119:** 492–502.
2. Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331:** 174–80. Correction. *ibid.*; 1035.
3. Escobar-Morreale HF, *et al.* Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metab* 2005; **90:** 4946–54.

Administration. *BIOEQUIVALENCE.* There has been controversy over the bioequivalence or otherwise of different brands of levothyroxine. Most studies and reports have come from the USA and results may have depended to some extent on the particular brands compared. Formulations may also have changed which makes comparison of results difficult. One study[1] concluded that 2 generic levothyroxine products were bioequivalent and interchangeable with 2 branded products.

In 2004 the FDA issued guidance on the bioequivalence of several levothyroxine products on the US market but this was heavily criticised in a joint statement by several American professional societies.[2] In response, these societies recommended to physicians that patients should be maintained on the same brand of levothyroxine and if the brand were changed then the patient's serum TSH should be retested and the dosage of levothyroxine re-titrated as necessary. Similar advice was issued in New Zealand in 2008, when a change in formulation within the same brand of levothyroxine resulted in a higher incidence of adverse drug reaction reporting.[3]

1. Dong BJ, *et al.* Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997; **277:** 1205–13.
2. American Association of Clinical Endocrinologists, The Endocrine Society, and American Thyroid Association. Joint position statement on the use and interchangeability of thyroxine products. Available at: https://www.aace.com/sites/default/files/AACE-TES-ATA-Thyroxine-Products.pdf (accessed 02/08/11) See also American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists. Joint Statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. *Thyroid* 2004; **14:** 486.
3. New Zealand Medicines and Medical Devices Safety Authority. Eltroxin formulation change - Monitor patients and adjust dosing if necessary (issued 26 June, 2008). Available at: http://www.medsafe.govt.nz/hot/alerts/eltroxin.asp (accessed 12/12/08)

ROUTE. Intra-amniotic injection of levothyroxine has been used to treat fetal goitrous hypothyroidism.[1,2] In one case, diagnosis was made at 36 weeks of gestation, and two doses of 300 micrograms of levothyroxine were injected into the maternal amniotic fluid between 37 and 38 weeks of gestation. Mild tachypnoea and an enlarged thyroid gland were noted in the neonate, who also required a further 2 weeks of oral levothyroxine for persistent neonatal hypothyroidism.[1] In a retrospective study of 12 infants, prenatal treatment varied widely in terms of levothyroxine dosage; intra-amniotic doses of between 200 to 800 micrograms were given. No adverse effects were seen, but all infants were hypothyroid at birth. The authors concluded that, while the method is feasible and safe and probably effective in decreasing goitre size, no guidelines can be developed until further studies are done.[2]

1. Miyata I, *et al.* Successful intrauterine therapy for fetal goitrous hypothyroidism during late gestation. *Endocr J* 2007; **54:** 813–17.
2. Ribault V, *et al.* French Fetal Goiter Study Group. Experience with intraamniotic thyroxine treatment in nonimmune fetal goitrous hypothyroidism in 12 cases. *J Clin Endocrinol Metab* 2009; **94:** 3731–9.

TIMING. Although levothyroxine is usually taken in the morning on an empty stomach for hypothyroidism (see Uses and Administration, above), a controlled study[1] found improved thyroid hormone concentrations when the dose was given at night; no significant changes in patients' plasma lipid concentrations or quality of life were seen.

The recommendation that levothyroxine be taken on an empty stomach has also been questioned; in particular, on the grounds that it may cause problems with adherence in infants and children. US expert bodies have suggested that consistent administration with regard to timing and meals is more important than the presence or absence of food (although giving it with iron or calcium should be avoided). In addition, soya-based infant formulas may impair absorption of levothyroxine, and frequent testing may be needed, particularly when there are changes in formula.[2]

1. Bolk N, *et al.* Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch Intern Med* 2010; **170:** 1996–2003.
2. Zeitler P, Solberg P. Pharmacy and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Food and levothyroxine administration in infants and children. *J Pediatr* 2010; **157:** 13–14.

Administration in children. It is especially important that children with hypothyroidism have their dosage individualised and treatment monitored. In the UK, the *BNFC* recommends the following oral doses of levothyroxine sodium:

- neonates: 10 to 15 micrograms/kg once daily (to a maximum of 50 micrograms daily) initially, adjusted in steps of 5 micrograms/kg every 2 weeks or as needed, to a usual maintenance dose of 20 to 50 micrograms daily
- children aged 1 month to 2 years: 5 micrograms/kg once daily (to a maximum of 50 micrograms daily) initially, adjusted in steps of 10 to 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual maintenance dose of 25 to 75 micrograms daily
- children aged 2 to 12 years: 50 micrograms once daily initially, adjusted in steps of 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual maintenance dose of 75 to 100 micrograms daily
- children aged 12 to 18 years: 50 micrograms once daily initially, then adjusted as for adults, see above

For discussion of the timing of dosage in infants and children see above.

Cardiomyopathies. Management of dilated cardiomyopathy (p. 1261.3) usually involves conventional therapy for heart failure, but a small study has reported benefit from short-term use of oral levothyroxine.[1] Levothyroxine was well tolerated but thyroid-stimulating hormone levels were reduced, which might limit long-term therapy. Simi-

lar results have been reported with short-term intravenous liothyronine.[2]

1. Moruzzi P, *et al.* Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. *Am J Med* 1996; **101:** 461–7.
2. Pingitore A, *et al.* Acute effects of triiodothyronine (T_3) replacement therapy in patients with chronic heart failure and low-T_3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2008; **93:** 1351–8.

Depression. While thyroid hormones may increase the activity of tricyclic antidepressants (see Thyroid Hormones, under Interactions of Amitriptyline, p. 407.2), the benefits in the augmentation treatment of depression (p. 398.1) are debatable. A meta-analysis[1] of 8 studies involving 292 patients with refractory depression treated with liothyronine in addition to tricyclic antidepressants indicated that such therapy was effective in a subgroup of cases but that the small number of patients studied made additional placebo-controlled data desirable.

In non-refractory depression a meta-analysis[2] also indicated a benefit when liothyronine was added to tricyclic antidepressants although it was acknowledged that many of the studies were old with methodological limitations. Subsequent studies have shown conflicting results. A controlled study of liothyronine with paroxetine could not confirm any advantage of additive therapy,[3] whereas another[4] found an improvement in response and remission when liothyronine was added to sertraline therapy. The authors of the latter study commented upon the conflicting results with the previous study, highlighting the difference in the proportion of patients with chronic depression; response to the combination of sertraline plus liothyronine was related to the duration of the current depressive episode, with duration being significantly shorter in those who responded.[4]

1. Aronson R, *et al.* Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry* 1996; **53:** 842–8.
2. Altshuler LL, *et al.* Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 2001; **158:** 1617–22.
3. Appelhof BC, *et al.* Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab* 2004; **89:** 6271–6.
4. Cooper-Kazaz R, *et al.* Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2007; **64:** 679–88.

Obesity. Thyroid drugs have been tried in the treatment of obesity (p. 2315.1) in euthyroid patients, but they produce only temporary weight loss, mainly of lean body-mass, and can produce serious adverse effects, especially cardiac complications.[1] Hypothyroidism has also been reported[2] when these drugs were withdrawn from previously euthyroid patients being treated for simple obesity. Levothyroxine appears to have been abused by some athletes to promote weight loss;[3] liothyronine has been abused similarly.[4] A systematic review[5] concluded that data were inconclusive as to the efficacy of thyroid hormone therapy for treating obesity. However, data supported the suggestion that thyroid hormone therapy induced subclinical hyperthyroidism in obese subjects, and therapy was not recommended in euthyroid patients.

1. Rivlin RS. Therapy of obesity with hormones. *N Engl J Med* 1975; **292:** 26–9.
2. Dornhorst A, *et al.* Possible iatrogenic hypothyroidism. *Lancet* 1981; **i:** 52.
3. MacAuley D. Drugs in sport. *BMJ* 1996; **313:** 211–15.
4. Hartung B, *et al.* Lethal thyroid storm after uncontrolled intake of liothyronine in order to lose weight. *Int J Legal Med* 2010; **124:** 637–40.
5. Kaptein EM, *et al.* Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *J Clin Endocrinol Metab* 2009; **94:** 3663–75.

Thyroid autoantibodies. A systematic review and meta-analysis[1] indicated that the presence of thyroid autoantibodies in women with normal thyroid function was strongly associated with an increased risk of miscarriage and preterm birth. There was some evidence suggesting that low-dose levothyroxine treatment during pregnancy might reduce these risks,[1] but further studies were needed and a prospective double-blind study (the TABLET study) was planned.[2]

1. Thangaratinam S, *et al.* Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* 2011; **342:** d2616.
2. Negro R, Stagnaro-Green A. Thyroid autoantibodies, preterm birth, and miscarriage. *BMJ* 2011; **342:** 1035–6.

Urticaria. There is some suggestion that chronic urticaria (p. 1689.2) may be associated with thyroid autoimmunity and that treatment with thyroid hormones may result in clinical remission.[1] In one study, a nine-year-old boy was successfully treated for chronic urticaria with levothyroxine therapy at doses of 50 to 100 micrograms daily.[2] The authors advised screening for thyroid function and anti-thyroid microsomal antibodies in cases of chronic urticaria as these patients may benefit from thyroid hormone therapy. A small investigative study concluded that treatment with levothyroxine sodium (in hypothyroid patients) or antithyroid drugs (in patients with Graves' disease) is of benefit in patients with severe chronic urticaria associated with thyroid autoimmunity.[3] A review[4] concluded that about 25% of patients with chronic idiopathic urticaria have serological evidence of thyroid autoantibodies, and that screening for thyroid autoimmunity may be useful in these patients. While acknowledging anecdotal reports of levothyroxine's efficacy in ameliorating urticaria, the authors concluded that definitive data were needed before any recommendation could be made for its use.

1. Rumbyrt JS, *et al.* Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; **96:** 901–5.
2. Dreyfus DH, *et al.* Steroid-resistant chronic urticaria associated with anti-thyroid microsomal antibodies in a nine-year-old boy. *J Pediatr* 1996; **128:** 576–8.
3. Gaig P, *et al.* Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. *J Investig Allergol Clin Immunol* 2000; **10:** 342–5.
4. Bagnasco M, *et al.* Urticaria and thyroid autoimmunity. *Thyroid* 2011; **21:** 401–10.

Adverse Effects and Treatment

The adverse effects of levothyroxine are generally associated with excessive dosage and correspond to symptoms of hyperthyroidism. They may include tachycardia, palpitations, cardiac arrhythmias, increase in blood pressure, anginal pain, headache, restlessness, excitability, insomnia, tremors, muscle weakness and cramps, heat intolerance, sweating, flushing, fever, weight loss, menstrual irregularities, diarrhoea, and vomiting. These adverse reactions usually disappear after dosage reduction or temporary withdrawal of treatment. Elevations in liver function tests and decreased bone mineral density have been reported. Hypersensitivity reactions can occur. Thyroid storm has occasionally been reported after massive or chronic intoxication and convulsions, cardiac arrhythmias, heart failure, coma, and death have occurred.

Treatment of overdose is usually symptomatic and supportive; propranolol may be useful in controlling the symptoms of sympathetic overactivity. The UK National Poisons Information Service states that the benefit of gastric decontamination in acute overdosage of levothyroxine is uncertain; oral activated charcoal may be considered for an adult or child presenting within 1 hour of ingestion of doses over 100 micrograms/kg. Levothyroxine overdosage requires an extended follow-up period as symptoms may be delayed for up to 6 days due to the gradual peripheral conversion of levothyroxine to tri-iodothyronine; glucocorticoids may be given to inhibit this conversion.

Carcinogenicity. An association between the use of thyroid hormones and an increased risk of breast cancer in women has been proposed,[1] but a further analysis of the data did not confirm such an association,[2] and nor did later studies.[3-5]

1. Kapdi CC, Wolfe JN. Breast cancer. Relationship to thyroid supplements for hypothyroidism. *JAMA* 1976; **236:** 1124–7.
2. Mustacchi P, Greenspan F. Thyroid supplementation for hypothyroidism. An iatrogenic cause of breast cancer? *JAMA* 1977; **237:** 1446–7.
3. Wallace RB, *et al.* Thyroid hormone use in patients with breast cancer. Absence of an association. *JAMA* 1978; **239:** 958.
4. Shapiro S, *et al.* Use of thyroid supplements in relation to the risk of breast cancer. *JAMA* 1980; **244:** 1685–7.
5. Hoffman DA, *et al.* Breast cancer in hypothyroid women using thyroid supplements. *JAMA* 1984; **251:** 616–19.

Effects on the bones. Hyperthyroidism is a known risk factor for osteoporosis and theoretically thyroid hormone therapy may also be a risk factor. A review of over 3000 patients from 63 studies summarised the available evidence on the association of levothyroxine and bone mineral density.[1] It was stressed that current findings were complex and confusing and poor methodological quality made comparison of results difficult. However, it was concluded that neither dose of levothyroxine nor duration of therapy had any relationship with bone mineral density (BMD): 31 studies showed no overall effect of levothyroxine, 23 studies provided partial negative and/or positive effects, while 9 showed overall negative effects. For postmenopausal women, particularly those with a history of hyperthyroidism, the review[1] recommended monitoring of thyroid hormone levels to avoid clinical hyperthyroidism, and screening for risk factors of osteoporosis; if warranted, bone densitometry, and appropriate management of any decline in BMD, should be used.

A retrospective case-control study[2] found a significant association between current levothyroxine use and increased risk of fracture in people over 70 years of age, with a strong dose-response relationship. An increased risk remained in those who had stopped levothyroxine therapy within the previous 6 months.

1. Schneider R, Reiners C. The effect of levothyroxine therapy on bone mineral density: a systematic review of the literature. *Exp Clin Endocrinol Diabetes* 2003; **111:** 455–70.
2. Turner MR, *et al.* Levothyroxine dose and risk of fractures in older adults: nested case-control study. *BMJ* 2011; **342:** d2238.

Effects on the muscles. A Taiwanese female with previous normal thyroid function developed thyrotoxic periodic paralysis (TPP) affecting the limbs after abusing levothyroxine, 100 micrograms twice daily for 2 weeks, in order to lose weight.[1] The attack subsided after treatment with intravenous potassium and withdrawal of the levothyroxine. Although TPP is a condition most commonly seen in patients of South Asian origin there is a report of TPP precipitated by excessive levothyroxine replacement therapy in a Caucasian patient with panhypopituitarism.[2]

1. Chen YC, *et al.* Thyrotoxic periodic paralysis in a patient abusing thyroxine for weight reduction. *Ren Fail* 2001; **23:** 139–42.
2. Hannon MJ, *et al.* Thyrotoxic periodic paralysis due to excessive L-thyroxine replacement in a Caucasian man. *Ann Clin Biochem* 2009; **46:** 423–5.

Effects on the nervous system. Two children aged 8 and 11 years developed pseudotumor cerebri (benign intracranial hypertension) shortly after starting levothyroxine for hypothyroidism.[1] There have been further reports on individual children[2-4] and infants.[5]

Partial complex status epilepticus, with confusion, agitation, and continuous myoclonic jerks in the left side of the face and left hand, was seen in a hypothyroid patient with Turner's syndrome who was receiving levothyroxine for myxoedema coma.[6] The condition responded to anticonvulsants; the patient subsequently remained seizure-free on a reduced dose of levothyroxine and concomitant phenytoin.

A 35-year-old woman with auto-immune thyroiditis, who increased her levothyroxine dosage to 300 micrograms daily in an attempt to lose weight, lost 20 kg over the next 6 months but developed incapacitating choreoathetosis.[7] However, all her symptoms had resolved a week after reducing her dosage back to 100 micrograms daily.

1. Van Dop C, *et al.* Pseudotumor cerebri associated with initiation of levothyroxine therapy for juvenile hypothyroidism. *N Engl J Med* 1983; **308:** 1076–80.
2. McVie R. Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309:** 731.
3. Hymes LC, *et al.* Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309:** 732.
4. Strickler C, Pilon AF. Presumed levothyroxine-induced pseudotumor cerebri in a pediatric patient being treated for congenital hypothyroidism. *Clin Ophthalmol* 2007; **1:** 545–9.
5. Raghavan S, *et al.* Pseudotumor cerebri in an infant after L-thyroxine therapy for transient neonatal hypothyroidism. *J Pediatr* 1997; **130:** 478–80.
6. Duarte J, *et al.* Thyroxine-induced partial complex status epilepticus. *Ann Pharmacother* 1993; **27:** 1139.
7. Kondziella D, *et al.* Choreathetosis due to abuse of levothyroxine. *J Neurol* 2009; **256:** 2106–8.

Hypersensitivity. A hypersensitivity reaction (fever, eosinophilia, and liver dysfunction) was reported[1] in a 63-year-old hypothyroid woman with Hashimoto's thyroiditis during treatment with liothyronine or levothyroxine. Symptoms disappeared when the drugs were stopped. After an interval of 4 months liothyronine was gradually reintroduced without adverse effect.

Urticaria and angioedema have been described in a patient who received thyroid and levothyroxine.[2] In a further case similar reactions were attributed to the presence of sunset yellow as colouring agent in the proprietary levothyroxine preparation.[3]

1. Shibata H, *et al.* Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. *Arch Intern Med* 1986; **146:** 1624–5.
2. Pandya AG, *et al.* Chronic urticaria associated with exogenous thyroid use. *Arch Dermatol* 1990; **126:** 1238–9.
3. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; **338:** 393.

Overdosage. In overdosage with thyroid drugs aggressive therapy is not normally justified in asymptomatic patients, although various regimens have been tried in large overdosage.

Massive overdoses of levothyroxine and liothyronine (up to 1000 times the normal dose over 2 to 12 days) have been described in small numbers of patients.[1-8] Symptoms of thyrotoxicosis can occur within the first 6 hours after ingestion of liothyronine but can be delayed for 2 to 5 days after levothyroxine, due to the time taken for metabolic conversion to liothyronine. Symptoms of thyrotoxicosis that have been reported include fever, arrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications, and coma.[1,2,5] Treatment of overdosage includes consideration of the use of activated charcoal and a beta blocker such as propranolol or metoprolol to treat tachyarrhythmia.[2,4,5] In most cases serious toxicity does not occur and patients recover with supportive therapy. Diuresis and haemodialysis do not enhance elimination because thyroid hormones are highly protein bound. It has also been concluded that plasmapheresis and haemoperfusion provide no significant clinical benefit.[4,6]

1. Kulig K, *et al.* Levothyroxine overdosage associated with seizures in a young child. *JAMA* 1985; **254:** 2109–10.
2. Binimelis J, *et al.* Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med* 1987; **13:** 33–8.
3. Golightly LK, *et al.* Clinical effects of accidental levothyroxine ingestion in children. *Am J Dis Child* 1987; **141:** 1025–7.

4. Henderson A, *et al.* Lack of efficacy of plasmapheresis in a patient overdosed with thyroxine. *Anaesth Intensive Care* 1994; **22:** 463–4.
5. Hack JB, *et al.* Severe symptoms following a massive intentional L-thyroxine ingestion. *Vet Hum Toxicol* 1999; **41:** 323–6.
6. Solá E, *et al.* Massive triiodothyronine intoxication: efficacy of hemoperfusion? *Thyroid* 2002; **7:** 637–40.
7. Tsutaoka BT, *et al.* Seizure in a child after an acute ingestion of levothyroxine. *Pediatr Emerg Care* 2005; **21:** 857–9.
8. Ho J, *et al.* Massive levothyroxine ingestion in a pediatric patient: case report and discussion. *CJEM* 2011; **13:** 165–8.

Precautions

Levothyroxine is contra-indicated in untreated hyperthyroidism. It has a narrow therapeutic index and should be used with extreme caution in patients with cardiovascular disorders including angina, heart failure, myocardial infarction, and hypertension; lower initial doses, smaller increments, and longer intervals between increases should be used as necessary. An ECG performed before starting treatment with levothyroxine may help to distinguish underlying myocardial ischaemia from changes induced by hypothyroidism. Levothyroxine should also be introduced very gradually in elderly patients and those with long-standing hypothyroidism to avoid any sudden increase in metabolic demands. It should not be given to patients with adrenal insufficiency without adequate corticosteroid cover otherwise the thyroid replacement therapy might precipitate an acute adrenal crisis. Care is also required when levothyroxine is given to patients with diabetes mellitus or diabetes insipidus. Thyroid hormones may affect the seizure threshold and care is needed when levothyroxine is given to patients with epilepsy.

Tests of thyroid function are subject to alteration by some nonthyroidal clinical conditions and by many drugs, some of which are mentioned under Interactions, below.

Abuse. For mention of abuse of levothyroxine by athletes for weight loss see Obesity, under Uses and Administration, p. 2340.1. For reference to periodic paralysis in a woman abusing levothyroxine as a slimming aid, see under Effects on the Muscles, p. 2340.2.

Adrenocortical insufficiency. Thyroid-hormone replacement without additional corticosteroids may precipitate acute adrenocortical insufficiency in patients with impaired adrenocortical function, including those with subclinical or unrecognised adrenocortical disease.[1] Prompt diagnosis and replacement of corticosteroids can prevent the development of a potentially fatal crisis. It has been pointed out that a raised concentration of thyroid-stimulating-hormone alone may not necessarily imply hypothyroidism in patients with chronic adrenocortical insufficiency.[2] Even confirmed hypothyroidism in these patients may not be permanent.

1. Fonseca V, *et al.* Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; **292:** 1185–6.
2. Davis J, Sheppard M. Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; **292:** 1595.

Anaemia. Four patients with iron deficiency anaemia and primary hypothyroidism developed palpitations and restlessness on treatment with levothyroxine sodium, and the drug had to be stopped. Upon correction of the anaemia with ferrous sulfate, all were able to tolerate levothyroxine therapy.[1] For a warning that ferrous sulfate reduces absorption of levothyroxine from the gastrointestinal tract, see Iron Salts under Interactions, p. 2342.1.

1. Shakir KMM, *et al.* Anemia: a cause of intolerance to thyroxine sodium. *Mayo Clin Proc* 2000; **75:** 189–92.

Breast feeding. Minimal amounts of thyroid hormones are distributed into breast milk. The last available guidance from the American Academy of Pediatrics noted that no effects had been seen in breast-fed infants whose mothers were taking levothyroxine and as such considered its use to be usually compatible with breast feeding.[1]

Although levothyroxine in breast milk will be insufficient to treat any hypothyroidism in the suckling newborn, it has been suggested that it may mask detection of any hypothyroidism in such a neonate.[2] However, the *BNF* considers that the amounts involved are too small to affect tests for neonatal hypothyroidism.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)
2. Anonymous. Can a woman on thyroxine safely breast-feed her baby? *BMJ* 1977; **2:** 1589.

Cardiovascular disorders. There is a complex relationship between the heart and thyroid.[1] Cardiovascular abnormalities may be associated with hypothyroidism as well as with levothyroxine replacement therapy, hence the need for caution.

1. Gammage M, Franklyn J. Hypothyroidism, thyroxine treatment, and the heart. *Heart* 1997; **77:** 189–90.

Myasthenia. Thyroid hormones may occasionally precipitate or exacerbate a pre-existing myasthenic syndrome.[1,2]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; **24:** 304–21.
2. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levothyroxine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pregnancy. Most authorities consider that thyroid hormones do not readily cross the placenta. Placental transfer has been reported,[1] but in amounts so limited that a mother with physiological concentrations of thyroxine and tri-iodothyronine would not provide normal thyroid hormone concentrations to a fetus with congenital hypothyroidism.[2-4]

Levothyroxine requirements increase in hypothyroid women during early pregnancy. A small study involving 20 pregnancies found that the dose requirement rose from the sixth to the sixteenth week of gestation before reaching a plateau; a mean dose increase of nearly 50% was eventually required in 17 cases.[5] The authors recommended that all hypothyroid women should have their levothyroxine dose increased by 30% as soon as pregnancy was confirmed, to avoid any risk of an initial period of hypothyroxinaemia before the first obstetric visit. Thereafter, dosage should be adjusted according to serum-thyrotropin concentrations. See also under Hypothyroidism, p. 2333.3.

For mention of the possible value of levothyroxine treatment in reducing miscarriage and premature births in euthyroid women with thyroid autoantibodies, see Thyroid Autoantibodies under Uses, p. 2340.1.

1. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989; **321:** 13–16.
2. Sack J, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1549–50.
3. Bachrach LK, Burrow GN. Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1549.
4. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1550.
5. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; **351:** 241–9.

Interactions

References.

1. Takahashi N, *et al.* Effect of thyroid hormone on the activity of CYP3A enzyme in humans. *J Clin Pharmacol* 2010; **50:** 88–93.

Antiarrhythmics. *Amiodarone*[1] may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine with a rise in the concentration of inactive reverse tri-iodothyronine.

1. Hershman JM, *et al.* Thyroxine and triiodothyronine kinetics in cardiac patients taking amiodarone. *Acta Endocrinol (Copenh)* 1986; **111:** 193–9.

Antibacterials. Enzyme induction by *rifampicin*[1,2] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones.

Two patients with previously stable thyroid function while receiving levothyroxine were found to have developed hypothyroidism 3 to 4 weeks after starting oral treatment with *ciprofloxacin*.[3] In one patient increasing the dose of levothyroxine was ineffective and thyroid function only returned to normal after ciprofloxacin was withdrawn. In the other patient, giving the drugs 6 hours apart was sufficient to overcome the interaction.

1. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; **15:** 71–6.
2. Nolan SR, *et al.* Interaction between rifampin and levothyroxine. *South Med J* 1999; **92:** 529–31.
3. Cooper JG, *et al.* Ciprofloxacin interacts with thyroid replacement therapy. *BMJ* 2005; **330:** 1002.

Anticoagulants. Thyroid hormones enhance the effects of *oral anticoagulants* (see under the interactions of Warfarin, p. 1535.2). Patients on anticoagulant therapy therefore require careful monitoring when treatment with thyroid drugs is started or altered as the oral anticoagulant dose may need to be adjusted.

Antidepressants. Some drugs such as *lithium* act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism.[1]

The effects of levothyroxine in hypothyroid patients may be decreased by use with *sertraline*, and the dose of levothyroxine may need to be increased.[2]

For the effects of thyroid hormones on *tricyclic antidepressants* see under Amitriptyline, p. 407.2.

1. Ramsay I. Drugs and non-thyroid induced changes in thyroid function tests. *Postgrad Med J* 1985; **61:** 375–7.
2. McCowen KC, *et al.* Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med* 1997; **337:** 1010–11.

Antidiabetics. As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism may affect other disease states and dosage of any drug treatment. In hypothyroid diabetics for instance, starting thyroid replacement therapy may increase their *insulin* or *oral hypoglycaemic* requirements.[1]

1. Refetoff S. Thyroid hormone therapy. *Med Clin North Am* 1975; **59:** 1147–62.

Antiepileptics. Enzyme induction by drugs such as *carbamazepine*,[1,2] *phenytoin*,[2,3] or *barbiturates*[4] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these drugs are also given[5] and a decrease if the enzyme-inducing drug is withdrawn.[6] *Phenytoin*,[3] and *carbamazepine* may reduce protein binding by displacing the thyroid hormones from their plasma-binding sites. As thyroid hormones are highly protein bound, changes in binding might be expected to influence requirements in thyroid replacement therapy, but in practice there is little clinical evidence of any problems except with thyroid-function testing.

1. Connell JMC, *et al.* Changes in circulating thyroid hormones during short-term hepatic enzyme induction with carbamazepine. *Eur J Clin Pharmacol* 1984; **26:** 453–6.
2. Larkin JG, *et al.* Thyroid hormone concentrations in epileptic patients. *Eur J Clin Pharmacol* 1989; **36:** 213–6.
3. Franklyn JA, *et al.* Measurement of free thyroid hormones in patients on long-term phenytoin therapy. *Eur J Clin Pharmacol* 1984; **26:** 633–4.
4. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; **15:** 71–6.
5. Blackshear JL, *et al.* Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. *Ann Intern Med* 1983; **99:** 341–2.
6. Hoffbrand BI. Barbiturate/thyroid-hormone interaction. *Lancet* 1979; **ii:** 903–4.

Antimalarials. Increased thyroid-stimulating hormone concentration has been noted after the use of *chloroquine* with *proguanil* for malaria prophylaxis in a patient stabilised on levothyroxine.[1] Induction of liver enzymes by chloroquine resulting in increased metabolism of levothyroxine was suggested as the mechanism.

1. Munera Y, *et al.* Interaction of thyroxine sodium with antimalarial drugs. *BMJ* 1997; **314:** 1593.

Antineoplastics. Eight patients taking levothyroxine, subsequent to thyroidectomy, developed raised concentrations of thyroid-stimulating hormone (TSH) and clinical hypothyroidism when they were given *imatinib*. Increasing the levothyroxine dose reversed hypothyroidism in only 3 patients, but TSH concentrations returned to normal in all patients when imatinib was stopped. In contrast, these effects did not occur in 3 other patients with a normal functioning thyroid. The authors reasoned that imatinib might have stimulated the clearance of thyroxine and tri-iodothyronine by inducing uridine diphosphate glucuronosyltransferases, but evidence is needed to confirm this mechanism. They suggested that the dose of levothyroxine should be at least doubled, with close monitoring of thyroid function, before imatinib is given to patients with hypothyroidism.[1]

1. de Groot JWB, *et al.* Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther* 2005; **78:** 433–8.

Antivirals. There have been reports of interactions between HIV-protease inhibitors and levothyroxine. An increased dose of levothyroxine was necessary with *ritonavir*[1] whereas a decreased dose was needed with *indinavir*.[2]

1. Tseng A, Fletcher D. Interaction between ritonavir and levothyroxine. *AIDS* 1998; **12:** 2235–6.
2. Lanzafame M, *et al.* Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* 2002; **30:** 54–5.

Beta blockers. Studies have indicated that plasma concentrations of *propranolol* are reduced in hyperthyroidism compared with the euthyroid state, probably due to increased clearance[1-4] and hypothyroid patients receiving chronic propranolol therapy have had a reduction in plasma-propranolol concentrations when given levothyroxine treatment.[2]

Propranolol may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine and a rise in the concentration of inactive reverse tri-iodothyronine.[5,6]

1. Feely J, *et al.* Increased clearance of propranolol in thyrotoxicosis. *Ann Intern Med* 1981; **94:** 472–4.
2. Feely J, *et al.* Plasma propranolol steady state concentrations in thyroid disorders. *Eur J Clin Pharmacol* 1981; **19:** 329–33.
3. Aro A, *et al.* Pharmacokinetics of propranolol and sotalol in hyperthyroidism. *Eur J Clin Pharmacol* 1982; **21:** 373–7.
4. Hallengren B, *et al.* Influence of hyperthyroidism on the kinetics of methimazole, propranolol, metoprolol, and atenolol. *Eur J Clin Pharmacol* 1982; **21:** 379–84.

5. Chambers JB, *et al*. The effects of propranolol on thyroxine metabolism and triiodothyronines production in man. *J Clin Pharmacol* 1982; **22:** 110–16.
6. Wilkins MR, *et al*. Effect of propranolol on thyroid homeostasis of healthy volunteers. *Postgrad Med J* 1985; **61:** 391–4.

Cardiac glycosides. Serum-digoxin concentrations appear to be lower in hyperthyroidism and higher in hypothyroidism,[1] which may contribute in part to the observed insensitivity of hyperthyroid patients to *digoxin* therapy,[2] although other mechanisms have been proposed.[3]

1. Croxson MS, Ibbertson HK. Serum digoxin in patients with thyroid disease. *BMJ* 1975; **3:** 566–8.
2. Huffman DH, *et al*. Digoxin in hyperthyroidism. *Clin Pharmacol Ther* 1977; **22:** 533–8.
3. Lawrence JR, *et al*. Digoxin kinetics in patients with thyroid dysfunction. *Clin Pharmacol Ther* 1977; **22:** 7–13.

Chelators and antidotes. *Lanthanum carbonate* reduced the absorption of levothyroxine, an effect that was thought to be due to the lanthanum ion binding with thyroid hormones in the gastrointestinal tract. An interval of at least 2 hours is suggested between taking the 2 drugs.[1] A similar effect has been seen with *sodium polystyrene sulfonate*[2] and sevelamer.[3-5]

1. Weitzman SP, *et al*. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. *Thyroid* 2009; **19:** 77–9.
2. McLean M, *et al*. Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* 1993; **341:** 1286.
3. Diskin CJ, *et al*. Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. *Int Urol Nephrol* 2007; **39:** 599–602.
4. John-Kalarickal J, *et al*. New medications which decrease levothyroxine absorption. *Thyroid* 2007; **17:** 763–5.
5. Arnadottir M, Johannesson AJ. Phosphate binders and timing of levothyroxine administration. *Nephrol Dial Transplant* 2008; **23:** 420.

Gastrointestinal drugs. *Sucralfate* reduces absorption of levothyroxine from the gastrointestinal tract[1,2] as does *aluminium hydroxide*,[3] and *calcium carbonate*.[4,5]

1. Sherman SI, *et al*. Sucralfate causes malabsorption of L-thyroxine. *Am J Med* 1994; **96:** 531–5.
2. Campbell JA, *et al*. Sucralfate and the absorption of L-thyroxine. *Ann Intern Med* 1994; **121:** 152.
3. Liel Y, *et al*. Nonspecific intestinal adsorption of levothyroxine by aluminium hydroxide. *Am J Med* 1994; **97:** 363–5.
4. Schneyer CR. Calcium carbonate and reduction of levothyroxine efficacy. *JAMA* 1998; **279:** 750.
5. Singh N, *et al*. Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* 2000; **283:** 2822–5.

General anaesthetics. Severe hypertension and tachycardia have been reported[1] when *ketamine* was used in patients taking levothyroxine.

1. Kaplan JA, Cooperman LH. Alarming reactions to ketamine in patients taking thyroid medication-treatment with propranolol. *Anesthesiology* 1971; **35:** 229–30.

Iron salts. *Ferrous sulfate* reduces absorption of levothyroxine from the gastrointestinal tract.[1]

1. Campbell NRC, *et al*. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 1992; **117:** 1010–13.

Lipid regulating drugs. Both decreased efficacy[1] and increased efficacy[2] of levothyroxine have been reported in individual patients given *lovastatin*. Increased thyroid stimulating hormone concentrations, requiring increased doses of levothyroxine, have been reported when *simvastatin* was begun.[3]

Colestyramine significantly reduces the absorption of levothyroxine by binding with thyroid hormones in the gastrointestinal tract. The malabsorption of levothyroxine is minimised by allowing an interval of 4 to 5 hours to elapse between taking the two drugs.[4] A similar effect has been seen with *colesevelam*, and a 4-hour interval is also recommended.[5,6]

1. Demke DM. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; **321:** 1341–2.
2. Gormley GJ, Tobert JA. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; **321:** 1342.
3. Kisch E, Segall HS. Interaction between simvastatin and L-thyroxine. *Ann Intern Med* 2005; **143:** 547.
4. Northcutt RC, *et al*. The influence of cholestyramine on thyroxine absorption. *JAMA* 1969; **208:** 1857–61.
5. Weitzman SP, *et al*. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. *Thyroid* 2009; **19:** 77–9.
6. Brown KS, *et al*. Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *J Clin Pharmacol* 2010; **50:** 554–65.

NSAIDs. Falsely low concentrations of levothyroxine (T_4) or tri-iodothyronine (T_3) have been reported during treatment with some anti-inflammatory drugs. Serum TSH measurements are less affected by NSAIDs and therefore TSH would be the optimal screening test in patients receiving an NSAID.[1]

1. Samuels MH, *et al*. Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; **88:** 5710–16.

Orlistat. A case of symptomatic hypothyroidism within 2 weeks of commencing orlistat has been reported in a woman stabilised on thyroxine therapy.[1] US licensed product information recommends monitoring patients for changes in thyroid function if they are taking both levothyroxine and orlistat, and to administer the drugs at least 4 hours apart.

1. Madhava K, Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine. *Clin Oncol (R Coll Radiol)* 2005; **17:** 492.

Sex hormones. *Oestrogen* therapy increases serum concentrations of thyroxine-binding globulin, thus increasing the amount of bound thyroxine. Normal thyroid function stimulates thyroxine synthesis to compensate for this effect and maintain normal free-thyroxine serum concentrations. In hypothyroidism, however, patients treated with exogenous levothyroxine who receive oestrogens, as in oral contraceptives or HRT,[1] may require an increase in levothyroxine dose. In contrast, *androgens* reduce the concentration of the binding globulin, which has resulted in clinical hyperthyroidism when given to postmenopausal women maintained on levothyroxine replacement therapy.[2]

Increased levothyroxine requirements were noted in two women when they took *raloxifene* at the same time as levothyroxine; the effect could be reversed by separating doses of the two drugs by about 12 hours.[3,4]

1. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* 2001; **344:** 1743–9.
2. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. *Ann Intern Med* 1994; **121:** 247–51.
3. Siraj ES, *et al*. Raloxifene causing malabsorption of levothyroxine. *Arch Intern Med* 2003; **163:** 1367–70.
4. Garwood CL, *et al*. Increased thyroid-stimulating hormone levels associated with concomitant administration of levothyroxine and raloxifene. *Pharmacotherapy* 2006; **26:** 881–5.

Sympathomimetics. Thyroid drugs increase metabolic demands and should therefore be used with caution with other drugs known to influence cardiac function, such as the *sympathomimetics*, as they may enhance this effect. In addition, thyroid hormones may increase receptor sensitivity to catecholamines.

Pharmacokinetics

Levothyroxine is variably absorbed from the gastrointestinal tract after oral doses. Fasting increases absorption. Once in the circulation, levothyroxine is extensively protein bound, mainly to thyroxine-binding globulin (TBG) but also to a lesser extent to thyroxine-binding pre-albumin (TBPA) or to albumin. Levothyroxine has a plasma half-life of about 6 to 7 days in euthyroid subjects; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Levothyroxine is mainly metabolised in the liver and kidney to tri-iodothyronine (liothyronine) and, about 40%, to inactive reverse tri-iodothyronine (reverse T_3) both of which undergo further deiodination to inactive metabolites. Further metabolites result from conjugation and decarboxylation; tetra-iodothyroacetic acid (tetrac) is one such metabolite. Further hydrolysis of the conjugates releases free hormone, which can be reabsorbed in the intestine to undergo enterohepatic recycling. Some conjugates reach the colon unchanged, then undergo hydrolysis, and are eliminated in the faeces as free hormone. Levothyroxine is mainly eliminated by the kidneys as free drug, deiodinated metabolites, or conjugates.

The distribution of thyroid hormones into breast milk and across the placenta is discussed under Breast Feeding and Pregnancy (p. 2341.1 and p. 2341.2).

Absorption. A study found that patients with multinodular goitre and impaired acid secretion (such as *Helicobacter pylori*-related gastritis or atrophic gastritis) required increased doses of levothyroxine, suggesting that normal gastric acid secretion is necessary for effective absorption of oral levothyroxine.[1]

1. Centanni M, *et al*. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *N Engl J Med* 2006; **354:** 1787–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Euthyrox; Synthroid; T4; ***Austral.***: Eutroxsig; Oroxine; ***Austria***: Euthyrox; Thyrex; ***Belg.***: Elthyrone; Euthyrox; Thyrax; ***Braz.***: Euthyrox; Levoid; Puran T4; Synthroid; Tetroid; Tiroidin; ***Canad.***: Eltroxin; Euthyrox; Synthroid; ***Chile***: Esaldox; Eutirox; Synthroid; ***China***: Euthyrox (优甲乐); Letrox (雷替斯); Nei Zhang Qing (内障清); You Xian (尤仙); Ze Ning (泽宁); ***Cz.***: Eltroxin; Euthyrox; Letrox; ***Denm.***: Eltroxin; Euthyrox; ***Fr.***: Levothyrox; ***Ger.***: Berlthyrox; Euthyrox; L-Thyrox†; Thevier; ***Gr.***: Euthyrox; Levothroid; Medithyrox; T4; Thyro-4; Thyrohormone; ***Hong Kong***: Eltroxin†; ***Hung.***: Euthyrox; Letrox; ***India***: Eltroxin; ***Indon.***: Euthyrox; Thyrax; ***Irl.***: Eltroxin; ***Israel***: Eltroxin; Euthyrox; ***Ital.***: Eutirox; Tiracrin; Tirosint; ***Jpn***: Thyradin-S; ***Malaysia***: Euthyrox; Oroxine; ***Mex.***: Abutiroi†; Cynocuatro; Eutirox; Karet; Leutiral; Tiroidine; ***Neth.***: Eltroxin; Euthyrox; Thyrax; Tirosint; ***Norw.***: Euthyrox; Levaxin; ***NZ***: Eltroxin; Eutroxsig; Synthroid; ***Philipp.***: Eltroxin; Eurolev; Euthyrox; Synthroid; Thyrax; Thyrohex†; ***Pol.***: Eferox†; Eltroxin; Euthyrox; Letrox; ***Port.***: Eutirox; Letequatro†; Letter; Thyrax; ***Rus.***: Bagothyrox (Баготирокс); Euthyrox (Эутирокс); ***S.Afr.***: Eltroxin; Euthyrox; Synthroid; ***Singapore***: Eltroxin; Euthyrox; Oroxine; Thyrosit; ***Spain***: Dexnon; Eutirox; Levothroid; ***Swed.***: Euthyrox; Levaxin; ***Switz.***: Eltroxine; Euthyrox; Tirosint; ***Thai.***: El-Thyro; Eltroxin; Euthyrox; Patroxin; Pondtroxin; Thyrosit; ***Turk.***: Euthyrox; Levotiron; Tefor; ***UK***: Eltroxin; Evotrox; ***Ukr.***: Euthirox (Эутирокс); Tivoral (Тиворал)†; ***USA***: Levothroid; Levoxyl; Novothyrox; Synthroid; Unithroid; ***Venez.***: Euthyrox; Thyrax.

Multi-ingredient Preparations. ***Arg.***: Eutroid; Levotrin; ***Austria***: Combithyrex; Jodthyrox; Novothyral; ***Belg.***: Novothyral; ***Chile***: Novothyral; ***Cz.***: Jodthyrox; Thyreotom; ***Fr.***: Euthyral; ***Ger.***: Jodthyrox; L-Thyrox Jod†; Novothyral; Prothyrid; Thyronajod; ***Gr.***: Dithyron; ***Ital.***: Dermocinetic; Somatoline; Tiroide Amsa; ***Mex.***: Cynoplus; Novotiral; ***Pol.***: Jodthyrox; Novothyral; ***Rus.***: Iodocomb (Йодокомб); Jodthyrox (Йодтирокс); Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); ***S.Afr.***: Diotroxin; ***Switz.***: Novothyral; ***Turk.***: Bitiron†; ***USA***: Thyrolar.

Homoeopathic Preparations. ***Austria***: Lymphomyosot; ***Cz.***: Lymphomyosot; ***Ger.***: Lymphomyosot N; Lymphomyosot; ***Hung.***: Lymphomyosot; ***S.Afr.***: Lymphomyosot; ***Ukr.***: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations

BP 2014: Levothyroxine Oral Solution; Levothyroxine Tablets;
USP 36: Levothyroxine Sodium Tablets; Liotrix Tablets.

Liothyronine Sodium *(BANM, rINNM)*

Liothyronin-Natrium; Liothyronin sodná sůl; Liothyronine sodique; Liothyroninum natricum; Liotironin Sodyum; Liotironina sódica; Liotironin-nátrium; Liotironino natrio druska; Liotyroniininatrium; Liotyronina sodowa; Liotyroninnatrium; Natrii Liothyroninum; Sodium Liothyronine; L-Triiodothyronine Sodium; Tri-iodotironin Sodyum; Натрий Лиотиронин; 3,5,3′-Tri-iodo-L-thyronine Sodium.

Sodium 4-*O*-(4-hydroxy-3-iodophenyl)-3,5-di-iodo-L-tyrosine.

$C_{15}H_{11}I_3NNaO_4$=673.0

CAS — 6893-02-3 (liothyronine); 55-06-1 (liothyronine sodium); 8065-29-0 (liotrix).

ATC — H03AA02.

ATC Vet — QH03AA02.

UNII — GCA9W7D2N.

NOTE. The abbreviation T_3 is often used for endogenous tri-iodothyronine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Liothyronine Sodium). A white or slightly coloured, hygroscopic powder. Practically insoluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Liothyronine Sodium). A light tan, odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Store in airtight containers.

Uses and Administration

Liothyronine is a thyroid hormone (see p. 2332.1). It is used in the treatment of hypothyroidism (p. 2333.3), and is believed to be more active than levothyroxine (p. 2339.2). The onset of action of liothyronine is rapid, developing within a few hours, and therefore it tends to be used in circumstances where this, and its short duration of action, are useful, particularly in hypothyroid (myxoedema) coma.

With regular dosing the peak therapeutic effect is usually achieved within 2 to 3 days; on withdrawal its effects may persist for 1 to 2 days.

The dose of liothyronine should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly. Although liothyronine is given as the sodium salt, doses can be expressed in terms of liothyronine sodium or liothyronine; the doses below are in terms of liothyronine sodium. Liothyronine sodium 10.3 micrograms is equivalent to about 10 micrograms of liothyronine. Liothyronine sodium 20 micrograms is generally considered to be equivalent in activity to about 100 micrograms of levothyroxine sodium.

In **hypothyroidism** the usual initial oral dose ranges from 5 to 25 micrograms daily, increased gradually to a maintenance dose of 60 to 75 micrograms daily in 2 or 3 divided doses, although up to 100 micrograms daily may be required in some patients. In elderly patients, in those with cardiovascular disorders, or in those with severe long-standing hypothyroidism, treatment should be introduced with doses at the low end of the range, with smaller increments, and longer intervals between increases, as necessary.

In **hypothyroid coma** liothyronine sodium may be given intravenously in a dose of 5 to 20 micrograms by slow intravenous injection, repeated as necessary, usually at intervals of 12 hours; the minimum interval between doses is 4 hours. An alternative regimen advocates an initial dose of 50 micrograms intravenously followed by further injections of 25 micrograms every 8 hours until improvement occurs; the dosage may then be reduced to 25 micrograms intravenously twice daily.

For the use of liothyronine in children, see below.

Liothyronine has also been given in the **diagnosis** of hyperthyroidism in adults. Failure to suppress the uptake of radio-iodine after several days of receiving liothyronine sodium suggests a diagnosis of hyperthyroidism.

For use as augmentation treatment with antidepressants, see Depression under Levothyroxine (p. 2340.1).

Liothyronine hydrochloride has also been used.

Administration in children. In the USA, liothyronine sodium may be given orally for the treatment of congenital hypothyroidism. An initial dose of 5 micrograms daily may be increased by 5 micrograms every 3 to 4 days, according to response, to the following usual maintenance doses:

- children below 1 year may require 20 micrograms daily
- children between 1 to 3 years may require 50 micrograms daily
- children over 3 years: as for adults, see p. 2342.3

In the UK, liothyronine sodium may be given orally to children for the treatment of hypothyroidism in a dose of 5 micrograms daily. However, the *BNFC* recommends that children aged 12 to 18 years can be given similar oral doses to those used in adults for hypothyroidism, namely 10 to 20 micrograms daily initially, increased gradually to 60 micrograms daily, in 2 or 3 divided doses. For the management of hypothyroid coma in children aged 12 to 18 years, intravenous doses are the same as for adults, see p. 2342.3.

Adverse Effects, Treatment, and Precautions

As for Levothyroxine Sodium, p. 2340.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies liothyronine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

As for Levothyroxine Sodium, p. 2341.2.

Pharmacokinetics

Liothyronine is readily and almost completely absorbed from the gastrointestinal tract. Once in the circulation, liothyronine binds mainly to thyroxine-binding globulin (TBG), although less strongly than levothyroxine; some is also bound to thyroxine-binding pre-albumin (TBPA). Liothyronine has a plasma half-life in euthyroidism of about 1 to 2 days; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Liothyronine is metabolised by deiodination to inactive di-iodothyronine and mono-iodothyronine. Iodine released by deiodination is largely reused within the thyroid cells. Further metabolites result from conjugation and decarboxylation; tiratricol (triac) is one such metabolite.

Thyroid hormones do not readily cross the placenta and minimal amounts are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tertroxin; ***Canad.***: Cytomel; ***China***: Nei Zhang Qing (内障清); ***Fr.***: Cynomel; ***Ger.***: Thybon; Thyrotardin†; ***Gr.***: Cynomel; T3; ***Irl.***: Tertroxin†; ***Ital.***: Liotir; Ti-Tre; ***Mex.***: Cynomel; Liotrex†; Triyotex; ***Neth.***: Cytomel; ***NZ***: Tertroxin†; ***Port.***: Neo-Tiroimade; ***S.Afr.***: Tertroxin; ***Turk.***: Tiromel; ***UK***: Triiodothyronine Injection; ***USA***: Cytomel; Triostat.

Multi-ingredient Preparations. ***Arg.***: Eutroid; Levotrin; Tresite F; ***Austria***: Combithyrex; Novothyral; ***Belg.***: Novothyral; ***Chile***: Novothyral; ***Cz.***: Thyreotom; ***Fr.***: Euthyral; ***Ger.***: Novothyral; Prothyrid; ***Gr.***: Dithyron; ***Ital.***: Tiroide Amsa; ***Mex.***: Cynoplus; Novotiral; Redotex; ***Pol.***: Novothyral; ***Rus.***: Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); ***S.Afr.***: Diotroxin; ***Switz.***: Novothyral; ***Turk.***: Bitiron†; ***USA***: Thyrolar.

Homoeopathic Preparations. ***Ger.***: NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations
BP 2014: Liothyronine Tablets;
USP 36: Liothyronine Sodium Tablets; Liotrix Tablets.

Perchlorates

Перхлораты.

Potassium Perchlorate

Chloran Potasu; Chloristan draselný; Kalii Perchloras; Kālija Perhlorāts; Kalijev Perklorat; Kalio perchloratas; Kaliumperchloraat; Kaliumperchlorat; Kaliumperkloraatti; Kaliumperklorat; Kálium-perklorát; Perclorato de Potássio; Perclorato di Potassio; Perclorato potásico; Potassium, perchlorate de; Potasyum Perklorat; Калиев Перхлорат; Перхлорат Калия.

$KClO_4$=138.5

CAS — 7778-74-7.
ATC — H03BC01.
ATC Vet — QH03BC01.
UNII — 42255P5X4D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Potassium Perchlorate). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; practically insoluble in alcohol.

USP 36: (Potassium Perchlorate). pH of a 0.1M solution in water is between 5.0 and 6.5.

Sodium Perchlorate

Chloristan Sodný; Natriumperchloraat; Natriumperchlorat; Natriumperkloraatti; Natriumperklorat; Perchlorate de Sodium; Perclorato de Sódio; Perclorato di Sodio; Perclorato sódico; Sodu nadchloran; Перхлорат Натрия.

$NaClO_4$=122.4

CAS — 7601-89-0 (anhydrous sodium perchlorate); 7791-07-3 (sodium perchlorate monohydrate).

Uses and Administration

Potassium and sodium perchlorate reduce the uptake and concentration of iodide, pertechnetate, and other anions by the thyroid, choroid plexus, gastric mucosa, and salivary glands, probably by competitive inhibition of active transport mechanisms.

They have been used **diagnostically** as adjuncts to pertechnetate (^{99m}Tc) to enhance visualisation of the brain, Meckel's diverticulum, or the placenta by reducing unwanted images of other organs. The usual oral dose of either potassium or sodium perchlorate was 200 to 400 mg given 30 to 60 minutes before the use of sodium pertechnetate (^{99m}Tc).

Potassium and sodium perchlorate have also been used with sodium iodide (^{131}I) in the perchlorate discharge test of thyroid function. The release of radio-iodine from the gland after an oral dose of perchlorate indicates a defect in the binding of iodide by the thyroid and thus a defect in thyroid hormone synthesis. The test has also been used to investigate the action of antithyroid drugs.

Potassium and sodium perchlorate have been used in the treatment of **hyperthyroidism** (p. 2332.2), but because of toxicity have been largely replaced by alternative treatments. However, perchlorates may be useful in patients with iodine-induced hyperthyroidism such as that associated with amiodarone therapy, by increasing responsiveness to conventional antithyroid drugs. A typical oral dose of potassium perchlorate in amiodarone-induced hyperthyroidism is 1 g daily.

References.

1. Bartalena L, *et al.* Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab* 1996; **81:** 2930–3.
2. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50:** 89–105.
3. Soldin OP, *et al.* Perchlorate clinical pharmacology and human health: a review. *Ther Drug Monit* 2001; **23:** 316–31.
4. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61:** 494–502.
5. Bogazzi F, *et al.* Potassium perchlorate only temporarily restores euthyroidism in patients with amiodarone-induced hypothyroidism who continue amiodarone therapy. *J Endocrinol Invest* 2008; **31:** 515–19.
6. Leung AM, *et al.* Perchlorate, iodine and the thyroid. *Best Pract Res Clin Endocrinol Metab* 2010; **24:** 133–41.
7. Bogazzi F, *et al.* Approach to the patient with amiodarone-induced thyrotoxicosis. *J Clin Endocrinol Metab* 2010; **95:** 2529–35.

Adverse Effects and Precautions

Potassium perchlorate seldom produces adverse effects when given as a single dose for diagnostic purposes. Prolonged use as an antithyroid drug has been associated with serious dose-related adverse effects. Aplastic anaemia (with some fatalities), agranulocytosis, eosinophilia, leucopenia, pancytopenia, and the nephrotic syndrome have been reported. Fever, rash, lymphadenopathy, gastrointestinal disturbances, arthralgia, and hypersensitivity reactions can occur. Hypothyroidism is common.

Effects on the blood. There have been reports of fatal aplastic anaemia[1,2] and of leucopenia and agranulocytosis[1] associated with the use of potassium perchlorate for the treatment of hyperthyroidism. A review[3] in 1998 noted that despite an increase in perchlorate use in recent years there did not appear to have been any further cases of aplastic anaemia since the 1960s.

1. Anonymous. Potassium perchlorate and aplastic anaemia. *BMJ* 1961; **i:** 1520–1.
2. Krevans JR, *et al.* Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. *JAMA* 1962; **181:** 182–4.
3. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50:** 89–105.

Handling. Potassium and sodium perchlorate have been used for the illicit preparation of explosives or fireworks; care is required with their supply. Great caution should be taken in handling perchlorates in solution or in the dry state as explosions may occur if brought into contact with organic or other readily oxidisable substances.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Irenat; ***Canad.***: Perchloracap†; ***Cz.***: Irenat; ***Ger.***: Irenat; ***Ital.***: Pertiroid; ***Pol.***: Irenat†.

Pharmacopoeial Preparations
USP 36: Potassium Perchlorate Capsules.

Prolonium Iodide *(rINN)*

Ioduro de prolonio; Prolonii Iodidum; Prolonium, Iodure de; Yoduro de prolonio; Пролония Йодид.

NN-(2-Hydroxytrimethylene)bis(trimethylammonium) di-iodide.

$C_9H_{24}I_2N_2O$=430.1

CAS — 123-47-7.
UNII — VKH95UNQ6N.

Pharmacopoeias. In *Chin.*

Profile

Prolonium iodide has been given by injection as a source of iodine (p. 2336.3) as part of the treatment of thyroid storm and for the pre-operative management of hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Luo Guan (洛冠).

Propylthiouracil *(BAN, rINN)*

Proiltiourasil; Propiltiouracil; Propiltiouracilas; Propiltiouracilo; Propylotiouracyl; Propylthiouracile; Propylthiouracilum; Propyltiouracil; Propyylitiourasiili; Пропилтиоурацил.

2,3-Dihydro-6-propyl-2-thioxopyrimidin-4(1*H*)-one; 2-Mercapto-6-propylpyrimidin-4-ol; 6-Propyl-2-thiouracil.

$C_7H_{10}N_2OS$=170.2

CAS — 51-52-5.
ATC — H03BA02.
ATC Vet — QH03BA02.
UNII — 721M9407IY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Propylthiouracil). White or almost white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 36: (Propylthiouracil). A white, powdery, crystalline substance. It is starch-like in appearance and to the touch. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol; soluble in ammonium hydroxide and in alkali hydroxides. Protect from light.

Uses and Administration

Propylthiouracil is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p. 2332.1); it also inhibits the peripheral deiodination of thyroxine to tri-iodothyronine. It is used in the management of hyperthyroidism (p. 2344.1), including the treatment of Graves' disease, preparation of hyperthyroid patients for thyroidectomy, use as an adjunct to radio-iodine therapy, and the treatment of thyroid storm.

Propylthiouracil is usually given orally. Initial doses range from 200 to 400 mg daily, although in severe cases initial doses of 600 to 1200 mg daily have been used. It has often been given in divided daily doses but once daily dosage is also possible. Improvement is usually seen in 1 to 3 weeks and control of symptoms is achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually

reduced to a maintenance dose, usually 50 to 150 mg daily. Treatment is usually continued for 1 to 2 years.

Doses should be reduced in renal impairment (below).

For the use of propylthiouracil in children and adolescents, see below.

Administration in children. In the UK, the *BNFC* recommends the following initial doses of oral propylthiouracil for children with hyperthyroidism (including Graves' disease), thyroid storm, and thyrotoxicosis:

- neonates: 2.5 to 5 mg/kg twice daily
- children aged 1 month to 1 year: 2.5 mg/kg three times daily
- children aged 1 to 5 years: 25 mg three times daily
- children aged 5 to 12 years: 50 mg three times daily
- children aged 12 to 18 years: 100 mg three times daily

These doses are given until the patient is euthyroid and then adjusted as needed; higher doses may be required, especially in thyroid storm.

In the USA, concerns about hepatotoxicity have prompted the FDA and others to advise against the routine use of propylthiouracil in children.[1,2]

1. FDA. Drug Safety Communication: new boxed warning on severe liver injury with propylthiouracil (issued 21st April, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm (accessed 29/06/10)
2. Rivkees SA, Mattison DR. Ending propylthiouracil-induced liver failure in children. *N Engl J Med* 2009; **360:** 1574–5.

Administration in renal impairment. The oral dosage of propylthiouracil may need to be reduced in patients with renal impairment. The *BNF* suggests the following adjustment according to estimated glomerular filtration rate (eGFR):

- eGFR 10 to 50 mL/min per 1.73 m^2: doses should be reduced by 25%
- eGFR less than 10 mL/min per 1.73 m^2: reduce doses by 50%

Alcoholic liver disease. Propylthiouracil has been said to reduce hyperoxic liver injury in hypermetabolic *animals* and despite reports of hepatotoxicity, including some fatalities, associated with propylthiouracil (see Effects on the Liver, under Carbimazole, p. 2335.3), it has been investigated in the treatment of patients with alcoholic liver disease. A systematic review,[1] however, concluded that there is no evidence to substantiate this use. Propylthiouracil was associated with adverse effects and it could not be shown to have any significant effects on mortality, liver related mortality, liver complications, and liver histology.

1. Fede G, *et al.* Propylthiouracil for alcoholic liver disease. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2011 (accessed 02/08/11).

Hyperthyroidism. Propylthiouracil has been one of the mainstays in the treatment of hyperthyroidism (p. 2332.2). However, in 2010, the FDA highlighted the risk of severe liver injury associated with propylthiouracil.[1] It recommended that when starting treatment for hyperthyroidism, propylthiouracil should only be used in patients who cannot tolerate thiamazole, or when radioiodine therapy or surgery is not appropriate. It also recommended that propylthiouracil should not be used in children, except when other treatments are not appropriate. However, the FDA did consider that propylthiouracil may be the treatment of choice in the first trimester of pregnancy.

1. FDA. Drug Safety Communication: new boxed warning on severe liver injury with propylthiouracil (issued 21st April, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm (accessed 29/06/10)

Psoriasis. Several reports have described benefit in patients with psoriasis (p. 1688.1) given propylthiouracil. An oral dose of 300 mg daily for 8 to 12 weeks has been used and is said not to produce clinical hypothyroidism.[1]

1. Elias AN. Anti-thyroid thioureylenes in the treatment of psoriasis. *Med Hypotheses* 2004; **62:** 431–7.

Adverse Effects, Treatment, and Precautions

As for Carbimazole, p. 2335.1, although cross-sensitivity to carbimazole does not necessarily occur.

Propylthiouracil has been associated with greater hepatotoxicity than other thiourea antithyroid drugs such as carbimazole or thiamazole (see Effects on the Liver, under Carbimazole, p. 2335.3). Patients or their carers should be told about this being a risk, especially in the first 6 months, how to recognise toxicity symptoms (e.g. anorexia, pruritus, jaundice, right upper quadrant pain), and that they should be advised to seek immediate medical attention. Doses may need to be reduced in hepatic impairment.

Propylthiouracil should be given with care, and in reduced doses, to patients with renal impairment.

Breast feeding. Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily; for references, see Breast Feeding, under Carbimazole, p. 2335.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propylthiouracil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pharmacokinetics

Propylthiouracil is rapidly absorbed from the gastrointestinal tract with a 50 to 75% bioavailability and with peak plasma concentrations occurring about 1 to 2 hours after oral doses. It is concentrated in the thyroid gland; since its duration of action is more closely related to the intrathyroidal drug concentration than its plasma half-life, prolonged antithyroid activity results from single daily doses. Propylthiouracil is about 80% bound to plasma proteins.

Propylthiouracil has an elimination half-life of about 1 to 3 hours. It undergoes rapid first-pass metabolism in the liver, and is mainly excreted in the urine as the glucuronic acid conjugate, with very little excreted as unchanged drug. The elimination half-life may be increased in renal or hepatic impairment.

Propylthiouracil crosses the placenta and is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Prothiucil; ***Braz.***: Propil; Propilracil; ***Canad.***: Propyl-Thyracil; ***China***: Ao Kang Xin (敖康欣); Bingsaiyou (丙赛优); Jiakang (甲康); ***Cz.***: Propycil; ***Fr.***: Proracyl; ***Ger.***: Propycil; ***Gr.***: Prothuril; ***Hong Kong***: CP-PTU; ***Hung.***: Propycil; ***Israel***: Propylthiocil; ***Pol.***: Thyrosan; ***Port.***: Propycil; ***Rus.***: Propycil (Пропицил); ***Singapore***: Propyl; ***Swed.***: Tiotil; ***Switz.***: Propycil; ***Thai.***: Peteyu; Propyl; PTU; Uracil; ***Turk.***: Propycil.

Pharmacopoeial Preparations

BP 2014: Propylthiouracil Tablets;
USP 36: Propylthiouracil Oral Suspension; Propylthiouracil Tablets.

Protirelin *(BAN, USAN, rINN)*

Abbott-38579; Lopremone; Protireliini; Protirelina; Protirelinas; Protiréline; Protirelinum; Synthetic TRH; Thyrotrophin-releasing Hormone; Thyrotropin-releasing Hormone; TRF; TRH; Протирелин.

L-Pyroglutamyl-L-histidyl-L-prolinamide; 1-[*N*-(5-Oxo-L-prolyl)-L-histidyl]-L-prolinamide; Glu-His-Pro-NH_2.

$C_{16}H_{22}N_6O_4$=362.4

CAS — 24305-27-9.

ATC — V04CJ02.

ATC Vet — QV04CJ02.

UNII — 5Y5F15120W.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*, which also includes the tartrate.

Ph. Eur. 8: (Protirelin). A synthetic tripeptide with the same sequence of amino acids as the natural hypothalamic neurohormone, that stimulates the release and synthesis of thyrotrophin. A white or yellowish-white hygroscopic powder. Very soluble in water; freely soluble in methyl alcohol. Store at a temperature of 2 degrees to 8 degrees. Protect from light and moisture.

Uses and Administration

Protirelin is a hypothalamic releasing hormone that stimulates the release of thyrotrophin (p. 2346.1) from the anterior lobe of the pituitary. It also has prolactin-releasing activity. It may be obtained by synthesis.

Protirelin may be used in the assessment of the hypothalamic-pituitary-thyroid axis in the diagnosis of mild hyperthyroidism (p. 2332.2) or hypothyroidism (p. 2333.3), and ophthalmic Graves' disease, although in many cases immunoassays for thyroid-stimulating hormone are now preferred. The response to protirelin may be used for differentiating between primary and secondary hypothyroidism but care is required in interpreting the results of the test and it should not be used alone in establishing the diagnosis. Protirelin is given with gonadorelin (p. 2280.3) in the assessment of anterior pituitary function.

Protirelin is given intravenously, usually in doses of 200 micrograms; doses up to 400 micrograms have been given. Protirelin is also given intranasally; 1 mg is sprayed into each nostril.

For the use of protirelin in children, see below.

Protirelin has been investigated in the treatment of neurological diseases, and in the prevention of neonatal respiratory distress syndrome, but results have been variable.

Protirelin tartrate has been given in the treatment of neurological disorders.

Administration in children. Protirelin is no longer available in the UK, but a single intravenous dose of 1 microgram/kg of protirelin was suggested for the assessment of thyroid function in children; the *BNFC* formerly recommended a single dose of 7 micrograms/kg (to a maximum of 200 micrograms), intravenously, for the diagnosis of hypopituitarism and hypothalamic disease.

Protirelin can also be given intranasally to children up to the age of 18 years; 1 mg is sprayed into one nostril only.

Lactation induction. Intranasal protirelin has been tried for stimulation of lactation (p. 2130.1) but good maternal education and support in techniques that promote physiological lactation are preferable to drug treatment.

Neonatal respiratory distress syndrome. The regulation of fetal lung development is under multihormonal control and thyroid hormones appear to stimulate pulmonary maturation. However, the thyroid hormones and thyrotrophin do not cross the placenta sufficiently for them to be given in premature labour where neonatal respiratory distress syndrome (p. 1608.3) may develop; therapy with protirelin has therefore been investigated.[1]

Protirelin has been given with corticosteroids to the mother and some beneficial effects have been noted.[1] One study using protirelin 400 micrograms every 8 hours for 4 doses indicated that antenatal protirelin reduced the incidence of chronic lung disease when given with corticosteroids but did not affect the incidence of respiratory distress syndrome.[2] However, 2 large multicentre studies had found that addition of protirelin to corticosteroid treatment had no beneficial effects on outcome compared with corticosteroids only;[3,4] in fact, in the earlier of these studies,[3] respiratory distress syndrome and the need for ventilation were greater in the offspring of mothers given protirelin. Subsequent follow-up appeared to confirm the disadvantages of protirelin in this cohort;[5] however the unexpected conclusions of this study aroused some controversy.[6-8] The second study noted no difference in outcome in the 2 groups of infants.[4] A meta-analysis concluded[9] that prenatal treatment with protirelin was not beneficial, and that it was associated with more adverse effects than the use of corticosteroids alone.

1. de Zegher F, *et al.* Prenatal treatment with thyrotrophin releasing hormone to prevent neonatal respiratory distress. *Arch Dis Child* 1992; **67:** 450–4.
2. Ballard RA, *et al.* Respiratory disease in very-low-birthweight infants after prenatal thyrotropin-releasing hormone and glucocorticoid. *Lancet* 1992; **339:** 510–5.
3. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 877–82.
4. Ballard RA, *et al.* Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. *N Engl J Med* 1998; **338:** 493–8.
5. Crowther CA, *et al.* Australian collaborative trial of antenatal thyrotropin-releasing hormone: adverse effects at 12-month follow-up. *Pediatrics* 1997; **99:** 311–17.
6. Ballard RA, *et al.* Thyrotropin-releasing hormone for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 1572.
7. Moya FR, Maturana A. Thyrotropin-releasing hormone for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 1572–3.
8. McCormick MC. The credibility of the ACTOBAT follow-up study. *Pediatrics* 1997; **99:** 476–8.
9. Crowther CA, *et al.* Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 16/09/05).

Neurological disorders. Reports of the use of protirelin in various neurological disorders.

1. Bonuccelli U, *et al.* Oral thyrotropin-releasing hormone treatment in inherited ataxias. *Clin Neuropharmacol* 1988; **11:** 520–8.
2. Filla A, *et al.* Sperimentazione cronica del TRH per via intramuscolare nelle degenerazioni spino-cerebellari: studio in doppio cieco cross-over su 30 soggetti. *Riv Neurol* 1989; **59:** 83–8.
3. Mellow AM, *et al.* A peptide enhancement strategy in Alzheimer's disease: pilot study with TRH-physostigmine infusions. *Biol Psychiatry* 1993; **34:** 271–3.
4. Chemaly R, *et al.* Myélinolyse extra-pontine: traitement par T.R.H. *Rev Neurol (Paris)* 1998; **154:** 163–5.
5. Tzeng AC, *et al.* A study of thyrotropin-releasing hormone for the treatment of spinal muscular atrophy: a preliminary report. *Am J Phys Med Rehabil* 2000; **79:** 435–40.
6. Kubek MJ, Garg BP. Thyrotropin-releasing hormone in the treatment of intractable epilepsy. *Pediatr Neurol* 2002; **26:** 9–17.

Adverse Effects

Protirelin given by rapid intravenous injection may cause nausea, a desire to micturate, flushing, dizziness, and a strange taste. These effects have been attributed to contraction of smooth muscles by the bolus injection. Similar adverse effects have been seen with intranasal application; bronchospasm can also occur. Transient increases in pulse rate, and changes in blood pressure have been reported with intravenous use. Convulsions have occurred in patients with predisposing conditions such as

epilepsy, brain lesions, or pituitary tumours. In patients with pituitary tumours given protirelin with gonadorelin, severe headaches with or without amaurosis have been reported, as has pituitary apoplexy requiring neurosurgical intervention.

Amaurosis. Of 4 patients with pituitary tumours who developed severe headache after protirelin injection, one also developed amaurosis, apparently associated with pituitary apoplexy.[1] Visual acuity improved after surgery.

1. Drury PL, *et al.* Transient amaurosis and headache after thyrotropin releasing hormone. *Lancet* 1982; **i:** 218–19.

Effects on the cardiovascular system. Increased blood pressure has been reported in women given protirelin antenatally,[1,2] and the view has been expressed that although the magnitude of the change is unlikely to be clinically significant in normotensive women, much greater rises have been seen in pre-eclamptic women[2,3] and may be severe enough to increase the risk of cerebral haemorrhage.[2]

1. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 877–82.
2. Peek MJ, *et al.* Hypertensive effect of antenatal thyrotropin-releasing hormone in pre-eclampsia. *Lancet* 1995; **345:** 793. Correction. *ibid.*; 1124.
3. Tan ASA, *et al.* Is maternal thyrotropin releasing hormone administration safe in the pregnant women with preeclampsia? *Am J Perinatol* 1997; **14:** 5–6.

Effects on the CNS. Adverse effects reported after injection of 400 micrograms of protirelin included unconsciousness, hypotension, and convulsions.[1] In another patient with a history of convulsions, a 500-microgram injection induced epileptic seizures.[2]

1. Dolva LØ, *et al.* Side effects of thyrotrophin releasing hormone. *BMJ* 1983; **287:** 532.
2. Maeda K, Tanimoto K. Epileptic seizures induced by thyrotropin releasing hormone. *Lancet* 1981; **i:** 1058–9.

Effects on the respiratory system. Bronchospasm occurred in an asthmatic boy given protirelin intravenously.[1]

For a report that protirelin provoked bronchospasm in patients with motor neurone disease, see under Precautions, below.

1. McFadden RG, *et al.* TRH and bronchospasm. *Lancet* 1981; **ii:** 758–9.

Effect on sexual function. On questioning, 7 of 16 women reported a sensation of mild vaginal sexual arousal occurring 1 to 3 minutes after intravenous injection of protirelin.[1] Four women also had urinary sensations, and 3 described an urge to urinate with no sexual component.

1. Blum M, Pulini M. Vaginal sensations after injection of thyrotropin releasing hormone. *Lancet* 1980; **ii:** 43.

Pituitary apoplexy. Pituitary apoplexy has been reported after combined testing of anterior pituitary function in patients with a pituitary tumour.[1,2] Of the drugs given, protirelin was thought most likely to have an aetiological role. Pituitary apoplexy has also been reported after the use of protirelin alone.[3]

See also Amaurosis, above.

1. Chapman AJ, *et al.* Pituitary apoplexy after combined test of anterior pituitary function. *BMJ* 1985; **291:** 26.
2. Dökmetaş HS, *et al.* Pituitary apoplexy probably due to TRH and GnRH stimulation tests in a patient with acromegaly. *J Endocrinol Invest* 1999; **22:** 698–700.
3. Szabolcs I, *et al.* Apoplexy of a pituitary macroadenoma as a severe complication of preoperative thyrotropin-releasing hormone (TRH) testing. *Exp Clin Endocrinol Diabetes* 1997; **105:** 234–6.

Precautions

Protirelin should be given with care to patients with ischaemic heart disease, obstructive airways disease, epilepsy, pituitary tumours, or severe hypopituitarism. Giving protirelin while the patient is lying down may reduce the incidence of hypotension.

Eclampsia. For the suggestion that the hypertensive effects of protirelin increase the risk of cerebral haemorrhage in pre-eclamptic women, see Effects on the Cardiovascular System under Adverse Effects, above.

Motor neurone disease. In some patients with amyotrophic lateral sclerosis, intravenous injection of protirelin resulted in acute bronchospasm.[1] Five of 25 patients had falls in FEV_1 of more than 20%; in 2, a 15% decrease in arterial-oxygen pressure occurred. Patients with sclerosis and weakened respiratory muscles should be warned of this potential adverse effect.

1. Braun SR, *et al.* Pulmonary effects of thyrotropin-releasing hormone in amyotrophic lateral sclerosis. *Lancet* 1984; **ii** 529–30.

Interactions

The thyroid-stimulating hormone (TSH) response to protirelin may be *decreased* by the thyroid hormones levothyroxine and liothyronine, barbiturates, bromocriptine, carbamazepine, corticosteroids (at pharmacological rather than physiological doses), cyproheptadine, dopamine, levodopa, lisuride, methysergide, morphine, phenothiazines (such as thioridazine), phentolamine, salicylates (such as aspirin), somatostatin, ranitidine, and X-ray contrast media.

An *increased* response may be seen with antithyroid drugs (if the patient is over-treated), gonadorelin and gonadorelin analogues, amiodarone, biperiden, clomifene, domperidone, haloperidol, iodides, metoclopramide, prostaglandins, spironolactone, and sulpiride. Since caffeine and theophylline also enhance the response, tea and coffee or other xanthine-containing beverages should be avoided for 12 to 14 hours before use of protirelin.

Oestrogens may also increase the response in men but not usually in women; when combined with a progestogen a slightly depressed response has been reported.

Variable responses have been seen with chlorpromazine and lithium.

Reviews.

1. Lamberg B-A, Gordin A. Abnormalities of thyrotrophin secretion and clinical implications of the thyrotrophin releasing hormone stimulation test. *Ann Clin Res* 1978; **10:** 171–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: TRH; Trhelea; ***Austria***: Antepan; ***Canad.***: Relefact TRH†; ***Fr.***: Stimu-TSH†; ***Ger.***: Antepan†; Thyroliberin†; TRH; ***Gr.***: Relefact†; TRH; ***Israel***: TRH; ***Jpn***: Hirtonin; ***Neth.***: Relefact TRH; ***Singapore***: TRH; ***Spain***: TRH Prem†; ***Turk.***: TRH.

Thiamazole *(BAN, rINN)*

Mercazolylum; Methimazole; Methylmercaptoimidazole; Metimazol; Thiamazol; Thiamazolum; Tiamatsoli; Tiamazol; Tiamazolas; Тиамазол.

1-Methylimidazole-2-thiol.

$C_4H_6N_2S$=114.2

CAS — 60-56-0.

ATC — H03BB02.

ATC Vet — QH03BB02.

UNII — 554Z48XN5E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Thiamazole). A white or pale brown, crystalline powder. Freely soluble in water and in dichloromethane; freely soluble or soluble in alcohol.

USP 36: (Methimazole). A white to pale buff crystalline powder having a faint characteristic odour. Soluble 1 in 5 of water, 1 in 5 of alcohol, 1 in 4.5 of chloroform, and 1 in 125 of ether. Its solutions are practically neutral to litmus. Protect from light.

Uses and Administration

Thiamazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p. 2332.1). It is used in the management of hyperthyroidism (p. 2332.2), including the treatment of Graves' disease, in the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Thiamazole is given orally usually in an initial dosage of 15 to 60 mg daily. It is usually given in three divided doses but single daily doses have also been used. When the patient is euthyroid the dose is gradually reduced to a maintenance dose, usually 5 to 15 mg daily. Maintenance treatment is usually continued for 1 to 2 years, although the optimum duration has not been established.

Thiamazole has also been used with supplemental levothyroxine as a *blocking-replacement regimen.*

Thiamazole doses of 80 to 240 mg daily, usually in 3 or 4 divided doses, have been given intravenously in the management of thyroid storm.

For the use of thiamazole in children, see below.

Administration in children. The initial oral dose of thiamazole for hyperthyroidism in children is 400 micrograms/kg daily, in 3 divided doses; the maintenance dose may be half of this.

Adverse Effects, Treatment, and Precautions

As for Carbimazole, p. 2335.1.

Breast feeding. The use of thiamazole during breast feeding is discussed under Carbimazole, p. 2335.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiamazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pharmacokinetics

The pharmacokinetics of thiamazole can be considered with those of carbimazole (p. 2336.2) since the latter is rapidly and completely metabolised to thiamazole in the body.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Danantizol; ***Belg.***: Strumazol; ***Braz.***: Tapazol; ***Canad.***: Tapazole; ***Chile***: Thyrozol; ***China***: Jia Qi Ya (佳累亚); Thyrozol (赛治); ***Cz.***: Thyrozol; ***Denm.***: Thycapzol; ***Fr.***: Thyrozol; ***Ger.***: Favistan; Methizol; Thyrozol; ***Gr.***: Unimazole; ***Hung.***: Metothyrin; ***India***: Methimez; ***Indon.***: Thyrozol; ***Israel***: Mercaptizol; ***Ital.***: Tapazole; ***Malaysia***: Timazol; ***Mex.***: Ganglioside; Tapazol; Tizorol; ***Neth.***: Strumazol; ***Philipp.***: Strumazol; Tapazole; Tapdin; Thyrazol; ***Pol.***: Metizol; Thyrozol; ***Port.***: Metibasol; ***Rus.***: Mercazolil (Мерказолил); Thyrozol (Тирозол); ***Singapore***: Thyrozol; ***Spain***: Tirodril; ***Swed.***: Thacapzol; ***Thai.***: Tapazole; Timazol; ***Turk.***: Thyromazol; ***Ukr.***: Metizol (Метизол); Thyrozol (Тирозол); ***USA***: Northyx; Tapazole; ***Venez.***: Tapazol.

Multi-ingredient Preparations. ***Ital.***: Bromazolo.

Pharmacopoeial Preparations

USP 36: Methimazole Tablets.

Thyroglobulin *(USAN, rINN)*

Thyreoglobulin; Thyreoglobuline; Thyroglobuline; Thyroglobulinum; Tireoglobulin; Tireoglobulina; Tiroglobulina; Tyreoglobuliini; Tyreoglobulina; Тироглобулин.

CAS — 9010-34-8.

UNII — NN2P9VPL7M.

Profile

Thyroglobulin is an extract obtained by the fractionation of porcine thyroid glands, that yields levothyroxine and liothyronine on hydrolysis. It has been used in the treatment of hypothyroidism, but such treatment with mixtures of thyroid hormones or preparations of animal extracts is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Tiroide Vister.

Thyroid

Dry Thyroid; Getrocknete Schilddrüse; Glandă Tiroidă; Glandula Thyreoidea; Glándula tiroides, extracto de; Kilpirauhanen; NSC-26492; Pajzsmirigy; Schildklier; Ščitnica; Sköldkörtel; Skydliaukė; Štítná Žláza; Štítna Žlijezda; Štítna Žľaza; Tarczyca; Theiroid; Thyreoidin; Thyroid Extract; Thyroid Gland; Thyroïde; Thyroidea; Thyroideum Siccum; Tiroide; Tiroide Secca; Tiroit Bezi; Vairogdziedzeris; Щитовидна Жлеза; Щитовидная Железа.

ATC — H03AA05.

ATC Vet — QH03AA05.

UNII — 0B4FDL9I6P.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Thyroid). It is the cleaned, dried, and powdered thyroid gland, previously deprived of connective tissue and fat, obtained from domesticated animals used for food by humans. On hydrolysis it yields not less than 90% and not more than 110% each of the labelled amounts of levothyroxine and liothyronine calculated on the dried basis. It is free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. It may contain a suitable diluent such as glucose, lactose, sodium chloride, starch, or sucrose. A yellowish to buff-coloured amorphous powder, having a slight, characteristic, meat-like odour. Store in airtight containers.

Profile

Thyroid has been used in the treatment of hypothyroidism, but treatment with mixtures of thyroid hormones or preparations of animal extracts is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Cinetic; ***Mex.***: Amet†; ***Thai.***: Thiroyd; Thyroid-S; TR; ***USA***: Nature Throid; Westhroid.

Multi-ingredient Preparations. ***Ger.***: FegaCoren; ***India***: Ebexid; ***Thai.***: Metharmon-F†.

Homoeopathic Preparations. ***Canad.***: Fucus L111†; Weight Control; ***Chile***: Fucus Especial; ***Fr.***: Fucus Complexe No 111; ***Ger.***: AntiFocal Nr 69-Sol L†; Glandulae-F-Gastreu R20; Hewethyreon N; NeyDil Nr 66†; NeyFoc Nr 69; NeyLing Nr 66; NeySol L 66†; ***Neth.***: Chavita 5.

Pharmacopoeial Preparations
USP 36: Thyroid Tablets.

Thyrotrophin *(BAN, rINN)*

Hormona tirotrófica; Thyroid-stimulating Hormone; Thyrotrophic Hormone; Thyrotrophine; Thyrotrophinum; Thyrotropin; Thyrotropinum; Tirotrofina; TSH; Tyrotropiini; Tyrotropin; Тиротропин.

CAS — 9002-71-5.
ATC — H01AB01; V04CJ01.
ATC Vet — QH01AB01; QV04CJ01.
UNII — 02KSI6Z9AK.

Description. Thyrotrophin is a glycoprotein from the anterior pituitary with a molecular weight in man of about 30 000.

Thyrotropin Alfa *(BAN, USAN, rINN)*

rhTSH; Thyrotropine Alfa; Thyrotropinum Alfa; Tirotropina alfa; Тиротропин Альфа.

CAS — 194100-83-9.
ATC — V04CJ01.
ATC Vet — QV04CJ01.
UNII — AVX3D5A4LM.

Units

0.037 units of human pituitary thyrotrophin for immunoassay and bioassay are contained in about 7.5 micrograms of thyrotrophin, with albumin 1 mg and lactose 5 mg, in one ampoule of the second International Reference Preparation (1983).

Uses and Administration

Thyrotrophin is a glycoprotein that is secreted by the anterior lobe of the pituitary and has an alpha subunit essentially the same as that of the gonadotrophins. Its main actions are to increase iodine uptake by the thyroid and the formation and secretion of the thyroid hormones. It may produce hyperplasia of thyroid tissue. Thyrotrophin secretion is controlled by a hypothalamic releasing hormone (Protirelin, p. 2344.2) and by circulating thyroid hormones; somatostatin (p. 1930.3) inhibits the release of thyrotrophin.

Thyrotrophin was used with radio-iodine in the diagnosis of hypothyroidism (p. 2333.3) and to differentiate between primary and secondary hypothyroidism, but direct radioimmunoassay of circulating endogenous thyroid-stimulating hormone has superseded this test.

Thyrotropin alfa is a recombinant form of thyrotrophin used as an adjunctive diagnostic tool for serum-thyroglobulin testing, with or without radio-iodine imaging, in the follow-up of patients with well-differentiated thyroid cancer. It is also used to increase radio-iodine uptake for ablation of thyroid remnant tissue in patients who have had a thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic disease. The usual thyrotropin alfa regimen consists of 2 doses of 900 micrograms, given 24 hours apart, by intramuscular injection into the buttock. Radio-iodine is given 24 hours after the second dose of thyrotropin alfa for radio-iodine imaging or remnant ablation. Diagnostic scanning is performed 48 to 72 hours after the radio-iodine has been given, but post-therapy scanning may be delayed by additional days to allow background activity to decline. Samples for serum-thyroglobulin testing should be taken 72 hours after the second thyrotropin alfa dose.

Goitre and thyroid nodules. Thyrotropin alfa has been investigated[1-4] as an adjunct to increase thyroid uptake of radio-iodine (^{131}I) in the treatment of selected patients with nodular goitre (p. 2332.1).

1. Nielsen VE, *et al.* The effects of recombinant human thyrotropin, in normal subjects and patients with goitre. *Clin Endocrinol (Oxf)* 2004; **61:** 655–63.
2. Duick DS, Baskin HJ. Significance of radioiodine uptake at 72 hours versus 24 hours after pretreatment with recombinant human thyrotropin for enhancement of radioiodine therapy in patients with symptomatic nontoxic or toxic multinodular goiter. *Endocr Pract* 2004; **10:** 253–60.
3. Nielsen VE, *et al.* Recombinant human thyrotropin markedly changes the ^{131}I kinetics during ^{131}I therapy of patients with nodular goiter: an evaluation by a randomized double-blinded trial. *J Clin Endocrinol Metab* 2005; **90:** 79–83.
4. Albino CC, *et al.* Recombinant human thyrotropin as adjuvant in the treatment of multinodular goiters with radioiodine. *J Clin Endocrinol Metab* 2005; **90:** 2775–80.

Malignant neoplasms of the thyroid. Patients with well-differentiated thyroid carcinoma (p. 716.1) undergo surgery, with or without iodine-131 treatment. They then receive thyroid hormone therapy to suppress thyrotrophin (TSH), because most differentiated thyroid cancers express TSH receptors and grow in response to thyrotrophin stimulation. Monitoring for tumour recurrence in subsequent years requires interruption of thyroid hormone treatment so that thyrotrophin levels rise, and stimulate the uptake of a subsequent dose of iodine-131 by any residual or recurrent tumour. However, this results in hypothyroidism, with associated symptoms that may be severe in some patients.[1]

Studies[2,3] have examined the use of thyrotropin alfa as an alternative prelude to radio-iodine scanning, and found that it did stimulate radio-iodine uptake, although the sensitivity of scanning may depend on the technique used; thyrotropin alfa might be considered a suitable alternative to thyroid hormone withdrawal. In patients with CNS or spinal metastases, or who have substantial disease in the thyroid bed, thyrotropin alfa may cause tumour expansion with acute complications; it has been recommended[1] that prophylactic corticosteroid therapy should be considered in these cases.

Thyroid hormone withdrawal is also used in the treatment of differentiated thyroid cancer, to increase uptake of radio-iodine for thyroid remnant ablation and treatment of metastatic disease. Thyrotropin alfa is also used as an alternative adjunct.[4]

1. Basaria M, *et al.* The use of recombinant thyrotropin in the follow-up of patients with differentiated thyroid cancer. *Am J Med* 2002; **112:** 721–5.
2. Ladenson PW, *et al.* Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997; **337:** 888–96.
3. Haugen BR, *et al.* A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab* 1999; **84:** 3877–85.
4. Robbins RJ, Robbins AK. Recombinant human thyrotropin and thyroid cancer management. *J Clin Endocrinol Metab* 2003; **88:** 1993–8.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with thyrotropin alfa are nausea and headache. Vomiting, diarrhoea, dizziness, paraesthesia, fatigue, and insomnia are also common. Hypersensitivity reactions have been reported rarely; manifestations include urticaria, rash, pruritus, flushing, and respiratory signs and symptoms. A transient flu-like illness has also been reported, which may include fever, chills, myalgia, and arthralgia. Other adverse effects include nasopharyngitis, tremors, palpitations, hyperhidrosis, and discomfort at the injection site.

Very rare cases of hyperthyroidism or atrial fibrillation have been seen when thyrotropin alfa has been given to patients with residual thyroid tissue. Fatalities due to drug-induced hyperthyroidism have been reported within 24 hours of use of thyrotropin alfa; these occurred in patients with multiple serious comorbidities, and caution is recommended in patients with cardiac disease, extensive metastases, or serious underlying illness. Enlargement of residual thyroid tissue or metastases can occur after treatment, which may cause pain and acute symptoms dependent on the location of the tissue; for example, hemiplegia, hemiparesis, or loss of vision have occurred in patients with CNS metastases. Laryngeal oedema with respiratory distress, necessitating tracheotomy, has been reported in patients with paratracheal metastases. Pretreatment with corticosteroids is recommended for patients in whom tumour enlargement might compromise vital anatomical structures.

The elimination of thyrotropin alfa is reduced in dialysis-dependent end-stage renal disease, resulting in prolonged elevation of thyroid-stimulating hormone concentrations after treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thyrotropin as not porphyrinogenic when used as a diagnostic agent; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Thyrogen; ***Belg.***: Thyrogen; ***Canad.***: Thyrogen; ***Chile***: Thyrogen; ***Cz.***: Thyrogen; ***Denm.***: Thyrogen; ***Fin.***: Thyrogen; ***Fr.***: Thyrogen; ***Ger.***: Thyrogen; ***Gr.***: Thyrogen; ***Hong Kong***: Thyrogen; ***Hung.***: Thyrogen; ***Irl.***: Thyrogen; ***Israel***: Thyrogen; ***Ital.***: Thyrogen; ***Jpn***: Thyrogen; ***Malaysia***: Thyrogen; ***Neth.***: Thyrogen; ***Norw.***: Thyrogen; ***Pol.***: Thyrogen; ***Port.***: Thyrogen; ***Singapore***: Thyrogen; ***Spain***: Thyrogen; ***Swed.***: Thyrogen; ***Switz.***: Thyrogen; ***Thai.***: Thyrogen; ***Turk.***: Thyrogen; ***UK***: Thyrogen; ***Ukr.***: Tirogen (Тироген); ***USA***: Thyrogen.

Tiratricol *(rINN)*

Tiratricolum; Tiratrikol; Tiratrikoli; Triac; Triiodothyroacetic Acid; Тиратрикол.

[4-(4-Hydroxy-3-iodophenoxy)-3,5-di-iodophenyl]acetic acid.

$C_{14}H_9I_3O_4$=621.9
CAS — 51-24-1.
ATC — D11AX08; H03AA04.
ATC Vet — QD11AX08; QH03AA04.
UNII — 29OQ9EU4R1.

NOTE. Tri-ac has also been used as a name for proprietary preparations containing other drugs.

Profile

Tiratricol, a metabolite of tri-iodothyronine, is given orally to suppress the secretion of thyroid-stimulating hormone (TSH). It is given with thyroxine in situations where thyroxine monotherapy is insufficient to suppress TSH secretion. It is reported to be less active than the thyroid hormones.

Obesity. Abnormal thyroid function tests, severe diarrhoea, fatigue, lethargy, and profound weight loss have occurred in patients taking dietary supplements containing tiratricol.[1-3] The FDA has warned that dietary supplements containing tiratricol may cause heart attacks and strokes.[4]

1. Anonymous. Triax: a harmful product sold on the internet. *WHO Drug Inf* 2000; **14:** 30.
2. Bauer BA, *et al.* Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. *Mayo Clin Proc* 2002; **77:** 587–90.
3. Ma RC, *et al.* Thyroid dysfunction due to over-the-counter usage of tiratricol. *Intern Med J* 2008; **38:** 611–12.
4. FDA. Safety alert for human medical products: tiratricol (triiodothyroacetic acid) (issued 22nd November 2000). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHuman-MedicalProducts/ucm173259.htm (accessed 18/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nulobes; Triacana; ***Fr.***: Teatrois.

Urological Drugs

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Urinary-tract infections, p. 2351

This chapter includes a number of drugs used in the management of certain urological or urogenital conditions such as urinary incontinence, benign prostatic hyperplasia, and erectile dysfunction.

Other drugs used in these conditions may be found elsewhere in *Martindale*: they include the tricyclic antidepressants such as imipramine (p. 426.2) and the serotonin and noradrenaline reuptake inhibitor duloxetine (p. 415.1), which are in the chapter on Antidepressants (p. 397.1); some alpha blockers such as doxazosin (p. 1369.1), phentolamine (p. 1468.3), and prazosin (p. 1473.3), as well as, more generally, diuretics and drugs such as ACE inhibitors which may be used to alter urological function, all of which are to be found in the chapter on Cardiovascular Drugs (p. 1242.1); and the various electrolytes (see p. 1775.1).

For the treatment of urogenital infections, see under Choice of Antibacterial, p. 172.2. For the management of urological and reproductive tract malignancies, see under Choice of Antineoplastic, p. 691.2.

Benign prostatic hyperplasia

Benign enlargement of the prostate gland is common in men with increasing age: at least 50% of men aged over 60 years have histological evidence of hyperplasia. Men with an enlarged prostate may have symptoms of lower urinary tract obstruction (often referred to as LUTS), such as acute or chronic urinary retention, or irritative symptoms such as frequency, urgency, nocturia, or occasionally urge incontinence, resulting from secondary bladder instability. Therapy is influenced by the severity of symptoms and their effect on the patient's quality of life. The three main options for management are watchful waiting (monitoring without active intervention), drug treatment, and surgery.[1-7]

Watchful waiting is suitable for men with mild to moderate symptoms that are not bothersome,[2,3] and for some men with moderate to severe LUTS who have not yet developed complications of benign prostatic hyperplasia such as renal impairment, urinary retention, or recurrent infection.[2] The patient is monitored and advised on lifestyle measures that may improve symptoms; these include decreasing fluid intake at specific times such as bedtime or when going out, reducing caffeine and alcohol intake in general, and bladder re-training techniques.

Drug treatment is essentially based on the use of *alpha$_1$-adrenoceptor blockers* and *5α-reductase inhibitors*, and is begun once symptoms become bothersome.

- Alpha$_1$-adrenoceptor blockers (such as alfuzosin, doxazosin, prazosin, indoramin, tamsulosin, or terazosin) apparently act on the smooth muscle tone within the prostate and the bladder neck, and can produce symptomatic relief within weeks.[1,3] They are considered to have similar efficacy[1-3,8] and choice between them may be influenced by adverse effect profile and ease of use.[8]
- The 5α-reductase inhibitors (finasteride and dutasteride) reduce prostate volume, although this takes a number of months.[1,3,8] They reduce the risk of progression to urinary retention and prostatic surgery, and are given particularly to men with urinary symptoms and large prostates.[1-3,8] However, they are less effective for symptomatic improvement than alpha$_1$-adrenoceptor blockers.[2]
- Combined treatment using an alpha$_1$-adrenoceptor blocker and a 5α-reductase inhibitor may be more effective than monotherapy,[1,3] and is considered to be suitable for patients with LUTS associated with demonstrable prostatic enlargement who are at significant risk of progression.[2,3,8]

More recently there has been interest in the use of *phosphodiesterase type-5 inhibitors* such as tadalafil, which cause smooth-muscle relaxation in the bladder neck, urethra, and prostate.[9]

Other drug therapies exist but are largely unproven or unsuitable for general use. Gonadorelin analogues such as leuprorelin or nafarelin can produce a reduction in prostate size, but adverse effects make these drugs unsuitable for indefinite therapy. More recently, gonadorelin antagonists such as cetrorelix have been tried. The antifungal mepartricin has been reported to produce symptomatic improvement, possibly by binding to oestrogen in the intestinal lumen and lowering plasma-oestrogen concentrations. Injection of botulinum A toxin into the prostate gland, for the treatment of chronic urinary retention, has shown some promise in small studies. A number of plant extracts such as saw palmetto (*Serenoa repens*) and *Pygeum africanum* are also in use. Systematic reviews of the latter[10] and of the phytosterol sitosterol[11] (a constituent of both plants) in benign prostatic hyperplasia have noted some benefits; however, most studies were short-term and used preparations that were not standardised, and a subsequent review of saw palmetto[12] found little evidence of efficacy. Although there have been concerns about the use of antimuscarinics in patients with symptomatic disease, some patients have symptoms suggestive of overactive bladder, and antimuscarinics such as oxybutynin may be useful to decrease hypercontractility of the detrusor muscle and reduce overactive bladder symptoms, either alone or as adjuncts (see also Urinary Incontinence and Retention, p. 2349.2).[2,3,6]

Surgery is recommended for men with more severe symptoms that do not respond to drug therapy, or who have complications such as acute urinary retention, gross haematuria, renal failure, bladder calculi, or recurrent urinary-tract infection. The mainstay of treatment is transurethral resection of the prostate (TURP),[1,2] which is more effective than drug treatment but is associated with a risk of complications such as impotence (although this may not be attributable to the surgery in all cases) and bladder neck contracture.[2] Transurethral incision of the prostate may be used as an alternative for smaller prostates[1,2] and open prostatectomy may be indicated for removal of very large glands. Various surgical alternatives to TURP use heat to destroy prostatic tissue surrounding the urethra.[1,2,13] These minimally invasive therapies include transurethral microwave thermotherapy, water-induced thermotherapy, radiofrequency transurethral needle ablation, interstitial laser treatment, and transrectal high-intensity focused ultrasound.

1. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; **361:** 1359–67. Correction. *ibid.*; **362:** 496.
2. McVary KT, *et al*. American Urological Association. American Urological Association guideline: management of benign prostatic hyperplasia (BPH) (revised 2010). Available at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=bph (accessed 18/04/11)
3. Oelke M, *et al*. European Association of Urology. Guidelines on conservative treatment of non-neurogenic male LUTS (2010). Available at: http://www.uroweb.org/gls/pdf/BPH%202010.pdf (accessed 18/04/11)
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7. Gur S, *et al*. Guide to drug therapy for lower urinary tract symptoms in patients with benign prostatic obstruction: implications for sexual dysfunction. *Drugs* 2008; **68:** 209–29.
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10. Ishani A, *et al*. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; **109:** 654–64.
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12. Tacklind J, *et al*. Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 17/03/10).
13. Larson TR. Rationale and assessment of minimally invasive approaches to benign prostatic hyperplasia therapy. *Urology* 2002; **59** (suppl 2A): 12–16.

Cystitis

Signs and symptoms of cystitis (inflammation of the bladder) include suprapubic pain, dysuria, frequency and urgency of urination, nocturia, and haematuria. It may have various causes but is usually associated with urinary-tract infections (see p. 213.1). Non-infectious cystitis can occur as an adverse effect of some drugs such as NSAIDs (notably tiaprofenic acid).[1] Pelvic radiotherapy and some drugs used for cancer chemotherapy can also cause haemorrhagic cystitis (below). Other inflammatory non-infectious forms of cystitis include interstitial cystitis (see p. 2348.1) and rare conditions such as eosinophilic cystitis.[2]

1. Bramble FJ, Morley R. Drug-induced cystitis: the need for vigilance. *Br J Urol* 1997; **79:** 3–7.
2. Teegavarapu PS, *et al*. Eosinophilic cystitis and its management. *Int J Clin Pract* 2005; **59:** 356–60.

Haemorrhagic cystitis. Haemorrhagic cystitis results from damage to the bladder wall that causes diffuse bleeding from the endothelial lining; damage may range from minor telangiectatic bleeding to diffuse necrotic ulceration.[1] Signs and symptoms include haematuria, dysuria, urgency, and increased frequency of urination.

Haemorrhagic cystitis may be associated with various diseases, drug and radiation therapies, infections, and toxins. Associated diseases include carcinoma of the bladder, rheumatoid arthritis, and amyloidosis.[1] Drugs that are often associated with haemorrhagic cystitis are antineoplastics, particularly the oxazaphosphorine alkylating agents cyclophosphamide and ifosfamide[1,2] (see also Effects on the Bladder under Cyclophosphamide, p. 772.3). Other drugs with which haemorrhagic cystitis has been reported include penicillins and NSAIDs.[2] Pelvic irradiation[3] for genito-urinary malignancies may cause acute symptoms that can occur up to 6 months after irradiation; some patients will develop chronic symptoms and in a small number the symptoms may become debilitating and refractory to conservative management. Viruses such as adenovirus, BK virus, and CMV can cause haemorrhagic cystitis, particularly in immunocompromised patients.[1,4] In some cases, bacterial or fungal infection, or parasitical infestation may be responsible.[2] Other causative agents have included toxins such as dyes, insecticides, and turpentine.[1]

Initial supportive **treatment** of haemorrhagic cystitis involves increasing fluid intake to hydrate the bladder and dilute the concentration of any toxic agent in the urine. Symptomatic relief with antispasmodics and analgesics may be indicated.[1] If haematuria does not improve or resolve, intravesical treatment may be considered. This usually begins with a continuous bladder irrigation of *sodium chloride 0.9%*, to remove existing clots.[1-3] For bleeding that persists or worsens, other treatments have been described, mostly in case reports or small series.[1-5] *Alum* irrigation has been used for its astringent properties, but its effect is rarely permanent. Adverse effects include suprapubic pain, fever, bladder spasm, and urinary retention or frequency; alum precipitation can block the catheter and aluminium toxicity may occur rarely. *Silver nitrate* instillation has a cauterising effect by coagulating proteins on the bladder mucosa, *phenol* causes a chemical cauterisation, and *formaldehyde* hydrolyses protein on the bladder wall, coagulating tissue and controlling bleeding in the mucosa and submucosa. However, the duration of effect of these cauterising agents is often short, they are contra-indicated in patients with ureteric reflux, and treatments are painful, necessitating anaesthesia. *Prostaglandins*, such as alprostadil, carboprost, and dinoprostone, have been instilled into the bladder for a cytoprotective effect, to stimulate platelet aggregation, and to cause local vasoconstriction.

There are also reports of successful systemic treatment in some cases that were refractory to intravesical therapy. *Conjugated oestrogens* have been given intravenously and orally.[1] The *antifibrinolytic drugs*, aminocaproic acid[1,2] and tranexamic acid[2] have been given intravenously and orally; aminocaproic acid has also been given intravesically. Oral

pentosan polysulfate sodium has been used in radiation-induced haemorrhagic cystitis.[3] *Hyperbaric oxygen* therapy increases tissue oxygenation and has been used particularly in radiation-induced haemorrhagic cystitis to treat radionecrosis and tissue ischaemia.[3,5] Cryosurgery using *liquid nitrogen* has been used rarely.[1] Systemic *antivirals* such as cidofovir have been used to treat virus-associated haemorrhagic cystitis after haematopoietic stem cell transplant.[4] *Clotting factors* such as eptacog alfa have also been used in haematopoietic stem cell transplant patients, although adverse effects limit use to refractory, life-threatening, acute haemorrhage.[4]

In cases that do not respond to drug treatment, *surgical* options include urinary diversion, internal iliac artery embolisation, unilateral hypogastric artery ligation, and if all else fails, cystectomy.[1-3] Hydrodistension, the application of pressure to the bladder wall by an inflated balloon, has also been used.[5] However, anaesthesia is required, its effect is short-lived, and it is associated with the risk of bladder perforation.[1,2,5]

Prophylaxis to reduce the risk of haemorrhagic cystitis associated with high-dose cyclophosphamide and ifosfamide includes intravenous hydration with diuresis, frequent voiding of the bladder or bladder catheterisation with sodium chloride 0.9% irrigation, and the use of *mesna* as a uroprotectant.[1,2] Improvements in radiotherapy techniques are reducing the risk of radiation-induced haemorrhagic cystitis.[3]

1. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; **17:** 696–706.
2. Traxer O, *et al*. Cystite hémorragique: étiologie et traitement. *Prog Urol* 2001; **11:** 591–601.
3. Crew JP, *et al*. Radiation-induced haemorrhagic cystitis. *Eur Urol* 2001; **40:** 111–23.
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5. Choong SKS, *et al*. The management of intractable haematuria. *BJU Int* 2000; **86:** 951–9.

Interstitial cystitis. Interstitial cystitis is a chronic inflammatory condition of the bladder that mainly affects middle-aged women.[1-5] There are also rare reports of the condition occurring in children, usually girls.[6] Symptoms include perineal and pelvic pain (that is often relieved by voiding), urinary frequency, urgency, and nocturia. Interstitial cystitis is a disease of unknown aetiology and suggested possible causes have included abnormal bladder epithelial permeability, neurogenic abnormalities, autoimmune disorders, and allergic reactions with increased mast-cell activation.[1,2] It is considered to be incurable; attempts at **management** have included local and systemic drug therapy and surgery. Non-drug therapies that may be tried include exercise, stress management, bladder training, and the avoidance of foods that patients have found to exacerbate symptoms, such as caffeine, artificial sweeteners, and acidic juices.[1,2,6] However, scientific data to support these strategies are lacking.[1,6]

Oral therapy with pentosan polysulfate sodium has been given to improve the protective glycosaminoglycan layer of the bladder, and has reduced symptoms in some patients. Benefits may take more than 3 months to become apparent.[1,2] Other oral treatments that have been used for symptom relief include amitriptyline and hydroxyzine;[1-4] cimetidine[3] and gabapentin[2] have also been tried. There has been some interest in quercetin.[4]

Intravesical instillation of dimethyl sulfoxide has been shown to improve symptoms of interstitial cystitis,[1-3] although the evidence was queried by a systematic review.[5] Heparin has also been given intravesically,[1,2] as have BCG vaccine, oxybutynin, and the capsaicin analogue resiniferatoxin.[5]

Cystoscopy under anaesthesia with bladder distension, a diagnostic procedure, has been reported to relieve symptoms by destruction of the mucosal nerve plexus and tension receptors in the bladder wall. Although some[1,3,6] support its use for diagnosis and treatment, others[2] suggest that it has limited efficacy. Surgery is reserved for intractable symptoms that have failed to respond to less drastic treatments.[1]

1. Selo-Ojeme DO, Onwude JL. Interstitial cystitis. *J Obstet Gynaecol* 2004; **24:** 216–25.
2. Kahn BS, *et al*. Management of patients with interstitial cystitis or chronic pelvic pain of bladder origin: a consensus report. *Curr Med Res Opin* 2005; **21:** 509–16.
3. Tincello DG, Walker ACH. Interstitial cystitis in the UK: results of a questionnaire survey of members of the Interstitial Cystitis Support Group. *Eur J Obstet Gynecol Reprod Biol* 2005; **118:** 91–5.
4. Theoharides TC. Treatment approaches for painful bladder syndrome/interstitial cystitis. *Drugs* 2007; **67:** 215–35.
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Diabetes insipidus

Diabetes insipidus deprives the kidney of its capacity to produce a concentrated urine, resulting in the passage of large volumes of dilute urine (polyuria) and excessive thirst (polydipsia). Patients generally have moderately raised serum-sodium concentrations but are prone to more severe hypernatraemia (p. 1778.1) when fluid is restricted.

The syndrome of diabetes insipidus is caused either:

- by a deficiency in secretion of antidiuretic hormone (ADH; vasopressin) from the posterior pituitary gland (cranial, pituitary, or neurogenic diabetes insipidus)
- or by a failure in activity of secreted ADH on renal tubules (nephrogenic diabetes insipidus)

Cranial diabetes insipidus is most commonly idiopathic (although it is now increasingly suspected to have an autoimmune basis) or occurs after surgery or trauma when it may be temporary. More rarely, it results from neoplasms, infections, or infiltrations of the CNS, or forms part of the familial DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Nephrogenic diabetes insipidus may occur as a familial X-linked recessive disorder in male infants, but is more often secondary to hypercalcaemia, hypokalaemia, or drug therapy (including lithium salts, foscarnet, and demeclocycline).

The mainstay of **diagnosis** of diabetes insipidus is measurement of serum and urine osmolality, urine specific gravity, and serum-sodium concentration. If these are found to be normal a formal water deprivation test may be performed, with careful monitoring of urine volume, osmolality, and body-weight. The test should be stopped if more than 3 litres of urine is passed or 3% of total body-weight is lost, although this is in any case virtually diagnostic of diabetes insipidus. A dose of ADH in the form of desmopressin is then given to test renal responsiveness—prompt urine concentration is indicative of cranial diabetes insipidus, while failure indicates the nephrogenic form.

Cranial diabetes insipidus is usually **treated** by replacement therapy with ADH in the form of intranasal desmopressin, although tablets are now also available and may be preferred in children; desmopressin has greater antidiuretic efficacy and considerably less vasoconstrictor activity than lypressin or vasopressin itself.

Nephrogenic diabetes insipidus is by definition unresponsive to ADH therapy and water replacement tends to be the mainstay of treatment. Thiazide diuretics, notably hydrochlorothiazide, are given with some restriction of sodium intake to patients with nephrogenic diabetes insipidus; the resultant mild sodium depletion enhances proximal renal tubular sodium and water resorption. Giving them with amiloride has been reported to have an additive effect while also preventing hypokalaemia.

Other drugs have also been tried in the management of diabetes insipidus. Chlorpropamide stimulates ADH secretion and augments the activity of residual ADH in patients with partial cranial disease and as in nephrogenic disease the thiazides may be useful. Clofibrate and carbamazepine have also been found to promote ADH secretion in these patients. Indometacin and other prostaglandin synthetase inhibitors decrease urine volume in all types of the condition. Combination of indometacin with a thiazide and desmopressin has been investigated.

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Erectile dysfunction

Erectile dysfunction (impotence) signifies inability of a male to achieve satisfactory erection of the penis during sexual intercourse. Estimates of prevalence depend to some extent upon the definitions that are used, but the problem is thought to be not uncommon, particularly in older men. The ***causes*** of erectile dysfunction may be psychological, organic, or a combination of both. Psychological factors include stress, mental depression, and anxieties about sexual performance. Organic causes include androgen deficiency as a result of hypogonadism, neurological dysfunction (including central or peripheral lesions due to malignancy or trauma), peripheral vascular disorders, and penile abnormalities such as Peyronie's disease or microphallus. Sometimes organic dysfunction may be secondary to another disease, such as diabetes mellitus in which neurological and vascular damage lead to erectile dysfunction in over one-third of all patients. In addition, erectile dysfunction may be drug-induced.

Approaches to the ***management*** of erectile dysfunction depend to some extent upon the causative factors.

In those few patients in whom erectile dysfunction is secondary to *androgen deficiency* in hypogonadism, androgen replacement, preferably by the intramuscular injection or transdermal application of a suitable testosterone ester, may be of value. Androgen replacement therapy is inappropriate in patients with normal testosterone concentrations and may carry significant health risks. In patients with hypogonadism secondary to hyperprolactinaemia addition of bromocriptine is often effective in improving sexual function.

Psychotherapy or behavioural therapy alone may be adequate in patients in whom no organic cause is detected, but even when organic factors play a role *psychosocial factors* are also important and should be addressed by appropriate counselling.

When causes of erectile dysfunction are partly or primarily *organic*, the main options are:

- use of a vacuum pump to induce erection by negative pressure, followed by constriction of the base of the penis with a band to maintain tumescence
- oral or sublingual drugs
- injection of vasoactive substances into the corpora cavernosa
- transurethral dosage of vasoactive substances
- implantation of a penile prosthesis is generally reserved for patients in whom other therapy has failed or is refused, but it may also be a suitable first-line choice for some patients

Vascular surgery may have a limited application, in vasogenic dysfunction, but its role is not clearly defined and there are some doubts about its long-term effectiveness.

Oral therapy for erectile dysfunction has had a chequered history, and most of the drugs tried have proved little more effective than placebo. However, with the advent of sildenafil and other inhibitors of phosphodiesterase type-5, oral therapy is now established in erectile dysfunction. Data from randomised controlled studies have shown efficacy of sildenafil in erectile dysfunction compared with placebo, including in men with diabetes mellitus and spinal-cord injury; it has no effect on the penis in the absence of sexual stimulation. It is generally more effective in erectile dysfunction of psychogenic origin and in mild to moderate cases of organic origin. There has, however, been concern about cardiac-related deaths associated with the use of sildenafil, although causality has not been firmly established. Visual disturbances and sudden hearing loss have also been reported. Other phosphodiesterase type-5 inhibitors also used are avanafil, tadalafil, and vardenafil.

Yohimbine, an α_2-adrenoceptor antagonist, may have some benefit, although more in erectile dysfunction of psychological than organic origin. Oral phentolamine is available for the treatment of erectile dysfunction in some countries and has been reported to be of benefit. Trazodone, a serotonin antagonist and reuptake inhibitor used in the treatment of depression, may rarely cause priapism and has therefore been investigated for the treatment of erectile dysfunction. Beneficial effects have been reported either alone or with yohimbine. Oral L-arginine, the precursor of nitric oxide, has also shown some promise in studies.

Sublingual apomorphine, a dopaminergic (D_1 or D_2) agonist, has also shown efficacy, but nausea may be a problem.

Intracavernosal injection therapy is the most effective pharmacological method of treating erectile dysfunction and, until the advent of effective oral therapy, was the most widely used. Unfortunately, one major disadvantage of this method is the need for repeated self-injection of the penis, and studies suggest that the long-term drop-out rate is high. However, it is still a valuable option in men unresponsive to, or unable to take, oral therapy. The drugs most commonly used are alprostadil, papaverine, and phentolamine. Alprostadil is preferred because it is more effective than papaverine (with or without phentolamine), and is associated with a lower incidence of priapism and fibrosis. However, the erection is frequently painful. Papaverine, a non-specific phosphodiesterase inhibitor, has been used alone or with phentolamine, an α-adrenoceptor antagonist. Erectile dysfunction of neurogenic or psychogenic origin generally responds better to papaverine than dysfunction of vascular origin. However, long-term use of intracavernosal papaverine may result in fibrosis, and it has been suggested that it should not be used more than three times a week or on two successive days. Priapism may also be a problem. Triple therapy, involving the combination of alprostadil, papaverine, and phentolamine, has been reported to be effective and to have a relatively low incidence of adverse effects. Other drugs that have been used for intracavernosal therapy include aviptadil (a smooth muscle relaxant used with phentolamine), ketanserin used with alprostadil, and moxisylyte.

The **transurethral route** is a less invasive but also less effective option than intracavernosal therapy. A transurethral pellet of alprostadil is reported to be effective, although efficacy is inconsistent; common adverse effects include penile pain and urethral pain or burning. Transurethral alprostadil as a cream or gel has also shown promise.

A number of studies have also investigated **transcutaneous** therapy. Results from pilot studies investigating transcutaneous delivery of glyceryl trinitrate, papaverine, minoxidil, or alprostadil from creams, gels, or pastes have been variable. Topical treatment with a cream containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone has also been tried, with mixed results.

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Glomerular kidney disease

For a description of the various forms of glomerular kidney disease and their management, see p. 1604.3.

Malignant neoplasms

Malignant neoplasms of the bladder are relatively common malignancies in the developed world; the management of bladder cancer is discussed on p. 700.2. Prostate cancer is one of the most common malignancies in men and a leading cause of cancer death; its management is covered on p. 712.3. For malignancies of the kidney see p. 708.3.

Micturition disorders

Normal micturition (awareness of the need to void urine as a result of bladder filling, postponement of urination until convenient, and the ability to empty the bladder voluntarily) is controlled by the detrusor muscle of the bladder (smooth muscle innervated mainly by parasympathetic nerves) and the external sphincter (sympathetic innervation). During urination parasympathetic stimulation causes the detrusor muscle to contract while reduced sympathetic tone allows the external sphincter to relax. Micturition disorders can occur through local effects on the bladder or urethra or may result through disturbances of their nervous control. They include nocturnal enuresis, urinary incontinence, and urinary retention. The terms 'neurogenic bladder' and 'neuropathic bladder' are used loosely to describe any bladder dysfunction resulting from neurological disturbance.

Nocturnal enuresis. Involuntary discharge of urine during sleep, termed nocturnal enuresis (bed-wetting), is a normal occurrence in young children, but may persist in up to 5% by the age of 10 years. Nocturnal enuresis is defined as primary if there has never been a period of dryness for more than 6 months, and secondary if the child was dry for such a period before the onset of bed-wetting.

Nonpharmacological approaches to **treatment** include bladder retention training, motivational therapy, and behaviour modification or conditioning therapy using moisture-sensitive alarms. Drug therapy may initially produce a more rapid response, but training and the use of alarms has generally appeared to be more effective and to have a lower relapse rate. The *BNFC* states that, for children under 5 years of age, reassurance and advice on the management of nocturnal enuresis can be useful for some families; drug therapy may be considered in children over 5 years depending on their maturity and motivation, the frequency of bed-wetting, and the needs of the child and their family. Drug therapy is probably most useful for intermittent use on special occasions such as sleeping away from home or when added to treatment in children who fail to respond to nonpharmacological methods alone. The long-term use of drugs for enuresis is controversial.

- Use of oral *desmopressin* at night can be effective in the short-term control of nocturnal enuresis and many now consider it to be the drug of choice in terms of safety. However, it should not be given when enuresis is due to polydipsia as desmopressin may provoke water intoxication and convulsions due to hyponatraemia.
- Tricyclic antidepressants have also been used and of these most experience has been with *imipramine*. Their mechanism of action in nocturnal enuresis is unclear. It may be partly the result of their antimuscarinic and antispasmodic actions.
- Antimuscarinics such as *oxybutynin* reduce uninhibited bladder contractions, but although they may be of benefit in diurnal enuresis they are rarely of benefit in nocturnal enuresis alone. Combination with desmopressin may improve response in some cases.

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Urinary incontinence and retention. Urinary incontinence is defined as an involuntary loss of urine that is objectively demonstrable and a social or hygienic problem. Nocturnal enuresis in children is discussed above. Depending on the cause patients may have symptoms of urinary frequency, nocturia, urgency, dribbling, or dysuria. Classifications of incontinence vary but the main types include: stress incontinence, urge incontinence and overactive bladder, and overflow incontinence (a consequence of urinary retention). Patients may also have mixed types, for example combined stress and urge incontinence. The term functional incontinence is used when the patient's condition is due to impaired mobility or mental function. It is important to determine the type and, where possible, cause of urinary incontinence before attempting treatment. Urinary-tract infections, constipation, and benign prostatic hyperplasia may mimic or cause the symptoms of urinary incontinence and should be excluded.

Stress incontinence is the commonest form of incontinence in women; some men may also develop stress incontinence e.g. after prostatectomy. The patient usually has urethral sphincter incompetence and loss of urine is associated with increases in intra-abdominal pressure such as may occur on standing or coughing. Initial management should be conservative: first-line treatment is likely to be pelvic floor exercises; other treatments may include electrical stimulation or biofeedback, the use of devices such as vaginal cones, surgery, or drugs.

- Drug therapy has had only a secondary role in the treatment of stress incontinence although the serotonin and noradrenaline reuptake inhibitor *duloxetine* is now licensed in several countries to increase urethral tone in the treatment of moderate to severe stress urinary incontinence, and may be an alternative to surgical treatment. Alpha-adrenoceptor agonists such as *ephedrine*, *phenylpropanolamine*, and *pseudoephedrine* have been used to increase tone in the muscles of the urethra and at the base of the bladder; they may prevent incontinence in certain stress situations, but long-term experience has been mostly disappointing. *Oestrogens* used with an alpha-adrenoceptor agonist such as phenylpropanolamine appear to be effective and may be of use for postmenopausal women with mild stress incontinence; unfortunately, addition of a progestogen (necessary in women with an intact uterus) might exacerbate the incontinence. The value of oestrogens used without an alpha-adrenoceptor agonist is less clear. Intra-urethral injections of *collagen* or *polytef* appear to be effective, but there are concerns over migration and granuloma formation with polytef.

In **urge incontinence**, also known as unstable bladder or detrusor instability, contractions of the detrusor muscle occur without warning and overcome urethral sphincter resistance, despite any attempt the patient might make to prevent it. Urge incontinence is the most common form of incontinence in the elderly and is often refractory to treatment. The cause is usually unknown and these cases are referred to as being due to **idiopathic detrusor instability**. When there is overt neurological disease, such as upper motor neurone lesions in spinal cord injury or multiple sclerosis, the term **detrusor hyperreflexia** is used. **Overactive bladder syndrome** is defined as urgency (a compelling desire to urinate) with or without actual urge incontinence; patients usually exhibit urinary frequency and nocturia. In men it is sometimes associated with benign prostatic hyperplasia (p. 2347.1).

Reduction of excessive fluid intake and avoidance of drinks containing alcohol or caffeine may control mild symptoms of urge incontinence or overactive bladder. Behavioural therapy may be helpful: bladder training for at least 6 weeks is a first-line option in women with urge or mixed incontinence. Women with mixed incontinence may also benefit from pelvic floor exercises. Other treatments that have been tried include hypnotherapy, acupuncture, and biofeedback.

- No drug treatment has been found to be universally effective. Drugs with antimuscarinic activity can be of significant clinical benefit. They inhibit unstable detrusor muscle contractions but the incidence of adverse effects can be high. As these drugs can increase bladder volume they should not be used in patients with urinary retention. The antimuscarinic *oxybutynin* also has direct smooth muscle relaxant properties and has been widely used, but adverse effects are common. Transdermal or extended-release formulations may be considered in women who cannot tolerate conventional formulations of oxybutynin. *Tolterodine*, *trospium*, and *propiverine* are other alternatives. (In the UK, propiverine is suggested for overactive bladder but not for incontinence.) *Fesoterodine* is also available for the management of overactive bladder syndrome. Selective M_3 antimuscarinics, *darifenacin* and *solifenacin*, may also be considered. They appear to be at least as effective as less selective antimuscarinics. The older antimuscarinics *flavoxate*, *propantheline*, and *emepronium* are not now recommended.
  Mirabegron, a $beta_3$-adrenoceptor agonist, is available in some countries for the management of overactive bladder syndrome. *Tricyclic antidepressants* have also been used in urge incontinence because of their antimuscarinic activity but their main use has been in nocturnal enuresis and nocturia (see above). *Desmopressin* is also mainly used in nocturnal enuresis and nocturia. Evidence for *oestrogens* is inconclusive, but they may be useful as adjuncts in postmenopausal women with vaginal atrophy and symptoms of urgency, frequency, and nocturia. Injection of *botulinum A toxin* into the detrusor muscle may be effective in the treatment of detrusor hyperreflexia that is resistant to antimuscarinics. Sacral nerve stimulation, using an implantable device, may be an option in cases that are resistant to drug treatment. Surgery is reserved for intractable cases.

Urge incontinence can also be due to abnormalities in bladder sensation; the causes of **sensory urgency** are often unknown but may be due to conditions such as urinary-tract infections or interstitial cystitis. Bladder retraining techniques and antimuscarinic therapy have been suggested when no underlying disorder can be identified.

Patients with **overflow incontinence** suffer from a continuous or frequent dribbling of urine as a consequence of an overdistended bladder produced by **urinary retention**. It may result from some form of urethral blockage or may be associated with drug treatment or conditions that reduce detrusor contractions or interfere with relaxation of the urethra. Overflow incontinence is uncommon in women and most patients are elderly men with urethral blockage due to benign prostatic hyperplasia (p. 2347.1). However, urinary retention may also occur postpartum or postoperatively. Treatment depends on the underlying condition. Catheterisation is used to relieve acute painful urinary retention or when no cause can be

found. Surgical procedures or dilatation are often used to correct any mechanical outflow obstruction.

- Alpha-adrenoceptor blocking drugs such as *alfuzosin, doxazosin, indoramin, prazosin, tamsulosin,* and *terazosin* may be given to patients waiting for surgery or to those unfit for surgery. They decrease outflow resistance and improve bladder emptying. Patients with detrusor hypotonicity have been given parasympathomimetics such as *bethanechol, carbachol,* and *distigmine* to increase detrusor muscle contractions but there have been doubts about their efficacy and safety. Use of parasympathomimetics for postoperative urinary retention has been superseded by catheterisation.

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Premature ejaculation

A universally accepted definition of premature ejaculation has not yet been established, but the American Urological Association has defined it as ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.[1]

Management may include psychological, behavioural, and drug treatment.[1] Several antidepressants have been evaluated for a therapeutic effect in premature ejaculation,[1-3] based on their adverse effects of anorgasmia and delayed ejaculation. The SSRIs fluoxetine, paroxetine, and sertraline, and the tricyclic antidepressant clomipramine, have been used successfully. However, the optimal dosing regimen for these drugs has not been established, and they have been given either on a continuous daily basis or as single doses only before intercourse. Doses that have been effective in premature ejaculation have usually been lower than those recommended for the treatment of depression. A rapidly absorbed short-acting SSRI, dapoxetine, is used specifically for on-demand treatment of premature ejaculation. Topical anaesthetics, such as lidocaine/prilocaine cream, have been applied to the penis to delay ejaculation.[1-3] Disadvantages of this therapy include loss of erection due to numbness associated with prolonged application, and numbness in the partner caused by residual topical anaesthetic.[1,3] Available commercial preparations intended for such use include benzocaine gels and lidocaine sprays. Sildenafil, a phosphodiesterase type-5 inhibitor used for erectile dysfunction, has also been tried with some success;[1] however, some consider that such drugs should only be used in patients with co-morbid erectile dysfunction.[3]

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Prostatitis

The term prostatitis is used to describe several clinical syndromes, including well-defined bacterial infections of the prostate gland, poorly-defined chronic pelvic pain, and asymptomatic inflammation of the prostate. Prostatitis is relatively common as a urological diagnosis, with about 30% of men having such symptoms at some time in their life.[1] The US National Institutes of Health classification system[1,2] for prostatitis consists of categories:

- I: acute bacterial prostatitis
- II: chronic bacterial prostatitis
- III: chronic prostatitis/chronic pelvic pain syndrome (subdivided into IIIA inflammatory and IIIB non-inflammatory)
- IV: asymptomatic inflammatory prostatitis

Acute bacterial prostatitis (category I) is most often due to Gram-negative pathogens, particularly *Escherichia coli* and other enterobacteriaceae. Symptoms include fever, chills, malaise and myalgia, with rectal, low back, or perineal pain. There is often bacteriuria with frequent and urgent dysuria. The prostate is enlarged, tender, and warm.[1-3] **Chronic bacterial prostatitis** (category II) is relatively rare, and may develop from acute bacterial prostatitis in some men. It is characterised by pelvic pain and recurrent urinary-tract infections. The prostate appears to be normal but in some cases is swollen or firm.[1] Bacterial prostatitis should be managed with appropriate antibacterial therapy[2-5] (see under Urinary-tract Infections, p. 213.1).

Chronic prostatitis/chronic pelvic pain syndrome (category III), which has also been described as abacterial prostatitis, is the most common form of prostatitis. The aetiology and pathogenesis remain unclear, and suggestions have included infection with atypical organisms that cannot be detected by conventional techniques, intraprostatic reflux, or immunological processes.[1] Neurological[6] or psychological factors[1,6] may also play a role in some patients. Symptoms of chronic pelvic pain syndrome include pelvic, perineal, and genital pain, lower urinary-tract symptoms, sexual dysfunction, and general symptoms such as headache and fatigue.[1,3] In inflammatory chronic pelvic pain syndrome (category IIIA), leucocytes can be found in expressed prostatic secretion, in the urine after prostatic massage, and in semen; no leucocytes can be detected in non-inflammatory chronic pelvic pain syndrome (category IIIB; previously called prostatodynia).[1,3,6]

There are no universally effective treatments for chronic pelvic pain syndrome; overall, studies of treatments have been small and of poor quality.[2,5-7] Many clinicians favour initial management with antibacterials despite negative cultures, in order to treat occult atypical infection.[2] An oral fluoroquinolone is the antibacterial of choice (or a tetracycline for patients allergic to fluoroquinolones). Recommended duration of treatment varies, but courses are generally of 4 to 8 weeks, depending on response in the first few weeks.[3,4,6] However, there is no strong evidence to support this practice,[2,7] and although there are some studies to suggest that antibacterial treatment may be beneficial in inflammatory chronic pelvic pain syndrome, there is less evidence for the non-inflammatory form.[4] Other treatments that have been tried, with variable results, include[2,3,5-9] the 5α-reductase inhibitor finasteride, alpha blockers such as alfuzosin, terazosin, or tamsulosin, fluoxetine, pentosan polysulfate sodium, mepartricin, pollen extract, quercetin, and NSAIDs. The role of allopurinol is controversial. Non-drug treatments that have shown some promise include transurethral or transrectal microwave thermotherapy[5-7] and sacral nerve stimulation.[6] Drugs used for symptomatic relief of neuropathic pain may include tricyclic antidepressants such as amitriptyline, or antiepileptics such as gabapentin. Anticholinergics such as oxybutynin or tolterodine may be used for urinary frequency.[6]

Asymptomatic inflammatory prostatitis (category IV) is often detected coincidentally during examination for other disorders.[1]

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Renal calculi

The solubility of calcium, oxalate, and phosphate in normal urine is maintained by a variety of inhibitors of crystallisation, both organic and inorganic. However, increases in the concentrations of crystalline substances in the urine, or decreases in the relative proportions of crystallisation inhibitors, may render individuals susceptible to urolithiasis, the formation of renal calculi (kidney stones). Renal calculi consist of crystalline components arranged around an organic matrix. They are typically formed in the calices or renal pelvis, and may become lodged in the ureter. Calcium-containing stones (usually calcium oxalate and calcium phosphate in variable proportions) account for the vast majority of occurrences although stones of other compositions including cystine, uric acid, or magnesium ammonium phosphate (also called struvite or infection stones), are occasionally seen.

The incidence and prevalence of renal calculi is increasing.[1,2] The lifetime risk of stone development varies between populations but is about 15% for white men and 6% for white women, with a lifetime recurrence rate of up to 50%.[3] Risk factors include obesity, low fluid intake, and a diet high in protein, refined carbohydrates, and salt.[1] Some conditions can promote calculi formation, including renal tubular acidosis, primary hyperparathyroidism, sarcoidosis, primary hyperoxaluria, inflammatory bowel disease, hyperuricaemic conditions, and cystic fibrosis.[4] Drug-induced calculi can be formed by crystallisation of poorly soluble drugs with a high urinary excretion, or by an effect on calcium oxalate or purine metabolism.[5]

Treatment. Most renal calculi are small, and stones that are less than 5 mm in diameter will usually pass spontaneously.[6-9] Patients may be asymptomatic or may pass small stones with relatively little discomfort, but passage of a larger stone down the ureter can be accompanied by excruciating pain (renal or ureteral colic) requiring analgesia (see Biliary and Renal Colic, p. 6.3). If there is no obstruction, infection, or other complication, conservative treatment is favoured, with the patient being monitored radiographically over several weeks to see if the stone will pass of its own accord.[10]

There is some interest in the possible use of drug treatment to ease the spontaneous passage of the stone. Small studies using a calcium-channel blocker (usually nifedipine) or an $alpha_1$-adrenoceptor blocker such as tamsulosin, sometimes with a corticosteroid such as deflazacort, have reported improvements in the rate of stone expulsion and expulsion time, and reductions in analgesic requirements, in patients with uncomplicated lower ureteral stones. A meta-analysis[11] of 9 studies confirmed the apparent benefit of such treatment, and a further meta-analysis[12] of 11 studies using alpha blockers in particular, found that patients had a 44% greater likelihood

of spontaneous stone passage than those not given these drugs. Although a suitable randomised controlled study is required to confirm efficacy, medical treatment may offer a viable alternative to lithotripsy or ureteroscopy.[11] A literature review[13] suggested that daily doses of nifedipine 30 mg, doxazosin 4 mg, tamsulosin 400 micrograms, or terazosin 5 mg given for 28 to 45 days are effective in enhancing expulsion of ureteral stones that are less than 15 mm in diameter. Another[14] considered alpha blockers to be more effective than calcium-channel blockers; little benefit was noted in small studies where a corticosteroid or an antimuscarinic was added to an alpha blocker.

Where intervention is considered necessary for stone removal the choice of technique depends on the size, composition, and location of the stone. Extracorporeal shock wave lithotripsy is generally favoured, but other procedures such as ureteroscopy or percutaneous nephrolithotomy are used for more complex cases.[7,8,15] Antibacterials may be needed for infection (see Urinary-tract Infections, p. 213.1).

Prevention. In the prevention of recurrence it is important to identify, and where possible correct, any underlying disease process or biochemical or anatomical abnormality. Certain general measures are also appropriate. Patients should drink at least 2 to 3 litres of fluid daily in order to maintain an adequate volume of urine.[1,3,7,16] In hot climates or working environments a higher volume of fluid should be taken.

In preventing the recurrence of **calcium stones**, a balanced diet that is low in protein and salt[1,3,10,17] and high in fibre[1,7] is generally advocated. In the past patients were advised to decrease their calcium intake, but studies have found an inverse relationship between dietary calcium intake and stone formation.[3,7,16,17] Also, because oxalate is bound by calcium in the gut, preventing its absorption, a low calcium intake can increase oxalate absorption and the risk of stone formation. Therefore, a normal level of dietary intake of calcium is now advised[1,3,7,17,18] (an exception to this is in patients with absorptive hypercalciuria type I, a rare condition of intestinal calcium hyperabsorption).[1] However, calcium supplements appear to increase the risk of stone formation and are generally avoided.[3,7,17] If they are used, they should be taken with meals to avoid hypercalciuria.[1,18] Excessive dietary oxalate intake should also be avoided;[3,7,10,17] foods containing large quantities of bioavailable oxalate include spinach, rhubarb, nuts, and cocoa.[17]

Where pharmacological therapy is indicated, choice of treatment depends on the underlying metabolic abnormality and stone composition. Alkaline citrate, usually given as potassium citrate, is commonly used to prevent the recurrence of calcium stones. It acts as a urinary alkaliniser and increases citrate excretion; citrate forms complexes with calcium to reduce urinary saturation of calcium salts and inhibits crystallisation.[2,7,16,18] Potassium citrate is the main treatment option in patients with hypocitraturia and renal tubular acidosis.[1,3,7] In hypercalciuria, a thiazide diuretic or indapamide can also be used to increase distal tubular calcium reabsorption;[1-3,6,7,10,16,19] potassium citrate can also prevent diuretic-induced hypokalaemia in these patients. In the prevention of calcium stones with hyperoxaluria, a restriction of oxalate-rich food and an adequate dietary calcium intake (or calcium supplements taken with meals) are advocated.[6,10,17,18] The use of magnesium has also been suggested[1] although it may be no better than placebo.[3,7] Some patients with primary hyperoxaluria may respond to high doses of pyridoxine.[1,3,7,10,18] In hyperuricosuria, reduced purine intake and allopurinol may be effective.[1,3,7,10]

Prevention of **uric acid stones** is based on adequate fluid intake, a low purine diet, and urinary alkalinisation with potassium citrate. Allopurinol may be used if there are high levels of urate.[1-3,6,7] Acetazolamide has been used short term.[6]

Struvite stones are caused by urease-producing bacteria. Antibacterials are used, and may be required long term, with urinary acidification using ammonium chloride[7] or methionine.[1,7] Dietary phosphate restriction may also be appropriate for patients with phosphate excretion of more than 35 mmol/day.[1] Acetohydroxamic acid, an inhibitor of bacterial urease, may be used as an adjunct in selected cases of severe infection,[7] but its use has been limited by adverse effects.[3,10]

Cystine stones are associated with cystinuria, see p. 1567.2.

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Renal colic

For the treatment of urological pain see Biliary and Renal Colic, p. 6.3.

Renal failure

For discussions of acute and chronic renal failure and their management, see p. 1779.1.

Sexually transmitted diseases

For discussion of sexually transmitted diseases and their treatment see p. 204.1.

Syndrome of inappropriate ADH secretion

In some patients secretion of antidiuretic hormone (ADH; vasopressin) occurs despite hypotonicity of the extracellular fluid and normal or raised fluid volume, and such patients are said to have the syndrome of inappropriate ADH secretion (SIADH). With severe water excess, the resultant hyponatraemia may result in symptoms ranging from lassitude or headache to profound neurological symptoms such as confusion, convulsions, or coma. Some patients may experience inappropriate thirst as well as ADH secretion, thus exacerbating their condition. For a discussion of sodium homoeostasis and dilutional hyponatraemia, see p. 1777.3 and p. 1778.1.

Conditions that can precipitate SIADH include CNS disorders, infections such as encephalitis and meningitis, head trauma, porphyria, or pulmonary diseases such as tuberculosis and pneumonia. ADH may also be secreted ectopically from malignancies, most commonly from small-cell bronchial carcinoma. SIADH may also be drug-induced; drugs associated with the condition include carbamazepine, chlorpropamide, cytotoxic drugs such as cyclophosphamide and the vinca alkaloids, oxytocin, some antipsychotics, tricyclic antidepressants, and SSRIs.

Diagnosis of SIADH is initially prompted by the presence of hyponatraemia and corresponding plasma hypo-osmolality with or without neurological symptoms. Hypervolaemia, persistent excess sodium excretion, lack of oedema, and normality of both renal and adrenal function are confirmatory.

Mild water excess is frequently asymptomatic and may not require specific therapy, but patients with SIADH often have a more severe disorder and treatment is best aimed at the underlying cause. If such treatment is not possible or if symptoms persist, water restriction may be considered. However, fluid restriction is unpleasant, particularly for patients who retain inappropriate thirst, and may not be tolerable. In these patients demeclocycline may be given to antagonise the effect of ADH on the renal tubules. Lithium has been given as an alternative but has a high frequency of adverse effects, and phenytoin has been used occasionally to inhibit pituitary ADH secretion. Diuretics such as furosemide (used with oral sodium chloride) have been tried in an attempt to optimise diuresis while retaining sodium. Oral urea has also been used in a small number of patients. In patients with life-threatening severe acute water intoxication (see Hyponatraemia, p. 1778.1), treatment initially involves cautious improvement of the profound hyponatraemia by intravenous infusion of hypertonic (usually 3%) or isotonic sodium chloride, often with furosemide or another loop diuretic to avoid volume expansion. Drugs that act directly in the renal tubules as vasopressin V_2 receptor antagonists such as tolvaptan are also used.

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Urinary-tract infections

The treatment of urinary-tract infections is discussed on p. 213.1.

Acetildenafil

Hongdenafil.

5-[2-Ethoxy-5-[2-(4-ethylpiperazine-1-yl)-acetyl]phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one.

$C_{25}H_{34}N_6O_3$=466.6

CAS — 831217-01-7.

Profile

Acetildenafil is an analogue of sildenafil (p. 2364.1) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction. Other drugs related to sildenafil detected in similar products include:

- aildenafil
- dimethyl sildenafil thione (sulfoaildenafil)
- homosildenafil
- hydroxyhomosildenafil.
- nor-acetildenafil
- sulfohomosildenafil

Alfuzosin Hydrochloride

(BANM, USAN, rINNM)

Alfutsosiinihydrokloridi; Alfuzosin Hidroklorür; Alfuzosina, hidrocloruro de; Alfuzosine, Chlorhydrate d'; Alfuzosin-hydrochlorid; Alfuzosinhydrochlorid; Alfuzosinhydroklorid; Alfuzosini Hydrochloridum; Alfuzozin-hidroklorid; Alfuzozino hidrochloridas; Hidrocloruro de alfuzosina; SL-77499-10; SL-77499 (alfuzosin); Альфузозина Гидрохлорид.

N-{3-[4-Amino-6,7-dimethoxyquinazolin-2-yl(methyl)amino] propyl}tetrahydro-2-furamide hydrochloride.

$C_{19}H_{27}N_5O_4$,HCl=425.9

CAS — 81403-80-7 (alfuzosin); 81403-68-1 (alfuzosin hydrochloride).

ATC — G04CA01.

ATC Vet — QG04CA01.

UNII — 75046A1XTN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Alfuzosin Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Alfuzosin Hydrochloride). A white to almost white, slightly hygroscopic, powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Uses and Administration

Alfuzosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1). It acts preferentially on receptors in the lower urinary tract and is therefore used in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction, including acute urinary retention.

Alfuzosin is given orally as the hydrochloride. Like other alpha$_1$-adrenoceptor blockers, it may cause collapse in some patients after the first dose, which should therefore be given just before bedtime to reduce the risk. Doses may need to be reduced in patients with hepatic or renal impairment (see p. 2352.1); the initial dose should also be reduced in the elderly.

In **benign prostatic hyperplasia,** the usual dose of alfuzosin hydrochloride is 2.5 mg three times daily, increased to 10 mg daily if necessary. In elderly patients, and those receiving treatment for hypertension, a lower

initial dose of 2.5 mg twice daily should be considered. A modified-release preparation may also be used in a dose of 10 mg once daily after a meal.

In patients aged over 65 years catheterised for **acute urinary retention** associated with benign prostatic hyperplasia, a modified-release preparation may be given in a dose of 10 mg once daily after a meal for 3 to 4 days.

Reviews.

1. Wilde MI, *et al*. Alfuzosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. *Drugs* 1993; **45:** 410–29.
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4. Weiner DM, Lowe FC. Alfuzosin for the management of benign prostate hyperplasia. *Expert Opin Pharmacother* 2003; **4:** 2057–63.
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Administration in hepatic or renal impairment. Alfuzosin should be avoided in patients with severe hepatic impairment; in those with mild to moderate impairment the initial oral dose of alfuzosin hydrochloride should be 2.5 mg daily, increased to 2.5 mg twice daily according to response.

The findings of a study[1] in 18 subjects with varying degrees of renal impairment (including 6 with severe impairment) given a single dose of alfuzosin 10 mg as a once-daily, modified-release formulation suggested that no dose reduction was needed in patients with impaired renal function. At most, slight pharmacokinetic modifications were found in those with renal impairment when compared with those with normal function. It should also be noted that the renal clearance of alfuzosin is a minor route of elimination (see Pharmacokinetics, below). Licensed product information recommends that patients with renal impairment are started on a dose of 2.5 mg twice daily, thereafter adjusted according to response.

1. Marbury TC, *et al*. Pharmacokinetics and safety of a single oral dose of once-daily alfuzosin, 10 mg, in male subjects with mild to severe renal impairment. *J Clin Pharmacol* 2002; **42:** 1311–17.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3 and p. 1475.1. Alfuzosin may be more selective for the urinary tract and vasodilator effects may be less frequent. Additional adverse effects of alfuzosin include rhinitis, bronchitis, sinusitis, pharyngitis, and upper respiratory-tract infections. Angina has occurred in patients with pre-existing ischaemic heart disease; if symptoms appear or worsen during treatment, alfuzosin should be stopped. Prolongation of the QT interval has been reported during alfuzosin treatment, and it should be used with caution in patients with acquired or congenital QT prolongation, or those who are taking other drugs that prolong the QT interval. Hepatocellular and cholestatic liver injury, including jaundice, has occurred and may require treatment to be stopped. Alfuzosin should be avoided in severe hepatic impairment, and doses may need to be reduced in mild to moderate hepatic impairment and in renal impairment (see above).

Incidence of adverse effects. In postmarketing surveillance involving 13 389 patients given oral alfuzosin 2.5 mg three times daily for benign prostatic hyperplasia, about 3.7% of patients failed to complete treatment because of adverse effects. These were mostly vasodilator effects (vertigo or dizziness, syncope or malaise, hypotension, and headache), and were more common in patients over 75 years of age and during the first week of treatment.[1]

1. Lukacs B, *et al*. Safety profile of 3 months' therapy with alfuzosin in 13,389 patients suffering from benign prostatic hypertrophy. *Eur Urol* 1996; **29:** 29–35.

Cataract surgery. Alpha blockers, including alfuzosin, have been associated with intraoperative floppy iris syndrome in cataract surgery patients. For further details, see under Tamsulosin, p. 2369.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alfuzosin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for Prazosin Hydrochloride, p. 1475.1. Potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, itraconazole, and ritonavir, may increase blood concentrations of alfuzosin.

Pharmacokinetics

Alfuzosin is readily absorbed after oral doses and peak plasma concentrations generally occur 0.5 to 3 hours after a dose; bioavailability is about 64%. Absorption from modified-release preparations is improved if given with food. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to inactive metabolites that are excreted primarily in faeces via the bile. Only about 11% of a dose is excreted unchanged in the urine. Alfuzosin has a plasma elimination half-life of 3 to 5 hours. It is 90% bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dalfaz; UroXatral; ***Austria***: Xatral; ***Belg.***: Xatral; ***Braz.***: Xatral; ***Canad.***: Xatral; ***Chile***: UroXatral; ***China***: Nuo Shu An (诺舒安); WeiPing (维平); Xatral (桑塔); ***Cz.***: Alfuzostad; Xatral; ***Denm.***: Danafusin; Prostazosin; Xatral; ***Fin.***: Danafusin; Lafunomyl; Xatral; ***Fr.***: Urion; Xatral; ***Ger.***: Alfunar; Alfusin†; Urion†; UroXatral†; ***Gr.***: Alcinin; Alfuprost; Alfural; Alfuzin; Innosensitive; Ofuxal; Rilif; Spedamyl; Xatral; Zoprost; Zoratral; ***Hong Kong***: Xatral; ***Hung.***: Alfetim; Alfugen; Alfuzostad; Fetamozin; ***India***: Alfoo; Alfusin; Efzu; Flotral; Fual; ***Indon.***: Xatral; ***Irl.***: Alfirum†; Alfu; Alzmeran; Tevax; Xatger; Xatral; ***Israel***: Alfu-Kal; Xatral; ***Ital.***: Mittoval; Xatral; ***Malaysia***: Xatral; ***Mex.***: Ranplasia; Xatral; ***Neth.***: Xatral; ***Norw.***: Xatral†; ***Philipp.***: Fozal; Profuzosin; Xatral; ***Pol.***: AlfuLEK; Alfuzostad; Alugen; Dalfaz; ***Port.***: Benestan; ***Rus.***: Dalfaz (Дальфаз); ***S.Afr.***: Rantral; Xatral; ***Singapore***: Xatral; ***Spain***: Benestan; Unibenestan; ***Swed.***: Danafusin; Lafunomyl; Xatral; ***Switz.***: Fuzocim; Xatral; ***Thai.***: Xatral; ***Turk.***: Xatral; ***UK***: Besavar; Vasran; Xatral; ***Ukr.***: Dalfusin (Дальфузин)†; ***USA***: UroXatral; ***Venez.***: Xatral.

Multi-ingredient Preparations. ***Hung.***: Alfin Combo; ***India***: Afdura; Dutalfa; ***Mex.***: Profidox.

Pharmacopoeial Preparations
BP 2014: Alfuzosin Tablets; Prolonged-release Alfuzosin Tablets;
USP 36: Alfuzosin Hydrochloride Extended-Release Tablets.

Alprostadil *(BAN, USAN, rINN)*

Alprostadiili; Alprostadilis; Alprostadilum; Alprosztadil; PGE_1; Prostaglandin E_1; U-10136; Алпростадил.

(*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprost-13-enoic acid; 7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}heptanoic acid.

$C_{20}H_{34}O_5$=354.5

CAS — 745-65-3.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

UNII — F5TD010360.

NOTE. In *Martindale* the term alprostadil is used for the exogenous substance and prostaglandin E_1 for the endogenous substance.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Alprostadil). A white or slightly yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in ethyl acetate.

USP 36: (Alprostadil). A white to off-white crystalline powder. M.p. about 110 degrees. Soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in chloroform and in ether; slightly soluble in ethyl acetate. Store between 2 degrees and 8 degrees in airtight containers.

Alprostadil Alfadex *(BAN, rINNM)*

Alprostadilum Alfadexum; α-Cyclodextrin Alprostadil; PGE_1 α-CD; Prostaglandin E_1 α-Cyclodextrin Clathrate Compound; Алпростадил Альфадекс.

$C_{20}H_{34}O_5.x[C_{36}H_{60}O_{30}]$

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Alprostadil is a prostaglandin (p. 2598.1) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostaglandin E_1. Alprostadil is used mainly in congenital heart disease and in erectile dysfunction (p. 2348.2).

In the management of **erectile dysfunction**, alprostadil is given by intracavernosal injection; preparations may contain alprostadil or alprostadil alfadex, but the dose is expressed in terms of the base. Alprostadil may also be given as an intra-urethral application.

By *intracavernosal injection*, the initial dose should be low, for example 2.5 micrograms, and is increased incrementally until a suitable dose is established. Normally, the second dose should be 5 micrograms if some response to the first dose is seen, or 7.5 micrograms if there is no response; increments should then be of 5 to 10 micrograms until an effective dose is reached. The usual dose range is 5 to 20 micrograms and the maximum recommended dose is 60 micrograms. In cases of erectile dysfunction of neurogenic origin secondary to spinal cord injury an initial dose of 1.25 micrograms has been given, with a second dose of 2.5 micrograms, a third dose of 5 micrograms, and subsequent increments of 5 micrograms. While finding a suitable dose, the interval between doses should be at least 1 day if there has been a partial response. If there is no response however, the next, higher dose may be given within 1 hour. Once established, the optimal dose should be given not more than once daily and not more than three times per week.

Alprostadil may also be injected intracavernosally in the diagnosis of erectile dysfunction in doses ranging from 5 to 20 micrograms.

By *intra-urethral (transurethral) application*, the initial dose is 250 micrograms. The dose may be increased incrementally to 500 or 1000 micrograms or decreased to 125 micrograms according to response. The optimal dose should be given not more than twice daily, and not more than seven times per week. A dose of 500 micrograms may be used diagnostically.

Alprostadil is also available in some countries as a *topical* formulation for the treatment of erectile dysfunction. There is also ongoing investigation of the use of topical formulations for female sexual dysfunction. An injectable liposomal formulation of alprostadil (lipo-prostaglandin E_1, lipo-PGE_1) has also been investigated for various uses.

For doses used in neonates with **congenital heart disease** to maintain the patency of the ductus arteriosus, see Administration in Children, below.

Administration in children. Alprostadil is used to maintain the patency of the ductus arteriosus in neonates with congenital heart disease until surgery is possible. It is given by continuous intravenous infusion beginning with doses of 50 to 100 nanograms/kg per minute; doses should be reduced as soon as possible to the minimum necessary to maintain response. Lower starting doses may be effective in some patients, and UK licensed product information advises that doses as low as 5 nanograms/kg per minute have been used successfully when transport of the infant is necessary. The *BNFC* suggests an initial dose of 5 nanograms/kg per minute, adjusted in steps of 5 nanograms/kg per minute according to response, to a maximum of 100 nanograms/kg per minute. The dose can be increased to 400 nanograms/kg per minute according to US licensed product information but, in general, higher infusion rates do not improve effect. Alprostadil may also be given by continuous infusion through an umbilical artery catheter placed at the ductal opening.

Ergotamine poisoning. Alprostadil[1,2] is one of many drugs that have been used to treat the circulatory disturbances in ergotamine poisoning (see Cardiovascular Effects, p. 674.3).

1. Levy JM, *et al*. Prostaglandin E_1 for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Intervent Radiol* 1984; **7:** 28–30.
2. Horstmann R, *et al*. Kritische Extremitätenischämie durch Ergotismus. *Dtsch Med Wochenschr* 1993; **118:** 1067–71.

Haemorrhagic cystitis. Bladder irrigation with alprostadil produced resolution of severe haemorrhagic cystitis in 5 of 6 children who had undergone bone marrow transplantation.[1] Alprostadil was given via a catheter and retained for 1 hour each day for at least 7 consecutive days.

1. Trigg ME, *et al*. Prostaglandin E_1 bladder instillations to control severe hemorrhagic cystitis. *J Urol (Baltimore)* 1990; **143:** 92–4.

Hearing loss. Alprostadil has been used in the treatment of sudden hearing loss to increase cochlear blood flow and oxygen supply. Results of a meta-analysis of 13 randomised studies suggested that those patients treated with alprostadil had an improvement in their hearing when compared with controls.[1]

1. Zhuo X-L, *et al*. Is the application of prostaglandin E_1 effective for the treatment of sudden hearing loss? An evidence-based meta-analysis. *J Int Med Res* 2008; **36:** 467–70.

Hepatic disorders. Benefit has been reported in patients with *viral hepatitis* (p. 952.1) given intravenous alprostadil alone or followed by oral dinoprostone or misoprostol.[1,2] Prostaglandins were studied because they had previously been shown to have a cytoprotective effect in experimentally induced hepatitis or in isolated hepatocytes, but the

mechanism by which they exerted a beneficial effect was uncertain.

Combined intravenous therapy with glucagon, insulin, and alprostadil formulated in lipid microspheres has also been found effective in preventing *acute fulminant hepatic failure* after hepatic arterial infusion of antineoplastic chemotherapy.[3]

1. Sinclair SB, *et al.* Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E: a preliminary report. *J Clin Invest* 1989; **84:** 1063–9.
2. Flowers M, *et al.* Prostaglandin E in the treatment of recurrent hepatitis B infection after orthotopic liver transplantation. *Transplantation* 1994; **58:** 183–92.
3. Ikegami T, *et al.* Randomized control trial of lipo-prostaglandin E_1 in patients with acute liver injury induced by Lipiodol-targeted chemotherapy. *Clin Pharmacol Ther* 1995; **57:** 582–9.

Organ and tissue transplantation. Alprostadil and other prostaglandin analogues have been investigated in regimens for the management of solid organ transplantation, with variable results. For reference to the use of alprostadil in intestinal grafts see p. 1935.1.

References.
1. Merion RM. Prostaglandins in liver transplantation. *Adv Exp Med Biol* 1997; **433:** 13–18.
2. Iberer F, *et al.* Prostaglandins in heart transplantation. *Adv Exp Med Biol* 1997; **433:** 19–22.
3. Ray JG. Prostaglandin E1 analogs do not improve renal function among either transplant or nontransplant patients: no further trials required. *Transplantation* 1998; **66:** 476–83.

Peripheral vascular disease. Various prostaglandins, including alprostadil,[1-7] have been used in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3) that is complicated by ulceration.

1. Clifford PC, *et al.* Treatment of vasospastic disease with prostaglandin E_1. *BMJ* 1980; **281:** 1031–4.
2. Telles GS, *et al.* Prostaglandin E_1 in severe lower limb ischaemia: a double-blind controlled trial. *Br J Surg* 1984; **71:** 506–8.
3. Mohrland JS, *et al.* A multiclinic, placebo-controlled, double-blind study of prostaglandin E_1 in Raynaud's syndrome. *Ann Rheum Dis* 1985; **44:** 754–60.
4. Sethi GK, *et al.* Intravenous infusion of prostaglandin E_1 (PGE_1) in management of limb ischemia. *Am Surg* 1986; **52:** 474–8.
5. Langevitz P, *et al.* Treatment of refractory ischemic skin ulcers in patients with Raynaud's phenomenon with PGE_1 infusions. *J Rheumatol* 1989; **16:** 1433–5.
6. The ICAI Study Group. Prostanoids for chronic critical leg ischemia: a randomized, controlled, open-label trial with prostaglandin E_1. *Ann Intern Med* 1999; **130:** 412–21.
7. Bartolone S, *et al.* Efficacy evaluation of prostaglandin E1 against placebo in patients with progressive systemic sclerosis and significant Raynaud's phenomenon. *Minerva Cardioangiol* 1999; **47:** 137–43.

Pulmonary hypertension. Alprostadil has shown some beneficial effects in patients with pulmonary arterial hypertension.[1,2]

1. Shen J, *et al.* Effects of lipo-prostaglandin E1 on pulmonary hemodynamics and clinical outcomes in patients with pulmonary arterial hypertension. *Chest* 2005; **128:** 714–19.
2. von Scheidt W, *et al.* Prostaglandin E1 testing in heart failure-associated pulmonary hypertension enables transplantation: the PROPHET study. *J Heart Lung Transplant* 2006; **25:** 1070–6.

Adverse Effects, Treatment, and Precautions

The adverse effects reported most commonly in **infants** with congenital heart disease treated with alprostadil are apnoea, fever, flushing, hypotension, bradycardia, tachycardia, diarrhoea, and convulsions. Other adverse effects reported include oedema, cardiac arrest, hypokalaemia, disseminated intravascular coagulation, and cortical proliferation of the long bones. Weakening of the wall of the ductus arteriosus and pulmonary artery may occur on prolonged infusion. Alprostadil should be avoided in neonates with respiratory distress syndrome and should be used with caution in those with bleeding tendencies; blood pressure and respiratory status should be monitored during infusion.

Adverse effects reported in **adults** given alprostadil have included headache, flushing, hypotension, diarrhoea, and pain and inflammation at the infusion site.

After intracavernosal or intra-urethral alprostadil for the treatment of erectile dysfunction, the most frequently reported adverse effect is pain during erection. Local reactions including penile fibrosis, fibrotic nodules, and Peyronie's disease have been reported. Priapism may occur (see below). Systemic effects are less common but hypotension and other adverse effects have been reported. Intracavernosal or intra-urethral use should be avoided in patients with complicating penile deformities or with sickle-cell disease, myeloma, leukaemias, or other conditions predisposing to prolonged erection.

In children. Reviews[1,2] of adverse effects associated with alprostadil in infants with congenital heart disease.

1. Lewis AB, *et al.* Side effects of therapy with prostaglandin E_1 in infants with critical congenital heart disease. *Circulation* 1981; **64:** 893–8.
2. Lucron H, *et al.* Complications du traitement par prostaglandines El des cardiopathies congénitales en réanimation médicale pédiatrique. *Arch Mal Coeur Vaiss* 2005; **98:** 524--30.

Effects on the bones. Periosteal or cortical hyperostosis has been reported in infants given alprostadil for cyanotic congenital heart disease.[1,2] A retrospective review of 30 infants[3] treated with alprostadil revealed radiographic signs of periosteal reactions in 5. Changes could be detected after even short courses of therapy; 3 developed relatively mild periosteal changes in the ribs after infusions ranging from 9 to 205 hours and one had involvement of the left femur after infusion for 71 hours. Resolution of lesions had occurred in most bones 6 to 12 months later. In a further study,[4] radiological evidence of cortical hyperostosis was found in 53 of 86 infant heart transplant recipients who had received alprostadil infusion pre-operatively. Of 53 of the infants who had received alprostadil for less than 30 days, 21 were affected (2 severely). Correspondingly, of those treated for 30 to 60 days, 18 of 22 were affected (13 severely). All 14 infants treated for more than 60 days were affected (7 severely). Since the associated bone changes may persist for months after stopping alprostadil, caution should be exercised to avoid misdiagnosis.

1. Kalloghlian AK, *et al.* Cortical hyperostosis simulating osteomyelitis after short-term prostaglandin E_1 infusion. *Eur J Pediatr* 1996; **155:** 173–4.
2. Estes K, *et al.* Cortical hyperostosis secondary to prostaglandin E_1 therapy. *J Pediatr* 2007; **151:** 441.
3. Ringel RE, *et al.* Periosteal changes secondary to prostaglandin administration. *J Pediatr* 1983; **103:** 251–3.
4. Woo K, *et al.* Cortical hyperostosis: a complication of prolonged prostaglandin infusion in infants awaiting cardiac transplantation. *Pediatrics* 1994; **93:** 417–20.

Effects on the gastrointestinal tract. Hyperplasia of the gastric mucosa, resulting in gastric outlet obstruction, has been reported in several neonates receiving alprostadil infusion.[1-3] It was suggested that this effect was dose-dependent.[1] Regression of the obstruction usually occurred after cessation of therapy.

For a report of necrotising enterocolitis in infants receiving alprostadil for congenital heart disease, see Dinoprostone, p. 2135.2.

1. Peled N, *et al.* Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992; **327:** 505–10.
2. Merkus PJFM, *et al.* Prostaglandin E1 and gastric outlet obstruction in infants. *Lancet* 1993; **342:** 747.
3. Kobayashi N, *et al.* Acute gastric outlet obstruction following the administration of prostaglandin: an additional case. *Pediatr Radiol* 1997; **27:** 57–9.

Effects on the metabolism. Severe hyperglycaemia with apparent ketoacidosis occurred during postoperative infusion of alprostadil in the infant of a diabetic mother.[1] The manufacturers had received reports of hyperglycaemia associated with alprostadil in 5 infants, one of whom had a diabetic mother. Hypoglycaemia has also been reported in a few infants.[2]

1. Cohen MH, Nihill MR. Postoperative ketotic hyperglycaemia during prostaglandin E_1 infusion in infancy. *Pediatrics* 1983; **71:** 842–4.
2. Lewis AB, *et al.* Side effects of therapy with prostaglandin E_1 in infants with critical congenital heart disease. *Circulation* 1981; **64:** 893–8.

Effects on the skin. A 63-year-old man with Peyronie's disease[1] developed toxic pustuloderma (acute generalised exanthematous pustulosis) 6 days after receiving a single intracavernosal injection of alprostadil to define the penile morphology. He was treated with antihistamines and topical corticosteroids and the condition resolved completely within a week.

1. Gallego I, *et al.* Toxic pustuloderma induced by intracavernous prostaglandin E_1. *Br J Dermatol* 1997; **136:** 975–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alprostadil as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Priapism. If priapism (p. 1430.2) occurs after the use of alprostadil for erectile dysfunction, its treatment should not be delayed more than 6 hours. The *BNF* recommends initial therapy by penile aspiration. If aspiration is unsuccessful sodium chloride 0.9% can be injected into one side of the corpus cavernosum and drained through the other side. If both aspiration and lavage have been unsuccessful, a sympathomimetic with action on alpha-adrenergic receptors is given by cautious intracavernosal injection, with continuous monitoring of blood pressure and pulse. Extreme caution is necessary in patients with coronary heart disease, hypertension, cerebral ischaemia, or if taking an antidepressant. Low doses and dilute solutions are recommended as follows:

- intracavernosal injection of phenylephrine 100 to 200 micrograms (0.5 to 1 mL of a 200 micrograms/mL solution) every 5 to 10 minutes; maximum total dose 1 mg

alternatively

- intracavernosal injection of adrenaline 10 to 20 micrograms (0.5 to 1 mL of a 20 micrograms/mL solution) every 5 to 10 minutes; maximum total dose 100 micrograms

alternatively

- intracavernosal injection of metaraminol may be used, but it should be noted that fatal hypertensive crises have been reported; metaraminol 100 micrograms (5 mL of a 20 micrograms/mL solution) may be given by careful slow injection every 15 minutes; a maximum total dose of up to 1 mg has been suggested

If necessary the sympathomimetic injections can be followed by further penile aspiration. If sympathomimetics are unsuccessful, urgent surgical referral is required.

Pharmacokinetics

On infusion alprostadil is rapidly metabolised by oxidation during passage through the pulmonary circulation. It is excreted in the urine as metabolites within about 24 hours. Systemic absorption of alprostadil occurs after intracavernosal injection.

References.
1. Cox JW, *et al.* Pulmonary extraction and pharmacokinetics of prostaglandin E_1 during continuous intravenous infusion in patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **137:** 5–12.
2. Cawello W, *et al.* Dose proportional pharmacokinetics of alprostadil (prostaglandin E_1) in healthy volunteers following intravenous infusion. *Br J Clin Pharmacol* 1995; **40:** 273–6.
3. Lea AP, *et al.* Intracavernous alprostadil: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in erectile dysfunction. *Drugs Aging* 1996; **8:** 56–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cardiobron; Prolisina VR; Prostavasin; ***Austral.***: Caverject; Prostin VR; ***Austria***: Alprostapint; Caverject; Minprog; Pridax; Prostavasin; ***Belg.***: Caverject; Prostin VR; ***Braz.***: Aplicav; Caverject; Prostavasin; ***Canad.***: Caverject; Muse; Prostin VR; ***Chile***: Caverject; Prostin Pediatrico; ***China***: Bi Fa Er (比法尔); Bolesi (勃乐斯); Kai Tong (凯彤); Kaishi (凯时); Prostavasin (保达新); Ruitong (锐通); Yu Ge (誉歌); ***Cz.***: Alprestil; Alprostan; Alprostapint; Caverject†; Karon; Muse†; Prostavasin; ***Denm.***: Caverject; Muse; Prostivas; ***Fin.***: Caverject; Muse; Prostivas; ***Fr.***: Caverject; Caverjectdual; Edex; Muse; Prostine VR; ***Ger.***: Caverject; Minprog; Muse; Pridax; Prostavasin; Viridal; ***Gr.***: Caverject; Edex; Muse; Prostavasin; Prostin VR; ***Hong Kong***: Befar; Caverject; Eglandin†; Prostavasin†; Prostin VR; ***Hung.***: Alprestil; Alprostapint†; Caverject; Prostavasin; Prostin VR; ***India***: Alpostin; Bioglandin; Prostin VR; ***Irl.***: Caverject; Muse; Viridal; ***Israel***: Alprostapint†; Caverject; Prostin VR; ***Ital.***: Alprostar; Caverject; Muse; Prostavasin; Prostin VR; Viridal†; ***Jpn***: Liple; Palux; Prostandin; ***Malaysia***: Caverject; Prostin VR; ***Mex.***: Caverject; ***Neth.***: Muse; Prostin VR; ***Norw.***: Bondil; Caverject; Prostivas; ***NZ***: Caverject; Prostin VR; ***Pol.***: Caverject†; Prostavasin; Prostin VR; ***Port.***: Caverject; Muse; Prostin VR; Vasoprost; ***Rus.***: Alprostan (Алпростан); Caverject (Каверджект); Prostin VR (Простин ВР); Vasaprostan (Вазапростан); ***S.Afr.***: Caverject; Muse†; Prostin VR; ***Singapore***: Caverject; Prostin VR; ***Spain***: Caverject; Muse; Sugiran; ***Swed.***: Bondil; Caverject; Prostivas; ***Switz.***: Caverject; Muse; Prostin VR; ***Thai.***: Prostin VR; ***UK***: Caverject; Muse; Prostin VR; Viridal; ***Ukr.***: Vazaprostan (Вазапростан); ***USA***: Caverject; Edex; Muse; Prostin VR; ***Venez.***: Caverject.

Multi-ingredient Preparations. ***USA***: Tri-Mix.

Pharmacopoeial Preparations
USP 36: Alprostadil Injection.

Aminotadalafil

Аминотадалафил.
6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-amino-pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione.
$C_{21}H_{18}N_4O_4$=390.4
UNII — FY501QO030.

Profile

Aminotadalafil is an analogue of tadalafil (p. 2368.1) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction.

Avanafil *(USAN, rINN)*

Avanafilo; Avanafilum; TA-1790; Аванафил.
4-[(3-Chloro-4-methoxybenzyl)amino]-2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]-*N*-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide.
$C_{23}H_{26}ClN_7O_3$=483.0
CAS — 330784-47-9.
UNII — DR5S136IVO.

Uses and Administration

Avanafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used orally in the management of erectile dysfunction (p. 2348.2). The usual dose is 100 mg taken about 30 minutes before sexual intercourse. The dose may be increased to 200 mg, or decreased to 50 mg, depending on response. Avanafil should not be taken more than once in 24 hours.

In patients stabilised on alpha blocker therapy, the initial dose of avanafil should be no more than 50 mg daily. A maximum dose of 50 mg daily is also advised in patients taking avanafil with moderate inhibitors of cytochrome P450 isoenzyme CYP3A4.

References.

1. Limin M, *et al.* Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. *Expert Opin Invest Drugs* 2010; **19:** 1427–37.
2. Alwaal A, *et al.* Future prospects in the treatment of erectile dysfunction: focus on avanafil. *Drug Des Devel Ther* 201 1; **5:** 435–43.
3. Goldstein I, *et al.* A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med* 2012; **9:** 1122–33.
4. Segal R, Burnett AL. Avanafil for the treatment of erectile dysfunction. *Drugs Today* 2012; **48:** 7–15.
5. Zhao C, *et al.* Efficacy and safety of avanafil for treating erectile dysfunction: results of a multicentre, randomized, double-blind, placebo-controlled trial. *BJU Int* 2012. Available at: doi:10.1111/j.1464-410X.2012.11095.x

Adverse Effects and Precautions

As for Sildenafil, p. 2365.2 and p. 2366.2. The use of avanafil is not recommended in patients with severe hepatic or renal impairment or in dialysis patients; however, this is due to a lack of data and no dosage adjustment is needed in mild or moderate hepatic (Child-Pugh class A or B) or renal (creatinine clearance of 30 to less than 90 mL/min) impairment.

Interactions

As for Sildenafil, p. 2366.3. Avanafil should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4. When given with moderate CYP3A4 inhibitors, dosage of avanafil must be reduced and suggested doses are given below (above). An enhanced hypotensive effect may be seen if avanafil is taken with substantial amounts of alcohol.

Pharmacokinetics

Avanafil is rapidly absorbed after an oral dose. Peak plasma concentrations occur within a median of 30 to 45 minutes; the rate of absorption is reduced when avanafil is given with a high-fat meal although this is considered to have minimal clinical significance. It is about 99% bound to plasma proteins.

Avanafil is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4 and to a minor extent by the CYP2C isoform. Two major metabolites are produced, one of which is active. Avanafil is excreted as metabolites mainly in the faeces (about 62%), and to a lesser extent in the urine (about 21%). The terminal elimination half-life is about 5 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Stendra.

Benzamidenafil

N-((3,4-dimethoxyphenyl)methyl)-2-(1-hydroxypropan-2-ylamino)-5-nitro-benzamide.
$C_{19}H_{23}N_3O_6$=389.4
CAS — 1020251-53-9.

Profile

Benzamidenafil is a phosphodiesterase type-5 inhibitor that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction.

References.

1. Zou P, *et al.* Identification of benzamidenafil, a new class of phosphodiesterase-5 inhibitor, as an adulterant in a dietary supplement. *J Pharm Biomed Anal* 2008; **47:** 255–9.

Dapoxetine *(rINN)*

Dapoxetina; Dapoxétine; Dapoxetinum; LY-210448; Дапоксетин.
(+)-(*S*)-*N*,*N*-Dimethyl-α-[2-(1-naphthyloxy)ethyl]benzylamine.
$C_{21}H_{23}NO$=305.4
CAS — 119356-77-3.
ATC — G04BX14.
ATC Vet — QG04BX14.
UNII — GB2433A4M3.

Dapoxetine Hydrochloride *(USAN, rINNM)*

Dapoxétine, Chlorhydrate de; Dapoxetini Hydrochloridum; Hidrocloruro de dapoxetina; Дапоксетина Гидрохлорид.
(+)-(*S*)-*N*, *N*-Dimethyl-alpha-[2-(l-naphthyloxy)ethyl]benzylamine hydrochloride.
$C_{21}H_{23}NO$, HCl=341.9
CAS — 129938-20-1.
ATC — G04BX14.
ATC Vet — QG04BX14.
UNII — U4OHT63MRI.

Profile

Dapoxetine is a rapidly absorbed short-acting SSRI used for on-demand treatment of premature ejaculation (p. 2350.2). Dapoxetine is usually given as the hydrochloride, but doses are expressed in terms of the base. A usual oral dose equivalent to dapoxetine 30 or 60 mg is taken 1 to 3 hours before sexual intercourse; this dose should not be taken more than once in 24 hours. Caution is required if the higher dose is given to patients who are taking potent cytochrome P450 isoenzyme CYP2D6 inhibitors or who are slow CYP2D6 metabolisers. A maximum dose of dapoxetine 30 mg is recommended for those taking moderate CYP3A4 inhibitors; dapoxetine is contra-indicated in patients taking potent CYP3A4 inhibitors.

Dapoxetine has been used to adulterate dietary supplements promoted for sexual health.

References.

1. Pryor JL, *et al.* Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet* 2006; **368:** 929–37.
2. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol* 2006; **46:** 301–9.
3. Andersson KE, *et al.* Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation. *BJU Int* 2006; **97:** 311–15.
4. Dresser MJ, *et al.* Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: impact of age and effects of a high-fat meal. *J Clin Pharmacol* 2006; **46:** 1023–9.
5. Shabsigh R, *et al.* Perceived control over ejaculation is central to treatment benefit in men with premature ejaculation: results from phase III trials with dapoxetine. *BJU Int* 2008; **102:** 824–8.
6. Kaufman JM, *et al.* Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. *BJU Int* 2009; **103:** 651–8.
7. Buvat J, *et al.* Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. *Eur Urol* 2009; **55:** 957–67.
8. Hellstrom WJG. Emerging treatments for premature ejaculation: focus on dapoxetine. *Neuropsychiatr Dis Treat* 2009; **5:** 37–46.
9. McMahon C, *et al.* Dapoxetine 3003 Study Investigators. Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. *J Sex Med* 2010; **7:** 256–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Extensil; ***Austria***: Priligy; ***Fin.***: Priligy; ***Ger.***: Priligy; ***Irl.***: Priligy; ***Ital.***: Priligy; ***Malaysia***: Priligy; ***Neth.***: Priligy; ***NZ***: Priligy; ***Port.***: Priligy; ***Singapore***: Priligy; ***Spain***: Priligy; ***Swed.***: Priligy; ***UK***: Priligy.

Darifenacin *(BAN, USAN, rINN)*

Darifenacina; Darifénacine; Darifenacinum; UK-88525; Дарифенацин.
(*S*)-1-[2-(2,3-Dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-3-pyrrolidineacetamide.
$C_{28}H_{30}N_2O_2$=426.6
CAS — 133099-04-4.
ATC — G04BD10.
ATC Vet — QG04BD10.
UNII — APG9B19VLM.

Darifenacin Hydrobromide

(BANM, USAN, rINNM)

Darifénacine, Bromhydrate de; Darifenacini Hydrobromidum; Hidrobromuro de darifenacina; UK-88525-04; Дарифенацина Гидробромид.
(*S*)-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide.
$C_{28}H_{30}N_2O_2$,HBr=507.5
CAS — 133099-07-7.
ATC — G04BD10.
ATC Vet — QG04BD10.
UNII — CR02EYQ8GV.

Uses and Administration

Darifenacin is a selective M_3 antimuscarinic with actions similar to those of atropine (p. 1310.3); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder.

Darifenacin is used in the management of urinary frequency, urgency, and incontinence in detrusor instability (p. 2349.2). It is given orally as the hydrobromide but doses are described in terms of the base: darifenacin hydrobromide 8.9 mg is equivalent to about 7.5 mg of darifenacin. The usual initial dose is the equivalent of darifenacin 7.5 mg once daily; after 2 weeks of treatment this may be increased to 15 mg once daily if necessary.

The starting dose of 7.5 mg should only be increased with caution in patients also receiving potent inhibitors of the cytochrome P450 isoenzyme CYP2D6, such as paroxetine and terbinafine. Darifenacin should be avoided, or a dose of 7.5 mg daily not exceeded, in patients also receiving potent inhibitors of CYP3A4, such as HIV-protease inhibitors, ketoconazole, and itraconazole. The dose of darifenacin should be increased with caution in the presence of moderate inhibitors of CYP3A4, such as macrolide antibacterials, fluconazole, and grapefruit juice.

Darifenacin should be used with caution in hepatic impairment, see below.

Darifenacin is being studied in irritable bowel syndrome.

References.

1. Haab F, *et al.* Darifenacin, an M_3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol* 2004; **45:** 420–9.
2. Chapple C, *et al.* A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M_3 selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* 2005; **95:** 993–1001.
3. Foote J, *et al.* Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M_3 selective receptor antagonist. *Eur Urol* 2005; **48:** 471–7.
4. Parsons M, *et al.* Darifenacin in the treatment of overactive bladder. *Int J Clin Pract* 2005; **59:** 831–8.
5. Hill S, *et al.* Long-term darifenacin treatment for overactive bladder in patients aged 65 years and older: analysis of results from a 2-year, open-label extension study. *Curr Med Res Opin* 2007; **23:** 2697–2704.
6. Dwyer P, *et al.* Long-term benefits of darifenacin treatment for patient quality of life: results from a 2-year extension study. *Neurourol Urodyn* 2008; **27:** 540–7.

Administration in hepatic impairment. Licensed product information states that the oral dose of darifenacin should not exceed 7.5 mg once daily in patients with moderate hepatic impairment (Child-Pugh category B), and its use should be avoided in severe impairment (Child-Pugh category C).

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Darifenacin should be used with caution in patients also receiving inhibitors of cytochrome P450 isoenzymes (see Interactions, below and Uses and Administration, above). It should also be used with caution in hepatic impairment (see Administration in Hepatic Impairment, above).

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Exposure to darifenacin may be increased by drugs that inhibit the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Inducers of CYP3A4 may reduce plasma concentrations of darifenacin. Dosage adjustment for darifenacin may be necessary (see Uses and Administration, above). Darifenacin itself is also a moderate inhibitor of CYP2D6.

Pharmacokinetics

After an oral dose, darifenacin is subject to extensive first-pass metabolism and has a bioavailability of about 15 to 19%. It is about 98% bound to plasma proteins. Darifenacin is metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The pharmacokinetics of darifenacin at steady state are dose-dependent because of the saturation of CYP2D6 metabolism. Most of a dose is excreted as metabolites in the urine and faeces.

References.

1. Kerbusch T, *et al.* Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability. *Br J Clin Pharmacol* 2003; **56:** 639–52.
2. Devineni D, *et al.* Pharmacokinetics of darifenacin, an M_3 selective receptor antagonist: effects of renal or hepatic impairment. *Br J Clin Pharmacol* 2005; **59:** 632–3.
3. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* 2006; **45:** 325–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Continex; Darisec; Enablex; Extracta†; ***Austral.***: Enablex; ***Belg.***: Emselex; ***Braz.***: Enablex; ***Canad.***: Enablex; ***Cz.***: Emselex; ***Denm.***: Emselex; ***Ger.***: Emselex;

Gr.: Emselex; *Hung.*: Emselex; *India*: Dariten-OD; *Irl.*: Emselex; *Neth.*: Emselex; *Norw.*: Emselex; *Pol.*: Emselex; *Port.*: Emselex; *Rus.*: Enablex (Энаблекс); *S.Afr.*: Enablex; *Swed.*: Emselex; *Switz.*: Emselex; *Turk.*: Emselex; *UK*: Emselex; *USA*: Enablex.

Desmopressin (BAN, rINN) ⊗

DDAVP; Desmopresina; Desmopresinas; Desmopressiini; Desmopressine; Desmopressinum; Dezmopresszin; Десмопрессин.

1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin; [1-Deamino,8-D-arginine]vasopressin.

$C_{46}H_{64}N_{14}O_{12}S_2$=1069.2

CAS — 16679-58-6.

ATC — H01BA02.

ATC Vet — QH01BA02.

UNII — ENR1LLB0FP.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Desmopressin). A synthetic cyclic nonapeptide, available as an acetate. A white or almost white, fluffy powder. Soluble in water, in alcohol, and in glacial acetic acid. Store in airtight containers at 2 degrees to 8 degrees. Protect from light.

Desmopressin Acetate (BANM, USAN, rINNM) ⊗

Acetato de desmopresina; Desmopresin Asetat; Desmopresina, acetato de; Desmopressine, Acétate de; Desmopressini Acetas; Десмопрессина Ацетат.

$C_{46}H_{64}N_{14}O_{12}S_2,C_2H_4O_2,3H_2O$=1183.3

CAS — 62288-83-9 (anhydrous desmopressin acetate); 62357-86-2 (desmopressin acetate trihydrate).

ATC — H01BA02.

ATC Vet — QH01BA02.

UNII — XB13HYU18U.

Pharmacopoeias. In *US.*

USP 36: (Desmopressin Acetate). A white, fluffy powder. Soluble in water, in alcohol, and in acetic acid. Store in airtight containers at a temperature not exceeding 25 degrees, but preferably between 2 degrees and 8 degrees. Protect from light.

Units

27 units of desmopressin are contained in about 27 micrograms of desmopressin (with 5 mg of human albumin and citric acid) in one ampoule of the first International Standard (1980).

Uses and Administration

Desmopressin is a synthetic analogue of vasopressin (p. 2642.3). It has greater antidiuretic activity and a more prolonged action than vasopressin or lypressin. It also stimulates factor VIII and plasminogen activator activity in the blood, but has little pressor activity.

Desmopressin is used in the diagnosis and treatment of cranial diabetes insipidus, in the treatment of nocturnal enuresis, in tests of renal function, and for post-dural puncture headache. It is also used in the management of mild or moderate haemophilia and type I von Willebrand's disease, and in tests of fibrinolytic response.

It is given as the acetate, orally, as a solution intranasally, and by injection. The intranasal dose is about ten times that required intravenously and the oral dose about ten times greater than the intranasal dose. Doses are usually expressed in terms of desmopressin acetate, but for some preparations they are given in terms of the base; 110.7 micrograms of desmopressin acetate is equivalent to about 100 micrograms of desmopressin.

In the control of **cranial diabetes insipidus**, desmopressin acetate is given orally in usual initial doses of 100 micrograms three times daily. Doses may be adjusted according to response, with maintenance doses usually between 100 and 200 micrograms three times daily though total doses of between 100 micrograms and 1200 micrograms daily have been used.

A sublingual lyophilisate preparation containing desmopressin acetate is also available in the UK, but doses are expressed in terms of the base. The initial dose is equivalent to 60 micrograms of desmopressin given sublingually three times daily. The dose may be adjusted, with usual maintenance doses between 60 and 120 micrograms three times daily, though total doses of up to 720 micrograms daily have been used.

Desmopressin acetate may also be used intranasally in usual doses of 10 to 40 micrograms daily as a single dose or in divided doses.

It may also be given subcutaneously, intramuscularly, or intravenously in a dose of 1 to 4 micrograms daily.

A single intranasal dose of 20 micrograms or 2 micrograms subcutaneously or intramuscularly has been given in the **diagnosis** of diabetes insipidus.

In the **testing of renal function**, desmopressin acetate has been given intranasally in single doses of 40 micrograms and subcutaneously or intramuscularly in doses of 2 micrograms.

For **post-dural puncture headache**, a dose of desmopressin acetate 4 micrograms may be given by subcutaneous or intramuscular injection, either immediately before lumbar puncture or when headache occurs, and repeated after 24 hours if necessary (but see also p. 2356.2).

In the management of **primary nocturnal enuresis**, desmopressin acetate is given at bedtime in usual oral doses of 200 to 400 micrograms. The sublingual lyophilisate preparation may be given in a dose equivalent to desmopressin 120 micrograms, increasing to 240 micrograms if needed. The need for continued treatment should be reassessed after 3 months by withdrawing desmopressin for at least 1 week. For the view that nasal preparations should not be used for primary nocturnal enuresis, see Effects on Electrolytes, under Adverse Effects, p. 2356.3. For the control of **nocturia** in multiple sclerosis desmopressin acetate 10 to 20 micrograms intranasally at bedtime is recommended (but see Urinary Incontinence, p. 2356.2).

Desmopressin acetate is used to boost concentrations of factor VIII before surgical procedures in patients with mild to moderate **haemophilia** or **type I von Willebrand's disease**. The usual dose is 300 or 400 nanograms/kg by slow intravenous infusion over 15 to 30 minutes, or by subcutaneous injection, just before surgery. Further doses may be given, although response is reduced with repeated dosage. It may be used similarly to treat spontaneous or trauma-induced bleeding episodes in these patients. It is also given intranasally in doses of 150 micrograms (in patients weighing less than 50 kg) or 300 micrograms; it should be given 0.5 to 2 hours before surgery. Further doses may be given, although response is reduced with repeated dosage.

For **testing of fibrinolytic response** desmopressin acetate may be given by intravenous infusion in doses of 300 or 400 nanograms/kg over 20 minutes, or by subcutaneous injection in a dose of 300 nanograms/kg. A sample of venous blood is taken 20 minutes after completing the infusion and tested for fibrinolytic activity on fibrin plates. Alternatively, a dose of 300 micrograms may be given intranasally 60 minutes before collecting the blood sample.

For details of uses and doses in children, see below.

Administration in children. Although some desmopressin preparations are licensed in the UK and the USA for paediatric use, the indications are generally fewer than for adults and the age ranges are often not specified.

The *BNFC*, however, lists doses for both licensed and unlicensed indications, and the full range of doses, given according to age, is as follows:

Treatment of diabetes insipidus

orally

- neonate: initially 1 to 4 micrograms 2 or 3 times daily, adjusted according to response
- 1 month to 2 years: initially 10 micrograms 2 or 3 times daily, adjusted according to response (range 30 to 150 micrograms daily)
- 2 to 12 years: initially 50 micrograms 2 or 3 times daily, adjusted according to response (range 100 to 800 micrograms daily)
- 12 to 18 years: initially 100 micrograms 2 or 3 times daily, adjusted according to response (range 200 to 1200 micrograms daily)

sublingually

- 2 to 18 years: initially 60 micrograms 3 times daily, adjusted according to response (range 40 to 240 micrograms 3 times daily)

intranasally

- neonate: initially 100 to 500 nanograms, adjusted according to response (range 1.25 to 10 micrograms daily as a single dose or in 2 divided doses)
- 1 month to 2 years: initially 2.5 to 5 micrograms once or twice daily, adjusted according to response
- 2 to 12 years: initially 5 to 20 micrograms once or twice daily, adjusted according to response
- 12 to 18 years: initially 10 to 20 micrograms once or twice daily, adjusted according to response

subcutaneously or *intramuscularly*

- neonate: initially 100 nanograms once daily, adjusted according to response (use the intramuscular route only)
- 1 month to 12 years: initially 400 nanograms once daily, adjusted according to response
- 12 to 18 years: initially 1 to 4 micrograms once daily, adjusted according to response

Test for suspected diabetes insipidus

intranasally

- 1 month to 2 years: 5 to 10 micrograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 10 to 20 micrograms as a single dose
- 12 to 18 years: 20 micrograms as a single dose

subcutaneously or *intramuscularly*

- 1 month to 2 years: 400 nanograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 0.5 to 1 microgram as a single dose
- 12 to 18 years: 1 to 2 micrograms as a single dose

Testing of renal function

intranasally

- 1 month to 1 year: 10 micrograms
- 1 to 15 years: 20 micrograms
- 15 to 18 years: 40 micrograms

subcutaneously or *intramuscularly*

- 1 month to 1 year: 400 nanograms
- 1 to 18 years: 2 micrograms

Test of antidiuretic hormone secretion (congenital deficiency suspected)

intranasally

- 1 month to 2 years: initially 100 to 500 nanograms as a single dose

Test of antidiuretic hormone secretion (congenital deficiency not suspected)

intranasally

- 1 month to 2 years: 1 to 5 micrograms as a single dose

Primary nocturnal enuresis

orally

- 5 to 18 years: 200 micrograms at bedtime, increased if necessary to 400 micrograms

sublingually

- 5 to 18 years: 120 micrograms at bedtime, increased if necessary to 240 micrograms

The need for continued treatment with either route should be reassessed after 3 months by withdrawing desmopressin for at least 1 week

Mild to moderate **haemophilia** or **von Willebrand's disease**

intravenously (infusion over 20 minutes) or *subcutaneously*

- 1 month to 18 years: 300 nanograms/kg as a single dose immediately before surgery or after trauma; the dose may be repeated at intervals of 12 hours if no tachycardia occurs

intranasally

- 1 to 18 years: 4 micrograms/kg as a single dose; for pre-operative use give 2 hours before the procedure

Testing of fibrinolytic response

intravenously (infusion over 20 minutes) or *subcutaneously*

- 2 to 18 years: 300 nanograms/kg as a single dose; blood is sampled after 20 minutes for fibrinolytic activity

Administration in renal impairment. While most UK licensed product information recommends caution when using desmopressin in patients with reduced renal function, *Desmospray (Ferring, UK)* and US licensed product information contra-indicates its use in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50 mL/min). This contra-indication has been questioned,[1] as the risk of hyponatraemia usually associated with desmopressin (see Effects on Electrolytes, p. 2356.3) is reduced in chronic kidney disease. This is due to a loss of urinary-concentrating ability (reducing the diuretic effect of desmopressin), and a limited volume of filtered water for the desmopressin to act on. Adjusting the dose according to response has been suggested as a suitable way of giving desmopressin to patients with chronic kidney disease.

1. Sica DA, Gehr TWB. Desmopressin: safety considerations in patients with chronic renal disease. *Drug Safety* 2006; **29:** 553–6.

Diabetes insipidus. Desmopressin is the usual treatment for cranial diabetes insipidus (p. 2348.2).

Haemorrhagic disorders. Desmopressin is used in the management of patients with mild haemophilia A, carriers of haemophilia with low factor VIII concentrations, and patients with acquired haemophilia who have low titres of antibodies to factor VIII (see Haemophilias, p. 1126.3). Desmopressin is also used in von Willebrand's disease (p. 1129.3). The use of desmopressin results in a two- to sixfold increase in plasma concentrations of factor VIII and von Willebrand factor,[1] and patients must have measurable baseline concentrations of these factors in order to respond to desmopressin.[1,2] In general, a baseline factor VIII concentration of 0.1 to 0.15 units/mL is needed to achieve post-injection concentrations of about 0.3 to 0.5 units/mL, which are generally sufficient for minor bleeding or lesser procedures. Concentrations of at least 0.7 to 1 unit/mL must be achieved for major surgery.[1] Desmopressin can be given subcutaneously, but the peak levels of factor VIII are reached later than after intra-

venous use. Intranasal use is also effective and allows patients to treat bleeding episodes themselves, without delay, outside hospital.[1] The use of desmopressin as an alternative to blood products has been recommended whenever possible in the treatment of these disorders, as a precaution against blood-borne infection.[1]

Bleeding due to liver disease has been controlled by desmopressin,[3,4] as has that associated with uraemia[5-8] (but for a report of tolerance to the effects of repeated doses of desmopressin in uraemic patients, see under Adverse Effects and Precautions, p. 2357.1), and there are reports of bleeding being controlled in other disorders such as telangiectasia[9] and platelet storage deficiency.[10-12] See also Haemorrhagic Disorders in Vasopressin (p. 2643.3), and Variceal Haemorrhage in Vasopressin (p. 2643.3) and Terlipressin (p. 2627.2). Desmopressin has also been tried for excessive or heavy menstrual bleeding with mixed results.[13]

Desmopressin has also had conflicting results in surgical procedures.[2] A meta-analysis, which mainly included studies in cardiac surgery, found no evidence that desmopressin reduces perioperative blood transfusion in patients who do not have congenital bleeding disorders.[14] A possible role for desmopressin has been proposed in the control of surgical bleeding in patients whose religious beliefs preclude the use of blood products.[15,16] It has also been reported to be effective in postoperative aspirin-related bleeding that was previously unresponsive to clotting factors.[17] However, studies of prophylactic desmopressin given to patients who had received aspirin in the 7 days before cardiac bypass surgery have produced conflicting results, with desmopressin either reducing blood loss[18] or having no effect.[19]

1. Lethagen S. Desmopressin in mild hemophilia A: indications, limitations, efficacy, and safety. *Semin Thromb Hemost* 2003; **29:** 101–5.
2. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90:** 2515–21.
3. Burroughs AK, *et al*. Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1985; **291:** 1377–81.
4. Rak K, *et al*. Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1986; **292:** 138.
5. Mannucci PM, *et al*. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983; **308:** 8–12.
6. Shapiro MD, Kelleher SP. Intranasal deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *Am J Nephrol* 1984; **4:** 260–1.
7. Viganò GL, *et al*. Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. *Am J Hematol* 1989; **31:** 32–5.
8. Jacquot C, *et al*. Addition of desmopressin to recombinant human erythropoietin in treatment of haemostatic defect of uraemia. *Lancet* 1988; **i:** 420.
9. Quitt M, *et al*. The effect of desmopressin on massive gastrointestinal bleeding in hereditary telangiectasia unresponsive to treatment with cryoprecipitate. *Arch Intern Med* 1990; **150:** 1744–6.
10. Nieuwenhuis HK, Sixma JJ. 1-Desamino-8-D-arginine vasopressin (desmopressin) shortens the bleeding time in storage pool deficiency. *Ann Intern Med* 1988; **108:** 65–7.
11. Castaman G, Rodeghiero F. Consistency of responses to separate desmopressin infusions in patients with storage pool disease and isolated prolonged bleeding time. *Thromb Res* 1993; **69:** 407–12.
12. Zatik J, *et al*. Variable response of Hermansky-Pudlak syndrome to prophylactic administration of 1-desamino 8D-arginine in subsequent pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2002; **104:** 165–6.
13. Fraser IS, *et al*. A benefit-risk review of systemic haemostatic agents, part 2: in excessive or heavy menstrual bleeding. *Drug Safety* 2008; **31:** 275–82.
14. Carless PA, *et al*. Desmopressin for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 15/09/05).
15. Martens PR. Desmopressin and Jehovah's witness. *Lancet* 1989; **i:** 1322.
16. Beholz S, *et al*. Use of desmopressin and erythropoietin in an anaemic Jehovah's Witness patient with severely impaired coagulation capacity undergoing stentless aortic valve replacement. *Perfusion* 2001; **16:** 485–9.
17. Chard RB, *et al*. Use of desmopressin in the management of aspirin-related and intractable haemorrhage after cardiopulmonary bypass. *Aust N Z J Surg* 1990; **60:** 125–8.
18. Sheridan DP, *et al*. Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Can J Surg* 1994; **37:** 33–6.
19. Pleym H, *et al*. Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. *Anesth Analg* 2004; **98:** 578–84.

Nocturnal enuresis. Desmopressin is one of the main drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of nocturnal enuresis in children (p. 2349.1). Secretion of vasopressin during the night in normal individuals reduces urine output and it has been suggested that nocturnal enuresis in some children might be due to impaired nocturnal secretion of vasopressin. However, other possible mechanisms include bladder instability and reduced nightly functional bladder capacity, and it has been proposed that treatment should be based on a greater consideration of nocturnal enuresis as a multifactorial condition.[1]

The synthetic vasopressin analogue desmopressin is used for its presumed antidiuretic effect on the kidney,[2] although there is some evidence that it may act by some other mechanism, possibly having a central effect.[3,4] It has been shown that desmopressin given at night can be effective in the short-term control of nocturnal enuresis[2,5] and many now consider it to be the drug of choice in terms of safety.[6,7] There is some evidence[8,9] that long-term use of desmopressin is also effective. However, a meta-analysis suggested that benefit might not be sustained once the drug was stopped.[10] Desmopressin should not be given when enuresis is due to polydipsia as it may provoke water intoxication and convulsions due to hyponatraemia. For precautions to be observed when desmopressin is used to treat enuresis, and the view that nasal formulations should not be used for this indication, see Effects on Electrolytes, below.

1. Butler RJ, *et al*. Investigating the three systems approach to complex childhood nocturnal enuresis. *Scand J Urol Nephrol* 2004; **38:** 117–21.
2. Müller D, *et al*. Comparative tolerability of drug treatment for nocturnal enuresis in children. *Drug Safety* 2004; **27:** 717–27.
3. Jonat S, *et al*. Effect of DDAVP on nocturnal enuresis in a patient with nephrogenic diabetes insipidus. *Arch Dis Child* 1999; **81:** 57–9.
4. Müller D, *et al*. Desmopressin for nocturnal enuresis in nephrogenic diabetes insipidus. *Lancet* 2002; **359:** 495–7.
5. Moffat MEK, *et al*. Desmopressin acetate and nocturnal enuresis: how much do we know? *Pediatrics* 1993; **92:** 420–5.
6. Van de Walle J, *et al*. Is there still a role for desmopressin in children with primary monosymptomatic nocturnal enuresis? A focus on safety issues. *Drug Safety* 2010; **33:** 261–71.
7. NICE. Nocturnal enuresis: the treatment of bedwetting in children and young people (issued October 2010). Available at: http://www.nice.org.uk/nicemedia/live/13246/51367/51367.pdf (accessed 18/11/10)
8. Hjälmås K, *et al*. Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multicentre study. *Br J Urol* 1998; **82:** 704–9.
9. Wolfish NM, *et al*. The Canadian Enuresis Study and Evaluation: short- and long-term safety and efficacy of an oral desmopressin preparation. *Scand J Urol Nephrol* 2003; **37:** 22–7.
10. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 15/09/05).

Orthostatic hypotension. The first drug tried in patients with orthostatic hypotension (p. 1634.3) who cannot be managed by nonpharmacological methods is usually fludrocortisone, but desmopressin is sometimes useful in patients with central neurological abnormalities.[1]

1. Mathias CJ, *et al*. The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. *BMJ* 1986; **293:** 353–4.

Post-dural puncture headache. Desmopressin acetate is licensed for use in the UK subcutaneously or intramuscularly for the treatment or prophylaxis of headache due to lumbar puncture. However, published evidence to support this appears to be scanty, and many patients respond to conservative treatment (see p. 1979.1).

References.
1. Durward WF, Harrington H. Headache after lumbar puncture. *Lancet* 1976; **ii:** 1403–4.
2. Widerlöv E, Lindström L. DDAVP and headache after lumbar puncture. *Lancet* 1979; **i:** 548.
3. Hansen PE, Hansen JH. DDAVP, a synthetic analogue of vasopressin, in prevention of headache after lumbar puncture and lumbar pneumoencephalography. *Acta Neurol Scand* 1979; **60:** 183–8.
4. Cowan JMA, *et al*. DDAVP in the prevention of headache after lumbar puncture. *BMJ* 1980; **280:** 224.

Renal colic. Intranasal desmopressin is being studied[1] in the management of the pain of acute renal colic (p. 6.3).

1. Zabihi N, Teichman JMH. Dealing with the pain of renal colic. *Lancet* 2001; **358:** 437–8.

Urinary incontinence. Desmopressin given intranasally appeared to be effective in reducing voiding frequency/incontinence when studied in 26 patients with multiple sclerosis whose bladder dysfunction had previously been unresponsive to antimuscarinics;[1] similar results have been reported in other small studies in patients with multiple sclerosis.[2] However, a review of studies using desmopressin to treat nocturia in such patients cast doubt on the clinical relevance of the limited reductions achieved in voiding frequency.[3] Nevertheless, beneficial long-term use of desmopressin for nocturia has been described, with some patients also using it intermittently during the daytime to control symptoms for special occasions.[4] Oral desmopressin has been reported to have a favourable effect on measures such as the number of nocturnal voids and duration of sleep until the first nocturnal void in women[5] and men[6] with nocturia. Beneficial effects were maintained or improved in many responders who were treated for a further 10 or 12 months.[7] In the management of daytime urinary incontinence in women, an improvement in the incidence of periods without leakage during the 4 hours after an intranasal dose of desmopressin has been reported.[8]

For the usual treatment of incontinence, see Urinary Incontinence and Retention, p. 2349.2.

1. Fredrikson S. Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. *Acta Neurol Scand* 1996; **94:** 31–4.
2. Cvetković RS, Plosker GL. Desmopressin: in adults with nocturia. *Drugs* 2005; **65:** 99–107.
3. Ferreira E, Letwin SR. Desmopressin for nocturia and enuresis associated with multiple sclerosis. *Ann Pharmacother* 1998; **32:** 114–16.
4. Tubridy N, *et al*. Long term use of desmopressin for urinary symptoms in multiple sclerosis. *Multiple Sclerosis* 1999; **5:** 416–17.
5. Lose G, *et al*. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003; **189:** 1106–13.
6. Mattiasson A, *et al*. Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int* 2002; **89:** 855–62.
7. Lose G, *et al*. Clinical experiences with desmopressin for long-term treatment of nocturia. *J Urol (Baltimore)* 2004; **172:** 1021–5.
8. Robinson D, *et al*. Antidiuresis: a new concept in managing female daytime urinary incontinence. *BJU Int* 2004; **93:** 996–1000.

Adverse Effects and Precautions

Adverse effects of desmopressin include headache, nausea, and mild abdominal cramps; there may be pain and swelling at the site of injection. With large intravenous doses hypotension, with tachycardia and facial flushing, may occur; some patients may experience an increase in blood pressure. Occasionally there may be cerebral or coronary thrombosis. Hypersensitivity reactions have also occurred. The antidiuretic action of desmopressin can produce water intoxication and hyponatraemia, occasionally leading to convulsions. The incidence of hyponatraemia may be higher with nasal formulations than with oral formulations. Nasal doses may cause local irritation, congestion, and epistaxis.

Precautions to be observed with desmopressin are similar to those for vasopressin (see p. 2644.1). It should not be given to patients with type IIB von Willebrand's disease, in whom the release of clotting factors may lead to platelet aggregation and thrombocytopenia. Caution is required with patients who have impaired renal function, see Administration in Renal Impairment, p. 2355.3. When desmopressin is used diagnostically, or for the treatment of enuresis, the fluid intake should be limited to a minimum and only to satisfy thirst from 1 hour before to 8 hours after use (see also Effects on Electrolytes, below).

Effects on the cardiovascular system. Facial flushing and warmth after intravenous desmopressin reflect a vasodilator action[1] or may be due to an opioid mechanism in the CNS.[2] A drop in diastolic blood pressure of about 14 mmHg and an increase in heart rate of 20 beats/minute are the rule during intravenous infusion of desmopressin in doses of 400 nanograms/kg or more.[1] The hypotensive effects of desmopressin were responsible for a serious reaction, involving cyanosis and dyspnoea, in a 21-month-old child with cyanotic heart disease.[3] Thrombosis (including myocardial infarction)[4-6] and cerebral infarction[7] have been associated rarely with the use of intravenous desmopressin. An analysis[8] of events in patients undergoing major surgery suggested, however, that co-existing conditions in elderly patients and the surgical procedures themselves were associated with a high risk of thrombosis, and that desmopressin did not increase the incidence of thrombotic events.

Licensed product information also warns of the possibility of an increase in blood pressure.

1. Brommer EJP, *et al*. Desmopressin and hypotension. *Ann Intern Med* 1985; **103:** 962.
2. Pigache RM. Facial flushing induced by vasopressin-like peptides lacking pressor activity. *J Clin Pharmacol* 1984; **17:** 369–71.
3. Israels SJ, Kobrinsky NL. Serious reaction to desmopressin in a child with cyanotic heart disease. *N Engl J Med* 1989; **320:** 1563–4.
4. Anonymous. Desmopressin and arterial thrombosis. *Lancet* 1989; **i:** 938–9.
5. Mannucci PM, Lusher JM. Desmopressin and thrombosis. *Lancet* 1989; **ii:** 675–6.
6. Hartmann S, Reinhart W. Fatal complication of desmopressin. *Lancet* 1995; **345:** 1302–3. Correction. *ibid.;* 1648.
7. Grunwald Z, Sather SDC. Intraoperative cerebral infarction after desmopressin administration in infant with end-stage renal disease. *Lancet* 1995; **345:** 1364–5.
8. Mannucci PM, *et al*. Desmopressin, surgery and thrombosis. *Thromb Haemost* 1994; **71:** 154–5.

Effects on electrolytes. There have been a number of reports of seizures due to hyponatraemia and water intoxication after intranasal[1-8] or intravenous[9] desmopressin. The UK CSM noted in March 1996 that it had received reports of hyponatraemic convulsions in 21 children and 3 adults receiving desmopressin (which it somewhat inaccurately described as vasopressin).[10] It was recommended that when this drug was used to treat primary nocturnal enuresis the risks of hyponatraemia should be minimised by

- avoiding concomitant use of drugs, such as *tricyclic antidepressants*, that increase endogenous ADH secretion
- keeping to the recommended starting dose
- avoiding excessive fluid intake, including ingestion of water during swimming
- stopping treatment temporarily if vomiting or diarrhoea occurred, to allow recovery of normal fluid and electrolyte balance

Some have suggested that no more than 240 mL of fluid should be ingested on nights when desmopressin is given.[7] Others have suggested that serum-sodium concentrations be measured 24 to 48 hours, 1 week, and 1 month after starting treatment with desmopressin.[8] A systematic review[11] of the risk in older patients being treated for nocturia, which found the incidence of hyponatraemia to be about 8%, also recommended regular monitoring. Others[12] have gone further and do not recommend desmopressin be used to treat nocturia or nocturnal polyuria in frail or elderly patients.

In April 2007, the MHRA requested that the indication for the treatment of primary nocturnal enuresis be removed from desmopressin nasal spray formulations in the UK. Compared with oral formulations, nasal forms were associated with most of the serious adverse effects reported in patients with primary nocturnal enuresis; these included hyponatraemia, water intoxication, and convulsions. Hyponatraemia was reported at a rate of about 15 cases per 100 000 years of patient exposure for nasal dosage forms, compared with 6 cases per 100 000 patient years for oral formulations; hyponatraemia was mainly associated with overdose, excessive fluid intake, or inappropriate use.[13] Similar warnings have been issued by other regulatory authorities, including the FDA.[14]

1. Simmonds EJ, *et al*. Convulsions and coma after intranasal desmopressin in cystic fibrosis. *BMJ* 1988; **297:** 1614.
2. Salvatoni A, *et al*. Hyponatremia and seizures during desmopressin acetate treatment in hypothyroidism. *J Pediatr* 1990; **116:** 835–6.
3. Davis RC, *et al*. Nocturnal enuresis. *Lancet* 1992; **340:** 1550.
4. Hamed M, *et al*. Hyponatraemic convulsion associated with desmopressin and imipramine treatment. *BMJ* 1993; **306:** 1169.
5. Hourihane J, Salisbury AJ. Use caution in prescribing desmopressin for nocturnal enuresis. *BMJ* 1993; **306:** 1545.
6. Robson WLM, Leung AKC. Hyponatraemia following desmopressin. *BMJ* 1993; **307:** 64–5.
7. Robson WLM, *et al*. Hyponatremia in patients with nocturnal enuresis treated with DDAVP. *Eur J Pediatr* 1996; **155:** 959–62.
8. Odeh M, Oliven A. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. *J Clin Pharmacol* 2001; **41:** 582–4.
9. Shepherd LL, *et al*. Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. *J Pediatr* 1989; **114:** 470–2.
10. CSM/MCA Hyponatraemic convulsions in patients with enuresis treated with vasopressin. *Current Problems* 1996; **22:** 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 21/01/09)
11. Weatherall M. The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. *Neurourol Urodyn* 2004; **23:** 302–5.
12. Schröder A. *et al*. European Association of Urology. Guidelines on urinary incontinence (updated April 2010). Available at: http://www.uroweb.org/gls/pdf/16_Urinary_Incontinence%202010.pdf (accessed 03/10/11)
13. MHRA. Desmopressin nasal spray: removal of the primary nocturnal enuresis (bedwetting) indication (issued 18th April 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2030795 (accessed 02/09/08)
14. FDA. Information for healthcare professionals: desmopressin acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray) (issued 4th December 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm (accessed 11/06/08)

Effects on the eyes. Pseudotumor cerebri associated with desmopressin treatment has been reported in a patient.[1]

1. Neely DE, *et al*. Desmopressin (DDAVP)-induced pseudotumor cerebri. *J Pediatr* 2003; **143:** 808.

Effects on mental function. Paranoid psychosis occurred after desmopressin therapy in a patient with Alzheimer's dementia.[1]

1. Collins GB, *et al*. Paranoid psychosis after DDAVP therapy for Alzheimer's dementia. *Lancet* 1981; **ii:** 808.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desmopressin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Tolerance. In 3 uraemic patients desmopressin infusion produced an initial shortening of the bleeding time but after repeated infusions this response was reduced and there was even some increase in baseline bleeding times.[1] Two infusions of desmopressin 300 nanograms/kg in one day appear to induce a near maximum response; different treatment is required subsequently.

1. Canavese C, *et al*. Reduced response of uraemic bleeding time to repeated doses of desmopressin. *Lancet* 1985; **i:** 867–8.

Interactions

As for Vasopressin, p. 2644.2. See also Effects on Electrolytes, p. 2356.3. NSAIDs, such as ibuprofen (see Effects on Electrolytes under Ibuprofen, p. 69.3) and indometacin, may enhance the antidiuretic effect of desmopressin.

Gastrointestinal drugs. In a study[1] in healthy subjects, *loperamide* caused a threefold increase in the gastrointestinal absorption of oral desmopressin, presumably by slowing gastrointestinal motility. In the same study, however, increased motility caused by *erythromycin* did not affect desmopressin absorption.

1. Callréus T, *et al*. Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur J Clin Pharmacol* 1999; **55:** 305–9.

Pharmacokinetics

Desmopressin is absorbed from the nasal mucosa with a bioavailability of 10 to 20%. After oral doses it is largely destroyed in the gastrointestinal tract but sufficient is absorbed from high doses to produce therapeutic effects. When given intravenously desmopressin exhibits biphasic pharmacokinetics, with half-lives of about 8 minutes and 75 minutes for the 2 phases respectively.

References.

1. Fjellestad-Paulsen A, *et al*. Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. *Clin Endocrinol (Oxf)* 1993; **38:** 177–82.
2. Lam KSL, *et al*. Pharmacokinetics, pharmacodynamics, long-term efficacy and safety of oral 1-deamino-8-D-arginine vasopressin in adult patients with central diabetes insipidus. *Br J Clin Pharmacol* 1996; **42:** 379–85.
3. Agersø H, *et al*. Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. *Br J Clin Pharmacol* 2004; **58:** 352–8.
4. Østerberg O, *et al*. Pharmacokinetics of desmopressin administrated [sic] as an oral lyophilisate dosage form in children with primary nocturnal enuresis and healthy adults. *J Clin Pharmacol* 2006; **46:** 1204–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Emosint; Octostim; Presinex; ***Austral.***: Minirin; Octostim; ***Austria***: Minirin; Nocutil; Octostim; ***Belg.***: Minirin; Octostim; ***Braz.***: D-Void; DDAVP; ***Canad.***: DDAVP; Minirin; Octostim; ***Chile***: DDAVP; Desmo-C; Octostim; ***China***: Minirin (弥朽); ***Cz.***: Desmospray†; Desmotabs†; Minirin; ***Denm.***: Desmoham; DesmoMelt; Desmopal; Minirin; Minirinmelt; Minurin; Nocutil; Octostim; ***Fin.***: Minirin; Octostim; ***Fr.***: Minirin; Minirinmelt; Octim; ***Ger.***: Desmogalen; Desmospray; Desmotabs; Minirin; Nocturin; Nocutil; Octostim; ***Gr.***: DDAVP; Defirin; Desmoprol; Esmon; Minirin; ***Hong Kong***: Minirin; Octostim; ***Hung.***: Desmopress†; Minirin; Nocutil; Octostim; ***India***: D-Pressin; D-Void; Des-Press; Minirin; ***Irl.***: DDAVP; Desmospray; Desmotabs; Nordurine; ***Israel***: Adin†; Minirin; Octostim; ***Ital.***: Emosint; Minirin/DDAVP; ***Jpn***: Minirinmelt; ***Malaysia***: Minirin; ***Mex.***: Minirin; Nafiset; Octostim; ***Neth.***: Adiuretin†; Minirin†; Minrin; Octostim; ***Norw.***: Minirin; Octostim; ***NZ***: Minirin; Octostim; ***Philipp.***: Minirin; Octostim; ***Pol.***: Minirin; Noctissin; ***Port.***: DDAVP; Desmospray; Minirin; Presinex; ***Rus.***: Emosint (Эмосинт); Minirin (Минирин); Presinex (Пресайнекс); ***S.Afr.***: DDAVP; ***Singapore***: Minirin; ***Spain***: Minurin; Octostim; Wetirin; ***Swed.***: Minirin; Nocutil; Octostim; ***Switz.***: Minirin; Nocutil; Octostim; ***Thai.***: Minirin; ***Turk.***: Desmovital; Minirin; Octostim; ***UK***: DDAVP; DesmoMelt; Desmospray; Desmotabs; Octim; Presinex†; ***Ukr.***: Adiupressin (Адиупрессин); Minirin (Минирин); Uropres (Уропрес); ***USA***: DDAVP; Minirin; Stimate.

Pharmacopoeial Preparations

BP 2014: Desmopressin Injection; Desmopressin Intranasal Solution; Desmopressin Tablets;

USP 36: Desmopressin Acetate Injection; Desmopressin Nasal Spray Solution.

Dutasteride *(BAN, USAN, rINN)*

Dutasterid; Dutasterida; Dutastéride; Dutasteridum; GG-745; GI-198745; GI-198745X; Дутастерид.

α,α,α,α′,α′,α′-Hexafluoro-3-oxo-4-aza-5α-androst-1-ene-17β-carboxy-2′,5′-xylidide; 3-Oxo-2′,5′-bis(trifluoromethyl)-4-aza-5α-androst-1-ene-17β-carboxanilide.

$C_{27}H_{30}F_6N_2O_2$=528.5

CAS — 164656-23-9.

ATC — G04CB02.

ATC Vet — QG04CB02.

UNII — O0J6XJN02I.

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Dutasteride). A white or pale yellow powder. Practically insoluble in water; soluble or sparingly soluble in anhydrous alcohol; freely soluble in dichloromethane.

Uses and Administration

Dutasteride, like finasteride (p. 2358.3), is an inhibitor of 5α-reductase. Unlike finasteride, it is claimed to inhibit both the type-1 and type-2 isoforms of the enzyme. Dutasteride is used in the treatment of benign prostatic hyperplasia (p. 2347.1); it may reduce the incidence of acute urinary retention and the need for surgery. Dutasteride is given in oral doses of 500 micrograms daily, either alone or with the alpha-blocker tamsulosin (p. 2369.1). Response may be delayed and treatment for 6 months may be required to assess whether benefit has been achieved.

Dutasteride is under investigation for the prevention of prostate cancer, and in the treatment of alopecia.

References.

1. Djavan B, *et al*. Dutasteride: a novel dual inhibitor of 5alpha-reductase for benign prostatic hyperplasia. *Expert Opin Pharmacother* 2005; **6:** 311–17. Correction. *ibid.*; 681.
2. Dolder CR. Dutasteride: a dual 5-α reductase inhibitor for the treatment of symptomatic benign prostatic hyperplasia. *Ann Pharmacother* 2006; **40:** 658–64.
3. Keam SJ, Scott LJ. Dutasteride: a review of its use in the management of prostate disorders. *Drugs* 2008; **68:** 463–85.
4. Fenter TC, *et al*. Dutasteride vs finasteride: assessment of differences in acute urinary retention rates and surgical risk outcomes in an elderly population aged ≥ 65 years. *Am J Manag Care* 2008; **14** (suppl 2): S154–S159.
5. Musquera M, *et al*. The REDUCE trial: chemoprevention in prostate cancer using a dual 5α-reductase inhibitor, dutasteride. *Expert Rev Anticancer Ther* 2008; **8:** 1073–9.
6. Rittmaster R, *et al*. Effect of dutasteride on intraprostatic androgen levels in men with benign prostatic hyperplasia or prostate cancer. *Urology* 2008; **72:** 808–12.
7. Roehrborn CG, *et al*. CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol* 2010; **57:** 123–31.
8. Andriole GL, *et al*. REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010; **362:** 1192–1202.

Adverse Effects and Precautions

As for Finasteride, p. 2359.2 and p. 2359.3.

Interactions

Dutasteride is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Dutasteride concentrations may be increased by moderate or potent inhibitors of CYP3A4 and a reduction of the dutasteride dosing frequency may be considered if adverse effects are noted.

Pharmacokinetics

Dutasteride is absorbed from the gastrointestinal tract, reaching a peak serum concentration in 1 to 3 hours, with a bioavailability of about 60%. It is highly bound to plasma proteins. Dutasteride is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and most of a dose is excreted as metabolites in the faeces. At steady state the elimination half-life is about 3 to 5 weeks.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avodart; ***Austral.***: Avodart; ***Austria***: Avodart; Avolve†; ***Belg.***: Avodart; ***Braz.***: Avodart; ***Canad.***: Avodart; ***Chile***: Avodart; ***Cz.***: Avodart; ***Denm.***: Avidart; Avodart; Duagen; ***Fin.***: Avodart; ***Fr.***: Avodart; ***Ger.***: Avodart; ***Gr.***: Avodart; Duagen; ***Hong Kong***: Avodart; ***Hung.***: Avodart; ***India***: Duprost; Dutagen; Dutas; ***Indon.***: Avodart; ***Irl.***: Avodart; ***Israel***: Avodart; ***Ital.***: Avodart; Duagen; ***Malaysia***: Avodart; ***Mex.***: Avodart; ***Neth.***: Avodart; ***Norw.***: Avodart; ***Philipp.***: Avodart; ***Pol.***: Avodart†; ***Port.***: Avodart; Avolve†; Duagen; ***Rus.***: Avodart (Аводарт); ***S.Afr.***: Avodart; ***Singapore***: Avodart; ***Spain***: Avidart; Duagen†; ***Swed.***: Avodart; ***Switz.***: Avodart; ***Thai.***: Avodart; ***Turk.***: Avodart; ***UK***: Avodart; ***Ukr.***: Avodart (Аводарт); ***USA***: Avodart.

Multi-ingredient Preparations. ***Austral.***: Duodart; ***Belg.***: Combodart; ***Canad.***: Jalyn; ***Cz.***: Duodart; ***Denm.***: Combodart; ***Fin.***: Duodart; ***Ger.***: Duodart; ***Gr.***: Duodart; ***India***: Afdura; Dutalfa; Dutas-T; ***Irl.***: Combodart; ***Israel***: Duodart; ***Neth.***: Combodart; ***Norw.***: Duodart; ***Pol.***: Duodart; ***Port.***: Combodart; ***Spain***: Duodart; ***Switz.***: Duodart; ***UK***: Combodart; ***USA***: Jalyn.

Elocalcitol *(rINN)*

BXL-628; Élocalcitol; Elocalcitolum; Эльокальцитол.

(1*S*,3*R*,5*Z*,7*E*,23*E*)-1-Fluoro-26,27-dihomo-9,10-secocholesta-5,7,10(19),16,23-pentaene-3,25-diol.

$C_{29}H_{43}FO_2$=442.7

CAS — 199798-84-0.

UNII — 2WDS5F2V6Q.

NOTE. Do not confuse with eldecalcitol (p. 1182.3).

Profile

Elocalcitol is a derivative of vitamin D (p. 2112.3) that is under investigation for benign prostatic hyperplasia, overactive bladder, and male infertility.

References.

1. Tiwari A. Elocalcitol, a vitamin D3 analog for the potential treatment of benign prostatic hyperplasia, overactive bladder and male infertility. *IDrugs* 2009; **12:** 381–93.

Emepronium Bromide *(BAN, rINN)*

Bromuro de emepronio; Emepronii Bromidum; Emepronio, bromuro de; Émépronium, Bromure d'; Emeproniumbromid; Emeproniumbromidi; Эмепрония Бромид.

Ethyldimethyl(1-methyl-3,3-diphenylpropyl)ammonium bromide.

$C_{20}H_{28}BrN$=362.4

CAS — 27892-33-7 (emepronium); 3614-30-0 (emepronium bromide).

ATC — G04BD01.

ATC Vet — QG04BD01.

UNII — WZM699L2TL.

Emepronium Carrageenate (BAN)

Emepronio, carragenato de.
ATC — G04BD01.
ATC Vet — QG04BD01.

Uses and Administration

Emepronium is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1310.3). It has been used orally as the bromide and the carrageenate in the treatment of urinary frequency and incontinence (p. 2349.2); the bromide has also been given by subcutaneous or intramuscular injection.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that emepronium should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2.

To avoid oesophageal ulceration, tablets of emepronium bromide should always be swallowed with an adequate volume of water, and patients should always be in the sitting or standing position while, and for 10 to 15 minutes after, taking the tablets. Emepronium is contra-indicated in patients with symptoms or signs of oesophageal obstruction or with pre-existing oesophagitis.

Buccal and oesophageal ulceration. Tablet-induced oesophageal damage is a widely recognised problem and is related to direct mucosal injury by the medication. Emepronium bromide has been frequently implicated in this type of mucosal injury, although it rarely results in stricture formation.[1]

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies emepronium as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Emepronium is incompletely absorbed from the gastrointestinal tract and is mainly excreted unchanged in the urine and faeces. It does not readily cross the blood-brain barrier at therapeutic doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Urikrat Novum.

Fesoterodine (BAN, rINN)

Fesoterodina; Fésotérodine; Fesoterodinum; Фезотеродин.
2-[(1*R*)-3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate.
$C_{26}H_{37}NO_3$=411.6
CAS — 286930-02-7.
ATC — G04BD11.
ATC Vet — QG04BD11.
UNII — 621G617227.

Fesoterodine Fumarate (BANM, USAN, rINNM)

Fésotérodine, Fumarate de; Fesoterodini Fumaras; Fumarato de fesoterodina; SPM-907; SPM-8272; Фезотеродина Фумарат.
$C_{26}H_{37}NO_3,C_4H_4O_4$=527.7
CAS — 286930-03-8.
UNII — EOS72165S7.

Uses and Administration

Fesoterodine is an antimuscarinic used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome (p. 2349.2). It is given orally as the fumarate; the usual initial dose is 4 mg once daily, increased to a maximum of 8 mg once daily if necessary, according to response. Patients should be re-evaluated after 8 weeks of treatment. In those taking moderate inhibitors of the cytochrome P450 isoenzyme CYP3A4, caution is advised when increasing the dose of fesoterodine fumarate to 8 mg once daily. UK and US licensed product information recommend that the dose of fesoterodine fumarate should not exceed 4 mg once daily in patients taking potent CYP3A4 inhibitors. In those taking CYP2D6 inhibitors, UK licensed product information suggests that the dose of fesoterodine fumarate may need to be reduced to 4 mg once daily. For doses in hepatic and renal impairment, see below.

References.

1. McKeage K, Keating GM. Fesoterodine. *Drugs* 2009; **69:** 731–8.
2. Tzefos M, *et al.* Fesoterodine for the treatment of overactive bladder. *Ann Pharmacother* 2009; **43:** 1992–2000.
3. Herschorn S, *et al.* Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int* 2010; **105:** 58–66.

Administration in hepatic impairment. UK licensed product information for fesoterodine fumarate states that patients with mild hepatic impairment should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed an oral dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with moderate impairment (Child-Pugh class B) should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended.

In the USA, no dose adjustments are recommended in patients with mild or moderate hepatic impairment.

Fesoterodine fumarate is contra-indicated in those with severe impairment (Child-Pugh class C), due to a lack of data.

Administration in renal impairment. UK licensed product information for fesoterodine fumarate states that patients with mild (GFR 50 to 80 mL/minute) or moderate (GFR 30 to 50 mL/minute) renal impairment, should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed an oral dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with severe impairment (GFR less than 30 mL/minute) should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended.

In the USA, no dose adjustments are recommended in patients with mild or moderate renal impairment; a maximum dose of fesoterodine fumarate 4 mg once daily is recommended in those with severe impairment.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Additional adverse effects reported with fesoterodine include dizziness, headache, increased liver enzyme values, and peripheral oedema. Angina and QT prolongation have been reported. Fesoterodine is contra-indicated in severe hepatic impairment; caution is required when used in patients with mild or moderate hepatic impairment or with renal impairment (see Administration in Hepatic Impairment and Administration in Renal Impairment, above). Caution is needed when used with potent or moderate CYP3A4 inhibitors, potent CYP3A4 inducers, or with potent CYP2D6 inhibitors (see Interactions and Uses and Administration, below and above, respectively). Fesoterodine should not be used in patients with moderate to severe hepatic or renal impairment who are also taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Fesoterodine is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Inhibitors or inducers of these enzymes can affect exposure to fesoterodine; dosage adjustments may be necessary (see Uses and Administration, above).

References.

1. Malhotra B, *et al.* Evaluation of drug-drug interactions with fesoterodine. *Eur J Clin Pharmacol* 2009; **65:** 551–60.

Pharmacokinetics

Fesoterodine is well absorbed orally, and rapidly hydrolysed to its active metabolite (5-hydroxymethyltolterodine) by plasma esterases. Bioavailability of the active metabolite is about 52%. Peak plasma concentrations occur around 5 hours after an oral dose. The active metabolite is about 50% bound to plasma proteins. It is further metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites; none of these metabolites has significant antimuscarinic activity. Exposure to the active metabolite of fesoterodine is higher in patients with hepatic or renal impairment, and in poor metabolisers of CYP2D6 compared with extensive metabolisers. Some 70% of an oral dose of fesoterodine is recovered in the urine as metabolites, and a smaller amount in the faeces. The terminal half-life of the active metabolite is about 7 hours after oral dosing, and about 4 hours after intravenous dosing.

References.

1. Malhotra B, *et al.* Pharmacokinetic profile of fesoterodine. *Int J Clin Pharmacol Ther* 2008; **46:** 556–63.
2. Malhotra B, *et al.* Assessment of the effects of renal impairment on the pharmacokinetic profile of fesoterodine. *J Clin Pharmacol* 2009; **49:** 477–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Toviaz; ***Belg.***: Toviaz; ***Canad.***: Toviaz; ***Cz.***: Toviaz; ***Denm.***: Toviaz; ***Ger.***: Toviaz; ***Gr.***: Toviaz; ***Irl.***: Toviaz; ***Israel***: Toviaz; ***Ital.***: Toviaz; ***Jpn***: Toviaz; ***Neth.***: Toviaz; ***Norw.***: Toviaz; ***Pol.***: Toviaz; ***Port.***: Toviaz; ***Spain***: Toviaz; ***Swed.***: Toviaz; ***Switz.***: Toviaz; ***Turk.***: Toviaz; ***UK***: Toviaz; ***USA***: Toviaz.

Finasteride (BAN, USAN, rINN)

Finasterid; Finasterida; Finasteridas; Finastéride; Finasteridi; Finasteridum; Finasterid; MK-0906; MK-906; YM-152; Финастерид.
N-tert-Butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.
$C_{23}H_{36}N_2O_2$=372.6
CAS — 98319-26-7.
ATC — D11AX10; G04CB01.
ATC Vet — QD11AX10; QG04CB01.
UNII — 57GNO57U7G.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Finasteride). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 36: (Finasteride). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Store in airtight containers.

Uses and Administration

Finasteride is an azasteroid that inhibits the type-2 isoform of 5α-reductase, the enzyme responsible for conversion of testosterone to the more active dihydrotestosterone, and therefore has anti-androgenic properties. It is given orally in a dose of 5 mg daily in the management of **benign prostatic hyperplasia** to cause regression of the enlarged prostate and to improve symptoms; it may reduce the incidence of acute urinary retention and the need for surgery. Response may be delayed and treatment may be required for 6 months or more to assess whether benefit has been achieved.

In the treatment of **male-pattern baldness** (alopecia androgenetica) in men, finasteride is given orally in a dose of 1 mg daily. In general, use for 3 months or more is required before benefit is seen, and effects are reversed within 12 months of ceasing therapy.

Alopecia. In men with male-pattern baldness (alopecia—see p. 1682.3), treatment with oral finasteride for 12 months resulted in an 11% increase in vertex hair count, which was maintained in those who continued therapy.[1] Extension of this study to 5 years found that long-term treatment with finasteride maintained beneficial effects, or at least slowed hair loss.[2] High baseline concentrations of 5α-dihydrotestosterone predict a good response to treatment with finasteride in patients aged 26 years and under.[3] The use of oral finasteride for male-pattern baldness has been reviewed.[4-6] Some efficacy has also been found with topical finasteride.[7]

Although finasteride is contra-indicated in women who are or may become pregnant (see Precautions, p. 2359.3), a dose of 2.5 mg daily has been used with an oral contraceptive containing drospirenone and ethinylestradiol for female pattern hair loss,[8] with some success. Finasteride has also been investigated in the treatment of male-pattern baldness in postmenopausal women; however, a 1-year placebo-controlled study[9] found no benefit. There have been reports of benefit from finasteride in women with hair loss due to hyperandrogenism[10] or androgen therapy.[11]

1. Kaufman KD, *et al.* Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998; **39:** 578–89.
2. The finasteride male pattern hair loss study group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol* 2002; **12:** 38–49.

3. Camacho FM, *et al*. Value of hormonal levels in patients with male androgenetic alopecia treated with finasteride: better response in patients under 26 years old. *Br J Dermatol* 2008; **158:** 1121–4.
4. McClellan KJ, Markham A. Finasteride: a review of its use in male pattern hair loss. *Drugs* 1999; **57:** 111–26.
5. Whiting DA. Advances in the treatment of male androgenetic alopecia: a brief review of finasteride studies. *Eur J Dermatol* 2001; **11:** 332–4.
6. Libecco JF, Bergfeld WF. Finasteride in the treatment of alopecia. *Expert Opin Pharmacother* 2004; **5:** 933–40.
7. Mazzerella F, *et al*. Topical finasteride in the treatment of androgenic alopecia. *J Dermatol Treat* 1997; **8:** 189–92.
8. Iorizzo M, *et al*. Finasteride treatment of female pattern hair loss. *Arch Dermatol* 2006; **142:** 298–302.
9. Price VH, *et al*. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. *J Am Acad Dermatol* 2000; **43:** 768–76.
10. Shum KW, *et al*. Hair loss in women with hyperandrogenism: four cases responding to finasteride. *J Am Acad Dermatol* 2002; **47:** 733–9.
11. Hong J-B, *et al*. A woman with iatrogenic androgenetic alopecia responding to finasteride. *Br J Dermatol* 2007; **156:** 754–5.

Benign prostatic hyperplasia. Finasteride[1,2] is used in the management of benign prostatic hyperplasia (p. 2347.1). It produces moderate reductions in prostate volume, although this takes a number of months and is not always associated with much symptomatic improvement; therapy must be continued indefinitely for benefit to be maintained. A 4-year study found that finasteride reduced the probability of surgery and acute urinary retention in men with symptomatic benign prostate hyperplasia with prostatic enlargement.[3] Although the need for prostatectomy was reduced by 55% it was pointed out[4] that only 6% of patients would benefit from treatment with finasteride, since for every 100 men treated, 7 finasteride and 13 placebo recipients required surgery. A 2-year, open-label follow-up[5] of this study reported that the reductions in probability of surgery and acute urinary retention were maintained. It was also found that in patients who switched from placebo to finasteride, these measures decreased to become similar to those recorded in men already receiving finasteride. A comparative 12-month study[6] found the alpha blocker terazosin to be more effective than finasteride in relieving symptoms and improving peak urine flow rates; the combination of finasteride plus terazosin was no more effective than terazosin alone. Moreover, although finasteride reduced prostatic volume, it was no more effective than placebo, a finding that is at odds with previous placebo-controlled studies. It has been suggested that the smaller median prostate size in this study may explain the negative findings,[7] and that men with larger prostates do benefit from finasteride. Similar results were reported in a 12-month study using doxazosin.[8] Later results[9,10] from a large study showed that over a longer period of 4 or more years the combination of doxazosin and finasteride reduced the risk of clinical progression more than either drug alone. The combination of an alpha blocker and 5α-reductase inhibitor is therefore considered to be a suitable option for patients with urinary symptoms and demonstrable prostatic enlargement, and who are at significant risk of progression.

1. Wilde MI, Goa KL. Finasteride: an update of its use in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1999; **57:** 557–81.
2. Smith AB, Carson CC. Finasteride in the treatment of patients with benign prostatic hyperplasia: a review. *Ther Clin Risk Manag* 2009; **5:** 535–45.
3. McConnell JD, *et al*. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostate hyperplasia. *N Engl J Med* 1998; **338:** 557–63.
4. Wasson JH. Finasteride to prevent morbidity from benign prostatic hyperplasia. *N Engl J Med* 1998; **338:** 612–13.
5. Roehrborn CG, *et al*. Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. *J Urol (Baltimore)* 2004; **171:** 1194–8.
6. Lepor H, *et al*. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996; **335:** 533–9.
7. Walsh PC. Treatment of benign prostatic hyperplasia. *N Engl J Med* 1996; **335:** 586–7.
8. Kirby RS, *et al*. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003; **61:** 119–26.
9. McConnell JD, *et al*. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; **349:** 2387–98.
10. Kaplan SA, *et al*. Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. *J Urol (Baltimore)* 2006; **175:** 217–20.

Hirsutism. Finasteride is reported to be effective for the treatment of hirsutism (p. 2262.1) in women.[1-7] It should be noted that finasteride should not be used in women who are or may become pregnant (see Precautions, below).

1. Falsetti L, *et al*. Comparison of finasteride versus flutamide in the treatment of hirsutism. *Eur J Endocrinol* 1999; **141:** 361–7.
2. Moghetti P. *et al*. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85:** 89–94.
3. Müderris II, *et al*. A prospective, randomized trial comparing flutamide (250mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. *Fertil Steril* 2000; **73:** 984–7.
4. Bayram F, *et al*. Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism. *Eur J Endocrinol* 2002; **147:** 467–71.
5. Lumachi F, Rondinone R. Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. *Fertil Steril* 2003; **79:** 942–6.
6. Beigi A, *et al*. Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Int J Gynaecol Obstet* 2004; **87:** 29–33.
7. Tartagni M, *et al*. Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women. *Fertil Steril* 2004; **82:** 752–5.

Malignant neoplasms of the prostate. Finasteride appears to have little effect in established prostate cancer,[1,2] but is under investigation for its prevention (p. 712.3), and guidelines for such use have been issued.[3] The results of 1 small study[4] of its effects on the prostate found little evidence to support its use for prevention of malignancy in patients at high risk. In healthy men, a large controlled study, the Prostate Cancer Prevention Trial (PCPT),[5] found that 7 years of finasteride prophylaxis reduced the incidence of prostate cancer by about 25% compared with placebo, but this benefit was offset by an increased risk of high-grade tumours associated with finasteride. The risk-benefit implications of these results have been debated, although some commentaries[6-9] suggest that preventive use would be justified, at least in selected patients. Further analysis[10] of the PCPT data found that finasteride had introduced a detection bias for both prostate cancer and for high-grade prostate cancer. Finasteride increased the sensitivity of prostate specific antigen (PSA) testing, implying that the PCPT primary findings of increased risk of high-grade tumours were due, at least in part, to improved detection. The reported 25% decrease in prostate cancer incidence was also likely to be an underestimate. The European Association of Urology has endorsed a recommendation that prostate cancer management guidelines be updated to reflect these findings.[11]

1. Presti JC, *et al*. Multicenter, randomized, double-blind placebo controlled study to investigate the effect of finasteride (MK-906) on stage D prostate cancer. *J Urol (Baltimore)* 1992; **148:** 1201–4.
2. Rittmaster RS. Finasteride. *N Engl J Med* 1994; **330:** 120–5.
3. Kramer BS, *et al*. American Society of Clinical Oncology Health Services Committee, American Urological Association Practice Guidelines Committee. Use of 5-α-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol* 2009; **27:** 1502–16. Correction. *ibid*.; 2742. Also available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668556/pdf/zlj1502.pdf (accessed 16/06/10)
4. Cote RJ, *et al*. The effect of finasteride on the prostate gland in men with elevated serum prostate-specific antigen levels. *Br J Cancer* 1998; **78:** 413–18.
5. Thompson IM, *et al*. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349:** 215–24.
6. Parnes HL, *et al*. Prevention of hormone-related cancers: prostate cancer. *J Clin Oncol* 2005; **23:** 368–77.
7. Unger JM, *et al*. Estimated impact of the Prostate Cancer Prevention Trial on population mortality. *Cancer* 2005; **103:** 1375–80.
8. Lotan Y, *et al*. Implications of the prostate cancer prevention trial: a decision analysis model of survival outcomes. *J Clin Oncol* 2005; **23:** 1911–20.
9. Vickers AJ, *et al*. Finasteride to prevent prostate cancer: should all men or only a high-risk subgroup be treated? *J Clin Oncol* 2010; **28:** 1112–16.
10. Thompson IM, *et al*. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006; **98:** 1128–33.
11. Teillac P, Abrahamsson P-A. The Prostate Cancer Prevention Trial and its implications for clinical practice: a european consensus. *Eur Urol Suppl* 2006; **5:** 640–6.

Adverse Effects

The most commonly reported adverse effects of finasteride are decreased libido, erectile dysfunction, ejaculation disorders, and reduced volume of ejaculate.

Breast tenderness and enlargement (gynaecomastia) may occur, and there have been reports of hypersensitivity reactions such as swelling of the lips and face, pruritus, urticaria, and rashes. Testicular pain has also been reported.

Incidence of adverse effects. In a study using prescription event monitoring data,[1] the most commonly reported adverse effects of finasteride in 14 772 patients were impotence or ejaculatory failure (2.1% of patients), reduced libido (1%), and breast disorders such as gynaecomastia (0.4%). Adverse effects reported in a single patient each, and verified on rechallenge, were exfoliative dermatitis, perioral numbness, and swollen glands. Finasteride appeared to be associated with ataxia in 1 patient and wheeziness in another.

1. Wilton L, *et al*. The safety of finasteride used in benign prostatic hypertrophy: a non-interventional observational cohort study in 14 772 patients. *Br J Urol* 1996; **78:** 379–84.

Effects on the breast. Gynaecomastia was the adverse effect of finasteride most frequently reported to the FDA between June 1992 and February 1995 (a total of 214 reports).[1] The onset after therapy ranged from 14 days to 2.5 years, and the condition could be unilateral or bilateral. Mastectomy was performed in 12 men. Of the 86 men for whom follow-up information was available, partial or complete remission of gynaecomastia occurred in 80%, and no change occurred in 20%. In 2 of the cases, primary intraductal breast carcinoma was subsequently found, although 1 probably had breast cancer before finasteride therapy.

A subsequent review by the MHRA[2] reported 53 cases of male breast cancer associated with the use of finasteride worldwide; most cases occurred within 5 years of starting treatment. There was a trend towards male breast cancer occurring more frequently with finasteride compared with placebo in clinical studies, although the overall incidence was not significantly different. There have also been 4 reports of breast cancer in women after unlicensed use of finasteride; cases occurred after relatively shorter periods of treatment (up to 1 year). Patients were advised to promptly report any changes in their breast tissue during finasteride treatment, such as lumps, pain, or nipple discharge. However, there was no strong evidence to suggest that gynaecomastia was a precursor to breast cancer as it occurs in only 9% of breast cancer cases, but has been reported in up to 50% of men in the general population.

1. Green L, *et al*. Gynecomastia and breast cancer during finasteride therapy. *N Engl J Med* 1996; **335:** 823.
2. MHRA. MHRA public assessment report: the risk of male breast cancer with finasteride (issued December 2009). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con06 (accessed 23/03/10)

Effects on mental function. Depression has been reported[1,2] in 20 patients given finasteride for the treatment of alopecia. In most cases the depression began about 3 to 4 months after starting finasteride, and resolved within a few weeks of stopping it. In 2 patients rechallenged with finasteride, depression recurred within 2 weeks of restarting the drug.[1]

1. Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. *J Dermatol* 2002; **29:** 665–9.
2. Health Canada. Finasteride: suspected association with depression. *Can Adverse React News* 2004; **14** (1): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1-eng.pdf (accessed 02/09/08)

Precautions

Finasteride should be used with caution in hepatic impairment. When used for benign prostatic hyperplasia, finasteride should be used with caution in men at risk of obstructive uropathy. Patients should be evaluated for prostatic carcinoma before and during therapy. Use of finasteride decreases concentrations of serum markers of prostate cancer such as prostate specific antigen (PSA) by up to 50% even when cancer is present, and reference values should be adjusted accordingly; the ratio of free to total PSA (percent free PSA) remains constant.

Studies in *animals* suggest finasteride could produce feminisation (hypospadia) of a male fetus if used in pregnant women; therefore, its use is contra-indicated in women who are or may become pregnant. In addition, it is recommended that women in this category should not handle crushed or broken finasteride tablets. Finasteride has been detected in semen, therefore use of a condom is recommended if the patient's sexual partner is, or may become, pregnant.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies finasteride as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pharmacokinetics

Finasteride is absorbed after oral doses, and peak plasma concentrations occur in 1 to 2 hours. The mean bioavailability has variously been reported as 63% and 80%. It is about 90% bound to plasma protein. Finasteride crosses the blood-brain barrier, and is distributed into semen. It is metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4, and excreted in urine and faeces as metabolites. The mean terminal half-life is about 6 hours in patients under 60 years of age but may be prolonged to about 8 hours in those 70 years of age or older.

References.

1. Steiner JF. Clinical pharmacokinetics and pharmacodynamics of finasteride. *Clin Pharmacokinet* 1996; **30:** 16–27.
2. Suzuki R, *et al*. Saturable binding of finasteride to steroid 5α-reductase as determinant of nonlinear pharmacokinetics. *Drug Metab Pharmacokinet* 2010; **25:** 208–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Andropel; Avertex; Capilfor; Daric; Finasterin; Finprostat; Finterac; Flutiamik; Folcres; HPB; Ivix Fin; Nasteril; Propecia; Proscar; Prosmin; Prostanil; Prostanovag; Prostene; Q-Prost Alopex; Q-Prost; Renacidin; Ridefin; Sutrico; Tealep; Tresaride; Tricofarma; Urofin; Urototal; Vetiprost; ***Austral.***: Finasta; Finnacar; Propecia; Proscar; ***Austria***: Androfin; Propecia; Proscar; ***Belg.***: Proscar; ***Braz.***: Alfasin; Capyla; Fendical; Finalop; Finapecia; Finarid; Finastec; Finastil; Flaxin; Nasterid A; Nasterid; Pracap†; Pronasteron; Propecia; Proscar; Prostide; ***Canad.***: Propecia; Proscar; ***Chile***: Folipil; Prohair; Proscar; Regenex; Saniprostol; Tricoplus; Vastus; ***China***:

The symbol † denotes a preparation no longer actively marketed

Ai Shi Lie (艾仕列); Bao Li An (葆利安); Duo Shai (多晒); Finatra (如川); Fu Lie (孚列); He Shu (合舒); Ji You (吉优); Jun Neng (俊能); Ka Bo (卡波); Kang Lie Su (康列苏); Kui An (奎安); Lan Le (蓝乐); Li Er Quan (利尔泉); Lie Qin (列沁); Lishu (沥舒); LiTong (立同); Long Tong (隆通); Propecia (保法止); Proscar (保列治); Pu Lie An (浦列安); Pu Luo Ping (普洛平); Qian Li Xin (前力欣); Qian Nuo Lin (千诺林); Shi Yi (士怡); Si Jun Yi (司君宜); Tian Shu Xin (恬舒新); Xian Li Xiao (先立晓); Xing Bao (星保); Yi An Lin (意安林); Yi Ru Te (易如特); Yi Shu Sheng (逸舒升); Yi Tong (亦通); Yi You Rui Xin (易优瑞欣); Zai An Lie (再安列); ***Cz.***: Androfin; Apo-Finas; Duromeran†; Edufil†; Finajelf; Finanorm; Finard; Finex; Finpros; Gefin; Hyplafin; Ibition†; Lekoprost; Mostrafin; Penester; Propecia; Proscar†; Radicut†; ***Denm.***: Finaprost; Finastad; Propecia; Proscar; ***Fin.***: Gefina; Propecia; Proscar; Tifisterid; ***Fr.***: Chibro-Proscar; Propecia; ***Ger.***: FinaHAIR†; Finamed; Finapil; Finascar; Finural; Propecia; Proscar; Prosmin; ***Gr.***: Alsteride; Avielid; Finaprost; Finar; Finastir; Finazil; Finescar; Fisterid; Glopisine; Pervil; Poruxin; Profin; Profinosa; Prohype; Propecia; Proplasia; Proscar; Prostafin; ***Hong Kong***: Fincar; Propecia; Proscar; ***Hung.***: Andofin; Finanorm; Finastep; Finpros; Hyplafin; Proscar; Prosterid; Sterakfin; ***India***: Finabald; Finalo; Finara; Finaride; Finast; Finastat; Finax; Fincar; Finpecia; Finster; Fintride; Fistide; Monast; ***Indon.***: Alopros; Finaxal†; Finpro; Proscar; Prostacom; Prostide; Reprostom; ***Irl.***: Finocar; Fintex; Fintrid; Profal; Proscar; ***Israel***: Pro-Cure; Propecia; ***Ital.***: Finastid; Folians; Genaprost; Pilus; Propecia; Proscar; Prostide; ***Malaysia***: Propecia; Proscar; ***Mex.***: Borealist; Philterin; Propeshia; Proscar; Riterid-Z; Syndrex; Tealep; Teriurin; Vanorid; ***Neth.***: Finagalen†; Finahold†; Finajelf†; Finaschwarz†; Finastad†; Propecia; Proscar; ***Norw.***: Proscar; ***NZ***: Finaccord; Fintral; Propecia; Proscar; ***Philipp.***: Atepros; Finarid; Finast; Pronax; Propecia; Proscar; Prostab; Prostanus; Prosteride; ***Pol.***: Ambulase†; Antiprost; Apo-Fina; Aprost; FinaGen; Finamef; Finanorm; Finaran; Finaride; Finaster; Finpros; Fintral; Finxta; Hyplafin; Lifin; Penester; Propecia; Proscar; Symasteride; Ulgafen; Zasterid; ***Port.***: Binpros†; Finox; Growancer†; Propecia; Proscar; Prostacide†; Prostafin; Zidoril†; Zylfina†; ***Rus.***: Alfinal (Альфинал); Finast (Финаст); Finpros (Финпрос); Penester (Пенестер); Proscar (Проскар); Prosterid (Простерид); Zerlon (Зерлон); ***S.Afr.***: Fincar; Finpecia; Finpro; Propecia; Proscar; ***Singapore***: Finas; Finast; Propecia; Proscar; ***Spain***: Alocare; Arahormo; Ativol†; Eucoprost†; Lambdaxel; Litace; Maxpil; Normomale; Propecia; Proscar; ***Swed.***: Propecia; Proscar; ***Switz.***: Alocapil; Finacapil; Finasterax; Propecia; Proscar; ***Thai.***: Firide; Harifin; Propecia; Proscar; Prosteride; Stercia; Sterzar; ***Turk.***: Alofin; Dilaprost; Finarid; Propecia; Proscar; Prosterit; ***UK***: Propecia; Proscar; ***Ukr.***: Adenosterid (Аденостерид-Здоровье); Finast (Финаст)†; Penester (Пенестер); Prosterid (Простерид)†; ***USA***: Propecia; Proscar; ***Venez.***: Nasterol; Propecia; Proscar; Prosdina.

Multi-ingredient Preparations. ***Arg.***: Prosdox Duo; ***Hung.***: Alfin Combo; Duamild; ***India***: Contiflo-OD-F; Finabald-T; Finast T; Flokind-F; Geriflo; Urimax F; ***Mex.***: Profidox.

Pharmacopoeial Preparations
BP 2014: Finasteride Tablets;
USP 36: Finasteride Tablets.

Flavoxate Hydrochloride

(BANM, USAN, rINNM)

DW-61; Flavoksat Hidroklorür; Flavoxate, Chlorhydrate de; Flavoxathydrochlorid; Flavoxati hydrochloridum; Flavoxato, hidrocloruro de; Hidrocloruro de flavoxato; NSC-114649; Rec-7-0040; Флавоксата Гидрохлорид.

2-Piperidinoethyl 3-methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylate hydrochloride.

$C_{24}H_{25}NO_4.HCl$=427.9

CAS — 15301-69-6 (flavoxate); 3717-88-2 (flavoxate hydrochloride).

ATC — G04BD02.

ATC Vet — QG04BD02.

UNII — 9C05J6089W.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*

Ph. Eur. 8: (Flavoxate Hydrochloride). A white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Flavoxate Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water, in alcohol, and in dichloromethane. Protect from light.

Uses and Administration

Flavoxate hydrochloride is described as a smooth muscle relaxant but it also has antimuscarinic actions (see, p. 1310.3); it is a tertiary amine. It is used for the symptomatic relief of pain, urinary frequency, and incontinence associated with inflammatory disorders of the urinary tract. It is also used for the relief of vesicourethral spasms resulting from instrumentation or surgery. A usual dose is 200 mg orally three times daily.

Urinary incontinence. Flavoxate is indicated mainly in the treatment of urge incontinence (p. 2349.2). Results of studies have sometimes been disappointing,[1,2] although adverse effects are said to be less marked than those seen with other antimuscarinics such as oxybutynin.[3] In the UK, guidelines issued by NICE suggest that flavoxate should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[4]

1. Chapple CR, *et al.* Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. *Br J Urol* 1990; **66:** 491–4.
2. Dahm TL, *et al.* Flavoxate treatment of micturition disorders accompanying benign prostatic hypertrophy: a double-blind placebo-controlled multicenter investigation. *Urol Int* 1995; **55:** 205–8.
3. Fehrmann-Zumpe P, *et al.* Using flavoxate as primary medication for patients suffering from urge symptomatology. *Int Urogynecol J* 1999; **10:** 91–5.
4. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Ocular effects, including increased intra-ocular pressure, are occasionally troublesome. Other adverse effects include sedation or fatigue, vertigo, and hypersensitivity reactions. Leucopenia or eosinophilia has been reported rarely.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Flavoxate is readily absorbed from the gastrointestinal tract and rapidly metabolised, about 50 to 60% of a dose being excreted in the urine within 24 hours as methyl flavone carboxylic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bladuril; ***Belg.***: Urispas; ***Braz.***: Genurin-S; ***Canad.***: Urispas; ***Chile***: Bladuril; Urodial; ***China***: Bei Si Qing (贝斯清); Chang Er Da (畅尔达); Du Luo Jie (渡洛捷); Genurin (津源灵); Ji Shi Da (吉时达); Luo Ao Ke (洛沃克); Soolda (舒尔达); You Bi Da (优必达); ***Denm.***: Urispadol; ***Fr.***: Urispas; ***Ger.***: Spasuret†; ***Gr.***: Verispasmin; ***Hong Kong***: Urispas; ***India***: Favate; Flavate; Flavoride; Flavospas; Urisol; Urispas; ***Indon.***: Uroxal; ***Irl.***: Urispas; ***Ital.***: Genurin; ***Jpn***: Bladderon; Lady Guard†; ***Malaysia***: Cleanxate; Uripax; Urispas; ***Mex.***: Bladuril; ***Neth.***: Urispas; Uronid†; ***Port.***: Urispas; ***S.Afr.***: Urispas; ***Singapore***: Cleanxate; Genurin; Lavoxen; Urispas; ***Spain***: Uronid; ***Switz.***: Urispas; ***Thai.***: Flavo-Spa; Flavorin; Spasdic; Spasuri; U-Spa; Urispas; Uroxate; Voxate; ***Turk.***: Urispas; ***UK***: Urispas; ***USA***: Urispas; ***Venez.***: Genurin.

Multi-ingredient Preparations. ***Arg.***: Algio-Bladuril; ***Ital.***: Cistalgan.

Pharmacopoeial Preparations
BP 2014: Flavoxate Tablets;
USP 36: Flavoxate Hydrochloride Tablets.

Imidafenacin *(rINN)*

Imidafenacina; Imidafénacine; Imidafenacinum; KRP-197; KRP-1979; Ono-8025; Имидафенацин.

4-(2-Methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide.

$C_{20}H_{21}N_3O$=319.4

CAS — 170105-16-5.

UNII — XJR8Y07LJO.

Profile

Imidafenacin is an antimuscarinic that is used in the treatment of urinary frequency, urgency, and incontinence (p. 2349.2). It is given in an oral dose of 100 micrograms twice daily, after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Staybla; Uritos.

Lodenafil Carbonate *(rINN)*

Carbonato de Lodenafilo; Lodénafil Carbonate; Lodenafili Carbonas; Лоденафиль Карбонат.

Bis[2-(4-{4-ethoxy-3-[1-methyl-7-oxo-3-propyl-4,7-dihydro-1*H*-pyrazolo(4,3-*d*)pyrimidin-5-yl]phenylsulfonyl}piperazin-1-yl)ethyl]carbonate.

$C_{47}H_{62}N_{12}O_{11}S_2$=1035.2

CAS — 398507-55-6.

Profile

Lodenafil carbonate is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2); it is used orally in the management of erectile dysfunction (p. 2348.2). A suggested dose is 80 mg taken 20 minutes to 1 hour before sexual intercourse.

References.
1. Glina S, *et al.* Efficacy and tolerability of lodenafil carbonate for oral therapy in erectile dysfunction: a phase II clinical trial. *J SexMed* 2009; **6:** 553–7.
2. Glina S, *et al.* Efficacy and tolerability of lodenafil carbonate for oral therapy of erectile dysfunction: a phase III clinical trial. *J Sex Med* 2010; **7:** 1928–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Helleva.

Mirabegron *(USAN, rINN)*

Mirabegrón; Mirabégron; Mirabegronum; YM-178; Мирабегрон.

2-(2-Amino-1,3-thiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide.

$C_{21}H_{24}N_4O_2S$=396.5

CAS — 223673-61-8.

ATC — G04BD12.

ATC Vet — QG04BD12.

UNII — MVR3JL3B2V.

Uses and Administration

Mirabegron is a beta$_3$-adrenoceptor agonist used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome (p. 2349.2). The usual oral dose is 25 to 50 mg once daily, which is usually effective within 8 weeks.

For doses in hepatic and renal impairment, see below.

References.
1. Gras J. Mirabegron for the treatment of overactive bladder. *Drugs Today* 2012; **48:** 25–32.
2. Bhide AA, *et al.* Use of mirabegron in treating overactive bladder. *Int Urogynecol J* 2012; **23:** 1345–8.

Administration in hepatic impairment. Licensed product information states that the oral dose of mirabegron should not exceed 25 mg once daily in patients with moderate hepatic impairment (Child-Pugh class B), and its use is not recommended in those with severe impairment (Child-Pugh class C) due to a lack of data; no dose adjustment is necessary in mild impairment (Child-Pugh class A).

It is also recommended that the dose of mirabegron is reduced in patients with hepatic impairment who are also taking strong inhibitors of cytochrome P450 isoenzyme CYP3A. In patients with mild hepatic impairment, a maximum dose of 25 mg daily may be given; co-administration is not recommended in patients with more severe hepatic impairment.

Administration in renal impairment. Licensed product information states that the oral dose of mirabegron should not exceed 25 mg once daily in patients with severe renal impairment (creatinine clearance [CC] 15 to 29 mL/minute), and its use is not recommended in those with end-stage renal disease (CC less than 15 mL/minute), or requiring haemodialysis, due to a lack of data; no dose adjustment is necessary in mild or moderate impairment (CC 30 to 89 mL/minute).

It is also recommended that the dose of mirabegron is reduced in patients with renal impairment who are also taking strong inhibitors of cytochrome P450 isoenzyme CYP3A. In patients with mild or moderate renal impairment a maximum dose of 25 mg daily of mirabegron may be used; co-administration is not recommended in patients with severe renal impairment.

Adverse Effects and Precautions

The most commonly reported adverse effects with mirabegron are hypertension, nasopharyngitis, urinary-tract infection, and headache. Other frequently reported adverse effects include nausea, diarrhoea, constipation, dizziness, tachycardia, and dry mouth.

Mirabegron is not recommended in patients with severe uncontrolled hypertension and blood pressure should be monitored in all patients, particularly those with hypertension. It should be used with caution in those with hepatic or renal impairment. Due to the risk of urinary retention, mirabegron should be given with caution to patients with clinically significant bladder outlet obstruction or those who are also taking antimuscarinics for the treatment of overactive bladder syndrome.

References.
1. Tyagi P, *et al.* Mirabegron: a safety review. *Expert Opin Drug Safety* 2011; **10:** 287–94.

Interactions

Strong inhibitors of cytochrome P450 CYP3A isoenzymes may increase mirabegron exposure, and a lower dose of mirabegron is recommended during concomitant therapy in patients with hepatic or renal impairment (see p. 2360.3).

Mirabegron is a moderate inhibitor of the cytochrome P450 isoenzyme CYP2D6 and concomitant use with substrates such as desipramine and metoprolol increases systemic exposure to these drugs. When used with mirabegron, appropriate monitoring and dose adjustment of CYP2D6 substrates may be necessary, particularly those with a narrow therapeutic index such as flecainide, propafenone, and thioridazine.

For the effect of mirabegron on digoxin, see p. 1358.1.

Pharmacokinetics

After oral doses of mirabegron, peak plasma concentrations occur in about 3.5 hours. It is about 71% bound to plasma proteins and widely distributed in the body. Mirabegron is metabolised via multiple pathways involving butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase in addition to cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Two major inactive metabolites are excreted in the urine and the faeces; about 25% of a dose is excreted unchanged in the urine. The terminal elimination half-life is about 50 hours. It has been detected in the milk of *rats*.

References.

1. Eltink C, *et al*. Single dose pharmacokinetics and absolute bioavailability of mirabegron, a β 3-adrenoceptor agonist for treatment of overactive bladder. *Int J Clin Pharmacol Ther* 2012; **50:** 838–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Betanis; ***UK***: Betmiga; ***USA***: Myrbetriq.

Naftopidil *(rINN)*

BM-15275; KT-611; Naftopidilum; Нафтопидил.
(±)-4-(*o*-Methoxyphenyl)-α-[(1-naphthyloxy)methyl]-1-piperazineethanol.
$C_{24}H_{28}N_2O_3$=392.5
CAS — 57149-07-2.
UNII — R9PHW59SFN.

Profile

Naftopidil is a peripheral alpha$_1$-adrenoceptor blocker that is structurally related to urapidil (p. 1520.2) and has similar general properties. It is used in benign prostatic hyperplasia to relieve symptoms of urinary obstruction.

References.

1. Yokoyama T, *et al*. Comparison of 25 and 75 mg/day naftopidil for lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective, randomized controlled study. *Int J Urol* 2006; **13:** 932–8.
2. Maruyama O, *et al*. Naftopidil monotherapy vs naftopidil and an anticholinergic agent combined therapy for storage symptoms associated with benign prostatic hyperplasia: a prospective randomized controlled study. *Int J Urol* 2006; **13:** 1280–5.
3. Masumori N, *et al*. Short-term efficacy and long-term compliance/treatment failure of the α 1 blocker naftopidil for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Scand J Urol Nephrol* 2007; **41:** 422–9.
4. Oh-oka H. Effect of naftopidil on nocturia after failure of tamsulosin. *Urology* 2008; **72:** 1051–5.
5. Ukimura O, *et al*. Naftopidil versus tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia with special reference to the storage symptom: a prospective randomized controlled study. *Int J Urol* 2008; **15:** 1049–54.
6. Garimella PS, *et al*. Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 23/03/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: DiShuang (帝爽); Eapidil (博帝); Ge Rui Jia (格瑞佳); Jun Lie Xin (君列欣); Kun Da (坤达); Lai Luo Er (来络尔); Na Tuo (那妥); Pu Chang (浦畅); Shu Er (疏尔); Sitandi (司坦迪); Yu Chang (愈畅); Zai Chang (再畅); ***Jpn***: Avishot†; Flivas.

Oxendolone *(USAN, rINN)*

Oxendolona; Oxendolonum; TSAA-291; Оксендолон.
16β-Ethyl-17β-hydroxyestr-4-en-3-one.
$C_{20}H_{30}O_2$=302.5
CAS — 33765-68-3.
UNII — MN4I850D4P.

Profile

Oxendolone is an anti-androgen that has been used in the treatment of benign prostatic hyperplasia.

Oxybutynin *(BAN, USAN, rINN)*

Oxibutinina; Oxybutynine; Oxybutyninum; Оксибутинин.
4-Diethylaminobut-2-ynyl 2-cyclohexyl-2-phenylglycolate; 4-(Diethylamino)-2-butynyl α-phenylcyclohexaneglycolic acid ester.
$C_{22}H_{31}NO_3$=357.5
CAS — 5633-20-5.
ATC — G04BD04.
ATC Vet — QG04BD04.
UNII — K9P6MC7092.

Oxybutynin Hydrochloride *(BANM, rINNM)*

5058; Hidrocloruro de oxibutinina; MJ-4309-1; Oksibütinin Hidroklorür; Oksibutinino hidrochloridas; Oksibutyniinihydrokloridi; Oksybutyniny chlorowodorek; Oxibutinina, hidrocloruro de; Oxibutinin-hidroklorid; Oxibutyninhydroklorid; Oxybutynin Chloride (USAN); Oxybutynin hydrochlorid; Oxybutynine, chlorhydrate d'; Oxybutyninhydrochlorid; Oxybutynini Hydrochloridum; Оксибутинина Гидрохлорид.
4-Diethylaminobut-2-ynyl α-cyclohexylmandelate hydrochloride; 4-(Diethylamino)but-2-ynyl (*RS*)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride.
$C_{22}H_{31}NO_3$,HCl=394.0
CAS — 1508-65-2.
ATC — G04BD04.
ATC Vet — QG04BD04.
UNII — L9F3D9RENQ.

Pharmacopoeias. In *Eur*. (see p. vii) and *US*.

Ph. Eur. 8: (Oxybutynin Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; practically insoluble in cyclohexane. Protect from light.

USP 36: (Oxybutynin Chloride). A white, practically odourless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; very soluble in chloroform and in methyl alcohol; slightly soluble in ether; very slightly soluble in hexane.

Uses and Administration

Oxybutynin hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3); it also has direct effects on smooth muscle. It is used for the management of urinary frequency, urgency, and incontinence in neurogenic bladder disorders and in idiopathic detrusor instability, and as an adjunct to nonpharmacological therapy for nocturnal enuresis.

Usual oral doses of oxybutynin hydrochloride are 5 mg two or three times daily, increased to 5 mg four times daily if required. In elderly patients lower doses of 2.5 or 3 mg twice daily initially, increased to 5 mg twice daily if necessary, may be adequate. Modified-release preparations of oxybutynin hydrochloride are also available. The initial dose is 5 mg once daily, increased by 5 mg at weekly intervals if necessary, up to a maximum of 20 or 30 mg daily, depending on the preparation.

Oxybutynin is also used topically. A transdermal patch is available that supplies 3.9 mg of oxybutynin daily. The patch should be applied to intact skin on the abdomen, hip, or buttocks and replaced every 3 to 4 days; re-application to the same site should be avoided for 7 days. Alternatively, oxybutynin can be applied as a gel in the management of overactive bladder syndrome; dosage depends on the brand used. *Gelnique* 10% gel (*Watson, USA*) contains 100 mg of oxybutynin hydrochloride in each sachet; the contents of one sachet is applied once daily to intact skin on the abdomen, thighs, upper arms, or shoulders. *Anturol* 3% gel (*Antares, USA*) delivers 28 mg of oxybutynin in each pump actuation; 3 actuations should be applied once daily to intact skin as for the sachet preparation.

For doses in children, see below.

Administration in children. Oxybutynin hydrochloride is licensed in the UK and USA for **neurogenic bladder disorders** in children. Additionally, in the UK, oxybutynin is also licensed for the treatment of **idiopathic overactive bladder** and **nocturnal enuresis**.

For these indications, children aged from over 5 to 12 years of age may be given the following doses:

- the *conventional oral formulation* may be given in an initial dose of 2.5 to 3 mg twice daily, increased to 5 mg twice or three times daily according to response; for nocturnal enuresis, the last dose should be given before bedtime
- as a *modified-release tablet* the initial dose is 5 mg once daily, increased by 5-mg increments at weekly intervals to a maximum daily dose of 15 or 20 mg, depending on the preparation, and according to response. Modified-release preparations are not recommended for children who are unable to swallow the tablet whole

In addition, for the treatment of idiopathic overactive bladder or neurogenic bladder disorders, the *BNFC* suggests that children aged 2 to 5 years may be given a dose of 1.25 to 2.5 mg as a *conventional oral formulation* 2 or 3 times daily.

Children from 12 years of age may be given adult doses (see Uses and Administration, above).

Oxybutynin may also be given by *intravesical instillation*, although unlicensed by this route. The *BNFC* suggests a dose of 5 mg (as the hydrochloride) in 30 mL of solution, 2 or 3 times daily, in children aged 2 to 18 years.

Benign prostatic hyperplasia. Although there have been concerns about the use of antimuscarinics in patients with symptomatic benign prostatic hyperplasia (p. 2347.1) some patients have lower urinary tract symptoms suggestive of overactive bladder, and antimuscarinics such as oxybutynin are increasingly being used for treatment, either alone or as adjuncts. In men who had incomplete relief of urinary storage symptoms (such as frequency, nocturia, and urge incontinence) with tamsulosin alone, addition of a prolonged-release formulation of oxybutynin gave further symptom relief compared with placebo.[1]

1. MacDiarmid SA, *et al*. Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2008; **83:** 1002–10.

Nocturnal enuresis. Antimuscarinics such as oxybutynin reduce uninhibited bladder contractions but, although they may be of use in diurnal enuresis, they are rarely of benefit in nocturnal enuresis (p. 2349.1) alone. Oxybutynin did not appear to be effective in treating primary nocturnal enuresis in children with normal bladders.[1] However, children with low bladder capacity and detrusor instability may derive some benefit from oxybutynin.[2,3]

1. Lovering JS, *et al*. Oxybutynin efficacy in the treatment of primary enuresis. *Pediatrics* 1988; **82:** 104–6.
2. Koşar A, *et al*. Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna: a clinical and urodynamic study. *Scand J Urol Nephrol* 1999; **33:** 115–18.
3. Nevéus T. Oxybutynin, desmopressin and enuresis. *J Urol (Baltimore)* 2001; **166:** 2459–62.

Urinary incontinence. In addition to its antimuscarinic effect, oxybutynin has a direct antispasmodic effect which helps reduce the number of uninhibited bladder contractions in urge incontinence (see p. 2349.2). It is effective when given orally[1-4] or via a transdermal patch.[5-7] NICE considers conventional oral oxybutynin formulations to be the drug of first choice in women with overactive bladder syndrome or mixed incontinence if bladder training has been ineffective.[8] However, adverse effects may limit its use; if immediate-release oxybutynin is not well tolerated, a controlled-release or transdermal formulation may be considered as an alternative.[8] The comparative pharmacokinetics and efficacy of the different formulations have been reviewed;[9] there is some evidence that transdermal formulations may be better tolerated in the elderly, although direct comparative studies are mostly lacking.

Oral oxybutynin can be useful in the management of neurogenic detrusor hyperreflexia in adults[10,11] and children.[12] Direct instillation of oxybutynin into the bladder has also been tried. In one study[13] that included patients aged 1 to 34 years, 21 out of 32 patients became totally continent using an intravesical dose of 300 micrograms/kg daily, given in 3 divided doses. A further 7 patients became continent with doses titrated up to a maximum of 900 micrograms/kg daily, but another 4 remained incontinent. Other reports[14,15] have used single or multiple doses of 5 mg, often prepared by dispersing a crushed 5-mg tablet in 30 mL of distilled water or sodium chloride 0.9%.

1. Riva D, Casolati E. Oxybutynin chloride in the treatment of female idiopathic bladder instability: results from double blind treatment. *Clin Exp Obstet Gynecol* 1984; **11:** 37–42.
2. Moore KH, *et al*. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. *Br J Urol* 1990; **66:** 479–85.
3. Tapp AJS, *et al*. The treatment of detrusor instability in postmenopausal women with oxybutynin chloride: a double blind placebo controlled study. *Br J Obstet Gynaecol* 1990; **97:** 521–6.
4. Siddiqui MA, *et al*. Oxybutynin extended-release: a review of its use in the management of overactive bladder. *Drugs* 2004; **64:** 885–912.
5. Davila GW, *et al*. A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol (Baltimore)* 2001; **166:** 140–5.
6. Dmochowski RR, *et al*. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol (Baltimore)* 2002; **168:** 580–6.
7. Dmochowski RR, *et al*. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003; **62:** 237–42.
8. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

9. Kennelly MJ. A comparative review of oxybutynin chloride formulations: pharmacokinetics and therapeutic efficacy in overactive bladder. *Rev Urol* 2010; **12:** 12–19.
10. O'Leary M, *et al*. Effect of controlled-release oxybutynin on neurogenic bladder function in spinal cord injury. *J Spinal Cord Med* 2003; **26:** 159–62.
11. Bennett N, *et al*. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? *J Urol (Baltimore)* 2004; **171:** 749–51.
12. Franco I, *et al*. Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. *J Urol (Baltimore)* 2005; **173:** 221–5.
13. Haferkamp A, *et al*. Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. *Spinal Cord* 2000; **38:** 250–4.
14. Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. *Spinal Cord* 1996; **34:** 284–7.
15. Lose G, Nørgaard JP. Intravesical oxybutynin for treating incontinence resulting from an overactive detrusor. *BJU Int* 2001; **87:** 767–73.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2.

Animal studies have shown reproductive toxicity with high doses of oxybutynin, hence the recommendation that it should be avoided during pregnancy; caution should also be observed during breast feeding.

Effects on body temperature. A 76-year-old man taking oxybutynin hydrochloride 5 mg three times daily suffered heatstroke on a day when the ambient temperature was about 37 degrees. He had had a similar febrile episode the previous summer while taking oxybutynin.[1]

1. Adubofour KO, *et al*. Oxybutynin-induced heatstroke in an elderly patient. *Ann Pharmacother* 1996; **30:** 144–7.

Effects on the eyes. After 4 weeks of treatment, the adverse ocular effects of oxybutynin and tolterodine were evaluated in 24 and 28 women, respectively, being treated for urge incontinence.[1] The incidence of adverse effects reported by the patients was similar for the 2 drugs. A burning sensation in the eyes occurred in about half the women, but reports of a foreign-body sensation and dry eyes were less frequent. There was a reduction in accommodation amplitude although this was statistically significant only for oxybutynin, and pupillary diameter in dim light was only significantly larger for tolterodine. Tear film stability was found to be reduced for both drugs, but intraocular pressure was not significantly affected.

Acute angle-closure glaucoma has been reported in an elderly woman taking oxybutynin for urge incontinence.[2]

1. Altan-Yaycioglu R, *et al*. Ocular side-effects of tolterodine and oxybutynin, a single-blind prospective randomized trial. *Br J Clin Pharmacol* 2005; **59:** 588–92.
2. Sung VCT, Corridan PG. Acute-angle closure glaucoma as a side-effect of oxybutynin. *Br J Urol* 1998; **81:** 634–5.

Effects on the gastrointestinal tract. Reflux oesophagitis has been reported[1] in a 36-year-old woman with cerebral palsy and hiatus hernia who had taken oxybutynin for 5 years to prevent urinary incontinence. Symptoms of gastro-oesophageal reflux resolved when oxybutynin was stopped.

1. Lee M, Sharifi R. Oxybutynin-induced reflux esophagitis. *DICP Ann Pharmacother* 1990; **24:** 583–5.

Effects on the nervous system. A review of adverse CNS effects associated with oxybutynin found 37 reports in children and 143 in adults. Hallucinations were the most common event reported in children, followed by agitation, sedation, confusion, amnesia, and nightmares. Children reported agitation more than twice as often as adults, whereas adults reported sedation more than twice as often as children. Confusion was the most common event reported for patients aged 60 years or over, reported three times as often as for younger patients.[1] A study[2] of healthy subjects, aged 65 years or older, also found oxybutynin to cause cognitive impairment.

1. Gish P, *et al*. Spectrum of central anticholinergic adverse effects associated with oxybutynin: comparison of pediatric and adult cases. *J Pediatr* 2009; **155:** 432–4.
2. Katz IR, *et al*. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 1998; **46:** 8–13.

Night terrors. Night terrors have been reported in 5 patients taking oxybutynin.[1] Four of the patients were young children and the fifth was an elderly woman. Rechallenge was positive in 2 cases.

1. Valsecia ME, *et al*. New adverse effect of oxybutynin: "night terror". *Ann Pharmacother* 1998; **32:** 506.

Overdosage. A report[1] of a 34-year-old woman who ingested 100 mg of oxybutynin. The main symptoms were antimuscarinic effects and included drowsiness, hallucinations, dilatation of pupils, and urinary retention. Tachycardia resolved shortly after admission to hospital but ventricular ectopic beats and bigeminy persisted for over 24 hours. The patient recovered with symptomatic treatment.

1. Banerjee S, *et al*. Poisoning with oxybutynin. *Hum Exp Toxicol* 1991; **10:** 225–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxybutynin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Itraconazole. Use of itraconazole with oxybutynin resulted in moderate increases of serum concentrations of the latter.[1] However, concentrations of the active metabolite of oxybutynin, *N*-desethyloxybutynin, were virtually unchanged and the interaction was considered to be of minor clinical significance.

1. Lukkari E, *et al*. Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. *Eur J Clin Pharmacol* 1997; **52:** 403–6.

Pharmacokinetics

After oral doses of oxybutynin, peak plasma concentrations are reached within one hour. Oxybutynin is also absorbed after application to the skin. It is highly bound to plasma proteins. Oxybutynin undergoes extensive first-pass metabolism, particularly by the cytochrome P450 isoenzyme CYP3A4, and systemic oral bioavailability has been reported to be only 6%. *N*-desethyloxybutynin is an active metabolite. Oxybutynin and its metabolites are excreted in the urine and faeces, and an elimination half-life of 2 to 3 hours has been reported. Oxybutynin has been detected in breast milk. Evidence suggests that it may cross the blood-brain barrier.

References.

1. Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. *J Clin Pharmacol* 1999; **39:** 289–96.
2. Appell RA, *et al*. Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc* 2003; **78:** 696–702.
3. Reiz JL, *et al*. Pharmacokinetics and pharmacodynamics of once-daily controlled-release oxybutynin and immediate-release oxybutynin. *J Clin Pharmacol* 2007; **47:** 351–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Delak; Ditropan; Oxi-Q; Oxitina; Oxyurin; Retebem; Retemicon; Soxsup†; Tinaxina; Urequin; ***Austral.***: Ditropan; Oxytrol; ***Austria***: Detrusan; Ditropan; Kentera; ***Belg.***: Ditropan; Kentera; ***Braz.***: Frenurin; Incontinol; Retemic; ***Canad.***: Ditropan; Gelnique; Nu-Oxybutyn; Oxytrol; Uromax; ***Chile***: Odranal; Urazol; Uricont; ***China***: Anrushan (安如山)†; Ao Ning (奥宁); Jie Sai (捷赛); Shuang Miao (爽妙); Yi Jing (依静); ***Cz.***: Ditropan; Kentera; Uroxal; ***Denm.***: Kentera; ***Fin.***: Cystrin; Kentera; ***Fr.***: Ditropan; Driptane; ***Ger.***: Dridase; Kentera; Lyrinel†; Oxybugamma; Oxybutin; Oxymedin†; Ryol†; Spasyt†; ***Gr.***: Ditropan; Kentera; Lyrinel; Oxybase; ***Hung.***: Ditropan; Uroxal; ***India***: Cystran; Nocturin; Oxybutin; Oxyspas; ***Irl.***: Cystrin; Ditropan; Kentera; Lyrinel XL; ***Israel***: Lyrinel; Novitropan; ***Ital.***: Ditropan; ***Jpn***: Neoxy; ***Malaysia***: Voxytane; ***Mex.***: Inprax; Lyrinel; Nefryl; Tavor; ***Neth.***: Dridase; Kentera; ***Norw.***: Kentera; ***NZ***: Oxytrol; ***Philipp.***: Driptane; ***Pol.***: Cystrin†; Ditropan; Driptane; Kentera; Uroton; ***Port.***: Ditropan; Kentera; Lyrinel; ***Rus.***: Driptane (Дриптан); Novitropan (Новитропан); ***S.Afr.***: Ditropan; Lenditro; Lyrinel; Oxyspas; Urihexal; ***Singapore***: Lyrinel; Obutin; ***Spain***: Ditropan; Dresplan; ***Swed.***: Ditropan; Kentera; ***Switz.***: Ditropan; Kentera; Lyrinel; ***Thai.***: Diutropan; Lyrinel; ***Turk.***: Uropan; ***UK***: Cystrin; Ditropan; Kentera; Lyrinel XL; ***Ukr.***: Driptane (Дриптан); Sibutin (Сибутин); ***USA***: Anturol†; Ditropan; Gelnique; Oxytrol; ***Venez.***: Reteven.

Pharmacopoeial Preparations

BP 2014: Oxybutynin Oral Solution; Oxybutynin Tablets; Prolonged-release Oxybutynin Tablets;

USP 36: Oxybutynin Chloride Extended-Release Tablets; Oxybutynin Chloride Syrup; Oxybutynin Chloride Tablets.

Papaverine *(BAN)*

Papaveriini; Papaverin; Papaverina; Papaverinum; Папаверин.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline.

$C_{20}H_{21}NO_4$=339.4

CAS — 58-74-2.

ATC — A03AD01; G04BE02.

ATC Vet — QA03AD01; QG04BE02.

UNII — DAA13NKG2Q.

NOTE. Papaverine should not be confused with papaveretum (p. 112.2).

Papaverine Hydrochloride *(BANM)*

Papaveriinihydrokloridi; Papaverina, hidrocloruro de; Papavérine, chlorhydrate de; Papaverin-hidroklorid; Papaverin-hydrochlorid; Papaverinhydrochlorid; Papaverinhydroklorid; Papaverini hydrochloridum; Papaverinii Chloridum; Papaverinium Chloride; Papaverino hidrochloridas; Papaweryny chlorowodorek; Папаверина Гидрохлорид.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride.

$C_{20}H_{21}NO_4$,HCl=375.8

CAS — 63817-84-5 (papaverine cromesilate); 61-25-6 (papaverine hydrochloride); 39024-96-9 (papaverine monophosadenine); 2053-26-1 (anhydrous papaverine sulfate).

ATC — A03AD01; G04BE02.

ATC Vet — QA03AD01; QG04BE02.

UNII — 23473EC6BQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Papaverine Hydrochloride). White or almost white crystals or crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.0.

USP 36: (Papaverine Hydrochloride). Odourless white crystals or white, crystalline powder. Soluble 1 in 30 of water and 1 in 120 of alcohol; soluble in chloroform; practically insoluble in ether. pH of a 2% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Papaverine is an alkaloid present in opium, although it is not related chemically or pharmacologically to the other opium alkaloids. Papaverine has a direct relaxant effect on smooth muscle which is attributed in part to its ability to inhibit phosphodiesterase. It has been given in the management of cerebral, peripheral, and coronary **vascular disorders**; it is also given as an **antispasmodic** for gastrointestinal disorders and coughs. However, there is little evidence to justify its clinical use in these conditions.

Papaverine hydrochloride has been given orally in doses of up to 600 mg daily. Sustained-release preparations have been used. The codecarboxylase derivative, cromesilate, hydrobromide, monophosadenine, nicotinate, sulfate, and teprosilate have also been used. Papaverine hydrochloride has also been given in doses of 30 to 120 mg by intramuscular or slow intravenous injection, repeated every 3 hours as needed (but see Adverse Effects and Precautions, below).

Papaverine hydrochloride has been given by injection into the corpus cavernosum of the penis for the treatment of **erectile dysfunction** (p. 2348.2). Doses have ranged from 2.5 to 60 mg, but must be initially titrated by the prescriber. Doses up to about 30 mg have been combined with phentolamine.

Adverse Effects and Precautions

Adverse effects of oral papaverine include gastrointestinal disturbance, flushing of the face, headache, malaise, drowsiness, skin rash, sweating, orthostatic hypotension, and dizziness. Jaundice, eosinophilia, and signs of altered liver function may occur, sometimes due to hypersensitivity. In addition high parenteral doses can result in cardiac arrhythmias; intravenous or intramuscular doses should be given slowly. Thrombosis has been reported at the injection site.

Intracavernosal injection can cause dose-related priapism and local fibrosis has been reported after long-term therapy.

Papaverine should be given with caution to patients with reduced gastrointestinal motility. Caution is also advised in the presence of cardiac conduction disorders or unstable cardiovascular disease, especially when papaverine is given parenterally. Intravenous dosage is contra-indicated in patients with complete AV block.

Glaucoma. There appeared to be no basis for the manufacturers' recommendation that papaverine should be used with caution in patients with glaucoma.[1] There was no obvious mechanism to support such a warning and only 1 report of an adverse reaction had been received by the FDA. The author had given papaverine intracavernosally to patients with glaucoma and had seen no deterioration.

1. Swartz DA, Todd MW. Intracavernous papaverine and glaucoma. *JAMA* 1990; **264:** 570.

Intracavernosal administration. Systemic adverse effects occurring after intracavernosal injection of papaverine are infrequent but include dizziness and syncope,[1,2] probably

related to the hypotensive effects of papaverine; abnormal liver function test results have also occurred.[1-3]

The most serious acute adverse effect is priapism[1,2,4] and patients should be instructed to seek medical help if an erection lasts for more than 4 hours. Detumescence can be effected by aspiration of blood from the corpus or by local injection of an alpha-adrenergic agonist such as adrenaline, metaraminol, or phenylephrine (see Priapism under Alprostadil, p. 2353.2). Other local effects include haematoma, infection, and, on long-term therapy, fibrosis and penile distortion.[1,2]

Dispensing errors have resulted in inadvertent injection of *papaveretum* with potentially fatal consequences.[2,5,6]

1. Krane RJ, *et al*. Impotence. *N Engl J Med* 1989; **321:** 1648–59.
2. Bénard F, Lue TF. Self-administration in the pharmacological treatment of impotence. *Drugs* 1990; **39:** 394–8.
3. Levine SB, *et al*. Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol (Baltimore)* 1989; **141:** 54–7.
4. Virag R. About pharmacologically induced prolonged erection. *Lancet* 1985; **i:** 519–20.
5. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.
6. Gregoire A. Self injection treatment for impotence. *BMJ* 1990; **300:** 537.

Interactions

Levodopa. For the effects of papaverine on levodopa, see p. 908.1.

Pharmacokinetics

The biological half-life of papaverine given orally is reported to be between 1 and 2 hours, but there is wide interindividual variation. It is about 90% bound to plasma proteins.

Papaverine is mainly metabolised in the liver and excreted in the urine, almost entirely as glucuronide-conjugated phenolic metabolites.

The reports of infrequent systemic effects after intracavernosal injection of papaverine indicate that there is some distribution to the systemic circulation from the corpus cavernosus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mesotina; ***China***: Bo Wei (泊威); Fei Lin (菲林); FuHong (福虹); Gai Yi (盖一); Kai Ge La Fei (凯格拉非); Kuo Shu (阔舒); Sai De Long (赛德隆); ***India***: Paparin; ***Venez.***: Atroveran; Papaveryl.

Multi-ingredient Preparations. ***Arg.***: Antipasmol; Antispasmina; Gastranil; Hepatodirectol; Neoastrin; ***Austria***: Androskat; ***Braz.***: Ductoveran; Espasmocron†; Monotrean B6; Monotrean; Sedalene; Sedalin†; Spasmotropin; Vagostesyl; ***Chile***: Buton; Colicor; Dipatropin; Dolospam; ***Fr.***: Acticarbine; ***Hong Kong***: Codolax†; Codoplex; Codoplex; Enterocin Compound†; Methor-Co†; Metoplex; Vickolax†; ***Hung.***: Meristin; Neo-Bilagit; Troparinum; ***India***: Brovon; ***Indon.***: Sanmag; Spaslic; Spasmal; Spasminal†; ***Israel***: Spasmalgin; ***Ital.***: Antispasmina Colica; ***Mex.***: Acilin; ***Neth.***: Androskat; ***Pol.***: Biospasmil†; Fortestomachicae; Spasticol; Tolargin†; ***Port.***: Antispasmina Colica†; ***Rus.***: Andipal (Андипал); Pagluferal (Паглюферал); Papazol (Папазол); ***Spain***: Sulmetin Papaver†; ***Swed.***: Spasmofen; ***Switz.***: Spasmosol†; ***UK***: Brovon; ***USA***: Tri-Mix; ***Venez.***: Atrobel.

Pharmacopoeial Preparations
BP 2014: Papaverine Injection;
USP 36: Papaverine Hydrochloride Injection; Papaverine Hydrochloride Tablets.

Propiverine Hydrochloride

(BANM, rINNM)

BUP-4 (propiverine); Hidrocloruro de propiverina; Propiverin Hidroklorür; Propiverina, hidrocloruro de; Propivérine, Chlorhydrate de; Propiverini Hydrochloridum; Пропиверина Гидрохлорид.

1-Methyl-4-piperidyl diphenylpropoxyacetate hydrochloride.

$C_{23}H_{29}NO_3$,HCl=403.9

CAS — 60569-19-9 (propiverine); 54556-98-8 (propiverine hydrochloride).

ATC — G04BD06.

ATC Vet — QG04BD06.

Uses and Administration

Propiverine hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used for the management of urinary frequency, urgency, and incontinence (p. 2349.2) in neurogenic bladder disorders and in idiopathic detrusor instability. Usual oral doses of propiverine hydrochloride are 15 mg two or three times daily, increased to 4 times daily if required. Some patients may respond to 15 mg once daily. A daily dose of 60 mg should not be exceeded. Propiverine hydrochloride can also be given as a modified-release preparation in a dose of 30 mg once daily.

Administration in hepatic impairment. Although UK licensed product information for propiverine does not recommend its use in patients with moderate or severe hepatic impairment some[1] suggest that on pharmacokinetic grounds it may be given to those with mild to moderate degrees of impairment at recommended doses without increasing the risk of adverse effects.

1. Siepmann M, *et al*. Pharmacokinetics and safety of propiverine in patients with fatty liver disease. *Eur J Clin Pharmacol* 1998; **54:** 767–71.

Urinary incontinence. Although propiverine is licensed in the UK for use in urinary frequency, urgency, and incontinence (see above), guidelines subsequently issued by NICE consider that although it should be an option for urinary frequency in women with overactive bladder syndrome, use in women with overt incontinence is not recommended.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Hypotension and drowsiness may also occur with propiverine. Propiverine is contra-indicated in patients with moderate or severe hepatic impairment (but see above). Liver enzyme values should be monitored in patients receiving long-term therapy. Skeletal retardation has occurred in the offspring of *animals* given high doses of propiverine during pregnancy and therefore its use is not recommended during pregnancy.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Hypotension may occur in patients treated with propiverine and isoniazid. Drowsiness may be enhanced by drugs with CNS-depressant properties.

Pharmacokinetics

Propiverine is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2.3 hours after oral doses. It undergoes extensive first-pass metabolism and the average absolute bioavailability is reported to be about 41%. Plasma concentrations of the principal metabolite, the *N*-oxide, greatly exceed those of the parent compound. Protein binding is about 90% for propiverine and 60% for the *N*-oxide metabolite. Propiverine and its metabolites are excreted in the urine, bile, and faeces. The elimination half-life is about 20 hours.

References.
1. Haustein K-O, Hüller G. On the pharmacokinetics and metabolism of propiverine in man. *Eur J Drug Metab Pharmacokinet* 1988; **13:** 81–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Mictonorm; ***China***: He Er Shu (贺尔舒); Hua Ke (华克); PeiNing (培宁); ***Cz.***: Mictonetten; Mictonorm; ***Ger.***: Mictonetten; Mictonorm; Propimedac; Propiver; ***Gr.***: Mictonorm; ***Hong Kong***: Mictonorm; ***Indon.***: Mictonorm; ***Irl.***: Detrunorm; Propinorm; ***Jpn***: BUP-4; ***Philipp.***: Mictonorm; ***Port.***: Mictonorm; ***S.Afr.***: Detrunorm; ***Singapore***: Mictonorm; ***Thai.***: Mictonorm†; ***Turk.***: Mictonorm; ***UK***: Detrunorm.

Pygeum Africanum

African Prune; Afrikankirsikkapuunkuori (pygeum africanum bark); Afrikinių slyvų žievė (pygeum africanum bark); Kůra slivoně africké (pygeum africanum bark); Pigeum; Pruni Africanae; Pruni africanae cortex (pygeum africanum bark); Prunier d'Afrique; Prunier d'Afrique, écorce de (pygeum africanum bark); Африканская Слива.

ATC — G04CX01.

ATC Vet — QG04CX01.

*ATC Herb — HG04CW5007 (*Prunus africana*: bark).*

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Pygeum Africanum Bark; Pygeum Bark BP 2014). The whole or cut, dried bark of the stems and branches of *Prunus africana* (*Pygeum africanum*).

USP 36: (Pygeum). The bark of *Prunus africana* (*Pygeum africanum*) (Rosaceae). It contains not less than 9.0% of extractable matter.

Profile

An extract from the bark of the tree *Prunus africana* (*Pygeum africanum*) is used in the treatment of benign prostatic hyperplasia (p. 2347.1). Like some other phytotherapies for this disorder, it appears to contain various sitosterols. A usual oral dosage is 100 mg daily.

Benign prostatic hyperplasia. Pygeum africanum appears to produce a modest benefit on urological symptoms and measures of urinary flow.

References.
1. Andro M-C, Riffaud J-P. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. *Curr Ther Res* 1995; **56:** 796–817.
2. Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996; **78:** 325–36.
3. Ishani A, *et al*. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; **109:** 654–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Prostem; ***China***: Tadenan (太得恩); ***Cz.***: Tadenan†; ***Fr.***: Tadenan; ***Gr.***: Foudaril; Rotamat; Tadenan; ***Ital.***: Pigenil; ***Mex.***: Tadenom; ***Philipp.***: Tadenan; ***Pol.***: Poldanen; Tadenan; ***Rus.***: Tadenan (Таденан); Trianol (Трианол); ***Spain***: Acubiron†; Bidrolar†; Pronitol†; Tuzanil; ***Switz.***: Tadenan; ***Thai.***: Tadenan; ***Ukr.***: Tadenan (Таденан); Trianol (Трианол)†.

Multi-ingredient Preparations. ***Arg.***: Catiz Plus; Normoprost Compuesto; Normoprost Plus; Ultracal; ***Belg.***: Prostatonin†; ***Braz.***: Prostem Plus; ***Canad.***: Prosta Ease; Prostease; ***Fr.***: Prosta-SecurA; ***Hong Kong***: Prostease; ***Hung.***: Prostatonin; ***Pol.***: Neo-poldanen†; ***Port.***: Neo Urgenin; ***Spain***: Neo Urgenin†; Prosturol; Tebetane Compuesto; ***Switz.***: Prostatonin; ***UK***: Potenzia.

Pharmacopoeial Preparations
USP 36: Pygeum Capsules.

Saw Palmetto

American Dwarf Palm; *Brahea serrulata*; *Sabal serrulata*; *Serenoa repens*; *Serenoa serrulatum*; PA-109; Palma enana americana; Palmera de Florida; Sabal; Sabal, fruit de (saw palmetto fruit); Sabalis Serrulatae; Sabalis serrulatae fructus (saw palmetto fruit); Sågpalmettofrukt (saw palmetto fruit); Sahapalmunhedelmä (saw palmetto fruit); Serenový plod (saw palmetto fruit); Šliaužiančiųjų serenojų vaisiai (saw palmetto fruit); Пальма Сереноа.

ATC — G04CX02.

ATC Vet — QG04CX02.

*ATC Herb — HG04CW5008 (*Serenoa repens*: fruit).*

*UNII — 487DXM62F2 (*Serenoa repens*); J7WWH9M8QS (*Serenoa repens *fruit).*

Pharmacopoeias. In *Eur.* (see p. vii) and *US*. *Eur.* and *US* also include the extract. *US* also includes the powdered form.

Ph. Eur. 8: (Saw Palmetto Fruit). The dried, ripe fruit of *Serenoa repens* (*Sabal serrulata*). It has a strong, but not rancid, odour. It contains not less than 11.0% of total fatty acids, calculated with reference to the dried drug.

USP 36: (Saw Palmetto). The partially dried, ripe fruit of *Serenoa repens* (Arecaceae). Store in airtight containers. Protect from light.

Profile

The dried fruit of the saw palmetto or American dwarf palm tree, *Serenoa repens* (Arecaceae), contains steroidal compounds with anti-androgenic and oestrogenic activities, one of which is sitosterol (p. 1471.2). Saw palmetto is used for the treatment of benign prostatic hyperplasia. Preparations of alcoholic or lipophilic extracts of the fruit have typically been given in oral doses of 160 mg twice daily, or 320 mg once daily.

Adverse effects. A systematic review of the adverse effects of saw palmetto, including data from international and national reporting schemes, clinical studies, case reports, and manufacturers, found the most frequent adverse effects to be gastrointestinal disturbances, abdominal pain, fatigue, headache, decreased libido, and rhinitis. There was one report of hypokalaemia leading to fatality received by the Australian national reporting scheme (ADRAC).[1]

1. Agbabiaka TB, *et al*. Serenoa repens (saw palmetto): a systematic review of adverse events. *Drug Safety* 2009; **32:** 637–47.

EFFECTS ON THE LIVER. Cholestatic hepatitis occurred in a man who took a herbal preparation containing saw palmetto for 2 weeks to treat nocturia and hesitancy.[1]

1. Hamid S, *et al*. Protracted cholestatic hepatitis after the use of Prostata. *Ann Intern Med* 1997; **127:** 169–70.

Uses. *BENIGN PROSTATIC HYPERPLASIA.* A lipid hexane extract of saw palmetto has been shown to be generally superior to placebo,[1,2] and of similar efficacy to finasteride[3] in the treatment of benign prostatic hyperplasia (p. 2347.1). However, a double-blind study[4] found that treatment for one year was not superior to placebo for improving

urinary symptoms and objective measures. A subsequent systematic review of 30 randomised studies of various saw palmetto extracts concluded that they did not improve urological symptoms and flow measures in men with benign prostatic hyperplasia.[5]

1. Champault G, *et al*. A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia. *Br J Clin Pharmacol* 1984; **18:** 461.
2. Plosker GL, Brogden RN. Serenoa repens (Permixon): a review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging* 1996; **9:** 379–95.
3. Carraro J-C, *et al*. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate* 1996; **29:** 231–40.
4. Bent S, *et al*. Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; **354:** 557–66.
5. Tacklind J, *et al*. Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 15/01/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Beltrax Uno; Permicaps; Permixon; Serecur; ***Austral.***: Pro-Guard†; Prostate Defence; ***Austria***: Permixon; Prosta-Urgenin; Prostasan; Sabal; ***Belg.***: Prosta-Urgenin; Prostaserene; ***Braz.***: Prostat; Prostatal; Renopen; ***Canad.***: Sabalasan; ***Chile***: Prostafort; Sabal; ***China***: Prostadyn (柏诺特); ***Cz.***: Capistan; Prosta-Urgenin; Prostakan Mono; Prostamol Uno; Spalda Sabal; ***Fin.***: Curbisal; Prostacaps†; Prostaforce; ***Fr.***: Permixon; Prodinan; Sabal; ***Ger.***: Cefasabal†; Eviprostat-S; Horphagen uno; Hyperprost; Prosta Urgenin Uno; Prostagutt mono; Prostagutt uno; Prostess; Remiprostan uno; Sabal uno; Sabal; Sabalvit; Sita†; Steiprostat; Strogen; Talso†; ***Gr.***: Libeprosta; Urisedon; ***Hong Kong***: Permixon; ***Hung.***: Prostamol Uno; Saballo; Strogen Uno; ***Indon.***: Lanaprost†; Prostakur†; ***Israel***: Permixon; ***Ital.***: Permixon; Prosteren; Rilaprost; Saba; Serpens; ***Malaysia***: Lanaprost; ***Mex.***: Permixon; Prostasan; Prostex; Urogutt; ***Norw.***: Curbisal; Fitoprost; ***Philipp.***: Prostacare; ProstActive; ***Pol.***: Bioprost; Fitoprost; Permixon†; Prostaforce; Prostamol Uno; Prostaplant; Sterko; ***Port.***: Permixon; Sereprosta; ***Rus.***: Permixon (Пермиксон); Prostamol Uno (Простамол Уно); Prostaplant (Простаплант); ***Singapore***: Lanaprost; Permixon; Prostakan; ***Spain***: Permixon; Sereprostat; ***Swed.***: Curbisal; Sabamin; ***Switz.***: Permixon; Prosta-Urgenine; Prostadyn; Prostagutt uno; ProstaMed; Prostasan; SabCaps; ***Thai.***: Blackmores Proseren; Permixon; Prosta-Urgenin; Sametto; Urogutt; ***Turk.***: Prostagood; ***UK***: Prostasan; Sabal; Sabalin; ***Ukr.***: Prosta Urgenin Uno (Проста Ургенин Уно)†; Prostacer (Простакер); Prostamol Uno (Простамол Уно); Prostaplant (Простаплант); ***Venez.***: Chronostim.

Multi-ingredient Preparations. ***Arg.***: ADX; Anastim; Argeal; Catiz Plus; Keracnyl; Keracnyl; Normoprost Plus; Novo Prostasan; PR21; Sabal; Troxac; Ultracal; ***Austral.***: Advanced Prostate Care; Extralife Flow-Care†; Masculine Herbal Complex; Mens Dual-Action Multi; Mens Super Soy/Clover†; Prosta Balance; ProstaCo; Prostate Health Formula; ***Austria***: Prostagutt; Spasmo-Urgenin; Urgenin; Urogutt; ***Belg.***: Prostalane†; Urgenin; ***Braz.***: Capilos; ***Canad.***: Prosta Ease; Prostease; Saw Palmetto Formula†; ***Chile***: Argeal; Keracnyl; ***Cz.***: Prostakan Forte; ***Fr.***: Argeal; Kelual DS; Keracnyl; Keracnyl; Kertyol Shampooing†; ProstaSecurA; ***Ger.***: Cefasabal†; Granu Fink Prosta; Nephroselect M; Prostagutt forte; ***Hong Kong***: Palmetto Plus†; Phyto-Ease; Prostease; Urgenin†; ***Hung.***: Prostazyn; ***Indon.***: Instink†; Maxirex; Menolia†; Reximax; Soprost†; ***Israel***: Urgenin†; ***Ital.***: Bioesse Plus; Biothymus M; Pluvio; Prostaplant; Sametrix; ***Malaysia***: Cefasabal; ***Mex.***: Prosgutt; ***Pol.***: Naturapia Prostata†; Penigra; ***Port.***: Efluvium Anti-caspa†; Efluvium Anti-seborreico†; Neo Urgenin; ***Rus.***: Prostagutt Forte (Простагут Форте); ***Singapore***: Palmetto Plus†; ***Spain***: Neo Urgenin†; Spasmo-Urgenin; Urgenin†; ***Switz.***: Granu Fink Prosta†; Prostagutt-F; ***Thai.***: Spasmo-Urgenin; ***UK***: Antiglan; Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Potenzia; Regina Royal Concorde; Strength; ***Ukr.***: Prostaplant Forte (Простаплант Форте); ***USA***: Alive Mens Energy; Clinical Nutrients 50-Plus Men; Udamin SP; ***Venez.***: Argeal; Sabal.

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; Cantharis Med Complex; Erbiode-Starkungstropfen; Gentos; Prosfortil; ***Canad.***: Breast Enhancer; Male +; Reneel†; ***Fr.***: Juniperus Complexe No 6; Sabal Serrulata Compose; ***Ger.***: Cysto Hevert; Hewesabal mono†; Homvio-Rin; Pascosabal; Prostamed Mikto; Prostasabal; Prostata-Entoxin N; Prostata-Gastreu N R25; Prostata-Komplex L Ho-Fu-Complex; Prostata-Komplex N Ho-Fu-Complex†; Urofossat; Urokatt; Urotruw N; Ursinol; ***Hung.***: Gentos; ***Neth.***: Reneel H; Sabal-Homaccord; ***Rus.***: Gentos (Гентос); Sabal-Homaccord (Сабаль-Гомаккорд); ***Switz.***: Regenaplex Nr. 49a; ***Ukr.***: Gentos (Гентос); Homvio-Prostan (Хомвио-Простан).

Pharmacopoeial Preparations
USP 36: Saw Palmetto Capsules.

Sildenafil Citrate *(BANM, USAN, rINNM)*

Citrato de sildenafilo; Sildénafil, citrate de; Sildenafil Sitrat; Sildenafili citras; Sildenafilo, citrato de; UK-92480-10; Сильденафила Цитрат.

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-*d*]pyrimidin-7-one citrate; 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazone citrate.

$C_{22}H_{30}N_6O_4S,C_6H_8O_7$=666.7

CAS — 139755-83-2 (sildenafil); 171599-83-0 (sildenafil citrate).
ATC — G04BE03.
ATC Vet — QG04BE03.
UNII — BW9B0ZE037.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Sildenafil Citrate). A white or almost white, slightly hygroscopic, crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in hexane. Store in airtight containers.

USP 36: (Sildenafil Citrate). A white or almost white, slightly hygroscopic, crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in hexane. Store in airtight containers.

Stability. Sildenafil citrate tablets were ground to a powder and combined with a 1:1 mixture of methylcellulose 1% and simple syrup (USNF), or with a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (both *Paddock, USA*), to a nominal concentration of 2.5 mg/mL sildenafil citrate in each suspension.[1] Both suspensions were found to be chemically and physically stable for 91 days in plastic bottles, at both 4 degrees and 25 degrees.

1. Nahata MC, *et al*. Extemporaneous sildenafil citrate oral suspensions for the treatment of pulmonary hypertension in children. *Am J Health-Syst Pharm* 2006; **63:** 254–7.

Uses and Administration

Sildenafil is a phosphodiesterase type-5 inhibitor used in the management of erectile dysfunction and pulmonary arterial hypertension (see below and p. 2365.1 respectively for more details). It can be given orally, or by intravenous injection, as the citrate although doses are expressed in terms of the base; 14 mg of sildenafil citrate is equivalent to about 10 mg of sildenafil.

In **erectile dysfunction**, it is given orally, in a usual dose equivalent to sildenafil 50 mg about one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 100 mg, and sildenafil should not be taken more than once in 24 hours.

- An initial dose of 25 mg has been suggested in the USA for patients over 65 years of age, though such initial reductions are not considered necessary in the UK.
- An initial dose of no more than 25 mg daily is advised in patients taking sildenafil with inhibitors of cytochrome P450 isoenzyme CYP3A4; the dose should not exceed 25 mg every 48 hours if given with ritonavir-boosted HIV-protease inhibitors, although such a combination is best avoided entirely (see Interactions, p. 2366.3).
- In patients stabilised on alpha blocker therapy, an initial dose of sildenafil 25 mg should be considered.

To improve exercise ability in **pulmonary arterial hypertension**, sildenafil is given orally in a dose of 20 mg three times daily. Alternatively, it may be given by intravenous injection in a dose of 10 mg three times daily if the oral route is not possible. Use of sildenafil for pulmonary arterial hypertension is not recommended with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir; use with other potencies of CYP3A4 inhibitor may require a reduction in the sildenafil dose. In the UK, a dose reduction to 20 mg twice daily orally, or 10 mg twice daily intravenously, should be considered in patients taking sildenafil with medium-potency CYP3A4 inhibitors like erythromycin or unboosted saquinavir. A reduction to 20 mg once daily orally, or 10 mg once daily intravenously, is advised in patients taking sildenafil with stronger CYP3A4 inhibitors like clarithromycin, telithromycin, and nefazodone.

For doses in children, see Administration in Children below.

For doses in hepatic and renal impairment, see below.

Administration in children. Sildenafil citrate may be given *orally* to children for the treatment of pulmonary arterial hypertension. In Europe it is licensed for use in those aged from 1 to 17 years. The dose for those weighing 20 kg or less is 10 mg three times daily, and for those weighing over 20 kg [about 6 years or older] it is 20 mg three times daily (the same as the licensed adult dose). The *BNFC* suggests that neonates and children up to 1 year may be given an initial dose of 250 to 500 micrograms/kg every 4 to 8 hours, adjusted according to response to a maximum of 30 mg daily. Tapered withdrawal is advised.

Although unlicensed in neonates and children, *intravenous* sildenafil has been used successfully. In a dose-finding study involving 36 neonates with persistent pulmonary hypertension,[1] an intravenous loading dose of 400 micrograms/kg given over 3 hours, followed by a maintenance infusion (for 48 hours to 7 days) of 1.6 mg/kg daily improved oxygenation scores and was well tolerated.

1. Steinhorn RH, *et al*. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. *J Pediatr* 2009; **155:** 841–7.

Administration in hepatic impairment. Sildenafil clearance is reduced in patients with hepatic impairment. Safety has not been established in patients with severe hepatic impairment (Child-Pugh class C) and its use is contra-indicated in these patients for this reason.

Licensed product information for patients with **erectile dysfunction** recommends an initial oral dose of 25 mg in patients with hepatic impairment.

Licensed product information for patients with **pulmonary arterial hypertension** states that initial dose adjustments are not needed for patients with mild or moderate hepatic impairment (Child-Pugh class A or B); in the UK, it is recommended that a reduction to 20 mg twice daily orally, or 10 mg twice daily intravenously, should be considered if therapy is not well tolerated.

Administration in renal impairment. Sildenafil clearance is reduced in patients with severe renal impairment.

Licensed product information for patients with **erectile dysfunction** recommends that in these patients, an initial oral dose of 25 mg should be considered. In the UK it is stated that the dose may be increased to 50 or 100 mg orally, if needed and tolerated.

Licensed product information for patients with **pulmonary arterial hypertension** states that no dose adjustments are required for patients with renal impairment, including those with severe renal impairment (creatinine clearance less than 30 mL/minute). However, in the UK, consideration of a reduction to 20 mg twice daily orally, or 10 mg twice daily intravenously, is suggested if therapy is not well tolerated.

Benign prostatic hyperplasia. Although not routinely recommended due to a lack of data, sildenafil has been used to treat lower urinary tract symptoms commonly associated with benign prostatic hyperplasia (p. 2347.1).[1]

1. Gales BJ, Gales MA. Phosphodiesterase-5 inhibitors for lower urinary tract symptoms in men. *Ann Pharmacother* 2008; **42:** 111–15.

Erectile dysfunction. Sildenafil, an inhibitor of phosphodiesterase type-5, is used as an oral therapy for erectile dysfunction (p. 2348.2). It is effective in erectile dysfunction of psychogenic causes and organic causes such as diabetes mellitus, spinal-cord injury, and prostatectomy.

References.

1. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. *Drugs* 1999; **57:** 967–89.
2. Montorsi F, *et al*. Efficacy and safety of fixed-dose oral sildenafil in the treatment of erectile dysfunction of various etiologies. *Urology* 1999; **53:** 1011–18.
3. Rendell MS, *et al*. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. *JAMA* 1999; **281:** 421–6.
4. Kedia S, *et al*. Treatment of erectile dysfunction with sildenafil citrate (Viagra) after radiation therapy for prostate cancer. *Urology* 1999; **54:** 308–12.
5. Zippe CD, *et al*. Role of Viagra after radical prostatectomy. *Urology* 2000; **55:** 241–5.
6. Fink HA, *et al*. Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2002; **162:** 1349–60.
7. Fedele D, *et al*. Experience with sildenafil in diabetes. *Diabetes Nutr Metab* 2002; **15:** 49–52.
8. Derry F, *et al*. Efficacy and safety of sildenafil citrate (Viagra) in men with erectile dysfunction and spinal cord injury: a review. *Urology* 2002; **60** (suppl): 49–57.
9. Raina R, *et al*. Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. *Urology* 2003; **62:** 110–15.
10. Carson CC. Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients. *Curr Urol Rep* 2003; **4:** 488–96.
11. Setter SM, *et al*. Phosphodiesterase 5 inhibitors for erectile dysfunction. *Ann Pharmacother* 2005; **39:** 1286–95.

Female sexual dysfunction. Improvements have been reported in women with antidepressant-associated sexual dysfunction after treatment with sildenafil compared with placebo.[1] A review[2] concluded that, although data suggest a possible role for sildenafil for the treatment of female sexual dysfunction, studies are small and of variable quality, and should be interpreted with caution.

1. Nurnberg HG, *et al*. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA* 2008; **300:** 395–404.
2. Brown DA, *et al*. Assessing the clinical efficacy of sildenafil for the treatment of female sexual dysfunction. *Ann Pharmacother* 2009; **43:** 1275–85.

High-altitude disorders. Hypoxic pulmonary hypertension associated with high altitude (p. 1276.2) may respond to sildenafil. Small studies have shown some promising results.[1-3]

1. Ghofrani HA, *et al*. Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: a randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med* 2004; **141:** 169–77.
2. Richalet JP, *et al*. Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 2005; **171:** 275–81.
3. Ricart A, *et al*. Effects of sildenafil on the human response to acute hypoxia and exercise. *High Alt Med Biol* 2005; **6:** 43–9.

Oesophageal motility disorders. Preliminary studies[1-3] have investigated the use of sildenafil in patients with oesophageal motility disorders (p. 1813.2) such as achalasia or nutcracker oesophagus. Although some benefit has been reported, further studies are needed.

1. Bortolotti M, *et al.* Effects of sildenafil on esophageal motility of patients with idiopathic achalasia. *Gastroenterology* 2000; **118:** 253–7.
2. Eherer AJ, *et al.* Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. *Gut* 2002; **50:** 758–64.
3. Lee JI, *et al.* The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. *Neurogastroenterol Motil* 2003; **15:** 617–23.

Premature ejaculation. Early reports have suggested that sildenafil may be effective in the management of premature ejaculation (p. 2350.2) and the rationale for such use has been reviewed.[1]

1. Abdel-Hamid IA. Phosphodiesterase 5 inhibitors in rapid ejaculation: potential use and possible mechanisms of action. *Drugs* 2004; **64:** 13–26.

Priapism. Sildenafil has been reported to be effective in the treatment of priapism in 3 patients with sickle-cell disease.[1] In 2 of these patients, sildenafil was also successful in preventing further episodes of priapism when it was taken at the onset of symptoms.

1. Bialecki ES. Sildenafil relieves priapism in patients with sickle cell disease. *Am J Med* 2002; **113:** 252.

Pulmonary hypertension. Oral phosphodiesterase type-5 inhibitors have produced beneficial responses in patients with pulmonary arterial hypertension (p. 1278.2), and sildenafil and tadalafil may be used as first- or second-line therapy in patients in functional class II or III. The results of short-term and long-term studies of phosphodiesterase type-5 inhibitors have been reviewed.[1-3] In a study[4] using single doses of phosphodiesterase type-5 inhibitors, it was found that sildenafil and tadalafil had greater selectivity for the pulmonary circulation than vardenafil, and that arterial oxygenation was improved by sildenafil only. Sildenafil, with which most experience lies, has been given either alone[5-7] or with other treatments such as inhaled nitric oxide,[6] inhaled iloprost,[8] intravenous epoprostenol,[9-11] oral beraprost,[12] or oral bosentan.[13,14] In a pivotal study,[7] sildenafil improved exercise capacity and haemodynamics in patients when given at 20, 40, or 80 mg orally three times daily. While there was no evidence of a dose-response relationship in the primary end-point of exercise capacity, there was a linear trend in the response in haemodynamic measures. In an extension study, all patients were treated with 80 mg orally three times daily if tolerated. Some have questioned whether the licensed dose of 20 mg three times daily is sufficient,[15] especially if patients are given bosentan at the same time (the two drugs interact—see Cardiovascular Drugs under Interactions, p. 2366.3). This led the authors of the original study to suggest that the licensed dose be used initially, with an increase to 40 or 80 mg three times daily in order to achieve or maintain favourable effects.[16]

Where there is associated cirrhosis (portopulmonary hypertension) it has been suggested that sildenafil may be useful in stabilising symptoms sufficiently to facilitate transplantation.[17]

Sildenafil has also been studied for paediatric pulmonary hypertension, including persistent pulmonary hypertension in neonates and in those with pulmonary arterial hypertension associated with congenital heart disease, or secondary to lung disease, or in postoperative pulmonary hypertension and in neonates who are difficult to wean from inhaled nitric oxide.[18-21] Licensed and unlicensed paediatric doses are given under Administration in Children, p. 2364.2.

Sildenafil has also been reported to be of benefit in high-altitude pulmonary hypertension,[22] and has been tried in pulmonary hypertension associated with chronic thromboembolic disorders.[23]

1. Croom KF, Curran, MP. Sildenafil: a review of its use in pulmonary arterial hypertension. *Drugs* 2008; **68:** 383–97.
2. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. *N Engl J Med* 2009; **361:** 1864–71.
3. Buckley MS, *et al.* Phosphodiesterase-5 inhibitors in management of pulmonary hypertension: safety, tolerability, and efficacy. *Drug Healthc Patient Saf* 2010; **2:** 151–61.
4. Ghofrani HA, *et al.* Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol* 2004; **44:** 1488–96.
5. Sastry BKS, *et al.* Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol* 2004; **43:** 1149–53.
6. Michelakis E, *et al.* Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation* 2002; **105:** 2398–2403.
7. Galiè N, *et al.* Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 2148–57.
8. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; **136:** 515–22.
9. Bhatia S, *et al.* Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. *Mayo Clin Proc* 2003; **78:** 1207–13.
10. Stiebellehner L, *et al.* Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003; **123:** 1293–5.
11. Simonneau G, *et al.* PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; **149:** 521–30. Correction. *ibid.* 2009; **150:** 63.
12. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45:** 286–9.
13. Hoeper MM, *et al.* Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; **24:** 1007–10.
14. Mathai SC, *et al.* Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 2007; **29:** 469–75.
15. Hoeper MM, Welte T. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1091.
16. Galiè N, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1092–3.
17. Hemnes AR, Robbins IM. Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. *Liver Transpl* 2009; **15:** 15–19.
18. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 18/01/08).
19. Leibovitch L, *et al.* Therapeutic applications of sildenafil citrate in the management of paediatric pulmonary hypertension. *Drugs* 2007; **67:** 57–73.
20. Huddleston AJ, *et al.* Sildenafil for the treatment of pulmonary hypertension in pediatric patients. *Pediatr Cardiol* 2009; **30:** 871–82.
21. Mourani PM, *et al.* Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009; **154:** 379–84.
22. Aldashev AA, *et al.* Phosphodiesterase type 5 and high altitude pulmonary hypertension. *Thorax* 2005; **60:** 683–7.
23. Suntharalingam J, *et al.* Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2008; **134:** 229–36.

Raynaud's syndrome. Sildenafil has been reported to be of benefit in Raynaud's phenomenon (see Vasospastic Arterial Disorders, p. 1275.3) resistant to vasodilator therapy.[1]

1. Fries R, *et al.* Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; **112:** 2980–5.

Adverse Effects

Adverse effects most commonly reported with sildenafil are headache, flushing, and dyspepsia. Also common are visual disturbances such as blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, pain and redness of the eyes. Retinal haemorrhage has occurred, and non-arteritic anterior ischaemic optic neuropathy (NAION) causing permanent loss of vision has been reported rarely. Other common adverse effects include dizziness, insomnia, anxiety, vertigo, epistaxis, nasal congestion, pyrexia, and gastrointestinal disturbances such as diarrhoea and vomiting. Priapism can occur.

Other adverse effects include skin rashes, erythema, alopecia, limb and/or back pain, myalgia, facial oedema, fluid retention, paraesthesia, and urinary-tract infection. Dyspnoea, cough, rhinitis, sinusitis, bronchitis, and cellulitis can occur. Sudden decrease or loss of hearing has been reported. Other reported effects include anaemia, leucopenia, gynaecomastia, urinary frequency or incontinence, haematuria, and seizures. Hypersensitivity reactions have been reported rarely.

Cerebrovascular haemorrhage and transient ischaemic attacks have occurred. There have also been reports of palpitations, syncope, hypertension, hypotension, and serious cardiovascular events including myocardial infarction, arrhythmias, tachycardia, unstable angina, and sudden cardiac death.

Reviews.

1. Vitezic D. A risk-benefit assessment of sildenafil in the treatment of erectile dysfunction. *Drug Safety* 2001; **24:** 255–65.
2. Padma-nathan H, *et al.* A 4-year update on the safety of sildenafil citrate (Viagra). *Urology* 2002; **60** (suppl 2): 67–90.
3. Tsertsvadze A, *et al.* Oral sildenafil citrate (Viagra) for erectile dysfunction: a systematic review and meta-analysis of harms. *Urology* 2009; **74:** 831–836.

Convulsions. A report[1] of 2 patients who had a first tonic-clonic seizure shortly after taking sildenafil.

1. Gilad R, *et al.* Tonic-clonic seizures in patients taking sildenafil. *BMJ* 2002; **325:** 869.

Effects on the blood. Thrombocytopenia has been reported in a patient taking sildenafil 25 mg three times daily. The patient's platelet count increased when sildenafil was stopped and decreased on rechallenge.[1]

1. Philip A, *et al.* Sildenafil-induced thrombocytopenia. *Ann Intern Med* 2008; **149:** 437–9.

Effects on the cardiovascular system. The effects of phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil) on the cardiovascular system,[1,2] and the potential risks of sexual activity in men with cardiovascular disease,[3] have been reviewed.

There has been considerable uncertainty about the potential cardiovascular risk associated with sildenafil treatment. Minor effects associated with vasodilatation, such as headache and flushing are relatively common, but in patients without pre-existing cardiovascular risk factors the risk of serious cardiovascular events associated with the drug appears to be low. However, there have been reports of myocardial infarction in patients who had no apparent risk factors,[4,5] and a consensus document issued by the American College of Cardiology and the American Heart Association (ACC/AHA) has pointed out that patients with erectile dysfunction are mostly over 45 years of age and are more likely to have risk factors predisposing them to cardiovascular disease.[6]

As of November 1998, 130 deaths in US patients taking sildenafil had been reported to the FDA; 3 of these were due to stroke and 77 to some other cardiovascular event.[7] The nature of the relationship between drug and event was considered unclear, but some of these patients were also receiving nitrates, a combination now contra-indicated because of the greatly increased risk of potentially life-threatening hypotension.[6] The Australian Adverse Drug Reactions Advisory Committee[8] stated in June 2002 that it had received 773 reports of adverse reactions associated with the use of sildenafil. There were 20 reports of myocardial infarction, including 4 fatalities; 9 of these 20 patients had pre-existing cardiovascular disease or diabetes or were considered to be at high risk of cardiovascular disease, and 1 patient was taking nitrates. Other cardiovascular effects reported included 26 reports of chest pain and 10 other fatalities (6 sudden unexplained deaths, 2 strokes, and 2 subarachnoid haemorrhages). However, it was pointed out that the timing of these adverse effects in relation to sildenafil ingestion was often not reported and that, since sildenafil is taken in the context of sexual activity and, in some cases, underlying coronary disease, the contribution of sildenafil to cardiac events was difficult to assess.

It is still uncertain whether patients with **pre-existing** cardiovascular disease are at increased risk when taking sildenafil without concomitant nitrates. The ACC/AHA consensus statement noted that the evidence was scanty and suggested that sildenafil could be used, but with caution, in patients with stable *coronary artery disease* provided that nitrates were not taken.[6] A later review[9] and studies using exercise testing[10,11] also concluded that sildenafil appeared to be well tolerated in most patients with chronic stable coronary artery disease. In men with mild to moderate chronic *heart failure*, small studies have found that sildenafil was well tolerated and effective for erectile dysfunction,[12-14] and improved measures of exercise capacity.[12] Analyses[15,16] of combined study data have examined the effects of sildenafil in men stabilised on antihypertensive treatment (including diuretics, beta blockers, alpha blockers, ACE inhibitors, and calcium-channel blockers) compared with men who did not have *hypertension*. Similar results were found for both groups in terms of sildenafil's efficacy for erectile dysfunction.[16] Also, changes in blood pressure and heart rate after a dose of sildenafil,[15] and the incidence of treatment-related adverse effects that were potentially related to blood pressure decrease,[16] were not significantly different between the groups. Evidence to assess the risk in other cardiovascular disorders is less extensive, although a case report of a patient with hypertrophic *cardiomyopathy* who had cardiovascular adverse effects after a dose of sildenafil suggested that the drug may precipitate an unstable haemodynamic state in this condition.[17]

1. Brindis RG, Kloner RA. Sildenafil in patients with cardiovascular disease. *Am J Cardiol* 2003; **92** (suppl): 26M–36M.
2. Kloner RA. Cardiovascular effects of the 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. *Circulation* 2004; **110:** 3149–55.
3. Kostis JB, *et al.* Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005; **96:** 313–21.
4. Feenstra J, *et al.* Acute myocardial infarction associated with sildenafil. *Lancet* 1998; **352:** 957–8.
5. Kekilli M, *et al.* Acute myocardial infarction after sildenafil citrate ingestion. *Ann Pharmacother* 2005; **39:** 1362–4.
6. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. ACC/AHA Expert Consensus Document. *J Am Coll Cardiol* 1999; **33:** 273–82. Correction. *ibid.*; **34:** 1850. Also available at: http://circ.ahajournals.org/cgi/reprint/99/1/168.pdf (accessed 29/11/05)
7. FDA. Postmarketing safety of sildenafil citrate (Viagra): summary of reports of death in Viagra users received from marketing (late March) through mid-November 1998. Available at: http://www.fda.gov/cder/consumerinfo/viagra/safety3.htm (accessed 29/11/05)
8. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; **21:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
9. Tran D, Howes LG. Cardiovascular safety of sildenafil. *Drug Safety* 2003; **26:** 453–60.
10. Arruda-Olson AM, *et al.* Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. *JAMA* 2002; **287:** 719–25.
11. Fox KM, *et al.* Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina. *Eur Heart J* 2003; **24:** 2206–12.
12. Bocchi EA, *et al.* Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure: a double-blind, placebo-controlled, randomized study followed by a prospective treatment for erectile dysfunction. *Circulation* 2002; **106:** 1097–1103.
13. Webster LJ, *et al.* Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-

controlled, double-blind crossover trial. *Arch Intern Med* 2004; **164:** 514–20.
14. Katz SD, *et al*. Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol* 2005; **95:** 36–42.
15. Zusman RM, *et al*. Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication. *J Hypertens* 2000; **18:** 1865–9.
16. Kloner RA, *et al*. Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens* 2001; **14:** 70–3.
17. Stauffer J-C, *et al*. Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med* 1999; **341:** 700–701.

Effects on the ears. As of October 2007, the US FDA had received a total of 29 postmarketing reports of sudden hearing loss with phosphodiesterase type-5 inhibitors. The problem was sometimes accompanied by tinnitus, vertigo, or dizziness. In most of the cases, the hearing loss involved one ear, and it was either a partial or complete loss of hearing. In about one-third of cases, the loss was temporary. While a causal relationship could not be established, patients should be advised that hearing loss may be related to these drugs, and to seek medical attention if affected.[1]

1. FDA. FDA announces revisions to labels for Cialis, Levitra and Viagra: potential risk of sudden hearing loss with ED drugs to be displayed more prominently (issued 18th October 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html (accessed 18/01/08)

Effects on the eyes. The Australian Adverse Drug Reactions Advisory Committee[1] stated in June 2002 that it had received 65 reports of abnormal vision from a total of 773 adverse reactions associated with use of sildenafil reported over 3 years. A bluish tinge or haze to vision and some increased light sensitivity has been reported by patients taking sildenafil, with the percentage of reports increasing with increasing dose.[2] The visual symptoms usually peak 1 to 2 hours after ingestion and resolve about 3 to 4 hours later. The effects of a single dose of sildenafil 100 mg were studied in 5 healthy subjects.[3] Electroretinogram measurements showed significant changes that correlated well with plasma-sildenafil concentrations, peaking at 1 hour after administration and showing complete recovery at the 6-hour measurements. Inhibition of phosphodiesterase type-6 in rod photoreceptors is the most likely mechanism of sildenafil-associated retinal dysfunction. A review of visual disorders associated with 5-phosphodiesterase inhibitors noted that pooled reports of disturbances of vision with sildenafil suggest an incidence of 2 to 5%; the frequency with vardenafil and tadalafil seems to be lower although the evidence is limited. There is also little evidence of retinal toxicity, but this class of drugs is not recommended for use in patients with hereditary degenerative retinal disorders since they have minor inhibitory effects on 6-phosphodiesterase which has an important role in the visual transduction cascade.[4]

Other visual disturbances reported in patients taking sildenafil have included temporary loss of vision and increased intra-ocular pressure.[5] A 69-year-old man who had permanent loss of vision in one eye a few hours after taking sildenafil 100 mg was found to have an occlusion in a retinal artery.[6] In another similar case of retinal artery occlusion[7] the patient also had uncontrolled hypertension; the authors suggested that embolisation by a pre-existing arteriosclerotic plaque of the carotid artery resulted from elevated blood pressure and cardiac workload during sexual activity, rather than as a direct adverse effect of sildenafil.

Several cases of persistent blurred vision and visual loss caused by nonarteritic anterior ischaemic optic neuropathy (NAION; vascular insufficiency and ischaemia at the optic nerve head) associated with sildenafil use have been reported.[8-11] Generally, visual defects developed in one eye only within 24 hours of sildenafil ingestion, although many of these men had taken doses of sildenafil on past occasions without adverse effect. A small number of cases have also been reported for tadalafil[11-14] and vardenafil.[11] However, many of these men had underlying anatomic or vascular risk factors for NAION, including low cup to disc ratio (crowded disc), age over 50, diabetes, hypertension, ischaemic heart disease, hyperlipidaemia, and smoking. A small, retrospective, case-control study suggested that men who use sildenafil or tadalafil and have a history of myocardial infarction may be at an increased risk of NAION.[15] As of May 2005 the FDA had concluded that it was not possible to determine whether NAION was directly related to the use of phosphodiesterase type-5 inhibitors, the patients' underlying vascular risk factors or anatomical defects, a combination of these factors, or other factors.[11] Later reviews came to similar conclusions,[4,16] and the estimated incidence of NAION in men receiving sildenafil has been calculated to be similar to estimates for the general population.[17]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; **21:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
2. Marmor MF. Sildenafil (Viagra) and ophthalmology. *Arch Ophthalmol* 1999; **117:** 518–19.
3. Vobig MA, *et al*. Retinal side-effects of sildenafil. *Lancet* 1999; **353:** 375.
4. Laties AM. Vision disorders and phosphodiesterase type 5 inhibitors: a review of the evidence to date. *Drug Safety* 2009; **32:** 1–18.
5. CSM/MCA Sildenafil (Viagra). *Current Problems* 1999; **25:** 16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 02/09/08)
6. Tripathi A, O'Donnell N. Branch retinal artery occlusion; another complication of sildenafil. *Br J Ophthalmol* 2000; **84:** 934–5.
7. Bertolucci A, *et al*. Hemi-retinal artery occlusion associated with sexual activity and sildenafil citrate (Viagra). *Acta Ophthalmol Scand* 2003; **81:** 198–200.
8. Boshier A, *et al*. A case of nonarteritic ischemic optic neuropathy (NAION) in a male patient taking sildenafil. *Int J Clin Pharmacol Ther* 2002; **40:** 422–3.
9. Pomeranz HD, *et al*. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002; **109:** 584–7.
10. Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra): a report of seven new cases. *J Neuroophthalmol* 2005; **25:** 9–13.
11. FDA. Alert 07/2005: Sildenafil (marketed as Viagra). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/sildenafilHCP.pdf (accessed 28/07/05)
12. Peter NM, *et al*. Tadalafil-associated anterior ischaemic optic neuropathy. *Eye* 2005; **19:** 715–17.
13. Escaravage GK, *et al*. Tadalafil associated with anterior ischemic optic neuropathy. *Arch Ophthalmol* 2005; **123:** 399–400.
14. Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. *Arch Ophthalmol* 2005; **123:** 400–401.
15. McGwin G, *et al*. Non-arteritic anterior ischaemic optic neuropathy and the treatment of erectile dysfunction. *Br J Ophthalmol* 2006; **90:** 154–7.
16. Danesh-Meyer HV, Levin LA. Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: casual or causal association? *Br J Ophthalmol* 2007; **91:** 1551–5.
17. Gorkin L, *et al*. Sildenafil citrate use and the incidence of nonarteritic anterior ischemic optic neuropathy. *Int J Clin Pract* 2006; **60:** 500–3.

Effects on mental function. There have been a few cases reported[1-3] of transient global amnesia after the use of sildenafil or tadalafil. Between January 1998 and February 2001, the FDA had received 35 reports of amnesia in which sildenafil was listed as the primary causal suspect.[4]

1. Gandolfo C, *et al*. Sildenafil and transient global amnesia. *Neurol Sci* 2003; **24:** 145–6.
2. Savitz SA, Caplan LR. Transient global amnesia after sildenafil (Viagra) use. *Neurology* 2002; **59:** 778.
3. Schiefer J, Sparing R. Transient global amnesia after intake of tadalafil, a PDE-5 inhibitor: a possible association? *Int J Impot Res* 2005; **17:** 383–4.
4. Milman HA, Arnold SB. Neurologic, psychological, and aggressive disturbances with sildenafil. *Ann Pharmacother* 2002; **36:** 1129–34.

Precautions

Caution is required in patients with hepatic or severe renal impairment, and dosage reduction of sildenafil may be necessary. Care is also needed in patients with anatomical deformation of the penis or haematological disorders that may predispose them to priapism. In the event of prolonged erection (for more than 4 hours), patients should seek medical assistance, as penile tissue damage and permanent loss of potency can occur. Patients are also advised to stop taking sildenafil and seek medical advice in cases of sudden visual or hearing loss. Sildenafil should not be given to those with loss of vision in one eye caused by non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this was in connection with previous phosphodiesterase type-5 inhibitors or not. Patients who experience dizziness or visual disturbances should not drive or operate hazardous machinery.

The safety of sildenafil is uncertain in patients with severe hepatic impairment, bleeding disorders, active peptic ulceration, hypotension, hypertension, a recent history of stroke, myocardial infarction, or life-threatening arrhythmia, unstable angina, heart failure, or retinal disorders such as retinitis pigmentosa (a minority of whom have genetic disorders of retinal phosphodiesterases). Licensed product information advises that it should not be used in these groups.

Cardiovascular disease. For mention of a consensus statement on the use of sildenafil in patients with cardiovascular disease, see p. 2365.2.

Contamination of herbal preparations. Sildenafil has been found in products marketed as dietary supplements or "herbal Viagra" for erectile dysfunction. Serious adverse effects have been reported and the FDA issued a warning highlighting the potential for interactions with prescription medication. Other drugs that have been identified as contaminants of such herbal preparations include glibenclamide and tadalafil.[1]

For mention of drugs related to sildenafil that have been used similarly in dietary supplements, see Acetildenafil p. 2351.3.

1. MHRA/CHM. Herbal products marketed for erectile dysfunction. *Drug Safety Update* 2008; 1(11): 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON017930&RevisionSelectionMethod=LatestReleased (accessed 13/11/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sildenafil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Sildenafil or other phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. Volatile nitrates and sodium nitroprusside will be similarly affected. Sildenafil may also enhance the hypotensive effect of nicorandil and use of the two drugs together should be avoided. Symptomatic hypotension may also occur when phosphodiesterase type-5 inhibitors are given with alpha blockers. Generally, the patient should be stabilised on alpha blocker therapy before the phosphodiesterase type-5 inhibitor is started at a low dose and adjusted according to response. Drugs that inhibit the cytochrome P450 isoenzyme CYP3A4, such as cimetidine, delavirdine, erythromycin, itraconazole, and ketoconazole, may reduce the clearance of phosphodiesterase type-5 inhibitors, necessitating a reduction in dosage. Plasma concentrations of phosphodiesterase type-5 inhibitors are significantly increased by HIV-protease inhibitors, and particularly so by ritonavir-boosted regimens. Such combinations should not be given unless absolutely essential. Grapefruit juice should be avoided with sildenafil or other phosphodiesterase type-5 inhibitors as it may increase their plasma concentrations. Inducers of CYP3A4, such as rifampicin, are likely to decrease plasma concentrations of phosphodiesterase type-5 inhibitors. Bosentan also reduces exposure to sildenafil.

Specific dosage recommendations have been made for the use of phosphodiesterase type-5 inhibitors with many of these drugs; see Uses and Administration under Avanafil (p. 2354.1), Sildenafil (p. 2364.2), Tadalafil (p. 2368.2), and Vardenafil (p. 2372.1).

Antivirals. Rises in sildenafil concentrations after use of *saquinavir* or *ritonavir* were consistent[1] with inhibition of metabolism mediated by the cytochrome P450 isoenzyme CYP3A4. The larger increases seen with ritonavir may be due to its additional inhibition of the isoenzyme CYP2C9. Fatal myocardial infarction has been reported[2] in a 47-year-old patient who took sildenafil 25 mg with ritonavir and saquinavir. In a study[3] of 6 HIV-positive men being treated with triple antiretroviral therapy that included *indinavir*, plasma concentrations of sildenafil were found to be significantly increased compared with historical controls.

1. Muirhead GJ, *et al*. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Pharmacol* 2000; **50:** 99–107.
2. Hall MCS, Ahmad S. Interaction between sildenafil and HIV-1 combination therapy. *Lancet* 1999; **353:** 2071–2.
3. Merry C, *et al*. Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS* 1999; **13:** F101–F107.

Cardiovascular drugs. For the effects of sildenafil in men stabilised on *antihypertensives* in general, see Effects on the Cardiovascular System, p. 2365.2. For mention of a possible interaction between sildenafil and *verapamil*, see Immunosuppressants, p. 2367.1.

A two-way interaction appears to exist between sildenafil and *bosentan*. In a placebo-controlled study[1] in 55 healthy subjects plasma concentrations of bosentan increased when taken with sildenafil, while those of sildenafil decreased. The combination was well tolerated however, and the clinical significance of the interaction was not clear.

In men with stable angina given sildenafil and sublingual *glyceryl trinitrate*, hypotensive symptoms occurred for at least 8 hours after dosing; the interaction was not considered synergistic after 6 hours, although there were still additive effects on blood pressure. The authors suggested that this data might support the cautious use of glyceryl trinitrate in patients hospitalised for angina who were haemodynamically stable but had taken sildenafil at least 6 hours previously.[2]

1. Burgess G, *et al*. Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Eur J Clin Pharmacol* 2008; **64:** 43–50.
2. Oliver JJ, *et al*. Time-dependent interactions of the hypotensive effects of sildenafil citrate and sublingual glyceryl trinitrate. *Br J Clin Pharmacol* 2009; **67:** 403–12.

Dihydrocodeine. The use of dihydrocodeine with sildenafil was associated with priapism in 2 men who had previously been treated successfully with sildenafil.[1] The first patient had two prolonged erections, lasting 4 and 5 hours, and the effect did not recur when the dihydrocodeine was stopped. The second patient had priapism on 3 occasions in the first week of dihydrocodeine treatment, but not in the subsequent 2 weeks despite continuing both drugs.

1. Goldmeier D, Lamba H. Prolonged erections produced by dihydrocodeine and sildenafil. *BMJ* 2002; **324:** 1555.

Food. *Grapefruit juice* has been shown to increase bioavailability but delay absorption of sildenafil in healthy subjects.[1]

1. Jetter A, *et al*. Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther* 2002; **71:** 21–9.

Immunosuppressants. Studies in men with erectile dysfunction who were receiving *tacrolimus* after kidney transplantation found that sildenafil had no effect on tacrolimus pharmacokinetics.[1,2] However, the pharmacokinetic profile of sildenafil differed from that reported in healthy subjects; the maximal plasma concentration was higher, the area under the concentration-time curve was increased, and the elimination half-life was prolonged.[1] Reductions in blood pressure were also found when sildenafil was given, although this may have been due to an interaction with *verapamil*. The authors suggested that an initial dose of 25 mg sildenafil should be used, and that on the days of sildenafil use the doses of antihypertensive drugs may need to be adjusted according to blood pressure response.[1,2]

1. Christ B, *et al.* Interactions of sildenafil and tacrolimus in men with erectile dysfunction after kidney transplantation. *Urology* 2001; **58:** 589–93.
2. Christ B, *et al.* Investigation on interaction between tacrolimus and sildenafil in kidney-transplanted patients with erectile dysfunction. *Int J Clin Pharmacol Ther* 2004; **42:** 149–56.

Nitrates. Giving sildenafil 50 mg to patients receiving *isosorbide mononitrate*, or sublingual *glyceryl trinitrate* given 1 hour after sildenafil, resulted in substantially greater decreases in blood pressure than when the nitrate was given alone in 2 crossover studies in patients with angina.[1] Treatment-related adverse effects were reported in 8 of 16 patients who received sildenafil with isosorbide mononitrate and 3 of 15 who took sildenafil with glyceryl trinitrate. The authors confirmed that sildenafil should not be taken with nitrates.

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; **36:** 25–31.

Pharmacokinetics

Sildenafil is rapidly absorbed after an oral dose, with a bioavailability of about 40%. Peak plasma concentrations occur within 30 to 120 minutes; the rate of absorption is reduced when sildenafil is given with food.

Sildenafil is widely distributed into tissues and is about 96% bound to plasma proteins. It is metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 (the major route) and CYP2C9. The major metabolite, *N*-desmethylsildenafil (UK-103320) also has some activity. The terminal half-lives of sildenafil and the *N*-desmethyl metabolite are about 4 hours.

Sildenafil is excreted as metabolites, mainly in the faeces, and to a lesser extent the urine. Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

References.

1. Nichols DJ, *et al.* Pharmacokinetics of sildenafil citrate after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol* 2002; **53** (suppl 1): 5S–12S.
2. Muirhead GJ, *et al.* The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. *Br J Clin Pharmacol* 2002; **53** (suppl 1): 21S–30S.
3. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.
4. Mukherjee A, *et al.* Population pharmacokinetics of sildenafil in term neonates: evidence of rapid maturation of metabolic clearance in the early postnatal period. *Clin Pharmacol Ther* 2009; **85:** 56–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Activil; Almaximo; Anaus; Bifort; Cagno; Egomax; Erectol; Expit; Falic; File; Firmel; Forzak; Gimonte Sildenafil; Gladium; Hepil; Incresil; Juvigor; Labsamax; Lorbinafil; Lumix; Magnus; Maxdosa; Maximo†; Nexofil†; Nitro; Openvas; Paramen; Permitil; Pluspen; Segurex; Sildefil†; Super-O; Tecnomax; Viagra; Vigor Plus; Vimax; Virilon; Viripotens; Vorst; ***Austral.***: Revatio; Viagra; ***Austria***: Revatio; Viagra; ***Belg.***: Revatio; Viagra; ***Braz.***: Dejavu; Escitan; Revatio; Sollevare; Tantrix; Vasifil; Viagra; Virineo; ***Canad.***: Revatio; Viagra; ***Chile***: Alfin; Dirtop; Disilden; Erosfil; Esantop; Helpin; Lifter; Novalif; Plusefec; Ripol; Seler†; Selerup; Siafil; Viagra; Vigorex; Vimax; Zilfic; ***China***: Viagra (万艾可); ***Cz.***: Amfidor; Ecriten; Fildlata; Revatio; Silaxa; Silfeldrem; Viagra; Vigrande; Vizarsin; ***Denm.***: Revatio; Viagra; ***Fin.***: Viagra; ***Fr.***: Revatio; Viagra; ***Ger.***: Revatio; Viagra; ***Gr.***: Revatio; Viagra; ***Hong Kong***: Revatio; Viagra; ***Hung.***: Revatio; Viagra; ***India***: Adams Delite; Air Bus; Alsigra; Androz; Be-Force; Bison; C-Gra; Caverta; Echarge; Edegra; Enthusia; Erec; Erectimax; Funtoosh; Hewon; Honygra; Intagra; Integra; Jean Siagra; Josh-IN; Juan; Kamagra; Leegra; Lovegra; Lupigra; Manforce; Manpower; Meriday; Moragara; N-Gra; Neogra; Niagra; Nyte; Penegra; Silagra; Viagra; ***Indon.***: Viagra; Vimax; ***Irl.***: Revatio; Sidena; Viagra; Vizarsin; ***Israel***: Revatio; Slider; Tarim; Via-Avenir; Viagra; ***Ital.***: Revatio; Viagra; ***Jpn***: Viagra; ***Malaysia***: Viagra; ***Mex.***: Apodefil; Patrex; Viagra; ***Neth.***: Afilon; Arifil; Azulsix; Enafilzil; Fildlata; Revatio; Silden; Sildenamed; Silderec; Sildrem; Silfeldrem; Tornetis; Viagra; Vilgendra; Vizarsin; ***Norw.***: Revatio; Viagra; ***NZ***: Avigra; Revatio; Silvasta; Vedafil; Viagra; ***Philipp.***: Adonix; Ambigra; Andros; Erefil; Neo-Up; Viagra; Zilden; ***Pol.***: Ecriten; Falsigra; Maxigra; Revatio; Viagra; Vigrande; Vizarsin; ***Port.***: Revatio; Viagra; ***Rus.***: Viagra (Виагра); Viasan-LF (Виасан-ЛФ); ***S.Afr.***: Avigra; Viagra; ***Singapore***: Revatio; Viagra; ***Spain***: Dragul; Oximum; Revatio; Viagra; Vizarsin; ***Swed.***: Revatio; Viagra; ***Switz.***: Revatio; Viagra; ***Thai.***: Elonza; Revatio; Sidegra; Viagra; ***Turk.***: Degra; Egira; Revatio; Sildegra; Viagra; Vigrande; ***UK***: Nipatra; Revatio; Viagra; Vizarsin; ***Ukr.***: Conegra (Конегра); Erasmo (Эрасмо)†; Erektil (Эректил); Eroton (Эротон); Extra (Экстра)†; Intagra (Интагра); Novygra (Новигра); Penimex (Пенимекс); Potentiale (Потенціале); Silada (Силада); Superviga (Супервига); Ulti-mate (Алти-Мет); Vecta (Векта)†; Viagra (Виагра); Vigrande (Вигранде); ***USA***: Revatio; Viagra; ***Venez.***: Duroval; Itaka; Viagra; Viasek; Viasil; Vigrasol; Viosex; Viridil.

Pharmacopoeial Preparations

USP 36: Sildenafil Citrate Oral Suspension.

Silodosin *(BAN, rINN)*

KAD-3213; KMD-3213; Selodosin; Silodosina; Silodosine; Silodosinum; Сильводозин.

(-)-1-(3-Hydroxypropyl)-5-[(2*R*)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1*H*-indole-7-carboxamide.

$C_{25}H_{32}F_3N_3O_4$=495.5

CAS — 160970-54-7.

ATC — G04CA04.

ATC Vet — QG04CA04.

UNII — CUZ39LUY82.

Uses and Administration

Silodosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) that is reported to be selective for the alpha$_{1A}$-adrenoceptor subtype. It is used orally in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction, in a usual dose of 8 mg daily with food, as a single dose or in 2 divided doses. Doses may need to be reduced in renal impairment, see below.

References.

1. Schilit S, Benzeroual KE. Silodosin: a selective α_{1A}-adrenergic receptor antagonist for the treatment of benign prostatic hyperplasia. *Clin Ther* 2009; **31:** 2489–2502.
2. Cantrell MA, *et al.* Silodosin for benign prostatic hyperplasia. *Ann Pharmacother* 2010; **44:** 302–10.

Administration in renal impairment. Exposure to silodosin may be increased in patients with renal impairment. No dosage adjustment is considered necessary in patients with mild renal impairment (creatinine clearance, CC, 50 mL/minute and above). In those with moderate renal impairment (CC 30 to 50 mL/minute), the oral dose should be reduced to 4 mg once daily; silodosin is contra-indicated in severe impairment (CC less than 30 mL/minute).

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3 and p. 1475.1. Additional adverse effects include ejaculation abnormalities such as retrograde ejaculation (reversible on stopping treatment), arrhythmias, increased blood triglycerides, and skin reactions. Intraoperative floppy iris syndrome has also been associated with the use of alpha blockers, see Cataract Surgery, under Tamsulosin p. 2369.3.

Silodosin should not be used in patients with severe renal impairment, and the dose may need to be adjusted in those with moderate renal impairment (see Administration in Renal Impairment, above). Increases in liver enzyme values, impaired hepatic function, and jaundice have been reported; silodosin should be avoided in patients with severe hepatic impairment. It should also not be used with strong inhibitors of cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein; caution is required when used with moderate CYP3A4 inhibitors (see Interactions, below).

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Silodosin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with CYP3A4 inhibitors may increase exposure to silodosin. Use with strong CYP3A4 inhibitors such as ketoconazole is contra-indicated; caution is advised with use of moderate CYP3A4 inhibitors. Silodosin is also metabolised by UDP-glucuronosyltransferase 2B7 (UGT2B7), and use with inhibitors of this enzyme may increase silodosin exposure.

Silodosin is a P-glycoprotein substrate, and use with P-glycoprotein inhibitors may increase exposure to silodosin; use with strong inhibitors such as ciclosporin is not recommended.

Pharmacokinetics

Peak concentrations of silodosin occur about 2.6 hours after an oral dose; absolute bioavailability is about 32%. Exposure to silodosin is decreased when given with a meal that is moderately high in fat and calories. Silodosin is about 97% protein bound. It undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 isoenzyme CYP3A4. The main metabolite is a glucuronide conjugate (KMD-3213G) that is formed via UDP-glucuronosyltransferase 2B7; it is active and has a half-life of about 24 hours, with a four times greater exposure than silodosin. The second major metabolite (KMD-3293) is formed by alcohol and aldehyde dehydrogenase; it is not expected to contribute to the overall activity. After oral dosing, about 34% is recovered in the urine and 55% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Silodyx; ***Canad.***: Rapaflo; ***Cz.***: Silodyx; Urorec; ***Fr.***: Silodyx; Urorec; ***Ger.***: Urorec; ***Gr.***: Silodyx; Urorec; ***Irl.***: Silodyx; Urorec; ***Jpn***: Urief; ***Neth.***: Silodyx; Urorec; ***Pol.***: Silodyx; Urorec; ***Port.***: Silodyx; Urorec; ***Rus.***: Urorec (Уророк); ***Spain***: Silodyx; Urorec; ***Ukr.***: Urorec (Уророк); ***USA***: Rapaflo.

Solifenacin Succinate

(BANM, USAN, rINNM)

Solifénacine, Succinate de; Solifenacini Succinas; Succinato de solifenacina; YM-905; YM-67905; Солифенацина Сукцинат.

(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate compound with butanedioic acid (1:1).

$C_{23}H_{26}N_2O_2,C_4H_6O_4$=480.6

CAS — 242478-37-1 (solifenacin); 242478-38-2 (solifenacin succinate).

ATC — G04BD08.

ATC Vet — QG04BD08.

UNII — KKA5DLD701.

Uses and Administration

Solifenacin succinate is a selective M_3 antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used in the treatment of urinary frequency, urgency, and incontinence in detrusor instability (p. 2349.2). Solifenacin succinate is given orally in usual doses of 5 mg once daily, increased to 10 mg once daily if required. Maximum doses of 5 mg once daily are recommended in patients receiving drugs such as ketoconazole or ritonavir that are strong inhibitors of the cytochrome P450 isoenzyme CYP3A4. For doses in hepatic or renal impairment, see below.

References.

1. Chapple CR, *et al.* Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; **93:** 303–10.
2. Cardozo L, *et al.* Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol (Baltimore)* 2004; **172:** 1919–24.
3. Haab F, *et al.* Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *Eur Urol* 2005; **47:** 376–84.
4. Chapple CR, *et al.* A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; **48:** 464–70.
5. Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. *Eur Urol* 2005; **48:** 483–7.
6. Payne CK. Solifenacin in overactive bladder syndrome. *Drugs* 2006; **66:** 175–90.
7. Garely AD, *et al.* Solifenacin for overactive bladder with incontinence: symptom bother and health-related quality of life outcomes. *Ann Pharmacother* 2007; **41:** 391–8.
8. Michel MC, *et al.* Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: a 12-week, open-label, post-marketing surveillance study. *Drug Safety* 2008; **31:** 505–14.
9. Pelman RS, *et al.* Solifenacin at 3 years: a review of efficacy and safety. *Postgrad Med* 2008; **120:** 85–91.
10. Cardozo L, *et al.* SUNRISE Study Group. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. *BJU Int* 2008; **102:** 1120–7.

Administration in hepatic and renal impairment. Oral doses of 5 mg of solifenacin succinate once daily are recommended in patients with moderate hepatic impairment (Child-Pugh category B) or severe renal impairment (creatinine clearance less than 30 mL/minute). It should not be used in patients with severe hepatic impairment (Child-Pugh category C) or in those undergoing haemodialysis.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Solifenacin succinate should be used with caution in patients also receiving inhibitors of the cytochrome P450 isoenzyme CYP3A4 (see Interactions, p. 2368.1 and Uses and Administration, above). It should also be used with caution in hepatic and renal impairment.

Effects on the cardiovascular system. A 12-week post-marketing surveillance study found solifenacin had no

effect on the heart rate or blood pressure of patients with overactive bladder syndrome, despite many patients having cardiovascular co-morbidities.[1] However, US licensed product information states that QT prolongation and torsade de pointes have been reported in association with solifenacin use, although causality and frequency could not be determined.

1. Michel MC, *et al.* Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: a 12-week, open-label, post-marketing surveillance study. *Drug Safety* 2008; **31:** 505–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies solifenacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Exposure to solifenacin succinate may be increased by drugs that inhibit the cytochrome P450 isoenzyme CYP3A4. Although there is a lack of data, licensed product information also warns of the potential for interaction between solifenacin succinate and substrates or inducers of CYP3A4. Dosage adjustment for solifenacin succinate may be necessary (see Uses and Administration, p. 2367.3).

Pharmacokinetics

After an oral dose, solifenacin succinate is absorbed from the gastrointestinal tract; peak plasma concentrations occur after 3 to 8 hours and bioavailability is about 90%. Solifenacin is about 98% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and has a terminal half-life of 45 to 68 hours. Solifenacin is excreted mainly as metabolites in urine and faeces.

References.

1. Kuipers ME, *et al.* Solifenacin demonstrates high absolute bioavailability in healthy men. *Drugs R D* 2004; **5:** 73–81.
2. Smulders RA, *et al.* Pharmacokinetics and safety of solifenacin succinate in healthy young men. *J Clin Pharmacol* 2004; **44:** 1023–33.
3. Doroshyenko O, Fuhr U. Clinical pharmacokinetics and pharmacodynamics of solifenacin. *Clin Pharmacokinet* 2009; **48:** 281–302.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vesicare; ***Austral.***: Vesicare; ***Austria***: Vesicare; ***Belg.***: Vesicare; ***Braz.***: Vesicade; Vesicare; ***Canad.***: Vesicare; ***China***: Vesicare (卫喜康); ***Cz.***: Asolfena; Vesicare; Zevesin; ***Denm.***: Vesicare; ***Fin.***: Vesicare; ***Fr.***: Vesicare; ***Ger.***: Vesikur; ***Gr.***: Vesicare; ***Hong Kong***: Vesicare; ***Hung.***: Vesicare; ***India***: Bispec; ***Indon.***: Vesicare; ***Irl.***: Vesitirim; ***Israel***: Vesicare; ***Ital.***: Vesiker; ***Jpn***: Vesicare; ***Malaysia***: Vesicare; ***Mex.***: Vesicare; ***Neth.***: Flomin; Uriclin†; Vesicare; ***Norw.***: Vesicare; ***NZ***: Vesicare; ***Philipp.***: Vesicare; ***Pol.***: Vesicare; ***Port.***: Flomin; Uriclin; Vesicare; ***Rus.***: Vesicare (Везикар); ***S.Afr.***: Vesicare; ***Singapore***: Vesicare; ***Spain***: Vesicare; ***Swed.***: Vesicare; ***Switz.***: Vesicare; ***Thai.***: Vesicare; ***Turk.***: Kinzy; ***UK***: Vesicare; ***Ukr.***: Vesicare (Везикар); ***USA***: Vesicare.

Tadalafil *(BAN, USAN, rINN)*

GF-196960; IC-351; Tadalafiili; Tadalafila; Tadalafilo; Tadalafilum; Тадалафил.

(6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione.

$C_{22}H_{19}N_3O_4$=389.4

CAS — 171596-29-5.

ATC — G04BE08.

ATC Vet — QG04BE08.

UNII — 742SXX0ICT.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of tadalafil:

Weekend Pill.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Tadalafil). A white or almost white powder. Practically insoluble in water; slightly soluble in dichloromethane; freely soluble in dimethyl sulfoxide.

USP 36: (Tadalafil). A white or almost white powder. Practically insoluble in water; slightly soluble in dichloromethane; freely soluble in dimethyl sulfoxide.

An oral suspension of tadalafil extemporaneously prepared from tadalafil tablets was stable for at least 91 days when stored in amber plastic bottles at room temperature.[1]

1. Pettit RS, *et al.* Stability of an extemporaneously prepared tadalafil suspension. *Am J Health-Syst Pharm* 2012; **69:** 592–4.

Uses and Administration

Tadalafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used in the management of erectile dysfunction (p. 2348.2), of benign prostatic hyperplasia (p. 2347.1), and of pulmonary arterial hypertension (p. 1278.2).

For **erectile dysfunction**, tadalafil is given orally in a usual dose of 10 mg at least 30 minutes before sexual intercourse and may be taken with or without food; the dose may be increased to 20 mg, or decreased to 5 mg, if necessary. Efficacy may persist for up to 36 hours after dosing. Tadalafil should not be taken more than once in 24 hours.

For those who respond to tadalafil when taken as needed, and anticipate frequent use (defined as at least twice weekly), a regular daily regimen may be considered suitable. In the UK the recommended dose in such patients is 5 mg once daily, taken at about the same time each day. The dose may be decreased to 2.5 mg once daily based on individual tolerability. In the USA, the recommended starting dose of tadalafil for daily use is 2.5 mg, taken at about the same time each day, which may then be increased to 5 mg, based on tolerability and efficacy. The lowest possible starting dose of tadalafil should be given if the patient is taking an alpha blocker.

For **benign prostatic hyperplasia** tadalafil is given in a dose of 5 mg daily, taken at the same time every day. Use with an alpha blocker is not recommended.

In patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole or ritonavir-boosted HIV-protease inhibitors, the dose of tadalafil when used *as needed* should not exceed 10 mg once every 72 hours; when used on a *regular daily basis* for erectile dysfunction, the dose should not exceed 2.5 mg.

To improve exercise ability in **pulmonary arterial hypertension**, tadalafil is given orally in a dose of 40 mg once daily. Tadalafil therapy should be stopped at least 24 hours before starting treatment with ritonavir. In patients who have been taking ritonavir for at least one week, tadalafil therapy can be started at 20 mg once daily, and increased to 40 mg once daily as tolerated. Tadalafil should be avoided in patients taking other potent inhibitors of CYP3A4 and in patients taking potent inducers of CYP3A4.

Dosage adjustments are not necessary in elderly patients; for recommendations in hepatic or renal impairment, see below.

References.

1. Brock GB, *et al.* Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol (Baltimore)* 2002; **168:** 1332–6. Correction. *ibid.* 2005; **173:** 664. [dosage error in abstract]
2. Brock GB. Tadalafil: a new agent for erectile dysfunction. *Can J Urol* 2003; **10** (suppl 1): 17–22.
3. Bella AJ, Brock GB. Tadalafil in the treatment of erectile dysfunction. *Curr Urol Rep* 2003; **4:** 472–8.
4. Curran MP, Keating GM. Tadalafil. *Drugs* 2003; **63:** 2203–12. Correction. *ibid.*; 2703.
5. Meuleman EJ. Review of tadalafil in the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2003; **4:** 2049–56.
6. Padma-Nathan H. Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction. *Am J Cardiol* 2003; **92** (suppl 1): 19M–25M.
7. Carson CC, *et al.* The efficacy and safety of tadalafil: an update. *BJU Int* 2004; **93:** 1276–81.
8. Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. *Expert Opin Pharmacother* 2005; **6:** 75–84.
9. Donatucci CF, *et al.* Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. *Curr Med Res Opin* 2008; **24:** 3383–92.
10. Galiè N, *et al.* Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; **119:** 2894–2903.
11. Andersson KE, *et al.* Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. *Neurourol Urodyn* 2011; **30:** 292–301.
12. Porst H, *et al.* for the LVHJ study team. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. *Eur Urol* 2011; **60:** 1105–13.

Administration in hepatic impairment. Exposure to tadalafil in patients with mild to moderate hepatic impairment is comparable to healthy subjects when an oral dose of 10 mg is used.

When used for **erectile dysfunction** or **benign prostatic hyperplasia**, licensed product information states the following:

- mild to moderate hepatic impairment (Child-Pugh Class A or B): the maximum oral dose is 10 mg; regular daily dosing has not been extensively evaluated and caution is required
- severe hepatic impairment (Child-Pugh Class C): insufficient data are available; in the UK, caution is advised, and in the USA use in this group is not recommended

For **pulmonary arterial hypertension**, licensed product information recommends a reduced starting dose of oral tadalafil 20 mg once daily for patients with mild to moderate hepatic impairment; again, use in patients with severe hepatic impairment is not recommended.

Administration in renal impairment. The clearance of tadalafil is reduced in renal impairment.

When used for **erectile dysfunction**, UK licensed product information for tadalafil recommends the following:

- mild to moderate renal impairment: no dose adjustment
- severe renal impairment: the maximum oral dose is 10 mg; regular daily dosing is not recommended in these patients

Dose recommendations in the USA for erectile dysfunction, when used *as needed*, in patients with renal impairment based on creatinine clearance (CC) are:

- mild (CC 51 to 80 mL/minute): no dose adjustment
- moderate (CC 30 to 50 mL/minute): an initial oral dose of 5 mg not more than once daily, with a maximum dose of 10 mg in 48 hours
- severe (CC less than 30 mL/minute or on haemodialysis): a maximum oral dose of 5 mg not more than once in every 72 hours

For patients taking tadalafil on a *regular daily basis* for erectile dysfunction only:

- mild or moderate (CC 30 mL/minute and over): no dosage adjustment
- severe (CC less than 30 mL/minute or on haemodialysis): not recommended

For patients taking tadalafil on a *regular daily basis* for **benign prostatic hyperplasia** (with or without erectile dysfunction):

- moderate (CC 30 to 50 mL/minute): a n initial oral dose of 2.5 mg once daily, increased to 5 mg once daily if necessary according to response
- severe (CC less than 30 mL/minute or on haemodialysis): not recommended

In **pulmonary arterial hypertension**, a starting dose of 20 mg orally once daily is recommended in patients with mild to moderate renal impairment (CC 31 to 80 mL/minute), increased to 40 mg once daily as tolerated. Due to a lack of clinical experience, use should be avoided in patients with severe renal impairment (CC less than 30 mL/minute) or those on haemodialysis; tadalafil is not eliminated by dialysis.

High-altitude disorders. Hypoxic pulmonary hypertension associated with high altitude (p. 1276.2) may respond to tadalafil. A small study[1] has shown some promising results in adults with a history of high-altitude pulmonary oedema.

1. Maggiorini M, *et al.* Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med* 2006; **145:** 497–506.

Adverse Effects and Precautions

As for Sildenafil, p. 2365.2 and p. 2366.2. Visual disturbances may occur less frequently with tadalafil than with sildenafil. Dosage reductions may be required in patients with hepatic or renal impairment.

References.

1. Montorsi F, *et al.* Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004; **45:** 339–44.

Contamination of herbal preparations. For mention of dietary supplements contaminated with drugs such as tadalafil, see Contamination of Herbal Preparations, under Sildenafil p. 2366.2.

Effects on the cardiovascular system. References.

1. KlonerRA, *et al.* Cardiovascular effects of tadalafil. *Am J Cardiol* 2003; **92:** 37M–46M.

Effects on the cerebrovascular system. Intracerebral haemorrhage[1] and subarachnoid haemorrhage[2] have been reported following single oral doses of tadalafil (40 mg and 20 mg, respectively) for erectile dysfunction.

1. Gazzeri R, *et al.* Intracerebral hemorrhage associated with use of tadalafil (Cialis). *Neurology* 2008; **70:** 1289–90.
2. Sheikh-Taha M, Alaywa RA. Subarachnoid hemorrhage associated with tadalafil. *Am J Health-Syst Pharm* 2011; **68:** 1195–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tadalafil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for Sildenafil, p. 2366.3.

Although phosphodiesterase type-5 inhibitors may be used cautiously with alpha blockers, UK licensed product information recommends against the use of tadalafil with doxazosin.

Antifungals. Priapism occurred in a man who took two separate doses of tadalafil 10 mg, at least one month apart, during *itraconazole* treatment.[1] He was able to take sildenafil during itraconazole treatment without adverse effect. See also Uses and Administration, p. 2368.2, for recommended tadalafil dosage when it is taken with inhibitors of the cytochrome P450 isoenzyme CYP3A4.

1. Galatti L, *et al.* Interaction between tadalafil and itraconazole. *Ann Pharmacother* 2005; **39:** 200.

Antivirals. A study in healthy subjects given tadalafil with *ritonavir-boosted tipranavir* showed a significant increase in tadalafil concentrations initially, but once at steady state these HIV-protease inhibitors had little effect on tadalafil pharmacokinetics.[1] See also Uses and Administration, p. 2368.2, for recommended tadalafil dosage when it is taken with inhibitors of the cytochrome P450 isoenzyme CYP3A4.

1. Garraffo R, *et al.* Effect of tipranavir/ritonavir combination on the pharmacokinetics of tadalafil in healthy volunteers. *J Clin Pharmacol* 2011; **51:** 1071–8.

Nitrates. Phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. An interaction between tadalafil and sublingual *glyceryl trinitrate* was reported to occur when glyceryl trinitrate was given within 24 hours after tadalafil but was no longer detectable at 48 hours.[1] Licensed product information recommends that if nitrate treatment is needed in a life-threatening situation then it should only be given at least 48 hours after the last dose of tadalafil and under close medical supervision.

1. Kloner RA, *et al.* Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003; **42:** 1855–60.

Pharmacokinetics

Tadalafil is well absorbed after an oral dose. Peak plasma concentrations occur within 2 hours; the rate and extent of absorption are not affected by food.

Tadalafil is widely distributed into tissues and is about 94% bound to plasma proteins. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolite, the methylcatechol glucuronide, is inactive. The mean half-life of tadalafil is about 17.5 hours.

Tadalafil is excreted, mainly as metabolites, in the faeces (61% of the dose), and to a lesser extent the urine (36% of the dose). Clearance may be reduced in the elderly and in patients with renal impairment.

References.

1. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.
2. Forgue ST, *et al.* Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 280–8.
3. Forgue ST, *et al.* Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol* 2007; **63:** 24–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cialis; ***Austral.***: Adcirca; Cialis; ***Austria***: Adcirca; Cialis; ***Belg.***: Adcirca; Cialis; ***Braz.***: Adcirca; Cialis; ***Canad.***: Adcirca; Cialis; ***Chile***: Cialis; ***China***: Cialis (希爱力); ***Cz.***: Adcirca; Cialis; ***Denm.***: Adcirca; Cialis; ***Fin.***: Cialis; ***Fr.***: Adcirca; Cialis; ***Ger.***: Adcirca; Cialis; ***Gr.***: Cialis; ***Hong Kong***: Cialis; ***Hung.***: Cialis; ***India***: Erectalis; Forzest; Getgo; Manforce More; Oneaid; Tadacip; Zydalis; ***Indon.***: Cialis; ***Irl.***: Cialis; ***Israel***: Cialis; ***Ital.***: Cialis; ***Malaysia***: Cialis; ***Mex.***: Cialis; ***Neth.***: Adcirca; Cialis; ***Norw.***: Adcirca; Cialis; ***NZ***: Cialis; ***Philipp.***: Cialis; ***Pol.***: Cialis; ***Port.***: Adcirca; Cialis; ***Rus.***: Cialis (Сиалис); ***S.Afr.***: Cialis; ***Singapore***: Cialis; ***Spain***: Adcirca; Cialis; ***Swed.***: Adcirca; Cialis; ***Switz.***: Adcirca; Cialis; ***Thai.***: Cialis; ***Turk.***: Cialis; Lifta; Longis; Pasport; ***UK***: Cialis; ***Ukr.***: Cialis (Сиалис); ***USA***: Adcirca; Cialis; ***Venez.***: Cialis.

Pharmacopoeial Preparations
USP 36: Tadalafil Tablets.

Tamsulosin Hydrochloride

(BANM, USAN, rINNM)

Amsulosin Hydrochloride; Hidrocloruro de tamsulosina; LY-253351; Tamsulosiinihydrokloridi; Tamsulosin Hidroklorür; Tamsulosina, hidrocloruro de; Tamsulosine, Chlorhydrate de; Tamsulosinhydrochlorid; Tamsulosinhydroklorid; Tamsulosini Hydrochloridum; YM-617; YM-12617-1; Тамсулозина Гидрохлорид; *R*-(-)-YM-12617.

(-)-(*R*)-5-(2-{[2-(*o*-Ethoxyphenoxy)ethyl]amino}-propyl)-2-methoxybenzenesulfonamide hydrochloride.

$C_{20}H_{28}N_2O_5S,HCl$=445.0

CAS — 106133-20-4 (tamsulosin); 106463-17-6 (tamsulosin hydrochloride).

ATC — G04CA02.

ATC Vet — QG04CA02.

UNII — 11SV1951MR.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tamsulosin Hydrochloride). A white or almost white powder. Slightly soluble in water and in anhydrous alcohol; freely soluble in formic acid.

USP 36: (Tamsulosin Hydrochloride). A white or almost white crystalline powder. Slightly soluble in water and in dehydrated alcohol; sparingly soluble in methyl alcohol; practically insoluble in ether; freely soluble in formic acid. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Tamsulosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1); it is reported to be more selective for the alpha$_{1A}$-adrenoceptor subtype, which accounts for about 70% of the α_1 adrenoceptors in the prostate. It is used in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction.

In benign prostatic hyperplasia, tamsulosin hydrochloride is given orally in a modified-release formulation, in a dose of 400 micrograms once daily. Licensed US product information states that the dose may be increased after 2 to 4 weeks, if necessary, to 800 micrograms once daily.

Reviews.

1. Wilde MI, McTavish D. Tamsulosin: a review of its pharmacological properties and therapeutic potential in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1996; **52:** 883–98.
2. Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. *Ann Pharmacother* 2000; **34:** 188–99.
3. Lyseng-Williamson KA, *et al.* Tamsulosin: an update of its role in the management of lower urinary tract symptoms. *Drugs* 2002; **62:** 135–67.
4. Ren R-M, *et al.* Efficacy and safety of tamsulosin for the treatment of benign prostatic hyperplasia: a meta analysis. *Chin Med J (Engl)* 2010; **123:** 234–8.

Antidepressant-induced genito-urinary disorders. Tamsulosin was used successfully[1] to treat urinary hesitancy in 6 male patients receiving reboxetine. Painful ejaculation associated with reboxetine was also treated successfully[2] in 2 men.

1. Demyttenaere K, *et al.* Tamsulosin as an effective treatment for reboxetine-associated urinary hesitancy. *Int Clin Psychopharmacol* 2001; **16:** 353–5.
2. Demyttenaere K, Huygens R. Painful ejaculation and urinary hesitancy in association with antidepressant therapy: relief with tamsulosin. *Eur Neuropsychopharmacol* 2002; **12:** 337–41.

Prostatitis. Alpha$_1$-adrenoceptor blockers are one of a number of classes of drugs that have been tried for symptomatic relief in men with chronic prostatitis (p. 2350.2). In a 6-week multicentre, double-blind placebo-controlled study involving 58 men with moderate to severe chronic prostatitis/chronic pelvic pain syndrome, tamsulosin 400 micrograms daily produced greater symptomatic relief than placebo;[1] the effect was considered clinically significant for men with severe prostatitis. The benefit appeared to take several weeks to develop, and it was considered possible that longer exposure would produce additional benefit.

1. Nickel JC, *et al.* Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J Urol (Baltimore)* 2004; **171:** 1594–7.

Renal calculi. In the conservative management of renal calculi (p. 2350.3) there is increasing interest in the possible use of drug treatment to ease the spontaneous passage of the stone down the ureter. Alpha$_1$-adrenoceptor blockers can decrease smooth muscle spasm in the ureter, reducing obstruction and improving urine flow. In studies[1-5] of patients with uncomplicated lower ureteral stones, tamsulosin has been reported to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements. Tamsulosin was generally given orally in a dose of 400 micrograms daily for up to 4 weeks. Comparison groups were treated with various other antispasmodics including benzodiazepines, phloroglucinol, and nifedipine; in most studies patients were also treated with antibacterial prophylaxis, deflazacort, and NSAIDs. A review and meta-analysis[6] considered that tamsulosin was of benefit in aiding the expulsion of lower urinary tract stones less than 10 mm in diameter; the number needed to treat was 3.

A review[7] found evidence suggesting that adjunctive tamsulosin is safe and effective in enhancing the clearance of renal stones with a larger diameter when used with extracorporeal shock wave lithotripsy. Although evidence regarding ureteral stone clearance is inconclusive, adjunctive tamsulosin has been reported to reduce painful episodes.

1. Červenàkov I, *et al.* Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker–tamsulosin. *Int Urol Nephrol* 2002; **34:** 25–9.
2. Dellabella M, *et al.* Efficacy of tamsulosin in the medical management of juxta vesical ureteral stones. *J Urol (Baltimore)* 2003; **170:** 2202–5.
3. Porpiglia F, *et al.* Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; **172:** 568–71.
4. Yilmaz E, *et al.* The comparison and efficacy of 3 different α 1-adrenergic blockers for distal ureteral stones. *J Urol (Baltimore)* 2005; **173:** 2010–12.
5. Dellabella M, *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; **174:** 167–72.
6. Arrabal-Martin M, *et al.* Treatment of ureteral lithiasis with tamsulosin: literature review and meta-analysis. *Urol Int* 2010; **84:** 254–9.
7. Losek RL, Mauro LS. Efficacy of tamsulosin with extracorporeal shock wave lithotripsy for passage of renal and ureteral calculi. *Ann Pharmacother* 2008; **42:** 692–6.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3 and p. 1475.1. Because tamsulosin is selective for α_1 receptors in the prostate the vasodilator effects may be less frequent. Tamsulosin may cause ejaculation abnormalities. Very rarely, Stevens-Johnson syndrome has been reported. Tamsulosin should be avoided in severe hepatic impairment.

Incidence of adverse effects. A study[1] using prescription event monitoring data for more than 12 000 patients treated with tamsulosin found that dizziness, headache, malaise, and hypotension were the adverse effects most commonly reported.

1. Mann RD, *et al.* The pharmacovigilance of tamsulosin: event data on 12 484 patients. *BJU Int* 2000; **85:** 446–50.

Cataract surgery. In 2005 the manufacturers[1,2] of tamsulosin warned that a syndrome of flaccidity of the iris, progressive miosis, and potential prolapse (intraoperative floppy iris syndrome; IFIS) had been reported in some patients undergoing cataract surgery who were taking or had taken, alpha blockers. One group of workers[3] had reported that in one series of 741 patients undergoing cataract surgery, 15 of the 16 who developed IFIS had received tamsulosin. An earlier retrospective study of 511 similar patients by the same workers[3] had found IFIS in 10 of the 16 patients with a history of tamsulosin treatment but no cases in any of the other patients, including 11 patients given other alpha blockers. A retrospective case-controlled analysis found that patients taking tamsulosin within 14 days of cataract surgery were more than twice as likely to have serious postoperative ophthalmic events; no such association was found among those previously exposed to tamsulosin or with other alpha blockers used to treat benign prostatic hyperplasia.[4] The US manufacturer[2] stated that although most cases had occurred in patients who had been taking alpha blockers concurrently or up to 2 weeks before surgery the benefit of stopping such therapy before cataract surgery has not been established; a few cases had included patients who stopped alpha blockers up to 9 months before surgery. The manufacturers of tamsulosin recommend that patients being considered for cataract surgery should be questioned to ascertain whether they are taking the drug.[1,2] A literature review[5] found that other alpha blockers, including alfuzosin, doxazosin, and terazosin, have also been associated with IFIS in this patient group; however, IFIS has been most strongly associated with the use of tamsulosin. In the UK, the MHRA[6] has required the inclusion of a warning in the labelling of all alpha blockers advising patients to inform their cataract surgeon about past and current use of these drugs.

1. Boehringer Ingelheim (Canada). Important safety information on intraoperative floppy iris syndrome (IFIS) (issued 14th October 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/flomax_hpc-cps-eng.pdf (accessed 02/09/08)
2. Boodee HW [Boehringer Ingelheim Pharmaceuticals, Inc (USA)]. Important drug information for physicians (issued November 2005) Available at: http://www.fda.gov/medwatch/safety/2005/Flomax_dearhcp_nov22_PI.pdf (accessed 01/12/05)
3. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. *J Cataract Refract Surg* 2005; **31:** 664–73.
4. Bell CM, *et al.* Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery. *JAMA* 2009; **301:** 1991–6.
5. Cantrell MA, *et al.* Intraoperative floppy iris syndrome associated with α $_1$-adrenergic receptor antagonists. *Ann Pharmacother* 2008; **42:** 558–63.
6. MHRA/CHM. α -1 adrenoceptor antagonists: intraoperative floppy iris syndrome. *Drug Safety Update* 2007:**1** (1): 4–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2031802 (accessed 17/06/08)

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Tamsulosin is metabolised by cytochrome P450 isoenzymes CYP2D6 and CYP3A4, and inhibitors of these isoenzymes may increase exposure to tamsulosin. It should be used with caution, if at all, with strong inhibitors of CYP3A4 and such combinations should be avoided in patients who are CYP2D6 poor metabolisers. Caution is also required when giving tamsulosin with a moderate inhibitor of CYP3A4, with strong or moderate inhibitors of CYP2D6, or in CYP2D6 poor metabolisers, particularly at oral tamsulosin doses higher than 400 micrograms daily.

Caution is also advised when tamsulosin is given with warfarin or diclofenac as the elimination of tamsulosin may be increased and therefore the exposure reduced. Furosemide may also reduce exposure, but tamsulosin concentrations remain within the normal range.

Pharmacokinetics

Tamsulosin is absorbed from the gastrointestinal tract and is almost completely bioavailable. The extent and rate of absorption are reduced by food. After oral doses of an immediate-release preparation, peak plasma concentrations occur after about 1 hour. Tamsulosin is about 99% bound to plasma proteins. It is metabolised slowly in the liver primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; it is excreted mainly in the urine as metabolites and some unchanged drug. The plasma elimination half-life has been reported to be between 4 and 5.5 hours.

Some of the pharmacokinetic values cited above may be altered when tamsulosin is given as a modified-release preparation, the form in which it is usually used; for instance, peak plasma concentrations occur about 6 hours after a dose and the apparent elimination half-life may be 10 to 15 hours.

Renal impairment. Plasma-tamsulosin concentrations were reported to be increased in patients with renal impairment when compared with subjects with normal renal function.[1,2] However, plasma concentrations of unbound, pharmacologically active drug were similar in both groups and it was suggested that the raised total plasma concentrations were due to an increase in plasma protein binding.

1. Koiso K, *et al.* Pharmacokinetics of tamsulosin hydrochloride in patients with renal impairment: effects of α_1-acid glycoprotein. *J Clin Pharmacol* 1996; **36:** 1029–38.
2. Wolzt M, *et al.* Pharmacokinetics of tamsulosin in subjects with normal and varying degrees of impaired renal function: an open-label single-dose and multiple-dose study. *Eur J Clin Pharmacol* 1998; **54:** 367–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aclosan; Biprokam; Controlpros; Espontal; Lostam; Omnic; Prostoklar; Reduprost; Secotex; Talosin; Tamsuna; Tansiloprost; Uralos; Uroprost-Q; ***Austral.***: Flomax†; Flomaxtra; ***Austria***: Aglandin; Alna; Tamsu; Tamsunova†; ***Belg.***: Omic; Ranomax; ***Braz.***: Contiflo; Omnic; Secotex; Tamsulon; ***Canad.***: Flomax; ***Chile***: Eupen; Gotely; Omnic; Prostall; Secotex; Sulix; Vi-Uril; ***China***: BenTe (本特); Bi Tan (必坦); Harnal (哈乐); Jida BenTe (积大本特); Qi Suo (齐索); ***Cz.***: Apo-Tamis; Damurgin; Fokusin; Lannatam; Omnic; Solesmin; Taflosin; Tamipro; Tamsec†; Tamsuda; Tamsulonorm; Tamurox; Tanyz; Urostad; Urotam; ***Denm.***: Cepalux; Masulin; Omnic; Omnistad; Prostacure; Ranomax; Tamsin; Tamsukon†; Tamsulogen†; Tamsunorm; ***Fin.***: Expros; Omnic; Promictan; Tamictor; Tamsact; Tamsin; Tamsu-Anlini; TamsuCinfa; Tamsu-Garan; Tamsulogen; Tamsumin; TamsuPli; ***Fr.***: Josir; Mecir; Omexel; Omix; ***Ger.***: Alna; Omnic; Prostacure; Prostadil; Prostazid†; Tadin; Tamsu-Q†; Tamsublock; Tamsulo-Isis†; Tamsumedin†; Tamsunar; ***Gr.***: Miktosan; Novelio; Omnic; Pradif; Prosolvin; Ranomax; Sintamel; Tamsol; Tamsolet; Tamsulijn; Zidrolin; ***Hong Kong***: Harnal; ***Hung.***: Flosin; Fokusin; Omipro; Omnic; Provosal; Ranomax; Tamsol; Tamsudil; Tamsugen; Tamsulonorm; Tanyz; Totalprost; Uro-Tam; Urostad; ***India***: Alfatam; Contiflo; Dynapres; Gotam; Urimax; ***Indon.***: Harnal; ***Irl.***: Kirnom; Omnexel; Omnic; Omsil; Prolosin; Tacap; Tamnexyl; Tamnic; Tamsu; Tamsulas†; ***Israel***: Omnic; Promnix; Tamsulin; ***Ital.***: Antunes; Botam; Lura; Omnic; Pradif; Probena; Tamlic; ***Jpn***: Harnal; ***Malaysia***: Harnal; ***Mex.***: Amzuvag; Asoflon; Fedpros; Hipebe; Jumslim; Secadryckel; Secotex; Suprosina; ***Neth.***: Mapelor; Omnic; Protam; Sebrane; Talpro; Taluso; Tamagsyn; Tamsin; Tamsuda; Tamsulijn; ***Norw.***: Cepalux; Omnic; ***NZ***: Flomax; Flomaxtra; ***Philipp.***: Harnal; Pimax; Prozelax; ***Pol.***: Apo-Tamis; Bazetham; Fokusin; Omipro; Omnic; Omsal; Prostamnic; Proximic; Ranlosin; Symlosin; Tamsec; Tamsudil; Tamsugen; TamsuLek; Tanyz; Uprox; Urostad; ***Port.***: Omnic; Pradif; Sulin; Tacap; ***Rus.***: Fokusin (Фокусин); Hyperprost (Гиперпрост); Omnic (Омник); Omsulosin (Омсулозин); Revokarin (Ревокарин); Sonizin (Сонизин); Tamsulon (Тамсулона); Tanyz (Таниз-К); Tulosin (Тулозин); ***S.Afr.***: Beniprosin; Flomax; Prostaflo; Tamsul; Uromax; ***Singapore***: Harnal; ***Spain***: Inreq; Manfredol†; Omnic; Sebrane; Urolosin; Vetevel†; Zuantrip; ***Switz.***: Omix; Pradif; Tamsunax; ***Thai.***: Harnal; ***Turk.***: Flomax; Floprost; Tamidra; Tamprost; Tocas; Uromax; ***UK***: Bazetham†; Contiflo; Cositam; Diffundox; Flomax; Flomaxtra; Galebon; Stronazon; Tabphyn; Tamfrex; ***Ukr.***: Adenorm (Аденорм); Flosin (Флосин); Fokusin (Фокусин); Omix (Омікс); Omnic (Омник); Omnimax (Омнимакс); Ranoprost (Ранопрост); Tamsol (Тамсол); Tamsonic (Тамсоник)†; Tamsulid (Тамсулид); Urofrin (Урофрин); ***USA***: Flomax; ***Venez.***: Secotex; Tamsulon.

Multi-ingredient Preparations. ***Austral.***: Duodart; ***Belg.***: Combodart; ***Canad.***: Jalyn; ***Cz.***: Duodart; ***Denm.***: Combodart; ***Fin.***: Duodart; ***Ger.***: Duodart; ***Gr.***: Duodart; ***Hung.***: Duamild; ***India***: Contiflo-OD-F; Dutas-T; Finabald-T; Finast T; Flokind-F; Geriflo; Urimax F; ***Irl.***: Combodart; ***Israel***: Duodart; ***Neth.***: Combodart; ***Norw.***: Duodart; ***Pol.***: Duodart; ***Port.***: Combodart; ***Spain***: Duodart; ***Switz.***: Duodart; ***UK***: Combodart; ***USA***: Jalyn.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Tamsulosin Capsules; Prolonged-release Tamsulosin Tablets;

USP 36: Tamsulosin Hydrochloride Capsules.

Tolterodine Tartrate *(BANM, USAN, rINNM)*

Kabi-2234 (tolterodine); PNU-200583E; Tartrato de tolterodina; Tolterodin Tartrat; Tolterodina, tartrato de; Tolterodine L-Tartrate; Toltérodine, Tartrate de; Tolterodini Tartras; Тольтеродина Тартрат.

(+)-(*R*)-2-{α-[2-(Diisopropylamino)ethyl]benzyl}-*p*-cresol tartrate.

$C_{22}H_{31}NO,C_4H_6O_6$=475.6

CAS — 124937-51-5 (tolterodine); 124937-52-6 (tolterodine tartrate).

ATC — G04BD07.

ATC Vet — QG04BD07.

UNII — 5T619TQR3R.

Uses and Administration

Tolterodine tartrate is a tertiary antimuscarinic with actions similar to those of atropine (p. 1310.3); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder. Tolterodine is used in the management of urinary frequency, urgency, and incontinence in detrusor instability. Usual oral doses of tolterodine tartrate are 2 mg twice daily; modified-release preparations are given in a usual dose of 4 mg once daily. Doses of 1 mg twice daily (or 2 mg daily as a modified-release preparation) are recommended in patients experiencing troublesome adverse effects. Licensed US product information advises that the dose of tolterodine should not exceed 2 mg daily in patients receiving potent CYP3A4 inhibitors; UK product information recommends against such combinations. See below for doses in patients with hepatic or renal impairment and for doses in children.

Administration in children. Although tolterodine is not licensed in the UK for use in children, the *BNFC* suggests that an oral dose of 1 mg daily, increased according to response to a maximum of 2 mg twice daily, may be used in children from 2 years of age for urinary frequency, urgency, and incontinence. A similar dose is given to children aged 5 years and above for the treatment of nocturnal enuresis; one dose should be given at bedtime. Children stabilised on 2 mg twice daily of a conventional formulation may be transferred to 4 mg once daily of a modified-release preparation.

Administration in hepatic or renal impairment. Oral doses of 1 mg of tolterodine tartrate twice daily (or 2 mg daily as a modified-release preparation) are recommended by UK and US licensed product information in patients with hepatic or severe renal impairment.

Benign prostatic hyperplasia. Although there have been concerns about the use of antimuscarinics in patients with symptomatic benign prostatic hyperplasia (p. 2347.1) some patients have lower urinary tract symptoms suggestive of overactive bladder, and antimuscarinics such as tolterodine are increasingly being used to treat such symptoms, either alone or as adjuncts.

References.
1. Kaplan SA, *et al.* Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol (Baltimore)* 2005; **174:** 2273–5.
2. Kaplan SA, *et al.* Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006; **296:** 2319–28. Correction. *ibid.*; **297:** 1195. Correction. *ibid.*; **298:** 1864.
3. Rovner ES, *et al.* Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. *J Urol (Baltimore)* 2008; **180:** 1034–41.

Nocturnal enuresis. Tolterodine has been tried with desmopressin for nocturnal enuresis (p. 2349.1) in children with an incomplete response to desmopressin.[1] A 66% reduction in the risk of bed-wetting episodes was reported with tolterodine and desmopressin treatment compared with desmopressin alone.

1. Austin PF, *et al.* Combination therapy with desmopressin and an anticholinergic medication for nonresponders to desmopressin for monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial. *Pediatrics* 2008; **122:** 1027–32.

Urinary incontinence. Tolterodine is used as an alternative to oxybutynin in the treatment of urge incontinence (see p. 2349.2). Tolterodine is said to have fewer adverse effects than oxybutynin, but the *BNF* states that its efficacy and adverse effects are comparable to modified-release oxybutynin.

References.
1. Harvey M-A, *et al.* Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. *Am J Obstet Gynecol* 2001; **185:** 56–61.
2. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. *Eur J Obstet Gynecol Reprod Biol* 2001; **98:** 97–102.
3. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). *Curr Med Res Opin* 2002; **18:** 177–84.
4. Swift S, *et al.* A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14:** 50–4.
5. Diokno AC, *et al.* Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003; **78:** 687–95.
6. Khullar V, *et al.* Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. *Urology* 2004; **64:** 269–74.
7. Sand PK, *et al.* A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; **15:** 243–8.
8. Nijman RJ, *et al.* Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. *J Urol (Baltimore)* 2005; **173:** 1334–9.
9. Rovner ES. Tolterodine for the treatment of overactive bladder: a review. *Expert Opin Pharmacother* 2005; **6:** 653–66.
10. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)
11. Jumadilova Z, *et al.* Retrospective evaluation of outcomes in patients with overactive bladder receiving tolterodine versus oxybutynin. *Am J Health-Syst Pharm* 2006; **63:** 2357–64.
12. Salvatore S, *et al.* Tolterodine for the treatment of overactive bladder. *Expert Opin Pharmacother* 2008; **9:** 1249–55.
13. Ulahannan D, Wagg A. The safety and efficacy of tolterodine extended release in the treatment of overactive bladder in the elderly. *Clin Interv Aging* 2009; **4:** 191–6.
14. Chung DE, Te AE. Tolterodine extended-release for overactive bladder. *Expert Opin Pharmacother* 2009; **10:** 2181–94.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. For a report of adverse ocular effects of tolterodine, see Effects on the Eyes under Oxybutynin, p. 2362.1. Tolterodine should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that high doses may cause fetal toxicity and it is recommended that tolterodine should be avoided during pregnancy.

Prolongation of the QT interval has occurred in controlled studies using both therapeutic and higher doses of tolterodine, and although changes from baseline did not cross the threshold of concern, the clinical implications are unclear. Licensed product information therefore warns that tolterodine should be used with caution in patients with QT prolongation or relevant risk factors, such as electrolyte disturbances, bradycardia, pre-existing cardiac disease, or the concomitant use of other drugs known to prolong the QT interval. Patients with raised tolterodine concentrations because of drug interactions (see below) would also be at increased risk, particularly poor metabolisers (see Pharmacokinetics, p. 2371.1).

References.
1. Layton D, *et al.* Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. *Drug Safety* 2001; **24:** 703–13.
2. Garely AD, Burrows L. Benefit-risk assessment of tolterodine in the treatment of overactive bladder in adults. *Drug Safety* 2004; **27:** 1043–57.
3. Malhotra BK, *et al.* Thorough QT study with recommended and supratherapeutic doses of tolterodine. *Clin Pharmacol Ther* 2007; **81:** 377–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tolterodine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

There is a risk of interactions between tolterodine and drugs that inhibit cytochrome P450 isoenzymes CYP2D6 (but see Antidepressants, below), or CYP3A4. For comment on dosage of tolterodine with potent CYP3A4 inhibitors (such as the macrolide antibacterials erythromycin or clarithromycin, or the azole antifungals ketoconazole, itraconazole, or miconazole), see Uses and Administration, above. Tolterodine can prolong the QT interval and should be used with caution in patients receiving other drugs known to have this effect, particularly class Ia and class III antiarrhythmics.

Anticholinesterases. For mention of an interaction between tolterodine and *donepezil* or *rivastigmine*, see Antimuscarinics, under Donepezil, p. 391.2.

Anticoagulants. For reference to the effect of tolterodine on the activity of *warfarin*, see under Antimuscarinics, p. 1532.2.

Antidepressants. The SSRI *fluoxetine* is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6 and use with tolterodine has resulted in more than a fourfold increase

All cross-references refer to entries in Volume A

in the area under the serum concentration-time curve (AUC) of tolterodine, associated with an approximate 20% decrease in the AUC of its 5-hydroxymethyl metabolite.[1] However, since both are active these changes were thought likely to result in little clinical difference, and licensed product information does not recommend a dose adjustment when tolterodine is given with fluoxetine.

1. Brynne N, *et al.* Fluoxetine inhibits the metabolism of tolterodine—pharmacokinetic implications and proposed clinical relevance. *Br J Clin Pharmacol* 1999; **48:** 553–63.

Gastrointestinal drugs. In a study[1] in healthy subjects, a dose of *antacid* was found to speed up the release of tolterodine from a modified-release preparation, probably as a result of the increase in gastric pH. Plasma-tolterodine concentrations were increased, but the half-life and area under the plasma concentration-time curve were not significantly affected. *Omeprazole* was reported to have a similar effect in another study.[2] The possible clinical effect of this change in drug release is unclear.

1. Sathyan G, *et al.* Effect of antacid on the pharmacokinetics of extended-release formulations of tolterodine and oxybutynin. *Clin Pharmacokinet* 2004; **43:** 1059–68.
2. Dmochowski R, *et al.* Effect of the proton pump inhibitor omeprazole on the pharmacokinetics of extended-release formulations of oxybutynin and tolterodine. *J Clin Pharmacol* 2005; **45:** 961–8.

Pharmacokinetics

Peak plasma concentrations of tolterodine occur 1 to 3 hours after an oral dose. It is highly bound to plasma proteins. Tolterodine is mainly metabolised in the liver by the cytochrome P450 isoenzyme CYP2D6 to the active 5-hydroxymethyl derivative (DD-01); in a minority of poor metabolisers tolterodine is metabolised by CYP3A4 isoenzymes to its inactive *N*-dealkylated derivative. The absolute bioavailability of tolterodine is normally about 17%, and the half-life is 2 to 3 hours; these increase in poor metabolisers to an absolute bioavailability of 65% and a half-life of about 10 hours. However, the clinical use of tolterodine is not affected by these differences in metabolism because the exposure to unbound tolterodine in poor metabolisers is similar to the combined exposure to unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolisers. Tolterodine is excreted primarily in the urine with about 17% appearing in the faeces; less than 1% of a dose is excreted as unchanged drug.

References.
1. Brynne N, *et al.* Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. *Int J Clin Pharmacol Ther* 1997; **35:** 287–95.
2. Brynne N, *et al.* Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. *Clin Pharmacol Ther* 1998; **63:** 529–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Breminal; Coli-Q; Detrusitol; Toltem; Urginol; ***Austral.***: Detrusitol; ***Austria***: Detrusitol; ***Belg.***: Detrusitol; ***Braz.***: Detrusitol; ***Canad.***: Detrol; ***Chile***: Detrusitol; Eltoven; ***China***: BeiKe (贝可); Bu Mai Ding (布迈定); Detrusitol (得妥); Le Zai (乐在); NeiQing (内青); Ning Tong (宁通); SheNiTing (舍尼亭); Te Su An (特苏安); ***Cz.***: Detrusitol; Uroflow; ***Denm.***: Detrusitol; ***Fin.***: Detrusitol; ***Fr.***: Detrusitol; ***Ger.***: Detrusitol; ***Gr.***: Detrusitol; ***Hong Kong***: Detrusitol; ***Hung.***: Detrusitol; ***India***: Detrusitol; Dezrolala; Flochek; Terol; ***Indon.***: Detrusitol; ***Irl.***: Detrusitol; ***Israel***: Detrusitol; ***Ital.***: Detrusitol; ***Malaysia***: Detrusitol; ***Mex.***: Detrusitol; Hipolter; ***Neth.***: Detrusitol; Tolespes; Tulerin; Uroline; ***Norw.***: Detrusitol; ***NZ***: Detrusitol; ***Pol.***: Defur; Detrusitol; Uroflow; ***Port.***: Detrusitol; ***Rus.***: Detrusitol (Детрузитол); Roliten (Ролитен); Urotol (Уротол); ***S. Afr.***: Detrusitol; ***Singapore***: Detrusitol; ***Spain***: Detrusitol; Urotrol; ***Swed.***: Detrusitol; ***Switz.***: Detrusitol; ***Thai.***: Detrusitol; ***Turk.***: Detrusitol; Toldin; Toltex; ***UK***: Blerone; Detrusitol; Inconex; Mariosea; Neditol; Preblacon; Santizor; ***Ukr.***: Detrusitol (Детрузитол); Roliten (Ролитен); Urotol (Уротол); ***USA***: Detrol; ***Venez.***: Detrusitol.

Trospium Chloride *(BAN, USAN, rINN)*

Cloruro de trospio; IP-631; Trospii Chloridum; Trospio chloridas; Trospio, cloruro de; Trospium, Chlorure de; Trospiumchlorid; Trospium-chlorid; Trospiumklorid; Trospiumkloridi; Trospiyum Klorür; Трospия Хлорид.

3α-Benziloyloxynortropane-8-spiro-1′-pyrrolidinium chloride.

$C_{25}H_{30}ClNO_3$=428.0

CAS — 10405-02-4.

ATC — G04BD09.

ATC Vet — QG04BD09.

UNII — 1E6682427E.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Trospium Chloride). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

USP 36: (Trospium Chloride). A colourless or white to slightly yellow crystalline powder. Very soluble in water; freely soluble in methyl alcohol. pH of a 1% solution in carbon dioxide-free water is 5.0 to 7.0. Protect from light.

Uses and Administration

Trospium chloride is a quaternary ammonium antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used for the management of urinary frequency, urgency, and incontinence in detrusor instability or detrusor hyperreflexia. It has also been used as an antispasmodic.

The immediate-release preparation is given orally in usual doses of 20 mg twice daily before meals on an empty stomach. Lower doses of 20 mg once daily may be warranted in patients aged 75 years and over. The need for continued treatment should be assessed at regular intervals of 3 to 6 months. A modified-release preparation is also available in some countries; the usual oral dose is 60 mg once daily in the morning, at least one hour before food. For use in patients with hepatic or renal impairment, see below.

Trospium chloride has also been given by slow intravenous injection. An inhaled formulation of trospium chloride for the treatment of chronic obstructive pulmonary disease is also being developed.

References.
1. Walter P, *et al.* Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: a pilot study. *Neurourol Urodyn* 1999; **18:** 447–53.
2. Frohlich G, *et al.* Trospium chloride in patients with detrusor overactivity: meta-analysis of placebo-controlled, randomized, double-blind, multi-center clinical trials on the efficacy and safety of 20 mg trospium chloride twice daily. *Int J Clin Pharmacol Ther* 2002; **40:** 295–303.
3. Halaska M, *et al.* Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol* 2003; **20:** 392–9.
4. Lopez Pereira P, *et al.* Trospium chloride for the treatment of detrusor instability in children. *J Urol (Baltimore)* 2003; **170:** 1978–81.
5. Zinner N, *et al.* Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol (Baltimore)* 2004; **171:** 2311–15.
6. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs* 2004; **64:** 2433–46.
7. Singh-Franco D, *et al.* Trospium chloride for the treatment of overactive bladder with urge incontinence. *Clin Ther* 2005; **27:** 511–30.
8. Rudy D, *et al.* Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006; **67:** 275–80.
9. Menarini M, *et al.* TcP128-Study Group. Trospium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? *Int J Clin Pharmacol Ther* 2006; **44:** 623–32.
10. Staskin D, *et al.* Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *J Urol (Baltimore)* 2007; **178:** 978–83.
11. Biastre K, Burnakis T. Trospium chloride treatment of overactive bladder. *Ann Pharmacother* 2009; **43:** 283–95.

Administration in hepatic impairment. Licensed product information for trospium chloride states that maximum plasma concentrations and area under the concentration-time curve were increased in patients with mild (Child-Pugh score 5 to 6) or moderate (Child-Pugh score 7 to 12) hepatic impairment compared with healthy subjects. There is no information regarding the use of trospium chloride in patients with severe hepatic impairment.

UK licensed product information advises caution in those with mild to moderate impairment, and advises against treatment in severe hepatic impairment. US licensed product information for both the immediate-release and the modified-release preparations advises caution in those with moderate to severe hepatic impairment. No specific dosage recommendations are given in either the UK or US product information.

Administration in renal impairment. Trospium chloride is mainly eliminated through active tubular secretion. Licensed product information states that increases in maximum plasma concentrations, area under the concentration-time curve, and half-life have been seen in patients with severe renal impairment given the immediate-release preparation; the pharmacokinetics of trospium chloride have not been studied in those with mild or moderate renal impairment.

UK licensed product information for the immediate-release preparation advises caution in those with mild to moderate renal impairment, while allowing for an oral dose of trospium chloride 20 mg once daily, or every alternate day, in those with severe renal impairment, defined as creatinine clearance (CC) of between 10 and 30 mL/minute per 1.73 m^2.

US licensed product information for the immediate-release preparation recommends a dose of 20 mg daily at bedtime for those with severe renal impairment (defined as CC less than 30 mL/minute). The modified-release preparation is not recommended for use in patients with severe renal impairment.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Trospium should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that trospium crosses the placenta and is distributed into breast milk; licensed product information therefore recommends that caution should be observed during pregnancy and breast feeding.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

After oral doses of trospium chloride, peak plasma concentrations occur in 4 to 6 hours. The bioavailability of trospium chloride is reduced by the simultaneous intake of food, especially with a high fat content. Plasma protein binding ranges from about 50% to about 80%. Trospium is excreted in the urine mainly by active renal tubular secretion as unchanged drug; about 10% appears as the spiroalcohol metabolite. The plasma half-life has been reported to be between 10 and 20 hours for the immediate-release preparation, and about 35 hours for the modified-release preparation. The mean half-life has been reported to be prolonged twofold in patients with severe renal impairment (creatinine clearance between 8 and 32 mL/minute). Trospium has been reported to cross the placenta and has been detected in the milk of *rats.*

Reviews.
1. Doroshyenko O, *et al.* Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet* 2005; **44:** 701–20.

For a study of the bioavailability of trospium chloride after intravesical instillation, see References, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Spasmex; ***Austria***: Inkontan; Rekont; Spasmolyt; Uraplex; Urivesc; ***Canad.***: Sanctura; Trosec; ***Chile***: Spasmex; ***China***: Spasmo-Lyt (顺睦利); ***Cz.***: Spasmed; Spasmex†; Uraplex; ***Denm.***: Ceris; Spasmo-Lyt; Spasmoplex†; Uraplex; Urivesc; ***Fin.***: Spasmo-Lyt; ***Fr.***: Ceris; ***Ger.***: Spasmex; Spasmo-Rhoival TC†; Spasmo-Urgenin TC; Spasmolyt; Trospi; Urivesc; ***Gr.***: Uraplex; Urivesc; ***Irl.***: Ceris; Flotros; Regurin; ***Israel***: Spasmex; Spasmo-Lyt; ***Ital.***: Uraplex†; Urivesc; ***Malaysia***: Spasmolyt; ***Port.***: Spasmoplex; Urivesc; ***Rus.***: Spasmex (Спазмекс); ***S.Afr.***: Uricon; ***Singapore***: Spasmolyt; ***Spain***: Uraplex; Urivesc; ***Switz.***: Spasmo-Urgenine Neo; ***Thai.***: Spasium; Spasmex; Spasmo-Lyt; Urivesc; ***Turk.***: Spasmex; ***UK***: Flotros; Regurin; ***Ukr.***: Spasmo-Lyt (Спазмо); ***USA***: Sanctura.

Multi-ingredient Preparations. ***Austria***: Spasmo-Urgenin; ***Spain***: Spasmo-Urgenin; ***Thai.***: Spasmo-Urgenin.

Pharmacopoeial Preparations
USP 36: Trospium Chloride Tablets.

Udenafil *(USAN, rINN)*

DA-8159; Udénafil; Udenafilo; Udenafilum; Уденафил.

3-(1-Methyl-7-oxo-3-propyl-4,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-*N*-{2-[(2*RS*)-1-methylpyrrolidin-2-yl]ethyl}-4-propoxybenzenesulfonamide.

$C_{25}H_{36}N_6O_4S$=516.7

CAS — 268203-93-6.

UNII — L5IB4XLY36.

Profile

Udenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used in the management of erectile dysfunction in an oral dose of 100 or 200 mg, 30 minutes to 2 hours before sexual intercourse. It should not be taken more than once in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Malaysia***: Zydena; ***Philipp.***: Zydena; ***Rus.***: Zydena (Зидена).

Vardenafil *(rINN)*

Vardénafil; Vardenafilum; Варденафил.

1-{[3-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*]-*as*-triazin-2-yl)-4-ethoxyphenyl]sulfonyl}-4-ethylpiperazine.

$C_{23}H_{32}N_6O_4S$=488.6

CAS — 224785-90-4.

ATC — G04BE09.

ATC Vet — QG04BE09.

UNII — UCE6F4125H.

The symbol † denotes a preparation no longer actively marketed

Vardenafil Dihydrochloride *(USAN, rINNM)*

Dihidrocloruro de vardenafil; Vardénafil, Dichlorhydrate de; Vardenafili Dihydrochloridum; Варденафила Дигидрохлорид.

$C_{23}H_{32}N_6O_4S,2HCl$=561.5

CAS — 224789-15-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

UNII — 5O8R96XMH7.

Vardenafil Hydrochloride *(USAN, rINNM)*

Bay-38-9456; Hidrocloruro de vardenafil; Vardénafil, Chlorhydrate de; Vardenafil Monohydrochloride; Vardenafili Hydrochloridum; Варденафила Гидрохлорид.

$C_{23}H_{32}N_6O_4S,HCl$=525.1

CAS — 224785-91-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

UNII — 5M8S2CU0TS.

Uses and Administration

Vardenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p. 2364.2). It is used in the management of erectile dysfunction (p. 2348.2). Vardenafil is given orally as the hydrochloride trihydrate although doses are expressed in terms of the base; vardenafil hydrochloride trihydrate 11.85 mg is equivalent to about 10 mg of vardenafil.

The usual dose of the *conventional oral formulation* is 10 mg taken about 25 minutes to one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 20 mg, and vardenafil should not be taken more than once in 24 hours. The dose may be taken with or without food, but onset of activity may be delayed if taken with a high-fat meal.

- An initial dose of 5 mg is recommended in elderly patients, which may be increased up to the maximum of 20 mg if necessary.
- In patients stabilised on alpha blocker therapy, the initial dose of vardenafil should be no more than 5 mg daily and it should not be taken within 6 hours of the alpha blocker, although this interval may not be necessary with alfuzosin or tamsulosin.
- A maximum daily dose of vardenafil 5 mg is advised in patients taking erythromycin (dose not specified in licensed product information), itraconazole (200 mg daily), or ketoconazole (200 mg daily). A daily dose of 2.5 mg is recommended for those taking clarithromycin (dose not specified in licensed product information), itraconazole (400 mg daily), or ketoconazole (400 mg daily).
- A maximum dose of vardenafil 2.5 mg every 24 hours is recommended in patients taking HIV-protease inhibitors. This dose should be reduced to 2.5 mg every 72 hours in those taking ritonavir-boosted regimens, although this combination may be best avoided (see also Interactions, below).

An *orodispersible formulation* that disintegrates on the tongue before swallowing is also available; the usual and maximum dose is 10 mg taken 25 minutes to one hour before sexual intercourse. The bioavailability of vardenafil after dosing with this formulation is greater than that with the conventional form and, consequently, the two forms are not bioequivalent.

For doses in hepatic or renal impairment, see below.

Reviews.

1. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs* 2003; **63:** 2673–2703.
2. Crowe SM, Streetman DS. Vardenafil treatment for erectile dysfunction. *Ann Pharmacother* 2004; **38:** 77–85.
3. Markou S, *et al.* Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. *Int J Impot Res* 2004; **16:** 470–8.
4. van Ahlen H, *et al.* The real-life safety and efficacy of vardenafil: an international post-marketing surveillance study—results from 29 358 German patients. *J Int Med Res* 2005; **33:** 337–48.
5. Reffelmann T, Kloner RA. Vardenafil: a selective inhibitor of phosphodiesterase-5 for the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2007; **8:** 965–74.
6. Eardley I, *et al.* Global experiences with vardenafil in men with erectile dysfunction and underlying conditions. *Int J Clin Pract* 2008; **62:** 1594–1603.
7. Morales AM, *et al.* Vardenafil for the treatment of erectile dysfunction: an overview of the clinical evidence. *Clin Interv Aging* 2009; **4:** 463–72.
8. Sanford M. Vardenafil orodispersible tablet. *Drugs* 2012; **72:** 87–98.

Administration in hepatic impairment. When given as the *conventional oral formulation*, an initial dose of 5 mg of vardenafil is recommended by UK licensed product information in patients with mild to moderate hepatic impairment (Child-Pugh category A to B), which may be increased if necessary, according to response and tolerability. The maximum dose recommended in patients with moderate hepatic impairment is 10 mg. Vardenafil has not been evaluated in severe hepatic impairment (Child-Pugh category C).

The *orodispersible formulation* should not be used in patients with moderate or severe hepatic impairment. It may be given, in a dose of 10 mg, to those with mild impairment who can tolerate a 5-mg dose of the conventional formulation.

Administration in renal impairment. No dose adjustment of vardenafil is needed in patients with mild to moderate renal impairment. An initial dose of 5 mg of the *conventional oral formulation* is recommended by UK licensed product information in patients with a creatinine clearance of less than 30 mL/minute; this may be increased to 10 mg and then to 20 mg if necessary, according to response and tolerability. US licensing information does not consider adjustment to be necessary. The *orodispersible formulation*, in a dose of 10 mg, may be given to those patients who can tolerate a 5-mg dose of the conventional formulation.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis.

Adverse Effects and Precautions

As for Sildenafil, p. 2365.2 and p. 2366.2. Photosensitivity has also been reported. Vardenafil may prolong the QT interval and is best avoided in patients with relevant risk factors such as hypokalaemia, congenital QT prolongation, or the use of antiarrhythmics of class Ia or class III. Dosage reductions may be required in patients with hepatic or renal impairment.

Effects on the cardiovascular system. References.

1. Thadani U, *et al.* The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002; **40:** 2006–12.

Interactions

As for Sildenafil, p. 2366.3. The use of vardenafil with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 (such as HIV-protease inhibitors, some azole antifungals, and macrolide antibacterials) is generally best avoided; if thought to be essential, dosage of vardenafil must be reduced and suggested doses are given above. Use with ketoconazole and itraconazole is contra-indicated in men older than 75 years of age. An enhanced hypotensive effect may be seen if vardenafil is taken with nifedipine. Vardenafil may prolong the QT interval and its use with antiarrhythmics of class Ia or class III should be avoided.

Pharmacokinetics

Vardenafil is rapidly absorbed after an oral dose, with a bioavailability of about 15%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when vardenafil is given with a high-fat meal.

Vardenafil is widely distributed into tissues and is about 95% bound to plasma proteins. It is metabolised in the liver primarily by cytochrome P450 isoenzymes CYP3A4 (the major route) as well as CYP3A5 and CYP2C isoforms. The major metabolite produced by desethylation of vardenafil also has some activity. The terminal half-life is about 4 to 5 hours.

Vardenafil is excreted as metabolites mainly in the faeces (91 to 95%), and to a lesser extent in the urine (2 to 6%). Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

References.

1. Rajagopalan P, *et al.* Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol* 2003; **43:** 260–7.
2. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Levitra; ***Austral.***: Levitra; ***Austria***: Levitra; Vivanza; ***Belg.***: Levitra; ***Braz.***: Levitra; Vivanza†; ***Canad.***: Levitra; ***Chile***: Levitra; ***China***: Levitra (艾力达); ***Cz.***: Levitra; Vivanza; ***Denm.***: Levitra; ***Fin.***: Levitra; ***Fr.***: Levitra; ***Ger.***: Levitra; ***Gr.***: Levitra; Vivanza; ***Hong Kong***: Levitra; ***Hung.***: Levitra; ***Indon.***: Levitra; ***Irl.***: Levitra; Vivanza; ***Israel***: Levitra; ***Ital.***: Levitra; ***Malaysia***: Levitra; ***Mex.***: Levitra; ***Neth.***: Levitra; Vivanza; ***Norw.***: Levitra; ***NZ***: Levitra; ***Philipp.***: Levitra; ***Pol.***: Levitra; Vivanza; ***Port.***: Levitra; Vivanza; ***Rus.***: Levitra (Левитра); ***S.Afr.***: Levitra; ***Singapore***: Levitra; ***Spain***: Levitra; Vivanza; ***Swed.***: Levitra; ***Switz.***: Levitra; Vivanza; ***Thai.***: Levitra; ***Turk.***: Levitra; ***UK***: Levitra; ***Ukr.***: Levitra (Левитра); ***USA***: Levitra; Staxyn; ***Venez.***: Levitra.

Yohimbine Hydrochloride *(BAN)*

Aphrodine Hydrochloride; Chlorhydrate de Québrachine; Corynine Hydrochloride; Hidrocloruro de Afrodina; Yohimbina, hidrocloruro de; Yohimbine, chlorhydrate de; Yohimbinhydrochlorid; Yohimbini hydrochloridum; Йохимбина Гидрохлорид.

Methyl 17α-hydroxy-yohimban-16α-carboxylate hydrochloride.

$C_{21}H_{26}N_2O_3,HCl$=390.9

CAS — 146-48-5 (yohimbine); 65-19-0 (yohimbine hydrochloride).

ATC — G04BE04.

ATC Vet — QG04BE04; QV03AB93.

UNII — NB2E1YP49F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Yohimbine Hydrochloride). A white or slightly yellowish, crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Yohimbine Hydrochloride). A white to yellow powder. Slightly soluble in water and in alcohol; soluble in boiling water. Store in airtight containers.

Profile

Yohimbine is the principal alkaloid of the bark of the yohimbe tree, *Pausinystalia yohimbe* (*Corynanthe yohimbi*) (Rubiaceae); it is also found in *Rauwolfia serpentina*. It is an alpha$_2$-adrenoceptor blocker with a short duration of action. It has an antidiuretic effect and produces increases in heart rate and blood pressure. It has been reported to cause CNS effects including anxiety and manic reactions. It has been given orally in the treatment of erectile dysfunction (p. 2348.2) and for its alleged aphrodisiac properties but convincing evidence of such an effect is lacking. It is contra-indicated in renal or hepatic disease.

Adverse effects. A warning about the potential adverse effects, including anxiety, manic reactions, bronchospasm, and a lupus-like syndrome, associated with yohimbine taken in health food products.[1] Interactions with tricyclic antidepressants and with phenothiazines might also occur. Acute severe neurotoxicity has been reported.[2]

1. De Smet PAGM, Smeets OSNM. Potential risks of health food products containing yohimbe extracts. *BMJ* 1994; **309:** 958.
2. Giampreti A, *et al.* Acute neurotoxicity after yohimbine ingestion by a body builder. *Clin Toxicol* 2009; **47:** 827–9.

Uses. References to the use of yohimbine in erectile dysfunction.

1. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomised clinical trials. *J Urol (Baltimore)* 1998; **159:** 433–6.
2. Tam SW, *et al.* Yohimbine: a clinical review. *Pharmacol Ther* 2001; **91:** 215–43.
3. Lebret T, *et al.* Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction. *Eur Urol* 2002; **41:** 608–13.
4. Guay AT, *et al.* Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial. *Int J Impot Res* 2002; **14:** 25–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Yocon; ***Belg.***: Yocoral; ***Braz.***: Yomax; ***Canad.***: Yocon†; ***Chile***: Yocon; ***Denm.***: Virigen†; ***Fr.***: Yocoral; ***Ger.***: Yocon; ***Port.***: Zumba; ***UK***: Prowess Plain; ***Ukr.***: Yochimbin Spiegel (Йохімбін Шпігель)†; ***USA***: Aphrodyne; Yocon.

Multi-ingredient Preparations. ***Arg.***: Ferona†; Optimina Plus; ***Braz.***: Libiplus; Tonaton; ***Hong Kong***: Sessoforte†; Wari-Procomil†; ***Indon.***: Sirec; ***UK***: Prowess; ***Ukr.***: Yohimbex-Garmonia (Йохимбекс-Гармония).

Homoeopathic Preparations. ***Fr.***: Kalium Phosphoricum Complexe No 100; ***Rus.***: Damiana-Plus (Дамиана-Плюс).

Pharmacopoeial Preparations

USP 36: Yohimbine Injection.

Vaccines Immunoglobulins and Antisera

The agents described in this section are immunological agents used for both active and passive immunisation.

Active immunisation is the exposure of the immune system to antigens in the form of micro-organisms or products of their activity in order to stimulate production of antibodies and acquired cell-mediated responses with a specific protective capacity. It may be a natural process after infection, or an artificial process induced by giving *vaccines*. It is inevitably a slow process dependent upon the rate at which the antibodies can be produced. Although the terms vaccination and immunisation are often used synonymously and interchangeably, *vaccination* simply refers to giving a vaccine whereas *immunisation* implies the development of protective levels of antibodies.

Passive immunisation, which results in immediate short-term protection, may be achieved by giving exogenous antibodies in the form of *antisera* (of animal origin) or *immunoglobulins*.

Antisera

Antisérums; Antisueros; Immunsera; Sueros inmunológicos; Антисыворотки.

Description

Antisera (immunosera) are sterile preparations containing immunoglobulins obtained from the serum of immunised animals by purification. The term antisera includes antitoxins, which are antibodies that combine with and neutralise specific toxins, and antivenins (antivenoms), which are antitoxins directed against the toxic principle of the venoms of poisonous animals such as certain snakes and arthropods.

Antisera are obtained from healthy animals immunised by injections of the appropriate toxins or toxoids, venins, or suspensions of micro-organisms or other antigens. The specific immunoglobulins may be obtained from the serum by fractional precipitation and enzyme treatment or by other chemical or physical means. A suitable antimicrobial preservative may be added, and is invariably added if the product is issued in multidose containers. The Ph. Eur. 8 directs that when antisera contain phenol, the concentration is not more than 0.25%. The antiserum is distributed aseptically into sterile containers, which are sealed so as to exclude micro-organisms. Alternatively they may be supplied as freeze-dried preparations for reconstitution immediately before use.

Uses and Administration

Antisera have the specific power of neutralising venoms or bacterial toxins, or combining with the bacterium, virus, or other antigen used for their preparation. Most antisera in current use are antitoxins or antivenins. The use of antisera to induce passive immunity has declined; immunoglobulins are preferred. Although antisera are defined as being of animal origin (see above), the term antisera has been used in some countries to describe antitoxins of human origin (immunoglobulins).

Adverse Effects and Precautions

Reactions are liable to occur after the injection of any serum of animal origin. Anaphylaxis (type I hypersensitivity reaction, p. 610.1) may occur, with hypotension, dyspnoea, urticaria, and shock, which requires management as a medical emergency (see Anaphylaxis and Anaphylactic Shock, p. 1293.2).

Serum sickness (type III hypersensitivity reaction, p. 610.1) may also occur, frequently 7 to 10 days after the injection of serum of animal origin.

Before injecting serum, information should be obtained whenever possible as to whether the patient is subject to hypersensitivity disorders or has received serum injections before. Sensitivity testing should be performed before giving antisera. The patient must be kept under observation after giving a full dose of antisera. Adrenaline injection and resuscitation facilities should be available.

Immunoglobulins

Immunglobuline; Inmunoglobulinas; Иммуноглобулины.

Description

Immunoglobulins are produced by B lymphocytes as part of the humoral response to foreign antigens. Immunoglobulins used in clinical practice are preparations containing antibodies, usually prepared from human plasma or serum, and mainly comprise IgG. Normal immunoglobulin, prepared from material from blood donors, contains several antibodies against infectious diseases prevalent in the general population, whereas specific immunoglobulins contain minimum specified levels of one antibody. Antibodies may also be prepared by genetic engineering techniques.

Uses and Administration

Immunoglobulins are used for passive immunisation, thus conferring immediate protection against some infectious diseases. They are preferred to antisera of animal origin as the incidence of adverse reactions is lower.

It is generally important to follow the conferment of passive immunity, which is largely an emergency procedure, by the injection of suitable antigens to produce active immunity.

Adverse Effects

Local reactions with pain and tenderness at the site of intramuscular injection may follow the use of immunoglobulins. Hypersensitivity reactions, including, rarely, anaphylactic reactions, have also been reported; such reactions, though, are far less frequent than after the use of antisera of animal origin.

Some immunoglobulins are available as intravenous preparations. Systemic reactions with fever, chills, facial flushing, headache, and nausea may occur, particularly at high rates of infusion.

Precautions

Strenuous efforts are made to screen human donor material used in the preparation of immunoglobulins; the transmission of infections, including hepatitis B and HIV, which has been associated with the use of certain blood products (see p. 1135.3), does not appear to be a problem with the immunoglobulins currently in use.

IgA, present in some immunoglobulin preparations, may give rise to the production of anti-IgA antibodies in patients with IgA deficiencies, with the consequent risk of anaphylactic reactions. For precautions in such patients, see Hypersensitivity under Adverse Effects and Precautions in Normal Immunoglobulins, p. 2407.3.

Interactions

Immunoglobulins may interfere with the ability of live vaccines to induce an immune response and a suitable interval should separate their use (see Vaccines, Interactions, p. 2375.3).

Vaccines

Vacunas; Вакцины.

Description

Vaccines are traditionally preparations of antigenic materials that are given with the objective of inducing in the recipient active immunity to specific infecting agents or toxins or antigens produced by them. They may contain living or killed micro-organisms, bacterial toxoids, or antigenic material from particular parts of the infecting organism, which may be derived from the organism or produced by recombinant DNA technology. Vaccines may be single-component vaccines or mixed combined vaccines. Vaccines against some non-infectious diseases are being developed.

Storage. All vaccines are sensitive to heat to differing extents, with oral poliomyelitis vaccines and measles vaccines the most heat-sensitive of the commonly used vaccines. Freeze-dried vaccines become much more heat-sensitive once reconstituted. The effect of heat on vaccines is generally irreversible loss of potency, but in some cases heat exposure may also cause the vaccine to become more reactogenic. The system used for storing and distributing vaccines at sufficiently low temperature is called the cold chain, and consists of a series of storage and transport links all designed to keep the vaccine at the correct temperature until it reaches the user. WHO recommends[1] that oral poliomyelitis vaccines be stored at -25 to -15 degrees and that, in general, freeze-dried vaccines should be stored at 2 to 8 degrees.

Some vaccines are also sensitive to freezing, notably hepatitis B vaccines and Haemophilus influenzae vaccines, and care should be taken not to store them at too low a temperature.[1]

In addition to temperature sensitivity, some vaccines are also sensitive to light, such as BCG vaccines, measles-containing vaccines, and rubella-containing vaccines. These are sometimes supplied in darker glass vials for protection, but care should be taken to protect them from sunlight and ultraviolet light, including fluorescent lights.[2]

Further advice concerning vaccine storage is given in the references below.[3-6] Preliminary study has suggested[7] that it may be possible to develop vaccines that are stable without refrigeration by drying the antigens in a suspension of sucrose and trehalose.

1. WHO. *Temperature sensitivity of vaccines.* Geneva: WHO, 2006. Also available at: http://www.who.int/vaccines-documents/DocsPDF06/847.pdf (accessed 23/04/10)
2. WHO. *Cold chain, vaccines and safe-injection equipment management.* Geneva: WHO, 2008. Also available at: http://www.who.int/immunization_delivery/systems_policy/MLM_module1.pdf (accessed 23/04/10)
3. Department of Vaccines and Other Biologicals. *Temperature monitors for vaccines and the cold chain.* Geneva: WHO, 1999. Also available at: http://www.who.int/vaccines-documents/DocsPDF/www9804.pdf (accessed 15/09/05)
4. CDC. Notice to readers: guidelines for maintaining and managing the vaccine cold chain. *MMWR* 2003; **52:** 1023–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5242.pdf (accessed 24/05/06)
5. Australian Government Department of Health and Ageing. National vaccine storage guidelines: strive for 5 (2005). Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/DF94731AD8CBF34ECA2575BD001C8129/$File/strive-4-five.pdf (accessed 27/08/10)
6. Public Health Agency of Canada. National vaccine storage and handling guidelines for immunization providers (2007). Available at: http://www.phac-aspc.gc.ca/publicat/2007/nvshglp-ldemv/pdf/nvshglp-ldemv-eng.pdf (accessed 27/08/10)
7. Alcock R, *et al*. Long-term thermostabilization of live poxviral and adenoviral vaccine vectors at supraphysiological temperatures in carbohydrate glass. *Sci Transl Med* 2010; **2:** 19ra12.

Uses and Administration

Vaccines are used for active immunisation as a prophylactic measure against some infectious diseases. They provide partial or complete protection for months or years. For inactivated vaccines, a slight and rather slow antibody response of primarily immunoglobulin M (IgM) (the primary response) is produced after the first or second dose but, when a further dose is given after a suitable interval, a prompt antibody response follows and high concentrations of IgG occur in the blood (the secondary response). Though the antibody concentration may later fall, a further dose of vaccine promptly restores it. For most live vaccines only one dose is required, although 3 doses of live (oral) poliomyelitis vaccines are needed to achieve complete immunisation. Some inactivated vaccines contain an adjuvant such as aluminium hydroxide or aluminium phosphate to enhance the immune response.

Protection against several infectious diseases may be provided in early life by active immunisation and national schedules for **childhood** immunisation are regularly reviewed and updated. Schedules for routine immunisation of infants and children are generally designed to fit in with routine health checks and landmark events such as school starting and leaving ages. National immunisation schedules should be consulted for full details of local recommendations.

In the **UK**, the following schedule of vaccination and immunisation is recommended:

- at 2 months of age, the first dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine (p. 2385.3), plus a first dose of pneumococcal conjugate vaccine (p. 2410.1) and a first dose of a rotavirus vaccine (p. 2416.1)
- at 3 months of age, a second dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, plus the first dose of meningococcal C conjugate vaccine (p. 2401.3) and a second dose of a rotavirus vaccine
- at 4 months of age, a third dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, plus a second dose of pneumococcal conjugate vaccine
- at about 12 to 13 months of age, a third dose of pneumococcal conjugate vaccine, plus a first dose of measles, mumps, and rubella vaccine (p. 2400.2), plus a booster dose of a combined *Haemophilus influenzae* and meningococcal C conjugate vaccine (p. 2388.1)

- at 3 years 4 months to 5 years, a reinforcing dose of a combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine (p. 2385.2) and a second dose of measles, mumps, and rubella vaccine
- at 12 to 13 years of age, 3 separate doses of human papillomavirus vaccine (p. 2392.2) for all girls
- at around 14 years, a booster dose of a low-dose diphtheria, tetanus, and poliomyelitis (inactivated) vaccine (p. 2386.2) and a meningococcal C conjugate vaccine

The following schedule is usually recommended in the **USA**:

- at birth, the first dose of hepatitis B vaccine (p. 2389.3)
- at age 1 to 2 months, a second dose of hepatitis B vaccine
- at 2 months, a first dose of diphtheria, tetanus, and pertussis (acellular component) vaccine (p. 2383.3), plus a *Haemophilus influenzae* vaccine (p. 2387.2), a pneumococcal conjugate vaccine (p. 2410.1), a poliomyelitis (inactivated) vaccine (p. 2411.1) and a rotavirus vaccine (p. 2416.1)
- at 2 to 18 months, a course of a meningococcal vaccine (p. 2401.3) with or without a *Haemophilus influenzae* vaccine to high-risk children
- at 4 months, a second dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, plus the second doses of a *Haemophilus influenzae* vaccine, pneumococcal conjugate vaccine, poliomyelitis (inactivated) vaccine, and rotavirus vaccine
- at 6 months, the third dose of *Haemophilus influenzae* vaccine if necessary (depending on the type of vaccine used), a third dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, a third dose of pneumococcal conjugate vaccine, and a third dose of rotavirus vaccine if necessary (depending on the type of vaccine used)
- at 6 to 18 months, the third doses of hepatitis B and poliomyelitis (inactivated) vaccines
- from 6 months to 18 years, annual influenza vaccine
- from 12 to 23 months, 2 doses (6 to 18 months apart) of a hepatitis A vaccine (p. 2388.3)
- at 12 to 15 months, a reinforcing dose of *Haemophilus influenzae* vaccine, the first dose of measles, mumps, and rubella vaccine, the first dose of varicella-zoster vaccine (p. 2423.3) and the fourth dose of pneumococcal conjugate vaccine
- at 15 to 18 months, the fourth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine
- at 2 to 18 years, pneumococcal polysaccharide vaccine (as an addition to previous dosage with pneumococcal conjugate vaccine) in certain high-risk groups
- at 2 to 10 years, meningococcal C conjugate vaccine (2 doses, 2 months apart) to children with terminal complement deficiencies or asplenia and other high-risk groups; meningococcal polysaccharide vaccine may alternatively be used
- at 4 to 6 years, the fifth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, the fourth dose of poliomyelitis (inactivated) vaccine, the second dose of measles, mumps, and rubella vaccine, and the second dose of varicella-zoster vaccine
- at age 11 to 12 years, a sixth dose of low-dose diphtheria, tetanus, and pertussis (acellular component) plus a first dose of quadrivalent meningococcal C conjugate vaccine in those not previously vaccinated (meningococcal polysaccharide vaccine may alternatively be used); the first dose of human papillomavirus vaccine (p. 2392.2) may be given to girls, the second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose
- at 16 years, a booster dose of meningococcal C conjugate vaccine (meningococcal polysaccharide vaccine may alternatively be used)

Immunisation schedules for older children and **adults** are also produced, along with recommendations for vaccination of high-risk groups, including the immunocompromised and the elderly, and of travellers.

In addition to vaccines directed against bacteria and viruses, advances are being made in producing vaccines against fungi, protozoa, and helminths, and for non-infective diseases including cancer (see p. 757.3) and auto-immune disorders.

Development of novel vaccine formulations and delivery methods is continuing, including transdermal and transmucosal systems. Genetic manipulation of foodstuffs is being investigated with the aim of producing edible vaccines.

Immunisation schedules. References to routine immunisation schedules in the UK[1] and USA.[2-4]

1. DoH. *Immunisation Against Infectious Disease* 2006 (updated 14th March, 2013): "The Green Book". Available at: https://www.gov.uk/government/publications/green-book-the-complete-current-edition (accessed 18/04/13)
2. CDC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for persons aged 0 through 18 years– United States, 2013. *MMWR Surveill Summ* 2013; **62** (suppl 1): 2–8. Correction. *ibid.*; 256. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a2.htm (accessed 21/03/13)
3. CDC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 Years and older– United States, 2013. *MMWR Surveill Summ* 2013; **62** (suppl 1): 9–19. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a3.htm (accessed 21/03/13)
4. Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule—United States, 2013. *Pediatrics* 2013; **131:** 397–8. Also available at: http://pediatrics.aappublications.org/content/131/2/397.full.pdf+html (accessed 22/05/13)

EXPANDED PROGRAMME ON IMMUNIZATION. In 1974 the World Health Assembly adopted a resolution creating the Expanded Programme on Immunization (EPI), the aim of which was to provide immunisation against 6 target diseases (diphtheria, measles, pertussis, poliomyelitis, tetanus, and tuberculosis) for all children throughout the world by 1990. Hepatitis B, pneumococcal, and *Haemophilus influenzae* infections were later added to the list of target diseases and more recently rotavirus, and, for girls, human papillomavirus vaccines were also added. Although the attention of WHO had been focussed mainly on the developing countries, it was emphasised that the programme was not created exclusively for these countries. Besides WHO, many other organisations, including UNICEF, are involved. Since 2000 much work has been carried out under the auspices of the Global Alliance for Vaccination and Immunisation (GAVI) and in 2006 UNICEF and WHO established the Global Immunization Vision and Strategy (GIVS) to raise global immunisation coverage for these common preventable diseases to at least 90% in every country over 5 years, and then to sustain coverage.

Although many cases of the target diseases and many deaths have been prevented, vaccine coverage, especially for measles and neonatal tetanus is still low. It is particularly important to immunise children as early in life as possible and not to withhold vaccines from those with minor illness or malnutrition. Vaccine uptake was around 70% in 1990 compared with less than 5% in 1974. By 2003, all 192 member states of WHO were routinely immunising against diphtheria, measles, pertussis, poliomyelitis, and tetanus before the age of 18 months. Also, 158 member states were routinely immunising against tuberculosis, but routine BCG vaccination has been stopped in some countries, including the UK, due to low risk and prevalence of disease.

A schedule designed to provide protection for all children at the earliest possible age broadly recommends:

- at birth, a dose of BCG vaccine (p. 2378.1). A monovalent hepatitis B vaccine (p. 2389.3) should be given as soon as possible after birth; further doses (which may be given as a combined vaccine) are then given at 6, 10 (optional), and 14 weeks. A dose of the poliomyelitis (OPV) vaccine (p. 2411.1) can be given at birth in endemic or recently endemic countries
- at 6 weeks, the first dose of a diphtheria, tetanus, and pertussis vaccine (p. 2383.3), plus a *Haemophilus influenzae* vaccine (p. 2387.2), a pneumococcal conjugate vaccine (p. 2410.1), a rotavirus vaccine (p. 2416.1), and a poliomyelitis vaccine (OPV)
- at 10 weeks, a second dose of diphtheria, tetanus, and pertussis vaccine, plus the second doses of a *Haemophilus influenzae* vaccine, a pneumococcal conjugate vaccine, a rotavirus vaccine, and a second (or third) dose of a poliomyelitis vaccine (OPV)
- at 14 weeks, the third dose of diphtheria, tetanus, and pertussis vaccine, plus the third doses of *Haemophilus influenzae* vaccine, a pneumococcal conjugate vaccine, rotavirus vaccine (only for those completing a course of *RotaTeq*), and a third (or fourth) dose of a poliomyelitis vaccine (OPV)
- at 9 to 12 months, the first dose of a measles vaccine (p. 2398.3) with a dose of rubella vaccine (p. 2417.1); a second dose of a measles vaccine should be given 4 weeks after the first dose
- at 1 to 6 years, the fourth (booster) dose of diphtheria, tetanus, and pertussis vaccine
- at age 9 to 13 years,the first dose of human papillomavirus (quadrivalent) vaccine (p. 2392.2) may be given to girls, the second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose. *Alternatively*, at age 10 to 13 years, the first dose of human papillomavirus (bivalent) vaccine may be given to girls, the second dose is given 1 month after the first dose and the third dose is given 6 months after the first dose

Inactivated polio vaccine (IPV) alone may be given as an alternative to OPV alone (or an IPV/OPV sequential schedule) in countries that have the lowest risk of both wild-strain polio viruses importation and transmission. A primary series of 3 doses should be started at 2 months of age and the next doses given at 4 to 8 week intervals. If the primary series starts earlier (e.g. at 6 weeks of age) then a booster dose should be given after an interval of 6 months or more.

In addition to these vaccines children living in certain areas may also be given Japanese encephalitis vaccine (p. 2396.2), tick-borne encephalitis vaccine (p. 2422.1), and/or yellow fever vaccine (p. 2424.3). Immunisation schedules for children in some high-risk populations, older children, and adults are also provided.

References.

1. WHO. WHO vaccine-preventable diseases: monitoring system 2010 global summary. Geneva: WHO, 2010. Also available at: http://whqlibdoc.who.int/hq/2010/WHO_IVB_2010_eng.pdf (accessed 10/04/13)
2. WHO. WHO recommendations for routine immunization–summary tables (issued 15 November, 2012). Available at: http://www.who.int/immunization/policy/immunization_tables/en/index.html (accessed 26/03/13)

Immunisation of immunocompromised patients. Immunocompromised patients may require immunisation against opportunistic infections but immune response to vaccination may be impaired (see Precautions, p. 2375.2), and there is a risk of disseminated infection with live vaccines.

Recommendations for immunisation of HIV-positive individuals have varied, particularly with regard to live vaccines.

It is generally recommended that vaccines used for routine immunisation in childhood may be given to asymptomatic HIV-positive persons, providing they are not immunosuppressed, but that BCG and yellow fever vaccines should not be given at all.[1,2] WHO recommends[3] that an extra dose of measles vaccine may be given at 6 months of age with the standard dose given as soon after 9 months of age as possible.

Some detailed guidance on vaccination of immunocompromised children is provided by the Royal College of Paediatrics and Child Health in the UK[4] and by the Children's HIV Association of UK and Ireland.[5] Guidance on immunisation of HIV-infected adults is provided by the British HIV Association.[6]

1. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 27/08/10)
2. Eley B. Immunization in patients with HIV infection: are practical recommendations possible? *Drugs* 2008; **68:** 1473–81.
3. WHO. Measles vaccines: WHO position paper. *Wkly Epidem Rec* 2009; **84:** 349–60. Also available at: http://www.who.int/wer/2009/wer8435.pdf (accessed 16/12/09)
4. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/doc.aspx?id_Resource=1768 (accessed 15/07/08)
5. Riordan A. Children's HIV Association of UK and Ireland. Immunisation of HIV-infected children, June 2007 [under review]. Available at: http://www.chiva.org.uk/health/guidelines/immunisation (accessed 27/08/10)
6. Geretti AM, *et al*. British HIV Association Immunisation Subcommittee. Immunisation guidelines for HIV-infected adults 2008. Available at: http://www.bhiva.org/documents/Guidelines/Immunisation/Immunization2008.pdf (accessed 10/02/10)

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO.[1] In 2010 the following information regarding certification of vaccination was given.

A *yellow fever* vaccination certificate is now the only one that may be mandated by international regulations, although some countries require other vaccinations before entry is permitted. The vaccine used must be approved by WHO and given at a designated centre. Vaccination is strongly recommended for travel outside the urban areas of countries in the yellow fever endemic zone even if these countries have not officially reported the disease and do not require evidence of vaccination on entry. Many countries require a certificate from travellers arriving from infected areas or from countries with infected areas, or who have been in transit through those areas. Some countries require a certificate from all entering travellers including those in transit; although there is no epidemiological justification for this requirement, and it is clearly in excess of the International Health Regulations (WHO recommendations for prevention of the international spread of diseases), travellers may find that it is strictly enforced, particularly for persons going to Asia from Africa or South America. The validity period of international certificates of vaccination against yellow fever is 10 years, beginning 10 days after vaccination.

Some polio-free countries require evidence of *polio* vaccination before travellers from endemic countries are permitted entry; Saudi Arabia also requires pilgrims to be vaccinated against *meningococcal* disease.

No country or territory any longer requires a certificate of *cholera* immunisation as the introduction of cholera into any country cannot be prevented by cholera vaccination.

Now that *smallpox* has been eradicated, smallpox vaccination is no longer required by any country.

Apart from vaccinations required by countries for entry to their territory, other vaccinations are either recommended by WHO for general protection against certain

diseases or advised in certain circumstances. A vaccination plan should be established, taking into account the traveller's destination, overall state of health and current immune status, the duration and type of travel, and the time available before travel.

Further information for international travellers is also often provided by national authorities including those in the UK[2] and USA.[3]

1. WHO. *International Travel and Health.* Geneva: WHO, 2010. Also available at: http://www.who.int/ith/en/ (accessed 02/07/10)
2. The National Travel Health Network and Centre. *Health Information for Overseas Travel.* Available at: http://www.nathnac.org/pro/yellowbook_revision.htm (accessed 16/11/9)
3. CDC. *The Yellow Book*:2010. Available at: http://wwwn.cdc.gov/travel/content/yellowbook/home-2010.aspx (accessed 16/11/09)

Infection eradication. Eradication of infectious diseases has proved more difficult than was hoped, and smallpox is the only disease to have been recognised officially as having been eradicated so far. Eradication is defined as the extinction of the pathogen that causes the infectious disease in question, whereas in elimination the disease disappears but the causative agent remains. Of the target diseases of WHO's Expanded Programme on Immunization (see p. 2374.2), many of the factors necessary for elimination are present for each of the diseases, but some are not. *Measles* is so highly communicable a disease that a vaccine efficacy rate of about 95% is probably not high enough even to eliminate, much less eradicate, the disease. However, immunisation campaigns have produced substantial reductions of infection rate in some countries, although repeated vaccination may be necessary. *Pertussis* is also highly infectious and the vaccine is almost certainly not effective enough. *Tetanus* is not eradicable as the causative organism is ubiquitous. However, elimination of neonatal tetanus may be possible although it depends on protection of more than 80% of infants at birth. This depends not only on maternal vaccination but also on delivery practices. For *poliomyelitis*, countries that are efficient at giving vaccines have proved remarkably successful not only in practically eliminating the disease but also in virtually eradicating the organism. *Tuberculosis* is clearly not eradicable at present and *diphtheria* has many features that suggest it cannot be easily eradicated. Prospects for eradicating *congenital rubella syndrome* are more encouraging and the prospects for elimination or eradication of *mumps* are probably similar to those of rubella.

Other factors that may contribute to the failure of vaccination policies in eradicating disease include: concern, often unfounded, over the safety of vaccines and the perpetuation of invalid contra-indications, the use of inappropriate indicators for the efficacy of vaccines, the suitability of different types of vaccine and of vaccination schedules, difficulties in vaccine supply, and social and behavioural pressures which reduce compliance with vaccination schedules.

Vaccine development. The WHO Initiative for Vaccine Research (IVR) supports and facilitates the development, clinical evaluation, and worldwide access to safe, effective, and affordable vaccines against infectious diseases of public health importance, especially in developing countries. The Global Vaccine Research Forum hosts an annual conference to discuss vaccine research and development issues, and to update research agendas. Information is frequently updated by WHO.[1,2]

1. WHO. State of the art of new vaccines: research and development (revised 2005). Available at: http://www.who.int/vaccine_research/documents/stateoftheart/en/index.html (accessed 29/04/06)
2. WHO. New vaccines against infectious diseases: research and development status (April 2005, updated February 2006). Available at: http://www.who.int/vaccine_research/documents/en/Status_Table.pdf (accessed 29/04/06)

Adverse Effects

Injection of a vaccine may be followed by a local reaction, possibly with inflammation and lymphangitis. An induration or sterile abscess may develop at the injection site. Fever, headache, and malaise may start a few hours after injection and last for 1 or 2 days. Hypersensitivity reactions may occur and anaphylaxis has been reported rarely.

Further details, if appropriate, of adverse effects of vaccines may be found in the respective individual monographs.

Anaphylaxis. In a retrospective study[1] in the USA conducted to quantify the risk of anaphylaxis after vaccination of children and adolescents, only 5 cases potentially associated with vaccines were identified from more than 7.5 million doses given. Vaccines implicated were generally given in combination and included the following components: diphtheria and tetanus; diphtheria, tetanus, and pertussis; hepatitis B; Haemophilus influenzae; measles, mumps, and rubella; and oral poliomyelitis. One case followed measles, mumps, and rubella vaccine given alone. It was concluded that vaccine-associated anaphylaxis is a rare event.

Recommendations[2] have been issued in the USA for the evaluation and management of patients with suspected allergy to vaccines.

1. Bohlke K, *et al.* Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; **112:** 815–20.
2. Kelso JM, *et al.* Joint Task Force on Practice Parameters for Allergy & Immunology. Adverse reactions to vaccines. *Ann Allergy Asthma Immunol* 2009; **103** (suppl 2): S1–S14.

Long-term effects. The introduction of routine childhood vaccination has been accompanied by concerns over the safety and possible long term sequelae of some commonly used vaccines. Difficulties have arisen in distinguishing temporal and causal associations and in some cases the perceived dangers of vaccination have impeded uptake. Among the disorders that have been temporally (but generally not causally) associated with childhood vaccination are neurological disorders, sudden infant death syndrome, type 1 diabetes mellitus, and demyelinating disorders. Information on adverse effects associated with specific vaccines can be found under diphtheria, tetanus, and pertussis vaccines (p. 2384.1), hepatitis B vaccines (p. 2390.3), influenza vaccines (p. 2394.3), measles, mumps, and rubella vaccines (p. 2400.2), and pertussis vaccines (p. 2409.1).

Additives or excipients have sometimes been alleged to be the cause of adverse reactions—see below for further details.

References.

1. Jefferson T. Vaccination and its adverse effects: real or perceived. *BMJ* 1998; **317:** 159–60.
2. Ball LK, *et al.* Risky business: challenges in vaccine risk communication. *Pediatrics* 1998; **101:** 453–8.
3. Hiltunen M, *et al.* Immunisation and type 1 diabetes mellitus: is there a link? *Drug Safety* 1999; **20:** 207–12.
4. Institute for Vaccine Safety Diabetes Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety workshop. *Pediatr Infect Dis J* 1999; **18:** 217–22.
5. Stratton K, *et al. Immunization safety review: multiple immunizations and immune dysfunction.* Washington DC: National Academy Press, 2002. Also available at: http://www.nap.edu/catalog.php?record_id=10306 (accessed 14/07/08)
6. Offitt PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003; **111:** 653–9.
7. Wraith DC, *et al.* Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003; **362:** 1659–66.
8. Stratton K, *et al. Immunization safety review: vaccinations and sudden unexpected death in infancy.* Washington DC: National Academy Press, 2003. Also available at: http://www.nap.edu/catalog.php?record_id=10649 (accessed 14/07/08)
9. CDC. Surveillance for safety after immunization: vaccine adverse event reporting system (VAERS) — United States, 1991–2001. *MMWR* 2003; **52** (SS-1): 1–24. Correction. *ibid.;* 113.
10. Hviid A, *et al.* Childhood vaccination and type 1 diabetes. *N Engl J Med* 2004; **350:** 1398–1404.
11. Koppen S, *et al.* No epidemiological evidence for infant vaccination to cause allergic disease. *Vaccine* 2004; **22:** 3375–85.
12. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine* 2005; **23:** 3876–86.

Effects of adjuvants. *Aluminium hydroxide* has been used frequently as an adsorbent in vaccines. A review[1] found significantly more erythema and induration with aluminium-containing vaccines than with plain ones. There was, however, no evidence of serious or long-lasting adverse effects that could be attributed to aluminium salts.

Thiomersal has been used as a preservative but because of alleged adverse effects is no longer used as widely as it once was (see Vaccines, under Thiomersal, p. 1772.2 for further details). However, the comment has been made that in developing countries far more benefit will be seen from protecting children with current, inexpensive, domestically-manufactured thiomersal-containing vaccines, than by investing in thiomersal-free alternatives.[2]

1. Jefferson T, *et al.* Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *Lancet Infect Dis* 2004;**4:** 84–90.
2. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; **28:** 89–101.

Effects on the nervous system. *GUILLAIN-BARRÉ SYNDROME.* Guillain-Barré syndrome (see under Musculoskeletal and Nerve Disorders, p. 2406.1) has occasionally been reported after vaccination, although causal relationships have been difficult to evaluate.[1] Such reports have been made after diphtheria and tetanus vaccines (p. 2383.2), haemophilus influenzae vaccines (p. 2387.3), hepatitis A vaccines (p. 2389.1), hepatitis B vaccines (p. 2391.1), a swine influenza vaccine (p. 2395.1), measles, mumps, and rubella vaccines (p. 2401.1), meningococcal vaccines (p. 2402.2), oral poliomyelitis vaccines (p. 2411.3), and rabies vaccines (p. 2414.3); the evidence is strongest for the association with swine influenza vaccine.

1. Haber P, *et al.* Vaccines and Guillain-Barré syndrome. *Drug Safety* 2009; **32:** 309–23.

Precautions

Most persons can safely receive the majority of vaccines. In a few individuals vaccination is contra-indicated or should be deferred.

All vaccines are contra-indicated in those who have had a previous confirmed anaphylactic reaction to a previous dose of a vaccine containing the same antigens or a confirmed anaphylactic reaction to another component contained in the relevant vaccine (for example, neomycin, polymyxin B, or streptomycin which may be present in trace amounts).

Some vaccines are prepared in egg cultures and are contra-indicated in persons with a confirmed anaphylactic reaction to egg.

Live vaccines are contra-indicated in immunosuppressed patients in these situations:

- severe primary immunodeficiency
- malignant disease being treated with either chemotherapy or radiotherapy and for at least 6 months after stopping such treatment
- solid organ transplant receiving immunosuppressive therapy
- bone marrow transplant during, and for at least 12 months after stopping, immunosuppressive therapy (or longer if graft-versus-host disease develops)
- all patients receiving high-dose systemic corticosteroids until at least 3 months after stopping treatment; this includes children receiving prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg for at least 1 week or 1 mg/kg for 1 month and adults receiving a daily dose of 40 mg for more than 1 week.
- HIV positive patients with immunosuppression

Vaccination may be delayed in persons who are acutely unwell and in those with evolving neurological conditions (until stabilised). In pregnancy, vaccination should be delayed until after delivery; termination of pregnancy is not recommended if a vaccine is inadvertently given during pregnancy.

If any alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination otherwise inactivation of live vaccines may occur.

Immunocompromised patients. For a discussion of the use of vaccines in HIV-infected and otherwise immunocompromised patients, see under Uses, p. 2374.3.

Premature infants. In the UK, the Royal College of Paediatrics and Child Health[1] and the Department of Health[2] consider that all routine childhood immunisations should be scheduled on the basis of the child's actual date of birth with no allowance being made for prematurity. In the USA, the American Academy of Pediatrics offers similar advice.[3] It is acknowledged that more studies are required into immunisation in prematurity, particularly in infants receiving corticosteroids.[1] There is some evidence that a minority of premature infants may fail to respond adequately to Haemophilus influenzae vaccines and to hepatitis B immunisation.[1] It has also been suggested that there may be an increased risk of apnoea and bradycardia in premature infants vaccinated with polyvalent vaccines,[4,5] and some licensed product information for pentavalent or hexavalent vaccines has been amended accordingly.

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3. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2013.
4. Schulzke S, *et al.* Apnoea and bradycardia in preterm infants following immunisation with pentavalent or hexavalent vaccines. *Eur J Pediatr* 2005; **164:** 432–5.
5. Cooper PA, *et al.* Apnea and its possible relationship to immunization in ex-premature infants. *Vaccine* 2008; **26:** 3410–3.

Interactions

The ability of vaccines to induce an immune response can be influenced by the recent use of other vaccines or immunoglobulins. Live vaccines should either be given simultaneously (but at different sites) or an interval of at least 3 weeks allowed between them. Live vaccines should normally be given at least 3 weeks before or at least 3 months after the use of immunoglobulin. However, travellers should receive appropriate vaccines regardless of these limitations if time is short.

Patients receiving immunosuppressant therapy, including antineoplastics or therapeutic doses of corticosteroids, may also display a reduced response to vaccines and deferral of immunisation is advised, see Precautions, above. For further details on immunisation in immunocompromised patients, see under Uses and Administration, p. 2374.3.

Any agent that is active against the bacterial or viral strain present in the vaccine may interfere with development of a protective immune response but treatment with antibacterials is not a contra-indication to immunisation.

Adenovirus Vaccines

Profile

Adenovirus type 4 and type 7 vaccine is a live, oral vaccine used to prevent febrile acute respiratory disease caused by adenovirus types 4 and 7. It is approved in the US for use in military personnel from 17 to 50 years of age. A single vaccine dose is given orally as 2 tablets; one tablet of adenovirus type 4 and one of adenovirus type 7. The tablets should be swallowed whole to avoid releasing the virus in the upper respiratory tract. The virus can be shed in the stool for up to 28 days after vaccination; proper personal hygiene should be followed during this period to reduce the risk of viral transmission.

The vaccine should not be given to pregnant women and pregnancy should be avoided for 6 weeks after receiving the vaccine. Vaccination should also be postponed in those with vomiting and/or diarrhoea.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Ke Rui (安柯瑞).

AIDS Vaccines

HIV Vaccines; Vacunas contra VIH; Vacunas del SIDA.

Profile

Many prototype vaccines against AIDS have been or are being developed but the results of clinical studies have generally been disappointing.

Despite the passage of more than two decades since the discovery of HIV, no effective vaccine has been found to either ameliorate the disease or to prevent infection.[1-14] Globally tens of millions of people are infected with HIV, with the overwhelming majority of infections occurring in developing countries that in many cases lack the resources and infrastructure to acquire and deliver costly antiretroviral therapy. A safe, effective, easily administered, and inexpensive AIDS vaccine is therefore desperately required.

There are many reasons why no such vaccine has so far been developed. Firstly, natural infection with HIV does not result in protective immunity; rather, it establishes persistent and lifelong infection and viral clearance and development of resistance to re-infection never occur. This means that there is no model of protective immunity to emulate through vaccination. Various aspects of the biology of the virus have also presented thus far insurmountable problems in vaccine development. The complex structure of the HIV envelope glycoprotein is inherently resistant to antibody attack and the virus has the capacity to evolve quickly in order to evade any neutralising antibody responses mounted by the host. In addition, the selective infection, progressive destruction, and impaired regeneration of CD4+ T helper cells, and the enormous genetic diversity of HIV with its continually evolving geographical distribution and prevalence have proven problematical. Finally, the ability of HIV to evade immune surveillance enables it to establish a state of proviral latency in long-lived CD4+ cells thus providing a persistent, yet immunologically invisible, reservoir of virus infection.

Despite these problems, research has continued[1-9,15] into developing AIDS vaccines from two distinct perspectives, namely prophylactic vaccines aimed at preventing primary infection and therapeutic vaccines aimed at reducing the rate of disease progression in HIV-infected individuals. Subunit recombinant viral envelope proteins, notably gp120, have been investigated as both prophylactic and therapeutic vaccines, but phase III clinical studies have proved disappointing.[9] In one, involving a bivalent formulation of recombinant gp120 proteins from HIV subtype B, predominant in North America and Europe (AIDSVAX B/B) given to 5009 subjects most of whom were homosexual men, no effect on the rate of HIV infection was found. In a second study in Thailand using AIDSVAX B/E, a related vaccine consisting of recombinant gp120 proteins from HIV subtypes B and E predominant in South-East Asia, no protection against HIV infection was found among 2546 HIV-negative injection drug users.[9] Despite these disappointing results, AIDSVAX B/E was evaluated in a further large study in a Thai population at community risk for HIV infection as the booster component of a combination immunisation prime-boost regimen that includes an attenuated canarypox vector prime (ALVAC vCP1521).[14] This regimen showed only a modest benefit with a trend toward reducing the risk of HIV infection but did not affect the early viral load or CD4+ T lymphocyte count in those who eventually became infected with HIV.

While typical HIV neutralising antibody responses are only transiently effective within a given individual and generally not cross-reactive with other isolates, several monoclonal antibodies have been derived from B cells or molecular clones of immunoglobulin genes obtained from HIV-infected persons during the course of natural infection, and have significant neutralisation activity against a wider array of HIV isolates. These monoclonal antibodies act by penetrating gp120 and other viral envelope proteins, thereby preventing CD4 attachment to the virus. Since they have activity against a broader range of isolates and may be produced in relatively large quantities by recombinant technology, passive delivery of a cocktail of monoclonal antibodies is being studied in *animal* models as a means of prophylaxis.[9] The cost of this approach may, however, potentially prohibit its future use on a wide scale in humans.

Efforts at understanding why it is so difficult to configure immunogens from the HIV envelope that more effectively elicit neutralising antibody responses continue but, in addition, attention has turned to what is termed the cytotoxic T lymphocyte (CTL) hypothesis.[9] This proposes that vaccination of uninfected individuals will not prevent infection but will induce an anti-HIV CTL (CD8+) response. If subsequently infected with HIV these immunised persons would be better able to control viral replication and progress to AIDS much more slowly or perhaps not at all and potentially decrease viral transmission. The validity of this hypothesis is at present uncertain but it has been supported by the observation of low level, yet detectable, HIV-specific CD8+ T cell responses in certain cohorts of highly exposed but uninfected individuals.

Additionally, new vaccine strategies are becoming available which it is thought will probably be able to elicit HIV-specific CTL responses of sufficient magnitude to allow direct testing of the concept in humans. Numerous *animal* studies are underway to assess the safety and immunogenicity of various replication-defective recombinant viral vectors (modified vaccinia Ankara strain, vesicular stomatitis virus, Venezuelan equine encephalitis virus, adeno-associated virus, and adenovirus) and also bacterial, yeast, and plasmid DNA vectors, all of which are designed to elicit antiviral CD8+ T cell responses.[9] However, initial analyses from a large study of an adenovirus-based vaccine designed to boost T cell responses (the STEP trial) provoked alarm since results suggested that it did not decrease susceptibility to HIV infection and might have increased it in some cases.[16] Final analysis of this study found that the vaccine did not prevent HIV-1 infection or reduce early viral levels.[17]

Recombinant plasmid DNA immunogens are also under investigation as potential AIDS vaccines because of their desirable safety profile and ability to express defined and discrete inserted HIV antigens. They are either used singly or as a priming immunogen in prime-boost regimens using different vaccine vectors for sequential immunisation. Initial results in preclinical *animal* studies were encouraging, but results have been disappointing in subsequent phase I human studies.[8]

Within the field of AIDS vaccine research, the decision to advance candidate vaccines from phase I or II to phase III efficacy studies is somewhat complex. At present there are no consistent criteria in place to provide guidance on such decisions and there is a need for a coordinated, objective, and rigorous process for prioritisation in order to facilitate vaccine development. To the same end, alternative designs for phase III studies are being considered, including the use of end-points such as reduction of viral load or preservation of CD4+ T cell counts for assessing vaccine efficacy rather than prevention of infection as the single primary endpoint. These and other measures may facilitate licensure of vaccines which currently would not occur.

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Anthrax Vaccines

Vacunas del carbunco.
ATC — J07AC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates)); Vaccinum Anthracis Adsorbatum ab Colato Culturarum ad Usum Humanum. A preparation of *Bacillus anthracis* antigens precipitated by aluminium potassium sulfate. The antigens are prepared from a sterile culture filtrate produced by a non-encapsulated strain, either avirulent or attenuated, of *B. anthracis*. The main virulence components of *B. anthracis* are the polyglutamic acid capsule and 2 binary anthrax toxins, namely lethal toxin and oedema toxin, formed from the respective combination of protective antigen with either lethal factor or oedema factor. In addition, the vaccine is likely to contain many other *B. anthracis* antigens, including membrane proteins, secreted proteins, cytoplasmic proteins, peptidoglycans, nucleic acids, and carbohydrates. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

An anthrax vaccine that is an alum precipitate of the antigen found in the sterile filtrate of suitable cultures of the Sterne strain of *Bacillus anthracis* is available in the UK for human use. It is used for active immunisation against anthrax (p. 173.2) and is recommended as *pre-exposure prophylaxis* for persons working with potentially infected animals or animal products. It is given in 4 doses, each of 0.5 mL by intramuscular injection. The first 3 doses are separated by intervals of 3 weeks and the fourth dose follows after an interval of 6 months; reinforcing doses of 0.5 mL are required each year. In the USA, an anthrax vaccine was originally licensed for subcutaneous use as a series of 6 doses given at 0, 2, and 4 weeks and 6, 12, and 18 months followed by yearly booster doses. In December 2008, the FDA approved a series of 5 intramuscular doses, each of 0.5 mL, given at 0 and 4 weeks and 6, 12, and 18 months; reinforcing doses of 0.5 mL are required at yearly intervals after the 18-month dose. Those with medical contraindications to intramuscular injections may be given the vaccine by the original 6-dose subcutaneous regimen. For *post-exposure prophylaxis* the FDA recommends that 3 doses of the vaccine, each of 0.5 mL, may be given subcutaneously at 0, 2, and 4 weeks in addition to recommended antibacterial therapy.

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Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Biothrax.

Pharmacopoeial Preparations
Ph. Eur.: Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates);
USP 36: Anthrax Vaccine Adsorbed.

Anti-D Immunoglobulins

Immunoglobulinas anti-D; Inmunoglobulinas anti-D; Inmunoglobulinas anti Rh.

ATC — J06BB01.

UNII — 48W7181FLP (human Rh_o (D) immune globulin).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Anti-D Immunoglobulin; Immunoglobulinum Humanum Anti-D; Anti-D (Rh_o) Immunoglobulin BP 2014). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is intended for intramuscular administration. It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies, such as anti-C, anti-E, anti-A, and anti-B. Normal immunoglobulin may be added. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored in an airtight container.

Ph. Eur. 8: (Human Anti-D Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Anti-D ad Usum Intravenosum; Anti-D Immunoglobulin for Intravenous Use BP 2014). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies. Human normal immunoglobulin for intravenous administration may be added. Storage requirements are similar to those for Human Anti-D Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25 degrees.

USP 36: (Rh_o (D) Immune Globulin). A sterile solution of globulins derived from human plasma containing antibody to the erythrocyte factor Rh_o (D). It contains 10 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Anti-D immunoglobulin is used to prevent a rhesus-negative mother actively forming antibodies to fetal rhesus-positive red blood cells that may pass into the maternal circulation during childbirth, abortion, or certain other sensitising events. In subsequent rhesus-positive pregnancies these antibodies could produce haemolytic disease of the newborn (erythroblastosis foetalis). The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. Anti-D immunoglobulin is also used in the management of some blood disorders, mainly immune thrombocytopenia.

Anti-D immunoglobulin products are available either for intramuscular use only or for intramuscular or intravenous use. Doses differ for these products and the manufacturer's recommendation should be followed for commercial products.

In the UK, recommendations produced by expert groups relate to the use of a non-proprietary product produced by the National Blood Transfusion Service. They recommend that **postnatal prophylaxis** with anti-D immunoglobulin should always be given to rhesus-negative mothers with no anti-D antibodies in their serum and who have just delivered rhesus-positive infants. It should be given as soon as possible after delivery but may give some protection even if treatment is delayed beyond 72 hours. A dose of 500 units (100 micrograms) by intramuscular injection will clear up to 4 mL of fetal red cells. An additional dose may be required depending on the amount of transplacental bleeding; for bleeds exceeding 4 mL an additional 125 units for each mL of red cells will be required.

For routine **antenatal prophylaxis**, two intramuscular doses of either 500 units or 1000 to 1650 units of anti-D immunoglobulin should be given at 28 and 34 weeks' gestation; alternatively a single dose of 1500 units may be given between 28 and 30 weeks gestation. Doses given depend on the preparation used. Postnatal prophylaxis is still necessary.

There is also a risk of sensitisation during pregnancy from spontaneous, induced, or threatened abortion, amniocentesis, or external version. Any rhesus-negative woman at **risk of transplacental haemorrhage** during pregnancy and not known to be sensitised should be given an intramuscular dose of 250 units at up to 20 weeks' gestation and 500 units of anti-D immunoglobulin after 20 weeks' gestation.

Anti-D immunoglobulin is also given to rhesus-negative women of child-bearing potential after the inadvertent **transfusion of Rh-incompatible blood**, or after receiving blood components containing rhesus-positive red cells or organ donations from rhesus-positive donors. The dose is based on the amount of red blood cells transfused; an intramuscular dose up to 125 units/mL of transfused cells may be used.

For **immune thrombocytopenia** (idiopathic thrombocytopenic purpura), a usual initial dose of 250 units/kg (50 micrograms/kg) of a licensed anti-D immunoglobulin product is given by intravenous injection; it may be given in two divided doses on separate days if desired. Maintenance doses usually range between 125 to 300 units/kg (25 to 60 micrograms/kg) depending on the clinical response. A reduced initial dose of 125 to 200 units/kg (25 to 40 micrograms/kg) is recommended in patients with pre-existing anaemia (haemoglobin below 10 g/dL).

Haemolytic disease of the newborn. Rhesus (Rh) incompatibility, in particular Rh(D) incompatibility, is a major cause of potentially severe haemolytic disease of the newborn,[1] although other blood group antibodies may also cause the disease. The use of anti-D immunoglobulin to suppress the production of anti-D antibodies in a Rh(D)-negative mother in response to leakage of red blood cells across the placenta from a Rh(D)-positive fetus has produced a major reduction in the incidence of this disorder.

Prophylaxis. Postnatal prophylaxis of Rh(D)-negative mothers after the birth of a Rh(D)-positive infant is well established. In 1971, WHO[2] suggested a standard intramuscular dose of 200 to 300 micrograms but stated that a 100-microgram dose was likely to have a success rate only slightly inferior to that of a 200-microgram dose, thus allowing optimum use to be made of a limited resource. Clinical experience in the UK has confirmed the efficacy of the 100-microgram (500 units) intramuscular dose and this is the amount officially recommended in the UK in such situations.[3,4] Doses do, however, vary considerably in other countries.

Despite the success of anti-D immunoglobulin prophylaxis, sensitisations have continued to occur. There are several possible reasons for this, the main one being immunisation during pregnancy where there has been no overt sensitising event. Postpartum doses may be omitted due to oversight or loss to follow-up. Assessment of the volume of any transplacental haemorrhage is essential to avoid inadequate dosing. Significantly large feto-maternal haemorrhage is likely to occur after traumatic deliveries including caesarean section, manual removal of the placenta, still-birth or intra-uterine death, abdominal trauma during the third trimester, delivery of twins, or unexplained hydrops fetalis.

The efficacy of postpartum prophylaxis is not in question but opinions differ on the need for prophylaxis during pregnancy. It is generally agreed that prophylaxis is necessary in all non-sensitised Rh(D)-negative women after therapeutic terminations at any stage of pregnancy, including medical termination utilising mifepristone, after ectopic pregnancy, spontaneous complete or incomplete miscarriage after 12 weeks' gestation, or threatened miscarriage after 12 weeks' gestation as evidenced by abnormal bleeding or abdominal pain. Recommendations have been made by the British Committee for Standards in Haematology for the management of these sensitising events.[4]

Prophylaxis should also be given to all non-sensitised Rh (D)-negative women after the following sensitising events during pregnancy: invasive prenatal diagnosis including amniocentesis, chorion villus sampling, or fetal blood sampling; other intra-uterine procedures such as insertion of shunts or embryo reduction; antepartum haemorrhage; external cephalic version of the fetus; closed abdominal injury; or intra-uterine death.[3,4] A dose of 50 micrograms (250 units) is recommended for prophylaxis after these events up to 20 weeks of pregnancy, and at least 100 micrograms (500 units) thereafter.

In the UK routine antenatal prophylaxis at 28 and 34 weeks' gestation is recommended for all Rh(D)-negative women[3-5] and should be given irrespective of whether anti-D prophylaxis had been given for other sensitising events during the same pregnancy or previous pregnancies.[4]

Treatment. In mild cases, the resultant hyperbilirubinaemia can be managed with phototherapy. In severe cases, exchange transfusions may be necessary and intra-uterine transfusions may be considered in pregnancies of less than about 34 weeks' gestation; beyond this, premature delivery is often preferable.[6] Some clinicians have reported treatment failures with intra-uterine transfusions but have found intravenous normal immunoglobulin 400 mg/kg daily for 5 days every 2 to 3 weeks to the mother to be effective. There are several case reports[7,8] of beneficial responses using similar doses, but no benefit was seen in 4 patients receiving 1000 mg/kg once a week.[9] This dose, however, appeared to reduce the severity of the disease in a patient with Kell sensitisation.[9] Reductions in bilirubin concentrations have been reported with intravenous normal immunoglobulin 500 mg/kg as a single dose in newborn infants,[10] and a systematic review[11] found that such treatment reduced the number of infants requiring exchange transfusion and the duration of hospital stay and phototherapy needed. Reports in small numbers of infants[12-16] suggest that epoetins may be of value in controlling anaemia which develops 2 to 8 weeks after birth.

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Immune thrombocytopenia. Normal immunoglobulin is used for immune thrombocytopenia (p. 1606.1), and anti-D immunoglobulin has been found to have similar properties. The potential role of anti-D immunoglobulin in the treatment of immune thrombocytopenia has been discussed in several reviews.[1-3] In general, despite many studies showing the clinical efficacy and low toxicity of intravenous anti-D immunoglobulin, its precise role has not been defined for several reasons. Firstly, the optimal dose has not been established: doses used have ranged from 12.5 to 25 micrograms/kg daily, given for at least 2 days, in early studies to later more promising single doses of 50 to 75 micrograms/kg. Secondly, no study has shown anti-D immunoglobulin to be as effective as corticosteroid therapy for initial treatment. Furthermore, despite suggestions that anti-D immunoglobulin may be safer and easier to give than normal immunoglobulin, good comparative data are scanty. Clinical studies have, however, shown the safety and efficacy of intravenous anti-D immunoglobulin in Rh(D)-positive, non-splenectomised patients with immune thrombocytopenia.[1] A prospective, randomised clinical study[4] in Rh(D)-positive children with immune thrombocytopenia found that a single intravenous dose of 75 micrograms/kg raised the platelet count more rapidly than a single intravenous dose of 50 micrograms/kg, and was as effective as a single intravenous dose of 800 mg/kg of normal immunoglobulin.

1. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 1998; **35** (suppl 1): 52–7.
2. Sandler SG. Treating immune thrombocytopenic purpura and preventing Rh alloimmunization using intravenous rho (D) immune globulin. *Transfus Med Rev* 2001; **15:** 67–76.
3. Sandler SG. Intravenous Rh immune globulin for treating immune thrombocytopenic purpura. *Curr Opin Hematol* 2001; **8:** 417–20. Correction. *ibid.* 2002; **9:** 179.
4. Tarantino MD, *et al.* Single dose of anti-D immune globulin at 75 μ g/kg is as effective as intravenous immune globulin at rapidly raising the platelet count in newly diagnosed immune thrombocytopenic purpura in children. *J Pediatr* 2006; **148:** 489–94.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

In patients given anti-D immunoglobulin for immune thrombocytopenia (ITP) there have been rare reports of back pain, shaking chills, fever, and discoloured urine; such signs and symptoms may be associated with intravascular haemolysis. Serious and sometimes fatal complications of intravascular haemolysis including anaemia, acute renal insufficiency, or disseminated intravascular coagulation have been rarely reported. Most reported cases of

haemolysis occurred within 4 hours of the dose; fatal outcomes and complications occurred most frequently in patients more than 65 years of age with comorbid conditions. Patients should be closely monitored for at least 8 hours after a dose of anti-D immunoglobulin.

For the treatment of ITP, anti-D immunoglobulin is contra-indicated in rhesus-negative or splenectomised patients. Patients with ITP who need a blood transfusion should be given rhesus-negative red blood cells so as not to exacerbate ongoing haemolysis. Those with low initial haemoglobin concentrations (less than 10 g/dL) should be given a reduced dosage of the immunoglobulin to minimise the risk of severe anaemia.

When given for prophylaxis of rhesus sensitisation, anti-D immunoglobulin should not be used in rhesus-positive individuals.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anti-D immunoglobulin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Igantid; Immunorho; Kam Rho-D; Partoben; Partogamma; Rhesogamma; Rhophylac; ***Austral.***: WinRho; ***Austria***: Partobulin; Rhesogam†; Rhophylac; ***Belg.***: RhoGAM; WinRho†; ***Braz.***: Matergam†; Partogama; Rhesonativ; Rhophylac; ***Canad.***: HyperRho S/D†; WinRho; ***Chile***: Igamad; Immunorho; Rhesogamma P†; ***Cz.***: Igamad; Partobulin; Rhesonativ; Rhophylac; ***Denm.***: Rhesonativ; Rhophylac; ***Fin.***: Rhesonativ; Rhophylac; ***Fr.***: Rhophylac; ***Ger.***: Partobulin†; Rhesonativ; Rhophylac; ***Gr.***: Rhesogamma P; Rhesuman; Rhophylac; WinRho; ***Hong Kong***: HyperRho-D; Partobulin; RhoGAM; WinRho; ***Hung.***: Rhesonativ; RhoGAM†; Rhophylac; ***India***: Anti-D; Matergam-P; Micrhogam; ***Indon.***: HyperRho S/D; ***Irl.***: Rhesonativ; Rhophylac; ***Israel***: BayRho-D†; KamRho-D; Rhophylac; WinRho; ***Ital.***: Igamad; Immunorho; Partobulin; Rhophylac; WinRho†; ***Mex.***: Octaglob D; Rhesogamma P; Rhophylac; ***Neth.***: RheDQuin; Rhesonativ; Rhophylac; WinRho†; ***Norw.***: Rhesonativ; Rhophylac; ***NZ***: RhoGAM; WinRho; ***Philipp.***: WinRho; ***Pol.***: Gamma Anty D; Partobulin; Rhesonativ; Rhophylac; ***Port.***: Rhesonativ; Rhophylac; WinRho†; ***Rus.***: HyperRho S/D (ГиперРОУ С/Д); Immunoro (Иммуноро); KamRHO (КамРОУ); Partobulin (Партобулин); Rhesonativ (Резонатив); ***S.Afr.***: Rhesugam; ***Singapore***: WinRho†; ***Spain***: Gamma Anti D†; Igamad; Rhesogamma†; Rhophylac; ***Swed.***: Rhesonativ; Rhophylac; ***Switz.***: Rhophylac; ***Thai.***: Igamad; Rhesonativ; ***Turk.***: BayRho-D; HyperRho-D; Immunorho; Partobulin; Rhesogamma P; Rhesuman; RhoGAM; Rhophylac; WinRho; ***UK***: D-Gam; Partobulin; Rhophylac; WinRho†; ***USA***: HyperRho S/D; MICRhoGAM; RhoGAM; Rhophylac; WinRho.

Pharmacopoeial Preparations

Ph. Eur.: Human Anti-D Immunoglobulin for Intravenous Administration; Human Anti-D Immunoglobulin;
USP 36: Rh_o (D) Immune Globulin.

Argentine Haemorrhagic Fever Vaccines

Junin Haemorrhagic Fever Vaccines; Vacunas de la fiebre hemorrágica argentina.

Profile

A live attenuated vaccine has been investigated for active immunisation against Argentine haemorrhagic fever.

References.

1. Maiztegui JI, *et al.* Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. *J Infect Dis* 1998; **177:** 277–83.
2. Feuillade MR, Enría DA. Análisis de la utilidad de la vacuna Candid 1 en la prevención de la fiebre hemorrágica argentina en niños. *Rev Panam Salud Publica* 2005; **18:** 100–106.

BCG Vaccines

Bacillus Calmette-Guérin Vaccines; Vacunas BCG; Вакцины БЦЖ.

ATC — J07AN01; L03AX03.

UNII — 0BQ62LY3KF (bacillus calmette-guerin live (attenuated) antigen); 5H5854UBMZ (bacillus calmette-guerin live antigen, B).

Pharmacopoeias. Many pharmacopoeias, including *Br.*, *Eur.* (see p. vii), and *US*, have monographs.

Ph. Eur. 8: (BCG Vaccine, Freeze-dried; Vaccinum Tuberculosis (BCG) Cryodesiccatum; Bacillus Calmette-Guérin Vaccine BP 2014). A freeze-dried preparation containing live bacteria obtained from a strain derived from the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity to protect against tuberculosis has been established. It may contain a stabiliser. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from direct sunlight.

The BP 2014 states that BCG may be used on the label.

The BP 2014 gives BCG Vaccine as an approved synonym.

BP 2014: (Percutaneous Bacillus Calmette-Guérin Vaccine). A suspension of living cells of an authentic strain of the bacillus of Calmette and Guérin with a higher viable bacterial count than Bacillus Calmette-Guérin Vaccine. It is supplied as a dried vaccine and is reconstituted immediately before use by the addition of a suitable sterile liquid. The dried vaccine should be stored at a temperature below -20 degrees and be protected from light.

The BP 2014 states that Tub/Vac/BCG (Perc) may be used on the label.

The BP 2014 gives Percut. BCG Vaccine as an approved synonym.

USP 36: (BCG Vaccine). A dried living culture of the bacillus Calmette-Guérin strain of *Mycobacterium tuberculosis* var. *bovis*; it is grown from a strain that has been maintained to preserve its capacity for conferring immunity. It contains an amount of viable bacteria such that inoculation, in the recommended dose, of tuberculin-negative persons results in an acceptable tuberculin conversion rate. It contains a suitable stabiliser and no antimicrobial agent. The dried vaccine should be stored in hermetically sealed containers at 2 degrees to 8 degrees. The reconstituted vaccine should be used immediately after preparation and any portion not used within 2 hours should be discarded.

Ph. Eur. 8: (BCG for Immunotherapy; BCG ad Immunocurationem). A freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity for treatment has been established. It may contain a stabiliser. The product should be stored at 2 degrees to 8 degrees and be protected from direct sunlight.

USP 36: (BCG Live). A freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (*Mycobacterium bovis*, var. BCG) for intravesical use only. It is reconstituted and further diluted aseptically with a sterile diluent before use. A reconstituted dose contains 1.0–19.2 X 10^8 colony-forming units (cfu). It does not contain a preservative.

BCG Live is sensitive to light and must be stored in a glass container, protected from direct light, and at 2 degrees to 8 degrees.

Uses and Administration

BCG vaccines are used for active immunisation against tuberculosis. A form suitable for immunotherapy is also used locally in the treatment and prophylaxis of carcinoma *in-situ* of the bladder, and the prophylaxis of recurrent early stage bladder papillomas after resection.

For vaccination against **tuberculosis** different strategies may be adopted, depending on the prevalence of the disease in local populations, the prevalence of HIV co-infection, the potential for infant exposure to these diseases, and the existence of infrastructure to diagnose infection and follow-up vaccinated persons. WHO considers that BCG vaccination of adults is not normally recommended, although it may be considered for tuberculin-negative subjects in unavoidable and close contact with drug-resistant tuberculosis. In countries with a high prevalence of tuberculosis, infant immunisation with a single dose of BCG as soon as possible after birth is ideally to be recommended. However, these populations tend to have a high prevalence of HIV infection as well, and BCG vaccination is contra-indicated in HIV-infected subjects. Nonetheless, WHO considers that children without HIV infection will particularly benefit from vaccination in these circumstances, and recommends that immunisation should be carried out in:

- infants born to women of unknown HIV status
- infants without obvious signs of HIV infection born to women known to be HIV-infected
- infants known to be HIV-negative as a result of virological testing

It considers that immunisation should be avoided in infants known to be infected with HIV, or whose HIV status is unknown but who are born to HIV-infected mothers and have signs or symptoms suggestive of HIV infection.

In contrast, a country such as the UK has a relatively low prevalence of tuberculosis, and routine immunisation is no longer carried out. Instead, immunisation is targeted at groups considered to be at increased risk:

- all neonates and infants (0 to 12 months) living in areas where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- all neonates and infants with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated children aged 1 to 5 years with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population; such children aged from 6 to 16 years should also be vaccinated if they have been shown to be tuberculin-negative
- previously unvaccinated, tuberculin-negative contacts of persons suffering from active respiratory tuberculosis
- previously unvaccinated, tuberculin-negative immigrants under 16 years of age who were born in, or lived in for at least 3 months, a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated, tuberculin-negative persons under 16 years of age intending to stay or work with local people for more than 3 months in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population.
- vaccination should be *withheld* in all those known or suspected to be HIV-infected, regardless of clinical status. Where vaccination is indicated, as in infants born to HIV-positive mothers, it should only be given after two appropriately timed negative postnatal tests for HIV infection.

Vaccination is also recommended in the UK for previously unvaccinated, tuberculin-negative persons under 35 years of age in the following groups:

- healthcare workers or laboratory staff at high risk of infection
- veterinary and other staff who handle animals known to be susceptible to tuberculosis
- staff in any institution where the incidence of tuberculosis is high

In the USA, CDC advises still more selective use, with BCG vaccination restricted essentially to tuberculin-negative children or health workers who are continually exposed to individuals with untreated or drug-resistant tuberculosis.

BCG vaccine is given intradermally (intracutaneously) at the insertion of the deltoid muscle in a dose of 0.1 mL; infants under 12 months of age are given 0.05 mL.

Contacts of patients with active pulmonary tuberculosis may require chemoprophylaxis (see under Tuberculosis, p. 210.2) despite previous vaccination. Neonates and children under 2 years of age should be given chemoprophylaxis and immunised, if appropriate, once the course is completed. An isoniazid-resistant form of the vaccine has been produced for use in patients who have received isoniazid, but its use is not recommended.

For use in immunotherapy of **bladder cancer** several regimens have been tried. A typical induction regimen consists of once-weekly intravesical instillation of a solution containing 1 to 16 X 10^8 colony forming units of BCG in about 50 mL of preservative-free saline 0.9%, for 6 consecutive weeks. Maintenance regimens vary widely from single doses or short courses (once a week for 3 weeks) at 3- to 6-monthly intervals, to instillation once a month; the period of suggested maintenance also varies from 6 months to 3 years. Some also favour a consolidation regimen of three further instillations, a week apart, carried out 6 weeks after completion of induction. Instillations should be retained in the bladder for 2 hours if possible, and then voided with the patient in a sitting position to minimise the risk of environmental contamination (see also Precautions, p. 2380.1).

References.

1. WHO. BCG vaccine: WHO position paper. *Wkly Epidem Rec* 2004; **79:** 27–38. Also available at: http://www.who.int/immunization/wer7904BCG_Jan04_position_paper.pdf (accessed 23/06/10)

Leprosy. BCG vaccination has been shown to protect recipients against leprosy[1,2] and is considered to be one of the factors responsible for the decrease in the incidence of leprosy. One meta-analysis[1] of studies using BCG vaccine to prevent leprosy found that the average protective effect was 26% for the clinical studies and 61% for the observational (cohort or case-controlled) studies. Protection was better for multibacillary forms rather than paucibacillary forms of leprosy. Age at the time of vaccination was not a predictor of vaccine efficacy, but in the observational studies the protective effect was found to decrease with age. Clinical studies indicated that an additional dose of BCG was more effective than a single dose. For further details concerning the use of BCG vaccines in both the immunoprophylaxis and immunotherapy of leprosy, see Leprosy Vaccines, p. 2397.2.

1. Setia MS, *et al.* The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis* 2006; **6:** 162–70.
2. Merle CSC, *et al.* BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines* 2010; **9:** 209–22.

Malignant neoplasms. Immunotherapy with BCG vaccines has been tried in various malignant disorders and is most successful when given locally. The possibility that

BCG vaccination might protect children against malignancies has been discussed.[1]

1. Grange JM, Stanford JL. BCG vaccination and cancer. *Tubercle* 1990; **71:** 61–4.

BLADDER. Immunotherapy with adjuvant intravesical BCG is used in the management of bladder cancers and is the treatment of choice for carcinoma *in situ* (p. 700.2), although debate about its exact role in non-muscle-invasive bladder cancer is ongoing.[1,2] It does not have a direct toxic effect on tumour cells, but produces a cascade of immune reactions that is reported to reduce tumour recurrence and disease progression. A systematic review[3] indicated that intravesical BCG after transurethral resection (TUR) reduced recurrence of Ta and T1 bladder cancers compared with TUR alone. Another systematic review[4] of intravesical therapy concluded that tumour recurrence was significantly reduced with BCG when compared with mitomycin C but only in patients at high risk of recurrence; there was no difference in terms of disease progression or survival. However, a meta-analysis[5] reported intravesical BCG to be better than mitomycin C in the prevention of tumour recurrences, particularly in those on BCG maintenance regime, irrespective of the risk of recurrence.

1. Ayres BE, *et al.* Is the role of intravesical bacillus Calmette-Guérin in non-muscle-invasive bladder cancer changing? *BJU Int* 2010; **105** (suppl 2): 8–13.
2. Gontero P, *et al.* The role of bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. *Eur Urol* 2010; **57:** 410–29.
3. Shelley M, *et al.* Intravesical bacillus Calmette-Guerin in Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 05/11/07).
4. Shelley M, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 05/11/07).
5. Böhle A, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol (Baltimore)* 2003; **169:** 90–5.

SKIN. Several studies have reported that BCG vaccine injected into intradermal metastases of melanoma (p. 714.3) can result in regression of the injected, and sometimes also the uninjected nodules. BCG therapy has been disappointing for visceral metastases. Many anecdotal reports and nonrandomised studies have shown benefit from BCG vaccine as adjuvant therapy, but these results have not been confirmed in large randomised, controlled studies.[1,2]

1. Ho VC, Sober AJ. Therapy for cutaneous melanoma: an update. *J Am Acad Dermatol* 1990; **22:** 159–76.
2. Agarwala SS, *et al.* Mature results of a phase III randomized trial of bacillus Calmette-Guerin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer stage I-III melanoma (E1673): a trial of the Eastern Oncology Group. *Cancer* 2004; **100:** 1692–8.

Tuberculosis. Studies from many parts of the world have evaluated the efficacy of BCG vaccine to protect against tuberculosis. Levels of protection have varied from 0 to over 80%.[1] Many explanations for such variability have been proposed: interaction with the immune response to other mycobacterial infections; antigenic, microbiological, or formulation differences between BCG vaccines; differences in the natural history of infection and disease; variations in host genetics or nutrition; or methodological differences between studies.[1,2] It has been noted that in general the efficacy of BCG vaccine in any region is proportional to its distance from the equator and this possibly reflects differences in exposure to environmental mycobacteria.[3] This could be the strongest influence on efficacy,[3] with the implication that BCG may be least effective in areas of the world where the risk of tuberculosis is greatest. BCG also appears to be more effective against systemic (miliary and meningitic tuberculosis) than against pulmonary tuberculosis. It is likely that BCG cannot produce complete protection against infection, and the development of new vaccines is ongoing.[4-6]

National policies of BCG vaccination vary widely. Some countries recommend routine vaccination; in others, such as the UK,[7] and USA[8] routine vaccination is no longer carried out and targeted immunisation aimed at infants and others at increased risk is performed (see Uses and Administration, p. 2378.2). Schedules throughout the world have varied from single intradermal vaccination at birth (as recommended by WHO),[9] to single vaccination at age 10 to 14, to repeated vaccination every few years (particularly in eastern Europe). The percutaneous route has been found to be as effective as the intradermal route.[10] These policy differences appear to be related as much to differences of opinion about the mechanism of action and efficacy of vaccines as to local differences in the epidemiology of tuberculosis.[1] WHO considers BCG vaccination to be an adjunct to case detection and treatment in the control of tuberculosis,[9,11] and recommends that neither tuberculin skin testing nor repeat vaccination should be used.

1. Fine PEM, Rodrigues LC. Modern vaccines: mycobacterial diseases. *Lancet* 1990; **335:** 1016–20.
2. Fine PEM. BCG vaccination against tuberculosis and leprosy. *Br Med Bull* 1988; **44:** 691–703.
3. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; **346:** 1339–45. Correction. *ibid.*; **347:** 340.
4. von Reyn CF, Vuola JM. New vaccines for the prevention of tuberculosis. *Clin Infect Dis* 2002; **35:** 465–74.
5. Orme IM. Tuberculosis vaccines: current progress. *Drugs* 2005; **65:** 2437–44.
6. Lambert PH, *et al.* New vaccines against tuberculosis. *Clin Chest Med* 2009; **30:** 811–26.
7. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
8. CDC. TB elimination: BCG vaccine. (issued November 2008). Available at: http://www.cdc.gov/tb/publications/factsheets/prevention/BCG.pdf (accessed 26/08/10)
9. Anonymous. WHO statement on BCG revaccination for the prevention of tuberculosis. *Bull WHO* 1995; **73:** 805–6.
10. Hawkridge A, *et al.* Efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis in South African infants: randomised trial. *BMJ* 2008; **337:** 1275–8.
11. WHO. BCG vaccine. *Wkly Epidem Rec* 2004; **79:** 27–38. Available at: http://www.who.int/entity/wer/2004/en/wer7904.pdf (accessed 01/11/07)

HIV-INFECTED PATIENTS. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients, including patients with symptomatic HIV infection or AIDS. WHO[1] states that HIV prevalence is one of the factors that should be considered when determining local policies on BCG vaccination (see Uses and Administration, p. 2378.2), and recommends that infants with known or likely HIV infection should not be vaccinated because of the increased risk in this group (see Immunocompromised Patients under Precautions, p. 2380.1). In the UK and USA, BCG vaccination is also not recommended for HIV-positive patients.

1. WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Wkly Epidem Rec* 2007; **82:** 193–6. Available at: http://www.who.int/wer/2007/wer8221.pdf (accessed 01/11/07)

Adverse Effects and Treatment

As for vaccines in general, p. 2375.1.

Serious adverse reactions to BCG vaccines used *for immunisation* against tuberculosis are rare, although the incidence may vary between strains. The normal therapeutic response involves induration and development of a lesion at the injection site, possibly with enlargement of local lymph nodes; this lesion may later ulcerate and heal over some months leaving a scar. In a few patients an exaggerated reaction, usually associated with overdose, inadvertent subcutaneous injection, or use in persons who are already tuberculin positive, may result in an abscess or discharging ulcer, or suppurative lymphadenitis. Non-specific systemic reactions may include fever and headache. Generalised reactions, possibly due to hypersensitivity, have been reported with a few fatalities. Disseminated BCG infection may occur and has also led to fatalities, particularly in immunocompromised patients. Disseminated BCG complications such as osteitis have been reported with some BCG vaccines. Very rarely, a lupoid type of reaction has occurred, mostly after multiple revaccination.

Intravesical use of BCG in the treatment and prophylaxis of bladder cancer is associated with an inflammatory response; transient dysuria and urinary frequency, sometimes with fever or a flu-like syndrome, and haematuria, are common, especially with repeated treatment (as in maintenance therapy). Rarely bladder contracture and epididymo-orchitis have been reported. As with vaccination, disseminated BCG infection has occurred rarely and may potentially be fatal. Fever lasting more than 24 hours should be investigated, and antimycobacterial therapy given if necessary. Other reported adverse effects have included hypersensitivity reactions such as rashes and arthralgia, and ocular symptoms including uveitis, conjunctivitis, iritis, and keratitis.

Reviews and studies of the adverse effects of BCG vaccines and their management.[1-6] An increased incidence of local effects has followed intradermal injection of high doses of BCG vaccines.[7,8] The incidence of adverse effects may vary between strains; an increase in incidence was reported in Ireland after withdrawal of a vaccine based on the Evans strain and its replacement with a vaccine containing the SSI strain of BCG.[9]

1. Lotte A, *et al.* Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 1988; **63:** 47–59.
2. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; **68:** 93–108.
3. Grange JM. Complications of bacille Calmette-Guérin (BCG) vaccination and immunotherapy and their management. *Commun Dis Public Health* 1998; **1:** 84–8.
4. FitzGerald JM. Management of adverse reactions to bacille Calmette-Guerin vaccine. *Clin Infect Dis* 2000; **31** (suppl 3): S75–S76.
5. Turnbull FM, *et al.* National study of adverse reactions after vaccination with bacille Calmette-Guérin. *Clin Infect Dis* 2002; **34:** 447–53.
6. Bellet JS, Prose NS. Skin complications of bacillus Calmette-Guérin immunization. *Curr Opin Infect Dis* 2005; **18:** 97–100.
7. Miles MM, Shaw RJ. Effect of inadvertent intradermal administration of high dose percutaneous BCG vaccine. *BMJ* 1996; **312:** 1014.
8. Puliyel JM, *et al.* Adverse local reactions from accidental BCG overdose in infants. *BMJ* 1996; **313:** 528–9.
9. Bolger T, *et al.* Complications associated with the bacille Calmette-Guérin vaccination in Ireland. *Arch Dis Child* 2006; **91:** 594–7.

Effects on the bones and joints. The risk of osteitis after BCG vaccination varies from country to country and appears to be linked to the strain of bacillus used.[1]

Osteitis or arthritis has also been reported after intravesicular use of BCG (see below).

1. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; **68:** 93–108.

Effects on the eyes. Follicular conjunctivitis occurred after accidental contamination of the eye with BCG vaccine.[1] The conjunctivitis responded to topical corticosteroid therapy, but a course of isoniazid was given as a precautionary measure.

For reference to uveitis after intravesical instillation see below.

1. Pollard AJ, George RH. Ocular contamination with BCG vaccine. *Arch Dis Child* 1994; **70:** 71.

Effects on the lymphatic system. Lymphadenitis associated with BCG vaccination has been reviewed.[1] It is the most common adverse effect of BCG vaccination and may develop 2 to 24 weeks after vaccination, with most cases occurring within 6 months. The incidence and severity depend on the dose, vaccine strain, the age at vaccination, and the immunological state of the patient. Suppurative BCG lymphadenitis in the form that develops in 30 to 80% of cases; neonates and immunodeficient patients are associated with an increased risk.

The treatment of BCG lymphadenitis remains controversial. Although antibacterials and antituberculous drugs such as isoniazid and rifampicin have been given, there is little evidence to support their use; the non-suppurative (simple) form regresses spontaneously without treatment while suppurating lymph nodes may be drained by needle aspiration and left to heal.

1. Goraya JS, Virdi VS. Bacille Calmette-Guerin lymphadenitis. *Postgrad Med J* 2002; **78:** 327–9.

Intravesicular administration. Intravesicular instillation of BCG can give rise to both localised and systemic adverse effects as a consequence of the immune stimulation required to eradicate cancer cells.[1-3] The most serious effects are due to disseminated infection and include severe sepsis with cardiorespiratory manifestations and a disseminated mycobacterial infection with granulomatous pneumonitis and hepatitis; prompt treatment with antimycobacterials is required.[1,4,5] Fatalities have occurred.[6,7] Other reports include severe haemophagocytic syndromes,[8] uveitis,[9,10] and arthritis and osteitis.[11,12] Epididymo-orchitis has also been reported up to 4 years after intravesicular BCG therapy.[13,14]

Initial findings of a study[15] involving 115 patients indicated that prophylactic use of ofloxacin, a fluoroquinolone with tuberculostatic activity, decreased the incidence of moderate to severe adverse effects associated with intravesical BCG without any significant decrease in recurrence-free survival at 12 months. Ofloxacin was given orally after each BCG instillation; a dose of 200 mg was given 6 hours after the first urination with a second dose about 10 to 12 hours later. Long-term study, however, was still needed to confirm these results.

1. Lamm DL. Efficacy and safety of bacille Calmette-Guérin immunotherapy in superficial bladder cancer. *Clin Infect Dis* 2000; **31:** S86–S90.
2. Rischmann P, *et al.* BCG intravesical instillations: recommendations for side-effects management. *Eur Urol* 2000; **37** (suppl 1): 33–6.
3. Huang TC. Management of complications of bacillus Calmette-Guerin immunotherapy in the treatment of bladder cancer. *Ann Pharmacother* 2000; **34:** 529–32.
4. Mooren FC, *et al.* Systemic granulomatous disease after intravesical BCG instillation. *BMJ* 2000; **320:** 219.
5. Gómez-Ferrer Lozano A, *et al.* Neumonitis granulomatosa por instilación endovesical de BCG. *Actas Urol Esp* 2006; **30:** 839–42.
6. Peyrière H, *et al.* Fatal systemic reaction after multiple doses of intravesical bacillus Calmette-Guérin for polyposis. *Ann Pharmacother* 2000; **34:** 1279–82.
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8. Schleinitz N, *et al.* Severe hemophagocytic syndrome after intravesical BCG instillation. *Am J Med* 2002; **112:** 593–4.
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11. Morgan MB, Iseman MD. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical administration of Bacille Calmette-Guérin. *Am J Med* 1996; **100:** 372–3.
12. Tinazzi E, *et al.* Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. *Rheumatol Int* 2006; **26:** 481–8.
13. Menke JJ, Heins JR. Epididymo-orchitis following intravesical bacillus Calmette-Guérin therapy. *Ann Pharmacother* 2000; **34:** 479–82.
14. Falkensammer C, *et al.* Late occurrence of bilateral tuberculous-like epididymo-orchitis after intravesical bacille Calmette-Guérin therapy for superficial bladder carcinoma. *Urology* 2005; **65:** 175.
15. Colombel M, *et al.* The effect of ofloxacin on bacillus Calmette-Guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol (Baltimore)* 2006; **176:** 935–9.

Precautions

As for vaccines in general, p. 2375.2.

BCG vaccines may be given with other live vaccines, but if they are not given at the same time it is preferable to allow an interval of 4 weeks between each although the period may be reduced to 10 days if absolutely necessary. However, routine primary immunisation in infants, including the use of live poliomyelitis vaccine, need not be delayed. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of lymphadenitis. BCG vaccination should be postponed in patients with fever or generalised skin infection. In patients with eczema, BCG vaccines should be given at a site free from lesions. Because of the possible risk of disseminated infections, BCG vaccines should not be given to immunocompromised patients including those with HIV infection. Infants born to HIV-positive mothers may be vaccinated once HIV infection has been ruled out; vaccination should be considered in infants of unknown status in areas of high tuberculosis prevalence if there are no signs suggestive of HIV infection. Vaccination is contra-indicated in patients taking antimycobacterial therapy, and those with a history of tuberculosis or a positive tuberculin skin test. Neonates in household contact with a known or suspected case of active tuberculosis should not be vaccinated.

The instillation of *intravesical* BCG should be postponed for 7 to 14 days after any trauma to the urinary tract including transurethral resection, biopsy, and trauma caused by catheterisation. Treatment should also be postponed in patients with acute febrile illness, urinary-tract infection, or gross haematuria. Use is contra-indicated in patients with active tuberculosis, a history of systemic reaction to BCG, or treatment with antimycobacterial therapy. As with vaccination, intravesical BCG should be avoided in immunocompromised patients, including those with HIV infection. Because BCG contains live mycobacteria that may be excreted in the urine, patients should be advised on the risk of contamination, and on appropriate infection control procedures to protect family and close contacts.

Immunocompromised patients. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients including those with symptomatic HIV infections and AIDS. An increased risk of disseminated BCG infection has been seen in infants and children with asymptomatic HIV infections,[1-3] leading to high mortality rates of about 80%. WHO Global Advisory Committee on Vaccine Safety therefore no longer recommends BCG vaccination of infants and children with known HIV infection (see Tuberculosis, HIV-infected Patients, p. 2379.2).

1. Hesseling AC, *et al.* Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006; **42:** 548–58.
2. Hesseling AC, *et al.* The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. *Vaccine* 2007; **25:** 14–18.
3. Azzopardi P, *et al.* Bacille Calmette-Guérin vaccine-related disease in HIV-infected children: a systematic review. *Int J Tuberc Lung Dis* 2009; **13:** 1331–44.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies BCG vaccine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Theophylline. For a report of increased theophylline half-life and serum concentrations after BCG vaccination, see under Theophylline Hydrate, p. 1236.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: ImmuCyst; ***Austral.***: ImmuCyst; OncoTICE; ***Austria***: ImmuCyst; OncoTICE; ***Belg.***: ImmuCyst; OncoTICE; ***Braz.***: ImmuCyst; Imunoest; ***Canad.***: ImmuCyst; OncoTICE; ***Chile***: ImmuCyst†; ***China***: Si Qi Kang (斯奇康); WeiKa (微卡); Wu Ti Lin Si (乌体林斯); ***Cz.***: ImmuCyst; ***Fin.***: OncoTICE†; ***Fr.***: ImmuCyst; ***Ger.***: ImmuCyst†; OncoTICE†; ***Gr.***: ImmuCyst; OncoTICE; ***Hong Kong***: ImmuCyst; ***Hung.***: ImmuCyst; ***India***: Onco-BCG; OncoTICE; ***Irl.***: ImmuCyst; ***Israel***: ImmuCyst; OncoTICE; ***Ital.***: ImmuCyst; OncoTICE; ***Malaysia***: Glutamate BCG; ImmuCyst; ***Mex.***: Cultivo BCG; OncoTICE; ***Neth.***: OncoTICE; ***Norw.***: OncoTICE; ***NZ***: ImmuCyst; OncoTICE; ***Philipp.***: Glovax; ***Pol.***: OncoTICE; Onko BCG; ***Port.***: ImmuCyst; OncoTICE; ***Rus.***: Imuron-Vac (Имурон-Вак); ***Singapore***: ImmuCyst; ***Spain***: ImmuCyst†; OncoTICE; Vejicur; ***Swed.***: OncoTICE; ***Switz.***: ImmuCyst; OncoTICE; ***Thai.***: ImmuCyst; ***Turk.***: ImmuCyst; OncoTICE; ***UK***: ImmuCyst; OncoTICE; ***Ukr.***: Onco-BCG (Онко БЦЖ); ***USA***: TheraCys; Tice; ***Venez.***: OncoTICE.

Pharmacopoeial Preparations
Ph. Eur.: BCG for Immunotherapy; Freeze-dried BCG Vaccine; **USP 36:** BCG Live; BCG Vaccine.

Botulism Antitoxins

Antitoxinas botulínicas; Antitoxinas del botulismo; Ботулинические Антитоксины.
ATC — J06AA04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Botulinum Antitoxin; Immunoserum Botulinicum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by type A, type B, type E, or any mixture of types A, B, and E, of *Clostridium botulinum*. It contains not less than 500 international units of each of type A and type B and not less than 50 units of type E per mL. It should be stored at 2 degrees to 8 degrees and not be allowed to freeze.

The BP 2014 states that Bot/Ser may be used on the label.

The BP 2014 states that when Mixed Botulinum Antitoxin or Botulinum Antitoxin is prescribed or demanded and the types to be present are not stated, Botulinum Antitoxin prepared from types A, B, and E shall be dispensed or supplied.

NOTE. Some antitoxins used in the UK have not conformed to the requirements of the BP 2014 and Ph. Eur. 8 (having a higher phenol content than the pharmacopoeias allow), and thus have been referred to as **botulism antitoxin** rather than botulinum antitoxin.

Uses and Administration

Botulism antitoxins are used in the postexposure prophylaxis and treatment of botulism. Treatment should be given as early as possible in the course of the disease.

Since the type of botulism toxin is seldom known the polyvalent antitoxin is usually given. Sensitivity testing should always be performed before using the antitoxin.

In the UK, equine-derived trivalent antitoxins containing antitoxin types A, B, and E have been used. One type has contained not less than 500 units/mL of each of the 3 antitoxins. For the treatment of botulism, 20 mL of this antitoxin would be diluted to 100 mL with sodium chloride 0.9% and given by slow intravenous infusion over at least 30 minutes; another 10 mL may be given 2 to 4 hours later if necessary, and further doses at 12- to 24-hour intervals if indicated. Persons who have been exposed to the toxin and in whom symptoms have not developed should be given 20 mL intramuscularly as a prophylactic measure.

A second preparation used for treatment of botulism in the UK has contained 750 units/mL of antitoxin type A, 500 units/mL of antitoxin type B, and 50 units/mL of antitoxin type E. Patients would be given 250 mL by slow intravenous infusion, followed by a further 250 mL by continuous drip infusion. A further 250 mL may be given 4 to 6 hours later if necessary according to response. Patients with severe intoxication should be given an intralumbar injection of 20 mL, particularly if intravenous treatment has produced no improvement; this procedure may be repeated at 24-hour intervals if required.

In the USA, a human-derived intravenous botulism immunoglobulin (BIG-IV) is available for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. The recommended dose of 1.5 mL/kg (75 mg/kg), given as a single intravenous infusion, provides a protective level of neutralising antibodies for at least 6 months. A heptavalent botulinum antitoxin active against toxin types A, B, C, D, E, F, and G is also available in the USA for the treatment of naturally occurring noninfant botulism.

Botulism. Botulism[1-4] is caused by the exotoxin of *Clostridium botulinum*, a spore-forming, Gram-positive anaerobe which occurs in soil and mud. There are 3 naturally occurring forms of botulism; *food-borne botulism* caused by ingestion of contaminated foodstuffs, *wound botulism* due to the growth of toxin-releasing organisms in the wound, and *intestinal botulism* (including infant botulism and adult intestinal toxaemia) caused by intestinal colonisation and toxin production. Accidental or intentional exposure to botulinum toxin may result in inhalation botulism (from aerosolisation of botulinum toxin) or iatrogenic botulism (from injection of the toxin). Seven types of *C. botulinum* can be distinguished (types A to G), each producing a different exotoxin; human disease is usually caused by types A, B, and E. The toxin is heat labile, but the spores can survive temperatures of up to 120 degrees.

All forms of botulism produce the same clinical syndrome. Symptoms arise as a result of the toxin blocking the release of acetylcholine at the neuromuscular junction and include symmetrical cranial nerve palsies and descending flaccid paralysis, orthostatic hypotension, dry mouth, and dilated pupils. Gastrointestinal symptoms occur with food-borne or intestinal colonisation botulism. Death is usually from respiratory arrest.

Treatment of botulism is with equine-derived antitoxins and intensive respiratory and supportive therapy. Antitoxins should be given as early as possible as only toxins that are not bound to nerve ending are neutralised; however, antitoxins may still be beneficial if treatment is delayed. Some patients may benefit from drugs, such as fampridine or guanidine, aimed at reversing the neuromuscular blockade. Vaccination has been investigated as a preventive measure in persons at high risk, but is problematic since it may preclude therapeutic or cosmetic use of the toxin.

Infant botulism is of increasing importance, especially in the USA where it is reported to be the most common form of botulism, with honey (see p. 2072.2) reputed to be the most frequent source of infection. In contrast to food-borne botulism, in infant botulism low doses of toxin continue to be released into the gut for some time. Treatment is with intensive supportive care; equine botulism antitoxin used in adults is not generally used for infant botulism because of its serious adverse effects (including serum sickness and anaphylaxis), its short half-life, and the possibility of life-long sensitisation to equine proteins.[5] A human-derived intravenous botulism immunoglobulin (BIG-IV) is available in the USA for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. Clinical studies[5] reported that treatment with BIG-IV within 7 days of hospital admission reduced the length of hospital stay and severity of illness in infant botulism type A or B; treatment given within 3 days was more effective than treatment given 4 to 7 days after admission.

1. Robinson RF, Nahata MC. Management of botulism. *Ann Pharmacother* 2003; **37:** 127–31.
2. Health Protection Agency. Guidelines for action in the event of a deliberate release: botulism (issued March 2009). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947315628 (accessed 26/08/10)
3. Sobel J. Botulism. *Clin Infect Dis* 2005; **41:** 1167–73.
4. Smith LA. Botulism and vaccines for its prevention. *Vaccine* 2009; **27** (suppl 4): D33–D39.
5. Arnon SS, *et al.* Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med* 2006; **354:** 462–71.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: BabyBIG.

Pharmacopoeial Preparations
Ph. Eur.: Botulinum Antitoxin.

Bovine Colostrum

Calostro bovino.
UNII — S256WJ3OFQ.

Profile

Bovine colostrum has been used similarly to antisera and human immunoglobulin preparations to provide passive immunity against infectious diseases. Hyperimmune bovine colostra have been prepared from cows previously immunised with specific antigens. In particular, these specific hyperimmune bovine colostra have been tried in cryptosporidiosis and in the prevention of rotavirus diarrhoea in infants. They may also have potential for use against *Helicobacter pylori*, *Shigella* spp., and measles.

Reviews.
1. Kelly GS. Bovine colostrums: a review of clinical uses. *Altern Med Rev* 2003; **8:** 378–94. Correction. *ibid.* 2004; **9:** 69.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: PM Auscolos; Travelan; ***India***: Istrum; Kairlact.

Multi-ingredient Preparations. ***Austral.***: PM IQShield; ***India***: Immunorm; ***Indon.***: Bd-GARD; Biostrum; Brainvit; Calostrum; Curbexon; Curmunos; Hepimun Plus; Idesar Plus; Igastrum Plus; Igastrum; Imustrum; Intrum Plus; Kolivit; Kuminta; Prokids; Stimox; Truvit; Vicotrum; Vistrum; Vitaplex; ***Ital.***: Colostrum.

Brucellosis Vaccines

Vacunas de la brucelosis.
ATC — J07AD01.

Profile

A brucellosis vaccine prepared from an antigenic extract of *Brucella abortus* has been used for active immunisation against brucellosis (p. 176.1) in persons at high risk of contracting the disease.

Campylobacter Jejuni Vaccines

Vacunas contra el Campylobacter jejuni.

Profile

An oral vaccine is under development to provide active immunisation against *Campylobacter jejuni* infection.

Cholera Vaccines

Vacunas del cólera.
ATC — J07AE01; J07AE02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Cholera Vaccine; Vaccinum Cholerae). A sterile homogeneous suspension of a suitable killed strain or strains of *Vibrio cholerae*. It consists of a mixture of equal parts of vaccines prepared from smooth strains of 2 main serological types, Inaba and Ogawa of the classical biotype with or without the El Tor biotype. A single strain or several strains of each type may be included. All strains must contain, in addition to their type O antigens, the heat-stable O antigen common to the Inaba and Ogawa types. If more than one strain each of Inaba and Ogawa are used they may be selected to contain other O antigens. It contains not less than 8000 million *V. cholerae* per dose, which does not exceed 1 mL. It contains not more than 0.5% of phenol. It should be stored at 2 degrees to 8 degrees and protected from light.

The BP 2014 states that Cholera may be used on the label.

Ph. Eur. 8: (Cholera Vaccine, Freeze-dried; Vaccinum Cholerae Cryodesiccatum). Cholera vaccine that is freeze-dried and reconstituted immediately before use by the addition of a suitable sterile liquid. Phenol may not be used in the preparation of the dried vaccine. It should be stored at 2 degrees to 8 degrees and be protected from light.

Ph. Eur. 8: (Cholera Vaccine (Inactivated, Oral); Vaccinum Cholerae Perorale Inactivatum). A homogeneous suspension of inactivated suitable strains of *Vibrio cholerae* serogroup O1, representing serotypes and biotypes of epidemic strains. The vaccine may contain the B subunit of cholera toxin (CTB). Just before ingestion, one dose of vaccine suspension is mixed with a suitable buffer as stated on the label. Store at 2 degrees to 8 degrees. Protect from light.

The BP 2014 states that Dried/Cholera may be used on the label.

Uses and Administration

Injectable inactivated whole-cell cholera vaccines have been used for active immunisation against cholera (p. 184.2) but are not considered to be very effective and the immunity conferred is short-lived. They have no role in the management of contacts of cases or in controlling the spread of infection.

Oral vaccines containing either live attenuated or inactivated strains are available in some countries and appear to be more effective than parenteral vaccines (see below). In the UK, an oral vaccine containing inactivated strains of *Vibrio cholerae* O1 and recombinant cholera toxin B subunit is available for use in adults and children aged over 2 years who are travelling to areas of risk. The vaccine is given as a suspension, in doses of 3 mL, mixed with sodium hydrogen carbonate solution. Adults and children aged over 6 years are given two doses, and children aged 2 to 6 years three doses, in each case at weekly intervals. Immunisation should be complete at least 1 week before potential exposure. Booster doses may be given after 2 years in adults and children over 6 years, or after 6 months in children aged 2 to 6 years, if continuous protection is required. Oral vaccines containing a live attenuated form of the *V. cholerae* strain CVD 103-HgR are available in some countries. They are effective against the O1 serogroup of cholera, but do not afford protection against the O139 serogroup. They may be given to adults and children aged over 2 years who are travelling to areas of risk and are given as a single-dose suspension in sodium hydrogen carbonate solution. Immunisation should be carried out at least 1 week before potential exposure. When necessary revaccination is recommended every 6 months.

The WHO International Health Regulations do not require cholera vaccination for travellers as the introduction of cholera into any country cannot be prevented by cholera vaccination. However, travellers may still be asked for evidence of immunisation at some borders.

References.

1. WHO. Cholera vaccines: WHO position paper. *Wkly Epidem Rec* 2010; **85:** 117–28. Also available at: http://www.who.int/wer/2010/wer8513.pdf (accessed 22/06/10)

Oral cholera vaccines. Since parenteral cholera vaccines are not considered to be very effective, providing at best 50% protection and confer immunity lasting only 3 to 6 months, attention has turned towards oral vaccines that stimulate intestinal immunity.[1] Both killed and live attenuated oral vaccines have been developed, and both types have been shown to be non-toxic and immunogenic.

Killed vaccines contain inactivated whole *Vibrio cholerae* O1 either alone or with B subunit component of cholera toxin. These vaccines typically produce a protective efficacy of about 60 to 70% and both modify established infections and prevent new ones. Although the vaccines are effective in areas where the El Tor biotype predominates, they are more effective against classical strains. Immunity particularly against El Tor may be less sustained in children under 5 years of age than in older children and adults. The main drawback is the need to give two or more doses at 1- to 2-week intervals to achieve a protective effect. The protective effect is rapidly established but diminishes over time and booster doses are necessary to maintain a high level of immunity.

A live attenuated vaccine is now available containing CVD 103-HgR in which the genes encoding the toxic A subunit are deleted by recombinant techniques.[2,3] This vaccine is effective 8 days after a single dose but less so against El Tor than against classical strains. It is not effective against *V. cholorae* O139.

Live oral vaccines effective against El Tor are now being developed,[4,5] and promising responses have also been reported with a live attenuated O139 vaccine.[6] A number of other candidate vaccines including some potentially more suitable for developing countries, are under development.[7]

The efficacy and cost-effectiveness of oral vaccines to control cholera outbreaks in refugee populations is uncertain.

1. Ryan ET, Calderwood SB. Cholera vaccines. *Clin Infect Dis* 2000; **31:** 561–5.
2. Tacket CO, *et al.* Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with Vibrio cholerae OI El tor inaba three months after vaccination. *Infect Immun* 1999; **67:** 6341–5.
3. Richie E, *et al.* Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area. *Vaccine* 2000; **18:** 2399–2410.
4. Tacket CO, *et al.* Volunteer studies investigating the safety and efficacy of live El Tor Vibrio cholerae O1 vaccine strain CVD 111. *Am J Trop Med Hyg* 1997; **56:** 533–7.
5. Sack DA, *et al.* Evaluation of Peru-15, a new live oral vaccine for cholera, in volunteers. *J Infect Dis* 1997; **176:** 201–5.
6. Coster TS, *et al.* Safety, immunogenicity, and efficacy of live attenuated Vibrio cholerae O139 vaccine prototype. *Lancet* 1995; **345:** 949–52.
7. Lopez AL, *et al.* Cholera vaccines for the developing world. *Hum Vaccin* 2008; **4:** 165–9.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Slight swelling, erythema, and tenderness occasionally occur at the injection site. Fever and malaise have been reported and general reactions, including anaphylaxis and hypersensitivity reactions, have occurred. Neurological and psychiatric reactions have occasionally occurred.

Gastrointestinal disturbances, headache, dizziness, and respiratory symptoms have followed use of oral cholera vaccine.

Blood group. Patients with blood group O are more likely to experience severe symptoms if infected with cholera of the El Tor or O139 types, and cholera vaccines offer them less protection.[1] It has been suggested that this increased vulnerability should be taken into account in epidemiological planning.

1. Holmner Å, *et al.* Molecular basis of cholera blood-group dependence and implications for a world characterized by climate change. *FEBS Lett* 2010; **584:** 2548–55.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies inactivated, whole cell cholera vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

The oral cholera vaccine available in the UK is acid labile; consequently food should not be consumed for 1 hour before and after use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Orochol; ***Austral.***: Dukoral; ***Austria***: Dukoral; ***Belg.***: Dukoral; ***Braz.***: Vacina Oral Contra Colera; ***Canad.***: Dukoral; ***Chile***: Dukoral; ***China***: Oravacs (可唯适); ***Cz.***: Dukoral; ***Denm.***: Dukoral; ***Fin.***: Dukoral; ***Fr.***: Dukoral; ***Ger.***: Dukoral; ***Hong Kong***: Dukoral; ***Hung.***: Dukoral; ***Irl.***: Dukoral; ***Ital.***: Dukoral; ***Malaysia***: Dukoral; ***Neth.***: Dukoral; ***Norw.***: Dukoral; ***NZ***: Dukoral; ***Philipp.***: Dukoral; Orochol†; ***Pol.***: Dukoral; ***Port.***: Dukoral; ***S.Afr.***: Dukoral; ***Singapore***: Dukoral; ***Spain***: Dukoral; ***Swed.***: Dukoral; ***Switz.***: Dukoral; ***Thai.***: Dukoral†; ***Turk.***: Dukoral†; ***UK***: Dukoral.

Pharmacopoeial Preparations

Ph. Eur.: Cholera Vaccine (Inactivated, Oral); Cholera Vaccine; Freeze-dried Cholera Vaccine.

Contraceptive Vaccines

Vacunas anticonceptivas.

Profile

Various approaches to development of a contraceptive vaccine are under investigation. The molecules being explored target either:

- gamete production (gonadotrophin releasing hormone, follicle-stimulating hormone, and luteinising hormone)
- gamete function (zona pellucida proteins and sperm antigens), or
- gamete outcome (human chorionic gonadotrophin)

Phase I and II clinical studies with human chorionic gonadotrophin vaccines have reported reversible efficacy and lack of immunotoxicity; however, vaccines targeting sperm antigens appear to be the most promising.

Reviews.

1. Delves PJ. The development of contraceptive vaccines. *Expert Opin Invest Drugs* 2002; **11:** 1225–37.
2. Aitken RJ. Immunocontraceptive vaccines for human use. *J Reprod Immunol* 2002; **57:** 273–87.
3. McLaughlin EA, *et al.* Contraceptive vaccines. *Expert Opin Biol Ther* 2003; **3:** 829–41.
4. Ferro VA, Mordini E. Peptide vaccines in immunocontraception. *Curr Opin Mol Ther* 2004; **6:** 83–9.
5. Naz RK. Contraceptive vaccines. *Drugs* 2005; **65:** 593–603.
6. Naz RK. Status of contraceptive vaccines. *Am J Reprod Immunol* 2009; **61:** 11–8.

Crimean-Congo Haemorrhagic Fever Immunoglobulins

Inmunoglobulinas contra la fiebre hemorrágica de Congo-Crimea.

Profile

Preparations containing antibodies against Crimean-Congo haemorrhagic fever have been used for passive immunisation against the disease.

References.

1. Vassilenko SM, *et al.* Specific intravenous immunoglobulin for Crimean-Congo haemorrhagic fever. *Lancet* 1990; **335:** 791–2.
2. Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. *Antiviral Res* 2008; **78:** 125–31.

Crimean-Congo Haemorrhagic Fever Vaccines

Profile

An inactivated vaccine against Crimean-Congo haemorrhagic fever, derived from *mouse* brains, is used in parts of eastern Europe.

Cytomegalovirus Immunoglobulins

Inmunoglobulinas contra el citomegalovirus.
ATC — J06BB09.
UNII — 129L90A25N (human cytomegalovirus immune globulin).

Description. Cytomegalovirus immunoglobulins containing high levels of specific antibody against CMV have been prepared from human plasma.

Uses and Administration

Cytomegalovirus immunoglobulins are used for passive immunisation against CMV infection. They are used prophylactically, especially in patients undergoing certain transplant procedures. In transplants from CMV-seropositive donors into seronegative recipients, prophylactic use of cytomegalovirus immunoglobulin with ganciclovir should also be considered.

In the USA, a cytomegalovirus immunoglobulin G is available for use in recipients of heart, kidney, liver, lung, and pancreas transplants, and for CMV-seronegative recipients of these organs other than kidney from CMV-seropositive donors. The dosage schedule for kidney transplant recipients is 150 mg/kg by intravenous infusion within 72 hours of transplantation, then 100 mg/kg once every 2 weeks for 4 doses, then 50 mg/kg every 4 weeks for 2 doses. The rate of infusion should start at 15 mg/kg per hour increasing gradually to a maximum rate of 60 mg/kg per hour. For recipients of transplants other than kidney, the recommended dosage schedule is 150 mg/kg within 72 hours of transplantation and then once every 2 weeks for 4 further doses, then 100 mg/kg every 4 weeks for 2 doses. In the UK, cytomegalovirus immunoglobulin is available on a named patient basis for prophylaxis in patients receiving immunosuppressive treatment.

The name sevirumab is applied to a χ-chain human monoclonal cytomegalovirus immunoglobulin G1.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Megalotect; ***Austral.***: CMV Immunoglobulin; ***Austria***: Cytotect; ***Belg.***: Ivegam-CMV; ***Canad.***: CytoGam; ***Chile***: Cytotect†; ***Cz.***: Cytotect; ***Ger.***: Cytotect; ***Gr.***: Megalotect; ***Hong Kong***: Cytotect†; ***Hung.***: Cytotect; ***Irl.***: Megalotect; ***Israel***: Megalotect; ***Ital.***: Cytotect; ***Neth.***: Megalotect; ***Pol.***: Cytotect; ***Port.***: Megalotect; ***Singapore***: Megalotect; ***Switz.***: Cytotect; ***Thai.***: Megalotect†; ***Turk.***: CytoGam; Cytotect; ***Ukr.***: Cytobiotect (Цитобиотект); ***USA***: CytoGam.

Cytomegalovirus Vaccines

Vacunas contra el citomegalovirus.

Profile

Several vaccines for active immunisation against CMV infection are under investigation, including some produced by recombinant technology. A live attenuated cytomegalovirus vaccine containing human CMV Towne strain has been investigated in humans since the late 1970s, particularly for the prevention of CMV infection in renal transplant recipients. However, there have been doubts over its safety.

Several promising candidate vaccines against human CMV infection have been developed; a 2004 review noted that 5 had been or were being tested in humans.[1] Attenuated CMV (Towne strain) vaccine was found to be erratic in efficacy and lost segments of its genetic material; to overcome this a second, more robust, vaccine was designed consisting of a chimera between the attenuated CMV and wild-type virus. The third vaccine developed, known as ALVAC, consisted of a canarypox vector with either a glycoprotein B envelope or a core antigen from CMV pp65, a protein found to be recognised by CD8+ T lymphocytes during naturally acquired infection. Fourthly, a protein subunit vaccine consisting of a recombinant envelope glycoprotein had been found to be safe and to induce a neutralising antibody response. The fifth vaccine developed was a mixture of synthetic peptides incorporating a T helper epitope known as CD8+ cytotoxic T cell epitope and a lipid tail. At that time the attenuated cytomegalovirus vaccine, the protein subunit vaccine, and the recombinant vector vaccine had been or were being tested in CMV-negative subjects, and the chimeric vaccine had been tested in CMV-positive patients as a precursor to testing in CMV-negative persons.[1] Further vaccine candidates that had been proposed included DNA vaccines and a vaccine based on recombinant technology.[1] Further development has continued,[2,3] but no candidate has yet come into general use. Some commentators[4] have suggested that reduction or prevention of cytomegalovirus disease may be a more realistic goal for a vaccine than prevention of infection.

1. Arvin AM, *et al*. Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. *Clin Infect Dis* 2004; **39:** 233–9.
2. Schleiss MR. Cytomegalovirus vaccine development. *Curr Top Microbiol Immunol* 2008; **325:** 361–82.
3. Herr W, Plachter B. Cytomegalovirus and varicella-zoster virus vaccines in hematopoietic stem cell transplantation. *Expert Rev Vaccines* 2009; **8:** 999–1021.
4. Khanna R, Diamond DJ. Human cytomegalovirus vaccine: time to look for alternative options. *Trends Mol Med* 2006; **12:** 26–33.

Dengue Fever Vaccines

Vacunas del dengue.

Profile

Live attenuated vaccines under study for active immunisation against dengue fever contain dengue virus types 1, 2, 3, and 4 alone or in various combinations. WHO considers that protection against only one or two dengue viruses might actually increase the risk of more serious disease. The ultimate aim is to produce a vaccine active against all types of dengue virus.

Recombinant vaccines are also under investigation.

References.
1. Velzing J, *et al*. Induction of protective immunity against dengue virus type 2: comparison of candidate live attenuated and recombinant vaccines. *Vaccine* 1999; **17:** 1312–30.
2. Kanesa-Thasan N, *et al*. Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. *Vaccine* 2001; **19:** 3179–88.
3. Rothman AL, *et al*. Induction of T lymphocyte responses to dengue virus by a candidate tetravalent live attenuated dengue virus vaccine. *Vaccine* 2001; **19:** 4694–99.
4. Sabchareon A, *et al*. Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. *Am J Trop Med Hyg* 2002; **66:** 264–72.
5. Sun W, *et al*. Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. *Am J Trop Med Hyg* 2003; **69** (suppl 6): 24–31.
6. Sabchareon A, *et al*. Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. *Pediatr Infect Dis J* 2004; **23:** 99–109.
7. Monath TP. Dengue and yellow fever—challenges for the development and use of vaccines. *N Engl J Med* 2007; **357:** 2222–5.
8. Edelman R. Dengue vaccines approach the finish line. *Clin Infect Dis* 2007; **45** (suppl 1): S56–60.
9. Hatch S, *et al*. Dengue vaccine: opportunities and challenges. *IDrugs* 2008; **11:** 42–5.
10. Webster DP, *et al*. Progress towards a dengue vaccine. *Lancet Infect Dis* 2009; **9:** 678–87.
11. Durbin AP, Whitehead SS. Dengue vaccine candidates in development. *Curr Top Microbiol Immunol* 2010; **338:** 129–43.
12. Miller N. Recent progress in dengue vaccine research and development. *Curr Opin Mol Ther* 2010; **12:** 31–8.

Dental Caries Vaccines

Vacunas de la caries dental.

Profile

Dental caries vaccines consisting of purified proteins from *Streptococcus mutans* or *Str. sobrinus* are under investigation. Monoclonal antibodies are also being studied for local passive immunisation.

Several *animal* studies of candidate vaccines for the prevention of dental caries have shown that immunisation with protein antigens from *Streptococcus mutans* or *Str. sobrinus* can induce salivary IgA antibodies which inhibit both sucrose-dependent or sucrose-independent accumulation of these organisms on tooth surfaces. It is thought that candidate vaccines for study in humans could be given by mucosal application since children are already naturally exposed to the antigens involved during the first years of life. Infection with *Str. mutans* normally occurs from the age of about 18 months and the intention is therefore to vaccinate 1-year-old children in order to intercept colonisation. However, progress towards a vaccine for active immunisation against dental caries requires further clinical evaluation. Passive administration of salivary antibodies to *Str. mutans* has also provided some protection in preclinical studies and small scale studies in humans.[1-4]

1. Koga T, *et al*. Immunization against dental caries. *Vaccine* 2002; **20:** 2027–44.
2. Smith DJ. Caries vaccines for the twenty-first century. *J Dent Educ* 2003; **67:** 1130–9.
3. Russell MW, *et al*. A caries vaccine? The state of the science of immunization against dental caries. *Caries Res* 2004; **38:** 230–5.
4. Smith DJ, Mattos-Graner RO. Secretory immunity following mutans streptococcal infection or immunization. *Curr Top Microbiol Immunol* 2008; **319:** 131–56.

Diphtheria Antitoxins

Antitoxinas diftéricas.
ATC — J06AA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria Antitoxin; Immunoserum Diphthericum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Corynebacterium diphtheriae*. It has a potency of not less than 1000 international units/mL when obtained from horse serum and not less than 500 international units/mL when obtained from other mammals. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Dip/Ser may be used on the label.

Uses and Administration

Diphtheria antitoxins neutralise the toxin produced by *Corynebacterium diphtheriae* locally at the site of infection and in the circulation.

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria and should be given without waiting for bacteriological confirmation of the infection. An antibacterial is also usually given (see p. 178.3). Diphtheria antitoxin is generally not used for the prophylaxis of diphtheria because of the risk of provoking a hypersensitivity reaction. Contacts of a diphtheria case should be promptly investigated, given antibacterial prophylaxis and active immunisation with a suitable diphtheria-containing vaccine as appropriate (see below), and kept under observation.

A test dose of diluted diphtheria antitoxin should always be given intradermally to exclude hypersensitivity. In the UK, diphtheria antitoxin is given by intravenous infusion for the treatment of diphtheria of mild to moderate severity in the following recommended doses:

- for *nasal* diphtheria, 10 000 to 20 000 units
- for *tonsillar* diphtheria, 15 000 to 25 000 units
- for *pharyngeal* or *laryngeal* diphtheria, 20 000 to 40 000 units

In cases of combined disease, or when diagnosis is delayed, 40 000 to 60 000 units should be given, and, in severe disease, doses up to 100 000 units used. For most cutaneous infections, diphtheria antitoxin is insufficiently absorbed and is therefore not given; however, if the ulcer is sufficiently large (more than 2 cm^2) and especially if it is membranous, then 20 000 to 40 000 units may be given. Higher doses have been used in some countries.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria Antitoxin.

Diphtheria Vaccines

Vacunas de la difteria.
ATC — J07AF01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria Vaccine (Adsorbed); Vaccinum Diphtheriae Adsorbatum). A preparation of diphtheria formol toxoid adsorbed on a mineral carrier. The formol toxoid is prepared from the toxin produced by the growth of *Corynebacterium diphtheriae*. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives, particularly those of the phenolic type. It contains not less than 30 international units per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Ph. Eur. 8: (Diphtheria Vaccine (Adsorbed, Reduced Antigen Content); Vaccinum Diphtheriae, Antigeniis Minutum, Adsorbatum). It is an adsorbed diphtheria vaccine containing not less than 2 international units per dose.

The BP 2014 states that for a vaccine for use in the UK, the amount of toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents per dose.

Uses and Administration

Diphtheria vaccines are used for active immunisation against diphtheria. The non-adsorbed vaccine has poor immunogenic properties and its effects are enhanced if given as an adsorbed preparation. For primary immunisation combined diphtheria vaccines, usually diphtheria, tetanus, and pertussis vaccines (p. 2383.3) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p. 2385.3), are used. A single-component diphtheria vaccine has sometimes been used, for example in the event of contact with an infected patient or a carrier. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Individuals coming into contact with a case of diphtheria or carrier of a toxigenic strain, or those travelling to an endemic or epidemic area should receive a complete primary course or a reinforcing dose according to age and immunisation history; those not previously immunised should receive a primary course of immunisation, and those previously immunised should receive a single reinforcing dose of a diphtheria-containing vaccine. Contacts of a case of diphtheria or carrier of a toxigenic strain should in

addition receive a prophylactic course of a suitable antibacterial (see p. 178.3). Individuals at repeated risk of exposure to infection may be offered booster doses every 10 years.

Schick testing (p. 2611.2) to ascertain immune status is no longer considered necessary before giving diphtheria vaccine to adults provided that a low dose is given; antibody testing is used to check immunity in those regularly exposed to diphtheria.

In some countries, booster doses of a diphtheria and tetanus vaccine are recommended every 10 years (see under Diphtheria and Tetanus Vaccines, below).

Conjugation to diphtheria toxoid has been used to increase the immunogenicity of other vaccines (see Haemophilus Influenzae Vaccines, p. 2387.2).

References.
1. WHO. Diphtheria vaccine: WHO position paper. *Wkly Epidem Rec* 2006; **81:** 24–32. Also available at: http://www.who.int/immunization/wer8103Diphtheria_Jan06_position_paper.pdf (accessed 23/06/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Local reactions may occur but are generally not severe in young children; the frequency and severity of reactions is reported to be less in children under 2 years of age than in older children and adults. If diphtheria vaccines or vaccines containing a diphtheria component need to be given to children over the age of 10 years or to adults, vaccines with a reduced content of diphtheria toxoid and intended for adults and adolescents should be used. For further details see Uses and Administration, p. 2382.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diphtheria vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Difterivaccine; ***NZ***: Di Anatoxal†.

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria Vaccine (Adsorbed); Diphtheria Vaccine (Adsorbed, Reduced Antigen Content).

Diphtheria and Tetanus Vaccines

Vacunas de la difteria y el tétanos; Vacunas dobles DT; Vacunas DT.
ATC — J07AM51.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria and Tetanus Vaccine (Adsorbed); Vaccinum Diphtheriae et Tetani Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid adsorbed on a mineral carrier. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid and not less than 40 international units of tetanus toxoid per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DT/Vac/Ads(Child) may be used on the label.

The BP 2014 gives Adsorbed Diphtheria-Tetanus Prophylactic as an approved synonym.

Ph. Eur. 8: (Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae et Tetani, Antigeni-o(-is) Minutum). It is diphtheria and tetanus vaccine (adsorbed) containing not less than 2 units of diphtheria toxoid and not less than 20 units of tetanus toxoid per dose.

The BP 2014 states that for a vaccine for use in the UK, the amount of diphtheria toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents of diphtheria toxoid per dose.

The BP 2014 states that dT may be used on the label.

Uses and Administration

Combined adsorbed diphtheria and tetanus vaccines may be used for active immunisation, although vaccines used for primary immunisation usually combine diphtheria, tetanus, and pertussis, and sometimes also Haemophilus influenzae and poliomyelitis. Diphtheria and tetanus vaccines are used in some countries for reinforcing doses after primary immunisation; in the USA they are given to adults every 10 years. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

The non-adsorbed combined diphtheria and tetanus vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Booster doses. In many countries, booster doses of combined diphtheria and tetanus vaccines are recommended every 10 years, and studies have been conducted to assess whether this is necessary. Since the incidence of clinical diphtheria in many countries in western Europe and North America approaches zero, it had been considered that there was no need for booster doses in adults, despite low antibody titres, so long as the policy of immunisation during infancy was maintained.[1,2] However, after a report[3] of an outbreak of clinical diphtheria in Sweden after a period of many years during which no indigenous cases of diphtheria had occurred and the disease was regarded as being eliminated from the country, the question of immunity in adults and the need for revaccination again arose. In the USA, it was considered[4] that re-immunisation every 10 years with a diphtheria and tetanus combined vaccine was mandatory and that this combined vaccine should be used whenever a tetanus vaccine was indicated as in treating emergency wounds. Outbreaks of diphtheria in Russia and neighbouring countries[5] have prompted recommendations for booster doses in travellers to these countries.

1. Mathias RG, Schechter MT. Booster immunisation for diphtheria and tetanus: no evidence of need in adults. *Lancet* 1985; **i:** 1089–91.
2. Anonymous. Diphtheria and tetanus boosters. *Lancet* 1985; **i:** 1081–2.
3. Rappuoli R, *et al.* Molecular epidemiology of the 1984–1986 outbreak of diphtheria in Sweden. *N Engl J Med* 1988; **318:** 12–14.
4. Karzon DT, Edwards KM. Diphtheria outbreaks in immunized populations. *N Engl J Med* 1988; **318:** 41–3.
5. Anonymous. Diphtheria immunisation—advice from the Chief Medical Officer. *Commun Dis Rep* 1993; **3:** 27.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1. See also under Diphtheria Vaccines, above, and Tetanus Vaccines, p. 2421.2. Diphtheria and tetanus vaccines are reported to produce fewer adverse effects than diphtheria, tetanus, and pertussis vaccines (see under Incidence of Adverse Effects, p. 2384.1).

Dose-related effects. A high incidence of adverse effects was reported in teenagers inadvertently given a high-dose diphtheria and tetanus vaccine intended for use in infants.[1] Most reactions were classified as mild or moderately severe, but severe local or systemic reactions occurred in a third of those reporting reactions.

1. Sidebotham PD, Lenton SW. Incidence of adverse reactions after administration of high dose diphtheria with tetanus vaccine to school leavers: retrospective questionnaire study. *BMJ* 1996; **313:** 533–4.

Effects on the nervous system. Encephalopathy is more common after vaccination with diphtheria, tetanus, and pertussis vaccine (p. 2384.1) than with diphtheria and tetanus vaccine. Several cases of encephalopathy occurred in a small region in Italy in children after immunisation against diphtheria and tetanus,[1] although it was not possible to infer a causal relationship. A case of polyradiculoneuritis has been reported in a patient after the use of a diphtheria-tetanus vaccine and was considered most likely to have been due to the tetanus component.[2]

1. Greco D. Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy. *Bull WHO* 1985; **63:** 919–25.
2. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. *Arch Neurol* 1983; **40:** 56–7.

GUILLAIN-BARRÉ SYNDROME. Evidence mainly from case reports and uncontrolled studies favoured a causal relationship between vaccination with diphtheria and tetanus vaccines or single-antigen tetanus vaccines and Guillain-Barré syndrome. The data came primarily from immunocompromised patients.[1] However, a later analysis of active surveillance epidemiological studies of Guillain-Barré syndrome and tetanus vaccination history concluded that if an association exists, it must be extremely rare and not of public health significance.[2]

1. Stratton KR, *et al.* Adverse events associated with childhood vaccines other than pertussis and rubella: summary of a report from the Institute of Medicine. *JAMA* 1994; **271:** 1602–5.
2. Tuttle J, *et al.* The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health* 1997; **87:** 2045–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria and tetanus vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Imovax DT; Vacuna Doble; ***Austral.***: ADT; CDT†; ***Austria***: DiTe Anatoxal†; DT-reduct; Td-pur; ***Belg.***: Tedivax; ***Braz.***: Dif-Tet-All†; ***Canad.***: Td Adsorbed; ***Chile***: Imovax DT; ***Denm.***: DiTe Booster; ***Fin.***: DiTe Booster; ***Ger.***: Td-Impfstoff; Td-pur; Td-Rix; ***Gr.***: Anatoxal Di Te Berna; DT Vax; ***Hong Kong***: Diftet; Imovax DT†; ***India***: DT-Vac†; Dual Antigen; ***Irl.***: Diftavax†; ***Israel***: Imovax DT; ***Ital.***: Dif-Tet-All; Diftavax; Ditanrix; ***Malaysia***: Adsorbed DT Vaccine; ***Norw.***: DiTe Booster; ***NZ***: ADT; CDT; DiTe Anatoxal†; ***Philipp.***: Di Te Anatoxal†; Td-pur; ***Pol.***: DT; ***Port.***: Ditanrix; DiTe Booster; DT Vax; ***S.Afr.***: DT Vax†; ***Singapore***: ADT; CDT; ***Spain***: Anatoxal Te Di†; Diftavax; Ditanrix; DiTe Booster; ***Swed.***: DiTe Booster; ***Switz.***: Ditanrix†; Td-pur; ***Thai.***: Adsorbed DT Vaccine; Td-pur; ***Turk.***: Di Te Anatoxal; ***USA***: Decavac.

Multi-ingredient Preparations. ***Irl.***: DiTe Booster.

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria and Tetanus Vaccine (Adsorbed); Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content).

Diphtheria, Tetanus, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos y Haemophilus influenzae.

Profile

Combined adsorbed diphtheria, tetanus, and *Haemophilus influenzae* type b vaccines have been used in some countries for active immunisation of infants. For discussion of immunisation schedules see under Vaccines, p. 2373.3. For concern over the antigenicity of *Haemophilus influenzae* type b vaccine in combined vaccines, see under Haemophilus Influenzae Vaccines, Interactions, p. 2387.3.

Diphtheria, Tetanus, and Hepatitis B Vaccines

ATC — J07CA07.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, and hepatitis B vaccines have been used in some countries for active immunisation.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Diphtheria, Tetanus and Hepatitis B (rDNA) Vaccine (Adsorbed).

Diphtheria, Tetanus, and Pertussis Vaccines

DTP Vaccines; Vacunas de la difteria, el tétanos y la tos ferina.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus and Pertussis (Whole Cell) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis ex Cellulis Integris Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid on a mineral carrier to which a suspension of killed *Bordetella pertussis* has been added. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international

units of diphtheria toxoid, not less than 40 international units if the test is performed in *guinea-pigs*, or 60 international units if the test is performed in *mice*, of tetanus toxoid, and not less than 4 international units of the pertussis component per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTwP may be used on the label.

Ph. Eur. 8: (Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Sine Cellulis ex Elementis Praeparatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTaP may be used on the label.

Uses and Administration

Combined diphtheria, tetanus, and pertussis vaccines are used for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Combined adsorbed vaccines may be given by deep subcutaneous or intramuscular injection (vaccines with acellular pertussis components are for intramuscular injection only) in usual doses of 0.5 mL. In the USA, a vaccine with an acellular pertussis component (DTaP) is used as part of the recommended schedule for primary immunisation. Three doses are given at intervals of 2 months (the first preferably at 2 months of age), a fourth dose at least 6 months after the third, and a fifth dose at 4 to 6 years. Specially formulated tetanus toxoid, reduced diptheria toxoid, and acellular pertussis (Tdap) vaccines are licensed for use in persons aged from 10 or 11 years to 64 years of age; it is given to adolescents at 11 to 12 years of age.

Vaccines containing an acellular pertussis component are now preferred to those containing a whole-cell component (see Vaccine Development, p. 2408.3). The non-adsorbed type of combined diphtheria, tetanus, and pertussis vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Reviews.

1. Pichichero ME, *et al*. An adolescent and adult formulation combined tetanus, diphtheria and five-component pertussis vaccine. *Expert Rev Vaccines* 2006; **5:** 175–87.
2. Wilson TR. Update on adolescent immunization: review of pertussis and the efficacy, safety, and clinical use of vaccines that contain tetanus-diphtheria-acellular pertussis. *J Pediatr Health Care* 2006; **20:** 229–37.
3. Frampton JE, Keating GM. Reduced-antigen, combined diphtheria, tetanus, and acellular pertussis vaccine (Boostrix): a review of its use as a single-dose booster immunization. *BioDrugs* 2006; **20:** 371–89.
4. Murphy TV, *et al*. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; **57** (RR-4): 1–51.
5. Plosker GL. Combined, reduced-antigen content tetanus, diphtheria, and acellular pertussis vaccine (Boostrix): a review of its use as a single-dose booster immunization in individuals aged 10-64 years in the US. *BioDrugs* 2009; **23:** 253–67.
6. Li WC, *et al*. Boostrix: a reduced-dose acellular pertussis vaccine for use in adolescents and adults. *Expert Rev Vaccines* 2009; **8:** 1317–27.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1. See also under Diphtheria Vaccines, p. 2383.1, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

The incidence of local reactions and fever is reported to be lower with accelerated immunisation schedules than with former schedules that spread primary immunisation over 6 months. Local reactions and pyrexia occur less commonly after acellular pertussis vaccines than whole-cell pertussis vaccines, especially in children older than 6 months.

In infants with a personal or close family history of seizures, precautions should be taken to avoid pyrexia. See under Pertussis Vaccines for further details of precautions and contra-indications in individuals with a history of neurological problems.

Incidence of adverse effects. The incidence of local reactions is lower with diphtheria and tetanus vaccines combined with an acellular pertussis component (DTaP) than with a whole-cell pertussis component, and is similar to that after diphtheria and tetanus (DT) vaccines. Such reactions are generally mild and self-limiting. Rarely, high fever, persistent or inconsolable crying (possibly as a reaction to pain), hypotonic-hyporesponsive collapse, or short-lived convulsions (frequently febrile convulsions) may occur, and have been reported after both DT and DTaP vaccines with equal frequency. These reactions do not appear to have any long-term consequences. Rare but serious acute neurological complications including encephalopathy and prolonged seizures have been reported after vaccines with a whole-cell pertussis component (see Effects on the Nervous System, p. 2409.1) but the association could be coincidental. Epidemiological studies have shown that such events are exceedingly rare and only occasionally followed by long-term neurological damage. Analysis of these studies has been difficult but authorities in the UK and USA concluded that the evidence was insufficient for a link.

A causal relationship between DTP vaccination and sudden infant death syndrome (SIDS) has not been established and any temporal relationship is likely to be due to chance.[1,2] There is evidence that the risk of SIDS is lower in infants who have been vaccinated.[3]

Immediate anaphylactic reactions have been reported and are regarded as a contra-indication to further use of DTP vaccine. However, the appearance of a rash is not generally regarded as a contra-indication to further doses.

For further details concerning the contra-indications and precautions to be observed for pertussis-containing vaccines, see p. 2409.2.

1. Hoffman HJ, *et al*. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. *Pediatrics* 1987; **79:** 598–611.
2. Griffin MR, *et al*. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *N Engl J Med* 1988; **319:** 618–23.
3. Mitchell EA, *et al*. Immunisation and the sudden infant death syndrome. *Arch Dis Child* 1995; **73:** 498–501.

Interactions

As for vaccines in general, p. 2375.3.

For a report of a diminished immune response to *Haemophilus influenzae* conjugated vaccine when mixed with diphtheria, tetanus, and acellular pertussis vaccine, see Haemophilus Influenzae Vaccines, p. 2387.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adacel; Bustrix; Triacel; Vacuna Triple; ***Austral.***: Adacel; Boostrix; Infanrix; Tripacel†; ***Austria***: Boostrix; ***Belg.***: Boostrix; ***Braz.***: Vacina Acel Ads Contra Dif, Tet e Coq; Vacina Comb. Contra Dif.-Tet,-Pert. Acel; Vacina Comb. Contra Dift.-Tet.-Coq.Acel; ***Canad.***: Adacel; Boostrix; Tripacel; ***Chile***: Adacel; ***China***: Infanrix (英芬立适); ***Cz.***: Adacel; Boostrix; Infanrix; ***Denm.***: Di-Te-Ki-Booster; Triaxis; ***Fin.***: Boostrix; Di-Te-Kik†; Infanrix†; Triaxis; ***Ger.***: Boostrix; Covaxis; Infanrix; ***Gr.***: Anatoxal Di Te Per; DT Coq; Infanrix; Triaxis; ***Hong Kong***: Boostrix; Diftetkok; Infanrix†; Tripacel†; ***Hung.***: Boostrix; ***India***: Infanrix; Triple Antigen; Tripvac; ***Indon.***: Infanrix; Tripacel; ***Irl.***: Infanrix; Triaxis; ***Israel***: Acelluvax DTP; Adacel Polio; Adacel; Boostrix; Infanrix; Tripacel; ***Ital.***: Boostrix; Infanrix; ***Malaysia***: Adacel; Boostrix†; DTP Vaccine; Infanrix; ***Mex.***: Boostrix; ***Neth.***: Boostrix; Infanrix†; Triaxis; ***Norw.***: Boostrix; ***NZ***: Adacel; Boostrix; DiTePer Anatoxal†; Infanrix; Tripacel†; Triple Antigen; ***Philipp.***: Adacel; Boostrix; DPT, DT COQ; Infanrix; Tripacel†; Tripavac; ***Pol.***: Boostrix; DT Coq†; DTaP; DTP; Infanrix DTPa; Tripacel; ***Port.***: Boostrix; Infanrix; ***Rus.***: Infanrix (Инфанрикс); ***S.Afr.***: DTP-Merieux†; Infanrix DTPa; ***Singapore***: Boostrix; DTP; Infanrix; Tripacel†; ***Spain***: Boostrix; Infanrix; Triaxis; ***Swed.***: Boostrix; Infanrix; Triaxis; ***Switz.***: Boostrix; ***Thai.***: Adacel; Boostrix; DTCoq/DTP†; DTP Vaccine; Infanrix; Tripacel†; ***Turk.***: Acelluvax DTP†; Di Te Per Anatoxal; Infanrix DTPa†; Tripacel; ***UK***: Trivax-AD; ***Ukr.***: Boostrix (Бустрикс); Infanrix (Инфанрикс); ***USA***: Adacel; Boostrix; Daptacel; Infanrix; Tripedia.

Multi-ingredient Preparations. ***Irl.***: Boostrix.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Diphtheria, Tetanus and Pertussis (Whole Cell) Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y Haemophilus influenzae.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product may be presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

Combined adsorbed diphtheria, tetanus, whole-cell or acellular pertussis, and *Haemophilus influenzae* type b vaccines are available in some countries for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p. 2373.3. Some combined vaccines are not licensed for use in primary immunisation regimens because of concerns over the response to the *Haemophilus influenzae* type b component (see under Interactions of Haemophilus Influenzae Vaccines, p. 2387.3).

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, above, Haemophilus Influenzae Vaccines, p. 2387.3, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actacel; ***Austral.***: Infanrix Hib; ***Braz.***: Vacina Comb. Contra Dif.-Tet,-Pert. Acel e HIB; ***Chile***: Actacel; Tetract-HIB; ***China***: Infanrix + Hib (英芬四联); ***Cz.***: Infanrix Hib; Tetract-HIB†; ***India***: Easy-4; ***Indon.***: Infanrix Hib; Tetract-HIB; ***Irl.***: Infanrix Hib; ***Israel***: Actacel; Infanrix Hib; Tetract-HIB†; ***Malaysia***: Infanrix Hib; ***NZ***: Infanrix Hib; ***Philipp.***: Infanrix IPV + HIB; Tetract-HIB; ***Port.***: Infanrix Hib; ***S. Afr.***: Actacel†; Combact-HIB†; ***Singapore***: Actacel†; Infanrix Hib; Tetract-HIB†; ***Spain***: Infanrix Hib†; ***Thai.***: Actacel†; Tetract-HIB†; ***Turk.***: Tetract-HIB; ***USA***: TriHIBit†; ***Venez.***: Vacuna Tetravalente.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Haemophilus Type b Conjugate Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Haemophilus Influenzae, and Hepatitis B Vaccines

ATC — J07CA11.

Profile

Combined diphtheria, tetanus, pertussis, *Haemophilus influenzae*, and hepatitis B vaccines are available in some countries for active immunisation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tritanrix HB-HIB; ***Chile***: Quinvaxem; ***Cz.***: Quintanrix†; ***India***: Easy-5; ***Mex.***: Tritanrix HB + Hiberix; ***Neth.***: Quintanrix†; ***Philipp.***: Quinvaxem; ***Thai.***: Quinvaxem.

Multi-ingredient Preparations. ***NZ***: Tritanrix HB + HIB†.

Diphtheria, Tetanus, Pertussis, and Hepatitis B Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y la hepatitis B.
ATC — J07CA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, pertussis, and hepatitis B vaccines are available in some countries for active immunisation.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, and hepatitis B vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Infanrix HepB†; ***Braz.***: Vacina Comb. Contra Dif.-Tet.-Pert.Acel e Hepat.B; ***China***: Yi Tai (益泰); ***Cz.***: Tritanrix HepB; ***Gr.***: Infanrix HepB; ***India***: Tritanrix HB; ***Indon.***: Tritanrix HB†; ***Malaysia***: Tritanrix HB; ***Mex.***: Tritanrix HB; ***Neth.***: Tritanrix-HepB; ***NZ***: Infanrix HepB; ***Philipp.***: Tritanrix HB; ***Port.***: Tritanrix HepB; ***S.Afr.***: Tritanrix HB; ***Spain***: Tritanrix HB†; ***Thai.***: DTP-HB; Tritanrix HB; ***Turk.***: Tritanrix HB.

Multi-ingredient Preparations. ***India***: Ecovac; ***Irl.***: Tritanrix HB.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis, and Haemophilus Influenzae Vaccines

ATC — J07CA09.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum, Hepatitidis B (ADNr), Poliomyelitidis Inactivatum et Haemophili Stirpe b Coniugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, hepatitis B surface antigen, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product may be presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before or during use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Profile

A combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and *Haemophilus influenzae* type b vaccine is available in some countries for active immunisation.

References.
1. Curran MP, Goa KL. DTPa-HBV-IPV/Hib vaccine (Infanrix hexa™). *Drugs* 2003; **63:** 673–82.
2. Dhillon S. DTPa-HBV-IPV/Hib Vaccine (Infanrix hexa™): a review of its use as primary and booster vaccination. *Drugs* 2010; **70:** 1021–58.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, heptitis B, poliomyelitis, and haemophilus influenzae vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Infanrix Hexa; ***Austral.***: Infanrix Hexa; ***Austria***: Infanrix Hexa; ***Belg.***: Infanrix Hexa; ***Braz.***: Infanrix Hexa†; Vacina Adsorvida Contra Dif, Tet, Coq Acel, Polio Inat Hepat B (Rec) e Hib Conj†; Vacina Comb. Contra Dif.-Tet,-Pert. Acel Hepat.B r-DNA, Polio Inat e HIB; ***Canad.***: Infanrix Hexa; ***Chile***: Hexavac†; Infanrix Hexa; ***Cz.***: Infanrix Hexa; ***Fr.***: Infanrixhexa; ***Ger.***: Infanrix Hexa; ***Gr.***: Hexavac; Infanrix Hexa; ***Hong Kong***: Infanrix Hexa; ***Hung.***: Hexavac†; ***Irl.***: Infanrix Hexa; ***Israel***: Infanrix Hexa; ***Ital.***: Infanrix Hexa; ***Malaysia***: Infanrix Hexa; ***Mex.***: Infanrix Hexa; ***Neth.***: Infanrix Hexa; ***NZ***: Infanrix Hexa; ***Philipp.***: Infanrix Hexa; ***Pol.***: Infanrix Hexa; ***Port.***: Infanrix Hexa; ***S.Afr.***: Infanrix Hexa; ***Singapore***: Infanrix Hexa; ***Spain***: Infanrix Hexa; ***Swed.***: Infanrix Hexa; ***Switz.***: Infanrix Hexa; ***Thai.***: Infanrix Hexa; ***Turk.***: Infanrix Hexa; ***Ukr.***: Infanrix Hexa (Инфанрикс Гекса); ***Venez.***: Infanrix Hexa; Vacuna Conjugada Hexavalente (Hexaca).

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, and Poliomyelitis Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y la poliomielitis.

ATC — J07CA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Poliomyelitidis Inactivatum Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Whole Cell) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis ex Cellulis Integris et Poliomyelitidis Inactivatum Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, an inactivated suspension of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTwP/IPV may be used on the label.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Poliomyelitidis Inactivatum, Antigeni-o(-is) Minutum, Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral adsorbent such as aluminium hydroxide or hydrated aluminium phosphate. The amount of diphtheria toxoid per single human dose is reduced compared with vaccines generally used for primary vaccination; the amounts of tetanus toxoid and pertussis components may also be reduced. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that dTaP/IPV may be used on the label.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine is used for active immunisation. For discussion of immunisation schedules see under Vaccines, p. 2373.3.

In the UK it is used as part of the recommended schedule and is given by intramuscular injection in a single dose of 0.5 mL as a booster at pre-school age (3 years 4 months to 5 years). It is used similarly in the USA. It is not suitable for primary immunisation.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, p. 2384.1, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, and poliomyelitis vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tetraxim; ***Austral.***: Adacel Polio; Boostrix IPV; Infanrix IPV; Quadracel; ***Austria***: Boostrix Polio; Repevax; Tetravac; ***Belg.***: Boostrix Polio; Infanrix IPV; Tetravac; ***Braz.***: Vacina Acel Ads Contra Dif, Tet e Coq Pol; Vacina Ads Cont Dift, Tet, Coq Acel Polio; ***Canad.***: Adacel-Polio; Quadracel; ***Cz.***: Adacel Polio; Boostrix Polio; Infanrix Polio; ***Denm.***: Di-Te-Ki-Pol; Infanrix Tetra; ***Fin.***: Boostrix Polio; Di-Te-Ki-Pol†; Infanrix Polio; Tetravac; ***Fr.***: Boostrixtetra; Infanrixtetra; Repevax; Tetravac; ***Ger.***: Boostrix Polio; Repevax; ***Gr.***: Boostrix Polio; Infanrix Tetra; Repevax; Tetracoq; Tetravac; ***Hong Kong***: Adacel Polio; Boostrix Polio; Infanrix IPV; Tetraxim; ***Hung.***: Boostrix Polio; Infanrix IPV; Tetraxim; ***Irl.***: Boostrix IPV; Infanrix IPV; Tetravac; ***Israel***: Boostrix Polio; Infanrix IPV; Tetracoq†; ***Ital.***: PolioBoostrix; PolioInfanrix; Tetravac; ***Jpn***: Quattrovac; Tetrabik; ***Malaysia***: Infanrix IPV; Tetraxim; ***Mex.***: Infanrix IPV; ***Neth.***: Boostrix Polio; Infanrix IPV; Triaxis Polio; ***Norw.***: Boostrix Polio; Repevax; Tetravac; ***NZ***: Adacel Polio; Boostrix IPV; Infanrix IPV; Quadracel; ***Philipp.***: Tetracoq†; Tetraxim; ***Pol.***: Boostrix Polio; DTaP-IPV; ***Port.***: Boostrix Polio; Infanrix Tetra; Repevax; Tetravac; ***S.Afr.***: Adacel Quadra; Tetraxim†; ***Singapore***: Boostrix Polio; ***Swed.***: Boostrix Polio; Infanrix Polio; Tetravac; ***Switz.***: Boostrix Polio; Infanrix DTPa-IPV; Tetravac; ***Thai.***: Adacel Polio; Boostrix Polio; Infanrix IPV; Tetraxim; ***Turk.***: Tetracoq; Tetraxim; ***UK***: Infanrix IPV; Repevax; ***Ukr.***: Infanrix IPV (Инфанрикс ИПВ); ***USA***: Kinrix; ***Venez.***: Vacuna Adsorbida Tetravalente.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content); Diphtheria, Tetanus, Pertussis (Whole Cell) and Poliomyelitis (Inactivated) Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos, la tos ferina, la poliomielitis y Haemophilus influenzae.

ATC — J07CA06.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum Poliomyelitidis Inactivatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product is presented either as a pentavalent liquid formulation in the same container, or as a tetravalent liquid formulation with the freeze-dried Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTaP/IPV/Hib may be used on the label.

Ph. Eur. 8: (Diphtheria, Tetanus, Pertussis (Whole Cell), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis ex Cellulis Integris, Poliomyelitidis Inactivatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, an inactivated suspension of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product is presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that DTwP/IPV/Hib may be used on the label.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* type b vaccine is used for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

In the UK it is used as part of the recommended schedule for primary immunisation. It is given by intramuscular injection in usual doses of 0.5 mL; three doses are given at intervals of one month, starting preferably at 2 months of age. Although it is not licensed for use after a child's fourth birthday, the national schedule considers it may be used up to the age of 10 years.

In the USA, it is licensed for use in infants and children from 6 weeks to 4 years of age and may be given as part of the recommended immunisation schedule at ages 2, 4, 6, and 15 to 18 months. It is not indicated for the booster dose at 4 to 6 years of age; however, if it is given accidentally to children 5 years and older, it may be counted as a valid dose.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, p. 2384.1, Haemophilus Influenzae Vaccines, p. 2387.3, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Premature neonates. In an observational study[1] of 78 very-low-birth-weight premature neonates given a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine before hospital discharge, increased incidences of apnoea, bradycardia, desaturation, or oxygen requirement occurred in 47% overall within 24 to 48 hours of vaccination. All neonates with increased events returned to baseline within 48 to 72 hours and there was no detrimental impact on clinical course. The authors considered that, although monitoring and appropriate intervention were required, delaying vaccination was not warranted, a view in line with UK and USA official recommendations (see p. 2375.3).

1. Pfister RE, *et al.* Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. *J Pediatr* 2004; **145:** 58–66.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pentaxim; ***Austral.***: Pediacel†; Poliacel†; ***Braz.***: Poliacel; Vacina Acel Ads Contra Dif, Tet, Coq e Polio Inat Comb C/Vac Conj Contra Hib†; Vacina Comb. Contra Dif.-Tet,-Pert. Acel, Polio Inat e HIB; ***Canad.***: Pediacel; Pentacel; ***Chile***: Pentact-HIB†; ***China***: Pentaxim (潘太欣); ***Cz.***: Infanrix IPV + Hib; Pediacel; ***Denm.***: Di-Te-Ki-Pol/Act-Hib; ***Fin.***: Infanrix Polio + Hib; Pentavac; ***Fr.***: Infanrixquinta; Pentavac; ***Ger.***: Infanrix IPV + Hib; Pentavac; ***Gr.***: Infanrix IPV + Hib; Pentavac; ***Hong Kong***: Infanrix IPV + Hib; Pediacel; Pentact-HIB†; Pentaxim; ***Hung.***: Infanrix IPV + Hib; Pentaxim; ***Indon.***: Pediacel; ***Irl.***: Infanrix IPV + Hib; Pediacel; Pentavac; ***Israel***: Infanrix Polio IPV - Hib; Pediacel; Pentact-HIB; Poliacel-Act-Hib; ***Ital.***: Pentavac; ***Malaysia***: Infanrix IPV + Hib; Pediacel; Pentaxim; ***Mex.***: Infanrix IPV + Hib; Pediacel; ***Neth.***: DKTP-Hib†; Infanrix IPV + Hib; Pediacel; ***Norw.***: Infanrix Polio + Hib; ***NZ***: Infanrix IPV + Hib; Poliacel†; ***Philipp.***: Pentact-HIB†; Pentaxim; ***Pol.***: Infanrix IPV + Hib; Pentaxim; ***Port.***: Infanrix IPV + Hib; Pediacel; Pentavac; ***S.Afr.***: Pentaxim; ***Singapore***: Infanrix IPV + Hib; Pediacel; ***Spain***: Infanrix IPV + Hib; Pentavac; ***Swed.***: Infanrix Polio + Hib; Pentavac; ***Switz.***: Infanrix DTPa-IPV+Hib; Pentavac; ***Thai.***: Infanrix IPV + Hib; Pediacel; Pentaxim; ***Turk.***: Infanrix IPV-HIB†; Pentact-HIB; Pentaxim; Poliacel; ***UK***: Infanrix IPV + Hib; Pediacel; ***USA***: Pentacel; ***Venez.***: Infanrix IPV + Hib; Vacuna Adsorbida Pentavalente.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Whole Cell), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hepatitis B Vaccines

ATC — J07CA12.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and hepatitis B vaccine is available in some countries for active immunisation of children.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria, Tetanus, and Pertussis Vaccines, p. 2384.1, Hepatitis B Vaccines, p. 2390.3, Pertussis Vaccines, p. 2409.1, and Tetanus Vaccines, p. 2421.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Infanrix Penta; ***Cz.***: Infanrix Penta; ***Gr.***: Infanrix Penta; ***Irl.***: Infanrix Penta; ***Ital.***: Infanrix Penta†; ***Neth.***: Infanrix Penta; ***NZ***: Infanrix Penta; ***Pol.***: Infanrix Penta; ***Port.***: Infanrix Penta; ***USA***: Pediarix.

Diphtheria, Tetanus, and Poliomyelitis Vaccines

Vacunas de la difteria, el tétanos y la poliomielitis.

ATC — J07CA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Diphtheria, Tetanus and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigens(s) Content); Vaccinum Diphtheriae, Tetani et Poliomyelitidis Inactivatum, Antigeni-o(-is) Minutum, Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, suitable strains of human polioviruses types 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral adsorbent such as aluminium hydroxide or hydrated aluminium phosphate. The amount of diphtheria toxoid per single human dose is reduced compared with vaccines generally used for primary vaccination; the amount of tetanus toxoid may also be reduced. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

A combined diphtheria, tetanus, and poliomyelitis (inactivated) vaccine is used for active immunisation. For discussion of immunisation schedules see under Vaccines, p. 2373.3.

In the UK it is used as part of the recommended schedule and is given by intramuscular injection in a single dose (usually 0.5 mL) as a booster at the ages of 13 to 18 years. It is not licensed for primary immunisation.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Diphtheria Vaccines, p. 2383.1, Diphtheria and Tetanus Vaccines, p. 2383.2, and Tetanus Vaccines, p. 2421.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Revaxis; ***Belg.***: Revaxis; ***Canad.***: Td-Polio; ***Fr.***: DT Polio†; Revaxis; ***Ger.***: Revaxis; Td-Virelon†; ***Gr.***: Revaxis; ***Hung.***: Dultavax; ***Irl.***: Revaxis; ***Israel***: Dultavax; ***Ital.***: Revaxis; ***Neth.***: Revaxis; ***Pol.***: Dultavax; ***Port.***: Revaxis; ***S.Afr.***: Td-Polio†; ***Switz.***: Revaxis; Td-Virelon†; ***UK***: Revaxis.

Pharmacopoeial Preparations

Ph. Eur.: Diphtheria, Tetanus, and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content).

Endotoxin Antibodies

Anticuerpos antiendotoxinas.

Profile

Antibodies against the endotoxin of Gram-negative bacteria have been tried as adjunctive therapy for the treatment and prevention of Gram-negative bacteraemia and shock.

Early preparations consisted of antisera prepared from the sera of donors immunised with *Escherichia coli* J5; these were superseded by human and murine IgM monoclonal antibodies. Nebacumab (HA-1A) is a human monoclonal IgM antibody that binds specifically to the lipid A domain of endotoxin. Lipid A in the circulation releases tumour necrosis factor and other cytokines from macrophages and endothelial cells which may ultimately culminate in physiological effects such as multiple organ failure. Despite early promising results of clinical studies the safety of nebacumab in patients without Gram-negative septicaemia was questioned and the product was withdrawn.

A murine monoclonal IgM antibody (edobacomab; E5) has also undergone clinical studies although results have been disappointing.

Epstein-Barr Virus Vaccines

Vacunas del virus de Epstein-Barr.

Profile

Several Epstein-Barr virus vaccines are under investigation for active immunisation against infectious mononucleosis and post-transplant lymphoproliferative disorders.

Epstein-Barr virus is a herpesvirus that is ubiquitous in the adult population. It only causes clinical illness where primary infection occurs in adolescence or adulthood, when it prompts the symptoms of infectious mononucleosis in about 50% of cases. More than 90% of the world's population, however, carry the virus as a lifelong latent infection of B-lymphocytes and, as a result, Epstein-Barr virus can also be associated with malignancies including lymphoproliferative diseases, Burkitt's lymphoma, gastric carcinoma, oral hairy leucoplakia, nasopharyngeal carcinoma, and Hodgkin's disease.

Vaccines against Epstein-Barr virus infection are under investigation[1-3] and the main focus has been towards the development of a vaccine to prevent primary infection or to minimise its consequences, namely infectious mononucleosis and post-transplant lymphoproliferative disease, rather than towards the malignancies associated with the virus which occur in relatively fewer patients. Two main approaches have been adopted, the first of which seeks to exploit the major envelope glycoprotein of the virus, gp340, because of its ability to induce neutralising antibodies. This vaccine may prevent infectious mononucleosis by moderating the initial viral replication and spread during primary infection, thereby curtailing the cytotoxic T-lymphocyte response to lytic antigens that would otherwise invoke the immunological processes responsible for clinical symptoms. The second approach is based on the induction of cytotoxic T-cells specific to Epstein-Barr virus, thereby aiming to reduce the clinical symptoms of infectious mononucleosis rather than to prevent primary infection.

Potential future vaccines for malignancies associated with Epstein-Barr virus are likely to be therapeutic rather than preventative and to exploit the presence of the virus in tumour cells; alternatively they may be focussed on tumour antigens not encoded by Epstein-Barr virus.[1,2]

1. Moss DJ, *et al.* Candidate vaccines for Epstein-Barr virus. *BMJ* 1998; **317:** 423–4.
2. Macsween KF, Crawford DH. Epstein-Barr virus—recent advances. *Lancet Infect Dis* 2003; **3:** 131–40.
3. Lockey TD, *et al.* Epstein-Barr virus vaccine development: a lytic and latent protein cocktail. *Front Biosci* 2008; **13:** 5916–27.

Escherichia Coli Vaccines

Vacunas de Escherichia coli.

Profile

Vaccines against enterotoxigenic strains of *Escherichia coli* are under investigation. Vaccine candidates include toxoids, inactivated whole bacteria, purified surface antigens, and live oral vaccines.

Infectious diarrhoea remains a major source of morbidity and mortality in the world and a significant proportion is caused by pathogenic strains of *Escherichia coli* While it is considered feasible to develop effective vaccines against *E. coli*, at present there are no such vaccines available. Current approaches against enteropathogenic *E. coli* (EPEC) and enterohaemorrhagic *E. coli* (EHEC) have focussed on three main areas: the EPEC and EHEC proteins involved in colonisation of the intestine, the EHEC O157-specific side-chain of lipopolysaccharides, and the immunogenicity of Shiga toxin produced by the organism. While vaccination against EPEC has to be directed towards susceptible human populations, there are two possible approaches with regard to EHEC, namely vaccination of either humans or the animal reservoir, cattle. Studies of vaccine candidates are ongoing *in vitro*, in *animal* models, and in healthy subjects. For both pathogens, however, the development of vaccines would not in itself serve to eradicate the spread of infections

and would need to be accompanied by public health campaigns to increase food hygiene and monitoring of water supplies and facilities.[1]

Enterotoxigenic *E. coli* (ETEC) is a major cause of travellers' diarrhoea. A phase II placebo-controlled study[2] found that a vaccine containing heat-labile enterotoxin from ETEC given as a skin patch (2 patches applied 2 to 3 weeks apart), reduced the risk of moderate to severe travellers' diarrhoea by 75% and severe diarrhoea by 84%. In vaccinated travellers who got diarrhoea, the illness was significantly shorter and milder.

Further references.[3-8]

1. Horne C, *et al*. Current progress in enteropathogenic and enterohemorrhagic Escherichia coli vaccines. *Expert Rev Vaccines* 2002; **1:** 483–93.
2. Frech SA, *et al*. Use of a patch containing heat-labile toxin from Escherichia coli against travellers' diarrhoea: a phase II, randomised, double-blind, placebo-controlled field trial. *Lancet* 2008; **371:** 2019–25.
3. Boedeker EC. Vaccines for enterotoxigenic Escherichia coli: current status. *Curr Opin Gastroenterol* 2005; **21:** 15–9.
4. Steffen R, *et al*. Vaccination against enterotoxigenic Escherichia coli, a cause of travelers' diarrhea. *J Travel Med* 2005; **12:** 102–7.
5. Walker RI, *et al*. Ad Hoc ETEC Technical Expert Committee. Analysis of strategies to successfully vaccinate infants in developing countries against enterotoxigenic E. coli (ETEC) disease. *Vaccine* 2007; **25:** 2545–66.
6. Goldwater PN. Treatment and prevention of enterohemorrhagic Escherichia coli infection and hemolytic uremic syndrome. *Expert Rev Anti Infect Ther* 2007; **5:** 653–63.
7. Serna A, Boedeker EC. Pathogenesis and treatment of Shiga toxin-producing Escherichia coli infections. *Curr Opin Gastroenterol* 2008; **24:** 38–47.
8. Svennerholm AM, Tobias J. Vaccines against enterotoxigenic Escherichia coli. *Expert Rev Vaccines* 2008; **7:** 795–804.

Gas-gangrene Antitoxins

Antitoxinas de la gangrena gaseosa.
ATC — J06AA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Gas-gangrene Antitoxin (Novyi); Immunoserum Gangraenicum (Clostridium Novyi)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium novyi*. It has a potency of not less than 3750 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Nov/Ser may be used on the label.

The BP 2014 gives Gas-gangrene Antitoxin (Oedematiens) as an approved synonym.

Ph. Eur. 8: (Gas-gangrene Antitoxin (Perfringens); Immunoserum Gangraenicum (Clostridium Perfringens)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium perfringens*. It has a potency of not less than 1500 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Perf/Ser may be used on the label.

Ph. Eur. 8: (Gas-gangrene Antitoxin (Septicum); Immunoserum Gangraenicum (Clostridium Septicum)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium septicum*. It has a potency of not less than 1500 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Sep/Ser may be used on the label.

Ph. Eur. 8: (Gas-gangrene Antitoxin, Mixed; Immunoserum Gangraenicum Mixtum). It is prepared by mixing Gas-gangrene Antitoxin (Novyi), Gas-gangrene Antitoxin (Perfringens), and Gas-gangrene Antitoxin (Septicum) in appropriate quantities. It has a potency of not less than 1000 international units/mL of Gas-gangrene Antitoxin (Novyi), not less than 1000 international units/mL of Gas-gangrene Antitoxin (Perfringens), and not less than 500 international units/mL of Gas-gangrene Antitoxin (Septicum). It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Gas/Ser may be used on the label.

Profile

Gas-gangrene antitoxins have been used for the treatment of gas gangrene and for prophylaxis in patients at risk after injury. They are now seldom used and have been superseded by antibacterials. Monovalent gas-gangrene antitoxins have been little used in practice owing to the difficulty of rapidly identifying the infecting organism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Aggs.

Pharmacopoeial Preparations

Ph. Eur.: Gas-gangrene Antitoxin (Novyi); Gas-gangrene Antitoxin (Perfringens); Gas-gangrene Antitoxin (Septicum); Mixed Gas-gangrene Antitoxin.

Gonococcal Vaccines

Gonorrhoea Vaccines; Vacunas de la gonorrea.

Profile

Experimental gonococcal vaccines, produced usually from the surface antigens of *Neisseria gonorrhoeae*, have been investigated.

Haemophilus Influenzae Vaccines

Vacunas de Haemophilus influenzae.
ATC — J07AG01 (B, purified antig. conjugate).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Haemophilus type b Conjugate Vaccine; Vaccinum Haemophili Stirpe B Conjugatum). A liquid or freeze-dried preparation of a polysaccharide, polyribosylribitol phosphate (PRP), derived from a suitable strain of *Haemophilus influenzae* type b, covalently bound to a carrier protein. The carrier protein, when conjugated to PRP, is capable of inducing a T-cell-dependent B-cell immune response to the polysaccharide. Carrier proteins currently approved are diphtheria toxoid, tetanus toxoid, CRM 197 diphtheria protein, and meningococcal group B outer membrane protein (OMP). It should be stored at 2 degrees to 8 degrees and protected from light.

The BP 2014 states that Hib may be used on the label.

Uses and Administration

Haemophilus influenzae (Hib) vaccines are used for active immunisation against *Haemophilus influenzae* type b infections. Vaccines are prepared from the capsular polysaccharide of *H. influenzae* type b and immunogenicity, especially in young children, is improved by linking the polysaccharide to a protein carrier to form a conjugate vaccine.

Different proprietary vaccines may be conjugated to differing proteins but are generally regarded as interchangeable.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria Toxoid Conjugate) (PRP-D) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to diphtheria toxoid.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (HbOC) consists of oligosaccharides derived from the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to a non-toxic variant of diphtheria toxin isolated from *Corynebacterium diphtheriae*.

Haemophilus Influenzae Conjugate Vaccine (Meningococcal Protein Conjugate) (PRP-OMP or PRP-OMPC) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to an outer membrane protein complex of *Neisseria meningitidis* group B.

Haemophilus Influenzae Conjugate Vaccine (Tetanus Toxoid Conjugate) (PRP-T) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to tetanus toxoid.

For primary immunisation either combined vaccines or single-component Haemophilus influenzae vaccines may be used.

In the UK, a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine (p. 2385.3) is used. Children over 1 year of age and under 10 years of age who have not been immunised against *Haemophilus influenza* or have not completed a primary vaccination course of diphtheria, tetanus, pertussis, or polio, should be given 3 doses of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine. Those who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio, should receive a single dose of a combined *Haemophilus influenzae* and meningococcal C conjugate vaccine. Routine use in children older than 10 years or adults is not recommended in the UK, but asplenic children (over 10 years of age) and adults who have not been previously immunised should receive two doses of combined *Haemophilus influenzae* and meningococcal C conjugate vaccine, two months apart.

In the USA, primary immunisation is also carried out in conjunction with diphtheria, tetanus, and pertussis vaccination. If a meningococcal protein conjugate vaccine is used, only 2 doses are given for the primary course. A reinforcing dose using any of the available vaccines is given at 12 to 15 months of age.

Where compatibility has been shown, Hib vaccines may be mixed immediately before use with diphtheria, tetanus, and pertussis vaccines (but see Interactions, below).

References.

1. WHO. WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. *Wkly Epidem Rec* 2006; **81:** 445–52. Also available at: http://www.who.int/immunization/REH_47_8_pages.pdf (accessed 23/06/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Erythema multiforme and transient cyanosis of the lower limbs have been reported rarely in children receiving haemophilus influenzae-containing vaccines.

Effects on the nervous system. Guillain-Barré syndrome has been reported[1] after vaccination with haemophilus influenzae conjugate vaccines in a small number of infants. In one report, onset of symptoms occurred within 1 week of vaccination of 3 infants with an haemophilus influenzae conjugate vaccine (diphtheria toxoid conjugate). However, a causal relationship has not yet been established.

1. D'Cruz OF, *et al*. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) after immunization with Haemophilus influenzae type b conjugate vaccine. *J Pediatr* 1989; **115:** 743–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies haemophilus influenzae vaccines as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Antineoplastics. Haemophilus influenzae infection occurred in a child who had received antineoplastic therapy despite having completed a primary course of immunisation before the neoplasia was diagnosed.[1] A subsequent booster dose produced an adequate antibody response. Antineoplastic therapy may have impaired the T-cell response to infection.

1. Jenkins DR, *et al*. Childhood neoplasia and Haemophilus influenzae type b vaccine failure. *Lancet* 1996; **348:** 131.

Diphtheria, tetanus, and pertussis vaccines. Some haemophilus influenzae conjugated vaccines may be mixed with diphtheria, tetanus, and pertussis vaccines before use without adversely affecting the immunogenicity of the components[1,2] although there has also been a report of reduced immunogenicity.[3] Manufacturers may provide further information on compatibility. The safety and efficacy of giving a conjugate haemophilus influenza vaccine with other childhood vaccines has been reviewed.[4,5]

1. Miller MA, *et al*. Safety and immunogenicity of PRP-T combined with DTP: excretion of capsular polysaccharide and antibody response in the immediate post-vaccination period. *Pediatrics* 1995; **95:** 522–7.
2. Mulholland EK, *et al*. The use of Haemophilus influenzae type b-tetanus toxoid conjugate vaccine mixed with diphtheria-tetanus-pertussis vaccine in Gambian infants. *Vaccine* 1996; **14:** 905–9.
3. Eskola J, *et al*. Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of Haemophilus influenzae type b conjugated vaccine. *Lancet* 1996; **348:** 1688–92.
4. Knuf M, *et al*. Immunogenicity of routinely used childhood vaccines when coadministered with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV). *Pediatr Infect Dis J* 2009; **28**(4 suppl): S97–S108.
5. Chevallier B, *et al*. Safety and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) when coadministered with routine childhood vaccines. *Pediatr Infect Dis J* 2009; **28**(4 suppl): S109–S118.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hiberix; PedvaxHIB; ***Austria***: Act-HIB; ***Belg.***: Act-HIB; ***Braz.***: PedvaxHIB; Vacina Conj Com Proteina Tetanica HIB; Vacina Conj Contra Haemophilus Influenzae Tipo B; ***Canad.***: Act-HIB; PedvaxHIB; ***Chile***: Act-HIB; ***China***: Act-HIB (安尔宝); He Er Bei (阿儿贝); Hiberix (贺新立适); PedvaxHIB (普泽欣); ***Cz.***: Act-HIB†; Hiberix; ***Denm.***: Act-HIB; ***Fin.***: Act-HIB; Hiberix; ***Fr.***: Act-HIB; ***Gr.***: Act-HIB; Hiberix; HibTITER; ***Hong Kong***: Act-HIB; Hiberix; Pedvax-HIB†; ***Hung.***: Act-HIB; ***India***: Act-HIB; Hiberix; HIBest; HibTITER; Vaxim HIB†; ***Indon.***: Act-HIB; Hiberix; PedvaxHIB; ***Irl.***: Act-HIB†; Hiberix†; ***Israel***: Act-HIB; Hiberix; ***Ital.***: Act-HIB; Hiberix; Vaxem Hib; ***Malaysia***: Hiberix; ***Mex.***: PedvaxHIB; ***Neth.***: Act-HIB; Hiberix; ***Norw.***: Act-HIB; ***NZ***: Act-HIB; Hiberix; ***Philipp.***: Act-HIB; Hiberix; Vaxem Hib; ***Pol.***: Act-HIB; Hiberix; HibTITER; PedvaxHIB; ***Port.***: Act-HIB; Hiberix; ***Rus.***: Hiberix (Хиберикс); ***S.Afr.***: Act-HIB†; Hiberix; ***Singapore***: Act-HIB†; Hiberix; HibTITER; ***Spain***: Hiberix; ***Swed.***: Act-HIB; ***Switz.***: Hiberix; ***Thai.***: Act-HIB; Hiberix; PedvaxHIB; Vaxem Hib;

The symbol † denotes a preparation no longer actively marketed

Turk.: Act-HIB; Hiberix; PedvaxHIB; ***UK***: Hiberix†; ***USA***: Act-HIB; Hiberix; OmniHIB; PedvaxHIB; ***Venez.***: Hiberix.

Pharmacopoeial Preparations
Ph. Eur.: Haemophilus Type b Conjugate Vaccine.

Haemophilus Influenzae and Hepatitis B Vaccines

Vacunas de Haemophilus influenzae y la hepatitis B.
ATC — J07CA08.

Uses and Administration

Haemophilus influenzae type b (Hib) conjugate and hepatitis B vaccines are available in some countries for active immunisation as part of the primary immunisation of infants born to HBsAg-negative mothers. In the USA, an *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine is used. It is given in a schedule of 3 doses, 0.5 mL being given intramuscularly at 2 months, 4 months, and 12 to 15 months of age. Use in infants less than 6 weeks old is not recommended.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Comvax; ***Cz.***: Procomvax†; ***Gr.***: Procomvax; ***Irl.***: Procomvax†; ***Mex.***: Comvax; ***Neth.***: Procomvax†; ***NZ***: Comvax; ***Pol.***: Procomvax†; ***Port.***: Procomvax†; ***Singapore***: Comvax; ***USA***: Comvax.

Haemophilus Influenzae and Meningococcal Vaccines

Pharmacopoeias. *Br.* includes a monograph.

BP 2014: (Haemophilus Type b and Meningococcal Group C Conjugate Vaccine). It is prepared from purified polysaccharides derived from a suitable strain of *Neisseria meningitidis* group C and from a suitable strain of *Haemophilus influenzae*, type b covalently bound to a carrier protein. A suitable adjuvant, a suitable antimicrobial preservative, and a stabiliser may be added to the bulk conjugates of the components. The product is presented as a combined lyophilisate of the haemophilus type b and meningococcal group C components together with the solvent in a separate container. The final product is prepared by mixing the contents of the two containers immediately before use. The label may state Hib/MenC.

Profile

A combined *Haemophilus influenza* type b and meningococcal C conjugate vaccine is available for active immunisation in some countries; in the UK a single dose may be given to children between 1 and 10 years of age who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio. A booster dose of the combination vaccine is recommended at 12 months for children who have received a complete primary course of three *Haemophilus influenza* type b-containing vaccines. Two doses given 2 months apart may be given to asplenic children (over 10 years of age) or adults who have not been previously immunised.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Menitorix; ***UK***: Menitorix; ***USA***: MenHibrix.

Pharmacopoeial Preparations
BP 2014: Haemophilus Type b and Meningococcal Group C Conjugate Vaccine.

Haemophilus Influenzae and Poliomyelitis Vaccines

ATC — J07CA04.

Profile

Combined haemophilus influenzae type b conjugate and inactivated poliomyelitis vaccines have been used in some countries for active immunisation of infants.

Haemorrhagic Fever with Renal Syndrome Vaccines

HFRS Vaccine; Vaccinum Haemorrhagia Febris cum Renis Sindronum; Vacunas de la fiebre de Korin; Vacunas de la fiebre hemorrágica con síndrome renal; Vacunas de la fiebre hemorrágica de Corea y Extremo Oriente; Vacunas de la fiebre renal epidémica; Vacunas de la nefrosonefritis hemorrágica.

Description. A fluid or freeze-dried preparation of a suitable hantavirus grown in the neural tissue of suckling rodents or in cell cultures and inactivated. The fluid vaccine should be stored at 2 degrees to 8 degrees and not allowed to freeze. The freeze-dried form should be stored below 10 degrees.

Profile

Inactivated viral vaccines against haemorrhagic fever with renal syndrome have been investigated and are available in some countries, but there have been problems producing a sufficient and sustained immune response.

References.
1. Sohn YM, *et al.* Primary humoral immune responses to formalin inactivated hemorrhagic fever with renal syndrome vaccine (Hantavax): consideration of active immunization in South Korea. *Yonsei Med J* 2001; **42:** 278–84.
2. Cho HW, *et al.* Review of an inactivated vaccine against hantaviruses. *Intervirology* 2002; **45:** 328–33.
3. Park K, *et al.* Protective effectiveness of hantavirus vaccine. *Emerg Infect Dis* 2004; **10:** 2218–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: HaBiVa (汉必威); HaPuVa (汉普威); You Er Jian (佑尔健).

Helicobacter Pylori Vaccines

Vacunas de Helicobacter pylori.

Profile

Vaccines against *Helicobacter pylori* are being developed for prophylaxis of peptic ulcer disease and gastric cancer.

Studies in *animals* have shown the feasibility of both prophylactic and therapeutic vaccination against *Helicobacter pylori* infection, but there have been few studies in humans. Encouraging results have been obtained with parenteral, multicomponent, aluminium hydroxide-based vaccines in terms of safety and immunogenicity. In contrast, preliminary results obtained with mucosally delivered single-component vaccines have been disappointing, partly due to the intrinsic difficulty in developing purified proteins that are sufficiently immunogenic following mucosal delivery. Studies are ongoing into the mechanisms by which the host's genetic make-up modifies the inflammatory and immunological response to *H. pylori* and the development of suitable adjuvants.[1-6]

1. Ruggiero P, *et al.* The quest for a vaccine against Helicobacter pylori: how to move from mouse to man? *Microbes Infect* 2003; **5:** 749–56.
2. Sutton P, Doidge C. Helicobacter pylori vaccines spiral into the new millennium. *Dig Liver Dis* 2003; **35:** 675–87.
3. Del Giudice G, Michetti P. Inflammation, immunity and vaccines for Helicobacter pylori. *Helicobacter* 2004; **9** (suppl 1): 23–8.
4. Agarwal K, Agarwal S. Helicobacter pylori vaccine: from past to future. *Mayo Clin Proc* 2008; **83:** 169–75.
5. Sijun H, Yong X. *Helicobacter pylori* vaccine: mucosal adjuvant & delivery systems. *Indian J Med Res* 2009; **130:** 115–24.
6. Velin D, Michetti P. Advances in vaccination against *Helicobacter pylori*. *Expert Rev Gastroenterol Hepatol* 2010; **4:** 157–66.

Hepatitis A Immunoglobulins

Inmunoglobulinas contra la hepatitis A.
ATC — J06BB11.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Hepatitis A Immunoglobulin; Immunoglobulinum Humanum Hepatitidis A). A sterile liquid or freeze-dried preparation containing human immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against the hepatitis A virus. Normal immunoglobulin may be added. It contains not less than 600 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container under vacuum or under an inert gas.

Profile

Immunoglobulins containing high levels of specific antibodies against hepatitis A have been used in some countries for passive immunisation against hepatitis A infection; in the UK, normal immunoglobulin is usually given.

References.
1. Liu JP, *et al.* Immunoglobulins for preventing hepatitis A. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 10/02/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Globuman Hepatite A.

Pharmacopoeial Preparations
Ph. Eur.: Human Hepatitis A Immunoglobulin.

Hepatitis A Vaccines

Vacunas de la hepatitis A.
ATC — J07BC02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Hepatitis A Vaccine (Inactivated, Adsorbed); Vaccinum Hepatitidis A Inactivatum Adsorbatum; Inactivated Hepatitis A Vaccine BP 2014). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures, inactivated by a validated method, and adsorbed on a mineral carrier. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Hep A may be used on the label.

Ph. Eur. 8: (Hepatitis A Vaccine (Inactivated, Virosome); Vaccinum Hepatitidis A Inactivatum Virosomale). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures and inactivated by a validated method. Virosomes composed of influenza proteins and phospholipids are used as adjuvants. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that HepA may be used on the label.

Uses and Administration

Hepatitis A vaccines are used for active immunisation against hepatitis A infection.

In the UK, the use of an inactivated vaccine is recommended as an alternative to normal immunoglobulin for frequent travellers to areas of high or moderate hepatitis A endemicity or for those staying for more than 3 months in such areas; in some countries a hepatitis A immunoglobulin (above) is available for those making shorter or less frequent journeys. Immunisation is also recommended in haemophiliacs, patients with chronic liver disease, and in those at risk of exposure to hepatitis A by virtue of their occupation, and should be considered in persons whose lifestyle is likely to place them at risk. The vaccine is given intramuscularly, except in haemophiliacs in whom it should be given by deep subcutaneous injection. In the UK, various vaccines are available and the dose (0.5 or 1 mL) depends on the product used and age of the patient. They may be prepared from several inactivated hepatitis A virus strains including CR326F, GBM, HM175, and RG-SB. The primary immunisation schedule for all vaccines consists of a single dose appropriate to the age of the patient and should be followed 6 to 12 months later by a booster dose. Immunity is provided for at least 10 years after these doses.

In the USA, immunisation from 12 to 23 months of age (with a second dose at least 6 months later) is recommended as part of the routine primary immunisation schedule. Postexposure prophylaxis is recommended in persons who have not previously received a hepatitis A vaccine. Vaccination is also recommended for travellers to countries with intermediate to high hepatitis A endemicity.

References.
1. WHO. Hepatitis A vaccines: WHO position paper. *Wkly Epidem Rec* 2000; **75:** 38–44. Also available at: http://www.who.int/immunization/wer7505Hepatitis%20A_Feb00_position_paper.pdf (accessed 23/06/10)
2. American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. *Pediatrics* 2007; **120:** 189–99. http://pediatrics.aappublications.org/cgi/reprint/120/1/189.pdf (accessed 15/07/08)
3. Koslap-Petraco MB, *et al.* Hepatitis A: disease burden and current childhood vaccination strategies in the United States. *J Pediatr Health Care* 2008; **22:** 3–11.
4. Nothdurft HD. Hepatitis A vaccines. *Expert Rev Vaccines* 2008; **7:** 535–45.

Vaccine development. Commercially available hepatitis A vaccines are usually produced from inactivated hepatitis A virus strains propagated in cell culture, commonly of human diploid fibroblast cells. 'Virosome' hepatitis A vaccines consisting of inactivated hepatitis A virus epitopes formulated into liposomes are also becoming available. Live attenuated hepatitis A vaccines have also been developed, although an oral live vaccine does not appear to have yet been produced.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

General references.

1. Niu MT, *et al.* Two-year review of hepatitis A vaccine safety: data from the Vaccine Adverse Event Reporting System (VAERS). *Clin Infect Dis* 1998; **26:** 1475–6.

Effects on the blood. WHO has received reports of 5 cases of thrombocytopenia, 3 with purpura, associated with hepatitis A vaccine.[1]

1. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; **345:** 1638.

Effects on the nervous system. Neurological symptoms resembling encephalitis have followed a third dose of hepatitis A vaccine.[1] Other serious neurological reactions reported in patients given inactivated hepatitis A vaccine include transverse myelitis, Guillain-Barré syndrome, and neuralgic amyotrophy.[2] Such reactions appear to be very rare, and, since other vaccines have often been given simultaneously, may not be directly attributable to hepatitis A vaccine.

1. Hughes PJ, *et al.* Probable post-hepatitis A vaccination encephalopathy. *Lancet* 1993; **342:** 302.
2. CSM/MCA Hepatitis A vaccination (Havrix). *Current Problems* 1994; **20:** 16. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 23/04/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hepatitis B vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Avaxim; Epaxal; Havrix; VAQTA; Virohep-A; ***Austral.***: Avaxim; Havrix; VAQTA; ***Austria***: Avaxim; Epaxal; Havrix; ***Belg.***: Epaxal; Havrix; ***Braz.***: Vacina Contra Hepatite A; ***Canad.***: Avaxim; Epaxal; Havrix; VAQTA; ***Chile***: Avaxim; Epaxal; Havrix; ***China***: Avaxim (巴维信); Epaxal (爱巴苏); Hai Wei Ke (海威克); Havrix (贺福立适); Healive (孩尔来福); VAQTA (维康特); Wei Sai Rui An (维赛瑞安); Wei Sai Rui Ji (维赛瑞吉); ***Cz.***: Avaxim; Havrix; VAQTA; ***Denm.***: Avaxim; Epaxal; Havrix; VAQTA; ***Fin.***: Avaxim†; Epaxal; Havrix; VAQTA†; ***Fr.***: Avaxim; Havrix; ***Ger.***: Havpur; Havrix; VAQTA; ***Gr.***: Avaxim; Epaxal; Havrix; VAQTA; ***Hong Kong***: Avaxim; Epaxal; Havrix; VAQTA; ***Hung.***: Avaxim; Havrix; VAQTA; ***India***: Avaxim; Biovac-A; Havpur; Havrix; ***Indon.***: Avaxim; Havrix; VAQTA; ***Irl.***: Avaxim; Epaxal; Havrix; VAQTA; ***Israel***: Avaxim; Epaxal; Havrix; VAQTA; ***Ital.***: Avaxim; Epaxal; Havrix; VAQTA; ***Malaysia***: Avaxim; Epaxal; Havrix; ***Mex.***: Avaxim; Havrix; VAQTA; ***Neth.***: Avaxim; Epaxal; Havrix; VAQTA; ***Norw.***: Epaxal; Havrix; ***NZ***: Avaxim; Epaxal†; Havrix; VAQTA; ***Philipp.***: Avaxim; Epaxal; Havrix; Mevac-A; ***Pol.***: Avaxim; Havrix; VAQTA; ***Port.***: Avaxim; Epaxal; Havrix; VAQTA; ***Rus.***: Avaxim (Аваксим); Havrix (Хаврикс); VAQTA (BAKTA); ***S.Afr.***: Avaxim; Havrix; ***Singapore***: Avaxim; Epaxal; Havrix; VAQTA; ***Spain***: Epaxal; Havrix; VAQTA; ***Swed.***: Avaxim; Epaxal; Havrix; ***Switz.***: Epaxal; Havrix; ***Thai.***: Avaxim; Epaxal; Havrix; VAQTA; ***Turk.***: Avaxim; Epaxal; Havrix; VAQTA; ***UK***: Avaxim; Epaxal; Havrix; VAQTA; ***Ukr.***: Havrix (Хаврикс)†; ***USA***: Havrix; VAQTA; ***Venez.***: Havrix.

Pharmacopoeial Preparations

Ph. Eur.: Hepatitis A Vaccine (Inactivated, Adsorbed); Hepatitis A Vaccine (Inactivated, Virosome).

Hepatitis B Immunoglobulins

Inmunoglobulinas contra la hepatitis B.
ATC — J06BB04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Hepatitis B Immunoglobulin; Immunoglobulinum Humanum Hepatitidis B). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having specific antibodies against hepatitis B surface antigen. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

Ph. Eur. 8: (Human Hepatitis B Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Hepatitidis B ad Usum Intravenosum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface antigen. Human normal immunoglobulin for intravenous administration may be added. It contains not less than 50 international units/mL. Storage requirements are similar to those for Human Hepatitis B Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25 degrees.

USP 36: (Hepatitis B Immune Globulin). A is a sterile solution consisting of globulins derived from the plasma of human donors who have high titres of antibodies against hepatitis B surface antigen. It contains 10 to 18% of protein, of which not less than 80% is monomeric immunoglobulin G. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Hepatitis B immunoglobulins are used for passive immunisation of persons exposed or possibly exposed to hepatitis B virus, including by sexual contact. They are not appropriate for treatment. Hepatitis B immunoglobulins should always be given in addition to active immunisation with hepatitis B vaccine in at-risk patients exposed to hepatitis B virus.

In the UK, a hepatitis B immunoglobulin containing 100 international units/mL is available for intramuscular use. The dose in adults and children over 10 years of age is a single dose of 500 international units by intramuscular injection given preferably within 48 hours of exposure and not more than 1 week after exposure. Children aged 5 to 9 years may be given 300 international units, and children under 5 years 200 international units. Hepatitis B immunoglobulin should also be given to newborn infants at risk whose mothers are persistent carriers of hepatitis B surface antigen or whose mothers are HBsAg-positive as a result of recent infection. The dose is 200 international units by intramuscular injection preferably at birth, and certainly within 24 hours of birth.

There is now a UK and European standard for a preparation for intravenous use containing not less than 50 international units/mL.

In the USA, a hepatitis B immunoglobulin containing 15 to 18% of protein is available for intramuscular use. The dose for adults is 0.06 mL/kg. A dose of 0.5 mL is given to infants perinatally exposed to hepatitis B; this appears to be a significantly lower dose than that used in the UK. A hepatitis B immunoglobulin is also available for the prevention of hepatitis B recurrence after liver transplantation in patients who are positive for hepatitis B surface antigen. It is given intravenously at a dose of 20 000 international units during surgery and then daily from day 1 to day 7 after transplant surgery, then every 2 weeks from week 2 to week 12, and then monthly from 4 months post-surgery.

Preparation strength. *The content of hepatitis B immunoglobulin may vary between countries and between manufacturers. Care should be taken in interpreting dosage recommendations which are not given in terms of international units.* Products available in the USA have their strength expressed with reference to an FDA standard but are considered to contain the equivalent of at least 200 international units/mL.

Monoclonal antibodies. The name tuvirumab is applied to a human hepatitis B monoclonal antibody. A murine monoclonal antibody has been tried in a few patients with primary antibody deficiency.[1]

1. Lever AML, *et al.* Monoclonal antibody to HBsAg for chronic hepatitis B virus infection with hypogammaglobulinaemia. *Lancet* 1990; **335:** 1529.

Organ and tissue transplantation. Studies[1-5] in patients positive for hepatitis B surface antigen undergoing liver transplantation (p. 1936.3) suggest that long-term passive immunisation with hepatitis B immunoglobulin could reduce hepatitis B re-infection and improve survival in these patients.

1. Samuel D, *et al.* Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991; **337:** 813–15.
2. Nymann T, *et al.* Prevention of hepatitis B recurrence with indefinite hepatitis B immune globulin (HBIG) prophylaxis after liver transplantation. *Clin Transplant* 1996; **10:** 663–7.
3. McGory RW, *et al.* Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996; **61:** 1358–64.
4. Terrault NA, *et al.* Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 1996; **24:** 1327–33.
5. Sanchez-Fueyo A, *et al.* Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; **31:** 496–501.

Postexposure prophylaxis. For discussion of the use of hepatitis B immunoglobulins in patients exposed to hepatitis B virus, see Postexposure Prophylaxis under Uses and Administration of Hepatitis B Vaccines, p. 2390.2.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Preparation strength. For a warning concerning possible lack of equivalence between different preparations of hepatitis B immunoglobulins, see under Uses and Administration, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hepatitis B immunoglobulin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antib; Igantibe; ***Austria***: Hepatect; Venbig; Zutectra; ***Belg.***: Hepacaf; ***Canad.***: HepaGam B; HyperHep B; ***Chile***: Igantibe; ***Cz.***: NeoHepatect; Zutectra; ***Denm.***: Venbig; ***Fr.***: IVheBex; Zutectra; ***Ger.***: Hepatect; Zutectra; ***Gr.***: Aunativ; Hepatect; Hepuman; Igantibe; Immuno HBS; IVheBex; Venbig; ***Hong Kong***: Hyper Hep B; ***Hung.***: Hepatect; ***India***: Aunativ; Hepabig; Hepaglob; ***Indon.***: HyperHep B; ***Irl.***: Hepatect; Zutectra; ***Israel***: HepaGam B; Hepatect; HyperHep B; Omri-Hep-B; ***Ital.***: Igantibe; ImmunoHBs; Neohepatect; Uman-Big; Venbig; Zutectra; ***Jpn***: Hebsbulin; ***Malaysia***: Hepabig; ***Neth.***: Hepatect; HepBQuin; ImmunoGam†; IVheBex; ***NZ***: HyperHep B; ***Philipp.***: BayHep B; Hepabig; ***Pol.***: Gamma Anty HBs; Hepatect; Zutectra; ***Port.***: Hepatect; IVheBex; Venbig; Zutectra; ***Rus.***: Antihep (Антиген); ***S.Afr.***: Hebagam; ***Spain***: Gamma Antihepatitis B†; Gammaglob Antihepatitis BP†; Hepatect; Igantibe; Niuliva; Zutectra; ***Swed.***: Venbig; Zutectra; ***Switz.***: Hepatect; Zutectra; ***Thai.***: Igantibe; ImmunoHBs; Venbig; ***Turk.***: BayHep B; Hep B Quin; Hepatect; Hepatitis B Ig-P; Hepuman; Hyper Hep B; IVheBex; ***UK***: Hepatect; Zutectra; ***USA***: HepaGam B; HyperHep B; Nabi-HB.

Pharmacopoeial Preparations

Ph. Eur.: Human Hepatitis B Immunoglobulin for Intravenous Administration; Human Hepatitis B Immunoglobulin;
USP 36: Hepatitis B Immune Globulin.

Hepatitis B Vaccines

Vacunas de la hepatitis B.
ATC — J07BC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) have monographs.

Ph. Eur. 8: (Hepatitis B Vaccine (rDNA); Vaccinum Hepatitidis B (ADNr)). A preparation of hepatitis B surface antigen, that is obtained by recombinant DNA technology. It should be stored at a temperature of 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light. Under these storage conditions it may be expected to retain its potency for 24 months.

The BP 2014 states that Hep B may be used on the label.

Uses and Administration

Hepatitis B vaccines are used for active immunisation against hepatitis B infection. Two types of vaccine have been available, each containing hepatitis B surface antigen (HBsAg) adsorbed onto aluminium hydroxide or a similar adsorbent. The type of vaccine in which the surface antigen is produced in yeast cells using recombinant DNA techniques is now widely used and there has been considerable interest in further developments to improve immunogenicity. The second type of vaccine, in which the surface antigen is obtained from plasma after purification and inactivation processes is now not generally available.

WHO had recommended that national immunisation policies should include routine hepatitis B immunisation for the whole population by 1997 and this has been implemented in some countries including the USA (see Administration, p. 2390.1). The current recommendations in the UK are for immunisation of persons at high risk of contracting hepatitis B. High-risk groups include:

- healthcare personnel, laboratory workers, or any other personnel who have direct contact with patients or their body fluids or tissues
- staff and residents of accommodation for those with severe learning difficulties
- patients with chronic liver disease
- patients with chronic renal failure including those requiring haemodialysis
- haemophiliacs and those receiving regular blood transfusions or blood products
- close family contacts or sexual partners of cases or carriers of hepatitis B

- families adopting children from countries with a high prevalence of hepatitis B
- foster carers
- individuals who frequently change sexual partners
- parenteral drug abusers
- inmates of custodial institutions
- some travellers to areas where hepatitis B is endemic
- infants born to women who are persistent carriers of hepatitis B surface antigen or infants born to women who are HBsAg-positive as a result of recent infection

Hepatitis C carriers who are not immunised against hepatitis B should also receive immunisation.

A basic immunisation schedule consists of 3 doses of a hepatitis B vaccine, with the second and third doses 1 and 6 months, respectively, after the first. In the USA, some products may be given in an alternative 2-dose regimen to adolescents with doses given 4 to 6 months apart. Doses should be given intramuscularly, with the deltoid region being the preferred site in adults and older children and the anterolateral thigh the preferred site in neonates, infants, and younger children; the gluteal region (buttock) should not be used as efficacy may be reduced. The subcutaneous route should be used in patients with haemophilia. The dose of the recombinant vaccine depends on the product used. Typical doses for adults are 10 or 20 micrograms and for infants and children 5 or 10 micrograms. Products containing 40 micrograms are available for adult dialysis and predialysis patients who have a reduced immune response to the vaccine. However, *the dose of one recombinant preparation should not be seen as equivalent to the dose of another.*

For pre-exposure prophylaxis in high-risk groups and for postexposure prophylaxis an accelerated schedule should be used. It may also be used where more rapid immunisation, for instance with travellers, is required. This schedule involves giving the third dose 2 months after the initial dose with a further booster at 1 year. In exceptional circumstances in adults travelling to an endemic area who commence their vaccination course within a month of departure, an even more rapid schedule involving injections at 0, 7, and 21 days has been used; when this schedule is used, a booster dose is recommended after 1 year.

For newborn infants at risk combined active and passive immunisation against hepatitis B is recommended. The first dose of vaccine should preferably be given at birth, and certainly within 24 hours of birth. A single dose of hepatitis B immunoglobulin (200 international units) should be given at the same time into a different site. Additionally, in any patient in whom immediate protection is required, combined active and passive immunisation may be considered with a single dose of 500 international units of hepatitis B immunoglobulin being the dose for adults. See under Hepatitis B Immunoglobulins, p. 2389.2, for children's doses.

General references.

1. Buynak EB, *et al*. Vaccine against human hepatitis B. *JAMA* 1976; **235:** 2832–4.
2. Douglas RG. The heritage of hepatitis B vaccine. *JAMA* 1996; **276:** 1796–8.
3. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; **336:** 196–204.
4. Keating GM, Noble S. Recombinant hepatitis B vaccine (Engerix-B): a review of its immunogenicity and protective efficacy against hepatitis B. *Drugs* 2003; **63:** 1021–51.
5. WHO. Hepatitis B vaccines: WHO position paper. *Wkly Epidem Rec* 2009; **84:** 405–20. Also available at: http://www.who.int/wer/2009/wer8440.pdf (accessed 22/06/10)

Administration. The major public health burden of hepatitis B infection in the developing world is due to the consequences of chronic carriage of hepatitis B virus (hepatocellular carcinoma and chronic cirrhosis) rather than acute infection. WHO[1] considered that the most important means of controlling hepatitis B on a global scale and of reducing mortality from its sequelae was mass immunisation of infants. It stated that hepatitis B vaccine should be incorporated into the Expanded Programme on Immunization (EPI) and many countries have since done so. WHO later reiterated this aim[2] stating that hepatitis B vaccine should be integrated into national immunisation programmes in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. WHO's aim was to reduce the incidence of new child carriers of hepatitis B by 80% by 2001. Results from Taiwan, where mass immunisation of infants has been in place since the mid-1980s have shown a marked decline in the number of child carriers under 10 years of age.[3,4] The incidence of hepatocellular carcinoma in children has also been reduced.[5,6]

Opinion has been divided in the UK regarding implementation of universal hepatitis B immunisation,[7-9] with some advising increased emphasis on alternative strategies already in place such as antenatal screening.[7,8]

The optimum vaccination strategy depends on the pattern of hepatitis B viral transmission in a particular country.[10] In hyperendemic regions where most infections are acquired early in life, the vaccine should be given shortly after birth and hepatitis B immunisation integrated into the EPI. Immunisation of all infants should be considered for population groups with chronic hepatitis B virus carrier rates greater than 2% and should be a public health priority where carrier rates are greater than 10%. Countries with a lower carrier rate might opt to immunise all adolescents as an alternative to infant immunisation. Immunisation of individuals at high risk of infection should be continued in addition to routine vaccination schedules[2] and, if hepatitis B is not integrated into infant vaccination schedules, screening pregnant women for HBsAg and immunising the infants of HBsAg-positive mothers should continue.[1]

If use of hepatitis B vaccine is integrated into the EPI, 3 doses should be given intramuscularly, the first dose being given as soon as possible after birth with the first EPI immunisation. The exact timing of these doses will depend on the risk of transmission at birth and the EPI schedule in operation. In the USA, these recommendations have been implemented by immunisation of all infants and of children at any age between 2 and 18 years who have not previously received 3 doses of vaccine. The recommended schedule is for all infants to be given an initial dose of the monovalent hepatitis B vaccine soon after birth; then 2 further doses with the monovalent vaccine or 3 further doses with a combination vaccine containing hepatitis B. Infants of HBsAg-positive mothers should receive hepatitis B vaccine plus hepatitis B immunoglobulin within 12 hours of birth. Infants whose mother's HBsAg status is unknown should receive a hepatitis B vaccine within 12 hours of birth and the maternal blood should be checked at delivery and, if positive for HBsAg, the infant given hepatitis B immunoglobulin as soon as possible (no later than 1 week of age). The second dose is given at 1 to 2 months of age and the final dose at 6 months of age or later. Infants who receive a combination vaccine after the birth dose may be given an additional dose at 4 months of age. Alternatively, some products may be given in a two-dose regimen, with doses given 4 to 6 months apart.

1. WHO. Progress in the control of viral hepatitis: memorandum from a WHO meeting. *Bull WHO* 1988; **66:** 443–55.
2. Anonymous. Hepatitis B vaccine. *WHO Drug Inf* 1993; **7:** 130–1.
3. Chen H-L, *et al*. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA* 1996; **276:** 906–8.
4. Hsu H-M, *et al*. Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis* 1999; **179:** 367–70.
5. Lee C-L, Ko Y-C. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics* 1997; **99:** 351–3.
6. Chang M-H, *et al*. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; **336:** 1855–9.
7. Mortimer PP, Miller E. Commentary: antenatal screening and targeting should be sufficient in some countries. *BMJ* 1997; **314:** 1036–7.
8. Dunn J, *et al*. Integration of hepatitis B vaccination into national immunisation programmes: alternative strategies must be considered before universal vaccination is adopted. *BMJ* 1997; **315:** 121–2.
9. Goldberg D, McMenamin J. The United Kingdom's hepatitis B immunisation strategy—where now? *Commun Dis Public Health* 1998; **1:** 79–83.
10. Rots NY, *et al*. Hepatitis B vaccination strategies tailored to different endemicity levels: some considerations. *Vaccine* 2010; **28:** 893–900.

BOOSTER DOSES. There has been considerable interest in the duration of immunity conferred by hepatitis B vaccination and the possible need for booster doses.[1-3]

In the UK it is now recommended that individuals at continuing risk of infection should be offered a *single* booster dose of vaccine, *once only*, about 5 years after primary immunisation. Boosters are also recommended if contamination of eyes, mouth, or fresh cuts on skin with blood from a HBsAg-positive person occurs, unless they are known to have protective concentrations of antibody. However, a meta-analysis[3] suggested that a 3-dose course of immunisation with hepatitis B vaccine in immunocompetent individuals resulted in good protection against infection for up to 20 years.

References.

1. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000; **355:** 561–5.
2. Banatvala JE, Van Damme P. Hepatitis B vaccine—do we need boosters? *J Viral Hepatitis* 2003; **10:** 1–6.
3. Poorolajal J, *et al*. Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. *Vaccine* 2010; **28:** 623–31.

Postexposure prophylaxis. A combination of passive immunisation with a hepatitis B immunoglobulin and active immunisation with a hepatitis B vaccine is generally recommended for postexposure prophylaxis against hepatitis B.

One group of patients who should be given postexposure prophylaxis are infants born to mothers who are persistent carriers of hepatitis B surface antigen (HBsAg). The risk is particularly high if the mother has detectable hepatitis Be antigen (HBeAg) or hepatitis B virus DNA or absence of detectable antibody to hepatitis Be antigen (anti-HBe). Postexposure prophylaxis is also recommended in the UK for persons accidentally inoculated, or who contaminate the eye or mouth or breaks to the skin with blood from a known HBsAg-positive person, as well as in sexual contacts (and sometimes close family contacts) of sufferers from acute hepatitis B and who are seen within a week of the onset of jaundice in the contact.

In the UK, the recommended schedule for postexposure prophylaxis is the first dose of vaccine given preferably within 48 hours of exposure and no later than one week after exposure, or, for neonates exposed to hepatitis B at birth, no later than 24 hours after birth, with a single dose of hepatitis B immunoglobulin given simultaneously at a separate site. The second and third doses of vaccine are given 1 and 2 months after the first dose, with a booster dose at 12 months. Healthcare workers who have been successfully immunised should be given a booster dose after subsequent contamination with blood from an infected person, unless they are known to have adequate antibody concentration.

Adverse Effects

As for vaccines in general, p. 2375.1.

In addition, abdominal pain and gastrointestinal disturbance, and musculoskeletal and joint pain and inflammation have been reported after hepatitis B vaccines. There may also be dizziness and sleep disturbance. Cardiovascular effects include occasional hypotension and, rarely, tachycardia. Other rare adverse effects include dysuria, visual disturbances, and earache.

General references.

1. McMahon BJ, *et al*. Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; **92:** 254–6.
2. Anonymous. Adverse events after hepatitis B vaccination. *Can Med Assoc J* 1992; **147:** 1023–6.
3. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. *Expert Opin Drug Safety* 2003; **2:** 225–31.
4. Autret-Leca E, *et al*. Tolérance du vaccin contre l'hépatite B: exemple d'une complémentarité notification spontanée/études pharmacoépidémiologiques. *Presse Med* 2007; **36:** 563–4.

Effects on the blood. Rare cases of thrombocytopenia[1-4] and pancytopenia[5] associated with hepatitis B vaccination have been reported.

1. Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994; **344:** 1293.
2. Meyboom RHB, *et al*. Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; **345:** 1638.
3. Ronchi F, *et al*. Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child* 1998; **78:** 273–4.
4. Nuevo H, *et al*. Thrombocytopenic purpura after hepatitis B vaccine: case report and review of the literature. *Pediatr Infect Dis J* 2004; **23:** 183–4.
5. Viallard JF, *et al*. Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol* 2000; **110:** 230–3.

Effects on bones and joints. Reactive arthritis[1-3] and Reiter's syndrome[2] have been reported after hepatitis B vaccination. There have also been isolated reports of rheumatoid arthritis occurring after hepatitis B vaccination[3,4] and a suggestion that hepatitis B vaccination may trigger the onset of underlying SLE.[5] Some reports of arthralgia have been received by the UK CSM and by the manufacturers of *Engerix B*.[2]

1. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301:** 345.
2. Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; **309:** 94–5.
3. Gross K, *et al*. Arthritis after hepatitis B vaccination: report of three cases. *Scand J Rheumatol* 1995; **24:** 50–2.
4. Pope JE, *et al*. The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998; **25:** 1687–93.
5. Maillefert JF, *et al*. Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology (Oxford)* 1999; **38:** 978–83.

Effects on the eyes. There have been isolated case reports of acute posterior uveitis,[1] visual loss associated with eosinophilia,[2] acute posterior multifocal placoid pigment epitheliopathy,[3] central retinal vein occlusion,[4] and multiple evanescent white dot syndrome[5] after vaccination against hepatitis B.

For mention of optic neuritis in patients receiving hepatitis B vaccine, see under Effects on the Nervous System, p. 2391.1.

1. Fried M, *et al*. Uveitis after hepatitis B vaccination. *Lancet* 1987; **ii:** 631–2.
2. Brézin AP, *et al*. Visual loss and eosinophilia after recombinant hepatitis B vaccine. *Lancet* 1993; **342:** 563–4.
3. Brézin AP, *et al*. Acute posterior multifocal placoid pigment epitheliopathy after hepatitis B vaccine. *Arch Ophthalmol* 1995; **113:** 297–300.
4. Devin F, *et al*. Occlusion of central retinal vein after hepatitis B vaccination. *Lancet* 1996; **347:** 1626.
5. Baglivo E, *et al*. Multiple evanescent white dot syndrome after hepatitis B vaccine. *Am J Ophthalmol* 1996; **122:** 431–2.

Effects on the kidneys. There have been case reports of acute glomerulonephritis in patients after hepatitis B vaccine.[1,2]

1. Carmeli Y, Oren R. Hepatitis B vaccine side-effect. *Lancet* 1993; **341:** 250–1.
2. Pennesi M, *et al*. Glomerulonephritis after recombinant hepatitis B vaccine. *Pediatr Infect Dis J* 2002; **21:** 172–3.

Effects on the liver. There have been occasional reports of transient abnormalities in liver function associated with hepatitis B vaccine.[1-3] The appearance of autoantibodies

has been reported in a patient,[2] and severe cytolysis consistent with an allergic mechanism in another.[3]

1. Rajendran V, Brooks AP. Symptomatic reaction to hepatitis B vaccine with abnormal liver function values. *BMJ* 1985; **290:** 1476.
2. Lilic D, Ghosh SK. Liver dysfunction and DNA antibodies after hepatitis B vaccination. *Lancet* 1994; **344:** 1292–3.
3. Germanaud J, *et al*. A case of severe cytolysis after hepatitis B vaccination. *Am J Med* 1995; **98:** 595.

Effects on the nervous system. In the years 1982 to 1985 the Centers for Disease Control, the FDA, and the manufacturer of plasma-derived hepatitis B vaccine received 41 reports of adverse neurological effects.[1] It was estimated that about 850 000 persons had received the vaccine in this time. Neurological events were convulsions (5 cases), Bell's palsy (10 cases), Guillain-Barré syndrome (9 cases), lumbar radiculopathy (5 cases), brachial plexus neuropathy (3 cases), optic neuritis (5 cases), and transverse myelitis (4 cases). In some analyses Guillain-Barré syndrome was reported significantly more often than expected. However, no conclusive epidemiological association could be made between any neurological adverse effect and the vaccine.

In France, spontaneous reports of multiple sclerosis and central demyelinating disease in patients who had received hepatitis B vaccine led to the suspension by the French authorities of hepatitis B vaccination in schools in 1998. This decision was widely condemned by many authorities including WHO, the US National Multiple Sclerosis Society, and the Viral Hepatitis Prevention Board, and there was a fear that reduced confidence in the vaccine could have a profound effect on uptake. Arguments[2] against a link between hepatitis B vaccine and multiple sclerosis include the lack of correlation between the incidence of hepatitis B infection and demyelinating diseases, data from clinical studies including extensive postmarketing surveillance, and analysis of the French cases which concluded that the incidence of multiple sclerosis amongst vaccine recipients was not higher than would be expected in the population as a whole. A consultative group concluded[3] that, in the light of the evidence, the benefits of hepatitis B vaccination supported current WHO recommendations that all countries should have universal infant and/or adolescent hepatitis B immunisation programmes and that adults at increased risk of infection should also be immunised. More recent studies[4,5] have also indicated no association between hepatitis B vaccine and multiple sclerosis, although one study[6] did suggest a threefold increase in risk.

A case-control analysis[7] reported that vaccination with a hepatitis B vaccine did not generally increase the risk of CNS inflammatory demyelination in childhood. However, data from vaccination with one specific hepatitis B vaccine (*Engerix B*) suggested a small risk increase, particularly for confirmed multiple sclerosis, in the longer term. A review[8] noted that in addition to reports of neuropathies there had also been reports of a temporal association of hepatitis B vaccination with myasthenia gravis, polyarteritis nodosa, and dermatomyositis, but that evidence was largely confined to weak case reports and could not be used to confirm causality.

1. Shaw FE, *et al*. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination: experience of the first three years. *Am J Epidemiol* 1988; **127:** 337–52.
2. Anonymous. Expanded Programme on Immunization (EPI): lack of evidence that hepatitis B vaccine causes multiple sclerosis. *Wkly Epidem Rec* 1997; **72:** 149–52.
3. Halsey NA, *et al*. Hepatitis B vaccine and central nervous system demyelinating diseases. *Pediatr Infect Dis J* 1999; **18:** 23–4.
4. Ascherio A, *et al*. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001; **344:** 327–32.
5. Mikaeloff Y, *et al*. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Arch Pediatr Adolesc Med* 2007; **161:** 1176–82.
6. Hernán MA, *et al*. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* 2004; **63:** 838–42.
7. Mikaeloff Y, *et al*. Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. *Neurology* 2009; **72:** 873–80.
8. Stübgen J-P. Neuromuscular disorders associated with hepatitis B vaccination. *J Neurol Sci* 2010; **292:** 1–4.

Effects on the skin. Skin reactions, which have been reported in a few individuals after hepatitis B vaccination, include erythema multiforme,[1,2] erythema nodosum,[3-5] lichen planus,[6-8] and vasculitis.[9]

1. Feldshon SD, Sampliner RE. Reaction to hepatitis B virus vaccine. *Ann Intern Med* 1984; **100:** 156–7.
2. Wakeel RA, White MI. Erythema multiforme associated with hepatitis B vaccine. *Br J Dermatol* 1992; **126:** 94–5.
3. Di Giusto CA, Bernhard JD. Erythema nodosum provoked by hepatitis B vaccine. *Lancet* 1986; **ii:** 1042.
4. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. *N Engl J Med* 1989; **321:** 1198–9.
5. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301:** 345.
6. Ciaccio M, Rebora A. Lichen planus following HBV vaccination: a coincidence? *Br J Dermatol* 1990; **122:** 424.
7. Ferrnado MF, *et al*. Lichen planus following hepatitis B vaccination. *Br J Dermatol* 1998; **139:** 350.
8. Usman A, *et al*. Lichenoid eruption following hepatitis B vaccination: first North American case report. *Pediatr Dermatol* 2001; **18:** 123–6.
9. de Carvalho JF, *et al*. Systemic polyarteritis nodosa following hepatitis B vaccination. *Eur J Intern Med* 2008; **19:** 575–8.

Hypersensitivity. There have been reports of hypersensitivity reactions after hepatitis B vaccination that have been attributed to components of the vaccines, including formaldehyde,[1] thiomersal,[2] and *Saccharomyces cerevisiae*.[3]

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patient. *Lancet* 1986; **ii:** 522–3.
2. Noel I, *et al*. Hypersensitivity to thiomersal in hepatitis B vaccine. *Lancet* 1991; **338:** 705.
3. Brightman CAJ, *et al*. Yeast-derived hepatitis B vaccine and yeast sensitivity. *Lancet* 1989; **i:** 903.

Precautions

As for vaccines in general, p. 2375.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hepatitis B vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Reduced immune response. The immune response to hepatitis B vaccine is dependent on both host- and immunisation-related factors.[1] Host-related factors that appear to diminish the response include increasing age, increasing body-weight, smoking,[1,2] and male sex;[3] particular HLA haplotypes may also be associated with poor response.[4] Failure of hepatitis B immunisation in infants could be related to high perinatal maternal viraemia[5] rather than to inherent resistance to the vaccine.

Some studies have found a defective response in chronic alcoholics[6,7] whereas others have not;[8] the degree of liver impairment may be a significant factor. It has been suggested that an increased dose of hepatitis B vaccine may be appropriate in those with a history of alcoholism.[9] Active infection with *Schistosoma mansoni* also appears to decrease the response to hepatitis B vaccination.[10] A diminished response occurs in HIV-positive patients[11-13] and in patients on haemodialysis;[1] an increased dose of hepatitis B vaccine is recommended in these patients. In patients with haemophilia who are not HIV-positive[14] immunity is reported to wane rapidly after vaccination and frequent booster doses may be required. Biological response modifiers such as thymopentin[15] and interferon[16] have been used successfully in some patients on haemodialysis to overcome the immune deficit. Use of interleukin-2 has met with variable success. Granulocyte-macrophage colony-stimulating factor has also been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[17]

The immune response to hepatitis B vaccine is affected by the site of intramuscular injection. The deltoid region is recommended for adults and the anterolateral thigh for infants. A diminished response has been associated with injection into the gluteal region (buttock).[1]

A related problem is posed by subjects who become infected with hepatitis B despite mounting an adequate response to immunisation. In one study, evidence of viral replication was detected in 44 of 1590 hepatitis B vaccinees despite development of protective titres of antibody.[18] Acute hepatitis occurred in one patient. Although the infection may have been incubating at the time of vaccination, the virus isolated from the child with acute disease was an escape mutant with a different DNA sequence from that isolated from the mother.

1. Hollinger FB. Factors influencing the immune response to hepatitis b vaccine, booster dose guidelines, and vaccine protocol recommendations. *Am J Med* 1989; **87** (suppl 3A): 36S–40S.
2. Horowitz MM, *et al*. Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. *Ann Intern Med* 1988; **108:** 185–9.
3. Morris CA, *et al*. Intradermal hepatitis B immunization with yeast-derived vaccine: serological response by sex and age. *Epidemiol Infect* 1989; **103:** 387–94.
4. Alper CA, *et al*. Genetic prediction of nonresponse to hepatitis B vaccine. *N Engl J Med* 1989; **321:** 708–12.
5. del Canho R, *et al*. Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol* 1994; **20:** 483–6.
6. Degos F, *et al*. Hepatitis B vaccination and alcoholic cirrhosis. *Lancet* 1983; **ii:** 1498.
7. Mendenhall C, *et al*. Hepatitis B vaccination: response of alcoholic with and without liver injury. *Dig Dis Sci* 1988; **33:** 263–9.
8. McMahon BJ, *et al*. Response to hepatitis B vaccine in Alaska Natives with chronic alcoholism compared with non-alcoholic control subjects. *Am J Med* 1990; **88:** 460–4.
9. Rosman AS, *et al*. Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* 1997; **103:** 217–22.
10. Ghaffar YA, *et al*. Response to hepatitis B vaccine in infants born to mothers with schistosomiasis. *Lancet* 1989; **ii:** 272.
11. Carne CA, *et al*. Impaired responsiveness of homosexual men with HIV antibodies to plasma derived hepatitis B vaccine. *BMJ* 1987; **294:** 866–8.
12. Collier AC, *et al*. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* 1988; **109:** 101–5.
13. Chan W, *et al*. Response to hepatitis B immunization in children with hemophilia: relationship to infection with human immunodeficiency virus type 1. *J Pediatr* 1990; **117:** 427–30.
14. Maris JM, *et al*. Loss of detectable antibody to hepatitis B surface antigen in immunized patients with hemophilia but without human immunodeficiency virus infection. *J Pediatr* 1995; **126:** 269–71.
15. Donati D, Gastaldi L. Controlled trial of thymopentin in hemodialysis patients who fail to respond to hepatitis B vaccination. *Nephron* 1988; **50:** 133–6.
16. Quiroga JA, Carreño V. Interferon and hepatitis B vaccine in haemodialysis patients. *Lancet* 1989; **i:** 1264.
17. Cruciani M, *et al*. Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; **25:** 709–18.
18. Carman WF, *et al*. Vaccine-induced escape mutant of hepatitis B virus. *Lancet* 1990; **336:** 325–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: AGB; Biovac HB; Engerix-B; HBVaxPro; Hepativax; Supervax; ***Austral.***: Engerix-B; H-B-Vax II; ***Austria***: Engerix-B; HBVaxPro; ***Belg.***: Engerix-B; Fendrix; HBVaxPro; ***Braz.***: Vacina Contra Hepatite B; ***Canad.***: Engerix-B; Recombivax HB; ***Chile***: Engerix-B; Heberbiovac HB; Hepavax-Gene; Recomvax B; ***China***: Engerix-B (安在时); Hepavax-Gene (益可欣); ***Cz.***: Engerix-B; Fendrix; HBVaxPro; ***Denm.***: Engerix-B; Fendrix†; HBVaxPro; ***Fin.***: Engerix-B; ***Fr.***: Engerix-B; Fendrix†; GenHevac B; HBVaxPro; ***Ger.***: Engerix-B; Fendrix; HBVaxPro; ***Gr.***: Engerix-B; Fendrix; HBVaxPro; Recombivax; ***Hong Kong***: Engerix-B; H-B-Vax II†; HBVaxPro; Hepavax-Gene; Sci-B-Vac; ***Hung.***: Engerix-B; HBVaxPro; ***India***: Bevac; Biovac-B; Engerix-B; Enivac-HB; Genevac-B; HB Vac; Hepaccine-B; Hepagen-Plus; Hepashield; Invac-B; LG Euvax B; Shanvac-B; ***Indon.***: Engerix-B; Euvax B; H-B-Vax II; Hepavax†; ***Irl.***: Engerix-B; Fendrix; HBVaxPro; ***Israel***: Engerix-B; Recombinant H-B Vax II; Sci-B-Vac; ***Ital.***: Engerix-B; Fendrix; HBVaxPro; ***Malaysia***: Engerix-B; Euvax B; HBVaxPro; Hepavax-Gene; ***Mex.***: Engerix-B; H-B-Vax II; Heberbiovac HB; Probivac-B; ***Neth.***: Engerix-B; Fendrix; HB-Vax-DNA†; HBVaxPro; ***Norw.***: Engerix-B; Fendrix; ***NZ***: Engerix-B; H-B-Vax II†; HBVaxPro; ***Philipp.***: Amvax; Engerix-B; Euvax B; Genvac-B; Hepavax-Gene; Hepliv; Recomvax B†; Shanvac-B; Temrevac-HB; ***Pol.***: Engerix-B; Euvax B; HBVaxPro; Hepavax-Gene; ***Port.***: Engerix-B; Fendrix; HBVaxPro; ***Rus.***: Biovac-B (Биовак-в)†; Engerix-B (Энджерикс B); H-B-Vax II (H-B-Вакс II); Regevac B (Регевак B); Shanvac-B (Шанвак-B); ***S.Afr.***: Engerix-B; H-B-Vax II†; Heberbiovac HB; Hepaccine-B†; ***Singapore***: Engerix-B; HBVaxPro; ***Spain***: Engerix-B; Fendrix; HBVaxPro; ***Swed.***: Engerix-B; Fendrix; HBVaxPro; ***Switz.***: Engerix-B; HBVaxPro; ***Thai.***: Engerix-B; Euvax B; H-B-Vax II†; HBVaxPro; Heberbiovac HB; Hepavax-Gene; Revac-Bmcf; Shanvac-B; ***Turk.***: Engerix-B; Euvax B; GenHevac B; HBVaxPro; Hepavax-Gene; ***UK***: Engerix-B; Fendrix; HBVaxPro; ***Ukr.***: Engerix-B (Энджерикс-B); ***USA***: Engerix-B; Recombivax HB; ***Venez.***: Engerix-B.

Pharmacopoeial Preparations

Ph. Eur.: Hepatitis B Vaccine (rDNA).

Hepatitis A and B Vaccines

Vacunas de las hepatitis A y B.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Hepatitidis A Inactivatum et Hepatitidis B (ADNr) Adsorbatum; Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine BP 2014). A suspension consisting of a suitable strain of hepatitis A virus, grown in cell cultures and inactivated by a validated method, and of hepatitis B surface antigen obtained by recombinant DNA technology; the antigens are adsorbed on a mineral carrier, such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that HepA/HepB may be used on the label.

Uses and Administration

Combined hepatitis A and B vaccines are used for active immunisation against hepatitis A and hepatitis B.

A hepatitis A and B vaccine (*Twinrix, GSK*) is available containing not less than 720 ELISA units of inactivated hepatitis A virus and not less than 20 micrograms of recombinant hepatitis B surface antigen (HBsAg) protein in 1 mL. For primary immunisation, three doses of 1 mL are given by intramuscular injection, with the second and third doses 1 and 6 months after the first. For children up to the age of 16 years a 0.5-mL dose is given.

Alternatively, in exceptional circumstances when travel is anticipated within one month or more after the first dose but when insufficient time is available for the standard course, adults may be given an accelerated schedule. In the UK, this consists of three doses at 0, 7 and 21 days. In the US the recommended schedule consists of doses at 0, 7, and 21 to 30 days plus a dose at 12 months.

Booster doses may be given as appropriate with the monovalent component vaccines since protection against hepatitis A and B declines at different rates, or a booster dose of the combined vaccine may be given after 5 years in adults

or 4 years in children. A booster is recommended 1 year after the accelerated schedule.

In the UK a similar vaccine (*Ambirix, GSK*) is licensed for primary immunisation in a 2-dose schedule for children aged 1 to 15 years; the second dose is given between 6 and 12 months after the first.

Reviews.

1. Murdoch DL, *et al.* Combined hepatitis A and B vaccines: a review of their immunogenicity and tolerability. *Drugs* 2003; **63:** 2625–49.
2. Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. *Expert Rev Vaccines* 2004; **3:** 249–67.
3. Zuckerman JN. Vaccination against hepatitis A and B: developments, deployment and delusions. *Curr Opin Infect Dis* 2006; **19:** 456–9.
4. Hewlett AT. Combined hepatitis A and B vaccine: providing a bright future for preventing hepatitis. *Expert Opin Biol Ther* 2009; **9:** 1235–40.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Hepatitis A Vaccines, p. 2389.1, and Hepatitis B Vaccines, p. 2390.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combined hepatitis A and B vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Twinrix; ***Austral.***: Twinrix; ***Austria***: Twinrix; ***Belg.***: Twinrix; ***Braz.***: Vacina Comb. Contra Hepatite A e B; ***Canad.***: Twinrix; ***Chile***: Twinrix; ***China***: Bilive (倍尔来); Twinrix (双福立适); ***Cz.***: Ambirix; Twinrix; ***Denm.***: Ambirix; Twinrix; ***Fin.***: Twinrix; ***Fr.***: Twinrix; ***Ger.***: Twinrix; ***Gr.***: Twinrix; ***Hong Kong***: Twinrix; ***Hung.***: Twinrix; ***Indon.***: Twinrix; ***Irl.***: Ambirix; Twinrix; ***Israel***: Twinrix; ***Ital.***: Twinrix; ***Malaysia***: Twinrix; ***Mex.***: Twinrix; ***Neth.***: Ambirix; Twinrix; ***Norw.***: Twinrix; ***NZ***: Twinrix; ***Philipp.***: Twinrix; ***Pol.***: Ambirix; Twinrix; ***Port.***: Ambirix; Twinrix; ***S.Afr.***: Twinrix; ***Singapore***: Twinrix; ***Spain***: Twinrix; ***Swed.***: Ambirix; Twinrix; ***Switz.***: Twinrix; ***Thai.***: Twinrix; ***Turk.***: Twinrix; ***UK***: Ambirix; Ambrix; Twinrix; ***Ukr.***: Twinrix (Твінрикс); ***USA***: Twinrix; ***Venez.***: Twinrix.

Pharmacopoeial Preparations

Ph. Eur.: Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Hepatitis A and Typhoid Vaccines

Vacunas de la hepatitis A y fiebre tifoidea.

ATC — J07CA10.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Hepatitis A (Inactivated, Adsorbed) and Typhoid Polysaccharide Vaccine; Vaccinum Hepatitidis A Inactivatum Adsorbatum et Febris Typhoidis Polysaccharidicum). A suspension consisting of a suitable strain of hepatitis A virus, grown in cell cultures and inactivated by a validated method, and of purified Vi capsular polysaccharide obtained from *Salmonella typhi* Ty 2 strain or some other suitable strain that has the capacity to produce Vi polysaccharide. The product is presented either as a liquid mixture containing both components or as 2 separate liquids which are mixed together immediately before use. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

Combined hepatitis A and typhoid vaccines are used for active immunisation. They contain either inactivated HM175 or GBM hepatitis A virus strains together with the Vi capsular polysaccharide from *Salmonella typhi* Ty 2 strain. Adults and adolescents over 15 years of age may be given a dose of 1 mL by intramuscular injection, at least 2 weeks before the risk of exposure to typhoid and hepatitis A. A booster dose may be given after 6 to 12 months to provide long-term protection.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vivaxim; ***Austria***: Hepatyrix; ViATIM; ***Canad.***: Vivaxim; ***Fr.***: Tyavax; ***Ger.***: Hepatyrix; ViATIM; ***Hong Kong***: Vivaxim; ***Irl.***: Hepatyrix; ViATIM; ***Israel***: Hepatyrix; ***Malaysia***: Vivaxim; ***Neth.***: ViATIM; ***NZ***: Hepatyrix; Vivaxim; ***Port.***: ViATIM; ***UK***: Hepatyrix; ViATIM.

Herpes Simplex Vaccines

Vacunas del herpes común; Vacunas del herpes simple.

Profile

Several types of vaccines against herpes simplex virus types 1 and 2 have been developed. They have been tried both in oral and genital herpes infections. They are also being studied for the prevention of infection in sexual partners of patients with genital herpes.

Herpes simplex virus types 1 and 2 are widespread in populations throughout the world. Herpes simplex virus type 2 causes lifelong infection with significant morbidity. Even with the availability of effective antiviral therapy, the increasing burden of herpes simplex virus infection makes it a suitable candidate for vaccine development. The incidence of neonatal herpes infections has also increased and this risk would also be addressed by development of appropriate vaccines. An additional benefit would be a reduced risk of acquiring HIV infection.

Vaccines for herpes simplex were first studied in the 1920s and many different types of vaccine have undergone evaluation. They have included auto-inoculation of live herpes simplex virus, whole inactivated vaccines, attenuated live virus vaccines, modified live virus subunit vaccines, cell culture-derived subunit vaccines, recombinant glycoprotein subunit vaccines, disabled infectious single cycle (DISC) vaccines, and nucleic acid (DNA) vaccines.[1,2]

Prophylactic vaccines against HSV-2 could be beneficial if they either shift the threshold of infection i.e. increase the titre of virus necessary to cause infection, or if they prevent clinical disease itself. An attenuated live virus vaccine based on modified HSV-1 has been tested in clinical studies but was poorly tolerated at the doses required to elicit an immune response. Prophylactic vaccines including subunit vaccines encoding virus glycoproteins and delivered with adjuvants have shown some benefits.[1,2]

To date, no randomised clinical studies have shown useful benefit from therapeutic vaccines for HSV-1 or HSV-2. A therapeutic vaccine should prevent recurrences or at least minimise their severity or duration. Heat killed, whole virus vaccines from HSV-1 (Lupidon H) and HSV-2 (Lupidon G), and inactivated subunit vaccines have been studied but have generally produced disappointing results.[1,2] Recombinant glycoprotein vaccines have also been tested but again results have been disappointing.[1,2]

1. Morrison LA. Vaccines against genital herpes: progress and limitations. *Drugs* 2002; **62:** 1119–29.
2. Stanberry LR. Clinical trials of prophylactic and therapeutic herpes simplex virus vaccines. *Herpes* 2004; **11** (suppl 3): 161A–169A.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Lupidon G; Lupidon H; ***Rus.***: Herpovax (Герповакс); Vitaherpavac (Витагерпавак); ***Switz.***: Lupidon H+G.

Human Papillomavirus Vaccines

HPV Vaccines; Human Papilloma Virus Vaccines; Vacunas del virus del papiloma humano.

ATC — J07BM01.

UNII — 23CVL7WF4J (human papillomavirus antigen); 61746O90DY (human papillomavirus type 6 L1 capsid protein antigen); Z845VHQ61P (human papillomavirus type 11 L1 capsid protein antigen); 6LTE2DNX63 (human papillomavirus type 16 L1 capsid protein antigen); J2D279PEM5 (human papillomavirus type 18 L1 capsid protein antigen); 7XB76X2V7T (human papillomavirus type 16 L1 capsid protein residues 2-471 antigen); M7H9CF9G0Z (human papillomavirus type 18 L1 capsid protein residues 2-472 antigen).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Papillomavirus Vaccine (rDNA); Vaccinum Papillomaviri Humani (ADNr)). A preparation of purified virus-like particles composed of the major capsid protein of one or more human papillomavirus (HPV) genotypes, that is obtained by recombinant DNA technology. It may contain an adjuvant. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

Uses and Administration

A **quadrivalent** recombinant human papillomavirus (HPV) vaccine, prepared from purified virus-like particles of the capsid protein L1, is used in girls and women from 9 to 26 years of age to prevent diseases such as genital warts, cervical cancer, and other pre-cancerous lesions (cervical, vulvar, and vaginal) caused by HPV types 6, 11, 16, and 18. In the USA it is also licensed for the prevention of vulvar and vaginal cancers, as well as for boys and men from 9 to 26 years of age to prevent genital warts, and in both groups for the prevention of anal cancer and anal intraepithelial neoplasia. It is also being studied for the prevention of cervical cancer in women between 27 and 45 years of age.

It is given in 3 doses of 0.5 mL intramuscularly. The first dose may be given at any time between 9 and 26 years of age; the second dose is given 2 months later, and the third dose 6 months after the first dose.

A similar **bivalent** recombinant HPV vaccine, prepared from a mixture of L1 capsid proteins of HPV types 16 and 18 and containing an adjuvant AS04, is licensed for the prevention of cervical cancer and pre-cancerous cervical lesions in girls and women from 9 to 25 years of age (or between 10 and 45 years of age in Australia). In Europe it is also licensed for the prevention of pre-cancerous vulvar and vaginal lesions. It is given intramuscularly in 3 doses of 0.5 mL. The first dose may be given at any age in the approved range; the second dose is given 1 month later, and the third dose 6 months after the first dose.

Further vaccines are under investigation for the treatment or prophylaxis of genital warts and several malignant neoplasms.

Reviews and studies.

1. Keam SJ, Harper DM. Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted, adsorbed) [Cervarix ®]. *Drugs* 2008; **68:** 359–72.
2. Stanley M. HPV vaccines: are they the answer? *Br Med Bull* 2008; **88:** 59–74.
3. Huang CM. Human papillomavirus and vaccination. *Mayo Clin Proc* 2008; **83:** 701–6.
4. Flaherty DK, Alkhateeb FM. Human papillomavirus quadrivalent vaccine: a look behind the numbers. *Ann Pharmacother* 2009; **43:** 740–4.
5. Muñoz N, *et al.* Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. *Lancet* 2009; **373:** 1949–57.
6. Romanowski B, *et al.* GlaxoSmithKline Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *Lancet* 2009; **374:** 1975–85.
7. Kenter GG, *et al.* Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. *N Engl J Med* 2009; **361:** 1838–47.
8. WHO. Human papillomavirus vaccines: WHO position paper. *Wkly Epidem Rec* 2009; **84:** 118–31. Also available at: http://www.who.int/wer/2009/wer8415.pdf (accessed 23/06/10)
9. Campo MS, Roden RB. Papillomavirus prophylactic vaccines: established successes, new approaches. *J Virol* 2010; **84:** 1214–20.
10. Garland SM, Smith JS. Human papillomavirus vaccines: current status and future prospects. *Drugs* 2010; **70:** 1079–98.
11. McCormack PL, Joura EA. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil): a review of its use in the prevention of premalignant genital lesions, genital cancer and genital warts in women. *Drugs* 2010; **70:** 2449–74.
12. Palefsky JM, *et al.* HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011; **365:** 1576–85.
13. Garnock-Jones KP, Giuliano AR. Quadrivalent human papillomavirus (HPV) types 6, 11, 16, 18 vaccine: for the prevention of genital warts in males. *Drugs* 2011; **71:** 591–602.
14. Giuliano AR, *et al.* Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med* 2011; **364:** 401–11. Correction. *ibid.*; 1481.
15. McKeage K, Romanowski B. AS04-adjuvanted human papillomavirus (HPV) types 16 and 18 vaccine (Cervarix): a review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. *Drugs* 2011; **71:** 465–88.
16. Swedish KA, *et al.* Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. *Clin Infect Dis* 2012; **54:** 891–8.

Vaccine development and efficacy. There are more than 100 known human papillomavirus (HPV) genotypes; at least 13 of these can cause cervical cancer and are also associated with other anogenital cancers and cancers of the head and neck. Genotypes 16 and 18 cause about 70% of all cervical cancers, while genotypes 6 and 11 can cause genital warts. HPV is highly transmissible with risk of infection being highest soon after sexual activity begins. Asymptomatic and transient infection occurs in most people at some time in their life. However, the fact that more than 99% of cases of cervical cancer diagnosed are associated with the presence of sexually transmitted human papillomavirus DNA has prompted the possibility of vaccine development.

Viral recombinant proteins are being studied as antigenic components of both prophylactic and therapeutic vaccines.[1-9] Prophylactic vaccines are based on the recombinant capsid proteins L1 or L2 which self-assemble into virus-like particles which induce antibodies that in turn neutralise the infecting virus. Two such vaccines (a quadrivalent HPV vaccine effective against types 6, 11, 16, and 18 and a bivalent, adjuvanted HPV vaccine effective against types 16 and 18) are licensed in several countries. The bivalent vaccine was also reported to be effective against non-vaccine types 31, 33, and 45.[10] The prophylactic vaccines have no therapeutic effects and therefore cannot be given to women with persistent HPV infection, who are at risk of developing cervical cancer. Furthermore, vaccination does not appear to provide protection against progression to cervical intraepithelial neoplasia induced by HPV present at the time of vaccination. However, analysis of pooled data from 2 follow-up studies[11] found that, irrespective of causal HPV type, previous vaccination with

the quadrivalent HPV vaccine in women who had been diagnosed and treated for cervical and vulvar or vaginal disease was associated with a 35 to 46% reduction of subsequent HPV related disease (including high grade diseases). The development of therapeutic vaccines would benefit those women already positive for HPV DNA.[9,12] Therapeutic vaccines are based on the viral oncogenic proteins E6 and E7 and are designed to induce cell-mediated immune responses to eliminate infected cells; vaccine candidates are undergoing phase II evaluation. There is also some preliminary study being conducted into the possibility of a 'chimeric' vaccine combining both prophylactic and therapeutic components, but the immunogenicity and efficacy of such vaccines are unknown.

For it to be claimed justifiably that a prophylactic vaccine prevents cervical cancer, it is necessary to show that such a vaccine not only prevents infection but also prevents cancer itself, or at least a defined precursor of disease. Since any placebo-controlled study defining established cancer as an end-point would clearly be unethical, an appropriate compromise is to use the appearance of high-grade dysplasia or pre-cancerous lesions as an end-point, this being regarded as a direct precursor to cervical cancer requiring treatment. However, true pre-cancerous lesions of this kind are relatively unusual in current practice and therefore phase III studies require tens of thousands of subjects in order to establish this efficacy.[3]

Guidance and technical information on HPV, HPV-related diseases, and HPV vaccines has been produced by WHO.[13] They consider HPV vaccines to be highly effective among females not exposed to HPV vaccine genotypes at the time of their first vaccination and that the target group for vaccination will probably be preadolescent girls (about 9 to 12 years of age). Guidelines for the use of HPV vaccine for the prevention of cervical cancer have been developed in the USA by the CDC,[14] the American Cancer Society[15] and the American Academy of Pediatrics (AAP).[16] These authorities recommend routine vaccination for all girls 11 to 12 years of age, although girls as young as 9 years of age may be vaccinated at the discretion of their doctor. Catch-up vaccinations may be given to older girls and young women who have not received or completed a vaccine course. Guidelines have also been developed in the USA[16,17] and Australia[18] for the use of quadrivalent HPV vaccine in males. The CDC and the AAP recommend routine vaccination of males 11 to 12 years of age, although the vaccination series can be started at 9 years of age. Catch-up vaccination courses are recommended for older males aged 13 to 21 years who have not received or completed a vaccine course; males aged 22 to 26 years may also be vaccinated. In the UK the Joint Committee on Vaccination and Immunisation[19] recommends routine vaccination of all girls 12 to 13 years of age. Catch-up vaccination is recommended for girls under 18 years of age.

1. Galloway DA. Papillomavirus vaccines in clinical trials. *Lancet Infect Dis* 2003; **3:** 469–75.
2. Lehtinen M, Paavonen J. Effectiveness of preventive human papillomavirus vaccination. *Int J STD AIDS* 2003; **14:** 787–92.
3. Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; **55:** 319–31.
4. Mandic A, Vujkov T. Human papillomavirus vaccine as a new way of preventing cervical cancer: a dream or the future? *Ann Oncol* 2004; **15:** 197–200.
5. Roden RBS, *et al*. Vaccination to prevent and treat cervical cancer. *Hum Pathol* 2004; **35:** 971–82.
6. Lowndes CM, Gill ON. Cervical cancer, human papillomavirus, and vaccination. *BMJ* 2005; **331:** 915–16.
7. Harper DM, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364:** 1757–65.
8. Poland GA, *et al*. Immunogenicity and reactogenicity of a novel vaccine for human papillomavirus 16: a 2-year randomized controlled clinical trial. *Mayo Clin Proc* 2005; **80:** 601–10.
9. Cid-Arregui A. Therapeutic vaccines against human papillomavirus and cervical cancer. *Open Virol J* 2009; **3:** 67–83.
10. Paavonen J, *et al*. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374:** 301–14. Correction. *ibid.*; **376:**1054.
11. Joura EA, *et al*. for the FUTURE I and II Study Group. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ* 2012; **344:** e1401.
12. Hildesheim A, *et al*. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. *JAMA* 2007; **298:** 743–53.
13. WHO. *Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals*. Geneva: WHO, 2007. Available at: http://www.who.int/vaccines-documents/DocsPDF07/866.pdf (accessed 26/06/07)
14. CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; **59:** 626–9. Correction. *ibid.*; 1184.
15. Saslow D, *et al*. American Cancer Society guidelines for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007; **57:** 7–28. Also available at: http://caonline.amcancersoc.org/cgi/reprint/57/1/7 (accessed 26/06/07)
16. American Academy of Pediatrics Committee on Infectious Diseases. HPV vaccine recommendations. *Pediatrics* 2012; **129:** 602–5. http://pediatrics.aappublications.org/content/129/3/602.full.html (accessed 04/04/12)
17. CDC. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011; **60:** 1705–8.
18. Department of Health and Ageing. *The Australian Immunisation Handbook* 10th edition, 2013. Available at: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/EE1905BC65D40BCFCA257B26007FC8CA/$File/part4.pdf (accessed 15/04/13)
19. Health Protection Report. HPV vaccination programme to begin in the UK in Autumn 2008 (issued 2 November, 2008). Available at: http://www.hpa.org.uk/hpr/archives/2007/news2007/news4407.htm (accessed 07/04/08)

Laryngeal papillomatosis. A 5-year-old girl with recurrent laryngeal papillomatosis due to human papillomavirus type 11, who had required frequent surgical treatment, recovered completely after receiving a 3-dose course of quadrivalent human papillomavirus vaccine; the patient was still disease free 17 months after vaccination.[1]

1. Mudry P, *et al*. Recurrent laryngeal papillomatosis: successful treatment with human papillomavirus vaccination. *Arch Dis Child* 2011; **96:** 476–7.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Breast feeding. In mothers given the quadrivalent recombinant human papillomavirus vaccine or placebo during clinical studies, the rates of adverse reactions in the mother and in the breast-fed infant, as well as vaccine immunogenicity, were comparable in the 2 groups. Based on apparently the same data the UK licensed product information states that the vaccine can be given to breast-feeding women whereas the US information recommends caution. UK licensed product information for the bivalent vaccine recommends it should only be used when the benefits outweigh the possible risks.

Effects on the nervous system. Demyelinating disease[1-3] and neuromyelitis optica[4] have been temporally associated with human papillomavirus vaccinations, although causality has not been confirmed.

1. Sutton I, *et al*. CNS demyelination and quadrivalent HPV vaccination. *Mult Scler* 2009; **15:** 116–19.
2. Álvarez-Soria MJ, *et al*. Trastornos neurológicos desmielinizantes y vacunación del papilomavirus humano. *Rev Neurol* 2011; **52:** 472–6.
3. Chang J, *et al*. Demyelinating disease and polyvalent human papilloma virus vaccination. *J Neurol Neurosurg Psychiatry* 2011; **82:** 1296–8.
4. Menge T, *et al*. Neuromyelitis optica following human papillomavirus vaccination. *Neurology* 2012; **79:** 285–7.

Incidence of adverse effects. Up to September 2009, more than 26 million doses of quadrivalent recombinant human papillomavirus vaccine (qHPV) had been distributed in the USA and 15 037 adverse events after vaccination had been reported to the Vaccine Adverse Event Reporting System (VAERS). Ninety three percent of these reports were considered to be non-serious and 7% serious. Non-serious adverse effects included syncope (sometimes with tonic-clonic movements and other seizure-like activity), pain and swelling at the injection site, dizziness, fever, nausea, headache, hypersensitivity reactions, and urticaria. Serious adverse effects reported after vaccination included Guillain-Barré syndrome, transverse myelitis, pancreatitis, auto-immune disorders, motor neurone disease, and anaphylaxis. Venous thromboembolic events had also been rarely reported; but most people who reported these adverse events had a risk factor, such as the use of an oral contraceptive. There had been 44 deaths reported after vaccination; 27 of which were confirmed and followed up.[1,2]

When compared with other vaccines, most of the adverse effects for qHPV were not more frequent. Furthermore, no unusual pattern or clustering of deaths or serious adverse effects was found that might suggest that the vaccine was responsible.[1,2]

In the UK the bivalent recombinant human papillomavirus vaccine is given as part of the immunisation programme. At the end of July 2009, at least 1.4 million doses had been given and 2195 reports of adverse events after vaccination had been received by the MHRA. The most commonly reported adverse effects were dizziness, headache, nausea, pain in extremity (mainly sore arm), syncope, vomiting, malaise, fatigue, fever, and rash. Other adverse effects reported include 13 reports of chronic fatigue syndrome, 1 report of Guillain-Barré syndrome, and 1 report of facial palsy.[3]

1. Slade BA, *et al*. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009; **302:** 750–7.
2. CDC. Reports of health concerns following HPV vaccination (as updated 5th November 2009). Available at: http://www.cdc.gov/vaccinesafety/Vaccines/HPV/gardasil.html (accessed 23/11/09)
3. MHRA. Human papillomavirus (HPV) immunisation programme—first year safety review. *Drug Safety Update* 2009: **3:** 5–8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON059813&RevisionSelectionMethod=LatestReleased (accessed 26/08/10)

Pregnancy. Although specific studies of the quadrivalent and bivalent recombinant human papillomavirus vaccines in pregnant women have not been conducted, some women during clinical development did receive the vaccine in pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in those who received the vaccine and those who received placebo. It is, nevertheless, recommended that vaccination should be postponed until after completion of pregnancy; if pregnancy occurs before the vaccination course has been completed, the remaining doses should be given after pregnancy completion.

These findings and recommendations are supported by a literature review[1] (up to August 2010) that found no increased risk of adverse pregnancy outcomes or malformations for the 369 pregnancies that occurred within 30 days of receiving a human papillomavirus vaccine.

1. Forinash AB, *et al*. Safety of the HPV bivalent and quadrivalent vaccines during pregnancy. *Ann Pharmacother* 2011; **45:** 258–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cervarix; Gardasil; ***Austral.***: Cervarix; Gardasil; ***Austria***: Cervarix; Gardasil; ***Belg.***: Cervarix; Gardasil; ***Canad.***: Cervarix; Gardasil; ***Chile***: Cervarix; Gardasil; ***Cz.***: Cervarix; Gardasil; Silgard; ***Denm.***: Cervarix; Gardasil; Silgard; ***Fr.***: Cervarix; Gardasil; ***Ger.***: Cervarix; Gardasil; ***Gr.***: Cervarix; Gardasil; ***Hong Kong***: Cervarix; Gardasil; ***Hung.***: Cervarix; Silgard; ***India***: Gardasil; ***Indon.***: Cervarix; Gardasil; ***Irl.***: Cervarix; Gardasil; Silgard; ***Israel***: Cervarix; Gardasil; ***Ital.***: Cervarix; Gardasil; ***Jpn***: Gardasil; ***Malaysia***: Cervarix; Gardasil; ***Neth.***: Cervarix; Gardasil; Silgard; ***Norw.***: Cervarix†; Gardasil; ***NZ***: Cervarix; Gardasil; ***Philipp.***: Cervarix; Gardasil; ***Pol.***: Cervarix; Gardasil; Silgard; ***Port.***: Cervarix; Gardasil; Silgard; ***Rus.***: Cervarix (Церварикс); Gardasil (Гардасил); ***S.Afr.***: Cervarix; Gardasil; ***Singapore***: Cervarix; Gardasil; ***Spain***: Cervarix; Gardasil; ***Swed.***: Cervarix; Gardasil; ***Switz.***: Cervarix; Gardasil; ***Thai.***: Cervarix; Gardasil; ***Turk.***: Cervarix; Gardasil; ***UK***: Cervarix; Gardasil; ***Ukr.***: Cervarix (Церварикс); Gardasil (Гардасил); ***USA***: Cervarix; Gardasil.

Pharmacopoeial Preparations

Ph. Eur.: Human Papillomavirus Vaccine (rDNA).

Influenza Vaccines

Flu Vaccines; Vacunas de la gripe; Противогриппозные Вакцины.

ATC — J07BB01; J07BB02; J07BB03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Influenza Vaccine (Whole Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Viris Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu may be used on the label.

The BP 2014 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 8: (Influenza Vaccine (Split Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Virorum Fragmentis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that the integrity of the virus particles has been disrupted without diminishing their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu may be used on the label.

The BP 2014 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 8: (Influenza Vaccine (Surface Antigen, Inactivated); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum). A sterile suspension consisting mainly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain

their antigenic properties. The stated amount of haemagglutinin antigen for each strain is usually 15 micrograms per dose. It may contain an adjuvant. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu or Flu(adj) may be used on the label as appropriate.

The BP 2014 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 8: (Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum Virosomale). A sterile aqueous suspension consisting mainly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties and reconstituted to virosomes with phospholipids and without reducing the antigenic properties of the antigens. The stated amount of haemagglutinin antigen for each strain is 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu may be used on the label.

Ph. Eur. 8: (Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Virisque Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu or Flu (adj) may be used on the label as appropriate.

Ph. Eur. 8: (Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Corticisque Antigeniis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu or Flu (adj) may be used on the label as appropriate.

Nomenclature of strains. The strain designation for influenza virus types A, B, and C contains: a description of the antigenic specificity of the nucleoprotein antigen (types A, B, or C) (an internal antigen, the matrix antigen, has also been described); the host of origin (if not man, including, if appropriate, the inanimate source); the geographical origin; the strain number; and the year of isolation; e.g. A/lake water/Wisconsin/1/79. For type A viruses the antigenic description follows (in parentheses) including the antigenic character of the haemagglutinin (e.g. H1) and the antigenic character of the neuraminidase (e.g. N1). There is no provision for describing subtypes of B and C viruses. Recombination between viruses within a type is readily accomplished; the letter R should be added after the strain description to indicate the recombinant nature of the virus, e.g. A/Hong Kong/1/68(H3N2)R. In addition the strain of origin of the H and N antigens of antigenic hybrid recombinant A and B viruses should be given, e.g. A/BEL/42(H1)—Singapore/1/57(N2)R.[1]

1. Assaad FA, *et al*. Revision of the system of nomenclature for influenza viruses: a WHO Memorandum. *Bull WHO* 1980; **58:** 585–91.

Uses and Administration

Influenza vaccines are used for active immunisation against seasonal influenza.

Three types of the influenza virus occur, namely types A, B, and C, and the formulation and composition of influenza vaccines is constantly reviewed with changes made to accommodate the antigenic shifts and drifts of the influenza virus. Recommendations concerning the antigenic nature of influenza vaccines are made annually by WHO. Currently, influenza vaccines are mainly of the inactivated type and are available as split-virion vaccines or as various surface-antigen vaccines (including virosomal products); whole-virion vaccines are now seldom used. Live attenuated influenza vaccines against influenza virus types A and B are also available.

Influenza vaccination is generally recommended for persons considered to be at special risk, particularly the elderly, those with chronic heart disease, chronic respiratory disease including asthma (but see Asthma, under Precautions, p. 2395.3), chronic hepatic, neurological, or renal disease, diabetes mellitus, and patients who are immunosuppressed. Vaccination is also recommended for residents, particularly elderly persons and children, in closed institutions. Medical personnel and other persons at risk from infection through contact with infected patients should also receive vaccination. In the USA, annual vaccination of all children from 6 months to 18 years of age and all adults from 50 years of age is recommended. Vaccination usually produces immunity after about 14 days, lasting for about 6 months to 1 year. Injections are therefore scheduled annually so that the period of maximum immunity coincides with the usual period of influenza infection. In the UK and USA, they are generally given between September and early November.

Influenza vaccines are usually given in the UK by deep *subcutaneous* injection or *intramuscular* injection. The preferred site for injection is the deltoid muscle in adults and older children and, in infants and young children, the anterolateral aspect of the thigh. The recommended dose is 0.5 mL for adults and children aged over 3 years. In children aged 6 months to 3 years, doses of 0.25 or 0.5 mL have been used. Children should be given a second dose at least 4 weeks after the first if receiving the vaccine for the first time. In the USA, a single intramuscular dose of 0.5 mL of a high-dose inactivated influenza vaccine, containing 60 micrograms per viral strain (180 micrograms per 0.5 mL), may be given for active immunisation of adults 65 years of age and older.

An inactivated *intradermal* seasonal influenza vaccine containing 9 micrograms of antigen per viral strain is available in the UK for use in adults from 18 to 59 years of age and a vaccine with 15 micrograms per viral strain is available for use in adults from 60 years of age; both are given as a single dose of 0.1 mL.

The live attenuated influenza vaccine is given *intranasally*, in a dose of 0.2 mL (0.1 mL in each nostril) in adults (up to 49 years of age) and children from 2 years of age. Children who have not previously been vaccinated against seasonal influenza should be given a second dose at least 4 weeks after the first if receiving the vaccine for the first time.

Current commercially available seasonal influenza vaccines are not effective against avian influenza virus H5N1 but most are effective against pandemic (H1N1) 2009 influenza. For further information on vaccines against these influenza strains, see below.

Reviews.

1. WHO. Influenza vaccines: WHO position paper. *Wkly Epidem Rec* 2005; **80:** 279–87. Also available at: http://www.who.int/immunization/wer8033influenza_August2005_position_paper.pdf (accessed 23/6/10)
2. Jefferson T, *et al*. Vaccines for preventing influenza in healthy children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).
3. Audsley JM, Tannock GA. Cell-based influenza vaccines: progress to date. *Drugs* 2008; **68:** 1483–91.
4. Goossen GM, *et al*. Influenza vaccination in children being treated with chemotherapy for cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 01/12/09).
5. Jefferson T, *et al*. Vaccines for preventing influenza in the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 26/08/10).
6. Jefferson T, *et al*. Vaccines for preventing influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2010 (accessed 26/08/10).
7. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2012-13 Influenza Season. *MMWR* 2012; **61:** 613–8. Also available at: http://www.cdc.gov/mmwr/pdf/wk/mm6132.pdf (accessed 20/09/12)

Avian influenza vaccine. Since 1997, infection of humans with avian influenza virus H5N1 has been reported and is associated with high mortality. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic. Candidate avian influenza vaccines have been investigated and *Sanofi Pasteur, USA* has developed a vaccine (monovalent, split virion, inactivated vaccine containing A/Vietnam/1203/2004 (H5N1) influenza virus strain). Although the vaccine will not be commercially available, it has been licensed by the FDA and will be included in the National Stockpile in the USA for use in the event that the H5N1 virus develops the ability to become readily transmissible from human to human.[1] In the EU, a monovalent, whole viron, vero-cell derived, inactivated vaccine containing the A/Vietnam/1203/2004 (H5N1) influenza virus strain is available (*Vepacel; Baxter, EU*). Targeted use of stockpiled prepandemic influenza vaccines during the pandemic alert period or in the early stages of a pandemic aims to reduce the consequences of an influenza outbreak while specific vaccines against the novel pandemic virus are being developed.[2]

1. FDA. FDA news: FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1 (issued 17th April, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108892.htm (accessed 26/08/10)
2. Plosker GL. A/H5N1 prepandemic influenza vaccine (whole virion, vero cell-derived, inactivated) [Vepacel]. *Drugs* 2012; **72:** 1543–57.

Pandemic (H1N1) 2009 influenza. An influenza outbreak in humans, first detected in Mexico in April 2009 and known as swine flu, was due to a new strain of influenza A virus, subtype H1N1 that transmitted sufficiently easily from person-to-person to be of concern for a pandemic. Infections have been reported worldwide and deaths have occurred; on 11th June 2009 WHO declared a worldwide pandemic. No effective vaccine was immediately available, and an evaluation by the CDC[1] found that vaccination with recent (2005 to 2009) seasonal influenza vaccines was unlikely to provide protection against the pandemic virus.

The first vaccines against this pandemic influenza A strain were approved in September 2009. Methods used to develop and produce these vaccines were similar to those used for seasonal influenza vaccine and the A/California/07/2009 (H1N1) strain of virus was used in their production. The FDA has approved 4 monovalent vaccines; 3 are inactivated and given intramuscularly, while 1 is a live vaccine and is given intranasally. The EMEA has approved 2 monovalent inactivated vaccines containing adjuvants; both are given by intramuscular injection. Guidelines for the use of these vaccines have been developed.[2-4] WHO has recommended that an A/California/07/2009 (H1N1) strain of virus be included in the influenza vaccine for the 2012-2013 northern hemisphere influenza season.[5]

1. CDC. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. *MMWR* 2009; **58:** 521–4. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5819.pdf (accessed 22/05/09)
2. National Center for Immunization and Respiratory Diseases, CDC. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* 2009; **58** (RR-10): 1–8. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5810.pdf (accessed 29/09/09)
3. WHO. WHO recommendations on pandemic (H1N1) 2009 vaccines: pandemic (H1N1) 2009 briefing note 2 (issued 13th July, 2009). Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/index.html (accessed 29/09/09)
4. DoH. Further details about the H1N1 swine flu vaccination programme 2009–2010. Message from the Chief Medical Officer, Sir Liam Donaldson (issued 13th August, 2009). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104315.pdf (accessed 27/08/10)
5. WHO. Recommended composition of influenza virus vaccines for use in the 2012-2013 northern hemisphere influenza season; February 2012. Available at: http://www.who.int/influenza/vaccines/virus/recommendations/201202_recommendation.pdf (accessed 16/03/12)

Adverse Effects

As for vaccines in general, p. 2375.1.

Local and systemic reactions may occur but are usually mild. Fever and malaise sometimes occur and severe febrile reactions have been reported particularly on giving whole-virion vaccine to children, although this type of vaccine is seldom used now. Flu-like symptoms may follow the use of live, attenuated vaccines.

Various neurological syndromes have been temporally associated with use of influenza vaccine, the most notable report being of the Guillain-Barré syndrome occurring after vaccination with inactivated swine influenza vaccine in 1976 (see p. 2395.1).

Effects on the blood. Autoimmune haemolytic anaemia has been reported in two elderly women 2 to 3 days after vaccination with an adjuvanted (MF59) influenza vaccine. Both women were treated with intravenous corticosteroids and other supportive treatment; one women died within 48 hours while the clinical condition of the other improved. The mechanism for this reaction is probably molecular mimicry, although the role of adjuvants cannot be excluded.[1]

1. Montagnani S, *et al*. Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases. *Ann Pharmacother* 2011; **45:** e8.

Effects on the eyes. For a discussion of bilateral eye redness, occurring as part of an oculorespiratory syndrome after influenza vaccination, see p. 2395.2.

Effects on the nervous system. *BELL'S PALSY.* Between October 2000 and April 2001, the Swiss Drug Monitoring Centre and the University of Zurich received 46 reports of Bell's palsy occurring in patients who had used an inactivated intranasal influenza vaccine (*Nasalflu*). The manufacturers suspended distribution of the vaccine and, after a subsequent study[1] suggested a strong association between the vaccine and the development of Bell's palsy, it was withdrawn from clinical use.

1. Mutsch M, *et al.* Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *N Engl J Med* 2004; **350:** 896–903.

ENCEPHALOMYELITIS SYNDROME. Three cases of acute encephalomyelitis syndrome have been reported in Australia following vaccination with a pandemic (H1N1) 2009 influenza vaccine in previously healthy adults. They were all treated with intravenous methylprednisolone for 3 to 5 days; symptoms improved and weakness resolved in all 3 patients, although, in one patient, the paraesthesia persisted for 3 weeks after treatment.[1]

1. Denholm JT, *et al.* Acute encephalomyelitis syndromes associated with H1N1 09 influenza vaccination. *Neurology* 2010; **75:** 2246–8.

GUILLAIN-BARRÉ SYNDROME. In 1976 a limited outbreak of influenza in the USA caused by a virus closely resembling the swine influenza virus led to the use of a killed swine influenza virus vaccine.[1] After about 45 million doses of the vaccine had been given the vaccination programme ceased because there was some evidence of a temporal association between vaccination and the onset of a paralytic polyneuropathy of the Guillain-Barré type. An epidemiologic and clinical evaluation of these cases suggested a definite link between vaccination and the onset of the syndrome with extensive paralysis but no association with the onset of limited motor lesions.

Surveillance systems have since investigated any possible link with the development of Guillain-Barré syndrome. The Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence was inadequate to either accept or reject a causal relationship with non-swine influenza vaccines used after 1976. This review had inspected reports submitted from 1990 to 2003 to VAERS (Vaccine Adverse Events Reporting System in the USA) but considered that such case reports were uninformative with respect to causality, although they were useful for hypothesis generation. One suggestion made by workers monitoring the VAERS data[3] was the question as to whether *Campylobacter* infection could be involved. Influenza vaccines have traditionally been made in chicken eggs. *Campylobacter* is endemic in chickens and a known cause of Guillain-Barré syndrome.

In October 2009, the CDC's Emerging Infections Program began active surveillance to assess the risk for Guillain-Barré syndrome after vaccination with the monovalent unadjuvanted pandemic (H1N1) 2009 influenza vaccine. Preliminary results showed an elevated, statistically significant association between vaccination and Guillain-Barré syndrome. If these findings are confirmed at the end-of-surveillance analysis, the excess risk for Guillain-Barré syndrome (about 0.8 excess cases per 1 million vaccinations) associated with pandemic (H1N1) 2009 influenza vaccine would be comparable to the excess reported for some trivalent seasonal influenza vaccine formulations (about 1 excess case per 1 million vaccinations) and much smaller than the risk seen during the 1976 swine influenza vaccination programme (about 10 excess cases per 1 million vaccinations).[4] From the 1st October until 24th November 2009, 12 possible cases of Guillain-Barré syndrome had been reported to VAERS. After a review of these cases, 4 met Brighton Collaboration criteria for Guillain-Barré syndrome and 4 did not meet the criteria; 4 were still being reviewed.[5] A multinational case-controlled study[6] in 5 European countries reported no increased risk of Guillain-Barré syndrome (after adjusting for flu-like illness and upper respiratory-tract infections) following vaccination with a monovalent adjuvanted pandemic (H1N1) 2009 influenza vaccine.

1. Anonymous. Influenza and the Guillain-Barré syndrome. *Lancet* 1984; **ii:** 850–1.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications.* Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog.php?record_id=10822 (accessed 26/08/10)
3. Haber P, *et al.* Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004; **292:** 2478–81.
4. CDC. Preliminary results: surveillance for Guillain-Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. *MMWR* 2010; **59:** 657–61.
5. CDC. Safety of influenza A (H1N1) 2009 monovalent vaccines United States, October 1-November 24, 2009. *MMWR* 2009; **58:** 1351–6.
6. Dieleman J, *et al.* Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. *BMJ* 2011; **343:** d3908.

MULTIPLE SCLEROSIS. Analysis[1] indicated that there was no association between the use in the USA during 1976 of influenza vaccines containing a swine virus component and the development of multiple sclerosis. Later analysis by the Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence favoured rejection of a causal relationship between influenza vaccines used in various years (including the swine vaccines of 1976) and relapse of multiple sclerosis but that the evidence was inadequate to either accept or reject a causal relationship with incident multiple sclerosis.

1. Kurland LT, *et al.* Swine flu vaccine and multiple sclerosis. *JAMA* 1984; **251:** 2672–5.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications.* Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog.php?record_id=10822 (accessed 26/08/10)

NARCOLEPSY. Cases of narcolepsy, especially in children and adolescents, have been reported following vaccination with monovalent adjuvanted pandemic (H1N1) 2009 influenza vaccines; in most cases *Pandemrix* (manufactured by GlaxoSmithKline) was given.[1-4]

In February 2011, the National Institute for Health and Welfare (THL) of Finland issued a preliminary statement following a retrospective registry-based review into cases of narcolepsy in Finland between 2009 to 2010. A total of 60 cases of narcolepsy were identified in children and adolescents aged 4 to 19 years during this time period and 52 (87%) of them had been vaccinated with *Pandemrix*. The risk of narcolepsy in this age group was calculated to be nine times higher for those vaccinated with *Pandemrix*than for non-vaccinated persons. No increased risk has been seen in those over 19 years of age; no cases were noted in children under 4 years.[2]

In June 2011 the Medical Products Agency (MPA) in Sweden published their results of a review of all cases of severe narcolepsy with cataplexy during 2009 to 2010. Their review also supported a link between vaccination with *Pandemrix* and the risk of narcolepsy in children and adolescents aged 19 years and younger. A total of 81 cases of narcolepsy were identified in children and adolescents during this time period and 69 (85%) of them had been given *Pandemrix* vaccination. Those vaccinated with *Pandemrix* were shown to have an almost 7-fold increased risk for diagnosis of narcolepsy with cataplexy compared with non-vaccinated persons.[3]

The number of cases reported from Sweden, Finland, and Iceland have been higher than for other countries; increased rates of narcolepsy have not been reported from several other European countries, or from Canada where a pandemic (H1N1) 2009 influenza vaccine similar to Pandemrix was used. An increased rate of narcolepsy has also not been reported following use of any other influenza vaccines or for vaccines against other diseases. It does not therefore appear that narcolepsy following vaccination against pandemic influenza is a general worldwide phenomenon and it may be that some unidentified additional factor was operating in Sweden and Finland.[1-4]

Nonetheless, in July 2011, and following a review of the available information, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that *Pandemrix* vaccine should only be given to persons under 20 years of age if the recommended seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is still needed. Their investigation confirmed an association between *Pandemrix* and narcolepsy and indicated a 6- to 13-fold increased risk of narcolepsy (with or without cataplexy) in vaccinated when compared with unvaccinated children and adolescents; this risk corresponded to about an extra 3 to 7 cases in every 100,000 vaccinated persons.[4]

1. WHO. Global Committee on Vaccine Safety: statement on narcolepsy and vaccination (issued 21st April, 2011). Available at: http://www.who.int/vaccine_safety/topics/influenza/pandemic/h1n1_safety_assessing/narcolepsy_statement/en/ (accessed 21/03/12)
2. National Institute for Health and Welfare. National narcolepsy task force; interim report, 31st January, 2011. Available at: http://www.thl.fi/thl-client/pdfs/dce182fb-651e-48a1-b018-3f774d6d1875 (accessed 21/03/12)
3. Medical Products Agency. Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations — results of a case inventory study by the MPA in Sweden during 2009—2010 (issued 30th June, 2011). Available at: http://www.lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandermrix_110630.pdf (accessed 21/03/12)
4. EMA. Assessment report: Pandemrix. (issued 21st July, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000832/WC500118056.pdf (accessed 21/03/12)

Effects on the respiratory tract. For a discussion of respiratory symptoms, occurring as part of an oculorespiratory syndrome after influenza vaccination, see below.

Henoch-Schönlein purpura. Influenza vaccination has been associated with both development[1] and exacerbation[2] of Henoch-Schönlein purpura.

1. Patel U, *et al.* Henoch-Schönlein purpura after influenza vaccination. *BMJ* 1988; **296:** 1800.
2. Damjanov I, Amato JA. Progression of renal disease in Henoch-Schönlein purpura after influenza vaccination. *JAMA* 1979; **242:** 2555–6.

Oculorespiratory syndrome. During 2000 to 2001, an increased incidence of ocular and respiratory effects was reported in Canada in 960 patients, 96% of whom had received a specific split virion influenza vaccine (*Fluviral S/F*).[1] Symptoms included bilateral redness of the eyes and facial oedema with coughing, wheezing, tightness of the chest, breathing difficulty, or sore throat and were collectively termed oculorespiratory syndrome.[1,2] It was postulated that the syndrome might be due to many microaggregates of unsplit viruses present in the vaccine. A study[3] using an improved formulation of the vaccine found that oculorespiratory symptoms still occurred in 6.3% of recipients and that, since the improved formulation was otherwise minimally reactogenic, such symptoms might be associated with influenza vaccines in general. A subsequent study[4] of influenza vaccination among persons previously afflicted by oculorespiratory syndrome was halted early owing to a 33% rate of recurrence of symptoms within 24 hours. The authors concluded that previously afflicted patients should be warned of the risk of recurrence but that episodes of recurrence were usually mild and well tolerated.[4]

1. National Advisory Committee on Immunization. Supplementary statement for the 2001-2002 season: influenza vaccination of persons who experienced oculo-respiratory syndrome following previous influenza vaccination. *Can Commun Dis Rep* 2001; **27** (Nov.15): 1–7.
2. Boulianne N, *et al.* Clinical manifestations and incidence of oculo-respiratory syndrome following influenza vaccination—Quebec, 2000. *Can Commun Dis Rep* 2001; **27:** 85–90.
3. Scheifele DW, *et al.* Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. *Clin Infect Dis* 2003; **36:** 850–7.
4. Skowronski DM, *et al.* Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis* 2003; **37:** 1059–66.

Precautions

As for vaccines in general, p. 2375.2.

Whole-virion influenza vaccine is not recommended for use in children because of the increased risk of febrile reactions. Split-virion and surface-antigen vaccines are, however, suitable for children and infants and are widely used in mass immunisation campaigns. Live, attenuated vaccines should not be given to children and adolescents younger than 18 years of age who are also receiving salicylates because of the association of Reye's syndrome with salicylates and wild-type influenza infection. Salicylates and salicylate-containing products should be avoided for 4 weeks following vaccination.

Recommendations on influenza vaccine use in subjects with egg allergy are discussed below.

Vaccination should be postponed in patients with active infection or acute febrile illness.

Asthma. There have been reports of exacerbations of asthma after influenza vaccination,[1,2] but reviews[3,4] have concluded that evidence of a causal relationship is lacking and that any risk of exacerbation which might exist is outweighed by the risk of influenza itself. Chronic respiratory disease, including asthma, is an indication for influenza vaccination in both the UK and USA. A systematic review has supported the use of inactivated vaccines for patients with chronic obstructive pulmonary disease.[5] A further systematic review, however, has concluded that, while there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination), uncertainty remains about the degree of protection that vaccination affords against asthma exacerbations after influenza infection.[6]

1. Hassan WU, *et al.* Influenza vaccination in asthma. *Lancet* 1992; **339:** 194.
2. Nicholson KG, *et al.* Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet* 1998; **351:** 326–31.
3. Watson JM, *et al.* Does influenza immunisation cause exacerbations of chronic airflow obstruction or asthma? *Thorax* 1997; **52:** 190–4.
4. Park CL, Frank A. Does influenza vaccination exacerbate asthma? *Drug Safety* 1998; **19:** 83–8.
5. Poole P, *et al.* Influenza vaccine for patients with chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 04/05/06).
6. Cates CJ, *et al.* Vaccines for preventing influenza in people with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).

Diagnostic tests. False-positive screening enzyme-linked immunosorbent assays (ELISAs) for antibodies to HIV-1, HTLV-1 and hepatitis C virus were reported in blood donors who had recently received influenza vaccine.[1] The reaction was attributed to cross-reactivity of the test kit in use at the time with non-specific IgM.

1. Anonymous. False-positive serologic tests for human T-cell lymphotropic virus type 1 among blood donors following influenza vaccination, 1992. *JAMA* 1993; **269:** 2076 and 2078.

Egg allergy. Since most influenza vaccines are grown in cell cultures of chick embryos and may contain residual egg protein (ovalbumin), licensed product information generally contra-indicates their use in individuals with a history of hypersensitivity reactions to egg. However, in recent years, influenza vaccines with a very low ovalbumin content (< 120 nanograms/mL) have become avail-

able and have been used safely in some patients with an allergy to eggs. Egg-free vaccines are also now available.

In the UK, the Department of Health has issued[1] the following advice when immunising subjects with an allergy to eggs:

- subjects with a history of *anaphylaxis to eggs* or with *egg allergy and uncontrolled asthma* should be given an egg-free vaccine or, if unavailable, a vaccine with an ovalbumin content of < 12 nanograms/mL can be given in a hospital setting.
- all other subjects with *allergies to eggs* may be given egg-free vaccine or a vaccine with an ovalbumin content of < 12 nanograms/mL.
- vaccines with ovalbumin content (> 120 nanograms/mL) or where content is not stated should not be given to egg-allergic individuals.

It should be noted that ovalbumin concentrations can vary from season to season and between lots for a given vaccine.

Guidelines for the use of influenza vaccines in persons with a history of egg allergy have also been provided by authorities in the USA.[2]

1. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 11/07/12)
2. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011; **60:** 1128–32. Also available at: http://www.cdc.gov/mmwr/pdf/wk/mm6033.pdf (accessed 13/07/12)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies influenza vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

For the effect of influenza vaccination on some other drugs see under Phenobarbital Sodium, p. 538.1, Phenytoin Sodium, p. 545.2, Theophylline Hydrate, p. 1236.3, and Warfarin Sodium, p. 1535.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agrippal; Begrivac; Fluad; Fluarix; Inflexal; Influvac; Isiflu Zonale; Istivac; Mutagrip; Nilgrip; Vaxigrip; ***Austral.***: Fluad; Fluarix; Fluvax; Influvac; Intanza; Panvax; Vaxigrip; ***Austria***: Addigrip†; Batrevac†; Begrivac†; Fluad; FluVaccinol; Inflexal; Influvac; Intanza; Sandovac; Vaxigrip; ***Belg.***: α-Rix; Agrippal†; Fluad; Inflexal†; Influvac S; Intanza; Pandemrix; Vaxigrip; ***Braz.***: Agrippal†; Vacina Contra Gripe; Vacina de Virus Inativado Contra Gripe; ***Canad.***: Agriflu; Arepanrix; Fluad; FluMist; Fluviral; Influenza A (H1N1) Monovalent Vaccine†; Influvac; Intanza; Vaxigrip; ***Chile***: Begrivac; Bio-Flu; Fluarix; Fluazur; Inflexal; Influvac; Mevac-Flu; Vaxigrip; ***China***: Agrippal (爱阁力保); Anflu (安尔来福); Fluad (复立达); Fluarix (福禄立适); Fluvax (扶洛凡); Fluviral; Inflexal (因福舒); Influvac (英伏可); Panflu 1 (盼尔来福); Shi Pu Li Er (适普利尔); Vaxigrip (凡尔灵); Ying Fu Ning (英扶宁); Ying Te Fu Lu (英特福禄); Yu Gan Ning (御感宁); ***Cz.***: Aflunov; Begrivac; Celvapan; Daronrix; Fluad; Fluarix; Fluenz; Focetria; Foclivia; IDflu; Inflexal†; Influvac; Intanza; Optaflu; Pandemrix; Preflucel; Prepandrix; Pumarix; Vaxigrip; ***Denm.***: Agrippal; Begrivac; Fluad; Fluarix; Fluenz; Inflexal; Influvac; Intanza; Mutagrip; Pandemrix†; Vaxigrip; ***Fin.***: Agrippal; Begrivac†; Fluarix; Flupar†; Fluvirin†; Inflexal; Influvac; Preflucel; Vaxigrip; ***Fr.***: Agrippal; Celvapan†; Fluarix; Fluvirine†; Focetria; Gripguard; Humenza†; Immugrip; Influvac; Intanza†; Mutagrip†; Pandemrix†; Panenza†; Previgrip†; Vaxigrip; ***Ger.***: Addigrip†; Afluria; Begrivac†; Fluad; FluVaccinol†; Infectovac Flu; Inflexal†; Influsplit SSW; Influvac; Intanza; Mutagrip; Preflucel; ***Gr.***: Addigrip; Agrippal; Evagrip; Fluarix; Inflexal; Influvac; Mutagrip; Vaxigrip; ***Hong Kong***: Agrippal; Fluad†; Fluarix; FluMist; Fluvax; Fluzone; Inflexal; Influvac; Intanza; Vaxigrip; ***Hung.***: Agrippal; Begrivac; Fluarix; Fluval; IDflu; Influvac; Vaxigrip; ***India***: Fluarix; ***Indon.***: Agrippal; Fluarix; Vaxigrip; ***Irl.***: Addiflu†; Aflunov; Agrippal; Begrivac; Celvapan; Daronrix; Enzira; Fluarix; Focetria; Foclivia; IDflu; Influvac; Intanza; Invivac†; Optaflu; Pandemrix; Preflucel; Prepandemic Influenza Vaccine; Prepandrix; Pumarix; ***Israel***: Agrippal; Fluad; Fluarix; FluMist; Fluvirin†; Focetria; Influvac; Pandemrix; Vaxigrip; ***Ital.***: Adiugrip; Agrippal; Fluad; Fluarix; Inflexal; Influpozzi; Influvac S; Influvirus†; Isiflu V; Isigrip Zonale; Mutagrip; Vaxigrip; ***Malaysia***: Agrippal; Fluarix; Fluvax; Inflexal; Influvac; Vaxigrip; ***Mex.***: Agrippal†; Fluarix; Fluzone; ***Neth.***: Aflunov; Afluria; Agrippal; Arepanrix†; Batrevac; Celvapan; Daronrix; Fluarix; Fluenz; Fluvax; Fluvirin†; Focetria; Foclivia; IDflu; Inflexal; Influject†; Influvac; Intanza; Invivac†; Mutagrip; Optaflu; Pandemrix; Preflucel; Prepandrix; Pumarix; Vacciflu; Vaxigrip; Vepacel; Xanaflu; ***Norw.***: Begrivac†; Celvapan; Fluarix; Influvac; Invivac†; Pandemrix; Preflucel; Vaxigrip; ***NZ***: Celvapan; Fluarix; Fluvax; Influvac; Intanza; Panvax; Vaxigrip; ***Philipp.***: Agrippal; Fluad†; Fluarix; Inflexal; Influvac; Vaxigrip; ***Pol.***: Aflunov; Arepanrix; Begrivac; Celvapan; Daronrix; Fluarix; Focetria; Foclivia; Humenza; IDflu; Inflexal; Influvac; Intanza; Optaflu; Pandemrix; Vaxigrip; ***Port.***: Addigrip†; Aflunov; Batrevac†; Celvapan; Chiroflu; Daronrix; Fluad; Fluarix; Fluvirin; Focetria; Foclivia; IDflu; Inflexal; Influvac; Intanza; Invivac; Istivac; Optaflu; Pandemrix; Prepandrix; Vaxigrip; ***Rus.***: Agrippal (Агриппал); Begrivac (Бегривак); Fluarix (Флюарикс); Fluvaxin (ФЛЮВАКСИН); Grifor (Грифор); Grippol (Гриппол); Grippovac (Грипповак); Inflexal (Инфлексал); Influvac (Инфлювак); MonoGrippol (МоноГриппол); OrniFlu (ОрниФлю); Pandeflu (Пандефлю); Ultravac (Ультравак); ***S.Afr.***: Agrippal; Fluarix; Fluvirin†; Influvac; Mutagrip†; Vaxigrip; ***Singapore***: Agrippal; Fluad†; Fluarix; Fluvax; Influvac; Intanza; Vaxigrip; ***Spain***: Chiroflu; Chiromas; Fluarix; Fluenz; Gripavac†; Influvac; Intanza; Levrison†; Mutagrip; Serinflu†; Vac Antigripal†; Vacuna Antigripal; Vaxigrip; ***Swed.***: Afluria; Fluarix; Inflexal; Influvac; Pandemrix; Preflucel; Vaxigrip; ***Switz.***: Agrippal; Celtura; Fluad; Fluarix; Focetria; Inflexal; Influvac; Mutagrip; ***Thai.***: Agrippal; Begrivac†; Fluad; Fluarix; Fluzone; Inflexal; Influvac; Intanza; Vaxigrip; ***Turk.***: Agrippal†; Fluarix; Inflexal; Influvac; Intanza; Vaxigrip; ***UK***: Agrippal; Begrivac; Celvapan†; Enzira; Fluarix; Fluenz; Fluvirin; Focetria; Imuvac; Influvac; Intanza; Invivac; Mastaflu†; Optaflu; Pandemrix†; Viroflu; ***Ukr.***: Inflexal (Инфлексал)†; Influvac (Инфлувак); ***USA***: Afluria; Agriflu†; Fluarix; Flublok; Flucelvax; FluLaval; FluMist; Fluvirin; Fluzone; Influenza A (H1N1) Monovalent Vaccine; Influenza A (H1N1) Monovalent Vaccine; Influenza A (H1N1) Monovalent Vaccine; Influenza A (H1N1) Monovalent Vaccine; ***Venez.***: Fluarix; Isiflu; Vacuna Purificada.

Homoeopathic Preparations. ***Austria***: Globuli gegen Grippe; Metavirulent; ***Fr.***: Homeomunil; ***Ger.***: metavirulent; ***Neth.***: Dolivaxil†; ***Switz.***: metavirulent.

Pharmacopoeial Preparations

Ph. Eur.: Inactivated Influenza Vaccine (Split Virion, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Influenza Vaccine (Whole Virion, Inactivated); Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures).

Japanese Encephalitis Vaccines

Vacunas de la encefalitis japonesa.

ATC — J07BA02.

Uses and Administration

Two types of inactivated Japanese encephalitis (JE) vaccine containing either the Nakayama or the Beijing-1 strain of the virus and grown in mouse-brain tissue have generally been used for active immunisation against encephalitis due to JE virus. The Nakayama strain vaccine produced in Japan was widely available internationally, but production has been stopped. Another inactivated JE vaccine is made in China from the Beijing-3 strain of JE virus and grown in Syrian hamster kidney-cell cultures. This vaccine has been replaced in the Chinese vaccination programme by a live, attenuated JE virus (strain SA 14-14-2) vaccine that is also produced on primary hamster cells. Most recently the vaccine IC-51 (an inactivated, adsorbed JE vaccine also based on the strain SA 14-14-2, and manufactured in cultivated Vero cells) has been approved for use in several countries. JE vaccines are widely used in China, Japan and other parts of Asia where JE is endemic and may form part of the WHO Expanded Programme on Immunization. Vaccination is recommended for visitors to rural areas of South East Asia and the Far East where infection is endemic and where the visit is to be for more than one month; it is also recommended for shorter visits in individuals likely to be at exceptional risk.

In the UK, two inactivated JE vaccines are available; one containing Nakayama strain grown in mouse brain and the other manufactured in cultivated Vero cells.

Children from 1 year of age to under 3 years of age who are non-immune travellers may be given 3 doses each of 0.5 mL of inactivated *mouse-brain vaccine* subcutaneously at 0, 7 to 14, and 28 to 30 days. Children from 3 to 17 years of age may be given 3 doses each of 1 mL; full immunity will take up to one month to develop after the last dose. An abbreviated dosage schedule has been suggested (for those aged 3 to 17 years) if time is not available for this standard schedule; two doses at 0 and 7 to 14 days *or* 3 doses at 0, 7, and 14 days may be given. A booster dose should be given 12 months after the primary immunisation course and then at 3-year intervals.

Infants and children from 2 months to under 3 years of age may be given 2 doses each of 0.25 mL of the inactivated *Vero cell vaccine* intramuscularly at 0 and 28 days. Children from 3 years of age and adults may be given 2 doses each of 0.5 mL; full immunity will take up to one week to develop after the last dose. A booster dose should be given to adults 12 to 24 months after the primary immunisation course, before potential re-exposure to JE virus. Those at continuous risk for acquiring Japanese encephalitis should receive a booster dose at month 12 after primary immunisation.

In the USA an inactivated vaccine manufactured in cultivated Vero cells is available. It is licensed for use in adults (or from the age of 17 years); the vaccination schedule is similar to that used in the UK. For those less than 17 years of age, the CDC recommends enrolment in an ongoing clinical study, giving the inactivated Vero cell vaccine off-label, or obtaining a vaccine at an international travellers' clinic in Asia.

In areas where JE is endemic, primary immunisation with inactivated vaccines has been given according to a different schedule. Although the ages and schedule of subsequent boosters varies in different countries, the same schedule is used for primary immunisation. The first dose is given at age 6 months to 3 years according to the country, but in all cases is followed by a second dose 1 to 4 weeks later and then a third after 1 year. Live attenuated Japanese encephalitis vaccines are also used, in single or 2-dose schedules (see below), in some countries in the Far East where disease is endemic.

Guidelines and recommendations.

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Inactivated Japanese encephalitis vaccines grown in mouse-brain tissue have been widely used in Asia for some years. In Japan, the incidence of the disease has decreased since the introduction of nationwide vaccination in the mid-1960s. Recently another inactivated vaccine, IC-51, based on the strain SA 14-14-2 and manufactured in cultivated Vero cells, has been approved for use.[1-4]

A live attenuated vaccine, SA14-14-2, is widely used in China and is replacing the use of inactivated vaccine. Studies[5,6] with the live attenuated vaccine showed that 2 doses given a year apart were 97% effective in an endemic region of rural China. Similar results were obtained when the interval between doses was reduced to 1 to 3 months. A further case-control study[7] in Nepal found that single-dose administration was more than 99% effective.

Other vaccines are under development including recombinant DNA and chimeric vaccines. Recombinant vaccines delivered using poxvirus vectors were also investigated but research appears to have been halted.[8]

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Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Hypersensitivity reactions including urticaria, angioedema, hypotension, and dyspnoea have been reported mainly in travellers from non-endemic areas. In May 2005 the Japanese government suspended routine vaccination with mouse brain-derived vaccine in response to a report of acute disseminated encephalomyelitis after vaccination; however, a causal link has not been established.

Persons with unstable neurological conditions, including convulsions in the past year, may be at higher risk of adverse events. It is suggested that vaccine should not be given to those who are recovering from acute disseminated encephalomyelitis or to those with Guillain-Barré syndrome, multiple sclerosis, or other demyelinating disorders.

The IC-51 vaccine, which is manufactured in cultured Vero cells and contains no gelatin or animal protein, should theoretically reduce the potential for hypersensitivity and neurological reactions.

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Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: JE-Vax†; Jespect; ***Austria***: Ixiaro; ***Belg.***: Ixiaro; ***Canad.***: Ixiaro; JE-Vax†; ***China***: Ai Pu Sheng (爱普生); An Kang (安康); Jieyiwei (杰益维); ***Cz.***: Ixiaro; ***Denm.***: Ixiaro; ***Fr.***: Ixiaro; ***Ger.***: Ixiaro; ***India***: Jencevac; ***Irl.***: Ixiaro; ***Israel***: Ixiaro; ***Jpn***: Encevac; Jebik V; ***Neth.***: Ixiaro; ***Norw.***: Ixiaro; ***NZ***: Jespect; ***Pol.***: Ixiaro; ***Port.***: Ixiaro; ***Spain***: Ixiaro; ***Swed.***: Ixiaro; ***Switz.***: Ixiaro; ***Thai.***: CD Jevax; JE-Vaccine†; ***UK***: Ixiaro; ***USA***: Ixiaro; JE-Vax†.

Jellyfish Venom Antisera

Antídoto contra las picaduras de medusa; Antisuero contra el veneno de la medusa; Jellyfish Antivenins; Jellyfish Antivenoms.

Uses and Administration

An antiserum for use in the management of severe stings by the box jellyfish or sea wasp *Chironex fleckeri* is available in Australia. The preparation contains the specific antitoxic globulins that neutralise the venom of *Chironex fleckeri* and is prepared from the serum of sheep immunised with the venom of the box jellyfish.

Box jellyfish antivenom is usually given by the intravenous route in a dose of 20 000 units. Alternatively, 60 000 units may be injected intramuscularly.

Jellyfish stings. Many stings caused by the box jellyfish *Chironex fleckeri* are of little consequence and can be managed by simple first aid measures; however, some can be rapidly fatal so immediate assessment is vital.[1] Fragments of tentacle adhering to the skin should be inactivated by the application of vinegar or 3 to 10% acetic acid solution. Cardiopulmonary resuscitation may be necessary in severe cases. The antiserum can be effective if given quickly and in adequate dosage,[2,3] although use is mainly reserved for those with cardiorespiratory instability, severe pain refractory to opioid analgesics, or at risk of significant scarring.[1,3] Some experimental evidence suggested that verapamil might be useful for treatment of the cardiotoxic effects of the venom and allow more time for the antiserum to exert its action,[1,4] but it is now considered to be contra-indicated.[3] Some have suggested that the *Chironex fleckeri* antiserum may be effective for severe envenomation by related species.[3,5]

Irukandji syndrome consists of several hypercatecholaminergic symptoms (such as generalised pain, distress, hypertension, cardiomyopathy, and pulmonary oedema) arising from envenomation with the small box jellyfish *Carukia barnesi*.[1,6,7] Treatment is essentially symptomatic and supportive. The *Chironex fleckeri* antivenom is not effective.[3,5,7] Acetic acid may also be helpful for stings by related species (see p. 2427.1).

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Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Leishmaniasis Vaccines

Vacunas de la leishmaniasis.

Profile

Vaccines containing *Leishmania* spp. are under investigation in an attempt to prevent cutaneous leishmaniasis.

The inoculation of an infective strain of a *Leishmania* sp. into the skin, a technique known as leishmanisation, has been used to protect against cutaneous leishmaniasis (p. 922.1). Although the technique has been standardised it is not generally recommended since large, slow-healing lesions have occurred in some patients. There is currently no effective vaccine for any form of leishmaniasis. First-generation vaccines containing killed leishmanial promastigotes, with or without BCG as an adjuvant, have been developed and tested in humans. These have conferred some protection against cutaneous disease but it has waned relatively quickly in some cases. They have not been found to confer protection against visceral leishmaniasis (p. 923.1). Studies are ongoing investigating the use of alum as an adjuvant. There is also further investigation into second-generation vaccines using different approaches such as the use of surface antigens (gp63 and lipophosphoglycan), promastigote antigen from *L. amazonensis*, enzyme receptor (LACK), Th1-driving adjuvant such as interleukin-12, oligodeoxynucleotides with leishmanial antigens, or recombinant leishmanial antigen (TSA, LmSTI-1), all of which have conferred some protection in *mice*. A glycoprotein-enriched *L. donovani* promastigote vaccine (*Leishmune*) is available for prophylactic veterinary use in Brazil. DNA constructs encoding gp63 and LACK have also conferred protection against *L. major* in *mice*. A chimeric vaccine has also been developed combining three leishmanial antigens (LeIF, LmSTI-1, and TSA) in monophosphoryl lipid A adjuvant but had, at best, mixed results in studies in *dogs*. Attenuated vaccines prepared by gene deletion have shown promise in *mice*. The saliva of sandflies (the vector) seems to enhance infectivity, and vaccines against salivary or gut antigens of the insect have also been investigated.

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Leprosy Vaccines

Vacunas de la lepra.

Profile

Vaccines against leprosy including those using *Mycobacterium leprae*, as well as other mycobacteria, are under investigation. A killed vaccine has been developed in India for use as an adjunct to standard multidrug therapy in the treatment of leprosy. Although studies of new vaccines are continuing, BCG vaccine (p. 2378.3) also appears to be effective.

Leprosy vaccines are being studied both to prevent infection with *M. leprae* (immunoprophylaxis) and to prevent disease in infected individuals (immunotherapeutic). Attempts to develop a vaccine against leprosy are based on the assumption that induction of a cell-mediated immune response to *Mycobacterium leprae* will lead to protection against the bacillus. Several vaccines have been studied and include BCG, BCG plus heat-killed *M. leprae*, heat-killed *Mycobacterium w*, and ICRC (Indian Cancer Research Centre) bacillus. The fortuitous finding that BCG vaccine, which is inexpensive and widely available, is effective against leprosy has important implications for leprosy control. Considerable **immunoprophylaxis** against leprosy is afforded by BCG vaccination (see p. 2378.3), and a study in Malawi showed that repeated vaccination provided additional protection.[1] However, the addition of killed *M. leprae* did not produce any further improvement, confirming preliminary results of a study in Venezuela.[2] However, in a report of their sixth meeting,[3] the WHO Technical Advisory Group on the Elimination of Leprosy reported superior vaccine efficacy for BCG plus heat-killed *M. leprae* than with BCG alone in a prophylactic leprosy vaccine study in south India. The study was begun in 1991 and involved 171 400 subjects who received either BCG alone, BCG plus heat-killed *M. leprae*, *Mycobacterium w*, ICRC bacillus, or placebo. Three surveys of the results have since been conducted by way of follow-up; the preliminary findings of the latest of these surveys revealed that the overall efficacy rates for the vaccines were 22% for BCG alone, 67% for BCG plus heat-killed *M.leprae*, 41% for *Mycobacterium w*, and 51% for ICRC bacillus. Within these results, the findings specifically for efficacy in contacts of patients with leprosy were 11% for BCG alone, 88% for BCG plus heat-killed *M. leprae*, 87% for *Mycobacterium w*, and 11% for ICRC bacillus. Further studies are being conducted in Brazil regarding the use of BCG for booster doses in schoolchildren, and also for its use in household contacts. There is also evidence that combining BCG vaccination with rifampicin chemoprophylaxis produces additive benefit.[4]

Beneficial responses have been reported[5-11] from the **immunotherapeutic** use of *Mycobacterium w* vaccine with standard multidrug therapy (p. 188.3) although a small increase in Type 1 lepra reactions has been seen.[10-12] A similar, and possibly identical, vaccine based on the ICRC bacillus has also been evaluated.[13,14] Immunotherapy with BCG and heat killed *M.leprae* has produced beneficial responses when given as an adjunct to chemotherapy.[15] WHO has suggested that the immunotherapeutic use of vaccines may ultimately prove to be more clinically relevant than the immunoprophylactic use,[13] and high compliance with immunotherapy appears to be attainable.[16]

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Immuvac.

Leptospirosis Vaccines

Leptospira Vaccines; Vacunas de la leptospirosis.

Profile

Leptospirosis vaccines prepared from killed *Leptospira interrogans* are available in some countries. They are used for active immunisation against leptospirosis icterohaemorrhagica (spirochaetal jaundice; Weil's disease) in persons at high risk of contracting the disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Spirolept.

Lyme Disease Vaccines

Vacunas de la enfermedad de Lyme.

Profile

Vaccines based on recombinant outer surface proteins of *Borrelia burgdorferi* were developed and used in some countries for active immunisation against Lyme disease in persons at risk of contracting the disease.

Lyme arthritis refractory to treatment with antibacterials has occurred rarely as an immune reaction to vaccine-derived outer surface proteins of *Borrelia burgdorferi*.

Malaria Vaccines

Vacunas de la malaria; Vacunas del paludismo.

Profile

Malaria vaccines acting against the sporozoite, asexual, and sexual stages of the *Plasmodium falciparum* life cycle are under investigation, as well as multicomponent vaccines consisting of combined antigens from various stages.

Vaccine development. Chemoprophylaxis of malaria is becoming increasingly problematical (see p. 644.1), resulting in the increased desirability of effective malaria vaccines, several of which have been, or are being, studied clinically. The various approaches to malaria vaccine development have been extensively reviewed.[1-15] Malaria vaccines can be categorised into 4 main groups:

- vaccines against pre-erythrocytic forms of the parasite, specifically the sporozoite and liver stages of infection. A sporozoite vaccine could prevent infection either via an antibody response to block invasion of liver cells or via a cell-mediated response to destroy infected liver cells by preventing release of parasites into the bloodstream. The most advanced of these vaccines are derived from the circumsporozoite antigen present on the sporozoite and the main vaccine candidate of this type is RTS,S. This vaccine is comprised of the antigenic C-terminus of the circumsporozoite gene from *Plasmodium falciparum* fused to hepatitis B surface antigen and formulated with different adjuvants. Encouraging results in early studies in endemic African areas have been reported with the variants RTS,S/AS02A,[16] RTS,S/AS02D,[17] and RTS,S/AS01E.[18] The US military is also investigating the possibility of DNA vaccines for malaria, including a liver-stage DNA candidate encoding the circumsporozoite (CS) protein of *P. falciparum*; however, this vaccine has so far failed to induce antigen-specific antibodies. A multiple-antigen version of this DNA vaccine, known as MuStDo5, encoding 5 different liver-stage antigens including CS is also under investigation. Some workers are investigating the prospect of priming with a DNA vaccine and boosting with recombinant antigen or viral vectors. There is also some development of vaccines that focus on the intracellular liver stage of the parasite, since some antigens expressed by sporozoites or merozoites can also be expressed by liver stage parasites
- vaccines against asexual erythrocytic stages, directed at the merozoite form of the parasite. These vaccines would be expected to reduce the severity and the duration of disease by decreasing the blood-parasite density; this effect correlates with reduced symptoms and risk of death. The most advanced asexual vaccine candidate is merozoite surface protein 1 (MSP-1), which forms part of a complex thought to be involved in erythrocyte invasion; antibodies to MSP-1 have been shown to block parasite entry to erythrocytes *in vitro*. Recombinant MSP-1 has also been shown to protect against lethal parasite challenge in *animal* studies. Several other merozoite surface proteins are also under development (MSP-2, 3, 4, 5, 8, and 9). A vaccine comprising MSP-1 and MSP-2 plus *P. falciparum* ring-infected erythrocyte (RESA) has recently shown a 62% reduction in parasite density in children in a study in Papua New Guinea. Two further promising asexual erythrocytic stage vaccine candidates are the apical membrane antigen-1 (AMA-1) and erythrocyte-binding antigen-175 (EBA-175)
- transmission-blocking vaccines to raise antibodies in humans against the gamete stage of the parasite present in the mosquito gut; these antibodies would then be taken up by the biting mosquito from in the blood and block further parasite development in the mosquito, thus rendering it non-infectious. Blocking transmission in this way could reduce infectivity of mosquitoes in that they would carry fewer parasites, and could extend the useful life of a pre-erythrocytic or erythrocytic vaccine by preventing transmission of antibody-resistant mutants. The most advanced candidate vaccines of this type contain the *P. falciparum* surface protein antigens Pfs-25 and Pfs-28 or the *P. vivax* homologues Pvs-25 and Pvs-28. Recombinant forms of these antigens are currently being investigated. Other similar sexual stage vaccines under development include Pfs-48/45 and Pfs-230
- vaccines against the toxins produced by the parasite that contribute to the disease itself. The glycosylphosphatidyl inositol (GPI) anchor, which binds several of the parasite's antigens to the erythrocyte membrane, has been shown to be highly toxic in *mouse* models, but has potential for disease attenuation if it can be detoxified and rendered safe.

A multi-antigen, multistage combination vaccine is thought to be the best approach to effective vaccination against malaria. One such vaccine, SPf66, a synthetic preparation of three antigens from the asexual phase of the parasite in the blood linked by a sporozoite antigen has been studied but little or no evidence for its protective efficacy has been found.[3] Another multicomponent vaccine, NYVAC-Pf7, using a recombinant vaccinia viral vector that expresses 7 proteins from different stages of malarial infection, has also been studied,[19] but results have been disappointing. A further multicomponent vaccine, CDC/NIIMALVAC-1 has provided encouraging preliminary results in *animals* and *in vitro*.[20]

1. Webster D, Hill AVS. Progress with new malaria vaccines. *Bull WHO* 2003; **81:** 902–9.
2. Moorthy VS, *et al*. Malaria vaccine developments. *Lancet* 2004; **363:** 150–6.
3. Graves PM, Gelband H. Vaccines for preventing malaria (SPf66). Available in The Cochrane Library; Issue 2. Chichester: John Wiley; 2006.
4. WHO. State of the art of new vaccines: research & development (January 2005). Available at: http://www.who.int/vaccine_research/documents/Dip%20814.pdf (accessed 27/08/10)
5. Graves PM, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/06/08).
6. Graves PM, Gelband H. Vaccines for preventing malaria (blood-stage). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/06/08).
7. Tetteh KK, Polley SD. Progress and challenges towards the development of malaria vaccines. *BioDrugs* 2007; **21:** 357–73.
8. Matuschewski K, Mueller AK. Vaccines against malaria - an update. *FEBS J* 2007; **274:** 4680–7.
9. Mikolajczak SA, *et al*. Preerythrocytic malaria vaccine development. *Curr Opin Infect Dis* 2007; **20:** 461–6. Correction. *ibid.*; 656.
10. Genton B, Reed ZH. Asexual blood-stage malaria vaccine development: facing the challenges. *Curr Opin Infect Dis* 2007; **20:** 467–75.
11. Saul A. Mosquito stage, transmission blocking vaccines for malaria. *Curr Opin Infect Dis* 2007; **20:** 476–81.
12. Sharma S, Pathak S. Malaria vaccine: a current perspective. *J Vector Borne Dis* 2008; **45:** 1–20.
13. Vekemans J, Ballou WR. Plasmodium falciparum malaria vaccines in development. *Expert Rev Vaccines* 2008; **7:** 223–40.
14. Pinzon-Charry A, Good MF. Malaria vaccines: the case for a whole-organism approach. *Expert Opin Biol Ther* 2008; **8:** 441–8.
15. Tyagi RK, *et al*. Various carrier system(s)-mediated genetic vaccination strategies against malaria. *Expert Rev Vaccines* 2008; **7:** 499–520.
16. Alonso PL, *et al*. Duration of protection with RTS,S/ASO2A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. *Lancet* 2005; **366:** 2012–12.
17. Abdulla S, *et al*. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *N Engl J Med* 2008; **359:** 2533–44.
18. Bejon P, *et al*. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. *N Engl J Med* 2008; **359:** 2521–32.
19. Ockenhouse CF, *et al*. Phase I/IIa safety, immunogenicity, and efficacy trial of NYVAC-Pf7, a pox-vectored, multiantigen, multistage vaccine candidate for Plasmodium falciparum malaria. *J Infect Dis* 1998; **177:** 1664–73.
20. Shi YP, *et al*. Immunogenicity and in vitro protective efficacy of a recombinant multistage Plasmodium falciparum candidate vaccine. *Proc Natl Acad Sci U S A* 1999; **96:** 1615–20.

Measles Immunoglobulins

Inmunoglobulinas contra el sarampión.
ATC — J06BB14.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Measles Immunoglobulin; Immunoglobulinum Humanum Morbillicum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the measles virus. Normal immunoglobulin may be added. It contains not less than 50 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Uses and Administration

Measles immunoglobulins may be used for passive immunisation against measles. They have been used to prevent or modify measles in susceptible persons who have been exposed to infection; in the UK, normal immunoglobulin is usually given.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Moruman.

Pharmacopoeial Preparations
Ph. Eur.: Human Measles Immunoglobulin.

Measles Vaccines

Vacunas del sarampión.
ATC — J07BD01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Measles Vaccine (Live); Vaccinum Morbillorum Vivum). A freeze-dried preparation of a suitable live attenuated strain of measles virus grown in cultures of chick-embryo cells or human diploid cells. It is prepared immediately before use by reconstitution from the dried vaccine. The virus concentration is not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Measles may be used on the label.

Uses and Administration

Measles vaccines are used for active immunisation against measles. Measles strains currently used in vaccines are usually the more attenuated Enders' attenuated Edmonston strain or the Schwarz strain. A high-potency measles vaccine prepared from the Edmonston-Zagreb strain of measles virus was formerly used but was stopped because of evidence of increased mortality (see High-titre Vaccines and Mortality, under Adverse Effects, p. 2399.2).

For primary immunisation a combined measles, mumps, and rubella vaccine (p. 2400.2) is usually used. For discussion of immunisation schedules, see below.

Measles vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response. However, they have been given to infants at 6 to 9 months of age in developing countries and in the USA in certain circumstances (such as during measles outbreaks) (see also Immunisation Schedules, below).

Single-antigen measles vaccines have also been used for prophylaxis after exposure to measles provided they are given within 72 hours of contact.

Administration. Several alternative routes of administration of measles vaccines have been investigated in an attempt to overcome some of the disadvantages of subcutaneous or intramuscular injection.[1] Aerosol administration has produced good responses in children over 9 months of age, although this route was not so effective in younger children.[2,3] Aerosol administration could be potentially useful for mass immunisation campaigns, a suggestion confirmed in a randomised study.[4]

Oral vaccines against measles, produced in edible plants, are under investigation.[5,6]

Work is currently underway to develop oral and/or nasal vaccines that will be suitable in infants less than 9 months of age, a time when they are vulnerable due to waning maternal antibodies.

1. Cutts FT, *et al*. Alternative routes of measles immunization: a review. *Biologicals* 1997; **25:** 323–38.
2. Hiremath GS, Omer SB. A meta-analysis of studies comparing the respiratory route with the subcutaneous route of measles vaccine administration. *Hum Vaccin* 2005; **1:** 30–6.
3. Low N, *et al*. Immunogenicity and safety of aerosolized measles vaccine: systematic review and meta-analysis. *Vaccine* 2008; **26:** 383–98.
4. Dilraj A, *et al*. Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: a randomised trial. *Lancet* 2000; **355:** 798–803.
5. Webster DE, *et al*. Appetising solutions: an edible vaccine for measles. *Med J Aust* 2002; **176:** 434–7.
6. Muller CP, *et al*. Immunogenic measles antigens expressed in plants: role as an edible vaccine for adults. *Vaccine* 2003; **21:** 816–19. Correction. *ibid.*; 3093.

Immunisation schedules. In the developed world measles vaccine (usually as measles, mumps, and rubella vaccine) is usually given in the second year of life. As a result of concern that measles vaccine would not elicit an appropriate immune response in young infants due to the persistence of maternal antibodies in circulation, vaccination has generally not been attempted in children under 12 months old. However, infants born to vaccinated mothers tend to have lower levels of maternal antibodies and are susceptible to measles infection at under 12 months of age; vaccination has been shown to be effective at 6 to 9 months of age in such children,[1-3] although antibody titres were lower in infants vaccinated at 6 months of age than in those vaccinated later.[1,4]

In the UK and USA, routine vaccination is given at between 12 and 15 months, with a second dose given at between 4 and 6 years (see the immunisation schedules summarised under Vaccines, p. 2373.3). Similar schedules are used in other countries. There is evidence that these 2-dose strategies will produce high levels of immunity in the community. During an outbreak of measles, vaccination may be given as early as 6 months of age;[5] revaccination is recommended in any child who is vaccinated before their first birthday. Vaccine may be given to non-immune persons of any age considered to be at risk of infection even if their immune status is uncertain.

For discussion of immunisation schedules in the developing world, see under Expanded Programme on Immunization, below.

1. Johnson CE, *et al*. Measles vaccine immunogenicity in 6- versus 15-month-old infants born to mothers in the measles vaccine era. *Pediatrics* 1994; **93:** 939–44.
2. Carson MM, *et al*. Measles vaccination of infants in a well-vaccinated population. *Pediatr Infect Dis J* 1995; **14:** 17–22.
3. Markowitz LE, *et al*. Changing levels of measles antibody titers in women and children in the United States: impact on response to vaccination. *Pediatrics* 1996; **97:** 53–8.
4. Gans HA, *et al*. Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *JAMA* 1998; **280:** 527–32.
5. De Serres G, *et al*. Effectiveness of vaccination at 6 to 11 months of age during an outbreak of measles. *Pediatrics* 1996; **97:** 232–5.

EXPANDED PROGRAMME ON IMMUNIZATION. Measles remains a leading cause of death among young children, despite the availability of a safe and effective vaccine for the past 40 years. WHO estimated 454 000 people, the majority of them children, died from measles and measles complications in 2004.

In the developed world measles vaccine (usually as measles, mumps, and rubella vaccine) is usually given in the second year of life. If given earlier, passively-acquired maternal antibodies against measles may interfere with development of protective immunity.

In the developing world, protection given by maternal antibodies is often rapidly lost and in hyperendemic areas, such as urban and peri-urban areas, clinical measles may occur in children as young as 5 to 6 months of age. Immunisation against measles is part of WHO's Expanded Programme on Immunization (see, p. 2374.2). The first dose of measles vaccine is given to children at the age of 9 months or shortly thereafter. A 'second opportunity' for immunisation is provided to all children (either through routine immunisation campaigns or by targeted supplementary activities depending on local need). This assures measles immunity in children who failed to receive a previous dose of measles vaccine, as well as in those who were vaccinated but failed to develop immunity following vaccination (about 10 to 15% of those children vaccinated at 9 months of age).

References.

1. WHO. Measles vaccines: WHO position paper. *Wkly Epidem Rec* 2009; **84:** 349–60. Also available at: http://www.who.int/wer/2009/wer8435.pdf (accessed 03/03/10)

Immunisation for travellers. WHO recommends that all travellers who have not been immunised should be offered measles vaccine. Infants who are travelling to areas where measles is highly endemic may receive a dose at the age of 6 months but those who receive the first dose of measles vaccine between the ages of 6 to 8 months should also receive the scheduled primary immunisation doses later.[1]

It is generally recommended that individuals with at least a moderate degree of immune deficiency should receive measles vaccine even when travelling to areas with a low risk of contracting the disease.[1]

1. WHO. *International travel and health* 2010 ed. Available at: http://www.who.int/entity/ith/ITH2010.pdf (accessed 27/08/10)

Adverse Effects

As for vaccines in general, p. 2375.1.

Fever and rashes may occur after measles vaccines. The fever generally starts about 1 week after the injection, lasts for about 2 or 3 days, and has sometimes been accompanied by convulsions. More serious effects reported rarely include encephalitis and thrombocytopenia.

Reviews.

1. Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Safety* 1998; **19:** 435–54.

Incidence of adverse effects. Some brief comments made by the Advisory Committee on Immunization Practices in the USA on adverse effects of standard measles vaccines.[1] An excellent safety record of measles vaccines has been indicated by the experience gained through the use of more than 240 million doses up to 1993. Fever with a temperature of 39.4 degrees or more may develop in 5 to 15% of vaccinees beginning 5-12 days after vaccination and usually lasts several days. Transient rashes have been reported in about 5% of vaccinees. CNS disorders, including encephalitis and encephalopathy, have been reported with a frequency of less than one case per million doses given. The incidence of encephalitis or encephalopathy after vaccination is lower than the incidence rate of encephalitis of unknown origin suggesting that such events after vaccination may be only temporally related to, rather than due to, vaccination.

1. Immunization Practices Advisory Committee. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996; **45** (RR 12): 1–35.

Atypical measles. The atypical-measles syndrome has occurred in persons vaccinated against measles and later exposed to the natural infection. The syndrome has been characterised by high fever and atypical rash; abdominal pain has been common and pneumonia almost universal.[1] Although atypical measles has occurred particularly in patients given killed vaccine[1] (no longer used) it has been reported in recipients of live measles vaccines.[2,3]

Measles occurring in patients previously vaccinated with live measles vaccines may be mild and go unrecognised. However, secondary vaccine failure does not appear to be a major problem (see Immunisation Schedules under Uses, p. 2398.3).

1. Anonymous. The atypical-measles syndrome. *Lancet* 1979; **i:** 962–3.
2. Chatterji M, Mankad V. Failure of attenuated viral vaccine in prevention of atypical measles. *JAMA* 1977; **238:** 2635.
3. Henderson JAM, Hammond DI. Delayed diagnosis in atypical measles syndrome. *Can Med Assoc J* 1985; **133:** 211–13.

Effects on hearing. For reports of sensorineural hearing loss after vaccination with monovalent measles vaccine or other measles-containing vaccines, see under Measles, Mumps and Rubella Vaccines, p. 2400.3.

Effects on the nervous system. *GUILLAIN-BARRÉ SYNDROME.* No association was found between measles vaccination and Guillain-Barré syndrome in an analysis of 2296 cases.[1]

1. da Silveira CM, *et al*. Measles vaccination and Guillain-Barré syndrome. *Lancet* 1997; **349:** 14–16.

OPTIC NEURITIS. For a report of optic neuritis in 2 children after being given measles and rubella vaccine, see under Adverse Effects of Measles and Rubella Vaccines, p. 2400.1.

SUBACUTE SCLEROSING PANENCEPHALITIS. Subacute sclerosing panencephalitis (SSPE) is a rare complication of measles infection (p. 961.2) and has been reported in children who have received measles vaccine but have no history of clinical disease. Nevertheless mass measles vaccination has been effective in reducing the incidence of SSPE in both developing and industrialised countries,[1,2] and the risks of remaining unimmunised are considered to be greater than those arising from immunisation.

1. Anonymous. SSPE in the developing world. *Lancet* 1990; **336:** 600.
2. Immunization Practices Advisory Committee. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996; **45** (RR 12): 1–35.

Effects on the skin. Stevens-Johnson syndrome was associated with measles vaccination in a 10-month-old infant.[1]

1. Hazir T, *et al*. Stevens-Johnson syndrome following measles vaccination. *J Pakistan Med Assoc* 1997; **47:** 264–5.

High-titre vaccines and mortality. After reports of excess mortality in children, especially among girls, who received high-titre Edmonston-Zagreb (EZ) measles vaccine,[1] WHO reversed its recommendation for the use of this vaccine in its Expanded Programme on Immunization in developing countries.[2,3] Subsequent study[4] of children who had received high-titre EZ vaccine showed adverse effects on the nutritional status in either sex, confirming a generally deleterious effect of the vaccine. Others, however, have argued that the problems associated with the use of EZ vaccine have been exaggerated.[5,6] A review[6] pointed out that excess mortality was not seen in all studies, and concluded that the problem was unlikely to be due to the vaccine itself.

1. Knudsen KM, *et al*. Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996; **25:** 665–73.
2. Anonymous. High-titre measles vaccines dropped. *Lancet* 1992; **340:** 232.
3. WHO. Expanded Programme on Immunization; safety of high-titre measles vaccines. *Wkly Epidem Rec* 1992; **67:** 357–61.
4. Garenne M. Effect of Edmonston-Zagreb high-titre vaccine on nutritional status. *Lancet* 1994; **344:** 261–2.
5. Bennett JV, *et al*. Edmonston-Zagreb measles vaccine: a good vaccine with an image problem. *Pediatrics* 1999; **104:** 1123–4.
6. Aaby P, *et al*. High-titer measles vaccination before 9 months of age and increased female mortality: do we have an explanation? *Semin Pediatr Infect Dis* 2003; **14:** 220–32.

Precautions

As for vaccines in general, p. 2375.2.

Measles vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response, but they have been given to younger infants when the risk of measles is particularly high (see Immunisation Schedules, under Uses, p. 2398.3, for further discussion).

Hypersensitivity. For discussion of precautions to be taken on giving measles vaccines to children allergic to egg, see Measles, Mumps, and Rubella Vaccines, p. 2401.1.

Immunocompromised patients. For a discussion of the use of live vaccines in immunocompromised patients including those with HIV infection, see Precautions on p. 2375.2.

As with other live vaccines, measles vaccine is generally not recommended for use in patients with impaired immunity, although combined measles, mumps, and rubella vaccine may be given to HIV-positive individuals unless they have severe immunosuppression or other contra-indications. WHO[1,2] recommend that children with suspected or confirmed HIV infection or in areas where there is a high incidence of both HIV infection and measles should receive a dose of measles vaccine at 6 months of age in addition to the scheduled dose at 9 months. Immunocompromised patients who come into contact with measles should be given normal immunoglobulin. Specific measles immunoglobulins (p. 2398.2) have been used in some countries. Although measles vaccines have been given to immunocompromised patients without causing adverse effects[3] there have been some reports of severe reactions; disseminated measles infection was reported in a child with severe congenital immunodeficiency,[4] and fatal giant-cell pneumonitis was reported in an adult with AIDS.[5]

1. WHO. Measles vaccines: WHO position paper. *Wkly EpidemRec* 2009; **84:** 349–60. Also available at: http://www.who.int/wer/2009/wer8435.pdf (accessed 12/02/10)
2. WHO. WHO recommendations for routine immunization–summary tables (issued 9 June 2010). Available at: http://www.who.int/immunization/policy/immunization_tables/en/print.html (accessed 27/08/10)
3. Krasinski K, Borkowsky W. Measles and measles immunity in children infected with human immunodeficiency virus. *JAMA* 1989; **261:** 2512–16.
4. Monafo WJ, *et al*. Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr* 1994; **124:** 273–6.
5. Angel JB, *et al*. Vaccine-associated measles pneumonitis in an adult with AIDS. *Ann Intern Med* 1998; **129:** 104–6.

Inflammatory bowel disease. Measles vaccination has been suggested as a possible factor in the development of inflammatory bowel disease.[1] However a case-control study involving 140 patients with inflammatory bowel disease provided no support for this hypothesis,[2] and measles virus has not been detected in biopsy specimens from patients with inflammatory bowel disease.[3] Later reviews[4-6] concluded that there is no evidence of any association between measles-containing vaccines and inflammatory bowel disease. A suggested link between measles vaccine-associated inflammatory bowel disease and autism is now refuted (see p. 2401.1).

1. Thompson NP, *et al*. Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 1995; **345:** 1071–4.
2. Feeney M, *et al*. A case-control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997; **350:** 764–6.
3. Afzal MA, *et al*. Absence of measles-virus genome in inflammatory bowel disease. *Lancet* 1998; **351:** 646–7.
4. Davis RL, Bohlke K. Measles vaccination and inflammatory bowel disease: controversy laid to rest? *Drug Safety* 2001; **24:** 939–46.
5. Seagroatt V, Goldacre MJ. Crohn's disease, ulcerative colitis, and measles vaccine in an English population, 1979-1998. *J Epidemiol Community Health* 2003; **57:** 883–7.
6. Demicheli V, *et al*. Vaccines for measles, mumps and rubella in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/05/06).

Interactions

As for vaccines in general, p. 2375.3

Vitamin A. Supplementation with vitamin A (see Deficiency States, p. 2099.2) is now included as part of WHO's Expanded Programme on Immunization.[1] There has been conflicting evidence of the effects of such supplementation on the response to measles vaccination. One study[2] reported a reduced immune response if vaccination occurs at 6 months (before the age at which measles vaccination is usually given in the EPI) while others[3,4] generally found no significant change in seroconversion or immune response in children vaccinated at 9 months (the age at which vaccination is generally started).

1. WHO. Measles vaccines: WHO position paper. *Wkly Epidem Rec* 2009; **84:** 349–60. Also available at: http://www.who.int/wer/2009/wer8435.pdf (accessed 12/02/10)
2. Semba RD, *et al*. Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet* 1995; **345:** 1330–2.
3. Benn CS, *et al*. Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, West Africa. *Lancet* 1997; **350:** 101–5.
4. Cherian T, *et al*. Effect of Vitamin A supplementation on the immune response to measles vaccination. *Vaccine* 2003; **23:** 2418–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Rimevax†; ***Cz.***: Movivac†; ***Fr.***: Rouvax; ***Ger.***: Masern-Impfstoff Merieux; ***Gr.***: Moraten; ***India***: M-Vac; ***Israel***: Rouvax†; ***Mex.***: Rimevax†; ***NZ***:

Rimevax; ***Philipp.***: Rouvax; ***Pol.***: Rouvax; ***S.Afr.***: Diplovax†; Morbilvax†; Rimevax†; Rouvax; ***Singapore***: Moraten; ***Spain***: Rimevax†; ***Turk.***: Moraten; Rouvax; ***USA***: Attenuvax†.

Pharmacopoeial Preparations
Ph. Eur.: Measles Vaccine (Live).

Measles and Mumps Vaccines

Vacuna del sarampión y las paperas; Vacunas del sarampión y la parotiditis.
ATC — J07BD51.

Uses and Administration

Measles and mumps vaccines may be used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (below) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.
See also under Measles Vaccines, p. 2399.1, and Mumps Vaccines, p. 2402.3.

Effects on the bones and joints. For a reference to arthritis occurring after measles and mumps vaccine, see under Adverse Effects and Precautions of Measles, Mumps, and Rubella Vaccines, below.

Effects on hearing. For reports of sensorineural hearing loss after vaccination with measles-containing vaccines, see under Measles, Mumps, and Rubella Vaccines, below.

Interactions

As for vaccines in general, p. 2375.3.
See also under Measles Vaccines, p. 2399.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Si Lin (思林); ***Cz.***: Mopavac†; ***Gr.***: Rouvax.

Measles and Rubella Vaccines

Vacunas del sarampión; Vacunas del sarampión y la rubéola.
ATC — J07BD53.

Uses and Administration

Measles and rubella vaccines may be used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (below) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.
See also under Measles Vaccines, p. 2399.1, and Rubella Vaccines, p. 2417.2.

Incidence of adverse effects. Eight million children aged between 5 and 16 years were immunised with a measles and rubella vaccine in 1994 in the UK. By October 1995 the UK CSM had received reports on 2735 suspected adverse reactions most of which were minor and self-limiting.[1] Serious suspected reactions were rare and generally the number of reported cases was consistent with the background frequency of the particular disorder.

1. CSM/MCA. Adverse reactions to measles rubella vaccine. *Current Problems* 1995; **21:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015633&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)

Effects on hearing. For reports of sensorineural hearing loss after vaccination with measles-containing vaccines, see under Measles, Mumps, and Rubella Vaccines, below.

Effects on the nervous system. Optic neuritis was reported in 2 children given measles and rubella vaccine 2 to 3 weeks previously.[1]

1. Stevenson VL, *et al.* Optic neuritis following measles/rubella vaccination in two 13-year-old children. *Br J Ophthalmol* 1996; **80:** 1110–11.

Interactions

As for vaccines in general, p. 2375.3.
See also under Measles Vaccines, p. 2399.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: MoRu-Viraten†; ***Chile***: MoRu-Viraten; ***Mex.***: Moruviraten†.

Measles, Mumps, and Rubella Vaccines

MMR Vaccines; Vacunas del sarampión, de la rubéola y de la parotiditis epidémica; Vacunas del sarampión, de la rubéola y de las paperas; Vacunas del sarampión, la parotiditis y la rubéola; Vacunas triples víricas.
ATC — J07BD52.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Measles, Mumps and Rubella Vaccine (Live); Vaccinum Morbillorum, Parotitidis et Rubellae Vivum). A freeze-dried preparation containing suitable live attenuated strains of measles virus, mumps virus (*Paramyxovirus parotitidis*), and rubella virus. The vaccine is prepared immediately before use by reconstitution from the dried vaccine. It contains in each dose not less than 3.0 log $CCID_{50}$ of infective measles virus, not less than 3.7 log $CCID_{50}$ of infective mumps virus, and not less than 3.0 log $CCID_{50}$ of infective rubella virus. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that MMR may be used on the label.

Uses and Administration

Measles, mumps, and rubella vaccines are used for active immunisation against measles, mumps, and rubella. They are used for primary immunisation in children 12 months of age or older and to protect susceptible contacts during an outbreak of measles. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

In the UK, it is recommended that all children receive two doses of 0.5 mL of a measles, mumps, and rubella vaccine by intramuscular injection (or subcutaneously if there is a bleeding disorder). These are usually given shortly after the first birthday and before school entry, but may be given at any age if routine vaccination has been omitted, allowing 3 months between doses. The combined vaccine may also be used for prophylaxis after exposure to measles provided it is given within 72 hours of contact. However, it is not considered to be effective for postexposure prophylaxis against either mumps or rubella. If the vaccine is given before 12 months of age, re-immunisation will be necessary starting at between 12 and 15 months with a further dose according to national schedules.

Similar schedules are used in the USA.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.
See also under Measles Vaccines, p. 2399.1, Mumps Vaccines, p. 2402.3, and Rubella Vaccines, p. 2417.2.

Events due to the measles component usually occur 6 to 11 days after vaccination and those due to the mumps and rubella components after 2 to 3 weeks but may occur up to 6 weeks after vaccination.

Adverse effects tend to be less frequent after the second dose of vaccine than after the first dose.

Measles, mumps, and rubella vaccines should not be given to individuals with a confirmed anaphylactic reaction to any antibacterial such as neomycin or kanamycin, that may be used in the manufacturing process.

Recommendations on vaccination in persons with egg allergy are discussed under Hypersensitivity, p. 2401.1.

Incidence of adverse effects. A double-blind placebo-controlled crossover study[1] in 581 pairs of twins showed that the frequency of adverse effects from the use of measles, mumps and rubella (MMR) vaccine was between 0.5 and 4.0%, indicating that adverse reactions are much less common than was previously thought. A study in the USA[2] showed that children given the vaccine at age 4 to 6 years had fewer adverse effects than those given it at 10 to 12 years. A later study[3] based on family reported symptoms was unable to detect any vaccine-related adverse effects when the second dose of MMR vaccine was given at either 4 to 6 years or 10 to 12 years. Vaccine-related adverse effects after the first dose of MMR vaccine were reported in about 17% in those vaccinated between the age of 12 and 20 months.

A further study[4] that assessed the effect of almost 3 million doses of vaccines in 1.8 million individuals revealed that 173 potentially serious reactions were claimed to have been caused by vaccination. There were 77 neurologic, 73 allergic, and 22 miscellaneous reactions recorded, and 1 death reported. However, 45% of the reactions were probably caused by some other factor. It was therefore concluded that serious events caused by MMR vaccine are rare and are greatly outweighed by the risks of the natural diseases.

1. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine: a double-blind placebo-controlled trial in twins. *Lancet* 1986; **i:** 939–42.
2. Davis RL, *et al.* MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the vaccine safety datalink project. *Pediatrics* 1997; **100:** 767–71.
3. LeBaron CW, *et al.* Evaluation of potentially common adverse events associated with the first and second doses of measles-mumps-rubella vaccine. *Pediatrics* 2006; **118:** 1422–30.
4. Patja A, *et al.* Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. *Pediatr Infect Dis J* 2000; **19:** 1127–34.

Effects on the blood. Thrombocytopenia occurs rarely in children receiving measles, mumps, and rubella (MMR) vaccine and usually resolves spontaneously. The rubella component is considered to be the most likely cause. An increased incidence of thrombocytopenia after the second dose of the vaccine has been reported in children who developed thrombocytopenia after the first dose.[1] A study[2] by the UK Public Health Laboratory Service suggested a link between MMR vaccine and the occurrence of immune thrombocytopenia, with an absolute risk of 1 in 22 300 of occurrence within 6 weeks of the first dose of the vaccine, and 2 out of every 3 cases attributable to it. Children with immune thrombocytopenia before receiving MMR vaccine had no vaccine-associated recurrences. A further study[3] of children aged 13 to 24 months and diagnosed with immune thrombocytopenia for the first time between January 1988 and December 1999 similarly found the attributable risk of developing it within 6 weeks of receiving the vaccine to be about 1 in 25 000. As a consequence of these findings, the UK CSM has recommended[4] that children developing immune thrombocytopenia within 6 weeks of vaccination with MMR vaccine, or any of its components, should have serological testing before their second dose is due; if this suggests that full immunity is not established, then a second dose should be given. A retrospective analysis of the CDC's Vaccine Safety Datalink between 1991 and 2000 also reported a strong association between MMR vaccination and the risk of immune thrombocytopenia in children 12 to 23 months of age. The association was strongest among those 12 to 15 months of age and was higher for boys than girls; the attributable risk of developing immune thrombocytopenia was 1 in 40 000 doses.[5]

1. Vlacha V, *et al.* Recurrent thrombocytopenic purpura after repeated measles-mumps-rubella vaccination. *Pediatrics* 1996; **97:** 738–9.
2. Miller E, *et al.* Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* 2001; **84:** 227–9.
3. Black C, *et al.* MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol* 2003; **55:** 107–11.
4. CSM/MCA. MMR vaccine and idiopathic thrombocytopenic purpura. *Current Problems* 2001; **27:** 15. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 24/05/06)
5. France EK, *et al.* Vaccine Safety Datalink Team. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics* 2008; **121:** e687–92.

Effects on the bones and joints. Arthralgia and arthritis occurring in patients given mumps, measles, and rubella vaccines have generally been attributed to the rubella component.[1] However, arthritis has been reported in an infant after vaccination with measles and mumps vaccine.[2]

1. Benjamin CM, *et al.* Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine. *BMJ* 1992; **304:** 1075–8.
2. Nussinovitch M, *et al.* Arthritis after mumps and measles vaccination. *Arch Dis Child* 1995; **72:** 348–9.

Effects on hearing. Hearing loss is a known complication of wild measles and mumps viral infections, and the live attenuated strains of these viruses used in the vaccines might therefore have the potential to affect hearing. There have been individual case reports of sensorineural hearing loss after measles vaccination.[1,2] Profound, irreversible sensorineural deafness was reported in a 27-year-old woman after administration of a measles and rubella vaccine.[3] Nine cases of sensorineural hearing loss after measles, mumps, and rubella (MMR) vaccine were reported to the UK CSM between 1988 and 1993.[4] Of these, 3 cases were judged not to have been associated with the vaccine. In the remaining 6, the mumps virus component was considered to be the most likely cause of deafness if the vaccine was to blame, but the risk was considered to be small compared with the risks of natural infection. In the USA, a review of reports to the Vaccine Adverse Events Reporting System (VAERS) between 1990 and 2003 identified 44 cases of sensorineural hearing loss after doses of live attenuated measles and/or mumps vaccines; an additional 11 cases were identified from published reports. The onset of hearing loss in most cases was in keeping with the incubation periods of wild measles and mumps viruses. Based on the annual usage of MMR

vaccine, an estimated rate of hearing loss was reported to be 1 in 6 to 8 million doses.[5]

1. Watson JG. Bilateral hearing loss in a 3-year-old girl following measles immunisation at the age of 15 months. *Int J Pediatr Otorhinolaryngol* 1990; **19:** 189–90.
2. Jayarajan V, Sedler PA. Hearing loss following measles vaccination. *J Infect* 1995; **30:** 184–5.
3. Hulbert TV, *et al.* Bilateral hearing loss after measles and rubella vaccination in an adult. *N Engl J Med* 1991; **325:** 134.
4. Stewart BJA, Prabhu PU. Reports of sensorineural deafness after measles, mumps, and rubella immunisation. *Arch Dis Child* 1993; **69:** 153–4.
5. Asatryan A, *et al.* Live attenuated measles and mumps viral strain-containing vaccines and hearing loss: Vaccine Adverse Event Reporting System (VAERS), United States, 1990–-2003. *Vaccine* 2008; **26:** 1166–72.

Effects on the nervous system. Although there have been case reports[1] linking Guillain-Barré syndrome with measles, mumps, and rubella vaccine, a retrospective study[2] that involved 189 patients with the syndrome and about 630 000 recipients of the vaccine could not find a causal association.

Prolonged tonic-clonic seizures were associated with prolonged hemiparesis in a 16-month-old girl 6 days after measles, mumps, and rubella vaccination.[3] There was evidence of transient encephalopathy. However, a causal relationship between measles-containing vaccines and encephalitis is generally considered to be unlikely. Other reported neurological effects after vaccination include gait disturbances,[4,5] and transverse myelitis.[6] However, a retrospective study[7] found no evidence for a causal association between vaccination and acute ataxia and the development of gait disturbances and suggested the original reports represented chance occurrence.

For discussion of meningitis and encephalitis occurring after measles, mumps, and rubella vaccination, see under Adverse Effects of Mumps Vaccines, p. 2402.3.

1. Morris K, Rylance G. Guillain-Barré syndrome after measles, mumps, and rubella vaccine. *Lancet* 1994; **343:** 60.
2. Patja A, *et al.* Risk of Guillain-Barré syndrome after measles-mumps-rubella vaccination. *J Pediatr* 2001; **138:** 250–4.
3. Sackey AH, Broadhead RL. Hemiplegia after measles, mumps, and rubella vaccination. *BMJ* 1993; **306:** 1169.
4. Plesner A-M. Gait disturbances after measles, mumps, and rubella vaccine. *Lancet* 1995; **345:** 316.
5. Plesner AM, *et al.* Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study. *Acta Paediatr* 2000; **89:** 58–63.
6. Joyce KA, Rees JE. Transverse myelitis after measles, mumps, and rubella vaccine. *BMJ* 1995; **311:** 422.
7. Miller E, *et al.* No evidence of an association between MMR vaccine and gait disturbance. *Arch Dis Child* 2005; **90:** 292–6.

Hypersensitivity. Since the measles and mumps components of measles, mumps, and rubella vaccines are grown in cell cultures of chick embryos the vaccine was formerly contra-indicated in individuals with a history of anaphylactic reactions to egg. In both the UK and USA, serious reactions to egg including anaphylaxis are no longer regarded as absolute contra-indications to vaccination although specialist advice should be obtained and vaccination performed only under controlled conditions. It is generally agreed that the vaccine can be given safely to children with less severe reactions to eggs.

A confirmed anaphylactic reaction to gelatin, kanamycin, or neomycin is a contra-indication to measles, mumps, and rubella vaccines.

Inflammatory bowel disease and autism. A controversial report[1] in 1998 linked measles, mumps, and rubella vaccination with the development of inflammatory bowel disease and behavioural abnormalities including autism. However, there is now overwhelming evidence from studies and analyses that the vaccine does not cause autism.[2-12] Similarly, the link between measles-containing vaccines and inflammatory bowel disease has not been substantiated (see under Precautions for Measles Vaccines, p. 2399.3).

1. Wakefield AJ, *et al.* Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351:** 637–41.
2. Peltola H, *et al.* No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet* 1998; **351:** 1327–8.
3. Roberts R. There is no causal link between MMR vaccine and autism. *BMJ* 1998; **316:** 1824.
4. Taylor B, *et al.* Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 1999; **353:** 2026–9.
5. Kaye JA, *et al.* Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 2001; **322:** 460–3. Correction. *ibid.*; 720.
6. Dales L, *et al.* Time trends in autism and in MMR immunization coverage in California. *JAMA* 2001; **285:** 1183–5.
7. Halsey NA, *et al.* Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the new challenges in childhood immunizations conference convened in Oak Brook, Illinois, June 12-13, 2000. Abstract: *Pediatrics* 2001; **107:** 1174. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/5/e84 (accessed 14/12/04)
8. Smeeth L, *et al.* MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004; **364:** 963–9.
9. Immunization Safety Review Committee. *Immunization safety review: vaccines and autism.* Washington DC: National Academy Press, 2004. Available at: http://www.nap.edu/catalog.php?record_id=10822 (accessed 26/08/10)
10. Demicheli V, *et al.* Vaccines for measles, mumps and rubella in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/05/06)
11. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 27/08/10)
12. Hornig M, *et al.* Lack of association between measles virus vaccine and autism with enteropathy: a case-control study. *PLoS One* 2008; **3:** e3140.

Orchitis. Orchitis is a common complication of wild-type mumps infection, particularly in post-pubertal males, and a few cases of bilateral and unilateral orchitis following vaccination with measles, mumps, and rubella vaccine have been reported.[1,2] An 18-year-old adolescent developed swelling 11 days after vaccination[1]; he was treated with NSAIDs and the swelling resolved.[1] A 12-month-old child developed scrotal and testicular swelling 2 weeks after vaccination which resolved spontaneously over several days, while 2 post-pubertal patients (36 and 37 years of age) developed swelling 3 days after vaccination; in both patients the swelling also spontaneously resolved within 1 to 5 weeks.[2]

1. Abdelbaky AM, *et al.* Unilateral epididymo-orchitis: a rare complication of MMR vaccine. *Ann R Coll Surg Engl* 2008; **90:** 336–7.
2. Clifford V, *et al.* Mumps vaccine associated orchitis: evidence supporting a potential immune-mediated mechanism. *Vaccine* 2010; **28:** 2671–3.

Interactions

As for vaccines in general, p. 2375.3.

See also under Measles Vaccines, p. 2399.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: MMR II; Trimovax; Triviraten; ***Austral.***: Priorix; ***Austria***: MMRVaxPro; Priorix; ***Belg.***: MMRVaxPro; Priorix; ***Braz.***: Vacina Comb. Contra Sarampo, Caxumba e Rubeola; Vacina Contra Sarampo, Caxumba e Rubeola; Vacina de Virus Vivos de Sarampo, Caxumba e Rubeola; ***Canad.***: MMR II; Priorix; ***China***: MMR II (默尔康); Priorix (普祥立适); ***Cz.***: MMR II†; MMRVaxPro; Priorix; Trivivac; ***Denm.***: MMR†; Priorix; ***Fin.***: MMR II†; Priorix; ***Fr.***: MMRVaxPro; Priorix; R.O.R.†; ***Ger.***: MMR Triplovax†; MMRVaxPro; Priorix; ***Gr.***: MMR II; MMRVaxPro; Pluserix; Priorix; ***Hong Kong***: MMR II; Priorix; Trimovax; ***Hung.***: MMR II†; Priorix; ***India***: Morupar; Tresivac; ***Indon.***: MMR II; Trimovax; ***Irl.***: MMR II†; MMRVaxPro; Priorix; ***Israel***: MMR II; Priorix; ***Ital.***: MMR II†; MMRVaxPro; Priorix; ***Malaysia***: MMR II; Priorix; ***Mex.***: MMR II; Priorix; ***Neth.***: MMRVaxPro; Priorix; ***Norw.***: MMR II†; MMRVaxPro; Priorix; ***NZ***: MMR II; Priorix; Triviraten†; ***Philipp.***: Priorix; Trimovax; Triviraten†; ***Pol.***: MMR II†; MMRVaxPro; Priorix; ***Port.***: MMR II†; MMRVaxPro; Priorix; ***Rus.***: MMR II (ММР II); Priorix (Приорикс); ***S.Afr.***: Priorix; Trimovax; ***Singapore***: MMR II; Priorix; ***Spain***: MMRVaxPro; Priorix; Vacuna Triple MSD†; ***Swed.***: MMR II†; MMRVaxPro; Priorix; ***Switz.***: MMRVaxPro; Priorix; ***Thai.***: MMR II; Priorix; Trimovax; ***Turk.***: MMR II; Priorix; Trimovax; Triviraten; ***UK***: MMR II†; MMRVaxPro; Priorix; ***USA***: MMR II; ***Venez.***: Priorix.

Pharmacopoeial Preparations

Ph. Eur.: Measles, Mumps, and Rubella Vaccine (Live).

Measles, Mumps, Rubella, and Varicella-Zoster Vaccines

MMRV Vaccines.

ATC — J07BD54.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Measles, Mumps, Rubella and Varicella Vaccine (Live); Vaccinum Morbillorum, Parotitidis, Rubellae et Varicellae Vivum). A freeze-dried preparation containing suitable live attenuated strains of measles virus, mumps virus (*Paramyxovirus parotitidis*), rubella virus, and human herpesvirus 3. The vaccine is prepared immediately before use by reconstitution from the dried vaccine. It contains in each dose not less than 3.0 log $CCID_{50}$ of infective measles virus, not less than 3.7 log $CCID_{50}$ of infective mumps virus, and not less than 3.0 log $CCID_{50}$ of infective rubella virus. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

Profile

Measles, mumps, rubella, and varicella-zoster vaccines are used for active immunisation against measles, mumps, rubella and varicella (chickenpox).

In the USA, the Advisory Committee on Immunization Practices (ACIP) states that the measles, mumps, rubella, and varicella (MMRV) vaccine may be given to children aged 12 months to 12 years for simultaneous vaccination against these viral diseases. Surveillance data indicate an increased risk of febrile seizure in children after their first dose of MMRV vaccine, compared with those who were given separate injections of measles, mumps, and rubella (MMR) vaccine and varicella vaccine at the same visit. The ACIP therefore no longer expresses a preference for use of the quadrivalent vaccine over separate injections of equivalent component vaccines.

Reviews.

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2. Ramet J. A new challenge for Europe: introducing a pediatric quadrivalent vaccine for measles, mumps, rubella, and varicella. *Int J Infect Dis* 2007; **11** (suppl 2): S49–S55.
3. Dhillon S, Curran MP. Live attenuated measles, mumps, rubella, and varicella zoster virus vaccine (Priorix-Tetra). *Paediatr Drugs* 2008; **10:** 337–47.
4. Czajka H, *et al.* A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. *Vaccine* 2009; **27:** 6504–11.
5. CDC. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; **59** (RR-3): 1–12. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5903.pdf (accessed 25/06/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Priorix-Tetra; ***Canad.***: Priorix-Tetra; ***Cz.***: Priorix-Tetra; ProQuad; ***Denm.***: Priorix-Tetra; ***Fin.***: Priorix-Tetra†; ***Ger.***: Priorix-Tetra; ***Gr.***: Priorix-Tetra; ***Irl.***: Priorix-Tetra; ProQuad; ***Israel***: Priorix-Tetra; ***Ital.***: Priorix-Tetra; ProQuad; ***Malaysia***: Priorix-Tetra; ***Neth.***: Priorix-Tetra; ProQuad; ***NZ***: Priorix-Tetra; ProQuad; ***Pol.***: ProQuad; ***Port.***: Priorix-Tetra; ProQuad; ***Singapore***: Priorix-Tetra; ***Switz.***: Priorix-Tetra; ***Thai.***: Priorix-Tetra; ***USA***: ProQuad.

Pharmacopoeial Preparations

Ph. Eur.: Measles, Mumps, Rubella and Varicella Vaccine (Live).

Meningococcal Vaccines

Vacunas de polisacáridos meningocócicos.

ATC — J07AH01; J07AH02; J07AH03; J07AH04; J07AH05; J07AH06; J07AH07; J07AH08; J07AH09; J07AH10.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Meningococcal Polysaccharide Vaccine; Vaccinum Meningitidis Cerebrospinalis). It consists of one or more purified capsular polysaccharides obtained from one or more suitable strains of *Neisseria meningitidis* group A, group C, group Y, and group W135; it may contain a single type of polysaccharide or any mixture of the types. It is prepared immediately before use by reconstitution from the stabilised freeze-dried vaccine with a suitable sterile liquid. The freeze-dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Men plus the relevant antigen may be used on the label (for example MenAC).

Ph. Eur. 8: (Meningococcal Group C Conjugate Vaccine; Vaccinum Meningococcale Classis C Coniugatum). A liquid or freeze-dried preparation of purified capsular polysaccharide derived from a suitable strain of *Neisseria meningitidis* group C covalently linked to a carrier protein. The vaccine may contain an adjuvant. The freeze-dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that MenC(conj) may be used on the label.

Uses and Administration

Meningococcal vaccines are used for active immunisation against *Neisseria meningitidis* infections, which include meningitis and septicaemia (see Meningococcal Infections, p. 192.1). They are preparations of purified polysaccharide antigens from *N. meningitidis* and may be monovalent, containing the antigen of only one serotype of *N. meningitidis* or polyvalent, containing antigens of two or more serotypes. Conjugation of the polysaccharide to a carrier such as diphtheria CRM_{197} protein or to tetanus toxoid protein increases the immunogenicity. While effective vaccines against some of the common serotypes of bacterial meningitis such as A, C, W135, and Y have been available and included in many national immunisation programmes, it has been more difficult to develop vaccines against the group B serotype. However, several avenues of research have now resulted in the production of an effective vaccine against this serotype.

In the UK, primary immunisation is recommended during childhood with a further dose given during adolescence, whereas in the USA routine immunisation is recommended during adolescence or for those at increased risk for meningococcal disease from 6 weeks of age. In the UK, a conjugate meningococcal C vaccine is used and is generally given by intramuscular injection with the subcutaneous route reserved for patients with haemophilia or thrombocytopenia. The primary immunisation course for infants consists of a single dose of 0.5 mL given at 3 months of age. The first booster dose with a combined conjugate

meningococcal C and *Haemophilus influenza* type b vaccine is recommended at 12 to 13 months of age with a further booster dose of conjugate meningococcal C vaccine given around 14 years of age. In the USA, routine immunisation with a single dose of a conjugate tetravalent vaccine from groups A, C, Y, and W135 is performed at 11 to 12 years of age, with a booster dose at 16 years of age. Catch up vaccinations may be given, however, routine vaccination of those aged 19 to 21 years who are not at increased risk for meningococcal disease is not recommended. For discussion of immunisation schedules see under Vaccines, p. 2373.3.

Asplenic persons or those who have terminal complement component deficiencies are at higher than normal risk of acquiring meningococcal infection and therefore they should be immunised. Either a conjugate meningococcal C vaccine or a tetravalent vaccine (A, C, Y, and W135, unconjugated or conjugated) may be used depending on availability and local immunisation guidelines.

Meningococcal vaccines are also indicated in persons travelling to countries where the risk of infection is high. They should receive a tetravalent meningococcal polysaccharide vaccine (either unconjugated or conjugated) rather than the group C conjugate vaccine, and should be immunised even if they have already received the latter. Vaccination is indicated particularly for visits of 1 month or more and for those backpacking or living or working with local residents. Vaccination is a visa requirement for pilgrims to Saudi Arabia.

Meningococcal vaccines may be given as an adjunct to chemoprophylaxis in contacts of persons with meningitis (see p. 191.1).

Strain-specific **meningitis B** vaccines based on bacterial outer membrane vesicles or proteins such as PorA, PorB, or NspA have successfully been used against epidemics in Norway, Cuba, and New Zealand. In 2013, an adsorbed meningococcal B vaccine containing 3 recombinant *N. meningitidis* group B proteins (NHBA fusion protein, NadA protein, and the fHbp fusion protein), and the outer membrane vesicles from *N. meningitidis* group B strain NZ 98/254 was approved for use in Europe. It is given by intramuscular injection in usual doses of 0.5 mL; primary immunisation consists of three doses given at intervals of one month, starting preferably at 2 months of age. A single reinforcing dose is recommended between 12 and 23 months of age.

Guidelines and recommendations.

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2. CDC. Updated recommendations for use of meningococcal conjugate vaccines—Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2011; **60:** 72–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a3.htm (accessed 14/03/13)
3. American Academy of Pediatrics. Committee on Infectious Diseases. Meningococcal conjugate vaccines policy update: booster dose recommendations. *Pediatrics* 2011; **128:** 1213–8. Also available at: http://pediatrics.aappublications.org/content/128/6/1213.full.pdf+html (accessed 04/04/13)
4. WHO. Meningococcal vaccines: WHO position paper, November 2011. *Wkly Epidem Rec* 2011; **86:** 521–39. Also available at: http://www.who.int/wer/2011/wer8647.pdf (accessed 08/03/13)
5. CDC. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013; **62** (RR-2): 1–28. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf (accessed 04/04/13)
6. CDC. Infant meningococcal vaccination: Advisory Committee on Immunization Practices (ACIP) recommendations and rationale. *MMWR* 2013; **62:** 52–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a3.htm (accessed 08/03/13)

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3. McNicholas A, *et al*. Surveillance of vaccine breakthrough cases following MeNZB vaccination. *N Z Med J* 2008; **121:** 38–46.
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5. Smith MJ. Meningococcal tetravalent conjugate vaccine. *Expert Opin Biol Ther* 2008; **8:** 1941–6.
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8. Lewis S, *et al*. Challenges and progress in the development of a serogroup B meningococcal vaccine. *Expert Rev Vaccines* 2009; **8:** 729–45.
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12. WHO: Initiative for Vaccine Research (IVR). Meningococcal disease. Information available at: http://www.who.int/vaccine_research/diseases/soa_bacterial/en/index1.html (accessed 08/04/13)
13. Findlow J, *et al*. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. *Clin Infect Dis* 2010; **51:** 1127–37.
14. Gossger N, *et al*. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 2012; **307:** 573–82.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Immunity to the unconjugated serogroup C polysaccharide in meningococcal vaccines may be insufficient to confer adequate protection against infection in infants under about 2 years of age.

Effects on the nervous system. From June 2005 to September 2006, 17 cases of Guillain-Barré syndrome were reported to the Vaccine Adverse Event Reporting System (VAERS) after use of a tetravalent (A, C, W135, and Y) meningococcal conjugate vaccine (Menactra). Whether the cases were caused by the vaccine or were coincidental was unknown.[1,2] The CDC recommends that persons with a history of Guillain-Barré syndrome should not be vaccinated with the tetravalent meningococcal conjugate vaccine.[2]

1. CDC. Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine - United States, June-July 2005. *MMWR* 2005; **54:** 1023–5.
2. CDC. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine— United States, June 2005-September 2006. *MMWR* 2006; **55:** 1120–4. Correction. *ibid.*; 1177.

Pregnancy and the neonate. A study[1] in 157 Asian women given a tetravalent polysaccharide vaccine in the third trimester of pregnancy found that immunisation was safe for both mothers and infants. Infants were provided with significantly increased levels of IgG for 2 to 3 months and of oral IgA for 6 months from breast feeding.

1. Shahid NS, *et al*. Placental and breast transfer of antibodies after maternal immunization with polysaccharide meningococcal vaccine: a randomized, controlled evaluation. *Vaccine* 2002; **20:** 2404–9.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antimeningococica A+C; Menjugate; Menomune; Menveo; NeisVac-C; Va-Mengoc-BC; ***Austral.***: Mencevax ACWY; Meningitec; Menjugate; Menomune; Menveo; NeisVac-C; ***Austria***: Mencevax ACWY; Meningitec†; Menjugate; Menveo; NeisVac-C; ***Belg.***: Mencevax ACWY; Meningitec; Menjugate; Menveo; NeisVac-C; Nimenrix; ***Braz.***: Vacina Meningococica A+C; Vacina Meningococica Conjugada Grupo C; Vacina Meningococica Conjugada Grupo C; ***Canad.***: Menactra; Meningitec; Menjugate; Menomune; Menveo; NeisVac-C; ***Chile***: Meningo A+C†; NeisVac-C; ***China***: Meng Ling Kang (梦灵康); MeningACon (盟纳康); Meningo A+C (美宁安 A+C); Menwayc (盟威克); Nao Man Ning (瑙幔宁); Yu Nao Ning (御脑宁); Yu Nao Ning A+C (御脑宁A+C); ***Cz.***: Menjugate; Menveo; NeisVac-C; ***Denm.***: Meningitec; Meningovax A+C†; Menjugate; Menveo; NeisVac-C; Nimenrix; ***Fin.***: Mencevax ACWY; Meningovax A+C†; Menjugate†; NeisVac-C; ***Fr.***: Mencevax; Meningitec; Meninvact†; Menjugate; Menomune†; Menveo; NeisVac; ***Ger.***: Mencevax ACWY; Meningitec; Meningokokken-Impfstoff A + C; Menjugate; Menveo; NeisVac-C; ***Gr.***: Meningitec; Meninvact; Menjugate; Menomune; Menveo; NeisVac-C; Vaccin Meningococcique; ***Hong Kong***: Mencevax ACWY; ***Hung.***: Mencevax ACWY; Meningitec; Meningo A+C; Menjugate; NeisVac-C; ***India***: Mencevax; ***Indon.***: Mencevax ACWY; ***Irl.***: Meningitec; Menjugate; Menveo; NeisVac-C; ***Israel***: Mencevax ACWY; Menveo; ***Ital.***: Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; ***Malaysia***: Mencevax ACWY; Menomune; ***Mex.***: Va-Mengoc-BC; ***Neth.***: Meningitec; Meningovax A+C†; Meninvact†; Menjugate; Menveo; NeisVac-C; Nimenrix; ***Norw.***: Meningitec†; Meningovax A+C†; Menveo; NeisVac-C; Nimenrix; ***NZ***: Mencevax ACWY; Meningitec; Menomune; MeNZB†; NeisVac-C; ***Philipp.***: Euro A & C; Menactra; Mencevax ACWY; Menomune; Menovac; ***Pol.***: Meningitec; Menveo; NeisVac-C; ***Port.***: Meningitec; Menjugate; Menveo; NeisVac-C; ***Rus.***: Mencevax ACWY (Менцевакс ACWY); ***S.Afr.***: Imovax Meningo A & C†; Mencevax; ***Singapore***: Menactra; Mencevax ACWY; Menomune†; ***Spain***: Mencevax AC†; Meningitec; Menjugate; Menveo; NeisVac-C; Nimenrix; ***Swed.***: Meningovax A+C†; Menveo; NeisVac-C; ***Switz.***: Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; ***Thai.***: Menomune; ***Turk.***: Imovax Meningo A+C†; ***UK***: ACWY Vax; Bexsero; Meningitec; Menjugate; Menveo; NeisVac-C; Nimenrix; ***USA***: Menactra; Menomune; Menveo.

Pharmacopoeial Preparations

Ph. Eur.: Meningococcal Group C Conjugate Vaccine; Meningococcal Polysaccharide Vaccine.

Multiple Sclerosis Vaccines

Vacunas de la esclerosis múltiple.

Profile

Vaccines based on T cells have been investigated for the management of multiple sclerosis.

The use of vaccine-derived polyclonal antibodies from the serum of goats is also under investigation.

References.

1. Hellings N, *et al*. T-cell vaccination in multiple sclerosis: update on clinical application and mode of action. *Autoimmun Rev* 2004; **3:** 267–75.
2. Sospedra M, Martin R. Antigen-specific therapies in multiple sclerosis. *Int Rev Immunol* 2005; **24:** 393–413.
3. Fontoura P, *et al*. Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. *Int Rev Immunol* 2005; **24:** 415–46.
4. Correale J, *et al*. Vaccines for multiple sclerosis: progress to date. *CNS Drugs* 2008; **22:** 175–98.

Mumps Immunoglobulins

Inmunoglobulinas contra la parotiditis; Inmunoglobulinas contra las paperas.

ATC — J06BB15.

Profile

Preparations containing antibodies against mumps virus have been used in some countries for passive immunisation against mumps.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Paruman.

Mumps Vaccines

Vacunas de la parotiditis; Vacunas de las paperas.

ATC — J07BE01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Mumps Vaccine (Live); Vaccinum Parotitidis Vivum). A freeze-dried preparation containing a suitable live attenuated strain of mumps virus (*Paramyxovirus parotitidis*) grown in cultures of human diploid cells or chick-embryo cells or the amniotic cavity of chick embryos. It is prepared immediately before use by reconstitution from the dried vaccine. The cell-culture medium may contain the lowest effective concentration of a suitable antibacterial. The virus concentration is not less than 3.7 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Mumps may be used on the label.

Uses and Administration

Mumps vaccines are used for active immunisation against mumps.

For primary immunisation a combined measles, mumps, and rubella vaccine (p. 2400.2) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Many different attenuated strains of mumps virus have been used in vaccines and those commonly used have included Jeryl Lynn, Urabe, Leningrad-3 (and adapted L-Zagreb), and Rubini strains. Efficacy seems to be broadly similar for these strains with the exception of Rubini which is reported to be less effective than Jeryl Lynn or Urabe.

In some countries, a single-antigen mumps vaccine has been used although combined vaccines are usually preferred.

References.

1. WHO. Mumps virus vaccines: WHO position paper. *Wkly Epidem Rec* 2007; **82:** 51–60. Also available at: http://www.who.int/immunization/wer8207mumps_Feb07_position_paper.pdf (accessed 25/06/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Parotid swelling may occur. Unilateral nerve deafness, aseptic meningitis, and encephalitis have occurred rarely (see below for further discussion).

Mumps vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Effects on hearing. For reports of sensorineural hearing loss after vaccination with measles, mumps, and rubella-containing vaccines, see p. 2400.3.

Effects on the nervous system. There have been a few reports of neurological reactions including meningitis and encephalitis after vaccination with measles, mumps, and rubella (MMR) vaccines. These reactions have been attributed to the mumps component. However, it has not been possible to isolate the virus from the CSF in every case and identify it as either the vaccine strain or a wild-type strain. Meningitis develops up to 35 days after immunisation, is mild, and sequelae are rare.[1,2] One study[3] found the incidence of virus-positive post-immunisation meningitis from the Urabe strain of mumps vaccine to be about 1 in 11 000 immunised children, with the incidence following Jeryl Lynn mumps vaccine being much lower. This

result was supported by the incidence of about 1 in 4000 in another study,[4] making it less likely that this was a chance result, and much higher than the estimates of up to 1 in 1 million reported previously.[5] Subsequent research[6] identified the Urabe vaccine strain in CSF samples from all of 20 children with post-vaccination meningitis in the UK, and no isolates of the Jeryl Lynn strain in patients with meningitis among 80 samples tested. Thus, vaccines containing the Urabe strain, including combined MMR vaccines are no longer used in the UK and some other countries.[7] A relatively high incidence of meningitis of about 1 in 1000 has also occurred after use of a measles and mumps vaccine prepared from the Leningrad-3 strain of mumps virus.[8,9]

Encephalitis has been associated with mumps vaccination less frequently than meningitis, but may be more serious.[1] The Advisory Committee on Immunization Practices in the USA has reported that the incidence of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses.[10] This is no higher than the background incidence for CNS dysfunction seen in the general population. There are also a few reports of acute disseminated encephalomyelitis following vaccination with mumps vaccine.[11]

In considering the above data it should be remembered that mumps is the most common cause of meningoencephalitis in children under 15 years of age in the UK and an important cause of permanent sensorineural deafness in childhood.[1] Meningitis after natural mumps infection is estimated to occur in 1 in 400 cases, an incidence that is very considerably above any reported with vaccination.

1. Anonymous. Mumps meningitis and MMR vaccination. *Lancet* 1989; **ii:** 1015–16.
2. Maguire HC, *et al*. Meningoencephalitis associated with MMR vaccine. *Commun Dis Rep* 1991; **1** (review 6): R60–R61.
3. Miller E, *et al*. Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* 1993; **341:** 979–82.
4. Colville A, Pugh S. Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet* 1992; **340:** 786. Correction. *ibid.*: 986.
5. McDonald JC, *et al*. Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. *Pediatr Infect Dis J* 1989; **8**: 751–5.
6. Forsey T, *et al*. Mumps vaccine and meningitis. *Lancet* 1992; **340:** 980.
7. Anonymous. Two MMR vaccines withdrawn. *Lancet* 1992; **340:** 722.
8. Čižman M, *et al*. Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J* 1989; **8:** 302–8.
9. Tešović G, *et al*. Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet* 1993; **341:** 1541.
10. Immunization Practices Advisory Committee. Mumps prevention. *MMWR* 1989; **38:** 388–400.
11. Japanese Pharmaceuticals and Medical Devices Safety Information. Important safety information—freeze-dried live attenuated mumps vaccine; no. 279 (issued May 2011). Available at: www.pmda.go.jp/english/service/pdf/precautions/PMDSI-279.pdf (accessed 03/04/12)

Orchitis. For mention of orchitis following vaccination with measles, mumps, and rubella vaccine see under Measles, Mumps, and Rubella Vaccine, p. 2401.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Pavivac; *Gr.*: Mumpsvax; *Turk.*: Mumaten; *USA*: Mumpsvax†.

Pharmacopoeial Preparations
Ph. Eur.: Mumps Vaccine (Live).

Mycobacterium Vaccae Vaccines

SRL-172; Vacunas de Mycobacterium vaccae.

Profile

Vaccines containing *Mycobacterium vaccae* are under investigation for the prevention and immunotherapy of tuberculosis and other mycobacterial infections. They are also being studied for therapeutic use in asthma, eczema, psoriasis, and some malignant neoplasms.

Asthma. Heat-killed *Mycobacterium vaccae* is a potent down-regulator of T-helper 2 cytokines which play a central role in asthma. In a double-blind, randomised, placebo-controlled study[1] in 24 asthmatic men, a bronchial allergen challenge was given 2 weeks before and 3 weeks after a single intradermal injection of *Mycobacterium vaccae* vaccine. The maximum fall in FEV, during the allergic response to the latter challenge was reduced by a mean of 34%, but this was not statistically significant compared with placebo.

1. Camporota L, *et al*. The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. *Eur Respir J* 2003; **21:** 287–93.

Eczema. In a double-blind, randomised, placebo-controlled study[1] in 41 children aged 5 to 18 years with moderate to severe atopic dermatitis, an intradermal injection of *Mycobacterium vaccae* vaccine resulted in a 48% reduction in the surface area of the skin affected after 3 months compared with 4% in those given placebo. In a later study[2] in 56 children aged 2 to 6 years, these results could not be replicated because the reduction in affected area was not found to be significantly different from placebo.

1. Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; **107:** 531–4.
2. Arkwright PD, David TJ. Effect of Mycobacterium vaccae on atopic dermatitis in children of different ages. *Br J Dermatol* 2003; **149:** 1029–34.

Malignant neoplasms. *Mycobacterium vaccae* vaccines have been used with limited success as adjunctive therapy in the management of a variety of cancers, notably prostate cancer, malignant melanoma, and non-small-cell lung cancer. In a preliminary study[1] 28 patients with inoperable non-small-cell lung cancer and mesothelioma were randomised to receive chemotherapy either with or without adjunctive intradermal injection of a heat-killed *Mycobacterium vaccae* vaccine (SRL-172). A trend towards improved response rate was found in those patients receiving combined therapy, together with improved median survival and 1-year survival rates; some patients given combined therapy were subsequently able to receive curative surgery or radical radiotherapy. A similar subsequent phase III study[2] in 419 patients found a significant improvement in patient quality of life after combined therapy, but the improvements in survival-time could not be replicated. Secondary analyses of these results[3] suggested an improvement in survival-time for patients with adenocarcinoma, but not for those with squamous cell carcinoma. There is also some evidence of beneficial effect in patients with metastatic renal cell carcinoma.[4]

1. O'Brien ME, *et al*. A randomized phase II study of SRL172 (Mycobacterium vaccae) combined with chemotherapy in patients with advanced inoperable non-small-cell lung cancer and mesothelioma. *Br J Cancer* 2000; **83:** 853–7.
2. O'Brien ME, *et al*. SRL172 (killed Mycobacterium vaccae) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* 2004; **15:** 906–14.
3. Stanford JL, *et al*. Successful immunotherapy with Mycobacterium vaccae in the treatment of adenocarcinoma of the lung. *Eur J Cancer* 2008; **44:** 224–7.
4. Patel PM, *et al*. An evaluation of a preparation of Mycobacterium vaccae (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 2008; **44:** 216–23.

Psoriasis. Preliminary studies have shown that heat-killed *Mycobacterium vaccae* vaccines may induce periods of remission when given intradermally. An open-label study[1] in 24 patients given 2 intradermal injections into lesion-free deltoid skin at a 3-week interval found, 12 weeks after starting treatment: marked improvement (14 patients), moderate improvement (2), no change (6), and worsening of symptoms (2). By 24 weeks, 11 of 22 patients continued to show a greater than 50% improvement and of these 5 had complete clearance of skin lesions lasting for 6 months or more. In another study,[2] a more potent heat-killed, delipidated, deglycolipidated vaccine was given similarly to 20 patients with moderate to severe psoriasis; after 12 weeks, 13 of the 20 patients showed a marked improvement, 3 were unchanged, 3 had worsened, and 1 withdrawn due to an exfoliative flare. At 24 weeks, 13 of 19 patients continued to show a greater than 50% improvement, and in some this lasted for 6 months or more. A double-blind, randomised, placebo-controlled study[3] with the latter vaccine in 36 patients with psoriatic arthritis found no improvement in psoriatic lesions compared with placebo, although there did appear to be some improvement in pain experienced. Another placebo-controlled study in patients with psoriasis also failed to show benefit.[4]

1. Balagon MV, *et al*. Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol* 2000; **39:** 51–8.
2. Balagon MV, *et al*. Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated Mycobacterium vaccae (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001; **26:** 233–41.
3. Dalbeth N, *et al*. A randomised placebo controlled trial of delipidated, deglycolipidated Mycobacterium vaccae as immunotherapy for psoriatic arthritis. *Ann Rheum Dis* 2004; **63:** 718–22.
4. Netto EM, *et al*. Phase II randomized, placebo-controlled trial of M. vaccae-derived protein (PVAC) for the treatment of psoriasis. *Vaccine* 2006; **24:** 5056–63.

Tuberculosis. *IMMUNISATION.* References.

1. von Reyn CF, *et al*. Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of Mycobacterium vaccae vaccine. *Clin Infect Dis* 1998; **27:** 1517–20.
2. Waddell RD, *et al*. Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clin Infect Dis* 2000; **30** (suppl 3): S309–S315.
3. Vuola JM, *et al*. Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial. *AIDS* 2003; **17:** 2351–5.
4. Yang XY, *et al*. Mycobacterium vaccae vaccine to prevent tuberculosis in high risk people: a meta-analysis. *J Infect* 2010; **60:** 320–30.
5. Beresford B, Sadoff JC. Update on research and development pipeline: tuberculosis vaccines. *Clin Infect Dis* 2010; **50** (suppl 3): S178–S183.

IMMUNOTHERAPY. A systematic review[1] found that immunotherapy with *Mycobacterium vaccae* produced no beneficial effects in patients with tuberculosis.

1. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/12/04).

Normal Immunoglobulins

Inmunoglobulinas inespecíficas.
ATC — J06BA01; J06BA02.
UNII — 66Y330CJHS (human immunoglobulin G).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Normal Immunoglobulin; Immunoglobulinum Humanum Normale). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG) antibodies, of normal subjects. Other proteins may be present; it contains not less than 10% and not more than 18% of total protein. It is intended for intramuscular or subcutaneous injection. It is obtained from the pooled plasma collected from at least 1000 donors who must be healthy and as far as can be ascertained be free from detectable agents of infection transmissible by transfusion of blood or blood components. No antibacterial is added to the plasma used. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. Multidose, but not single dose, preparations contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 5.0 to 7.2. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in an airtight, colourless, glass container.

Ph. Eur. 8: (Human Normal Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Normale ad Usum Intravenosum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG); other proteins may be present and the total protein content is not less than 3%. It contains IgG antibodies of normal subjects; the standard does not apply to products intentionally prepared to contain fragments or chemically modified IgG. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. It does not contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 4.0 to 7.4. Storage requirements are similar to those for Human Normal Immunoglobulin, except that the freeze-dried preparation is stored in an airtight container at a temperature not exceeding 25 degrees.

USP 36: (Immune Globulin). A sterile solution of globulins that contains many antibodies normally present in human adult blood. It is prepared from pooled material (approximately equal quantities of blood, plasma, serum, or placentas) from not fewer than 1000 donors. It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It is intended for intramuscular injection. It contains glycine as a stabiliser, and a suitable preservative. It contains antibodies against diphtheria, measles, and poliomyelitis. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Normal immunoglobulin is available as two distinct preparations and formulations:

- an *intramuscular* injection (Human Normal Immunoglobulin (Ph. Eur. 8) and Immune Globulin (USP 36)) generally containing 16% of protein is used for passive immunisation, and sometimes also for primary antibody deficiencies
- the preparation formulated for *intravenous* use (Human Normal Immunoglobulin for Intravenous Administration (Ph. Eur. 8)) is used in disorders such as primary and secondary antibody deficiencies, as an immunomodulatory agent for immune thrombocytopenia, and to treat chronic inflammatory and immune-mediated diseases; solutions generally contain about 3 to 6% of protein, although some may contain up to 12%

Doses of normal immunoglobulin often appear confusing, being expressed variously in terms of weight (protein or immunoglobulin G content) or in terms of volume to be given, and the two do not always appear to correspond. It should be remembered that there may be differences between intravenous preparations of normal immunoglobulin including differing IgA content and IgG subclass distribution.

Normal immunoglobulin, being derived from the pooled plasma of blood donors, contains antibodies to bacteria and viruses currently prevalent in the general population; in the UK, and also in some other countries, typical antibodies

present include those against hepatitis A, measles, mumps, rubella, and varicella. Normal immunoglobulin therefore may be used to provide passive immunisation against such diseases.

Normal immunoglobulin may be used to control outbreaks of **hepatitis A**, the recommended intramuscular dose for close contacts being 250 mg in those under 10 years of age and 500 mg in older children and adults. It may also be used for prophylaxis against hepatitis A in immunocompromised patients if their response to hepatitis A vaccine is unlikely to be adequate.

Normal immunoglobulin may be used to prevent or possibly modify an attack of **measles** in children and adults at special risk (such as those who are immunocompromised) but should be given as soon as possible after contact with measles. In the UK recommended doses, given intramuscularly, for the prevention or attenuation of an attack are 250 mg for those under 1 year of age, 500 mg for those aged 1 to 3 years, and 750 mg for those aged 3 years and over.

Normal immunoglobulin does not prevent **rubella** infection and is not recommended for the protection of pregnant women exposed to rubella; it should only be considered where termination of pregnancy is unacceptable. The dose is 750 mg by intramuscular injection.

Normal immunoglobulin may be used in the management of patients with **primary antibody deficiencies** such as congenital agammaglobulinaemia, hypogammaglobulinaemia, or **immunocompromised patients** including those with immunodeficiency syndromes; the immunoglobulin is given to provide protection against infectious diseases that such patients may suffer. The intramuscular preparation has been used but the intravenous route is usually preferred as it is less painful for the doses required. Alternatively, the subcutaneous route may be used. For intravenous infusion the dose, expressed in terms of weight (protein or immunoglobulin G content), is usually 400 to 800 mg/kg initially, then 200 mg/kg every 3 weeks adjusted as necessary according to trough-immunoglobulin concentrations; the maintenance dose is usually 200 to 800 mg/kg per month. In patients with secondary immunodeficiency syndromes, doses of 200 to 400 mg/kg every 3 to 4 weeks have been recommended. Other dosage regimens have been used. Subcutaneous doses are 200 to 500 mg/kg as an initial loading dose (divided over several days), followed by maintenance doses at repeated intervals to achieve a cumulative monthly dose of 400 to 800 mg/kg. When infused intravenously, normal immunoglobulin should always be given very carefully and slowly with gradual increases in the rate of infusion.

For prophylaxis of infection after **bone marrow transplantation**, normal immunoglobulin is given intravenously in a dose of 500 mg/kg weekly, adjusted according to response.

Intravenous infusion of normal immunoglobulin is also used to raise the platelet count in patients with **immune thrombocytopenia** (idiopathic thrombocytopenic purpura). Doses of 400 mg/kg are given daily for 2 to 5 consecutive days. Alternatively, a dose of 800 to 1000 mg/kg may be given on day 1 and repeated within 3 days if necessary. Further doses may be given as necessary.

For **Kawasaki disease**, normal immunoglobulin (used with aspirin) is given intravenously in a dose of 1.6 to 2 g/kg in divided doses over 2 to 5 days, or 2 g/kg given as a single dose. Similar doses of intravenous normal immunoglobulin have been tried in a range of disorders believed to have an auto-immune origin. The precise mode of action of normal immunoglobulin in such disorders is unknown.

For the treatment of **Guillain-Barré syndrome**, normal immunoglobulin is given intravenously in a dose of 400 mg/kg for 5 consecutive days, repeated every 4 weeks if required.

References.

1. Anonymous. Intravenous immunoglobulin (IVIG). *Med Lett Drugs Ther* 2006; **48:** 101–3.
2. Gürcan HM, Ahmed AR. Efficacy of various intravenous immunoglobulin therapy protocols in autoimmune and chronic inflammatory disorders. *Ann Pharmacother* 2007; **41:** 812–23.
3. Provan D, *et al*. UK Immunoglobulin Expert Working Group. Prescribing intravenous immunoglobulin: summary of Department of Health guidelines. *BMJ* 2008; **337:** 990–2.
4. Anonymous. I.V. immunoglobulin therapy for infectious diseases. *Drug Ther Bull* 2010; **48:** 57–60.

Administration. Oral dosage with normal immunoglobulins has been proposed to reduce the incidence and severity of gastrointestinal infections, particularly in patients with defective immune systems including neonates. Although the main immunoglobulin secreted into the gastrointestinal tract in subjects with a normal immune system is IgA, which is not present in large quantities in commercial normal immunoglobulins, beneficial responses, especially in viral infections, have been reported after oral use. Systematic reviews have not, however, supported routine use of oral immunoglobulin for the prevention or treatment of gastrointestinal infections.[1-3] Preparations of immunoglobulin A are available in some countries and have been tried, mainly in bacterial gastrointestinal infections.[4,5]

1. Mohan P, Haque KN. Oral immunoglobulin for the prevention of rotavirus infection in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
2. Mohan P, Haque KN. Oral immunoglobulin for the treatment of rotavirus diarrhoea in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
3. Foster JP, Cole MJ. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/03/05).
4. Tjellström B, *et al*. Oral immunoglobulin A supplement in treatment of Clostridium difficile enteritis. *Lancet* 1993; **341:** 701–2.
5. Hammarström V, *et al*. Oral immunoglobulin treatment in Campylobacter jejuni enteritis. *Lancet* 1993; **341:** 1036.

Blood disorders. Intravenous normal immunoglobulins are used in the treatment of symptomatic severe immune thrombocytopenia (p. 1606.1). Other blood disorders in which normal immunoglobulins have been tried include agranulocytosis[1] and haemolytic disease of the newborn (p. 2377.2), haemolytic anaemias (p. 1122.2), red cell aplasia caused by parvovirus B19 infections (see under Passive Immunisation, p. 2406.3), thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies p. 1159.1), and thrombocytopenia with a variety of causes.[2-10]

1. Fasth A. Immunoglobulin for neonatal agranulocytosis. *Arch Dis Child* 1986; **61:** 86–7.
2. Hoffman DM, *et al*. Human immunodeficiency virus-associated thrombocytopenia. *DICP Ann Pharmacother* 1989; **23:** 157–160.
3. Frame JN, *et al*. Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; **111:** 946–7.
4. Howrie DL, *et al*. Use of iv immune globulin for treatment of phenytoin-induced thrombocytopenia. *Clin Pharm* 1989; **8:** 734–7.
5. Landonio G, *et al*. HIV-related severe thrombocytopenia in intravenous drug users: prevalence, response to therapy in a medium-term follow-up, and pathogenic evaluation. *AIDS* 1990; **4:** 29–34.
6. Goulder P, *et al*. Intravenous immunoglobulin in virus associated haemophagocytic syndrome. *Arch Dis Child* 1990; **65:** 1275–7.
7. Larner AJ, *et al*. Life threatening thrombocytopenia in sarcoidosis: response to vincristine, human immunoglobulin, and corticosteroids. *BMJ* 1990; **300:** 317–19.
8. Ray JB, *et al*. Intravenous immune globulin for the treatment of presumed quinidine-induced thrombocytopenia. *DICP Ann Pharmacother* 1990; **24:** 693–5.
9. Salzman MB, Smith EM. Phenytoin-induced thrombocytopenia treated with intravenous immune globulin. *J Pediatr Hematol Oncol* 1998; **20:** 152–3.
10. Majluf-Cruz A, *et al*. Usefulness of a low-dose intravenous immunoglobulin regimen for the treatment of thrombocytopenia associated with AIDS. *Am J Hematol* 1998; **59:** 127–32.

Bowel disorders. Intravenous normal immunoglobulin may be beneficial[1-3] in inducing remission of Crohn's disease and ulcerative colitis and in antibiotic-associated or pseudomembranous colitis associated with *Clostridium difficile* infection.[4,5]

1. Rohr G, *et al*. Treatment of Crohn's disease and ulcerative colitis with 7S-immunoglobulin. *Lancet* 1987; **i:** 170.
2. Knoflach P, *et al*. Crohn disease and intravenous immunoglobulin G. *Ann Intern Med* 1990; **112:** 385–6.
3. Körber J, *et al*. A case of Crohn's disease with increased CD8 T-cell activation and remission during therapy with intravenous immunoglobulins. *Scand J Gastroenterol* 1998; **33:** 1113–17.
4. Leung DYM, *et al*. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. *J Pediatr* 1991; **118:** 633–7.
5. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea. *J Antimicrob Chemother* 2004; **53:** 882–4.

Complex regional pain syndrome. It has been suggested that the immune system may be involved in sustaining complex regional pain syndrome (CRPS—p. 8.1) and a small double-blind crossover pilot study in patients who had CRPS for between 6 and 30 months that was refractory to standard treatment suggested that low-dose intravenous normal immunoglobulin (250 mg/kg daily on 2 consecutive days) could substantially reduce the intensity of pain and improve autonomic limb symptoms.[1]

1. Goebel A, *et al*. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. *Ann Intern Med* 2010; **152:** 152–8.

Epilepsy. Normal immunoglobulins have sometimes been of benefit[1-3] in the treatment of children with intractable epilepsy, including Lennox-Gastaut syndrome or West's syndrome, but a review of the literature found that few well controlled studies had been conducted,[4] and a Canadian evidence-based guideline recommended against its use.[5] Although a positive trend in favour of intravenous immunoglobulin therapy for refractory epilepsy was noted in one double-blind controlled study[6] involving 61 patients, the results were not considered to be statistically significant.

1. Ariizumi M, *et al*. High dose gammaglobulin for intractable childhood epilepsy. *Lancet* 1983; **ii:** 162–3.
2. Sandstedt P, *et al*. Intravenous gammaglobulin for post-encephalitic epilepsy. *Lancet* 1984; **ii:** 1154–5.
3. van Engelen BGH, *et al*. High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome: an add-on study. *Eur J Pediatr* 1994; **153:** 762–9.
4. Duse M, *et al*. Intravenous immune globulin in the treatment of intractable childhood epilepsy. *Clin Exp Immunol* 1996; **104** (suppl 1): 71–6.
5. Feasby T, *et al*. Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21** (suppl 1): S57–S107.
6. van Rijckevorsel-Harmant K, *et al*. Treatment of refractory epilepsy with intravenous immunoglobulins: results of the first double-blind/dose finding clinical study. *Int J Clin Lab Res* 1994; **24:** 162–6.

Hypogammaglobulinaemia. See under Primary Antibody Deficiency, below.

Immunocompromised patients. Immunodeficiency states may arise from primary disorders of the immune system, or, more commonly, they are secondary to immunosuppressive therapy, HIV infection, or haematological malignancies. Premature neonates may have deficits in their immune systems due to their immaturity; placental transfer of maternal antibodies usually occurs after about 32 weeks of gestation. Such patients and neonates may be deficient in gammaglobulins and they could potentially benefit from the use of normal immunoglobulins to address their increased susceptibility to infection. For information on the use of immunoglobulins in specific conditions, see the following sections and under Neonatal Infection, p. 2406.2.

MALIGNANCIES. Hypogammaglobulinaemia and the effects of treatment may increase the susceptibility to infection of patients with *chronic lymphocytic leukaemia*.[1] In a study[2] of 81 patients with chronic lymphocytic leukaemia considered to be at an increased risk of infection, intravenous normal immunoglobulin 400 mg/kg given every 3 weeks for one year reduced the incidence of bacterial infection compared with saline placebo. The incidence of viral and fungal infections was not affected. A study in 34 patients[3] suggested that a dose of normal immunoglobulin 250 mg/kg per month was adequate for routine prophylaxis in most patients. Beneficial effects on infection rates have been reported in patients with *multiple myeloma* receiving normal immunoglobulins.[4] A systematic review[5] concluded that there was no benefit in terms of mortality in patients with lymphoproliferative disorders given prophylactic normal immunoglobulin, but that there was a substantial reduction in infections which might justify such use.

1. Wierda WG. Immunologic monitoring in chronic lymphocytic leukaemia. *Curr Oncol Rep* 2003; **5:** 419–25.
2. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled clinical trial. *N Engl J Med* 1988; **319:** 902–7.
3. Chapel H, *et al*. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *Br J Haematol* 1994; **88:** 209–12.
4. Chapel HM, *et al*. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. *Lancet* 1994; **343:** 1059–63.
5. Raanani P, *et al*. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/02/10).

PRIMARY ANTIBODY DEFICIENCY. There are 3 major forms of primary antibody deficiency (primary immune deficiency): X-linked agammaglobulinaemia (XLA, Bruton's agammaglobulinaemia), common variable immunodeficiency (CVID) which includes IgG subclass and specific antibody deficiencies, and selective IgA deficiency. The disease is characterised by a wide range of infective complications as well as auto-immune disorders. Management is by replacement therapy with normal immunoglobulin accompanied by appropriate antimicrobial therapy for breakthrough infections.[1-5] Immunisation against infection is of little value (although some patients with CVID may occasionally respond)[5] and is contra-indicated for live viral vaccines.

Normal immunoglobulin was traditionally given by the intramuscular route. However, the maximum dose that could be reasonably given by this route was 25 mg/kg weekly, and it was therefore only satisfactory for patients with mild disease.[6] The introduction of intravenous preparations of normal immunoglobulin allowed high doses to be used in those with severe disease. This route should therefore be used for all patients with XLA and for patients with CVID who have more than mild disease.[1] The use of intravenous normal immunoglobulin in IgG subclass deficiency, with or without IgA deficiency, or in specific antibody deficiency is successful, though less well established. The dose and frequency of administration of intravenous normal immunoglobulin is variable and should be adjusted to prevent breakthrough infection. It has been suggested that different normal immunoglobulin products may not be equivalent; however, a Canadian guideline considered that they could be used interchangeably from the standpoint of efficacy, although individual patients might have fewer adverse reactions to a particular product, and be unwilling to change.[5] Most patients require 200 to 600 mg/kg every 2 or 3 weeks to maintain optimum protection.[6] In one study,[7] doses of between 260 and

1120 mg/kg every 3 weeks were necessary to maintain residual serum IgG concentrations above 500 mg/dL. These doses were found to be effective in reducing the incidence of severe acute bacterial infections and pulmonary insufficiency in children with XLA. Surgical procedures should be covered with additional normal immunoglobulin and appropriate prophylactic antibacterials. Home treatment with intravenous normal immunoglobulin has been used successfully in several countries in both adults and children.[5,6,8-11] Adverse reactions have been few and generally mild.[6,9,10] They are most likely to occur during the first infusion and during intercurrent illness, and may be precipitated by a high infusion rate.[11] Long-term treatment of children with antibody deficiencies with intravenous normal immunoglobulin has been shown to lead to normal growth and similar rates of infection to those found in non-immunodeficient children.[12]

Immunoglobulin replacement can alternatively be given by subcutaneous infusion as an alternative to intravenous therapy.[2,4,13,14] Subcutaneous use is considered as effective as intravenous in protecting against infection, and may be more convenient for giving at home, although evidence of equivalence is lacking for patients with severe autoimmune symptoms. A suggested starting dose in most patients is 100 to 150 mg/kg weekly.[5] The intraventricular route has been of benefit in some patients with echovirus encephalitis.[6,15]

1. Carrock Sewell WA, *et al*. Therapeutic strategies in common variable immunodeficiency. *Drugs* 2003; **63:** 1359–71.
2. Schwartz SA. Intravenous immunoglobulin treatment of immunodeficiency disorders. *Pediatr Clin North Am* 2000; **47:** 1355–69.
3. Empson M, *et al*. The assessment and management of primary antibody deficiency. *N Z Med J* 2004; **117:** U914.
4. Durandy A, *et al*. Immunoglobulin replacement therapy in primary antibody deficiency diseases—maximizing success. *Int Arch Allergy Immunol* 2005; **136:** 217–29.
5. Shehata N, *et al*. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. *Transfus Med Rev* 2010; **24** (suppl 1): S28–S50.
6. Spickett GP, *et al*. Primary antibody deficiency in adults. *Lancet* 1991; **337:** 281–4.
7. Quartier P, *et al*. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999; **134:** 589–96.
8. Ochs HD, *et al*. Intravenous immunoglobulin home treatment for patients with primary immunodeficiency diseases. *Lancet* 1986; **i:** 610–11.
9. Ryan A, *et al*. Home intravenous immunoglobulin therapy for patients with primary hypogammaglobulinaemia. *Lancet* 1988; **ii:** 793.
10. Kobayashi RH, *et al*. Home self-administration of intravenous immunoglobulin therapy in children. *Pediatrics* 1990; **85:** 705–9.
11. Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. *BMJ* 1994; **308:** 581–5.
12. Skull S, Kemp A. Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973-93. *Arch Dis Child* 1996; **74:** 527–30.
13. Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs* 2007; **21:** 105–16.
14. Helbert M, Farragher A. Subcutaneous immunoglobulin for patients with antibody deficiency. *Br J Hosp Med* 2007; **68:** 206–10.
15. Erlendsson K, *et al*. Successful reversal of echovirus encephalitis in x-linked hypogammaglobulinemia by intraventricular administration of immunoglobulin. *N Engl J Med* 1985; **312:** 351–3.

TRANSPLANTATION. Normal immunoglobulin may be used in patients undergoing haematopoietic stem cell transplantation (HSCT—see p. 1933.1) with the aim of decreasing the incidence of bacterial and of symptomatic CMV infection, and that of graft-versus-host disease.[1,2] A 1990 National Institutes of Health consensus considered that intravenous normal immunoglobulin was useful for both purposes in these immunosuppressed patients.[3] However, later results have not tended to support this. Reviews and meta-analyses have concluded that there is little evidence to support any benefit of normal immunoglobulin in reducing infection,[1,2,4] or all-cause mortality.[4] Although there is some evidence to suggest that the risk of interstitial pneumonitis may be reduced, this seems to be counterbalanced by an increased risk of hepatic veno-occlusive disease.[4] Evidence for any benefit in reducing graft-versus-host disease is at best equivocal[1] or absent.[4] It has been concluded therefore, that normal immunoglobulin does not have a role for routine prophylaxis in HSCT.[2,4]

Normal immunoglobulin is also increasingly used in the setting of solid organ transplantation. A Canadian evidence-based guideline[5] concluded that there was sufficient evidence to support its use in renal transplantation where the patient would receive a kidney from a living donor to whom he or she was sensitised, and for use after plasmapheresis in patients with acute antibody-mediated rejection. There was insufficient evidence to support use in cardiac, liver, or lung transplantation.

1. Sokos DR, *et al*. Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2002; **8:** 117–30.
2. Raanani P, *et al*. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/02/10).
3. NIH. Intravenous immunoglobulin: prevention and treatment of disease. *NIH Consens Statement Online* 1990; **8:** 1–23. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hsnihcdc&part=A7621 (accessed 24/02/10)
4. Raanani P, *et al*. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. *J Clin Oncol* 2009; **27:** 770–81.
5. Shehata N, *et al*. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. *Transfus Med Rev* 2010; **24** (suppl 1): S7–S27.

Kawasaki disease. Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood, occurs mainly in children under 5 years of age. It is epidemic and endemic worldwide but is a particular problem in Japan. Kawasaki disease presents with high fever which persists for at least 5 days and may be followed by bilateral conjunctivitis, changes in the oropharyngeal mucosa, signs of vasculitis in the extremities, rash, and cervical lymphadenopathy. The major complications of Kawasaki disease are cardiac effects including coronary artery aneurysm, aortic or mitral incompetence, myocarditis, and pericarditis with effusion. The cause of the disease is unknown, although an infective aetiology has been suggested. Early diagnosis, expert cardiac assessment, and immediate treatment are essential for improved outcome.

Treatment aims to reduce inflammation, particularly in the coronary arterial wall and myocardium, and therefore prevent the development of cardiac complications. Long-term antiplatelet treatment is given as necessary to prevent coronary thrombosis.

Initial treatment is with aspirin and normal immunoglobulin.[1-3] Despite the anti-inflammatory and antiplatelet properties of aspirin it does not appear to lower the incidence of coronary abnormalities in Kawasaki disease when used alone; however, high-dose aspirin and intravenous high-dose normal immunoglobulin appear to possess an additive anti-inflammatory effect when used together and a decreased incidence of coronary-artery abnormalities has been found after such a combination as compared with aspirin alone. Treatment should begin if possible within 10, and preferably within 7, days of the onset of illness. Treatment before day 5 appears to offer no more advantage in preventing cardiac sequelae than treating from days 5 to 7, but it may be associated with an increased need for re-treatment with normal immunoglobulin. Treatment should be given to children presenting after the tenth day of illness if they have either persistent unexplained fever or aneurysms with ongoing systemic inflammation.[2]

Normal immunoglobulin has been given by intravenous infusion in divided doses over 2 to 5 days, but high-dose administration as a single dose is now recommended; a meta-analysis[4] and a systematic review[5] have concluded that single-dose therapy is associated with a lower incidence of coronary abnormalities after 30 days than multiple-dose treatment. The optimum dosage and duration of treatment with aspirin is unknown, but the usual practice is to use an anti-inflammatory regimen until the fever has settled and then to convert to an antithrombotic regimen. A few patients fail to respond to treatment with aspirin and normal immunoglobulin. Re-treatment with normal immunoglobulin may be considered for those with persistent or recurring fever.[2,6]

Evidence for the use of corticosteroids remains inconclusive.[1] They have been given in some centres[7] but since the introduction of immunoglobulin therapy they have not been routinely used as there is a risk that they may exacerbate coronary artery aneurysms. Nevertheless, their use has received renewed attention; randomised studies comparing the adjunctive use of corticosteroids with standard therapy alone have suggested they may be of benefit.[8-10] Corticosteroids have also been tried as an alternative to a second course of intravenous normal immunoglobulin, and a study[11] reported that intravenous pulse corticosteroid treatment was as effective as a second course of normal immunoglobulin. However, most experts do not use them unless fever continues after the second course of normal immunoglobulin.[2]

Alternative suggested drugs for patients refractory to normal immunoglobulin include ulinastatin,[12] which has been used for adjunctive therapy in Japan, but its efficacy remains currently unproven. Abciximab has been used to treat patients with large coronary aneurysms; in one study,[13] patients given abciximab in addition to standard therapy showed a greater regression in aneurysm diameter. Other treatments that have been tried in patients unresponsive to initial normal immunoglobulin include pentoxifylline,[2] the use of cyclophosphamide with corticosteroids in particularly refractory cases,[2] and infliximab;[14,15] an analysis of treatment of resistant Kawasaki disease in the United States between 2001 and 2006 noted a trend towards the increased use of infliximab.[16]

Long-term management. Low-dose aspirin is commonly continued for about 6 weeks after the onset of illness and then stopped if there are no coronary abnormalities.[1,2] Some practitioners use aspirin and dipyridamole as antithrombotic therapy although it is unknown whether this provides benefit over aspirin alone. Dipyridamole may be used as an alternative antithrombotic agent for patients who cannot tolerate aspirin. Aspirin is usually continued for at least one year if coronary abnormalities are present and should be continued indefinitely if coronary aneurysms persist. Anticoagulation with warfarin or heparin in addition to aspirin may be necessary in some patients such as those with giant or multiple aneurysms.

1. Harnden A, *et al*. Kawasaki disease. *BMJ* 2009; **338:** 1133–8.
2. Newburger JW, *et al*. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; **114:** 1708–33. Correction. *ibid*. 2005; **115:** 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 25/05/06) Also published in *Circulation* 2004; **110:** 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
3. WoodLE, Tulloh RM. Kawasaki disease in children. *Heart* 2009; **95:** 787–92.
4. Durongpisitkul K, *et al*. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; **96:** 1057–61.
5. Oates-Whitehead RM, *et al*. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/03/05).
6. Sundel RP, *et al*. Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993; **123:** 657–9.
7. Shinohara M, *et al*. Corticosteroids in the treatment of the acute phase of Kawasaki disease. *J Pediatr* 1999; **135:** 465–9.
8. Sundel RP, *et al*. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003; **142:** 611–16.
9. Okada Y, *et al*. Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003; **143:** 363–7.
10. Wooditch AC, Aronoff SC. Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: a meta-analysis of 862 children. *Pediatrics* 2005; **116:** 989–95.
11. Furukawa T, *et al*. Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. *Arch Dis Child* 2008; **93:** 142–6.
12. Zaitsu M, *et al*. Ulinastatin, an elastase inhibitor, inhibits the increased mRNA expression of prostaglandin H2 synthase-type 2 in Kawasaki disease. *J Infect Dis* 2000; **181:** 1101–9.
13. Williams RV, *et al*. Does abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease? Abstract: *Pediatrics* 2002; **109:** 132. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/1/e4 (accessed 24/03/05)
14. Burns JC, *et al*. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.
15. Burns JC, *et al*. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008; **153:** 833–8.
16. Son MB, *et al*. Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics* 2009; **124:** 1–8.

Kidney disorders. Treatment with normal immunoglobulin has been of benefit in some patients with haemolytic-uraemic syndrome and in those with lupus nephritis (see under Musculoskeletal and Nerve Disorders, below). For mention of the use of normal immunoglobulin in IgA nephropathy, see Glomerular Kidney Disease, p. 1604.3.

Musculoskeletal and nerve disorders. High-dose intravenous normal immunoglobulin has been tried with some benefit in various disorders of the nerves, muscles, joints, and connective tissues which may have an auto-immune basis.[1] These include multiple sclerosis,[2-4] chronic inflammatory demyelinating polyneuropathy,[5,6] polymyositis and dermatomyositis,[7-12] myasthenia gravis,[13-17] stiff-man syndrome,[18-22] chronic systemic juvenile arthritis,[23-25] SLE[26] including lupus nephritis,[27] Guillain-Barré syndrome (see p. 2406.1), and motor neurone disease (see also p. 2406.1). It is also being investigated in Alzheimer's disease.[28] Guidelines issued by an expert committee in Canada[29] included recommendations on the use and dose of normal immunoglobulin for acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis and polymyositis, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome and myasthenia gravis, multifocal motor neuropathy, multiple sclerosis, opsoclonus-myoclonus, neuropsychiatric disorders associated with streptococcal infections in children, short-term management of Rasmussen's encephalitis, and stiff man syndrome.

1. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; **291:** 2367–75.
2. Fazekas F, *et al*. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997; **349:** 589–93.
3. Hommes OR, *et al*. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004; **364:** 1149–56.
4. Achiron A, *et al*. Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2004; **61:** 1515–20.
5. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology* 2002; **59** (suppl 6): S13–S21.
6. Brannagan TH. Intravenous gammaglobulin (IVIg) for treatment of CIDP and related immune-mediated neuropathies. *Neurology* 2002; **59** (suppl 6): S33–S40.
7. Cherin P, *et al*. Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. *Am J Med* 1991; **91:** 162–8.
8. Lang BA, *et al*. Treatment of dermatomyositis with intravenous gammaglobulin. *Am J Med* 1991; **91:** 169–72.
9. Dalakas MC, *et al*. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; **329:** 1993–2000.
10. Brownell AKW. Intravenous immune globulin for dermatomyositis. *N Engl J Med* 1994; **330:** 1392.

11. Collet E, *et al*. Juvenile dermatomyositis: treatment with intravenous gammaglobulin. *Br J Dermatol* 1994; **130:** 231–4.
12. Cherin P, *et al*. Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. *Arthritis Rheum* 2002; **46:** 467–74.
13. Bassan H, *et al*. High-dose intravenous immunoglobulin in transient neonatal myasthenia gravis. *Pediatr Neurol* 1998; **18:** 181–3.
14. Jongen JLM, *et al*. High-dose intravenous immunoglobulin therapy for myasthenia gravis. *J Neurol* 1998; **245:** 26–31.
15. Howard JF. Intravenous immunoglobulin for the treatment o f acquired myasthenia gravis. *Neurology* 1998; **51** (suppl 5): S30–S36.
16. Selcen D, *et al*. High-dose intravenous immunoglobulin therapy in juvenile myasthenia gravis. *Pediatr Neurol* 2000; **22:** 40–3.
17. Zinman L, *et al*. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology* 2007; **68:** 837–41.
18. Karlson EW, *et al*. Treatment o f stiff-man syndrome with intravenous immune globulin. *Arthritis Rheum* 1994; **37:** 915–18.
19. Amato AA, *et al*. Treatment of stiff-man syndrome with intravenous immunoglobulin. *Neurology* 1994; **44:** 1652–4.
20. Barker RA, Marsden CD. Successful treatment of stiff man syndrome with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1997; **62:** 426–7.
21. Khanlou H, Eiger G. Long-term remission of refractory stiff-man syndrome after treatment with intravenous immunoglobulin. *Mayo Clin Proc* 1999; **74:** 1231–2.
22. Dalakas MC, *et al*. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345:** 1870–6.
23. Groothoff JW, van Leeuwen EF. High dose intravenous gammaglobulin in chronic systemic juvenile arthritis. *BMJ* 1988; **296:** 1362–3.
24. Giannini EH, *et al*. Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. *J Rheumatol* 1996; **23:** 919–24.
25. Uziel Y, *et al*. Intravenous immunoglobulin therapy in systemic onset juvenile rheumatoid arthritis: a followup study. *J Rheumatol* 1996; **23:** 910–18.
26. Francioni C, *et al*. Long term IV Ig treatment in systemic lupus erythematosus. *Clin Exp Rheumatol* 1994; **12:** 163–8.
27. Lin C-Y, *et al*. Improvement of histological and immunological change in steroid and immunosuppressive drug-resistant lupus nephritis by high-dose intravenous gamma globulin. *Nephron* 1989; **53:** 303–10.
28. Dodel R, *et al*. Intravenous immunoglobulins as a treatment for Alzheimer's disease: rationale and current evidence. *Drugs* 2010; **70:** 513–28.
29. Feasby T, *et al*. Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21** (suppl 1): S57–S107.

GUILLAIN-BARRÉ SYNDROME. Guillain-Barré syndrome[1,2] (acute idiopathic inflammatory polyneuropathy; acute idiopathic demyelinating neuropathy; acute infectious polyneuropathy) may follow an infection or, more rarely, immunisation, but very often no predisposing factor can be identified. An association with infection with *Campylobacter jejuni* is frequent,[2,3] but the syndrome is also commonly associated with infection with CMV, Epstein-Barr virus, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*.[1,2] Reversible demyelination results in pain and progressive flaccid paralysis. An auto-immune aetiology seems likely. Severely affected patients require cardiovascular monitoring and respiratory support if respiratory muscles are affected or autonomic instability is present. Corticosteroids have been given but are generally considered to be of little value.[2,4] Plasma exchange (see p. 1158.3) is effective if given early,[5] but is not universally available and is not suitable for all patients. Intravenous normal immunoglobulin, again ideally given within 2 weeks of onset, has therefore become the treatment of choice in many centres.[2] A systematic review[6] has concluded that use of normal immunoglobulins is at least as effective as plasma exchange, but that there is no advantage from combining the two forms of treatment. Deterioration has also been noted in some patients after immunoglobulin therapy,[7,8] although one study[9] found that the incidence of relapse was greater after plasma exchange than after normal immunoglobulin.

1. Kuwabara S. Guillain Barré syndrome: epidemiology, pathophysiology and management. *Drugs* 2004; **64:** 597–610.
2. van Doorn PA, *et al*. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. *Lancet Neurol* 2008; **7:** 939–50.
3. Rees JH, *et al*. Campylobacter jejuni infection and Guillain-Barré syndrome. *N Engl J Med* 1995; **333:** 1374–9.
4. Hughes RAC, *et al*. Corticosteroids for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 27/08/10).
5. Raphaël JC, *et al*. Plasma exchange for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 29/03/05).
6. Hughes RAC, *et al*. Intravenous immunoglobulin for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 05/08/10).
7. Irani DN, *et al*. Relapse in Guillain-Barré syndrome after treatment with human immune globulin. *Neurology* 1993; **43:** 872–5.
8. Castro LHM, Ropper AH. Human immune globulin infusion in Guillain-Barré syndrome: worsening during and after treatment. *Neurology* 1993; **43:** 1034–6.
9. Romano JG, *et al*. Relapses in the Guillain-Barré syndrome after treatment with intravenous immune globulin or plasma exchange. *Muscle Nerve* 1998; **21:** 1327–30.

MOTOR NEURONE DISEASE. Several studies and a systematic review have shown normal immunoglobulins to be of benefit in the treatment of multifocal motor neuropathy, a form of motor neurone disease (p. 2605.2) associated with anti-GM_1 antibody formation.[1-7] In most patients, however, improvement has to be maintained with periodic infusion and some become less responsive to therapy over time, requiring higher doses. A retrospective study[8] of 10 patients with multifocal motor neuropathy treated with normal immunoglobulins showed that while the initial response could be maintained for several years, efficacy decreased during prolonged treatment even when doses were progressively adjusted. During the first few years of therapy, increased dosage restored the efficacy of normal immunoglobulins, but was found to be less able to do so later in follow-up.

1. Van den Berg LH, *et al*. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; **59:** 248–52.
2. Meucci N, *et al*. Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1997; **63:** 765–9.
3. Van den Berg LH, *et al*. The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. *Brain* 1998; **121:** 421–8.
4. Ellis CM, *et al*. Use of human intravenous immunoglobulin in lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 1999; **67:** 15–19.
5. Federico P, *et al*. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; **55:** 1256–62.
6. Léger JM, *et al*. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; **124:** 145–53.
7. van Schaik IN, *et al*. Intravenous immunoglobulin for multifocal motor neuropathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 14/02/06).
8. Terenghi F, *et al*. How long is IVIg effective in multifocal motor neuropathy? *Neurology* 2004; **62:** 666–8.

Neonatal disorders. *HAEMOLYTIC DISEASE OF THE NEWBORN.* For a discussion of haemolytic disease of the newborn and its management, including the use of intravenous immunoglobulin as an alternative to exchange transfusions in affected pregnancies, see p. 2377.2.

NEONATAL INFECTION. Sepsis is a serious problem in premature infants despite appropriate antimicrobial therapy. Preterm infants are born with low serum-immunoglobulin concentrations that decrease over the next several weeks of life. There is also a deficiency of antibodies to specific organisms such as group B streptococci, *Staphylococcus epidermidis*, and *Escherichia coli*.

Some, but not all, studies suggest that prophylactic use of intravenous normal immunoglobulin in premature infants shortly after birth can decrease the incidence of septicaemia.[1] Aspects of the methodology of these studies have, however, been criticised[2] and a systematic review[3] concluded that prophylactic use of intravenous immunoglobulin for prevention of infection in preterm or low birthweight neonates was of at best marginal benefit only, and of no benefit in preventing sepsis, and did not recommend routine use. Some benefit has been seen after use of intravenous immunoglobulin to treat infants with suspected sepsis[1] and it may improve the response to antibacterials,[4] although a further systematic review[5] found insufficient evidence to support routine use in infants with suspected, or subsequently proved, neonatal infection.

The optimum dosage of intravenous immunoglobulin is not established. A prophylactic dose of 500mg/kg on admission repeated every 1 to 2 weeks has been suggested for units where infection is common in very low birthweight infants.[1] Others have suggested adjusting the dose to maintain a specified serum-immunoglobulin concentration. Alternatively, normal immunoglobulin could be given only to infants with immunoglobulin concentrations below a certain level, or be reserved for immediate use in those who become ill with suspected sepsis.[1]

Normal immunoglobulin cannot protect against all types of infection. Normal immunoglobulin preparations from different manufacturers may have, for a specific pathogen, differing levels of specific antibody and differing levels of functional activity or there may be lot-to-lot variability in functional activity for normal immunoglobulin from a specific manufacturer. Such variability, resulting in low concentrations of functional antibodies in the 4 batches of immunoglobulins used in the National Institute of Child Health Study,[6] was held responsible for the lack of demonstrable efficacy of immunoglobulins in that study, one of the largest to date.

1. Whitelaw A. Treatment of sepsis with IgG in very low birthweight infants. *Arch Dis Child* 1990; **65:** 347–8.
2. Noya FJD, Baker CJ. Intravenously administered immune globulin for premature infants: a time to wait. *J Pediatr* 1989; **115:** 969–71.
3. Ohlsson A, Lacy J. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 29/03/05).
4. Christensen RD, *et al*. Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991; **118:** 606–14.
5. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 28/06/10).
6. Fanaroff AA, *et al*. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. *N Engl J Med* 1994; **330:** 1107–13.

Neuropsychiatric disorders. Benefit has been shown from plasma exchange or intravenous immunoglobulin in children with exacerbations of obsessive-compulsive disorder or tic disorders including Tourette's syndrome associated with streptococcal infection.[1] These results suggested that these disorders may respond to immunomodulatory therapy in a subgroup of patients with paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), believed to be due to cross-reaction of antistreptococcal antibodies with neural tissue. In a double-blind, placebo-controlled study[2] of the use of normal immunoglobulins in 30 patients with tic disorders, despite initial improvement compared with placebo over 8 weeks no significant differences were found in the severity of obsessions and compulsions beyond this time.

1. Perlmutter SJ, *et al*. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999; **354:** 1153–8.
2. Hoekstra PJ, *et al*. Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. *J Clin Psychiatry* 2004; **65:** 537–42.

Passive immunisation. *CMV INFECTION.* See Transplantation, under Immunocompromised Patients, p. 2405.1.

HEPATITIS C. In a randomised, placebo-controlled study[1] in seronegative sexual partners of patients positive for antibody to hepatitis C, normal immunoglobulin given intramuscularly every 2 months was found to significantly reduce the incidence of subsequent seroconversion. One of 450 subjects who received normal immunoglobulin became seropositive during follow-up compared with 6 of 449 who had received placebo.

1. Piazza M, *et al*. Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin: a randomized controlled trial. *Arch Intern Med* 1997; **157:** 1537–44.

PARVOVIRUS B19 INFECTION. Persistent infection with human parvovirus B19 can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients. Normal immunoglobulins contain antibodies able to neutralise parvovirus B19 and have been used in various groups of infected patients.[1] Resolution of anaemia and clearance of parvovirus B19 from the circulation have been reported after use of normal immunoglobulin in a patient who had had red cell aplasia for 10 years.[2] Normal immunoglobulin was given by intravenous infusion in a dose of 400 mg/kg daily for 10 days and then periodically for several months. Successful treatment of anaemia due to parvovirus B19-induced red cell aplasia with plasmapheresis and intravenous immunoglobulin has been described in a liver transplant recipient.[3] Efficacy has also been found in recipients of other solid-organ transplants including heart, kidney, and lung.[1] Clearance of parvovirus B19 from the circulation has been reported in patients who also have AIDS, but the presence of concomitant opportunistic infections may prevent resolution of the anaemia.[4,5]

Normal immunoglobulin given to patients with parvovirus B19-associated chronic fatigue syndrome has also resulted in clearance of the virus from the circulation and resolution of symptoms.[6,7]

Beneficial responses to intravenous immunoglobulin have also been reported in a few patients with parvovirus B19 infections associated with vasculitic syndromes.[8,9]

1. Mouthon L, *et al*. Intravenous immunoglobulins in autoimmune- or parvovirus B19-mediated pure red-cell aplasia. *Autoimmun Rev* 2005; **4:** 264–9.
2. Kurtzman G, *et al*. Pure red-cell aplasia of 10 years' duration due to persistent parvovirus B19 infection and its cure with immunoglobulin therapy. *N Engl J Med* 1989; **321:** 519–23.
3. Ramage JK, *et al*. Parvovirus B19-induced red cell aplasia treated with plasmapheresis and immunoglobulin. *Lancet* 1994; **343:** 667–8.
4. Frickhofen N, *et al*. Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. *Ann Intern Med* 1990; **113:** 926–33.
5. Bowman CA, *et al*. Red cell aplasia associated with human parvovirus B19 and HIV infection: failure to respond clinically to intravenous immunoglobulin. *AIDS* 1990; **4:** 1038–9.
6. Kerr JR, *et al*. Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003; **36:** e100–e106. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/374666 (accessed 15/07/08)
7. McGhee SA, *et al*. Persistent parvovirus-associated chronic fatigue treated with high dose intravenous immunoglobulin. *Pediatr Infect Dis J* 2005; **24:** 272–4.
8. Finkel TH, *et al*. Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? *Lancet* 1994; **343:** 1255–8.
9. Viguier M, *et al*. Treatment of parvovirus B19-associated polyarteritis nodosa with intravenous immune globulin. *N Engl J Med* 2001; **344:** 1481–2.

TOXIC SHOCK SYNDROME. For a discussion of toxic shock syndrome and its treatment, including reference to improved survival after administration of intravenous normal immunoglobulins, see p. 209.3.

Pregnancy. Fetal loss has been attributed in some cases to the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin) in the mother. Successful pregnancy outcome has been reported after use of intravenous normal immunoglobulin during pregnancy to a few such women.[1]

1. Triolo G, *et al*. IVIG in APS pregnancy. *Lupus* 2004; **13:** 731–5.

Skin disorders. Normal immunoglobulins have been tried in a few patients with blistering skin diseases.[1-3] The usual treatment for pemphigus and pemphigoid is with systemic corticosteroids; intravenous normal immunoglobulins in

high doses have produced generally transient improvement when used alone,[4] although corticosteroid-sparing effects have been reported.[5,6] Successful treatment with high doses of intravenous normal immunoglobulin plus rituximab has also been reported in some patients with refractory pemphigus vulgaris.[7] There have been case reports of patients with severe epidermolysis bullosa acquisita responding to therapy with high-dose intravenous immunoglobulins.[8,9] Studies have been conducted into the use of high-dose normal immunoglobulin for the treatment of other blistering conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis.[10] One retrospective analysis[11] of 48 consecutive cases of toxic epidermal necrolysis found a beneficial effect with survival in 42 patients. In contrast, a prospective open study[12] in 34 consecutive patients admitted to hospital with Stevens-Johnson syndrome or toxic epidermal necrolysis suggested that normal immunoglobulin might actually be associated with an increase in mortality. Further retrospective analyses, however, did find a reduction in mortality in 16 consecutive patients admitted with toxic epidermal necrolysis[13] and in 7 children with Stevens-Johnson syndrome.[14] Normal immunoglobulin has also produced benefit in patients with pyoderma gangrenosum.[15-19]

Clinical benefit was noted in 9 of 10 patients with autoimmune chronic urticaria who were given a 5-day course of intravenous immunoglobulins, 2 of whom had prolonged remission over 3 years of follow-up.[20] Benefit has also occurred after high-dose intravenous immunoglobulin therapy for atopic dermatitis,[21] psoriasis,[22] and pityriasis rubra pilaris.[23] The cutaneous lesions in a young child with juvenile dermatomyositis were successfully treated with high-dose intravenous immunoglobulin.[24]

Intramuscular normal immunoglobulin has been used with some success either alone or in combination therapy for recalcitrant suppurative skin diseases such as hidradenitis suppurativa, folliculitis decalvans, or chronic recurrent furunculosis or folliculitis.[25]

1. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; **140:** 865–74.
2. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol* 2003; **139:** 1051–9.
3. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol* 2006; **6:** 557–78.
4. Godard W, *et al.* Bullous pemphigoid and intravenous gammaglobulin. *Ann Intern Med* 1985; **103:** 965.
5. Beckers RCY, *et al.* Adjuvant high-dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. *Br J Dermatol* 1995; **133:** 289–93.
6. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001; **45:** 825–35.
7. Ahmed AR, *et al.* Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355:** 1772–9.
8. Mohr C, *et al.* Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *Br J Dermatol* 1995; **132:** 824–6.
9. Gourgiotou K, *et al.* Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol* 2002; **16:** 77–80.
10. Mittmann N, *et al.* Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. *Am J Clin Dermatol* 2006; **7:** 359–68.
11. Prins C, *et al.* Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol* 2003; **139:** 26–32.
12. Bachot N, *et al.* Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; **139:** 33–6.
13. Trent JT, *et al.* Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami experience. *Arch Dermatol* 2003; **139:** 39–43.
14. Metry DW, *et al.* Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003; **112:** 1430 6.
15. Dirschka T, *et al.* Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. *J Am Acad Dermatol* 1998; **39:** 789–90.
16. Hagman JH, *et al.* The use of high-dose immunoglobulin in the treatment of pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 19–22.
17. Dobson CM, *et al.* Superficial granulomatous pyoderma treated with intravenous immunoglobulin. *J Am Acad Dermatol* 2003; **48:** 456–60.
18. Cummins DL, *et al.* Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007; **157:** 1235–9.
19. Kreuter A, *et al.* Intravenous immunoglobulin for pyoderma gangrenosum. *Br J Dermatol* 2008; **158:** 856–7.
20. O'Donnell BF, *et al.* Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138:** 101–6.
21. Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clin Exp Dermatol* 2002; **27:** 3–7.
22. Gurmin V, *et al.* Psoriasis: response to high-dose intravenous immunoglobulin in three patients. *Br J Dermatol* 2002; **147:** 554–7.
23. Kerr AC, Ferguson J. Type II adult-onset pityriasis rubra pilaris successfully treated with intravenous immunoglobulin. *Br J Dermatol* 2007; **156:** 1055–6.
24. Amano H, *et al.* Successful treatment of cutaneous lesions in juvenile dermatomyositis with high-dose intravenous immunoglobulin. *Br J Dermatol* 2007; **156:** 1390–2.
25. Goo B, *et al.* Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases. *Br J Dermatol* 2007; **157:** 563–8.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2. Intravenous immunoglobulin preparations should be used with caution in patients with renal impairment. Immunoglobulin products containing sucrose may be associated with an increased risk of inducing acute renal failure (see Effects on the Kidneys, below). Thromboembolic events such as myocardial infarction, stroke, pulmonary embolism, and deep-vein thrombosis have been reported after use of intravenous immunoglobulins; these products should be used with caution in obese patients and in patients with pre-existing risk factors for thrombotic events.

Antibody titres for some common pathogens can vary widely not only between products from different manufacturers, but also from lot to lot. Formulations of intravenous immunoglobulins should therefore not be regarded as equivalent.

Reviews.

1. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoglobulin therapy. *Drug Safety* 1999; **21:** 171–85.
2. Wittstock M, *et al.* Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol* 2003; **50:** 172–5.
3. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003; **17:** 241–51.
4. Ameratunga R, *et al.* Increased risk of adverse events when changing intravenous immunoglobulin preparations. *Clin Exp Immunol* 2004; **136:** 111–13.
5. Singh-Grewal D, *et al.* A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch Dis Child* 2006; **91:** 651–4.
6. Katz U, *et al.* Safety of intravenous immunoglobulin (IVIG) therapy. *Autoimmun Rev* 2007; **6:** 257–9.
7. Carbone J. Adverse reactions and pathogen safety of intravenous immunoglobulin. *Curr Drug Safety* 2007; **2:** 9–18.
8. Bonilla FA. Intravenous immunoglobulin: adverse reactions and management. *J Allergy Clin Immunol* 2008; **122:** 1238–9.

Effects on the blood. Adverse effects on the blood have occasionally been reported after intravenous use of normal immunoglobulin to increase the platelet count in patients with immune thrombocytopenia and in the management of other auto-immune diseases. Reduced platelet adhesiveness with multiple subcutaneous haematomas occurred in one patient.[1] Thrombotic events have occurred after intravenous use,[2-4] particularly in elderly subjects (sometimes fatal) suggesting that a rising platelet count during normal immunoglobulin treatment may represent a risk in patients with severe atherosclerotic disease.[2] However, a review of 34 patients over 60 years of age treated with normal immunoglobulin could not confirm the association.[5]

Haemolytic reactions, including haemolytic disease of the newborn, have sometimes been noted[6-8] and passive transfer of anti-A, anti-B, or anti-D antibodies or active immunisation by blood group substances from normal immunoglobulin preparations has been implicated. It has been suggested[7] that blood phenotyping be carried out before treatment with normal immunoglobulin is started.

Transient neutropenia has occurred after use of normal immunoglobulin in patients with immune thrombocytopenia, but the clinical significance of this effect has been disputed.[9-11]

1. Ljung R, Nilsson IM. High-dose intravenous gammaglobulin: a cautionary note. *Lancet* 1985; **i:** 467.
2. Woodruff RK, *et al.* Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; **ii:** 217–18.
3. Go RS, Call TG. Deep venous thrombosis of the arm after intravenous immunoglobulin infusion: case report and literature review of intravenous immunoglobulin-related thrombotic complications. *Mayo Clin Proc* 2000; **75:** 83–5.
4. Marie I, *et al.* Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. *Br J Dermatol* 2006; **155:** 714–21.
5. Frame WD, Crawford RJ. Thrombotic events after intravenous immunoglobulin. *Lancet* 1986; **ii:** 468.
6. Potter M, *et al.* ABO alloimmunisation after intravenous immunoglobulin infusion. *Lancet* 1988; **i:** 932–3.
7. Nicholls MD, *et al.* Haemolysis induced by intravenously-administered immunoglobulin. *Med J Aust* 1989; **150:** 404–6.
8. Gordon DJ, *et al.* A pediatric case series of acute hemolysis after administration of intravenous immunoglobulin. *Am J Hematol* 2009; **84:** 771–2.
9. Majer RV, Green PJ. Neutropenia caused by intravenous immunoglobulin. *BMJ* 1988; **296:** 1262.
10. Veys PA, *et al.* Neutropenia following intravenous immunoglobulin. *BMJ* 1988; **296:** 1800.
11. Ben-Chetrit E, Putterman C. Transient neutropenia induced by intravenous immune globulin. *N Engl J Med* 1992; **326:** 270–1.

Effects on the kidneys. There have been case reports of renal failure or impairment associated with the use of intravenous normal immunoglobulin.[1-3] The incidence of renal failure appears to be greatest with immunoglobulin products containing sucrose.[1,4] The FDA in the USA had issued a warning alerting physicians to the potential risks of acute renal failure associated with intravenous use of normal immunoglobulin products, particularly those containing sucrose.[5]

1. Orbach H *et al.* Intravenous immunoglobulin and the kidney—a two-edged sword. *Semin Arthritis Rheum* 2004; **34:** 593–601.
2. Itkin YM, Trujillo TC. Intravenous immunoglobulin-associated acute renal failure: case series and literature review. *Pharmacotherapy* 2005; **25:** 886–92.
3. Shah S, Vervan M. Use of i.v. immune globulin and occurrence of associated acute renal failure and thrombosis. *Am J Health-Syst Pharm* 2005; **62:** 720–5.
4. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; **93:** 901–4.
5. FDA. Important drug warning: potential risk of acute renal failure reported to be associated with administration of immune globulin intravenous (human) (issued 24 September 1999). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105901.htm (accessed 27/08/10)

Effects on the nervous system. Aseptic meningitis has been reported after intravenous use of normal immunoglobulin.[1-5]

Migraine, associated with intravenous immunoglobulin therapy in a patient on 2 occasions, did not recur after prophylaxis with propranolol was started.[6]

Hemiplegia has been reported in a 4-year-old child given intravenous immunoglobulin for immune thrombocytopenic purpura.[7]

1. Kato E, *et al.* Administration of immune globulin associated with aseptic meningitis. *JAMA* 1988; **259:** 3269–71.
2. Casteels-Van Daele M, *et al.* Intravenous immune globulin and acute aseptic meningitis. *N Engl J Med* 1990; **323:** 614–15.
3. Sekul EA, *et al.* Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994; **121:** 259–62.
4. Picton P, Chisholm M. Aseptic meningitis associated with high dose immunoglobulin: case report. *BMJ* 1997; **315:** 1203–4.
5. Boyce TG, Spearman P. Acute aseptic meningitis secondary to intravenous immunoglobulin in a patient with Kawasaki syndrome. *Pediatr Infect Dis J* 1998; **17:** 1054–6.
6. Constantinescu CS, *et al.* Recurrent migraine and intravenous immune globulin therapy. *N Engl J Med* 1993; **329:** 583–4.
7. Tsiouris J, Tsiouris N. Hemiplegia as a complication of treatment of childhood immune thrombocytopenic purpura with intravenously administered immunoglobulin. *J Pediatr* 1998; **133:** 717.

Effects on the skin. Diffuse alopecia has been reported[1] in 3 women within 1 to 4 weeks of treatment with intravenous normal immunoglobulin. There have been reports[2,3] of severe and extensive eczema in elderly patients up to 3 weeks after receiving normal immunoglobulin intravenously. There has also been a report of cutaneous vasculitic rash on the face of a woman receiving intravenous normal immunoglobulin.[4] Severe cutaneous vasculitis has been reported in a patient who received intravenous normal immunoglobulin for type II mixed cryoglobulinaemia.[5] An erythematous eruption occurred on the hands and feet of a patient 3 days after completing a 5-day treatment course of normal immunoglobulin for chronic inflammatory demyelinating polyneuropathy;[6] the lesions resolved 2 to 3 weeks after completion of therapy. A similar eruption had occurred following normal immunoglobulin therapy in 5 previous occasions. Vesiculobullous eruptions have been seen in a patient being treated with intravenous normal immunoglobulin for Stevens-Johnson syndrome.[7]

For mention of a patient with AIDS who developed erythema characteristic of fifth disease following intravenous normal immunoglobulin, see Infection, p. 2408.1.

1. Chan-Lam D, *et al.* Alopecia after immunoglobulin infusion. *Lancet* 1987; **i:** 1436.
2. Barucha C, McMillan JC. Eczema after intravenous infusion of immunoglobulin. *BMJ* 1987; **295:** 1141.
3. Whittam LR, *et al.* Eczematous reactions to human immune globulin. *Br J Dermatol* 1997; **137:** 481–2.
4. Howse M, *et al.* Facial vasculitic rash associated with intravenous immunoglobulin. *BMJ* 1998; **317:** 1291.
5. Yebra M, *et al.* Severe cutaneous vasculitis following intravenous infusion of gammaglobulin in a patient with type II mixed cryoglobulinemia. *Clin Exp Rheumatol* 2002; **20:** 225–7.
6. Mutasim DF, Sheth PB. An eruption secondary to intravenous immunoglobulin therapy. *Cutis* 2002 **69:** 35–6, 38.
7. Lin WL, *et al.* Intravenous immunoglobulin-induced, non-eczematous, vesiculobullous eruptions in Stevens-Johnson syndrome. *Am J Clin Dermatol* 2009; **10:** 339–42.

Hypersensitivity. Hypersensitivity reactions may occasionally occur after intramuscular or intravenous use of normal immunoglobulins particularly in hypogammaglobulinaemic or agammaglobulinaemic patients. Both immediate and late[1] reactions have occurred.

The IgA content of normal immunoglobulins can result in the development of IgE and IgG anti-IgA antibodies in immunodeficient patients with IgA deficiency. It has been suggested by some[2] that the IgE anti-IgA antibodies are responsible for anaphylaxis although others have disagreed.[3] Two patients who had reactions to conventional normal immunoglobulin preparations tolerated preparations with a low content of IgA.[2] Some manufacturers of normal immunoglobulin preparations recommend that they should not be used in patients with selective IgA deficiencies who have known antibody against IgA.

The IgE content of some preparations has also been suggested as a cause of hypersensitivity reactions[4] although this has been disputed.[5] Complement-activating IgG aggregates may also be involved although the anticomplementary activity of the products does not appear to be related to the incidence of adverse effects.[5]

1. Hachimi-Idrissi S, *et al.* Type III allergic reaction after infusion of immunoglobulins. *Lancet* 1990; **336:** 55.
2. Burks AW, *et al.* Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. *N Engl J Med* 1986; **314:** 560–4.

3. Hammarström L, Smith CIE. Anaphylaxis after administration of gamma globulin for hypogammaglobulinemia. *N Engl J Med* 1986; **315:** 519.
4. Tovo P-A, *et al*. IgE content of commercial intravenous IgG preparations. *Lancet* 1984; **i:** 458.
5. Newland AC, *et al*. IgE in intravenous IgG. *Lancet* 1984; **i:** 1406–7.

Infection. An association between use of certain intravenous immunoglobulin preparations and hepatitis C infections led to changes in manufacturing procedures and withdrawal of the affected products from the market.[1-3]

In addition, there has been a report[4] of a patient with AIDS who developed fifth disease (erythema infectiosum) after intravenous normal immunoglobulin treatment for infection with parvovirus. Paradoxically, there has also been a report[5] of life-threatening parvovirus B19 infection, resulting in pure red cell aplasia and aggravation of hepatitis and fulminant disease, from the use of normal immunoglobulin to treat a patient with existing hepatic dysfunction caused by coxsackie B4 virus infection.

1. Quinti I, *et al*. Intravenous gammaglobulin may still infect patients. *BMJ* 1994; **308:** 856.
2. Bader J-M. HCV and Gammagard in France. *Lancet* 1994; **343:** 1628. Corrections. *ibid.*; **344:** 201 and 206.
3. Anonymous. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. *JAMA* 1994; **272:** 424–5.
4. French AL, *et al*. Fifth disease after immunoglobulin administration in an AIDS patient with parvovirus-induced red cell aplasia. *Am J Med* 1996; **101:** 108–9.
5. Hayakawa F, *et al*. Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* 2002; **118:** 1187–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies normal immunoglobulin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Normal immunoglobulin may interfere with the immune response to live viral vaccines. Such vaccines should therefore be given at least 3 weeks before, or 3 months after, normal immunoglobulin. This does not apply to yellow fever vaccine for immunoglobulins prepared in the UK, nor for booster doses of oral poliomyelitis vaccines. Where such an interval is impractical for immunisation preceding foreign travel it may have to be ignored.

Poliomyelitis vaccine. For a study indicating that normal immunoglobulin has no effect on the antibody response to oral poliomyelitis vaccine, see p. 2412.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Beriglobina; Citax F; Endobulin; Flebogamma; Gammaglobulina; Isiven; Kiovig; Pentaglobin; Sandoglobulina; Seroglubin; Vigam; ***Austral.***: Intragam; Octagam; Sandoglobulin†; ***Austria***: Beriglobin; Endobulin†; Gammagard; Gammanorm; Gamunex; Ig Vena; Intraglobin†; Intratect; Kiovig; Octagam; Pentaglobin; Privigen; Sandoglobulin†; Subcuvia; Vivaglobin; ***Belg.***: Gammagard SD; Gammanorm; Hizentra; Kiovig; Multigam; Nanogam; Octagam; Privigen; Sandoglobuline; Subcuvia; Vivaglobin; ***Braz.***: Armoglobulina†; Beriglobina; Endobulin; Gama-Venina†; Octagam; Sandoglobulina; Venimmuna†; ***Canad.***: Gamastan; Gammagard; Gamunex; Hizentra; Privigen; Sandoglobulin†; Vivaglobin; ***Chile***: Beriglobina P†; Flebogamma; Ig Vena N; Pentaglobin; ***China***: Bo Xin (博欣); Chang Sheng Xun Kang (长生迅抗); Gama Laishi (伽玛莱士); ***Cz.***: Endobulin†; Flebogamma; Flebogammadif; Gammagard; Gammanorm; Gamunex; Igamplia; Kiovig; Octagam; Pentaglobin†; Privigen; Subcuvia; Venimmun N†; Vivaglobin†; ***Denm.***: Beriglobin; Endobulin†; Gammanorm; Gamunex; Hizentra; Kiovig; Octagam; Privigen; Subcuvia; Vivaglobin; ***Fin.***: Gammagard; Gammanorm; Gamunex; Nanogam; Octagam; Subcuvia; Vivaglobin†; ***Fr.***: Clairyg; Gammagard; Gammanorm; Hizentra; Kiovig; Octagam; Privigen; Sandoglobuline; Subcuvia; Tegeline; Vivaglobin; ***Ger.***: Beriglobin; Endobulin†; Flebogamma†; Flebogammadif; Gammagard; Gammanorm; Gamunex; Hizentra; Ig Vena; Intratect; Kiovig; Octagam; Pentaglobin; Privigen; Sandoglobulin†; Subcuvia; Vivaglobin†; ***Gr.***: Anosoglobin; Beriglobin; Flebogamma; Gamimune; Gaminex; Gamma-Venin; Gammagard; Globuman; Ig Vena; Intraglobin F; Intratect; Kiovig; Octagam; Omr-IgG; Pentaglobin; Privigen; Sandoglobulin; Subcuvia; Vivaglobin; ***Hong Kong***: Baygam†; Flebogamma†; Gamimune N†; Gammagard; Intragam P; Intraglobin F; Kiovig; Octagam†; Pentaglobin; ***Hung.***: Gammagard†; Gammanorm; Humaglobin; Intratect; Octagam; Pentaglobin; Vivaglobin; ***India***: Bharglob; Cytotect; Flebogamma; Gama-Glob; Gamafine; Gamaglobin; Gamma-IV; Histoglob; Immunorel; IV-Globulin; Iviglob; Norglobin; Octagam; ***Indon.***: Gamimune N†; Gammaraas; Gamunex; ***Irl.***: Flebogamma; Flebogammadif; Gammagard; Gammanorm; Hizentra; Intraglobin†; Intratect; Kiovig; Nanogam; Privigen; Subcuvia; ***Israel***: Beriglobin P; Flebogamma; Gammagard; Gammaplex; Gamunex; Intraglobin F; Intratect; Kiovig; Octagam; Omr-IgG; Privigen; Sandoglobulin; Venoglobulin; Vigam; ***Ital.***: Endobulin; Flebogamma; Gammagard; Ig Vena; Intraglobin†; Intratect; Keyven; Kiovig; Octanorm; Pentaglobin; Sandoglobulina; Subcuvia; Venital; Vivaglobin; ***Jpn***: Venilon†; Venoglobulin; ***Malaysia***: Flebogamma; Gamma-Globulin; IV-Globulin; Vigam; ***Mex.***: Beriglobina P; Gamma-Venin P†; Octagam; Pentaglobin; Sandoglobulina; Vigam; ***Neth.***: Flebogamma; Gammagard; Gammanorm; GammaQuin; Gamunex; Hizentra; Intratect; Kiovig; Nanogam; Octagam; Privigen; Subcuvia; Vivaglobin†; ***Norw.***: Gammanorm; Hizentra; Kiovig; Octagam; Privigen; Subcuvia†; ***NZ***: Flebogamma; Gammanorm; Intragam; Octagam; Privigen; Sandoglobulin; ***Philipp.***: Gamimune N; Gammagard; IV-Globulin S; Vizcarra; ***Pol.***: Endobulin; Gamma-Globulina†; Gammagard; Intraglobin F; Intratect; Kiovig; Pentaglobin; Privigen; Sandoglobulin; Subcuvia; Venimmun; Vivaglobin; ***Port.***: Flebogamma; Flebogammadif; Gammagard; Gammanorm; Gamunex; Ig Vena; Kiovig; Octagam; Privigen; Sandoglobulina; Subcuvia; Tegeline; Vivaglobin; ***Rus.***: Flebogamma (Флебогамма); Gabriglobine (Габриглобин); Gamimune N (Гамимун Н); Gamunex (Гамунекс); Humaglobin (Хумаглобин); Immunovenin (Иммуновенин); Intraglobin (Интраглобин); Intratect (Интратект); Octagam (Октагам); Pentaglobin (Пентаглобин); ***S.Afr.***: Beriglobin; Intragam; Intraglobin F†; Pentaglobin†; Polygam; ***Singapore***: Flebogamma; Gammagard; Intragam; Intraglobin F; Octagam†; Pentaglobin; Venoglobulin; Vigam; ***Spain***: Beriglobina P; Endobulin†; Flebogamma; Gammagard; Gammaglobulina†; Hizentra; Igamplia; Intratect; Kiovig; Octagamocta; Privigen; Vivaglobin†; ***Swed.***: Beriglobin; Flebogamma; Gammagard; Gammanorm; Gamunex; Hizentra; Kiovig; Octagam; Privigen; Subcuvia; Vivaglobin†; Xepol†; ***Switz.***: Beriglobin; Endobulin†; Gammanorm; Gamunex; Hizentra; Ig Vena; Intratect; Kiovig; Octagam; Privigen; Redimune; Subcuvia; Vivaglobin; ***Thai.***: Flebogamma; Gammagard†; Gammaraas; Ig Vena; Intraglobin†; Kiovig; LIV-Gamma; Octagam; Pentaglobin; Vigam; ***Turk.***: Endobulin; Flebogamma; Gamimune N; Gammar; Gamunex; Globuman†; Ig Vena; Intraglobin; Isiven†; Kiovig; Octagam; Pentaglobin; Subcuvia†; Tegeline; Vigam; ***UK***: Aragam; Flebogamma; Flebogammadif; Gammagard; Gammanorm; Gammaplex; Gamunex; Hizentra; Intratect; Kiovig; Octagam; Privigen; Sandoglobulin; Subcuvia; Subgam; Vigam; Vivaglobin†; ***Ukr.***: Bioven Mono (Биовен Моно); ***USA***: Bivigam; Carimune; Flebogamma; Gamastan; Gammagard; Gammaplex; Gamunex†; Hizentra; Octagam; Privigen; Vivaglobin†; ***Venez.***: Flebogamma.

Multi-ingredient Preparations. ***Arg.***: Histaglobin; ***Austria***: Histaglobin†; ***India***: Histaglobulin; ***Pol.***: Histaglobulina; ***Rus.***: Kipferon (Кипферон); ***S.Afr.***: Histaglobin†.

Pharmacopoeial Preparations
Ph. Eur.: Human Normal Immunoglobulin for Intravenous Administration; Human Normal Immunoglobulin;
USP 36: Immune Globulin.

Pertussis Immunoglobulins

Inmunoglobulinas contra la tos ferina.
ATC — J06BB13.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 36: (Pertussis Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with pertussis vaccine. It may contain glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Pertussis immunoglobulins have been used for passive immunisation against pertussis (whooping cough) and to prevent or modify pertussis in susceptible persons who have been exposed to infection.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Tosuman; ***Turk.***: Tosuman.

Pharmacopoeial Preparations
USP 36: Pertussis Immune Globulin.

Pertussis Vaccines

Vacunas de la tos ferina.
ATC — J07AJ01; J07AJ02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Pertussis Vaccine (Whole Cell, Adsorbed); Vaccinum Pertussis ex Cellulis Integris Adsorbatum). A sterile suspension of inactivated whole cells of one or more strains of *Bordetella pertussis* in saline to which hydrated aluminium phosphate or aluminium hydroxide has been added. It may contain a suitable antimicrobial preservative. The estimated potency is not less than 4 units per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that wP may be used on the label.

Ph. Eur. 8: (Pertussis Vaccine (Acellular, Component, Adsorbed); Vaccinum Pertussis sine Cellulis ex Elementis Praeparatum Adsorbatum). A preparation of individually prepared and purified antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It contains either a suitably prepared pertussis toxoid or a pertussis toxin-like protein free from toxic properties produced by expression of a genetically modified form of the corresponding gene. It may also contain filamentous haemagglutinin, pertactin, and other defined antigens such as fimbrial-2 and fimbrial-3 antigens. The final vaccine contains not more than 100 units of bacterial endotoxin per dose. It may contain a suitable antimicrobial preservative. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that aP may be used on the label.

Ph. Eur. 8: (Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Vaccinum Pertussis Sine Cellulis Copurificatum Adsorbatum). A preparation of antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that aP may be used on the label.

Uses and Administration

Pertussis vaccines are used for active immunisation against pertussis (whooping cough) (p. 198.3). Acellular pertussis vaccines have taken the place of whole-cell vaccines in several countries including the UK and the USA.

For primary immunisation combined pertussis vaccines, usually diphtheria, tetanus, and pertussis vaccines (p. 2383.3) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p. 2385.3) are used. For pre-school boosters diphtheria, tetanus, pertussis, and poliomyelitis vaccines (p. 2385.2) are sometimes given. For discussion of immunisation schedules, see below.

References.
1. Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. *Drugs* 2005; **65:** 1367–89.
2. WHO. Pertussis vaccines–WHO position paper. *Wkly Epidem Rec* 2005; **80:** 31–9. Also available at: http://www.who.int/immunization/topics/wer8004pertussis_Jan_2005.pdf (accessed 10/12/09)
3. Guiso N. Bordetella pertussis and pertussis vaccines. *Clin Infect Dis* 2009; **49:** 1565–9.

Immunisation schedules. Pertussis is a common, highly infectious, respiratory disease, mainly affecting children, and for which there is no effective treatment. WHO estimates that 20 to 40 million cases of pertussis occur annually and that the disease is responsible for 200 000 to 400 000 deaths each year. The highest incidence of pertussis occurs in developing countries where immunisation is low.

Combined vaccines are now used in most countries but both the strength of the pertussis component and production methods vary, leading to vaccines of different potencies. The considerably higher cost of acellular over whole-cell pertussis vaccines means that the latter are still used widely in developing countries.

Depending upon the country, the age at which a child is given the first dose of a combined vaccine varies from 5 weeks to 6 months. (For summaries of immunisation schedules in the UK and USA, see under Vaccines, p. 2373.3.) In countries with a high incidence of pertussis, WHO recommends that immunisation should start at 6 weeks of age and that the schedule involve 3 doses at monthly intervals followed by a booster dose at 18 months to 6 years of age. In the UK and USA, booster doses should be given after the end of the primary series of 3 injections before entry to school. Several reports have described the use of a 2-dose widely-spaced primary immunisation schedule and this would indeed simplify procedures in developing countries; however, the limitation of such a schedule is the long period of risk between doses without adequate protection and unless the interval can be shortened to 4 weeks, the wide use of such a schedule is not advisable in endemic areas.

Vaccine development. Dissatisfaction with whole-cell vaccines in the 1970s because of adverse reactions led to reduced uptake and a resurgence of pertussis in several countries. In Japan, research into less reactogenic pertussis vaccines resulted in the introduction of acellular vaccines for routine vaccination in the early 1980s. Acellular pertussis vaccines can contain a variety of pertussis components:

- pertussis toxin (PT; also formerly known as lymphocytosis-promoting factor, LPF)
- filamentous haemagglutinin (FHA)
- pertactin (PRN)
- fimbrial agglutinogens (FIM) 2 and 3

The acellular vaccines commonly used are a 3-component vaccine containing PT/FHA/PRN and a 5-component vaccine containing PT/FHA/PRN/FIM2/FIM3. The vaccine used in combination vaccines for primary immunisation in the UK is the 5-component vaccine. The 3-component vaccine does not provide the same level of protection against whooping cough in primary immunisation. Both 3-component and 5-component vaccines may be used in combination vaccines for pre-school boosting. The combination vaccine used for pre-school boosting that contains 5-component pertussis vaccine does not provide the recommended strength of diphtheria to be used for primary immunisation.

Acellular vaccines are recommended in the UK and USA for both primary immunisation in infants and for the booster doses in young children before school entry. Whole-cell vaccines are still, however, widely used in other countries, particularly in the developing world.

Adverse Effects

As for vaccines in general, p. 2375.1.

Local reactions may occur at the site of injection of pertussis vaccines or pertussis-containing vaccines and use may be followed by fever and irritability. Local reactions and fever occur less frequently with the acellular vaccine than with whole-cell vaccine, especially in children over 6 months of age and adults. However, booster doses of acellular pertussis-containing vaccines are associated with an increased risk of injection site reactions.

Severe reactions which have been reported include persistent screaming and generalised collapse but these effects were generally associated with an earlier type of vaccine and the reactions are rarely seen with the currently available vaccines.

Rare neurological adverse reactions have included convulsions and encephalopathy. There has been much debate, however, on the causal role of pertussis vaccine in such reactions (see below for detailed discussion). It should be remembered that neurological complications occur more frequently as a consequence of pertussis infection than from vaccination.

Asthma. A higher incidence of asthma was reported in 243 children who had received whole-cell pertussis vaccine than in 203 children who had not.[1] However, follow-up of a large Swedish study[2] showed no difference in the incidence of wheezing or allergic reactions between children who had received diphtheria, tetanus, and whole-cell pertussis vaccines and those who had not. A later prospective study[3] also found no evidence that whole-cell pertussis vaccination increased the risk of wheezing illness in young children. Furthermore, no association was found between pertussis vaccination in infancy and development of asthma in children aged up to 7 years in a later study of the same group of children.[4] A population-based cohort study[5] also reported no evidence of an increased risk of wheezing or asthma in more than 6000 children 8 to 12 years after vaccination in infancy with either an acellular or whole-cell pertussis vaccine.

1. Odent MR, *et al*. Pertussis vaccination and asthma: is there a link? *JAMA* 1994; **272:** 592–3.
2. Nilsson L, *et al*. Lack of association between pertussis vaccination and symptoms of asthma and allergy. *JAMA* 1996; **275**: 760.
3. Henderson J, *et al*. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. *BMJ* 1999; **318:** 1173–6.
4. Maitra A, *et al*. Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. *BMJ* 2004; **328:** 925–6.
5. Spycher BD, *et al*. Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study. *Pediatrics* 2009; **123:** 944–50. Correction. *ibid.*; 1437.

Effects on the nervous system. There has been continuing debate over several decades concerning the perceived link between pertussis vaccination and brain damage. Anxiety among both the public and health-care professionals in the UK in the mid-1970s over the safety of whole-cell pertussis vaccines led to a fall in the acceptance rates for infant vaccination and major epidemics of pertussis in 1977/79 and 1981/83. Since that time confidence has been restored and, with the introduction of acellular vaccines, the vast majority of infants now receive the vaccine before their second birthday. Comparison of whole-cell vaccines with acellular vaccines has since confirmed that the latter are associated with a greatly reduced incidence of serious neurological disorders.[1]

The consensus of opinion now seems to be that there is a temporal, but not necessarily causal, relationship between whole-cell pertussis vaccine and acute neurological illness that may occasionally lead to long-term dysfunction, and that risks of not immunising are greater than the potential risks associated with the vaccine.

The difficulty in ascertaining whether a causal relationship exists between whole-cell pertussis vaccine (usually given as diphtheria, tetanus, and pertussis (DTP) vaccine) and acute neurological reactions arises partly because primary vaccination is given at an age when neurological dysfunction with other causes is often first manifested. The temporal relationship seen may be entirely coincidental, may result from indirect factors such as pyrexia after vaccination, or may represent a direct effect of DTP vaccine. Much of the evidence is based on large epidemiological studies,[2-7] in particular the National Childhood Encephalopathy Study (NCES)[8] from the UK and its 10-year follow-up.[9] Serious acute neurological illnesses reported to the NCES[8] were found to be more common in infants immunised within 7 days (relative risk 2.4), and especially within 72 hours of onset, than in unimmunised children. For previously normal children, irrespective of outcome, the risk was estimated as 1 in 110 000 injections. In a subset of cases diagnosed as infantile spasms,[10] no link with vaccination was found overall, but there was a small excess of cases of infantile spasm in previously normal children who had received either DTP or diphtheria and tetanus vaccines during the previous 7 days (relative risk 2.0-2.5) followed by a corresponding deficit during the next 3 weeks. This suggested that vaccination may trigger the onset of spasms in a child with an underlying predisposition.

In 1991, the USA Institute of Medicine reviewed the available data, including the NCES results, and concluded that a causal relationship between the whole-cell pertussis component of DTP vaccine and acute encephalopathy probably existed, with an estimated excess risk of 0 to 10.5 per million vaccinations.[11] They concurred with the conclusion that a causal relationship between vaccination and infantile spasm was unlikely.

The NCES 10-year follow-up found that children who had had a serious acute neurological illness (excluding infantile spasms) had an increased risk of death or long-term dysfunction, but the risk was no greater in children given DTP vaccine in the 7 days before the original acute illness.[9] The National Vaccines Advisory Committee concluded that the results were insufficient to determine whether DTP vaccine influenced the development of chronic neurological dysfunction, and this conclusion has been accepted by both the Advisory Committee on Immunization Practices[12] and the American Academy of Pediatrics.[13]

1. Geier DA, Geier MR. An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. *Brain Dev* 2004; **26:** 296–300.
2. Pollock TM, Morris J. A 7-year survey of disorders attributed to vaccination in North West Thames Region. *Lancet* 1983; **i:** 753–7.
3. Pollock TM, *et al*. Symptoms after primary immunisation with DTP and with DT vaccine. *Lancet* 1984; **ii:** 146–9.
4. Walker AM, *et al*. Neurologic events following diphtheria-tetanus-pertussis immunization. *Pediatrics* 1988; **81:** 345–9.
5. Shields WD, *et al*. Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. *J Pediatr* 1988; **113:** 801–5.
6. Griffin MR, *et al*. Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. *JAMA* 1990; **263:** 1641–5.
7. Gale JL, *et al*. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine: a population-based case-control study. *JAMA* 1994; **271:** 37–41.
8. Miller DL, *et al*. Pertussis immunisation and serious acute neurological illness in children. *BMJ* 1981; **282:** 1595–9.
9. Miller D, *et al*. Pertussis immunisation and serious acute neurological illnesses in children. *BMJ* 1993; **307:** 1171–6.
10. Bellman MH, *et al*. Infantile spasms and pertussis immunisation. *Lancet* 1983; **i:** 1031–4.
11. Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines: summary of a report of the Institute of Medicine. *JAMA* 1992; **267:** 392–6.
12. CDC. Update: vaccine side effects, adverse reactions, contraindications, and precautions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996; **45** (RR-12): 1–45. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4512.pdf (accessed 25/05/06)
13. Committee on Infectious Disease, American Academy of Pediatrics. The relationship between pertussis vaccine and central nervous system sequelae: continuing assessment. *Pediatrics* 1996; **97:** 279–81.

Precautions

As for vaccines in general, p. 2375.2. The precautions and contra-indications to the use of pertussis vaccines have sometimes been more stringent than is now considered necessary because of the controversy about their potential adverse effects, especially neurotoxicity (see Effects on the Nervous System, above). In the UK it is now recommended that immunisation should continue with acellular pertussis vaccine even when episodes of fever (irrespective of severity), hypotonic-hyporesponsive episodes, persistent crying or screaming, or severe local reactions (irrespective of extent) have occurred after a preceding dose. Children who have had a local or general reaction to a whole-cell pertussis vaccine should complete their immunisation with acellular pertussis vaccine.

Whether or not children with a personal or family history of convulsions or epilepsy or who have suffered cerebral damage in the neonatal period should receive pertussis vaccines appears to have been the most difficult question to resolve in the past. In the UK it is now considered that a family history of seizures is not a contra-indication to immunisation. When a child has a history of seizures associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal; advice on the prevention of fever should be given at the time of immunisation (see Fever and Hyperthermia, p. 11.3 for comments on the prevention of fever after immunisation). Similarly when there is a history of seizures not associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal. If a seizure associated with fever occurs within 72 hours of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 24 hours. Immunisation should also be carried out in children with a history of cerebral damage in the neonatal period unless there is evidence of an evolving neurological abnormality. In children with a neurological problem that is still evolving it is recommended that immunisation should be deferred until the condition is stable. If a child develops encephalopathy or encephalitis within 7 days of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 7 days.

A personal or family history of hypersensitivity reactions is not generally considered to be a contra-indication to the use of pertussis vaccines, and neither are stable neurological conditions such as spina bifida, congenital brain abnormality, or perinatal hypoxic ischaemic encephalopathy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pertussis vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Acellulair†.

Pharmacopoeial Preparations

Ph. Eur.: Pertussis Vaccine (Acellular Component, Adsorbed); Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Pertussis Vaccine (Whole Cell, Adsorbed).

Pigbel Vaccines

Vacuna de Pigbel; Vacunas de la enteritis necrotizante.

Profile

A vaccine against pigbel (necrotising enteritis), a disease occurring mainly in children in the highlands of Papua New Guinea, is used for active immunisation against the disease. The vaccine consists of an adsorbed *Clostridium perfringens* type C toxoid.

An immunisation programme, in which pigbel vaccine was given to children at 2, 4, and 6 months of age and, initially, to older children, was introduced in Papua New Guinea in 1980.[1] A survey found a sustained overall fall in the incidence of severe pigbel in children coincident with the increased induced immunity. However, protection may be relatively short-lived and boosters may be necessary for full protection of young children. A later review[2] conducted to inform vaccination policy, noted that a newer vaccine was available but that the disease continued to be a problem.

1. Lawrence GW, *et al*. Impact of active immunisation against enteritis necroticans in Papua New Guinea. *Lancet* 1990; **336:** 1165–7.
2. Poka H, Duke T. In search of pigbel: gone or just forgotten in the highlands of Papua New Guinea? *P N G Med J* 2003; **46:** 135–42.

Plague Vaccines

Vacunas de la peste.

ATC — J07AK01.

Uses and Administration

Plague vaccines have been used for active immunisation against plague in those occupationally exposed to the organism and in some field workers in infected areas. They may reduce morbidity and mortality in bubonic plague but their activity against pneumonic plague is unknown.

References.

1. Cornelius C, *et al*. Protective immunity against plague. *Adv Exp Med Biol* 2007; **603:** 415–24.
2. Smiley ST. Current challenges in the development of vaccines for pneumonic plague. *Expert Rev Vaccines* 2008; **7:** 209–21.

3. Smiley ST. Immune defense against pneumonic plague. *Immunol Rev* 2008; **225:** 256–71.
4. Alvarez ML, Cardineau GA. Prevention of bubonic and pneumonic plague using plant-derived vaccines. *Biotechnol Adv* 2010; **28:** 184–96.
5. Feodorova VA, Corbel MJ. Prospects for new plague vaccines. *Expert Rev Vaccines* 2009; **8:** 1721–38.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Interactions

As for vaccines in general, p. 2375.3.

Pneumococcal Vaccines

Vacunas neumocócicas.
ATC — J07AL01; J07AL02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Pneumococcal Polysaccharide Vaccine; Vaccinum Pneumococcale Polysaccharidum). A mixture of purified polysaccharide capsular antigens from 23 differing serotypes of *Streptococcus pneumoniae*. Each 0.5-mL dose contains 25 micrograms of each of the 23 polysaccharide types. An antimicrobial preservative may be added. The vaccine has a pH of 4.5 to 7.4. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Pneumo may be used on the label.

Ph. Eur. 8: (Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed); Vaccinum Pneumococcale Polysaccharidicum Coniugatum Adsorbatum). A sterile suspension of purified capsular polysaccharides obtained from *Streptococcus pneumoniae* serotypes individually conjugated to a carrier protein. The carrier protein used may vary for the various polysaccharide conjugates contained in a multivalent vaccine. The vaccine may be adsorbed on a suitable adjuvant or adsorbant. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Pneumo(conj) may be used on the label.

Uses and Administration

Of the many serotypes of *Streptococcus pneumoniae* the 23 from which antigens are obtained for the most commonly available pneumococcal vaccine are considered to cause up to 96% of pneumococcal disease.

Pneumococcal vaccines are used for active immunisation in those at increased risk from infection with the types of *Streptococcus pneumoniae* contained in the vaccine. Pneumococcal vaccines may be in the form of an unconjugated 23-valent polysaccharide vaccine (PPV; suitable only for patients over 2 years of age) or as a conjugate vaccine (PCV) containing 7 serotypes (suitable for infants aged 2 months to 5 years). A conjugated vaccine containing 13 serotypes (PCV-13), suitable for infants and children aged 6 weeks to 17 years of age, has been approved for use in some countries and has replaced the vaccine containing 7 serotypes in routine childhood immunisation programmes. The PCV-13 vaccine may also be used in adults aged 50 years and older.

In the UK, it is recommended that immunisation should be part of the routine childhood immunisation programme and considered in all persons for whom pneumococcal infection is likely to be more common and/or serious, such as those aged 65 years and over and those aged two months and over in clinical risk groups. At-risk groups are considered to be:

- those who have undergone splenectomy and those with splenic dysfunction, including that due to sickle-cell anaemia and coeliac disease
- patients with immunodeficiency or immunosuppression due to disease or treatment, including HIV infection at all stages
- persons with chronic cardiac, pulmonary, hepatic, or renal impairment, including nephrotic syndrome, or diabetes mellitus
- persons with CSF shunts
- persons with cochlear implants

An antibody response develops by the third week, and usually lasts about 5 years. The antibody response is less reliable and declines more rapidly in young children and persons with impaired immune function.

A single dose of 0.5 mL of the 23-valent vaccine, containing 25 micrograms of each of the 23 polysaccharide types, is given to at-risk adults and children over 2 years of age by intramuscular injection (or subcutaneously if there are bleeding disorders). Previously unvaccinated children and adults undergoing elective splenectomy, chemotherapy, or other immunosuppressive treatment are at increased risk of pneumococcal disease and should be vaccinated accordingly (see below). The vaccine should be given at least 2 weeks (but preferably 4 to 6 weeks) before treatment. Revaccination is not generally recommended except, after 5 years, in patients likely to have rapidly declining antibody concentrations (for example, those with asplenia or splenic dysfunction and those with nephrotic syndrome).

The 7- and 13-valent pneumococcal conjugate vaccines are given by intramuscular injection. In the UK, the 13-valent PCV is suitable for infants and children from 6 weeks of age and is recommended as part of the routine immunisation schedule; doses of 0.5 mL are given at 2 and 4 months and a reinforcing dose is given at 13 months of age. A single dose of a 23-valent PPV is given to all adults 65 years and over. Additional recommendations are included in the vaccination schedule for the clinical risk groups above:

- *children 2 to 12 months of age (including those with asplenia, splenic dysfunction, or who are immunocompromised)*: vaccinate with a 13-valent PCV according to the routine immunisation schedule, followed by a single dose of a 23-valent PPV after their second birthday
- *children, aged 12 months to under 5 years*: give one dose of a 13-valent PCV, followed by a single dose of a 23-valent PPV after their second birthday (and at least 2 months after the dose of PCV)
  for those in the above group with asplenia, splenic dysfunction, or who are immunocompromised: give 2 doses of a 13-valent PCV, at least 2 months apart, followed by a single dose of a 23-valent PPV after their second birthday (and at least 2 months after the final dose of PCV)
- *from 5 years of age*: a single dose of a 23-valent PPV

In the USA, the 13-valent PCV is recommended for infants and children from 2 to 59 months of age as part of the primary immunisation schedule and for children aged 60 to 71 months of age with underlying medical conditions. Three doses are recommended as part of the routine primary immunisation schedule at 2, 4, and 6 months of age and a reinforcing dose is given at 12 to 15 months of age. A supplementary dose of the 13-valent PCV should be given to high-risk groups through to 71 months who have previously completed vaccination with 7-valent PCV. A dose of the 23-valent PPV should also be given to high-risk groups at 2 years of age (or as soon as possible after a high-risk chronic illness is diagnosed in those older than 2 years) and at least 2 months after the final dose of 13-valent PCV. A second dose of 23-valent PPV is recommended 5 years after the first dose in those with sickle-cell disease, asplenia, splenic dysfunction, HIV-infection, or who are immunocompromised.

Guidelines and recommendations.

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2. WHO. 23-valent pneumococcal polysaccharide vaccine: WHO position paper. *WklyEpidem Rec* 2008; **83:** 373–84. Also available at: http://www.who.int/wer/2008/wer8342.pdf (accessed 05/03/13)
3. American Academy of Pediatrics, Committee on Infectious Diseases. Policy Statement—Recommendations for the prevention of *Streptococcus pneumoniae* infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). *Pediatrics* 2010; **126:** 186–90. Also available at: http://pediatrics.aappublications.org/cgi/reprint/126/1/186 (accessed 05/03/13)
4. CDC. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; **59:** 1–18. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf (accessed 05/03/13)
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7. WHO. Pneumococcal vaccines WHO position paper - 2012 - recommendations. *Vaccine* 2012; **30:** 4717–18. Also available at: http://www.who.int/wer/2012/wer8714.pdf (accessed 05/03/13)

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2. Davies EG, *et al*. Pneumococcal vaccines for sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/04/06).
3. Lin PL, *et al*. Safety and immunogenicity of the American Academy of Pediatrics-recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. *Pediatrics* 2005; **116:** 160–7.
4. Bernatoniene J, Finn A. Advances in pneumococcal vaccines: advantages for infants and children. *Drugs* 2005; **65:** 229–55.
5. Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for protection. *Clin Infect Dis* 2008; **47:** 1328–38.
6. Adamkiewicz TV, *et al*. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics* 2008; **121:** 562–9.
7. Jansen AGSC, *et al*. Pneumococcal conjugate vaccines for preventing otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 11/12/09).
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10. Bryant KA, *et al*. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010; **125:** 866–75. Also available at: http://pediatrics.aappublications.org/cgi/reprint/125/5/866 (accessed 29/07/10)
11. Duggan ST. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) [Prevenar 13]. *Drugs* 2010; **70:** 1973–86.
12. Sucher AJ, *et al*. Prevnar 13, the new 13-valent pneumococcal conjugate vaccine. *Ann Pharmacother* 2011; **45:** 1516–24.
13. Paradiso PR. Advances in pneumococcal disease prevention: 13-valent pneumococcal conjugate vaccine for infants and children. *Clin Infect Dis* 2011; **52:** 1241–7.
14. Sanford M. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed): in older adults. *Drugs* 2012; **72:** 1243–55.
15. Moberley S, *et al*. Vaccines for preventing pneumococcal infection in adults. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2013 (accessed 05/03/13).

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1. Unless otherwise stated, the information below refers to the unconjugated polyvalent vaccine.

Revaccination of adults is not routinely recommended because of the increased incidence and severity of adverse reactions.

Pneumococcal vaccination is relatively ineffective in patients with multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, especially during treatment, and in chronic alcoholism. In patients with Hodgkin's disease the use of pneumococcal vaccines is not recommended in those who have received extensive chemotherapy or nodal irradiation. Pneumococcal vaccines should be given at least 2 weeks (and preferably 4 to 6 weeks) before starting immunosuppressive therapy or be delayed until at least 3 months after completion of therapy.

A satisfactory response to the unconjugated polyvalent pneumococcal vaccines is not obtained in children less than 2 years of age and therefore immunisation of this age group with this vaccine is not recommended. However, a pneumococcal conjugate vaccine is available that may be given to infants from 2 months of age.

Effects on the blood. Relapses have occurred on rare occasions in patients with stabilised immune thrombocytopenia at 2 to 14 days after vaccination against pneumococcal infections, lasting for up to 2 weeks. One such case was reported[1] following revaccination less than 2.5 years after an uneventful primary vaccination with pneumococcal vaccine.

1. Neil VS. Long term management after splenectomy: revaccination may cause relapse. *BMJ* 1994; **308:** 339.

Effects on the kidneys. Glomerulonephritis was described[1] in a splenectomised patient after use of pneumococcal vaccine. It was postulated that high antibody titres from a recent pneumococcal infection could have contributed. Minimal change nephrotic syndrome with mild interstitial nephritis following pneumococcal vaccination was suggested as the cause of oedema of the face and legs, visual disturbance suggestive of uveitis, and massive proteinuria in a 67-year-old woman who had been vaccinated about 4 months earlier.[2]

1. Tan SY, Cumming AD. Vaccine related glomerulonephritis. *BMJ* 1993; **306:** 248.
2. Kikuchi Y, *et al*. Minimal change nephrotic syndrome, lymphadenopathy and hyperimmunoglobulinemia after immunization with a pneumococcal vaccine. *Clin Nephrol* 2002; **58:** 68–72.

Effect of nutritional status. An impaired antibody response to pneumococcal vaccine was reported[1] in elderly patients with low serum concentrations of vitamin B_{12}.

1. Fata FT, *et al*. Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B12 levels. *Ann Intern Med* 1996; **124:** 299–304.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pneumococcal vaccine (unconjugated) as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Pneumo 23; Pneumovax 23; Prevenar; Prote-Neu; Synflorix; ***Austral.:*** Pneumovax 23; Prevenar 13; Prevenar; Synflorix; ***Austria:*** Pneumo 23; Prevenar 13; Prevenar; Synflorix; ***Belg.:*** Pneumo 23; Prevenar; Synflorix; ***Braz.:*** Vacina Pneumococica Conjugada 7-Valente; Vaci-

na Pneumococica Polivalente; ***Canad.***: Pneumo 23; Pneumovax 23; Prevnar 13; Prevnar; Synflorix; ***Chile***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; ***China***: Hui Yi Kang (惠益康); Pneumo 23 (优博 23); Pneumovax (纽莫法); Prevenar (沛儿); ***Cz.***: Pneumo 23; Prevenar; Synflorix; ***Denm.***: Pneumovax; Prevenar; ***Fin.***: Pneumovax; Prevenar; ***Fr.***: Pneumo 23; Pneumovax†; Prevenar 13; Prevenar†; ***Ger.***: Pneumovax 23; Prevenar; Synflorix; ***Gr.***: Pneumo 23; Pneumovax 23; Pnu-Imune 23; Prevenar; Synflorix; ***Hong Kong***: Pneumo 23; Pneumovax 23; Prevenar; Synflorix; ***Hung.***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; ***Indon.***: Pneumo 23; Prevenar; Synflorix; ***Irl.***: Pneumovax II; Prevenar; Synflorix; ***Israel***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; ***Ital.***: Pneumo 23†; Pneumovax; Prevenar; ***Malaysia***: Pneumo 23; Prevenar; Synflorix; ***Mex.***: Prevenar; Pulmovax; ***Neth.***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; ***Norw.***: Pneumovax; Prevenar 13; Prevenar†; Synflorix†; ***NZ***: Pneumo 23; Pneumovax 23; Prevenar; Synflorix; ***Philipp.***: Pneumo 23; Pneumovax; Prevenar; ***Pol.***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; ***Port.***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; ***Rus.***: Prevenar (Превенар); ***S.Afr.***: Imovax Pneumo 23; Pneumovax 23; Prevenar; ***Singapore***: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar†; Synflorix; ***Spain***: Pneumo 23; Pneumovax 23; Prevenar; Synflorix; ***Swed.***: Pneumo 23†; Pneumovax; Prevenar 13; Prevenar; Synflorix; ***Switz.***: Pneumovax 23; Prevenar 13; Prevenar†; ***Thai.***: Pneumo 23; Pneumovax 23; Prevnar 13; Prevnar†; Synflorix; ***Turk.***: Pneumo 23; Prevenar; Synflorix; ***UK***: Pneumovax II; Prevenar; Synflorix; ***Ukr.***: Prevenar 13 (Превенар 13); Synflorix (Синфлорикс); ***USA***: Pneumovax 23; Prevnar; ***Venez.***: Prevenar.

Pharmacopoeial Preparations

Ph. Eur.: Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed); Pneumococcal Polysaccharide Vaccine.

Poliomyelitis Vaccines

Polio Vaccines; Poliovirus Vaccines; Vacunas de la polio; Vacunas de la poliomielitis.

ATC — J07BF01; J07BF02; J07BF03; J07BF04.

NOTE. Inactivated poliomyelitis vaccines are sometimes termed Salk Vaccine and live (oral) poliomyelitis vaccines are sometimes termed Sabin Vaccine.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Poliomyelitis Vaccine (Inactivated); Vaccinum Poliomyelitidis Inactivatum). A liquid preparation of suitable strains of poliomyelitis virus, types 1, 2, and 3, grown in suitable cell cultures and inactivated by a suitable method. Permitted antibacterials may be used in its production and it may contain preservatives. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that IPV may be used on the label.

Ph. Eur. 8: (Poliomyelitis Vaccine (Oral); Vaccinum Poliomyelitidis Perorale; Poliomyelitis Vaccine, Live (Oral) BP 2014). A liquid preparation of suitable live attenuated strains of poliomyelitis virus, types 1, 2, or 3, grown in suitable, approved cell cultures; it may contain any one of the 3 virus types or combinations of them. The trivalent vaccine is standardised for virus titre which is not less than 6.0 log $CCID_{50}$ for type 1, not less than 5.0 log $CCID_{50}$ for type 2, and not less than 5.5 log $CCID_{50}$ for type 3 per dose. Permitted antibacterials may be used in its production. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that OPV may be used on the label.

Uses and Administration

Poliomyelitis vaccines are used for active immunisation against poliomyelitis. For discussion of immunisation schedules, see under Vaccines, p. 2373.3. There are 3 serotypes of poliovirus, and both live trivalent (oral) and inactivated trivalent poliomyelitis vaccines are used in routine immunisation programmes. Monovalent oral poliomyelitis vaccines against either wild poliovirus types 1 or 3 are used during supplementary immunisation activities in the highest-risk areas; an oral bivalent poliomyelitis vaccine is also being tried. The oral vaccine stimulates the formation of antibodies both in the blood and in the mucosal tissues of the gastrointestinal tract.

In the UK, a trivalent inactivated poliomyelitis vaccine is recommended for the primary immunisation of all age groups, given as a course of 3 doses at intervals of 4 weeks. It is given intramuscularly as a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine. For children who received primary immunisation during infancy, reinforcing doses are recommended at school entry (diphtheria, tetanus, pertussis, and poliomyelitis) and before leaving school (diphtheria, tetanus, and poliomyelitis). Further reinforcing doses are necessary only in adults exposed to infection including travellers to countries where poliomyelitis is epidemic or endemic and healthcare workers in contact with poliomyelitis cases. A single dose is given, repeated every 10 years if necessary.

In the USA, the recommended schedule consists of four doses of inactivated vaccine given at 2 months, 4 months, 6 to 18 months, and 4 to 6 years of age.

On the occurrence of a single case of paralytic poliomyelitis from wild virus, a single dose of the oral vaccine is recommended for all persons in the neighbourhood, regardless of whether they have previously been immunised. A primary course should be completed in previously unimmunised individuals.

References.

1. CDC. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. *MMWR* 2009; **58:** 829–30. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5830a3.htm (accessed 30/06/10)
2. WHO. Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. *Wkly Epidem Rec* 2010; **85:** 213–28. Also available at: http://www.who.int/wer/2010/wer8523.pdf (accessed 30/06/10)

Choice of vaccine. Two types of poliomyelitis vaccine are available: live attenuated oral poliomyelitis vaccine (OPV) and inactivated (killed) poliomyelitis vaccine (IPV) given by injection. Both vaccines are highly effective against all 3 types of poliovirus but there are advantages and disadvantages associated with their use.

The *advantages* of OPV are:

- it produces an immune response in both the blood and in the lining of the gut, thus preventing both spread of infection to the CNS and multiplication of the virus in the gastrointestinal tract and hence transmission via the stools and saliva
- it is given orally and is therefore easy to give without specialist training
- it is relatively inexpensive, an important consideration in developing countries in particular.

The *disadvantage* of OPV is:

- it causes very rare cases of vaccine-associated paralytic poliomyelitis (VAPP).

The *advantage* of IPV is:

- it is not a live vaccine and as such carries no risk of VAPP.

The *disadvantages* of IPV are:

- it confers very little immunity in the gastrointestinal tract, hence when an individual immunised with IPV is infected with wild poliovirus the virus can still multiply in the intestines and be shed in the stools, thus risking continued transmission
- trained health workers are required to give it by injection
- it costs far more than OPV.

Poliomyelitis has now been eradicated from most countries in the world (see below) and hence many, including the UK and the USA, consider it appropriate to use IPV exclusively for routine immunisation. However, the Global Polio Eradication Initiative will continue to use OPV where necessary until global eradication is achieved, at which time it has stated that the use of OPV should cease as soon as possible while population immunity against poliomyelitis and surveillance sensitivity for paralysis remain high, and be replaced by routine use of IPV.[1]

1. WHO. Framework for national policy makers in OPV-using countries: cessation of routine oral polio vaccine (OPV) use after global polio eradication. Geneva: WHO, 2005. Also available at: http://www.polioeradication.org/content/publications/OPVCessationFrameworkEnglish.pdf (accessed 12/10/05)

Eradication of infection. By the mid-1980s poliomyelitis was declining in many regions of the world due to mass oral poliomyelitis vaccine immunisation activities and in 1988, WHO announced the goal of eradicating poliomyelitis by the year 2000. Other bodies joined the project which became known as the Global Polio Eradication Initiative.[1] Although the goal was not achieved in 2000, very considerable progress has been made. In 1988, wild poliovirus (WPV) was endemic in 125 countries and more than 1000 children became paralysed every day. The last cases of WPV type 2 were reported in October 1999[2] and by 2006 indigenous transmission of WPV2 infection had been interrupted globally;[3] by 2008 transmission of indigenous WPV types 1 and 3 (WPV1 and WPV3) still occurred in 4 countries (Afghanistan, India, Nigeria, and Pakistan).[2-4] These countries remain a source of WPV that may be reintroduced into countries where transmission had previously stopped; in 2009, 207 cases were reported from 15 countries after WPV importation.[2]

Once global WPV transmission has been interrupted, the greatest risk of poliomyelitis being reintroduced will be from the attenuated viruses contained in oral poliomyelitis vaccine, which in rare cases can result in vaccine-associated paralytic polio (VAPP) and outbreaks due to vaccine-derived polioviruses (VDPV).[1] The first report of circulating VDPV occurred in 2000 and in 2009 VDPVs were detected in 6 countries;[2] VDPVs can circulate even in well-immunised communities and produce polio outbreaks in areas with low rates of oral polio vaccine coverage. Furthermore, they can replicate for years in immunocompromised persons.[4] This led to the realisation that complete eradication of poliomyelitis must eventually also include the eradication of the live oral vaccine and that a high level of universal immunity against poliomyelitis will need to be maintained, with the current inactivated poliomyelitis vaccine or a new generation inactivated poliomyelitis vaccine, even after wild poliovirus is eradicated.[5]

1. Global Polio Eradication Initiative. Information available at: http://www.polioeradication.org (accessed 14/12/09)
2. CDC. Progress towards interruption of wild poliovirus transmission—worldwide, 2009. *MMWR* 2010; **59:** 545–50. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5918a1.htm (accessed 30/06/10)
3. CDC. Wild poliovirus type 1 and type 3 importations—15 countries, Africa, 2008–2009. *MMWR* 2009; **58:** 357–62. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5814a1.htm (accessed 14/12/09)
4. CDC. Update on vaccine-derived polioviruses—worldwide, January 2008–June 2009. *MMWR* 2009; **58:** 1002–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5836a3.htm (accessed 14/12/09)
5. Chumakov K, Ehrenfeld E. New generation of inactivated poliovirus vaccines for universal immunization after eradication of poliomyelitis. *Clin Infect Dis* 2008; **47:** 1587–92.

Adverse Effects

As for vaccines in general, p. 2375.1.

Vaccine-associated paralytic poliomyelitis has been reported rarely in recipients of oral poliomyelitis vaccines and in contacts of recipients (see p. 2412.1).

Carcinogenicity. Some poliomyelitis vaccines given in the 1950s and 1960s were found to be contaminated with Simian virus (SV40) from the monkey cell cultures used in the manufacturing process.[1] Once the contamination was realised, steps were taken to eliminate it from future vaccines. However, SV40 is believed to possess biological properties consistent with cancer-causing viruses and epidemiological studies have consequently been conducted to assess whether vaccine recipients have subsequently developed cancer. Although these studies did not find any increased cancer risk, a report by the USA Institute of Medicine in 2002 concluded that these studies were sufficiently flawed to preclude any conclusion being reached. Studies have also assessed the risk to offspring of women given these vaccines during pregnancy (see p. 2412.1). Vaccines now in use do not contain SV40 as they are not manufactured using monkey cell cultures.

1. Stratton K, *et al.*, eds., Institute of Medicine of the National Academies. SV40 contamination of polio vaccine and cancer. *Immunization Safety Review.* Washington D.C.: National Academies Press, 2003. Also available at: http://www.nap.edu/openbook.php?isbn=0309086108 (accessed 15/07/08)

Effects on the nervous system. There have been several case reports of the isolation of poliovaccine virus from the CSF after use of oral poliomyelitis vaccine. A 7-year-old girl who had previously been vaccinated with inactivated poliomyelitis vaccine in infancy was given oral vaccine and developed prolonged headache, vomiting, and fever but no paralysis;[1] poliovirus was subsequently isolated from her CSF 34 days after she had received the oral vaccine, and it was concluded that her previous immunisations had been ineffective. In a further report,[2] poliovirus was isolated from the CSF of 2 infants with ventriculoperitoneal shunts who had developed aseptic meningitis without paralysis after oral poliomyelitis vaccination. A neurovirulent variant of Sabin type 2 oral poliomyelitis vaccine virus was detected in both the CSF and stools of an infant with transient hypogammaglobulinaemia who developed meningoencephalitis, retinitis, and irreversible hearing loss after oral poliomyelitis vaccination.[3] A 6-year-old girl given oral poliomyelitis vaccine at 1 and 2 years developed acute disseminated encephalomyelitis and a mutated form of poliovirus was isolated from her CSF;[4] it was thought that she had been infected with the mutated virus from extrafamilial contacts and that the cause of her condition may have been related to her HLA type.

1. Rantala H, *et al.* Poliovaccine virus in the cerebrospinal fluid after oral polio vaccination. *J Infect* 1989; **19:** 173–6.
2. Gutierrez K, Abzug MJ. Vaccine-associated poliovirus meningitis in children with ventriculoperitoneal shunts. *J Pediatr* 1990; **117:** 424–7.
3. Inaba H, *et al.* Polio vaccine virus-associated meningoencephalitis in an infant with transient hypogammaglobulinemia. *Scand J Infect Dis* 2001; **33:** 630–1.
4. Ozawa H, *et al.* Acute disseminated encephalomyelitis associated with poliomyelitis vaccine. *Pediatr Neurol* 2000; **23:** 177–9.

GUILLAIN-BARRÉ SYNDROME. A small cluster of cases of Guillain-Barré syndrome was seen[1] in children after a mass oral poliomyelitis vaccination campaign in Finland in 1985. An increased frequency of Guillain-Barré syndrome was also seen in adults. However, a direct link with poliovaccine virus infection could not be established and no link between Guillain-Barré syndrome and oral polio vaccine was found by a subsequent, epidemiological study in California.[2]

1. Uhari M, *et al.* Cluster of childhood Guillain-Barré cases after an oral poliovaccine campaign. *Lancet* 1989; **ii:** 440–1.
2. Rantala H, *et al.* Epidemiology of Guillain-Barré syndrome in children: relationship of oral polio vaccine administration to occurrence. *J Pediatr* 1994; **124:** 220–3.

VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS. Although generally considered safe and effective, in extremely rare cases the live attenuated virus in oral poliomyelitis vaccines can cause vaccine-associated paralytic poliomyelitis (VAPP) in either the vaccine recipient or in a close contact. There is no such risk associated with inactivated poliomyelitis vaccines. The incidence of VAPP is about 1 case in every 2.5 million doses of vaccine and may be increased in immunocompromised patients. A case control study[1] identified intramuscular injections given within 30 days of vaccination as a risk factor in the development of VAPP. This phenomenon, known as provocation paralysis or provocation poliomyelitis, has been described with the wild virus[2] and has been recognised as a factor in vaccine-associated paralysis in the UK and USA.[3] Paralytic poliomyelitis in contacts of vaccine recipients can be further reduced by ensuring that parents without evidence of previous immunisation receive the vaccine at the same time as their children. The benefits of oral poliomyelitis vaccination are considered to greatly outweigh the small risk involved, however, and many countries where the risk of wild virus-caused poliomyelitis has been reduced to zero are now considering combined immunisation schedules with both oral and inactivated poliomyelitis vaccines. It has been suggested that inactivated poliomyelitis vaccine should be introduced globally.[4]

1. Strebel PM, *et al.* Intramuscular injections within 30 days of immunization with oral poliovirus vaccine—a risk factor for vaccine-associated paralytic poliomyelitis. *N Engl J Med* 1995; **332:** 500–6.
2. Anonymous. Provocation paralysis. *Lancet* 1992; **340:** 1005–6.
3. Wyatt HV. Vaccine-associated poliomyelitis. *Lancet* 1994; **343:** 610.
4. Heinsbroek E, Ruitenberg EJ. The global introduction of inactivated polio vaccine can circumvent the oral polio vaccine paradox. *Vaccine* 2010; **28:** 3778–83.

Precautions

As for vaccines in general, p. 2375.2.

Poliomyelitis vaccine may contain trace amounts of antibacterials such as neomycin, polymyxin B, and streptomycin and should be used with caution in patients with severe hypersensitivity to these antibacterials.

Oral poliomyelitis vaccines should not be given to patients with diarrhoea or vomiting.

Because the vaccine virus of oral poliomyelitis vaccines is excreted in the faeces for up to 6 weeks, the contacts of recently vaccinated babies and infants should be advised of the need for strict personal hygiene, particularly hand washing after napkin changing, in order to reduce the possibility of infection in unimmunised contacts. Unimmunised adults can be immunised at the same time as their children.

Immunocompromised patients are at increased risk of developing vaccine-associated paralytic poliomyelitis. Oral poliomyelitis vaccines should not be given to immunocompromised patients or their household contacts and in these persons an inactivated vaccine should be used. Asymptomatic HIV-positive persons may receive oral poliomyelitis vaccines but faecal excretion of the vaccine virus may continue for longer than in uninfected individuals. For symptomatic HIV-positive persons the use of inactivated poliomyelitis vaccine may be considered.

Intramuscular injections given after the oral vaccine may also increase the risk of vaccine-associated paralytic poliomyelitis (see above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trivalent inactivated poliomyelitis vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Live vaccines such as *oral poliomyelitis vaccines* are generally contra-indicated in pregnancy because of a theoretical risk to the fetus. Population-wide mass vaccination programmes become impossible, however, if pregnant mothers and women of child-bearing age are to be excluded.[1] In February 1985, mass vaccination with live oral poliomyelitis vaccine was started during a poliomyelitis outbreak in Finland.[1] Pregnant women were advised to take the vaccine. An analysis of all reported congenital malformations in the years 1982 to 1986 suggested that oral poliomyelitis vaccine had no harmful effects on fetal development as measured by overall prevalence of malformations or by the incidence of either CNS or orofacial defects. The results did not, however, exclude an effect measurable by other criteria of fetal development.

The incidence of spontaneous abortions was measured during a mass poliomyelitis vaccination campaign in Israel.[2] The number of spontaneous abortions did not differ between controls and women vaccinated during the first trimester of pregnancy; the percentage of spontaneous abortions in relation to live births was also similar. Microscopic examination of placentas from spontaneous abortions indicated no effect of oral poliomyelitis vaccine on the frequency or type of pathological changes. In addition, subsequent epidemiological study[3] found no increases in congenital malformations or in premature births during the period of and immediately after the vaccination campaign compared with those born before the campaign.

The Collaborative Perinatal Project (CPP) in the USA[4] followed up 50 897 pregnancies to examine risk factors for the development of malignancies in offspring born between 1959 and 1966. In 18 342 children whose mothers were vaccinated during pregnancy with *inactivated poliomyelitis vaccines*, there were 14 malignancies (7.6 per 10 000), while in 32 555 non-exposed children there were 10 malignancies (3.1 per 10 000). There were 7 tumours derived from neural tissue in the exposed children (3.8 per 10 000) and one in non-exposed children (0.3 per 10 000). Thus there was an excess of neural tumours but not of leukaemias or other malignancies in children exposed *in utero* to inactivated poliomyelitis vaccine. No malignancies occurred among the children born to 3056 women who received oral poliomyelitis vaccine. Serum samples collected from mothers on entry into the CPP and at delivery were subsequently analysed[5] for the presence of antibodies to Simian virus 40 (SV40). None of the serum samples from 8 mothers of infants with neural tumours had antibodies to SV40. Two of the 7 mothers of infants with leukaemia had SV40 antibodies, but only one had conversion during pregnancy. None of the samples from the 7 mothers of children with other types of cancer had antibodies. Three of 36 controls had antibodies, but in both the first and second samples. The association between use of inactivated poliomyelitis vaccine in mothers and neural tumours in their offspring could not be attributed to contamination of vaccine with SV40. A later analysis[6] of 54 796 children enrolled in the CPP found an increased risk of neural tumours and of haematological malignancy in children whose mothers were given pre-1963 poliomyelitis vaccine, but concluded that this was unlikely to have been due to transmission of SV40.

1. Harjulehto T, *et al.* Congenital malformations and oral poliovirus vaccination during pregnancy. *Lancet* 1989; **i:** 771–2.
2. Ornoy A, *et al.* Spontaneous abortions following oral poliovirus vaccination in first trimester. *Lancet* 1990; **i:** 800.
3. Ornoy A, Ben Ishai P. Congenital anomalies after oral poliovirus vaccination during pregnancy. *Lancet* 1993; **341:** 1162.
4. Heinonen OP, *et al.* Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973; **2:** 229–35.
5. Rosa FW, *et al.* Absence of antibody response to simian virus 40 after inoculation with killed-poliovirus vaccine of mothers of offspring with neurologic tumors. *N Engl J Med* 1988; **318:** 1469.
6. Engels EA, *et al.* Poliovirus vaccination during pregnancy, maternal seroconversion to simian virus 40, and risk of childhood cancer. *Am J Epidemiol* 2004; **160:** 306–16.

Interactions

As for vaccines in general, p. 2375.3.

Normal immunoglobulins. Although the use of live vaccines and immunoglobulins at the same time is generally not recommended, normal immunoglobulin had no effect on the antibody response to oral poliomyelitis vaccine when the 2 preparations were given together to 50 subjects.[1]

1. Green MS, *et al.* Response to trivalent oral poliovirus vaccine with and without immune serum globulin in young adults in Israel in 1988. *J Infect Dis* 1990; **162:** 971–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Imovax Polio; Opvero; Polioral; Sabin†; ***Austral.***: Ipol; ***Belg.***: Imovax Polio; ***Braz.***: IPV†; ***Canad.***: Imovax Polio; ***China***: Imovax Polio (爱宝维); ***Cz.***: Imovax Polio; IPV-Virelon†; VeroPol; ***Fin.***: Imovax Polio; VeroPol; ***Fr.***: Imovax Polio; ***Ger.***: IPV Merieux; IPV-Virelon†; ***Gr.***: Poliorix; Vaccin Antipoliomyelitique/Merieux; ***Hong Kong***: Imovax Polio; ***Hung.***: Imovax Polio; ***India***: Imovax Polio; OPV; ***Indon.***: Imovax Polio; ***Israel***: Imovax Polio; Polio Sabin; ***Ital.***: Imovax Polio; Poliovax-IN†; ***Jpn***: Imovax Polio; ***Malaysia***: Polio Sabin; ***Mex.***: Polio Sabin†; Polioral†; ***Norw.***: Imovax Polio; ***NZ***: Imovax Polio; Ipol; ***Philipp.***: Imovax Polio; Polio Sabin; Polioral; Poliorix†; ***Pol.***: Imovax Polio; Polio Sabin†; ***Port.***: Imovax Polio; ***Rus.***: Imovax Polio (Имовакс Полио); Poliorix (ПОЛИОРИКС); ***S.Afr.***: OPV-Merieux; Polioral; ***Singapore***: Imovax Polio; Polio Sabin; ***Spain***: Vac Polio Sabin†; Vac Poliomielitica†; ***Swed.***: Imovax Polio; VeroPol; ***Switz.***: Poliorix; ***Thai.***: Opvero; Polio Sabin; Polioral; ***Turk.***: Buccapol; OPV; Polio Sabin†; Poliorix†; ***USA***: Ipol.

Pharmacopoeial Preparations

Ph. Eur.: Poliomyelitis Vaccine (Inactivated); Poliomyelitis Vaccine (Oral).

Pseudomonas Vaccines

Vacunas de pseudomonas.

Profile

Candidate *Pseudomonas aeruginosa* vaccines are under investigation for the prevention of pseudomonal infections in different disease states.

Pseudomonas aeruginosa is notably resistant to many antibacterials and there has consequently been considerable interest in developing an effective vaccine against it.[1-4] However, disappointing clinical results and improvements in antibacterial management have meant that no such vaccine is yet available for clinical use.

Early attempts in the 1960s at developing a vaccine focused on cell wall components (lipopolysaccharides). Multivalent lipopolysaccharide vaccines were tested in *animals* and in patients, including burns patients and patients with various forms of cancer and acute and chronic lung disease but, despite some positive results, these vaccines never gained clinical acceptance because of problems associated with the use of lipopolysaccharides. Vaccines designed at targeting the toxic exoproduct of *Ps. aeruginosa*, exotoxin A, produced mixed results at best; there has also been interest in exotoxin A toxoid plus other protective immunogens and in multicomponent and conjugate vaccines. There was brief interest in ribosomes and ribosomal RNA vaccines but these fell out of favour.

The discovery that motility was associated with *Ps. aeruginosa* virulence prompted research into the use of flagella as protective immunogens. The organism normally has two types of flagellum and a divalent vaccine has been tested, but with only modest benefit. There has also been some interest in development of vaccines against pili, bacterial appendages used for attachment.

Some investigators tried the use of high-molecular-weight polysaccharides as potential vaccine candidates but interest in this area has declined. Another defunct area of research is the use of pseudomonal alginate and mucoid exopolysaccharide; these were suggested for use in cystic fibrosis patients but did not progress beyond *animal* studies.

From the 1980s, there was considerable interest in the use of a variety of outer membrane proteins to develop a vaccine, partly because outer membrane proteins are exposed on the cell surface and at least one, protein F, is common to all serotypes. Encouraging results were obtained in *animal* models of infected burns and of chronic lung disease. Preliminary studies in healthy humans yielded large and sustained increases in antibody titres and found outer membrane proteins to be well tolerated. Multicomponent vaccines have been developed consisting of toxoids of known pseudomonal virulence factors such as proteases, elastases, and exotoxin A. Conjugate vaccines have been shown to be effective in *animal* models and to elicit a high antibody titre in cystic fibrosis patients.

In recent years, attention has also turned to the development of DNA vaccines, and to the use of some novel immunological approaches such as the use of pooled monoclonal antibodies directed against a variety of *Ps. aeruginosa* virulence antigens and of epitopes of pseudomonal elastase. In addition, research has shown that both active and passive immunisation with the purified type III translocation protein (PcrV) from *Ps. aeruginosa* is effective in *mouse* models of lung infection and burns, although results of combined active and passive immunisation in clinical studies were disappointing. Finally, there has been interest in obtaining immunological protection by presenting *Pseudomonas* antigens via mucous membranes, particularly in the gastrointestinal tract or intranasally.

1. Johansen HK, Gøtzsche PC. Vaccines for preventing infection with Pseudomonas aeruginosa in cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 27/08/10).
2. Cachia PJ, Hodges RS. Synthetic peptide vaccine and antibody therapeutic development: prevention and treatment of Pseudomonas aeruginosa. *Biopolymers* 2003; **71:** 141–68.
3. Holder IA. Pseudomonas vaccination: a historical overview. *Vaccine* 2004; **22:** 831–9.
4. Döring G, Pier GB. Vaccines and immunotherapy against Pseudomonas aeruginosa. *Vaccine* 2008; **26:** 1011–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jia Dai Bao (佳代胞); Lv Mu An (绿慕安); ***Pol.***: Pseudovac.

Q Fever Vaccines

Vacunas de la fiebre Q.

Profile

A Q fever vaccine consisting of a purified killed suspension of *Coxiella burnetii* is available in Australia. It is prepared

from Phase I Henzerling strain of *C. burnetii* grown in the yolk sacs of embryonated eggs. A single 0.5-mL subcutaneous dose is given for active immunisation in individuals at high risk of Q fever. These include abattoir workers, veterinarians, farmers and others exposed to farm animals, and laboratory workers handling potentially infected tissue.

Before immunisation, patients should be tested for their serum antibody titre and a skin test performed; giving the vaccine to persons already sensitised to Q fever antigens may cause serious hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Q-Vax.

Rabies Antisera

Antisuero de la rabia; Suero antirrábico.
ATC — J06AA06.

Profile

Rabies antisera have been used to provide passive immunisation against rabies but the use of rabies immunoglobulins (see below) is preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Mirv-HDC.

Rabies Immunoglobulins

Inmunoglobulinas contra la rabia.
ATC — J06BB05.
UNII — 95F619ATQ2 (human rabies virus immunoglobulin).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Rabies Immunoglobulin; Immunoglobulinum Humanum Rabicum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from donors immunised against rabies and contains specific antibodies that neutralise the rabies virus. Normal immunoglobulin may be added. It contains not less than 150 international units/mL. The liquid preparation should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

USP 36: (Rabies Immune Globulin). A sterile solution of globulins derived from plasma or serum from selected adult human donors who have been immunised with rabies vaccine and have developed high titres of rabies antibody. It contains 10 to 18% of protein of which not less than 80% is monomeric immunoglobulin G. It has a potency of 150 international units/mL. It contains glycine as a stabilising agent, and a suitable preservative. A solution diluted to contain 1% of protein has a pH of 6.4 to 7.2. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Rabies immunoglobulins are used for passive immunisation against rabies. They are combined with active immunisation by rabies vaccines (see below) in postexposure treatment for the prevention of rabies in previously unimmunised persons who have been bitten by rabid animals or animals suspected of being rabid. There are 2 types of immunoglobulin available: human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose of HRIG is 20 international units/kg; for ERIG products it is 40 international units/kg. The recommended dose should be infiltrated in and around the cleansed wound; if infiltration of the whole volume is not possible, any remaining immunoglobulin should be given intramuscularly (in the anterolateral thigh and not the gluteal region) at a different site to that at which the vaccine was given.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Imogam Rabia; ***Austral.***: Imogam; ***Austria***: Berirab; ***Canad.***: HyperRab; Imogam; ***China***: Yi Sheng Bao Er (依生保尔); ***Cz.***: Favirab; ***Fr.***: Favirab; Imogam Rage; ***Ger.***: Berirab; Tollwutglobulin; ***Gr.***: Berirap; ***Hong Kong***: Berirab; HyperRab; ***India***: Berirab-P; Carig; Equirab; Erig; HRIG; Imogam Rabies; Imorab; ***Indon.***: Imogam; ***Israel***: Berirab; HyperRab; Imogam Rabies; KamRab; ***Mex.***: Berirab-P; Kamrab†; ***Philipp.***: BayRab; Berirab-P; Equirab; Favirab; ***S.Afr.***: Rabigam; ***Spain***: Imogam Rabia; ***Switz.***: Berirab; ***Thai.***: Berirab; Favirab; Imogam Rabies†; KamRAB; TRCS ERIG; ***Turk.***: BayRab; Favirab; Imogam†; ***USA***: HyperRab; Imogam Rabies.

Pharmacopoeial Preparations
Ph. Eur.: Human Rabies Immunoglobulin;
USP 36: Rabies Immune Globulin.

Rabies Vaccines

Vacunas de la rabia.
ATC — J07BG01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Rabies Vaccine for Human Use Prepared in Cell Cultures; Vaccinum Rabiei ex Cellulis ad Usum Humanum; Rabies Vaccine BP 2014). A sterile freeze-dried suspension of inactivated rabies virus; a suitable strain is grown in an approved cell culture. The cell-culture medium may contain suitable antibacterials at the smallest effective concentration. The vaccine is prepared immediately before use by the addition of a suitable sterile liquid. The estimated potency is not less than 2.5 international units per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Rab may be used on the label.

Uses and Administration

Rabies vaccines are used for active immunisation against rabies. They are used as part of postexposure treatment to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. Infection does not take place through unbroken skin but is possible through uninjured mucous membranes and has been reported after the inhalation of virus in the laboratory. Rabies vaccines are also used for pre-exposure prophylaxis against rabies in persons exposed to a high risk of being bitten by rabid or potentially rabid animals.

Schedules for prophylaxis and treatment of rabies are recommended by WHO (see Pre-exposure Immunisation and Postexposure Treatment, p. 2414.1) and many countries have immunisation schedules based on these.

In the UK, two types of rabies vaccine are available. The first type is prepared from inactivated Wistar rabies virus strain PM/WI38 1503-3M cultured on human diploid cells, and the second type is prepared from inactivated Flury LEP virus strain produced on purified chick embryo cells. Each contains not less than 2.5 international units/mL. The purified chick embryo-cell vaccine is given intramuscularly into the deltoid region in adults but into the anterolateral aspect of the thigh in children. The human diploid-cell vaccine is given intramuscularly into the deltoid region in both adults and children. Other cell culture-derived vaccines, such as Vero cell rabies vaccine, are available in other countries.

For **pre-exposure prophylaxis** against rabies, the recommended schedule in the UK is 3 doses, each of 1 mL, by intramuscular injection on days 0, 7, and 28; the third dose may in some instances be given on day 21 if there is insufficient time before travel. For persons at regular and continuous risk, a single reinforcing dose should be given 1 year after completion of the primary course with further doses at 3- to 5-year intervals. For those at intermittent risk, a booster dose should be given from 2 years after completion of the primary course.

For **postexposure treatment**, thorough cleansing of the wound with soap and water is imperative. The recommended schedule in the UK for unimmunised or incompletely immunised persons is 5 doses, each of 1 mL, by intramuscular injection on days 0, 3, 7, 14, and 30. (In some countries 4-dose regimens are favoured, see p. 2414.1.) In fully immunised persons two doses of vaccine should be given intramuscularly, one each on day 0 and day 3. Vaccination should be started as soon as possible after exposure, and may be stopped if it is proved that the patient was not at risk. In previously unimmunised patients at high risk, rabies immunoglobulin (see above) should also be given at the same time as the first dose of vaccine.

Rabies. Rabies is caused by infection with a rhabdovirus of the genus Lyssavirus. Rabies has a worldwide distribution, mainly in domesticated and wild dogs but also in bats and other warm-blooded animals, although some countries, including the UK, most of Australasia, and Antarctica are designated as rabies-free areas. Transmission of the rabies virus to humans is usually by the bite of an infected animal or contamination of broken skin by saliva. Infection is possible via intact mucous membranes and by aerosol transmission, but infection is unlikely after contamination of intact skin. Other body fluids such as urine and tears should be regarded as potentially infectious; rabies virus transmission has also been reported after organ transplantation from misdiagnosed donors.

Human rabies is almost always fatal once symptoms have appeared. The incubation period varies from 2 weeks to 6 years (average of 2 to 3 months) depending on the distance of the bite site from the brain and the amount of virus in the inoculum. There are 2 types of clinical presentations of rabies; encephalitic (furious) and paralytic (dumb). Encephalitic rabies presents with periods of hyperexcitability accompanied by severe agitation and bizarre behaviour alternating with periods of lucidity. Severe spasms of the larynx and pharynx may be provoked by attempts at swallowing (leading to hydrophobia) or by air blown at the face (aerophobia). Other symptoms include hypersalivation, fever, and convulsions. In the paralytic form, progressive flaccid paralysis develops in the bitten limb and ascends in a symmetrical or asymmetrical manner. Patients not dying through respiratory or cardiac arrest during the acute phase may develop various complications culminating in coma and death or (very rarely) recovery; only a few patients are documented as having survived after the onset of coma, and all had received either pre- or postexposure immunisation.

National control programmes involve epidemiological surveillance, mass canine immunisation campaigns, and dog population management. The development of oral animal vaccines delivered on baited food has met with considerable success in some areas and has become an essential tool for eliminating rabies in wild animals. Rigorously applied controls of international transfer of animals including certification of vaccination and quarantine for animals entering rabies-free areas are necessary to prevent re-introduction of rabies.

Although some treatments have been tried including antivirals, interferons, high doses of rabies immunoglobulin, and corticosteroids, none has shown evidence of efficacy. Postexposure treatment after contact with a suspected or confirmed rabid animal may be effective in preventing death; it includes prompt and thorough cleansing of the contaminated site and the early use of rabies vaccine with or without rabies immunoglobulins. For a brief outline of postexposure treatment, see p. 2414.1.

Pre-exposure prophylaxis is recommended in persons at high risk of exposure, either due to their occupation or those travelling in enzootic areas. The main obstacle to mass pre-exposure vaccination appears to be the high cost of cell culture vaccines. See under Pre-exposure Immunisation (p. 2414.1) for outlines of recommended vaccination schedules.

CHOICE OF VACCINES. Many different rabies vaccines are available for human use. Some are derived from nerve tissue of animals, some from avian tissues (duck embryos), and some prepared in cell cultures. The first rabies vaccine was based on attenuated virus from desiccated nerve tissue. Later, inactivated nervous tissue-derived vaccines were prepared from rabid sheep, goat (Semple vaccines) or suckling mouse brains (Feunzalida Palacios vaccine). A complete postexposure treatment course of nerve-tissue vaccine consists of up to 23 injections and is associated with severe neurological reactions and a significant failure rate. WHO therefore strongly recommends that nerve-tissue vaccines should not be used, and that production should be stopped. Cell-derived rabies vaccines were subsequently developed; the human diploid cell rabies vaccine (HDCV) was introduced in 1967 and later less expensive purified chick embryo-cell vaccine (PCECV) and purified Vero-cell rabies vaccines (PVRV) entered use. There appears to be little difference in terms of safety and antigenicity between HDCV, PCECV, and PVRV in recommended regimens. The incidence of severe hypersensitivity reactions should, however, be lower with PVRV and PCECV than with HDCV since the purification process removes most human serum albumin in the cell-growth medium before virus inactivation (see Hypersensitivity, under Adverse Effects and Precautions, p. 2414.3). A purified duck-embryo vaccine (PDEV) provided similar efficacy and safety to vaccines produced from cell cultures, but is no longer manufactured.

There are few data concerning the efficacy of rabies vaccines. It appears that nerve-tissue vaccines afford limited protection after minor exposures to rabies virus, are less effective after head bites, and are of little use after very severe exposures. Failure rates for HDCV, PCECV, and PVRV (including cases with less than the recommended therapy) have been estimated as less than 1 in 80 000 treatments in the USA, Canada, and Europe, 1 in 12 000 to 20 000 in Thailand, and 1 in 30 000 in the remaining tropical countries. Reported failures of these vaccines are usually associated with severe lesions on or near the head and/or errors in treatment, such as deviation from recommendations, incorrect site of vaccine administration, or delay in treatment. WHO recommends a minimum potency of

2.5 international units per intramuscular dose for all cell-derived rabies vaccines.

The cost of cell-derived rabies vaccines is prohibitively high in the developing world. Although the adverse effects of nerve-tissue vaccines preclude their use for pre-exposure prophylaxis, they are still used in some countries for postexposure prophylaxis. WHO is anxious that nerve-tissue vaccines should be replaced with affordable cell-derived vaccines as soon as possible. In the meantime, cost-cutting regimens have been devised for use of cell-derived rabies vaccines by the intradermal route. Rapid immunisation is achieved by the use of several sites of injection; fewer injections are required than with traditional intramuscular regimens.

PRE-EXPOSURE IMMUNISATION. WHO[1,2] has developed guidelines as to who should receive pre-exposure vaccination with rabies vaccines. However, national policies may vary somewhat from that of WHO, depending on the local risk of contracting rabies and the vaccines available; it is generally recommended for use in persons at high risk of infection with rabies virus. Where available, the vaccines produced in cell culture or from purified embryonated eggs are preferred over the vaccines produced in animal tissues (see under Choice of Vaccine, p. 2413.3). WHO recommends[1,2] pre-exposure prophylaxis for persons regularly at high risk of exposure, such as certain laboratory workers, veterinarians, animal handlers, and wildlife officers, and those living in or travelling to areas where rabies is endemic (particularly in children under 15 years of age). The immunisation schedule should preferably consist of 3 injections of a rabies vaccine of potency at least 2.5 international units given on days 0, 7, and either day 21 or 28, but variation of a few days is unimportant. Vaccine should be given into the deltoid area of the arm or for young children into the anterolateral area of the thigh. Titres of virus-neutralising antibodies can be checked in serum samples collected 1 to 3 weeks after the last dose. Those who work with the live virus should have their antibody titres checked every 6 months and if the figure falls below 0.5 international units/mL they should receive a booster.[1,2] Other individuals at continuing risk should have their titres checked every 12 months and a booster given if the titre is below 0.5 international units/mL.[1] Where serological testing is unavailable, a booster vaccination every 5 years may be an acceptable alternative.[2]

WHO also suggests intradermal use of rabies vaccine in doses of 0.1 mL on days 0, 7, and either day 21 or 28 but intramuscular injection is preferable and is mandatory in those taking malaria prophylaxis.

In the UK,[3] the schedule for immunisation (see Uses and Administration, p. 2413.2) is similar to that recommended by WHO.

In the USA, immunisation with a human diploid cell vaccine or a purified chick embryo cell vaccine is carried out similarly to the WHO schedule, with serum-antibody titres determined every 6 months to 2 years, depending upon the level of exposure, and booster doses given as necessary. Vaccines for intradermal use are no longer available in the USA.[4]

1. WHO. *Current WHO guide for rabies pre and post-exposure prophylaxis in humans* (revised December 2007, June 2009). Available at: http://www.who.int/rabies/PEP_prophylaxis_guidelines_June09.pdf (accessed 14/12/09)
2. WHO. Rabies vaccines. WHO position paper. *Wkly Epidem Rec* 2007; **82:** 425–35. Also available at: http://www.who.int/wer/2007/wer8249_50.pdf (accessed 14/12/09) Correction *ibid.* 2008; **83:** 15–16.
3. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 27/08/10)
4. CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; **57** (RR-3): 1–28. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5703.pdf (accessed 14/12/09)

POSTEXPOSURE TREATMENT. WHO guidelines[1,2] emphasise the importance of prompt local treatment for all bite wounds and scratches that may be contaminated with rabies virus and that, depending on the category of animal contact, rabies vaccine on its own or with rabies immunoglobulin should be given. The combination of these measures immediately after exposure is considered to guarantee almost complete protection. Pregnancy and infancy are not contra-indications to postexposure vaccination. These measures should be instituted even in patients who present months after having been bitten.

First aid or local treatment consists of immediate thorough flushing and washing of the wound with water, or soap and water, or detergent followed by the application of alcohol 70% or tincture or aqueous solution of iodine. Medical care may then consist of the instillation of rabies immunoglobulin into the depth of the wound and infiltration around the wound. Ideally the wound should not be sutured, but if suturing is necessary then it is essential that it be preceded by rabies immunoglobulin as above. Antimicrobials and tetanus vaccine may also be given as necessary.

The use of rabies vaccine and of rabies immunoglobulin depends on the category of animal contact. WHO classifies the type of contact with a suspect or rabid animal into 3 categories:

- category I covers touching or feeding of animals and licks on intact skin
- category II covers nibbling of uncovered skin, minor scratches or abrasions without bleeding
- category III covers single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membranes with the animal's saliva, and exposure to bats

Generally no treatment is required for category I contact. Patients who have had category II contact should be given rabies vaccine but the course may be stopped if the contact has been with a cat or dog that remains healthy throughout an observation period of 10 days or if postmortem study of the contact animal shows it to be negative for rabies. Immunocompromised patients with category II contact should also be given rabies immunoglobulin. Patients with category III contact should be given rabies vaccine preceded by rabies immunoglobulin infiltrated around the wound and instilled into it as described above.

There are 2 types of immunoglobulin available; human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose for HRIG is 20 international units/kg and for ERIG products is 40 international units/kg. As much as possible of the dose should be infiltrated into and around the wound, with the remainder being injected intramuscularly into a site remote from that where vaccine was given, such as the anterior thigh.

The potency of rabies vaccines should be at least 2.5 international units per single human dose. For intramuscular vaccination schedules one dose should be given on days 0, 3, 7, 14, and 28 into the deltoid region or, for small children, into the anterolateral area of the thigh. An abbreviated multisite intramuscular schedule (the 2-1-1 regimen) induces an early antibody response and may be particularly effective when postexposure treatment has not included a rabies immunoglobulin. This schedule consists of one dose given in the right arm and one in the left arm on day 0, and one dose intramuscularly into the deltoid region on days 7 and 21.

Intradermal vaccination reduces the volume of injection required and is therefore suited to situations where vaccine or money is in short supply. For intradermal vaccination one dose (0.1 mL) of purified chick embryo-cell or purified Vero-cell vaccine may be given at each of two sites, usually the left and right upper arm, on days 0, 3, 7, and 28. Alternatively, in emergency situations when no rabies immunoglobulin is available, either human diploid cell or purified chick embryo-cell rabies vaccine may be given intradermally in one dose at each of 8 sites on day 0, in one dose at 4 sites on day 7, and subsequently in one dose at one site on days 28 or 30 and 90.

For postexposure treatment of previously vaccinated patients, WHO recommends local treatment of wounds followed by rabies vaccine given on days 0 and 3, either as a standard intramuscular dose or as one intradermal dose per site. No rabies immunoglobulin should be given. Patients who previously received vaccines of unproven potency or who have failed to develop an acceptable rabies neutralising antibody titre should be given full treatment as for those previously unimmunised.

In the UK,[3] rabies immunoglobulin is given if the patient is previously unimmunised and at high risk. Vaccine is given on days 0, 3, 7, 14, and 30 (five doses) in unimmunised persons (although the UK licensed product information for human diploid cell vaccine also recommends a sixth dose on day 90); two doses, one each on day 0 and day 3 are given to previously fully immunised persons.

In the USA, a human diploid-cell vaccine or a purified chick embryo cell vaccine may be used for postexposure treatment.[4] In previously unimmunised individuals, a 5-dose intramuscular regimen similar to that of WHO was formerly recommended,[4] but with increasing evidence of the value of an abbreviated 4-dose regimen[5] the CDC now recommends[6] a 1-mL dose of vaccine intramuscularly on days 0, 3, 7, and 14, with rabies immunoglobulin as in the WHO schedule. In previously immunised individuals, two doses of vaccine are given on days 0 and 3, and rabies immunoglobulin is not required.

1. WHO. *Current WHO guide for rabies pre and post-exposure prophylaxis in humans* (revised December 2007, June 2009). Available at: http://www.who.int/rabies/PEP_prophylaxis_guidelines_June09.pdf (accessed 14/12/09)
2. WHO. Rabies vaccines. WHO position paper. *Wkly Epidem Rec* 2007; **82:** 425–35. Also available at: http://www.who.int/wer/2007/wer8249_50.pdf (accessed 14/12/09) Correction. *ibid.* 2008; **83:** 15–16.
3. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 27/08/10)
4. CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; **57** (RR-3): 1–28. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5703.pdf (accessed 14/12/09)
5. Rupprecht CE, *et al.* Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine* 2009; **27:** 7141–8.
6. CDC/ACIP. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2010; **59** RR-2: 1–9. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5902.pdf (accessed 30/04/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Patients receiving human diploid-cell or purified chick embryo-cell rabies vaccines may have pain, erythema, and induration at the injection site. Systemic reactions including abdominal pain, diarrhoea, nausea and vomiting, headache, chills, dizziness, fever, malaise, convulsions, encephalitis, lymphadenopathy, arthralgia and myalgia, dyspnoea and wheezing, or rash may also occur. Reactions may become more severe with repeated doses. Hypersensitivity reactions including anaphylaxis occur more commonly with vaccines prepared from non-human sources than with human diploid-cell vaccine. However, these reactions have also been associated with the presence of β-propiolactone-altered human albumin in the human diploid-cell vaccine.

Neurological reactions (meningoencephalitis, meningoencephalomyelitis, mononeuritis multiplex, transverse myelitis, or ascending paralysis) have been associated with the use of animal nerve-tissue vaccines. WHO considers that nerve-tissue vaccines should no longer be used. There are only isolated reports of neurological reactions after use of human diploid-cell vaccines.

Patients known to be hypersensitive to a particular vaccine or its components should be given an alternative product if available, although there are no absolute contra-indications to postexposure treatment. Pre-exposure prophylaxis should be delayed in patients with febrile illness until fever has resolved.

Effects on the nervous system. Rabies vaccines were originally prepared from infected animal brain tissue. The incidence of neurological complications with these vaccines was about 1 in 1 600, with an overall mortality of 15%.[1] Neurological adverse effects were attributed to myelin basic proteins present in these vaccines.[1-4] Subsequently, a highly immunogenic rabies vaccine was produced from the relatively myelin-free nerve tissue of suckling mice. However, neuroparalytic complications were reported in about 1 in 8 000 persons treated.[1,5] Most of these complications were of a Guillain-Barré-type illness, and had a fatality rate of 20 to 50%.[1]

Neuroparalytic reactions occur less frequently (1 in 32 000 persons treated) with vaccines prepared from duck embryo tissue;[1,5] however, these vaccines are no longer manufactured.[5]

Cell-derived rabies vaccines have been developed with better safety profiles.[1,5,6]

Isolated cases of neuroparalytic reactions have been reported with human diploid-cell or chick embryo-cell vaccines, mostly manifesting as a Guillain-Barré-type illness.[1,7-10]

1. Bernard KW, *et al.* Neuroparalytic illness and human diploid cell rabies vaccine. *JAMA* 1982; **248:** 3136–8.
2. WHO. WHO expert committee on rabies: eighth report. *WHO Tech Rep Ser 824* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_824.pdf (accessed 15/10/07)
3. Kulkarni V, *et al.* Biphasic demyelination of the nervous system following anti-rabies vaccination. *Neurol India* 2004; **52:** 106–8.
4. Siddiqui A, *et al.* Guillain-Barre syndrome occurring after rabies vaccination. *J Pakistan Med Assoc* 2005; **55:** 87–8.
5. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; **77:** 109–19.
6. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2004. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)
7. Knittel T, *et al.* Guillain-Barré syndrome and human diploid cell rabies vaccine. *Lancet* 1989; **i:** 1334–5.
8. Tornatore CS, Richert JR. CNS demyelination associated with diploid cell rabies vaccine. *Lancet* 1990; **335:** 1346–7.
9. Mortiere MD, Falcone AL. An acute neurologic syndrome temporally associated with postexposure treatment of rabies. *Pediatrics* 1997; **100:** 720–1.
10. Chakravarty A. Neurologic illness following post-exposure prophylaxis with purified chick embryo cell antirabies vaccine. *J Assoc Physicians India* 2001; **49:** 927–8.

Hypersensitivity. Systemic hypersensitivity reactions[1] have occurred in up to 6% of patients receiving booster immunisation with human diploid-cell rabies vaccine (HDCV), with onset after 2 to 21 days. Presenting features include generalised or pruritic rash or urticaria, angioedema, arthralgias, fever, nausea, and vomiting. These reactions have been linked to the presence of β-propiolactone-altered human albumin in HDCV. A lower risk of hypersensitivity reaction should exist with newer cell-derived vaccines that contain little or no human albumin, such as purified chick embryo cell rabies vaccines (PCECV) or purified Vero-cell rabies vaccines (PVRV). A review[2] noted that patients given booster immunisation with PCECV did not generally have systemic hypersensitivity reactions; data from the US Vaccine Adverse Event

Reporting System covering 336 reported adverse events to PCECV between October 1997 and December 2005 included only 20 reports classified as possible anaphylaxis, of which only 3 were considered serious.[3] In a comparison study[4] involving 400 children, patients receiving a new chromatographically purified Vero-cell vaccine were found to have a lower incidence of systemic hypersensitivity (0.7%) than those in the HDCV group (1.2%) after booster immunisation.

1. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; **77:** 109–19.
2. Dreesen DW. A global review of rabies vaccines for human use. *Vaccine* 1997; **15** (suppl): S2–S6.
3. Dobardzic A, *et al.* Safety review of the purified chick embryo cell rabies vaccine: data from the Vaccine Adverse Event Reporting System (VAERS), 1997–2005. *Vaccine* 2007; **25:** 4244–51.
4. Sabchareon A, *et al.* A new Vero cell rabies vaccine: results of a comparative trial with human diploid cell rabies vaccine in children. *Clin Infect Dis* 1999; **29:** 141–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rabies vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Spongiform encephalopathies. Possible transmission of Creutzfeldt-Jakob disease associated with sheep-brain rabies vaccine has been reported from India.[1] It was suggested that transmission of the abnormal prion protein from sheep with scrapie might be implicated.

1. Arya SC. Acquisition of spongiform encephalopathies in India through sheep-brain rabies vaccination. *Natl Med J India* 1992; **4:** 311–12.

Interactions

As for vaccines in general, p. 2375.3.

Antimalarials. Studies have suggested that continuous antimalarial chemoprophylaxis with *chloroquine* during primary immunisation with human diploid-cell rabies vaccine, given intradermally for pre-exposure prophylaxis, may be associated with a poor antibody response.[1,2] WHO[3] recommends that people currently taking malaria prophylaxis or those unable to complete the 3-dose rabies pre-exposure regime before starting malaria prophylaxis should receive pre-exposure rabies vaccination by the intramuscular route instead.

1. Taylor DN, *et al.* Chloroquine prophylaxis associated with a poor antibody response to human diploid cell rabies vaccine. *Lancet* 1984; **i:** 1405.
2. Pappaioanou M, *et al.* Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *N Engl J Med* 1986; **314:** 280–4.
3. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2005. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Verorab; ***Austral.***: Rabipur; ***Austria***: Rabipur; ***Belg.***: Rabipur; ***Braz.***: HDCV†; Vacina Anti-Rabica Humana†; ***Canad.***: Imovax Rabies; RabAvert; ***Chile***: Lyssavac N; Verorab; ***China***: Fu Er Bo (福尔博); Rabipur (瑞必补尔); Verorab (维尔博); Wu Sheng Wang Ning (武生旺宁); ***Cz.***: Rabipur; Verorab; ***Denm.***: Rabies-Imovax; Rabipur; ***Fin.***: Rabies-Imovax; ***Fr.***: Rabipur; ***Ger.***: Rabipur; Tollwut-Impfstoff (HDC); ***Hong Kong***: Verorab; ***India***: Imovax Rabies; Rabipur; Rabivax; ***Indon.***: Verorab; ***Israel***: Rabipur; Verorab; ***Ital.***: Imovax Rabbia†; Rabipur; ***Malaysia***: Verorab; ***Neth.***: Rabipur; ***Norw.***: Rabies-Imovax; Rabipur; ***NZ***: Verorab; ***Philipp.***: Abhayrab; Indirab; Lyssavac N; Rabiesvax; Rabipur; Speeda; V-Rab; Verorab; ***Pol.***: Verorab; ***Port.***: Rabipur; ***Rus.***: Rabipur (Рабипур); ***S.Afr.***: Rabipor; Verorab; ***Singapore***: Rabipur; ***Spain***: Rabipur; Vacuna Antirrabica; ***Swed.***: Rabies-Imovax; ***Switz.***: Rabipur; ***Thai.***: Abhayrab; Lyssavac N†; Rabipur; Rabivax; Speeda; Verorab; ***Turk.***: HDCV†; Rabivac; ***UK***: Rabipur; ***USA***: Imovax Rabies; RabAvert; ***Venez.***: Verorab.

Pharmacopoeial Preparations

Ph. Eur.: Rabies Vaccine for Human Use Prepared in Cell Cultures.

Raxibacumab *(USAN, rINN)*

Raxibacumabum; Раксибакумаб.

Immunoglobulin G1, anti-(anthrax protective antigen) (human monoclonal PA heavy chain), disulfide with human monoclonal PA λ-chain, dimer.

CAS — 565451-13-0.

UNII — 794PGL549S.

NOTE. The name ABthrax has been used as a trade mark for raxibacumab.

Uses and Administration

Raxibacumab is a monoclonal antibody that neutralises the toxin secreted by *Bacillus anthracis* by binding to its protective antigen. Raxibacumab has not been tested in humans with anthrax; its efficacy is based on *animal* studies. It is used with antibacterials for the treatment of inhalation anthrax (p. 173.2), and for prophylaxis where no alternative therapy exists.

Raxibacumab is given intravenously as a single dose of 40 mg/kg. It is diluted using sodium chloride 0.9% to a final volume of 250 mL and given over 2 hours and 15 minutes. The infusion rate is 15 mL/hour for the first 20 minutes and then increased to 125 mL/hour for the remainder of the dose. Diphenhydramine should be given up to 1 hour before the infusion to reduce the incidence and severity of infusion reactions; however, if a reaction occurs the infusion may be slowed or interrupted.

For use in children, see below.

References.

1. Mazumdar S. Raxibacumab. *MAbs* 2009; **1:** 531–8.
2. Migone T-S, *et al.* Raxibacumab for the treatment of inhalational anthrax. *N Engl J Med* 2009; **361:** 135–44.
3. Anonymous. Raxibacumab for anthrax. *Med Lett Drugs Ther* 2013; **55:** 27–8.

Administration in children. Raxibacumab is given intravenously as a single dose based on body-weight:

- less than or equal to 15 kg: 80 mg/kg
- greater than 15 kg to 50 kg: 60 mg/kg
- greater than 50 kg: the usual adult dose is given, see above

Raxibacumab is diluted with sodium chloride 0.45% or 0.9% to a volume ranging from 7 to 250 mL depending on the weight of the child. The infusion is given over about 2 hours and 15 minutes; it is given slowly for the first 20 minutes and then the infusion rate may be increased for the remainder of the dose. Diphenhydramine should be given up to 1 hour before the infusion; if a reaction does occur then the infusion should be slowed or interrupted.

Adverse Effects and Precautions

Raxibacumab commonly causes infusion reactions including rash, urticaria, and pruritus, and it is recommended that diphenhydramine is given up to 1 hour before treatment. Other common adverse effects are pain in the extremities and somnolence. Less common effects include anaemia, leucopenia, lymphadenopathy, palpitations, flushing, hypertension, peripheral oedema, vasovagal syncope, vertigo, fatigue, insomnia, back pain, and muscle spasms. Increases in blood amylase and creatine phosphokinase concentrations, and prolonged prothrombin time have been seen.

Pharmacokinetics

There is some tissue distribution of raxibacumab after intravenous infusion, but it does not cross the blood-brain barrier. Raxibacumab has a half-life of about 20 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Raxibacumab Injection.

Respiratory Syncytial Virus Immunoglobulins

Inmunoglobulinas contra el virus sincitial respiratorio.

Palivizumab *(BAN, rINN)*

MEDI-493; Palivitsumabi; Palivizumabum; Паливизумаб.

Immunoglobulin G 1 (human-mouse monoclonal MEDI-493 γ1-chain antirespiratory syncytial virus protein F), disulfide with human-mouse monoclonal MEDI-493 κ-chain, dimer.

CAS — 188039-54-5.

ATC — J06BB16.

UNII — DQ448MW7KS.

Uses and Administration

Respiratory syncytial virus immunoglobulin (RSVI) is available in some countries for the passive immunisation of infants against lower respiratory-tract infections caused by RSV. It is prepared from the pooled plasma of adults selected for high titres of antibodies that neutralise the virus. Each mL of RSVI contains about 50 mg of protein.

In the USA, children under 2 years of age with chronic lung disease of prematurity (bronchopulmonary dysplasia) or a history of premature birth have received a prophylactic intravenous infusion once a month during the RSV season (typically November to April or early May). The drug has been given in a dose of up to 750 mg/kg at an initial rate of 75 mg/kg per hour for 15 minutes, followed by 180 mg/kg per hour until the end of the infusion.

Palivizumab, a humanised monoclonal antibody to RSV, is available in some countries for the prevention of RSV in premature infants (born at 35 weeks of gestation or less) and in children less than 2 years of age needing treatment for chronic lung disease of prematurity, as well as those with haemodynamically significant congenital heart disease. It is used intramuscularly in a dose of 15 mg/kg monthly during the RSV season. Ideally the first dose should be given before the start of the RSV season; up to 5 doses are usually given. Children undergoing cardiac bypass should be given an extra dose of palivizumab as soon as they are stable after surgery; doses are subsequently resumed monthly thereafter.

The American Academy of Pediatrics has issued revised indications for the use of palivizumab which no longer include recommendations for the use of respiratory syncytial virus immunoglobulin (RSVI).[1] Palivizumab prophylaxis should be considered for infants younger than 2 years of age with chronic lung disease of prematurity (bronchopulmonary dysplasia) who have required medical therapy for their condition within 6 months of the anticipated start of the RSV season. Infants born before 32 weeks 0 days gestation may also benefit from prophylaxis even if they do not have chronic lung disease. Palivizumab, may in addition be given to children under 2 years of age with haemodynamically significant congenital heart disease. Although prophylaxis has been shown to reduce hospitalisation for infants born between 32 and 35 weeks gestation, the cost for this large group of infants should be considered carefully. In general, the AAP recommends a maximum of 5 doses for all infants with haemodynamically significant congenital heart disease, chronic lung disease, or birth before 32 weeks 0 days gestation. In infants with a gestational age of between 32 weeks 0 days and 34 weeks 6 days who do not have haemodynamically significant congenital heart disease or chronic lung disease, prophylaxis has been restricted to those at higher risk; AAP now recommends a maximum of 3 doses in this group if they are born within 3 months of or during the RSV season and either attend child care or one or more other children in the household are under 5 years of age. Doses are only recommended while children are below 3 months of age.

In the UK, the Joint Committee on Vaccination and Immunisation[2] recommends a maximum of 5 doses of palivizumab in certain classes of premature infant depending on their chronological age at the start of the RSV season and gestational age, as follows:

- those with chronic lung disease
  - born at less than 35 weeks of gestation and with a chronological age of 1 to < 1.5 months
  - born at 32 weeks of gestation or less and with a chronological age of 1.5 to 3 months
  - born at 28 weeks of gestation or less and with a chronological age of 3 to 6 months
  - born at 24 weeks of gestation or less and with a chronological age of 6 to 9 months
- haemodynamically significant, acyanotic congestive heart disease
  - born at 32 weeks of gestation or less and with a chronological age of < 1.5 months
  - born at 30 weeks of gestation or less and with a chronological age of 1.5 to 3 months
  - born at 26 weeks of gestation or less and with a chronological age of 3 to 6 months

They also advise that palivizumab be given during the RSV season to children under the age of 24 months who have severe combined immunodeficiency syndrome (until immune reconstituted) and to long-term ventilated children aged less than 12 months (or less than 24 months with additional co-pathology) at the start of the RSV season.

Both palivizumab and RSVI have been shown to decrease the risk of severe RSV infection in high-risk infants and children. Palivizumab is preferred over RSVI for most high-risk children because of its comparative ease of administration, safety, and efficacy (the latter is no longer available in the USA). Monthly use of palivizumab during the RSV season results in a 45 to 55% reduction in hospitalisation. Although palivizumab is usually preferred, RSVI may also decrease the incidence of other respiratory-tract infections in addition to those caused by RSV, and this may be of benefit for infants younger than 6 months who are not eligible for influenza immunisation and those with severe pulmonary disease who may be more prone to other respiratory-tract infections. Palivizumab has not been shown to affect the rate of hospitalisation for non-RSV infections or the incidence of otitis media.

1. Committee on Infectious Diseases of the American Academy of Pediatrics. Policy statements–modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics* 2009; **124:** 1694–1701. Also available at: http://pediatrics.aappublications.org/cgi/reprint/124/6/1694 (accessed 17/12/09)
2. DoH. Joint Committee on Vaccination and Immunisation statement on immunisation for respiratory syncytial virus (issued 11th October 2010). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_120395.pdf (accessed 30/11/10)

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies palivizumab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for immunoglobulins in general, p. 2373.2.

There is some evidence that antibody responses to diphtheria, tetanus, pertussis, and Haemophilus influenzae vaccines may be reduced in infants also receiving respiratory syncytial virus immunoglobulins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Synagis; ***Austral.***: Synagis; ***Austria***: Synagis; ***Belg.***: Synagis; ***Braz.***: Synagis; ***Canad.***: Synagis; ***Chile***: Synagis; ***Cz.***: Synagis; ***Denm.***: Synagis; ***Fin.***: Synagis; ***Fr.***: Synagis; ***Ger.***: Synagis; ***Gr.***: Synagis; ***Hong Kong***: Synagis; ***Hung.***: Synagis; ***Irl.***: Synagis; ***Israel***: Abbosynagis; ***Ital.***: Synagis; ***Jpn***: Synagis; ***Malaysia***: Synagis; ***Mex.***: Synagis; ***Neth.***: Synagis; ***Norw.***: Synagis; ***NZ***: Synagis; ***Pol.***: Synagis; ***Port.***: Synagis; ***Rus.***: Synagis (Синагис); ***S.Afr.***: Synagis; ***Singapore***: Synagis; ***Spain***: Synagis; ***Swed.***: Synagis; ***Switz.***: Synagis; ***Turk.***: Synagis; ***UK***: Synagis; ***USA***: RespiGam†; Synagis; ***Venez.***: Synagis.

Respiratory Syncytial Virus Vaccines

Vacunas del virus sincitial respiratorio.

Profile

Vaccines containing RSV protein subunit are being studied for active immunisation.

Development of an effective and safe vaccine against RSV has been hampered by several factors.[1-3] The target population for a vaccine is mainly young infants who may not respond adequately to vaccination owing to the antigenic diversity of RSV, immunological immaturity, or the presence of maternal antibodies. In the early 1960s, a formalin inactivated respiratory syncytial virus vaccine known as FI-RSV (also sometimes called Lot 100) was tested in infants and children aged 2 months to 7 years but failed to protect against subsequent infection with wild-type virus; it also led to a catastrophically exaggerated clinical response to wild-type virus in infants who were naive to RSV before vaccination, resulting in hospitalisation for the majority of recipients and 2 fatalities. Since that time, some candidate vaccines have subsequently been developed including live attenuated virus and viral protein subunit vaccines.[1,2] Several of the live attenuated vaccine candidates have been investigated in humans but results have generally been disappointing. More recently, genetically engineered live attenuated vaccine candidates have been generated, and some are currently being investigated in clinical studies.[1,2]

Subunit vaccines are composed of the F and G glycoproteins from RSV since these are the glycoproteins that induce antibody responses.[1,2] They are most likely to be of use in older persons and in high-risk children and might also be used for maternal immunisation. A chimeric FG fusion protein vaccine was evaluated in phase I studies but is no longer in development.

1. Durbin AP, Karron RA. Progress in the development of respiratory syncytial virus and parainfluenza virus vaccines. *Clin Infect Dis* 2003; **37:** 1668–77.
2. Kneyber MCJ, Kimpen JLL. Advances in respiratory syncytial virus vaccine development. *Curr Opin Investig Drugs* 2004; **5:** 163–70.
3. Power UF. Respiratory syncytial virus (RSV) vaccines—two steps back for one leap forward. *J Clin Virol* 2008; **41:** 38–44.

Rift Valley Fever Vaccines

Vacunas de la fiebre del valle del Rift.

Profile

An inactivated rift valley fever vaccine has been developed for the active immunisation of persons at high risk of contracting the disease.

Rotavirus Vaccines

Vacunas de rotavirus.
ATC — J07BH01; J07BH02.

Pharmacopoeias. In *Eur* (see p. vii).

Ph. Eur. 8: (Rotavirus Vaccine (Live, Oral); Vaccinum Rotaviri Vivum ad Peroralia). A preparation of one or more suitable virus serotypes, grown in an approved cell substrate and presented in a form suitable for oral administration. The vaccine is a clear liquid or it may be a freeze-dried preparation to be reconstituted immediately before use, as stated on the label, to give a slightly turbid liquid. The vaccine ready for administration may be coloured owing to the presence of a pH indicator. The vaccine is formulated so as to avoid inactivation by gastric fluids. It should be stored at 2 degrees to 8 degrees, and be protected from light.

Uses and Administration

Several live oral rotavirus vaccines for use in the prevention of childhood diarrhoea have been developed and some are now licensed. Since April 2009, the WHO Strategic Advisory Group of Experts (SAGE) on immunisation has recommended that rotavirus vaccines be included in all national childhood immunisation programmes.

A live attenuated oral monovalent rotavirus vaccine (based on the human RIX4414 strain) is available in some countries. Two doses are given, the first at 6 weeks of age onwards and the subsequent dose at least 4 weeks later; the course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks. A live oral pentavalent reassortant rotavirus vaccine (based on human and bovine strains) is also available in the USA. Three doses are given, the first at 6 to 12 weeks of age and the two subsequent doses at 4- to 10-week intervals; the third dose should not be given after 32 weeks of age.

A live oral tetravalent rotavirus vaccine (RRV-TV) was formerly available in the USA but was withdrawn by the manufacturer in October 1999 after reports of intussusception associated with its use.

Guidelines and recommendations.

1. DoH. *Immunisation Against Infectious Disease* 2006 (updated 14th March, 2013): "The Green Book". Available at: https://www.gov.uk/government/publications/green-book-the-complete-current-edition (accessed 23/05/13)
2. CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009; **58** (RR-2): 1–25. Correction. *ibid.* 2010; **59:** 1074. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5802.pdf (accessed 23/05/13)
3. Committee on Infectious Diseases. American Academy of Pediatrics. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics* 2009; **123:** 1412–20. Also available at: http://pediatrics.aappublications.org/cgi/reprint/123/5/1412 (accessed 23/05/13)
4. WHO. Rotavirus vaccines: WHO position paper–January 2013. *Wkly Epidem Rec* 2013; **88:** 49–64. Also available at: http://www.who.int/wer/2013/wer8805.pdf (accessed 23/05/13)

References.

1. Vesikari T, *et al.* Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; **354:** 23–33.
2. Ruiz-Palacios GM, *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; **354:** 11–22.
3. Buttery JP, Kirkwood C. Rotavirus vaccines in developed countries. *Curr Opin Infect Dis* 2007; **20:** 253–8.
4. Cunliffe N, Nakagomi O. Introduction of rotavirus vaccines in developing countries: remaining challenges. *Ann Trop Paediatr* 2007; **27:** 157–67.
5. Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev* 2008; **21:** 198–208.
6. Desselberger U, *et al.* Rotaviruses and rotavirus vaccines. *Br Med Bull* 2009; **90:** 37–51.
7. Ward RL, Bernstein DI. Rotarix: a rotavirus vaccine for the world. *Clin Infect Dis* 2009; **48:** 222–8.
8. Plosker GL. Pentavalent rotavirus vaccine (RotaTeq): a review of its use in the prevention of rotavirus gastroenteritis in Europe. *Drugs* 2010; **70:** 1165–88.
9. Soares-Weiser K, *et al.* Vaccines for preventing rotavirus diarrhoea: vaccines in use. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2012 (accessed 23/05/13).

Vaccine development. Rotaviruses are an important cause of severe diarrhoea in both developed and developing countries (see Gastro-enteritis, p. 951.3); rates of illness are similar in both and improvement in water quality and general hygiene does not have much effect on viral transmission. The disease infects almost all children before the age of 5 years but is most severe among children 4 to 23 months of age.[1] Human rotavirus diarrhoea is caused by group A, B, or C rotaviruses.[2] While an initial infection does not produce complete immunity, it does appear to be protective against further severe gastroenteritis. Vaccination therefore aims to produce a similar effect.[1,3] Development of a suitable vaccine has been made difficult by the diversity of rotaviruses.[2] Initial attempts at vaccine development used single bovine or rhesus monkey strains but these were associated with variable efficacy and adverse effects.[4-6]

To overcome these problems reassortant rotavirus (RRV) strains were constructed. These combined animal rotavirus strains with human rotavirus genes coding for serotype-specific antigens, enabling polyvalent vaccines to be produced against the major rotavirus serotypes causing disease. Some such candidate vaccines are under development[7] and some are now licensed.[8]

1. CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009; **58** (RR-2): 1–25. Correction. *ibid.* 2010; **59:** 1074. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5802.pdf (accessed 17/12/09)
2. Anonymous. Puzzling diversity of rotaviruses. *Lancet* 1990; **335:** 573–5.
3. Committee on Infectious Diseases. American Academy of Pediatrics. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics* 2009; **123:** 1412–20. Also available at: http://pediatrics.aappublications.org/cgi/reprint/123/5/1412 (accessed 17/12/09)
4. Levine MM. Modern vaccines: enteric infections. *Lancet* 1990; **335:** 958–61.
5. Bernstein DI, *et al.* Evaluation o f WC3 rotavirus vaccine and correlates of protection in healthy infants. *J Infect Dis* 1990; **162:** 1055–62.
6. Flores J, *et al.* Protection against severe rotavirus diarrhoea by rhesus rotavirus vaccine in Venezuelan infants. *Lancet* 1987; **i:** 882–4.
7. Glass RI, *et al.* The future of rotavirus vaccines: a major setback leads to new opportunities. *Lancet* 2004; **363:** 1547–50.
8. Heaton PM, Ciarlet M. Vaccines: the pentavalent rotavirus vaccine: discovery to licensure and beyond. *Clin Infect Dis* 2007; **45:** 1618–24.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

The most common adverse effects reported in subjects receiving rotavirus vaccines (attenuated monovalent human strain or pentavalent reassortant rotavirus vaccine) are fever, fatigue, irritability, and gastrointestinal disturbances. Otitis media, nasopharyngitis, bronchospasm, and haematochezia (blood in the stools) have also been reported with the pentavalent vaccine. A few cases of Kawasaki disease have been reported with the pentavalent vaccine but no causal relationship has been established.

There has been much debate on the causal role of rotavirus vaccines for intussusception (see below); cases have been reported since marketing.

Both the attenuated monovalent human strain vaccine and the pentavalent reassortant vaccine are contra-indicated in infants with a history of intussusception, with congenital malformations of the gastrointestinal tract, or with severe combined immunodeficiency (SCID) disorder. Caution is also generally advised in those with gastrointestinal illnesses, growth retardation, or who are immunocompromised, and use may be postponed in children suffering from diarrhoea or vomiting. Use of a rotavirus vaccine should be carefully considered before being given to infants with a close family contact who is immunocompromised; if given precautions should be taken to avoid transmission of any excreted vaccine virus.

Intussusception. A live oral tetravalent vaccine (RRV-TV) became available in the USA in August 1998 but was withdrawn from the market by the manufacturer in October 1999 after reports of intussusception (a condition when part of the intestine prolapses into the lumen of an adjacent part causing an obstruction). From September 1998 until July 1999, 15 patients with intussusception had been reported to the Vaccine Adverse Event Reporting System (VAERS), 12 of whom developed symptoms within a week of vaccination.[1] While this evidence was considered inconclusive, further studies were expected to clarify the risks associated with routine use of this vaccine. One such study,[2] in which 429 infants with intussusception were retrospectively analysed, found that 74 (17.2%) had received RRV-TV compared with 226 of 1763 controls (12.8%) and concluded that there was evidence of a causal relationship with the vaccine. Another retrospective study,[3] however, found that there was no evidence of an increase in hospital admissions due to intussusception during the period of RRV-TV availability and recommended that a large, randomised, double-blind vaccine study be performed to determine the absolute risk. Further analysis of the incidence of intussusception associated with RRV-TV has prompted discussion as to whether the absolute risk might in fact be sufficiently low that withholding the vaccine results in greater mortality than would be caused by intussusception.[4] Reassessment of the data on RRV-TV and intussusception has suggested that the risk for intussusception was age-dependent; relative risk for intussusception following the first dose of RRV-TV increased with increasing age.[5,6] However, WHO Global Advisory Committee on Vaccine Safety found that there was insufficient evidence available to determine whether use of RRV-TV before 60 days of age was associated with a lower risk for intussusception but confirmed the association of a high risk of intussusception in infants immunised after day 60.[7] Such considerations have implications for the ongoing evaluation of other candidate live attenuated rotavirus vaccines in that, should cases of intussusception occur, a decision might be required as to what constitutes an acceptable rate.[4]

From February 2006 until February 2007, 35 patients with confirmed intussusception had been reported to VAERS after vaccination with the pentavalent reassortant vaccine; 17 of whom developed symptoms within 21 days of vaccination, including 11 that occurred within 7 days of vaccination. However, this number of cases is not higher than the age adjusted background rates for intussusception.[8]

The safety of the currently marketed mono- and pentavalent live vaccines has been reviewed.[9]

1. CDC. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR* 1999; **48:** 577–81.
2. Murphy TV, *et al*. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001; **344:** 564–72. Correction. *ibid.*; 1564.
3. Simonsen L, *et al*. Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception. *Lancet* 2001; **358:** 1224–9.
4. Murphy BR, *et al*. Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. *J Infect Dis* 2003; **187:** 1301–8.
5. Rothman KJ, *et al*. Age dependence of the relation between reassortant rotavirus vaccine (RotaShield) and intussusception. *J Infect Dis* 2006; **193:** 898.
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7. WHO. Global Advisory Committee on Vaccine Safety, 1–2 December 2005. *Wkly Epidem Rec* 2006; **81:** 15–19.
8. CDC. Postmarketing monitoring of intussusception after RotaTeq® vaccination—United States, February 1, 2006–February 15, 2007. *MMWR* 2007; **56:** 218–22.
9. Patel MM, *et al*. Intussusception and rotavirus vaccination: a review of the available evidence. *Expert Rev Vaccines* 2009; **8:** 1555–64.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rotarix; RotaTeq; ***Austral.***: Rotarix; RotaTeq; ***Austria***: Rotarix; RotaTeq; ***Belg.***: Rotarix; RotaTeq; ***Canad.***: Rotarix; RotaTeq; ***Chile***: Rotarix; ***China***: Luo Te Wei (罗特威); ***Cz.***: Rotarix; RotaTeq; ***Denm.***: Rotarix; RotaTeq†; ***Fr.***: Rotarix; RotaTeq; ***Ger.***: Rotarix; RotaTeq; ***Gr.***: Rotarix; RotaTeq; ***Hong Kong***: Rotarix; RotaTeq; ***Hung.***: Rotarix; RotaTeq; ***Irl.***: Rotarix; RotaTeq; ***Israel***: Rotarix; RotaTeq; ***Ital.***: Rotarix†; RotaTeq; ***Jpn***: Rotarix; RotaTeq; ***Malaysia***: Rotarix; RotaTeq; ***Mex.***: Rotarix; ***Neth.***: Rotarix; RotaTeq; ***Norw.***: Rotarix; RotaTeq; ***NZ***: Rotarix; RotaTeq; ***Philipp.***: Rotarix; RotaTeq; ***Pol.***: Rotarix; RotaTeq; ***Port.***: Rotarix; RotaTeq; ***S.Afr.***: Rotarix; ***Singapore***: Rotarix; RotaTeq; ***Spain***: Rotarix†; RotaTeq; ***Swed.***: Rotarix; RotaTeq; ***Switz.***: Rotarix; ***Thai.***: Rotarix; RotaTeq; ***Turk.***: Rotarix; RotaTeq; ***UK***: Rotarix; ***Ukr.***: Rotarix (Ротарикс); ***USA***: Rotarix; RotaTeq; ***Venez.***: Rotarix.

Rubella Immunoglobulins

Inmunoglobulinas contra la rubéola.
ATC — J06BB06.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Rubella Immunoglobulin; Immunoglobulinum Humanum Rubellae). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the rubella virus. Normal immunoglobulin may be added. It contains not less than 4500 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Uses and Administration

Rubella immunoglobulins may be used for passive immunisation against rubella (German measles). They have been used to prevent or modify rubella in susceptible persons.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Human Rubella Immunoglobulin.

Rubella Vaccines

Vacunas de la rubéola.
ATC — J07BJ01.
UNII — 52202H034Z (rubella virus live antigen); U751HEX436 (rubella virus antigen).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Rubella Vaccine (Live); Vaccinum Rubellae Vivum). A freeze-dried preparation of a suitable live attenuated strain of rubella virus grown in human diploid cell cultures. It is reconstituted immediately before use. The cell-culture medium may contain a permitted antibacterial at the smallest effective concentration, and a suitable stabiliser may be added to the bulk vaccine. The final vaccine contains not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Rubella may be used on the label.

Uses and Administration

Rubella vaccines are used for active immunisation against rubella (German measles). The symptoms of rubella infection are generally mild except in the early stages of pregnancy when it leads to fetal damage in most infants.

For primary immunisation combined measles, mumps, and rubella vaccine (p. 2400.2) is usually given. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Women of child-bearing age should also be vaccinated with the combined vaccine if they are seronegative; women who are found to be seronegative during pregnancy should be vaccinated in the early postpartum period. Effective precautions against pregnancy must be observed for at least one month after vaccination. To avoid the risk of transmitting rubella to pregnant patients, all health service staff, both male and female, should be screened and those found to be seronegative should be vaccinated.

In some countries, a single-antigen rubella vaccine has been used although combined vaccines are usually preferred.

References.

1. WHO. Rubella vaccines: WHO position paper. *Wkly Epidem Rec* 2000; **75:** 161–69. Also available at: http://www.who.int/immunization/wer7520rubella%20_May00_position_paper.pdf (accessed 30/06/10)

Adverse Effects

As for vaccines in general, p. 2375.1.

Generally, adverse effects have not been severe. Those occurring most commonly are rashes, pharyngitis, fever, and lymphadenopathy; arthralgia and arthritis may also occur. Thrombocytopenia (including immune thrombocytopenia) has been reported rarely.

Effects on bones and joints. Although acute arthralgia or arthritis occurs in up to 30% of women after rubella vaccination,[1] a retrospective analysis found no evidence of an increased risk of chronic arthropathies.[2]

1. Tingle AJ, *et al*. Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet* 1997; **349:** 1277–81.
2. Ray P, *et al*. Risk of chronic arthropathy among women after rubella vaccination. *JAMA* 1997; **278:** 551–6.

Effects on hearing. For a report of irreversible sensorineural deafness associated with use of measles and rubella vaccine, see p. 2400.3.

Effects on the nervous system. For a report of optic neuritis in 2 children after use of measles and rubella vaccine, see under Adverse Effects of Measles and Rubella Vaccines, p. 2400.1.

Precautions

As for vaccines in general, p. 2375.2.

Rubella vaccines should not be given during pregnancy. In the UK it is recommended that patients should be advised not to become pregnant within 1 month of vaccination. However, no case of congenital rubella syndrome has been reported after the inadvertent use of rubella vaccines shortly before or during pregnancy and there is no evidence that the vaccines are teratogenic. Inadvertent use of rubella vaccines during pregnancy should not therefore result in a recommendation to terminate the pregnancy. There is no risk to a pregnant woman from contact with recently vaccinated persons as the vaccine virus is not transmitted.

Rubella vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Vaccines may contain traces of neomycin and/or polymyxin and should therefore not be given to individuals with a history of anaphylaxis to these antibacterials.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rubella vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Since 1971 the US CDC has followed up women given rubella vaccines within 3 months before or after conception.[1] Up to 1979 vaccines containing either the Cendehill or HPV-77 strains of rubella virus were available. None of the 290 infants born to the 538 women given these vaccines had defects indicative of congenital rubella syndrome; this included 94 live-born infants of women who were known to be susceptible to rubella before receiving the vaccine. In 1979 a rubella vaccine containing the Wistar RA 27/3 strain was introduced. None of 212 infants born live to 254 women known to be susceptible to rubella and who had received the RA 27/3 rubella vaccine from 1979 to 1988 had defects indicative of congenital rubella syndrome. These results are consistent with experiences in Germany[2] and the UK.[3,4] However, because of evidence that rubella vaccine viruses can cross the placenta and infect the fetus a theoretical risk to the fetus cannot be completely ruled out.[1] Thus in both the UK and USA pregnancy is considered a contra-indication to rubella vaccination, and patients are also advised not to become pregnant within one month of vaccination. However, in neither country is termination of pregnancy recommended if the vaccine is inadvertently given during pregnancy.

1. Anonymous. Rubella vaccination during pregnancy—United States, 1971–1988. *JAMA* 1989; **261:** 3374–83.
2. Enders G. Rubella antibody titers in vaccinated and nonvaccinated women and results of vaccination during pregnancy. *Rev Infect Dis* 1985; **7** (suppl 1): S103–S107.
3. Sheppard S, *et al*. Rubella vaccination and pregnancy: preliminary report of a national survey. *BMJ* 1986; **292:** 727.
4. Tookey PA, *et al*. Rubella vaccination in pregnancy. *Commun Dis Rep* 1991; **1**(review 7): R86–R88.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rudivax; ***Austral.***: Ervevax†; Meruvax II; ***China***: Rudivax (护贝法); ***Fr.***: Rudivax; ***Gr.***: Rubeaten; Vaccin Rubeole; ***India***: R-Vac; ***Israel***: Rudivax; ***Mex.***: Ervevax†; ***NZ***: Ervevax; ***Port.***: Rudivax†; ***Rus.***: Ervevax (Эрвевакс)†; Rudivax (Рудивакс); ***S.Afr.***: Rudivax†; ***UK***: Almevax; ***USA***: Meruvax II†.

Pharmacopoeial Preparations
Ph. Eur.: Rubella Vaccine (Live).

Rubella and Mumps Vaccines

Vacunas de la rubéola y la parotiditis; Vacunas de la rubéola y las paperas.
ATC — J07BJ51.

Uses and Administration

Rubella and mumps vaccines have been used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (p. 2400.2) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Mumps Vaccines, p. 2402.3, and Rubella Vaccines, above.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Biavax II†.

Schistosomiasis Vaccines

Bilharzia Vaccines; Vacunas de la esquistosomiasis.

Profile

Vaccines against schistosomiasis are under development.

Despite attempts since the 1960s, development of an effective vaccine against schistosomiasis has proved difficult.[1,2] The worms themselves are not thought to be responsible for the disease but the eggs elicit a powerful and damaging immune response when they are trapped in tissue.

As only the very young in endemic areas will not have been exposed to schistosomiasis a protective antigen for a candidate vaccine must be one that will attack the adult parasite without cross reacting with egg antigens thus increasing the risk of developing chronic disease in those already affected. Most antigen vaccine candidates tested to date have at best resulted in 50 to 60% protection in *animal* models although repeated immunisation with irradiated cercariae in *murine* models has resulted in almost 80%

protection. Consequently it has been questioned whether sterilising immunity should be the aim. It might be more realistic to develop a vaccine which can reduce the overall worm burden and the fecundity of surviving worms, thus reducing the number of eggs released and deposited in the liver. This in turn would lead to lower rates of infection by reducing the numbers of miracidia available to infect snails. Such a vaccine would, however, only be effective in terms of infection and morbidity rates after a considerable period of time, probably more than 20 years. Alternatively, vaccine candidates that specifically attack particular stages of the parasite life cycle might be feasible. Some potential vaccine candidate antigens have been identified and clinical studies have taken place with the glutathione-*S*-transferase antigen from *S. haematobium*, Sh28 GST. Use of antigens with recombinant cytokines in order to enhance immune response, or with the B subunit of cholera toxin in order to suppress harmful inflammatory responses, has also been investigated. There is also some suggestion that it might be possible to develop a multicomponent vaccine consisting of multiple antigens that will give protection against different stages in the parasite cycle.[1]

1. Lebens M, *et al.* Current status and future prospects for a vaccine against schistosomiasis. *Expert Rev Vaccines* 2004; **3:** 315–28.
2. McManus DP, Loukas A. Current status of vaccines for schistosomiasis. *Clin Microbiol Rev* 2008; **21:** 225–42.

Scorpion Venom Antisera

Antídoto contra las picaduras de escorpión o alacrán; Antisuero contra el veneno de escorpión; Scorpion Antivenins; Scorpion Antivenoms.

Uses and Administration

Some scorpion stings are dangerous and even fatal. The use of a scorpion venom antiserum suitable for the species of scorpion can prevent symptoms, provided that it is given with the least possible delay; other general supportive measures and symptomatic treatment are also needed. The efficacy of scorpion venom antisera is disputed by some clinicians.

Scorpion stings. Scorpion stings are common throughout the tropics, but the most dangerous and potentially fatal species are found in India, North Africa and the Middle East, the southern states of North America and Mexico, Latin America and the Caribbean, and southern Africa. Local symptoms after scorpion stings include intense pain and swelling. Systemic symptoms result from excitation of nerve and muscle cells by the venom; the pattern of symptoms depends upon the species of scorpion. Symptoms such as hypersalivation, vomiting, and diarrhoea are generally followed by adrenergic features, with release of catecholamines producing hypertension, toxic myocarditis, arrhythmias, heart failure, and pulmonary oedema. The cardiotoxic effects are prominent features of stings in India, North Africa, and the Middle East. Neurotoxic effects such as fasciculations, spasms, and respiratory paralysis are seen with stings from North American species. Stings by the black scorpion of Trinidad may also produce pancreatitis.

Pain is treated with local infiltration or peripheral nerve block with local anaesthetics; opioid analgesics may be necessary, but are regarded as dangerous after stings by some North American species. An appropriate antiserum may be given as soon as possible after envenomation, although the efficacy of some antisera has been questioned and in some countries they are no longer considered of benefit. Supportive treatment for cardiotoxic effects includes alpha blockers, calcium-channel blockers, and ACE inhibitors. The use of cardiac glycosides, beta blockers, and atropine is controversial. Phenobarbital and benzodiazepines have been suggested for neurotoxic effects.

References.

1. el Amin EO, *et al.* Scorpion sting: a management problem. *Ann Trop Paediatr* 1991; **11:** 143–8.
2. Bond GR. Antivenin administration for Centruroides scorpion sting: risks and benefits. *Ann Emerg Med* 1992; **21:** 788–91.
3. Warrell DA, FennerPJ. Venomous bites and stings. *Br Med Bull* 1993; **49:** 423–39.
4. Müller GJ. Scorpionism in South Africa: a report of 42 serious scorpion envenomations. *S Afr Med J* 1993; **83:** 405–11.
5. Gateau T, *et al.* Response to specific centruroides sculpturatus antivenom in 151 cases of scorpion stings. *Clin Toxicol* 1994; **32:** 165–71.
6. Sofer S, *et al.* Scorpion envenomation and antivenom therapy. *J Pediatr* 1994; **124:** 973–8.
7. Karalliedde L. Animal toxins. *Br J Anaesth* 1995; **74:** 319–27.
8. Abroug F, *et al.* Serotherapy in scorpion envenomation: a randomised controlled trial. *Lancet* 1999; **354:** 906–9.
9. Isbister GK, *et al.* Scorpion stings in Australia: five definite stings and a review. *Intern Med J* 2004; **34:** 427–30.
10. Gazarian KG, *et al.* Immunology of scorpion toxins and perspectives for generation of anti-venom vaccines. *Vaccine* 2005; **23:** 3357–68.
11. Bencheikh RS, *et al.* Conduite à tenir devant une piqûre de scorpion au Maroc. *Ann Fr Anesth Reanim* 2008; **27:** 317–22.
12. Boyer LV, *et al.* Arizona Envenomation Investigators. Antivenom for critically ill children with neurotoxicity from scorpion stings. *N Engl J Med* 2009; **360:** 2090–8.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Alacramyn; ***USA***: Anascorp.

Shigella Vaccines

Dysentery Vaccines; Shigellosis Vaccines; Vacunas contra Shigella; Vacunas de la disentería; Vacunas de la shigellosis.

Profile

Shigella vaccines have been under investigation since the 1960s but early prototypes were unsatisfactory. Live attenuated oral vaccines, parenteral conjugated vaccines, and intranasal vaccines are now also under development.

Natural or experimental exposure to *Shigella* antigens has been shown to induce clinical immunity, and there has been some work towards developing an effective vaccine.[1,2] There have been 3 main approaches to vaccination under investigation.[1] Firstly, workers at the USA National Institutes of Health have developed a series of vaccines in which the O antigen of *S. sonnei*, *S. flexneri* 2a strain, or *S. dysenteriae* type 1 is conjugated to *Pseudomonas aeruginosa* recombinant exoprotein A. These vaccines are given intramuscularly and have elicited strong immune responses in adults and children tested, and some have reached phase III studies. A second approach has been to deliver *Shigella* lipopolysaccharide intranasally in proteasomes, which are purified outer membrane proteins that form a multimolecular vesicular complex around the antigen; these vaccines are being tested in phase I studies. The third approach is the use of live attenuated oral vaccines, attenuated by creating deletions in genes that govern vital metabolic processes within the organism or by mutating genes that encode specific virulence factors.

A major challenge in the development of a shigella vaccine is to provide protection against all of the many serotypes that appear epidemiologically important. Most experts agree that for a shigella vaccine to be totally effective globally it must protect against *S. dysenteriae* type 1, *S. sonnei*, and all 15 classical *S. flexneri* serotypes. However, it has been shown that a composite of 3 *S. flexneri* serotypes (2a, 3a, and 6) can provide cross protection against the remaining 12. Hence the ultimate plan is to develop a pentavalent vaccine comprising these 3 *S. flexneri* serotypes with *S. sonnei* and *S. dysenteriae* type 1.[1] Shigella vaccines have been licensed for use in China.[2]

1. Kotloff KL. Progress in Shigella vaccine development. In: de Quadros CA, ed. *Vaccines: Preventing Disease and Protecting Health.* Washington D.C., 2004: 130–9.
2. Kweon MN. Shigellosis: the current status of vaccine development. *Curr Opin Infect Dis* 2008; **21:** 313–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Shigelat (Шигеллвак).

Smallpox Vaccines

Vacunas de la viruela.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Smallpox Vaccine (Live)). A liquid or freeze-dried preparation of live vaccinia virus grown in the membranes of the chick embryo, in cell cultures, or in the skin of living animals. The cell culture medium may contain suitable antibacterials at the lowest effective concentration. Store at 2 degrees to 8 degrees and protect from light. The liquid vaccine should not be allowed to freeze.

Uses and Administration

After the global eradication of smallpox in 1980, vaccination against smallpox (using first generation vaccinia virus vaccine) has been indicated for those considered to be at high risk such as laboratory workers handling certain orthopoxviruses, and key emergency, healthcare, and military personnel who may have to respond to a bioterrorist release of smallpox. A second generation smallpox vaccine has been licensed in the USA for inclusion to the National Stockpile for vaccination of those considered to be at high risk for smallpox infection. Persons at high risk and who have received primary vaccination against smallpox, should be re-vaccinated every 3 to 10 years depending on their exposure risk. Vaccination is not recommended for persons working with highly attenuated strains of orthopoxviruses.

WHO considers that mass vaccination against smallpox is currently not appropriate, although individuals who may be at risk of exposure to smallpox or those with confirmed infection may be vaccinated.

Recombinant vaccinia viruses are being investigated as vectors of foreign antigens, for example in a candidate AIDS vaccine (p. 2376.1).

Vaccine development. Smallpox[1] is an acute contagious and sometimes fatal disease caused by variola virus, a member of the Poxviridae family and of the orthopoxvirus genus. There is substantial cross-protection between poxviruses of the same genus; the very effective first generation smallpox vaccine used in the global vaccination programme was created from an orthopoxvirus, vaccinia. In 1980 WHO declared smallpox to have been globally eradicated.

There has since been concern that smallpox may be used as a terrorist weapon (although WHO considers this risk to be extremely low in most countries). Therefore, research into safer vaccines against smallpox has continued. First generation vaccine was produced from vaccinia strains grown on the skin of live animals or calf lymph. Despite purification processes, the vaccine contained some bacteria, animal proteins, and adventitious animal viruses, and produced a high incidence of adverse effects, some of which were extremely serious (see Adverse Effects and Precautions, below). Second generation vaccines are single clones of vaccinia isolated from the set of genetically related viruses that made up the first generation ones; they are grown in tissue culture (rather than on animal skin or calf lymph) and are free of bacteria and adventitious animal viruses. A second generation vaccine has been found to be effective and is licensed in the USA for inclusion to the National Stockpile. However, this vaccine still has a high incidence of adverse effects. Third generation vaccines[2] are in the early stages of development. They are being developed from vaccinia strains attenuated by serial passage on non-human tissue or by genetic manipulation, and are expected to be safer than either first or second generation vaccines. Interest has also been shown in monoclonal variola antibodies for passive immunisation.[1,3]

Stocks of smallpox (variola) virus are being kept in a few secure laboratories in the USA and Russia. Since the eradication of smallpox, WHO maintains a stockpile of smallpox vaccine, and recommends vaccination for people with occupational exposure to fully potent orthopoxviruses, such as certain laboratory and healthcare workers. Because of concern that smallpox may be used for bioterrorism, WHO and several countries have increased the number of doses kept in stock.[1] Policies for the use of smallpox vaccine, including bioterrorism preparedness, have been developed in many countries such as the USA[4,5] and UK[6,7] with some countries recommending vaccination for key emergency and military personnel.

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Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Both first and second generation live smallpox vaccines have been associated with a high incidence of adverse effects. The most common adverse effects are injection site reactions, fatigue, fever, headache, malaise, myalgia, erythema, and generalised rash. Rarely there may be generalised vaccinial infection, or severe skin or CNS infection resulting in encephalitis, encephalomyelitis, encephalopathy, necrotising skin infection (progressive vaccinia, vaccinia necrosum, vaccinina gangrenosum, or disseminated vaccinia), eczema vaccinatum, and erythema multiforme (including Stevens-Johnson syndrome). Fatalities have occurred, particularly from post-vaccination encephalitis and progressive vaccinia. Inadvertent contamination of other body sites (such as the face, mouth, nose, lips, and genitalia) from the site of vaccination also occurs frequently; autoinoculation of the eye (ocular vaccinia)

may result in blindness. Benign and malignant lesions have also been reported at the vaccination site.

There have been reports of myocarditis or pericarditis or both, including some fatalities, associated with smallpox vaccination. Smallpox vaccination is not recommended for infants under 12 months of age, for persons with a history of eczema or other skin conditions, those who are immunocompromised, for pregnant women, or for women who breast feed. Household contacts of these groups should also not be vaccinated. Vaccination is best avoided in persons with known cardiac disease.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: En Zai Shi (恩再适); ***USA***: ACAM2000; Dryvax†.

Pharmacopoeial Preparations
Ph. Eur.: Smallpox Vaccine (Live).

Snake Venom Antisera

Antídoto contra las mordeduras de serpiente; Antisuero contra el veneno de serpiente; Snake Antivenins; Snake Antivenoms.

ATC — J06AA03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Viper Venom Antiserum, European; Immunoserum Contra Venena Viperarum Europaearum). A preparation containing the specific antitoxic globulins that have the power of neutralising the venom of one or more species of viper (*Vipera ammodytes, V. aspis, V. berus,* or *V. ursinii*). The globulins are obtained by fractionation of the serum of animals that have been immunised against the venom or venoms. Each mL neutralises the venoms in not less than 100 mouse LD_{50} of *V. ammodytes,* 100 of *V. aspis,* 50 of *V. berus,* or 50 of *V. ursinii*. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that the only poisonous snake native to the British Isles is the adder or common viper, *Vipera berus*. In a geographical region where other species of snake (including elapids) are found, antisera able to neutralise the venoms of the species of snake indigenous to the region should be used. When the preparation is intended to neutralise the venom or venoms of one or more snakes other than vipers, the title Snake Venom Antiserum is used.

Uses and Administration

Venomous snakes comprise the Viperidae (vipers), Elapidae (cobras, kraits, and mambas), and the Hydrophiidae (sea snakes).

The venom of snakes is a complex mixture chiefly of proteins, many of which have enzymatic activity, and may provoke local inflammatory reactions. The venom may have profound effects on tissue, blood vessels and other organs, blood cells, coagulation, and myotoxic or neurotoxic effects with sensory, motor, cardiac, renal, and respiratory involvement.

Snake venom antisera are the only specific treatment available for venomous snake bites, but can produce severe adverse reactions. They are generally only used if there are clear indications of systemic involvement, severe local involvement, or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement. Adrenaline should be available in case of anaphylactic reactions to the antiserum; premedication with adrenaline, corticosteroids, and/or antihistamines is widely practiced but is regarded as controversial.

In Great Britain, the only indigenous poisonous snake is the adder, *Vipera berus*; its bite is rarely fatal but European Viper Venom Antiserum (or Zagreb antivenom) may sometimes be indicated as part of the overall treatment. The usual dose for adults and children is 10 mL by intravenous injection over 10 to 15 minutes or by intravenous infusion over 30 minutes after diluting in 5 mL/kg body-weight of sodium chloride 0.9%; the dose may be repeated after about 1 to 2 hours if symptoms of systemic envenoming persist.

In the USA, a polyvalent crotalidae antiserum against *Bothrops atrox, Crotalus adamanteus, C. atrox,* and *C. durissus terrificus,* and an antiserum against the North American coral snake, *Micrurus fulvius,* are available. In Australia, polyvalent antisera against the brown snake, death adder, taipan, and tiger snake, plus either the king brown snake or black snake, are available. A variety of polyvalent and monovalent antisera are also available as appropriate to the indigenous species of snakes in many other countries.

Snake bites. Most snake species are non-venomous and belong to the colubrid family although a few colubrids are technically venomous. The 3 families of venomous front-fanged snakes are the elapids, vipers, and sea snakes. Elapids include cobras, mambas, kraits, coral snakes, and the Australasian venomous land snakes. Vipers are subdivided into crotalids (pit vipers) and viperids. Viper bites are much more common than elapid bites, except in Australasia, where vipers do not occur naturally. Sea snake bites occur among fishermen of the Asian and western Pacific coastal areas. Although there are some notable exceptions, viper bites tend to cause vasculotoxicity, elapids cause neurotoxicity, and sea snakes cause myotoxicity.

Only a few snakes are known to be of medical importance. Of the vipers these include *Bothrops atrox* (Central and South America), *Bitis arietans* (Africa), *Echis carinatus* (Africa and Asia), *Vipera russelli* (Asia), and *Agkistrodon rhodostoma* (south-east Asia). In a few restricted areas of Africa and Asia, cobra bites are common; bites by mambas (Africa) and kraits (Asia) are rare. The carpet viper, *Echis pyramidum,* and saw-scaled viper, *Echis carinatus,* can justifiably be labelled the most dangerous snakes in the world and they cause more deaths and serious poisoning than any other snake.

Management of snake bite involves general supportive care and monitoring of vital functions but in systemic snake-bite poisoning, specific snake venom antiserum is the most effective therapeutic agent available. If used correctly, it can reverse systemic poisoning when given hours or even days after the bite. It is highly desirable to wait for clear clinical evidence of systemic poisoning before giving an antiserum and therefore it should not be given routinely in all cases of snake bite. Monospecific antisera are more effective, and less likely to cause reactions, than polyvalent antisera. The dosage of antiserum to be used is dependent on the species of snake and the consequent potency of the requisite antiserum. The antiserum should be given intravenously diluted in isotonic saline, either by infusion or bolus injection (see under Adverse Effects and Precautions, below). First aid measures including incisions and suction to remove the venom and application of tourniquets are generally to be discouraged. In most cases, the bitten limb should be immobilised and the victim transferred to a medical facility, with the snake if possible. For bites by elapids, when respiratory failure may occur before the patient reaches hospital, a tourniquet may be justified to delay the onset of neurotoxicity. Supportive treatment is necessary even in patients who have received an adequate dose of antiserum. Local pain may be treated with a suitable analgesic. Artificial respiration may be required in patients with symptoms of neurotoxicity. Anticholinesterases may be of benefit against the neurotoxic effects of some snake venoms and it has been recommended that an intravenous test dose of edrophonium preceded by atropine should be tried in patients with severe symptoms of neurotoxicity. For those patients who respond, treatment with neostigmine should be started but anticholinesterases are unlikely to affect outcome in patients who already require assisted respiration. Hypovolaemia should be corrected cautiously with parenteral fluids. Hypotension may be treated with subcutaneous adrenaline or, in patients bitten by Russell's viper, a response to dopamine has been noted. Patients with renal impairment may require dialysis if they do not respond to rehydration, diuretics, and dopamine. Broad spectrum antibacterials and a tetanus vaccine should be given as prophylactic measures. Surgical decompression and debridement of necrotic tissue may be necessary once normal haemostasis has been restored.

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3. Warrell DA. Snake venoms in science and clinical medicine: 1. Russell's viper: biology, venom and treatment of bites. *Trans R Soc Trop Med Hyg* 1989; **83:** 732–40.
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Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Serum sickness is not uncommon and anaphylactic reactions may occur.

Anaphylaxis. Conjunctival or cutaneous hypersensitivity testing failed to predict early (anaphylactic) reactions to the antivenom given in a study of patients in Nigeria with systemic envenoming by the saw-scaled or carpet viper (*Echis carinatus*) and in Thailand with local or systemic envenoming by green pit vipers (*Trimeresurus albolabris* and *T. macrops*), the monocellate Thai cobra (*Naja kaouthia*), or the Malayan pit viper (*Calloselasma rhodostoma*). It was considered that conventional hypersensitivity testing has no predictive value for the occurrence of allergic reactions to antivenom and that it is not justifiable to delay treatment for 20 or 30 minutes to read the results of these tests. Although the rate at which antiserum can be given is more easily controlled by intravenous infusion, this method has serious practical disadvantages in the rural tropics where most cases of snake bite occur and an advantage of the intravenous push injection is that the person giving the antiserum must remain with the patient during the period when most severe anaphylactic reactions develop.

Pretreatment with low-dose subcutaneous adrenaline may reduce the incidence of anaphylaxis and other acute adverse reactions to the antiserum.[1] However, premedication with adrenaline, antihistamines, and corticosteroids, although widely practiced, is controversial. In one study,[2] prophylaxis with promethazine was ineffective in preventing anaphylaxis from antiserum against *Bothrops* envenomation.

1. Premawardhena AP, *et al*. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ* 1999; **318:** 1041–3.
2. Fan HW, *et al*. Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999; **318:** 1451–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Suero Antiofidico Polivalente; ***Austral.***: Black Snake Antivenom; Polyvalent Snake Antivenom; ***Fr.***: Viperfav; ***Hong Kong***: Sea Snake Antivenene; Tiger Snake; ***India***: Antisnake Venom; ASVS; ***Mex.***: Antivipmyn; Coralmyn; ***Singapore***: Polyvalent Snake Antivenom; Sea Snake Antivenom; ***USA***: CroFab.

Multi-ingredient Preparations. ***Hung.***: Crotalgin Forte; Crotalgin; Kovitox.

Pharmacopoeial Preparations
Ph. Eur.: European Viper Venom Antiserum.

Spider Venom Antisera

Antídoto contra el veneno de las arañas; Antisuero contra el veneno de arañas; Spider Antivenins; Spider Antivenoms.

Uses and Administration

The use of a spider venom antiserum suitable for the species of spider can prevent symptoms, provided that it is done with the least possible delay; other general supportive measures and symptomatic treatment may also be needed.

The symbol † denotes a preparation no longer actively marketed

An antiserum against the black widow spider (*Latrodectus mactans*) is available in the USA and Canada. The contents of a vial containing at least 6000 antivenin units is the usual dose for adults and children. In severe cases and in children under 12 years of age it is given by intravenous infusion in sodium chloride 0.9% over 15 minutes; in less severe cases, it may be given by intramuscular injection.

Antivenoms are also available against other *Latrodectus* species, including the Australian red-back spider (*L. hasselti*) and the South African button spiders. An antiserum against the funnel-web spider (*Atrax robustus*) is available in Australia.

Antivenoms have also been developed against *Loxosceles* spiders and against *Phoneutria* spiders, but there is little evidence of their efficacy.

Spider bites. Although many species of spider are venomous, relatively few pose a danger to man. Two main clinical syndromes are recognised; necrotic araneism, produced mainly by members of the genus *Loxosceles* which includes the brown recluse spider *L. reclusa*, and neurotoxic araneism produced by members of the genera *Latrodectus* (including the black widow and red-back spiders), *Phoneutria* (South American banana spiders), and *Atrax* (funnel-web spiders).

Necrotic araneism presents as local pain and erythema at the site of the bite, commonly developing into a necrotic lesion with a black eschar that sloughs after a few weeks, sometimes leaving an ulcer that heals gradually. The area affected can be extensive. Rarely, systemic symptoms including intravascular coagulation, haemolytic anaemia, respiratory distress, and renal failure, occur and may be life-threatening. Some therapies have been suggested, but conservative management is usually adequate with surgical repair of any persistent defects if necessary. Dapsone is reported to produce beneficial effects on healing. Treatment for systemic manifestations is supportive. Antisera are available in some countries.

Neurotoxic araneism may involve severe pain, headache, vomiting, tachycardia, hypertension, muscle spasms, and occasionally pulmonary oedema, and coma, depending upon the species. Antisera are available and reported to be more effective than those for necrotic araneism, but should be reserved for serious envenomation. Intravenous injection of calcium gluconate 10% has been suggested to relieve muscle spasm as an alternative to conventional muscle relaxants.

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2. Isbister GK, *et al.* Antivenom treatment in arachnidism. *J Toxicol Clin Toxicol* 2003; **41:** 291–300.
3. Nimorakiotakis B, Winkel KD. The funnel web and common spider bites. *Aust Fam Physician* 2004; **33:** 244–51.
4. Saucier JR. Arachnid envenomation. *Emerg Med Clin North Am* 2004; **22:** 405–22, ix.
5. Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; **352:** 700–707.
6. Vetter RS, Isbister GK. Medical aspects of spider bites. *Annu Rev Entomol* 2008; **53:** 409–29.
7. Cabrerizo S, *et al.* Loxoscelismo: epidemiología y clínica de una patología endémica en el país. *Arch Argent Pediatr* 2009; **107:** 152–9.
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Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Aracmyn; Reclusmyn.

Staphylococcal Immunoglobulins

Profile

Staphylococcal immunoglobulins are under investigation for passive immunisation against infection with *Staphylococcus aureus*.

Two antistaphylococcal immunoglobulins, INH A-21 and *Altastaph*, have been used in Phase II and III studies for prevention of staphylococcal infections in very low birthweight neonates, but a systematic review failed to find any significant reduction in the rate of bacterial infection.[1] Phase II and III studies for other antistaphylococcal immunoglobulins (Pagibaximab, Tefibazumab, and *Aurograb*) are underway.[1,2]

1. Shah PS, Kaufman DA. Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 15/12/09).
2. Deresinski S. Antistaphylococcal vaccines and immunoglobulins: current status and future prospects. *Drugs* 2006; **66:** 1797–1806.

Staphylococcal Vaccines

Vacunas estafilocócicas.

Profile

Staphylococcal vaccines have been developed for the prophylaxis of staphylococcal infections.

A vaccine containing *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A showed promise[1] in early studies in patients with end-stage renal disease who were receiving haemodialysis; however, later work failed to confirm benefit and its development was stopped.[1,2]

1. Shinefield H, *et al.* Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. *N Engl J Med* 2002; **346:** 491–6.
2. Deresinski S. Antistaphylococcal vaccines and immunoglobulins: current status and future prospects. *Drugs* 2006; **66:** 1797–1806.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Estafiloide†; ***China***: Bo Ke Le Wei (博克乐威); ***Cz.***: Polystafana†; Stafal†; ***USA***: SPL.

Stone Fish Venom Antisera

Antídoto contra el veneno del pez piedra estuarino; Antisuero contra el veneno del pez piedra estuarino; Stone Fish Antivenins; Stone Fish Antivenoms.

Uses and Administration

An antiserum for use in the management of stings by the stone fish (*Synanceja trachynis*) is available in Australia. The antiserum is prepared from the serum of horses that have been immunised with the venom of the stone fish. Other symptomatic and supportive treatments are given in addition.

Stone fish venom antiserum may be given by intramuscular injection or, in more severe cases, by intravenous infusion. When given by intravenous infusion, it should be diluted 1 in 10 with an intravenous solution. The initial dose of stone fish antivenom given to both adults and children is dependent on the number of visible puncture sites: 1 to 2 puncture sites, 2000 units; 3 to 4 puncture sites, 4000 units; and 5 or more puncture sites, 6000 units. The initial dose may be repeated if necessary should symptoms persist.

References to the management of stone fish envenomation.

1. Sutherland SK. Stone fish bite. *BMJ* 1990; **300:** 679–80.
2. Lehmann DF, Hardy JC. Stonefish envenomation. *N Engl J Med* 1993; **329:** 510–11.
3. Brenneke F, Hatz C. Stonefish envenomation—a lucky outcome. *Travel Med Infect Dis* 2006; **4:** 281–5.
4. Grandcolas N, *et al.* Piqûres par poisson-pierre: une antalgie difficile, un risque notable de complications. *Presse Med* 2008; **37:** 395–400.
5. Prentice O, *et al.* Stonefish envenomation. *Am J Emerg Med* 2008; **26:** 972.e1–972.e2.
6. Ngo SY, *et al.* Stonefish envenomation presenting to a Singapore hospital. *Singapore Med J* 2009; **50:** 506–9.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Streptococcus Group B Vaccines

Vacunas contra estreptococos del grupo B.

Profile

Vaccines for active immunisation against group B streptococcal infections are being developed. Giving a vaccine to pregnant women to prevent neonatal infection has been proposed.

References.
1. Baker CJ, Edwards MS. Group B streptococcal conjugate vaccines. *Arch Dis Child* 2003; **88:** 375–8.

Tetanus Antitoxins

Antitoxinas del tétanos; Antitoxinas tetánicas.
ATC — J06AA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Tetanus Antitoxin for Human Use; Immunoserum Tetanicum ad Usum Humanum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Clostridium tetani*. It is obtained by fractionation from the serum of horses, or other mammals, that have been immunised against tetanus toxin. For prophylactic use, it has a potency of not less than 1000 international units/mL, and for therapeutic use not less than 3000 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Tet/Ser may be used on the label.

Profile

Tetanus antitoxins neutralise the toxin produced by *Clostridium tetani* and have been used to provide temporary passive immunity against tetanus, but tetanus immunoglobulins (below) are preferred. A test dose of tetanus antitoxin should always be given to identify those who might suffer hypersensitivity reactions.

Whenever a non-immune patient is seen because of injury, a course of active immunisation should be instituted (see Tetanus Vaccines, p. 2421.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Anti-Tet (ATS); ***Philipp.***: Antitet; Tetanox; Toxigen.

Pharmacopoeial Preparations
Ph. Eur.: Tetanus Antitoxin for Human Use.

Tetanus Immunoglobulins

Inmunoglobulinas contra el tétanos.
ATC — J06BB02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Tetanus Immunoglobulin; Immunoglobulinum Humanum Tetanicum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the toxin of *Clostridium tetani*. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

USP 36: (Tetanus Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with tetanus vaccine. It contains not less than 50 units of tetanus antitoxin/mL. It contains 10 to 18% of protein of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Tetanus immunoglobulins are used for passive immunisation against tetanus.

The use of tetanus immunoglobulins is recommended in the UK and the USA as part of the management of tetanus-prone wounds in persons unimmunised or incompletely immunised against tetanus, in persons whose immunisation history is unknown, in those who have received the last dose of tetanus vaccine more than 10 years previously, and in patients with impaired immunity. Active immunisation with a tetanus vaccine (p. 2421.1) should also be started simultaneously, and antibacterials and symptomatic therapy given as appropriate (see p. 209.2 and p. 2029.2). The usual dose of tetanus immunoglobulin is 250 units by intramuscular injection but, if more than 24 hours have elapsed since the wound was sustained, or if there is a risk of heavy contamination, or after burns, 500 units should be given irrespective of the immunisation history.

Tetanus immunoglobulin is also used in the treatment of tetanus, a recommended dose being 150 units/kg in total, given intramuscularly into multiple sites.

A preparation suitable for intravenous use is available in some countries. It is given for the treatment of tetanus in a dose of 5000 to 10 000 units by intravenous infusion.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Tetanus immunoglobulins will neutralise tetanus toxoid and should not be injected into the same site or in the same syringe as a tetanus vaccine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gammatet; Igantet; IT SD-T; Tetabulin; ***Austria***: Tetabulin; Tetagam; ***Belg.***: Tetabuline; ***Braz.***: Tetanogamma; ***Canad.***: Hypertet; ***Chile***: Igantet; ***Cz.***:

Tetabulin; ***Fr.***: Gammatetanos; ***Ger.***: Tetagam; Tetanobulin†; ***Gr.***: Igantet; Tetagam-P; Tetanosson; Tetuman; ***Hong Kong***: Hyper-Tet; Tetagam; ***Hung.***: Tetig; ***India***: Beats; Igantet; Tetagam-P; ***Indon.***: Tetagam P; ***Irl.***: Tetabulin; ***Israel***: HyperTET; ***Ital.***: Gamma-Tet P; Igantet; Tetabulin; Tetanus-Gamma; ***Malaysia***: Igantet; Sero-Tet; ***Mex.***: Tetanogamma; ***Neth.***: Teta-Quin; ***Philipp.***: BayTet†; IG Tetano†; Sero-Tet; Tetagam-P; Tetanea; ***Pol.***: Tetabulin; ***Port.***: Tetagam; ***S.Afr.***: Tetagam; ***Singapore***: Igantet; ***Spain***: Gamma Antitetanos; Tetagamma P†; ***Switz.***: Tetagam; ***Thai.***: Tetagam; Tetanus Gamma; ***Turk.***: Bay-Tet; Tetanea; Tetaquintetatus; Tetuman†; ***USA***: BayTet†.

Pharmacopoeial Preparations
Ph. Eur.: Human Tetanus Immunoglobulin;
USP 36: Tetanus Immune Globulin.

Tetanus Vaccines

Vacunas del tétanos.
ATC — J07AM01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Tetanus Vaccine (Adsorbed); Vaccinum Tetani Adsorbatum). It is prepared from tetanus formol toxoid adsorbed on a mineral carrier which may be hydrated aluminium phosphate or aluminium hydroxide. The resulting mixture is isotonic with blood. Suitable antimicrobial preservatives may be added. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type and these should not be added to the vaccine. It contains not less than 40 units per dose. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Tet may be used on the label.

The BP 2014 directs that when Tetanus Vaccine is prescribed or demanded and the form is not stated, Tetanus Vaccine (Adsorbed) may be dispensed or supplied.

BP 2014: (Tetanus Vaccine). It is prepared from tetanus toxin produced by the growth of *Clostridium tetani*. The toxin is converted to tetanus formol toxoid by treatment with formaldehyde solution. It contains suitable non-phenolic antimicrobial preservatives. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Tet/Vac/FT may be used on the label.

The BP 2014 directs that when Tetanus Vaccine is prescribed or demanded and the form is not stated, Tetanus Vaccine (Adsorbed) may be dispensed or supplied.

Uses and Administration

Tetanus vaccines are used for active immunisation against tetanus.

For primary immunisation combined tetanus vaccines, usually diphtheria, tetanus, and pertussis vaccines (p. 2383.3) or diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae vaccines (p. 2385.3), are used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3. In adults requiring primary immunisation combined vaccines such as diphtheria and tetanus vaccines (p. 2383.1) or diphtheria, tetanus, and poliomyelitis vaccines (p. 2386.2) are used.

In children who complete the primary course in infancy, reinforcing doses are given at school entry (about 4 to 6 years) and in adolescence using the recommended appropriate combined vaccines. In adults, a reinforcing dose is desirable 10 years later with a further dose after a further 10 years.

Tetanus vaccines should be part of wound management if primary immunisation is incomplete or boosters are not up-to-date. For tetanus-prone wounds, tetanus immunoglobulin (see p. 2420.3) may also be required. Tetanus vaccine and tetanus immunoglobulin may be given at the same time, but not at the same site. In the event of injury in non-immunised persons or if immunisation status is uncertain, the opportunity is usually taken to start a course of primary immunisation. Since this provides no immediate protection, prophylactic treatment with tetanus immunoglobulin is recommended for tetanus-prone wounds. Suitable antibacterial therapy may also be given (see p. 209.2).

References.
1. WHO. Tetanus vaccines: WHO position paper. *Wkly Epidem Rec* 2006; **75:** 198–208. Also available at: http://www.who.int/immunization/wer8120tetanus_May06_position_paper.pdf (accessed 30/05/10)

Neonatal tetanus. In 1989 WHO adopted a resolution to eliminate neonatal tetanus after estimates revealed that worldwide (but excluding China) it was the cause of 800 000 neonatal deaths each year, a figure representing about 50% of all such deaths in developing countries. Control of neonatal tetanus may be achieved by ensuring adequate hygiene during delivery and by ensuring protective immunity of the mother in late pregnancy. However, by mid-2000 there were 57 countries that had still not eliminated maternal and neonatal tetanus and WHO, UNICEF, and UNFPA agreed to set a target date of 2005 for elimination (defined as a rate of neonatal tetanus below 1 in 1000 live births at district level). However, by the end of 2007, 47 countries were still considered to have not achieved elimination.

Tetanus vaccine is given to all women of child-bearing age as part of WHO's Expanded Programme on Immunization. For pregnant women, 2 doses of vaccine should be given, the second dose at least 4 weeks after the first and at least 2 weeks before delivery; this may provide the newborn infant with about 80% protection against tetanus. For all women of child-bearing age, 3 doses of vaccine, with at least 4 weeks between the first two doses and 6 to 12 months between the second and third doses, provide 95 to 98% protection for at least 5 years. Fourth and fifth doses, each at least one year after the previous dose, prolong the immunity for 10 and 20 years respectively.

Reinforcing doses in adults. Although the current recommendation in the UK is that 5 doses of tetanus vaccine (as a 3-dose primary course in infancy and 2 reinforcing doses at pre-school and in adolescence) is sufficient to produce satisfactory long-term protection in most circumstances, there has been concern about immunity in the elderly, and in particular women. Routine primary immunisation against tetanus was introduced in the UK in 1961, so individuals born before that year would not have been immunised in infancy, and unless they had been in the armed forces, may never have received a full primary course. Unless there is a clear immunisation history immunity to tetanus may be difficult to assess. It is also recommended in the UK that travellers to areas where medical attention may not be accessible, and who had the last dose of vaccine more than 10 years previously, should receive a booster even if they have had 5 doses previously.

Studies in the USA,[1] Australia,[2] and Austria[3] have shown that at least half of healthy people over 50 years of age did not have adequate circulating tetanus antibodies. However, the level of circulating antibodies in the absence of an antigen challenge may not be an appropriate measure of the immune status. The low incidence of clinical tetanus in adults provides circumstantial evidence of an adequate inducible antibody response on exposure to tetanus despite a decline in antibody concentrations with increasing age.[4,5] Conversely, there have been reports of tetanus occurring despite high antibody concentrations.[6,7] There have been calls for the introduction of regular booster injections in adults,[3,7-9] as is standard practice in the USA or alternatively a single booster in late middle age[10,11] or giving a primary course to elderly persons who have never received one.[1]

1. Gergen PJ, *et al.* A population-based serologic survey of immunity to tetanus in the United States. *N Engl J Med* 1995; **332:** 761–6.
2. Heath TC, *et al.* Tetanus immunity in an older Australian population. *Med J Aust* 1996; **164:** 593–6.
3. Steger MM, *et al.* Vaccination against tetanus in the elderly: do recommended vaccination strategies give sufficient protection? *Lancet* 1996; **348:** 762.
4. Bowie C. Tetanus toxoid for adults—too much of a good thing. *Lancet* 1996; **348:** 1185–6.
5. Baily G. Are the elderly inadequately protected against tetanus? *Lancet* 1996; **348:** 1389–90.
6. Passen EL, Andersen BR. Clinical tetanus despite a 'protective' level of toxin-neutralising antibody. *JAMA* 1986; **255:** 1171–3.
7. Bowman C, *et al.* Tetanus toxoid for adults. *Lancet* 1996; **348:** 1664.
8. Rethy LA, Rethy L. Can tetanus boosting be rejected? *Lancet* 1997; **349:** 359–60.
9. Sehgal R. Tetanus toxoid for adults. *Lancet* 1997; **349:** 573.
10. Balestra DJ, Littenberg B. Tetanus immunization in adults. *JAMA* 1994; **272:** 1900.
11. Gardner P, LaForce FM. Protection against tetanus. *N Engl J Med* 1995; **333:** 599.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Local reactions, usually after the use of adsorbed vaccines, and mild systemic reactions may occur. The incidence and severity of reactions increases with the number of doses given.

Anaphylaxis and neurological reactions have been reported rarely.

Although vaccination is usually postponed in patients suffering from an acute febrile illness, tetanus vaccine should be given to such patients in the presence of a tetanus-prone wound.

With the exception of the first booster dose of tetanus vaccine (which is usually given before school entry and about 3 years after the primary course), further boosters should not generally be given at intervals of less than 10 years because of an increased risk of severe local reactions.

Effects on the nervous system. Neuropathies have been reported rarely with tetanus vaccination. Optic neuritis and myelitis occurred[1] in an 11-year-old girl after a routine booster dose. Corticosteroids and immunoglobulin were given, and both vision and muscle power were restored after 11 months. Acute transverse myelitis was reported[2] in a 50-year-old man who received a tetanus vaccine and immunoglobulin after an injury. Neurological deficits were unchanged after 1 month despite use of corticosteroids. Other causes could not be ruled out in either case. Brachial neuritis that developed in 2 infants after immunisation with diphtheria, tetanus, and pertussis vaccine was attributed to the tetanus component.[3]

1. Topaloglu H, *et al.* Optic neuritis and myelitis after booster tetanus toxoid vaccination. *Lancet* 1992; **339:** 178–9.
2. Read SJ, *et al.* Acute transverse myelitis after tetanus toxoid vaccination. *Lancet* 1992; **339:** 1111–12.
3. Hamati-Haddad A, Fenichel GM. Brachial neuritis following routine childhood immunization for diphtheria, tetanus, and pertussis (DTP): report of two cases and review of the literature. *Pediatrics* 1997; **99:** 602–3.

GUILLAIN-BARRÉ SYNDROME. For a discussion on the relationship between tetanus-containing vaccines and Guillain-Barré syndrome, see Diphtheria and Tetanus Vaccines, p. 2383.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetanus vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Pregnancy. No connection has been found between use of tetanus vaccine during pregnancy and either congenital malformations[1] or spontaneous abortion.[2]

1. Silveira CM, *et al.* Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. *Bull WHO* 1995; **73:** 605–8.
2. Catindig N, *et al.* Tetanus toxoid and spontaneous abortions: is there epidemiological evidence of an association? *Lancet* 1996; **348:** 1098–9.

Interactions

As for vaccines in general, p. 2375.3.

Tetanus immunoglobulins will neutralise tetanus toxoid and should not be injected into the same site or in the same syringe as a tetanus vaccine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tetanol; Tetavax; ***Austral.***: Tet-Tox†; ***Austria***: Tetanol; ***Chile***: Tetavax; ***Cz.***: Alteana; Tetanol; Tetavax; ***Ger.***: Tetanol; ***Gr.***: Anatoxal-Te-Berna; Tetanol; ***Hong Kong***: Te Anatoxal†; Tetatox; Tetavax; ***Hung.***: Tetanol; ***India***: Bett; ***Ital.***: Anatetall; Imovax Tetano; ***Malaysia***: TT Vaccine; ***Mex.***: Tetamyn†; Tetanol; Tetinox; ***Norw.***: Tetavax; ***NZ***: Te Anatoxal†; Tet-Tox; ***Philipp.***: Anatetall; Imatet; T-Vac; Te Anatoxal†; Tet-vac; Tetavax; Tetliv; Tetox; ***S.Afr.***: Tetavax; ***Singapore***: Tetavax; ***Spain***: Anatoxal Tedi; ***Switz.***: Tetanol pur; ***Thai.***: Anatetall; Bio-TT; Te Anatoxal†; Tetavax; TT Vaccine; ***Turk.***: Anatetall†; Tetavax; ***USA***: Te Anatoxal.

Pharmacopoeial Preparations
Ph. Eur.: Tetanus Vaccine (Adsorbed).

Tetanus and Influenza Vaccines

Vacunas del tétanos y la gripe.

Profile

Tetanus and influenza vaccines are available in some countries for active immunisation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Tetagrip†.

Tetanus and Poliomyelitis Vaccines

Vacunas del tétanos y la poliomielitis.

Profile

Tetanus and poliomyelitis (inactivated) vaccines have been used in some countries for active immunisation against tetanus and poliomyelitis.

Tick Venom Antisera

Antídoto contra las picaduras de garrapata; Antisuero contra el veneno de garrapata; Tick Antivenins; Tick Antivenoms.

Profile

An antiserum is available in Australia for treatment of the neurotoxic effects of envenomation by the tick *Ixodes*

holocyclus. The antiserum is prepared from the serum of dogs that have been immunised with tick venom.

Tick venom antiserum is given by slow intravenous infusion.

Tick-borne Encephalitis Immunoglobulins

Inmunoglobulinas de la encefalitis transmitida por garrapatas.
ATC — J06BB12.

Profile

Preparations containing antibodies against tick-borne encephalitis are available in some countries for passive immunisation against the disease.

Tick-borne Encephalitis Vaccines

Vacunas de la encefalitis transmitida por garrapatas.
ATC — J07BA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Tick-borne Encephalitis Vaccine (Inactivated); Vaccinum Encephalitidis Ixodibus Advectae Inactivatum). A liquid preparation of a suitable strain of tick-borne encephalitis virus grown in cultures of chick-embryo cells or other suitable cell cultures and inactivated by a suitable method. It should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Tic/enceph may be used on the label.

Uses and Administration

A vaccine is available in some countries for active immunisation against tick-borne viral encephalitis.

In the UK, vaccination against tick-borne encephalitis is recommended for those who anticipate prolonged exposure to the infective agent, for example persons visiting or working in the warm forested parts of Europe and Scandinavia. The vaccine is given by intramuscular injection in adult doses of 0.5 mL. The primary course consists of three doses, the second being given 4 to 12 weeks after the initial dose, and a third dose 5 to 12 months later. In children over 1 year of age and below 16 years of age, 3 doses of 0.25 mL of the junior formulation of the vaccine are given; the intervals between each dose are the same as for the adult schedule. To achieve rapid short-term protection in adults and children, the second dose may be given 2 weeks after the first dose. Booster doses for adults and children at continued risk should be given within 3 years of the last primary vaccination or booster dose.

References.
1. Demicheli V, *et al.* Vaccines for preventing tick-borne encephalitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 18/12/09).

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Effects on the nervous system. Severe progressive sensorimotor spastic paralysis occurred in a 54-year-old man after a second booster dose of tick-borne encephalitis vaccine.[1] Partial recovery was noted after about 6 months.

1. Bohus M, *et al.* Myelitis after immunisation against tick-borne encephalitis. *Lancet* 1993; **342:** 239–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tick-borne encephalitis vaccine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria:*** Encepur; FSME-Immun; ***Belg.:*** FSME-Immun; ***Canad.:*** FSME-Immun; ***China:*** Sen Tai Bao (森泰保); ***Cz.:*** Encepur; FSME-Immun; ***Denm.:*** Encepur; TicoVac; ***Fin.:*** Encepur; TicoVac; ***Fr.:*** Encepur; TicoVac; ***Ger.:*** Encepur; FSME-Immun; ***Gr.:*** Encepur; ***Hung.:*** Encepur; FSME-Immun; ***Irl.:*** TicoVac; ***Ital.:*** TicoVac; ***Neth.:*** FSME-Immun; ***Norw.:*** TicoVac; ***Pol.:*** Encepur; FSME-Immun; ***Port.:*** FSME-Immun; ***Rus.:*** Encepur (Энцепур); Encevir (Энцевир); ***Swed.:*** Encepur; FSME-Immun; ***Switz.:*** Encepur; FSME-Immun; ***UK:*** TicoVac.

Pharmacopoeial Preparations
Ph. Eur.: Tick-borne Encephalitis Vaccine (Inactivated).

Trichomoniasis Vaccines

Vacunas de la tricomoniasis.

Profile

A trichomoniasis vaccine containing inactivated *Lactobacillus* spp. is available in some countries for the prophylaxis of recurrent vaginal trichomoniasis. The vaccine is reported to stimulate production of antibodies against the aberrant coccoid forms of the lactobacilli associated with trichomoniasis and also, by cross-reaction, against the trichomonads themselves.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.:*** Booster-Gynatren; Gynatren.

Tularaemia Vaccines

Vacunas de la tularemia.

Profile

A tularaemia vaccine prepared from a live attenuated strain of *Francisella tularensis* has been used for active immunisation against tularaemia in persons at high risk of contracting the disease.

References.
1. Titball R, Oyston P. A vaccine for tularaemia. *Expert Opin Biol Ther* 2003; **3:** 645–53.
2. Conlan JW. Vaccines against Francisella tularensis: past, present and future. *Expert Rev Vaccines* 2004; **3:** 307–14.
3. Oyston PC. Francisella tularensis vaccines. *Vaccine* 2009; **27** (suppl 4): D48–D51.
4. Pechous RD, *et al.* Working toward the future: insights into Francisella tularensis pathogenesis and vaccine development. *Microbiol Mol Biol Rev* 2009; **73:** 684–711.

Typhoid Vaccines

Vacunas de la fiebre tifoidea.
ATC — J07AP01; J07AP02; J07AP03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Typhoid Vaccine; Vaccinum Febris Typhoidi). A sterile suspension of inactivated *Salmonella typhi* containing not less than 500 million and not more than 1000 million bacteria per dose which does not exceed 1 mL. It is prepared from a suitable strain of *S. typhi* such as Ty 2. The bacteria are inactivated by heat, or by treatment with acetone, formaldehyde, or phenol, or by phenol and heat. The vaccine should be stored at 2 degrees to 8 degrees, and be protected from light.

The BP 2014 states that Typhoid may be used on the label.

Ph. Eur. 8: (Typhoid Vaccine, Freeze-dried; Vaccinum Febris Typhoidi Cryodesiccatum). A freeze-dried preparation of inactivated *Salmonella typhi* containing not less than 500 million and not more than 1000 million bacteria per dose which does not exceed 1 mL. It is prepared from a suitable strain of *S. typhi* such as Ty 2. The bacteria are inactivated by heat, or by treatment with acetone or formaldehyde. Phenol may not be used in the preparation. The vaccine should be stored at 2 degrees to 8 degrees, and be protected from light. It is reconstituted by the addition of suitable sterile liquid and should be used within 8 hours.

The BP 2014 states that Typhoid may be used on the label.

Ph. Eur. 8: (Typhoid Vaccine (Live, Oral, Strain Ty 21a); Vaccinum Febris Typhoidis Vivum Perorale (Stirpe Ty 21a)). A freeze-dried preparation of live *S. typhi* strain Ty 21a grown in a suitable medium. It contains not less than 2×10^9 bacteria per dose. It should be stored at 2 degrees to 8 degrees, and be protected from light.

The BP 2014 states that Typhoid(live,oral) may be used on the label.

Ph. Eur. 8: (Typhoid Polysaccharide Vaccine; Vaccinum Febris Typhoidis Polysaccharidicum). A preparation of purified Vi capsular polysaccharide obtained from *S. typhi* Ty2 strain or some other suitable strain that has the capacity to produce Vi polysaccharide. It contains 25 micrograms of polysaccharide per dose. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Typhoid may be used on the label.

Uses and Administration

Typhoid vaccines are used for active immunisation against typhoid fever. As with many vaccines, the efficacy of typhoid vaccine is not complete and the importance of maintaining attention to hygiene should be emphasised to those travelling to endemic areas.

Typhoid vaccination is advised for laboratory workers handling specimens which may contain typhoid organisms and for persons travelling to areas where typhoid fever is endemic. In the UK, vaccination of contacts of a known typhoid carrier is not recommended; in the USA such persons are advised to receive the vaccine. Typhoid vaccine is not useful in controlling outbreaks of the disease in non-endemic areas.

In the UK, two vaccines are used: a capsular polysaccharide vaccine for parenteral use, and a live oral vaccine.

The capsular polysaccharide typhoid vaccine contains 25 micrograms of the Vi polysaccharide antigen per dose. A single dose of 0.5 mL is given by deep subcutaneous or intramuscular injection. Booster doses may be given every 3 years to those who remain at risk. The response in children under 18 months of age may be suboptimal, and the decision to vaccinate will be governed by the risk of exposure to infection.

The live oral typhoid vaccine contains an attenuated strain of *Salmonella typhi*, Ty 21a, and is given as enteric-coated capsules containing not less than 2×10^9 bacteria per dose. A primary immunisation schedule of one capsule every other day for 3 doses is given.

In the USA, the Vi capsular polysaccharide vaccine and the live oral Ty 21a vaccine are available. The capsular polysaccharide vaccine is given intramuscularly similarly to that in the UK, with a booster dose suggested every 2 years. For the oral vaccine, 4 doses on alternate days are recommended for both primary immunisation and boosters, which are given every 5 years if exposure continues.

In areas where typhoid is endemic WHO advises that immunisation should be considered as part of the routine schedules; either the Vi capsular polysaccharide vaccine or the Ty 21a live oral vaccine should be given to schoolchildren over the age of 2 years. Immunisation of the whole community should also be considered during an outbreak of typhoid; if this is not possible, persons aged 2 to 19 years should be the target group.

References.
1. WHO. Typhoid vaccines: WHO position paper. *Wkly Epidem Rec* 2008; **83:** 49–59. Also available at: http://www.who.int/wer/2008/wer8306.pdf (accessed 30/06/10)

Immunisation for travellers. In most developed countries where typhoid is not endemic, the main use for typhoid vaccine is for non-immune travellers visiting endemic areas. The highest incidence of the disease is associated with travel to the Indian subcontinent and parts of tropical South America, although immunisation is also recommended for travellers to lower risk areas of Africa, Asia, and south-east Europe. By far the most important form of protection against gastrointestinal infection is strict attention to personal, food, and water hygiene, although in practice this advice is often difficult to follow.[1]

None of the vaccines used has been 100% effective in preventing disease. Their efficacy has generally been assessed in field studies in the populations of endemic areas. Such populations acquire a degree of natural immunity due to continued exposure and it may not be possible to equate protection rates in these populations to non-immune travellers. The live oral vaccine has been shown to confer a useful degree of immunity in field studies but the dose used may have been insufficient to protect non-immune individuals. The degree of immunity induced may be increased by the use of higher inocula or liquid preparations. In addition, compliance with dosing and storage requirements may further limit the efficacy of this dosage form.

Large field studies have verified the efficacy of the capsular polysaccharide vaccine but its efficacy has not been assessed in non-immune populations. However, it does have the advantage of being given as a single dose.

Whole-cell vaccines are generally no longer used because they are frequently associated with adverse effects.

1. WHO. *The diagnosis, treatment and prevention of typhoid fever.* Geneva: WHO, 2003. Also available at: http://www.who.int/vaccine_research/documents/en/typhoid_diagnosis.pdf (accessed 20/02/06)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Oral live typhoid and parenteral polysaccharide vaccines have been associated with fewer adverse effects than parenteral killed typhoid vaccines and have replaced them in many countries.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies typhoid vaccines (live oral and polysaccharide) as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

Conflicting advice has been issued about the use of live oral typhoid vaccines with antibacterials or antimalarials (particularly mefloquine or proguanil). WHO has stated that all these drugs should be stopped from 3 days before until 3 days after receiving the Ty 21a live oral vaccine. The UK licensed product information advises a separation of 3 days for antibacterials, 12 hours for mefloquine (although licensed product information for mefloquine recommends at least 3 days), and 3 days for other antimalarials (but the fixed-dose combination of atovaquone and proguanil may be given with the vaccine). The US product information has indicated that mefloquine (and chloroquine) can be given with the vaccine but that proguanil should only be taken 10 days after the vaccine. US licensed product information for mefloquine, however, advises waiting at least 3 days after vaccination is completed before starting mefloquine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Typhim Vi; Vivotif; ***Austral.***: Typherix; Typhim Vi; Vivotif; ***Austria***: Typherix; Typhim Vi; Vivotif; ***Belg.***: Typherix; Typhim Vi; Vivotif; ***Canad.***: Typherix; Typhim Vi; Vivotif; ***Chile***: Typhim Vi; Vivotif; ***China***: Typhim Vi (达恩Vi); ***Cz.***: Typherix; Typhim Vi; ***Denm.***: Typherix; Typhim Vi; Vivotif; ***Fin.***: Typherix; Typhim Vi; Vivotif; ***Fr.***: Typherix; Typhim Vi; ***Ger.***: Typherix; Typhim Vi; Typhoral L; ***Gr.***: Typherix; Vivotif; ***Hong Kong***: Typherix†; Typhim Vi; Vivotif; ***Hung.***: Typherix; Typhim Vi; ***India***: Biovac Typhoid; Typhim Vi; Typhoral; Vactyph; ***Indon.***: Typherix; Typhim Vi; Vivotif; ***Irl.***: Typherix; Typhim Vi; ***Israel***: Typherix; Typhim Vi; ***Ital.***: Typherix; Typhim Vi; Vivotif; ***Malaysia***: Typherix; Typhim Vi; Vivotif; ***Neth.***: Typherix; Typhim Vi; Vivotif; ***Norw.***: Typherix; Typhim Vi; Vivotif; ***NZ***: Typh-Vax; Typherix; Typhim Vi; Vivotif; ***Philipp.***: Typherix; Typhim Vi; Vivotif; ***Pol.***: Typhim Vi; ***Port.***: Typherix; Typhim Vi; ***S.Afr.***: Typherix; Typhim Vi; ***Singapore***: Typherix; Typhim Vi; Vivotif; ***Spain***: Typherix; Typhim Vi; Vivotif; ***Swed.***: Typherix; Typhim Vi; Vivotif; ***Switz.***: Vivotif; ***Thai.***: Typbar; Typhim Vi; Vivotif†; ***Turk.***: Typhim†; ***UK***: Typherix; Typhim Vi; Vivotif; ***USA***: Typhim Vi; Vivotif.

Pharmacopoeial Preparations

Ph. Eur.: Freeze-dried Typhoid Vaccine; Typhoid Polysaccharide Vaccine; Typhoid Vaccine (Live, Oral, Strain Ty 21a); Typhoid Vaccine.

Vaccinia Immunoglobulins

Inmunoglobulinas contra el virus de la vacuna.
ATC — J06BB07.
UNII — 7UB4J759TD (human vaccinia virus immunoglobulin).

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 36: (Vaccinia Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with vaccinia virus (smallpox vaccine). It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable antimicrobial agent. It should be stored at 2 degrees to 8 degrees.

Profile

Vaccinia immunoglobulins have been used intramuscularly for the treatment of clinical complications of smallpox vaccination. They are not effective for postviral encephalitis. An intravenous vaccinia immunoglobulin is available in the USA.

References.

1. Hopkins RJ, *et al.* Safety and pharmacokinetic evaluation of intravenous vaccinia immune globulin in healthy volunteers. *Clin Infect Dis* 2004; **39:** 759–66.
2. Hopkins RJ, Lane JM. Clinical efficacy of intramuscular vaccinia immune globulin: a literature review. *Clin Infect Dis* 2004; **39:** 819–26.

Preparations

Pharmacopoeial Preparations

USP 36: Vaccinia Immune Globulin.

Varicella-Zoster Immunoglobulins

Inmunoglobulinas contra el herpesvirus 3 humano; Inmunoglobulinas contra el virus de la varicela zóster.
ATC — J06BB03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Varicella Immunoglobulin; Immunoglobulinum Humanum Varicellae). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against *Herpesvirus varicellae*. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under inert gas.

Ph. Eur. 8: (Human Varicella Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Varicellae ad Usum Intravenosum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having antibodies against human herpesvirus 3 (varicella-zoster virus 1). Human normal immunoglobulin for intravenous administration may be added. It contains not less than 25 international units/mL. Storage requirements are similar to those for Human Varicella Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25 degrees.

USP 36: (Varicella-Zoster Immune Globulin). A sterile solution of globulins derived from the plasma of adult donors selected for high titres of varicella-zoster antibodies. It contains 15 to 18% of globulins, of which not less than 99% is immunoglobulin G with traces of immunoglobulin A and immunoglobulin M. It contains glycine as a stabilising agent and thiomersal as a preservative. It contains not less than 125 units of specific antibody in not more than 2.5 mL of solution. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Varicella-zoster immunoglobulins are used for passive immunisation against varicella (chickenpox) in susceptible persons considered to be at high risk of developing varicella-associated complications after exposure to varicella or herpes zoster (shingles).

In the UK, varicella-zoster immunoglobulins are recommended for individuals who are at high risk of severe varicella and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox or herpes zoster. Those at increased risk include immunosuppressed patients, neonates including those whose mothers develop chickenpox (but not herpes zoster) in the period 7 days before to 7 days after delivery, and pregnant women. Varicella-zoster immunoglobulin does not prevent infection when given after exposure but may modify the course of disease. Treatment with antivirals may be necessary in severe disease (see p. 956.2).

The doses, given by deep intramuscular injection, of the varicella-zoster immunoglobulin available in the UK are: 250 mg for children up to 5 years of age; 500 mg for those aged 6 to 10 years; 750 mg for those aged 11 to 14 years; and 1 g for all those 15 years of age or older. A further dose is required if a second exposure occurs more than 3 weeks later. Varicella-zoster immunoglobulin should be given as soon as possible and not later than 10 days after exposure. Preparations of normal immunoglobulin for intravenous use may be used to provide an immediate source of antibody.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Varitect; ***Austria***: Varitect; ***Canad.***: VariZIG; ***Ger.***: Varicellon; Varitect; ***Gr.***: Varitect; ***Hong Kong***: Varitect†; ***Irl.***: Varitect†; ***Israel***: Varitect; ***Ital.***: Varitect; ***Neth.***: VariQuin; ***Pol.***: Varitect†; ***Port.***: Varitect†; ***S.Afr.***: Vazigam; ***Singapore***: Varitect†; ***Switz.***: Varitect; ***Thai.***: Varitect†; ***Turk.***: Immunozig†; Varitect; ***USA***: Varizig.

Pharmacopoeial Preparations

Ph. Eur.: Human Varicella Immunoglobulin for Intravenous Administration; Human Varicella Immunoglobulin;
USP 36: Varicella-Zoster Immune Globulin.

Varicella-Zoster Vaccines

Vacunas de la varicela zóster; Ветряночные Вакцины.
ATC — J07BK01.

Pharmacopoeias. Many pharmacopoeias have monographs including *Eur.* (see p. vii).

Ph. Eur. 8: (Shingles (Herpes Zoster) Vaccine (Live); Vaccinum Zonae Vivum). A freeze-dried preparation of a suitable attenuated strain of human herpesvirus 3 grown in cultures of human diploid cells. The culture medium may contain suitable antibiotics at the smallest effective concentration. It is reconstituted immediately before use to give a clear or slightly opalescent liquid, almost white suspension, or pale yellow liquid that may be coloured owing to the presence of a pH indicator. It is intended for use in adults. The dried vaccine should be stored at 2 degrees to 8 degrees. Protect from light.

Ph. Eur. 8: (Varicella Vaccine (Live); Vaccinum Varicellae Vivum). A freeze-dried preparation of a suitable attenuated strain of human herpesvirus 3 grown in cultures of human diploid cells. The culture medium may contain suitable antibiotics at the smallest effective concentration. It is reconstituted immediately before use to give a clear liquid that may be coloured owing to the presence of a pH indicator; it may contain a stabiliser. The dried vaccine should be stored at 2 degrees to 8 degrees. Protect from light.

The BP 2014 states that Var(Live) may be used on the label.

Uses and Administration

Live attenuated varicella-zoster vaccines may be used for active immunisation against varicella (chickenpox) and herpes zoster (shingles).

In the UK, vaccination against **varicella** is recommended only for persons considered to be at high risk of contracting the infection or highly susceptible to any complications it might cause; such patients include susceptible healthcare workers, and healthy contacts of immunocompromised patients when continuing close contact is unavoidable. Children from 1 year of age and adults may be given two doses (of 0.5 mL each), either intramuscularly or subcutaneously (depending on the product used); doses must be given 4 to 8 weeks apart.

In the USA, a 2-dose vaccination regimen against varicella is recommended as part of the primary immunisation schedule of infants and children (see under Vaccines, p. 2373.3). The first dose of 0.5 mL is given subcutaneously to children aged 12 to 15 months and the second dose at 4 to 6 years of age. Routine vaccination is also recommended for persons over the age of 7 years without evidence of immunity; two doses are given at an interval of at least 3 months in those aged 7 to 12 years and at least 28 days apart in those 13 years of age and older. Those who only received 1 dose should receive a second, catch-up dose.

In the USA, a high potency vaccine (containing a minimum of 19 400 plaque-forming units) against **herpes zoster** is recommended for persons 60 years of age and older. A single dose of 0.65 mL is given subcutaneously. In the UK, use of this vaccine is recommended for adults aged 70 years old.

A combination vaccine of measles, mumps, rubella, and varicella (MMRV) is available in the USA for use in children aged 12 months to 12 years.

References.

1. WHO. Varicella vaccines: WHO position paper. *Wkly Epidem Rec* 1998; **73:** 241–48. Also available at: http://www.who.int/immunization/wer7332varicella_Aug98_position_paper.pdf (accessed 30/06/10)
2. Oxman MN. Zoster vaccine: current status and future prospects. *Clin Infect Dis* 2010; **51:** 197–213.

Results of studies of varicella-zoster vaccines for active immunisation against chickenpox in healthy and leukaemic children have been largely favourable. Protective **efficacy** in healthy children appears to be over 90%. In healthy adolescents and adults, adding a second dose 4 or 8 weeks after the first increased seroconversion rates from about 70 to 80% to 97% or better.[1] A protective efficacy of about 85% has been reported in leukaemic children given one dose of varicella-zoster vaccine[2,3] and interruption of chemotherapy for vaccination does not appear necessary in terms of immunogenicity of the vaccine.[2,4]

The **duration of immunity** after a 1-dose regimen for active immunisation against chickenpox is also under debate; despite at least 70 to 90% efficacy, some consider that a single dose does not provide sufficient herd immunity levels to prevent outbreaks, especially in school settings.[5,6] Initial studies show that the immunity induced by natural infection with wild type virus is superior to that induced by the vaccine. In one study,[3] antibodies were absent in about one-quarter of all vaccinees (both leukaemic children and

healthy adults) 1 year after a second dose of vaccine, but were still present after up to 6 years in all those who had breakthrough varicella infection.

However, immunity to varicella-zoster is complex, depending not only on circulating antibody but also on cellular immunity and secretory antibody. Thus, although a person may become seronegative after vaccination, protection from varicella may remain, albeit partial.[2] Both humoral and cell mediated immunity have been shown to persist for up to 20 years after vaccination.[7] Leukaemic children seen up to 6 years after immunisation have continued to be well protected[2] and varicella in previously-vaccinated persons is usually mild.[5,6]

Surveillance data collected from 11 356 children in the USA between 1995 and 2004 found that annual rates of breakthrough varicella increased significantly with time. Children aged 8 to 12 years at the onset of disease who had been vaccinated 5 years or more previously were 2.6 times more likely to have moderate or severe breakthrough varicella than those vaccinated less than 5 years previously.[8] The efficacy of a 2-dose vaccination regimen (doses given 3 months apart) was assessed in 2216 children over a period of 9 to 10 years.[9] Children vaccinated with the 2-dose regimen were 3.3 times less likely to develop varicella more than 42 days after vaccination than those who had received a single dose. During the 10-year follow-up period most breakthrough cases occurred in years 2 to 5, for both treatment regimens. No breakthrough cases were reported in years 7 to 10 for those who received the 2-dose regimen, while 10 cases were reported for those who received the 1-dose regimen. Since June 2007 the US Advisory Committee on Immunization Practices (ACIP) has recommended that children between the ages of 4 and 6 years receive a second dose of varicella vaccine.[6]

A systematic review suggests that varicella-zoster vaccine may prevent or modify varicella if given to children within 3 days of exposure to the infection.[10] It may be useful as an **adjunct** to varicella-zoster immunoglobulin. The treatment of varicella-zoster infections with antivirals is discussed on p. 956.2.

One concern of varicella-zoster vaccination has been the possibility of an **increased risk of herpes zoster** (shingles) in immunised children. Although herpes zoster has been reported in vaccinated persons, a study involving 346 leukaemic children and 84 matched controls concluded that the incidence of herpes zoster following varicella-zoster vaccine was no greater than that following natural varicella infection.[11] The study did suggest that the risk of herpes zoster may be lowered by vaccination but this must be confirmed by long-term follow-up. Postmarketing surveys[12] of almost 90 000 vaccine recipients also showed a low incidence of herpes zoster. The vaccine strain of varicella-zoster virus is transmissible, particularly from vaccinees who develop a rash. There is no evidence of reversion to virulence of the vaccine strain with secondary transmission.

Another concern is that vaccination of children could result in more severe infections in later life after immunity has waned. However, studies have shown that in general varicella is less severe in previously immunised than in non-immunised patients.[13,14]

The risk of zoster increases with age reflecting the waning of the specific cell-mediated immunity to the virus. Thus, the use of a high-potency varicella-zoster vaccine has been investigated in elderly subjects.[15,16] In a randomised, double-blind, placebo-controlled study in over 38 000 subjects aged 60 years or more the vaccine reduced the burden of illness due to herpes zoster by 61.1% and the incidence of herpes zoster and of postherpetic neuralgia by 51.3% and 66.5% respectively.[17] A high-potency varicella-zoster vaccine is recommended by some authorities for all people 60 years of age and older,[18,19] including those who have already had an episode of shingles.[18] The efficacy of the varicella-zoster vaccine in preventing further infections in such patients has not been shown in clinical studies,[20] although immunogenicity of this vaccine 4 weeks after vaccination has been shown.[21]

1. Kuter BJ, *et al*. Safety, tolerability, and immunogenicity of two regimens of Oka/Merck varicella vaccine (Varivax) in healthy adolescents and adults. *Vaccine* 1995; **13:** 967 72.
2. Gershon AA, *et al*. Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. *N Engl J Med* 1989; **320:** 892–7.
3. Gershon AA, *et al*. Live attenuated varicella vaccine: protection in healthy adults compared with leukemic children. *J Infect Dis* 1990; **161:** 661–6.
4. Arbeter AM, *et al*. Immunization of children with acute lymphoblastic leukemia with live attenuated varicella vaccine without complete suspension of chemotherapy. *Pediatrics* 1990; **85:** 338–44.
5. Lopez AS, *et al*. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? *Pediatrics* 2006; **117:** 2253–4. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/6/e1070 (accessed 06/07/07)
6. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-4): 1–40. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5604.pdf (accessed 06/07/07)
7. Asano Y, *et al*. Experience and reason: twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. *Pediatrics* 1994; **94:** 524–6.
8. Chaves SS, *et al*. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med* 2007; **356:** 1121–9.
9. Kuter B, *et al*. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J* 2004; **23:** 132–7.
10. Macartney K, McIntyre P. Vaccines for post-exposure prophylaxis against varicella (chickenpox) in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 18/12/09).
11. Lawrence R, *et al*. The risk of zoster after varicella vaccination in children with leukemia. *N Engl J Med* 1988; **318:** 543–8.
12. Black S, *et al*. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* 1999; **18:** 1041–6.
13. Watson BM, *et al*. Modified chickenpox in children immunized with the Oka/Merck varicella vaccine. *Pediatrics* 1993; **91:** 17–22.
14. Bernstein HH, *et al*. Clinical survey of natural varicella compared with breakthrough varicella after immunization with live attenuated Oka/Merck varicella vaccine. *Pediatrics* 1993; **92:** 833–7.
15. Sanford M, Keating GM. Zoster vaccine (Zostavax): a review of its use in preventing herpes zoster and postherpetic neuralgia in older adults. *Drugs Aging* 2010; **27:** 159–76.
16. Keating GM. Shingles (herpes zoster) vaccine (Zostavax(®)): a review of its use in the prevention of herpes zoster and postherpetic neuralgia in adults aged ≥ 50 years. *Drugs* 2013; **73:** 1227–44.
17. Oxman MN, *et al*. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005; **352:** 2271–84.
18. CDC. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; **57:** 1–30. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm (accessed 12/02/10)
19. Public Health England. Shingles vaccine special edition (issued September 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239832/vaccine_update_12_9_v3.pdf (accessed 24/10/13)
20. Adams EN, *et al*. Herpes zoster and vaccination: a clinical review. *Am J Health-Syst Pharm* 2010; **67:** 724–7.
21. Mills R, *et al*. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. *Vaccine* 2010; **28:** 4204–9.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Varicella vaccines for active immunisation against chickenpox are generally well tolerated. Rashes may occur at the injection site and generalised varicella-like rashes elsewhere have been reported. The vaccine strain of virus can become latent, which could result in late development of zoster infections, but the incidence of herpes zoster is lower after vaccination than in an unvaccinated population. Breakthrough cases of chickenpox have been reported after single- and 2-dose vaccination regimens, but were in most cases milder. The incidence of breakthrough varicella is markedly lower after the 2-dose regimen.

High potency varicella vaccines licensed for active immunisation against herpes zoster (shingles) should not be used for active immunisation against varicella (chickenpox). Such vaccines are contra-indicated in patients with a history of anaphylactic reactions to neomycin or gelatin.

Transmission of the vaccine strain of the virus may occur rarely between those who developed a varicella-like rash after vaccination and susceptible contacts. The vaccines are contra-indicated in patients with severe immunosuppression and those with active untreated tuberculosis should not be vaccinated.

General references.
1. Black S, *et al*. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* 1999; **18:** 1041–6.
2. Simberkoff MS, *et al*. Safety of herpes zoster vaccine in the Shingles Prevention Study: a randomized trial. *Ann Intern Med* 2010; **152:** 545–54.

Effects on the eye. See Effects on the Nervous System, below.

Effects on the nervous system. Twenty months after immunisation with varicella-zoster virus vaccine a 3½-year-old immunocompetent child developed herpes zoster opthalmicus and encephalitis; molecular analysis confirmed the vaccine strain as the causative agent. The child made a full recovery with no neurologic sequelae after treatment with intravenous and topical aciclovir.[1]

1. Chouliaras G, *et al*. Vaccine-associated herpes zoster ophthalmicus and encephalitis in an immunocompetent child. *Pediatrics* 2010; **125:** 807. Full version: http://www.pediatrics.org/cgi/content/full/125/4/e969 (accessed 10/11/10)

Pregnancy. Normally occurring varicella zoster infection may cause fetal harm, therefore as a precautionary measure, vaccination of pregnant women against varicella is generally contra-indicated; advice is also given to avoid pregnancy for 3 months after the last dose of vaccine. However, surveillance of women inadvertently vaccinated during pregnancy has not identified any increased risk, either in terms of congenital varicella or for congenital abnormalities.

It should also be noted that the vaccine strain of varicella-zoster virus is transmissible, particularly from vaccinees who develop a rash.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Varicela Biken; Varilrix; ***Austral.***: Varilrix; Varivax; Zostavax; ***Austria***: Varilrix; Varivax; Zostavax; ***Belg.***: Provarivax; Varilrix; ***Braz.***: Vacina Contra A Varicela (Virus Atenuado); Vacina Contra Varicela; ***Canad.***: Varilrix; Varivax; Zostavax; ***Chile***: Biken; Varilrix; ***China***: Huiliwei (惠立维); Varilrix (威可檬); Wei Zhi Wei (维稚维); Weiruile (维瑞乐); ***Cz.***: Varilrix; Zostavax; ***Denm.***: Varilrix; ***Fin.***: Varilrix; ***Fr.***: Varilrix; Varivax; ***Ger.***: Varilrix; Varivax; Zostavax†; ***Gr.***: Varilrix; Varirix; Varivax; ***Hong Kong***: Okavax; Varilrix; Varivax; ***Hung.***: Varilrix; ***India***: Okavax; Varilrix; Varipox†; ***Indon.***: Okavax; Varilrix; ***Irl.***: Varivax; Zostavax; ***Israel***: Varilrix; Zostavax; ***Ital.***: Varilrix; Varivax; ***Malaysia***: Okavax; Varilrix; ***Mex.***: Okavax; Varilrix; Varivax; ***Neth.***: Provarivax; Zostavax; ***Norw.***: Varilrix; ***NZ***: Varilrix; Varivax; Zostavax; ***Philipp.***: Okavax; V-Z Vax; Varilrix; ***Pol.***: Varilrix; Zostavax; ***Port.***: Varilrix; Varivax; Zostavax; ***Rus.***: Okavax (Окавакс); Varilrix (Варилрикс); ***S.Afr.***: Varilrix; ***Singapore***: Okavax; Varilrix; ***Spain***: Varilrix; Varivax; ***Swed.***: Varilrix; ***Switz.***: Varilrix; Varivax; Zostavax; ***Thai.***: Okavax; Varilrix; ***Turk.***: Okavax; Varilrix; ***UK***: Varilrix; Varivax; Zostavax; ***Ukr.***: Varilrix (Варилрикс); ***USA***: Varivax; Zostavax; ***Venez.***: Varilrix.

Pharmacopoeial Preparations

Ph. Eur.: Shingles (Herpes Zoster) Vaccine (Live); Varicella Vaccine (Live).

Yellow Fever Vaccines

Vacunas de la fiebre amarilla.

ATC — J07BL01.

UNII — 4G601DAM77 (yellow fever virus antigen); PY4EET359T (yellow fever virus live antigen).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Yellow Fever Vaccine (Live); Vaccinum Febris Flavae Vivum). A freeze-dried preparation of yellow fever virus derived from the 17D strain and grown in fertilised hen eggs. It is reconstituted immediately before use. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Yel(live) may be used on the label.

Uses and Administration

Yellow fever vaccines are used for active immunisation against yellow fever. Immunity is usually established within about 10 days of administration and persists for many years. Only one dose is required for immunisation and is given by deep subcutaneous injection; the dose (0.5 mL) is the volume containing at least 1000 mouse LD_{50} units.

In the UK, immunisation against yellow fever is recommended for laboratory workers handling infected material, for persons travelling through or living in areas of infection, and for travellers entering countries which require an International Certificate of Vaccination. The immunity produced may last for life although officially an International Certificate of Vaccination against yellow fever is valid only for 10 years starting 10 days after the primary immunisation and only if the vaccine used has been approved by WHO and given at a designated centre.

Vaccination under 9 months of age is not generally recommended (see Adverse Effects and Precautions, p. 2425.1).

General references.
1. Barrett ADT. Yellow fever vaccines. *Biologicals* 1997; **25:** 17–25.
2. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–59. Also available at: http://www.who.int/wer/2003/en/wer7840.pdf (accessed 30/06/10)
3. Barnett ED. Yellow fever: epidemiology and prevention. *Clin Infect Dis* 2007; **44:** 850–6.
4. Barrett AD, Teuwen DE. Yellow fever vaccine - how does it work and why do rare cases of serious adverse events take place? *Curr Opin Immunol* 2009; **21:** 308–13.
5. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; **59** (RR-7): 1–27. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5907.pdf (accessed 02/09/10)

Immunisation schedules. The 17D (Rockefeller) yellow fever vaccine is now the only yellow fever vaccine produced.[1,2] The quantity available in the world has been limited and its relatively short half-life does not permit the accumulation of large stocks. The demand for the vaccine is also somewhat irregular, being suddenly high during epidemics and low during inter-epidemic periods.

In Africa and in South America two different strategies for yellow fever immunisation have been followed.[1,2] Firstly, an emergency immunisation programme takes place once an outbreak has begun, in an attempt to limit the spread of infection by immunising all persons in the focus, regardless of their former immune status. One disadvantage is that immunity does not appear until 7 days after immunisation and deaths may be expected to occur in the interim period. Secondly, a routine mass immunisation

programme for yellow fever is aimed at immunising in advance all populations considered to be at risk. Yellow fever vaccine is included in the WHO Expanded Programme on Immunization; there are obvious logistic advantages in giving it at the age of 9 months at the same time as measles vaccine. In rural areas of the endemic zone that are considered at high risk, the minimum age for routine immunisation may be lowered to 6 months (see Vaccine-associated Neurotropic Disease, below).

1. WHO. *Prevention and control of yellow fever in Africa*. Geneva: WHO, 1986.
2. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–60.

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO. Information is provided concerning the countries in Africa and South America where yellow fever is endemic and also countries requiring a traveller to hold a valid vaccination certificate. For some further details, see p. 2374.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Local and general reactions are not common after vaccination for yellow fever. Very rarely encephalitis has occurred, generally in infants under 9 months of age. Therefore, yellow fever vaccine is not usually given to infants under 9 months (but see Vaccine-associated Neurotropic Disease, below).

There are as yet limited data on the safety of yellow fever vaccine in HIV-positive individuals. In the UK, it is recommended that specialist advice should be sought regarding the use of yellow fever vaccine in such individuals. WHO notes that the vaccine has been given to HIV-positive individuals who are symptomatic. For further information on the use of yellow fever vaccine in HIV-infected individuals, see below.

Breast feeding. In the USA, the Advisory Committee on Immunization Practices[1] recommends that yellow fever vaccination of nursing mothers be avoided, except when travel to high-risk yellow fever-endemic areas cannot be avoided or postponed.

1. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR* 2002; **51** (RR-17): 1–11. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5117.pdf (accessed 25/05/06)

HIV Infection. There is a high prevalence of HIV infection in many countries where yellow fever is endemic, but immunogenicity and safety data on the use of the 17D yellow fever vaccine in HIV-infected individuals are limited. A study[1] of 102 HIV-infected individuals (with mainly mild to moderate immunodeficiency) vaccinated with the 17D yellow fever vaccine reported no serious adverse events after vaccination, but noted that the immunogenicity of the vaccine was impaired in HIV-infected individuals compared with those not infected with HIV. HIV-infected individuals with undetectable HIV RNA levels and higher CD4+ T lymphocyte counts had a better response to the vaccine. Furthermore, the authors considered that a booster vaccination every 10 years for HIV-infected individuals was probably insufficient and suggested that determination of neutralisation titre or revaccination should be considered after 2 to 5 years in the event of potential exposure.

1. Veit O, *et al*. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* 2009; **48:** 659–66.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies yellow fever vaccine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Although yellow fever vaccine has been given to women during pregnancy without producing adverse effects in the infants,[1] fetal infection has been reported.[2] In the USA recommendations[3] therefore advise that the safety of yellow fever vaccination during pregnancy has not been established and the vaccine should only be given to pregnant women if travel to an endemic area is unavoidable and if an increased risk of exposure exists. Infants born to these women should be monitored closely for evidence of congenital infection or other adverse effects.

1. Nasidi A, *et al*. Yellow fever vaccination and pregnancy: a four-year prospective study. *Trans R Soc Trop Med Hyg* 1993; **87:** 337–9.
2. Tsai TF, *et al*. Congenital yellow fever virus infection after immunization in pregnancy. *J Infect Dis* 1993; **168:** 1520–3.
3. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR* 2002; **51** (RR-17): 1–11. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5117.pdf (accessed 25/05/06)

Vaccine-associated neurotropic disease. Yellow fever vaccine has been associated with rare reports of encephalitis, now termed vaccine-associated neurotropic disease (YEL-AND). WHO has stated[1] that, since 1945, there have been at least 26 cases of proven or probable YEL-AND of which 16 occurred in infants aged less than 6 months. Of the 26 cases, 24 recovered without further complications and there were 2 fatalities.[1] Vaccine virus recovered from one of the fatalities, a 3-year-old child, revealed that mutation had occurred in the envelope gene of the virus, but it is unknown whether similar mutations occurred in the other cases. The other fatality occurred in an immunocompromised adult with HIV infection. As a precaution against possible encephalitis, infants less than 9 months of age are not generally immunised, although it may be advisable to immunise at 6 to 8 months of age during epidemics.

A laboratory-confirmed case of yellow fever vaccine-associated neurologic disease occurred in an infant due to the transmission of yellow fever vaccine virus through breast milk. The infant recovered completely with antibacterial and antiviral treatment for meningoencephalitis and follow-up of the infant showed normal neurodevelopment and growth through age 6 months.[2]

1. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–59.
2. CDC. Transmission of yellow fever vaccine virus through breast-feeding - Brazil, 2009. *MMWR* 2010; **59:** 130–2.

Vaccine-associated viscerotropic disease. Yellow fever vaccine has been associated with rare reports of multiple organ failure, now termed yellow fever vaccine-associated viscerotropic disease (YEL-AVD). WHO has stated[1] that, between 1996 and 2001, there were 7 recorded cases (6 fatal) of YEL-AVD of which 2 occurred in Brazil,[2] 4 in the USA,[3] and one in Australia.[4] A further case, also leading to fatality, was reported to have occurred in Spain in 2004,[5] and 5 cases, 4 fatal, in 2007 in Peru.[6] It has been suggested that the most likely explanation is an idiosyncratic host susceptibility to the 17D vaccine strain rather than a reversion of the vaccine strain to a wild-type strain.[5] There is also some evidence to suggest that the risk of YEL-AVD is greater in patients aged over 60 years.[7]

1. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–59.
2. Vasconcelos PFC, *et al*. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. *Lancet* 2001; **358:** 91–7. Corrections. *ibid.*; 336. *ibid.*; 1018.
3. Chan RC, *et al*. Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. *Lancet* 2001; **358:** 121–2.
4. Martin M, *et al*. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. *Lancet* 2001; **358:** 98–104.
5. Agencia Española del Medicamentos y Productos Sanitarios. A death associated with yellow fever vaccination reported in Spain. Available at: http://www.eurosurveillance.org/ew/2004/041104.asp (accessed 25/08/05)
6. Whittembury A, *et al*. Viscerotropic disease following yellow fever vaccination in Peru. *Vaccine* 2009; **27:** 5974–81.
7. Khromava AY, *et al*. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* 2005; **23:** 3265–63.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Stamaril; ***Austral.***: Stamaril†; ***Austria***: Stamaril; ***Belg.***: Stamaril; ***Canad.***: YF-Vax; ***Chile***: Stamaril; ***Cz.***: Stamaril; ***Denm.***: Stamaril; ***Fin.***: Arilvax†; Stamaril; ***Fr.***: Stamaril; ***Ger.***: Stamaril; ***Hong Kong***: Stamaril†; ***Hung.***: Stamaril; ***Irl.***: Stamaril; ***Israel***: Arilvax†; Stamaril; ***Ital.***: Stamaril; ***Malaysia***: Stamaril; ***Neth.***: Arilvax†; Stamaril; ***Norw.***: Stamaril; ***NZ***: Stamaril; ***Pol.***: Stamaril; ***Port.***: Stamaril; ***S.Afr.***: Arilvax†; Stamaril; ***Singapore***: Stamaril; ***Spain***: Stamaril; ***Swed.***: Stamaril; ***Switz.***: Stamaril; ***Turk.***: Stamaril†; ***UK***: Arilvax; Stamaril; ***USA***: YF-Vax.

Pharmacopoeial Preparations

Ph. Eur.: Yellow Fever Vaccine (Live).

Miscellaneous Drugs and Other Substances

This chapter includes some drugs not easily classified, herbal medicines, new drugs whose place in therapy is not yet clear, and drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

Abrus

Abrus Seed; Bejuco de peonia; Indian Liquorice; Jequirity Bean; Jumble Beads; Prayer Beads; Regaliz americano; Rosary Beans; Semillas del regaliz americano.

Profile

Abrus consists of the seeds of *Abrus precatorius* (Leguminosae), one of whose constituents is abrin. Abrin, which is closely related to ricin, is considered responsible for the toxic effects of the seeds. Children have died from eating one or more seeds. Toxicity may be less likely to occur if the seeds are swallowed whole, than if they are chewed, because of the hard seed coat. Toxic effects may occur within a few hours or may be delayed for several days after ingestion. Signs and symptoms of abrin poisoning are similar to those described for ricin, p. 2604.2.

Abrus has been used as an oral contraceptive in herbal medicine.

Homoeopathy

Abrus has been used in homoeopathic medicines under the following names: Jequirity.

References.

1. Aslam M, Shaw JMH. Abrus in Asian medicine. *Pharm J* 1998; **261:** 822–4.
2. Fernando C. Poisoning due to Abrus precatorius (jequirity bean). *Anaesthesia* 2001; **56:** 1178–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Enkasari; Ika Sariawan; ***Rus.***: Travisil (Трависил); ***Ukr.***: Travisil (Трависил).

Homoeopathic Preparations. ***Austral.***: Sedatif†; ***Canad.***: Sedatil; ***Cz.***: Sedatif PC; ***Fr.***: Sedatif PC; ***Hung.***: Sedatif; ***Neth.***: Sedatif PC; ***Port.***: Sedatif PC; ***Rus.***: Homeostres (Гомеострес); ***Switz.***: Sedatif PC; ***Ukr.***: Sedatif PC (Седатив ПЦ).

Absinthium

Absinthe; Absinthii herba; Absintio; Ajenjo; Ajorizo; Artemisa; Assenzio; Fehér üröm fű; Hierba santa; Incienso de Andalucía; Karčiųjų kiečių žolė; Losna; Mali, Koiruoho; Malört; Pelin; Pelyňková nať; Wermutkraut; Wormwood; Ziele piołunu; Полынь Горькая.

CAS — 546-80-5 (α-thujone); 471-15-8 (β-thujone).

ATC Herb — HA03AW5004 (Artemisia absinthium: *herb); HA05AW5002* (Artemisia absinthium: *herb); HA09WA5002* (Artemisia absinthium: *herb); HP02WA5001* (Artemisia absinthium: *herb).*

UNII — F84709P2XV.

NOTE. The name Hierba Santa (yerba santa) has been applied to many plants including species of the genus *Eriodictyon* (p. 1665.2).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of absinthium:

Green Fairy; Green Goddess; La Fée Verte.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Wormwood). The leaves or flowering tops, or a mixture of these dried, whole or cut organs of wormwood, *Artemisia absinthium*. It contains not less than 2 mL/kg of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Absinthium has been used as a bitter. It is also used in small quantities as a flavour in alcoholic beverages, although it is considered in some countries to be unsafe for use in foods, beverages, or drugs. Habitual use or large doses cause absinthism, which is characterised by restlessness, vomiting, vertigo, tremors, and convulsions. Thujone, related to camphor, is the major constituent of the essential oil derived from absinthium.

Absinthium has been investigated in the treatment of inflammatory bowel disease.

Homoeopathy

Absinthium has been used in homoeopathic medicines under the following names: Artemisia absinthium; Artemisia absinthium ex herba siccata; Absinth.

References.

1. Weisbord SD, *et al*. Poison on line—acute renal failure caused by oil of wormwood purchased through the Internet. *N Engl J Med* 1997; **337:** 825–7.
2. Skyles AJ, Sweet BV. Wormwood. *Am J Health-Syst Pharm* 2004; **61:** 239–42.
3. Omer B, *et al*. Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. *Phytomedicine* 2007; **14:** 87–95.
4. Krebs S, *et al*. Wormwood (*Artemisia absinthium*) suppresses tumour necrosis factor alpha and accelerates healing in patients with Crohn's disease—a controlled clinical trial. *Phytomedicine* 2010; **17:** 305–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Nat Pelynku Praveho†.

Multi-ingredient Preparations. ***Austral.***: Wormwood Complex; ***Austria***: Abdomilon N; Magentee St Severin; Mariazeller; Pervivo; Sigman-Haustropfen; ***Braz.***: Camomila; ***Canad.***: Gallexier†; Para-Gard; ***Cz.***: Original Schwedenbitter; Zaludecni Cajova Smes; ***Fr.***: Tisane Hepatique de Hoerdt†; ***Ger.***: Abdomilon N; Amara-Tropfen; Floradix Multipretten N; Gallemolan forte†; Gallexier; Gastritol; Pascopankreat; ventri-loges N†; ***Hung.***: Bittner; ***Pol.***: Artemisol; Krople Zoladkowe†; Krople Zoladkowe; Pervivo; ***Rus.***: Gastroguttal (Гастрогуттал); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Amara†; ***Switz.***: Baume Zeller; Gouttes Amara; Kernosan Heidelberger Poudre; Metabol; Pommade au Baume; Wala Elixir amer; ***Ukr.***: Gastritol (Гастритол); Maraslavin (Мараславин).

Homoeopathic Preparations. ***Canad.***: Amaratopfen†; Formula ES 211; ***Fr.***: Carominthe; Yucca Complexe No 110; ***Ger.***: Cefatropin N†; Gastritis Complex; K 1000; Magen-Darm-Entoxin N; Magen-Darmtropfen N; Ventrigutt M; ***Rus.***: Nux Vom-Plus (Нукс Вом-Плюс); ***UK***: Nausyn.

Acedoben *(pINN)*

Acedobén; Acédobène; Acedobenum; Ацедобен.

p-Acetamidobenzoic acid.

$C_9H_9NO_3$=179.2

CAS — 556-08-1.

UNII — 04Z20NMK31.

Profile

Acedoben is a component of inosine pranobex (p. 988.3), and has been given orally as the potassium salt in the treatment of skin disorders. Acedoben and its sodium salt have been applied topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Hongosan†.

Aceglutamide *(rINN)*

Aceglutamida; Acéglutamide; Aceglutamidum; Ацеглутамид.

N^2-Acetyl-L-glutamine; 2-Acetylamino-L-glutaramic acid.

$C_7H_{12}N_2O_4$=188.2

CAS — 2490-97-3.

UNII — 01J18G9G97.

Profile

Aceglutamide has been given in an attempt to improve memory and concentration. Aceglutamide aluminium (p. 1814.3) is used as an antacid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ai Li Su (爱立苏); Ai Lu Na (艾鲁那); Ai Sen Ao (艾森澳); Ao Li Xi (奥立喜); Ao Yi Ning (奥怡宁); Dan Nuo (丹诺); De Yi Fen (德益芬); Di Yi (迪依); Fu Ao (扶奥); Gan Fen (干芬); Han Xue (涵雪); He Di Xin (赫迪新); Hui Le (慧乐); Jian Yi (健意); Jin Jie Shu (劲截纾); Jun Da Ke (均达柯); Kang Da Li Cun (康达利存); Kang Pa Si (康帕斯); Li Shu Kang (力枢康); Long Ge Xian (隆格先); Long Sheng Tai (龙胜泰); Lu Si Kai (路斯开); Meng Qing (梦清); Miao Si Ning (妙司宁); Nuo An Ping (诺安平); Nuoyi (诺依); Qi Shi (奇势); Rui Ke An (瑞可安); Sa Ni Ka (萨尼卡); Sai Pu Li Er (赛普利尔); ShengDi (胜迪); Shuai Ning (帅宁); Su Yi Ning (苏忆宁); Tian Xing (天醒); Tu Er (土尔); Wan Xin Neng (万欣能); Xun Bo (讯博); Yi Ming (忆明); Yi Pei (一培); YiQing (意清); YiXin (宜信); You Ni Sheng (尤尼生); Yun Ke Shu (云可舒).

Multi-ingredient Preparations. ***Chile***: Cebrocal; ***Ital.***: Acutil Fosforo; ***Mex.***: Italviron.

Acemannan *(USAN, rINN)*

Acemanán; Acémannan; Acemannanum; Polymanoacetate; Ацеманнан.

CAS — 110042-95-0.

UNII — UZ29E6L2X8.

Profile

Acemannan is a highly acetylated, polydispersed, linear mannan obtained from the mucilage of *Aloe vera* (*A. barbadensis*). It has immunomodulating properties and is an ingredient of topical wound dressing products including those formulated for the oral mucosa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Carrasyn; DiaB Gel; Oral Wound Rinse; RadiaGel; SaliCept; Ultrex.

Acetic Acid

Acide acétique; Ácido acético; Ácido etanóico; Ácido etílico; Ácido metanocarboxílico; Acidum Aceticum; Acto rūgštis; Asetik Asit; Ättiksyra; E260; Ecetsav; Eisessig (glacial acetic acid); Essigsäure; Etanoico; Ethanoic Acid; Etikkahappo; Kwas octowy; Kyselina octová.

$C_2H_4O_2$=60.05

CAS — 64-19-7.

ATC — G01AD02; S02AA10.

ATC Vet — QG01AD02; QS02AA10.

UNII — Q40Q9N063P.

NOTE. The nomenclature of acetic acid often leads to confusion over whether concentrations are expressed as percentages of glacial acetic acid ($C_2H_4O_2$) or of a diluted form. In *Martindale*, the percentage figures given against acetic acid represent the amount of $C_2H_4O_2$.

Pharmacopoeias. Glacial acetic acid is included in *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Solutions containing about 30 to 37% are included in *Br.* (33%), *Chin.* (36 to 37%), *Int.*, *Jpn* (30 to 32%), and *Swiss* (30%). Also in *USNF* (36 to 37%).

Dilute acetic acid (6%) is included in *Br.* and *Int.* Also in *USNF*.

Ph. Eur. 8: (Acetic Acid, Glacial; Acidum Aceticum Glaciale). A crystalline mass or a clear colourless volatile liquid. F.p. not lower than 14.8 degrees. Miscible with water, with alcohol, and with dichloromethane. Store in airtight containers.

BP 2014: (Acetic Acid (33 per cent)). It contains 32.5 to 33.5% w/w of $C_2H_4O_2$. It is a clear colourless liquid with a pungent odour. Miscible with water, with alcohol, and with glycerol.

BP 2014: (Acetic Acid (6 per cent)). It contains 5.7 to 6.3% w/w of $C_2H_4O_2$. It is prepared by diluting Acetic Acid (33 per cent).

USP 36: (Glacial Acetic Acid). A clear colourless liquid with a pungent characteristic odour. B.p. about 118 degrees.

Miscible with water, with alcohol, and with glycerol. Store in airtight containers.

USNF 31: (Acetic Acid). It contains 36 to 37% w/v of $C_2H_4O_2$. It is a clear colourless liquid with a strong characteristic odour. Miscible with water, with alcohol, and with glycerol. Store in airtight containers.

USNF 31: (Diluted Acetic Acid). It contains 5.7 to 6.3% w/v of $C_2H_4O_2$. It is prepared by diluting Acetic Acid. Store in airtight containers.

Uses and Administration

Glacial acetic acid has been used as an escharotic. Diluted forms have been used as an antibacterial (it is reported to be effective against *Haemophilus* and *Pseudomonas* spp.), antifungal, and antiprotozoal in vaginal gels and douches, irrigations, topical preparations for the skin and nails, and in ear drops. Diluted forms have also been used as an expectorant, an astringent lotion, and as treatments for warts (p. 1689.3), callosities, and for certain jellyfish stings (see below). Solutions have also been used to soften ear wax (p. 1836.3) and in the treatment of otitis externa (p. 195.1). Visual inspection of the uterine cervix with acetic acid (VIA) is being investigated as a screening method for cervical cancer, particularly where facilities for cytological methods may be limited.

A solution containing 4% w/v $C_2H_4O_2$ is known as artificial vinegar or non-brewed condiment. Vinegar is a product of fermentation.

Jellyfish sting. Vinegar or acetic acid 3 to 10% is applied to box jellyfish stings to inactivate any fragments of adherent tentacle (see p. 2397.1). Acetic acid solutions have been reported to be useful in stings by related species[1] although they may produce further discharge of venom in some jellyfish.[2]

1. Fenner PJ, *et al.* "Morbakka", another cubomedusan. *Med J Aust* 1985; **143:** 550–5.
2. Fenner PJ, Fitzpatrick PF. Experiments with the nematocysts of Cyanea capillata. *Med J Aust* 1986; **145:** 174.

Wounds and burns. Infection of wounds (p. 1690.1) and burns (p. 1683.1) with *Pseudomonas aeruginosa* may delay healing. Acetic acid has been used, in concentrations of up to 5%, to eradicate these infections.[1]

1. Milner SM. Acetic acid to treat Pseudomonas aeruginosa in superficial wounds and burns. *Lancet* 1992; **340:** 61.

Adverse Effects and Treatment

Local or topical application of acetic acid preparations may produce stinging or burning. Ingestion of glacial acetic acid can produce similar adverse effects to those of hydrochloric acid (p. 2529.1), which may be treated similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cutinova; Hexa-Defital Crema Enjuague; Otopreven; Pelo Libre Protectora; ***Austral.***: Summer's Eve Douche; ***Fr.***: Para Lentes†; ***Ger.***: Liberanit†; ***Gr.***: Instaret; ***UK***: EarCalm; Meltus Baby; ***USA***: Feminique; Massengill Disposable; Summer's Eve Disposable; ***Venez.***: Duvagin; Fem Ducha; Gynovit.

Multi-ingredient Preparations. ***Arg.***: Aglio†; Callicida; Detebencil Nit; Fuera Bicho†; Hexa-Defital Plus; Microsona Otica; Uze Active; ***Austral.***: Aqua Ear; Ear Clear for Swimmers Ear; ***Belg.***: Aporil; ***Braz.***: A Curitybina; Lacto Vagin; ***Canad.***: Acid Concentrate; Haemosol H†; Naturalyte H; Viron Wart Lotion; ***Chile***: Concentrado Acido; ***China***: Solcoderm (思可得); ***Fr.***: Anticor†; Dialysol Acide†; Nitrol†; Ysol 206†; ***Ger.***: AdaptaCide PAA-C; Gehwol Huhneraugen-Tinktur; Solco-Derman; ***Gr.***: Otocort; ***Hong Kong***: Baby Cough with Antihistamine†; Solcoderm†; ***Hung.***: Strand; ***India***: Otek-O; Perfocyn†; ***Irl.***: Phytex†; ***Ital.***: Cue Soluzione Otologica; Oleo Calcarea; ***NZ***: VoSoL; ***Pol.***: Acifungin; Solcogyn; ***Rus.***: Bubil (Бубил)†; Solcoderm (Солкодерм); Solcovagin (Солковагин); ***Spain***: Callicida Cor Pik†; Callicida Rojo†; Keranin†; Nitroina; Quocin; ***Switz.***: Solcoderm; Solcogyn; Waruzol; ***Thai.***: Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; ***Turk.***: Dilan†; Rendializat Sodyum; SH-206; Tuba; ***UK***: Ellimans; Goddards Embrocation; Phytex; Potters Gees Linctus; Sanderson's Throat Specific; ***Ukr.***: Solcoderm (Солкодерм); Solcovagin (Солковагин); ***USA***: AABP; Acetasol HC; Acetasol; Acid Jelly†; Borofair Otic†; Burow's; Fem pH; Klout; Otic Domeboro; Otic Edge†; Star-Otic; VoSoL HC; ***Venez.***: Kayivis; Saxacid.

Pharmacopoeial Preparations

BP 2014: Strong Ammonium Acetate Solution;
USP 36: Acetic Acid Irrigation; Acetic Acid Otic Solution; Hydrocortisone and Acetic Acid Otic Solution.

Acetohydroxamic Acid *(USAN, rINN)*

Acetohidroxámico, ácido; *N*-Acetyl Hydroxyacetamide; Acide Acétohydroxamique; Ácido acetohidroxámico; Acidum Acetohydroxamicum; AHA; Ацетогидроксамовая Кислота.

$C_2H_5NO_2$=75.07
CAS — 546-88-3.
ATC — G04BX03.
ATC Vet — QG04BX03.
UNII — 4RZ82L2GY5.

Pharmacopoeias. In *US*.

USP 36: (Acetohydroxamic Acid). White, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform. Store in airtight containers at a temperature between 8 degrees and 15 degrees.

Uses and Administration

Acetohydroxamic acid inhibits bacterial urease and thus decreases urinary ammonia concentration and alkalinity. It is used as an adjunct in the treatment of chronic urinary-tract infections (p. 213.1). It has also been used in the prophylaxis of struvite renal calculi (p. 2350.3), although the benefits have not been clearly established.

Acetohydroxamic acid is given orally in a usual dose of 250 mg three or four times daily. The total dose should not exceed 1.5 g daily. For doses in children and in patients with renal impairment, see below.

Administration in children. Children with chronic recalcitrant urea-splitting urinary infection have been given acetohydroxamic acid orally in doses of 10 mg/kg daily in 2 or 3 divided doses for periods of up to 1 year. However close monitoring should be carried out since dosage and dose intervals have not been established in clinical studies.

Administration in renal impairment. Acetohydroxamic acid should not be given to patients with serum-creatinine concentrations in excess of about 220 micromoles/litre. If the concentration is between 160 and 220 micromoles/litre, the maximum daily dose given orally should be 1 g and the dosing interval should be extended to every 12 hours.

Adverse Effects and Precautions

Phlebitis, thromboembolism, haemolytic anaemia, and iron-deficiency anaemia have occurred. Bone-marrow depression has been reported in *animal* studies. Other adverse effects include headache, gastrointestinal disturbances, alopecia, rash (particularly after ingestion of alcohol), trembling, and mental symptoms including anxiety and depression. Blood counts and renal function should be monitored regularly during treatment. Patients with acute renal failure should not be given acetohydroxamic acid.

Pregnancy. Studies in *animals* indicate that acetohydroxamic acid is teratogenic.

Interactions

Acetohydroxamic acid chelates iron given orally, resulting in reduced absorption of both. Ingestion with alcohol may precipitate a rash.

Pharmacokinetics

Acetohydroxamic acid is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 1 hour. The plasma half-life is reported to be up to 10 hours, but may be longer in patients with impaired renal function. Acetohydroxamic acid is partially metabolised to acetamide, which is inactive; up to about two-thirds of a dose may be excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Uronefrex; ***USA***: Lithostat.

Pharmacopoeial Preparations

USP 36: Acetohydroxamic Acid Tablets.

Acetylleucine *(rINN)*

Acetileucina; Acétylleucine; Acetylleucinum; RP-7542; Ацетиллейцин.

N-Acetyl-DL-leucine.
$C_8H_{15}NO_3$=173.2
CAS — 99-15-0.
ATC — N07CA04.
ATC Vet — QN07CA04.
UNII — K76S41V71X.

Profile

Acetylleucine has been used in the treatment of vertigo (p. 612.3) in usual oral doses of up to 2 g daily, in divided doses, or 1 g daily by intravenous injection. Higher doses have occasionally been used.

References.

1. Ferber-Viart C, *et al.* Effects of acetyl-DL-leucine in vestibular patients: a clinical study following neurotomy and labyrinthectomy. *Audiol Neurotol* 2009; **14:** 17–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Tanganil.

Acexamic Acid *(BAN, rINN)*

Acexámico, ácido; Acide Acexamique; Ácido acexámico; Acidum Acexamicum; CY-153; Epsilon Acetamidocaproic Acid; Ацексамовая Кислота.

6-Acetamidohexanoic acid.
$C_8H_{15}NO_3$=173.2
CAS — 57-08-9 (acexamic acid); 70020-71-2 (zinc acexamate).
UNII — 7IC4BO7D3R.

Pharmacopoeias. *Eur.* (see p. vii) includes Zinc Acexamate.

Profile

Acexamic acid is related structurally to the antifibrinolytic agent aminocaproic acid (p. 1131.3). Acexamic acid, usually as the calcium or sodium salt, has been used topically or systemically to promote the healing of ulcers and various other skin lesions. Zinc acexamate has been given for peptic ulcer disease.

References.

1. Reis AM, *et al.* Allergic contact dermatitis to acexamic acid. *Contact Dermatitis* 2008; **58:** 241–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Plastenan; Restaurene; ***China***: An Yi (安易); Wei Ke Xin (卫可欣); ***Fr.***: Plastenan; ***Mex.***: Recoveron; ***Spain***: Copinal.

Multi-ingredient Preparations. ***Arg.***: Bagoderm; Cicatrizol; Lisoderma; Plastenan con Neomicina; ***Mex.***: Dermatolona; Recoveron N; Recoveron NC.

Achillea

Achillée millefeuille; Aquilea; Cickafarkfű; Cientoenrama; Kraujažolių žolė; Milenrama; Milfoil; Milhojas; Millefolii Herba; Rölleka; Schafgarbe; Schafgarbenkraut; Siankärsämö; Řebříčková nať; Yarrow; Ziele krwawnika; Тысячелистник Обыкновенный.

CAS — 8022-07-9 (yarrow root oil).
*ATC Herb — HA03AW5001 (*Achillea millefolium*: herb); HA09WA5001 (*Achillea millefolium*: herb); HA05AW5001 (*Achillea millefolium*: herb); HC05AW5001 (*Achillea millefolium*: herb); HA03WX5001 (*Achillea millefolium*: herb); HG02WA5001 (*Achillea millefolium*: herb); HR05YA5001 (*Achillea millefolium*: herb); HM01AW5001 (*Achillea millefolium*: herb); HN02BG5001 (*Achillea millefolium*: herb).*
UNII — 2FXJ6SW4PK.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Yarrow). The whole or cut, dried flowering tops of yarrow, *Achillea millefolium*. It contains not less than 2 mL/kg of essential oil and not less than 0.02% of proazulenes, expressed as chamazulene ($C_{14}H_{16}$ = 184.3), both calculated with reference to the dried drug. Protect from light.

Profile

Achillea has been used in herbal medicine. It has been stated to have diaphoretic, anti-inflammatory, and other miscellaneous properties. It has been reported to cause contact dermatitis.

Yarrow root oil is used in aromatherapy.

Homoeopathy

Achillea has been used in homoeopathic medicines under the following names: Achillea millefolium; Millefolium; Achillea ex herba; Millef.

References.

1. Anonymous. Final report on the safety assessment of yarrow (Achillea millefolium) extract. *Int J Toxicol* 2001; **20** (suppl 2): 79–84.
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3. Nemeth E, Bernath J. Biological activities of yarrow species (*Achillea* spp.). *Curr Pharm Des* 2008; **14:** 3151–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Nat Rebricku†; Rebrickovy Caj, Rebrickova Nat†; ***Mex.***: Blancaler.

Multi-ingredient Preparations. ***Austral.***: DiaCo; Flavons†; Masculine Herbal Complex; ***Austria***: Abfuhrtee St Severin; Amersan; Gallen- und Lebertee St Severin; Mariazeller; Menodoron; ***Canad.***: Cystoforce†; Floradix Kindervital†; Honey Herb Cough Drops†; Natraway Sport 1 & 2†; Natraway Sport 3†; Original Herb Cough Drops†; ***Cz.***: Amersan; Cicaderma; Projimava; Species Urologicae Planta; Zaludecni Cajova Smes; ***Fr.***: Afra†; Colitisane†; Dexsil Articulations; Gonaxine; Tisane Hepatique de Hoerdt†; Tisane Provencale no 5†; ***Ger.***: Alasenn; Amara-Tropfen; Floradix Multipretten N; Gallexier; Hevert Stoffwechsel-Tee N†; Imupret; Menodoron; Sedovent†; ***Hung.***: Gallexier; Gastrosol; Hemorid; Hemorid; Majvedo es Detoxikalo; Menofit; Mensesyl; Salus Multipretten; Szent Lukacs; Urogin; Uroherb; ***India***: Bonnisan; Geriforte; Geriforte; Hepaliv; Liv 52; ***Ital.***: Bulboshap†; Forticrin; Lik-Gel†; Lozione Same Urto; Pik Gel; ***Malaysia***: Bonnisan; ***Pol.***: Amarosal; Artecholin†; Artecholwex†; Cholavisol; Dyspepsin; Enterosol; Gastrobonisol; Hemorol; Liv 52; Nefrobonisol; Nervosan†; Reumosol; Salviasept; Sanofil; ***Port.***: Cicaderma; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); Evalar (Эвалар); Fitantis (Фитантис); GeKaTon (Жекатон); Kliophyt (Клиофит); Laxantis Species No 1 (Слабительный Сбор 1); Liv 52 (Лив 52); Liv 52 (Лив 52); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Phytohepatol No 2 (Фитогепатол 2); Polygemostat (Полигемостат); Proctophytol (Проктофитол); Rotocan (Ротокан); Tonsilgon N (Тонзилгон Н); ***S.Afr.***: Amara†; Clairo†; Menodoron†; ***Singapore***: Disco; Liv 52; Liv 52; ***Swed.***: Multipretten; ***Switz.***: Baume Zeller; Gastrosan; Gouttes Amara; Kernosan 24; Kernosan 26; Kernosan Heidelberger Poudre; Liv 52; Menodoron; Pommade au Baume; Tisane hepatique et biliaire; Tisane pour l'estomac; Venaphyt N; ***UK***: Catarrh-eeze; Rheumatic Pain Remedy; Spotner; Tabritis; Wellwoman; ***Ukr.***: Ambovit (Амбовит); Clotrex (Клотрекс); Imupret (Имупрет); Liv 52 (Лив 52); Tonsilgon N (Тонзилгон)†.

Homoeopathic Preparations. ***Austral.***: Echine†; ***Austria***: Traumeel; ***Canad.***: Amaratopfen†; Cicaderma†; Traumeel; ***Chile***: Variplex; ***Cz.***: Traumeel; ***Fr.***: Arnica Complexe no 1; Cicaderma; Diacure; Millefolium Complexe No 7†; ***Ger.***: Heweven Complex; Infihepan; Regenaplex Haut W; Traumeel S; Venokatt; ***Hung.***: Traumeel; ***Neth.***: Achilite; Apo-STOM; Cystilite; Traumeel H; Traumeel S; ***Rus.***: Cicaderma (Цикадерма); Traumeel S (Траумель С); ***S.Afr.***: Achillea Comp†; Chamomilla/Millefolium Comp†; Traumeel S; ***Switz.***: Regenaplex Nr. 25b; Regenaplex Nr. 31c; Regenaplex Nr. 59b; Traumeel; ***UK***: Laxadoron; Menodoron; ***Ukr.***: Traumeel S (Траумель С); ***USA***: Traumeel; ***Venez.***: Traumeel.

Acid Alpha Glucosidase

Acid Maltase; Alfa Glucosidasa; Amyloglucosidase; EC 3.2.1.3; Glucan 1,4-α-Glucosidase; α-Glucosidasa; Lysosomal α-glucosidase; Альфа-глюкозидаза.

CAS — 9032-08-0.

Alglucosidase Alfa *(BAN, USAN, rINN)*

Alglucosidasa alfa; Alglucosidasum Alfa; rhGAA; Альглюкозидаза Альфа.

CAS — 420784-05-0.
ATC — A16AB07.
ATC Vet — QA16AB07.
UNII — DTI67O9503.

NOTE. The name Pompase has been used as a trade mark for alglucosidase alfa.

Uses and Administration

Alglucosidase alfa is a recombinant form of human acid alpha glucosidase given as enzyme replacement therapy for the treatment of Pompe disease (see below). It is given intravenously using an infusion pump in doses of 20 mg/kg once every 2 weeks. The total volume of fluid, which is determined by the patient's body-weight, should be infused over about 4 hours. The infusion rate should be increased gradually: the initial rate should not exceed 1 mg/kg per hour; once the patient can tolerate this rate, it may be increased every 30 minutes by 2 mg/kg per hour with monitoring of vital signs before each increase; the maximum infusion rate is 7 mg/kg per hour.

Administration in children. Licensed product information mentions that there is no evidence for special consideration when alglucosidase alfa is used in children or adolescents for the treatment of Pompe disease and the *BNFC* notes that the usual adult dose (see above) may be given to neonates as well as infants and older children.

Pompe disease. Pompe disease (glycogen storage disease type II; glycogenosis type II; acid maltase deficiency) is a rare fatal autosomal recessive disorder caused by a deficiency of acid α-glucosidase, which cleaves α-1,4- and α-1,6-glucosidic linkages in lysosomal glycogen to liberate glucose. Glycogen accumulation results in progressive myopathy, especially of the respiratory and skeletal muscles, and the heart. Infantile-onset Pompe disease is rapidly progressive leading to cardiopulmonary failure in the first year of life. In juvenile and adult-onset forms of Pompe disease glycogen accumulation is limited mainly to the skeletal muscles and is more slowly progressive producing muscle weakness and varying degrees of respiratory weakness; a small proportion of patients may also have some cardiac involvement. Pompe disease is a multisystem disorder and extensive supportive treatment is required. Alglucosidase alfa is a recombinant form of human acid alpha glucosidase given as enzyme replacement therapy for Pompe disease with greatest benefit seen following treatment at an early stage of infantile-onset disease whereas evidence of efficacy in late-onset disease is limited.

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Adverse Effects, Treatment, and Precautions

Fever, flushing, diarrhoea, vomiting, rash, urticaria, cough, upper respiratory-tract infections, otitis media, pneumonia, tachycardia, tachypnoea, and hypoxia have been commonly reported with alglucosidase alfa. Cardiac arrest has also been reported. Patients with an acute illness at the time of infusion are at greater risk of developing cardiorespiratory failure. Severe cutaneous reactions including ulcerative and necrotising lesions have also been seen with alglucosidase alfa.

Infusion reactions are common with alglucosidase alfa; symptoms may resolve on decreasing the infusion rate, temporarily stopping the infusion, and/or use of antihistamines, corticosteroids, or antipyretics, which may also be given as pre-treatment. Severe reactions may require stopping the infusion immediately. Serious hypersensitivity reactions, including anaphylactic shock, have also been reported during infusion of alglucosidase alfa. Patients with advanced Pompe disease may have compromised cardiac function and should be monitored closely since they may be predisposed to a higher risk of severe complications from infusion reactions.

IgG antibodies to alglucosidase alfa develop in the majority of patients within the first 3 months of treatment, although the effect on long-term efficacy is not clear. The presence of antibodies may predispose patients to developing infusion reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Myozyme; ***Belg.***: Myozyme; ***Braz.***: Myozyme; ***Canad.***: Myozyme; ***Cz.***: Myozyme; ***Denm.***: Myozyme; ***Fr.***: Myozyme; ***Ger.***: Myozyme; ***Gr.***: Myozyme; ***Hong Kong***: Myozyme; ***Irl.***: Myozyme; ***Israel***: Myozyme; ***Ital.***: Myozyme; ***Malaysia***: Myozyme; ***Neth.***: Myozyme; ***Norw.***: Myozyme; ***NZ***: Myozyme; ***Pol.***: Myozyme; ***Port.***: Myozyme; ***Spain***: Myozyme; ***Swed.***: Myozyme; ***Switz.***: Myozyme; ***UK***: Myozyme; ***USA***: Lumizyme; Myozyme.

Multi-ingredient Preparations. ***Canad.***: Digesta.

Acid Fuchsine

Acid Magenta; Acid Roseine; Acid Rubine; CI Acid Violet 19; Colour Index No. 42685; Fucsina ácida; Rubina ácida; Кислый Фуксин.

CAS — 3244-88-0.

Profile

Acid fuchsine is the disodium or diammonium salt of the trisulfonic acid of magenta. It is used as a microscopic stain and a pH indicator.

Acitazanolast *(rINN)*

Acitazanolastum; WP-871; Ацитазаноласт.

3′-(1*H*-tetrazol-5-yl)oxanilic acid.

$C_9H_7N_5O_3$=233.2

CAS — 114607-46-4.

UNII — 99Y8VJ356G (anhydrous acitazanolast); U6SU9ZSU4K (acitazanolast hydrate).

Profile

Acitazanolast is a leukotriene inhibitor used as the hydrate in a concentration of 0.1% in eye drops for the treatment of allergic conjunctivitis (p. 611.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Zepelin.

Aconite

Acetylbenzoylaconine (aconitine); Aconit.; Aconit napel; Aconite Root; Aconiti Tuber; Acónito; Aconitum napellus; Amapelo; Anapelo; Matalobos; Monkshood Root; Napelo; Radix Aconiti; Vedegambre azul; Wolfsbane Root; Аконит; Борец; Царь-зелье.

8-Acetoxy-3,11,18-trihydroxy-16-ethyl-1,6,19-trimethoxy-4-methoxymethylaconitan-10-yl benzoate (aconitine).

$C_{34}H_{47}NO_{11}$=645.7 (aconitine)

CAS — 8063-12-5 (aconite); 302-27-2 (aconitine).

ATC Herb — HM02AX5001 (Aconitum napellus: *root*).

UNII — U0NQ8555JD (Aconitum napellus); *KPD2N7348X* (Aconitum napellus, *root*).

NOTE. Wolfsbane is also used as a common name for arnica flower (p. 2447.2).

Description. Aconite consists of the dried tuberous root of *Aconitum napellus* agg. (Ranunculaceae). It contains several alkaloids, the main pharmacologically active one being aconitine.

Pharmacopoeias. *Chin.* and *Jpn* include the root of various *Aconitum* spp.

Uses and Administration

Aconite liniments have been used in the treatment of neuralgia, sciatica, and rheumatism. Sufficient aconitine may be absorbed through the skin to cause poisoning; liniments should never be applied to wounds or abraded surfaces. Aconite should not be used internally because of its low therapeutic index and variable potency; however it is reported to be a common ingredient in traditional Chinese remedies and is also an ingredient of some cough mixtures.

Homoeopathy

Aconite has been used in homoeopathic medicines under the following names: Aconitum, radix; Aconitum, rad.

The whole plant, Aconitum napellus (Aconitum nap), is also used in homoeopathic medicine as is the root of the related plant Aconitum ferox (Aconitum fer).

Adverse Effects and Treatment

Aconite has variable effects on the heart leading to heart failure. It also affects the CNS.

Symptoms of aconite poisoning may appear within minutes or up to 2 hours after oral ingestion; in fatal poisoning death usually occurs within 12 hours, although with larger doses it may be instantaneous.

Initial symptoms (and an important diagnostic feature) are tingling sensations of the tongue, mouth, fingers, and toes followed by generalised paraesthesia. Other symptoms include nausea, vomiting, diarrhoea, muscle weakness, skeletal muscle paralysis, and difficult respiration; also sweats, chills and a feeling of intense cold may occur. Respiratory paralysis, hypotension, and cardiac arrhythmias may develop in severe cases.

Although the benefits of gastric decontamination are uncertain, gastric lavage may be tried in patients within one hour of life-threatening oral poisoning; activated charcoal may also be considered. Patients should be observed and

monitored, and corrective and supportive treatment given as necessary. Arrhythmias are relatively resistant to treatment, although atropine has been tried for bradycardia.

Poisoning. References to poisoning with aconite.

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5. Imazio M, *et al.* Malignant ventricular arrhythmias due to Aconitum napellus seeds. *Circulation* 2000; **102:** 2907–8.
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8. Chan TY. Aconite poisoning. *Clin Toxicol* 2009; **47:** 279–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: No-Tos Adultos; ***Austria***: Rheuma; ***Belg.***: Saintbois; ***Braz.***: Expectomel; Melagriao; ***Cz.***: Pleumolysin; ***Jpn***: Daibofuto; Keishikajutsubuto; Maobushi-saishinto; Shimbuto; ***Pol.***: Padma 28; ***Rus.***: Wantong Artiplas (Ваньтун Артиплас); ***Switz.***: Arteria-vita; Padma 28; Padmed Circosan; ***UK***: Padma 28.

Homoeopathic Preparations. ***Austral.***: Calm; Childrens Cold and Flu Relief; Childrens Cough Relief; Childrens Sleep; Pain & Fever Relief; Respatona Dry Cough & Nasal Congestion; Respatona Head Cold; Sedatif†; Teething Relief; ***Austria***: Aconitum Med Complex; Aflubin; Apozema Allium Cepa compositum; Ferrum Phosphoricum comp; Gripp Heel; Infludo; Lobelia Med Complex; Luffa Med Complex; Meditonsin; Metavirulent; Nisylen†; Otovowen; Pneumodoron Nr 1; toxi-loges; Traumeel; ***Canad.***: Aches & Pains; Arum Triphyllum Plex†; Barijodeel†; Bryaconeel†; Calms Forte 4 Kids; Calnor†; Calsom†; Cold Tablets with Zinc†; Comp-Drops 3 Bowel Support†; Cough Syrup with Honey†; Crou Complex†; Echinacea Compositum; Formula INF; Homeovox; Hylands Formula CS; Hylands Formula CZ; Hylands LCQ; Hylands Leg Cramps; Ivernax; L52 Cough & Cold; Leg Cramps with Quinine; Sedatil; Spascupreel; Traumeel; ***Chile***: Bioactiv Z; ***Cz.***: Gripp Heel; Homeovox; Lehnigrip†; Sedatif PC; Spascupreel S†; Traumeel; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 18†; Abbe Chaupitre no 1†; Abbe Chaupitre no 20†; Abbe Chaupitre no 25†; Abbe Chaupitre no 66†; Abbe Chaupitre no 6; Abbe Chaupitre no 91†; Aconitum Compose†; Arnica Complexe no 1; Arum Triphyllum Compose; Baudry; Boripharm No 11†; Boripharm No 1†; Crataegus Complexe No 15; Euphrasia Complexe No 115; Gelsemium Complexe No 70; Geranium Complexe No 108†; Homeogrippe†; Homeovox; Infludo; Iodum Complexe No 118; L 52; Pates Pectorales; Pulsatilla Complexe No 60†; Ranunculus Complexe No 79; Rheumadoron; Rhododendron Complexe No 42†; Rhus Toxicodendron Complexe No 80; Sclero-Drainol†; Sedatif PC; Urtica Complexe No 82†; Uva Ursi Complexe No 9; ***Ger.***: Aconitum Nicotiana comp†; Anovin; Arnica comp/Apis†; Arnica Oligoplex; Arnica/Symphytum comp; Asthmavowen-N†; Aurum-Gastreu S R2; Cefagrippin†; Contramutan; Echinacin akut; Erkaltungs-Entoxin; Eupatorium N Oligoplex; Febrocyl L Ho-Len-Complex; Ferrum phosphoricum comp; Gelsemium Comp; Gelsemium Comp; Gelsemium N Oligoplex; Gnaphalium Injektopas SL; Gripp-Heel; Grippe-Gastreu S R6; Gripps; HanoToxin M; Hanotoxin M; Infekt 1-Injektopas N; Infekt-Komplex L Ho-Fu-Complex; Infi-Echinacea; Infigripp; Infihepan; Infludo; Influex; Influvit; Jowidarmin; Jsoskleran; Mato; Meditonsin; metavirulent; Migrane Hevert†; Migrane Hevert; Natuimmun†; Neuralgie-Gastreu R70; Nisylen; Original-Tinktur N Truw; Otofren; Otovowen; Pascoleucyn; phono Gripp; Pneumodoron 1; Rheumodoron 102 A; Rheumodoron 1; Rufebran neuro†; Schworotox A; Spascupreel; Tonsillosyx; toxi-loges; toxi-loges; Traumeel S; Tussistin; Viscum album H†; Wiedimmun N†; Wiedimmun; ***Hung.***: Aflubin; Gripp-Heel; Homeovox; Sedatif; Spascupreel; Traumeel; ***Neth.***: Arnilite; Cold Care; Echilite; Febrilite; Gripp-Heel H; Grippe-Gastreu R6; Head Care; Homeocare Revito; Homeovox; Infludo; Kind 0-6 Kinditherm; Kind 0-6 Nisykind; Kruidvat Homeopathie Influcomplex†; Nervival; Nisyleen; Sedatif PC; Traumeel S; ***Port.***: Homeovox; Sedatif PC; ***Rus.***: Aflubin (Афлубин); Belladonna-Plus (Белладонна-Плюс); Briacon (Бриакон); Homeostres (Гомеострес); Homeovox (Гомеовокс); Influcid (Инфлюцид); Traumeel S (Траумель С); ***S.Afr.***: Ferrum Phos Comp†; Gripp-Heel; Infludo†; Pneumodoron 1†; Rheumadoron†; Traumeel S; ***Switz.***: Gripp-Heel; Homeovox; Influaforce†; Infludo; metavirulent; Regenaplex Nr 41a; Regenaplex Nr. 21c; Regenaplex Nr. 31c; Rheumadoron; Sedatif PC; Traumeel; ***UK***: Infludo; Rheumadoron; Rheumadoron; ***Ukr.***: Aflubin (Афлубин); Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Homeovox (Гомеовокс); Influcid (Инфлюцид); Sedatif PC (Седатив ПЦ); Traumeel S (Траумель С); ***USA***: Preferred Remedies Cold & Flu; Traumeel; ***Venez.***: Traumeel.

Acridine Orange

Naranja de acridina; Акридиновый Оранжевый.
3,6-Bis(dimethylamino)acridine.
$C_{17}H_{19}N_3$=265.4
CAS — 494-38-2.
UNII — F30N4O6XVV.

Profile

Acridine orange is a dye with antiseptic properties. It has been used as a diagnostic stain in microbiology.

For details of the antiseptic properties of acridine derivatives, see p. 1732.3.

Diagnostic use. Acridine orange has been used for the diagnostic staining of malarial parasites in the quantitative buffy coat (QBC) technique.[1-6] Acridine orange stains the DNA of the malarial parasites in a blood sample that is then centrifuged, and the area just below the buffy coat is examined under a fluorescence microscope. It has been described as easier and quicker to use than the standard examination of stained blood films, and is therefore seen to be advantageous when urgent diagnosis is needed, and in endemic areas where a high number of tests need to be performed in a short period of time and/or technical staff are inexperienced. However, malarial species identification is not always possible and sensitivity may be poor particularly at low levels of parasitaemia. Additionally, the initial outlay for special equipment such as a micro-centrifuge and a fluorescence or adapted light microscope and ongoing expense of the QBC kits may be prohibitive in developing countries.

The QBC technique has also been used in the diagnosis of other diseases such as babesiosis, filariasis, and trypanosomiasis.

Acridine orange has also been tried for the staining of blood slides.[7-10]

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2. WHO. WHO expert committee on malaria: twentieth report. *WHO Tech Rep Ser892* 2000. Available at: http://libdoc.who.int/trs/WHO_TRS_892.pdf (accessed 18/08/09)
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5. Parija SC, *et al.* A comparative study of blood smear, QBC and antigen detection for diagnosis of malaria. *Indian J Pathol Microbiol* 2009; **52:** 200–2.
6. Tangpukdee N, *et al.* Malaria diagnosis: a brief review. *Korean J Parasitol* 2009; **47:** 93–102.
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9. Tarimo DS, *et al.* Appraisal of the acridine orange method for rapid malaria diagnosis at three Tanzanian district hospitals. *East Afr Med J* 1998; **75:** 504–7.
10. Lema OE, *et al.* Comparison of five methods of malaria detection in the outpatient setting. *Am J Trop Med Hyg* 1999; **60:** 177–82.

Acrolein

Acraldehyde; Acrialdehído; Acroleína; Acrylaldehyde; Acrylic Aldehyde; Alilaldehído; Propenal.
Prop-2-enal.
C_3H_4O=56.06
CAS — 107-02-8.
UNII — 7864XYD3JJ.

Profile

Acrolein is a volatile, highly flammable liquid at ordinary temperature and pressure. It has various industrial uses, but is also a toxic byproduct of combustion and may be present in exhaust gases, tobacco smoke, and smoke from fires. It is irritant to the skin and may cause skin burns. Ingestion of acrolein produces severe gastrointestinal distress. The vapour causes lachrymation and pulmonary irritation. Inhalation may cause pulmonary oedema and permanent lung damage.

Acrolein is a metabolite of cyclophosphamide (p. 771.1) and may be responsible for the latter's bladder toxicity.

References.
1. WHO. Acrolein. *IPCS Health and Safety Guide 67.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg067.htm (accessed 23/07/08)
2. WHO. Acrolein. *Environmental Health Criteria 127.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc127.htm (accessed 23/07/08)
3. Stevens JF, Maier CS. Acrolein: sources, metabolism, and biomolecular interactions relevant to human health and disease. *Mol Nutr Food Res* 2008; **52:** 7–25.
4. Faroon O, *et al.* Acrolein health effects. *Toxicol Ind Health* 2008; **24:** 447–90.

Acrylamide

Acrilamida; Akryloamid; Amida acrílica; Etilencarboxamida; Vinil amida.
Propenamide.
C_3H_5NO=71.08
CAS — 79-06-1.
UNII — 20R035KLCI.

Profile

Acrylamide is highly toxic and irritant; it can be absorbed through unbroken skin. Symptoms of poisoning include burning and ulceration of the mouth and throat following ingestion. Excessive sweating is common and other symptoms may include numbness of limbs, paraesthesias, and muscle weakness. CNS effects such as somnolence, confusion, hallucinations, ataxia, tremors, dysarthria, and nystagmus may occur depending on the severity of exposure. Peripheral neuropathies may appear several weeks after severe acute exposure or as a result of chronic exposure. Gastric lavage may be tried in patients within one hour of ingestion, although some recommend gastric aspiration instead of lavage; activated charcoal may also be considered, but ipecacuanha-induced emesis is not recommended because of the risk of CNS depression and seizures. Contamination of eyes and skin should be irrigated and treated as for burns. Patients should be monitored, and corrective and supportive treatment given as necessary.

Acrylamide has various industrial applications, including use as a plasticiser and a waterproof 'chemical grout'.

References.
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2. WHO. Acrylamide. *IPCS Health and Safety Guide 45.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg045.htm (accessed 31/03/06)
3. Exon JH. A review of the toxicology of acrylamide. *J Toxicol Environ Health B* 2006; **9:** 397–412.

Food toxicity. Concerns have been expressed by the Swedish National Food Administration about the level of acrylamide they found in certain cooked foods, particularly those exposed to very high temperatures such as fried foods, and the potential carcinogenic risk. However, it was acknowledged that, although the results have been replicated in other international laboratories, the total sample size was small and none of the methods being used have so far been validated.[1] One subsequent population-based study failed to find any excess risk or convincing trend of cancer of the bowel, bladder, or kidney in high consumers of foods with a high or moderate acrylamide content.[2] The joint FAO/WHO Expert Committee on Food Additives (JECFA)[3] reviewed data provided by 24 countries on acrylamide in food analysed between 2002 and 2004. Their recommendations were for re-evaluation of the effects of acrylamide on completion of studies of carcinogenicity and neurotoxicity, and that efforts to reduce the concentrations of acrylamide in food should continue.

1. Kapp C. WHO urges more research into acrylamide in food. *Lancet* 2002; **360:** 64.
2. Mucci LA, *et al.* Dietary acrylamide and cancer of the large bowel, kidney, and bladder: absence of an association in a population-based study in Sweden. *Br J Cancer* 2003 **88:** 84–9.
3. FAO/WHO. Evaluation of certain food contaminants: sixty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 930* 2006. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_930_eng.pdf (accessed 18/07/08)

Actinoquinol Sodium *(USAN, rINNM)*

Actinoquinol sódico; Actinoquinol Sodique; Natrii Actinoquinolum; Sodium Etoquinol; Sodium Tequinol; Натрий Актинохинол.
Sodium 8-ethoxy-5-quinolinesulfonate.
$C_{11}H_{10}NNaO_4S$=275.3
CAS — 15301-40-3 (actinoquinol); 7246-07-3 (actinoquinol sodium).
UNII — 8PW272ITDS.

Profile

Actinoquinol and actinoquinol sodium have been used as ingredients in eye drop preparations intended to protect the eyes from the effects of light.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Uvicol†; ***Ger.***: duraultra†; ***Ital.***: Fotofil.

Ademetionine *(rINN)*

Ademethionine; Ademetioniini; Ademetionin; Adémétionin; Ademetionina; Ademetioninum; *S*-Adenosyl-L-methionine; Methioninyl adenylate; SAMe; Адеметионин.
(*S*)-5′-[(3-Amino-3-carboxypropyl)methylsulphonio]-5′-deoxyadenosine hydroxide, inner salt.
$C_{15}H_{22}N_6O_5S$=398.4

CAS — 29908-03-0; 485-80-3; 17176-17-9.
ATC — A16AA02.
ATC Vet — QA16AA02.
UNII — 7LP2MPO46S.

Ademetionine Sulfate Tosilate

Ademetionine Disulfate Tosylate; *S*-Adenosyl-L-methionine Sulfate Tosilate; FO-1561.
CAS — 55722-12-8.
UNII — 564ROC9U09.

Pharmacopoeias. In *US.*

USP 36: (*S*-Adenosyl-L-methionine Disulfate Tosylate). A white powder. Freely soluble in water. Store in airtight containers in a refrigerator at a temperature between 2 degrees and 8 degrees. Protect from light.

Profile

Ademetionine is a naturally occurring molecule found in virtually all body tissues and fluids. It acts as a methyl group donor in many transmethylation reactions and therefore is involved in the synthesis or metabolism of several compounds that maintain normal cell function. Ademetionine sulfate tosilate and ademetionine butanedisulfonate are stable forms of ademetionine that have been promoted for the treatment of depression (see below), liver disorders, and musculoskeletal and joint disorders such as osteoarthritis and fibromyalgia (see below).

References.

1. Bottiglieri T, *et al.* The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders. *Drugs* 1994; **48:** 137–52.
2. Chavez M. SAMe: S-adenosylmethionine. *Am J Health-Syst Pharm* 2000; **57:** 119–23.
3. Fetrow CW, Avila JR. Efficacy of the dietary supplement S-adenosyl-L-methionine. *Ann Pharmacother* 2001; **35:** 1414–25.
4. Bottiglieri T. S-Adenosyl-L-methionine (SAMe): from the bench to the bedside—molecular basis of a pleiotrophic molecule. *Am J Clin Nutr* 2002; **76** (suppl): 1151S–1157S.
5. Gören JL, *et al.* Bioavailability and lack of toxicity of S-adenosyl-L-methionine (SAMe) in humans. *Pharmacotherapy* 2004; **24:** 1501–7.

Depression. Ademetionine has been given orally or parenterally in the management of depression (p. 398.1). It appears to be of similar efficacy to the tricyclic antidepressants but evidence is limited to small, heterogeneous groups of patients studied over short periods of time; additionally many studies have involved parenteral rather than oral therapy.

References.

1. Bressa GM. S-Adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand* 1994; **154** (suppl): 7–14.
2. Mischoulon D, Fava M. Role of *S*-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am J Clin Nutr* 2002; **76:** 1158S–1161S.
3. Papakostas GI, *et al.* S-Adenosyl-methionine in depression: a comprehensive review of the literature. *Curr Psychiatry Rep* 2003; **5:** 460–6.
4. Williams AL, *et al.* S-adenosylmethionine (SAMe) as treatment for depression: a systematic review. *Clin Invest Med* 2005; **28:** 132–9.

Liver disorders. Some workers have found that ademetionine produced clinical improvement in patients with **intrahepatic cholestasis**,[1,2] including that associated with pregnancy.[3,4] Pruritus associated with the condition has also been relieved. Other studies,[5,6] however, have not found any benefit.

Ademetionine produced a good or excellent clinical response in patients with **hepatic steatosis**.[7] In a study[8] of patients with **alcoholic liver cirrhosis**, treated with ademetionine for 2 years, there was a trend towards reduced overall mortality or need for liver transplantation, but only in patients with less severe hepatic dysfunction. However, a systematic review[9] of 9 randomised placebo-controlled studies, which included the latter study could not find evidence to support or refute the claim that ademetionine has a beneficial effect in patients with alcoholic liver diseases, and larger high quality randomised placebo-controlled studies are needed.

1. Frezza M, *et al.* Oral S-adenosylmethionine in the symptomatic treatment of intrahepatic cholestasis: a double-blind, placebo-controlled study. *Gastroenterology* 1990; **99:** 211–15.
2. Almasio P, *et al.* Role of S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis. *Drugs* 1990; **40** (suppl 3): 111–23.
3. Bonfirraro G, *et al.* S-Adenosyl-L-methionine (SAMe)-induced amelioration of intrahepatic cholestasis of pregnancy: results of an open study. *Drug Invest* 1990; **2:** 125–8.
4. Frezza M, *et al.* S-Adenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy: results of a controlled clinical trial. *Hepatogastroenterology* 1990; **37** (suppl 2): 122–5.
5. Ribalta J, *et al.* S-Adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: a randomized, double-blind, placebo-controlled study with negative results. *Hepatology* 1991; **13:** 1084–9.
6. Floreani A, *et al.* S-Adenosylmethionine versus ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: preliminary results of a controlled trial. *Eur J Obstet Gynecol Reprod Biol* 1996; **67:** 109–13.
7. Caballeria E, Moreno J. Therapeutic effects of S-adenosylmethionine (SAMe) in hepatic steatosis. *Acta Ther* 1990; **16:** 253–64.
8. Mato JM, *et al.* S-Adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol* 1999; **30:** 1081–9.
9. Rambaldi A, Gluud C. S-Adenosyl-L-methionine for alcoholic liver diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/04/08).

Musculoskeletal and joint disorders. Ademetionine has been reported[1-5] to possess therapeutic efficacy in the treatment of osteoarthritis (p. 12.3) and similar conditions, possibly due to an effect on cartilage metabolism and formation of anti-inflammatory mediators within the cell; it may also inhibit leukotrienes but does not appear markedly to interfere with prostaglandin synthesis. However, a systematic review[6] found that available studies were mainly small and of questionable quality, and therefore the routine use of ademetionine for osteoarthritis of the knee or hip could not be recommended until further evaluation through larger randomised controlled studies. Possible benefit in fibromyalgia (see under Soft-tissue Rheumatism, p. 14.2) has also been shown.[5]

1. Domljan Z, *et al.* A double-blind trial of ademethionine vs naproxen in activated gonarthrosis. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 329–33.
2. Bradley JD, *et al.* A randomized, double blind, placebo controlled trial of intravenous loading with S-adenosylmethionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. *J Rheumatol* 1994; **21:** 905–11.
3. Soeken KL, *et al.* Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. *J Fam Pract* 2002; **51:** 425–30.
4. Najm WI, *et al.* S-Adenosyl methionine (SAMe) versus celecoxib for the treatment of osteoarthritis symptoms: a double-blind cross-over trial. *BMC Musculoskelet Disord* 2004; **5:** 6.
5. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)
6. Rutjes AW, *et al.* S-Adenosylmethionine for osteoarthritis of the knee or hip. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 15/07/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tunik; ***China***: Transmetil (思美泰); ***Cz.***: Transmetil; ***Ger.***: Gumbaral†; ***India***: Ostisave; ***Ital.***: Donamet; Samyr; Transmetil; ***Mex.***: Samyr; ***Rus.***: Heptor (Гептор); Heptral (Гептрал); ***Singapore***: Heptral; ***Ukr.***: Heptral (Гептрал).

Multi-ingredient Preparations. ***Arg.***: Tunik B12; ***Ital.***: Selene.

Adenine

Adeniini; Adenin; Adenina; Adeninas; Adénine; Adeninum; Vitamin B_4; Vitamina B_4; Аденин.
6-Aminopurine; 1,6-Dihydro-6-iminopurine.
$C_5H_5N_5$=135.1
CAS — 73-24-5.
UNII — JAC85A2161.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Adenine). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 36: (Adenine). Odourless white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in boiling water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Profile

Adenine is a purine base and one of the components of adenosine nucleotides that form nucleic acids (p. 2573.1). It is also a constituent of many coenzymes. It has been used to extend the storage life of whole blood (p. 1135.2) and has also been given for the management of white blood cell disorders and alcoholism. Adenine hydrochloride has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Leuco-4†.

Multi-ingredient Preparations. ***Philipp.***: Godex; Inlex; Mitocore; Mitonerb; Mivex; ***Rus.***: Lidevine (Лидевин); ***Spain***: Pleon†; ***Ukr.***: Hepadif (Гепадиф); Lidevin (Лидевин).

Pharmacopoeial Preparations

USP 36: Anticoagulant Citrate Phosphate Dextrose Adenine Solution.

Adenosine Phosphate *(BAN, USAN, rINN)*

A-5MP; Adenosina, fosfato de; Adenosine 5′-Monophosphate; Adenosine Monophosphate; Adénosine, Phosphate d'; Adenosine-5′-(dihydrogen phosphate); Adenosine-5′-phosphoric Acid; Adenosini Phosphas; AMP; Fosfato de adenosina; Monophosadénine; Muscle Adenylic Acid; NSC-20264; Аденозина Фосфат; 5′-Adenylic Acid.
6-Amino-9-β-D-ribofuranosylpurine 5′-(dihydrogen phosphate).
$C_{10}H_{14}N_5O_7P$=347.2
CAS — 61-19-8.
ATC — C01EB10.
ATC Vet — QC01EB10.
UNII — 415SHH325A.

Pharmacopoeias. *Ger.* includes the disodium salt ($C_{10}H_{12}N_5Na_2O_7P,xH_2O$).

Profile

Adenosine phosphate is an endogenous adenine nucleotide involved in many biological processes. Adenosine monophosphate (AMP) is a vasodilator and has been included in preparations for venous insufficiency, haemorrhoids, and varicose veins. It has also been used in pain and inflammation. Adenosine diphosphate and its disodium salt have also been used. AMP is also used in bronchial challenge tests to assess airway hyper-responsiveness in asthma and other respiratory disorders.

Unlike adenosine (p. 1291.1) or adenosine triphosphate (below), adenosine phosphate is not used in supraventricular tachycardias.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ming Sheng (铭生); Tian An Xin (天安欣); Wei An (韦安); Wo Ping (沃平); Xiao Shan Ping (肖山平); ***Fr.***: Adenyl; ***Rus.***: Phosphaden (Фосфаден).

Multi-ingredient Preparations. ***Fr.***: Surelen†; ***Gr.***: Arkadin; ***Indon.***: Nevradin†; ***Spain***: Artri†; Pleo Vitamin†.

Adenosine Triphosphate

Ácido adeniltrifosfórico; Ácido adenosintrifosfórico; Adenosina, trifosfato de; Adenosine 5′-Triphosphate; Adenylpyrophosphoric Acid; ATP; Trifosadenina; Triphosadénine; Аденозинтрифосфат; 5′-Adenyldiphosphoric Acid.
Adenosine 5′-(tetrahydrogen triphosphate).
$C_{10}H_{16}N_5O_{13}P_3$=507.2
CAS — 56-65-5.
ATC — C01EB10.
ATC Vet — QC01EB10.
UNII — 8L70Q75FXE.

Pharmacopoeias. *Ger.* includes the disodium salt ($C_{10}H_{14}N_5Na_2O_{13}P_3$ = 551.1).

Profile

Adenosine triphosphate (ATP) is an endogenous adenine nucleotide with a fundamental role in cellular energy transformation; ATP is hydrolysed to adenosine diphosphate (ADP) releasing energy stored in phosphate bonds. In addition, extracellular ATP influences many biological processes.

ATP is a vasodilator that has been used in varied disorders. The sodium and disodium salts have been used in cerebral and peripheral vascular disorders and also for the treatment of supraventricular tachycardias, although adenosine (p. 1291.1) is the form generally used as an antiarrhythmic. ATP has also been investigated for use in cachexia in patients with cancer.

Reviews.

1. Agteresch HJ, *et al.* Adenosine triphosphate: established and potential clinical applications. *Drugs* 1999; **58:** 211–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xin Long Ning (新隆宁); ***Fr.***: Atepadene†; Striadyne; ***Hong Kong***: ATP Daiichi; ***Jpn***: Adetphos; ***Philipp.***: Adepos; Nutaphake; ***Rus.***: Fosfobion (Фосфобион); ***Spain***: Atepodin.

Multi-ingredient Preparations. ***Arg.***: Fospartan Ginseng; ***Canad.***: Vitathion-ATP†; ***China***: Ai Nuo Ji (艾诺吉); Jia You (佳优); ***Indon.***: Bio-ATP; Enerplus; Myoviton; Nichoviton; Pro ATP; Vitap; ***Jpn***: Panion; ***Spain***: Refulgin†; Tomevit†; ***Ukr.***: Cocarnit (Кокарнит).

Adiphenine *(rINN)*

Adifenina; Adiphénine; Adipheninum; Адифенин.
2-Diethylaminoethyl diphenylacetate.
$C_{20}H_{25}NO_2$=311.4
CAS — 64-95-9.
UNII — YKG6OR043Q.

Adiphenine Hydrochloride *(USAN, rINNM)*

Adifenina, hidrocloruro de; Adiphénine, Chlorhydrate d'; Adiphenini Hydrochloridum; Cloridrato de Adifenina; Hidrocloruro de adifenina; NSC-129224; Spasmolytine; Адифенина Гидрохлорид.

$C_{20}H_{25}NO_2$,HCl=347.9

CAS — 50-42-0.

UNII — 42B4PDY0AV.

Profile

Adiphenine and adiphenine hydrochloride have been used as antispasmodics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Dorilen; Doriless; Lisador; Lisantil; Sedador; Sedalene; Sedalin†; ***Chile***: Abalgin; Abalgin; SAE; ***Turk.***: Spasmo-Panalgine.

Adipic Acid

Acide adipique; Ácido hexanodioico; Acidum adipicum; Adípico, ácido; Adipiinihappo; Adipinsäure; Adipinsav; Adipinsyra; Adipo rūgštis; Hexanedioic Acid; Kwas adypinowy; Kyselina adipová; Адипиновая Кислота.

1,4-Butanedicarboxylic acid.

$C_6H_{10}O_4$=146.1

CAS — 124-04-9.

UNII — 76A0JE0FKJ.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Adipic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water; freely soluble in alcohol and in methyl alcohol; soluble in acetone.

USNF 31: (Adipic Acid). A white, crystalline powder. Slightly soluble in water; soluble in boiling water and in acetone; freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Profile

Adipic acid is used as an acidifier in pharmaceutical products and in foods and has been included in preparations for the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Bouillet.

Adonis Vernalis

Adonide; Adonidis Vernalis Herba; Adonis; Adonis de primavera; Adonis vernal; Adoniskraut; False Hellebore; Herba Adonidis; Vernal Pheasant's Eye; Ziele miłka wiosennego; Горицвет Весенний.

ATC Herb — HC01AX5001 (Adonis vernalis: herb).

UNII — DX3ZNI25WK.

Pharmacopoeias. In *Ger.* and *Pol.*

Profile

Adonis vernalis, the dried aerial parts of *Adonis vernalis* (Ranunculaceae), contains cardiac glycosides which have actions similar to those of digoxin (p. 1353.3).

Homoeopathy

Adonis vernalis has been used in homoeopathic medicines under the following names: Adonis; Adonis v.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Ritmoneuran; Serenus; ***Ger.***: Miroton†; ***Mex.***: Verisan Triplex; ***Rus.***: Cardiovalen (Кардиовален).

Homoeopathic Preparations. ***Austria***: Homviocorin; ***Fr.***: Vespa Complexe No 46†; ***Ger.***: Angioton H; Angioton S†; Convallocor; Convallysan M; Lowe-Komplex Nr 10; Truw Gold; ***Ukr.***: Homviocorin-N (Хомвиокорин-N).

Adrenalone *(USAN, pINN)* ⊗

Adrenalon; Adrenalona; Adrénalone; Adrenaloni; Adrenalonum; Адреналон.

3′,4′-Dihydroxy-2-(methylamino)acetophenone.

$C_9H_{11}NO_3$=181.2

CAS — 99-45-6.

ATC — A01AD06; B02BC05.

ATC Vet — QA01AD06; QB02BC05.

UNII — EGU41QL329.

Adrenalone Hydrochloride *(pINNM)* ⊗

Adrenalona, hidrocloruro de; Adrénalone, Chlorhydrate d'; Adrenaloni Hydrochloridum; Adrenalonu chlorowodorek; Hidrocloruro de adrenalona; Адреналона Гидрохлорид.

$C_9H_{11}NO_3$,HCl=217.6

CAS — 62-13-5.

ATC — A01AD06; B02BC05.

ATC Vet — QA01AD06; QB02BC05.

UNII — NN82YWE2IC.

Profile

Adrenalone hydrochloride is used as a local haemostatic and vasoconstrictor. It has also been used with adrenaline in eye drops for glaucoma.

Aesculus

Aesculus hippocastanum; Castaño de indias; Falso castaño; Hippocastani semen; Horse-chestnut; Marron d'Inde; Rosskastaniensamen; Spanish Chestnut; Конский Каштан.

CAS — 6805-41-0 (aescin); 11072-93-8 (β-aescin); 531-75-9 (anhydrous esculoside).

*ATC Herb — HA07XA5001 (*Aesculus hippocastanum*; bark); HD03WX5001 (*Aesculus hippocastanum*; bark); HR05DB5001 (*Aesculus hippocastanum*; leaf); HC05CW5001 (*Aesculus hippocastanum*; leaf); HC05CW5002 (*Aesculus hippocastanum*; seed); HC05BW5001 (*Aesculus hippocastanum*; seed).*

*UNII — 2331W47PSX (*Aesculus hippocastanum*); 7U76MXL14N (*Aesculus hippocastanum *bark); KK0Z92II8M (*Aesculus hippocastanum *flower); Z49U891FNQ (*Aesculus hippocastanum *leaf); 3C18L6RJAZ (*Aesculus hippocastanum *seed).*

NOTE. The name Spanish Chestnut has been applied both to Aesculus and to Sweet Chestnut (p. 2625.1).

Pharmacopoeias. In *Fr., Ger., It.,* and *US.*

US also includes the powdered form and powdered extract.

Ger. also includes esculoside in the sesquihydrate form.

USP 36: (Horse Chestnut). The dried seeds of *Aesculus hippocastanum* (Hippocastanaceae), harvested in the autumn. It contains not less than 3.0% of triterpene glycosides, calculated on the dried basis as aescin. Protect from light and moisture.

Uses and Administration

The seeds (conkers) and other parts of the horse-chestnut, *Aesculus hippocastanum,* contain several active principles including esculoside (aesculin or esculin; 6-β-D-glucopyranosyloxy-7-hydroxycoumarin, $C_{15}H_{16}O_9$ = 340.3) and aescin (escin), which is a mixture of saponins.

Aescin and esculoside, the major active principles of aesculus, have been used in the prevention and treatment of various peripheral vascular disorders, including haemorrhoids (p. 1808.1). They have been given orally, by intravenous injection (in the form of sodium aescinate), by rectal suppository, and applied topically. Aescin has also been given intravenously in the prevention and treatment of postoperative oedema.

Other derivatives such as sodium aescin polysulfate have also been used.

Homoeopathy

Aesculus has been used in homoeopathic medicines under the following names: Aesculus hippocastanum; Aesculus hipp; Aesculus cortex; Aesculus hippocastanum ex cortice; Aesc. hip.; Aesculus hippocastanum, flos; Aesculus hipp, flos.

Related plants are also used in homoeopathic medicines under the following names: Aesculus carnea, flos; Aesculus glabra; Aesculus glab.

Esculoside has been used in homoeopathic medicines under the following names: Aesculinum; Aescul.

General references.

1. WHO. Semen Hippocastani. *WHO Monographs on Selected Medicinal Plants,* volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/15.html (accessed 04/02/10)

The use of aesculus has been reviewed;[1-3] although there is some evidence suggesting benefit in chronic venous insufficiency, more rigorous studies are needed.[2]

1. Sirtori CR. Aescin: pharmacology, pharmacokinetics and therapeutic profile. *Pharmacol Res* 2001; **44:** 183–93.
2. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 31/03/06).
3. Anonymous. Aesculus hippocastanum (Horse chestnut). *Altern Med Rev* 2009; **14:** 278–83.

Adverse Effects

Ingestion of aesculus may cause nausea, vomiting, diarrhoea, abdominal colic, delirium, and with large doses respiratory arrest (but see under Poisoning, below).

Effects on the kidneys. A report of the incidence of acute renal failure in patients after cardiac surgery and implicating high-dose intravenous aescin therapy.[1] In 70 patients given a mean maximum daily dose of 340 micrograms/kg, no alteration of renal function was seen; in 16 receiving 360 micrograms/kg, mild renal impairment occurred; and in 40 given 510 micrograms/kg, acute renal failure developed.

1. Hellberg K, *et al.* Medikamentös bedingtes post-operatives Nierenversagen nach herzchirurgischen Eingriffen. *Thoraxchirurgie* 1975; **23:** 396–400.

Effects on the respiratory tract. Bronchial asthma associated with aescin inhalation has been reported in a worker in the pharmaceutical industry.[1]

1. Muñoz X, *et al.* Occupational asthma related to aescin inhalation. *Ann Allergy Asthma Immunol* 2006; **96:** 494–6.

Effects on the skin. Contact dermatitis[1] to esculoside and contact urticaria[2] to aescin have been reported after the use of topical preparations that contained these extracts. Both reactions were confirmed by positive skin tests.

1. Comaish JS, Kersey PJ. Contact dermatitis to extract of horse chestnut (esculin). *Contact Dermatitis* 1980; **6:** 150–1.
2. Escribano MM, *et al.* Contact urticaria due to aescin. *Contact Dermatitis* 1997; **37:** 233.

Poisoning. There have been reports of poisoning in children from eating the seeds, or drinking infusions made from the leaves and twigs of horse-chestnut trees.[1] The toxic substance is considered to be esculoside. Symptoms of poisoning were muscle twitching, weakness, lack of coordination, dilated pupils, vomiting, diarrhoea, paralysis, and stupor.

The UK National Poisons Information Service considers, however, that given the bitterness of the seeds and the poor gastrointestinal absorption of esculoside, significant poisoning is unlikely.

1. Nagy M. Human poisoning from horse chestnuts. *J AMA* 1973; **226:** 213.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Grafic Retard; Herbaccion Venotonico; Nadem; Venastat; Venostasin; ***Austria***: Aesculaforce; Provenen†; Reparil; Venosin; Venostasin; ***Belg.***: Reparil; Traumatil; Veinofytol; Venoplant; ***Braz.***: Phytovein; Reparil; Reparil; Varilise; Venafort; Venotac; Zarv; ***Chile***: Venastat; ***China***: Ou Kai (欧开); ***Cz.***: Reparil; Venitan; Yellon†; ***Fin.***: Venaforce†; ***Fr.***: Flogencyl; ***Ger.***: Aescorin Forte; Aescusan; Aescuven; Essaven Neu†; Essaven†; Heweven Phyto†; Hoevenol; Noricaven; Plissamur; Reparil; Venalot; Venen-Tabletten; Venen-Tropfen N†; Venentabs; veno-biomo†; Venoplant; Venopyronum†; Venorutin retard Rosskastanie†; Venostasin; Venostasin; ***Hong Kong***: Reparil; ***Hung.***: Venastat; ***Irl.***: Venaforce; ***Ital.***: Edeven†; Edevexin; Flebostasin; Ginoven; Reparilexin; ***Mex.***: Alevarin; Venastat; ***Norw.***: Venastat; ***Pol.***: Aescuven; Esceven; Hiposem; Reparil; Sapoven; Venastat; Venitan; Venoplant; Venotonin; ***Port.***: Varison; ***Rus.***: Escizane (Эсцизан); Rectaktiv (Ректактив); Venitan (Венитан); Venoplant (Веноплант); ***Spain***: Flebostasin; Thrombescina; Varicid†; ***Swed.***: Venastat; ***Switz.***: Aesculaforce; AesculaMed; Bio-Venaphyt†; Phlebostasin; Venavit N; Venostasin; ***Thai.***: Reparil; Reparil; ***Turk.***: Reparil; Venotrex; ***UK***: Venaforce; ***Ukr.***: Aescusan (Эскузан); Aesplant (Эсплант); Eskuvit (Эскувит); Venitan (Венитан); Venoplant (Веноплант); ***Venez.***: Vasoplant.

Multi-ingredient Preparations. ***Arg.***: CVP Cellulite; Escina Forte; Escina Omega; Esculeol P; Flaval; Grafic Forte; Troxeven; Tubarine; Venofol; Venostasin; Venostasin; VNS 45; ***Austral.***: Aesculus & Ruscus Compound; Extralife Leg-Care†; Horsechestnut Complex; Sleep Remedy; Vein Relief; Zellulean with Escin†; ***Austria***: Amphodyn†; Augentropfen Stulln†; Heparin Comp; Opino; Opino; Reparil; Urelium Neu; ***Belg.***: Rectovasol; Reparil; ***Braz.***: Hematom; Novarrutina; Proctosan; Reparil; Reparil; Venocur Triplex; ***Canad.***: Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; ***Chile***: Pectokast; Proctoplex; Repariven; ***China***: Ou Lai (欧莱); Reparil-Gel N (利百素凝胶); Stulln (施图伦); Stulln (施图伦); ***Cz.***: Anavenol; Ophthalmo-Evercil; Reparil-Gel N; ***Denm.***: Proctosedyl; ***Fin.***: Proctosedyl; ***Fr.***: Aphloine P; Arterase; Climaxol; Escinogel†; Evarose†; Histo-Fluine P; Intrait de Marron d'Inde P; Opo-Veinogene; Pelvimag; Phlebocreme; Phlebogel†; Phlebosedol†; Phlebosup; Phytomelis; Rap Phyto; Rap Phyto; Reparil; Sedorrhoide; Veinophytum†; Veinostase; Veinotonyl; Vivene†; ***Ger.***: Aescusan†; Augentropfen Stulln Mono; Cefasabal†; Diu Venostasin; Fagorutin Rosskastanien-Balsam N†; Hoevenol; Intradermi†; PC 30 V; Ratanhia comp†; Reparil-Gel N; Schnupfencreme; Sportupac M†; Trauma-cyl†; Varicylum-S†; Weleda Hamorrhoidalzapfchen; ***Gr.***: Opino; ***Hong Kong***: Reparil; ***Hung.***: Aranyer Elleni; Reparil N; Venen; ***India***: Proctosedyl; ***Indon.***: Lanaven Plus†; Lanaven; Opino†; ***Irl.***: Proctosedyl; ***Ital.***: Algorex; Altadrine; Angiovein; Binfolipase; Binfonorm†; Blogofort†; Capill Venogel; Capill; Centella Complex; Centella Complex; Centeril H;

Centeril H; Clebolider†; Criotonal; Dermocinetic; Edeven; Enatus; Essaven; Flavion; Flavion; Flebo-Si†; Flebolider; Flebovis materna; Flebozin; Flodolor; Flogofort Cremagel; Flogofort; Flogovis IdroGel; Flogovis; Gefion; Inflamase IdroGel; Inflamase; Levital Plus; Lik-Gel†; Linfonorin Cremagel; Liotontrauma; Muscoril Trauma; Osmogel; Osteolip Crema; Pik Gel; Plogovis†; Proctopure; Proctosedyl; Proctosedyl; Recto-Reparil; Reparil CM; Sidenol; Signum; Snell Cell†; Somatoline; Vasotonal; Venactive; Venalta; Venoplant; Venoplant; Venoton; Wasotonal†; ***Malaysia***: Cefasabal; Proctosedyl; Reparil-Gel N; ***Mex.***: Almodin; Varicyl; Verisan Triplex; ***Mon.***: Fluon+; Fluon; Phytospray; ***Norw.***: Proctosedyl; ***Philipp.***: Proctosedyl; Reparil N; ***Pol.***: Aesculan; Anavenol†; Arcalen; Arnisol; Emorect; Escalar; Fitoven; Hemorol; Neo-Aesculan; Proctosone†; Proktosedon; Reparil N; Sapoven AT†; Sapoven T; Savarix; Venacorn; Venescin; Venoforton; Venozel; ***Port.***: Synchrocell; Venoparil; ***Rus.***: Aescusan (Эскузан); Anavenol (Анавенол); Evalar (Эвалар); Herbion Aesculus (Гербион Эскулюс); Proctosedyl (Проктоседил); Proctosedyl M (Проктоседил М); Reparil-Gel N (Репарил-Гель Н); Venitan Forte (Венитан Форте); ***S.Afr.***: Proctosedyl; Reparil; Stibium Comp†; ***Singapore***: Erase; Proctosedyl; Reparil-Gel N; ***Spain***: Contusin; Essavenon†; Feparil; Urgenin†; Venacol†; ***Swed.***: Proctosedyl†; ***Switz.***: Augentonicum; Demoven N; DUL-X Cool; Flavovenyl; Flavovenyl; Hametum-N; Ipasin; Lapidar 4; PC 30 V; Reparil N; Suppositoires contre les hemorroides; Venaphyt N; ***Thai.***: Essaven; Proctosedyl; Reparil; Veno-Gel†; ***Turk.***: Prepagel; ***Ukr.***: Aescusan (Эскузан); Eskuvit (Эскувит); Fitoval Lotion (Фитовал Лосьон); Herbion Aesculus (Гербион Эскулус); Proctosedyl (Проктоседил); Reparil-Gel N (Репарил-Гель Н); Venen Theiss (Венен Тайсс); Venitan Forte (Венитан); Venosan (Веносан); ***USA***: Bioflex; Flexgen; ***Venez.***: Gelsem.

Homoeopathic Preparations. ***Austria***: Haemex; Venodril; Vensa; Wirbelsaule- und Gelenkstropfen Nr 2†; ***Canad.***: Avenoc†; Cutisitum†; Formula CI 207†; Formula Homeo QR 209†; Ginkgo-Comp†; Hae 2 Complex†; Hylands Hemorrhoids; ***Chile***: Calcarea fluor Compuesta; Variplant; Variplex; ***Fr.***: Abbe Chaupitre no 15†; Abbe Chaupitre no 64†; Aesculus Complexe No 103; Aesculus Compose; Avenoc; Boripharm No 1†; Hamamelis Compose; Homeodose 20†; Sepia Compose; Vascoflor; Veinosium†; ***Ger.***: Conisan A†; Conisan B†; Conjunctisan-AN†; Conjunctisan-BN†; Haemorrhoid-Gastreu N; Heweven Complex; Neuri-cyl N Ho-Len-Complex; Phonix Silybum spag; phono Ven; Reproven N; Rheuma-Hevert†; Secale-Gastreu; Secalosan N; Varicylum N; Venen-Komplex Ho-Fu-Complex; Veno-Injektopas; veno-loges N; Venokatt; Venoselect N; Wibotin HM; ***Neth.***: Achilite; Acidolite; Aesculus Comp; Ambheel; Homeocare Vasco; Omnilite; Venafleur; ***Port.***: Avenoc; ***Rus.***: Menalgin (Менальгин); Mercure-Plus (Меркур-Плюс); Paeonia-Plus (Пеония-Плюс); Vensa (Венза); ***S.Afr.***: Achillea Comp†; ***Switz.***: Gastronol; Regenaplex Nr 38b; Regenaplex Nr. 12; Regenaplex Nr. 24c; Regenaplex Nr. 25a; Regenaplex Nr. 25c; Regenaplex Nr. 31a; Regenaplex Nr. 31b; Regenaplex Nr. 31c; Regenaplex Nr. 51c; Regenaplex Nr. 59b; ***UK***: Catarrh Cream; Haemorrhoid Cream; Medicinal Gargle.

Afegostat Tartrate *(USAN, rINNM)*

Afégostat, Tartrate d'; Afegostati Tartras; AT-2101; HGT-3410; Isofagomine Tartrate; Tartrato de afegostat; Афегостата Тартрат.

(3*R*,4*R*,5*R*)-5-(Hydroxymethyl)piperidine-3,4-diol hydrogen tartrate.

$C_6H_{13}NO_3.C_4H_6O_6$=297.3

CAS — 169105-89-9 (afegostat); 161302-93-8 (afegostat hydrochloride); 919364-56-0 (afegostat tartrate).

UNII — 285ZJJ9773.

NOTE. The name Plicera has been used as a trade mark for afegostat tartrate. The code AT-2101 has also been applied to a topical formulation of diclofenac in hyaluronic acid used in the treatment of actinic keratoses.

Profile

Afegostat tartrate is an iminosugar under investigation for oral therapy of Gaucher disease (p. 2433.3). It is a pharmacological chaperone that stabilises the variant lysosomal glucocerebrosidase facilitating its folding and transport from the endoplasmic reticulum into lysosomes, thereby increasing the pool of active endogenous enzyme.

Afelimomab *(rINN)*

Afélimomab; Afelimomabum; MAK-195F; Афелимомаб.

Immunoglobulin G3, anti-(human tumor necrosis factor α) F (ab')2 fragment (mouse monoclonal LU54107 γ3-chain), disulfide with mouse monoclonal LU54107 κ-chain, dimer.

CAS — 156227-98-4.

ATC — L04AB03.

ATC Vet — QL04AB03.

NOTE. The name Segard has been used as a trade mark for afelimomab.

Profile

Afelimomab is a monoclonal tumour necrosis factor antibody that has been investigated for the treatment of sepsis.

References.

1. Vincent JL. Afelimomab. *Int J Clin Pract* 2000; **54:** 190–3.
2. Reinhart K, *et al.* Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES study. *Crit Care Med* 2001; **29:** 765–9.
3. Gallagher J, *et al.* A multicenter, open-label, prospective, randomized, dose-ranging pharmacokinetic study of the anti-TNF-alpha antibody afelimomab in patients with sepsis syndrome. *Intensive Care Med.* 2001; **27:** 1169–78.
4. Panacek EA, *et al.* Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* 2004; **32:** 2173–82.

Aflatoxins

Aflatoxinas.

CAS — 1162-65-8 (aflatoxin B_1); 7220-81-7 (aflatoxin B_2); 1165-39-5 (aflatoxin G_1); 7241-98-7 (aflatoxin G_2); 6795-23-9 (aflatoxin M_1); 6885-57-0 (aflatoxin M_2).

Profile

Aflatoxins are toxic metabolites produced by many strains of *Aspergillus flavus* and *A. parasiticus*, growing on many vegetable foods, notably maize and peanuts. Several forms, including aflatoxins B_1, B_2, G_1, and G_2 have been identified. Aflatoxins M_1 and M_2 are metabolites produced by *animals* after ingestion of aflatoxins B_1 and B_2; they may be detected in cows' milk.

Aflatoxins can cause hepatitis and cirrhosis. They have been implicated in liver cancer, and may act as co-carcinogens with hepatitis B virus. Aflatoxin B_1 is reported to be one of the most potent carcinogens known in *animals*. It has been reported that aflatoxins have been developed in some countries as biological weapons.

References.

1. Ross RK, *et al.* Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 1992; **339:** 943–6.
2. Jackson PE, Groopman JD. Aflatoxin and liver cancer. *Baillieres Best Pract Res Clin Gastroenterol* 1999; **13:** 545–55.
3. Peraica M, *et al.* Toxic effects of mycotoxins in humans. *Bull WHO* 1999; **77:** 754–66.
4. Pitt JI. Toxigenic fungi and mycotoxins. *Br Med Bull* 2000; **56:** 184–92.

Agnus Castus ⊗

Agni Casti; Agni Casti Fructus; Agnocasto; Chaste Tree Fruit; Chasteberry; Drmkový plod; Gattilier, fruit de; Keuschlamm; Mönchspfeffer; Monk's Pepper; Munkpeppar; Owoc niepokalanka zwyczajnego; Sauzgatillo; Siveydenpuunhedelmä; Zerolo; Монаший Перец.

ATC — G02CX03.

ATC Vet — QG02CX03.

*ATC Herb — HG02WX5005 (*Vitex agnus-castus*: fruit).*

UNII — 433OSF3U8A.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Agnus Castus Fruit). The whole, ripe, dried fruit of *Vitex agnus castus*. It contains a minimum 0.08% of casticin calculated with reference to the dried drug. Protect from light.

USP 36: (Chaste Tree). The dried ripe fruits of *Vitex agnus-castus* (Verbenaceae). It contains not less than 0.05% of agnuside and not less than 0.08% of casticin, calculated on the dried basis.

Uses and Administration

Agnus castus is reported to affect the secretion of luteinising hormone, follicle stimulating hormone, and prolactin by the pituitary. Both inhibition and stimulation of prolactin secretion have been reported, and may be dose-dependent. Agnus castus is included in herbal preparations for the symptoms of premenstrual syndrome, including mastalgia; it has also been used for menstrual cycle irregularities or menopausal disorders, but should be avoided in patients receiving exogenous sex hormones, including oral contraceptives.

Homoeopathy

Agnus castus has been used in homoeopathic medicines under the following names: Vitex agnus-castus; Agn. cast.; Agnus.

References.

1. Houghton P. Agnus castus. *Pharm J* 1994; **253:** 720–1.
2. Christie S, Walker AF. Vitex agnus-castus L.: (1) a review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners. *Eur J Herbal Med* 1997; **3:** 29–45.
3. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; **322:** 134–7.
4. Chrubasik S, Roufogalis BD. Chaste tree fruit for female disorders. *Aust J Pharm* 2001; **82:** 156–7.
5. Wuttke W, *et al.* Chaste tree (Vitex agnus-castus)—pharmacology and clinical indications. *Phytomedicine* 2003; **10:** 348–57.
6. Döll M. Das prämenstruelle Syndrom: Wirksamkeit von Vitex agnus castus. *Med Monatsschr Pharm* 2009; **32:** 186–91.
7. van Die MD, *et al.* *Vitex agnus-castus* (Chaste-Tree/Berry) in the treatment of menopause-related complaints. *J Altern Complement Med* 2009; **15:** 853–62.

Adverse Effects and Precautions

The adverse effects of agnus castus are reported to be mild and reversible, with acne, erythematous rash, headache, gastrointestinal disorders, menstrual disorders, nausea, and pruritus being the most frequently reported.[1] Toxicity data for use of agnus castus during pregnancy and breast feeding are sparse and its safety is therefore unclear.[1,2] In view of its pharmacological actions, use is not recommended.[1] There is a theoretical possibility of drug interactions between agnus castus and dopamine antagonists.[1]

1. Daniele C, *et al.* Vitex agnus castus: a systematic review of adverse events. *Drug Safety* 2005; **28:** 319–32.
2. Dugoua J-J, *et al.* Safety and efficacy of chastetree (*Vitex agnus-castus*) during pregnancy and lactation. *Can J Clin Pharmacol* 2008; **15:** e74–e79.

Interactions

For reference to potential interactions with agnus castus and dopamine antagonists, see above. For a suggestion of a potential interaction between agnus castus and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Premular; ***Austria***: Agnofem; Agnucaston; Agnumens†; ***Braz.***: Lutene†; Nalle; Tenag; Vitenon; Vitex; ***Chile***: Dimenox; ***Cz.***: Agnucaston; Cesrafemme†; ***Ger.***: Agnolyt; Agnucaston; Agnus; Biofem†; Castufemin; Cefanorm†; Femicur N; Feminon A; Femisana mens†; Gynocastus; Sarai†; Strotan; ***Hung.***: Agnucaston; Cefanorm; PreMens; ***Indon.***: Agnu Gyne†; Agnucaston†; ***Mex.***: Cicloplant†; ***Norw.***: Femicur†; ***Pol.***: Agufem; Castagnus; Cyclodynon; Feminon PMS; ***Rus.***: Agnucaston (Агнукастон); Cyclodynon (Циклодинон); ***Spain***: Dismegyn; Femiplante†; ***Swed.***: Femicur; ***Switz.***: Cyclodynon†; Oprane; Prefemine; PreMens; ***Turk.***: Agnucaston; Biofem†; ***UK***: Cyclopret; Herbal Premens; Kira Prem; Periagna; Premherb; ***Ukr.***: Cyclodynon (Циклодинон).

Multi-ingredient Preparations. ***Austral.***: Dong Quai Complex†; Extralife Meno-Care†; Extralife PMS-Care†; Femi-Nan; Feminine Herbal Complex; Femme-F; PM H-Regulator; PM LifePro Max for Women; PMT-Eze†; Prosense for Women†; ***Canad.***: Natural HRT; Phytoestrin; ***Hong Kong***: Phytoestrin†; ***India***: Evepearl-PMS; ***Indon.***: Herbalacta†; ***Ital.***: Bioestril Ginseng; Bioestril Valeriana; Climil Complex; Climil-80; Ginecast; Spm-OK; ***Singapore***: Phytoestrin†; ***UK***: Flash Fighters; ***Ukr.***: Evica (Евика)†.

Homoeopathic Preparations. ***Austria***: Erbiode-Starkungstropfen; Mastodynon; Pascofemin; ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Amphosca†; Ervopax†; Fatigue; Homeo-Form F†; ***Cz.***: Mastodynon; ***Fr.***: Agnus Castus Complexe No 2†; Amphosca Orchitine; Amphosca Ovarine; Boripharm No 31; Nervopax; ***Ger.***: Agnurell; Agnus castus comp†; Agnus femin; Antimast†; Antimast TN†; Bomaklim; Emasex-A vitex; Feminon N; Klimaktosin; Mastodynon; Pascofemin; Phyto-L; Viragil; Virilis-Gastreu S R41; ***Neth.***: Emvita 10; Homeocare Cyclo; Mastodynon†; Mulimen H; ***Rus.***: Damiana-Plus (Дамиана-Плюс); Dysmenorm (Дисменорм); Mastodynon (Мастодинон); ***Switz.***: Menosan†; ***Thai.***: Mastodynon†; ***Ukr.***: Dysmenorm (Дисменорм.); Mastodynon (Мастодинон).

Agrimony

Agrimoña; Agrimonia; Agrimoniae Herba; Aigremoine; Cafetí; Dirvuolių žolė; Hierba bacera; Hierba de San Guillermo; Hierba del podador; Maarianverijuuri; Odermennigkraut; Párlófű; Småborre; Řepíková nať; Репешок Аптечный.

*ATC Herb — HA01WA5001 (*Agrimonia eupatoria*: herb); HD02WX5001 (*Agrimonia eupatoria*: herb).*

*UNII — EBU0U94820 (*Agrimonia eupatoria*); GYD07VBS73 (*Agrimonia eupatoria *flowering top).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Agrimony). The dried flowering tops of *Agrimonia eupatoria* containing a minimum of 2.0% of tannins expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Agrimony, the aerial parts of *Agrimonia eupatoria* (Rosaceae) or more rarely *A. procera* (*A. odorata*; fragrant agrimony), has astringent and diuretic properties. It is used internally for diarrhoea, biliary and other gastrointestinal disorders, and

urinary-tract disorders; it has also been used for inflammatory mouth and throat disorders. It has been used externally for wound healing and skin disorders.

A. pilosa is used in traditional Chinese medicine. It contains the tannin agrimoniin which is reported to be an inducer of interleukin-1 production.

Homoeopathy

Agrimony has been used in homoeopathic medicines under the following names: Agrimonia eupatoria; Agrimonia eup; Agrimonia eupatoria, flos; Agrimonia eup, flos; Agrimonia odorata, flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Repikovy Caj, Repikova Nat.

Multi-ingredient Preparations. ***Austral.***: Detox Program; Digestive Bitters; ***Austria***: Amersan; Gallen- und Lebertee St Severin; ***Cz.***: Amersan; Herbadent; Species Cholagogae Planta†; Stomaran; The Salvat; Zlucnikova Cajova Smes; ***Fr.***: Tisane Hepatique de Hoerdt†; ***Hung.***: Majvedo es Detoxikalo; Urogin; Vesevedo; ***Rus.***: Herbion Drops for the Gallbladder (Гербион Капли Желчегонные)†; ***Switz.***: Kernosan 24; ***UK***: Piletabs; ***Ukr.***: Herbion Drops for the Gallbladder (Гербион Капли Желчегонные).

Homoeopathic Preparations. ***Fr.***: Poconeol no 57; Poconeol no 81†; ***Switz.***: Regenaplex Nr. 25b; Regenaplex Nr. 35b; Regenaplex Nr. 79; Regenaplex Nr. 80aN.

Alfalfa

Alfaz; Lucerne; Mielga; Purple medick; Люцерна.

CAS — 543-38-4 (canavanine).

ATC Herb — HG04BW5022 (Medicago sativa: *herb*); *HA10BX5004* (Medicago sativa: *herb*).

UNII — SQI2NBY9KR (alfalfa top); HY3L927V6M (alfalfa leaf); DJO934BRBD (alfalfa).

Pharmacopoeias. *Br.* includes a form for homoeopathic preparations.

BP 2014: (Medicago Sativa for Homoeopathic Preparations). The fresh whole flowering plant of *Medicago sativa*.

Profile

Alfalfa is the plant *Medicago sativa* (Leguminosae) which is cultivated as an animal feedstuff. The seeds and sprouts of alfalfa contain canavanine (2-amino-4-(guanidinooxy) butyric acid), a toxic amino acid structurally related to arginine; content is reported to represent about 1.5% of the dry weight. A syndrome resembling SLE has been recorded in *monkeys* fed alfalfa.

Alfalfa is used in herbal preparations for a variety of disorders.

Homoeopathy

Alfalfa has been used in homoeopathic medicines under the following names: Alfa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Esterin.

Multi-ingredient Preparations. ***Arg.***: Calmag D; Daily Nutrilite; ***Austral.***: Irontona†; Vitatona†; ***Chile***: Calcio 520; ***Fr.***: Gonaxine; ***Ukr.***: Alfagin (Алфагин).

Homoeopathic Preparations. ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Alfalfa Tonic; Comp-Drops 1 Stress†; Fatigue; Homeo-Form F†; Homeo-Form P†; Motherwort Combination 3†; ***Fr.***: Soreal; ***Switz.***: Nelsons Noctura†; ***UK***: Noctura.

Alfaprostol *(BAN, USAN, rINN)*

Alfaprostolum; K-11941; Ro-22-9000; Альфапростол.

Methyl (*Z*)-7-{(1*R*,2*S*,3*R*,5*S*)-2-[(3*S*)-5-cyclohexyl-3-hydroxypent-1-ynyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.

$C_{24}H_{38}O_5$=406.6

CAS — 74176-31-1.

ATC Vet — QG02AD94.

UNII — 4XKL2JJ08I.

Profile

Alfaprostol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Alglucerase *(BAN, USAN, rINN)*

Alglucerasa; Alglucérase; Alglucerasum; Glucosylceramidase; Macrophage-targeted β-Glucocerebrosidase; Альглюцераза.

CAS — 143003-46-7.

ATC — A16AB01.

ATC Vet — QA16AB01.

UNII — 27T56C7KK0.

Description. Alglucerase is a modified form of human placental β-glucocerebrosidase (ceramide glucosidase; β-D-glucosyl-*N*-acylsphingosine glucohydrolase). It is a monomeric glycoprotein of 497 amino acids with glycosylation making up about 6% of the molecule.

Imiglucerase *(BAN, USAN, rINN)*

Imiglucerasa; Imiglucérase; Imiglucerasum; Imiglukeraasi; Imiglukeras; Imigluseraz; r-GCR; Recombinant Macrophage-targeted β-Glucocerebrosidase; Имиглюцераза.

CAS — 154248-97-2.

ATC — A16AB02.

ATC Vet — QA16AB02.

UNII — Q6U6J48BWY.

Description. Imiglucerase is a recombinant modified form of human β-glucocerebrosidase. It is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites. Imiglucerase differs from placental glucocerebrosidase by 1 amino acid at position 495, where histidine is substituted for arginine.

Taliglucerase Alfa *(USAN, rINN)*

prGCD; Taliglucerasa Alfa; Taliglucérase Alfa; Taliglucerasum Alfa; Талиглюцераза Альфа.

CAS — 37228-64-1.

ATC — A16AB11.

ATC Vet — QA16AB11.

UNII — 0R4NLX88O4.

Description. Taliglucerase alfa is a recombinant modified form of human β-glucocerebrosidase. It is a monomeric glycoprotein containing 4 N-linked glycosylation sites. Taliglucerase alfa differs from human glucocerebrosidase by 2 amino acids at the N-terminal and up to 7 amino acids at the C-terminal.

The name Uplyso has been used as a trade mark for taliglucerase alfa.

Velaglucerase Alfa *(BAN, USAN, rINN)*

Velaglucerasa alfa; Vélaglucérase alfa; Velaglucerasum alfa; Велаглюцераза Альфа.

CAS — 884604-91-5.

ATC — A16AB10.

ATC Vet — QA16AB10.

UNII — 23HYE36B0I.

Description. Velaglucerase alfa is produced by gene activation technology in a human cell line and has the same amino acid sequence as human glucocerebrosidase. It contains 5 potential N-linked glycosylation sites, 4 of which are occupied by glycan chains.

Uses and Administration

The enzyme β-glucocerebrosidase is given as imiglucerase, taliglucerase alfa, velaglucerase alfa, or occasionally alglucerase for long-term enzyme replacement therapy in patients with Gaucher disease (see below). The oligosaccharide chains of the enzyme are modified to terminate with mannose residues to ensure uptake into macrophages.

Alglucerase, imiglucerase, taliglucerase alfa, and velaglucerase alfa are used in the management of type 1 Gaucher disease; imiglucerase may also be used in patients with type 3 who have clinically significant non-neurological manifestations of the disease. The usual dose for each of these is 60 units/kg given once every 2 weeks by intravenous infusion over 1 to 2 hours. The solution should be filtered through a low-protein-binding 0.2 micrometre in-line filter during administration. The dose should be individualised according to disease severity and adjusted according to response. Doses ranging as low as 15 units/kg once every 2 weeks have been used, and initial doses of imiglucerase 2.5 units/kg given 3 times weekly have been reported.

For administration in children, see below.

Reviews.

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2. Morris JL. Velaglucerase alfa for the management of type 1 Gaucher disease. *Clin Ther* 2012; **34:** 259–71.
3. Deegan PB, Cox TM. Imiglucerase in the treatment of Gaucher disease: a history and perspective. *Drug Des Devel Ther* 2012; **6:** 81–106.
4. Hollak CEM. An evidence-based review of the potential benefits of taliglucerase alfa in the treatment of patients with Gaucher disease. *Core Evid* 2012; **7:** 15–20.

Administration in children. Alglucerase, imiglucerase, and velaglucerase alfa may be given to children in the same dosing regimen as that usually used in adults (see above). However, licensed product information states that safety and efficacy have not been established for alglucerase and imiglucerase in children younger than 2 years of age, or for velaglucerase alfa in those aged less than 4 years.

The *BNFC* suggests that imiglucerase may be used similarly in neonates and infants, and that doses up to 120 units/kg once every 2 weeks by intravenous infusion may be given to patients with type 3 Gaucher disease.

Gaucher disease. Gaucher disease (glucocerebrosidosis) is a rare, autosomal recessive disorder, although it is the commonest lysosomal storage disorder. It is caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase (acid β-glucosidase, ceramide glucosidase, β-D-glucosyl-*N*-acylsphingosine glucohydrolase, or glucosylceramidase) which catalyses the hydrolysis of glucocerebroside, a lipid component of cell membranes, to glucose and ceramide. Deficiency of β-glucocerebrosidase results in accumulation of glucocerebroside in the lysosomes of reticuloendothelial cells, particularly macrophages.[1-5]

Gaucher disease is **classified** into three main forms based on clinical signs and symptoms. Hepatosplenomegaly occurs in all forms. **Type 1 Gaucher disease** (chronic adult non-neuronopathic disease) accounts for 90% or more of cases and occurs especially in Ashkenazi Jews. More than half of all patients with type 1 disease are diagnosed before the age of 10 years.[6] The disease follows a chronic course of variable severity and onset, with hepatosplenomegaly and blood and bone disorders being the main features; there is no neurological involvement. In **type 2 Gaucher disease** (acute infantile neuronopathic disease), neurological involvement predominates. Patients show developmental delay by the age of 6 months, suffer seizures, pulmonary infections, and usually die in early childhood. **Type 3 Gaucher disease** is a subacute neuronopathic form and is slowly progressive.[4] There are 3 subtypes varying in severity and prognosis: in type 3a, there is slow progressive neurological deterioration with death usually occurring during childhood; in type 3b (Norrbotten disease) there is slow cognitive deterioration and patients may survive to adulthood; type 3c typically affects patients of Palestinian, Arab, or Japanese descent, with possible survival to the teenage years.

Treatment of Gaucher disease was previously limited to symptomatic management until the development of enzyme replacement therapy with β-glucocerebrosidase. Due to the rarity of Gaucher disease, early clinical studies were limited mainly to small case series of patients with type 1 disease. β-Glucocerebrosidase is given as imiglucerase or velaglucerase alfa, or occasionally as alglucerase or taliglucerase alfa. Use of such therapy has been shown to reverse hepatosplenomegaly and the haematological abnormalities;[7,8] effects may be seen within a few months, although in many the response is poor during the first 6 to 9 months and then improves rapidly.[2] Return to normal haemoglobin values within 6 to 12 months has been reported, as has reduction in liver size by 20 to 30% within 2 years and 30 to 40% by 5 years; a 50% reduction in spleen size also occurred.[9] Bone symptoms respond more slowly. Decreases in bone pain during the first year of treatment have been reported although there was no radiological improvement.[8] Existing bone manifestations are slow to respond or refractory to enzyme replacement therapy, but alendronate has been shown to be of benefit as adjunctive therapy for osteopenia in 36 adults with negative lumbar bone mineral density scores who had been receiving glucocerebrosidase for at least 2 years.[10] Normalised growth velocity has been reported in children[11] and radiographical assessments have shown improvements in bone density and mineralisation.[12] There is evidence that long-term enzyme replacement therapy for up to 8 years completely or partially ameliorates anaemia, thrombocytopenia, organomegaly, and bone pain in patients with type 1 Gaucher disease, as well as preventing further deterioration.[9,13] However, successful symptom control is dependent on the degree of damage that has already occurred, and early initiation of therapy is recommended for a more favourable prognosis.[5,14] Enzyme replacement therapy in Gaucher disease is lifelong and relapses occur with prolonged interruptions to therapy.[6,15] Taliglucerase alfa[16] and velaglucerase alfa[17] are used similarly to imiglucerase in the treatment of type 1 Gaucher disease. Alglucerase has also been tried in rare cases of Gaucher disease affecting the heart[18] or the eye.[19] It is not yet known whether enzyme replacement therapy is able to prevent the development of symptoms in asymptomatic patients.

The efficacy of enzyme replacement therapy in managing neurological symptoms in patients with type 2 or type 3 disease[20] is unproven. Most of the patients with type 3 Gaucher disease in a small study[21] did not deteriorate neurologically when treated with doses that reversed almost all the systemic manifestations. However, it was pointed out that the amount of enzyme that crosses the blood-brain barrier is unlikely to be significant, and other forms of treatment specifically for neuronopathic Gaucher disease need to be developed.

For those patients with type 1 Gaucher disease in whom enzyme replacement therapy may be unsuitable, miglustat may be used. It reduces the synthesis of glucocerebroside by inhibiting glucosyltransferase, one of the early enzymes in the sphingolipid biosynthetic pathway. However, the balance of benefits versus adverse affects with miglustat is less favourable than with imiglucerase, which remains the standard treatment where possible; the two drugs should not be used together.[22]

Haematopoietic stem cell transplantation has produced favourable outcomes in patients with Gaucher disease and could potentially provide a permanent cure. However, the procedure is not without risk of death or significant morbidity, and until these are reduced to an acceptable level by further technological advances supported by data from good clinical studies, it is reserved as a late treatment option, by which time a complete cure is less likely.[23]

Possible future therapies under investigation for Gaucher disease include oral therapy with the pharmacological chaperone afegostat tartrate, and gene therapy. Other modified forms of β-glucocerebrosidase are also under investigation to improve uptake into the affected macrophages.

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Adverse Effects and Precautions

Reactions occurring during or shortly after infusion of alglucerase, imiglucerase, taliglucerase alfa, or velaglucerase alfa can include fever, chills, pruritus, flushing, and gastrointestinal symptoms including cramps, diarrhoea, nausea, and vomiting. Some of these may be hypersensitivity reactions; other hypersensitivity reactions, including urticaria and angioedema, respiratory symptoms, and hypotension have also occurred. Anaphylactoid reactions have occurred rarely with imiglucerase and taliglucerase alfa. Caution is required in patients who have shown signs of hypersensitivity; reduction of the rate of infusion, and pretreatment with antihistamines and/or corticosteroids may permit further treatment. Antibodies have developed in about 15% of patients during the first year of therapy with alglucerase or imiglucerase. The development of antibodies to taliglucerase alfa and velaglucerase alfa has also been reported. Patients who develop antibodies are at increased risk of hypersensitivity reactions and periodic assessment for antibody formation is recommended.

Pain and irritation at the injection site may occur. Other adverse effects reported include fatigue, dizziness, headache, backache, peripheral oedema, mouth ulcers, and disturbances in sense of smell.

Alglucerase is prepared from human placentas and its infusion therefore carries a risk of transmission of infections although this is minimised by the manufacturing process. Chorionic gonadotrophin, a naturally occurring hormone in human placentas, has been detected in alglucerase. The presence of this hormone may produce early virilisation in young boys if sufficient is given, and has the potential to produce false positive results in pregnancy tests that rely on the detection of this hormone. Alglucerase should be used with caution, if at all, in patients with androgen-sensitive malignancies.

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Effects on the lungs. Pulmonary hypertension developed in 2 patients with Gaucher disease after starting treatment with alglucerase.[1] Neither patient had evidence of parenchymal lung infiltration with Gaucher cells.

1. Dawson A, *et al*. Pulmonary hypertension developing after alglucerase therapy in two patients with type 1 Gaucher disease complicated by the hepatopulmonary syndrome. *Ann Intern Med* 1996; **125:** 901–4.

Pharmacokinetics

After intravenous infusion, plasma enzymatic activities of alglucerase and imiglucerase decline rapidly from steady state, with an elimination half-life of between 3.6 and 10.4 minutes. Taliglucerase alfa is cleared with a terminal half-life of 18.9 to 28.7 minutes, and velaglucerase alfa has a half-life of 5 to 12 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cerezyme; ***Austria***: Cerezyme; ***Belg.***: Cerezyme; ***Braz.***: Cerezyme; ***Canad.***: Cerezyme; ***Chile***: Cerezyme; ***China***: Cerezyme (思而赞); ***Cz.***: Cerezyme; ***Denm.***: Cerezyme; VPRIV; ***Fin.***: Cerezyme; ***Fr.***: Cerezyme; VPRIV; ***Ger.***: Cerezyme; VPRIV; ***Gr.***: Cerezyme; ***Hong Kong***: Cerezyme; ***Irl.***: Cerezyme; VPRIV; ***Israel***: Cerezyme; Elelyso; VPRIV; ***Ital.***: Cerezyme; ***Jpn***: Cerezyme; ***Malaysia***: Cerezyme; ***Neth.***: Cerezyme; VPRIV; ***Norw.***: Cerezyme; VPRIV; ***NZ***: Cerezyme; ***Pol.***: Cerezyme; VPRIV; ***Port.***: Cerezyme; VPRIV; ***Rus.***: Cerezyme (Церезим); ***S.Afr.***: Cerezyme; ***Spain***: Cerezyme; Vpriv; ***Swed.***: Cerezyme; VPRIV; ***Switz.***: Cerezyme; ***Thai.***: Cerezyme; ***Turk.***: Cerezyme; ***UK***: Cerezyme; VPRIV; ***Ukr.***: Cerezyme (Церезим); ***USA***: Ceredase†; Cerezyme; Elelyso; VPRIV.

Alibendol *(rINN)*

Alibendolum; Алибендол.

5-Allyl-*N*-(2-hydroxyethyl)-3-methoxysalicylamide.

$C_{13}H_{17}NO_4$=251.3

CAS — 26750-81-2.

UNII — A8CO1VZK2Z.

Profile

Alibendol is a choleretic used in the treatment of gastrointestinal disorders.

Alipogene Tiparvovec *(rINN)*

AAV1-LPL^{S447X}; Alipogén tiparvovec; Alipogène tiparvovec; Alipogenum tiparvovecum; AMT-011; Алипоген Типарвовек.

Recombinant adeno-associated virus serotype 1 (AAV1) vector expressing the S447X variant of the human lipoprotein lipase (LPL) gene.

CAS — 929881-05-0.

ATC — C10AX10.

ATC Vet — QC10AX10.

Profile

Alipogene tiparvovec is a gene therapy product (p. 2511.2) used in the treatment of adult patients with familial lipoprotein lipase (LPL) deficiency who have severe or recurrent pancreatitis. It is made from a nonreplicating adeno-associated viral vector (AAV1) that carries a gene for LPL. Alipogene tiparvovec is licensed for use as a single injection series, using a solution that contains 3×10^{12} genome copies per mL. The maximum total dose is 1×10^{12}/kg. Multiple injections should be made intramuscularly into the legs and the use of spinal or regional anaesthesia is advised; the recommended dose per injection site is 1.5×10^{12}.

For 3 days before, and for 12 weeks after, treatment, immunosuppressive therapy should be given; ciclosporin (3 mg/kg daily) and mycophenolate mofetil (2 g daily) have been suggested. In addition, an intravenous dose of methylprednisolone (1 mg/kg) should be given 30 minutes before starting treatment.

It is also under investigation for the treatment of type V hyperlipoproteinaemia, syndrome X, and non-alcoholic steatohepatitis.

References.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Glybera.

Allergen Products

Alergenos; Allergeenivalmisteet; Allergenprodukter; Producta Allergenica; Produits allergènes.

Uses and Administration

Allergen products are used diagnostically in skin tests and provocation tests to confirm the cause of a suspected hypersensitivity reaction. They are also used for allergen immunotherapy in certain patients with hypersensitivity reactions, particularly to insect venoms such as bee or wasp venom, pollen (p. 2593.3), house dust, and house-dust mite. Preparations for allergen immunotherapy are given by subcutaneous injection or sublingually. Other routes (such as oral, nasal, or bronchial) have also been tried.

Administration. Allergen vaccines used for allergen immunotherapy (see p. 2435.1) should be well characterised and standardised for total allergenic potency, biological activity, and shelf-life. Whenever possible, the same batch of allergen should be used during a course of treatment because of possible differences in potency between batches. Injections for allergen immunotherapy are given subcutaneously as aqueous extracts or combined with adjuvants to reduce adverse effects while retaining or enhancing immunogenicity. Such modified vaccines are slow-release formulations and therefore the interval between injections is increased. Vaccines can be physically modified by adsorption onto an inert carrier such as aluminium or calcium salts, or tyrosine, or chemically modified with glutaral, formaldehyde, or liposomes. Combinations of the two types of modified vaccine may also be used.

Dosage regimens for allergen immunotherapy are as recommended by the manufacturers and depend on the sensitivity of the patient. During the initial build-up phase, the dose of allergen vaccine is slowly increased (by increasing the concentration and/or the dose volume) until the maintenance dose is reached. However, the dose should be reduced after a systemic reaction, or stopped if the reaction is severe. Likewise, the dose might need to be reduced or not given at all to highly sensitised patients during periods of natural exposure to the allergen.

In *conventional* build-up schedules, injections of aqueous extracts are given once or twice weekly, with maintenance expected to be reached in 4 to 6 months. Depot preparations are given every 1 to 2 weeks. *Modified dosage schedules* have been used where maintenance needs to be achieved more quickly; such regimens may, however, be associated with an increased risk of adverse reactions, although this can be ameliorated by premedication with an antihistamine. Aqueous extracts should be used for modified schedules until the maintenance dose is reached. In *cluster schedules* several injections may be given on the same day, usually at 30-minute intervals, once or twice a week on non-consecutive days. Fewer total injections are used than with conventional schedules and maintenance therapy can be reached in as little as 4 weeks. There might be a slight increase in risk of systemic reactions. *Rush schedules* are more rapid than cluster schedules and several injections are given at specified intervals once daily on consecutive days allowing maintenance doses to be reached in a matter of days; naturally, this does increase the risk of systemic adverse effects and patients need to be monitored more closely and for longer than with conventional schedules. *Ultrarush schedules* are even faster and may be used to accelerate desensitisation to stinging insects in highly sensitive individuals. When the maintenance dose has been

reached, the injection interval is progressively increased as necessary according to safety and efficacy. Injection intervals are typically 2 to 4 weeks for aeroallergens and 8 weeks for insect venom. The optimal duration of allergen immunotherapy is unknown, but a period of 3 to 5 years is usually recommended; the decision to discontinue therapy will depend on individual response. Some patients will remain desensitised after stopping allergen immunotherapy but others will relapse.

The sublingual route is also used for allergen immunotherapy, with the vaccine given daily either as a solution or as oral lyophilisate tablets. It is considered to be a good alternative to the subcutaneous route in terms of safety and efficacy, although the optimal vaccine dose in relation to efficacy and duration of treatment is still undetermined. The oral, nasal, and bronchial routes have also been tried for allergen immunotherapy, although efficacy or safety has not always been shown.

Modification of allergens is being investigated as an alternative way to increase safety and efficacy, and developments include recombinant proteins, peptides, plasmid DNA vaccines, and immunostimulatory sequences of DNA conjugated to specific allergens. Other immunomodulatory methods include use of allergen-specific antibodies or fragments, and humanised anti-IgE monoclonal antibodies (e.g. omalizumab, p. 1216.3). Also, more efficient adjuvants such as monophosphoryl lipid A are being tried.

References.

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Allergen immunotherapy. Allergic reactions are type I (immediate) hypersensitivity reactions mediated by IgE antibodies (see under Hypersensitivity, p. 610.1) that are usually managed by anti-allergic medication or, where possible, allergen avoidance. For patients in whom these treatment methods are inadequate or unsuitable, allergen immunotherapy (desensitisation or hyposensitisation) may be tried. Specific allergen immunotherapy (SIT) is the administration of gradually increasing quantities of an allergen vaccine to a patient with diagnosed IgE-mediated allergy until a maintenance dose is reached that is effective in ameliorating symptoms associated with subsequent exposure to the allergen.[1-4] The mechanism of action is thought to be through T-helper (Th) cell switching by rectifying the balance between Th1 and Th2 lymphocytes and increasing the levels of protective IgG while decreasing the levels of IgE.[2,4-6] Long-lasting benefit is conferred, and the quality of life improved in patients for whom allergen avoidance is difficult or impossible. Patients must have demonstrable evidence of specific IgE antibodies before undergoing allergen immunotherapy (see Diagnostic Use below), and it is generally recommended that diagnosis of allergies and allergen immunotherapy should only be carried out in specialist centres. Subcutaneous injection immunotherapy (SCIT) is the traditional method of administration and has a long history of use. Sublingual immunotherapy (SLIT) is now also widely used, and other routes have been tried—see Administration, p. 2434.3. Reports of severe and sometimes fatal hypersensitivity reactions to injected allergen preparations prompted recommendations to reduce the risk of systemic reactions (see under Adverse Effects, p. 2436.2).

The use of allergen immunotherapy has been reviewed[4,7] and recommendations have been published.[2,3,8,9] The incidence and severity of allergic disease is increasing as a result of environmental changes, and allergies represent a major cause of illness in developed countries; in the UK for example, they are estimated to affect 1 in 3 people. Of particular concern is the rise in multi-system allergies.[4] Common sources of allergens include: pollen and fungal spores producing seasonal allergic rhinitis and conjunctivitis (hay fever); house dust, house-dust mites, and animal dander producing perennial allergic rhinitis; venom from bees, wasps, and stinging ants; latex rubber, flour, and other allergens giving rise to occupational rhinitis; drugs (e.g. penicillins, anaesthetics); and some foods (e.g. nuts, shellfish).[4] Allergic reactions are a common cause of childhood asthma and are also associated with atopic eczema.[4]

Not all allergies are suitable for treatment with specific allergen immunotherapy and recommendations made by the CSM[10] in the UK are that allergen immunotherapy should only be used for seasonal allergic rhinitis (hay fever) in patients not responsive to anti-allergic drugs, and for hypersensitivity to bee and wasp venoms; warnings against use in patients with asthma are also given (although allergen immunotherapy is used in some countries for the treatment of allergic asthma—see below). The UK CSM[10] also concludes that there is inadequate evidence of benefit from desensitisation to allergens such as house dust, house-dust mites, animal dander, and foods, and therefore does not recommend allergen immunotherapy in these cases.

Allergen immunotherapy is used in **children** and is thought to be more effective than in adults.[2] It has been suggested that its use in children with allergic rhinoconjunctivitis may also prevent the development of asthma.[3] Review of controlled studies and meta-analyses[11] confirmed that allergen injection immunotherapy is effective in allergic asthma in children, and early intervention may prevent progression to multiple allergen hypersensitivity. However, since adverse effects of allergen immunotherapy are more likely in asthmatics, it is contra-indicated in unstable asthma (see also below). Therapy is generally not recommended for children younger than 5 or 6 years of age[2,3,8] because it is less well tolerated, cooperation with a young child might be difficult,[3] and in this age group the differential diagnosis between allergic rhinitis and viral infection of the respiratory tract may not be clear.[2]

Allergen immunotherapy for seasonal **allergic rhinitis** and **conjunctivitis** triggered by pollen has generally been reserved for severely affected patients when anti-allergic drugs have failed.[2,3,8] A systematic review[5] of controlled studies concluded that there is a significant reduction in symptoms and use of medication in suitably selected patients who have not responded adequately to anti-allergic drugs, together with a known and relatively low risk of serious adverse effects with no long-term consequences. The sublingual route is a means of ameliorating the severe systemic reactions associated with injection immunotherapy, and it also offers a more convenient form of dosing.[12] A systematic review[6] of studies using sublingual immunotherapy in patients with seasonal and perennial allergic rhinitis supported the promotion of this route because rhinitis symptoms and use of anti-allergic medication were reduced significantly in adults and no systemic adverse effects were reported. However, it was difficult to assess the magnitude of the effect and compare this route with injection immunotherapy. The treatment effect in children was not significant. However, a meta-analysis[13] of more controlled studies involving a greater total number of children concluded that sublingual immunotherapy was effective in children with allergic rhinitis.

There is some evidence that allergen immunotherapy for allergies such as rhinitis may prevent the development of **asthma**[3] and thus earlier use may be warranted.[14] A systematic review[15] of randomised controlled studies confirmed that allergen immunotherapy in asthmatic patients reduced the symptoms of asthma and the use of asthma medication, although it was not possible to quantify the benefits compared with other forms of therapy, and the possibility of severe or fatal anaphylaxis remains. Recommendations for the use of allergen immunotherapy in patients with asthma vary. Guidelines issued in the UK[10] in 1994 recommended that asthmatic patients should not be treated with allergen immunotherapy because they are more likely to develop severe adverse effects (although asthma is not considered a contra-indication to allergen immunotherapy for anaphylaxis caused by Hymenoptera spp.). Others,[3,9] including WHO,[2] consider that allergen immunotherapy for allergic rhinoconjunctivitis can be given to patients whose asthma is stable and not severe (FEV_1 is not less than 70% of predicted value),[2] when avoidance of allergens has not been sufficient or is not possible, and drug treatment has failed. Allergen immunotherapy should not be given to patients whose asthma can be controlled by antiasthmatic drugs and allergen avoidance.[16]

Allergen immunotherapy is indicated for patients with specific IgE antibodies who have had severe anaphylaxis after **insect stings**, particularly those of Hymenoptera (bees, wasps, and stinging ants).[2,3,8,17,18] Vaccines containing purified venom are available for most Hymenoptera spp. and have replaced whole body extract preparations, which were generally found to be ineffective. Venom immunotherapy is very effective in decreasing the risk of systemic reactions to venom in susceptible people.[18] Venom vaccines are not available for stinging ants but whole body extract vaccines may contain sufficient venom antigens to be effective.[2,3,18] Allergen immunotherapy for rhinoconjunctivitis and asthma due to house-dust mite or animal dander can be considered when the allergen is unavoidable.[2,3,9,15] A review[19] considering both injection and sublingual mite immunotherapy in adults and children with asthma and/or rhinitis confirms efficacy, although it is not possible to assess safety relative to other forms of allergen immunotherapy such as pollen vaccines. One multicentre, randomised, dose-response study[20] found that specific mite injection immunotherapy for 1 year improved eczema in patients with atopic dermatitis allergic to house-dust mite. Limited data indicate that allergen immunotherapy might be effective for atopic dermatitis associated with aeroallergen sensitivity.[3] However, more controlled studies are needed to confirm its place in treatment.[4]

Allergen immunotherapy for **drug hypersensitivity** may be warranted on the rare occasions when continued use is considered essential, possibly with penicillins or insulin.[8,21] In most cases the effect of desensitisation is temporary and if the medication is required again in the future, the process must be repeated.[22]

Allergen immunotherapy has also been tried in **other disorders** such as urticaria and food allergies, but there is insufficient evidence to support such use[3,4,8,10] and its use is not recommended. The traditional method of allergen immunotherapy in peanut allergy has an unacceptably high rate of systemic adverse reactions and other immunotherapeutic interventions are being sought.[23]

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Diagnostic use. Sensitivity testing can be used to confirm that suspected allergens are mainly responsible for the symptoms of a suspected hypersensitivity reaction. It is

necessary before patients with allergies are managed either by allergen avoidance or treated with allergen immunotherapy (see p. 2435.1). However, sensitivity testing should not form the sole basis of the treatment of hypersensitivity reactions.

Type IV (delayed) hypersensitivity reactions such as contact dermatitis are normally diagnosed using patch tests. Several standard techniques are available, but in general they all involve maintaining a standard amount of the test substance in contact with the skin for 48 to 72 hours. A positive response is shown by erythema, swelling, or vesiculation. The sensitivity of different parts of the body varies, and this should be accounted for in applying test substances and controls. The test results are normally read 30 to 60 minutes after removal of the patches to allow any pressure effects of the patches to subside. Patch testing with mixtures of allergens may be necessary to diagnose contact dermatitis in patients hypersensitive to multiple allergens.

Type I (immediate) hypersensitivity reactions such as allergic rhinitis, allergic asthma, and insect-sting hypersensitivity are tested using skin-prick or intradermal tests. Since the allergen is introduced through the skin in these tests, the risk of systemic reactions is greater than patch testing, and adrenaline injection should be kept available. The skin-prick test involves pricking the epidermis through a drop of allergen in solution, and comparing the result after 15 to 20 minutes with positive and negative controls. This test is inexpensive and the results available rapidly. The intradermal (intracutaneous) test is used if the skin-prick test result does not agree with a strong clinical suspicion, although now that potent allergen extracts are used for skin-prick tests, the intradermal test offers few advantages and has greater risk of systemic reactions. Skin testing is unreliable for evaluating hypersensitivity to drugs, except for penicillins and for certain macromolecules. Skin test titration, that is testing with a series of dilutions, has been used to determine a safe starting dose for allergen immunotherapy.

Provocation tests are designed to reproduce symptoms of hypersensitivity by controlled exposure to a suspected allergen. They are used when skin or laboratory tests are unavailable, or IgE is not involved in the mechanism. Provocation may be by the bronchial, oral, nasal, or ocular routes. Facilities for full cardiopulmonary resuscitation should be immediately available.

In-vitro methods for measuring antigen-specific IgE include immunoassays such as the enzyme-linked immunosorbent assay (ELISA), which has now replaced the radioallergosorbent test (RAST). These tests can be used in place of skin-prick tests but they are expensive and the results not available as quickly.

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Adverse Effects and Treatment

Adverse effects to allergen products can range from mild local reactions to severe generalised reactions that may be fatal, especially reactions to bee and wasp venom. Hypersensitivity reactions may be immediate or delayed.

Adverse effects with **skin-prick testing** are uncommon, although swelling and irritation at the injection site, rhinitis, urticaria, wheezing, and chest tightness might occur, and rarely, anaphylactic shock.

Allergen immunotherapy injections may give rise to swelling, irritation, redness, and hardness at the injection site. Systemic reactions include itching eyes, sneezing, cough, wheezing, chest tightness, atopic eczema, urticaria, and oedema. Anaphylactic shock or severe delayed reactions may also occur. Commonly reported adverse effects with allergen preparations given **sublingually** include oral oedema, pruritus, and paraesthesia, throat irritation, sneezing, rhinitis, nasal congestion, itching of the eyes and ears, and headache; systemic reactions may occur if the dosage regimen is not adhered to.

Severe reactions to allergen products normally occur within 30 minutes and should be treated promptly with intramuscular adrenaline injection 1 in 1000 (1 mg/mL). Full supportive measures should be implemented and treatment with antihistamines and corticosteroids may be required (for a discussion of the treatment of anaphylaxis and anaphylactic shock, see p. 1293.2). Further allergen immunotherapy should be stopped or continued at reduced dosage depending on the severity of the reaction and in accordance with the licensed product information.

Reviews.

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In 1986 the UK CSM reported[1] that hyposensitising vaccines have the potential to induce severe bronchospasm and anaphylaxis, and that these reactions had caused 26 deaths in the UK since 1957. The majority of patients had no reaction to previous hyposensitising injections. In 1989 the FDA reported that since 1980, the American Academy of Allergy and Immunology and the FDA had received 14 reports of death after allergen immunotherapy, and 4 deaths after skin testing for allergies.[2] The most common clinical factor in these patients was a history of asthma.

In view of these and other reports, recommendations have been made to minimise the risks of systemic reactions.[3-6] Allergen immunotherapy should only be used for seasonal allergic rhinoconjunctivitis not responding to anti-allergic drugs, and for severe hypersensitivity to Hymenoptera stings. In the UK[4] such treatment has usually been avoided in patients with asthma (although asthma is not an absolute contra-indication to Hymenoptera allergen immunotherapy), but elsewhere[3,5,6] asthmatic patients whose asthma is stable and not severe may be treated. Hyposensitising agents should be used only where facilities for full cardiopulmonary resuscitation are immediately available. The recommended length of time after injection that patients should be kept under medical observation varies from 30 minutes[3] to 1 hour.[4] If the patient develops even mild symptoms of a general reaction, observation should be extended until they are completely resolved. The observation period should also be extended for patients at high risk of reactions.

Of 12 samples of *Aspergillus* extract used for allergen immunotherapy, 4 were found to contain aflatoxin (p. 2432.2), one being highly mutagenic as determined by the Ames' test. The results suggested that careful screening of commercially available mould extracts was warranted.[7]

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Precautions

Patients should be observed for at least 30 to 60 minutes after administration of allergen products because of the risk of anaphylaxis (see also under Adverse Effects, above). Patients should avoid taking beta blockers since adrenaline may be ineffective if hypersensitivity reactions occur. Antiallergic medication taken concomitantly may mask the patient's reactivity.

Skin-prick testing should not be carried out in areas where there are skin lesions. Patients should be instructed not to rub or scratch the test site. Antiallergic medication should be stopped before allergen testing to prevent false negative reactions. Systemic or long-term topical use of potent corticosteroids may also mask skin reactivity.

Allergen immunotherapy should not be used in patients with serious immunological illness, cancer, disorders of amino acid metabolism, bleeding disorders, or hyperthyroidism. It should also be avoided during infections or febrile conditions, and administration of an allergen preparation delayed for 24 to 48 hours after recovery. Allergen immunotherapy should be avoided during pregnancy because of the risk to the fetus of any systemic reactions in the mother. Patients with asthma may be more susceptible to hypersensitivity reactions with allergen products and it is considered that allergen immunotherapy should be avoided or used with caution. Injection immunotherapy should be avoided in children under 6 years of age, and sublingual immunotherapy in children under 2 years. Sublingual immunotherapy is contra-indicated in patients with severe oral inflammatory conditions such as lichen planus with ulcerations, or severe mycosis. Sublingual immunotherapy should be stopped for 7 days in patients who have oral surgery, including dental extraction, and also in children shedding a deciduous tooth, to allow the wounds to heal.

Allergen immunotherapy should be avoided or used with caution in patients with cardiovascular or pulmonary insufficiency, or severe eczema. Rarely, patients may have drowsiness with allergen immunotherapy preparations and, if affected, should avoid driving or operating machinery.

Allergen immunotherapy injections should only be given where facilities for full cardiopulmonary resuscitation are immediately available. Injections for immunotherapy should be given subcutaneously and not intravenously or intramuscularly. Patients should avoid strenuous exercise for at least 12 hours after injection immunotherapy, or 1 hour before and after sublingual immunotherapy. It is also recommended to avoid heavy meals and alcohol around the time of injection with some products. Severe anaphylactoid reactions have been reported in patients undergoing allergen immunotherapy who are also receiving ACE inhibitors (see Hypersensitivity, p. 1287.1). Some manufacturers suggest that the reaction could be avoided by temporarily withholding ACE inhibitor therapy during each desensitisation. Allergen immunotherapy preparations and vaccines against infectious diseases should not be given within at least a week of each other or until all possible reactions to either vaccine have disappeared.

Interactions

For precautions to be observed in using allergen products in patients receiving ACE inhibitors, antiallergic drugs, beta blockers, corticosteroids, or vaccines see Precautions, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Albay†; Allpyral†; ***Austria***: Grazax; Oralair; ***Belg.***: Alyostal; Oralair; Pharmalgen; True Test†; ***Braz.***: Nikkho Vac; ***Canad.***: Oralair; Pharmalgen†; Pollinex-R; Venomil; ***China***: Alutard SQ (安脱达); ChangDi (畅迪); Novo-Helisen (阿罗格); ***Cz.***: Alutard SQ; Alyostal; D-Al; Grazax; H-AL; Oralair; Pangramin; Pollinex; Soluprick SQ; Staloral; ***Denm.***: ALK; Alutard SQ; Aquagen SQ; Grazax; Nixema†; Pharmalgen; Soluprick; True Test; ***Fin.***: Grazax; ***Fr.***: Albey; Alyostal; ASAD†; Diallertest; Grazax; True Test; ***Ger.***: Acaroid; ALK; Allergovit; Clustoid; Depiquick; Depot-Hal; Grazax; Hymnox†; Novo-Helisen; Oralair; Oralvac; Phostal; Pollinex Quattro; Purethal; Reless; Roxoid; Staloral; TA Baume; TA Graser; TA Krauter top; TA MIX†; Tol†; TyroMILBE; Tyrosin TU; Venomenhal; Venomil; ***Gr.***: Alyostal; Grazax; Staloral; ***Hung.***: Alustal; Alyostal; Lais; Pangramin; Purethal; Staloral; Venomenhal; ***Irl.***: Grazax; ***Israel***: Ingestants Extracts; Inhalants And Epidermal Extracs; Insects Extracts; Mold & Smuts Extracts; True Test; ***Ital.***: Grazax; Phostal†; Staloral†; ***Neth.***: Allergopharma; Allergovit; Alutard; ARTU; Artuvac; Bencard Priktestoplossing; Depot-Hal; Grazax; HAL; Keolium; Nixema†; Novo-Helisen†; Oralair; Oralgen; Pharmalgen; Pollinex; Purethal; Soluprick Controlevloeistoffen; Soluprick SQ; ***Norw.***: Alutard; Grazax; Soluprick SQ; ***NZ***: Albey; True Test; ***Pol.***: Allergovit; Alutard SQ; Alyostal; Catalet; Grazax; Novo-Helisen; Perosall; Pharmalgen; Phostal; Pollinex; Purethal; Staloral; Venomenhal; ***Port.***: Grazax; Soluprick; Truetest; ***Rus.***: Fostal (Фосталь); Ungapiven (Унгапивен); ***S.Afr.***: Albay†; Albey†; Allpyral Pure Mite†; Allpyral Special Grass†; ***Spain***: Grazax; Oralair; ***Swed.***: Alutard SQ; Aquagen SQ; Grazax; Mekostest; Soluprick SQ; ***Switz.***: ALK; Allergovit; Alutard SQ; Alyostal†; Grazax; Novo-Helisen; Oralair; Pharmalgen; Phostal; Polvac; Soluprick SQ; Staloral; ***Turk.***: Acaril; Acarosan; Allergodip; Allergopen; Allergovit; Apsi; Novo-Helisen; ***UK***: Bencard Skin Testing Solutions; Grazax; Pharmalgen; Pollinex; Soluprick SQ; ***USA***: Albay†; Allpyral; Center-Al; Pharmalgen; True Test; Venomil†.

Multi-ingredient Preparations. ***Arg.***: Summavac; ***Braz.***: Alergoral; Aminovac; Urtivac; Vag Oral†; ***Canad.***: Center-AL; True Test; ***Cz.***: Phostal; ***Fin.***: Alutard SQ; Aquagen SQ; Soluprick SQ; ***Ger.***: Alustal; Avanz; BU Pangramin SLIT†; Depigoid; Deposit; Slit One; Sublivac; Sulgen; ***Gr.***: Allergopharm; ***Ital.***: Alustal†; ***Neth.***: Trolab; True Test; ***NZ***: Alustal; ***Switz.***: Alustal; True Test.

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; Tonsillopas; ***Ger.***: Schworosin; Tonsillopas; ***Switz.***: Regenaplex Nr 28b; Regenaplex Nr 41a; Regenaplex Nr. 25b.

Allyl Isothiocyanate *(USAN)*

Аллилизотиоцианат.

Isothiocyanato-1-propene.

C_4H_5NS=99.15

CAS — 57-06-7.

UNII — BN34FX42G3.

Pharmacopoeias. *Fr.* and *US*

USP 36: (Allyl Isothiocyanate). A colourless to pale yellow, very refractive, liquid with a pungent, irritating odour and an acrid taste. Slightly soluble in water; miscible with

alcohol, with carbon disulfide, and with ether. Store in airtight containers.

Profile

Allyl isothiocyanate is the main constituent of volatile mustard oil (p. 2646.1) derived from black mustard seeds (p. 2566.1). It is an extremely powerful irritant that has been used as a counter-irritant and rubefacient.

Handling. Allyl isothiocyanate is a potent lachrymator, with a pungent irritating odour. Care should be taken to protect the eyes, to prevent inhalation of fumes, and to avoid tasting.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Apisarthron; ***Ukr.***: Apisarthron (Апизартрон).

Almond Oil

Aceite de Almendra; Aceite de almendras; Almendras dulces, aceite de; Amande, huile d'; Amygdalae Oleum; Badem Yağı; Bitter Almond Oil; Expressed Almond Oil; Huile d'Amande; Mandelöl; Mandelolja; Mandlový olej; Mandulaolaj; Manteliöljy; Migdolų aliejus; Ol. Amygdal.; Olej migdałowy; Oleo de Amêndoas; Olio di Mandorla; Sweet Almond Oil; Миндальное Масло.

CAS — 8007-69-0.
*ATC Herb — HD02WB5008 (*Prunus dulcis*: oil).*
UNII — 66YXD4DKO9 (almond oil); 6TQK77W0EX (bitter almond oil).

Pharmacopoeias. In *USNF*.

Eur (see p. vii) includes the virgin oil and a refined oil.

Fr. also specifies Huile de Noyaux, an oil obtained from various species of *Prunus*.

Ph. Eur. 8: (Almond Oil, Virgin; Amygdalae Oleum Virginale). A yellow, clear, liquid. It is the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* var. *amara* or *P. dulcis* var. *dulcis* or a mixture of both varieties. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

Ph. Eur. 8: (Almond Oil, Refined; Amygdalae Oleum Raffinatum). The fatty oil obtained by refining and deodorisation of Almond Oil. It may contain a suitable antoxidant. A pale yellow, clear liquid. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

USNF 31: (Almond Oil). The refined fixed oil expressed from the kernels of varieties of *Prunus dulcis*[*Prunus amygdalus*] (Rosaceae). It may contain suitable antoxidants. A clear, colourless or pale straw-coloured, oily liquid with a bland taste. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in well-filled, airtight containers. Protect from light.

Profile

Almond oil, which consists mainly of glycerides of oleic acid with smaller amounts of linoleic and palmitic acid, has nutritive and demulcent properties. It is used as an emollient and to soften ear wax. It is also used as a vehicle in some injections.

Reviews.

1. Ahmad Z. The uses and properties of almond oil. *Complement Ther Clin Pract* 2010; **16:** 10–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Laderm; ***Gr.***: Karelyne.

Multi-ingredient Preparations. ***Arg.***: Caien†; ***Austral.***: Curash Babycare Medicated Nappy Rash Cream; ***Canad.***: Pure Gardens; ***Chile***: Akerat; ***Cz.***: Balmandol; ***Fr.***: Aromadetox†; ***Ger.***: Neuroderm; ***Irl.***: Earex†; ***Ital.***: Activ Dopo Puntura†; Baby Zanzara†; Babygella; Babysteril; ***Mex.***: Liniderm; ***NZ***: Am-O-Lin†; Snorenz; ***Port.***: Cuidaderma; Olidermil; ***Singapore***: Earex; Snoreeze; ***Spain***: Pasta Lassar Imba; ***Switz.***: Antidry; Antidry; Antidry; Balmandol; Viola; ***Turk.***: Balmandol; Metamorfoz; Myo-Oil; Snoreless; ***UK***: Calendula Nappy Change Cream; Earex; Imuderm†; Infaderm; Skin Perfecting Oil; Snor-Away.

Pharmacopoeial Preparations
BP 2014: Almond Oil Ear Drops;
USP 36: Rose Water Ointment.

Alpha Fetoprotein

ABI-001 (recombinant AFP); α-Fetoprotein; MM-093 (recombinant AFP).

Profile

Alpha fetoprotein (AFP) is a naturally occurring alpha globulin of similar molecular weight to albumin. It is the most abundant plasma protein found in the human fetus and screening of AFP concentrations in maternal serum and amniotic fluid may be used for the detection of developmental abnormalities. Elevated concentrations of alpha fetoprotein are used as a marker test for various cancers and as a way of monitoring treatment in hereditary tyrosinaemia type 1 (see p. 2572.2).

Recombinant alpha fetoprotein has been investigated in the treatment of auto-immune diseases, but concerns about a potential oncogenic effect have been raised.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Profetal (Профеталь).

Alpha Galactosidase A

α-D-Galactosidase; α-Galactosidase A; α-D-Galactoside Galactohydrolase; Альфа-галактозидаза А.

*UNII — 6215K8E2M8 (*Aspergillus niger *alpha-galactosidase).*

Agalsidase Alfa *(BAN, USAN, rINN)*

Agalsidasa alfa; Agalsidasum Alfa; Агальсидаза Альфа.

CAS — 104138-64-9 (protein moiety).
ATC — A16AB03.
ATC Vet — QA16AB03.
UNII — 2HLC17MX9G.

Agalsidase Beta *(rINN)*

Agalsidasa β; Agalsidasum Beta; Agalsidaz Beta; Alfasidasa β; Агальсидаза Бета.

CAS — 104138-64-9 (protein moiety).
ATC — A16AB04.
ATC Vet — QA16AB04.
UNII — RZD65TSM9U.

Uses and Administration

Alpha galactosidase A is an endogenous enzyme that hydrolyses terminal α-D-galactose residues in oligosaccharides and galactolipids into more easily digestible mono- and disaccharides. A form derived from a fungal source is used to prevent intestinal gas.

Agalsidase alfa and beta are recombinant forms of alpha galactosidase A used for the long-term enzyme replacement therapy of Fabry disease (see below).

Agalsidase alfa is given by intravenous infusion in a dose of 200 micrograms/kg over 40 minutes, repeated every alternate week.

Agalsidase beta is given by intravenous infusion in a dose of 1 mg/kg at an initial rate of no more than 250 micrograms/minute; once tolerance has been established, for patients weighing ≥ 30 kg, the rate of administration may be gradually increased by 50 to 80 micrograms/minute in each subsequent infusion. The dose should be repeated every alternate week.

Administration in children. Licensed product information suggests that agalsidase alfa may be given to children aged 7 years and older, and agalsidase beta to children 8 years and over, for the treatment of Fabry disease in the doses outlined above.

Fabry disease. Fabry disease (Anderson-Fabry disease) is a rare X-linked recessive lysosomal storage disorder. It mainly affects males, although female carriers may sometimes have clinical manifestations. It is characterised by a deficiency of the enzyme alpha galactosidase A resulting in the intracellular accumulation of globotriaosylceramide (Gb_3) and other glycosphingolipids, especially in vascular endothelium and smooth muscle. Symptoms include severe neuropathies, fevers, skin blemishes (angiokeratomas), corneal and lenticular opacities, and gastrointestinal disturbances. Cardiac, cerebrovascular, and renal deterioration is progressive placing patients at increased risk for early-onset myocardial infarction, stroke, and renal failure.[1-7]

Symptomatic treatment was the only option until the development of enzyme replacement therapy[3,6] with agalsidase alfa[2,8] and beta.[7,9] Results from controlled studies show this form of therapy to be effective in clearing deposits from the kidneys, heart, and skin[10-14] as well as improving peripheral neuropathy.[15] An open-label extension study[16] of agalsidase beta in the 58 patients formerly studied in a 20-week controlled phase III study[12] confirmed the continued safety and efficacy of enzyme replacement therapy after 30 months of treatment. Benefit continued in these patients followed up for a further 24 months,[17] and kidney biopsies in 8 of the patients confirmed complete clearance of globotriaosylceramide. A systematic review[6] of prospective randomised controlled and open-label studies concluded that the evidence for enzyme replacement therapy with agalsidase beta at a dose of 1 mg/kg every other week was more robust than that for agalsidase alfa at a dose of 200 micrograms/kg every other week, although the benefit with either dose or drug was variable. The cardiac effects of Fabry disease have been reviewed,[18] and both agalsidase alfa and beta have been reported to improve left ventricular structure and function. Further studies[19-21] confirmed regression of left ventricular hypertrophy with agalsidase alfa or beta, but improvement in myocardial function or exercise capacity is more likely to occur in patients started on enzyme replacement therapy before myocardial fibrosis is evident.[21] Although most studies have been in adults, enzyme replacement therapy has been shown to be safe in children over 6 years of age.[22] Expert opinion generally recommends that treatment is begun as soon as clinical signs and symptoms are seen.[4,23] Gene therapy[24] is also under investigation.

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2. Mehta A. Agalsidase alfa: specific treatment for Fabry disease. *Hosp Med* 2002; **63:** 347–50.
3. Desnick RJ, *et al.* Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med* 2003; **138:** 338–46.
4. Desnick RJ, *et al.* Fabry disease in childhood. *J Pediatr* 2004; **144:** S20–S26.
5. Clarke JTR. Narrative review: Fabry disease. *Ann Intern Med* 2007; **146:** 425–33.
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9. Keating GM, Simpson D. Agalsidase beta: a review of its use in the management of Fabry disease. *Drugs* 2007; **67:** 435–55.
10. Moore DF, *et al.* Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001; **104:** 1506–12.
11. Schiffmann R, *et al.* Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001; **285:** 2743–9.
12. Eng CM, *et al.* Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001; **345:** 9–16.
13. Moore DF, *et al.* Elevated cerebral blood flow velocities in Fabry disease with reversal after enzyme replacement. *Stroke* 2002; **33:** 525–31.
14. Wraith JE, *et al.* Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. *J Pediatr* 2008; **152:** 563–70.
15. Hilz MJ, *et al.* Enzyme replacement therapy improves function of C-, Aδ-, and Aβ-nerve fibers in Fabry neuropathy. *Neurology* 2004; **62:** 1066–72.
16. Wilcox WR, *et al.* Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am J Hum Genet* 2004; **75:** 65–74.
17. Germain DP, *et al.* Sustained, long-term renal stabilization after 54 months of agalsidase β therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007; **18:** 1547–57.
18. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart* 2007; **93:** 528–35.
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20. Imbriaco M, *et al.* Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: a prospective long-term cardiac magnetic resonance imaging study. *Heart* 2009; **95:** 1103–7.
21. Weidemann F, *et al.* Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. *Circulation* 2009; **119:** 524–9.
22. Ries M, *et al.* Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics* 2006; **118:** 924–32.
23. Banikazemi M, *et al.* Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007; **146:** 77–86.
24. Siatskas C, Medin JA. Gene therapy for Fabry disease. *J Inherit Metab Dis* 2001; **24** (suppl 2): 25–41.

Adverse Effects, Treatment, and Precautions

Infusion reactions have been reported in about 14% of patients given agalsidase alfa, and in about 67% of patients treated with agalsidase beta. The frequency of onset of these reactions decreases with continued use, with the majority of reports occurring during the first 2-4 months after the start of treatment, although onset after 1 year has also been reported. Symptoms generally start during, or within 1 hour of, infusion. The most common symptoms have included chills, dyspnoea, facial flushing, headache, nausea, fever, and fatigue. Other reported symptoms include abdominal pain, diarrhoea, vomiting, nasal congestion, throat tightness, chest pain, dizziness, paraesthesia, myalgia, stridor, hypoxia, hypertension, bradycardia, tachycardia, and pruritus, urticaria, and angioedema; anaphylactic shock has also been noted rarely. The infusion may be interrupted for about 5 to 10 minutes and restarted once symptoms have subsided. Pre-treatment with oral antihistamines, paracetamol, ibuprofen, and/or corticosteroids 1 to 24 hours before infusion has been used to prevent subsequent reactions. Patients with compromised cardiac function due to Fabry disease should be monitored closely since they may be predisposed to a higher risk of severe complications arising

from infusion reactions. IgG antibodies to agalsidase alfa develop in some patients, and to agalsidase beta in the majority of patients. The presence of antibodies increases the risk of infusion reactions. Serious hypersensitivity reactions including anaphylactic shock have been reported during infusion with agalsidase alfa or beta.

Interactions

Agalsidase alfa or beta should not be used with amiodarone, chloroquine, monobenzone, or gentamicin, which all have the potential to inhibit intracellular α-galactosidase activity.

Pharmacokinetics

The pharmacokinetic properties of agalsidase alfa appear to be unaffected by dose; the elimination half-life from blood after a single dose has been reported to be about 100 minutes. The pharmacokinetics of agalsidase beta indicate a saturated clearance; the elimination half-life after a single dose has been reported to range from 45 to 100 minutes.

Most pharmacokinetic parameters of agalsidase alfa in children with Fabry disease were similar to those in adult patients after single and repeated doses, except for serum clearance, which was age dependent being significantly increased in children.[1] However, there was no difference in pharmacodynamics between the age groups.

1. Ries M, *et al.* Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. *J Clin Pharmacol* 2007; **47:** 1222–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fabrazyme; Replagal; ***Austria***: Fabrazyme; Replagal; ***Belg.***: Fabrazyme; Replagal; ***Braz.***: Fabrazyme; ***Canad.***: Beano; Fabrazyme; Gaz Away†; Replagal; ***Chile***: Fabrazyme; ***Cz.***: Fabrazyme; Replagal; ***Denm.***: Fabrazyme; Replagal; ***Fin.***: Fabrazyme; ***Fr.***: Fabrazyme; Replagal; ***Ger.***: Fabrazyme; Replagal; ***Gr.***: Fabrazyme; Replagal; ***Hong Kong***: Fabrazyme; ***Hung.***: Fabrazyme; Replagal; ***India***: Galazyme-A; Galazyme-Pro; Leno; ***Irl.***: Fabrazyme; Replagal; ***Israel***: Fabrazyme; Replagal; ***Ital.***: Fabrazyme; Replagal; ***Jpn***: Fabrazyme; ***Malaysia***: Fabrazyme; ***Neth.***: Fabrazyme; Replagal; ***Norw.***: Fabrazyme; Replagal; ***NZ***: Fabrazyme; Replagal; ***Pol.***: Fabrazyme; Replagal; ***Port.***: Fabrazyme; Replagal; ***Rus.***: Fabrazyme (Фабразим); Replagal (Реплагал); ***Spain***: Fabrazyme; Replagal; ***Swed.***: Fabrazyme; Replagal; ***Switz.***: Fabrazyme; Replagal; ***Turk.***: Fabrazyme; ***UK***: Beano; Fabrazyme; Replagal; ***USA***: Beano; Fabrazyme.

Multi-ingredient Preparations. ***India***: Blotamax; Gastica Plus; Leno-EZ; ***Ital.***: No Gas Enzimi.

Alpha$_1$-proteinase Inhibitor

alpha-1-Antitrypsinum; Alpha$_1$ Antitrypsin; Antitrypsine alpha-1; Inhibidor de la α_1-proteinasa; Альфа1 Антитрипсин.

ATC — B02AB02.

ATC Vet — QB02AB02.

UNII — F43I396OIS (alpha$_1$-proteinase inhibitor human).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Human α-1-Proteinase Inhibitor). A sterile liquid or freeze-dried preparation of a plasma protein fraction containing mainly human α-1-proteinase inhibitor. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Other plasma proteins may be present. It may contain excipients such as stabilisers. Freeze-dried products are hygroscopic, white or pale yellow or pale brown powders or friable solids; liquid products are clear or slightly opalescent, colourless or pale yellow or pale green or pale brown. pH of 6.5 to 7.8. Store in airtight and sterile containers at a temperature not exceeding 25 degrees.

Uses and Administration

Endogenous alpha$_1$-proteinase inhibitor is a serum glycoprotein synthesised in the liver that acts as an elastase inhibitor, mainly inhibiting neutrophil elastase. Alpha$_1$-proteinase inhibitor, prepared from pooled human plasma, is used as replacement therapy in patients with emphysema who have congenital alpha$_1$ antitrypsin deficiency (see below). It is given in a dose of 60 mg/kg once a week by intravenous infusion at a rate of about 0.08 mL/kg per minute (usually corresponding to a 15 to 30 minute infusion).

A recombinant form of alpha$_1$-proteinase inhibitor is under investigation for nebulised delivery in congenital alpha$_1$ antitrypsin deficiency and cystic fibrosis (see below).

Alpha$_1$-proteinase inhibitor has also been investigated for the prevention of bronchopulmonary dysplasia (p. 1602.1) in preterm neonates.

Alpha$_1$ antitrypsin deficiency. Alpha$_1$ antitrypsin deficiency (alpha$_1$-proteinase inhibitor deficiency) is characterised by chronic obstructive pulmonary disease (COPD) and chronic liver disease associated with a lack of alpha$_1$-proteinase inhibitor.[1,2] This inhibitor is produced in the liver but exerts its main effects in the lungs as an inhibitor of neutrophil elastase, an enzyme released in response to inflammation. Congenital deficiency of the inhibitor thus leaves the lungs vulnerable to destruction by elastase, leading to the development of emphysema (see Chronic Obstructive Pulmonary Disease, p. 1199.1), usually in the third or fourth decade of life. Hepatic manifestations of deficiency include hepatitis, cirrhosis, and hepatoma. Panniculitis and vasculitis may also occur less frequently in some phenotypes.[3,4]

Management of COPD associated with the deficiency involves avoidance of factors (mainly cigarette smoking) that cause pulmonary inflammation, and supportive treatment with bronchodilators and oxygen as appropriate. Augmentation therapy with alpha$_1$-proteinase inhibitor to raise serum concentrations above the protective threshold is also of benefit in some patients.[3,5] Intravenous infusion of the drug has been shown to correct the biochemical abnormality[6] and has been recommended in those patients with some deterioration of lung function.[3,7] In a short-term study[8] serum and secretion concentrations of alpha$_1$-proteinase inhibitor as well as markers of neutrophilic inflammation were monitored in 12 patients receiving augmentation therapy over 4 weeks. Results showed a rise in serum levels of alpha$_1$-proteinase inhibitor to above the protective threshold, and reduction in elastase activity and levels of leukotriene B_4 levels (thought to be important in producing airway inflammation in alpha$_1$ antitrypsin deficiency). A small placebo-controlled study[9] found that the rate of decline of FEV_1 was not affected in patients treated for at least 3 years. Data[10] from a large registry of patients also suggested that, overall, treatment did not affect the rate of decline of FEV_1, but that it decreased mortality, although this may be influenced by other factors. Evaluation[7] of 2 of these studies[9,10] and one other concluded that replacement therapy might reduce the progression of disease in selected patients, but that further randomised placebo-controlled studies were required to provide conclusive evidence for overall clinical efficacy. The Canadian Thoracic Society[11] recommends that replacement therapy should be reserved for patients with an FEV_1 between 35 and 65% predicted who are no longer smoking and on optimal medical therapy but continuing to show a rapid decline in FEV_1. In a retrospective cohort study[12] in 96 patients followed up for a minimum of 12 months, results indicated that the rate of progression of pulmonary emphysema was reduced during the time that the patients received augmentation therapy, and patients with well-maintained lung function and a rapid decline in FEV_1 benefited most from therapy. These authors recommended early diagnosis to identify patients at risk and to start augmentation even if lung function is greater than 65% predicted.

Liver involvement does not respond to treatment with alpha$_1$-proteinase inhibitor and is managed symptomatically.[3]

Several new approaches to treatment of alpha$_1$ antitrypsin deficiency are under investigation:[3,4,13] plasma-derived and recombinant forms of alpha$_1$-proteinase inhibitor for inhalation; synthetic elastase inhibitors for oral use; synthetic chaperones to block intrahepatic polymerisation of the inhibitor and other methods to improve serum concentrations; retinoids; inhaled hyaluronic acid; and gene therapy.

1. Köhnlein T, Welte T. Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. *Am J Med* 2008; **121:** 3–9.
2. Silverman EK, Sandhaus RA. Alpha$_1$-antitrypsin deficiency. *N Engl J Med* 2009; **360:** 2749–57.
3. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; **168:** 818–900. Also available at: http://www.thoracic.org/sections/publications/statements/pages/respiratory-disease-adults/alphal.html (accessed 14/07/06)
4. Stoller JK, Aboussouan LS. α_1-Antitrypsin deficiency. *Lancet* 2005; **365:** 2225–36.
5. Juvelekian GS, Stoller JK. Augmentation therapy for α_1-antitrypsin deficiency. *Drugs* 2004; **64:** 1743–56.
6. Coakley RJ, *et al.* α 1-Antitrypsin deficiency: biological answers to clinical questions. *Am J Med Sci* 2001; **321:** 33–41.
7. Abboud RT, *et al.* Alpha$_1$-antitrypsin deficiency: a position statement of the Canadian Thoracic Society. *Can Respir J* 2001; **8:** 81–8.
8. Stockley RA, *et al.* The effect of augmentation therapy on bronchial inflammation in α 1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2002; **165:** 1494–8.
9. Dirksen A, *et al.* A randomized clinical trial of α_1-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; **160:** 1468–72.
10. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV_1 decline in individuals with severe deficiency of α_1-antitrypsin. *Am J Respir Crit Care Med* 1998; **158:** 49–59.
11. O'Donnell DE, *et al.* Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can Respir J* 2007; **14** (suppl B): 5B–32B.
12. Wencker M, *et al.* Longitudinal follow-up of patients with α_1-protease inhibitor deficiency before and during therapy with IV α_1-protease inhibitor. *Chest* 2001; **119:** 737–44.
13. Sandhaus RA. α_1-Antitrypsin deficiency 6: new and emerging treatments for α_1-antitrypsin deficiency. *Thorax* 2004; **59:** 904–9.

Cystic fibrosis. Some of the inflammatory damage that occurs in the lungs of patients with cystic fibrosis is thought to be caused by excessive amounts of elastase released locally. Alpha$_1$-proteinase inhibitor given by nebuliser is therefore under investigation[1-3] in patients with cystic fibrosis (p. 177.2).

1. Martin SL, *et al.* Safety and efficacy of recombinant alpha$_1$-antitrypsin therapy in cystic fibrosis. *Pediatr Pulmonol* 2006; **41:** 177–83.
2. Cantin AM, *et al.* Prolastin aerosol therapy and sputum taurine in cystic fibrosis. *Clin Invest Med* 2006; **29:** 201–7.
3. Griese M, *et al.* α_1-Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. *Eur Respir J* 2007; **29:** 240–50.

Adverse Effects and Precautions

Adverse effects of intravenous alpha$_1$-proteinase inhibitor include asthenia, chills, increase in cough, dizziness, dyspnoea, flu-like symptoms, headache, hypotension, pain at the injection site, paraesthesias, pharyngitis, pruritus, rashes, somnolence, and tachycardia. The infusion should be interrupted or the rate reduced if adverse effects occur and resumed at a more tolerable rate once the symptoms have subsided; the infusion should be stopped immediately in the event of anaphylactic or anaphylactoid reactions, and full supportive measures implemented. Preparations derived from pooled human plasma carry a risk of transmission of infection (see Blood, p. 1135.3).

The drug is contra-indicated in patients with selective IgA deficiencies who have known antibody against IgA since they are at risk of severe reactions to IgA that may be present in the product.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aralast; Prolastin; Trypsan; ***Austria***: Prolastin; ***Canad.***: Prolastin; ***Chile***: Trypsan; ***Cz.***: Trypsone; ***Denm.***: Prolastina; ***Fin.***: Prolastina; ***Fr.***: Alfalastin; ***Ger.***: Prolastin; ***Gr.***: Aralast; Prolastin; ***Irl.***: Prolastin; ***Israel***: Glassia; ***Ital.***: Prolastina; ***Neth.***: Prolastin; ***Port.***: Prolastin; ***Spain***: Prolastina; Trypsone; ***Swed.***: Prolastina; ***Switz.***: Prolastin; ***USA***: Aralast; Prolastin; Zemaira.

Althaea

Altea; Alteablad (marshmallow leaf); Altearot (marshmallow root); Alteeanjuuri (marshmallow root); Alteeanlehti (marshmallow leaf); Alteia; Alth.; Althaca; Althaea folium (marshmallow leaf); Althaeae radix (marshmallow root); Bismalva; Eibisch; Guimauve; Guimauve, feuille de (marshmallow leaf); Guimauve, racine de (marshmallow root); Hierba cañamera; Korzeń prawoślazu (marshmallow root); Liść prawoślazu (marshmallow leaf); Malvavisco; Marshmallow; Orvosizilíz-gyökér (marshmallow root); Orvosizilíz-levél (marshmallow leaf); Proskurníkový kořen (marshmallow root); Proskurníkový list (marshmallow leaf); Svilarožių lapai (marshmallow leaf); Svilarožių šaknys (marshmallow root); Алтей.

ATC — R05CA05.

ATC Vet — QR05CA05.

*ATC Herb — HD02WA5002 (*Althaea officinalis*: root); HA01WB5001 (*Althaea officinalis*: root); HR05DB5002 (*Althaea officinalis*: root).*

*UNII — TRW2FUF47H (*Althaea officinalis *root).*

Pharmacopoeias. *Eur.* (see p. vii) includes the root and the leaf. *Fr.* also includes the flower.

Ph. Eur. 8: (Marshmallow Root; Althaeae Radix). The peeled or unpeeled, whole or cut, dried root of marshmallow, *Althaea officinalis*. Protect from light.

Ph. Eur. 8: (Marshmallow Leaf; Althaea Folium). The whole or cut dried leaf of *Althaea officinalis*. Protect from light.

Profile

Althaea is demulcent and emollient and has been used for irritation and inflammation of the mucous membranes of the mouth and pharynx, and relief of associated dry cough. It has also been used in traditional remedies for a variety of disorders including gastrointestinal disturbances.

General references.

1. WHO. Radix Altheae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/3.html (accessed 04/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Colluvoxyl†; Primadrill†; ***Ger.***: Phytohustil; ***Pol.***: Althagem; Althamel; Rubital; ***Ukr.***: Alteyka (Алтейка); Althemix (Алтемикс)†; Mucaltin Forte (Мукалтин Форте).

Multi-ingredient Preparations. ***Arg.***: Pansoral Primeros Dientes; ***Austral.***: Althaea Complex†; Digestive Aid; Garlic and Horseradish + C Complex†; Herbal Throat Spray; Ultra Allergy Defense; ***Austria***: Heumann's Bronchialtee; Hustensaft Weleda; The Chambard-Tee; Tuscalman; ***Belg.***: Sedemol; Sulfa-Sedemol; ***Canad.***: Bilonat; Honey Herb Cough Drops†; Original Herb Cough Drops†; ***Cz.***: Detska Cajova Smes; Detsky Caj s Hermankem; Pruduskova; Pulmoran; Species Pectorales Planta; ***Fr.***: Apilaxe; Boribel Tisane No 13†; Boribel Tisane No 6†; Colitisane†; Pansoral Premieres Dents; Pectoflorine†; Tisane D'Ars†; Tisane Provencale no 1; Tisane Saint-Urbain†; ***Ger.***: Heumann Bronchialtee Solubifix T; Imupret; Weleda Hustenelixier; ***Hung.***: Majvedo es Detoxikalo; ***Indon.***: Silex; ***Ital.***: Altuss; Bron 6; Enatus; Gastrotuss; ***Neth.***: Verzachtende Hoestsiroop met tijm; ***Pol.***: Bronchial†; Gastrosan fix†; Rubital Compositum; Syrop Prawoslazowy Zlozony; Tabulettae Laxantes; ***Rus.***: Linkus (Линкас); Mixture Conta Tussis for Children (Микстура От Кашля Для Детей); Pansoral Teething (Пансорал Первые Зубы); Pectorales Species No 1 (Грудной Сбор 1); Pectorales Species No 3 (Грудной Сбор 3); Tonsilgon N (Тонзилгон Н); ***S.Afr.***: Cough Elixir†; ***Singapore***: Pansoral Teething†; ***Switz.***: Elixir contre la toux†; Malveol; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; Tisane Provencale no 1; Tuscalman; ***UK***: Herb and Honey Cough Elixir; Herbheal Ointment; Modern Herbals Cold & Catarrh; Potter's Catarrh Pastilles; Sinotar; ***Ukr.***: Bronchostop (Бронхостоп); Imupret (Имупрет); Linkus (Линкас); Mucaltin Forte с Vitamini C (Мукалтин Форте с витамином С); Tonsilgon N (Тонзилгон)†; ***Venez.***: Novacodin.

Homoeopathic Preparations. ***Fr.***: Poconeol no 37; ***UK***: Cough Elixir.

Alum

Alaun; Allume; Aluin; Alumbre; Alumen; Aluminium Kalium Sulfuricum; Aluminium Potassium Sulfate; Aluminium Potassium Sulphate; Aluminiumkaliumsulfat; Alumínium-kálium-szulfát; Aluminum Potassium Sulfate; Alun; Aluna; Alūnas; E522; Glinowo-potasowy siarczan; Glinu potasu siarczan; Kalii Aluminii Sulfas Dodecahydricus; Potash Alum; Potassium Alum; Síran draselno-hlinitý dodekahydrát; Sulfato alumínico potásico; Sulfato de aluminio potasio; Квасцы; Алюм.

Potassium aluminium sulphate dodecahydrate.

$AlK(SO_4)_2,12H_2O$=474.4

CAS — 7784-24-9 (alum dodecahydrate); 10043-67-1 (anhydrous alum).

ATC — S01XA07.

ATC Vet — QS01XA07.

UNII — 1L24V9R23S (alum); 09OXB01F3O (anhydrous alum).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

US also includes dodecahydrated ammonia alum (Ammonium Alum). *Jpn* also includes dried alum.

Ph. Eur. 8: (Alum). Colourless, transparent, crystalline masses or a granular powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. A 10% solution in water has a pH of 3.0 to 3.5.

USP 36: (Potassium Alum). A white powder or large, colourless crystals or crystalline fragments. It is odourless. Soluble 1 in 7 of water and 1 in 0.3 of boiling water; insoluble in alcohol; freely but slowly soluble in glycerol. Its solutions are acid to litmus. Store in airtight containers.

Uses and Administration

Alum precipitates proteins and is a powerful astringent. It is often included in preparations used as mouthwashes or gargles and in dermatological preparations.

Alum, either as a solid or as a solution, may be used as a haemostatic. Intravesical instillation of alum, typically as a 1% solution, has been used as a treatment for haemorrhagic cystitis (p. 2347.3).

Alum has been used as an adjuvant in the preparation of vaccines. It is also used as a mordant in the dyeing industry.

Adverse Effects and Precautions

Large doses of alum are irritant and may be corrosive; gum necrosis and gastrointestinal haemorrhage have occurred. Systemic absorption from bladder irrigation solutions can cause acute aluminium toxicity (see under Aluminium below) including encephalopathy.

Acute encephalopathy has been reported[1,2] after bladder irrigation with alum solutions in the treatment of bladder haemorrhage. Anecdotal evidence would suggest that this practice should be avoided in patients with renal insufficiency.[1]

1. Phelps KR, *et al.* Encephalopathy after bladder irrigation with alum: case report and literature review. *Am J Med Sci* 1999; **318:** 181–5.
2. Nakamura H, *et al.* Acute encephalopathy due to aluminium toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; **40:** 296–300.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Stepton; Varikopax.

Multi-ingredient Preparations. ***Arg.***: Bentophyto; ***Austria***: EST; ***Braz.***: Lucretin; ***Canad.***: Fletchers Sore Mouth Medicine; ***Fr.***: Supro; ***Ger.***: Retterspitz Ausserlich; Retterspitz Innerlich; ***India***: Feel Chill†; ***Irl.***: Pedamed; ***Ital.***: Lavanda Sofar; ***Mex.***: Forcremol; ***Neth.***: Trachitol; ***NZ***: Grans Remedy; ***Spain***: Co Bucal; Lindemil; ***USA***: BFI; Massengill; Mycinette; ***Venez.***: Borogin.

Homoeopathic Preparations. ***Fr.***: Poconeol no 82†; Sulfur Complexe No 12.

Aluminium

Aluminio; Aluminum; E173; Glin; Алюминий.

Al=26.9815386

CAS — 7429-90-5.

UNII — CPD4NFA903 (aluminium); 3XHB1D032B (aluminium ion).

Description. Aluminium is a malleable and ductile soft silvery-white metal, becoming coated with a thin layer of oxide.

Pharmacopoeias. *Br.* includes Aluminium Powder.

BP 2014: (Aluminium Powder). An odourless or almost odourless, silvery-grey powder. It consists mainly of metallic aluminium in very small flakes, usually with an appreciable quantity of aluminium oxide. It is lubricated with stearic acid to protect the metal from oxidation. Practically insoluble in water and in alcohol; it dissolves in dilute acids and in aqueous solutions of alkali hydroxides, with the evolution of hydrogen.

Handling. Aluminium powder has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Incompatibility. Incompatibilities have been reported between aluminium in injection equipment and metronidazole,[1,2] and between aluminium and various antineoplastics including cisplatin, daunorubicin, and doxorubicin.[3-6] The suitability of aluminium caps for sugar-containing liquids has also been questioned. Abrasion of the aluminium cap by sugar from *Ceporex Syrup*[cefalexin] has resulted in the formation of a black slime.[7]

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bohart RD, Ogawa G. An observation on the stability of cis-dichlorodiammineplatinum (II): a caution regarding its administration. *Cancer Treat Rep* 1979; **63:** 2117–18.
4. Gardiner WA. Possible incompatibility of doxorubicin hydrochloride with aluminum. *Am J Hosp Pharm* 1981; **38:** 1276.
5. Williamson MJ, *et al.* Doxorubicin hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1983; **40:** 214.
6. Ogawa GS, *et al.* Dispensing-pin problems. *Am J Hosp Pharm* 1985; **42:** 1042.
7. Tressler LJ. Medicine bottle caps. *Pharm J* 1985; **235:** 99.

Uses and Administration

Aluminium is used in packaging and in injection equipment. The foil is also used as a dressing and for insulation. Aluminium may also be employed as a colouring agent for some foodstuffs. Aluminium powder alone and in paste form with zinc oxide has been used as a dressing. Astringent aluminium salts are used as antiperspirants. Aluminium hydroxide (p. 1817.2) is used as an antacid.

Aluminium oxide (p. 1690.3) has been used as an abrasive agent.

Homoeopathy

Aluminium has been used in homoeopathic medicines under the following names: Aluminium metallicum; Alumin met; Al. met.

Adverse Effects, Treatment, and Precautions

Aluminium toxicity is well recognised in patients with renal impairment. Patients on dialysis have developed encephalopathy, osteodystrophy, and anaemia associated with an aluminium salt taken as a phosphate binder or with aluminium present in the water supply. For this reason, aluminium-free phosphate binders are often used in dialysis patients and the concentration of aluminium in dialysis fluid has been limited to not more than 10 micrograms/litre (see Aluminium Overload under Dialysis Solutions, p. 1779.3). Serum-aluminium concentrations should be monitored regularly in patients undergoing dialysis.

Aluminium toxicity has followed the use of parenteral fluids and infant feeds with a high concentration of aluminium.

Aluminium toxicity may be treated by removal of the aluminium with desferrioxamine (p. 1544.1).

The adverse effects of aluminium salts and precautions to be taken are described under Aluminium Hydroxide, p. 1817.3.

A review of aluminium toxicity[1] lists possible sources of aluminium including water, antacids, phosphate-binding gels, total parenteral nutrition solutions, processed human serum albumin, fluids used in infants, and environmental pollution; cooking utensils and beverages such as tea have also been suggested as possible sources of aluminium. It has been suggested that over-the-counter preparations of antacids, which can contain significant amounts of aluminium, represent the most important quantitative source of aluminium exposure.[2] Toxicity tends to occur when the gastrointestinal barrier to aluminium absorption is circumvented, as in intravenous fluid use or dialysis, or if the excretion of aluminium is reduced, as in renal impairment. Infants, especially preterm infants, form a special risk group.[3-7]

Accidental deposition of 20 tonnes of aluminium sulfate in a reservoir in Cornwall, UK in 1988 led to contamination of a nearby town's water supply.[8] Symptoms reported included diarrhoea, mouth ulcers or blisters, malaise, joint symptoms (mainly deterioration of existing symptoms), and memory defects (usually beginning 2 to 3 months after the incident). Although some medical experts considered that no long-term toxic effects were to be expected,[8] aluminium deposits were found in the bones of 2 individuals 6 to 7 months later.[9] In a study[10] undertaken 3 years after the incident, 55 adults who claimed to have suffered cerebral damage performed poorly in psychomotor testing. The authors attributed this to aluminium exposure, but the study's design and conclusions have been criticised.[11-13] An inquiry by the UK DoH[14] did not anticipate that exposure to aluminium from this incident would have caused long-term health problems in people who were adults or toddlers at the time, although this possibility should be explored further in those who were bottle-fed infants (i.e. below one year of age) at that time. Further studies were also recommended on the neuropsychological status and prevalence of joint problems in the population who consumed the contaminated water.

1. Monteagudo FSE, *et al.* Recent developments in aluminium toxicology. *Med Toxicol* 1989; **4:** 1–16.
2. Reinke CM, *et al.* Aluminium in over-the-counter drugs: risks outweigh benefits? *Drug Safety* 2003; **26:** 1011–25.
3. Bishop N, *et al.* Aluminium in infant formulas. *Lancet* 1989; **i:** 490.
4. Lawson M, *et al.* Aluminium and infant formulae. *Lancet* 1989; **i:** 614–15.
5. Anonymous. Aluminium content of parenteral drug products. *WHO Drug Inf* 1990; **4:** 70.
6. American Academy of Pediatrics Committee on Nutrition. Aluminum toxicity in infants and children. *Pediatrics* 1996; **97:** 413–16.
7. Fewtrell MS, *et al.* Aluminum exposure from parenteral nutrition in preterm infants: bone health at 15-year follow-up. *Pediatrics* 2009; **124:** 1372–9. Correction. *ibid.*; 1709.
8. Anonymous. Camelford two years on. *Lancet* 1990; **336:** 366.
9. Eastwood JB, *et al.* Aluminium deposition in bone after contamination of drinking water supply. *Lancet* 1990; **336:** 462–4.
10. Altmann P, *et al.* Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *BMJ* 1999; **319:** 807–11.
11. David A. Cerebral dysfunction after water pollution incident in Camelford: results were biased by self selection of cases. *BMJ* 2000; **320:** 1337.
12. Esmonde TFG. Cerebral dysfunction after water pollution incident in Camelford: study has several methodological errors. *BMJ* 2000; **320:** 1337–8.
13. McMillan TM. Cerebral dysfunction after water pollution incident in Camelford: study may prolong the agony. *BMJ* 2000; **320:** 1338.
14. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Subgroup Report on the Lowermoor Water Pollution Incident. DoH (issued 26th January, 2005). Available at: http://cot.food.gov.uk/pdfs/lowermoorreport05.pdf (accessed 16/08/10)

Burns. Thermal burns have been reported in patients undergoing magnetic resonance imaging (MRI) procedures when wearing transdermal medication patches containing aluminium in the backing material.[1] Aluminium is a conductive material and could induce a concentration of electrical currents sufficient to cause serious burns if placed in the MRI field; a similar phenomenon could also occur with external defibrillation.

1. Health Canada. Association of transdermal drug patches with thermal burns during magnetic resonance imaging procedures (issued 26th April 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/mri-irm_patch-timbre_nth-ah_e.pdf (accessed 03/04/08)

Effects on mental function. Encephalopathy with seizures has been associated with the use of aluminium-containing materials used for bone reconstruction.[1,2] In each case, reconstruction of areas of the skull resulted in high concentrations of aluminium in the CSF.

1. Renard JL, *et al.* Post-otoneurosurgery aluminium encephalopathy. *Lancet* 1994; **344:** 63–4.
2. Hantson P, *et al.* Encephalopathy with seizures after use of aluminium-containing bone cement. *Lancet* 1994; **344:** 1647.

ALZHEIMER'S DISEASE. The role of aluminium in the aetiology of Alzheimer's disease (see Dementia, p. 388.1) is, at best, unclear.[1-4] Circumstantial evidence of a positive association arises from *animal* and *in-vitro* data, together with clinical observations that aluminium is present in senile plaques and neurofibrillary tangles occurring in Alzheimer's disease, that giving aluminium chelators to Alzheimer patients may slow the progression of the disease, and that the risk of brain changes is increased in people living in areas with a high aluminium content in the drinking water supply. Some of these findings have been criticised, disproved, or not confirmed by other workers. Listed below are some of the studies which point to an association between aluminium intake and Alzheimer's disease,[5-8] some criticisms,[9-13] and some negative findings.[14,15]

There does not appear to be a risk of aluminium accumulation from normal use of aluminium-containing antacids by patients with normal renal function; consequently use of these antacids by such patients should not be considered to put them at risk of Alzheimer's disease.[16,17]

1. Crapper McLachlan DR, *et al.* Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? *Can Med Assoc J* 1991; **145:** 793–804.
2. Anonymous. Is aluminium a dementing ion? *Lancet* 1992; **339:** 713–14.
3. Munoz DG. Is exposure to aluminium a risk factor for the development of Alzheimer disease?—No. *Arch Neurol* 1998; **55:** 737–9.
4. Forbes WF, Hill GB. Is exposure to aluminium a risk factor for the development of Alzheimer disease?—Yes. *Arch Neurol* 1998; **55:** 740–1.
5. Martyn CN, *et al.* Geographical relation between Alzheimer's disease and aluminium in drinking water. *Lancet* 1989; **i:** 59–62.
6. Crapper McLachlan DR, *et al.* Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 1991; **337:** 1304–8.
7. Good PF, *et al.* Selective accumulation of aluminum and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study. *Ann Neurol* 1992; **31:** 286–92.
8. Harrington CR, *et al.* Alzheimer's-disease-like changes in tau protein processing: association with aluminium accumulation in brains of renal dialysis patients. *Lancet* 1994; **343:** 993–7.
9. Ebrahim S. Aluminium and Alzheimer's disease. *Lancet* 1989; **i:** 267.
10. Schupf N, *et al.* Aluminium and Alzheimer's disease. *Lancet* 1989; **i:** 267.
11. Lindesay J. Aluminium and Alzheimer's disease. *Lancet* 1989; **i:** 268.
12. Birchall JD, Chappell JS. Aluminium, water chemistry, and Alzheimer's disease. *Lancet* 1989; **i:** 953.
13. Whalley LJ, *et al.* Aluminium and dementia. *Lancet* 1992; **339:** 1235–6.
14. Markesbery WR, *et al.* Instrumental neutron activation analysis of brain aluminum in Alzheimer's disease and aging. *Ann Neurol* 1981; **10:** 511–16.
15. Wettstein A, *et al.* Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. *Int Arch Occup Environ Health* 1991; **63:** 97–103.
16. Anonymous. Aluminium salts and Alzheimer's disease. *Pharm J* 1991; **246:** 809.
17. Flaten TP, *et al.* Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; **45:** 203–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Podexine Exfoliante.

Multi-ingredient Preparations. ***Braz.***: Belagin†; ***Chile***: Podexine Anti-Transpirante; ***Ital.***: Rino Get; ***Mex.***: Dicentril†; Ulgel.

Homoeopathic Preparations. ***Fr.***: Abbe Chaupitre no 10†; Abbe Chaupitre no 22†.

Pharmacopoeial Preparations
BP 2014: Compound Aluminium Paste.

Aluminium Acetate

Aluminio, acetato de; Aluminum Acetate; Ацетат Алюминия; Уксуснокислый Алюминий.
$C_6H_9AlO_6$=204.1
CAS — 139-12-8.
UNII — 80EHD8I43D.

Profile

Aluminium acetate is prepared from aluminium sulfate and acetic acid.

Solutions containing aluminium acetate are astringent. Ear drops, which correspond to a solution of aluminium acetotartrate in that they are prepared from aluminium sulfate with the aid of acetic acid and tartaric acid, reduce oedema and inflammation of the ear in conditions such as otitis externa (p. 195.1) by producing an acidic environment hostile to pathogenic bacteria; they are also hygroscopic. Solutions, usually prepared from glacial acetic acid and an aluminum subacetate topical solution (which is itself prepared from aluminium sulfate and acetic acid), have also been used in dermatology as astringent lotions for irritating skin conditions.

Various preparations containing aluminium acetate have been known as Burow's creams, emulsions, lotions, or solutions.

Aluminium acetotartrate and aluminium subacetate (basic aluminium acetate) are also used as topical astringents.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Buro-Sol; ***Ger.***: Alsol; Essigsaure Tonerde-Salbe; Essitol; ***Hung.***: Alsol; Cremor; ***Pol.***: Altacet; Altaziaja; Altix; ***Switz.***: Euceta†; ***USA***: Bite Rx; ***Venez.***: Acid Mantle.

Multi-ingredient Preparations. ***Arg.***: Epiprocto†; ***Austral.***: Xyloproct; ***Austria***: Acetonal†; Nasanal; ***Braz.***: Xyloproct; ***Fr.***: Gel a l'Acetotartrate d'Alumine Defresne†; ***Gr.***: Xyloproct; ***Hong Kong***: Haemoral†; ***Indon.***: Haemocaine; ***Irl.***: Xyloproct†; ***Israel***: Proctozorin-N; ***Ital.***: Betaderm†; Micofoot; Oleo Calcarea; Vegetallumina; ***Malaysia***: Xyloproct; ***Mex.***: Dermanol; Litiset; Xyloproct Plus; ***Norw.***: Xyloproct†; ***NZ***: Xyloproct; ***Pol.***: Kamagel; ***Rus.***: Kamagel (Камагель); ***Spain***: Avril; ***Swed.***: Xyloproct; ***Switz.***: Euceta avec camomille et arnica; Fenipic; Fortacet†; Mikutan N†; Realderm; Topaceta†; ***Turk.***: Hemoralgine; ***UK***: Xyloproct; ***Ukr.***: Camagel (Камагель); ***USA***: Borofair Otic†; Burow's; Otic Domeboro; Star-Otic.

Pharmacopoeial Preparations
BP 2014: Aluminium Acetate Ear Drops;
USP 36: Aluminum Subacetate Topical Solution.

Aluminium Lactate

Aluminio, lactato de; Aluminum Lactate; Алюминия Лактат.
Tris(lactato)aluminium.
$C_9H_{15}AlO_9$=294.2
CAS — 537-02-0; 18917-91-4.
UNII — V797H4GG0Z.

Profile

Aluminium lactate is used in the local treatment of various disorders of the mouth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Etiaxil; ***Ital.***: Aluctyl†.

Multi-ingredient Preparations. ***Israel***: Aronal Forte; ***Ital.***: Lacalut; ***Port.***: Gartun; ***Switz.***: Deaftol; Drossadinetten; Drossadinol.

Aluminium Sulfate

Aliuminio sulfatas; Alumiinisulfaatti; Aluminii Sulfas; Aluminii Sulfas Hydricus; Aluminio, sulfato de; Aluminium, sulfate d'; Aluminium Sulfuricum; Aluminium Sulphate; Aluminium Trisulphate; Aluminiumsulfat; Alumínium-szulfát; Aluminum Sulfate; E520; Glinu siarczan; Síran hlinitý hydrát; Сульфат Алюминия.
$Al_2(SO_4)_3.xH_2O$=342.1 (anhydrous)
CAS — 10043-01-3 (anhydrous aluminium sulfate); 17927-65-0 (aluminium sulfate hydrate).
UNII — 34S289N54E (aluminium sulfate hydrate); I7T908772F (anhydrous aluminium sulfate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Aluminium Sulfate). Colourless lustrous crystals or crystalline masses. It contains 51 to 59% of $Al_2(SO_4)_3$. Soluble in cold water; freely soluble in hot water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Aluminum Sulfate). Contains 54 to 59% of $Al_2(SO_4)_3$. An odourless, white, crystalline powder, shining plates, or crystalline fragments. Soluble 1 in 1 of water; insoluble in alcohol. The pH of a 5% solution in water is not less than 2.9.

Profile

Aluminium sulfate has an action similar to that of alum (p. 2439.1) but is more astringent. Topical preparations containing 20% aluminium sulfate have been used for the treatment of envenomation by certain insects and marine organisms. The aluminium may cause precipitation of the proteins contained within the venoms thus reducing local toxicity. Aluminium sulfate is also included in astringent preparations intended to soothe irritating skin conditions.

Aluminium sulfate is also used in the preparation of aluminium acetate solutions.

Adverse effects. Possible adverse effects or toxicity associated with aluminium, or aluminium salts such as aluminium sulfate, in the public water supply are discussed under Aluminium, p. 2439.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Stingose; ***Hong Kong***: Stingose†; ***NZ***: Stingose; ***UK***: Stingose.

Multi-ingredient Preparations. ***Canad.***: Boropak†; ***Mex.***: Domeboro; ***USA***: Domeboro; Ostiderm; Pedi-Boro Soak Paks†.

Pharmacopoeial Preparations
USP 36: Aluminum Subacetate Topical Solution; Aluminum Sulfate and Calcium Acetate for Topical Solution; Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution.

Amber Oil

Oleum Succini; Rectified Amber Oil.
CAS — 9000-02-6 (amber); 8002-67-3 (amber oil).

Profile

Amber oil is formed by the destructive distillation of Baltic amber, a fossilised tree resin that contains succinic acid. It has properties and uses similar to those of turpentine oil.

The 'amber oils' used in aromatherapy are generally derived from non-fossilised tree resins or gums mixed with essential oils and other ingredients.

Homoeopathy

Amber has been used in homoeopathic medicines under the following names: Bernstein; Electron; Succinum

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Puma Balm; ***UK***: Nine Rubbing Oils; ***Ukr.***: Bezornil (Безорнил).

Ambergris

CAS — 8038-65-1 (ambergris); 473-03-0 (ambrein).
UNII — XTC0D02P6C.

Profile

Ambergris is a waxy solid produced in the intestines of sperm whales. It consists mainly of ambrein (a triterpene alcohol), cholesterol, and benzoic acid. Both ambergris and ambrein are used in perfumery.

Homoeopathy

Ambergris has been used in homoeopathic medicines under the following names: ambra grisea; ambre gris.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Ambra Med Complex; Asarum Med Complex; Avena Med Complex; Lobelia Med Complex; Mefem; Relax; Vertigoheel; Vertigopas; ***Canad.***: Amphosca†; Biomag†; Men Complex†; ***Cz.***: Vertigoheel; ***Fr.***: Amphosca Orchitine; Amphosca Ovarine; Biomag; Gastro-Drainol†; Kalium Phosphoricum Complexe No 100; Sepia Complexe No 20; ***Ger.***: Ambrax; Infinerval; Manuia; Nervo-Plantin†; Nervoid N; Pascolibrin; Presselin Nervenkomplex; Presselin Nervennahrung N†; Tondinel H; Vertigoheel; Vertigopas; Vertizin; ***Hung.***: Vertigoheel; ***Neth.***: Acidolite; Cerebrum comp; Homeocare neusspray; Neurovita; Sinufleur; ***Rus.***: Sambucus-Plus (Самбукус-Плюс); Valeriana-Plus (Валериана-Плюс); ***S.Afr.***: Vertigoheel; ***Switz.***: HerBalance; Vertigoheel; ***Ukr.***: Homvio-Nervin (Хомвио-Нервин); ***USA***: Preferred Remedies Stress; Vertigoheel.

Ambucetamide *(BAN, rINN)*

A-16; Ambucetamida; Ambucétamide; Ambucetamidum; Dibutamide; Амбуцетамид.
2-Dibutylamino-2-(4-methoxyphenyl)acetamide.
$C_{17}H_{28}N_2O_2$=292.4
CAS — 519-88-0.
UNII — 131B408RZI.

Profile

Ambucetamide is an antispasmodic and has been given for the relief of dysmenorrhoea. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Neth.***: Femerital†.

Ambutonium Bromide *(BAN)*

Ambutonii Bromidum; Ambutoniumbromid; Ambutoniumbromidi; BL-700B; R-100; Амбутония Бромид.
(3-Carbamoyl-3,3-diphenylpropyl)ethyldimethylammonium bromide.
$C_{20}H_{27}BrN_2O$=391.4
CAS — 14007-49-9 (ambutonium); 115-51-5 (ambutonium bromide).
UNII — 9J8YA3ZT14.

Profile

Ambutonium bromide is a quaternary ammonium antimuscarinic that has been used in gastrointestinal disorders with smooth muscle spasm.

Amilomer *(rINN)*

Amilomère; Amilómero; Amilomerum; Амиломер.
CAS — 42615-49-6.

Profile

Amilomer consists of microspheres produced by reaction of partially hydrolysed starch with epichlorohydrin, quickly degradable by amylase (with a half-life of less than 120 minutes); the name is followed by a hyphenated numerical code in which the number preceding the hyphen indicates the half-life in minutes and that following the hyphen indicates the mean diameter of the microspheres in μm.

Amilomer is used in transarterial chemoembolisation procedures in the management of hepatic malignancies.

Aminohippuric Acid

Ácido *p*-aminohipúrico; Ácido paraminohipúrico; Acidum Aminohippuricum; *p*-Aminobenzoylglycine; *p*-Aminohippuric Acid; Aminohippurihappo; Aminohippursyra; Aminohipúrico, ácido; Kwas aminohipurowy; PAHA; Para-aminohippuric Acid; Аминогиппуровая Кислота.
N-4-Aminobenzoylaminoacetic acid.
$C_9H_{10}N_2O_3$=194.2
CAS — 61-78-9 (aminohippuric acid); 94-16-6 (sodium aminohippurate).
ATC — V04CH30.
ATC Vet — QV04CH30.
UNII — Y79XT83BJ9.

Pharmacopoeias. In *US.*

USP 36: (Aminohippuric Acid). A white crystalline powder which discolours on exposure to light. Soluble 1 in 45 of water, 1 in 50 of alcohol, and 1 in 5 of 3N hydrochloric acid; very slightly soluble in carbon tetrachloride, in chloroform, in ether, and in benzene; freely soluble in alkaline solutions with some decomposition, and in diluted hydrochloric acid. Store in airtight containers. Protect from light.

Uses and Administration

Aminohippuric acid is excreted mainly by proximal tubular secretion, with some glomerular filtration. It is given as sodium aminohippurate (aminohippurate sodium; $C_9H_9N_2NaO_3$ = 216.2) for the estimation of effective renal plasma flow. It is given by intravenous infusion in a suggested priming dose of 6 to 10 mg/kg followed by an infusion dose of 10 to 24 mg per minute to achieve a plasma sodium aminohippurate concentration of 2 mg/100mL; at these concentrations about 90% of aminohippurate is cleared from the renal bloodstream in a single circuit in patients with normal renal function. Sodium aminohippurate has also been used for the assessment of the renal tubular secretory mechanism. Doses for this purpose are infused slowly to achieve a plasma concentration of 400 to 600 micrograms/mL to saturate the tubular secretion. These tests are used mainly in research procedures.

Adverse Effects and Precautions

Sodium aminohippurate may cause nausea and vomiting, hypersensitivity reactions, vasomotor disturbances, flushing, tingling, cramps, and a feeling of warmth. Patients may develop an urge to urinate or defaecate after infusion.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aminohippuric acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/10/11)

Interactions

The estimation of sodium aminohippurate may be affected in patients taking procaine, sulfonamides, or thiazosulfone. Probenecid diminishes the excretion of aminohippuric acid. Clearance is also affected by penicillins, salicylates, and other drugs that compete for the same excretory pathways.

Preparations

Pharmacopoeial Preparations
USP 36: Aminohippurate Sodium Injection.

Ammi Visnaga

Bishop's Weed; Biznaga; Kela; Khella; Khellah; Picktooth Fruit; Visnaga; Амми зубная (*Ammi visnaga*).
*ATC Herb — HC01DW5001 (*Ammi visnaga*: fruit); HA03WA5001 (*Ammi visnaga*: fruit); HR03WB5001 (*Ammi visnaga*: leaf).*
*UNII — JZM4T38Q8A (*Ammi visnaga*); 3UN285QN0C (*Ammi visnaga *fruit).*

NOTE. The name Bishop's Weed is commonly used to refer to the related medicinal herb *Ammi majus*. It is also used for *Aegopodium podagraria* (Apiaceae) (Goutweed, Ground Elder).

Profile

The fruit of *Ammi visnaga* (Apiaceae) is used in herbal preparations. It is also a source of khellin (p. 2538.1) and visnadine (p. 2646.1).

Homoeopathy

Ammi visnaga has been used in homoeopathic medicines under the following names: Ammi vis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Ammifurin (Аммифурин); Avisan (Ависан).

Multi-ingredient Preparations. ***Austria***: Urelium Neu; ***Ger.***: Cefadrin†; ***Pol.***: Kelicardina; Nefrol; ***Ukr.***: Flavia (Флавия); Phytolyt (Фитолит).

Homoeopathic Preparations. ***Ger.***: A-Bomin; Asthmakhell N; Cefangipect H†; Cefangipect†; Cefaspasmon N†; Cefavora Cor; Lowe-Komplex Nr 10; Pollinosan†; Pulmo Bronchialcomplex; ***Neth.***: Asakell; Asthmakhell†; Holergie; ***Switz.***: A Vogel Spray contre le rhume des foins; Pollinosan†.

Ammonia

Amoníaco, solución diluida de; Amonowy wodorotlenek; Amonyak.
CAS — 7664-41-7.
UNII — 5138Q19F1X.

NOTE. The food additive number E527 is used for ammonium hydroxide. Solutions of ammonia in water have been referred to as ammonium hydroxide solutions. Strong solutions of ammonia have also been described by the synonyms Ammoniaca, Ammoniacum, Ammoniaque Officinale, and Liquor Ammoniae Fortis. Dilute solutions of ammonia have also been referred to as Ammonia Water, Ammonium Hydricum Solutum, Liquor Ammoniae, and Liquor Ammoniae Dilutus.

Pharmacopoeias. Strong ammonia solutions are included in *Chin.* (25 to 28%), *Eur.* (see p. vii) (25 to 30%), and *USNF* (27 to 31%). Dilute ammonia solutions are included in *Br.*, *Chin.*, *Ger.*, *Jpn*, and *Swiss* (all about 10%).

Ph. Eur. 8: (Ammonia Solution, Concentrated; Ammoniae Solutio Concentrata; Strong Ammonia Solution BP 2014). It contains between 25% and 30% (w/w) of ammonia, NH_3. A clear colourless liquid. Very caustic. Miscible with water and with alcohol. Store at a temperature not exceeding 20 degrees in airtight containers.

BP 2014: (Dilute Ammonia Solution). It is prepared by diluting Strong Ammonia Solution with freshly boiled and cooled purified water. It contains 9.5 to 10.5% w/w of NH_3.

NOTE. The BP directs that when Ammonia Solution is prescribed or demanded, Dilute Ammonia Solution shall be dispensed or supplied.

USNF 31: (Strong Ammonia Solution). It contains between 27% and 31% (w/w) of NH_3. On exposure to air, it loses ammonia rapidly. A clear colourless liquid with an exceedingly pungent characteristic odour. Store at a temperature not exceeding 25 degrees in airtight containers.

Handling. Strong ammonia solutions should be handled with great care because of the caustic nature of the solutions and the irritating properties of the vapour. Cool the container well before opening and avoid inhalation of the vapour.

Uses and Administration

Dilute solutions of ammonia have been used as reflex stimulants either as smelling salts or oral solutions. They have also been used as rubefacients and counter-irritants (see p. 6.3) and to neutralise insect stings. Users should always be aware of the irritant properties of ammonia.

Hartshorn and Oil was sometimes used as a name for an ammonia liniment. Household ammonia and cloudy ammonia have been used as names for cleaning preparations of ammonia with oleic acid or soap respectively. A saturated solution containing about 35% w/w and known as '0.880 ammonia' has been used in many chemical and industrial applications.

Stings. Bathers who were stung by Portuguese men-of-war (*Physalia physalis*) were rapidly and effectively relieved of discomfort, paresis, irritation, and other symptoms by the application of aromatic ammonia spirit compresses.[1]

1. Frohman IG. Treatment of physalia stings. *JAMA* 1966; **197:** 733.

Adverse Effects

Ingestion of strong solutions of ammonia causes severe pain in the mouth, throat, and gastrointestinal tract, as well as severe local oedema and salivation, with cough, vomiting, and shock. Burns to the oesophagus and stomach may result in perforation. Stricture formation, usually in the oesophagus, can occur weeks or months later. Ingestion may also cause oedema of the respiratory tract and pneumonitis, though this may not develop for a few hours.

Inhalation of ammonia vapour causes sneezing and coughing and in high concentration causes pulmonary oedema. Asphyxia has been reported after oedema or spasm of the glottis. Ammonia vapour is irritant to the eyes and causes weeping; there may be conjunctival swelling and temporary blindness.

Ammonia solution in contact with skin and eyes produces blistering and vesiculation; ammonia burns feel 'soapy' because of saponification of the tissues. Strong solutions on the conjunctiva cause a severe reaction with conjunctival oedema, corneal damage, and acute glaucoma. Late complications include angle-closure glaucoma, opaque corneal scars, atrophy of the iris, and formation of cataracts. Ammonia burns have resulted from treating insect bites and stings with the strong solution, and even with the dilute solution, especially if a dressing is subsequently applied.

References.

1. Beare JDL, *et al.* Ammonia burns of the eye: an old weapon in new hands. *BMJ* 1988; **296:** 590.
2. WHO. Ammonia health and safety guide. *IPCS Health and Safety Guide 37.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/hsg/hsg/hsg037.htm (accessed 04/04/06)
3. Payne MP, Delic JI. Ammonia. In: *Toxicity Review 24.* London: HMSO, 1991: 1–12.
4. Payne MP, *et al. Toxicology of substances in relation to major hazards: ammonia.* London: HMSO, 1991.
5. Leduc D, *et al.* Acute and long term respiratory damage following inhalation of ammonia. *Thorax* 1992; **47:** 755–7.
6. Michaels RA. Emergency planning and the acute toxic potency of inhaled ammonia. *Environ Health Perspect* 1999; **107:** 617–27.
7. Amshel CE, *et al.* Anhydrous ammonia burns case report and review of the literature. *Burns* 2000; **26:** 493–7.
8. Kerstein MD, *et al.* Acute management of exposure to liquid ammonia. *Mil Med* 2001; **166:** 913–14.

Toxicity from mixing cleaning agents. For reference to the adverse effects of mixing ammonia-based and hypochlorite-based cleaning agents see Sodium Hypochlorite, p. 1769.2.

Treatment of Adverse Effects

Ingestion of ammonia solutions should not be treated by lavage or emesis. Milk or water have been given as diluents, but small volumes should be used to reduce the risk of inducing emesis. Appropriate measures should be taken to alleviate pain, shock, and pulmonary oedema, and maintain an airway.

Contaminated skin and eyes should be flooded immediately with water and the washing continued for at least 15 minutes. Any affected clothing should be removed while flooding is being carried out.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: After Bite†; ***Irl.***: After Bite; ***Israel***: Afterbite; ***Spain***: After Bite; Calmapica; Goipic; ***Switz.***: After Bite; ***UK***: After Bite.

Multi-ingredient Preparations. ***Austral.***: Senega and Ammonia; ***Austria***: Rowalind; ***Canad.***: Calmapic†; SJ Liniment†; ***Chile***: Rhus Opodeldoc; ***Fr.***: Hypneine†; Lipothymal†; ***Irl.***: Blistex Relief; ***Ital.***: Activ Dopo Puntura†; Baby Zanzara†; ***Rus.***: Pectorales Elixir (Грудной Эликсир); ***S.Afr.***: Enterodyne†; ***Spain***: Masagil†; ***UK***: Blistex Relief; Goddards Embrocation; Mackenzies Smelling Salts; Pickles Smelling Salts; ***USA***: Emergent-Ez.

Homoeopathic Preparations. ***Austral.***: Respatona Sore Throat.

Pharmacopoeial Preparations
BP 2014: Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Strong Ammonium Acetate Solution; White Liniment.

Ammonium Citrate

Ammon. Cit.; Amonowy cytrynian; E380; Triammonium Citrate; Цитрат Аммония.
$C_6H_5O_7(NH_4)_3$=243.2
CAS — 3458-72-8.
UNII — J90A52459R.

Profile

Ammonium citrate is used as a food additive and has been used in respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Ambrotos; Mucobrol; ***India***: HB Rich.

Ammonium Phosphate ⊗

545 (ammonium polyphosphates); Amonowy wodorofosforan; Diammonium Hydrogen Phosphate; Dibasic Ammonium Phosphate; Fosfato de amonio; Фосфат Аммония.
Diammonium hydrogen orthophosphate.
$(NH_4)_2HPO_4$=132.1
CAS — 7783-28-0.
UNII — 10LGE70FSU.

Pharmacopoeias. In *USNF*.

USNF 31: (Ammonium Phosphate). Colourless or white granules or powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 7.6 to 8.2. Store in airtight containers.

Profile

Ammonium phosphate was formerly used as a diuretic. It may be used as a buffering agent in pharmaceutical preparations.

Ammonium biphosphate (monobasic ammonium phosphate; $NH_4H_2PO_4$ = 115.0) has been used to acidify urine and as a phosphate supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Phosphore Alko; ***Pol.***: Phosphor†.

Homoeopathic Preparations. ***Chile***: Ikoplex No 5; ***Ger.***: Girheulit HM†; Girheulit HOM; Rufebran rheumo†.

Amnion

Amnios; Амнион.

Profile

Human extra-embryonic fetal membranes comprise an inner amniotic membrane, the amnion, and an outer membrane, the chorion. Amnion is used in ocular surgery for a range of conditions. Both amnion and combined membranes have been used as a dressing for raw wounds including chronic ulcers and burns.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: FegaCoren.

Homoeopathic Preparations. ***Ger.***: Neydin-F†; Neydin-M†; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A.

Amylase

Amilasa; Amylaza; Diastasa; Diastase; EC 3.2.1.1 (α-amylase); EC 3.2.1.2 (β-amylase); EC 3.2.1.3 (glucoamylase); Glucogenasa; Glucogenase; Ptialina; Ptyalin; Амилаза.
CAS — 9000-92-4 (amylase); 9000-85-5 (bacterial α-amylase); 9000-90-2 (porcine α-amylase, pancreatic); 9001-19-8 (takadiastase); 9000-91-3 (β-amylase); 9032-08-0 (glucoamylase).
ATC — A09AA01.
ATC Vet — QA09AA01.
UNII — 1909J9CFAT (α-amylase a type-1/2).

Pharmacopoeias. In *Fr.* and *Jpn*.

Uses and Administration

The term amylase refers to an enzyme catalysing the hydrolysis of α-1,4-glucosidic linkages of polysaccharides such as starch, glycogen, or their degradation products. Amylases may be classified according to the manner in which the glucosidic bond is attacked. Endoamylases attack the α-1,4-glucosidic linkage at random. Alpha-amylases are the only types of endoamylases known and yield dextrins, oligosaccharides, and monosaccharides. The more common alpha-amylases include those isolated from human saliva, mammalian pancreas, *Bacillus subtilis*, *Aspergillus oryzae*, and barley malt. Exoamylases attack the α-1,4-glucosidic linkage only from the non-reducing outer polysaccharide chain ends. They include beta-amylases and glucoamylases (amyloglucosidases or gamma-amylases) and are of vegetable or microbial origin. Beta-amylases yield beta-limit dextrins and maltose, and glucoamylases yield glucose.

Amylase is used in the production of predigested starchy foods and for the conversion of starch to fermentable sugars in the baking, brewing, and fermentation industries.

Amylase from various sources has been used as an ingredient of preparations of mixed digestive enzymes, and has been given orally for its supposed activity in reducing respiratory-tract inflammation and local swelling and oedema. Pancreatic enzymes such as pancreatin (p. 2579.3) and pancrelipase (p. 2580.1) have amylase activity.

Adverse Effects

Hypersensitivity reactions have been reported.

Hypersensitivity. References to asthma developing after occupational exposure to amylases used in the flour milling[1-3] and detergent[4,5] manufacturing industries, and studies[6-8] to assess the likelihood of developing amylase hypersensitivity after ingesting wheat products including bread.

1. Smith TA, *et al*. Respiratory symptoms and wheat flour exposure: a study of flour millers. *Occup Med (Lond)* 2000; **50:** 25–9.
2. Cullinan P, *et al*. Allergen and dust exposure as determinants of work-related symptoms and sensitization in a cohort of flour-exposed workers; a case-control analysis. *Ann Occup Hyg* 2001; **45:** 97–103.
3. Quirce S, *et al*. Glucoamylase: another fungal enzyme associated with baker's asthma. *Ann Allergy Asthma Immunol* 2002; **89:** 197–202.
4. Hole AM, *et al*. Occupational asthma caused by bacillary amylase used in the detergent industry. *Occup Environ Med* 2000; **57:** 840–2.
5. Cullinan P, *et al*. An outbreak of asthma in a modern detergent factory. *Lancet* 2000; **356:** 1899–1900.
6. Cullinan P, *et al*. Clinical responses to ingested fungal alpha-amylase and hemicellulase in persons sensitized to Aspergillus fumigatus? *Allergy* 1997; **52:** 346–9.
7. Sander I, *et al*. Is fungal alpha-amylase in bread an allergen? *Clin Exp Allergy* 2000; **30:** 560–5.
8. Simonato B, *et al*. IgE binding to soluble and insoluble wheat flour proteins in atopic and non-atopic patients suffering from gastrointestinal symptoms after wheat ingestion. *Clin Exp Allergy* 2001; **31:** 1771–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Orenzym; ***Fr.***: Flaviastase†; Maxilase; Megamylase; Oromylase†; ***India***: Galazyme-Pro; ***Mon.***: Amylodiastase; ***Port.***: Maxilase.

Multi-ingredient Preparations. ***Arg.***: Docechol; Dom-Polienzim; Gastridin-E; Homocisteon Compuesto; Pakinase; Polienzim; Tridigestivo Soubeiran; ***Austral.***: Enzyme; Vegie Digestaid; ***Austria***: Wobenzym; ***Belg.***: Digestomen; ***Braz.***: Essen; Peptopancreasi†; Primeral; Thiomucase; ***Canad.***: Digesdyn; Digesta; Digestolax; Dipan†; Multi-Zyme†; Pancre Zyme†; Synergy Defense; ***Chile***: Flapex E; ***China***: Dages (达吉); Wei Tai Kang (谓泰康); YiMei (怡美); ***Cz.***: Wobenzym; ***Hong Kong***: Appezym; Bio-Tomosan†; Caricose†; Digezym; Enzyme Co†; Enzyplex; Magesto; Uni-Paptase†; ***India***: Afizyme; Aglozyme; Aglozyme; Aldezyme; Alzyme; Aniwel DPS; Anzykair; Anzykair; Aquadil-P; Aristozyme; Arizyme; Asizyme; Astozyme; Atopep; Bactzyme; Bestozyme P; Bestozyme; Bestozyme; Biota-P; Biozyme; Canzyme; Cascazyme; Catalyd; Catazyme-P; Catazyme; Daffozyme; Dewzym; Digems-CT; Digeplex-T; Digeplex; Digeplex; Digestomen-P; Digitage; Dipep; Dipep; Disnizyme; Dorzy DPS; Dorzy; Duozyme; E-Pep; Eaze; Elfazyme; Endos; Entozyme; Entrozyme; Enzar; Enzofast; Enzofast; Enzytel; Estzyme; Everzyme; Extrazyme; Farizym; Ferizyme; Fozyme; Fullzyme; Fyzyme; Gaskit; Gaskit; Gastrofit; Gastrozyme; Gastrozyme; Genozyme; Genozyme; Glozyme; Hanzyme; HG Zyme; Ifyzyme; Indozyme; Infazyme; Intazyme; Intazyme; Intrazyme Tonic; Intrazyme; Jayzyme; Kairase; Kamozyme; KDZyme; Kingzyme; Lac-B; Lavazyme; Lavazyme; Laxzyme; Leno-EZ; Litzyme; Lupizyme; Lyzyme; M-Zyme; Maprazyme; Martiz; Merozyme-C; NBGest; Nectozyme; Neopeptine; Neopeptine; Neopeptine; Nifazyme; Novazyme Elachi; Nutrozyme; Nutrozyme; Nutrozyme; Onazyme; Optizyme; Panzyme; Papytazyme; PP Bio; PP Tage; Sanzyme-DS; Unienzyme; Unienzyme; Vitazyme; Vitazyme; ***Indon.***: Aludonna; Enzyplex; Excelase-E; Librozym Plus†; Librozym†; Vitazym; Xepazym; ***Jpn***: Cabagin†; ***Malaysia***: Biotase; Enzyme Digest; Enzyplex†; Pepfiz; ***Mex.***: Ochozim; Wobenzym; Zimotris; ***Port.***: Modulanzime; ***Rus.***: Pepfiz (Пепфиз); Unienzyme с MPS (Юниэнзим с МПС); Wobenzym (Вобэнзим); ***Singapore***: Biotase; Enzyplex; Weisen-U; ***Spain***: Demusin†; Digestomen Complex; ***Thai.***: Corisul; Diasgest; Digestin; Enzyplex†; Flataco; Flatulence†; Magesto; Mesto-Of; Patarsul; Pepfiz; Pepsitase; Polyenzyme-I†; ***UK***: Enzyme Digest; Enzyme Plus; ***Ukr.***: Wobenzym (Вобэнзим); ***USA***: Bio-Zyme; Digex†; Enzyme; Ku-Zyme†; Kutrase†; Papaya Enzyme; Similase Jr; ***Venez.***: Festal Reformulado.

Anagrelide Hydrochloride *(BANM, USAN, rINNM)*

Anagrelida, hidrocloruro de; Anagrélide, Chlorhydrate d'; Anagrelidi Hydrochloridum; BL-4162a; BMY-26538-01; Hidrocloruro de anagrelida; Анагрелида Гидрохлорид.
6,7-Dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin-2(3*H*)-one hydrochloride.
$C_{10}H_7Cl_2N_3O$,HCl=292.5
CAS — 68475-42-3 (anagrelide); 58579-51-4 (anagrelide hydrochloride); 823178-43-4 (anagrelide hydrochloride monohydrate).
ATC — L01XX35.
ATC Vet — QL01XX35.
UNII — VNS4435G39 (anagrelide hydrochloride); YTM763Y5C8 (anagrelide hydrochloride monohydrate).

Pharmacopoeias. In *US*.

USP 36: (Anagrelide Hydrochloride). An off-white to pale pinkish powder. Very slightly soluble in water; sparingly soluble in dimethyl sulfoxide and dimethylformamide. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III that reduces platelet production and, at higher than therapeutic doses, inhibits platelet aggregation. It is used to treat primary (essential) thrombocythaemia (p. 695.2) in patients intolerant of, or unresponsive to, other therapy, and also in thrombocythaemia secondary to other myeloproliferative disorders.

Anagrelide is given orally as the hydrochloride monohydrate ($C_{10}H_7Cl_2N_3O$,HCl,H_2O = 310.6) but doses are expressed in terms of the base; 1.2 mg of anagrelide hydrochloride monohydrate is equivalent to about 1 mg of anagrelide. The initial dose is the equivalent of anagrelide 1 mg daily in 2 divided doses. After at least a week, the dose is adjusted, by increasing the daily dose by not more than 500 micrograms in any one week, until the platelet count is maintained within the normal range. The usual maintenance dose is 1 to 3 mg daily. The dose should not exceed 10 mg daily or 2.5 mg as a single dose. In the USA, a higher initial dose of 2 mg daily, divided into 2 or 4 doses, is used. For doses to be used in children and in patients with hepatic impairment, see below.

The effects of anagrelide therapy must be regularly monitored: platelet counts should be measured every 2 days during the first week of treatment and then at least weekly until the maintenance dose is reached.

References.

1. Spencer CM, Brogden RN. Anagrelide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of thrombocythaemia. *Drugs* 1994; **47:** 809–22.
2. Chintagumpala MM, *et al*. Treatment of essential thrombocythemia with anagrelide. *J Pediatr* 1995; **127:** 495–8.
3. Oertel MD. Anagrelide, a selective thrombocytopenic agent. *Am J Health-Syst Pharm* 1998; **55:** 1979–86.
4. Lackner H, *et al*. Treatment of children with anagrelide for thrombocythemia. *J Pediatr Hematol Oncol* 1998; **20:** 469–73.
5. Pescatore SL, Lindley C. Anagrelide: a novel agent for the treatment of myeloproliferative disorders. *Expert Opin Pharmacother* 2000; **1:** 537–46.
6. Dingli D, Tefferi A. Anagrelide: an update on its mechanisms of action and therapeutic potential. *Expert Rev Anticancer Ther* 2004; **4:** 533–41.
7. Steurer M, *et al*. Anagrelide for thrombocytosis in myeloproliferative disorders: a prospective study to assess efficacy and adverse event profile. *Cancer* 2004; **101:** 2239–46.
8. Wagstaff AJ, Keating GM. Anagrelide: a review of its use in the management of essential thrombocythaemia. *Drugs* 2006; **66:** 111–31.
9. Christoforidou A, *et al*. Hydroxyurea and anagrelide combination therapy in patients with chronic myeloproliferative diseases resistant or intolerant to monotherapy. *Acta Haematol (Basel)* 2008; **120:** 195–8.
10. Emadi A, Spivak JL. Anagrelide: 20 years later. *Expert Rev Anticancer Ther* 2009; **9:** 37–50.

Administration in children. The recommended initial daily dose of anagrelide in children aged 7 years and over is 500 micrograms orally for one week followed by adjustment of the daily dose in increments of 500 micrograms at weekly intervals until the platelet count is maintained within the normal range. The usual maintenance dose is 1 to 3 mg daily; the dose should not exceed 10 mg daily or 2.5 mg as a single dose.

Administration in hepatic impairment. UK licensed product information recommends that anagrelide should not be given to patients with moderate or severe hepatic impairment. In the USA, anagrelide therapy is not recommended in patients with severe hepatic impairment, although patients with moderate hepatic impairment have been given anagrelide in an initial oral daily dose of 500 micrograms, which should be maintained for a minimum of 1 week and with cardiovascular monitoring; the daily dose may then be increased cautiously as above.

Adverse Effects

Adverse effects most commonly reported with anagrelide include headache, palpitations and tachycardia, fluid retention, diarrhoea, nausea, and abdominal pain; fatigue, dizziness, flatulence, vomiting, dyspnoea, rashes, and anaemia have also occurred. Cardiovascular effects also include vasodilatation and positive inotropic effects; myocardial infarction, cardiomyopathy and heart failure have been reported. Anagrelide has been shown to be embryotoxic and fetotoxic in *animal* studies.

Effects on the heart. High-output heart failure occurred in a patient given anagrelide for essential thrombocytosis.[1] Clinical and haemodynamic adverse effects resolved almost immediately on stopping anagrelide.

1. Engel PJ, *et al.* High-output heart failure associated with anagrelide therapy for essential thrombocytosis. *Ann Intern Med* 2005; **143:** 311–13.

Effects on the lungs. Severe life-threatening hypersensitivity pneumonitis has been associated with anagrelide.[1]

1. Raghavan M, *et al.* Severe hypersensitivity pneumonitis associated with anagrelide. *Ann Pharmacother* 2003; **37:** 1228–31.

Erectile dysfunction. Erectile dysfunction associated with anagrelide therapy has been reported in a patient.[1]

1. Braester A, Laver B. Anagrelide-induced erectile dysfunction. *Ann Pharmacother* 2002; **36:** 1291.

Precautions

Anagrelide is mainly removed from the body by hepatic metabolism, and its use is contra-indicated in patients with severe hepatic impairment. In the UK it is additionally contra-indicated in those with moderate impairment, but in the USA its use is permitted in such patients at reduced doses (see p. 2442.3). Licensed product information in the UK also contra-indicates its use in those with moderate to severe renal impairment (creatinine clearance less than 50 mL/minute).

Anagrelide should be used with caution in patients with cardiovascular disease. Cardiac function should be assessed in patients before and during treatment, and patients monitored for cardiovascular adverse effects during treatment. For precautions in patients taking anagrelide with aspirin, see Interactions, below.

Platelet counts should be monitored closely, especially at the start of treatment (see Uses and Administration, p. 2442.3). Haemoglobin, white blood cells, and hepatic and renal function should also be monitored until a maintenance dose is established.

Dizziness may affect the performance of skilled tasks such as driving.

Anagrelide should not be used during pregnancy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anagrelide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

There is the theoretical possibility that inhibitors of the cytochrome P450 isoenzyme CYP1A2 could reduce the clearance of anagrelide. Anagrelide itself has limited inhibitory activity towards CYP1A2. Anagrelide may exacerbate the effects of other phosphodiesterase inhibitors such as amrinone, cilostazol, enoximone, milrinone, and olprinone that also produce positive inotropic effects.

Potentiation of the effects of other drugs that modify platelet function when given with anagrelide is a theoretical possibility. Although no clinically significant effects have been seen when given with aspirin to patients with essential thrombocythaemia, enhancement of antiplatelet aggregation effects of anagrelide and aspirin has been reported in a study after co-administration to healthy subjects compared with aspirin alone. The UK manufacturers consequently recommend that before starting concomitant treatment of these 2 drugs, the potential risks should be assessed in patients with a high-risk profile for haemorrhage.

Pharmacokinetics

Anagrelide is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 hour after an oral dose on an empty stomach, increasing in the presence of food, although this appears to have no clinically significant effect on bioavailability. It is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP1A2, and eliminated in the urine; less than 1% of a dose is excreted unchanged. The plasma half-life is about 1.3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agrelid; ***Austral.***: Agrylin; ***Austria***: Thromboreductin; ***Belg.***: Xagrid; ***Canad.***: Agrylin; ***Cz.***: Thromboreductin; Xagrid; ***Denm.***: Xagrid; ***Fin.***: Xagrid; ***Fr.***: Xagrid; ***Ger.***: Xagrid; ***Gr.***: Agrylin†; Xagrid; ***Hong Kong***: Agrylin; Thromboreductin; ***Hung.***: Thromboreductin; ***Indon.***: Agrylin; Thromboreductin; ***Irl.***: Xagrid; ***Israel***: Agrylin; Anagrid; ***Ital.***: Xagrid; ***Malaysia***: Thromboreductin; ***Neth.***: Xagrid; ***Norw.***: Xagrid; ***Philipp.***: Agrylin; ***Pol.***: Xagrid; ***Port.***: Xagrid; ***S.Afr.***: Agrylin; Thromboreductin; ***Singapore***: Agrylin†; ***Spain***: Xagrid; ***Swed.***: Xagrid; ***Switz.***: Thromboreductin; Xagrid; ***Thai.***: Agrylin; Thromboreductin; ***Turk.***: Thromboreductin; ***UK***: Xagrid; ***USA***: Agrylin.

Pharmacopoeial Preparations
USP 36: Anagrelide Capsules.

Andrographis

Chuanxinlian; Kalmegh; Kariyat; Kirayat.
CAS — 5508-58-7 (andrographolide).
*ATC Herb — HA05BA5001 (*Andrographis paniculata*: herb); HN02BG5002 (*Andrographis paniculata*: herb).*
UNII — 0P49L952WZ.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Andrographis). Andrographis is the dried stems and leaves of *Andrographis paniculata* (Acanthaceae). It contains not less than 1% of diterpene lactones calculated on the dried basis, as the sum of andrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographolide, and andrograpanin. Protect from light and moisture.

Profile

Andrographis is the dried entire plant or leaves and shoots of *Andrographis paniculata* (Acanthaceae). It has been used as a traditional herbal medicine in Asia. Andrographolide is one of its main constituents.

General references.

1. WHO. Herba Andrographidis. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/4.html (accessed 05/02/10)

Respiratory-tract infections. References to the use of andrographis in upper respiratory-tract infections.

1. Coon JT, Ernst E. Andrographis paniculata in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy. *Planta Med* 2004; **70:** 293–8.
2. Poolsup N, *et al. Andrographis paniculata* in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2004; **29:** 37–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cold Combat; ***Canad.***: Restorin; ***Thai.***: Fa-Thalai-Chon.

Multi-ingredient Preparations. ***Austral.***: Andrographis Complex; Andrographis Compound; Echinacea Royale; Gartech†; Immune Boost with Andrographis; ***Fr.***: Lactibiane Defenses; ***Hung.***: Livfit; ***India***: Agloliv; Agloliv; Cytozen; Hepaliv; Hipatop; Li-Verve; Livasa; Livasa; Livomyn; Livomyn; Livosil-H; Livotone; Livto; Liyurto; Megacure-DS; ***Indon.***: Neoboost; ***Ital.***: Angiovein; ***Philipp.***: Bo-D-Fense†; ***Rus.***: Dipana (Дипана); ***Singapore***: Hemoglo; ***Ukr.***: Detoxopirol (Детоксопирол).

Anecortave *(rINN)*

AL-3789; Anecortava; Anécortave; Anecortave Acetate (USAN); Anecortavum; Анекортав.
17,21-Dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate.
$C_{23}H_{30}O_5$=386.5
CAS — 7753-60-8.
ATC — S01LA02.
ATC Vet — QS01LA02.
UNII — Y0PC411K4T.

NOTE. The name Retaane has been used as a trade mark for anecortave.

Profile

Anecortave is an angiostatic cortisene under investigation for the treatment of patients with neovascular (wet) age-related macular degeneration (p. 880.2). It is similar in structure to cortisol acetate but without any glucocorticoid activity and is able to inhibit several steps of the neovascularisation process. It is given by posterior juxtascleral depot injection and is available in some countries for compassionate use on a named-patient basis.

References.

1. Clark AF. Mechanism of action of the angiostatic cortisene anecortave acetate. *Surv Ophthalmol* 2007; **52** (suppl 1): S26–S34.
2. Regillo CD, *et al.* Clinical safety profile of posterior juxtascleral depot administration of anecortave acetate 15 mg suspension as primary therapy or adjunctive therapy with photodynamic therapy for treatment of wet age-related macular degeneration. *Surv Ophthalmol* 2007; **52** (suppl 1): S70–S78.
3. Russell SR, *et al.* Anecortave acetate for the treatment of exudative age-related macular degeneration—a review of clinical outcomes. *Surv Ophthalmol* 2007; **52** (suppl 1): S79–S90.
4. Geltzer A, *et al.* Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 08/04/08).
5. Robin AL, *et al.* Reduction of intraocular pressure with anecortave acetate in eyes with ocular steroid injection-related glaucoma. *Arch Ophthalmol* 2009; **127:** 173–8.

Anethole

Anethol; Anetol; *p*-Propenylanisole; Анетол.
(*E*)-1-Methoxy-4-(prop-1-enyl)benzene.
$C_{10}H_{12}O$=148.2
CAS — 104-46-1; 4180-23-8 (E isomer).
UNII — Q3JEK5DO4K (natural anethole); A79C64YD3Q (synthetic anethole).

NOTE. Distinguish from Anethole Trithione (below).

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 31: (Anethole). Obtained from anise oil or other sources or prepared synthetically. At or above 23 degrees anethole is a colourless or faintly yellow liquid with a sweet taste and the aromatic odour of aniseed. Very slightly soluble in water; soluble 1 in 2 by volume of alcohol; readily miscible with chloroform and with ether. Store in airtight containers. Protect from light.

Profile

Anethole has similar properties to those of anise oil (p. 2444.3). It is also included in mixed terpene preparations used in urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Rowatinex; ***Austria***: Rowatinex; Wick Erkaltungssirup fur die Nacht; ***Canad.***: Bronco Asmol†; ***Chile***: Rowatinex; ***Cz.***: Rowatinex; ***Ger.***: Rowatinex; ***Hong Kong***: Neo-Rowatinex; Rowatinex; ***Hung.***: Rowatinex; ***Indon.***: Listerine Coolmint†; ***Irl.***: Rowatinex; ***Israel***: Rowatinex; ***Malaysia***: Rowatinex; ***Philipp.***: Listerine Coolmint; Rowatinex; ***Pol.***: Rowatinex; ***Rus.***: Rowatinex (Роватинекс); ***Spain***: Pulmofasa; Rowanefrin; ***Thai.***: Rowatinex; ***Ukr.***: Angi Sept Dr Theiss (Анги Септ Др Тайсс); ***Venez.***: Rowatinex.

Anethole Trithione

Anethole Dithiolthione; Anetholtrithion; Anetol tritiona; SKF-1717; Trithioparamethoxyphenylpropene; Анетола Тритион.
5-(4-Methoxyphenyl)-3*H*-1,2-dithiole-3-thione.
$C_{10}H_8OS_3$=240.4
CAS — 532-11-6.
ATC — A16AX02.
ATC Vet — QA16AX02.
UNII — QUY32964DJ.

NOTE. Distinguish from Anethole (above).

Profile

Anethole trithione has been given orally in the management of dry mouth (p. 2175.3) and as a choleretic. The usual daily dose is 75 mg, generally in 3 divided doses before meals. Anethole trithione may cause discoloration of the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Sulfarlem; ***Canad.***: Sialor; ***China***: Zhengrui (正瑞); ***Fr.***: Sulfarlem; ***India***: Hepasulfol; ***Switz.***: Sulfarlem; ***Turk.***: Sulfarlem.

Multi-ingredient Preparations. ***India***: Hepasulfol-AA.

Angelica

Andělikový kořen; Angélica; Angelicae Archangelicae Radix; Angelicae radix; Angelikarot; Angélique, racine d'; Angyalgyökér; Archangelica; Archangelicae Radix; Korzeń arcydzięgla; Šventagaršvių šaknys; Väinönputkenjuuri; Ангелика; Дудник.
CAS — 8015-64-3 (angelica oils).
*ATC Herb — HG04BW5003 (*Angelica archangelica*: root); HA03AW5003 (*Angelica archangelica*: root); HR05YA5002 (*Angelica archangelica*: root).*
*UNII — 3W51R3EK30 (*Angelica acutiloba *root); DTN01M69SN (*Angelica archangelica *root); 0MF1EI01KJ (*Angelica pubescens *root).*

Pharmacopoeias. In *Eur.* (see p. vii).

Jpn has separate monographs for *Angelica acutiloba* (Japanese Angelica) and *A. dahurica.*

Chin. specifies *A. dahurica*, *A. dahurica* var. *formosana*, *A. pubescens*, and *A. sinensis.*

Ph. Eur. 8: (Angelica Archangelica Root). The whole or cut, carefully dried rhizome and root of *Angelica archangelica* (*Archangelica officinalis*) containing a minimum of 0.2% v/w of essential oil, calculated with reference to the dried drug.

Profile

Angelica (*Angelica archangelica*) is widely used in herbal medicine. The root is used as a bitter to stimulate the appetite. Angelica also has diaphoretic and expectorant properties and has been used for circulatory and respiratory disorders.

Angelica oil is used in aromatherapy.

Angelica contains furanocoumarins and may cause photosensitivity reactions or interfere with anticoagulant therapy.

Other *Angelica* spp. that are used in herbal medicine include *A. acutiloba* (Japanese angelica), *A. dahurica*, *A. pubescens*, and *A. sinensis* (see Dong Quai, p. 2497.1).

Angelica stems are candied for culinary use.

Homoeopathy

Angelica has been used in homoeopathic medicines under the following names: Archangelica; Angelica archangelica; Angelica archangelica var. archangelica.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Sigmafem; Wunderbalsam; ***Austral.***: Irontona†; Toxicol; Vitatona†; ***Austria***: Abdomilon N; Iberogast; Klosterfrau Melissengeist; Pervivo; ***Belg.***: Eau Des Carmes; ***Canad.***: Formula T4†; ***Cz.***: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Iberogast; Klosterfrau Melisana; Original Schwedenbitter; Stomaran; Valofyt Neo†; ***Fr.***: Boribel Tisane No 6†; Boribel Tisane No 7†; Dystolise; Mediflor Digestive No 3; NurAiD; Santane C_6†; Tigre de Chine; ***Ger.***: Abdomilon N; Gastritol; Iberogast; Infi-tract V; Klosterfrau Melissengeist; Melissengeist; Schwedentrunk Elixier; ***Hung.***: Antipoll; Bano Svedkeseru; Bittner; Iberogast; Klosterfrau Melisana; ***Ital.***: Florelax; ***Jpn***: Bofutsushosan; Choreitogoshimotsuto; Daibofuto; Gorinsan; Hochuekkito; Jiinkokato; Jiinshihoto; Junchoto; Juzentaihoto; Kamikihito; Kamishoyosan; Keigairengyoto; Kihito; Kyukikyogaito; Ninjin'yoeito; Nyoshinsan; Otsujito; Ryutanshakanto; Saikoseikanto; Seihaito; Seishoekkito; Shichimotsukokato; Shimotsuto; Shiunko; Shofusan; Sokeikaketsuto; Tokiinshi; Tokikenchuto; Tokishakuyakusan; Tokishigyakukagoshuyushokyoto; Tokito; Tsudosan; Unkeito; Unseiin; Yokuininto; Yokukansan; Yokukansankachimpihange; ***Neth.***: Iberogast; ***Philipp.***: BSI Medicated Plaster; Hemofer; Zilongjin; ***Pol.***: Iberogast; Melis-Tonic; Melisal; Melisana Klosterfrau; Melissed; Nervosol; Pervivo; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Melissa (Доппельгерц Мелисса); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Wantong Artiplas (Ваньтун Артиплас); ***S.Afr.***: Melissengeist†; Spiritus Contra Tussim Drops†; ***Spain***: Agua del Carmen; Iberogast; ***Swed.***: Iberogast; ***Switz.***: Gastrosan; Iberogast; ***UK***: Digestion Calming Drops; Melissa Comp.; ***Ukr.***: Gastritol (Гастритол); Huato Pills (Болюсы Хуато); Iberogast (Иберогаст); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***USA***: Mucotrol.

Homoeopathic Preparations. ***Switz.***: Regenaplex Nr 28a; Regenaplex Nr 41a; Regenaplex Nr. 3; ***UK***: Cough Drops.

Animal Tissue Extracts

Mammalian Tissue Extracts

Mamiferos, extractos tisulares; Экстракты из Млекопитающей Ткани.

Profile

Many medicinal preparations with definite pharmacological activity and valid clinical uses are of mammalian origin and are described under their appropriate monographs—for example, calcitonin, corticotropin, hydrocortisone (cortisol), some enzymes, heparin, insulin, parathyroid hormone, pituitary hormones, some sex hormones, and thyroid.

Other preparations of animal origin have been promoted for various disorders. Evidence of pharmacological activity is generally lacking and such preparations are often of doubtful benefit.

Homoeopathy

Animal tissues that have been used in homoeopathic preparations include the following: Anas Barbariae Hepatis et Cordis; Bufo Bufo; Cerebellum; Diencephalon; Gingiva Bovis; Pituitary Gland; Sus Scrofa Umbilical Cord; Tonsillae Palatinae Bovis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Raw Prostate; Renacenz; Sigmatrofic; Solcoseryl; ***Austria***: Actovegin; Cerebrolysin; Enzynorm; Solcoseryl; ***Chile***: Renacenz; ***China***: Actovegin (爱维治); Ao De Jin (奥德金); Cerebrolysin (脑活素); Fu Ke Tuo (复可托); Hong Yuan (鸿源); Lang Du (朗度); Sheng Qi (生祺); Shuai Qi (帅奇); Xin Ou Rui (新欧瑞); Xin Wei Zhi (欣维治); ***Cz.***: Cerebrolysin; Solcoseryl; ***Fr.***: Eurobiol; ***Ger.***: Actihaemyl; Actovegin†; Cerebrolysin†; ***Gr.***: Actovegin; Solcoseryl; ***Hong Kong***: Actovegin; Cerebrolysin; Levident†; Solcoseryl; ***Hung.***: Actovegin†; ***India***: Placentrex; ***Indon.***: Solcoseryl†; ***Ital.***: Cellulin Retinale; Liposom; ***Jpn***: Solcoseryl; ***Malaysia***: Solcoseryl; ***Mex.***: Aninegalem; Reposton†; ***Philipp.***: Cerebrolysin; Solcoseryl; ***Pol.***: Cerebrolysin; Solcoseryl; ***Port.***: Cerebrolysine†; ***Rus.***: Actovegin (Актовегин); Cerebrolysin (Церебролизин); Cortexin (Кортексин); Laennec (Лаеннек); Prostacor (Простакор); Prostatilen (Простатилен); Retinalamin (Ретиналамин); Samprost (Сампрост); Sirepar (Сирепар)†; Solcoseryl (Солкосерил); Uroprost (Уропрост); Vitaprost (Витапрост); ***Singapore***: Solcoseryl; ***Switz.***: Solcoseryl; ***Thai.***: Cerebrolysin; Hepavit; Sirepar†; Solcoseryl; ***Ukr.***: Actovegin (Актовегин); Cerebrocurin (Цереброкурин); Cerebrolysin (Церебролизин); Ceregin (Церегин); Cortexin (Кортексин); Haematogen (Гематоген); Inflamafertin (Инфламафертин); Propes (Пропес); Retinalamin (Ретиналамин); Solcoseryl (Солкосерил); Vitaprost (Витапрост).

Multi-ingredient Preparations. ***Arg.***: ITE-B12 Forte; Melagel; Pat-Chobet; Peptonum; Tricomax; ***Austral.***: Hepasol; ***Austria***: Aktivanad; Intestinol†; Solcoseryl Dental; Wobe-Mugos; ***Braz.***: Dobiron; Extrato Hepatico Composto; Ferrocomplex; Fol Sang†; Hematiase B12; Lisotox; Panvitrop; Rubrargil; Xantinon B12; ***Canad.***: Digestolax; Super Energex Plus†; ***Chile***: Rumalon; Tonopron Fuerte Con Vit. B12; ***Ger.***: Aktivanad-N; Dia-Aktivanad-N; Enzym Comp; Enzym-Harongan; Enzynorm f; Factor AF2; FegaCoren; NeyDesib Nr 78; Solcoseryl akut†; Solcoseryl Dental†; ***Hong Kong***: Fortifer; Solcoseryl Dental; ***Hung.***: Dipankrin; Neogranormon; ***India***: Bayers Tonic; Deferon; Hepatoglobine; Iberol; Lederplex; Livogen; Mynberrys Compound; Neo-Hepatex; Plastules B-12; Surbex T; ***Indon.***: Bioplacenton; Centabio; Cyltabs; LaktaFit; Milmor; Moloco + B12; Neocenta; Solcoseryl Dental†; Tonikum Bode; Viliron; ***Irl.***: Ferybar†; ***Ital.***: Biotrefon Plus; Gastro-Pepsin; Vigogel; ***Malaysia***: Solcoseryl Dental; ***Mex.***: Cholal Modificado; ***Philipp.***: Godex†; Godex; Mitodex; Solcoseryl Dental; ***Port.***: Cognicer; ***Rus.***: Cholenzim (Холензим); Erbisol (Эрбисол); Prohepar (Прогепар); Solcoseryl Dental (Солкосерил Дентальная); ***S.Afr.***: Liviton; Prohep†; Zeel; Zeel; ***Singapore***: Solcoseryl Dental; ***Spain***: Hepadif; Policolinosil; ***Switz.***: Solcoseryl Dentaire; Wala Echinacea; ***Thai.***: Intricon; Solcoseryl Dental; Vitaral; ***Turk.***: Solcoseryl; ***UK***: Hematinic; S.P.H.P.; ***Ukr.***: Hepadif (Гепадиф); Hepadif (Гепадиф); Solcoseryl Dental (Солкосерил Дентальная); ***USA***: Albafort; Feocyte; FeoGen; Geritonic; I-L-X; Iron Complex; Multigen; Trimagen†; Vitagen Advance.

Homoeopathic Preparations. ***Austral.***: Oscillococcinum; ***Austria***: Berberis Cosmoplex†; ***Canad.***: Complete Flu Care 4 Kids†; Fibromyalgie; Homeocoksinum; Hylands Flu; Hylands Formula F; Oscillococcinum; ***Cz.***: Dolicoccil†; Stodal; Zeel Salbe†; ***Fr.***: Enterokinasum Compose; Hepatodrainol; Hypophysis Complexe No 31†; Oscillococcinum; ***Ger.***: AntiFocal Nr 69-Sol L†; Conisan A†; Conisan B†; Conjunctisan-AN†; Conjunctisan-BN†; Crataegus comp; EK Burger†; Glandulae-F-Gastreu R20; Hepar comp; Hepar-Magnesium; Hepar-Stannum†; Hewelymphon N†; Infihepan; Mucosa compositum; Ney Opin Nr 58; NeyArthros Nr 43-Sol†; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; NeyAthos Nr 43; NeyChon Nr 68; NeyChondrin Nr 68-Sol†; NeyDil Nr 66†; NeyDIL Nr 70; Neydin-F†; Neydin-M†; NeyDop Nr 97; Ney-Faexan Nr 55; NeyFegan Nr 26; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A; NeyIm Nr 73 pro injectione; NeyImmun Nr 73-Sol†; NeyLing Nr 66; Ney-Normin Nr 65; NeyPson Nr 5; NeySol L 66†; NeyTroph Nr 96 oral†; NeyTroph Nr 96 pro injectione; NeyTroph Nr96-Sol†; Sanochond; ***Hung.***: Dolicoccil; Oscillococcinum; Zeel; ***Neth.***: Chavita 6; Emvita 10; Emvita 11; Emvita 26; Geovita; Hepatodrainol†; Neurovita; Oscillococcinum; Urtizon complex; ***Port.***: Hepatodrainol; Oscillococcinum; ***Rus.***: Oscillococcinum (Оциллококцинум); Zeel T (Цель Т); ***Switz.***: Fluzinum; Influostim; Oscillococcinum; ***Ukr.***: Oscillococcinum (Оцилококцинум); Stodal (Стодаль).

Aniseed

Anice; Anis; Anis, fruit d'; Anís, semilla de; Anis Verde; Anis Vert; Anise; Anise Fruit; Anise Seed; Anisi fructus; Ánizstermés (fruit); Anyžių vaisiai (fruit); Anýzový plod (fruit); Owoc anyżu (fruit); Анис.

UNII — 21C2F5E8RE.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Aniseed; Anisi Fructus). The whole dried fruit of *Pimpinella anisum*, containing not less than 2% v/w of essential oil calculated with reference to the anhydrous drug. It has an odour reminiscent of anethole. Protect from light.

Profile

Aniseed is carminative and mildly expectorant; it is used mainly as anise oil or as preparations of the oil. It may cause contact dermatitis, probably due to its anethole content.

Aniseed is the source of anise oil (below).

References.

1. Chandler RF, Hawkes D. Aniseed—a spice, a flavor, a drug. *Can Pharm J* 1984; **117:** 28–9.
2. Fraj J, *et al.* Occupational asthma induced by aniseed. *Allergy* 1996; **51:** 337–9.
3. Garcia-Gonzalez JJ, *et al.* Occupational rhinoconjunctivitis and food allergy because of aniseed sensitization. *Ann Allergy Asthma Immunol* 2002; **88:** 518–22.
4. Gázquez García V, *et al.* Aniseed-induced nocturnal tongue angioedema. *J Investig Allergol Clin Immunol* 2007; **17:** 406–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Wunderbalsam; ***Austral.***: Colon Care; Detox Program; HRF; Neo-Cleanse; ***Austria***: Asthmatee EF-EM-ES; Brady's-Magentropfen; Euka; Hustensaft Weleda; ***Braz.***: Balsamo Branco; Camomila; ***Canad.***: Digestol; Floradix Kindervital†; Formula T4†; Herbal Laxative†; ***Chile***: Paltomiel; ***Fr.***: Elixir Bonjean†; Herbesan; Mucinum a l'Extrait de Cascara; Tisane Provencale no 5†; ***Ger.***: Floradix Multipretten N; Weleda Hustenelixier; ***Hung.***: Herbalakt; Salus Multipretten; ***Israel***: Jungborn†; ***Ital.***: Cadifen; Cadimint; Dicalmir; Tisana Kelemata; ***Neth.***: Verzachtende Hoestsiroop met tijm; ***Pol.***: Apinorm†; Syrop Sosnowy Zlozony; ***Port.***: Mucinum; ***Rus.***: Kliophyt (Клиофит); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Pectorales Species No 3 (Грудной Сбор 3); ***S.Afr.***: Clairo†; Cough Elixir†; Fragador†; ***Spain***: Crislaxo; Laxante Sanatorium†; ***Swed.***: Alpenkraft; Multipretten; ***Switz.***: Elixir contre la toux†; Kernosan Elixir; Kernosan Heidelberger Poudre; Metabol; Tisane favorisant l'allaitement; ***Turk.***: Naneson; ***UK***: Herb and Honey Cough Elixir; Revitonil; ***Ukr.***: Liponorm (Липонорм); Vitrum Beauty Elite (Витрум Бьюти Элит).

Homoeopathic Preparations. ***Canad.***: Voxpax†; ***Fr.***: Voxpax; ***UK***: Cough Elixir; Fragador; Laxadoron.

Anise Oil

Anís, aceite esencial de; Anis, huile essentielle d'; Aniseed Oil; Anisi Aetheroleum; Anisi Etheroleum; Anisöl; Anisolja; Anisöljy; Ánizsolaj; Anyžių eterinis aliejus; Anýzová silice; Esencia de Anís; Essence d'Anis; Olejek anyżowy; Oleum Anisi; Анисовое Масло.

*ATC Herb — HR05WA5032 (*Pimpinella anisum*: essential oil); HA03AW5048 (*Pimpinella anisum*: fruit); HR05WA5033 (*Pimpinella anisum*: fruit); HA03AW5047 (*Pimpinella anisum*: essential oil).*

UNII — 6Y89129C8H.

NOTE. The name anise oil is also applied to Star Anise Oil, p. 2622.2.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8 (Anise Oil; Anisi Aetheroleum). An essential oil obtained by steam distillation from the dry ripe fruits of *Pimpinella anisum*. It contains less than 1.5% linalol, 0.5 to 5.0% estragole, less than 1.2% α-terpineol, 0.1 to 0.4% *cis*-anethole, 87 to 94% *trans*-anethole, 0.1 to 1.4% anisaldehyde, and 0.3 to 2.0% pseudoisoeugenyl 2-methylbutyrate. A clear, colourless or pale yellow liquid. Relative density 0.980 to 0.990. F.p. 15 degrees to 19 degrees. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Anise Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* (Apiaceae) or from the dried ripe fruit of *Illicium verum* (Illiaceae). Congealing temperature not lower than 15 degrees. Soluble 1 in 3 of alcohol (90%). Store in well-filled airtight containers. If solid material has separated, carefully warm the oil until it is completely liquefied, and mix before using.

Incompatibility. PVC bottles softened and distorted fairly rapidly in the presence of anise oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Profile

Anise oil is carminative and mildly expectorant and is a common ingredient of cough preparations. It is also a flavour. Anise oil is used in aromatherapy.

It may cause contact dermatitis, probably due to its anethole content.

For references to aniseed and anise oil, see Aniseed, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Paranix; ***Austral.***: Digestive Aid; Gartech†; Moov Head Lice Shampoo; ***Austria***: Bradosol; Bronchostop; Heumann's Bronchialtee; Kamillosan; Luuf-Hustentee; Neo-Angin; ***Canad.***: Anifen†; ***Cz.***: Bronchosan†; Neo-Angin; Stopangin; Stopangin; ***Fr.***: Aromadetox†; Aromadigest†; Paregorique†; ***Ger.***: Bronchoforton†; Ephepect-Pastillen N; Floradix Multipretten N; Heumann Bronchialtee Solubifix T; Kamillosan Mundspray†; Paranix; Pulmotin; Repha-Os†; Salviathymol N; Sinuforton†; Verdauungstropfen Gastrofunkten†; ***Hong Kong***: Ephepect Blocker; ***Hung.***: Carmol; Salus Multipretten; ***India***: Bestozyme P; Bestozyme; Kamillosan-N; Merozyme-C; Neopeptine; ***Indon.***: Bital; Minyak Telon Cap Tiga Anak†; OBH; Silex; Telon 3 Anak; ***Neth.***: Bronchicum; ***Philipp.***: Kamillosan M; ***Pol.***: Carmolis; Herbolen D†; Tobacoff; ***Rus.***: Bronchosan (Бронхосан); Carmolis (Кармолис); Carmolis

Fluid (Кармолис Жидкость); Mixture Conta Tussis for Adults (Микстура От Кашля Для Взрослых); Mixture Conta Tussis for Children (Микстура От Кашля Для Детей); Pectorales Elixir (Грудной Эликсир); Stopangin (Стопангин); ***S.Afr.***: Borsdruppels; Paragoriese-Elikser†; Puma Cough Balsam†; ***Spain***: Carminativo Juventus; H Tussan†; ***Switz.***: DemoPectol; Impuls pastilles pour les bronches; Kamillosan; Makaphyt Gouttes antitussives†; Odontal; Paranix; Pastilles bronchiques S; Pastilles pectorales du Dr. Welti; Penta†; Rotpunkt Apotheke pastilles pour les bronches avec codeine; ***Thai.***: Corinap; Gas-Nep; Mesto-Of; Rheum; ***Turk.***: Myo-Oil; ***UK***: Hactos; Honey & Molasses; Lightning Cough Remedy; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Slippery Elm Stomach Tablets; Vegetable Cough Remover; Zubes Blackcurrant; Zubes; ***Ukr.***: Bronchial Balsam Bells (Бронхиальный Бальзам Беллс); Bronchosan (Бронхосан)†; Kofanol (Кофанол)†; Stopangin (Стопангин); Stopangin (Стопангин).

Pharmacopoeial Preparations

BP 2014: Camphorated Opium Tincture; Compound Orange Spirit; Concentrated Anise Water; Concentrated Camphorated Opium Tincture;

USNF 31: Compound Orange Spirit.

Anisodamine

6-Hydroxy-hyoscyamine.

$C_{17}H_{23}NO_4$=305.4

CAS — 55869-99-3.

UNII — 01343Q8EL8.

Pharmacopoeias. *Chin.* has a monograph for Raceanisodamine and Anisodamine Hydrobromide.

Profile

Anisodamine is an alkaloid isolated from *Scopolia tangutica* (*Anisodus tanguticus*), a plant used as a traditional medicine in China. It is related to atropine and hyoscyamine and has similar antimuscarinic properties (p. 1310.3). Anisodamine is given orally for its spasmolytic actions in the treatment of gastrointestinal spasm. It has also been tried in circulatory disorders, septic shock, and organophosphorus poisoning.

References.

1. Poupko JM, *et al.* The pharmacological properties of anisodamine. *J Appl Toxicol* 2007; **27:** 116–21.
2. Fu XH, *et al.* Effect of intracoronary administration of anisodamine on slow reflow phenomenon following primary percutaneous coronary intervention in patients with acute myocardial infarction. *Chin Med J (Engl)* 2007; **120:** 1226–31.

Antimony

Antimoine; Antimon; Antimonio; Stibium; Сурьма.

Sb=121.76

CAS — 7440-36-0.

UNII — 9IT35J3UV3 (antimony); 069647RPT5 (antimony ion Sb^{3+}).

Antimony Arsenate

AsO_4Sb=260.7

CAS — 28980-47-4.

UNII — WE3458XNFT.

Antimony Pentasulfide

Antimonial Saffron; Antimonium Sulfuratum Aureum; Antimony Red; Golden Antimony Sulfide.

Sb_2S_5=403.8

CAS — 1315-04-4.

UNII — 1433F1186N.

Antimony Trisulfide

Antimonous Sulfide; Antimony Glance; Antimony Sulfide; Antimony Sulphide; Antimony Trisulfide Colloid (USAN); Antimony Trisulphide; Needle Antimony; Stibnite.

Sb_2S_3=339.8

CAS — 1345-04-6.

UNII — F79059A38U.

Profile

Antimony is a semi-metal or metalloid. It exists in several oxidation states, of which the trivalent (3+) and pentavalent (5+) are most important. Antimony and its compounds (antimonials) have industrial uses and toxicity has been reported from occupational exposure. They have also been used medicinally, but less toxic compounds are usually preferred; trivalent antimony compounds (p. 151.2) have been used as anthelmintics while pentavalent antimony compounds (p. 926.3) are used in leishmaniasis.

Antimony trisulfide, as kohl, has been used in cosmetics. An antimony trisulfide colloid labelled with technetium-99m has been used in lymphoscintigraphy.

Homoeopathy

Antimony and its compounds, including the trisulfide, pentasulfide, and arsenate have been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Hamorrhoidal-Zapfchen.

Multi-ingredient Preparations. ***S.Afr.***: Heilsalbe†; Stibium Comp†; Wecesin†; ***Switz.***: Suppositoires contre les hemorroides; Wecesin.

Homoeopathic Preparations. ***Austral.***: IBS Eze; ***Austria***: Birkenkohle comp; Frostsalbe†; Gastricumeel; Globuli gegen Husten Nr 2; Lymphdiaral; ***Canad.***: Adrisin†; Cold Sores & Fever Blisters; Formula ES 211; Formula Homeo QR 209†; Fucus L111†; Headache & Migraine; Homeo-Form MI†; Homeoknop Bioactiv O Weight Loss Aid†; Hylavir FB†; Ind Complex†; War Complex†; ***Chile***: Bioactiv O; Lessfat; ***Fr.***: Abbe Chaupitre no 10†; Cina Compose; Fucus Complexe No 111; Ipeca Compose; Silicea Complexe No 11; Slimum†; Soreal; Verrulia; ***Ger.***: Birkenkohle comp; Broncho-Injektopas; Bronchopas; Gastritis Complex; Hautfunktionstabletten N; Hautfunktionstropfen N; Infifer N; Lymphdiaral sensitive N; Lymphdiaral; Nuxal comp; Nuxal H; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Rufebran bronchot; Sinupas; Tussistin S; Wecesin; Weleda Heilsalbe; ***Neth.***: Apo-STOM; Cutis comp; Gastricumeel; Kind 0-6 Tussikind; Kind 0-6 Tussikind; Lymphdiaral; Phonix Hydrargyrum; Phonix Solidago comp; Tussistin; ***S.Afr.***: Achillea Comp†; Hamamelis Comp†; ***Switz.***: Gastricumeel; ***UK***: Balsamicum; Frost Cream; WCS Dusting Powder.

Apis Mellifera

Abeille domestique; Abeja de la Miel; The honey bee; Медоносная Пчела Домашняя.

UNII — 7S82P3R43Z (Apis mellifera); 76013O881M (Apis mellifera venom).

Pharmacopoeias. *Eur.* (see p. vii) includes the live worker honey bee for homoeopathic preparations.

Ph. Eur. 8: (Honey Bee for Homoeopathic Preparations; Apis Mellifera ad Praeparationes Homoeopathicas). Live worker honey bee, *Apis mellifera.*

Profile

The honey bee, *Apis mellifera*, is a source of purified honey (p. 2072.1), royal jelly (p. 2608.1), propolis (p. 2597.3), beeswax (p. 2170.2) and bee pollen (see Pollen and Pollen Extracts, p. 2593.3).

Homoeopathy

Preparations of *Apis mellifera* have been used in homoeopathic medicines under the following names: Apis; Apis mellifica; Apis mel; Apis mell.

Allergen immunotherapy. For reference to the use of whole body extracts or venom from Hymenoptera spp. for allergen immunotherapy in allergic subjects, see p. 2435.1.

Arthritis. Bee venom has traditionally been used in the treatment of arthritis.[1,2] Studies *in vitro* have shown that bee venom has anti-inflammatory activity similar to that of cyclophosphamide. Melittin appears to be the active constituent, and seems to act by interfering with superoxide radical production from human leucocytes.[1]

1. Somerfield SD. Bee venom and arthritis: magic, myth or medicine? *N Z Med J* 1986; **99:** 281–3.
2. Caldwell JR. Venoms, copper and zinc in the treatment of arthritis. *Rheum Dis Clin North Am* 1999, **25:** 919–28.

Hypersensitivity. There were 14 reports of suspected adverse effects (10 considered serious), including allergic reactions, involving bee products such as bee pollen (p. 2593.3), propolis (p. 2597.3), and royal jelly (p. 2608.1) reported to the Canadian health authorities (Health Canada) between January 1998 and October 2004.[1]

There have also been reports of allergic contact dermatitis to **propolis** identified through patch testing,[2,3] and a case of occupational contact dermatitis.[4]

Anaphylactoid reactions[5] and acute severe exacerbations of asthma[6-9] (one fatal[7]) have occurred in atopic individuals who took **royal jelly**.

Hypersensitivity reactions to topical **beeswax** (p. 2170.2) products have been reported rarely. Contact dermatitis from use of a beeswax-based nipple protector has been reported,[10] and cheilitis from beeswax lip products has also occurred.[11] In some,[10,12] but not all,[11] cases, sensitivity may be related to propolis content in beeswax.

1. Health Canada. Products derived from bees: serious adverse reactions. *Can Adverse React News* 2005; **15** (2): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2eng.pdf (accessed 08/08/08)
2. Giusti F, *et al.* Sensitization to propolis in 1255 children undergoing patch testing. *Contact Dermatitis* 2004; **51:** 255–8.
3. Walgrave SE, *et al.* Allergic contact dermatitis from propolis. *Dermatitis* 2005; **16:** 209–15.
4. Lieberman HD, *et al.* Allergic contact dermatitis to propolis in a violin maker. *J Am Acad Dermatol* 2002; **46** (suppl): S30–S31.
5. Takahama H, Shimazu T. Food-induced anaphylaxis caused by ingestion of royal jelly. *J Dermatol* 2006; **33:** 424–6.
6. Thien FCK, *et al.* Royal jelly-induced asthma. *Med J Aust* 1993; **159:** 639.
7. Bullock RJ, *et al.* Fatal royal jelly-induced asthma. *Med J Aust* 1994; **160:** 44.
8. Peacock S, *et al.* Respiratory distress and royal jelly. *BMJ* 1995; **311:** 1472.
9. Thien FCK, *et al.* Asthma and anaphylaxis induced by royal jelly. *Clin Exp Allergy* 1996; **26:** 216–22.
10. García M, *et al.* Allergic contact dermatitis from a beeswax nipple-protective. *Contact Dermatitis* 1995; **33:** 440–1.
11. Lucente P, *et al.* Contact cheilitis due to beeswax. *Contact Dermatitis* 1996; **35:** 258.
12. Jacob SE, *et al.* Allergic contact dermatitis to propolis and carnauba wax from lip balm and chewable vitamins in a child. *Contact Dermatitis* 2008; **58:** 242–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Joint & Muscle Cream; ***Canad.***: Libeeda for Men; ***Cz.***: Apisarthron†; ***Hung.***: Apisarthron; Melliora; Rheudol; ***Rus.***: Apisarthron (Апизартрон); ***S. Afr.***: Bolus Eucalypti Comp†; ***Ukr.***: Apisarthron (Апизартрон).

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Joint & Muscle Oral Spray†; Respatona Sore Throat; Snore Eze; Sports Ice Joint & Muscle; ***Austria***: Apozema Allium Cepa compositum; Apozema Apis compositum; Bolus Eucalypti Comp; Erbiode Allergie; Erysidoron Nr 1; Globuli gegen Halsweh Nr 2; Globuli gegen Heiserkeit; Iris Med Complex; ***Canad.***: Angeel†; Arnica-Heel Comp†; Arthritic Pain; Cruroheel S†; EnurAid; Erysidoron 1†; Execalm†; Hay Fever; Hives; Homeo-Form AR†; Hylands Formula E; Larydol†; Lympatox; Pollen Plus; Renelix; SK Complex†; ***Chile***: Apis Compuesto; ***Cz.***: Angin-Heel S; Galium; ***Fr.***: Aconitum Compose†; Agnus Castus Complexe No 2†; Angipax; Boripharm No 10†; Dermo-Drainol†; Euphrasia Complexe No 115; Mercurius Cyanatus Complexe No 43†; Natrum Carbonicum Complexe No 10†; ***Ger.***: Allergo-Loges; Angi Truw N; Angina-Gastreu S R1; Arnica comp/Apis†; Arthriplex; Arthrokatt; Dermi-cyl L Ho-Len-Complex; Desarell; Erysidoron 1; Febro-cyl L Ho-Len-Complex; Flenin; Genu-cyl L Ho-Len-Complex; HanoToxin M; Hanotoxin M; Hevertotox; Hewallergia Complex; Infekt-Komplex L Ho-Fu-Complex; Influex; Lowe-Komplex Nr 13; Lowe-Komplex Nr 5 Echinacea; Ossidal; Pascodem; Pascorenal N; Pascorenal-Injektopas; Pulmosan Infekt; Regasinum antallergicum; Sinusitis Hevert SL; Solidago Hevert Complex; Solidagosan N; toxi-loges; Toxiselect; Zahnungstropfen Escatitona; ***Hung.***: Angin-Heel; ***Neth.***: Akutur spag; Arnilite; Belachin-Gastreu R1; Echilite; Emvita 15; Emvita 20; Emvita 3; Emvita 4; Gynaelite; Homeocare keelspray; Lergilite; Prurilite; Urtizon complex; Vinceel H; ***Rus.***: Climaxan (Климаксан); Dysmenorm (Дисменорм); Ruta-Plus (Рута-Плюс); Urtica-Plus (Уртика-Плюс); ***S.Afr.***: Berberis/Cantharis Comp†; Erysidoron 1†; ***Switz.***: Akutur; HerbAllerg; Regenaplex Nr 28a; Regenaplex Nr. 50b; ***UK***: Bolus Eucalypti Comp; Erysidoron 1; ***Ukr.***: Dysmenorm (Дисменорм.); Incena (Инцена); ***USA***: Preferred Remedies Allergy.

Apricot

Абрикос.

UNII — 10TCS27K2T (Prunus armeniaca); 269CJD5GZ9 (Prunus armeniaca fruit); YX3B7ZG375 (Prunus armeniaca juice); 0X5YG5R83N (Prunus armeniaca leaf); 75356789IW (Prunus armeniaca seed).

Pharmacopoeias. *Chin.* includes Bitter Apricot Seed, the kernel obtained from various species of *Prunus*. *Jpm* includes a monograph for Apricot Kernel.

Profile

The kernels of the apricot, *Prunus armeniaca* (*Armeniaca vulgaris*; *P. tiliifolia*) (Rosaceae), are used in Chinese medicine for disorders of the respiratory tract and for constipation.

Apricot is a source of persic oil (p. 2587.1). Amygdalin, the major cyanogenic glycoside of apricot kernels, is the major constituent of laetrile (p. 2539.3). Apricot kernels are also a source of pangamic acid (p. 2582.1).

Apricot fruits are used as a food.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Jpn***: Colgen Maoto; Gokoto; Junchoto; Makyokansekito; Makyoyokukanto; Maoto; Mashiningan; Ryokankyomishingeninto; Seihaito; Shimpito; ***Singapore***: New Tonin Troche; ***Ukr.***: Ventero-Nova (Вентеро-Нова).

Aptiganel *(pINN)*

Aptiganelum; Аптиганел.

1-(*m*-Ethylphenyl)-1-methyl-3-(1-naphthyl)guanidine.

$C_{20}H_{21}N_3$=303.4

CAS — 137159-92-3.
UNII — 46475LV84I.

Aptiganel Hydrochloride *(USAN)*

CNS-1102.
$C_{20}H_{21}N_3$,HCl=339.9
CAS — 137160-11-3.
UNII — 40PWH14OXW.

NOTE. The name Cerestat has been used as a trade mark for aptiganel hydrochloride.

Profile

Aptiganel is a guanidine derivative that antagonises the effects of the excitatory amino-acid neurotransmitter glutamate at NMDA-receptors. It has been given intravenously in the investigation of the prevention of ischaemic brain damage in patients with traumatic head injury or stroke.

After dose-ranging studies of aptiganel in healthy subjects[1] and in patients,[2] adverse effects reported[3] in patients with acute ischaemic stroke, at doses that had been neuroprotective in *animals*, included an increase in systolic blood pressure and an excess of CNS effects. A randomised controlled study[4] in patients with acute ischaemic stroke was suspended because of a lack of efficacy and a potential imbalance in mortality compared with placebo.

1. Muir KW, *et al.* Pharmacological effects of the non-competitive NMDA antagonist CNS 1102 in normal volunteers. *Br J Clin Pharmacol* 1994; **38:** 33–8.
2. Block GA, *et al.* Final results from a dose-escalating safety and tolerance study of the non-competitive NMDA antagonist CNS1102 in patients with acute cerebral ischaemia. *Stroke* 1995; **26:** 185.
3. Dyker AG, *et al.* Safety and tolerability study of aptiganel hydrochloride in patients with an acute ischemic stroke. *Stroke* 1999; **30:** 2038–42.
4. Albers GW, *et al.* Aptiganel hydrochloride in acute ischemic stroke: a randomized controlled trial. *JAMA* 2001; **286:** 2673–82.

Arachidonic Acid

(all-*Z*)-Eicosatetraenoic Acid.
(5*Z*,8*Z*,11*Z*,14*Z*)-5,8,11,14-Eicosatetraenoic acid.
$C_{20}H_{32}O_2$=304.5
CAS — 506-32-1 ((all-Z)-eicosatetraenoic acid); 7771-44-0 (eicosatetraenoic acid).
UNII — 27YG812J1I.

Profile

Arachidonic acid is an omega-6 polyunsaturated fatty acid and is an important component of mammalian cell membranes; it acts as a precursor for the production of some eicosanoids such as prostaglandins (see p. 2598.1). Arachidonic acid is a n essential fatty acid and has been used in nutritional supplements for infants. Its role as a supplement in adults is controversial.

References.
1. Calder PC. Dietary arachidonic acid: harmful, harmless or helpful? *Br J Nutr* 2007; **98:** 451–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Cycloferon (Циклоферон); ***Ukr.***: Cycloferon (Циклоферон).

Multi-ingredient Preparations. ***Indon.***: Biolysin Smart; Brainvit; Cerebrofort AA+DHA; Cerebrofort Gold; Curfos; Curvit CL; Folamil Genio; Lysmin Plus; Mulsanol; Natavit; Prokids; ***NZ***: Efanatal; ***Singapore***: Dhaxtra; Mumomega Equazen†; Nata-Boost; Natal Care.

Arachis Oil

Aceite de maní; Arachide, huile d', raffinée; Arachidis Oleum; Arachidis Oleum Raffinatum; Cacahuete, aceite de; Earth-nut Oil; Erdnussöl; Finomított földimogyoróolaj; Ground-nut Oil; Huile d'Arachide; Jordnötolja, raffinerad; Maapähkinäöljy, puhdistettu; Nut Oil; Ol. Arach.; Olej arachidowy oczyszczony; Óleo de Amendoim; Oleum Arachis; Peanut Oil; Podzemnicový olej čištěný; Refined Arachis Oil; Žemės riešutų aliejus; Yerfıstığı Yağı; Масло Земляного Ореха; Арахисовое Масло.
*ATC Herb — HB05BA5001 (*Arachis hypogaea*: oil); HD02WB5001 (*Arachis hypogaea*: oil).*
UNII — 5TL50QU0W4.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn*. Also in *USNF*.

Eur. also includes hydrogenated arachis oil.

Ph. Eur. 8: (Arachis Oil, Refined; Arachis Oil BP 2014). The refined fatty oil obtained from the shelled seeds of *Arachis hypogaea*. A suitable antoxidant may be added. It is a clear, yellowish viscous liquid consisting of glycerides, chiefly of oleic and linoleic acids, with smaller amounts of other acids. It solidifies at about 2 degrees. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

The BP 2014 gives Ground-nut Oil and Peanut Oil as approved synonyms.

Ph. Eur. 8: (Arachis Oil, Hydrogenated; Arachidis Oleum Hydrogenatum). Arachis oil that has been refined, bleached, hydrogenated, and deodorised. It is a white or faintly yellowish soft mass that melts to a clear pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65 degrees to 70 degrees). Protect from light.

USNF 31: (Peanut Oil). The fully-refined (alkali-refined, bleached, and deodorised at 230 degrees to 260 degrees) oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* (Leguminosae). It is a colourless or pale yellow, oily liquid with a bland taste; it may have a characteristic nutty odour. Very slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Profile

Emulsions containing arachis oil are used in nutrition. Arachis oil is given as an enema for softening impacted faeces. It is used in drops for softening ear wax (see under Docusates, p. 1836.3) and in emollient creams. Arachis oil is given orally, usually with sorbitol, as a gallbladder evacuant before cholecystography.

Precautions. It has been suggested that the use during infancy of preparations containing arachis oil, including infant formulas and topical preparations, may be responsible for sensitisation to peanut, with a subsequent risk of hypersensitivity reactions.[1-3] The arachis oil used in such preparations is refined oil and it has been pointed out that such oil should not contain the proteins that produce allergic reactions in susceptible people.[4,5] In the USA, heating of arachis oil during preparation, to further reduce protein content, has been proposed.[6] Nonetheless, some consider that sufficient protein may be present in refined oil to cause sensitisation.[7] However, others have pointed out that to date, there are no reliable data about doses of topical arachis oil needed to induce sensitisation via the epidermal route and that the benefit of protecting skin barrier functions in atopic patients with products using refined arachis oil outweigh possible risks of sensitisation.[8] In the UK, the CSM considered that there was not enough evidence to conclude that medicinal products containing arachis oil could lead to sensitisation.[9] However, although they considered the risk of a reaction to be low, they recommended that patients known to be allergic to peanuts should not use medicines containing arachis oil (nor, because of the possibility of cross-sensitivity, should patients allergic to soya), and that such medicines should include an appropriate warning in the labelling.

1. de Montis G, *et al.* Sensitisation to peanut and vitamin D oily preparations. *Lancet* 1993; **341:** 1411.
2. Lever LR. Peanut and nut allergy: creams and ointments containing peanut oil may lead to sensitisation. *BMJ* 1996; **313:** 299.
3. Lack G, *et al.* Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; **348:** 977–85.
4. Hourihane J O'B, *et al.* Randomised, double blind, crossover challenge study of allergenicity of peanut oil in subjects allergic to peanuts. *BMJ* 1997; **314:** 1084–8.
5. Committee on Toxicity of chemicals in Food, Consumer Products and the Environment. *Peanut allergy.* London: DoH, 1998.
6. Wilkin JK, *et al.* Peanut allergy. *N Engl J Med* 2003; **349:** 302.
7. Lack G, *et al.* Peanut allergy. *N Engl J Med* 2003; **349:** 302–3.
8. Ring J, Möhrenschlager M. Allergy to peanut oil — clinically relevant? *J Eur Acad Dermatol Venereol* 2007; **21:** 452–5.
9. CSM/MHRA. Medicines containing peanut (arachis) oil. *Current Problems* 2003; **29:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074508&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Oilatum†; ***Denm.***: Olie†; ***Fin.***: Calogen; ***Ger.***: Olbad Cordes F†; ***Indon.***: Oilatum Cream†; ***Irl.***: Fletcher's Arachis Oil†; ***Ital.***: Calogen; ***Mex.***: Dermo Bell; Nutrisil; Oilatum; ***NZ***: Calogen; ***S.Afr.***: Oilatum Cream†; ***UK***: Calogen.

Multi-ingredient Preparations. ***Austral.***: Cerumol; ***Austria***: Balneum F; ***Cz.***: Balneum Hermal F; ***Ger.***: Balneum F; ***Hung.***: Balneum Hermal F; ***India***: Oliade Bath; ***Irl.***: Cerumol; Earex†; Polytar Emollient; Polytar; ***Israel***: Balneum F; Cerumol; ***Ital.***: Balneum Hermal Forte; ***Pol.***: Balneum Hermal F†; ***S.Afr.***: Cerumol; Haarlemensis; ***Singapore***: Cerumol; Earex; ***Spain***: Emolytar†; ***Switz.***: Balmed Hermal F; ***UK***: Cerumol; Earex; Hewletts†; Nowax; Red Oil; Soothol; ***Venez.***: Nutricap.

Pharmacopoeial Preparations
BP 2014: Arachis Oil Enema.

Areca

Areca Nuts; Arecae Semen; Arekasame; Betel; Betel Nuts; Noix d'Arec; Nuez de areca; Nuez de betel; Арека.
UNII — 483O0360NZ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of areca:
Daka; Gua; Maag; Mak; Marg; Pan parag; Pinang; Pugua; Puwak; Supai; Suparim.

Pharmacopoeias. In *Chin.* and *Jpn*.

Uses and Administration

Areca consists of the dried ripe seeds of *Areca catechu* (Palmae) containing the alkaloid arecoline.

Areca is used in Asian countries as a masticatory. It has sialogogue properties and is chewed for its mild intoxicant and euphoriant effects. The usual custom is to chew pieces of areca seed (areca nut; betel nut) wrapped with lime (calcium hydroxide) in the leaf of the betel pepper (betelvine) (*Piper betle*, which is unrelated to areca). This preparation is known as 'betel quid' (betel) or 'paan' (pan-masala), and produces a red juice when chewed, which stains the saliva, teeth and mucosa. Other ingredients that might be added include catechu gum, spices, or tobacco.

Areca was formerly used in the treatment of tapeworm infection, and arecoline has been used in veterinary medicine as a purgative and taenifuge.

Adverse Effects

Arecoline and arecaidine (produced by the hydrolysis of arecoline when chewed with lime—see Uses and Administration, above) have cholinergic activity, and adverse effects that may occur with initial or heavy use of areca include excessive salivation, sweating, lachrymation, urinary incontinence, or diarrhoea. An increased incidence of oral submucosal fibrosis, oral leucoplakia, and oral squamous cell carcinoma has been reported following habitual use.

Areca chewing. Discussions of the health risks associated with the chewing of preparations containing areca nut by indigenous populations in Asia[1-3] and immigrant groups in the UK,[4] USA,[5] and New Zealand,[6] including acute effects.[2,3,5] See also Adverse Effects of Tobacco Products under Nicotine (p. 2571.2) for reference to mixtures of areca and tobacco.

1. Mack TM. The new pan-Asian paan problem. *Lancet* 2001; **357:** 1638–9.
2. Deng JF, *et al.* Acute toxicities of betel nut: rare but probably overlooked events. *J Toxicol Clin Toxicol* 2001; **39:** 355–60.
3. Chu NS. Effects of betel chewing on the central and autonomic nervous systems. *J Biomed Sci* 2001; **8:** 229–36.
4. Warnakulasuriya S, *et al.* Areca nut use: an independent risk factor for oral cancer. *BMJ* 2002; **324:** 799–800.
5. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
6. Yoganathan P. Betel chewing creeps into the New World. *N Z Dent J* 2002; **98:** 40–5.

Carcinogenicity. Precancerous and cancerous conditions of the oral cavity have been attributed to the chewing of preparations containing areca (see Uses and Administration, above). In betel-chewer's mucosa, the oral mucosa is discoloured and there is desquamation or peeling of the oral epithelium from the traumatic effect of chewing and possibly a chemical action of the constituents. This condition may be a precursor of oral submucosal fibrosis, which is considered to be precancerous.[1] Oral leucoplakia is another precancerous condition that is reported. The role of areca in the development of these conditions and oral squamous cell carcinoma has been debated. The effects may be due to the arecaidine content of areca, the alkalinity of the lime, presence of tobacco, or a combination of these.[2,3] Results from a case-controlled study[4] point to an independent association between oral squamous cell carcinoma and chewing areca seeds in preparations without tobacco compared with non-users of areca. A review[5] of available evidence strongly supports this association.

1. Reichart PA, Philipsen HP. Betel chewer's mucosa—a review. *J Oral Pathol Med* 1998; **27:** 239–42.
2. Norton SA. Betel: consumption and consequences. *J Am Acad Dermatol* 1998; **38:** 81–8.
3. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
4. Merchant A, *et al.* Paan without tobacco: an independent risk factor for oral cancer. *Int J Cancer* 2000; **86:** 128–31.
5. Nair U, *et al.* Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis* 2004; **19:** 251–62.

Effects on the lungs. Evidence suggesting that there is an association between betel-nut chewing and bronchoconstriction in asthmatic patients.[1,2]

1. Taylor RFH, *et al.* Betel-nut chewing and asthma. *Lancet* 1992; **339:** 1134–6.
2. Kiyingi KS. Betel nut chewing and asthma. *Lancet* 1992; **340:** 59–60.

Effects on the nervous system. Areca-nut (betel-nut) chewing is associated with habituation, addiction, and dependence,[1] and CNS symptoms of withdrawal have been described in 2 patients.[2] A case of neonatal withdrawal syndrome in an infant born to a chronic areca-nut user has also been reported.[3] Psychosis has also been reported.[1]

It has been suggested that the muscarinic action of areca alkaloids may have a beneficial effect on symptoms of schizophrenia, and a study of such patients in a Micronesian population provides some support for this idea.[4] However, severe extrapyramidal symptoms followed betel-nut chewing in 2 patients with chronic schizophrenia who were also receiving antipsychotic therapy.[5]

1. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
2. Wiesner DM. Betel-nut withdrawal. *Med J Aust* 1987; **146:** 453.
3. López-Vilchez MA, *et al*. Areca-nut abuse and neonatal withdrawal syndrome. Abstract: *Pediatrics* 2006; **117:** 203. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/1/e129.pdf (accessed 16/08/10)
4. Sullivan RJ, *et al*. Effects of chewing betel nut (Areca catechu) on the symptoms of people with schizophrenia in Palau, Micronesia. *Br J Psychiatry* 2000; **177:** 174–8.
5. Deahl MP. Psychostimulant properties of betel nuts. *BMJ* 1987; **294:** 841.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Good Time; Herr; Himplasia; Lukol; ***Jpn***: Nyoshinsan; ***Ukr.***: Evica (Евика)†.

Aristolochia

Serpentaria.

CAS — 313-67-7 (aristolochic acid).

NOTE. *Aristolochia clematitis* has also been known as asarabacca (p. 2449.3).

Pharmacopoeias. In *Chin.* as Herba Aristolochiae (Tianxianteng; Dutchman's Pipe Vine), which allows *Aristolochia debilis* or *A. contorta*.

Uses and Administration

Aristolochia spp. (birthworts) including *A. clematitis* and *A. labiata (A. brasiliensis)* have been used in herbal medicine. Chinese medicine has employed various species of *Aristolochia* including *A. contorta, A. debilis,* and *A. manshuriensis*. The terms Mu Tong and Fangji have been used for *Aristolochia* spp. in traditional medicine.

Serpentary (serpentaria) is the dried rhizome and roots of *Aristolochia serpentaria* (Virginian snakeroot) and of *A. reticulata* (Texan snakeroot) (Aristolochiaceae). However, snakeroot is also used as a common name to describe poisonous *Eupatorium* spp. Preparations of serpentary have been used as bitters.

The active ingredient is aristolochic acid, which has been tried in inflammatory disorders, mainly in folk medicine; the sodium salt of aristolochic acid has also been used. However, there is concern over the use of *Aristolochia* and aristolochic acid because of serious toxicity and preparations have been banned in some countries—see below

Adverse Effects

Chronic ingestion of aristolochic acid present in *Aristolochia* spp. has been associated with serious nephrotoxicity and carcinogenicity.

Effects on the kidneys. Progressive interstitial fibrosis of the kidney related to a slimming regimen containing Chinese herbs had been reported in 70 patients in Belgium by 1993; 30 of these patients had terminal renal failure.[1] Renal failure has also been reported[2] in 2 patients in the UK after ingestion of Chinese herbal medicines that were later found to contain aristolochic acid, a known nephrotoxin;[3] one of these patients subsequently developed invasive urothelial carcinoma.[4] Inadvertent ingestion of aristolochic acid can originate as a result of the substitution of *Aristolochia* spp. (probably *A. manshuriensis*) for other innocuous herbal substances;[2,5] the Belgian cases were probably as a result of substitution of *A. fangchi* extracts for *Stephania tetrandra*.[1] As a result of these cases, the UK MCA issued a permanent ban on *Aristolochia* preparations in 1999. Similar bans have been made in several other countries;[3] in 2004, the Chinese regulatory authority also banned the use of *A. fangchi* and *A. debilis* in traditional medicine formulations. Examination of 39 patients in Belgium with nephropathy associated with *A. fangchi* ingestion had revealed 18 cases of urothelial carcinoma and evidence of mild to moderate dysplasia in 19 patients.[6] There had appeared to be a higher risk of carcinoma with total doses of *A. fangchi* in excess of 200 g.

Aristolochic acid has been proposed as the cause of endemic (Balkan) nephropathy,[7] which is confined to a very specific rural geographical distribution and first described in the 1950s. Data supporting this hypothesis included findings of DNA damage linked to aristolochic acid in kidney samples from affected patients, as well as renal failure in horses who had grazed in the local fields. *Aristolochia clematitis* is endemic to the region and has been found in fields cultivated for wheat grain. It is possible that the local population could be exposed to toxic amounts of aristolochic acid over time from bread made with grain contaminated with *A. clematitis* seeds.

1. Vanhaelen M, *et al*. Identification of aristolochic acid in Chinese herbs. *Lancet* 1994; **343:** 174.
2. Lord GM, *et al*. Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999; **354:** 481–2.
3. Cosyns JP. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. *Drug Safety* 2003; **26:** 33–48.
4. Lord GM, *et al*. Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 2001; **358:** 1515–6.
5. But PP, Ma S-c. Chinese-herb nephropathy. *Lancet* 1999; **354:** 1731–2.
6. Nortier JL, *et al*. Urothelial carcinoma associated with the use of a chinese herb (Aristolochia fangchi). *N Engl J Med* 2000; **342:** 1686–92.
7. Grollman AP, *et al*. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A* 2007; **104:** 12129–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Euserpina Cellulite.

Multi-ingredient Preparations. ***S.Afr.***: Borstol Cough Remedy†.

Homoeopathic Preparations. ***Canad.***: Detox L37; ***Switz.***: Menstruasan.

Arjuna

Arjun; Arjun Myrobalan.

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis,* Emblic Myrobalan — see Indian Gooseberry, p. 2532.2), *Prunus* (*P. cerasifera,* Myrobalan Plum), and *Terminalia* (*T. arjuna,* Arjun Myrobalan — Arjuna, above; *T. bellirica* — see Beleric Myrobalan, p. 2453.2; and *T. chebula* — see Chebulic Myrobalan, p. 2474.3). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. In *Br.*

BP 2014: (Terminalia Arjuna Stem Bark). The cut dried bark of the stems of *Terminalia arjuna*. It contains not less than 6% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The bark of arjuna, *Terminalia arjuna* (Combretaceae), is used in Ayurvedic medicine mainly for cardiovascular disorders. It is also included in herbal preparations for liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Herbadict; ***Pol.***: Liv 52; ***Rus.***: Liv 52 (Лив 52); Liv 52 (Лив 52); ***Singapore***: Liv 52; Liv 52; ***Switz.***: Liv 52; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Liv 52 (Лив 52); Trypsidan (Трипсидан)†.

Arnica

Árnica; Arnica, fleur d' (arnica flower); Arnicae Anthodium; Arnicae flos (arnica flower); Arnikų žiedai (arnica flower); Arnikablomma (arnica flower); Arnikinkukka (arnica flower); Arnikový květ (arnica flower); Hegyi árnika virág (arnica flower); Koszyczek arniki (arnica flower); Leopard's Bane; Mountain Tobacco; Wolf's Bane; Wolfsbane; Арника.

*ATC Herb — HD03WX5003 (*Arnica montana*: flower).*

*UNII — OZ0E5Y15PZ (*Arnica montana *flower); O80TY208ZW (*Arnica montana*); MUE8Y11327 (*Arnica montana *root).*

NOTE. Wolfsbane is also used as a common name for aconite (p. 2428.3).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Arnica Flower; Arnica Flos). It consists of the whole or partially broken, dried flowerheads of *Arnica montana*. It contains not less than 0.4% w/w of total sesquiterpene lactones expressed as dihydrohelenalin tiglate, calculated with reference to the dried drug. It has an aromatic odour. Protect from light.

Profile

Arnica is generally used in the form of the flowerheads of *Arnica montana* (Compositae).

Arnica flower is irritant to mucous membranes and when ingested has produced severe symptoms including gastrointestinal and nervous system disturbances, both tachycardia and bradycardia, and collapse. Tincture of arnica may cause dermatitis when applied to the skin of sensitive persons.

Preparations of arnica flower and arnica root are used as astringents for topical application to unbroken skin in conditions such as sprains and bruises; such preparations are not considered suitable for internal use. Arnica flowers are the source of arnica oil, which has been used similarly.

Herbal preparations containing arnica are available for oral use.

Brazilian arnica (*Solidago chilensis*, arnica do campo) has been used for external application similarly to arnica.

Homoeopathy

Arnica has been used in homoeopathic medicines under the following names: Arnica montana; Arnica, Flos; Arnica montana e flore; Arnica montana ex herba; Arnica, Planta tota; Arnica montana ex planta tota; Arnica montana, radix; Arnica, rad; Arn. mont. Some homoeopathic preparations are available for oral use.

References.

1. Leivers K. Unravelling the confusion around arnica's herbal and homoeopathic use. *Pharm J* 2005; **275:** 289–91.
2. Kouzi SA, Nuzum DS. Arnica for bruising and swelling. *Am J Health-Syst Pharm* 2007; **64:** 2434–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Sports Ice Bruising Relief; ***Belg.***: Arnican; ***Chile***: Arnikaderm; ***China***: Haojishi (Cool) (好及施 (冷感)); ***Fr.***: Arnicagel; Arnican; Arnigel; Pharmadose teinture d'arnica; ***Ger.***: Arnikatinktur; Arthrosenex N; Doc; ***Irl.***: Atrogel; ***Mex.***: Balsamo Nordin; Estimul; ***Port.***: Arnigel; ***Singapore***: SinEccH; ***Spain***: ArnicaMed; ***Switz.***: A Vogel Gel en cas de rhumatisme; AtroMed; ***UK***: Arnicare; Atrogel; Bumps & Bruises.

Multi-ingredient Preparations. ***Arg.***: CVP Cellulite; Fluido Spineda; Lavandula Oligoplex; ***Austral.***: Accelerex painEASE; Accelerex painEASE; Hernidisc; Joint & Muscle Cream; Percutane†; ***Austria***: Arnicet†; Asthmatee EF-EM-ES; Berggeist; Cional; Dynexan; Heparin Comp; Rheuma; ***Belg.***: Algi-Cool†; Purigel Crisp†; Purigel NF; ***Canad.***: Arnica Ointment†; ***Chile***: K-Gel; Lefkaflam; Matikomp; ***Cz.***: Arnidol; ***Fr.***: Arnicadol†; Decramp; Decramp; Dolores; Evarose†; Rap Phyto; Tigre de Chine; ***Ger.***: Combudoron; Dolo-cyl†; Gothaplast Rheumamed AC†; Kneipp Arnika Salbe S; Retterspitz Ausserlich; Retterspitz Quick Muskel; Sportino Akut†; Trauma-cyl†; Varicylum-S†; Weleda Hauttonikum†; ***Hong Kong***: New Patecs A†; ***Hung.***: Forte Hirudo; Kobralgin; Kovitox; Medhirud; Melliora; Rheudol; ***Irl.***: Combudoron†; Massage Balm with Arnica; ***Ital.***: Clebolider†; Criotonal; Flebolider; Flodolor; Lactacyd Lentivo; Proctocella Complex; Vaginol; Vasotonal; Venalta; Venoplant; Wasotonal†; ***Malaysia***: A-Bruzzy; Arnica Comp; ***Mex.***: Arnident; Norex; Reudol; ***Neth.***: Bioforce; ***Pol.***: Arcalen; Arnisol; Dentosept A; Dentosept; Emorect; Escalar; Prostapol; Reumobonisol; Stomatosol; Uroprost; Venoforton; ***Rus.***: Stomatophit (Стоматофит); ***S. Afr.***: Arnica Massage Oil; Combudoron†; Dynexan; Lotio Pruni Comp cum Cupro†; Muscle Rub†; Wecesin†; Zeel; ***Singapore***: A-Bruzzy; Scar Esthetique; ***Switz.***: Combudoron; DUL-X Cool; DUL-X warm; DUL-X; Euceta avec camomille et arnica; Fortacet†; Gel de consoude†; Mucosan†; Onguent aux herbes Keller; Perskindol Cool Arnica; Topaceta†; Venadoron; Wecesin; ***Turk.***: Symphosan; ***UK***: Arnica Massage Balm; Hansaplast Herbal Heat Plaster; Profelan; ***Ukr.***: Fitoval Shampoo Anti-Hair Loss (Фитовал шампунь против выпадения волос); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); ***USA***: Zim's Max Freeze; ***Venez.***: Andantol Jalea; Gelsem.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Echine†; Sports Ice Joint & Muscle; ***Austria***: Arnica Komplex†; Arnica Med Complex; Aurumheel; Frostsalbe†; Ledum Med Complex; Memoria; Pumpan; Remasan; Repisan; Rheuma; Rhus Med Complex; Secale Med Complex; Thuja Med Complex; Traumeel; Tropfen bei Verletzungen; Zom; ***Canad.***: Aches & Pains; Adrisin†; Angeel†; Arnica + Pain Relief; Arnica Cream†; Arnica-Heel Comp†; Arnicaid; Art Complex†; Arthritic Pain; Arthritis Pain Formula; Artis-Heel†; Ateria-Heel†; Aurumheel†; Backache with Arnica†; Barijodeel†; Bioactiv E†; Bioactiv R†; Bumps and Bruises; Calnor†; Capsicum + Arthri-Cream; Comp-Drops 9†; Drosera Complex; Drosera Plex†; Echinacea Compositum; Echinacea L40†; EnurAid; Fibromyalgie; Formula CI 207†; Formula Homeo QR 209†; Ginkgo-Comp†; Homeo-Form AR†; Homeo-S-Asp; Hylagesic APF; Hylands Formula E; Hylands Leg Cramps; Ikoplex 12†; Ivernax; Jet Lag; Kids Cough & Cold Phytux; Kids' Teething; L52 Cough & Cold; Lympatox; Osteel†; Phytotux H; Roxalia; Soludor†; Sportenine; Traumeel; Zeel Comp; ***Chile***: Anacardio con Fosforo; Arnica Compuesta; Arnica Hamamelis Compuesta; Bioactiv E; Bioactiv R; Grippakit; Ikoplex No 12; ***Cz.***: Angin-Heel S; Drosetux; Homeogene 9; Lehnigrip†; Paragrippe; Traumeel; Zeel Compositum; Zeel Salbe†; ***Fr.***: Abbe Chaupitre no 10†; Abbe Chaupitre no 13; Abbe Chaupitre no 15†; Abbe Chaupitre no 25†; Abbe Chaupitre no 30†; Acidum Phosphoricum Compose†; Aconitum Compose†; Actheane; Arnica Complexe no 1; Arthro-Drainol; Boripharm No 1†; Calendula Complexe No 89; Crataegus Complexe No 15; Dolisedal†; Drosera Compose; Drosetux; Echinacea Complexe No 40; Gelsemium Complexe No 70; grippe†; Homeofortil†; Homeogene 41†; Homeogene 9; Hypericum Complexe No 26; Kalium Iodatum Complexe No 84†; L

52; Natrum Carbonicum Complexe No 10†; Oenanthe Crocata Complexe No 78; Paragrippe; Poconeol no 61†; Rheumadoron; Rhododendron Complexe No 42†; Sepia Compose; Soludor; Sportenine; Symphytum Complexe No 48†; Tabacum Compose; Veino-Drainol†; Veinosium†; Zincum Cyanidum Complexe No 101†; ***Ger.***: Aderplus spezial Dr Hagedorn†; Arnica comp/Apis†; Arnica Comp; Arnica Oligoplex; Arnica/Betula comp; Arnica/Symphytum comp; Arnicarell; Aurum-Gastreu S R2; Capillaron Vertigo; Cardioselect N; Cefadolor Arnica Komplex†; Cefadybasin SE†; Cerebral-Do; Chirofossat; Convallysan M; Corvipas SL; Derivatio H; Derivatio; Goldtropfen S; Infifer N; Infigripp; Infihepan; Jowidarmin; Jsoskleran; K 1000; Kattwicor; Lowe-Komplex Nr 10; Mandragora comp; Myonasan; Odonton-Echtroplex; Ossidal; Pascoe-Agil HOM; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Plantacard N; Regenaplex Haut G; Regenaplex Haut W; Rheumodoron 102 A; Rheumodoron 1; Roth's RKT Tropfen; Roth's Rotacard; Ruta-Gastreu N R55; Santa Flora S; Secalosan N; Strophanthus comp; Symphytum Rowo†; Trauma SL; Traumakatt; Traumeel S; Uwobletten Arteriosklerose-Complex†; Varicylum N; Venen-Komplex Ho-Fu-Complex; veno-loges N; Venokatt; Wecesin; Wibotin HM; Zeel comp; ***Hung.***: Angin-Heel; Aurumheel; Drosetux; Homeogene 9; Traumeel; Zeel; ***Neth.***: Achilite; Apo-Rheum†; Arniflor; Arnigel†; Arnilite; Artifleur; Auriculite; Cephalite; Combudoron; Echilite; Gynaelite; Homeocare Vasco; Homeogene 9†; Muscle Care; Myamolite; Omnilite; Paragrippe†; Phonix Hydrargyrum; Phonix Solidago comp; Reudol; Rhumeel; Sportenine†; Traumeel H; Traumeel S; Venafleur; Zeel comp N; ***Port.***: Homeogene 9; Paragrippe; ***Rus.***: Anabar (Анабар); Aurum Plus (Аурум-Плюс); Memoria (Мемория); Mercure-Plus (Меркур-Плюс); Paeonia-Plus (Пеония-Плюс); Pumpan (Пумпан); Repisan (Реписан); Traumeel S (Траумель С); Zeel T (Цель Т); ***S.Afr.***: Rheumadoron†; Traumeel S; ***Switz.***: Arnigel; Contusin; Drosetux; Exsepta; Homeogene 9; Nelsons Traumatica†; Regenaplex Nr 41a; Regenaplex Nr 86a; Regenaplex Nr. 12; Regenaplex Nr. 24c; Regenaplex Nr. 25a; Regenaplex Nr. 25b; Regenaplex Nr. 31c; Regenaplex Nr. 3; Regenaplex Nr. 49a; Regenaplex Nr. 50b; Regenaplex Nr. 51c; Regenaplex Nr. 88b; Rheuma-Heel; Rheumadoron; Traumeel; ***UK***: Combudoron; Frost Cream; Pyrethrum Spray; Rheumadoron; Rheumadoron; WCS Dusting Powder; ***Ukr.***: Aurocard (Аурокард); Memoria (Мемория); Pumpan (Пумпан); Traumeel S (Траумель С); ***USA***: Preferred Remedies Aches & Pains; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations

Ph. Eur.: Arnica Tincture.

Arsenic Triiodide

Arsen. Triiod.; Arsenicum Triioduratum; Arsenii Iodetum; Arsenious Iodide; Arsenium Iodatum; Arsenous Iodide.

AsI_3=455.6

CAS — 7784-45-4.

UNII — 3029988O2T.

Profile

Arsenic triiodide is a trivalent arsenic salt and shares the toxicity of these compounds (see Arsenic Trioxide, below). It was formerly used in the management of some skin conditions.

Homoeopathy

Arsenic triiodide has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Hay Fever; ***Austria***: Luffa compositum-Heel; Tartephedreel; ***Canad.***: Detox L37; Eczema L87; ***Chile***: Flucoccinum; Influk; ***Cz.***: Husteel; Luffeel; ***Fr.***: Aurum Complexe No 38†; Euphorbium Complexe No 88; Hypericum Complexe No 26; Hypophysis Complexe No 31†; Myosotis Complexe No 63†; Scabiosa Complexe No 87; Sclero-Drainol†; Staphysagria Complexe No 92†; Thuya Complexe No 37; Vespa Complexe No 46†; ***Ger.***: Luffeel Comp; Lymphaden Lymphdrusentabletten; Otofren; Rufebran lympho†; Sinasal; Sinusitis Hevert†; Sinusyx; Uwobletten Arteriosklerose-Complex†; ***Hung.***: Husteel; Luffeel; ***Neth.***: Homeocare Allerlo; Husteel; Luffeel H; Sinufleur; ***Switz.***: Regenaplex Nr. 24c.

Arsenic Trioxide *(USAN)*

Acidum Arsenicosum Anhydricum; Anhídrido arsenioso; Arseni Trioxydum; Arsenic; Arsenic Oxide; Arsénico, trióxido de; Arsenicum Album; Arsénieux, anhydride; Arsenii trioxidum; Arsenious Acid; Arsenous Oxide; White Arsenic. Diarsenic trioxide.

As_2O_3=197.8

CAS — 1327-53-3.

ATC — L01XX27.

ATC Vet — QL01XX27.

UNII — S7V92P67HO.

Pharmacopoeias. In *Jpn.*

Eur. (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Arsenious Trioxide for Homoeopathic Preparations; Arsenii Trioxidum ad Praeparationes Homoeopathicae). A white or almost white powder. Practically insoluble to sparingly soluble in water; it dissolves in solutions of alkali hydroxides and carbonates.

Uses and Administration

Arsenic trioxide is used for induction of remission and consolidation in acute promyelocytic leukaemia (see below). It is given as an intravenous infusion over 1 to 2 hours to patients who are refractory to, or who have relapsed from, conventional therapy with retinoids and antineoplastics; if acute vasomotor reactions occur, the rate of infusion may be slowed and up to 4 hours may be taken. For induction, a dose of 150 micrograms/kg is given once daily until remission occurs; no more than 50 doses should be given (in the USA, the maximum number of induction doses allowed is 60). Treatment for consolidation must begin 3 to 4 weeks after completion of induction (or 3 to 6 weeks in the USA). The dose for consolidation is 150 micrograms/kg once daily given for 25 doses spread over a period of up to 5 weeks; the regimen suggested in the UK is to give the daily dose for 5 days each week followed by 2 days without dosing.

Arsenic trioxide is used in certain Asian herbal remedies. Arsenic anhydride has also been used.

Arsenic trioxide has been widely used as a constituent of weedkillers and sheepdips and as a rodenticide.

Arsenic trioxide and arsenic triiodide (above) were formerly used internally as solutions or externally as ointments in the treatment of various skin diseases, but such use is generally no longer recommended. Such oral solutions were usually prepared with arsenic trioxide and potassium hydroxide or a potassium salt and were known as Fowler's Solution or Potassium Arsenite Solution. Externally, arsenic trioxide has a caustic action.

Homoeopathy

Arsenic trioxide has been used in homoeopathic medicines under the following names: Arsenious trioxide; Arsenici trioxidum; Arsenicum album; Acidum arsenicosum; Arsenicum alb; Ars. alb.

Acute myeloid leukaemias. The use of arsenic trioxide in the management of patients with acute promyelocytic leukaemia (p. 693.1) has been reviewed.[1-5] Remission was achieved in patients who had relapsed despite conventional therapy with retinoids and antineoplastics.[6,7] Arsenic trioxide is also being investigated for postremission therapy and in conjunction with transplantation.[4] Treatment was also successful in newly-diagnosed patients but severe liver toxicity occurred in some cases.[6]

For references to adverse effects occurring in patients receiving arsenic trioxide for acute promyelocytic leukaemia, see under Adverse Effects, p. 2449.1.

1. Soignet SL. Clinical experience of arsenic trioxide in relapsed acute promyelocytic leukemia. *Oncologist* 2001; **6** (suppl 2): 11–6.
2. Murgo AJ. Clinical trials of arsenic trioxide in hematologic and solid tumors: overview of the National Cancer Institute Cooperative Research and Development Studies. *Oncologist* 2001; **6** (suppl 2): 22–8.
3. Slack JL, *et al.* Advances in the management of acute promyelocytic leukemia and other hematologic malignancies with arsenic trioxide. *Oncologist* 2002; **7** (suppl 1): 1–13.
4. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol* 2005; **23**: 2396–2410.
5. Leu L, Mohassel L. Arsenic trioxide as first-line treatment for acute promyelocytic leukemia. *Am J Health-Syst Pharm* 2009; **66:** 1913–18.
6. Niu C, *et al.* Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 1999; **94:** 3315–24.
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Multiple myeloma. Arsenic trioxide is under investigation for the treatment of relapsed or refractory multiple myeloma (p. 699.2).

References.

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2. Munshi NC, *et al.* Clinical activity of arsenic trioxide for the treatment of multiple myeloma. *Leukemia* 2002; **16:** 1835–7.
3. Bahlis NJ, *et al.* Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res* 2002; **8:** 3658–68.
4. Berenson JR, Yeh HS. Arsenic compounds in the treatment of multiple myeloma: a new role for a historical remedy. *Clin Lymphoma Myeloma* 2006; **7:** 192–8.

Myelodysplastic syndromes. The use of arsenic trioxide for the treatment of myelodysplastic syndromes (p. 694.3) is also under investigation.

References.

1. List A, *et al.* Opportunities for Trisenox (arsenic trioxide) in the treatment of myelodysplastic syndromes. *Leukemia* 2003; **17:** 1499–1507.
2. Vey N. Arsenic trioxide for the treatment of myelodysplastic syndromes. *Expert Opin Pharmacother* 2004; **5:** 613–21.
3. Schiller GJ, *et al.* Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. *J Clin Oncol* 2006; **24:** 2456–64.
4. Vey N, *et al.* Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study. *J Clin Oncol* 2006; **24:** 2465–71.
5. Sekeres MA. New data with arsenic trioxide in leukemias and myelodysplastic syndromes. *Clin Lymphoma Myeloma* 2007; **8** (suppl 1): S7–S12.

Adverse Effects

The toxicity of arsenic compounds varies according to chemical composition, solubility, and valency. Inorganic arsenic compounds are much more toxic than organic compounds and elemental arsenic is the least toxic. Toxicity increases with increasing solubility, and trivalent (arsenite) compounds are more toxic than pentavalent (arsenate) compounds. Arsenic exerts its effects through a variety of pathophysiological mechanisms such as induction of oxidative stress and binding to sulfydryl groups in enzymes, and it has the potential to affect most of the major organ systems in the body; it also induces alteration in gene expression.

Acute poisoning. Estimates of lethal and toxic oral doses vary: the lethal dose of arsenic trioxide has been reported to be around 1 to 3 mg/kg; a dose of 1 mg/kg of arsenic may be lethal in children; acute toxic doses of arsenic compounds have been reported to range from 1 mg to 10 g. Symptoms of acute poisoning occur within 30 minutes to several hours after ingestion and food delays the onset.

Early features of acute arsenic poisoning after ingestion involve the gastrointestinal tract with common symptoms of a metallic or garlic taste, a burning sensation in the mouth, dysphagia, abdominal pain, severe nausea, projectile vomiting, haemorrhagic gastritis, and profuse 'rice-water' diarrhoea leading to hypovolaemic shock; the breath may have an odour of garlic. In the absence of adequate treatment, death can occur within 24 hours of a severely toxic dose. Absorption of arsenic may produce multisystem toxicity days or weeks later, which could include cardiomyopathy, anaemia, leucopenia, skin disorders, acute respiratory distress syndrome, hepatitis, renal failure, encephalopathy, and peripheral polyneuropathy.

Arsenic compounds are irritant and corrosive when inhaled or in contact with the skin or eyes; acute systemic effects may occur after inhalation or skin contact.

Chronic poisoning. Arsenic is widely distributed in the environment: the smelting industry (non-ferrous metals) is a major industrial source of arsenic contamination in the soil, water, and air; mining residues and arsenical pesticides and wood preservatives also contribute to soil and water contamination. Seafood is a source of organic arsenic. Occupational exposure is a potential cause of chronic arsenic toxicity but in the general population, food and drinking water is usually the source of arsenic.

Chronic arsenic poisoning or occupational exposure typically produces varied skin disorders appearing over 1 to 10 years, particularly hyperkeratosis, especially affecting the palms and soles, and changes in skin pigmentation. Transverse white lines (Mee's lines) may appear in the nails several weeks after absorption. Gastrointestinal disturbances may occur, although are less likely with chronic exposure. Hypertension, cardiovascular disorders, and diabetes mellitus have been associated with chronic arsenic poisoning. Jaundice may occur as a result of hepatomegaly and portal hypertension may eventually develop. Encephalopathy and peripheral neuropathies may also occur. Arsenic is toxic to the bone marrow and produces blood disorders including leucopenia and aplastic anaemia. Chronic exposure to arsenic has been associated with neoplasms of the skin, lungs, bladder, liver, and kidney. Chronic inhalation of arsenic salts may result in perforation of the nasal septum.

Adverse effects of therapeutic use. Reported adverse effects of arsenic trioxide therapy in patients with acute promyelocytic leukaemia (APL) include leucocytosis, neutropenia, raised liver enzyme values, gastrointestinal disturbances, fatigue, oedema, hyperglycaemia, hypokalaemia, dyspnoea, cough, rashes, pruritus, pyrexia, headaches, paraesthesia, and dizziness. Prolongation of the QT interval and other cardiac arrhythmias have occurred. The so-called 'leucocyte activation syndrome' ('APL differentiation syndrome') similar to one that develops with tretinoin therapy (see Retinoic Acid Syndrome, p. 1726.2) has occurred in some patients. Sudden death has been reported in a few patients.

References,[1-9] including discussion of epidemic toxicity due to arsenic-contaminated drinking water.[4,6-8]

1. Health and Safety Executive. Inorganic arsenic compounds. *Toxicity Review 16*. London: HMSO,1986.
2. Shannon RL, Strayer DS. Arsenic-induced skin toxicity. *Hum Toxicol* 1989; **8:** 99–104.
3. Gebel T. Confounding variables in the environmental toxicology of arsenic. *Toxicology* 2000; **144:** 155–62.

4. WHO. Arsenic and arsenic compounds. *Environmental Health Criteria 224*. Geneva: WHO, 2001. Also available at: http://www.inchem.org/documents/ehc/ehc/ehc224.htm (accessed 11/04/08)
5. Borak J, Hosgood HD. Seafood arsenic: implications for human risk assessment. *Regul Toxicol Pharmacol* 2007; **47:** 204–12.
6. Flora SJ, *et al*. Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review. *J Environ Biol* 2007; **28** (2 suppl): 333–47.
7. Islam LN, *et al*. Association of respiratory complications and elevated serum immunoglobulins with drinking water arsenic toxicity in human. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; **42:** 1807–14.
8. Guha Mazumder DN. Arsenic and non-malignant lung disease. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; **42:** 1859–67.
9. Navas-Acien A, *et al*. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA* 2008; **300:** 814–22.

Adulteration. Arsenical compounds have reportedly been used to "cut" cocaine and symptoms of arsenic poisoning may occur in cocaine abusers.[1] Toxicity due to the presence of arsenic in various ethnic remedies has also been reported.[2-4]

1. Lombard J, *et al*. Arsenic intoxication in a cocaine abuser. *N Engl J Med* 1989; **320:** 869.
2. Kew J, *et al*. Arsenic and mercury intoxication due to Indian ethnic remedies. *BMJ* 1993; **306:** 506–7.
3. Ernst E, Thompson Coon J. Heavy metals in traditional Chinese medicines: a systematic review. *Clin Pharmacol Ther* 2001; **70:** 497–504.
4. Ernst E. Heavy metals in traditional Indian remedies. *Eur J Clin Pharmacol* 2002; **57:** 891–6.

Treatment of leukaemia. References[1-6] to and a review[7] of adverse effects in patients receiving arsenic trioxide for the treatment of acute promyelocytic leukaemia, including a report of sudden death occurring in 3 patients in a dose-finding study.[5]

1. Huang SY, *et al*. Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. *Br J Haematol* 1998; **103:** 1092–5.
2. Huang CH, *et al*. Complete atrioventricular block after arsenic trioxide treatment in an acute promyelocytic leukemic patient. *Pacing Clin Electrophysiol* 1999; **22:** 965–7.
3. Camacho LH, *et al*. Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol* 2000; **18:** 2620–5.
4. Ohnishi K, *et al*. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med* 2000; **133:** 881–5.
5. Westervelt P, *et al*. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood* 2001; **98:** 266–71.
6. Cashin R, *et al*. Acute renal failure, gastrointestinal bleeding, and cardiac arrhythmia after administration of arsenic trioxide for acute promyelocytic leukemia. *Am J Health-Syst Pharm* 2008; **65:** 941–6.
7. Rust DM, Soignet SL. Risk/benefit profile of arsenic trioxide. *Oncologist* 2001; **6** (suppl 2): 29–32.

Treatment of Adverse Effects

Acute poisoning due to the ingestion of arsenic compounds should be treated by immediate gastric lavage if the patient presents within 1 hour and has not already vomited. Activated charcoal has been used to reduce absorption but is unlikely to be of benefit unless a significant amount of arsenic has been ingested. Intravenous replacement of fluids and electrolytes should be undertaken as necessary to correct dehydration and electrolyte imbalance; pressor agents may be required.

Chelation therapy should be considered in patients with symptoms of arsenic poisoning or with urine-arsenic concentrations above 200 nanograms/mL. In the UK, the therapy of choice for acute arsenic poisoning is unithiol (p. 1579.1) given intravenously initially, especially in cases of gastrointestinal toxicity; stabilised patients can then be changed to the oral route. Oral succimer (p. 1576.3) may be used as an alternative in the absence of gastrointestinal disturbances. Dimercaprol (p. 1549.3) is no longer recommended as first choice therapy in the UK because of its adverse effects. In the USA, dimercaprol, succimer, penicillamine (p. 1567.1), or unithiol have been used as chelation therapy for arsenic poisoning. Courses of chelation therapy should be repeated until urine-arsenic concentrations fall below 50 nanograms/mL and/or there is marked symptomatic improvement. Patients with chronic arsenic poisoning should be removed from the source of contamination as soon as possible. Starting oral chelation therapy will depend on the patient's clinical condition and laboratory results of arsenic in urine, hair, and nails. In the UK, intravenous unithiol is recommended, although the oral route has also been used. Succimer is not considered to be beneficial in chronic arsenic poisoning.

If renal failure occurs haemodialysis may be required.

Poisoning. The treatment of 3 patients who had ingested massive doses of arsenic has been described.[1,2] An adult survived after ingesting 54g of arsenic trioxide:[1] in addition to standard supportive measures, attempts to remove the arsenic from his gastrointestinal tract included lavage, endoscopic removal, manual removal after gastrotomy, and cleansing enemas, plus chelation therapy. Of 2 siblings who ingested solubilised inorganic arsenic in a pesticide solution,[2] one child (aged 4 months) was estimated to have ingested 428 mg/kg arsenic and died despite aggressive attempts at removal of the arsenic, including chelation therapy, extracorporeal membrane oxygenation, exchange transfusion, and haemodialysis. The other child, aged 2 years, was estimated to have ingested 14.6 mg/kg arsenic, received standard chelation therapy and survived.

1. Dueñas-Laita A, *et al*. Acute arsenic poisoning. *Lancet* 2005; **365:** 1982.
2. Lai MW, *et al*. Acute arsenic poisoning in two siblings. *Pediatrics* 2005; **116:** 249–57.

Precautions

Patients receiving arsenic trioxide for acute promyelocytic leukaemia should have their ECG, blood sugar, electrolytes, blood count, and coagulation monitored at least twice weekly during induction and at least weekly during consolidation. More frequent monitoring may be needed in clinically unstable patients. Arsenic trioxide should be used with caution in renal impairment since renal excretion is the main route of elimination.

Pharmacokinetics

Water-soluble arsenic acids and their salts are more rapidly absorbed from the gastrointestinal tract than poorly soluble arsenicals such as arsenic trioxide. The absorption of arsenic trioxide is dependent upon the physical form of the compound and coarsely powdered material may be eliminated in the faeces before significant dissolution and absorption can occur. Soluble arsenic salts may also be absorbed after inhalation and through skin.

Once absorbed, arsenic is stored mainly in the liver, kidneys, heart, and lungs, with smaller amounts in the muscles and nervous tissue. About 2 weeks after ingestion, arsenic is deposited in the hair and nails and remains fixed to the keratin for years. It is also deposited in the bones and skin.

Although pentavalent arsenic is reduced to some degree *in vivo* to the more toxic trivalent form, trivalent arsenic is slowly and extensively oxidised to pentavalent arsenic. Both forms are methylated and excreted in the urine, mainly as dimethylarsinic acid, with smaller amounts appearing as monomethylarsonic acid and inorganic arsenic compounds. Although about 60% of a dose may be eliminated in the urine within 8 days, small amounts may continue to be excreted for several weeks after a single dose. Less significant amounts of arsenic are excreted in the faeces and sweat and via the lungs and skin. It is also distributed into breast milk and readily crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Phenasen; ***Austria***: Trisenox; ***Belg.***: Trisenox; ***Braz.***: Trisenox; ***China***: Yi Tai Da (伊泰达); ***Cz.***: Trisenox; ***Fr.***: Trisenox; ***Ger.***: Trisenox; ***Gr.***: Trisenox; ***India***: Arsenox; Arsikem; ***Irl.***: Trisenox; ***Israel***: Trisenox; ***Ital.***: Trisenox; ***Jpn***: Trisenox; ***Neth.***: Trisenox; ***Pol.***: Trisenox; ***Port.***: Trisenox; ***Spain***: Trisenox; ***Thai.***: Asadin†; ***UK***: Trisenox; ***USA***: Trisenox.

Multi-ingredient Preparations. ***Fr.***: Caustinerf Arsenical; Devitasol Arsenical†; Yranicid Arsenical; ***Ital.***: Pasta Arsenicale; ***Neth.***: Diarrheel S.

Homoeopathic Preparations. ***Austral.***: Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Childrens Sleep; Hangover Relief; Hay Fever; Homoderma; IBS Eze; Respatona Head Cold; Respatona Sore Throat; Vitatona Energy†; ***Austria***: Apozema Allium Cepa compositum; Daram; Echinacea-Cosmoplex; Erbiode Allergie; Erbiode Haarvital; Famulan; Gastricumeel; Lymphdiaral; Pulsatilla Med Complex; ***Canad.***: Allergies; Cat Complex†; Diarrex; Hives; Kids Allergies; Kids' Earache; ***Chile***: Bioactiv H; Formula II Especial; Ikoplex No 24; ***Fr.***: Abbe Chaupitre no 19†; Abbe Chaupitre no 20†; Abbe Chaupitre no 30†; Abbe Chaupitre no 43†; Abbe Chaupitre no 59†; Abbe Chaupitre no 64†; Abbe Chaupitre no 67†; Abbe Chaupitre no 83†; Abbe Chaupitre no 88†; Abbe Chaupitre no 90†; Agnus Castus Complexe No 2†; Aloe Compose; Boripharm No 12†; Cistus Canadensis Complexe No 86†; Conium Complexe No 36†; Crataegus Complexe No 15; Dermo-Drainol†; Diabene; Diaralia; Euphrasia Complexe No 115; Ferrum Complexe No 29; Gastro-Drainol†; Gelsemium Complexe No 70; Geranium Complexe No 108†; Grindelia Complexe No 58; Kalmia Complexe No 18; L 107; Natrum Carbonicum Complexe No 10†; Nervopax; Nux Vomica Complexe No 49; Oenanthe Crocata Complexe No 78; Pareira Brava Compose; Silicea Complexe No 11; Sulfur Complexe No 12; Tonique Vegetal; Urtica Complexe No 82†; Voxpax; ***Ger.***: Allergie-Injektopas; Araniforce arthro; BN dolo†; Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Curare comp; Entzundungstropfen; Flenin; Gripps; Herniol Injekt; Hewesoor N†; Intercostal-Gastreu; Jowidarmin; Kinolymphat†; Lymphaden Complex; Lymphaden; Lymphdiaral; Neuri-cyl N Ho-Len-Complex; Phonix Silybum spag; Phonix Urtica-Arsenicum spag; Presselin All; Rufebran gastro†; ***Neth.***: Ailgeno spag; Emvita 21; Emvita 26; Emvita 6; Enulite; Gastricumeel; Kind 0-6 Kindigest; Lymphdiaral; Okugest; ***Rus.***: Atma (Атма); Famulan (Фамулан); ***Switz.***: Diarrheel S; Gastricumeel; Regenaplex Nr 28a; Regenaplex Nr 28b; Regenaplex Nr 41a; Regenaplex Nr 86a; Regenaplex Nr. 12; Regenaplex Nr. 24b; Regenaplex Nr. 35b; ***Ukr.***: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); Atma (Атма); Gastrokind (Гастрокинд).

Arsine

Arsenic Trihydride; Arsina; Hydrogen Arsenide; Trihidruro de arsénico.

AsH_3=77.95

CAS — 7784-42-1.

Profile

Arsine is a heavy colourless gas with a garlic-like odour, which has no clinical uses but is an environmental or occupational hazard. It is highly toxic and causes severe haemolysis which may result in acute renal failure. It is potentially toxic below the odour threshold of 0.5 ppm and dangerously toxic after exposure to as little as 3 ppm; there may be a latent period of up to 24 hours after exposure before symptoms develop. Symptoms of arsine gas poisoning include generalised weakness, muscle cramps, thirst, headache, abdominal pain, nausea, vomiting, anorexia, jaundice, bronze skin coloration, haemolytic anaemia, haematuria, oliguria, and anuria. Pulmonary oedema, ECG abnormalities, and peripheral neuropathy have also been reported. Treatment involves exchange transfusions and haemodialysis; dimercaprol and other chelating agents have been used but are of no value in the acute stage and do not prevent haemolysis.

References.

1. Fowler BA, Weissberg JB. Arsine poisoning. *N Engl J Med* 1974; **291:** 1171–4.
2. Hesdorffer CS, *et al*. Arsine gas poisoning: the importance of exchange transfusions in severe cases. *Br J Ind Med* 1986; **43:** 353–5.
3. Pakulska D, Czerczak S. Hazardous effects of arsine: a short review. *Int J Occup Med Environ Health* 2006; **19:** 36–44.

Asafetida

Asafétida; Asafoetida; Asant; Devil's Dung; Gum Asafetida; Асафетида.

*ATC Herb — HA03AW5026 (*Ferula gummosa*: resin); HA03AW5025 (*Ferula assafoetida*: gum); HR05WA5011 (*Ferula assafoetida*: resin); HR05WA5012 (*Ferula gummosa*: resin).*

UNII — W9FZA51AS1.

Pharmacopoeias. In *Chin.*

Profile

Asafetida is an oleo-gum resin obtained from various species of *Ferula* (Umbelliferae). It has been used as a carminative and antispasmodic. It was also formerly used as an expectorant. It is used in cooking and is an ingredient of certain foods.

References.

1. Kelly KJ, *et al*. Methemoglobinemia in an infant treated with the folk remedy glycerited asafoetida. *Pediatrics* 1984; **73:** 717–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Duiwelsdrekdruppels.

Multi-ingredient Preparations. ***India***: Coliwell; Garlill; Lunarex; Tummy Ease†; ***S.Afr.***: Entressdruppels HM; Stuidruppels; ***Thai.***: Corisul; Flataco; Flatulence†; Patarsul; ***UK***: Daily Tension & Strain Relief.

Homoeopathic Preparations. ***Canad.***: Homeo-Form ST†; Hylands Gas; Kids Calm; Osteel†; Stress L72†; Stress; ***Cz.***: Ypsiloheel; ***Fr.***: Abbe Chaupitre no 90†; Basilicum Complexe No 96; Cina Complexe No 55†; Homeodose 8†; L 72; Poconeol no 82†; Symphytum Complexe No 48†; ***Ger.***: Gnaphalium Injektopas SL; Metaharonga; Nervoregin comp; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rytesthin; Schwoneural N; Sedaphin†; Ypsiloheel N; ***Hung.***: Osteoheel; ***Neth.***: Discus comp H; Nervival; ***Switz.***: Osteoheel.

Asarabacca

Ásaro europeo; Bacará; Hazelwort; Rhizoma Asari; Wild Nard; Копытень Европейский.

UNII — H0876AL67A.

NOTE. Asarabacca has also been used as a common name for *Aristolochia clematitis* (see Aristolochia, p. 2447.1).

Profile

Asarabacca is the dried rhizome, roots, and leaves of *Asarum europaeum* (Aristolochiaceae), which is an ingredient of snuffs. It is also an irritant emetic and has been used in rodent poisons. Asarabacca is an ingredient of preparations given for respiratory disorders.

Homoeopathy

Asarabacca has been used in homoeopathic medicines under the following names: Asarum; Asarum europaeum; Asarum eur; Asar. eur.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Asarum Med Complex; Migrenopas†; ***Fr.***: Gastro-Drainol†; ***Rus.***: Nux Vom-Plus (Нукс Вом-Плюс).

Asbestos

Amianto; Asbesto.

Profile

The name asbestos is applied to several naturally occurring and widely distributed fibrous mineral silicates of the serpentine and amphibole groups. They include amosite (brown asbestos), anthophyllite, chrysotile (white asbestos), and crocidolite (blue asbestos).

Asbestos has properties of heat resistance, insulation, and reinforcement and has been used extensively for heat or electrical insulation, fire protection, in friction materials, and in the construction industry in many materials including cement, pipes, and tiles.

When inhaled, asbestos fibres can cause asbestosis (pulmonary fibrosis), lung cancer, and mesothelioma of the pleura and peritoneum. Mesothelioma has been reported in persons exposed to relatively small amounts of asbestos after an average latent period of 30 to 40 years. An association between occupational exposure and an increased incidence of gastrointestinal, laryngeal, and other cancers has also been reported. Some types of asbestos are more hazardous than others; crocidolite (a member of the amphibole group) is considered to be the most dangerous.

References.

1. Landrigan PJ, *et al*. The hazards of chrysotile asbestos: a critical review. *Ind Health* 1999; **37:** 271–80.
2. Browne K, Gee JB. Asbestos exposure and laryngeal cancer. *Ann Occup Hyg* 2000; **44:** 239–50.
3. Bourdes V, *et al*. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Eur J Epidemiol* 2000; **16:** 411–7.
4. Bolton C, *et al*. Asbestos-related disease. *Hosp Med* 2002; **63:** 148–51.
5. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med* 2004; **170:** 691–715. Also available at: http://www.thoracic.org/sections/publications/statements/pages/eoh/asbestos.html (accessed 24/07/08)
6. Uibu T, *et al*. Asbestos exposure as a risk factor for retroperitoneal fibrosis. *Lancet* 2004; **363:** 1422–6.
7. Hessel PA, *et al*. Asbestos, asbestosis, and lung cancer: a critical assessment of the epidemiological evidence. *Thorax* 2005; **60:** 433–6.
8. O'Reilly KM, *et al*. Asbestos-related lung disease. *Am Fam Physician* 2007; **75:** 683–8.
9. British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007; **62** (suppl 2): ii1–ii19. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Malignant%20Mesothelioma/Guidelines/statement%20on%20malignant%20mesothelioma2007.pdf (accessed 24/07/08)

Ash

Askblad (ash leaf); Chinese Ash (*Fraxinus chinensis*); Common Ash; Esche; European Ash (*Fraxinus excelsior*); Fraxini folium (ash leaf); Frêne; Frêne Élevé (*Fraxinus excelsior*); Frêne, feuille de (ash leaf); Fresno; Jasanový list (ash leaf); Magas kőrisfa levél (ash leaf); Saarnenlehti (ash leaf); Uosių lapai (ash leaf); Ясень.

*UNII — 9F7B1YGJ59 (Ash); R6KCX5H8I2 (*Fraxinus excelsior *bark); RC38362Q7M (*Fraxinus excelsior *leaf); 7G2O12V1NZ (*Fraxinus excelsior *seed).*

Pharmacopoeias. *Chin.* includes Ash Bark (Cortex Fraxini, Qinpi). *Eur.* (see p. vii) includes Ash Leaf.

Ph. Eur. 8: (Ash Leaf; Fraxini Folium). The dried leaf of *Fraxinus excelsior* or *Fraxinus angustifolia* (*F. oxyphylla*) or of hybrids of these 2 species or of a mixture. It contains a minimum of 2.5% of total hydroxycinnamic acid derivatives, expressed as chlorogenic acid ($C_{16}H_{18}O_9 = 354.3$), calculated with reference to the dried drug.

Profile

The leaf of the European ash (*Fraxinus excelsior*) is included in herbal remedies for the treatment of rheumatic and joint disorders, urinary-tract disorders, and constipation. The leaf of *F. oxyphylla* is also used.

Ash bark has been used to reduce fever and as a tonic.

The bark of the Chinese ash, *F. chinensis* or related species is used in traditional Chinese medicine for disorders including acute dysentery and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Phytodolor; ***Austria***: Phytodolor; ***Cz.***: Phytodolor†; ***Fr.***: Arthritisanet†; Arthroflorine†; Azema†; Boribel Tisane No 17†; Boribel Tisane No 9; Calmiflorine†; Hydrastart; Mediflor Contre la Constipation Passagere No 7; Mediflor Diuretique No 4†; Mediflor Douleurs Articulaires no 2†; Mediflor no 1; Obeflorine†; Provencale No 2†; Santane OI; Tisane de Sante†; Tisane Provencale no 2†; Tisane Provencale no 6†; Urotisan†; ***Ger.***: Phytodolor.

Ashwagandha

Winter Cherry; Витания Снотворная (*Withania somnifera*).

*UNII — GD1Z9GY1FW (*Withania somnifera*); 2HZ95R7082 (*Withania somnifera *flower); J337CNM3CW (*Withania somnifera *leaf); V038D626IF (*Withania somnifera *root).*

NOTE. The name Winter Cherry has been applied to several plants including *Physalis alkekengi* (see p. 2590.1) and *Cardiospermum halicacabum*, as well as *Withania somnifera*. Ashwagandha has also been known as Indian ginseng and should not be confused with other ginsengs (see p. 2513.3).

Pharmacopoeias. *US* includes Ashwagandha Root.

Br. includes Withania Somnifera Root.

USP 36: (Ashwagandha Root). Ashwagandha Root is the dried mature roots of *Withania somnifera* (Solanaceae). It contains not less than 0.3% of withanolides calculated on the dried basis, as the sum of withanolide aglycones, calculated as withanolide A, and withanolide glycosides, calculated as withanoside IV. Protect from light and moisture.

BP 2014: (Withania Somnifera Root). The dried mature roots of *Withania somnifera*. It contains not less than 0.01% withaferin A ($C_{28}H_{38}O_6 = 470.6$) and not less than 0.01% withanolide A ($C_{29}H_{42}O_7 = 502.6$). Store in airtight containers.

Profile

The root of ashwagandha, *Withania somnifera* (*Physalis somnifera*) (Solanaceae), has traditionally been used in Ayurvedic medicine and is included in herbal preparations for many conditions. The berries are also used.

References.

1. Kulkarni SK, Dhir A. *Withania somnifera*: an Indian ginseng. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 1093–1105.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Ad Baby; Cebrotone; Eat Ease; Milano; One All Caps; One BE.

Multi-ingredient Preparations. ***Austral.***: Fe-Max; Femi-Nan; Ginsynergy plus Rhodiola; Humulus Compound; Lavandula Compound; Memory and Vitality Formula; Mindac; Thyroid Complex; Ultra Calm; Withania Complex; Withania Compound; Women's D-Stress; ***Fr.***: Apaisance†; ***Hung.***: Herbadict; Munipyrin; ***India***: Abana; Addyzoa; Aptizooom; Arthrella; Arthrill; Artrex; Aswal Plus; Attentio; Daash; Femi Forte; Fortege; G-Advit; G-Calvit; Galakol; Geriforte; Geriforte; Glowone; Gynoset; Herr; Imunocin; Lactare; Laforte; Laviril; M2-Tone; Manoll; Memtone; Mentat; Mentofer; Mezica; Mustong; Nevromine; Ojus; ***Ital.***: Euroton; ***Malaysia***: 30 Plus†; ***Rus.***: Fitovit (Фитовит); Tentex (Тентекс); Verona (Верона); ***Singapore***: Artrex; ***Ukr.***: Вон-Apetit (Бон-Аппетит); Fitovit (Фитовит); Gynopower (Гинопауэр); Trypsidan (Трипсидан)†; Verona (Верона); ***USA***: Adrenoid.

Asparagus

Asperge; Garden Asparagus; Sparrow Grass; Sparrowgrass; Аспарагус; Спаржа.

UNII — Z1EJP3037Z.

NOTE. Distinguish from wild asparagus (see under Shatavari, p. 2614.2).

Pharmacopoeias. In *Fr.*

Profile

The roots and aerial parts of asparagus, *Asparagus officinalis* (Asparagaceae), have diuretic and laxative properties and have been included in herbal preparations for urinary tract disorders and constipation. The young shoots are used as a food stuff and their ingestion is followed by excretion of various sulfur compounds that produce a characteristic strong odour in the urine.

Homoeopathy

Asparagus has been used in homoeopathic medicines under the following names: Asparagus officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Neo-Cleanse; Wild Yam Complex; ***Fr.***: Biofirm; ***Ger.***: Asparagus-P; ***Hung.***: Herbadict; Lactonic; ***Jpn***: Jiinkokato; Seihaito; ***Rus.***: Fitovit (Фитовит); ***UK***: AsParAid; ***Ukr.***: Andropower (Андропауэр); Gynopower (Гинопауэр).

Homoeopathic Preparations. ***Fr.***: Abbe Chaupitre no 20†; Poconeol no 67.

Aspens

NOTE. The term Aspen has been used variously in the literature and reference sources to denote different species of *Populus* or parts thereof. It is therefore often difficult to determine exactly what is intended when this term has been used. Likewise, the term *Populus*, which is used in botanical classifications to denote a genus of plants, and the name Poplar have been applied to similar plants or parts thereof and care should therefore be taken with medicines that use any of the above terms to describe their ingredients.

Populus Alba

Abele; Álamo Blanco; *Populus alba*; Peuplier Blanc; Silber-Pappel; White Poplar.

*UNII — Y05EGY83Y4 (*Populus alba*).*

Populus Tremula

Asp; Aspen Poplar; Bævre-Asp; Espe; European Aspen; Haapa; *Populus tremula*; Peuplier Tremble; Quaking Aspen; Zitter-Pappel.

*ATC Herb — HN02BA5004 (*Populus tremula*: leaf); HG04CW5004 (*Populus tremula*: leaf); HC01EB5018 (*Populus tremula*: bud); HN02BA5003 (*Populus tremula*: bud); HR05WA5044 (*Populus tremula*: bud); HN02BA5002 (*Populus tremula*: bark); HG04CW5003 (*Populus tremula*: bark).*

*UNII — U755Q6LFAH (*Populus tremula*); 5Q01F7TPJJ (*Populus tremula *flowering top).*

Populus Tremuloides

Álamo Temblón; American Aspen; American Poplar; Amerikanische Espe; *Populus aurea*; *Populus tremuloides*; Peuplier Faux-tremble; Quaking Aspen; Tremble; Trembling Aspen; White Poplar.

*ATC Herb — HN02BA5007 (*Populus tremuloides*: leaf); HG04CW5006 (*Populus tremuloides*: leaf); HR05WA5045 (*Populus tremuloides*: bud); HN02BA5006 (*Populus tremuloides*: bud); HC01EB5019 (*Populus tremuloides*: bud); HN02BA5005 (*Populus tremuloides*: bark); HG04CW5005 (*Populus tremuloides*: bark).*

*UNII — MUN0TBE4PE (*Populus tremuloides*); 5543O0CEID (*Populus tremuloides *bark); 7IIH57D9E0 (*Populus tremuloides *leaf).*

Profile

Various species of *Populus* (Salicaceae), such as *P. tremula*, and *P. tremuloides*, which are sometimes referred to as aspens, are used for their salicin-rich leaves and bark in herbal medicine for prostate disorders and rheumatic conditions. In some sources the species *P. alba* has been grouped with the aspens.

Homoeopathy

Species of aspen have been used in homoeopathic medicines under the following names: Populus tremuloides; Populus trem.

The flowers of *Populus tremula* are also used in homoeopathic medicines under the following names: Populus tremula, flos; Populus trem, flos.

References.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 29/04/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Phytodolor; ***Austria***: Phytodolor; Prostagutt; ***Canad.***: Cystoforce†; ***Cz.***: Phytodolor†; ***Ger.***: Eviprostat N; Phytodolor; Prostamed; ***Indon.***: Eviprostat; ***Jpn***: Eviprostat; ***Singapore***: Eviprostat; ***UK***: Gerard House Reumalex; Peerless Composition Essence; Tabritis; ***Ukr.***: Prostamed (Простамед).

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Canad.***: Homeodel 15†; ***Ger.***: Cysto Hevert; Hewecyst Blasen-Nieren†; Homvio-Rin; Homvio-Rin; Inconturina mono; Prostamed Mikto; Prostarell; Prostata-Entoxin N; Prostata-Gastreu N R25; Urokatt; Urotruw N; Ursinol; ***Neth.***: Akutur spag; Cystilite; Homeocare Uro; Reneel H; ***Ukr.***: Homvio-Prostan (Хомвио-Простан).

Astragalus

Bei Qi; Chinese Astragalus; Huang Qi; Huangqi; Membranous Milk Vetch (*A. Membranaceus*); Meng Gu Huang Qi (*A. mongholicus*); Milk Vetch; Milkvetch.

UNII — QP4TY1M906 (Astragalus mongholicus); 59DK50719X (Astragalus mongholicus root); IJI7YZ55VS (Astragalus propinquus); 922OP8YUPF (Astragalus propinquus root).

NOTE. Distinguish from *Astragalus gummifer*, the source of Tragacanth (p. 2217.1).

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Astragalus Mongholicus Root). The whole dried root of *Astragalus mongholicus* (*A. membranaceus*) freed from rootlets and rootstock, collected from spring to autumn.

Profile

Astragalus is a large genus of about 3 000 species of herbs and small shrubs belonging to the legume family Fabaceae. Many species carry the common name milkvetch.

The root of *A. membranaceus* (*Phaca membranacea*; *A. propinquus*) is used as a tonic in traditional Chinese medicine where it is known by the name huang qi. The closely related species *A. mongholicus* is used similarly. The taxonomy of some species of *Astragalus* is debatable and some authorities regard *A. membranaceus*, *A. mongholicus*, and *A. propinquus* as the same species whereas others consider them to be two or three separate species.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Echinacea Royale; Masculine Herbal Complex; Olf†; Withania Compound; ***Canad.***: Defense; ***Ital.***: Eutears; ***Jpn***: Boiogito; Daibofuto; Hangebyakujutsutemmato; Hochuekkito; Juzentaihoto; Kamikihito; Kihito; Ninjin'yoeito; Ogikenchuto; Seishinrenshiin; Seishoekkito; Shichimotsukokato; Tokiinshi; Tokito; ***Malaysia***: Elgucare; NeuroAid; Shine Growell; ***Philipp.***: Hemofer; ***Rus.***: Raylis (Райлис); ***Singapore***: NeuroAid.

Avena

Aven; Avione; Cultivated White Oats; Hafer; Oatmeal; Oats; Овёс.

ATC Herb — HN06BX5001 (Avena sativa: fresh herb).

UNII — 8PI54V663Y (oatmeal); Z6J799EAJK (Avena sativa grain).

Pharmacopoeias. *US* includes colloidal oatmeal.

USP 36: (Colloidal Oatmeal). The powder resulting from the grinding and further processing of whole oat grain. When dried at 120 degrees for 4 hours it loses not more than 10% of its weight.

Profile

Avena is the grain of *Avena sativa* (Gramineae). It is used in herbal medicine and is reputed to have sedative activity.

A colloidal fraction extracted from avena is used in the preparation of emollient dermatological preparations.

Whether avenin, a protein present in oats, is harmful to patients with coeliac disease is controversial.

Homoeopathy

Avena has been used in homoeopathic medicines under the following names: Avena sativa; Avena e planta tota; Aven. sat.

References.

1. Haboubi NY, *et al*. Coeliac disease and oats: a systematic review. *Postgrad Med J* 2006; **82:** 672–8.
2. Kurtz ES, Wallo W. Colloidal oatmeal: history, chemistry and clinical properties. *J Drugs Dermatol* 2007; **6:** 167–70.
3. Garsed K, Scott BB. Can oats be taken in a gluten-free diet? A systematic review. *Scand J Gastroenterol* 2007; **42:** 171–8.
4. Butt MS, *et al*. Oat: unique among the cereals. *Eur J Nutr* 2008; **47:** 68–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermopan; ***Austral.***: Aveeno Preparations; DermaVeen; Nyal Eczema Relief; ***Canad.***: Aveeno Preparations; ***Chile***: Dermopan; ***Fr.***: Aveeno Preparations; Sensifluid; ***Hong Kong***: DermaVeen†; ***Ital.***: Avalon; Aveeno Preparations; Emulave; ***NZ***: DermaVeen; ***Port.***: Aveeno Preparations†; Emulave†; ***Singapore***: DermaVeen; ***UK***: Aveeno Preparations; ***USA***: ActiBath; ***Venez.***: Dermopan.

Multi-ingredient Preparations. ***Arg.***: Aristaloe; Dermalibour; Dermomega; Epitheliale A-Derma; Epitheliale AH; Exomega; Lactoplus; Proavenal Omegatopic; Purasoft; Valeriana Oligoplex; ***Austral.***: Avena Complex†; Calmo†; Dong Quai Complex†; Executive B Stress Formula; For Women Active Woman Formula†; GR² Control Appetite Reducer; Masculine Herbal Complex; Olf†; The Blue One†; Tranquil Night; ***Canad.***: Cystoforce†; ***Chile***: Cytelium; Dermalibour; Epithelial AH; Exomega Barrera; Exomega; Proaven; ***Cz.***: Valofyt Neo†; ***Fr.***: A-Derma Lait Solaire†; Apaisance†; Biocarde; Cytelium; Derm'Intim; Dermalibour; Dermalibour; Epitheliale; Eryase†; Exomega; Filigel†; Gonaxine; Saugella Girl; Saugella HydraSerum; ***Ger.***: Requiesan†; Vollmers praparierter gruner N; ***India***: Elovera; ***Indon.***: Menolia†; ***Irl.***: Avena Sativa Comp; ***Ital.***: Acnaveen; ***Mex.***: Aveendix; Bonaven; Fruticoline; Suavene; ***Neth.***: Plantival; ***Philipp.***: Dermablend Colloidal Oatmeal Lotion; ***Pol.***: Sedomix; ***Port.***: Micaveen†; ***Rus.***: Cedoflor (Седофлор); ***S.Afr.***: Avena Sativa Comp†; ***Singapore***: Dermavive; Sativa; ***Switz.***: Mucilar Avena; The d'avoine verte Vollmers†; ***UK***: Avena Sativa Comp; Daily Overwork & Mental Fatigue Relief; Daily Tension & Strain Relief; Napiers Herbal Stress & Sleep Aid; Outlook; ***Ukr.***: Herbastress (Гербастресс); Pravenor (Правенор); ***USA***: Aveeno Cleansing Bar†; ***Venez.***: Avensyl; Bonaven; Cytelium; Dagenol; Epitheliale AH; Exomega; Fiberfull.

Homoeopathic Preparations. ***Austria***: Acidum phosphoricum Med Complex; Avena Med Complex; Avena Rihom Komplex†; Globuli gegen Schlafstorungen; Notta; Pasconal; Valerianaheel; ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Alfalfa Tonic; Calms Forte; Comp-Drops 1 Stress†; Comp-Drops 7 Sleepless†; Fatigue; Hepar Compositum; Homeo-Form F†; Homeo-Form I†; Homeo-Form ST†; Hylands Formula C; Hylands Formula CF; Insomnia Passiflora†; Insomnia; Kids Calm; Soludor†; Stress L72†; Stress; Ton 2 Complex†; Valerianaheel Comp†; Vegetal Tonic; ***Chile***: Melinerv; ***Fr.***: Acidum Phosphoricum Compose†; Cereales Germees; Eudyne†; L 72; Passiflora GHL; Sativol†; Slipeol†; Soludor; Stressdoron; Tonique Vegetal; Zincum Cyanidum Complexe No 101†; ***Ger.***: Alho-Sedosan; Avena sativa comp†; Cefaneuro; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; Dormosyx; Hepar comp; Infinerval; Jsoskleran; Liquidorm N; Lycoaktin; Nervo-Plantin†; Nervoid N; Nervoregin H; Nervoregin; Neurexan; Neuro-Ginsan N; Pasconal Nerventropfen; Passiflora Complex†; Seda-Do; Sedacalman; Sedakatt; Sedaselect; Sedativa-Injektopas; Thyreo-Injektopas; Tondinel H; Tondinel; ***Hung.***: PSY-Stabil; ***Neth.***: Hyperilite; PSY-stabil; Sativol†; Weleda Avena Valeriana; ***Rus.***: Notta (Нотта); ***Switz.***: Nelsons Noctura†; ***UK***: Noctura; ***Ukr.***: Notta (Нотта); ***USA***: Preferred Remedies Sleep.

Avocado

Aguacate; Ahuacate; Alligator Pear; Аллигаторова Груша; Авокадо.

UNII — SDS87L369F.

Profile

Avocado, *Persea americana* (*P. persea*; *P. gratissima*) (Lauraceae), is included in herbal preparations mainly for respiratory-tract and hepatic disorders. Several parts of the plant, including the fruit and leaves, have been used for a variety of disorders.

The fruit is a dietary source of vitamin E, vitamin B_6, vitamin K, and iron.

Avocado oil is used topically as an emollient and as a neutral carrier for essential oils in aromatherapy. It may also be taken orally.

Osteoarthritis. A mixture comprising one-third avocado oil and two-thirds soya oil (p. 2092.3), and known as avocado-soybean unsaponifiables (ASU) has been given as a dietary supplement to patients with osteoarthritis; an evidence-based report[1] by the Arthritis Research Campaign in the UK considered that it was safe and possibly effective in reducing pain and problems associated with walking and other daily activities.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Piascledine.

Multi-ingredient Preparations. ***Arg.***: Derrumal; ***Austral.***: Macro Natural Vitamin E Cream; ***Braz.***: Piascledine; ***Chile***: Codetol PM; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil†; Paltomiel Plus; Paltomiel; Paltomiel; Piascledine; Pulmosina; ***Cz.***: Piascledine; ***Fr.***: Piascledine; ***Ital.***: Piascledine; Pluvio; ***Mex.***: Piascledine; ***NZ***: Mr Nits; ***Pol.***: Piascledine; ***Port.***: Biureol†; Nutraisdin; ***Rus.***: Piascledine (Пиаскледин); ***USA***: Sonafine.

Homoeopathic Preparations. ***Fr.***: Poconeol no 25; Poconeol no 76; Poconeol no 7.

Azadirachta

Margosa; Neem; Nim; Ним.

UNII — 3TE8A92UPM (neem extract); G580B439YI (Aazadirachta indica bark).

Pharmacopoeias. In *Br.*

BP 2014: (Azadirachta Indica Leaf). The dried leaf of *Azadirachta indica*. It contains not less than 1.0% of tetranortriterpinoids, expressed as salannin, calculated with reference to the dried drug. Protect from moisture.

Uses and Administration

Azadirachta is the dried stem bark, root bark, and leaves of *Azadirachta indica* (*Melia azadirachta*) (Meliaceae), which has been used as a bitter. It is widely used in South Asia and has been reported to have insecticidal, antimalarial, and spermicidal properties. Azadirachta oil (neem oil, margosa oil) expressed from the seeds has also been used.

References.

1. Prakash A, *et al*. A preliminary field study on repellency of neem oil against *Anopheles dirus* (Diptera:Culicidae) in Assam. *J Commun Dis* 2000; **32**: 145–7.
2. Boeke SJ, *et al*. Safety evaluation of neem (*Azadirachta indica*) derived pesticides. *J Ethnopharmacol* 2004; **94:** 25–41.
3. Subapriya R, Nagini S. Medicinal properties of neem leaves: a review. *Curr Med Chem Anticancer Agents* 2005; **5:** 149–56.
4. Maity P, *et al*. The use of neem for controlling gastric hyperacidity and ulcer. *Phytother Res* 2009; **23:** 747–55.

Adverse Effects

Effects on the skin. Report of a patient who developed contact dermatitis of the face and ears 1 week after she started using neem oil for the treatment of alopecia areata.[1]

1. Reutemann P, Ehrlich A. Neem oil: an herbal therapy for alopecia causes dermatitis. *Dermatitis* 2008; **19:** E12–E15.

Poisoning. Severe poisoning has occurred in Indian children given neem oil as a remedy for minor ailments.[1]

1. Sinniah D, Baskaran G. Margosa oil poisoning as a cause of Reye's syndrome. *Lancet* 1981; **i:** 487–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Malaysia***: Moz-Away; ***UK***: Nice 'n Clear.

Multi-ingredient Preparations. ***India***: Flexi-muv†; ***Indon.***: Bionam; ***Ital.***: Keromicil; Keromicil; ***NZ***: Mr Nits; ***Philipp.***: Cogent db+; ***Rus.***: Pilex (Пайлекс); ***Singapore***: Hemoglo; ***UK***: Dr Johnsons Nit & Lice; Hemocyl; MozzyOff Cocktail; Padma Circosan; ***Ukr.***: Pilex (Пилекс).

Azapentacene Sulfonate Sodium

Натрия Азапентацена Полисульфонат.

Disodium 5,12-dihydroquinoxalino[2,3-*b*]phenazine disulfonate.

$C_{18}H_{12}N_4O_6S_2Na_2$=490.4

CAS — 1790-56-3 (azapentacene disulfonic acid); 3863-80-7 (azapentacene disulfonate disodium).

Profile

Azapentacene sulfonate sodium has been used topically in the management of cataracts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Luisar; ***Hong Kong***: Quinax; ***Indon.***: Pentacin†; ***Mex.***: Lutrax; ***Philipp.***: Quinax; ***Pol.***: Quinax; ***Rus.***: Quinax (Квинакс); ***Singapore***: Quinax; ***Thai.***: Quinax; ***Ukr.***: Quinax (Квинакс).

Azintamide *(rINN)*

Azintamida; Azintamidum; Azinthiamide; ST-9067; Азинтамид.

2-[(6-Chloro-3-pyridazinyl)thio]-*N*,*N*-diethylacetamide.

$C_{10}H_{14}ClN_3OS$=259.8

CAS — 1830-32-6.

UNII — ACZ6L64B41.

Profile

Azintamide has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Biluen Enzimatico; ***China***: Mite (泌特); ***Port.***: Colerin-F†; ***Spain***: Oragalin Espasmolitico.

Azovan Blue *(BAN)*

Azovanum Caeruleum; Azuł azován; Azul de Evans; CI Direct Blue 53; Colour Index No. 23860; Evans Blue; T-1824; Эванс Голубой.

Tetrasodium 1,1′-diamino-8,8′-dihydroxy-7,7′-(2,2′-dimethylbiphenyl-4,4′-diylbisdiazo)di-(naphthalene-2,4-disulphonate); Tetrasodium 6,6′-[3,3′-dimethylbiphenyl-4,4′-diylbis(azo)]bis[4-amino-5-hydroxynaphthalene-1,3-disulphonate].
$C_{34}H_{24}N_6Na_4O_{14}S_4$=960.8
CAS — 314-13-6.
UNII — 45PG892GO1.

Profile

Azovan blue is a dye that has been given intravenously for the determination of blood volume; it is firmly bound to plasma proteins and is slow to leave the circulation. Some patients may have staining of the skin.

Azulene

Atsuleeni; Azulen; Azuleno; Azulenum; Cyclopentacycloheptene; Азулен.
$C_{10}H_8$=128.2
CAS — 275-51-4.
UNII — 82R6M9MGLP.

NOTE. The name 'Azulene' has also been used for several derivatives of azulene including azulene sodium sulfonate, chamazulene, guaiazulene, and sodium gualenate.

Profile

Azulene has been used in preparations for anorectal and skin disorders, and for oral hygiene. The sodium sulfonate salt has been used in preparations for mouth and throat disorders and for dyspepsia; sodium gualenate has also been used in gastrointestinal disorders.

Hypersensitivity. Allergic cheilitis occurred in a patient after long-term use of a toothpaste containing azulene.[1]

1. Balato N, *et al.* Allergic cheilitis to azulene. *Contact Dermatitis* 1985; **13:** 39–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Kamil Blue.

Multi-ingredient Preparations. ***Arg.***: Domuderm; Ninderm; ***Braz.***: Eritrex A; Proctosan; ***China***: She Lan (舍兰); Zi Mo (兹末); ***Hong Kong***: Eye-Ruby Violet†; ***India***: Glutazene; ***Israel***: Kamil Blue; Kamil Blue; ***Ital.***: AZ 15; ***Rus.***: Eucasept (Эвкасепт).

Bacopa

Becopa; Brahmi; Herb of Grace; Thyme Leaved Gratiola; Water Hyssop; Бакопа.

Pharmacopoeias. In *Br. US* includes Bacopa as well as a powdered form and a powdered extract.

BP 2014: (Bacopa Monnieri). The dried aerial parts of *Bacopa monnieri*. It contains not less than 1.0% w/w of bacopa saponins, expressed as bacopaside II ($C_{47}H_{76}O_8$ = 769.1-), calculated with reference to the dried drug.

USP 36: (Bacopa). The dried stems and leaves of *Bacopa monnieri* (Scrophulariaceae). It contains not less than 2.5% of triterpene glycosides. Protect from light and moisture.

Profile

Bacopa consists of the dried whole plant, preferably the leaves and stem, of *Bacopa monnieri* (*B. monnieria, Gratiola monnieria, Herpestis monniera, Lysimachia monnieri*) Scrophulariaceae (sometimes placed in Plantaginaceae). It is used in Ayurvedic medicine for a variety of indications, and is included in herbal preparations for memory and cognitive disorders.

References.
1. Anonymous. Bacopa monniera. *Altern Med Rev* 2004; **9:** 79–85.
2. Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant: an overview. *Phytomedicine* 2005; **12:** 305–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: KeenMind; PM Branin; PM Golbimac; ***Philipp.***: Memo Plus Gold; ***UK***: Memory Plus.

Multi-ingredient Preparations. ***Austral.***: Bacopa & Ginkgo Compound; Bacopa Complex; Brahmi Super Learning Complex; Ginkgo Brahmi; Mens Dual-Action Multi; Mindac; NA Neurocard; PM Kids Intelligent; PM LifeBrain; Thyroid Complex; Ultra Calm; ***Indon.***: Bilotec; ***Philipp.***: Memory DD†; Premium Memori Plus; ***Rus.***: Dipana (Дипана); Fitovit (Фитовит); ***Singapore***: Memomet; ***Ukr.***: Fitovit (Фитовит); Intellan (Интеллан); Osteoartisi Max (Остеоартизи Макс); Trypsidan (Трипсидан)†.

Bactericidal Permeability Increasing Protein

Proteína bactericida incrementadora de la permeabilidad; Бактерицидный Белок, Увеличивающий Проницаемость Клеточной Мембраны.

Opebacan *(BAN, USAN, rINN)*

Opébacan; Opebacán; Opebacanum; rBPI-21; Опебакан.
132-L-Alanine-1-193-bactericidal/permeability-increasing protein (human).
CAS — 206254-79-7.

Profile

Bactericidal permeability increasing protein is produced by human leucocytes and possesses both Gram-negative bactericidal and endotoxin-neutralising properties. It also inhibits angiogenesis. Several derivatives have been developed and are under investigation. Opebacan is a modified recombinant fragment of bactericidal permeability increasing protein that is under investigation for the treatment of Crohn's disease and meningococcal septicaemia. Other derivatives of bactericidal permeability increasing protein are under investigation for retinopathies and acne.

Bactericidal permeability increasing protein also possesses antifungal activity.

References.
1. Giroir BP, *et al.* Preliminary evaluation of recombinant amino-terminal fragment of human bactericidal/permeability-increasing protein in children with severe meningococcal sepsis. *Lancet* 1997; **350:** 1439–43.
2. Levin M, *et al.* Recombinant bactericidal/permeability-increasing protein ($rBPI_{21}$) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. *Lancet* 2000; **356:** 961–7.
3. Levy O. A neutrophil-derived anti-infective molecule: bactericidal/permeability-increasing protein. *Antimicrob Agents Chemother* 2000; **44:** 2925–31.
4. van der Schaft DW, *et al.* The antiangiogenic properties of bactericidal/permeability-increasing protein (BPI). *Ann Med* 2002; **34:** 19–27.

Barium

Bario; Baryum; Барий.
Ba=137.327
CAS — 7440-39-3.
UNII — V645272HLN (barium ion); 24GP945V5T (barium).

Description. Barium is a soft, highly reactive, silvery-white metal.

Uses and Administration

The soluble barium salts are not used in therapeutics but are widely used in industry. For the uses of barium chloride and barium hydroxide lime, see below. Barium sulfide has been used as a depilatory and barium carbonate was used as a rodenticide. The insoluble barium sulfate (p. 1583.2) is used as a contrast medium.

Homoeopathy

Barium salts have been used in homoeopathic medicines under the following names:
- Barium acetate: Acétate de baryum; Barium aceticum; Bariumacetat; Baryta acetica
- Barium carbonate: Barii carbonas; Barium carbonicum; Baryta Carbonica; Carbonate de baryum
- Barium citrate: Baryta citrica; Citrate de baryum
- Barium iodide: Barii iodidum; Barium iodatum; Bariumiodid; Baryta iodata; Iodure de baryum; Barium jodatum
- Barium oxalosuccinate: barium oxalsuccinum

Other barium salts used in homoeopathy and described elsewhere include: barium chloride (below).

Adverse Effects and Treatment

All barium salts that are water- or acid-soluble are very toxic. The symptoms of barium poisoning arise from stimulation of all forms of muscle and include vomiting, excess salivation, colic, diarrhoea, slow or irregular pulse, hypertension, dysarthria, confusion, dizziness, paraesthesias, vertigo, muscle tremors, seizures, muscular paralysis, and respiratory or metabolic acidosis. Hypokalaemia is common. Renal impairment has been reported. Death from cardiac or respiratory failure may occur.

In acute poisoning, emptying the stomach by lavage is recommended if possible. Magnesium or sodium sulfate may be given to convert barium to insoluble barium sulfate. Hypokalaemia and metabolic acidosis should be corrected and ventilation assisted if necessary. Excretion may be increased by diuresis. Haemodialysis may be used in severe poisoning.

Reports of barium intoxication.

1. Lewi Z, Bar-Khayim Y. Food poisoning from barium carbonate. *Lancet* 1964; **ii:** 342–3.
2. Diengott D, *et al.* Hypokalaemia in barium poisoning. *Lancet* 1964; **ii:** 343–4.
3. Gould DB, *et al.* Barium sulfide poisoning: some factors contributing to survival. *Arch Intern Med* 1973; **132:** 891–4.
4. Berning J. Hypokalaemia of barium poisoning. *Lancet* 1975; **i:** 110.
5. Wetherill SF, *et al.* Acute renal failure associated with barium chloride poisoning. *Ann Intern Med* 1981; **95:** 187–8.
6. Phelan DM, *et al.* Is hypokalaemia the cause of paralysis in barium poisoning? *BMJ* 1984; **289:** 882.
7. WHO. Barium. *Environmental Health Criteria 107*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc107.htm (accessed 24/07/08)
8. Sigue G, *et al.* From profound hypokalemia to life-threatening hyperkalemia: a case of barium sulfide poisoning. *Arch Intern Med* 2000; **160:** 548–51.
9. Wells JA, Wood KE. Acute barium poisoning treated with hemodialysis. *Am J Emerg Med* 2001; **19:** 175–7.
10. Jacobs IA, *et al.* Poisoning as a result of barium styphnate explosion. *Am J Ind Med* 2002; **41:** 285–8.
11. Bahlmann H, *et al.* Acute barium nitrate intoxication treated by hemodialysis. *Acta Anaesthesiol Scand* 2005; **49:** 110–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Barium Jodatum Oligoplex.

Homoeopathic Preparations. ***Austria***: Barium Med Complex; ***Canad.***: Ateria-Heel†; Barijodeel†; Ginkgo-Comp†; Hylands Sore Throat; Itires; Sore Throat; ***Chile***: Bioactiv M; Silik; ***Fr.***: Badiaga Complexe No 47; Phytogargarisme†; Sabal Serrulata Compose; ***Ger.***: Antihypertonicum N†; Antihypertonicum-Tropfen N†; Cefadybasin SE†; Lowe-Komplex Nr 3; Zitronensaurezyklus-Heel; ***Neth.***: Bronchilite; Co-Hypert; Gastrifleur; Homeocare keelspray; Lymfelite; Lymphomyosot; Myamolite; ***Rus.***: Anabar (Анабар); Aurum Plus (Аурум-Плюс); Phytolacca-Plus (Фитолакка-Плюс).

Barium Chloride

Barii Chloridum; Bario chloridas; Bariumklorid; Bariumkloridi; Baru chlorek; Baryum, chlorure de; Бария Хлорид.
$BaCl_2$=208.2
CAS — 10361-37-2 (anhydrous barium chloride); 10326-27-9 (barium chloride dihydrate).
UNII — 0VK51DA1T2 (anhydrous barium chloride); EL5GJ3U77E (barium chloride dihydrate).

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Barium Chloride Dihydrate for Homoeopathic Preparations; Barii Chloridum Dihydricum ad Praeparationes Homoeopathicas). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble or practically insoluble in alcohol.

Profile

Barium chloride has several industrial uses including the manufacture of pigments and dyes, leather tanning, boiler detergents, water softeners, and aluminium refining.

Barium chloride is a soluble salt and therefore potentially toxic if ingested. Systemic toxicity arising from burns to skin from molten barium chloride has been reported. For the adverse effects and treatment of barium and barium salts, and reference to barium chloride poisoning, see under Barium, above.

Homoeopathy

Barium chloride has been used in homoeopathic medicines under the following names: Barium chloratum; Baryta muriatica; Baryta mur; Bar. mur.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Arnica Med Complex; Secale Med Complex; ***Canad.***: HPB Complex†; ***Fr.***: Pulmo-Drainol†; Sclero-Drainol†; ***Ger.***: RauwolfiaViscomp; ***Neth.***: Rinileen†; ***Rus.***: Aurum Plus (Аурум-Плюс).

Barium Hydroxide Lime

Bario, cal con hidróxido de; Бариевая Известь.
CAS — 17194-00-2 (anhydrous barium hydroxide); 12230-71-6 (barium hydroxide octahydrate).

Pharmacopoeias. In *US*.

USP 36: (Barium Hydroxide Lime). A mixture of barium hydroxide octahydrate and calcium hydroxide; it may also contain potassium hydroxide. White or greyish-white granules, or coloured with an indicator to show when absorptive power is exhausted. It absorbs not less than 19% of its weight of carbon dioxide. Store in airtight containers.

Profile

Barium hydroxide lime is used similarly to soda lime to absorb carbon dioxide in closed-circuit anaesthetic apparatus. Barium hydroxide lime contains a soluble form

of barium and is toxic if swallowed. For the adverse effects and treatment of barium poisoning, see p. 2452.2.

Precautions. Excessive drying out of barium hydroxide lime in anaesthetic apparatus, which may occur if oxygen flow through the equipment is left on for prolonged periods, can lead to the production of carbon monoxide and the risk of inducing carboxyhaemoglobinaemia in patients undergoing anaesthesia using the apparatus.[1]

1. CSM/MCA. Safety issues in anaesthesia: volatile anesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Basil

Albahaca; Basil Herb; Basilic; Basilici Herba; Basilienkraut; Sweet Basil; Базилик.

*ATC Herb — HA01WA5002 (*Ocimum basilicum*: herb); HA03AW5044 (*Ocimum basilicum*: leaf); HR05YA5016 (*Ocimum basilicum*: leaf); HD11AX5003 (*Ocimum basilicum*: leaf); HA03AW5043 (*Ocimum basilicum*: herb).*

UNII — 2U0KZP0FDW.

Pharmacopoeias. In *Fr.*

Profile

The aerial parts of basil, *Ocimum basilicum* (Lamiaceae), are used in preparations for gastrointestinal disorders and as a diuretic. It is also used as a culinary herb.

Basil oil is an essential oil with antiseptic properties. It is used in perfumery and cosmetics and also in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Aromadetox†; Aromadigest†; Aromazen†; ***Ger.***: Weleda-Rheumasalbe M†; ***Ital.***: Citrosystem; ***Rus.***: Bronchitussin (Бронхитусен); Bronchocin (Бронхоцин); Bronchoton (Бронхотон); Travisil (Трависил).

Homoeopathic Preparations. ***Canad.***: Indigestion†; ***Fr.***: Basilicum Complexe No 96; ***Ger.***: Phyto-C.

Bay Oil

Aceite esencial de malagueta; Laurel dulce, aceite esencial de; Myrcia Oil; Oleum Myrciae; Масло бея.

UNII — 3T5GC5CQ33.

NOTE. Distinguish from Laurel Leaf Oil (Bay Leaf Oil) which is obtained from the leaves of *Laurus nobilis* (Lauraceae).

Profile

Bay oil is a yellow volatile oil that darkens rapidly on exposure to air and has a pleasant odour and spicy taste. It is obtained by distillation from the leaves of *Pimenta racemosa* (Myrtaceae) and probably other allied species. The principal use of bay oil is in the preparation of bay rum, which is used as a hair lotion and as an astringent application. Bay oils from both *P. racemosa* and *Laurus nobilis* are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Aromadetox†; Aromadigest†; Percutalgin'Phyto; ***UK***: Adiantine; Medicated Extract of Rosemary.

Bayberry

Árbol de la cera; Bayberry Bark; Candle Berry Bark; Chak-lol; Guanacalá; Huacanalá; Mirto ceroso; Myrica; Wax Myrtle Bark; Восковница Восконосная (*Myrica cerifera*).

*UNII — 29B6F0441G (*Myrica cerifera*); 2VZ27D14UH (*Myrica cerifera *fruit); L41B20QT0M (*Myrica cerifera *fruit wax); 58Z237VK03 (*Myrica cerifera *leaf); S46HJ3710D (*Myrica cerifera *root bark).*

NOTE. Bayberry has also been used as a synonym for bog myrtle (see p. 2458.3).

Profile

Bayberry, the root bark of *Myrica cerifera* (Myricaceae), is used in upper respiratory-tract disorders and as a gargle for sore throat. It has also been used in gastrointestinal disorders, to treat vaginal discharge, and topically on ulcers and sores.

Homoeopathy

Bayberry has been used in homoeopathic medicines under the following names: Myrica cerifera; Myrica; Myri. cer.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: HRF; ***UK***: EP&C Essence; Peerless Composition Essence.

Bearberry

Aguavilla; Bärentraubenblätter; Bearberry Leaves; Busserole; Busserole, feuille de; Gayuba; Liść mą; Medvědicový list; Medveszőlőlevél; Meškauogių lapai; Mjölonrisblad; Ptarmiganberry Leaves; Sianpuolukanlehti; Uva de oso; Uva-Ursi; Uvaduz; Uvae ursi folium; Медвежье Ушко.

*ATC Herb — HJ01WB5003 (*Arctostaphylos uva-ursi*: leaf).*

*UNII — 37SXO36KR7 (*Arctostaphylos uva-ursi*); 3M5V3D1X36 (*Arctostaphylos uva-ursi *leaf).*

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bearberry Leaf). The whole or fragmented dried leaves of the bearberry, *Arctostaphylos uva-ursi*. It contains not less than 7.0% of anhydrous arbutin, calculated with reference to the dried drug. Protect from light.

Profile

Bearberry has been reported to be a diuretic, bacteriostatic, and astringent and has been used in the treatment of urinary-tract disorders.

Homoeopathy

Bearberry has been used in homoeopathic medicines under the following names: Uva ursi; Uva ur.

Adverse effects. Bilateral bull's-eye maculopathy that developed in a 56-year-old woman was suspected to be due to regular ingestion of uva ursi as a tea over a 3-year period, since uva ursi can inhibit melanin metabolism.[1]

1. Wang L, Del Priore LV. Bull's-eye maculopathy secondary to herbal toxicity from uva ursi. *Am J Ophthalmol* 2004; **137:** 1135–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Urocystil; ***Braz.***: Uromed; ***Ger.***: Cystinol Akut; Uvalysat; ***Ital.***: Ginocap; ***Pol.***: Uversan; ***Rus.***: Uriflorin (Урифлорин); ***Ukr.***: Cystinol Akut (Цистинол Акут).

Multi-ingredient Preparations. ***Arg.***: Ajolip; Cellasene†; Herbaccion Antioxidante; KLB6 Fruit Diet; Prostamen; Ripped Max; Varicura; ***Austral.***: Althaea Complex†; Colon Care; Cranberry Complex†; Cranberry Complex; Cranbiotic Super†; De Witts New Pills†; Detox Program; Extralife Fluid-Care†; Extralife PMS-Care†; Extralife Uri-Care†; PMT-Eze†; ***Austria***: Uropurat†; ***Canad.***: Bio Renal†; Cellutex; Cystoforce†; Diurenat†; Diuretic Formula; Diuretic Tablets; Eliminex; Entwasserungstee†; Hepaflor†; Herbal Diuretic†; Herbal Diuretic; Salusan†; ***Cz.***: Species Urologicae Planta; Urcyston Planta; Urologicka Cajova Smes; ***Fr.***: Boribel Tisane No 17†; Mediflor Diuretique No 4†; Uromil; Urophytum†; ***Ger.***: Arctuvan; Cystinol N; ***Hung.***: Urogin; Uroherb; ***Israel***: Jungborn†; ***Ital.***: Bionefrol; Ginecistin; Litostop; ***Mex.***: Noxivid†; ***Pol.***: Nefrosept; Urofort; ***Port.***: Rilastil Dermo Solar; ***Rus.***: Diureticae Species No2 (Мочегонный Сбор 2); Herbion Urological Drops (Гербион Урологические Капли); Phytonefrol (Фитонефрол); Urokam (Урокам); ***Singapore***: Disco; ***Spain***: Genurat; ***Switz.***: Demonatur Dragees pour les reins et la vessie†; Dragees S pour les reins et la vessie; Femicin Tisane pour reins/vessie†; Impuls dragees pour la vessie et les reins; Sabrinin dragees pour les reins et la vessie; Strath Gouttes pour les reins et la vessie; Tisane pour les reins et la vessie; Urinex; ***UK***: Antitis; Aqua Ban Herbal; Backache Relief; Backache; Backache; Boots Water Relief; Cascade; De Witt's K & B Pills; Diuretabs; HealthAid Boldo-Plus; HRI Water Balance; Kas-Bah; Lowater; Modern Herbals Water Retention; Potenzia; Prementaid; Sciargo; Tabritis; Uvacin; Watershed; ***Ukr.***: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Uro-Control (Уро-Контрол); Urocran (Урокран); ***USA***: Cardiopress.

Homoeopathic Preparations. ***Canad.***: Goldenrod Combination†; ***Fr.***: Pareira Brava Compose; Urocalm; Uva Ursi Complexe No 9; ***Ger.***: HanoNephrin; Levisticum S; ***Rus.***: Cistoit-GF (Цистоит-ГФ); ***Switz.***: Regenaplex Nr 86a; Regenaplex Nr. 49a.

Beleric Myrobalan

Belleric Myrobalan.

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan — see Indian Gooseberry, p. 2532.2), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — see Arjuna, p. 2447.2; *T. bellirica*, Beleric Myrobalan, above; and *T. chebula* — see Chebulic Myrobalan, p. 2474.3). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. In *Br.*

BP 2014: (Terminalia Belerica Fruit). The pericarp of dried ripe fruits of *Terminalia belerica*. It contains not less than 10% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The fruit of beleric myrobalan, *Terminalia bellirica* (*T. bellerica*; *T. belerica*) (Combretaceae), is used in Ayurvedic medicine for a range of conditions including cough and other respiratory-tract disorders. The unripe fruit is used for constipation while the ripe fruit is used for diarrhoea.

The traditional Ayurvedic medicine triphala is a combination of beleric myrobalan, chebulic myrobalan (p. 2474.3), and Indian gooseberry (p. 2532.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Triphala; ***Hung.***: Munipyrin; ***India***: Flexi-muv†; FN-T-Tus†; ***Philipp.***: Cogent db+; ***Rus.***: Doktor Mom (Доктор Мом); Pilex (Пайлекс); Travisil (Трависил); ***Singapore***: Hemoglo; Imunomet; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Doktor Mom (Доктор Мом сироп); Eve Care (Ив Кер)†; Septilin (Септилин); Travisil (Трависил); Trypsidan (Трипсидан)†.

Belladonna

Belladon; Belladona; Belladone; Belladone, feuille de (belladonna leaf); Belladonnablad (belladonna leaf); Belladonnablätter (belladonna leaf); Belladonnae folium (belladonna leaf); Belladonnanlehti (belladonna leaf); Deadly Nightshade; Liść pokrzyku (belladonna leaf); Nadragułyalevél (belladonna leaf); Rulikový list (belladonna leaf); Šunvyšnių lapai (belladonna leaf); Tollkirschen; Белладонна.

ATC — A03BA04.

ATC Vet — QA03BA04.

*ATC Herb — HN05CW5002 (*Atropa belladonna*: leaf); HA03YA5002 (*Atropa belladonna*: leaf); HA03YA5001 (*Atropa belladonna*: herb); HN05CW5001 (*Atropa belladonna*: herb).*

*UNII — WQZ3G9PF0H (*Atropa belladonna*); 6GZW20TIOI (belladonna leaf); 6MW97Q6E8M (belladonna radix).*

NOTE. Distinguish from Russian belladonna (see Scopolia, p. 2611.3).

Pharmacopoeias. *Eur.* (see p. vii) and *US* include a monograph for Belladonna Leaf. *Chin.* includes Belladonna Herb.

Eur. also includes Prepared Belladonna Leaf, Standardised Belladonna Leaf Tincture, and Standardised Belladonna Leaf Dry Extract.

Jpn includes only Belladonna Root.

Ph. Eur. 8: (Belladonna Leaf; Belladonnae Folium). It consists of the dried leaf, or dried leaf and flowering, and occasionally fruit-bearing, tops of *Atropa belladonna*. It contains not less than 0.30% of total alkaloids, calculated as hyoscyamine. The alkaloids consist mainly of hyoscyamine with smaller amounts of hyoscine. It has a slightly nauseous odour. Protect from light.

The BP 2014 directs that when Belladonna Herb, Belladonna Leaf, or Powdered Belladonna Herb is prescribed, Prepared Belladonna Herb shall be dispensed.

Ph. Eur. 8: (Belladonna, Prepared; Belladonnae Pulvis Normatus; Prepared Belladonna Herb BP 2014). It is belladonna leaf powder adjusted to an alkaloidal content of 0.28 to 0.32% of total alkaloids, calculated as hyoscyamine. Store in airtight containers. Protect from light.

USP 36: (Belladonna Leaf). It consists of the dried leaf and flowering or fruiting top of *Atropa belladonna* (Solanaceae). It yields not less than 0.35% of the alkaloids of belladonna leaf. When moistened, its odour is slight, somewhat tobacco-like. Avoid long exposure to direct sunlight. Protect powdered Belladonna Leaf from light.

Stability in mixtures. Atropine in belladonna preparations was unstable at alkaline pH and would quickly be degraded in mixtures with a pH above 7.[1] Such mixtures in the BPC 1973 included Aluminium Hydroxide and Belladonna Mixture, Cascara and Belladonna Mixture, and Magnesium Trisilicate and Belladonna Mixture.

1. *PSGB Lab Report P/71/9* 1971.

Uses and Administration

Belladonna has the actions of antimuscarinics (see under Atropine, p. 1310.3). Belladonna herb and its preparations have been used for their antimuscarinic actions in many conditions, including the relief of gastrointestinal and

urinary-tract disorders associated with smooth muscle spasm, but they are generally regarded as an outmoded form of treatment.

Belladonna liniments and plasters have been used as counter-irritants for the relief of pain but there is little evidence that they have a beneficial effect and adverse effects have occurred.

Homoeopathy

Belladonna has been used in homoeopathic medicines under the following names: Atropa bella-donna; Belladonna, radix; Belladonna, rad; Bell.

References.

1. Ulbricht C, *et al.* An evidence-based systematic review of belladonna by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2004; **4:** 61–90.
2. Lee MR. Solanaceae IV: Atropa belladonna, deadly nightshade. *J R Coll Physicians Edinb* 2007; **37:** 77–84.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

References.

1. Mateo Montoya A, *et al.* Acute anticholinergic syndrome from Atropa belladonna mistaken for blueberries. *Eur J Ophthalmol* 2009; **19:** 170–2.
2. Bogan R, *et al.* Plasma level of atropine after accidental ingestion of Atropa belladonna. *Clin Toxicol* 2009; **47:** 602–4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bellanorm; ***Ger.***: Belladonnysat Burger†; ***Pol.***: Bellapan; ***Rus.***: Bellacehol (Беллацехол); ***Venez.***: Atroveran.

Multi-ingredient Preparations. ***Arg.***: Antipasmol; Benitol; Cascara Sagrada Bouzen; Cascara Sagrada Oligoplex; Dioxicolagol; Gastranil; Hepacur; Hepatodirectol; Opobyl; Passacanthine; ***Austral.***: Joint & Muscle Cream; ***Belg.***: Saintbois; ***Braz.***: Acridin; Broncol†; Bronquidex; Brontoss; Calminex Atleta; Calminex H; Cystex; Ductoveran; Gastrobene; Gastrobene; Gotas Preciosas; Hemofleb; Pilulas Ross; Solvobil; ***Canad.***: Bellergal; Cystoforce†; ***Chile***: Broncodeina; Ergobelan; Fenokomp 39; Gruben; Ramistos; ***China***: Aoweishu (澳谓舒); ***Cz.***: Capsicolle; ***Fin.***: Tannopon†; ***Hung.***: Kefalgin; ***India***: Aldiamycin; Ergophen; Gynedol; Magnine; Migranil; ***Indon.***: Bellapheen; Spasmal; Spasminal†; Stomadon†; ***Israel***: Laxative Compound; ***Ital.***: Antiemorroidali†; Antispasmina Colica; ***Jpn***: Colgen Kowa for Rhinitis; ***Mex.***: Chofabol; Parche Negro Belladona; Reudol; ***Pol.***: Alax; Bellergot; Biospasmil†; Cholitol; Hemorol; Kapsiplast; Spasticol; ***Port.***: Antispasmina Colica†; Cephyl†; Doce Alivio; Migretil; ***Rus.***: Anusol (Анузол); Becarbon (Бекарбон); Bellasthesin (Белластезин); Bellataminal (Беллатаминал); Besalol (Бесалол); Bethiol (Бетиол); Gastroguttal (Гастрогуттал); Solutan (Солутан)†; Theophedrinum-N (Теофедрин-Н); Valocormid (Валокормид); Zelenin (Зеленин); ***S.Afr.***: Bennetts Colic Mixture†; Bolus Eucalypti Comp†; ***Spain***: Alofedina; Carminativo Juventus; Crislaxo; Dolokey†; Laxante Bescansa Aloico†; Tanagel; ***Switz.***: Bromocod N†; Cafergot-PB†; Demo Elixir pectoral N†; Escotussin; Nican†; Phol-Tux; ***Thai.***: Belacid; Benera†; Delta Charcoal; Neuramizone; New Gel; Pro ABS; ***Turk.***: Bellergal; ***UK***: Opazimes; ***Ukr.***: Bellalgin (Беллалгин); Bellasthesin (Белластезин); Distonin (Дистонин)†; Gastropin (Гастропин); ***USA***: B & O Supprettes No. 15A; B & O Supprettes No. 16A; Bel-Phen-Ergot S†; Bellamine†; Bellergal-S; Butibel; Cafatine-PB; Folergot-DF; Phenerbel-S; ***Venez.***: Atrobel; Ervostal; Traveget.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Calm; Childrens Cough Relief; Childrens Sleep; Earache Relief†; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Pain & Fever Relief; Respatona Dry Cough & Nasal Congestion; Respatona Sinus Relief; Respatona Sore Throat; Sedatif†; Snorestop; Sports Ice Joint & Muscle; Teething Relief; ***Austria***: Aconitum Med Complex; Apozema Apis compositum; Bolus Eucalypti Comp; Bronchalis-Heel; Cantharis Med Complex; Echinacea-Cosmoplex; Erbiode Regelbeschwerden; Erysidoron Nr 1; Exangina†; Globuli gegen Fieber und Grippe Nr 2; Globuli gegen Halsweh Nr 2; Gripagil Husten- und Bronchialtropfen; Nux Med Complex; Pertudoron†; Schnarchex; Spigelon; Taraxacum Med Complex; Tartephedreel; Tonsan akut; Traumeel; Vocara; ***Canad.***: Aches & Pains; Angeel†; Bed Wetting†; Bioactiv N†; Bioactiv R†; Breathe More; Bronkeel†; Calnor†; Camilia; Carduus Plex†; Comp-Drops 5 Expectorant†; Coryzalia; Cough & Cold; Den 141†; Diarrhea; Drosera Complex; Drosera Plex†; Earache; Endoteel†; EnurAid; Erysidoron 1†; Formula DM 210†; Formula ES 211; Homeo-Form R†; Homeovox; Husteel†; Hyalgesic HP†; Hylands Formula E; Hylands Headache; Hylands Kinder-BW; Hylands Kinder-T†; Hylands Sore Throat; Ikoplex 12†; Indigestion†; Insomnia Passiflora†; Ivernax; Kids Cough & Cold Phytux; Kids' Earache; L52 Cough & Cold; Larydol†; Pertudoron 1†; Phytotux H; Roxalia; Sedatil; Sinus Ease; Sinusalia; Sinuspax†; Snore No More; Sore Throat; Spascupreel; Spigelon†; Tee Complex†; Teething; Traumeel; Viburcol; ***Chile***: Allium Compuesto; Bioactiv N; Bioactiv R; Bioactiv Z; Grippakit; Ikoplex No 12; Influk; ***Cz.***: Angin-Heel S; Bronchalis-Heel; Coryzalia; Drosetux; Homeogene 9; Homeovox; Husteel; Lehnigrip†; Paragrippe; Sedatif PC; Traumeel; Viburcol; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 13; Abbe Chaupitre no 1†; Abbe Chaupitre no 22†; Abbe Chaupitre no 23†; Abbe Chaupitre no 25†; Abbe Chaupitre no 66†; Abbe Chaupitre no 6; Abbe Chaupitre no 88†; Abbe Chaupitre no 91†; Agnus Castus Complexe No 2†; Allium Cepa Compose; Aloe Compose; Angipax; Arnica Complexe no 1; Basilicum Complexe No 96; Baudry; Boripharm No 10†; Boripharm No 12†; Boripharm No 1†; Boripharm No 22†; Boripharm No 31; Cholesterolum Complexe No 112†; Cocculus Complexe No 73; Coryzalia; Diabene; Drosera Complexe No 64; Drosera Compose; Drosetux; Euphrasia Complexe No 115; Formica Rufa Compose; Gelsemium Complexe No 70; Grindelia Complexe No 58; grippe†; Hedera Complexe No 120; Helonias Compose; Homeogene 9; Homeogrippe†; Homeovox; Hypericum Complexe No 26; Ipeca Complexe No 65; Juniperus Complexe No 6; Kalium Iodatum Complexe No 84†; Kalium Muriaticum Complexe No 41†; L 107; L 52; L 8; Mercurius Cyanatus Complexe No 43†; Millefolium Complexe No 7†; Momordica Complexe No 109†; Paragrippe; Passiflora GHL; Pertudoron; Pulsatilla Complexe No 60†; Pulviplasmine†; Rubia Complexe No 3; Santaherba; Scrofularia Compose; Sedatif PC; Sinuspax; Tabacum Compose; Urtica Complexe No 82†; Uva Ursi Complexe No 9; Vespa Complexe No 46†; ***Ger.***: Angina-Gastreu S R1; Arnica Oligoplex; Broncho-Entoxin N; Cocculus Oligoplex; Contramutan; Echinacin akut; Entzundungstropfen; Enuroplant N; Erysidoron 1; Febro-cyl L Ho-Len-Complex; Gastritis Complex; Gastro-Pasc; HanoTussan; Heweurat N; Infekt-Komplex L Ho-Fu-Complex; Infigripp; Infihepan; Jutussin; Lithiascyl L Ho-Len-Complex; Mato; Mucosa compositum; Mullersche Tabletten; Original-Tinktur N Truw; Pascorenal-Injektopas; Pascosabal; Pertudoron 1; Phonix Silybum spag; Pulmo Bronchialcomplex; Pulmosan; Schworotox; Solidago Hevert Complex; Stoma-Gastreu S R5; Traumeel S; Ulco-cyl L Ho-Len-Complex; Ventrigutt M; Viburcol N; Weleda Fieber- und Zahnungszapfchen; Wiedimmun N†; ***Hung.***: Angin-Heel; Bronchalis-Heel; Coryzalia; Drosetux; Homeogene 9; Homeovox; Husteel; Sedatif; Spigelon; Traumeel; Viburcol; ***Neth.***: Apo-STOM; Auriculite; Belachin-Gastreu R1; Bronchalis; Chelidonium-Homaccord N; Coryzalia; Cystilite; Echilite; Febrilite; Head Care; Hemorrolite; Homeocare keelspray; Homeogene 9†; Homeovox; Husteel; Jutussin R9; Kind 0-3 Chamodent; Kind 0-6 Kinditherm; Mercurius-Heel; Myamolite; Paragrippe†; Red Skin; Sedatif PC; Snurdim; Tonsiotreen; Traumeel S; Viburcol H; Vinceel H; ***Port.***: Coryzalia; Homeogene 9; Homeovox; Paragrippe; Sedatif PC; ***Rus.***: Belladonna-Plus (Белладонна-Плюс); Cistoit-GF (Цистоит-ГФ); Coryzalia (Коризалия); Homeostres (Гомеострес); Homeovox (Гомеовокс); Pharyngomed (Фарингомед); Phytolacca-Plus (Фитолакка-Плюс); Tonsan-Akut (Тонзан-акут); Traumeel S (Траумель С); Vocara (Вокара); ***S.Afr.***: Chamomilla/Millefolium Comp†; Erysidoron 1†; Pertudoron Drops†; Traumeel S; Viburcol; ***Switz.***: Alceprin-N; Bronchalis-Heel; Coryzalia; Drosetux; Homeogene 9; Homeovox; Regenaplex Nr 38b; Regenaplex Nr. 24b; Regenaplex Nr. 3; Sedatif PC; Spigelon; Traumeel; Viburcol N; ***UK***: Bolus Eucalypti Comp; Erysidoron 1; ***Ukr.***: Coryzalia (Коризалия); Dentokind (Дентокинд); Homeovox (Гомеовокс); Incena (Инцена); Sedatif PC (Седатив ПЦ); Traumeel S (Траумель С); Vocara (Вокара); ***USA***: Preferred Remedies Cold & Flu; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations

Ph. Eur.: Belladonna Leaf Dry Extract, Standardised; Belladonna Leaf Tincture, Standardised;

USP 36: Belladonna Extract Tablets; Belladonna Extract; Belladonna Tincture.

Bellis Perennis

Bellis; Bruisewort; Common Daisy; Daisy; English Daisy; European Daisy; Gänseblümchen; Kaunokainen; Lawn Daisy; Lawndaisy; Massliebchen; Pâquerette; Petite Marguerite; Tausendschön; Tausendschönchen; Tusensköna; Vellorita.

UNII — 2HU331I03UY (Bellis perennis extract).

Profile

The flowers, leaves, and roots of *Bellis perennis* (Asteraceae) have been given orally in herbal medicine for a variety of disorders and externally for wounds and skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Joint & Muscle Cream.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Austria***: Traumeel; ***Canad.***: Arnicaid; Bumps and Bruises; Eczema L87; Jet Lag; Traumeel; ***Cz.***: Traumeel; ***Fr.***: Calendula Complexe No 89; Scabiosa Complexe No 87; ***Ger.***: Delto-cyl Ho-Len-Complex; Ekzem-Entoxin N; Infihepan; Phytocortal; Regenaplex Haut W; Roth's RKT Tropfen; Symphytum Rowo†; Traumeel S; ***Hung.***: Traumeel; ***Neth.***: Opsonat; Traumeel H; Traumeel S; ***Rus.***: Traumeel S (Траумель С); ***S. Afr.***: Traumeel S; ***Switz.***: Regenaplex Nr 41a; Traumeel; ***Ukr.***: Traumeel S (Траумель С); ***USA***: Traumeel; ***Venez.***: Traumeel.

Bendazol Hydrochloride *(rINNM)*

Bendazol, Chlorhydrate de; Bendazol, hidrocloruro de; Bendazoli Hydrochloridum; Dibazol; Hidrocloruro de bendazol; Бендазола Гидрохлорид.

2-Benzylbenzimidazole hydrochloride.

$C_{14}H_{12}N_2$,HCl=244.7

CAS — 621-72-7 (bendazol); 1212-48-2 (bendazol hydrochloride).

Profile

Bendazol hydrochloride is used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Andipal (Андипал); Cytovir (Цитовир); Papazol (Папазол).

Bentiromide *(BAN, USAN, rINN)*

Bentiromid; Bentiromida; Bentiromidi; Bentiromidum; BTPA-BA; BT-PABA; E-2663; PFT; Ro-11-7891; Бентиромид.

4-(*N*-Benzoyl-L-tyrosylamino)benzoic acid.

$C_{23}H_{20}N_2O_5$=404.4

CAS — 37106-97-1.

ATC — V04CK03.

ATC Vet — QV04CK03.

UNII — 239IF5W61J.

Profile

Bentiromide has been given orally as a noninvasive test of exocrine pancreatic function (see under Pancreatitis, p. 2580.2), the amount of *p*-aminobenzoic acid and its metabolites excreted in the urine being taken as a measure of the chymotrypsin-secreting activity of the pancreas. Headache and gastrointestinal disturbances have been reported in patients receiving bentiromide. The bentiromide test has given misleading results in patients with gastrointestinal, liver, or kidney disorders, or in patients receiving certain foods or drugs that are excreted as arylamines. Some of these drugs included benzocaine, chloramphenicol, lidocaine, paracetamol, procaine, procainamide, sulfonamides, and some diuretics.

References.

1. Hoek FJ, *et al.* Improved specificity of the PABA test with p-aminosalicylic acid (PAS). *Gut* 1987; **28:** 468–73.
2. Puntis JWL, *et al.* Simplified oral pancreatic function test. *Arch Dis Child* 1988; **63:** 780–4.

Benzyl Cinnamate

Benzylu cynamonian; Cinnamein; Бензилциннамат.

Phenylmethyl 3-phenyl-2-propenoate.

$C_{16}H_{14}O_2$=238.3

CAS — 103-41-3.

UNII — V67O3RO97U.

Profile

Benzyl cinnamate is a constituent of various balsams and resins, including Peru balsam (p. 2587.1), to which it has been used similarly. It is also used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Pulmex Baby; Pulmex†; ***Braz.***: Ozonyl; ***Irl.***: Sudocrem; ***UK***: Sudocrem; ***Ukr.***: Sudocrem (Судокрем).

Benzyl Isothiocyanate

Bencilo, isotiocinato de; Benzyl Mustard Oil; Benzylsenföl; Oleum Tropaeoli; Бензилгорчичное Масло; Бензилизотиоцианат.

C_8H_7NS=149.2

CAS — 622-78-6.

UNII — 871J6YOR8Q.

Pharmacopoeias. *Fr.* includes Capucine (*Tropaeolum majus*).

Profile

Benzyl isothiocyanate is an oil obtained from *Tropaeolum majus* (Capuchin cress; common nasturtium) (Tropaeolaceae) that has been given as an antibacterial.

Tropaeolum majus has been used in herbal medicine.

Homoeopathy

Tropaeolum majus has been used in homoeopathic medicines under the following names: Tropaeolum.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Angocin Anti-Infekt N; Nephroselect M.

Homoeopathic Preparations. ***Ger.***: Jsostoma S.

Benzyl Mandelate

Benzyl Phenylglycolate; Benzylin; Benzylis Mandelas; Benzylium Amygdalicum; Benzyl-DL-mandelate; Mandelsäurebenzylester; Бензил Манделат.

$C_{15}H_{14}O_3$=242.3

CAS — 890-98-2.

UNII — 2QN49PWH71.

Profile

Benzyl mandelate has been used for its antispasmodic actions. It has also been included in preparations with analgesics in an attempt to increase the analgesic effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Spasmo Claim†; ***Turk.***: Spalt.

Berberine

Berberina.

5,6-Dihydro-9,10-dimethoxybenzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizinium.

$C_{20}H_{18}NO_4$=336.4

CAS — 2086-83-1 (berberine); 633-65-8 (berberine chloride); 633-66-9 (berberine sulfate).

UNII — 0I8Y3P32UF.

Pharmacopoeias. *Chin.* includes berberine chloride. *Jpn* includes berberine chloride hydrate and berberine tannate. *Viet.* includes berberine chloride dihydrate.

Profile

Berberine is a quaternary alkaloid present in hydrastis, in various species of *Berberis*, and in many other plants. It has been used as a bitter and as a flavour in food and alcoholic drinks. It possesses antimicrobial activity and has also been tried as various salts in some infections.

References.

1. Khin-Maung-U, *et al.* Clinical trial of berberine in acute watery diarrhoea. *BMJ* 1985; **291**: 1601–5.
2. Rabbani GH, *et al.* Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. *J Infect Dis* 1987; **155**: 979–84.
3. Vennerstrom JL, *et al.* Berberine derivatives as antileishmanial drugs. *Antimicrob Agents Chemother* 1990; **34**: 918–21.
4. Phillipson JD, Wright CW. Medicinal plants in tropical medicine: 1 Medicinal plants against protozoal diseases. *Trans R Soc Trop Med Hyg* 1991; **85**: 18–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Murine; ***China***: Si Na Ge (斯娜格).

Multi-ingredient Preparations. ***Braz.***: Neo Quimica Colirio†; Visazul; Visolon; ***Fr.***: Sedacollyre†; ***Hong Kong***: Berber CO†; ***UK***: Hemocyl.

Bergamot Oil

Bergamot Essence; Bergamota, aceite esencial de; Esencia de bergamota; Oleum Bergamottae; Бергамотное Масло.

UNII — 39W1PKE3JI.

Pharmacopoeias. In *Fr.* and *It.*

Uses and Administration

Bergamot oil is a greenish or brownish-yellow volatile oil with a characteristic fragrant odour and a bitter aromatic taste, obtained by expression from the fresh peel of fruit of *Citrus bergamia* (Rutaceae). Constituents include linalyl acetate and 5-methoxypsoralen (p. 1714.1).

Bergamot oil is used in perfumery and as a flavour in Earl Grey tea. It has been included in some preparations for upper respiratory-tract disorders and hyperhidrosis. It is also used in aromatherapy.

Adverse Effects

Photosensitivity reactions have occurred following the topical use of preparations containing bergamot oil.

Effects on the muscles. Muscle cramps have been reported[1] in a patient who drank up to 4 litres of 'Earl Grey' tea daily.

1. Finsterer J. Earl Grey tea intoxication. *Lancet* 2002; **359**: 1484.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Nopucid Bio Citrus; ***Ital.***: Bergacid†; ***Philipp.***: Kamillosan M; ***Switz.***: Perskindol Classic.

Beta-glucans

Beta-glucani; Beta-glucanos; Betaglukaner; β-D-Glucans; β-Glucans; Бета-глюканы.

CAS — 39464-87-4 (betasizofiran); 9013-94-9 (chrysolaminaran); 104074-36-4 (grifolan); 54724-00-4 (curdlan); 9008-22-4 (laminaran); 9037-88-1 (pachyman); 51052-65-4 (paramylon); 159940-37-1 (pleuran); 9010-72-4 (zymosan).

Pharmacopoeias. In *US.*

USP 36: (Beta Glucan). It is obtained by extraction from the cell wall of fermented and thermally processed *Saccharomyces cerevisiae*. It is comprised mainly of β-(1,3)/(1,6) branched glucan polymers. Small amounts of β-(1,6)-glucan and chitin are also expected to be present in the final product. It contains not less than 70% beta glucan, calculated as glucose after enzymatic hydrolysis, on the dried basis. Store in airtight containers. Protect from light.

Profile

Beta-glucans are a heterogeneous group of naturally occurring polysaccharides consisting of a backbone of β-1→3 linked D-glucopyranosyl moieties to which some D-glucopyranosyl moieties are randomly connected by β-1→6, β-1→3, or β-1→4 linkages as side-chains or branches.

There are numerous beta-glucans and their physical characteristics, such as solubility, and their biological activities vary according to the length of the main chain, the type and degree of branching, and the length of the side-chains. Common sources include: yeasts, mushrooms (reishi, shiitake, maitake) and other fungi; seaweeds and other algae; cereals (oats, barley); and bacteria. There can be considerable variation in the structure of beta-glucans not only between those derived from different sources but also within different batches of the same source. Unfortunately the literature is often vague as to the nature of the beta-glucan used or fails to state its source.

Some beta-glucans and typical sources include:

Algae:
- Chrysolaminaran (chrysolaminarin; leucosin) (*Chaetoceros muelleri*)
- Paramylon (*Euglena gracillis*)

Bacteria:
- Curdlan (*Alcaligenes faecalis*)

Fungi:
- Betasizofiran (scleroglucan) (*Athelia rolfsii*; *Sclerotium glucanicum*; *Sclerotium rolfsii*)
- Glomerellan (*Glomerella cingulata*)
- Grifolan (*Grifola frondosa*; maitake)
- Lentinan (*Lentinula edodes*; shiitake; see p. 2543.2)
- Pachyman (*Wolfiporia extensa*; *Poria cocos*)
- Pleuran (*Pleurotus ostreatus*)
- Polysaccharide-K (*Trametes versicolor*; *Coriolus versicolor*; see p. 2594.1)
- Sizofiran (*Schizophyllum commune*; see p. 857.2)

Seaweeds:
- Laminaran (Laminarin) (*Laminaria digitata*; *Laminaria hyperborea*; see p. 2540.1)

Yeasts:
- PGG-glucan (*Saccharomyces cerevisiae*)
- Macrogard(*Saccharomyces cerevisiae*)
- Zymosan (*Saccharomyces cerevisiae*)

Many beta-glucans are reported to have immunomodulating activity and some such as lentinan, polysaccharide-K (a beta-glucan protein complex), and sizofiran are used as adjuncts in the treatment of malignant neoplasms. Others are being studied in various diseases where manipulation of the immune system would be of benefit or as adjuncts in the management of diabetes. Some beta-glucans are promoted as dietary supplements.

It has been reported that soluble beta-glucans tend to be stronger immunostimulants than insoluble ones and modification of the glucan side-chain to produce derivatives such as carboxymethylated compounds has been reported to increase activity.

References.

1. Akramienė. D, *et al.* Effects of β -glucans on the immune system. *Medicina (Kaunas)* 2007; **43**: 597–606.
2. Chen J, Raymond K. Beta-glucans in the treatment of diabetes and associated cardiovascular risks. *Vasc Health Risk Manag* 2008; **4**: 1265–72.
3. Soltanian S, *et al.* Beta-glucans as immunostimulant in vertebrates and invertebrates. *Crit Rev Microbiol* 2009; **35**: 109–38.
4. Novak M, Vetvicka V. Glucans as biological response modifiers. *Endocr Metab Immune Disord Drug Targets* 2009; **9**: 67–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Decon Nasale; Evacream; Glucanet; Immuwash; Viscoblast Mono; ***Turk.***: Imuneks.

Multi-ingredient Preparations. ***Braz.***: Minesol; ***Fr.***: Herpclair; ***Ital.***: Biorag; Edodes; Glucanoos; Immun-up Junior; Immun-up; Imoviral Junior; Imoviral; Linfoflu; Proctocella Complex; Rinotrofina C; Ripavir; Viscoblast; ***Singapore***: Bios Life; ***USA***: Better Cholesterol.

Betahistine *(BAN, rINN)*

Betahistiini; Betahistin; Betahistina; Bétahistine; Betahistinum; Бетагистин.

N-Methyl-2-(2-pyridyl)ethylamine.

$C_8H_{12}N_2$=136.2

CAS — 5638-76-6.

ATC — N07CA01.

ATC Vet — QN07CA01.

UNII — X32KK4201D.

Betahistine Hydrochloride *(USAN, rINNM)*

Betahistiinidihydrokloridi; Betahistin Dihidroklorür; Betahistina, hidrocloruro de; Betahistin-dihydrochlorid; Betahistindihydrochlorid; Betahistindihydroklorid; Bétahistine, Chlorhydrate de; Bétahistine, dichlorhydrate de; Betahistine Dihydrochloride (BANM); Betahistini dihydrochloridum; Betahistini Hydrochloridum; Betahistino dihidrochloridas; Hidrocloruro de betahistina; PT-9; Бетагистина Гидрохлорид.

N-Methyl-2-(2-pyridyl)ethylamine dihydrochloride.

$C_8H_{12}N_2$,2HCl=209.1

CAS — 5579-84-0.

ATC — N07CA01.

ATC Vet — QN07CA01.

UNII — 49K58SMZ7U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Betahistine Dihydrochloride). A white to slightly yellow, very hygroscopic, powder. Very soluble in water; soluble in alcohol; practically insoluble in isopropyl alcohol. A 10% solution in water has a pH of 2.0 to 3.0. Store in airtight containers.

USP 36: (Betahistine Hydrochloride). A white to almost yellow, very hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in isopropyl alcohol. pH of a 10% solution in water is between 2.0 and 3.0.

Betahistine Mesilate *(BANM, rINNM)*

Betahistiinimesilaatti; Betahistina, mesilato de; Betahistindimesilat; Betahistin-dimesylát; Bétahistine, Mésilate de; Betahistine Mesylate; Betahistini Dimesilas; Betahistini mesilas; Betahistinmesilat; Betahistino mesilatas; Betahisztin-mezilát; Mesilato de betahistina; Бетагистина Мезилат.

N-Methyl-2-(2-pyridyl)ethylamine bismethanesulphonate.

$C_8H_{12}N_2$,$(CH_4O_3S)_2$=328.4

CAS — 54856-23-4.

ATC — N07CA01.

ATC Vet — QN07CA01.

UNII — X1L0E3R43Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Betahistine Mesilate). A white or almost white, crystalline, very hygroscopic powder. Very soluble in water; freely soluble in alcohol; very slightly soluble in isopropyl alcohol. A 10% solution in water has a pH of 2.0 to 3.0. Store in airtight containers.

Uses and Administration

Betahistine is an analogue of histamine and is claimed to improve the microcirculation of the labyrinth resulting in reduced endolymphatic pressure. It is used to reduce the symptoms of vertigo (p. 612.3), tinnitus (p. 1990.1), and hearing loss associated with Ménière's disease (p. 611.2).

Betahistine is given orally as the hydrochloride or mesilate. The usual initial dose of the hydrochloride is 16 mg three times daily taken preferably with meals; maintenance doses are generally in the range of 24 to 48 mg daily. Betahistine mesilate is used in similar doses.

References.

1. Lacour M, Sterkers O. Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. *CNS Drugs* 2001; **15**: 853–70.

2. James A, Burton MJ. Betahistine for Ménière's disease or syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 30/05/06).
3. Della Pepa C, *et al.* Betahistine in the treatment of vertiginous syndromes: a meta-analysis. *Acta Otorhinolaryngol Ital* 2006; **26:** 208–15.
4. Phillips JS, Prinsley PR. Prescribing practices for betahistine. *Br J Clin Pharmacol* 2008; **65:** 470–1.
5. Barak N. Betahistine: what's new on the agenda? *Expert Opin Invest Drugs* 2008; **17:** 795–804.

Adverse Effects

Gastrointestinal disturbances, headache, rashes, and pruritus have been reported.

References.
1. De Riu G, *et al.* An elderly female patient with tardive oromandibular dystonia after prolonged use of the histamine analog betahistine. *J Clin Neurosci* 2010;.

Precautions

Betahistine should not be given to patients with phaeochromocytoma. It should be given with care to patients with asthma, peptic ulcer disease, or a history of peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Betaserc; Meniex; Microser; Ronistina; Travelmin; ***Austral.***: Seniere; Seniere; Serc; ***Austria***: Bestin; Betaserc; ***Belg.***: Betahistop†; Betaserc; Docbetahi†; ***Braz.***: Betaserc; Labirin; ***Canad.***: Serc; ***Chile***: Microser; Vasomotal; ***China***: Merislon (敏使朗); Xi Qi Ting (西其汀); ***Cz.***: Avertin; Bestin; Betaserc; Emperin; Marbeta; Microser; Polvertic; Vertibetis; Vertisan; Zenostig; ***Denm.***: Betaserc; Serc; ***Fin.***: Acuver; Betaserc; ***Fr.***: Betaserc; Extovyl; Lectil; Serc; ***Ger.***: Aequamen; Betavert; Vasomotal; ***Gr.***: Antivom; Betaserc; Betavert; Katabexin; Ribrain; Riva; ***Hong Kong***: Alfinor; Beta-Synto; Betaserc; Meniero†; Merislon; ***Hung.***: Acuver; Betagen; Betarevin; Betaserc; Elven; Emperin; Microser; Polvertic; Zenostig; ***India***: Arotin; Balanse; Betahist; Betavert; Biobet; Carelet; Divert; Hestin-B; Histavert; Histigo; Hybet; Intrabet; Invert; Meni; Nanovert; Neuvert; Oshvert; Vertin; ***Indon.***: Betaserc; Darvon; Histigo; Merislon; Mertigo; Noverty; Vastigo; Vercure; Versilon; Vertex; ***Irl.***: Betahecon; By-Vertin; Serc; Vertigon; ***Israel***: Agiserc; Betistine; ***Ital.***: Betaserc; Fortamid; Microser; Sincrover; Vertiserc; ***Jpn***: Merislon; ***Malaysia***: Alfinor; Betaserc; Merislon; ***Mex.***: Serc; ***Neth.***: Betabare; Betakele; Betakile; Betakole†; Betakule; Betalane; Betalase; Betalene; Betalese; Betaline†; Betalose; Betalune; Betaluse; Betarave†; Betareze; Betarive; Betarove; Betaruve†; Betaserc; Betazela; Divetrin; Marbeta; Polvertic; Zenostig; ***NZ***: Serc; Vergo; ***Philipp.***: Exigo; Merislon; Normini; Serc; Verdiz; Verist; Vert; Vertegra; Vertilate; ***Pol.***: Betalan; Betanil; Betaserc; Histigen; Histimerck; Lavistina; Microser; Neatin; Polvertic; Verhist; Vertigen; Vertix; Vestibo; Zenostig; ***Port.***: Betaserc; Nucleus†; ***Rus.***: Asniton (Аснитон); Betacentrine (Бетацентрин); Betannorm (Бетанорм); Betaserc (Бетасерк); Betaver (Бетавер); Microser (Микрозер); Tagista (Тагиста); Vasoserc (Вазосерк); Vestibo (Вестибо); ***S.Afr.***: Serc; ***Singapore***: Betaserc; Merislon; ***Spain***: Fidium; Serc; ***Switz.***: Betaserc; ***Thai.***: Behistin; Betahis; Betahist-B†; Betris; Merislon; Merlin; Mertigo; Serc; Stei; ***Turk.***: Betaris; Betaserc; Betateva; Medisense; Vasoserc; Vertiserc; Vestibo; ***UK***: Serc; ***Ukr.***: Betagis (Бетагис); Betanorm (Бетанорм); Betaserc (Бетасерк); Vasoserc (Вазосерк); Vestibo (Вестібо); Vestinorm (Вестинорм); ***Venez.***: Microser; Serc.

Pharmacopoeial Preparations
BP 2014: Betahistine Dihydrochloride Tablets.

Betaine

Betaína; Glicina Betaina; Glicolol Betaina; Glycine Betaine; Glycocoll Betaine; Lycine; Trimethylglycine; Бетаин.
(Carboxymethyl)trimethylammonium hydroxide inner salt.
$C_5H_{11}NO_2$=117.1
CAS — 107-43-7.
ATC — A16AA06.
ATC Vet — QA16AA06.
UNII — 3SCV180C9W.

Betaine Hydrochloride

Betaiinihydrokloridi; Betaína, hidrocloruro de; Betainhydrokloríd; Betaini Hydrochloridum; Trimethylglycine Hydrochloride; Бетаина Гидрохлорид.
(Carboxymethyl)trimethylammonium hydroxide inner salt hydrochloride.
$C_5H_{11}NO_2$,HCl=153.6
CAS — 590-46-5.
ATC — A09AB02.
ATC Vet — QA09AB02.
UNII — JK8U8K4D6K.

Pharmacopoeias. In *US.*

USP 36: (Betaine Hydrochloride). A white crystalline powder. Soluble in water and in alcohol; practically insoluble in chloroform and in ether. A 25% solution in water has a pH of 0.8 to 1.2.

Profile

Betaine is used as a methyl donor to remethylate homocysteine to methionine in the treatment of patients with homocystinuria (see Amino Acid Metabolic Disorders, p. 2042.2). It is given orally in a usual dose of 3 g twice daily. Doses are adjusted according to plasma-homocysteine concentrations; up to 20 g daily has been required in some patients. For doses in children, see below.

Severe cerebral oedema and hypermethioninaemia have been reported in a few patients, and it is recommended that plasma-methionine concentrations should be monitored at the start of betaine treatment and periodically thereafter. Patients being treated for cystathionine beta-synthase deficiency may pose particular problems because betaine may further raise their already elevated methionine concentrations increasing the risk of cerebral oedema.

Betaine has also been used as a variety of salts in preparations for liver and gastrointestinal disorders. The hydrochloride has been given as a source of hydrochloric acid in the treatment of hypochlorhydria.

Administration in children. In the UK, betaine is given orally to children under 10 years of age in a usual daily dose of 100 mg/kg in 2 divided doses, adjusted according to response up to a maximum of 150 mg/kg daily. However, in the USA, licensed product information recommends this lower dose only for children under 3 years of age, and recommends the usual adult dose (see above) for children over 3 years.

Adverse effects. References.
1. Devlin AM, *et al.* Cerebral edema associated with betaine treatment in classical homocystinuria. *J Pediatr* 2004; **144:** 545–8.

Homocystinuria. References.
1. Smolin LA, *et al.* The use of betaine for the treatment of homocystinuria. *J Pediatr* 1981; **99:** 467–72.
2. Wilcken DEL, *et al.* Homocystinuria—the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983; **309:** 448–53.
3. Holme E, *et al.* Betaine for treatment of homocystinuria caused by methylenetetrahydrofolate reductase deficiency. *Arch Dis Child* 1989; **64:** 1061–4.
4. Anonymous. Betaine for homocystinuria. *Med Lett Drugs Ther* 1997; **39:** 12.

Liver disorders. Betaine has also been investigated for the treatment of nonalcoholic steatohepatitis.

References.
1. Miglio F, *et al.* Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis: a double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittelforschung* 2000; **50:** 722–7.
2. Abdelmalek MF, *et al.* Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. *Am J Gastroenterol* 2001; **96:** 2711–7.

Pharmacokinetics. References.
1. Schwahn BC, *et al.* Pharmacokinetics of oral betaine in healthy subjects and patients with homocystinuria. *Br J Clin Pharmacol* 2003; **55:** 6–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cystadane; ***Austria***: Cystadane; ***Belg.***: Cystadane; ***Canad.***: Cystadane; ***Cz.***: Cystadane; ***Denm.***: Cystadane; ***Fr.***: Cystadane; ***Ger.***: Cystadane; ***Irl.***: Cystadane; ***Israel***: Cystadane; ***Ital.***: Cystadane; ***Neth.***: Cystadane; ***Norw.***: Cystadane; ***Pol.***: Cystadane; ***Port.***: Cystadane; ***Spain***: Cystadane; ***Swed.***: Cystadane; ***USA***: Cystadane.

Multi-ingredient Preparations. ***Arg.***: Skin Hair & Nails; ***Austral.***: Betaine Digestive Aid; Digestaid; Digestive Zyme†; ***Austria***: Oroacid†; ***Belg.***: Digestomen; ***Braz.***: Abcler; Anekron; Biohepax†; Chofrafig; Colachofra; Enterofigon; Epocler; Hepalin; Hepatox; Metiocolin Composto; Necro B6; Xantinon Complex; ***Canad.***: Digesdyn; Digest; Formula 17605 Diaplex; Formula 3358†; Mega Zyme†; Multi-Zyme†; ***Fr.***: Actigess†; Citrarginine†; Hepagrume; Nivabetol†; ***Ger.***: Flacar; ***Gr.***: Efkalsol; Kloref; ***Hong Kong***: Jetepar†; ***Hung.***: Betacid; ***India***: Homocyst; ***Indon.***: DFM; ***Ital.***: Citroepatina†; Ri-Donna; ***Malaysia***: Enzyme Digest; Jetepar; ***Neth.***: Gastrobul†; ***Philipp.***: Jetepar; ***S.Afr.***: Kloref†; ***Singapore***: Jetepar†; ***Switz.***: Halipepsin†; ***UK***: Enzyme Digest; Enzyme Plus; Kloref†; Magnesium-B; ***Ukr.***: Citrarginine (Цитраргинин); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Clinical Nutrients 50-Plus Men; Mimyx†; Panplex 2-Phase; Sunnie; Tyler Prenatal.

Bethanechol Chloride *(BAN)*

Betanecol, cloruro de; Betanekolikloridi; Betanekolklorid; Bethanecholi Chloridum; Carbamylmethylcholine Chloride; Бетанехола Хлорид.
(2-Carbamoyloxypropyl)trimethylammonium chloride.
$C_7H_{17}ClN_2O_2$=196.7
CAS — 674-38-4 (bethanechol); 590-63-6 (bethanechol chloride).
ATC — N07AB02.
ATC Vet — QN07AB02.
UNII — H4QBZ2LO84.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Bethanechol Chloride). Colourless or white crystals, or white crystalline powder, usually having a slight, amine-like odour. It is hygroscopic and exhibits polymorphism. Freely soluble in water and in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 5.5 and 6.5. Store in airtight containers.

Stability. References to the stability of oral liquid preparations of bethanechol chloride prepared extemporaneously from tablets.
1. Schlatter JL, Saulnier J-L. Bethanechol chloride oral solutions: stability and use in infants. *Ann Pharmacother* 1997; **31:** 294–6.
2. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1804–9.

Sterilisation. The US manufacturers state that solutions of bethanechol chloride may be autoclaved at 120 degrees for 20 minutes without discoloration or loss of potency.

Uses and Administration

Bethanechol chloride, a choline ester, is a quaternary ammonium parasympathomimetic that mainly exhibits the muscarinic actions of acetylcholine (p. 2003.2). It is not inactivated by cholinesterases so its actions are more prolonged than those of acetylcholine. Bethanechol chloride has little if any nicotinic activity and is used for its actions on the bladder and gastrointestinal tract. It has been used as an alternative to catheterisation in the treatment of urinary retention and has also been used for gastric atony and retention, abdominal distension following surgery, congenital megacolon, and gastro-oesophageal reflux disease.

Bethanechol chloride is given in usual doses of 10 to 50 mg orally up to 4 times daily, but dosage must be adjusted individually. Doses should be taken on an empty stomach. Bethanechol has also been given subcutaneously. For a warning to avoid intravenous or intramuscular use, see under Precautions, below.

Decreased gastrointestinal motility. Parasympathomimetics such as bethanechol enhance gastric contractions and increase intestinal motility and form just one of many treatments that have been used in conditions associated with decreased gastrointestinal motility (p. 1805.2).

Gastro-oesophageal reflux disease. Prokinetic drugs such as bethanechol have been tried in gastro-oesophageal reflux disease (p. 1807.2).

References.
1. Thanick KD, *et al.* Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. *Ann Intern Med* 1980; **93:** 805–8.
2. Saco LS, *et al.* Double-blind controlled trial of bethanechol and antacid versus placebo and antacid in the treatment of erosive esophagitis. *Gastroenterology* 1982; **82:** 1369–73.
3. Thanick K, *et al.* Bethanechol or cimetidine in the treatment of symptomatic reflux esophagitis: a double-blind control study. *Arch Intern Med* 1982; **142:** 1479–81.
4. Strickland AD, Chang JHT. Results of treatment of gastroesophageal reflux with bethanechol. *J Pediatr* 1983; **103:** 311–15.

Urinary incontinence and retention. Bethanechol is one of the parasympathomimetics that have been given to increase detrusor activity in patients with overflow incontinence, but there have been doubts about the efficacy of such treatment (see p. 2349.2). Bethanechol was also one of the parasympathomimetics used in the management of postoperative urinary retention but they have generally been superseded by catheterisation.

References.
1. Finkbeiner AE. Is bethanechol chloride clinically effective in promoting bladder emptying: a literature review. *J Urol (Baltimore)* 1985; **134:** 443–9.
2. Kemp B, *et al.* Prophylaxis and treatment of bladder dysfunction after Wertheim-Meigs operation: the positive effect of early postoperative detrusor stimulation using the cholinergic drug betanecholchloride. *Int Urogynecol J Pelvic Floor Dysfunct* 1997; **8:** 138–41.
3. Riedl CR, *et al.* Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test. *J Urol (Baltimore)* 2000; **164:** 2108–11.

Adverse Effects and Treatment

As described for choline esters under Acetylcholine Chloride, p. 2003.2.

Precautions

As described for choline esters under Acetylcholine Chloride, p. 2003.3.

Bethanechol should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse

effects are liable to occur, calling for emergency use of atropine.

Autonomic neuropathy. Patients with autonomic neuropathy might be more susceptible to the adverse effects of bethanechol and they should be started on low-dosage regimens and observed closely for signs of toxicity.[1]

1. Caraco Y, *et al.* Bethanechol-induced cholinergic toxicity in diabetic neuropathy. *DICP Ann Pharmacother* 1990; **24:** 327–8.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Bethanechol chloride is poorly absorbed from the gastrointestinal tract. It is not hydrolysed by cholinesterases. At standard doses bethanechol does not cross the blood-brain barrier.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Miotonachol; ***Austral.***: Urocarb; ***Austria***: Myocholine; ***Belg.***: Myocholine; ***Braz.***: Liberan; ***Canad.***: Duvoid; Myotonachol†; ***Ger.***: Myocholine; ***India***: Bethacol; Urotone; Urotonin; ***Philipp.***: Uriflow; ***Switz.***: Myocholine; ***Thai.***: Ucholine; Urecholine; ***UK***: Myotonine; ***USA***: Myotonachol; Urecholine.

Pharmacopoeial Preparations
USP 36: Bethanechol Chloride Injection; Bethanechol Chloride Oral Solution; Bethanechol Chloride Oral Suspension; Bethanechol Chloride Tablets.

Bibrocathol *(rINN)*

Bibrocathin; Bibrocatholum; Bibrocatol; Bibrokatol; Bibrokatoli; Bismuth Tetrabrompyrocatechinate; Tetrabromopyrocatechol Bismuth; Биброкатол.

4,5,6,7-Tetrabromo-2-hydroxy-1,3,2-benzodioxabismole.

$C_6HBiBr_4O_3$=649.7

CAS — 6915-57-7.

ATC — S01AX05.

ATC Vet — QS01AX05.

UNII — 0KJ20H1BLJ.

Profile

Bibrocathol is a bismuth-containing compound that has been applied topically in the treatment of eye disorders, wounds, and burns.

References.

1. Behrens-Baumann W, *et al.* Bibrocathol-Augensalbe ist wirksam bei Blepharitis. Ergebnisse einer randomisierten, doppelblinden, kontrollierten klinischen Studie. *Ophthalmologe* 2006; **103:** 960–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bibrocathol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 31/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Noviform†; Posiformin; ***Swed.***: Noviform; ***Switz.***: Posiformin.

Bicyclol

Бициклол.

4,4′-Dimethoxy-5,6,5′,6′-bis(methylene-dioxy)-2-hydroxymethyl-2′methoxycarbonyl biphenyl.

$C_{19}H_{18}O_9$=390.3

Profile

Bicyclol has been used as a hepatoprotectant in the management of hepatitis. It has been given orally in a dose of 25 or 50 mg three times daily for at least 6 months.

References.

1. Liu Q, *et al.* A useful agent for chemoprevention of hepatocellular carcinoma? *Cancer Biol Ther* 2006; **5:** 1674–6.
2. Wu T, *et al.* Bicyclol for chronic hepatitis B. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/05/08).
3. Yang X, *et al.* Bicyclol for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 01/05/08).
4. Liu GT. Bicyclol: a novel drug for treating chronic viral hepatitis B and C. *Med Chem* 2009; **5:** 29–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bai Sai Nuo (百赛诺).

Bifendate

Dimethyl 7,7′-dimethoxy-(4,4′-bi-1,3-benzodioxole)-5,5′-dicarboxylate.

$C_{20}H_{18}O_{10}$=418.4

CAS — 73536-69-3.

Pharmacopoeias. In *Chin.*

Profile

Bifendate is derived from schisandra (see p. 2611.2). It is used in Chinese medicine for chronic hepatitis.

Bifendate has been reported to reduce blood concentrations of ciclosporin (see p. 1953.2).

Bile Acids and Salts

Biliares, ácidos y sales; Желчные Кислоты и Соли Желчных Кислот.

CAS — 81-25-4 (cholic acid); 11006-55-6 (sodium tauroglycocholate); 361-09-1 (sodium cholate).

Pharmacopoeias. *Jpn* includes bear bile.

Profile

The principal primary bile acids, cholic acid and chenodeoxycholic acid (p. 2475.1), are produced in the liver from cholesterol and are conjugated with glycine or taurine to give glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid, before being secreted into the bile where they are present as the sodium or potassium salts (bile salts). Secondary bile acids are formed in the colon by bacterial deconjugation and 7α-dehydroxylation of cholic acid and chenodeoxycholic acid, producing deoxycholic acid and lithocholic acid, respectively. Ursodeoxycholic acid (p. 2638.1) is a minor bile acid in man although it is the principal bile acid in *bears*. Dehydrocholic acid (p. 2492.1) is a semisynthetic bile acid.

The total body pool of bile salts is about 3 g, and most of the secreted bile salts are reabsorbed in a process of enterohepatic recycling, so that only a small fraction of this amount must be synthesised *de novo* each day.

Bile salts are strongly amphiphilic; with the aid of phospholipids they form micelles and emulsify cholesterol and other lipids in bile. Oral administration of chenodeoxycholic acid also reduces the synthesis of cholesterol in the liver, while ursodeoxycholic acid reduces biliary cholesterol secretion apparently by increasing conversion of cholesterol to other bile acids. The bile acids (but not the bile salts) also have a choleretic action, increasing the secretion of bile, when given orally.

Chenodeoxycholic acid and ursodeoxycholic acid are given orally in the management of cholesterol-rich gallstones (p. 2639.1) in patients unsuited to, or unwilling to undergo, surgery. Ursodeoxycholic acid is also used in some chronic liver diseases (p. 2638.2) including primary biliary cirrhosis (p. 2638.3).

Preparations containing bile salts have been used to assist the emulsification of fats and absorption of fat-soluble vitamins in conditions in which there is a deficiency of bile in the gastrointestinal tract. Ox bile has also been used in the treatment of chronic constipation. Cholic acid is used for the treatment of inborn errors in primary bile synthesis.

Sodium cholate has been used for its spermicidal properties in barrier contraceptives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Desicol†; ***Mex.***: Virulizin; ***Rus.***: Festal (Фестал); ***S.Afr.***: Bilron†; ***Ukr.***: Allocholum (Аллохол); ***Venez.***: Hepa-Desicol.

Multi-ingredient Preparations. ***Arg.***: Bibol Leloup; Bil 13; Bilagol Antigas; Bilidren; Carbogasol Digestivo; Cascara Sagrada Bouzen; Digesplen; Hepatalgina; Nilflux; Opobyl; Veracolate†; Zimerol; ***Austral.***: Digestaid; Enzyme; ***Austria***: Buccalin; Helopanzym; Intestinol†; Silberne†; ***Belg.***: Buccaline†; ***Braz.***: B-Vesil†; Dasc†; Figatil; ***Canad.***: Artechol†; Articho-Nat; Bicholate†; Colibyl†; Digesdyn; Digestolax; Formula B-1†; Hepartichaut†; Lipozyme†; Multi-Zyme†; Regubil; ***Chile***: Combizym Compositum†; Flapex E; Hepabil; K.C.M.C; Katin; ***China***: Fufang Dan An Pian (复方胆氨片); Wei Tai Kang (谓泰康); ***Cz.***: Combizym Compositum†; ***Fr.***: Rectopanbiline; ***Hong Kong***: Enzyplex; Hepatofalk†; Protectaid; ***India***: Cyltabs; Digeplex-T; Disseptal; Enzovit; Festal; Kamozyme-EP; Livotone; Merckenzyme†; Mumzyme; Papytazyme; ***Indon.***: Benozym; Berzymplex; Cotazym Forte; Enzymfort; Enzyplex; Eviprostat; Pankreon Comp; ***Israel***: Encypalmed; Protectaid; ***Ital.***: Solvobil†; ***Malaysia***: Enzyplex†; ***Mex.***: Dixiflen; Espaven Enzimatico; Ochozim; Zimeton; ***NZ***: Buccaline; ***Philipp.***: SG-Glutergen; ***Port.***: Fermetone Composto; ***Rus.***: Biofestal (Биофесталь); Cholenzim (Холензим); Ipental (Ипентал)†; Pheresthal (Ферестал); ***Singapore***: Enzyplex; ***Swed.***: Combizym Compositum†; ***Switz.***: Buccaline; Combizym Compositum; ***Thai.***: Combizym Compositum†; Enzyplex†; Patarcolate; Veracolate†; ***Turk.***: Flaton; Intestinol; Multanzim†; Pankreon Comp; Pankrodigest†; ***UK***: Protectaid; ***Ukr.***: Choliver (Холивер)†; Festal (Фестал); ***USA***: Digepepsin; Panplex 2-Phase; ***Venez.***: Combizym Forte; Nutizym Compositum; Pankreon Compositum; Stamyl.

Homoeopathic Preparations. ***Canad.***: Carduus Plex†; ***Fr.***: Bilinum Complexe No 113; Hepatodrainol.

Birch Leaf

Abedul, hojas de; Beržų lapai; Betulae Folium; Březový list; Birkenblätter; Björkblad; Bouleau; Bouleau, feuille de; Koivunlehti; Liść brzozy; Nyírfalevél; Silver Birch Leaf; Берёзовый Лист.

*ATC Herb — HG04BW5005 (*Betula pendula*: leaf).*

UNII — 5HW39H9KDH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Birch Leaf). The whole or fragmented dried leaves of *Betula pendula* and/or *B. pubescens* as well as hybrids of both species. It contains not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4), with reference to the dried drug. Protect from light.

Profile

Birch leaf is used in herbal medicine, particularly for urinary-tract disorders. Birch leaf oil has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Betulacur†; Urorenal†; ***Hung.***: Salus Diuretic.

Multi-ingredient Preparations. ***Arg.***: Sequals G; ***Austria***: Blasentee St Severin; Heumann's Blasen- und Nierentee; Rheuma; Solubitrat†; ***Canad.***: Bio Renal†; Entschlackungstee N†; Entwasserungstee†; Rheuma Heilkrauter Tee†; ***Chile***: Cellenergy; ***Cz.***: Fytokliman Planta; Reduktan; Species Urologicae Planta; Urologicka Cajova Smes; ***Fr.***: B.O.P.; Depuratum; Detoxifiance; Drainactil†; Mediflor Douleurs Articulaires no 2†; Silibiol; Urotisan†; ***Ger.***: Antihypertonicum S; BioCyst†; Biofax†; Dr Wiemanns Rheumatonikum†; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee†; Harntee 400 N; Harntee-Steiner†; Heumann Blasen- und Nierentee Solubitrat uro; Hevert-Blasen-Nieren-Tee N†; Nephroselect M; Renob Blasen- und Nierentee†; ***Hung.***: Kilo-Nit; Mensesyl; Urogin; Uroherb; ***Ital.***: Flebonorm; Gemiol Plus; Ginoday; Linfonorm; Lipaven; Listerine Fresh Citrus; Slimmer Plus; ***Pol.***: Betasol; Diabetofort; Herbaton†; Nefrobonisol; NeoFitolizyna†; Urosan†; Urosept; ***Rus.***: Herbion Urological Drops (Гербион Урологические Капли); Sibectan (Сибектан); Urokam (Урокам); ***S.Afr.***: Arnica Massage Oil; ***Spain***: Diurinat; Genurat; ***Switz.***: Dragees S pour les reins et la vessie; Impuls dragees pour la vessie et les reins; Nephrosolid; Sabrinin dragees pour les reins et la vessie; Tisane Diuretique; Tisane pour le coeur et la circulation; Tisane pour les reins et la vessie; Urinex; ***UK***: Massage Balm with Calendula; ***Ukr.***: Ambovit (Амбовит); Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Urochol (Урохол)†; Uronephron (Уронефрон).

Homoeopathic Preparations. ***Canad.***: Homeodel 15†; Nixotinex; Urarthone†; ***Cz.***: Galium; ***Fr.***: Berberis Complexe No 83; Rheumadoron; Sclerocalcine; Urarthone; ***Ger.***: Arnica comp/Apis†; Arnica/Betula comp; Arnica/Symphytum comp; K 1000; Levisticum S; Mandragora comp; Rheumodoron 102 A; ***Switz.***: Rheumadoron; ***UK***: Rheumadoron; Rheumadoron.

Black Catechu

Cutch; Акация-катеху (*Acacia catechu*).

CAS — 8001-76-1.

UNII — 55J167EEON.

NOTE. Distinguish from Catechu (p. 2472.3).

Pharmacopoeias. In *Chin.*

Profile

Black catechu is an extract from *Acacia catechu* (Leguminosae) that is used as an astringent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Herbadict; ***India***: Arowash†; Koflet; ***Ukr.***: Travisil (Трависил).

Black Currant

Blackcurrant; Cassis; Grosella negra (casis); Rib. Nig.; Чёрная Смородина (*Ribes nigrum*).

*ATC Herb — HR05YA5019 (*Ribes nigrum*: fruit); HA07XA5011 (*Ribes nigrum*: fruit).*

*UNII — 9755T40D11 (*Ribes nigrum *fruit); Z46FSZ2M25 (*Ribes nigrum *leaf).*

Pharmacopoeias. *Br.* includes the fruit.

Eur. (see p. vii) includes the leaf.

BP 2014: (Black Currant). The fresh ripe fruits of *Ribes nigrum* with their pedicels and rachides. It has a strong, characteristic odour and a pleasantly acidic taste.

Profile

Black currant fruit is a source of vitamin C (p. 2110.3). It is used to prepare black currant syrup, which is used as a nutritional supplement and as a flavour.

Black currant leaf is included in herbal preparations for urinary, musculoskeletal, and gastrointestinal disorders. Black currant is reported to contain bioflavonoids and is also included in preparations for vascular disorders. It has also been used as a diuretic in folk medicine.

Black currant seed oil (below) is used as a source of gamolenic acid (see p. 2509.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Tiliv†.

Multi-ingredient Preparations. ***Austria***: Amersan; ***Cz.***: Amersan; ***Fr.***: Arkophytum†; Arthritisane†; Arthroflorine†; Chondrosteo; Drainactil†; Expuryl; Glucarthroz; Hydracur; IgeE†; Mediflor Douleurs Articulaires no 2†; Mincifit†; Resource Rhubagil†; Rhumadol; Santane A_4†; Santane O1; Santane R_8†; Silibiol; Tisane Provencale no 6†; Urotisan†; Veinobiase; ***Hung.***: Crategil; ***Ital.***: Anaribes Plus; Flebotrofine; Gemiol Plus; Imoviral; Nepiros; Ribovir; ***Pol.***: Melisal; Melissed; ***S.Afr.***: Vitaforce Acerola C†; ***Spain***: Exodren; Fitosvelt†; ***Ukr.***: Vitokan (Витокан).

Pharmacopoeial Preparations
BP 2014: Black Currant Syrup.

Black Currant Seed Oil

Blackcurrant seed oil.

UNII — GKE1188837.

Profile

Black currant seed oil is derived from the seeds of *Ribes nigrum* (Grossulariaceae). It contains gamolenic acid (p. 2509.2) and is used similarly to evening primrose oil (p. 2502.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Solaire; ***UK***: Skin Perfecting Oil; ***Ukr.***: Perfectil Plus (Перфектил Плюс).

Black Haw

American Sloe; Nanny Bush; Stag Bush; Калина Сливолистная.

UNII — J411UTU0HN (Viburnum prunifolium bark).

Pharmacopoeias. In *Fr.*

Profile

The bark of black haw, *Viburnum prunifolium* (Adoxaceae) is claimed to have spasmolytic activity on uterine and other smooth muscle. It is included in herbal preparations for peripheral vascular disorders and menstrual disorders. The root bark is also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Aphloine P; Climaxol; Jouvence de l'Abbe Soury; Jouvence de l'Abbe Soury; Phlebosedol†; ***Mon.***: Fluon.

Homoeopathic Preparations. ***Fr.***: Aesculus Compose; Hamamelis Compose; Veino-Drainol†; ***Ger.***: Pascofemin spasmo.

Black Nightshade

Hierba mora; Morelle Noire; Solano negro; Tomatillos del diablo; Паслён Чёрный.

*UNII — 0FMD6WV47M (*Solanum nigrum*); XA101YYV55 (*Solanum nigrum *fruit); O4G5C1G3W5 (*Solanum nigrum *top).*

Profile

Black nightshade is the leaves and flowering tops of the black or garden nightshade, *Solanum nigrum* (Solanaceae). It contains solanine and its allied alkaloids. Black nightshade is distributed throughout most of the world as a weed of cultivation. It appears to have little medicinal value although it has been used in some herbal products and in liniments, poultices, and decoctions for external application. Ingestion can cause typical antimuscarinic effects that may require treatment as described under Atropine, p. 1312.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Pol.***: Liv 52; ***Rus.***: Bonjigar (Бонджигар); Dipana (Дипана); Liv 52 (Лив 52); Liv 52 (Лив 52); ***Singapore***: Liv 52; Liv 52; ***Ukr.***: Bonjigar (Бонджигар); Eve Care (Ив Кер)†; Liv 52 (Лив 52); Pilex (Пилекс).

Homoeopathic Preparations. ***Canad.***: Arnica-Heel Comp†; Ateria-Heel†; ***Fr.***: Poconeol no 71.

Blackthorn

Black Thorn; Épine noir; Prugnolo; Prunellier; Schlehe; Schwarzdorn; Sloe; Тёрн; Терновник.

*ATC Herb — HA06AX5008 (*Prunus spinosa*: flower).*

*UNII — 5342MY2M3P (*Prunus spinosa*); 53Y84VPS2W (*Prunus spinosa *flower bud); 181707E6S0 (*Prunus spinosa *flower water); 3MLB4858X7 (*Prunus spinosa *fruit); UU3NL9WVML (*Prunus spinosa *wood).*

Pharmacopoeias. *Br.* includes Prunus Spinosa Fruit for Homoeopathic Preparations.

BP 2014: (Prunus Spinosa Fruit for Homoeopathic Preparations). The fresh ripe fruit of *Prunus spinosa.*

Profile

The flowers of the blackthorn or sloe, *Prunus spinosa* (Rosaceae), are included in herbal preparations for constipation and urinary-tract disorders.

The fruit (sloes) are used for mild inflammation of oral and pharyngeal mucosa.

Culinary uses of sloes include preserves and as a flavour in alcoholic beverages.

Homoeopathy

Blackthorn is used in homoeopathic medicines under the following names: Prunus spin; Prunus spinosa; Prunus spinosa e summitatibus Rh; Prunus spinosa, Summitates Rh.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Schlehen Elixir†.

Multi-ingredient Preparations. ***Ger.***: Schnupfencreme; Weleda Hauttonikum†; ***S.Afr.***: Lotio Pruni Comp cum Cupro†; ***Switz.***: Venadoron; Wala Baume nasal doux; Wala Baume nasal.

Homoeopathic Preparations. ***Neth.***: Weleda Sleedoorn†; ***UK***: Catarrh Cream.

Blue Cohosh

Caulófilo; Caulophyllum; Papoose Root; Squaw Root; Стеблелист Василистниковидный (*Caulophyllum thalictroides*).

*UNII — 518LV969O6 (*Caulophyllum thalictroides*); JTJ6HH6YEH (*Caulophyllum thalictroides *root).*

NOTE. Distinguish from Black Cohosh, which is Cimicifuga, p. 2478.1.

Uses and Administration

Blue cohosh, the rhizome and roots of *Caulophyllum thalictroides* (Berberidaceae), has uterotonic and antirheumatic properties. It is used for menstrual and other gynaecological disorders.

Homoeopathy

Blue cohosh has been used in homoeopathic medicines under the following names: Caulophyllum; Caulophyllum thalictroides; Caulph.

References.

1. Dugoua JJ, *et al.* Safety and efficacy of blue cohosh (Caulophyllum thalictroides) during pregnancy and lactation. *Can J Clin Pharmacol* 2008; **15:** e66–e73.

Adverse Effects

Effects on the cardiovascular system. Acute myocardial infarction associated with profound congestive heart failure and shock has been reported in a newborn infant whose mother ingested blue cohosh to promote uterine contractions.[1]

A case of cerebral infarct, resulting in motor seizures affecting the right arm, has also been reported[2] in a neonate born to a mother who used blue cohosh; screening revealed the presence of a cocaine metabolite, benzoylecgonine, in the herb, but it was unclear if this was due to contamination, or was a false-positive reaction caused by some other component.[3]

1. Jones TK, Lawson BM. Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication. *J Pediatr* 1998; **132:** 550–2.
2. Finkel RS, Zarlengo KM. Blue cohosh and perinatal stroke. *N Engl J Med* 2004; **351:** 302–3.
3. Finkel RS, Zarlengo KM. More on blue cohosh and perinatal stroke. *N Engl J Med* 2004; **351:** 2240–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Dyzco†.

Homoeopathic Preparations. ***Austria***: Mastodynon; Pascofemin; ***Canad.***: Comp-Drops 9†; Hylands PMS; Hylaprin; ***Cz.***: Mastodynon; ***Ger.***: Dysmenorrhoe-Gastreu S R75; Mastodynon; Naranofem†; Pascofemin spasmo; Pascofemin; ***Neth.***: Mastodynon†; ***Rus.***: Mastodynon (Мастодинон); ***Thai.***: Mastodynon†; ***Ukr.***: Mastodynon (Мастодинон).

Bog Myrtle

Sweet Gale; Восковница Обыкновенная (*Myrica gale*).

NOTE. Bog myrtle has also been used as a common name for *Menyanthes trifoliata* (see Menyanthes, p. 2554.2). Bayberry (see p. 2453.1) has also been used as a synonym for bog myrtle.

Profile

The essential oil obtained from bog myrtle, *Myrica gale* (Myricaceae), has been used as an insect repellent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: MozzyOff Cocktail.

Boldo

Boldi Folium; Boldo, feuille de; Boldo Folium; Boldo Leaves; Boldoblad; Boldólevél; Boldonlehti; Boldovníkový list; Hojas de boldo; Kvapiųjų čilmedžių lapai; Liść boldo; Peumus; Больдо.

CAS — 476-70-0 (boldine); 1398-22-7 (boldoglucin).

*ATC Herb — HA05AW5013 (*Peumus boldus*: leaf); HG04BW5028 (*Peumus boldus*: leaf).*

UNII — Q4EWM09M3O.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes Boldo Leaf Dry Extract.

Fr. includes Boldine.

Ph. Eur. 8: (Boldo Leaf). The whole or fragmented dried leaf of *Peumus boldus*. It contains not more than 4% v/w of essential oil calculated with reference to the anhydrous drug. It contains not less than 0.1% of total alkaloids, expressed as boldine ($C_{19}H_{21}NO_4$ = 327.4), calculated with reference to the anhydrous drug. It has a characteristic odour especially when rubbed. Protect from light.

Profile

Boldo is employed in herbal medicine as a diuretic, for hepato-biliary disorders and for gastrointestinal disorders such as constipation. The alkaloid boldine is also used.

Homoeopathy

Boldo has been used in homoeopathic medicines under the following names: Peumus boldus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Hepatilon; Prinachol; ***Canad.***: Cholarex; ***Mex.***: Bliz†.

Multi-ingredient Preparations. ***Arg.***: Alcachofa Plus; Bil 13; Boldina; Chofitol Plus; Digenat; Dioxicolagol; Drenocol; Fegalgina; Hepacur; Hepatalgina; Hepatalgina; Hepatodirectol; Incaico; Metiogen; Opobyl; Palatrobil; Radicura; Sabelin; Wunderbalsam; ***Austral.***: Berberis Complex†; ***Austria***: St Bonifatius-Tee†; ***Braz.***: Colachofra; Ductoveran; Eparema; Figatil; Gotas Digestivas; Gotas Preciosas; Solvobil; ***Canad.***: Hepaflor†; Hepaticol;

Hepatol; Herbaraphanus†; Phyto-Marinex; ***Chile***: Hepabil; Nature Complex Reduct-Te; Reduc-Te; Te Laxante†; ***Cz.***: The Salvat; ***Fr.***: Afra†; Azema†; Bolcitol†; Boldoflorine; Boldoflorine; Boribel Tisane No 7†; Drainactil†; Elixir Spark†; Gastrotisane†; Hepaclem†; Hepatoflorine†; Jecopeptol†; Maalox Digestion Difficile; Mediflor Hepatique No 5; Mucinum a l'Extrait de Cascara; Opobyl†; Oxyboldine; Petites Pilules Carters†; Santane C_6†; Santane F_{10}†; Solution Stago Diluee; Tisane Garfield†; Tisane Hepatique de Hoerdt†; ***Ger.***: Heumann Verdauungstee Solu-Lipar; ***Ital.***: Amaro Medicinale; Boldina He; Caramelle alle Erbe Digestive; Cistefi; Colax†; Confetti Lassativi CM; Dis-Cinil Complex; Eparema-Levul; Eparema; Eupatol; Hepatos B12; Hepatos; Solvobil†; ***Mex.***: Chofabol; Hepedren; Ifuchol; Peptochol; ***Pol.***: Boldaloin; Boldovera; ***Port.***: Mucinum; ***Spain***: Nico Hepatocyn; Opobyl; Resolutivo Regium†; Solucion Schoum; ***Swed.***: Cynaramin; ***Switz.***: Boldocynara; Kernosan 24; Tisane hepatique et biliaire; ***UK***: Adios; Aquella; Boldex; Digestisan; HealthAid Boldo-Plus; Milk Thistle Complex; Weight Loss Aid; ***Venez.***: Cynascool; Natrossil.

Homoeopathic Preparations. ***Canad.***: Cynara Complex†; Digestion; Formula FV 213; Hecocur†; ***Chile***: Cynara Compuesta; Digherbal; ***Fr.***: Aesculus Complexe No 103; L 114; Poconeol no 7; ***Ger.***: EAP-61; ***Neth.***: Apo-Hepat.

Boneset

Feverwort; Hierba de la fiebre; Thoroughwort; Посконник Прободённый (*Eupatorium perfoliatum*).

*ATC Herb — HR05YA5006 (*Eupatorium perfoliatum*: herb).*

NOTE. Boneset has also been used as a common name for *Symphytum officinale* (see Comfrey, p. 2484.2). Purple boneset is Gravel Root, p. 2522.1. The name Feverwort has also been used for *Centaurium erythraea* (see Centaury, p. 2473.2).

Profile

Boneset, the aerial parts of *Eupatorium perfoliatum* (Compositae), has diaphoretic and immunostimulant properties and has been used in the treatment of fever, influenza, the common cold, and other upper respiratory-tract disorders.

Homoeopathy

Boneset has been used in homoeopathic medicines under the following names: Eupatorium perfoliatum; Eupatorium perf; Eup. perf.

References.

1. Habtemariam S, Macpherson AM. Cytotoxicity and antibacterial activity of ethanol extract from leaves of a herbal drug, boneset (Eupatorium perfoliatum). *Phytother Res* 2000; **14:** 575–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Flavons†; ***Switz.***: Spagymun; ***UK***: Catarrh Mixture.

Homoeopathic Preparations. ***Austral.***: Childrens Cold and Flu Relief; Echine†; ***Austria***: Ferrum Phosphoricum comp; Globuli gegen Grippe; Gripp Heel; Infludo; Nisylen†; toxi-loges; ***Canad.***: C-Plus; Comp-Drops 5 Expectorant†; Complete Flu Care 4 Kids†; Echinacea Compositum; Formula INF; Hylands Flu; Hylands Formula F; Ikoplex 12†; Ivernax; L52 Cough & Cold; ***Chile***: Ikoplex No 12; Influk; Similibus; ***Cz.***: Gripp Heel; Lehnigrip†; Paragrippe; ***Fr.***: Aconitum Compose†; Boripharm No 11†; grippe†; Infludo; L 52; Paragrippe; ***Ger.***: Anovin; Broncho-Injektopas; Cefagrippin†; Contramutan; Echinacea comp; Eupatorium N Oligoplex; Ferrum phosphoricum comp; Gripp-Heel; Grippe-Gastreu S R6; Gripps; Immunorell; Infi-Echinacea; Infigripp; Infludo; Influvit; Jowidarmin; Nisylen; Pascoleucyn N; Pascoleucyn; phono Gripp; toxi-loges; toxi-loges; Wiedimmun N†; Wiedimmun; ***Hung.***: Gripp-Heel; ***Neth.***: Echilite; Echinacea comp; Febrilite; Gripp-Heel H; Grippe-Gastreu R6; Homeocare Revito; Infludo; Kind 0-6 Nisykind; Kruidvat Homeopathie Influ-complex†; Nisyleen; Paragrippe†; ***Port.***: Paragrippe; ***Rus.***: Berberis Comp (Барбарис Комп); Influcid (Инфлюцид); ***S.Afr.***: Ferrum Phos Comp†; Gripp-Heel; Infludo†; ***Switz.***: Gripp-Heel; Influaforce†; Infludo; ***UK***: Infludo; ***Ukr.***: Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Influcid (Инфлюцид); ***USA***: Preferred Remedies Cold & Flu.

Borage

Borraja; Bourrache; Огуречник; Бораго.

*ATC Herb — HJ01WB5005 (*Borago officinalis: *herb); HM01AW5003 (*Borago officinalis: *herb); HR05DB5003 (*Borago officinalis: *herb).*

UNII — 7X23S1OW1N (borage flower); PB618V0K2W (borage leaf).

Pharmacopoeias. *Fr.* includes monographs for flowers and flowering tops.

Profile

The aerial parts of borage *Borago officinalis* (Boraginaceae), have been used in herbal medicine as a demulcent and emollient. However, it contains pyrrolizidine alkaloids that may be toxic and internal use is not recommended.

Borage seeds are the source of borage oil (below), which is used as a source of gamolenic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Dexol.

Multi-ingredient Preparations. ***Canad.***: Natraway Sport 1 & 2†; Natraway Sport 3†; ***Chile***: Celltech; ***Ital.***: Sclerovis H Plus; ***Mex.***: Aveendix; ***NZ***: Mr Nits.

Homoeopathic Preparations. ***Chile***: TBR/X.

Borage Oil

Boraginis Oleum; Borago Officinalis Oleum; Borraja, aceite de; Bourrache, huile de; Brutnákový olej; Gurkörtolja; Purasruohoöljy; Starflower Oil; Vaistinių agurklių aliejus; Масло Бурачника.

UNII — F8XAG1755S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Borage (Starflower) Oil, Refined; Refined Borage Oil BP 2014). The fatty oil obtained from seeds of *Borago officinalis* by extraction and/or expression. It is then refined. A suitable antoxidant may be added. A clear, light yellow or yellow liquid. Relative density about 0.921. Practically insoluble in water and in alcohol; miscible with petroleum spirit. Store in well-filled, airtight containers under an inert gas. Protect from light.

The BP 2014 gives Refined Starflower Oil as an approved synonym.

Profile

Borage oil is a source of essential fatty acids, mainly gamolenic acid (p. 2509.2). It is included in dietary supplements, often with fish oils or other sources of omega-3 fatty acids (see p. 1460.1).

Eczema. For the effects of borage oil on eczema, see under Gamolenic Acid, p. 2509.3.

Rheumatoid arthritis. For the use of borage oil as a source of gamolenic acid for the management of rheumatoid arthritis, see under Gamolenic Acid, p. 2510.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Tiliv L; ***Fr.***: Omegaline; ***Pol.***: Neoglandyna; ***UK***: Floresse.

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; Cellasene†; La Edad De Oro; Ureadin Facial; ***Braz.***: Borag; Gamaline-V; Livten Vit; Primorist; Votag O6; ***Canad.***: Primanol Borage Oil†; ***Chile***: Ureadin Facial Antiarrugas; Ureadin Facial; ***Fr.***: Actymine†; Alphalarm; Alpharegul Femme; Alpharegul Homme; Androlistica; Effadiane relipidantes; Elteans; Feminabiane Cycle Feminin; Feminabiane Meno'Confort; GliSODine Solaire; Menolistica; Omegaline Solaire; Phytophanere†; Phytosolaire†; Topialyse Sensitive; Topialyse Sensitive; Topialyse Sensitive; Topialyse; ***Hung.***: Fumago; Klimin; Memolife; Obesmin; ***Ital.***: Biophase Complex†; LCP; Secril; Spm-OK; Topialyse; ***Port.***: Antiestrias; Bioclin Sebo Care; Hidratante VV; Nutraisdin; Nutraisdin; Rilastil Anti-Oxidante; Rilastil Dermo Solar; Ureadin Facial; ***Singapore***: Androlistica; Manhae; Seven Seas EPO Plus Starflower Oil; ***UK***: Arheumacare; Super Antioxidant Plus; ***Ukr.***: Wellwoman (Велвумен).

Borax

Booraksi; Boraksas; Borato de sodio decahidratado; Bórax; Disodium Tetraborate; Disodu tetraboran; E285; Heptaoxotetraborato de sodio decahidratado; Natrii Tetraboras; Natrii Tetraboras Decahydricus; Natrium Boricum; Natriumtetraborat; Nátrium-tetraborát; Purified Borax; Sodium Biborate; Sodium Borate; Sodium Pyroborate; Sodium Tetraborate; Sodu tetraboran; Tetraborato de sodio; Tetraboritan sodný dekahydrát; Бура; Боракс.

$Na_2B_4O_7.10H_2O$=381.4

CAS — 1330-43-4 (anhydrous borax); 61028-24-8 (anhydrous borax); 1303-96-4 (borax decahydrate).

ATC — S01AX07.

ATC Vet — QS01AX07.

UNII — 91MBZ8H3QO (sodium borate decahydrate); 8191EN8ZMD (anhydrous sodium borate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Borax). Colourless crystals or crystalline masses, or white or almost white, crystalline powder. It effloresces. Soluble in water; very soluble in boiling water; freely soluble in glycerol. A 4% solution in water has a pH of 9.0 to 9.6.

The BP 2014 gives Sodium Borate and Sodium Tetraborate as official synonyms.

USNF 31: (Sodium Borate). Odourless transparent colourless crystals or white crystalline powder. Its solutions are alkaline to phenolphthalein. It effloresces in warm dry air. Soluble 1 in 16 of water, 1 in 1 of boiling water, and 1 in 1 of glycerol; insoluble in alcohol. Store in airtight containers.

Boric Acid

Acide borique; Ácido bórico; Acidum boricum; Boorihappo; Boracic Acid; Borato rūgštis; Borsäure; Bórsav; Borsyra; E284; Kwas borowy; Kyselina boritá; Orthoboric Acid; Sal Sedativa de Homberg; Борная Кислота.

H_3BO_3=61.83

CAS — 10043-35-3.

ATC — S02AA03.

ATC Vet — QS02AA03.

UNII — R57ZHV85D4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF.*

Ph. Eur. 8: (Boric Acid). Colourless shiny plates greasy to the touch, or white or almost white crystals, or white or almost white crystalline powder. Soluble in water and in alcohol; freely soluble in boiling water and in glycerol (85%). A 3.3% solution in water has a pH of 3.8 to 4.8.

USNF 31: (Boric Acid). Odourless, colourless, somewhat pearly lustrous scales, or crystals, or white powder, slightly unctuous to the touch. Soluble 1 in 18 of water, 1 in 4 of boiling water, 1 in 18 of alcohol, 1 in 6 of boiling alcohol, and 1 in 4 of glycerol.

Stability. Boric acid volatilises in steam. It forms a complex with glycerol which is a stronger acid than boric acid.

Uses and Administration

Boric acid possesses weak bacteriostatic and fungistatic properties; it has generally been superseded by more effective and less toxic disinfectants. It is used as a pesticide against ants and cockroaches.

Boric acid is used, usually with borax, as a buffer and antimicrobial in eye drops, and was formerly used as a soluble lubricant in solution-tablets. It is also used as a preservative for urine samples. Boric acid and borax are not used internally.

In the UK, the use of boric acid in cosmetics and toiletries is restricted (see Adverse Effects, p. 2460.1).

Borax is used similarly to boric acid and has also been used externally as a mild astringent and as an emulsifier in creams. Preparations of borax in glycerol or in honey (Borax Glycerin; Honey of Borax) were formerly used as paints for the throat, tongue, and mouth, but should not be used because of the risk of toxicity.

Other salts of boric acid, including potassium and zinc salts, have been used.

Homoeopathy

Boric acid has been used in homoeopathic medicines under the following names: Acidum boricum; Acidum Boracicum; Ac. boric.; Boricum acidum; Boricum ac.

Borax has been used in homoeopathic medicines under the following names: Natrium tetraboracicum.

Urine preservation. Boric acid in concentrations of about 2% may be a suitable preservative for urine samples in transit requiring bacteriological examination.[1,2] However, overnight storage of specimens preserved with boric acid may significantly alter culture results.[3]

1. Porter IA, Brodie J. Boric acid preservation of urine samples. *BMJ* 1969; **2:** 353–5.
2. Lum KT, Meers PD. Boric acid converts urine into an effective bacteriostatic transport medium. *J Infect* 1989; **18:** 51–8.
3. Gillespie T, *et al.* The effect of specimen processing delay on borate urine preservation. *J Clin Pathol* 1999; **52:** 95–8.

Vaginitis. Vaginal candidiasis (p. 564.1) caused by *Candida glabrata* and other non-*albicans* species frequently responds to topical boric acid.[1,2] Satisfactory clinical and mycological responses to topical boric acid were reported in 2 patients with *Candida glabrata* vaginitis who had not responded to repeated courses of azole antifungals.[3] Treatment with boric acid effected clinical and mycological cure in 4 of 6 patients with refractory vaginitis caused by *C. krusei*.[4] Long-term boric acid treatment showed promise in the treatment and prevention of relapses of vulvovaginal candidiasis, but its efficacy ended when treatment was stopped.[5] Similarly, a study in diabetic women[6] found that although initial response to a 14-day course of topical boric acid was better than with fluconazole, relapse was common over the subsequent 3 months.

1. Sobel JD, Chaim W. Treatment of Torulopsis glabrata vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 1997; **24:** 649–52.

2. Pappas PG, *et al*. Infectious Diseases Society of America. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; **38:** 161–89. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/380796 (accessed 24/07/08)
3. Redondo-Lopez V, *et al*. Torulopsis glabrata vaginitis: clinical aspects and susceptibility of antifungal agents. *Obstet Gynecol* 1990; **76:** 651–5.
4. Singh S, *et al*. Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy. *Clin Infect Dis* 2002; **35:** 1066–70.
5. Guaschino S, *et al*. Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2001; **184:** 598–602.
6. Ray D, *et al*. Prolonged (3-month) mycological cure rate after boric acid suppositories in diabetic women with vulvovaginal candidiasis. *J Infect* 2007; **55:** 374–7.

Adverse Effects, Treatment, and Precautions

The main symptoms of acute boric acid poisoning are vomiting and diarrhoea, abdominal pain, an erythematous rash involving both skin and mucous membranes, followed by desquamation, and stimulation or depression of the CNS. There may be convulsions and hyperpyrexia. There may also be renal tubular damage. Abnormal liver function and jaundice have been reported rarely. Death, resulting from circulatory collapse and shock, may occur within several days.

The slow excretion of boric acid can lead to cumulative toxicity during repeated use. Symptoms of chronic intoxication include anorexia, gastrointestinal disturbances, debility, confusion, dermatitis, menstrual disorders, anaemia, convulsions, and alopecia.

Fatalities have occurred most frequently in young children after the accidental ingestion of solutions of boric acid or after the application of boric acid powder to abraded skin.

In the UK the use of boric acid, borates, and tetraborates in cosmetics is controlled: the concentration is limited to 5% in talcs, to 0.1% in products for oral hygiene, and to 3% in other cosmetic products; tetraborates are limited to 8% in hair waving products and 18% in bath products. Such cosmetic products should not be used in children under 3 years of age; preparations used for oral hygiene should not be swallowed; and topical preparations containing greater than the equivalent of 1.5% of boric acid should not be applied to peeling or irritated skin.

Deaths have resulted from absorption after lavage of body cavities with solutions of boric acid, and this practice is no longer recommended.

Inhaled boric acid and borax are pulmonary irritants.

Treatment of poisoning is symptomatic. The stomach should be emptied if the patient presents within 1 hour of ingesting a large amount of boric acid; activated charcoal is not effective. Haemodialysis may be of value in severe cases.

In Great Britain pharmacists have been advised not to sell boric acid as such for use as a dusting powder (see also above). Pharmacists have also been advised not to supply Borax Glycerin or Honey of Borax, even with an appropriate warning, because of the hazards associated with the use of these preparations in infants.

Pharmacokinetics

Boric acid is absorbed from the gastrointestinal tract, from damaged skin, from wounds, and from mucous membranes. It does not readily penetrate intact skin. About 50% of the amount absorbed is excreted in the urine within 24 hours and most of the remainder is excreted within 96 hours of ingestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Eye Wash; ***China***: Yin Tai (殷泰); ***Fr.***: Dacryum; Hydralin Classic; ***Ital.***: AB 300; ***Mon.***: Steridose; ***Pol.***: Aphtin; Borasol; Gemiderma; ***Thai.***: Glycerin of Borax; ***Turk.***: Bibora; ***Venez.***: Sax.

Multi-ingredient Preparations. ***Arg.***: Anusol-HC; Anusol†; Baby-Tex; Bentophyto; Calcusan Bebe; Cutidermin Bebe Polvo†; Fil Olor; Fungocop; Gineseptina; Griseoplus; Hipoglos Cicatrizante; Hipoglos con Hidrocortisona; Irigal; Lemil; Phylarm; Prurisedan; Sebulex; ***Austral.***: Joint Formula Advanced; ***Austria***: Coldophthal; Ophtaguttal; ***Belg.***: Alcasol; Boradrine†; Borostyrol; Sedemol; Sulfa-Sedemol; ***Braz.***: Cloraseptic; Colpagex-N†; Dinill; Gynax-N; Higicler; Hipodermon; Lucretin; Malvona; Oturga; Po Antisseptico†; Pomaderme; Vagitrin-N; Visiplex; ***Canad.***: Refresh Ultra; ***Chile***: Dexagin; Frescansol; Hipoglos; Pediaderm; Perfungol; ***China***: Bi Zhi Ke (比之可); ***Cz.***: Caltrate Plus; Herbadent; Ophtal; Ophthalmo-Septonex; Pityol; ***Fin.***: Otiborin; ***Fr.***: Borostyrol; Dacryoboraline†; Dacryoserum; Dacudoses; Eau Precieuse†; Homeoplasmine; Hydralin Classic; Ophtalmine†; Paps†; PhyLarm; Sophtal; Supro; ***Gr.***: Oulogram; Septobore; Vaseline Borique; ***Hong Kong***: Eye Glo Plus; Eye Glo Regular; Eye Wash; Gly Thymol; Hydralin; ***India***: Andre; Boroswift; Borozin; Coldtaur; Decomic; Dermal; Distone; Feel Chill†; Fista; Gencart; Geocal; Healing Dust; I-Top; Irimist; Itchasia; Mil; Moisol; Naflin; New Eye Lotion†; NPBor; Oculear; Osmotic-6; Proto-Boric†; ***Indon.***: Skintex†; Verile; ***Irl.***: Phytex†; ***Israel***: Claritone; Gargol; ***Ital.***: Bergacid†; Boma; Fotofil; Fucsina Fenica; ***Mex.***: Clarex; Forcremol; Hipoglos; Lav Ofteno; Lowila; Oftaboril; Tokolirio; ***Mon.***: Boroclarine†; Glyco-Thymoline; ***Philipp.***: Soothing Eye Wash; United Home Burn Ointment; ***Pol.***: Acifungin; Afronis; Antypot; Dentosept A; Gargarin; Hemorectal; Neo-Tormentil; Tormentile Forte; Tormentiol; ***Rus.***: Calcemin (Кальцемин); Combutec-2 (Комбутек-2); Contraceptin T (Контрацептин Т); Fucaseptol (Фукасептол); Fucorcin (Фукорцин); Linin (Линин); Lysoplac (Лизоплак)†; Oftalmol (Офтальмол); Olasol (Олазоль); Osarbon (Осарбон); Ottoslavin (Оттославин); Teimurov (Теймурова); ***S.Afr.***: Anugesic†; Caloplast†; Prep†; Universal Eye Drops†; Vagarsol; ***Singapore***: Castellani's Paint; Eye Mo; ***Spain***: Banoftal†; Cloram Hemidex†; Coliriocilina Adren Astr†; Dermomycose Liquido; Fungusol; Milrosina; Natusan; Oftalmol Ocular; Vaselina Boricada†; Zolina; ***Thai.***: Eye Mo; Eye-Gene Soft; Eye-Gene; Mano; Opplin; Opsil; Optal; Optic; Quinradon-N†; Visotone; Visotone; ***Turk.***: Dermikolin; Undo-Talk; ***UK***: Oxy Clean Facial Scrub; Phytex; ***Ukr.***: Calcemin Advance (Кальцемин Адванс); Pilex (Пилекс); Vitrum Osteomag (Витрум Остеомаг); ***USA***: BFI; Castaderm; Collyrium for Fresh Eyes†; Columbia Antiseptic Powder; Ear-Dry; Paladin; Palomar E; Phylorinol; RA Lotion; Saratoga; Seale's Lotion; Star-Otic; Trimo-San; ***Venez.***: Ademina; Borocanfor; Borogin; Micofeet; Sebaxyl.

Homoeopathic Preparations. ***Austria***: Otodolor; Otovowen; ***Canad.***: Bioactiv H†; Cold Sores & Fever Blisters; Homeoplasmine; Hylavir FB†; Kids' Teething; ***Chile***: Bioactiv H; ***Fr.***: Aftosium; Boripharm No 10†; Gastro-Drainol†; Homeoaftyl; Poconeol no 82†; Staphysagria Complexe No 92†; ***Ger.***: Hewesoor N†; Otovowen; ***Rus.***: Avia-Mor (Авиа-Море); ***Switz.***: Regenaplex Nr 28b; ***USA***: Succus Cineraria Maritima†.

Pharmacopoeial Preparations
BP 2014: Kaolin Poultice;
BPC 1973: Magenta Paint; Surgical Chlorinated Soda Solution;
USP 36: Rose Water Ointment.

Borneol

Baros Camphor; Bhimsaim Camphor; Borneo Camphor; Borneokampfer; Bornyl Alcohol; Camphol; Dryobalanops Camphor; Malayan Camphor; Sumatra Camphor; Борнеол.

endo-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol.

$C_{10}H_{18}O$=154.3

CAS — 507-70-0.

UNII — M89NIB437X.

Pharmacopoeias. In *Chin* as synthetic borneol (Borneolum Syntheticum).

Profile

Borneol is a constituent of several essential oils. It has antiseptic and antispasmodic actions and is included in preparations for the treatment of biliary- and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Rowatinex; ***Austria***: Rowachol; Rowatinex; ***Chile***: Rowatinex; ***Cz.***: Rowachol; Rowatinex; ***Ger.***: Rowachol; Rowatinex; ***Hong Kong***: Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.***: Rowachol; Rowatinex; ***Indon.***: Penfri; Stobled; ***Irl.***: Rowachol; Rowatinex; ***Israel***: Rowachol; Rowatinex; ***Malaysia***: Rowachol; Rowatinex; ***Mex.***: Cholex; ***Philipp.***: Mentopas; Rowachol; Rowatinex; ***Pol.***: Rowachol; Rowatinex; Terpichol; ***Rus.***: Rowatinex (Роватинекс); Wantong Artiplas (Ваньтун Артиплас); ***Spain***: Rowachol; Rowanefrin; ***Thai.***: Rowachol; Rowatinex; ***UK***: Rowachol; ***Ukr.***: Bezornil (Безорнил); Koronatera (Коронатера); ***Venez.***: Rowachol; Rowatinex.

Bornyl Acetate *(USAN)*

Borneol Acetate; Bornilo, acetato de; Bornylu octan; Борнилацетат.

1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate.

$C_{12}H_{20}O_2$=196.3

CAS — 76-49-3 (bornyl acetate); 125-12-2 (isobornyl acetate).

UNII — 213431586X.

Profile

Bornyl acetate is a constituent of some essential oils. It has been used in aromatic preparations in the treatment of coughs, other respiratory-tract disorders, and musculoskeletal and joint disorders. Isobornyl acetate has been used similarly; it has also been used in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Jabonacid; ***Chile***: Expanden; ***Ger.***: Rheubalmin Bad; ***Hung.***: Nozi; ***Switz.***: Perskindol Classic.

Bromelains *(BAN, USAN, rINN)* ⊗

Bromelaiinit; Bromelaina; Bromelaína; Bromelainer; Bromelainy; Bromélaïones; Bromelins; EC 3.4.22.33; Plant Protease Concentrate; Бромелаины.

CAS — 9001-00-7.

ATC — B06AA11.

ATC Vet — QB06AA11.

ATC Herb — HA09AA5001 (Ananas comosus: extract); HD03WX5002 (Ananas comosus: extract).

UNII — U182GP2CF3 (bromelains); F0ZCA6O9QT (fruit bromelain).

Units

One Rorer unit of protease activity has been defined as that amount of enzyme which hydrolyses a standardised casein substrate at pH 7 and 25 degrees so as to cause an increase in absorbance of 0.00001 per minute at 280 nm. FIP units are also defined in terms of rate of hydrolysis of bromelain activity of a casein preparation under standard conditions.

Activity has also been described in terms of milk-clotting units.

Uses and Administration

Bromelains are a concentrate of proteolytic enzymes derived from the pineapple plant, *Ananas comosus* (*A. sativus*) (Bromeliaceae). They are used as an adjunct in the treatment of soft-tissue inflammation and oedema associated with trauma and surgery. Bromelains have also been given as an aid to digestion, and used in the treatment of partial deep dermal and full thickness burns.

References.
1. Kane S, Goldberg MJ. Use of bromelain for mild ulcerative colitis. *Ann Intern Med* 2000; **132:** 680.
2. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci* 2001; **58:** 1234–45.

Adverse Effects

Bromelains may cause nausea, vomiting, and diarrhoea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma.

Effects on the respiratory system. Bronchial asthma occurred in 2 patients after exposure to bromelains.[1] Of 6 workers sensitised to papain, 5 had positive skin tests to bromelains and 2 of them also had immediate asthmatic reactions after bronchial challenge with bromelains.[2]

1. Galleguillos F, Rodriguez JC. Asthma caused by bromelin inhalation. *Clin Allergy* 1978; **8:** 21–4.
2. Baur X, Fruhmann G. Allergic reactions, including asthma, to the pineapple protease bromelain following occupational exposure. *Clin Allergy* 1979; **9:** 443–50.

Precautions

Bromelains should be given with care to patients with coagulation disorders or with severe hepatic or renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Ananase Forte; ***Fr.***: Extranase; ***Ger.***: Dontisanin†; Mucozym†; Phlogenzym mono; Proteozym; Traumanase; Wobenzym mono†; ***Hong Kong***: Internase; ***Ital.***: Ananase; ***Neth.***: NexoBrid; ***Port.***: Ananase; ***Switz.***: Traumanase; ***Venez.***: Ananase.

Multi-ingredient Preparations. ***Arg.***: Varicofem; ***Austral.***: Bio-Disc†; Digest Aid; Digestaid; Hernidisc; Tresos B PluSe; Vegie Digestaid; ***Austria***: Phlogenzym; Rutozym; Traumazym; Wobenzym; ***Braz.***: Monocetin†; Plasil Enzimatico; Sintozima†; ***Canad.***: Mega Zyme†; Multi Enzyme†; Multi-Zyme†; Wobenzym; ***Cz.***: Phlogenzym; Wobenzym; ***Ger.***: Phlogenzym†; Wobenzym plus; ***Hung.***: Phlogenzym; Salus Multipretten; ***India***: Baknil; Bree-C; Disperzyme; Enractin; Merckenzyme†; ***Indon.***: Benozym; Elsazym; ***Ital.***: Algorex; Flogofort; Flogovis IdroGel; Flogovis; Inflamase IdroGel; Inflamase; Plogovis†; Signum; ***Jpn***: Kimotab†; ***Malaysia***: Enzyme Digest; ***Mex.***: Phlogenzym; Plasil Enzimatico; Wobenzym; ***Philipp.***: Lungcaire Plus; ***Rus.***: Phlogenzym (Флогэнзим); Wobenzym (Вобэнзим); ***Singapore***: Essentials†; ***Turk.***: Ultimate; ***UK***: BackOsamine; Enzyme Digest; ***Ukr.***: Ektis (Эктис); Phlogenzym (Флогэнзим); Wobenzym (Вобэнзим); ***USA***: Bio-Zyme; ***Venez.***: Nutizym Compositum; Phlogenzym; Wobenzym N.

Bromides

Bromuros; Бромиды.

ATC — N05CM11.

ATC Vet — QN05CM11.

Ammonium Bromide

Ammon. Brom.; Ammonii Bromidum; Ammonium Bromatum; Ammonium, bromure d'; Ammónium-bromid; Ammoniumbromid; Ammoniumbromidi; Amonio bromidas; Amonowy bromek; Brometo de Amônio; Bromid amonný; Бромид Аммония; Бромистый Аммоний.

NH_4Br=97.94

CAS — 12124-97-9.

UNII — R0JB3224WS.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ammonium Bromide). A white or almost white, hygroscopic crystalline powder or colourless crystals. It becomes yellow when exposed to light or air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers. Protect from light.

Potassium Bromide

Brometo de Potássio; Bromid draselný; Bromure de Potassium; Kalii bromidum; Kalio bromidas; Kalium Bromatum; Kaliumbromid; Kálium-bromid; Kaliumbromidi; Pot. Brom.; Potassii Bromidum; Potassium, bromure de; Potasu bromek; Бромистый Калий.

KBr=119.0

CAS — 7758-02-3.

UNII — OSD78555ZM.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn, US,* and *Viet.*

Ph. Eur. 8: (Potassium Bromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

USP 36: (Potassium Bromide). A white crystalline powder or colourless, cubical crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

Sodium Bromide

Brometo de Sódio; Bromid sodný; Bromure de Sodium; Natrii bromidum; Natrio bromidas; Natrium Bromatum; Natriumbromid; Nátrium-bromid; Natriumbromidi; Sod. Brom.; Sodii Bromidum; Sodium, bromure de; Sodu bromek; Бромистый Натрий.

NaBr=102.9

CAS — 7647-15-6.

UNII — LC1V549NOM.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn, US,* and *Viet.*

Ph. Eur. 8: (Sodium Bromide). A slightly hygroscopic, white or almost white, granular powder, or small, colourless, transparent, or opaque crystals. Freely soluble in water; soluble in alcohol. Store in airtight containers.

USP 36: (Sodium Bromide). A white crystalline powder or colourless, cubical crystals. Freely soluble in water; soluble in alcohol.

Uses and Administration

Bromides depress the CNS. Calcium, potassium, and sodium bromide have been used as sedatives and anticonvulsants, but have generally been replaced by more effective, less toxic drugs. Ammonium and strontium bromide have been used similarly, as have bromoform and dilute hydrobromic acid. Bromides have also been used in multi-ingredient preparations for the treatment of coughs.

Homoeopathy

Hydrobromic acid and various bromides have been used in homoeopathic medicines under the following names:

- Hydrobromic acid: Hydr. ac.
- Ammonium bromide: Ammonium bromatum; Ammonium bromidum; Amm. brom.; Ammon brom
- Arsenic bromide: Arsenicum bromatum; Arsenicum brom; Ars. brom.
- Cadmium bromide: Cadmium bromatum; Cadmium brom; Cad. brom.
- Calcium bromide: Calcarea bromata; Calc. bro.
- Ferrous bromide: Ferrum bromatum; Ferrum brom; Fer. brom.
- Potassium bromide: Kalium bromatum; Kali bromatum; Kali brom;Kali. br.
- Sodium bromide: Natrum bromatum; Nat. brom.
- Radium bromide: Radium bromatum; Radium brom; Rad. br.
- Zinc bromide: Zincum bromatum; Zinc brom; Zinc. br.

Adverse Effects and Precautions

During prolonged exposure bromide accumulation may occur giving rise to bromide intoxication or bromism. Symptoms include nausea and vomiting, anorexia, confusion, behavioural disturbances, slurred speech, memory impairment, drowsiness, irritability, ataxia, tremors, hallucinations, mania, delirium, psychoses, stupor, coma, and other manifestations of CNS depression. Rashes of various types may occur and toxic epidermal necrolysis has been reported. Death after acute poisoning appears to be rare as vomiting follows the ingestion of large doses.

There have been reports of neonatal bromide intoxication and growth defects associated with maternal bromide ingestion during pregnancy.

Breast feeding. The American Academy of Pediatrics[1] considers that intake of bromides is usually compatible with breast feeding, although rashes, weakness, and absence of crying have been reported in the infant after maternal intake. Exposure to bromides in photographic laboratories may also result in potential absorption and transfer into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid;* 1029. Also available at: http://pediatrics.aappublications.org/cgi/content/full/108/3/776 (accessed 22/07/08)

Treatment of Adverse Effects

In acute poisoning, the stomach should be emptied (if emesis has not already occurred), and sodium chloride should be given by intravenous infusion. Glucose may also be used and furosemide may be given to aid diuresis.

In chronic poisoning, bromides are stopped and sodium chloride is given intravenously or orally with adequate amounts of fluid. Ammonium chloride has been given but is no longer recommended as it may precipitate metabolic acidosis. Diuretics are of value. In severe cases of bromide intoxication, or when the usual treatments cannot be used, haemodialysis may be of benefit.

Pharmacokinetics

Bromides are readily absorbed from the gastrointestinal tract. They displace chloride in extracellular body fluids and have a half-life in the body of about 12 days. They may be distributed into breast milk and cross the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Dibro-Be Mono.

Multi-ingredient Preparations. ***Braz.***: Frenotosse; ***Chile***: Gruben; Pectokast; Ramistos; ***Fr.***: Galirene†; Sedatif Tiber†; Sel D; ***Ger.***: Adelheid-Jodquelle, Tolzer; ***Hung.***: Yam; ***India***: Gynedol; ***Indon.***: Thymcal; ***Ital.***: Fertomcidina-U; ***Pol.***: Sal Ems Factitium; ***Rus.***: Amtersol (Амтерсол); Bromenval (Броменвал); Cardiovalen (Кардиовален); Pertussin (Пертуссин); Valocormid (Валокормид).

Homoeopathic Preparations. ***Austria***: Exangina†; Nervoheel; Sensicare; Tonsillopas; Valerianaheel; ***Canad.***: Acne; Nervita; Quietude; ***Cz.***: Sedalia; Spascupreel S†; ***Fr.***: Abbe Chaupitre no 1†; Abbe Chaupitre no 91†; Quietude; ***Ger.***: Drufusan N†; Liquidorm N; Mato; Mullersche Tabletten; Roth's RKT Tropfen; Rytesthin; Sedacalman; Sedaphin†; Spascupreel; Tonsillopas; ***Hung.***: Nervoheel; Spascupreel; ***Neth.***: Gynaelite; Nervoheel; Quietude†; ***Rus.***: Psorilom (Псорилом); ***Switz.***: Nelsons Noctura†; Nervoheel; Quietude; ***UK***: Noctura; ***USA***: Eczemol.

Bromine

Brom; Brome; Bromium; Bromo; Bromum; Бром.

Br_2=159.808

CAS — 7726-95-6.

UNII — S8V4XY874G.

Description. Bromine is a dark reddish-brown, heavy, mobile liquid that gives off intensely irritating brown fumes.

Uses and Administration

Bromine is widely used in industry. It was formerly used, in the form of an adduct with a quaternary ammonium compound, in the treatment of plantar warts.

Adverse Effects

Bromine is intensely irritating and corrosive to eyes and mucous membranes; it may cause severe gastro-enteritis if swallowed. Contact with the skin can produce severe burns, and inhalation of the vapour causes violent irritation of the respiratory tract and pulmonary oedema.

Treatment of Adverse Effects

Milk or water should be given as soon as possible after ingestion of bromine. Gastric lavage, activated charcoal, ipecacuanha, and neutralisation are not recommended. If bromine vapour has been inhaled, oxygen should be given and assisted ventilation may be necessary. The use of prophylactic corticosteroids for laryngeal and pulmonary oedema is controversial. Splashes on the skin and eyes should be immediately washed off; washing with copious amounts of water should continue for at least 15 minutes after skin exposure, and with sodium chloride 0.9% for at least 30 minutes after eye exposure.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Canad.***: Roxalia; ***Cz.***: Homeogene 9; ***Fr.***: Homeogene 9; ***Hung.***: Homeogene 9; ***Neth.***: Homeogene 9†; ***Port.***: Homeogene 9; ***Rus.***: Valeriana-Plus (Валериана-Плюс); ***Switz.***: Homeogene 9.

Bryonia

Brionia; Bryony; Nueza; Переступень; Бриония.

*ATC Herb — HA06AB5004 (*Bryonia dioica*: root).*

UNII — T7J046Y12B.

Profile

Bryonia, the root of *Bryonia alba* or *B. dioica* (Cucurbitaceae), is an ingredient of preparations that have been used in respiratory-tract infections and inflammatory disorders. Toxic symptoms and fatalities have been reported after ingestion of the berries.

Homoeopathy

Bryonia has been used in homoeopathic medicines under the following names: Bryonia cretica; Bryonia e radice; Bry. cre.; Bryonia alba; Bry. alba.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Homeoplasmine; ***Ger.***: Schnupfencreme; ***Mex.***: Reudol; ***Port.***: Stodal.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Arthritis Relief; Childrens Cold and Flu Relief; Childrens Cough Relief; Colic Relief; Joint & Muscle Oral Spray†; Respatona Dry Cough & Nasal Congestion; Respatona Sore Throat; Sports Ice Joint & Muscle; ***Austria***: Aconitum Med Complex; Aflubin; Ferrum Phosphoricum comp; Infludo; Nisylen†; Pneumodoron Nr 1; Rhus Med Complex; Sulfur Med Complex; Tonsan akut; toxiloges; ***Canad.***: Aches & Pains; Arnica-Heel Comp†; Arthflex; Artis-Heel†; Bronkeel†; Bryaconeel†; Calnor†; Comp-Drops 3 Bowel Support†; Comp-Drops 5 Expectorant†; Complete Flu Care 4 Kids†; Cou Complex†; Echinacea Compositum; Fibromyalgie; Formula DM 210†; Formula INF; Homeo-Form C†; Homeo-Form G†; Homeo-Form ME†; Homeoplasmine; Homeovox; Hylagesic APF; Hylands Cough; Hylands Flu; Hylands Formula F; Ivernax; Kids Cough & Cold Phytux; Menopause L122; Menopause; Phytotux H; Roxalia; Spigelon†; Stodal; Toxex; ***Chile***: Bioactiv V; Influk; Similibus; ***Cz.***: Bronchalis-Heel; Gripp Heel; Homeogene 9; Homeovox; Lehnigrip†; Stodal; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Abbe Chaupitre no 25†; Abbe Chaupitre no 6; Abbe Chaupitre no 88†; Aconitum Compose†; Aloe Compose; Arthro-Drainol; Baudry; Boripharm No 23; Bryonia Opodeldoch; Cholesterolum Complexe No 112†; Homeogene 14†; Homeogene 9; Homeogrippe†; Homeovox; Infludo; Ipeca Compose; Kalium Muriaticum Complexe No 41†; L 107; Lachesis Complexe No 122; Nux Vomica Complexe No 49; Nux Vomica Compose; Pates Pectorales; Pulmo-Drainol†; Pulsatilla Complexe No 60†; Ranunculus Complexe No 79; Stodal; Stodal; ***Ger.***: Arthrokatt; Bronchi-Do; Bronchiselect; Bryorheum N; Capillaron Vertigo; Echinacin akut; Entzundungstropfen; Eupatorium N Oligoplex; Ferrum phosphoricum comp; G1-Injektopas; Gelenk Albin; Genu-cyl L Ho-Len-Complex; Gripp-Heel; Grippe-Gastreu S R6; Gripps; Hevertotox; Hewerheum N†; Infekt 1-Injektopas N; Infi-Echinacea; Infigripp; Infludo; Jutussin; Lowe-Komplex Nr 6; Mato; Nisylen; Nux Vomica N Oligoplex; Pascoe-Agil HOM; Pascoleucyn; Pascoleucyn; Pneumodoron 1; Pulmo-cyl Ho-Len-Complex; Pyrogenium; Rheucostan R; Rheuma-Hevert; Rheuma-Hevert; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; Rheumeda; Rheumodoron 1; Rhus toxicodendron N Oligoplex; Schworotox; toxi-loges; Toxiselect; Traumakatt; Tussistin S; Tussistin; ***Hung.***: Aflubin; Gripp-Heel; Homeogene 9; Homeovox; Spigelon; Stodal; ***Neth.***: Bronchalis; Echinacea comp; ***Port.***: Homeogene 9; Homeoplasmine†; Homeovox; ***Rus.***: Aflubin (Афлубин); Belladonna-Plus (Белладонна-Плюс); Briacon (Бриакон); Capsicum-Plus (Капсикум-Плюс); Homeovox (Гомеовокс); Influcid (Инфлюцид); Sambucus-Plus (Самбукус-Плюс); Stodal (Стодаль); Tonsan-Akut (Тонзан-акут); ***S.Afr.***: Ferrum Phos Comp†; Gripp-Heel; Infludo†; Pneumodoron 1†; ***Switz.***: Infludo; metaossylen N; Regenaplex Nr 38b; Regenaplex Nr 41a; Regenaplex Nr. 35b; Regenaplex Nr. 50b; TussEx; ***UK***: Sootha; ***Ukr.***: Aflubin (Афлубин); Homeovox (Гомеовокс); Homvio-Reuman (Хомвио-Ревман); Influcid (Инфлюцид); Stodal (Стодаль).

Buchu

Barosma; Bucco; Buchú; Buchu Leaves; Diosma; Folia Bucco; Hojas de buchú; Бучу.

CAS — 68650-46-4 (buchu leaf oil).

ATC Herb — HG04BW5002 (Agathosma betulina: leaf); HJ01WB5001 (Agathosma betulina: leaf).
UNII — 369DDH39Z0 (Agathosma betulina leaf); KOS935A04V (buchu leaves extract).

Pharmacopoeias. In *Fr.*, which allows the dried leaves of *Agathosma betulina* (short or round buchu), *A. crenulata* (oval buchu), and *A. serratifolia* (long buchu).

Profile

Buchu, the dried leaves of 'short' or 'round' buchu, *Agathosma betulina* (*Barosma betulina*) (Rutaceae), is a weak diuretic and urinary antiseptic that has been used in multi-ingredient preparations for the treatment of urinary-tract disorders. Oval or long buchu, the leaves of *Agathosma crenulata* (*B. crenulata*), has also been used. The name long buchu is also applied to *A. serratifolia* (*B. serratifolia*). The leaves of *A. serratifolia* are also used medicinally.

Buchu leaf oil, usually from *A. betulina*, is occasionally promoted for use in aromatherapy, although it is rarely used in practice.

Homoeopathy

Buchu has been used in homoeopathic medicines under the following names: Barosma; Barosma crenata; Bar. cren.; Barosma serratifolia; Bar. ser.

References.

1. Moolla A, Viljoen AM. Buchu'–*Agathosma betulina* and *Agathosma crenulata* (Rutaceae): a review. *J Ethnopharmacol* 2008; **119:** 413–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Althaea Complex†; Cranberry Complex†; Cranberry Complex; Cranbiotic Super†; De Witts New Pills†; Extralife Uri-Care†; ***Canad.***: Bio Renal†; Cellutex; Diurenat†; Diuretic Tablets; Hepaflor†; Herbal Diretic; Herbal Diuretic†; Herbal Diuretic; Herbal Laxative plus Yogurt†; Saw Palmetto Formula†; Stomach Ease; ***Cz.***: Epilobin; ***Fr.***: Phytemag; Urophytum†; ***S.Afr.***: Borstol Cough Remedy†; Doans Backache Pills†; ***Switz.***: Urinex; ***UK***: Antitis; Backache Relief; Backache; De Witt's K & B Pills; Diuretabs; HRI Water Balance; Kas-Bah; Lowater; Skin Eruptions Mixture; Watershed; Watershed; ***Ukr.***: Uro-Control (Уро-Контрол); ***USA***: Cardio-press.

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Ger.***: Cysto Hevert.

Bucillamine *(rINN)*

Bucilamina; Bucillaminum; DE-019; SA-96; Tiobutarit; Буцилламин.
N-(2-Mercapto-2-methylpropionyl)-L-cysteine.
$C_7H_{13}NO_3S_2$=223.3
CAS — 65002-17-7.
ATC — M01CC02.
ATC Vet — QM01CC02.
UNII — R80LRA5WTF.

Pharmacopoeias. In *Jpn*.

Profile

Bucillamine is structurally related to penicillamine (p. 1567.1) and is reported to be an immunomodulator that has been used in the treatment of rheumatoid arthritis.

Adverse effects. Bucillamine has been implicated in the development of skin,[1] kidney,[2,3] and lung disorders.[4]

1. Ogata K, *et al*. Drug-induced pemphigus foliaceus with features of pemphigus vulgaris. *Br J Dermatol* 2001; **144:** 421–2.
2. Nagahama K, *et al*. Bucillamine induces membranous glomerulonephritis. *Am J Kidney Dis* 2002; **39:** 706–12.
3. Hoshino J, *et al*. Outcome and treatment of bucillamine-induced nephropathy. *Nephron Clin Pract* 2006; **104:** c15–c19.
4. Saito Y, *et al*. A case of bucillamine-induced interstitial pneumonia with positive lymphocyte stimulation test for bucillamine using bronchoalveolar lavage lymphocytes. *Intern Med* 2007; **46:** 1739–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Rimatil.

Buckwheat

Blé Noir; Boekweit; Boveteört (aerial parts); Buchweizen; Buchweizenkraut (aerial parts); Fagopyri Herba (aerial parts); Grano Turco; Grikių žolė (aerial parts); Pohanková nať (aerial parts); Sarrasin; Sarrasin Commun; Viljatatar (aerial parts); Ziele gryki; Гречиха Обыкновенная.
ATC Herb — HC05CW5003 (Fagopyrum esculentum: herb).
UNII — N0Y68724R3 (Fagopyrum esculentum grain); B10M69172N (Fagopyrum esculentum).

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Buckwheat Herb; Fagopyri Herba). The whole or fragmented aerial parts of *Fagopyrum esculentum*, collected in the early flowering period prior to fruiting and dried immediately. It contains a minimum 3.0% of rutoside, calculated with reference to the dried drug.

Profile

The aerial parts of buckwheat, *Fagopyrum esculentum* (Polygonaceae), are included in herbal preparations for chronic venous insufficiency.

Buckwheat contains flavonoids and is a source of rutoside (see p. 2505.3).

Homoeopathy

Buckwheat has been used in homoeopathic medicines under the following names: Fagopyrum; Fagopyrum esculentum; Fago. esc.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Fagorutin Buchweizen†.

Multi-ingredient Preparations. ***Fr.***: Tone; ***Ger.***: Fagorutin Buchweizen†; ***Pol.***: Betasol; Fitoven.

Homoeopathic Preparations. ***Austria***: Globuli gegen Sonnenallergie.

Bucladesine Sodium *(rINNM)*

Bucladesina sódica; Bucladésine Sodique; DBcAMP (bucladesine); Dibutyryl Cyclic AMP Sodium; DT-5621 (bucladesine); Natrii Bucladesinum; Натрий Букладезин.
N-(9-β-D-Ribofuranosyl-9*H*-purin-6-yl)butyramide cyclic 3′,5′-(hydrogen phosphate) 2′-butyrate sodium.
$C_{18}H_{24}N_5O_8PNa$=492.4
CAS — 362-74-3 (bucladesine); 16980-89-5 (bucladesine sodium).
ATC — C01CE04.
ATC Vet — QC01CE04.
UNII — 4DZN2C97A7.

Profile

Bucladesine sodium has been reported to have cardiotonic properties when given intravenously. It has been applied topically for the treatment of bedsores.

Bufotenine

Bufotenin; Bufotenina; 5-Hydroxy-*NN*-dimethyltryptamine; Mappine; *NN*-Dimethylserotonin; Буфотенин.
3-(2-Dimethylaminoethyl)indol-5-ol.
$C_{12}H_{16}N_2O$=204.3
CAS — 487-93-4.
UNII — 0A31347TZK.

Profile

Bufotenine is an indole alkaloid obtained from the seeds and leaves of *Piptadenia peregrina*, from which the hallucinogenic snuff cohoba is prepared, and *P. macrocarpa* (Mimosaceae). It was first isolated from the skin glands of toads (*Bufo* spp.) and has also been isolated from species of *Amanita* (Agaricaceae). Bufotenine has serotonergic activity and is reported to have hallucinogenic properties. It has no therapeutic use.

Bugleweed

Profile

The term bugleweed usually refers to species of the genus *Lycopus* (Lamiaceae), although some species of *Ajuga* (Lamiaceae) are also known by this common name.

In herbal medicine, the names bugleweed, sweet bugle, water bugle, and water horehound are applied to both the European bugleweed (*L. europaeus*) and the Virginia bugleweed (*L. virginicus*) which are used mainly for mild hyperthyroidism and menstrual disorders. The American bugleweed (*L. americanus*) is used similarly.

Zelan, the dried aerial part of the hirsute shiny bugleweed (*L. lucidus*) is used in traditional Chinese medicine.

Homoeopathy

Bugleweed has been used in homoeopathic medicines under the following names: Lycopus virginicus; Lycopus virgin.; Lycopus virg.; Lycopus europaeus; Lycopus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: thyreo-loges; Thyreogutt mono.

Homoeopathic Preparations. ***Austria***: Asarum Med Complex; ***Canad.***: Motherwort Combination 3†; ***Fr.***: Badiaga Complexe No 47; Hypophysis Complexe No 31†; Poconeol no 61†; Vespa Complexe No 46†; ***Ger.***: Hewethyreon N; Lycoaktin; Neuroselect; Rufebran thyreo†; Thyreo-Injektopas; thyreo-loges comp; Thyreo-Pasc.

Buphenine Hydrochloride *(BANM, rINNM)* ⊗

Bufenina, hidrocloruro de; Buphénine, Chlorhydrate de; Buphenini Hydrochloridum; Hidrocloruro de bufenina; Nylidrin Hydrochloride; Nylidrinium Chloride; Буфенина Гидрохлорид.
1-(4-Hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)propan-1-ol hydrochloride.
$C_{19}H_{25}NO_2$,HCl=335.9
CAS — 447-41-6 (buphenine); 849-55-8 (buphenine hydrochloride).
ATC — C04AA02; G02CA02.
ATC Vet — QC04AA02; QG02CA02.
UNII — EC69E3PW7E.

Uses and Administration

Buphenine produces peripheral vasodilatation through beta-adrenoceptor stimulation and a direct action on the arteries and arterioles of the skeletal muscles.

Buphenine has been used in the treatment of peripheral vascular and cerebrovascular disease. Doses of buphenine hydrochloride in the range of 12 to 48 mg daily in 3 or 4 divided doses have been given orally. It has also been used in preparations for rhinitis and nasal congestion.

An intravenous infusion of buphenine hydrochloride has been used to arrest premature labour. It has also been given orally as a prophylactic tocolytic agent.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; buphenine has mainly beta-agonist effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Arlidin; ***India***: Arlidin; ***Mex.***: Arlidin; Nilken.

Multi-ingredient Preparations. ***Austria***: Opino; Opino; ***Fr.***: Phlebogel†; ***Gr.***: Opino; ***Indon.***: Opino†; ***Mex.***: Flumil; ***Switz.***: Arbid†; Visaline†.

Burnet

Garden Burnet; Greater Burnet; Pimpinela mayor; Salad Burnet; Sanguisorba; Кровохлёбка.
UNII — 4NYV2HT01X (burnet extract).

NOTE. Distinguish from Burnet Saxifrage (p. 2463.1).

Pharmacopoeias. In *Chin.* and *Eur*. (see p. vii).

Ph. Eur. 8: (Sanguisorba Root). The whole or fragmented, dried underground parts of *Sanguisorba officinalis* without rootlets. The adventitious roots are about 5 to 25 cm long and up to 2 cm in diameter. They contain a minimum 5.0% of tannins, expressed as pyrogallol ($C_6H_6O_3$ = 126.1) calculated with reference t o the dried drug.

Profile

Burnet, the aerial parts and roots of *Sanguisorba officinalis* (*Poterium officinalis*) (Rosaceae), has antihaemorrhagic and astringent properties. It has been used internally to treat menorrhagia and gastrointestinal disorders and is also used topically for eczema, burns, and other skin disorders.

Burnet is also used as an animal fodder and salad vegetable, and as an ingredient in beer making.

Homoeopathy

Burnet has been used in homoeopathic medicines under the following names: Sanguisorba officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Tormentan; ***Indon.***: Ambeven†.

Homoeopathic Preparations. ***Fr.***: Cetraria Complexe No 61; Geranium Complexe No 108†.

Burnet Saxifrage

Bibernell; Boucage; Pimpinella; Бедренец Камнеломковый (*Pimpinella saxifraga*).
ATC Herb — HA01WA5003 (Pimpinella major: root); HR05WA5034 (Pimpinella major: herb); HR05WA5037 (Pimpinella saxifraga: root); HJ01WB5011 (Pimpinella saxifraga: root); HA03AW5050 (Pimpinella saxifraga: root); HA01WA5004 (Pimpinella saxifraga: root); HR05WA5036 (Pimpinella saxifraga: herb); HC05BW5003 (Pimpinella major: herb); HC05BW5004 (Pimpinella saxifraga: herb); HA09WX5001 (Pimpinella major: herb); HA09WX5002 (Pimpinella saxifraga: herb); HR05WA5035 (Pimpinella major: root); HJ01WB5010 (Pimpinella major: root); HA03AW5049 (Pimpinella major: root).
UNII — 8O53J9196C (Pimpinella); 5Y05905N7G (Pimpinella saxifraga).

NOTE. Distinguish from Burnet (p. 2462.3).

Profile

The root of burnet saxifrage, *Pimpinella saxifraga* (Apiaceae), or greater burnet saxifrage, *P. major* is included in herbal preparations for coughs and minor upper respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Expectosan Hierbas y Miel; ***Canad.***: Honey Herb Cough Drops†; Original Herb Cough Drops†; ***Ger.***: Cefabronchin; ***Neth.***: Bronchicum; ***Pol.***: Bronchicum Eliksir†; ***Switz.***: Kernosan Elixir; Kernosan Heidelberger Poudre; Makaphyt Gouttes antitussives†.

Butcher's Broom

Box Holly; Dygiųjų pelždiežių šakniastiebiai; Kłącze ruszczyka; Listnatcový kořen; Mäusedornwurzelstock; Petit houx; Rautamyrtinjuurakko; Rusci Radix; Rusci rhizoma; Stickmyrtenrot; Иглица Шиповатая (*Ruscus aculeatus*).
ATC Herb — HC05AW5006 (Ruscus aculeatus: rhizome); HC05BW5005 (Ruscus aculeatus: rhizome).
UNII — 5KEZB2GMGU (Ruscus aculeatus); ZW12V95I1Q (Ruscus aculeatus root).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Butcher's Broom; Rusci Rhizoma). The dried, whole or fragmented underground parts of *Ruscus aculeatus*. It contains a minimum of 1.0% of total sapogenins, expressed as ruscogenins (mixture of neoruscogenin ($C_{27}H_{40}O_4$ = 428.6) and ruscogenin), calculated with reference to the dried drug. Protect from light.

Profile

The dried rhizome and root of butcher's broom is used in herbal preparations for chronic venous insufficiency and haemorrhoids. It contains steroidal saponins including the sapogenin ruscogenin (see p. 2608.3) which is used for similar purposes. The dose may be expressed in terms of total ruscogenins.

References.

1. Anonymous. *Ruscus aculeatus* (butcher's broom). *Altern Med Rev* 2001; **6:** 608–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Venoserin; ***Ger.***: Cefadyn; Fagorutin Ruscus†; Phlebodril Venenkapsein; ***Spain***: Arkocapsulas Rusco; ***Switz.***: Impuls pour les veines; ***UK***: Phytovein; ***Ukr.***: Cyclo 3 Fort (Цикло 3 Форт).

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; Celu-Atlas; Cistidac; CVP Cellulite; CVP Flebo; Cyclo 3; Fiblast; Nolen; Varicofem; Varicura; Venart Crema; Venart; Venidium; ***Austral.***: Aesculus & Ruscus Compound; Extralife Leg-Care†; Horsechestnut Complex; ***Braz.***: Capilos; ***Chile***: Anastim; Celu-Atlas; ***Cz.***: Cyclo 3 Fort; ***Fr.***: Anaphase; Avene Antirougeurs; Bicirkan; Climaxol; Creme au Melilot Composee†; Cyclo 3 Fort; Cyclo 3; Diveine; Evarose†; Rap Phyto; Veinobiase; ***Ger.***: Phlebodril†; ***Gr.***: Cyclo 3 Forte; ***Indon.***: Haemogal; Venos; ***Ital.***: Angiorex Complex; Capill Venogel; Clebolider†; Flebolider; Slimmer Plus; Wasotonal†; ***Mex.***: Fabroven; ***Pol.***: Cyclo 3 Fort; ***Port.***: Creme Laser Hidrante†; Cyclo 3; ***Rus.***: Cyclo 3 (Цикло 3); Cyclo 3 Fort (Цикло-3 Форт); ***Singapore***: Cyclo 3 Fort; Cyclo 3†; Pedimed Foot Care Cream; ***Spain***: Fabroven†; Fabroven; ***Switz.***: Phlebodril N; Phlebodril; Silence†; ***Thai.***: Cyclo 3 Fort; ***Venez.***: Anastim.

Butinoline Phosphate *(rINN/M)*

Butinolina, fosfato de; Butinoline, Phosphate de; Butinolini Phosphas; Fosfato de butinolina; Бутинолина Фосфат.

1,1-Diphenyl-4-pyrrolidino-1′-yl but-2-yn-1-ol phosphate.
$C_{20}H_{21}NO,H_3PO_4$=389.4
CAS — 968-63-8 (butinoline); 54118-66-0 (butinoline phosphate).
UNII — EB2657YYBG.

Profile

Butinoline phosphate is used as an antispasmodic in preparations for gastrointestinal disorders.

Butterbur

Белокопытник.
ATC Herb — HN02CW5003 (Petasites hybridus: leaf); HR03WX5007 (Petasites hybridus: leaf); HA03WX5005 (Petasites hybridus: rhizome); HG02WB5005 (Petasites hybridus: leaf); HG04BX5001 (Petasites hybridus: rhizome); HA03WX5004 (Petasites hybridus: leaf); HN02CW5004 (Petasites hybridus: rhizome); HR03WX5008 (Petasites hybridus: rhizome).

Profile

The leaves and roots of butterbur, *Petasites hybridus* (*P. officinalis*) (Asteraceae), have antispasmodic and anti-inflammatory properties and have been used in herbal preparations for a variety of disorders, including gastrointestinal and respiratory-tract disorders, and migraine. However, the MHRA in the UK advises against its use because of reports of hepatotoxicity (see Effects on the Liver, below).

References.

1. Schapowal A. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *BMJ* 2002; **324:** 144–6.
2. Lee DK, *et al.* Butterbur, a herbal remedy, attenuates adenosine monophosphate induced nasal responsiveness in seasonal allergic rhinitis. *Clin Exp Allergy* 2003; **33:** 882–6.
3. Diener HC, *et al.* The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol* 2004; **51:** 89–97.
4. Jackson CM, *et al.* The effects of butterbur on the histamine and allergen cutaneous response. *Ann Allergy Asthma Immunol* 2004; **92:** 250–4.
5. Lipton RB, *et al.* Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004; **63:** 2240–4.
6. Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache* 2005; **45:** 196–203.
7. Giles M, *et al.* Butterbur: an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2005; **5:** 119–43.
8. Käufeler R, *et al.* Efficacy and safety of butterbur herbal extract Ze 339 in seasonal allergic rhinitis: postmarketing surveillance study. *Adv Therapy* 2006; **23:** 373–84.
9. Agosti R, *et al.* Effectiveness of Petasites hybridus preparations in the prophylaxis of migraine: a systematic review. *Phytomedicine* 2006; **13:** 743–6.
10. Sadler C, *et al.* American Academy of Pediatrics Provisional Section on Complementary, Holistic, and Integrative Medicine. Complementary, holistic, and integrative medicine: butterbur. *Pediatr Rev* 2007; **28:** 235–8. Correction [dose error]. *ibid.*; 385.
11. Sutherland A, Sweet BV. Butterbur: an alternative therapy for migraine prevention. *Am J Health-Syst Pharm* 2010; **67:** 705–11.

Effects on the liver. Butterbur contains pyrrolizidine alkaloids and sesquiterpenes which have been implicated in serious liver damage and organ failure; 40 cases of hepatotoxicity associated with butterbur preparations have been reported in the literature including 9 cases of acute hepatitis, 2 of which required transplantation. Consequently, the MHRA in the UK has advised against their use.[1]

1. MHRA. Press release: unlicensed herbal remedy could cause liver and organ damage (issued 1st February, 2012). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON143514 (accessed 23/02/12)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Petadolex†; ***Switz.***: Pollivita; Tesalin Allergy†; Tesalin N.

Multi-ingredient Preparations. ***Switz.***: Dragees aux figues avec du sene; Dragees pour la detente nerveuse†; Relaxane; Valverde Constipation dragees; Valverde Detente dragees; Wala Baume pectoral au plantain; Wala Pulmonium suc contre la toux.

Homoeopathic Preparations. ***Fr.***: Kalium Muriaticum Complexe No 41†; Santalum Complexe No 30†; ***Switz.***: metaneuron N.

Butternut

Butternussbaum (Butternussbaum); Juglans; Lemon Walnut; Nogal Ceniciento; Noyer Cendré; Oil Nut; White Walnut.

NOTE. Distinguish from English Walnut (p. 2646.1) and Black Walnut (p. 2646.1). The name Juglans has also been applied to English Walnut.

Profile

The inner bark or inner root bark of the butternut, *Juglans cinerea* (*J. cathartica*; *J. oblonga*; *Wallia cinerea*), Juglandaceae, is reported to have stimulant laxative properties. It is included in herbal preparations for gastrointestinal and biliary disorders. It has also been used for skin disorders.

Homoeopathy

Butternut has been used in homoeopathic medicines under the following names: Juglans cinerea; Juglans cin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Colax†; GR² Control Thermogenic Enhancer; ***Canad.***: Para-Gard; ***UK***: Adios; Boldex.

Homoeopathic Preparations. ***Fr.***: Agnus Castus Complexe No 2†; Cistus Canadensis Complexe No 86†; ***Ger.***: Cholo 2-injektopas; Relivora Komplex.

Butyl Nitrite

n-Butyl Nitrite; Nitrito de butilo; Nitrous Acid Butyl Ester; Бутилнитрит.
$C_4H_9NO_2$=103.1
CAS — 544-16-1.
UNII — 44P8QG0F3T.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of butyl nitrite:

Bolt; Climax; Locker room; Poppers; Rush; Snappers; Video head cleaner.

Profile

Butyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p. 1540.3).

Cadmium

Cadmio; Kadm; Kadmium; Кадмий.
Cd=112.411
CAS — 7440-43-9.
UNII — 00BH33GNGH.

Cadmium Sulfate

Cadmii Sulfas; Cadmium, sulfate de; Kadmiumsulfaatti; Kadmiumsulfat; Kadmu siarczan.
$CdSO_4$=208.5
CAS — 10124-36-4.
UNII — 947UNF3Z6O.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Cadmium Sulfate Hydrate for Homoeopathic Preparations; Cadmii Sulfas Hydricus ad Praeparationes Homoeopathicas). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol.

Profile

Cadmium is used in many manufacturing processes and cadmium poisoning presents a recognised industrial hazard. Inhalation of cadmium fumes during welding procedures may not produce symptoms until 12 to 36 hours have passed and these symptoms include respiratory distress leading to pulmonary oedema. Ingestion of cadmium or its salts has the additional hazard of severe gastrointestinal effects. Cadmium has a long biological half-life and accumulates in body tissues, particularly the liver and kidneys. Chelation therapy is not generally recommended for cadmium poisoning, although sodium calcium edetate has been used after acute ingestion. However, chelators do not increase cadmium elimination in chronic poisoning and use of dimercaprol may increase cadmium toxicity and should be avoided. Chronic exposure to cadmium results in progressive renal impairment and other effects (see p. 2464.1).

Cadmium sulfide has been used topically in some countries for the treatment of skin and scalp conditions. Cadmium sulfate has been included in some preparations for the treatment of eye irritation.

Homoeopathy

Cadmium and some cadmium compounds have been used in homoeopathic medicines under the following names:

- Cadmium metallicum; Cadmium met; Cad. met.
- Cadmium chloride: Cadmium muriaticum; Cadmium mur

- Cadmium iodide: Cadmium iodatum; Cadmium iod
- Cadmium sulfate: Cadmium sulfuricum; Cadmium sulphuricum; Cad. sul.
- Cadmium sulphide: Cadmium sulphuratum; Cad. sulph.

For other cadmium compounds used in homoeopathic medicines see Cadmium Bromide, under Sodium Bromide, p. 2461.1.

Adverse effects. The toxicity of cadmium has been reviewed.[1] Environmental or occupational exposure to cadmium has been associated with renal dysfunction,[2-5] although this may be reversible if exposure is reduced.[6] A reduction in bone density may also occur.[7] Fatalities due to industrial exposure or self-poisoning have also been reported.[8,9] No effect on testicular endocrine function was noted in 77 industrial workers exposed to cadmium.[3]

An increased incidence of cancer of the prostate has been reported in subjects exposed to high levels of cadmium but the evidence is not conclusive.[10] There may be an association between cadmium exposure and lung cancer, although observations on this type of cancer are difficult to interpret because of exposure to other hazards such as smoking.

1. Fielder RJ, Dale EA. Cadmium and its compounds. *Toxicity Review 7*. London: HMSO, 1983.
2. Buchet JP, *et al*. Renal effects of cadmium body burden of the general population. *Lancet* 1990; **336:** 699–702. Correction. *ibid*. 1991; **337:** 1554.
3. Mason HJ. Occupational cadmium exposure and testicular endocrine function. *Hum Exp Toxicol* 1990; **9:** 91–4.
4. Cai S, *et al*. Renal dysfunction from cadmium contamination of irrigation water: dose-response analysis in a Chinese population. *Bull WHO* 1998; **76:** 153–9.
5. Satarug S, *et al*. Safe levels of cadmium intake to prevent renal toxicity in human subjects. *Br J Nutr* 2000; **84:** 791–802.
6. Hotz P, *et al*. Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. *Lancet* 1999; **354:** 1508–13.
7. Staessen JA, *et al*. Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. *Lancet* 1999; **353:** 1140–44.
8. Taylor A, *et al*. Poisoning with cadmium fumes after smelting lead. *BMJ* 1984; **288:** 1270–1.
9. Buckler HM, *et al*. Self poisoning with oral cadmium chloride. *BMJ* 1986; **292:** 1559–60. Correction. *ibid*.; **293:** 236.
10. Bell GM. Carcinogenicity of cadmium and its compounds. *Toxicity Review 24*. London: HMSO,1991.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Biocadmio†.

Homoeopathic Preparations. ***Fr.***: Conium Complexe No 36†; ***Ger.***: Rufebran gastro†.

Cajuput Oil

Cajeput Oil; Cajuput Essence; Cayeput, aceite esencial de; Esencia de cayeput; Oleum Cajuputi; Каепутовое Масло.
UNII — J3TO6BUQ37.

NOTE. Do not confuse with Cineole (p. 2479.1), which has the similar synonyms, cajupetol and cayeputol.

Profile

Cajuput oil is a volatile oil obtained by distillation from the fresh leaves and twigs of *Melaleuca cajuputi* (*M. leucadendron*) (Myrtaceae). It contains cineole (p. 2479.1). Cajuput oil has been applied externally as a stimulant and mild rubefacient in rheumatism. It is also used with other volatile agents in preparations for the relief of respiratory-tract disorders and nasal congestion. It is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Goanna Heat Cream; Tiger Balm Oil; Tiger Balm Red; Tiger Balm White; ***Austria***: Babix; Tiger Balsam Rot; Tiger Balsam Weiss; ***Belg.***: Olbas; ***Canad.***: External Anti-Pain Oil†; Penetrating Rub†; Tiger Balm Arthritis Rub; Tiger Balm Red; Tiger Balm Ultra; Tiger Balm White; Youngflex Massage 168; ***Fr.***: Tigre de Chine; ***Ger.***: Liniplant; Olbas; Tiger Balm rot N; Tiger Balm weiss; ***Gr.***: Tiger Balm; ***Hong Kong***: BF-Analgesic Balm†; Vida Salirub†; ***Hung.***: Tiger Balm Red; Tiger Balm White; ***India***: Flexi-muv†; ***Indon.***: Balsam Sakti†; Minyak Telon Cap Tiga Anak†; Minyak Telon†; Telon 3 Anak; ***Irl.***: Olbas; Olbas; Tiger Balm Red; Tiger Balm White; ***Israel***: Tiger Balm Red; Tiger Balm White; ***Neth.***: Olbas†; ***Philipp.***: Begesic; ***Pol.***: Argol Rheuma; Olbas; Olbas; ***S. Afr.***: Muscle Rub†; ***Swed.***: Oleum Basileum; Oleum Salvum; ***Switz.***: Baume du Tigre blanc; Baume du Tigre rouge; Novital; Olbas†; Olbas; Olbas; Wala Baume nasal; ***Thai.***: Dexalin Balm; Hot Ize; ***UK***: Bells Muscle Rub; Olbas for Children; Olbas; Olbas; Soothol; Tiger Balm; Vadarex; ***USA***: Tiger Balm.

Calamus

Acore Vrai; Ácoro aromático; Ácoro verdadero; Cálamo aromático; Calamus Rhizome; Kalmus; Sweet Flag Root; Аир Обыкновенный (*Acorus calamus*).
CAS — 8015-79-0 (calamus oil).
ATC Herb — HA03AW5002 (Acorus calamus: *rhizome*).
UNII — XY1K7KIQ0F (Acorus calamus).

Pharmacopoeias. In *Chin.* and *Swiss*.

Profile

Calamus, the dried rhizome of the sweet flag, *Acorus calamus* (Acoraceae), has been used as a bitter and carminative; it is also used as a source of calamus oil, which is employed in perfumery. The FDA in the USA has prohibited marketing calamus as a food or food additive; the oil (Jammu variety) is reported to be a carcinogen.

Homoeopathy

Calamus has been used in homoeopathic medicines under the following names: Calamus aromaticus; Acorus calamus.

References.

1. Björnstad K, *et al*. Bioanalytical investigation of asarone in connection with Acorus calamus oil intoxications. *J Anal Toxicol* 2009; **33:** 604–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Koren Puskvorce†.

Multi-ingredient Preparations. ***Austria***: Abdomilon N; Pervivo; ***Canad.***: Gallexier†; ***Cz.***: Dr Theiss Schwedenbitter†; Original Schwedenbitter; Stomaran; ***Fr.***: Jouvence de l'Abbe Soury; NurAiD; ***Ger.***: Abdomilon N; ventri-loges N†; ***Hung.***: Bano Svedkeseru; Bittner; ***Israel***: Rekiv†; ***Pol.***: Dentosept A; Gastro†; Krople Zoladkowe†; Krople Zoladkowe; Pervivo; Seboren; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Phytogastrol (Фитогастрол); Stomatophit (Стоматофит); Vicair (Викаир); Vicalin (Викалин); ***Singapore***: NeuroAid; ***Switz.***: Kernosan 26; Kernosan Elixir; Tisane pour l'estomac; Urinex; Wala Elixir amer; ***UK***: Pegina; ***Ukr.***: Pilex (Пилекс); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trypsidan (Трипсидан)†; Vicair (Викаир); Vicalin (Викалин); Vitokan (Витокан).

Homoeopathic Preparations. ***Fr.***: Carominthe; ***Ger.***: Infi-Symphytum; Steirocall.

Calcium Carbimide *(rINN)*

Calcii Carbimidum; Calcium Cyanamide; Carbimida cálcica; Carbimide Calcique; Cyanamide; Кальция Карбимид.
$CCaN_2$=80.1
CAS — 156-62-7 (calcium carbimide); 8013-88-5 (citrated calcium carbimide).
ATC — N07BB02.
ATC Vet — QN07BB02; QV03AA02.
UNII — ZLR270912W.

NOTE. The name cyanamide is also used to designate carbimide, which is used in veterinary medicine.

Profile

Calcium carbimide has actions and uses similar to those of disulfiram (p. 2495.3). It is an aversive agent used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p. 1734.1) and causes a reaction in patients who have consumed alcohol similar to that seen with disulfiram (see p. 2496.1). It is given orally in a dose of up to 60 mg twice daily. Citrated calcium carbimide has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Colme†; ***Rus.***: Colme (Колме); ***Spain***: Colme.

Calcium Dihydrogen Phosphate

Acid Calcium Phosphate; Calcium Dihydrogenphosphoricum; E341; Fosfato monocálcico; Monobasic Calcium Phosphate; Monobasic Calcium Phosphate, Monohydrate; Monocalcium Phosphate; Кальция Дигидрофосфат.
Calcium tetrahydrogen diorthophosphate monohydrate.
$Ca(H_2PO_4)_2,H_2O$=252.1
CAS — 7758-23-8 (anhydrous calcium dihydrogen phosphate).
UNII — 701EKV9RMN (anhydrous calcium dihydrogen phosphate); 0N4E6L5449 (calcium dihydrogen phosphate monohydrate).

Pharmacopoeias. In *Jpn* and *Swiss*.

Profile

Calcium dihydrogen phosphate is used in fertilisers. It is also used as an antoxidant in baking powders and flours and as a source of calcium in some mineral supplement preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Phosphoneuros; ***India***: Caracsol; ***Ukr.***: Pregnavit (Прегнавит).

Calcium Dobesilate *(rINN)*

205E; Calcii Dobesilas; Calcium, dobésilate de; Calcium Doxybenzylate; CLS-2210; Dobesilan vápenatý; Dobésilate de Calcium; Dobesilato de calcio; Kalcio dobesilatas; Kalciumdobesilat; Kalcium-dobezilát; Kalsiumdobesilaatti; Kalsiyum Dobesilat; Кальция Добезилат.
Calcium 2,5-dihydroxybenzenesulphonate.
$C_{12}H_{10}CaO_{10}S_2$=418.5
CAS — 88-46-0 (dobesilic acid); 20123-80-2 (calcium dobesilate).
ATC — C05BX01.
ATC Vet — QC05BX01.
UNII — 5921X1560Q (anhydrous calcium dobesilate); M0ROX9374L (calcium dobesilate monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii) which specifies the monohydrate.

Ph. Eur. 8: (Calcium Dobesilate Monohydrate). A white or almost white hygroscopic powder. Very soluble in water; freely soluble in dehydrated alcohol; practically insoluble in dichloromethane; very slightly soluble in isopropyl alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Profile

Calcium dobesilate is claimed to reduce capillary permeability and has been used in various peripheral circulatory disorders including diabetic retinopathy and haemorrhoids (p. 1808.1). Gastrointestinal disturbances have occurred with its use, and there are also reports of hypersensitivity reactions.

Calcium dobesilate is given orally in usual doses of 0.5 to 1.5 g daily in divided doses. It is also given rectally for haemorrhoids and is an ingredient of some preparations given for various skin disorders.

Adverse effects. Agranulocytosis has been reported[1-3] in a few patients after treatment with calcium dobesilate, and in 2 cases recurred on rechallenge.[1,2] However, a later review[4] of the safety profile of calcium dobesilate concluded that the overall risk of adverse effects was low with the most prominent symptoms being fever, arthralgias, and gastrointestinal disturbances. Reports of agranulocytosis were rare and the authors concluded that there may have been methodological bias in previous assessments of risk.

1. Kulessa W, *et al*. Wiederholte Agranulozytose nach Einnahme von Calciumdobesilat. *Dtsch Med Wochenschr* 1992; **117:** 372–4.
2. Cladera Serra A, *et al*. Agranulocitosis inducida por dobesilato calcico. *Med Clin (Barc)* 1995; **105:** 558–9.
3. García Benayas E, *et al*. Calcium dobesilate-induced agranulocytosis. *Pharm World Sci* 1997; **19:** 251–2.
4. Allain H, *et al*. Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. *Drug Safety* 2004; **27:** 649–60.

Uses. Although there have been reports from small studies of a positive effect of calcium dobesilate in patients with diabetic retinopathy, the conclusion from a large multicentre, randomised, double-blind, placebo-controlled study was that it neither prevented the occurrence of nor reduced the probability of developing clinically significant macular oedema during the 5-year follow-up period in patients with type 2 diabetes mellitus and mild-to-moderate non-proliferative diabetic retinopathy.[1]

1. Haritoglou C, *et al*. Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2009; **373:** 1364–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Doxium; Duflemina; Eflevar; ***Austria***: Doxium; ***Chile***: Doxium; ***China***: An Duo Ming (安多明); Dashiming (达士明); Doxium (导升明)†; Hao Chang (昊畅); Keyuan (可元); Li Bei Si (利倍思); Medoril (美多瑞); ***Cz.***: Danium; Dobica; Doxium; ***Ger.***: Dexium†; Dobica†; ***Gr.***: Difilina; Doxytrex; Nugatex; Stifarol; ***Hong Kong***: Doxium; ***Hung.***: Doxilek; Doxium; ***India***: Cabisyl; Caldob; Cocalate; DBS; Dobesil; Dobest; Dobilet; Dobkair; Dosil; Doxium; Eflo; Mobium; ***Ital.***: Doxium; ***Malaysia***: Doxium; ***Mex.***: Doxium; ***Mon.***: Doxium; ***Philipp.***: Doxium; ***Pol.***: Doxium; Galvenox; ***Port.***: Doxi-Om; Doxivenil; ***Rus.***: Doxi-Hem (Докси-хем); ***S.Afr.***: Doxium†;

Spain: Doxium; ***Switz.***: Doxium; ***Turk.***: Doxium; Modet; ***Venez.***: Deoxical; Doxium.

Multi-ingredient Preparations. ***Cz.***: Dobexil; Doxiproct Plus; Doxiproct; ***Hung.***: Doxiproct Plus; Doxiproct; Doxivenil†; ***Ital.***: Doxiproct; ***Mex.***: Doxiproct Plus; Vasculflow; ***Port.***: Doxiproct Plus; Doxiproct; ***Switz.***: Doxiproct Plus; Doxiproct; Doxivenil†; ***Venez.***: Doxivenil.

Calcium Hopantenate *(rINNM)*

Calcii Hopantenas; Calcium Homopantothenate; Hopanténate de Calcium; Hopantenato cálcico; Кальций Гопантенат.

Calcium D-(+)-4-(2,4-dihydroxy-3,3-dimethylbutyramido) butyrate hemihydrate.

$Ca(C_{10}H_{18}NO_5)_2.½H_2O$=513.6

CAS — 18679-90-8 (hopantenic acid); 17097-76-6 (anhydrous calcium hopantenate); 1990-07-4 (calcium hopantenate hemihydrate).

UNII — LK8EOC1M6K (anhydrous calcium hopantenate); RQA63PEI5Q (calcium hopantenate hemihydrate).

Profile

Calcium hopantenate is a homologue of pantothenic acid (p. 2085.2) and has been given orally in the treatment of various behavioural, extrapyramidal, and other neurological disorders. Its use is limited by severe metabolic adverse effects and fatalities have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Gopantam (Гопантам); Pantocalcin (Пантокальцин); Pantogam (Пантогам); ***Ukr.***: Pantocalcin (Пантокальцин); Pantogam (Пантогам)†.

Calcium Hydroxide

Cal apagada; Cal hidratada; Calcii Hydroxidum; Calcium Hydrate; Calcium, hydroxyde de; Calciumhydroxid; E526; Hidróxido cálcico; Hydroxid vápenatý; Kalcio hidroksidas; Kalcium-hidroxid; Kalciumhydroxid; Kalsiumhydroksidi; Slaked Lime; Wapnia wodorotlenek; Гидроокись Кальция; Гашёная Известь.

$Ca(OH)_2$=74.09

CAS — 1305-62-0.

UNII — PF5DZW74VN.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Calcium Hydroxide). A fine white or almost white powder. Practically insoluble in water.

USP 36: (Calcium Hydroxide). A white powder with a slightly bitter alkaline taste. Soluble 1 in 630 of water and 1 in 1300 of boiling water; insoluble in alcohol; soluble in glycerol and in syrup. Store in airtight containers.

Profile

Calcium hydroxide is a weak alkali. It is used in the form of Calcium Hydroxide Solution (lime water) in some skin lotions and oily preparations to form calcium soaps of fatty acids which produce water-in-oil emulsions.

Calcium hydroxide pastes are used in dentistry. A paste made from a mixture of calcium hydroxide and potassium hydroxide and known as Vienna paste was used as an escharotic. Soda lime (p. 2617.2) is a mixture of calcium hydroxide and potassium hydroxide and/or sodium hydroxide. With sulfur, calcium hydroxide forms sulfurated lime solution (p. 1721.3).

Homoeopathy

Calcium hydroxide has been used in homoeopathic medicines under the following names: Calcarea caustica; Cal. caus.; Calc caust.

Adverse effects. A report of ocular alkali burns in children, leading to severe visual loss, caused by packets of calcium hydroxide ('Chuna') popularly consumed in India as an additive to chewing tobacco.[1]

For the use of sodium edetate in the treatment of calcium hydroxide burns of the eye, see p. 1551.1.

1. Agarwal T, Vajpayee RB. A warning about the dangers of chuna packets. *Lancet* 2003; **361:** 2247.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Calcipulpe†; ***Ger.***: Dermi-cyl†; ***Mex.***: Oleoderm.

Multi-ingredient Preparations. ***Gr.***: Calvicef; ***Mex.***: Liniderm; Oleoderm Plus; ***Pol.***: Acne Sulf†; ***Spain***: Cremsol†.

Pharmacopoeial Preparations

BP 2014: Calcium Hydroxide Solution;
USP 36: Calcium Hydroxide Topical Solution.

Calcium Oxide

Cal viva; Calcii Oxidum; Calcium Oxydatum; Calcium, oxyde de; Calx; Calx Usta; Chaux Vive; E529; Gebrannter Kalk; Lime; Óxid cálcico; Oxid vápenatý; Óxido de calcio; Quicklime; Wapnia tlenek; Окись Кальция.

CaO=56.08

CAS — 1305-78-8.

ATC Vet — QP53AX18.

UNII — C7X2M0VVNH.

Pharmacopoeias. In *Jpn*, *Pol.*, and *US.*

USP 36: (Lime). Hard, odourless, white or greyish-white masses, granules, or powder. When it is moistened with water a reaction occurs, heat being evolved and calcium hydroxide formed. Slightly soluble in water; very slightly soluble in boiling water. Store in airtight containers.

Uses and Administration

Calcium oxide has been used in various dermatological preparations. A paste made from a mixture of calcium oxide and sodium hydroxide and known as London paste was used as an escharotic.

Adverse Effects and Treatment

Calcium oxide may cause burns on contact with moist skin and mucous membranes; it is particularly irritant to the eyes. Washing or flooding of affected areas may need to be prolonged. Pneumonitis may follow inhalation.

For the use of sodium edetate in the treatment of calcium oxide burns of the eye, see p. 1551.1.

Preparations

Proprietary Preparations (details are given i n Volume B)

Multi-ingredient Preparations. ***Ital.***: Oleo Calcarea.

Dried Calcium Sulfate

Calcii Sulfas Hemihydricus; Calcined Gypsum; Calcium Sulfuricum ad Usum Chirurgicum; Calcium Sulphuricum Ustum; Dried Calcium Sulphate; Exsiccated Calcium Sulphate; Gebrannter Gips; Gêsso; Gypsum Siccatum; Plaster of Paris; Plâtre Cuit; Síran vápenatý hemihydrát; Sulfato cálcico anhidro; Sulfato de calcio anhidro; Sulphate of Lime; Yeso Blanco; Yeso de París; Сульфат Кальция (calcium sulfate); Сернокислый Кальций (calcium sulfate).

$CaSO_4.½H_2O$=145.1

CAS — 10034-76-1 (calcium sulfate hemihydrate); 26499-65-0 (calcium sulfate hemihydrate).

UNII — 3RW091J48V.

Pharmacopoeias. In *Br.*, *Chin.*, *Ger.*, *Jpn*, *Pol.*, and *Viet.*

BP 2014: (Dried Calcium Sulfate). A white or almost white, odourless or almost odourless hygroscopic powder. It may contain suitable setting accelerators or decelerators. Slightly soluble in water; more soluble in dilute mineral acids; practically insoluble in alcohol.

The BP gives Exsiccated Calcium Sulphate and Plaster of Paris as approved synonyms.

Profile

Dried calcium sulfate is used for the preparation of Plaster of Paris Bandage, which is used for the immobilisation of limbs and fractures. It is also employed for making dental casts and has been used as a bone graft substitute.

Calendula

Caléndula; Calendulae Anthodium; Calendulae Flos; Flor de muerto; Gold-bloom; Kehäkukka; Körömvirág; Koszyczek nagietka; Maravilla; Marigold; Marybud; Medetkų žiedai; Mercadela; Měsíčkový květ; Pot Marigold; Ringblomma; Souci; Ноготки.

*ATC Herb — HD02WX5002 (*Calendula officinalis*: flower); HD03WX5004 (*Calendula officinalis*: flower); HC05AW5002 (*Calendula officinalis*: flower); HD03WX5005 (*Calendula officinalis*: herb).*

*UNII — 18E7415PXQ (calendula); P0M7O4Y7YD (*Calendula officinalis *flower).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Calendula Flower). It consists of the whole or cut, dried, and fully opened flowers which have been detached from the receptacle of the cultivated, double-flowered varieties of *Calendula officinalis*. It contains not less than 0.4% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$=464.4) calculated with reference to the dried drug. Protect from light.

Profile

Calendula has antiseptic, anti-inflammatory, and astringent properties. It is used in external preparations for minor skin disorders, and also internally for gastrointestinal and menstrual disorders. Calendula is also included in many herbal preparations to improve their appearance.

Calendula oil is also used.

Homoeopathy

Calendula has been used in homoeopathic medicines under the following names: Calendula officinalis; Calend.

References.

1. Anonymous. Final report on the safety assessment of Calendula officinalis extract and Calendula officinalis. *Int J Toxicol* 2001; **20** (suppl 2): 13–20.
2. WHO. Flos Calendulae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO; 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/6.html (accessed 04/02/10)
3. Basch E, *et al*. Natural Standard Research Collaboration. Marigold (*Calendula officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2006; **6:** 135–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Spin-Care; ***Cz.***: Dr Theiss Ringelblumen Salbe†; Mesickovy†; ***Fr.***: Calendulene†; ***Hung.***: Plerico; ***Irl.***: Calendolon; ***Mex.***: Cicadin; ***Pol.***: Calendulin†; ***UK***: Calendolon.

Multi-ingredient Preparations. ***Arg.***: Acnetrol; Albion; Aristaloe; Brunavera; Bushi; Capson; Control Acne; Eurocolor Post Solar; Lactoscrub; Lavandula Oligoplex; Talquisedan; ***Austral.***: Aloe Vera Gel; Arctium & Zinc Compound; Bio-Oil; Eczema Relief†; Herbal Throat Spray; Nappy Rash Relief Cream; Skin Support; ***Austria***: Nasenol; The Chambard-Tee; ***Braz.***: Cetrilan; Malvatricin Natural†; ***Canad.***: Formula T13 Tea†; Formula T4†; Pure Gardens; ***Chile***: Matikomp; Talquisedan; ***Cz.***: Cicaderma; Epilobin; ***Fr.***: Blue Berry; Cicatridine; Dida; Glycepure; Homeoplasmine; Olioseptil Gorge-Larynx; Santane F_{10}†; Saugella allaitment anti-crevasses; Saugella douceur Poligyn; Saugella Girl; Saugella HydraSerum; Stimunal; ***Ger.***: Euphrasia comp; Unguentum lymphaticum†; Weleda Nasenol; ***Hong Kong***: Calmiderm; Pregnacare; ***Hung.***: Aranyer Elleni; Depsorin; Gastrosol; Plerudin; Rheuvit; Szent Lukacs; Venen; ***India***: Dermec; ***Ital.***: Alkagin; Allerlux; Babygella; Decon Ovuli; Emoform Alifresh; Faringel; Fito Stomygen†; Lenirose; Nevril; Proctopure; Sclerovis H Plus; Vaginol; Zeadema Crono; ***Malaysia***: A-Bruzzy; Arnica Comp; Bio-Oil; Natberry Extra; ***Mex.***: Aloemagnolia; Sanicut; Suavene; Supranettes Naturalag; ***Neth.***: Bioforce; ***Philipp.***: Lactaderm†; ***Pol.***: Arcalen; Azucalen; Dyspepsin; Escalar; Mucosit; Padma 28; Reumosol; Sanofil; Scaldex; ***Port.***: Alkagin; Alkagin; Alkagin; Cicaderma; ***Rus.***: Alorom (Алором); Elecasol (Элекасол); GeKaTon (Жекатон); Kliophyt (Клиофит); Pectorales Species No 4 (Грудной Сбор 4); Phytonefrol (Фитонефрол); Rotocan (Ротокан); ***S.Afr.***: Heilsalbe†; Oleum Rhinale Nasal Oil†; Wecesin†; ***Singapore***: A-Bruzzy; Nu-Derm Toner; ***Spain***: Banoftal†; ***Switz.***: Arteria-vita; Echinadoron; Gel de consoude†; Impuls a la consoude; Keppur; Onguent aux herbes Keller; Urinex; Venaphyt N; Wala Echinacea; Wecesin; Ziegella†; ***Turk.***: Alkagin; ***UK***: Calendula Nappy Change Cream; Eucanol; Massage Balm with Calendula; Padma Circosan; Supranettes; ***Ukr.***: Clotrex (Клотрекс); Elecasol (Элткасол); Pilex (Пилекс); Tazalok (Тазалок); Venen Theiss (Венен Тайсс); Vitokan (Витокан); ***USA***: Miaderm Radiation Relief; Nasal-Ease; ***Venez.***: Andantol Jalea; Flucirac; Gelsem; Linfoderm.

Homoeopathic Preparations. ***Austral.***: Echine†; Homoderma; Sedatif†; ***Austria***: Calendumed; Lymphdiaral; Lymphdiaral; Repisan; Sonnenbrandspray; Traumeel; Tropfen bei Verletzungen; ***Canad.***: Arnica Cream†; Calendula +; Calendula Ointment†; Capsicum + Arthri-Cream; Cicaderma†; ClearAc Cleanser†; Erinol†; Formula MBC†; Homeoplasmine; Homeovox; Optalia†; Sedatil; Traumeel; ***Chile***: Calendaderm; Calendula Echinacea Comp; Matico Compuesto; Ovukalen; ***Cz.***: Homeovox; Sedatif PC; Traumeel; ***Fr.***: Calendula Complexe No 89; Cicaderma; Endhometrol; Homeoptic; Homeovox; Sedatif PC; Symphytum Complexe No 48†; ***Ger.***: Arnica Comp; Calendumed; Cefalymphat H†; Cefalymphat†; Infihepan; Lymphdiaral sensitive N; Lymphdiaral; Lymphdiaral; Naranotox comp; Odonton-Echtroplex; Ruta-Gastreu N R55; Traumeel S; Wecesin; Weleda Heilsalbe; ***Hung.***: Calendumed; Homeovox; Sedatif; Traumeel; ***Neth.***: Achilite; Calendulan; Calendulan; Dermalite; Homeoptic†; Homeovox; Lymphdiaral; Lymphdiaral; Mercurialis zalf; Omnilite; Sedatif PC; Traumeel H; Traumeel S; Vinceel H; ***Port.***: Homeodent†; Homeoplasmine†; Homeovox; Sedatif PC; ***Rus.***: Cicaderma (Цикадерма); Homeostres (Гомеострес); Homeovox (Гомеовокс); Mercure-Plus (Меркур-Плюс); Repisan (Реписан); Traumeel S (Траумель С); Urtica-Plus (Уртика-Плюс); ***S.Afr.***: Traumeel S; ***Switz.***: Contusin; Homeoplasmine; Sedatif PC; Traumeel; ***UK***: Balsamicum; Burns Cream; Haemorrhoid Cream; Healing Cream; Hypercal; Oleum Rhinale; Pyrethrum Spray; WCS Dusting Powder; ***Ukr.***: Homeovox (Гомеовокс); Sedatif PC (Седатив ПЦ); Traumeel S (Траумель С); ***USA***: Traumeel; ***Venez.***: Traumeel.

California Poppy

Californian Poppy; Eschscholtzia; Gold Poppy; Goldmohn; Kalifornian tuliunikko; Kalifornischer Kappenmohn; Pavot de Californie; Schlafmützchen; Sömntuta; Tuliunikko.

ATC Herb — HN05CW5003 (Eschscholzia californica: herb).

UNII — 9315HN272X (Eschscholzia californica); 023XWA119J (Eschscholzia californica flowering top).

NOTE. *Eschscholzia californica* was the first named member of the genus *Eschscholzia*, named in honour of the botanist Johann Friedrich von Eschscholtz. It should be noted that the "t" in the personal surname is generally now not included in the scientific botanical name but many sources still spell the genus as *Eschscholtzia* or even as *Escholtzia*.

Pharmacopoeias. In *Fr.*

Profile

The dried aerial parts of the California poppy, *Eschscholzia californica* (Papaveraceae), are used in herbal preparations for anxiety disorders and insomnia.

The herb contains several alkaloids, reported to include cryptopine and protopine.

Homoeopathy

California poppy has been used in homoeopathic medicines under the following names: Eschscholtzia californica; Eschscholtzia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Sedagin.

Multi-ingredient Preparations. ***Austral.***: The Blue One†; ***Fr.***: Calmiflorine†; Fibromyalgine Fort; Panxeol†; Phytozac; Plenesia; Sedalozia†; Sedopal; Sympathyl; ***Ger.***: Requiesan†; ***Ital.***: Alosen†; Dormil; Fisioreve CM; Fitosonno; Vagostabil Junior; ***Rus.***: Sympathyl (Симпатил).

Homoeopathic Preparations. ***Ger.***: Dormi-Gastreu S R14; ***Rus.***: Passidorm (Пассидорм).

Calumba

Calumba Root; Colombo; Raíz de colombo; Калумба.

UNII — V36I2B8LD5.

Pharmacopoeias. In *Jpn.*

Profile

Calumba, the dried root of *Jateorhiza palmata* (*J. columba*) (Menispermaceae), has been used as a bitter and as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Wunderbalsam; ***Switz.***: Padma-Lax; Padmed Laxan; ***UK***: Appetiser Mixture; Pegina.

Camostat Mesilate (pINNM) ⊗

Camostat, Mésilate de; Camostat, mesilato de; Camostat Mesylate; Camostati Mesilas; FOY-305; Mesilato de camostat; Камостата Мезилат.

N,N-Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy) phenylacetate methanesulphonate.

$C_{20}H_{22}N_4O_5,CH_4O_3S$=494.5

CAS — 59721-28-7 (camostat); 59721-29-8 (camostat mesilate).

ATC — B02AB04.

ATC Vet — QB02AB04.

UNII — 451M50A1EQ.

Pharmacopoeias. In *Jpn.*

Profile

Camostat mesilate is a proteolytic enzyme inhibitor that has been given orally for the treatment of postoperative reflux oesophagitis (see Gastro-oesophageal Reflux Disease, p. 1807.2) in a dose of 100 mg 3 times daily, and for remission of the acute symptoms of chronic pancreatitis (p. 2580.2) in a dose of 200 mg 3 times daily.

References

1. Ashizawa N, *et al.* Efficacy of camostat mesilate compared with famotidine for treatment of functional dyspepsia: is camostat mesilate effective? *J Gastroenterol Hepatol* 2006; **21:** 767–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Foipan.

Camphene

Kamfen; Камфен.

2,2-Dimethyl-3-methylenebicyclo[2.2.1]heptane.

$C_{10}H_{16}$=136.2

CAS — 79-92-5.

UNII — G3VG94Z26E.

Profile

Camphene is a constituent of several essential oils. It has antiseptic and antispasmodic actions and is included in preparations for the treatment of biliary- and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Rowatinex; ***Austria***: Rowachol; Rowatinex; ***Chile***: Rowatinex; ***Cz.***: Rowachol; Rowatinex; ***Ger.***: Rowachol; Rowatinex; ***Hong Kong***: Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.***: Rowachol; Rowatinex; ***Irl.***: Rowachol; Rowatinex; ***Israel***: Rowachol; Rowatinex; ***Malaysia***: Rowachol; Rowatinex; ***Mex.***: Cholex; ***Philipp.***: Rowachol; Rowatinex; ***Pol.***: Rowachol; Rowatinex; Terpichol; ***Rus.***: Rowatinex (Роватинекс); ***Spain***: Rowachol; Rowanefrin; ***Thai.***: Rowachol; Rowatinex; ***UK***: Rowachol; ***Venez.***: Rowachol; Rowatinex.

Camphor

Alcanfor; 2-Camphanone; D-Camphor (natural); Camphora; Camphora D; Camphre; Camphre Droit (natural); Camphre du Japon (natural); Cânfora; D-Kafr; Kafr; Kamfer; Kamferi; Kámfor; Kamfora; Kamparas; Камфора.

Bornan-2-one; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one.

$C_{10}H_{16}O$=152.2

CAS — 76-22-2 (± camphor); 21368-68-3 (± camphor); 464-49-3 (+ camphor); 464-48-2 (- camphor).

ATC — C01EB02.

ATC Vet — QC01EB02.

UNII — 5TJD82A1ET (synthetic DL-camphor); N20HL7Q941 (natural D-camphor).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*; some only describe natural camphor and some only synthetic camphor;

Eur. and *Jpn* have separate monographs for natural and racemic or synthetic camphor.

Ph. Eur. 8: (Camphor, Racemic). A white or almost white, crystalline powder or friable crystalline masses, highly volatile even at room temperature. Slightly soluble in water; very soluble in alcohol and in petroleum spirit; very slightly soluble in glycerol; freely soluble in fatty oils.

Ph. Eur. 8: (D-Camphor; Natural Camphor BP 2014). A white or almost white, crystalline powder or friable crystalline masses, highly volatile even at room temperature. Slightly soluble in water; very soluble in alcohol and in petroleum spirit; very slightly soluble in glycerol; freely soluble in fatty oils.

USP 36: (Camphor). A ketone obtained from *Cinnamomum camphora* (Lauraceae) or produced synthetically. The natural product is dextrorotatory and the synthetic product is optically inactive.

Colourless or white crystals, granules, or crystalline masses, or colourless to white, translucent, tough masses with a penetrating characteristic odour. It slowly volatilises at ordinary temperatures.

Soluble 1 in 800 of water, 1 in 1 of alcohol, 1 in 0.5 of chloroform, and 1 in 1 of ether; freely soluble in carbon disulfide, in petroleum spirit, and in fixed and volatile oils. Store at a temperature not exceeding 40 degrees in airtight containers.

Compounding. A liquid or soft mass is formed when camphor is triturated with cloral hydrate, menthol, phenol, and many other substances. Camphor is readily powdered by triturating with a few drops of alcohol, ether, or chloroform.

Uses and Administration

Applied externally, camphor acts as a rubefacient and mild analgesic (see p. 6.3) and is used in liniments as a counter-irritant in fibrositis, neuralgia, and similar conditions. It is also an ingredient of many inhaled nasal decongestant preparations but it is of doubtful efficacy. The use of camphor liniment (camphorated oil) is discouraged because of its potential toxicity. It has been withdrawn from the market in both the UK and the USA. In the USA the concentration of camphor in preparations for external use may not exceed 11% and use is controlled or limited, particularly in children, in many countries.

Camphor oil is occasionally used in aromatherapy.

Taken internally camphor has irritant and carminative properties and has been used as a mild expectorant. It has also been used in mixed preparations for cardiovascular disorders.

Adverse Effects

In addition to accidental ingestion of preparations containing camphor, poisoning has also occurred after giving camphorated oil (camphor liniment) to children in mistake for castor oil. The symptoms include nausea, vomiting, epigastric pain, headache, dizziness, oropharyngeal burning, delirium, muscle twitching, epileptiform convulsions, depression of the CNS, and coma. Breathing is difficult and the breath has a characteristic odour; anuria may occur. Death from respiratory failure or status epilepticus may occur; fatalities in children have been recorded from 1 g. There have been reports of instant collapse in infants following the local application of camphor to their nostrils.

Effects on the nervous system. Although the use of camphor in medicinal products is controlled in many countries (see under Uses and Administration above), sporadic cases of toxicity continue to be reported.[1] Three cases of seizures in children aged from 15 to 36 months in the USA were associated with imported camphor preparations used as natural remedies or pesticides by some ethnic groups. In 2 of the cases, the camphor-containing preparation was ingested, while the third patient was exposed to toxic concentrations of camphor through repetitive topical application.

1. Khine H, *et al.* A cluster of children with seizures caused by camphor poisoning. *Pediatrics* 2009; **123:** 1269–72.

Treatment of Adverse Effects

Supportive care, including anticonvulsant therapy, is the mainstay of treatment of camphor intoxication. The benefits of gastric decontamination are uncertain, but oral activated charcoal, or gastric lavage after potentially life-threatening overdose, may be considered if the patient presents within 1 hour of ingestion; any convulsions must be controlled first. Haemodialysis with a lipid dialysate or haemoperfusion have been tried but are of doubtful value.

Precautions

Camphor should not be applied to the nostrils of infants even in small quantities, as this may cause immediate collapse.

The UK Committee on the Review of Medicines[1] recommended that camphor should not be included in products intended for the treatment of hepatic and biliary disorders, gallstones, colic, renal disorders, urinary-tract infections, or ureteral stones. The use of camphor parenterally or as irrigants was considered undesirable due to the associated safety hazard.

1. Anonymous. Camphorated oil: licensing authority takes action on camphor products. *Pharm J* 1984; **232:** 792.

Pharmacokinetics

Camphor is readily absorbed from all administration sites. It is hydroxylated in the liver to yield hydroxycamphor metabolites which are then conjugated with glucuronic acid and excreted in the urine. Camphor crosses the placenta.

For reference to a study on the dermal absorption of camphor, menthol, and methyl salicylate, see Menthol, p. 2554.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Band-Aid Anti-Itch†; Jointflex†; Watkins Liniment†; ***Fr.***: Camphrice Du Canada; ***Ger.***: Camphoderm N; Korovit Kreislauf; Mulmicor†; Pectocor N; Rheunervol N; Vaopin N†; ***India***: Capsigyl-D; ***Pol.***: Migrenol†; ***Port.***: Vicks Vaporub; ***Switz.***: Bronchomed; ***UK***: Rohto Zi; ***USA***: Benadryl Children's Anti-Itch; Benadryl Children's Itch Cooling.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Austria***: Schnarchex; ***Canad.***: Eczema L87; Soludor†; ***Fr.***: Boripharm No 15†; Scabiosa Complexe No 87; Soludor; Strophantus Compose; Vinicard†; ***Ger.***: Aktivon; Chamoca M; Conva-cyl Ho-Len-Complex; Corselect N; Corvipas SL; Crataegus comp; Diacard; Grippe-Gastreu S R6; Hevert-Activon Kreislauftropen†; Infi-Camphora; Infifer N; Korolinda; Myonasan; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Procordal; Roth's Rotacard; Santa Flora S; ***Neth.***: Calendulan; Grippe-Gastreu R6; Phonix Solidago comp; ***Rus.***: Tonginal (Тонгинал); ***Switz.***: Gouttes d'Or; ***UK***: Catarrh Cream; ***Ukr.***: Tonginal (Тонгинал).

Pharmacopoeial Preparations

BP 2014: Camphorated Opium Tincture; Concentrated Camphor Water; Concentrated Camphorated Opium Tincture;

USP 36: Camphor Spirit; Camphorated Phenol Topical Gel; Flexible Collodion.

Camphor Monobromide

Alcanfor Bromuro; Bromkampfer; Camphor Monobromate; Camphora Monobromata; Camphre Bromé; Kamferimonobromaatti; Kamfermonobromat; Monobromated Camphor.

3-Bromocamphor; 3-Bromo-2-bornanone.

$C_{10}H_{15}BrO$=231.1

CAS — 76-29-9.

Profile

Camphor monobromide was formerly used for its sedative properties, similarly to other bromides (see p. 2460.3). It has also been used in preparations for urinary disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Mictasol Azul; ***Belg.***: Mictasol; ***Braz.***: Mictasol.

Camylofin Hydrochloride *(rINNM)*

Acamylophenine Hydrochloride; Camilofina, hidrocloruro de; Camylofin Dihydrochloride; Camylofine, Chlorhydrate de; Camylofini Hydrochloridum; Hidrocloruro de camilofina; Камилофина Гидрохлорид.

Isopentyl 2-(2-diethylaminoethylamino)-2-phenylacetate dihydrochloride.

$C_{19}H_{32}N_2O_2$,2HCl=393.4

CAS — 54-30-8 (camylofin); 5892-41-1 (camylofin hydrochloride).

ATC — A03AA03.

ATC Vet — QA03AA03.

UNII — MO02H82C7M.

Profile

Camylofin is used as an antispasmodic, usually in combination preparations. It is usually used as the hydrochloride; the noramidopyrine mesilate and the sodium salts have also been used.

Overdosage. Ingestion of large doses of camylofin by 2 infants produced symptoms similar to those of opioid intoxication.[1] Both infants responded to treatment with naloxone.

1. Schvartsman S, *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; **ii:** 1246.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Anafortan.

Multi-ingredient Preparations. ***Arg.***: Apasmo; ***Austria***: Avamigran; ***Braz.***: Espasmo Silidron; ***India***: Anafortan-N; Anafortan; Anaspas; ***Ukr.***: Nomigren (Номигрен).

Cannabidiol ⊗

CBD; Каннабидиол.

(3*R*, 4*R*)-2-*p*-Mentha-1,8-dien-3-yl-5-pentylresorcinol.

$C_{21}H_{30}O_2$=314.5

CAS — 13956-29-1.

UNII — 19GBJ60SN5.

Profile

Cannabidiol is a cannabinoid present in cannabis (below) that is being used or under investigation for several potential therapeutic uses. For the use of a buccal spray preparation containing cannabis extracts, whose main active ingredients are dronabinol and cannabidiol, (see Nabiximols, p. 2566.3).

For references to the potential uses of cannabidiol, see under Cannabis, p. 2468.1.

Cannabis ⊗

Cáñamo Indiano; Cannab.; Cannabis Indica; Chanvre; Hanfkraut; Indian Hemp.

CAS — 8063-14-7.

*ATC Herb — HA04WA5001 (*Cannabis sativa: *herb).*

*UNII — 8X454SZ22D (*Cannabis sativa *subsp.* sativa *flowering top); FTS5RM302N (*Cannabis sativa *subsp.* indica *top).*

Description. Cannabis consists of the dried flowering or fruiting tops of the pistillate plant of *Cannabis sativa* (Cannabinaceae). In the UK cannabis is defined by law as any part of any plant of the genus *Cannabis*. *Marihuana* usually refers to a mixture of the leaves and flowering tops. *Bhang, dagga, ganja, kif,* and *maconha* are commonly used in various countries to describe similar preparations. *Hashish* and *charas* are names often applied to the resin, although in some countries *hashish* is applied to any cannabis preparation.

A series of cannabinoids has been extracted from the plant, the most important being Δ^9-tetrahydrocannabinol (dronabinol), Δ^8-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid, cannabinol, and cannabidiol.

Street names. Cannabis and cannabis preparations have also been known by the following names, many of which are 'street names' (see p. vii) or slang names:

30s; 50; 420; 4.20; 4:20; 4/20; Abu-Sufian; Acapulco; Acapulco gold; Acapulco red; Ace; Afgani indica; Afghan; Afghan black; Afghanais; Afi; African; African black; African bush; Airplane; Ait makhlif; Ak-47; Al Green; Al Sharpton; Aliamba; Amsterdam; Anassa; Angola; Angolaise; Anhascha; Arathi; Arathi Highlands; Ashes; Assassin of Youth; Assyuni; Astro turf; Atshitshi; Aunt Mary; Baby; Baby belong; Baby bhang; Babysitter; Bad One; Bad seed; Bale; Bamba; Bambalacha; Bambia; Bammer; Bammies; Bammy; Bangi-Aku; Bango; Bangoo; Bangue; Banji; Bank Head Bud; Banzai Buds; Bar; Barbara Jean; Barn Man; Bash; BC bud; BC budd; BC Kindbud; Beaster; Beat N Sleep; Belyando spruce; Bergspinasie; Bhang; Bhangaku; Bheng; Biff; Bigfoot; Biggy; Birthday Cake; Black; Black bart; Black ganga; Black gold; Black gungi; Black gunion; Black Maria; Black mo; Black moat; Black powder; Black Russian; Blah; Blast; Blaze; Block; Blonde; Blonde hash; Blow; Blowhead; Blowing smoke; Blue de hue; Blue sage; Blue sky blond; Blueberry; Bo; Bob Hope; Bobby Brown; Bo-bo; Bobo bush; Bohd; Boi; Boléia; Bomb; Bombay Black; Bomb-dizzle; Bone; Boo; Boo boo bama; Boom; Bowgma-Chuff; Brass; Bread; Brick; Bristol Brown; Broccoli; Brown; Brown Frown; B-ster; Bubble gum; Bubonic Chronic; Bud; Buda; Buddha; Buddha grass; Buds; Buen; Bueno; Bullyon; Bunk; Burnie; Burrito; Bush; Butt; Butter; Butter flower; Buzzles; Cabbage; Cable; Caca; Caca de Chango; Cam red; Cam trip; Cambodian red; Can; Canadian black; Canamo; Canapa; Canappa; Cangonha; Canhama; Cann; Cannabis tea; Cannacoro; Can-Yac; Carmabis; Caroçuda; Cavite All Star; Cavite All Stars; CDs; Cereal; Cess; Cest; Chamom; Chara; Charas; Charge; Charris; Cheeba; Cheebong; Cheech and Chong; Cheeo; Cheese; Chemo; Chiba chiba; Chicago black; Chicago green; Chillums; Chippie; Chira; Chitari; Chocolate; Chocolate Thai; Choof; Chrin; Christmas bud; Christmas tree; Chro; Chron; Chron Chron; Chronic; Chucky; Chunky; Chur ganja; Churrus; Churus; Chus; Chutras; Chutsao; Citral; Citrol; Clone; Club; Cochornis; Coconut Rabbi; Colarado cocktail; Colas; Coli; Coliflor tostao; Collie Weed; Colombian; Colombo; Columbia; Columbian; Columbus black; Compresses; Cosa; Costo; Crazy weed; Creeper; Creeper Weed; Crippy; Crown Town Brown; Crying weed; Cryppie; Cryptonie; C.S.; Cubes; Culican; Cumming Air; Cung; Curro; Cush; D Nugs; Da-boa; Dacha; Dagga; Dak; Dancouver; Dan K; Dank; Darakte-Bang; Dark; Dawamesk; Deaf; Dew; Diamba; Diambista; Diggidy; Diggity; Dimba; Ding; Dinkie dow; Dirijo; Dirt; Dirt grass; Ditch; Ditch weed; Ditchweed; Dizz; Djamba; Djoma; Do a joint; Doctor Kissinger's Crutch; DoggyNuggz; Doja; Dokka; Dolja; Domestic; Don jem; Don Juan; Dona Juana; Dona Juanita; Donajuanita; Doob; Doobee; Doobie; Dooko; Dope; Doradilla; Dormilona; Doshia; Double zero; Doug; Doug Funnie; Downtown brown; Dozer; Draf; Draf weed; Drag weed; Draw; Dread; Dro; Droski; Drottleneck; Dry high; Dubbe; Dube; Duby; Durban Poison; Durijo; Durog; Durong; Duros; Dustwallow Marsh; Ebenieghber; El Gallo; Electric Puha; Elephant; Elva; Endo; Erva do norte; Erva maligna; Esra; Esrar; Exotics; Fallbrook redhair; Faso; Feeling; Fêmea; Feng Shui inner tam-tam; Fine stuff; Finger; Finger lid; Fininha; Finote; Fir; Fire; Firebush; Firewood; Flack Juice; Flame; Flower; Flower tops; Fokkra; Food; Four twenty; Fraho; Frajo; Friend; Fruit; Fu; Fuma D'Angola; Fumo brabo; Fumo de caboclo; Funk; Funny stuff; Fur; Gage; Gandia; Ganga; Gange; Gangster; Ganj; Ganja; Ganjila; Garaouich; Garawiche; Garbage; Garoarsch; Gash; Gauche butt; Gauge; Gauge butt; Gauja; Gear; Gerp; Ghana; Ghanja; Giggle smoke; Giggle weed; Gnaoui; Goblet of jam; Gold; Gold star; Golden; Golden leaf; Gong; Gongo; Gonj; Good giggles; Good Goods; Good stuff; Goody-goody; Goof; Goof butt; Gorge; Gozah; Grahni Sherdool; Grain; Grand Pants; Gram; Grapefruit Hydro; Grass; Grass brownies; Grasshopper; Grata; Greefe; Green; Green buds; Green Candy; Green cheesy wham; Green Funk; Green Goblin; Green goddess; Green Jesus Love; Green paint; Green Penis; Greens; Greeter; Grefa; Grefer; Greta; Grey shields; Griefo; Griefs; Grifa; Griff; Griffa; Griffa-griffo; Griffo; Grim Creeper; Grimmy; Grolid; Guabza; Guaza; Gunga; Gungeon; Gungun; Gunja; Gunjah; Gunney; Gunney sack; Gunza; Gweeler; H; H caps; Hachiche; Haircut; Hairy Ogre; Hameni; Hamp; Hang Liu; Hanhich; Haouzi; Harm reducer; Harry Potter; Harsh; Has; Hascisc; Hash; Hash oil; Hashish; Hasis; Hasji's; Hasjisj; Haszysz; Hawaiian; Hawaiian Black; Hawiian homegrown hay; Hax; Haxixe; Hay; Haze; Headies; Heady Nugs; Heat; Heloua; Hemp; Hen-Nab; Herb; Herba; Herbals; Herbalz; High; High-Grade; Hippie Lettuce; Hocus; Hola-wola-shupidy-doo; Home Grown; Homegrown; Hooch; Hooda; Hooter; Huile; Humboldt Green; Hursini; Hydro; Hydrophonic; Hyge; Ice Cream; Igbo; Indian boy; Indian hay; Indian hemp; Indiana ditchweed; Indiana hay; Indica; Indische-hennepkruid; Indisk hampa; Indo; Indonesian bud; Indoor; Instaga; Instagu; Intianhamppu; Intsangu; Isangu; Ish; IZM; Jamaican gold; Jamaican red; Jamaican red hair; Jane; Janjah; Janjaweed; Jatiphaladya churna; Jay smoke; Jea; Jive; Jive stick; Johnson grass; Jolly green; Jonko; Joy smoke; Juan Valdez; Juana; Juanita; Juja; Kabak; Kaff; Kajees; Kalakit; Kali; Kamonga; Kanab; Kansas Grass; Karpura rasa; Kate bush; Kawaii electric; Kaya; KB; K.B.; Kee; Keif; Kentucky blue; Key; KGB; K.G.B.; Khanh-Chha; Khanje; Khayf; Khif-kiff; Ki; Kief; Kif; Kif Ktami; Kiff; Kill; Killer; Killer green bud; Killer weed; Kilroy; Kilter; Kind; Kind bud; Kind-Bud; Kine-Bud; King bud; Kinnab; Kitt; Kolto; Kona gold; Kraut; Krippies; Krippy; Kryptonite; Kumba; Kush; Kushempeng; Kutchie; Kynd; Kynd-Bud; La-LaLa; Ladies; Lakbay diva; Lakbay viva; Lamb's bread; Lang; Laughing grass; Laughing weed; Leaf; Lebanese; Lebanese blonde; Lebanese gold; Leno; Leon Mcarthy; Leon Punders; LG; Liamba; Lianda; Light Green; Light stuff; Lima; Limbo; Lime green; Little green friends; Little smoke; L.L.; Llesca; Loaf; Lobo; Local weed; Loco; Loco Weed; Locoweed; Longbottom Leaf; Loose shank; Love nuggets; Love weed; Lows; Lubage; Lucas; Lumber; M; Macaroni; Machinery; Macon; Maconha; Maconia; Madi; Mafu; Maggie; Magic smoke; Magiyam; Majat; Makhlif; Malak; Malawi Cob; Malawi Gold; Malawi grass; Malawian gold; Malva; Manhattan silver; Manitoba Hydro; Manzul; Marachuan; Maraguango; Marajuana; Marie Jeanne; Marie-Jane; Marie-Juana; Marigongo; Marihuana; Marijuana; Marimba; Mariquita; Marley; Maroc; Marocaine; Maruamba; Mary; Mary Ann; Mary Jane; Mary and Johnny; Mary Jonas; Mary Warner; Mary Weaver; Mary-Ann; Mary-Jane; Mary-Jonas; Matekwane; Maui wauie; Maui-wowie; May Ann; Mbanje; Meck; Meconha; Meg; Meggie; Merda; Merde; Mersh; Messorole; Method; Methtical; Mex; Mexican brown; Mexican green; Mexican locoweed; Mexican red; Mezz; Mid-Grade; Middies; Middys; Midies; Mids; Mighty mite; Mint; Misari; Mister Brownstone; M.J.; Mnoana; Mo; M.O.; Modams; Mohasky; Mohasty; Momea; Momeka; Monte; Mooca; Moocah; Mooster; Moota; Mooters; Mootie; Mootos; Mor a grifa; Moragrifa; Moroc; Mota; Motah; Mother; Moto; Mr. Piff; Mu; M.U.; Muggie; Muggle; Muggles; Mulatinha; Mull; Mundyadi vatika; Murphy; Musty Marty; Muta; Mutah; Mutha; Nail; Namba; Nederweed; Nederwiet; Neihe; Nigra; Nordle; Northern lights; N'rama; Ntsangu; Nug; Nugget; Nuggets; Nuggs; Nugglets; Nwonkaka; Oboy; O.J.; Old Toby; Oleo; Olja; Ooh-Wee; Orange Cat; Oregano; Out-Do; Owl; Ozone; Paca lolo; Pack; Pack a bowl; Pakaloco; Pakalolo; Paki black; Pakistani black; Panama cut; Panama gold; Panama red; Pappa C's funky space boots; Parsley; Passa; Pasta; Pasto; Pat; Pétard; Peinka; Penek; Penka; Philip Drummond; Philly blunts; Piff; Pin; Pine; Pito; Pizza; Platters; Plow; Pocket rocket; Pod; Poison; Poke; Poke Smot; Politics; Po-Pa; Porro; Pot; Potlikker; Potten bush; P.R.; Pretendica; Pretendo; Pretinha; Pretties; Pretty Ladies; Puff; Purp; Purple; Purple haze; Purple Urple; Purps; Quarter moon; Queen Ann's lace; Rafe; Rafi; Rafo; Ragweed; Railroad weed; Rainy day woman; Rangood; Rasta Plant; Rasta weed; RB; Red bud; Red cross; Red dirt; Red oil; Red seal; Redge; Reef; Reefer; Reggies; Reggiwegs; Regs; Regular; Relish; Resin; R.G.B.; Riamba; Righteous bush; Rip; RIP; Roacha; Rocky; Rongony; Root; Rope; Rora; Rosa Maria; Rose Maria; Rose Marie; Rose-Marie; Rough stuff; Rube; Rubia; Ruderalis; Rugs; Sabsi; Sadda; Salad; Salt and pepper; Santa Marta; Sasfras; Sativa; Schwag; Schwagg; Schwamp; Scissors; Scraps; Scrapes; Scrub; Seeds; Sen; Sense; Sensemilia; Sensi; Sess; Sezz; Shake; Sheeba; Sheebz; Shit; Shmagma; Shrimp; Shrubs; Shwig; Shwiggity Shwag; Shwag; Shwuggets; Siddhi; Siddi; Sighirma; Sins; Sinse; Sinsemilla; Sizzla; Skunk; Skunkweed; Sky; Smokage; Smoke; Smoke a bowl; Smoke Canada; Smoochywoochypoochy; Snop; Soap bar; Soles; Soñadora; Soruma; Soul Flower; Soussi; Speed boat; Splim; Square mackerel; Stack; Stank; Stank-a-dank; Stash; Stems; Stick; Sticks; Sticky; Sticky Black; Sticky brown; Sticky Icky; Sticky Icky Icky; Stink weed; Stinkweed; Stinky; Stoney weed; Stress; Strijj; Stuff; Subji; Sugar weed; Summitates cannabis; SupaDank; Super grass; Super pot; Supergrass; Suruma; Swag; Swamp Grass; Swazi Gold; SWED; Sweet Leaf; Sweet Lucy; T; Tablete; Tack; Tahgalim; Tai Alon; Taima; Takkouri; Takrouri; Tea; Tedrika; Teloeut; Tempel; Temple; Temple balls; Teriaki; Texas pot; Texas Red; Texas tea; Tex-mex; Thai Sticks; That Shit; THC; The Dank; The Peeping Jesus; The Pig Farmer's laptop; The Shit That Killed Elvis; The Wizard; Thirteen; Thumb; Thump! Thump! Thump!; Tia; Tical; Tijuana; Time; Time Machine's Glory; TJ; Tochi; Toke; Torch; Towels; Transkei; Trauma; Trees;

Triple A; Tronadora; Trupence bag; Turtle; Tustin; Tweed; Tweeds; Twenty Twen Twen; Tweny Bag; Umya; Unotque; Urumogi; Utilities; Vipe; Viper's weed; Wacky Baccy; Wacky Backy; Wacky Tabacky; Wacky terbacky; Wacky tobaccky; Wacky weed; Wag; Wake and Bake; Wasch; Weasel feed; Wee; Weed; Weed tea; Weed tear; Wewe; Whack; Whackatabacky; Wheat; White Rhino; White Russian; White Widow; White-haired lady; Woo blunts; Woodle; Woof; Wooz; Wooze; X; Yaa; Yamba; Yandi; Yarndi; Yeah; Yeh; Yellow submarine; Yen pop; Yerba; Yerhia; Yesca; Yesco; Yeska; Ying; Yoda; Yoruba; Yum Yum; Zacate chino; Zacatecas purple; Zambi; Zani; Zerouali; Ziele konopi indyjskich; Zig Zag man; Zol; Zoot.

Pharmacopoeias. In *Chin.* and *Jpn.*

Uses and Administration

Cannabis contains about 60 cannabinoids of which the main active constituent is Δ^9-tetrahydrocannabinol. Two types of specific endogenous cannabinoid-binding receptors have been identified. CB_1 receptors are distributed throughout the CNS and some peripheral tissues and are involved in modulation of various neurotransmitters, which is thought to be responsible for the clinical effects of cannabinoids. CB_2 receptors are expressed mainly in immune cells and are thought to be involved in modulation of the immune system. Cannabinoid receptor agonists and antagonists have also been identified.

Therapeutic use. Cannabis was formerly used therapeutically as a sedative or narcotic. The cannabinoid Δ^9-tetrahydrocannabinol (dronabinol, p. 1840.1) and a synthetic cannabinol (nabilone, p. 1865.2) are used as antiemetics in patients receiving cancer chemotherapy. Dronabinol is also used to stimulate appetite in HIV patients with cachexia. Nabiximols (p. 2566.3) is a combination of cannabis extracts, whose main active ingredients are dronabinol and cannabidiol (p. 2467.1). It is used as adjunctive treatment for the symptomatic relief of spasticity and neuropathic pain in multiple sclerosis in adults. This same preparation is also used as adjunctive analgesic treatment in adult patients with advanced cancer who have moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Cannabinoids are also being investigated for other potential therapeutic uses, including relief of spasticity in multiple sclerosis, in spinal cord injury, and in various forms of pain, including diabetic neuropathy and other types of neuropathic pain, and pain associated with rheumatoid arthritis. Cannabis reduces intra-ocular pressure and it has been reported to be of benefit in glaucoma. Vaporisation is being investigated as a means of delivering therapeutic doses of cannabinoids.

Abuse. Cannabis is widely abused as a psychoactive agent and has a long history of such use. The amount of Δ^9-tetrahydrocannabinol in cannabis depends on its geographical source. Proportions also differ depending on the form used and have been reported as: 1 to 4% in the leaves and flowering tops, or even up to 15% in some varieties bred for a high yield of cannabinoids (so-called skunk); 5 to 12% in sinsemilla (obtained from unpollinated female plants); 3 to 6% in the dried resin (hashish); and 30 to 50% in hashish oil expressed from the pressed resin. The usual route of abuse is by smoking cigarettes containing the dried leaves and flowering parts of the plant or the more potent dried resin (hashish); inhalation using water pipes or vaporisers are alternative methods. Cannabis is also ingested in cakes or sweets. Less commonly, cannabis extract or hashish oil is injected intravenously.

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Dependence

Prolonged heavy use of cannabis may lead to tolerance and psychological dependence but the existence of physical dependence remains somewhat controversial. Reported withdrawal symptoms have included anorexia, agitation, apprehension, aggression, anxiety, insomnia, irritability, restlessness, fever, sweating, tremor, dysphoria, rhinorrhoea, headache, and nausea.

Symptoms of withdrawal have been reported in neonates born to mothers who used cannabis during pregnancy, and have included jitteriness and tremulousness, crying, and disturbances in sleep and response to light occurring up to 30 days after birth.

References.

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Adverse Effects, Treatment, and Precautions

Cannabis is widely abused for its psychological effects and the most important psychoactive cannabinoid is Δ^9-tetrahydrocannabinol. The toxicity of cannabis is dose-related and when used recreationally depends to a large extent on the experience of the user and degree of tolerance. The effects may also be affected by CNS depressants taken at the same time.

The psychological effects produced by low doses of cannabis include calmness, euphoria, relaxation, drowsiness, a feeling of well-being, heightened sensory awareness, and alterations in perception of time, space, colour, or sound. Sedation may occur some time later after the initial effects. Anxiety or panic reactions may also occur at low doses.

As the level of intoxication increases, the user may experience feelings of depersonalisation, disorientation, decreased inhibition, altered mood, memory impairment, and difficulty in maintaining attention. Symptoms of heavy intoxication include incoordination, ataxia, skeletal muscle jerks, and slurred speech. Distrust, dysphoria, poor concentration, slowed reaction times, lethargy, and sedation may also occur. Fear, panic attacks in apprehensive patients, hallucinations, and transient paranoia or psychosis have also been reported.

Cannabis additionally affects several physiological body systems and symptoms of intoxication include tachycardia, palpitations, paroxysmal atrial fibrillation, and orthostatic hypotension; life-threatening ventricular tachycardia may occur after large doses. Decrease in intra-ocular pressure, conjunctival injection, cough, dry mouth, increased appetite, and reduced bowel motility have also been reported.

The toxicity of cannabis is increased with intravenous use. Gastrointestinal disturbances have been reported including nausea and vomiting, abdominal pain, and diarrhoea. Other symptoms include headache, rigors, fever, dyspnoea, cardiovascular irregularities, jaundice, shock, disseminated intravascular coagulation, renal impairment, and death.

Ingestion of cannabis by children is potentially fatal. Mydriasis, hypotonia, hyporeflexia, ataxia, hypothermia, tachycardia, respiratory depression, drowsiness, stupor, and coma have been reported.

Chronic use of cannabis has been reported to reduce resistance to infection, produce persistent neurotoxicity, and the carcinogens present in cannabis smoke potentially increase the risk of cancer. However, there is little conclusive evidence for the long-term effects of cannabis.

Cannabis has been presumed to affect driving because of slowed reaction times, effects on cognition, and perceptual alterations, although there is no conclusive evidence to this effect, and it has not been possible to correlate cannabis blood concentration with specific levels of impaired driving performance.

The risks of gastrointestinal decontamination after ingestion of cannabis may outweigh the benefits if the patient is drowsy or agitated. However, activated charcoal has been recommended within one hour of ingestion of a potentially toxic dose. Ipecacuanha given within 30 to 90 minutes of ingestion has been used as an alternative. Treatment of an overdose or acute toxicity following ingestion or inhalation of cannabis products is symptomatic and supportive. Adults often require little more than reassurance as clinical toxicity is rarely serious and recovery usually occurs spontaneously within several hours. Patients should be monitored for 6 hours after intravenous injection of cannabis products. Children should also be observed for 6 hours after ingestion. Agitated patients may require sedation with diazepam; lorazepam or midazolam have also been used. Haloperidol or ziprasidone are alternatives to benzodiazepines.

Reviews.

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Breast feeding. The American Academy of Pediatrics deprecates[1] the use of cannabis as a drug of abuse by breast-feeding mothers; a published report[2] indicated that cannabinoids were secreted into breast milk and absorbed by nursing infants, and while no adverse effect was reported to have occurred, some components do have a very long half-life.

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2. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol* 2002; **42** (11 suppl): 64S–70S.

Effects on the cerebrovascular system. References.

1. Herning RI, *et al.* Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. *Neurology* 2005; **64:** 488–93.

Effects on the CNS. References to, and reviews of, the CNS effects of cannabis, including effects on cognition,[1-5] anxiety and depression,[6] and psychosis,[7-13] including schizophrenia.[14,15] Coma, reversed by flumazenil, has been reported in 2 children who had ingested cannabis.[16]

1. Pope HG Jr, *et al.* Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry* 2001; **58:** 909–15.
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Effects on the eyes. A report of persistent visual abnormalities in a patient after discontinuation of heavy abuse of cannabis.[1] No organic cause for the effects, which were accompanied by less persistent mental changes, could be found.

1. Laffi GL, Safran AB. Persistent visual changes following hashish consumption. *Br J Ophthalmol* 1993; **77:** 601–2.

Effects on the gastrointestinal tract. There have been several reports of heavy cannabis use producing recurrent episodes of severe nausea and vomiting accompanied by abdominal pain; the symptoms are temporarily relieved by taking hot baths or showers, which can lead patients into a compulsive bathing habit. The mechanism of action of

this so-called cannabinoid hyperemesis syndrome is unknown. Stopping cannabis use will prevent further episodes but no other treatment is known.

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1. Allen JH, *et al.* Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut* 2004; **53:** 1566–70.
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Hyperthermia. Life-threatening hyperthermia was reported[1] in a 24-year-old man who went jogging after smoking cannabis.

1. Walter FG, *et al.* Marijuana and hyperthermia. *J Toxicol Clin Toxicol* 1996; **34:** 217–21.

Peripheral vascular disease. References.
1. Combemale P, *et al.* Cannabis arteritis. *Br J Dermatol* 2005; **152:** 166–9.

Pregnancy. Cannabis has effects on sperm and can alter reproductive hormonal systems. Infants born to mothers exposed to cannabis during pregnancy tend to have a lower birth-weight[1,2] and may suffer from increased excitation in the postnatal period.[3]

1. Zuckerman B, *et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; **320:** 762–8.
2. Frank DA, *et al.* Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *J Pediatr* 1990; **117:** 622–6.
3. Silverman S. Interaction of drug-abusing mother, fetus, types of drugs examined in numerous studies. *JAMA* 1989; **261:** 1689, 1693.

Interactions

Cannabis and alcohol have additive effects. The sedative effects of cannabis may be potentiated by other CNS depressants. Additive antimuscarinic effects, for example tachycardia, may occur with drugs such as tricyclic antidepressants. Cannabis induces microsomal enzymes and therefore interactions with many drugs that are metabolised by these enzymes might be expected (see, for example, Theophylline, p. 1235.3).

Anticoagulants. For a report of cannabis smoking increasing the effect of warfarin, see p. 1533.2.

Disulfiram. Limited evidence indicates that use of disulfiram with cannabis may produce a hypomanic state.[1]

1. Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *Am J Psychiatry* 1983; **140:** 243–4.

Pharmacokinetics

Time to onset and duration of effects of cannabis vary with factors such as route of administration and the user's experience. The active principles of cannabis are readily absorbed from the lungs. Systemic bioavailability of Δ^9-tetrahydrocannabinol from smoked cannabis generally ranges between about 10 and 35%, with regular users achieving a higher efficiency. This produces an effect within minutes, reaches a peak in about 30 minutes, and lasts for about 3 to 4 hours. The pharmacokinetics of cannabis after injection are similar to smoking.

Δ^9-Tetrahydrocannabinol absorption may be slow and erratic from the gastrointestinal tract, and extensive first-pass liver metabolism reduces the systemic bioavailability to less than 20% with high interindividual variation. Effects peak in about 1 to 4 hours and last for up to 6 hours.

Δ^9-Tetrahydrocannabinol is lipophilic and becomes widely distributed in the body. Plasma protein binding is about 97 to 99%. Δ^9-Tetrahydrocannabinol is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP2C subfamily, mainly to the active 11-hydroxy derivative.

Within 72 hours of an oral dose, 10 to 15% is excreted in the urine mainly as conjugates and metabolites, and 35 to 50% in faeces mainly as unconjugated metabolites. About 80 to 90% of a dose is excreted within 5 days after ingestion. Duration of detectability of urinary metabolites varies greatly and can be several weeks for heavy chronic users.

Cannabis crosses the placenta and is distributed into breast milk.

Review.
1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42:** 327–60.

Canola Oil

Cánola, aceite de; Масло Канолы.
CAS — 120962-03-0.
UNII — 331KBJ17RK.

Profile

Canola oil is a form of rapeseed oil (p. 2602.3) from strains selected for low erucic acid content. It is used as an edible oil and in pharmaceutical manufacturing and cosmetics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *NZ:* Mr Nits.

Cantharides

Blistering Beetle; Cantáridas; Cantharis; Insectes Coléoptères Hétéromères; Lytta; Méloides; Russian Flies; Spanish Fly; Шпанские Мушки.
UNII — 3Q034RO3BT.

Uses and Administration

Cantharides is the dried beetle *Cantharis vesicatoria* (*Lytta vesicatoria*) (Meloidae) or other spp., containing not less than 0.6% of cantharidin, which is a protective exudate produced by the beetles. The properties of cantharides are those of its active principle, cantharidin (below).

Mylabris (Chinese blistering beetle; Chinese cantharides; Indian blistering beetle), the dried beetles of the species *Mylabrus sidae* (= *M. phalerata*), *M. cichorii*, and *M. pustulator*, has been used as a substitute for cantharides and as a source of cantharidin (see below) in the East.

Homoeopathy

Cantharides has been used in homoeopathic medicines under the following names: Cantharis; Lytta vesicatoria; Canthr.

Adverse Effects

The adverse effects of cantharides are those of its active component, cantharidin, below.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Canad.***: Bladder Irritation; Calendula +; EnurAid; Hylands Formula E; Reneel†; ***Fr.***: Amanita Complexe No 75; Cistus Canadensis Complexe No 86†; Geranium Complexe No 108†; Juniperus Complexe No 6; ***Ger.***: Cysto-cyl L Ho-Len-Complex; Hewecyst Blasen-Nieren†; Levisticum S; metasolidago S†; Pascorenal-Injektopas; Solidago Hevert Complex; Urofossat; Uroselect; ***Neth.***: Opsonat; ***Rus.***: Cistoit-GF (Цистоит-ГФ); ***S.Afr.***: Berberis/Cantharis Comp†; ***Switz.***: Regenaplex Nr 28b; Regenaplex Nr 86a.

Cantharidin

Cantaridina; Кантаридин.
Hexahydro-3aα,7aα-dimethyl-4β,7β-epoxyisobenzofuran-1,3-dione.
$C_{10}H_{12}O_4$=196.2
CAS — 56-25-7.
UNII — IGL471WQ8P.

Uses and Administration

Cantharidin is obtained from cantharides or mylabris (see under Cantharides, above). Cantharidin has vesicant activity and a solution of 0.7% in flexible collodion is applied for the removal of warts and molluscum contagiosum. Preparations of cantharides and cantharidin have also been used externally as rubefacients and counter-irritants. Owing to the intensely irritating nature of cantharidin it should not be taken internally. Also it should not be applied over large surfaces because of the risk of absorption.

Preparations of cantharides and cantharidin were formerly promoted for hair loss but their use in cosmetic products is now prohibited in the UK by law.

Molluscum contagiosum. References.
1. Silverberg NB, *et al.* Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol* 2000; **43:** 503–7.
2. Moed L, *et al.* Cantharidin revisited: a blistering defense of an ancient medicine. *Arch Dermatol* 2001; **137:** 1357–60.
3. Ross GL, Orchard DC. Combination topical treatment of molluscum contagiosum with cantharidin and imiquimod 5% in children: a case series of 16 patients. *Australas J Dermatol* 2004; **45:** 100–2.
4. Hanna D, *et al.* A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol* 2006; **23:** 574–9.

Adverse Effects and Treatment

The adverse effects of cantharidin, a protective exudate produced by blistering beetles (see under Cantharides above), are a result of its irritant and vesicant properties and may occur after exposure to preparations of cantharidin or to the beetle itself. Cantharidin produces blistering of mucous membranes. After ingestion of cantharidin there is burning pain in the throat and stomach, difficulty in swallowing, nausea, vomiting, haematemesis, abdominal pain, diarrhoea (sometimes bloody), tenesmus, renal pain, frequent micturition, dysuria, priapism, haematuria, proteinuria, renal failure, severe hypotension, and circulatory failure. Severe gastrointestinal disturbances can produce significant morbidity. Oral doses of cantharidin ranging from 10 to 80 mg have been lethal, although there have been reports of survival after doses up to 175 mg. Cantharidin is lipid soluble and oral bioavailability is increased in the presence of fatty substances.

Dermatological exposure may produce dermatitis, blisters, and ulceration, although symptoms may not appear until several hours later. Significant dermal exposure can give rise to systemic toxicity. Keratoconjunctivitis, iritis, and oedema may result from contact with the eyes or surrounding tissues.

Cantharidin has been abused as a sex stimulant.

Treatment of cantharidin poisoning is largely supportive. Emesis must be avoided following oral ingestion because of the severe irritant effect of cantharidin on mucous membranes. Activated charcoal has been tried, although it is not certain whether it binds to cantharidin.

Poisoning. References.
1. Hundt HKL, *et al.* Post-mortem serum concentration of cantharidin in a fatal case of cantharides poisoning. *Hum Exp Toxicol* 1990; **9:** 35–40.
2. Polettini A, *et al.* A fatal case of poisoning with cantharidin. *Forensic Sci Int* 1992; **56:** 37–43.
3. Karras DJ, *et al.* Poisoning from "Spanish fly" (cantharidin). *Am J Emerg Med* 1996; **14:** 478–83.
4. Tagwireyi D, *et al.* Cantharidin poisoning due to "Blister beetle" ingestion. *Toxicon* 2000; **38:** 1865–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Canthacur; Cantharone; ***China***: You Si Luo (尤斯洛); ***Turk.***: Canthacur.

Multi-ingredient Preparations. ***Canad.***: Canthacur-PS; Cantharone Plus; ***Turk.***: Canthacur-PS.

Capsicum

Capsic.; Capsici fructus; Cayennepfeffer; Chillies; Espanjanpippuri; Paprikų vaisiai; Paprikový plod; Piment de cayenne; Piment Rouge; Pimentão; Red Pepper; Spanischer Pfeffer; Spansk peppar; Перец Красный.
ATC Herb — HM02AB5001 (Capsicum annuum: fruit); HA03AW5006 (Capsicum annuum: fruit).
UNII — 6M47G7C4SY (red pepper); T5KDM4J239 (Capsicum spp. fruit).

NOTE. Ground cayenne pepper of commerce is normally a blend of varieties of capsicum. Paprika is from *Capsicum annuum* var. *longum*; it is milder than capsicum.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Eur. and *US* also include capsicum oleoresin (capsicin).

Ph. Eur. 8: (Capsicum). The dried ripe fruits of *Capsicum annuum* var. *minimum* and small-fruited varieties of *C. frutescens*. It contains a minimum of 0.4% of total capsaicinoids expressed as capsaicin, calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Capsicum Oleoresin, Refined and Standardised). A red or brown mobile extract that contains 12.0 to 18.0% of capsaicinoids expressed as capsaicin. It is produced from the herbal drug and alcohol by an appropriate procedure.

Ph. Eur. 8: (Capsicum Soft Extract, Standardised). A reddish-brown glutinous extract that contains 2.0 to 2.4% of capsaicinoids expressed as capsaicin. It is produced from the herbal drug and alcohol by an appropriate procedure.

USP 36: (Capsicum). The dried ripe fruit of various capsicum species. It contains not less than 0.3% of total capsaicinoids, calculated as the sum of capsaicin, dihydrocapsaicin, nordihydrocapsaicin, nonivamide, decanylvanillinamide, and homocapsaicin, and the nonivamide content is not more than 5% of the total capsaicinoids, calculated on the dried basis. During storage, a few drops of chloroform may be added from time to time to prevent attack by insects.

USP 36: (Capsicum Oleoresin). An alcoholic extract of the dried ripe fruits of capsicum. It contains not less than 6.5% of total capsaicinoids, calculated as the sum of capsaicin, dihydrocapsaicin, nordihydrocapsaicin, nonivamide, decanylvanillinamide, and homocapsaicin, calculated on the anhydrous basis. The nonivamide content is not more than 5% of the total capsaicinoids, calculated on the anhydrous basis. It is a powerful irritant, and even in minute quantities produces an intense burning sensation when it comes in contact with the eyes and tender parts of the skin. Contact with the skin and eyes is to be avoided. It is a dark red, oily liquid. Soluble in alcohol, in acetone, in chloroform, in ether, and in volatile oils; soluble with opalescence in fixed oils. Store in airtight containers.

Uses and Administration

Capsicum has a carminative action but it is mainly used externally, often in the form of capsicum oleoresin, as a counter-irritant (see Rubefacients and Topical Analgesia, p. 6.3). It is also included in preparations for the management of cough and cold symptoms. Capsaicin (p. 35.1), the active ingredient of capsicum, is also used in topical preparations in the treatment of painful skin conditions.

Capsicum oleoresin is used in 'pepper sprays' for law enforcement and self defence.

Capsicum also has culinary uses.

Homoeopathy

Capsicum has been used in homoeopathic medicines under the following names: Capsicum annuum; Cap. a.

Adverse Effects

Preparations of capsicum and capsicum oleoresin can be very irritant to the skin and mucous membranes.

Adverse effects of pepper sprays. References to the toxic effects of 'pepper sprays' containing capsicum oleoresin.

1. Brown L, *et al.* Corneal abrasions associated with pepper spray exposure. *Am J Emerg Med* 2000; **18:** 271–2.
2. Zollman TM, *et al.* Clinical effects of oleoresin capsicum (pepper spray) on the human cornea and conjunctiva. *Ophthalmology* 2000; **107:** 2186–9.
3. Chan TC, *et al.* The effect of oleoresin capsicum "pepper" spray inhalation on respiratory function. *J Forensic Sci* 2002; **47:** 299–304.
4. Das S, *et al.* Capsicum spray injury of the eye. *Int Ophthalmol* 2005; **26:** 171–3.
5. Miller JJ, Skolnick J. Inhalation injury after capsaicin exposure. *J Ky Med Assoc* 2006; **104:** 103–5.

Effects on the gastrointestinal tract. The initial response to the ingestion of a hot pepper is a hot or burning sensation in the mouth, which is attributed to the binding of capsaicin to receptors in the oral cavity.[1] Casein-containing substances such as milk can reverse this burning sensation, apparently by displacing capsaicin, this being due to their lipophilicity.

Spicy meals have long been associated with gastrointestinal discomfort and ingestion of meals containing 1.5 g of red or black pepper has been shown to cause signs of gastric mucosal damage comparable with those caused by a 625-mg dose of aspirin.[2] However, other studies in *animals*[3] and humans[4,5] suggest that capsaicin may have a protective effect on gastric mucosa. Ingestion of about 30 g of jalapeño peppers (a capsicum fruit) caused no visible damage to the duodenal or gastric mucosa of 12 healthy subjects[6] and daily ingestion of meals containing a total of 3 g of chilli powder did not affect the clinical progress of patients with duodenal ulcers given antacids.[7]

1. Henkin R. Cooling the burn from hot peppers. *JAMA* 1991; **266:** 2766.
2. Myers BM, *et al.* Effect of red pepper and black pepper on the stomach. *Am J Gastroenterol* 1987; **82:** 211–14.
3. Holzer P. Peppers, capsaicin, and the gastric mucosa. *JAMA* 1989; **261:** 3244–5.
4. Kang JY, *et al.* Chili—protective factor against peptic ulcer? *Dig Dis Sci* 1995; **40:** 576–9.
5. Yeoh KG, *et al.* Chili protects against aspirin-induced gastroduodenal mucosal injury in humans. *Dig Dis Sci* 1995; **40:** 580–3.
6. Graham DY, *et al.* Spicy food and the stomach: evaluation by videoendoscopy. *JAMA* 1988; **260:** 3473–5.
7. Kumar N, *et al.* Do chillies influence healing of duodenal ulcer? *BMJ* 1984; **288:** 1803–4.

Poisoning. References.

1. Snyman T, *et al.* A fatal case of pepper poisoning. *Forensic Sci Int* 2001; **124:** 43–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Hansaplast ABC Warme-Pflaster; ***Braz.***: Hercap; ***Chile***: Dolorub Capsico; Parche Leon Fortificante†; ***China***: Haojishi (Warm) (好及施 (温感)); ***Denm.***: Termo; ***Ger.***: Advel†; Capsamol; Dolobene Hot; Finalgon CPD; Rheumamed; Thermo Burger; ***Gr.***: Hansaplast Leontos†; ***India***: Capsigyl-D; Capsola Medi; ***Irl.***: Elastoplast; ***Israel***: Dragon Plaster; ***Ital.***: Thermogene; ***Port.***: Neodor; ***Spain***: Alacapsin; Ipsodol; Katrum; Sor Virginia; ***Swed.***: Termo; ***Switz.***: Hansaplast ABC; ***UK***: Fiery Jack; ***USA***: Salonpas Hot.

Multi-ingredient Preparations. ***Arg.***: Bifena; Sebulex; Veracolate†; ***Austral.***: Airborne Immunity; Euphrasia Complex; Euphrasia Compound; For Peripheral Circulation Herbal Plus Formula 5†; Goanna Heat Cream; GR² Control Thermogenic Enhancer; Joint Mobility†; Masculine Herbal Complex; Metabolift Fat Burner; Metabolism Advantage; Osteo-Relief; Percutane†; The Blue One†; ***Austria***: Trauma-Salbe warmend; ***Belg.***: Rado-Salil; Stilene; Thermocream; ***Braz.***: Capilos; Pilulas Ross; ***Canad.***: Absorbine Arthritis†; Hot Stuff†; Le Baume Ehrlich†; Natraway Sport 3†; Saw Palmetto Formula†; ***Chile***: Cellenergy; ***Fr.***: Baume Saint-Bernard; Curomal; Geldolor; Tigre de Chine; ***Ger.***: Gothaplast Rheumamed AC†; ***Hong Kong***: Salonsip Hot Patch†; Sloan's Liniment†; ***India***: Agile; Algipan; Capsigyl-D; Capsigyl; Capsitop; Capsola Plus; Cartigen; Flexi-muv†; Inflazone; Micronac; Myolaxin; Pane Free; Relaxyl; ***Indon.***: Lafalos Plus; Osteor-C; Sloan's Liniment†; ***Irl.***: Menthol & Wintergreen; Ralgex; ***Israel***: Dragon Massage Cream; Ment-O-Cap†; Radian-B; Rublex Massage Cream; ***Ital.***: Altadrine; Capso; Capsolin; Criotonal; Gefion; Gelovis; Sloan†; Valcap; Vasotonal; Wasotonal†; ***Mex.***: Parche Negro Belladona; ***Neth.***: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; ***Pol.***: Kapsiplast; ***Port.***: Balsamo Analgesico Sanitas; Medalginan; ***Rus.***: Efcamon (Эфкамон); Espol (Эспол); Percamf (Перкамф); ***S.Afr.***: Brooklax Pills†; Infrarub†; Moultons Pain Paint†; Muscle Rub†; SB 3 Triple Action Pills†; SB Shisalene†; Sloan's Heat Rub; Sloan's Liniment Rub†; Tandpyndruppels†; ***Singapore***: Lafalos Plus; ***Spain***: Dolokey†; Embrocacion Gras†; Linimento Naion; Termosan; ***Thai.***: Carminative Patar; Carminative Sahakarn; Flataco; Flatulence†; Meloids; Mist Carminative; Patarcolate; Patarsul; Veracolate†; ***Turk.***: Algo-Wax; Capsalgine; Capsi-Gel; Gelocaps; ***UK***: Allens Dry Tickly Cough; Balmosa; Buttercup Syrup; Catarrh Mixture; Cremalgin†; Fiery Jack; Hactos; Hansaplast Herbal Heat Plaster; Herbal Indigestion Naturtabs; Honey & Molasses; Indian Brandee; Indian Brandee; Indigestion and Flatulence; Indigestion Relief; Jamaican Sarsaparilla; Kilkof; Life Drops; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Radian-B; Ralgex†; Rheumatic Pain Relief; Sanderson's Throat Specific; Sanderson's Throat Specific; Vegetable Cough Remover; ***Ukr.***: Bronchial Balsam Bells (Бронхиальный Бальзам Беллс); Liponorm (Липонорм); ***USA***: Adrenoid; Duraflex Comfort; Pharmacists Creme; Pharmacists Lotion; Salonpas Gel Patch Hot; Throat Discs; Xoten-C; ***Venez.***: Ehrlich Balsamo.

Homoeopathic Preparations. ***Austral.***: Sleep & Insomnia Relief; ***Austria***: Berberis Cosmoplex†; Otodolor; Otovowen; Robinia Med Complex; ***Canad.***: Capsicum + Arthri-Cream; Earache; Kids' Earache; ***Fr.***: Euphrasia Complexe No 115; Grindelia Complexe No 58; Slimum†; ***Ger.***: Otovowen; Tonsipret; ***Neth.***: Oteel H; Ricura; ***Rus.***: Capsicum-Plus (Капсикум-Плюс); Tonsipret (Тонзипрет); ***Switz.***: Regenaplex Nr. 24b; ***Ukr.***: Incena (Инцена); Tonsipret (Тонзипрет).

Pharmacopoeial Preparations

Ph. Eur.: Capsicum Tincture, Standardised.

Caraway

Alcarahueya; Alcaravea; Alcaravia; Caraway Fruit; Caraway Seed; Carum; Carvi; Carvi fructus; Carvia; Cumin des Prés; Fructus Carvi; Frutos de la alcaravea; Kminový plod; Kmynų vaisiai; Köménytermés; Kumina; Kümmel; Kummin; Owoc kminku; Тмин.

*ATC Herb — HA03AW5008 (*Carum carvi: *fruit).*

UNII — W2FH8O2BBE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Caraway Fruit; Caraway BP 2014). The whole, dried fruits of *Carum carvi*. It contains not less than 3.0% v/w of essential oil, calculated with reference to the dried drug. It has an odour reminiscent of carvone. Protect from light.

The BP 2014 directs that when Powdered Caraway is prescribed or demanded, material containing not less than 2.5% v/w of essential oil shall be dispensed or supplied.

USNF 31: (Caraway). The dried, ripe fruit of *Carum carvi* (Apiaceae). Preserve against attack by insects.

Profile

Caraway is an aromatic carminative, and is used in gastrointestinal disorders and as a flavour. The seeds have culinary uses. It is the source of caraway oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Iberogast; Mag Kottas Krauterexpress Abfuhrtee; Midro Tee; Montana; ***Braz.***: Balsamo Branco; ***Canad.***: Anti Dyspepsia Digestive Aid†; Clear Capsules†; Formula T4†; ***Cz.***: Iberogast; ***Fr.***: Santane C_6†; Santane D_5†; Santane F_{10}†; Santane O1; Santane O1; ***Ger.***: Carminativum Hofmann†; Carminativum-Hetterich; Floradix Multipretten N; Iberogast; Iberomint†; Montana N; Pascoventral; ***Hung.***: Iberogast; Montana; Salus Multipretten; ***India***: Bonnispaz; Coliwell; ***Israel***: Jungborn†; Lido Tea†; Midro-Tea; ***Ital.***: Cadifen; Cadimint; Florelax; Midro; Relaxcol; ***Neth.***: Iberogast; ***Pol.***: Apinorm†; Iberogast; Laxantol†; Melis-Tonic; Normosan†; Rhelax; Tabletki Przeciw Niestrawnosci; Tabulettae Laxantes; ***Rus.***: Herbion Drops for the Gallbladder (Гербион Капли Желчегонные)†; Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Kliophyt (Клиофит); ***S.Afr.***: Clairo†; ***Spain***: Iberogast; ***Swed.***: Alpenkraft; Iberogast; Multipretten; ***Switz.***: Kernosan Heidelberger Poudre; Tisane favorisant l'allaitement; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Iberogast (Иберогаст).

Homoeopathic Preparations. ***Canad.***: Cynara Complex†; ***UK***: Laxadoron.

Pharmacopoeial Preparations

USNF 31: Compound Cardamom Tincture.

Caraway Oil

Alcaravea, aceite esencial de; Carvi aetheroleum; Carvi Etheroleum; Carvi, huile essentielle de; Kminová silice; Kuminaöljy; Kümmelöl; Kumminolja; Olejek kminkowy; Oleum Cari; Oleum Carui; Oleum Carvi; Тминное Масло.

*ATC Herb — HA03AW5007 (*Carum carvi: *essential oil).*

UNII — C2J9B08Q3I.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Caraway Oil). The oil obtained by steam distillation from the dry fruits of *Carum carvi*. A clear, colourless or yellow liquid. Relative density 0.904 to 0.920. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Caraway Oil). The volatile oil distilled from caraway. It contains not more than 50% v/v of carvone ($C_{10}H_{14}O$). Soluble 1 in 8 of alcohol (80%). Store in airtight containers. Protect from light.

Profile

Caraway oil is an aromatic carminative and is used in gastrointestinal disorders and as a flavour. It is also employed as caraway water for infant colic (see Gastrointestinal Spasm, p. 1807.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Balyfen†.

Multi-ingredient Preparations. ***Austria***: Parodontax†; Sigman-Haustropfen; Spasmo Claim†; ***Ger.***: Enteroplant; Floradix Multipretten N; Gastrysat†; Verdauungstropfen Gastrofunkten†; ***Hung.***: Enteroplant†; Salus Multipretten; Stompax; ***India***: Aniwel DPS; Aquadil-P; Bestozyme P; Bestozyme; Catalyd; Catazyme; Dorzy DPS; Gastrozyme; Gastrozyme; Hanzyme; Lavazyme; Litzyme; Merozyme-C; Neopeptine; Vitazyme; ***Ital.***: Relaxcol; ***Mex.***: Enterokan; ***Singapore***: Enterokan; ***Swed.***: Multipretten; ***Switz.***: Flatulex; Huile Po-Ho A. Vogel; ***Thai.***: Corinap; Gas-Nep; Gripe Mixture; ***UK***: Atkinson & Barker's Gripe Mixture; Nurse Harvey's Gripe Mixture.

Pharmacopoeial Preparations

BP 2014: Aromatic Cardamom Tincture; Compound Cardamom Tincture.

Carbon-13

Carbono 13; Углерод-13.

CAS — 14762-74-4.

Profile

Carbon-13 is a naturally occurring, non-radioactive, stable isotope of carbon. It has been used to label organic compounds, such as urea (p. 1727.3), for use in diagnostic tests, including breath tests for the diagnosis of *Helicobacter pylori* infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Pylobactell; ***Denm.***: Diabact UBT; Helicobacter Test†; ***Fin.***: Diabact UBT; ***Fr.***: Heli-Kit; Ubit†; ***Ger.***: Diabact UBT; Helicobacter Test; ***Gr.***: Helicobacter Test; Pylobactell; ***Irl.***: Diabact UBT; ***Israel***: C13-Urea; ***Ital.***: Breathquality-UBT; Citredici UBT Kit; Expirobacter; Helicokit; ***Neth.***: Helico State; Pylobactell; UBTest†; ***Norw.***: Diabact UBT; ***Pol.***: Pylobactell; ***Port.***: Helico-teste; Helicobacter Test; Pylobactell; Ubit; ***Spain***: Tau Kit; Ubtest; ***Swed.***: Diabact UBT; ***Switz.***: Helicobacter Test; Pylori 13; ***UK***: Diabact UBT; Pylobactell; ***USA***: Meretek UBT.

Multi-ingredient Preparations. ***Irl.***: Helicobacter Test; Pylobactell; ***USA***: Ez-HBT.

Pharmacopoeial Preparations

USP 36: Urea C 13 for Oral Solution.

All cross-references refer to entries in Volume A

Cardamom

Cardamomi; Cardamomo, fruto del; Кардамон.
UNII — 8BC4CUT4JL.

Pharmacopoeias. In *Br.* and *Jpn.* Also in *USNF.*

BP 2014: (Cardamom Fruit). The dried, nearly ripe fruit of *Elettaria cardamomum* var. *minuscula*. Only the seeds are used in making preparations of cardamom and they are used immediately after removal from the fruit. The seeds should not be stored after removal from the fruit. They have a strongly aromatic odour and taste and contain not less than 4% v/w of volatile oil.

USNF 31: (Cardamom Seed). The dried ripe seed of *Elettaria cardamomum* (Zingiberaceae), recently removed from the capsule. Preserve against attack by insects.

Profile

Preparations of cardamom are used as carminatives and as flavours. The seeds have culinary uses. Cardamom seeds are the source of cardamom oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Peritone; ***Austria***: Klosterfrau Melissengeist; Mariazeller; ***Cz.***: Dr Theiss Schwedenbitter†; Klosterfrau Melisana; ***Fr.***: Dida; ***Ger.***: Gallexier; Klosterfrau Melissengeist; Montana N; Schwedentrunk Elixier; ***Hung.***: Klosterfrau Melisana; ***India***: Abana; Manix; Paedritone; ***Malaysia***: Bonnisan; ***Pol.***: Melisana Klosterfrau; Padma 28; ***Rus.***: Sodecor (Содекор); Suprima-Broncho (Суприма-бронхо); ***S. Afr.***: Alma†; Enterodyne†; Helmontskruie†; ***Switz.***: Arteriavita; Padma Digestin; Stomacine; ***Thai.***: Carminative Patar; Carminative Sahakarn; Caryopin; Mist Carminative; ***UK***: Indian Brandee; Padma Circosan; Pegina; ***Ukr.***: Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trypsidan (Трипсидан)†.

Pharmacopoeial Preparations
USNF 31: Compound Cardamom Tincture.

Cardamom Oil

Cardamomo, aceite esencial de; Ol. Cardamom; Кардамоновое Масло.
ATC Herb — HA03AW5024 (Elettaria cardamomum: *essential oil*).
UNII — JM0KJ091HZ.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Cardamom Oil). A clear, colourless or pale yellow liquid, visibly free from water, with an odour of cardamom fruit. It is distilled from crushed cardamom fruit. At 20 degrees it is soluble 1 in 6 of alcohol (70%). Store at a temperature not exceeding 25 degrees in well-filled containers. Protect from light.

USNF 31: (Cardamom Oil). The volatile oil obtained from cardamom seed. Soluble 1 in 5 of alcohol (70%). Store in airtight containers. Protect from light.

Profile

Preparations of cardamom oil are used as carminatives and as flavours.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Aromadigest†; ***India***: Aniwel DPS; Aquadil-P; Carmicide; Catalyd; Catazyme; Digeplex; Dorzy DPS; Gastrozyme; Gastrozyme; Hanzyme; Lavazyme; Litzyme; Vitazyme; ***Thai.***: Corinap; Gas-Nep.

Pharmacopoeial Preparations
BP 2014: Aromatic Cardamom Tincture; Compound Cardamom Tincture; Compound Rhubarb Tincture.

Carglumic Acid *(USAN, rINN)*

Acide Carglumique; Ácido carglúmico; Acidum Carglumicum; Carglutamic Acid; Karglumik Asit; OE-312; Карглумовая Кислота.
N-Carbamoyl-L-glutamic acid.
$C_6H_{10}N_2O_5$=190.2
CAS — 1188-38-1.
ATC — A16AA05.
ATC Vet — QA16AA05.
UNII — 5L0HB4V1EW.

Profile

Carglumic acid is used for the treatment of hyperammonaemia in patients with *N*-acetylglutamate synthase deficiency. The initial oral dose ranges from 100 to 250 mg/kg daily, adjusted thereafter to maintain normal plasma levels of ammonia. Individual responsiveness to carglumic acid should be tested before starting long-term therapy; daily maintenance doses range from 10 to 100 mg/kg. The total daily dose should preferably be taken as 2 to 4 divided doses before food.

References to the use of carglumic acid in the management of hyperammonaemia due to *N*-acetylglutamate synthase deficiency.

1. Bélanger-Quintana A, *et al.* Hyperammonaemia as a cause of psychosis in an adolescent. *Eur J Pediatr* 2003; **162:** 773–5.
2. Caldovic L, *et al.* Restoration of ureagenesis in N-acetylglutamate synthase deficiency by N-carbamylglutamate. *J Pediatr* 2004; **145:** 552–4.
3. Gebhardt B, *et al.* N-carbamylglutamate protects patients with decompensated propionic aciduria from hyperammonaemia. *J Inherit Metab Dis* 2005; **28:** 241–4.
4. Guffon N, *et al.* Neonatal hyperammonemia: the N-carbamoyl-L-glutamic acid test. *J Pediatr* 2005; **147:** 260–2.
5. Jones S, *et al.* N-Carbamylglutamate for neonatal hyperammonaemia in propionic acidaemia. *J Inherit Metab Dis* 2008. Available at: doi: 10.1007/s10545-008-0777-1

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Carbaglu; ***Belg.***: Carbaglu; ***Cz.***: Carbaglu; ***Denm.***: Carbaglu; ***Fr.***: Carbaglu; ***Ger.***: Carbaglu; ***Gr.***: Carbaglu; ***Irl.***: Carbaglu; ***Israel***: Carbaglu; ***Ital.***: Carbaglu; ***Neth.***: Carbaglu; ***Pol.***: Carbaglu; ***Port.***: Carbaglu; ***Spain***: Carbaglu; ***Swed.***: Carbaglu; ***UK***: Carbaglu; ***USA***: Carbaglu.

Caroverine *(pINN)*

Caroverina; Carovérine; Caroverinum; Кароверин.
1-[2-(Diethylamino)ethyl]-3-(*p*-methoxybenzyl)-2(1*H*)-quinoxalinone.
$C_{22}H_{27}N_3O_2$=365.5
CAS — 23465-76-1.
ATC — A03AX11.
ATC Vet — QA03AX11.
UNII — XJ73B0K6KB.

Profile

Caroverine is a smooth muscle relaxant with calcium-channel blocking and glutamate-antagonist properties. It is used as the base or the hydrochloride in conditions associated with painful smooth muscle spasm. Typical oral doses (expressed as the base) are 20 to 40 mg three or four times daily. It may also be given by slow intravenous or intramuscular injection in doses of 40 to 80 mg. Caroverine has also been given rectally. It is also used in cerebral circulatory disorders and in tinnitus.

References.

1. Denk DM, *et al.* Caroverine in tinnitus treatment: a placebo-controlled blind study. *Acta Otolaryngol* 1997; **117:** 825–30.
2. Ehrenberger K. Clinical experience with caroverine in inner ear diseases. *Adv Otorhinolaryngol* 2002; **59:** 156–62.
3. Quint C, *et al.* The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Otolaryngol* 2002; **122:** 877–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Delirex†; Spasmium; Tinnitin.

Carqueja

Baccharis.

NOTE. The name carqueja has also been applied to the unrelated plant *Krameria tomentosa* (Krameriaceae).

Profile

Carqueja consists of the aerial stems of several *Baccharis* species (Asteraceae), particularly *B. articulata* and *B. genistelloides* var. *trimera* (*B. trimera*).

Carqueja is used in traditional medicine in South America and is included in herbal remedies mainly for gastrointestinal and hepatic disorders.

Homoeopathy

Carqueja has been used in homoeopathic medicines under the following names: Baccharis trimera.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Alcachofa Plus; Boldina; Digenat; HDG; Hepacur; Hepatodirectol; Radicura; Sabelin; ***Braz.***: Gotas Preciosas.

Homoeopathic Preparations. ***Fr.***: Poconeol no 37; Poconeol no 74†.

Cartilage and Cartilage Extracts

Хрящ и Хрящевые Экстракты.
UNII — D5P3K3V822 (autologous cultured chondrocytes).

Profile

Preparations containing cartilage or cartilage extracts from various sources have been used in musculoskeletal and joint disorders and as nutritional supplements. Autologous cultured chondrocytes are used for the repair of symptomatic cartilage defects of the femoral condyle in the knee. A product derived from shark cartilage (AE-941, p. 735.3) is under investigation as an antineoplastic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Car-ti-buron; Cartilago Vital; Cartimax; CT1000; ***Austral.***: Cartilag†; PM Cartisak; ***Austria***: ChondroCelect; ***Belg.***: ChondroCelect; ***Cz.***: ChondroCelect; ***Indon.***: Fellafit; Sharko Inside; ***Irl.***: ChondroCelect; ***Pol.***: ChondroCelect; ***Port.***: ChondroCelect; ***Spain***: ChondroCelect.

Multi-ingredient Preparations. ***Arg.***: Car-ti-buron Flex; Cartiflex; Collagen T2-Gag; Rep-Cartil; ***Chile***: Cartilago T-500†; Rumalon; ***Fr.***: Captafer; Corvitec; ***Mex.***: Mex-Amina; ***Rus.***: Rumalon (Румалон); ***S.Afr.***: Zeel; Zeel; ***Thai.***: Cal-ups Join.

Homoeopathic Preparations. ***Cz.***: Zeel Salbe†; ***Ger.***: NeyArthros Nr 43-Sol†; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; NeyAthos Nr 43; ***Hung.***: Zeel; ***Rus.***: Zeel T (Цель Т).

Oriental Cashew

Anacardier d'orient; Anacardium; Cashew-pähkinä; Indisk nöt; Marking Nut Tree; Markingnut Tree; Nanercz wschodni; Semecarpus anacardium; Восточный Анакардовый Орех.
UNII — Y0F0BU8RDU (Semecarpus anacardium *juice*); *1SNJ70152E* (Semecarpus anacardium).

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Oriental Cashew for Homoeopathic Preparations; Semecarpus Anacardium ad Praeparationes Homoeopathicas). The dried fruit of *Semecarpus anacardium* (*Anacardium orientale*). It contains a minimum 6.0% of total phenol derivatives expressed as eugenol.

Profile

Various parts of the oriental cashew, *Semecarpus anacardium* (Anacardiaceae), and their preparations are used in traditional Indian medicine. The oil contains bhilawanols, irritant substances reputed to have cytotoxic action.

Homoeopathy

The dried ripe fruit of oriental cashew is used in homoeopathic medicines under the following names: Anacardium; Semecarpus anacardium; Anacardium orientale; Anacard or; Anac. or.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Astomera; ***Canad.***: Barijodeel†; Formula ES 211; Nervita; ***Chile***: Anacardio con Fosforo; Bioactiv M; ***Fr.***: Abbe Chaupitre no 6; Acidum Phosphoricum Compose†; Anxietum; Euphorbium Complexe No 88; ***Ger.***: Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Lowe-Komplex Nr 6; Mucosa compositum; Nervoid N; Rytesthin; Sedaphin†; Stoma-Gastreu S R5; Ventrigutt M; ***Hung.***: PSY-Stabil; ***Neth.***: Cerebrum comp; Emvita 7; Mucosa comp H; Nervofleur; PSY-stabil; ***Rus.***: Anabar (Анабар); ***Switz.***: Regenaplex Nr. 25a.

Cassia Oil

Aceite de Casia; Canela de la China, aceite de; Cannelier, huile essentielle de; Cassiaöl; Chinese Cinnamon Oil; Cinnamomi Cassiae Aetheroleum; Cinnamomi Cassiae Etheroleum; Kassiakaneliöljy; Kassiaolja; Kínai fahéjolaj; Kininių cinamonų eterinis aliejus; Oleum Cassiae; Oleum Cinnamomi; Oleum Cinnamomi Cassiae; Silice skořicovníku čínského; Масло Кассии.
UNII — A4WO0626T5.

NOTE. In *Martindale*, 'Cinnamon' is used for material obtained from *Cinnamomum verum* and 'Cassia' for material from *Cinnamomum cassia*. However, some of the literature and some pharmacopoeias use the term 'Cinnamon' to describe products from *C. cassia*. Care should be taken to differentiate between the botanical sources.

Pharmacopoeias. In *Eur.* (see p. vii).

Chin. P. under the title of Oleum Cinnamomi specifies oil from *Cinnamomum cassia*. *JpnP.* under the title Cinnamon Oil

allows oil from either *C. cassia* or from *C. zeylanicum* [*C. verum*].

Chin. and *Jpn* also include bark (cassia bark) from *Cinnamomum cassia* although the titles are Cortex Cinnamomi and Cinnamon Bark respectively.

Ph. Eur. 8: (Cassia Oil). The oil obtained by steam distillation of the leaves and young branches of *Cinnamomum cassia* (*C. aromaticum*). It contains 70 to 90% of cinnamaldehyde. A clear, mobile, yellow to reddish-brown liquid, with a characteristic odour of cinnamaldehyde. Store in well-filled airtight containers. Protect from heat.

Profile

Cassia oil, obtained from *Cinnamomum cassia*, has properties resembling those of cinnamon oil (p. 2479.3) and is used similarly as a carminative and flavour. It has also been used in aromatherapy. Hypersensitivity to cinnamaldehyde, the main constituent of cassia oil, has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Tiger Balm Red; ***Cz.***: Klosterfrau Melisana; ***Hung.***: Klosterfrau Melisana; ***India***: Abana; Diakof; Himcolin; Kofarest-H; Koflet; ***Malaysia***: Shine Maxtra; ***Rus.***: Sodecor (Содекор); ***S.Afr.***: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Entressdruppels HM; Moultons Pain Paint†; Stuidruppels; ***UK***: Dragon Balm; ***Ukr.***: Bronchomed (Бронхомед); Huato Pills (Болюсы Хуато).

Castor

Castoreum.

Profile

Castor is the dried scent-glands (preputial follicles) of the beaver, *Castor fiber* and *Castor canadensis*. It has been used in perfumery.

Homoeopathy

Castor has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Bano Svedkeseru; ***Ukr.***: Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Castor Oil

Aceite de Ricino; Hintyağı; Huile de Ricin; Ol. Ricin.; Oleum Ricini; Ricini Oleum; Ricini Oleum Virginale; Ricino, aceite de; Ricinolja (jungfruolja); Ricinový olej panenský; Ricinusolaj; Risiiniöljy, neitsytöljy; Rizinusöl; Клещевинное Масло; Касторка; Касторовое Масло.

ATC — A06AB05.

ATC Vet — QA06AB05.

ATC Herb — HD02WB5010 (Ricinus communis: oil); HS01XW5001 (Ricinus communis: oil); HA06AB5016 (Ricinus communis: oil).

UNII — D5340Y2I9G.

NOTE. CASOIL is a code approved by the BP 2014 for use on single unit doses of eye drops containing castor oil where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Eur. also includes hydrogenated castor oil and refined castor oil. *USNF* includes hydrogenated castor oil.

Ph. Eur. 8: (Castor Oil, Virgin). The fatty oil obtained by cold expression from the seeds of *Ricinus communis*. During the expression step the temperature of the oil must not exceed 50 degrees. A suitable antoxidant may be added. Relative density about 0.958. It is a clear, at 40 degrees, slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit. Store in well-filled airtight containers. Protect from light.

Ph. Eur. 8: (Castor Oil, Hydrogenated; Ricini Oleum Hydrogenatum). The oil obtained by hydrogenation of castor oil. It consists mainly of the triglyceride of 12-hydroxystearic acid. Almost white to pale yellow fine powder, masses, or flakes. M.p. 83 degrees to 88 degrees. Practically insoluble in water and in petroleum spirit; very slightly soluble in dehydrated alcohol; slightly soluble in dichloromethane. Store in well-filled containers.

Ph. Eur. 8: (Castor Oil, Refined). The fatty oil obtained by cold expression from the seeds of *Ricinus communis* and then refined. A suitable antoxidant may be added. Relative density about 0.958. It is a clear, almost colourless or slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit. Store in well-filled, airtight containers. Protect from light.

USP 36: (Castor Oil). The fixed oil obtained from the seed of *Ricinus communis* (Euphorbiaceae). It is a pale yellowish or almost colourless, transparent, viscid liquid. Has a faint, mild odour; is free from foreign and rancid odour; and has a bland, characteristic taste. Soluble in alcohol; miscible with dehydrated alcohol, with chloroform, with ether, and with glacial acetic acid. Store in airtight containers at a temperature not exceeding 40 degrees.

USNF 31: (Hydrogenated Castor Oil). Refined, bleached, hydrogenated, and deodorised castor oil, consisting mainly of the triglyceride of hydroxystearic acid. A white, crystalline wax. M.p. 85 degrees to 88 degrees. Insoluble in water and in most common organic solvents. Store in airtight containers at a temperature not exceeding 40 degrees.

Uses and Administration

Castor oil is used externally for its emollient effect. It has also been used topically to allay irritation due to foreign bodies in the eye. Castor oil may be used as a solvent in some injections, and as a plasticiser.

Hydrogenated castor oil is used as a stiffening agent. Polyoxyl castor oils (p. 2202.3) are used as emulsifying and solubilising agents.

Castor oil has been used as a laxative, but such use is obsolete.

Adverse Effects and Precautions

Oral administration of castor oil, particularly in large doses, may produce nausea, vomiting, colic, and severe purgation. Castor oil should not be given when intestinal obstruction is present.

The seeds of *Ricinus communis* contain a toxic protein, ricin (p. 2604.2). Allergic reactions have been reported in subjects handling the seeds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Laxol; ***Ger.***: Laxopol†; ***Israel***: Laxopol; ***Mex.***: Ricitel†; ***Switz.***: Rical; ***Turk.***: Ricilaks; Riciment; Ricipan; ***USA***: Emulsoil; Neoloid†.

Multi-ingredient Preparations. ***Canad.***: Refresh Ultra; ***Chile***: Node DS†; ***Cz.***: Suspensio Visnevski cum Pice Liquida HBF; ***Ger.***: Itax†; ***India***: Coliwell; ***Pol.***: Salicylol; ***Rus.***: Urocholesan (Урохолесан); Urolesan (Уролесан); ***Spain***: Callicida Cor Pik†; Keranin†; Linitul; Otocerum; ***Switz.***: Peru Stick; ***Ukr.***: Urolesan (Уролесан); ***USA***: Allanderm-T†; Boudreaux's All Natural Butt Paste; Boudreaux's Butt Paste; Dermuspray; Dr Dermi-Heal; Granulderm†; Granulex; GranuMed; Mammol; Optase; Proderm; Vasolex; Venelex; Xenaderm.

Homoeopathic Preparations. ***Switz.***: Silacten.

Pharmacopoeial Preparations

BP 2014: Chloroxylenol Solution; Flexible Collodion; Zinc and Castor Oil Ointment;

USP 36: Aromatic Castor Oil; Castor Oil Capsules; Castor Oil Emulsion; Flexible Collodion.

Catalase

Caperase; Catalasa; EC 1.11.1.6; Equilase; Optidase; Каталаза.

CAS — 9001-05-2.

Profile

Catalase is an enzyme obtained from many biological sources including animal liver (hepatocatalase) and certain bacteria and fungi. It is a protein composed of 4 polypeptide subunits, the precise composition of which varies according to the source, and has a molecular weight of about 240 000. Catalase has the ability to promote the decomposition of hydrogen peroxide to water and oxygen.

It has been applied to wounds and skin ulcers and has also been used in the treatment of vitiligo. It has sometimes been used with glucose oxidase (p. 2516.3) in food preservation to break down hydrogen peroxide produced during oxidation of glucose, and is also included in preparations for contact lens care to neutralise hydrogen peroxide.

Catalase is a free-radical scavenger and has been investigated for its ability to limit reperfusion injury thought to be related to free-radical production. Combinations of catalase with superoxide dismutase have also been investigated.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Citrizan.

Multi-ingredient Preparations. ***Arg.***: Arion Cronos; ***Canad.***: UltraCare†; ***Gr.***: Pulvo 47; Pulvo-Hexa; ***Ital.***: Citrizan Antibiotico; ***Mex.***: Avitil; ***NZ***: Oxysept 1 Step; ***Thai.***: Pulvo 47†; ***Turk.***: Pulvo 47; ***USA***: UltraCare.

Catechu

Gambier; Gambir; Pale Catechu; Гамбир.

CAS — 8001-48-7.

ATC Herb — HA07XA5013 (Uncaria gambir: extract); HA01WA5008 (Uncaria gambir: extract).

UNII — 3NJQ5D856N.

NOTE. Distinguish from Black Catechu (p. 2457.3).

Pharmacopoeias. In *Jpn*. Also in *BP(Vet)*.

BP(Vet) 2014: (Catechu). A dried aqueous extract of the leaves and young shoots of *Uncaria gambier* occurring as dull pale greyish-brown to dark reddish-brown cubes. Odourless or almost odourless.

Profile

Catechu is an astringent and has been given in preparations for the treatment of diarrhoea and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Diarcalm†; ***Fr.***: Elixir Bonjean†; ***Indon.***: Entrodiar†; ***Ital.***: Flavion; Imoviral; ***Rus.***: Travisil (Трависил); ***S.Afr.***: Enterodyne†; SB Diarrhoea Mixture†; Tandpyndruppels†; ***Thai.***: Patarver; ***UK***: Chesty Cough Relief; Spanish Tummy Mixture.

CD4 Antibodies

Anti-CD4 Monoclonal Antibodies; Anticuerpos CD4; CD4mAb; Monoclonal CD4 Antibodies; Антитела Против СД4-Клеток.

Profile

Monoclonal antibodies raised against CD4 receptors are under investigation in the treatment of immunologically mediated disorders, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma, cutaneous T-cell lymphoma, psoriasis, and various other skin disorders, with the aim of decreasing and eliminating circulating helper T lymphocytes. They have also been tried in transplantation. CD4 antibodies investigated include: clenoliximab, keliximab, priliximab, and zanolimumab.

Cedar Wood Oil

Eastern Red Cedar Stem Oil; Oleum Cedri; *Juniperus virginiana* Oil; *Juniperus virginiana* Stem Oil; Red Cedar Oil; Red Cedar Stem Oil; Red Cedarwood Oil.

CAS — 8000-27-9.

UNII — PAD4FN7P2G.

NOTE. Distinguish cedar wood oil, obtained from species of *Juniperus virginiana*, and cedar leaf oil, obtained from *Thuja occidentalis* (see Thuja, p. 2629.3).

Profile

Cedar wood oil (cedarwood oil; red cedar oil) is obtained from red cedar, *Juniperus virginiana* (Cupressaceae). Cedar wood oil is used in perfumery and is included in preparations for nasal congestion and various skin disorders. It is also used in aromatherapy. Atlantic cedarwood oil (Atlas cedarwood oil) from *Cedrus atlantica* (Pinaceae) and oils from the wood of other species of *Juniperus* and *Cedrus* are used similarly.

Homoeopathy

Red cedar has been used in homoeopathic medicines under the following names: Juniperus virginiana; Juniperus virg.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Wick Vaporub; ***Canad.***: Artriben†; ***Fr.***: Activox; ***Gr.***: EKS; Revigel; ***Hung.***: Kinder Luuf Balsam; ***India***: Healplus; ***Mon.***: Dermagor Betacade; ***NZ***: Vicks Vaporub; ***Port.***: Betacade; ***Swed.***: Vicks Vaporub; ***UK***: No-Sor Vapour Rub.

Celery

Apio; Apium; Celery Fruit; Celery Seed; Сельдерей.

CAS — 8015-90-5 (celery oil).

ATC Herb — HA03WA5003 (Apium graveolens: fruit); HM01AW5002 (Apium graveolens: fruit); HA03WA5002 (Apium graveolens: essential oil); HG04BW5004 (Apium graveolens: fruit).
UNII — 15V0BLB71G (celery); XSZ4RMF8NF (celery juice); 1240X980BZ (celery root); 1G1EAA320L (celery seed); 44IDY6DTKX (celery stem/top).

Uses and Administration

Celery consists of the dried ripe fruits of *Apium graveolens* (Umbelliferae). Other parts of the plant are also used. Celery is reported to have diuretic properties and has been included in herbal preparations for rheumatic disorders. Celery oil has also been used similarly. Allergic and photoallergic reactions have been reported.

Celery also has culinary uses. Celery seed oil is used in aromatherapy.

Homoeopathy

Celery has been used in homoeopathic medicines under the following names: Apium graveolens; Apium. gr.

References.
1. Houghton P. Bearberry, dandelion and celery. *Pharm J* 1995; **255:** 272–3.

Insect repellent. A hexane extraction of celery seed has shown promise as a mosquito repellent.[1]

1. Tuetun B, *et al.* Repellent properties of celery, *Apium graveolens* L., compared with commercial repellents, against mosquitoes under laboratory and field conditions. *Trop Med Int Health* 2005; **10:** 1190–8.

Interactions

For a report of severe phototoxicity occurring in a patient who had consumed celery soup before undergoing PUVA therapy, see Interactions under Methoxsalen, p. 1714.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Calmtabs; ***Austral.***: Arthri Plus†; Arthriforte†; Arthritic Pain Herbal Formula 1†; Arthro-Eze; Boswellia Complex; Celery 3000; Devils Claw Plus†; Masculine Herbal Complex; Olf†; ***Canad.***: Herbal Diretic; Herbal Diuretic; ***Chile***: Draineur; ***Fr.***: Biofirm; ***India***: Agloliv; Aptizooom; Flexi-muv†; Gasex; Himcospaz; Ojus; ***Indon.***: Tensigard; ***Philipp.***: Ruflex; ***Singapore***: Ruflex; ***UK***: Mixed Vegetable Tablets; Modern Herbals Rheumatic Pain; Rheumatic Pain Relief; Rheumatic Pain; Vegetex; ***Ukr.***: Nephrocare (Нефрокеа); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Tazalok (Тазалок).

Cellobiose

Glucobiosa; Целлобиоза.
4-*O*-β-D-Glucopyranosyl-D-glucose.
$C_{12}H_{22}O_{11}$=342.3
CAS — 528-50-7.

Profile

Cellobiose is an indigestible disaccharide that has been used to assess intestinal permeability. It has been used as an alternative to lactulose in the differential sugar absorption test (p. 1851.1).

Cellulase *(USAN)*

Celulasa; EC 3.2.1.4; Целлюлаза.
CAS — 9012-54-8.

Profile

Cellulase is a concentrate of cellulose-splitting (cellulolytic) enzymes derived from *Aspergillus niger* or other sources. It is used in food processing and has been given orally with other digestive enzymes for its supposed benefit in minor digestive disorders such as dyspepsia and flatulence. Hemicellulase has been given for similar purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Pancrelase; ***Rus.***: Festal (Фестал).

Multi-ingredient Preparations. ***Arg.***: Arnol; Biletan Enzimatico; Biluen Enzimatico; Dom-Polienzim; Gastridin-E; Pakinase; Pankreon Total; Polienzim; ***Austral.***: Vegie Digestaid; ***Belg.***: Digestomen; ***Braz.***: Dasc†; Digecap-Zimatico; Essen; Sintozima†; ***Canad.***: Digesdyn; Digesta; Multi-Zyme†; Synergy Defense; ***China***: Dages (达吉); Mite (泌特); ***India***: Dipep; Enzovit; Festal; ***Indon.***: Cotazym Forte; ***Mex.***: Dixiflen; Espaven Enzimatico; Ochozim; Onoton; ***Philipp.***: Spasmo-Canulase; ***Port.***: Colerin-F†; Espasmo Canulase†; Fermetone Composto; ***Rus.***: Biofestal (Биофесталь); Ipental (Ипентал)†; Pheresthal (Ферестал); ***S.Afr.***: Spasmo-Canulase†; ***Switz.***: Spasmo-Canulase; ***Turk.***: Flaton; ***Ukr.***: Festal (Фестал); ***USA***: Digex†; Enzyme; Similase Jr; ***Venez.***: Stamyl.

Centaury

Centáurea menor; Centaurée, petite; Centaurii Herba; Centaurii Minoris Herba; Ezerjófű; Feverwort; Hiel de la tierra; Petite Centaurée; Rohtorantasappi; Širdažolių žolė; Tausendgüldenkraut; Tusengyllenört; Zemėžlučová nať; Ziele centurii.
ATC Herb — HA09WA5004 (Centaurium erythraea: herb).
UNII — 57X4TSH585 (Centaurium erythraea); B204P54Z1F (Centaurium erythraea extract); ZL25KMM82T (Centaurium erythraea flowering top).

NOTE. The name Feverwort has also been used as a common name for *Eupatorium perfoliatum* (see Boneset, p. 2459.1).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Centaury). The whole or fragmented dried flowering aerial parts of *Centaurium erythraea.* It has a bitter taste. Protect from light.

Uses and Administration

Centaury is used as a bitter, including for appetite loss and dyspepsia.

Adverse Effects

Effects on the liver. A report[1] of hepatotoxicity possibly associated with the use of *Copaltra,* a herbal preparation marketed as an adjunct in the treatment of diabetes mellitus and containing centaury and *Coutarea latiflora* (copalchi) (p. 2487.3). A further 5 cases had been reported to the French pharmacovigilance network.

1. Wurtz A-S, *et al.* Possible hepatotoxicity from Copaltra, an herbal medicine. *Ann Pharmacother* 2002; **36:** 941–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: China-Eisenwein†; Magentee St Severin; Mariazeller; Pervivo; ***Braz.***: Camomila; ***Canad.***: Floradix Tab†; Formula T4†; ***Cz.***: Stomaran; ***Fr.***: Diatisan†; Tisane D'Ars†; Tisane Hepatique de Hoerdt†; ***Ger.***: Amara-Tropfen; Canephron N; Montana N; ***Hung.***: Bittner; ***Pol.***: Pervivo; ***Rus.***: Canephron N (Канефрон Н); Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Amara†; Clairo†; ***Switz.***: Gastrosan; Gouttes Amara; Kernosan 24; Kernosan 26; Metabol; Tisane pour l'estomac; ***UK***: Cystipret; ***Ukr.***: Canephron N (Канефрон Н); Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Vitokan (Витокан).

Homoeopathic Preparations. ***Canad.***: Amaratopfen†; ***Fr.***: Diacure; ***Ger.***: Gastrin-Do; Gastroplant; ***UK***: Laxadoron.

Cereus

Cacto grandifloro; Cactus; Night-blooming Cereus; Pitahaya; Reina de la noche; Селеницереус Крупноцветковый (*Selenicereus grandiflorus*).

Profile

Cereus, the flowers and stems of night-blooming cereus (*Selenicereus grandiflorus*; *Cactus grandiflorus*) (Cactaceae), is thought to have cardiac stimulant actions and has been used in various cardiovascular disorders. It has also been used as an anthelmintic and in the treatment of rheumatism.

Homoeopathy

Cereus has been used in homoeopathic medicines under the following names: Cactus; Selenicereus grandiflorus; Cactus grandiflorus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UAE***: Mebo Scar.

Multi-ingredient Preparations. ***Switz.***: Femisan.

Homoeopathic Preparations. ***Austria***: Cactus compositum; Corasan; ***Canad.***: Menopause L122; Soludor†; ***Chile***: Ikoplex No 6; Lachess; ***Fr.***: Abbe Chaupitre no 20†; Crataegus Complexe No 15; Lachesis Complexe No 122; Poconeol no 31; Poconeol no 5; Soludor; Strophantus Compose; Vinicard†; ***Ger.***: A-Bomin; Angioton H; Angioton S†; Arte-cyl Ho-Len-Complex; Aurum-Gastreu S R2; Cardioselect N; Cefangipect H†; Cefangipect†; Cefavora Cor; Confludin N; Conva-cyl Ho-Len-Complex; Cor Plus; Cor; Corselect N; Corvipas SL; Crataegus comp; Crataegus Herzcomplex; Derivatio H; Derivatio; Diacard; HanoCor N; Homviotensin; Infi-Camphora; Lowe-Komplex Nr 10; Lycoaktin; Myonasan; Naranocor HM; Pectapas CPL; Pectapas SL; Pectapas; Schworocard; Steicardin N†; Strophanthus comp; Truw Gold; ***Neth.***: Cralonin H; ***Switz.***: Gouttes d'Or.

Ceruletide *(BAN, USAN, rINN)*

Caerulein; Cerulein; Ceruleína; Ceruletid; Ceruletida; Cérulétide; Ceruletidum; FI-6934; 883-S; Seruletidi; Церулетид.
$C_{58}H_{73}N_{13}O_{21}S_2$=1352.4
CAS — 17650-98-5 (ceruletide); 71247-25-1 (ceruletide diethylamine).
ATC — V04CC04.
ATC Vet — QV04CC04.
UNII — 888Y089718.

NOTE. The name Ceruleinum has been applied to Indigo Carmine (p. 2532.2).

Description. Ceruletide is a decapeptide amide originally isolated from the skin of the Australian frog, *Hyla caerulea,* and other amphibians. Ceruletide may exist as a salt with 1 to 3 moles of diethylamine (ceruletide diethylamine).

Uses and Administration

Ceruletide is structurally related to pancreozymin (p. 2582.1) and has similar actions. When given parenterally it stimulates gallbladder contraction and relaxes the sphincter of Oddi; it also causes an increase in the secretion of pancreatic enzymes and stimulates intestinal muscle.

As ceruletide diethylamine it is used as an aid to diagnostic radiology and in the management of paralytic ileus. It has also been used in tests of pancreatic exocrine function (see under Pancreatitis, p. 2580.2), sometimes with secretin (p. 2612.2); these studies generally require duodenal intubation of the patient and examination of duodenal aspirate and are rarely performed.

For most radiographic procedures of the biliary and digestive tracts ceruletide diethylamine has been given by intramuscular injection in a dose equivalent to 300 nanograms/kg of ceruletide. Doses equivalent to 1 to 2 nanograms/kg per minute have been given by intravenous infusion in pancreatic function tests and in the treatment of paralytic ileus.

Adverse Effects

Ceruletide stimulates gallbladder contraction and gastrointestinal muscle and may give rise to abdominal discomfort. Hypotensive reactions may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Takus†.

Cetyl Myristoleate

CMO; Hexadecyl Myristoleate; Palmityl Myristoleate; Цетил Миристолеат.
Hexadecyl (*Z*)-tetradec-9-enoate.
CAS — 64660-84-0.
UNII — 87P8K33Q5X.

Profile

Cetyl myristoleate is a cetyl ester (p. 2178.2) that has been suggested to be associated with resistance to arthritis in *mice.* Mixtures of cetyl esters containing mainly cetyl myristoleate have been given orally as nutritional supplements and have also been used topically in the management of osteoarthritis and musculoskeletal disorders.

References.
1. Diehl HW, May EL. Cetyl myristoleate isolated from Swiss albino mice: an apparent protective agent against adjuvant arthritis in rats. *J Pharm Sci* 1994; **83:** 296–9.
2. Hesslink R, *et al.* Cetylated fatty acids improve knee function in patients with osteoarthritis. *J Rheumatol* 2002; **29:** 1708–12.
3. Kraemer WJ, *et al.* Effect of a cetylated fatty acid topical cream on functional mobility and quality of life of patients with osteoarthritis. *J Rheumatol* 2004; **31:** 767–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Cartizole Plus; Celadrin; ***Indon.***: Flexasur; Flexasur; ***Malaysia***: Flexasur.

Cevimeline Hydrochloride *(USAN, rINNM)*

AF-102; AF-102B; Cevimelina, hidrocloruro de; Céviméline, Chlorhydrate de; Cevimelini Hydrochloridum; FKS-508; Hidrocloruro de cevimelina; SND-5008; SNI-2011; SNK-508; Цевимелина Гидрохлорид.

(±)-*cis*-2-Methylspiro[1,3-oxathiolane-5,3′-quinuclidine] hydrochloride hemihydrate.
$C_{10}H_{17}NOS,HCl,½H_2O$=244.8
CAS — 107233-08-9 (cevimeline); 153504-70-2 (cevimeline hydrochloride).
ATC — N07AX03.
ATC Vet — QN07AX03.
UNII — P81Q6V85NP.

Uses and Administration

Cevimeline is a selective muscarinic M_1 agonist used to improve the symptoms of dry mouth (see p. 2175.3) in patients with Sjögren's syndrome. It is given orally as the hydrochloride in doses of 30 mg 3 times daily.

Reviews.
1. Weber J, Keating GM. Cevimeline. *Drugs* 2008; **68:** 1691–8.

Dementia. Muscarinic M_1 agonists such as cevimeline have proved unsuccessful in relieving the symptoms of Alzheimer's disease (see p. 388.1).

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2 and p. 688.3.

Sweating is a common problem with cevimeline; patients who sweat excessively should be advised to drink extra fluids to avoid dehydration. Cevimeline should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision may affect the performance of skilled tasks. In addition cevimeline should be given with care to those with renal calculi or with biliary-tract disorders. It should also be used with caution in patients deficient in the cytochrome P450 isoenzyme CYP2D6 who may be at a higher risk of adverse effects.

Interactions

As for Neostigmine, p. 688.3.

Drugs that inhibit cytochrome P450 isoenzymes CYP2D6, CYP3A3, or CYP3A4 inhibit the metabolism of cevimeline.

Pharmacokinetics

After oral doses cevimeline is absorbed from the gastrointestinal tract; peak concentrations are reached in 1.5 to 2 hours. The rate and extent of absorption are decreased when given with food. Cevimeline is less than 20% bound to plasma proteins. It is metabolised in the liver by cytochrome P450 isoenzymes CYP2D6, CYP3A3, and CYP3A4. Cevimeline is mainly excreted in the urine, mainly as metabolites; about 0.5% of a dose is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Evoxac.

Chamomile

Camomila; Camomille romaine, fleur de (chamomile flower, Roman); Chamomillae romanae flos (chamomile flower, Roman); Heřmánkový květ (matricaria flower); Kamillavirágzat (matricaria flower); Kamomillankukka (matricaria flower); Kamomillankukka, roomalainen (chamomile flower, Roman); Kamomillblomma (matricaria flower); Kamomillblomma, romersk (chamomile flower, Roman); Koszyczek rumianku (matricaria flower); Květ heřmánku římského (chamomile flower, Roman); Manzanilla; Matricaire, fleur de (matricaria flower); Matricariae flos (matricaria flower); Ramunėlių žiedai (matricaria flower); Rómaikamilla-virág (chamomile flower, Roman); Tauriųjų didramunių žiedai (chamomile flower, Roman); Ромашка.
*ATC Herb — HA09WA5006 (*Chamaemelum nobile*: flower); HA03WB5001 (*Chamaemelum nobile*: flower); HA03AW5010 (*Chamaemelum nobile*: flower); HN05CM5013 (*Matricaria recutita*: flower); HM01AW5014 (*Matricaria recutita*: flower); HA01WX5001 (*Chamaemelum nobile*: flower); HD03WX5011 (*Matricaria recutita*: flower); HG02WB5001 (*Chamaemelum nobile*: flower); HA03WB5002 (*Matricaria recutita*: flower); HA03AW5034 (*Matricaria recutita*: flower).*
*UNII — FGL3685T2X (chamomile tea); G0R4UBI2ZZ (*Matricaria recutita*).*

Description. The name Chamomile is used for the dried flowerheads from 2 species of *Compositae* having similar medicinal properties:

- Chamomile from *Anthemis nobilis* (*Chamaemelum nobile*) is known as Chamomile Flowers, Chamomillae Romanae Flos, Manzanilla Romana, or Roman Chamomile Flower.
- Chamomile from *Matricaria recutita* (*Chamomilla recutita*) is known as Camomile Allemande, Camomilla, Chamomilla, Chamomillae Anthodium, Flos Chamomillae, Flos Chamomillae Vulgaris, German Chamomile, Hungarian Chamomile, Kamillenblüten, Manzanilla Ordinaria, Matricaria Flower, or Matricariae Flos

Pharmacopoeias. *Eur.* (see p. vii) includes chamomile from *Anthemis nobilis* and *Matricaria recutita*. *US* includes chamomile from *Matricaria recutita*.

Eur. also includes Matricaria Oil.

Ph. Eur. 8: (Chamomile Flower, Roman; Chamomile Flowers BP 2014). The dried flowerheads obtained from the cultivated double variety of *Anthemis nobilis* (*Chamaemelum nobile*), containing not less than 0.7% v/w of essential oil, calculated with reference to the dried drug. It has a strong characteristic odour. Protect from light.

Ph. Eur. 8: (Matricaria Flower; Matricariae Flos; Matricaria Flowers BP 2014). The dried flowerheads obtained from *Matricaria recutita* (*Chamomilla recutita*), containing not less than 0.4% v/w of blue essential oil and 0.25% of apigenin-7-glucoside, calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Matricaria Oil; Matricariae Aetheroleum). The blue essential oil obtained by steam distillation from the fresh or dried flower-heads or flowering tops of *Matricaria recutita* (*Chamomilla recutita*). There are 2 types of matricaria oil which are characterised as rich in bisabolol oxides, or rich in levomenol. Store in a well-filled, airtight container at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Chamomile). The dried flowerheads of *Matricaria recutita* (*Matricaria chamomilla, Matricaria chamomilla* var. *courrantiana, Chamomilla recutita*) (Asteraceae alt. Compositae). It contains not less than 0.4% of blue volatile oil, not less than 0.3% of apigenin-7-glucoside, and not less than 0.15% of bisabolane derivatives, calculated as levomenol. Protect from light.

Uses and Administration

Chamomile has been applied externally as a poultice in the early stages of inflammation, and preparations containing chamomile or extracts of chamomile (including the oil or a constituent, chamazulene), have been used for skin disorders, including the prevention and treatment of cracked nipples and nappy rash. Chamomile German oil and Chamomile Roman oil are used in aromatherapy. 'Chamomile tea' is a domestic remedy for indigestion and has also been reported to have hypnotic properties.

Homoeopathy

Chamomile has been used in homoeopathic medicines under the following names: Anthemis nobilis; Anthemis nob; Chamomilla; Cham.

Reviews.
1. Berry M. The chamomiles. *Pharm J* 1995; **254:** 191–3.
2. WHO. Flos Chamomillae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO; 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/11.html (accessed 04/02/10)
3. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). *Phytother Res* 2006; **20:** 519–30.
4. Gardiner P. Complementary, holistic, and integrative medicine: chamomile. *Pediatr Rev* 2007; **28:** e16–e18.

Adverse Effects

Chamomile has been reported to produce contact sensitivity and anaphylaxis.

Hypersensitivity. References.
1. Van Ketel WG. Allergy to Matricaria chamomilla. *Contact Dermatitis* 1987; **16:** 50–1.
2. McGeorge BC, Steele MC. Allergic contact dermatitis of the nipple from Roman chamomile ointment. *Contact Dermatitis* 1991; **24:** 139–40.
3. Rodriguez-Serna M, *et al*. Allergic and systemic contact dermatitis from Matricaria chamomilla tea. *Contact Dermatitis* 1998; **39:** 192–3.
4. Jensen-Jarolim E, *et al*. Fatal outcome of anaphylaxis to camomile-containing enema during labor: a case study. *J Allergy Clin Immunol* 1998; **102:** 1041–2.
5. Giordano-Labadie F, *et al*. Allergic contact dermatitis from camomile used in phytotherapy. *Contact Dermatitis* 2000; **42:** 247.
6. Foti C, *et al*. Contact urticaria from Matricaria chamomilla. *Contact Dermatitis* 2000; **42:** 360–1.
7. de la Torre Morín F, *et al*. Clinical cross-reactivity between Artemisia vulgaris and Matricaria chamomilla (chamomile). *J Investig Allergol Clin Immunol* 2001; **11:** 118–22.
8. Vandenplas O, *et al*. Occupational asthma caused by chamomile. *Allergy* 2008; **63:** 1090–2.
9. Andres C, *et al*. Anaphylactic reaction to camomile tea. *Allergol Int* 2009; **58:** 135–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kamillosan; ***Belg.***: Babygencal†; Kamillosan; ***Braz.***: Ad-Muc; Kamillosan; ***Canad.***: Paraterol†; ***Cz.***: Hermankovy; Kamillosan†; ***Fr.***: Camolid; ***Ger.***: Kamillen-Bad Ritsert†; Kamillenbad Intradermi†; Kamillin; Kamillosan†; Matmille†; PC 30 N†; ***Hong Kong***: Camoderm†; ***India***: Kamillosan; Kamillosan; ***Indon.***: Kamillosan; ***Irl.***: Kamillosan; ***Ital.***: Ceru Spray; Milla; ***Mex.***: Balsamo Nordin; Kamillosan; ***Pol.***: Azulan; Azuseptol; ***Port.***: Kamilosan; ***Rus.***: Romasulan (Ромазулан); ***S.Afr.***: Ashton & Parsons Infants Powders†; Kamillosan†; ***Switz.***: Kamillex; Kamillin Medipharm; Kamillofluid; Kamillosan; ***Turk.***: Parodontax; ***UK***: Ashton & Parsons Infants Powders; Kamillosan; ***Venez.***: Kamillen; Kamillosan.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Calm; Childrens Sleep; Colic Relief; Earache Relief†; Sleep & Insomnia Relief; Teething Relief; ***Austria***: Avena Med Complex; Birkenkohle comp; Daram; Echinacea-Cosmoplex; Erbiode Regelbeschwerden; Notta; Ohrentropfen Similasan; Osanit Chamomilla; Osanit Zahnungskugelchen; Otodolor; Otovowen; Traumeel; Valerianaheel; Zahnkugelchen; ***Canad.***: Calms Forte 4 Kids; Calms Forte; Calsom†; Camilia; Col 138†; Colic; Den 141†; Diarrex; Diarrhea; Earache; Formula DM 210†; Hylands Formula C; Hylands Formula CF; Hylands Kinder-CL†; Hylands Kinder-T†; Indigestion†; Jet Lag; Kid's Colic; Kids' Teething; Lemon Balm†; Quietude; Spascupreel; Tee Complex†; Teething; Traumeel; Valerianaheel Comp†; Viburcol; ***Chile***: Gug/X†; ***Cz.***: Sedalia; Spascupreel S†; Traumeel; Viburcol; ***Fr.***: Abbe Chaupitre no 18†; Abbe Chaupitre no 30†; Abbe Chaupitre no 43†; Abbe Chaupitre no 7; Abbe Chaupitre no 83†; Arthro-Drainol; Basilicum Complexe No 96; Camilia; Gelsemium Complexe No 70; Hedera Complexe No 120; Hypophysis Complexe No 31†; L 107; L 25; Poconeol no 37; Quietude; Ricinus Compose; ***Ger.***: A-Bomin; Angi Truw N; Birkenkohle comp; Cefaspasmon N†; Cocculus Oligoplex; dysto-loges N; Entero-Gastreu S R4; Entzundungstropfen; Galloselect; Gastrin-Do; Gastro-Plantin N†; Infihepan; Jsostoma S; Magen-Darmtropfen N; Meno-cyl L Ho-Len-Complex; Osanit; Otovowen; Passiflora Complex†; Rapako comp; Regenaplex Haut W; Roth's Rotacard; Sedacalman; Spascupreel; Spasmosyx F; Stoma-Gastreu S R5; Traumeel S; Viburcol N; Weleda Fieber- und Zahnungszapfchen; Zahnungstropfen Escatitona; Zappelin N; ***Hung.***: Spascupreel; Traumeel; Viburcol; ***Neth.***: Artifleur; Auriculite; Collite; Entero-Gastreu R4; Gastrifleur; Homeocare Digesto; Homeocare keelspray; Kind 0-3 Chamodent; Kind 0-3 Cinababy; Kind 0-6 Kinditherm; Omnilite; Oteel H; Quietude†; Spascupreel H; Traumeel H; Traumeel S; Viburcol H; ***Rus.***: Menalgin (Менальгин); Notta (Нотта); Traumeel S (Траумель С); ***S.Afr.***: Chamomilla/Millefolium Comp†; Traumeel S; Viburcol; ***Switz.***: Camilia; Quietude; Regenaplex Nr. 35b; Regenaplex Nr. 79; Traumeel; Viburcol N; ***UK***: Teetha; ***Ukr.***: Dentokind (Дентокинд); Enterocind (Энтерокинд); Kindinorm (Киндинорм); Notta (Нотта); Traumeel S (Траумель С); ***USA***: Preferred Remedies Sleep; Preferred Remedies Stress; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations
Ph. Eur.: Matricaria Liquid Extract.

Chaparral

Gobernadora; Чапаррель.
*UNII — PK0TXD049P (*Larrea tridentata*).*

Uses and Administration

Chaparral is derived from the creosote bush, *Larrea tridentata* (Zygophyllaceae). It has been included in various herbal preparations but recommendations that products containing chaparral should not be consumed have been made in several countries because of serious toxicity—see below.

Masoprocol is an antineoplastic isolated from the creosote bush.

Effects on the liver. References.
1. Gordon DW, *et al*. Chaparral ingestion: the broadening spectrum of liver injury caused by herbal medications. *JAMA* 1995; **273:** 489–90.
2. Batchelor WB, *et al*. Chaparral-induced hepatic injury. *Am J Gastroenterol* 1995; **90:** 831–3.
3. Sheikh NM, *et al*. Chaparral-associated hepatotoxicity. *Arch Intern Med* 1997; **157:** 913–19.
4. Kauma H, *et al*. Toxic acute hepatitis and hepatic fibrosis after consumption of chaparral tablets. *Scand J Gastroenterol* 2004; **39:** 1168–71.

Adverse Effects

Ingestion of chaparral has been associated with severe hepatotoxicity including permanent liver failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Ger.***: Pollinosan†; ***Switz.***: A Vogel Spray contre le rhume des foins; Pollinosan†.

Chebulic Myrobalan

Haritaki; He Zi; Ink Nut; Inknut; Jangi Harara; Myrobalan.
*UNII — SH421PVG8O (*Terminalia chebula*); T6755WMN6R (*Terminalia chebula *bark); S8R4V700NK (*Terminalia chebula *fruit); 2UH38Y7160 (*Terminalia chebula *root).*

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan — see Indian Gooseberry, p. 2532.2), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — see Arjuna, p. 2447.2; *T. bellirica* — see

Beleric Myrobalan, p. 2453.2; and *T. chebula*, Chebulic Myrobalan, above). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. In *Br.*

BP 2014: (Terminalia Chebula Fruit). The pericarp of mature fruits of *Terminalia chebula*. It contains not less than 20% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The fruit of chebulic myrobalan, *Terminalia chebula* (Combretaceae), is used in Ayurvedic medicine as a tonic and for a variety of disorders including both diarrhoea and constipation. The unripe fruit is also known as black myrobalan.

Other parts of the plant may also be used medicinally.

The traditional Ayurvedic medicine triphala is a combination of chebulic myrobalan, beleric myrobalan (p. 2453.2), and Indian gooseberry (p. 2532.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Triphala; ***Hung.***: Herbadict; Livfit; Munipyrin; ***India***: Abana; Ampucare; Bonnisan; Diabasic; Flexi-muv†; Geriforte; Geriforte; Herbolax; Intraliv; Jaundif; Koflet; Livasa; Liyurto; Megacure-DS; Menosan; Mentat; New-Livfit; Paedritone; ***Malaysia***: Bonnisan; ***Philipp.***: Cogent db+; ***Rus.***: Fitovit (Фитовит); Pilex (Пайлекс); Travisil (Трависил); ***Singapore***: Hemoglo; Imunomet; ***Switz.***: Padma-Lax; Padmed Laxan; ***UK***: Padma Circosan; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Eve Care (Ив Кер)†; Fitovit (Фитовит); Imunin (Иммунин)†; Septilin (Септилин); Softovak (Софтовак); Travisil (Трависил); Trypsidan (Трипсидан)†.

Chenodeoxycholic Acid *(BAN, rINN)*

Acide Chénodésoxycholique; Ácido quenodeoxicólico; Acidum Chenodeoxycholicum; CDCA; Chenic Acid; Chenodeoksicholio rūgštis; Chenodesoxycholsäure; Chenodiol (USAN); Kenodeoksikolik Asit; Kenodeoksikoolihappo; Kenodeoxicholsyra; Kenodezoxikólsav; Kyselina chenodeoxycholová; Quenodeoxicólico, ácido; Хенодезоксихолевая Кислота.

3α,7α-Dihydroxy-5β-cholan-24-oic acid.

$C_{24}H_{40}O_4$=392.6

CAS — 474-25-9.

ATC — A05AA01.

ATC Vet — QA05AA01.

UNII — 0GEI24LG0J.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Chenodeoxycholic Acid). A white or almost white powder. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.

Uses and Administration

Chenodeoxycholic acid is a naturally occurring bile acid (p. 2457.2). When given orally it reduces hepatic synthesis of cholesterol and provides additional bile salts to the pool available for solubilisation of cholesterol and lipids. It has been used for the dissolution of cholesterol-rich gallstones (p. 2639.1) in patients with a functioning gallbladder, in usual doses of about 15 mg/kg daily. The daily dose may be divided unequally and the larger dose given before bedtime to counteract the increase in biliary cholesterol concentrations seen overnight. Treatment may need to be given for up to 2 years, depending on the size of the stone. It should be continued for about 3 months after radiological disappearance of the stones. Chenodeoxycholic acid is also used in reduced doses with ursodeoxycholic acid (p. 2638.1).

Chenodeoxycholic acid has been used as a dietary supplement in neonates and children with inborn errors of bile acid synthesis: it has been used in the treatment of cerebrotendinous xanthomatosis; with cholesterol in the Smith-Lemli-Opitz syndrome; and with cholic acid for bile acid synthesis defects.

Cerebrotendinous xanthomatosis. Cerebrotendinous xanthomatosis is a rare autosomal recessive inborn error of bile acid metabolism. Accumulation of cholestanol in multiple organs and absence of chenodeoxycholic acid from bile results in a shift of bile acid metabolism to the cholestanol pathway. In a case report[1] of 4 family members with cerebrotendinous xanthomatosis followed up for 14 years after starting chenodeoxycholic acid therapy, 2 sisters who were started on treatment early at ages 2 and 7 years respectively, remained asymptomatic whereas only moderate improvement was seen in their 2 uncles who started treatment when already severely affected at ages 16 and 27 years respectively.

1. Berginer VM, *et al.* Chronic diarrhea and juvenile cataracts: think cerebrotendinous xanthomatosis and treat. *Pediatrics* 2009; **123:** 143–7.

Adverse Effects and Precautions

As for Ursodeoxycholic Acid, p. 2639.2. Diarrhoea may occur more frequently than with ursodeoxycholic acid. A transient rise in liver-function test values and hypercholesterolaemia (low-density lipoprotein) have been reported with chenodeoxycholic acid.

Chenodeoxycholic acid is embryotoxic in some *animals*.

Interactions

As for Ursodeoxycholic Acid, p. 2639.3.

Pharmacokinetics

Chenodeoxycholic acid is absorbed from the gastrointestinal tract and undergoes first-pass metabolism and enterohepatic recycling. It is partly conjugated in the liver before being excreted into the bile and, under the influence of intestinal bacteria, the free and conjugated forms undergo 7α-dehydroxylation to lithocholic acid. Some lithocholic acid is excreted directly in the faeces and the rest absorbed, mainly to be conjugated and sulfated by the liver before excretion in the faeces. Chenodeoxycholic acid also undergoes epimerisation to ursodeoxycholic acid.

References.

1. Crosignani A, *et al.* Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet* 1996; **30:** 333–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Chenofalk†; Xenbilox; ***Gr.***: Theramatic; ***Indon.***: Chenofalk†; ***Israel***: Chenofalk†; ***Mex.***: Sulobil; ***Neth.***: Chenofalk; ***Port.***: Xebyl; ***Rus.***: Chenofalk (Хенофальк); ***Turk.***: Chenofalk; ***USA***: Chenodal.

Multi-ingredient Preparations. ***Ger.***: Lithofalk†; ***Gr.***: Lithofalk; ***Ital.***: Bilenor.

Cherry Laurel

Cherry Bay; English Laurel; Kirschlorbeer; Kirschlorbeerbaum; Laakerikirsikka; Lagerhägg; Laurier-Cerise; Laurier-amande; Lorbeerkirsche.

UNII — 516S28LU0T (Prunus laurocerasus); G3X35793OV (Prunus laurocerasus fruit oil); F26P2D4757 (Prunus laurocerasus leaf).

Pharmacopoeias. In *Fr.*

Profile

The leaves of cherry laurel, *Prunus laurocerasus* (*Cerasus laurocerasus*; *Laurocerasus officinalis*) (Rosaceae), are included in herbal medicines for cough. They contain the glycoside prulaurasin (laurocerasin; DL-mandelonitrile-D-glucoside) which decomposes to glucose, hydrocyanic acid (p. 2156.2), and benzaldehyde (p. 2171.1). They have been used in the preparation of Cherry-laurel Water and as the source of Oil of Cherry Laurel.

Cherry-laurel water was formerly used for nausea and vomiting, and as an eye lotion. The oil, with the hydrocyanic acid removed, has been used as a flavour.

Adverse effects are due to the content of hydrocyanic acid, and overdosage can be fatal.

Homoeopathy

Cherry laurel has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Cellutex; ***Ital.***: Balsamina Kroner; ***S.Afr.***: Spiritus Contra Tussim Drops†; ***Spain***: Caltoson Balsamico†; Eupnol; ***Switz.***: Sano Tuss.

Homoeopathic Preparations. ***Fr.***: Boripharm No 31; ***Ger.***: Cor Plus; Hypotonie-Gastreu R44; Pulmo-cyl Ho-Len-Complex; ***UK***: Cough Drops.

Chicory

Achicoria de Bruselas; Achicoria de Café; Achicoria de Raíz; Belgium Endive; Blue Daisy; Blue Sailors; Chicoreé; Chicorée Amère; Chicorée de Bruxelles; Chicorée Sauvage; Chicória; Cikoria; Coffee Chicory; Coffee Weed; Common Chicory; Cykoria Podróżnik; French Endive; Hinduba; Kaffeezichorie; Radicchio; Radicheta; Salatzichorie; Succory; Wegwarte; Wild Chicory; Wilde Zichorie; Witloof; Wurzelzichorie.

UNII — 1KE45XD28S (chicory); HW54500A89 (chicory flower); WBQ249COFR (chicory leaf); 090CTY533N (chicory root).

NOTE. The names Chicory and Endive are applied to several species of *Cichorium*.

Pharmacopoeias. In *Chin.*

Pol. includes the root.

Profile

The root and leaves of *Cichorium intybus* (Asteraceae) are included in herbal preparations for gastrointestinal disorders, biliary and hepatic disorders, and in tonics.

The roasted root has been used as a substitute for coffee and the leaves are eaten as a vegetable.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Draineur; ***Fr.***: Biofirm; Detoxifiance; Obeflorine†; ***Ger.***: Amara-Tropfen; ***Hung.***: Diabess; Livfit; Majvedo es Detoxikalo; ***Indon.***: Jesscool†; ***Malaysia***: Bonnisan; ***Pol.***: Liv 52; Urosan†; ***Rus.***: Bonjigar (Бонджигар); Liv 52 (Лив 52); Liv 52 (Лив 52); ***S.Afr.***: Amara†; ***Singapore***: Liv 52; Liv 52; ***Switz.***: Gouttes Amara; Kernosan 24; Liv 52; Metabol; ***Ukr.***: Bonjigar (Бонджигар); Liv 52 (Лив 52).

Homoeopathic Preparations. ***Canad.***: Amaratopfen†; ***Fr.***: Poconeol no 67.

Chlorella

UNII — 591BV50NV8.

NOTE. *Chlorella vulgaris* and *Chlorella pyrenoidosa* are regarded as separate species by some sources.

Profile

The green alga *Chlorella vulgaris* (*C. pyrenoidosa*) (Oocystaceae) has been promoted as a nutritional supplement and as an adjunct to management of a range of diseases. Related species may be used similarly. The nutritional content varies with the method of preparation.

Chlorella is claimed to contain a substance known as Chlorella Growth Factor.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Growee; ***Ital.***: Ginoday; ***Philipp.***: Bomvital; Ceegeefer†; Celermin†; Cherifer; Chlorvytol†; Dreamvite; Dynavit; Enersel; EZ-Grow; Flexivit; Growee with Chlorella; Healthy Kidz; Kiddie Estamin; Kiddie Prime; Kiddirel; Lysadam Plus; Megavit; Multigen Plus; Multigrow; Nerveplex; Nutrazinc; Nutricaire; Nutrigrow Plus; Nutrigrow†; Nutrigrow; Optigrow; Pediafortan Forte-GE; Propan TLC; Pryce-Kidz; Regeron Vita with Chlorella; Regeron Vita with Chlorella; Restor-F; Restor; Strevit; Supranutrol; Time-Cee; TLC Vita; Vigorvit; Vita SL Plus; Vitakids; ***Singapore***: Growee†.

Chloroacetophenone

1-Chloroacetophenone; Cloroacetofenona; CN; CN Gas; Phenacyl Chloride; ω-Chloroacetophenone.

2-Chloroacetophenone.

C_8H_7ClO=154.6

CAS — 532-27-4.

UNII — 88B5039IQG.

NOTE. The name mace is applied to solutions of chloroacetophenone.

Profile

Chloroacetophenone is a lachrymatory which is irritant to the skin and eyes. It has been used in a riot-control gas; it is described as a tear gas.

References.

1. Hu H, *et al.* Tear gas—harassing agent or toxic chemical weapon? *JAMA* 1989; **262:** 660–3.
2. Treudler R, *et al.* Occupational contact dermatitis due to 2-chloracetophenone tear gas. *Br J Dermatol* 1999; **140:** 531–4.
3. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; **22:** 103–10.
4. Carron PN, Yersin B. Management of the effects of exposure to tear gas. *BMJ* 2009; **338:** 1554–8.

8-Chlorotheophylline

Chlortheophylline.

8-Chloro-3,7-dihydro-1,3-dimethyl-1*H*-purin-2,6-dione.

$C_7H_7ClN_4O_2$=214.6

CAS — 85-18-7.

UNII — GE2UA340FM.

Profile

8-Chlorotheophylline is a xanthine derivative that forms stable compounds (teoclates) with various drugs. It is used in the manufacture of antihistamines such as promethazine teoclate (p. 638.2) and dimenhydrinate (p. 625.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Switz.***: Detensor.

Chondroitin Sulfate Sodium

Chondroitin 4-Sulfate (chondroitin sulfate A); Chondroitin Sulphate Sodium; Chondroïtine, sulfate sodique de; Chondroitini natrii sulfas; Chondroitinsulfat-Natrium; Chondroitin-sulfát sodná sůl; Chondroityny sodu siarczan; CSA (chondroitin sulfate A); Sodium Chondroitin Sulfate; Sodyum Kondroitin Sülfat; Хондроитин Сульфат Натрия.

$(C_{14}H_{19}NO_{14}SNa_2)_n$

CAS — 9007-28-7 (chondroitin sulfate); 9082-07-9 (chondroitin sulfate sodium); 24967-93-9 (chondroitin sulfate A); 39455-18-0 (chondroitin sulfate A sodium); 25322-46-7 (chondroitin sulfate C); 12678-07-8 (chondroitin sulfate C sodium).

ATC — M01AX25.

ATC Vet — QM01AX25.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Chondroitin Sulfate Sodium). A natural copolymer based mainly on the two disaccharides obtained from cartilage of both terrestrial and marine origins. Depending on the animal species of origin, it shows different proportions of 4-sulfate and 6-sulfate groups. A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers. Protect from light.

USP 36: (Chondroitin Sulfate Sodium). The sodium salt of the sulfated linear glycosaminoglycan obtained from bovine, porcine, or avian cartilages of healthy and domestic animals used for food by humans. It consists mostly of the sodium salt of the sulfate ester of *N*-acetylchondrosamine (2-acetamido-2-deoxy-β-D-galactopyranose) and D-glucuronic acid copolymer. These hexoses are alternately linked β-1,4 and β-1,3 in the polymer. Chondrosamine moieties in the prevalent glycosaminoglycan are monosulfated mainly on position 4 and less so on position 6. Chondroitin sulfate sodium is extremely hygroscopic once dried. Store in airtight containers.

Uses and Administration

Chondroitin sulfate is an acid mucopolysaccharide that is a constituent of most cartilaginous tissues. It is used as the sodium salt, chondroitin sodium sulfate. It is given orally in reactive arthritides (see under Spondyloarthropathies, p. 14.3), such as gonococcal arthritis, and is often given with glucosamine (p. 2515.3) for its supposed chondroprotective action in musculoskeletal and joint disorders including osteoarthritis (see under Glucosamine, p. 2515.3). It is also used for its visco-elastic properties as an adjunct to ocular surgical procedures, including cataract extraction and intra-ocular lens implantation, and has been used for the relief of dry eye. A medium containing chondroitin sulfate A has been used to preserve corneas for transplantation. Chondroitin sulfate sodium has also been used as a means of replacing the glycosaminoglycan layer in the bladder in the treatment of interstitial cystitis (p. 2348.1). Chondroitin sulfate A and C are components of the heparinoid danaparoid (p. 1349.2).

Interactions

For reference to the effect of preparations containing chondroitin with glucosamine on warfarin, see under Dietary Supplements, p. 1533.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bioflogil; Dunason; Liquiprin; Lubrictin; Prof†; Structum; ***Austria***: Condrosulf; ***Belg.***: Lacrypos†; ***Braz.***: Dunason; ***Canad.***: Cell-fX; Uracyst; ***Chile***: Condrosulf; ***China***: An Pu Nuo Xin (安谱诺欣); Fu Zhi Ping (伏旨平); Xin Qi Si (欣奇思); ***Cz.***: Condral†; Condrosulf; Structum†; ***Fin.***: Artosolv†; Cartexan; ***Fr.***: Chondrosulf; Lacrypos†; Structum; ***Ger.***: Gepan Instill; Sanaven; Uropol; ***Hung.***: Condrosulf; ***Indon.***: Viostin S; ***Irl.***: Chondromel; ***Ital.***: Condrosulf; ***Malaysia***: Chondril†; Consulf; ***Mex.***: Condrosulf; Dunason; Maxus; Structum; ***Pol.***: Condral; Recalcin; Structum; ***Port.***: Condrosulf†; Ossin; Structum; ***Rus.***: Artra Chondroitin (Артра Хондроитин); Chondrogard (Хондрогард); Chondroitine-Akos (Хондроитин-Акос); Chondrolife (Хондролайф); Chondrolon (Хондролон); Chondroxide (Хондроксид); Mucosat (Мукосат); Structum (Структум); ***Singapore***: Consulf†; ***Spain***: Condrosan; Condrosulf; ***Switz.***: Condrosulf; Structum; ***Ukr.***: Arthron Chondrex (Артрон Хондрекс); Hondra-Syla (Хондра-Сила); Mucosat Neo (Мукосат Neo); Structum (Структум).

Multi-ingredient Preparations. ***Arg.***: Adaxil Forte; Adaxil Plus; Artrilase Complex; Artrocaptin; Asotrex; Baliartrin Duo; Cartiflex Forte; Ecosamina; Etinox; Etinox; Finartrit; Findol Plus; Gluco Arrumalon Duo; Glucometil 3; Glucotrin Forte; Glucotrin VL; Lacrimax†; Maxus; Mecanyl Duo; Mecanyl K Duo; Optilac; Ostatac Duo; Reumosan Compuesto; Sigmaflex; Vartalon Duo K; Vartalon Duo; Viscoat†; ***Austral.***: AB Ausbiobone; AB Carsa Giox; Bioflex†; Bonlutin; Duovisc; Formula for Joints; GenFlex 3†; GenFlex Plus†; Joint Formula Advanced with MSM Booster; Joint Formula Advanced; MeticGlucotin; Osteo-Relief Plus MSM; OsteoEze Active + MSM; OsteoEze Active; PM Metic-Glucotin; Viscoat†; ***Braz.***: Artrolive; Condroflex; ***Canad.***: Uracyst Test Kit†; ***Chile***: Artridol Duo; Dinaflex Duo; Eniflex Duo; Euroflex; Flexure; Hiperflex; Osteo Bi-Flex†; ***China***: Frecoseryl (润尔乐); Kang Ming (康明); ***Fr.***: Arthrobiane; Capsaine; Chondrosteo; Dexsil Articulations; Dexsil Sport; Fleximax; Synotabs; Viscoat†; ***Ger.***: DisCoVisc; Duovisc; Mobilat DuoAktiv; Viscoat; ***Gr.***: Viscoat; ***Hong Kong***: Arthritil Plus†; Doctor's Choice Fortified Joint Support†; ***Hung.***: Porcerosito; ***India***: Arth; Arthocare DS; Arthocare; Artifix; Bonit Join; Carticare; Cartifix; Cartigen Plus; Cartilamine DS; Cartilamine Forte; Cartisark; Cartivit; Cartiwel; Cartiz; Cartup; Conjoint; Flexi Cap; Flexibel; Freeflex; GC Flex; Gencart; Glutin; Intecar; Joint Guard; Jointace Forte; Jonty; Kondro; Mega Freeflex; Mobijoint; Necare; Orbone; Osteocip; Osteoflex; Ostiwel; Ostofit; Ostop; Ostovit; ***Indon.***: Aptivium Optimum Joint Formula†; Artriox†; Artritin; Artro Plus; Artro; Bonic Plus; Bonic; Cartiflex; Cartin; Chondro-PA; Fitbon Plus; Flexor; Fripos; GCM; Joint Care Plus; Joint Care; Jointfit; Lavarix; Maxitrin†; Naturema; Nutrijoint; OA Forte; OA Plus; OA; Osamin; Ositin; Osmetin 3; Oste; Ostela; Osteoflam; Osteokom Forte; Osteokom; Osteokom; Osteonic; Osteor Plus; Osteor-C; Osteor; Osteotin; Ostine; Ostrimix; Osvion Plus; Rebone; Rheumatin Forte; Rheumatin; Risteon; Triflexor; Triostee; Viopor-M Forte; Viopor-M; Viopor; Viostin Com DS; Viostin Com; Viostin-X; Vostem; Vosteon; ***Irl.***: Seven Seas Active Sport†; ***Israel***: Mega Gluflex with MSN; Mega Gluflex; ***Ital.***: Cartago; Cartijoint†; Condrorexil; DisCoVisc†; Fitogenase; Ginepausil; Joint Support; Reumil; Reumilase Plus; Reumilase SD; Viscoat; ***Malaysia***: Conart; Cosamine Plus; Duovisc†; Viscoat†; ***Mex.***: Actiman; Artiflex; Humylub Ofteno; Mex-Amina; Splash Tears; Vartalon Compositum; ***Mon.***: Algicuivre; ***NZ***: Viscoat; ***Philipp.***: Artiflex; Cartifast-C; Flexxbon; Osteoaid; Viscoat; ***Rus.***: Artra (Артра); Chondroitine-Akos (Хондроитин-Акос); Chondroxide (Хондроксид); Hondrofen (Хондрофен); KONDROnova (КОНДРОнова); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); ***S.Afr.***: Duovisc†; Viscoat; ***Singapore***: Artril C†; Artrilase; BCC; Duovisc; Glutilage Plus; Joint Care; JointFlex; Seven Seas JointCare; Viscoat†; ***Spain***: Droglican; ***Thai.***: Artrofort Complex; DisCoVisc; Duovisc; Viscoat; ***Turk.***: Duovisc†; Jointace; Ultimate; Viscoat; ***UK***: BackOsamine; Flexeze; GlucOsamax; Joint Action; Jointace; Jointace; Jointace; ***Ukr.***: Arthron Complex (Артрон Комплекс); Arthron-Triactive (Артрон Триактив); Artritosamin (Артритозамин); Chondrasil (Хондрасил)†; Chondroitin Complex (Хондроитин Комплекс); Chondroxide (Хондроксид); Flex-A-Min Complex (Флекс-А-Мин Комплекс)†; Hondra-Syla (Хондра-Сила); Movex Active (Мовекс Актив); Movex Comfort (Мовекс Комфорт); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); ***USA***: Cosamin; DisCoVisc; Viscoat; ***Venez.***: Artrosamin.

Pharmacopoeial Preparations

USP 36: Chondroitin Sulfate Sodium Tablets; Glucosamine and Chondroitin Sulfate Sodium Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets.

Chrome Alum

Chromium Potassium Sulfate; Chromium Potassium Sulphate; Cromo, alumbre de; Хромовые Квасцы.

$KCr(SO_4)_2,12H_2O=499.4$

CAS — 10141-00-1 (anhydrous chrome alum); 7788-99-0 (chromium potassium sulfate dodecahydrate).

Profile

Chrome alum is used in leather tanning, as a mordant in dyeing, and for hardening gelatin in photographic materials. It has been used as a sclerosant in medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Scleremo.

Homoeopathic Preparations. ***Ger.***: Pascallerg.

Chromium Trioxide

Anhídrido Crómico; Chromic Acid; Chromic Anhydride; Chromu(VI) tlenek; Cromo, trióxido de.

$CrO_3=99.99$

CAS — 1333-82-0.

UNII — 8LV49809UC.

Potassium Dichromate

Bichromate of Potash; Potassium Bichromate; Potasu dichromian.

$K_2Cr_2O_7=294.2$

CAS — 7778-50-9.

UNII — T4423S18FM.

Pharmacopoeias. *Eur.* (see p. vii) includes for homoeopathic preparations.

Ph. Eur. 8: (Potassium Dichromate for Homoeopathic Preparations; Kalii Bichromas ad Praeparationes Homoeopathicas). Orange crystals. Freely soluble in water; practically insoluble in alcohol.

Profile

Chromium trioxide is a hexavalent chromium salt. Although chromium is an essential trace element (see p. 2055.3) hexavalent salts are mainly used in industry and are associated with acute and chronic toxicity; they are more dangerous than di- or trivalent compounds.

Hexavalent chromium salts are oxidising agents and solutions are corrosive. Repeated contact may cause eczematous dermatitis, particularly in hypersensitive persons and can also cause deep perforating ulcers known as 'chrome holes'. If inhaled, chromic dusts cause rhinitis and painless ulcers which may perforate the nasal septum; inhalation may cause severe lung damage and inflammation of the eyes. There may also be involvement of the CNS and there is an increased risk of lung cancer.

Acute poisoning after ingestion of hexavalent chromium salts may cause intense thirst, dizziness, abdominal pain with vomiting, and diarrhoea; hepatic injury, acute renal failure with anuria or oliguria, and peripheral vascular collapse may also result. Fatalities have occurred due to renal or hepatic damage.

Treatment of acute chromium poisoning is symptomatic and supportive. Protective measures should be taken when handling or working with chromium and its salts.

Chromium trioxide was formerly used as a caustic and astringent. Potassium dichromate has been used similarly.

Homoeopathy

Potassium dichromate has been used in homoeopathic medicines under the following names: kali bichromicum; kalium bichromicum; kaliumdichromat; kalii dichromas; kali-bi.

Adverse effects. The toxicity of chromium[1-4] is mainly associated with hexavalent chromium compounds and there have been reports of poisoning with ammonium dichromate,[5] chromium trioxide,[6] potassium dichromate,[7-9] and sodium dichromate.[10] Although treatment with ascorbic acid has been suggested there is little evidence of benefit and it is not generally recommended.[11]

1. WHO. Chromium. *Environmental Health Criteria 61*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/ehc/ehc/ehc61.htm (accessed 30/07/08)
2. Health and Safety Executive. The toxicity of chromium and inorganic chromium compounds. *Toxicity Review 21*. London: HMSO, 1989.
3. Barceloux DG. Chromium. *J Toxicol Clin Toxicol* 1999; **37:** 173–94.
4. Dayan AD, Paine AJ. Mechanisms of chromium toxicity, carcinogenicity and allergenicity: review of the literature from 1985 to 2000. *Hum Exp Toxicol* 2001; **20:** 439–51.
5. Meert KL, *et al*. Acute ammonium dichromate poisoning. *Ann Emerg Med* 1994; **24:** 748–50.
6. Matey P, *et al*. Chromic acid burns: early aggressive excision is the best method to prevent systemic toxicity. *J Burn Care Rehabil* 2000; **21:** 241–5.
7. Michie CA, *et al*. Poisoning with a traditional remedy containing potassium dichromate. *Hum Exp Toxicol* 1991; **10:** 129–31.
8. Stift A, *et al*. Liver transplantation for potassium dichromate poisoning. *N Engl J Med* 1998; **338:** 766–7.
9. Kolacinski Z, *et al*. Acute potassium dichromate poisoning: a toxicokinetic case study. *J Toxicol Clin Toxicol* 1999; **37:** 785–91.
10. Ellis EN, *et al*. Effects of hemodialysis and dimercaprol in acute dichromate poisoning. *J Toxicol Clin Toxicol* 1982; **19:** 249–58.
11. Bradberry SM, Vale JA. Therapeutic review: is ascorbic acid of value in chromium poisoning and chromium dermatitis? *J Toxicol Clin Toxicol* 1999; **37:** 195–200.

Handling. Chromium trioxide is a powerful oxidising agent and is liable to explode in contact with small quantities of alcohol, ether, glycerol, and other organic substances.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Childrens Cough Relief; Childrens Runny Nose Relief; Earache Relief†; Respatona Chesty Cough & Nasal Congestion; Respatona Dry Cough & Nasal Congestion; Respatona Head Cold; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; Snore Eze; Snorestop; ***Austria***: Asinis; Globuli gegen Schnupfen Nr 3; Luffa Med Complex; Metasinusit; Nebenhohlen-Tropfen Nr 26†; Tonsillopas; Tonsiotren; ***Canad.***: Bioactiv H†; Bronchial Cough; Cat Complex†; Comp-Drops 5 Expectorant†; Coryzalia; Cough & Cold; Detox L37; Homeo-Form R†; Homeodel 21†; Homeovox;

Hylagene; Hylands Formula S; Hylands Sinus†; Hylaquell BC; Indigestion; Nareel†; Rhinar†; Sinus Ease; Sinus; Sinuspax†; Snore Stop; ***Chile***: Rinoplex; ***Cz.***: Coryzalia; Homeovox; ***Fr.***: Allium Cepa Compose; Coryzalia; Homeoaftyl; Homeodose 8†; Homeovox; Iodum Complexe No 118; Mercurius Cyanatus Complexe No 43†; Sinuspax; Thuya Complexe No 37; ***Ger.***: Angina-Gastreu S R1; Gripps; Hevertotox; Hewallergia Complex; Muco-cyl L Ho-Len-Complex; Mucosa compositum; Odonton-Echtroplex; Rufebran gastro†; Schleimhaut-Komplex L Ho-Fu-Complex; Sinasal; Sinuselect N; Sinusitis Hevert SL; Sinusitis Hevert†; Sinusitis-Weliplex†; Tonsillopas; Tonsiotren H; ***Hung.***: Coryzalia; Homeovox; Naso-Heel S; ***Neth.***: Belachin-Gastreu R1; Coryzalia; Homeovox; Mucosa comp H; Snurdim; ***Port.***: Coryzalia; Homeovox; ***Rus.***: Asinis (Асинис); Cinnabsin (Циннабсин); Coryzalia (Коризалия); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); ***Switz.***: A Vogel pour les sinus; Alceprin-N; Coryzalia; Homeovox; metasinusit; Nelsons Sinusit†; Sinusin; Sinuspax†; ***Ukr.***: Asinis (Асинис); Cinnabsin (Циннабсин); Coryzalia (Коризалия); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); ***USA***: Preferred Remedies Sinus.

Chromocarb Diethylamine *(rINNM)*

Chromocarbe, Diéthylamine de; Chromocarbi Diethylaminum; Cromocarbo, dietilamina de; Dietilamina de cromocarbo; Хромокарба Диэтиламин.

The diethylamine salt of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid .

$C_{14}H_{17}O_4N$=263.3

CAS — 4940-39-0 (chromocarb).

UNII — R0O8TF63DH.

Profile

Chromocarb diethylamine is used to reduce capillary haemorrhage (including conjunctival haemorrhage) associated with various disorders, and for venous insufficiency. It is given orally in a dose of 200 mg 3 times daily. It is also used as eye drops; 1 or 2 drops of a 10% solution have been instilled up to 6 times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Fludarene; ***Port.***: Fradilen; ***Spain***: Activadone.

Chrysoidine Hydrochloride Citrate

Crisoidina, hidrocloruro del citrato de.

4-Phenylazobenzene-1,3-diamine hydrochloride citrate; Azobenzene-2,4-diamine hydrochloride citrate.

$C_{12}H_{12}N_4HCl,C_6H_8O_7$=440.8

CAS — 532-82-1 (chrysoidine hydrochloride); 5909-04-6 (chrysoidine hydrochloride citrate).

Profile

Chrysoidine hydrochloride citrate has been used as a dye but has been associated with tumours of the bladder.

Carcinogenicity. The development of tumours of the urinary bladder in anglers was possibly associated with the use of chrysoidine hydrochloride (chrysoidine Y; CI Basic Orange 2; Colour Index No. 11270) for colouring the maggots used as bait.[1-3]

1. Searle CE, Teale J. Chrysoidine-dyed bait: a possible carcinogenic hazard to anglers? *Lancet* 1982; **1**: 564.
2. Sole GM. Maggots dyed with chrysoidine: a possible risk to anglers. *BMJ* 1984; **289**: 1043–4.
3. Massey JA, *et al.* Maggots dyed with chrysoidine. *BMJ* 1984; **289**: 1451–2.

Chymopapain *(BAN, USAN, rINN)* ⊗

BAX-1526; Chymopapaïne; Chymopapainum; EC 3.4.22.6; Kymopapaiini; Kymopapain; NSC-107079; Quimopapaina; Quimopapaína; Химопапаин.

CAS — 9001-09-6.

ATC — M09AB01.

ATC Vet — QM09AB01.

ATC Herb — HA09AA5002 (Carica papaya: extract).

UNII — 1UK146T40N.

Description. Chymopapain is a proteolytic enzyme isolated from the latex of papaya (*Carica papaya*), differing from papain in electrophoretic mobility, solubility, and substrate specificity. Molecular weight about 27 000.

Units

One nanokatal (nKat) is defined as the amount of chymopapain which produces 1 nanomole of *p*-nitroaniline per second from DL-benzoylarginine-*p*-nitroanilide substrate at pH 6.4 and 37 degrees.

In some countries CTE units have been used, defined as the amount of chymopapain that produces a hydrolysate from acid-denatured haemoglobin at pH 4.0 in one minute with an optical density at 275 nm equivalent to that of a tyrosine solution 0.0001%.

Uses and Administration

Chymopapain is used as an injection into the intervertebral disc in the treatment of sciatic pain and other symptoms secondary to herniation of intervertebral discs of the lumbar spine (chemonucleolysis).

Chymopapain injection should preferably be given under local, rather than general, anaesthesia. The dose for a single intervertebral disc is 2 to 4 nanokatals, with a maximum dose per patient of 8 nanokatals.

Chemonucleolysis. Dissolution of the disc by injection of chymopapain or other enzymes (chemonucleolysis) has been used as an effective alternative to surgery in patients with lumbar disc herniation (see Low Back Pain, p. 9.2). However, concerns about its safety have led to a decline in its use, and discectomy is often preferred.

References.

1. Nordby EJ, *et al.* Chemonucleolysis. *Spine* 1996; **21**: 1102–5.
2. Brown MD. Update on chemonucleolysis. *Spine* 1996; **21** (24 suppl): 62S–68S.
3. Poynton AR, *et al.* Chymopapain chemonucleolysis: a review of 105 cases. *J R Coll Surg Edinb* 1998; **43**: 407–9.
4. Wittenberg RH, *et al.* Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study. *Spine* 2001; **26**: 1835–41.

Adverse Effects

The most important adverse effect of chymopapain is anaphylaxis, which can occur in up to about 1% of patients. It has resulted in fatalities and restricts use to a single treatment session per patient. Typical symptoms include angioedema, hypotension, laryngeal oedema and bronchospasm, shock, and cardiac arrest. Allergic skin reactions may also occur. Other reported reactions include headache, nausea and vomiting, paralytic ileus, urinary retention, thrombophlebitis, paraesthesias, foot-drop, and discitis. Severe muscle spasm and an increase in back pain are common. Paraplegia, acute transverse myelitis, and intracerebral and subarachnoid haemorrhage have occurred.

Incidence of adverse effects. A 1984 postmarketing surveillance study on a US chymopapain preparation for intradiscal injection (*Chymodiactin*) involved data from 29 075 patients (representing about 50% of the total number of vials sold).[1] Anaphylactic reactions were confirmed in 194 patients (0.67%), 2 of whom died. The incidence was higher in women than in men. In 52 cases the reaction occurred after the test dose. Serious neurological reactions reported were: cerebral haemorrhage (6 cases, 3 fatal; autopsy revealed that they had underlying cerebrovascular abnormalities); paraplegia (11 cases, 5 of which may have been due to incorrect needle placement); transverse myelitis with paraplegia (2 cases, after 2 and 3 weeks, with subsequent recovery); and seizures (2 cases on injection and 1 several days after the procedure). Twenty-two patients had discitis with severe back pain and spasm. In 9 cases bacteria could be cultured, and 1 patient subsequently developed fatal *Staphylococcus aureus* meningitis.

Another review[2] of serious reactions associated with chymopapain between 1982 and 1991 (including data from the earlier postmarketing study) involved 121 reports among about 135 000 patients. They included fatal anaphylaxis (7 cases), infections (24 cases), haemorrhage (32 cases), and neurological reactions (32 cases).

Both reviews concluded that careful attention to proper patient selection and correct techniques of intradiscal needle placement are the most important factors in avoiding adverse effects with chymopapain.

1. Agre K, *et al.* Chymodiactin postmarketing surveillance: demographic and adverse experience data in 29075 patients. *Spine* 1984; **9**: 479–85.
2. Nordby EJ, *et al.* Safety of chemonucleolysis: adverse effects reported in the United States, 1982–1991. *Clin Orthop* 1993; **293**: 122–34.

Precautions

Chymopapain should not be used in those patients with a known sensitivity to papaya proteins or in patients with progressive paralysis, or tumours of the spinal cord, or lesions of the cauda equina. Severe spondylolisthesis is also a contra-indication. It should not be given to patients with heart failure, coronary artery disease, or respiratory failure who may be at increased risk if anaphylaxis occurs, nor to patients receiving beta blockers.

Care is required in administering chymopapain to ensure that the injection is into the disc and not intrathecal. However, discography is not recommended since the use of contrast media may exacerbate neurotoxicity and may inactivate the enzyme.

The risk of allergic reactions associated with chymopapain is so high that no patient should ever receive it more than once. Tests to identify those most at risk and pretreatment with antihistamines (H_1 and H_2) and corticosteroids may be used, but facilities for the emergency management of anaphylactic reactions should always be to hand when giving patients chymopapain. The risk of anaphylaxis is higher in women.

Injection of more than one disc is associated with an increased frequency of neurological reactions; therefore, such injection should only be carried out after confirmation of definite further disc involvement.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Chymodiactin†.

Chymotrypsin *(BAN, rINN)* ⊗

Chimotripsinas; α-Chymotrypsin; Chymotrypsine; Chymotrypsinum; EC 3.4.21.1; Kimotripszin; Kymotrypsiini; Kymotrypsin; Quimotripsina; Химотрипсин.

CAS — 9004-07-3.

ATC — B06AA04; S01KX01.

ATC Vet — QB06AA04; QS01KX01.

UNII — BVS505O332.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Chymotrypsin). A proteolytic enzyme obtained by the activation of chymotrypsinogen extracted from the pancreas of beef. It contains not less than 5 microkatals in each mg. A white or almost white, crystalline or amorphous powder; the amorphous form is hygroscopic. Sparingly soluble in water. A 1% solution in water has a pH of 3.0 to 5.0. Solutions have a maximum stability at pH 3 and a maximum activity at about pH 8. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Chymotrypsin). A proteolytic enzyme crystallised from an extract of the pancreas gland of the ox, *Bos taurus* (Bovidae). It contains not less than 1000 USP units in each mg, calculated on the dried basis. A white to yellowish-white, crystalline or amorphous, odourless powder. An amount equivalent to 100 000 USP units is soluble in 10 mL of water and in 10 mL of sodium chloride 0.9%. Store in airtight containers at a temperature not exceeding 40 degrees.

Units

Various methods have been used to assay the potency of chymotrypsin. Ph. Eur. 8 expresses activity in terms of microkatals while USP 36 expresses in terms of USP units. Other units that may be encountered are FIP units, Armourunits, and Denver (or Wallace or Wampole) units.

Uses and Administration

Chymotrypsin is a proteolytic enzyme that has been used in ophthalmology for the dissection of the zonule of the lens, thus facilitating intracapsular cataract extraction and reducing trauma to the eye. For this purpose a solution of chymotrypsin in a sterile diluent such as sodium chloride 0.9% has been injected to irrigate the posterior chamber.

Chymotrypsin has also been given, usually orally or topically, for its supposed action in reducing soft-tissue inflammation and oedema associated with surgery or traumatic injuries, and in patients suffering from upper respiratory-tract disorders.

Hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Wobenzym; ***Braz.***: Parenzyme Analgesico; Parenzyme†; Thiomucase; ***Canad.***: Wobenzym; ***Cz.***: Wobenzym; ***Gr.***: Chymoral; Itastab; Tricuval; ***India***: Alfapsin D; Alfapsin; Ceze; Chymase; Chymin; Chymobel Plus; Chymobel; Chymoral; Chymosoz-D; Chymotas; Chymotrip; Chymutrip; Ficlo-Forte; Flamotryp; K-Trip Plus; K-Trip; Kymovil Plus; Omotrip; Optase-DC; Orthal Forte; Orthotime; Solu-zyme; ***Mex.***: Ochozim; Quimotrip†; Ribotripsin; Wobe-Mugos; Wobenzym; Zimotris; ***Port.***: Chimar; ***Rus.***: Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); ***Spain***: Dertrase; Dosil Enzimatico; Doxiten Enzimatico; Quimodril; ***Ukr.***: Wobe-Mugos E (Вобэ-Мугос Е)†; Wobenzym (Вобэнзим); ***USA***: Bio-Zyme; ***Venez.***: Wobenzym N.

Pharmacopoeial Preparations

USP 36: Chymotrypsin for Ophthalmic Solution.

Ciliary Neurotrophic Factor

CNTF; Factor neurotrófico ciliar; Цилиарный Нейротрофический Фактор.

NOTE. The name Axokine has been used as a trade mark for a neurotrophic factor related to ciliary neurotrophic factor. The name Axokine has also been used for a proprietary preparation of hydroxychloroquine sulfate (p. 655.2).

Profile

Ciliary neurotrophic factor (CNTF) is a nerve growth factor produced in neural tissues and released in response to injury. Recombinant CNTF has been investigated in motor neurone disease (p. 2605.2), peripheral neuropathy, and obesity. CNTF is also under investigation for the treatment of retinitis pigmentosa and atrophic (dry) age-related macular degeneration as an intra-ocular polymer implant containing human retinal epithelial cells that have been genetically modified to secrete CNTF.

References.

1. Miller RG, *et al.* A placebo-controlled trial of recombinant human ciliary neurotrophic (rhCNTF) factor in amyotrophic lateral sclerosis. *Ann Neurol* 1996; **39:** 256–60.
2. Ettinger MP, *et al.* Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *JAMA* 2003; **289:** 1826–32.
3. Sieving PA, *et al.* Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proc Natl Acad Sci U S A* 2006; **103:** 3896–901.

Cimicifuga

Actée à grappes; Black Cohosh; Black Snakeroot; Bugbane; Cimicifuga; Cimicifugae rhizoma; Cohosh negro; Herbe aux Punaises; Цимицифуга.

ATC — G02CX04.

ATC Vet — QG02CX04.

ATC Herb — HG03WA5001 (Cimicifuga racemosa: rhizome); HM01AW5006 (Cimicifuga racemosa: rhizome).

UNII — K73E24S6X9 (Cimicifuga racemosa root); 1D114JZ36B (Cimicifuga dahurica root).

NOTE. Distinguish from Blue Cohosh, p. 2458.2.

Pharmacopoeias. *Chin.* includes the rhizome of *Cimicifuga heracleifolia, C. dahurica,* and *C. foetida.*

Eur. (see p. vii) and *US* include the rhizome and roots of *C. racemosa. US* also includes the powdered form.

Jpn includes the rhizome of *C. simplex, C. heracleifolia, C. dahurica,* and *C. foetida.*

Ph. Eur. 8: (Black Cohosh; Cimicifugae Rhizoma). The dried, whole or fragmented rhizome and root of *Cimicifuga racemosa* (*Actaea racemosa*). It contains not less than 1.0% of triterpene glycosides, expressed as monoammonium glycyrrhizate ($C_{42}H_{65}NO_{16}$ = 840.0) calculated with reference to the dried drug.

USP 36: (Black Cohosh). The dried rhizome and roots of *Actaea racemosa* (*Cimicifuga racemosa*). It contains not less than 0.4% triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$ = 660.8) with reference to the dried drug. Protect from light and moisture.

Uses and Administration

Cimicifuga, the roots of *Cimicifuga racemosa* (*Actaea racemosa*) (Ranunculaceae), is used for menopausal and gynaecological disorders and is included in preparations for coughs.

Homoeopathy

Cimicifuga has been used in homoeopathic medicines under the following names: Actaea racemosa; Actaea rac.; Cimicifuga racemosa; Cim. rac.

General references.

1. WHO. Rhizoma Cimicifugae Racemosae. *WHO Monographs on Selected Medicinal Plants,* volume 2. WHO: Geneva; 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/8.html (accessed 04/02/10)

Menopausal disorders. Cimicifuga is used in menopausal disorders, particularly for the relief of hot flushes but opinion varies as to its efficacy. While some systematic reviews[1,2] consider that its use is not supported by conclusive evidence others suggest that overall it might be of some benefit.[3]

1. Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*) for menopausal symptoms: a systematic review of its efficacy. *Pharmacol Res* 2008; **58:** 8–14.
2. Palacio C, *et al.* Black cohosh for the management of menopausal symptoms: a systematic review of clinical trials. *Drugs Aging* 2009; **26:** 23–36.
3. Shams T, *et al.* Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis. *Altern Ther Health Med* 2010; **16:** 36–44.

Adverse Effects

A systematic review of the limited data available on adverse effects for cimicifuga concluded that adverse effects are generally mild and transient.[1] It has been reported that cimicifuga may cause dizziness, vertigo, headache, vomiting, and gastrointestinal irritation when taken in large doses.[2] From January 1998 to February 2005, Health Canada[3] had received 7 reports of adverse effects suspected of being associated with black cohosh, including dizziness, rash, pruritus, oedema, increased pulse, bradycardia, atrial fibrillation, changes in plasma-thyroid hormone concentration, vaginal bleeding, and convulsions. However, lack of data meant that causality could not be proved.

As of March 2006, the UK MHRA[2] had received 21 reports of **hepatotoxicity** associated with cimicifuga ingestion since 1998, which represented more than two-thirds of the total number of reports for any reaction related to cimicifuga. Likewise, there have been similar reports of hepatotoxicity in other countries including the USA, Germany, and Sweden.[2] Up to April 2006, 11 cases of liver impairment associated with cimicifuga had also been reported in Australia.[4] Adverse liver reactions reported worldwide have included abnormal liver function tests, jaundice, hepatitis, and liver failure.[2] In general, patients showed signs of recovery on stopping ingestion.[2] Some regulatory authorities consider that the available evidence supports a rare association between cimicifuga and risk of liver toxicity, even though the level of risk is difficult to determine.[2,5,6] They have recommended that warnings regarding potential adverse liver reactions should be added to product information and consumers are advised to stop taking cimicifuga if they develop symptoms of liver damage;[2,5-7] also, patients who have previously had liver or other serious health problems should consult their doctor before starting to take cimicifuga.[2,6]

1. Huntley A, Ernst E. A systematic review of the safety of black cohosh. *Menopause* 2003; **10:** 58–64.
2. MHRA. UK Public Assessment Report. Black Cohosh (issued 31st July 2006). Available at: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalmedicines/CON2024279 (accessed 16/08/10)
3. Health Canada. Black cohosh: international reports of liver toxicity. *Can Adverse React News* 2005; **15** (3): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3_e.pdf (accessed 31/10/05)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Hepatotoxicity with black cohosh. *Aust Adverse Drug React Bull* 2006; **25:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0604.pdf (accessed 25/05/06)
5. EMEA. EMEA Public statement on herbal medicinal products containing cimicifuga racemosae rhizoma (black cohosh, root) — serious hepatic reactions (issued 18th July 2006). Available at: http://www.emea.europa.eu/pdfs/human/hmpc/26925906en.pdf (accessed 01/11/07)
6. Australian Government Department of Health and Ageing: Therapeutic Goods Administration. Black cohosh (*Cimicifuga racemosa*): new labelling requirements and consumer information for medicines containing black cohosh (issued 29th May 2007). Available at: http://www.tga.gov.au/cm/0705blkcohosh.htm (accessed 01/11/07)
7. Health Canada. Health Canada is advising consumers about a possible link between black cohosh and liver damage (issued 18th August 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html (accessed 05/11/07)

Interactions

For a suggestion of a potential interaction between cimicifuga and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Pharmacokinetics

In a study[1] to investigate the pharmacokinetics of 23-epi-26-deoxyactein, one of the most abundant triterpene glycosides of black cohosh, the maximum concentration and area under the curve increased proportionately with dosage, and the half-life was about 2 hours. Less than 0.01% of 23-epi-26-deoxyactein was recovered in the urine after 24 hours. No acute toxicity or oestrogenic hormone effects were seen after single oral doses of a 75% ethanol extract of black cohosh containing 1.4, 2.8, or 5.6 mg of 23-epi-26-deoxyactein given to 15 healthy, menopausal women.

1. van Breemen RB, *et al.* Pharmacokinetics of 23-epi-26-deoxyactein in women after oral administration of a standardized extract of black cohosh. *Clin Pharmacol Ther* 2010; **87:** 219–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Menofem; ***Austral.***: Femular; ***Austria***: Agnukliman; Jinda†; Klimadynon; Remifemin; Sanvita Meno; ***Braz.***: Amenopam†; Aplause; Clifemin; Mencirax; Menocalm; Menocimed†; Tensiane†; ***Canad.***: Women's Formula; ***Chile***: Ginemaxim; ***China***: Remifemin (莉芙敏); ***Cz.***: Cesracimi; Cimisan†; Menofem; ***Denm.***: Remifemin; ***Fr.***: Cimipax†; ***Ger.***: Cefakliman mono†; Cimisan†; Femi; Femikliman uno†; Femilla†; Feminon C; Galafem; Jinda; Klimadynon; Kofemin; Natu-fem; Remifemin; Sinei†; ***Hong Kong***: Klimadynon; ***Hung.***: Cefakliman mono; Cimicin; Femitan†; Klimapur†; Remifemin; ***Indon.***: Klimadynon†; Remifemin†; ***Malaysia***: Cefakliman; Remifemin; ***Mex.***: Avala; Clifenal†; Mensifem; ***Norw.***: Remifemin; ***Philipp.***: Remifemin; ***Pol.***: Klimasol†; Menofem; Remifemin; ***Rus.***: Klimadynon (Климадинон); ***Singapore***: Klimadynon; Nopause; Remifemin; ***Spain***: Aquimicix†; Avala†; Klimadynon; Remifemin; ***Swed.***: Remifemin; ***Switz.***: Cimifemine; Climavita; Femicine; Feminelle; Klimadynon; Maxifem†; Sanafem; ***Thai.***: Femosa; Remifemin; ***Turk.***: Klimadynon; ***UK***: DiaBlack; DiaCimi; Femiplant; MenoCool; Menoherb; Menopret; Rumatix; ***Ukr.***: Klimadynon (Климадинон).

Multi-ingredient Preparations. ***Austral.***: Bone Complex; Cimicifuga Compound; Dong Quai Complex†; Dyzco†; Extralife Meno-Care†; Extralife PMS-Care†; Femi-Nan; Meno Support Plus; PM Meno-Care; Wild Yam Complex; ***Austria***: Remifemin plus; ***Canad.***: Calm-Aid†; Natural HRT Nightime; Natural HRT; Phytoestrin; ***Cz.***: Dr Theiss Schwedenbitter†; ***Ger.***: Cimicifuga comp; Remifemin plus; ***Hong Kong***: Phytoestrin†; ***Hung.***: Remifemin Plus; ***India***: Evepearl-MP; ***Indon.***: Anstrep; Femosa; Menose; Menoxa†; Osteopor; Pectum; Voldilex; ***Ital.***: Biomineral Donna†; Hiperogyn; Pausanil; ***Jpn***: Otsujito; Rikkosan; Shin'iseihaito; ***Malaysia***: Gyno-Plus; ***Pol.***: Klimax; Naturapia Menopauza; ***Singapore***: Phytoestrin†; ***UK***: DiaMenoCalm; Flash Fighters; Gerard House Reumalex; Menomood; Modern Herbals Rheumatic Pain; St Johnswort Compound; Vegetable Cough Remover; Vegetex; ***Ukr.***: Lifemin (Лайфемин); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***USA***: Estrocare.

Homoeopathic Preparations. ***Austral.***: Pain & Fever Relief; ***Austria***: Klimaktoplant; Mefem; Orgafem; Pascofemin; Remens; ***Canad.***: Arthritis Pain Formula; Comp-Drops 9†; Headache & Migraine L77; Homeo-Form PMT†; Hylagesic APF; Hylands Formula MC; Hylands Menstrual Cramps†; Men Complex†; PMS; ***Cz.***: Gelsemium-Homaccord; ***Fr.***: Actheane; Cimicifuga Complexe No 21†; Helonias Compose; L 25; Phapax; ***Ger.***: Agnus castus comp†; Agnus femin; Bomaklim; Calmvalera; Cefakliman N†; Cefakliman S; Cefakliman†; Cimicifuga N Oligoplex; DolorA; Dysmenorrhoe-Gastreu S R75; Elana†; Feminon N; Gelenk Albin; HanoFemin; Infi-Symphytum; Klimaktoplant N; Klimax-Gastreu S R10; Migrane-Gastreu R16; Naranofem†; Nervoid N; Neuro-Ginsan N; Ovarell; Pascofemin; Pascolibrin; Rheuma-Pasc; Zincum Hevert N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Cimicifuga-Homaccord; Gelsemium-Homaccord; ***Neth.***: Homeocare Cyclo; Klimaktolan; Klimax-Gastreu R10; Kruidvat Homeopathie Meno†; Mulimen H; ***Rus.***: Climaxan (Климаксан); Diet-Comfort (Диет-Комфорт); Klimaktoplan (Климактоплан); Mirticam (Миртикам); Remens (Ремене); Uspokoi (Успокой); ***Switz.***: Menosan†; Menstruasan; Regenaplex Nr. 21c; ***Ukr.***: Capadol (Кападол); Homvio-Reuman (Хомвио-Ревман); Klimaktoplan N (Климактоплан Н); Remens (Ремене); ***USA***: Estrex.

Pharmacopoeial Preparations

USP 36: Black Cohosh Fluidextract; Black Cohosh Tablets; Powdered Black Cohosh Extract.

Cinametic Acid *(rINN)*

Acide Cinamétique; Ácido cinamético; Acidum Cinameticum; Cinamético, ácido; Цинаметовая Кислота.

4-(2-Hydroxyethoxy)-3-methoxycinnamic acid.

$C_{12}H_{14}O_5$=238.2

CAS — 35703-32-3.

UNII — 3E3106052Y.

Profile

Cinametic acid has been used as a choleretic.

Cinchona Bark

Chinae Cortex; Chinarinde; Chininmedžių žievė; Chinovníková kůra; Cinchona; Cinchonae Cortex; Cinchonae Succirubrae Cortex; Jesuit's Bark; Kiinankuori; Kinabark; Peruvian Bark; Quina; Quina Vermelha; Quino, corteza del; Quinquina; Quinquina Rouge; Red Cinchona Bark; Vöröskinafa-kéreg; Хинная Кора.

ATC Herb — HA09WA5007 (Cinchona pubescens: bark); HN02BW5003 (Cinchona pubescens: bark); HP01BC5001 (Cinchona pubescens: bark).

UNII — 292E43P4I9 (cinchona bark); 03DF2I0XP1 (Cinchona pubescens); S96N10R972 (Cinchona pubescens bark); 056KT7S4VM (Cinchona calisaya); 77H72B7O3D (Cinchona calisaya bark).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Cinchona Bark). The whole or cut, dried bark of *Cinchona pubescens* (*Cinchona succirubra*), of *C. calisaya,* of *C. ledgeriana,* or of its varieties or hybrids. It contains a minimum of 6.5% of total alkaloids, of which 30 to 60% are quinine-type alkaloids. It has an intensely bitter, somewhat astringent taste. Protect from light.

Profile

Cinchona contains several alkaloids, including two pairs of optical isomers: quinine (p. 665.1) and quinidine, (p. 1481.1) and cinchonine and cinchonidine. Cinchona alkaloids have long been used for their antimalarial activity either singly, as quinine or quinidine, or in mixtures, such as totaquine. Quinidine is also used for its antiarrhythmic properties.

Cinchona bark is used as a bitter and is also employed in herbal remedies.

Homoeopathy

Cinchona bark has been used in homoeopathic medicines under the following names: Cinchonae cortex; China; China pubescens; China rubra; Cinchona succirubra; China officinalis; Cinchona; Cinchona officinalis; Cinc. of.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Albion; Bifena; ***Austria***: Brady's-Magentropfen; China-Eisenwein†; Mariazeller; ***Braz.***: Agua Inglesa†; ***Fr.***: Quinimax; Quintonine†; ***Ger.***: Amara-Pascoe; ***Ital.***: Bulboshap†; Lozione Same Urto; ***Pol.***: Melisana Klosterfrau; ***S.Afr.***: Borstol Cough Remedy†; Versterkdruppels; ***Switz.***: Enuton†.

Homoeopathic Preparations. ***Austral.***: Vitatona Energy†; ***Austria***: Acidum phosphoricum Med Complex; China Med Complex; Colchicum Med Complex; Gripagil-Grippetropfen mit Echinacea; Pertudoron†; Schnarchex; toxi-loges; ***Canad.***: Aches & Pains; Bioactiv E†; Calms Forte 4 Kids; Carduus Plex†; Diarrhea; Formula ES 211; Formula FV 213; Formula Homeo QR 209†; Hepar Compositum; Hylagene; Hylands LCQ; Indigestion; Infilex†; L52 Cough & Cold; Leg Cramps with Quinine; Ton 2 Complex†; Vegetal Tonic; ***Chile***: Bioactiv A; Bioactiv E; Bioactiv L; ***Cz.***: Hepeel; Lehnigrip†; ***Fr.***: Abbe Chaupitre no 18†; Abbe Chaupitre no 82†; Abbe Chaupitre no 88†; Adenocynesine†; Amanita Complexe No 75; Arnica Complexe no 1; Basilicum Complexe No 96; Boripharm No 15†; Boripharm No 1†; Chelidonium Compose; Cina Compose; Diaralia; Gastro-Drainol†; Grindelia Complexe No 58; Hepatocynesine†; Homeogene 22†; Hydrastis Compose; Hypophysis Complexe No 31†; L 107; L 25; L 28; L 52; Ledum Complexe No 81; Millefolium Complexe No 7†; Momordica Complexe No 109†; Nux Vomica Complexe No 49; Pertudoron; Tonique Vegetal; ***Ger.***: Aletris Oligoplex†; Arnica Oligoplex; Capillaron Vertigo; Conva-cyl Ho-Len-Complex; Febro-cyl L Ho-Len-Complex; HanoToxin M; Hanotoxin M; Hepa-Gastreu N R7; Hepar comp; Infi-China; Infi-Symphytum; Infigripp; Infihepan; Jowidarmin; Mato; Milzimmunosyx; Monapax; Nux Vomica N Oligoplex; Pertudoron 1; Rheuma-Pasc; Spasmo-Entoxin; toxi-loges; Ventrigutt M; ***Hung.***: Hepeel; PSY-Stabil; ***Neth.***: Ailgeno spag; Febrilite; Hepa-Gastreu R7; Infragil; Lymphomyosot; Neurovita; PSY-stabil; Restructa H; ***Rus.***: Nux Vom-Plus (Нукс Вом-Плюс); Ruta-Plus (Рута-Плюс); ***S.Afr.***: Pertudoron Drops†; ***Switz.***: Hepeel; Regenaplex Nr. 35b; Regenaplex Nr. 59b; Silacten; ***Ukr.***: Enterocind (Энтерокинд).

Cineole

Cajuputol; Cayeputol; Cineol; Cineolas; Cinéole; Cineolum; Cyneol; Eucaliptol; Eucalyptol (USAN); Eucalyptol; Eucalyptolum; Sineoli; Цинеол.

1,8-Epoxy-*p*-menthane; 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane.

$C_{10}H_{18}O$=154.3

CAS — 470-82-6.

UNII — RV6J6604TK.

NOTE. Do not confuse with Cajuput Oil (p. 2464.1), which has synonyms similar to cajupetol and cayeputol that are used for Cineole.

Description. Cineole is a colourless liquid, with an aromatic camphoraceous odour, obtained from eucalyptus oil, cajuput oil, and other oils.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Cineole). A clear colourless liquid. It solidifies at about 0.5 degrees. Practically insoluble in water; miscible with alcohol and with dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Eucalyptol). It is obtained from eucalyptus oil and from other sources. Store in airtight containers.

Profile

Cineole has the actions and uses of eucalyptus oil (p. 2501.2). It has been used in counter-irritant ointments and in dental products. It has also been used in nasal preparations, but oily solutions inhibit ciliary movement and may cause lipoid pneumonia. Preparations containing cineole with other volatile substances have been used in the treatment of renal and biliary calculi.

References.

1. Kehrl W, *et al.* Therapy for acute nonpurulent rhinosinusitis with cineole: results of a double-blind, randomized, placebo-controlled trial. *Laryngoscope* 2004; **114:** 738–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Soledum Balsam; Soledum; ***Switz.***: Bronchomed.

Multi-ingredient Preparations. ***Arg.***: Aseptobron N; Aseptobron; Aseptobron; Atomo Desinflamante Familiar; Atomo Desinflamante G; Atomo Desinflamante; Bronco Etersan; Di-Neumobron; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; No-Tos Adultos; Pervinox Extra Mint; Pervinox Fresh Mint; Pervinox Fruit; Refenax Caramelos Expectorantes; Rowatinex; ***Austral.***: Bosisto's Vaporising Ointment†; Euky Bearub; Nasex†; Spray-Tish Menthol; ***Austria***: Rhinospray Plus; Rowachol; Rowatinex; Wick SinexAloe; ***Belg.***: Eucalyptine Pholcodine; Eucalyptine†; Eucalyptine; Eucalyptine; Eucalyptine; Inhalo Rhinathiol; Inopectol†; Olbas; Pulmex Baby; Pulmex†; ***Braz.***: Algice; Angino-Rub; Bromil Grip†; Bromil; Bromil; Fluomint†; Gripsay; Inhalante Yatropan; Ozonyl Aquoso; Ozonyl Expectorante; Ozonyl; Pastilhas Valda†; Penetro; Tetrapulmo†; Transpulmin Balsamo; Transpulmin; Vick Pastilhas†; ***Canad.***: Antiseptic Mouthwash; Cal Mo Dol†; Carboseptol†; Demo-Cineol†; Glenalgesic Forte†; Larynsol†; Listerine Antiseptic Tartar Control; Listerine Antiseptic with Fluoride; Listerine; Mielocol†; Naturub; Original Antiseptic Mouthwash†; Orthorub†; Rhino-Vaccin†; ***Chile***: Listerine; Oralfresh Citrus†; Oralfresh Clasico†; Rowatinex; ***China***: Qie Nuo (切诺); ***Cz.***: Rowachol; Rowatinex; ***Denm.***: Otrivin Menthol; ***Fin.***: Otrivin Menthol; ***Fr.***: Bi-Qui-Nol; Dinacode avec codeine†; Essence Algerienne; Eucalyptine Le Brun; Eucalyptine; Eucalyptine; Hexapneumine†; Listerine protection dents et gencives; Listerine Stay White; Neuriplege Sport; Pectoderme†; Pholcones Bismuth; Pulmofluide Simple; Valda†; ***Ger.***: Rhinospray Plus; Rowachol; Rowatinex; Transpulmin Balsam†; ***Hong Kong***: BF-Analgesic Balm†; Listerine Cool Mint; Listerine Tartar Control; Listerine Teeth and Gum Defence; Listerine; Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.***: Rhinospray Plus; Rowachol; Rowatinex; ***India***: Aerway; Cool Mint Listerine; Coriminic-Vaporise; Dristan Nasal Drops†; Endrine Mild; Endrine; Genvol Plus; Karvol Plus; Kolq Inhalant; Listerine; Sinarest Vapocaps; ***Indon.***: Dactylen; Listerine Coolmint†; Listerine†; Transpulmin BB Balsam; ***Irl.***: Rowachol; Rowatinex; ***Israel***: Gargol; Rowachol; Rowatinex; ***Ital.***: Abiostil; Balsamico; Calyptol; Lipobalsamo; Listerine Fresh Citrus; Listerine Tartar Control; Neo Borocillina Decong; Pumilene Vapo; Rinogutt; Rinovit; Transpulmina Gola; Transpulmina Tosse†; Vicks Sinex; ***Malaysia***: Rowachol; Rowatinex; ***Mex.***: Bronkitose Mielimon; Cholex; Duals Nordin; Guayalin; Iodex Cristal; Listerine; ***Mon.***: Bronchodermine; Bronchodermine; Calyptol; Glyco-Thymoline; ***Neth.***: Balsoclase Compositum†; Balsoclase-E†; Otrivin Menthol; Rhinospray met eucalyptus; ***Norw.***: Otrivin med mentol; ***NZ***: Listerine Citrus Fresh; Listerine Tartar Control†; Listerine Teeth Defence; Listerine; Tixylix Chest Rub; Vicks Sinex†; ***Philipp.***: Kamillosan M; Listerine Coolmint; Listerine Fresh Citrus; Listerine Freshburst; Listerine Original; Listerine Tartar Control; Listerine Teeth & Gum Defense; Rhea Superscent Oil†; Rowachol; Rowatinex; Supercent; Transpulmin Balsam†; ***Pol.***: Rowachol; Rowatinex; Salviasept; Terpichol; ***Port.***: Transpulmina; Transpulmina; ***Rus.***: Nazol Advance (Назол Адванс); Rowatinex (Роватинекс); Sleepex (Слипекс); ***S.Afr.***: Respisniffers†; Woodwards Inhalant; ***Singapore***: Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; ***Spain***: Brota Rectal Balsamico†; Caltoson Balsamico†; Diminex Antitusigeno; Dolmitin†; Eupnol; Mentobox; Pastillas Pectorales Kely†; Pulmofasa; Rinobanedif; Rowachol; Rowanefrin; Sinus Inhalaciones; Vitavox†; ***Swed.***: Otrivin Menthol; ***Switz.***: Denosol; Mucosan†; Nasobol Inhalo; Onguent aux herbes Keller; Parapic; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; Resorbane; Transpulmin N; Vicks Sinex; ***Thai.***: Dexalin Balm; Hot Ize; Rowachol; Rowatinex; Sore Mouth Gel†; ***Turk.***: Bugumentol; Bugusan; Buguseptil; Gelocaps; Mentimol†; Mentimol; Mentolin; Mentoseptol; Oka Mentol; Otaci Oka Mentol; Otaci Salvia; Otrivine Mentol; Rinolar; Sulfarhin; ***UK***: Dubam; Listerine Antiseptic Mouthwash; Lockets; Nostroline; Nowax; Rowachol; ***Ukr.***: Nasol Kids (Назол Кидс); Nazol Advans (Назол Адванс); ***USA***: Babee; BFI; Listerine; Nostrilla Conditioning Double Moisture; Pfeiffer's Cold Sore; Rid-a-Pain; Saratoga; Sting-Eze; Toetal Fresh; ***Venez.***: Rowachol; Rowatinex; Transmin.

Cinnamedrine *(USAN, rINN)* ⊗

Cinamedrina; Cinnamédrine; Cinnamedrinum; *N*-Cinnamylephedrine; Циннамедрин.

α-{1-[Methyl(3-phenyl-2-propenyl)amino]ethyl}benzenemethanol.

$C_{19}H_{23}NO$=281.4

CAS — 90-86-8.

UNII — Y1245J8012.

Cinnamedrine Hydrochloride *(rINNM)* ⊗

Cinamedrina, hidrocloruro de; Cinnamédrine, Chlorhydrate de; Cinnamedrini Hydrochloridum; *N*-Cinnamylephedrine Hydrochloride; Hidrocloruro de cinamedrina; Циннамедрина Гидрохлорид.

$C_{19}H_{23}NO,HCl$=317.9

UNII — T4B6SPQ0UF.

Profile

Cinnamedrine hydrochloride is reported to have sympathomimetic actions resembling those of ephedrine. It was formerly used with analgesics in the symptomatic relief of dysmenorrhoea.

Cinnamon

Canela; Canela do Ceilão; Cannelle dite de Ceylan; Ceylon Cinnamon; Ceylonzimt; Cinamonų žievė; Cinnam.; Cinnamomi cortex; Cinnamon Bark; Fahéj; Kanel; Kaneli; Skořicovníková kůra; Zimt; Zimtrinde; Корица.

UNII — 5S29HWU6QB.

NOTE. In *Martindale*, 'Cinnamon' is used for material obtained from *Cinnamomum verum* and 'Cassia' for material from *Cinnamomum cassia.* However, some of the literature and some pharmacopoeias use the term 'Cinnamon' to describe products from *C. cassia.* Care should be taken to differentiate between the botanical sources.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Cinnamon). The dried bark, freed from the outer cork and the underlying parenchyma, of the shoots grown on cut stock of *Cinnamomum verum* containing not less than 1.2% v/w of essential oil. It has a characteristic, aromatic odour.

The BP 2014 directs that when Powdered Cinnamon is prescribed or demanded, material containing not less than 1.0% v/w of essential oil shall be dispensed or supplied.

Profile

Cinnamon, the bark of *Cinnamomum verum* (*C. zeylanicum*), is carminative and slightly astringent. It is included in some preparations for gastrointestinal disorders and is being studied for its potential as an adjunct in the management of type 2 diabetes mellitus. It is also used as a flavour. It is a source of cinnamon oil (below).

References.

1. WHO. Cortex Cinnamomi. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/12.html (accessed 04/02/10)
2. Dugoua JJ, *et al.* From type 2 diabetes to antioxidant activity: a systematic review of the safety and efficacy of common and cassia cinnamon bark. *Can J Physiol Pharmacol* 2007; **85:** 837–47.
3. Chase CK, McQueen CE. Cinnamon in diabetes mellitus. *Am J Health-Syst Pharm* 2007; **64:** 1033–5.
4. Pham AQ, *et al.* Cinnamon supplementation in patients with type 2 diabetes mellitus. *Pharmacotherapy* 2007; **27:** 595–9.
5. Barceloux DG. Cinnamon (*Cinnamomum* species). *Dis Mon* 2009; **55:** 327–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Detox Program; Digestive Bitters; Gluco Support; Olf†; ***Austria***: Brady's-Magentropfen; China-Eisenwein†; Klosterfrau Melissengeist; Mariazeller; Montana; ***Belg.***: Eau Des Carmes; ***Braz.***: Balsamo Branco; Paratonico†; ***Canad.***: Magen- und Darmtee N†; ***Cz.***: Dr Theiss Schwedenbitter†; Klosterfrau Melisana; Passedan†; ***Fr.***: Afra†; Feminabiane Confort Urinaire; Glycepure; Quintonine†; Santane D_5†; Santane F_{10}†; Santane R_8†; Tavmet; ***Ger.***: Amara-Pascoe; Klosterfrau Melissengeist; Melissengeist; Montana N; Schwedentrunk Elixier; Sedovent†; ***Hung.***: Klosterfrau Melisana; Montana; ***India***: Aptizooom; Eugynin; Koflet; Manix; ***Indon.***: Astadiab; Cinula; Oncoxin; ***Ital.***: Biophase Shampoo; Dam; ***Jpn***: Anchusan; Colgen Maoto; Goreisan; Goshajinkigan; Goshakusan; Hachimijiogan; Inchingoreisan; Ireito; Jidabokuippo; Juzentaihoto; Kakkonto; Kakkontokasenkyushin'i; Keishibukuryogan; Keishibukuryogankayokuinin; Keishikajutsubuto; Keishikaryukotsuboreito; Keishikashakuyakudaioto; Keishikashakuyakuto; Keishininjinto; Keishito; Maoto; Mokuboito; Ninjin'yoeito; Nyoshinsan; Ogikenchuto; Orento; Ryokeijutsukanto; Saikokaryukotsuboreito; Saikokeishikankyoto; Saikokeishito; Saireito; Shakanzoto; Shokenchuto; Shoseiryuto; The Guard Seichojo; Tokakujokito; Tokikenchuto; Tokishigyakukagoshuyushokyoto; Tokito; Unkeito; Yokuininto; ***Malaysia***: Taisho Kampo; ***Mex.***: Varicyl; ***Pol.***: Reumpapai; ***Rus.***: Doppelherz Melissa (Доппельгерц Мелисса); Himcolin (Химколин); Wantong Artiplas (Ваньтун Артиплас); ***S.Afr.***: Melissengeist†; Rooilavental; Spiritus Contra Tussim Drops†; ***Spain***: Agua del Carmen; ***Switz.***: Baume Zeller; Odontal; Padma Digestin; Tisane pour les problemes de prostate; ***Thai.***: Meloids; ***Turk.***: Keten; ***UK***: Digestion Calming Drops; Melissa Comp.; ***Ukr.***: Imunin (Иммунин)†; Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Clinical Nutrients 50-Plus Men; ***Venez.***: Aftil; Ocoxin.

Homoeopathic Preparations. ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Vegetal Tonic; ***Fr.***: Tonique Vegetal; ***Ger.***: Rytesthin; ***UK***: Cough Drops.

Pharmacopoeial Preparations

Ph. Eur.: Cinnamon Tincture;
USNF 31: Compound Cardamom Tincture.

Cinnamon Oil

Aetheroleum Cinnamomi Zeylanici; Canela, aceite esencial de; Cinnam. Oil; Esencia de Canela; Essence de Cannelle de Ceylan; Oleum Cinnamomi; Zimtöl; Коричное Масло.

CAS — 8015-91-6.

UNII — E5GY4I6YCZ.

NOTE. In *Martindale*, 'Cinnamon' is used for material obtained from *Cinnamomum verum* and 'Cassia' for material from *Cinnamomum cassia.* However, some of the literature and some pharmacopoeias use the term 'Cinnamon' to describe products from *C. cassia.* Care should be taken to differentiate between the botanical sources.

Pharmacopoeias. *Eur.* (see p. vii) includes oil from both the bark and the leaf of *Cinnamomum verum.*

Jpn under the title Cinnamon Oil specifies oil from either *Cinnamomum cassia* or *Cinnamomum zeylanicum*[*C. verum*].

Cinnamon Bark Oil

Cannelle dite de Ceylan, huile essentielle de; Ceilonինių cinamonų žievės eterinis aliejus; Ceylon Cinnamon Bark Oil; Ceyloni fahéjfakéreg-olaj; Cinnamomi zeylanicii corticis aetheroleum; Cinnamoni Zeylanicii Corticus Aetheroleum; Kaneliöljy, Ceylonin; Kanelolja, ceylonesisk; Silice kůry skořicovníku cejlonského; Коричное Масло Из Коры.
ATC Herb — HA03AW5011 (Cinnamomum verum: essential oil); HA03AW5012 (Cinnamomum verum: bark).
UNII — XE54U569EC.

Pharmacopoeias. In *Eur.* (see p. vii) and Jpn.

Ph. Eur. 8: (Cinnamon Bark Oil, Ceylon). The oil obtained by steam distillation of the bark of the shoots of *Cinnamomum verum*. It contains 55 to 75% of cinnamaldehyde and less than 7.5% of eugenol. A clear, mobile, light yellow liquid becoming reddish over time, with a characteristic odour of cinnamaldehyde. Store in well-filled airtight containers. Protect from heat.

Cinnamon Leaf Oil

Cannelier dit de Ceylan (feuille de), huile essentielle de; Ceiloninių cinamonų lapų eterinis aliejus; Ceyloni fahéjfalevél-olaj; Cinnamomi Zeylanici Folii Aetheroleum; Cinnamomi Zeylanici Folii Etheroleum; Kanelbladolja, ceylonesisk; Kanelinlehtiöljy, Ceylonin; Ol. Cinnam. Fol; Silice listu skořicovníku cejlonského; Коричное Масло Из Листьев.
UNII — S92U8SQ71V.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Cinnamon Leaf Oil, Ceylon). The oil obtained by steam distillation of the leaves of *Cinnamomum verum*. It contains less than 3% of cinnamaldehyde, and 70 to 85% of eugenol. A clear, mobile, reddish brown to dark brown liquid, with a characteristic odour of eugenol. Store in well-filled airtight containers. Protect from heat.

Profile

Cinnamon bark oil has properties and uses similar to those of cinnamon (p. 2479.3). It is also included in preparations for musculoskeletal and joint disorders and for respiratory-tract disorders. There have been reports of hypersensitivity to cinnamaldehyde and other constituents of cinnamon oil. Cinnamon leaf oil has also been used, although the amounts of eugenol and cinnamaldehyde are different from the bark oil. Cinnamon bark or leaf oil is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Austria***: Tiger Balsam Rot; ***Canad.***: Amol†; DSO Dressing; Melisana†; Tiger Balm Red; Tiger Balm Ultra; ***Chile***: Agua del Carmen; Agua Melisa Carminativa; ***Cz.***: Amol; ***Fr.***: Aromasol; Aromavital†; Dida; Esculape†; Gouttes aux Essences; Olioseptil Nez-Gorge; Resistim; Stomargil; Tigre de Chine; Tigridol; ***Ger.***: Amol Heilkrautergeist N; esto-gast; Melissengeist; Salviathymol N; Verdauungstropfen Gastrofunkten†; ***Hong Kong***: Magesto; ***Hung.***: Amol; Carmol; Cholasyl; Tiger Balm Red; ***India***: Aniwel DPS; Aquadil-P; Artrex; Bestozyme P; Carmicide; Cartigen; Catalyd; Catazyme; Coliwell; Digeplex; Dorzy DPS; Everzyme; Gastrozyme; Gastrozyme; Hanzyme; Lavazyme; Litzyme; Merispas; Sensur; Sensur; Vitazyme; ***Indon.***: Corsabalm; ***Irl.***: Tiger Balm Red; ***Israel***: Karvol; ***Ital.***: Relaxcol; Valda Propoli†; ***NZ***: Karvol; ***Pol.***: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; ***Rus.***: Efcamon (Эфкамон); ***S.Afr.***: Enterodyne†; Karvol†; ***Singapore***: Karvol; ***Spain***: Depurativo Richelet†; ***Switz.***: Baume du Tigre rouge; Echinarom; Pirom; Spagyrom; ***Thai.***: Caryopin; Magesto; Mesto-Of; ***UK***: Slippery Elm Stomach Tablets.

Pharmacopoeial Preparations
BP 2014: Aromatic Cardamom Tincture; Compound Cardamom Tincture; Concentrated Cinnamon Water; Tolu-flavour Solution.

Citicoline *(pINN)*

CDP-Choline; Citicolina; Citicolinum; Citidoline; Cytidine Diphosphate Choline; Cytidine diphosphocholine; Cytidyl Diphosphocholine; IP-302; Цитиколин.
Choline cytidine-5′-pyrophosphate.
$C_{14}H_{26}N_4O_{11}P_2$=488.3
CAS — 987-78-0.
ATC — N06BX06.
ATC Vet — QN06BX06.
UNII — 536BQ2JVC7.

Citicoline Sodium *(USAN, pINNM)*

Citicolina sódica; Citicoline Sodique; Natrii Citicolinum; Sodium Citicoline; Sodium Cytidine Diphosphate Choline; Натрий Цитиколин.
Cytidine 5′-(sodium *P*′-[2-(trimethylammonio)-ethyl] hydrogen diphosphate), inner salt.
$C_{14}H_{25}N_4NaO_{11}P_2$=510.3
CAS — 33818-15-4.
UNII — 7XQ5AKD9YD.

Pharmacopoeias. In *Chin.*

Profile

Citicoline is a derivative of choline and cytidine that is involved in the biosynthesis of lecithin. It is claimed to increase blood flow and oxygen consumption in the brain and has been given in the treatment of cerebrovascular disorders (including ischaemic stroke, p. 1269.2), parkinsonism, and head injury. It is given by intravenous or intramuscular injection in doses of up to 1 g daily or orally in divided doses of 200 to 600 mg daily.

Citicoline sodium has also been used.

References.

1. Secades JJ, Lorenzo JL. Citicoline: pharmacological and clinical review, 2006 update. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl B): 1–56.
2. Anonymous. Citicoline. *Altern Med Rev* 2008; **13**: 50–7.

Cerebrovascular disorders. Citicoline has shown some short- to medium-term benefit for disturbances of memory and behaviour associated with cerebrovascular disorders.[1]

1. Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/05/06).

Strabismus. Experimental studies have shown that centrally-acting drugs such as citicoline may improve vision in patients with amblyopia (see Strabismus, p. 2000.3). However, their role in clinical practice is unknown.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2**: 91–100.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Complegel Novo; Nimo-Somazina; Reagin; Somazina; ***Austria***: Startonyl; ***Braz.***: Somazina; ***Chile***: Somazina; ***China***: Ai Xing Dan (爱星丹); Ao Ge Er (奥格尔); Bin Shu (滨舒); Bo Lang Rui Ning (博朗瑞宁); Chen Wang (辰旺); De Yi Rong (德益荣); Feng Hai Qing (丰海清); Jia Jian (加简); Jie Wei Su (洁维苏); Jiu An Suxin (久安苏欣); Lan Gui (兰桂); Li Shu (理枢); Li Tuo Gan (立拓感); Nicholin (尼可林); Ou Mai (欧迈); PiDi Ming (彼迪明); Pu Mei La Tai (普美拉泰); Sai Li Ao (赛立奥); Shu Mo Ta (舒莫它); Si Kao Lin (思考林); Si Ke Lin (思可林); Su Bu Lin (苏布林); Xian Li Ke (先立科); Xin Ke Lai (欣可来); Xin Tong (鑫通); Yi Dan (亿丹); Yi Luo Qing (益落清); You Xin (友欣); ***India***: Ceham; Citilin; Citinova; Clinaxon; Col; Costrok; Inticol; Mycostar; Neocit; Neurospark; Onlyciti; ***Indon.***: Beclov; Brainact; Brainolin; Bralin; Cercul; Cholimed; Cholinaar; Cibren; Citicholine; Crolin; Incelin; Lancolin; Neuciti; Neulin; Neurolin; Nicholin; Recolin; Serfac; Simciti; Soholin; Strolin; Takelin; Zeufor; ***Ital.***: Brassel; Cebroton†; Cidilin; Difosfocin; Gerolin; Logan; Neurex; Neuroton; Nicholin†; Nicolsint; Sintoclar; ***Jpn***: Nicholin; ***Mex.***: Onquevit; Somazina; Zunun; ***Philipp.***: Cholinerv; Citilin; Nicholin; Somazine; Zynapse; ***Port.***: Hipercol; Somazina; Startonyl; Trausan; ***Rus.***: Ceraxon (Цераксон); ***Spain***: Numatol; Somazina; ***Thai.***: Somazina; ***Ukr.***: Ceraxon (Цераксон); Neuroxon (Нейроксон); Somazina (Сомазина); ***Venez.***: Somazina.

Multi-ingredient Preparations. ***Arg.***: Nimodilat Plus; Nimoreagin; Nivas Plus; Reagin Vascular; ***China***: Ying Di Te (英迪特); ***Fr.***: Cebrolux; ***India***: Nervijen-CT; Nutam Plus; ***Ital.***: Cebrolux.

Citral

Cytral; Цитраль.
3,7-Dimethyl-2,6-octadienal.
$C_{10}H_{16}O$=152.2
CAS — 5392-40-5 (citral); 141-27-5 (geranial); 106-26-3 (neral).
UNII — T7EU0O9VPP.

Profile

Citral is a terpenoid constituent of lemon oil (p. 2543.1), lemon grass oil (p. 2543.2), melissa oil (p. 2553.2), and many other essential oils; it exists as 2 isomers, *trans*-citral (geranial) and *cis*-citral (neral). It has been used in preparations for respiratory-tract, musculoskeletal, and other disorders. It is also used as a flavour and perfume.

Hypersensitivity. References.

1. Heydorn S, *et al.* Citral a fragrance allergen and irritant. *Contact Dermatitis* 2003; **49**: 32–6.
2. Lalko J, Api AM. Citral: identifying a threshold for induction of dermal sensitization. *Regul Toxicol Pharmacol* 2008; **52**: 62–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Bronchorectine a u Citral.

Anhydrous Citric Acid

Acidum Citricum; Acidum Citricum Anhydricum; Cítrico anhidro, ácido; Citrinų rūgštis, bevandenė; Citrique (acide) anhydre; Citronensäure; Citronsyra, vattenfri; E330; Kyselina citronová; Sitruunahappo, vedetön; Vízmentes citromsav; Лимонная Кислота Безводная.
2-Hydroxypropane-1,2,3-tricarboxylic acid.
$C_6H_8O_7$=192.1
CAS — 77-92-9.
ATC — A09AB04.
ATC Vet — QA09AB04.
UNII — XF417D3PSL.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Citric Acid, Anhydrous). Colourless crystals or granules or a white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol.

USP 36: (Anhydrous Citric Acid). Colourless, translucent crystals, or a white, granular to fine, crystalline powder. Soluble 1 in 0.5 of water, 1 in 2 of alcohol, and 1 in 30 of ether. Store in airtight containers.

Citric Acid Monohydrate

Ácido del Limón; Acidum Citricum Monohydricum; Cítrico monohidrato, ácido; Citrinų rūgštis monohidratas; Citrique (acide) monohydraté; Citromsav-monohidrát; Citronensäure-Monohydrat; Citronsyramonohydrat; Hydrous Citric Acid; Kwas cytrynowy jednowodny; Kyselina citronová monohydrát; Sitruunahappomonohydraatti; Лимонная Кислота Моногидрат.
$C_6H_8O_7.H_2O$=210.1
CAS — 5949-29-1.
ATC — A09AB04.
ATC Vet — QA09AB04.
UNII — 2968PHW8QP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Citric Acid Monohydrate). Efflorescent, colourless crystals or granules, or a white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 36: (Citric Acid Monohydrate). Colourless, translucent crystals, or a white, granular to fine, crystalline powder. It is efflorescent in dry air. Soluble 1 in 0.5 of water, 1 in 2 of alcohol, and 1 in 30 of ether. Store in airtight containers.

Uses and Administration

Citric acid is used in effervescing mixtures; the monohydrate is used in the preparation of effervescent granules.

Citric acid monohydrate is used as a synergist to enhance the efficacy of antoxidants.

Preparations containing citric acid are used in the management of dry mouth (p. 2175.3) and to dissolve renal calculi, alkalinise the urine, and prevent encrustation of urinary catheters. Citric acid is an ingredient of citrated anticoagulant solutions. Citric acid has also been used in preparations for the treatment of coughs, gastrointestinal disturbances, and metabolic acidosis.

Adverse Effects and Precautions

Citric acid ingested frequently or in large quantities may cause erosion of the teeth and have a local irritant action.

Interactions

Aluminium hydroxide. Intestinal absorption of aluminium ions may be enhanced by oral doses of citrates. Caution is needed in patients with chronic renal disease receiving aluminium hydroxide as a phosphate binder who are given a calcium supplement in the form of effervescent tablets that contain citric acid.[1]

1. Mees EJD, Basçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; **59**: 322.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Urologic G; ***Gr.***: Citrolithin; ***India***: Revici; ***Mex.***: Lipocinetic†; ***Pol.***: Citrolyt; ***S.Afr.***: Crystacit; ***Venez.***: Policitra.

Multi-ingredient Preparations. ***Arg.***: Alikal; Alka-Seltzer Doble Accion; Azodac; Fegalgina; Sal de Fruta Eno; Uvasal; ***Austral.***: Alka-Seltzer; Citralite†; Citravescent; Eno; Gastrolyte; PicoPrep;

Ural; ***Austria***: Alka-Seltzer; Blanel; Helo-acid; Kalioral; ***Braz.***: Alka-Seltzer; Control†; Digestbem; Emidrat; Estomazil; Sadol†; Sal de Andrews; Sal de Fruta Eno; Sonrisal; ***Canad.***: Alka-Seltzer; Bromo Madelon†; Enfalyte; Pico-Salax; Picodan; Purg-Odan; ***Chile***: Disfruta; Fenokomp 39; Kanacitrin; Sal de Fruta Eno; Uroalquine; Yasta; ***Cz.***: Alka-Seltzer; Blemaren N; Carbocit; Herbadent; Picoprep; ***Denm.***: CitraFleet; Picoprep; Samarin; ***Fin.***: Alka-Seltzer†; CitraFleet; Picoprep; ***Fr.***: Actigess†; Alhydrate†; Alka-Seltzer; Bactigyn; CitraFleet; Citrocholine†; Fanolyte; Hepargitol; Hydrigoz†; Novalac Hydranova; Picolite; Picoprep; ***Ger.***: Alka-Seltzer; Blemaren N; CitraFleet; Pepzitrat†; Picoprep; Retterspitz Ausserlich; Retterspitz Innerlich; Weleda Heuschnupfenspray; ***Gr.***: E-Z-Gas; Gastrovison; ***Hong Kong***: Alka-Seltzer†; Eno†; Picolax; ***Hung.***: Alka-Seltzer; Blemaren N; E-Z-Gas; Egaver Plusz; Egaver; Picoprep; ***India***: Ableed; Alkacos; Alkamax; Alkasym; Carmicide; Citro-Soda; Distone; Dristan Expectorant; Icey; K-Cit; Kezar; Kufma; Manzer; Maxoza; Merispas; Oralka-K; Orfix; Urisoda; ***Indon.***: Koffex for Children; Promethazine Ikapharmindo; ***Irl.***: Alka-Seltzer; Andrews; CitraFleet; Cymalon; Lemsip Dry Cough; Picolax; Rehidrat†; Resolve†; ***Israel***: E-Z-Gas II; Minerali; Pico-Salax; Urikal; ***Ital.***: Alka-Seltzer; Citroepatina†; Citromagnesiaca; Duogas; Geffer; Lavanda Sofar; ***Malaysia***: Alka-Seltzer; Ezee; pH Care; Picoprep†; Potcit; U-Lite; Ural; Urisoda; ***Mex.***: Kaposalt; Uroclasio NF; ***Mon.***: Foncitril; ***Neth.***: Alka-Seltzer; Gastrogas†; Picoprep; ***Norw.***: CitraFleet; Picoprep; ***NZ***: Alka-Seltzer; Picoprep; Ural; ***Philipp.***: Alka-Seltzer†; Ural; ***Pol.***: Citropepsin; ***Port.***: CitraFleet; Creme Laser Hidrante†; Detoxergon; Eno†; ***Rus.***: Alka-Seltzer (Алка-Зельтцер); Blemaren (Блемарен); Limontar (ЛИМОНТАР); ***S.Afr.***: Adco-Sodasol; Alkafizz; Citro-Soda; Effersol; Picoprep†; Pneucid†; Quatro-Soda; Uri-Alk; Vicks Cough Syrup†; ***Singapore***: Alka-Seltzer; Bio-Taches†; Citravescent; Dicitrate; K-Mix; Potcit; Uricalm; ***Spain***: Cardi-Braun; Citorsal; CitraFleet; Justegas; Sal de Fruta Eno; Uralyt Urato; ***Swed.***: Alka-Seltzer†; CitraFleet; Picoprep; Renapur; Samarin; Samarin; ***Switz.***: Alka-Seltzer; E-Z-Gas II; Picoprep; Siesta-1; ***Thai.***: Alka-Seltzer; Polyvit; ***Turk.***: Alka-Seltzer; Historan; ***UK***: Alka-Seltzer XS; Alka-Seltzer; Allens Junior Cough; Andrews; Carbex; Cymalon; Effercitrate; Eno; Entrocalm Replace; Hill's Balsam Chesty Cough for Children; Lemsip Cough & Cold Dry Cough; O.R.S.; Oralyte; Potters Children's Cough Pastilles; Resolve; Uriflex G; Uriflex R; Uro-Tainer Solution R; Uro-Tainer Suby G; Zubes Blackcurrant; Zubes Honey & Lemon; ***Ukr.***: Alka-Seltzer (Алка-Зельтцер); Blemaren (Блемарен); Citramon Forte (Цитрамон-Форте); ***USA***: Alka-Seltzer Antacid; Alka-Seltzer Heartburn Relief; Alka-Seltzer with Aspirin; Alka-Seltzer; Bicitra†; Bromo Seltzer Effervescent Granules†; Cytra-2; Cytra-3; Cytra-K; Cytra-LC†; E-Z-Gas II; Extra Strength Alka-Seltzer Effervescent Tablets; Gold Alka-Seltzer; Lycelle; Oracit; Original Alka-Seltzer Effervescent Tablets; Prepopik; Renacidin; Resol; SalivaSure; Sparkles; Taron; Zee-Seltzer; ***Venez.***: Alka-Seltzer; Eno.

Homoeopathic Preparations. ***Canad.***: Ubicoenzyme; ***Ger.***: Citrokehl; HanoOxygen E; Zitronensaurezyklus-Heel.

Pharmacopoeial Preparations

BP 2014: Lemon Syrup; Paediatric Compound Tolu Linctus; Paediatric Simple Linctus; Potassium Citrate Mixture; Simple Linctus;

Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);

USP 36: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation; Magnesium Carbonate and Citric Acid for Oral Solution; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Magnesium Citrate Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Sodium Citrate and Citric Acid Oral Solution; Tricitrates Oral Solution.

Citronella Oil

Citrinžolių eterinis aliejus; Citronela, aceite esencial de; Citronellae Aetheroleum; Citronellae Etheroleum; Citronellaolaj; Citronellöl; Citronellolja; Citronelová silice; Citronnelle, huile essentielle de; Esencia de citronela; Oleum Citronellae; Sitronellaöljy; Цитронелловое Масло.

UNII — QYO8Q067D0.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Citronella Oil). The oil obtained by steam distillation from the fresh or partially dried aerial parts of *Cymbopogon winterianus*. It contains 30.0 to 45.0% citronellal, 9.0 to 15.0% citronellol, 2.0 to 4.0% citronellyl acetate, less than 2.0% geranial, 20.0 to 25.0% geraniol, 3.0 to 8.0% geranyl acetate, 1.0 to 5.0% limonene, and less than 2.0% neral. A pale yellow to brownish-yellow liquid with a very strong odour of citronellal. Store in well-filled containers. Protect from light.

Profile

Citronella oil is used as a perfume and insect repellent. It is also used in aromatherapy. Hypersensitivity has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aulo Gelio Repelente; Aulo Gelio Toallitas; Exilet; Moscut; Rep Repelente; ***Malaysia***: Moz-Away; ***UK***: Mozzie Patch; Natrapel.

Multi-ingredient Preparations. ***Arg.***: Aulo Repelente De Piojos; Max Repel; Max Repel; Rep Locion Repelente; Rep Repelente; ***Austral.***: Apex Repel Natural; ***Belg.***: Mouskito Travel Stick; ***Canad.***: Natrapel Plus; ***Cz.***: Amol; ***Fr.***: Ephydrol; Ysol 206†; ***Ger.***: esto-gast; Melissengeist; ***Hung.***: Carmol; ***Indon.***: Corsabalm; ***Ital.***: Citrosystem; Mistick Verde; Pungino; ***Mon.***: Akipic; ***Pol.***: Carmolis; ***Rus.***: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); ***S.Afr.***: Melissengeist†; ***Switz.***: Baume du Chalet; Novital; ***UK***: Repelselect; Snowfire; ***USA***: Treo.

Clivers

Amor de hortelano; Azotalenguas; Bardana; Cleavers; Galii Aparinis Herba; Galium; Goosegrass; Presera; Липушник.

UNII — Z4B6561488.

Profile

Clivers is the dried aerial parts of *Galium aparine* (Rubiaceae). It has been used in herbal medicine, mainly as a diuretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: DermaCo; ***UK***: Antitis; Aqua Ban Herbal; Athera; Backache; Boots Water Relief; Cascade; Gerard House Water Relief Tablets; HealthAid Boldo-Plus; Kas-Bah; Modern Herbals Menopause; Modern Herbals Water Retention; Napiers Herbal Slimming Aid; Psorasolv; Quantrim Herbal Slimming Tablets; Sciargo; Skin Cleansing; Slimwell Herbal Slimming Tablets; Tabritis; Water Naturtabs; Watershed; ***Ukr.***: Tazalok (Тазалок).

Homoeopathic Preparations. ***Canad.***: Cutisitum†; Essigen†; Itires; Toxex; Tyglan†; Visceel†; Yellow Dock Combination†; ***Cz.***: Galium; ***Hung.***: Toxex; ***Neth.***: Toxex.

Cloprostenol Sodium *(BANM, USAN, rINNM)*

Cloprostenol sódico; Cloprosténol Sodique; Cloprostenoli natricum; ICI-80996; Natrii Cloprostenolum; Натрий Клопростенол.

Sodium (±)-(*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(*E*)-(3*R*)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.

$C_{22}H_{28}ClNaO_6$=446.9

CAS — 40665-92-7 (cloprostenol); 55028-72-3 (cloprostenol sodium).

UNII — 886SAV9675.

Pharmacopoeias. In *BP(Vet)* and *US* for veterinary use only.

BP(Vet) 2014: (Cloprostenol Sodium). A white or almost white amorphous hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in acetone. Protect from light and moisture.

USP 36: (Cloprostenol Sodium). A white or almost white, amorphous hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

Profile

Cloprostenol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). The sodium salt is used as a luteolytic in veterinary medicine. It should be used with caution as it is reported to be readily absorbed through the skin.

Clove

Caryoph.; Caryophylli Flos; Caryophyllum; Clavo; Clou de girofle; Cloves; Cravinho; Cravo-da-Índia; Gewürznelke; Gewürznelken; Giroflier; Gvazdikėliai; Hřebíčkovcový květ; Kryddnejlika; Mausteneilikka; Szegfűszeg; Tropical Myrtle; Гвоздика.

ATC Herb — HA03AW5056 (Syzygium aromaticum: flower bud).

UNII — K48IKT5321.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Clove). The whole flower buds of *Syzygium aromaticum* (*Eugenia caryophyllus*), containing not less than 15% v/w of volatile oil, dried until they become reddish-brown, and with a characteristic aromatic odour. Protect from light.

The BP 2014 directs that when Powdered Clove is prescribed or demanded, material containing not less than 12.0% v/w of essential oil shall be dispensed or supplied.

Uses and Administration

Clove is a carminative and is used as a flavour. It is the source of clove oil (below).

Clove and clove oil have been abused in the form of cigarettes.

Adverse Effects

Abuse. Smoking of cigarettes composed of a mixture of tobacco and cloves (kretek) is a habit that originated in Indonesia and has spread to other countries including the UK and the USA. There have been reports of severe and sometimes fatal respiratory illness related to smoking clove cigarettes and there is also evidence from *animal* studies that clove cigarette smoke and eugenol (the principal constituent of clove oil) have harmful pulmonary effects. The Council on Scientific Affairs of the American Medical Association considers that in addition to the hazards associated with smoking tobacco, clove cigarettes may also produce severe lung injury in certain susceptible individuals and could also induce pulmonary aspiration in healthy individuals due to diminution of the gag reflex produced by the local anaesthetic action of eugenol.[1] The American Academy of Pediatrics has also alerted paediatricians in the USA to clove-cigarette smoking by young people and warned of the risks.[2]

1. American Medical Association Council on Scientific Affairs. Evaluation of the health hazard of clove cigarettes. *JAMA* 1988; **260:** 3641–4.
2. Committee on Substance Abuse. Hazards of clove cigarettes. *Pediatrics* 1991; **88:** 395–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Klosterfrau Melissengeist; Mariazeller; Pervivo; ***Belg.***: Eau Des Carmes; ***Braz.***: Balsamo Branco; Vitonico; ***Canad.***: Clear Capsules†; Intestinal Bulking Agent II†; Kalenite†; Para-Gone; Special Formula Bulking Agent†; ***Cz.***: Klosterfrau Melisana; ***Fr.***: Dida; Saugella Homme; ***Ger.***: Klosterfrau Melissengeist; Melissengeist; ***Hung.***: Bittner; Klosterfrau Melisana; ***India***: Abana; Eugynin; Fortege; Pallrywyn Forte; ***Ital.***: Biophase Shampoo; Saugella Uomo; ***Jpn***: Cabe 2 New; Jidabokuippo; Nyoshinsan; ***Pol.***: Padma 28; Pervivo; ***Rus.***: Doppelherz Melissa (Доппельгерц Мелисса); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Clairo†; Melissengeist†; Spiritus Contra Tussim Drops†; ***Singapore***: Stop Snoring; ***Switz.***: Arteria-vita; Kernosan Eau Dentifrice†; Odontal; Padmed Circosan; Tisane pour les problemes de prostate; ***UK***: Melissa Comp.; Padma 28; Padma Circosan; Revitonil; ***Ukr.***: Imunin (Иммунин)†; Normoton (Нормотон); Olesan (Олесан); Trypsidan (Трипсидан)†.

Homoeopathic Preparations. ***UK***: Cough Drops; Laxadoron.

Clove Oil

Caryophylli floris aetheroleum; Caryophylli Floris Etheroleum; Clavo, aceite esencial de; Clou de girofle, huile essentielle de; Esencia de Clavo; Essence de Girofle; Gvazdikėlių eterinis aliejus; Neilikkaöljy; Nejlikolja; Nelkenöl; Ol. Caryoph.; Oleum Caryophylli; Silice hřebíčkovcového květu; Szegfűszegolaj; Гвоздичное Масло.

ATC Herb — HN01BW5001 (Syzygium aromaticum: essential oil); HA03AW5055 (Syzygium aromaticum: essential oil); HA01WC5005 (Syzygium aromaticum: essential oil).

UNII — 57B389D6D0.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Clove Oil). A clear yellow liquid obtained by steam distillation from clove containing 75.0 to 88.0% of eugenol. It becomes brown on exposure to air. Miscible with dichloromethane, with toluene, and with fatty oils. Store in well-filled airtight containers. Protect from light and heat.

USNF 31: (Clove Oil). The volatile oil distilled with steam from clove. It contains not less than 85.0% of phenolic substances, chiefly eugenol. Soluble 1 in 2 of alcohol (70%). Store in well-filled airtight containers.

Incompatibility. PVC bottles softened and distorted fairly rapidly in the presence of clove oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Uses and Administration

Clove oil is a carminative that is sometimes used in the treatment of flatulent colic. It is also used as a flavour.

Applied externally clove oil is irritant but can produce local anaesthesia. It is used as a domestic remedy for toothache, a plug of cotton wool soaked in the oil being inserted in the cavity of the carious tooth; repeated application may damage the gingival tissues. Mixed with

zinc oxide, it is used as a temporary anodyne dental filling, although eugenol (p. 2501.3), one of its constituents, is often preferred. Clove oil is included as a counter-irritant in preparations for musculoskeletal and joint disorders. It is also used in aromatherapy.

Adverse Effects

The eugenol present in clove oil may act as an irritant to skin and mucous membranes; it may also cause hypersensitivity. For references to the adverse effects of clove oil abused in the form of cigarettes, see under Clove p. 2481.3.

Poisoning. Severe toxicity after ingestion of clove oil by young children has been reported.[1-4] Adverse effects included coma, acidosis, a generalised seizure, disordered blood clotting, and acute liver damage.

1. Lane BW, *et al.* Clove oil ingestion in an infant. *HumExp Toxicol* 1991; **10:** 291–4.
2. Hartnoll G, *et al.* Near fatal ingestion of oil of cloves. *Arch Dis Child* 1993; **69:** 392–3.
3. Eisen JS, *et al.* N-acetylcysteine for the treatment of clove oil-induced fulminant hepatic failure. *J Toxicol Clin Toxicol* 2004; **42:** 89–92.
4. Janes SE, *et al.* Essential oil poisoning: N-acetylcysteine for eugenol-induced hepatic failure and analysis of a national database. *Eur J Pediatr* 2005; **164:** 520–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Naeltjie-Olie; ***UK***: Dentogen; Soothake Toothache Gel.

Multi-ingredient Preparations. ***Austral.***: Herbal Throat Spray; Oral-Eze; Tiger Balm Oil; Tiger Balm Red; Tiger Balm White; Wormwood Complex; ***Austria***: Parodontax†; Tiger Balsam Rot; Tiger Balsam Weiss; ***Braz.***: Dentisan†; ***Canad.***: Amol†; DSO Dressing; External Anti-Pain Oil†; Muscle Mist; Tiger Balm Arthritis Rub; Tiger Balm Red; Tiger Balm Ultra; Tiger Balm White; Wonder Oil; ***Chile***: Agua del Carmen; Agua Melisa Carminativa; ***Cz.***: Amol; Herbadent; Stopangin; ***Fr.***: Arnicadol†; Aromasol; Aromavital†; Baume Aroma; Capsaine; Esculape†; Gouttes aux Essences; Nazinette du Docteur Gilbert; Percutalgin'Phyto; Tigre de Chine; Tigridol; ***Ger.***: Amol Heilkrautergeist N; esto-gast; Melissengeist; Repha-Os†; Salviathymol N; Tiger Balm weiss; Verdauungstropfen Gastrofunkten†; ***Gr.***: Tiger Balm; ***Hong Kong***: Magesto; ***Hung.***: Amol; Carmol; China-Balsam; Gingisol; Hustagil Anticold Cream; Tiger Balm Red; Tiger Balm White; ***India***: Arowash†; Olesan Oil; Sensur; Sensur; ***Indon.***: Balsam Sakti†; Corsabalm; ***Irl.***: Olbas; Olbas; Soothake Toothache Tincture; Tiger Balm Red; Tiger Balm White; ***Israel***: Tiger Balm Red; Tiger Balm White; ***Ital.***: Dentosan Azione Intensiva; Dentosan Mese; Fialetta Odontalgica Dr Knapp; ***Neth.***: Olbas†; ***NZ***: Electric Blue Headlice; Electric Blue Headlice; ***Pol.***: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; Olbas; Salviasept; ***Rus.***: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Efcamon (Эфкамон); ***S.Afr.***: Alpha Toothache Essence†; Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Enterodyne†; Helmontskruie†; Moultons Pain Paint†; Muscle Rub†; Prep†; Puma Balm; SB Toothache Drops†; ***Singapore***: Teenstick; ***Spain***: Otogen Calmante; ***Switz.***: Baume du Tigre blanc; Baume du Tigre rouge; Echinarom; Olbas; Spagyrom; ***Thai.***: Caryopin; Magesto; Masaga; Mesto-Of; ***Turk.***: Disinol; Piyraleks; Sena-Oil; ***UK***: Hactos; Nine Rubbing Oils; Olbas for Children; Olbas; Olbas; Potters Sugar Free Cough Pastilles; Red Oil; Repelselect; Snowfire; Soothake Toothache Tincture; Teenstick; Tiger Balm; ***Ukr.***: Stopangin (Стопангин); ***USA***: Dentapaine; Tiger Balm; Toothache Gel.

Homoeopathic Preparations. ***UK***: Medicinal Gargle.

Pharmacopoeial Preparations
BP 2014: Aromatic Cardamom Tincture.

Red Clover

Cow Clover; Meadow Clover; Purple Clover; Trébol rojo; Trefoil; Красный Клевер; Луговой Клевер.
UNII — L9153EKV2Y.

Pharmacopoeias. In *US*, which also includes the powdered form and powdered extract.

USP 36: (Red Clover). The dried inflorescence of *Trifolium pratense* (Fabaceae). It contains not less than 0.5% of isoflavones, calculated on the dried basis as the sum of daidzein (p. 2620.3), genistein (p. 2620.3), formononetin, and biochanin A. Protect from light and moisture.

Profile

The flowerheads of red clover have been used in herbal medicine. The isoflavones present in red clover have been investigated, similarly to other phytoestrogens, for their potential endocrine effects.

References.

1. Booth NL, *et al.* Clinical studies of red clover (Trifolium pratense) dietary supplements in menopause: a literature review. *Menopause* 2006; **13:** 251–64.
2. Coon JT, *et al. Trifolium pratense* isoflavones in the treatment of menopausal hot flushes: a systematic review and meta-analysis. *Phytomedicine* 2007; **14:** 153–9.
3. Sabudak T, Guler N. Trifolium L. a review on its phytochemical and pharmacological profile. *Phytother Res* 2009; **23:** 439–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Promensil; Trinovin; ***Braz.***: Climadil; Clinet; Promensil; ***Canad.***: Promensil; ***Indon.***: Promeno; Trinovin; ***Singapore***: Fem-E; ***UK***: Menoflavon; Promensil; ***Ukr.***: Kleverol (Клеверол).

Multi-ingredient Preparations. ***Austral.***: Bone Complex; Femi-Nan; Mens Super Soy/Clover†; PM Meno-Care; Soy Power Plus†; ***Canad.***: Libeeda for Women; ***Indon.***: Femosa; Fitogen; Osteopor; ***Ital.***: Bioestril Ginseng; Bioestril Valeriana; Ginepausil; ***Philipp.***: Nutrafem; Thinber Fiber Complex†; ***Rus.***: Cedoflor (Седофлор); Sedativae Species No 3 (Седативный Сбор 3); ***Spain***: Fitogyn; Soyred†; ***Switz.***: Metabol; ***UK***: Napiers Oral Skin Soother Herbal Relief; ***USA***: Detox.

Homoeopathic Preparations. ***Canad.***: Essigen†; Yellow Dock Combination†.

Pharmacopoeial Preparations
USP 36: Red Clover Tablets.

Cnicus Benedictus

Blessed Thistle; Cardo bendito; Cardo Santo; Centáurea bendita; Centáurea Sudorífica; Chardon Bénit; Holy Thistle; Kardobenediktenkraut; Кникус Аптечный.
*ATC Herb — HA09WA5010 (*Cnicus benedictus*: herb).*
*UNII — 6L5ZL09795 (*Cnicus benedictus*); NJN80GZ34N (*Cnicus benedictus *flowering top).*

Profile

Cnicus benedictus, the flowering tops of *Cnicus benedictus* (*Carbenia benedicta; Carduus benedictus*) (Compositae), has been used as a bitter.

Homoeopathy

Cnicus benedictus has been used in homoeopathic medicines under the following names: Carduus benedictus; Carduus ben.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Mariazeller; Pervivo; ***Ger.***: Gallexier; Gastritol; ***Hung.***: Bittner; ***Pol.***: Artecholin†; Artecholwex†; Pervivo; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Essens Amara of Groen Amara; ***Switz.***: Gastrosan; Kernosan 24; Kernosan 26; ***UK***: Bio-Strath Artichoke Formula; Sure-Lax (Herbal); ***Ukr.***: Gastritol (Гастритол); Hepahealth (Гепахелс).

Homoeopathic Preparations. ***Ger.***: Heweberberol; Rufebran heparo†; ***USA***: Preferred Remedies Detoxin.

Cobalt

Cobalto; Cobaltum; Kobalt; Кобальт.
Co=58.933195
CAS — 7440-48-4.
UNII — 3G0H8C9362.

Cobalt Chloride

Cloruro cobaltoso; Cobalto, cloruro de; Cobaltous Chloride; Kobaltu(II) chlorek; Хлористый Кобальт.
$CoCl_2.6H_2O$=237.9
CAS — 7646-79-9 (anhydrous cobalt chloride); 7791-13-1 (cobalt chloride hexahydrate).
UNII — EVS87XF13W (cobalt chloride); 17AVG63ZBC (cobalt chloride hexahydrate).

Cobalt Oxide

Cobalto, óxido de; Óxido cobaltoso-cobáltico; Tetraóxido de tricobalto; Tricobalt Tetroxide; Кобальт Оксид; Окись Кобальта.
Co_3O_4=240.8
CAS — 1308-06-1.
UNII — USK772NS56.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Cobalt Oxide). It consists of cobalt (II, III) oxide (tricobalt tetroxide) with a small proportion of cobalt (III) oxide (dicobalt trioxide). A black powder. Practically insoluble in water; dissolves in mineral acids and in solutions of alkali hydroxides.

Uses and Administration

Cobalt is a trace mineral required in the synthesis of vitamin B_{12} and compounds such as the acetate, gluconate, sulfate, and sodium gluconate have sometimes been included in dietary supplements. Although it has been reported that cobalt chloride can produce reticulocytosis and raise the erythrocyte count such use in the treatment of anaemias has been deprecated.

In veterinary medicine various cobalt salts are given to ruminants as a dietary supplement.

Adverse Effects

Reactions to cobalt have included anorexia, nausea and vomiting, diarrhoea, precordial pain, cardiomyopathy, flushing of the face and extremities, rashes, tinnitus, temporary nerve deafness, renal injury, diffuse thyroid enlargement, and hypothyroidism. In large doses it may reduce the production of erythrocytes.

References.

1. Kennedy A, *et al.* Fatal myocardial disease associated with industrial exposure to cobalt. *Lancet* 1981; **i:** 412–4.
2. Cugell DW, *et al.* The respiratory effects of cobalt. *Arch Intern Med* 1990; **150:** 177–83.
3. Evans P, *et al.* Cobalt and cobalt compounds. *Toxicity Review 29*. London: HMSO,1993.
4. Torresani C, *et al.* Erosive oral lichen planus due to sensitization to cobalt chloride. *Clin Exp Dermatol* 1994; **19:** 535–6.
5. Krakowiak A, *et al.* Occupational asthma caused by cobalt chloride in a diamond polisher after cessation of occupational exposure: a case report. *Int J Occup Med Environ Health* 2005; **18:** 151–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Infladase Forte.

Multi-ingredient Preparations. ***Arg.***: Gingeron; Total Magnesiano Sport; ***Fr.***: Stimuplexe†; ***Hung.***: Ferrocomp; Humet-R; ***Indon.***: Emineton; Nonemi; ***Philipp.***: Ferroplex.

Homoeopathic Preparations. ***Canad.***: Formula FA 224†; Formula PC 223†; Weight Loss Kit†; ***Ger.***: Chirofossat; Infi-China.

Cobicistat *(USAN, rINN)*

Cobicistatum; GS-9350; Кобицистат.
(1,3-Thiazol-5-yl)methyl (5*S*,8*R*,11*R*)-8,11-dibenzyl-2-methyl-5-[2-(morpholin-4-yl)ethyl]-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-3,6-dioxo-2,4,7,12-tetraazatridecan-13-oate.
$C_{40}H_{53}N_7O_5S_2$=776.0
CAS — 1004316-88-4.
ATC — V03AX03.
ATC Vet — QV03AX03.
UNII — LW2E03M5PG.

Profile

Cobicistat is a pharmacokinetic enhancer used similarly to low-dose ritonavir (p. 1013.1) to boost the concentrations of antiretrovirals; it has no antiretroviral activity itself. Cobicistat (150 mg) is given as a component of a four-drug, fixed-dose combination product (*Stribild, Gilead, USA* and also referred to as the Quad pill) with elvitegravir (p. 976.2), emtricitabine (p. 976.3), and tenofovir (p. 1018.1) for the treatment of HIV infection and AIDS (p. 957.2) in antiretroviral treatment-naive patients. The recommended dose is one tablet taken orally once daily with food.

Fixed-dose antiretroviral combination products containing cobicistat and atazanavir or darunavir are also being developed.

Cobicistat is metabolised mainly by the cytochrome P450 isoenzyme CYP3A and to a lesser extent CYP2D6; it is also an inhibitor of the same isoenzymes. It is an inhibitor of P-glycoprotein, breast cancer resistanance protein (BCRP), and the organic anion transporting polypeptides (OATP1B1 and OATP1B3). Concomitant use of cobicistat with drugs that are metabolised by these isoenzymes or that are substrates for these transporters may result in increased plasma concentrations of such drugs. Drugs that induce CYP3A may decrease the plasma concentration of cobicistat, while drugs that inhibit CYP3A may increase its plasma concentration.

References.

1. von Hentig N, Haberl A. Safety of pharmacoenhancers for HIV therapy. *Expert Rev Clin Pharmacol* 2012; **5:** 557–68.
2. Olin JL, *et al.* Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet for HIV-1 infection treatment. *Ann Pharmacother* 2012; **46:** 1671–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Tybost.

Multi-ingredient Preparations. ***Jpn***: Stribild; ***UK***: Stribild; ***USA***: Stribild.

Coccidioidin

Coccidioidina; Кокцидиоидин.
CAS — 12622-73-0.
UNII — ZP77O7YY70.

Profile

Coccidioidin contains antigens from the fungus *Coccidioides immitis*. It has been used as an aid to the diagnosis of coccidioidomycosis and, in conjunction with other antigens, to assess the status of cell-mediated immunity. A usual dose of 0.1 mL of a 1 in 100 dilution by intradermal (intracutaneous) injection has been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Spherulin†.

Cocculus

Cocculus indicus; Coque du Levant; Fischkörner; Fish Berry; Indian Berry; Kokkelskörner; Levant Nut; Oriental Berry; Poison-berry.
UNII — 810258W28U.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Anamirta Cocculus for Homoeopathic Preparations). The dried, ripe fruit of *Anamirta paniculata*. It contains not less than 0.80% of picrotoxinin, ($C_{15}H_{16}O_6 = 292.3$), calculated with reference to the dried drug.

Profile

Cocculus, the dried fruit of *Anamirta cocculus* (*A. paniculata*; *Menispermum cocculus*) (Menispermaceae) has been used in herbal medicines for nervous system disorders and topically as a parasiticide, but is highly toxic and has been generally superseded. The main active constituent is picrotoxin, a CNS and respiratory stimulant.

Traditionally, the berries have been used as a fish poison.

Homoeopathy

Cocculus has been used in homoeopathic medicines under the following names: Anamirta cocculus; Cocculus.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus.

Homoeopathic Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus; Travellers Relief; ***Austria***: Nausyn; Travelex; Vertigoheel; Vertigopas; ***Canad.***: Cocculine; Hylands Motion Sickness; Hylands PMS; Hylaprin; Kids Calm; Nixotinex; Travel Sickness; ***Chile***: Bioactiv V; ***Cz.***: Cocculine; Vertigoheel; Vita C-R15 forte†; Vita C-R15†; ***Fr.***: Apomorphinum Complexe No 97†; Cocculine; Cocculus Complexe No 73; Dolitravel†; Homeogene 21†; Nausetum; Oenanthe Crocata Complexe No 78; Tabacum Compose; Tarentula Complexe No 71; ***Ger.***: Calmvalera; Cerebral-Do; Cocculus Oligoplex; Curare comp; Femi-cyl L Ho-Len-Complex; Gelsemium Comp; Gelsemium Comp; Homvio-Em; Infi-China; Naranofem†; Nervoregin H; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pascolibrin; Passiflora Complex†; Procordal vertigo; Schwoneural N; Vertigo Hevert SL; Vertigo-Hevert; Vertigo-Hevert; Vertigoheel; Vertigopas; Viscum album H†; Viscum Album HM†; Zerosorin SN†; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Cocculine; Vertigoheel; ***Neth.***: Cerebrum comp; Co-Hypert; Cocculine; Coconium-Gastreu; Gravifem†; Travelin; Vertigoheel; ***Port.***: Cocculine; ***Rus.***: Aurum Plus (Аурум-Плюс); Avia-Mor (Авиа-Море); Cocculine (Коккулин); ***S.Afr.***: Vertigoheel; ***Switz.***: Cocculine; Nelsons Travella†; Vertigoheel; ***UK***: Nausyn; Travella; ***USA***: Vertigoheel.

Cocoyl Caprylocaprate

Coco-Caprylate/Caprate; Cocoylcaprylocaprat; Cocoyle, caprylocaprate de; Cocoylis Caprylocapras; Cocoylis Octanodecanoas; Kokoilo kaprilokapratas; Kokoyl oktanodekanoát; Kokoylkaprylokaprat; Kokoyylikaprylokapraatti; Kókuszalkoholok kaprilátjai és kaprátjai; Коко-каприлат/капрат.
CAS — 95912-86-0.
UNII — 8D9H4QU99H.

NOTE. The name Cetiol LC has been used as a trade mark for cocyl caprylocaprate.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Cocoyl Caprylocaprate). A mixture of esters of saturated C_{12} to C_{18} alcohols with caprylic (octanoic) and capric (decanoic) acids obtained by the reaction of these acids with vegetable saturated fatty alcohols. Relative density about 0.86. Viscosity about 11 mPa s. A slightly yellowish liquid. Practically insoluble in water; miscible with alcohol and with liquid paraffin.

Profile

Cocoyl caprylocaprate is used as an emollient.

Coenzyme A

CoA; CoASH; Coenzima A; Кофермент А.
5′-*O*-{3-Hydroxy-3-[2-(2-mercaptoethylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl}adenosine-3′-dihydrogenphosphate-5′-trihydrogendiphosphate.
$C_{21}H_{36}N_7O_{16}P_3S = 767.5$
CAS — 85-61-0.
UNII — SAA04E81UX.

Profile

Formed from adenosine triphosphate, cysteine, and pantothenic acid, coenzyme A is involved in the body in many physiological roles, including the formation of citrate, the oxidation of pyruvate, the oxidation and synthesis of fatty acids, the synthesis of triglycerides, cholesterol, and phospholipids, and the acetylation of amines, choline, and glucosamine. It has been given by injection in a variety of metabolic disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Redumax; ***Philipp.***: Enervon-C; ***S.Afr.***: Zeel; Zeel.

Homoeopathic Preparations. ***Cz.***: Zeel Salbe†; ***Hung.***: Zeel; ***Rus.***: Zeel T (Цель Т).

Cogalactoisomerase Sodium

Cogalactoisomerasa sódica; UDPG; Uridine-5′-diphosphoglucose Sodium; Уридиндифосфатглюкоза Натрий.
$C_{15}H_{22}N_2Na_2O_{17}P_2.3H_2O = 664.3$
CAS — 133-89-1 (cogalactoisomerase).

Profile

Cogalactoisomerase sodium has been used in various hepatic disorders.

Colforsin *(USAN, rINN)*

Boforsin; Colforsina; Colforsine; Colforsinum; Forscolin; Forskolin; HL-362; L-75-1362B; Колфорсин.
(3*R*,4a*R*,5*S*,6*S*,6a*S*,10*S*,10a*R*,10b*S*)-Dodecahydro-5,6,10,10b-tetrahydroxy-3,4a,7,7,10a-pentamethyl-3-vinyl-1*H*-naphtho[2,1-*b*]pyran-1-one, 5-acetate.
$C_{22}H_{34}O_7 = 410.5$
CAS — 66575-29-9.
UNII — 1F7A44V6OU.

Colforsin Daropate Hydrochloride *(rINNM)*

Colforsin Dapropate Hydrochloride; Colforsine, Chlorhydrate de Daropate de; Colforsini Daropatis Hydrochloridum; Hidrocloruro del daropato de colforsina; Milaforsin Hydrochloride; NKH-477; Колфорсина Даропата Гидрохлорид.
$C_{27}H_{43}NO_8.HCl = 546.1$
CAS — 138605-00-2.

Profile

Colforsin is an adenylate cyclase stimulator derived from the plant *Plectranthus barbatus* (*Coleus forskohlii*) (Labiatae). It has been investigated for several conditions, including glaucoma and impotence. It is reported to have positive inotropic and bronchodilator effects. It has been used in the form of colforsin daropate hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn.***: Adehl.

Collagen

ARG-201 (type 1 bovine collagen); Colágeno; Коллаген.
ATC — B02BC07; G04BX11.
ATC Vet — QB02BC07; QG04BX11.

Pharmacopoeias. *US* includes Bovine Acellular Dermal Matrix and Scaffold Human Dermis.

USP 36: (Bovine Acellular Dermal Matrix). A remodelable collagen scaffold derived from fetal or neonatal bovine skin. It is presented as a flat white sheet that is cut to size and hydrated in sterile saline solution before implantation. It is utilised as a structural scaffold in orthopaedic, neurosurgical, urogynaecological, dermatological, plastic, and other reconstructive procedures. The source fetal or neonatal bovine skin is mechanically and chemically processed to isolate the dermis and remove cells and cellular components. To prevent the transmission of infectious disease, the manufacturing process is validated to inactivate viruses potentially present in the source material. To prevent the spread of transmissible spongiform encephalopathies, the source material is acquired from appropriate geographic locations. Store at 15 degrees to 30 degrees.

USP 36: (Scaffold Human Dermis). It is derived from donated allograft human dermis that is processed to remove cells and freeze-dried to remove moisture while preserving biologic components and structure of the dermal matrix. It is biocompatible and supports remodeling by the recipient's own tissue. The matrix is composed of native human dermal architecture, consisting of collagen (mainly collagen type I, with additional components of collagen types III and IV), chondroitin sulfate and hyaluronic acid glycosaminoglycans, and elastin. The product can be provided in a sheet or powder form. The donated human skin is processed in a manner that removes all cellular components, including the epidermal layer and dermal cells. The resulting product is then rendered into a particulate form (microsized), with a mean particle size of less than 100 micrometres, by processing with a freezer mill. Scaffold Human Dermis does not contain intact cells, cell nuclei, or chemically induced crosslinks. Human skin used to produce Scaffold Human Dermis is obtained from sources that have passed applicable donor eligibility requirements for relevant communicable diseases.

Profile

Collagen is a fibrous protein component of mammalian connective tissue making up almost one third of the total body protein.

Collagen, processed in a variety of ways, has been used in surgery as a haemostatic and as a repair and suture material. For cosmetic purposes it has been injected into the dermis to correct scars and other contour deformities of the skin. Collagen implants have been used to block tear outflow in the management of dry eye (p. 2190.1).

Intraurethral administration o f collagen has been used in the treatment of stress incontinence (p. 2349.2). There has also been interest in the use of oral collagen to suppress the inflammatory process in rheumatoid arthritis (p. 13.2), osteoarthritis (p. 12.3), and scleroderma (p. 1938.3).

Elastin, another component of connective tissue, is an ingredient, often with collagen, of various topical preparations promoted for skin disorders.

References.

1. Herschorn S, *et al.* Early experience with intraurethral collagen injections for urinary incontinence. *J Urol (Baltimore)* 1992; **148:** 1797–1800.
2. Sieper J, *et al.* Oral type II collagen treatment in early rheumatoid arthritis: a double-blind, placebo-controlled, randomized trial. *Arthritis Rheum* 1996; **39:** 41–51.
3. Stanton SL, Monga AK. Incontinence in elderly women: is periurethral collagen an advance? *Br J Obstet Gynaecol* 1997; **104:** 154–7.
4. Anonymous. GAX collagen for genuine stress incontinence. *Drug Ther Bull* 1997; **35:** 86–7.
5. Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum* 2000; **30:** 87–99.
6. Hamraoui K, *et al.* Efficacy and safety of percutaneous treatment of iatrogenic femoral artery pseudoaneurysm by biodegradable collagen injection. *J Am Coll Cardiol* 2002; **39:** 1297–1304.
7. Corcos J, *et al.* Multicenter randomized clinical trial comparing surgery and collagen injections for treatment of female stress urinary incontinence. *Urology* 2005; **65:** 898–904.
8. Bello AE, Oesser S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. *Curr Med Res Opin* 2006; **22:** 2221–32.
9. Poon CI, Zimmern PE. Is there a role for periurethral collagen injection in the management of urodynamically proven mixed urinary incontinence? *Urology* 2006; **67:** 725–9.
10. Sakamoto K, *et al.* Long-term subjective continence status and use of alternative treatments by women with stress urinary incontinence after collagen injection therapy. *World J Urol* 2007; **25:** 431–3.
11. Postlethwaite AE, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of oral type I collagen treatment in patients with diffuse cutaneous systemic sclerosis: I. oral type I collagen does not improve skin in all patients, but may improve skin in late-phase disease. *Arthritis Rheum* 2008; **58:** 1810–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Covadenyl; Eurohair; Hidroplus CL; Medic-S; Membracel; Skinderm CL; ***Austral.***: Ionil Rinse†; Zyderm†; Zyplast†; ***Chile***: Artrimax; Cosmoplast†; ***Ger.***: Catrix†; Colloss†; Hemocol; Medifome†; TissuCone; TissuFleece; TissuFoil; ***Gr.***: Colgen; Gelfix; ***India***: Collafex; Gelfix; ***Ital.***: Condress; Idroskin; Suprasorb C; ***Malaysia***: Bio Coll; ***Mex.***: Fibroquel; ***NZ***: Contigen; Zyderm; Zyplast; ***Singapore***: CosmoDerm; CosmoPlast; Terraflex; ***UK***: Contigen; ***USA***: Avitene†.

Multi-ingredient Preparations. ***Arg.***: Amenite E; Amenite Plus; Aristaloe; Colageno + C; Collagen T2-Gag; Dayflex C; E-Devit; Estri-Atlas; Fibracol Plus; Galenic Restaurador Capilar; Hairplus; Hidrosam T; Hidrosam; HSN; Lociherp Liposomas Antiage; Lociherp Liposomas Vitaminado; Medicreme; Piroctol; Pityrum; Puraloe Nutritiva; Rep-Cartil; Rominafort; Skinderm R; Totalos Plus; Turgent Colageno; Ukase Lulitis; Zinc-S Plus; ***Belg.***: Duracoll; ***Chile***: Acnoxyl Gel Humectante; Estri-Atlas; ***Fr.***: Flex-Tonic; Lubri-Mucal; Osteocalm; Taido; ***Ger.***: Collapat II; Septocoll; Targobone†; ***Hong Kong***: TachoComb; ***Indon.***: Biolastin; Colaskin; Jointfit; Legreskin; OA Plus; ***Ital.***: Artrodue; Biomineral 5-Alfa Shampoo; Emofix; Osteoclar; Promogran Prisma; Promogran; Reumilase Plus; Reumilase SD; Reumilase; Secril; Unidermo; Vitreoclar Crono; ***Malaysia***: Balance Elastin E; Evelle; ***Philipp.***: Gloww; ***Rus.***: Combutec-2 (Комбутек-2); Methuracol (Метуракол); TachoComb (ТахоКомб); ***Singapore***: Articolase (w/glucosamine); BCC; Evelle; Glow; RejuvaSkin Anti-Aging Serum; Seven Seas JointCare Max; TachoComb; ***Switz.***: Gorgonium; ***UK***: Collatamp EG; Jointace; JointCare Max; ***Ukr.***: TachoComb (Тахокомб); ***USA***: PDP Liquid Protein; ***Venez.***: Artrosamin.

Collagenase ⊗

Clostridiopeptidas; Clostridiopeptidasa A; Clostridiopeptidase A; Clostridiopeptidasum A; Colagenasa; EC 3.4.24.3; Klostridiopeptidaasi A; Коллагеназа.

CAS — 9001-12-1.

ATC — D03BA02.

ATC Vet — QD03BA02.

UNII — 9X7O8V25IT (collagenase Clostridium histolyticum *gene colh isoenzyme aux-II); 231982L46K (collagenase* Clostridium histolyticum *gene colg isoenzyme aux-I); 15Z7208B52 (collagenase* Clostridium histolyticum*).*

Units

Collagenase potency is expressed in units based on the amount of enzyme required to degrade a standard preparation of undenatured collagen.

Uses and Administration

Collagenase is a proteolytic enzyme derived from the fermentation of *Clostridium histolyticum* and has the ability to break down collagen. Preparations containing collagenase are used topically for the debridement of dermal ulcers and burns, and possibly other necrotic lesions, to facilitate granulation and epithelialisation. Collagenase is given by intralesional injection in the treatment of Dupuytren's contracture. It is injected in a dose of 580 micrograms into a palpable cord with a contracture of a metacarpophalangeal joint or proximal interphalangeal joint. The injection may be given up to 3 times per cord at intervals of 4 weeks if the contracture remains. Only one cord may be injected at a time; if patients have multiple contractures with palpable cords, each cord should be treated in a sequential order. Collagenase has also been given by injection into the intervertebral disc for chemonucleolysis in the treatment of lumbar disc herniation (see Low Back Pain, p. 9.2). Collagenase is under investigation for use in Peyronie's disease and frozen shoulder.

Chemonucleolysis. Collagenase has been studied as an alternative to chymopapain (p. 2477.1) for chemonucleolysis because of the risk of anaphylaxis with the latter. Although early studies with collagenase reported benefit, there were also reports of back pain and muscle spasm.[1] Collagenase was not as effective as chymopapain in a comparative study,[2] and further study may be warranted before a firm recommendation can be made.

1. Brown MD. Update on chemonucleolysis. *Spine* 1996; **21** (24 suppl): 62S–68S.
2. Wittenberg RH, *et al*. Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study. *Spine* 2001; **26**: 1835–41.

Dupuytren's disease. Collagenase has been reported to be of benefit in the treatment of Dupuytren's contracture.[1,2]

1. Badalamente MA, Hurst LC. Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg (Am)* 2007; **32**: 767–74.
2. Hurst LC, *et al*. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med* 2009; **361**: 968–79.

Peyronie's disease. Beneficial effects have been reported with intralesional collagenase in men with Peyronie's disease.[1-3]

1. Gelbard MK, *et al*. The use of collagenase in the treatment of Peyronie's disease. *J Urol (Baltimore)* 1985; **134**: 280–3.
2. Gelbard MK, *et al*. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. *J Urol (Baltimore)* 1993; **149**: 56–8.
3. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med* 2008; **5**: 180–7.

Adverse Effects and Precautions

Hypersensitivity reactions to collagenase may occur.

Local burning, erythema, and pain have been reported at the site of application when used topically. It has been suggested that debridement of infected wounds may increase the risk of bacteraemia and that patients should be watched for signs of systemic bacterial infection. The activity of collagenase may be reduced by antiseptics containing detergents, hexachlorophene, and heavy metal ions.

Injection of collagenase into tendons, nerves, blood vessels, or other collagen-containing structures in the hand should be avoided because of the risk of permanent injury such as tendon rupture or damage to ligaments. Collagenase injections should be used with caution in patients with coagulation disorders or in those who have received anticoagulants (excluding low-dose aspirin) within 7 days before the injection because of the risk of ecchymosis, bruising or injection-site haemorrhage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Xiapex; ***Belg.***: Iruxol Mono; Xiapex; ***Braz.***: Iruxol Mono; Kollagenase; ***Canad.***: Santyl; ***Cz.***: Xiapex; ***Denm.***: Xiapex; ***Fin.***: Xiapex; ***Fr.***: Xiapex; ***Ger.***: Xiapex; ***Gr.***: Iruxol Mono; Xiapex; ***Hong Kong***: Iruxol Mono†; ***Hung.***: Xiapex; ***Irl.***: Xiapex; ***Ital.***: Noruxol; Xiapex; ***Neth.***: Novuxol; Xiapex; ***Norw.***: Xiapex; ***Pol.***: Xiapex; ***Port.***: Ulcerase; Xiapex; ***Rus.***: Kollalysin (Коллализин); ***Spain***: Xiapex; ***Swed.***: Xiapex; ***Switz.***: Iruxol Mono; Xiapex; ***Turk.***: Novuxol; ***UK***: Xiapex; ***USA***: Santyl; Xiaflex; ***Venez.***: Iruxol.

Multi-ingredient Preparations. ***Arg.***: Iruxol; ***Braz.***: Gino Kollagenase; Gyno Iruxol; Iruxol; Kollagenase com cloranfenicol; ***Cz.***: Iruxol Mono; ***Fin.***: Iruxol Mono; Iruxol†; ***Hung.***: Iruxol Mono†; ***Indon.***: Plasmin; ***Irl.***: Iruxol Mono; ***Ital.***: Iruxol; ***Malaysia***: Iruxol Mono; ***Mex.***: Ulcoderma†; ***Philipp.***: Plasmin; ***Rus.***: Iruxol (Ируксол)†; ***S.Afr.***: Iruxol Mono; ***Spain***: Iruxol Mono; Iruxol Neo.

Colophony

Colofonia; Coloph.; Colophane; Colophonium; Kalafuna; Kanifolija; Kolofoni; Kolofónium; Kolofonium; Kolophonium; Resin; Resina Pini; Resina Terebinthinae; Rosin; Канифоль.

UNII — 88S87KL877.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Colophony). The residue remaining after distillation of the volatile oil from the oleoresin obtained from various species of *Pinus*. Translucent, pale yellow to brownish-yellow, angular, irregularly shaped, brittle, glassy pieces of different sizes the surfaces of which bear conchoidal markings. Do not reduce to a fine powder.

Profile

Colophony is an ingredient of some collodions and plastermasses. It has been used as an ingredient of ointments and dressings for wounds and minor skin disorders. Skin sensitisation and allergic respiratory symptoms have been reported.

Hypersensitivity. Reviews.

1. Downs AM, Sansom JE. Colophony allergy: a review. *Contact Dermatitis* 1999; **41**: 305–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Biopin (Биопин).

Multi-ingredient Preparations. ***Arg.***: Adhesol; ***Austria***: Ehrenhofer-Salbe; Vulpuran; ***Gr.***: Ilon; ***Ital.***: Fialetta Odontalgica Dr Knapp; ***Mex.***: Parche Negro Belladona; ***UK***: Dispello; Herbheal Ointment; Pickles Corn Caps.

Pharmacopoeial Preparations

BP 2014: Flexible Collodion.

Comfrey

Boneset; Comfrey Root; Common Comfrey; Consolidae Radix; Consuelda; Sínfito mayor; Symphytum; Окопник Лекарственный.

*ATC Herb — HM02AX5004 (*Symphytum officinale*: root); HA02WX5003 (*Symphytum officinale*: herb); HA02WB5001 (*Symphytum officinale*: root); HD03WC5002 (*Symphytum officinale*: root); HD03WC5001 (*Symphytum officinale*: herb).*

UNII — D05HXK6R3G (comfrey); DG4F8T839X (comfrey leaf); M9VVZ08EKQ (comfrey root).

NOTE. Boneset is also a common name used for *Eupatorium perfoliatum* (see p. 2459.1). Purple boneset is Gravel Root, p. 2522.1.

Pharmacopoeias. *Br.* includes Symphytum Officinale Root for Homoeopathic Preparations and Symphytum Officinale Root, Ethanol. decoctum for Homoeopathic Preparations.

BP 2014: (Symphytum Officinale Root for Homoeopathic Preparations). The fresh root of *Symphytum officinale*.

BP 2014: (Symphytum Officinale Root, Ethanol Decoction for Homoeopathic Preparations). The fresh root of *Symphytum officinale*.

Uses and Administration

Comfrey consists of the dried root and rhizome of *Symphytum officinale* (Boraginaceae); the leaf has also been used. It contains about 0.7% of allantoin, large quantities of mucilage, and some tannin. It may also contain pyrrolizidine alkaloids.

Comfrey was formerly used as an application to wounds and ulcers to stimulate healing and was also given systemically for gastric ulceration. It has been applied topically in the treatment of inflammatory disorders. The healing action of comfrey has been attributed to the presence of allantoin (p. 1693.1).

Oral preparations of comfrey have been withdrawn or banned in some countries because of toxicity—see below.

Homoeopathy

Comfrey has been used in homoeopathic medicines under the following names: Symphytum officinale; Symph. of.; Symphytum.

References.

1. Stickel F, Seitz HK. The efficacy and safety of comfrey. *Public Health Nutr* 2000; **3**: 501–8.
2. Grube B, *et al*. Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial. *Phytomedicine* 2007; **14**: 2–10.
3. D'Anchise R, *et al*. Comfrey extract ointment in comparison to diclofenac gel in the treatment of acute unilateral ankle sprains (distortions). *Arzneimittelforschung* 2007; **57**: 712–16.

Adverse Effects

Ingestion of comfrey has been associated with hepatotoxicity.

Effects on the liver. Toxic pyrrolizidine alkaloids have been isolated from several species of comfrey plants including common comfrey (*Symphytum officinale*), prickly comfrey (*S. asperum*), and Russian comfrey (*S. uplandicum*). Ingestion of plants containing pyrrolizidine alkaloids is a common cause of hepatic veno-occlusive disease in developing countries[1] and pyrrolizidine alkaloid hepatotoxicity presumably due to comfrey has been reported in North America and Europe.[1,2] Pulmonary endothelial hyperplasia and carcinogenic activity have also been reported in *animals*.[1,2]

1. Ridker PM, McDermott WV. Comfrey herb tea and hepatic veno-occlusive disease. *Lancet* 1989; **i**: 657–8.
2. Bach N, *et al*. Comfrey herb tea-induced hepatic veno-occlusive disease. *Am J Med* 1989; **87**: 97–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Flexagil; ***Austria***: Traumaplant; ***Belg.***: Flexagile; ***Chile***: Traumaplant; ***Cz.***: Traumaplant; ***Fr.***: Epidermine†; ***Ger.***: Kytta-Plasma f; Kytta-Salbe f; Traumaplant; ***Hung.***: Flexagil; ***Indon.***: Mediflor†; ***Israel***: Traumaplant; ***Ital.***: Kytta; ***Port.***: Elas; ***Switz.***: Kytta Pommade; Symphosan†; Traumaplant; ***UK***: Comfrelieve; ***Venez.***: Traumaplant.

Multi-ingredient Preparations. ***Arg.***: Lavandula Oligoplex; ***Austral.***: Joint & Muscle Cream; ***Canad.***: Natraway Sport 1 & 2†; Natraway Sport 3†; ***Fr.***: Cicactive; Tigre de Chine; ***Ger.***: Kytta-Balsam f; Rhus-Rheuma-Gel N; ***Israel***: Comfrey Plus; ***S.Afr.***: Zeel; Zeel; ***Switz.***: DUL-X Cool; Gel de consoude†; Impuls a la consoude; Keppur; Keppur; Kytta Baume†; Perskindol Cool Consoude; ***Turk.***: Symphosan; ***Ukr.***: Perfectil Plus (Перфектил Плюс).

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Austria***: Osteoplex; Repisan; Steiroplex; Traumeel; Wirbelsaule- und Gelenkstropfen Nr 2†; ***Canad.***: Arnica + Pain Relief; Calendula Ointment†; Capsicum + Arthri-Cream; Traumeel; ***Chile***: Osteofix; ***Cz.***: Traumeel; Zeel Salbe†; ***Fr.***: Symphytum Complexe No 48†; ***Ger.***: Araniforce rheuma†; Arnica/Symphytum comp; Chirofossat; Infi-Symphytum; Infihepan; Infiossan; Odonton-Echtroplex; Osteoplex; Ruta-Gastreu N R55; Steirocall; Steiroplex†; Symphytum Rowo†; Traumeel S; ***Hung.***: Traumeel; Zeel; ***Neth.***: Arnilite; Homeocare Exercito; Kruidvat Homeopathie Spier- en gewrichtsgel†; Spiroflor; Traumeel H; Traumeel S; ***Rus.***: Repisan (Реписан); Rewma-Gel (Ревма-Гель); Traumeel S (Траумель С); Zeel T (Цель Т); ***S. Afr.***: Traumeel S; ***Switz.***: Contusin; Nelsons Traumatica†; Omida Gel Antirhumatismal; Regenaplex Nr. 88b; Traumeel; ***Ukr.***: Reuma-Gel (Ревма-Гель); Traumeel S (Траумель С); ***USA***: Traumeel; ***Venez.***: Traumeel.

Complement Blockers

Inhibidores del complemento; Блокаторы Комплемента.

Profile

Complement is a group of plasma and cellular proteins contributing to the innate immune system and is so called because it complements the microbicidal action of antibodies. The complement system is activated by the antigen-antibody complex followed by a cascade reaction of complement proteins culminating in microbial cell lysis. Complement also plays a part in many other physiological processes and regulatory mechanisms are in place to prevent inflammatory damage to host tissues through the inappropriate activation of complement. Hereditary or acquired abnormalities of the complement system are associated with a variety of disorders depending on which part of the system is affected, and include recurrent infections, partial lipodystrophy, hereditary angioedema, paroxysmal nocturnal haemoglobinuria, non-specific vasculitis, glomerulonephritis, cardiovascular disease, rheumatoid arthritis, sepsis, asthma, acute respiratory distress syndrome, psoriasis, SLE, bullous pemphigoid, discoid lupus, and graft survival after solid organ transplantation.

Several substances are used or are under investigation for their ability to block activation of the complement system:

- complement C1 esterase inhibitor (below) is given as replacement therapy in the treatment of hereditary angioedema
- eculizumab (p. 2499.1) is a monoclonal antibody that targets the terminal C5 protein of complement and is given in the treatment of paroxysmal nocturnal haemoglobinuria
- pexelizumab (p. 2587.2) is a similar substance under investigation in patients undergoing coronary artery revascularisation procedures
- mirococept (APT-070, SCR1-3) is a derivative of soluble complement receptor type 1 (SCR1) under investigation for the prevention of post transplantation graft dysfunction
- TP-10, a form of SCR1 has also been investigated for respiratory disorders
- myristoylated-peptidyl-recombinant human CD59 is under investigation for paroxysmal nocturnal haemoglobinuria

References.

1. Bhole D, Stahl GL. Therapeutic potential of targeting the complement cascade in critical care medicine. *Crit Care Med* 2003; **31** (suppl): S97–S104.
2. Brook E, *et al*. Opportunities for new therapies based on the natural regulators of complement activation. *Ann N Y Acad Sci* 2005; **1056:** 176–88.

Complement C1 Esterase Inhibitor

Factor de inhibición de la C1 esterasa; Inhibidor de la C1 esterasa; C1-Ингибитор Комплемента.

ATC — B06AC01.
ATC Vet — QB06AC01.
UNII — 6KIC4BB60G.

Conestat Alfa *(rINN)*

Conestatum alfa; rhC1INH; Конестат Альфа.

Human plasma protease C1 inhibitor (C1 esterase inhibitor) (*N,O*-glycosylated recombinant protein expressed in the mammary gland of transgenic rabbits), glycoform α.

CAS — 80295-38-1.
ATC — B06AC04.
ATC Vet — QB06AC04.
UNII — 5QS67N4551.

NOTE. The name Rhucin has been used as a trade mark for conestat alfa.

Uses and Administration

Complement C1 esterase inhibitor is an endogenous complement blocker (above) that plays a role in regulation of the complement system. It is prepared from human plasma and given as replacement therapy in hereditary angioedema (below), in which there is a deficiency of natural complement C1-esterase inhibitor. In the treatment of an acute attack, or for prophylaxis before surgical procedures, a dose of 20 units/kg is given by slow intravenous injection or infusion. Further doses may be necessary, according to patient response. For routine prophylaxis, a dose of 1000 units may be given once every 3 or 4 days. For doses used in children, see below.

Conestat alfa is recombinant human complement C1 esterase inhibitor used in the treatment of acute attacks in patients with hereditary angioedema. It is given by intravenous injection over about 5 minutes in a dose of 50 units/kg in patients weighing up to 84 kg, or for patients of 84 kg and over, in a dose of 4200 units. In most cases, one dose should be sufficient to arrest the attack but if required, a second dose of 50 units/kg up to a maximum of 4200 units may be given. No more than 2 doses should be given in 24 hours. Conestat alfa is also under investigation in the treatment of capillary leak syndrome, for the prevention of delayed graft function in organ transplantation, and as a means of limiting reperfusion injury in patients with acute myocardial infarction (below).

Administration in children. Complement C1 esterase inhibitor may be used in neonates, infants, and children for the treatment of acute attacks of hereditary angioedema, or as prophylaxis before surgical procedures. A dose of 20 units/kg is given by slow intravenous injection or infusion, and may be repeated according to patient response.

Hereditary angioedema. Hereditary angioedema, formerly known as hereditary angioneurotic oedema, is a rare autosomal dominant disease caused by either a deficiency of complement C1 esterase inhibitor or, more rarely, a lack of functioning inhibitor.[1-6] The disease presents as episodic attacks of oedema, usually of the extremities and face, and often involving the gastrointestinal mucosa producing abdominal pain. A non-pruritic rash may also occur. A few patients develop life-threatening laryngeal oedema. Attacks generally last about 1 to 3 days and may occur as frequently as weekly or there may be years between attacks. The first attack may occur at any age although initial presentation in childhood is most common. Trauma, especially dental surgery, illness, and emotional stress may provoke an attack although often there is no precipitating factor. Some medications such as ACE inhibitors or oestrogens found in hormonal contraceptives or HRT can act as triggers.

Treatment of the acute attack is essentially supportive. If laryngeal oedema is present adrenaline may be given (as for Anaphylaxis, p. 1293.2) even though patients with hereditary angioedema often fail to respond adequately; antihistamines and corticosteroids are generally considered to be ineffective. The mainstay of treatment of an acute attack is replacement therapy with complement C1 esterase inhibitor.[1-5] A recombinant form, conestat alfa, is also available.[6] Fresh frozen plasma has been used although there is a risk of initially exacerbating the oedema due to the presence of other complements in the plasma. Tracheostomy or tracheal intubation may be necessary. If complement C1 esterase inhibitor is not available, androgens or antifibrinolytics may be tried in higher doses than normally used for prophylaxis.[1,4] However, these generally have limited efficacy and are slow to act. More recently, ecallantide (an inhibitor of human plasma kallikrein) and icatibant acetate (a selective bradykinin B_2 antagonist) have become available for the treatment of acute attacks.[6]

Once the acute attack has subsided most patients will not require further treatment, but those who have life-threatening attacks, repeated episodes of swelling around the face or neck, or incapacitating attacks require long-term **prophylactic therapy**. A synthetic androgen (danazol or stanozolol) or an antifibrinolytic (aminocaproic acid or tranexamic acid) is effective for long-term prophylaxis.[1,2,4,5] Danazol and stanozolol raise serum concentrations of C1 esterase inhibitor possibly by enhancing its synthesis in the liver.[2] Aminocaproic acid and tranexamic acid may act by inhibiting plasmin activation.[7] A synthetic androgen is often preferred because these seem to be more effective than antifibrinolytics. In children, however, androgens are generally avoided because of their adverse effects. Nevertheless, they may be used in children, with close monitoring, when antifibrinolytics have been ineffective.[3] In some cases, long-term prophylaxis with once or twice weekly C1 esterase inhibitor may be indicated for adults when antifibrinolytics and androgens are ineffective, not tolerated, or contra-indicated.[2,4,6]

Short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental work.[2-5] Complement C1 esterase inhibitor is usually given 1 hour before the procedure, or fresh frozen plasma may be used if this is not available. Alternatively, a synthetic androgen or antifibrinolytic may be used, but these must be started several days before the procedure and continued for 2 days after.

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.
2. Gompels MM, *et al*. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]
3. Farkas H, *et al*. Management of hereditary angioedema in pediatric patients. Abstract: *Pediatrics* 2007; **120:** 635. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/3/e713 (accessed 10/12/09)
4. Bowen T, *et al*. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008; **100** (suppl 2): S30–S40.
5. Zuraw BL. Hereditary angioedema. *N Engl J Med* 2008; **359:** 1027–36.
6. Epstein TG, Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs* 2008; **68:** 2561–73.
7. Ritchie BC. Protease inhibitors in the treatment of hereditary angioedema. *Transfus Apheresis Sci* 2003; **29:** 259–67.

Myocardial infarction. Complement C1 esterase inhibitor is being studied as a means of limiting reperfusion injury in patients with acute myocardial infarction.[1-3]

1. de Zwaan C, *et al*. Continuous 48-h C1-inhibitor treatment, following reperfusion therapy, in patients with acute myocardial infarction. *Eur Heart J* 2002; **23:** 1670–7.
2. Thielmann M, *et al*. Administration of C1-esterase inhibitor during emergency coronary artery bypass surgery in acute ST-elevation myocardial infarction. *Eur J Cardiothorac Surg* 2006; **30:** 285–93.
3. Fattouch K, *et al*. Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: a randomised double-blind study. *Eur J Cardiothorac Surg* 2007; **32:** 326–32.

Adverse Effects and Precautions

There have been rare reports of hypersensitivity reactions, including urticaria, wheezing, and anaphylaxis, in patients given complement C1 esterase inhibitor, including conestat alfa Headache, chills, fever, and injection site reactions including redness and pain have also occurred. Thrombosis was reported in studies using doses of complement C1 esterase inhibitor higher than those licensed for hereditary angioedema.

As for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

Conestat alfa is derived from the milk of transgenic rabbits and patients should be tested for the presence of IgE antibodies against rabbit allergens. Treatment may only be started if the results are negative, and the test should be repeated once each year during treatment, or after 10 treatments, whichever occurs first.

Pharmacokinetics

In patients with hereditary angioedema, the half-life reported after intravenous injection of complement C1 esterase inhibitor during an attack-free period ranges from about 20 to 60 hours, depending on the preparation. It is slightly shorter in children and in patients with severe attacks.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Berinert P; ***Austral.***: Berinert; ***Austria***: Berinert; ***Belg.***: Berinert; ***Canad.***: Berinert; ***Cz.***: Berinert; Ruconest; ***Denm.***: Berinert; Cinryze; Ruconest; ***Fin.***: Berinert; Cebitor; ***Fr.***: Berinert; Ruconest; ***Ger.***: Berinert; Cinryze; Ruconest; ***Gr.***: Berinert; ***Hung.***: Berinert P; ***Irl.***: Cinryze; Ruconest; ***Israel***: Berinert; ***Neth.***: Berinert; Cetor; Cinryze; Ruconest; ***Norw.***: Berinert; Cinryze; Ruconest; ***Pol.***: Ruconest; ***Port.***: Berinert; Ruconest; ***Spain***: Berinert; Cinryze; ***Swed.***: Berinert; Ruconest; ***Switz.***: Berinert; ***Turk.***: Cetor; ***UK***: Berinert; Cinryze; Ruconest; ***USA***: Berinert; Cinryze.

Condurango

Condurango Bark; Condurango cortex; Condurango, écorce de; Eagle-vine Bark; Кондуранго.

ATC Herb — HA09WA5017 (Marsdenia cundurango: *bark*).
UNII — R23QIR6YBA.

Pharmacopoeias. In *Jpn* and *Swiss*.

Profile

Condurango, the dried stem bark of *Marsdenia condurango* (*Gonolobus condurango*) (Asclepiadaceae), has been used as a bitter.

Homoeopathy

Condurango has been used in homoeopathic medicines under the following names: Marsdenia cundurango; Cond.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Sigman-Haustropfen; ***Braz.***: Camomila; ***Ger.***: Pascopankreat; ***Hung.***: Kilo-Nit; ***Pol.***: Herbaton†; ***Switz.***: Kernosan 26; Padma-Lax; Padmed Laxan; Stomacine.

Homoeopathic Preparations. ***Austria***: Lymphdiaral; ***Fr.***: Gastro-Drainol†; Hydrastis Compose; Nux Vomica Compose; ***Ger.***: Antimas†; Flenin; Hewesoor N†; Juv 110; Lowe-Komplex Nr 6; Mucosa compositum; ***Neth.***: Lymphdiaral; ***USA***: Preferred Remedies Antacid.

Congo Red

CI Direct Red 28; Colour Index No. 22120; Czerwień Kongo; Rojo Congo; Rubrum Congoensis; Конго Красный.

Disodium 3,3′-[biphenyl-4,4′-diylbis(azo)]bis[4-aminonaphthalene-1-sulphonate].

$C_{32}H_{22}N_6Na_2O_6S_2$=696.7

CAS — 573-58-0.
UNII — 3U05FHG59S.

Profile

Congo red is used as a stain in the diagnosis of amyloidosis. It causes amyloid in tissue samples to fluoresce under polarised light.

Conivaptan Hydrochloride (rINNM) ⊗

CI-1025; Conivaptan, Chlorhydrate de; Conivaptán, hidrocloruro de; Conivaptani Hydrochloridum; YM-087 (conivaptan or conivaptan hydrochloride); Конивантана Гидрохлорид.

4″-[(4,5-Dihydro-2-methylimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]-2-biphenylcarboxanilide hydrochloride.

$C_{32}H_{26}N_4O_2$,HCl=535.0

CAS — 210101-16-9 (conivaptan); 168626-94-6 (conivaptan hydrochloride).

ATC — C03XA02.

ATC Vet — QC03XA02.

UNII — 75L57R6X36.

Uses and Administration

Conivaptan hydrochloride is a vasopressin V_{1a} and V_2 receptor antagonist. In the management of hyponatraemia it acts mainly at V_2 receptors in the renal collecting ducts to increase the excretion of free water. It is used to treat euvolaemic and hypervolaemic hyponatraemia (p. 1778.1). It has also been studied for heart failure, but safety has not been established and it should only be used if the benefits outweigh the risks.

Conivaptan hydrochloride is given by intravenous infusion. To minimise infusion site irritation, it should be diluted in glucose 5% infusion and given through a large vein; the infusion site should be changed every 24 hours. A loading dose of 20 mg is given over 30 minutes, followed by a continuous infusion of 20 mg over 24 hours. Treatment may be continued at a dose of 20 mg daily for 1 to 3 days titrated to a maximum of 40 mg daily if required. The maximum duration of the infusion is 4 days. If a rapid rise in serum-sodium occurs (more than 12 mmol/litre in 24 hours) conivaptan should be stopped, and serum-sodium and neurological status should be carefully monitored because of the risk of osmotic demyelination syndrome. If hypovolaemia or hypotension develop, conivaptan should be stopped and volume status and vital signs should be monitored. Conivaptan may be resumed at a lower dose, if still indicated, when the rise in serum-sodium has stopped, if there is no evidence of adverse neurological effects and the patient is euvolaemic and no longer hypotensive. For dosage reductions in hepatic and renal impairment, see below.

References.

1. Walter KA. Conivaptan: new treatment for hyponatremia. *Am J Health-Syst Pharm* 2007; **64:** 1385–95.

Administration in hepatic impairment. In patients with hepatic impairment (Child-Pugh Class A, B, or C), conivaptan should be given intravenously in an initial loading dose of 10 mg followed by a continuous infusion of 10 mg over 24 hours for 2 to 4 days. If serum sodium does not rise at the desired rate, the dose may be titrated upwards to 20 mg over 24 hours.

Administration in renal impairment. In patients with moderate renal impairment (creatinine clearance 30 to 60 mL/min) conivaptan should be given intravenously in an initial loading dose of 10 mg followed by a continuous infusion of 10 mg over 24 hours for 2 to 4 days. If serum sodium does not rise at the desired rate, the dose may be titrated upwards to 20 mg over 24 hours. Conivaptan is not recommended in patients with severe renal impairment or anuria (see below).

Adverse Effects and Precautions

The most common adverse effects of conivaptan are infusion site reactions such as erythema, pain, phlebitis, and swelling, which are usually mild but can be severe enough in some patients that infusion must be stopped. Other adverse effects include atrial fibrillation, gastrointestinal disturbances, pyrexia, thirst, electrolyte disturbances, headache, and hypertension or hypotension.

Conivaptan is contra-indicated in hypovolaemic hyponatraemia, and is not indicated for the treatment of patients with congestive heart failure. Rapid correction of serum-sodium concentrations with conivaptan could increase the risk of osmotic demyelination syndrome. Conivaptan should be used with caution in hepatic or renal impairment because systemic exposure can be increased. It is not recommended at all in patients with severe renal impairment or those who are anuric because of unlikely benefit.

Interactions

As a substrate of the cytochrome P450 isoenzyme CYP3A4, concentrations of conivaptan can be increased by CYP3A4 inhibitors. The use of conivaptan with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contra-indicated. Conivaptan itself is also a potent inhibitor of CYP3A4 and may increase the concentrations of other substrates of this isoenzyme, including amlodipine, midazolam, and simvastatin.

For the effect of conivaptan on digoxin, see p. 1358.1.

Pharmacokinetics

Conivaptan is metabolised by the cytochrome P450 isoenzyme CYP3A4, but inhibits its own metabolism. Using a regimen of intravenous loading dose followed by continuous infusion, concentrations of conivaptan initially decrease from the loading dose peak over about 12 hours, then gradually increase. After stopping the infusion, conivaptan has an elimination half-life of about 5 hours. Conivaptan is highly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Vaprisol.

Convallaria

Convalaria; Convallariae Herba; Lily of the Valley; Lirio Convalio; Lirio de los Valles; Maiblume; Maiglöckchenkraut; May Lily; Muguet; Mugueta; Muguete; Ziele konwalii; Ландыш.

CAS — 3253-62-1 (convallatoxol); 13473-51-3 (convalloside); 13289-19-5 (convallatoxoloside); 508-75-8 (convallatoxin).

ATC Herb — HC01AX5002 (Convallaria majalis: *herb).*

UNII — 4R8IGU6CQ3 (Convallaria majalis*); 261W7X975U* (Convallaria majalis *bulb); T84WVY4I0G* (Convallaria majalis *flower); QHH4HVF5QE* (Convallaria majalis *flowering); 4G7VTP9FC4* (Convallaria majalis *flowering top).*

Pharmacopoeias. In *Ger.* and *Pol.* (from *C. majalis*or closely related species).

Profile

Convallaria consists of the dried flowers, herb, or the rhizomes and roots of lily of the valley, *Convallaria majalis* (Liliaceae). Several crystalline glycosides have been obtained from the plant including convallarin, convalloside, convallatoxoloside, and convallatoxin.

Convallaria contains cardiac glycosides and has actions on the heart similar to those of digoxin (p. 1353.3). Convallaria is used in herbal medicine.

Homoeopathy

Convallaria has been used in homoeopathic medicines under the following names: Convallaria majalis; Conval. m.

Convallaria majalis has been designated unsafe for inclusion in foods, beverages, or drugs by the FDA in the USA.[1]

1. Larkin T. *FDA Consumer* 1983; **17**(Oct.): 5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Convafort; ***Ukr.***: Corglycon (Коргликон).

Multi-ingredient Preparations. ***Arg.***: Passacanthine; ***Ger.***: Miroton†; ***Mex.***: Verisan Triplex; ***Pol.***: Cardiol C; Kelicardina; Neocardina; ***Rus.***: Carniland (Карниланд); Valocormid (Валокормид); Zelenin (Зеленин).

Homoeopathic Preparations. ***Austria***: Aurumheel; Homviocorin; Pumpan; ***Canad.***: Aurumheel†; ***Ger.***: Angioton H; Angioton S†; Asthmavowen-N†; Cardioject; Confludin N; Conva-cyl Ho-Len-Complex; Convallocor; Convallysan M; Convastabil; Cor Plus; Cor-loges; Goldtropfen S; HanoCor N; Homviocorin spezial; Infi-Camphora; Lowe-Komplex Nr 10; Lowe-Komplex Nr 13; Naranocor HM; Roth's Rotacard; Schworocard; Steicardin N†; ***Hung.***: Aurumheel; ***Rus.***: Pumpan (Пумпан); ***Switz.***: Gouttes d'Or; ***Ukr.***: Aurocard (Аурокард); Homviocorin-N (Хомвиокорин-N); Pumpan (Пумпан).

Copper Acetate

Cuivre, acétate de; Cupri acetas; Cupric Acetate; Kopparacetat; Kuparisetaatti; Miedzi(II) octan; Vario acetatas; Ацетат Меди; Уксуснокислая Медь.

$(C_2H_3O_2)_2Cu,H_2O$=199.6

CAS — 142-71-2 (anhydrous).

UNII — 39M11XPH03.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Copper Acetate Monohydrate for Homoeopathic Preparations; Cupri Acetas Monohydricus ad Praeparationes Homoeopathicas). Greenish-blue crystals or green powder. Soluble in water; slightly soluble or very slightly soluble in alcohol.

Profile

Copper acetate has been used in a variety of dermatological preparations. It is now more usually used complexed with a tripeptide in the form of prezatide copper acetate (p. 1718.1). This acts as a source of ionic copper, which is needed by lysyl oxidase, a copper-dependent enzyme that has a crucial role in the crosslinking of collagen and elastin. For the nutritional and other uses of copper and its salts, see p. 2057.2.

Homoeopathy

Copper acetate has been used in homoeopathic medicines under the following names: Cuprum aceticum; Cuprum acet; Cup. acet.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Verel; ***Mex.***: Emplasto Monopolis.

Homoeopathic Preparations. ***Austria***: Dalektro; Gripagil Husten- und Bronchialtropfen; ***Canad.***: Drosera Homaccord; Homeo-Form I†; Husteel†; Insomnia; Pertudoron 2†; Spascupreel; ***Cz.***: Husteel; ***Fr.***: Amanita Complexe No 75; Cina Complexe No 55†; Drosera Complexe No 64; Geranium Complexe No 108†; Lobelia Complexe No 74†; Momordica Complexe No 109†; Nervopax; Oenanthe Crocata Complexe No 78; Pulsatilla Complexe No 60†; Rhododendron Complexe No 42†; Zincum Cyanidum Complexe No 101†; ***Ger.***: Bomapect N; Cocculus Oligoplex; Jutussin; Pertudoron 2; Presselin All; Pulmosan; Vasa-Gastreu N R63; Viropect; ***Hung.***: Husteel; ***Neth.***: Homeocare Nervo; Husteel; Jutussin R9; Neurovita; ***Switz.***: Regenaplex Nr. 12; Regenaplex Nr. 24b.

Corbadrine (rINN) ⊗

Corbadrina; Corbadrinum; *l*-3,4-Dihydroxynorephedrine; Levonordefrin; *l*-Nordefrin; Корбадрин.

(-)-2-Amino-1-(3,4-dihydroxyphenyl)propan-1-ol.

$C_9H_{13}NO_3$=183.2

CAS — 829-74-3 (corbadrine); 6539-57-7 (nordefrin); 61-96-1 (nordefrin hydrochloride).

UNII — V008L6478D.

Pharmacopoeias. In *US.*

USP 36: (Levonordefrin). A white to buff-coloured, odourless, crystalline solid. Practically insoluble in water; slightly soluble in alcohol, in acetone, in chloroform, and in ether; freely soluble in aqueous solutions of mineral acids.

Profile

Corbadrine is a sympathomimetic (p. 1507.3) that has been added to local anaesthetic preparations in dentistry to diminish absorption and to localise the effect; a concentration of 1 in 20 000 has been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations.

Used as an adjunct in:. ***Canad.***: Isocaine; Polocaine; Scandonest; ***S.Afr.***: Carbocaine; ***USA***: Carbocaine with Neo-Cobefrin; Isocaine; Polocaine; Scandonest.

Pharmacopoeial Preparations

USP 36: Mepivacaine Hydrochloride and Levonordefrin Injection; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection.

Coriander

Chinese Parsley; Coentro; Coriand.; Coriander Fruit; Coriander Seed; Coriandre; Coriandri Fructus; Coriandro; Fruto del cilantro; Kalendrų vaisiai; Koriander; Koriandertermés; Koriandrový plod; Korianteri; Owoc kolendry; Perejil chino; Кориандр.

ATC Herb — HA03AW5019 (Coriandrum sativum: *fruit).*

UNII — 1OV56052IK.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Coriander). The dried cremocarp of *Coriandrum sativum*, containing not less than 0.3% v/w of essential oil,

calculated with reference to the dried substance. Protect from light.

The BP 2014 directs that when Powdered Coriander is prescribed or demanded material containing not less than 0.2% v/w of essential oil shall be dispensed or supplied.

Profile

Coriander is the source of coriander oil (below). It is a carminative and is used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Salutaris.

Multi-ingredient Preparations. ***Arg.***: Wunderbalsam; ***Austria***: Brady's-Magentropfen; Mariazeller; Planta Lax; ***Belg.***: Eau Des Carmes; ***Braz.***: Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; ***Canad.***: Digestol; Floradix Kindervital†; Formula T4†; ***Fr.***: Azema†; Calmiflorine†; Mediflor Digestive No 3; Tisane Provencale no 5†; ***Ger.***: Floradix Multipretten N; ***Gr.***: Tamarine; ***Hung.***: Babynos; Menofit; Salus Multipretten; Tamarinlax; ***India***: Alka; Britesite; Gasex; Livomyn; Livomyn; ***Ital.***: Cadifen; Cadimint; Dicalmir; Tamarine; ***Mex.***: MD Lax; Naturetti; ***Pol.***: Cholesol; Diges-Tonic; ***Rus.***: Babynos (Бебинос); Cedoflor (Седофлор); Evalar (Эвалар); Kliophyt (Клиофит); Phytohepatol No 2 (Фитогепатол 2); Proctophytol (Проктофитол); Sodecor (Содекор); ***S.Afr.***: Melissengeist†; Spiritus Contra Tussim Drops†; ***Spain***: Agua del Carmen; Jarabe Manceau; Pruina; ***Swed.***: Multipretten; ***Switz.***: Femisan; ***UK***: Melissa Comp.; ***Ukr.***: Вол-Апетит (Бон-Аппетит); Carminativum Babynos (Карминативум Бебинос); Intellan (Интеллан).

Homoeopathic Preparations. ***Fr.***: Poconeol no 27; ***UK***: Cough Drops.

Coriander Oil

Cilantro, aceite esencial de; Coriandre, huile essentielle de; Coriandri Aetheroleum; Coriandri Etheroleum; Kalendrų eterinis aliejus; Koriander öl; Korianderolja; Koriandrová silice; Koriantеriöljy; Ol. Coriand; Oleum Coriandri; Кориандровое Масло.

*ATC Herb — HA03AW501B (*Coriandrum sativum*: essential oil).*
UNII — 7626GC95E5.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. & (Coriander Oil). An essential oil obtained by steam distillation from the fruits of *Coriandrum sativum*. A clear colourless or pale yellow liquid, with the characteristic spicy odour. It contains not less than 65% and not more than 78% of linalol. Relative density 0.860 to 0.880. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Coriander Oil). The volatile oil obtained by steam distillation from coriander. Specific gravity 0.863 to 0.875. Soluble 1 in 3 of alcohol (70%). Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Coriander oil is aromatic and carminative and is used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Floradix Multipretten N; Gastrysat†; ***Hung.***: Salus Multipretten; ***India***: Niltan; ***Ital.***: Valda Propoli†; ***Pol.***: Argol Essenza Balsamica; Argol Grip; Argol Rheuma; ***Rus.***: Espol (Эспол); ***Swed.***: Multipretten.

Pharmacopoeial Preparations
BP 2014: Compound Orange Spirit; Compound Rhubarb Tincture;
USNF 31: Compound Orange Spirit.

Corn Silk

Barbas de Elote; Maíz, barba del; Stigma Maydis; Zea; Кукурузные Столбики С Рыльцами.

*ATC Herb — HG04BW5043 (*Zea mays*: style).*
UNII — 7D3VB244UX.

Pharmacopoeias. In *Fr.*

Profile

Corn silk, the stigma and style of maize (*Zea mays*) (Gramineae), has diuretic properties and is used for urinary-tract disorders including renal calculi.

Maize is widely used as a food and has also been used in herbal medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Insadol†; ***Rus.***: Insadol (Инсадол); ***Switz.***: Insadol†; ***UK***: Protat.

Multi-ingredient Preparations. ***Austral.***: Althaea Complex†; ***Canad.***: Saw Palmetto Formula†; ***Fr.***: Alpha Renol; Urotisan†; ***Hung.***: Zeatax; ***Pol.***: Neopoldanen†; ***Spain***: Diurinat; ***UK***: Elixir Damiana and Saw Palmetto; ***Ukr.***: Urochol (Урохол)†; Urocran (Урокран).

Couch-grass

Agropyron; Chiendent; Chiendent, rhizome de; Dogs Grass; Grama; Grama del norte; Graminis rhizoma; Juolavehnänjuurakko; Kłącze perzu; Kvickrot; Pýrový oddenek; Quackgrass; Tarackbúza-gyökértörzs; Triticum; Twitch; Varpučių šakniastiebiai; Пырей Ползучий.

*ATC Herb — HG04BW5010 (*Elymus repens*: rhizome); HR05WA5007 (*Elymus repens*: rhizome).*
UNII — 8K1MK5E1FY.

NOTE. Distinguish from Wheat, *Triticum aestivum* (see p. 2647.1).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Couch Grass Rhizome). The whole or cut, washed and dried rhizome of *Agropyron repens* (*Elymus repens*); the adventitious roots are removed. Protect from light.

Profile

Couch-grass is a mild diuretic that has been used in herbal medicine in the treatment of urinary-tract disorders. It contains glucose, mannitol, inositol, and triticin (a carbohydrate resembling inulin). The Latin binomials *Elytrigia repens* and *Triticum repens* have also been applied to couch-grass.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Urophyton; ***Indon.***: Renalof.

Multi-ingredient Preparations. ***Belg.***: Herbesan; ***Canad.***: Bio Renal†; Floradix Tab†; ***Fr.***: Alpha Renol; Drainuryl; Fibromyalgine; Herbesan; Hydrastart; Mediflor Diuretique No 4†; Obeflorine†; Tisane D'Ars†; Tisane de Sante†; Tisane Hepatique de Hoerdt†; Urotisan†; ***Ger.***: Hevert-Blasen-Nieren-Tee N†; Renob Blasen- und Nierentee†; ***Hung.***: Menofit; ***Ital.***: Cistefi; Emmenoiasi; Litostop; Tisana Kelemata; ***Neth.***: Herbesan†; ***Pol.***: Dentosept; Diabetofort; Diabetosol; Laxantol†; NeoFitolizyna†; ***Spain***: Diurinat; ***UK***: Antitis; Kas-Bah.

Homoeopathic Preparations. ***Fr.***: Poconeol no 57; Poconeol no 79; ***Ger.***: Urofossat.

Coumarin

1,2-Benzopyrone; 5,6-Benzo-α-pyrone; Cumarin; Cumarina; Kumaryna; Tonka Bean Camphor; Кумарин.

2*H*-1-Benzopyran-2-one.
$C_9H_6O_2$=146.1
CAS — 91-64-5.
UNII — A4VZ22K1WT.

Pharmacopoeias. In *Ger.*

Profile

Coumarin is the odorous principle of Tonka seed (Tonka or Tonquin bean); it may be prepared synthetically. Coumarin has been given to reduce excess tissue protein and associated fluid in the treatment of lymphoedema (see below). It has also been used as a fixative in perfumery and as a flavour. It is reported to be an immunostimulant and has been tried in the treatment of malignant neoplasms.

Coumarin derivatives are used as anticoagulants; coumarin itself is not an active anticoagulant.

Effects on the liver. Coumarin has been classified as hepatotoxic based on studies in *animals* and effects ranging from elevated liver enzymes to serious organ damage has been reported in humans. Seventeen of 2173 patients enrolled in a study of coumarin developed elevated liver enzyme values;[1] the majority of patients were given 100 mg coumarin daily for 1 month followed by 50 mg daily for 2 years. However, none of the patients developed permanent liver damage and liver enzyme values returned to normal in 5 patients who continued taking coumarin. Results from 5 studies supported by the Lymphoedema Association of Australia, in which patients received 400 mg daily for a mean duration of 14.6 months, showed 2 cases of hepatotoxicity among 1106 patients.[2] In the period of 14 months up to May 1995, the Australian Drug Evaluation Committee received 10 reports of suspected adverse reactions to coumarin,[3] including 6 cases of jaundice in women who had taken 400 mg daily for 1 to 4 months. Periportal and lobular necrosis were found on biopsy in 1 case and another had a fatal outcome due to massive hepatic necrosis.

Reports of hepatotoxicity have led to the withdrawal of coumarin in several countries.

1. Cox D, *et al.* The rarity of liver toxicity in patients treated with coumarin (1,2-benzopyrone). *Hum Toxicol* 1989; **8:** 501–6.
2. Casley-Smith JR, Casley-Smith JR. Frequency of coumarin hepatotoxicity. *Med J Aust* 1995; **162:** 391.
3. Anonymous. Lodema and the liver. *Aust Adverse Drug React Bull* 1995; **14:** 11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/07/08)

Lymphoedema. Benzopyrones such as coumarin are reported to reduce excess protein in tissues with high-protein oedema, hence the use of coumarin in lymphoedema of various causes, including postmastectomy, and filarial lymphoedema and elephantiasis.[1-5] Evidence for its efficacy is, however, conflicting;[4-6] at best the action is slow and treatment may need to be given for 6 months to 2 years before any benefit is seen.

1. Jamal S, *et al.* The effects of 5,6 benzo-[a]-pyrone (coumarin) and DEC on filaritic lymphoedema and elephantiasis in India: preliminary results. *Ann Trop Med Parasitol* 1989; **83:** 287–90.
2. Turner CS. Congenital lymphedema. *J AMA* 1990; **264:** 518.
3. Casley-Smith JR, *et al.* Treatment of lymphedema of the arms and legs with 5,6-benzo-[α]-pyrone. *N Engl J Med* 1993; **329:** 1158–63.
4. Casley-Smith JR, *et al.* Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-α-pyrone (coumarin). *BMJ* 1993; **307:** 1037–41.
5. Casley-Smith JR. Benzo-pyrones in the treatment of lymphoedema. *Int Angiol* 1999; **18:** 31–41.
6. Loprinzi CL, *et al.* Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med* 1999; **340:** 346–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Esberiven; ***Ital.***: Linfovenodren†.

Multi-ingredient Preparations. ***Arg.***: Esberiven; Microsuy; ***Braz.***: Angiolot; Varicoss; Venalot H; Venalot; ***Ger.***: Venalot†; ***Ital.***: Flebolider; ***Mex.***: Venalot.

Homoeopathic Preparations. ***Switz.***: Regenaplex Nr. 24b.

Coutarea Latiflora

Copalchi.

*ATC Herb — HG04BW5014 (*Hintonia latiflora*: bark); HA09WA5014 (*Hintonia latiflora*: bark); HA10BX5003 (*Hintonia latiflora*: bark); HN02BG5006 (*Hintonia latiflora*: bark).*

NOTE. The name copalchi has also been applied to *Croton niveus* (Euphorbiaceae).

Uses and Administration

Coutarea latiflora (*Hintonia latiflora*) is an ingredient of herbal remedies used in the management of diabetes mellitus.

Adverse Effects

For a report of hepatotoxicity associated with a preparation containing *Coutarea latiflora* see Centaury, p. 2473.2.

Rhabdomyolysis. Rhabdomyolysis and haemolysis occurred in a 58-year-old man 2 days after starting treatment with *Coutarea latiflora*.[1] The patient had a similar reaction 4 years earlier after taking the same product.

1. Roca B. Rhabdomyolysis and hemolysis after use of Coutarea latiflora. *Am J Med* 2003; **115:** 677.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Sucontral†.

Cowberry

Alpine Cranberry; Arándano rojo; Liść brusznicy (leaf); Mirtilo rojo; Red Whortleberry; Vitis Idaeae Folium (leaf); Брусника.

Pharmacopoeias. In *Pol.*

Profile

The leaves of the cowberry, *Vaccinium vitis-idaea* (Ericaceae), have astringent properties and have been used as a domestic remedy for diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Pol.***: Diuronis; Urosan†; ***USA***: Prenate AM with Quatrefolic.

CR Gas

EA-3547; Gas CR.
Dibenz[*b,f*][1,4]oxazepine.
$C_{13}H_9NO$=195.2
CAS — 257-07-8.

Profile

A riot-control gas with irritant and lachrymatory properties similar to those of CS gas (p. 2489.1); it is described as a tear gas. CR gas is reported not to be hydrolysed by water and therefore to be suitable for use in water cannons.

References.
1. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; **22:** 103–10.
2. Carron PN, Yersin B. Management of the effects of exposure to tear gas. *BMJ* 2009; **338:** 1554–8.

Cranberry

Arándano; Клюква.
UNII — 0MVO31Q3QS.

Pharmacopoeias. *US* includes a liquid preparation.

USP 36: (Cranberry Liquid Preparation). The bright red juice derived from the fruits of *Vaccinium macrocarpon* or *V. oxycoccos* (Ericaceae). It contains no added substances and is for manufacturing purposes only. pH between 2.4 and 2.6. Store at 2 degrees to 8 degrees.

Uses and Administration

Cranberry consists of the fruit of *Vaccinium macrocarpon*, the American cranberry or *V. oxycoccus*, the European cranberry. Cranberry juice has been reported to reduce the incidence of urinary-tract infections.

Urinary-tract infections. Cranberries and cranberry juice have been used widely for many years for both the prevention and treatment of urinary-tract infections. A systematic review[1] of available data concluded that there was some evidence that cranberry juice for prevention may decrease the number of symptomatic urinary-tract infections in women over a 12 month period, particularly those with recurrent infections. However, evidence for efficacy in the elderly is inconclusive, and currently lacking in patients with neurogenic bladder. The authors recommended further controlled studies in all susceptible patient groups, and also into more acceptable dosage formulations. However, another such review[2] assessing the efficacy of cranberry for treatment concluded that there was no good quality evidence to suggest that it is effective.

The mechanism of action of cranberry in preventing urinary-tract infections appears to be through inhibition of adhesion of uropathogens such as *Escherichia coli* to urinary-tract mucosa, thus reducing bacterial colonisation. There is reasonable evidence that this is due to its content of anthocyanidins and proanthocyanidins.[3]

1. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 02/12/09).
2. Jepson RG, *et al*. Cranberries for treating urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 02/12/09).
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Interactions

For reports of interactions between cranberry juice and *warfarin*, see p. 1533.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Urosedac; ***Chile***: Gelcive; ***Fr.***: Cys Control; GynDelta; Uriform; ***India***: Cranbe; ***Ital.***: Cistiflux; Ivumir; ***Singapore***: Seven Seas Cranberry Forte.

Multi-ingredient Preparations. ***Arg.***: Aulis; Uridon; Urosedac Probiotic; ***Austral.***: Advanced Urinary Tract Care; Cranberry 10,000; Cranberry Complex†; Cranberry Complex; Cranbiotic Super†; Extralife Uri-Care†; Flavonoid Complex; ***Canad.***: Prostease; ***Fr.***: Acyprost; Duab; Feminabiane Confort Urinaire; GynDelta PRIM; Gynelys; Prostaform; ***Hong Kong***: Prostease; ***Ital.***: Cistefi; Litostop; Rubis; ***Pol.***: Diabetosol; Urosept; ***Rus.***: Evalar (Эвалар); Urokam (Урокам); ***Ukr.***: Ektis (Эктис); Lekran (Лекран); Nephrocare (Нефрокеа); Uro-Control (Уро-Контрол); Urocran (Урокран); ***Venez.***: Diamel; Optibiol.

Crataegus

Aubépine; Aubépine, baie d' (hawthorn berries); Aubépine, feuille et fleur d' (hawthorn leaf and flowers); Biancospino; Calabrice; Crataegi folium cum flore (hawthorn leaf and flowers); Crataegi fructus (hawthorn berries); Crataegi Inflorescentia (hawthorn leaf and flowers); English Hawthorn; Espinalbo; Espino albar; Espino blanco; Galagonyatermés (hawthorn berries); Gudobelių vaisiai (hawthorn berries); Hagtornsbär (hawthorn berries); Haw; Hlohový plod (hawthorn berries); Kwiatostan głogu (hawthorn leaf and flowers); May; Mehlbeerbaum; Orapihlajanmarja (hawthorn berries); Owoc głogu (hawthorn berries); Pilriteiro; Weissdorn; Whitethorn; Боярышник.
ATC — C01EB04.
ATC Vet — QC01EB04.
*ATC Herb — HC01EB5008 (*Crataegus monogyna*; flower); HC01EB5004 (*Crataegus laevigata*; leaf); HC01EB5003 (*Crataegus laevigata*; fruit); HC01EB5002 (*Crataegus laevigata*; flower); HC01EB5012 (*Crataegus monogyna*; leaf with flower with fruit); HC01EB5010 (*Crataegus monogyna*; leaf); HC01EB5013 (*Crataegus monogyna*; leaf with fruit); HC01EB5009 (*Crataegus monogyna*; fruit); HC01EB5011 (*Crataegus monogyna*; leaf with flower); HC01EB5007 (*Crataegus laevigata*; leaf with fruit); HC01EB5006 (*Crataegus laevigata*; leaf with flower with fruit); HC01EB5005 (*Crataegus laevigata*; leaf with flower).*
UNII — 6OM09RPY36 (hawthorn leaf with flower); Q21UUL2105 (crataegus fruit).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Hawthorn Berries; Crataegi Fructus). The dried false fruits of *Crataegus oxyacantha* (*C. laevigata*), or *C. monogyna*, or their hybrids or a mixture of these false fruits. They contain not less than 0.06% of procyanidins, calculated as cyanidin chloride ($C_{15}H_{11}ClO_6$ = 322.7) with reference to the dried drug.

Ph. Eur. 8: (Hawthorn Leaf and Flower; Crataegi Folium cum Flore). The whole or cut, dried flower bearing branches of *Crataegus oxyacantha* (*C. laevigata*), or *C. monogyna*, or their hybrids or, more rarely, other European *Crataegus* species including *C. pentagyna*, *C. nigra*, and *C. azarolus*. It contains not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug.

USP 36: (Hawthorn Leaf with Flower). The dried tips of the flower-bearing branches up to 7 cm in length of *Crataegus monogyna* or *C. laevigata*, also known as *C. oxyacantha* (Rosaceae). It contains not less than 0.6% of *C*-glycosylated flavones, expressed as vitexin ($C_{21}H_{20}O_{10}$ = 432.4), and not less than 0.45% of *C*-glycosylated flavones, expressed as hyperoside, calculated with reference to the dried drug. Protect from light.

Profile

Crataegus contains flavonoid glycosides with cardiotonic properties similar to those of digoxin (p. 1353.3). Crataegus is used in herbal medicine.

Homoeopathy

Crataegus has been used in homoeopathic medicines under the following names: Crataegus oxyacantha; Crat. oxy.

Crataegus is used in herbal medicine for cardiovascular disorders.[1-6] A systematic review[5] of controlled studies concluded that it shows significant benefit compared with placebo as an adjunctive treatment for chronic heart failure. However, results from a large randomised, double-blind, placebo-controlled, multicentre study (the SPICE trial) involving 2681 patients showed that a crataegus extract used as adjunctive treatment for heart failure had no significant effect on measures of primary outcome defined as a composite of cardiac death, non-fatal myocardial infarction, and hospitalisation due to progressive heart failure, although it might reduce sudden cardiac death in patients with left ventricular ejection fraction between 25 and 35%.[6] Crataegus is rarely associated with serious adverse affects, although the authors of another systematic review[4] noted that problems may occur with its unsupervised use, especially if given with other drugs.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bericard; Crataefortan; Crataegan; Crataegutt; ***Belg.***: Aubeline; ***Braz.***: Dekatin; ***Chile***: Cratenox; ***Cz.***: Caj z Hlohu; Hloh†; ***Fr.***: Aubeline†; Cardiocalm; ***Ger.***: Ardeycordal mono; Born†; Chronocard N; Cordapur Novo†; Craegium†; Cratae-Loges; Crataegutt; Dr Niedermaier Herztonikum†; Esbericard novo; Faros; Koro-Nyhadin; Natucor; Orthangin novo†; Oxacant-mono; Protecor Herz-Schutz†; Protecor novo†; Regulacor-POS†; Septacord mono†; Stenocrat mono; ***Pol.***: Cardiplant; Chronocard; Cratonic; ***Rus.***: Doppelherz Cardiovital (Доппельгерц Кардиовитал); Novo-Passit (Ново-Пассит); Phytorelax (Фиторелакс); ***Singapore***: Crataegutt†; ***Switz.***: Cardiodyn; Cardiplant; Crataegisan; Crataegitan; Faros; Kardionin; Vitacor; ***Ukr.***: Cardiplant (Кардиплант)†.

Multi-ingredient Preparations. ***Arg.***: Barium Jodatum Oligoplex; Hepatodirectol; Passacanthine; Sequals G; ***Austral.***: Asa Tones†; Bioage Peripheral†; ChelaCo; Coleus Complex†; Dan Shen Compound; For Peripheral Circulation Herbal Plus Formula 5†; ***Austria***: Korodin; Rutiviscal; Wechseltee St Severin; ***Belg.***: Natudor; Sedinal; Seneuval; ***Braz.***: Calman; Calmiplan; Floriny; Pasalix; Pasic; Passiflorine; Serenus; Sominex; ***Canad.***: Calmane; Floradix Tab†; Salusan†; ***Chile***: Armonyl; ***Cz.***: Alvisan Neo; Doppelherz Energie-Tonikum†; Fytokliman Planta; Hypotonicka†; Novo-Passit; Valofyt Neo†; ***Fr.***: Biocarde; Calmiflorine†; Euphytose; Lenicalm†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Natudor; Neuroflorine†; Neuropax†; Nicoprive; Nocvalene†; Okimus; Omezelis; Passiflorine; Passinevryl†; Provencale No 4†; Santane N_9; Sedalozia†; Sedatif Tiber†; Sedopal; Spasmine; Sympathyl; Sympavagol†; Tisane Provencale no 4†; Tranquital; Vagostabyl; ***Ger.***: Antihypertonicum S; Bomacorin; Cardio-Kreislauf-Longoral; Ilja Rogoff; Korodin; Oxacant-sedativ; Passin; Protecor; Saluscor Herz-Schutz†; Septacord; Tornix; ***Gr.***: Passiflorine; Passinevrol; ***Hung.***: Antipoll; Crategil; Doppelherz Energie Tonikum N; Kardalept; Mensesyl; Salus Herz-Schutz; Sam-Ginseng Royal; Sanhelios 333; Worishofener; ***India***: Nutiva-Lyco; ***Indon.***: Procardio†; ***Israel***: Nerven-Dragees; Passiflora; ***Ital.***: Anevrasi; Bioestril Ginseng; Controller; Lenicalm; Mirtiros; Noctis; Parvisedil; Passiflorine; Sedatol; Sedatol; Sedopuer F; Vagostabil; ***Jpn***: Keihito; ***Malaysia***: Circarol; ***Mex.***: Ifupasil; ***Philipp.***: Circulan; ***Pol.***: Alliorut†; Biovital N†; Cardiactiv; Cardiobonisol; Cardiol C; Cardiotonic; Cravisol; Doppelherz Energovital Tonik K; Doppelherz Energovital Tonik†; Fitoven; Gerovital Zdrovit; Ginkgocard†; Herbaton†; Kelicardina; Melis-Tonic; Melisal; Melissed; Neocardina; Neospasmina; Neospasmol†; Nerwobonisol; Nerwonal; Passibil; Passispasmin; Passispasmol†; Perfocrat†; Sedomix; Tabletki Tonizujace; Venoforton; ***Rus.***: Biovital (Биовитал); Bromenval (Броменвал); Cardiovalen (Кардиовален); Cedoflor (Седофлор); Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Evalar (Эвалар); Herbion Drops for the Heart (Гербион Сердечные Капли)†; Kliophyt (Клиофит); Passifit (Пассифит); Phyto Novo-Sed (Фито Ново-Седа); Sympathyl (Симпатил); Valemidin (Валемидин); ***Singapore***: Cardio-Essentials; ***Spain***: Passiflorine; Sedonat; Valeriana Leo; ***Switz.***: Arterosan Plus†; Cardiaforce; Cardiophyt A; Circulan†; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Femisan; Gouttes pour le coeur et les nerfs; Ipasin; Passiflor; Tai Ginseng†; Tisane pour le coeur et la circulation; Valverde Coeur; ***Ukr.***: Central-B (Централ-Б); Cratal (Кратал); Gerovital Dr. Theiss (Геровитал Др. Тайсс); Herbion Drops for Heart (Гербион Сердечные Капли)†; Neokardil (Неокардил); Normoton (Нормотон); Novo-Passit (Ново-Пассит); Persen Cardio (Персен Кардио); Sedafiton (Седафитон); Sedavit (Седавит); Vitokan (Витокан); ***USA***: Bioflex; Cardio Tone; Cardiopress; Flexgen; ***Venez.***: Equaliv; Ervostal; Pasidor; Pasifluidina; Passiflorum.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; ***Austria***: Arnica Med Complex; Aurumheel; Cactus compositum; Cefavora; Cora; Corasan; Cralonin; Homviocorin; Homviotensin; Pumpan; Rytmopasc; Selenium Med Complex; Valerianaheel; ***Canad.***: Aurumheel†; Tyglan†; ***Chile***: Melinerv; ***Fr.***: Adenocynesine†; Boripharm No 41; Calmodren; Crataegus Complexe No 15; Homeogene 14†; Hydrastis Compose; Kalium Iodatum Complexe No 84†; Santaherba; Sclerocalcine; Soludor; Strophantus Compose; ***Ger.***: Aktivon; Angioton H; Angioton S†; Antihypertonicum-Tropfen N†; Aurum-Gastreu S R2; Cardioject; Cardioselect N; Cefangipect H†; Cefangipect†; Cefavora Cor; Cefavora†; Confludin N; Conva-cyl Ho-Len-Complex; Convallocor; Convallysan M; Convastabil; Cor-loges; Cororell; Corselect N; Corvipas SL; Cralonin; Crataegus comp; Crataegus comp; Crataegus Herzcomplex; Diacard; Emocrat N†; Goldtropfen S; Habstal-Cor N; HanoCor N; Hevert-Activon Kreislauftropen†; Homviocorin spezial; Homviotensin; Hypotonie-Gastreu R44; Infi-Camphora; Kattwicor; Korolinda; Lowe-Komplex Nr 10; Lowe-Komplex Nr 3; Naranocor HM; Oto-cyl Ho-Len-Complex; Pectapas CPL; Pectapas SL; Pectapas; Phonix Silybum spag; Plantacard N; Procordal; RauwolfiaViscomp; Roth's Rotacard; Rytmopasc; Santa Flora S; Schworocard; Steicardin N†; Strophanthus comp; Uwobletten Arteriosklerose-Complex†; ***Hung.***: Aurumheel; ***Neth.***: Cralonin H; Cralonin; Nervofleur; ***Rus.***: Crataegus-Plus (Кратегус-Плюс); Pumpan (Пумпан); Valeriana-Plus (Валериана-Плюс); ***Switz.***: Cralonin; Gouttes d'Or; ***Ukr.***: Aurocard (Аурокард); Cefavora (Цефавора); Homviocorin-N (Хомвиокорин-N); Homviotensin (Хомвиотензин); Pumpan (Пумпан).

Pharmacopoeial Preparations
Ph. Eur.: Hawthorn Leaf and Flower Dry Extract.

Creatine

Креатин.
N-(Aminoiminomethyl)-*N*-methylglycine.
$C_4H_9N_3O_2$=131.1

CAS — 57-00-1 (creatine); 6020-87-7 (creatine monohydrate).
UNII — MU72812GK0 (creatine); 9603LN7R2Q (creatine monohydrate).

Creatine Phosphate

Creatina, fosfato de; Creatine Phosphoric Acid; Fosfocreatine; Phosphocreatine; Креатинфосфат.

N-[Imino(phosphonoamino)-methyl]-*N*-methylglycine.

$C_4H_{10}N_3O_5P$=211.1

CAS — 67-07-2 (creatine phosphate); 922-32-7 (creatine phosphate disodium).
ATC — C01EB06.
ATC Vet — QC01EB06.
UNII — 020IUV4N33.

Profile

Creatine is an endogenous substance found mainly in skeletal muscle of vertebrates. Creatine phosphate and its disodium salt have been tried in the treatment of cardiac disorders. Creatine phosphate has also been added to cardioplegic solutions. Creatine monohydrate has been tried in metabolic disorders and used as a dietary supplement. It is also under investigation for the treatment of Parkinson's disease, motor neurone disease (p. 2605.2), Duchenne muscular dystrophy, and Huntington disease.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Neoton (里尔统); ***Cz.***: Neoton; ***Ital.***: Creatile; ***Pol.***: Neoton; ***Rus.***: Neoton (Неотон).

Multi-ingredient Preparations. ***Arg.***: Gel Fitotonico; ***Indon.***: Hemaviton Action; ***Ital.***: Anasten Plus; Creavit; Enercomplex; Fortium; NeoBros C; Neovis; Vitalmix Fast; ***Switz.***: Carnidyn.

Crotalaria

Кроталярия.

Profile

Crotalaria spp. have been used in herbal teas but liver damage has been reported after their ingestion, possibly due to their content of pyrrolizidine alkaloids.

CS Gas

CS Gazi; CS Spray; Gas CS.

$C_{10}H_5ClN_2$=188.6

CAS — 2698-41-1.

Profile

CS gas (more properly CS spray) is the name commonly given to a particulate dispersion of α-(*o*-chlorobenzylidene) malonitrile, used as a riot-control agent or 'tear gas'. Its toxic effects include irritation of the eyes and nose, with copious lachrymation and rhinorrhoea; blepharospasm; a burning sensation of the mouth and throat; tightness in the chest, with difficulty in breathing; coughing; an increase in salivation; and retching and vomiting. These effects usually disappear within 15 minutes after exposure ends. The effects of pre-existing disease of the respiratory tract may be exacerbated. Erythema and blistering of the skin may occur.

If symptoms persist, the patient should be removed to a well ventilated area. Treatment is symptomatic. Contaminated skin may be washed with soap and water, but only if symptoms persist since exposure to water may initially exacerbate symptoms. If contamination of the eyes has been severe they should be irrigated with physiological saline or water.

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Cubeb

Cubeb Berries; Cubeb Fruit; Cubeba; Java Pepper; Tailed Pepper; Кубеба.

UNII — Z99L7429MA.

Profile

The unripe seeds of cubeb, *Piper cubeba* (Piperaceae), are the source of cubeb oil, which is used in perfumery and aromatherapy. Cubeb is an ingredient of various herbal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Pervivo; ***Hung.***: Bittner; ***Pol.***: Pervivo; ***Rus.***: Doktor Mom (Доктор Мом); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***Ukr.***: Doktor Mom (Доктор Мом сироп).

Homoeopathic Preparations. ***Switz.***: Regenaplex Nr. 49a.

Cucurbita

Abóbora; Calabacera; Calabaza, semillas de; Kürbissamen; Melon Pumpkin Seeds; Pepo; Pipas de la calabaza; Semence de Courge; Семена Тыквы.

*ATC Herb — HP02DW5001 (*Cucurbita pepo*: seed); HG04CW5001 (*Cucurbita pepo*: seed).*

Pharmacopoeias. In *Ger.*

Profile

Cucurbita consists of the seeds of *Cucurbita pepo* (Cucurbitaceae) or related species. It was formerly used for the expulsion of tapeworms (*Taenia*).

It is an ingredient of several herbal preparations used in urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Lefkur; ***Fr.***: ViTiX; ***Ger.***: Cysto-Urgenin†; Granu Fink Kurbiskern†; Granu Fink Prosta forte; Nomon mono; Prosta Fink forte†; Urgenin Cucurbitae oleum; Uvirgan mono†; Vesiherb; ***Hung.***: Peponen; ***Indon.***: Inkurin; ***Pol.***: Peponen; Peposterol; ***Rus.***: Peponen (Пепонен); Tycveolum (Тыквеол); Vitanorm (Витанорм); ***Switz.***: Kurbin†; ***Ukr.***: Peponen (Пепонен).

Multi-ingredient Preparations. ***Arg.***: Cellskinlab Phyto Spot; Clean-AC; Cleanance; Cleanance; Cleanance; Prostafit; ***Austral.***: In-Control; ProstaCo; ***Canad.***: Optomega; Prosta Ease; Prostease; Saw Palmetto Formula†; ***Chile***: Clean-AC; Cleanance; Cleanance; ***Fr.***: Acyprost; Alpharegul Femme; Alpharegul Homme; Androlistica; Cleanance K; Cleanance; Prostabiol; ProstaSecurA; ***Ger.***: Granu Fink Blase Kurbiskern†; Granu Fink Femina; Granu Fink Prosta; Prostamed; ***Hong Kong***: Prostease; ***Hung.***: Uroherb; ***Indon.***: Soprost†; ***Ital.***: Biomineral 5-Alfa; ***Philipp.***: Castoria; ***Port.***: Bioclin Sebo Care; ***Rus.***: Bioprost (Биопрост); ***Singapore***: Androlistica; ***Switz.***: Granu Fink Prosta†; Herbaprosta-Caps N†; ***UK***: Ymea; ***Ukr.***: Prostamed (Простамед); ***Venez.***: Argeal.

Homoeopathic Preparations. ***Fr.***: Sels Calcaires Nutritifs; ***Ger.***: Vomistop; ***S.Afr.***: Aufbaukalk I†; ***UK***: Apatite.

Curcuminoids

Куркуминоиды.

Pharmacopoeias. In *US.*

USP 36: (Curcuminoids). A partially purified natural complex of diaryl heptanoid derivatives isolated from turmeric (*Curcuma longa*). It contains not less than 95.0% of curcuminoids, calculated on the dried basis, as the sum of curcumin, desmethoxycurcumin, and bisdesmethoxycurcumin. It contains not less than 70.0% and not more than 80.0% of curcumin, not less than 15.0% and not more than 25.0% of desmethoxycurcumin, and not less than 2.5% and not more than 6.5% of bisdesmethoxycurcumin. Protect from light and moisture.

Profile

Curcuminoids are phenolic compounds found in turmeric (p. 2218.1). The principal ones are curcumin (p. 2180.1), desmethoxycurcumin, and bisdesmethoxycurcumin, all of which contribute to the yellow colour of turmeric. Curcuminoids are used as dietary supplements. There is considerable interest in potential medicinal uses, and curcuminoids have been reported to have anti-angiogenic, anti-cancer, anti-inflammatory, antimicrobial, antoxidant, anti-thrombotic, and immunomodulatory actions. Hydrogenation of curcuminoids produces tetrahydrocurcuminoids, which are colourless and therefore have potential uses in colourless food products and cosmetics.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Longin.

Multi-ingredient Preparations. ***India***: Melaglow; ***Indon.***: Apecur; Bevita; Biofos†; Heparviton NF; Heparviton; Hepatin; Prokids; Proliver; Reliv†; Vitagrow; Ximun.

Pharmacopoeial Preparations

USP 36: Curcuminoids Capsules; Curcuminoids Tablets.

Cusparia

Angostura; Angostura Bark; Carony Bark; Cusparia Bark; Ангостура.

UNII — 104010O5VU.

NOTE. 'Angostura Bitters' (*Dr. J.G.B. Siegert*) contains gentian and various aromatic ingredients but no cusparia; it is named after the town in which it was first made.

Profile

Cusparia, the bark of *Galipea officinalis* (Rutaceae), has been used as a bitter.

Cyanoacrylate Adhesives

Cianoacrilato, adhesivos de; Цианакрилатные Клеи.

Bucrilate *(rINN)*

Bucrilato; Bucrilatum; Bucrylate (USAN); Bucrylate; IBC; IBCA; Isobutyl Cyanoacrylate; Букрилат.

Isobutyl 2-cyanoacrylate.

$C_8H_{11}NO_2$=153.2

CAS — 1069-55-2.
UNII — 2HJV1F859Z.

Enbucrilate *(BAN, rINN)*

n-Butyl Cyanoacrylate; Enbucrilato; Enbucrilatum; NBCA; Энбукрилат.

Butyl 2-cyanoacrylate.

$C_8H_{11}NO_2$=153.2

CAS — 6606-65-1.
UNII — F8CEP82QNP.

Ethyl Cyanoacrylate

ECA; Этилцианакрилат.
Ethyl 2-cyanoacrylate.
$C_6H_7NO_2$=125.1
CAS — 7085-85-0.
UNII — 2G95FOH7SF.

Mecrilate *(rINN)*

Cyanoacrylate; MCA; Mécrilate; Mecrilato; Mecrilatum; Mecrylate (USAN); Mecrylate; Мекрилат.
Methyl 2-cyanoacrylate.
$C_5H_5NO_2$=111.1
CAS — 137-05-3.
UNII — WN7979561R.

Ocrilate *(rINN)*

Ocrilato; Ocrilatum; Ocrylate (USAN); Ocrylate; Окрилат.
Octyl 2-cyanoacrylate.
$C_{12}H_{19}NO_2$=209.3
CAS — 6701-17-3.
UNII — 6C655P1XVG.

Uses and Administration

Several cyanoacrylate compounds have been used as surgical tissue adhesives including bucrilate, enbucrilate, ethyl cyanoacrylate, mecrilate, and ocrilate.

Some cyanoacrylates are used for household purposes and as nail fixatives and others have been investigated as tubal occlusive agents for female sterilisation, for sclerotherapy in bleeding gastric varices (see under Monoethanolamine, p. 2563.1), and for embolisation of intracranial vascular lesions. Cyanoacrylate adhesives have also been used to plug corneal perforations until donor tissue is available.

References to the use of cyanoacrylate adhesives,[1-10] including bucrilate,[1,2] enbucrilate,[3,4] and ocrilate.[5-9]

1. Kind R, *et al.* Bucrylate treatment of bleeding gastric varices: 12 years' experience. *Endoscopy* 2000; **32:** 512–9.
2. Shepler TR, Seiff SR. Use of isobutyl cyanoacrylate tissue adhesive to stabilize external eyelid weights in temporary treatment of facial palsies. *Ophthal Plast Reconstr Surg* 2001; **17:** 169–73.
3. Schonauer F, *et al.* Use of Indermil tissue adhesive for closure of superficial skin lacerations in children. *Minerva Chir* 2001; **56:** 427–9.
4. Sinha S, *et al.* A single blind, prospective, randomized trial comparing n-butyl 2-cyanoacrylate tissue adhesive (Indermil) and sutures for skin closure in hand surgery. *J Hand Surg (Br)* 2001; **26:** 264–5.
5. Kutcher MJ, *et al.* Evaluation of a bioadhesive device for the management of aphthous ulcers. *J Am Dent Assoc* 2001; **132:** 368–76.
6. Puri P. Tissue glue aided lid repositioning in temporary management of involutional entropion. *Eur J Ophthalmol* 2001; **11:** 211–4.
7. Bernard L, *et al.* A prospective comparison of octyl cyanoacrylate tissue adhesive (dermabond) and suture for the closure of excisional wounds in children and adolescents. *Arch Dermatol* 2001; **137:** 1177–80.
8. Mattick A, *et al.* A randomised, controlled trial comparing a tissue adhesive (2-octylcyanoacrylate) with adhesive strips (Steristrips) for paediatric laceration repair. *Emerg Med J* 2002; **19:** 405–7.
9. Magee WP, *et al.* Use of octyl-2-cyanoacrylate in cleft lip repair. *Ann Plast Surg* 2003; **50:** 1–5.
10. Singer AJ, *et al.* The cyanoacrylate topical skin adhesives. *Am J Emerg Med* 2008; **26:** 490–6.

Adverse Effects and Treatment

Cyanoacrylate adhesives are considered to be non-toxic since they set within seconds of exposure to air. However, heat is evolved on solidification of cyanoacrylate and in rare cases may cause tissue burns. Mild irritation may occur particularly when bonded surfaces are separated mechanically, and contact dermatitis may occur after chronic exposure. Ocular contact with cyanoacrylate adhesives causes eyelids to seal rapidly and may also strip the skin; corneal abrasion, conjunctivitis, and loss of eyelashes may also occur.

In the event of accidental adhesion of the skin the bonded surfaces may be separated after application of acetone, prolonged soaking in warm (not hot) soapy water, and/or mixtures of alcohol and water. Application of liquid paraffin may help in removal from the skin. If necessary, the surfaces may be peeled or rolled apart with the aid of a spatula; attempts should not be made to pull the surfaces directly apart. Acetone and alcohol should not be used near or in the eyes. Solvents such as nitromethane, toluene, or xylene may be used to aid skin detachment from solid objects. Solvents should be used with care and should not be introduced into the oropharynx. Eyelids stuck together or bonded to the eyeball should be washed thoroughly with saline or water at room temperature for 15 minutes and a gauze patch applied; the eye will open without further action in 1 to 4 days. Manipulative attempts to open the eyes should not be made. Although cyanoacrylate introduced into the eyes may cause double vision and lachrymation there is usually no residual damage. If lips are accidentally stuck together plenty of warm water should be applied and maximum wetting from saliva inside the mouth encouraged. Lips should be peeled or rolled apart and not pulled. Adhesive introduced into the mouth solidifies and adheres, but saliva will lift the adhesive in ½ to 2 days. Care should be taken to avoid choking.

Reports of inadvertent application of cyanoacrylate adhesives to the eyes,[1,2] mouth,[3] and ears.[4,5] Pulmonary embolisation of ocrilate has been reported[6] when it was used to obliterate gastric varices in a patient.

1. Lyons C, *et al.* Superglue inadvertently used as eyedrops. *BMJ* 1990; **300:** 328.
2. DeRespinis PA. Cyanoacrylate nail glue mistaken for eye drops. *JAMA* 1990; **263:** 2301.
3. Cousin GCS. Accidental application o f cyanoacrylate to the mouth. *Br Dent J* 1990; **169:** 293–4.
4. O'Donnell JJ, *et al.* Cyanoacrylate adhesive mistaken for ear drops. *J Accid Emerg Med* 1997; **14:** 199.
5. Persaud R. A novel approach to the removal of superglue from the ear. *J Laryngol Otol* 2001; **115:** 901–2.
6. Rickman OB, *et al.* Pulmonary embolization of 2-octyl cyanoacrylate after endoscopic injection therapy for gastric variceal bleeding. *Mayo Clin Proc* 2004; **79:** 1455–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermabond†; ***Gr.***: Histoacryl; ***India***: Cutseal; Gesika; ***UK***: Dermabond; Histoacryl; Indermil; LiquiBand; SuperSkin.

Multi-ingredient Preparations. ***Ger.***: Epiglu; ***Irl.***: Epiglu†; ***UK***: Epiglu.

Cyclamen

Cyclamen d'Europe.
UNII — G728143D8Q.

NOTE. The name Cyclamen Europaeum has been applied to several related species of *Cyclamen* but strictly applies to *C. purpurascens*. The name Sowbread is applied to several species of *Cyclamen* but usually applies to *C. hederifolium*.

Profile

The tuber of *Cyclamen purpurascens* (*C. europaeum*) (Primulaceae) has been used in herbal medicine for a range of indications; it is reported to be a drastic purgative. An extract of the tuber has been used for sinusitis.

The related species *C. hederifolium* has also been used.

Homoeopathy

Cyclamen has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Nasodren; ***Rus.***: Sinuforte (Синуфорте).

Homoeopathic Preparations. ***Austria***: Mastodynon; Migrenopas†; ***Canad.***: Alfalfa Tonic; Formula DM 210†; Headache & Migraine L77; Headache & Migraine; Homeo-Form MI†; ***Cz.***: Hormeel S; Mastodynon; ***Fr.***: Phapax; ***Ger.***: Antimast TN†; Antimigren; Biodolor; Cefanalgin†; Cephaloplant†; Dolfin; DolorA; Femin-Do; Mastodynon; Neuro-Do; Pflugerplex Gelsemium; ***Hung.***: Hormeel S; ***Neth.***: Homeocare Nervo; Hormeel H; Hyperilite; Mastodynon†; ***Rus.***: Hormeel SN (Гормель СН); Mastodynon (Мастодинон); ***Switz.***: Menstruasan; Multiplex 1; ***Thai.***: Mastodynon†; ***Ukr.***: Capadol (Кападол); Mastodynon (Мастодинон).

Cyclobutyrol Sodium *(rINNM)*

Ciclobutirol sódico; Cyclobutyrol Sodique; Natrii Cyclobutyrolum; Натрий Циклобутирол.
Sodium 2-(1-hydroxycyclohexyl)butyrate.
$C_{10}H_{17}NaO_3$=208.2
CAS — 512-16-3 (cyclobutyrol); 1130-23-0 (cyclobutyrol sodium).
ATC — A05AX03.
ATC Vet — QA05AX03.
UNII — 9EA1G6PR44.

Profile

Cyclobutyrol sodium is a choleretic that has been given orally. Cyclobutyrol betaine, cyclobutyrol calcium, and cyclobutyrol nicotinamide have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Sugarbil†.

Cyclovalone *(rINN)*

Ciclovalona; Cyclovalonum; Циковалон.
2,6-Divanillylidenecyclohexanone.
$C_{22}H_{22}O_5$=366.4
CAS — 579-23-7.
UNII — 6M4YJ3FA16.

Profile

Cyclovalone has been used as a choleretic and for dyspepsia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vanilone.

Cymene

Cimeno; *p*-Cimeno; *p*-Cymene; *p*-Cymol; p-Cymen; Цимол; Цимен.
4-Isopropyl-1-methylbenzene; 4-Isopropyltoluene.
$C_{10}H_{14}$=134.2
CAS — 25155-15-1; 99-87-6 (p-cymene).
UNII — 1G1C8T1N7Q.

Profile

Cymene is used in perfumery. It has also been used as a topical local analgesic for the relief of pain in rheumatic conditions.

Cynara

Alcachofa; Alcachôfra; Alcacil; Artichaut; Artichaut, feuille d'; Artichoke Leaf; Artičokový list; Artischockenblätter; Cynarae folium; Liść karczocha; Лист Артишока.
ATC Herb — HG04BW5007 (Cynara cardunculus: *leaf*); *HA05AW5007* (Cynara cardunculus: *leaf*); *HC10AW5006* (Cynara cardunculus: *leaf*).
UNII — B71UA545DE.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract prepared from the leaves.

Ph. Eur. 8: (Artichoke Leaf). The whole or cut, dried leaf of *Cynara cardunculus* (*C. scolymus*). It contains a minimum 0.8% of chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated with reference to the dried drug. Protect from light.

Profile

Cynara, the leaf of the globe artichoke, *Cynara scolymus* (Compositae), is reputed to have diuretic and choleretic properties. It may also have some hypolipidaemic activity. Cynara is the source of cynarine (p. 2491.1).

References.

1. Joy JF, Haber SL. Clinical uses of artichoke leaf extract. *Am J Health-Syst Pharm* 2007; **64:** 1904–9.
2. Wider B, *et al.* Artichoke leaf extract for treating hypercholesterolaemia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 04/02/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Chofitol; Cynarex; Lorhepatic; ***Austria***: Cynarix; Hepar-POS†; ***Belg.***: Cholaplus; Cynarol; Hebucol; ***Braz.***: Alcachofrax; Alcagest; Chophytol; ***Fr.***: Chophytol; Hepanephrol; ***Ger.***: aar gamma N; Ardeycholan; Aristochol Gallekapsein†; Cefacynar†; Cholagogum; Cynacur†; Hepacyn; Hepagallin N†; Hepar SL; Hepar-POS; Heparstad; Hewechol Artischockendragees†; Natu-Hepa; ***Pol.***: Cynacholin; Cynarex; Digestiol; Hepacynar; Liproxal; ***Rus.***: Chophytol (Хофитол); ***Spain***: Cirkuhep; ***Switz.***: Chophytol; Hepa-S; Legadyn; Natu-Hepa; ***Turk.***: Digestor; ***UK***: Cypar Artichoke; DigestAid; Digestherb; Phytocleanse; ***Ukr.***: Artihol (Артихол); Bilicur (Биликур); Chophytol (Хофитол); Cynarix (Цинарикс).

Multi-ingredient Preparations. ***Arg.***: Adelgazar; Alcachofa Plus; Arceligasol; Bagohepat; Bilidren; Boldina; Chofitol Plus; Digenat; Dioxicolagol; Fegalgina; HDG; Hepachofa; Hepacur; Hepatalgina; Hepatalgina; Hepatodirectol; Lorbihepatic†; Lorhepatic; Metiogen; Palatrobil; Palatrobil; Wunderbalsam; ***Austral.***: Digest Aid; Extralife Liva-Care†; KickStart Detox; Liver Detox; Liver Tonic Complex; Livton Complex; PM Syrin; ***Austria***: Cynarix comp; Gallesyn neu; Gallesyn neu; ***Belg.***: Cynactil; ***Braz.***: Chofranina†; Colachofra; Figatil; Gotas Preciosas; Lisotox; Solvobil; ***Canad.***: Artechol†; Articho-Nat; Duo-Bil; Gallexier†; Hepartichaut†; Hepartichaut; Hepaticol; Hepatol; Herbaraphanus†; Milk Thistle†; Phyto-Marinex; ***Fr.***: Actibil†; Aromadetox†; Benetransit†; Biofirm; Canol; Elixir Spark†; Expuryl; Hepaclem†; Hepatoflorine†; ***Ger.***: Carmol Magen-Galle-Darm†; Gallexier; Gallexier; ***Hong Kong***: Hepatofalk†; Wellman†; ***Hung.***: Gallexier; ***Indon.***: Biocholes†; Hepagard; ***Ital.***: Cinarepa; Colax†; ***Mex.***: Bagohepat†; Chofabol; Hepedren; Ifuchol; ***Philipp.***: Hepamin; ***Pol.***: Cardiobonisol; Rapacholin AC†; Rapacholin C; Sylicynar; ***Rus.***: Herbion Drops for the Gallbladder (Гербион Капли Желчегонные)†; ***Singapore***: Vidaylin MiniBear; ***Spain***: Cynaro Bilina†; Laxadinas†; Lipograsil†; Nico Hepatocyn; ***Swed.***: Cynaramin; Galexir; ***Switz.***: Bilifuge; Boldocynara; Kernosan 24; Strath Gouttes pour le foie et la bile; Tisane hepatique et biliaire; ***UK***: Bio-Strath Artichoke Formula;

Digestisan; Milk Thistle Complex; Pure Plan; ***Ukr.***: Choliver (Холивер)†; Detoxil (Детоксил); Ektis (Эктис); Farcovit B12 (Фарковит B12)†; Hepahealth (Гепахелс); Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); PM Sirin (ПМ Сирин); ***Venez.***: Cynascool.

Homoeopathic Preparations. ***Canad.***: Cynara Complex†; Formula FV 213; Formula Homeo QR 209†; Hecocur†; Hepar Compositum; ***Chile***: Cynara Compuesta; Digherbal; ***Fr.***: Homeogene 22†; ***Ger.***: Hepar comp; Infihepan; ***Neth.***: Apo-Hepat; Gletar; Hepeel H; ***USA***: Preferred Remedies Detoxin.

Pharmacopoeial Preparations
Ph. Eur.: Artichoke Leaf Dry Extract.

Cynarine *(rINN)*

Cinarina; Cynarin; Cynarinum; Cynaryna; 1,5-Dicaffeoylquinic Acid; Цинарин.
1-Carboxy-4,5-dihydroxy-1,3-cyclohexylene bis(3,4-dihydroxycinnamate).
$C_{25}H_{24}O_{12}$=516.5
CAS — 1182-34-9; 1884-24-8.
UNII — 85D81U9JAV.

Profile

Cynarine is an active ingredient of cynara (p. 2490.3). It has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: HDG.

Cypress

Italian Cypress; Mediterranean Cypress.

Profile

Italian or Mediterranean cypress (*Cupressus sempervirens*, Cupressaceae) is included in preparations for peripheral vascular disorders.

It is the source of cypress oil. Cypress oil is used in preparations for the relief of cough and cold symptoms and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Arterase; Circulatonic†; Olioseptil Nez-Gorge; Veino Gomenol; Veinostase; ***Ital.***: Colostrum; Venalta; ***Spain***: Vapores Pyt†; ***Switz.***: Eucapinol; Novital.

Cytidine

Cytosine Riboside; Цитидин.
4-Amino-1-β-D-ribofuranosyl-2-(1*H*)-pyrimidinone.
$C_9H_{13}N_3O_5$=243.2
CAS — 65-46-3.
UNII — 5CSZ8459RP.

Profile

Cytidine is an endogenous cytosine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). Cytidine is used in preparations containing other nucleosides in the treatment of corneal damage. It has also been used in preparations for liver disorders, anaemias, and as a tonic. Disodium cytidine phosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; the triphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kun Bang (坤邦).

Multi-ingredient Preparations. ***Braz.***: Etna; Nucleo CMP; ***Chile***: Citoneuron; ***Ger.***: Keltican N†; ***Hong Kong***: Vitacic†; ***Ital.***: Centrum; ***Mex.***: Nucleo CMP; ***Mon.***: Vitacic; ***Spain***: Nucleo CMP; ***Ukr.***: Keltican (Келтикан); Nucleo CMF Forte (Нуклео ЦМФ Форте).

Cytisine

Baptitoxine; Laburnine; Sophorine; Ulexine; Цитизин.
1,2,3,4,5,6-Hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one.
$C_{11}H_{14}N_2O$=190.2
CAS — 485-35-8.
UNII — 53S5U404NU.

Profile

Cytisine is a highly toxic alkaloid found in laburnum (p. 2538.3) and some other leguminous plants. It resembles nicotine (p. 2569.3) in its actions and has been given orally as an aid to smoking cessation (p. 2570.2). The dose is 1.5 mg 6 times daily for 3 days which is then gradually reduced over the next 3 weeks to 1.5 mg twice daily for the final 5 days of treatment. Treatment of adverse effects of cytisine is as described for Nicotine, p. 2571.1.

A 0.15% solution of cytisine known as Cytitone has been used intravenously or intramuscularly in some countries as a respiratory stimulant.

References.

1. Etter J-F. Cytisine for smoking cessation: a literature review and a meta-analysis. *Arch Intern Med* 2006; **166:** 1553–9.
2. Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep* 2006; **58:** 777–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Bulg.***: Tabex (Табекс); ***Pol.***: Tabex; ***Rus.***: Tabex (Табекс); ***Ukr.***: Tabex (Табекс).

Multi-ingredient Preparations. ***Rus.***: Theophedrinum-N (Теофедрин-Н).

Cytochrome C

Citocromo C; Цитохром С.

Pharmacopoeias. *Chin.* includes Cytochrome C Solution and preparations for injection.

Profile

Cytochrome C is a haemoprotein occurring in the body and involved in electron and hydrogen transport in biological oxidation processes. It has been given intravenously in various hypoxic conditions.

Cytochrome C is an ingredient of some eye drops used for the treatment of cataract but its actions, if any, are unclear.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Sai Tuo (赛托); ***Ital.***: Citophase; ***Jpn***: Cytorest†.

Multi-ingredient Preparations. ***Gr.***: Collyre Vitaphakol; Suprin; ***Rus.***: Oftan Catachrom (Офтан Катахром).

Cytokines

Citocinas; Citokinas; Citoquinas; Цитокины.

Profile

Cytokines are a group of endogenous soluble peptides produced by many different cell types in response to noxious stimuli. In contrast to peptide hormones, they tend to act locally. Cytokines affect expression of genes influencing changes at the cellular level and have a regulatory function, acting as growth factors in cellular differentiation and/or proliferation. Cytokines are also involved in host responses to disease such as infection or inflammation. Some cytokines induce inflammation whereas others have an anti-inflammatory action through inhibition of proinflammatory cytokines. Cytokines are classified by their biological activity rather than structure and most are pleiotropic (i.e. they are multifunctional). A large number of cytokines alter endothelial function affecting permeability and may also cause cellular damage or death. Some cytokines are involved in the pathophysiology of diseases, particularly immune, inflammatory, and infectious diseases; they may also be involved in the development of cardiovascular disease.

Cytokines that are used clinically include:
- granulocyte colony-stimulating factors such as filgrastim (p. 1151.3)
- granulocyte-macrophage colony-stimulating factors such as molgramostim (p. 1156.2)
- interferons (p. 989.2)
- some interleukins (p. 2533.3)
- oprelvekin (p. 1157.2), a platelet growth factor
- palifermin (p. 2579.1), a keratinocyte growth factor
- somatomedins (p. 1929.1)
- thrombopoietin (p. 1164.1)
- trafermin (p. 1725.1), a fibroblast growth factor
- tumour necrosis factor (p. 878.1)
- urogastrone (p. 1894.3), an epidermal growth factor

Anticytokine-based therapy may involve suppressing the action of single or related cytokines by specific soluble cytokine receptors, antagonists to the cytokine receptor, or antibodies against the cytokine. Alternatively, the synthesis of several unrelated cytokines may be suppressed by a single therapeutic agent. Fusion toxins in which protein sequences from cytokines or natural growth factors are combined with a bacterial toxin have also been produced to target specific cytokines.

References.

1. Xing Z, Wang J. Consideration of cytokines as therapeutics agents or targets. *Curr Pharm Des* 2000; **6:** 599–611.
2. Schooltink H, Rose-John S. Cytokines as a therapeutic drugs. *J Interferon Cytokine Res* 2002; **22:** 505–16.
3. Andreakos ET, *et al.* Cytokines and anti-cytokine biologicals in autoimmunity: present and future. *Cytokine Growth Factor Rev* 2002; **13:** 299–313.
4. Stevceva L. Cytokines and their antagonists as therapeutic agents. *Curr Med Chem* 2002; **9:** 2201–7.
5. Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. *Curr Drug Targets* 2006; **7:** 675–81.
6. Villar CC, *et al.* Therapeutic modulation of cytokines in chronic infectious diseases. *Curr Pharm Des* 2006; **12:** 2329–48.
7. Feurino LW, *et al.* Current update of cytokines in pancreatic cancer: pathogenic mechanisms, clinical indication, and therapeutic values. *Cancer Invest* 2006; **24:** 696–703.

Damiana

Hierba de la pastora; Itamo real; Turnera; Дамиана.
UNII — RQ2CFA7WWJ.

Profile

Damiana is the dried leaves and stem of *Turnera diffusa* var. *aphrodisiaca* (Turneraceae) and possibly other species of *Turnera*. Damiana is drunk as a tea, and is used in herbal medicine for a variety of indications. It has a reputation as an aphrodisiac, but there is no evidence for this.

Homoeopathy

Damiana has been used in homoeopathic medicines under the following names: Turnera diffusa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Malaysia***: Cefagil.

Multi-ingredient Preparations. ***Arg.***: ADX; Vitalsex; ***Austral.***: Enhance for Men; For Women Active Woman Formula†; Herbal Rest & Relax; Masculine Herbal Complex; Meno Support Plus; Mens Performance Multi; Mens Super Soy/Clover†; Nevaton; Olf†; The Blue One†; Tribulus & Epimedium Compound; ***Canad.***: Libeeda for Men; Libeeda for Women; ***Hong Kong***: Sessoforte†; ***Indon.***: Instink†; Maxirex; Menolia†; Neo Hormoviton; Tripote†; Tristan†; ***Ital.***: Argidam; Dam; Euroton; ***Mex.***: Zumba; ***Pol.***: Tripoten; ***UK***: Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Regina Royal Concorde; Strength; Zotrim.

Homoeopathic Preparations. ***Austria***: Cefagil; Erbiode-Starkungstropfen; Orgafem; ***Canad.***: Goldenrod Combination†; ***Fr.***: Amphosca Orchitine; Amphosca Ovarine; Selenium Complexe No 99; ***Ger.***: Cefagil; Manuia; Testerell; Virilis-Gastreu S R41; ***Hung.***: Cefagil; ***Rus.***: Damiana-Plus (Дамиана-Плюс); ***Ukr.***: Cefagil (Цефагил).

Danshen

Chinese Sage; Chinese Salvia; Chinesischer Salbei; Dan Shen; Red Sage; Redroot Sage; Red-rooted Sage; Rotwurzsalbei; Tan Shen; Tan-shen; Шалфей многокорневищный.
CAS — 79483-68-4 (danshen root extract).
UNII — 3VOZ2N8O39.

NOTE. Distinguish from Dang Shen, the root of *Codonopsis pilosula* (Campanulaceae). The name Tan Shen is also applied to the dried roots of the related species *Salvia bowleyana* and *S. przewalskii*. The term Red Sage has been used for both *Salvia officinalis* (Sage, p. 2608.3) and *Salvia miltiorrhiza* (Danshen).

Pharmacopoeias. In *Chin.* and *US. Eur.* (see p. vii) includes Salvia Miltiorrhiza Root and Rhizome. *Br.* includes a separate monograph for Processed Salvia Miltiorrhiza Rhizome and Root. *US* includes Powdered Chinese Salvia.

Ph. Eur. 8: (Salvia Miltiorrhiza Root and Rhizome; Salviae Miltiorrhizae Radix et Rhizoma). The dried, whole or fragmented rhizome and root of *Salvia miltiorrhiza*, collected in spring or autumn. It contains not less than 3.0% of salvianolic acid B, ($C_{36}H_{30}O_{16}$ = 718.6), and not less than 0.12% of tanshinone II_A, ($C_{19}H_{18}O_3$ = 294.4), calculated with reference to the dried drug.

BP 2014: (Processed Salvia Miltiorrhiza Rhizome and Root). Salvia Miltiorrhiza Rhizome and Root that has been processed. It is collected in spring or autumn, separated from soil, washed, softened, sliced longitudinally or transversely, and dried. It may be stir baked with wine. It contains not less than 0.04% of tanshinone II_A ($C_{19}H_{18}O_3$ = 294.4), not less than 0.17% of rosmarinic acid ($C_{18}H_{16}O_8$ = 360.3), and not less than 3.0% of salvianolic acid B ($C_{36}H_{36}O_{16}$ = 724.7), calculated with reference to the dried material. Protect from moisture.

USP 36: (Chinese Salvia). It consists of the dried roots and rhizomes of *Salvia miltiorrhiza*, collected in spring or autumn. It contains not less than 0.1% of tanshinone IIA; not less than 0.2% of total tanshinones, calculated as the sum of cryptotanshinone, tanshinone I, and tanshinone IIA; and not less than 3.0% of salvianolic acid B; calculated on the dried basis. Protect from light and moisture.

Uses and Administration

Danshen is the dried root and rhizome of *Salvia miltiorrhiza* (Lamiaceae). It is used in traditional Chinese medicine mainly for cardiovascular disorders including ischaemic heart disease, ischaemic stroke, and hyperlipidaemias.

A root extract containing methylenetanshinquinone and 1,2-dihydrotanshinquinone has been described.

References.

1. Zhou L, *et al.* Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. *J Clin Pharmacol* 2005; **45:** 1345–59.
2. Cheng TO. Cardiovascular effects of danshen. *Int J Cardiol* 2007; **121:** 9–22.
3. Qiu F, *et al.* Effect of danshen extract on the activity of CYP3A4 in healthy volunteers. *Br J Clin Pharmacol* 2010; **69:** 656–62.

Interactions

For mention of a possible interaction between *warfarin* and Chinese herbal remedies including danshen, see Chinese Herbal Remedies, p. 1533.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Bupleurum Complex†; Dan Shen Compound; ***Indon.***: Procardio†; ***Malaysia***: Elgucare; NeuroAid; ***Singapore***: NeuroAid.

Dehydrocholic Acid *(BAN, rINN)*

Acide Déhydrocholique; Ácido dehidrocólico; Acidum Dehydrocholicum; Chologon; Dehidrocólico, ácido; Dehydrocholsyra; Dehydrokoolihappo; Triketocholanic Acid; Дегидрохолевая Кислота.

3,7,12-Trioxo-5β-cholan-24-oic acid.

$C_{24}H_{34}O_5$=402.5

CAS — 81-23-2 (dehydrocholic acid); 145-41-5 (sodium dehydrocholate).

UNII — NH5000009I.

Pharmacopoeias. In *Chin.*, *It.*, *Jpn*, and *US*.

USP 36: (Dehydrocholic Acid). A white, fluffy, odourless powder. Practically insoluble in water; soluble 1 in 100 of alcohol, 1 in 135 of acetic acid at 15 degrees, 1 in 130 of acetone at 15 degrees, 1 in 35 of chloroform, 1 in 2200 of ether at 15 degrees, 1 in 135 of ethyl acetate at 15 degrees, and 1 in 960 of benzene at 15 degrees; solutions in alcohol and in chloroform are usually slightly turbid; soluble in glacial acetic acid and in solutions of alkali hydroxides and carbonates.

Profile

Dehydrocholic acid is a semisynthetic bile acid (p. 2457.2) that is given for its hydrocholeretic properties, increasing the volume and water content of the bile without appreciably altering the content of bile acids. It has been used to improve biliary drainage and has also been given for the temporary relief of constipation. The usual oral dose is 250 to 500 mg three times daily after meals.

Dehydrocholic acid is contra-indicated in significant cholelithiasis, complete mechanical biliary obstruction, and in severe hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Dycholium; ***USA***: Cholan-HMB; Decholin.

Multi-ingredient Preparations. ***Arg.***: Arnol; Bagohepat; Bibol Leloup; Bil 13 Enzimatico; Bil 13; Bilagol Antigas; Carbogasol Digestivo; Digenorflat; Hepachofa; Hepatalgina; Lorbihepatic†; Lorhepatic; Pakinase; Palatrobil; Pankreon Total; Zimerol; ***Braz.***: B-Vesil†; Essen; Plasil Enzimatico; Sintozima†; ***Canad.***: Hepartichaut†; Hepartichaut; Regubil; ***Hung.***: Neo-Bilagit; ***Mex.***: Bagohepat†; Plasil Enzimatico; ***Philipp.***: Spasmo-Canulase; ***Pol.***: Rapacholin C; Rapacholin Forte; ***Port.***: Espasmo Canulase†; ***S.Afr.***: Spasmo-Canulase†; ***Spain***: Nulacin Fermentos†; ***Switz.***: Spasmo-Canulase; ***Thai.***: Vitana-EZ; Vitaral.

Pharmacopoeial Preparations

USP 36: Dehydrocholic Acid Tablets.

Delmopinol Hydrochloride *(rINNM)*

Delmopinol, Chlorhydrate de; Delmopinoli Hydrochloridum; Hidrocloruro de delmopinol; M-1650; Дельмопинола Гидрохлорид.

±-3-(4-Propylheptyl)-4-morpholineethanol hydrochloride.

$C_{16}H_{33}NO_2$,HCl=307.9

CAS — 79874-76-3 (delmopinol); 98092-92-3 (delmopinol hydrochloride).

Profile

Delmopinol prevents the formation of dental plaque by coating the teeth and preventing adhesion of bacteria. The hydrochloride is used as a mouth rinse in the treatment and prevention of gingivitis.

References.

1. Addy M, *et al.* Meta-analyses of studies of 0.2% delmopinol mouth rinse as an adjunct to gingival health and plaque control measures. *J Clin Periodontol* 2007; **34:** 58–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Auxinol; ***Israel***: Decapinol; ***UK***: Decapinol.

Demelverine Hydrochloride *(rINNM)*

Démelvérine, Chlorhydrate de; Demelverini Hydrochloridum; Hidrocloruro de demelverina; Methphenaethamine Hydrochloride; *N*-Methyldiphenethylamine Hydrochloride; Демельверина Гидрохлорид.

N-Methyl-*N*-(2-phenylethyl)-benzeneethanamine hydrochloride.

$C_{17}H_{21}N$,HCl=275.8

CAS — 13977-33-8 (demelverine); 18719-09-0 (demelverine hydrochloride).

UNII — T568N7L7GE.

Profile

Demelverine hydrochloride is an antispasmodic that has been used in the treatment of smooth muscle spasm.

Deoxyribonucleic Acid

ADN; Animal Nucleic Acid; Desoxirribonucleico, ácido; Desoxypentose Nucleic Acid; Desoxyribonucleic Acid; Desoxyribose Nucleic Acid; DNA; Thymus Nucleic Acid; ДНК; Дезоксирибонуклеиновая Кислота.

UNII — 8JCB80Q5K1.

Profile

Deoxyribonucleic acid (DNA) is a nucleic acid (p. 2573.1) in which the pentose sugar moiety of the nucleotides is deoxyribose, the purine bases are adenine (p. 2430.2) and guanine, and the pyrimidine bases are cytosine and thymine. Hydrogen bonds between complementary pairs of purine and pyrimidine bases link 2 polynucleotide strands, which are twisted to form a double helix with the bases on the inside of the structure and the sugar-phosphate backbone on the outside. Pairing of bases between complementary strands of DNA is always the same: adenine with thymine and cytosine with guanine. DNA is present in cell nuclei and its function is to carry the genetic material of cellular organisms and DNA viruses. It also provides the template for the production of ribonucleic acid (p. 2604.1). For the role of DNA in gene therapy, see p. 2511.2.

Proprietary preparations of DNA are marketed in some countries for a variety of debilitating and convalescent conditions; the sodium and magnesium salts of DNA have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: ADN†; ***Ital.***: Placentex; ***Rus.***: Derinat (Деринат).

Multi-ingredient Preparations. ***Arg.***: RNA DNA; ***Fr.***: Osteogen†; ***India***: Placentrex.

Dextran Sulfate *(BANM, rINNM)*

Dextran, Sulfate de; Dextran Sulfate Sodium; Dextran Sulphate; Dextran Sulphate Sodium; Dextrani Sulfas; Dextrano, sulfato de; Sulfato de dextran; Декстрана Сульфат.

CAS — 9011-18-1.

ATC — B05AA05.

ATC Vet — QB05AA05.

Pharmacopoeias. In *Jpn*.

Profile

Dextran sulfate is the sodium salt of sulfuric acid esters of dextran. It has been used as an anticoagulant and as a lipid regulating drug, and has been investigated for its antiviral activity. Dextran sulfate potassium has also been used.

Interactions. As mentioned on p. 1287.1 (under Hypersensitivity), anaphylactoid reactions have occurred in patients receiving ACE inhibitors during low-density lipoprotein apheresis using a dextran sulfate-cellulose column.[1,2] Withdrawal of the ACE inhibitor for 1 to 3 days before apheresis may prevent the reaction.[2]

1. Olbricht CJ, *et al.* Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. *Lancet* 1992; **340:** 908–9.
2. Agishi T. Anion-blood contact reaction (ABC reaction) in patients treated by LDL apheresis with dextran sulfate-cellulose column while receiving ACE inhibitors. *JAMA* 1994; **271:** 195–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dextran as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Diroseal; ***Chile***: Cicapost; Diroseal; Ureadin Rx DB; ***Fr.***: Avene Antirougeurs; Creme au Melilot Composee†; Dextrarine Phenylbutazone; Diroseal†; ***Hung.***: Doxivenil†; ***Ital.***: Stranoval; ***Port.***: Cicapost; ***Switz.***: Doxivenil†; ***Venez.***: Doxivenil.

Dextrorphan *(BAN, pINN)*

Dextrorfano; Dextrorphane; Dextrorphanum; Ro-1-6794; Декстрорфан.

17-Methyl-9α,13α,14α-morphinan-3-ol.

$C_{17}H_{23}NO$=257.4

CAS — 125-73-5.

UNII — 04B7QNO9WS.

Dextrorphan Hydrochloride

(BANM, USAN, pINNM)

Dextrorfano, hidrocloruro de; Dextrorphane, Chlorhydrate de; Dextrorphani Hydrochloridum; Hidrocloruro de dextrorfano; Ro-01-6794/706; Декстрорфана Гидрохлорид.

$C_{17}H_{23}NO$,HCl=293.8

CAS — 69376-27-8.

Profile

Dextrorphan, a metabolite of dextromethorphan (p. 1660.1), is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It possesses some cough suppressant activity and has been investigated as a neuroprotective agent in the management of stroke.

References.

1. Albers GW, *et al.* Safety, tolerability, and pharmacokinetics of the N-methyl-D-aspartate antagonist dextrorphan in patients with acute stroke. *Stroke* 1995; **26:** 254–8.

Dichlorodiethylsulfide

Dichlorodiethylsulphide; Gas mostaza; Iperita; Mustard Gas; Sulfur Mustard; Sulfuro de dicloroetileno; Yellow Cross Liquid; Yperite.

Bis(2-chloroethyl)sulphide.

$C_4H_8Cl_2S$=159.1

CAS — 505-60-2.

UNII — T8KEC9FH9P.

Profile

Dichlorodiethylsulfide was developed for use in chemical warfare and has even more severe vesicant and irritant properties than its nitrogen analogue, chlormethine (p. 765.2). It was formerly used topically in the treatment of psoriasis.

Reviews of the toxicology of dichlorodiethylsulfide,[1-4] and debate on the management of casualties injured by dichlorodiethylsulfide and other chemical warfare agents.[5-11] Most patients exposed to dichlorodiethylsulfide recover largely or completely and only a small proportion will have severe long-term eye or lung damage,[12,13] although death from respiratory, renal, and bone-marrow

failure may occur.[11] A combination of 1% phenol and 1% menthol applied topically produced significant relief of pruritus compared with placebo in a randomised study of 80 war veterans with chronic skin lesions after exposure to dichlorodiethylsulfide.[14]

Eleven fishermen who accidentally retrieved corroded and leaking gas shells containing dichlorodiethylsulfide from underwater dumps, presented with very inflamed skin, especially in the axillary and genitofemoral regions, yellow blisters on the hands and legs, painful irritation of the eyes, and transient blindness. Two developed pulmonary oedema.[15] There was evidence of a mutagenic effect and in view of the increased risk of lung cancer in soldiers and workers exposed to the gas it is reasonable to assume that fishermen heavily exposed to dichlorodiethylsulfide also have an increased cancer risk.

1. Smith KJ, *et al*. Sulfur mustard: its continuing threat as a chemical warfare agent, the cutaneous lesions induced, progress in understanding its mechanism of action, its long-term health effects, and new developments for protection and therapy. *J Am Acad Dermatol* 1995; **32:** 765–76.
2. Dacre JC, Goldman M. Toxicology and pharmacology of the chemical warfare agent sulfur mustard. *Pharmacol Rev* 1996; **48:** 289–326.
3. Kehe K, Szinicz L. Medical aspects of sulphur mustard poisoning. *Toxicology* 2005; **214:** 198–209.
4. Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. *Fundam Clin Pharmacol* 2005; **19:** 297–315.
5. Heyndrickx A, Heyndrickx B. Management of war gas injuries. *Lancet* 1990; **ii:** 1248–9.
6. Fouyn T, *et al*. Management of chemical warfare injuries. *Lancet* 1991; **337:** 121.
7. Willems JL, *et al*. Management of chemical warfare injuries. *Lancet* 1991; **337:** 121–2.
8. Maynard RL, *et al*. Management of chemical warfare injuries. *Lancet* 1991; **337:** 122.
9. Newman-Taylor AJ, Morris AJR. Experience with mustard gas casualties. *Lancet* 1991; **337:** 242.
10. Heyndrickx A. Chemical warfare injuries. *Lancet* 1991; **337:** 430.
11. Rees J, *et al*. Mustard gas casualties. *Lancet* 1991; **337:** 430.
12. Murray VSG, Volans GN. Management of injuries due to chemical weapons. *BMJ* 1991; **302:** 129–30.
13. Khateri S, *et al*. Incidence of lung, eye, and skin lesions as late complications in 34 000 Iranians with wartime exposure to mustard agent. *J Occup Environ Med* 2003; **45:** 1136–43.
14. Panahi Y, *et al*. Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. *Singapore Med J* 2007; **48:** 392–5.
15. Wulf HC, *et al*. Sister chromatid exchanges in fishermen exposed to leaking mustard gas shells. *Lancet* 1985; **i:** 690–1.

Digitalin

Amorphous Digitalin; Digitalina; Digitalinum Purum Germanicum.
UNII — Q15ECE254B.

NOTE. Distinguish from Digitaline Cristallisée (digitoxin, p. 1353.1) which is very much more potent.

Profile

Digitalin is a standardised mixture of glycosides from *Digitalis purpurea*. It has actions similar to those of digoxin (p. 1353.3). Because of its ready solubility in water it was formerly used for the preparation of solutions for injection. It is also present in some ophthalmic preparations.

Dihydroxydibutylether

Dihidroxidibutiléter; Hydroxybutyloxide.
4,4′-Oxybis(butan-2-ol).
$C_8H_{18}O_3$=162.2
CAS — 821-33-0.

Profile

Dihydroxydibutylether is a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Dyskinebyl (保丹健素).

Multi-ingredient Preparations. ***Arg.***: Binvex; ***Ital.***: Dis-Cinil Complex.

Dill

Aneth; Anethum; Eneldo; Укроп.
UNII — Y05PC4JZRH.

NOTE. Indian Dill is the dried ripe fruits of *Anethum sowa*.

Pharmacopoeias. *Br.* includes Anethum Graveolens Sowa Fruit. *Fr.* includes dill fruit.

BP 2014: (Anethum Graveolens Sowa Fruit). The dried ripe fruit of *Anethum graveolens*. It contains not less than 0.3% of essential oil calculated with reference to the anhydrous drug.

Profile

Dill (*Anethum graveolens*, Apiaceae) is a culinary herb and has also been used in herbal medicine. It is the source of dill oil (see below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Colax†; Colax; ***Hung.***: Lactonic.

Homoeopathic Preparations. ***Canad.***: Lemon Balm†; ***Fr.***: Billerol.

Dill Oil

Aceite esencial de aneto; Aceite esencial de hinojo hediondo; Aceite esencial del falso anis; Eneldo, aceite esencial de; European Dill Seed Oil; Oleum Anethi; Укропное Масло.
CAS — 8016-06-6.
UNII — 86T27UW55G.

Pharmacopoeias. In *Br.*

BP 2014: (Dill Oil). A clear colourless or pale yellow liquid, visibly free from water, obtained by distillation from the dried ripe fruits of *Anethum graveolens*. It darkens with age and has a characteristic odour of the crushed fruit. It contains 43 to 63% of carvone. At 20 degrees, soluble 1 in 1 or more of alcohol (90%) and 1 in 10 or more of alcohol (80%). Store at a temperature not exceeding 25 degrees in well-filled containers. Protect from light.

Profile

Dill oil, usually in the form of dill water, is used as an aromatic carminative, although the efficacy of such traditional remedies in infant colic is considered dubious (see Gastrointestinal Spasm, p. 1807.1). It has also been used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Woodwards Gripe Water; ***Fr.***: Aromadetox†; Aromadigest†; Aromazen†; ***Hong Kong***: Infant-Sed†; ***Hung.***: Woodward's Gripe Water; ***India***: Bestozyme P; Bestozyme; Betip; Carmicide DPS; Colicaid; Coliky; Coliza; Cymbi; Decolic Infant; DP-Spas DPS; Gastica; Merispas; Merozyme-C; Neopeptine; Panoric; ***Israel***: Dentinox; Nurse Harvey's Gripe Mixture; Woodwards Gripe Water; ***Malaysia***: Bonnisan; ***Rus.***: Solutan (Солуган)†; ***Singapore***: Dentinox Colic Drops; ***Thai.***: Baby Gripe†; Bebidol; Gripe Mixture; Woodwards Gripe Water†; ***UK***: Atkinson & Barker's Gripe Mixture; Neo Baby Gripe Mixture; Neo Gripe Mixture; Nurse Harvey's Gripe Mixture; Woodwards Gripe Water.

Dimecrotic Acid *(rINN)*

Acide Dimécrotique; Ácido dimecrótico; Acidum Dimecroticum; Димекротовая Кислота.
2,4-Dimethoxy-β-methylcinnamic acid.
$C_{12}H_{14}O_4$=222.2
CAS — 7706-67-4.
UNII — R46Y1C0ZR2.

Profile

Dimecrotic acid has been used as the magnesium salt as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hepadial; ***Port.***: Hepadoddi; Hepaquifa†; ***Spain***: Fisiobil.

Dimethoxymethane

Dimethoximethane; Dimetoximetano; Formal; Formaldehído dimetilacetal; Formaldehyde Dimethyl Acetal; Methylal; Metilal; Метилаль; Диметоксиметан.
$CH_2(OCH_3)_2$=76.10
CAS — 109-87-5.
UNII — 7H1M4G2NUE.

Profile

Dimethoxymethane has been used in perfumery. It has been included in preparations for topical analgesia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: PR Freeze Spray.

Dimethyl Sulfone

Dimethyl Sulphone; Dimetylosulfon; $DMSO_2$; Methyl Sulphone; Methylsulfonylmethane; Methylsulphonylmethane; MSM; Sulfonylbismethane; Диметилсульфон.
$C_2H_6O_2S$=94.13
CAS — 67-71-0.
UNII — 9H4PO4Z4FT.

Pharmacopoeias. In *US.*

USP 36: (Methylsulfonylmethane). A white powder or flake crystal. Freely soluble in water, in alcohol, in acetone, and in methyl alcohol; sparingly soluble in ether.

Profile

Dimethyl sulfone is an oxidation product of dimethyl sulfoxide (p. 2182.2) and has been used similarly as an organic solvent. It may be responsible for some of the pharmacological actions of dimethyl sulfoxide and has been tried in disorders including osteoarthritis, allergic rhinitis, and interstitial cystitis. It has also been used as a nutritional supplement.

References.

1. Ely A, Lockwood B. What is the evidence for the safety and efficacy of dimethyl sulfoxide and methylsulfonylmethane in pain relief? *Pharm J* 2002; **269:** 685–7.
2. Anonymous. Methylsulfonylmethane (MSM). *Altern Med Rev* 2003; **8:** 438–41.
3. Brien S, *et al*. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2008**16:** 1277–88.

Musculoskeletal and joint disorders. An evidence-based report[1] into the use of complementary medicines to treat rheumatic diseases concluded that dimethyl sulfone may have a moderate effect in improving symptoms of osteoarthritis, although the evidence is limited and from short-term studies.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Synchrorose.

Multi-ingredient Preparations. ***Arg.***: Glucometil 3; Glucometil K Duo; ***Austral.***: Joint Formula Advanced with MSM Booster; Osteo-Relief Plus MSM; OsteoEze Active + MSM; ***Fr.***: Rhumadol; ***India***: Altocerin-GM; Baknil; Bonjo Aid; Cartigen Plus; Cartivit; Cartiwel; Cartizole Plus; Compensate; Conjoint; Cool-Joint; DN Plus; Fremov-ME; Fremov; Joint Guard; Jointace-DN; Jointop; Jonty; Mecocas-Ortho; Mobijoint; Necare; Nurokind Ortho; OA Plus; Orbone; Orthocerin-G; Osicare; Ostawin; Osteojoin-D; Ostiwel Forte; Paclo-GMD; ***Indon.***: Aptivium Optimum Joint Formula†; Artriox†; Artritin; Artro Plus; Bonic Plus; Cartiflex; GCM; Joint Care Plus; Jointace; Maxitrin†; OA Plus; Ositin; Osteoflam; Osteokom Forte; Osteokom; Osteor Plus; Ostrimix; Osvion Plus; Rebone; Risteon; Triflexor; Triostee; Viopor-M Forte; Viopor-M; Viostin-X; ***Israel***: Mega Gluflex with MSN; ***Ital.***: Artrosulfur; Broncosulfur; Condrorexil; Neosulfur†; Osteoclar; Osteolip Crema; Reumafort; Rino Get; ***Mex.***: Mex-Amina; ***Philipp.***: Lungcaire Plus; Osteoaid; ***Port.***: Synchrorose Intensivo; ***S.Afr.***: ProFLEX 750†; ***UK***: GlucOsamax; NatraFlex; PainEaze; ***Ukr.***: Arthron-Triactive (Артрон Триактив); Artritosamin (Артритозамин); Flex-A-Min Complex (Флекс-А-Мин Комплекс)†; ***USA***: Stopain Cold Extra Strength.

Pharmacopoeial Preparations
USP 36: Glucosamine and Methylsulfonylmethane Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets; Methylsulfonylmethane Tablets.

p,α-Dimethylbenzyl Alcohol

Tolinol; *p*-Tolylmethylcarbinol; Tolynolum.
1-(*p*-Tolyl)ethanol.
$C_9H_{12}O$=136.2
CAS — 536-50-5.

NOTE. The name tolynol has been applied to both *p*,α-dimethylbenzyl alcohol and mephenesin (p. 2025.2).

Profile

p,α-Dimethylbenzyl alcohol has been used as a choleretic in the treatment of hepatic disorders and is an ingredient of preparations for gastrointestinal disorders. *p*,α-Dimethylbenzyl alcohol nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Apozema†; Galle-Donau; Spasmo Claim†; ***China***: Galle-Donau (加诺).

Dimethyltryptamine

Dimetiltriptamina; DMT; *N,N*-Dimethyltryptamine.
3-(2-Dimethylaminoethyl)indole.
$C_{12}H_{16}N_2$=188.3
CAS — 61-50-7.
UNII — WUB601BHAA.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dimethyltryptamine:

45 Minute Psychosis; 45 Minute Trip; AMT; Businessman's LSD; Businessman's special; Businessman's trip; DET; Disneyland; Disneyworld; Dmitri; DMT; Fantasia; Instant psychosis; Psychosis.

Profile

Dimethyltryptamine is an active principle obtained from the seeds and leaves of *Piptadenia peregrina* (Mimosaceae) from which the hallucinogenic snuff cohoba is prepared. It may also be obtained from other South American plants. It has been reported to be present in the tropical legume *Mucuna pruriens*.

Dimethyltryptamine produces hallucinogenic and sympathomimetic effects that are similar to those of lysergide (p. 2547.1), but of shorter duration. It has no therapeutic use. Related synthetic hallucinogens subject to abuse include:

- diethyltryptamine (DET)
- dipropyltryptamine (DPT)
- 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DiPT; Foxy; Foxy Methoxy; Methoxy Foxy)

References.

1. Alatrash G, *et al.* Rhabdomyolysis after ingestion of "foxy," a hallucinogenic tryptamine derivative. *Mayo Clin Proc* 2006; **81:** 550–1.

Dimevamide *(rINN)*

Aminopentamide; Dimevamida; Dimévamide; Dimevamidum; Димевамид.
α-[2-(Dimethylamino)propyl]-α-phenylbenzeneacetamide.
$C_{19}H_{24}N_2O$=296.4
CAS — 60-46-8.
UNII — IP1B47L61M.

Dimevamide Sulfate *(rINNM)*

Aminopentamide Sulfate; Dimevamida, sulfato de; Diméva-mide, Sulfate de; Dimevamidi Sulfas; Sulfato de dimevamida; Димевамида Сульфат.
$C_{19}H_{24}N_2O,H_2SO_4$=394.5
CAS — 35144-63-9 (xH_2SO_4).
UNII — 20P9NI883O.

Pharmacopoeias. In *US* for veterinary use only.

Profile

Dimevamide is a tertiary amine and has been used as an antimuscarinic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Kantrexil.

2,4-Dinitrochlorobenzene

2,4-Dinitroclorobenceno; DNCB; 2,4-Динитрохлорбензол.
1-Chloro-2,4-dinitrobenzene.
$C_6H_3ClN_2O_4$=202.6
CAS — 97-00-7.

Profile

2,4-Dinitrochlorobenzene is a potent sensitiser that has been applied topically in the evaluation of delayed hypersensitivity. It has also been used as an immunostimulant in various conditions including some forms of cancer, and in the treatment of alopecia and warts. It has also been investigated in HIV infection and leprosy.

2,4-Dinitrochlorobenzene has been reported to be mutagenic *in vitro*.

References.

1. Happle R. The potential hazards of dinitrochlorobenzene. *Arch Dermatol* 1985; **121:** 330–2.
2. Todd DJ. Topical treatment with dinitrochlorobenzene. *Lancet* 1995; **346:** 975.
3. Stricker RB, Goldberg B. Safety of topical dinitrochlorobenzene. *Lancet* 1995; **346:** 1293.
4. Strobbe LJ, *et al.* Topical dinitrochlorobenzene combined with systemic dacarbazine in the treatment of recurrent melanoma. *Melanoma Res* 1997; **7:** 507–12.
5. Yoshizawa Y, *et al.* Successful immunotherapy of chronic nodular prurigo with topical dinitrochlorobenzene. *Br J Dermatol* 1999; **141:** 387–9.
6. Yoshizawa Y, *et al.* Topical dinitrochlorobenzene therapy in the treatment of refractory atopic dermatitis: systemic immunotherapy. *J Am Acad Dermatol* 2000; **42:** 258–62.
7. Yoshizawa Y, *et al.* Systemic immunotherapy with topical dinitrochlorobenzene as additional treatment of alopecia areata. *Acta Derm Venereol* 2002; **82:** 136–8.
8. von Nida J, Quirk C. Successful treatment of in-transit melanoma metastases using topical 2-4 dinitrochlorobenzene. *Australas J Dermatol* 2003; **44:** 277–80.

Dioxins

NOTE. The name Dioxin has also been applied to dimethoxane.

Profile

The term 'dioxins' encompasses a large group of closely related chemicals known as polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). The most toxic is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

Dioxins are byproducts in the manufacture of commercial chemical products such as chlorinated phenols and polychlorinated biphenyls (PCBs), and can also be produced in smaller quantities by combustion processes and industrial waste. They first came to public attention during the Vietnam war, when they were found to be present in the herbicide Agent Orange used as a defoliant. They are incriminated as causing chloracne (a severe and persistent acne caused by chlorinated compounds). They are potent teratogens and carcinogens in *animals*. An increased incidence of cancer at different organs due to dioxins has been claimed but this has not been substantiated by clinical and follow-up studies. An effect on cell-mediated immunity has been noted.

Exposure should be limited to the lowest feasible concentration.

Adverse effects. The impact of dioxins in food and the environment has been reviewed.[1-4]

An excess of soft tissue sarcomas was found in workers exposed to chlorophenoxy herbicides including those contaminated with TCDD,[5] but cautious interpretation of these results was advised.[6] In Vietnam veterans the risk of non-Hodgkin's lymphoma was about 50% higher than control subjects, but was not related to exposure to Agent Orange, nor was there evidence for an increase in other cancers.[7] Exposure to TCDD was implicated in an increase in cancer mortality in chemical workers,[8,9] but confounding factors such as smoking may have been present.[9,10] Other studies[11,12] have not shown an association between dioxin exposure and an increase in the incidence of human cancer, and epidemiological studies after occupational or accidental exposures have found no clear persistent systemic effects, except for chloracne, and no clear association with carcinogenesis or reproductive disorders.[1,2] Decreased plasma immunoglobulin G concentrations were measured in people after exposure to TCDD 20 years earlier as a result of accidental environmental contamination in Seveso, Italy.[13] A statistically significant increase in the incidence of breast cancer related to serum levels of TCDD was seen in a cohort of 981 women who ranged in age from infancy to 40 years in 1976 at the time of the Seveso accident.[14] The authors pointed out that this cohort is relatively young and continued follow-up would clarify any possible pathogenic role of TCDD.

In the USA, the National Academy of Sciences' Institute of Medicine is reported to have carried out an evaluation of publications on herbicide exposure, largely in industrial and agricultural workers.[15] They concluded that exposure to herbicides or dioxin was associated with soft-tissue sarcomas, Hodgkin's disease, non-Hodgkin lymphoma, chloracne, and porphyria cutanea tarda, and that there was limited evidence of an association with respiratory and prostate cancers and multiple myeloma. An update to the report has also suggested a link between Agent Orange exposure and spina bifida in veterans' offspring.[16] There is some evidence that exposure of men to TCDD is associated with a decreased male to female sex ratio in their offspring.[17] Results from studies[18-20] suggest that prenatal exposure to PCBs has an effect on mental and motor development in early childhood, although this may be counteracted by an advantageous home environment. However, virtually no adverse effects in relation to postnatal exposure to PCBs present in breast milk were shown.[20]

1. Food Standards Agency UK. Dioxins and PCBs in the UK diet: 1997 Total Diet Study (Number 04/00) (issued September 2000). Available at: http://www.food.gov.uk/science/surveillance/fsis2000/4diox (accessed 24/07/08)
2. DEFRA. Dioxins and dioxin-like PCBs in the UK environment (issued October 2002). Available at: http://www.scotland.gov.uk/Resource/Doc/1052/0002248.pdf (accessed 24/07/08)
3. WHO. Dioxins and their effects on human health (issued November 2007). Available at: http://www.who.int/mediacentre/factsheets/fs225/en/print.html (accessed 24/07/08)
4. FAO. Dioxins in the food chain: prevention and control of contamination (issued April 2008). Available at: http://www.fao.org/ag/agn/agns/files/Dioxin_fact%20sheet.pdf (accessed 24/07/08)
5. Saracci R, *et al.* Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991; **338:** 1027–32.
6. Peto R. Occupational exposure to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991; **338:** 1392.
7. Suskind R. The association of selected cancers with service in the US military in Vietnam. *Arch Intern Med* 1990; **150:** 2449–50.
8. Manz A, *et al.* Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 1991; **338:** 959–64.
9. Fingerhut MA, *et al.* Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 1991; **324:** 212–18.
10. Triebig G. Is dioxin carcinogenic? *Lancet* 1991; **338:** 1592.
11. Coggon O, *et al.* Mortality and incidence of cancer at four factories making phenoxy herbicides. *Br J Ind Med* 1991; **48:** 173–8.
12. Green LM. A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. *Br J Ind Med* 1991; **48:** 234–8.
13. Baccarelli A, *et al.* Immunologic effects of dioxin: new results from Seveso and comparison with other studies. *Environ Health Perspect* 2002; **110:** 1169–73.
14. Warner M, *et al.* Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect* 2002; **110:** 625–8.
15. McCarthy M. Agent Orange. *Lancet* 1993; **342:** 362.
16. Stephenson J. New IOM report links Agent Orange Exposure to risk of birth defect in Vietnam vets' children. *JAMA* 1996; **275:** 1066–7.
17. Mocarelli P, *et al.* Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 2000; **355:** 1858–63.
18. Walkowiak J, *et al.* Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *Lancet* 2001; **358:** 1602–7.
19. Vreugdenhil HJ, *et al.* Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. *J Pediatr* 2002; **140:** 48–56.
20. Jacobson JL, Jacobson SW. Association of prenatal exposure to an environmental contaminant with intellectual function in childhood. *J Toxicol Clin Toxicol* 2002; **40:** 467–75.

Diphemanil Metilsulfate *(BAN, rINN)*

Difemanilo, metilsulfato de; Diphemanil Methylsulfate; Diphemanil Methylsulphate; Diphémanil, Métilsulfate de; Diphenanili Metilsulfas; Diphenmethanil Methylsulphate; Metilsulfato de difemanilo; Vagophemanil Methylsulphate; Дифеманила Метилсульфат.
4-Benzhydrylidene-1,1-dimethylpiperidinium methylsulphate.
$C_{20}H_{24}N,CH_3SO_4$=389.5
CAS — 62-97-5.
ATC — A03AB15.
ATC Vet — QA03AB15.
UNII — W2ZG23MGYI.

Profile

Diphemanil metilsulfate is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used topically as a 2% cream or powder to treat hyperhidrosis (p. 1685.1).

Diphemanil metilsulfate, given orally, has been used for the treatment of symptomatic bradycardia in infants.

References.

1. Vidal AM, *et al.* Pharmacokinetics of diphemanil methylsulphate in healthy subjects. *Eur J Clin Pharmacol* 1992; **42:** 689–91.
2. Vidal AM, *et al.* Pharmacokinetics of diphemanil methylsulphate in infants. *Eur J Clin Pharmacol* 1993; **45:** 89–91.
3. Pariente-Khayat A, *et al.* Pharmacokinetics of diphemanil methylsulphate in neonates and in premature infants. *Eur J Clin Pharmacol* 1996; **50:** 429–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Prantal; ***NZ***: Prantal†.

Diphenyl

Bifenilo; Difenilo; E230; Fenilbenceno; Phenylbenzene; Дифенил.
Biphenyl.
$C_{12}H_{10}$=154.2
CAS — 92-52-4.
UNII — 2L9GJK6MGN.

Profile

Diphenyl is fungistatic against a limited number of moulds and has been employed for impregnating the material used for wrapping citrus fruits.

Adverse effects. Workers exposed to high concentrations of diphenyl (up to 128 mg/m^3) developed toxic symptoms that included irritation of the throat and eyes, headache, nausea, diffuse abdominal pain, numbness, aching of limbs, and general fatigue.[1] One of the workers, who also had somnolence, icterus, ascites, and oedema of the legs,

died; at autopsy, the liver showed necrosis. Chronic hepatitis was reported in a woman exposed over a 25-year period to diphenyl in the paper used to pack citrus fruit.[2] There has also been a report[3] of a small cluster of cases of parkinsonism associated with diphenyl exposure.

1. Häkkinen I, *et al.* Diphenyl poisoning in fruit paper production. *Arch Environ Health* 1973; **26:** 70–4.
2. Carella G, Bettolo PM. Reversible hepatotoxic effects of diphenyl: report of a case and a review of the literature. *J Occup Med* 1994; **36:** 575–6.
3. Wastensson G, *et al.* Parkinson's disease in diphenyl-exposed workers—a causal association? *Parkinsonism Relat Disord* 2006; **12:** 29–34.

Dipivefrine *(BAN, rINN)* ⊗

Dipivalyl Epinephrine; Dipivefriini; Dipivefrin (USAN); Dipivefrina; Dipivéfrine; Dipivefrinum; DPE; Дипивефрин.

$C_{19}H_{29}NO_5$=351.4

CAS — 52365-63-6.

ATC — S01EA02.

ATC Vet — QS01EA02.

UNII — 8Q1PVL543G.

Dipivefrine Hydrochloride *(BANM, rINNM)* ⊗

Dipivalyl Adrenaline Hydrochloride; Dipivalyl Epinephrine Hydrochloride; Dipivefriinihydrokloridi; Dipivefrin Hydrochloride; Dipivefrina, hidrocloruro de; Dipivéfrine, chlorhydrate de; Dipivefrinhydrochlorid; Dipivefrin-hydrochlorid; Dipivefrinhydroklorid; Dipivefrini Hydrochloridum; Dipivefrino hidrochloridas; Dipiwefryny chlorowodorek; Hidrocloruro de dipivefrina; Дипивефрина Гидрохлорид.

(*RS*)-4-[1-Hydroxy-2-(methylamino)ethyl]-*o*-phenylene dipivalate hydrochloride.

$C_{19}H_{29}NO_5$,HCl=387.9

CAS — 64019-93-8.

ATC — S01EA02.

ATC Vet — QS01EA02.

UNII — 5QTH9UHV0K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Dipivefrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane; very soluble in methyl alcohol.

USP 36: (Dipivefrin Hydrochloride). White, crystalline powder or small crystals, having a faint odour. Very soluble in water. Store in airtight containers.

Profile

Dipivefrine is an ester and prodrug of adrenaline (p. 1292.1). A 0.1% solution of the hydrochloride is used topically as eye drops to reduce intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (p. 1999.1).

References.

1. Parrow KA, *et al.* Is it worthwhile to add dipivefrin HCl 0.1% to topical β_1-, β_2-blocker therapy? *Ophthalmology* 1989; **96:** 1338–41.
2. Drake MV, *et al.* Levobunolol compared to dipivefrin in African American patients with open angle glaucoma. *J Ocul Pharmacol* 1993; **9:** 91–5. Correction. *ibid.*; 385.
3. Albracht DC, *et al.* A double-masked comparison of betaxolol and dipivefrin for the treatment of increased intraocular pressure. *Am J Ophthalmol* 1993; **116:** 307–13.
4. Widengard I, *et al.* Effects of latanoprost and dipivefrin, alone or combined, on intraocular pressure and on blood-aqueous barrier permeability. *Br J Ophthalmol* 1998; **82:** 404–6.
5. Vilaplana J, *et al.* Contact dermatitis by dipivefrine. *Contact Dermatitis* 2005; **52:** 169–70.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dipivefrine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 31/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dipoquin†; Propine†; ***Belg.***: Propine†; ***Braz.***: Propine; ***Canad.***: Propine†; ***Denm.***: Propine†; ***Fin.***: Propine†; ***Fr.***: Propine†; ***Ger.***: d Epifrin†; Glaucothil†; ***Gr.***: Diopine; Glaucodose; Pivefrin; Prodren; Thilodrin; ***Hong Kong***: Propine†; ***Irl.***: Propine†; ***Israel***: Difrin†; ***Ital.***: Propine; ***Jpn***: Pivalephrine; ***Neth.***: Diopine†; ***Norw.***: Propine†; ***NZ***: Propine†; ***Singapore***: Propine†; ***Spain***: Diopine†; ***Swed.***: Propine†; ***Thai.***: Propine; ***UK***: Propine†; ***USA***: AkPro†; Propine.

Multi-ingredient Preparations. ***Austria***: Thiloadren†; ***Canad.***: Probeta†; ***Ger.***: Thilodigon†; ***Gr.***: Ryvina; Thilocombin; Thilodigon.

Pharmacopoeial Preparations

BP 2014: Dipivefrine Eye Drops;

USP 36: Dipivefrin Hydrochloride Ophthalmic Solution.

Diquafosol Tetrasodium *(BANM, USAN, rINNM)*

Dicuafosol tetrasódico; Diquafosol tetrasodique; Diquafosolum tetranatricum; INS-365; Диквафозол Тетранатрий.

Uridine(5′)tetraphospho(5′)uridine tetrasodium.

$C_{18}H_{22}N_4Na_4O_{23}P_4$=878.2

CAS — 211427-08-6.

UNII — X8T95BH9LL.

NOTE. The code KPY-998 has been variously applied to diquafosol and to diquafosol tetrasodium. The name Prolacria has been used as a trade mark for diquafosol tetrasodium.

Profile

Diquafosol is a $P2Y_2$-receptor agonist and has mucolytic properties. It is used as the tetrasodium salt in the management of dry eyes and has also been studied in respiratory disorders including cystic fibrosis.

References.

1. Nichols KK, *et al.* Diquafosol tetrasodium: a novel dry eye therapy. *Expert Opin Invest Drugs* 2004; **13:** 47–54.
2. Tauber J, *et al.* Double-masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. *Cornea* 2004; **23:** 784–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Diquas.

Disodium Guanylate

Disodium Guanosine-5′-monophosphate; E627; Guanilato disódico; Sodium 5′-Guanylate; Гуанилат Натрия Двузамещенный.

Guanosine 5′-(disodium phosphate).

$C_{10}H_{12}N_5Na_2O_8P.xH_2O$=407.2 (anhydrous)

CAS — 5550-12-9 (anhydrous disodium guanylate).

UNII — B768T44Q8V.

Profile

Disodium guanylate is used in preparations containing other nucleosides in the treatment of corneal damage. Disodium guanylate has been used as a flavour enhancer in foods. The term sodium 5′-ribonucleotide (disodium 5′-ribonucleotide) has been used to refer to a mixture of disodium guanylate with disodium inosinate (see below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Mon.***: Vitacic.

Disodium Inosinate

Disodium Inosine-5′-monophosphate; E631; Inosinato disódico; Inosinato sódico; Sodium 5′-Inosinate; Инозинат Натрия Двузамещённый; 5′-Inosinato disódico; 5′-Inosinato sódico.

Inosine 5′-(disodium phosphate).

$C_{10}H_{11}N_4Na_2O_8P.xH_2O$=392.2 (anhydrous)

CAS — 4691-65-0 (anhydrous disodium inosinate).

UNII — T2ZYA7KC05.

Profile

Disodium inosinate has been used as a flavour enhancer in foods. It has also been given orally and been applied topically in the treatment of visual disturbance. The term sodium 5′-ribonucleotide has been used to refer to a mixture of disodium inosinate with disodium guanylate (above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Inokat; Lumiclar; Opacout; ***Fr.***: Catacol; Correctol; ***Ger.***: Antikataraktikum N†.

Disodium Uridine Monophosphate

Disodium UMP; Уридин Монофосфат Динатрия.

5′-Uridylic acid, disodium salt; disodium 5′ uridylate.

$C_9H_{11}N_2O_9PNa_2$=368.1

CAS — 3387-36-8.

Profile

Uridine monophosphate is an endogenous uracil nucleotide involved in many biological processes. Disodium uridine monophosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; disodium uridine diphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Keltican N†; ***Spain***: Nucleo CMP; ***Ukr.***: Keltican (Келтикан); Nucleo CMF Forte (Нуклео ЦМФ Форте).

Disulfiram *(BAN, rINN)*

Dissulfiramo; Disulfiraami; Disulfiramas; Disulfirame; Disulfiramo; Disulfiramum; Diszulfirám; Éthyldithiourame; TTD; Дисульфирам.

Tetraethylthiuram disulphide; Bis(diethylthiocarbamoyl) disulfide.

$C_{10}H_{20}N_2S_4$=296.5

CAS — 97-77-8.

ATC — N07BB01; P03AA04.

ATC Vet — QN07BB01; QV03AA01.

UNII — TR3MLJ1UAI.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Disulfiram). A white or almost white, crystalline powder. M.p. 70 degrees to 73 degrees. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Disulfiram). A white to off-white, odourless crystalline powder. M.p. 69 degrees to 72 degrees. Very slightly soluble in water; soluble 1 in 30 of alcohol and 1 in 15 of ether; soluble in acetone, in carbon disulfide, and in chloroform. Store in airtight containers. Protect from light.

Stability. Studies[1,2] on the stability of disulfiram preparations.

1. Gupta VD. Stability of aqueous suspensions of disulfiram. *Am J Hosp Pharm* 1981; **38:** 363–4.
2. Philips M, *et al.* Stability of an injectable disulfiram formulation sterilized by gamma irradiation. *Am J Hosp Pharm* 1985; **42:** 343–5.

Uses and Administration

Disulfiram is used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p. 1734.1). Disulfiram is not a cure and the treatment is likely to be of little value unless it is undertaken with the willing cooperation of the patient and is used with supportive psychotherapy.

Disulfiram inhibits aldehyde dehydrogenase, the enzyme responsible for the oxidation of acetaldehyde, a metabolite of alcohol. The resulting accumulation of acetaldehyde in the blood is widely believed to be responsible for many of the unpleasant symptoms of the disulfiram-alcohol reaction which occur when alcohol is taken, even in small quantities, after disulfiram (see Adverse Effects and Treatment, p. 2496.1). Symptoms can arise within 10 minutes of the ingestion of alcohol and last from half an hour in mild cases to several hours in severe cases. It is advisable to carry out the initial treatment in hospital or in a specialised unit where the patient can be kept under close supervision.

Disulfiram is given orally. In the UK, the dose is 800 mg, taken as a single dose, on the first day of treatment, reduced by 200 mg daily to a maintenance dose which is usually 100 to 200 mg daily. In the USA, where doses above 500 mg daily are not recommended, an initial dose of 500 mg daily for 1 to 2 weeks is given, followed by a maintenance dose of 250 mg daily or within the range of 125 to 500 mg daily. Treatment should be reviewed after no longer than 6 months. Maintenance therapy with disulfiram may need to be continued for months or years, until the patient is fully recovered socially and a basis for permanent self-control has been established.

A test dose of alcohol has been given under close supervision when the patient is receiving maintenance doses of disulfiram, in order to demonstrate the nature of the disulfiram-alcohol reaction. However, these challenge tests are not routinely recommended, and should not in any case be used in patients over 50 years of age. Many authorities consider that an explicit description of the reaction is sufficient.

Disulfiram implants have been used in an attempt to overcome problems of patient compliance but have been largely abandoned due to lack of clinical efficacy.

Alcoholism. References.

1. Wright C, Moore RD. Disulfiram treatment of alcoholism. *Am J Med* 1990; **88:** 647–55.
2. Hughes JC, Cook CCH. The efficacy of disulfiram: a review of outcome studies. *Addiction* 1997; **92:** 381–95.
3. O'Shea B. Disulfiram revisited. *Hosp Med* 2000; **61:** 849–51.
4. Brewer C, *et al.* Does disulfiram help to prevent relapse in alcohol abuse? *CNS Drugs* 2000; **14:** 329–341.
5. Suh JJ, *et al.* The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006; **26:** 290–302.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; disulfiram is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (see Cocaine Withdrawal Syndrome, p. 1986.1).

References.
1. Carroll KM, *et al*. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004; **61:** 264–72.

Adverse Effects and Treatment

Drowsiness and fatigue are common during initial treatment with disulfiram. Other adverse effects reported include a garlic-like or metallic aftertaste, gastrointestinal upsets, body odour, bad breath, headache, impotence, and allergic dermatitis. Peripheral and optic neuropathies, psychotic reactions, and hepatotoxicity may occur.

Disulfiram-alcohol reaction. The use of disulfiram in the management of alcoholism is based on the extremely unpleasant, but generally self-limiting, systemic effects that occur when a patient receiving the drug ingests alcohol. These effects begin with flushing of the face and, as vasodilatation spreads, throbbing in the head and neck and a pulsating headache may develop. Respiratory difficulties, nausea, copious vomiting, sweating, thirst, chest pain, tachycardia, palpitations, marked hypotension, giddiness, weakness, blurred vision, and confusion may follow. The intensity and duration of symptoms is very variable and even small quantities of alcohol may result in alarming reactions. In addition to the above effects, severe reactions have included respiratory depression, cardiovascular collapse, cardiac arrhythmias, myocardial infarction, acute heart failure, unconsciousness, convulsions, and sudden death.

Severe reactions require intensive supportive therapy; oxygen and intravenous fluids may be necessary. Potassium concentrations should be monitored. Giving intravenous ascorbic acid, ephedrine sulfate, or antihistamines has been suggested.

Reviews.
1. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Safety* 1999; **20:** 427–35.

Effects on the blood. There were isolated reports of blood dyscrasias associated with disulfiram in the 1960s. US licensed product information recommends that blood counts should be performed during treatment.

Effects on the liver. A review of 18 cases of hepatitis in patients receiving disulfiram.[1] Symptoms have appeared between 10 days and 6 months after starting disulfiram, and clinical improvement has been seen within 2 weeks of stopping the drug, although liver enzyme values may not return to normal for several months. Fatal hepatic coma had been reported in 7 patients. The clinical picture of disulfiram-induced hepatitis is consistent with a hypersensitivity reaction. Another review[2] evaluated 82 cases of liver injury thought to be due to disulfiram and reported to the Swedish Adverse Drug Reactions Advisory Committee between 1966 and 2002. All but one of the cases were of hepatocellular liver damage, and 4 patients died and 4 underwent liver transplantation. Although there was some evidence that hypersensitivity played a role, it might not be the only mechanism of disulfiram-induced liver disease.

1. Mason NA. Disulfiram-induced hepatitis: case report and review of the literature. *DICP Ann Pharmacother* 1989; **23:** 872–4.
2. Björnsson E, *et al*. Clinical characteristics and prognostic markers in disulfiram-induced liver injury. *J Hepatol* 2006; **44:** 791–7.

Effects on the nervous system. *ENCEPHALOPATHY.* A 2% incidence of reversible toxic encephalopathy has been reported in patients receiving disulfiram.[1] Onset varies from days to months following the start of therapy and early signs include impaired concentration, memory deficits, anxiety, depression, and somnolence. Confusion and disorientation follow, often accompanied by paranoid delusions and sometimes hallucinations. Other symptoms may include ataxia, loss of fine motor coordination, slurred speech, and intention tremor. The encephalopathy usually resolves within 3 days to 2 weeks of stopping disulfiram, although symptoms may persist for 6 weeks. There are conflicting opinions on whether this psychosis is a toxic reaction to disulfiram or a response to abstinence from alcohol, but the authors suspected that most cases represent a toxic encephalopathy. However, psychosis without any suggestion of encephalopathy has been reported.[2]

1. Hotson JR, Langston JW. Disulfiram-induced encephalopathy. *Arch Neurol* 1976; **33:** 141–2.
2. Rossiter SK. Psychosis with disulfiram prescribed under probation order. *BMJ* 1992; **305:** 763.

PERIPHERAL NEUROPATHY. Reports of peripheral neuropathy associated with disulfiram and reference to previously reported cases.[1,2] Onset of neuropathy varied from days to months after starting disulfiram treatment and could develop with doses of 250 or 500 mg daily. The most common symptom reported was pins and needles, but numbness, pain/burning, and weakness were frequently described; usually both muscle weakness and sensory loss were noted. Optic atrophy has also been described. Although there might be some improvement immediately after disulfiram withdrawal, the neurological deficit only improved slowly and symptoms might persist for as long as 2 years.[1]

1. Watson CP, *et al*. Disulfiram neuropathy. *Can Med Assoc J* 1980; **123:** 123–6.
2. Frisoni GB, Di Monda V. Disulfiram neuropathy: a review (1971-1988) and report of a case. *Alcohol Alcohol* 1989; **24:** 429–37.

Effects on the respiratory tract. Bronchospasm and hypertension occurred in an asthmatic patient taking disulfiram after an alcohol challenge test.[1]

1. Zapata E, Orwin A. Severe hypertension and bronchospasm during disulfiram-ethanol test reaction. *BMJ* 1992; **305:** 870.

Effects on the skin. Orange-coloured palms and soles, provoking an initial diagnosis of jaundice, developed in a 55-year-old man who had been taking disulfiram for about 2 months.[1] It was postulated that the discoloration was due to accumulation of carotenes in the skin as a result of inhibition of vitamin A metabolism by disulfiram. The discoloration disappeared soon after disulfiram was stopped.

1. Santonastaso M, *et al*. Yellow palms with disulfiram. *Lancet* 1997; **350:** 266.

Overdosage. A 6-year-old boy had disulfiram intoxication after receiving disulfiram 250 mg four times daily to a total of 13 doses; he recovered later.[1] Of 6 previous reports one child died and 3 had moderate or severe brain damage. The syndrome of disulfiram intoxication in children is distinct from the disulfiram-alcohol interaction or acute disulfiram intoxication in adults. It is characterised by lethargy or somnolence, weakness, hypotonia, and vomiting, beginning about 12 hours after ingestion and progressing to stupor or coma. Dehydration, moderate tachycardia, and marked tachypnoea occur frequently, muscle tone is greatly decreased, and deep-tendon reflexes may be weak or absent.

Severe neurological damage has also been reported[2] in a 5-year-old girl after acute disulfiram intoxication which was initially diagnosed as diabetic ketoacidosis.

1. Benitz WE, Tatro DS. Disulfiram intoxication in a child. *J Pediatr* 1984; **105:** 487–9.
2. Mahajan P, *et al*. Basal ganglion infarction in a child with disulfiram poisoning. *Pediatrics* 1997; **99:** 605–8.

Precautions

Disulfiram is contra-indicated in the presence of cardiovascular disease or psychosis or severe personality disorders, and should not be given to patients known to be hypersensitive to it or to other thiuram compounds, such as those used in rubber vulcanisation or pesticides. It should be used with caution in the presence of diabetes mellitus, epilepsy, impaired hepatic or renal function, respiratory disorders, cerebral damage, or hypothyroidism. Caution is also advised when giving disulfiram to those who are addicted to other drugs in addition to alcohol. It is probably best avoided in pregnancy.

Disulfiram should not be given until at least 24 hours after the last ingestion of alcohol. Patients beginning therapy should be fully aware of the disulfiram-alcohol reaction and should be warned to avoid alcohol in any form, including alcohol-containing medicines and alcohol-based topical preparations. Reactions to alcohol may occur as long as 2 weeks after the cessation of disulfiram.

The US manufacturers have recommended that regular blood counts and liver function tests should be performed during long-term therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies disulfiram as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Pregnancy. A report of 2 infants with severe limb-reduction anomalies whose mothers had taken disulfiram during pregnancy.[1] Only 2 similar cases had previously been reported.

1. Nora AH, *et al*. Limb-reduction anomalies in infants born to disulfiram-treated alcoholic mothers. *Lancet* 1977; **ii:** 664.

Interactions

Disulfiram inhibits hepatic enzymes and may interfere with the metabolism of other drugs taken at the same time. It enhances the effects of phenytoin and coumarin anticoagulants and their dosage may need to be reduced. It also inhibits the metabolism and excretion of rifampicin. Toxic reactions have occurred when disulfiram was given with isoniazid or metronidazole. Disulfiram may inhibit the metabolism of paraldehyde leading to an accumulation of acetaldehyde and these drugs should not be used together.

In a study[1] to evaluate the effects of disulfiram on cytochrome P450 isoenzymes, the results suggested that disulfiram-mediated inhibition is mainly selective for CYP2E1 after both acute and chronic dosage.

1. Frye RF, Branch RA. Effect of chronic disulfiram administration on the activities of CYP1A2, CYP2C19, CYP2D6, CYP2E1, and N-acetyltransferase in healthy human subjects. *Br J Clin Pharmacol* 2002; **53:** 155–62.

Analgesics. The potential of disulfiram to impair drug metabolism was shown[1] when it was found to prolong the plasma half-life of *phenazone*, probably by inhibiting the hepatic microsomal mixed function oxidases. It was also suggested[1] that disulfiram alters catecholamine metabolism since urinary excretion of vanilmandelic acid was significantly reduced and that of homovanillic acid was increased.

1. Vesell ES, *et al*. Impairment of drug metabolism by disulfiram in man. *Clin Pharmacol Ther* 1971; **12:** 785–92.

Antidepressants. It has been reported[1] that *amitriptyline* appeared to enhance the disulfiram-alcohol reaction. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *tricyclic antidepressants* or those inhibiting the same enzymes as disulfiram, such as *MAOIs*.[2]

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; **i:** 313.
2. Sellers EM, *et al*. Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Antiprotozoals. For reference to toxicity associated with *metronidazole* given to alcoholic patients who were also receiving disulfiram, see Alcohol, under Interactions of Metronidazole, p. 939.2.

Antipsychotics. It has been suggested[1] that phenothiazine antiemetics such as *chlorpromazine* might increase hypotension because of their α-adrenoceptor blocking activity and should therefore be contra-indicated in patients taking disulfiram. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *phenothiazines*.[2]

1. Kwentus J, Major LF. Disulfiram in the treatment of alcoholism: a review. *J Stud Alcohol* 1979; **40:** 428–46.
2. Sellers EM, *et al*. Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Benzodiazepines. *Diazepam* was reported[1] to reduce the intensity of the disulfiram-alcohol reaction.

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; **i:** 313.

Cannabis. For a suggestion that a combination of disulfiram and *cannabis* may produce a hypomanic state, see p. 2469.1.

Cardiovascular drugs. Clinically serious pharmacodynamic interactions might be anticipated during the disulfiram-alcohol reaction in patients taking other drugs that impair blood pressure regulation, such as *alpha blockers*, *beta blockers*, or *vasodilators*.[1]

1. Sellers EM, *et al*. Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Macrolides. Fatal toxic epidermal necrolysis and fulminant hepatitis have been reported[1] after starting *clarithromycin* treatment in a patient who was receiving disulfiram.

1. Masiá M, *et al*. Fulminant hepatitis and fatal toxic epidermal necrolysis (Lyell disease) coincident with clarithromycin administration in an alcoholic patient receiving disulfiram therapy. *Arch Intern Med* 2002; **162:** 474–6.

Pharmacokinetics

Disulfiram is absorbed variably from the gastrointestinal tract and is rapidly reduced to diethyldithiocarbamate (ditiocarb, p. 1550.2), mainly by the glutathione reductase system in the erythrocytes; reduction may also occur in the liver. Diethyldithiocarbamate is metabolised in the liver to its glucuronide and methyl ester and to diethylamine, carbon disulfide, and sulfate ions. Metabolites are excreted mainly in the urine; carbon disulfide is exhaled in the breath.

There was marked intersubject variability in plasma concentrations of disulfiram and its metabolites in a study of 15 male alcoholics given single oral 250-mg doses of disulfiram and repeated dosing with 250 mg daily for 12 days.[1] Variability might result from the marked lipid solubility of disulfiram, differences in plasma protein binding, or enterohepatic cycling. Average times to reach peak plasma concentrations after single or repeated doses

were 8 to 10 hours for disulfiram, diethyldithiocarbamate, diethyldithiocarbamate-methyl ester, and diethylamine, and for carbon disulfide in breath; peak plasma concentrations of carbon disulfide occurred after 5 to 6 hours. Plasma concentrations of disulfiram were negligible within 48 hours of a dose, although concentrations of some metabolites were still raised. In urine, 1.7 and 8.3% of a disulfiram dose was eliminated as diethyldithiocarbamate-glucuronide in the 24 hours after a single and repeated dose respectively, while diethylamine accounted for 1.6 and 5.7%, respectively. In the 24 hours after a single and repeated dose 22.4 and 31.3%, respectively, was eliminated as carbon disulfide in the breath.

1. Faiman MD, *et al.* Elimination kinetics of disulfiram in alcoholics after single and repeated doses. *Clin Pharmacol Ther* 1984; **36:** 520–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abstensyl; Disulfix; ***Austral.***: Antabuse; ***Austria***: Antabus; ***Belg.***: Antabuse; ***Braz.***: Antietanol; Sarcoton; ***Chile***: Antabus; Toleranе†; ***Cz.***: Antabus; ***Denm.***: Antabus; ***Fin.***: Antabus; ***Fr.***: Esperal; ***Ger.***: Antabus†; ***Hung.***: Antaethyl; ***India***: Chronol; De-Quit; Deadict; DFM; Diabuse; Esperal†; Medibuse; NT-Addict; ***Irl.***: Antabuse; ***Ital.***: Antabuse; Etiltox; ***Mex.***: Etabus; ***Neth.***: Antabus; Refusal; ***Norw.***: Antabus; ***NZ***: Antabuse; ***Pol.***: Anticol; ***Port.***: Tetradin; ***Rus.***: Antabus (Антабус); Esperal (Эспераль); Teturam (Тетурам); ***S.Afr.***: Antabuse; ***Singapore***: Antabuse†; ***Spain***: Antabus; ***Swed.***: Antabus; ***Switz.***: Antabus; ***Thai.***: Alcobuse†; Anta-al; Antinol†; Chronol; Difiram; ***Turk.***: Antabus; ***UK***: Antabuse; ***Ukr.***: Esperal (Эспераль); Tetlong (Тетлонг); Teturam (Тетурам); ***USA***: Antabuse.

Multi-ingredient Preparations. ***Rus.***: Lidevine (Лидевин); ***Swed.***: Tenutex; ***Ukr.***: Lidevin (Лидевин).

Pharmacopoeial Preparations
BP 2014: Disulfiram Tablets;
USP 36: Disulfiram Tablets.

Dizocilpine Maleate *(USAN, rINNM)*

Dizocilpina, maleato de; Dizocilpine, Maléate de; Dizocilpini Maleas; Maleato de dizocilpina; MK-801; Дизоцилпина Малеат.

(+)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]-cycloheptene-5,10-imine maleate.

$C_{16}H_{15}N.C_4H_4O_4$=337.4

CAS — 77086-21-6 (dizocilpine); 77086-22-7 (dizocilpine maleate).

UNII — 6LR8C1B66Q.

Profile

Dizocilpine is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It has been investigated for its antiepileptic properties as well as for a potential role in various other neurological disorders including the prevention of damage due to cerebral ischaemia.

Dizocilpine has good anticonvulsant activity but as it causes alarming psychotropic effects it was abandoned as a possible therapy for epilepsy.[1] Interest in its use as a possible therapy for stroke continued.

1. Richens A. New antiepileptic drugs. *Br J Hosp Med* 1990; **44:** 241.

Dolomite

Доломит.

UNII — UG9H2002BF.

Profile

Dolomite is a naturally occurring mineral composed of calcium and magnesium carbonate. It has been used as a nutritional supplement but may contain lead and other toxic metals and is not generally recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Frutin†; ***USA***: Dolomite.

Dong Quai

Angelica Sinensis; Chinese Angelica; Dang Gui; Dang Qui; Danggui; Донг Квай.

UNII — 697D19QDBN (Angelica sinensis); B66F4574UG (Angelica sinensis root).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii), which specify the root.

Br. includes separate monographs for Angelica Sinensis Root and Processed Angelica Sinensis Root.

Ph. Eur. 8: (Angelica Sinensis Root; Angelicae Sinensis Radix; Processed Angelica Sinensis Root BP 2014). The smoke-dried, whole or fragmented root, with rootlets removed, of *Angelica sinensis*. Diels collected in late autumn. It contains not less than 0.050% of *trans*-ferulic acid, ($C_{10}H_{10}O_4$ = 194.2), calculated with reference to the dried drug.

BP 2014: (Angelica Sinensis Root). The dried whole root of *Angelica sinensis* (*A. polymorpha* var. *sinensis*). It consists of the top (uppermost part), main body, and small lateral roots (tails) collected in late autumn, removed from rootlets and dried. It contains not less than 0.1% of *Z*-ligustilide ($C_{12}H_{14}O_2$ = 190.2), calculated with reference to the dried material. Protect from moisture.

Profile

Dong quai is the dried root of Chinese angelica, *Angelica sinensis* (*A. polymorpha* var. *sinensis*) (Apiaceae). It is used in traditional Chinese medicine in the treatment of menstrual and menopausal disorders, respiratory disorders, and herpes zoster infections.

Other *Angelica* spp. employed in herbal medicine are described on p. 2443.3.

Homoeopathy

Dong quai has been used in homoeopathic medicines under the following names: Angelica sinensis, radix; Angelica sin.

General references.

1. WHO. Radix Angelicae Sinensis. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/5.html (accessed 04/02/10)

Interactions. For a suggestion of a potential interaction between dong quai and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Capsella Complex; Dong Quai Complex†; Extralife Meno-Care†; Femi-Nan; Feminine Herbal Complex; Olf†; PM Meno-Care; ***Canad.***: Natural HRT; Phytoestrin; ***Hong Kong***: Phytoestrin†; ***Philipp.***: BSI Medicated Plaster; Spigrow for Girls; ***Singapore***: NeuroAid; Phytoestrin†; ***Ukr.***: Huato Pills (Болюсы Хуато); Lifemin (Лайфемин).

Drosera

Atrapamoscas; Droséra; Droserae Herba; Herba Rorellae; Hierba de la gota; Rorela; Ros Solis; Rossolis; Sonnentau; Sundew; Росянка Круглолистная (*Drosera rotundifolia*).

*ATC Herb — HR03WX5002 (*Drosera rotundifolia*: herb).*

*UNII — 75O014T1HG (*Drosera rotundifolia*).*

Profile

Drosera consists of the air-dried entire plant *Drosera rotundifolia* (Droseraceae) and other *Drosera* spp. Preparations of drosera have been used for its reputed value in respiratory disorders.

Homoeopathy

Drosera has been used in homoeopathic medicines under the following names: Drosera rotundifolia; Dros rot.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Asa Tones†; ***Austria***: Hustensaft Weleda; Pilka Forte; Pilka; ***Belg.***: Saintbois; ***Chile***: Fitotos; Pectoral Pasteur; Pulmagol; Ramistos; ***Cz.***: Tussilen†; ***Fr.***: Pastilles Monleon†; Tussidoron; ***Ger.***: Drosithym-N†; Weleda Hustenelixier; ***India***: Lung-KR; ***Indon.***: Silex; ***Israel***: Pilka; ***Ital.***: Enatus; ***Mex.***: Citos; Fen-y-Tos; ***Port.***: Broncodiazina†; Stodal; ***S.Afr.***: Cough Elixir†; ***Spain***: Pazbronquial; Pilka; ***Switz.***: Bromocod N†; Demo Elixir pectoral N†; DemoPectol; DemoTussil; Drosinula; Elixir contre la toux†; Escotussin; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Nican†; Pastilles bronchiques S; Pilka; Sirop pectoral contre la toux S; Siropectan; Wala Baume pectoral au plantain; ***Venez.***: Codebromil; Dromil Sauco; Pi-Fedrin.

Homoeopathic Preparations. ***Austral.***: Childrens Cough Relief; ***Austria***: Globuli gegen Husten Nr 1; Gripagil Husten- und Bronchialtropfen; Pertudoron†; ***Canad.***: Arum Triphyllum Plex†; Brocosin; Cough & Cold; Drosera Complex; Drosera Homaccord; Drosera Plex†; Homeo-Form R†; Kids Cough & Cold Phytux; L52 Cough & Cold; Pertudoron 1†; Phytotux H; Stodal; ***Chile***: Drosemiel; Pertussin; ***Cz.***: Drosetux; Lehnigrip†; Stodal; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Arum Triphyllum Compose; Baudry; Boripharm No 11†; Drosera Complexe No 64; Drosera Compose; Drosetux; Homeogene 14†; Ipeca Compose; L 52; Pates Pectorales; Pertudoron; Stodal; ***Ger.***: A-Bomin; Asthmavowen-N†; Bomapect N; Bronchi-Do; Bronchiselect; Broncho-Entoxin N; Broncho-Injektopas; Drosera-Weliplex†; Erkaltungs-Entoxin; HanoTussan; Infigripp; Jutussin; Monapax; Neolin-Entoxin; Pertudoron 1; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Pulmosan; Relivora Komplex; Roth's RKT Tropfen; Tussiflorin Hom; Tussisana; Tussistin S; Viropect; ***Hung.***: Drosetux; Stodal; ***Neth.***: Bronchilite; Drosinula; Homeocare siroop; Jutussin R9; Kind 0-6 Tussikind; Kind 0-6 Tussikind; Nectadyn H; Stodal; Tussistin; ***Rus.***: Briacon (Бриакон); Sambucus-Plus (Самбукус-Плюс); Stodal (Стодаль); ***S.Afr.***: Pertudoron Drops†; ***Switz.***: Drosetux; Regenaplex Nr 38b; Stodal; TussEx; ***UK***: Cough Elixir; ***Ukr.***: Stodal (Стодаль).

Drotaverine *(rINN)*

Drotaverina; Drotavérine; Drotaverinum; Дротаверин.

1-(3,4-Diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline.

$C_{24}H_{31}NO_4$=397.5

CAS — 14009-24-6 (drotaverine); 985-12-6 (drotaverine hydrochloride).

ATC — A03AD02.

ATC Vet — QA03AD02.

UNII — 98QS4N58TW.

Pharmacopoeias. *Pol.* includes Drotaverine Hydrochloride.

Profile

Drotaverine is used as an antispasmodic in the management of biliary-tract, urinary-tract, and gastrointestinal spasm, in usual oral doses of 120 to 240 mg daily in divided doses. It has also been given by intramuscular or intravenous injection.

References.

1. Bolaji OO, *et al.* Pharmacokinetics and bioavailability of drotaverine in humans. *Eur J Drug Metab Pharmacokinet* 1996; **21:** 217–21.
2. Romics I, *et al.* The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int* 2003; **92:** 92–6.
3. Singh KC, *et al.* Drotaverine hydrochloride for augmentation of labor. *Int J Gynaecol Obstet* 2004; **84:** 17–22.
4. Gupta B, *et al.* Drotaverine hydrochloride versus hyoscine-N-butylbromide in augmentation of labor. *Int J Gynaecol Obstet* 2008; **100:** 244–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: No-Spa (诺仕帕); ***Cz.***: No-Spa; ***Hung.***: No-Spa; ***India***: Atd; Baralgan-D; Cindot; Cyclofas; Detrim; Dortsil; Dotacid; Dotarin; Dotariv; Dotra; Doverin; Dozee; Drobel; Dromac; Dropain; Drot; Drotaspa; Drotikind; Drotin; Drotis; Drotwell; Droty; Drovera; Drovet; Drovit; Dudot; Duraspas; DVN; Eldrot; Emverin; Enzodrot; Inorine; Kydrot; Mefdi; Merispas; Mudot; ***Malaysia***: No-Spa; Zepid; ***Philipp.***: Deolin†; No-Spa†; ***Pol.***: Galospa; No-Spa; ***Rus.***: Bezpa (Беспа)†; No-Spa (Но-Шпа); Nos-Bra (Нош-Бра); Spacovin (Спаковин); Spasmol (Спазмол); Spasmonet (Спазмонет); Spazoverin (Спазоверин); ***Thai.***: Deolin; No-Spa†; Spablock†; Spacovin; Sparax; Sparta; Toverine; ***Ukr.***: No-Spa (Но-Шпа).

Multi-ingredient Preparations. ***Hung.***: Algoflex-M; Algopyrin Complex; No-Spalgin; Paniverin†; Quarelin; ***India***: Abdowin; Abdrot; Apodrot; Baralgan-DM; Coease-M; Detrim; Divo-M; Dora-M; Dortsil-M; Dotarin-MF; Dotra-M; Dozee-M; Drat-MF; Drobel-MF; Drofem; Drofic; Drolid-M; Drolid; Dropar; Drosym-MF; Drotikind-M; Drotin Plus; Drotin-M; Drotmic; Drotwell-M; Dutora-M; DVN Plus; DVN-Forte; Eldrot-Plus; Emverin-MF; Esnil; Fodro-M; Inorine-M; Maff-D; Majispa; Masai; MD-MF; Mefdi; Mefnic-D; Mefsaid-D; Nobel Spas; Novaspas; Ospas; ***Rus.***: Nicospan (НИКОШПАН); No-Spalgin (Но-Шпалгин); Pentalgin (Пенталгин); Unispaz (Юниспаз); Unispaz N (Юниспаз Н); ***Ukr.***: No-Spalgin (Но-Шпалгин)†; Unispas (Юниспаз).

Dulcamara

Argamiel; Bittersüss; Bittersweet; Douce-Amère; Dulcamarae Caulis; Dulce amargo; Hierba mora; Matagallinas; Uvas del diablo; Vid silvestre; Woody Nightshade; Паслён Сладко-горький (*Solanum dulcamara*).

*ATC Herb — HM01AW5022 (*Solanum dulcamara*: stem).*

*UNII — KPS1B1162N (*Solanum dulcamara *top); K4QR93EG7I (*Solanum dulcamara*).*

Profile

Dulcamara consists of the dried stems and branches of *Solanum dulcamara* (Solanaceae). It was formerly a popular remedy for chronic rheumatism and skin eruptions and was given as an infusion.

All parts of the plant are poisonous due to the presence of solanaceous alkaloids. The berries have caused poisoning in children. Adverse effects are treated as described under Atropine, p. 1312.2.

Homoeopathy

Dulcamara has been used in homoeopathic medicines under the following names: Solanum dulcamara; Dulc.

The flowers of *Solanum dulcamara* are also used in homoeopathic medicines under the following names: Dulcamara, Flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Dulcacefak; ***Ger.***: Cefabene; ***Swed.***: Efabene.

Multi-ingredient Preparations. ***Austria***: Dermatodoron; Hustensaft Weleda; ***Ger.***: Dermatodoron; Weleda Hustenelixier; ***S.Afr.***: Cough Elixir†; Dermatodoron†; Zeel; Zeel; ***Switz.***: Elixir contre la toux†.

Homoeopathic Preparations. ***Austria***: Echinacea-Cosmoplex; ***Canad.***: Angeel†; Arnica-Heel Comp†; Arthflex; Calnor†; Detox L37; Eczema L87; Formula D Doron†; Homeo-S-Asp; Urarthone†; Viburcol; Zeel Comp; ***Cz.***: Angin-Heel S; Viburcol; Zeel Compositum; Zeel Salbe†; ***Fr.***: Abbe Chaupitre no 18†; Amanita Complexe No 75; Arthro-Drainol; Dermo-Drainol†; Euphrasia Complexe No 115; Homeogene 41†; Homeogrippe†; Juniperus Complexe No 6; Scabiosa Complexe No 87; Soreal; Thuya Complexe No 37; Urarthone; ***Ger.***: Bryorheum N; Cysto-Gastreu S R18; Drosera-Weliplex†; Dularell N; G1-Injektopas; Genu-cyl L Ho-Len-Complex; Hewecyst Blasen-Nieren†; Lumbago-Gastreu S R11; Rheuma-Hevert; Rheuma-Hevert; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Symphytum Rowo†; Zeel comp; ***Hung.***: Angin-Heel; Viburcol; Zeel; ***Neth.***: Apo-Rheum†; Cystilite; Cysto-Gastreu R18; Dulcarhus-Gastreu R11; Gletar; Homeocare Exercito; Omnilite; Prurilite; Reudol; Spiroflor; Zeel comp N; ***Rus.***: Atma (Атма); Zeel T (Цель Т); ***S.Afr.***: Viburcol; ***Switz.***: Regenaplex Nr 28b; Regenaplex Nr 86a; Viburcol N; ***UK***: Dermatodoron; ***Ukr.***: Atma (Атма).

Ebselen *(rINN)*

DR-3305; Ebsélène; Ebseleno; Ebselenum; PZ-51; Эбселен.

2-Phenyl-1,2-benzisoselenazolin-3-one.

$C_{13}H_9NOSe$=274.2

CAS — 60940-34-3.

UNII — 40X2P7DPGH.

Profile

Ebselen has antoxidant activity and inhibits lipid peroxidation. It has been investigated as a neuroprotectant in stroke.

References.

1. Yamaguchi T, *et al.* Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. *Stroke* 1998; **29:** 12–17.
2. Saito I, *et al.* Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 1998; **42:** 269–78.

Echinacea

Black Sampson; Blyškiųjų ežiuolių šaknys (pale coneflower root); Brauneria; Coneflower; Echinacea angustifolia, racine d' (narrow-leaved coneflower root); Echinacea pallida, racine d' (pale coneflower root); Echinacea purpurea, parties aériennes fleuries d' (purple coneflower herb); Echinacea purpurea, racine d' (purple coneflower root); Echinaceae angustifoliae radix (narrow-leaved coneflower root); Echinaceae pallidae radix (pale coneflower root); Echinaceae purpureae herba (purple coneflower herb); Echinaceae purpureae radix (purple coneflower root); Equinácea; Kaitapäivänhatunjuuri (narrow-leaved coneflower root); Kořen třapatky bledé (pale coneflower root); Kořen třapatky úzkolisté (narrow-leaved coneflower root); Läkerudbeckiarot (pale coneflower root); Liten läkerudbeckiarot (narrow-leaved coneflower root); Rohtopäivänhatunjuuri (pale coneflower root); Rudbeckia; Siauralapių ežiuolių šaknys (narrow-leaved coneflower root); Sonnenhutkraut; Эхинацея.

*ATC Herb — HL03AW5004 (*Echinacea angustifolia*: root); HL03AW5003 (*Echinacea angustifolia*: herb); HL03AW5010 (*Echinacea purpurea*: whole plant); HL03AW5008 (*Echinacea purpurea*: herb); HL03AW5006 (*Echinacea pallida*: herb); HL03AW5009 (*Echinacea purpurea*: root); HL03AW5005 (*Echinacea angustifolia*: whole plant); HL03AW5007 (*Echinacea pallida*: root).*

*UNII — 4N9P6CC1DX (echinacea); VB06AV5U58 (*Echinacea angustifolia*); D982V7VT3P (*Echinacea angustifolia *root); 904CK3270L (*Echinacea pallida*); MGY2W95GWO (*Echinacea pallida *root); QI7G114Y98 (*Echinacea purpurea*); OS64WTR4KU (*Echinacea purpurea *root); 2EMS3QFX65 (*Echinacea purpurea *flowering top).*

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Narrow-Leaved Coneflower Root; Echinaceae Angustifoliae Radix). The dried, whole, or cut underground parts of *Echinacea angustifolia*. It contains a minimum 0.5% of echinacoside ($C_{35}H_{46}O_{20}$=786.7), calculated with reference to the dried drug. Store uncomminuted. Protect from light.

Ph. Eur. 8: (Pale Coneflower Root; Echinaceae Pallidae Radix). The dried, whole, or cut underground parts of *Echinacea pallida*. It contains a minimum 0.2% of echinacoside calculated with reference to the dried drug. Store uncomminuted. Protect from light.

Ph. Eur. 8: (Purple Coneflower Herb; Echinaceae Purpureae Herba). The dried, whole or cut flowering aerial parts of *Echinacea purpurea*. It contains a minimum of 0.1% of the sum of caftaric acid ($C_{13}H_{12}O_9$=312.2) and cichoric acid ($C_{22}H_{18}O_{12}$=474.4). Store uncomminuted.

Ph. Eur. 8: (Purple Coneflower Root; Echinaceae Purpureae Radix). The dried, whole or cut underground parts of *Echinacea purpurea*. It contains a minimum of 0.5% of the sum of caftaric acid ($C_{13}H_{12}O_9$=312.2) and cichoric acid ($C_{22}H_{18}O_{12}$=474.4). Store uncomminuted.

USP 36: (Echinacea Angustifolia). It consists of the dried rhizome and roots of *Echinacea angustifolia* (Asteraceae), harvested in the autumn after 1 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 36: (Echinacea Pallida). It consists of the dried rhizome and roots of *Echinacea pallida* (Asteraceae), harvested in the autumn after 3 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 36: (Echinacea Purpurea Root). It consists of the dried rhizome and roots of *Echinacea purpurea* (Asteraceae), harvested in the autumn after 3 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 36: (Echinacea Purpurea Aerial Parts). The aerial parts of *Echinacea purpurea* (Asteraceae) harvested during the flowering stage. It contains not less than 1.0% of chicoric acid, and not less than 0.01% of dodecatetraenoic acid isobutylamides ($C_{16}H_{25}NO$), calculated on the dried basis. Store in airtight containers. Protect from light.

Uses and Administration

Echinacea, the dried, whole, or cut underground parts of *Echinacea angustifolia* (*Brauneria angustifolia*), *E. pallida* (*B. pallida*), or *E. purpurea*, or the aerial parts of *E. purpurea*, is reported to have immunostimulant properties. It is used in herbal preparations for the prophylaxis of bacterial and viral infections.

Homoeopathy

Echinacea has been used in homoeopathic medicines under the following names: Echinacea purp; Echinacea purpurea; Echinacea purpurea ex planta tota; Echinacea purpurea, Planta tota; Echinacea angustifolia; Echin. an.

General references.

1. WHO. Radix Echinaceae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/15.html (accessed 04/02/10)
2. WHO. Herba Echinaceae Purpurae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/16.html (accessed 04/02/10)

Respiratory disorders. Echinacea is widely used in herbal preparations to treat upper respiratory-tract infections such as the common cold. Studies[1-4] have produced conflicting results, but systematic reviews suggest that most have methodological flaws[5] rendering evidence of efficacy unconvincing.[5,6] A meta-analysis[7] of 14 randomised controlled studies suggested that echinacea does have a benefit in decreasing the incidence and duration of the common cold, although it was acknowledged that larger prospective studies controlling for several variables (e.g. species) are needed before it can be routinely recommended. Comparative evaluation of specific preparations is also difficult because of varying composition. Evaluation of the effect of 3 extracts of *Echinacea angustifolia* root, each produced by a different extraction method and with defined phytochemical profiles, showed no clinically significant effects by any of them on experimental rhinovirus infection or ensuing illness compared with placebo.[8] Alkamides, polysaccharides, and caffeic acid derivatives, which have been proposed as the active components of echinacea preparations, were present in varying amounts in the extracts.

1. Turner RB, *et al.* Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. *Antimicrob Agents Chemother* 2000; **44:** 1708–9.
2. Barrett BP, *et al.* Treatment of the common cold with unrefined echinacea: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002; **137:** 939–46.
3. Taylor JA, *et al.* Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. *JAMA* 2003; **290:** 2824–30.
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6. Linde K, *et al.* Echinacea for preventing and treating the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 31/07/08).
7. Shah SA, *et al.* Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. *Lancet Infect Dis* 2007; **7:** 473–80.
8. Turner RB, *et al.* An evaluation of Echinacea angustifolia in experimental rhinovirus infections. *N Engl J Med* 2005; **353:** 341–8.

Adverse Effects and Precautions

The most common adverse effects reported on short-term use of echinacea were gastrointestinal and skin-related; these were generally transient and reversible.[1] Hypersensitivity reactions including anaphylaxis have been reported.[1-4] The MHRA in the UK advises[5] against the use of oral echinacea in children under 12 years of age, because the benefits are outweighed by the low, but potentially severe, risk of allergic reactions in this age group.

1. Huntley AL, *et al.* The safety of herbal medicinal products derived from Echinacea species. *Drug Safety* 2005; **28:** 387–400.
2. Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002; **88:** 42–51.
3. Health Canada. Natural health products and adverse reactions. *Can Adverse React News* 2004; **14**(1): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1_e.pdf (accessed 11/08/05)
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5. MHRA. Press release: echinacea herbal products should not be used in children under 12 years old. (issued 20 August, 2012). Available at: http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con180628.pdf (accessed 07/02/13)

Pharmacokinetics

The pharmacokinetics of alkamides extracted from *Echinacea angustifolia* roots have been studied[1] in human subjects. Fast absorption of some alkamides was shown after oral use; highly lipophilic alkamides could not be detected in plasma.

1. Woelkart K, *et al.* Bioavailability and pharmacokinetics of alkamides from the roots of Echinacea angustifolia in humans. *J Clin Pharmacol* 2005; **45:** 683–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Echinacin†; ***Austria***: Echinacin; Echinaforce; ***Belg.***: Echinacin; ***Braz.***: Enax; Imunax; Imunnal†; Imunogreen†; ***Canad.***: Echinaforce; Echinamide; Super LSN Plus†; Triple Blend Echinacea†; ***Cz.***: Echinacin; Immunal; ***Ger.***: aar vir; Echiherb†; Echinacin; Echinaforce†; Echinapur†; Echinatur†; Episcorit; Esberitox mono; Immunobion; Lymphozil; Pascotox Purpurea†; Resistan mono; toxiloges†; ***Gr.***: Echinacin†; ***Hung.***: Echinacin; ***Ital.***: EuMunil; ***Mex.***: Regripax; ***Norw.***: Revitonil; ***Pol.***: Echinapur; Echinerba; Immunal; Lymphozil; Purex†; ***Rus.***: Estifan (Эстифан); Immunal (Иммунал); Immunex (Иммунекс); Immunorm (Иммунорм); ***Spain***: Echinacin; EchinaMed; Ekian†; Revitonil†; ***Swed.***: Echinaforce; Echinagard; Echinatex†; Salva vid munsar; ***Switz.***: Echinacin; Echinaforce; EchinaMed; Echinapur; Echiplant†; ***Thai.***: Echinacin†; Echinax; ***Turk.***: Parodontax; ***UK***: Cold-n-Flu-Eze; Duchy Herbals Echinacea Relief; Echinaboost; Echinacea; Echinacin; Echinaflu; Echinaforce; Echinapret; EchinEeze; Ekinaclear; Ekinalife; Phytocold; Skin Clear; ***Ukr.***: Echinacin (Эхинацин); Immunal (Иммунал); Immuno Theiss (Иммуно Тайсс); Immunoplus (Иммуноплюс); ***Venez.***: Flucaps.

Multi-ingredient Preparations. ***Arg.***: Novo Prostasan; Parodontax Fluor; SX-22; ***Austral.***: Airborne Immunity; Andrographis Complex; Andrographis Compound; Arctium & Zinc Compound; Astragalus Complex; Broncafect; Calporo†; Cats Claw Complex†; Cats Claw-Echine; Cold & Flu Day/Night; DiaCo; Echinacea 4000†; Echinacea ACE + Zinc; Echinacea Citrus Throat; Echinacea Complex†; Echinacea Lozenges; Echinacea Plus Garlix; Echinacea Royale; Esberitox N; Euphrasia Complex; Flavons†; Gartech†; Herbal Throat Spray; Lemsip First Signs Cold & Flu Day + Night; Lemsip First Signs Cold & Flu; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Olive Leaf Plus; Skin Support; Throat-Clear; ***Austria***: Esberitox; Parodontax†; Spasmo-Urgenin; Urgenin; ***Belg.***: Medica Junior; Urgenin; ***Braz.***: Malvatricin Natural Organic†; Malvatricin Natural Soft†; Malvatricin Natural†; Parodontax†; ***Canad.***: Cystoforce†; Defense; Echinamide Cold and Cough†; Immune Formula†; ***Chile***: Citro-C; Paltomiel Plus; ***China***: Esberitox (施保利通); ***Cz.***: Lymphozil†; ***Fr.***: Alvityl Defenses; Olioseptil Gorge-Larynx; ProstaSecurA; ***Ger.***: Esberitox; Euphrasia comp; Schnupfencreme; ***Hong Kong***: Perfectil; Urgenin†; Vita Coldycin Echinacea Plus†; ***Hung.***: Flu-Vit; Telma; ***Indon.***: Actimmune; Bd-GARD; Biofos†; Curmunos; Echinox; Eftian; Ekinase; Elanos Kids; Elanos; Erphacea; Ezygard; Flavin; Formuno; Hepasil; Hepatin; Idesar Plus; Imboost C; Imboost Force; Imboost; Imforce Plus; Imforce; Immu-cea; Immu-cea; Imodul; Imodul; Imox; Imudator; Imufor; Imumax; Imunal Plus; Imunogard; Imunos; Imunos; Imunvit Plus; Imunvit; Kidimun; Neoboost Kids; Neoboost; Norflam; Nufit; Nufit; Ocu-V; Opinacea; Opinacea; Primunox; Proimbus†; Proza; Proza; Stamino; StarMuno; StarMuno; Stimox; Tribost; Vidoran Imun Up; Ximun; ***Israel***: Urgenin†; ***Ital.***: Body Guard; Cistefi; Coryfin C senza Zucchero; Dermilia Flebozin†; Golatux; Immumil Plus†; Immun-up Junior; Immun-up; Imoviral Junior; Influ-Zinc; Influtux; Lesiorepar; Nepiros; Probigol; Promix 3; Ribovir; Sclerovis H Plus; Ulceclar; ***Malaysia***: Esberitox N; ***Mex.***: Biomax Kid; ***NZ***: Lice Blaster; Strepsils Echinacea Defence†; ***Pol.***: Alchinal; Cardiobonisol; Echinasal; Esberitox N; Immunofort; Pectobonisol; Plantifort; Reumaherb; ***Port.***: Neo Urgenin; Vitace; ***Rus.***: Perfectil (Перфектил); Phyto Novo-Sed (Фито Ново-Седа); Prostanorm (Ипростанорм); ***S.Afr.***: Wecesin†; ***Singapore***: Proza; Robovites Multivitamins; ***Spain***: Neo Urgenin†; Spasmo-Urgenin; Urgenin†; ***Swed.***: Esberitox; Kan Jang; ***Switz.***:

A Vogel Spray pour la gorge; Demonatur Capsules contre les refroidissements; Demonatur Dragees pour les reins et la vessie†; Echinadoron; Echinarom; Esberitop; Gel de consoude†; Impuls a la consoude; Kernosan Eau Dentifrice†; Resiston; Resiston; Spagymun; Spagyrom; Wala Echinacea; Wecesin; ***Thai.***: Spasmo-Urgenin; ***Turk.***: Immuzinc; ***UK***: Allerclear; Antifect; Echinacea; Echinaforce Sore Throat Spray; Fuerte; Goodypops; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Modern Herbals Cold & Catarrh; Napiers Elixir of Echinacea Complex; Potters Elixir of Echinacea Plus; Revitonil; Sinotar; ***Ukr.***: Esberitox (Эсберитокс); Immuno Theiss (Иммуно Тайсс); Immuno-Ton (Ймуно-Тон); Perfectil (Перфектил); Uro-Control (Уро-Контрол); Vitokan (Витокан); ***USA***: PowerMate.

Homoeopathic Preparations. ***Austral.***: Echine†; Respatona Sore Throat; ***Austria***: Echinacea-Cosmoplex; Exangina†; Gripagil-Grippetropfen mit Echinacea; Lymphdiaral; Lymphdiaral; Oculoheel; Otovowen; Sonnenbrandspray; toxi-loges; Traumeel; Zom; ***Canad.***: Acne; Angeel†; Arnica-Heel Comp†; Calendula +; Calnor†; Candida Yeast Relief; ClearAc†; Echinacea Compositum; Echinacea L40†; Echinaction†; Euphorbium Compositum; Homeo-Form C†; Hylands Formula CA; Infilex†; Itires; Larydol†; Plant Spray†; Toxex; Traumeel; Yellow Dock Combination†; ***Chile***: Calendula Echinacea Comp; Ovukalen; ***Cz.***: Dolicoccil†; Galium; Traumeel; ***Fr.***: Amanita Complexe No 75; Cistus Canadensis Complexe No 86†; Echinacea Complexe No 40; Hamamelis Compose; Mercurius Cyanatus Complexe No 43†; Symphytum Complexe No 48†; ***Ger.***: A-Bomin; Angi Truw N; Cefasept N; Cefasept†; Cefasept; Contramutan; EAP-61; Echinacea comp; Echinacea Urtinktur†; Echinacin akut; Echinaject; Echinarell; Entzundungstropfen; Erkaltungs-Entoxin; Eupatorium N Oligoplex; Flenin; HanoToxin M; Hanotoxin M; Hevertotox; Hevertotox; Immudynal; Immunorell; Infekt 1-Injektopas N; Infekt-Komplex L Ho-Fu-Complex; Infi-Echinacea; Infihepan; Influex; Jowidarmin; Jsoskleran; Lowe-Komplex Nr 5 Echinacea; Lymphdiaral Halstabletten; Lymphdiaral; Lymphozil H; Mato; metabiarex; Mullersche Tabletten; Naranotox; Natuimmun†; Odonton-Echtroplex; Original-Tinktur N Truw; Ortitruw; Otovowen; Pascoleucyn N; Pascoleucyn; Pesendorfer; Phonix Thuja-Lachesis spag; phono Gripp; Pulmosan Infekt; Pyrogenium; Regenaplex Haut G; Regenaplex Haut W; Relivora Komplex; Schworotox A; Schworotox; Sinusitis Hevert SL; toxi-loges; toxi-loges; Toxiselect; Traumeel S; Wecesin; Weleda Fieber- und Zahnungszapfchen; Wiedimmun N†; Wiedimmun; ***Hung.***: Dolicoccil; Oculoheel; Toxex; Traumeel; ***Neth.***: Cold Care; Echilite; Echinacea comp; Febrilite; Homeocare Revito; Infragil; Kruidvat Homeopathie Bzzz†; Lymphdiaral; Mercurius-Heel; Oculoheel; Omnilite; Prrrikweg; Ricura; Rinileen†; Sniffle Care; Toxex; Traumeel S; Vinceel H; ***Rus.***: Anabar (Анабар); Cinnabsin (Циннабсин); Mercure-Plus (Меркур-Плюс); Traumeel S (Траумель С); ***S.Afr.***: Traumeel S; ***Switz.***: Akutur; Contusin; Exsepta; Influaforce†; Multiplex 1; Regenaplex Nr 41a; Traumeel; TussEx; ***UK***: Burns Cream; Catarrh Cream; Pyrethrum Spray; WCS Dusting Powder; ***Ukr.***: Cinnabsin (Циннабсин); Traumeel S (Траумель С); ***USA***: Preferred Remedies Cold & Flu; Traumeel; ***Venez.***: Traumeel.

Eculizumab *(BAN, USAN, rINN)*

Éculizumab; Eculizumabum; h5G1.1; Экулизумаб.
Immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G1.1 light chain, dimer.
CAS — 219685-50-4.
ATC — L04AA25.
ATC Vet — QL04AA25.
UNII — A3ULP0F556.

Uses and Administration

Eculizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker (p. 2485.1) by inhibiting terminal complement activation at the C5 protein. It is used to reduce haemolysis in patients with paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia (p. 1122.2). Eculizumab is also used to inhibit thrombotic microangiopathy in patients with atypical haemolytic-uraemic syndrome (p. 1159.1); it is not indicated for haemolytic-uraemic syndrome associated with Shiga toxin producing *Escherichia coli*.

In paroxysmal nocturnal haemoglobinuria, eculizumab is given in a dose of 600 mg once every 7 days for the first 4 weeks, followed by 900 mg 7 days later, and then 900 mg every 12 to 16 days thereafter.

In atypical haemolytic-uraemic syndrome, a dose of 900 mg is given once every 7 days for the first 4 weeks, followed by 1.2 g given 7 days later, and then 1.2 g every 12 to 16 days thereafter. In patients also treated with plasmapheresis or plasma exchange, a supplemental dose of eculizumab 600 mg should be given within 60 minutes after each session. In those given fresh frozen plasma, a supplemental dose of eculizumab 300 mg should be given 60 minutes before each unit of plasma infusion.

Eculizumab is given by intravenous infusion over 25 to 45 minutes. The infusion should be diluted to 5 mg/mL in sodium chloride 0.45% or 0.9%, glucose 5%, or Ringer's injection. The infusion rate may be decreased in the event of infusion reactions but the total infusion time should not exceed 2 hours; the infusion may be stopped in severe reactions. Patients should be monitored for at least one hour after the infusion for signs of infusion reactions. Patients who stop treatment altogether should be monitored for serious reactions (see Adverse Effects, Treatment, and Precautions, below).

Eculizumab should only be given after ensuring adequate vaccination cover, especially meningococcal vaccination (see below).

For the use of eculizumab in children, see below.

Eculizumab is also under investigation in the treatment of neuromyelitis optica.

References.

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2. Kelly RJ, *et al*. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood* 2011; **117:** 6786–92.
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4. McKeage K. Eculizumab: a review of its use in paroxysmal nocturnal haemoglobinuria. *Drugs* 2011; **71:** 2327–45.
5. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011; **6:** 60. Available at: http://www.ojrd.com/content/pdf/1750-1172-6-60.pdf (accessed 03/05/12)
6. Lapeyraque A-L, *et al*. Eculizumab in severe Shiga-toxin-associated HUS. *N Engl J Med* 2011; **364:** 2561–3.
7. Hodgkins KS, *et al*. Clinical grand rounds: atypical hemolytic uremic syndrome. *Am J Nephrol* 2012; **35:** 394–400.
8. Daina E, *et al*. Eculizumab in a patient with dense-deposit disease. *N Engl J Med* 2012; **366:** 1161–3. Correction. *ibid.*; 1454.
9. Vivarelli M, *et al*. Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012; **366:** 1163–5.
10. Radhakrishnan S, *et al*. Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012; **366:** 1165–6.

Administration in children. Eculizumab may be used in children and adolescents in the treatment of atypical haemolytic-uraemic syndrome and of paroxysmal nocturnal haemoglobinuria. For both indications, it is given by intravenous infusion and dosed according to body-weight:

- 5 to < 10 kg: 300 mg weekly in weeks 1 and 2, then once every 3 weeks thereafter
- 10 to < 20 kg: 600 mg in week 1, 300 mg in week 2, then 300 mg every 2 weeks thereafter
- 20 to < 30 kg: 600 mg once weekly for 3 doses, then once every 2 weeks thereafter
- 30 to < 40 kg: 600 mg once weekly for 2 doses, 900 mg at week 3, then 900 mg every 2 weeks thereafter
- 40 kg and over: adult doses (see above)

In patients with atypical haemolytic-uraemic syndrome and also treated with plasmapheresis or plasma exchange, a supplemental dose of eculizumab should be given within 60 minutes after each session. The supplemental dose should be 300 mg when the most recent dose was 300 mg, and should be 600 mg when the most recent dose was 600 mg or more. In patients given fresh frozen plasma, a supplemental dose of eculizumab 300 mg should be given 60 minutes before each unit of plasma infusion.

The concentration and administration of eculizumab infusion is the same as that used in adults (see above), although the infusion time for children less than 12 years of age may be extended to 4 hours if the infusion is slowed because of adverse effects.

Adverse Effects, Treatment, and Precautions

Use of eculizumab increases susceptibility to meningococcal infections and patients should be vaccinated at least 2 weeks before receiving the first dose of eculizumab and receive booster vaccinations according to current guidelines. Prophylactic antibacterial therapy is recommended until 2 weeks after vaccination in patients who are less than 2 years old and those treated with eculizumab less than 2 weeks after vaccination. Patients should be monitored during treatment for early signs of meningococcal infections and treated as required. Patients up to 18 years of age must also be vaccinated against haemophilus influenzae and pneumococcal infections. Susceptibility to other infections may also increase and eculizumab should be used with caution in patients with systemic infection. Other adverse effects that have been reported with eculizumab include hypertension, headache, dizziness, fever, nasopharyngitis, back pain, nausea, vomiting, diarrhoea, leucopenia, thrombocytopenia, and anaemia. Infusion site reactions can include paraesthesia or pain, and hypersensitivity reactions including anaphylaxis have occurred.

Patients who stop eculizumab treatment are at risk for serious reactions. Those with paroxysmal nocturnal haemoglobinuria are at risk of serious haemolysis and should be monitored for at least 8 weeks. Management includes blood transfusion or exchange transfusion, anticoagulation, corticosteroids, or restarting eculizumab. Patients with atypical haemolytic-uraemic syndrome should be monitored for thrombotic microangiopathy for at least 12 weeks after stopping eculizumab. If severe complications occur, restarting eculizumab should be considered, with plasma therapy or appropriate organ-specific supportive care.

Breast feeding. Eculizumab is expected to be distributed into breast milk, but the effect on the breast-fed infant is unknown. See also Pregnancy, below.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eculizumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Eculizumab is expected to cross the placenta, and UK licensed product information suggests that female patients should use effective contraception during and for up to 5 months after stopping therapy. However, the use of eculizumab for the management of paroxysmal nocturnal haemoglobinuria during pregnancy in 8 women has been reported.[1,2] In 3 cases they received the drug in the first trimester, in 3 cases it was continued throughout pregnancy, and in 1 case was given from week 27; in 1 case eculizumab was given in the first 5 weeks of gestation before elective termination. Eculizumab was either undetected or found at very low levels in cord blood at delivery.[1] All babies were healthy at delivery, and found to be developing normally at follow-up, the eldest at 16 months of age.[1,2] It was noted that higher doses of eculizumab were needed to maintain complement blockade in the later stages of pregnancy.[1] Breast milk was analysed in 1 woman during the 10 days after delivery and eculizumab was not detected.[1]

1. Kelly R, *et al*. The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. *Br J Haematol* 2010; **149:** 446–50.
2. Marasca R, *et al*. Pregnancy in PNH: another eculizumab baby. *Br J Haematol* 2010; **150:** 707–8.

Pharmacokinetics

Eculizumab has an elimination half-life of about 11 to 12 days. Plasma exchange significantly increases eculizumab clearance, and a 1-hour session may reduce concentrations by about 50%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Soliris; ***Belg.***: Soliris; ***Canad.***: Soliris; ***Cz.***: Soliris; ***Denm.***: Soliris; ***Fr.***: Soliris; ***Ger.***: Soliris; ***Irl.***: Soliris; ***Israel***: Soliris; ***Ital.***: Soliris; ***Jpn***: Soliris; ***Neth.***: Soliris; ***Norw.***: Soliris; ***Pol.***: Soliris; ***Port.***: Soliris; ***Spain***: Soliris; ***Swed.***: Soliris; ***Switz.***: Soliris; ***UK***: Soliris; ***USA***: Soliris.

Eledoisin *(rINN)*

ELD-950; Eledoisina; Élédoïsine; Eledoisinum; Эледоизин.
5-Oxo-Pro-Pro-Ser-Lys-Asp-Ala-Phe-Ile-Gly-Leu-Met-NH_2.
$C_{54}H_{85}N_{13}O_{15}S$=1188.4
CAS — 69-25-0 (eledoisin); 10129-92-7 (eledoisin trifluoroacetate).
UNII — OKY3285J18.

Profile

Eledoisin is a peptide extracted from the posterior salivary glands of certain small octopuses (*Eledone* spp., Mollusca), or obtained by synthesis. Its actions resemble those of substance P; it is a potent vasodilator and increases capillary permeability. It has been given as the trifluoroacetate in eye drops to stimulate lachrymal secretion in Sjögren's syndrome and other dry eye conditions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Eloisin.

Eniluracil *(BAN, USAN, rINN)*

776C85; Eniluracilo; Eniluracilum; Энилурацил.
5-Ethynyluracil.
$C_6H_4N_2O_2$=136.1
CAS — 59989-18-3.
UNII — 2E2W0W5XIU.

Profile

Eniluracil inactivates the enzyme dihydropyrimidine dehydrogenase, which plays an important role in the metabolism of the antineoplastic fluorouracil (p. 798.1). Eniluracil increases the bioavailability of fluorouracil,

particularly when the latter is given orally. It is being investigated as an adjunct to fluorouracil therapy in the treatment of colorectal, breast, and pancreatic cancer. However, the optimal dose and regimen remains to be determined.

Entsufon Sodium *(USAN, rINNM)*

Entsufón sódico; Entsufon Sodique; Natrii Entsufonum; Натрий Энтсуфон.

Sodium 2-[2-[2-(*p*-1,3,3-tetramethylbutylphenoxy)ethoxy]ethoxy]ethanesulfonate.

$C_{20}H_{33}NaO_6S$=424.5

CAS — 55837-16-6 (entsufon); 2917-94-4 (entsufon sodium).

UNII — L6867H5FR4.

Profile

Entsufon sodium is a detergent used as a soap substitute for cleansing the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: pHisoHex; ***USA***: pHisoHex.

Eprodisate Disodium *(USAN, rINNM)*

Éprodisate Disodique; Eprodisato disódico; Eprodisatum Dinatricum; NC-503; Динатрий Эпродисат.

Disodium propane-1,3-disulfonate.

$C_3H_6Na_2O_6S_2$=248.2

CAS — 36589-58-9.

UNII — 5X0D9H16IU.

NOTE. The names Fibrillex and Kiacta have been used as trade marks for eprodisate disodium.

Profile

Eprodisate disodium is a glycosaminoglycan mimetic under investigation for the prevention of amyloid fibril formation and deposition in the treatment of AA amyloidosis.

References.

1. Dember LM, *et al.* Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; **356:** 2349–60.
2. Manenti L, *et al.* Eprodisate in amyloid A amyloidosis: a novel therapeutic approach? *Expert Opin Pharmacother* 2008; **9:** 2175–80.

Equisetum

Åkerfräken; Asiūklių žolė; Cola de Caballo; Equiseti Herba; Equiseto; Herba Equiseti; Horsetail; Peltokorte; Přesličková nať; Prêle; Prêle, tige de; Schachtelhalmkraut; Ziele skrzypu; Хвощ.

*ATC Herb — HD03WX5006 (*Equisetum arvense*: herb); HG04BW5011 (*Equisetum arvense*: herb); HG04CW5002 (*Equisetum arvense*: herb).*

*UNII — 1DP6Y6B65Z (*Equisetum arvense *top); 1L0VKZ185E (*Equisetum arvense *branch).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Equisetum Stem; Horsetail BP 2014). The whole or cut, dried sterile aerial parts of *Equisetum arvense*. It contains a minimum of 0.3% of total flavonoids expressed as isoquercitroside ($C_{21}H_{20}O_{12}$ = 464.4), calculated with reference to the dried drug.

Profile

Equisetum is an ingredient of herbal preparations that have been used in the treatment of genito-urinary and respiratory disorders. Similar preparations have been used in the treatment of cardiovascular disorders, rheumatic disorders, liver disorders, constipation, and as a tonic.

The related species *Equisetum hyemale* (*Equisetum hiemale*) is used in China for the treatment of eye disorders.

Homoeopathy

Equisetum has been used in homoeopathic medicines under the following names: Equisetum arvense; Equisetum arv.

Equisetum hyemale has been used in homoeopathic medicines under the following names: Equisetum hyem.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Silica-Vite†; ***Cz.***: Preslicka†; Preslickova†; ***Fr.***: Siliprele†; ***Ger.***: Nieron E; Redaxa fit†; Salus Zinnkraut; ***Ital.***: Bioequiseto†.

Multi-ingredient Preparations. ***Arg.***: Adelgazar; Arceligasol; Centella Queen Complex; Centellase Gel; Delgacin; Doctor 10 Body; Natural Diet; Silueta Plus†; ***Austral.***: Advanced Bladder Care; Advanced Prostate Care; Advanced Urinary Tract Care; Asa Right Powder†; Cal Alkyline†; Calporo†; Extralife Fluid-Care†; Hair Skin & Nails; Hernidisc; Nails Hair and Skin; Super One-a-Day Multi; ***Austria***: Blasentee St Severin; Entschlackender Abfuhrtee EF-EM-ES; Nierentee St Severin; Pneumopan†; St Bonifatius-Tee†; Uropurat†; ***Canad.***: Floradix Kindervital†; Salusan†; ***Chile***: Nature Complex Reduct-Te; Perfect Body; Reduc-Te; ***Cz.***: Alvisan Neo; Antirevmaticky Caj†; Urcyston Planta; ***Fr.***: Alpha Renol; Arterase; Cicatendon; Obeflorine†; Phytemag; Provencale No 2†; Silibiol; Tisane Provencale no 2†; ***Ger.***: Equisil N†; Eviprostat N; Hevert-Blasen-Nieren-Tee N†; Imupret; Nephroselect M; Solidagoren; ***Hung.***: Urogin; Vensaxa; Vesevedo; ***Indon.***: Eviprostat; ***Ital.***: Ginecast; Lik-Gel†; Osteo Complex; Osteosil Calcium; Pik Gel; Slimmer Plus; Tripondil; ***Jpn***: Eviprostat; ***Mex.***: Nordibela; ***Philipp.***: Gloww; ***Pol.***: Betasol; Cholesol; Doppelherz Energovital Tonik†; Nefrobonisol; NeoFitolizyna†; Reumosol; Sanofil; Urosan†; ***Rus.***: Arfazetin-E (Арфазетин-Э); Herbion Urological Drops (Гербион Урологические Капли); Polygemostat (Полигемостат); Tonsilgon N (Тонзилгон Н); ***Singapore***: Cystone; Eviprostat; ***Spain***: Diurette†; Diurinat; Resolutivo Regium†; ***Switz.***: Nephrosolid; Tisane Diuretique; Urinex; ***UK***: Antiglan; Antitis; Aqualette; Kas-Bah; ***Ukr.***: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Imupret (Имупрет); Phytolyt (Фитолит); Tonsilgon N (Тонзилгон)†; Urochol (Урохол)†; Uronephron (Уронефрон); Vitokan (Витокан); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***Venez.***: Demerung; Rheu-Tarx 1.

Homoeopathic Preparations. ***Canad.***: Formula Homeo Q R 209†; Hylands Formula E; Hylands Kinder-BW; ***Fr.***: Millefolium Complexe No 7†; Poconeol no 56; Symphytum Complexe No 48†; Urocalm; ***Ger.***: Araniforce rheuma†; Cysto Hevert; Enuroplant N; HanoNephrin; Heweberberol; Infi-Symphytum; Levisticum S; Mandragora comp; Nephroplex; RauwolfiaViscomp; Roth's Rotacard; Steirocall.

Etaden

Ethaden; Этаден.

2-[(6-Amino-1*H*-purin-8-yl)amino]ethanol; 8-[(2-Hydroxyethyl)amino]adenine.

$C_7H_{10}N_6O$=194.2

CAS — 66813-29-4 (etaden); 91297-65-3 (etaden hydrobromide).

Profile

Etaden is used as the hydrobromide monohydrate (dihydrobromide monohydrate) in the form of eye drops to stimulate epithelial regrowth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Etadexe-Mez (Этадекс-Мэз).

Ethanethiol

Ethyl Mercaptan Thioethyl Alcohol; Ethylmercaptan; Этантиол; Этил Меркаптан.

C_2H_6S=62.13

CAS — 75-08-1.

UNII — M439R54A1D.

Profile

Mercaptans such as ethanethiol have an extremely disagreeable odour that is detectable by humans at very low concentrations and therefore they are added as a safety measure to odourless gases such as natural gas. Inhalation of high concentrations of ethanethiol can cause dizziness, headache, nausea, vomiting, and unconsciousness.

Ethaverine Hydrochloride *(rINNM)*

Etaverina, hidrocloruro de; Éthavérine, Chlorhydrate d'; Ethaverini Hydrochloridum; Hidrocloruro de etaverina; Этаверина Гидрохлорид.

6,7-Diethoxy-1-(3,4-diethoxybenzyl)isoquinoline hydrochloride.

$C_{24}H_{29}NO_4$,HCl=432.0

CAS — 486-47-5 (ethaverine); 985-13-7 (ethaverine hydrochloride).

UNII — 6Z6T599E49.

Profile

Ethaverine is the tetraethoxy analogue of papaverine (p. 2362.2) and has been used as the hydrochloride as an antispasmodic in respiratory-tract, biliary, gastrointestinal, and genito-urinary disorders. It has also been used in migraine, vascular disorders and as an antiarrhythmic.

Ethaverine sulfamate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Thai.***: Elzym†.

Ethyl Nitrite

Nitrous Acid Ethyl Ester; Nitrous Ether; Этилнитрит.

$C_2H_5NO_2$=75.07

CAS — 109-95-5.

UNII — 8C7CJ279RV.

NOTE. Do not confuse with *O*-nitrosoethanol, a substance that has been referred to in the literature as 'ethyl nitrite gas'.

Profile

Ethyl nitrite has vasodilator effects similar to other volatile nitrites (see Amyl Nitrite, p. 1540.2). Alcoholic solutions of ethyl nitrite (Ethyl Nitrite Spirit; Nitrous Ether Spirit; Sweet Nitre Spirit; Sp. Aether. Nitros.) have been used as a diaphoretic in the treatment of colds and fevers.

Methaemoglobinaemia occurred in 2 infants given a folk remedy containing ethyl nitrite. Despite treatment with methylthioninium chloride 1 infant died.[1]

1. Chilcote RR, *et al.* Sudden death in an infant from methemoglobinemia after administration of "sweet spirits of nitre". *Pediatrics* 1977; **59:** 280–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Witdulsies.

Ethylene Glycol

Alcohol etilénico; Ethylene Alcohol; Etilen Glikol; Etilenglicol; Glicol; Glikol etylenowy; Glycol.

Ethane-1,2-diol.

$C_2H_6O_2$=62.07

CAS — 107-21-1.

UNII — FC72KVT52F.

Uses

Ethylene glycol is commonly encountered in antifreeze solutions and has been used illicitly to sweeten some wines. Diethylene glycol has been used similarly.

Adverse Effects

Toxic effects arising from ingestion of ethylene glycol result from its major metabolites: aldehydes, glycolate, lactate, and oxalate. Clinical features may be divided into three stages depending on the time elapsed since ingestion. In the first 12 hours, the patient may show signs of drunkenness and have nausea and vomiting. Convulsions and neurological defects may occur. From 12 to 24 hours, there may be tachycardia, mild hypertension, pulmonary oedema, and heart failure. Between 24 and 72 hours, patients with severe ethylene glycol poisoning may have flank pain and renal involvement with associated decreased plasma concentrations of calcium and bicarbonate, metabolic acidosis, deposition of oxalate in tissues and kidney tubules, proteinuria, oxaluria, haematuria, and renal failure. There may be respiratory failure, cardiovascular collapse, and sometimes coma and death. The fatal dose is reported to be about 100 mL.

Skin irritation and penetration have been reported after topical application.

Diethylene glycol produces similar toxicity, except that there is no conversion to oxalate and there is greater nephrotoxicity; hepatotoxicity is common. Poisoning has followed adulteration of medicinal products with diethylene glycol.

References.

1. Anonymous. Some wine to break the ice. *Lancet* 1985; **ii:** 254.
2. Vale JA, Buckley BM. Metabolic acidosis in diethylene glycol poisoning. *Lancet* 1985; **ii:** 394.
3. Buckley BM, Vale JA. Poisoning by alcohols and ethylene glycol. *Prescribers' J* 1986; **26:** 110–15.
4. Lewis LD, *et al.* Delayed sequelae after acute overdoses or poisonings: cranial neuropathy related to ethylene glycol ingestion. *Clin Pharmacol Ther* 1997; **61:** 692–9.
5. Hasbani MJ, *et al.* Encephalopathy and peripheral neuropathy following diethylene glycol ingestion. *Neurology* 2005; **64:** 1273–5.
6. Schier JG, *et al.* Medication-associated diethylene glycol mass poisoning: a review and discussion on the origin of contamination. *J Public Health Policy* 2009; **30:** 127–43.
7. Schep LJ, *et al.* Diethylene glycol poisoning. *Clin Toxicol* 2009; **47:** 525–35.

Treatment of Adverse Effects

The stomach may be emptied by gastric aspiration if ingestion of ethylene glycol was within the preceding hour. Severe metabolic acidosis should be corrected. Hypocalcaemia may require correction with calcium gluconate in

severe cases, although this is not usually done routinely because it may increase the formation of calcium oxalate crystals. Haemodialysis may be of value. Alcohol may be given orally or intravenously as it is a competitor of the metabolism of ethylene glycol. Alternatively fomepizole (p. 1553.1), an alcohol-dehydrogenase inhibitor, may be used for the treatment of ethylene glycol poisoning. The value of alcohol or fomepizole in the treatment of diethylene glycol poisoning is unclear.

References.

1. Harry P, *et al.* Ethylene glycol poisoning in a child treated with 4-methylpyrazole. *Pediatrics* 1998; **102:** E31.
2. Barceloux DG, *et al.* American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *Clin Toxicol* 1999; **37:** 537–60.
3. Brent J, *et al.* Fomepizole for the treatment of ethylene glycol poisoning. *N Engl J Med* 1999; **340:** 832–8.
4. Borron SW, *et al.* Fomepizole in treatment of uncomplicated ethylene glycol poisoning. *Lancet* 1999; **354:** 831.
5. Baum CR, *et al.* Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics* 2000; **106:** 1489–91.
6. Brent J. Current management of ethylene glycol poisoning. *Drugs* 2001; **61:** 979–88.
7. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother* 2002; **36:** 1085–9.

Pharmacokinetics

Ethylene glycol is absorbed from the gastrointestinal tract and is metabolised, chiefly in the liver, by alcohol dehydrogenase. Its breakdown products account for its toxicity and include aldehydes, glycolate, lactate, and oxalate.

References.

1. Sivilotti ML, *et al.* Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. *Ann Emerg Med* 2000; **36:** 114–25.

Etiproston Trometamol *(rINNM)*

Etiprostón trometamol; Etiproston Tromethamine; Étiprostone Trométamol; Etiprostonum Trometamolum; Этипростон Трометамол.

Trometamol salt of (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-2-[2-(phenoxymethyl)-1,3-dioxolan-2-yl]vinyl]cyclopentyl]-5-heptenoic acid.

$C_{24}H_{32}O_7.C_4H_{11}NO_3$=553.6

CAS — 59619-81-7 (etiproston).

Profile

Etiproston trometamol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Eucalyptus Leaf

Blahovičníkový list; Eucalypti Folium; Eucalyptus, feuille d'; Eucalyptusblätter; Eukaliptų lapai; Eukaliptuszlevél; Eukalyptuksenlehti; Eukalyptusblad; Лист Эвкалипта.

ATC Herb — HR05WA5010 (Eucalyptus globulus: *leaf*); *HR05WA5009* (Eucalyptus globulus: *gum*).

UNII — S546YLW6E6 (Eucalyptus globulus *leaf*).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur.: (Eucalyptus Leaf). It consists of the whole or cut dried leaves of older branches of *Eucalyptus globulus*. The whole drug contains not less than 2% v/w of essential oil and the cut drug not less than 1.5% v/w of essential oil, both calculated with reference to the anhydrous drug. It has an aromatic odour of cineole. Protect from light.

Profile

Eucalyptus leaf has been used in oral preparations for coughs and associated respiratory-tract disorders. It is also used as a flavour. It is a source of eucalyptus oil (see below).

General references.

1. WHO. Folium Eucalypti. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/12.html (accessed 04/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Chlorophyllipt (Хлорофиллипт); Eucalimin (Эвкалимин); Galenofillipt (Галенофиллипт).

Multi-ingredient Preparations. ***Arg.***: Farinop; Pre Calent; Repelente Zasu; ***Austria***: Euka; ***Braz.***: Broncol†; ***Canad.***: Formula T13 Tea†; ***Chile***: Codetol PM; Paltomiel Plus; Paltomiel; Paltomiel; Pectox; Propolis C; Propolkit; Propolkit; Pulmosina; ***Fr.***: Balsofumine; Dolirhume; Olioseptil Gorge-Larynx; Thiopectol; ***Ger.***: Cefabronchin; ***Hong Kong***: Glycerine Thymol Co†; Uni-Bana†; Vita Coldycin Echinacea Plus†; ***India***: Movefast; ***Indon.***: Neo Rheumacyl Neck and Shoulder; ***Ital.***: Altuss; Fosfoguaiacol†; ***Mex.***: Vipooll; ***NZ***: Cepacol Sore Throat; Otrivine Menthol; ***Rus.***: Elecasol (Элекасол); Evcarom (Эвкаром); Inhaphytol No 2 (Ингафитол 2); Insti (Инсти); Mixture for Inhalations (Смесь Для Ингаляций); ***S.Afr.***: Bolus Eucalypti Comp†; ***Singapore***: Arkopharma Propolis Spray; ***Spain***: Vapores Pyt†; ***Switz.***: Eau Precieuse; Silence†; Wala Echinacea; ***UK***: Calrub; Collins Elixir Decongesant Pasilles; No-Sor Nose Balm; PainEaze; Revitonil; Sinose; Sudarub; ***Ukr.***: Elecasol (Элткасол); Insti (Інсті); ***Venez.***: Mixagel.

Homoeopathic Preparations. ***Austria***: Bolus Eucalypti Comp; Ferrum Phosphoricum comp; Infludo; Tonsan akut; ***Canad.***: Arnica-Heel Comp†; L52 Cough & Cold; ***Cz.***: Lehnigrip†; ***Fr.***: Cetraria Complexe No 61; Infludo; L 52; ***Ger.***: Anovin; Arnica Oligoplex; Gripps; Infigripp; Infludo; Tussistin S; Tussistin; ***Neth.***: Grippe-Gastreu R6; Infludo; Kind 0-6 Tussikind; Kruidvat Homeopathie Influ-complex†; Nisyleen; Tussistin; ***Rus.***: Phytolacca-Plus (Фитолакка-Плюс); Tonsan-Akut (Тонзан-акут); ***Switz.***: Infludo; Regenaplex Nr. 50b; TussEx; ***UK***: Bolus Eucalypti Comp; Infludo.

Eucalyptus Oil

Blahovičníková silice; Esencia de eucalipto; Essence d'Eucalyptus Rectifiée; Eucalipto, aceite esencial de; Eucalypti aetheroleum; Eucalypti Etheroleum; Eucalyptus, huile essentielle d'; Eucalyptusöl; Eukaliptų eterinis aliejus; Eukaliptuszolaj; Eukalyptusolja; Eukalyptusöljy; Ökaliptüs Yağı; Olejek eukaliptusowy; Oleum Eucalypti; Эвкалиптовое Масло.

ATC Herb — HR05WA5008 (Eucalyptus globulus: *essential oil*); *HM02AW5004* (Eucalyptus globulus: *essential oil*).

UNII — 2R04ONI662.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Eucalyptus Oil). A colourless or pale yellow liquid with a characteristic aromatic camphoraceous odour. It is obtained by steam distillation and rectification from the fresh leaves or terminal branches of various species of *Eucalyptus* rich in cineole. The species mainly used are *E. globulus*, *E. polybractea*, and *E. smithii*. It contains not less than 70% w/w of cineole. Relative density 0.906 to 0.927. Soluble 1 in 5 of alcohol (70%). Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Eucalyptus oil has been taken orally for catarrh and coughs and is an ingredient of many preparations. It has been used as an inhalation often with other volatile substances. Eucalyptus oil has also been applied as a rubefacient and is used as a flavour. It is also used in aromatherapy.

Adverse Effects and Precautions

The symptoms of poisoning with eucalyptus oil include gastrointestinal symptoms such as epigastric burning, nausea and vomiting, and CNS depression, including coma. Cyanosis, ataxia, miosis, pulmonary damage, delirium, and convulsions may occur. Deaths have been reported.

Oily solutions of eucalyptus oil were formerly used in nasal preparations, but this use is now considered unsuitable as the vehicle inhibits ciliary movements and may cause lipoid pneumonia.

References.

1. Patel S, Wiggins J. Eucalyptus oil poisoning. *Arch Dis Child* 1980; **55:** 405.
2. Spoerke DG, *et al.* Eucalyptus oil: 14 cases of exposure. *Vet Hum Toxicol* 1989; **31:** 166–8.
3. Webb NJA, Pitt WR. Eucalyptus oil poisoning in childhood: 41 cases in south-east Queensland. *J Paediatr Child Health* 1993; **29:** 368–71.
4. Tibballs J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Med J Aust* 1995; **163:** 177–80.
5. Anpalahan M, Le Couteur DG. Deliberate self-poisoning with eucalyptus oil in an elderly woman. *Aust N Z J Med* 1998; **28:** 58.
6. Darben T, *et al.* Topical eucalyptus oil poisoning. *Australas J Dermatol* 1998; **39:** 265–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bosisto's Eucalyptus Spray; ***Ger.***: Aspecton Eukaps; Broncho-Truw Erkaltungsbalsam†; Exeu†; Pinimenthol Erkaltungsbad fur Kinder; Pulmotin Inhalat; Rinupret; Schnupfen Kapseln†; Tussidermil N; ***Irl.***: MOOV Head Lice†; ***Pol.***: Migrenol†; ***Port.***: Vicks Vaporub; ***Ukr.***: Hedelix Eucaps (Геделикс Эвкапс).

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***UK***: Catarrh Cream; Medicinal Gargle; Oleum Rhinale.

Eugenol

Ácido cariofílico; Ácido eugénico; 4-Allylguaiacol; Eugen.; Eugenic Acid; Eugénol; Eugenoli; Eugenolis; Eugenolum; Эвгенол.

4-Allyl-2-methoxyphenol.

$C_{10}H_{12}O_2$=164.2

CAS — 97-53-0.

UNII — 3T8H1794QW.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Eugenol). A colourless or pale yellow liquid with a strong odour of clove. Practically insoluble in water and in glycerol; freely soluble in alcohol (70%); miscible with alcohol, with glacial acetic acid, with dichloromethane, and with fatty oils. Eugenol darkens in colour on exposure to air. Store in well-filled containers. Protect from light.

USP 36: (Eugenol). It is obtained from clove oil or from other sources. A colourless or pale yellow liquid having a strongly aromatic odour of clove. Upon exposure to air, it darkens and thickens. Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers. Protect from light.

Profile

Eugenol is a constituent of clove oil (p. 2481.3) and some other essential oils. It is used in dentistry, often mixed with zinc oxide, as a temporary anodyne dental filling, and is an ingredient in oral hygiene preparations. Eugenol has been used as a flavour.

Eugenol is an irritant and sensitiser and can produce local anaesthesia. It is reported to inhibit prostaglandin synthesis.

For the pulmonary effects of eugenol inhalation from clove cigarettes, see Abuse, under Clove, p. 2481.3.

References.

1. Sarrami N, *et al.* Adverse reactions associated with the use of eugenol in dentistry. *Br Dent J* 2002; **193:** 257–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Analgesico Dental; ***Israel***: Mentholatum Toothache Kit; ***USA***: Red Cross Toothache.

Multi-ingredient Preparations. ***Arg.***: Carnot Topico; ***Belg.***: Dentophar†; Olbas; ***Chile***: Astrijesan; Listermint Con Fluor†; Parodium; ***Cz.***: Alvogyl; ***Fr.***: Alodont; Alvogyl; Fluocaril dents sensibles†; Iodopengha†; Pectoderme†; Post-Pengha; Pulparthrol; Pulperyl; Sedapulpe†; Yranol Eugenole; ***Gr.***: Counterpain; ***Hong Kong***: Counterpain†; Flanil; ***Indon.***: Counterpain-PXM; Counterpain; Flexozin; Lafalos Plus; Lafalos; Molakrim; Neo Rheumacyl; Nostren; Nufasic; Painkila; Remakrim†; Stop X; Zeropain; ***Irl.***: Ledermix; ***Israel***: Alvogyl; Dentin; ***Ital.***: Creosoto Composto; Eugenol-Guaiacolo Composto; Gocce Odontalgiche; Odongi; ***Malaysia***: Flanil; ***Philipp.***: Begesic; Counterpain†; ***Rus.***: Parodontocide (Пародонтоцид); ***S.Afr.***: Counterpain; ***Singapore***: Antipain; Begesic; Counterpain; Flanil; Lafalos Plus; Muscalax; ***Spain***: Alvogil†; Piorlis†; ***Switz.***: Alvogyl; Benzocaine PD; Ledermix; ***Thai.***: Analgen; Analgesic Balm; Begesic; Centropain; Contac Pain; Counterpain Plus; Counterpain; Flanil; Heat Cream; Hot Ize; Masabalm; Methyl Salicylate Cream, Compound; Muscalax; Muscort; Neotica; Nox-Pain; Painza; Patarpain; Reduxpain; Rid-O-Pain; Sancago; SP gel; Stopain; TO Balm; U-Gesic Balm; Voltex; X-Pain; Yapircam; ***UK***: Ledermix; ***Venez.***: Flemicaine.

Euphorbia

Euforbia; Pill-bearing Spurge; Snake Weed; Молочай.

ATC Herb — HR03WX5003 (Euphorbia hirta: *herb*).

UNII — 310FI8DJBG (euphorbia); L13YF113GN (Euphorbia pilulifera); *243K8QF0MS* (Euphorbia pilulifera *extract*).

Pharmacopoeias. *Chin.* includes monographs for *Euphorbia humifusa* or *E. maculata* herb and *E. pekinensis* root.

Profile

Euphorbia, the aerial parts of *Euphorbia hirta* (*E. pilulifera*, *Chamaesyce hirta*) (Euphorbiaceae), has sedative and expectorant properties and is used in the treatment of asthma and other respiratory-tract disorders. It has also been used for intestinal amoebiasis.

Other *Euphorbia* spp. are used for a variety of disorders. The seeds and latex of *E. lathyrus* (caper spurge) have been used as a purgative but are too toxic for general use. Many species have been used as arrow poisons.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Tafedim; ***India***: Thank God.

Multi-ingredient Preparations. ***Austral.***: Asa Tones†; Euphorbia Complex†; ResCo; ***Belg.***: Toularynx; ***Canad.***: Sirop Cocillana Codeine; ***Hong Kong***: Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Compound Cocillana†; Coolding†; ***India***: Nefid; ***Thai.***: Lactagogue; ***UK***: Antibron.

Homoeopathic Preparations. ***Austria***: Sensicare; ***Canad.***: Loprax†; ***Ger.***: Regenaplex Haut G; ***Neth.***: Echilite; ***Switz.***: Regenaplex Nr. 71b.

Euphrasia

Augentrost; Eufrasia; Euphraise; Eyebright; Очанка.
ATC Herb — HS01BW5001 (Euphrasia officinalis: herb).
UNII — C9642I91WL.

Profile

Euphrasia, the aerial parts of various *Euphrasia* spp. including *E. rostkoviana* and *E. officinalis* (Scrophulariaceae), has been used topically for blepharitis, conjunctivitis, and other eye disorders. However, such use is not generally recommended. Euphrasia has also been used for nasal catarrh and sinusitis, and to prevent snoring.

Homoeopathy

Euphrasia has been used in homoeopathic medicines under the following names: Euphrasia officinalis; Euphrasia ex planta tota; Euph. of.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Allerclear; Snore Calm.

Multi-ingredient Preparations. ***Austral.***: Bilberry Plus†; Euphrasia Complex; Euphrasia Compound; Eye Health Herbal Plus Formula 4†; ***Ger.***: Euphrasia comp; Herba-Vision Augenbad; Herba-Vision Augentrost; ***Indon.***: Oculosan; Proview; ***Ital.***: Altacura Ipragocce; Eulux; Iridil; ***Singapore***: EyeMax; ***Switz.***: Collypan; Herba-Vision Euphrasia; Oculosan; ***UK***: Se-Power; Vital Eyes; ***Ukr.***: Oko-Health (Око-хелс).

Homoeopathic Preparations. ***Austral.***: Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Hay Fever; Respatona Head Cold; ***Austria***: Apozema Allium Cepa compositum; Apozema Apis compositum; Famulan; Oculoheel; ***Canad.***: Allergies; C-Plus; Complete Flu Care 4 Kids†; Endoteel†; Hay Complex†; Hayfever; Homeo-Form SI†; Homeo-S-Asp; Homeodel 15†; Hylamine HF; Hylands Flu; Hylands Formula F; Kids Allergies; Optalia†; Sabalia; Sinus; ***Cz.***: Rhinallergy; ***Fr.***: Abbe Chaupitre no 66†; Allium Cepa Compose; Dolistamine†; Euphrasia Complexe No 115; Homeoptic; Polyrhinium; Rhinallergy; Uva Ursi Complexe No 9; ***Ger.***: ISO-Augentropfen C; Neolin-Entoxin; ***Hung.***: Oculoheel; Pro-Aller; ***Neth.***: Gletar; Homeoptic†; Oculoheel; ***Rus.***: Famulan (Фамулан); Mirticam (Миртикам); ***Switz.***: Alceprin-N; Nelsons Pollenna†; Polyrhinium; Regenaplex Nr. 3; Rhinallergy; Spagyrhin; ***UK***: Pollenna; ***USA***: Preferred Remedies Allergy.

European Barberry

Barberry; Berberry; Jaundice Berry; Oregon Grape; Pepperidge; Pepperidge Bush; Pipperidge; Pipperidge Bush; Sow Berry; Sowberry; Барбарис Обыкновенный (*Berberis vulgaris*).
ATC Herb — HA05AW5003 (Berberis vulgaris: root bark); HA04WX5002 (Berberis vulgaris: root bark).
UNII — 492B79913J (Berberis vulgaris); 6XEF22AHC3 (Berberis vulgaris fruit); 1TH8Q20J0U (Berberis vulgaris root bark); ITJ40JX79U (Berberis vulgaris root).

NOTE. The names Barberry, Oregon Grape, and Sowberry have been applied to both European Barberry and Oregon Grape (see p. 2577.1).

Profile

The stem or root bark of the European barberry (*Berberis vulgaris* (Berberidaceae)) is used orally in herbal medicine mainly for hepatic and biliary disorders, as a bitter for dyspepsia, and for some infective diseases. It is used topically in preparations for chronic skin conditions, and in eye washes. The fruit is used for disorders of the gastrointestinal tract and respiratory tract, and as a source of vitamin C.

Berberis vulgaris is a source of berberine (p. 2455.1).

Homoeopathy

European barberry has been used in homoeopathic medicines under the following names: Berberis; Berberis vulgaris; Berber vulg; Berb. vul.; Berberis, fructus; Berberis vulgaris e fructibus; Berberis vulgaris, fructus; Berber vulg, fruct.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Berberis Complex†; Bupleurum Compound; Caprilate†; Gartech†; ***Austria***: Amersan; ***Canad.***: Biliherb; Bilonat; Depuratif des Trappistes; Herbanat†; Para-Gard; Para-Gone; ***Cz.***: Amersan; ***Ger.***: Schnupfencreme; ***India***: Ampucare; Hepaliv; ***Indon.***: Kalkurenal; ***Switz.***: Bilifuge; Wala Baume nasal doux; Wala Baume nasal.

Homoeopathic Preparations. ***Austria***: Acidum picrinicum Med Complex†; Berberis Cosmoplex†; Erbiode Akne; Erbiode Blasen und Nieren; ***Canad.***: Berberis-Homaccord†; Bioactiv R†; Chelidonium Plex†; ClearAc†; Comp-Drops 8 Uri-Tract†; Cynara Complex†; Formula CI 207†; Formula Homeo QR 209†; Hylands Formula CA; Male +; Reneel†; Renelix; Sinall Formula†; ***Chile***: Bioactiv R; ***Fr.***: Abbe Chaupitre no 6; Berberis Complexe No 83; Boripharm No 1†; Boripharm No 22†; Cholesterolum Complexe No 112†; Cina Compose; Diacure; Digeodren; Hepatodrainol; L 8; Natrum Carbonicum Complexe No 10†; Pareira Brava Compose; Rhus Toxicodendron Compose; Ricinus Compose; Rubia Complexe No 3; Sabal Serrulata Compose; Saponaria Compose; Vascodran; ***Ger.***: Alho-Arthrosan N; Anore rheumat; Araniforce arthro; Arthriselect; Arthrokatt; Berberell; Berberis N Oligoplex; Cefarheumin S†; Chola-Plantin N†; Colchicum Complex; Cysto-Gastreu S R18; Doloject; G1-Injektopas; Harnsauretropfen F; Heparanox H; Hevertnier Complex N†; Heweberberol; Heweurat N; Hexacyl; Leber-Galletropfen; Lithias-cyl L Ho-Len-Complex; Lumbago-Gastreu S R11; Nierentropfen Cosmochema; Pesendorfer; Rheucostan R; rheumaloges; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; uro-loges; ***Neth.***: Acidolite; Cystilite; Cysto-Gastreu R18; Dermalite; Dulcarhus-Gastreu R11; Enulite; Hepalite; Hepatodrainol†; Homeocare Uro; Reneel H; Restructa H; ***Port.***: Hepatodrainol; ***Rus.***: Berberis Comp (Барбарис Комп); Berberis-Plus (Берберис-Плюс); Helidonium-Plus (Хелидониум-Плюс); Psorilom (Псорилом); ***Switz.***: Akutur; metaheptachol; Regenaplex Nr. 21e; Regenaplex Nr. 31b; Regenaplex Nr. 49a; Regenaplex Nr. 51c; ***UK***: Catarrh Cream; ***Ukr.***: Choledius (Холедиус).

Evening Primrose

King's Cureall; Onagre; Энотера.
ATC Herb — HR03WX5006 (Oenothera biennis: herb).
UNII — 76UI55V071 (Oenothera biennis).

Profile

Evening primrose, the aerial parts of *Oenothera biennis* (Onagraceae) and related species of *Oenothera*, is reported to have sedative and astringent properties. It has been used in herbal preparations for respiratory and gastrointestinal disorders.

Evening primrose seed is the source of evening primrose oil (below), which is a source of essential fatty acids.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Sclerovis H Plus.

Evening Primrose Oil

Aceite de prímula; Helokkiöljy; Nakvišų aliejus; Nattljusolja; Oenotherae oleum; Olej wiesiołkowy; Olej wiesiołkowy bezpośredniego tłoczenia (virgin evening primrose oil); Onagra, aceite de; Onagre, huile d'; Pupalkový olej; Масло Энотеры.
ATC Herb — HD11AX5004 (Oenothera biennis: oil); HG02WB5004 (Oenothera biennis: oil).
UNII — 3Q9L08K71N.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Evening Primrose Oil, Refined; Oenotherae Oleum Raffinatum). The fatty oil obtained from the seeds of *Oenothera biennis* or *O. lamarkiana* by extraction and/or expression, and then refined. A suitable antoxidant may be added. A clear, light yellow or yellow liquid. Relative density about 0.923. Practically insoluble in water and in alcohol; miscible with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store in well-filled, airtight containers under an inert gas. Protect from light.

Uses and Administration

Evening primrose oil is a source of linoleic and gamolenic acid, which are essential fatty acids of the omega-6 series that act as prostaglandin precursors (see p. 2509.2). Evening primrose oil has been given orally for the symptomatic relief of atopic eczema in usual doses of up to 3 grams twice daily; it is also used topically as a cream for the relief of dry or inflamed skin. Evening primrose oil has also been given orally for mastalgia. Evening primrose oil has been studied in a variety of other disorders including multiple sclerosis, rheumatoid arthritis, and the premenstrual syndrome. Mixtures of essential fatty acids (including EF-4, EF-12, and EF-27) derived from evening primrose oil and other oils have also been investigated in various disorders, including diabetic neuropathy, restenosis after angioplasty, and skin damage after radiotherapy.

General references.

1. Kleijnen J. Evening primrose oil. *BMJ* 1994; **309:** 824–5.

Eczema. For the use of evening primrose oil as a source of essential fatty acids for the management of eczema, see under Gamolenic Acid, p. 2509.3.

Mastalgia. For the use of evening primrose oil as a source of gamolenic acid for the management of mastalgia, see p. 2509.3.

Menopausal disorders. Although there are anecdotal reports of benefit, a controlled study[1] found that evening primrose oil was no more effective than placebo for managing menopausal vasomotor symptoms (p. 2245.1).

1. Chenoy R, *et al.* Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994; **308:** 501–3.

Multiple sclerosis. For the use of evening primrose oil in the management of multiple sclerosis, see under Gamolenic Acid, p. 2509.3.

Premenstrual syndrome. For conflicting results from the use of evening primrose oil in premenstrual syndrome see under Gamolenic Acid, p. 2510.1.

Rheumatoid arthritis. For the use of evening primrose oil as a source of gamolenic acid for the management of rheumatoid arthritis, see p. 2510.1.

Adverse Effects and Precautions

See Gamolenic Acid, p. 2510.1.

Effects on the nervous system. Temporal lobe epilepsy was diagnosed after treatment with evening primrose oil in 3 patients who had previously been diagnosed as schizophrenic.[1] Tonic-clonic (grand mal) seizures occurred in 2 additional schizophrenic patients during treatment with evening primrose oil.[2] All of these patients had received or were taking phenothiazine antipsychotics.

1. Vaddadi KS. The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. *Prostaglandins Med* 1981; **6:** 375–9.
2. Holman CP, Bell AFJ. A trial of evening primrose oil in the treatment of chronic schizophrenia. *J Orthomol Psychiatry* 1983; **12:** 302–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Primrose Micelle†; ***Fr.***: Osmonagre; ***Ger.***: Epogam; Linola gamma; Neobonsen; ***Gr.***: Epogam; ***Hung.***: Epovit; ***India***: Elprim; Simrose; ***Irl.***: Naudicelle†; ***Malaysia***: Bio-Enhanced Evening Primrose Oil; ***NZ***: Efamol; ***Philipp.***: Eveprim; ***Pol.***: Linoeparol†; Oeparol†; ***S.Afr.***: Primolin†; ***Swed.***: Efamol; ***Switz.***: Epogam; ***UK***: Efamol; Evening Gold; Evoprim; Linola Gamma†; ***Venez.***: Eve 500.

Multi-ingredient Preparations. ***Arg.***: La Edad De Oro; ***Austral.***: Arthri Plus†; Arthro-Eze; EFA Compound; For Women Multi Plus EPO†; Ginger-Vite Forte†; Maxepa Evening Primrose Oil; Once Daily Womens Multi; Primrose-E†; Womens One-a-Day Multi; Zellulean with Escin†; ***Braz.***: Primoris†; ***Canad.***: Primanol Borage Oil†; Restorativ Glucosamine Muscle and Joint; ***Fr.***: Anacaps tri-Activ; Anacaps†; Corvitec; Derm; Diomega; Dioptec; Donaclim; Donalis; Feminabiane Cycle Feminin; Phaneres; Regederm; Trioptec; ***Hong Kong***: Mumomega; Pregnacare; ***Hung.***: Allithera; Obesmin; ***India***: Bevitplus; Ease-PMS; Edge-P Plus; Edge-P; Goldprim; Multivite Woman; N-Care Forte; ***Indon.***: Epocaldi; ***Ital.***: Biomineral 5-Alfa; Edemalt; ***Malaysia***: Evening Primrose Oil Plus; Prim E; Tocovid Emulsion Plus; ***Mex.***: Rodan; ***NZ***: Efalex; Efamarine; Efamax†; Mr Nits; ***S.Afr.***: CalmolinADD†; Femolin PMS†; ***Singapore***: Mumomega Equazen†; Robovites Multivitamins; Seven Seas EPO Plus Starflower Oil; Vita Natal; VitaEPA Plus; ***Swed.***: Efalex; Efanatal†; ***UK***: Efalex; Efamarine; Efamol PMP; Efanatal; PMT Formula; ***Ukr.***: Wellwoman (Велвумен); ***USA***: Eucerin Itch-Relief.

Febuprol *(rINN)*

Fébuprol; Febuprolí; Febuprolum; Фебупрол.
1-Butoxy-3-phenoxy-2-propanol.
$C_{13}H_{20}O_3$=224.3
CAS — 3102-00-9.
UNII — B5RKR9Y63Y.

Profile

Febuprol is a choleretic that has been given orally in the treatment of biliary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Valbil†.

Felypressin *(BAN, USAN, rINN)* ⊗

Felipresina; Felipresinas; Felipressin; Felypresin; Felypressiini; Félypressine; Felypressinum; Phelypressine; PLV2; Фелипрессин.
[2-Phenylalanine,8-lysine]vasopressin; Cys-Phe-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2.
$C_{46}H_{65}N_{13}O_{11}S_2$=1040.2

CAS — 56-59-7.
UNII — 17N2918V6G.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Felypressin). A synthetic nonapeptide available as an acetate. A white or almost white powder or flakes. Freely soluble in water; practically insoluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Felypressin is a synthetic analogue of vasopressin (p. 2642.3) with similar actions. Its antidiuretic effects are less than those of vasopressin. It is used as a vasoconstrictor in local anaesthetic injections for dental use when sympathomimetics should be avoided. It is also an ingredient of preparations that have been used in the treatment of pain and inflammation of the mouth.

Preparations

Proprietary Preparations (details are given in Volume B)

Used as an adjunct in:. ***Braz.***: Citanest com Octapressin; Citocaina; ***Denm.***: Citanest Octapressin; ***Fin.***: Citanest Octapressin; ***Ger.***: Xylonest; ***Hong Kong***: Citanest Octapressin†; ***Mex.***: Pristesin F; ***Neth.***: Citanest Octapressine; ***Norw.***: Citanest Octapressin; ***Singapore***: Citanest Octapressin; ***Swed.***: Citanest Octapressin; ***Turk.***: Citanest Octapressin†; ***UK***: Citanest with Octapressin.

Fenchone

Fenchon; Фенхон.
1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one.
$C_{10}H_{16}O$=152.2
CAS — 4695-62-9 ((+)-fenchone); 7787-20-4 ((-)-fenchone); 1195-79-5 ((±)-fenchone).

Profile

Fenchone is a constituent of several essential oils. It has been used in preparations in the treatment of biliary and urinary-tract disorders. It is reported to have counter-irritant properties. Fenchone is also used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Rowatinex; ***Austria***: Rowatinex; ***Chile***: Rowatinex; ***Cz.***: Rowatinex; ***Ger.***: Rowatinex; ***Hong Kong***: Neo-Rowatinex; Rowatinex; ***Hung.***: Rowatinex; ***Irl.***: Rowatinex; ***Israel***: Rowatinex; ***Malaysia***: Rowatinex; ***Philipp.***: Rowatinex; ***Pol.***: Rowatinex; ***Rus.***: Rowatinex (Роватинекс); ***Spain***: Rowanefrin; ***Thai.***: Rowatinex; ***Venez.***: Rowatinex.

Fencibutirol *(USAN, rINN)*

Fencibutirolum; Mg-4833; Фенцибутирол.
2-(1-Hydroxy-4-phenylcyclohexyl)butyric acid.
$C_{16}H_{22}O_3$=262.3
CAS — 5977-10-6.
UNII — H2V165956A.

Profile

Fencibutirol is a choleretic that has been used in the treatment of constipation and biliary-tract disorders.

Fenipentol *(rINN)*

Fénipentol; Fenipentolum; Фенипентол.
1-Phenylpentan-1-ol; α-Butylbenzyl alcohol.
$C_{11}H_{16}O$=164.2
CAS — 583-03-9.
UNII — X3FZE77O60.

Profile

Fenipentol is a choleretic that has been given orally for the treatment of hepatic and biliary-tract disorders in doses of 100 to 200 mg three times daily. The hemisuccinate and sodium hemisuccinate have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Febichol.

Multi-ingredient Preparations. ***Venez.***: Cholipin.

Fennel

Édeskömény termés (bitter fennel); Fänkål, bitter (bitter fennel); Fänkål, söt (sweet fennel); Fenchel; Fenkoli, karvas (bitter fennel); Fenkoli, makea (sweet fennel); Fennel Fruit; Fennel Seed; Fenouil; Fenouil Amer; Fenouil amer, fruit de (bitter fennel); Fenouil doux, fruit de (sweet fennel); Foeniculi amari fructus (bitter fennel); Foeniculi dulcis fructus (sweet fennel); Foeniculum; Fruto de Hinojo; Funcho; Hinojo; Kartieji pankolių vaisiai (bitter fennel); Kerti édeskömény termés (sweet fennel); Owoc kopru włoskiego (bitter fennel); Plod fenyklu obecného pravého (bitter fennel); Plod fenyklu obecného sladkého (sweet fennel); Saldieji pankolių vaisiai (sweet fennel); Фенхель.
ATC Herb — HA03AW5028 (Foeniculum vulgare: fruit); HR05WA5013 (Foeniculum vulgare: fruit).
UNII — 557II4LLC3 (fennel); G3QC02NIE6 (fennel seed).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Fennel, Bitter; Foeniculi Amari Fructus). It consists of the dry, cremocarps and mericarps of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare*. It contains not less than 4.0% v/w of essential oil, calculated with reference to the anhydrous drug. The oil contains not less than 60.0% of anethole and not less than 15.0% of fenchone. Bitter fennel is greenish-brown, brown, or green. Protect from light and moisture.

Ph. Eur. 8: (Fennel, Sweet; Foeniculi Dulcis Fructus). It consists of the dry, cremocarps and mericarps of *Foeniculum vulgare*, subsp. *vulgare*, var. *dulce*. It contains not less than 2.0% v/w of essential oil, calculated with reference to the anhydrous drug. The oil contains not less than 80.0% of anethole. Sweet fennel is pale green or pale yellowish-brown. Protect from light and moisture.

Profile

Fennel is the source of fennel oil (below). It is used as a flavour and carminative, although the efficacy of such traditional remedies in infant colic is considered dubious (see Gastrointestinal Spasm, p. 1807.1). It is also used in herbal remedies for respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Fenyklovy Caj; ***Pol.***: Plantex; ***Rus.***: Plantex (Плантекс); ***Ukr.***: Plantex (Плантекс).

Multi-ingredient Preparations. ***Arg.***: Adelgazar; Arceligasol; ***Austral.***: Bupleurum Compound; Colon Care; Crampeze Stomach Cramps; Detox Program; Digest Aid; Digestaid; Digestive Aid; ***Austria***: Brady's-Magentropfen; Euka; Laxalpin†; Mag Kottas Krauterexpress Abfuhrtee; Planta Lax; ***Belg.***: Herbesan; ***Braz.***: Balsamo Branco; ***Canad.***: Cellutex; Clear Capsules†; Entschlackungstee N†; Floradix Kindervital†; Formula T4†; Gallexier†; Herbal Laxative plus Yogurt†; Herbal Laxative†; ***Chile***: Bebe Flat; Draineur; Instalax; Reduc-Te; ***Cz.***: Cajova Smes pri Nachlazeni; Detska Cajova Smes; Detsky Caj s Hermankem; Diabetan; Nervova Cajova Smes; Projimava; Pulmoran; Reduktan; Species Pectorales Planta; Stomaran; Zaludecni Cajova Smes; ***Fr.***: Afra†; Benetransit†; Bolcitol†; Gastrotisane†; Hepatoflorine†; Mediflor Contre la Constipation Passagere No 7; Mediflor Digestive No 3; Mediflor Diuretique No 4†; Santane D_5†; ***Ger.***: Carminativum-Hetterich; Cefabronchin; Floradix Multipretten N; Gallexier; Gastricholan-L; Kneipp Husten- und Bronchial-Tee†; ***Hung.***: Babynos; Gallexier; Herbalakt; Mensesyl; Salus Multipretten; Tamarinlax; ***India***: Abana; Anti Dysp; Apimore; Aptivate OS; Gasex; Lactacrat; Laxive; Liyurto; Mentat; Naptizer; Paedritone; ***Israel***: Jungborn†; ***Ital.***: Actenacol; Cadifen; Cadimint; Colimil; Dicalmir; Evamilk; Plurilac; Promolax; Relaxcol; Tripondil; ***Jpn***: Anchusan; Cabe 2 New; The Guard Seichojo; ***Malaysia***: Taisho Kampo; ***Neth.***: Herbesan†; ***Pol.***: Amarosal; Bobofen†; DexaPini; Diges-Tonic; Herbapini; Rhelax; Salviasept; Sirupus Pini Compositus; Sirupus Tussipini D; Sirupus Tussipini; Syrop Sosnowy Zlozony†; ***Rus.***: Babynos (Бебинос); Insti (Инсти); Phytogastrol (Фитогастрол); Phytonefrol (Фитонефрол); Travisil (Трависил); ***Singapore***: Stop Snoring; ***Spain***: Crislaxo; ***Swed.***: Alpenkraft; Multipretten; ***Switz.***: Femisan; Kernosan 24; Kernosan 26; Kernosan Eau Dentifrice†; Kernosan Elixir; Kernosan Heidelberger Poudre; Metabol; Tisane favorisant l'allaitement; Tisane laxative; Tisane pectorale et antitussive; Tisane pour nourissons et enfants; ***UK***: Cleansing Herbs; Herbal Indigestion Naturtabs; Indigestion and Flatulence; Lion Cleansing Herbs; Lustys Herbalene; Out-of-Sorts; Pure Plan; Revitonil; Senokot Dual Relief; Sure-Lax (Herbal); ***Ukr.***: Apitol (АПИТОЛ); Carminativum Babynos (Карминативум Бебинос); Insti (Інсті); Lipomin (Липомин); Liponorm (Липонорм); Softovak (Софтовак); Travisil (Трависил); Trypsidan (Трипсидан)†.

Homoeopathic Preparations. ***Chile***: Cynara Compuesta; ***Fr.***: Poconeol no 54.

Fennel Oil

Aetheroleum Foeniculi; Bitterfänkålsolja (bitter-fennel fruit oil); Esencia de Hinojo; Essência de Funcho; Fenouil amer (fruit de), huile essentielle de (bitter-fennel fruit oil); Foeniculi amari fructus aetheroleum (bitter-fennel fruit oil); Hinojo, aceite esencial; Karčiųjų pankolių vaisių eterinis aliejus (bitter-fennel fruit oil); Karvasfenkoliöljy (bitter-fennel fruit oil); Olejek kopru włoskiego (bitter-fennel fruit oil); Oleum Foeniculi; Rezene Yağı; Silice fenyklu hořkého (bitter-fennel fruit oil); Фенхелевое Масло.
ATC Herb — HA03AW5027 (Foeniculum vulgare: essential oil).
UNII — 59AAO5F6HT (fennel oil).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Bitter-Fennel Fruit Oil; Foeniculi Amari Fructus Aetheroleum). The essential oil obtained by steam distillation from the ripe fruits of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare*. It contains 12.0 to 25.0% fenchone and 55.0 to 75.0% anethole. A clear, colourless or pale yellow liquid with a characteristic odour. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Ph. Eur. 8: (Bitter-Fennel Herb Oil; Foeniculi Amari Herbae Aetheroleum). The essential oil obtained by steam distillation of the aerial parts of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare* collected during fruiting. A clear, pale or intense yellow liquid with an anise-like odour. Store at a temperature not exceeding 25 degrees. The label states that the content is Spanish-type or Tasmanian-type oil.

USNF 31: (Fennel Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Foeniculum vulgare* (Apiaceae). Congealing temperature not lower than 3 degrees. Soluble 1 in 1 of alcohol (90%). If solid matter has separated, carefully warm the oil until it is completely liquefied, and mix before using. Store in airtight containers.

Profile

Fennel oil is used as an aromatic flavour and carminative (but see the comment under Fennel, above); the German expert committee for herbal drugs and preparations (Commission E) considers that the use of fennel oil in infants and toddlers is contra-indicated. It is also used in herbal remedies for respiratory-tract disorders and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Babyfen†; Senefen†; ***Pol.***: Plantex; ***Rus.***: Plantex (Плантекс); ***Ukr.***: Plantex (Плантекс).

Multi-ingredient Preparations. ***Austral.***: PulmaCo; ResCo; Throat-Clear; ***Austria***: Eucarbon; Luuf-Hustentee; Spasmo Claim†; ***Canad.***: Anifen†; ***Chile***: Calmatol; ***Cz.***: Biotussil; Bronchosan†; Herbadent; Ophthalmo-Septonex; ***Fr.***: Dida; ***Ger.***: Ephepect-Pastillen N; Floradix Multipretten N; Gastrysat†; Salviathymol N; Verdauungstropfen Gastrofunkten†; Weleda Bronchialbalsam; ***Hong Kong***: Magesto; ***Hung.***: Cholasyl; Salus Multipretten; Stompax; ***India***: Betip; Carmicide DPS; Colicaid; Coliky; Coliwell; Coliza; Cymbi; Decolic Infant; DP-Spas DPS; Gastica; Merispas; Panoric; ***Indon.***: Minyak Telon†; ***Israel***: Novicarbon†; ***Ital.***: Relaxcol; Selezime; ***Malaysia***: Eucarbon; ***Pol.***: Woodwards Gripe Water; ***Rus.***: Bronchosan (Бронхосан); ***S.Afr.***: Borsdruppels; Oleum Salviae Comp†; ***Swed.***: Alpenkraft; Multipretten; ***Switz.***: Eau pour les yeux†; Flatulex; Huile Po-Ho A. Vogel; Laxasan; ***Thai.***: Corinap; Gas-Nep; Magesto; ***Turk.***: Eucarbon; ***Ukr.***: Bronchosan (Бронхосан)†; Eucarbon (Эукарбон); Softovak (Софтовак).

Fenoverine *(rINN)*

Fenoverina; Fénovérine; Fenoverinum; Феноверин.
10-[(4-Piperonyl-1-piperazinyl)acetyl]phenothiazine.
$C_{26}H_{25}N_3O_3S$=459.6
CAS — 37561-27-6.
ATC — A03AX05.
ATC Vet — QA03AX05.
UNII — N274ZQ6PZJ.

Profile

Fenoverine has been used as an antispasmodic but has been withdrawn in some countries after reports of rhabdomyolysis.

Adverse effects. Reports of rhabdomyolysis associated with fenoverine,[1-3] including a fatality.[1] A genetic predisposition has been suggested.[2]

1. Chariot P, *et al.* Fenoverine-induced rhabdomyolysis. *Hum Exp Toxicol* 1995; **14:** 654–6.
2. Jouglard J, *et al.* Research into individual predisposition to develop acute rhabdomyolysis attributed to fenoverine. *Hum Exp Toxicol* 1996; **15:** 815–20.
3. Chen CW, Chang MH. Rhabdomyolysis induced by fenoverine: a case report and literature review. *Acta Neurol Taiwan* 2005; **14:** 143–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Spasmopriv; ***Philipp.***: Spasmopriv; ***Singapore***: Spasmopriv; ***Thai.***: Spasmopriv†.

Fenpipramide *(BAN, rINN)*

Fenpipramid; Fenpipramida; Fenpipramidi; Fenpipramidum; Фенпипрамид.

2,2-Diphenyl-4-piperidinobutyramide.

$C_{21}H_{26}N_2O$=322.5

CAS — 77-01-0.

UNII — 88445508X3.

Fenpipramide Hydrochloride *(BANM, rINNM)*

Fenpipramide, Chlorhydrate de; Fenpipramidi Hydrochloridum; Hidrocloruro de fenpipramida; Фенпипрамида Гидрохлорид.

$C_{21}H_{26}N_2O$,HCl=358.9

CAS — 14007-53-5.

UNII — KJ2V75P034.

Fenpiverinium Bromide *(rINN)*

Bromuro de fenpiverinio; Fenpipramide Methobromide; Fenpipramide Methylbromide; Fenpiverinii Bromidum; Fenpiverinio, bromuro de; Fenpivérinium, Bromure de; Фенпивериния Бромид.

1-(3-Carbamoyl-3,3-diphenylpropyl)-1-methylpiperidinium bromide; 2,2-Diphenyl-4-piperidinobutyramide methyl bromide.

$C_{22}H_{29}BrN_2O$=417.4

CAS — 125-60-0.

ATC — A03AB21.

ATC Vet — QA03AB21.

UNII — 36479UA8GL.

Profile

Fenpipramide (as the hydrochloride) and its methobromide, fenpiverinium bromide, have been used as antispasmodics. Fenpipramide hydrochloride is also used for its antimuscarinic actions in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Algifen; Analgin; Spasmopan; ***India***: Combispas; Nidi Spas; Nobel Spas; Novaspas; ***Pol.***: Spasmalgon; ***Rus.***: Bioralgin (Биоралгин); Bral (Брал); Bralangine (Бралангин); Maxigan (Максиган); Nebalgan (Небалган); Novigan (Новиган); Plenalgin (Пленалгин); Renalgan (Реналган); Revalgin (Ревалгин); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); ***Thai.***: Donagan; Kanegan†; ***Ukr.***: Baralginus (Баралгинус)†; Novigan (Новиган); Spasgan (Спазган); Spasmadol (Спазмадол)†; Spasmalgon (Спазмалгон); Spasmil-M (Спазмил-М); ***Venez.***: Flemibar.

Fenugreek

Alforva; Alholva; Bockhornsfrö; Bockshornsame; Bockshornsamen; Faenum-Graecum; Fenogreco; Fenugrec; Görögszénamag; Greek hay; Ožragių sėklos; Sarviapilansiemen; Semen Foenugraeci; Semen Trigonellae; Semeno pískavice řeckého sena; Trigonella Foenugraeci Semen; Trigonellae Foenugraeci Semen; Пажитник.

UNII — 5610HF69OB (fenugreek); 654825W09Z (fenugreek seed); P9K34XXG87 (fenugreek seed resin); 487RI96K8Z (fenugreek leaf).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Fenugreek). The dried ripe seeds of *Trigonella foenum-graecum*. It has a strong characteristic odour. Protect from light.

Uses and Administration

Fenugreek has been used as an appetite stimulant and as an ingredient in preparations for respiratory disorders. It also has emollient properties. The tops and seeds are used in cooking.

References.

1. Basch E, *et al.* Therapeutic applications of fenugreek. *Altern Med Rev* 2003; **8:** 20–7.
2. Ulbricht C, *et al.* Fenugreek (*Trigonella foenum-graecum* L. Leguminosae): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2007; **7:** 143–77.

Adverse Effects

A 5-week-old infant lost consciousness after drinking herbal tea containing fenugreek.[1] On recovery the infant and his urine had an aroma characteristic of that found in 'maple syrup urine disease', an inborn condition involving defective metabolism of branched-chain amino acids. Further investigation revealed that the infant did not have the disease; the aroma was due to the presence of sotolone in the fenugreek seeds used to prepare the tea.

1. Sewell AC, *et al.* False diagnosis of maple syrup urine disease owing to ingestion of herbal tea. *N Engl J Med* 1999; **341:** 769.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Fenugrene.

Multi-ingredient Preparations. ***Austral.***: Bilberry Plus†; Garlic and Horseradish + C Complex†; Super Strength Horseradish Garlic + C; Ultra Allergy Defense; ***Fr.***: Phytheol Force†; Trimada; ***India***: Diabasic; Dialife; Happy'tizer†; Lactare; Nobese; ***Indon.***: Lactamam; Milmor NF; Provigor†; ***Malaysia***: Shine Maxtra; ***Philipp.***: Cogent db+; Lungcaire Plus; ***Singapore***: LactaGreek; ***Ukr.***: Alfagin (Алфагин); Pravenor (Правенор); Uronephron (Уронефрон).

Homoeopathic Preparations. ***Ger.***: Regenaplex Haut G.

Ferric Chloride

Chlorid železitý hexahydrát; Chlorure Ferrique; Cloruro de hierro III; Ferr. Perchlor.; Ferri Chloridum Hexahydricum; Férrico, cloruro; Ferrikloridhexahydrat; Ferrikloridiheksahydraatti; Ferrique (chlorure) hexahydraté; Ferrum Sesquichloratum; Geležies(III) chloridas heksahidratas; Iron Perchloride; Iron Sesquichloride; Iron Trichloride; Tricloruro de hierro; Vas(III)-klorid-hexahidrát; Železa(III) chlorek; Хлорид Железа.

$FeCl_3,6H_2O$=270.3

CAS — 7705-08-0 (anhydrous ferric chloride); 10025-77-1 (ferric chloride hexahydrate).

UNII — U38V3ZVV3V (ferric chloride); 0I2XIN602U (ferric chloride hexahydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ferric Chloride Hexahydrate). A very hygroscopic, crystalline mass or orange-yellow to brownish-yellow crystals. Very soluble in water and in alcohol; freely soluble in glycerol. Store in airtight containers. Protect from light.

Profile

Ferric chloride has the general properties of iron salts (p. 2073.1) but is exceptionally astringent. It has been used mainly by local application for its styptic and astringent properties. Local application of ferric chloride or other iron salts may cause permanent discoloration of the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Emostat†; ***Ital.***: Cotone Emostatico; ***Rus.***: Hemofer (Гемофер); ***S.Afr.***: Staaldruppels.

Multi-ingredient Preparations. ***UK***: Glykola.

Homoeopathic Preparations. ***Cz.***: Ferrum Homaccord†; ***Ger.***: Infi-China; ***Switz.***: metaossylen N.

Fibronectins

Fibronectina; Фибронектины.

Profile

Fibronectins are high molecular weight endogenous adhesive glycoproteins found in plasma and in the extracellular matrix. Plasma fibronectin was originally known as cold-insoluble globulin. Fibronectins are mainly involved in cellular attachment and migration in normal physiological processes as well as in various malignant diseases. They have an important role in the function of the extracellular matrix, and in morphogenesis and tissue remodelling. They also play a part in aggregation of platelets, and are used in combinations with other blood products in wound-sealant preparations. Manipulation of the activity of fibronectins (for example with fibronectin inhibitors or fibronectin fragments) is being investigated in the treatment of connective tissue diseases, malignancies, and wound healing. Fibronectin itself has potential use as a research tool for the study of cell adhesion and migration processes.

References.

1. Kaspar M, *et al.* Fibronectin as target for tumor therapy. *Int J Cancer* 2006; **118:** 1331–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Tisseel Duo†; ***Austria***: Evicel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Quixil†; Tissucol Duo; Tissucol Kit; ***Canad.***: Tisseel; ***Cz.***: Evicel; Tissucol; ***Denm.***: Evicel; Quixil; Tisseel Duo Quick; ***Fin.***: Quixil; Tisseel Duo Quick; ***Fr.***: Evicel; Tissucol; ***Ger.***: Evicel; Quixil†; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Evicel; ***Hong Kong***: Tisseel; ***Hung.***: Tissucol-Kit; ***Irl.***: Evicel; ***Israel***: Tisseel†; ***Ital.***: Quixil; ***Neth.***: Quixil†; Tissucol Duo; Tissucol; ***Norw.***: Evicel; ***NZ***: Tisseel Duo; ***Pol.***: Evicel; ***Rus.***: Tissucol Kit (Тиссукол Кит); ***Spain***: Tissucol Duo; ***Swed.***: Evicel; Quixil†; Tisseel Duo Quick; ***Switz.***: Quixil; Tissucol Duo S†; Tissucol†; ***UK***: Tisseel.

Fingolimod *(rINN)*

Fingolimodum; Финголимод.

2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol.

$C_{19}H_{33}NO_2$=307.5

CAS — 162359-55-9.

ATC — L04AA27.

ATC Vet — QL04AA27.

UNII — 3QN8BYN5QF.

Fingolimod Hydrochloride *(USAN)*

Fingolimod, Chlorhydrate de; Fingolimod Hydrochloride [rINNM (en)] (rINNM); Fingolimodi Hydrochloridum; FTY-720; Hidrocloruro de fingolimod; Финголимода Гидрохлорид.

$C_{19}H_{33}NO_2$,HCl=343.9

CAS — 162359-56-0.

ATC — L04AA27.

ATC Vet — QL04AA27.

UNII — G926EC510T.

Uses and Administration

Fingolimod is an immunomodulator used in the treatment of patients with relapsing forms of multiple sclerosis (p. 996.3), the aim of treatment being to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate, which binds to sphingosine 1-phosphate receptors blocking the emergence of lymphocytes from the lymph nodes thereby reducing the number of lymphocytes into peripheral blood. It is presumed that this reduces the migration of lymphocytes into the CNS.

Fingolimod is given orally as the hydrochloride once daily in a dose equivalent to 500 micrograms of the base. Patients should be observed for 6 hours after the first dose of fingolimod to monitor for signs and symptoms of bradycardia (see Adverse Effects and Precautions, below).

Fingolimod is also under investigation for prophylaxis of acute rejection in kidney transplantation.

References.

1. Kappos L, *et al.* Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med* 2006; **355:** 1124–40.
2. O'Connor P, *et al.* Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. *Neurology* 2009; **72:** 73–9.
3. Leypoldt F, *et al.* Hemorrhaging focal encephalitis under fingolimod (FTY720) treatment: a case report. *Neurology* 2009; **72:** 1022–4.
4. Kovarik JM, *et al.* Ketoconazole increases fingolimod blood levels in a drug interaction via CYP4F2 inhibition. *J Clin Pharmacol* 2009; **49:** 212–18.
5. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol* 2009; **158:** 1173–82.
6. Kappos L, *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.
7. Cohen JA, *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 402–15.

Adverse Effects and Precautions

The most common adverse effects reported with fingolimod include back pain, cough, diarrhoea, headache, influenza, and elevated liver enzymes.

Reduction in heart rate occurs within one hour of starting fingolimod treatment with maximum reduction in up to 6 hours. Patients should therefore be observed for signs and symptoms of bradycardia for 6 hours after the first dose. Most patients with bradycardia are asymptomatic, but dizziness, fatigue, palpitations, and chest pain may occur in some. After the second dose, a further reduction in heart rate may also occur compared with the heart rate immediately before this second dose, although this change is of smaller magnitude than the reduction on day one. With continued dosing, the heart rate returns to baseline levels within one month of starting treatment. Transient atrioventricular (AV) conduction delays have also occurred at the start of fingolimod treatment, and it is therefore recommended that before treatment starts, a baseline ECG should be obtained for patients at risk of bradyarrhythmia if one has not already been done in the preceding 6 months. These effects on heart rate and AV conduction may recur on

reintroduction of fingolimod if treatment has been stopped for more than 2 weeks, and the precautions for re-initiating treatment outlined above should be followed.

Fingolimod may increase the risk of developing infections due to the reduction in peripheral lymphocyte count (see Uses and Administration, p. 2504.3), and treatment should not be started in patients without a recent full blood count taken within the previous 6 months. Fingolimod should not be started in patients with active acute or chronic infections. Patients should be monitored for signs and symptoms of infection during treatment and for 2 months after treatment has stopped. Stopping fingolimod should be considered if a patient develops a serious infection during treatment, and then the risks versus benefits reassessed before treatment is resumed.

Patients without a history of chickenpox or who have not received varicella-zoster vaccination should be tested for antibodies to varicella-zoster virus. Vaccination should be considered in antibody-negative patients before starting fingolimod treatment, which should then be delayed for one month after vaccination. Giving any live attenuated vaccine should be avoided during, and for 2 months after stopping, fingolimod treatment because of the risk of infection.

Macular oedema has been reported in some patients taking fingolimod, and ophthalmologic evaluation should be carried out before starting treatment and routinely about 3 to 4 months later, and at any time if patients report visual disturbances during treatment. Patients with a history of uveitis and those with diabetes mellitus are at increased risk of developing macular oedema during treatment with fingolimod.

Dyspnoea has been reported with fingolimod and a decrease in lung function tests has been seen in patients as early as 1 month after starting treatment. When considered clinically appropriate, spirometric evaluation of respiratory function and evaluation of diffusion lung capacity for carbon monoxide should be obtained.

Fingolimod may increase liver transaminases and treatment should not be started without results of recent transaminase and bilirubin levels taken within the previous 6 months. Liver enzymes should also be monitored during treatment in patients with signs and symptoms of hepatic impairment, and treatment stopped if significant impairment occurs. The risk of adverse effects with fingolimod may be greater in patients with severe hepatic impairment and consequently they should be monitored closely or treatment avoided.

Hypertension has been reported in patients treated with fingolimod and blood pressure should therefore be monitored during treatment.

Breast feeding. Although there are no human data for excretion of fingolimod in breast milk, it is excreted in the milk of *rats*; therefore, because of the potential for serious adverse reactions in a nursing infant, licensed product information recommends that fingolimod is not compatible with breast feeding.

Pregnancy. Although there are only limited human data for use of fingolimod in pregnancy, developmental toxicity has been shown in *rats* and *rabbits*, and since the sphingosine 1-phosphate receptor is involved in vascular formation during embryogenesis, US licensed product information recommends that fingolimod should only be used during pregnancy if the potential benefit outweighs potential risks to the fetus, which may persist for 2 months after stopping treatment. Additionally, women of child-bearing potential are advised to use effective contraception during fingolimod treatment and for 2 months after treatment stops.

Interactions

Fingolimod should be used with caution at the same time as antineoplastics, immunosuppressants, and immunomodulators because of the increased risk of immunosuppression. Caution should also be exercised when switching patients to fingolimod from long-acting drugs such as *natalizumab* and *mitoxantrone*.

Ketoconazole increases the blood concentrations of fingolimod and fingolimod phosphate, and so patients taking the two drugs together should be closely monitored.

Patients taking *beta blockers*, or class Ia or class III *antiarrhythmics* should be closely monitored when given fingolimod because of the risk of decreased heart rate (see Adverse Effects and Precautions, p. 2504.3).

For use of *vaccines* with fingolimod, see Adverse Effects and Precautions, p. 2504.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gilenya; ***Canad.***: Gilenya; ***Denm.***: Gilenya; ***Fr.***: Gilenya; ***Ger.***: Gilenya; ***Gr.***: Gilenya; ***Irl.***: Gilenya; ***Israel***: Gilenya; ***Jpn***: Gilenya; Imusera; ***Neth.***: Gilenya; ***Norw.***: Gilenya; ***Spain***: Gilenya; ***Swed.***: Gilenya; ***Switz.***: Gilenya; ***Turk.***: Gilenya; ***UK***: Gilenya; ***USA***: Gilenya.

Flavonoid Compounds

Bioflavonoides; Bioflavonoids; Flavonoides; Vitamin P Substances; Vitaminas P; Флавоноиды.

Benzquercin *(rINN)*

Benzquercina; Benzquercine; Benzquercinum; Бензкверцин.
3,3′,4′,5,7-Pentakis(benzyloxy)flavone.
$C_{50}H_{40}O_7$=752.9
CAS — 13157-90-9.
UNII — 499L710905.

Diosmin *(BAN, rINN)*

Barosmin; Buchu Resin; Diosmetin 7-Rutinoside; Diosmiini; Diosmina; Diosminas; Diosmine; Diosminum; Diozmin; Диосмин.
3′,5,7-Trihydroxy-4′-methoxyflavone 7-[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside].
$C_{28}H_{32}O_{15}$=608.5
CAS — 520-27-4.
ATC — C05CA03.
ATC Vet — QC05CA03.
UNII — 7QM776WJ5N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Diosmin). A greyish-yellow or light yellow hygroscopic powder. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

USP 36: (Diosmin). Store in airtight containers.

Ethoxazorutoside *(rINN)*

Aethoxazorutin; Aethoxazorutoside; Ethoxazorutin; Éthoxazorutoside; Ethoxazorutosidum; Etoxazorutósido; Oxarutinum; Этоксазорутозид.
2-Morpholinoethylrutin.
$C_{33}H_{41}NO_{17}$=723.7
CAS — 30851-76-4.

Flavodate Sodium *(rINNM)*

Flavodate de Sodium; Flavodate Disodium; Flavodato sódico; Natrii Flavodas; Натрий Флаводовая.
Disodium (4-oxo-2-phenyl-4*H*-chromene-5,7-diyldioxy) diacetate.
$C_{19}H_{12}Na_2O_8$=414.3
CAS — 37470-13-6 (flavodic acid); 13358-62-8 (flavodate disodium).

Hesperidin

Hesperidiini; Hesperidina; Hesperidinum; Hesperydyna; Гесперидин.
5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl rutinoside.
$C_{28}H_{34}O_{15}$=610.6
CAS — 520-26-3 (hesperidin); 24292-52-2 (hesperidin methyl chalcone).
UNII — E750O06Y6O.

Description. Hesperidin is a flavonoid isolated from the rind of certain citrus fruits.

Leucocianidol *(rINN)*

Leucocianidolum; Leucocyanidin; Leucocyanidol; Лейкоцианидол.
2-(3,4-Dihydroxyphenyl)chroman-3,4,5,7-tetrol.
$C_{15}H_{14}O_7$=306.3
CAS — 480-17-1.
UNII — RAP1D6110C.

Monoxerutin *(rINN)*

Monohidroxietilrutósidos; Monohydroxyethylrutosides; Monokserutiini; Monoxerutina; Monoxérutine; Monoxerutinum; Моноксерутин.
7-(β-Hydroxyethyl)rutoside.
$C_{29}H_{34}O_{17}$=654.6
CAS — 23869-24-1.
ATC — C05CA02.
ATC Vet — QC05CA02.
UNII — EKF7043SBU.

Oxerutins *(BAN)*

Hidroxietilrutósidos; Hydroxyethylrutosides; Oxerutinas; Оксерутины.

Description. Oxerutins consist of a mixture of 5 different *O*-(β-hydroxyethyl)rutosides, not less than 45% of which is troxerutin (trihydroxyethylrutoside, below), but which also includes monohydroxyethylrutoside, dihydroxyethylrutoside, and tetrahydroxyethylrutoside.

Quercetin

Quercetina; Кверцетин; 3,3′,4′,5,7-Pentahydroxyflavone.
2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one.
$C_{15}H_{10}O_7$=302.2
CAS — 117-39-5.
UNII — 9IKM0I5T1E (quercetin); 53B03V78A6 (quercetin dihydrate).

Rutoside *(BAN, rINN)*

Rutin; Rutina; Rutosid; Rutosid-Trihydrat; Rutoside trihydraté; Rutosidi; Rutosiditrihydraatti; Rutósido; Rutosidtrihydrat; Rutosidum; Rutosidum Trihydricum; Rutozidas trihidratas; Rutozid-trihidrát; Rutozyd; Rutyna; Рутозид.
2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4-oxo-4*H*-chromen-3-yl rutinoside trihydrate; 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl 6-*O*-(α-L-rhamnosyl)-β-D-glucoside.
$C_{27}H_{30}O_{16}.3H_2O$=664.6
CAS — 153-18-4 (anhydrous rutoside).
ATC — C05CA01.
ATC Vet — QC05CA01.
UNII — 5G06TVY3R7 (anhydrous rutoside); RF4N03853G (rutoside trihydrate).

Description. Rutoside is a flavonoid obtained from buckwheat, *Fagopyrum esculentum* (Polygonaceae), or from other sources which include the flower buds of the Japanese pagoda-tree, *Sophora japonica*, and the leaves of several species of *Eucalyptus.*

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Rutoside Trihydrate). A yellow or greenish-yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane; soluble in methyl alcohol. It dissolves in solutions of alkali hydroxides. Protect from light.

Troxerutin *(BAN, rINN)*

THR; Trihidroxietilrutina; Trihydroxyethylrutoside; Trioxietilrutina; Trioxyethylrutin; Trokserutiini; Trokserutyna; Troxerutina; Troxérutine; Troxerutinum; Троксерутин.
3′,4′,7-Tris[*O*-(2-hydroxyethyl)]rutin; 5-Hydroxy-7-(2-hydroxyethoxy)-2-[3,4-bis(2-hydroxyethoxy)phenyl]-4-oxo-4*H*-chromen-3-yl rutinoside.
$C_{33}H_{42}O_{19}$=742.7
CAS — 7085-55-4.
ATC — C05CA04.
ATC Vet — QC05CA04.
UNII — 7Y4N11PXO8.

Description. Troxerutin is the principal component of oxerutins, above.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Troxerutin). A yellowish-green, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Flavonoids are naturally occurring phenolic compounds that are widely distributed in plants, occurring in the free state and also as glycosides. The main types of flavonoids are anthocyanins, chalcones, flavonols, flavones, and flavonones. Flavonoids act as antoxidants and claims have been made for many medicinal uses. Preparations containing natural or semisynthetic flavonoids are thought to improve capillary function by reducing abnormal leakage. They have been given to relieve capillary impairment and venous insufficiency of the lower limbs, and for haemorrhoids.

It has been suggested that flavonoids present in some foods, such as fruit, vegetables, tea, and red wine may protect against the development of atherosclerosis (p. 1250.2).

References.

1. Knekt P, *et al.* Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ* 1996; **312:** 478–81.
2. Hertog MGL, *et al.* Antioxidant flavonols and coronary heart disease risk. *Lancet* 1997; **349:** 699.
3. Youdim KA, *et al.* Dietary flavonoids as potential neuroprotectants. *Biol Chem* 2002; **383:** 503–19.

4. Lopez-Lazaro M. Flavonoids as anticancer agents: structure-activity relationship study. *Curr Med Chem Anticancer Agents* 2002; **2:** 691–714.
5. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* 2003; **63:** 71–100.
6. Alonso-Coello P, *et al*. Meta-analysis of flavonoids for the treatment of haemorrhoids. *Br J Surg* 2006; **93:** 909–20.
7. Cermak R. Effect of dietary flavonoids on pathways involved in drug metabolism. *Expert Opin Drug Metab Toxicol* 2008; **4:** 17–35.

Interactions. For a report of quercetin increasing the bioavailability and concentration of ciclosporin, see p. 1954.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermasistem; Flebon; Flebotropin; Flevomax; Jatamansin NF; Rutilina; Rutosidos; Terbenol; Venoruton; Venosmil; ***Austral.***: Paroven; ***Austria***: Venoruton; ***Belg.***: Docrutosi†; Veinamitol; Ven-Detrex; Venoruton; ***Braz.***: Daflon; Flavonid; Venoruton; ***Canad.***: Poly C; ***Chile***: Flebopex; Insuven; Venoruton; ***China***: An Ti Wei Le (安体维乐); Bo Shi Duo Ning (博士多宁); Bu Luo Wei Xin (布络威欣); Bu Rui Jin (布瑞金); Di Wei Xin (迪维欣); Fu Chang (弗畅); FuRui (符瑞); Gai Qu (盖曲); He Tong (禾通); Jiu Ren (久仁); Ka Lun (卡伦); Kai Li Jin Si (凯利金斯); Lang Ning (朗宁); Lin Yuan Luo Ke (林源络克); Lu Ding Nuo (路丁诺); Qi Li (其力); Shi Dan (世丹); Shuai Xing (帅星); Tai Wei Sheng (太韦盛); Wei Qi Ting (卫起汀); WeiXin (纬欣); Xin Chang Fu (欣畅福); Yan Quan (言全); Yi Qu Shan (易曲善); Yi Xin Jing (益新静); You Ni Ping (尤尼平); Yuan Ting (元汀); ZhiLi (质力); ***Cz.***: Cilkanol; Venoruton; ***Denm.***: Venoruton; ***Fr.***: Dio; Diovenor; Endium†; Flavan; Flebosmil†; Intercyton; Mediveine; Preparation H Veinotonic†; Rheoflux; Sedorrhoide Veinotonique†; Titanoral; Veinamitol; Venaclar; Venirene; ***Ger.***: Posorutin†; Rutin-Kapsein; Tovene†; Troxeven; Veno SL; Venoruton†; Venotrulan Trox†; ***Gr.***: Liosmin; Radiavit; Rioven; Venoruton; ***Hong Kong***: Venosmine; ***Hung.***: Dio-PP; Venoruton; ***India***: Venusmin; ***Indon.***: Ardium; Probien; Venaron; Venosmil; ***Israel***: Venoruton; ***Ital.***: Alven†; Alvenex; Arvenum; Diosven; Doven; Flebil; Venolen; Venoruton; Venosmine; ***Mex.***: Phlebodia; Sies; Teboven; ***Neth.***: Venoruton; ***NZ***: Paroven; ***Philipp.***: Varemoid; Venoruton; ***Pol.***: Aflavic; DIH; Diohespan; Diosminex; Otrex; Pelethrocin; Phlebodia; Posorutin; Procto-Hemolan Control; Rutinoven†; Rutoven†; Troxeratio; Venolan; Venoruton; Venotrex; ***Port.***: Arvenum†; Arvenum; Hepacalmina; Muralion†; Venex; Veno V; Venoruton; Venosmil; Veroven; ***Rus.***: Phlebodia (Флебодиа); Troxevazin (Троксевазин); Venoruton (Венорутон); ***S.Afr.***: Paroven†; ***Spain***: Esberiven; Venolep; Venorugel; Venoruton; Venosmil; ***Switz.***: Hemerven; Pur-Rutin; Venoruton; Venutabs; ***Thai.***: Flavon; Heteroid; Venoruton; ***Turk.***: Daflon; Natrol Ester C; Vendios; Venoruton; ***UK***: Colladeen; Paroven; ***Ukr.***: Cyclo 3 Fort (Цикло 3 Форт); Flebodia (Флебодиа); Quertin (Квертин); Troxegel (Троксегель); Vasoket (Вазокет); Venolan (Венолан)†; Venosmil (Веносмил); ***USA***: Citro-Flav; Limbrel; ***Venez.***: Diovenor; Flavol; Hyflon; Verutil.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Ger.***: Infi-China; Infihepan; Varicylum N.

Flibanserin *(USAN, rINN)*

BIMT-17; BIMT-17BS; Flibanserina; Flibansérine; Flibanserinum; Флибансерин.

1-{2-[4-(α,α,α-Trifluoro-*m*-tolyl)-1-piperazinyl]ethyl}-2-benzimidazolinone.

$C_{20}H_{21}F_3N_4O$=390.4

CAS — 167933-07-5.

ATC — G02CX02.

UNII — 37JK4STR6Z.

Profile

Flibanserin is a 5-HT_{1A}-receptor agonist and 5-HT_{2A}-receptor antagonist that has been investigated in the management of hypoactive sexual desire disorder in premenopausal women.

Flopropione *(rINN)*

Flopropiona; Flopropionum; Fluropropiofenone; Phlorapropiophenone; RP-13907; Флопропион.

2′,4′,6′-Trihydroxypropiophenone.

$C_9H_{10}O_4$=182.2

CAS — 2295-58-1.

UNII — 05V5NVB5Y1.

Pharmacopoeias. In *Jpn*.

Profile

Flopropione is an antispasmodic that has been given orally in doses of 40 to 80 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cospanon.

Fluorescein *(BAN)*

Fluoresceina; Fluoresceína; Fluorescéine; Fluoresceinum; Флуоресцеин.

3′,6′-Dihydroxyspiro[isobenzofuran-1(3*H*),9′(9*H*)xanthen]-3-one.

$C_{20}H_{12}O_5$=332.3

CAS — 2321-07-5.

ATC — S01JA01.

ATC Vet — QS01JA01.

UNII — TPY09G7XIR.

Pharmacopoeias. In *Eur* (see p. vii) and *US*.

Ph. Eur. 8: (Fluorescein). An orange-red, fine powder. Practically insoluble in water; soluble in hot alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Fluorescein). A yellowish-red to red, odourless powder. Insoluble in water; soluble in dilute alkali hydroxides. Store in airtight containers.

Fluorescein Dilaurate *(BANM)*

Fluoresceína, dilaurato de; Флуоресцеина Дилаурат.

$C_{44}H_{56}O_7$=696.9

CAS — 7308-90-9.

ATC — S01JA01.

ATC Vet — QS01JA01.

UNII — 939U41013O.

Fluorescein Sodium *(BANM)*

CI Acid Yellow 73; Colour Index No. 45350; D & C Yellow No. 8; Fluorescein Natrium; Fluorescein-Natrium; Fluorescein sodná sůl; Fluoresceína sódica; Fluoresceína soluble; Fluorescéine sodique; Fluoresceinnatrium; Fluoresceino natrio druska; Fluoresceinum natricum; Fluoreseiininatrium; Fluoresein Sodyum; Fluoreszcein-nátrium; Obiturin; Resorcinolphthalein Sodium; Sodium Fluorescein; Soluble Fluorescein; Uranin; Uranina; Флуоресцин Натрий.

Disodium fluorescein.

$C_{20}H_{10}Na_2O_5$=376.3

CAS — 518-47-8.

ATC — S01JA01.

ATC Vet — QS01JA01.

UNII — 93X55PE38X.

NOTE. FLN is a code approved by the BP 2014 for use on single unit doses of eye drops containing fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information. LIDFLN is a similar code approved for eye drops containing lidocaine hydrochloride and fluorescein sodium, and PROXFLN a code for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Fluorescein Sodium). An orange-red, fine hygroscopic powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane and in hexane. A 2% solution in water has a pH of 7.0 to 9.0. Store in airtight containers. Protect from light.

USP 36: (Fluorescein Sodium). An orange-red, hygroscopic, odourless powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Uses and Administration

Fluorescein sodium stains damaged cornea and disrupted ocular fluids and is applied to the eye for the detection of corneal lesions and foreign bodies, as an aid to the fitting of hard contact lenses, and in various other diagnostic ophthalmic procedures. It is applied as a 1 or 2% solution as eye drops or as sterile papers impregnated with fluorescein sodium. It may also be given with a local anaesthetic, typically as a 0.25% solution with lidocaine hydrochloride, oxybuprocaine hydrochloride, or proxymetacaine hydrochloride.

Fluorescein sodium may be given by rapid intravenous injection, usually as a solution equivalent to fluorescein 10 or 25%, for retinal angiography. The usual dose is the equivalent of 500 mg of fluorescein. A dose of 7.5 mg/kg has been suggested for children. The oral route has also been tried for angiography. Other uses of intravenous fluorescein sodium have included the differentiation of healthy from diseased or damaged tissue and visualisation of the biliary tract.

Fluorescein dilaurate has been given orally for the assessment of exocrine pancreatic function (see below). Pancreatic enzymes hydrolyse the ester and the amount of free fluorescein excreted in the urine can therefore be taken as a measure of pancreatic activity. A dose of 348.5 mg of fluorescein dilaurate, equivalent to 0.5 mmol of fluorescein, is given with a standard meal, and urine collected for the next 10 hours. The manufacturers give instructions concerning the type and amount of liquid and food which may be taken during this period. A control dose of 188.14 mg of fluorescein sodium, also equivalent to 0.5 mmol of fluorescein, is given on the next day under the same conditions.

Pancreatic function test. Studies of the fluorescein dilaurate test have considered it to be a useful noninvasive screening test for the exclusion of pancreatic exocrine failure in outpatients (see under Pancreatitis, p. 2580.2), particularly those presenting with steatorrhoea[1-3] or chronic diarrhoea.[4] However, low specificity (a relatively high rate of false-positive responses) has been reported with the fluorescein dilaurate test in some patient populations,[2,5] and the need for careful patient instruction in performance of the test has been emphasised.[3] In order to avoid the prolonged collection of urine necessary in the standard test, serum concentrations of fluorescein may be measured several hours after taking the test substance.[6]

The test has been used successfully in children,[7] particularly when the doses of fluorescein dilaurate and fluorescein sodium are reduced and fluid intake modified,[8] although the manufacturers recommend that the commercially available test is not used for this age group. In children, a simplified, single-day test using dual markers, fluorescein dilaurate and mannitol, has been investigated with encouraging results.[9] The fluorescein dilaurate test was found to be more sensitive than the faecal elastase 1 (FE-1) test for the diagnosis of mild-to-moderate exocrine pancreatic insufficiency in a study involving 40 patients.[10] However, a later study[11] involving 45 patients found that the pancreolauryl test was not as accurate at predicting the response to pancreatic enzyme supplements as the FE-1 test.

1. Barry RE, *et al*. Fluorescein dilaurate—tubeless test for pancreatic exocrine failure. *Lancet* 1982; **ii:** 742–4.
2. Boyd EJS, *et al*. Prospective comparison of the fluorescein-dilaurate test with the secretin-cholecystokinin test for pancreatic exocrine function. *J Clin Pathol* 1982; **35:** 1240–3.
3. Gould SR, *et al*. Evaluation of a tubeless pancreatic function test in patients with steatorrhoea in a district general hospital. *J R Soc Med* 1988; **81:** 270–3.
4. Murray IA, *et al*. Retrospective audit of the value of the pancreolauryl test in a district general hospital. *Postgrad Med J* 2003; **79:** 471–3.
5. Braganza JM. Fluorescein dilaurate test. *Lancet* 1982; **ii:** 927–8.
6. Dimagno EP. A perspective on the use of tubeless pancreatic function tests in diagnosis. *Gut* 1998; **43:** 2–3.
7. Cumming JGR, *et al*. Diagnosis of exocrine pancreatic insufficiency in cystic fibrosis by use of fluorescein dilaurate test. *Arch Dis Child* 1986; **61:** 573–5.
8. Dalzell AM, Heaf DP. Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis. *Arch Dis Child* 1990; **65:** 788–9.
9. Green MR, *et al*. Dual marker one day pancreolauryl test. *Arch Dis Child* 1993; **68:** 649–52.
10. Leodolter A, *et al*. Comparison of two tubeless function tests in the assessment of mild-to-moderate exocrine pancreatic insufficiency. *Eur J Gastroenterol Hepatol* 2000; **12:** 1335–8.
11. Elphick DA, Kapur K. Comparing the urinary pancreolauryl ratio and faecal elastase-1 as indicators of pancreatic insufficiency in clinical practice. *Pancreatology* 2005; **5:** 196–200.

Pediculosis. Infestation of the eyelashes or eyebrows with pubic lice (p. 2147.3) has been successfully treated with a single application of a 20% solution of fluorescein.[1]

1. Mathew M, *et al*. A new treatment of pthiriasis palpebrarum. *Ann Ophthalmol* 1982; **14:** 439–41.

Retinal angiography. Fluorescein is usually given intravenously for retinal angiography, but a study in 20 healthy subjects concluded that an oral dose of fluorescein sodium 25 mg/kg could produce good quality retinal angiograms in the majority of subjects.[1] This study used specially prepared 500-mg capsules of fluorescein sodium; the authors commented that previous oral studies had used the liquid preparation intended for intravenous use. Only mild reactions, possibly due to hypersensitivity, appear to have been reported with oral fluorescein.

1. Watson AP, Rosen ES. Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules. *Br J Ophthalmol* 1990; **74:** 458–61.

Adverse Effects and Precautions

The intravenous injection of fluorescein sodium may produce nausea and vomiting. Extravasation is painful. Hypersensitivity reactions range from urticaria to occasional instances of severe anaphylaxis. Cardiac arrest and fatalities have occurred rarely. Concern that impurities or a defect in manufacturing processes might be responsible for the serious reactions led to a review of the BP specification in the early 1980s and a reduction in the permitted level of impurities. Facilities for resuscitation should be available whenever fluorescein sodium is used intravenously.

Adverse effects after ocular instillation are rare. Allergic-type reactions have been reported and may include allergic conjunctivitis, periorbital oedema, and rashes and urticaria

or angioedema; anaphylaxis has also been reported. Intraocular fluorescein can produce transient blurring of vision, and patients should be warned not to drive or operate machinery until vision is clear.

Transient yellow discoloration of the skin and urine may occur with fluorescein sodium treatment. Contact with fluorescein sodium can stain skin and clothing. Soft contact lenses should not be worn while fluorescein sodium is being used because of the risk of staining.

Oral fluorescein dilaurate should not be given to patients with acute necrotising pancreatitis. Sulfasalazine may interfere with estimations of fluorescein in the fluorescein dilaurate test.

Two large studies have examined the incidence of adverse reactions after intravenous fluorescein angiography. An international survey[1] collected information concerning 594 687 angiographic procedures; the incidence of serious reactions was 1 in 18 020, and that of fatal reactions, 1 in 49 557. Reactions included anaphylactic shock, cardiac arrest, myocardial infarction, and shock with hypotension or respiratory distress. A US survey of 221 781 fluorescein angiograms[2] reported frequency rates of 1 in 63 for a moderate reaction (urticaria, syncope, thrombophlebitis, pyrexia, tissue necrosis, or nerve palsy) and 1 in 1900 for severe reactions (respiratory or cardiac events or tonic-clonic seizures); there was one death.

Individual reports of adverse reactions to intravenous fluorescein sodium include pancreatitis,[3] painful crises in patients with sickle-cell disease,[4] psoriasiform drug eruption,[5] and photoallergy[6] and phototoxicity.[7]

1. Zografos L. Enquête internationale sur l'incidence des accidents graves ou fatals pouvant survenir lors d'une angiographie fluoresceinique. *J Fr Ophtalmol* 1983; **6:** 495–506.
2. Yannuzzi LA, *et al.* Fluorescein angiography complication survey. *Ophthalmology* 1986; **93:** 611–17.
3. Morgan LH, Martin JM. Acute pancreatitis after fluorescein. *BMJ* 1983; **287:** 1596.
4. Acheson R, Serjeant G. Painful crises in sickle cell disease after fluorescein angiography. *Lancet* 1985; i: 1222.
5. Mayama M, *et al.* Psoriasiform drug eruption induced by fluorescein sodium used for fluorescein angiography. *Br J Dermatol* 1999; **140:** 982–4.
6. Hochsattel R, *et al.* Photoallergic reaction to fluorescein. *Contact Dermatitis* 1990; **22:** 42–4.
7. Kearns GL, *et al.* Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985; **107:** 796–8.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of fluorescein by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluorescein as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fluorescite; Grant; ***Austral.***: Disclo-Plaque†; Fluorescite; Fluorets†; Retinofluor; ***Canad.***: Ak-Fluor; Bio Glo; Diofluor; Fluorescite; Fluorets; ***China***: Fluorescite (荧设得); ***Cz.***: Fluorescite; ***Fin.***: Fluorescite; ***Fr.***: Fluocyne; ***Gr.***: AK-Fluor; Fluocyne; ***Hong Kong***: Fluorescite; Fluorets; ***India***: Fluore Stain Strips; Fluresin; ***Irl.***: Anatera; Fluorets; ***Israel***: Fluorescite; ***Ital.***: Fluoralfa; ***Malaysia***: Fluorescite; Fluorets; ***Mex.***: Optifluor†; ***Neth.***: Fluorescite; ***Norw.***: Anatera; ***NZ***: Fluorescite; Fluorets; ***Pol.***: Fluorescite; ***Port.***: Fluorescite; ***Rus.***: Fluorescite (Флюоресцит); ***S.Afr.***: Fluorescite; Fluorets; ***Singapore***: Fluorescite; Fluorets; ***Swed.***: Fluorescite; ***Thai.***: Fluorescite; ***Turk.***: Fluorescite; ***UK***: Fluorets; ***USA***: Ak-Fluor; Bio Glob; Fluor-I-Strip; Fluorescite; Fluorets; Ful-Glo; Funduscein; Ophthifluor.

Multi-ingredient Preparations. ***Austral.***: Fluress†; ***Austria***: Flurekain†; ***Canad.***: Fluoracaine†; Fluress; ***Fin.***: Oftan Flurekain; ***Ger.***: Thilorbin; ***Port.***: Fluotest; ***Spain***: Fluotest; ***Swed.***: Fluress; ***USA***: Fluoracaine; Fluorocaine; Fluorox; Flurate†; Fluress; Flurox; Healon Yellow†.

Pharmacopoeial Preparations

BP 2014: Fluorescein Eye Drops; Fluorescein Injection;

USP 36: Fluorescein Injection; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Fluorescein Sodium Ophthalmic Strips.

Formic Acid

Ácido amínico; Ácido formílico; Ácido metánico; Acidum Formicum; Ameisensäure; Aminic Acid; E236; E237 (formiato sódico); E237 (sodium formate); E238 (calcium formate); E238 (formiato cálcico); Fórmico, ácido; Kwas mrówkowy.

CH_2O_2=46.02

CAS — 64-18-6.

ATC Vet — QP53AG01.

UNII — 0YIW783RG1.

Pharmacopoeias. In *Pol.*

Profile

Formic acid resembles acetic acid in its properties (see p. 2427.1) but is more irritating and pungent. The acid and its sodium and calcium salts are used as preservatives in food. Solutions containing about 60% formic acid have been marketed for the removal of lime scale from kettles. Formic acid has also been used for the removal of tattoos. It is an ingredient of some external preparations promoted for the relief of musculoskeletal and joint disorders, and has been used with benzyl alcohol to aid the removal of nits.

In a report of 3 patients who swallowed descaling agents containing 40 or 55% formic acid, the major complications included local corrosive effects, metabolic acidosis, derangement of blood-clotting mechanisms, and acute onset of respiratory and renal failure.[1] All 3 patients died between 5 and 14 days after admission to hospital. A further report of 53 cases of formic acid ingestion included 15 fatalities.[2]

1. Naik RB, *et al.* Ingestion of formic acid-containing agents — report of three fatal cases. *Postgrad Med J* 1980; **56:** 451–6.
2. Rajan N, *et al.* Formic acid poisoning with suicidal intent: a report of 53 cases. *Postgrad Med J* 1985; **61:** 35–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Acimont; Berggeist; ***Ital.***: Rubjovit; ***Mex.***: Aminoyodarsencal; ***Switz.***: Fortalis; ***Ukr.***: Medichronal (Медихронал).

Homoeopathic Preparations. ***Austria***: Apozema Allium Cepa compositum; ***Canad.***: Adrisin†; Cutisitum†; ***Fr.***: Rhus Toxicodendron Compose; ***Ger.***: Acirufan; Allergie-Injektopas; Allergo-Loges; Desarell; Formasan; Formidium; Formisoton; Heweformica; metabiarex; Pascallerg; Presselin All; Regasinum antallergicum; Rufebran rheumo†; ***Neth.***: Geovita; Habifac.

Fosfocreatinine *(rINN)*

Fosfocreatinina; Fosfocréatinine; Fosfocreatininum; Phosphocreatinine; Фосфокреатинин.

(1-Methyl-4-oxo-2-imidazolidinylidene)phosphoramidic acid.

$C_4H_8N_3O_4P$=193.1

CAS — 5786-71-0 (fosfocreatinine); 19604-05-8 (fosfocreatinine sodium).

UNII — RG2371KXDE.

Profile

Fosfocreatinine or fosfocreatinine sodium has been used in muscle disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Sustenium.

Fosfructose Trisodium *(USAN, rINNM)*

CPC-111; Fosfructosa trisódica; Fosfructose Trisodique; Fosfructosum Trinatricum; Sodium Fructose-1,6-diphosphate; Тринатрий Фосфруктоза.

D-Fructose 1,6-bis(dihydrogen phosphate) trisodium octahydrate.

$C_6H_{11}Na_3O_{12}P_2.8H_2O$=550.2

CAS — 488-69-7 (fosfructose); 6055-82-9 (fosfructose calcium); 38099-82-0 (fosfructose trisodium); 81028-91-3 (fosfructose trisodium octahydrate).

ATC — C01E807.

UNII — 463VBZ2YVD.

Profile

Fosfructose is a metabolic intermediate. It is used as the trisodium salt as a source of phosphate in deficiency states and in total parenteral nutrition, and has also been used to protect against ischaemic tissue damage. Fosfructose calcium has also been promoted for a variety of disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bo Wei He (博维赫); Esafosfina (爱赛福); Fodi (佛迪); Luo Pu Xin (洛普欣); Ruianji (瑞安吉); Wei Sai Xin (威赛欣); ***Hong Kong***: Esafosfina; ***Ital.***: Esafosfina; FDP; ***Thai.***: Esafosfina†.

Multi-ingredient Preparations. ***Hong Kong***: Esafosfina Glutammica.

Frankincense

Encens; Franchincenso; Kadidlo; Kamanyang; Olibaanihartsi; Oliban; Olibano; Olibanum; Røgelse; Ru Xiang; Tamjan; Tāmāie; Tus; Uunsi; Uvumba; Virak; Weihrauch; Ладан; Тамян.

CAS — 8016-36-2 (frankincense oil).

ATC Herb — HA03AW5005 (Boswellia sacra: resin); HD03WA5001 (Boswellia sacra: resin); HM01AW5004 (Boswellia sacra: resin).

UNII — R9XLF1R1WM.

NOTE. Distinguish from Indian Frankincense, below.

Profile

Frankincense is the aromatic gum resin of *Boswellia sacra* (*B. carteri*) (Burseraceae) or other species of *Boswellia*. It is used in incense and as a fumigant.

Frankincense (ru xiang) is also used in Chinese medicine. Frankincense oil is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Painease; Restorativ Glucosamine Muscle and Joint; ***Fr.***: Capsaine; Tigre de Chine; ***Philipp.***: BSI Medicated Plaster.

Homoeopathic Preparations. ***Canad.***: Voxpax†; ***Fr.***: Voxpax.

Indian Frankincense

Encens indien; Indian Olibanum; Olibanum indicum; Salai Guggal; Weihrauch, Indischer.

UNII — 4PW41QCO2M.

NOTE. Indian frankincense is obtained from *Boswellia serrata* and should be distinguished from Frankincense (above) obtained from other species of *Boswellia*.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Indian Frankincense). Air-dried gum-resin exudate, obtained by incision in the stem or branches of *Boswellia serrata*. It contains a minimum of 1.0% of 11-keto-β-boswellic acid ($C_{30}H_{46}O_4$ = 470.7) and a minimum of 1.0% of acetyl-11-keto-β-boswellic acid ($C_{32}H_{48}O_5$ = 512.7) calculated with reference to the dried drug.

USP 36: (Boswellia Serrata). The oleogum resin obtained by incision or produced by spontaneous exudation from the stem and branches of *Boswellia serrata* (Burseraceae). It contains not less than 1% of the keto-derivatives of β-boswellic acid calculated on the dried basis, as the sum of 11-keto-β-boswellic acid and 3-acetyl-11-keto-β-boswellic acid. Store at a temperature between 8 degrees and 15 degrees. Protect from light and moisture.

Profile

Indian frankincense is the gum resin of *Boswellia serrata* (*B. glabra*) (Burseraceae). It has anti-inflammatory activity and is included in herbal preparations for musculoskeletal and joint disorders. It is also under investigation for use in inflammatory bowel disease and asthma. Boswellic acids extracted from the gum resin of *B. serrata* have also been tried for their anti-inflammatory actions in similar disorders.

References

1. Anonymous. *Boswellia serrata*. *Altern Med Rev* 2008; **13:** 165–7.
2. Ernst E. Frankincense: systematic review. *BMJ* 2008; **337:** a2813. Available at: http://www.bmj.com/cgi/reprint/337/dec17_2/a2813 (accessed 07/04/10)

Anti-inflammatory use. References to the use of Indian frankincense for its anti-inflammatory action.

1. Gupta I, *et al.* Effects of Boswellia serrata gum resin in patients with ulcerative colitis. *Eur J Med Res* 1997; **2:** 37–43.
2. Gupta I, *et al.* Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res* 1998; **3:** 511–14.
3. Gupta I, *etal.* Effects of gum resin of Boswellia serrata in patients with chronic colitis. *Planta Med* 2001; **67:** 391–5.
4. Ammon HPT. Boswellic acids in chronic inflammatory diseases. *Planta Med* 2006; **72:** 1100–16.
5. Abdel-Tawab M, *et al. Boswellia serrata*: an overall assessment of *in vitro*, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet* 2011; **50:** 349–69.

OSTEOARTHRITIS. Indian frankincense has been used in the treatment of osteoarthritis of the knee and an evidence-based report[1] by the Arthritis Research Campaign in the UK considered that it was safe and possibly effective in reducing pain and problems associated with walking and other daily activities, and that this effect might last for a period of time after stopping treatment.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and

fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Vedica; ***USA***: 5-Loxin.

Multi-ingredient Preparations. ***Arg.***: Glucobefol†; ***Austral.***: Boswellia Complex; Boswellia Compound; Full Motion; Joint Ease; Joint Mobility†; ***Chile***: Ruboril AI; ***Fr.***: Arthro; Prostaform; ***India***: Arthrill Forte; Artrex; Cartigen; Jointil Orthopedic oil; Jointil; Mobijoint; Niltan; Nucart-OA; ***Indon.***: Ositin; ***Ital.***: Actires; Fitogenase; Reumafort; Valedol; ***Malaysia***: Rumalaya; ***Philipp.***: Arthrid; ***Singapore***: Artrex; Muvease; ***Turk.***: Ultimate; ***UK***: NatraFlex; PainEaze; ***Ukr.***: Artritosamin (Артритозамин).

Homoeopathic Preparations. ***Ger.***: Olibanum RA.

Fructo-oligosaccharides

Oligofructans; Oligofructose; Polyfructoses.

Profile

Fructo-oligosaccharides are fructans, sugar polymers containing a chain of fructose units, with or without a glucose unit at the start. They may be classified in several ways, depending on the degree of polymerisation and the type of glycosidic linkage present. Inulin (p. 2534.3) is a long-chain linear fructan with mainly β2→1 linkages and is the main fructan found in plants. Fructo-oligosaccharides usually contain 3 to 10 fructose units and are obtained by partial hydrolysis of inulin or by synthesis from sucrose; the name oligofructose is sometimes used specifically for those produced from inulin.

Fructo-oligosaccharides are a form of dietary fibre and are also known to have a prebiotic effect, stimulating the growth of certain colonic bacteria. They are used as dietary supplements and have been given with probiotic organisms (see p. 2596.3) in the management of gastrointestinal disorders; they have also been used to improve the absorption of dietary minerals. Fructo-oligosaccharides are also used as low-calorie sweetening agents.

Reviews.

1. Kelly G. Inulin-type prebiotics—a review: part 1. *Altern Med Rev* 2008; **13:** 315–29.
2. Kelly G. Inulin-type prebiotics—a review: part 2. *Altern Med Rev* 2009; **14:** 36–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Singapore***: Protexin.

Multi-ingredient Preparations. ***Braz.***: Control†; ***Fr.***: Immunostim; Maxi-Flore; Transifine; ***Hong Kong***: Protexin Balance+; Protexin Balance; Protexin Restore; Protexin Vitality; ***India***: Bioform; Biota-P; Colonise; Darolac Plus; Eubioz; Favolife; Flora-SB; Florablend; Goodlac; Gutrite; Hiact-P; IMM-4; Immunorm; Laff; New Probiza; Og-Lac; PP Bio; PP Tage; ***Indon.***: Apecur; Biofos†; Calix†; Calvitran; Curfos; Curvit CL; Dhavit; Mulsanol; Obical; Protexin; Protexin; Seltifort Gold; Synbio; Vistrum; Vitacur; Vitagrow; Vitamam 1; Vitamam 2; Vitamam 3; Xanda; ***Israel***: Biolax Protect; Biolax†; Co-Biotic Kid; ***Ital.***: Estilax; Fervidus; Lactomaior; Ramnoflor Plus; Relaxcol; ***Malaysia***: Obical; ***Mex.***: Pedialyte FOS; ***Philipp.***: Exofat; ***Singapore***: Obical; Pro-4; Pro-Gut; ***UK***: Beneflora; Culture Care.

Fucoidan

Fucoidin; Fucoidine; Nemacystus Mucilage; Фукоидан.
CAS — 9072-19-9.

Profile

Fucoidan is a sulfated polysaccharide, based mainly on L-fucose, that is extracted from brown seaweed. It is reported to have anticoagulant, antithrombotic, and antineoplastic activity and has been promoted for a wide-range of disorders and as a food supplement.

References.

1. Mourão PA. Use of sulfated fucans as anticoagulant and antithrombotic agents: future perspectives. *Curr Pharm Des* 2004; **10:** 967–81.

Nomenclature. Fucans are a class of sulfated polysaccharides first isolated from marine algae. Their nomenclature can be somewhat varied and confusing. The original polysaccharide isolated from algae was termed fucoidin and this was later changed to fucoidan. These polysaccharides have also been found in marine invertebrates and improved analytical and separation techniques have allowed different types of sulfated polysaccharides to be identified. It has been suggested that the term sulfated fucan should be defined as a polysaccharide based mainly on sulfated L-fucoses, with less than 10% other monosaccharides.[1] This term has been applied to the sulfated fucans of marine invertebrates, whereas the term fucoidan has been used for fucans extracted from algae. Some define fucoidan as a sulfated polysaccharide of L-fucose and D-galactose extracted from brown seaweed although others have used this term for sulfated polysaccharide complexes having a content of L-fucose of only 60% or less. Other terms that have been coined for these compounds include fucansulfate and fucan sulfate.

1. Berteau O, Mulloy B. Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology* 2003; **13:** 29R–40R.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Fucobac; Fucosa; Fucotrap; Fudan; Gafudan; Mozuku.

Fumitory

Conejillos; Erdrauchkraut; Fumaria; Fumariae Herba; Fumeterre; Zemědýmová nať; Ziele dymnicy; Дымянка Лекарственная; Дымовая Трава.
*ATC Herb — HA05AW5009 (*Fumaria officinalis*: herb).*
*UNII — VH659J61ZL (*Fumaria officinalis *flowering top).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fumitory). The whole or fragmented, dried aerial parts of *Fumaria officinalis* harvested in full bloom. It contains a minimum of 0.40% of total alkaloids, expressed as protopine ($C_{20}H_{19}NO_5 = 353.4$). Protect from light.

Profile

Fumitory comprises the dried or fresh flowering plant *Fumaria officinalis* (Papaveraceae) and is used in herbal medicine. It is an ingredient of preparations used mainly for gastrointestinal and biliary-tract disorders.

Homoeopathy

Fumitory has been used in homoeopathic medicines under the following names: Fumaria; Fumaria officinalis.

Irritable bowel syndrome. Neither fumitory nor Javanese turmeric (p. 2636.2) was effective in a study[1] in patients with irritable bowel syndrome.

1. Brinkhaus B, *et al*. Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial. *Scand J Gastroenterol* 2005; **40:** 936–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bilobene; Oddibil; ***Braz.***: Oddibil; ***Fr.***: Oddibil; ***Ger.***: Bilobene†; ***Hung.***: Bilobene; ***Pol.***: Amphochol†.

Multi-ingredient Preparations. ***Austria***: Hepabene†; ***Fr.***: Actibil†; Azema†; Bolcitol†; Boribel Tisane No 7†; Depuratif Parnel†; Depuratum; Schoum; Tisane de Sante†; ***Hung.***: Fumago; Hepabene; Livfit; ***Ital.***: Soluzione Schoum; ***Pol.***: Boldovera; ***Rus.***: Hepabene (Гепабене); ***Spain***: Solucion Schoum; ***UK***: Echinacea; Napiers Elixir of Echinacea Complex; Potters Elixir of Echinacea Plus; Skin Cleansing; ***Ukr.***: Hepabene (Гепабене).

Homoeopathic Preparations. ***Austria***: Lymphomyosot; ***Canad.***: Eczema; ***Cz.***: Lymphomyosot; ***Fr.***: Saponaria Compose; ***Ger.***: Haut-Gastreu R60; Heweberberol; Lymphomyosot N; Lymphomyosot; ***Hung.***: Lymphomyosot; ***Rus.***: Psorilom (Псорилом); ***S. Afr.***: Lymphomyosot; ***Ukr.***: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Gabexate Mesilate *(rINNM)*

Gabexate, Mésilate de; Gabexate Mesylate; Gabexati Mesilas; Gabexato, mesilato de; Mesilato de gabexato; Габексата Мезилат.
Ethyl 4-(6-guanidinohexanoyloxy)benzoate methanesulphonate.
$C_{16}H_{23}N_3O_4,CH_4SO_3$=417.5
CAS — 39492-01-8 (gabexate); 56974-61-9 (gabexate mesilate).
UNII — E3Q07L0649.

Pharmacopoeias. In *Jpn.*

Profile

Gabexate mesilate is a proteolytic enzyme inhibitor that has been used for the treatment of pancreatitis (p. 2580.2) in an initial dose of 100 to 300 mg daily given by intravenous infusion. The dose may be reduced, or a further 100 to 300 mg given on the same day, according to response. It has also been used for disseminated intravascular coagulation (p. 1126.1) in a dose of 20 to 39 mg/kg given as a continuous intravenous infusion over 24 hours. Hypersensitivity reactions including anaphylaxis have occurred.

References.

1. Messori A, *et al*. Effectiveness of gabexate mesilate in acute pancreatitis: a metaanalysis. *Dig Dis Sci* 1995; **40:** 734–8.
2. Cavallini G, *et al*. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. *N Engl J Med* 1996; **335:** 919–23.
3. Matsukawa Y, *et al*. Anaphylaxis induced by gabexate mesylate. *BMJ* 1998; **317:** 1563.
4. Ranucci M, *et al*. Gabexate mesilate and antithrombin III for intraoperative anticoagulation in heparin pretreated patients. *Perfusion* 1999; **14:** 357–62.
5. Matsukawa Y, *et al*. Fatal cases of gabexate mesilate-induced anaphylaxis. *Int J Clin Pharmacol Res* 2002; **22:** 81–3.
6. Masci E, *et al*. Comparison of two dosing regimens of gabexate in the prophylaxis of post-ERCP pancreatitis. *Am J Gastroenterol* 2003; **98:** 2182–6.
7. Andriulli A, *et al*. Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate. *Clin Gastroenterol Hepatol* 2004; **2:** 713–18.
8. Hsu JT, *et al*. Efficacy of gabexate mesilate on disseminated intravascular coagulation as a complication of infection developing after abdominal surgery. *J Formos Med Assoc* 2004; **103:** 678–84.
9. Rudin D, *et al*. Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials. *J Gastroenterol Hepatol* 2007; **22:** 977–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Foy; Gabesato; ***Jpn***: Foy.

Galactan Sulfate

Galactan Polysulfate; Galactane Sulphate.

Profile

Galactans are polysaccharides composed of repeating galactose units and can consist of branched or unbranched chains in any linkages. Sulfated galactans are found in marine algae and other marine organisms and examples such as carrageenan (p. 2176.3) and agar (p. 2167.2) are used as gelling agents. Sulfated galactans have also been used in gastrointestinal disorders and some are under investigation for their antithrombotic properties.

Reviews.

1. Pomin VH, Mourão PAS. Structure, biology, evolution, and medical importance of sulfated fucans and galactans. *Glycobiology* 2008; **18:** 1016–27.
2. Pomin VH. Structural and functional insights into sulfated galactans: a systematic review. *Glycoconj J* 2010; **27:** 1–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Acidrine; ***Chile***: Sinacid†; ***Fr.***: Acidrine; ***Indon.***: Acidrine; ***Ital.***: Acidrine; ***Turk.***: Acidrine.

Galactomannan

Galactomanà; Galactomannaan; D-Galacto-D-mannan; Galactomannane; Галактоманнаны.
CAS — 11078-30-1.

Profile

Galactomannans are natural gums consisting of hydrocolloidal polysaccharides formed from polymers of galactose and mannose. They occur in the endosperms of various seeds, particularly legumes, and are a source of dietary fibre. They have thickening, gelling, and hydrating properties and are used as pharmaceutical excipients, food additives, and in cosmetics; they also have many industrial applications. Examples include guar gum (p. 475.1) and ceratonia (p. 2178.1); other plant sources include fenugreek (p. 2504.1) and tara (*Caesalpinia spinosa*, Fabaceae).

Galactomannans are also found in the cell walls of some fungi, including *Aspergillus*, and tests to detect galactomannans in the blood have been used in the diagnosis of aspergillosis (p. 563.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Glucoman; Sirmiogel.

Gall

Agallas de roble; Aleppo Galls; Blue Galls; Duběnka; Galla; Galläpfel; Galls; Noix de Galle; Nutgall; Чернильный Орешек.

Pharmacopoeias. In *Chin.*

Profile

Gall is the excrescences on the twigs of *Quercus infectoria* (Fagaceae), resulting from the stimulus given to the tissues

of the young twigs by the development of the larvae of the gall-wasp, *Adleria gallae-tinctoriae* (*Cynips gallae-tinctoriae*) (Cynipidae). It contains about 50 to 70% of gallotannic acid.

Gall is an astringent and has been used in ointments and suppositories for the treatment of haemorrhoids. It is a source of tannic acid (p. 2625.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Good Time; ***Thai.***: Relief Mouth Ulcer; ***Ukr.***: Entoban (Энтобан).

Homoeopathic Preparations. ***Ger.***: Juv 110.

Galsulfase *(BAN, USAN, rINN)*

BM-102; Galsulfasa; Galsulfasum; recombinant human arylsulfatase B; rhASB; Гальсульфас.

N-Acetylgalactosamine 4-sulfatase.

CAS — 552858-79-4.

ATC — A16AB08.

ATC Vet — QA16AB08.

UNII — 59UA429E5G.

NOTE. The name Aryplase has been used as a trade mark for galsulfase.

Uses and Administration

Galsulfase is recombinant human *N*-acetylgalactosamine 4-sulfatase used as enzyme replacement therapy in the treatment of mucopolysaccharidosis VI (see below). Galsulfase is given by intravenous infusion in a dose of 1 mg/kg once a week. Galsulfase should be reconstituted to a final volume of 250 mL in sodium chloride 0.9% and given using an infusion pump. The initial infusion rate should be 6 mL/hour for the first hour, which may then be increased to 80 mL/hour if well tolerated. The total infusion time should be at least 4 hours to minimise the risk of infusion reactions, but may be extended to up to 20 hours, or interrupted, if necessary, in the event of infusion reactions. Patients weighing 20 kg and under may be susceptible to fluid overload and a smaller infusion volume of 100 mL should be considered, in which case, the infusion rate should be decreased accordingly so that the total infusion time is not less than 4 hours.

Administration in children. Licensed product information for galsulfase in the treatment of mucopolysaccharidosis VI notes that children under 5 years of age were not included in phase III studies but nevertheless considers that patients in this age group with severe disease should be treated with the doses outlined above.

Mucopolysaccharidosis VI. Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) is a rare progressive disorder characterised by inherited deficiency of the enzyme *N*-acetylgalactosamine 4-sulfatase, which is necessary to catalyse the hydrolysis of the sulfate moiety of the glycosaminoglycan, dermatan sulfate. This results in accumulation of dermatan sulfate in the lysosomes producing widespread irreversible cellular and tissue damage, and organ dysfunction. There is a rapidly advancing form of the disease that presents in the first year of life characterised by short stature, skeletal and joint deformities, dysmorphic facial features, upper airway obstruction requiring tracheostomy, and recurrent ear infections. There is also a more slowly advancing form that progresses over many decades. Both forms result in significant morbidity and functional problems with a reduced lifespan.[1]

Treatment is supportive and symptomatic involving many body systems; physical and occupational therapy is also necessary.[1] Haematopoietic stem-cell transplantation to supply the deficient enzyme is of benefit to some patients, although it is associated with significant morbidity and mortality.[1] Enzyme replacement therapy with galsulfase has been reported to confer benefit with an acceptable safety profile.[1,2]

1. Giugliani R, *et al.* Management guidelines for mucopolysaccharidosis VI. *Pediatrics* 2007; **120:** 405–18.
2. Harmatz P, *et al.* Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human *N*-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J Pediatr* 2006; **148:** 533–9.

Adverse Effects, Treatment, and Precautions

Infusion reactions have been reported in over half of patients treated with galsulfase and common symptoms have included fever, chills, rigor, rash, and urticaria. Other reported symptoms have included abdominal pain, nausea, vomiting, headache, malaise, angioedema, joint pain, hypotension, dyspnoea, bronchospasm, retrosternal pain, and respiratory distress. Antihistamines and/or antipyretics may relieve symptoms of infusion reactions. A reduction in the rate of infusion to half the rate at which the reaction occurred should also be considered for mild or moderate reactions; for severe reactions, the infusion should be stopped until symptoms have subsided, and then restarted at one-half to one-quarter the rate at which the reaction occurred. Pre-treatment with antihistamines and/or antipyretics about 30 to 60 minutes before infusion is recommended to prevent reactions.

IgG antibodies to galsulfase develop in the majority of patients within the first 4 to 8 weeks of treatment, although the effect on long-term efficacy or safety is not clear.

References.

1. Kim KH, *et al.* Successful management of difficult infusion-associated reactions in a young patient with mucopolysaccharidosis type VI receiving recombinant human arylsulfatase B (galsulfase [Naglazyme]). Abstract: *Pediatrics* 2008; **121:** 609. Full version: http://pediatrics.aappublications.org/cgi/content/full/121/3/e714 (accessed 01/05/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Naglazyme; ***Cz.***: Naglazyme; ***Denm.***: Naglazyme; ***Fr.***: Naglazyme; ***Ger.***: Naglazyme; ***Gr.***: Naglazyme; ***Irl.***: Naglazyme; ***Israel***: Naglazyme; ***Ital.***: Naglazyme; ***Mex.***: Naglazyme; ***Neth.***: Naglazyme; ***Pol.***: Naglazyme; ***Port.***: Naglazyme; ***Rus.***: Naglazym (Наглазим); ***Spain***: Naglazyme; ***Swed.***: Naglazyme; ***Switz.***: Naglazyme; ***USA***: Naglazyme.

Gamma-aminobutyric Acid

Ácido aminobutírico; Ácido gamma-aminobutírico; Ácido piperídico; Acidum Aminobutyricum Gamma; Aminobutyric Acid; GABA; Gamma-aminosmörsyra; Gamma-aminovoihappo; Piperidic Acid; γ-Aminobutírico, ácido; Гамма-аминобутировая Кислота.

4-Aminobutyric acid.

$C_4H_9NO_2$=103.1

CAS — 56-12-2.

ATC — N03AG03.

ATC Vet — QN03AG03.

UNII — 2ACZ6IPC6I.

Profile

Gamma-aminobutyric acid is a principal inhibitory neurotransmitter in the CNS. It has been claimed to be of value in cerebral disorders and to have an antihypertensive effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Gammar; ***China***: An Luo (安罗); Chang Rui (常瑞); Ge Le Si Te (格勒斯特); Hui You (慧友); Kai Luo (凯络); Li Sheng Bei Fen (丽生贝芬); Lu Bi An (卢必安); Sheng Mai Fu (升迈福); Ti Ta Ding (替他宁); Tu Tu (图图); Tuo Tai (拓泰); Wei Ding (为丁); Xin Nuo Shu (欣诺舒); Yi An Fen (异安芬); Yu Hui Luo (亿辉洛); Zhu Zhong Xin (竹中欣); ***Hong Kong***: Gammalon; ***Rus.***: Aminalon (Аминалон); ***Thai.***: Bainto; Gammalon†; ***Ukr.***: Aminalon (Аминалон).

Multi-ingredient Preparations. ***Arg.***: Butineuron; Cadencial Plus; ***Braz.***: Complevit†; Gaballon; Gabax†; Organoneuro Cerebral; ***Chile***: Actebral; Cebrocal; Gamalate B6; Gamavit B6; ***Spain***: Gamalate B6; ***Ukr.***: Gamalate B6 (Гамалате B6); Olatropil (Олатропил).

Gamolenic Acid *(BAN, rINN)*

Acide Gamolénique; Ácido gamolénico; Ácido γ-linolénico; Acidum Gamolenicum; Gamolénico, ácido; GLA; γ-Linolenic Acid; Гамоленовая Кислота.

(*Z,Z,Z*)-Octadeca-6,9,12-trienoic acid.

$C_{18}H_{30}O_2$=278.4

CAS — 506-26-3.

ATC — D11AX02.

ATC Vet — QD11AX02.

UNII — 78YC2MAX4O.

Linoleic Acid

Kwas linołowy; Linoleico, ácido; Linolic Acid; Linolsäure; Линолевая Кислота.

(*Z,Z*)-Octadeca-9,12-dienoic acid.

$C_{18}H_{32}O_2$=280.5

CAS — 60-33-3.

UNII — 9KJL21T0QJ.

Uses and Administration

Gamolenic and linoleic acid are essential fatty acids of the omega-6 series that act as prostaglandin precursors. Endogenous gamolenic acid is derived from linoleic acid, which is present in many plant oils and is an essential constituent of the diet. The most widely-used source of these acids is evening primrose oil (see p. 2502.2). Gamolenic and linoleic acids have been used in skin disorders and mastalgia, and have been investigated in other disorders including multiple sclerosis, rheumatoid arthritis, and the premenstrual syndrome.

Preparations containing essential fatty acids (formerly known collectively as vitamin F), including arachidonic acid, linoleic acid, linolenic acid (α-linolenic acid, p. 1460.2), oleic acid, and their derivatives, have been used similarly. Conjugated linoleic acid (CLA), a mixture of isomers in which *cis*-9,*trans*-11-octadecadienoic acid and *trans*-10,*cis*-12-octadecadienoic acid predominate, has also been used.

Products containing gamolenic-acid rich plant oils are promoted in many countries as dietary supplements, often in combination with fish oils or other sources of omega-3 fatty acids (see p. 1460.1).

A derivative of gamolenic acid, lithium gamolenate, has been investigated in pancreatic cancer.

Eczema. Atopic eczema (p. 1684.1) may be due to a defect in essential fatty acid metabolism[1,2] and some beneficial symptomatic effects have been reported with evening primrose oil.[1,3] Meta-analysis of 9 studies involving 311 patients[4] has reported improvement in disease symptoms, especially itching, but a subsequent study in 123 patients found no therapeutic effect of evening primrose oil, alone or with fish oil.[5] Although the design and interpretation of this study has been criticised by the manufacturers of evening primrose oil,[6] the authors consider such criticism invalid,[7] and point out that an earlier large study yielded similar results.[8] No difference was found between placebo and evening primrose oil in a further study[9] in children with eczema, and there was also no effect on asthma symptoms in those patients suffering from both disorders. Studies[10,11] of borage oil (another source of gamolenic acid) also found no overall efficacy in adults or children with atopic eczema, although one study noted a suggestion of benefit in a subgroup of patients.[10] In a study[12] of a group of formula-fed infants with a high maternal familial risk of developing atopic eczema, borage oil supplementation did not prevent the expression of atopy, although it showed a tendency to alleviate the severity of the condition later in infancy.

Benefit has been reported in infants with seborrhoeic dermatitis from local application of borage oil.[13]

1. Wright S. Essential fatty acids and the skin. *Br J Dermatol* 1991; **125:** 503–15.
2. Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. *Am J Clin Nutr* 2000; **71** (suppl): 367S–372S.
3. Rustin MHA. Dermatology. *Postgrad Med J* 1990; **66:** 894–905.
4. Morse PF, *et al.* Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema: relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989; **121:** 75–90.
5. Berth-Jones J, Graham-Brown RAC. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; **341:** 1557–60. Correction. *ibid.*; **342:** 564.
6. Shield MJ, *et al.* Essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; **342:** 377.
7. Berth-Jones J, *et al.* Essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; **342:** 377–8. Correction. *ibid.*; 752.
8. Bamford JTM, *et al.* Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol* 1985; **13:** 959–65.
9. Hederos C-A, Berg A. Epogam evening primrose oil treatment in atopic dermatitis and asthma. *Arch Dis Child* 1996; **75:** 494–7.
10. Henz BM, *et al.* Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol* 1999; **140:** 685–8.
11. Takwale A, *et al.* Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ* 2003; **327:** 1385–7.
12. van Gool CJ, *et al.* γ -Linolenic acid supplementation for prophylaxis of atopic dermatitis—a randomized controlled trial in infants at high familial risk. *Am J Clin Nutr* 2003; **77:** 943–51.
13. Tollesson A, Frithz A. Borage oil, an effective new treatment for infantile seborrhoeic dermatitis. *Br J Dermatol* 1993; **129:** 95.

Mastalgia. Gamolenic acid (usually given in the form of evening primrose oil) has fewer adverse effects than drugs such as danazol or bromocriptine and has been preferred for mastalgia (p. 2265.1), especially in patients with less severe symptoms or those who require prolonged or repeated treatment. However, there is no clear evidence of efficacy.

Multiple sclerosis. There is some evidence that modifying the intake of dietary fats and supplementing the diet with omega-6 polyunsaturated fatty acids, such as linoleic acid, could influence the clinical course of multiple sclerosis (p. 996.3) and many patients practise dietary modification, including taking evening primrose oil. One study[1] has shown a reduction in severity and duration of relapse in patients taking linoleic acid supplements (as sunflower oil), and another[2] has reported benefit in patients who limited their intake of dietary saturated fatty acids and supplemented their diet with polyunsaturated fatty acids. A systematic review[3] of the relationship between dietary interventions (including linoleic acid supplements) and

MS concluded that there was insufficient evidence to determine their benefits or risks.

1. Millar JHD, *et al*. Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *BMJ* 1973; **1:** 765–8.
2. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 1990; **336:** 37–9.
3. Farinotti M, *et al*. Dietary interventions for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Premenstrual syndrome. Progressive improvement in premenstrual syndrome (p. 2272.3) was reported over 5 cycles in an open pilot study in 19 patients receiving evening primrose oil.[1] However, subsequent results have not shown any benefit.[2-4] Evening primrose oil has been considered for cyclical mastalgia (see p. 2509.3).

1. Larsson B, *et al*. Evening primrose oil in the treatment of premenstrual syndrome: a pilot study. *Curr Ther Res* 1989; **46:** 58–63.
2. Khoo SK, *et al*. Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust* 1990; **153:** 189–92.
3. Collins A, *et al*. Essential fatty acids in the treatment of premenstrual syndrome. *Obstet Gynecol* 1993; **81:** 93–8.
4. Budeiri DJ, *et al*. Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials* 1996; **17:** 60–8.

Rheumatoid arthritis. Patients with rheumatoid arthritis (p. 13.2) taking NSAIDs have shown subjective improvement after 12 months of treatment with evening primrose oil, with or without fish oil, when compared with placebo.[1] A clinically important reduction in signs and symptoms of disease activity has also been seen in patients treated with gamolenic acid in the form of borage oil.[2] During treatment with evening primrose oil patients with rheumatoid arthritis have increased plasma concentrations of gamolenic, dihomo-gamma-linolenic, and arachidonic acids, and decreased plasma concentrations of oleic and eicosapentaenoic acids and apolipoprotein B.[3] The increase in plasma-arachidonic acid and decrease in eicosapentaenoic acid might be unfavourable in such patients, since arachidonic acid is the precursor of inflammatory prostaglandins and eicosapentaenoic acid may have an anti-inflammatory role. However, a systematic review[4] of these and other studies concluded that there does appear to be some potential benefit for the use of gamolenic acid in rheumatoid arthritis, although optimum dosage and duration of treatment is unknown.

1. Belch JJF, *et al*. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann Rheum Dis* 1988; **47:** 96–104.
2. Leventhal LJ, *et al*. Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 1993; **119:** 867–73.
3. Jäntti J, *et al*. Evening primrose oil in rheumatoid arthritis: changes in serum lipids and fatty acids. *Ann Rheum Dis* 1989; **48:** 124–7.
4. Little CV, Parsons T. Herbal therapy for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 23/05/06).

Adverse Effects and Precautions

Gamolenic and linoleic acids from evening primrose oil, and presumably other sources, can produce minor gastrointestinal disturbances and headache. They can precipitate symptoms of undiagnosed temporal lobe epilepsy, and should be used with caution in patients with a history of epilepsy or those taking epileptogenic drugs, in particular phenothiazines. Hypersensitivity reactions may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: CLA 500; Metabolic CLA; ***Ger.***: Sanyrene; ***Hong Kong***: Welsan Dual Shower Oil; ***India***: GLA; Linocid; ***Ital.***: Triene; Vitef; ***Pol.***: Dermovit F; Linola; Linomag; ***UK***: Super GLA.

Multi-ingredient Preparations. ***Arg.***: Atomo Ordenador; Dial-ND; Epasterol; KW; Macbirs; Omeganorm†; Proavenal Omegatopic; Quelodin F; Revi-Atlas; ***Austria***: Mamellin; Sulgan 99; ***Braz.***: Glavit†; Oleo de Primula; ***Canad.***: Bionagre plus E†; ***Chile***: Delgadol Slim; Effaclar H; Infor; Proaven; Revi-Atlas; Ureadin Pediatrics; ***Cz.***: Linola-Fett; Linola; ***Fr.***: Sun Vue; Trimada; ***Ger.***: Hydro Cordes; Linola-Fett; Linola; Lipo Cordes; Unguentacid†; ***Gr.***: Striafissan; ***Hong Kong***: Doctor's Choice Multivitamins and Minerals for Eyes; Eye Q; Welsan Lipocream; ***Hung.***: Linola; ***India***: Accept; Alphaneuron; Cobal Plus; Combinac; Diptase; Efaderm; GLA-M; GMab Plus; Nimulid Nugel; Onerve; ***Ital.***: Dermagan; Derman-Oil; Dermana Crema; Dermana Pasta; Efagel; Esterol; Medilar; Neuralfa; Osteolip; Pasta Dicofarm; Tiofort; Topialyse; Trofinerv Antiox; ***Malaysia***: Pharmaton†; ***Mex.***: Nutrem; ***NZ***: Efamast†; Efanatal; ***Philipp.***: K-A Plus; Pharmaton; ***Port.***: Geriso; Thiospot; ***Singapore***: Eye Q Equazen†; Manhae; ***Spain***: Dermisone Epitelizante†; Doctofril Antiinflamat†; Nutracel; Vitamina F99 Topica†; ***Switz.***: Linola gras; Linola migras†; Linola; Sulgan N; Vitafissan N; ***UK***: Lacrima.

Gangliosides

Gangliósidos; Ганглиозиды.

Profile

Gangliosides are endogenous substances present in mammalian cell membranes, especially in the cortex of the brain. They are glycosphingolipids composed of a hydrophilic oligosaccharide chain, characterised by sialic acid residues, attached to a lipophilic moiety. The four major gangliosides found in the mammalian brain are referred to as G_{M1}, G_{D1a}, G_{D1b}, and G_{T1b}.

Experimental studies have reported that gangliosides may have a neuroprotective effect on the CNS and peripheral nervous system. Preparations of gangliosides from bovine brain have been given for peripheral neuropathies and cerebrovascular disorders and their role in spinal cord injury has also been investigated. The modified ganglioside siagoside has been studied in patients with Parkinson's disease.

Concern was expressed about the development of Guillain-Barré syndrome and other motor neurone disorders in some patients, and it was suggested that gangliosides were contra-indicated in Guillain-Barré syndrome and all auto-immune disorders. Subsequently these concerns over safety and doubts about efficacy led to the withdrawal of ganglioside preparations in many countries.

References.

1. Geisler FH, *et al*. Recovery of motor function after spinal-cord injury—a randomized, placebo-controlled trial with GM-1 ganglioside. *N Engl J Med* 1991; **324:** 1829–38.
2. Raschetti R, *et al*. Guillain-Barré syndrome and ganglioside therapy in Italy. *Lancet* 1992; **340:** 60.
3. Figueras A, *et al*. Bovine gangliosides and acute motor polyneuropathy. *BMJ* 1992; **305:** 1330–1.
4. Roberts JW, *et al*. Iatrogenic hyperlipidaemia with GM-1 ganglioside. *Lancet* 1993; **342:** 115.
5. Landi G, *et al*. Guillain-Barré syndrome after exogenous gangliosides in Italy. *BMJ* 1993; **307:** 1463–4.
6. Nobile-Orazio E, *et al*. Gangliosides: their role in clinical neurology. *Drugs* 1994; **47:** 576–85.
7. Candelise L, Ciccone A. Gangliosides for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 23/05/06).
8. Fredman P, *et al*. Gangliosides as therapeutic targets for cancer. *BioDrugs* 2003; **17:** 155–67.
9. Govoni V, *et al*. Is there a decrease in Guillain-Barré syndrome incidence after bovine ganglioside withdrawal in Italy? A population-based study in the Local Health District of Ferrara, Italy. *J Neurol Sci* 2003; **216:** 99–103.
10. Chinnock P, Roberts I. Gangliosides for acute spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/05/06).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Sinaxial; Sygen; ***China***: Shen Jie (申捷); Sygen (重塑杰); ***Gr.***: Sygen; ***Singapore***: Cronassial; Sygen.

Garcinia Cambogia

Brindall Berry; Brindleberry; Malabar Tamarind; Гарциния Камбоджа.

CAS — 90045-23-1 (Garcinia cambogia extract).

*UNII — BLL7J4KMB5 (*Garcinia cambogia*); D0QJI8UQVR (*Garcinia cambogia *fruit); 253B88SCZ4 (*Garcinia cambogia *fruit rind).*

Pharmacopoeias. *US* includes Garcinia Cambogia as well as a powdered form. There is also a standard for a powdered hydroxycitrate extract which may be prepared from either *Garcinia cambogia* or *G. indica*.

USP 36: (Garcinia Cambogia). The dried pericarp of the fruits of *Garcinia gummi-gutta* (*G. cambogia*) (Clusiaceae). It contains not less than 12% of the sum of (-)-hydroxycitric acid and (-)-hydroxycitric acid lactone, on the dried basis. Protect from light and moisture.

Profile

Extracts of Garcinia cambogia (*Garcinia gummi-gutta*, Clusiaceae) are a source of hydroxycitric acid and are included in preparations for the treatment of obesity.

Several species of *Garcinia* are used in traditional medicine, as a food source, and as a source of the pigment gamboge.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Terocaps.

Multi-ingredient Preparations. ***Arg.***: Adel; Desgras Burner Fat; Garcinia + Fucus; Garcinia Cambogia Compuesta; Garcinol Max; Indian Health - Garcinia; Mermelax; Metabolic; Reductase; Redudiet; Ripped Max; Silueta Plus†; ***Austral.***: 3B Beer Belly Buster†; Citri Slim+Trim†; Metabolift Fat Burner; ***India***: Obedeuce; ***Indon.***: Betaslim; Combes†; Vitaslim; ***Ital.***: Altadrine; Fibrovit; Snell Cell†; ***Mex.***: Slim-D†; ***Singapore***: Chitosano; Mincifit Body Shaper; ***Ukr.***: Liponorm (Липонорм); Stifimol (Стифимол).

Garlic

Aglio; Ail; Ail, poudre d' (garlic powder); Ajo; Allii sativi bulbi pulvis (garlic powder); Allium; Allium Sativum; Cibule česneku setého práškovaná (garlic powder); Fokhagymapor (garlic powder); Knoblauch; Valkosipuli; Vitlök; Česnakų milteliai (garlic powder); Чеснок.

CAS — 8008-99-9 (garlic extract).

*ATC Herb — HJ01WB5002 (*Allium sativum*: bulb); HJ01WA5001 (*Allium sativum*: bulb); HC10AW5002 (*Allium sativum*: bulb).*

*UNII — IIF21WT8O3 (*Allium sativum*); V1V998DC17 (*Allium sativum *bulb).*

Pharmacopoeias. In *US*, which also includes Garlic Fluidextract, Powdered Garlic, and Powdered Garlic Extract. *Eur.* (see p. vii) includes Garlic Powder.

Eur. also includes Garlic for Homoeopathic Preparations.

Ph. Eur. 8: (Garlic Powder). It is produced from garlic that has been cut, freeze-dried or dried at a temperature not exceeding 65 degrees, and powdered. It contains not less than 0.45% of allicin, calculated with reference to the dried drug. It is a light yellowish powder. Protect from light.

Ph. Eur. 8: (Garlic for Homoeopathic Preparations). The fresh bulb of *Allium sativum*. Store in airtight containers. Protect from light.

USP 36: (Garlic). The fresh or dried compound bulbs of *Allium sativum* (Liliaceae). It contains not less than 0.5% of alliin and not less than 0.2% of γ-glutamyl-(*S*)-allyl-L-cysteine, calculated on the dried basis. Store in a dry place at a temperature of 8 degrees to 15 degrees. Protect from light.

USP 36: (Powdered Garlic). It is produced from garlic that has been cut, freeze-dried or dried at a temperature not exceeding 65 degrees, and powdered. It contains not less than 0.3% of alliin and not less than 0.1% of γ-glutamyl-(*S*)-allyl-L-cysteine, calculated on the dried basis. Store in a dry place at a temperature of 8 degrees to 15 degrees. Protect from light.

Uses and Administration

The constituents of garlic include alliin, allicin, diallyl disulfide, and ajoene. It has traditionally been reported to have expectorant, diaphoretic, disinfectant, and diuretic properties. More recently, it has been investigated for antimicrobial, antihypertensive, lipid-lowering, fibrinolytic, antiplatelet, and cancer protective effects. Garlic oil has also been used.

Homoeopathy

Garlic has been used in homoeopathic medicines under the following names: Allium sativum; Allium sat; All. sat.

References.

1. Kleijnen J, *et al*. Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol* 1989; **28:** 535–44.
2. Mansell P, Reckless JPD. Garlic. *BMJ* 1991; **303:** 379–80.
3. McElnay JC, Po ALW. Garlic. *Pharm J* 1991; **246:** 324–6.
4. Kiesewetter H, *et al*. Effect of garlic on platelet aggregation in patients with increased risk of juvenile ischaemic attack. *Eur J Clin Pharmacol* 1993; **45:** 333–6.
5. Deshpande RG, *et al*. Inhibition of Mycobacterium avium complex isolates from AIDS patients by garlic (Allium sativum). *J Antimicrob Chemother* 1993; **32:** 623–6.
6. Dorant E, *et al*. Garlic and its significance for the prevention of cancer in humans: a critical review. *Br J Cancer* 1993; **67:** 424–9.
7. WHO. Bulbus Alii Sativi. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/4.html (accessed 04/02/10)
8. Ackermann RT, *et al*. Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med* 2001; **161:** 813–24.
9. Tattelman E. Health effects of garlic. *Am Fam Physician* 2005; **72:** 103–6.
10. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. *J Nutr* 2006; **136** (suppl): 736S–740S.
11. Reinhart KM, *et al*. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Ann Pharmacother* 2008; **42:** 1766–71.

Common cold. Although garlic is used as a remedy for the common cold because it is believed to have antibacterial and antiviral properties, a systematic review[1] found insufficient evidence of benefit from clinical studies and that claims of efficacy have come from poor quality evidence.

1. Lissiman E, *et al*. Garlic for the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 02/12/09).

Hyperlipidaemia. Garlic has been widely promoted for use in the treatment of hyperlipidaemia (p. 1248.1). Several early placebo-controlled studies[1,2] and meta-analyses[3,4] showed that garlic significantly decreased total serum-cholesterol concentrations. However, more recent data suggest that the effect is at best modest[5] or that there

is no significant difference[6-9] when compared with placebo.

1. Jain AK, *et al*. Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med* 1993; **94:** 632–5.
2. Kenzelmann R, Kade F. Limitation of the deterioration of lipid parameters by a standardized garlic-ginkgo combination product: a multicenter placebo-controlled double-blind study. *Arzneimittelforschung* 1993; **43:** 978–81.
3. Warshafsky S, *et al*. Effect o f garlic o n total serum cholesterol: a meta-analysis. *Ann Intern Med* 1993; **119:** 599–605.
4. Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. *J R Coll Physicians Lond* 1994; **28:** 39–45.
5. Stevinson C, *et al*. Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials. *Ann Intern Med* 2000; **133:** 420–9.
6. Neil HAW, *et al*. Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and a meta-analysis. *J R Coll Physicians Lond* 1996; **30:** 329–34.
7. Berthold HK, *et al*. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. *JAMA* 1998; **279:** 1900–2.
8. Isaacsohn JL, *et al*. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Intern Med* 1998; **158:** 1189–94.
9. Gardner CD, *et al*. Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial. *Arch Intern Med* 2007; **167:** 346–53.

Adverse Effects

Effects on the skin. Reports of burns or skin lesions after topical application of garlic to children,[1,2] and to adults,[3,4] including self-inflicted injury.[5]

1. Garty B-Z. Garlic burns. *Pediatrics* 1993; **91:** 658–9.
2. Canduela V, *et al*. Garlic: always good for the health? *Br J Dermatol* 1995; **132:** 161–2.
3. Farrell AM, Staughton RCD. Garlic burns mimicking herpes zoster. *Lancet* 1996; **347:** 1195.
4. Eming SA, *et al*. Severe toxic contact dermatitis caused by garlic. *Br J Dermatol* 1999; **141:** 391–2.
5. Lachter J, *et al*. Garlic: a way out of work. *Mil Med* 2003; **168:** 499–500.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ajo Vital; Ajomast; Alliocaps; ***Austral.***: Garlix†; ***Austria***: Kwai; ***Fr.***: Inod'ail; ***Ger.***: Kwai; Sapec; Strongus†; ***Hung.***: Allidex; ***India***: Garlee; Garlic Pearls; ***Ital.***: Kwai; ***Malaysia***: Kyolic; ***Pol.***: Aliovital†; Alitol; Geriacaps; ***Swed.***: Kyolic; ***Thai.***: Cilrag; ***Turk.***: Cirkulin; ***UK***: Garlimega; Kwai; Kyolic; ***Ukr.***: Allocholum (Аллохол); Herbion Allium (Гербион Аллиум); Revital Garlic Pearls (Ревайтл Чесночные Жемчужины)†.

Multi-ingredient Preparations. ***Arg.***: Aglio†; Ajo 1000 + C; Ajo Forte†; Ajo Mas Vitamina C; Ajolip; Exail; Varisedan; ***Austral.***: Airborne Immunity; ChelaCo; Daily Plus Max†; Echinacea Plus Garlix; Garlic Allium Complex; Garlic and Horseradish + C Complex†; Gartech†; Lemsip First Signs Cold & Flu Day + Night; Lemsip First Signs Cold & Flu; Menevit; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Odourless Garlic; Olive Leaf Plus; Super Strength Horseradish Garlic + C; Ultra Allergy Defense; ***Austria***: Rutiviscal; ***Canad.***: Defense; Kyolic 101†; Kyolic 102†; Para-Gone; ***Fr.***: Arterase; Dida; ProstaSecur A; ***Ger.***: Ilja Rogoff; Klosterfrau Aktiv†; Lipidavit†; ***Hong Kong***: Bio-Kult Candea; Cardioace; Doctor's Choice Multivitamins and Minerals for Eyes; Wellman; ***Hung.***: Allithera; Antisklerin; Sanhelios 333; ***India***: Arthrill; Full-24; Garlill; GGG-24; Lactare; Multivite Gold; ***Indon.***: Garlic-Plus; Imox; Naturlesterol; Resvica†; Sotens†; ***Ital.***: Angiovein; Artedin; Valcap; ***Malaysia***: Circarol; ***Mex.***: Hepafol-F; Supravital; ***Philipp.***: Circulan; Nutrotal; ***Pol.***: Alchinal; Alliofil; Alliorut†; Cepasmel; Cepastil; Doppelherz Vital Kapseln†; Klosterfrau Aktiv; ***Rus.***: Wellman (Велмен); ***Singapore***: Bio-Kult Candea; ***Switz.***: Allium Plus†; Arterosan Plus†; Keli-med; ***UK***: Allerclear; Antifect; Cardioace; Clogar; Fishogar; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Liqufruta Garlic Cough Medicine; Super Antioxidant Plus; ***Ukr.***: Gold Ray (Голд Рей); Grinvitals Cereloba Plus (Гринвитал Церелоба Плюс); Vitokan (Витокан); Wellman (Велмен); ***USA***: Cardiopress; Fitness Tabs for Men; Fitness Tabs for Women; Immunicare.

Homoeopathic Preparations. ***Canad.***: Mucan; ***Chile***: Flucoccinum; ***Ger.***: Nux Vomica N Oligoplex; RauwolfiaViscomp; ***Switz.***: Regenaplex Nr 38b; Regenaplex Nr. 50b.

Pharmacopoeial Preparations
USP 36: Garlic Delayed-Release Tablets.

Gavestinel *(BAN, USAN, rINN)*

Gavestinelum; GV-150526X; Гавестинел.
4,6-Dichloro-3-[(*E*)-2-(phenylcarbamoyl)vinyl]indole-2-carboxylic acid.
$C_{18}H_{12}Cl_2N_2O_3$=375.2
CAS — 153436-22-7.
UNII — 318X4QY113.

Profile

Gavestinel is a glycine antagonist that has been investigated as a neuroprotectant in stroke.

Stroke. Gavestinel has been tried for its supposed neuroprotective properties in acute stroke, but two major multicentre, randomised controlled studies have failed to show any benefit over placebo in acute ischaemic stroke.[1,2] Analysis of the data from these two studies in patients with primary intracerebral haemorrhage found no benefit of gavestinel in this subgroup either.[3]

1. Lees KR, *et al*. Glycine antagonist (gavestinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial. *Lancet* 2000; **355:** 1949–54.
2. Sacco RL, *et al*. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. *JAMA* 2001; **285:** 1719–28.
3. Haley EC, *et al*. Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. *Stroke* 2005; **36:** 1006–10.

Gelsemium

Gelsemium Root; Jessamine; Madreselva; Raíz del gelsemio; Raíz del jazmín amarillo; Yellow Jasmine Root; Корень Желтого Жасмина.
CAS — 509-15-9 (gelsemine).
UNII — 639KR60Q1Q.

Profile

Gelsemium consists of the dried rhizome and roots of *Gelsemium sempervirens* (Loganiaceae). It contains toxic indole alkaloids including gelsemine ($C_{20}H_{22}N_2O_2$ = 322.4). It depresses the CNS and has been used mainly in neuralgic conditions, particularly trigeminal neuralgia and migraine.

Homoeopathy

Gelsemium has been used in homoeopathic medicines under the following names: Gelsemium sempervirens; Gels.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Coquelusedal Nourrissons; Coquelusedal Paracetamol Nourrissons†; Coquelusedal Paracetamol; Coquelusedal; ***Port.***: Cephyl†.

Homoeopathic Preparations. ***Austral.***: Childrens Cold and Flu Relief; Childrens Sleep; Hangover Relief; Pain & Fever Relief; Sleep & Insomnia Relief; ***Austria***: Aconitum Med Complex; Cranagil; Globuli gegen Kopfschmerzen; Metavirulent; Migrenopas†; Nisylen†; Rytmopasc; Spigelon; ***Canad.***: Bioactiv N†; C-Plus; Calsom†; Cold Tablets with Zinc†; Complete Flu Care 4 Kids†; Coryzalia; Echinacea Compositum; Hea Complex†; Headache & Migraine L77; Herpes Soothing Cream; Homeo-Form CA†; Homeo-Form M†; Hyalgesic HP†; Hylands Flu; Hylands Formula CZ; Hylands Formula F; Hylands Headache; Hylands PMS; Hylaprin; Ikoplex 12†; Ivernax; L52 Cough & Cold; Loprax†; Mental Alertness; Nervita; Nixotinex; Quietude; Spascupreel; Spigelon†; ***Chile***: Allium Compuesto; Bioactiv N; Drosemiel; Flucoccinum; Grippakit; Ikoplex No 12; Lumboplex; TBR/X; ***Cz.***: Coryzalia; Gelsemium-Homaccord; Lehnigrip†; Paragrippe; Sedalia; Spascupreel S†; ***Fr.***: Acidum Phosphoricum Complexe No 5; Acidum Phosphoricum Compose†; Anxietum; Boripharm No 31; Boripharm No 3; Coryzalia; Gelsemium Complexe No 70; grippe†; L 52; Paragrippe; Phapax; Quietude; Ranunculus Complexe No 79; Slipeol†; Zenalia; Zincum Cyanidum Complexe No 101†; ***Ger.***: A-Bomin; Anovin; Antimigren; Biodolor; Cefagrippin†; Cefanalgin†; Cefaneuro; Cefatropin N†; Chirofossat; Cranio-cyl Ho-Len-Complex; Curare comp; DolorA; dysto-loges N; dysto-loges S; Echinacea comp; Febrocyl L Ho-Len-Complex; Gelsemium Comp; Gelsemium Comp; Gelsemium N Oligoplex; Grippe-Gastreu S R6; Gripps; HanoFemin; HanoToxin M; Hanotoxin M; Infekt-Komplex L Ho-Fu-Complex; Infi-Echinacea; Infi-Symphytum; Infigripp; Influvit; Jowidarmin; metavirulent; Migrane Hevert†; Migrane Hevert; Migrane-Gastreu R16; Neuralgie-Injektopas SL; Neuro-Do; Neuro-Ginsan N; Neuroselect; Nisylen; Pascallerg; Pflugerplex Gelsemium; Rephalgin N; Rytmopasc; Schworotox A; Sedaselect; Spascupreel; Wiedimmun; Zahnungstropfen Escatitona; Zerosorin SN†; ***Hung.***: Coryzalia; Gelsemium-Homaccord; Spascupreel; Spigelon; ***Neth.***: Arnilite; Cephalite; Coryzalia; Grippe-Gastreu R6; Homeocare Nervo; Hyperilite; Kind 0-6 Kinditherm; Kind 0-6 Nisykind; Kruidvat Homeopathie Influ-complex†; Mulimen H; Nervofleur; Nisyleen; Paragrippe†; Quietude†; Spascupreel H; ***Port.***: Coryzalia; Paragrippe; ***Rus.***: Aurum Plus (Аурум-Плюс); Briacon (Бриакон); Coryzalia (Коризалия); Crataegus-Plus (Кратегус-Плюс); Influcid (Инфлюцид); Mirticam (Миртикам); ***Switz.***: Coryzalia; Influaforce†; metavirulent; Quietude; Regenaplex Nr. 3; Spigelon; ***UK***: Coldenza; ***Ukr.***: Capadol (Кападол); Coryzalia (Коризалия); Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Influcid (Инфлюцид); ***USA***: Preferred Remedies Cold & Flu.

Gene Therapy

Terapéutica génica; Генотерапия.

Profile

Gene therapy is a product of the increasing knowledge of genetic function and the availability of methods to examine and manipulate the genome. Exogenous genetic material, which may be synthetic or recombinant nucleic acids (p. 2573.1), is introduced into somatic cells (transfection) in such a way that the cells are able to express the products of the new genes. It may be used for therapeutic, prophylactic, or diagnostic purposes. Gene therapy should be distinguished from the use of products derived from organisms (usually micro-organisms) whose genome has been manipulated by similar recombinant DNA technology, for example the use of recombinant cytokines (p. 2491.2), monoclonal antibodies (p. 2561.1), or antisense products.

Gene therapy is under investigation in three main areas:
- the replacement of abnormal or defective genes in patients with inherited disease
- the alteration of the characteristics of cells to change their relative susceptibility to other therapies (for example by making haematopoietic stem cells more resistant to the adverse effects of antineoplastics, or by making tumour cells selectively express an enzyme that converts an otherwise non-toxic prodrug into a cytotoxic agent)
- for localised production of a biologically active substance that cannot be given directly or would have unacceptable effects if used systemically.

To date, all gene therapy in humans has been of differentiated somatic cells. Alteration of the human genome in a manner transmissible to offspring, either by treating the germ cells or the early embryo, is considered at present to pose insuperable ethical problems.

Various methods for delivery of genetic material have been investigated, none of which is yet completely satisfactory. These include biological vectors (e.g. viruses or plasmids) or stem cells that have been genetically modified, oncolytic viruses, nucleic acids, either naked plasmids or carried by delivery vehicles, and genetic vaccines. Antisense techniques to modify, correct, or silence aberrant genes are also being developed, as is RNA interference. Xenotransplantation of animal cells may also be an option. Removal of donor cells from the patient followed by *ex vivo* transfer of the new gene (by physical or viral methods) and return of the modified cells may be feasible for modifying haematopoietic stem cells. However, for most tissues, methods of *in vivo* transfer are required. Modified viruses rendered incapable of replicating have been widely studied as vectors for gene therapy. Retroviruses have the advantage that the DNA they carry is integrated into the host genome, resulting in permanent expression of the gene, but there has been some concern that they may disrupt existing genetic material with possibly oncogenic effect; in addition, their small size limits the size of gene that they can carry, and they are largely ineffective in infecting non-dividing cells. Adenoviruses are more stable and can infect non-dividing as well as dividing cells, but their genetic freight is not integrated into the chromosome and transmitted to the cell's progeny, and the gene products are therefore only expressed transiently; they are also highly immunogenic which limits repeated use. Some other viral types, including herpes simplex viruses, adeno-associated viruses, and lentiviruses, are also under investigation. Viruses with tropisms for a particular tissue may be useful in producing localised effects.

Chemical or physical methods for DNA delivery have been extensively investigated. Such methods include direct injection of DNA, the use of DNA complexes bound to a ligand which can be taken up by cells, formulation of DNA in liposomes which can fuse with cell membranes and allow the DNA to enter the cell, and more exotic methods such as 'gene guns', in which DNA-coated gold particles are fired into the cells. Although gene expression can be achieved after use of such methods, it is again transient because the new genetic material is not integrated with that of the host, and physical methods are currently less efficient and more limited in scope than viral ones.

Many clinical studies are being carried out. The first successful therapy was for severe combined immunodeficiency, a single-gene disorder due to deficiency of the enzyme adenosine deaminase. Transfection of the gene for this enzyme into the patient's T-cells *ex vivo* and re-infusion of the modified T-cells has been shown to produce substantial clinical improvement, although therapy must be repeated periodically because of the limited lifespan of the lymphocytes.

Studies in patients with cystic fibrosis have also shown some success, and several other single-gene disorders, including alpha$_1$ antitrypsin deficiency, Gaucher disease, the haemoglobinopathies and haemophilias, and Duchenne muscular dystrophy are being studied or have been proposed as possible candidates. Alipogene tiparvovec (p. 2434.2), a nonreplicating adeno-associated viral vector (AAV1) that carries a gene for lipoprotein lipase, is used for the treatment of familial lipoprotein lipase deficiency.

Gene therapy is also under investigation in various acquired diseases, particularly in the management of various types of cancer. Strategies being studied include modification of tumour cells either to increase their immunogenicity or to render them selectively sensitive to antineoplastics, transfection of tumour cells with tumour suppressor genes, and transfection of healthy cells to

produce cancer killing substances. Other disorders being studied clinically include HIV infection, rheumatoid arthritis, Parkinson's disease and atherosclerosis.

Some reviews and references concerning gene therapy are listed below. See also under the discussions of individual diseases for comments on gene therapy in the context of their conventional treatment.

1. Hu WS, Pathak VK. Design of retroviral vectors and helper cells for gene therapy. *Pharmacol Rev* 2000; **52:** 493–511.
2. WHO. Gene transfer medicinal products. *WH O Drug Inf* 2002; **16:** 275–82.
3. Tomanin R, Scarpa M. Why do we need new gene therapy viral vectors? Characteristics, limitations and future perspectives of viral vector transduction. *Curr Gene Ther* 2004; **4:** 357–72.
4. DoH. Recommendations of the GTAC/CSM working party on retroviruses. Internet Document: May 2005. Available at: http://www.advisorybodies.doh.gov.uk/genetics/gtac/Finalrecommendations-June2005.pdf (accessed 11/02/08)
5. Basu J, Willard HF. Artificial and engineered chromosomes: non-integrating vectors for gene therapy. *Trends Mol Med* 2005; **11:** 251–8.
6. Barzon L, *et al*. Versatility of gene therapy vectors through viruses. *Expert Opin Biol Ther* 2005; **5:** 639–62.
7. Sinn PL, *et al*. Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors—design, biosafety, and production. *Gene Ther* 2005; **12:** 1089–98.
8. Wierdl M, Potter PM. Update on gene therapy approaches for cancer. *Curr Hematol Rep* 2005; **4:** 294–9.
9. Hart SL. Lipid carriers for gene therapy. *Curr Drug Deliv* 2005; **2:** 423–8.
10. Kaplan JM. Adenovirus-based cancer gene therapy. *Curr Gene Ther* 2005; **5:** 595–605.
11. Ohlfest JR, *et al*. Nonviral vectors for cancer gene therapy: prospects for integrating vectors and combination therapies. *Curr Gene Ther* 2005; **5:** 629–41.
12. Dobson J. Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene Ther* 2006; **13:** 283–7.
13. Pelletier R, *et al*. RNA based gene therapy for dominantly inherited diseases. *Curr Gene Ther* 2006; **6:** 131–46.
14. Park F, Gow KW. Gene therapy: future or flop. *Pediatr Clin North Am* 2006 **Aug:** 621–38.
15. Lavigne MD, Gorecki DC. Emerging vectors and targeting methods for nonviral gene therapy. *Expert Opin Emerg Drugs* 2006; **11:** 541–57.
16. Chan S, Harris J. The ethics of gene therapy. *Curr Opin Mol Ther* 2006; **8:** 377–83.
17. Cavazzana-Calvo M, Fischer A. Gene therapy for severe combined immunodeficiency: are we there yet? *J Clin Invest* 2007; **117:** 1456–65.
18. Kohn DB, Candotti F. Gene therapy fulfilling its promise. *N Engl J Med* 2009; **360:** 518–21.

Gentian

Bitter Root; Enzianwurzel; Genciana; Genciana mayor; Gencijonų šaknys; Gentian Root; Gentiana; Gentianae Radix; Gentianarot; Gentiane; Gentiane, racine de; Genziana; Hořcový kořen; Katkeronjuuri; Korzeń goryczki; Raíz de Genciana; Tárnicsgyökér; Горький Корень.

ATC Herb — HA05AW5010 (Gentiana lutea: *root*); *HA09WA5013* (Gentiana lutea: *root*).

UNII — S72O3284MS.

Pharmacopoeias. In *Eur.* (see p. vii), and *Jpn.*

Jpn includes Japanese Gentian, from *G. scabra* and other species. *Chin.* also specifies *G. scabra* and other species.

Ph. Eur. 8: (Gentian Root; Gentian BP 2014). The dried, fragmented underground organs of *Gentiana lutea* yielding not less than 33% of water-soluble extractive. It has a characteristic odour. Protect from light.

Profile

Gentian is used as a bitter. An alcoholic infusion of gentian, bitter-orange peel, and lemon peel has been used as an ingredient in bitter mixtures.

Homoeopathy

Gentian has been used in homoeopathic medicines under the following names: Gentiana lutea; Gentiana lut; Gent. lut.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Underberg†.

Multi-ingredient Preparations. ***Austral.***: Calmo†; Detox Program; Digest Aid; DiGest; Digestaid; Digestive Aid; Digestive Bitters; Extralife Sleep-Care†; Sinupret; Toxicol; ***Austria***: Abdomilon N; Brady's-Magentropfen; China-Eisenwein†; Klosterfrau Melissengeist; Mariazeller; Montana; Pervivo; Sigman-Haustropfen; Sinupret; Solvopret†; ***Braz.***: Camomila; Gotas Digestivas; Gotas Preciosas; ***Canad.***: Gallexier†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Para-Gard; Para-Gone; Stomach Ease; ***Cz.***: Biotussil; Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Klosterfrau Melisana; Original Schwedenbitter; Sinupret; ***Fr.***: Diatisan†; Quintonine†; ***Ger.***: Abdomilon N; Amara-Pascoe; Amara-Tropfen; Gallexier; Infi-tract V; Klosterfrau Melissengeist; Montana N; Schwedentrunk Elixier; Sedovent†; Sinupret; ventri-loges N†; ***Hong Kong***: Sinupret; ***Hung.***: Bano Svedkeseru; Bittner; Gallexier; Kalms; Klosterfrau Melisana; Montana; Sinupret; ***Indon.***: Sinupret†; ***Ital.***: Amaro Medicinale; Bulboshap†; Caramelle alle Erbe Digestive; ***Malaysia***: Sinupret; ***Mex.***: Bisolsinus; ***Philipp.***: Sinupret; ***Pol.***: Dyspepsin; Kalms; Melisana Klosterfrau; Pervivo; Sinupret; ***Rus.***: Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Sinupret (Синупрет); ***S.Afr.***: Amara†; Enzian Anaemodoron Drops†; Helmontskruie†; Lewensessens; Versterkdruppels; Wonderkroonessens; ***Singapore***: Sinupret; ***Spain***: Depurativo Richelet†; ***Swed.***: Galexir; Sinova; ***Switz.***: Gastrosan; Gouttes Amara; Kernosan 26; Metabol; Padma-Lax; Padmed Laxan; Sinupret; Strath Gouttes pour l'estomac; Wala Elixir amer; ***Thai.***: Pepsitase; Sinupret†; ***UK***: Acidosis; Appetiser Mixture; Effico; Indigestion Mixture; Kalms; Quiet Tyme; Scullcap & Gentian Tablets; Sinueeze; Sinuherb; Stomach Mixture; ***Ukr.***: Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Sinupret (Синупрет); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***Venez.***: Nov'Hepar B-12.

Homoeopathic Preparations. ***Austria***: Aflubin; Lymphomyosot; Metavirulent; ***Canad.***: Amaratopfen†; Vegetal Tonic; ***Chile***: Bioactiv A; ***Cz.***: Lymphomyosot; ***Fr.***: Cereales Germees; Gentiana Complexe No 33†; Sativol†; Tonique Vegetal; ***Ger.***: Gastrin-Do; K 1000; Lymphomyosot N; Lymphomyosot; Magen-Darmtropfen N; metavirulent; ***Hung.***: Aflubin; Lymphomyosot; ***Neth.***: Sativol†; ***Rus.***: Aflubin (Афлубин); ***S.Afr.***: Achillea Comp†; Lymphomyosot; ***Ukr.***: Aflubin (Афлубин); Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations

BP 2014: Acid Gentian Mixture; Alkaline Gentian Mixture; Compound Gentian Infusion; Concentrated Compound Gentian Infusion;

Ph. Eur.: Gentian Tincture.

Geraniol

Lemonol; Гераниол.

(*E*)-3,7-Dimethyl-2,6-octadien-1-ol.

$C_{10}H_{18}O$=154.3

CAS — 106-24-1.

UNII — L837108USY.

Profile

Geraniol is a constituent of several essential oils and is used in insect repellent preparations. It was formerly used as an anthelmintic. Geraniol is also used as a flavour and in perfumery. Contact dermatitis has been reported.

References.

1. Yamamoto A, *et al*. Contact urticaria from geraniol. *Contact Dermatitis* 2002; **46:** 52.
2. Murphy LA, White IR. Contact dermatitis from geraniol in washing-up liquid. *Contact Dermatitis* 2003; **49:** 52.
3. Tamagawa-Mineoka R, *et al*. Allergic contact cheilitis due to geraniol in food. *Contact Dermatitis* 2007; **56:** 242–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Cholestin.

Multi-ingredient Preparations. ***Canad.***: Natrapel Plus.

Geranium Oil

Aetheroleum Pelargonii; Geranii Etheroleum; Geranio, aceite esencial de; Geraniová silice; Oleum Geranii; Pelargonium Oil; Rose Geranium Oil; Гераниевое Масло.

UNII — 5Q1I94P4WG.

Profile

Geranium oil is a volatile oil obtained by distillation from the aerial parts of various species and hybrid forms of *Pelargonium* (Geraniaceae). It contains geraniol (above). It is used to perfume various preparations and has been included in insect repellent preparations. It is also used in aromatherapy.

Postherpetic neuralgia. A study[1] involving 30 patients has indicated that topically applied geranium oil is of benefit in the management of the pain of postherpetic neuralgia. Pain relief was obtained within a few minutes but further study is required to determine the duration of effect beyond 1 hour. Adverse effects were considered to be minor and included burning in the eye, rash, and lightheadedness.

1. Greenway FL, *et al*. Temporary relief of postherpetic neuralgia pain with topical geranium oil. *Am J Med* 2003; **115:** 586–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Entom Nature.

Multi-ingredient Preparations. ***Austral.***: Advanced Menopause Care; ***Fr.***: Euvanol; ***India***: Nasoclear Aloegel; ***Ital.***: Dentosan Azione Intensiva; Dentosan Mese; Mistick Verde; ***NZ***: Mr Nits; ***Singapore***: Teenstick; ***UK***: Medicated Extract of Rosemary; Nostroline; Repelselect; Teenstick.

Homoeopathic Preparations. ***UK***: Medicinal Gargle.

Germanium

Germanio; Германий.

Ge=72.630

CAS — 7440-56-4.

UNII — 00072J7XWS (germanium); TY8J0G7KOD (germanium ion).

Profile

Germanium compounds have been used in dietary supplements promoted for conditions including cancer, chronic fatigue syndrome, and immunodeficiency disorders. However, germanium compounds can produce severe renal damage and their use should be discouraged.

Germanium has also been used in dental alloys and has various industrial uses.

Effects on the kidneys. In the UK the DoH has recommended that germanium should not be taken as a dietary supplement because of a significant incidence of renal toxicity. There have been several reports of severe renal damage, including fatalities, resulting from germanium ingestion.

References.

1. Okada K, *et al*. Renal failure caused by long-term use of a germanium preparation as an elixir. *Clin Nephrol* 1989; **31:** 219–24.
2. van der Spoel JI, *et al*. Dangers of dietary germanium supplements. *Lancet* 1990; **336:** 117. Correction. *ibid*. 1991; **337:** 864.
3. Schauss AG. Nephrotoxicity in humans by the ultratrace element germanium. *Ren Fail* 1991; **13:** 1–4.
4. Hess B, *et al*. Tubulointerstitial nephropathy persisting 20 months after discontinuation of chronic intake of germanium lactate citrate. *Am J Kidney Dis* 1993; **21:** 548–52.
5. Tao SH, Bolger PM. Hazard assessment of germanium supplements. *Regul Toxicol Pharmacol* 1997; **25:** 211–19.
6. Swennen B, *et al*. Epidemiological survey of workers exposed to inorganic germanium compounds. *Occup Environ Med* 2000; **57:** 242–8.

Gevokizumab *(USAN, rINN)*

Gévokizumab; Gevokizumabum; XOMA-052; Гевокизумаб.

Immunoglobulin G2, anti-(human interleukin 1β) (human-*Mus musculus* XOMA 052 heavy chain), disulfide with human-*Mus musculus* XOMA 052 κ-chain, dimer.

CAS — 1129435-60-4.

UNII — QX3JU54GYQ.

Profile

Gevokizumab is a humanised anti-interleukin-1β monoclonal antibody that is under investigation for the treatment of non-infectious uveitis such as Behçet's disease.

References.

1. Owyang AM, *et al*. XOMA 052, a potent, high-affinity monoclonal antibody for the treatment of IL-1 β -mediated diseases. *MAbs* 2011; **3:** 49–60.
2. Gül A, *et al*. Interleukin-1 β -regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behcet's disease: an open-label pilot study. *Ann Rheum Dis* 2012; **71:** 563–6.

Ginkgo Biloba

Árbol de los cuarenta escudos; EGB-761; Fossil Tree; GBE-761; Ginkgo, feuille de (ginkgo leaf); Ginkgo folium (ginkgo leaf); Ginkgoblad (ginkgo leaf); Ginkmedžių lapai (ginkgo leaf); Jinanový list (ginkgo leaf); Kew Tree; Maidenhair Tree; Neidonhiuspuunlehti (ginkgo leaf); *Salisburia adiantifolia*; Páfrányfenyőlevél (ginkgo leaf); Гинкго Билоба.

ATC — N06DX02.

ATC Vet — QN06DX02.

ATC Herb — HN07CA5001 (Ginkgo biloba: *leaf*); *HC04AW5001* (Ginkgo biloba: *leaf*); *HN06DX5001* (Ginkgo biloba: *leaf*).

UNII — 660486U6OI (Ginkgo biloba); *19FUJ2C58T* (Ginkgo biloba *leaf*); *Y5967KO1JH* (Ginkgo biloba *leaf water*); *1XUK686051* (Ginkgo biloba *root*); *8CQ734K3W7* (Ginkgo biloba *seed*).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US. Eur.* (see p. vii) also includes Ginkgo Dry Extract, Refined and Quantified. *US* includes a powdered extract.

Ph. Eur. 8: (Ginkgo Leaf). The whole or fragmented dried leaf of *Ginkgo biloba* containing not less than 0.5% of flavonoids, calculated as flavone glycosides with reference to the dried drug. The leaf is greyish or yellowish-green or yellowish-brown.

USP 36: (Ginkgo). The dried leaf of *Ginkgo biloba* (Ginkgoaceae) containing not less than 0.5% of flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7, and not less than 0.1% of terpene lactones, both on the dried basis. The leaf is khaki green to greenish-brown. Protect from light and moisture.

Uses and Administration

An extract from the leaves of *Ginkgo biloba* has been used in cerebrovascular and peripheral vascular disorders. It is also being investigated in Alzheimer's disease, multi-infarct dementia, and in tinnitus. *Ginkgo biloba* is a source of ginkgolides (below).

Homoeopathy

Ginkgo biloba has been used in homoeopathic medicines under the following names: Ginkgo.

General references.

1. WHO. Folium Ginkgo. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/18.html (accessed 04/02/10)

Cerebrovascular disorders. A systematic review[1] of 10 randomised or quasi-randomised studies concluded that the routine use of ginkgo biloba extracts to promote recovery after ischaemic stroke was not supported by any convincing evidence, and that larger better quality studies were required.

1. Zeng X, *et al*. Ginkgo biloba for acute ischaemic stroke. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 23/05/06).

Dementia. Ginkgo biloba extracts have been tried in the treatment of dementia including Alzheimer's disease (p. 388.1). Meta-analyses[1,2] have found the extracts to be more effective than placebo in some cases. However, a later systematic review[3] concluded that there is inconsistent and unreliable evidence that ginkgo biloba has any benefit for people with dementia or cognitive impairment. Furthermore, these authors felt that conventional studies for its use in the treatment of acquired cognitive impairment were unlikely to prove useful, although studies in patients with neuropsychiatric symptoms might be warranted. A study[4] assessing whether ginkgo biloba can prevent cognitive decline in very elderly people with normal memory function found positive effects only after adjustment for noncompliance. However, more cases of stroke or transient ischaemic attacks were noted in those given ginkgo biloba although further study is required to confirm any link. Another study[5] investigating the effect of ginkgo biloba in reducing the incidence of dementia in people over 75 years of age with normal cognition or mild cognitive impairment found that it was ineffective.

1. Oken BS, *et al*. The efficacy of ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol* 1998; **55:** 1409–15.
2. Ernst E, Pittler MH. Ginkgo biloba for dementia: a systematic review of double-blind, placebo-controlled trials. *Clin Drug Invest* 1999; **17:** 301–8.
3. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 08/12/09).
4. Dodge HH, *et al*. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. *Neurology* 2008; **70:** 1809–17.
5. DeKosky ST, *et al*. Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA* 2008; **300:** 2253–62. Correction. *ibid.*; 2730.

Peripheral vascular disorders. Ginkgo biloba extracts have been tried in the treatment of peripheral vascular disorders (p. 1272.3). A meta-analysis[1] found the extracts to be more effective than placebo in the symptomatic treatment of intermittent claudication, although the authors considered the size of the effect to be modest and of uncertain clinical relevance. A later systematic review[2] found no evidence of a clinically significant benefit for patients with peripheral arterial disease.

1. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000; **108:** 276–81.
2. Nicolaï SPA, *et al*. Ginkgo biloba for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 08/12/09).

Tinnitus. Ginkgo biloba extracts have been tried in the treatment of tinnitus (p. 1990.1). A systematic review[1] of 5 randomised controlled studies cautiously concluded that these results were favourable, although a later systematic review[2] failed to show benefit.

1. Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. *Clin Otolaryngol* 1999; **24:** 164–7.
2. Hilton MP, Stuart EL. Ginkgo biloba for tinnitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 08/12/09).

Adverse Effects and Precautions

Adverse effects of ginkgo biloba include headaches, dizziness, palpitations, gastrointestinal disturbances, bleeding disorders, and skin hypersensitivity reactions.

Poisoning. Convulsions are a known effect of consuming large amounts of ginkgo seeds.[1,2] The effect is considered to be due to ginkgotoxin (4-metoxypyridoxine, 4′-*O*-methylpyridoxine), which is present in the raw seeds in amounts of up to 85 micrograms per seed.[3] It is also present in smaller amounts in the leaves, and has been detected in proprietary products in variable quantities that would correspond to a daily dose of up to about 60 micrograms. There have been a few reports of convulsions associated with ginkgo biloba products, and it has been suggested that they should be used with caution in patients with epilepsy.[3] Giving suitable quantities of a vitamin-B_6 source might be of benefit in preventing ginkgotoxin-induced convulsions.[2]

1. Miwa H, *et al*. Generalized convulsions after consuming a large amount of gingko nuts. *Epilepsia* 2001; **42:** 280–1.
2. Kajiyama Y, *et al*. Ginkgo seed poisoning. *Pediatrics* 2002; **109:** 325–7.
3. Leistner E, Drewke C. *Ginkgo biloba* and ginkgotoxin. *J Nat Prod* 2010; **73:** 86–92.

Pregnancy and breast feeding. There is weak evidence from *animal* and *in-vitro* studies that ginkgo biloba has antiplatelet activity and therefore its use during labour could possibly prolong bleeding time.[1] There are no data on its safety during breast feeding.

1. Dugoua J-J, *et al*. Safety and efficacy of ginkgo (Ginkgo biloba) during pregnancy and lactation. *Can J Clin Pharmacol* 2006; **13:** e277–e284.

Interactions

It has been suggested that ginkgo biloba should be used with caution in patients receiving anticoagulants or drugs that affect platelet aggregation. For reference to a possible interaction with *warfarin*, see p. 1534.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clarvix; Kalter; Tanakan; ***Austral.***: Ginkgoforte; PM Remem; ***Austria***: Cerebokan; Ceremin; Gingol†; Tebofortan; Tebonin; ***Belg.***: Tanakan; Tavonin; ***Braz.***: Binko; Bioflavin†; Clibium; Dinaton; Equitam; Gibilon; Ginbiloba; Gincobem; Gincolin; Ginkoba; Ginkogreen; Ginkolab; Ginkomed; Ginkoplus†; Ginkotab; Gyncobem; Kirsan; Oxian†; Tanakan; Tebiloba; Tebonin; Tekasan; ***Chile***: Ginkomax; Kiadon; Memokit†; Nokatar; Rokan; ***China***: Ginaton (金纳多); Tanakan (达纳康); Yin Ke Luo (银可络); ***Cz.***: Gingio; Tanakan; Tebokan; ***Fr.***: Ginkogink; Tanakan; Tramisal; Vitalogink; ***Ger.***: Duogink†; Floragink; Gingiloba†; Gingium†; Gingobeta†; Gingopret; Ginkobil; Ginkodilat†; Ginkopur; Kaveri; Rokan; Tebonin; ***Gr.***: Tanacain; Tebokan; ***Hong Kong***: Ebamin†; Ginkolin†; Tanakan; ***Hung.***: Bilobil; Gingium; Salus Floragink; Tanakan†; Tebofortan; ***India***: Avon; Bilovas; Cerestar; Geritisin; Gibil; Gincer; Ginkoba; Ginkocer; Ginkoriv; Ginvas; ***Indon.***: Brenax; Gingkan†; Ginkgoforce; Ginkona; Lanaginkola; Tebokan; ***Ital.***: Ginkoba; ***Malaysia***: Giloba; Gincare; Lanaginkola; Tanakan; Tebonin; ***Mex.***: Nemoril; Tebonin; Vasodil; ***Neth.***: Tavonin; ***Norw.***: Bio-Biloba; Memoplant†; Seredrin†; ***Philipp.***: Ginkocer†; Tebokan; Tebonin; ***Pol.***: Bilobil; Flavobil; Geriacaps; Ginkgofol; Ginkgomax†; Ginkofar; Herbabiloba†; Memoplant; Tanakan; ***Port.***: Abolibe; Biloban; Gincoben; Vasactife; ***Rus.***: Bilobil (Билобил); Gingium (Гингиум); Ginkgoum (Гинкоум); Ginos (Гинос); Memoplant (Мемоплант); Tanakan (Танакан); ***Singapore***: Giloba; Gincare; Ginkapran; Ginkosen; Gitako; Neuroxin†; Tanakan; Tebonin; ***Spain***: Fitokey Ginkgo†; Ginkgold; Ginkokan; Incebral; Normoginkgo; Tanakene; ***Swed.***: Bio-Biloba; ***Switz.***: Demonatur Ginkgo†; Geriaforce; Gingosol†; Sanapens†; Symfona; Symfonel; Talert†; Tanakene†; Tebofortin; Tebokan; ***Thai.***: Tanakan; Tebonin; ***Turk.***: Gineksin F; Gingobil; Tanakan; ***UK***: Gingkoforce; Ginkovital; ***Ukr.***: Bilobil (Билобил); Giloba (Гилоба); Memoplant (Мемоплант); Tanakan (Танакан); Vobilon (Вобилон); ***USA***: BioGinkgo; ***Venez.***: Kiadon; Neukob; Tanakan; Tebokan; Varginko.

Multi-ingredient Preparations. ***Arg.***: ADX; Aulis; Biovital Pro Q10; Cellasene Gold; Cellasene†; Centella Queen Complex; Centellase de Centella Queen; Ciprovit Energizante; CVP Cellulite; Desgras Piel Naranja; Fioton; Flebitol; GB 100; Gentianella; Ginkgo Biloba Forte; Ginkgo Biloba Memo Diates†; Ginkgo Forte; Herbaccion Celfin; Herbaccion Memory; Ivix; Lopecian; Neuroton†; SCV 300; Snell Patch; Snell Progress; Varicofem; Venoful; Vita 1000 Plus; VNS 45; ***Austral.***: Aesculus & Ruscus Compound; Bacopa & Ginkgo Compound; Bilberry Plus Eye Health†; Clements Tonic; Extralife Extra-Brite†; Extralife Eye-Care†; Extralife Leg-Care†; Eye Health Herbal Plus Formula 4†; For Peripheral Circulation Herbal Plus Formula 5†; Gincosan; Ginkgo Brahmi; HerbaVital; Horsechestnut Complex; Mens Dual-Action Multi; Mens Performance Multi; Mindac; Multi + Ginkgo for 55+†; PM LifeBrain; PM LifePro Max for Men; Prosense for Men†; PulmaCo; ViG; Vision-Eze†; Zellulean with Escin†; ***Braz.***: Minesol; ***Canad.***: Libeeda for Women; ***Chile***: Celltech; Gincosan; Mentania; Perfect Body; Podexine Pie Diabetico; Sebium AKN†; ***China***: Ginkor Fort (静可福); ***Cz.***: Bilobil Duo; Gincosan; Ginkor Fort; ***Fr.***: Diozinac KS; Diozinac; Ginkor Fort; Ginkor†; Memoptic; OM3memory†; ProstaSecurA; Sebium AKN; ***Ger.***: Trium; ***Hong Kong***: Doctor's Choice Multivitamins and Minerals for Eyes; Flavo-C†; Ginkgo-PS†; Ginkor Fort; ***Hung.***: Gincosan; Ginkor Fort†; ***India***: Bil-B; Bio-Loba; Enlarge; Full-24; GGG-24; Ginkoriv Plus; Goldcare; Jini; Multivite Gold; Multivite Woman; ***Indon.***: Bilotec; Cerebrovit Senior; Cereton; Ginokan†; Hemaviton Brain Nutrient†; Proseval; Proview; ***Ital.***: Angioton; Angiovein; Artedin; Blunorm; Criotonal; Eccarvit Plus; Energeia; Flavogin Plus; Fon Wan Memory; Forticrin; Fosfaserin; Ginkoftal; Ginkoret; Lik-Gel†; Macvit; Memovigor; Mentvis; Neuralta Migren; Otobrain; Pik Gel; Pulsalux; Vasobrain Plus; Vasobrain; Vasopt; Vasotonal; Venalta; Vertiginkgo; Vitalmix Fos; ***Malaysia***: Circarol; Gincosan; Ginkor Fort; ***Mex.***: Biometrix†; Maxibiloba; ***Mon.***: Phytospray; ***Philipp.***: Circulan; Nutricap; Nutrotal; ***Pol.***: Bioginko; Cardiobonisol; Ginkgocard†; Intelektan†; Passibil; Venoforton; ***Rus.***: Ginkor Fort (Гинкор Форт); Ginkor Gel (Гинкор Гель); ***Singapore***: Ginkgo-PS†; NutraMX; Robovites Multivitamins; Vitaton Gold; ***Switz.***: Allium Plus†; Arterosan Plus†; Gincosan; ***Thai.***: Gilomax; Ginkor Fort; ***UK***: Goldcare; Neuro Nutrients; ProBrain; ***Ukr.***: Ginkor Fort (Гинкор Форт); Ginkor Gel (Гинкор Гель); Goldcare (Голдкеа); Grinvitals Cereloba Plus (Гринвитал Церелоба Плюс); Intellan (Интеллан); Memory Booster (Мемори Бустер); Neokardil (Неокардил); Osteoartisi Max (Остеоартизи Макс); Theravit Antistress (Теравит Антистресс); Vitrum Memory (Витрум Мемори); ***USA***: Aphrofem; Blood Sugar Balance; Cavigen; Diabetiks; Dorofen; Gentaplex; PowerMate; Sunnie; ***Venez.***: Sebium AKN; Sengobil.

Homoeopathic Preparations. ***Austria***: Cefavora; Memoria; ***Canad.***: Formula CI 207†; Formula Homeo QR 209†; Ginkgo-Comp†; ***Ger.***: Cefavora G†; Cefavora†; Geriaforce†; Ginkgo biloba comp; Ginkgobakehl; Ginkgorell; metaginkgo†; ***Rus.***: Memoria (Мемория); ***Switz.***: Ginkgobakehl; metaginkgo; ***Ukr.***: Cefavora (Цефавора); Memoria (Мемория).

Pharmacopoeial Preparations

USP 36: Ginkgo Capsules; Ginkgo Tablets.

Ginkgolides

Ginkgólidos; Гинкголиды.

CAS — 15291-75-5 (ginkgolide A); 15291-77-7 (ginkgolide B); 15291-76-6 (ginkgolide C).

Profile

Ginkgolides are terpenoid molecules isolated from *Ginkgo biloba* (p. 2512.3), with platelet-activating factor (PAF) antagonist properties. They have been investigated as BN-52063, a mixture of ginkgolides A (BN-52020), B (BN-52021), and C (BN-52022), for asthma and other inflammatory and allergic disorders, and also in immune disorders such as endotoxic shock and graft rejection; ginkgolide B, which has the most potent PAF antagonist properties, has been tried alone in similar conditions.

Other ginkgolides, including ginkgolide M (BN-52023) and ginkgolide J (BN-52024), have also been identified.

References.

1. Braquet P. The ginkgolides: potent platelet-activating factor antagonists isolated from Ginkgo biloba L: chemistry, pharmacology and clinical applications. *Drugs Of The Future* 1987; **12:** 643–99.
2. Kleijnen J, Knipschild P. Ginkgo biloba. *Lancet* 1992; **340:** 1136–9.
3. Houghton P. Ginkgo. *Pharm J* 1994; **253:** 122–3.
4. Brochet B, *et al*. The Ginkgolide Study Group in Multiple Sclerosis. Double blind placebo controlled multicentre study of ginkgolide B in treatment of acute exacerbations of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; **58:** 360–2.
5. Maclennan KM, *et al*. The CNS effects of Ginkgo biloba extracts and ginkgolide B. *Prog Neurobiol* 2002; **67:** 235–57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Bilokan; Seremaks; Tebokan.

Multi-ingredient Preparations. ***Ital.***: Perfluxi Cremagel.

Ginseng

Ginseng radix; Ginsengwurzel; Ginzenggyökér; Jintsam; Ninjin; Panax; Pannag; Renshen; Schinsent; Všehojový kořen; Ženšenių šaknys; Корень Жизни; Женьшень.

ATC Herb — HN06WA5002 (Panax ginseng: root).

UNII — CUQ3A77YXI (Panax ginseng root).

Description. Ginseng is the dried root of *Panax ginseng* (*P. schinseng*) (Araliaceae). Other varieties of ginseng include *Panax quinquefolius* (American Ginseng) and *P. pseudoginseng*. The root commonly known as Siberian or Russian ginseng belongs to the same family, Araliaceae, but is an entirely different plant, *Eleutherococcus senticosus* (see Siberian Ginseng, p. 2614.3). Brazilian ginseng is reported to be derived from another unrelated plant, *Pfaffia paniculata*. The name Indian Ginseng is used for the Ayurvedic medicine, Ashwagandha (see p. 2450.2).

Ginseng contains complex mixtures of saponins termed ginsenosides or panaxosides. At least 13 saponins have been isolated from extracts of *P. ginseng* roots.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *US* (as Asian Ginseng and American Ginseng). *US* includes additionally powdered forms of these two varieties of ginseng. *Eur.* also includes the dry extract.

Jpn also includes Red Ginseng, the dried root of *P. ginseng* which has been steamed.

Chin. and *Jpn* also include the rhizome of *Panax japonicus*. *Eur.* (see p. vii) also includes Notoginseng Root from *P. notoginseng*. *Chin.* also includes Radix Notoginseng from *P. notoginseng*, and Rhizoma Panacis Majoris from *P. japonicus* var. *major* and *P. japonicus* var. *bipinnatifidus*.

Ph. Eur. 8: (Ginseng). The whole or cut dried root of *Panax ginseng*. It contains not less than 0.4% of combined

ginsenosides, Rg1 ($C_{42}H_{72}O_{14}$,$2H_2O$ = 837.1) and Rb1 ($C_{54}H_{92}O_{23}$,$3H_2O$ = 1163.4), calculated with reference to the dried drug. Protect from light.

USP 36: (Asian Ginseng). The dried roots of *Panax ginseng* (Araliaceae). It contains not less than 0.2% of ginsenoside Rg_1 and not less than 0.1% of ginsenoside Rb_1, both calculated on the dried basis. Store in a dry place at a temperature of 8 degrees to 15 degrees.

USP 36: (American Ginseng). The dried roots of *Panax quinquefolius* (Araliaceae). It contains not less than 4.0% of total ginsenosides, calculated on the dried basis. Store in airtight containers. Protect from light and heat.

Uses and Administration

Ginseng is reported to enhance the natural resistance and recuperative power of the body and to reduce fatigue. It is available commercially as roots, powdered roots, tablets, capsules, teas, oils, or extracts.

General references.

1. WHO. Radix Ginseng. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/19.html (accessed 04/02/10)

Adverse Effects

A 2-year study[1] of ginseng in 133 subjects who had used commercial preparations including roots, capsules, tablets, teas, extracts, cigarettes, chewing gum, and candies reported that the majority of preparations were taken orally, but a few subjects had experimented with intranasal or parenteral routes, and topical preparations had also been used. The stimulant effects of ginseng were confirmed but there was also a high incidence of adverse effects including 47 cases of morning diarrhoea, 33 of skin eruptions, 26 of sleeplessness, 25 of nervousness, 22 of hypertension, 18 of euphoria, and 14 of oedema. The 'ginseng abuse syndrome' defined as hypertension, nervousness, sleeplessness, skin eruptions, and morning diarrhoea was experienced by 14 subjects who took ginseng root material orally in an average daily dose of 3 g. Abrupt withdrawal precipitated hypotension, weakness, and tremor in 1 user. About 50% of the subjects had stopped the use of ginseng within the 2 years. Oestrogenic effects have also been reported from the use of ginseng,[2-4] and a case of Stevens-Johnson syndrome has also occurred.[5]

A systematic review[6] of some of these and other studies and case reports concluded that single-ingredient preparations of ginseng were well tolerated when data from clinical studies were examined. Adverse effects were generally mild and reversible, the most common being headache, sleep disturbances, and gastrointestinal disorders. It was more difficult to determine causality from the evidence given in isolated case reports; likewise, interpretation of data involving combination products was difficult.

Ginseng was also reported[7] to be well tolerated in a paediatric study in which 46 children aged between 3 and 12 years were randomly assigned to receive ginseng or placebo as a 3-day treatment course for upper respiratory-tract infections.

1. Siegel RK. Ginseng abuse syndrome: problems with the panacea. *JAMA* 1979; **241:** 1614–15.
2. Palmer BV, *et al.* Gin Seng and mastalgia. *BMJ* 1978; **1:** 1284.
3. Punnonen R, Lukola A. Oestrogen-like effect of ginseng. *BMJ* 1980; **281:** 1110.
4. Greenspan EM. Ginseng and vaginal bleeding. *JAMA* 1983; **249:** 2018.
5. Dega H, *et al*. Ginseng as a cause for Stevens-Johnson syndrome? *Lancet* 1996; **347:** 1344.
6. Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Safety* 2002; **25:** 323–44.
7. Vohra S, *et al*. Safety and tolerability of North American ginseng extract in the treatment of pediatric upper respiratory tract infection: a phase II randomized, controlled trial of 2 dosing schedules. *Pediatrics* 2008; **122:** 428. Full version: http://pediatrics.aappublications.org/cgi/reprint/122/2/e402.pdf (accessed 16/08/10)

Interactions

For reports of interactions between *phenelzine* and ginseng, see p. 446.2. For details of an interaction between *warfarin* and ginseng, see p. 1534.2. For a suggestion that ginseng may interfere with *digoxin* assays, see p. 1355.3. For a suggestion of a potential interaction between ginseng and *tamoxifen*, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ginsana; Herbaccion Bioenergizante; ***Austria***: Ginsana; ***Belg.***: Ginsana†; ***Braz.***: Bioplus; Enerseng†; Fortilan; Fotilan; Ginsana; Ginsex; Revigonal; ***Canad.***: Cold-FX; Nurite; ***Cz.***: Ginsana†; ***Fr.***: Gerimax Toniquet†; Tonigin†; ***Ger.***: Ardey-aktiv; Ginsana; IL HWA; Orgaplasma; ***Irl.***: Ginsana; ***Ital.***: Fon Wan Ginsenergy; Ginsana; ***Jpn***: Koujin; ***Malaysia***: Ginsana†; ***Mex.***: Rutying; Sanjin Royal Jelly; ***Norw.***: Ginsana; ***Pol.***: Ginsana†; Ginsenol; Panaxan†; ***Port.***: Ginsana; ***Rus.***: Gerimax Ginseng (Геримакс Женьшень); Ginsana (Гинсана); Herbion Zen Sen (Гербион Женьшень); ***Singapore***: Ginsana†; ***Spain***: Bio-Star†; Energin; Redseng; ***Swed.***: Ginsana; ***Switz.***: Ginsana; Ginsor; IL HWA; KintaVital; ***Thai.***: Ginsana†; Ginsroy; Pharmagin; ***UK***: Korseng; Red Kooga; ***Ukr.***: Gerimax Ginseng (Геримакс Женьшень).

Multi-ingredient Preparations. ***Arg.***: ADX; CTabs-Total Vit; Dynamisan; Energizante Vital con ginseng; Energy Plus; Fospartan Ginseng; Galenic Restaurador Capilar; Gingeron; Ginseng Bioplus Diates†; Herbaccion Ginseng y Magnesio; Holomagnesio Vital; Inmunofit; KH3†; Level Up; Magnesio 102 Plus; Marathon; Masvitalin Ginseng; Megamax; Merebral; Neuroton†; Optimina Fem; Optimina Plus; Pharmafort; Pharmaton Complex; Pharmaton; Plenovit; Polper Ginseng†; Stimulnerv; Tanvimil Ginseng; Total Magnesiano con Ginseng; Total Magnesiano con Vitaminas y Minerales; Total Magnesiano E; Total Magnesiano Sport; Vifortol; Vitagenol Plus; ***Austral.***: Aloe Vera Plus; Clements Tonic; Daily Plus Max†; Everyday Stress Formula; Extralife Extra-Brite†; Gincosan; Ginsynergy plus Rhodiola; Hairy Lemon; HerbaVital; Irontona†; Memory and Vitality Formula; Nervatona Focus; PM LifePro Max for Women; Prosense for Women†; ViG; Vitatona†; Wild Yam Complex; Withania Complex; ***Austria***: Geriatric Pharmaton; ProAktiv; ***Belg.***: Ostrin Q10; ***Braz.***: Geriaton; Geriavite; Gerilon; Gerin; Gerovital; Natus Gerin; Pharmaton; Poliseng; Vita Senior; Vitergan Master; ***Canad.***: Libeeda for Men; ***Chile***: Bedovit Pharmaton; Biocord-E; Biocord; Capilet Locion Capilar; Diltotal; Dynamisan; Enerday; Fortavil; Gincosan; Infor; Marathon; Mentania; Nectaday†; Pantiban†; Pharmaton; Salubion Ginseng; Supradyn Ginseng; Tolgin†; Tonopron Ginseng; Ultrac E; Ultrac Q10; Ultrac; Vitamix; ***China***: Supradyn (维多宝); ***Cz.***: Bilobil Duo; Geriavit; Gincosan; Pharmaton Activit; ***Fr.***: Alvityl Tonus; Aromavital†; Bion 3 Seniors; Bryssidine; Cicatendon; Dynabiane; Elusanes Starphyt†; Fibromyalgine Fort; Gerimax adultes†; Gestarelle S; Magneginseng†; Normalite 1000; Pharmaton†; Tigre de Chine; Tonactil†; ***Ger.***: Pharmaton; ***Gr.***: Pharmaton Geriatric; ***Hong Kong***: Pharmaton; Sanjukei Panax Ginseng; Wellman†; Wellman; ***Hung.***: Flu-Vit; Gerimax; Gincosan; Pharmaton Vital; Sam-Ginseng Royal; ***India***: Anvital; Ashwita; Beminal; Biostar; Biotone-TD; Biovital; Cad-Vital; Canzeal; Curevital; Cuvital; Dayvital; Elvital-SG; Enlarge; Everfit; Full-24; GB-Lex; Gen-One; Genmac; Gevital; GGG-24; Ginkoriv Plus; Ginsiplex; Gintox; Ginvit; Glofit Plus; Goldcare; GS Forte; GVM; Intavital; Keep-Fit; Lupivital; Lycopol; Lyrich-G; Malvit; Mezica; Minero; Minvital; Multiging; Multiphar; Multivite Gold; Nu-Seng; Omnigen Forte; Orovital-G; Trinergic; Vitacip; ***Indon.***: Armovit; Berocca Performance; Cerebrovit Active; Ginokan†; Hemaviton Action; Hemaviton Brain Nutrient†; Hemaviton Energy Drink; Hemaviton Jreng; Hemaviton Stamina Plus; Instink†; Maxirex; Menolia†; Neo Hormoviton Greng; Neo Hormoviton; Neo Hormoviton; Oramin-G; Penfri; Pharmaton Formula; Pharmaton Vit; Procur Plus; Proseval; Provital Plus; Provital; Ratax; Sirec; Stobled; Tripid; Tristan†; ***Irl.***: Pharmaton; Seven Seas Active Sport†; ***Israel***: Gerimax NF†; Pharmaton; Polyvit 30 Plus; ***Ital.***: Alvear con Ginseng; Apergan; Bioestril Ginseng; Bioton; Enercomplex; Energeia; Euroton; Forticrin; Fosfarsile Forte†; Fosfarsile Forte; Fosfaserin; Gegorvit; Ginsana Ton; Multi Up; Neoplus; Ocustress; Ottovis; Pollingel Ginseng; Taingel; The Ginseng King†; Vitalmix Complex; Vitalmix Fast; ***Jpn***: Bakumondoto; Bukuryoin; Bukuryoingohangekobokuto; Byakkokaninjinto; Chikujountanto; Chotosan; Daibofuto; Daikenchuto; Eki Cabe A†; Eki Cabe S; Goshuyuto; Hangebyakujutsutemmato; Hangeshashinto; Hochuekkito; Jinsoin; Juzentaihoto; Kamikihito; Keihito; Keishininjinto; Kihito; Mokuboito; Ninjin'yoeito; Ninjinto; Nyoshinsan; Orento; Q & P Gold; Rikkunshito; Saibokuto; Saikanto; Saikokaryukotsuboreito; Saikokeishito; Saireito; Seishinrenshiin; Seishoekkito; Shakanzoto; Shikunshito; Shosaikoto; Shosaikotokakikyosekko; Tokito; Unkeito; ***Malaysia***: 30 Plus†; Adult Citrex Multivitamin + Ginseng + Omega 3; Appeton; Enervon with Ginseng & Vitamin E; Gincosan; Ginsomin; Imuvit; NeuroAid; Pharmaton with Selenium; Pharmaton†; Proviton; Revital; Shine Growell; Shine Maxtra; ***Mex.***: Biometrix†; Dynamisan; Pharmaton Complex; Pharmaton; Vitalaif; Wilvit; ***Philipp.***: Arcostrong†; BSI Medicated Spray; Energel; Ginsomin; Havitall; Homtamin-G Plus; Immuvit; K-A Plus; Korgivit-E†; Memovit-E†; Nutricap; Nutrotal; Pharmaton; Polynerv-E with lecithin; Rejuvenex; Restor-F; Revicon Max; Rogin-E; SG-Glutergen; Supranutrol; Ultima; Vita SL; Vitaginseng; ***Pol.***: Bioginko; Doppelherz Vital Kapseln†; Geriatrix; Geriavit†; Geronpol†; Ginjal; Intelektan†; Witagin; ***Rus.***: Doppelherz Ginseng Aktiv (Доппельгерц Женьшень Актив); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Geriavit (Гериавит)†; Gerimax (Геримакс); Raylis (Райлис); Revital Ginseng Plus (Ревайтл Гинсенг Плюс)†; Theravit Tonic (Теравит Тоник); Vitamax (Витамакс)†; Wellman (Велмен); ***S.Afr.***: Activex 40 Plus†; Gericomplex†; Pharmaton†; ***Singapore***: Enervon with Ginseng & Vitamin E; Gin-Vita; Gingviton; Ginsomin; Immuvital; Neovita; Neovita; NutraMX; Pharmaton with Selenium; Pharmaton†; Provital; Vitaton Gold; Vitaton; ***Spain***: Cinfavit Complex; Forcemil; Pharmaton Complex†; Redseng Polivit†; Ton Was; Vitestable; ***Swed.***: Gericomplex; ***Switz.***: Biorganic Geri; Biovital Ginseng; Burgerstein Top-Vital; Enuton†; Gincosan; Imuvit†; Imuvital†; Pharmaton Vital Geriavit; Pharmatovit Ginseng; ProActive; Supradyn Vital 50+; Tai Ginseng†; Tonique D liquide†; ***Thai.***: Geriatric Pharmaton; Imugins; Imuvit; Multilim RG; Pharmaton Fizzi; Pharmaton; Revitan; ***Turk.***: Pharmaton; ***UAE***: Ginsavit; ***UK***: Multiron; Neovita; Pharmaton; Red Kooga Co-Q-10 and Ginseng; Regina Royal Concorde; ***Ukr.***: Alfagin (Алфагин); Energin (Энергин); Ginsomin (Гинсомин); Huato Pills (Болюсы Хуато); Mammoleptin (Маммолептин); Rotavit Royal (Ротавит Ройял); Theravit Antistress (Теравит Антистресс); Theravit Tonic (Теравит Тоник)†; Vitrum Energy (Витрум Энерджи); Wellman (Велмен); Yohimbex-Garmonia (Йохимбекс-Гармония); ***USA***: Clinical Nutrients 50-Plus Men; Dexatrim Max Daytime Appetite Control; Immunicare; ***Venez.***: Energyvit; Hivit; Kinerton; Multivit Natura; Pharmorat; Sengobil; Vigoran.

Homoeopathic Preparations. ***Austral.***: Nervatona Focus; ***Austria***: Erbiode-Starkungstropfen; Memoria; Orgafem; Selenium Med Complex; ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Formula FA 224†; ***Cz.***: Vita C-R15 forte†; ***Fr.***: Selenium Complexe No 99; ***Ger.***: K 1000; Manuia; Neuri-cyl N Ho-Len-Complex; Neuro-Ginsan N; Schworocor A; Tondinel; ***Rus.***: Damiana-Plus (Дамиана-Плюс); Memoria (Мемория); ***Ukr.***: Memoria (Мемория).

Pharmacopoeial Preparations

USNF 31: American Ginseng Capsules;
USP 36: American Ginseng Tablets; Asian Ginseng Tablets.

Glatiramer Acetate *(BAN, USAN)*

COP-1; Copolímero i; Copolymer 1; Glatirameeriasetaatti; Glatiramer, acetato de; Glatiramer Asetat; Glatirameracetat; Glatirameri Acetas; Глатирамер Ацетат.

L-Glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate.

CAS — 28704-27-0 (glatiramer); 147245-92-9 (glatiramer acetate).
ATC — L03AX13.
ATC Vet — QL03AX13.
UNII — 5M691HL4BO.

Uses and Administration

Glatiramer acetate, a random polymer of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, is a polypeptide that has some structural resemblance to myelin basic protein. It is used to reduce the frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis (p. 996.3), including patients with a well defined first clinical episode and deemed to be at high risk of developing clinically definite multiple sclerosis. Although its precise mechanism of action in multiple sclerosis is unknown, it is thought to modify immune processes involved in the pathogenesis. Glatiramer acetate is given by subcutaneous injection in a dose of 20 mg once daily. It should not be given by the intravenous or intramuscular route. An oral formulation has been investigated with disappointing results.

Multiple sclerosis. Reviews[1,2] and a meta-analysis[3] of controlled studies of glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis concluded that it is of benefit, although one systematic review[4] questioned this and failed to find evidence to support its routine use. It also produced similar results to interferon beta-1b in a comparative study[5] that assessed disease activity through monthly MRI scans for up to 2 years. Early treatment with glatiramer acetate in patients with clinically isolated syndrome who are at risk of developing multiple sclerosis significantly reduced the frequency of conversion to clinically definite disease and delayed the occurrence of a second attack.[6]

The mechanism of action of glatiramer acetate has also been reviewed.[7,8]

1. Simpson D, *et al*. Glatiramer acetate: a review of its use in relapsing-remitting multiple sclerosis. *CNS Drugs* 2002; **16:** 825–50.
2. Ruggieri M, *et al*. Glatiramer acetate in multiple sclerosis: a review. *CNS Drug Rev* 2007; **13:** 178–91.
3. Boneschi FM, *et al*. Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials. *Multiple Sclerosis* 2003; **9:** 349–55.
4. Munari L, *et al*. Therapy with glatiramer acetate for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 09/01/08).
5. Cadavid D, *et al*. Efficacy of treatment of MS with IFN β -1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology* 2009; **72:** 1976–83.
6. Comi G, *et al*. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1503–11.
7. Schrempf W, Ziemssen T. Glatiramer acetate: mechanisms of action in multiple sclerosis. *Autoimmun Rev* 2007; **6:** 469–75.
8. Racke MK, *et al*. The mechanism of action of glatiramer acetate treatment in multiple sclerosis. *Neurology* 2010; **74** (suppl 1): S25–S30.

Adverse Effects and Precautions

Immediate post-injection reactions are common with glatiramer acetate and include chest pain, palpitations or tachycardia, dyspnoea, throat constriction, urticaria, flushing (vasodilatation), and anxiety. These reactions are generally short-lived and resolve spontaneously. They have generally occurred only some months after treatment with glatiramer was started. Other common adverse effects include asthenia, nausea, vomiting, constipation, rash, arthralgia, back pain, and dizziness. Convulsions and anaphylactoid reactions have been reported rarely.

Antibodies to the drug develop with chronic therapy but are of unknown clinical significance. Pain, erythema, inflammation, mass, pruritus, and induration may occur at the injection site; localised lipoatrophy and, rarely, skin necrosis has also been reported.

Glatiramer acetate should be given with caution to patients with pre-existing cardiac disorders; such patients should be followed up regularly during treatment.

References.

1. Ziemssen T, *et al.* Risk-benefit assessment of glatiramer acetate in multiple sclerosis. *Drug Safety* 2001; **24:** 979–90.

Anaphylaxis. A systemic anaphylactic reaction to glatiramer acetate developed in a patient who showed a strong immunoglobulin response including specific immunoglobulin E.[1]

1. Rauschka H, *et al.* Severe anaphylactic reaction to glatiramer acetate with specific IgE. *Neurology* 2005; **64:** 1481–2.

Effects on the skin. Localised lipoatrophy at the injection site developed in 6 patients receiving glatiramer acetate.[1] Examination of 76 patients over a 6-month period in one centre[2] revealed evidence of lipoatrophy in at least one injection site in 34 patients; of these, 5 cases were severe. Prevalence of lipoatrophy was much higher than expected, and in some cases, it occurred only a few months after treatment started.[2]

Erythema nodosum confirmed by biopsy has been reported in one patient;[3] spontaneous resolution occurred without stopping treatment.

1. Drago F, *et al.* Localized lipoatrophy after glatiramer acetate injection in patients with remitting-relapsing multiple sclerosis. *Arch Dermatol* 1999; **135:** 1277–8.
2. Edgar CM, *et al.* Lipoatrophy in patients with multiple sclerosis on glatiramer acetate. *Can J Neurol Sci* 2004; **31:** 58–63.
3. Thouvenot E, *et al.* Erythema nodosum and glatiramer acetate treatment in relapsing-remitting multiple sclerosis. *Multiple Sclerosis* 2007; **13:** 941–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glatiramer acetate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 31/10/11)

Interactions

UK licensed product information reports that an increased incidence of injection-site reactions to glatiramer acetate has been seen in patients also given corticosteroids.

Pharmacokinetics

A substantial fraction of a subcutaneous dose of glatiramer is believed to be hydrolysed locally. Some of the injected dose is also presumed to enter the lymphatic system, either intact or partially hydrolysed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Copaxone; ***Austral.***: Copaxone; ***Austria***: Copaxone; ***Belg.***: Copaxone; ***Braz.***: Copaxone; ***Canad.***: Copaxone; ***Cz.***: Copaxone; ***Denm.***: Copaxone; ***Fin.***: Copaxone; ***Fr.***: Copaxone; ***Ger.***: Copaxone; ***Gr.***: Copaxone; ***Hung.***: Copaxone; ***Irl.***: Copaxone; ***Israel***: Copaxone; ***Ital.***: Copaxone; ***Mex.***: Copaxone†; ***Neth.***: Copaxone; ***Norw.***: Copaxone; ***NZ***: Copaxone; ***Pol.***: Copaxone; ***Port.***: Copaxone; ***Rus.***: Copaxone (Копаксон); ***S.Afr.***: Copaxone; ***Spain***: Copaxone; ***Swed.***: Copaxone; ***Switz.***: Copaxone; ***Turk.***: Copaxone; ***UK***: Copaxone; ***Ukr.***: Copaxone (Копаксон); ***USA***: Copaxone.

Glicofosfopeptical

AM-3; Fosfoglicopeptical; Glycophosphopeptical; Immunoferon; Иммуноферон.
CAS — 87139-86-4.

Profile

Glicofosfopeptical is a polysaccharide-protein complex that is reported to possess immunostimulant properties. It has been given orally in doses of 1 g every eight hours.

References.

1. Alvarez-Mon M, *et al.* Treatment with the immunomodulator AM3 improves the health-related quality of life of patients with COPD. *Chest* 2005; **127:** 1212–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Inmunol; ***Port.***: Imunoferon; ***Spain***: Inmunoferon.

Glucomannan

E425; Glucomanano; Harina de Konjac; Konjac Flour; Konjac Mannan; Глюкоманнан.
UNII — 36W3E5TAMG.

Profile

Glucomannan, a powdered extract from the tubers of *Amorphophallus konjac*, has been promoted as an anorectic. It has been claimed to reduce the appetite by absorbing liquid in the gastrointestinal tract. It is also used in the treatment of constipation and hyperlipidaemia. Glucomannan has been investigated as a dietary adjunct in the management of diabetes mellitus.

There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if it is swallowed dry. Therefore, it should always be taken with sufficient fluid and should not be taken immediately before going to bed. It should be avoided in patients who have difficulty swallowing.

References.

1. Henry DA, *et al.* Glucomannan and risk of oesophageal obstruction. *BMJ* 1986; **292:** 591–2.
2. Renard E, *et al.* Noninsulin-dependent diabetes and glucose intolerance: effect of glucomannan fibre on blood glucose and serum insulin. *Sem Hop Paris* 1991; **67:** 153–7.
3. Vuksan V, *et al.* Beneficial effects of viscous dietary fiber from konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. *Diabetes Care* 2000; **23:** 9–14.
4. Staiano A, *et al.* Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. *J Pediatr* 2000; **136:** 41–5.
5. Loening-Baucke V, *et al.* Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Abstract: *Pediatrics* 2004; **113:** 259. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/3/e259.pdf (accessed 16/08/10)
6. Keithley J, Swanson B. Glucomannan and obesity: a critical review. *Altern Ther Health Med* 2005; **11:** 30–4.
7. Vanderbeek PB, *et al.* Esophageal obstruction from a hygroscopic pharmacobezoar containing glucomannan. *Clin Toxicol* 2007; **45:** 80–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Dietmann; ***Ital.***: Cadicioc; Dicoplus; Dietoman; NormaLine; ***Mex.***: Dietoman; Esbeltex; ***Singapore***: Dulcofibre.

Multi-ingredient Preparations. ***Arg.***: Adelgacin; Green Diet; KLB6 Fruit Diet; ***Chile***: Delgadol Fibra; ***Fr.***: Filigel†; ***Ital.***: Agioslim; Ecamannan; Fibrovit; Glucoman; Lactomannan; ***Philipp.***: Thinber Fiber Complex†.

Gluconic Acid

Dextronic Acid; E574; Glycogenic Acid; Maltonic Acid; Pentahydroxycaproic Acid; Глюконовая Кислота.
D-Gluconic acid.
$C_6H_{12}O_7$=196.2
CAS — 526-95-4.
UNII — R4R8J0Q44B.

Gluconolactone

E575; Glucono delta-lactone; Glucono-delta-lactone; 1,5-Gluconolactone; D-Glucono-1,5-lactone; Глюконолактон.
D-Gluconic acid δ-lactone.
$C_6H_{10}O_6$=178.1
CAS — 90-80-2.
UNII — WQ29KQ9POT.

Pharmacopoeias. In *US.*

USP 36: (Gluconolactone). A fine, white, practically odourless, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Profile

Gluconolactone is hydrolysed to gluconic acid, a polyhydroxy acid. It has similar properties to the alpha hydroxy acids glycolic acid (p. 1704.3) and mandelic acid (p. 320.3) and has been used in skin disorders and for urinary catheter care. Gluconolactone and gluconic acid are also used as food additives.

References.

1. Grimes PE, *et al.* The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis* 2004; **73** (suppl 2): 3–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: NeoStrata.

Multi-ingredient Preparations. ***Arg.***: Neoceuticals Gel de Limpieza Facial; NeoStrata; ***Austral.***: NeoStrata; ***Canad.***: NeoStrata†; ***Chile***: NeoStrata; NeoStrata; NeoStrata; Teen Derm K; ***Fr.***: Ruboderm; ***Indon.***: Hidrogel†; ***Turk.***: NeoStrata; ***UK***: Uriflex R; Uro-Tainer Solution R; ***USA***: Renacidin.

Glucosamine *(USAN, rINN)*

Chitosamine; Glucosamina; Glucosaminum; NSC-758; Глюкозамин.
2-Amino-2-deoxy-β-D-glucopyranose.
$C_6H_{13}NO_5$=179.2
CAS — 3416-24-8.
ATC — M01AX05.
ATC Vet — QM01AX05.
UNII — N08U5BOQ1K.

Glucosamine Hydrochloride *(rINNM)*

Chitosamine Hydrochloride; Glucosamina, hidrocloruro de; Glucosamine, Chlorhydrate de; Glucosamini Hydrochloridum; Glukozaminy chlorowodorek; Hidrocloruro de glucosamina; Глюкозамина Гидрохлорид.
$C_6H_{13}NO_5$,HCl=215.6
CAS — 66-84-2.
UNII — 750W5330FY.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Glucosamine Hydrochloride). It is isolated from natural sources or produced by fermentation. A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 3.0 to 5.0.

USP 36: (Glucosamine Hydrochloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Glucosamine Sulfate Potassium Chloride

$(C_6H_{14}NO_5)_2SO_4$,2KCl=605.5

Pharmacopoeias. In *US.*

USP 36: (Glucosamine Sulfate Potassium Chloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Glucosamine Sulfate Sodium Chloride

$(C_6H_{14}NO_5)_2SO_4$,2NaCl=573.3

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Glucosamine Sulfate Sodium Chloride). It is prepared from glucosamine hydrochloride isolated from natural sources or produced by fermentation, and sodium sulfate. A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 3.0 to 5.0.

USP 36: (Glucosamine Sulfate Sodium Chloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Uses and Administration

Glucosamine is a natural substance found in chitin, mucoproteins, and mucopolysaccharides. It is involved in the manufacture of glycosaminoglycan, which forms cartilage tissue in the body; glucosamine is also present in tendons and ligaments. Glucosamine must be synthesised by the body but the ability to do this declines with age. Glucosamine has therefore been given for its supposed chondroprotective action in musculoskeletal and joint disorders including osteoarthritis (see below). Glucosamine may be isolated from chitin or prepared synthetically; it has also been given as the hydrochloride, sulfate, and hydroiodide salts, or as complexes such as glucosamine sulfate potassium chloride, glucosamine sulfate sodium chloride, and glucosamine hydrochloride magnesium sulfate.

Osteoarthritis. Glucosamine and its salts are widely available as licensed products or so-called 'health supplements' used for the management of osteoarthritis (p. 12.3); they may be combined with other substances supposed to be of benefit, including chondroitin (p. 2476.1), vitamins, and various herbs. Meta-analyses[1,2] of randomised placebo-controlled studies concluded that while there was some evidence for efficacy of glucosamine and chondroitin in the treatment of osteoarthritis, methodological flaws and publication bias had led to exaggeration of its potential benefit,[1] and that further studies are needed to fully characterise their disease-modifying properties.[2] A systematic review[3] of the use of glucosamine for osteoarthritis that included later controlled studies concluded that glucosamine is as safe as placebo but there was little evidence of improvement in pain or function. A further randomised controlled study[4] in 222 patients with hip osteoarthritis found no benefit after treatment with glucosamine for 2 years compared with placebo, and a meta-analysis[5] of controlled studies of chondroitin for osteoarthritis of the knee or hip concluded that chondroitin had minimal or no ben-

The symbol † denotes a preparation no longer actively marketed

efit. Further research is needed to confirm whether there are differences in efficacy between glucosamine salts, preparations, or routes, and when used with other agents (e.g. chondroitin) or in different patient subgroups.[3] A large multicentre double-blind study[6] in 1583 patients with symptomatic knee osteoarthritis to compare glucosamine and chondroitin, either alone or in combination, found no clear evidence of benefit in pain reduction compared with placebo or celecoxib, although there was a tendency to more positive results in a subset of patients with moderate to severe knee pain. An evidence-based report[7] into the use of complementary medicines to treat rheumatic diseases concluded that despite some mixed results, the majority of controlled studies of glucosamine sulfate showed significant clinical benefit whereas the evidence for glucosamine hydrochloride was either unavailable or less convincing. For chondroitin, the evidence from controlled studies was inconsistent, although the majority showed significant clinical benefit for pain reduction.

1. McAlindon TE, *et al*. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000; **283:** 1469–75.
2. Richy F, *et al*. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003; **163:** 1514–22.
3. Towheed T, *et al*. Glucosamine therapy for treating osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 14/05/08).
4. Rozendaal RM, *et al*. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008; **148:** 268–77.
5. Reichenbach S, *et al*. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007; **146:** 580–90.
6. Clegg DO, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; **354:** 795–808.
7. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Adverse Effects and Precautions

Effects on glucose metabolism. Glucosamine has a role in glucose metabolism, increasing insulin resistance in skeletal muscle,[1,2] and this has raised concerns about its safety profile in diabetic patients.[3] However, alteration of glycaemic homoeostasis was not found in a 3-year randomised controlled study in patients without diabetes.[4] A review[5] of the literature found limited data on diabetic patients taking glucosamine supplements, and recommended close monitoring of blood glucose levels in this group until more data are available.

1. Adams ME. Hype about glucosamine. *Lancet* 1999; **354:** 353–4.
2. Chan NN, *et al*. Drug-related hyperglycemia. *JAMA* 2002; **287:** 714–15.
3. Chan NN, *et al*. Glucosamine sulphate and osteoarthritis. *Lancet* 2001; **357:** 1618–9.
4. Reginster JY, *et al*. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; **357:** 251–6.
5. Stumpf JL, Lin SW. Effect of glucosamine on glucose control. *Ann Pharmacother* 2006; **40:** 694–8.

Effects on the skin. The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] has received 51 reports of allergic skin reactions with glucosamine, including erythematous rash, angioedema, urticaria, rash, and pruritus. It was noted that some preparations contain glucosamine sourced from seafood and therefore people with an allergy to shellfish may be at greater risk for hypersensitivity reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Skin reactions with glucosamine. *Aust Adverse Drug React Bull* 2005; **24:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0512.pdf (accessed 14/05/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glucosamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/10/11)

Interactions

For reference to the effect of glucosamine on warfarin, see Dietary Supplements under Interactions of Warfarin, p. 1533.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adaxil; Artrilase; Asoglutan; Baliartrin Potasico; Baliartrin; Belmalen Plus; Findol; Gluco Arrumalon; Glucometil K; Glucotrin Flex; Glucotrin Pro-Flex; Mecanyl K; Mecanyl; Ostatac; Pertinar; Vartalon Complemento; Vartalon K; ***Austral.***: GenFlex†; Joints in Motion; PM Joint-Aid†; ***Austria***: Dona; Flexove; Progona; ***Belg.***: Dolenio; Donacom; Voltaflex†; ***Braz.***: Artoglico; Dinaflex; Faximin; Glucoreumin; Injeflex; Ortosamin; Sulglic; ***Chile***: Artridol; Bioflex†; Dinaflex; Reufin; ***China***: Bao Jie Li (保节力); Bu Mai Xin (步迈新); Duan Zheng (端正); Jiu Li (九力); Liu Pu An (留普安); Peitil (培古立); Pu Li (葡立); Pu Li De (普力得); Viartril S (维固力); Wei Er Gu (维尔固); Yi Suo Jie (伊索佳); ***Cz.***: Bayflex; Chondrostad; Dona; Flexove; Gool; Mediflex†; Voltadyn†; ***Denm.***: Dolenio; Giscosamine; Glucomed†; Perigona; ***Fin.***: Arthrimel; Arthryl; Comfora; G-Lenk†; Glucadol; Glucorix; Glucosine; Perigona; ***Fr.***: Dolenio; Flexea; Osaflexan; Oscart†; Structoflex; Voltaflex; ***Ger.***: Dona; Leka; Mobilat Glucosamin†; Progona; Voltaflex†; ***Gr.***: Anarthril; Arthroloc; Best; Dolenio; Donamin; Donarot; Donarthril; Effer-Activ; Elimer; Energorot; Fragilis; Gioral; Glucasulf; Glucosamil; Glucozant; Glukotral; Gluminal; Glunarot; Glusamon; Gluvedus; Glycefort; Laraned; Lasanol; Lipathrec; Medomin; Minedon; Nerita; Painoff; Recosine; Sacrum; Samiclar; Sufigal; Taredon; Viartril; Viremax; Voltaflex; Xanalife; Zacosteo; ***Hong Kong***: Arthritil†; Aussamin; Cartril-S; Chitaq; Doctor's Choice for Joints; Donna†; F-Vialin†; MarinEx; Vialbone†; Viartril S; Vidatril†; Vitoport; Vocarxil; Voltaflex; ***Hung.***: Dona; Gool; ***India***: Artica; Cartiel; Cartigen; Cartilamine; Dietmann; Flextra; Glucart; Glucosam; Jointace; Kondro-OD; Lubrijoint; Osicare-DS; ***Indon.***: Cartos; Fitbon; Mediflex; Oste OD; Reflexor; ***Irl.***: Arthriaid; Arthrimel; Dolenio; Dona; Glusamin; Osteoeze; Osteole; Viartril S; ***Israel***: Arthryl; ***Ital.***: Dona; Glexar; Minarex; Xicil; ***Malaysia***: Artril; Artronil; Cartril-S; Cosamine†; Coxium; Donna; Flexsa; Osteofree; Procosa†; Viartril S; ***Mex.***: Artriman; Faximin; Flaxblutriz; Vartalon; ***Neth.***: Cartimin; Dolenio; Donacom; Glucofleks†; Glucomed; Voltaflex Glucosamine; ***Norw.***: Donacom; Gluxine†; Movere†; Perigona; Samin; ***Philipp.***: Cartrosyn; Flexsa; Glucart; Poly-Nag†; Sancom; Synotec; Viartril S; ***Pol.***: Actistav; Arthryl; Flexove; ***Port.***: Arthramina†; Dolenio; Glarzena; Glucomed; Glucosine; Glufan; Glusina; Minitil; Rieg†; Viartril S; ***Rus.***: Dona (Дона); Elbona (Эльбона); Pharmaskin (Фармаскин); ***Singapore***: ArthriCare; Artril†; Artrilase; Artronil†; Cartril-S†; Coxium; Flexsa; Gluco-S; Glutilage; Olivenol Livin' Active; Osteofree; Viartril S; Vital; ***Spain***: Acenam; Arafisio; Cartisorb; Coderol; Glucomed†; Glufan; Gluniro; Hespercorbin; Mascartil; Xicil; ***Swed.***: Artrox; Comfora; Donacom†; Glucomed; Glucosine; Perigona; ***Switz.***: Voltaflex†; ***Thai.***: Arthro-S; Artronil; Athril; Bio-Glucosamine; Biotril-s; BOS; Caseal; Coxium; Cuine; Flexsa; Gaxium; Gluco-S; Glucosa; Glucosamate; Glucotril; Glumesa; Glusa†; Glusafex; Glusamine†; Kosamine; Osamine; Prosulf; Rheutril; Viaflex; Viartril S; Viartril S; Zynotril; ***Turk.***: Dona; ***UK***: Alateris; Dolenio; Flexeze; Flexi-Melt; Glusartel; Joint-e-Licious; ***Ukr.***: Arthron Flex (Артрон Флекс); Artiflex (Артифлекс); Dona (Дона); Flex-A-Min Glucosamin (Флекс-А-Мин Глюкозамин)†; Sinarta (Синарта); ***Venez.***: Vartalon; Viartril S.

Multi-ingredient Preparations. ***Arg.***: Adaxil Forte; Adaxil Plus; Artrilase Complex; Artrocaptin; Asotrex; Baliartrin Duo; Cartiburon Flex; Cartiflex Forte; Dolo Asotrex; Dolo Baliartrin; Ecosamina; Etinox; Etinox; Finartrit; Findol Plus; Gluco Arrumalon Duo; Glucobefol†; Glucocartiflex; Glucometil 3; Glucometil K Duo; Glucometil Plus; Glucosamina Sport; Glucotrin Forte; Glucotrin VL; Mecanyl Duo; Mecanyl K Duo; Nectar G; Ostatac Duo; Reumosan Compuesto; Sigmaflex; Vartalon Duo K; Vartalon Duo; ***Austral.***: AB Ausbiobone; AB Carsa Giox; AB Oriostin; Accelerex; Arthro-Eze; Bioflex†; Bonlutin; Formula for Joints; Full Motion; GenFlex 3†; GenFlex NKO†; GenFlex Plus†; Joint Ease; Joint Formula Advanced with MSM Booster; Joint Formula Advanced; Joint Mobility†; MeticGlucotin; Osteo-Relief Plus MSM; Osteo-Relief; OsteoEze Active + MSM; OsteoEze Active; OsteoEze Bone & Joint; PM Joint-Care; PM Metic-Glucotin; ***Braz.***: Artrolive; Condroflex; ***Canad.***: Procosa; Restorativ Glucosamine Muscle and Joint; ***Chile***: Artridol Duo; Dinaflex Duo; Eniflex Duo; Euroflex; Flexure; Hiperflex; Osteo Bi-Flex†; ***China***: Ai Mei Xing (爱美幸); ***Fr.***: Arthrobiane; Capsaine; Chondrosteo; Cicatendon; Cuivramine; Dexsil Articulations; Dexsil Sport; Fleximax; Glucarthroz; Kinesamine; Rhumadol; Synotabs; ***Hong Kong***: Arthritil Plus†; Doctor's Choice Fortified Joint Support†; Procosa II†; ***Hung.***: Porcerosito; ***India***: Admine; Alnamax-G; Altocerin-GM; Arth; Arthar; Artheal; Arthocare DS; Arthocare; Arthocerin-G; Arthodia-G; Arthrovit Plus; Artifix; Baknil; Bigjoint; Bonit Join; Bonjo Aid; Carticare; Cartifix; Cartigen Plus; Cartigen; Cartilamine DS; Cartilamine Forte; Cartilamine Total; Cartilamine-SR; Cartimost GM; Cartipro; Cartisafe; Cartisark; Cartispan; Cartivit; Cartiwel; Cartiz-GM; Cartiz; Cartizole Plus; Cartup; Compensate; Conjoint; Cool-Joint; Cool-Joint; Cosa-G; Cosantin; Dicimax-G; Difirin Plus; Dims-GM; DN Plus; Durajoint-GM; Dycerin-GM; Flexi Cap; Flexibel; Flextra-D; Free M; Freeflex; Fremov-ME; Fremov; GC Flex; Gencart; Glortho Forte; Glucomade-500; Glucomade; Glucovit Plus; Glutin; GSO4; Icerin-GM; Intecar; Jaizzy-GM; Joint Guard; Jointace Forte; Jointace-DN; Jointop; Jonty; Kalhar; Kondro; Lecerein-GM; Lefax-G; Mecocas-Ortho; Mega Freeflex; Mericart; Mobijoint; Mycer G; Necare; Neuromed; Nucart-OA; Nurokind Ortho; OA Plus; Orbone Forte; Orbone; Ordi-G; Orthocerin-G; Osicare; Ostakair; Ostawin; Osteocip; Osteoflex; Osteojoin-D; Ostifin-G; Ostiwel Forte; Ostiwel; Ostodia-G; Ostofit; Ostop; Ostovit-G; Ostovit; Paclo-GMD; ***Indon.***: Aptivium Optimum Joint Formula†; Artriox†; Artritin; Artro Plus; Artro; Aviter; Bonic Plus; Bonic; Bonilav; Cartiflex; Cartin; Chondro-PA; Fitajoint; Fitbon Plus; Flexor; Fripos; GCM; Joint Care Plus; Joint Care; Jointace; Jointfit; Jointfit; Jointfit; Lavarix; Maxitrin†; Naturema; Nutrijoint; OA Forte; OA Plus; OA; Osamin; Ositin; Osmetin 3; Oste; Ostela; Osteoflam; Osteokom Forte; Osteokom; Osteokom; Osteonic; Osteor Plus; Osteor-C; Osteor; Osteotin; Ostine; Ostrimix; Osvion Plus; Rebone; Rheumatin Forte; Rheumatin; Risteon; Triflexor; Triostee; Viopor-M Forte; Viopor-M; Viopor; Viostin Com DS; Viostin Com; Viostin-X; Viusid; Vostem; Vosteon; ***Irl.***: Seven Seas Active Sport†; ***Israel***: Mega Gluflex with MSN; Mega Gluflex; ***Ital.***: Cartago; Cartijoint†; Condrorexil; Fitogenase; Ginepausil; Joint Support; Osteoclar; Reumil; Reumilase Plus; Reumilase SD; Reumilase; Synchrocell; Vitreoclar Crono; Vitreolux; ***Malaysia***: Conart; Cosamine Plus; ***Mex.***: Actiman; Artiflex; Artrifar; Mex-Amina; Procosa II; Vartalon Compositum; ***Mon.***: Algicuivre; ***Philipp.***: Artiflex; Cartifast-C; Flexxbon; Osteoaid; Ruflex; ***Port.***: Synchrocell; Synchrovit; ***Rus.***: Artra (Артра); KONDROnova (КОНДРОнова); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); ***S.Afr.***: ProFLEX 750†; ProFLEX†; ***Singapore***: Arthro-Flex; Articolase (w/glucosamine); Artril C†; Artrilase; Cartipro; Glucocal; Glutilage Plus; Joint Care; JointFlex; Procosa II†; Ruflex; Scar Esthetique; Seven Seas JointCare Max; Seven Seas JointCare; ***Spain***: Droglican; ***Thai.***: Artrofort Complex; ***Turk.***: Jointace; Ultimate; ***UK***: Arheumacare; BackOsamine; Flexeze; GlucOsamax; GlucoSelene; Healtheries Musseltone & Glucosamine; Joint Action; Jointace; Jointace; Jointace; JointCare Max; ***Ukr.***: Arthron Complex (Артрон Комплекс); Arthron-Triactive (Артрон Триактив); Artritosamin (Артритозамин); Chondroitin Complex (Хондроитин Комплекс); Flex-A-Min Complex (Флекс-А-Мин Комплекс)†; Hondra-Syla (Хондра-Сила); Movex Active (Мовекс Актив); Movex Comfort (Мовекс Комфорт); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Osteoartisi Max (Остеоартизи Макс); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); ***USA***: Arthritis Free; Cosamin; Dorofen; Duraflex Comfort; Stopain Cold Extra Strength; ***Venez.***: Artrosamin.

Pharmacopoeial Preparations

USP 36: Glucosamine and Chondroitin Sulfate Sodium Tablets; Glucosamine and Methylsulfonylmethane Tablets; Glucosamine Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets.

Glucose Oxidase *(USAN)*

Corylophyline; EC 1.1.3.4; β-D-Glucopyranose aerodehydrogenase; Glucosa oxidasa; GO; Microcide; Notatin; P-FAD; Глюкооксидаза.

CAS — 9001-37-0.

UNII — 0T8392U5N1.

Profile

Glucose oxidase is an enzyme obtained from certain fungi that catalyses the oxidation of glucose to gluconic acid with the concomitant production of hydrogen peroxide. It is used for its preservative properties as an additive in certain foods, sometimes with catalase (p. 2472.2). It is also used in fertility tests and tests of diabetic control. It has been used as an ingredient of topical oral preparations for the treatment of dry mouth (p. 2175.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Flaminal; ***Singapore***: Biotene†; Biotene; Biotene; OralSeven; OralSeven; OralSeven; ***UK***: Biotene Dry Mouth; Biotene Oralbalance; Flaminal; ***USA***: Biotene with Calcium.

Pharmacopoeial Preparations

USP 36: Glucose Enzymatic Test Strip.

Glucose Tests

Glucosa, pruebas de.

Profile

Several tests are available so that patients with diabetes mellitus (p. 461.1) can monitor their disease. Tests can be used to detect the presence of glucose in the urine and some of the preparations are used to detect several substances in the urine. These tests are easy to carry out but are not considered reliable enough for insulin-dependent patients who should ideally check their blood-glucose concentrations using one of the available blood tests. Diabetic clinics often measure the degree of haemoglobin glycation (HbA_{1c}) as an indicator of mean blood-glucose control over a period of weeks or months.

Urine tests generally use either the copper-reduction method or the glucose-oxidase method and both produce a colour change in the presence of glucose. Blood tests generally use the glucose-oxidase method; they may be read visually or by means of a meter. A meter gives the more precise reading. Patients should be properly trained in the use of these tests and in the interpretation of the results; they should be aware that concomitant drug therapy might affect the result.

Precautions. Preparations that contain, or are metabolised to, maltose (p. 2081.1), galactose (p. 1588.1), or xylose (p. 2649.2) may interfere with the results from glucose tests based on dehydrogenase pyrroloquinolinequinone

(GDH-PQQ) monitoring systems as these are non-specific for glucose. Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. MHRA. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Accu-Chek; Accutrend Glucosa; Achtung; Ascensia; Betachek; Contour TS; Dextrostix; Diastix; Elite†; Glucostix; One Touch; Precision Plus; Prestige; Prodigy Autocode; Sure Step; ***Austral.***: Accu-Chek; Ascensia†; Betachek; BM-Test BG†; BM-Test Glycemie 20-800†; Clinistix†; Clinitest†; Diabur-Test 5000†; Diastix; Esprit†; Glucoflex-R; Glucostix; Glucotrend†; Medi-Test Glucose†; Omnitest; Optium; Precision Plus†; ***Braz.***: Accu-Chek; Accutrend†; Glicofita Plus†; Haemo-Glukotest†; ***Canad.***: Accu-Chek†; Ascensia Elite; Chemstrip bG†; Clinistix†; Clinitest†; Diastix†; One Touch†; Sof-Tact†; ***Chile***: Accu-Chek; Accutrend Glucosa†; Ascencia; Contour; Major II; ***Fr.***: Accu-Chek; Ascensia; Caresens N; Glucomen†; Medisense†; One Touch; ***India***: Diastix†; Haemo-Glukotest; ***Irl.***: Accu-Chek; BM-Accutest†; Clinistix†; Clinitest†; Combina Glucose; Diabur-Test 5000†; Diastix; Freestyle†; Glucomen†; Glucometer Elite†; Glucostix†; Glucotide†; One Touch†; PocketScan†; ***Ital.***: Accu-Chek; Accutrend Glucose; Ascensia; Clinistix; Clinitest; Diabur-Test 5000; Diastix; Euroflash; EZ Smart; Finetouch; Freestyle; Glucocard; Glucoscan; One Touch; Optium Plus; Uni-Check†; ***Mex.***: Accu-Chek; Accutrend Glucose†; Clinitest; Dextrostix; Diabur-Test 5000†; Diastix; Haemo-Glukotest 20-800†; ***NZ***: Accu-Chek; Clinistix†; Clinitest†; Diabur-5000†; Diastix†; ***Port.***: Clinistix†; Glucocard†; Glucodisc; Glucostix†; One Touch; ***UK***: Ascensia Glucodisc; BM-Accutest; BM-Test 1-44; Breeze 2; Clinistix; Clinitest; Contour; Diabur-Test 5000; Diastix; ExacTech; Freestyle; Glucoflex-R; Glucomen; Hypoguard Supreme Plus; Medi-Test Glucose; Medisense; Optium Plus; ***USA***: Accu-Chek Advantage; Choice DM; Diascan; First Choice; Glucofilm; Glucostix; One Touch.

Pharmacopoeial Preparations

USP 36: Glucose Enzymatic Test Strip.

Glucuronic Acid

Глюкуроновая Кислота.

D-Glucuronic acid.

$C_6H_{10}O_7$=194.1

CAS — 576-37-4 (D,L-glucuronic acid); 6556-12-3 (D-glucuronic acid).

UNII — 8A5D83Q4RW.

Glucurolactone *(rINN)*

Glucurolactona; Glucurolactonum; D-Glucuronic Acid Lactone; Glucuronolactone; Глюкуролактон.

D-Glucofuranuronic acid γ-lactone.

$C_6H_8O_6$=176.1

CAS — 63-29-6; 32449-92-6.

UNII — XE4Y3016M9.

Glucuronamide *(BAN, rINN)*

Glucuronamida; Glucuronamidum; Глюкуронамид.

β-D-Glucopyranuronamide.

$C_6H_{11}NO_6$=193.2

CAS — 3789-97-7 (glucuronamide); 3574-23-0 (D-glucuronamide); 61914-43-0 (β-D-glucuronamide).

UNII — 1Q5MP1Z8HW.

Sodium Glucuronate

Sodu glukuronian; Глюкуронат Натрия.

$C_6H_9NaO_7$=216.1

CAS — 14984-34-0.

UNII — 631391W27S.

Profile

Glucuronic acid is one of the components of hyaluronic acid (p. 2526.2) and also has an important role in the metabolism of many endogenous substances, drugs, and toxins. It has been used topically as a potential precursor of hyaluronic acid, and has also been used as a nutritional supplement. Glucuronamide, glucurolactone (glucuronic acid lactone), diolamine glucuronate, and other glucuronates have also been used as supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Qi Gu Le (奇谷乐); Wei Mei Le (唯每乐); Xiu Fu (休孚); You Ni Kai (尤尼凯).

Multi-ingredient Preparations. ***Arg.***: Stimulnerv; ***Belg.***: Guronsan†; ***Fr.***: Guronsan; Sarvit a la glucuronamide†; ***Hong Kong***: Jetepar†; ***Ital.***: Reumilase; Synchrocell; ***Malaysia***: Jetepar; ***Philipp.***: Jetepar; ***Port.***: Guronsan; Synchrocell; Synchrovit; ***S.Afr.***: Guronsan C; ***Singapore***: Jetepar†; ***Spain***: Guronsan†.

Gluten

Глютен.

UNII — 1534K8653J (wheat gluten).

Profile

Gluten is a mixture of 2 proteins, gliadin and glutenin, and is present in wheat flour and to a lesser extent in barley and rye. Gliadin is a prolamine, one of the 2 chief groups of plant proteins, and glutenin belongs to the other main group termed glutelins.

Gluten is of medicinal and pharmaceutical interest in that patients with coeliac disease (p. 2043.1) are sensitive to the protein fraction of gluten contained in the normal diet. Treatment consists of the use of gluten-free diets; gluten-free foods are available.

A gluten-free diet may also be beneficial in patients with dermatitis herpetiformis (p. 1683.2).

Glycerol *(rINN)* ⊗

E422; Glicerin; Glicerina; Glicerol; Glicerolis; Gliserin; Gliserol; Glisin; Glycerin; Glycerine; Glycérol; Glycerolum; Glyseroli; Глицерол.

Propane-1,2,3-triol.

$C_3H_8O_3$=92.09

CAS — 56-81-5.

ATC — A06AG04; A06AX01.

ATC Vet — QA06AG04; QA06AX01; QA16QA03.

UNII — PDC6A3C0OX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Eur. and *Int.* also include Glycerol (85 per cent).

Ph. Eur. 8: (Glycerol). A clear, colourless or almost colourless, very hygroscopic, syrupy liquid, unctuous to the touch. Miscible with water and with alcohol; slightly soluble in acetone; practically insoluble in fixed oils and in essential oils. Store in airtight containers.

USP 36: (Glycerin). A clear, colourless, hygroscopic, syrupy liquid. Has not more than a slight characteristic odour, which is neither harsh nor disagreeable. Miscible with water and with alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Its solutions are neutral to litmus. Store in airtight containers.

Incompatibility. Strong oxidising agents form explosive mixtures with glycerol. Black discoloration has been reported with glycerol and bismuth subnitrate or zinc oxide when exposed to light.

Sterilisation. Sterilisation of glycerol by membrane filtration is described.[1]

1. McCluskey SV. Sterilization of glycerin. *Am J Health-Syst Pharm* 2008; **65:** 1173–6.

Uses and Administration

Glycerol is an osmotic dehydrating agent with hygroscopic and lubricating properties. When given orally or parenterally, glycerol increases the plasma osmolality, resulting in the movement of water by osmosis from the extravascular spaces into the plasma.

Glycerol is given orally for the short-term reduction of vitreous volume and intra-ocular pressure before and after ophthalmic surgery, and as an adjunct in the management of acute glaucoma (p. 1999.1). Its onset of action is rapid, with a maximal reduction in intra-ocular pressure occurring about 1 to 1½ hours after a dose; the duration of action is about 5 hours. The usual initial dose of glycerol is 1 to 1.8 g/kg given as a 50% solution. There can be problems of palatability when glycerol solutions are given orally; chilling or flavouring the solutions may help.

Glycerol may be applied topically to reduce corneal oedema, but as the effect is only transient its use is largely limited to an adjunct in eye examination and diagnosis. Glycerol eye drops can be painful on instillation and use of a local anaesthetic beforehand has been recommended.

Glycerol has also been given orally or intravenously to reduce intracranial pressure (see below).

Glycerol may be used rectally as suppositories or a solution in single doses to promote faecal evacuation in the management of constipation (p. 1804.3). It usually acts within 15 to 30 minutes. Glycerol is commonly classified as an osmotic laxative but may act additionally or alternatively through its local irritant effects; it may also have lubricating and faecal softening actions.

Glycerol is used as a demulcent in cough preparations (p. 1651.2).

Glycerol has many applications in pharmaceutical formulation; these include its use as a vehicle and solvent, as a sweetening agent, as a preservative in some liquid medications, as a plasticiser in tablet film-coating, and as a tonicity adjuster. It is often included in topical preparations such as eye drops, creams, and lotions as a lubricant and also for its moisturising properties since, when absorbed, its hygroscopic action can enhance moisture retention. Ear drops for the removal of ear wax often contain glycerol as a lubricating and softening agent.

Glycerol is also used as a cryoprotectant in cryopreservation.

Diagnosis of Ménière's disease. Glycerol has been used[1] in the diagnosis of Ménière's disease (p. 611.2) to distinguish potentially reversible cochlear dysfunction from the relatively irreversible pathology of advanced disease, or to predict the results of endolymphatic sac surgery. Glycerol is given orally to reduce the endolymphatic fluid volume and pressure and any transient improvement in hearing is measured. However, the adverse effects of glycerol such as headache, nausea, and vomiting can be a problem and the test has been reported to have low sensitivity and to give false-positive results. See also under Effects on the Ears, p. 2518.1.

1. Skalabrin TA, Mangham CA. Analysis of the glycerin test for Meniere's disease. *Otolaryngol Head Neck Surg* 1987; **96:** 282–8.

Raised intracranial pressure. Glycerol has been given intravenously or orally for its osmotic diuretic effect to reduce cerebral oedema and hence decrease the intracranial pressure (p. 1271.3). It is also reported to be able to increase blood flow to areas of brain ischaemia. It has been used in a variety of clinical conditions[1] including cerebral infarction or stroke,[2] Reye's syndrome,[3] and meningitis.[4,5] It has been postulated[5] that glycerol's beneficial action in preventing the neurological sequelae in bacterial meningitis is due to its effects in increasing cerebral plasma osmolality, which reduces cerebral oedema and enhances cerebral circulation by reducing the excretion of cerebrospinal fluid, and that this may be more important than the decrease in intracranial pressure induced by osmotic diuresis. Glycerol has been reported to be ineffective in hepatic coma.[6] Some patients have had serious adverse effects including haemolysis, haemoglobinuria, and renal failure.[7,8]

1. Frank MSB, *et al.* Glycerol: a review of its pharmacology, pharmacokinetics, adverse reactions, and clinical use. *Pharmacotherapy* 1981; **1:** 147–60.
2. Righetti E, *et al.* Glycerol for acute stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/05/06).
3. Nahata MC, *et al.* Variations in glycerol kinetics in Reye's syndrome. *Clin Pharmacol Ther* 1981; **29:** 782–7.
4. Kilpi T, *et al.* Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. *Pediatr Infect Dis J* 1995; **14:** 270–8.
5. Peltola H, *et al.* Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2007; **45:** 1277–86.
6. Record CO, *et al.* Glycerol therapy for cerebral oedema complicating fulminant hepatic failure. *BMJ* 1975; **ii:** 540.
7. Hägnevik K, *et al.* Glycerol-induced haemolysis with haemoglobinuria and acute renal failure: report of three cases. *Lancet* 1974; **i:** 75–7.
8. Welch KMA, *et al.* Glycerol-induced haemolysis. *Lancet* 1974; **i:** 416–17.

Skin disorders. The use of glycerol in skin disorders has been reviewed.[1] The hydrophilic hydroxyl groups present in glycerol are responsible for its properties of hygroscopicity and water solubility, and endogenous glycerol (synthesised in the pilosebaceous unit) has been shown to play a role in skin homoeostasis and maintenance of the function of the epidermal barrier. Glycerol has a long history of use in topical skin formulations and is widely used as an emollient and to improve skin smoothness. A greater understanding of the biological and biophysical effects of glycerol on the skin suggests additional properties of glycerol as a keratolytic, anti-irritant, skin barrier, or UV protectant. It is also reported to have antimicrobial properties, and to promote wound healing.

1. Fluhr JW, *et al.* Glycerol and the skin: holistic approach to its origin and functions. *Br J Dermatol* 2008; **159:** 23–34.

Trigeminal neuralgia. Selective destruction of pain-bearing nerves is reserved for patients who do not respond to conventional drug therapy for trigeminal neuralgia (p. 11.2). This may be achieved by the instillation of glycerol among the trigeminal rootlets (percutaneous retrogasserian glycerol rhizolysis).[1-5] The efficacy and safety of this procedure have been debated,[1,4] but some centres report

good long-term results in the majority of patients.[5] It has been suggested that variations in viscosity and osmolality may influence results.[2]

1. Sweet WH. The treatment of trigeminal neuralgia (tic douloureux). *N Engl J Med* 1986; **315:** 174–7.
2. Waltz TA, Copeland BR. Treatment of trigeminal neuralgia. *N Engl J Med* 1987; **316:** 693.
3. Young RF. Glycerol rhizolysis for treatment of trigeminal neuralgia. *J Neurosurg* 1988; **69:** 39–45.
4. Burchiel KJ. Percutaneous retrogasserian glycerol rhizolysis in the management of trigeminal neuralgia. *J Neurosurg* 1988; **69:** 361–6.
5. Jho H-D, Lunsford LD. Percutaneous retrogasserian glycerol rhizotomy: current technique and results. *Neurosurg Clin N Am* 1997; **8:** 63–74.

Adverse Effects and Precautions

The adverse effects of glycerol are mainly due to its dehydrating action.

When taken orally glycerol may cause headache, nausea, and vomiting; diarrhoea, thirst, dizziness, and mental confusion may occur less frequently. Cardiac arrhythmias have been reported.

Glycerol increases plasma osmolality resulting in the withdrawal of water from the extravascular spaces. The consequent expansion of extracellular fluid, especially if sudden, can lead to circulatory overload, pulmonary oedema, and heart failure; glycerol must therefore be used with caution in patients at risk, such as those with hypervolaemia, cardiac failure, or renal disease. Severe dehydration can occur and glycerol should be used cautiously in dehydrated patients. Patients with diabetes mellitus may additionally develop hyperglycaemia and glycosuria after metabolism of glycerol. Nonketotic hyperosmolar hyperglycaemic coma is rare, but fatalities have been reported.

Haemolysis, haemoglobinuria, and acute renal failure have also been associated with glycerol when given intravenously (see Raised Intracranial Pressure, p. 2517.3).

Glycerol can cause irritation when given topically or rectally. A local anaesthetic may be used before application of glycerol to the cornea to reduce the likelihood of a painful response.

For incompatibilities with glycerol, including the risk of explosive mixtures, see p. 2517.2.

Effects on the cardiovascular system. A 73-year-old man, free of cardiac complaints but who had previously had an acute myocardial infarction, developed severe pulmonary oedema after use of glycerol orally for elevated intra-ocular pressure.[1] The necessity for detailed cardiac evaluation before the use of oral glycerol was emphasised.

1. Almog Y, *et al.* Pulmonary edema as a complication of oral glycerol administration. *Ann Ophthalmol* 1986; **18:** 38–9.

Effects on the ears. A 56-year-old man given 100 mL of glycerol and 100 mL of sodium chloride 0.9% as part of a test for Ménière's disease developed temporary hearing loss in the non-involved ear. Two previous reports of deterioration in hearing associated with the glycerol test were reviewed by the author.[1]

1. Mattox DE, Goode RL. Temporary loss of hearing after a glycerin test. *Arch Otolaryngol* 1978; **104:** 359–61.

Effects on the eyes. Caution in applying glycerol to the cornea has been recommended. Studies in *animals*[1] and in man[2] have indicated that the topical application of glycerol to the eye can damage the endothelial cells of the cornea.

1. Sherrard ES. The corneal endothelium in vivo: its response to mild trauma. *Exp Eye Res* 1976; **22:** 347–57.
2. Goldberg MH, *et al.* The effects of topically applied glycerin on the human corneal endothelium. *Cornea* 1982; **1:** 39–44.

Hyperosmolar nonketotic coma. Hyperosmolar nonketotic coma has been associated with the oral use of glycerol[1] and deaths have occurred.[2] The most susceptible patients are maturity-onset elderly diabetics with acute or chronic disease predisposing to fluid deprivation, and in these patients oral glycerol may be best avoided.[1] If glycerol is used in patients with predisposing conditions, adequate measures should be taken to recognise the development of hyperosmolar nonketotic hyperglycaemia and prevent dehydration.[1,2]

1. Oakley DE, Ellis PP. Glycerol and hyperosmolar nonketotic coma. *Am J Ophthalmol* 1976; **81:** 469–72.
2. Sears ES. Nonketotic hyperosmolar hyperglycemia during glycerol therapy for cerebral edema. *Neurology* 1976; **26:** 89–94.

Overdosage. References.

1. Singh R, *et al.* Reversible neurologic manifestations after glycerol: a short report. *Neurol India* 2001; **49:** 320–1.
2. Bingel U, *et al.* Acute encephalopathy due to glycerol over-consumption. *J Neurol* 2006; **253:** 125–6.
3. Andresen H, *et al.* Severe glycerol intoxication after Menière's disease diagnostic—case report and overview of kinetic data. *Clin Toxicol* 2009; **47:** 312–16.

Pharmacokinetics

Glycerol is readily absorbed from the gastrointestinal tract and undergoes extensive metabolism, mainly in the liver; it may be used in the synthesis of lipids, metabolised to glucose or glycogen, or oxidised to carbon dioxide and water. It may also be excreted in the urine unchanged.

References.

1. Nahata MC, *et al.* Variations in glycerol kinetics in Reye's syndrome. *Clin Pharmacol Ther* 1981; **29:** 782–7.
2. Heinemeyer G. Clinical pharmacokinetic considerations in the treatment of increased intracranial pressure. *Clin Pharmacokinet* 1987; **13:** 1–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Refenax Lagrimas; Vixorfit; ***Austral.***: Bausch & Lomb Computer Eye Drops†; Becoderm†; ***Braz.***: Endura; Glicel; ***Canad.***: Bandi†; Synovisol; Universal Brand Enema†; ***Chile***: Fleet Babylax; ***China***: Xin Long (信龙); ***Fin.***: Miniderm; ***Fr.***: Bebegel; Cristal; ***Ger.***: Babylax; Glycerosteril; Glycilax; Milax; Nene-Lax; Otodolor Soft; ***Gr.***: Babylax; Glicerolo microclismi; Gly Care; Microclismata†; Pikefi; ***Hong Kong***: Computer Eye Drops; Fleet Babylax†; Glyceol; Wet Stuff; ***India***: Hidrate; ***Irl.***: Babylax; ***Ital.***: Bonlax; Verolax; Zetalax; ***Jpn***: Glyceol; ***Malaysia***: Egozite Protective Baby Lotion†; Fleet Babylax†; ZenCare; ***Mex.***: Estrin; Fleet Adulto†; Fleet Infantil†; Fleet Pedialax†; Micronovag; Neutrobar; PC; Supositorios Senosiain; ***Philipp.***: Babylax; Computer Eye Drops; Novas; United Home Glydolax; ***Port.***: Bebegel; Dolorecto†; Glycelax; Rectiole; Verolax; ***Rus.***: Glycelax (Глицелакс); ***S.Afr.***: Regard†; ***Singapore***: Fleet Babylax; Optive; ***Spain***: Adulax; Comosup; Dulcoenema; Gely†; Glicerotens; Kanova; Normovagil; Paidolax; Supogliz†; Verolax; Vitrosups†; ***Switz.***: Bulboid; Practomil; ***Thai.***: Glyceol; Glycerosteril; ***UAE***: Laxolyne; ***UK***: Benylin Childrens Apple Flavour Cough Syrup; Benylin Tickly Coughs; Boots Constipation Relief; Boots Cough Syrup 3 Months Plus; CalCough Children's Soothing Syrup; CalCough Infant Syrup; CalCough Tickly†; Neutrogena Norwegian Formula Dermatological Cream; Nirolex Dry Cough; Senokot Direct Relief; Tixylix; ***Ukr.***: Adulax (Адюлакс); Peidolax (Пейдолакс); ***USA***: Colace Infant/Child; Eye-Lube-A; Fleet Babylax; Listermint Arctic Mint Mouthwash; Osmoglyn†; Pedia-Lax; Sani-Supp; ***Venez.***: Fleet Babylax.

Multi-ingredient Preparations. ***Arg.***: Aftersun; Cutidermin Crema Antibacterial†; Endura; Irix Lagrimas; Keracnyl; Micronema; Optive; Sincerum Dry; Tears Naturale Forte; Tears Naturale†; Ureadin Facial; Visine Lagrimas; ***Austral.***: Anusol†; EgoPsoryl TA; Gentlees; Hamilton Dry Skin; Hamilton Skin Active Urederm Cream; Magnoplasm; Micolette; Optive; QV Flare Up; SM-33; Soothe'n Heal†; ***Belg.***: Aloplastine†; Laxavit; ***Braz.***: Dermamina; Optive; Trisorb; ***Canad.***: Agarol Plain; Auralgan; Bausch & Lomb Moisture Eyes; Clear Eyes for Dry Eyes Plus Redness Relief; Clear Eyes for Dry Eyes; Epi-Lyt; Refresh Ultra; Tears Naturale Forte; Tucks†; ***Chile***: Acnoxyl Jabon Liquido†; Agarol†; Cicapost; Ictyane; Keracnyl; Nasivin; Optive; Tears Visine†; Ureadin Rx DB; Ureadin Rx RD; ***China***: Bu Rui De (布瑞得); Ganruining (甘瑞宁); Tears Naturale Forte (新泪然); ***Denm.***: Glyoktyl; Pectyl; ***Fr.***: Aloplastine; Derm'Intim; Dexeryl; Ictyane HD; Ictyane; Kertyol PSO; Kertyol-S†; Lubri-Mucal; Naturophta Macula; Pharyndol; Pharyndol; PSO†; Rectopanbiline; Saugella Antiseptic; Saugella Dermoliquide; Scleremo; Taido; Topicrem†; Totephan†; Urgo Cicatrices; ***Ger.***: Dexeryl; GeloBacin; InfectoGripp; Lacrisic; Lubricano; Norgalax Miniklistier†; Norgalax Rektalgel; Optive; Otodolor; Silence; Zinksalbe; ***Hong Kong***: Acnederm Wash; Acnederm; Asonor; Baby Cough with Antihistamine†; Ego Skin Cream; Egopsoryl TA; Gly Thymol; Moisture Eyes; Optive; Tears Naturale Forte; Visine for Contacts†; ***Hung.***: Strand; ***India***: Alv; Clenora; Clenorush; Coldtaur; Dentra; Dermamoist; Dew Derm; Diafoot; Dordent; Glyvin; Glyvine-S; Icee; Kratol; Mannigyl; Mengy; Neotomic; Neurotol; Novaglow; Otogesic; ***Indon.***: Isotic Tearin; Laxadine; ***Irl.***: Lemsip Dry Cough; Micolette; ***Israel***: Claritone; DryEars; Kamil Blue; Microlet; Optive; ***Ital.***: Cue Soluzione Otologica; Dropyal; Evasen Dischetti; Evasen Liquido; Glicerolax; Lipimix; Microclismi Marco Viti†; Naturalass; Novilax; Rinogutt Atlantic; Salviette H; Solecin†; ***Malaysia***: AcneCare; Acnederm Foaming Wash; Aqua Care; Cationorm; Ego Skin Cream; Lanakeloid-E; Panoff; pH Care; Prelactic; ***Mex.***: Moisture Eyes; Nasalub; Nutrasorb; Optive; ProcalAmine; Varicyl; ***NZ***: Acnederm Foaming Wash†; Auralgan; Ego Skin Cream; Rosken Skin Repair; Silic; ***Philipp.***: BioSil†; Lactaderm†; Medisnore; Moisture Eyes; Optive; pH Care; Visine Refresh; ***Pol.***: Rektiolax; Unibasis; ***Port.***: Cicapost; Dagragel; Hidratante VG; Nutraisdin; Ureadin Facial; Ureadin Manos; ***Rus.***: Proposol-N (Пропосол-Н); ***S.Afr.***: Auralyt†; Caloplast†; ***Singapore***: Acnederm Foaming Wash; Acnederm; Arkopharma Propolis Spray; Bio-Taches Masque†; Ego Skin Cream; Endura; Lanakeloid-E; Minica S; Panoff; pH Care Intimate Wash; Silence; Snoreeze; Topicrem; Tropex; ***Spain***: Enofosforina Vigor†; ***Switz.***: Dexeryl; Lacrycon; Neo-Decongestine; Optive; Realderm; Silence†; Silence; ***Thai.***: Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; Endura; Optive; ***Turk.***: Gleitgelen; Kalmosan; Kansilak; Libalaks; Sabalaks; Snoreless; ***UK***: Allens Junior Cough; Asonor; Beehive Balsam; Earex Plus†; Feminesse; Glycerdex; Honey & Molasses; Imuderm†; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets Medicated Linctus; Lockets; Meltus Honey & Lemon; Micolette; Murine Dry & Tired Eyes; Optive; Relaxit; Swim-Ear; ***Ukr.***: Optive (Оптиве); ***USA***: Allergen; Astroglide; Auralgan; Aurax; Cetaklenz; Clearasil Antibacterial; Dri/Ear; Entertainer's Secret; Epi-Lyt; Episil; Formulation R; Hemorid For Women; Maxilube; Mimyx†; Moisture Drops; MuGard; N'ice; Neosalus; Neotic†; Ocean Nasal Moisturizer; Otic Edge†; Otozin; Preparation H; Refresh Dry Eye Therapy; Summer's Eve Anti-Itch; Surgel; Therevac Plus; Therevac SB; Tonsiline; Trimo-San; Tucks; Visine Maximum Redness Relief; Visine Pure Tears; Visine Tears; Visine Tired Eye Relief; Visine Totality Multi-Symptom Relief.

Pharmacopoeial Preparations

BP 2014: Glycerol Eye Drops; Glycerol Suppositories; Phenol and Glycerol Injection;

USP 36: Antipyrine and Benzocaine Otic Solution; Calamine Topical Suspension; Glycerin Ophthalmic Solution; Glycerin Oral Solution; Glycerin Suppositories.

Glycerol Phenylbutyrate *(USAN, pINN)*

Fenilbutirato de Glicerol; Glyceroli Phenylbutyras; Glyceryl Tri (4-Phenylbutyrate); HPN-100; Phénylbutyrate de Glycérol; Глицеролфенилбутират.

Propane-1,2,3-triyl tris(4-phenylbutanoate).

$C_{33}H_{38}O_6$=530.7

CAS — 611168-24-2.

ATC — A16AX09.

ATC Vet — QA16AX09.

UNII — ZH6F1VCV7B.

Sodium Phenylbutyrate *(BAN, USAN)*

Fenilbutirato de sodio; Natrii phenylbutyras; Natriumfenylbutyrat; Natriumfenyylibutyraatti; Natriumphenylbutyrat; Sodium, phénylbutyrate de; Sodyum Fenilbutirat; Фенилбутират Натрия.

Sodium 4-Phenylbutyrate.

$C_{10}H_{11}NaO_2$=186.2

CAS — 1716-12-7.

ATC — A16AX03.

ATC Vet — QA16AX03.

UNII — NT6K61736T.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Phenylbutyrate). A white or yellowish-white powder. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5.

Uses and Administration

Sodium phenylbutyrate is a prodrug for sodium phenylacetate (p. 2619.2) and glycerol phenylbutyrate is a prodrug for phenylbutyrate. They provide alternative metabolic routes for the excretion of waste nitrogen and are used as adjunctive therapy in the chronic treatment of hyperammonaemia (p. 2049.3) in patients with urea cycle disorders.

Both are given orally in equally divided doses with meals. The daily dose is adjusted according to protein tolerance and the required dietary protein intake for growth and development. In adolescents and adults the usual total daily dose of sodium phenylbutyrate is 9.9 to 13.0 g/m^2 to a maximum of 20 g daily. Glycerol phenylbutyrate is a liquid containing 1.1 g/mL, and is given in a total daily dose ranging from 4.5 to 11.2 mL/m^2 (5 to 12.4 g/m^2), to a maximum daily dose of 17.5 mL (about 19 g). To provide the same dose of phenylbutyric acid when converting between the two:

$$\text{glycerol phenylbutyrate (mL)} = \text{sodium phenylbutyrate (g)} \times 0.86$$

For doses used in children, see p. 2519.1.

Sodium phenylbutyrate is also under investigation for the treatment of some sickle-cell disorders (p. 1123.2) and for use as a potential differentiation-inducing agent in malignant glioma and acute myeloid leukaemia. Sodium phenylbutyrate is also under investigation for spinal muscular atrophy, which is caused by homozygous absence of the SMN1 gene, after reports that it significantly increased SMN transcript expression in both fibroblast cultures and leucocytes from these patients.

References.

1. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl 1): S46–S55. Correction. *ibid.* 2002; **140:** 490.
2. Mercuri E, *et al.* Randomized, double-blind, placebo-controlled trial of phenylbutyrate in spinal muscular atrophy. *Neurology* 2007; **68:** 51–5.
3. Caruthers RL, Johnson CE. Stability of extemporaneously prepared sodium phenylbutyrate oral suspensions. *Am J Health-Syst Pharm* 2007; **64:** 1513–15.
4. Lee B, *et al.* Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. *Mol Genet Metab* 2010; **100:** 221–8.
5. Lichter-Konecki U, *et al.* Ammonia control in children with urea cycle disorders (UCDs); phase 2 comparison of sodium phenylbutyrate and glycerol phenylbutyrate. *Mol Genet Metab* 2011; **103:** 323–9.
6. Iannitti T, Palmieri B. Clinical and experimental applications of sodium phenylbutyrate. *Drugs R D* 2011; **11:** 227–49.

Administration in children. Sodium phenylbutyrate and glycerol phenylbutyrate are used as adjunctive therapy in the chronic treatment of hyperammonaemia in infants and children with urea cycle disorders. They are given orally in equally divided doses with each meal or feed. The daily dose is adjusted according to protein tolerance and the required dietary protein intake for growth and development.

The usual total daily dose of sodium phenylbutyrate for patients weighing under 20 kg is 450 to 600 mg/kg. Those weighing 20 kg or more may be given the adult dose (see p. 2518.3). Alternatively, the *BNFC* suggests a dose of 75 to 150 mg/kg given 3 or 4 times daily for neonates and children up to 18 years of age.

Glycerol phenylbutyrate may be used in children aged 2 years and older; doses are calculated using the same regimen as that used in adults. There is limited data on the safety and efficacy of its use in children aged 2 months to 2 years, and it is contra-indicated in those less than 2 months old.

For the treatment of acute hyperammonaemia due to urea cycle disorders in neonates and children up to 18 years of age, the *BNFC* includes an unlicensed dose of sodium phenylbutyrate given by continuous intravenous infusion. An initial dose of 250 mg/kg is given over 90 minutes, followed by 20 mg/kg per hour adjusted according to response.

Adverse Effects and Precautions

Adverse effects of sodium phenylbutyrate include gastrointestinal disturbances, decreased appetite, taste disturbance, rashes, dizziness, headache, fatigue, depression, oedema, and weight gain. Abnormal body odour, probably caused by the metabolite phenylacetate, is commonly reported. Amenorrhoea or irregular menstruation is very common. Reported haematological disturbances include anaemia, thrombocytopenia, leucopenia, thrombocytosis, and leucocytosis.

Electrolyte disturbances, metabolic acidosis, alkalosis, and renal tubular acidosis are common. Increases in hepatic enzymes, bilirubin, and uric acid can occur. Sodium phenylbutyrate should be used with caution, if at all, in patients with congestive heart failure or severe renal impairment because of its high sodium content (see Sodium Content, below). It should also be used with caution in patients with milder renal impairment, hepatic impairment, or inborn errors of beta oxidation.

Adverse effects of glycerol phenylbutyrate are similar to those of sodium phenylbutyrate, although diarrhoea and flatulence may be more common. Glycerol phenylbutyrate is contra-indicated in children younger than 2 months old; their immature pancreatic exocrine function may not produce sufficient lipases for intestinal hydrolysis to release phenylbutyrate. Similarly, the efficacy of glycerol phenylbutyrate may be reduced in patients with pancreatic insufficiency or conditions of intestinal malabsorption.

Sodium content. Each g of sodium phenylbutyrate contains about 5.4 mmol of sodium.

Interactions

Probenecid may inhibit the renal excretion of the metabolites of sodium phenylbutyrate and glycerol phenylbutyrate.

Pharmacokinetics

Sodium phenylbutyrate is rapidly absorbed from the gastrointestinal tract and oxidised to phenylacetate, which undergoes glutamine conjugation via acetylation in the liver and kidney to form phenylacetylglutamine. Peak plasma concentrations of phenylacetate and phenylacetylglutamine occur after about 3 to 4 hours. About 80 to 100% of a dose of sodium phenylbutyrate is renally excreted as phenylacetylglutamine within 24 hours, providing an alternative route for nitrogen excretion. Phenylacetate also undergoes some hydrolysis by esterases in the blood and liver.

After oral administration, glycerol phenylbutyrate is hydrolysed by pancreatic lipases in the gastrointestinal tract to release phenylbutyrate, which is rapidly absorbed and metabolised as described above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ammonaps; ***Belg.***: Ammonaps; ***Cz.***: Ammonaps; ***Denm.***: Ammonaps; ***Fr.***: Ammonaps; ***Ger.***: Ammonaps; ***Gr.***: Ambutyrate; ***Irl.***: Ammonaps; ***Ital.***: Ammonaps; ***Jpn***: Buphenyl; ***Mex.***: Fegabiral; ***Neth.***: Ammonaps; ***Norw.***: Ammonaps; ***Pol.***: Ammonaps; ***Port.***: Ammonaps; ***Spain***: Ammonaps; ***Swed.***: Ammonaps; ***UK***: Ammonaps; ***USA***: Buphenyl; Ravicti.

Pharmacopoeial Preparations
USP 36: Sodium Phenylbutyrate Oral Suspension.

Glycerophosphoric Acid

Glicerofosfórico, ácido; Glycerylphosphoric Acid; Monoglycerylphosphoric Acid; Глицерофосфорная Кислота.

$C_3H_9O_6P$=172.1

CAS — 27082-31-1; 57-03-4 (α-glycerophosphoric acid); 17181-54-3 (β-glycerophosphoric acid); 5746-57-6 (L-α-glycerophosphoric acid); 1509-81-5 (DL-α-glycerophosphoric acid).

UNII — MG976Z29OM.

Sodium Glycerophosphate *(USAN)*

Glycerofosforečnan sodný; Natrii glycerophosphas; Natrio glicerofosfatas; Natrium Glycerophosphoricum; Nátriumglicerofoszfát; Natriumglycerofosfat; Natriumglyserofosfaatti hydratoitu; Sodium, glycérophosphate de; Sodium Glycerylphosphate; Глицерофосфат Натрия.

$C_3H_9O_6P,2Na,xH_2O$=218.1 (anhydrous)

CAS — 1334-74-3 (anhydrous sodium glycerophosphate); 1555-56-2 (anhydrous α-sodium glycerophosphate); 819-83-0 (anhydrous β-sodium glycerophosphate); 55073-41-1 (sodium glycerophosphate).

ATC — B05XA14.

ATC Vet — QB05XA14.

UNII — YP1H63LJ2K.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Glycerophosphate, Hydrated). A mixture of variable proportions of sodium (2*RS*)-2,3-dihydroxypropyl phosphate and sodium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate. It may contain various amounts of other glycerophosphate esters. The degree of hydration is 4 to 6. A white or almost white, crystalline powder or crystals. Freely soluble in water; practically insoluble in alcohol and in acetone.

Profile

Glycerophosphoric acid and various glycerophosphates have been used in tonics. They were once considered as a suitable means of providing phosphorus. Calcium and magnesium glycerophosphates (see p. 1783.3 and p. 1787.2, respectively) may be considered as a source of calcium or magnesium.

Reference to the use of sodium glycerophosphate as a source of phosphorus in infant parenteral nutrition.[1]

1. Costello I, *et al.* Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. *Arch Dis Child* 1995; **73:** F44–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium glycerophosphate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Glycophos (格利福斯); ***Denm.***: Glycophos; ***Fin.***: Glycophos; ***Gr.***: Glycophos; ***Hong Kong***: Glycophos; ***Malaysia***: Glycophos†; ***Neth.***: Glycophos; ***NZ***: Glycophos; ***Pol.***: Glycophos; ***Port.***: Glycophos; ***Spain***: Glycophos; ***Swed.***: Glycophos; ***Switz.***: Glycophos; ***Thai.***: Glycophos; ***Turk.***: Glycophose; ***UK***: Glycophos.

Multi-ingredient Preparations. ***Braz.***: Ferrotrat B12 Plus; ***Canad.***: Hemarexin†; ***Chile***: Paralymphine; ***China***: Diweijia (迪维佳); ***Fr.***: Biotone; Phosphore Alko; Stimuplexe†; Verrulyse-Methionine; ***India***: Deferon; Neurophosphates-Iron; ***Indon.***: Tonikum Bode; ***Irl.***: Metatone; ***Israel***: Babyzim; ***Ital.***: Glicero-Valerovit; Neurol; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); ***Spain***: Enofosforina Vigor†; ***UK***: Metatone.

Glycogen

Animal Starch; Liver Starch.

$(C_6H_{10}O_5)_n$.

CAS — 9005-79-2.

UNII — 309GSC92U1.

Profile

Glycogen is a polysaccharide composed of glucose subunits and is the main storage form for carbohydrate in animals. It has been used with lactic acid in preparations for vaginal disorders since it has been suggested that vaginal bacteria may utilise glycogen to produce an acidic environment, but this is not established.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Geliofil; ***Ger.***: Gelifend; ***Israel***: Femina Lactal; ***Ital.***: Geliofil; ***Singapore***: Luvena Prebiotic; ***UK***: Balance Activ RX; ***Ukr.***: Fitoval Shampoo Anti-Hair Loss (Фитовал шампунь против выпадения волос).

Homoeopathic Preparations. ***UK***: Fragador.

Glycopyrronium Bromide *(BAN, rINN)*

AHR-504; Bromuro de glicopirronio; Glicopirronio, bromuro de; Glikopironyum Bromür; Glycopyrrolate (USAN); Glycopyrronii Bromidum; Glycopyrronium, bromure de; Glykopyrroniumbromid; Glykopyrroniumbromidi; NVA-237; Гликопиррония Бромид.

3-(α-Cyclopentylmandeloyloxy)-1,1-dimethylpyrrolidinium bromide.

$C_{19}H_{28}BrNO_3$=398.3

CAS — 596-51-0; 51186-83-5.

ATC — A03AB02; R03BB06.

ATC Vet — QA03AB02; QR03BB06.

UNII — V92SO9WP2I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Glycopyrronium Bromide). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in dichloromethane.

USP 36: (Glycopyrrolate). A white, odourless, crystalline powder. Soluble 1 in 4.2 of water, 1 in 30 of alcohol, 1 in 260 of chloroform, and 1 in 35 000 of ether. Store in airtight containers.

Incompatibility. Glycopyrronium bromide is incompatible with alkalis.

Stability. Investigation of the compatibility of glycopyrronium bromide with infusion solutions and additives showed that the stability of glycopyrronium bromide is questionable above a pH of 6, owing to ester hydrolysis.[1]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; **36:** 508–10. Correction. *ibid.*; 745.

Uses and Administration

Glycopyrronium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). After intramuscular doses, onset of effects is within 15 to 30 minutes; vagal blocking effects last for 2 to 3 hours and antisialagogue effects persist for up to 7 hours. After intravenous doses, onset of actions occurs within 1 minute.

Glycopyrronium bromide is used similarly to atropine in anaesthetic practice (below). It has also been used in the iontophoretic treatment of hyperhidrosis (p. 2520.1) and as an adjunct in the treatment of peptic ulcer disease (p. 2520.1). It is also used for the treatment of chronic severe drooling in children (p. 2520.1) and as a bronchodilator in the maintenance treatment of chronic obstructive pulmonary disease (p. 2520.1).

Administration in children. Doses of glycopyrronium bromide in children are given below under Anaesthesia (below), Drooling (p. 2520.1), and Palliative Care (p. 2520.1).

Anaesthesia. Glycopyrronium bromide is given as a premedicant before general anaesthesia (see under Atropine, p. 1311.1) to diminish the risk of vagal inhibition of the heart and to reduce salivary and bronchial secretions. It is given in doses of 200 to 400 micrograms intravenously or intramuscularly before the induction of anaesthesia; alternatively, it may be given in a dose of 4 to 5 micrograms/kg to a maximum of 400 micrograms. If necessary, similar doses may be given intravenously during the operation and repeated if required. A suggested dosage for premedication in neonates is 5 micrograms/kg given intravenously or intramuscularly; doses in children aged 1 month and over are 4 to 8 micrograms/kg up to a maximum of 200 micrograms.

Glycopyrronium bromide is given before or with anticholinesterases to counteract their muscarinic effects when they are used to reverse the effects of competitive muscle relaxants (see Neostigmine, p. 687.2). The dose is glycopyrronium bromide 200 micrograms intravenously per 1 mg of neostigmine (or per 5 mg of pyridostigmine); alternatively, it may be given in a dose of 10 to 15 micrograms/kg intravenously with neostigmine 50 micrograms/kg. A suggested dosage for neonates and children is 10 micrograms/kg intravenously with neostigmine 50 micrograms/kg up to a maximum of glycopyrronium bromide 500 micrograms. Glycopyrronium bromide can be given mixed in the same syringe with the

anticholinesterase, and it has been suggested that greater cardiovascular stability results from use in this way.

Drooling. Glycopyrronium bromide is given orally to reduce chronic severe drooling in children aged 3 to 16 years with neurologic conditions such as cerebral palsy. The starting dose is 20 micrograms/kg 3 times daily increased in increments of 20 micrograms/kg every 5 to 7 days according to response and adverse effects over a 4-week titration period. The maximum recommended dose is 100 micrograms/kg 3 times daily, but not to exceed 1.5 to 3 mg per dose based on weight. The dose should be taken at least 1 hour before, or 2 hours after, meals.

Gastrointestinal disorders. Antimuscarinics, including glycopyrronium bromide, have a limited role as antispasmodics (see p. 1803.3), and have been used as adjuncts in the treatment of peptic ulcer disease (see p. 1813.2).

As an adjunct in the treatment of peptic ulcer disease the usual initial oral dose of glycopyrronium bromide has been 3 to 6 mg daily in divided doses adjusted according to response to a maximum of 8 mg daily; a maintenance dose of 1 mg twice daily is often adequate. Doses of 100 to 200 micrograms have been given by intramuscular or intravenous injection.

Hyperhidrosis. Adverse effects generally preclude oral use of antimuscarinics for the management of hyperhidrosis (p. 1685.1), but glycopyrronium, has been applied topically as an alternative to aluminium salts.

In studies involving 22 patients with the Frey syndrome (localised flushing and sweating on eating) glycopyrronium bromide as 1 and 2% cream or roll-on solution gave good control of symptoms;[1] patients tended to prefer the roll-on lotion as it was easier to apply. Topical hyoscine as 0.25, 1, or 3% solution or cream also controlled sweating, but was associated with a much higher incidence of adverse effects. Reports of adverse effects produced by systemic absorption of topical glycopyrronium bromide used for hyperhidrosis include urinary retention[2] and dilated pupils;[3] ocular adverse effects may also be produced following peri-ocular contamination.[4] Patients with diabetic gustatory sweating have also noted a reduction in the frequency and severity of episodes after applying glycopyrronium 0.5% cream.[5]

Glycopyrronium bromide has also been used as a 0.05% solution in the iontophoretic treatment of hyperhidrosis.

Oral glycopyrronium bromide has been tried successfully in a patient with diabetic gustatory sweating.[6] Oral use was also shown to be of benefit in a retrospective analysis[7] of patients who had been treated for idiopathic hyperhidrosis over the previous 4 years. Out of 19 patients evaluated, only 4 stopped treatment due to lack of response; however, a further 5 stopped treatment because of intolerable adverse effects, mainly dry mouth.

1. Hays LL, *et al.* The Frey syndrome: a simple, effective treatment. *Otolaryngol Head Neck Surg* 1982; **90:** 419–25.
2. Madan V, Beck MH. Urinary retention caused by topical glycopyrrolate for hyperhidrosis. *Br J Dermatol* 2006; **155:** 634–5.
3. Panting KJ, *et al.* Dilated pupils caused by topical glycopyrrolate for hyperhidrosis. *Br J Dermatol* 2008; **158:** 187–8.
4. Izadi S, *et al.* Mydriasis and accommodative failure from exposure to topical glycopyrrolate used in hyperhidrosis. *J Neuroophthalmol* 2006; **26:** 232–3.
5. Shaw JE, *et al.* A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia* 1997; **40:** 299–301.
6. Edick CM. Oral glycopyrrolate for the treatment of diabetic gustatory sweating. *Ann Pharmacother* 2005; **39:** 1760.
7. Bajaj V, Langtry JAA. Use of oral glycopyrronium bromide in hyperhidrosis. *Br J Dermatol* 2007; **157:** 118–21.

Palliative care. Glycopyrronium bromide is used in palliative care as an alternative to hyoscine to reduce excessive respiratory secretions. A dose of 200 micrograms may be given subcutaneously or intramuscularly every 4 hours to adults. Alternatively, a dose of 0.6 to 1.2 mg may be given by continuous subcutaneous infusion over 24 hours.

For the control of upper airways secretion and hypersalivation in children aged 1 month and over, the *BNFC* recommends a dose of 40 to 100 micrograms/kg given orally 3 or 4 times daily adjusted according to response up to a maximum of 2 mg. Alternatively, children aged 1 month to 12 years may be given glycopyrronium bromide by subcutaneous infusion in a dose of 12 to 40 micrograms/kg over 24 hours up to a maximum of 1.2 mg; children over 12 years of age may receive the same dose by continuous subcutaneous infusion as for adults (see above).

References.

1. Kintzel PE, *et al.* Anticholinergic medications for managing noisy respirations in adult hospice patients. *Am J Health-Syst Pharm* 2009; **66:** 458–64.

Respiratory-tract disorders. Antimuscarinics have potent bronchodilatory activity and some, such as ipratropium (p. 1211.3), may be used in the management of reversible airways obstruction. Glycopyrronium bromide is also used in the maintenance treatment of chronic obstructive pulmonary disease, although it is not suitable for the initial treatment of acute bronchospasm. It can be given as inhalation powder in capsules containing 63 micrograms of glycopyrronium bromide, equivalent to 50 micrograms of glycopyrronium, and supplying 44 micrograms of glycopyrronium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled once daily, at the same time each day.

References.

1. Schroeckenstein DC, *et al.* Twelve-hour bronchodilation in asthma with a single aerosol dose of the anticholinergic compound glycopyrrolate. *J Allergy Clin Immunol* 1988; **82:** 115–19.
2. Gilman MJ, *et al.* Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. *Chest* 1990; **98:** 1095–8.
3. Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1995; **25:** 470–3.
4. Buhl R, Banerji D. Profile of glycopyrronium for once-daily treatment of moderate-to-severe COPD. *Int J Chron Obstruct Pulmon Dis* 2012; **7:** 729–41.
5. Ulrik CS. Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit. *Int J Chron Obstruct Pulmon Dis* 2012; **7:** 673–8.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glycopyrronium bromide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Renal impairment. A comparison[1] of the pharmacokinetics of intravenous glycopyrronium in 11 uraemic and 7 control patients indicated that the renal elimination of glycopyrronium is considerably prolonged in patients with uraemia. The mean amount of a dose excreted in the urine within 3 hours of a dose was 0.7% in the uraemic patients and 50% in the control patients; 24-hour excretion was 7% and 65%, respectively. The authors concluded that repeated or large doses of glycopyrronium should be avoided or perhaps the drug should not be used in patients with uraemia.

1. Kirvelä M, *et al.* Pharmacokinetics of glycopyrronium in uraemic patients. *Br J Anaesth* 1993; **71:** 437–9.

Interactions

As for Atropine Sulfate, p. 1312.3.

Pharmacokinetics

Glycopyrronium bromide is poorly absorbed from the gastrointestinal tract; about 10 to 25% is absorbed after an oral dose. Glycopyrronium bromide penetrates the blood-brain barrier only poorly. Glycopyrronium is excreted in bile and urine.

References.

1. Kaltiala E, *et al.* The fate of intravenous [^{3}H]glycopyrrolate in man. *J Pharm Pharmacol* 1974; **26:** 352–4.
2. Ali-melkkilä TM, *et al.* Pharmacokinetics of IM glycopyrronium. *Br J Anaesth* 1990; **64:** 667–9.
3. Rautakorpi P, *et al.* Pharmacokinetics of glycopyrrolate in children. *J Clin Anesth* 1994; **6:** 217–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acpan; ***Austral.***: Robinul; ***Austria***: Robinul; ***Belg.***: Robinul; ***Denm.***: Robinul; Seebri; ***Fin.***: Robinul; ***Ger.***: Robinul; ***Gr.***: Robinul; ***India***: Glyco-P; Glyprolate; Lycolate; ***Irl.***: Robinul; ***Israel***: Seebri; ***Jpn***: Seebri; ***Neth.***: Enurev; Seebri; Tovanor; ***Norw.***: Robinul; ***NZ***: Robinul; ***S.Afr.***: Robinul; ***Spain***: Seebri; ***Swed.***: Robinul; ***UK***: Robinul†; Robinul; Seebri; ***USA***: Cuvposa; Glycate; Robinul.

Multi-ingredient Preparations. ***India***: Myo-Pyrolate.

Used as an adjunct in:. ***Belg.***: Robinul-Neostigmine; ***Denm.***: Robinul-Neostigmin; ***Fin.***: Glycostigmin; Robinul-Neostigmin; ***Norw.***: Robinul-Neostigmin; ***Swed.***: Robinul-Neostigmin; ***Switz.***: Robinul-Neostigmine; ***UK***: Robinul-Neostigmine†.

Pharmacopoeial Preparations
BP 2014: Glycopyrronium Bromide Oral Solution;
USP 36: Glycopyrrolate Injection; Glycopyrrolate Tablets.

Glycyrrhizic Acid

Glycyrrhizin; Glycyrrhizinic Acid; Глицирризин; Глицирризиновая Кислота.
$C_{42}H_{62}O_{16}$=822.9
CAS — 1405-86-3.
ATC — A05BA08.
ATC Vet — QA05BA08.
UNII — 6FO62043WK.

Ammonium Glycyrrhizate

Ammonii Glycyrrhizas; Ammonium, glycyrrhizate d'; Ammonium Glycyrrhizinate; Ammónium-glicirrizát; Ammoniumglycyrrhizat; Ammoniumglykyrritsaatti; Amonio glicirizatas; Amonium-glycyrrhizát; Glycyrram; Monoammonium Glycyrrhizinate; Аммония Глицирризат.
$C_{42}H_{65}NO_{16}$=840.0
CAS — 53956-04-0.
UNII — 3VRD35U26C (ammonium glycyrrhizate); 1Z1Y4QY887 (anhydrous ammonium glycyrrhizate).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Ammonium Glycyrrhizate). A white or yellowish-white, hygroscopic powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides. Store in airtight containers.

USNF 31: (Ammonium Glycyrrhizate). A white or yellowish-white, hygroscopic powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides. It is a mixture of ammonium 18α- and 18β-glycyrrhizate (ammonium salt of (20β)-3β-[[2-*O*-(β-D-glucopyranosyluronic acid)-α-D-glucopyranosyluronic acid]oxy]-11-oxoolean-12-en-29-oic acid), and the 18β-isomer is the main component. It contains not less than 78.0% and not more than 102.0% of ammonium 18α- and 18β-glycyrrhizate, on the anhydrous basis. Store in airtight containers.

Dipotassium Glycyrrhizate

Potassium Glycyrrhizinate; Дикалия Глицеризат.
$C_{42}H_{60}K_2O_{16}$=899.1
CAS — 68039-19-0 (potassium glycyrrhizate); 42294-03-1 (monopotassium glycyrrhizate); 68797-35-3 (dipotassium glycyrrhizate).
UNII — CA2Y0FE3FX.

Profile

Glycyrrhizic acid is a constituent of liquorice (p. 1853.2). The mild anti-inflammatory and mineralocorticoid properties of liquorice have been attributed to the presence of glycyrrhizic acid and its metabolite glycyrrhetinic acid (Enoxolone, p. 54.2).

Glycyrrhizic acid and its ammonium and potassium salts have been used in products promoted for the relief of coughs, viral infections, and gastrointestinal, liver, and skin disorders. Ammonium glycyrrhizate has also been used as a sweetener, flavour enhancer, and as an emulsifying and gel-forming agent in foodstuffs and cosmetics.

Other derivatives of glycyrrhizic acid include metoclopramide glycyrrhizinate (p. 1862.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Epigen; ***China***: Ai Fu Bi (艾扶必); An Xin Fu Ning (安欣福宁); Dai Te (代特); Dan Wei (丹薇); Fu Luo Xin (福罗欣); Ming Ze (明择); Pu Gan Jing (普甘静); Tai Ka (泰卡); Tong Zhou (同洲); Wei Heng (维恒); WeiDing (卫丁); Xi Xin Sheng (喜心生); Xin Er Luo (信尔洛); Yong Bang (永邦); Yu Lu An (虞庐安); Zhen Li Xin (振力幸); Zhi Gan Bao (知甘保); Zhuo Fang (卓方); ***Indon.***: Glizigen; Neo-Minophagen C; ***Jpn***: Glycyron; Neo-Minophagen C†; Neophagen C; ***Mex.***: Epigen; ***Rus.***: Epigen (Эпиген); Glycyram (Глицирам).

Multi-ingredient Preparations. ***Chile***: Keracnyl Stop Bouton; ***China***: BiFu (比孚); Bo Luo Ni (博罗尼); Gan Mu Shu (甘木舒); Gan Wei Xin (甘维欣); Gan You Lin (感佑林); Jun Qiang (君强); Kang Er Ning (康尔宁); LiWeiEr (里威尔); Neo-Minophagen C (美能); Neo-Minophagen C (美能); NuoHao (诺豪); Ruo Jing (若菁); Shu Kang Lin (抒康林); Tuo Di (妥迪); Wei Suan Su (卫算苏); Wei Yi Xing (卫伊兴); Xin Le Dun (新乐敦); XinKang (昕康); Ye Xin (业欣); Yi Nuo Wei (依诺维); Yi Xin (易新); YouNiDi (尤尼迪); Yu Li Sen (宇立森); ***Fr.***: Herpclair; Keracnyl stop bouton; Photerpes; ***Hong Kong***: Scassh Trouch Lozenge; ***Indon.***: Aviter; Viusid; ***Ital.***: Biorag; Biothymus DS; Cue Soluzione Otologica; ***Jpn***: Colgen Gargle†; Colgen Kowa for Rhinitis; ***Port.***: Alkagin; Bexident; ***Venez.***: Viusid.

GMDP

Glucosaminylmuramyl Dipeptide; ГМДП.
N-acetylglucosaminyl-β1-4-*N*-acetylmuramyl-alanyl-D-isoglutamine.
$C_{25}H_{43}N_5O_{13}$=653.6
CAS — 97590-38-0.

Profile

GMDP, a component of bacterial cell walls, is reported to have immunomodulator properties and is used in many

diseases stated to be associated with secondary immunodeficiency.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Licopid (Липопид); ***Ukr.***: Likopid (Ликопид).

Gold

Aurum; E175; Or; Oro; Золото.
Au=196.966569
CAS — 7440-57-5.
UNII — 79Y1949PYO (gold); 7XM25QYI14 (gold ion).

Profile

Gold is a bright-yellow, malleable, and ductile metal; the finely divided powder may be black, ruby, or purple. The main use of metallic gold in healthcare is now in dentistry. Gold may also be used as a colouring agent for some foodstuffs. In the treatment of rheumatoid arthritis, gold is used in the form of compounds such as auranofin (p. 27.3), aurothioglucose (p. 28.2), and sodium aurothiomalate (p. 130.2). Gold nanoparticles are under investigation as adjuncts in diagnostic imaging, as sensitisers for phototherapy, and in delivery systems for drugs and gene therapy. There have been rare reports of hypersensitivity reactions to metallic gold.

Gold chlorides (see below) have been used as a source of gold for medicinal uses.

Homoeopathy

Gold has been used in homoeopathic medicines under the following names: Aurum; Aurum met.; Aurum metallicum; Aur. met.

References.

1. Merchant B. Gold, the noble metal and the paradoxes of its toxicology. *Biologicals* 1998; **26:** 49–59.
2. Ehrlich A, Belsito DV. Allergic contact dermatitis to gold. *Cutis* 2000; **65:** 323–6.
3. Demann ET, *et al.* Gold as an implant in medicine and dentistry. *J Long Term Eff Med Implants* 2005; **15:** 687–98.
4. Han G, *et al.* Multi-functional gold nanoparticles for drug delivery. *Adv Exp Med Biol* 2007; **620:** 48–56.
5. Sperling RA, *et al.* Biological applications of gold nanoparticles. *Chem Soc Rev* 2008; **37:** 1896–1908.
6. Boisselier E, Astruc D. Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity. *Chem Soc Rev* 2009; **38:** 1759–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Oligocure; ***Ger.***: Goldlily.

Homoeopathic Preparations. ***Austral.***: Respatona Sore Throat; ***Austria***: Relax; ***Canad.***: Earache; HPB Complex†; Menopause; PMS; Ton 2 Complex†; ***Chile***: Rinoplex; Silik; ***Cz.***: Galium; ***Fr.***: Abbe Chaupitre no 10†; Abbe Chaupitre no 1†; Kalium Iodatum Complexe No 84†; Rhododendron Complexe No 42†; Sclero-Drainol†; Soludor; Stressdoron; Symphytum Complexe No 48†; ***Ger.***: Antihypertonicum N†; Aurum/Lavandula comp.; Aurumarell Kreislauf-Spezifikum; Cor; Crataegus comp; Derivatio H; Derivatio; Disci Bamb; Ginkgo biloba comp; Infekt 1-Injektopas N; Infi-China; Neurodoron; Otofren; Schworocard; Tondinel H; ***Neth.***: Gynaelite; ***S.Afr.***: Kalium Phos Comp†; ***Switz.***: HerBalance; Regenaplex Nr. 24b; Regenaplex Nr. 24c; Regenaplex Nr. 71b; Regenaplex Nr. 79; Regenaplex Nr. 88b.

Gold Chloride

Aurous Chloride; Gold (I) Chloride.
Gold monochloride.
AuCl=232.4
CAS — 10294-29-8; 11118-27-7.
UNII — 15443PR153.

Gold Acid Chloride

Auric Acid; Chloroauric Acid; Gold Acid Tetrachloride; Gold Acid Trichloride; Gold Trichloride Hydrochloride; Hydrochloroauric Acid; Tetrachloroauric (III) Acid.
Hydrogen (*SP*-4-1)-tetrachloroaurate(1-).
$HAuCl_4$=339.8
CAS — 16903-35-8 (anhydrous gold acid chloride); 16961-25-4 (gold acid chloride trihydrate); 1303-50-0 (gold acid chloride tetrahydrate).
UNII — 8H372EGX3V.

Gold Trichloride

Auric Chloride; Auric Trichloride; Gold (III) Chloride.
$AuCl_3$=303.3
CAS — 13453-07-1.

Sodium Tetrachloroaurate

Gold Chloride Sodium; Gold Sodium Chloride; Sodium Chloroaurate (III).
Sodium tetrachloroaurate (III).
$AuCl_4Na$=361.8
CAS — 15189-51-2.
UNII — 7FT6QUT299.

Pharmacopoeias. *Eur.* (see p. vii) includes the dihydrate for homoeopathic preparations.

Ph. Eur. 8: (Sodium Tetrachloroaurate Dihydrate for Homoeopathic Preparations; Natrii Tetrachloroauras Dihydricus ad Praeparationes Homoeopathicas). Orange-yellow, hygroscopic powder or crystals. Very soluble or freely soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Gold forms several compounds with chlorine depending on its oxidation state. Gold acid chloride and gold trichloride are gold chlorides in which the gold is in the +3 (auric) oxidation state. They have been used as sources of gold for industrial and medicinal purposes. Sodium tetrachloroaurate, the sodium salt of gold acid trichloride, has been used similarly.

Homoeopathy

Gold chloride and its derivatives have been used in homoeopathic medicines under the following names:

- Gold chloride: aurum chloratum; aurum chlor; aurum chlorat; aurum muriaticum
- Sodium tetrachloroaurate: aurum chloratum natronatum; auri et natri chloridum; aurum et natrum muriaticum; aurum muriaticum natronatum; chlorure d'or et de sodium; chlorure d'or jaune; gold chloride, sodium; natrium-goldchlorid; natrium tetrachloroauratum; sodium gold chloride; sodium tetrachloroaurate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Irontona†; Vitatona†.

Homoeopathic Preparations. ***Austria***: Aurumheel; ***Canad.***: Aurumheel†; ***Fr.***: Aurum Complexe No 38†; Cimicifuga Complexe No 21†; Homeodose 8†; Mercurius Solubilis Complexe No 39; Sativol†; Selenium Complexe No 99; Strophantus Compose; Urarthone; Vinicard†; ***Ger.***: Acirufan; Aurum-Gastreu S R2; Goldtropfen S; HanoCor N; Infi-Camphora; Infi-China; Lowe-Komplex Nr 10; Myonasan; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; ***Hung.***: Aurumheel; Naso-Heel S; ***Neth.***: Co-Hypert; Gletar; Phonix Solidago comp; Sativol†; ***Switz.***: Gouttes d'Or; Regenaplex Nr. 12; Regenaplex Nr. 71b; ***Ukr.***: Aurocard (Аурокард).

Gold Iodide

CAS — 10294-31-2 (gold monoiodide); 13453-24-2 (gold triiodide).
UNII — T1UDV7ES1A.

Profile

Iodides of gold (above) include gold monoiodide (aurous iodide; gold (I) iodide) and gold triiodide (auric iodide; gold (III) iodide).

Homoeopathy

Gold iodide, a mixture of gold monoiodide and gold triiodide, has been used in homoeopathic medicine under the following names: Aurum iodatum Aurum jodatum Aurum jodat.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Ger.***: Roth's Rotacard; ***Rus.***: Aurum Plus (Аурум-Плюс).

Gossypol

Gosipol; Госсипол.
2,2′-Bis(1,6,7-trihydroxy-3-methyl-5-isopropylnaphthalene-8-carboxaldehyde).
$C_{30}H_{30}O_8$=518.6
CAS — 303-45-7.
UNII — KAV15B369O.

Profile

Gossypol is a pigment extracted from cottonseed oil (p. 2180.1). It possesses antispermatogenic activity and has been studied, especially in China, as a male contraceptive. It has also been investigated for its antineoplastic, antiprotozoal, antiviral, and spermicidal activity and has been studied in women in the treatment of gynaecological disorders.

Adverse effects have included fatigue, changes in appetite, gastrointestinal effects, burning sensation of the face and hands, some loss of libido, and persistent oligospermia. Hypokalaemia has occurred.

The pharmacology and therapeutic potential of gossypol have been reviewed.[1] Although controlled studies[2,3] have shown gossypol to be an effective male contraceptive, WHO concluded[4] that gossypol would not be acceptable as a male antifertility drug because of the occurrence of adverse effects such as hypokalaemia and irreversible testicular damage resulting in azoospermia or severe oligozoospermia.

1. Wu D. An overview of the clinical pharmacology and therapeutic potential of gossypol as a male contraceptive agent and in gynaecological disease. *Drugs* 1989; **38:** 333–41.
2. Coutinho EM, *et al.* Antispermatogenic action of gossypol in men. *Fertil Steril* 1984; **42:** 424–30.
3. Liu G, *et al.* Clinical trial of gossypol as a male contraceptive drug part I: efficacy study. *Fertil Steril* 1987; **48:** 459–61.
4. Waites GMH, *et al.* Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug. *Int J Androl* 1998; **21:** 8–12.

Grape

Grapevine; Rebe; Vigne Rouge; Weinstock; Виноград.
ATC Herb — HC05BW5006 (Vitis vinifera: leaf).
UNII — 6X543N684K (grape); 3GOV20705G (wine grape); 3XQ5L209OF (golden raisin); 22E661250J (Vitis vinifera); R1H893D80E (Vitis vinifera leaf); C34U15ICXA (Vitis vinifera seed).

NOTE. Distinguish from grape bark, Cocillana, p. 1659.2.

Pharmacopoeias. *Fr.* includes Red Vine Extract (Extrait de Vigne Rouge (Sec)), prepared from the leaves. *US* includes Grape Seeds Oligomeric Proanthocyanidins.

USP 36: (Grape Seeds Oligomeric Proanthocyanidins). A fraction of an extract of the ripe seeds of *Vitis vinifera*. It contains not less than 75% of oligomeric proanthocyanidins. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Profile

The seeds and the leaves of the grape, *Vitis vinifera* (Vitaceae), are used in herbal medicine. The dried fruit (raisins) have laxative and demulcent properties.

Many parts of the plant including the fruit skin, seeds, and leaves are used. Both dietary sources and various extracts are promoted for their antioxidant properties in venous insufficiency and capillary impairment, and it has been suggested that they may protect against atherosclerosis.

A standardised red vine leaf extract (AS-195) has been given for the management of chronic venous insufficiency.

Grape seed and grape seed extracts have been included in preparations for peripheral vascular disorders and venous insufficiency and for prophylaxis of cardiovascular disorders. Extracts of grape seed proanthocyanidins, including IH636, are being investigated for a range of other disorders in which antoxidant and free-radical scavenging activity is thought to be beneficial, including cancer prevention, hepatic disorders, radiation-induced fibrosis, cataracts, and macular degeneration, although there is currently little evidence of efficacy.

Resveratrol, a compound present in grapes, (see p. 2603.2) is also promoted as an antoxidant.

Grape seed oil is included in topical preparations.

The fresh and dried fruits of the grape and the leaves are used as foodstuffs.

Review.

1. Bombardelli E, Morazzoni P. *Vitis vinifera* L. *Fitoterapia* 1995; **66:** 291–317.
2. Nassiri-Asl M, Hosseinzadeh H. Review of the pharmacological effects of *Vitis vinifera* (grape) and its bioactive compounds. *Phytother Res* 2009; **23:** 1197–1204.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flebo Ikatral; Ikatral; Mikonos; Viticalm; ***Austria***: Antistax; Pedopur; ***Braz.***: Antistax; Celox†; Radifree; Vinera; ***Chile***: Endotelon†; Uvanox; Viticalm; ***Cz.***: Antistax; ***Fr.***: Endotelon; ***Ger.***: Antistax; ***Hung.***: Endotelon; ***Ital.***: Antistax; Perfluxi; ***Mex.***: Antistax; ***Pol.***: Endotelon†; ***Rus.***: Antistax (Антистакс); Endotelon (Эндотелон); ***Singapore***: French Parad'ox Plus; ***Spain***: Antistax; ***Switz.***: Antistax; ***Turk.***: Antistax; ***UK***: Antistax; ***Ukr.***: Endotelon (Эндотелон).

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; Cistidac; CVP Cellulite; HSN; Ikatral Periferico; Laxiruela; Procto-Ikatral;

Austral.: Anthogenol; Antioxidant Forte Tablets†; Arthro-Eze; Atopiclair†; Bio ACE Excell; Flavonoid Complex; Homme-F; Joint Ease; PM Joint-Care; Pygno-Vite†; Radiance; ResveratoX; Vein Relief; Vitanox; Zellulean with Escin†; ***Austria***: Hepatodoron; ***Canad.***: Immune Formula†; Proflavanol 90†; ***Chile***: Celltech; Seresis; ***Fr.***: Anthylline†; Anti-oxydant F4; Blue Berry; Cledist; Corvitec; Derm; Diveine; Imedeen Prime Renewal†; Imedeen Time Perfection†; Mediflor Circulation du Sang No 12†; Nutrof Total; Omegaline Solaire; Ophtalmine†; Opo-Veinogene; Pharyndol; Pharyndol; Phlebosedol†; Tisane Provencale no 3†; Veinophytum†; ***Ger.***: Hepatodoron; ***Hong Kong***: Proflavanol†; ***India***: Calorex; Dayvital; Diakof; Ecome-LY; Eldervit-ZC; Elgrape; Elmega-3; Elnutra-M; Geriforte; Hair-stim-HGF; Koflet; L-Bex; Lycobond; Lycominvit; Lyconerve; Morvit; Natoz; Nislutin; Orymax; Orymax; Oxitard; Oxy-Grape; ***Indon.***: Antox; Atopiclair; Kapset; Lanaven Plus†; Legres; Legreskin; Liproqy; Lycoq†; Lyphen; Noros; Oxan; Proview; Resvica†; ***Israel***: Atopiclair; Xclair; ***Ital.***: Angiovein; Betaeffe Complex; Blunorm; Capill; Deproctol; Deroidal; DMS Control; Flavion; Mirtilux; Neosulfur†; Traumaven; Venalta; Venalta; Visu-len; Visu-ton; Vitreoclar; Zeadema Crono; Zeadema; ***Malaysia***: Glow; Proflavanol†; Seresis; ***Mex.***: Proflavanol; Seresis; ***Mon.***: Fluon+; ***Philipp.***: Gloww; ***S.Afr.***: Hepatodoron†; ***Singapore***: Atopiclair; Bio-Taches Masque†; Bio-Taches†; Cardio Cocktail; Claricof; Glow; Proflavanol†; Scar Esthetique; Seresis†; ***Swed.***: Vitadoron; ***Switz.***: Hepatodoron; ***UK***: Atopiclair; Xclair; ***Ukr.***: Artritosamin (Артритозамин); Bon-Apetit (Бон-Аппетит); Imunin (Иммунин)†; Perfectil Plus (Перфектил Плюс); Vitrum Beauty Elite (Витрум Бьюти Элит); Vitrum Beauty Q10 (Витрум Бьюти Q10)†; ***USA***: Atopiclair; Cardio Tone; Immunicare; Protegra; Pycnogenol Plus.

Homoeopathic Preparations. ***Canad.***: Formula CI 207†; Formula HEPA†; Formula Homeo QR 209†.

Graphite

Black Lead; Mineral Carbon; Plumbago.
CAS — 7782-42-5.
UNII — 4QQN74LH4O.

NOTE. Plumbago, as well as being a synonym for graphite, may be used to refer to lead ores and to a genus of flowering plants (the leadworts).

Profile

Graphite is a crystalline form of carbon containing a small amount of iron and other minerals. Graphite is used as a drawing material, and when mixed with a clay binder, it forms the core in pencils commonly referred to as 'lead' pencils. It also has industrial uses. Exposure to graphite dust can lead to respiratory disorders.

Homoeopathy

Graphite has been used in homoeopathic medicines under the following names: graphites; plumbago.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Homoderma; ***Austria***: Acidum picrinicum Med Complex†; Crimax; Erbiode Akne; Gracil; ***Canad.***: Adrisin†; Endoteel†; Execalm†; Ikoplex 11 Digestion Aid†; ***Chile***: Bioactiv F; Bioactiv Q; Ikoplex No 7; Lessfat; ***Fr.***: Abbe Chaupitre no 22†; Abbe Chaupitre no 23†; Slimum†; Veino-Drainol†; ***Ger.***: Derma-Plantin†; Dermi-cyl L Ho-Len-Complex; Ekzem-Entoxin N; Hautfunktionstabletten N; Hautfunktionstropfen N; Otofren; Steiroderm; ***Neth.***: Cutis comp; Habifac; ***Rus.***: Psorilom (Псорилом); Urtica-Plus (Уртика-Плюс); ***Switz.***: Exsepta; Regenaplex Nr. 24c; Regenaplex Nr. 25a.

Gravel Root

Joe Pye Weed; Purple Boneset; Queen of the Meadow; Raíz de eupatorio; Посконник Пурпуровый (*Eupatorium purpureum*).
UNII — 0VYG5PVN5Q (Eupatorium purpureum).

NOTE. Distinguish from Boneset, *Eupatorium perfoliatum* (see p. 2459.1). Boneset is also used as a common name for *Symphytum officinale* (see Comfrey, p. 2484.2). The name Queen of the Meadow has also been applied to Meadowsweet (p. 2550.2).

Profile

Gravel root is the root of *Eupatorium purpureum* (*Eutrochium purpureum*) (Compositae) and has diuretic, antilithic, and antirheumatic properties. It is used for renal and urinary calculus and other urinary-tract disorders, and has also been used for gout and rheumatism.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Backache.

Homoeopathic Preparations. ***Canad.***: Goldenrod Combination†; ***Ger.***: Cysto-Gastreu S R18; ***Neth.***: Cysto-Gastreu R18.

Greater Celandine

Celidonia; Chélidoine; Chelidonii Herba; Chelidonium; Hierba golondrinera; Hierba verruguera; Keltamo; Schöllkraut; Skelört; Tetterwort; Ugniažolių žolė; Vérehulló fecskefű; Vlašťovičníková vňať; Ziele glistnika; Гистотел Большой.
ATC Herb — HN02BW5002 (Chelidonium majus: *root*); *HA05AW5004* (Chelidonium majus: *herb*).
UNII — 7E889U5RNN (Chelidonium majus).

NOTE. The name Tetterwort has also been used for Sanguinaria (p. 2610.1).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Greater Celandine). The dried, whole, or cut aerial parts of *Chelidonium majus* collected during flowering. It contains a minimum of 0.6% of total alkaloids expressed as chelidonine ($C_{20}H_{19}NO_5 = 353.4$), calculated with reference to the dried drug.

Uses and Administration

Greater celandine has sedative and spasmolytic properties and the aerial parts are used for liver, biliary, and gastrointestinal disorders, and have also been used for respiratory-tract disorders. The latex has been used externally for warts and other skin conditions.

Homoeopathy

Greater celandine has been used in homoeopathic medicines under the following names: Chelidonium; Chelidonium majus; Chelidonium maj; Chelidonium majus, radix; Chelidonium, rad; Chelidonium, Flos; Chelidonium majus e floribus; Che. maj.

Effects on the liver. References.

1. Benninger J, *et al*. Acute hepatitis induced by greater celandine (Chelidonium majus). *Gastroenterology* 1999; **117:** 1234–7.
2. Stickel F, *et al*. Acute hepatitis induced by Greater Celandine (Chelidonium majus). *Scand J Gastroenterol* 2003; **38:** 565–8.
3. Moro PA, *et al*. Hepatitis from Greater celandine (*Chelidonium majus* L.): review of literature and report of a new case. *J Ethnopharmacol* 2009; **124:** 328–32.

Adverse Effects

Greater celandine has been reported to cause acute cholestatic hepatitis, stomatitis, gastroenteritis, and dermatitis. Fatalities have occurred after haemorrhagic gastritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Paverysat forte N†.

Multi-ingredient Preparations. ***Arg.***: Quelodin F; ***Austral.***: Berberis Complex†; Extralife Liva-Care†; Toxicol; ***Austria***: Choleodoron; Iberogast; ***Belg.***: Aporil; ***Cz.***: Iberogast; ***Fr.***: Nitrol†; ***Ger.***: Chol-Kugeletten Neu†; Cholhepan N; Gallemolan forte†; Iberogast; ***Hong Kong***: Hepatofalk Planta†; Hepatofalk†; ***Hung.***: Depsorin; Herpesil; Iberogast; Vesevedo; ***Indon.***: Lanagogum; ***Neth.***: Iberogast; ***Pol.***: Artecholin†; Artecholwex†; Chelicur; Cholavisol; Cholitol; Enterosol; Iberogast; Neoazarina; Sirupus Pini Compositus; Sirupus Tussipini D; Sirupus Tussipini; Syrop Sosnowy Zlozony†; Syrop Sosnowy Zlozony; ***S.Afr.***: Choleodoron†; ***Singapore***: Hepatofalk Planta†; ***Spain***: Iberogast; Nitroina; ***Swed.***: Iberogast; ***Switz.***: Choleodoron; Iberogast; ***Ukr.***: Iberogast (Иберогаст); ***Venez.***: Demerung.

Homoeopathic Preparations. ***Austral.***: IBS Eze; Sedatif†; Stomach Calm; ***Austria***: Galstena; Lymphdiaral; Taraxacum Med Complex; ***Canad.***: Carduus Plex†; Chelidonium Plex†; Choleodoron†; Dandelion Combination†; Digestion; Formula FV 213; Formula Homeo QR 209†; Headache & Migraine L77; Hepar Compositum; Sedatil; ***Cz.***: Hepeel; Sedatif PC; ***Fr.***: Abbe Chaupitre no 35†; Adenocynesine†; Amanita Complexe No 75; Boripharm No 15†; Chelidonium Compose; Choleodoron; Conium Complexe No 36†; Digeoslor; Gastro-Drainol†; Grindelia Complexe No 58; Hepatodrainol; Hepatopan†; Hydrastis Compose; Juniperus Complexe No 6; Kreosotum Complexe No 62; L 114; Phapax; Sedatif PC; Yucca Complexe No 110; ***Ger.***: Chelidonium comp; Chol-Do; Choleodoron†; Cholo 2-injektopas; Derivatio H; Derivatio; Flenin; Galloselect; HanoHepan; Hepa-Gastreu N R7; Hepa-Loges N; Hepar comp; Hepar-Hevert N; Hepar-Hevert; Hepar-Hevert; Homviohepan; Infihepan; Leber-Galletropfen; Lymphdiaral; Marianon Hepar; Phonix Silybum spag; Phyto-L; Phytocortal; Rufebran heparo†; Spasmo-Bomaleb†; ***Hung.***: Hepeel; Sedatif; ***Neth.***: Actelite; Chelidonium-Homaccord N; Choleodoron; Collite; Echilite; Hepa-Gastreu R7; Hepalite; Hepatodrainol†; Lymphdiaral; Sedatif PC; ***Port.***: Hepatodrainol; Sedatif PC; ***Rus.***: Berberis-Plus (Берберис-Плюс); Galstena (Галстена); Helidonium-Plus (Хелидониум-Плюс); Homeostres (Гомеострес); ***Switz.***: Hepeel; metaheptachol; Regenaplex Nr. 79; Sedatif PC; ***UK***: Choleodoron; ***Ukr.***: Choledius (Холедиус); Galstena (Галстена); Sedatif PC (Седатив ПЦ); ***USA***: Preferred Remedies Detoxin.

Green-lipped Mussel

Extracto de mejillón de labios verdes; Зеленого Губчатого Моллюска.
UNII — 1L5332YQ7U.

Profile

An extract from the green-lipped mussel *Perna canaliculus* (Mytilidae), stated to contain omega-3 polyunsaturated fatty acids, amino acids, fats, carbohydrates, and minerals, has been promoted for the treatment of rheumatic disorders including rheumatoid arthritis (p. 13.2). It has also been tried in asthma.

Musculoskeletal and joint disorders. Reviews of the investigation of green-lipped mussel in the treatment of arthritis have not revealed conclusive evidence of its usefulness,[1-4] although it might be of benefit in osteoarthritis when taken with paracetamol or NSAIDs.[3]

1. Li Wan Po A, Maguire T. Green-lipped mussel. *Pharm J* 1990; **244:** 640–1.
2. Cobb CS, Ernst E. Systematic review of a marine nutriceutical supplement in clinical trials for arthritis: the effectiveness of the New Zealand green-lipped mussel *Perna canaliculus*. *Clin Rheumatol* 2006; **25:** 275–84.
3. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)
4. Brien S, *et al*. Systematic review of the nutritional supplement *Perna canaliculus* (green-lipped mussel) in the treatment of osteoarthritis. *Q J Med* 2008; **101:** 167–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Lyprinol; ***UK***: Healtheries Musseltone; Lyprinol; Mobilyzer; Oceantone; Seatone; Supplex.

Multi-ingredient Preparations. ***Ital.***: Osteoclar; ***UK***: Healtheries Musseltone & Glucosamine.

Griffonia Simplicifolia

Гриффония.
UNII — 8M5FTG8LCS (Griffonia simplicifolia); *LUS5142TMY* (Griffonia simplicifolia *seed*).

Profile

The leaf, stem, and twigs of *Griffonia simplicifolia* (Fabaceae) have been used for a variety of disorders in its native West Africa. It is included in herbal and nutritional supplements. It is a source of lectins and has insecticidal properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Safralite; ***Ital.***: Brioplus; Calmason; Climil Complex; Ginecast; Spm-OK.

Grindelia

Gum Plant; Gumweed; Tar Weed; Гринделия Крупная (*Grindelia camporum*).
ATC Herb — HR05WA5016 (Grindelia humilis: *herb*); *HR05WA5015* (Grindelia camporum: *herb*); *HR03WX5004* (Grindelia camporum: *herb*).
UNII — IDB0NAZ6AI (grindelia); E9Q71VSJ15 (Grindelia robusta).

Pharmacopoeias. In *Fr.* which allows *Grindelia camporum*, *G. humilis*, *G. robusta*, and *G. squarrosa*.

Profile

Various *Grindelia* spp. (Asteraceae) have been included in herbal preparations used for respiratory-tract disorders.

Homoeopathy

Grindelia has been used in homoeopathic medicines under the following names: Grindelia robusta; Grind. ro.

References.

1. Canavan D, Yarnell E. Successful treatment of poison oak dermatitis treated with *Grindelia* spp. (Gumweed). *J Altern Complement Med* 2005; **11:** 709–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Expectosan Hierbas y Miel; ***Austral.***: Asa Tones†; Euphorbia Complex†; PulmaCo; ResCo; ***Chile***: Ramistos; ***Fr.***: Coquelusedal Nourrissons; Coquelusedal Paracetamol Nourrissons†; Coquelusedal Paracetamol; Coquelusedal; Ephydion†; Neo-Codion; Neo-Codion; Pectoflorine†; Vegetoserum; ***Hung.***: Bronchicum; Bronchicum; ***Indon.***: Pec-

tum; ***Ital.***: Broncosedina; Broncosedina; Cistefi; ***Neth.***: Bronchicum; ***Pol.***: Bronchicum Eliksir†; Echinasal; ***Rus.***: Bronchicum (Бронхикум)†; Bronchicum Husten (Бронхикум Сироп от Кашля)†; Neo-Codion (Нео-Кодион)†; Neo-Codion Babies (Нео-Кодион Для Младенцев)†; ***Spain***: Pazbronquial; ***Switz.***: Neo-Codion N; Nican†; ***Venez.***: Novacodin.

Homoeopathic Preparations. ***Canad.***: Arum Triphyllum Plex†; ***Fr.***: Arum Triphyllum Compose; Grindelia Complexe No 58; ***Ger.***: A-Bomin; Aralis; Asthmakhell N; Bronchi-Do; Bronchopas; Bronchosyx comp; Drosera-Weliplex†; Neolin-Entoxin; Pulmo Bronchialcomplex; Pulmo Bronchialcomplex; Pulmorell; Santa Flora S; ***Neth.***: Ailgeno spag; Asakell; Asthmakhell†.

Ground Ivy

Ale-hoof; Gundelrebe; Gundermann; Hiedra terrestre; Lierre Terrestre; Nepeta Glechoma; Будра Плющевидная.
UNII — L6O7WQK912 (Glechoma hederacea).

Pharmacopoeias. In *Chin.* and *Fr.*

Profile

Ground ivy, the aerial parts of *Glechoma hederacea* (*Nepeta hederacea*) (Labiatae) has been used for respiratory-tract and gastrointestinal disorders.

Homoeopathy

Ground ivy has been used in homoeopathic medicines under the following names: Glechoma; Glechoma hederacea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Gerard House Water Relief Tablets; Water Naturtabs.

Homoeopathic Preparations. ***Canad.***: Toxex; ***Hung.***: Toxex; ***Neth.***: Ailgeno spag; Habifac; Opsonat; Speci-chol; Toxex; ***Switz.***: Regenaplex Nr 28a.

Guaiacum Resin

Guaiac; Guaiacum; Guajakharz; Gwajakowa żywica; Resina de guayaco; Гваяковая Смола.
CAS — 9000-29-7.
UNII — N0K2Z502R6 (Guaiacum officinale resin); 03C8A0DFJ8 (guaiac).

Profile

Guaiacum resin is obtained from guaiacum wood (lignum vitae; *Guaiacum officinale* or *G. sanctum*) (Zygophyllaceae) and has been used in the treatment of rheumatism. It is used in herbal medicine.

Guaiacum resin is used in the detection of occult blood in the faeces. The accuracy of the guaiacum test has been questioned and some drugs may interfere with the result.

Homoeopathy

Guaiacum resin has been used in homoeopathic medicines under the following names: Guaiacum; Guajacum; Guaic.

References.

1. Ko CW, *et al.* Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003; **115:** 111–14.
2. Tannous B, *et al.* Comparison of conventional guaiac to four immunochemical methods for fecal occult blood testing: implications for clinical practice in hospital and outpatient settings. *Clin Chim Acta* 2009; **400:** 120–2.
3. Loitsch SM, *et al.* Stool test for colorectal cancer screening—it's time to move! *Clin Lab* 2008; **54:** 473–84.
4. Guittet L, *et al.* Comparison of a guaiac and an immunochemical faecal occult blood test for the detection of colonic lesions according to lesion type and location. *Br J Cancer* 2009; **100:** 1230–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Boswellia Compound; ***Ital.***: Tisana Kelemata; ***Switz.***: Pommade au Baume; ***UK***: Gerard House Reumalex; Rheumatic Pain Relief; Rheumatic Pain Remedy; Rheumatic Pain.

Homoeopathic Preparations. ***Austria***: Anfokali; Globuli gegen Halsweh Nr 1; ***Canad.***: Arthritis Pain Formula; ***Chile***: Artroplex; ***Ger.***: Cefadolor H†; Homvioartrin; Infekt-Komplex L Ho-Fu-Complex; Tonsipret; ***Hung.***: Anfokali; ***Neth.***: Apo-Rheum†; Reudol; ***Rus.***: Tonsipret (Тонзипрет); ***Ukr.***: Tonsipret (Тонзипрет).

Guaiazulene

Gayazulen; Guayazuleno; Gwajazulen; Гвайазулен.
1,4-Dimethyl-7-isopropylazulene.
$C_{15}H_{18}$=198.3
CAS — 489-84-9.
ATC — S01XA01.
ATC Vet — QS01XA01.
UNII — 2OZ1K9JKQC.

Profile

Guaiazulene has been reported to have anti-allergic, anti-inflammatory, antipyretic, and antiseptic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Azulon; ***Austria***: Azulenal; ***Cz.***: Ophthalmo-Azulen; ***Fr.***: Azulene†; ***Hung.***: Azulenol; Garmastan; ***Turk.***: Garmastan.

Multi-ingredient Preparations. ***Arg.***: Sodorant; ***Austria***: Piniment; Spasmo Claim†; Thrombocid; ***Cz.***: Dermazulen; Ophthalmo-Septonex; Pinosol; Pityol; ***Fr.***: Cicatryl; Pepsane; ***Ger.***: Thrombocid; ***Hong Kong***: Thrombocid; ***Hung.***: Pinosol; ***Israel***: Aronal Forte; ***Mex.***: Pepsane; ***Pol.***: Pinosol†; ***Port.***: Thrombocid; ***Rus.***: Pepsane-R (Пепсан-Р); Pinosol (Пиносол); Pinovitum (Пиновитум); ***Switz.***: Bain extra-doux; ***Ukr.***: Pepsane (Пепсан); Pinosol (Пиносол)†.

Guanidine Hydrochloride

Carbamidine Hydrochloride; Guanidina, hidrocloruro de; Guanidyny chlorowodorek; Iminourea Hydrochloride; Гуанидина Гидрохлорид.
CH_5N_3,HCl=95.53
CAS — 113-00-8 (guanidine); 50-01-1 (guanidine hydrochloride).
UNII — 3YQC9ZY4YB.

Profile

Guanidine hydrochloride enhances the release of acetylcholine from nerve terminals. It has been given orally to reverse neuromuscular blockade in patients with botulism (p. 2380.2), but its efficacy has not been established. Guanidine hydrochloride has also been tried in Eaton-Lambert myasthenic syndrome (p. 684.1) and other neurological disorders, but its use has been associated with bone-marrow suppression in some patients.

References.

1. Kaplan JE, *et al.* Botulism, type A, and treatment with guanidine. *Ann Neurol* 1979; **6:** 69–71.
2. Critchley EMR, *et al.* Outbreak of botulism in North West England and Wales. *Lancet* 1989; **ii:** 849–53.
3. Neal KR, Dunbar EM. Improvement in bulbar weakness with guanoxan in type B botulism. *Lancet* 1990; **335:** 1286–7.
4. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; **20:** 1146–52.

Guanosine

Guanine Riboside; NSC-19994; Vernine; Гуанозин.
2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6(1*H*)-one.
$C_{10}H_{13}N_5O_5$=283.2
CAS — 118-00-3.
UNII — 12133JR80S.

Profile

Guanosine is an endogenous guanine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). Guanosine is included in preparations for peripheral and cerebral vascular disorders and myopathies; guanosine monophosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Vitacic†; ***Spain***: Nutracel.

Guggul

Guggal; Guggulu; Gugul; Indian Bdellium; Mukul Myrrh.
UNII — 34969JX79R.

Pharmacopoeias. In *US.*

USP 36: (Guggul). The oleo-gum-resin obtained by incision or produced by spontaneous exudation from the stem and branches of *Commiphora wightii*. Store at 8 degrees to 15 degrees. Protect from light and moisture.

Profile

Guggul is the oleo-gum resin obtained from *Commiphora wightii* (*C. mukul*; *Balsamodendrum wightii*; *B. mukul*) (Burseraceae), a tree native to India. Guggul extracts have long been used in Ayurvedic medicine. Guggulipid (guglip; guglipid; gugulipid) is a standardised ethyl acetate extract of the gum resin that is produced commercially and used in dietary supplement preparations for lipid disorders, weight loss, and arthritis. The ketonic steroids *E*- and *Z*-guggulsterone are believed to be the bioactive compounds in guggulipid and other guggul extracts; they are thought to inhibit cholesterol synthesis through antagonism of the farsenoid X and bile-acid receptors.

Guggul should not be confused with myrrh (p. 2566.1) to which it is related.

Although plausible mechanisms of action have been shown for guggulsterones, the active plant sterols in the dietary supplement guggulipid, there is no scientific evidence to support use in practice to improve lipid profiles.[1-4]

1. Szapary PO, *et al.* Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. *J AMA* 2003; **290:** 765–72.
2. Sahni S, *et al.* Guggulipid use in hyperlipidemia: case report and review of the literature. *Am J Health-Syst Pharm* 2005; **62:** 1690–2.
3. Ulbricht C, *et al.* Natural Standard Research Collaboration. Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. *Complement Ther Med* 2005; **13:** 279–90.
4. Nohr LA, *et al.* Resin from the mukul myrrh tree, guggul, can it be used for treating hypercholesterolemia? A randomized, controlled study. *Complement Ther Med* 2009; **17:** 16–22.

Adverse effects. References.

1. Kölönte A, *et al.* Allergic contact dermatitis to guggul extract contained in an anticellulite gel-cream. *Contact Dermatitis* 2006; **54:** 226–7.
2. Salavert M, *et al.* Allergic contact dermatitis to guggul in a slimming cream. *Contact Dermatitis* 2007; **56:** 286–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Flexi-muv†; Karnim; ***Malaysia***: Rumalaya; ***Rus.***: Pilex (Пайлекс).

Pharmacopoeial Preparations

USP 36: Guggul Tablets; Native Guggul Extract; Purified Guggul Extract.

Gutta Percha

Gummi Plasticum; Gutapercha; Gutt. Perch.; Гуттаперча.
ATC Herb — HA01AD5001 (Palaquium gutta: gum).
UNII — 6Z9BZ8Q1D0.

Pharmacopoeias. In *US.*

USP 36: (Gutta Percha). The coagulated, dried, purified latex of the trees of the genera *Palaquium* and *Payena* and most commonly *Palaquium gutta* (Sapotaceae). It occurs in lumps or blocks of variable size; externally brown or greyish-brown to greyish-white in colour; internally reddish-yellow or reddish-grey and having a laminated or fibrous appearance. It is flexible but only slightly elastic. Has a slight, characteristic odour. Insoluble in water; partly soluble in carbon disulfide, in turpentine oil, and in benzene; about 90% soluble in chloroform. Store under water. Protect from light.

Profile

Gutta percha has been used in various dressings. In dentistry, gutta percha has been used as a filling material and as the basis of compounds for taking dental impressions.

Haematoporphyrin

Hematoporfirina.
$C_{34}H_{38}N_4O_6$=598.7
CAS — 14459-29-1.

Profile

Haematoporphyrin is an iron-free red pigment obtained from haematin. It is an ingredient of preparations promoted as tonics, particularly for the elderly, and has been used in the treatment of depression. Derivatives of haematoporphyrin are used as photosensitisers in the photodynamic therapy of malignant neoplasms (see Porfimer Sodium, p. 849.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hemedonine.

Multi-ingredient Preparations. ***Austria***: KH3; ***Chile***: Actebral; ***Gr.***: KH3; ***Hong Kong***: KH3; ***Ital.***: Porfirin 12; Tonogen; ***NZ***: KH3; ***Thai.***: KH3†.

Hamamelis

Amamelide; Csodamogyorólevél (hamamelis leaf); Hamamelių lapai (hamamelis leaf); Hamamelidis; Hamamelidis folium (hamamelis leaf); Hamameliksenlehti (hamamelis

leaf); Hamamélis de virginie; Hamamélis, feuille d' (hamamelis leaf); Hamamelisblad (hamamelis leaf); Trollhassel; Vilínový list (hamamelis leaf); Virginsk Troldnød; Witch Hazel; Zauberhasel; Zaubernuss; Гамамелис.

ATC Herb — HD03WA5004 (Hamamelis virginiana: *leaf); HC05AW5003* (Hamamelis virginiana: *leaf); HD03WX5007* (Hamamelis virginiana: *leaf with twig); HD03WA5003* (Hamamelis virginiana: *bark).*

UNII — V663Q8TEFU (Hamamelis virginiana*); IH3063S9MY* (Hamamelis virginiana *bark); 222MYC9QUV* (Hamamelis virginiana *flower water); T07U1161SV* (Hamamelis virginiana *leaf); 8FP93ED6H2* (Hamamelis virginiana *leaf water); T7S323PKJS* (Hamamelis virginiana *root bark/stem bark); UDA30A2JJY* (Hamamelis virginiana *top); NT00Y05A2V* (Hamamelis virginiana *top water); 101I4J0U34* (Hamamelis virginiana *twig water).*

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Hamamelis Leaf). The whole or cut dried leaves of *Hamamelis virginiana* containing not less than 3% tannins, expressed as pyrogallol ($C_6H_6O_3$ = 126.1), calculated with reference to the dried drug. Protect from light.

USP 36: (Witch Hazel). A clear, colourless distillate prepared from recently cut and partially dried dormant twigs of *Hamamelis virginiana.* pH between 3.0 and 5.0. Store in airtight containers at a temperature not exceeding 40 degrees.

Profile

Hamamelis has astringent properties and contains gallic acid, a bitter principle, and a trace of volatile oil. It is used in preparations for the symptomatic relief of haemorrhoids (p. 1808.1). Hamamelis water is used as a cooling application and has been applied as a haemostatic.

Hamamelis is used in herbal preparations for a variety of disorders.

Homoeopathy

Hamamelis has been used in homoeopathic medicines under the following names: Hamamelis virginiana; Hamamelis, Folium; Hamamelis virginiana e foliis; Hamamelis virginiana ex cortice summitatibusque; Hamamelis virginica; Ham. virg.

General references.

1. WHO. Folium et Cortex Hamamelidis. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/14.html (accessed 04/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Optrex; ***Austria***: Hametum; ***Braz.***: Hemoproct; ***Canad.***: Nik + Aid†; Optrex; ***Fr.***: Optrex; ***Ger.***: Faktu mit Hamamelis; Haenal Hamamelis; Hametum; Posterine; ***Hong Kong***: Optrex; ***Irl.***: Optrex; ***Ital.***: Acqua Virginiana; Derminiol; Optrex; ***Malaysia***: Optrex; ***Mex.***: Tia Puppy; ***NZ***: Optrex; ***Pol.***: Phlogderm†; ***Port.***: Optrex; ***Singapore***: Optrex; Preparation H; ***Spain***: Derminiol†; Hemo Derminiol†; Optrex; Suaviplant†; ***Switz.***: Hametum; Mavena Anal-Gen; Optrex; ***Thai.***: Optrex; ***Turk.***: Hametan; ***UK***: Optrex; Preparation H Clear Gel; Witch Doctor; Witch Sunsore; ***USA***: A-E-R; Neutrogena Drying.

Multi-ingredient Preparations. ***Arg.***: Astriluge; Dermacne; Domuderm; Ecnagel; Esculeol P; Lavandula Oligoplex; Manzan; Varicura; Venoful; VNS 45; Xyloprocto Toallas; ***Austral.***: Anusol†; Gentlees; Hemocane; Optrex Medicated†; ***Austria***: Arnicet†; Inotyol; Inotyol; Mirfulan; Sulgan 99; ***Belg.***: Hemorhinol†; Purigel Crisp†; Rectovasol; ***Braz.***: Hemodotti†; Hemofleb; Higicler; Malvatricin Natural Organic†; Proctosan; Visionom; ***Canad.***: Onrectal†; Preparation H-PE Gel; Tucks†; ***Chile***: Keracnyl Stop Bouton; Normaderm Barra de Limpieza; Normaderm Concentrado Activo; Normaderm Gel de Limpieza; Proctoplex; ***Fr.***: Anastase; Anthylline†; Aphloine P; Climaxol; Diveine; Evarose†; HEC; Histo-Fluine P; Inotyol; Jouvence de l'Abbe Soury; Jouvence de l'Abbe Soury; Keracnyl eau nettoyante†; Keracnyl stop bouton; Mediflor Circulation du Sang No 12†; Ophtalmine†; Pastilles Monleon†; Phlebosedol†; Phytomelis; Santane V_3†; Tisane Provencale no 3†; Veinostase; ***Ger.***: Aescusan†; Eulatin NH; Mirfulan; Trauma-cyl†; Varicylum-S†; Weleda Hamorrhoidalzapfchen; Weleda Hauttonikum†; ***Hong Kong***: Eye Glo Plus; ***Indon.***: Oculosan; ***Irl.***: Optrex Clear Eyes; ***Israel***: Derma Care; Inotyol; ***Ital.***: Altacura Ipragocce; Centella Complex; Centella Complex; Centeril H; Centeril H; Decon Ovuli; Dermilia Flebozin†; Dermitina; Eulux; Fito Stomygen†; Gefion; Ginoxil Ecoschiuma; Intim; Iridil; Mirtiros; Nevril; Proctopure; Sacnel; Salviette H; Steril Zeta; Venactive; Venalta; ***Malaysia***: Dermaheal DeAkni; ***Mex.***: Almodin; Prespir; Supranettes Naturalag; ***Mon.***: Fluon+; Fluon; ***Neth.***: Bioforce; ***NZ***: Optrex Red-Eye Relief; ***Port.***: Hemofissural; ***S.Afr.***: Lotio Pruni Comp cum Cupro†; Stibium Comp†; ***Singapore***: Nu-Derm Toner; Stop-Itch Plus; ***Spain***: Banoftal†; Ojosbel Azul†; Ojosbel; Solucion Schoum; ***Switz.***: Baume Dalet; Collypan; Haemolan†; Hametum-N; HEC†; Mavena Proctal-Gen†; Oculosan; Optrex compresses†; Suppositoires contre les hemorroides; Venadoron; ***Thai.***: Opplin; ***Turk.***: Symphosan; ***UK***: Adiantine; Eye Dew; Heemex; Lacto Calamine; Lacto Calamine; Modern Herbals Pile; Optrex Red Eyes; Supranettes; Swarm; Tea Tree & Witch Hazel Cream; Varicose Ointment; Vital Eyes; ***USA***: Bioflex; Clearasil Double Clear; Flexgen; Preparation H Cooling Gel; Tucks; ***Venez.***: Camolyn Plus; Camolyn; Flucirac.

Homoeopathic Preparations. ***Austria***: Hamamelis-Homaccord; Traumeel; Venodril; Vensa; ***Canad.***: Avenoc†; Cruroheel S†; Formula CI 207†; Formula Homeo QR 209†; Hae 1 Complex†; Lympatox; Traumeel; ***Chile***: Arnica Hamamelis Compuesta; Calcarea fluor Compuesta; Variplant; Variplex; ***Cz.***: Traumeel; ***Fr.***: Abbe Chaupitre no 15†; Abbe Chaupitre no 20†; Abbe Chaupitre no 64†; Aesculus Complexe No 103; Aesculus Compose; Avenoc; Calendula Complexe No 89; Hamamelis Compose; Homeodose 20†; L 28; Poconeol no 51; Pulviplasmine†; Sepia Compose; Thlascose†; Vascoflor; Veino-Drainol†; Veinosium†; ***Ger.***: Agnus castus comp†; EAP-61; Haemorrhoid-Gastreu N; Heweven Complex; Infihepan; ISO-Augentropfen C; Pesendorfer; phono Ven; Regenaplex Haut W; Reproven N; Ruta-Gastreu N R55; Secale-Gastreu; Traumeel S; Varicylum N; Venen-Komplex Ho-Fu-Complex; Veno-Injektopas; Venokatt; Venorell; Wibotin HM; ***Hung.***: Traumeel; ***Neth.***: Aesculus Comp; Ambheel; Hemorrolite; Homeocare Vasco; Omnilite; Traumeel S; Venafleur; ***Port.***: Avenoc; Homeodent†; ***Rus.***: Mercure-Plus (Меркур-Плюс); Paeonia-Plus (Пеония-Плюс); Traumeel S (Траумель С); Vensa (Венза); ***S.Afr.***: Achillea Comp†; Hamamelis Comp†; Traumeel S; ***Switz.***: Regenaplex Nr. 25c; Regenaplex Nr. 31a; Regenaplex Nr. 31b; Regenaplex Nr. 31c; Regenaplex Nr. 49a; Regenaplex Nr. 59b; Traumeel; ***UK***: Haemorrhoid Cream; ***Ukr.***: Traumeel S (Траумель С); ***USA***: Succus Cineraria Maritima†; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations

USP 36: Witch Hazel.

Harmaline

Harmalina.

3,4-Dihydroharmine.

$C_{13}H_{14}N_2O$=214.3

CAS — 304-21-2.

UNII — CN58I4TOET.

Description. Harmaline is an alkaloid obtained from peganum, the dried seeds of *Peganum harmala* (Zygophyllaceae).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of harmaline or preparations containing harmaline:

Caapi; Huasca; Purga, la; Vine; Yage.

Harmine

Harmina; 7-Methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole; Хармин.

$C_{13}H_{12}N_2O$=212.3

CAS — 442-51-3.

UNII — 4FHH5G48T7.

Description. Harmine is an alkaloid obtained from peganum, the dried seeds of *Peganum harmala* (Zygophyllaceae), also known as Syrian rue.

Harmine is identical with an alkaloid known as banisterine or telepathine obtained from *Banisteriopsis caapi* (Malpighiaceae).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of harmine or preparations containing harmine:

Rue.

Profile

Harmine and harmaline are the main active principles of a hallucinogenic drink, known in South American regions as 'ayahuasca', 'caapi', or 'yagé', that is made from closely related plants of the family Malpighiaceae. They have no therapeutic use.

Hedge Mustard

Erysimum; Hederichkraut; Herbe aux Chantres; Scrambling Rocket; Singer's Plant; St. Barbara's Hedge Mustard; Thalictroc; Vägsenap; Wegrauke; Wegsenf; Гулявник Лекарственный.

NOTE. The name English Watercress has been applied to Hedge Mustard, but it is more usually applied to *Nasturtium officinalis.*

Profile

The aerial parts of hedge mustard *Sisymbrium officinale* (*Erysimum officinale*) (Brassicaceae), have been used in herbal medicine mainly for sore throats and coughs. It has been given orally for respiratory, urinary, and gastrointestinal disorders. It is reported to contain cardioactive glycosides.

Hedge mustard also has culinary uses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Euphon; ***Fr.***: Drill Enrouement; Euphon; Voxyl†; ***Port.***: Euphon; ***Singapore***: Euphon.

Multi-ingredient Preparations. ***Fr.***: Activox; Clarix Toux Seche†; Euphon; Humex Gorge Irritee†; Pectoflorine†; Pholcodyl†; Polery; Polery; Vocadys; ***Malaysia***: Euphon; ***Port.***: Euphon; ***Rus.***: Cardiovalen (Кардиовален).

Homoeopathic Preparations. ***Fr.***: Pulviplasmine†; Voxpax.

Helonias

Blazing Star; Chamaelirium; False Unicorn; Helicornio falso; Starwort.

UNII — 4TT3575T8B (Chamaelirium luteum*); DQV54Y5H3U* (Chamaelirium luteum *root).*

Profile

Helonias is the root of *Chamaelirium luteum* (*Helonias dioica*) (Liliaceae). It is used in herbal medicine particularly for gynaecological disorders.

Homoeopathy

Helonias has been used in homoeopathic medicines under the following names: Chamaelirium luteum; Helonias dioica; Helon.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Capsella Complex; Nervatona Calm; Nervatona Focus; ***UK***: Period Pain Relief.

Homoeopathic Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus; ***Austria***: Pascofemin; ***Canad.***: Formula CA 205†; Motherwort Combination 1†; ***Chile***: Calendula Echinacea Comp; Ovukalen; ***Cz.***: Vita C-R15 forte†; Vita C-R15†; ***Fr.***: Diabene; Endhometrol; Helonias Compose; Sativol†; ***Ger.***: Aletris N Oligoplex; Aletris Oligoplex†; Femin-Do; HanoFemin; Infi-China; Naranofem†; Pascofemin; ***Neth.***: Sativol†.

Hemlock

Beaver Poison; Carrot Fern; Ciguë Tachée; Ciguë Tachetée; Conium; Deadly Hemlock; Fool's Parsley; Gefleckter Schierling; Herb Bennet; Kecksies; Kex; Myrkkykatko; Odört; Poison Hemlock; Poison Parsley; Schierling; Spotted Corobane; Spotted Cowbane; Spotted Hemlock; Spotted Parsley; St. Bennett's Herb; Болиголов Пятнистый; Бучиниш.

UNII — Q28R5GF371 (conium); 8N34F5Z76Y (hemlock).

NOTE. Distinguish from Hemlock Spruce (*Tsuga canadensis*, also known as Hemlock), water hemlock (applied to various *Cicuta* spp., notably *Cicuta virosa*, and also to *Oenanthe aquatica*), and hemlock water dropwort (*Oenanthe crocata*, also known as water hemlock). The name Herb Bennet, sometimes applied to hemlock, is more usually used for Avens, *Geum urbanum.* The name Wild Carrot has been applied to Hemlock but usually refers to *Daucus carota* (see p. 2647.2). The name Cicuta has been applied to Hemlock, but belongs to a different genus.

Profile

The fresh or dried leaves and unripe fruit of hemlock, *Conium maculatum* (Apiaceae) have traditionally been used in herbal medicines for their sedative and antispasmodic properties. Hemlock contains the alkaloid coniine, which has actions similar to nicotine (p. 2571.1); poisoning causes paralysis of the peripheral nervous system and skeletal muscles. Death is due to respiratory failure arising from paralysis of the muscles of respiration. All parts of the plant are poisonous, but accidental poisoning with the fresh plant is rare because of its unpleasant odour.

Homoeopathy

Hemlock has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Unguentum lymphaticum†; ***Venez.***: Linfoderm.

Homoeopathic Preparations. ***Austria***: Gentos; Lymphdiaral; Memoria; Selenium Med Complex; Vertigoheel; Vertigopas; ***Canad.***: Ginkgo-Comp†; Itires; Tyglan†; ***Chile***: Bioactiv F; Bioactiv V; ***Cz.***: Vertigoheel; ***Fr.***: Adenocynesine†; Conium Complexe No 36†; Dolitravel†; Kalmia Complexe No 18; Sabal Serrulata Compose; Scrofularia Compose; Selenium Complexe No 99; ***Ger.***: Flenin; ISO-Augentropfen C; Lymphaden Complex; Lymphdiaral sensitive N; Lymphdiaral; Lymphdiaral; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pesendorfer; Prostata-Gastreu N R25; Vertigo Hevert SL; Vertigo-Hevert; Vertigoheel; Vertigopas; Zerosorin SN†; ***Hung.***: Gentos; Vertigoheel; ***Neth.***: Cerebrum comp; Coconium-Gastreu; Dolilite;

Emvita 3; Lymphdiaral; Omnilite; Vertigoheel; ***Rus.***: Diet-Comfort (Диет-Комфорт); Gentos (Гентос); Mastopol (Мастопол); Memoria (Мемория); ***S.Afr.***: Vertigoheel; ***Switz.***: Vertigoheel; ***Ukr.***: Gentos (Гентос); Memoria (Мемория); ***USA***: Vertigoheel.

Henna

Alheña; Henna Leaf; Henné; Hoja de henna; Lawsonia; Хенна; Хна.
UNII — E5818YZ355.

Profile

Henna is the dried leaves of *Lawsonia inermis* (*L. alba*) (Lythraceae), containing lawsone (p. 2541.2). Powdered henna is used for dyeing the hair, skin, and nails.

Adverse effects. Allergic skin reactions to henna used to dye or temporarily tattoo the skin have been reported but are usually due to additives used to darken the colour and shorten the application time of the dye; allergic reactions to 'plain' henna are rare.[1] The most common cause of reactions is paraphenylenediamine—for further discussion and references, see Hypersensitivity under Paraphenylenediamine, p. 2583.3.

The suggestion that henna may cause neonatal hyperbilirubinaemia is discussed under Lawsone, p. 2541.3.

1. Lestringant GG, *et al.* Cutaneous reactions to henna and associated additives. *Br J Dermatol* 1999; **141:** 598–600.

Heptaminol Hydrochloride *(BANM, rINNM)* ⊗

Heptaminol, Chlorhydrate d'; Heptaminol, chlorhydrate de; Heptaminol, hidrocloruro de; Heptaminol hydrochlorid; Heptaminol-hidroklorid; Heptaminolhydrochlorid; Heptaminolhydroklorid; Heptaminoli Hydrochloridum; Heptaminolihydrokloridi; Heptaminolio hidrochloridas; Hidrocloruro de heptaminol; RP-2831; Гептаминола Гидрохлорид.
6-Amino-2-methylheptan-2-ol hydrochloride.
$C_8H_{19}NO,HCl$=181.7
CAS — 372-66-7 (heptaminol); 543-15-7 (heptaminol hydrochloride).
ATC — C01DX08.
ATC Vet — QC01DX08.
UNII — XB3RM40HIR.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Heptaminol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Profile

Heptaminol hydrochloride is a cardiac stimulant and vasodilator and has been given in the treatment of cardiovascular disorders. Heptaminol and heptaminol adenosine phosphate have also been used.

References.

1. Gharibi L, *et al.* Hair lightening in an hemodialysis patient treated by heptaminol (heptamyl). *Dermatol Online J* 2009; **15:** 16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ampecyclal; Hept-A-Myl; ***Indon.***: Hept-A-Myl.

Multi-ingredient Preparations. ***Arg.***: Flebitol; ***China***: Ginkor Fort (静可福); ***Cz.***: Ginkor Fort; ***Fr.***: Debrumyl; Ginkor Fort; ***Gr.***: Doprene; ***Hong Kong***: Ginkor Fort; ***Hung.***: Ginkor Fort†; ***Malaysia***: Ginkor Fort; ***Port.***: Debrumyl; Forticol; ***Rus.***: Ginkor Fort (Гинкор Форт); ***Spain***: Denubil; ***Thai.***: Ginkor Fort; ***Ukr.***: Ginkor Fort (Гинкор Форт).

Herniaria

Bruchkraut; Herba Herniariae; Herniary; Rompepiedras; Rupture-wort; Rupturewort; Грыжник.
*UNII — 51O769531P (*Herniaria glabra*); E8SAX233E7 (*Herniaria glabra *flowering).*

Profile

Herniaria consists of the dried leaves and flowering tops of various species of rupture-wort, chiefly *Herniaria glabra* and *H. hirsuta* (Caryophyllaceae). It has astringent and diuretic properties and has been given in urinary-tract disorders.

Homoeopathy

Herniaria has been used in homoeopathic medicines under the following names: Herniaria glabra; Hern. gla.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Blasentee St Severin; Uropurat†; ***Cz.***: Urologicka Cajova Smes.

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Fr.***: L 8.

Hibiscus

Guinea Sorrel; Hibisci Flos (flowers); Hibisci Sabdariffae Flos (flowers); Hibiscusblüten (flowers); Jamaica Sorrel; Jamaikinių hibiskų žiedai (flowers); Karkadé; Květ ibišku sudánského (flowers); Oseille de Guinée; Red Sorrel; Rosella; Rosellenkukka (flowers); Roselihibiskusblomma (flowers); Rozella (flowers); Кислица Ямайская; Гибискус Сабдарифа.
UNII — 584J2XT260.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Roselle; Hibisci Sabdariffae Flos). The whole or cut dried calyces and epicalyces of *Hibiscus sabdariffa* collected during fruiting.

Profile

Hibiscus is a large genus of flowering plants in the Malvaceae family. The flowers of roselle, *Hibiscus sabdariffa,* are included in herbal preparations for loss of appetite and a range of disorders of the upper respiratory and gastrointestinal tracts.

Culinary uses of *H. sabdariffa* include hibiscus tea, a refreshing caffeine-free beverage made from the flowers.

Homoeopathy

Hibiscus sabdariffa has been used in homoeopathic medicines under the following names: Sabdariffa.

Hibiscus sabdariffa has been used in folk medicine for the treatment of high blood pressure and while recent studies indicate that it might have antihypertensive[1] and hypolipidaemic effects,[2] a systematic review[3] considered that there was no reliable evidence to support its use in hypertension.

1. McKay DL, *et al. Hibiscus sabdariffa* L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. *J Nutr* 2010; **140:** 298–303.
2. Mozaffari-Khosravi H, *et al.* Effects of sour tea (*Hibiscus sabdariffa*) on lipid profile and lipoproteins in patients with type II diabetes. *J Altern Complement Med* 2009; **15:** 899–903.
3. Wahabi HA, *et al.* The effectiveness of *Hibiscus sabdariffa* in the treatment of hypertension: a systematic review. *Phytomedicine* 2010; **17:** 83–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ukr.***: Aflazin (Афлазин).

Multi-ingredient Preparations. ***Fr.***: Hydracur; ***Hung.***: Telma; ***USA***: Cardiopress.

Histamine

Histamiini; Histamin; Histamina; Histaminum; Гистамин.
2-(Imidazol-4-yl)ethylamine.
$C_5H_9N_3$=111.1
CAS — 51-45-6.
ATC — V04CG03.
ATC Vet — QV04CG03.
UNII — 820484N8I3.

Histamine Hydrochloride

Dihidrocloruro de histamina; Histamiinidihydrokloridi; Histamina, hidrocloruro de; Histamin-dihydrochlorid; Histamindihydrochlorid; Histamindihydroklorid; Histamine, dichlorhydrate d'; Histamine Dihydrochloride (USAN); Histamini Dihydrochloridum; Histamino dihidrocloridas; Histaminy dichlorowodorek; Hisztamin-dihidroklorid; Гистамина Гидрохлорид.
$C_5H_9N_3,2HCl$=184.1
CAS — 56-92-8.
ATC — L03AX14; V04CG03.
ATC Vet — QL03AX14; QV04CG03.
UNII — 3POA0Q644U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Histamine Dihydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. Very soluble in water; soluble in alcohol. A 5% solution in water has a pH of 2.85 to 3.60. Protect from light.

Histamine Phosphate

Difosfato de histamina; Histamiinifosfaatti; Histamin difosfát monohydrát; Histamina, fosfato de; Histamine Acid Phosphate; Histamine Diphosphate; Histamine, phosphate d'; Histaminfosfat; Histamini Diphosphas Monohydricus; Histamini phosphas; Histamino fosfatas; Histaminphosphat; Histaminy fosforan; Hisztamin-foszfát; Гистамина Фосфат.
$C_5H_9N_3,2H_3PO_4,H_2O$=325.2
CAS — 51-74-1 (anhydrous histamine phosphate).
ATC — V04CG03.
ATC Vet — QV04CG03.
UNII — QWB37T4WZZ.

Pharmacopoeias. *Chin.* and *US* specify the anhydrous substance.

USP 36: (Histamine Phosphate). Anhydrous histamine phosphate occurs as colourless, odourless, long prismatic crystals. Is stable in air but is affected by light. Soluble 1 in 4 of water. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. A study concluded that solutions of histamine phosphate could be sterilised by heating in an autoclave with little degradation.[1] Autoclaved solutions could be stored for a minimum of 4 months.

1. McDonald C, *et al.* Stability of solutions of histamine acid phosphate after sterilization by heating in an autoclave. *J Clin Pharm Ther* 1990; **15:** 41–4.

Uses and Administration

Histamine causes stimulation of smooth muscle, especially of the bronchioles, and lowers blood pressure by dilating the arterioles and capillaries. It also stimulates exocrine gland secretion, especially the gastric glands.

Intradermal injection of histamine produces the characteristic 'triple response' of erythema, flare, and wheal. This is used as a control response in skin testing for hypersensitivity. Also, since it is mediated in part by axon reflexes, it has been used to test the integrity of sensory nerves, for example in leprosy.

Inhalation of histamine causes bronchoconstriction and is used as a test of bronchial reactivity.

Histamine has also been given subcutaneously to identify the causes of achlorhydria and intravenously in the diagnosis of phaeochromocytoma, but safer tests are generally preferred.

Histamine is included in some combination topical preparations for musculoskeletal disorders.

Histamine hydrochloride is given subcutaneously as adjunctive treatment with interleukin-2 to patients with acute myeloid leukaemia in first remission after consolidation therapy—see p. 810.3 for further details including doses. Histamine hydrochloride has also been tried as an adjunct to interferons and other drugs in the management of hepatitis C.

Adverse Effects, Treatment, and Precautions

Injection of histamine salts can produce adverse effects including headache, fatigue, pyrexia, dizziness, flushing of the skin, general vasodilatation with a fall in blood pressure, tachycardia, bronchial constriction and dyspnoea, visual disturbances, vomiting, diarrhoea, and other gastrointestinal effects. These reactions can be severe; excessive dosage can produce collapse and shock, and may be fatal. Reactions may occur at the injection site.

Some of these effects may be relieved by an antihistamine, but adrenaline may be required and should always be available.

Histamine salts should be used with care in patients with asthma or other hypersensitivity disorders, in elderly patients, and in patients with cardiovascular disorders. Histamine salts should also be given with caution to patients with severe renal impairment because they may be more sensitive to the blood pressure lowering effects of histamine. Adverse effects such as dizziness and blurred vision may affect the patient's ability to drive or operate machinery after receiving histamine salts.

Interactions

The performance of histamine skin tests can be altered by co-administration of some drugs. Response to histamine is suppressed by antihistamines and can last from 1 to 40 days depending on the antihistamine. Tricyclic antidepressants decrease skin reactivity to histamine that may last for several weeks. Intravenous infusion of dopamine has also been reported to inhibit the histamine skin test response. There is the theoretical possibility that oral terbutaline and parenteral ephedrine might reduce the histamine skin test response since they have been shown to decrease allergen-induced wheal. Conversely the histamine skin test response can be significantly increased by propranolol.

Patients receiving histamine hydrochloride as adjunctive treatment with interleukin-2 for acute myeloid leukaemia (see p. 810.3) should not be given histamine H_2-antagonists such as cimetidine that have imidazole structures similar to histamine, systemic corticosteroids, or clonidine. Drugs that should be avoided or used with caution with exogenous histamine include antihistamines, as well as antipsychotics

that have histamine H_1-antagonist activity, and antidepressants, which may have histamine H_1- and H_2-antagonist activity. Concurrent administration of antihypertensive drugs, including beta blockers, increases the toxicity of exogenous histamine and the combination should be used with caution or avoided. MAOIs, antimalarials, and antitrypanosomal drugs may alter the metabolism of exogenous histamine and should also be used with caution or avoided. Endogenous histamine may be released by neuromuscular blockers, opioid analgesics, and some contrast media, which should be taken into consideration if histamine is given exogenously to patients before undergoing surgical or diagnostic procedures.

Pharmacokinetics

Histamine salts exert a rapid, though transient, effect when given parenterally. Histamine is rapidly metabolised by methylation and oxidation; the metabolites are excreted in the urine.

References.

1. Middleton M, *et al.* Pharmacokinetics of histamine dihydrochloride in healthy volunteers and cancer patients: implications for combined immunotherapy with interleukin-2. *J Clin Pharmacol* 2002; **42:** 774–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Histatrol; ***Cz.***: Ceplene; ***Ger.***: Ceplene; ***Irl.***: Ceplene; ***Mex.***: Destamin; ***Neth.***: Ceplene; Soluprick Controlevloeistoffen; ***Norw.***: Ceplene; ***Pol.***: Ceplene; ***Port.***: Ceplene; Soluprick; ***Swed.***: Ceplene; ***UK***: Ceplene; ***USA***: Histatrol.

Multi-ingredient Preparations. ***Arg.***: Histaglobin; ***Austria***: Histaglobin†; ***Fr.***: Algipan†; ***India***: Algipan; Histaglobulin; ***Neth.***: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; ***Pol.***: Histaglobulina; ***S.Afr.***: Histaglobin†; Infrarub†; ***Switz.***: Radalgin†.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Snore Eze; Snorestop; ***Canad.***: Adrisin†; Hepar Compositum; Homeodel 15†; Luffeel Nasal Spray; Sabalia; Snore Stop; ***Chile***: Apis Compuesto; Similibus; ***Cz.***: Luffeel; Rhinallergy; ***Fr.***: Dolistamine†; Polyrhinium; Rhinallergy; ***Ger.***: Hepar comp; Luffeel Comp; ***Hung.***: Luffeel; ***Neth.***: Homeocare Allerlo; Luffeel H; Prurilite; Snurdim; Urtizon complex; ***Switz.***: Polyrhinium; Rhinallergy.

Pharmacopoeial Preparations

USP 36: Histamine Phosphate Injection.

Histoplasmin

Histoplasmina; Гистоплазмин.

CAS — 9008-05-3.

Profile

Histoplasmin contains standardised culture filtrates of the fungus *Histoplasma capsulatum.* It has been given intradermally as an aid to the diagnosis of histoplasmosis. However, the diagnostic value of the test has been questioned and it may interfere with serological tests for histoplasmosis.

Histoplasmin has also been used, in conjunction with other antigens, to assess cell-mediated immunity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Histolyn-CYL†.

Homocysteine Thiolactone Hydrochloride

3-Aminodihydro-2(3*H*)-thiophenone hydrochloride.

C_4H_8ClNOS=153.6

CAS — 10593-85-8 (homocysteine thiolactone); 3622-59-1 (homocysteine thiolactone hydrochloride).

Profile

Homocysteine thiolactone has been used in preparations for the treatment of liver disorders. Its hydrochloride salt has been used as a mucolytic. Homocysteine thiolactone is a metabolite of homocysteine and has been implicated in the pathogenesis of some cardiovascular diseases (see p. 2063.3).

References.

1. Chwatko G, Jakubowski H. Urinary excretion of homocysteine-thiolactone in humans. *Clin Chem* 2005; **51:** 408–15.
2. Jakubowski H. The molecular basis of homocysteine thiolactone-mediated vascular disease. *Clin Chem Lab Med* 2007; **45:** 1704–16.

Horseradish

Armoracia; Meerrettich; Rábano picante; Rábano rusticano; Raifort; Хрен.

UNII — 8DS6G120HJ.

Profile

Horseradish, the root of *Cochlearia armoracia* (*Armoracia rusticana*; *Nasturtium armoracia*; *Radicula armoracia*) (Cruciferae), has diuretic and antiseptic properties and stimulates the digestion. It is used in gastrointestinal, respiratory-tract, and urinary-tract disorders, and has also been used externally.

Horseradish is widely used as a food flavouring and condiment.

Homoeopathy

Horseradish has been used in homoeopathic medicines under the following names: Cochlearia armoracia; Cochlearia arm; Coch. ar.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Garlic and Horseradish + C Complex†; Nyal Cold + Flu Fighter Day + Night; Nyal Cold + Flu Fighter; Nyal Cough, Cold & Flu Day + Night; Nyal Sinus Relief Day + Night; Nyal Sinus Relief; Super Strength Horseradish Garlic + C; Ultra Allergy Defense; ***Ger.***: Angocin Anti-Infekt N; ***Switz.***: Kernosan Elixir; Sanogencive; ***UK***: Mixed Vegetable Tablets.

Homoeopathic Preparations. ***Austria***: Asinis; ***Fr.***: Poconeol no 34; ***Port.***: Homeodent†; ***Rus.***: Asinis (Асинис); ***Ukr.***: Asinis (Асинис).

Hyaluronic Acid *(BAN)*

Hialurónico, ácido; Гиалуроновая Кислота.

(1→3)-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-*O*-β-D-glucopyranosiduronan.

CAS — 9004-61-9.

ATC — D03AX05; M09AX01; R01AX09; S01KA01.

ATC Vet — QD03AX05; QM09AX01; QR01AX09; QS01KA01.

NOTE. The term Hyaluronan is used to cover both hyaluronic acid and sodium hyaluronate.

Sodium Hyaluronate *(BANM)*

Hialuronato sódico; Hyaluronate Sodium (USAN); Natrii Hyaluronas; Natrio hialuronatas; Nátrium-hialuronát; Natriumhyaluronaatti; Natriumhyaluronat; Natrium-hyaluronát; NRD-101; Sodium, hyaluronate de; Sodyum Hiyalüronat; Гиалуронат Натрия.

CAS — 9067-32-7.

ATC — D03AX05; M09AX01; S01KA01.

ATC Vet — QD03AX05; QM09AX01; QS01KA01.

UNII — YSE9PPT4TH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Hyaluronate). The sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units. It is extracted from cocks' combs or obtained by fermentation from streptococci (Lancefield Groups A and C). A white or almost white, very hygroscopic powder or a fibrous aggregate. Sparingly soluble to soluble in water; practically insoluble in dehydrated alcohol and in acetone. A 0.5% solution in water has a pH of 5.0 to 8.5. Store in airtight containers. Protect from light and humidity.

Uses and Administration

Hyaluronic acid is widely distributed in body tissues and intracellular fluids, including the aqueous and vitreous humour, and synovial fluid; it is a component of the ground substance or tissue cement surrounding cells.

A viscous solution of sodium hyaluronate is used during surgical procedures on the eye, for example for cataract extraction. Introduction of the solution into the anterior or posterior chamber via a fine cannula or needle allows tissues to be separated during surgery and protects them from trauma. Sodium hyaluronate eye drops 0.1% are also used for the relief of dry eye and as a contact lens lubricant.

Sodium hyaluronate is given by intra-articular injection in the treatment of osteoarthritis of the knee. Doses vary according to the preparation used, but are of the order of 20 to 25 mg once weekly for 5 weeks or up to 30 mg once weekly for 3 or 4 weeks; it is generally recommended that the treatment course for any individual joint should not be repeated within 6 months. Sodium hyaluronate is also used during arthroscopic procedures to flush out irrigating solutions and act as a temporary substitute for synovial fluid.

Hyaluronic acid is applied topically to promote wound healing. Zinc hyaluronate has also been used. A film containing sodium hyaluronate and carmellose is used to prevent surgical adhesion. Sodium hyaluronate has also been used in the management of lesions of the oral mucosa.

Hylans, which are polymers derived from hyaluronic acid, are used similarly for osteoarthritis and wound care.

Sodium hyaluronate instilled intravesically has been used as a temporary replacement of the glycosaminoglycan layer in the bladder for the symptomatic treatment of interstitial cystitis.

Topical formulations of diclofenac in hyaluronic acid (CT-1101, AT-2101) are used in the treatment of actinic keratoses (but distinguish from an oral formulation of afegostat tartrate (p. 2432.1) under investigation for use in Gaucher disease that also carries the code AT-2101).

Hyaluronic acid has been used as a dermal filler for the correction of moderate to severe facial wrinkles and folds (see Photoageing, p. 1686.2).

Reviews.

1. Goa KL, Benfield P. Hyaluronic acid: a review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs* 1994; **47:** 536–66.
2. Adams ME, *et al.* A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Safety* 2000; **23:** 115–30.

Actinic keratoses. For references to the use of diclofenac in a hyaluronic acid gel in the treatment of actinic keratoses, see p. 49.2.

Dry eye. The usual management of dry eye (p. 2190.1) is with artificial tears. Sodium hyaluronate has also been reported to be of some benefit. Alleviation of symptoms[1-3] and an increase in tear film stability[1,2] has been shown after topical application of sodium hyaluronate solution (0.1 or 0.2%) compared with saline-based placebo solutions. However, another study[4] failed to show any advantage over placebo, although it has been suggested[4,5] that sodium hyaluronate might play a role in maintaining a healthy corneal epithelium.

1. Mengher LS, *et al.* Effect of sodium hyaluronate (0.1%) on break-up time (NIBUT) in patients with dry eyes. *Br J Ophthalmol* 1986; **70:** 442–7.
2. Sand BB, *et al.* Sodium hyaluronate in the treatment of keratoconjunctivitis sicca: a double masked clinical trial. *Acta Ophthalmol (Copenh)* 1989; **67:** 181–3.
3. Condon PI, *et al.* Double blind, randomised, placebo controlled, crossover, multicentre study to determine the efficacy of a 0.1% (w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome. *Br J Ophthalmol* 1999; **83:** 1121–4.
4. Shimmura S, *et al.* Sodium hyaluronate eyedrops in the treatment of dry eyes. *Br J Ophthalmol* 1995; **79:** 1007–11.
5. Aragona P, *et al.* Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *Br J Ophthalmol* 2002; **86:** 181–4.

Osteoarthritis. In osteoarthritis, the size and concentration of hyaluronic acid molecules naturally present in synovial fluid is reduced. Thus, one approach in the management of osteoarthritis (p. 12.3) of the knee is viscosupplementation of the synovial fluid by the intra-articular injection of hyaluronic acid or its derivatives. Such injections may reduce pain over 1 to 6 months but may be associated with a short-term increase in knee inflammation; there is some suggestion that any benefit is longer lasting than with intra-articular corticosteroids. Some studies suggest that viscosupplementation may be an effective option for patients who are unable to take oral NSAIDs or have regular intra-articular corticosteroids, and who are unsuitable candidates for joint replacement surgery, although there appears to be considerable variability in clinical response between products, as well as in the variables being assessed and length of treatment.

References.

1. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. *J Rheumatol* 1998; **25:** 2203–12. Correction. *ibid.* 1999; **26:** 1216.
2. Anonymous. Hyaluronan or hylans for knee osteoarthritis? *Drug Ther Bull* 1999; **37:** 71–2.
3. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)* 1999; **38:** 602–7.
4. Wobig M, *et al.* The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther* 1999; **21:** 1549–62.
5. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. *Arch Intern Med* 2002; **162:** 245–7.
6. Lo GH, *et al.* Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; **290:** 3115–21.
7. Bellamy N, *et al.* Viscosupplementation for the treatment of osteoarthritis of the knee. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/05/06).

Wound healing. Hyaluronic acid has been used to aid wound healing,[1,2] the overall management of which is discussed on p. 1690.1.

1. Soldati D, *et al.* Mucosal wound healing after nasal surgery: a controlled clinical trial on the efficacy of hyaluronic acid containing cream. *Drugs Exp Clin Res* 1999; **25:** 253–61.
2. Harris PA, *et al.* Use of hyaluronic acid and cultured autologous keratinocytes and fibroblasts in extensive burns. *Lancet* 1999; **353:** 35–6.

Adverse Effects

There have been reports of a transient rise in intra-ocular pressure when sodium hyaluronate was given into the eye. When injected into the knee, pain and inflammation may

occur at the injection site. There have also been occasional reports of hypersensitivity, including, rarely, anaphylaxis.

Effects on the eyes. Crystalline deposits on intra-ocular lenses have been reported in patients after use of a high viscosity sodium hyaluronate preparation during cataract surgery.[1]

1. Jensen MK, *et al*. Crystallization on intraocular lens surfaces associated with the use of Healon GV. *Arch Ophthalmol* 1994; **112:** 1037–42.

Effects on the skin. A cutaneous granulomatous reaction has been reported in a woman 5 weeks after treatment with synthetic hyaluronic acid for cosmetic use as a dermal filler.[1] All cutaneous lesions resolved spontaneously within 3 months without scarring.

1. Ghislanzoni M, *et al*. Cutaneous granulomatous reaction to injectable hyaluronic acid gel. *Br J Dermatol* 2006; **154:** 755–8.

Inflammatory reaction. Severe peritoneal inflammation has been reported[1] after use of a sodium hyaluronate-based bioresorbable membrane to prevent postoperative adhesion formation.

1. Klingler PJ, *et al*. Seprafilm-induced peritoneal inflammation: a previously unknown complication: report of a case. *Dis Colon Rectum* 1999; **42:** 1639–43.

Precautions

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hyaluronic acid given by injection for the treatment of musculoskeletal disorders as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acuaiss; Aquify; Artflex; Cystistat; Dropstar; Gengigel; Hialudorf; Hyabak; Hyalart; Hyalofill-F; Hyalomb; Hyasol; Iuronicoderm; Maxiostenil; Miniostenil; Osmolagrimas; Provisc†; Synvisc; Viscoderm; ***Austral.***: AMO Vitrax†; Healon; Luxyal; Ophthalin†; Provisc; Synvisc; ***Austria***: Artzal; Bionect; Hyalgan; ***Belg.***: Gengigel; Hyalgan; ***Braz.***: Densitium; Fermathron; Healon†; Hyaludermin; Polireumin; Suplasyn; Suprahyal; Synvisc; ***Canad.***: Cystistat; Durolane; Hyalgan; Monovisc; NeoVisc; Orthovisc; Suplasyn; Synvisc; ***Chile***: Biolon; Eucerin Emulsion†; Healon†; Hyalgan; Hylaform†; Lagricel Ofteno; Neolucid Ultra HR; Suprahyal; Synvisc; Toptear; ***China***: ARTZ (阿尔治); Hialid (爱丽); Hyal (哈艾路); Iviz (爱维); Runjie (润洁); Shipeike (施沛克); Sofast (施沛特); ***Cz.***: Hyalgan; ***Denm.***: Artz; Hyalgan; ***Fin.***: Artzal; Hyalgan; ***Fr.***: Adant; Aftamed; Amvisc†; Arthrum H; Biovisc†; Coxarthrum; Durolane; Effidia†; Euflexxa; Go-On; Hyabak; Hyalgan; Hyaline; Hyalugel; Hyaluzinc; Hylo-COMOD; Hylovis; Ialuset; Idune; Ostenil; Oxens; Provisc; Sinovial; Structovial; Succeev; Suplasyn†; Synocrom; Synvisc; Vitrax†; ***Ger.***: Artelac Splash; Artroject; Biolan; Biolon†; Curavisc; Cystistat†; Endogel; Fermathron; Gelbag; Genteal HA; Go-On; Hy-GAG; Hyaject; Hya-Ophtal; Hyabak; Hyalart; Hyalubrix; Hyaluron†; Hylan; Hylo-COMOD; Hylo-Gel; Hylo-Lasop; Hylo-Parin; Hylo-Vision; Hysan; Laservis; Monovisc; Orthovisc; Ostenil; Oxyal; Provisc; Recosyn; Sinovial; Suplasyn†; Synvisc; TwinVisc; Uni-Injekt; Unike; Viscoseal; Visiol; Vislube; Vismed; VisThesia; Xidan EDO; ***Gr.***: Arthryal; Biolon; Gonilert; Healon; Hyalart; Provisc; Viscure; Yardel; ***Hong Kong***: Artelac Advanced; Connettivina; Go-On; Healon†; Hialid; Hyalgan; Hyruan; Jonexa; Synocrom; Synvisc; Vismed; ***Hung.***: Curiosin; Hyalgan; ***India***: Fain; Halonix; Healon; Hymoist; Hyopt; Hyvisc; LG Hyal; LG Hyruan; Synvisc; Visial; ***Indon.***: Adant; Bionect; Cytistat; Durolane; Hialid; Hyalgan; Hyaloph; Lydium; Osflex; Sanorine; Suplasyn; ***Irl.***: Hyalgan; Suplasyn†; ***Israel***: Adant†; Arthrease; Biolon; Curavisc; Eyecon; Healon; Hylo-COMOD; Hysan; Orthovisc†; Suplasyn; Synvisc; ***Ital.***: Artelac Advanced; Artz; Cicatridina; Connettivina; Dropstar; Durolane; Fillast; Go-On; Hy-Drop; Hyabak; Hyalart; Hyalgan; Hyalistil; Hyalofill-F; Hyalubrix; Hylo-COMOD; Hyluprotect; Ial; Ialoclean; Ialum; Ialurex; Irilens; Jaloskin; Oftaial; Opisial†; Oxyal; Provisc; Rugantil†; Skin-B†; Skin-R†; Synocrom; Synvisc; Vismed; ***Jpn***: Hyalein; Suvenyl; Synvisc; ***Malaysia***: Adant; Aftamed; Curiosin; Gengigel; Go-On; Hyal; Hyalgan; Hylo-COMOD; Hyruan; Jointmax; Provisc†; Sinovial; Suplasyn; Synvisc; Viscoseal; Visiol; Vislube†; Vismed; ***Mex.***: Biolon; Dropstar; Eyestil; Hyasol; Lagricel; Suprahyal; Synvisc; Zonaker; ***Mon.***: Oxyal†; ***NZ***: Healon; Hyalgan; Hylaform; Juvederm; Ophthalin†; Provisc; Restylane; Synvisc; ***Philipp.***: Curiosin; Go-On; Hialid; Provisc; Synove; ***Pol.***: Hyalgan; Synvisc; ***Port.***: Artz; Hyalart; ***Rus.***: Curiosin (Куриозин); Healon (Хеалон); Hyalgan (Гиалган); Hylo-COMOD (Хило-КОМОД); Hylomax-COMOD (Хиломакс-КОМОД); ***S. Afr.***: AMO Vitrax†; Biolon†; Biolone; Healon; Microvisc; Provisc; Suplasyn; ***Singapore***: Curiosin; Cystistat†; Go-On; Hialid; Hyalgan; Hylaform†; Juvederm; Monovisc; Orthovisc; Provisc†; Sanorine; Suplasyn; Synvisc; Vislube†; Vismed; ***Spain***: Hyabak†; Hyalart; Hyalgan; ***Swed.***: Artzal; Hyalgan; Synvisc; ***Switz.***: Fermavisc; Hyalur; HycoSan5; Hylo-COMOD; Hylo-Gel; Hysan†; Ial; Ialugen; Laservis; Ostenil; Rhinogen; Sinovial; Suplasyn; Synvisc†; Viscoseal; Visiol; Vislube; Vismed; ***Thai.***: Adant; Go-On; Hialid; Hyalgan; Hyruan; Ial; Juvederm Ultra XC; Ophthalin†; Provisc; Suplasyn; Synvisc; Vislube; ***Turk.***: Adant; Amvisc; Biolon; Healon; Hyalgan; Ial†; Ophtalin Plus†; Orthovisc; Ostenil; Provisc†; Synvisc; ***UK***: Arthrease; Clinitas; Cystistat; Euflexxa; Fermathron; Gengigel; Hyabak; Hyalgan; Hyalofill; Hycosan; Hylo-Forte; Hylo-Tear; Lubristil; Lumecare Extra Gentle; Ocusan; Ophthalin; Optrex Contact Lens Friendly Eye Drops; Orthovisc; Ostenil; Oxyal; Suplasyn; Synocrom; Synvisc; Viscoseal; Vismed; ***Ukr.***: Curiosin (Куриозин); Hyaral (Гиарал); Kuriosin (Куриозин); Synhyal (Сингиал); ***USA***: AMO Vitrax†; Amvisc; Bionect; Coease; Euflexxa; Healon; Hyalgan; HyGel; Hylaform†; Hylase; Hylira; Juvederm; Orthovisc; Perlane; ProVisc; Restylane; Shellgel; Supartz; Synvisc; ***Venez.***: Hyalgan; Lagricel Ofteno; Suprahyal; Synvisc; Toptear.

Multi-ingredient Preparations. ***Arg.***: Alosol; Blink Contacts; Cellskinlab Hydragel B5; Culuflex H†; Epitheliale AH; Estri-Atlas; Fusimed; Hyalcrom NF; Hyalcrom; Hyalogran; Hyalomatrix-PA; Hydratone; Ingebrax†; Iuronico Biotic; Lacrimax†; Maxilac†; Maxus; Muvar; Natura Confort; Neoprost; Ocusun; Panoxi; Revi-Atlas; Vera Plus; Viscoat†; Vita-C Derms's; Yusin Tears II; ***Austral.***: Atopiclair†; Blink Contacts; Duovisc; Viscoat†; ***Belg.***: Physiologica Nasal; ***Braz.***: Seprafilm; ***Chile***: Epithelial AH; Estri-Atlas; Gelclair; Hyaluron; Hydragel B5 CKL; Hydraphase Ojos; Hydrating B5 Gel†; Redermic Piel; Redermic XL; Revi-Atlas; Ureadin Rx RD; ***China***: CP Bright (正大维他); Frecoseryl (润尔乐); Fredex (科恒); Run Jie (润洁); ***Cz.***: Ialugen Plus; ***Fr.***: Bactigyn; Cicaplast; Cicatridine; Cicatridine; Flexi-max; Ialuset Plus; Ilast Care; Ilast Hydra; Ilast O'Clean; Ilast Post-Op; Mucogyne; Mycoress; Navitae; Saugella Antiseptic; Saugella Dermoliquide; Saugella douceur Poligyn; Urgo Cicatrices; Veganix; Viscoat†; Vitrecor; ***Ger.***: Aliamare; Bepanthen Augentropfen; DisCoVisc; Duovisc; Gelclair; Herba-Vision Augenbad; Herba-Vision Augentrost; Herba-Vision Blaubeere; Hya-ject Plus; Hylo-Care; Hylo-Vision HD Plus; Ialunara; Ilast Care; Trium; Viscoat; ***Gr.***: Viscoat; ***Hung.***: Ialugen Plus; ***Indon.***: Aloclair; Atopiclair; Vitadrop; ***Israel***: Aphtagone†; Aptha-X†; Atopiclair; Salinagel; Xclair; ***Ital.***: Altergen; Biolastic T5; Cartijoint†; Connettivina Plus; DisCoVisc†; Dropyal; Hyalogran; Hyalosilver; Hylo-Care; Idroskin C; Lesiorepar; Migel; Naset; Osmogel; Respifree; Resvelife; Sirmiogel; Trofo 5; Ulceclar; Vaginol; Viscoat; Xanternet; ***Malaysia***: Aloclair; Aqua Care; Duovisc†; Hyiodine; Prelactic; Seprafilm; Viscoat†; Vitadrop; ***Mex.***: Cetopic; Emolin Neo; Grimal; Humylub Ofteno; Hyalcrom NF; Hyalox; ***Mon.***: Monasens; ***NZ***: Viscoat; ***Philipp.***: Viscoat; ***Port.***: Synchrorose Intensivo; Synchrovit; ***Rus.***: Hyaferone (Гиаферон); Hylozar-COMOD (Хилозар-КОМОД); ***S.Afr.***: Duovisc†; Viscoat; ***Singapore***: Atopiclair; BCC; Duovisc; RejuvaSkin Anti-Aging Serum; Scar Esthetique; Seprafilm; Viscoat†; ***Switz.***: Alphastria; Hylo-Care; Ialugen Plus; Lacrycon; Nasmer 3plus; Nasmer free; ***Thai.***: DisCoVisc; Duovisc; Viscoat; ***Turk.***: Duovisc†; Viscoat; ***UK***: Artelac Rebalance; Atopiclair; Blink Intensive Tears; Gelclair; Hylo-Care; Rohto Dry Eye Relief; Seprafilm; Xclair; Zuidex; ***Ukr.***: Curiosin (Куриозин); Kuriosin (Куриозин); ***USA***: Atopiclair; Deflux; DisCoVisc; Gelclair; Healon Yellow†; Miaderm Radiation Relief; Ocean Nasal Moisturizer; RadiaPlex Rx; Seprafilm; Solesta; Viscoat; Zacare Kit; ***Venez.***: Cepin; Epitheliale AH.

Hyaluronidase *(BAN, rINN)*

Hialuronidasa; Hialuronidazė; Hialuronidáz; Hiyalüronidaz; Hyaluronidaasi; Hyaluronidas; Hyaluronidasa; Hyaluronidasum; Гиалуронидаза.

CAS — 9001-54-1.

ATC — B06AA03.

ATC Vet — QB06AA03.

UNII — 8KOG53Z5EM (bovine hyaluronidase); 64R4OHP8T0 (ovine hyaluronidase).

NOTE. The name Kinetin (p. 1710.2) has also been used as a proprietary name for hyaluronidase.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). *US* includes as an injectable form.

Ph. Eur. 8: (Hyaluronidase). An enzyme capable of hydrolysing mucopolysaccharides of the hyaluronic acid type. It is prepared from the testes of mammals by a method that has been shown to reduce contamination by known infectious agents to acceptable limits; a suitable stabilising agent may be added to the purified preparation. A white or yellowish-white, amorphous powder; it contains not less than 300 international units of hyaluronidase activity per mg, calculated with reference to the dried substance. Soluble in water; practically insoluble in alcohol and in acetone. A 0.3% solution in water has a pH of 4.5 to 7.5. Store at 2 degrees to 8 degrees in airtight containers.

Units

The international and USP units are equivalent. One international or USP unit is equivalent to one turbidity-reducing unit or about 3.3 viscosity-reducing units.

Uses and Administration

Hyaluronidase is an enzyme that reversibly depolymerises hyaluronic acid (p. 2526.2), a component of the ground substance or tissue cement surrounding cells, thereby temporarily reducing its viscosity and rendering the tissues more readily permeable to injected fluids.

Hyaluronidase is used to increase the speed of absorption and reduce discomfort due to subcutaneous or intramuscular injection of fluids, to promote resorption of excess fluids and extravasated blood in the tissues, and to increase the efficacy of local anaesthesia.

In the UK, the usual dose as an adjunct to subcutaneous or intramuscular injection is 1500 units, added directly to the injection. To aid the dispersal of extravasated fluids or blood, the same dose is given in 1 mL of Water for Injections or 0.9% sodium chloride into the affected area. Lower doses of hyaluronidase are used in some countries; in the USA, the usual dose is 150 units.

In hypodermoclysis, hyaluronidase is used to aid the subcutaneous administration of relatively large volumes of fluids, especially in infants and young children, where intravenous injection is difficult. Care should be taken in the treatment of children and the elderly to control the speed and total volume given and to avoid overhydration. Hyaluronidase may be added to the injection fluid or may be injected into the site before the fluid is given. In the UK, 1500 units of hyaluronidase is generally given with each 500 to 1000 mL of fluid for subcutaneous use, but in the USA, 150 units of hyaluronidase is considered adequate for each litre of hypodermoclysis solution.

In the UK, the diffusion of local anaesthetics is accelerated by the addition of 1500 units of hyaluronidase to the anaesthetic solution. It has also been used in ophthalmology as an aid to local anaesthesia at recommended doses of 15 units/mL of local anaesthetic solution. Hyaluronidase has also been used for the treatment of vitreous haemorrhage and diabetic retinopathy.

To improve the resorption of radiopaque agents in subcutaneous urography, hyaluronidase is injected subcutaneously in a dose of 75 units over each scapula followed by injection of the contrast medium at the same site.

Recombinant human hyaluronidase is used for the preparation of oocytes during IVF.

Hyalosidase (GL enzyme) is a highly purified form of hyaluronidase that has been studied.

General references.

1. Etesse B, *et al*. Hyaluronidase: plaidoyer pour un retour. *Ann Fr Anesth Reanim* 2009; **28:** 658–65.
2. Dunn AL, *et al*. Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management. *Expert Opin Biol Ther* 2010; **10:** 127–31.

Ophthalmic surgery. In a study[1] involving 150 consecutive patients undergoing surgery for senile cataract, retrobulbar anaesthesia with lidocaine 2% solution plus adrenaline 1:100 000 and hyaluronidase 15 units/mL produced successful anaesthesia in 69 of 75 cases (92%), which was significantly better than 42 of 75 treated with lidocaine plus adrenaline alone. Although poor results have been reported from hyaluronidase and a local anaesthetic without adrenaline to restrict local anaesthetic absorption, the use of the enzyme and adrenaline was recommended as an aid to achieving complete ocular akinesia and anaesthesia in cataract surgery. Hyaluronidase has also been used with a mixture of bupivacaine and lidocaine for peribulbar anaesthesia, but results have been conflicting. In a study[2] in 50 patients, addition of hyaluronidase 25 units/mL of local anaesthetic mixture had no significant effect on time to satisfactory anaesthesia. However, in a second study[3] involving 200 patients, addition of hyaluronidase 50 or 300 units/mL improved the quality of the peribulbar block and, in the case of the higher concentration, also increased the speed of onset.

1. Thomson I. Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract. *Br J Ophthalmol* 1988; **72:** 700–2.
2. Prosser DP, *et al*. Re-evaluation of hyaluronidase in peribulbar anaesthesia. *Br J Ophthalmol* 1996; **80:** 827–30.
3. Dempsey GA, *et al*. Hyaluronidase and peribulbar block. *Br J Anaesth* 1997; **78:** 671–4.

Adverse Effects and Precautions

Sensitivity to hyaluronidase occasionally occurs. Because of the danger of spreading infection, the enzyme generally should not be injected into or around an infected area. It has been suggested that the presence of malignancy may similarly be a contra-indication to the use of hyaluronidase. It should not be given by intravenous injection nor should it be used for anaesthetic procedures in cases of unexplained premature labour. Hyaluronidase should not be applied directly to the cornea. It should not be used to reduce the swelling of bites or stings.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Unidasa; ***Austral.***: Hyalase; ***Austria***: Hylase; ***Braz.***: Hyalozima; ***Cz.***: Hylase; ***Ger.***: Hylase; ***Gr.***: Hyalase; ***Hong Kong***: Hyalase†; ***India***: Facidase; Hylorase;

Hynidase; ***Irl.***: Hyalase; ***Israel***: Hyalase; ***Neth.***: Hyason; ***NZ***: Hyalase; ***Rus.***: Longidaza (Лонгидаза); Lydase (Лидаза); Lyrase (Лираза); Nydase (Нидаза); ***S.Afr.***: Hyalase†; ***Singapore***: Hyalase; ***UK***: Hyalase; ***USA***: Amphadase; Hydase†; Hylenex; Vitrase.

Multi-ingredient Preparations. ***Arg.***: Nilflux; ***Braz.***: Oto-Xilodase; Postec; Xilodase; ***Gr.***: Lasonil; ***Ital.***: Lido-Hyal; ***Pol.***: Helason; ***Switz.***: Lido-Hyal†.

Pharmacopoeial Preparations
BP 2014: Hyaluronidase Injection;
USP 36: Hyaluronidase for Injection; Hyaluronidase Injection.

Hydrangea

Hidrangea; Raíz de hortensia; Seven Barks; Smooth Hydrangea; Wild Hydrangea; Гортензия.
*UNII — Z82ZU9MJ6M (*Hydrangea arborescens*); MRX3W33KCB (*Hydrangea arborescens *bark); SFK828Q2DE (*Hydrangea arborescens *root).*

Profile

Hydrangea, the root of *Hydrangea arborescens* (Hydrangeaceae), has diuretic and litholytic properties and is used for genito-urinary disorders including renal and urinary calculi.

Homoeopathy

Hydrangea has been used in homoeopathic medicines under the following names: Hydrangea arborescens; Hydrang.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Antiglan; Backache.

Homoeopathic Preparations. ***Ger.***: Pascosabal.

Hydrastine Hydrochloride

Hidrastina, hidrocloruro de; Hydrastyny chlorowodorek; Гидрастина Гидрохлорид.
6,7-Dimethoxy-3-(5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one hydrochloride.
$C_{21}H_{21}NO_6$,HCl=419.9
CAS — 118-08-1 (hydrastine); 5936-28-7 (hydrastine hydrochloride).
UNII — 562PDC2I9K.

Profile

Hydrastine hydrochloride, the hydrochloride of an alkaloid obtained from *Hydrastis canadensis* (Ranunculaceae) (see Hydrastis, below), has been reputed to cause uterine contractions and arrest uterine haemorrhage but it is of doubtful value. It was also formerly used in gastrointestinal disorders. Toxic doses are reported to cause strychnine-like convulsions and relaxation of the gut.

Hydrastinine Hydrochloride

Idrastinina Cloruro; Гидрастинина Гидрохлорид.
5,6,7,8-Tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-ol hydrochloride.
$C_{11}H_{11}NO_2$,HCl=225.7
CAS — 6592-85-4 (hydrastinine); 4884-68-8 (hydrastinine hydrochloride).
UNII — S8253P6A1G.

Profile

Hydrastinine is a derivative of the alkaloid hydrastine (above) and has been used similarly. It has vasoconstrictor properties and has been used as the hydrochloride as an ingredient of topical preparations for minor eye disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Haemanal.

Hydrastis

Cúrcuma canadiense; Golden Seal; Goldenseal; Hidraste; Hidrastis; Hydrast.; Hydrastidis Radix; Hydrastis Rhizoma; Hydrastisjuuri; Hydrastisrot; Idraste; Kanadinių auksašaknių šakniastiebiai; Sello de oro; Vodilkový kořen; Желтокорень Канадский (*Hydrastis canadensis*); Yellow Root.
UNII — ZW3Z11D0JV (goldenseal).

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Eur.* also includes a form for homoeopathic preparations.

Ph. Eur. 8: (Goldenseal Rhizome; Goldenseal Root BP 2014). The whole or cut, dried rhizome and root of *Hydrastis canadensis* containing not less than 2.5% of hydrastine and not less than 3.0% of berberine, calculated on the dried basis. Protect from light.

Ph. Eur. 8: (Hydrastis Canadensis for Homoeopathic Preparations). Prepared from the whole or cut, dried rhizome and root of *Hydrastis canadensis*. Protect from light.

USP 36: (Goldenseal). The dried roots and rhizomes of *Hydrastis canadensis* (Ranunculaceae), containing not less than 2.0% of hydrastine and not less than 2.5% of berberine, calculated on the dried basis. Store in airtight containers. Protect from light, moisture, and heat.

Profile

Hydrastis was formerly used to arrest excessive uterine haemorrhage. It is included in some herbal preparations for gastrointestinal disorders and peripheral vascular disorders. The pharmacological activity of hydrastis is attributed mainly to 2 of its constituent alkaloids, berberine (p. 2455.1) and hydrastine (above).

Homoeopathy

Hydrastis has been used in homoeopathic medicines under the following names: Hydrastis canadensis; Hyrdr. can.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Bilberry Plus†; Cats Claw-Echine; Echinacea Royale; Euphrasia Complex; ***Canad.***: Natraway Sport 1 & 2†; Natraway Sport 3†; Para-Gard; Para-Gone; ***Fr.***: Climaxol; ***Spain***: Solucion Schoum; ***Turk.***: Ma-Ka-Ta; ***UK***: Digestive; HRI Golden Seal Digestive; Wind & Dyspepsia Relief.

Homoeopathic Preparations. ***Austral.***: Childrens Runny Nose Relief; Snorestop; Stomach Calm; ***Austria***: Asinis; Lymphdiaral; Metasinusit; Nebenhohlen-Tropfen Nr 26†; Otovowen; Robinia Med Complex; ***Canad.***: Eczema L87; Formula CI 207†; Formula FV 213; Homeo-Form PMT†; Homeo-Form SI†; Homeodel 21†; Hylagene; Hylands Formula S; Hylands Sinus†; Indigestion; Mucan; Nareel†; PMS; Rhinar†; Sinus Ease; Sinus; Sinus; Snore Stop; Toxex; Ubicoenzyme; ***Chile***: Calendula Echinacea Comp; Ovukalen; ***Cz.***: Lamioflur†; ***Fr.***: Adenocynesine†; Aesculus Compose; Allium Cepa Compose; Chelidonium Compose; Cimicifuga Complexe No 21†; Conium Complexe No 36†; Endhometrol; Hepatodrainol; Hepatopan†; Homeogene 22†; Hydrastis Compose; L 25; L 28; Pulviplasmine†; Ricinus Compose; Scabiosa Complexe No 87; Sinuspax; Thlascose†; ***Ger.***: Aletris Oligoplex†; Antimas†; Gastro-Pasc; Jsostoma S; Lymphdiaral; Lymphdiaral; Mucosa compositum; Otovowen; Rapako comp; Sinuselect N; Ulco-cyl L Ho-Len-Complex; ***Hung.***: Naso-Heel S; Toxex; ***Neth.***: Hepatodrainol†; Lymphdiaral; Mucosa comp H; Nectadyn H; Omnilite; Opsonat; Rinileen†; Sinufleur; Snurdim; Toxex; ***Port.***: Hepatodrainol; ***Rus.***: Asinis (Асинис); Cinnabsin (Циннабсин); Mastopol (Мастопол); ***Switz.***: A Vogel pour les sinus; Alceprin-N; metasinusit; Nelsons Sinusit†; Regenaplex Nr. 59b; Regenaplex Nr. 71b; Sinusin; Sinuspax†; ***Ukr.***: Asinis (Асинис); Cinnabsin (Циннабсин); ***USA***: Preferred Remedies Sinus.

Hydrazine Sulfate

Hidrazina, sulfato de; Hidrazine Sulfate; Hydrazine Sulphate; Hydrazyny siarczan.
$H_6N_2O_4S$=130.1
CAS — 302-01-2 (hydrazine); 10034-93-2 (hydrazine sulfate).
UNII — 1N369SAT01.

Profile

Hydrazine sulfate is employed in various industrial processes. It is used in the preparation of hydrazine hydrate which is applied after a solution of platinic chloride for corneal tattooing. It has been tried, but with little if any benefit, in the management of cancer-related anorexia and cachexia.

Adverse effects and treatment. References to adverse effects resulting from exposure to hydrazine.[1-5] Pyridoxine has been used in the management of hydrazine intoxication.[6-8]

1. Albert DM, Puliafito CA. Choroidal melanoma: possible exposure to industrial toxins. *N Engl J Med* 1977; **296:** 634–5.
2. DurantPJ, Harris RA. Hydrazine and lupus. *N EnglJ Med* 1980; **303:** 584–5.
3. WHO. Hydrazine. *Environmental Health Criteria 68.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc68.htm (accessed 24/07/08)
4. WHO. Hydrazine health and safety guide. *IPCS Health and Safety Guide 56.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg056.htm (accessed 24/07/08)
5. Hainer MI, *et al.* Fatal hepatorenal failure associated with hydrazine sulfate. *Ann Intern Med* 2000; **133:** 877–80.
6. Kirklin JK, *et al.* Treatment of hydrazine-induced coma with pyridoxine. *N Engl J Med* 1976; **294:** 938–9.
7. Harati Y, Niakan E. Hydrazine toxicity, pyridoxine therapy, and peripheral neuropathy. *Ann Intern Med* 1986; **104:** 728–9.
8. Nagappan R, Riddell T. Pyridoxine therapy in a patient with severe hydrazine sulfate toxicity. *Crit Care Med* 2000; **28:** 2116–18.

Anorexia and cachexia. References[1-3] to the use of hydrazine sulfate in patients with anorexia or cachexia associated with cancer.

1. Tayek JA, *et al.* Effect of hydrazine sulphate on whole-body protein breakdown measured by ^{14}C-lysine metabolism in lung cancer patients. *Lancet* 1987; **ii:** 241–4.
2. Loprinzi CL, *et al.* Cancer-associated anorexia and cachexia: implications for drug therapy. *Drugs* 1992; **43:** 499–506.
3. Kaegi E. Unconventional therapies for cancer: hydrazine sulfate. *Can Med Assoc J* 1998; **158:** 1327–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Sehydrin (Сегидрин); ***Ukr.***: Sehydrin (Сегидрин).

Hydrochloric Acid

Acide chlorhydrique; Acidum Hydrochloricum; Acidum Hydrochloridum; Clorhídrico, ácido; Cloruro de hidrógeno; E507; Kloorivetyhappo; Kwas solny; Kyselina chlorovodíková; Saltsyra; Salzsäure; Sósav; Suolahappo; Vandenilio chlorido rūgštis; Vetykloridihappo.
HCl=36.46
CAS — 7647-01-0.
ATC — A09AB03; B05XA13.
ATC Vet — QA09AB03; QB05XA13.
UNII — QTT17582CB.

NOTE. The impure acid of commerce is known as Spirits of Salt and as Muriatic Acid.

Pharmacopoeias. *Chin., Eur.* (see p. vii), *Int., Jpn, Swiss,* and *Viet.* include various concentrations. Also in *USNF.*

Ph. Eur. 8: (Hydrochloric Acid, Concentrated; Acidum Hydrochloridum Concentratum; Hydrochloric Acid BP 2014). It contains 35.0 to 39.0% w/w of HCl. A clear, colourless, fuming liquid. Miscible with water. Store below 30 degrees in stoppered containers of glass or other inert material.

Ph. Eur. 8: (Hydrochloric Acid, Dilute; Acidum Hydrochloridum Dilutum). It contains 9.5 to 10.5% w/w of HCl prepared by mixing hydrochloric acid 274 g with water 726 g.

USNF 31: (Hydrochloric Acid). It contains 36.5 to 38.0% w/w of HCl. A colourless, fuming liquid having a pungent odour. It ceases to fume when it is diluted with 2 volumes of water. Store in airtight containers.

USNF 31: (Diluted Hydrochloric Acid). It contains 9.5 to 10.5% w/v of HCl and may be prepared by mixing hydrochloric acid 226 mL with sufficient water to make 1000 mL. A colourless, odourless liquid. Store in airtight containers.

Uses and Administration

Hydrochloric acid has been used as an escharotic. It has been used in the diluted form for the treatment of achlorhydria and other gastrointestinal disorders. It has also been given intravenously in the management of metabolic alkalosis (p. 1775.3). An acid perfusion test using hydrochloric acid has been used in the diagnosis of oesophageal disorders. When taken orally, it should be sipped through a straw to protect the teeth.

Homoeopathy

Hydrochloric acid has been used in homoeopathic medicines under the following names: Acidum hydrochloricum; Muriaticum acidum; Muriaticum ac; Hydrochloridum acidum; Chlorhydricum acidum; Acidum muriaticum; Ac. mur.

Diagnosis and testing. References and comments on the use of an acid perfusion test in the diagnosis of oesophageal disorders,[1-5] such as gastro-oesophageal reflux disease (p. 1807.2) and oesophageal motility disorders (p. 1813.2). The test involves intra-oesophageal perfusion of 0.1M hydrochloric acid; subsequent development of pain indicates an acid-sensitive oesophagus. This test has also been used in the differential diagnosis of angina.[2]

1. Sladen GE, *et al.* Oesophagoscopy, biopsy, and acid perfusion test in diagnosis of "reflux oesophagitis". *BMJ* 1975; **1:** 71–6.
2. Anonymous. Angina and oesophageal disease. *Lancet* 1986; **i:** 191–2.
3. Hewson EG, *et al.* Acid perfusion test: does it have a role in the assessment of non cardiac chest pain? *Gut* 1989; **30:** 305–10.
4. de Caestecker JS, Heading RC. Acid perfusion in the assessment of non-cardiac chest pain. *Gut* 1989; **30:** 1795–7.
5. Howard PJ, *et al.* Acid perfusion is a good screening test for symptomatic oesophageal reflux. *Gut* 1989; **30:** A1445.

Pregnancy. Heartburn during pregnancy may be due to reflux of alkaline duodenal contents. A dilute solution of hydrochloric acid (pH 2) taken after meals and at bedtime

produced improvements in heartburn in pregnant women.[1]

1. Anonymous. Heartburn in pregnancy. *Drug Ther Bull* 1990; **28:** 11–12.

Adverse Effects

Hydrochloric acid is highly irritant and corrosive and ingestion has proved fatal. The corrosive effect causes chemical burns and severe pain. There may be violent vomiting, haematemesis, and circulatory collapse; acids can also produce intravascular coagulation and haemolysis. Ulceration may lead to perforation and patients can suffer strictures and pyloric stenosis. Asphyxiation may result from laryngeal oedema. Inhalation of acid fumes or aspiration of ingested acids may cause pneumonitis.

References.

1. WHO. Chlorine and hydrogen chloride. *Environmental Health Criteria 21*. Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc21.htm (accessed 16/06/04)
2. Munoz Munoz E, *et al*. Massive necrosis of the gastrointestinal tract after ingestion of hydrochloric acid. *Eur J Surg* 2001; **167:** 195–8.

Treatment of Adverse Effects

Treatment of ingestion is mainly symptomatic. Gastric lavage and activated charcoal are not generally appropriate and emetics must *not* be used. Small amounts of water or milk may be given to dilute the acid but larger volumes may increase the risk of emesis and hence of further damage. Neutralising agents are not recommended because of the possibility of heat being produced during exothermic reactions, which may increase the injury further. Opioid analgesia may be required for pain. Endoscopy should be performed and surgical intervention may be necessary. There is little evidence to support the value of corticosteroids in preventing stricture formation.

Acid burns of the skin should be flooded immediately with water and the washing should be copious and prolonged. Any affected clothing should be removed while flooding is being carried out. For burns in the eye, the lids should be kept open and the eye flushed with a steady stream of water at room temperature or sodium chloride 0.9%. A few drops of a local anaesthetic solution will relieve lid spasm and facilitate irrigation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Mixtura Pepsini.

Multi-ingredient Preparations. ***Ital.***: Gastro-Pepsin; ***S.Afr.***: Sentinel Ulcer Mixture†.

Homoeopathic Preparations. ***Austral.***: Vitatona Energy†; ***Canad.***: Hae 2 Complex†; ***Ger.***: Kinolymphat†; Lowe-Komplex Nr 6; ***Switz.***: Regenaplex Nr 28a; Regenaplex Nr. 21e.

Hydrofluoric Acid

Fluohydric Acid; Fluorhídrico, ácido; Fluoric Acid; Fluoruro de hidrógeno; Kwas fluorowodorowy.

HF=20.01

CAS — 7664-39-3.

UNII — RGL5YE86CZ.

Description. Hydrofluoric acid is a solution of hydrogen fluoride in water. Various strengths are used. It attacks glass strongly.

Uses

Hydrofluoric acid is used in industry. Its main use has been for the production of fluorocarbons for use as refrigerants and propellants. It has also been used as an ingredient of preparations for glass etching and rust removal.

Homoeopathy

Hydrofluoric acid has been used in homoeopathic medicines under the following names: Fluoricum acidum; Acidum hydrofluoricum; Ac. fluor.; Hydrofluoricum acidum; Hydrofluoricum ac.

Adverse Effects

As for Hydrochloric Acid, above. Although the corrosive effects of hydrofluoric acid tend to predominate, absorption may produce systemic fluoride poisoning as described under Sodium Fluoride, p. 2090.1.

The pain from contact with weak solutions may be delayed, so that the patient is not aware of being burnt until some hours later, when the area begins to smart; intense pain then sets in and this may persist for several days. Destruction of tissue proceeds under the toughened coagulated skin, so that the ulcers extend deeply, heal slowly, and leave a scar.

The fumes of hydrofluoric acid are highly irritant.

Treatment of Adverse Effects

The initial treatment of poisoning after oral exposure to hydrofluoric acid is similar to that described for hydrochloric acid, see above. Calcium gluconate should also be given intravenously to correct known or suspected hypocalcaemia. Calcium chloride has also been given. Nebulised calcium gluconate may also be considered for severe poisoning by inhalation.

For ocular burns, the eye should be irrigated thoroughly for at least 30 minutes with Hexafluorine (*Prevor, Fr.*), a product containing amphoteric and chelating salts; if Hexafluorine is not available copious amounts of water or sodium chloride 0.9% should be used. Calcium gluconate has been used but there is little evidence of efficacy, and it may damage the conjunctiva.

In the event of skin burns with hydrofluoric acid, contaminated clothing or articles should be removed and the skin washed with copious amounts of cold water; Hexafluorine may be used if available. A calcium gluconate gel is sometimes used and it may be necessary to infiltrate the affected areas with calcium gluconate intradermally or subcutaneously. Regional intravenous infusion of calcium gluconate may be necessary in severe burns of the forearm, hand, or fingers; if ineffective, intra-arterial infusion for burns of the fingers may be considered. Hydrofluoric acid passes through finger- and toe-nails without causing any apparent damage; nails will therefore have to be removed or perforated to be able to treat the underlying tissues. Other first-aid measures reported to be effective include prolonged soaks in iced solutions of benzalkonium chloride; iced water has sometimes been used as has iced magnesium sulfate solution. Local anaesthesia may be needed. Burn eschars should be excised and necrotic tissue debrided. Absorption may lead to systemic fluoride toxicity and the need for intravenous calcium gluconate to manage hypocalcaemic symptoms.

References to the treatment of hydrofluoric acid burns.

1. Browne TD. The treatment of hydrofluoric acid burns. *J Soc Occup Med* 1974; **24:** 80–9.
2. MacKinnon MA. Hydrofluoric acid burns. *Dermatol Clin* 1988; **6:** 67–74.
3. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.
4. Kirkpatrick JJR, *et al*. Hydrofluoric acid burns: a review. *Burns* 1995; **21:** 483–93.
5. Sanz-Gallen P, *et al*. Hypocalcaemia and hypomagnesaemia due to hydrofluoric acid. *Occup Med (Lond)* 2001; **51:** 294–5.
6. Martin HCO, Muller MJ. Hydrofluoric acid burns from a household rust remover. *Med J Aust* 2002; **176:** 296.
7. Foster KN, *et al*. Hydrofluoric acid burn resulting from ignition of gas from a compressed air duster. *J Burn Care Rehabil* 2003; **24:** 234–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Gel-Kam Dentinbloc; Perfect Solutions 1-Minute†; Perfect Solutions In Office Rinse†.

Homoeopathic Preparations. ***Austria***: Crimax; Erbiode Haarvital; ***Chile***: Bioactiv P; ***Fr.***: Hamamelis Compose; Veino-Drainol†; ***Switz.***: Regenaplex Nr. 21e; Regenaplex Nr. 31b.

Hydroquinine Hydrobromide

Dihydrochinin Hydrobromide; Dihydroquinine Hydrobromide; Hidroquinina, hidrobromuro de; Hydrochinin Hydrobromide; Methylhydrocupreine Hydrobromide; Гидрохинина Гидробромид.

8α,9*R*-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrobromide.

$C_{20}H_{26}N_2O_2$,HBr=407.4

CAS — 522-66-7 (hydroquinine).

ATC — M09AA01.

ATC Vet — QM09AA01.

UNII — Q26K81T6MC.

NOTE. Do not confuse with Hydroquinone (p. 1705.1).

Profile

Hydroquinine is a derivative of quinine (p. 665.1) used similarly in the treatment of nocturnal muscle cramps. It is given as the hydrobromide in an oral dose of 200 mg with the evening meal and a further 100 mg at bedtime for 14 days.

Muscle spasm. Quinine and its derivatives such as hydroquinine have traditionally been used for the prevention of nocturnal cramps (p. 2014.1) but there has been concern over their efficacy and potential for adverse effects, especially in the elderly.

References.

1. Jansen PHP, *et al*. Randomised controlled trial of hydroquinine in muscle cramps. *Lancet* 1997; **349:** 528–32.
2. van Kan HJM, *et al*. Hydroquinine pharmacokinetics after oral administration in adult patients with muscle cramps. *Eur J Clin Pharmacol* 2000; **56:** 263–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Inhibin.

Hydroxyamfetamine Hydrobromide

(BANM, rINNM) ⊗

Bromhidrato de Hidroxianfetamina; Hidrobromuro de hidroxianfetamina; Hidroxianfetamina, hidrobromuro de; Hydroxyamfétamine, Bromhydrate d'; Hydroxyamfetamini Hydrobromidum; Hydroxyamphetamine Hydrobromide; *p*-Hydroxyamphetamine Hydrobromide; Oxamphetamine Hydrobromide; Parahydroxyamphetamine Hydrobromide; Гидроксиамфетамина Гидробромид.

(±)-4-(2-Aminopropyl)phenol hydrobromide.

$C_9H_{13}NO$,HBr=232.1

CAS — 103-86-6 (hydroxyamfetamine); 1518-86-1 ((±)-hydroxyamfetamine); 306-21-8 (hydroxyamfetamine hydrobromide); 140-36-3 ((±)-hydroxyamfetamine hydrobromide).

UNII — 59IG47SZ0E.

Pharmacopoeias. In *US.*

USP 36: (Hydroxyamphetamine Hydrobromide). A white, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Its solutions in water are slightly acid to litmus, having a pH of about 5. Protect from light.

Profile

Hydroxyamfetamine hydrobromide is a sympathomimetic with an action similar to that of ephedrine (p. 1663.2), but it has little or no stimulant effect on the CNS. It was formerly used as a vasopressor and in the management of some cardiac disorders.

In ophthalmology, hydroxyamfetamine hydrobromide has been used in a 1% solution as a mydriatic and in the diagnosis of Horner's syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Paremyd.

Pharmacopoeial Preparations

USP 36: Hydroxyamphetamine Hydrobromide Ophthalmic Solution.

Hydroxyapatite *(BAN)*

542 (edible bone phosphate); Durapatite (USAN); Hidroxiapatite; Hidroxiapatito; Hidroxilapatito; Hydroxylapatite; Win-40350; Гидроксиапатит.

Decacalcium dihydroxide hexakis(orthophosphate).

$3Ca_3(PO_4)_2$,$Ca(OH)_2$=1004.6; $Ca_5(OH)(PO_4)_3$=502.3

CAS — 1306-06-5.

UNII — 91D9GV0Z28.

Profile

Hydroxyapatite is a natural mineral with composition similar to that of the mineral in bone. Hydroxyapatite for therapeutic purposes is prepared from bovine bone and contains, in addition to calcium and phosphate, trace elements, fluoride and other ions, proteins, and glycosaminoglycans. It is given orally to patients requiring both calcium and phosphorus supplementation. Hydroxyapatite with tricalcium phosphate has been used in bone grafts.

Hydroxyapatite derived from marine coral has been used in the construction of orbital implants for use after surgical removal of the eye. A form of hydroxyapatite referred to as calcium hydroxyapatite (calcium hydroxylapatite; CaHA) is used for the correction of facial lipoatrophy in patients with HIV infection and as a cosmetic filler for moderate to severe facial wrinkles and folds.

Adverse effects. Reference to problems associated with the use of coral-derived orbital implants[1] and synthetic calcium hydroxyapatite.[2]

1. Shields CL, *et al*. Problems with the hydroxyapatite orbital implant: experience with 250 consecutive cases. *Br J Ophthalmol* 1994; **78:** 702–6.
2. Sankar V, McGuff HS. Foreign body reaction to calcium hydroxylapatite after lip augmentation. *J Am Dent Assoc* 2007; **138:** 1093–96.

Uses. A mixture of calcium phosphates with calcium carbonate could be combined to form a paste that could be injected into acute fractures;[1] under physiological conditions the paste hardened within minutes, due to the formation of dahllite, a carbonated apatite, and held the bones in place as it was progressively replaced by living bone.

1. Constantz BR, *et al*. Skeletal repair by in situ formation of the mineral phase of bone. *Science* 1995; **267:** 1796–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ossopan; ***Braz.***: Ossopan; ***Cz.***: Osteogenon; ***Fr.***: Ossopan; ***Ger.***: Calcibon; Endobon; ***Hung.***: Osteogenon; ***India***: Calex; Calstron; Natcal; Orgacal; Ossopan; ***Indon.***: Ossopan; Ossoral; ***Irl.***: Ossopan†; ***Ital.***: Apagen; ***Mex.***: Ossopan; ***Pol.***: Ossopan; Osteogenon; ***Port.***: Ossopan†; ***Rus.***: Osteogenon (Остеогенон); ***Spain***: Osteopor; ***Switz.***: Ossopan; ***Thai.***: Ossopan; ***UK***: Osteo Support; ***Ukr.***: Osteogenon (Остеогенон); ***USA***: Radiesse.

Multi-ingredient Preparations. ***Arg.***: Totalos Plus; ***Austral.***: Bone Builder; PM NextG Cal; ***Canad.***: Osteo-Guard†; ***Ger.***: Collapat II; ***India***: Odical; ***Indon.***: Vossecal; ***Ital.***: Eugune.

Hydroxymethylnicotinamide

Hidroximetilnicotinamida; *N*-Hydroxymethylnicotinamide; Nicotinylmethylamide; Nicotinylmethylamidum; Nikotynylometyloamid; Гидроксиметилникотинамид.

N-Hydroxymethylpyridine-3-carboxamide.

$C_7H_8N_2O_2$=152.2

CAS — 3569-99-1.

ATC — A05AB01.

ATC Vet — QA05AB01.

Pharmacopoeias. In *Pol.*

Profile

Hydroxymethylnicotinamide is a cholagogue and has been used in the treatment of various disorders of the gallbladder.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Bilamide†.

Multi-ingredient Preparations. ***India***: Jetositol.

Hydroxyquinoline Sulfate

Chinosolum; Hidroxiquinolina, sulfato de; Hydroxyquinoline Sulphate; Oksikinoliinisulfaatti; Oxichinolini Sulfas; Oxikinolinsulfat; Oxine Sulphate; Oxiquinol; Oxyquinol; Oxyquinoline Sulfate (USAN); Sulfate d'Orthoxyquinoléine; Гидроксихинолина Сульфат.

Quinolin-8-ol sulphate; 8-Quinolinol sulphate.

$(C_9H_7NO)_2,H_2SO_4$=388.4

CAS — 148-24-3 (hydroxyquinoline); 134-31-6 (hydroxyquinoline sulfate).

ATC — A01AB07; D08AH03; G01AC30; R02AA14.

ATC Vet — QA01AB07; QD08AH03; QG01AC30; QR02AA14.

UNII — 61VUG75Y3P.

Pharmacopoeias. In *Fr.* and *Swiss.* Also in *USNF.*

USNF 31: (Oxyquinoline Sulfate). A yellow powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether; freely soluble in methyl alcohol.

Potassium Hydroxyquinoline Sulfate

Oxiquinol potásico; Oxyquinol Potassium; Potassii Hydroxyquinolini Sulphas; Potassium Hydroxyquinoline Sulphate; Potassium Oxyquinoline Sulphate; Sulfato de hidroxiquinolina potásica.

CAS — 14534-95-3.

ATC — A01AB07; D08AH03; G01AC30; R02AA14.

ATC Vet — QA01AB07; QD08AH03; QG01AC30; QR02AA14.

Pharmacopoeias. In *Br.*, *Fr.*, and *Ger.*

BP 2014: (Potassium Hydroxyquinoline Sulfate). An equimolecular mixture of potassium sulfate and quinolin-8-ol sulfate monohydrate. It contains 50.6 to 52.6% of quinolin-8-ol and 29.5 to 32.5% of potassium sulfate, calculated with reference to the anhydrous substance. A pale yellow, odourless or almost odourless, microcrystalline powder. Freely soluble in water; insoluble in ether. On extraction with hot dehydrated alcohol a residue of potassium sulfate and a solution of quinolin-8-ol sulfate are obtained.

Profile

Hydroxyquinoline sulfate and potassium hydroxyquinoline sulfate have antibacterial, antifungal, and deodorant properties, and have been used similarly in the topical treatment of skin, oropharyngeal, and vaginal disorders. Potassium hydroxyquinoline sulfate is often used with benzoyl peroxide.

Derivatives of hydroxyquinoline including the salicylate, benzoate, borate, hydrofluoride, iodochloride, silicofluoride, and sodium hydroxyquinoline sulfate have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Leioderm†; ***Ital.***: Aftir Shampoo; ***Neth.***: Superol†.

Multi-ingredient Preparations. ***Arg.***: Curisept; ***Braz.***: Andolba; Cerumin; Colpolase†; Lacto Vagin; Malvatricin Ginecologico†; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvatricin; ***Canad.***: Racestyptine; ***Chile***: Diproquin; ***Fr.***: Chromargon; Dermacide; Nestosyl†; Nestosyl; ***Ger.***: Chinosol; Leioderm P; ***Gr.***: Dermacide; ***Irl.***: Quinoderm; ***Ital.***: Disinfene†; Ustiosan; ***Port.***: Queimax; ***Rus.***: Combutec-2 (Комбутек-2); Contraceptin T (Контрацептин Т); ***S. Afr.***: Oto-Phen Forte†; Quinoderm†; Universal Earache Drops†; ***Switz.***: Benzocaine PD; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; ***UK***: Quinoderm; Valderma; ***USA***: Acid Jelly†; Aurax; Auroguard Otic; Fem pH; Oxyzal; Stypto-Caine; Trimo-San; Triv; ***Venez.***: Borogin.

Pharmacopoeial Preparations

BP 2014: Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream.

Hymecromone *(BAN, USAN, rINN)*

Himecromona; Himekromon; Himekromonas; Hymechromon; Hymecromon; Hymécromone; Hymecromonum; Hymekromon; Hymekromoni; Imecromone; LM-94; Гимекромон.

7-Hydroxy-4-methylcoumarin.

$C_{10}H_8O_3$=176.2

CAS — 90-33-5.

ATC — A05AX02.

ATC Vet — QA05AX02.

UNII — 3T5NG4Q468.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Hymecromone). An almost white crystalline powder. Very slightly soluble in water; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol. It dissolves in dilute solutions of ammonia. Protect from light.

Profile

Hymecromone is a choleretic and biliary antispasmodic. It has been given orally in doses of 400 mg three times daily at mealtimes. It has also been given as the sodium salt by slow intravenous injection as an adjunct to diagnostic procedures. Diarrhoea may occasionally occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Unichol†; ***Belg.***: Cantabiline; ***Cz.***: Cholestil; Isochol; ***Fr.***: Cantabiline; ***Ger.***: Chol-Spasmoletten; Cholspasmin; ***Gr.***: Cantabiline; Choliren; ***Ital.***: Cantabilin; ***Pol.***: Cholestil; ***Rus.***: Odeston (Одестон); ***Turk.***: Cantabilin.

Hyoscyamus

Banotu; Beleño; Bilsenkraut; Bolmört; Giusquiamo; Henbane; Hullukaali; Hyoscy.; Hyoscyami; Hyoscyami folium (hyoscyamus leaf); Jusquiame; Jusquiame Noire; Jusquiame noire, feuille de (hyoscyamus leaf); Meimendro; Белена.

ATC Herb — HR03BB5002 (Hyoscyamus niger: seed); HA03YA5004 (Hyoscyamus niger: herb); HA03YA5006 (Hyoscyamus niger: seed); HA03YA5005 (Hyoscyamus niger: leaf).

UNII — 34412PDT5E (Hyoscyamus niger); 4WRK2153H3 (Hyoscyamus niger flowering); 32IT7G8BAW (Hyoscyamus niger leaf).

Pharmacopoeias. *Chin.* specifies only the seeds.

Eur. (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Hyoscyamus for Homoeopathic Preparations; Hyoscyamus Niger ad Praeparationes Homoeopathicas). The whole, fresh flowering plant of *Hyoscyamus niger*. Protect from light.

Profile

Hyoscyamus contains the alkaloid hyoscyamine with varying amounts of hyoscine and has peripheral and central effects similar to those of atropine (p. 1312.1); its preparations have been used mainly for the relief of visceral spasm. The fresh whole flowering plant (*Hyoscyamus niger*) as well as the dried leaves have been used in herbal and medicine.

Homoeopathy

Hyoscyamus has been used in homoeopathic medicines under the following names: Hyoscyamus leaf; Hyoscyamus niger; Hyos. nig.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kelosoft; ***Switz.***: Kelosoft; ***Venez.***: Atroveran.

Multi-ingredient Preparations. ***Arg.***: Hepacur; ***Austria***: Cardiodoron; ***Braz.***: Ductoveran; Glicodin; MM Expectorante; ***China***: Kang Ming (康明); ***Fr.***: Laccoderme a l'huile de cade†; ***Ger.***: Cardiodoron; Cimicifuga comp; Unguentum lymphaticum†; ***India***: Elixir Efelin; Memtone; Neo-Cordial; ***Port.***: Doce Alivio; ***S.Afr.***: Cardiodoron†; ***Switz.***: Cardiodoron; Keli-med; Sirop pectoral contre la toux S; ***UK***: Onopordon Comp B; ***Venez.***: Atrobel; Linfoderm.

Homoeopathic Preparations. ***Austral.***: Respatona Dry Cough & Nasal Congestion; Sleep & Insomnia Relief; ***Austria***: Bronchalis-Heel; ***Canad.***: Bronkeel†; Formula C Doron†; Formula C Doroon†; Homeo-Form I†; Homeo-Form PMT†; Homeogene 46; Hylands Insomnia; Insomnia; Kids Calm; PMS; Quietude; Spa Complex†; Stress L72†; ***Cz.***: Bronchalis-Heel; Sedalia; ***Fr.***: Abbe Chaupitre no 7; Boripharm No 3; Dolirelax†; Homeogene 46; Ipeca Complexe No 65; L 72; Lobelia Complexe No 74†; Oenanthe Crocata Complexe No 78; Quietude; Tarentula Complexe No 71; Zincum Cyanidum Complexe No 101†; ***Ger.***: Ambrax; Aralis; Bomapect N; Bronchi-Do; Broncho-Entoxin N; Cordiodoron†; Crataegus comp; Monapax; Passiflora Complex†; Roth's RKT Tropfen; Tussiflorin Hom; Zincum Hevert N; ***Hung.***: Bronchalis-Heel; ***Neth.***: Bronchalis; Quietude†; ***Rus.***: Valeriana-Plus (Валериана-Плюс); ***Switz.***: Bronchalis-Heel; Quietude; ***Ukr.***: Homvio-Nervin (Хомвио-Нервин).

Hypoglycin A

Hipoglicina A.

L-2-Amino-3-(2-methylenecyclopropyl)propionic acid.

$C_7H_{11}NO_2$=141.2

CAS — 156-56-9.

Profile

Hypoglycin A is a toxic substance present in the arillus of unripe ackee (akee), the fruit of *Blighia sapida* (Sapindaceae). It is responsible for Jamaican vomiting sickness, with symptoms of acute and severe vomiting, hypoglycaemia, muscular weakness, CNS depression, convulsions, and coma, frequently fatal. Glycine has been suggested for the management of hypoglycin A toxicity.

Hypophosphorous Acid

Ácido fosfínico; Acidum Hypophosphorosum; Hipofosforoso, ácido; Phosphinic Acid; Гипофосфористая Кислота; Фосфорноватистая Кислота.

H_3PO_2=66.0

CAS — 6303-21-5; 14332-09-3.

Pharmacopoeias. In *USNF.*

USNF 31: (Hypophosphorous Acid). It contains 30 to 32% of H_3PO_2. A colourless or slightly yellow, odourless liquid. Store in airtight containers.

Profile

Hypophosphorous acid is used as an antioxidant. Salts of hypophosphorous acid (hypophosphites or phosphinates) have been used in tonics, although they are not considered a suitable source of phosphorus.

Homoeopathy

Calcium hypophosphite has been used in homoeopathic medicines under the following names: Calcarea hypophosphorosa; Calc. hyp.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pectobron; ***Braz.***: Rhum Creosotado†; ***Canad.***: Tonimine†; ***Gr.***: Calvicef; ***Hong Kong***: Scott's Emulsion Orange†; Scott's Emulsion Original†; ***Hung.***: China; ***India***: Kalzana; ***Indon.***: Bionutrion; Curvit CL; Scott's Emulsion Vita; Scott's Emulsion Vita; Scott's Emulsion; Vical; Vidoran Emulsion Rasa; ***UK***: Dispello; S.P.H.P..

Homoeopathic Preparations. ***Fr.***: Jenoverine†; L 25; ***Ger.***: Ekzem-Entoxin N; Psychoneuroticum (Rowo-578)†; ***Neth.***: Jenoverine†; ***Ukr.***: Kindinorm (Киндинорм).

Hyssop

Herba Hyssopi; Hysope; Hyssop Wort; Ysop; Иссоп.

ATC Herb — HR05YA5010 (Hyssopus officinalis: herb); HR05YA5009 (Hyssopus officinalis: essential oil).

UNII — X7HKN4FOJI (hyssop); 173D71924B (hyssop oil); 0IQW001KPE (Hyssopus officinalis).

Pharmacopoeias. In *Fr.*

Profile

Hyssop is the fresh or dried aerial parts of *Hyssopus officinalis* (Lamiaceae). The herb and its preparations are included in herbal preparations mainly for disorders of the gastrointestinal and upper respiratory tracts.

It is the source of hyssop oil which is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Adelgazar; Arceligasol; ***Austria***: The Chambard-Tee; ***Canad.***: Clear Capsules†; Swiss Herb Cough Drops; ***Hung.***: Gombarex; ***Ital.***: Tisana Kelemata; ***Pol.***: Pectosol; ***Rus.***: Linkus (Линкас); Linkus Lor (Линкас Лор); ***Spain***: Agua del Carmen; ***UK***: Catarrh Mixture; Covonia Catarrh Relief; Tickly Cough & Sore Throat Relief; Vegetable Cough Remover; ***Ukr.***: Linkus (Линкас); Pectolvan Phyto (Пектолван Фито).

Ibogaine

Ibogaina; NIH-10567.
12-Methoxyibogamine.
$C_{20}H_{26}N_2O$=310.4
CAS — 83-74-9.
UNII — 35814I130U.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of ibogaine or preparations containing ibogaine:

Iboga.

Profile

Ibogaine is a hallucinogenic indole alkaloid extracted from the West African shrub *Tabernanthe iboga* (Apocynaceae). It has been investigated as an aid to withdrawal from drug addiction.

References.

1. Popik P, *et al.* 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. *Pharmacol Rev* 1995; **47:** 235–53.
2. Alper KR, *et al.* Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* 1999; **8:** 234–42.
3. Pace CJ, *et al.* Novel iboga alkaloid congeners block nicotinic receptors and reduce drug self-administration. *Eur J Pharmacol* 2004; **492:** 159–67.
4. Hittner JB, *et al.* Combating substance abuse with ibogaine: pre- and posttreatment recommendations and an example of successive model fitting analyses. *J Psychoactive Drugs* 2004; **36:** 191–9.
5. Maciulaitis R, *et al.* Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. *Hum Exp Toxicol* 2008; **27:** 181–94.
6. Hoelen DWM, *et al.* Long-QT syndrome induced by the antiaddiction drug ibogaine. *N Engl J Med* 2009; **360:** 308–9.

Icatibant Acetate *(BANM, USAN, rINNM)*

Acetato de icatibanto; Hoe-140 (icatibant or icatibant acetate); Icatibant, Acétate d'; Icatibanti Acetas; JE-049 (icatibant); Икатибанта Ацетат.
(*R*)-Arginyl-(*S*)-arginyl-(*S*)-prolyl-(2*S*,4*R*)-(4-hydroxyprolyl)glycyl-(*S*)-[3-(2-thienyl)alanyl]-(*S*)-seryl-(*R*)-[(1,2,3,4-tetrahydro-3-isoquinolyl)-carbonyl]-(2*S*,3a*S*,7a*S*)-[(hexahydro-2-indolinyl)-carbonyl]-(*S*)-arginine acetate.
$C_{59}H_{89}N_{19}O_{13}S.xC_2H_4O_2$
CAS — 130308-48-4 (icatibant); 138614-30-9 (icatibant acetate).
ATC — B06AC02.
ATC Vet — QB06AC02.
UNII — 325O8467XK.

Profile

Icatibant acetate is a selective bradykinin B_2 antagonist used in the symptomatic treatment of acute attacks of hereditary angioedema (p. 2485.2) in adults with complement C1 esterase inhibitor deficiency.

Icatibant acetate is given by subcutaneous injection, preferably into the abdomen, in a dose equivalent to 30 mg of icatibant. Due to the large injection volume of 3 mL, it should be given slowly. A single dose is usually enough to treat an acute attack but a second dose may be given after 6 hours if required. Not more than 3 doses should be given in a 24-hour period, each given at 6-hourly intervals.

Mild and transient injection-site reactions, including erythema, swelling, warm sensation, burning, itching, and skin pain are common. Nausea, vomiting, headache, dizziness, asthenia, nasal congestion, and rashes have also been reported.

Icatibant should be given with caution to patients with acute ischaemic heart disease or unstable angina pectoris, and to patients who have recently had a stroke.

Reviews.

1. Cruden NL, Newby DE. Therapeutic potential of icatibant (HOE-140, JE-049). *Expert Opin Pharmacother* 2008; **9:** 2383–90.
2. Dubois EA, Cohen AF. Icatibant. *Br J Clin Pharmacol* 2010; **69:** 425–6.
3. Cicardi M, *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; **363:** 532–41. Correction. *ibid.*; 1486.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Firazyr; ***Austria***: Firazyr; ***Cz.***: Firazyr; ***Denm.***: Firazyr; ***Fr.***: Firazyr; ***Ger.***: Firazyr; ***Gr.***: Firazyr; ***Irl.***: Firazyr; ***Israel***: Firazyr; ***Neth.***: Firazyr; ***Norw.***: Firazyr; ***Pol.***: Firazyr; ***Port.***: Firazyr; ***Rus.***: Firazyr (Фиразир); ***Spain***: Firazyr; ***Swed.***: Firazyr; ***Switz.***: Firazyr; ***UK***: Firazyr; ***USA***: Firazyr.

Iceland Moss

Islandinių kerpenų gniužulas; Isländisches Moos; Isländisches Moos/Isländische Flechte; Islandslav; Islanninjäkälä; Izlandi zuzmó; Lichen d'Islande; Lichen Islandicus; Lišejník islandský; Porost islandzki; Исландский Мох.
*ATC Herb — HA01WB5002 (*Cetraria islandica*: thallus); HR05WA5003 (*Cetraria islandica*: thallus); HA09WA5005 (*Cetraria islandica*: thallus).*
UNII — BJ7YPN79A1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Iceland Moss; Lichen Islandicus). The whole or cut dried thallus of *Cetraria islandica*. Protect from light.

Profile

Iceland moss, *Cetraria islandica* (Parmeliaceae), is a lichen with demulcent and mild antimicrobial activity. It is included in herbal medicines for dry cough, and irritation or inflammation of the oral and pharyngeal mucosa. It is also used as a bitter to stimulate the appetite.

Iceland moss has been used as a foodstuff and a flavouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Tetesept Hals-activ; ***Ukr.***: Isla-Mint (Исла-Минт); Isla-Moos (Исла-Мос).

Multi-ingredient Preparations. ***Ger.***: Cefabronchin; ***Ital.***: Enatus; Kevis; Sclerovis H Plus; ***Pol.***: Padma 28; Pectosol; ***Port.***: Bioclin Sebo Care; ***Switz.***: Arteria-vita; Kernosan Elixir; Padma 28; Padmed Circosan; Tisane pectorale et antitussive; ***UK***: Herb and Honey Cough Elixir; Padma 28; Padma Circosan; ***Ukr.***: Pectolvan Phyto (Пектолван Фито).

Homoeopathic Preparations. ***Canad.***: Kids Cough & Cold Phytux; Phytotux H; ***Fr.***: Cetraria Complexe No 61; ***Ger.***: A-Bomin; Cerivikehl; Drosera-Weliplex†; HanoTussan.

Idanpramine

Idampramina; Иданпрамин.
5,5-Bis(4-methoxyphenyl)-3-[2-(1-piperidinyl)ethyl]-2,4-imidazolidinedione.
$C_{24}H_{29}N_3O_4$=423.5
CAS — 25466-44-8.
ATC — A03AX06.
ATC Vet — QA03AX06.
UNII — 8WIO2013UA.

Idanpramine Hydrochloride

Иданпрамина Гидрохлорид.
$C_{24}H_{29}N_3O_4$,HCl=460.0
CAS — 25466-21-1.
ATC — A03AX06.
ATC Vet — QA03AX06.
UNII — 4B1367ZCIP.

Idanpramine Sulfate

Idampramina Sulfato; Иданпрамина Сульфат.
ATC — A03AX06.
ATC Vet — QA03AX06.

Profile

Idanpramine is an antimuscarinic that has been used as the hydrochloride and sulfate salts in the relief of visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Gastroidam†.

Idursulfase *(BAN, USAN, rINN)*

Iduronate-2-sulfatase; Idursulfasa; Idursulfasum; Idusulfase; Идурсульфас.
α-L-Iduronate sulfate sulfatase.
CAS — 50936-59-9.
ATC — A16AB09.
ATC Vet — QA16AB09.
UNII — 5W8JGG2651.

Uses and Administration

Idursulfase is recombinant human iduronate-2-sulfatase used as enzyme replacement therapy in the treatment of mucopolysaccharidosis II (see below). It is given by intravenous infusion in a dose of 500 micrograms/kg once a week. Idursulfase should be diluted in 100 mL of sodium chloride 0.9% and infused over 1 to 3 hours. The initial infusion rate should be 8 mL/hour for the first 15 minutes, which may then be increased by 8 mL/hour every 15 minutes if well tolerated, up to a maximum rate of 100 mL/hour. If the infusion rate is decreased because of infusion reactions (see below), the infusion time should not exceed 8 hours.

Administration in children. Children aged 16 months or older may be given idursulfase in the treatment of mucopolysaccharidosis II; the dosage is as described for adults, see Uses and Administration, above. Clinical experience with idursulfase treatment in children less than 5 years of age is limited; however, decreases in liver and spleen volumes and a reduction in the urine output of glycosaminoglycans similar to that seen in older children and adults have been reported.[1,2]

1. Muenzer J, *et al.* Idursulfase treatment of Hunter syndrome in children younger than 6 years: results from the Hunter Outcome Survey. *Genet Med* 2011; **13:** 102–9.
2. Giugliani R, *et al.* A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4–7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy. *Genet Med* 2013;. Available at: doi: 10.1038/gim.2013.162

Mucopolysaccharidosis II. Mucopolysaccharidosis II (Hunter syndrome) is a rare X-linked progressive disorder occurring almost exclusively in males and characterised by inherited deficiency of the enzyme iduronate-2-sulfatase, which is necessary to catalyse a step in the breakdown of glycosaminoglycans. This results in accumulation of dermatan and heparan sulfate in lysosomes and produces widespread irreversible cellular and tissue damage and organ dysfunction. Clinical manifestations include severe respiratory obstruction, facial dysmorphism, skeletal and joint deformities, cardiomyopathy, and neurological decline, with death usually in the second decade of life, although patients with milder disease may survive well into adulthood.[1-3]

Significant morbidity and functional problems occur and treatment is supportive and symptomatic involving many body systems; physical and occupational therapy is also necessary. Idursulfase is recombinant human iduronate-2-sulfatase used as enzyme replacement therapy and has been reported to confer benefit with an acceptable safety profile. It is anticipated that greatest benefit would be seen when treatment is started as early in the course of the disease as possible, especially before serious neurological involvement has occurred since idursulfase does not cross the blood-brain barrier. Haematopoietic stem-cell transplantation to supply the deficient enzyme has been tried in some patients, although results have been disappointing and the procedure is associated with significant morbidity and mortality.[1-3]

1. Wraith JE, *et al.* Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. *Eur J Pediatr* 2008; **167:** 267–77.
2. Martin R, *et al.* Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). *Pediatrics* 2008; **121:** e377–e386. Available at: http://pediatrics.aappublications.org/cgi/content/full/121/2/e377 (accessed 23/02/10)
3. Muenzer J, *et al.* Multidisciplinary management of Hunter syndrome. *Pediatrics* 2009; **124:** e1228–e1239. Available at: http://pediatrics.aappublications.org/cgi/content/full/124/6/e1228 (accessed 23/02/10)

Adverse Effects, Treatment, and Precautions

Infusion reactions are common with idursulfase and have included rash, pruritus, urticaria, flushing, fever, headache, and hypertension. Treatment with antipyretics, antihistamines with or without corticosteroids, or a reduction in infusion rate may be necessary. Stopping the infusion should be considered in severe reactions. Anaphylactoid reactions have been reported, in some cases up to 24 hours after the infusion. Serious adverse effects that have also been reported with idursulfase include hypoxia, pulmonary embolism, cyanosis, respiratory failure, cardiac arrhythmias, and arthralgia.

IgG antibodies to idursulfase develop in about half of patients. The presence of antibodies may predispose patients to developing infusion or allergic reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Elaprase; ***Belg.***: Elaprase; ***Canad.***: Elaprase; ***Cz.***: Elaprase; ***Denm.***: Elaprase; ***Fr.***: Elaprase; ***Ger.***: Elaprase; ***Gr.***: Elaprase; ***Hong Kong***: Elaprase; ***Hung.***: Elaprase; ***Irl.***: Elaprase; ***Israel***: Elaprase; ***Jpn***: Elaprase; ***Malaysia***: Elaprase; ***Neth.***: Elaprase; ***Norw.***: Elaprase; ***NZ***: Elaprase; ***Pol.***: Elaprase; ***Port.***: Elaprase; ***Spain***: Elaprase; ***Swed.***: Elaprase; ***Switz.***: Elaprase; ***UK***: Elaprase; ***USA***: Elaprase.

Ignatia

Fève de Saint-Ignace; Ignatia amara; Ignatius Bean; Lu Song Guo; St Ignatius' Bean.

ATC Herb — HA09WA5023 (Strychnos ignatii: seed).

UNII — 1NM3M2487K.

Profile

Ignatia consists of the dried ripe seeds of *Strychnos ignatii* (*S. tieute*; *I. amara*) (Loganiaceae). Ignatia contains strychnine (p. 2623.2) in higher concentrations than those found in Nux Vomica (p. 2573.3), plus similar concentrations of brucine, and has been used in herbal tonic preparations and as a bitter.

Homoeopathy

Ignatia has been used in homoeopathic medicines under the following names: Iamara; Ignatia amara; Ign.; Strychnos ignatii.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus.

Homoeopathic Preparations. ***Austral.***: Childrens Sleep; Nervatona Calm; Nervatona Focus; Smoke Eze; ***Austria***: Berberis Cosmoplex†; Ignatia-Homaccord; Klimaktoplant; Mandragora Med Complex; Mastodynon; Nervoheel; Pascofemin; Pasconal; Relax; Vomitusheel; ***Canad.***: Fibromyalgie; Hylands Gas; Hylands Insomnia; Kids Calm; Nixotinex; Sedilor†; Stress L72†; Stress; ***Chile***: Bioactiv O; ***Cz.***: Hormeel S; Mastodynon; Vita C-R15 forte†; Vita C-R15†; Ypsiloheel; ***Fr.***: Abbe Chaupitre no 7; Anxietum; Boripharm No 3; Dolirelax†; Dolisedal†; Dolitravel†; L 72; Lobelia Complexe No 74†; Neurocynesine†; Passiflora Compose; Soludor; Staphysagria Complexe No 92†; Stressdoron; Tabacum Compose; Tarentula Complexe No 71; Vinicard†; Zenalia; ***Ger.***: Ambrax; Antimast TN†; Calmvalera; Cefaneuro; Corselect N; Cranio-cyl Ho-Len-Complex; Gastroplant; Goldtropfen S; Hyperforat Nervo; Klimaktoplant N; Mastodynon; Myonasan; Nervoject F; Nervoregin comp; Pascofemin; Pascolibrin; Pasconal Nerventropfen; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rowo Rytesthin Ro-Plex (Rowo-318); Rytesthin; Sedaphin†; Sedaselect; Sedativa-Injektopas; Sepia comp; Ypsiloheel N; Zincum Hevert N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Hormeel S; Klimakt-Heel; Nervoheel; PSY-Stabil; ***Neth.***: Cerebrum comp; Echilite; Emvita 11; Hyperilite; Klimaktolan; Mastodynon†; Nervival; Nervofleur; Nervoheel; Neurocynesine†; PSY-stabil; ***Rus.***: Crataegus-Plus (Кратегус-Плюс); Hormeel SN (Гормель СН); Klimaktoplan (Климактоплан); Mastodynon (Мастодинон); Uspokoi (Успокой); Valeriana-Plus (Валериана-Плюс); ***Switz.***: Ignatia-Homaccord; Menosan†; Nervoheel; Vomitusheel; ***Thai.***: Mastodynon†; ***Ukr.***: Aurocard (Аурокард); Homvio-Nervin (Хомвио-Нервин); Klimaktoplan N (Климактоплан Н); Mastodynon (Мастодинон); ***USA***: Preferred Remedies Fatigue; Preferred Remedies Sleep.

Indian Barberry

Chitra; Indian Berberry; Tree Turmeric; Барбарис Остистый (*Berberis aristata*).

Pharmacopoeias. In *Br.*

BP 2014: (Berberis Aristata). The dried cut stem of *Berberis aristata*. It contains not less than 1.4% of berberine calculated with reference to the dried material.

Protect from moisture.

Profile

The stem and root bark of the Indian barberry (*Berberis aristata* (Berberidaceae)) is used orally in herbal medicine mainly for fevers, and in hepatic and gastrointestinal disorders and topically for skin lesions. The fruit and other parts of the plant are also used.

Berberis aristata is a source of berberine (p. 2455.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Antisept†; Britesite; Diabecon; Entrostat; Femi Forte; Geriforte; Geriforte; Herbinol; Livomyn; Livomyn; Livto; Marc Free; Paedritone; ***Ital.***: Berart; ***Rus.***: Bonjigar (Бонджигар); Entoban (Энтобан); Pilex (Пайлекс); ***Ukr.***: Bonjigar (Бонджигар); Entoban (Энтобан).

Indian Gooseberry

Amalaki; Amla; Emblic; Emblic Myrobalan; Филлантус Лекарственный.

ATC Herb — HA02WX5002 (Phyllanthus emblica: fruit); HA03AW5046 (Phyllanthus emblica: fruit); HA06AX5007 (Phyllanthus emblica: fruit); HA11WA5003 (Phyllanthus emblica: fruit); HA06AX5006 (Phyllanthus emblica: flower).

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan or Indian Gooseberry, above), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — see Arjuna, p. 2447.2; *T. bellirica* — see Beleric Myrobalan, p. 2453.2; and *T. chebula* — see Chebulic Myrobalan, p. 2474.3). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. *Br.* includes Phyllanthus Emblica Pericarp.

BP 2014: (Phyllanthus Emblica Pericarp). The pericarp of dried mature fruits of *Phyllanthus emblica* (*E. officinalis*). It contains not less than 6.0% tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The fruits of the Indian Gooseberry, *Phyllanthus emblica* (*Emblica officinalis*, *Mirobalanus embilica*) (Euphorbiaceae), have traditionally been used in Ayurvedic medicine and are included in herbal preparations.

The traditional Ayurvedic medicine triphala is a combination of Indian gooseberry, beleric myrobalan (p. 2453.2), and chebulic myrobalan (p. 2474.3). The fruits are reputed to contain large amounts of vitamin C, and are also used as a foodstuff.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Vita Jam; ***Thai.***: Compound Makham Pom.

Multi-ingredient Preparations. ***Arg.***: Recover Whitening; ***Austral.***: Ultra Calm; ***Fr.***: Triphala; ***Hung.***: Herbadict; Munipyrin; ***India***: Anti Dysp; Flexi-muv†; ***Malaysia***: Bonnisan; ***Philipp.***: Cogent db+; ***Rus.***: Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Fitovit (Фитовит); Pilex (Пайлекс); Travisil (Трависил); ***Singapore***: Hemoglo; Imunomet; Septilin; Septilin; ***Thai.***: Couffee Mixture; Iyara Ma-Weang; ***Ukr.***: Alfagin (Алфагин); Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Eve Care (Ив Кер)†; Fitovit (Фитовит); Imunin (Иммунин)†; Intellan (Интеллан); Septilin (Септилин); Travisil (Трависил); Trypsidan (Трипсидан)†.

Indigo Carmine

Blue X; Carmín de índigo; Ceruleinum; CI Food Blue 1; Colour Index No. 73015; Disodium Indigotin-5,5′-disulphonate; E132; FD & C Blue No. 2; Indicarminum; Indigo Karmin; Indigotina; Indigotindisulfonate Sodium; Indigotine; Indygokarmin; Sodium Indigotindisulphonate; Индигокармин.

Disodium 3,3′-dioxo-2,2′-bi-indolinylidene-5,5′-disulphonate.

$C_{16}H_8N_2Na_2O_8S_2$=466.3

CAS — 483-20-5 (indigotin-5,5′-disulphonic acid); 860-22-0 (indigo carmine).

ATC — V04CH02.

ATC Vet — QV04CH02.

UNII — X7OI7JF73P (indigotin-5,5′-disulphonic acid); D3741U8K7L (indigo carmine); L06K8R7DQK (FD & C blue no 2).

NOTE. The name Cerulein has been applied to Ceruletide (p. 2473.3).

Although the name FD & C Blue No.2 is widely used to denote indigo carmine it is actually defined as being mainly indigo carmine with smaller amounts of the disodium salt of 2-(1,3-dihydro-3-oxo-7-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid (*CAS*—54947-75-0) and the sodium salt of 2-(1,3-dihydro-3-oxo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid (*CAS*—605-18-5).

Pharmacopoeias. In *It.*, *Jpn*, and *US*.

USP 36: (Indigotindisulfonate Sodium). A dusky, purplish-blue powder, or blue granules having a coppery lustre. Soluble 1 in 100 of water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Its solutions have a blue or bluish-purple colour. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

On intravenous injection indigo carmine is rapidly excreted, mainly by the kidneys. It has been used in a test of renal function, but has largely been replaced by agents that give more precise results. It is used as a marker dye, particularly in urological procedures, when it is given in a usual dose of 40 mg, preferably by intravenous injection but sometimes intramuscularly. It has also been used as a marker dye in amniocentesis.

Indigo carmine has been used as a blue dye in medicinal preparations but it is relatively unstable. It has also been investigated as a dye-spray in the detection of colorectal adenomas. It is used as a food colour.

Adverse Effects and Precautions

Indigo carmine may cause nausea, vomiting, hypertension, and bradycardia, and occasionally, hypersensitivity reactions such as rashes, pruritus, and bronchoconstriction. Skin discoloration may occur after large parenteral doses, particularly in children and underweight patients.

Hypersensitivity. Cardiac arrest after a dose of indigo carmine 80 mg intravenously resulted in the deaths of 2 elderly patients.[1] Both had a history of asthmatic bronchitis. A life-threatening anaphylactoid reaction associated with indigo carmine use has also been reported, although the authors commented that such events are rare.[2]

1. Voiry AM, *et al.* Deux accidents mortels lors d'une injection peropératoire de carmin d'indigo. *Ann Med Nancy* 1976; **15:** 413–19.
2. Gousse AE, *et al.* Life-threatening anaphylactoid reaction associated with indigo carmine intravenous injection. *Urology* 2000; **56:** 508.

Preparations

Pharmacopoeial Preparations

USP 36: Indigotindisulfonate Sodium Injection.

Indocyanine Green

Verde de indocianina; Индоцианин Зелёный.

Sodium 2-{7-[1,1-dimethyl-3-(4-sulphobutyl)benz[*e*]indolin-2-ylidene]hepta-1,3,5-trienyl}-1,1-dimethyl-1*H*-benz[*e*]indolio-3-(butyl-4-sulphonate).

$C_{43}H_{47}N_2NaO_6S_2$=775.0

CAS — 3599-32-4.

UNII — IX6J1063HV.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Indocyanine Green). An olive-brown, dark green, blue-green, dark blue, or black powder. Is odourless or has a slight odour. It contains not more than 5.0% of sodium iodide, calculated on the dried basis. Soluble in water and in methyl alcohol; practically insoluble in most other organic solvents. Its solutions are deep emerald-green in colour. pH of a 0.5% solution in water is about 6. Its aqueous solutions are stable for about 8 hours. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Indocyanine green is an indicator dye used for assessing cardiac output and liver function, and for examining the choroidal vasculature in ophthalmic angiography. It is also used to assess blood flow and haemodynamics in various organs including the liver.

The usual dose for cardiac assessment is 5 mg injected rapidly via a cardiac catheter. A suggested dose for children is 2.5 mg, and for infants 1.25 mg. Several doses need to be given to obtain a number of dilution curves. However, the total dose should not exceed 2 mg/kg.

The usual dose of indocyanine green for testing liver function is 500 micrograms/kg given intravenously.

Administration in children. Doses of indocyanine green for cardiac assessment in infants and children are given under Uses and Administration, above.

Diagnostic use. Indocyanine green has been used to assess blood flow to various organs and in other haemodynamic studies. However, some methods of determination of indocyanine green clearance as a measure of liver blood flow have been questioned on the grounds that extraction of the dye by the liver is not complete as is often assumed.[1] Interindividual variability in indocyanine clearance may introduce further error.[2]

There have been reports of the use of indocyanine green to assess cerebral blood flow in children during cardiopulmonary bypass[3] and to measure plasma volume in

neonates.[4] In ophthalmology, indocyanine green angiography is used to visualise the choroidal circulation,[5,6] and as a stain during surgical repair of macular holes.[7,8]

1. Skak C, Keiding S. Methodological problems in the use of indocyanine green to estimate hepatic blood flow and ICG clearance in man. *Liver* 1987; **7:** 155–62.
2. Bauer LA, *et al.* Variability of indocyanine green pharmacokinetics in healthy adults. *Clin Pharm* 1989; **8:** 54–5.
3. Roberts I, *et al.* Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet* 1993; **342:** 1425.
4. Anthony MY, *et al.* Measurement of plasma volume in neonates. *Arch Dis Child* 1992; **67:** 36–40.
5. Owens SL. Indocyanine green angiography. *Br J Ophthalmol* 1996; **80:** 263–6.
6. Dzurinko VL, *et al.* Intravenous and indocyanine green angiography. *Optometry* 2004; **75:** 743–55.
7. Rodrigues EB, *et al.* Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes. *Ophthalmologica* 2005; **219:** 251–62.
8. Lee KL, *et al.* A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; **89:** 420–4.

Adverse Effects and Precautions

Indocyanine green is reported to be well tolerated. Anaphylaxis and urticaria have been reported. Solutions contain a small amount of sodium iodide and should be used with caution in patients hypersensitive to iodine. Clearance of indocyanine green may be altered by drugs that interfere with liver function.

References.

1. Jackson TL. Indocyanine green accused. *Br J Ophthalmol* 2005; **89:** 395–6.
2. Cheng SN, *et al.* Ocular toxicity of intravitreal indocyanine green. *J Ocul Pharmacol Ther* 2005; **21:** 85–93.
3. Gandorfer A, *et al.* Toxicity of indocyanine green in vitreoretinal surgery. *Dev Ophthalmol* 2008; **42:** 69–81.

Hypersensitivity. A report of anaphylactoid reactions to indocyanine green in 3 patients.[1] The authors commented that of 20 reactions that had been reported 9 involved anaphylactoid shock (with 2 subsequent deaths) and 11 involved hypotension or bronchospasm; they suggested that such reactions were dose-dependent and had a non-immune mechanism.

1. Speich R, *et al.* Anaphylactoid reactions after indocyanine-green administration. *Ann Intern Med* 1988; **109:** 345–6.

Pharmacokinetics

After intravenous injection indocyanine green is rapidly bound to plasma protein. It is taken up by the liver and is rapidly excreted unchanged into the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Infracyanine; ***Ger.***: ICG-Pulsion; ***Gr.***: ICG-Pulsion; ***Hong Kong***: Diagnogreen†; ***Irl.***: ICG-Pulsion; ***Israel***: IC Green†; ICG-Pulsion; ***Neth.***: ICG-Pulsion; ***Singapore***: ICG-Pulsion; ***USA***: IC Green.

Pharmacopoeial Preparations

USP 36: Indocyanine Green for Injection.

Inhibin

Inhibina; Ингибин.

CAS — 57285-09-3.

NOTE. The name inhibin has also been used as a proprietary name for hydroquinine hydrobromide (p. 2529.2).

Profile

Inhibin is a dimeric glycoprotein secreted by the testes and ovaries that suppresses secretion of follicle-stimulating hormone by the pituitary. As a member of the transforming growth factor-β family, it is also involved in mediation and regulation of many other physiological processes. Its two isoforms inhibin A and inhibin B have been widely investigated for their potential as markers of male infertility, ovarian cancer, and placental function. It has also been studied as a prognostic indicator of ovarian function in women undergoing assisted reproduction.

References.

1. Kumanov P, *et al.* Significance of inhibin in reproductive pathophysiology and current clinical applications. *Reprod Biomed Online* 2005; **10:** 786–812.

Inosine *(rINN)*

Hipoxantina ribósido; Hypoxanthine Riboside; Inosina; Inosinum; Инозин.

6,9-Dihydro-9-β-D-ribofuranosyl-1*H*-purin-6-one.

$C_{10}H_{12}N_4O_5$=268.2

CAS — 58-63-9.

ATC — D06BB05; G01AX02; S01XA10.

ATC Vet — QD06BB05; QG01AX02; QS01XA10.

UNII — 5A614L51CT.

Pharmacopoeias. In *Chin.*

Profile

Inosine has been used in the treatment of anaemias and cardiovascular, liver, and skin disorders and has been used as a tonic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Jie Di Lin (安洁迪林); An Qi Mi Rui (安琪米瑞); Ba Quan (巴泉); Dan Ze (丹泽); De Yi Mei (德益美); Di Li (迪力); En Li Ke (恩立克); Fu Li Ding (复力定); Fu Li Xin (复力欣); Gan Ke (甘可); Gan Quan (甘全); Hu Yue (湖月); Ke Mi Ya (科米雅); Lai Mei Kang (莱美康); Lan Xu (兰旭); Li Fu (力孚); PiDi Gan (彼迪甘); Pu Fu (普辅); Qi Fang Neng (奇方能); Quan Zhu (全助); WeiMeiJia (卫每加); Xin Feng (欣丰); Yan Luo Qi (延罗祺); Yi Rong Xin (易荣欣); Yong Rui Neng (永瑞能); Ze Bei (泽贝); Zhu Lu (竹路); Zuo He (左禾); ***Rus.***: Ribonosin (Рибонозин); ***Ukr.***: Riboxin (Рибоксин).

Multi-ingredient Preparations. ***China***: Li Sheng Si Tai (丽生斯泰); Ying Di Te (英迪特); ***Ital.***: Neo-Eparbiol; ***Rus.***: Cytoflavin (Цитофлавин); Remaxol (Ремаксол); ***Spain***: Nutracel; ***Ukr.***: Corargin (Кораргин); Cytoflavin (Цитофлавин).

Inositol

i-Inositol; Inositoli; Inositolum; *meso*-Inositol; mio-Inozytol; myo-Inositol; myo-Inositoli; Myo-Inositolum; *myo*-Inositolum; Инозитол.

myo-Inositol.

$C_6H_{12}O_6$=180.2

CAS — 87-89-8.

ATC — A11HA07.

ATC Vet — QA11HA07.

UNII — 4L6452S749.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (*myo*-Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in alcohol.

USNF 31: (Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Inositol, an isomer of glucose, has traditionally been considered to be a vitamin B substance although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. Sources of inositol include whole-grain cereals, fruits, and plants, in which it occurs as the hexaphosphate, fytic acid. It also occurs in both vegetables and meats in other forms. The usual daily intake of inositol from the diet is about 1 g. It is an ingredient of many vitamin preparations and dietary supplements, and of preparations promoted for many disorders.

Inositol appears to be involved physiologically in lipid metabolism and has been tried, with little evidence of efficacy, in disorders associated with fat transport and metabolism. It has been investigated in the treatment of depression and anxiety, in diabetic neuropathy, and in neonatal respiratory distress syndrome and retinopathy of prematurity.

Neonatal respiratory distress syndrome. Inositol supplementation has been tried in premature infants with respiratory distress syndrome (p. 1608.3). A meta-analysis[1] found that infants given inositol had improved survival and lower rates of bronchopulmonary dysplasia and retinopathy of prematurity than those given placebo.

1. Howlett A, Ohlsson A. Inositol for respiratory distress syndrome in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 19/04/06).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Inositech.

Multi-ingredient Preparations. ***Arg.***: Bifena; Cistidac; Desgras Burner Fat; Desgras Piel Naranja; Ripped Max; Skin Hair & Nails; ***Austral.***: Metabolift Fat Burner; Natal Plus; PM Syrin; ***Braz.***: Geriavite; Metiocolin B12; Xantinon Complex; ***Canad.***: Emulsi Factors; Formula 17605 Diaplex; Formula 3358†; Formula AO†; Glycopro; Lipofactors & Niacin†; Liv-Gd; Liv-Gd; Live-Rite; Nia-Plex; ***Chile***: Hepabil; Tonopron Jarabe; ***Fr.***: Hepagrume; ***Hong Kong***: Anti-Stress Hi B Plus C†; B Complex 50; Executive Stress†; Lipochol; Mega-Antioxidant†; Super Vita Vim; Vita Stress†; ***India***: Alcrin-M; Alcrin; Alphamix-BT; Cherrytone; Delphicol†; Dianuron; Diapill; Efcoben; Felicita-OD; Jetositol; Meconerv Forte; N-Care Forte; Nervijen-D; Nervz-B; Neuractin Forte; Neuroglow-B; Neurosoz-MC; ***Indon.***: Carni Plus; DFM; Elkana; Fitkom; Hemaviton Energy Drink; Minicerонal†; Vidaylin L; Xanda; Zamel; Zevit Grow; ***Ital.***: Hepatos B12; Konorderm; Lipoenergy; Porfirin 12; ***Malaysia***: Pharmaton†; Revital; Vi-Daylin; ***Mex.***: Bedoyecta; ***Philipp.***: Arcostrong†; Completia†; Enerzip; K-A Plus; Optigrow; Pharmaton; Rejuvenex; Revicon Forte (Improved); ***Rus.***: Prohepar (Прогепар); ***S.Afr.***: Clusivol; Hepavite†; Prohep†; ***Singapore***: Essentials†; NutraMX; ***Spain***: Dertrase; Policolinosil; Tri Hachemina†; ***Switz.***: Vitiron; ***Thai.***: Lipochol; Liporon; Vita Multicap; Vitop; ***UK***: Lipotropic Factors; Skin Care Nutrients; ***Ukr.***: Hepahealth (Гепахелс); PM Sirin (ПМ Сирин); Vitiron (Витирон); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Advanced Ear Health Formula; Alive Once Daily Womens 50+ Ultra Potency; Amino-Cerv; Biotect Plus; Cholinoid†; Clinical Nutrients 50-Plus Men; Megavite Fruits & Veggies; One A Day Vitacraves; PowerVites; Totalday; Tyler Prenatal; ***Venez.***: Hepasil; Yacriton.

Interleukins

Интерлейкины.

Profile

Interleukins are cytokines (p. 2491.2) that are thought to target leucocytes. As with other cytokines, interleukins are involved in the regulation of normal immune and inflammatory responses and have both proinflammatory and anti-inflammatory actions. Interleukins used clinically include interleukin-1 (below), interleukin-2 (p. 810.1), and aldesleukin (recombinant interleukin-2) (p. 810.1). Interleukins under investigation include interleukin-3 (p. 1155.2), ilodecakin (recombinant interleukin-10) (p. 2534.2), and edodekin alfa (recombinant interleukin-12) (p. 2534.2).

Interleukins have also been implicated in the pathogenesis of some diseases, and inhibitors of interleukins or their receptors may therefore be of therapeutic value.

Antagonists acting against interleukin receptors used clinically include anakinra (recombinant interleukin-1 receptor antagonist) (p. 21.2), basiliximab (p. 1944.1), and daclizumab (p. 1957.1), which are all interleukin-2 receptor antibodies, and tocilizumab (recombinant interleukin-6 receptor antibody) (p. 77.3) Inolimomab (p. 1959.3) is an interleukin-2 receptor antibody under investigation.

Antibodies targeting interleukins have been developed and include canakinumab (p. 34.2), a recombinant human monoclonal antibody against interleukin-1β, while those under investigation include mepolizumab (recombinant interleukin-5 antibody) (p. 1214.2) and elsilimomab (recombinant interleukin-6 antibody) (p. 2534.1).

Interleukin fusion toxins are produced by combining interleukin protein sequences with a bacterial toxin (e.g. diphtheria or pseudomonas) with the aim of inhibiting specific interleukin activity. Those under investigation include interleukin-2 fusion toxins (p. 2534.1), interleukin-4 fusion toxins, and cintredekin besudotox (p. 766.1), an interleukin-13 fusion toxin.

Soluble interleukin receptors may have therapeutic value and are also being tried therapeutically: rilonacept (p. 2604.3) is an interleukin-1 blocker used in the treatment of a group of rare inherited auto-inflammatory disorders; interleukin-4 receptor is also being investigated.

Inhibitors of cysteine protease IL-1β converting enzyme (ICE) have been investigated as a means of reducing secretion of interleukin-1β (below).

Interleukin-1

Catabolin; Endogenous Pyrogen; Haematopoietin-1; IL-1; Interleucina 1; Leucocyte Endogenous Mediator; Lymphocyte Activating Factor; Интерлейкин-1.

UNII — 8666ZWZ3E1 (interleukin-1α); X62226112J (interleukin-1β).

Profile

Interleukin-1 is one of several polypeptides known collectively as interleukins (above). It is produced in blood and a variety of tissues by mononuclear phagocytes involved in the complex regulation of immune responses. It enhances the immune response and has proinflammatory and pyrogenic properties. There are two distinct forms, interleukin-1α and interleukin-1β.

Interleukin-1 may also be produced by recombinant DNA technology, and human recombinant interleukin-1β has been used as an adjunct to cancer chemotherapy or radiotherapy for its haematopoietic activity. It has also been investigated for its immunotropic effects in purulent infections of the lung and ear, although it has no intrinsic antibacterial activity. Adverse effects of interleukin-1 include fever, chills, flu-like symptoms, hypotension, and pain, swelling, and erythema at the site of subcutaneous injection.

Interleukin-1 is also implicated in the pathogenesis of some diseases, particularly auto-immune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Betaleukin (Беталейкин).

Interleukin-1 Receptor Antagonists

Antagonista del Receptor de la Interleucina 1; IL-1i; IL-1ra; Interleukin-1 Inhibitors.

Profile

Endogenous antagonists to interleukin-1 receptor block the actions of interleukin-1 (p. 2533.3) and recombinant forms have been investigated in inflammatory and immune-modulated disorders.

Anakinra (p. 21.2) is a human recombinant interleukin-1 receptor antagonist used in the treatment of rheumatoid arthritis.

Interleukin-2 Fusion Toxins

Toxinas de fusión de interleucina 2.

Profile

Interleukin-2 fusion toxin is produced by replacing the receptor binding domain of diphtheria toxin with sequences from interleukin-2, thus producing specific cytotoxicity in cells expressing the interleukin-2 receptor. The interleukin-2 fusion toxin denileukin diftitox (p. 780.2) is used in the treatment of cutaneous T-cell lymphoma. The related compound DAB_{486} interleukin-2 has also been investigated in a variety of disorders.

Interleukin-6

B-cell Stimulatory Factor-2; BSF-2; Hepatocyte-Stimulating Factor; Hybridoma Growth Factor; IFN-β_2; IL-6; Interferon-β2; Интерлейкин-6.

UNII — 92QVL9080Y.

NOTE. The name Sigosix has been used as a trade mark for atexakin alfa (human recombinant interleukin-6).

Profile

Interleukin-6 is one of several polypeptides known collectively as interleukins (p. 2533.3). It is produced by many cell types and induces differentiation of B-lymphocytes and activation of T-cells. It has proinflammatory and pyrogenic properties and is involved in the regulation of immune responses and inflammation. Interleukin-6 has also been implicated in haematopoiesis.

Atexakin alfa is human recombinant interleukin-6 that has been investigated.

Since overproduction of interleukin-6 plays a crucial role in the pathogenesis of chronic inflammatory diseases, interleukin-6 antibodies (below) and interleukin-6 receptor antagonists (p. 77.3) are being investigated or used as therapeutic agents.

Interleukin-6 Antibodies

IL-6 Antibody.

Elsilimomab *(rINN)*

Elsilimomabum; Эльсилимомаб.

Immunoglobulin G1, anti-(human interleukin 6) (mouse monoclonal B-E8 heavy chain), disulfide with mouse monoclonal B-E8 κ-chain, dimer..

CAS — 468715-71-1.

Profile

Monoclonal antibodies to interleukin-6 (above) are under investigation for the treatment of disorders including post-transplant lymphoproliferative disorders and renal cell carcinoma.

Elsilimomab is an interleukin-6 monoclonal antibody under investigation.

Interleukin-10

CSIF; Cytokine synthesis inhibitory factor; IL-10; Интерлейкин-10.

CAS — 130068-27-8.

UNII — 95C4O216V9.

Ilodecakin *(USAN, rINN)*

Ilodecakina; Ilodécakine; Ilodecakinum; Interleukin-10 (human clone pH15C); rhIL-10; Sch-52000; Илодекакин.

CAS — 149824-15-7.

UNII — 6GY6UY4UR7.

NOTE. The names Prevascar and Tenovil have been used for ilodecakin.

Profile

Interleukin-10 is one of several polypeptides known collectively as interleukins (p. 2533.3). It regulates the differentiation and proliferation of several immune cells including T-cells and B-cells. It is postulated that it has immunostimulant as well as immunosuppressive properties; it also has anti-inflammatory actions. Interleukin-10 is under investigation for inflammatory bowel disease, malignant neoplasms, skin disorders including psoriasis and reduction of scarring, rheumatoid arthritis, hepatitis C, and organ transplantation.

Ilodecakin is a recombinant form of interleukin-10 under investigation.

References.

1. Asadullah K, *et al.* Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* 2003; **55:** 241–69.
2. Braat H, *et al.* Interleukin-10-based therapy for inflammatory bowel disease. *Expert Opin Biol Ther* 2003; **3:** 725–31.
3. Weiss E, *et al.* The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. *J Am Acad Dermatol* 2004; **50:** 657–75.
4. Asadullah K, *et al.* Interleukin-10: an important immunoregulatory cytokine with major impact on psoriasis. *Curr Drug Targets Inflamm Allergy* 2004; **3:** 185–92.
5. Vicari AP, Trinchieri G. Interleukin-10 in viral diseases and cancer: exiting the labyrinth? *Immunol Rev* 2004; **202:** 223–36.
6. Mocellin S, *et al.* Interleukin-10 and the immune response against cancer: a counterpoint. *J Leukoc Biol* 2005; **78:** 1043–51.
7. Mege JL, *et al.* The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis* 2006; **6:** 557–69.

Interleukin-12

IL-12; Интерлейкин-12.

UNII — 02FXP10O2U (interleukin-12 human recombinant).

Edodekin Alfa *(USAN, rINN)*

Edodekina alfa; Édodékine Alfa; Edodekinum Alfa; Ro-24-7472/000; Эдодекин Альфа.

CAS — 187348-17-0.

UNII — 31Z82G8ME1.

Description. A recombinant human interleukin-12.

Profile

Interleukin-12 is one of several polypeptides known collectively as interleukins (p. 2533.3). It is produced by macrophages and dendritic cells and enhances cellular immunity through induction of the activity of interferon-γ and cytotoxic T-lymphocytes. It has been investigated for the treatment of severe infections such as mycobacterial infections; it is worthy of note that children with a rare inherited susceptibility to fatal mycobacterial infections have mutations in the interleukin-12 gene. Interleukin-12 is also under study for the treatment of various cancers, including as adenovirus-mediated gene therapy.

Edodekin alfa is human recombinant interleukin-12 under investigation for the treatment of renal cell carcinoma.

References.

1. Mazzolini G, *et al.* Gene therapy of cancer with interleukin-12. *Curr Pharm Des* 2003; **9:** 1981–91.
2. Kikuchi T, *et al.* Vaccination of glioma patients with fusions of dendritic and glioma cells and recombinant human interleukin 12. *J Immunother* 2004; **27:** 452–9.
3. Trudeau C, *et al.* A single administration of recombinant human interleukin-12 is associated with increased expression levels of interferon-gamma and signal transducer and activator of transcription in healthy subjects. *J Clin Pharmacol* 2005; **45:** 649–58.
4. Sangro B, *et al.* Gene therapy of cancer based on interleukin 12. *Curr Gene Ther* 2005; **5:** 573–81.
5. Little RF, *et al.* Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood* 2006; **107:** 4650–7.

Intrinsic Factor

Antianemic Factor; Castle's Intrinsic Factor; Gastric Intrinsic Factor; Внутренне Присущий Фактор.

CAS — 9008-12-2.

Profile

Intrinsic factor, a glycoprotein secreted by the parietal glands in the stomach, is required for absorption of vitamin B_{12} in the small intestine. Deficiency in intrinsic factor leads to vitamin B_{12} deficiency disorders and pernicious anaemia.

Intrinsic factor is given orally with cyanocobalamin in the Schilling test in the differential diagnosis of pernicious anaemia (see Uses and Administration of Vitamin B_{12}, p. 2108.1). It is also included in some oral preparations containing cyanocobalamin, presumably as an aid to absorption.

Difficulty in obtaining intrinsic factor and/or radio-labelled cyanocobalamin for the original Schilling test prompted studies using a recombinant human intrinsic factor in a new vitamin B_{12} absorption test. Initial results with this recombinant form were promising.[1]

1. Hvas A-M, *et al.* The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B 12 deficiency. *Haematologica* 2006; **91:** 805–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Biosanbe; Habebion†; Hemafort; Inbion; Nichobion; Sangofer; ***Philipp.***: TriHEMIC; ***S. Afr.***: Autrin†; ***Singapore***: Hemacaps†; ***USA***: Chromagen†; Contrin; Ferotrinsic; Fetrin; Livitrinsic-f†; Pronemia Hematinic; TL Icon; TriHEMIC; Trinsicon†.

Inulin *(BAN)*

Alant Starch; Inulina; Инулин.

CAS — 9005-80-5.

UNII — JOS53KRJ01.

Pharmacopoeias. In *US.*

USP 36: (Inulin). A polysaccharide which, on hydrolysis, yields mainly fructose. A white, friable, chalk-like, amorphous, odourless powder. Soluble in hot water; slightly soluble in cold water and in organic solvents. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Inulin is a fructan or fructose polymer. It is used intravenously as a diagnostic agent to measure the glomerular filtration rate. Although an accurate test, it is complex to perform and is generally reserved for research purposes. Crystals of inulin may be deposited on storage of the injection; they should be dissolved by heating for not more than 15 minutes before use and the injection cooled to a suitable temperature before use.

Polyfructosan, an inulin analogue of lower average molecular weight, has been used similarly.

Inulin and related fructans, such as fructo-oligosaccharides (p. 2508.1), are a form of dietary fibre and have been used as dietary supplements, particularly for their prebiotic effects.

Pharmacokinetics

Inulin is rapidly removed from the circulation after intravenous doses but is not metabolised. A trace may be found in the bile and may cross the placenta, but it is mainly eliminated in the urine by glomerular filtration without secretion or reabsorption in the renal tubule.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Philipp.***: Fibersweet.

Multi-ingredient Preparations. ***Arg.***: Invisifiber; XLS; ***Chile***: Reduc-Te; Reducform-F; ***Fr.***: Actyfilus; Arkolevure; Cebrolux; Effadiane relipidantes; Maxi-Flore; ***Ger.***: Laxatan M; ***Hong Kong***: LactoGG; Lepicol; ***Indon.***: Becombion Grow Syrup; ***Ital.***: Cistefi; Enterolactis Duo; Enteroseven; Fibrovit; Floragermina 6; Lactolas; Naturalass; Plurilac; Serilact; Snell'it; Valcap; ***Malaysia***: Probio Lact Active Formula; ***Philipp.***: Culturelle With Lactobacillus GG†; ***Ukr.***: Zacofalk (Закофальк); ***USA***: Preorbotic.

Homoeopathic Preparations. ***Neth.***: Drosinula.

Pharmacopoeial Preparations

USP 36: Inulin in Sodium Chloride Injection.

Iris Versicolor

Blue Flag; Iris Virginica; Lirio azul; Касатик Разноцветный (*Iris versicolor*); Ирис Разноцветный (*Iris versicolor*).

UNII — PYC571247P (Iris versicolor); *X43D4L3DQC* (Iris versicolor *root*).

Profile

The rhizomes of *Iris versicolor* (Iridaceae) are used in herbal preparations for skin and gastrointestinal disorders.

Homoeopathy

Iris versicolor has been used in homoeopathic medicines under the following names: Iris; Iris ver.; Iris vers.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Weleda Hauttonikum†; ***Port.***: Cephyl†; ***Switz.***: Venadoron; ***UK***: HRI Clear Complexion; Skin Eruptions Mixture.

Homoeopathic Preparations. ***Austria***: Globuli gegen Kopfschmerzen; Iris Med Complex; Mastodynon; ***Canad.***: Bioactiv N†; Chelidonium Plex†; Formula DM 210†; Hea Complex†; Headache & Migraine L77; Hyalgesic HP†; Hylands Headache; ***Chile***: Bioactiv N; Lumboplex; ***Cz.***: Mastodynon; ***Fr.***: Neurocynesine†; Phapax; ***Ger.***: Antimigren; Cefanalgin†; Cephaloplant†; Dolfin; DolorA; Infifer N; Mastodynon; Migrane Hevert†; Migrane Hevert; Migrane-Gastreu R16; Rephalgin N; Schwoneural N; ***Neth.***: Cephalite; Lymphomyosot; Mastodynon†; Neurocynesine†; Speci-chol; ***Rus.***: Iris-Plus (Ирис-Плюс); Mastodynon (Мастодинон); ***Switz.***: Multiplex l; ***Thai.***: Mastodynon†; ***Ukr.***: Mastodynon (Мастодинон).

Isobutyl Nitrite

Изобутилнитрит.

$C_4H_9NO_2$=103.1

CAS — 542-56-3.

UNII — GW9WAB6QOM.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of isobutyl nitrite:

Aroma of men; Bolt; Bullet; Climax; Hardware; Krypt tonight; Locker room; Poppers; Quicksilver; Rush; Rush Snappers; Snappers; Thrust; White out; Whiteout.

Profile

Isobutyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p. 1540.3).

Isometheptene *(BAN, rINN)* ⊗

Isometepteno; Isométheptène; Isometheptenum; Изометептен.

1,5-Dimethylhex-4-enyl(methyl)amine; 1,5,*N*-Trimethylhex-4-enylamine.

$C_9H_{19}N$=141.3

CAS — 503-01-5.

ATC — A03AX10.

ATC Vet — QA03AX10.

UNII — Y7L24THH6T.

Isometheptene Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de isometepteno; Isométheptène, Chlorhydrate d'; Isomethepteni Hydrochloridum; Изометептена Гидрохлорид.

$C_9H_{19}N$,HCl=177.7

CAS — 6168-86-1.

ATC — A03AX10.

ATC Vet — QA03AX10.

UNII — 9Z4CJC3O5F.

Isometheptene Mucate *(BANM, rINNM)* ⊗

Isometepteno, mucato de; Isométheptène, Mucate d'; Isomethepteni Mucas; Mucato de isometepteno; Изометептена Мукат.

Isometheptene galactarate.

$(C_9H_{19}N)_2C_6H_{10}O_8$=492.7

CAS — 7492-31-1.

ATC — A03AX10.

ATC Vet — QA03AX10.

UNII — 8O120FDS6P.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Isometheptene Mucate). A white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 5.4 to 6.6. Store in airtight containers. Protect from light.

USP 36: (Isometheptene Mucate). A white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 6.0 and 7.5.

Uses and Administration

Isometheptene is an indirect-acting sympathomimetic (p. 1507.3). It is included for its vasoconstrictor effect, usually as the mucate, in some analgesic combination products used to treat acute migraine attacks (p. 670.3). Typical oral doses of isometheptene mucate in migraine are 130 mg at the beginning of an attack, with 65 mg hourly thereafter as necessary, up to a total maximum dose of 325 mg in a 12-hour period.

Isometheptene hydrochloride has also been used in the management of migraine and smooth muscle spasm; it has been given orally, as well as by intramuscular, or occasionally subcutaneous, or slow intravenous, injection. The mucate has also been used in the management of muscle spasms.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3.

Interactions

As for Sympathomimetics, p. 1508.3. Isometheptene has been reported to produce severe hypertensive reactions in patients receiving MAOIs.

Bromocriptine. For a report of hypertension and life-threatening complications after use of isometheptene and *bromocriptine*, see under Sympathomimetics, p. 899.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Octinum.

Multi-ingredient Preparations. ***Braz.***: Besodin; Cefaldina†; Doralgina; Dorgil; Doridina; Dorsedin; Migranette; Neosaldina; Neuralgina; Sedalgina; Sedamed; Sedol; Tensaldin; ***India***: Acudrin; ***UK***: Midrid; ***USA***: Epidrin; Midrin; Migragesic IDA; MigraTen; Migrazone; Nodolor; Prodrin.

Pharmacopoeial Preparations

USP 36: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Isospaglumic Acid *(rINN)*

Acide Isospaglumique; Ácido isospaglúmico; Acidum Isospaglumicum; Isospaglúmico, ácido; NAAGA; Изоспаглумовая Кислота.

N-(*N*-Acetyl-L-α-aspartyl)-L-glutamic acid.

$C_{11}H_{16}N_2O_8$=304.3

CAS — 3106-85-2.

UNII — 1W8M12WXYL.

Spaglumic Acid *(rINN)*

Acide Spaglumique; Ácido espaglúmico; Acidum Spaglumicum; Спаглумовая Кислота.

N-(*N*-Acetyl-L-β-aspartyl)-L-glutamic acid.

CAS — 4910-46-7.

ATC — R01AC05; S01GX03.

ATC Vet — QR01AC05; QS01GX03.

UNII — X81L78B3RB.

Profile

N-Acetyl-L-aspartylglutamate is a mast cell stabiliser and has been used as the sodium or magnesium salts of spaglumic or isospaglumic acids in eye drops for allergic eye conditions and in nasal solutions for allergic rhinitis.

N-Acetyl-L-aspartylglutamate also has a role as a neurotransmitter and has been investigated in CNS disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Naabak; ***Austria***: Rhinaaxia†; ***Braz.***: Naabak; Naaxia; ***Chile***: Alerbak†; Naaxia†; ***Fr.***: Naabak; Naaxia; Naaxiafree†; Rhinaaxia†; ***Gr.***: Rhinaaxia; ***Hong Kong***: Naaxia; ***Hung.***: Naaxia†; ***Ital.***: Naaxia; Rhinaaxia; ***Philipp.***: Naaxia; ***Port.***: Naabak; ***Singapore***: Naabak; ***Spain***: Naaxia; ***Switz.***: Naabak; ***Turk.***: Naaxia; ***Venez.***: Naabak.

Multi-ingredient Preparations. ***Gr.***: Naaxia.

Isoxsuprine Hydrochloride *(BANM, rINNM)*

Caa-40; Hidrocloruro de isoxsuprina; Isoksupriinihydrokloridi; Isoxsuprin hydrochlorid; Isoxsuprina, hidrocloruro de; Isoxsuprine, chlorhydrate d'; Isoxsuprinhydrochlorid; Isoxsuprinhydroklorid; Isoxsuprini Hydrochloridum; Izokszuprino hidrochloridas; Izoxszuprin-hidroklorid; Phenoxyisopropylnorsuprifen; Изоксуприна Гидрохлорид.

1-(4-Hydroxyphenyl)-2-(1-methyl-2-phenoxyethylamino) propan-1-ol hydrochloride.

$C_{18}H_{23}NO_3$,HCl=337.8

CAS — 395-28-8 (isoxsuprine); 579-56-6 (isoxsuprine hydrochloride).

ATC — C04AA01.

ATC Vet — QC04AA01.

UNII — V74TEQ36CO.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Isoxsuprine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Isoxsuprine Hydrochloride). A white, odourless, crystalline powder. Soluble 1 in 500 of water, 1 in 100 of alcohol and of 0.1N sodium hydroxide solution, and 1 in 2500 of 0.1N hydrochloric acid; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 6.0. Store in airtight containers.

Uses and Administration

Isoxsuprine is a vasodilator that also stimulates beta-adrenergic receptors. It causes direct relaxation of vascular and uterine smooth muscle and its vasodilating action is greater on the arteries supplying skeletal muscles than on those supplying skin. Isoxsuprine also produces positive inotropic and chronotropic effects.

Isoxsuprine hydrochloride has been used to arrest premature labour (p. 2131.1), but drugs with a more selective action are now preferred. It has also been given in the treatment of cerebral and peripheral vascular disease.

For use as a vasodilator, isoxsuprine hydrochloride is given orally in doses of 10 to 20 mg 3 or 4 times daily.

To arrest premature labour, isoxsuprine hydrochloride is given initially by intravenous infusion in doses of 200 to 500 micrograms/minute, adjusted according to the patient's response, until control is achieved. It is now common practice to give beta agonists by syringe pump when using them to delay premature labour. Maternal blood pressure and hydration, and maternal and fetal heart rates should be monitored during the infusion. Once labour has been arrested intramuscular injections of 10 mg are given every 3 to 8 hours. $Beta_2$ agonist therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3). Oral or rectal therapy is no longer recommended in premature labour because of a lack of evidence of benefit from treatment given by these routes of administration, although prophylactic oral doses of isoxsuprine hydrochloride 30 to 90 mg daily were formerly used after parenteral therapy.

The resinate has also been used similarly.

Adverse Effects

Isoxsuprine may cause transient flushing, hypotension, tachycardia, rashes, and gastrointestinal disturbances. Maternal pulmonary oedema and fetal tachycardia have been reported after intravenous use in premature labour.

Pulmonary oedema. Pulmonary oedema has been reported in mothers given isoxsuprine for premature labour.[1,2]

1. Nagey DA, Crenshaw MC. Pulmonary complications of isoxsuprine therapy in the gravida. *Obstet Gynecol* 1982; **59** (suppl): 38S–42S.
2. Nimrod C, *et al.* Pulmonary edema associated with isoxsuprine therapy. *Am J Obstet Gynecol* 1984; **148:** 625–9.

Precautions

Isoxsuprine is contra-indicated after recent arterial haemorrhage. It should not be given immediately post partum, nor should it be used for premature labour if there is infection.

In women being treated for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p. 1222.3, apply.

Pregnancy. Ileus was found to be more common in the offspring of mothers who received isoxsuprine than in matched controls.[1] The incidence of respiratory distress syndrome also rose as the isoxsuprine concentration in cord blood exceeded 10 nanograms/mL; likewise the incidence of hypocalcaemia and hypotension rose progressively with increasing concentrations. The cord concentrations correlated inversely with the drug-free interval before delivery and it was suggested that with frequent assessment of uterine response it should be possible to avoid delivering infants at a time when they have high plasma-isoxsuprine concentrations.[1]

In another study[2] of the association between ruptured membranes, beta-adrenergic therapy, and respiratory distress syndrome, it was found that both therapy with isoxsuprine and premature rupture of membranes were individually associated with a lowered incidence of respiratory distress syndrome, but when present together they resulted in an increased risk of respiratory distress syndrome. It was suggested that therapy with beta-adrenergic drugs including isoxsuprine should be restricted to patients with intact membranes.[1]

1. Brazy JE, *et al.* Isoxsuprine in the perinatal period II: relationships between neonatal symptoms, drug exposure, and drug concentration at the time of birth. *J Pediatr* 1981; **98:** 146–51.
2. Curet LB, *et al.* Association between ruptured membranes, tocolytic therapy, and respiratory distress syndrome. *Am J Obstet Gynecol* 1984; **148:** 263–8.

Pharmacokinetics

Isoxsuprine hydrochloride is well absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 1 hour after an oral dose. A plasma half-life of about 1.5 hours has been reported. Isoxsuprine is excreted in the urine mainly as conjugates.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duvadilan; Isodilan; Isotenk; Protelium†; Samaruc†; Uterine; ***Braz.***: Inibina; ***Gr.***: Cerebrovin; Duvadilan; ***India***: Adilin; B-Prox; Cuprox; Dulovas; Duvabel; Duvadilan; Elprox; Feprox; Fisox; Idilan; Ioril; Isarin; Iscom; Isopreg; Isoriv; Isowin; Isox; Isoxsan; Myprox; ***Indon.***: Duvadilan; Hystolan; Proterine; ***Ital.***: Vasosuprina; ***Mex.***: Vadosilan; ***Philipp.***: Duvadilan; Duvaprine; Isoxilan; ***Port.***: Dilum; ***USA***: Vasodilan; Voxsuprine; ***Venez.***: Duvadilan.

Pharmacopoeial Preparations

USP 36: Isoxsuprine Hydrochloride Injection; Isoxsuprine Hydrochloride Tablets.

Ivacaftor *(USAN, rINN)*

Ivacaftorum; VX-770; Ивакафтор.

N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide.

$C_{24}H_{28}N_2O_3$=392.5

CAS — 873054-44-5.

ATC — R07AX02.

ATC Vet — QR07AX02.

UNII — 1Y740IIL1Z.

Uses and Administration

Ivacaftor is stated to be a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. It is used in the treatment of cystic fibrosis (p. 177.2) in patients aged 6 years and above who have a G551D mutation in the CFTR gene; it is not effective in those who are homozygous for the F508del mutation in the CFTR gene and has not been studied in other mutations.

The recommended oral dose of ivacaftor is 150 mg every 12 hours, to be taken with a fat-containing food. The dose should be reduced to 150 mg once daily in patients also taking a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A; those taking a potent inhibitor of CYP3A should receive 150 mg twice weekly. For dosing in patients with hepatic impairment, see below.

References.

1. Accurso FJ, *et al.* Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010; **363:** 1991–2003.
2. Davis PB, *et al.* Ivacaftor. *Nat Rev Drug Discov* 2012; **11:** 349–50.
3. Flume PA, *et al.* VX08-770-104 Study Group. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest* 2012; **142:** 718–24.
4. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *Ann Pharmacother* 2012; **46:** 1065–75.

Administration in children. For doses of ivacaftor in children, see Uses and Administration, above.

Administration in hepatic impairment. In patients with moderate or severe hepatic impairment (Child-Pugh class B or C), the oral dose of ivacaftor should be reduced to 150 mg once daily; less frequent use may also be necessary in those with severe impairment.

Adverse Effects and Precautions

The most common adverse effects noted with ivacaftor are headache, oropharyngeal pain, upper respiratory-tract infections, nasal congestion, nasopharyngitis, abdominal pain, diarrhoea, nausea, rash, arthralgia, and dizziness.

Elevated transaminase levels have also been reported. Liver function should be measured before starting ivacaftor, and monitored during therapy (every 3 months for the first year, and annually thereafter). Ivacaftor should be stopped if levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are greater than 5 times the upper limit of normal; treatment may be restarted when levels return to normal.

Interactions

Ivacaftor is a substrate for the cytochrome P450 isoenzyme, CYP3A. Strong inducers of this isoenzyme such as rifampicin and St John's wort can significantly reduce ivacaftor levels and decrease its effectiveness; their use together is not recommended.

Conversely, moderate and potent inhibitors of CYP3A such as fluconazole and ketoconazole, respectively can significantly increase ivacaftor exposure and a reduced dose of ivacaftor may be appropriate (for further details, see Uses and Administration, above). Grapefruit juice, another CYP3A inhibitor, should be avoided during ivacaftor treatment.

Ivacaftor, itself, is a weak inhibitor of CYP3A and P-glycoprotein; caution is recommended when giving ivacaftor with other CYP3A or P-glycoprotein substrates, such as midazolam, digoxin, and tacrolimus.

Pharmacokinetics

Ivacaftor is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 4 hours after a single oral dose. Absorption is increased two- to fourfold when given with fat-containing food. Plasma protein binding is 99%. Ivacaftor is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP3A; one of its two major metabolites is considered to be pharmacologically active. About 88% of a dose is eliminated in the faeces as metabolites; a negligible amount is excreted in the urine as unchanged drug. The terminal half-life is about 12 hours.

Distribution of ivacaftor into milk has been found in studies in *rats.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Kalydeco; ***Neth.***: Kalydeco; ***Norw.***: Kalydeco; ***UK***: Kalydeco; ***USA***: Kalydeco.

Ivy

Břečťanový list (ivy leaf); Efeu; Gebenių lapai (ivy leaf); Hederae folium (ivy leaf); Herba Hederae Helicis; Lierre, feuille de (ivy leaf); Lierre Grimpant; Muratinlehti (ivy leaf); Murgröneblad (ivy leaf); Плющ Обыкновенный (*Hedera helix*).

ATC — R05CA12.

ATC Vet — QR05CA12.

ATC Herb — HR05WA5018 (Hedera helix: *leaf*).

UNII — 4REE45G68Q (Hedera helix); *3D10KUA6BM* (Hedera helix *flowering twig*); *ZP9XFG71A7* (Hedera helix *leaf*); *379040L9FW* (Hedera helix *leaf water*).

Pharmacopoeias. *Eur.* (see p. vii) includes the leaf and also a form for homoeopathic preparations.

Ph. Eur. 8: (Ivy Leaf; Hederae Folium). The whole or cut, dried leaves of *Hedera helix*, collected in spring and summer. It contains a minimum of 3% of hederacoside C ($C_{59}H_{96}O_{26}$ = 1221.4), calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Hedera Helix for Homoeopathic Preparations; Hedera Helix ad Praeparationes Homoeopathicas). The fresh, young, fully developed but not yet lignified branch of *Hedera helix*, harvested immediately before or at the beginning of flowering. Protect from light.

Profile

The dried leaves of ivy, *Hedera helix* (Araliaceae), contain saponins, and extracts are reported to have expectorant and spasmolytic actions. Ivy leaf is used for catarrh and chronic inflammation of the respiratory tract. It has also been applied externally.

Fresh ivy leaves can cause allergic contact dermatitis.

Homoeopathy

Ivy has been used in homoeopathic medicines under the following names: Hedera helix; Hedera; Hed. hel.

References.

1. Hofmann D, *et al.* Efficacy of dry extract of ivy leaves in children with bronchial asthma—a review of randomized controlled trials. *Phytomedicine* 2003; **10:** 213–220.
2. Hannu T, *et al.* Occupational asthma to ivy (*Hedera helix*). *Allergy* 2008; **63:** 482–3.
3. Jones JM, *et al.* Allergic contact dermatitis to English ivy (*Hedera helix*)—a case series. *Contact Dermatitis* 2009; **60:** 179–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Athos; Cedric; Celit; Funciobron H; No-Tos Hedera; Qura Tos; ***Austral.***: Cough Combat; ***Austria***: Alpinamed; Prospan; ***Braz.***: Abrilar; Fluijet; Hederax; Respiratus; ***Chile***: Aeromed; Arliv; Fluidox; Heberin; Hedilar; Hiedrix; Muxelix; Sintosin; ***Cz.***: Hedelix; Helixir; Prospan; ***Fr.***: Activox Expectorant†; Activox Lierre; Prospan; ***Ger.***: Bronchilon†; Bronchoforton†; Bronchostad Hustenloser; Drosithym Efeu Mono; Efeu; Efeusaft hysan; Gallith; Hedelix; Prospan; Sedotussin Efeu†; Sinuc†; Tuma; ***Gr.***: Prospan; ***Hung.***: Hedelix; Prospan; ***Indon.***: Prospan; ***Ital.***: Vertuss; ***Malaysia***: Prospan; ***Mex.***: Panoto-S; ***Neth.***: Prospan; ***Norw.***: Prospan; ***Pol.***: Bronchopect†; Hedelix; Hederasal; Hederoin; Helical; Prospan; ***Rus.***: Hedelix (Геделикс); ***Singapore***: Abrilar; Antihus; Prospan; ***Spain***: Abrilar†; Arkotux; Prospantus; ***Swed.***: Prospan; ***Switz.***: DemoPectol Junior; Prospan; Prospanex; Sanabronch; ***UK***: Activox; DiaCough; ***Ukr.***: Hedelix (Геделикс); Hederin (Гедерин); Pectolvan Hedera (Пектолван Плющ); Prospan (Проспан); ***Venez.***: Prospan.

Multi-ingredient Preparations. ***Arg.***: Athos-B; Cedric Pocket; Celu-Atlas; Expectosan Hierbas y Miel; Nio Marine; Snell Patch; Ukase Lulitis; Varisedan Gel; ***Austria***: Bronchipret; ***Chile***: Cellenergy; Celu-Atlas; Pectox; ***Cz.***: Bronchipret Tymian a Brect'an; ***Ger.***: Bronchipret; Broncholitan; ***Hung.***: Bronchipret; ***Indon.***: Bronchipret†; ***Ital.***: Balsamina Kroner; Binfolipase; Binfonorm†; Clebolider†; Dicotuss; Flebolider; Golatux; Hederix; Linfonorm Cremagel; Wasotonal†; ***Norw.***: Bronchosan†; ***Pol.***: ApiHelix†; Hedelicum; PiniHelix; ***Rus.***: Bronchipret (Бронхипрет); Insti (Инсти); ***Singapore***: Mincifit Body Shaper; ***Spain***: H Tussan†; ***Switz.***: Bronchosan; Demo Elixir pectoral N†; DemoPectol; DemoPectol; DemoPectol; Drosinula; Hederix; Kernosan Elixir; Liberol Dragees contre la toux†; Liberol Sirop contre la toux†; Sirop pectoral; ***Thai.***: Solvopret†; ***UK***: Broncholforce Chesty Cough Ivy Complex; ***Ukr.***: Bronchipret (Бронхипрет).

Homoeopathic Preparations. ***Canad.***: Tyglan†; ***Cz.***: Galium; ***Fr.***: Hedera Complexe No 120; Ipeca Complexe No 65; ***Ger.***: Echinaject; Hewethyreon N; Monapax; ***Neth.***: Drosinula; Gletar; Speci-chol.

Jamaica Dogwood

Fish Poison Bark; Piscidia.

UNII — 58JV0P12FY.

Profile

Jamaica dogwood, the root bark of *Piscidia erythrina* (*P. piscipula*; *Ichthyomethia piscipula*) (Leguminosae), has analgesic, antispasmodic, and sedative properties. It is mainly used for insomnia due to neuralgia or nervous tension. The bark and twigs of Jamaica dogwood have been used as a fish poison.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Sleep Easy; ***Fr.***: Jouvence de l'Abbe Soury; Schoum; ***Ital.***: Sedatol; Sedatol; Soluzione Schoum; ***Spain***: Solucion Schoum; ***UK***: Anased; HRI Calm Life; Nodoff; Slumber; ***Venez.***: Femendol.

Homoeopathic Preparations. ***Fr.***: Slipeol†.

Java Tea

Arbatinių inkstažolių lapai; Jaavalainen tee, Intialainen munuaistee; Jávai vesetealevél; Javate; Orthosiphon; Orthosiphonblätter; Orthosiphonis folium; Ortosifón; Té de java; Trubkovcový list; Яванский Чай.

ATC Herb — HG04BW5025 (Orthosiphon aristatus: *herb*).

UNII — DSS8V86H3Y.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Java Tea). The fragmented, dried leaves and tops of stems of *Orthosiphon stamineus* (*O. aristatus*; *O. spicatus*). Protect from light.

Profile

Java tea is used in herbal medicine mainly for the treatment of urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Urosiphon; ***Ger.***: Ardeynephron; Carito mono; Diufluxx Mono; Diurevit Mono†; Nephronorm med; Repha Orphon; ***Neth.***: Reinosan.

Multi-ingredient Preparations. ***Austria***: Solubitrat†; ***Fr.***: Dellova†; Santane O1; Tealine†; Teaslim†; ***Ger.***: Aqualibra; BioCyst†; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee†; Harntee 400 N; Harntee-Steiner†; Hevert-Blasen-Nieren-Tee N†; ***Indon.***: Renax; Tensigard; ***Ital.***: Dren'it; Linfoguard†; Lipa-

ven; Slimmer Plus; ***Pol.***: Ginjal; Uromix†; ***Spain***: Tealine; ***Switz.***: Bilifuge; Demonatur Dragees pour les reins et la vessie†; Herbaprosta-Caps N†; Tisane pour les reins et la vessie; Urinex; ***Ukr.***: Urochol (Урохол)†.

Homoeopathic Preparations. ***Ger.***: Phonix Silybum spag; Phonix Urtica-Arsenicum spag.

Jin Bu Huan

Uses and Administration

Jin bu huan is a traditional Chinese remedy used as a sedative and analgesic and variously stated to contain *Lycopodium serratum* or *Polygala chinensis*.

Adverse Effects

Adverse effects of jin bu huan include CNS depression and acute hepatotoxicity and have been attributed to its alkaloidal content of L-tetrahydropalmatine.

Acute hepatitis has been reported in 7 previously healthy patients after taking jin bu huan; symptoms occurred again in 2 after re-use.[1] It was noted that the content of plant material did not seem to correspond to the labelled species. Hepatitis and extreme fatigue have also been reported in 3 adults after taking jin bu huan for periods ranging from 6 days to 6 months.[2]

Accidental ingestion of jin bu huan by 3 children[2] produced profound lethargy and muscle weakness. Two of the children also developed respiratory depression and bradycardia.

1. Woolf GM, *et al*. Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med* 1994; **121:** 729–35.
2. Horowitz RS, *et al*. The clinical spectrum of jin bu huan toxicity. *Arch Intern Med* 1996; **156:** 899–903.

Juniper

Baccae Juniperi; Boróka tobozbogyó; Enbär; Enebro; Enebro enano; Genièvre; Iuniperi Pseudo-fructus; Jalovcový plod; Juniper Berry; Juniper Fruit; Juniperi Fructus; Juniperi Galbulus; Juniperi Pseudo-fructus; Kadagių vaisiai; Katajanmarja; Szyszkojagoda jałowca; Wacholderbeeren; Zimbro; Можжевельник.

*ATC Herb — HG04BW5016 (*Juniperus communis*: fruit); HA03AW5029 (*Juniperus communis*: fruit).*

*UNII — 464910T5N9 (*Juniperus communis*); O84B5194RL (*Juniperus communis *fruit).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Juniper; Juniperi galbulus). The dried ripe cone berry of *Juniperus communis*. It contains not less than 1% v/w of essential oil, calculated with reference to the anhydrous drug. It has a strongly aromatic odour, especially if crushed.

Profile

Juniper is the source of juniper oil (below). It has carminative, diuretic, antiseptic, and anti-inflammatory properties. It is used in herbal medicine and as a flavour in gin.

Homoeopathy

Juniper has been used in homoeopathic medicines under the following names: Juniperus communis; Juniperus communis sicc.; Juniperus communis e fructibus siccatis; Juniperus com; Junip. c.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Sidina.

Multi-ingredient Preparations. ***Arg.***: Albion; Wunderbalsam; ***Austral.***: Arthritic Pain Herbal Formula 1†; PMT-Eze†; ***Austria***: Mariazeller; St Bonifatius-Tee†; ***Canad.***: Diurenat†; Diuretic Formula; Diuretic Tablets; Herbal Diuretic†; Herbal Diuretic; Herbal Laxative plus Yogurt†; Stomach Ease; ***Fr.***: Alpha Renol; Depuratum; Diatisan†; Urotisan†; ***Ger.***: Amara-Tropfen; ***Hung.***: Antipoll; ***Ital.***: Broncosedina; Broncosedina; ***Pol.***: Cholesol; ***Rus.***: Diureticae Species No2 (Мочегонный Сбор 2); ***S.Afr.***: Amara†; ***Switz.***: Gouttes Amara; Kernosan Heidelberger Poudre; Metabol; Tisane pour les reins et la vessie; ***UK***: Backache; Watershed; ***Ukr.***: Uro-Control (Уро-Контрол); ***USA***: Cardiopress.

Homoeopathic Preparations. ***Canad.***: Amaratopfen†; Nixotinex; ***Fr.***: Juniperus Complexe No 6; Poconeol no 44; ***Ger.***: HanoNephrin; Levisticum S; Magen-Darm-Entoxin N; Magen-Darmtropfen N; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Solidago Hevert Complex; ***Neth.***: Chavita 2; Phonix Solidago comp.

Juniper Oil

Aceite de bayas de enebro; Borókaolaj; Enbärsolja; Enebro, aceite esencial de; Essence de Genièvre; Genièvre, huile essentielle de; Iuniperi aetheroleum; Jalovcová silice; Juniper Berry Oil; Juniperi Aetheroleum; Juniperi Etheroleum; Kadagių vaisių eterinis aliejus; Katajanmarjaöljy; Oleum Juniperi; Wacholderöl; Можжевеловое Масло.

*ATC Herb — HG04BW5015 (*Juniperus communis*: essential oil).*

UNII — YNW2QPG8YK (juniper oil); SZH16H44UY (juniper berry oil).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Juniper Oil; Juniperi aetheroleum). The essential oil obtained by steam distillation from the ripe, non-fermented berry cones of *Juniperus communis*. A suitable antoxidant may be added. A mobile, colourless to yellowish liquid with a characteristic odour. Store at a temperature not exceeding 25 degrees.

Profile

Juniper oil has been used as a carminative and as an ingredient of herbal remedies for urinary-tract disorders and muscle and joint pain. It is also used in aromatherapy. Prolonged use may cause gastrointestinal irritation and there may be a risk of renal damage from high doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Roleca Wacholder.

Multi-ingredient Preparations. ***Austria***: Berggeist; ***Belg.***: Olbas; ***Braz.***: Solvobil; ***Fr.***: Aromadigest†; Veino Gomenol; ***Ger.***: Dolocyl†; Kneipp Rheumabad Spezial†; Olbas; Weleda Bronchialbalsam; ***Irl.***: Olbas; Olbas; ***Ital.***: Flodolor; ***Neth.***: Olbas†; ***Pol.***: Analgol; Olbas; Olbas; Pinimentol; Pulmonil; ***S.Afr.***: Oleum Salviae Comp†; ***Singapore***: Mincifit Hodeol; ***Spain***: Emolytar†; Polytar†; ***Switz.***: Echinarom; Huile Po-Ho A. Vogel; Liberol Baby N; Olbas; Olbas; Spagyrom; Wiewohl†; Ziegella†; ***UK***: Diuretabs; HealthAid Boldo-Plus; Olbas for Children; Olbas; Olbas; Sciargo; St Johnswort Compound.

Kallidinogenase *(BAN, rINN)*

Calicreína; Callicrein; EC 3.4.21.35; Kalidinogenasa; Kalléone; Kallidinogenaasi; Kallidinogenas; Kallidinogénase; Kallidinogenasum; Kallikrein; Каллидиногеназа.

CAS — 9001-01-8.

ATC — C04AF01.

ATC Vet — QC04AF01.

Pharmacopoeias. In *Jpn*.

Profile

Kallidinogenase is an enzyme isolated from the pancreas and urine of mammals. It converts kininogen into the kinin, kallidin. Kallidinogenase has been used in male infertility (p. 2253.1) since the kallikrein-kinin system has a physiological role in the male genital tract. It also has vasodilating properties and has been used in the treatment of peripheral vascular disorders (p. 1272.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Padutin; ***China***: Guangle (广乐); Kai Li Kang (凯力康); Kainike (凯妮可).

Kalmia Latifolia

American Laurel; Breitblättrige Lorbeerrose; Broad-leafed Laurel; Calico Bush; Ivybush; Lambkill; Mountain Laurel; Sheep Laurel; Spoonwood.

*ATC Herb — HD11AX5001 (*Kalmia latifolia*: leaf).*

*UNII — P1SWF7DK1Y (*Kalmia latifolia*); 79N6542N18 (*Kalmia latifolia *leaf).*

NOTE. The name Spoonwood has also been used for *Mallotus philippensis*. The name Laurel has been applied to a number of unrelated species, including *Kalmia latifolia*.

Profile

The leaves of *Kalmia latifolia* (*Chamaedaphne latifolia*) (Ericaceae) are used in herbal medicine in topical preparations for a variety of skin disorders. It was formerly used orally, but its use is limited by toxicity; severe poisoning can be fatal. The plant has the reputation of being poisonous to some livestock.

Homoeopathy

Kalmia latifolia has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Joint & Muscle Cream.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Canad.***: Formula DM 210†; ***Chile***: Bioactiv Z; ***Fr.***: Abbe Chaupitre no 20†; Boripharm No 23; Kalmia Complexe No 18; ***Ger.***: Genu-cyl L Ho-Len-Complex; HanoCor N; Hewerheum N†; Myonasan; Naranocor HM; Neuralgie-Gastreu R70; Rheuma-Hevert†; Strophanthus comp; ***Neth.***: Discus comp H.

Kava

Kava-Kava; Кава.

CAS — 500-64-1 (kawain); 495-85-2 (methysticin); 500-62-9 (yangonin).

*ATC Herb — HN05BW5001 (*Piper methysticum*: rhizome extract); HN05CM5020 (*Piper methysticum*: rhizome).*

*UNII — 3P3065300W (*Piper methysticum*); BOW48C81XP (*Piper methysticum *root); M832AIJ6HX (methysticin); R970U49V3C (yangonin).*

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of kava:

'ava; Ava-ava; 'awa; Grog; Intoxicating pepper; Kawa; Kawa Kawa; Lewena; Sakau; Waka; Wati; Yangona; Yaqona.

Uses and Administration

Kava is the rhizome of *Piper methysticum* (Piperaceae), a shrub indigenous to islands of the South Pacific. It contains pyrones including kawain, methysticin, and yangonin. Kava has been used in the South Pacific to produce an intoxicating beverage used for recreational purposes and during convalescence. It is reported to have sedative, skeletal muscle relaxant, and anaesthetic properties. It is given in some anxiety- and stress-related disorders. It was formerly used as an antiseptic and diuretic in inflammatory conditions of the genito-urinary tract in the form of a liquid extract. Kawain has also been used for nervous disorders and as a tonic. Preparations of kava for internal use have been withdrawn in the UK and some other western countries on account of its potential for serious hepatotoxic effects—see Adverse Effects below.

Homoeopathy

Kava has been used in homoeopathic medicines under the following names: Piper methysticum; Piper. m.; Piper meth.

General reviews.

1. Anonymous. Kava. *Lancet* 1988; **ii:** 258–9.
2. Pepping J. Kava: *Piper methysticum*. *Am J Health-Syst Pharm* 1999; **56:** 957–60.
3. WHO. Rhizoma Piperis Methystici. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/23.html (accessed 04/02/10)
4. Sarris J, Kavanagh DJ. Kava and St. John's wort: current evidence for use in mood and anxiety disorders. *J Altern Complement Med* 2009; **15:** 827–36.

Adverse Effects

A characteristic rash resembling that of pellagra occurs in some heavy consumers of kava. Extrapyramidal effects have also been reported. There have been reports of hepatotoxicity associated with kava ranging from mild changes in liver function to irreversible damage requiring liver transplantation or resulting in death.

References.

1. Anonymous. Tonga trouble. *Pharm J* 1990; **245:** 288.
2. Ruze P. Kava-induced dermopathy: a niacin deficiency? *Lancet* 1990; **335:** 1442–5.
3. Schelosky L, *et al*. Kava and dopamine antagonism. *J Neurol Neurosurg Psychiatry* 1995; **58:** 639–40.
4. Spillane PK, *et al*. Neurological manifestations of kava intoxication. *Med J Aust* 1997; **167:** 172–3.
5. Anonymous. Kava extract linked to hepatitis. *WHO Drug Inf* 2000; **14:** 98.
6. Escher M, *et al*. Hepatitis associated with kava, a herbal remedy for anxiety. *BMJ* 2001; **322:** 139.
7. Anonymous. Hepatic toxicity possibly associated with kava-containing products—United States, Germany, and Switzerland, 1999-2002. *MMWR* 2002; **51:** 1065–7. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm (accessed 15/07/04)
8. Stickel F, *et al*. Hepatitis induced by Kava (Piper methysticum rhizoma). *J Hepatol* 2003; **39:** 62–7.
9. Clouatre DL. Kava kava: examining new reports of toxicity. *Toxicol Lett* 2004; **150:** 85–96.
10. Perez J, Holmes JF. Altered mental status and ataxia secondary to acute Kava ingestion. *J Emerg Med* 2005; **28:** 49–51.
11. Ulbricht C, *et al*. Safety review of kava (Piper methysticum) by the Natural Standard Research Collaboration. *Expert Opin Drug Safety* 2005; **4:** 779–94.
12. Teschke R, *et al*. Kava hepatotoxicity: a European view. *N Z Med J* 2008; **121:** 90–8.

Interactions

References

1. Anke J, Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.). *J Ethnopharmacol* 2004; **93:** 153–60.
2. Singh YN. Potential for interaction of kava and St. John's wort with drugs. *J Ethnopharmacol* 2005; **100:** 108–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Ansiopax; Calmonex; Kavagren†; Kavahexal†; Kavakan; Kavamed; Kavasedon; Laitan; ***Mex.***: Laikan.

Multi-ingredient Preparations. ***Ital.***: Controller.

Homoeopathic Preparations. ***Austria***: Lakrima; ***Ger.***: metakaveron; ***Hung.***: PSY-Stabil; ***Neth.***: PSY-stabil; ***Switz.***: metaneuron N; metaossylen N.

Keracyanin *(rINN)*

Cyaninoside; Keracianina; Kéracyanine; Keracyaninum; Керацианин.

3-[6-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyloxy]-3′,4′,5,7-tetrahydroxyflavylium chloride.

$C_{27}H_{31}ClO_{15}$=631.0

CAS — 18719-76-1.

UNII — V0N2VMB4FV.

Profile

Keracyanin is claimed to improve visual function in poor light conditions and has been given orally in vision disorders.

Keratin

CAS — 68238-35-7.

Profile

Keratin is a group of proteins found in hair, horn, nails, and similar materials. It has been used as an enteric coating for tablets. Keratin extracts and modified keratins have been investigated for use as biomaterials. Keratin preparations have also been promoted for topical and oral use in cosmetics and nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Esmalfort; Pantogar; ***Ger.***: Pantovigar; ***Hong Kong***: Pantogar; ***Indon.***: Pantogar; ***Ital.***: Biomineral 5-Alfa Shampoo; ***Mex.***: Pantogar; ***Rus.***: Pantovigar (Пантовигар); ***Singapore***: Pantogar; ***Switz.***: Pantogar; ***Turk.***: Pantogar; ***Ukr.***: Pantogar (Пантогар).

Keratinase ⊗

Queratinasa; Кератиназа.

CAS — 9025-41-6.

Profile

Keratinase is a proteolytic enzyme that has been obtained from cultures of *Streptomyces fradiae*. It can digest keratin, which is resistant to most proteolytic enzymes, in the presence of trace amounts of metal ions. It is used in the commercial separation of hair from animal hides, and has been tried as a depilatory; it has also been included in some topical antibacterial ointments, presumably to aid penetration of the active substances.

Khellin *(rINN)*

Kelina; Khelline; Khellinum; Visammin; Келлин.

4,9-Dimethoxy-7-methyl-5*H*-furo[3,2-*g*]chromen-5-one.

$C_{14}H_{12}O_5$=260.2

CAS — 82-02-0.

UNII — 5G117T0TJZ.

Profile

Khellin is a vasodilator obtained from *Ammi visnaga* fruit (p. 2441.2) or by synthesis and has been used in angina pectoris. It also has a bronchodilatory action and has been used in asthma. Khellin has also been tried in conjunction with UV light to treat vitiligo (see Pigmentation Disorders, p. 1687.2).

References.

1. Hofer A, *et al.* Long-term results in the treatment of vitiligo with oral khellin plus UVA. *Eur J Dermatol* 2001 **11:** 225–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Vicalin (Викалин); ***Ukr.***: Vicalin (Викалин).

Kinkeliba

Combreti Folium; Combreto; Kinkéliba.

*UNII — 02ACS1U93N (*Combretum micranthum*).*

Pharmacopoeias. In *Fr.*

Profile

Kinkeliba is the dried leaves of *Combretum micranthum* (*C. altum*; *C. raimbaultii*) (Combretaceae), a shrub indigenous to West Africa. It has been used as an ingredient of herbal remedies given for the treatment of biliary, liver, and gastrointestinal disorders. Other species of *Combretum* are also used.

Homoeopathy

Kinkeliba has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Azema†; Hepaclem†; Jecopeptol†; Mediflor Hepatique No 5; Romarene†; Solution Stago Diluee; ***Mon.***: Romarinex; ***Switz.***: Bilifuge.

Klebsiella Pneumoniae Glycoprotein

Glucoproteína de Klebsiella pneumoniae; RU-41740.

Profile

Klebsiella pneumoniae glycoprotein is an immunostimulant that has been used in the management of respiratory-tract infections, wounds, and burns.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Biostim; ***Cz.***: Biostim†; ***Gr.***: Biostim; ***Mex.***: Biostim.

Knotgrass

Knotweed; Nať rdesna ptačího; Pihatatar; Polygoni avicularis herba; Renouée des Oiseaux; Takažolių žolė; Trampgräs; Vogelknöterichkraut; Ziele rdestu ptasiego; Спорыш.

*ATC Herb — HR05WA5043 (*Polygonum aviculare*: herb).*

*UNII — M990N03611 (*Polygonum aviculare*); ZCD6009IUF (*Polygonum aviculare *top).*

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Knotgrass; Polygoni Avicularis Herba). It consists of the whole or fragmented, dried flowering aerial parts of *Polygonum aviculare*. It contains not less than 0.3% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$=464.4) calculated with reference to the dried drug.

Profile

Knotgrass, *Polygonum aviculare* (*P. heterophyllum*) (Polygonaceae), is included in herbal preparations for mild catarrh and associated upper respiratory-tract disorders.

Homoeopathy

Knotgrass has been used in homoeopathic medicines under the following names: Polygonum aviculare.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Pulmoran; Species Urologicae Planta; ***Pol.***: Cholesol; Padma 28; Reumosol; ***Swed.***: Alpenkraft; ***Switz.***: Arteria-vita; Padma 28; Padmed Circosan; ***UK***: Padma Circosan; ***Ukr.***: Ambovit (Амбовит); Phytolyt (Фитолит); Urochol (Урохол)†; Uronephron (Уронефрон); Vitokan (Витокан).

Krebiozen

Crebiocén; Кребиозен.

CAS — 9008-19-9.

Profile

Krebiozen is the name of a preparation that was formerly promoted as a 'cancer cure' in the USA, but totally discredited by the FDA. It was stated to be obtained from the blood of horses previously injected with an extract of *Actinomyces bovis*.

Kveim Antigen

Antígeno de Kveim; Антиген Квейма.

Profile

Kveim antigen is a fine suspension in physiological saline of sarcoid tissue prepared from spleens taken from patients with active sarcoidosis. It has been used as an intradermal injection in the Kveim (Kveim-Siltzbach) test for the diagnosis of sarcoidosis (p. 1612.2).

References.

1. James DG, Williams WJ. Kveim-Siltzbach test revisited. *Sarcoidosis* 1991; **8:** 6–9.

The safety of the Kveim test has been questioned, particularly with reference to the risk of transmission of sarcoidosis, and of hepatitis B, HIV, and Creutzfeldt-Jakob disease.[1] However, the procedure to identify acceptable sarcoid spleens and the method of preparation were considered sufficient to reduce the risk of transmission of infections[2] and of Creutzfeldt-Jakob disease.[3]

1. Wigly RD. Moratorium on Kveim tests. *Lancet* 1993; **341:** 1284.
2. du Bois RM, *et al.* Moratorium on Kveim tests. *Lancet* 1993; **342:** 173.
3. de SilvaRN, Will RG. Moratorium on Kveim tests. *Lancet* 1993; **342:** 173.

Laburnum

Citiso; Codeso europeo; Golden Chain; Golden Rain; Laburno; Lluvia de oro; Золотой Дождь Обыкновенный.

*UNII — A3V9296222 (*Laburnum anagyroides*).*

Profile

All parts of laburnum, *Laburnum anagyroides* (*L. vulgare*; *Cytisus laburnum*) (Leguminosae), are toxic. The toxic principle is cytisine (p. 2491.1) which has actions similar to nicotine.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Ger.***: Cocculus Oligoplex.

Lachesis Muta

Lachesis muta; *Lachesis mutus*; South American Bushmaster; Surucucu; Ляхезис мутус; Бушмейстер.

*UNII — 6Y582I290C (*Lachesis mutus*); VSW71SS07I (*Lachesis mutus *venom).*

Profile

Lachesis muta is a venomous snake belonging to the Crotalidae family (pit vipers). It is commonly known as the South American bushmaster snake.

Homoeopathy

Lachesis muta venom has been used in homoeopathic medicines under the following names: Lachesis; Lachesis mutus.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Lymphozil†.

Homoeopathic Preparations. ***Austral.***: Echine†; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Respatona Sore Throat; ***Austria***: Echinacea-Cosmoplex; Globuli gegen Grippe; Globuli gegen Halsweh Nr 2; Gripp Heel; Remens; Vensa; Vocara; ***Canad.***: Menopause; ***Chile***: Flucoccinum; Lachess; ***Cz.***: Gripp Heel; Ypsiloheel; ***Fr.***: Actheane; Lachesis Complexe No 122; Thlascose†; Veino-Drainol†; ***Ger.***: Cefakliman H†; Cefakliman N†; Cefasept N; Cefasept†; Cefasept; Corloges; Echinacea comp; Entzundungstropfen; Femi-cyl L Ho-Len-Complex; Gelsemium Comp; Gelsemium Comp; Gripp-Heel; HanoToxin M; Hanotoxin M; Hevertotox; Hevertotox; Hovnizym HM; Infekt 1-Injektopas N; Infi-Echinacea; Influex; Jowidarmin; Klimax-Gastreu S R10; Lachemistol; Lymphaden Complex; Lymphaden Lymphdrusentabletten; Lymphaden; Lymphozil H; Miburell; Mucosa compositum; Naranotox comp; Natuimmun†; Ossidal; Pascoleucyn N; Pascoleucyn; Pascoleucyn; Phonix Thuja-Lachesis spag; Pyrogenium; Schworotox A; Sinusitis Hevert SL; toxi-loges; Toxiselect; veno-loges N; Wibotin HM; Wiedimmun; Ypsiloheel N; ***Hung.***: Gripp-Heel; Klimakt-Heel; ***Neth.***: Emvita 10; Emvita 15; Emvita 6; Emvita 7; Gripp-Heel H; Homeocare Revito; Infragil; Klimaktolan; Klimax-Gastreu R10; Mercurius-Heel; Opsonat; ***Rus.***: Climaxan (Климаксан); Klimaktoplan (Климактоплан); Remens (Ременс); Vensa (Венза); Vocara (Вокара); ***S.Afr.***: Gripp-Heel; ***Switz.***: Gripp-Heel; Influaforce†; Menosan†; Menstruasan; Regenaplex Nr 28a; Regenaplex Nr. 24b; Regenaplex Nr. 25c; Regenaplex Nr. 35b; Regenaplex Nr. 79; ***Ukr.***: Incena (Инцена); Remens (Ременс); Vocara (Вокара); ***USA***: Estrex.

Lactic Acid

Acide lactique; Acidum lacticum; E270; E326 (potassium lactate); Kwas mlekowy; Kyselina mléčná; Láctico, ácido; Laktik Asit; Maitohappo; Milchsäure; Mjölksyra; Pieno rūgštis; Tejsav; Молочная Кислота.

2-Hydroxypropionic acid; 2-Hydroxypropanoic acid.

$C_3H_6O_3$=90.08

CAS — 50-21-5; 79-33-4 ((+)-lactic acid); 10326-41-7 ((-)-lactic acid); 598-82-3 ((±)-lactic acid).

ATC — G01AD01.

ATC Vet — QG01AD01; QP53AG02.

UNII — 33X04XA5AT (lactic acid); 3B8D35Y7S4 (dl-lactic acid); F9S9FFU82N (l-lactic acid).

Pharmacopoeias. In *Chin.*, *Int.*, *Jpm*, and *US*.

Eur. (see p. vii) includes monographs for the racemate and the (*S*)-enantiomer.

Ph. Eur. 8: (Lactic Acid). A mixture of lactic acid, its condensation products, such as lactoyl-lactic acid and other polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It is usually the racemate (*RS*-lactic acid), and contains the equivalent of 88 to 92% w/w of $C_3H_6O_3$. A colourless or slightly yellow, syrupy liquid. Miscible with water and with alcohol.

Ph. Eur. 8: ((*S*)-Lactic Acid). A mixture of (*S*)-lactic acid, its condensation products, such as lactoyl-lactic acid and other polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It contains the equivalent of 88 to 92% w/w of $C_3H_6O_3$, of which not less than 95% is the (*S*)-enantiomer. A colourless or slightly yellow, syrupy liquid. Miscible with water and with alcohol.

USP 36: (Lactic Acid). A mixture of lactic acid and lactic acid lactate equivalent to a total of 88 to 92% w/w of $C_3H_6O_3$. It is obtained by the lactic fermentation of sugars or is prepared synthetically. Lactic acid obtained by fermentation of sugars is laevorotatory, while that prepared synthetically is racemic.

A colourless or yellowish, hygroscopic, practically odourless, syrupy liquid. When it is concentrated by boiling, lactic acid lactate is formed. Miscible with water, with alcohol, and with ether; insoluble in chloroform. Store in airtight containers.

Uses and Administration

Lactic acid has actions similar to those of acetic acid (p. 2427.1) and has been used similarly in the treatment of skin and vaginal disorders. It has been used in the preparation of lactate injections and infusions to provide a source of bicarbonate for the treatment of metabolic acidosis (for the problems of using lactate in metabolic acidosis, see p. 1775.2). It is applied topically in the treatment of warts (p. 1689.3), often with salicylic acid, and in emollient creams. Other uses include the treatment of severe aphthous stomatitis in terminally ill, immunocompromised patients.

Lactic acid has also been used as a food preservative and as an ingredient of cosmetics.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1, although in the concentrations used it is less corrosive.

Neonates. There was evidence that neonates had difficulty in metabolising *R*-(-)-lactic acid and this isomer and the racemate should not be used in foods for infants less than 3 months old.[1]

1. FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications: seventeenth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 539* 1974. Also available at: http://libdoc.who.int/trs/WHO_TRS_539.pdf (accessed 13/05/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lactibon; ***Austria***: Espritin†; Warzin; ***Belg.***: Lacta-Gynecogel; ***Braz.***: Kit Rosaclean; ***Canad.***: Dermalac; ***Chile***: Eucerin; ***China***: Lactacyd FH (令特仕); ***Ger.***: KadeFungin Milchsaurekur; Relactagel; ***India***: Lacgel; Lactacyd; Lactal; ***Irl.***: Relactagel; ***Ital.***: Saugella Intilac; Unigyn; ***Mex.***: Acid-Lac; Avecyde†; Lactibon; ***Philipp.***: Lactacyd VG; naFlora; ***Pol.***: Keratolysin†; ***Spain***: Keratisdin†; ***Swed.***: Calmuril; ***Switz.***: Vagoclyss; ***UK***: Relactagel; ***USA***: Lactinol; Lactrex†; ***Venez.***: Dermalact; Lactibon.

Multi-ingredient Preparations. ***Arg.***: Acilac; Akerat; Callicida; Callicida; Callicida; Cellskinlab C + AHA; Control Acne; Dermocridin; Duofilm; Hidrolac; Keracnyl; Lactacyd; Lacticare; Lactoplus; Muvar; Opoenterol; Oxidermos; Pasem; Punto G†; Ureadin Facial; Urecrem; Verruclean; Verrutopic; ***Austral.***: Aussie Tan Skin Moisturiser†; Calmurid; Dermadrate; Dermatech Wart Treatment; Duofilm; Elucent Skin Refining Day Cream; ***Austria***: Anthozym†; Calmurid; Duofilm; Helo-acid; Hemosol; Hylak forte; Hylak; Lavagin†; Prismasol; ***Belg.***: Aporil; ***Braz.***: Calotrat; Colpolase†; Dermacyd; Dermafree; Duofilm; Kalicid; Kalloplast; Lacticare; Lacto Vagin; Salic; Verrux; ***Canad.***: Duofilm; Duoplant†; Epi-Lyt; P & S; Prismasol O; Prismasol; Prismocal; Viron Wart Lotion; ***Chile***: Akerat; Biopiel; Cuidado Intimo†; Duofilm; Eucerin Higiene Intima; Eucerin Piel Grasa†; Lactacyd; Node DS†; Ureadin 30; Verrufilm; ***China***: Bi Zhi Ke (比之可); Gan Bi Mei (干彼美); Lactacyd (乐特喜); Solcoderm (思可得); ***Cz.***: Duofilm; Hemosol; ***Denm.***: Prismasol; Verucid; ***Fin.***: Calmuril; Hemosol; Prismasol Kalium; Wicnelact; ***Fr.***: Akerat; Cleanance K; Duofilm; Effidigest; Geliofil; Hemosol B0; Keracnyl; Kerafilm; Lacticare†; Novophane DS; Novophane K; Prismasol; Propy-Lacticare†; Saugella Antiseptic; Saugella Antiseptic; Saugella Dermoliquide; Saugella Homme; Sebium AKN; Verrufilm; Verrupan; ***Ger.***: Akaderm N†; Clabin; Duofilm; Gelifend; Solco-Derman; Vagisan; W-Tropfen; ***Gr.***: Duofilm; ***Hong Kong***: Collomack†; Dermadrate; Dermatech Wart Treatment; Duofilm; Eubos Feminin; Lactacyd; Mithra-Intim; Solcoderm†; Verrufilm; ***Hung.***: Duofilm; Genia; ***India***: Alovit-AF; Basic; Carofit; Clomic-S; Copriderm; Cotaryl; Dew Derm; Diprosis; Diprovate-MF; Duofilm; Epicort-MK; Foot Care; Gowet; Heelcare; Lobate-S; Moisturex-AF; Moisturex; Oxylac; ***Indon.***: Exfoliac†; Lactacyd; Lacticare†; ***Irl.***: Calmurid HC; Calmurid; Cuplex†; Duofilm; Hemosol BO; Lacticare†; Prismasol; Salactol; Salatac; ***Israel***: Agisten 1; Calmurid†; Femina Lactal; Hemosol; Salatac; U-Lactin Foot Cream; U-Lactin; ***Ital.***: Babygella; Bruciaporri; Decon Lavanda; Duofilm; Eudermico; Fibranorm; Gastro-Pepsin; Geliofil; Geroderm Zolfo; Ginil†; Ipso Urea; Kerafilmver; Lactacyd Derma; Lactacyd Intimo; Lactacyd Lentivo; Saugella Salviettine; Sensigel; Sensiquell; Synchrobase Duo; Thiospot; Unidermo; Vaginol; Verel; Verunec; ***Malaysia***: Duofilm; Lactacyd; Lacticare; Prelactic; ***Mex.***: Duofilm; Kinor; Lacticare; Rug-Derm; Urader Lactato; ***Mon.***: Serelys; ***Neth.***: Calmurid HC; Calmurid; Duofilm; Hemosol; Prismasol; ***Norw.***: Prismasol; Verucid; ***NZ***: Dermadrate†; Duofilm; ***Philipp.***: Duofilm; Intima†; Kene; Lactacyd; Lacticare; Mithra-Intim; ***Pol.***: ABE-Plyn; Acerin; Brodacid; Duofilm; Masc na Odciski; ***Port.***: Bioclin Sebo Care†; Calicida Indiano; Calmurid; Creme Laser Hidrante†; Despigmentante†; Hemosol; Pansebase Composto; Pansebase; Prismasol; Secpel Composto†; Secpel†; Ureadin Manos; Verrucare; ***Rus.***: Collomac (Колломак); Duofilm (Дуофилм); Solcoderm (Солкодерм); ***S. Afr.***: Duofilm; Kroko; Lacticare†; ***Singapore***: Bio-Taches†; Dermadrate; Dermatech Wart Treatment; Duofilm; Lactacyd; Lacticare; Nu-Derm Exfoderm Forte; O'Yes Feminine Hygiene Wash; Octenisan; Sato Uonome Solution; U-Lactin†; ***Spain***: Antiverrugas; Callicida Cor Pik†; Callix†; Ginejuvent; Keranin†; Prismasol; Unguento Callicida Naion; Verufil; ***Swed.***: Hemosol; Prismasol; ***Switz.***: Calmurid; Clabin; Duofilm; Hemosol B0; Prismasol; Solcoderm; Va-t'en; Waruzol; Warz-ab Extor; ***Thai.***: Collomak; Duofilm; Lactacyd†; Lacticare; ***Turk.***: Duoderm; ***UK***: Balance Activ RX; Bazuka; Calmurid HC; Calmurid; Cuplex; Duofilm; Salactol; Salatac; ***Ukr.***: Collomak (Колломак); Duofilm (Дуофилм); Solcoderm (Солкодерм); ***USA***: AmLactin AP†; Epi-Lyt; Lacticare; Lactinol-E†; ***Venez.***: Akerat; Collomack; Kayivis.

Homoeopathic Preparations. ***Austria***: Aflubin; Metavirulent; ***Canad.***: Homeo-Form P†; Sportenine; ***Fr.***: Homeofortil†; Sportenine; ***Ger.***: HanoOxygen E; Lactopurum†; metavirulent; Sanuvis; ***Hung.***: Aflubin; ***Neth.***: Sportenine†; ***Rus.***: Aflubin (Афлубин); ***Switz.***: Lactovis; metavirulent; Regenaplex Nr. 21c; Regenaplex Nr. 21e; ***Ukr.***: Aflubin (Афлубин).

Pharmacopoeial Preparations

BP 2014: Lactic Acid Pessaries;

USP 36: Compound Clioquinol Topical Powder.

Lactobionic Acid

Acide Lactobionique; Acidum Lactobionicum; Kwas laktobionowy; Kyselina laktobionová; Lactobionsäure; Laktobionihappo; Laktobiono rūgštis; Laktobionsyra; Лактобионовая Кислота.

CAS — 96-82-2 (4-O-β-D-galactopyranosyl-D-gluconic acid).

UNII — 65R938S4DV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Lactobionic Acid). A mixture in variable proportions of 4-*O*-β-D-galactopyranosyl-D-gluconic acid ($C_{12}H_{22}O_{12}$ = 358.3) and 4-*O*-β-D-galactopyranosyl-D-glucono-1,5-lactone ($C_{12}H_{20}O_{11}$ = 340.3). A white or almost white powder. Freely soluble in water; slightly soluble in anhydrous ethanol, methyl alcohol, and glacial acetic acid.

USP 36: (Lactobionic Acid). A mixture in variable proportions of 4-*O*-β-D-galactopyranosyl-D-gluconic acid and 4-*O*-β-D-galactopyranosyl-D-glucono-1,5-lactone. A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in anhydrous alcohol, in methyl alcohol, and in glacial acetic acid.

Profile

Lactobionic acid is used to form water-soluble salts of drugs such as calcium and the macrolide antibacterials clarithromycin and erythromycin. It is present, in the form of potassium lactobionate, in preservation fluids such as UW (University of Wisconsin) solution for organ transplantation; the lactobionate anion acts as an impermeant and provides an osmotic force to oppose cellular oedema in the stored organ. Lactobionic acid has similar properties to gluconic acid (p. 2515.2) and is being tried in skin care products.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: NeoStrata.

Lactoferrin

Lactotransferrin; Лактоферрин.

Profile

Lactoferrin is an iron-binding protein found in milk, saliva, and other exocrine secretions. It has antimicrobial actions and has been used in preparations for the management of dry mouth (p. 2175.3) and other mouth disorders.

Lactoferrin and other whey proteins have also been used as nutritional supplements. Recombinant forms of lactoferrin such as talactoferrin alfa (p. 860.1) are under investigation.

Reviews.

1. Marshall K. Therapeutic applications of whey protein. *Altern Med Rev* 2004; **9:** 136–56.
2. Valenti P, *et al.* Lactoferrin functions: current status and perspectives. *J Clin Gastroenterol* 2004; **38** (suppl 2): S127–S129.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: BeWell†; Immune Boost†; ***Ital.***: Elleffe; Endvir Simplex.

Multi-ingredient Preparations. ***Austral.***: ImmunoDefence; TotalCare†; ***Fr.***: Photerpes; ***India***: Mvimin; ***Indon.***: Bd-GARD; Laktobion; ***Ital.***: Eutears; Floragermina 6; Liverton; Nepiros; Puraflor; Rivuclin; Rubrojunior; Rubrovital; Vitalmix Junior; ***Singapore***: Biotene; Biotene; Luvena Prebiotic; OralSeven; OralSeven; OralSeven; ***UK***: Biotene Dry Mouth; ***USA***: Biotene with Calcium.

Lactoperoxidase

EC 1.11.1.7; Лактопероксидаза.

CAS — 9003-99-0.

UNII — 01UIN5OC49 (bovine lactoperoxidase).

Profile

Lactoperoxidase is a peroxidase enzyme that is present in milk and saliva. It reacts with hydrogen peroxide and thiocyanate to produce an antibacterial effect and has been used in preparations for the management of dry mouth (p. 2175.3) and other mouth disorders. It has also been used for its preservative action in cosmetics and skin-care products.

In the lactoperoxidase system for milk preservation, sodium thiocyanate and sodium percarbonate (a source of hydrogen peroxide) are added to fresh bovine milk to activate the lactoperoxidase it contains.

Reviews.

1. Kussendrager KD, van Hooijdonk AC. Lactoperoxidase: physico-chemical properties, occurrence, mechanism of action and applications. *Br J Nutr* 2000; **84** (suppl 1): S19–S25.
2. Tenovuo J. Clinical applications of antimicrobial host proteins lactoperoxidase, lysozyme and lactoferrin in xerostomia: efficacy and safety. *Oral Dis* 2002; **8:** 23–9.
3. Lönnerdal B. Nutritional and physiologic significance of human milk proteins. *Am J Clin Nutr* 2003; **77** (suppl): 1537S–1543S.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Flaminal; ***Singapore***: Biotene†; Biotene; Biotene; Luvena Prebiotic; OralSeven; OralSeven; OralSeven; ***UK***: Biotene Dry Mouth; Biotene Oralbalance; Flaminal; ***USA***: Biotene with Calcium.

Laetrile

CAS — 1332-94-1 (laetrile); 29883-15-6 (amygdalin).

Profile

Laetrile is the term used for a product consisting chiefly of amygdalin, which is the major cyanogenic glycoside of apricot kernels. Amygdalin is *R*-α-cyanobenzyl-6-*O*-β-D-glucopyranosyl-β-D-glucopyranoside ($C_{20}H_{27}NO_{11}$ = 457.4). Laetrile is also used as a term for *R*-α-cyanobenzyl-6-*O*-β-D-glucopyranosiduronic acid ($C_{14}H_{15}NO_7$ = 309.3).

Laetrile was claimed to be preferentially hydrolysed in cancer cells by β-glucosidases to benzaldehyde and hydrogen cyanide, which killed the cell, but amygdalin

does not appear to be absorbed from the gastrointestinal tract, and both normal and malignant cells contain only traces of β-glucosidases. Laetrile has also been claimed to be 'vitamin B_{17}', the deficiency of which is said to result in cancer; there is no evidence for this view and laetrile is of no known value in human nutrition.

There have been several reports of cyanide poisoning and other adverse reactions associated with the use of laetrile, especially when taken orally.

A systematic review[1] concluded that data from controlled studies do not support the claims of efficacy for laetrile in cancer patients. Further references[2-4] to laetrile, including case reports[3,4] of toxic effects.

1. Milazzo S, *et al*. Laetrile treatment for cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 17/07/08).
2. Chandler RF, *et al*. Controversial laetrile. *Pharm J* 1984; **232:** 330–2.
3. Bromley J, *et al*. Life-threatening interaction between complementary medicines: cyanide toxicity following ingestion of amygdalin and vitamin C. *Ann Pharmacother* 2005; **39:** 1566–9.
4. O'Brien B, *et al*. Severe cyanide toxicity from 'vitamin supplements'. *Eur J Emerg Med* 2005; **12:** 257–8.

Laminaria

Stipites Laminariae; Styli Laminariae; Thallus Eckloniae; Thallus Laminariae; Ламинария.

UNII — NXA595GQ1K.

Pharmacopoeias. In *Chin.*

Uses and Administration

Laminaria is the dried stalks of the seaweeds *Laminaria japonica*, *L. digitata*, and possibly other species of *Laminaria*. The stalks swell in water to about 6 times their volume and have been used surgically to dilate cavities and to dilate the cervix in labour or abortion induction.

An extract of various species of *Laminaria* has been used as a dietary supplement (see Seaweeds, Kelps, and Wracks, p. 2612.1).

References.
1. Mazouni C, *et al*. Cervical preparation with laminaria tents improves induction-to-delivery interval in second- and third-trimester medical termination of pregnancy. *Contraception* 2009; **80:** 101–4.
2. Ben-Ami I, *et al*. Safety of late second-trimester pregnancy termination by laminaria dilatation and evacuation in patients with previous multiple cesarean sections. *Am J Obstet Gynecol* 2009; **201:** 154.e1–5.

Adverse Effects

Hypersensitivity. Anaphylaxis[1-3] and toxic shock syndrome[4] have been reported after the insertion of laminaria for cervical dilatation.

1. Nguyen MT, Hoffman DR. Anaphylaxis to laminaria. *J Allergy Clin Immunol* 1995; **95:** 138–9.
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3. Chanda M, *et al*. Hypersensitivity reactions following laminaria placement. *Contraception* 2000; **62:** 105–6.
4. Sutkin G, *et al*. Toxic shock syndrome after laminaria insertion. *Obstet Gynecol* 2001; **98:** 959–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Fitotranzit (Фитотранзит); Okovidit (Оковидит).

Multi-ingredient Preparations. ***Fr.***: Marinol; Node DS+; ***Rus.***: Evalar (Эвалар); Hyporolam (Гипоролам); Limanovit E (Лимановит Е).

Lappa

Bardana; Bardanae Radix; Bardane (Grande); Burdock; Burdock Root; Lampazo menor; Lappa Root; Лопух Лечебный.

*UNII — 597E9BI3Z3 (*Arctium lappa *root); EA541308MV (*Arctium lappa *fruit).*

Pharmacopoeias. In *Fr.*

Chin. and *Jpn* include the fruits.

Profile

Lappa is the dried root of the great burdock, *Arctium lappa* (*A. majus*), and other species of *Arctium* (Compositae). It was formerly used in the form of a decoction as a diuretic and diaphoretic but there is little evidence of its efficacy. Herbal preparations containing lappa have been used in the treatment of skin, musculoskeletal, and gastrointestinal disorders. The leaves and fruits of *Arctium* spp. have also been used.

Homoeopathy

Lappa has been used in homoeopathic medicines under the following names: Lappa major; Lap. maj.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Philipp.***: Saforelle; ***Port.***: Saforelle; ***Venez.***: Saforelle.

Multi-ingredient Preparations. ***Austral.***: Arctium & Zinc Compound; Burdock Complex; DermaCo; KickStart Detox; Percutane†; ***Canad.***: Depuratif des Trappistes; Eliminex; Herbal Laxative†; Milk Thistle Extract Formula; Natraway Sport 1 & 2†; Natraway Sport 3†; Natural HRT; ***Chile***: Capilet Locion Capilar; ***Cz.***: Diabetan; ***Fr.***: Arbum; Depuratif Parnel†; Mycoress; Topialyse Sensitive; Topialyse Sensitive; Zeniac LP; Zeniac; ***Ger.***: Weleda Hauttonikum†; ***Hong Kong***: Perfectil; ***Hung.***: Depsorin; ***Ital.***: Allerlux; ***Jpn***: Shofusan; ***Pol.***: Betasol; Immunofort; Seboren; ***Port.***: Erpecalm; ***Rus.***: Perfectil (Перфектил); ***S.Afr.***: Lotio Pruni Comp cum Cupro†; ***Singapore***: Purifying Gel; ***Switz.***: Venadoron; ***UK***: Aqua Ban Herbal; Aquella; Backache; Boots Water Relief; Cascade; Catarrh Mixture; Covonia Catarrh Relief; GB Tablets; Gerard House Skin; Gerard House Water Relief Tablets; HRI Clear Complexion; Modern Herbals Water Retention; Napiers Oral Skin Soother Herbal Relief; Pure Plan; Rheumatic Pain Remedy; Skin Cleansing; Skin Eruptions Mixture; Tabritis; Water Naturtabs; ***Ukr.***: Perfectil (Перфектил); Vitokan (Витокан); ***USA***: Detox.

Homoeopathic Preparations. ***Austral.***: Echine†; ***Canad.***: Adrisin†; Common Mallow Combination†; Cutisitum†; Echinacea L40†; Essigen†; Formula Homeo QR 209†; ***Fr.***: Digeodren; Echinacea Complexe No 40; Homeodose 24†; Saponaria Compose; Staphysagria Complexe No 92†; ***Ger.***: Regenaplex Haut G; ***Switz.***: Regenaplex Nr. 80aN.

Laronidase *(USAN, rINN)*

Alpha-L-iduronidase; Alronidase; Laronidasa; Laronidasum; Laronidaz; Ларонидаз.

8-L-Histidine-α-L-iduronidase (human).

CAS — 210589-09-6.

ATC — A16AB05.

ATC Vet — QA16AB05.

UNII — WP58SVM6R4.

Uses and Administration

Laronidase is recombinant human α-L-iduronidase and is used as enzyme replacement therapy for the treatment of the non-neurological manifestations of mucopolysaccharidosis I (see below). It is given by intravenous infusion in a dose of 100 units/kg each week. The initial infusion rate should be 2 units/kg per hour, increased every 15 minutes during the first hour, as tolerated, to a maximum of 43 units/kg per hour such that the infusion is completed in about 3 to 4 hours (but see also under Adverse Effects, Treatment, and Precautions, below). In some countries, the dose is expressed as mg/kg: 100 units is equivalent to about 580 micrograms of laronidase.

Administration in children. Licensed product information for laronidase in the treatment of mucopolysaccharidosis I does not mention any specific age group, although the *BNFC* notes that the usual adult dose (see above) may be given to patients from 1 month of age.

Mucopolysaccharidosis I. Mucopolysaccharidosis I is a progressive disorder characterised by deficiency of the enzyme α-L-iduronidase, which is necessary to catalyse the hydrolysis of terminal α-L-iduronic residues of the glycosaminoglycans, dermatan sulfate and heparan sulfate. This results in their accumulation in tissues, with many clinical manifestations including hepatomegaly, skeletal abnormalities, pulmonary disease, eye disease, and progressive deterioration of the CNS. Mucopolysaccharidosis I has traditionally been classified into three main forms based on clinical symptoms and severity: Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome. Hurler syndrome is the most severe form with a life expectancy of less than 10 years. However, there is a degree of overlap between the syndromes and they are indistinguishable by routine enzyme or urine tests.

Treatment was previously limited to symptomatic management but other options to halt disease progression are now available. Haematopoietic stem-cell transplantation using bone marrow or umbilical cord blood is of benefit in systemic disease and can prevent (but not usually reverse) CNS deterioration. However, substantial adverse effects limit its use to patients with severe disease. Enzyme replacement therapy with laronidase has been reported to confer benefit on the systemic manifestations of the disease, but since it does not cross the blood-brain barrier in appreciable amounts, beneficial effect on CNS symptoms is again predicted to be unlikely. However, the improvements conferred by enzyme replacement therapy might make haematopoietic stem-cell transplantation easier to tolerate.

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5. Muenzer J, Fisher A. Advances in the treatment of mucopolysaccharidosis type I. *N Engl J Med* 2004; **350:** 1932–4.
6. Staba SL, *et al*. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *N Engl J Med* 2004; **350:** 1960–9.
7. Wraith JE, *et al*. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human α -L-iduronidase (laronidase). *J Pediatr* 2004; **144:** 581–8.
8. Grewal SS, *et al*. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. *Genet Med* 2005;**7:** 143–6.
9. Miebach E. Enzyme replacement therapy in mucopolysaccharidosis type I. *Acta Paediatr Suppl* 2005; **94** (suppl 447): 58–60.
10. Wraith JE, *et al*. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human α -L-iduronidase (laronidase). Abstract: *Pediatrics* 2007; **120:** 158. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/1/e37 (accessed 07/02/08)
11. Muenzer J, *et al*. International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines. *Pediatrics* 2009; **123:** 19–29. Also available at: http://pediatrics.aappublications.org/cgi/content/full/123/1/19 (accessed 18/02/10)
12. Clarke LA, *et al*. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. *Pediatrics* 2009; **123:** 229–40.
13. Wynn RF, *et al*. Use of enzyme replacement therapy (laronidase) before hematopoietic stem cell transplantation for mucopolysaccharidosis I: experience in 18 patients. *J Pediatr* 2009; **154:** 135–9.
14. Martins AM, *et al*. Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr* 2009; **155** (suppl 2): S32–S46.

Adverse Effects, Treatment, and Precautions

Anaphylactic and other infusion reactions, sometimes delayed in onset, have been reported in patients given laronidase and facilities for resuscitation should be available whenever it is used. Common symptoms include flushing, fever, headache, and rash. Other adverse effects commonly reported include abdominal pain, arthralgia, back pain, nausea, vomiting, diarrhoea, cough, dyspnoea, urticaria, angioedema, pruritus, chills, paraesthesia, dizziness, tachycardia, increased blood pressure, and decreased oxygen saturation. Bronchospasm, tachypnoea, cyanosis, and extravasation have also been reported. Patients with existing respiratory disease may be at risk of more severe reactions. Antihistamines and/or antipyretics (e.g. paracetamol or ibuprofen) may relieve symptoms. A reduction in the rate of infusion to half the rate at which the reaction occurred should also be considered for mild or moderate reactions; for severe reactions, the infusion should be stopped until symptoms have subsided, and then restarted at one-half to one-quarter the rate at which the reaction occurred. Adrenaline should be used with caution because there is a greater incidence of coronary artery disease in patients with mucopolysaccharidosis I. Pre-treatment with antihistamines and/or antipyretics about 60 minutes before infusion is recommended to prevent reactions. IgG antibodies to laronidase are expected to develop within 3 months of starting treatment in the majority of patients, although the effect of this on safety and efficacy is not clear. However, such patients may be at increased risk of hypersensitivity reactions and should be treated with caution. Injection site reactions have also been reported.

Interactions

Licensed product information for laronidase recommends that it should not be given with chloroquine or procaine because of the potential risk of interference with the intracellular uptake of the enzyme.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aldurazyme; ***Austria***: Aldurazyme; ***Belg.***: Aldurazyme; ***Braz.***: Aldurazyme; ***Canad.***: Aldurazyme; ***Chile***: Aldurazyme; ***Cz.***: Aldurazyme; ***Denm.***: Aldurazyme; ***Fin.***: Aldurazyme; ***Fr.***: Aldurazyme; ***Ger.***: Aldurazyme; ***Gr.***: Aldurazyme; ***Hong Kong***: Aldurazyme; ***Israel***: Aldurazyme; ***Ital.***: Aldurazyme; ***Malaysia***: Aldurazyme; ***Neth.***: Aldurazyme; ***Norw.***: Aldurazyme; ***NZ***: Aldurazyme; ***Pol.***: Aldurazyme; ***Port.***: Aldurazyme; ***Spain***: Aldurazyme; ***Swed.***: Aldurazyme; ***Switz.***: Aldurazyme; ***Thai.***: Aldurazyme; ***Turk.***: Aldurazyme; ***UK***: Aldurazyme; ***Ukr.***: Aldurasim (Альдуразим)†; ***USA***: Aldurazyme.

Laropiprant *(BAN, USAN, rINN)*

Laropiprantum; MK-0524; Ларопипрант.

(-)-[(3*R*)-4-(4-Chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta(*b*)indol-3-yl]acetic acid.

$C_{21}H_{19}ClFNO_4S$=435.9

CAS — 571170-77-9.

UNII — G7N11T8O78.

NOTE. The name Cordaptive has been used as a trade mark for a combination product of laropiprant and nicotinic acid.

Profile

Laropiprant is a prostaglandin D_2 receptor 1 antagonist that inhibits nicotinic-acid induced flushing. It has been used in a modified-release combination preparation with nicotinic acid to reduce the flushing that occurs when nicotinic acid is used in high doses for the treatment of hyperlipidaemias, but the formulation was discontinued when it was found to have no benefit over statin therapy and an increased rate of adverse effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Pelzont†.

Multi-ingredient Preparations. ***Arg.***: Cordaptive; ***Austria***: Pelzont†; Tredaptive†; ***Belg.***: Tredaptive†; ***Braz.***: Cordaptive; ***Cz.***: Pelzont†; Tredaptive†; Trevaclyn†; ***Denm.***: Tredaptive†; ***Fr.***: Tredaptive†; ***Ger.***: Tredaptive†; ***Gr.***: Tredaptive†; ***Hong Kong***: Tredaptive†; ***Irl.***: Tredaptive†; Trevaclyn†; ***Israel***: Tredaptive†; ***Mex.***: Cordaptive; ***Neth.***: Pelzont†; Tredaptive†; Trevaclyn†; ***Norw.***: Tredaptive†; ***NZ***: Tredaptive†; ***Philipp.***: Tredaptive†; ***Pol.***: Pelzont†; Tredaptive†; Trevaclyn†; ***Port.***: Pelzont†; Tredaptive†; Trevaclyn†; ***Singapore***: Tredaptive†; ***Spain***: Tredaptive†; ***Swed.***: Tredaptive†; ***Switz.***: Tredaptive†; ***UK***: Tredaptive†.

Lavender

English Lavender; Kwiat lawendy (lavender flower); Lavande, fleur de (lavender flower); Lavande Vrai; Lavandulae flos (lavender flower); Lavendelblomma (lavender flower); Lavendelblüten; Laventelinkukka (lavender flower); Levandų žiedai (lavender flower); Levandulový květ (lavender flower); Levendulavirág (lavender flower); Лаванда Узколистная (*Lavandula angustifolia*).

ATC Herb — HN05CM5011 (Lavandula angustifolia: *flower); HG04BW5019* (Lavandula angustifolia: *flower); HA05AW5011* (Lavandula angustifolia: *flower); HA03AW5033* (Lavandula angustifolia: *flower).*

UNII — 9YT4B71U8P (lavender); 19AH1RAF4M (lavender extract).

Pharmacopoeias. *Eur.* (see p. vii) includes lavender flower.

Ph. Eur. 8: (Lavender Flower; Lavandulae flos). It consists of the dried flower of *Lavandula angustifolia* (*L. officinalis*). It contains not less than 1.3% v/w of essential oil, calculated with reference to the anhydrous drug. Protect from light.

Profile

Lavender flower is used as a sedative. It has also been used as a cholagogue. It is an ingredient of herbal remedies used for a variety of disorders.

Lavender flowers are the source of lavender oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Lavandula Oligoplex; ***Austral.***: Cimicifuga Compound; Lavandula Compound; Tranquil Night; ***Austria***: Euka; ***Braz.***: Balsamo Branco; Traumac†; ***Cz.***: Calmonal†; Valofyt Neo†; ***Fr.***: Hepato-Solutines†; Santane R_8†; ***NZ***: Botanica Hayfever; ***Pol.***: Lumewal; Nervinolum; Nervinum†; Nervosol; Reumobonisol; ***Port.***: Erpecalm; ***S.Afr.***: Krampdruppels; ***Singapore***: Stop Snoring; ***Spain***: Linimento Naion; ***Switz.***: Femisan; ***UK***: Vital Eyes; ***Ukr.***: Vitrum Beauty Elite (Витрум Бьюти Элит).

Lavender Oil

English Lavender Oil (from *L. intermedia*); Esencia de Alhucema; Esencia de Espliego; Essência de Alfazema; Foreign Lavender Oil (from *L. officinalis*); Huile Essentielle de Lavande; Lavanda, aceite esencial de; Lavande, huile essentielle de; Lavandulae aetheroleum; Lavandulae Etheroleum; Lavanta Yağı; Lavendelöl; Lavendelolja; Lavender Flower Oil; Laventeliöljy; Levandų eterinis aliejus; Levandulová silice; Olejek lawendowy; Oleum Lavandulae; Лавандовое Масло.

ATC Herb — HP03BX5002 (Lavandula angustifolia: *essential oil); HA03AW5032* (Lavandula angustifolia: *essential oil).*

UNII — ZBP1YXW0H8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lavender Oil). An essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* (*L. officinalis*). A colourless or pale yellow clear liquid with a characteristic odour, reminiscent of linalyl acetate. Relative density 0.878 to 0.892. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Lavender oil has been used as a carminative and as a flavour. It is sometimes applied externally as an insect repellent. Its chief use is in perfumery and it is occasionally used in ointments and other pharmaceutical preparations to cover disagreeable odours. It has been suggested that lavender oil may have sedative properties after inhalation. It is also used in aromatherapy.

References.

1. Cavanagh HM, Wilkinson JM. Biological activities of lavender essential oil. *Phytother Res* 2002; **16:** 301–8.

Insomnia. Ambient exposure to lavender oil produced similar sleep patterns to conventional sedatives in 4 elderly patients.[1]

1. Hardy M, *et al.* Replacement of drug treatment for insomnia by ambient odour. *Lancet* 1995; **346:** 701.

Adverse Effects

Lavender oil has been reported to produce nausea, vomiting, headache, and chills when inhaled or absorbed through the skin. It may cause contact allergy and phototoxicity.

There have been reports of contact dermatitis associated with lavender oil in a shampoo,[1] and facial dermatitis after application of the oil to pillows for its sedative properties.[2] A suggestion that topical exposure to products containing lavender and melaleuca oils was associated with the development of gynaecomastia in 3 prepubertal boys,[3] was questioned by others (including manufacturers of such products).[4-7]

1. Brandão FM. Occupational allergy to lavender oil. *Contact Dermatitis* 1986; **15:** 249–50.
2. Coulson IH, Khan ASA. Facial 'pillow' dermatitis due to lavender oil allergy. *Contact Dermatitis* 1999; **41:** 111.
3. Henley DV, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; **356:** 479–85.
4. Kemper KJ, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; **356:** 2541–2.
5. Kalyan S, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; **356:** 2542.
6. Kurtz JL, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; **356:** 2542–3.
7. Dean CJ, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; **356:** 2543.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Lasea; ***Pol.***: Lawenol; ***Ukr.***: Тавипес (Тавипек).

Multi-ingredient Preparations. ***Arg.***: Nopucid Bio II; ***Austral.***: Apex Repel Natural; Bio-Oil; Bosisto's Antiseptic Spray; Bosisto's Eucalyptus Inhalant; Bosisto's EucoSteam Inhalant; Bosisto's Nasal Inhaler; Crampeze Pain Relief; NeutraLice; Vicks Baby Balsam; ***Austria***: Berggeist; Rowalind; ***Belg.***: Mouskito Travel Milk†; ***Braz.***: Aliviol; Benegel; Gelflex; Inhalante Yatropan; Nevrol†; ***Canad.***: Amol†; Vicks Vapo Steam†; ***Chile***: Migrastick; ***Cz.***: Amol; Ondrejova Mast; ***Fr.***: Aromasol; Arthro; Balsofumine; Dolirhume; Dystolise; Esculape†; Gouttes aux Essences; Maghora†; Paps†; Perubore; Poudre du Marcheur†; Resistim; Respirea†; Tigre de Chine; ***Ger.***: Amol Heilkrautergeist N; Dolo-cyl†; Enelbin-Paste†; ***Hong Kong***: Calmiderm; ***Hung.***: Amol; Carmol; Inno Rheuma; Szent Lukacs; ***India***: LTT Cleanser; ***Indon.***: Fitajoint; ***Irl.***: Massage Balm with Arnica; ***Israel***: Headache Pads; ***Ital.***: Citrosystem; Controller; Mistick Verde; Narhinel Balsamico Bambini; Venalta; ***Malaysia***: Bio-Oil; ***NZ***: Electric Blue Headlice; Electric Blue Headlice; Vicks Baby Balsam; ***Pol.***: Amol; Aromatol; Carmolis; ***Rus.***: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Espol (Эспол); ***S.Afr.***: Arnica Massage Oil; Entressdruppels HM; Rooilavental; ***Spain***: Dolokey†; Termosan; ***Switz.***: Baume du Chalet; Baume du Tigre huile; Echinarom; Oculosan; Perskindol Classic; Perskindol Classic; Pulmex; Spagyrom; Ziegella†; ***Turk.***: Algo-Wax; Myo-Oil; ***UK***: Arnica Massage Balm; Eucanol; Eucanol; Larch Resin comp.; Massage Balm with Calendula; Migrastick; Repelselect; ***USA***: Nasal Jelly.

Homoeopathic Preparations. ***Ger.***: Aurum/Lavandula comp.; ***UK***: Medicinal Gargle.

Lawsone

Lawsonia; Лаусон.

2-Hydroxy-1,4-naphthoquinone.

$C_{10}H_6O_3$=174.2

CAS — 83-72-7.

UNII — TLH4A6LV1W.

Profile

Lawsone is a dye present in henna (p. 2525.1), the leaves of *Lawsonia* spp., and may also be prepared synthetically. It has been used with dihydroxyacetone in sunscreen preparations. There appears to be no evidence that it has any sunscreening properties when used alone.

Adverse effects. Observation that lawsone causes oxidative damage to red blood cells *in vitro* supported a suggestion that percutaneous absorption of henna could contribute to unexplained neonatal hyperbilirubinaemia in countries where the ceremonial use of henna is widespread.[1]

1. Zinkham WH, Oski FA. Henna: a potential cause of oxidative hemolysis and neonatal hyperbilirubinemia. *Pediatrics* 1996; **97:** 707–9.

Lead

Blei; Plomb; Plomo; Plumbum; Свинец.

Pb=207.2

CAS — 7439-92-1.

UNII — 2P299V784P.

Description. Lead is a grey, malleable and ductile metal.

Uses

Lead compounds were formerly used as astringents, but the medicinal use of preparations containing lead is no longer recommended. The lead salts or compounds that have been used have included lead acetate and lead subacetate (for lead lotion, still known sometimes as lotio plumbi), lead carbonate, lead monoxide, and lead oleate (for lead plastermass).

Adverse Effects

Lead poisoning (plumbism) may be due to inorganic or organic lead and may be acute or, more often, chronic. It has followed exposure to many compounds and objects from which lead may be absorbed following ingestion or inhalation. Some of those that have been incriminated include paint, pottery glazes, crystal glassware, domestic water supplies, petrol, poteen, cosmetics (particularly home-made or traditional forms such as kohl or surma), herbal or folk remedies, including traditional Chinese medicines, newsprint, and retained bullets. Children are often the victims of accidental poisoning and may be vulnerable to chronic exposure to lead from environmental pollution.

Acute effects of lead poisoning include metallic taste, abdominal pain, diarrhoea, vomiting, hypotension, muscle weakness and cramps, fatigue, abnormal liver function tests, and acute interstitial nephritis. Encephalopathy may occur and is more common in children. Symptoms of chronic poisoning with inorganic lead include anorexia, abdominal pain, constipation, anaemia, headache, fatigue, irritability, peripheral neuropathy, and encephalopathy with convulsions and coma. There may be kidney damage and impairment of mental function. Children with elevated lead concentrations may be asymptomatic apart from intellectual deficits and behavioural disorders.

Organic lead poisoning produces mainly CNS symptoms; there can be gastrointestinal and cardiovascular effects, and renal and hepatic damage.

General references to lead exposure, adverse effects, screening, and management,[1-15] and case reports of specific sources of lead exposure.[16-21]

1. WHO. Recommended health-based limits in occupational exposure to heavy metals: report of a WHO study group. *WHO Tech Rep Ser647* 1980. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_647.pdf (accessed 08/07/08)
2. WHO. Lead—environmental aspects. *Environmental Health Criteria 85.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc85.htm (accessed 08/07/08)
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5. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; **116:** 1036–46.
6. Kordas K, *et al.* Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. *J Pediatr* 2005; **147:** 632–9.
7. Stewart WF, *et al.* Past adult lead exposure is linked to neurodegeneration measured by brain MRI. *Neurology* 2006; **66:** 1476–84.
8. Zimmermann MB, *et al.* Iron fortification reduces blood lead levels in children in Bangalore, India. *Pediatrics* 2006; **117:** 2014–21.
9. Téllez-Rojo MM, *et al.* Longitudinal associations between blood lead concentrations lower than 10 micrograms/dL and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 2006; **118:** e323–e330. Available at: http://pediatrics.aappublications.org/cgi/content/full/118/2/e323 (accessed 08/07/08)
10. Yuan W, *et al.* The impact of early childhood lead exposure on brain organization: a functional magnetic resonance imaging study of language function. *Pediatrics* 2006; **118:** 971–7.
11. Menke A, *et al.* Blood lead below 0.48 micromol/L (10 micrograms/dL) and mortality among US adults. *Circulation* 2006; **114:** 1388–94.
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13. Gracia RC, Snodgrass WR. Lead toxicity and chelation therapy. *Am J Health-Syst Pharm* 2007; **64:** 45–53.

14. Chen A, *et al*. Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: does lead affect behavior only by lowering IQ? *Pediatrics* 2007; **119:** e650–e658. Available at: http://pediatrics.aappublications.org/cgi/content/full/119/3/e650 (accessed 08/07/08)
15. CDC Advisory Committee on Childhood Lead Poisoning Prevention. Interpreting and managing blood lead levels <10 micrograms/dL in children and reducing childhood exposures to lead: recommendations of CDC's Advisory Committee on Childhood Lead Poisoning Prevention. *MMWR* 2007; **56 (RR-8)**: 1–16. Correction. *ibid.*; **56 (47)**: 1241. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5608a1.htm (accessed 05/08/08)
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Treatment of Adverse Effects

The main aim in the management of both acute and chronic lead poisoning is to control the symptoms and reduce the concentration of lead in the body. Patients should be removed from the source of exposure and iron and calcium deficiencies corrected.

Treatment of symptomatic poisoning entails supportive therapy including intravenous fluids. Renal and hepatic function should also be monitored and convulsions controlled with a benzodiazepine. Encephalopathy, which is rare in adults but more common in children, requires urgent treatment.

Acute ingestion of lead or its salts should be treated if appropriate by activated charcoal or gastric lavage if within 1 hour of ingestion of a potentially life-threatening dose. Emesis is not recommended for organic lead compounds.

In severe cases of inorganic or organic lead poisoning, chelation therapy may be required to facilitate removal of lead from the body. A lead mobilisation test that measures urinary excretion of lead after a standard dose of sodium calcium edetate (p. 1573.2) has been used as a means of assessing the need for therapy. However, because of difficulties in administering the test and uncertainties in interpreting results, some authorities have recommended blood-lead concentrations as a guide to treatment. The lead mobilisation test in addition to measurement of blood-lead concentrations may be useful in determining the necessity for chelation therapy in children (see below). Blood-lead concentrations should be obtained before starting chelation therapy, and then again after the first course since mobilisation of stored lead from body tissues may cause blood-lead concentrations to rebound after an initial drop; further courses of chelator may then be required. Raised blood-lead concentrations despite chelation therapy could also indicate continued exposure.

Blood-lead concentrations for chelation therapy and the chelating regimens used differ slightly between the UK and USA. In the UK, children with blood-lead concentrations between 10 and 50 micrograms per 100 mL are monitored but not routinely given chelation therapy, and the lead mobilisation test is no longer recommended. For blood-lead concentrations between 50 and 70 micrograms per 100 mL, oral succimer (p. 1576.3) or intravenous sodium calcium edetate (p. 1573.2) should be given. For blood-lead concentrations greater than 70 micrograms per 100 mL, intravenous sodium calcium edetate should be given. While dimercaprol (p. 1549.3) has been used in the UK, it is not currently recommended as first-line treatment for lead poisoning. In the USA, chelation therapy is not indicated for children with a blood-lead concentration less than 25 micrograms per 100 mL. Children with a blood-lead concentration of 25 to 44micrograms per 100 mL and a positive sodium calcium edetate mobilisation test should be considered for treatment. All children with blood-lead concentrations ≥45 micrograms per 100 mL should be treated, and chelators that have been used include dimercaprol, sodium calcium edetate, penicillamine (p. 1567.1), or succimer. If encephalopathy is present, dimercaprol should be given followed 4 hours later by parenteral sodium calcium edetate.

It is considered that asymptomatic adults with a blood-lead concentration less than 50 micrograms per 100 mL and who are not pregnant do not generally require chelation therapy. However, all adults with blood-lead concentrations ≥ 50 micrograms per 100 mL should be considered for treatment. Those without encephalopathy may be treated with oral succimer or intravenous sodium calcium edetate; alternatives are unithiol or penicillamine. Adults with encephalopathy should be treated with parenteral sodium calcium edetate. As with children (see above), dimercaprol is given with sodium calcium edetate in the USA but not in the UK.

Lead foreign bodies may need to be removed surgically or endoscopically to prevent further exposure. Long-term management of chronic lead poisoning involves eliminating environmental lead exposure. Chelation therapy is not a substitute for environmental controls in those suffering occupational exposure.

Results from one study[1] indicated that succimer did not improve scores on tests of cognition, behaviour, or neuropsychological function despite lowering blood levels of lead in children who had initial levels of less than 45 micrograms per 100 mL. The authors suggested that, since succimer is as effective a chelator as any other currently available, chelation therapy in general may not be beneficial in children with these blood-lead levels.

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Lead in the Environment

Many countries have taken action to reduce lead exposure from environmental sources, including food, paint, and petrol, by limiting or banning altogether the use of lead compounds in such sources. Such measures have been of value in reducing childhood exposure to lead. Screening of all children to detect those at risk of chronic lead poisoning and developmental deficit has been advocated, but selective screening in areas perceived as high risk may be more appropriate in countries where the overall level of lead contamination is low.

Pharmacokinetics

Lead is absorbed from the gastrointestinal tract. It is also absorbed by the lungs from dust particles or fumes.

Inorganic lead is not absorbed through intact skin, but organic lead compounds may be absorbed rapidly.

Lead is distributed in the soft tissues, with higher concentrations in the liver and kidneys. In the blood it is associated with the erythrocytes. Over a period of time lead accumulates in the body and is deposited in calcified bone, hair, and teeth. Lead crosses the placental barrier. It is excreted in the faeces, urine, and sweat, and also appears in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Vulpuran; ***Mex.***: Emplasto Monopolis; ***Rus.***: Teimurov (Теймурова).

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; Scleron; ***Canad.***: Biomag†; Reneel†; Scleron; Travel Sickness; ***Fr.***: Abe Chaupitre no 19†; Biomag; Cocculus Complexe No 73; ***Ger.***: Arnica/Betula comp; Cefadybasin SE†; Curare comp; Gelsemium Comp; Gelsemium Comp; Lobelia comp; metaginkgo†; Scleron; ***Neth.***: Chavita 6; Collite; Emvita 26; ***S.Afr.***: Scleron†; ***Switz.***: metaginkgo; Regenaplex Nr. 25a.

Lecithin

E322; E442 (ammonium phosphatides); Lécithine; Lecithinum; Lecitina; Lesitinler; Лецитин.

CAS — 8002-43-5.

UNII — 1Z74184RGV (egg lecithin); 1DI56QDM62 (soybean lecithin).

NOTE. The term phosphatidylcholine, a synonym for phosphatidyl choline (p. 2588.3), one of the ingredients of lecithin, is also sometimes used for lecithin itself.

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 31: (Lecithin). A complex mixture of acetone-insoluble phosphatides, which consists chiefly of phosphatidyl choline, phosphatidyl olamine, phosphatidyl serine, and phosphatidyl inositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. It contains not less than 50% of acetone-insoluble matter.

The consistency of both natural grades and refined grades of lecithin may vary from plastic to fluid, depending upon the content of free fatty acid and oil, and upon the presence or absence of other diluents. Its colour varies from light yellow to brown, depending on the source, on crop variations, and on whether it is bleached or unbleached.

It is odourless or has a characteristic, slight nutlike odour. It is partially soluble in water, but readily hydrates to form emulsions. The oil-free phosphatides are soluble in fatty acids, but are practically insoluble in fixed oils. When all phosphatide fractions are present, lecithin is partially soluble in alcohol and practically insoluble in acetone. Protect from light and from excess heat and moisture.

Profile

Lecithin is an emulsifying and stabilising agent used in both the pharmaceutical and the food industries.

Lecithin has also been used as a source of choline in the treatment of dementia (p. 388.1) but with little evidence of clinical benefit. Phosphatidyl serine (p. 2589.1) has been used similarly. Other constituents of lecithin such as phosphatidyl olamine and phosphatidyl inositol may be found in natural pulmonary surfactants (p. 2599.2).

Lecithin is also a n ingredient o f preparations promoted as tonics and dietary supplements in an enormous range of disorders.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Herbaccion Lecitina; Reducin†; ***Austral.***: Buerlecithin†; ***Austria***: Buerlecithin Compact†; ***Ger.***: Ocutears†; ***Hung.***: Buerlecithin; ***India***: Elivee; Essentiale-L; Lecivit; Livage; Livintact; ***Mex.***: Leciderm†; ***Pol.***: Lecitan†; ***Venez.***: Lecivar.

Multi-ingredient Preparations. ***Arg.***: Ayton; Cellasene Gold; Cellasene†; Fosfovita; Herbaccion Memory; KLB6 Fruit Diet; Lecitina E; No-Gras; Tanvimil Isoflavonas; Triconal; ***Austral.***: Berberis Complex†; Daily Plus Max†; Extralife Arthri-Care†; Extralife Extra-Brite†; Extralife Liva-Care†; Hair Skin & Nails; Joint Ease; Natal Plus; PM Joint-Care; Vitamin E Complex; Zellulean with Escin†; ***Austria***: Buerlecithin; Geriatric Pharmaton; Lecikur†; ***Chile***: Bedovit Pharmaton; Biocord-E; Biocord; Cartilago T-500†; Diltotal; ***Cz.***: Geriavit; ***Fr.***: Magneginseng†; Neurovitol; ***Ger.***: Lipidavit†; Tears Again; ***Hong Kong***: Cardioace; Ginkgo-PS†; Pharmaton; Profile B Plus Fat Burner†; Slimming Aid†; Wari-Procomil†; ***Hung.***: Antisklerin; Memolife; Pharmaton Vital; ***India***: Lecivit-S; Mynberrys Compound; ***Indon.***: Artovit; BIO-EPL†; Cholesvit; Curson†; Epatin; Hepachol; Heparsitin; Lanagogum; Lanaven Plus†; Lanavision Plus; Lecitrol; Lesichol; Lesifit; Lesipar; Letropar; Letrosil; Life 10; Lipirol; Maxivit; Neurochol; Nutriflam; Obdhamin; Oramin-G; Pharmaton Formula; Picula; Provital Plus; Vercithin; Verona; Vitachol; Vitalux; ***Israel***: Pharmaton; Tears Again†; ***Ital.***: Eavit Plus; Eavit; Fosfaserin; Granvit; Nutrigel; Ottovis; Solecin†; Tricortin; Valcap; Vitalux Plus; Vitalux; ***Malaysia***: Livguard; Livovid; Pharmaton†; Proviton; ***Mex.***: Pharmaton Complex; Pharmaton; ***Philipp.***: Bio-Termin Plus with Lecithin; Heltine Plus; Homtamin-G Plus; Korgivit-E†; Leginsol-E; Liverine; Megavit; Memory DD†; Memory Plus; Memovit-E†; Multramin; Nutricap; Polynerv-E with lecithin; Premium Memori Plus; Restor-F; Rogin-E; SG-Glutergen; Vigor-ACE; Vita SL with lecithin†; Vita SL; Vitaginseng; ***Pol.***: Geriavit†; Lecytyna E; Vita Buerlecithin; ***Port.***: Geriso; Pansebase Composto; Pansebase; Secpel Composto†; Secpel†; ***Rus.***: Geriavit (Гериавит)†; Kinder Biovital (Киндер Биовиталь); Livolin (Ливолин); ***S.Afr.***: Gericomplex†; Neurotone; Pharmaton†; Vitaforce Nutri-B†; ***Singapore***: Gingviton; Ginkgo-PS†; Hepasil DTX†; Neovita; Pharmaton with Selenium; Pharmaton†; Snoreeze; Vigor-Ace; Vitaton; ***Switz.***: Biovital Ginseng; Pharmaton Vital Geriavit; Vita Buerlecithin; ***Thai.***: Geriatric Pharmaton; Gilomax; Pharmaton; ***Turk.***: Liponit; Pharmaton; ***UK***: Cardioace; Episil; Kelp Plus 3; Neovita; Pharmaton; S.P.H.P.; Skin Care Nutrients; ***Ukr.***: Esavit (Эсавит)†; Fitoval Shampoo (Фитовал шампунь); Hepahealth (Гепахелс); Kinder Biovital (Кіндер Біовіталь); Lioliv (Ліолів)†; Lipoflavon (Ліпофлавон)†; Rotavit Royal (Ротавит Ройял); ***USA***: Episil; KLB6; NeevoDHA; SaltStable Lo; ***Venez.***: Hepasil; Lecivar Plus; Nutricap; Provax.

Homoeopathic Preparations. ***Ger.***: NeyArthrosome (Revitorgan-Dilution)†; NeyGeront Vitalkapsein A.

Leishmanin

Leishmanina.

Profile

Leishmanin is a suspension of *Leishmania* promastigotes used in an intradermal test to indicate previous exposure to leishmanial antigens. Its chief use is in epidemiological studies of leishmaniasis (p. 922.1). The leishmanin skin test has also been known as the Montenegro test.

Lemon

Лимон.

UNII — 24RS0A988O.

Pharmacopoeias. *Br.* includes dried lemon peel and *Swiss* includes fresh lemon peel.

BP 2014: (Dried Lemon Peel). The dried outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus limon*. It contains not less than 2.5% v/w of volatile oil.

Profile

Lemon, *Citrus limon* (*Citrus limonum*) (Rutaceae), is an ingredient of herbal remedies used for gastrointestinal disorders and as tonics. The juice is traditionally included in preparations for colds and coughs. Lemon is a source of bioflavonoids used to improve capillary function (see Flavonoid Compounds, p. 2505.2). The peel is the source of

lemon oil (below). Citrus fruits are a source of vitamin C (p. 2110.3).

Photosensitivity is associated with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Varicura; ***Austria***: Gencydo; ***Braz.***: Balsamo Branco; ***Canad.***: Salusan†; ***Fr.***: Amana Cellium; Anastase; ***Ger.***: Gencydo; Weleda Hauttonikum†; ***India***: Gludibit; ***Ital.***: Flavion; ***Port.***: Erpecalm; ***Rus.***: Doppelherz Melissa (Доппельгерц Мелисса); ***Singapore***: Stop Snoring; ***Switz.***: Gencydo; Venadoron.

Homoeopathic Preparations. ***Fr.***: Gencydo; ***UK***: Gencydo.

Pharmacopoeial Preparations
BP 2014: Concentrated Compound Gentian Infusion;
USNF 31: Lemon Tincture.

Lemon Oil

Aetheroleum Citri; Citri Etheroleum; Citrinų eterinis aliejus; Citromolaj; Citron, huile essentielle de; Citronenöl; Citronolja; Citronová silice; Esencia de Cidra; Essence de Citron; Essência de Limão; Limón, aceite esencial de; Limonis aetheroleum; Ol. Limon.; Olejek cytrynowy; Oleum Citri; Oleum Limonis; Sitruunaöljy; Лимонное Масло.

*ATC Herb — HA03AW5014 (*Citrus limon*: essential oil).*
UNII — I9GRO824LL.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. & (Lemon Oil). The essential oil obtained by suitable mechanical means without the aid of heat from the fresh peel of *Citrus limon*. It contains a maximum of 0.5% β-caryophyllene, 0.5 to 2.3% geranial, 0.1 to 0.8% geranyl acetate, 56.0 to 78.0% limonene, 0.3 to 1.5% neral, 0.2 to 0.9% neryl acetate, 7.0 to 17.0% β-pinene, 1.0 to 3.0% sabinene, 6.0 to 12.0% γ-terpinene, and a maximum of 0.6% α-terpineol.

A clear mobile pale yellow to greenish-yellow liquid with a characteristic odour. It may become cloudy at low temperatures. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light. Where applicable the label should state that the contents are Italian-type lemon oil.

USNF 31: (Lemon Oil). The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus* X *limon* (Rutaceae), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral, is not less than 2.2% and not more than 3.8% for California-type lemon oil, and not less than 3.0% and not more than 5.5% for Italian-type lemon oil. Store in well-filled airtight containers.

Profile

Lemon oil is chiefly used in perfumery and as a flavour. It is used in the preparation of terpeneless lemon oil (below). It has also been used with other volatile agents in rubefacient preparations and preparations for respiratory-tract disorders. Both lemon oil and lemon petitgrain oils (prepared from the leaves and twigs) are used in aromatherapy.

Photosensitivity reactions and contact dermatitis have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Spasmo Claim†; ***Chile***: Agua del Carmen; Agua Melisa Carminativa; ***Cz.***: Amol; Coldastop; ***Fr.***: Aromadetox†; Aromadigest†; Oliosептil Gorge-Larynx; Poudre du Marcheur†; ***Ger.***: Amol Heilkrautergeist N; GeloSitin; Melissengeist; ***Hung.***: Amol; Carmol; ***Ital.***: Valda Timo e Limone; Venalta; ***NZ***: Electric Blue Headlice; ***Pol.***: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; ***Rus.***: Carmolis (Кармолис); ***S.Afr.***: Balsem Vita GEEL†; Balsem Vita ROOI†; Spiritus Contra Tussim Drops†; ***Swed.***: Alpenkraft; ***Switz.***: DUL-X Sport; Perskindol Classic; Perskindol Classic; Pirom; Sibrovita†; Venadoron; ***Turk.***: Nevrol Cemal; SH-206; ***UK***: Melissa Comp.; ***USA***: Mexsana.

Homoeopathic Preparations. ***UK***: Cough Drops.

Pharmacopoeial Preparations
BP 2014: Aromatic Ammonia Spirit;
USNF 31: Compound Orange Spirit.

Terpeneless Lemon Oil

Limón exento de terpeno, aceite esencial de; Oleum Limonis Deterpenatum.

Pharmacopoeias. In *Br.*

BP 2014: (Terpeneless Lemon Oil). A clear colourless or pale yellow liquid, visibly free from water, with the characteristic odour and taste of lemon, prepared by concentrating lemon oil under reduced pressure until most of the terpenes have been removed, or by solvent partition. It contains not less than 40% w/w of aldehydes calculated as citral. Soluble 1 in 1 of alcohol (80%). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Terpeneless lemon oil is used as a flavour. It has the advantages of being stronger in taste and odour and more readily soluble than the natural oil and is used in the preparation of lemon spirit and lemon syrup.

Photosensitivity is associated with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Lemsip Cough & Cold Dry Cough; Meltus Honey & Lemon.

Pharmacopoeial Preparations
BP 2014: Compound Orange Spirit; Lemon Spirit; Lemon Syrup.

Lemon Grass Oil

Essência de Capim-Limão; Indian Melissa Oil; Indian Verbena Oil; Lemongrass, aceite de; Lemongrass Oil; Oleum Graminis Citrati; Лемонграссовое Масло.

*ATC Herb — HA03AW5022 (*Cymbopogon citratus*: essential oil).*
UNII — 5BIA40E9ED.

Profile

Lemon grass oil is the volatile oil obtained by distillation from *Cymbopogon flexuosus* or *C. citratus* (Gramineae). It contains citral (p. 2480.2) and citronellal.

Lemon grass oil was formerly given as a carminative. It has been used in perfumery and as a flavour. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Apex Repel Natural; ***Canad.***: Salusan†; ***Fr.***: Aromavital†; ***India***: Artrex.

Lemon Verbena

Herba Lippiae Citriodorae; Herba Verbenae Odoratae; Hierba luisa; Verbenae citriodoratae folium (lemon verbena leaf); Verveine Odorante; Verveine odorante, feuille de (lemon verbena leaf); Вербена Лимонная.

UNII — 9B1F4HKA9O.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lemon Verbena Leaf). The whole or fragmented, dried leaves of *Aloysia citriodora* (*A. triphylla, Verbena triphylla, Lippia citriodora*). It contains a minimum of 2.5% acteoside ($C_{29}H_{36}O_{15}$ = 624.6) expressed as ferulic acid and not less than 0.3% v/w essential oil for the whole drug and 0.2% v/w essential oil for the fragmented drug, all calculated with reference to the dried drug. After grinding it has a characteristic odour reminiscent of lemon.

Profile

Lemon verbena, the flowering tops or leaves of *Lippia citriodora* (*Aloysia triphylla*; *Verbena triphylla*) (Verbenaceae), has antispasmodic and sedative actions and has been used for gastrointestinal disorders and as a tonic. It is most commonly used as an ingredient of herbal teas.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Agua del Carmen.

Lentinan

LC-33; Lentinano; Лентинан.

CAS — 37339-90-5.
ATC — L03AX01.
ATC Vet — QL03AX01.
UNII — 6751655D1D.

Profile

Lentinan is a β-1,3-D-glucan extracted from the shiitake mushroom *Lentinula edodes* (*Lentinus edodes*). It appears to act as an immunostimulant and has been tried in the treatment of malignant neoplasms and in HIV infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tian Di Xin (天地欣); ***Jpn***: Lenacut.

Multi-ingredient Preparations. ***USA***: Immunicare.

Lepromin

Lepromina; Лепромин.

CAS — 63163-81-5.

Profile

Lepromin is a suspension of killed *Mycobacterium leprae* prepared from the skin of heavily infected patients suffering from lepromatous leprosy (lepromin H) or from armadillo tissue infected with *M. leprae* (lepromin A). It has been used in an intradermal skin test for the classification of leprosy (p. 188.3) and the assessment of immune responsiveness to *M. leprae*. The test is not diagnostic for leprosy.

The original lepromin (of Mitsuda and Hayashi), a suspension of the whole autoclaved homogenised leproma including some tissue elements, is sometimes called integral lepromin, whereas purified bacillary suspensions are sometimes called bacillary lepromins.[1] Leprolins are the soluble proteins of the bacilli with or without proteins of the lepra, not coagulated by heating, and do not elicit the early reaction. The Dharmendra antigen is neither a lepromin nor a leprolin and is used especially for testing the early reactions; it gives only a weak late reaction. Purified protein derivatives of *Mycobacterium leprae*, such as leprosin A,[2] have also been developed.

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Leptin

Leptina; OB protein; Лептин.

Profile

Leptin, an endogenous peptide hormone produced mainly by white adipocytes in adipose tissue, is involved in the long-term maintenance of body-weight through regulation of food intake and energy expenditure. Leptin has a negative feedback effect on hypothalamic control of neurotransmitters involved in the control of appetite: thus, an increase in adipose tissue mass results in an increase in leptin concentrations that in turn suppresses expression of appetite stimulatory peptides and vice versa. Mutations of either the leptin receptor or the *ob* gene that encodes the leptin protein result in failure of leptin's control over appetite producing forms of morbid early-onset obesity. However, it is not clear that common obesity (p. 2315.1) is associated with similar genetic mutations or, as also postulated, is associated with functional leptin resistance caused by sustained high leptin concentrations.

Leptin is produced in other tissues, and studies have suggested additional functions and properties including modulation of neuroendocrine, immune, and reproductive processes. The potential role of leptin in a variety of disease states including syndromes of insulin resistance, autoimmune diseases, and cardiovascular disorders is also being studied.

Replacement therapy with recombinant leptin is under investigation in the management of obesity as well as some other disorders including generalised lipodystrophy and hypothalamic amenorrhoea secondary to energy deficits or low body-weight.

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Lerdelimumab *(rINN)*

Lérdelimumab; Lerdelimumabum; Лерделимумаб.
Immunoglobulin G4, anti-(human transforming growth factor β2) (human monoclonal CAT-152 γ4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer.
CAS — 285985-06-0.

Profile

Lerdelimumab is a human monoclonal antibody specific for transforming growth factor β2 that has been investigated for the prevention of excessive postoperative scarring after glaucoma surgery.

Levomenol *(rINN)*

(-)-α-Bisabolol; Lévoménol; Levomenolum; Lewomenol; Левоменол.
(-)-6-Methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol.
$C_{15}H_{26}O$=222.4
CAS — 23089-26-1.
UNII — 24WE03BX2T.

Profile

Levomenol is a sesquiterpene isolated from the volatile oil of chamomile (p. 2474.1). It has been tried as a transepidermal penetration enhancer and is present in many emollient preparations.

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Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aftersun; Confortel; Keracnyl; ***Austria***: Sensicutan; ***Belg.***: Purigel Crisp†; ***Chile***: Cuidado Intimo†; Effaclar H; Eucerin Higiene Intima; Eucerin Piel Grasa†; Queratopil; Ruboril; Suavigel; ***Cz.***: Sensicutan; ***Fr.***: Clean-AC; Dermophil Indien; Ephydrol; Keracnyl eau nettoyante†; Keracnyl; Seborheane†; Squaphane E; ***Ger.***: Mirfulan Spray N; Sensicutan; ***Hong Kong***: Mithra-Intim; ***Israel***: Xclair; ***Ital.***: Alceclar†; Biothymus DS; Broxo al Fluoro; Decon Lavanda; Intim; Pitiren; Resvelife; Saugella Poligyn; Tial-Z; ***Malaysia***: pH Care; ***Mex.***: Aveendix; ***Philipp.***: Mithra-Intim; Nap; ***Port.***: Hidratante VV; ***Singapore***: Bio-Taches Masque†; ***Switz.***: Antidry; Dermophil Indien; Tenderdol; ***Turk.***: Numis; ***UK***: Skin Perfecting Oil; Xclair.

Lexipafant *(BAN, USAN, rINN)*

BB-882; DO-6; Lexipafantum; Лексипафант.
Ethyl *N*-methyl-*N*-[α-(2-methylimidazo[4,5-*c*]pyridin-1-yl) tosyl]-L-leucinate.
$C_{23}H_{30}N_4O_4S$=458.6
CAS — 139133-26-9.
UNII — H14917M9YW.

Profile

Lexipafant is a platelet-activating factor antagonist that is being investigated in the prevention of neurological and renal complications after cardiac surgery. It has also been studied for possible applications in asthma, sepsis, and pancreatitis.

Lignin

Ligniini; Lignină; Lignín; Lignina; Ligninas; Lignine; Лигнин.
CAS — 9005-53-2.

Profile

Lignin is a polymer occurring in plant fibrous tissue; it has been reported to adsorb bile salts and acids, and has been used in the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Filtrum (Фильтрум); Polyphan (Полифан); Polyphepan (Полифепан); ***Ukr.***: Filtrum (Фильтрум)†.

Multi-ingredient Preparations. ***Rus.***: Lactofiltrum (Лактофильтрум); ***Ukr.***: Lactofiltrum-ECO (Лактофильтрум-Эко).

Linseed

Flaxseed; Leinsamen; Lenmag; Lin; Lin, graine de; Linaza; Linfrö; Linho; Lini Semen; Lini Semina; Linum; Lněné semeno; Nasienie lnu; Pellavansiemen; Semilla de Lino; Sėmenys; Льняное Семя.
ATC — A06AC05.
ATC Vet — QA06AC05.
*ATC Herb — HJ01WB5009 (*Linum usitatissimum*: seed); HR05WA5023 (*Linum usitatissimum*: seed); HD02WB5005 (*Linum usitatissimum*: seed); HA06AC5007 (*Linum usitatissimum*: seed).*
UNII — 4110YT348C.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Linseed). The dried ripe seeds of *Linum usitatissimum*. Protect from light.

Profile

Preparations of linseed have been administered for their demulcent and laxative actions. Crushed linseed has been used as a poultice. Linseed is the source of linseed oil, below. Linseed has also been tried as a dietary supplement to improve postmenopausal symptoms, and has been investigated for its potential in reducing the risk of disorders including cardiovascular disease, diabetes mellitus, and malignant neoplasms.

General references.

1. Hall C, *et al.* Flaxseed. *Adv Food Nutr Res* 2006; **51:** 1–97.
2. Basch E, *et al.* Flax and flaxseed oil (Linum usitatissimum): a review by the Natural Standard Research Collaboration. *J Soc Integr Oncol* 2007; **5:** 92–105.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Linoforce; Optomega; ***Chile***: Aloelax; Instalax; ***Fin.***: Femarelle; ***Fr.***: Alpharegul Homme; Feminabiane Meno'Confort; ***Gr.***: Femarelle; ***Hong Kong***: Femarelle; ***India***: Femarelle; ***Israel***: Femarelle†; ***Ital.***: Lignamid; ***Mex.***: Tofupill; ***Norw.***: Femarelle; ***Pol.***: Laxantol†; Ulventroten†; ***Singapore***: Femarelle; ***Spain***: Femarelle; LinoMed; ***Swed.***: Femarelle; ***Switz.***: Linoforce; LinoMed; ***UK***: Femarelle; Linoforce; Salinum; ***USA***: Femarelle; Numoisyn.

Linseed Oil

Aceite de Linaza; Flaxseed Oil; Huile de Lin; Leinöl; Lenolaj; Lin, huile de; Linaza, aceite de; Lini Oleum; Linolja; Lněný olej; Oleum Lini; Pellavaöljy; Sėmenų aliejus; Льняное Масло.
ATC — A06AC05.
ATC Vet — QA06AC05.
*ATC Herb — HD02WB5004 (*Linum usitatissimum*: oil).*
UNII — 84XB4DV00W.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Linseed Oil, Virgin). The oil obtained by cold expression from ripe seeds of *Linum usitatissimum*. A suitable antoxidant may be added. A clear, yellow or brownish-yellow liquid. It turns dark and gradually thickens on exposure to air. When cooled, it becomes a soft mass at about -20 degrees. Relative density about 0.931. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in airtight containers. Protect from light.

Profile

Linseed oil is used in veterinary medicine as a purgative for horses and cattle. In man, linseed oil is included in topical preparations for a variety of skin disorders. It has been tried as a vegetable source of omega-3 fatty acids (p. 1460.1).

Boiled linseed oil ('boiled oil') is linseed oil heated with litharge, manganese resinate, or other driers, to a temperature of about 150 degrees so that metallic salts of the fatty acids are formed and cause the oil to dry more rapidly. It must not be used for medicinal purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Linna-Oil; ***Mex.***: Omelina.

Multi-ingredient Preparations. ***Austral.***: Advanced Menopause Care; Once Daily 50+ Multi; ***Austria***: Dermowund†; ***Canad.***: Prosta Ease; Pure Gardens; ***Fr.***: Kotor Articulations; Neurovitol; ***India***: Adlin; Amizox; Ankare; Arflur; Artifen-D; Artilov; Binpain; Bioflex; Buta-Proxyvon†; Culin; Dacpar; Delaxin-M; Depain; DFO; Diclogen Plus; Dicloran-MS; Dicloriz; Diclowin Active; Dicnac Gelino; Dicnap; Difenac; Difin Plus; Dinecol; Divon; Dofec Plus; Dolobid-M; Dolopar; Dolowin; Duoflam Gel; Duoflam Spy; Elwin-Plus; Enzoflam; Felini; Flexibel; Fortafen; Gelospi; Hooky; Inflahit; Intagesic; Intragesic; Jusgo; Kloser-D; KMR; Lenex; Lenin-D; Linif; Mahadol; Medicreme-Strong; Micronac; Mobigel; Mosvar; Muscodac; Muskel; Nacmol Plus; Nacpo; Nicip Supergel; Nifgel; Noctel; Novalini; Novogel; Novonac; Nugesia; Oligel; Omni; Omnigel; Onspot; Opinac; Orthocos; Orthocure; Orthodac; Orthoris; Osteoflam; Panace; ***Ital.***: Pentaker; ***Mex.***: Optivision; ***Philipp.***: SG-Glutergen; ***Rus.***: Dicloran Plus (Диклоран Плюс); ***Spain***: Cremsol†; ***UK***: Nine Rubbing Oils; ***Ukr.***: Denebol Gel (Денебол Гель); Dicloran Plus (Диклоран Плюс); Dolaren (Доларен).

Lithium Benzoate ⊗

Litio, benzoato de.
$C_7H_5LiO_2$=128.1
CAS — 553-54-8.
UNII — R9Z042Z19E.

Profile

Lithium benzoate has been used as a diuretic and urinary disinfectant. Its use cannot be recommended because of the pharmacological effect of the lithium ion (p. 427.3). Each g contains 7.8 mmol of lithium.

Homoeopathy

Lithium Benzoate has been used in homoeopathic medicines under the following names: Lithium benzoicum; Lithium benz.

Lixivaptan *(USAN, rINN)* ⊗

Lixivaptán; Lixivaptanum; VPA-985; WAY-VPA-985; Ликсиваптан.
3′-Chloro-5-fluoro-4′-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-*o*-toluanilide.
$C_{27}H_{21}ClFN_3O_2$=473.9
CAS — 168079-32-1.
UNII — 8F5X4B082E.

Profile

Lixivaptan is a selective vasopressin V_2-receptor antagonist under investigation for the treatment of hyponatraemia in patients with heart failure.

References.

1. Abraham WT, *et al.* Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol* 2006; **47:** 1615–21.
2. Ku E, *et al.* Lixivaptan: a novel vasopressin receptor antagonist. *Expert Opin Invest Drugs* 2009; **18:** 657–62.

Lobenzarit Sodium *(USAN, rINNM)*

CCA; Lobenzarit disódico; Lobenzarit sódico; Lobenzarit Sodique; Natrii Lobenzaritum; Натрий Лобензарит.
4-Chloro-2,2′-iminodibenzoate disodium.
$C_{14}H_8ClNNa_2O_4$=335.7
CAS — 63329-53-3 (lobenzarit); 64808-48-6 (lobenzarit sodium).
UNII — 7Z9SP74BXF.

Profile

Lobenzarit sodium has been used as an immunomodulator in rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Carfenil.

Lodoxamide *(BAN, rINN)*

Lodoksamidi; Lodoxamid; Lodoxamida; Lodoxamidum; U-42585; Лодоксамид.
N,N′-(2-Chloro-5-cyano-*m*-phenylene)dioxamic acid.
$C_{11}H_6ClN_3O_6$=311.6
CAS — 53882-12-5.
ATC — S01GX05.

ATC Vet — QS01GX05.
UNII — SPU695OD73.

Lodoxamide Ethyl *(BANM, USAN, rINNM)*

Ethylum Lodoxamidum; Lodoxamida etilo; Lodoxamide Ethyle; U-42718; Этил Лодоксамид.
Diethyl *N,N'*-(2-Chloro-5-cyano-*m*-phenylene)dioxamate.
$C_{15}H_{14}ClN_3O_6$=367.7
CAS — 53882-13-6.
UNII — TQY1B8145B.

Lodoxamide Trometamol *(BANM, rINNM)*

Lodoksamid Trometamin; Lodoxamida trometamol; Lodoxamide Trométamol; Lodoxamide Tromethamine (USAN); Lodoxamidum Trometamolum; U-42585E; Лодоксамид Трометамол.
N,N'-(2-Chloro-5-cyano-*m*-phenylene)dioxamic acid compound with trometamol.
$C_{11}H_6ClN_3O_6.2C_4H_{11}NO_3$=553.9
CAS — 63610-09-3.
ATC — S01GX05.
ATC Vet — QS01GX05.
UNII — 50LV9A548L.

Uses and Administration

Lodoxamide has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1225.3). Lodoxamide trometamol is used in eye drops for non-infectious allergic conjunctivitis (p. 611.1), such as vernal keratoconjunctivitis, giant papillary conjunctivitis, and allergic-atopic conjunctivitis; a concentration equivalent to 0.1% of lodoxamide is used, 1 or 2 drops usually being instilled into the eye four times daily.

Lodoxamide has also been studied for its prophylactic effect in the treatment of asthma, but has not proved to be of benefit; it has usually been given orally as the ethyl ester or by inhalation as the trometamol salt.

Conjunctivitis. Lodoxamide is an effective treatment for vernal keratoconjunctivitis.[1,2] There is some evidence that it may be more effective than sodium cromoglicate for this purpose (see Rhinitis and Conjunctivitis, p. 1227.1).

1. Anonymous. Lodoxamide for vernal keratoconjunctivitis. *Med Lett Drugs Ther* 1994; **36:** 26.
2. Lee S, Allard TRFK. Lodoxamide in vernal keratoconjunctivitis. *Ann Pharmacother* 1996; **30:** 535–7.

Adverse Effects

Lodoxamide eye drops may cause local irritation. Reported effects include burning or stinging, and itching. Flushing and dizziness have also been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alomide; ***Austral.***: Lomide; ***Belg.***: Alomide; ***Braz.***: Alomide; ***Canad.***: Alomide; ***Chile***: Alomide†; ***China***: Alomide (阿乐迈); ***Cz.***: Alomide†; ***Denm.***: Alomide; ***Fin.***: Alomide; ***Fr.***: Almide; Lodoxal†; ***Ger.***: Alomide; ***Gr.***: Alomide; Thilomide; ***Hong Kong***: Alomide; ***Hung.***: Alomide; ***Indon.***: Alomide; ***Irl.***: Alomide; ***Israel***: Alomide; ***Ital.***: Alomide; ***Malaysia***: Alomide; ***Mex.***: Alomide; ***Norw.***: Alomide†; ***NZ***: Lomide; ***Philipp.***: Alconmide†; ***Pol.***: Alomide; ***Port.***: Alomide†; ***Rus.***: Alomide (Аломид)†; ***S.Afr.***: Alomide; ***Singapore***: Alomide†; ***Spain***: Alomide; ***Thai.***: Alomide†; ***Turk.***: Alomide; Thilomide; ***UK***: Alomide; ***Ukr.***: Alomid (Аломид); ***USA***: Alomide; ***Venez.***: Alomide.

Lomifylline *(rINN)*

Lomifilina; Lomifyllinum; Ломифиллин.
7-(5-Oxohexyl)theophylline.
$C_{13}H_{18}N_4O_3$=278.3
CAS — 10226-54-7.
UNII — NA91GV8GDJ.

Profile

Lomifylline is a theophylline derivative that has been used in preparations for cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cervilane; Micerfin; ***Braz.***: Norogil; ***Chile***: Cervilane; ***Mex.***: Cervilan.

Loosestrife

Blutweiderichkraut; Fackelblomster; Kyprejová nať; Lythri Herba; Purple Loosestrife; Rantakukka; Raudoklių žolė; Réti fűzényfű; Salicaire; Дербенник.

NOTE. Do not confuse with yellow willowherb, *Lysimachia vulgaris* which is also known as loosestrife.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Loosestrife; Lythri Herba). The dried flowering tops, whole or cut, of *Lythrum salicaria*. It contains not less than 5.0 % of tannins, expressed as pyrogallol and calculated with reference to the dried drug. Protect from light.

Profile

Purple loosestrife, *Lythrum salicaria* (Lythraceae), is used in herbal medicine for the treatment of diarrhoea. It is also used for its astringent and antimicrobial properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Salicairine.

Multi-ingredient Preparations. ***Fr.***: Saugella Dermoliquide; Saugella douceur Poligyn; ***Ital.***: Gynegella P.

Lorenzo's Oil

Lorenzo, aceite de; Масло Лоренцо.

Glyceryl Trierucate

Trierucin.
1,2,3-Propanetriol tri(13-docosenoate).
$C_{69}H_{128}O_6$=1053.8
CAS — 2752-99-0.
UNII — I0IDQ0M20R.

Glyceryl Trioleate

Triolein; Триолеин.
1,2,3-Propanetriol tri(9-octandecenoate).
$C_{57}H_{104}O_6$=885.5
CAS — 122-32-7.
UNII — O05EC62663.

Profile

Lorenzo's oil is a liquid containing glyceryl trierucate (a source of erucic acid) and glyceryl trioleate (a source of oleic acid), in the ratio 1 part to 4 parts respectively. It has been used with dietary modification for the treatment of adrenoleucodystrophy, a genetic disorder characterised by demyelination, adrenal cortical insufficiency, and accumulation of saturated 'very-long-chain fatty acids'.

Adrenoleucodystrophy. Adrenoleucodystrophy is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids results in diffuse and multifocal demyelination of the nervous system and adrenocortical insufficiency. The most common form usually affects children and is characterised mainly by cerebral demyelination; it is usually fatal within a few years. In the adult variant, called adrenomyeloneuropathy, demyelination of the spinal cord and peripheral neuropathy progress slowly over many years.[1,2]

There appears to be no effective treatment for adrenoleucodystrophy or its variants. A high dietary intake of long-chain monounsaturated fatty acids, as provided by the mixture Lorenzo's oil (glyceryl trierucate with glyceryl trioleate), has been tried, the idea being to monopolise the specific enzyme involved in the conversion of long-chain fatty acids to very-long-chain fatty acids. Although dietary therapy with Lorenzo's oil has reduced plasma concentrations of saturated very-long-chain fatty acids, there is no evidence that this improves or delays progression of adrenoleucodystrophy or adrenomyeloneuropathy.[3-6] However, it has been suggested that these disorders may not respond to correction of the biochemical abnormality once neurological damage has occurred.[5] The efficacy of treatment before the appearance of neurological symptoms is currently being studied with some encouraging results.[7] There is some evidence to suggest that the childhood form may have an immunological component, but results using immunosuppressants or immunoglobulins have been reported to be disappointing.[5] Bone marrow transplants may improve symptoms but should only be tried in those with mild cerebral involvement.[1] Lovastatin can also reduce plasma concentrations of very-long-chain fatty acids.[8]

1. van Geel BM, *et al.* X linked adrenoleukodystrophy: clinical presentation, diagnosis, and therapy. *J Neurol Neurosurg Psychiatry* 1997; **63:** 4–14.
2. Moser HW, *et al.* Adrenoleukodystrophy: new approaches to a neurodegenerative disease. *JAMA* 2005; **294:** 3131–4.
3. Aubourg P, *et al.* A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. *N Engl J Med* 1993; **329:** 745–52.
4. Kaplan PW, *et al.* Visual evoked potentials in adrenoleukodystrophy: a trial with glycerol trioleate and Lorenzo oil. *Ann Neurol* 1993; **34:** 169–74.
5. Rizzo WB. Lorenzo's oil—hope and disappointment. *N Engl J Med* 1993; **329:** 801–2.
6. van geel BM, *et al.* Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil". *J Neurol Neurosurg Psychiatry* 1999; **67:** 290–9.
7. Moser HW, *et al.* Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. *Arch Neurol* 2005; **62:** 1073–80.
8. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; **69:** 312–22.

Adverse effects. Thrombocytopenia has been reported in patients receiving Lorenzo's oil, although patients are often asymptomatic.[1] It is possible that giant platelets which retain most of their function are produced and that these are not counted by automatic counting procedures giving a false impression of thrombocytopenia.[2]

Lymphocytopenia with an increased incidence of infection has also been reported in few patients.[3]

1. Zinkham WH, *et al.* Lorenzo's oil and thrombocytopenia in patients with adrenoleukodystrophy. *N Engl J Med* 1993; **328:** 1126–7.
2. Stöckler S, *et al.* Giant platelets in erucic acid therapy for adrenoleukodystrophy. *Lancet* 1993; **341:** 1414–15.
3. Unkrig CJ, *et al.* Lorenzo's oil and lymphocytopenia. *N Engl J Med* 1994; **330:** 577.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: GTO Oil.

Lovage Root

Gelsvių šaknys; Korzeń lubczyka; Lestyángyökér; Levistici Radix; Levístico; Libečkový kořen; Libstickerot; Liebstöckelwurzel; Liperinjuuri; Livèche (racine de); Livèche, racine de; Корень Любистока.
UNII — 46QZ19OEX8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lovage Root). The whole or cut, dried rhizome and root of *Levisticum officinale*. The whole drug contains not less than 0.4% v/w of essential oil and the cut drug not less than 0.3% v/w of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Lovage root is used in herbal medicine for gastrointestinal and urinary-tract disorders. The leaves and seeds or fruit of lovage are used as a culinary herb and flavouring.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Ehrenhofer-Salbe; ***Cz.***: Zaludecni Cajova Smes; ***Fr.***: NurAiD; ***Ger.***: Canephron N; Nephroselect M; ***Rus.***: Canephron N (Канефрон Н); Wantong Artiplas (Ваньтун Артиплас); ***Switz.***: Tisane pour les reins et la vessie; ***UK***: Cystipret; ***Ukr.***: Canephron N (Канефрон Н); Uronephron (Уронефрон).

Homoeopathic Preparations. ***Ger.***: Levisticum S; Regenaplex Haut G; ***Switz.***: Regenaplex Nr. 79; ***UK***: Fragador.

Luffa

Loofah; Люффа.
UNII — F0R3Y60C6V.

Profile

Luffas are tropical and subtropical vines of the genus *Luffa* (Cucurbitaceae). The dried fibre of the fruits (luffa sponge) of *Luffa acutangula, L. aegyptiaca,* and *L. operculata* has traditionally been used in herbal medicine for symptoms of upper respiratory-tract disorders; the fruit pulp of some species was also used as a purgative.

The young fruits of some species are eaten as a vegetable. Luffa sponge is also used as a mildly abrasive bathing sponge.

Homoeopathy

Luffa has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Sinustrat.

Homoeopathic Preparations. ***Austria***: Delufen; Erbiode Heuschnupfen; Euphorbium Compositum; Globuli gegen Schnupfen

Nr 2; Globuli gegen Schnupfen Nr 3; Heuschnupfenmittel DHU†; Luffa compositum-Heel; Luffa Med Complex; Metavirulent; Rhododendroneel; ***Canad.***: Euphorbium Compositum; Euphorbium Compositum; Luffeel Nasal Spray; ***Cz.***: Euphorbium Compositum; Luffeel; Luffeel; ***Ger.***: Allergo-Loges; Allergokatt; Cefaluffa†; Euphorbium comp SN; Heuschnupfenmittel; Heuschnupfenmittel; Luffa Nasentropfen; Luffasan; Luffeel Comp; Luffeel Comp; metavirulent; Pollinosan†; Schleimhaut-Komplex L Ho-Fu-Complex; Sinupas; Sinusitis Hevert SL; Sinusitis-Weliplex†; ***Hung.***: Luffeel; Luffeel; ***Neth.***: Bronchilite; Euphorbium comp; Holergie; Homeocare Allerlo; Homeocare neusspray; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Lergilite; Luffanil; Luffeel H; Luffeel H; Nisyspray; Ricura; Sinufleur; ***Rus.***: Aphlubin-Naze (Афлубин-Назе); Delufen (Делуфен); Rhinital (Ринитал); ***S.Afr.***: Euphorbium Compositum S†; ***Switz.***: A Vogel pour les sinus; A Vogel Spray contre le rhume des foins; HerbAllerg; Pollinosan†; ***Ukr.***: Delufen (Делуфен); Rhinital (Ринитал).

Lungmoss

Lung Lichen; Lunglav; Lungwort; Oak Lungwort; Tree Lungwort.

UNII — D1YM0P5Z2T.

NOTE. The names lungmoss, lungwort, and oak lungs have also been applied to the plant *Pulmonaria officinalis*.

Profile

Lungmoss, the lichen *Lobaria pulmonaria* (*Sticta pulmonaria*) (Lobariaceae), is included in herbal medicines for pulmonary disorders.

Homoeopathy

Lungmoss has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Port.***: Stodal.

Homoeopathic Preparations. ***Austral.***: Hay Fever; ***Austria***: Anfokali; Bronchalis-Heel; ***Canad.***: Allergies; Bronkeel†; Hay Fever; Homeo-Form AL†; Homeo-Form SI†; Kids Allergies; Nareel†; Sinus; ***Cz.***: Bronchalis-Heel; Stodal; ***Fr.***: Homeodose 8†; Stodal; Stodal; ***Ger.***: Jutussin; Pulmo Bronchialcomplex; Pulmo Bronchialcomplex; Schleimhaut-Komplex L Ho-Fu-Complex; ***Hung.***: Anfokali; Bronchalis-Heel; Naso-Heel S; Stodal; ***Neth.***: Bronchalis; Jutussin R9; Stodal; ***Rus.***: Stodal (Стодаль); ***Switz.***: Bronchalis-Heel; Regenaplex Nr. 24c; Stodal; ***Ukr.***: Stodal (Стодаль); ***USA***: Preferred Remedies Allergy; Preferred Remedies Sinus.

Luprostiol *(BAN, rINN)*

Luprostioli; Luprostiolum; Лупростиол.

(±)-(*Z*)-7-{(1*S*,2*R*,3*R*,5*S*)-2-[(2*S*)-3-(3-Chlorophenoxy)-2-hydroxypropylthio]-3,5-dihydroxycyclopentyl}hept-5-enoic acid.

$C_{21}H_{29}ClO_6S$=445.0

CAS — 67110-79-6.

ATC Vet — QG02AD91.

UNII — HWR60H5GZB.

Profile

Luprostiol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Lupulus

Apynių spurgai; Chmelová šištice; Hop Strobile; Hopfenzapfen; Hops; Houblon; Houblon, cône de; Humalankukka; Humlekotte; Humulus; Komlótoboz; Lupuli flos; Lupuli Strobulus; Lúpulo; Strobili Lupuli; Szyszka chmielu.

ATC Herb — HN05CM5004 (Humulus lupulus: cone); HA09WA5015 (Humulus lupulus: cone); HN05CM5005 (Humulus lupulus: glandular hair).

UNII — 01G73H6H83.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hop Strobile). The dried, generally whole, female inflorescences (strobiles) of the hop plant *Humulus lupulus*. It has a characteristic aromatic odour. Protect from light.

Profile

Lupulus has been used as a bitter, and supplies the characteristic flavour of beers. It is used in herbal and folk medicine as a sedative.

Homoeopathy

Lupulus has been used in homoeopathic medicines under the following names: Humulus lupulus; Lupulinum; Humulus lupulus e glandulis; Humulus; Lupul.

All cross-references refer to entries in Volume A

References.

1. Zanoli P, Zavatti M. Pharmacognostic and pharmacological profile of *Humulus lupulus* L. *J Ethnopharmacol* 2008; **116:** 383–96.

Interactions. For a suggestion of a potential interaction between lupulus and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Novo-Passit (Ново-Пассит); ***Swed.***: Valerina; ***Switz.***: Klosterfrau Nervenruh Dragees.

Multi-ingredient Preparations. ***Arg.***: Calmtabs; ***Austral.***: Chill Pill; Cold & Flu Day/Night; Executive Sleep Formula; Extralife Sleep-Care†; Humulus Compound; Natural Deep Sleep†; Passionflower Plus†; PM Dreamtime; ReDormin; Sleep Easy; Tranquil Night; ***Austria***: Baldracin; Hova; Montana; Nervenruh; Nerventee St Severin; Schlaf- und Beruhigungsdragees; Wechseltee St Severin; ***Braz.***: Remilev; ***Canad.***: Calm-Aid†; Detente†; Herbal Insomnia†; Herbal Nerve†; Myoplex†; Relax Plus; Relaxant; Relaxol; Salusan†; Sleep Relax; ***Chile***: Cellenergy; Valupass; ***Cz.***: Baldracin†; Calmonal†; Detsky Caj s Hermankem; Doppelherz Energie-Tonikum†; Fytokliman Planta; Hova; Novo-Passit; Sanason†; Species Nervinae Planta; Valofyt Neo†; ***Fr.***: Diatisan†; Santane N_9; Tone; ***Ger.***: Alluna Nacht†; Allunapret; Ardeysedon; Avedorm duo†; Baldrian-Dispert Nacht†; Einschlaf-Kapsein extra†; Granu Fink Femina; Ilja Rogoff; Kneipp Gute Nacht†; Kytta-Sedativum; Moradorm S; Nervenkapseln; Pascosedon; Sedacur; Sedaselect D; Selon; ***Gr.***: Vivinox; ***Hung.***: Cirkulin Valeriana; Doppelherz Energie Tonikum N; Hova; Kalms; Montana; ReDormin; Sedacur; ***Irl.***: Avena Sativa Comp; Quiet Life; ***Israel***: Nerven-Dragees; Redormin Night; ***Ital.***: Altadrine Firming†; Calmason; Emmenoiasi; Eugune; Osteo Complex; ***Jpn***: Eki Cabe A†; ***Mex.***: Ivel†; Nervinetas; ***Neth.***: Plantival; ***Norw.***: Valerina Natt; ***Philipp.***: Sleepasil; ***Pol.***: Calmina; Doppelherz Energovital Tonik†; Hova; Kalms; Klimax; Lekosen†; Lumewal; Lunapret; Nervendragees; Nervinolum; Nervinum†; Nervomix; Nervosol; Nerwobonisol; Passispasmin; Passispasmol†; Sedomix; Somnoten†; Tabletki Uspokajajace; Vallup†; Valuherb; Valused; ***Rus.***: Cedoflor (Седофлор); Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Kliophyt (Клиофит); Passifit (Пассифит); Sanason (Санасон); Sedativae Species No 2 (Седативный Сбор 2); Urocholesan (Урохолесан); Urolesan (Уролесан); ***S.Afr.***: Avena Sativa Comp†; ***Spain***: Tranquigor; ***Swed.***: Dormeasan; Sedacur; ***Switz.***: Baldriparan; Dormeasan; Dragees pour la detente nerveuse et le sommeil†; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Femisan; Gouttes pour le coeur et les nerfs; Hova; Hyperiforce comp; Nervinetten; ReDormin; Relaxo; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; Valverde Coeur; Valverde Sommeil; Zeller Sommeil; ***UK***: Anased; Avena Sativa Comp; Chamomile Blend; Dormeasan; Estroven Nighttime; Gerard House Serenity; Gerard House Somnus; Goodnight; HRI Calm Life; HRI Night; Kalms Day; Kalms Sleep; Kalms; Natrasleep; Neurotone; Newrelax; Nodoff; Nytol Herbal; Puncto SleepTight; Quiet Days; Quiet Life; Quiet Nite; Quiet Tyme; Relax B*; Slumber; Sominex Herbal; Stressless; Unwind Herbal Nytol; Valerian Passiflora and Hops; Valerina Night-Time; Ymea; ***Ukr.***: Florised (Флорисед); Herbastress (Гербастресс); Herbion Sedative Drops (Гербион Успокаивающие Капли)†; Lifemin (Лайфемин); Novo-Passit (Ново-Пассит); Sanason (Санасон)†; Sedavit (Седавит); Trivalumen (Тривалумен); Urochol (Урохол)†; Urolesan (Уролесан); ***Venez.***: Insocaps; Lupassin; Nervinetas.

Homoeopathic Preparations. ***Austral.***: Sleep & Insomnia Relief; ***Austria***: Valerianaheel; ***Canad.***: Calms Forte; Calsom†; Hylands Formula C; Hylands Formula CF; Valerianaheel Comp†; ***Ger.***: Alho-Sedosan; Antimast TN†; Avena sativa comp†; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; Nervoregin; Neuro-Ginsan N; Passiflora Complex†; Seda-Do; Sedacalman; Sedaphin†; Thyreo-Injektopas; Tondinel H; ***Neth.***: Weleda Avena Valeriana; ***Rus.***: Passidorm (Пассидорм); ***Switz.***: Nelsons Noctura†; ***USA***: Preferred Remedies Sleep.

Lycopene

E160(d); Ликопин.

$C_{40}H_{56}$=536.9

CAS — 502-65-8 (all-trans lycopene).

UNII — SB0N2N0WV6.

Pharmacopoeias. In *US* which also includes Tomato Extract Containing Lycopene.

USP 36: (Lycopene). A mixture of geometrical isomers of lycopene. Store in airtight containers under an inert gas at a temperature of 8 degrees to 15 degrees. Protect from light.

Profile

Lycopene is a carotenoid responsible for the red colour of tomatoes and some other fruits including rose fruit (p. 2607.1). Many isomeric forms of lycopene are possible but the *all-trans* lycopene is the most common form present in food. Lycopene is used as a colouring agent and antoxidant. Much interest has been expressed in the antoxidant properties of lycopene for the potential prevention of diseases such as cardiovascular disease and some cancers, particularly of the prostate gland. Lycopene is used as a dietary supplement and is also an ingredient of some skin preparations; it has also been included in oral tanning preparations.

References.

1. Rao AV, *et al.* Lycopene. *Adv Food Nutr Res* 2006; **51:** 99–164.
2. Riccioni G, *et al.* Protective effect of lycopene in cardiovascular disease. *Eur Rev Med Pharmacol Sci* 2008; **12:** 183–90.

Malignant neoplasms. There has been continuing interest in the potential role of tomatoes and lycopene in the prevention of various cancers.[1,2] However, an evidence-based review of the literature by the FDA[3] concluded that there was no credible evidence to support claims that tomatoes or tomato-based foods reduced the risk for lung, colorectal, breast, cervical, or endometrial cancer. The FDA also concluded that there was very limited credible evidence for qualified health claims for tomatoes or tomato sauce and a reduced risk of prostate, gastric, ovarian, and pancreatic cancers. They also found no credible evidence to support health claims for lycopene and a reduced risk of any of the cancers evaluated.

1. Everson KM, McQueen CE. Lycopene for prevention and treatment of prostate cancer. *Am J Health-Syst Pharm* 2004; **61:** 1562–6.
2. Dahan K, *et al.* Lycopene in the prevention of prostate cancer. *J Soc Integr Oncol* 2008; **6:** 29–36.
3. Kavanaugh CJ, *et al.* The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. *J Natl Cancer Inst* 2007; **99:** 1074–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Licopenox; ***Braz.***: Licco; ***Chile***: Lycoprost; ***India***: Lycbound; Lycorich Plus; ***UK***: Ateronon.

Multi-ingredient Preparations. ***Arg.***: Natubrown; Prostamen; Reversal; Selder; ***Austral.***: Advanced Prostate Care; Homme-F; Menevit; Prostate Care; Womens Multi; ***Braz.***: Licopene†; Licovit; Licoxid; Lymium; Tomat; ***Chile***: Dennov; ***Fr.***: Actymine†; Actypral†; Anti-oxydant 200; Anti-oxydant F4; Corvitec; GliSODine Solaire; Imedeen Prime Renewal†; Imedeen Tan Optimizer†; Oxelio Topique; Phytosolaire†; ***Hong Kong***: Palmetto Plus†; ***India***: Actioner; Adrovit; Alcored; Aritom-L; Asi-Min MV; Aza Cap; Basix-LB; Betagan Forte; Betonin-XT; C-Rich; Cad-11; Cadred; Calorex; Calorex; Cardistim; Coq Forte; Crotec-EC; Diasafe; Doravit Forte; Ecome-LY; Elgrape; Elnutra-M; Elnutra; Enduranz; Evion Forte; Exerge; Feribest-L; Fol-G2; Furtipil-L; Gardian; Gatdor; Gemvit; GV-24; Hi-Q; Hyrase; Immunace Forte; Imuvit; Ipene; Joyce; Keeper Plus; L-Bex; L-Mato; L-Nit; L-Vit-Z; Layo; Leclub; Legain; Lifored; Lizace; Lutamin; Lutivit; Lyco-First; Lyco-First; Lycoact; Lycoage; Lycobal Forte; Lycobel; Lycobel; Lycobig; Lycobion; Lycobond; Lycocare; Lycocos; Lycoden-M; Lycodric; Lycofact Plus; Lycofit; Lycofol; Lycofresh; Lycogold; Lycogreen; Lycolar; Lycolife; Lycomato; Lycomato; Lycomax; Lycomin; Lycomint; Lycominvit; Lyconerve; Lyconet Green; Lyconia; Lyconova; Lycoral-Z; Lycored; Lycos-CZ; Lycosel; Lycoshine; Lycosim; Lycosta; Lycostar-CM; Lycostar; Lycoswift; Lycosym; Lycosym; Lycour; Lycovit; Lycoxy; Lycozin; Lycra; Lynet; Lyrich-G; Lyrich; Lyrich; Lyto; Lytox; Megagin; Memi-LB; Mitavin; Momvita; Multilipius; Multivite Gold; Multivite Vision; Multivite Woman; Multoxid; Myco-L; N-Rich; Natoz; NBOxid; Nervic Plus; Neuroage Plus; Neuroage Plus; Niloxid; Nislutin; Nutiva-Lyco; Olyco Plus; Omaato; Oncovit; Orymax; Orymax; Oxyla-AL; Oxylyco; ***Indon.***: Amaropo Plus; Antox; Kapset; Legres; Legreskin; Liproqy; Lycoq†; Lycoten; Lycoxy; Lyphen; Noros; Ocu-V; Optha-LL; Optimax Plus; Optimax; Oxypen; Reticopen; Retivit Plus; Stacare; ***Israel***: Multivitamin; Quantum; ***Ital.***: Adrusen; Zeadema Crono; ***Malaysia***: Glow; Lycovid; Pynocare-white; ***Philipp.***: Gloww; Havitall; Nutricap; Nutrotal; Polynerv-E with lecithin; ***Singapore***: Glow; Palmetto Plus†; Vitaton Gold; ***Turk.***: Prostamen; ***Ukr.***: Oko-Health (Око-хелс); OxyLic (ОксиЛик); ***USA***: Alive Mens Energy; Bladder 2.2; Cardio Tone; Certavite Senior with Antioxidant Nutrients; Clinical Nutrients 50-Plus Men; Corvita; Corvite Free; Fitness Tabs for Men; Fitness Tabs for Women; Immunicare; Ocuvite Eye + Multi; One A Day Men's Health Formula; PreQue 10; REQ49+; Triveen-Ten; Udamin SP; Udamin.

Lycopodium

Blitzpulver; Hexenmehl; Licopodio; Lycopod; Lycopode; Streupulver; Vegetable Sulfur; Vegetable Sulphur; Witch Meal.

CAS — 8023-70-9.

ATC Herb — HD02WX5003 (Lycopodium clavatum: spore).

UNII — C88X29Y479.

Profile

Lycopodium, the spores of *Lycopodium clavatum* (see p. 2547.1) and related species, has been used as a pharmaceutical excipient and in herbal medicines for liver and biliary-tract disorders. It was also formerly used for bladder disorders and in dusting powder for skin conditions.

Lycopodium is flammable and has been included in explosives and fireworks.

Homoeopathy

Lycopodium has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Magnesia Phosphorica I Oligoplex.

Homoeopathic Preparations. ***Austral.***: Homoderma; IBS Eze; Stomach Calm; ***Canad.***: Bioactiv R†; Bioactiv S†; Calms Forte 4 Kids; Comp-Drops 8 Uri-Tract†; Cynara Complex†; Earache; Formula ES 211; Formula FV 213; Indigestion†; ***Chile***: Arnica Hamamelis Compuesta; Bioactiv R; Bioactiv S; Silik; ***Fr.***: Abbe Chaupitre no 59†; Abbe Chaupitre no 79†; Amphosca Orchitine; Amphosca Ovarine; Basilicum Complexe No 96; Boripharm No 15†; Grindelia Complexe No 58; Homeodose 24†; L 114; Myosotis Complexe No 63†; Natrum Carbonicum Complexe No 10†; Yucca Complexe No 110; ***Ger.***: Bomagall; Cholo 2-injektopas; Galloselect; Haemorrhoid-Gastreu N; Hepa-Gastreu N R7; Hepa-Loges N; Hepar comp; Hevertnier Complex N†; Hexacyl; Juv 110; Leber Albin; Lymphdiaral; Pancreas-Gastreu N; Stoma-Gastreu S R5; Tondinel.

Lycopodium Clavatum

Almindelig Ulvefod; Bärlapp; Buck Horn; Clavatum; Club Moss; Common Clubmoss; Elk-moss; Foxtail; Ground Pine; Katinlieko; Keulenbärlapp; Mattlummer; Metsäkatinlieko; Plavúň Obyčajný; Plavuň Vidlačka; Running Clubmoss; Shen Jin Cao; Stag's-horn Clubmoss; Vanlig Mattlummer; Wolf's Claw.

ATC Herb — HG04BW5021 (Lycopodium clavatum: herb).

UNII — 005ICF6L27.

Profile

The aerial parts of *Lycopodium clavatum* (Lycopodiaceae) have traditionally been used in herbal medicine for bladder and kidney disorders. Several species of *Lycopodium* are reported to contain toxic alkaloids. The spores of *Lycopodium clavatum*, known as Lycopodium, are also used (see p. 2546.3).

Homoeopathy

Lycopodium clavatum has been used in homoeopathic medicine.

References.

1. Ma X, Gang DR. The Lycopodium alkaloids. *Nat Prod Rep* 2004; **21:** 752–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Toxicol; ***Malaysia***: Elgucare.

Homoeopathic Preparations. ***Austral.***: Respatona Nasal Spray Decongestant; ***Austria***: Lymphdiaral; Nux Vomica-Homaccord; ***Canad.***: Adrisin†; Amphosca†; Carduus Plex†; Cruroheel S†; Digestion; Headache & Migraine; Hecocur†; Hepar Compositum; Homeo-Form MI†; Homeo-Form PMT†; Hylands Gas; Jet Lag; PMS; Rhinar†; ***Chile***: Artroplex; Bioactiv F; Bioactiv I; ***Cz.***: Hepeel; ***Fr.***: Cimicifuga Complexe No 21†; ***Ger.***: Asthmakhell N; Choanol N; Colintest-Gastreu; Heparanox H; Lowe-Komplex Nr 6; Marianon Hepar; Nuxal comp; Nuxal H; Ventrigutt M; ***Hung.***: Hepeel; ***Neth.***: Acidolite; Aesculus Comp; Ambheel; Apo-Hepat; Asakell; Asthmakhell†; Bronchilite; Colintest-Gastreu R37; Dermafleur; Dermalite; Dolilite; Emvita 26; Emvita 7; Hemorrolite; Hepa-Gastreu R7; Hepalite; Hepeel H; Lymphdiaral; Nux Vomica-Homaccord; ***Rus.***: Iris-Plus (Ирис-Плюс); Rhus-Plus (Рус-Плюс); ***Switz.***: Hepeel; Regenaplex Nr. 31b; Regenaplex Nr. 51c; ***Ukr.***: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); ***USA***: Preferred Remedies Stress.

Lysergide *(BAN, rINN)*

Lisergida; Lisérgido; LSD; LSD-25; Lysergic Acid Diethylamide; Lysergidum; Лизергид.

(+)-*NN*-Diethyl-D-lysergamide; (6a*R*,9*R*)-*NN*-Diethyl-4,6,6a,7,8,9-hexahydro-7-methylindolo[4,3-*fg*]quinoline-9-carboxamide.

$C_{20}H_{25}N_3O$=323.4

CAS — 50-37-3.

UNII — 8NA5SWF92O (lysergide); 5S94F6A36E (l-lysergide).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of lysergide:

25; 25s; 100s; A; Acid; Acid tabs; Acido; Aeon flux; Alice; Alphabet; Angel tears; Angry paper; Animal; Barrels; Bart Simpson; Battery acid; Beast; Beavis & Butthead; Bells; Bevis & Butthead; Big D; Big daddy; Bird head; Birdhead; Black acid; Black star; Black sunshine; Black tabs; Blackbird; Blaze; Blotter; Blotter acid; Blotter cube; Blotters; Blue acid; Blue barrels; Blue chairs; Blue cheers; Blue fly; Blue heaven; Blue heavens; Blue microdot; Blue mist; Blue moons; Blue star; Blue tabs; Blue vials; Boomers; Brown bombers; Brown dots; Buvard; California sunshine; Cap; Caps; Casper the ghost; Caviar; Cheap basing; Cheers; Chief; Chinese dragons; Cid-drip the entertainer; Chocolate chips; Church; Cid; Class; Coffee; Colors; Comic book; Conductor; Contact lens; Crackers; Crystal; Crystal tea; Cube; Cupcakes; D; Deeda; Dental floss; Diablo; Dinosaurs; Domes; Dose; Doses; Dosure; Dots; Double dome; Dragon; DSL; El Cid; Electric Kool Aid; Ellis Day; Elvis; Eye Candy; Felix; Felix the Cat; Fields; Flash; Flashers; Flat blues; Flats; Flying triangle; Frogs; Fry; Gel; Gel caps; Gelatine squares; Geltab; Ghost; God's flesh; Golden dragon; Golf balls; Goofy's; Gooney birds; Grape parfait; Green double domes; Green single dome; Green single domes; Green wedge; Grey shields; Groovy lemon; Hats; Hawaiian sunshine; Hawk; Haze; Head light; Head lights; Headlights; Heaven; Heavenly; Heavenly blue; Illusions; Infinity; Instant zen; Jesus Christ acid; Kaliedescope; Keys to the kingdom; L; LAD; Lake Shore Drive; Laogor; Lason daga; Lason sa daga; Lavender; LBJ; Leary's; Lenos; Lens; Lids; Lime acid; Little smoke; Live, Spit and Die; Logor; Loony Toons; LSD; LSD-25; Lucy; Lucy in the sky with diamonds; Magic Tickets; Mellow yellow; Mickey's; Microdot; Microdots; Midnight Quinn; Mighty Quinn; Mikes; Mind blow; Mind detergent; Mist; Mister Natural; Monstre rouge; Monstre vert; Monterey Purple; Moons; Mother of God; Newspapers; One way; One-way; Optical illusions; Orange ba; Orange barrels; Orange cubes; Orange haze; Orange micro; Orange sunshine; Orange wedges; Owsley; Owsley's acid; Owsley's blue dot; Ozzie's stuff; Pane; Paper; Paper acid; Peace; Peace tablets; Peaks; Pearly gates; Pellets; Pepa; Phoenix; Pills; Pink blotters; Pink panther; Pink robots; Pink wedge; Pink wedges; Pink witche; Pink witches; Pizza; Potato; Pure love; Purple barrels; Purple dome; Purple dots; Purple flats; Purple gel tabs; Purple haze; Purple hearts; Purple mikes; Purple ozoline; Purple wedge; Pyramid; Pyramids; Rain Drops; Rainbow; Recycle; Red lips; Rips; Royal blue; Royal blues; Roz-rox; Russian sickles; Sacrament; Sandoz; Serenity; Sheets; Shields; Sherman; Sid; Smears; Smiley; Snowmen; South parks; Specks; Square dancing tickets; Squirrel; Stamp; Stanley's stuff; Star; Strawberries; Strawberry; Strawberry fields; Sugar; Sugar cubes; Sugar lumps; Sunrise; Sunshine; Sunshine Acid; Superman; Syd; T; Tab; Tabs; Tail lights; Teddy bears; The Ghost; The Hawk; Ticket; Tickets; Ticket to ride; Timothy Leary; Timothy Leary Ticket; Trip; Trippers; Trips; Twenty-five; Uncle Sid; Uncle Sidney; Valley dolls; Vodka acid; Volcano 5; Vulcoes; Wafer; Waffles; Watercolors; Wedding bells; Wedge; Wedges; White dust; White lightning; White Owsley's; Window glass; Window pane; Woodstock; Yellow; Yellow dimples; Yellow sunshine; Yellows; Ying Yang; Zen; Zig Zag man.

Profile

Lysergide was formerly used therapeutically but is now encountered as a drug of abuse for its hallucinogenic and psychedelic properties.

There is considerable variation in individual reaction to lysergide. Disorders of visual perception are among the first and most constant reactions to lysergide. Subjects may be hypersensitive to sound. Extreme alterations of mood, depression, distortion of body image, depersonalisation, disorders of thought and time sense, and synaesthesia may be experienced. Anxiety, often amounting to panic, may occur (a 'bad trip'). Duration of effects may last for up to 12 hours after ingestion, although hallucinations can sometimes last up to 48 hours and psychoses for up to 4 days. The effects of lysergide may recur months after ingestion of lysergide; the recurrence or 'flashback' may be spontaneous or induced by alcohol, other drugs, stress, or fatigue.

The subjective effects of lysergide may be preceded or accompanied by somatic effects that are mainly sympathomimetic in nature and include mydriasis, tremor, hyperreflexia, hyperthermia, piloerection, muscle weakness, and ataxia. There may be nausea and vomiting and increased heart rate and blood pressure. Derangement of blood clotting mechanisms has been described. In addition, respiratory arrest, convulsions, and coma may result from overdoses. There is no evidence of fatal reactions to lysergide in man, although accidental deaths, suicides, and homicides have occurred during lysergide intoxication.

Tolerance develops to the behavioural effects of lysergide after several days and may be lost over a similar period. There is cross-tolerance between lysergide, mescaline, and psilocybine and psilocin, but not to amfetamine or to cannabis.

Physical dependence on lysergide does not seem to occur.

Mace Oil

Macis, aceite de; Мацисовое Масло.

ATC Herb — HM02AW5010 (Myristica fragrans: essential oil); HA03AW5040 (Myristica fragrans: essential oil).

UNII — 9KKX6I0U7Z.

NOTE. Mace has also been used as a name for solutions of chloroacetophenone (p. 2475.3), a tear gas.

Profile

Mace oil is a volatile oil obtained by distillation from mace, the arillus of the seed of *Myristica fragrans* (Myristicaceae).

Nutmeg (p. 2573.1) is the dried kernel of the seed of *M. fragrans*.

Mace is used as a flavour and carminative similarly to nutmeg. It has also been used with herbal substances and other volatile agents in preparations for musculoskeletal and respiratory-tract disorders. As with nutmeg, large doses of mace may cause epileptiform convulsions and hallucinations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: China-Eisenwein†; ***Cz.***: Dr Theiss Schwedenbitter†; Original Schwedenbitter; ***Hung.***: Bano Svedkeseru; ***Rus.***: Himcolin (Химколин).

Macrogols

Macrogola; Macrogole; Macrogoles; Macrogoller; Makrogoler; Makrogoliai; Makrogolit; Makrogolok; Makrogoly; PEGs; Polietilen Glikoller; Polietilenglicoles; Polyethylene Glycols; Polyoxyethylene Glycols; Макроголы.

$CH_2(OH)(CH_2OCH_2)_nCH_2OH$. Alternatively some authorities use the general formula $H(OCH_2CH_2)_nOH$ when the number assigned to *n* for a specified macrogol is 1 more than that of *m* in the first formula.

CAS — 25322-68-3 (macrogols); 37361-15-2 (macrogol 300).

ATC — A06AD15.

ATC Vet — QA06AD15.

Nomenclature. Macrogol is *BAN* and *rINN*. The name is followed by a figure which corresponds approximately to its average molecular weight.

Pharmacopoeias. Macrogols of various molecular weights are included in many pharmacopoeias.

Eur. (see p. vii) has a general monograph describing macrogol 300, 400, 600, 1000, 1500, 3000, 3350, 4000, 6000, 8000, 20 000, and 35 000. *USNF* has a general monograph describing Polyethylene Glycol which requires that it be labelled with the average nominal molecular weight as part of the official title.

Ph. Eur. 8: (Macrogols). Mixtures of polymers with the general formula $H(OCH_2CH_2)_nOH$, where *n* represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

Macrogol 300, 400, and 600 are clear, viscous, colourless or almost colourless, hygroscopic liquids. Miscible with water; very soluble in alcohol, in acetone, and in dichloromethane.

Macrogol 1000 is a white or almost white, hygroscopic solid with a waxy or paraffin-like appearance. Very soluble in water; freely soluble in alcohol and in dichloromethane.

Macrogol 1500 is a white or almost white solid with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; freely soluble in alcohol.

Macrogol 3000 and 3350 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; very slightly soluble in alcohol.

Macrogol 4000, 6000, and 8000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; practically insoluble in alcohol.

Macrogol 20 000 and 35 000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water; practically insoluble in alcohol; soluble in dichloromethane.

All macrogols are practically insoluble in fatty oils and in mineral oils. All macrogols should be stored in airtight containers.

USNF 31: (Polyethylene Glycol). Addition polymers of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups. They may contain a suitable antoxidant. Each macrogol is usually designated by a number that corresponds approximately to its average molecular weight. As the average molecular weight

increases, the water solubility, hygroscopicity, and solubility in organic solvents decrease, while the viscosity increases.

Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids, having a slight, characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material having a consistency similar to beeswax, or as creamy-white flakes, beads, or powders. Liquid grades are miscible with water; solid grades are freely soluble in water; all grades are soluble in alcohol, in acetone, in chloroform, in ethoxyethanol, in ethyl acetate, and in toluene; all grades are insoluble in ether and in hexane. The pH of a 5% solution of a macrogol in water is between 4.5 and 7.5.

Store in airtight containers.

Incompatibility. Macrogols can have oxidising activity leading to incompatibilities. The activity of bacitracin or benzylpenicillin may be reduced in a macrogol base. Some plastics are softened by macrogols.

Uses and Administration

Macrogols are relatively stable, non-toxic compounds which have a range of properties depending on their molecular weight. They are widely used in pharmaceutical manufacturing as water-soluble bases for topical preparations and suppositories, as solvents and vehicles, and as solubilising agents, tablet binders, plasticisers in film coating, and tablet lubricants. Macrogols of high molecular weight such as macrogol 4000 have been used as inert markers in studies on intestinal absorption and excretion.

A mixture of macrogol 3350 or 4000 with electrolytes is used for **bowel preparation** before colonoscopy, radiological procedures, or surgery. These preparations have been formulated so that the osmotic activity of the macrogol and concentrations of the electrolytes result in a minimum net effect on the fluid and electrolyte balance. Reconstituted aqueous solutions of different preparations contain about 59 g, 60 g, 100 g, or 105 g of the macrogol per litre. The method of administration is similar for most preparations irrespective of the concentration of macrogol in the final solution. Adults are given 200 to 300 mL of the reconstituted aqueous solution, which should be swallowed rapidly, and this is repeated every 10 to 15 minutes until the rectal effluent is clear, or until a total of 3 to 4 litres of the solution has been consumed. Alternatively, 2 litres of reconstituted solution is taken in the evening preceding the clinical procedure, and a further 2 litres early in the morning on the day of the procedure. Bowel evacuation usually begins about 1 hour after starting dosage and is complete in about 4 hours. Patients should take no solid food for at least 2 hours before starting the course, although best results are obtained if the period of fasting is 3 to 4 hours. The manufacturer of one preparation containing 100 g of macrogol 3350 per litre recommends a different regimen of just 2 litres of reconstituted solution for the whole course: one litre is drunk over a period of 1 to 2 hours followed by a further litre after 1.5 hours on the evening before the procedure; alternatively, the course can be split into one litre on the evening before and one litre on the morning of the procedure so that the course finishes at least one hour before the procedure. An additional one litre of clear fluid should also be consumed during the course and no solid food should be taken from the start of the course until after the clinical procedure. Some manufacturers recommend that the reconstituted solution is more palatable if chilled, although chilled solutions are not recommended for infants. There has also been a report of hypothermia developing in a patient after consuming a large volume of the chilled solution. Additional flavouring ingredients, sugar, or other sweeteners should not be added to the solution. If distension or pain occur, dosage should be temporarily stopped or the interval between drinks extended. Some preparations may also be given by nasogastric tube at a rate of 20 to 30 mL/min.

A solution containing 105 g of macrogol 3350 per litre is used for the treatment of **chronic constipation** in a usual oral dose of 125 mL up to three times daily. For some preparations, the solution is made up to a lower volume of 62.5 mL although the final concentration of macrogol 3350 remains at 105 g per litre. The maximum course is 2 weeks, which may be repeated if necessary; extended use may be required in some circumstances in which case a reduction in dose could be considered.

A solution containing 105 g of macrogol 3350 per litre is used in the management of **faecal impaction**; one litre of this solution should be consumed within 6 hours each day for a maximum of 3 days. Patients with impaired cardiovascular function should take no more than 250 mL in any one hour.

For doses of macrogol preparations in children, see Administration in Children below.

Conjugation of drugs and therapeutic proteins with macrogols (**pegylation**) has been tried in an attempt to improve their pharmacokinetic profiles and to reduce their adverse effects. Pegylation may also reduce the immunogenicity of therapeutic proteins. Examples of pegylated proteins include pegademase (p. 2584.3), pegaspargase (p. 743.3), and peginterferon alfa (see Uses and Administration of Interferon Alfa, p. 989.2).

Administration in children. Solutions of macrogols with electrolytes are used for **bowel preparation** in children in varying dosage regimens. A solution containing 105 g of macrogol 3350 per litre may be given orally or by nasogastric tube to children aged over 6 months in a dose of 25 mL/kg per hour until the rectal effluent is clear; children under 2 years of age should be monitored for hypoglycaemia since these solutions contain no caloric substrate. A solution containing 59 g of macrogol 4000 per litre may be given to children aged over 5 years and weighing over 20 kg in an oral dose of one litre of solution per 15 to 20 kg. For general details on administration of macrogol solutions, see under Uses and Administration above.

A solution containing 105 g of macrogol 3350 per litre is given orally to children with **chronic constipation**. The usual initial daily dose for those aged 2 to 6 years is 62.5 mL, and for those aged 7 to 11 years, 125 mL. Thereafter, the dose should be increased or decreased as necessary to produce regular soft stools; the usual maximum dose is 250 mL daily. Treatment for prolonged periods may be required in children, although safety and efficacy have only been proved for up to 3 months of treatment. It is recommended that treatment is stopped gradually and resumed if constipation occurs. The *BNFC* also recommends a dose of 31.25 to 62.5 mL daily in children under 1 year for the treatment of chronic constipation.

A solution containing 105 g of macrogol 3350 per litre is given orally to children aged 5 to 11 years for **faecal impaction** in an escalating dose until disimpaction occurs up to a maximum of 7 days. Four doses of 62.5 mL of solution are given initially on the first day, increasing by 2 doses daily to a maximum of 12 doses daily on days 5 to 7; the total daily dose should be divided and consumed within a 12-hour period. Doses for prevention of recurrence of faecal impaction in children are as for children's doses for chronic constipation (see above). The *BNFC* recommends that children aged 1 to 5 years with faecal impaction may be given two doses of 62.5 mL of solution on the first day, then four doses daily for 2 days, then 6 doses daily for 2 days, and finally 8 doses daily until impaction resolves. It also recommends a dose of 31.25 to 62.5 mL daily in children under 1 year.

Doses of macrogols for the treatment of chronic constipation and faecal impaction for those aged 12 years and over are given under Uses and Administration above.

Drug delivery systems. References to the use of macrogols in delivery systems for drugs and proteins.

1. Reddy KR. Controlled-release, pegylation, liposomal formulations: new mechanisms in the delivery of injectable drugs. *Ann Pharmacother* 2000; **34:** 915–23.
2. Harris JM, *et al*. Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet* 2001; **40:** 539–51.

Phenol poisoning. Washing with liquid macrogols has been recommended in the emergency treatment of skin contamination with phenol, see p. 1764.3.

Adverse Effects and Precautions

Macrogols appear to have relatively low toxicity, although any toxicity appears to be greatest with the macrogols of low molecular weight. They may cause stinging when used topically, especially on mucous membranes, and have been associated with hypersensitivity reactions such as urticaria. Hyperosmolality, metabolic acidosis, and renal failure have been reported after topical application of macrogols to burn patients. Topical preparations with a macrogol base should therefore be used with caution in patients with renal impairment and/or large areas of raw surfaces, burns, or open wounds.

Patients undergoing bowel cleansing with mixtures of macrogols (3350 or 4000) and electrolytes commonly have local gastrointestinal discomfort, bloating, and nausea. Abdominal cramps, vomiting, and anal irritation may also occur and there have been rare reports of possible hypersensitivity reactions. These colonic lavage solutions are contra-indicated in gastrointestinal obstruction or perforation, ileus, gastric retention, peptic ulcer disease, and toxic megacolon; caution is advisable in patients with ulcerative colitis. Since aspiration may be a problem, they should be used with caution in patients with an impaired gag reflex, reflux oesophagitis, or diminished levels of consciousness. They should be given with caution to diabetic patients. Drugs taken within one hour of starting colonic lavage with an oral macrogol and electrolyte mixture may be flushed from the gastrointestinal tract unabsorbed.

Effects on fluid and electrolyte homoeostasis. A syndrome of elevated total serum calcium (with a concomitant decrease in ionised calcium), hyperosmolality, metabolic acidosis, and renal failure has been seen in *animals*[1] and in burn patients[2] after the topical application of preparations with a macrogol base. The FDA has recommended that topical preparations containing macrogols should be used with caution in burn patients with known or suspected renal impairment, as macrogols absorbed through denuded skin and not excreted normally by a compromised kidney could lead to symptoms of progressive renal impairment.[3]

The use of macrogol and electrolyte solutions for bowel preparation has also been associated with sodium and water retention, resulting in exacerbation of heart failure in a patient with diabetic gastroparesis,[4] and with the development of pulmonary oedema possibly due to aspiration in a child without cardiac or renal disease.[5]

1. Herold DA, *et al*. Toxicity of topical polyethylene glycol. *Toxicol Appl Pharmacol* 1982; **65:** 329–35.
2. Bruns DE, *et al*. Polyethylene glycol intoxication in burn patients. *Burns* 1982; **9:** 49–52.
3. Anonymous. Topical PEG in burn ointments. *FDA Drug Bull* 1982; **12:** 25–6.
4. Granberry MC, *et al*. Exacerbation of congestive heart failure after administration of polyethylene glycol-electrolyte lavage solution. *Ann Pharmacother* 1995; **29:** 1232–5.
5. Paap CM, Ehrlich R. Acute pulmonary edema after polyethylene glycol intestinal lavage in a child. *Ann Pharmacother* 1993; **27:** 1044–7.

Hypersensitivity. Hypersensitivity to macrogols is uncommon but both immediate urticarial reactions and delayed allergic contact dermatitis have been reported after the topical application of preparations with a macrogol vehicle or base.[1] An anaphylactic reaction has been associated with the ingestion of macrogols in a multivitamin tablet.[2] The manufacturers of preparations containing macrogols and electrolytes for bowel cleansing have reported isolated instances of skin reactions and rhinorrhoea.

1. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978; **4:** 135–8.
2. Kwee YN, Dolovich J. Anaphylaxis to polyethylene glycol (PEG) in a multivitamin tablet. *J Allergy Clin Immunol* 1982; **69:** 138.

Overdosage. Ingestion of 2 litres of a colonic lavage solution containing macrogol 400 instead of macrogol 4000 resulted in a patient developing severe metabolic acidosis due to systemic absorption of the macrogol. The patient rapidly became comatose but was successfully treated with intravenous bicarbonate and dialysis.[1]

1. Bélaïche J, *et al*. Coma acidosique après préparation colique par du polyèthylène glycol. *Gastroenterol Clin Biol* 1983; **7:** 426–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies macrogols as not porphyrinogenic; they may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Toxicity. For reports of macrogol (polyethylene glycol) 400 toxicity when included in some preparations of benzodiazepines, see under Propylene Glycol, p. 2205.3.

Pharmacokinetics

Liquid macrogols may be absorbed when taken orally but macrogols of high molecular weight, such as macrogol 3350, are not significantly absorbed from the gastrointestinal tract. There is evidence of absorption of macrogols when applied to damaged skin. Macrogols entering the systemic circulation are mainly excreted unchanged in the urine; low-molecular-weight macrogols may be partly metabolised.

References.

1. DiPiro JT, *et al*. Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. *Clin Pharm* 1986; **5:** 153–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Osmolagrimas; ***Austral.***: OsmoLax; ***Austria***: DrinkaLax†; Forlax; MixaLax†; ***Belg.***: Forlax; ***Braz.***: Harmolax; ***Canad.***: Lax-a-Day; Pegalax; Relaxa; Restoralax; Sealax†; ***China***: Chang Song (长松); Forlax (福松); Run Ke Long (润可隆); You Sai Le (优赛乐); ***Cz.***: Forlax; Oripeg; ***Denm.***: Nuvolax; ***Fin.***: Pegorion; ***Fr.***: Biopeg; Forlax; ***Ger.***: Bellymed; Dulcolax M Balance; Glandomed; Laxofalk; ***Gr.***: Tanilas; Transorbin; ***Hong Kong***: Forlax; ***Hung.***: Forlax; ***India***: Ezlax; Laxopeg; ***Irl.***: Idrolax; ***Israel***: Moviprep; Normalax; Peglax; ***Ital.***: Kronys; Onlipeg; Paxabel; Pergidal; ***Malaysia***: Blink Intensive Tears; Forlax; ***Mex.***: Contumax; ***Neth.***: Forlax; ***Pol.***: Forlax; Olopeg; Prolaxatan†; ***Port.***: Forlax; Philenterol†; Transipeg†; ***Rus.***: Forlax (Форлакс); Osmogol (Осмоголь); Polyoxidin (Полиоксидин); Realaxan (Реалаксан); ***Singapore***: Blink Intensive Tears; Forlax; ***Spain***: Casenlax; Micralax Macrogol; ***Swed.***: Forlax; ***Thai.***: Forlax; ***Turk.***: Transipeg†; ***UK***: Dulcobalance; PegLax; ***Ukr.***: Diagnol (Диагнол); Forlax (Форлакс); ***USA***: Dulcolax Balance; GaviLAX; GlycoLax; MiraLax.

Multi-ingredient Preparations. ***Arg.***: Adital; Barex; Irix Lagrimas; Systane; Tractoclin; Transipeg; Visine Lagrimas; Visine Plus; ***Austral.***: Colonlytely; Colonprep; Glycoprep-C; Glycoprep; Movicol; Prep Kit-C; Systane; Visine Advanced Relief; ***Austria***: Endofalk; Klean-Prep; Molaxole; Movicol; Moviprep; ***Belg.***: Colofort; Colopeg; Delpeg†; Endofalk; Endopeg; Klean-Prep; Laxido; Molaxole; Movicol; Moviprep; Precosol; Transipeg; ***Braz.***: Mirugell; Muvinlax; NuLytely; ***Canad.***: Bi-PegLyte; CoLyte; GoLytely; Klean-Prep; Lubricating Nasal Gel; Lubricating Nasal Mist; Moviprep; Peglyte; Rhinaris; Salinex Nasal Lubricant; Secaris; Systane; Visine Advance Triple Action; Visine Cool; ***Chile***: Endofalk; Systane; Tears Visine†; ***China***: Fortrans (福静清); Movicol (默维可); ShuTaiQing (舒泰清); Systane (思然); ZhengQing (正清); ***Cz.***: Fortrans; Maxellax; Molaxole; Movicol†; Moviprep; ***Denm.***: Encol; Endofalk; Gangiden; Lacrofarm; Magenterol; Movicol; Moviprep; Moxalole; ***Fin.***: Colonsoft; Colonsteril; Endofalk; Klean-Prep†; Lacrofarm; Laxido; Laxiriva; Movicol; Moviprep; Moxalole; Olopeg; ***Fr.***: Colopeg; Fortrans; Klean-Prep; Movicol; Moviprep; Moxalole; SST†; Systane; Transipeg; ***Ger.***: Darmspulpulver; Darmspulung†; Delcoprep; Endofalk; Isomol; Klean-Prep; Laxatan M; Lefax Activolax; Macrogol; Movicol; Moviprep; Oralav; ***Gr.***: Endofalk; Fortrans; GoLytely; Izetafin; Klean-Prep; Movicol; ***Hong Kong***: Clinac OC; Fortrans; Hypotears; Klean-Prep; Movicol†; Systane; Visine Moisturizing†; ***India***: Coloclean; Colopeg; Endopeg; ***Indon.***: Laxarec; Microlax; Niflec; Systane; Visine Extra; ***Irl.***: Klean-Prep; Laxido; Molaxole; Movicol; Movilief; Moviprep; Movitev; Transipeg†; ***Israel***: Meroken New; Systan UL; Systane; ***Ital.***: Hypotears; Isocolan; Klean-Prep; Macro-P; Molaxole; Movicol; Moviprep; Selg-Esse; Selg; Systane; ***Malaysia***: Fortrans; Hypotears; Systane; ***Mex.***: NuLytely; Systane; Visine Extra; ***Neth.***: Colofort; Eleprep†; Endofalk; Klean-Prep; Laxtra; Molaxole; Movicolon; Moviprep; Transipeg; ***Norw.***: Endofalk; Laxabon; Movicol; Moviprep; Moxalole; ***NZ***: Klean-Prep; Movicol; Moviprep; Prepkit-C; Visine Advanced Relief; ***Philipp.***: Moisturizing All Clear; Systane; Visine Refresh; ***Pol.***: Fortrans; ***Port.***: Endofalk; Fortrans; Klean-Prep; Movicol; Pecol; ***Rus.***: Endofalk (Эндофальк); Fortrans (Фортранс); Lavacole (Лавакол); Transipeg (Транзипег); ***S.Afr.***: GoLytely; Klean-Prep; Movicol; Pegicol; ***Singapore***: Fortrans; Klean-Prep; Movicol; Peglyte; Systane; ***Spain***: Casenglicol; Evacuante Simple; Klean-Prep; Molaxole; Movicol; Moviprep; Solucion Evacuante; ***Swed.***: Endofalk; Lacrofarm; Laxabon; Laxido; Laxiriva; Movicol; Movprep; Moxalole; Omnicol; Omnilax; ***Switz.***: Colo-Sol; Cololyt; Fordtran†; Hypotears; Isocolan; Klean-Prep; Molaxole; Movicol; Moviprep; Nose Fresh; Pegicol; Transipeg; ***Thai.***: Niflec; Systane; ***Turk.***: Endofalk; GoLytely; Movicol; Systane; ***UK***: Artelac Rebalance; Blink Intensive Tears; Klean-Prep; Laxido; Molaxole; Movicol; Moviprep; SST; Zerozole†; ***Ukr.***: Endofalk (Эндофальк); Fortrans (Фортранс); ***USA***: Advanced Relief Visine; Blink Gel Tears; CoLyte; GaviLyte; GoLytely; HalfLytely and Bisacodyl Bowel Prep Kit; Hypotears; MoviPrep; Nu-Tears II; NuLytely; OCL; Suclear; Systane; TriLyte; Visine Maximum Redness Relief; Visine Pure Tears; Visine Tears; Visine Tired Eye Relief; Visine Totality Multi-Symptom Relief; ***Venez.***: Systane.

Pharmacopoeial Preparations
USP 36: PEG 3350 and Electrolytes for Oral Solution.

Magnesium Glutamate Hydrobromide

Bromoglutamato magnésico; Glutamato magnésico, hidrobromuro de; Hidrobromuro de alfa-aminoglutamato magnésico; Magnesium α-Aminoglutarate Hydrobromide; Magnesium Bromoglutamate.
$(C_5H_8NO_4)_2Mg,HBr$=397.5
CAS — 53459-38-4.

Profile

Magnesium glutamate hydrobromide has been used as a sedative and hypnotic in the treatment of insomnia, neuroses, and behavioural disorders. The use of bromides is generally deprecated (see p. 2460.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Onyric; ***Spain***: Psicosoma.

Multi-ingredient Preparations. ***Chile***: Gamalate B6; Gamavit B6; ***Spain***: Gamalate B6; Psicosoma; ***Ukr.***: Gamalate B6 (Гамалате B6).

Malabar Nut

Adhatoda; Adotodai; Adulsa; Arusa; Malabar Nut Tree; Malabarnöt; Malabarnuss; Pavettia; Vasaca; Vasaka.
CAS — 6159-55-3 (vasicine).
*ATC Herb — HR038B5003 (*Justicia adhatoda*: leaf); HR05WA5019 (*Justicia adhatoda*: leaf).*
*UNII — 9GL9VCO10F (*Justicia adhatoda*); HH159XOV81 (*Justicia adhatoda *leaf); 3J544964HZ (*Justicia adhatoda *root).*

Pharmacopoeias. *US* includes a monograph for Malabar-Nut-Tree Leaf and the powdered form and powdered extract.

USP 36: (Malabar-Nut-Tree, Leaf). The dried leaves of *Justicia adhatoda* (*Adhatoda vasica*) (Acanthaceae). It contains not less than 0.6% of vasicine, calculated on the dried basis. Protect from light and moisture.

Profile

The leaves, flowers, and roots of the malabar nut, *Justicia adhatoda* (*Adhatoda vasica*; *A. zeylanica*) Acanthaceae, are used in Indian traditional medicine, mainly as an expectorant and antispasmodic in preparations for cough and other respiratory-tract disorders. The principal constituents are adhatodic acid and the alkaloid vasicine (peganine).

Homoeopathy
Malabar nut has been used in homoeopathic medicines under the following names: Adhatoda vasica; Justicia; Justicia adhatoda.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: PulmaCo; ***India***: Aglotus; Arjin; Arthopack; Arthopack; Astha; Astha; Diakof; Evecare; Evecare; FN-T-Tus†; Geriforte; Geriforte; Haleezy; Honitus; Kof-Rid; Kofarest-H; Koflet; Leuko-G; Livomyn; Livomyn; Lukol; Myron; ***Malaysia***: Strepsils Cough Lozenge†; Strepsils Cough Syrup†; ***NZ***: Lice Blaster; ***Rus.***: Doktor Mom (Доктор Мом); Insti (Инсти); Linkus (Линкас); Linkus Lor (Линкас Лор); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); ***Singapore***: Claricof; Strepsils Cough Lozenge (with natural herbs); Strepsils Cough Syrup†; ***Swed.***: Kan Jang; ***Ukr.***: Bronchomed (Бронхомед); Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Eve Care (Ив Кер)†; Imunin (Иммунин)†; Insti (Інсті); Linkus (Линкас); Olesan (Олесан)†; Olesan (Олесан); Travisil (Трависил).

Homoeopathic Preparations. ***Ger.***: Klosterfrau Allergin; Syxyl Heuschnupfen.

Malic Acid

Acide Malique; Ácido de las manzanas; Ácido hidroxisuccínico; Acidum Malicum; Acidum Malicum Racemicum; Äpfelsäure; Äppelsyra; Apple Acid; E296; Hydroxysuccinic Acid; Kyselina jablečná racemická; Málico, ácido; Obuolių rūgštis; Omenahappo; Яблочная Кислота.
(2*RS*)-2-Hydroxybutanedioic acid.
$C_4H_6O_5$=134.1
CAS — 6915-15-7 (malic acid); 636-61-3 ((+)-malic acid); 97-67-6 ((-)-malic acid); 617-48-1 ((±)-malic acid).
UNII — 817L1N4CKP ((±)-malic acid); J3TZF807X5 ((-)-malic acid).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.
Ger. also includes the *S*-form ((-)-malic acid).

Ph. Eur. 8: (Malic Acid). A white or almost white, crystalline powder. Freely soluble in water and in alcohol, sparingly soluble in acetone.

USNF 31: (Malic Acid). A white or practically white, crystalline powder or granules. Very soluble in water; freely soluble in alcohol.

Profile

Malic acid is used in pharmaceutical formulations as an acidifier, flavour, and as an alternative to citric acid in effervescent powders. It is used with butylated hydroxytoluene as an antoxidant in vegetable oils. It is used topically with benzoic acid and salicylic acid for desloughing of ulcers, burns, and wounds, and systemically with arginine (p. 2049.1) in preparations for the treatment of liver disorders. Pastilles containing malic acid are also used in the management of dry mouth (p. 2175.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Acerbine; Leberinfusion; ***Chile***: Secand; ***Cz.***: Ringerfundin; ***Denm.***: Ringerfundin; ***Fin.***: Ringerfundin; Xerodent; ***Fr.***: Isofundine; Squaphane; SST†; ***Hung.***: Egaver Plusz; Egaver; ***Indon.***: Aviter; Viusid; ***Ital.***: Keraflex; Sterofundin; ***Neth.***: Sterofundin Iso; ***Norw.***: Ringerfundin; Xerodent; ***Rus.***: Hepasol A (Гепасол А); ***S.Afr.***: Aserbine; ***Singapore***: Bio-Taches†; ***Spain***: Acerbiol†; ***Swed.***: Ringerfundin; Xerodent; ***Switz.***: Ringerfundin; ***UK***: Hydrotab; Salivix; SST; ***Ukr.***: Acerbin (Ацербин); Hepasol A (Гепасол А); ***USA***: Saliva-Sure; ***Venez.***: Lecivar Plus; Viusid.

Homoeopathic Preparations. ***Ger.***: Hepar comp; Zitronensaurezyklus-Heel.

Mallow

Erdei mályvavirág (mallow flower); Květ slézu lesního (mallow flower); Liść ślazu (mallow leaf); Malvablomma (mallow flower); Malvae folium (mallow leaf); Malvae sylvestris flos (mallow flower); Malvenblätter (mallow leaf); Malvenblüten (mallow flower); Mauve des Bois (*Malva silvestris*); Mauve, feuille de (mallow leaf); Mauve, fleur de (mallow flower); Metsämalvankukka (mallow flower); Miškinių dedešvų žiedai (mallow flower); Мальва Лесная (*Malva sylvestris*); Просвирник Лесной (*Malva sylvestris*).
*ATC Herb — HD02WA5003 (*Malva sylvestris*: seed); HA16AX5003 (*Malva sylvestris*: leaf); HA01WB5003 (*Malva sylvestris*: flower); HR05WA5027 (*Malva sylvestris*: leaf); HN02BG5007 (*Malva sylvestris*: seed); HR05WA5026 (*Malva sylvestris*: flower).*

Pharmacopoeias. *Eur.* (see p. vii) includes Mallow Flower and Mallow Leaf.

Ph. Eur. 8: (Mallow Flower; Malvae sylvestris flos). The whole or fragmented dried flower of *Malva sylvestris* or its cultivated varieties. Protect from light.

Ph. Eur. 8: (Mallow Leaf; Malvae Folium). The whole or fragmented dried leaf of *Malva sylvestris*, *M. negleita*, or a mixture of both species. Protect from light.

Profile

Mallow flower and leaf act as demulcents and are ingredients of herbal remedies for coughs and cold symptoms. Mallow flower is used to enhance the colour of herbal teas and other foodstuffs. Mallow is also included in herbal remedies for gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Malvatrikids Baby; ***Cz.***: Slezovy Kvet†; ***Ital.***: Malvina; ***Switz.***: Tisane contre le toux irritative.

Multi-ingredient Preparations. ***Arg.***: Acnetrol; Aristaloe; KW; Lactoscrub; Maprosol Gel; Mictasol Azul; Prurigel; Xyloprocto Toallas; ***Austral.***: Neo-Cleanse; ***Austria***: Midro Tee; ***Belg.***: Mictasol; ***Braz.***: Malvatricin Natural Soft†; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvatrikids F; Malvatrikids Junior; Malvodon†; Mictasol; ***Canad.***: Bilonat; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; ***Fr.***: Angiodrop; Apaisance†; Boribel Tisane No 13†; Erygine†; Mediflor Hepatique No 5; Mediflor Pectorale d'Alsace no 8†; Mucogyne; Pectoflorine†; Santane C_6†; Santane O1; Santane O1; Saugella Girl; Tisane Saint-Urbain†; Veganix; Yerbalaxa; ***Hung.***: Telma; ***Israel***: Midro-Tea; ***Ital.***: Alkagin; Cistefi; Dentaton; Fito Stomygen†; Glicerolax; Iridil; Microclismi Marco Viti†; Mictasone†; Neoderma 47; Nevril; Ninfagin; Perfluxi Cremagel; Piodermina; Plurilac; ***Port.***: Alkagin; Alkagin; Alkagin; ***Rus.***: Herbion Plantain Syrup (Гербион Сироп Подорожника); ***Singapore***: Arkopharma Propolis Spray; ***Switz.***: Malveol; ***UK***: Spotner; ***Ukr.***: Herbion Plantaginis Syrup (Гербион Сироп Подорожника).

Homoeopathic Preparations. ***Canad.***: Common Mallow Combination†; Goldenrod Combination†.

Malotilate *(USAN, rINN)*

Malotilato; Malotilatum; NKK-105; Малотилат.
Diisopropyl 1,3-dithiole-$\Delta^{2,\alpha}$-malonate.
$C_{12}H_{16}O_4S_2$=288.4
CAS — 59937-28-9.
UNII — RV59PND975.

Profile

Malotilate is used for a protective effect on liver function in patients with chronic hepatic disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xin Yi Gan (辛益甘); Ya Bao Xin (亚宝欣); ***Jpn***: Kantec.

Mannose Triflate

Tetraacetyl Mannose Triflate.
1,3,4,6-Tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose.
$C_{15}H_{19}F_3O_{12}S$=480.4
CAS — 92051-23-5.
UNII — 0KI8FFQ6TT.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tetra-*O*-acetyl-mannose Triflate for Radiopharmaceutical Preparations). A white or almost white crystalline hygroscopic powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane; very soluble in acetonitrile. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Mannose triflate is a synthetic carbohydrate used as a precursor in the production of fludeoxyglucose (^{18}F) injection (see p. 2224.1).

Manuka

New Zealand Tea Tree; Манука.

Profile

The oil of manuka (*Leptospermum scoparium*) is used for its antimicrobial properties as an alternative to melaleuca oil (p. 2551.1). It is also used in aromatherapy. Manuka honey has also been used as a wound dressing (p. 2072.2).

References.
1. Cooper RA, *et al.* The sensitivity to honey of Gram-positive cocci of clinical significance isolated from wounds. *J Appl Microbiol* 2002; **93:** 857–63.
2. Cooper RA, *et al.* The efficacy of honey in inhibiting strains of Pseudomonas aeruginosa from infected burns. *J Burn Care Rehabil* 2002; **23:** 366–70.
3. English HK, *et al.* The effects of manuka honey on plaque and gingivitis: a pilot study. *J Int Acad Periodontol* 2004; **6:** 63–7.
4. Jull A, *et al.* Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg* 2008; **95:** 175–82.
5. Mavric E, *et al.* Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. *Mol Nutr Food Res* 2008; **52:** 483–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Antiac; Sinose.

Marjoram

Majoranae Herba; Marjolaine; Sweet Marjoram; Ziele majeranku; Майоран.

ATC Herb — HG04BW5024 (Origanum majorana: *herb); HR05DB5008* (Origanum majorana: *herb); HN06AW5004* (Origanum majorana: *herb); HN02CW5002* (Origanum majorana: *herb); HA03WX5003* (Origanum majorana: *herb).*

UNII — G9Z40ZYU6P (Origanum majorana *top); R40XM3HU5X* (Origanum majorana).

NOTE. Distinguish from wild marjoram (see Oregano, p. 2576.3).

Pharmacopoeias. In *Pol.*

Profile

The dried leaves and flowers of marjoram, *Origanum majorana* (*Majorana hortensis*) (Lamiaceae), and the essential oil obtained from them have antibacterial properties. They are used, either separately or in combination, in herbal remedies for a variety of disorders. Marjoram is also used as a culinary herb.

Marjoram oil is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Menodoron; ***Fr.***: Dystolise; ***Ger.***: Menodoron; ***Hung.***: Antipoll; Herbalakt; ***Neth.***: Luuf Verkoudheidsbalsem (voor baby's); ***Pol.***: Salviasept; ***Port.***: Erpecalm; ***Rus.***: Urolesan (Уролесан); ***S.Afr.***: Menodoron†; ***Switz.***: Menodoron.

Homoeopathic Preparations. ***Cz.***: Hormeel S; ***Fr.***: Boripharm No 41; ***Hung.***: Hormeel S; ***Rus.***: Hormeel SN (Гормель СН).

Marsh Tea

Crystal Tea; Ledi palustris herba; Lédon des marais; Marsh Cistus; Marsh Labrador Tea; Sumpf-Porst; Sumpfporstkraut; Wild Rosemary.

ATC Herb — HD11AX5002 (Ledum palustre: *herb); HR05WA5022* (Ledum palustre: *herb).*

UNII — 877L01IZ0P.

NOTE. The names James' Tea and Labrador Tea have been applied to marsh tea (*Ledum palustre*) but are also used for the related species *L. groenlandicum* (*L. latifolium*; *Rhododendron groenlandicum*).

Although the synonym Wild Rosemary has been used for Marsh Tea, Rosemary (p. 2607.2) is an unrelated plant.

Profile

The dried aerial parts of marsh tea, *Ledum palustre* (*L. tomentosum*; *Rhododendron tomentosum*; *R. palustre*) (Ericaceae) have been used in herbal preparations mainly for rheumatic and respiratory tract disorders. It contains an irritant essential oil and has been abused as an abortifacient.

Homoeopathy

Marsh tea has been used in homoeopathic medicines under the following names: Ledum; Ledum palustre.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Joint & Muscle Cream; ***Cz.***: Cicaderma; ***Ger.***: Rhus-Rheuma-Gel N; ***Mex.***: Sanicut; ***Port.***: Cicaderma; ***Rus.***: Pectorales Species No 4 (Грудной Сбор 4).

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Joint & Muscle Oral Spray†; Sports Ice Joint & Muscle; ***Austria***: Ledum Med Complex; Proagil; Rhus Med Complex; Thuja Med Complex; ***Canad.***: Adrisin†; Arnicaid; Cicaderma†; Cutisitum†; Hylands LCQ; Hylands Leg Cramps; Rudistrol†; Toxex; ***Chile***: Artroplex; ***Fr.***: Abbe Chaupitre no 13; Abbe Chaupitre no 23†; Cicaderma; Ledum Complexe No 81; Urtica Complexe No 82†; ***Ger.***: Anore rheumat; Arthrokatt; Arthrorell N; Berberis N Oligoplex; Bomarthros Harpagophytum Complex; Colchicum Complex; Doloject; G1-Injektopas; Hewerheum N†; Homvioartrin; Rheucostan R; Rheuma-Hevert; Rheuma-Hevert; rheumaloges; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; Rheumeda; Steirocall S†; ***Neth.***: Arnilite; Homeocare Exercito; Kruidvat Homeopathie Bzzz†; Kruidvat Homeopathie Spier- en gewrichtsgel†; Prrrikweg; Prurilite; Rudistrol†; Spiroflor; Urtizon complex; ***Rus.***: Cicaderma (Цикадерма); Rewma-Gel (Ревма-Гель); ***Switz.***: Omida Gel Antirhumatismal; Regenaplex Nr. 21c; ***UK***: Pyrethrum Spray; ***Ukr.***: Reuma-Gel (Ревма-Гель).

Mastic

Almáciga; Mastiche; Mastiksi; Mastix; Pistacijų mastika; Мастика.

ATC Herb — HA01AD5002 (Pistacia lentiscus: *resin).*

UNII — 7446H202QW.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Mastic). The dried resinous exudate obtained from stems and branches of *Pistacia lentiscus* var. *latifolius*. It contains a minimum of 1% v/w of essential oil, calculated with reference to the anhydrous drug. It should not be powdered.

Profile

Solutions of mastic in alcohol, chloroform, or ether have been used, applied on cotton wool, as temporary fillings for carious teeth. Compound Mastic Paint (BP 1980) was formerly used as a protective covering for wounds and to hold gauze in position.

Mastic gum has been used in the management of peptic ulcer disease.

Peptic ulcer disease. Mastic has traditionally been used in the treatment of gastrointestinal disorders such as peptic ulcer. It has been suggested that any effect may be related to its *in vitro* activity against *Helicobacter pylori*[1,2] and although one small study[3] found that it had little effect on the load of *H. pylori in vivo*, a later study sponsored by the manufacturers produced somewhat more encouraging results.[4]

1. Huwez FU, *et al.* Mastic gum kills Helicobacterpylori. *N Engl J Med* 1998; **339:** 1946. Correction. *ibid.*:**340:** 576 [dose].
2. Paraschos S, *et al.* In vitro and in vivo activities of Chios mastic gum extracts and constituents against Helicobacter pylori. *Antimicrob Agents Chemother* 2007; **51:** 551–9.
3. Bebb JR, *et al.* Mastic gum has no effect on Helicobacter pylori load in vivo. *J Antimicrob Chemother* 2003; **52:** 522–3.
4. Dabos KJ, *et al.* The effect of mastic gum on Helicobacter pylori: a randomized pilot study. *Phytomedicine* 2009. Available at: doi: 10.1016/j.phymed.2009.09.010

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Mastika†.

Meadowsweet

Älgört; Filipendulae Ulmariae Herba; Mädesüsskraut; Mesiangervo; Voňavý tužebník jilmový; Pelkinių vingiorykščių žolė; Queen of the Meadows; Reina de los prados; Reine des Prés; Reine des prés, sommité fleurie de; Spiraeae Herba; Ulmaria; Лабазник; Таволга.

ATC Herb — HJ01WB5008 (Filipendula ulmaria: *herb); HA16AX5002* (Filipendula ulmaria: *herb); HR05YA5007* (Filipendula ulmaria: *flower); HG04BW5012* (Filipendula ulmaria: *flower); HN02BA5001* (Filipendula ulmaria: *herb).*

UNII — 3LH0M209LN (Filipendula ulmaria*); 06L18L32G6* (Filipendula ulmaria *flower); 7495ZGS5HI* (Filipendula ulmaria *flowering top); 37GVN739ZQ* (Filipendula ulmaria *leaf); 997724QNDS* (Filipendula ulmaria *root).*

NOTE. The name Queen of the Meadow has also been applied to Gravel Root (p. 2522.1).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Meadowsweet). The whole or cut, dried flowering tops of *Filipendula ulmaria* (*Spiraea ulmaria*). It contains a minimum of 0.1% v/w of essential oil (dried drug). It has an aromatic odour of methyl salicylate after crushing.

Profile

Meadowsweet is used in herbal medicine as a diuretic and in gastrointestinal and rheumatic disorders.

Homoeopathy

Meadowsweet has been used in homoeopathic medicines under the following names: Filipendula ulmaria; Spiraea; Spiraea ulmaria; Spiraea ulmaria ex herba; Filip. ul.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Detox Program; Digestive Bitters; HiPep; ***Canad.***: Cellutex; ***Cz.***: Antirevmaticky Caj†; ***Fr.***: Arthritisane†; Arthroflorine†; Chondrosteo; Dolores; Drainuryl; Fibromyalgine; Hydracur; Mediflor Diuretique No 4†; Mediflor Douleurs Articulaires no 2†; OM3flex†; Santane A_4†; Santane O1; Santane R_8†; Tisane de Sante†; Tisane Provencale no 2†; Tisane Provencale no 6†; ***Ital.***: Flodolor; Lik-Gel†; Neuralta Migren; Pik Gel; ***Mex.***: Rodan; ***Mon.***: Algicuivre; ***Pol.***: Infektoten†; Reumaherb; ***Switz.***: Urinex; ***UK***: Acidosis; Acidosis; Indigestion Mixture; Pure Plan; ***Ukr.***: Tazalok (Тазалок); ***USA***: Amerigel.

Homoeopathic Preparations. ***Cz.***: Ferrum Homaccord†; ***Fr.***: Urodren; ***Ger.***: Colchicum Complex; Gelenk Albin; Hewerheum N†; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Rheuma-Hevert†; Rheuma-Hevert; Rheuma-Hevert; Rheumeda; ***Neth.***: Phonix Solidago comp; Rhodolith-Gastreu R46; ***Ukr.***: Homvio-Reuman (Хомвио-Ревман).

Meclofenoxate Hydrochloride

(BANM, rINNM) ⊗

Centrophenoxine Hydrochloride; Clofenoxine Hydrochloride; Clophenoxate Hydrochloride; Deanol 4-Chlorophenoxyacetate Hydrochloride; Hidrocloruro de meclofenoxato; Meclofenoxane Hydrochloride; Méclofénoxate, Chlorhydrate de; Meclofenoxati Hydrochloridum; Meclofenoxato, hidrocloruro de; Меклофеноксата Гидрохлорид.

2-Dimethylaminoethyl 4-chlorophenoxyacetate hydrochloride.

$C_{12}H_{16}ClNO_3,HCl$=294.2

CAS — 51-68-3 (meclofenoxate); 3685-84-5 (meclofenoxate hydrochloride).

ATC — N06BX01.

ATC Vet — QN06BX01.

UNII — 5BK3070BDY.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Meclofenoxate hydrochloride has been claimed to aid cellular metabolism in the presence of diminished oxygen concentrations. It has been given mainly for mental changes in the elderly, or after strokes or head injury.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Lucidril.

Meglumine *(BAN, rINN)*

Meglumiini; Meglumin; Meglumina; Megluminas; Méglumine; Megluminum; Меглюмин.

N-Methylglucamine; 1-Methylamino-1-deoxy-D-glucitol.

$C_7H_{17}NO_5$=195.2

CAS — 6284-40-8.

UNII — 6HG8UB2MUY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Meglumine). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane.

USP 36: (Meglumine). White to faintly yellowish-white, odourless crystals or powder. Freely soluble in water; sparingly soluble in alcohol.

Profile

Meglumine is an organic base used for the preparation of salts of organic acids including many used as contrast media.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Contrastin; ***Rus.***: Remaxol (Ремаксол).

Melaleuca Oil

Australian Tea Tree Oil; Melaleuca, aceite de; Mélaleuca, huile essentielle de; Melaleucae Aetheroleum; Melaleucae Etheroleum; Mirtenių eterinis aliejus; Oleum Melaleucae; Silice kajeputu střídavolistého; Tea Tree Oil; Teebaumöl; Teepuuöljy; Teträdolja; Масло Чайного Дерева.

CAS — 68647-73-4; 8022-72-8.

*ATC Herb — HD08AW5001 (*Melaleuca alternifolia*: essential oil); HA03AW5035 (*Melaleuca leucadendra*: essential oil); HP03AX5001 (*Melaleuca leucadendra*: essential oil); HM02AW5008 (*Melaleuca leucadendra*: essential oil); HP03BX5003 (*Melaleuca leucadendra*: essential oil); HR05WA5029 (*Melaleuca leucadendra*: essential oil).*

UNII — VIF565UC2G.

NOTE. Though the synonym Ti-tree Oil has been used for melaleuca oil (e.g. in BPC 1949), the name Ti-tree is also applied to species of *Cordyline* (Liliaceae) indigenous to New Zealand.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tea Tree Oil). The essential oil obtained by steam distillation from the foliage and terminal branchlets of *Melaleuca alternifolia, M. linariifolia, M. dissitiflora,* and/or other species of *Melaleuca.* It contains less than 7.0% aromadendrene, less than 15% cineole, 0.5 to 12.0% *p*-cymene, 0.5 to 4.0% limonene, 1.0 to 6.0% α-pinene, less than 3.5% sabinene, 5.0 to 13.0% α-terpinene, 10.0 to 28.0% γ-terpinene, minimum of 30% terpinen-4-ol, 1.5 to 8.0% α-terpineol, and 1.5 to 5.0% terpinolene.

A clear, mobile, colourless to pale yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Melaleuca oil has bactericidal and fungicidal properties and is used topically for various skin disorders. It is also used in aromatherapy.

References.

1. Carson CF, *et al.* Efficacy and safety of tea tree oil as a topical antimicrobial agent. *J Hosp Infect* 1998; **40:** 175–8.
2. Allen P. Tea tree oil: the science behind the antimicrobial hype. *Lancet* 2001; **358:** 1245.
3. Satchell AC, *et al.* Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol* 2002; **43:** 175–8.
4. Hammer KA, *et al.* In vitro activity of Melaleuca alternifolia (tea tree) oil against dermatophytes and other filamentous fungi. *J Antimicrob Chemother* 2002; **50:** 195–9.
5. Satchell AC, *et al.* Treatment of dandruff with 5% tea tree oil shampoo. *J Am Acad Dermatol* 2002; **47:** 852–5.
6. Koh KJ, *et al.* Tea tree oil reduces histamine-induced skin inflammation. *Br J Dermatol* 2002; **147:** 1212–7.
7. Mozelsio NB, *et al.* Immediate systemic hypersensitivity reaction associated with topical application of Australian tea tree oil. *Allergy Asthma Proc* 2003; **24:** 73–5.
8. Perrett CM, *et al.* Tea tree oil dermatitis associated with linear IgA disease. *Clin Exp Dermatol* 2003; **28:** 167–70.
9. Hammer KA, *et al.* Antifungal effects of Melaleuca alternifolia (tea tree) oil and its components on Candida albicans, Candida glabrata and Saccharomyces cerevisiae. *J Antimicrob Chemother* 2004; **53:** 1081–5.
10. Hammer KA, *et al.* A review of the toxicity of Melaleuca alternifolia (tea tree) oil. *Food Chem Toxicol* 2006; **44:** 616–25.
11. Carson CF, *et al.* Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev* 2006; **19:** 50–62.

For a disputed association between products containing melaleuca and lavender oils and the development of prepubertal gynaecomastia, see under Lavender Oil, p. 2541.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Clean Skin Anti Acne†; Moov Insect Repellent; Rapaid Itch Relief; ***Chile***: Acnoxyl Acondicionador; Sebolic; ***Fr.***: Myleuca; ***Hung.***: Tebamol; ***Irl.***: MOOV Head Lice†; ***Israel***: Burnshield; ***Malaysia***: MOOV; ***Mon.***: Onykoleine; ***Singapore***: Moov; Rapaid; ***UK***: Burnshield Gel; Melavir; Vosene Kids 3 in 1.

Multi-ingredient Preparations. ***Arg.***: Sebosoap; ***Austral.***: Apex Repel Natural; Bosisto's Antiseptic Spray; Clean Skin Face Wash†; Elmore Oil; Moov Head Lice Solution; NeutraLice; Nyal Nasal Spray; Rapaid Rash-Relief; ***Chile***: Acnoxyl Abrasivo†; Acnoxyl Gel Humectante; Acnoxyl Jabon Liquido†; Acnoxyl Locion Tonica; ***Fr.***: Cicatridine; Esculape†; Mycogel†; Navi Blef; Olioseptil Gorge-Larynx; Olioseptil Nez-Gorge; Phytosquame†; Squaphane P; ***Hong Kong***: Mycogel†; Vita Coldycin Echinacea Plus†; ***India***: Acneguard; Acnestal; Climdan; Clin-3; Dandruff Plus; Evaren; LTT Cleanser; Moiste; ***Irl.***: Skin Clear†; ***Israel***: Acti Talc; ***Ital.***: Keromicil; Keromicil; Naturocil; Vaginol; ***Malaysia***: T3 Acne; ***NZ***: Electric Blue Headlice; Electric Blue Headlice; Lice Blaster; ***Philipp.***: Enfacare; ***Singapore***: Burnaid; Purifying Gel; Rapaid; Regulator; T3; Teenstick; ***Thai.***: Fungicon; Gynecon-T; ***UK***: Dr Johnsons Nit & Lice; Sinose; Skin Clear; Tea Tree & Witch Hazel Cream; Teenstick; ***USA***: Zim's Max Freeze.

Melanocyte-stimulating Hormone

β Hormone; Chromatophore Hormone; Hormona melanocitoestimulante; Intermedin; Intermedina; Melanotropin; Melanotropina; MSH; Pigment Hormone; Меланоцитостимулирующий Гормон.

CAS — 9002-79-3.

Profile

Melanocyte-stimulating hormone is a polypeptide isolated from the pars intermedia of the pituitary of fish and amphibia which causes dispersal of melanin granules in the skin of fish and amphibia and allows adaptation to the environment.

In adult humans, the pituitary gland lacks a distinct intermediate lobe, and the pituitary is not thought to secrete melanocyte-stimulating hormone (MSH) directly. However, the precursor molecule, pro-opiomelanocortin, is cleaved in the pituitary into corticotropin (p. 1628.3), the glycoprotein β-lipotrophin (β-LPH), and an amino-terminal peptide. Subsequent processing in other tissues, such as the brain and gastrointestinal tract, may yield three forms of MSH: α-MSH (via corticotropin cleavage), β-MSH, and γ-MSH. The presence and function of these melanocyte-stimulating hormones in man are uncertain. A receptor analogous to that in amphibians is apparently lacking in humans; effects on skin pigmentation emanating from the pituitary are mainly mediated by corticotropin.

Release of melanocyte-stimulating hormone is inhibited in *animals* by melanostatin; there is also evidence for a hypothalamic releasing factor (MRF).

Melanocyte-stimulating hormone is under investigation, as α-MSH, in the prevention and treatment of ischaemic intrinsic acute renal failure. Afamelanotide (4-L-norleucine-7-D-phenylalanine-α-MSH; melanotan-I), a synthetic analogue of α-MSH, is under investigation as a photoprotective agent in skin conditions such as erythropoietic protoporphyria, phototoxicity associated with photodynamic therapy, polymorphous light eruptions, actinic keratosis, and solar urticaria. Another α-MSH synthetic analogue, melanotan-II, was under investigation for sexual dysfunction although this has been abandoned. However, its metabolite, bremelanotide (PT-141), is under investigation for haemorrhagic shock. Afemelanotide and melanotan II are widely abused as lifestyle drugs (see below).

Abuse. Analogues of α-melanocyte-stimulating hormone (α-MSH) are illicitly manufactured and supplied as lifestyle drugs. Afamelanotide (melanotan I) is widely abused to obtain a cosmetic tan. Some people also use it for medical conditions such as rosacea and fibromyalgia. Another α-MSH analogue, melanotan II, is abused to increase sexual desire and induce penile erections.[1] Illicit supply and use of such drugs raises several concerns.[1,2] The safety, quality, and efficacy of unregulated compounds is always questionable and there is the additional concern of sterility of the preparation since α-MSH analogues are reconstituted in bacteriostatic water and given by subcutaneous injection. Endogenous α-MSH has many regulatory functions in humans and therefore use of exogenous α-MSH analogues could adversely affect several physiological systems, especially as there is the potential for long-term use if abused for lifestyle reasons. Illicit use of α-MSH for tanning has also been associated with a change in size and pigmentation of pre-existing moles[3] and a rapid increase in the number of new moles.[4,5]

1. Evans-Brown M, *et al.* Use of melanotan I and II in the general population. *BMJ* 2009; **338:** 424–5.
2. MHRA. "Tan jab" is an unlicensed medicine and may not be safe — warns medicines regulator. Press release (issued 17 November 2008). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON031009 (accessed 04/06/09)
3. Langan EA, *et al.* Change in moles linked to use of unlicensed "sun tan jab". *BMJ* 2009; **338:** 251.
4. Cardones AR, Grichnik JM. α-Melanocyte-stimulating hormone-induced eruptive nevi. *Arch Dermatol* 2009; **145:** 441–4.
5. Cousen P, *et al.* Eruptive melanocytic naevi following melanotan injection. *Br J Dermatol* 2009; **161:** 707–8.

Erythropoietic protoporphyria. Afamelanotide as a modified-release resorbable implant given subcutaneously at a dose of 20 mg and repeated after an interval of 60 days has shown benefit in the treatment of erythropoietic protoporphyria in 5 patients in an open-label study.[1]

1. Harms J, *et al.* An α-melanocyte-stimulating hormone analogue in erythropoietic protoporphyria. *N Engl J Med* 2009; **360:** 306–7.

Melanostatin

Hormona inhibidora de la melanotropina; Intermedin-inhibiting Factor; Melanocyte-stimulating-hormone-release-inhibiting Factor; Melanostatina; Melanotropin Release-inhibiting Factor; MIF; Меланостатин.

Pro-Leu-Gly-NH_2.

CAS — 9083-38-9.

Profile

Melanostatin is a tripeptide, obtained from the hypothalamus, that inhibits the release of melanocyte-stimulating hormone (see above) in *animals*. However, there is little evidence of its activity in man. It has been tried in the treatment of depression and parkinsonism but with little benefit.

Melatonin

N-Acetyl-5-methoxytryptamine; Melatoniini; Melatonina; Melatoninum.

N-[2-(5-Methoxyindol-3-yl)ethyl]acetamide.

$C_{13}H_{16}N_2O_2$=232.3

CAS — 73-31-4.

ATC — N05CH01.

ATC Vet — QN05CH01.

UNII — JL5DK93RCL.

Pharmacopoeias. In *Br* and *US*.

BP 2014: (Melatonin). A white to off-white crystalline powder. Slightly soluble in water; soluble in methyl alcohol, in acetone, and in ethyl acetate. Store at a temperature not exceeding 30 degrees. Protect from light.

USP 36: (Melatonin). Store in airtight containers. Protect from light.

Uses and Administration

Melatonin is a hormone produced in the pineal gland from the amino acid tryptophan. Results mainly from *animal* studies indicate that melatonin increases the concentration of aminobutyric acid and serotonin in the midbrain and hypothalamus and enhances the activity of pyridoxal-kinase, an enzyme involved in the synthesis of aminobutyric acid, dopamine, and serotonin. Melatonin is involved in the inhibition of gonadal development and in the control of oestrus. It is also involved in protective changes in skin coloration. There appears to be a diurnal rhythm of melatonin secretion; it is secreted during hours of darkness and may affect sleep pattern. Because of its possible role in influencing circadian rhythm, melatonin has been tried in the alleviation of jet lag and other disorders resulting from delay of sleep. Melatonin is given orally as a modified-release preparation in doses of 2 mg once daily, 1 to 2 hours before bedtime and after food, for the short-term management of primary insomnia in patients aged 55 or over; the dosage may be continued for up to 13 weeks. Melatonin has also been studied in various depressive disorders including seasonal affective disorder, and in large doses for its contraceptive activity.

For doses in children, see p. 2552.1.

Several melatonin analogues are being developed.

Melatonin has been tried in several disorders[1] including, in large doses, as an adjunct to conventional chemotherapy for malignant neoplasms[2,3] and, with norethisterone, as a contraceptive.[4] It is possible that contraceptive use of melatonin may be associated with a reduced risk of breast cancer.[5] For mention of response to melatonin in 2 patients with sarcoidosis, see p. 1612.2. Preliminary studies have also suggested that melatonin may be beneficial in hyperlipidaemias,[6] cluster headaches,[7] tinnitus,[8] alopecia in women,[9] and irritable bowel syndrome associated with sleep disturbances.[10] Repeated bedtime doses may also play a part in reducing nocturnal blood pressure in patients with essential hypertension.[11] Claims for its value as an anti-ageing treatment and for use in conditions such as Alzheimer's disease and AIDS are unfounded.[2,12] The effects of long-term use of melatonin have yet to be assessed.

1. Wetterberg L. Melatonin and clinical application. *Reprod Nutr Dev* 1999; **39:** 367–82.
2. Pepping J. Melatonin. *Am J Health-Syst Pharm* 1999; **56:** 2520–7.
3. Lissoni P, *et al.* Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer* 1999; **35:** 1688–92.
4. Short RV. Melatonin. *BMJ* 1993; **307:** 952–3.
5. Cohen M, *et al.* Hypotheses: melatonin/steroid combination contraceptives will prevent breast cancer. *Breast Cancer Res Treat* 1995; **33:** 257–64.
6. Pittalis S, *et al.* Effect of a chronic therapy with the pineal hormone melatonin on cholesterol levels in idiopathic hypercholesterolemic patients. *Recenti Prog Med* 1997; **88:** 401–2.
7. Leone M, *et al.* Melatonin versus placebo in the prophylaxis of cluster headache; a double-blind pilot study with parallel groups. *Cephalalgia* 1996; **16:** 494–6.

8. Rosenberg SI, *et al*. Effect of melatonin on tinnitus. *Laryngoscope* 1998; **108:** 305–10.
9. Fischer TW, *et al*. Melatonin increases anagen hair rate in women with androgenetic alopecia or diffuse alopecia: results of a pilot randomized controlled trial. *Br J Dermatol* 2004; **150:** 341–5.
10. Song GH, *et al*. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study. *Gut* 2005; **54:** 1402–7.
11. Scheer FAJL, *et al*. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 2004; **43:** 192–7.
12. Brzezinski A. Melatonin in humans. *N Engl J Med* 1997; **336:** 186–95.

Administration in children. Although melatonin is unlicensed in the UK for use in children, the *BNFC* suggests that it may be used for the treatment of sleep-onset insomnia and delayed sleep phase syndrome associated with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, autism, and learning difficulties in children aged 1 month to 18 years. Suggested oral doses are 2 to 3 mg once daily initially, increased if necessary after 1 to 2 weeks to 4 to 6 mg up to a maximum of 10 mg daily. However, little is known about the long-term effects of melatonin in children, including its effects on other circadian rhythms such as endocrine or reproductive hormone secretion, and use in children should therefore be reviewed every 6 months. Unlicensed immediate-release formulations of melatonin may be more suitable for use in children rather than the licensed modified-release formulation used in adults (see p. 2551.3), but in this case, prescribers should specify the manufacturer because of variability in clinical effect between unlicensed preparations.

Melatonin is also sometimes used in children before magnetic resonance imaging (MRI), computed tomography (CT), or EEG investigations.

Insomnia. Although melatonin is considered[1-6] to be potentially useful in the management of various forms of insomnia (p. 1033.2), especially those associated with circadian rhythm disturbances, there is little evidence of efficacy from large studies[7] and its long-term safety is unknown. A meta-analysis[8] of randomised controlled studies concluded that melatonin does not have a significant effect on sleep onset latency in secondary sleep disorders or those accompanying sleep restriction such as jet lag and shift work. In healthy subjects melatonin has been reported[9,10] to reduce the time to onset of sleep and to increase the time spent asleep. Whether this is due to adjustment of the 'body clock' or any hypnotic action of melatonin is unclear. Measurement of nocturnal urinary excretion of the major metabolite, 6-sulfatoxymelatonin, showed that low nocturnal melatonin production is associated with insomnia in patients over 55 years of age, and might identify those more likely to respond to treatment with melatonin.[11] Improved quality of sleep has been reported in elderly patients treated with melatonin for insomnia,[12] and it might be of use in delayed sleep phase syndrome[13] and insomnia in shift workers and totally blind people, although some[14,15] have found no beneficial effects of melatonin in night shift workers or emergency medicine employees. There has also been a report[16] of a patient with somnolence associated with melatonin deficiency after pinealectomy who responded to treatment with melatonin. A preliminary report[17] has suggested that use of melatonin may enable benzodiazepine therapy for insomnia to be stopped without impairing the quality of sleep. However, melatonin might adversely affect sleep patterns in some circumstances.[18] Melatonin has been tried with some benefit in improving sleep patterns in patients with end-stage renal disease undergoing daytime haemodialysis.[19] Transdermal melatonin may have advantages over fast-release oral formulations in improving plasma-melatonin concentrations.[20]

1. Haimov I, Lavie P. Potential of melatonin replacement therapy in older patients with sleep disorders. *Drugs Aging* 1995; **7:** 75–8.
2. Brown GM. Melatonin in psychiatric and sleep disorders: therapeutic implications. *CNS Drugs* 1995; **3:** 209–26.
3. Anonymous. Melatonin. *Med Lett Drugs Ther* 1995; **37:** 111–12.
4. Arendt J. Melatonin. *BMJ* 1996; **312:** 1242–3.
5. Lamberg L. Melatonin potentially useful but safety, efficacy remain uncertain. *JAMA* 1996; **276:** 1011–14.
6. Skene DJ, *et al*. Use of melatonin in the treatment of phase shift and sleep disorders. *Adv Exp Med Biol* 1999; **467:** 79–84.
7. Anonymous. Melatonin for primary insomnia? *Drug Ther Bull* 2009; **47:** 74–7.
8. Buscemi N, *et al*. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Abridged version: *BMJ* 2006; **332:** 385–8. Full version: http://www.bmj.com/cgi/reprint/332/7538/385.pdf (accessed 25/07/08)
9. Zhdanova IV, *et al*. Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther* 1995; **57:** 552–8.
10. Attenburrow MEJ, *et al*. Low dose melatonin improves sleep in middle-aged subjects. *Psychopharmacology (Berl)* 1996; **126:** 179–81.
11. Leger D, *et al*. Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. *Am J Med* 2004; **116:** 91–5.
12. Garfinkel D, *et al*. Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 1995; **346:** 541–4.
13. Nagtegaal JE, *et al*. Effects of melatonin on the quality of life in patients with delayed sleep phase syndrome. *J Psychosom Res* 2000; **48:** 45–50.
14. Wright SW, *et al*. Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. *Ann Emerg Med* 1998; **32:** 334–40.
15. Jockovich M, *et al*. Effect of exogenous melatonin on mood and sleep efficiency in emergency medicine residents working night shifts. *Acad Emerg Med* 2000; **7:** 955–8.
16. Lehmann ED, *et al*. Somnolence associated with melatonin deficiency after pinealectomy. *Lancet* 1996; **347:** 323.
17. Garfinkel D, *et al*. Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 1999; **159:** 2456–60.
18. Middleton BA, *et al*. Melatonin and fragmented sleep patterns. *Lancet* 1996; **348:** 551–2.
19. Koch BC, *et al*. The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study). *Br J Clin Pharmacol* 2009; **67:** 68–75.
20. Aeschbach D, *et al*. Use of transdermal melatonin delivery to improve sleep maintenance during daytime. *Clin Pharmacol Ther* 2009; **86:** 378–82.

Jet lag. Melatonin has been reported to alleviate jet lag after long flights.[1-5] The most appropriate dosing schedule has yet to be determined but will depend on both the direction of travel and the distance travelled. A systematic review[6] concluded that melatonin was effective in preventing or reducing jet lag in those travelling across 5 or more time zones, particularly in an easterly direction, and especially if jet lag had been experienced previously; travellers crossing 2 to 4 time zones might also derive benefit. However, a meta-analysis[7] of randomised controlled studies concluded that melatonin does not have a significant effect on sleep onset latency accompanying jet lag.

1. Waterhouse J, *et al*. Jet-lag. *Lancet* 1997; **350:** 1611–16.
2. Arendt J. Jet-lag. *Lancet* 1998; **351:** 293–4.
3. Arendt J. Jet-lag and shift work: (2) therapeutic use of melatonin. *J R Soc Med* 1999; **92:** 402–5.
4. Waterhouse J, *et al*. Jet lag: trends and coping strategies. *Lancet* 2007; **369:** 1117–29.
5. Sack RL. Jet lag. *N Engl J Med* 2010; **362:** 440–7.
6. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 28/04/05).
7. Buscemi N, *et al*. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Abridged version: *BMJ* 2006; **332:** 385–8. Full version: http://www.bmj.com/cgi/reprint/332/7538/385.pdf (accessed 25/07/08)

Adverse Effects and Precautions

The most commonly reported adverse effects with melatonin are headache, nasopharyngitis, back pain, and arthralgia.

Melatonin should not be used in patients with autoimmune disease or hereditary galactose intolerance disorders, LAPP lactase deficiency, or glucose-galactose malabsorption. Melatonin should not be used in patients with hepatic impairment because of reports of decreased clearance in such patients.

Effects on the nervous system. An increase in seizure activity was noted in 4 of 6 children with severe neurological deficits during treatment with melatonin for sleep disorders.[1] Seizure activity returned to baseline values when melatonin was stopped and recurred on rechallenge.

1. Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998; **351:** 1254.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies melatonin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Cytochrome P450 isoenzymes CYP1A1 and CYP1A2 are involved in the metabolism of melatonin and consequently other drugs that inhibit or induce these isoenzymes may affect melatonin levels. Melatonin should not be taken with fluvoxamine, methoxsalen, cimetidine, or oestrogens, all of which increase melatonin concentrations through inhibition of its metabolism. Tobacco smoking has been reported to decrease melatonin concentrations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Armonil Noche; Buenas Noches; Melatol; ***Austral.***: Circadin; ***Austria***: Circadin; ***Belg.***: Circadin; ***Cz.***: Circadin; ***Denm.***: Circadin; ***Fr.***: Circadin; ***Ger.***: Circadin; ***Gr.***: Circadin; ***Hung.***: Bio-Melatonin; Circadin; ***India***: Meloset; ***Irl.***: Circadin; ***Israel***: Circadin; ***Ital.***: Armonia; Melamil†; ***Mex.***: Benedorm; Cronocaps; Normolem; Remedin; ***Neth.***: Circadin; ***Norw.***: Circadin; ***NZ***: Circadin; ***Philipp.***: Sleepwell; ***Pol.***: Circadin; ***Port.***: Circadin; ***Rus.***: Circadin (Циркадин); Melaxen (Мелаксен); ***Spain***: Circadin; ***Swed.***: Circadin; ***Switz.***: Circadin; ***Thai.***: Circadin; ***UK***: Circadin; ***Ukr.***: Melaxen (Мелаксен); ***USA***: Transzone.

Multi-ingredient Preparations. ***Arg.***: Plenovit Melatonina; ***India***: Alprax Z; Destres; Eternex†; Meloprax; Stresnil; ***Ital.***: Nervocel†; Pineal Notte; Pineal Notte; Stressout; ***Philipp.***: Sleepasil; ***USA***: Bevitamel; Melagesic PM; PowerSleep.

Pharmacopoeial Preparations
BP 2014: Melatonin Capsules;
USP 36: Melatonin Tablets.

Melilot

Barkūno žolė; Gelber Steinklee; Komonicová vňať; Mélilot; Meliloti herba; Rohtomesikkä; Sötväppling; Steinkleekraut; Sweet Clover; Yellow Melilot; Yellow Sweet Clover; Ziele nostrzyka; Донник.

ATC Herb — HC05BW5002 (Melilotus officinalis: *herb*).
UNII — DJR90OLD7P (Melilotus officinalis); *GM6P02J2DX* (Melilotus officinalis *top*).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Melilot; Meliloti Herba). The whole or cut, dried aerial parts of *Melilotus officinalis*. It contains a minimum of 0.3% coumarin, calculated with reference to the dried drug. Protect from light.

Profile

Melilot is used internally in herbal preparations for chronic venous insufficiency. It contains coumarin (see p. 2487.2) and its derivatives, and the dose may be expressed in terms of coumarin. The German expert committee for herbal drugs and preparations (Commission E) also allows the addition or substitution of *M. altissimus* (tall melilot), tall yellow sweet clover.

Melilotus officinalis is also used externally.

Homoeopathy

Melilot has been used in homoeopathic medicines under the following names: Melilotus officinalis; Melilotus off; Mel. off.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Varizil; Vecasten; Venolise; ***Ger.***: Meli Rephastasan†; ***Ital.***: Linfodermina.

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; Cellasene†; Gentianella; Snell Patch; Snell Progress; Varicura; Venart Crema; ***Austral.***: Zellulean with Escin†; ***Canad.***: Natraway Sport 1 & 2†; ***Chile***: Celltech; ***Fr.***: Anthylline†; Antinerveux Lesourd†; Creme au Melilot Composee†; Cyclo 3; Esberiven Fort; Esberiven; Evarose†; Mediflor Circulation du Sang No 12†; Santane V_3†; Sedopal; ***Ital.***: Binfolipase; Binfonorm†; Capill Venogel; Cumadren; Deproctol; Dermilia Flebozin†; Deroidal; Diosmina Complex; Facosmina; Flebo-Si†; Flebofort; Flebonorm; Flebovis materna; Flebovis; Flebozin; Fraxiven; Gefion; Levital Plus; Linfoguard†; Linfonorm Cremagel; Lipaven; Pulsalux; Tractoven; Traumaven; Venodin; Venoplant; Venoplant; Venoton; ***Pol.***: Masc na Odciski; Tabletki Tonizujace; ***Rus.***: Cyclo 3 (Цикло 3); Herbion Aesculus (Гербион Эскулюс); ***Singapore***: Cyclo 3†; ***Spain***: Fabroven†; ***Switz.***: Phlebodril; ***Ukr.***: Herbion Aesculus (Гербион Эскулус); Pravenor (Правенор).

Homoeopathic Preparations. ***Austria***: Spigelon; Venodril; ***Canad.***: Headache & Migraine L77; Headache & Migraine; Homeo-Form MI†; Nareel†; Spigelon†; ***Fr.***: Hypericum Complexe No 26; Phapax; ***Ger.***: Biodolor; Cefanalgin†; Neuro-Do; Pflugerplex Gelsemium; Schwoneural N; veno-loges N; ***Hung.***: Naso-Heel S; Spigelon; ***Neth.***: Aesculus Comp; Cephalite; Co-Hypert; Gynaelite; ***Switz.***: Spigelon.

Melissa

Balm, Lemon; Citromfűlevél; Lemon Balm; Liść melisy; Meduňkový list; Melisų lapai; Melisa; Meliss; Melissae folium; Mélisse, feuille de; Melissenblatt; Sitruunamelissanlehti; Toronjil; Мелисса Лекарственная.

ATC Herb — HN02CW5001 (Melissa officinalis: *leaf*); *HA03AW5036* (Melissa officinalis: *leaf*); *HN05CM5015* (Melissa officinalis: *leaf*); *HR05YA5013* (Melissa officinalis: *leaf*).
UNII — YF70189L0N (Melissa officinalis *whole*); *50D2ZE9219* (Melissa officinalis *leaf*).

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract prepared from the leaves.

Ph. Eur. 8: (Melissa Leaf). The dried leaf of *Melissa officinalis*. It contains not less than 1% of rosmarinic acid ($C_{18}H_{16}O_8 = 360.3$), calculated with reference to the dried drug. It has an odour reminiscent of lemon. Protect from light.

Profile

Melissa has been used as a carminative and sedative. It is an ingredient of herbal remedies used for a variety of disorders. It is also reported to have virustatic activity and has been applied topically for herpes labialis. The chief constituent of

melissa is citral (p. 2480.2). Hypersensitivity reactions to melissa have been reported.

Melissa is the source of melissa oil (see below).

Homoeopathy

Melissa has been used in homoeopathic medicines under the following names: Melissa officinalis.

References.

1. Ballard CG, *et al*. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with melissa. *J Clin Psychiatry* 2002; **63:** 553–8.
2. WHO. Folium Melissae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/18.html (accessed 05/02/10)
3. Ulbricht C, *et al*. Natural Standard Research Collaboration. Lemon balm (*Melissa officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2005; **5:** 71–114.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lomaherpan; ***Belg.***: Dormiplant†; ***Canad.***: Erpecalm†; ***Chile***: Citromel; ***Cz.***: Medunkovy; ***Ger.***: Gastrovegetalin; Lomaherpan; ***Rus.***: Lomaherpan (Ломагерпан); Novo-Passit (Ново-Пассит); ***Swed.***: Valerina; ***Switz.***: Valverde Boutons de fievre creme.

Multi-ingredient Preparations. ***Arg.***: Alcachofa Plus; Nervocalm; Sabelin; Valeriana Compuesta; Valeriana Oligoplex; Valeriana Relax Diates†; ***Austral.***: Executive Sleep Formula; Herbal Rest & Relax; Natural Deep Sleep†; Nyal Night-Time Cough; Nyal Sleep Aid; Sleep Sound Formula; ***Austria***: Abdomilon N; Baldracin; Baldrian comp; Iberogast; Klosterfrau Melissengeist; Mariazeller; Passedan; Sedogelat; The Chambard-Tee; Wechseltee St Severin; ***Belg.***: Calmiplant; Eau Des Carmes; Minhavez; Songha†; ***Braz.***: Balsamo Branco; Bronquiogen†; Calmapax; Camomila; Passaneuro; Sedantol; Sonhare; ***Canad.***: Bilonat; Detente†; Dormane Plus; Formula T4†; Natural HRT Nighttime; Relaxant; Relaxol; Salusan†; Swiss Herb Cough Drops; ***Chile***: Bebe Son; Melipass; Perfect Body; Recalm†; ***Cz.***: Alvisan Neo; Baldracin†; Euvekan†; Fytokliman Planta; Hypotonicka†; Iberogast; Klosterfrau Melisana; Nervova Cajova Smes; Novo-Passit; Passedan†; Passit; Persen; Species Nervinae Planta; Valofyt Neo†; ***Denm.***: Relana†; ***Fr.***: Aromazen†; Azema†; Biocarde; Boribel Tisane No 6†; Calmotisan†; DNV; Dystolise; Elixir Bonjean†; Herpclair; Mediflor Circulation du Sang No 12†; Mediflor Pectorale d'Alsace no 8†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Omezelis; Phytozac; Phytozac; Santane C_6†; Santane D_5†; Santane N_9; Vagostabyl; ***Ger.***: Abdomilon N; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee†; Euvegal Entspannungs- und Einschlaftropfen; Euvegal; Heumann Beruhigungstee Tenerval; Iberogast; Klosterfrau Melissengeist; Melissengeist; Oxacant-sedativ; Pascosedon; Phytonoctu; Plantival forte; Plantival novo; Sandrin; Seda-Plantina N; Sedacur; Sedariston plus†; Valeriana Beruhigungsdragees; Vivinox Day; ***Hung.***: Antifront; Antifront; Antipoll; Carmol; Crategil; Euvekan†; Herbalakt; Herpesil; Iberogast; Klosterfrau Melisana; Menofit; Mensesyl; Sedacur; Sedogelat; Telma; Travelon; Worishofener; ***Israel***: Songha Night; ***Ital.***: Actenacol; Calmason; Colimil; Dormiplant; Emmenoiasi; Enatus; Ginepausil; Lenifren; Sedatol; Tisana Kelemata; Vagostabil Junior; Vagostabil; ***Malaysia***: Circarol; ***Mex.***: Nordimenty; Plantival; ***Neth.***: Iberogast; ***Norw.***: Euvekan†; Sobal†; Songha Natt; Valerina Natt; ***NZ***: Botanica Hayfever; Mr Nits; ***Philipp.***: Circulan; ***Pol.***: Amarosal; Aromatol; Bobofen†; Calmina; Carmolis; Cravisol; DexaCaps; Doppelherz Energovital Tonik K; Dormiplant; Iberogast; Klimax; Lumewal; Melisal; Melisana Klosterfrau; Melissed; Nervinolum; Nervinum†; Nervomag; Nervomix; Nervosan†; Nervosol; Nerwobonisol; Perfocrat†; Persen; Psychotonisol†; Relana†; Sedomix; Somnoten†; Tabletki Uspokajajace; Ulventroten†; ***Rus.***: Cedoflor (Седофлор); Doppelherz Melissa (Доппельгерц Мелисса); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Dormiplant (Дормиплант); Persen (Персен); Phyto Novo-Sed (Фито Ново-Седа); ***S.Afr.***: Melissengeist†; Spiritus Contra Tussim Drops†; ***Singapore***: Stop Snoring; ***Spain***: Agua del Carmen; Dormiplant†; Iberogast; Melival; Nervikan; Relana†; Resolutivo Regium†; Solucion Schoum; ***Swed.***: Iberogast; Sedacur; ***Switz.***: Arterosan Plus†; Baldriparan; Cardiaforce; Dormiplant; Dragees pour la detente nerveuse et le sommeil†; Dragees pour la detente nerveuse†; Femisan; Gastrosan; Hyperiforce comp; Iberogast; Kernosan 26; Metabol; Relaxane; Relaxo; Songha Night; Tisane calmante pour les enfants; Tisane favorisant l'allaitement; Tisane pour l'estomac; Tisane pour le coeur et la circulation; Tisane pour le sommeil et les nerfs; Tisane pour nourissons et enfants; Valverde Detente dragees; ***Turk.***: Nervikan; Nevrol Cemal; ***UK***: DiaDay & Night; DiaRelax; Digestion Calming Drops; Melissa Comp.; Puncto SleepTight; Spotner; Valerina Day Time; Valerina Night-Time; ***Ukr.***: Antifront (Антифронт); Antifront (Антифронт); Dormiplant (Дормиплант); Herbion Sedative Drops (Гербион Успокаивающие Капли)†; Iberogast (Иберогаст); Klimased (Климасед); Normoton (Нормотон); Novo-Passit (Ново-Пассит); Persen (Персен); Relaxil (Релаксил); Sedasen (Седасен); ***Venez.***: Euvekan; Sedival.

Homoeopathic Preparations. ***Austria***: Valerianaheel; ***Canad.***: Lemon Balm†; Motherwort Combination 3†; Valerianaheel Comp†; ***Chile***: Melinerv; ***Ger.***: Myonasan; Roth's RKT Tropfen; ***Neth.***: Neurovita; ***UK***: Cough Drops.

Melissa Oil

Balm Oil; Esencia de Melisa; Lemon Balm Oil; Мелиссовое Масло.

CAS — 8014-71-9.

*ATC Herb — HN05CM5014 (*Melissa officinalis*: essential oil).*

UNII — MJ76269K9S.

Profile

Melissa oil is the essential oil obtained from melissa (*Melissa officinalis*), p. 2552.3. It is used in preparations with other essential oils in a variety of disorders. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Opino; ***Canad.***: Melisana†; ***Chile***: Agua del Carmen; Agua Melisa Carminativa; ***Cz.***: Thrombocid; ***Fr.***: Stomargil; ***Ger.***: Amol Heilkrautergeist N; Thrombocid; ***Gr.***: Opino; ***Hung.***: Amol; Pasta Cool; ***Indon.***: Opino†; ***Ital.***: Altadrine Firming†; Dentosan Azione Intensiva; Dentosan Mese; Neuralta Migren; ***Pol.***: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Doppelherz Energovital Tonik†; ***Port.***: Thrombocid; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энготоник); ***Switz.***: DUL-X warm; DUL-X.

Menbutone *(BAN, rINN)*

Menbuton; Menbutona; Menbutoni; Menbutonum; SC-1749 (menbutone sodium); Менбутон.

4-(4-Methoxy-1-naphthyl)-4-oxobutyric acid.

$C_{15}H_{14}O_4$=258.3

CAS — 3562-99-0.

ATC Vet — QA05AX90.

UNII — 341YM32546.

Profile

Menbutone is used as a choleretic to stimulate gastrointestinal function in veterinary medicine.

Menfegol *(rINN)*

Menfégol; Menfegolum; Menphegol; Менфеголь.

α-[*p*-(*p*-Menthyl)phenyl]-ω-hydroxypoly(oxyethylene).

$C_{16}H_{23}(OCH_2CH_2)_nOH$

CAS — 57821-32-6.

Profile

Menfegol is a macrogol aryl ether nonionic surfactant (p. 2164.2). It is used as a spermicide.

Adverse effects. Frequent use of menfegol in spermicidal foaming tablets has been associated with a high incidence of genital ulceration, which could increase the risk of infection by HIV.[1]

1. Goeman, J. *et al*. Frequent use of menfegol spermicidal vaginal foaming tablets associated with a high incidence of genital lesions. *J Infect Dis* 1995; **171:** 1611–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Neo Sampoon†; ***Malaysia***: Neo Sampoon; ***Philipp.***: Neo Sampoon; ***Singapore***: Neo Sampoon†.

Menthol

Hexahydrothymol; Mentholum; Mentol; Mentoli; Mentolis; Ментол.

p-Menthan-3-ol; 2-Isopropyl-5-methylcyclohexanol.

$C_{10}H_{20}O$=156.3

CAS — 1490-04-6 (menthol); 15356-60-2 ((+)-menthol); 2216-51-5 ((-)-menthol); 89-78-1((±)-menthol).

UNII — L7T10EIP3A.

Description. Menthol is either the laevo-isomer, levomenthol (*BAN*, *rINN*), or a racemic mixture, racementhol (*BAN*, *rINN*). The laevo-isomer may be obtained from the volatile oils of various species of *Mentha* (Labiatae) or it may be prepared synthetically.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* *Eur.* and *Jpn* have separate monographs for laevo-menthol (levomenthol) and racemic menthol (racementhol).

Ph. Eur. 8: (Levomenthol). It occurs as colourless, acicular or prismatic shiny crystals. M.p. about 43 degrees. Practically insoluble in water; very soluble in alcohol and in petroleum spirit; freely soluble in fatty oils and in liquid paraffin; very slightly soluble in glycerol.

Ph. Eur. 8 (Menthol, Racemic; Racementhol BP 2014). It occurs as colourless, acicular or prismatic shiny crystals or as a free-flowing or agglomerated crystalline powder. M.p. about 34 degrees. Practically insoluble in water; very soluble in alcohol and in petroleum spirit; freely soluble in fatty oils and in liquid paraffin; very slightly soluble in glycerol.

USP 36: (Menthol). An alcohol obtained from diverse mint oils or prepared synthetically. It may be laevorotatory (*l*-menthol), from natural or synthetic sources, or racemic (*dl*-menthol). It occurs as colourless, hexagonal crystals, usually needle-like, or in fused masses, or crystalline powder. Has a pleasant, peppermint-like odour. M.p. of *l*-menthol 41 degrees to 44 degrees. Slightly soluble in water; very soluble in alcohol, in chloroform, in ether, and in petroleum spirit; freely soluble in glacial acetic acid, in fixed and volatile oils, and in liquid paraffin. Store in airtight containers preferably at a temperature of 15 degrees to 30 degrees.

Compounding. A liquid or soft mass is formed when menthol is triturated with camphor, cloral hydrate, phenol, and many other substances.

Methods of preparing menthol 1% w/w in aqueous cream BP and the stability of the resultant product have been discussed.[1]

1. Cable C. The preparation of menthol (1 per cent w/w) in aqueous cream BP. *Pharm J* 2005; **274:** 469.

Uses and Administration

Menthol is chiefly used to relieve symptoms of bronchitis, sinusitis, and similar conditions. For this purpose it may be used as an inhalation, usually with benzoin or eucalyptus oil, as pastilles, or as an ointment with camphor and eucalyptus oil for application to the chest or nostrils (but see Adverse Effects below). However, as mentioned under the section on the management of cough (p. 1651.2), the use of menthol in inhalations is unlikely to provide any additional benefit.

When applied to the skin menthol dilates the blood vessels, causing a sensation of coldness followed by an analgesic effect. It relieves itching and is used in creams, lotions, or ointments in pruritus and urticaria. It has also been applied to the forehead, presumably as a counter-irritant, for the relief of headache.

In small oral doses menthol has a carminative action.

A review[1] of menthol's actions and uses noted that menthol elicited a cool sensation by acting on the TRPM8 receptor, a thermosensitive cation channel that is also activated by low temperature.

1. Patel T, *et al*. Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol* 2007; **57:** 873–8.

Neuropathic pain. Topical application of 0.5% menthol in calamine cream twice daily has been reported to relieve severe neuropathic pain induced by bortezomib in a 69-year-old man.[1]

1. Colvin LA, *et al*. From bench to bedside: a case of rapid reversal of bortezomib-induced neuropathic pain by the TRPM8 activator, menthol. *J Clin Oncol* 2008; **26:** 4519–20.

Adverse Effects, Treatment, and Precautions

Menthol may give rise to hypersensitivity reactions including contact dermatitis. Ingestion of significant quantities of menthol is reported to cause symptoms similar to those seen after ingestion of camphor (p. 2466.3), including severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma; they may be managed similarly. There have been reports (below) of apnoea and instant collapse in infants after the local application of menthol to their nostrils.

Administration to infants. Instillation of decongestant preparations containing menthol directly into the nostrils of infants and young children has resulted in acute respiratory distress with cyanosis[1] and respiratory arrest,[2] and must be avoided. In one case,[1] nasal application was associated with concurrent chemical conjunctivitis.

1. Wyllie JP, Alexander FW. Nasal instillation of 'Olbas Oil' in an infant. *Arch Dis Child* 1994; **70:** 357–8.
2. Blake KD. Dangers of common cold treatments in children. *Lancet* 1993; **341:** 640.

Effects on the nervous system. A 13-year-old boy developed ataxia, confusion, euphoria, nystagmus, and diplopia after inhaling 5 mL of Olbas oil instead of the recommended few drops.[1] It was considered probable that the menthol in the preparation was responsible for the symptoms; the amount of menthol inhaled was about 200 mg.

1. O'Mullane NM, *et al*. Adverse CNS effects of menthol-containing Olbas oil. *Lancet* 1982; **i:** 1121.

Pharmacokinetics

After absorption, menthol is excreted in the urine and bile as a glucuronide.

Absorption. The systemic absorption of camphor, menthol, and methyl salicylate from dermal patches containing all three ingredients has been studied.[1] The absolute bioavailability of these compounds could not be determined from this study, but there did not appear to be any substantial systemic accumulation even after unrealistically high exposure for prolonged periods.

1. Martin D, *et al.* Dermal absorption of camphor, menthol, and methyl salicylate in humans. *J Clin Pharmacol*.2004; **44:** 1151–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flex-All; Rati Salil Ice; ***Austral.***: Dencorub Arthritis Ice; Ice Gel; Vicks Vapodrops Butter and Menthol†; ***Canad.***: Absorbine Jr Roll-on Ice†; Absorbine Jr; Absorbine Power Gel; Artic Ice†; Blue Ice Rub; Certified Ice†; Cough Lozenges; Deep Cold; Everflex; Formula G9†; Formula TT†; Formula TTO†; Gel Glace†; Glenalgesic Blue†; Ice Gel Therapy; Medicated Foot Powder†; Polar Ice†; Rub A-535 Antiphlogistine Ice; Soothing Ice Rub†; Vicks VapoDrops; ***Chile***: Friorub; Hielorub†; Mentholatum Patch; ***Hong Kong***: Bengay Patch; Counterpain†; ***Hung.***: Salonpas Gel-Patch; ***India***: Capsigyl-D; Dolocide Plus; Icegel; ***Indon.***: Blue Cap; Counterpain Cool; ***Irl.***: Deep Freeze Cold Gel; Meggezones; ***Jpn***: Minclea; ***Malaysia***: Menzza Ice; ***NZ***: Vicks Throat Drops; Vicks Vapodrops; ***Pol.***: Migrenol†; ***Port.***: Vicks Vaporub; ***Singapore***: Bengay Patch; Bengay Vanishing; Counterpain Cool; ***Spain***: Prulit†; ***Switz.***: Perskindol Cool; ***Thai.***: Centropain; Counterpain Cool; Painza Cool; Stopain; ***UK***: 4Head; Arjun Cream; Benylin Mucus Cough Menthol; Deep Freeze Cold Gel; Dermacool; Happinose; Ice Cool Stress & Tension Relief; Meggezones; Quool; Vicks Cough Syrup with Honey for Dry & Irritating Coughs; Vicks Vaposyrup for Tickly Coughs; ***USA***: Absorbine Jr; Ben-Gay Patch; Ben-Gay Vanishing; Biofreeze; Cepacol Regular Strength; Cepacol Sore Throat Post Nasal Drip; Cold & Hot Pain Relief Therapy Patch; Extra Strength Vicks Cough Drops; Halls-Plus Maximum Strength; Icy Hot Back Pain Relief; Icy Hot Pain Relieving; Icy Hot PM; Icy Hot Pop & Peel; Icy Hot Pro-Therapy; Icy Hot Roll; Kof-Eze; Mineral Freez Gel; N'ice 'n Clear; N'ice; Ricola Herb; Salonpas Aqua Patch†; Sportscreme Ice; Stopain Cold; Therapeutic Mineral Ice; Therapy Ice; Vicks Cough Drops; Wonder Ice; ***Venez.***: Dencorub Ice.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Austria***: Exangina†; ***Ger.***: Mullersche Tabletten.

Pharmacopoeial Preparations
BP 2014: Levomenthol Cream; Menthol and Benzoin Inhalation; **USP 36:** Benzocaine and Menthol Topical Aerosol; Menthol Lozenges; Tetracaine and Menthol Ointment.

Menthol Esters

Menthyl Esters.

Menthyl acetate

Menthol Acetate; Mentylu octan.
5-Methyl-2-(1-methylethyl)cyclohexyl acetate.
$C_{12}H_{22}O_2$=198.3
CAS — 89-48-5; 16409-45-3.
UNII — W8C5F4H1OA.

Menthyl Isovalerate

Menthol Isovalerate; Menthyl Valerate.
5-Methyl-2-(1-methylethyl)cyclohexyl 3-methylbutanoate.
$C_{15}H_{28}O_2$=240.4
CAS — 28221-20-7; 89-47-4; 16409-46-4.
UNII — E6QE751102.

NOTE. The name Validol has been used both as a synonym for menthyl isovalerate and as a proprietary name for a preparation containing it.

Menthyl Lactate

Menthol Lactate; *l*-Menthyl Lactate.
5-Methyl-2-(1-methylethyl)cyclohexyl 2-hydroxypropanoate.
$C_{13}H_{24}O_3$=228.3
CAS — 59259-38-0.
UNII — 2BF9E65L7I.

Profile

Esters of menthol such as the acetate, isovalerate, and lactate are readily hydrolysed to menthol (p. 2553.2) and have similar properties. They are used as flavourings and perfumes, and for their cooling properties in skin-care products.

Menthyl isovalerate also shares some properties with isovaleric acid (p. 2641.2) and has been used similarly. Preparations containing what has been variously described as menthyl isovalerate or a solution of menthol in menthyl isovalerate have been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Darvalidol†; Mentowal; Validol; ***Rus.***: Validol (Валидол); ***Ukr.***: Corvalment (Корвалмент); Validol (Валидол).

Multi-ingredient Preparations. ***Belg.***: Purigel Crisp†; Purigel NF; ***Hung.***: Nicobrevin; ***Irl.***: Nicobrevin†; ***Ital.***: Blogofort†; Flogofort Cremagel; Pitiren; ***NZ***: Nicobrevin; ***Rus.***: Barboval (Барбовал); Carniland (Карниланд); ***UK***: Nicobrevin; ***Ukr.***: Barboval (Барбовал).

Menthone

(*dl*)-menthone; Menton; Ментон; (±)-menthone.
(2*R*,5*S*)-*rel*-5-Methyl-2-(1-methylethyl)cyclohexanone.
$C_{10}H_{18}O$=154.3
CAS — 3391-87-5 ((+)-menthone); 14073-97-3 ((-)-menthone); 89-80-5 ((±)-menthone); 1196-31-2 ((+)-isomenthone); 491-07-6 ((±)-isomenthone).

Profile

Menthone is a constituent of several essential oils. Of the 4 possible stereoisomers of menthone, (-)-menthone (*l*-menthone) is the most abundant in nature. Menthone is reported to be a cholagogue and has been used in preparations for biliary-tract and liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Rowachol; ***Cz.***: Rowachol; ***Ger.***: Rowachol; ***Hong Kong***: Neo-Rowachol; Rowachol; ***Hung.***: Rowachol; ***Irl.***: Rowachol; ***Israel***: Rowachol; ***Malaysia***: Rowachol; ***Mex.***: Cholex; ***Philipp.***: Rowachol; ***Pol.***: Rowachol; Terpichol; ***Thai.***: Rowachol; ***UK***: Rowachol; ***Venez.***: Rowachol.

Menyanthes

Bitterklee; Bogbean; Buckbean; Folia Trifoli Fibrini; Liść bobrka (bogbean leaf); Marsh Trefoil; Ménynanthe; Menyanthidis Folium (bogbean leaf); Menyanthidis trifoliatae folium; Raatteenlehti (bogbean leaf); Tréboł acuático; Trébol de agua; Trébol fabrino; Trèfle d'Eau; Trifolii Fibrini Folium (bogbean leaf); Trilapių pupalaiškių lapai (bogbean leaf); Vachtový list (bogbean leaf); Vattenklöverblad (bogbean leaf); Vidrafűlevél (bogbean leaf); Вахта Трёхлистная.
ATC Herb — HA09WA5019 (Menyanthes trifoliata: *leaf*).
UNII — 7H0QTZ446K (Menyanthes trifoliata); *GYG64DIH9P* (Menyanthes trifoliata *leaf*); *38S191W4O2* (Menyanthes trifoliata *root*).

NOTE. Bog myrtle (see p. 2458.3) has also been used as a common name for *Menyanthes trifoliata*.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bogbean Leaf). The dried, entire or fragmented leaf of *Menyanthes trifoliata*. It has a very bitter and persistent taste.

Profile

Menyanthes has been used as a bitter. It is used in herbal medicine for rheumatic, gastrointestinal, and biliary-tract disorders. It is also used in folk medicine.

Homoeopathy

Menyanthes has been used in homoeopathic medicines under the following names: Menyanthes trifoliata; Menyan. t.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Mariazeller; Pervivo; ***Canad.***: Gallexier†; ***Fr.***: Tisane Hepatique de Hoerdt†; ***Ger.***: Gallexier; ***Hung.***: Bittner; ***Pol.***: Krople Zoladkowe†; Krople Zoladkowe; Pervivo; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***UK***: Modern Herbals Rheumatic Pain; Rheumatic Pain Relief; Rheumatic Pain Remedy; Rheumatic Pain; Vegetex; ***Ukr.***: Trivalumen (Тривалумен).

Homoeopathic Preparations. ***Austral.***: Echine†; ***Canad.***: Alfalfa Tonic; ***Fr.***: Cereales Germees.

Mercaptamine *(BAN, rINN)*

Cysteamine (USAN); Cysteamine; L-1573; MEA; Mercamine; Mercaptamina; Mercaptaminum; Merkaptamiini; Merkaptamin; Меркаптамин.
2-Aminoethanethiol.
C_2H_7NS=77.14
CAS — 60-23-1.
ATC — A16AA04.
ATC Vet — QA16AA04.
UNII — 5UX2SD1KE2.

NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine (p. 820.3) and mercaptamine (formerly cysteamine) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

Mercaptamine Bitartrate *(BANM, rINNM)*

Bitartrato de mercaptamina; Cysteamine Bitartrate; Mercaptamina, bitartrato de; Mercaptamine, Bitartrate de; Mercaptamini Bitartras; Меркаптамина Битартрат.
C_2H_7NS, $C_4H_6O_6$=227.2
CAS — 27761-19-9.
ATC — A16AA04.
ATC Vet — QA16AA04.
UNII — QO84GZ3TST.

Mercaptamine Hydrochloride *(BANM, rINNM)*

CI-9148; Cysteamine Hydrochloride (USAN); Hidrocloruro de mercaptamina; Mercaptamina, hidrocloruro de; Mercaptamine, Chlorhydrate de; Mercaptamini Hydrochloridum; Меркаптамина Гидрохлорид.
C_2H_7NS,HCl=113.6
CAS — 156-57-0.
ATC — A16AA04.
ATC Vet — QA16AA04.
UNII — IF1B771SVB.

Uses and Administration

Mercaptamine reduces intracellular cystine levels and is given orally as the bitartrate and as eye drops containing the hydrochloride in the treatment of cystinosis (see p. 2555.1). Doses are expressed in terms of the base; 2.94 g of the bitartrate or 1.47 g of the hydrochloride are each equivalent to 1 g of mercaptamine.

In the treatment of nephropathic cystinosis, mercaptamine bitartrate is given in an initial dose that is one-sixth to one-quarter of the expected maintenance dose, and is then increased gradually over 4 to 6 weeks. The usual maintenance dose in patients over 12 years of age and weighing over 50 kg is 2 g daily of the base in divided doses. Daily doses above 1.95 g/m² are not recommended. Immediate-release preparations are given in 4 divided doses with or after food and modified-release preparations are given twice daily at least 2 hours after or 30 minutes before eating. Doses are given in conjunction with monitoring of leucocyte-cystine levels, which should be kept below 1 nanomol of hemicystine per mg of protein. Doses for children under 12 years of age or weighing under 50 kg are given below.

Phosphocysteamine, a phosphorothioester of mercaptamine, has been said to be more palatable, and has been used similarly.

Mercaptamine is also used in the treatment of corneal cystine crystal deposits in patients with cystinosis. It is administered as eye drops containing mercaptamine hydrochloride 6.5 mg/mL (equivalent to mercaptamine 0.44%); one drop is instilled into each eye every hour. Eye drops containing mercaptamine 0.11% or 0.55% have also been used.

Mercaptamine is under investigation for the treatment of Huntington's disease and nonalcoholic fatty liver disease in children.

Administration in children. Doses of mercaptamine for the treatment of cystinosis in children should be calculated on the basis of body-surface because of a risk of Ehlers-Danlos-like syndrome with high doses (see Adverse Effects p. 2555.1). The recommended maintenance dose of mercaptamine given orally to children up to 12 years of age or weighing under 50 kg is 1.3 g/m²(about 50 mg/kg) daily in divided doses. Doses should be reduced if any skin or bone abnormalities appear. Daily doses above 1.95 g/m² are not recommended. Lower starting doses and monitoring of leucocyte-cystine levels are recommended as described under Uses and Administration, above.

For children at risk of aspiration or who have difficulty swallowing, the contents of immediate-release capsules may be sprinkled on food, although not in acidic drinks.

Similarly, the contents of modified-release capsules may be mixed with a small amount of liquid or soft food, for example orange juice or apple sauce.

Cystinosis. Mercaptamine is used in the treatment of cystinosis, a rare autosomal recessive metabolic disorder characterised by the intracellular accumulation of cystine. Cystinosis is marked by growth retardation, rickets, Fanconi syndrome, and renal failure necessitating transplantation; acute episodes of acidosis and dehydration may occur. Hypothyroidism generally develops and puberty is delayed in males.[1,2] Photophobia and loss of visual acuity are associated with deposition of cystine in the eye.[3]

Oral mercaptamine treatment is given to increase cystine clearance from cells. It can delay the development of end-stage renal disease, reduce the incidence of extrarenal complications,[4-7] and improve life expectancy.[5,7] Treatment is most effective when started early, at the time of diagnosis in infancy or early childhood.[7,8]

Mercaptamine eye drops are used to dissolve corneal cystine crystals because oral therapy is ineffective.[9] Treatment must be applied frequently throughout the day; photophobia may be relieved within weeks[2] and crystals dissolved over several months.[1]

1. Wilmer MJ, *et al.* Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol* 2011; **26:** 205–15.
2. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr Nephrol* 2013; **28:** 51–9.
3. Dureau P, *et al.* Evolution of ocular manifestations in nephropathic cystinosis: a long-term study of a population treated with cysteamine. *J Pediatr Ophthalmol Strabismus* 2003; **40:** 142–6.
4. Gahl WA, *et al.* Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* 1987; **316:** 971–7.
5. Gahl WA, *et al.* Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med* 2007; **147:** 242–50.
6. Greco M, *et al.* Long-term outcome of nephropathic cystinosis: a 20-year single-center experience. *Pediatr Nephrol* 2010; **25:** 2459–67.
7. Brodin-Sartorius A, *et al.* Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney Int* 2012; **81:** 179–89.
8. Markello TC, *et al.* Improved renal function in children with cystinosis treated with cysteamine. *N Engl J Med* 1993; **328:** 1157–62.
9. Kaiser-Kupfer MI, *et al.* A randomized placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. *Arch Ophthalmol* 1990; **108;** 689–93.

Adverse Effects and Precautions

Mercaptamine can be unpalatable and may cause breath and body odour. It may cause gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, and abdominal pain, and occasionally, gastrointestinal ulceration. Other adverse effects may include drowsiness, lethargy, headache, rashes, fever, and encephalopathy. Mercaptamine may cause leucopenia, increases in liver enzyme values, and nephrotic syndrome. Nervousness, hallucinations, and benign intracranial hypertensionhave also been reported. A few cases of Ehlers-Danlos-like syndrome (a connective tissue disorder) affecting the elbows have been reported in children treated with high doses of mercaptamine. Skin should be monitored regularly and bones examined by X-ray as necessary; the patient and their parents should also be advised to examine the skin regularly. Recommended doses should not be exceeded—see Administration in Children, p. 2554.3.

The most common adverse effects reported with mercaptamine eye drops are sensitivity to light, eye pain and irritation, visual field defects, and headache.

Mercaptamine is contra-indicated in patients with penicillamine hypersensitivity.

Intolerance. Three patients with nephropathic cystinosis developed fever, maculopapular eruption, leucopenia, or headache within 2 weeks of starting oral mercaptamine at doses of 53, 67, and 75 mg/kg daily, respectively.[1] These adverse effects resolved within 48 hours of drug withdrawal and all 3 patients were able to tolerate mercaptamine when restarted at a dose of 10 mg/kg daily, slowly increased to therapeutic levels over 2 to 3 months. Higher doses of mercaptamine had been associated with lethargy and seizures.

1. Schneider JA, *et al.* Cysteamine therapy in nephropathic cystinosis. *N Engl J Med* 1981; **304:** 1172.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mercaptamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Mercaptamine is absorbed from the gastrointestinal tract, and the peak plasma concentration is reached in about 1.4 hours. It is about 54% bound to plasma proteins, mainly albumin. Mercaptamine has a terminal elimination half-life of about 4.8 hours, and most of a dose is excreted as the sulfate.

Children. Results of a pharmacokinetic-pharmacodynamic study[1] in paediatric patients with nephropathic cystinosis showed that although mercaptamine is rapidly cleared from plasma, dosing every 6 hours was sufficient to maintain the content of cystine in the white blood cells below the target value (see p. 2554.3).

1. Belldina EB, *et al.* Steady-state pharmacokinetics and pharmacodynamics of cysteamine bitartrate in paediatric nephropathic cystinosis patients. *Br J Clin Pharmacol* 2003; **56:** 520–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cystagon; ***Austria***: Cystagon; ***Belg.***: Cystagon†; ***Cz.***: Cystagon; ***Denm.***: Cystagon; ***Fin.***: Cystagon; ***Fr.***: Cystagon; ***Ger.***: Cystagon; ***Irl.***: Cystagon; ***Ital.***: Cystagon; ***Neth.***: Cystagon; ***Norw.***: Cystagon; ***Pol.***: Cystagon; ***Port.***: Cystagon; ***Spain***: Cystagon; ***Swed.***: Cystagon; ***UK***: Cystagon; ***USA***: Cystagon; Cystaran; Procysbi.

Mercuric Chloride

Bicloruro de Mercurio; Chlorid rtuťnatý; Cloreto Mercúrico; Corrosive Sublimate; Gyvsidabrio dichloridas; Higany(II)-klorid; Hydrarg. Perchlor.; Hydrargyri Dichloridum; Hydrargyri Perchloridum; Hydrargyrum Bichloratum; Kvicksilverdiklorid; Mercuric Chlor.; Mercúrico, cloruro; Mercurique (Chlorure); Mercurique, chlorure; Mercury Bichloride; Mercury Perchloride; Merkuridikloridi; Quecksilberchlorid; Quecksilber(II)-chlorid; Rtęci(II) chlorek.

$HgCl_2$=271.5

CAS — 7487-94-7.

ATC — D08AK03.

ATC Vet — QD08AK03.

UNII — 53GH7MZT1R.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Mercuric Chloride). A white or almost white, crystalline powder, or colourless or white or almost white crystals or heavy crystalline masses. Soluble in water and in glycerol; freely soluble in alcohol. Protect from light.

Profile

The use of mercuric chloride as an antibacterial substance is limited by its toxicity, its precipitating action on proteins, its irritant action on raw surfaces, its corrosive action on metals, and by the fact that its activity is greatly reduced in the presence of excreta or body fluids.

Details of the adverse effects of inorganic mercury compounds are provided under Mercury, p. 2556.1.

Homoeopathy

Mercuric chloride has been used in homoeopathic medicines under the following names: Chlorure mercurique; Corrosive sublimate; Hydrargyri bichloridum; Mercurius corrosivus; Quecksilberchlorid; Sublimé corrosif.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Neth.***: Diarrheel S.

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Canad.***: Detox L37; PMS; ***Fr.***: Abbe Chaupitre no 18†; Agnus Castus Complexe No 2†; Angipax; Cimicifuga Complexe No 21†; Cina Complexe No 55†; Cistus Canadensis Complexe No 86†; Echinacea Complexe No 40; Geranium Complexe No 108†; Hedera Complexe No 120; Iodum Complexe No 118; Juniperus Complexe No 6; Kalium Muriaticum Complexe No 41†; L 107; Pareira Brava Compose; Pulsatilla Complexe No 60†; Rhus Toxicodendron Complexe No 80; Symphytum Complexe No 48†; Thuya Complexe No 37; Uranthone; Urtica Complexe No 82†; ***Ger.***: Angina-Gastreu S R1; Entero-Gastreu S R4; Hewesoor N†; Kinolymphat†; Pascorenal-Injektopas; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; ***Neth.***: Belachin-Gastreu R1; Entero-Gastreu R4; Phonix Hydrargyrum; Phonix Solidago comp; ***Switz.***: Diarrheel S.

Yellow Mercuric Oxide

Gelbes Quecksilberoxyd; Hydrargyri Oxidum Flavum; Hydrargyri Oxydum Flavum; Mercúrico amarillo, óxido; Mercurique (Oxyde) Jaune; Oxido Amarillo de Mercurio; Óxido de mercurio amarillo; Yellow Precipitate; Жёлтая Окись Ртути.

HgO=216.6

CAS — 21908-53-2.

Pharmacopoeias. In *Fr.* and *It.*

Profile

Yellow mercuric oxide has been used in eye ointments for the local treatment of minor infections including the eradication of pubic lice from the eyelashes. Absorption can occur and produce the adverse effects of inorganic mercury (see Mercury, p. 2556.1).

Pediculosis. Yellow mercuric oxide 1% eye ointment was considered to be a safe and effective treatment in pediculosis (p. 2147.3) of the eyelashes caused by pubic lice (pthiriasis palpebrarum).[1]

1. Ashkenazi I, *et al.* Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrarum. *Br J Ophthalmol* 1991; **75:** 356–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Pomada Amarilla; ***Fr.***: Ophtergine; Pommade Maurice†.

Multi-ingredient Preparations. ***India***: Bell Diono Resolvent†; Bell Resolvent†.

Mercurous Chloride

Quecksilberchlorür; Calomel; Calomelanos; Cloreto Mercuroso; Hydrarg. Subchlor.; Hydrargyri Subchloridum; Hydrargyrosi Chloridum; Hydrargyrum Chloratum (Mite); Mercureux (Chlorure); Mercurioso, cloruro; Mercurius Dulcis; Mercury Monochloride; Mercury Subchloride; Mild Mercurous Chloride; Monocloruro de mercurio; Protocloruro de Mercurio.

HgCl = 236.0; Hg_2Cl_2 = 472.1

CAS — 7546-30-7 (HgCl); 10112-91-1 (Hg_2Cl_2).

UNII — J2D46N657D.

NOTE. Precipitated Mercurous Chloride (Hydrargyri Subchloridum Praecipitatum), is a white amorphous powder, for which the synonym 'White Precipitate' (Praecipitatum Album) has been used. White Precipitate has also been used as a name for Ammoniated Mercury.

Pharmacopoeias. In *Chin.* as Hg_2Cl_2.

Profile

Mercurous chloride was formerly given as a laxative and was applied topically as an antibacterial. It was one of the mercury compounds used in the management of syphilis in the pre-antibiotic era.

The mercurous form of mercury does not possess the corrosive properties of the mercuric form and is not absorbed to any great extent. However, the mercurous form can be converted to the mercuric, with consequent toxicity as described under Mercury (see p. 2556.1).

Homoeopathy

Mercurous chloride has been used in homoeopathic medicines under the following names: Mercurius dulcis; Merc dulc.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Fr.***: Abbe Chaupitre no 88†; Aconitum Compose†; Allium Cepa Compose; Hepatocynesine†; Scrofularia Compose; ***Neth.***: Oteel H; ***Switz.***: Alceprin-N.

Mercury

Azogue; Hidrargirio; Hydrarg.; Hydrargyrum; Hydrargyrum Depuratum; Mercure; Mercurio; Quecksilber; Quicksilver; Rtęć; Ртуть.

Hg=200.592

CAS — 7439-97-6.

ATC — D08AK05.

UNII — FXS1BY2PGL (mercury); ED30FJ8Y42 (mercuric ion).

Description. Mercury is a shining, silvery white, very mobile liquid, easily divisible into globules, which readily volatilises on heating.

Uses

The hazards associated with mercury generally outweigh any therapeutic benefit and its clinical use has largely been abandoned. The use of mercurial diuretics such as mersalyl has generally been superseded by other diuretics. Ointments containing mercurials, such as ammoniated mercury (p. 1711.3) have also generally been replaced by less toxic preparations. Mercurials were formerly used as spermicides.

Some ionisable inorganic mercury salts and certain organic compounds of mercury have been used as disinfectants, and some mercury salts are effective parasiticides and fungicides. Organic mercurials such as phenylmercuric acetate, borate, and nitrate are also used as preservatives (p. 1765.1). Mercury is a component of dental amalgams.

Other mercury salts that have been used for their antibacterial activity include mercuric chloride, yellow mercuric oxide, mercurous chloride (above), and thiomersal (p. 1771.3).

Homoeopathy

Mercury and some mercury compounds have been used in homoeopathic medicines. The precise identity of the substances is not always clear but the following names have been used:

- Mercury: Hydrargyrum metallicum; Mercurius vivus; Merc. viv.
- Mercuric cyanide: Hydrargyrum bicyanatum; Mercurius cyanatus; Merc cyan
- Mercuric iodide: Mercurius iodatus flavus; Merc iod flav; Merc. i. f.
- Red mercuric iodide: Hydrargyrum biiodatum; Mercurius bijodatus; Mercurius iodatus ruber;Merc iod rub; Merc. i. r.
- Mercurous nitrate: Hydrargyrum nitricum oxydulatum; Mercurius nitricus oxydulatus; Mercurius nitricus; Merc. nit.
- Red mercuric sulfide: Hydrargyrum sulfuratum rubrum; Cinnabaris; Cinbar.
- Ammoniated mercuric nitrate: Mercurius solubilis; Mere. sol.
- Potassium mercuric iodide: Mercurius et kali iodatus; Merc. ki.
- Red mercuric oxide: Hydrargyri Oxidum Rubrum; Red Precipitate; Oxyde Rouge de Mercure; Mercurius Praecipitatus Ruber
- Mercuric sulfate: Mercurius sulphuricus; Hydrargyrum sulfuricum; Mercurius sulfuricus; Hydrargyricus sulfas

See also Ammoniated Mercury (p. 1711.2), Mercuric Chloride (p. 2555.2), and Mercurous Chloride (p. 2555.3).

Adverse Effects

Poisoning with liquid mercury or inorganic mercury salts has arisen from sources such as batteries, cosmetics, dental materials, medical equipment, and jewellery manufacture. Barometers, sphygmomanometers, and thermometers are still sources of liquid mercury. Trace amounts of organic and inorganic mercury may also be ingested in the diet.

The effects of **acute** exposure depend on the nature of the compound.

- *Elemental (liquid) mercury* if ingested is poorly absorbed and, unless there is aspiration or pre-existing gastrointestinal disorders, is not considered to be a severe toxicological hazard. The greatest dangers from elemental mercury arise from the inhalation of mercury vapour, which can cause gastrointestinal effects including nausea, vomiting, and diarrhoea; more importantly it is toxic to the respiratory system and this effect can be fatal. Some CNS involvement has also been reported. Adverse effects have also been reported after accidental or intentional parenteral dosage.
- *Inorganic salts* such as mercuric chloride are corrosive when ingested causing severe nausea, vomiting, pain, bloody diarrhoea, and necrosis. The kidney is also involved and tubular necrosis may develop. Mercurous salts are considered to be less hazardous, but the mercurous form can be converted to the mercuric.
- *Organic mercurial compounds* produce similar toxic effects to inorganic compounds, but they have a more selective action on the CNS that has proved difficult to treat. The degree of toxicity varies; those used as preservatives or disinfectants are less toxic than the ethyl or methyl compounds that are not used pharmaceutically or clinically. Methylmercury is notorious for its toxicity; there have been cases of fetal neurotoxicity during outbreaks of methylmercury poisoning.

Chronic mercury poisoning may result from inhalation of mercury vapour, skin contact with mercury or mercury compounds, or ingestion of mercury salts over prolonged periods. It is characterised by many symptoms including tremor, motor and sensory disturbances, mental deterioration, gastrointestinal symptoms, dermatitis, kidney damage, salivation, and gingivitis. A blue line may be present on the gums. There is little difference between acute and chronic poisoning with organic mercurials.

The syndrome of *acrodynia* (pink disease), with symptoms of sweat, rash, erythema of the extremities, photophobia, wasting, weakness, hypertension, tachycardia, and diminished reflexes, occurred in children given mercury in teething powders or in ointments or dusting powders. Such preparations have long since been withdrawn from use. However, the syndrome is still a feature of mercury poisoning from other sources.

Hypersensitivity to mercury and mercurial compounds has been reported.

Mercurialentis has been reported in patients treated with eye drops containing an organomercurial preservative.

Chronic exposure. Acute *occupational exposure* to mercury vapour in 53 men resulted in an initial phase described as metal fume fever, an intermediate phase of severe symptoms with CNS, gastrointestinal, respiratory, and urological involvement, and a late phase with persistent CNS symptoms, dysuria, and pain on ejaculation.[1,2] Although persistent hyperchloraemia was noted in the 11 patients with the highest mercury levels, renal impairment tended to be temporary.[2]

Long-term follow-up of a patient who had an intravenous *injection* of mercury 12 years previously also revealed no persistent renal impairment,[3] despite the presence of mercury microemboli in lungs, kidneys, liver, and subcutaneous tissues and high concentrations in the urine. At this time, the patient had residual reductions in respiratory function, polyneuropathy, and marked asthenozoospermia. Spermatozoal abnormalities may also have contributed to his wife's miscarriage. Mercury deposits mimicking gallbladder cancer were found in the gallbladder of a patient 35 years after he had injected himself with elemental mercury.[4]

Fetal neurotoxicity after *maternal exposure* to methylmercury is well recognised, and there has been widespread concern about the effect of maternal diets on the developing fetus because of mercury concentrations in freshwater and marine organisms. Results from a study in the Faroe Islands showed an association between delays in neurological development in children and maternal consumption of pilot whale meat.[5] Follow-up studies of this population when they reached 14 years of age suggest that the neurotoxic effects of methylmercury might compromise brain development into the teenage years,[6] as well as affecting autonomic regulation of heart function.[7] However, data from a study conducted in a fish-consuming population in the Seychelles failed to find a similar connection.[8]

There has been considerable concern over the systemic absorption of mercury from *dental amalgam*, which typically contains between 40 and 70% of mercury. However, the quantity absorbed from amalgam fillings is reported to be relatively small[9,10] and current evidence suggests that the use of dental amalgam for tooth restoration is both safe and effective.[11-14] The main risks appear to be occupational exposure of dental staff and environmental pollution. Some patients with hypersensitivity to mercury (manifest most commonly as local lichenoid reactions) may benefit from removal of amalgam fillings.[15-17]

Ethylmercury is contained in *thiomersal*, which is used as a preservative in some vaccines for infants and children, thus representing a potential source of mercury exposure. The safety of these vaccines has been a matter of considerable debate worldwide for many years although it is now usually accepted that there is no evidence of neurotoxicity. However, some countries have phased out vaccines containing thiomersal in favour of alternative preservatives. For further details and references, see Thiomersal p. 1772.2.

The symptoms of *acrodynia* have been mistaken for those of phaeochromocytoma.[18-21]

1. Bluhm RE, *et al*. Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part I: history, neuropsychological findings and chelator effects. *Hum Exp Toxicol* 1992; **11:** 201–10.
2. Bluhm RE, *et al*. Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part II: hyperchloraemia and genitourinary symptoms. *Hum Exp Toxicol* 1992; **11:** 211–15.
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4. Zippel D, *et al*. Quicksilver cholecystitis. *Ann Intern Med* 2006; **144:** 941.
5. Grandjean P, *et al*. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol* 1997; **19:** 417–28.
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13. Bellinger DC, *et al*. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. *JAMA* 2006; **295:** 1775–83.
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15. Ibbotson SH, *et al*. The relevance and effect of amalgam replacement in subjects with oral lichenoid reactions. *Br J Dermatol* 1996; **134:** 420–3.
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17. Laeijendecker R, *et al*. Oral lichen planus and allergy to dental amalgam restorations. *Arch Dermatol* 2004; **140:** 1434–8.
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19. Velzeboer SCJM, *et al*. A hypertensive toddler. *Lancet* 1997; **349:** 1810.
20. Wössmann W, *et al*. Mercury intoxication presenting with hypertension and tachycardia. *Arch Dis Child* 1999; **80:** 556–7.
21. Torres AD, *et al*. Mercury intoxication and arterial hypertension: report of two patients and review of the literature. Abstract: *Pediatrics* 2000; **105:** 627. Full version: http://pediatrics.aappublications.org/cgi/reprint/105/3/e34.pdf (accessed 14/07/06)

Effects on the kidneys. The kidneys are one of the main sites for the accumulation of mercury in the body. All forms of mercury (liquid mercury, inorganic mercury, and organic mercury) may be toxic to the kidney although the inorganic forms are the most nephrotoxic.[1]

1. Zalups RK. Molecular interactions with mercury in the kidney. *Pharmacol Rev* 2000; **52:** 113–43.

Hypersensitivity. Systemic contact dermatitis in a patient apparently sensitised by red, mercury-based tattoo pigments, developed when he ate raw swordfish and alfonsino, both renowned for high mercury levels.[1]

1. Tsuruta D, *et al*. A red tattoo and a swordfish supper. *Lancet* 2004; **364:** 730.

Treatment of Adverse Effects

The treatment of **acute** mercury toxicity depends on the form of mercury, the route of exposure, and the dose. Supportive measures may be needed with all types of toxicity. Ingestion of elemental mercury seldom requires active treatment since it is poorly absorbed by this route, although inhalation or aspiration of elemental mercury vapour is a potentially serious problem. Poisoning due to organic mercury is difficult to treat and supportive measures are the mainstay of treatment. Acute exposure to mercury by injection requires mainly supportive therapy, although excision of the affected area has been recommended after subcutaneous or intramuscular injection. Mercurials on the skin should be removed by copious washing with soap and water; for contamination in the eye, irrigation with water at room-temperature for at least 15 minutes should be performed.

Acute oral poisoning due to inorganic mercury salts should be treated if appropriate by activated charcoal or gastric lavage to reduce absorption if within 1 hour of ingestion of a potentially life-threatening dose. Decontamination is not usually necessary after ingestion of small amounts such as elemental mercury from a thermometer. Some inorganic mercury compounds may be corrosive to the gastrointestinal tract when ingested, which can make gastrointestinal decontamination problematic; induction of emesis is not recommended. Gastric decontamination may be tried for organic mercury compounds, although the benefits are uncertain.

In severe cases of toxicity with all forms of mercury poisoning, chelation therapy may be required to facilitate the removal of mercury from the body. Unithiol (p. 1579.1) is the chelating agent of choice in the UK and should be considered in symptomatic patients with a blood-mercury concentration of 100 micrograms/litre, and in asymptomatic patients with a blood-mercury concentration of 200 micrograms/litre. Other chelating agents that may be used are succimer (p. 1576.3), dimercaprol (p. 1549.3), and penicillamine (p. 1567.1). The treatment of choice may vary in other countries depending on local policies and availability of the above chelating agents. Penicillamine may be associated with more adverse effects than other chelating agents and should be reserved for use when others are unavailable or not tolerated. Dimercaprol should be avoided in poisoning with metallic mercury or methylmercury because it may exacerbate neurological effects through redistribution of mercury to the brain from other sites.

Some centres start haemodialysis early in the course of treatment; others wait until renal failure develops. Giving a thiol resin complex to prevent the reabsorption of mercury from the bile has also been tried.

The management of **chronic** toxicity is generally symptomatic although chelation therapy has been used in some patients if the blood-mercury concentration is raised or the patient is symptomatic.

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2. Ferguson L, Cantilena LR. Enhanced mercury clearance during hemodialysis with chelating agents. *Clin Pharmacol Ther* 1991; **49:** 131.
3. Florentine MJ, Sanfilippo DJ. Elemental mercury poisoning. *Clin Pharm* 1991; **10:** 213–21.
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7. Aaseth J, *et al*. Treatment of mercury and lead poisonings with dimercaptosuccinic acid and sodium dimercaptopropanesulfonate: a review. *Analyst* 1995; **120:** 853–4.
8. Isik S, *et al*. Subcutaneous metallic mercury injection: early, massive excision. *Ann Plast Surg* 1997; **38:** 645–8.
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Pharmacokinetics

There is little absorption of elemental mercury from globules in the gastrointestinal tract. The main hazard of elemental mercury is from absorption after inhalation of mercury vapour; this mercury is widely distributed before being oxidised to the mercuric form. Concentrations can be detected in the brain.

Soluble inorganic mercuric salts are absorbed from the gastrointestinal tract and can also be absorbed through the skin. The mercury is distributed throughout the soft tissues with high concentrations in the kidneys; it is mainly excreted in the urine and faeces with an elimination half-life of about 60 days, although it may take years to eliminate mercury from the brain; elimination from other tissues can take several months.

Organic alkyl mercury compounds are more readily absorbed from both the gastrointestinal and the respiratory tracts. They are widely distributed and can produce high concentrations in the brain. Alkyl mercury compounds are excreted in urine and in the faeces with extensive enterohepatic recycling. The biological half-life varies but is longer than that of inorganic mercury.

Organic mercury, and to some extent inorganic mercury, diffuse across the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Coldophthal; Nasenol; ***Ger.***: Iscador c Hg; Schnupfencreme; Weleda Nasenol; ***Spain***: Oftalmol Ocular.

Homoeopathic Preparations. ***Austral.***: Earache Relief†; Elimitona Slim & Detox; Elimitona; Joint & Muscle Oral Spray†; Pain & Fever Relief; Respatona Sore Throat; Teething Relief; ***Austria***: Apozema Apis compositum; Asinis; Delufen; Echinacea-Cosmoplex; Euphorbium Compositum; Exangina†; Globuli gegen Halsweh Nr 2; Globuli gegen Hautausschlage; Globuli gegen Schnupfen Nr 3; Lymphdiaral; Lymphdiaral; Meditonsin; Metasinusit; Nebenhohlen-Tropfen Nr 26†; Ohrentropfen Similasan; Otovowen; Rhododendroneel; Tonsan akut; Tonsillopas; Tonsiotren; Traumeel; Vocara; Zom; ***Canad.***: Cough & Cold; Diarrex; Earache; Euphorbium Compositum; Homeovox; Hylands Sore Throat; Roxalia; Sinus Ease; Sinuspax†; Sore Throat; ***Chile***: Bioactiv H; ***Cz.***: Angin-Heel S; Traumeel; ***Fr.***: Aftosium; Calendula Complexe No 89; Dolistamine†; Hepatodrainol; Homeodose 24†; Homeogene 9; Homeovox; Mercurius Cyanatus Complexe No 43†; Mercurius Solubilis Complexe No 39; Phytogargarisme†; Silicea Complexe No 11; Sinuspax; ***Ger.***: Anovin; Cefasept N; Cefasept†; Cefasinu; Entzundungstropfen; Euphorbium comp SN; Hevertotox; Humoval; Infihepan; Lymphaden Complex; Lymphaden; Lymphdiaral Halstabletten; Lymphdiaral sensitive N; Lymphdiaral; Mato; Meditonsin; Mercurell; Muco-cyl L Ho-Len-Complex; Mullersche Tabletten; Otovowen; Pyrogenium; Rufebran lympho†; Schworosin; Sinasal; Sinfrontal; Sinuselect N; Sinusitis Hevert SL; Sinusitis Hevert†; Sinusitis-Weliplex†; Tonsillopas; Tonsillosyx; Tonsiotren H; Traumeel S; Zahnungstropfen Escatitona; ***Hung.***: Angin-Heel; Homeogene 9; Homeovox; Naso-Heel S; Osteoheel; Traumeel; ***Neth.***: Discus comp H; Euphorbium comp; Hepalite; Hepatodrainol†; Homeogene 9†; Homeovox; Lymphdiaral; Mercurius-Heel; Myamolite; Oteel H; Ricura; Rinileen†; Tonsiotreen; Traumeel H; Traumeel S; ***Port.***: Hepatodrainol; Homeogene 9; Homeovox; ***Rus.***: Aphlubin-Naze (Афлубин-Назе); Asinis (Асинис); Belladonna-Plus (Белладонна-Плюс); Cinnabsin (Циннабсин); Delufen (Делуфен); Homeovox (Гомеовокс); Mercure-Plus (Меркур-Плюс); Plantago-Plus (Плантаго-Плюс); Tonsan-Akut (Тонзан-акут); Tonsilotren (Тонзилотрен); Traumeel S (Траумель С); Vocara (Вокара); ***S.Afr.***: Euphorbium Compositum S†; Traumeel S; Zinnober D6†; ***Switz.***: A Vogel pour les sinus; Homeogene 9; metasinusit; Osteoheel; Sinfrontal; Sinusin; Sinuspax†; Traumeel; ***UK***: Catarrh Cream; Oleum Rhinale; ***Ukr.***: Asinis (Асинис); Cinnabsin (Циннабсин); Delufen (Делуфен); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); Traumeel S (Траумель С); Vocara (Вокара); ***Venez.***: Traumeel.

Mescaline

Mescalina; Mescalinum; Meskaliini; Meskalin.
3,4,5-Trimethoxyphenethylamine
$C_{11}H_{17}NO_3$=211.3
CAS — 54-04-6.
UNII — RHO9910JVC.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for mescaline or peyote:

Bad seed; Beans; Big chief; Black button; Blue caps; Britton; Buttons; Cactus; Cactus buttons; Cactus head; Chief; Crystal; Dusty; Full moon; Green button; Half moon; Hikori; Hikula; Hikuli; Hyatari; Indians; M; Mesc; Mesca; Mescal; Mescalito; Mescap; Mescy; Mese; Mess; Mezc; Moon; Musk; Nubs; P; Peyote; Peyotl; Pixie sticks; San Pedro; Seni; Shaman; Topi; Tops.

Profile

Mescaline is an alkaloid obtained from the cactus *Lophophora williamsii* (*Anhalonium williamsii, A. lewinii*) (Cactaceae), which grows in the northern regions of Mexico. The cactus is known in those areas by the Aztec name 'peyote' or 'peyotl' and dried slices of the cactus are called 'mescal buttons'.

Mescaline produces hallucinogenic and sympathomimetic effects similar to those produced by lysergide (see p. 2547.1), but it is less potent. Its effects last for up to 12 hours. It has no therapeutic use. Both Mexican and North American Indians have used peyote in religious ceremonies on account of its hallucinogenic activity.

Botulism. Peyote consumed during a ceremonial ritual was believed to have caused botulism in three men.[1] The sample was found to contain type B botulinum toxin when assayed.

1. Hashimoto H, *et al.* Botulism from peyote. *N Engl J Med* 1998; **339:** 203–4.

Mesoglycan Sodium

Mesoglicano sódico; Sodium Mesoglycan.

Profile

Mesoglycan sodium is a mucopolysaccharide complex (glycosaminoglycan) extracted from calf aorta, containing mainly suleparoid (heparan sulfate) (p. 1507.2) and dermatan sulfate (p. 1350.3). It has been claimed to have antithrombotic, antiplatelet, and antihyperlipidaemic properties.

References.

1. Forconi S, *et al.* A randomized, ASA-controlled trial of mesoglycan in secondary prevention after cerebral ischemic events. *Cerebrovasc Dis* 1995; **5**: 334–41.
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3. Arosio E, *et al.* A placebo-controlled, double-blind study of mesoglycan in the treatment of chronic venous ulcers. *Eur J Vasc Endovasc Surg* 2001; **22:** 365–72.
4. Nenci GG, *et al.* Treatment of intermittent claudication with mesoglycan—a placebo-controlled, double-blind study. *Thromb Haemost* 2001; **86:** 1181–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Prisma; ***Port.***: Prisma.

Metamfepramone Hydrochloride *(rINNM)* ⊗

Dimepropion Hydrochloride (BANM); Hidrocloruro de metanfepramona; Métamfépramone, Chlorhydrate de; Metamfepramoni Hydrochloridum; Metamfepyramone Hydrochloride; Metanfepramona, hidrocloruro de; Метамфепрамона Гидрохлорид.
2-Dimethylaminopropiophenone hydrochloride.
$C_{11}H_{15}NO.HCl$=213.7
CAS — 15351-09-4 (metamfepramone); 10105-90-5 (metamfepramone hydrochloride).
UNII — 6Y816E97O1.

Profile

Metamfepramone, the dimethyl analogue of diethylpropion (p. 2321.1) and a derivative of cathinone (p. 2318.2), is a sympathomimetic that has been used as the hydrochloride in the treatment of hypotension and in preparations for the symptomatic relief of the common cold. It was formerly used as an anorectic agent. It is also subject to abuse (see Abuse, under Catha, p. 2318.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Tempil N†.

Metergoline *(BAN, rINN)*

FI-6337; MCE; Metergolinii; Metergolin; Metergolina; Métergoline; Metergolinum; Methergoline; Метэролин.
Benzyl (8*S*,10*S*)-(1,6-dimethylergolin-8-ylmethyl)carbamate.
$C_{25}H_{29}N_3O_2$=403.5
CAS — 17692-51-2.
ATC — G02CB05.
ATC Vet — QG02CB05.
UNII — 1501393LY5.

Profile

Metergoline, an ergot derivative, is a dopamine agonist with actions and uses similar to those of bromocriptine (p. 895.3). It is also a serotonin antagonist. Metergoline has been used similarly to bromocriptine in disorders associated with hyperprolactinaemia in usual oral doses of 12 mg daily in divided doses; up to 24 mg daily has been given in hyperprolactinaemic men. It has also been used orally to inhibit lactation, for the treatment of gastrointestinal disorders, and for the prophylaxis of migraine and other vascular headaches.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p. 2252.2). Metergoline has been tried in patients intolerant of bromocriptine.[1] In this report metergoline lowered plasma-prolactin concentrations, although not to normal, in 3 men and 8 women with hyperprolactinaemia. Galactorrhoea was abolished and/or a regular menstrual cycle established in 5 of the women. Prolactin concentrations and symptoms were unchanged in 3 further women with normoprolactinaemic galactorrhoea.

1. Casson IF, *et al.* Intolerance of bromocriptine: is metergoline a satisfactory alternative? *BMJ* 1985; **290:** 1783–4.

Migraine. Although metergoline has been used in some countries for the prophylaxis of migraine (p. 670.3) it is not usually considered to be the drug of choice or even one of the main alternatives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Liserdol; ***Ital.***: Liserdol.

Metesculetol Sodium *(rINNM)*

Metesculetol sódico; Métesculétol Sodique; Methesculétol Sodique; Methyl-4-esculetol Monoethanoate Sodium; Natrii Metesculetolum; Натрий Метэскулетол.
[(7-Hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-6-yl)oxy] acetate sodium.
$C_{12}H_9NaO_6$=272.2
CAS — 52814-39-8 (metesculetol); 53285-61-3 (metesculetol sodium).

Profile

Metesculetol is included in preparations for peripheral vascular disorders and haemorrhoids. It is also present in some oral hygiene preparations. Metescufylline is a compound of metesculetol and etamiphylline (p. 1208.2) that has been given orally for its reputed vasoprotectant effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Diencil; Parogencyl Bi-Actif†; Vitis Encias Colutorio; Vitis Encias Pasta; ***Fr.***: Intrait de Marron d'Inde P; Parogencyl prevention gencives†; Parogencyl sensibilite gencives†; Veinotonyl; ***Hong Kong***: Pyodontyl†; ***Ital.***: Parogencyl; ***Mon.***: Fluon.

Methacholine Chloride *(BAN, rINN)*

Acetyl-β-methylcholine Chloride; Amechol Chloride; Cloruro de metacolina; Metacolina, cloruro de; Méthacholine, Chlorure de; Methacholini Chloridum; Methacholinium Chloratum; Метахолиния Хлорид.
(2-Acetoxypropyl)trimethylammonium chloride.
$C_8H_{18}ClNO_2$=195.7
CAS — 55-92-5 (methacholine); 62-51-1 (methacholine chloride).
UNII — GW5ETF9M2K.

Pharmacopoeias. In *Fr., Swiss,* and *US.*

USP 36: (Methacholine Chloride). Colourless or white crystals, or a white crystalline powder. It is odourless or has a slight odour, and is very hygroscopic. Soluble 1 in 1.2 of water, 1 in 1.7 of alcohol, and 1 in 2.1 of chloroform. Its solutions are neutral to litmus. Store in airtight containers.

Uses and Administration

Methacholine is a quaternary ammonium parasympathomimetic with the muscarinic actions of acetylcholine (p. 2003.2). It is hydrolysed by acetylcholinesterase at a considerably slower rate than acetylcholine and is more resistant to hydrolysis by non-specific cholinesterases so that its actions are more prolonged.

Inhalation of nebulised solutions of methacholine chloride are used to provoke bronchoconstriction in the diagnosis of bronchial airway hypersensitivity (but see Precautions, below).

Methacholine chloride has been used in eye drops as a miotic for diagnostic purposes.

References.
1. Crapo RO, *et al.* Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000; **161:** 309–29. Also available at: http://ajrccm.atsjournals.org/cgi/reprint/161/1/309.pdf (accessed 30/05/08)
2. Swartz E, Lang D. When should a methacholine challenge be ordered for a patient with suspected asthma? *Cleve Clin J Med* 2008; **75:** 37–40.

Adverse Effects and Treatment

As for Acetylcholine Chloride, p. 2003.2. Severe adverse cholinergic effects have followed the oral and parenteral use of methacholine and these routes are no longer used.

Precautions

As for Neostigmine, p. 688.3.

Methacholine has the potential to produce severe bronchoconstriction and it should not be used for inhalation challenge tests in patients with clinically apparent asthma, wheezing, or poor pulmonary function.

Methacholine should not be given orally or parenterally.

Interactions

As for Neostigmine, p. 688.3. Methacholine is slowly hydrolysed by acetylcholinesterase, and its effects are markedly enhanced if used after anticholinesterases.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Provocholine; ***Israel***: Provocholine; ***Spain***: Provocholine; ***USA***: Mecholyl; Provocholine.

Methiosulfonium Chloride

Methylmethionine Sulfonium Chloride; Metiosulfonio, cloruro de; Vitamin U; Метиосульфония Хлорид.

(3-Amino-3-carboxypropyl)dimethylsulphonium chloride.

$C_6H_{14}ClNO_2S$=199.7

CAS — 1115-84-0.

ATC — A02BX04.

ATC Vet — QA02BX04.

UNII — G9CUR2204U.

Profile

Methiosulfonium chloride has been used for its reputed protective effect on the liver and gastrointestinal mucosa. The bromide has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cabagin-U.

Multi-ingredient Preparations. ***China***: Aoweishu (澳谓舒); Rudd-U (立愉); Wei Tai Kang (谓泰康); ***Jpn***: Cabagin S New; Cabagin†; Cabe 2†; The Guard Seichojo; ***Singapore***: Weisen-U.

Methyl Fluorosulfate

Fluorosulfato, metilo de; Magic Methyl; Methyl Fluorosulphate; Methyl Fluorosulphonate.

CH_3FO_3S=114.1

CAS — 421-20-5.

UNII — N015VFJ94Z.

Profile

Methyl fluorosulfate has been used as a laboratory methylating agent. Pulmonary oedema has occurred after inhalation, and concern has been expressed concerning possible carcinogenicity.

Methylenedioxycinnamic Acid

Метилендиоксикоричная Кислота.

3,4-Methylenedioxycinnamic acid.

$C_{10}H_8O_4$=192.2

CAS — 2373-80-0.

Profile

Methylenedioxycinnamic acid and its potassium salt have been used in preparations for the treatment of liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vacuobil.

Multi-ingredient Preparations. ***Arg.***: Vacuobil Plus.

Methylhydroxyquinoline Metilsulfate

Methylhydroxyquinoline Methylsulphate; Metilhidroxiquinolina, metilsulfato de; Метилгидроксихинолина Метилсульфат.

1-Methyl-8-hydroxyquinolinium methyl sulphate.

$C_{10}H_{10}NO.CH_3O_4S$=271.3

CAS — 19104-24-6.

Profile

Methylhydroxyquinoline metilsulfate has been used topically to treat eye irritation.

Methylmethacrylate

Metacrilato de metilo; Méthacrylate de méthyle; Methyl Methacrylate; Methylis methacrylas; Метилметакрилат.

Methyl 2-methylacrylate; Methyl 2-methylpropenoate.

$C_5H_8O_2$=100.1

CAS — 80-62-6.

UNII — 196OC77688.

Uses and Administration

Methylmethacrylate forms the basis of acrylic bone cements used in orthopaedic surgery. A liquid consisting chiefly of methylmethacrylate monomer with a polymerisation initiator is mixed with a powder consisting of polymethylmethacrylate (PMMA) or a methylmethacrylate ester copolymer. The reaction is exothermic. Barium sulfate or zirconium dioxide may be added as a contrast medium. PMMA beads containing gentamicin have been implanted for the prophylaxis and treatment of bone infections and some soft-tissue infections. Bone cements containing antibacterials such as gentamicin or erythromycin are also available.

PMMA has also been used as a material for intra-ocular lenses, for denture bases, as a cement for dental prostheses, and in composite resins for dental restoration.

Several polymers based on methacrylic acid are used in pharmaceutical technology mainly as film coating agents and binders.

Ph. Eur. 8 includes:
- Ammonio Methacrylate Copolymer (Type A) (a copolymer of acrylic and methacrylic acid esters)
- Ammonio Methacrylate Copolymer (Type B) (a copolymer of acrylic and methacrylic acid esters)
- Basic Butylated Methacrylate Copolymer
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:1)
- Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:2)

USNF 31 includes:
- Methacrylic Acid Copolymer (a copolymer of methacrylic acid and an acrylic or methacrylic ester)
- Amino Methacrylate Copolymer
- Ammonio Methacrylate Copolymer
- Ethyl Acrylate and Methyl Methacrylate Copolymer
- Methacrylic Acid and Ethyl Acrylate Copolymer
- Partially-Neutralized Methacrylic Acid and Ethyl Acrylate Copolymer
- Methacrylic Acid and Methyl Methacrylate Copolymer

Bone disorders. Polymethylmethacrylate bone cements are used in orthopaedics; typically they are injected percutaneously into vertebral fractures or lesions to relieve pain and stabilise the damaged vertebra, and are used in joint replacement.[1-7] The technique has been used in the treatment of metastatic bone lesions and myeloma (p. 700.3 and p. 699.2) as well as for vertebral compression fractures due to osteoporosis (p. 1168.1). Complications[5,8-11] are uncommon but may include both local and systemic effects (including pulmonary embolism) due to leakage of the cement and sudden drop in blood pressure, probably due to the monomer.

1. Barr JD, *et al.* Percutaneous vertebroplasty for pain relief and spinal stabilization. *Spine* 2000; **25:** 923–8.
2. Lingar L. Percutaneous polymethacrylate vertebroplasty. *Radiol Technol* 2004; **76:** 109–13.
3. Burton AW, *et al.* Vertebroplasty and kyphoplasty: a comprehensive review. *Neurosurg Focus* 2005; **18:** e1. Available at: http://www.medscape.com/viewarticle/501670 (accessed 11/11/09)
4. Suresh SP, Whitehouse RW. Vertebroplasty and kyphoplasty. *J Br Menopause Soc* 2005; **11:** 28–32.
5. Guglielmi G, *et al.* Percutaneous vertebroplasty: indications, contraindications, technique, and complications. *Acta Radiol* 2005; **46:** 256–68.
6. Hochmuth K, *et al.* Percutaneous vertebroplasty in the therapy of osteoporotic vertebral compression fractures: a critical review. *Eur Radiol* 2006; **16:** 998–1004.
7. Webb JCJ, Spencer RF. The role of polymethylmethacrylate bone cement in modern orthopaedic surgery. *J Bone Joint Surg Br* 2007; **89:** 851–7.
8. Laredo JD, Hamze B. Complications of percutaneous vertebroplasty and their prevention. *Semin Ultrasound CT MR* 2005; **26:** 65–80.
9. Barragan-Campos HM, *et al.* Percutaneous vertebroplasty for spinal metastases: complications. *Radiology* 2006; **238:** 354–62.
10. Health Canada. Complications associated with the use of bone cements in vertebroplasty and kyphoplasty procedures (issued 30th May, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bone_cement-ciment_acrylique_nth-aah_2_e.pdf (accessed 30/5/08)
11. Venmans A, *et al.* Frequency and outcome of pulmonary polymethylmethacrylate embolism during percutaneous vertebroplasty. *AJNR Am J Neuroradiol* 2008; **29:** 1983–5.

Adverse Effects and Precautions

Occupational exposure to methylmethacrylate monomer vapour during preparation of the bone cement may irritate the respiratory tract, eyes, and skin. Cases of occupational asthma have been reported. Contact dermatitis, dizziness, nausea and vomiting may also occur. Methylmethacrylate monomer may be harmful to the liver.

Methylmethacrylate monomer acts as a peripheral vasodilator and has caused hypotension and, rarely, cardiac arrest and death when absorbed during the use of polymethylmethacrylate (PMMA) as a bone cement during orthopaedic surgery (see also Bone Disorders under Uses and Administration, above). Other adverse effects associated with the use of PMMA as a bone cement include thrombophlebitis, pulmonary embolism, haemorrhage, haematoma, short-term irregularities in cardiac conduction, cerebrovascular accident, compression of the spinal cord and/or nerve roots, and new fractures in adjacent non-augmented vertebrae. Recommendations when using PMMA include monitoring with high quality imaging systems to detect leakage, and close monitoring of blood pressure during and immediately after the procedure.

References.
1. Leggat PA, Kedjarune U. Toxicity of methyl methacrylate in dentistry. *Int Dent J* 2003; **53:** 126–31.
2. Leggat PA, *et al.* Surgical applications of methyl methacrylate: a review of toxicity. *Arch Environ Occup Health* 2009; **64:** 207–12.

Effects on the nervous system. Sensory polyneuropathy has been reported in a dental technician after occupational exposure to methylmethacrylate monomer.[1]

1. Sadoh DR, *et al.* Occupational exposure to methyl methacrylate monomer induces generalised neuropathy in a dental technician. *Br Dent J* 1999; **186:** 380–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Palacos R†; ***Ger.***: Biomet Bone Cement R; Biomet Plus Bone Cement†; flint; SmartSet HV; ***Gr.***: Palacos; ***Port.***: Septopal; ***Singapore***: Palacos R; ***Thai.***: Biomet; Palacos R†; ***UK***: Palacos R.

Multi-ingredient Preparations. ***Austral.***: Palacos E with Garamycin†; Palacos R with Garamycin†; Septopal†; ***Austria***: Septopal; ***Belg.***: Septopal; ***Braz.***: Septopal; ***Chile***: Palacos E con Gentamicina†; Palacos R con Gentamicina†; Perlas De PMMA con Gentamicina†; ***China***: Septopal (塞透派勒); ***Denm.***: Septopal†; ***Fin.***: Septopal; ***Fr.***: Septopal†; ***Ger.***: Epiglu; Heraeus PMMA Kette G; Palasept G†; Refobacin Bone Cement R; Refobacin Plus Bone Cement; Refobacin Revision; Septopal; SmartMix Cemvac GHV; SmartSet GHV; ***Gr.***: Palacos R with Gentamycin; Septopal; ***Hong Kong***: Septopal†; ***Hung.***: Septopal†; ***India***: Septopal†; ***Irl.***: Epiglu†; ***Neth.***: Septopal; ***Norw.***: Septopal; ***NZ***: Antibiotic Simplex; CMW Gentamicin; Palacos with Garamycin; Smartmix; Smartset; Vacu-Mix Plus with CMW gentamicin; ***Philipp.***: Septopal; ***S.Afr.***: Palacos R with Garamycin; Septopal; ***Singapore***: Refobacin Bone Cement R†; Septopal; ***Switz.***: Septopal; ***Thai.***: Refobacin Bone Cement R; Septopal; ***UK***: Epiglu; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal.

Metochalcone *(rINN)*

CB-1314; Methochalcone; Metocalcona; Métochalcone; Metochalconum; Trimethoxychalcone; Метохалкон.

2′,4,4′-Trimethoxychalcone.

$C_{18}H_{18}O_4$=298.3

CAS — 18493-30-6.

UNII — 1754ZE4075.

Profile

Metochalcone has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Neocolan†.

All cross-references refer to entries in Volume A

Metocinium Iodide *(pINN)*

Ioduro de metocinio; Metocinii Iodidum; Métocinium, Iodure de; Метоциния Йодид.
(2-Hydroxyethyl)trimethylammonium iodide benzilate.
$C_{19}H_{24}INO_3$=441.3
CAS — 2424-71-7.
UNII — R11SBP9F2B.

Profile

Metocinium iodide is used as an antispasmodic.

Metyrapone *(BAN, USAN, rINN)*

Metirapon; Metirapona; Metyrapon; Métyrapone; Metyraponi; Metyraponum; Su-4885 (metyrapone tartrate); Метирапон.
2-Methyl-1,2-di(3-pyridyl)propan-1-one.
$C_{14}H_{14}N_2O$=226.3
CAS — 54-36-4.
ATC — V04CD01.
ATC Vet — QV04CD01.
UNII — ZS9KD92H6V.

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2014: (Metyrapone). A white to light amber crystalline powder with a characteristic odour. M.p. 50 degrees to 53 degrees. Sparingly soluble in water; freely soluble in alcohol and in chloroform; it dissolves in dilute mineral acids. Protect from light.

USP 36: (Metyrapone). A white to light amber, fine, crystalline powder, having a characteristic odour. It darkens on exposure to light. Sparingly soluble in water; soluble in chloroform and in methyl alcohol; forms water-soluble salts with acids. Store in airtight containers. Protect from heat and light.

Uses and Administration

Metyrapone inhibits the enzyme 11β-hydroxylase responsible for the synthesis of the glucocorticoids cortisone and hydrocortisone (cortisol) as well as aldosterone from their precursors. The consequent fall in the plasma concentrations of circulating glucocorticoids stimulates the anterior pituitary gland to produce more corticotropin. This, in turn, stimulates the production of more 11-deoxycortisol and other precursors which are metabolised in the liver and excreted in the urine where they can be measured. Metyrapone is therefore used as a test of the feedback hypothalamic-pituitary mechanism in the differential diagnosis of ACTH-dependent Cushing's syndrome, although the dexamethasone suppression test (p. 1632.1) may be preferred.

After demonstration of the responsiveness of the adrenal cortex, metyrapone is given orally, usually in a dose of 750 mg every 4 hours for 6 doses. Taking doses with milk or after a meal may minimise the gastrointestinal adverse effects of metyrapone. For doses in children, see below. In patients with a normally functioning pituitary gland excretion of 17-hydroxycorticosteroids is increased two- to fourfold and that of 17-ketosteroids about twofold.

Metyrapone is also used in the management of Cushing's syndrome (below) when doses may range from 250 mg to 6 g daily.

Since metyrapone inhibits the synthesis of aldosterone it has been used to treat some cases of resistant oedema; it is given with a glucocorticoid to suppress the normal corticotropin response to low plasma concentrations of glucocorticoids. The suggested usual dosage of metyrapone in resistant oedema is 3 g daily in divided doses.

Metyrapone tartrate has also been used.

Administration in children. The oral dose of metyrapone in children aged 1 month and over for the differential diagnosis of ACTH-dependent Cushing's syndrome is 15 mg/kg, with a minimum dose of 250 mg, every four hours for 6 doses.

Cushing's syndrome. Cushing's syndrome is the result of a chronic excess of glucocorticoids.[1] It may be independent of the secretion of adrenocorticotrophic hormone (ACTH; corticotropin), either due to an adrenal tumour secreting cortisol, or to exogenous corticosteroids, or it may be ACTH-dependent, such as Cushing's disease proper, which is caused by excessive ACTH secretion from a pituitary adenoma; other ACTH-dependent forms may be due to pituitary hyperplasia, or an ectopic ACTH-secreting tumour elsewhere—usually bronchus or lung cancer. About two-thirds of all cases are due to Cushing's disease, which is 8 times more common in women than men.

Symptoms may develop insidiously over several years and include obesity, particularly of the trunk, rounding of the face, atrophy of the skin leading to striae, poor wound healing, muscle weakness, osteoporosis, hypertension, diabetes mellitus, and depression and other psychological disturbances. Hypokalaemia is rare in Cushing's disease but common in other forms of the syndrome. Women may have hirsutism due to adrenal androgen secretion, and both sexes may develop hypogonadism and loss of libido.

Diagnosis of Cushing's syndrome can be problematic because no test is wholly reliable.[1-5] Where there is suspicion, options for initial screening include measurement of urinary cortisol, late-night salivary cortisol, midnight plasma-cortisol, and overnight low-dose dexamethasone suppression testing. A dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism. Once a diagnosis of Cushing's syndrome has been made, plasma-ACTH measurements are used to distinguish between ACTH-dependent and ACTH-independent forms. High-dose dexamethasone suppression testing and corticorelin stimulation testing have been used to differentiate between pituitary and ectopic ACTH-dependent Cushing's syndrome, but they both have disadvantages and their usefulness has been debated. The conclusion from one review[6] was that measurement of urinary free cortisol and the dexamethasone suppression test have most evidence supporting their use while there is limited evidence supporting the use of salivary and serum midnight cortisol tests. For further discussion of dexamethasone suppression testing, see p. 1632.1, and for corticorelin stimulation testing, see p. 1628.2. Imaging techniques and sampling of central (petrosal) venous blood are additional procedures that may be used for localising tumours.

Appropriate **treatment** depends on accurate identification of the cause of the syndrome.[1] The usual treatment[7] in Cushing's disease is transsphenoidal resection of the tumour, which when carried out by an experienced surgeon produces a successful response in the majority of patients. Pituitary radiotherapy is slower than surgery to take effect, produces a lower remission rate, and is more likely to produce hypopituitarism. It is therefore usually used as second-line therapy when initial surgery has not been curative and a second operation is considered unsuitable. If pituitary surgery or radiotherapy fails, bilateral adrenalectomy may be considered (although this has some risks including that of Nelson's syndrome due to hyperactivity of residual pituitary tumour). Patients who undergo such surgery require glucocorticoid and mineralocorticoid replacement therapy for life. Surgery is also the treatment of choice for a resectable adrenal tumour or ectopic ACTH-secreting tumour; even where there is metastasis it may be useful in moderating symptoms.

Pasireotide, which has a high affinity for somatostatin receptor subtype 5, may be used for medical treatment of ACTH-secreting pituitary adenoma when surgery is not possible or has failed.[8] Several other drugs have been used in patients with Cushing's disease, but their role appears to be mainly adjuvant.[1,7,9] Those acting at the hypothalamic-pituitary level, aimed at reducing ACTH secretion, do not seem to be of much value; there have been occasional reports of benefit with bromocriptine, cyproheptadine, and sodium valproate. Drugs that inhibit steroid synthesis in the adrenal gland are more effective, and include mitotane, metyrapone, and ketoconazole. These may be used to control severe complications quickly, prepare patients for surgery, or provide cover while radiotherapy takes effect. Mifepristone acts as a glucocorticoid receptor antagonist, and has been used successfully in a few patients with Cushing's syndrome. Etomidate can be useful for acute control of hypercortisolaemia if the oral route is not available.

In patients with the ectopic ACTH syndrome in whom surgery is unsuitable or ineffective, chemotherapy aimed at the primary tumour is the treatment of choice but is likely to be only palliative. Inhibitors of steroid synthesis can be used to control symptoms, and somatostatin analogues such as octreotide may decrease ACTH secretion by ectopic tumours that have somatostatin receptors.[1]

Surgery is the preferred treatment for an adrenal tumour but, although this is usually curative for adrenal adenoma, it is less successful for adrenal carcinoma.[1]

In patients who are successfully treated for Cushing's syndrome, adrenocortical replacement therapy (see p. 1600.2) is usually required until the hypothalamic-pituitary-adrenal axis recovers normal function, a process which may take many months.

1. Newell-Price J, *et al.* Cushing's syndrome. *Lancet* 2006; **367:** 1605–17.
2. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
3. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.
4. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab* 2006; **91:** 3746–53.
5. Nieman LK, *et al.* The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; **93:** 1526–40. Also available at: http://www.endo-society.org/guidelines/final/upload/Cushings_Guideline.pdf (accessed 06/08/08)
6. Elamin MB, *et al.* Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and metaanalyses. *J Clin Endocrinol Metab* 2008; **93:** 1553–62.
7. Biller BMK, *et al.* Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008; **93:** 2454–62.
8. Colao A, *et al.* Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med* 2012; **366:** 914–24. Correction. *ibid.;* **367:** 780.
9. Nieman LK. Medical therapy of Cushing's disease. *Pituitary* 2002; **5:** 77–82.

Adverse Effects

Metyrapone may give rise to nausea and vomiting, abdominal pain, headache, sedation, dizziness, hypotension, and hypersensitivity rashes. Hypoadrenalism, hirsutism, and bone marrow depression may occur rarely. Long-term use of metyrapone can cause hypertension.

Alopecia. Reports of alopecia[1,2] associated with administration of metyrapone for Cushing's syndrome.

1. Harris PL. Alopecia associated with long-term metyrapone use. *Clin Pharm* 1986; **5:** 66–8.
2. Harries-Jones R, Overstall P. Metyrapone-induced alopecia. *Postgrad Med J* 1990; **66:** 584.

Precautions

Metyrapone should be used with extreme caution, if at all, in patients with gross hypopituitarism or with reduced adrenal secretory activity because of the risk of precipitating acute adrenal failure. Thyroid dysfunction or liver cirrhosis may alter the response to metyrapone.

Dizziness and sedation may affect the performance of skilled tasks such as driving.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metyrapone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Phenytoin is reported to increase the metabolism of metyrapone; doubling the dose of metyrapone may counteract the interaction. Drugs reported to interfere with the metyrapone test include antidepressants such as amitriptyline, antithyroid drugs, antipsychotics such as chlorpromazine, barbiturates, corticosteroids, cyproheptadine, and hormones that affect the hypothalamic-pituitary axis such as oestrogens and progestogens.

Pharmacokinetics

Metyrapone is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after ingestion. It is metabolised by rapid reduction to metyrapol and excreted in the urine mainly as glucuronide conjugates of metyrapone and metyrapol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Metopirone; ***Fr.***: Metopirone; ***Gr.***: Metopirone; ***Hong Kong***: Metopirone; ***Irl.***: Metopirone; ***Israel***: Metopirone; ***Neth.***: Metopiron; ***NZ***: Metopirone; ***Switz.***: Metopirone; ***UK***: Metopirone; ***USA***: Metopirone.

Pharmacopoeial Preparations
BP 2014: Metyrapone Capsules;
USP 36: Metyrapone Tablets.

Miglustat *(BAN, USAN, rINN)*

Butyldeoxynojirimycin; *n*-Butyl-deoxynojirimycin; Miglustaatti; Miglustatum; OGT-918; OXAIDS; SC-48334; Миглустат.
1,5-(Butylimino)-1,5-dideoxy-D-glucitol;(2*R*,3*R*,4*R*,5*S*)-1-Butyl-2-(hydroxymethyl)piperidine-3,4,5-triol.
$C_{10}H_{21}NO_4$=219.3
CAS — 72599-27-0.
ATC — A16AX06.
ATC Vet — QA16AX06.
UNII — ADN3S497AZ.

Uses and Administration

Miglustat is an inhibitor of the enzyme glucosylceramide synthase, responsible for the first step in the synthesis of glucosylceramide and most other glycolipids. It is used to help prevent the accumulation of glucosylceramide in patients with mild to moderate type 1 Gaucher disease (p. 2433.3) who cannot be treated with enzyme replacement therapy. It is also used for the treatment of

progressive neurological manifestations of Niemann-Pick type C disease. The initial dose in type 1 Gaucher disease is 100 mg orally 3 times daily; reduction to 100 mg once or twice daily may be necessary in some patients because of diarrhoea. The dose for the treatment of Niemann-Pick type C disease is 200 mg orally three times daily; temporary dose reduction may be necessary in some patients because of diarrhoea. For doses to be used in children, see below. For details of reduced doses in patients with renal impairment, see below.

References.
1. McCormack PL, Goa KL. Miglustat. *Drugs* 2003; **63:** 2427–34.
2. Weinreb NJ, *et al.* Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol* 2005; **80:** 223–9.
3. Giraldo P, *et al.* Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica* 2006; **91:** 703–6.
4. Elstein D, *et al.* Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood* 2007; **110:** 2296–2301.
5. Patterson MC, *et al.* Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007; **6:** 765–72.

Administration in children. Doses of miglustat given orally for the treatment of Niemann-Pick type C disease in children are adjusted on the basis of body-surface:
- greater than 1.25 m^2: 200 mg three times daily
- between 0.88 and 1.25 m^2: 200 mg twice daily
- between 0.73 and 0.88 m^2: 100 mg three times daily
- between 0.47 and 0.73 m^2: 100 mg twice daily
- equal to or less than 0.47 m^2: 100 mg daily

Administration in renal impairment. The initial dose of miglustat given orally should be reduced in renal impairment according to the patient's creatinine clearance (CC). For the treatment of **type 1 Gaucher disease**, reduced doses are:
- CC 50 to 70 mL/minute per 1.73 m^2: 100 mg twice daily
- CC 30 to 50 mL/minute per 1.73 m^2: 100 mg once daily
- CC less than 30 mL/minute per 1.73 m^2: not recommended

For the treatment of **Niemann-Pick type C disease**, reduced doses are:
- CC 50 to 70 mL/minute per 1.73 m^2: 200 mg twice daily
- CC 30 to 50 mL/minute per 1.73 m^2: 100 mg twice daily
- CC less than 30 mL/minute per 1.73 m^2: not recommended Doses for Niemann-Pick type C disease in children below the age of 12 years with renal impairment should be adjusted for body-surface. See Administration in Children, above for doses in children with normal renal function.

Adverse Effects and Precautions

Diarrhoea and other gastrointestinal disturbances, weight loss, tremor, dizziness, headache, cramps in legs, and visual disturbances are frequent in patients receiving miglustat, and some patients may have paraesthesias, peripheral neuropathy, or thrombocytopenia. Studies in *animals* have indicated an effect on spermatogenesis; male patients should not attempt conception during, or for 3 months after stopping, treatment. Care is required in renal impairment.

Pharmacokinetics

Miglustat is rapidly absorbed after oral doses and peak plasma concentrations occur in about 2 hours. It is mainly excreted in the urine with some also excreted in the faeces; the average elimination half-life is 6 to 7 hours.

Food. The average peak plasma concentration was reduced by 37% when miglustat was taken with food by 24 healthy subjects. However, there was no clinically significant effect on the extent of absorption (area under the curve was decreased by 14%).[1] Licensed product information states that miglustat may be taken with or without food.

1. van Giersbergen PLM, Dingemanse J. Influence of food intake on the pharmacokinetics of miglustat, an inhibitor of glucosylceramide synthase. *J Clin Pharmacol* 2007; **47:** 1277–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zavesca; ***Austria***: Zavesca; ***Belg.***: Zavesca; ***Braz.***: Zavesca; ***Canad.***: Zavesca; ***Cz.***: Zavesca; ***Denm.***: Zavesca; ***Fin.***: Zavesca; ***Fr.***: Zavesca; ***Ger.***: Zavesca; ***Gr.***: Zavesca; ***Hung.***: Zavesca; ***Irl.***: Zavesca; ***Israel***: Zavesca; ***Ital.***: Zavesca; ***Jpn***: Brazaves; ***Neth.***: Zavesca; ***Norw.***: Zavesca; ***NZ***: Zavesca; ***Pol.***: Zavesca; ***Port.***: Zavesca; ***Rus.***: Zaveska (Завеска); ***Spain***: Zavesca; ***Swed.***: Zavesca; ***Switz.***: Zavesca; ***UK***: Zavesca; ***USA***: Zavesca.

Dementholised Mint Oil

Csökkentett mentoltartalmú mezei mentaolaj (partly dementholised mint oil); Menta, aceite esencial desmentolado de; Mentha arvensis, huile essentielle partiellement démentholée de (mint oil, partly dementholised); Menthae arvensis aetheroleum partim mentholum depletum (mint oil, partly dementholised).

CAS — 68917-18-0 (cornmint oil).

Pharmacopoeias. In *Eur.* (see p. vii).

Mentha oil is in *Jpn.*

Ph. Eur. 8: (Mint Oil, Partly Dementholised; Menthae Arvensis Aetheroleum Partim Mentholum Depletum; Dementholised Mint Oil BP 2014). The essential oil obtained by steam distillation from the fresh, flowering aerial parts, recently gathered from *Mentha canadensis* (*M. arvensis* var. *glabrata*; *M. arvensis* var. *piperascens*) followed by partial separation of menthol by crystallisation. A colourless or pale yellow to greenish-yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Dementholised mint oil is used as a flavour. *Mentha arvensis* is used in herbal medicine as a febrifuge and for rheumatic disorders. Cornmint oil, obtained from *M. arvensis*, is used in aromatherapy as an adulterant or substitute for peppermint oil. Peppermint oil (p. 1877.1) and spearmint oil (p. 2621.2) are used as carminatives and flavours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Japol; ***Ger.***: Japanol; JHP Rodler; Novopin MIG neu; Retterspitz Muskel- und Nervenol; ***Pol.***: Migrenol†; ***Swed.***: Japol.

Multi-ingredient Preparations. ***Austral.***: Tiger Balm Oil; Tiger Balm Red; Tiger Balm White; ***Austria***: Parodontax†; ***Canad.***: Tiger Balm Arthritis Rub; Tiger Balm Patch Warm; ***Chile***: Astrijesan; Calmatol; ***Fr.***: Esculape†; Tigre de Chine; ***Ger.***: Dreierlei; ***Hung.***: Salonpas Liniment; Tiger Balm Red; Tiger Balm White; ***Irl.***: Olbas; Tiger Balm Red; Tiger Balm White; ***Israel***: Tiger Balm Red; Tiger Balm White; ***Ital.***: Broncosedina; Listerine Fresh Citrus; Listerine Tartar Control; Venalta; ***Malaysia***: Eucarbon; ***Neth.***: Olbas†; ***Pol.***: Argol Essenza Balsamica; Milocardin; Mucosit; Rapacholin C; Rapacholin Forte; Rhin-Bac; Salviasept; ***Switz.***: Baume du Tigre blanc; Baume du Tigre rouge; DemoPectol; Kernosan Eau Dentifrice†; Malveol; Novital; Odontal; Onguent nasal Ruedi; Phlogantin†; Pommade nasale de Nager†; Pommade nasale de Ruedi†; Radix†; Tyrothricin†; Unathene†; ***Turk.***: Sandolin†; ***UK***: Olbas for Children; Olbas; Sinose; ***Ukr.***: Phytolysin Plus (Фитолизин Плюс); ***USA***: Tiger Balm.

Miracle Fruit

Fruta milagrosa; Магический Фрукт.

NOTE. The name Miracle Fruit has also been applied to *Gymnema sylvestre* and *Thaumatococcus daniellii*.

Profile

Miracle fruit is the fruit of *Synsepalum dulcificum* (*Richardella dulcifica*) (Sapotaceae). It contains a glycoprotein 'miraculin' with no apparent taste of its own but which is able to make sour substances taste sweet and to improve the flavour of foods. Its activity is reduced by heating.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ukr.***: Lipomin (Липомин); Liponorm (Липонорм).

Mistletoe

European Mistletoe; Gui; Mistelkraut; Muérdago; Tallo de Muérdago; Visci Caulis; Visci herba; Viscum; Viscum Album; Омела.

ATC Herb — HC02KA5003 (Viscum album: extract); HL01CW5001 (Viscum album: herb).

UNII — E6839Q6DO1 (Viscum album); P83EQ521R3 (Viscum album fruit); BK9092J5MP (Viscum album fruiting top).

Pharmacopoeias. In *Ger.*

Uses and Administration

Mistletoe is the dried, evergreen, dioecious semi-parasite, *Viscum album* (Loranthaceae), which grows on the branches of deciduous trees, chiefly apple, poplar, and plum. It occurs as a mixture of broken stems and leaves and occasional fruits. Mistletoe has a vasodilator action and has been used in herbal preparations for hypertension and cardiovascular disorders although its activity when taken orally is questionable. It has also been used in nervous disorders.

Mistletoe contains lectins with cytotoxic and immunomodulatory actions *in vitro* and preparations have been given by injection in neoplastic disease.

Homoeopathy

Mistletoe has been used in homoeopathic medicines under the following names: Viscum; Viscum album; Vis. alb.

Malignant neoplasms. Reviews[1-3] of the use of mistletoe for the treatment of malignant neoplasms revealed that studies have been of variable quality, and have produced conflicting results; it has been suggested that the more rigorous studies do not show benefit.[3] A systematic review[4] of 21 randomised controlled studies found major methodological flaws in most of the studies and concluded that there was insufficient evidence to provide guidelines for the use of mistletoe extracts in oncology.

1. Mansky PJ. Mistletoe and cancer: controversies and perspectives. *Semin Oncol* 2002; **29:** 589–94.
2. Kienle GS, *et al.* Mistletoe in cancer—a systematic review on controlled clinical trials. *Eur J Med Res* 2003; **8:** 109–19.
3. Ernst E, *et al.* Mistletoe for cancer? A systematic review of randomised clinical trials. *Int J Cancer* 2003; **107:** 262–7.
4. Horneber M, *et al.* Mistletoe therapy in oncology. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 03/06/08).

Adverse Effects

Ingestion of the berries and other parts of mistletoe has been reported to cause nausea, vomiting, diarrhoea, and bradycardia.

A review of mistletoe.[1] There are about 1300 species of mistletoe representing 36 genera of the Loranthaceae, and what is called the "common mistletoe" varies from country to country: in Europe the term describes *Viscum album* while in the USA it describes *Phoradendron flavescens*. The toxicity of aqueous extracts of mistletoe has been found to depend upon the nature of the host plant. Three classes of cytotoxic compounds are present in the leaves and stems of *V. album* although the berries are generally considered to be the most toxic part of the plant. These are alkaloids, viscotoxins, and lectins. The viscotoxins have been shown to cause hypotension, bradycardia, arterial vasoconstriction, and a negative inotropic effect, and may act as acetylcholine agonists. The lectins show toxic effects in *animals* similar to those seen with ricin.

There have been reports of hepatitis after the ingestion of herbal remedies containing mistletoe.[2,3] Severe delayed hypersensitivity has been reported[4] in a patient given intravenous chemotherapy for breast cancer concurrently with subcutaneous injections of a mistletoe extract. It was thought that mistletoe had stimulated the reaction to methotrexate and gemcitabine.

1. Anderson LA, Phillipson JD. Mistletoe—the magic herb. *Pharm J* 1982; **229:** 437–9.
2. Harvey J, Colin-Jones DG. Mistletoe hepatitis. *BMJ* 1981; **282:** 186–7.
3. Weeks GR, Proper JS. Herbal medicines—gaps in our knowledge. *Aust J Hosp Pharm* 1989; **19:** 155–7.
4. Shaw HS, *et al.* Delayed-type hypersensitivity reaction with Iscador M given in combination with cytotoxic chemotherapy. *J Clin Oncol* 2004; **22:** 4432–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Eurixor; Helixor; Iscador; Isorel; Lektinol; ***Cz.***: Nat Jmeli†; ***Ger.***: Abnobaviscum; Cefalektin†; Eurixor†; Helixor; Iscador; Iscucin; Lektinol; Mistel Curarina; Mistel-Krautertabletten; Misteltropfen Hofmanns; Salus Mistel-Tropfen; Viscysat†; ***Switz.***: Helixor; Iscador.

Multi-ingredient Preparations. ***Austral.***: Calmo†; ***Austria***: Rutiviscal; Wechseltee St Severin; ***Canad.***: Herbal Insomnia†; Salusan†; ***Cz.***: Alvisan Neo; Hypotonicka†; ***Ger.***: Antihypertonicum S; Ilja Rogoff; Iscador c Arg; Iscador c Cu; Iscador c Hg; ***Hung.***: Sam-Ginseng Royal; Sanhelios 333; ***Pol.***: Cravisol; Doppelherz Energovital Tonik†; Venoforton; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); Herbion Drops for the Heart (Гербион Сердечные Капли)†; ***Ukr.***: Herbion Drops for Heart (Гербион Сердечные Капли)†.

Homoeopathic Preparations. ***Austria***: Cefavora; Homviotensin; Veratrum Med Complex; ***Canad.***: Ateria-Heel†; Candida Yeast Relief; Ginkgo-Comp†; Homeo-Form C†; HPB Complex†; Hylands LCQ; Hylands Leg Cramps; Leg Cramps with Quinine; Urarthone†; Visceel†; ***Fr.***: Hypophysis Complexe No 31†; Kalium Iodatum Complexe No 84†; L 25; Poconeol no 43; Poconeol no 5; Poconeol no 65†; Tarentula Complexe No 71; Urarthone; ***Ger.***: Antihypertonicum N†; Antihypertonicum-Tropfen N†; Arthrocalman; Cefavora†; Derivatio H; Derivatio; Evisco Mistel Urtinktur; Evisco Misteltropfen N; Flenin; Hewerheum N†; Homviotensin; Juv 110; Kattwicor; Lachemistol; Lowe-Komplex Nr 3; Lymphdiaral; Miburell; Panalgan; Phyto-C; Plantacard N; Plenosol; RauwolfiaViscomp; Roth's Rotacard; Uwobletten Arteriosklerose-Complex†; Vertizin; Viscum album H†; Viscum Album HM†; Viscum-Entoxin N; ***Neth.***: Actelite; Chavita 6; Co-Hypert; ***Rus.***: Crataegus-Plus (Кратегус-Плюс); ***Ukr.***: Cefavora (Цефавора); Homviotensin (Хомвиотензин).

Mitratapide *(USAN, rINN)*

Mitratapid; Mitratapida; Mitratapidum; R-103757; Митратапид.

2-[(2*R*)-Butan-2-yl]-4-(4-{4-[4-({(2*S*,4*R*)-2-(4-chlorophenyl)-2-[(4-methyl-4*H*-1,2,4-triazol-3-ylsulfanyl)methyl]-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

$C_{36}H_{41}ClN_8O_4S$=717.3

CAS — 179602-65-4.

ATC Vet — QA08AB90.

UNII — FVW7T75XP4.

Profile

Mitratapide is an inhibitor of the microsomal triglyceride transfer protein. It is used in veterinary medicine as an aid to management of obesity in *dogs*.

Monoclonal Antibodies

Nomenclature

The official nomenclature of monoclonal antibodies discussed here is intended to identify the specific therapeutic target of the antibody and the origin of its immunoglobulin sequence, which is discussed further under Uses and Administration, below.

The prefix of a name is unique to each specific monoclonal antibody, but names for all monoclonal antibodies have the suffix **-mab**.

The prefix of a name is followed by a substem that gives an indication of the pharmacological category or therapeutic target of the monoclonal antibody, for example:

-b(a)- bacterial
-c(i)- cardiovascular
-f(u)- fungal
-k(i)- interleukin
-l(i)- immunomodulator
-s(o)- bone
-t(u)- tumour
-v(i)- viral

Another substem indicating the genetic origin of the immunoglobulin sequence of the monoclonal antibody follows the therapeutic substem and immediately precedes the suffix, for example:

-o- murine
-xi- chimeric
-zu- humanised
-u- fully human

Examples of monoclonal antibodies named under this system are:

- elsilimomab (p. 2534.1) – immunomodulator, murine
- tositumomab (p. 874.2) – antitumour, murine
- abciximab (p. 1281.1) – cardiovascular, chimeric
- infliximab (p. 74.2) – immunomodulator, chimeric
- palivizumab (p. 2415.2) – RSV antibody, humanised
- tocilizumab (p. 77.3) – immunomodulator, humanised
- trastuzumab (p. 875.3) – antitumour, humanised
- canakinumab (p. 34.2) – interleukin-1β inhibitor, human
- denosumab (p. 1182.1) – bone disorders, human
- panitumumab (p. 843.1) – antitumour, human

The system for indicating therapeutic category is not, however, completely reliable, especially for a monoclonal antibody that has more than one use, or one that is used for an indication that was not its original intended target. Names of earlier monoclonal antibodies also include therapeutic substems that have been excluded from later nomenclature lists, for example edrecolomab (p. 786.1) used for colorectal cancer and oregovomab (p. 838.1) investigated for ovarian cancer.

If a monoclonal antibody is radiolabelled or conjugated to another substance such as a toxin or antineoplastic drug, this should be reflected by use of a second word to form the name (e.g. gemtuzumab ozogamicin, p. 802.2). Likewise, pegylated monoclonal antibodies are named using a second word 'pegol' (e.g. certolizumab pegol, p. 39.1) or related designation, although the prefix **peg-** has also been used.

References.

1. WHO. *General policies for monoclonal antibodies.* Geneva: WHO, 2009. Available at: http://www.who.int/medicines/services/inn/Generalpoliciesformonoclonalantibodies2009.pdf (accessed 06/04/10)
2. AMA (USAN). Monoclonal antibodies. Available at: http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies_print.html (accessed 06/04/10)

Uses and Administration

In order to understand the structure and function of monoclonal antibodies and the rationale for their use, it is necessary to understand the basic structure of antibodies in general.

Antibodies (immunoglobulins) are high-molecular-weight glycoproteins produced by B lymphocytes in response to antigenic stimulation. They are made up of 4 amino acid chains comprising two heavy chains and two light chains arranged in a Y-shape. The heavy chains (Fc domain; complement binding) constitute the constant region of the molecule and determine its effector function—for example, whether it binds to Fc receptors on immune cells or activates the complement cascade; the amino acid sequence of the Fc domain is identical for all antibodies within a class (e.g. IgA, IgD, IgE, IgG, IgM). The light chains (Fab domain; fragment antigen binding) constitute the variable region of the molecule and form the antigen binding site; specific amino acid sequences (the complementarity-determining region) determine the ability of the antibody to bind to the epitope (the antigenic determinant) of the target molecule and the degree of binding. There may be several different epitopes on one antigen and a usual antibody response *in vivo* will therefore produce polyclonal antibodies (e.g. antisera, see p. 2373.1). **Monoclonal antibodies**, on the other hand, are identical antibodies produced by a single clone of B lymphocytes that will bind only to a specific epitope on the target antigen. Monoclonal antibodies interact with, and influence, the function of target molecules through binding, blocking, or signalling, depending on the Fab region of the antibody.

Monoclonal antibodies were first produced by hybridoma technology, which was described by Köhler and Milstein in 1975, although the first therapeutic monoclonal antibody for human use, muromonab-CD3 (p. 1960.1), was not developed until 1986. In the original hybridoma technique, mice were immunised with a specific antigen to stimulate B-lymphocytes to produce antibodies against that antigen. The B-lymphocytes were extracted from the mice spleen cells and fused with cultured tumour cells to form immortal hybrid cell lines (hybridomas) that were then screened for monoclonal antibodies of interest. In this way, identical antibodies could be produced in large quantities over a prolonged period. Unfortunately, murine monoclonal antibodies can be unreliable, have short half-lives and limited efficacy, and generate production of antibodies with the potential for serious adverse effects (see p. 2562.2). Using recombinant DNA technology, chimeric monoclonal antibodies can be produced in which the Fab region of the mouse-derived antibody is combined with the Fc region of a human antibody to try and improve the safety profile (e.g. infliximab, p. 74.2 and rituximab, p. 852.1). The total human genetic component of chimeric monoclonal antibodies is between 60 and 90%, and while safer than murine monoclonal antibodies, there are still problems with adverse effects. Further developments in genetic engineering have produced humanised antibodies in which the amino acid sequences of the complementarity-determining region from the mouse Fab region are incorporated into the Fab region of a human antibody to increase the total human genetic component to around 90 to 95% (e.g. bevacizumab, p. 747.1 and trastuzumab, p. 875.3). Fully human monoclonal antibodies with 100% human genetic composition (e.g. adalimumab, p. 17.2 and panitumumab, p. 843.1) can now be developed through new biotechnologies such as antibody phage display in which human antibody sequences are cloned or designed, or the use of transgenic mice carrying human antibody genes. Other developments include modification of monoclonal antibodies to produce a fragment that lacks the Fc region (e.g. abciximab, p. 1281.1 and ranibizumab, p. 2602.1). Monoclonal antibodies can also be attached to another drug such as a cytotoxic drug (e.g. gemtuzumab ozogamicin, p. 802.2), a radioactive isotope (e.g. ibritumomab tiuxetan chelated with indium-111 or yttrium-90, see p. 804.3), or a toxin (e.g. zolimomab aritox); these are called conjugated monoclonal antibodies, whereas unconjugated monoclonal antibodies are referred to as 'naked'. The nomenclature of monoclonal antibodies reflects the genetic origin of the immunoglobulin sequence of monoclonal antibodies and is discussed above, under Nomenclature.

Monoclonal antibodies have been produced for a variety of different uses, including diagnostics, therapeutics, veterinary practice, food industry, agriculture, and vaccine preparation. Therapeutic uses include neovascular (wet) age-related macular degeneration, allergic asthma, bacterial and viral infections, cardiovascular disorders, immunosuppression in transplant recipients, inflammatory bowel disease, inflammatory joint disorders, malignant neoplasms, multiple sclerosis, paroxysmal nocturnal haemoglobinuria, and plaque psoriasis.

References.

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2. Anonymous. Understanding monoclonal antibodies. *Drug Ther Bull* 2007; **45:** 55–6.
3. Martin-Mateos MA. Monoclonal antibodies in pediatrics: use in prevention and treatment. *Allergol Immunopathol (Madr)* 2007; **35:** 145–50.
4. Samaranayake H, *et al.* Challenges in monoclonal antibody-based therapies. *Ann Med* 2009; **41:** 322–31.
5. Steinitz M. Three decades of human monoclonal antibodies: past, present and future developments. *Hum Antibodies* 2009; **18:** 1–10.
6. Wang DD, *et al.* Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *J Clin Pharmacol* 2009; **49:** 1012–24.
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Cardiovascular disorders. Abciximab (p. 1281.1) is a chimeric monoclonal antibody Fab fragment that targets the glycoprotein IIb/IIIa-receptor on the surface of human platelets and prevents the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa-receptor sites on activated platelets. Abciximab thus inhibits platelet aggregation and is used as an adjunct to heparin and aspirin therapy in patients undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p. 1259.2).

Cryopyrin-associated periodic syndromes. Canakinumab (p. 34.2) is a human monoclonal antibody that binds to interleukin-1β and blocks its interaction with interleukin-1 receptors, thus preventing activation of the interleukin-1β-induced gene and the production of inflammatory mediators. It is used in the treatment of cryopyrin-associated periodic syndromes including familial cold auto-inflammatory syndrome and Muckle-Wells syndrome, which are rare inherited auto-inflammatory disorders.

Dermatological disorders. Monoclonal antibodies that target the inflammatory cytokine tumour necrosis factor (TNF) are used in the treatment of plaque psoriasis (p. 1688.1), and examples of monoclonal TNF antibodies used in clinical practice include the chimeric antibody infliximab (p. 74.2) and the human antibody adalimumab (p. 17.2). Ustekinumab (p. 1728.2) is a human monoclonal antibody that binds to interleukins 12 and 23 and is also used in the treatment of plaque psoriasis. Efalizumab (p. 1702.2) is a humanised monoclonal antibody that binds to CD11a on leucocytes to inhibit the activation of T-lymphocytes. It has been used to treat plaque psoriasis but was withdrawn from the market in the USA and Europe because of reports of progressive multifocal leukoencephalopathy.

Inflammatory bowel disease. Monoclonal antibodies that target the inflammatory cytokine tumour necrosis factor (TNF) are used in the treatment of inflammatory bowel diseases (p. 1808.3) such as Crohn's disease and ulcerative colitis, and examples of monoclonal TNF antibodies used in clinical practice include the chimeric antibody infliximab (p. 74.2) and the human antibody adalimumab (p. 17.2). Certolizumab pegol (p. 39.1) is a pegylated humanised TNF antibody fragment used in the treatment of Crohn's disease.

Inflammatory joint disorders. Monoclonal antibodies that target the inflammatory cytokine tumour necrosis factor (TNF) are used in the treatment of inflammatory joint disorders such as rheumatoid arthritis (p. 13.2), juvenile idiopathic arthritis (p. 12.1), psoriatic arthritis (see under Spondyloarthropathies, p. 14.3), and ankylosing spondylitis (see under Spondyloarthropathies, p. 14.3). Examples of monoclonal TNF antibodies used in clinical practice for various arthritides include the chimeric antibody infliximab (p. 74.2), the humanised antibody tocilizumab (p. 77.3), the pegylated humanised TNF antibody fragment certolizumab pegol (p. 39.1), and the human antibodies adalimumab (p. 17.2) and golimumab (p. 66.3). Rituximab (p. 852.1) is a chimeric anti-CD20 monoclonal antibody used as adjunctive treatment for rheumatoid arthritis.

Lymphoproliferative disorders. Tocilizumab (p. 77.3) is a humanised monoclonal antibody that specifically targets both soluble and membrane-bound interleukin-6 receptors thereby inhibiting interleukin-6 signalling. It is used for the treatment of Castleman's disease, a rare lymphoproliferative disorder.

Malignant neoplasms. Tumour cells express several different antigens each of which is a potential target for development of a specific monoclonal antibody that can generate immune responses with consequential direct or indirect anti-tumour effects. Monoclonal antibodies can also be conjugated with antineoplastic drugs, toxins, or radioisotopes and specifically targeted to tumour receptors in order to avoid damaging healthy tissue.

Trastuzumab (p. 875.3) is a humanised monoclonal antibody directed against the cell surface protein produced by the human epidermal growth receptor 2 (HER2) gene. HER2 protein is overexpressed in some tumours, and trastuzumab is used in the treatment of breast cancer (p. 702.1). Other monoclonal antibodies that bind to the epidermal growth factor receptor include the chimeric antibody cetuximab (p. 762.3) used in the treatment of

metastatic colorectal cancer (p. 706.3) and cancers of the head and neck (p. 708.1), the humanised antibody nimotuzumab (p. 836.3) used in the treatment of glioma (see under Malignant Neoplasms of the Brain, p. 701.2) and cancers of the head and neck, and the human antibody panitumumab (p. 843.1) used in the treatment of metastatic colorectal cancer in patients with disease progression after other therapies.

Bevacizumab (p. 747.1) is a humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis. It is used with fluoropyrimidine-based chemotherapy in the treatment of metastatic colorectal cancer, with paclitaxel in the treatment of metastatic breast cancer, with platinum-based chemotherapy in the treatment of non-small cell lung cancer (p. 710.2), and with interferon alfa in the treatment of renal cell carcinoma (p. 708.3). Bevacizumab is also used for progressive glioblastoma (see under Malignant Neoplasms of the Brain, p. 701.2).

Edrecolomab (p. 786.1) is a murine monoclonal antibody directed at epithelial cell surface glycoproteins that has been used as adjuvant therapy after surgery for colorectal cancer.

Rituximab (p. 852.1) is a chimeric monoclonal antibody targeted to the CD20 antigen of B lymphocytes that is used in the treatment of non-Hodgkin's lymphoma (p. 696.3). Alemtuzumab (p. 737.1) is a humanised monoclonal antibody directed against the CD52 antigen of lymphocytes that is used in the treatment of chronic lymphocytic leukaemia (p. 693.3).

Catumaxomab (p. 762.2) is a rat-mouse hybrid monoclonal antibody used for the treatment of malignant ascites (see under Malignant Effusions, p. 700.1) in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

Gemtuzumab ozogamicin (p. 802.2) is a humanised monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. It is used for the second-line treatment of CD33-positive acute myeloid leukaemia (p. 693.1) in elderly patients unable to tolerate conventional chemotherapy.

Ibritumomab is a murine monoclonal antibody targeted to the CD20 antigen of B lymphocytes that is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. In the management of non-Hodgkin's lymphoma, ibritumomab tiuxetan (p. 804.3) is chelated with indium-111 and used for imaging, whereas it is chelated with yttrium-90 and used for radio-immunotherapy. Likewise, tositumomab (p. 874.2) is a murine monoclonal antibody also targeted to the CD20 antigen and radiolabelled with iodine-131 for use in the treatment of non-Hodgkin's lymphoma.

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2. Fanale MA, Younes A. Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma. *Drugs* 2007; **67:** 333–50.
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Multiple sclerosis. Natalizumab (p. 2567.2) is a humanised monoclonal antibody that binds to α4β1-integrin, which is highly expressed on the surface of all leucocytes, with the exception of neutrophils, thereby preventing transmigration of mononuclear leucocytes across the endothelium into inflamed parenchymal tissue. It has been found to decrease the frequency of exacerbations in relapsing-remitting multiple sclerosis (p. 996.3) but it has been associated with an increased risk of progressive multifocal leukoencephalopathy and its use is therefore restricted. Alemtuzumab (p. 737.1) is also licensed for use in the treatment of multiple sclerosis; when compared with interferon beta-1a, it significantly reduced the rate of relapse in previously untreated patients with relapsing-remitting multiple sclerosis and also in patients who had relapsed after first-line treatment. Other monoclonal antibodies are being investigated for the treatment of multiple sclerosis and include daclizumab (p. 1957.1) and rituximab (p. 852.1).

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1. Simpson BS, Coles AJ. Rationale for cytotoxic monoclonal antibodies in MS. *Int MS J* 2007; **14:** 48–56.
2. Di Pauli F, *et al.* Monoclonal antibodies in the treatment of multiple sclerosis. *Curr Med Chem* 2009; **16:** 4858–68.
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4. Cohen JA, *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1819–28.
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Ocular disorders. Ranibizumab (p. 2602.1) is a humanised monoclonal antibody Fab fragment that binds to and inhibits vascular endothelial growth factor A (VEGF-A), thereby preventing its action in endothelial cell proliferation and neovascularisation, as well as vascular leakage. Ranibizumab is used for the treatment of neovascular (wet) age-related macular degeneration (p. 880.2). Bevacizumab (p. 747.1) is a related humanised monoclonal antibody also used to treat this condition, although it is unlicensed for such use and has been associated with adverse effects.

1. Rodrigues EB, *et al.* Therapeutic monoclonal antibodies in ophthalmology. *Prog Retin Eye Res* 2009; **28:** 117–44.

Organ and tissue transplantation. Muromonab-CD3 (p. 1960.1) is a murine monoclonal antibody that targets the T3 (CD3) antigen of human T-lymphocytes, which is essential to antigen recognition and response. Binding to T-cells activates complement, which depletes T-cell populations. Muromonab-CD3 is used in the treatment of acute allograft rejection in organ transplant recipients (see p. 1932.2).

Monoclonal antibodies that target CD25, a subunit of the interleukin-2 receptor, are also used as immunosuppressants in transplantation. The binding of interleukin-2 to the T-cell is blocked by the monoclonal antibody, and thus inhibits T-cell activation. Basiliximab (p. 1944.1) is a chimeric monoclonal antibody that functions as an interleukin-2 receptor antagonist. It used in combined immunosuppressive regimens for the prevention of acute graft rejection following renal transplantation (p. 1935.2). Daclizumab (p. 1957.1) is a humanised monoclonal antibody used similarly.

Paroxysmal nocturnal haemoglobinuria. Eculizumab (p. 2499.1) is a humanised monoclonal antibody that acts as a complement blocker by inhibiting terminal complement activation at the C5 protein. It is used to reduce haemolysis in patients with paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia (p. 1122.2).

Respiratory disorders. Omalizumab (p. 1216.3) is a humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and reduces the amount of free IgE available to trigger the allergic cascade. It is used in the prophylactic management of allergic asthma (p. 1195.2).

Palivizumab (p. 2415.2) is a humanised monoclonal antibody to respiratory syncytial virus (RSV) for the passive immunisation of infants against RSV infection (p. 961.3).

1. Schachter EN, Neuman T. The use of monoclonal antibodies and related agents in the treatment of respiratory disease. *Drugs Today* 2009; **45:** 533–48.

Adverse Effects and Precautions

Early murine monoclonal antibodies were associated with serious immune-mediated adverse effects, and although later development of chimeric, humanised, and fully human monoclonal antibodies (described under Uses and Administration, p. 2561.1) has improved their safety profile, these substances can still present problems due to their potent interaction with the immune system. Patients with significantly compromised immune systems should not generally be given monoclonal antibodies.

Serious hypersensitivity reactions, including anaphylaxis, can occur with monoclonal antibodies, although the mechanism of action is not clear in many cases since the production of specific immunoglobulin E has been rarely shown. Infusion reactions associated with a cytokine release syndrome commonly occur at the start of a monoclonal antibody infusion. Injection site reactions have also been reported. Antibodies to the monoclonal antibody develop in some patients, although it is not entirely clear how this affects safety and efficacy.

Monoclonal antibodies have been associated with an increased incidence of serious infections and should therefore be given with caution to patients with active infections, a history of recurring infections, or underlying conditions that may predispose them to developing infections. Treatment should not be started or continued in patients with severe infections that require treatment. There have been cases of progressive multifocal leukoencephalopathy (PML) reported with some monoclonal antibodies such as efalizumab (p. 1702.2), natalizumab (p. 2568.1), and rituximab (p. 854.1).

The adverse effects of monoclonal antibodies are discussed in greater detail in specific monographs.

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Monoctanoin *(BAN, USAN)*

Glycerol Monocaprylate; Glyceroli Monocaprylas; Glycerolmonocaprylat; Glyceryl Caprylate; Glyceryl Mono-octanoate; Monocaprylin; Monoctanoína; Monooctanoin; Monooctanoin.

CAS — 26402-26-6 (glyceryl mono-octanoate).

UNII — VFU0OU98LO (monoctanoin); TM2TZD4G4A (glyceryl mono-octanoate); 197M6VFC1W (glyceryl mono-decanoate); SA9937IP23 (glyceryl di-octanoate).

NOTE. Monoctanoin (*BAN, USAN*) is a semisynthetic mixture containing 80 to 85% of glyceryl mono-octanoate ($C_{11}H_{22}O_4 = 218.3$), 10 to 15% of glyceryl mono-decanoate (glyceryl caprate) ($C_{13}H_{26}O_4 = 246.3$) and glyceryl di-octanoate (glyceryl dicaprylate) ($C_{19}H_{36}O_5 = 344.5$), and a maximum of 2.5% of free glycerol ($C_3H_8O_3 = 92.09$).

Pharmacopoeias. *Eur.* (see p. vii) includes Glycerol Monocaprylate.

Ph. Eur. 8: (Glycerol Monocaprylate). A mixture of monoacylglycerols, mainly mono-*O*-octanoylglycerol, (glyceryl mono-octanoate; glyceryl caprylate), containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with octanoic acid, followed by a distillation step in the case of glycerol monocaprylate (type II). Content of glycerol monocaprylate (type I): monoacylglycerols: 45 to 75%; diacylglycerols: 20 to 50%; triacylglycerols: maximum 10%. Content of glycerol monocaprylate (type II): monoacylglycerols: minimum 80%; diacylglycerols: maximum 20%; triacylglycerols: maximum 5%. A colourless or slightly yellow, oily liquid or soft mass. Practically insoluble in water; very soluble in alcohol; freely soluble in dichloromethane.

Profile

Monoctanoin is a mixture of glyceryl esters (p. 2186.3) containing mainly glyceryl monocaprylate. It has been given by continuous perfusion through a catheter inserted directly into the common bile duct to dissolve cholesterol gallstones (p. 2639.1) retained after cholecystectomy. Similar mixtures, known as glyceryl monocaprylates, are used as solvents and emulsifiers in pharmaceutical preparations.

Monoethanolamine

Colamine; Моноэтаноламин.

2-Hydroxyethylamine; 2-Aminoethanol.

$C_2H_7NO = 61.08$

CAS — 141-43-5.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Ethanolamine). A clear, colourless, or pale yellow liquid with a slight odour. It is alkaline to litmus. Miscible with water and with alcohol; slightly soluble in ether.

USNF 31: (Monoethanolamine). A clear, colourless, moderately viscous liquid having a distinctly ammoniacal odour. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerol; immiscible with ether, with petroleum spirit, and with fixed oils, although it dissolves many essential oils. Store in airtight containers. Protect from light.

Monoethanolamine Oleate *(rINN)*

Ethanolamine Oleate (USAN); Monoetanolamina, oleato de; Monoéthanolamine, Oléate de; Monoethanolamini Oleas; Oleato de monoetanolamina; Моноэтаноламина Олеат.

2-Hydroxyethylamine compound with oleic acid; 2-Aminoethanol compound with oleic acid.

$C_2H_7NO,C_{18}H_{34}O_2 = 343.6$

CAS — 2272-11-9.

ATC — C05BB01.
ATC Vet — QC05BB01.
UNII — U4RY8MRX7C.

Uses and Administration

Monoethanolamine oleate is used as a sclerosant in the treatment of varicose veins and oesophageal varices. For sclerotherapy of varicose veins, 2 to 5 mL of a 5% solution of monoethanolamine oleate is injected slowly into empty isolated sections of vein, divided between 3 or 4 sites. Injection into full veins is also possible. For sclerotherapy of oesophageal varices, the dose is 1.5 to 5 mL of a 5% solution per varix to a maximum total dose of 20 mL per treatment session. Treatment may be given in the initial management of bleeding varices, then repeated at intervals until the varices are occluded.

Variceal haemorrhage. Portal hypertension may occur in many conditions that affect the liver, and leads to the development of collateral channels linking the portal and systemic circulations. Enlargement of such blood vessels beneath the oesophageal and gastric mucosa produces varices which have about a 30% risk of rupture and bleeding. Oesophageal varices are more often a cause of haemorrhage than gastric varices. Capillaries and veins in the gastric mucosa may also become swollen, a condition known as portal hypertensive gastropathy, and clinically important bleeding may occur in severe cases.

Variceal haemorrhage is usually severe, with mortality as high as 50% for the initial episode; the recurrence rate may be as high as 100% in patients who survive without treatment. Bleeding may stop spontaneously, but in those who continue to bleed, control of haemorrhage is difficult and patients should be referred to a centre with appropriate specialist facilities. Treatment to stabilise the patient may be necessary before they can be safely transferred.

Acute management. Initial treatment is supportive and requires measures to prevent aspiration and maintain a clear airway, and volume replacement with colloid and blood. Emergency endoscopy should be performed to establish the site of haemorrhage and exclude non-variceal sources of bleeding. The choice of treatment depends on the site of haemorrhage.[1-11] ***Endoscopic methods*** have been favoured for initial management. Injection sclerotherapy or banding ligation are used for bleeding oesophageal varices but the optimum management of bleeding gastric varices remains to be defined; the value of injection sclerotherapy varies with their location. Intravariceal injection of bovine or human thrombin, or cyanoacrylate tissue adhesives, has been used in gastric varices. Where the source of haemorrhage is non-variceal and due to gastropathy, portal decompressive surgery is effective, although it is associated with a high incidence of encephalopathy in cirrhotic patients. Small studies have shown propranolol to be effective in arresting haemorrhage.[12]

Injection sclerotherapy for variceal haemorrhage may be performed during the emergency endoscopy procedure. Intravariceal injection, paravariceal injection, or a combination of the two have been used. The most widely used sclerosants are monoethanolamine oleate and sodium tetradecyl sulfate for intravariceal injection and lauromacrogol 400 for paravariceal injection. Sclerotherapy controls bleeding in up to 95% of cases. Ulceration and stricture formation occur frequently following injection sclerotherapy.

An alternative technique is ***endoscopic banding ligation***, where elastic bands are placed around the varices. The tissue subsequently necroses to leave a superficial ulcer. This technique is more successful than injection sclerotherapy, but may be more difficult to perform if active bleeding is occurring. Procedures may be repeated if bleeding continues or restarts.

Where endoscopy is unavailable, drug therapy or balloon tamponade may be used until the patient can be transferred to a specialist centre. These techniques may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy[13] or endoscopy.[14]

Drug therapy is aimed at controlling portal venous pressure, although it is ineffective in massive haemorrhage and its effects cease once the drug is stopped. Two meta-analyses[13,15] have examined data from studies comparing drug therapy with endoscopic methods for the treatment of acute variceal bleeding. Sclerotherapy did not appear to be superior to vasoactive drugs as the first single treatment, and was associated with more frequent adverse effects.[13] Adjunctive drug therapy improved the efficacy of endoscopic therapy (injection sclerotherapy or banding ligation) compared with endoscopic methods alone, although overall mortality was not affected; severe adverse effects were similar in both groups.[15]

Drugs used include vasopressin and its analogue terlipressin and, more recently, somatostatin and its analogue octreotide. Vasopressin controls haemorrhage in about 50% of patients. It is given by continuous intravenous infusion, with glyceryl trinitrate, which counteracts the adverse cardiac effects of vasopressin, while potentiating its reduction of portal pressure. Terlipressin has the advantage of a longer therapeutic action, enabling bolus doses to be given. A comparison[16] of terlipressin and sclerotherapy found them to be equally effective for the control of acute variceal bleeding. A systematic review[17] of studies comparing terlipressin with placebo, or other drugs or interventions, also gave favourable results. However, somatostatin,[2] and particularly octreotide,[2,18,19] which may be given by bolus injection, are now generally preferred as they are thought to have similar efficacy to vasopressin but fewer adverse effects. A systematic review[20] of studies comparing somatostatin or its analogues octreotide and vapreotide with either placebo or no drug treatment suggested a small benefit in controlling bleeding; however, no mortality benefit has yet been shown. Clinical studies with recombinant factor VIIa to control acute variceal bleeding have produced beneficial results.[14]

Balloon tamponade controls bleeding by direct pressure on the varices. Although it is a very effective means of controlling haemorrhage, there is a high incidence of rebleeding once pressure is removed and the incidence of complications is high. It is useful in cases of massive haemorrhage when drug therapy is ineffective and sclerotherapy is difficult.

Surgery, such as the formation of a shunt or oesophageal transection, may be necessary if the above measures fail to control the bleeding. However, such techniques have been associated with high mortality in some series. Formation of a transjugular intrahepatic portal-systemic shunt (TIPS) is now generally preferred.[4] It may be particularly useful in candidates for liver transplantation. Limited data suggest that the shunt may remain patent in the majority of patients for at least 3 years.[21]

Short-term ***antibacterial prophylaxis*** has been proposed[22] for cirrhotic patients with gastrointestinal bleeding, including variceal bleeding, because reduced rates of infection and improved short-term survival have been reported in a few studies, although there is no benefit on overall mortality.[23]

Long-term management. Once the acute bleeding has been controlled measures are needed to prevent rebleeding.[10,11] Endoscopic therapy is widely used, with injection sclerotherapy or banding ligation being repeated until the varices are obliterated. Banding ligation is now the treatment of choice; it eradicates varices in fewer treatment sessions than injection sclerotherapy and reduces the risk of ulceration and stricture formation.[24,25] Sucralfate has been given following sclerotherapy as it may reduce the frequency of stricture formation and reduce bleeding from treatment-related ulcers. It seems to have no influence on ulcer healing following banding ligation.[26] Some practitioners carry out regular endoscopic checks and repeat sclerotherapy or banding ligation when varices reappear, although this approach is no more effective in terms of improving survival than giving treatment once bleeding occurs. Drug therapy is an alternative to endoscopic methods.[27] Beta blockers (mainly propranolol) reduce the incidence of recurrent variceal bleeding and may improve survival.[25,28,29] A combination of nadolol with isosorbide mononitrate has been reported to reduce the risk of rebleeding more than repeated sclerotherapy, although there was no significant effect on mortality.[30] Drug therapy has also been used as an adjunct to endoscopic methods to control rebleeding in the period before variceal obliteration has occurred, or for long-term management following endoscopic therapy, although studies comparing endoscopic banding ligation with combination drug therapy have produced variable results.[31] However, results from a meta-analysis[32] of 23 studies found that a combination of drug and endoscopic therapy is better than either treatment alone in the prevention of overall and variceal rebleeding; this effect was the same with either endoscopic injection sclerotherapy or banding ligation. Long-term octreotide therapy following sclerotherapy has also been investigated and may reduce recurrent variceal bleeding.[33] Several studies[34-36] have compared TIPS with endoscopic treatment, but no clear benefit has been shown and there may be an increased risk of encephalopathy with the use of shunts. Surgery, including liver transplantation, should be considered in patients with recurrent life-threatening haemorrhage. Propranolol may also have a role in patients with portal hypertensive gastropathy. In a controlled study, propranolol reduced the incidence of recurrent bleeding from portal hypertensive gastropathy in patients with cirrhosis.[37]

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed, but should probably be given to patients with cirrhosis and varices thought to be at high risk of bleeding.[11] A reliable system that will identify those at high risk of haemorrhage has yet to be devised. The NIEC (North Italian Endoscopic Club) system is probably the best so far,[38,39] and is based on size of the varices, presence of red wale marks on the varices, and Child-Pugh class; amendments to improve the traditional index have been suggested.[39] Sclerotherapy had been considered as a method of prophylaxis, but its value has not been clearly established. Studies show that beta blockers decrease the incidence of a first bleed[29,40] and are probably the treatment of choice if prophylaxis is to be given. Banding ligation may be a suitable alternative for patients who are unable to take beta blockers.[41] Others consider banding ligation to be the standard therapy for prophylaxis.[9] A meta-analysis[42] of 9 randomised controlled studies concluded that variceal banding ligation was superior to beta blockers in preventing a first variceal bleed, whereas a systematic review[43] of 16 randomised controlled studies found both treatments to be effective and suggested that the estimated effect of banding ligation in some studies may be biased and was associated with shorter duration of follow-up.

It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought, and isosorbide mononitrate[9,44,45] (as adjunctive therapy with a beta blocker) and clonidine[46] have been investigated for the prophylaxis of a first bleed and prevention of recurrent haemorrhage in patients with portal hypertension.

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Varicose veins. Varicose veins are tortuous, protruding veins in the legs, that occur when weak vein walls and valve incompetence result in venous reflux and dilatation. Symptoms associated with varicose veins include heaviness, tension, aching, and itching of the legs. Complications include oedema, thrombophlebitis, deep venous thrombosis, lipodermatosclerosis, and venous ulceration. Risk factors for varicose veins include increasing age, pregnancy, and occupations that involve prolonged standing.[1]

The management of varicose veins has been reviewed.[1-5] Conservative management using compression hosiery may be effective for relief of symptoms in some patients[4] but longer-term compliance is poor.[3,5] Surgery or sclerotherapy are other treatment options, depending on the veins affected. Surgical treatment, which is the gold standard for treatment of more severe varicose veins, may involve ligation of the affected vein, stripping of the affected stem vein, or avulsions of the varicosities.[3] In sclerotherapy, which may be the treatment of choice for thread veins,[2,4] a sclerosant is injected into the affected vein where it irritates and damages the lining of the vein causing local thrombosis, fibrosis, and stenosis. Detergent sclerosants include monoethanolamine oleate, sodium tetradecyl sulfate, lauromacrogol 400, and sodium morrhuate; osmotic sclerosants include hypertonic sodium chloride solutions, and hypertonic mixtures of sodium chloride and glucose; caustic sclerosants include chromated glycerol, and a mixture of iodine and sodium iodide. Graduated compression dressings are usually applied after sclerotherapy to minimise the time taken for the surrounding tissue to absorb the damaged segment of vein. Compression may also help to reduce complications of sclerotherapy including hyperpigmentation, oedema, aching, thrombophlebitis, and deep venous thrombosis. A systematic review[6] of randomised controlled studies of injection sclerotherapy failed to determine its place in the overall management of varicose veins, since the type of sclerosant, formulation, local pressure dressing, or degree and length of compression do not appear to have a significant effect on efficacy. However, the evidence supports its current place in practice, which is in the treatment of recurrent varicose veins following surgery, and thread veins. In another systematic review,[7] the use of surgery or sclerotherapy for the management of primary varicose veins was compared. There was a tendency for better early outcomes with sclerotherapy whereas surgery produced more long-term benefits. However, there was insufficient evidence to recommend the use of one form of treatment over the other, and the extent of the varicose veins ultimately governs the choice.

New methods of treatment being tried include foam sclerotherapy, in which a detergent-like sclerosant is mixed with air to create a foam,[2,4,5] ambulatory phlebectomy, endovenous laser therapy, and radiofrequency ablation.[3-5,8]

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Adverse Effects and Precautions

Monoethanolamine oleate is irritant to skin and mucous membranes. Local injection may cause sloughing, ulceration, and, in severe cases, necrosis. Pain may occur at the site of injection. Patients receiving treatment for oesophageal varices may develop pleural effusion or infiltration. Hypersensitivity reactions have been reported.

Sclerotherapy should not be used to treat varicose veins of the legs in patients unable to walk, with obese legs, with thrombosis or a tendency to thrombosis, or with acute phlebitis, marked arterial, cardiac, or renal disease, local or systemic infections, or uncontrolled metabolic disorders such as diabetes mellitus. Monoethanolamine oleate should not be used in patients taking oral contraceptives.

Effects on the kidneys. Acute renal failure, which cleared spontaneously within 3 weeks, occurred in 2 obese women given sclerosing injections of 15 to 20 mL of a solution containing monoethanolamine oleate 5% and benzyl alcohol 2%.[1]

1. Maling TJB, Cretney MJ. Ethanolamine oleate and acute renal failure. *N Z Med J* 1975; **82:** 269–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Ethamolin; ***Jpn***: Oldamin; ***USA***: Ethamolin.

Pharmacopoeial Preparations
BP 2014: Ethanolamine Oleate Injection.

Motherwort

Agripalma; Agripaume, herbe de; Cardíaca; Cola de león; Herzgespannkraut; Hjärtstilla; Leonuri cardiacae herba; Leonuri Herba; Leonurus; Motherwort Herb; Nukula; Srdečníková nať; Sukatžolių žolė; Пустырник Сердечный.
ATC Herb — HN05CM5012 (Leonurus cardiaca: herb); HC01EB5016 (Leonurus cardiaca: herb).
UNII — 8NC0C2YXK0 (Leonurus cardiaca); IJ4SXX96Y4 (Leonurus cardiaca flowering top).

Pharmacopoeias. In *Eur.* (see p. vii). *Chin.* includes the fruit.

Ph. Eur. 8: (Motherwort). The whole or cut, dried, flowering aerial parts of *Leonurus cardiaca*. It contains not less than 0.2% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug. Protect from light.

Profile

Motherwort is given in herbal medicine for nervous and cardiac disorders; it is also used in products promoted for mild hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Biocarde; ***Ger.***: Cimicifuga comp; Oxacant-sedativ; ***Irl.***: Quiet Life; ***Pol.***: Biovital N†; Gerovital Zdrovit; Klimax; Lumewal; Nervinolum; Nerwobonisol; Tabletki Tonizujace; Tabletki Uspokajajace; ***Rus.***: Biovital (Биовитал); Cedoflor (Седофлор); Kliophyt (Клиофит); Phyto Novo-Sed (Фито Ново-Седа); Sedativae Species No 2 (Седативный Сбор 2); Sedativae Species No 3 (Седативный Сбор 3); Valemidin (Валемидин); ***Switz.***: Tisane pour le coeur et la circulation; ***UK***: Menopause Relief; Modern Herbals Stress; Period Pain Relief; Prementaid; Quiet Life; SuNerven; Valerian Passiflora and Hops; Wellwoman; ***Ukr.***: Cratal (Кратал); Flavia (Флавия); Florised (Флорисед); Gerovital Dr. Theiss (Геровитал Др. Тайсс); Normoton (Нормотон); Sedafiton (Седафитон).

Homoeopathic Preparations. ***Canad.***: Motherwort Combination 1†; Motherwort Combination 3†; ***Fr.***: Hypophysis Complexe No 31†; ***Ger.***: Arrhythmie-Gastreu N; Crataegus Herzcomplex; Hewethyreon N; ***Neth.***: Nervival; ***Rus.***: Valeriana-Plus (Валериана-Плюс).

Moxaverine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moxaverina; Meteverine Hydrochloride; Moxaverina, hidrocloruro de; Moxavérine, Chlorhydrate de; Moxaverini Hydrochloridum; Моксаверина Гидрохлорид.
1-Benzyl-3-ethyl-6,7-dimethoxyisoquinoline hydrochloride.
$C_{20}H_{21}NO_2$,HCl=343.9
CAS — 10539-19-2 (moxaverine); 1163-37-7 (moxaverine hydrochloride).
ATC — A03AD30.
ATC Vet — QA03AD30.

Profile

Moxaverine has a similar structure to papaverine (p. 2362.2) and the hydrochloride has been given orally and by intravenous infusion in the treatment of vasospastic disorders and as an antispasmodic in gastrointestinal and biliary-tract spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Kollateral†.

Mozavaptan *(rINN)* ⊗

Manavaptan; Mozavaptán; Mozavaptane; Mozavaptanum; OPC-31260; Мозаваптан.
N-(4-[[(5*RS*)-5-(Dimethylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl]phenyl)-2-methylbenzamide.
$C_{27}H_{29}N_3O_2$=427.5
CAS — 137975-06-5.
UNII — 17OJ42922Y.

Profile

Mozavaptan is a selective vasopressin V_2-receptor antagonist used as the hydrochloride for the treatment of hyponatraemia in cancer-related syndrome of inappropriate antidiuretic hormone secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Physuline.

Mucoproteose

Profile

Mucoproteose is a component of gastric mucus and has been included in some oral iron preparations to protect the gastrointestinal mucosa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Tardyferon; ***Belg.***: Tardyferon; ***Cz.***: Tardyferon; ***Ger.***: Tardyferon; ***Hung.***: Tardyferon; ***Pol.***: Tardyferon; ***Port.***: Tardyferon; ***Turk.***: Oroferon; Tardyferon; ***Ukr.***: Tardyferon (Тардиферон).

Multi-ingredient Preparations. ***Arg.***: Tardyferon; ***Austria***: Tardyferon-Fol; ***Cz.***: Tardyferon-Fol; ***Fr.***: Tardyferon B_9; Tardyferon; ***Ger.***: Tardyferon-Fol; ***Hung.***: Tardyferon-Fol; ***Pol.***: Tardyferon-Fol; ***Port.***: Tardyferon-Fol; ***Rus.***: Gyno-Tardyferon (Гино-тардиферон); ***Switz.***: Gyno-Tardyferon; Tardyferon; ***Turk.***: Gyno-Tardyferon; Gynoferon; ***Ukr.***: Gyno-Tardyferon (Гино-Тардиферон).

Mulungu

Мулунгу.

Profile

The bark of the mulungu tree, *Erythrina verna* (*E. mulungu*) Fabaceae, has traditionally been used in South America as a sedative and as a hypotensive.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Calmapax; Passaneuro; Passaneuro; Ritmoneuran.

Mumps Skin Test Antigen

Parotiditis, prueba cutánea contra el antígeno de la.

Profile

Recovery from mumps produces skin hypersensitivity to mumps virus. Mumps skin test antigen, a preparation of inactivated mumps virus, has been used with other antigens to assess the status of cell-mediated immunity. A positive reaction may indicate previous infection with mumps virus

but it is not considered to be very reliable. It should not be given to patients hypersensitive to egg protein.

Muramidase Hydrochloride

N-Acetylmuramide Glycanohydrolase Hydrochloride; E1105 (muramidase); Globulin G_1 Hydrochloride; Hidrocloruro de lisozima; Lysozyme Hydrochloride; Muramidasa, hidrocloruro de; Лизоцима Гидрохлорид.

CAS — 9001-63-2 (muramidase); 9066-59-5 (muramidase hydrochloride).

ATC — D06BB07; J05AX02.

ATC Vet — QD06BB07; QJ05AX02.

UNII — 4YRW73H69V.

Pharmacopoeias. In *Jpn.*

Profile

Muramidase is a mucopolysaccharidase normally present in saliva and other tissues and secretions. It is active against Gram-positive bacteria, possibly by transforming the insoluble polysaccharides of the cell wall to soluble mucopeptides. It is also thought to be active against some viruses and some Gram-negative bacteria.

Muramidase has been given, usually as the hydrochloride, to patients with herpes zoster and other painful viral infections, and for mouth and respiratory-tract disorders. It has been used with antibacterials in an attempt to enhance their activity. Sensitivity reactions have been reported.

Adverse effects. A report[1] of a toxic epidermal necrolysis-type drug eruption in a patient who took an oral cold preparation containing muramidase chloride, which was considered to be the probable cause. The patient's condition improved after intravenous corticosteroid therapy.

1. Kobayashi M, *et al.* A case of toxic epidermal necrolysis-type drug eruption induced by oral lysozyme chloride. *J Dermatol* 2000; **27:** 401–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Murazyme; ***Hong Kong***: CP-Lyso; Eurozyme; Flemizyme; Jemizym; Leftose†; Lysosmin†; Neuzym; Qualizyme; Uni-Zyme†; Visozyme†; ***Jpn***: Leftose; Neuzym; ***Malaysia***: E-Zyme; Neuzym; Noflux; ***Singapore***: Leftose; Lyzyme; Neuflo; Neuzym; ***Thai.***: Leftose†.

Multi-ingredient Preparations. ***Braz.***: Colpistar; Tricomax; ***Fr.***: Cantalene; Glossithiase; Hexalyse; Lyso-6; Lysopaine; ***Ger.***: Frubienzym†; ***Gr.***: Lyso-6; Lysopaine; Lysoril; Sopain-Plus; ***Hong Kong***: Eye-Ruby L†; Hexalyse; Quadezyme; ***Ital.***: Narlisim; ***Port.***: Narizima; ***Rus.***: Bifilis (Бифилиз); Hexalyse (Гексализ); Lysobact (Лизобакт); ***Singapore***: Biotene; Biotene; Luvena Prebiotic; OralSeven; OralSeven; OralSeven; ***Spain***: Lizipaina; Rino Dexa; Trofalgon; ***Switz.***: Arbid-top; Lysopaine N; Lysopaine†; Mebucasol f†; Sangerol; ***Thai.***: Siduol; ***UK***: Biotene Dry Mouth; ***Ukr.***: Hexalyse (Гексализ); Lisak (Лизак); Lizak (Лизак); Lysobact (Лисобакт); ***USA***: Bio-Zyme; Biotene with Calcium.

Poisonous Mushrooms or Toadstools

Champignons vénéneux; Giftpilze; Setas venenosas.

CAS — 23109-05-9 (α-amanitin); 21150-22-1 (β-amanitin); 21150-23-2 (γ-amanitin); 58919-61-2 (coprine); 16568-02-8 (gyromitrin); 2552-55-8 (ibotenic acid); 60-34-4 (methylhydrazine); 300-54-9 (muscarine); 2763-96-4 (muscimol); 37338-80-0 (orellanine); 17466-45-4 (phalloidin); 28227-92-1 (phalloin); 39412-56-1 (phallolysin).

Classification

This monograph describes poisonous mushrooms often known as toadstools, their toxins, toxic effects, and the treatment of those effects. Their only use is in homoeopathic medicine (see below). *Amanita muscaria* and *Psilocybe* spp. are abused for their psychoactive properties (see also Psilocin, p. 2599.1).

Mushrooms can be classified into 8 groups according to their principal toxins and toxic effects:

- *Group I.* Most deaths due to mushroom poisoning follow the ingestion of mushrooms containing cyclopeptides and among these mushrooms *Amanita phalloides* ('death cap') has been reported to be responsible for 90% of all mushroom fatalities. The cyclopeptides are a group of heat-stable cyclic polypeptides with molecular weights ranging from 800 to 1100 and include the amatoxins (α-, β-, γ-amanitin) and phallotoxins (phalloidin, phaloin, phallolysin). Other mushrooms containing cyclopeptides include *A. verna* ('deadly agaric', 'fool's mushroom'), *A. virosa*, ('destroying angel') and *A. bisporigera* ('white destroying angel'), and *Galerina autumnalis*, *G. marginata*, and *G. venenata*.
- *Group II.* Although *A. muscaria* ('fly agaric') and *A. pantherina* ('panther cap', 'false blusher') may contain small amounts of muscarine, the antimuscarinic effects of the hallucinogenic agent muscimol and the insecticidal agent ibotenic acid usually predominate.
- *Group III.* Many species of *Gyromitra* contain toxins known as gyromitrins that decompose to release methylhydrazine (monomethylhydrazine; MMH) an inhibitor of the coenzyme pyridoxal phosphate.
- *Group IV.* Mushrooms whose principal toxin is muscarine include many of the *Clitocybe* and *Inocybe* spp. *A. muscaria* and *A. pantherina* (see above) may also contain small amounts.
- *Group V. Coprinus atramentarius* ('ink cap') contains the compound coprine, one of whose metabolites is an inhibitor of acetaldehyde dehydrogenase and it may therefore produce 'disulfiram-like' symptoms after drinking alcohol.
- *Group VI.* Mushrooms that may contain the hallucinogenic indoles psilocin and psilocybine include species of *Psilocybe*, *Panaeolus*, *Gymnopilus*, *Stropharia*, and *Conocybe*.
- *Group VII.* Many mushrooms that only act as gastrointestinal irritants and do not produce systemic effects are included in this group.
- *Group VIII.* A further group has sometimes been used to classify some species of *Cortinarius* that contain a renal toxin thought by some to be orellanine, but whose exact nature remains to be determined.

Uses

Several types of poisonous mushrooms have been used in homoeopathic medicines under the following names:

- *Amanita phalloides*: Agaricus phalloides; Agaricus phal; Agaricus bulbosus
- *Amanita muscaria*: Agaricus muscarius; Agaricus musc; Agar. m.
- *Coprinus stercorarius* (*Stropharia stercoraria*): Agaricus stercorarius; Agaricus ster; Aga. ster.
- *Russula emetica*: Agaricus emeticus; Agaricus emet; Agar. e.

Adverse Effects

The clinical course of poisoning due to mushrooms is related to their principal toxins:

- *Group I.* Initial symptoms may occur 6 to 24 hours after ingestion of mushrooms containing cyclopeptides, and usually consist of gastrointestinal effects such as abdominal pain, nausea, severe vomiting, and profuse diarrhoea similar to that in cholera. The patient may then appear to recover and be symptom-free for 2 to 3 days, although liver-enzyme values may be increasing. After this phase, the more serious toxic effects of the amatoxins become apparent and there are signs of hepatic, renal, cardiac, and CNS toxicity. Symptoms include jaundice, oliguria, anuria, hypoglycaemia, coagulopathies, circulatory collapse, convulsions, and coma. The mortality rate is high in this third phase, with death usually being due to hepatic failure following hepatic necrosis. Up to 90% of untreated patients may die, though the rate can be as low as 15 to 30% after treatment.
- *Group II.* The adverse effects of mushrooms containing ibotenic acid and muscimol usually occur within 2 hours of ingestion. Symptoms may include ataxia, euphoria, delirium, and hallucinations associated with other antimuscarinic effects. Fatalities are rare.
- *Group III.* Patients who have ingested mushrooms containing gyromitrins usually develop symptoms of poisoning within 6 to 24 hours. These consist initially of nausea, vomiting, abdominal pain, and muscle cramps, headache, dizziness and fatigue. Delirium, convulsions, coma, methaemoglobinaemia and haemolysis may also occur. Occasionally jaundice and hepatic necrosis lead to hepatic failure and death. Up to 40% of patients die.
- *Group IV.* Symptoms typical of 'cholinergic crisis' (see Adverse Effects of Neostigmine, p. 688.2) may appear about 30 minutes to 2 hours after ingestion of mushrooms containing muscarine. These include bradycardia, bronchospasm, salivation, perspiration, lachrymation, rhinorrhoea, involuntary urination and defaecation, and diarrhoea. Miosis, hypotension, and cardiac arrhythmias may also occur. Rarely death may follow due to cardiac arrest or respiratory-tract obstruction.
- *Group V.* Since one of the metabolites of coprine is an acetaldehyde dehydrogenase inhibitor, drinking alcohol, even up to several days after ingestion of mushrooms containing this compound, will produce symptoms similar to those of the 'disulfiram-alcohol' interaction (see Disulfiram, Adverse Effects, p. 2496.1). Fatalities are rare.
- *Group VI.* The adverse effects of ingestion of mushrooms containing psilocin and psilocybine are similar to those described under lysergide (p. 2547.2). Symptoms usually occur within about 30 minutes to 2 hours. Fatalities are rare.
- *Group VII.* Generally no treatment is required for adverse gastrointestinal effects seen with this group of mushrooms.
- *Group VIII.* There may be a delay of as long as 14 to 20 days before symptoms of poisoning due to *Cortinarius* appear. Patients will develop an intense thirst. Other symptoms usually include nausea, vomiting, diarrhoea, and anorexia. Muscle aching and spasms and a feeling of coldness may also occur. In severe cases renal failure may lead to death. It has been reported that up to 15% of patients die.

Pregnancy. α-Amanitine does not appear to cross the placental barrier, even during the acute phase of intoxication.[1]

1. Belliardo F, *et al.* Amatoxins do not cross the placental barrier. *Lancet* 1983; **i:** 1381.

Treatment of Adverse Effects

As there are no specific antidotes for the majority of cases of mushroom poisoning and the species involved is often unknown, treatment consists mainly of symptomatic and supportive measures. The stomach may be emptied by gastric lavage if the patient has not already vomited spontaneously. However, if presentation is delayed (because of the slow onset of symptoms seen with some types of mushrooms) measures to empty the stomach are unlikely to be beneficial. Activated charcoal may be of use in binding toxins in the gastrointestinal tract and preventing absorption. Determining the interval between ingestion and the onset of symptoms often helps to identify the type of mushrooms ingested. If possible specimens of the mushrooms or a sample of the stomach contents should be sent to an expert mycologist for identification. Particular attention should be paid to intravenous replacement of fluids and electrolytes especially if vomiting and diarrhoea are severe. If the ingestion of hepatotoxic or nephrotoxic mushrooms is suspected liver and renal function should be monitored.

Since some mushrooms contain a wide range of toxins and patients may have ingested more than one species, specific therapy should only be instituted after positive identification.

- *Group I.* There is little clinical evidence to support the efficacy of specific agents or treatments for the management of cyclopeptide poisoning. Drugs such as benzylpenicillin, silymarin or silibinin have been given to try to protect the liver against the hepatotoxic effects of the amatoxins. Exchange transfusions, haemodialysis, or charcoal haemoperfusion have been tried to facilitate amatoxin removal. The removal of bile via a duodenal tube left *in situ* has been suggested to reduce enterohepatic circulation of amatoxins. Forced diuresis has also been advocated. Liver transplantation may be required for progressive hepatic failure. A radioimmunoassay for the detection of amatoxins is available in some countries to confirm a diagnosis of cyclopeptide poisoning.
- *Group II.* Specific treatment is usually only required if symptoms are severe. Physostigmine has been used to treat antimuscarinic symptoms. As mushrooms containing ibotenic acid and muscimol may also contain small amounts of muscarine, atropine may be required to control muscarinic symptoms.
- *Group III.* Pyridoxine hydrochloride has been given as an intravenous infusion as specific therapy to overcome the inhibition of pyridoxal phosphate by methylhydrazine, but the use of large doses of pyridoxine might itself produce adverse neurological effects. Methylthioninium chloride may be required if methaemoglobinaemia is severe.
- *Group IV.* Atropine sulfate may be required to control the symptoms of muscarine poisoning but it should only be used if definite muscarinic symptoms are present.
- *Group V.* There is no specific treatment for the 'disulfiram-alcohol' reaction except for the maintenance of blood pressure.
- *Group VI.* If symptoms are severe some patients may require sedation with diazepam.

General reviews.

1. Köppel C. Clinical symptomatology and management of mushroom poisoning. *Toxicon* 1993; **31:** 1513–40.

Amanita phalloides. The use of specific antidotes in the treatment of poisoning due to *Amanita phalloides* remains controversial. Acetylcysteine, benzylpenicillin, sulfamethoxazole, thioctic acid, cytochrome C, ascorbic acid, insulin, growth hormone, silymarin or silibinin, and corticosteroids have all been used or suggested. Evidence to support most of these is lacking;[1,2] there is limited evidence to support the use of silibinin and acetylcysteine, but benzylpenicillin, although widely used, does not have

proven efficacy.[1] In patients who develop fulminant liver failure the definitive treatment is liver transplantation.[1,2]

1. Enjalbert F, *et al*. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40:** 715–57.
2. Berger KJ, Guss DA. Mycotoxins revisited: part I. *J Emerg Med* 2005; **28:** 53–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Hung.***: Spascupreel.

Black Mustard

Graine de Moutarde Noire; Mostarda Preta; Mostaza negra; Moutarde Jonciforme; Schwarzer Senfsame; Semen Sinapis; Semilla de Mostaza; Sinapis Nigra; Горчица Чёрная.

ATC Herb — HM02AW5003 (Brassica nigra: seed).

UNII — 8LTY55LQ8D.

Description. Black mustard is the dried ripe seeds of *Brassica nigra* (*B. sinapioides*) (Cruciferae).

Pharmacopoeias. In *Swiss* which allows *B. nigra, B. juncea,* and other species.

White Mustard

Mostaza blanca; Sinapis Alba; Горчица Белая.

UNII — 66SFD3EC0P (Sinapis alba); 25VR943RPP (Sinapis alba seed).

Description. White mustard is the dried ripe seeds of *Brassica alba* (Cruciferae).

Pharmacopoeias. *Chin.* allows *B. alba* or *B. juncea.*

Uses and Administration

Black and white mustard seeds have been used as emetics, in counter-irritant and rubefacient preparations, and as condiments. Black mustard seeds are the source of volatile mustard oil (p. 2646.1), which is composed largely of allyl isothiocyanate (p. 2436.3).

Adverse Effects

Hypersensitivity. A report of 2 cases of IgE-mediated anaphylaxis to mustard condiment.[1]

1. Vidal C, *et al*. Anaphylaxis to mustard. *Postgrad Med J* 1991; **67:** 404.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mon.***: Autoplasme Vaillant; Sinapisme Rigollot.

Multi-ingredient Preparations. ***Pol.***: Reumobonisol.

Homoeopathic Preparations. ***Austral.***: Hay Fever; ***Austria***: Delufen; ***Ger.***: Sinapis nigra N Oligoplex; ***Rus.***: Aphlubin-Naze (Афлубин-Назе); Delufen (Делуфен); ***Ukr.***: Delufen (Делуфен).

Myrrh

Gum Myrrh; Gummiresina Myrrha; Mira; Mirhami; Mirra; Mirrha; Myrhovníková klejopryskyřice; Myrra; Myrrha; Myrrhe; Мирра.

CAS — 9000-45-7 (Myrrh); 8016-37-3 (myrrh oil).

ATC Herb — HA03AW5016 (Commiphora myrrha: resin); HA01WC5002 (Commiphora myrrha: resin).

UNII — JC71GJ1F3L.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Myrrh). A gum-resin, hardened in air, obtained from the stem and branches of *Commiphora molmol* and/or other species of *Commiphora.* Protect from light.

USP 36: (Myrrh). The oleo-gum resin obtained from the stems and branches of *Commiphora molmol* and other related species of *Commiphora* (Burseraceae) other than *C. mukul.* Store in airtight containers in a dry place.

Profile

The principal source of myrrh is *Commiphora myrrha* (*C. molmol*) (Burseraceae). Myrrh is astringent to mucous membranes; the tincture is used in mouthwashes and gargles for inflammatory disorders of the mouth and pharynx. It has also been used as a carminative. Myrrh has been tried in the treatment of schistosomiasis and fascioliasis.

Myrrh should not be confused with guggul (p. 2523.2) to which it is related.

Myrrh oil is used in aromatherapy.

Contact dermatitis has been reported.

Helminth infections. Myrrh was of benefit in a small study[1] of 7 patients with fascioliasis and in another study[2] of 204 patients with schistosomiasis. However, it showed low cure rates in the treatment of schistosomiasis when compared with praziquantel.[3,4]

1. Massoud A, *et al*. Preliminary study of therapeutic efficacy of a new fasciolicidal drug derived from Commiphora molmol (myrrh). *Am J Trop Med Hyg* 2001; **65:** 96–9.
2. Sheir Z, *et al*. A safe, effective, herbal antischistosomal therapy derived from myrrh. *Am J Trop Med Hyg* 2001; **65:** 700–4.
3. Botros S, *et al*. Efficacy of mirazid in comparison with praziquantel in Egyptian Schistosoma mansoni-infected school children and households. *Am J Trop Med Hyg* 2005; **72:** 119–23.
4. Barakat R, *et al*. Efficacy of myrrh in the treatment of human schistosomiasis mansoni. *Am J Trop Med Hyg* 2005; **73:** 365–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Inspirol P†; ***Rus.***: Myrtoplex (Миртоплекс).

Multi-ingredient Preparations. ***Arg.***: Parodontax Fluor; ***Austral.***: Eczema Relief†; Herbal Throat Spray; ***Austria***: Brady's-Magentropfen; Dentinox†; Parodontax†; Pervivo; ***Braz.***: Paratonico†; Parodontax†; Vitonico; ***Chile***: Astrijesan; ***Cz.***: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Original Schwedenbitter; ***Denm.***: Dolodent; ***Fr.***: Tigre de Chine; ***Ger.***: Infi-tract V; Mint-Lysoform; Myrrhinil-Intest; Ratanhia comp†; Repha-Os†; ***Hong Kong***: Ad-Muc; ***Hung.***: Bano Svedkeseru; Bittner; ***Philipp.***: BSI Medicated Plaster; ***Pol.***: Pervivo; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Helmontskruie†; Lewensessens; ***Spain***: Buco Regis; ***Switz.***: Baume Zeller; Kernosan Eau Dentifrice†; Pommade au Baume; Sanogencive; ***UK***: Herbal Indigestion Naturtabs; HRI Golden Seal Digestive; Indigestion and Flatulence; Vocalzone; Wind & Dyspepsia Relief; ***Ukr.***: Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Homoeopathic Preparations. ***UK***: Medicinal Gargle.

Pharmacopoeial Preparations

Ph. Eur.: Myrrh Tincture;

USP 36: Myrrh Topical Solution.

Myrtillus

Baccae Myrtilli; Bilberry; Blåbär (bilberry fruit); Blaeberry; Borůvkový plod; Fekete áfonya termés (bilberry fruit); Heidelbeere; Huckleberry; Hurtleberry; Mirtilo; Mėlynių uogos, džiovintos (bilberry fruit); Mustikka (bilberry fruit); Myrtille, fruit de (bilberry fruit); Myrtilli Fructus; Myrtilli fructus (bilberry fruit); Whortleberry; Черника Обыкновенная.

ATC Herb — HD08AW5005 (Vaccinium myrtillus: leaf); HA07XA5015 (Vaccinium myrtillus: fruit); HA10BX5005 (Vaccinium myrtillus: leaf).

UNII — 9P2U39H18W (Vaccinium myrtillus fruit); Y4U591OU70 (Vaccinium myrtillus leaf).

Pharmacopoeias. In *Eur.* (see p. vii). *US* includes Powdered Bilberry Extract.

Ph. Eur. 8: (Bilberry Fruit, Dried; Dried Bilberry BP 2014; Bilberry Fruit, Fresh; Fresh Bilberry BP 2014). The ripe fruit of *Vaccinium myrtillus.* It has a sweet and slightly astringent taste. The dried fruit contains a minimum of 1.0% of tannins, expressed as pyrogallol, calculated with reference to the dried drug. The fresh or frozen fruit contains a minimum of 0.30% of anthocyanins, expressed as cyanidin-3-glucoside chloride (chrysanthemin, $C_{21}H_{21}ClO_{11} = 484.8$), calculated with reference to the dried drug. The frozen fruit should be stored at or below -18 degrees.

Profile

Myrtillus has diuretic and astringent properties. It has been used for ophthalmic and circulatory disorders and for diarrhoea.

Homoeopathy

Myrtillus has been used in homoeopathic medicines under the following names: Vaccinium myrtillus; Vaccinium; Vac. myrt.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Miralis; ***Ger.***: Difrarel†; ***India***: Gloeye; ***Indon.***: Lanavision; ***Ital.***: Mirtilene Forte; Tegens; ***Malaysia***: Natberry; ***Pol.***: Bilberin†; Fibs; ***Port.***: Difrarel; Tegens; ***Rus.***: Mirtilene Forte (Миртилене Форте); ***Switz.***: Myrtaven.

Multi-ingredient Preparations. ***Arg.***: Chiafibra; ***Austral.***: Bilberry Plus Eye Health†; Bilberry Plus†; Extralife Eye-Care†; Extralife Leg-Care†; PM Eye Tonic; Pygno-Vite†; St Mary's Thistle Plus†; Vision-Eze†; ***Austria***: Amersan; ***Canad.***: Visionex; ***China***: Difrarel (递法明); ***Cz.***: Amersan; Diabetan; Diabeticka Cajova Smes-Megadiabetin†; Tormentan; Urcyston Planta; ***Fr.***: Antioxydant F4; Bion 3 Seniors; Blue Berry; Cledist; Difrarel E; Difrarel; Difravision; Glycepure; Phyltalzeal; Stomargil; Sun Vue; Tone; ***Hong Kong***: Mega-Antioxidant†; PM Eye Tonic†; ***Hung.***: Diabess; Difrarel E†; ***India***: GV-24; I-Lute; ***Indon.***: Berry Vision; Bioretin†; Eyebright; Eyevit; Kapset; Lanavision Plus; Lanavision; Lubire; Lutevision Extra; Lutevision†; Matase; Matovit AX; Matovit Fifty; Matovit; Natureyes; nutrivision; Nuvision; Ocu-V; Ocugard; Oculex; Oculex; Opibright; Opthall; Optimax Plus; Optimax; Proliva; Proview; Retop; Visivit; Vita-Vision; Vitop; ***Israel***: Opti-Safe†; ***Ital.***: Alvear con Ginseng; Angiorex Complex; Angioton; Api Baby; Bebimix†; Biolactine; Capill; Dermilia Flebozin†; Eu-Visus; Euretin; Evamilk; Flavogin Plus; Flebo-Si†; Flebofort; Flebofort; Ginecistin; Lactovit; Levital Plus; Lik-Gel†; Lipaven; Macvit; Memovigor; Mentvis; Mirtex P; Mirtilene; Mirtilux; Mirtilux; Mirtiros; Neomyrt Plus; Nerex; Pik Gel; Promix 3; Retinovit; Rivuclin; The Ginseng King†; Troca Vit; Tussol; Ultravisin; Visu-ton; Vitalmix Complex; Vitreolux; ***Malaysia***: Natberry Extra; Natberry Plus; ***Philipp.***: iiCare; ***Pol.***: Biovision; Pelogel; Reumosol; ***Rus.***: Brusniver (Бруснивер); Multimax for Eyes (Мультимакс Для Глаз); Strix (Стрикс); ***Singapore***: EyeMax; Nutrivision†; Visionex†; ***Spain***: Mirtilus†; ***Switz.***: Herba-Vision Myrtillus; ***UK***: Se-Power; Visio-Max; ***Ukr.***: Lipomin (Липомин); Liponorm (Липонорм); Memory Booster (Мемори Бустер); Oko-Health (Око-хелс); Osteoartisi Max (Остеоартизи Макс); Vitrum Foreyes Forte (Вітрум Форайз Форте); Vizivit (Визивит); ***USA***: Clinical Nutrients 50-Plus Men; Diabetiks.

Homoeopathic Preparations. ***Fr.***: Diabene; Diacure; Poconeol no 35; ***Rus.***: Mirticam (Миртикам).

Pharmacopoeial Preparations

Ph. Eur.: Fresh Bilberry Fruit Dry Extract, Refined and Standardised.

Myrtle

Arrayán; Mirto; Myrte; Мирт Обыкновенный.

CAS — 8008-46-6 (myrtle oil); 8002-55-9 (myrtol).

UNII — 367E55FXGW.

NOTE. Distinguish from Myrtillus, above, derived from *Vaccinium myrtillus.*

Profile

Myrtle (*Myrtus communis*, Myrtaceae) has been included in herbal preparations for cough.

Myrtle oil is obtained from the leaves and twigs. Myrtle oil is included in preparations for disorders of the upper respiratory tract and is used in aromatherapy.

The term myrtol has been used to describe an extract of myrtle, standardised on its content of α-pinene, *d*-limonene, and cineole. It is used for respiratory-tract disorders.

References.

1. Matthys H, *et al*. Efficacy and tolerability of myrtol standardized in acute bronchitis. A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. *Arzneimittelforschung* 2000; **50:** 700–11.
2. Gündüz GT, *et al*. Efficacy of myrtle oil against Salmonella typhimurium on fresh produce. *Int J Food Microbiol* 2009; **130:** 147–50.
3. Babaee N, *et al*. The efficacy of a paste containing Myrtus communis (myrtle) in the management of recurrent aphthous stomatitis: a randomized controlled trial. *Clin Oral Investig* 2010; **14:** 65–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Gelomyrtol; ***Fr.***: Myrtine; ***Ger.***: Gelomyrtol; ***Gr.***: Gelomyrtol; ***Hong Kong***: Gelomyrtol; ***Neth.***: Gelodurat; ***Rus.***: Gelomyrtol (Геломиртол); ***Switz.***: Gelomyrtol; ***Thai.***: Gelomyrtol†; ***Ukr.***: Gelomyrtol (Геломиртол).

Multi-ingredient Preparations. ***Austria***: Tetra-Gelomyrtol†; ***Fr.***: Nazinette du Docteur Gilbert; Percutalgin'Phyto; ***Ger.***: Tetra-Gelomyrtol; ***Rus.***: Entoban (Энтобан); ***Switz.***: Gelodurat; ***Ukr.***: Entoban (Энтобан).

Nabiximols *(USAN)*

GW-1000.

CAS — 56575-23-6.

ATC — N02BG10.

ATC Vet — QN02BG10.

UNII — K4H93P747O.

Description. Nabiximols is defined as a mixture of two cannabis extracts:

Component A, which is a highly characterized botanical extract of a defined chemotype of *Cannabis sativa* L. The major chemical constituent is the cannabinoid dronabinol (Δ⁹-tetrahydrocannabinol; THC). Minor constituents include related cannabinoids and non-cannabinoid components α - and *trans*-caryophyllenes.

Component B, which is a highly characterized botanical extract of a defined chemotype of *Cannabis sativa* L. The major chemical constituent is the cannabinoid cannabidiol (CBD). Minor constituents include related cannabinoids and non-cannabinoid components α - and *trans*-caryophyllenes.

The names Tetranabinex and Nabidiolex have been used as trade marks for components A and B, respectively.

Profile

Nabiximols is a combination of two cannabis (p. 2467.1) extracts obtained from chemically and genetically characterised plants of *Cannabis sativa*. The principal active components of the extracts are the cannabinoids, dronabinol (Δ^9-tetrahydrocannabinol, see p. 1840.1) and cannabidiol (p. 2467.1). Nabiximols is used in a buccal spray preparation as adjunctive treatment for the symptomatic relief of moderate to severe spasticity due to multiple sclerosis in adults who have not responded adequately to other therapy and who show clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. It may also be of benefit as adjunctive analgesic treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis. This same preparation is also used as adjunctive analgesic treatment in adult patients with advanced cancer who have moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Nabiximols is given in a dose equivalent to 2.7 mg dronabinol and 2.5 mg cannabidiol in each 100 microlitre spray. The dose is titrated over 14 days to find the optimum dose, which is normally between 4 and 8 sprays daily, up to a usual maximum of 12 sprays daily. The dose on the first day is 1 spray once or twice daily, with gradual incremental increases thereafter of no more than 1 additional spray per day. The gap between sprays should be at least 15 minutes. The timing of sprays varies between patients but in general the morning dose should be taken before midday, and the afternoon/evening dose between 4 pm and bedtime. Once the optimum daily dose has been reached, patients may spread the dose throughout the day depending on individual response and tolerability. The spray should be directed at different sites on the oromucosal surface changing the site with each use. The spray should not be directed towards the pharynx, nor should it be inhaled, and it should not be used intranasally.

Use is contra-indicated in patients with a history of psychosis or other serious psychiatric disorders (other than reactive depression). Nabiximols is also not recommended in patients with serious cardiovascular disease. Mild or moderate dizziness is common during the first few weeks of treatment.

For references to studies of nabiximols and other potential uses of cannabinoids, see under Cannabis, p. 2468.1.

Breast feeding. Nabiximols is contra-indicated in breast feeding because of the considerable levels of cannabinoids likely in maternal breast milk and the potential for developmental adverse effects in the nursing infant.

Pregnancy. Licensed product information for nabiximols generally contra-indicates use in pregnancy, and advises that female patients of child-bearing potential, or male patients with partners in this category, should use reliable contraceptive precautions during treatment and for 3 months afterwards.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Sativex; ***Cz.***: Sativex; ***Denm.***: Sativex; ***Fin.***: Sativex; ***Ger.***: Sativex; ***Israel***: Sativex; ***Neth.***: Sativex; ***Norw.***: Sativex; ***NZ***: Sativex; ***Spain***: Sativex; ***Swed.***: Sativex; ***UK***: Sativex.

Nadide *(BAN, USAN, rINN)*

Co-I; Codehydrogenase I; Coenzima I; Coenzyme I; Difosfopiridina nucleótido; Diphosphopyridine Nucleotide; DPN; NAD; Nadida; Nadidum; Nicotinamida adenina dinucleot; Nicotinamide Adenine Dinucleotide; NSC-20272; Надид.

1-(3-Carbamoylpyridinio)-β-D-ribofuranoside 5-(adenosine-5′-pyrophosphate).

$C_{21}H_{27}N_7O_{14}P_2$=663.4

CAS — 53-84-9.

UNII — 0U46U6E8UK.

Profile

Nadide is a naturally occurring coenzyme claimed to be of value in the treatment of alcohol and opioid addiction. The reduced form of nadide, NADH, has been used in the management of chronic fatigue syndrome.

Parkinsonism. The reduced form of nadide, NADH (β-NADH; reduced DPN) and its phosphate derivative (NADPH) have been given in the management of Parkinson's disease in an attempt to enhance endogenous dopamine synthesis by stimulating the enzyme tyrosine hydroxylase. Although some beneficial effects have been reported in several case series, a placebo-controlled study failed to find any evidence of efficacy and the routine use of NADH has not been recommended.[1]

1. Swerdlow RH. Is NADH effective in the treatment of Parkinson's disease? *Drugs Aging* 1998; **13:** 263–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: DPN†; ***Spain***: Nad†.

Multi-ingredient Preparations. ***Philipp.***: Enervon-C.

Homoeopathic Preparations. ***Canad.***: Cutisitum†; Hepar Compositum; Ubicoenzyme; ***Cz.***: Zeel Salbe†; ***Hung.***: Zeel; ***Rus.***: Zeel T (Цель Т).

Nafamostat Mesilate *(rINNM)*

FUT-175; Mesilato de nafamostat; Nafamostat, Mésilate de; Nafamostat, mesilato de; Nafamostat Mesylate (USAN); Nafamostati Mesilas; Нафамостата Мезилат.

6-Amidino-2-naphthyl *p*-guanidinobenzoate dimethanesulfonate.

$C_{21}H_{25}N_5O_8S_2$=539.6

CAS — 81525-10-2 (nafamostat); 82956-11-4 (nafamostat mesilate).

UNII — 1D2T74921W.

Pharmacopoeias. In *Jpn.*

Profile

Nafamostat is a proteolytic enzyme inhibitor that has been used as the mesilate in the treatment of acute pancreatitis and disseminated intravascular coagulation, and as an anticoagulant in haemodialysis.

Hyperkalaemia has been reported.

References.

1. Yanamoto H, *et al.* Therapeutic trial of cerebral vasospasm with the serine protease inhibitor, FUT-175, administered in the acute stage after subarachnoid hemorrhage. *Neurosurgery* 1992; **30:** 358–63.
2. Akizawa T, *et al.* Nafamostat mesilate: a regional anticoagulant for haemodialysis in patients at high risk for bleeding. *Nephron* 1993; **64:** 376–81.
3. Miyata T, *et al.* Effectiveness of nafamostat mesilate on glomerulonephritis in immune-complex diseases. *Lancet* 1993; **341:** 1353.
4. Murase M, *et al.* Nafamostat mesilate reduces blood loss during open heart surgery. *Circulation* 1993; **88:** 432–6.
5. Kitagawa H, *et al.* Hyperkalaemia due to nafamostat mesylate. *N Engl J Med* 1995; **332:** 687.
6. Yamazato M, *et al.* Severe abdominal pain associated with allergic reaction to nafamostat mesilate in a chronic hemodialysis patient. *Intern Med* 2002; **41:** 864–6.
7. Kaminishi Y, *et al.* Effects of nafamostat mesilate and minimal-dose aprotinin on blood-foreign surface interactions in cardiopulmonary bypass. *Ann Thorac Surg* 2004; **77:** 644–50.
8. Ota T, *et al.* Cardiopulmonary bypass using nafamostat mesilate for patients with infective endocarditis and recent intracranial hemorrhage. *Interact Cardiovasc Thorac Surg* 2007; **6:** 270–3.

Naphthylacetic Acid

Naftilacético, ácido; 1-Naphthaleneacetic Acid; 1-Naphthylacetic Acid; Нафтилуксусная Кислота.

$C_{12}H_{10}O_2$=186.2

CAS — 86-87-3.

UNII — 33T7G7757C.

Profile

Naphthylacetic acid has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Galle-Donau; ***China***: Galle-Donau (加诺).

Natalizumab *(BAN, rINN)*

Natalizumabum; Натализумаб.

Immunoglobulin G 4 (human-mouse monoclonal AN100226 4-chain antihuman integrin 4), disulfide with human-mouse monoclonal AN100226 light chain, dimer.

CAS — 189261-10-7.

ATC — L04AA23.

ATC Vet — QL04AA23.

UNII — 3JB47N2Q2P.

NOTE. The name Antegren has been used as a trade mark for natalizumab.

Uses and Administration

Natalizumab is a recombinant humanised monoclonal antibody raised against human α4 integrin that is used as monotherapy to prevent relapses and delay progression of disability in patients with highly active relapsing-remitting multiple sclerosis. It is also used for inducing and maintaining response and remission in moderate to severe Crohn's disease (see Inflammatory Bowel Disease, p. 1808.3). However, because of an increased risk of progressive multifocal leukoencephalopathy (PML) its availability is restricted, and use is limited to patients who have had an inadequate response to, or are unable to tolerate, other therapies. A baseline magnetic resonance imaging scan must be done before natalizumab is started in order to differentiate newly developed lesions from pre-existing lesions. Patients should be evaluated for signs and symptoms of PML at 3 and 6 months after the first dose, then every 6 months thereafter. Natalizumab must be discontinued at the first sign of PML or other opportunistic infection developing; treatment may resume if this diagnosis is excluded, but should be permanently discontinued if confirmed.

Patients who were previously taking interferon beta or glatiramer acetate may switch directly to natalizumab provided there are no treatment-related adverse effects such as neutropenia; blood counts must return to normal before starting natalizumab. Patients who have been receiving immunosuppressants such as azathioprine and cyclophosphamide must not start natalizumab until it has been confirmed that they are no longer immunocompromised. Likewise, the pharmacodynamic effects of natalizumab remain for about 12 weeks after stopping treatment, and therefore a wash-out period may be appropriate on stopping natalizumab before giving immunosuppressive drugs.

Natalizumab 300 mg is given by intravenous infusion once every 4 weeks. The dose is diluted in 100 mL of sodium chloride 0.9% and given over about 1 hour. The patient should be observed during the infusion and for a further hour after it is complete; the infusion should be stopped if a hypersensitivity reaction occurs and treatment with natalizumab permanently discontinued. Treatment should also be discontinued if there is evidence of persistent raised antibodies to natalizumab since these reduce efficacy and increase the risk of hypersensitivity reactions. Continuation of therapy in multiple sclerosis patients who have shown no benefit after 6 months should be reconsidered. In the treatment of Crohn's disease, natalizumab should be stopped if patients have not obtained therapeutic benefit after 12 weeks of induction therapy or when patients are unable to discontinue chronic concomitant corticosteroid use within 6 months of starting natalizumab.

Natalizumab has also been investigated for the treatment of ulcerative colitis.

References.

1. Sweet BV. Natalizumab update. *Am J Health-Syst Pharm* 2007; **64:** 705–16.

Inflammatory bowel disease. The efficacy and safety of natalizumab in the treatment of *Crohn's disease* have been reviewed, including proposed mechanisms for the role of α4 integrins in the immunopathogenesis of inflammatory bowel disease (p. 1808.3).[1,2] A systematic review[3] of controlled studies of the use of natalizumab in the treatment of Crohn's disease concluded that it is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease, particularly those with active inflammation or chronically active disease despite use of conventional treatment. However, this benefit must be weighed against the risks of developing progressive multifocal leukoencephalopathy.

Natalizumab is also under investigation for *ulcerative colitis*.[4]

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; **39:** 1833–43.
2. Lanzarotto F, *et al.* Novel treatment options for inflammatory bowel disease: targeting α 4 integrin. *Drugs* 2006; **66:** 1179–89.
3. MacDonald JK, McDonald JWD. Natalizumab for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
4. Feagan BG, *et al.* Treatment of ulcerative colitis with a humanized antibody to the α 4 β 7 integrin. *N Engl J Med* 2005; **352:** 2499–2507.

Multiple sclerosis. The efficacy and safety of natalizumab in the treatment of multiple sclerosis (p. 996.3) have been reviewed,[1-4] including proposed mechanisms for the role of α4 integrins in its immunopathogenesis.[5,6] Randomised controlled studies[7-10] showed beneficial results in suppressing inflammatory lesions and reducing the frequency of relapse. Subsequent review[11] of the data from the AFFIRM[8] and SENTINEL studies[9] showed reduction of visual loss. In the SENTINEL study,[9] natalizumab was given with interferon beta, a combination that may have contributed to the development of progressive multifocal leukoencephalopathy in 2 of the study patients, one of whom died (see Infections, p. 2568.2). In the GLANCE study,[12] the rate of development of new active MRI lesions was lower when natalizumab was given as add-on therapy to patients who had suffered at least one relapse while taking glatiramer acetate than with glatiramer acetate alone. Although there was no evidence of PML during this study, further study of natalizumab given with glatiramer acetate was stopped because of the occurrence of PML

The symbol † denotes a preparation no longer actively marketed

reported by other workers when natalizumab was given as add-on therapy to interferon beta. Natalizumab is currently licensed only as monotherapy. New and enlarging lesions seen in patients 15 months after stopping natalizumab treatment[13] has raised the possibility of a rebound effect resulting in disease progression. However, data from another study[14] that followed up patients for 14 months after stopping therapy do not support these findings. Due to differing numbers of natalizumab exposures per patient between these two studies, it has been suggested[15] that a rebound effect is more likely to occur in patients who have short-term treatment.

1. Keeley KA, *et al*. Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; **39:** 1833–43.
2. Ransohoff RM. Natalizumab for multiple sclerosis. *N Engl J Med* 2007; **356:** 2622–9.
3. Goodin DS, *et al*. The use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; **71:** 766–73.
4. Anonymous. Natalizumab for multiple sclerosis? *Drug Ther Bull* 2008; **46:** 69–72.
5. Rice GPA, *et al*. Anti-α 4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology* 2005; **64:** 1336–42.
6. Kivisäkk P, *et al*. Natalizumab treatment is associated with peripheral sequestration of proinflammatory T cells. *Neurology* 2009; **72:** 1922–30.
7. Miller DH, *et al*. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003; **348:** 15–23.
8. Polman CH, *et al*. AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.
9. Rudick RA, *et al*. SENTINEL investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 911–23.
10. Miller DH, *et al*. AFFIRM Investigators. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; **68:** 1390–1401.
11. Balcer LJ, *et al*. AFFIRM and SENTINEL investigators. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 2007; **68:** 1299–1304.
12. Goodman AD, *et al*. GLANCE Investigators. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. *Neurology* 2009; **72:** 806–12.
13. Vellinga MM, *et al*. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. *Neurology* 2008; **70:** 1150–1.
14. Stüve O, *et al*. Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. *Neurology* 2009; **72:** 396–401.
15. Schiess N, Calabresi PA. Natalizumab: bound to rebound? *Neurology* 2009; **72:** 392–3.

Adverse Effects and Precautions

Natalizumab commonly causes infusion-related reactions including headache, dizziness, fatigue, urticaria, pruritus, rash, fever, rigors, nausea, hypotension, flushing, dyspnoea, and chest pain. Serious hypersensitivity reactions such as anaphylaxis can also occur. These reactions are usually associated with antibodies to natalizumab. The presence of these antibodies results in reduced serum concentrations and efficacy of natalizumab. The risk of infection is increased and there have been a few cases of progressive multifocal leukoencephalopathy (PML) reported; all patients should be monitored and if signs or symptoms of PML appear treatment should be withheld pending investigation. The risk of developing PML increases with treatment duration. Immune reconstitution inflammatory syndrome has been reported in patients who discontinued natalizumab after developing PML, and in almost all cases, it occurred after plasma exchange was used to eliminate natalizumab from the circulation. Clinically significant hepatotoxicity has also been reported with natalizumab and treatment should be stopped if there is evidence of jaundice or other significant liver injury.

Natalizumab is contra-indicated in patients who have previously had PML. It is also contra-indicated in patients with, or at risk for, opportunistic infections, and in those with malignancies. Patients with significantly compromised immune systems should not generally be given natalizumab.

Antibody formation. The incidence and clinical effects of antibody formation to natalizumab therapy in patients with relapsing multiple sclerosis were studied in the AFFIRM and SENTINEL studies.[1] Of 625 patients treated with natalizumab in the AFFIRM study 20 (3%) were transiently positive for antibodies to natalizumab and 37 (6%) were persistently positive. Equivalent figures for 585 natalizumab-treated patients in the SENTINEL study were 32 (5%) and 38 (6%) respectively. Overall the presence of antibodies was generally correlated with reduced serum concentrations of natalizumab and a poorer treatment response, efficacy being restored in those patients who became antibody-negative during therapy. Antibody-positive patients also had a higher incidence of infusion-related adverse effects, including hypersensitivity reactions (17 of the 37 persistently positive patients in the AFFIRM study). It is recommended that patients with suboptimal response to natalizumab or persistent infusion-related adverse effects should be considered for antibody testing. UK licensed product information warns that therapy should not be restarted in patients who remain positive for antibodies 6 weeks after interrupting an initial short exposure to natalizumab.

1. Calabresi PA, *et al*. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 2007; **69:** 1391–1403.

Hypersensitivity. A review[1] of the data for patients who had hypersensitivity reactions in the AFFIRM study,[2] which included 627 patients in the natalizumab treatment group, found that there was a low incidence (< 1%) of serious reactions described as anaphylactoid or anaphylactic. All patients with hypersensitivity reactions responded promptly to discontinuation of the infusion and standard pharmacotherapy as necessary (adrenaline, oxygen, and antihistamines with or without corticosteroids); all recovered fully about 1 to 2 hours after the end of the infusion. UK licensed product information warns that patients should be counselled on the importance of uninterrupted dosing, particularly in the early months of treatment; the risk for hypersensitivity reactions is greatest with early infusions and in patients who, after an initial short exposure to natalizumab, are re-exposed after a treatment-free period of 3 or more months.

1. Phillips JT, *et al*. Infusion-related hypersensitivity reactions during natalizumab treatment. *Neurology* 2006; **67:** 1717–18. Correction. *ibid*. 2007; **68:** 473.
2. Polman CH, *et al*. AFFIRM investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.

Infections. Three cases of progressive multifocal leukoencephalopathy (an opportunistic infection of the brain caused by JC virus, a human polyomavirus) have been described in patients given natalizumab.[1-3] One patient[1] died after receiving natalizumab with azathioprine for Crohn's disease. The other patients[2,3] were given natalizumab with interferon beta for multiple sclerosis; one of these[2] also died. After these reports, the use of natalizumab was restricted (see Uses and Administration, p. 2567.2). A subsequent retrospective evaluation[4] of more than 3000 patients who had received natalizumab found no further cases. However, 2 further cases have subsequently been reported[5] in patients taking natalizumab as monotherapy for 14 months and 17 months; one of the patients had previously taken immunosuppressants. Further cases of PML continue to be reported[6] but the rate in patients who have received at least one infusion of natalizumab is below 1 in 1000 patients. However, the risk for developing PML appears to increase with the number of infusions and based on current worldwide data, the rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1000 patients.

1. Van Assche G, *et al*. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353:** 362–8.
2. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; **353:** 369–74.
3. Langer-Gould A, *et al*. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005; **353:** 375–81.
4. Yousry TA, *et al*. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; **354:** 924–33.
5. FDA. Information for healthcare professionals: natalizumab injection for intravenous use (marketed as Tysabri) (issued Aug. 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126592.htm (accessed 11/03/10)
6. FDA. Information on natalizumab (marketed as Tysabri) (issued Sep. 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm (accessed 11/03/10)

Melanoma. Long-standing naevi in two women developed into melanoma shortly after starting natalizumab treatment for multiple sclerosis.[1]

1. Mullen JT, *etal*. Melanoma complicating treatment with natalizumab for multiple sclerosis. *N Engl J Med* 2008; **358:** 647–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies natalizumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Use with antineoplastics, immunosuppressants, or immunomodulators may further increase the risk of opportunistic infections including progressive multifocal leukoencephalopathy associated with natalizumab. Concurrent treatment with interferon beta or glatiramer acetate is contra-indicated.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tysabri; ***Austria***: Tysabri; ***Belg.***: Tysabri; ***Braz.***: Tysabri; ***Canad.***: Tysabri; ***Cz.***: Tysabri; ***Denm.***: Tysabri; ***Fr.***: Tysabri; ***Ger.***: Tysabri; ***Gr.***: Tysabri; ***Hung.***: Tysabri; ***Irl.***: Tysabri; ***Israel***: Tysabri; ***Ital.***: Tysabri; ***Neth.***: Tysabri; ***Norw.***: Tysabri; ***NZ***: Tysabri; ***Pol.***: Tysabri; ***Port.***: Tysabri; ***Spain***: Tysabri; ***Swed.***: Tysabri; ***Switz.***: Tysabri; ***UK***: Tysabri; ***Ukr.***: Tizabri (Тизабри); ***USA***: Tysabri.

Neroli Oil

Aceite esencial de las flores del naranjo amargo; Aceite esencial de Neroli; Aurantii amari floris aetheroleum; Aurantii Amari Floris Aetheroleum (bitter-orange flower oil); Aurantii Amari Floris Etheroleum; Azahar, aceite esencial de; Bitter-Orange Flower Oil; Esencia de Azahar; Essência de Flor de Laranjeira; Karčiavaisių citrinmedžių žiedų eterinis aliejus (bitter-orange flower oil); Keserű narancs virág olaj (bitter-orange flower oil); Neroli aetheroleum; Néroli, huile essentielle de; Neroliöl/Bitterorangenblütenöl; Neroliolja; Neroliöljy; Olejek z kwiatu pomarańczy gorzkiej; Oleum Neroli; Orange Flower Oil; Orange-flower Oil; Silice květů hořkého pomeranče; Неролиевое Масло.

UNII — D4BGE91OXH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Neroli Oil). A clear, pale yellow or dark yellow liquid with a characteristic odour obtained by steam distillation from the fresh flowers of *Citrus aurantium* subsp. *aurantium* (*C. aurantium* subsp. *amara*) (see under Bitter Orange, p. 2575.3). Relative density 0.863 to 0.880. Store in well-filled airtight containers at a temperature below 25 degrees. Protect from light.

Profile

Neroli oil is used as a flavour and in perfumery. It is also used in aromatherapy. Photosensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Agua Melisa Carminativa; ***Cz.***: Stopangin; ***Ital.***: Controller; ***Rus.***: Stopangin (Стопангин); ***Switz.***: Kemeol†; Nasmer free; Oculosan; ***Turk.***: Nevrol Cemal; ***Ukr.***: Stopangin (Стопангин).

Nerve Agents

Gases nerviosos.

Sarin

GB; Sarín.

Isopropyl methylphosphonofluoridate.

$C_4H_{10}FO_2P$=140.1

CAS — 107-44-8.

UNII — B4XG72QGFM.

Soman

GD; Somán.

Pinacolyl methylphosphonofluoridate.

$C_7H_{16}FO_2P$=182.2

CAS — 96-64-0.

Tabun

GA; Tabún.

Ethyl *N*-dimethylphosphoramidocyanidate.

$C_5H_{11}N_2O_2P$=162.1

CAS — 77-81-6.

VX

Methylphosphonothioic acid S-{2-[bis(1-methylethyl)amino] ethyl} *O*-ethyl ester.

$C_{11}H_{26}NO_2PS$=267.4

CAS — 50782-69-9.

UNII — 9A4381183B.

Profile

The nerve agents, sarin, soman, tabun, and VX (also referred to as 'nerve gases') used in chemical warfare are extremely potent inhibitors of cholinesterase. The effects of poisoning due to these agents, and their treatment, are similar to those for organophosphorus insecticides (p. 2158.3) but as the nerve agents have a much greater intrinsic toxicity the symptoms of poisoning are more severe. Pyridostigmine has been given prophylactically to personnel at risk from exposure to nerve agents (see p. 689.3).

References.

1. Ministry of Defence. *Medical manual of defence against chemical agents*. London: HMSO, 1987. (JSP312)
2. World MJ. Toxic gas trauma. *Lancet* 1995; **346:** 260–1.

3. Nozaki H, *et al.* A case of VX poisoning and the difference from sarin. *Lancet* 1995; **346:** 698–9.
4. Okumura T, *et al.* Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med* 1996; **28:** 129–35.
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6. Holstege CP, *et al.* Chemical warfare: nerve agent poisoning. *Crit Care Clin* 1997; **13:** 923–42.
7. Ministry of Defence. Use of medical countermeasures to protect armed forces during the Gulf War: background to the use of medical countermeasures to protect British forces during the Gulf War (Operation Granby) (issued October 1997). Available at: http://www.mod.uk/NR/rdonlyres/86D81B65-F0B0-46E4-8BCC-50DD4F1FF584/0/Oct97MedicalCountermeasurepaper1.pdf (accessed 30/06/10)
8. United States Army. *Medical Management of Chemical Casualties Handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense;1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/Red-Handbook/001TitlePage.htm (accessed 24/07/08)
9. Weinbroum AA, *et al.* Anaesthesia and critical care considerations in nerve agent warfare trauma casualties. *Resuscitation* 2000; **47:** 113–23.
10. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; **44:** 1–3.
11. Janowsky DS. Central anticholinergics to treat nerve-agent poisoning. *Lancet* 2002; **359:** 265–6.
12. Anonymous. Nerve agents. *J R Army Med Corps* 2002; **148:** 344–57.
13. Lee EC. Clinical manifestations of sarin nerve gas exposure. *JAMA* 2003; **290:** 659–62.
14. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; **112:** 648–58.
15. Newmark J. The birth of nerve agent warfare: lessons from Syed Abbas Foroutan. *Neurology* 2004; **62:** 1590–6.

Neutral Red

CI Basic Red 5; Colour Index No. 50040; Neutral Red Chloride; Nuclear Fast Red; Rojo neutro; Rojo toluileno; Toluylene Red; Нейтральный Красный.

3-Amino-7-dimethylamino-2-methylphenazine hydrochloride.

$C_{15}H_{16}N_4$,HCl=288.8

CAS — 553-24-2.

UNII — 261QK3SSBH.

Profile

Neutral red is used as an indicator for alkalinity and for preparing neutral-red paper. It is also used as a stain in microscopy.

It is a photoactive dye that has been tried in photodynamic therapy of recurrent herpes simplex infections, but with limited success.

Niaouli Oil

Aceite esencial de niauli; Essence de Niaouli; Gomenol; Ниаули Масло.

UNII — D50IC2T8FU (Melaleuca viridiflora oil); 22K2F1YSHD (Melaleuca quinquenervia oil).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Niaouli Oil, Cineole Type; Niaouli Typo Cineolo Aetheroleum). An essential oil obtained by steam distillation from young leafy branches of *Melaleuca quinquenervia*. A colourless or pale yellow liquid with an aromatic odour of cineole. Store at a temperature below 25 degrees.

Profile

Niaouli oil is a volatile oil, obtained by distillation from the fresh leaves of *Melaleuca viridiflora* or *Melaleuca quinquenervia* (Myrtaceae). It contains cineole (p. 2479.1) and has similar actions to eucalyptus oil (p. 2501.2). It is an ingredient of many preparations. Typical indications include respiratory-tract congestion. Cajuput oil (p. 2464.1) and melaleuca oil (p. 2551.1) are also prepared from *Melaleuca* spp.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Gomenol; Gomenoleo; Huile Gomenolee; ***Switz.***: Bronchomed.

Multi-ingredient Preparations. ***Arg.***: Aseptobron; Aseptobron; Di-Neumobron; Medex Rub; No-Tos Adultos; Refenax Caramelos Expectorantes; ***Braz.***: Algice; Gripsay; Ozonyl Aquoso; Ozonyl Expectorante; Ozonyl; Tetrapulmo†; ***Fr.***: Arthro; Balsolene; Biogaze; Coquelusedal; Euphonyl Expectorant; Euvanol; Euvanol; Hexaquine; Olioseptil Nez-Gorge; Terpone Nourrisson†; Terpone; Thermo Gomenol; Vaseline Gomenolee; Veganix; Veino Gomenol; ***Ital.***: Bron 6; Rinopaidolo; Rinovit; ***Pol.***: Argol Grip; ***Spain***: Brota Rectal Balsamico†; Pastillas Pectorales Kely†; Rinobanedif; Vapores Pyt†; Vitavox†; ***Switz.***: DUL-X warm; Pulmex; Resorbane; ***Turk.***: Buguseptil; Rinolar.

Nicergoline *(BAN, USAN, rINN)*

FI-6714; Nicergolin; Nicergolina; Nicergolinas; Nicergolinum; Nisergoliini; Nisergolin; Ницерголин.

10α-Methoxy-1,6-dimethylergolin-8β-ylmethyl 5-bromonicotinate.

$C_{24}H_{26}BrN_3O_3$=484.4

CAS — 27848-84-6.

ATC — C04AE02.

ATC Vet — QC04AE02.

UNII — JCV8365FWN.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Nicergoline). A fine to granular white or yellowish powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane.

Uses and Administration

Nicergoline is an ergot derivative. It has been used similarly to codergocrine mesilate (p. 389.3) to treat symptoms of mental deterioration associated with cerebrovascular insufficiency (see Dementia, p. 388.1) and has also been used in peripheral vascular disorders (p. 1272.3). Nicergoline has been given orally in doses of up to 60 mg daily in divided doses. It has also been given by intramuscular injection and by intravenous infusion. Nicergoline tartrate has been used in parenteral dosage forms.

References.

1. Ronchi F, *et al.* Symptomatic treatment of benign prostatic obstruction with nicergoline: a placebo controlled clinical study and urodynamic evaluation. *Urol Res* 1982; **10:** 131–4.
2. Bousquet J, *et al.* Double-blind, placebo-controlled study of nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J Allergy Clin Immunol* 1989; **83:** 825–8.
3. Saletu B, *et al.* Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. *Psychopharmacology (Berl)* 1995; **117:** 385–95.
4. Herrmann WM, *et al.* A multicenter randomized double-blind study on the efficacy and safety of nicergoline in patients with multi-infarct dementia. *Dementia Geriatr Cogn Disord* 1997; **8:** 9–17.
5. Fioravanti M, Flicker L. Nicergoline for dementia and other age associated forms of cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/04/05).
6. Felisati G, *et al.* Nicergoline in the treatment of dizziness in elderly patients: a review. *Arch Gerontol Geriatr Suppl* 2004; 163–70.
7. Winblad B, *et al.* Therapeutic use of nicergoline. *Clin Drug Investig* 2008; **28:** 533–52.

Adverse Effects and Precautions

Adverse effects that may occur after nicergoline include gastrointestinal disturbances and, particularly after parenteral doses, hypotension.

Incidence of adverse effects. Adverse effects occurred in 25 of 359 patients with cerebrovascular insufficiency treated with nicergoline for 1 month;[1] the drug had to be withdrawn in 11. The reactions included 6 cases of hot flushes, 8 of general malaise, 2 of agitation, 3 of hyperacidity, 1 of nausea, 3 of diarrhoea, and 2 of dizziness and somnolence.

1. Dauverchain J. Bedeutung von Nicergolin bei der symptomatischen Behandlung des arteriellen Hochdrucks und der chronischen, zerebrovaskulären Insuffizienz. *Arzneimittelforschung* 1979; **29:** 1308–10.

Interactions

For a study indicating that nicergoline enhances the cardiac depressant action of propranolol, see Ergot Derivatives, in Interactions of Beta Blockers, p. 1322.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cergodun; Sermion; ***Austria***: Ergotop; Nicergin; Sermion; ***Braz.***: Sermion; ***Chile***: Sermion; ***China***: Chen Rang (辰让); Fulutong (富路通); Jin Yi Xin (金亿新); Kai Er (凯尔); Lexilin (乐喜林); Nixo (尼舒); Sernion (思尔明); Shi Nuo Da (史诺达); Ya Run Ji (雅润基); ***Cz.***: Ergotop; Sermion; ***Fr.***: Sermion; ***Ger.***: Ergobel; Nicergobeta†; Nicerium†; ***Gr.***: Albotyl; Gustosal; Inelin; Sermion; ***Hong Kong***: Cergodun; Qualigoline; Sermion; ***Hung.***: Ergotop; Sermion; ***India***: Cholergol; Nicerbium; ***Indon.***: Serolin; ***Ital.***: Sermion; ***Jpn***: Sermion; ***Mex.***: Sermion; ***Philipp.***: Nicerbium; Sermion†; ***Pol.***: Adavin; Circulat†; Nicerin; Niglostin; Nilogrin; Sermion; ***Port.***: Sermion; ***Rus.***: Nilogrin (Нилогрин)†; Sermion (Сермион); ***Spain***: Sermion; Varson; ***Switz.***: Sermion†; ***Thai.***: Sergoline; Sermion; ***Turk.***: Sermion; ***Ukr.***: Nicerium (Ницериум); Sergolin (Серголин); Sermion (Сермион); ***Venez.***: Sermion.

Multi-ingredient Preparations. ***Arg.***: Sibelium Plus.

Nicotinaldehyde

3-Formylpyridine; Nicotinic Aldehyde; 3-Pyridinaldehyde; Pyridine-3-aldehyde.

3-Pyridinecarboxaldehyde.

C_6H_5NO=107.1

CAS — 500-22-1.

UNII — 840R4IDQ1T.

Profile

Nicotinaldehyde has been used topically in preparations for musculoskeletal and respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Rowalind.

Nicotine *(BAN)*

Nicotin; Nicotina; Nicotinum; Nikotiini; Nikotin; Nikotinas.

(*S*)-3-(1-Methylpyrrolidin-2-yl)pyridine.

$C_{10}H_{14}N_2$=162.2

CAS — 54-11-5.

ATC — N07BA01.

ATC Vet — QN07BA01; QP53AX13.

UNII — 6M3C89ZY6R.

Description. Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae) (see p. 2632.2). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Nicotine). A colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water; miscible with dehydrated alcohol. Store under nitrogen in airtight containers. Protect from light.

USP 36: (Nicotine). It should be stored under nitrogen at a temperature below 25 degrees. Protect from light and moisture.

Nicotine Polacrilex *(BANM, USAN)*

CAS — 96055-45-7.

ATC — N07BA01.

ATC Vet — QN07BA01.

Pharmacopoeias. In *US*.

USP 36: (Nicotine Polacrilex). A weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. Store in airtight containers.

Nicotine Resinate *(BANM)*

Nicotine, résinate de; Nicotini Resinas; Nicotinresinat; Nikotiiniresinaatti; Nikotino rezinatas; Nikotin-resinát; Nikotin-rezinát.

ATC — N07BA01.

ATC Vet — QN07BA01.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nicotine Resinate). A complex of nicotine with a weak cationic exchange resin. It may contain glycerol. A white or slightly yellowish powder. Practically insoluble in water. Store in airtight containers. Protect from light.

Nicotine Tartrate

Nicotine Bitartrate (USAN); Nicotine Bitartrate (BANM).

$C_{10}H_{14}N_2$,$2C_4H_6O_6$,$2H_2O$=498.4

CAS — 65-31-6 (anhydrous nicotine tartrate).

ATC — N07BA01.

ATC Vet — QN07BA01.

UNII — 7892ZN5G41 (anhydrous nicotine tartrate); R7M676M8YV (nicotine tartrate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nicotine Ditartrate Dihydrate). A white or almost white powder. Soluble in water and in alcohol. A 10% solution in water has a pH of 3.0 to 3.4. Protect from light.

Uses and Administration

The main physiological action of nicotine is paralysis of all autonomic ganglia, preceded by stimulation. Centrally, small doses cause respiratory stimulation, while larger doses produce convulsions and arrest of respiration. The effects on skeletal muscle are similar to those on ganglia.

Nicotine chewing gum, transdermal patches, lozenges, sublingual tablets, nasal spray, or inhalator are used as aids for smoking cessation (p. 2570.2) and many such products are also used to reduce the amount smoked. For smoking *cessation*, treatment is usually continued for up to 3 months, then gradually withdrawn. For smoking *reduction*, it may be continued for up to 6 months, and an attempt to quit then made. If use is to be continued beyond 9 months, additional advice from a healthcare professional should be sought.

- *Chewing gum* is available in strengths of 2 mg and 4 mg; the nicotine may be present in the gum in the form of a complex with methacrylic acid polymer (nicotine

polacrilex). Individuals who smoke 20 cigarettes or less daily should start with the 2-mg strength gum chewed slowly over about 30 minutes when the urge to smoke occurs. Those who smoke over 20 cigarettes daily or require more than 15 pieces daily of the 2-mg gum should receive the 4-mg strength. Not more than 15 pieces should be used daily.

- *Sublingual tablets* containing the equivalent of 2 mg of nicotine as a β-cyclodextrin complex may be used: the recommended dose is 1 or 2 tablets sublingually every hour, increased to a maximum of 40 tablets daily if necessary. Nicotine tartrate has also been used sublingually.
- *Lozenges* containing 1, 1.5, 2, or 4 mg of nicotine (as the polacrilex or tartrate) are available. For abrupt cessation of, or temporary abstinence from smoking, the initial dose is one lozenge every 1 to 2 hours, or for gradual cessation of smoking, one lozenge whenever there is a strong urge to smoke. The usual daily dose is 8 to 12 lozenges with a maximum daily dose of 30 of the 1-mg lozenges or 15 lozenges for all higher strengths.
- Adhesive *transdermal patches* are designed to be worn for 16 or 24 hours and are available in different strengths that deliver from 5 to 25 mg during the recommended wearing time. One patch should be applied daily, on waking, to a dry, non-hairy area of skin on the hip, trunk, or upper arm, usually beginning with the highest strength or with a dose determined by the previous daily consumption of cigarettes. A different site of application should be used each day with 24 hours or more elapsing before the patch is applied to the same area of skin.
- A suggested initial dosage for a *nasal spray* containing 500 micrograms per spray is one spray administered into each nostril up to twice hourly as required up to a maximum of 80 sprays daily for the first 8 weeks and reduced gradually thereafter. Treatment for more than 3 months is not recommended.
- Nicotine *inhalator cartridges* contain nicotine 10 mg for use in an appropriate inhaler mouthpiece. The initial dose is 6 to 16 cartridges daily for up to 12 weeks and is reduced gradually over a further 4 to 12 weeks.

Nicotine has been used as a horticultural insecticide.

Alzheimer's disease. The use of nicotine as a cholinergic agonist is one of several methods being studied[1] to overcome brain cholinergic deficits in patients with Alzheimer's disease (see Dementia, p. 388.1). Preliminary studies[2,3] using nicotine patches have been of limited duration and were inconclusive. Transdermal nicotine has been used for the control of behavioural symptoms such as agitation in a small number of patients with Alzheimer's disease.[4] A systematic review[5] was unable to present any conclusions on the efficacy and safety of nicotine in Alzheimer's disease because of a lack of adequate randomised controlled studies.

1. Baldinger SL, Schroeder DJ. Nicotine therapy in patients with Alzheimer's disease. *Ann Pharmacother* 1995; **29:** 314–15.
2. Wilson AL, *et al*. Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 1995; **51:** 509–14.
3. Snaedal J, *et al*. The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. *Dementia* 1996; **7:** 47–52.
4. Rosin RA, *et al*. Transdermal nicotine for agitation in dementia. *Am J Geriatr Psychiatry* 2001; **9:** 443–4.
5. López-Arrieta JLA, Sanz FJ. Nicotine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 28/04/05).

Blepharospasm. Nicotine nasal spray was reported to be of benefit in a patient with blepharospasm (p. 2018.1) refractory to botulinum A toxin.[1] However, a subsequent study in 4 patients with blepharospasm reported no improvement with the use of nicotine nasal spray.[2]

1. Dursun SM, *et al*. Treatment of blepharospasm with nicotine nasal spray. *Lancet* 1996; **348:** 60.
2. Dressler D, *et al*. Nicotine nasal spray is not reliable treatment for blepharospasm: results of a pilot study. *Mov Disord* 1998; **13:** 190.

Extrapyramidal disorders. Nicotine transdermal patches have been reported to produce beneficial effects[1] in schizophrenic patients with antipsychotic-induced akathisia (p. 1049.2). Because of an apparent inverse association between smoking and Parkinson's disease (p. 889.1), transdermal nicotine patches have been investigated in the treatment of parkinsonian symptoms, but with little evidence of overall benefit.[2,3]

1. Anfang MK, Pope HG. Treatment of neuroleptic-induced akathisia with nicotine patches. *Psychopharmacology (Berl)* 1997; **134:** 153–6.
2. Vieregge A, *et al*. Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. *Neurology* 2001; **57:** 1032–5.
3. Lemay S, *et al*. Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28:** 31–9.

Skin disorders. There have been anecdotal reports of nicotine producing beneficial effects in various skin disorders, including pyoderma gangrenosum,[1] and dermatitis due to fluorouracil therapy.[2]

1. Kanekura T, *et al*. Nicotine for pyoderma gangrenosum. *Lancet* 1995; **345:** 1058.
2. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; **120:** 813.

Smoking cessation. Smoking is the single most important cause of preventable illness and premature death in the UK and USA; it is estimated that around 1 in 5 deaths are due to smoking-related illnesses. The financial burden of smoking-related diseases on healthcare providers is also substantial. Many governments have undertaken initiatives to promote smoking cessation for which there is substantial evidence of a decline in the risk of disease[1] and death.[2] As the abstinence period increases, the reduced risk of disease in former smokers may even approach, although rarely does it ever equal, that of people who have never smoked.[1]

Nicotine dependence and the development of a characteristic withdrawal syndrome (see Dependence and Withdrawal, p. 2571.1) make stopping smoking very difficult. Many individuals relapse when trying to give up or need several attempts before successfully stopping. Both nonpharmacological and pharmacological treatments can improve the abstinence rate and are most effective when the two approaches are combined.[3-12]

Nonpharmacological methods include counselling, training in coping skills, and support groups; although the abstinence rate increases with the intensity of the support, even brief advice is effective in encouraging cessation.

The first-line pharmacological intervention is *nicotine replacement therapy* (NRT) which is an effective treatment for reducing the cravings associated with stopping smoking. NRT is available in several formulations: chewing gum, transdermal patches, inhalators, nasal sprays, sublingual tablets, and lozenges. A systematic review[9] of NRT found abstinence was more than doubled when compared with controls, regardless of the intensity of any additional nonpharmacological support. However, a later meta-analysis[13] concluded that most of the evidence comes from studies with behavioural support and it is unclear whether using NRT without regular contact would be as effective.

Choice of formulation is based on patient preference, tolerance, and previous treatments, if any. The transdermal patch is easiest to use and compliance is greatest with this route but local effects may be troublesome. The gum has an unpleasant taste initially and some find the chewing action difficult. The sublingual tablet may be useful for those who have difficulty chewing the gum. The nasal spray has a fast onset of action but may cause local irritation. The inhalator has the advantage of simulating cigarette smoking but may cause local irritation of the mouth and throat. The lozenge has the advantage that it can be sucked discreetly. Patients who are unable to tolerate one type of NRT may benefit from a course of an alternative NRT preparation.

Combination therapy with different types of NRT (patches with either the nasal spray, inhalator, or chewing gum) has also been tried as a means of increasing efficacy.[14,15]

NRT for smoking cessation is usually continued for about 3 months before being withdrawn. Although the manufacturers advise gradual withdrawal, others[6] have found that this offers no advantage and recommend abrupt withdrawal. NRT for smoking reduction is typically continued for longer periods. NRT has also been used long-term and may be of particular benefit in those patients who feel they would relapse if NRT was stopped or in those who have persistent withdrawal symptoms.

There has been concern over the use of NRT in patients with cardiovascular disease (see Effects on the Cardiovascular System, p. 2571.2) but clinical experience and studies have shown that NRT can be used with caution in these patients. The use of NRT in those who have suffered a recent myocardial infarction or those with severe arrhythmias or unstable angina is, however, contra-indicated as such patients have not been adequately studied.

Several other drugs have also been used to achieve abstinence from smoking.[16-18] *Bupropion* is effective and recommended by some as a first-line alternative to NRT; its action is said to be independent of its antidepressant activity. Bupropion with NRT has been used successfully. Evidence to support the use of most other antidepressants is lacking,[19] but *nortriptyline* appears to be effective and is used as a second-line drug. A study[20] found, however, that there was no advantage in combining nortriptyline with NRT. *Clonidine* is also effective but adverse effects limit its usefulness.[18] Preliminary investigations suggest that *selegiline* and *mecamylamine* may be effective.[16,18] The cannabinoid-1 receptor antagonist *rimonabant* has produced promising results in early studies,[16,17] although a systematic review[21] of 3 randomised controlled studies found the evidence to be inconclusive. A systematic review[22] of studies on the use of the oral nicotine receptor partial agonists *varenicline* and *cytisine* concluded that both drugs have a potential place in smoking cessation. Varenicline compared favourably with placebo and bupropion in helping smokers to quit, but its efficacy in preventing relapse still remains to be fully established. Like bupropion, varenicline is recommended by some as a first-line alternative to NRT. Cytisine is widely used in central and eastern Europe but the current evidence for efficacy is limited and better designed studies are required to test earlier findings. There is little or no evidence to support the efficacy of other treatments such as *silver acetate*, *lobeline*, or *anxiolytics* such as *buspirone*, and their use is not recommended. A *vaccine* for the prevention of smoking relapse is under investigation.[16,17]

1. Dresler CM, *et al*. Reversal of risk upon quitting smoking. *Lancet* 2006; **368:** 348–9.
2. Vollset SE, *et al*. Smoking and deaths between 40 and 70 years of age in women and men. *Ann Intern Med* 2006; **144:** 381–9.
3. Hudmon KS, Corelli RL. ASHP therapeutic position statement on the cessation of tobacco use. *Am J Health-Syst Pharm* 2009; **66:** 291–307.
4. Anonymous. Nicotine replacement to aid smoking cessation. *Drug Ther Bull* 1999; **37:** 52–4.
5. West R, *et al*. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000; **55:** 987–99.
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13. Moore D, *et al*. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. Abridged version: *BMJ* 2009; **338:** 867–71. Full version: http://www.bmj.com/cgi/content/full/338/apr02_3/b1024?view=long&p-mid=19342408 (accessed 17/06/10)
14. Steinberg MB, *et al*. Triple-combination pharmacotherapy for medically ill smokers: a randomized trial. *Ann Intern Med* 2009; **150:** 447–54.
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22. Cahill K, *et al*. Nicotine receptor partial agonists for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 28/06/07).

Spasticity. There have been anecdotal reports[1] of beneficial responses to nicotine in spastic dystonia.

1. Vaughan CJ, *et al*. Treatment of spastic dystonia with transdermal nicotine. *Lancet* 1997; **350:** 565.

Tics. Tourette's syndrome (see Tics, p. 1030.1) is characterised by motor and vocal tics and behavioural disturbances. Nicotine[1-5] has been reported to be of benefit when used alone or with the more usual treatment of haloperidol in patients with Tourette's syndrome whose symptoms were not satisfactorily controlled with haloperidol alone. It is hoped that the use of transdermal nicotine patches will avoid the reported problems of compliance associated with the taste and gastrointestinal effects of nicotine gum.

1. McConville BJ, *et al*. The effects of nicotine plus haloperidol compared to nicotine only and placebo nicotine only in reducing tic severity and frequency to Tourette's disorder. *Biol Psychiatry* 1992; **31:** 832–40.
2. Silver AA, Sanberg PR. Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome. *Lancet* 1993; **342:** 182.
3. Dursun SM, *et al*. Longlasting improvement of Tourette's syndrome with transdermal nicotine. *Lancet* 1994; **344:** 1577.
4. Sanberg PR, *et al*. Nicotine for the treatment of Tourette's syndrome. *Pharmacol Ther* 1997; **74:** 21–5.
5. Silver AA, *et al*. Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study. *J Clin Psychiatry* 2001; **62:** 707–14.

Ulcerative colitis. Investigation of the use of nicotine in ulcerative colitis (see Inflammatory Bowel Disease, p. 1808.3) has been prompted by the observation that this condition is rare in smokers.[1] A systematic review[2] found that transdermal nicotine was more effective than placebo in producing remission in patients with active ulcerative

colitis, but appeared to be no more effective than standard therapy with a corticosteroid or aminosalicylate, and was associated with more adverse effects. It appears to be ineffective in maintaining disease remission.[3] Any role is likely to be limited to patients who do not respond to standard therapy and who can tolerate the adverse effects.[2] Local delivery to the colon, in the form of enemas[4-6] and oral modified-release capsules,[7] is under investigation as a means of reducing the adverse effects of nicotine.

1. Guslandi M. Nicotine treatment for ulcerative colitis. *Br J Clin Pharmacol* 1999; **48:** 481–4.
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3. Thomas GAO, *et al.* Transdermal nicotine as maintenance therapy for ulcerative colitis. *N Engl J Med* 1995; **332:** 988–92.
4. Sandborn WJ, *et al.* Nicotine tartrate liquid enemas for mildly to moderately active left-sided ulcerative colitis unresponsive to first-line therapy: a pilot study. *Aliment Pharmacol Ther* 1997; **11:** 663–71.
5. Ingram JR, *et al.* Nicotine enemas for treatment of ulcerative colitis: a study of the pharmacokinetics and adverse events associated with three doses of nicotine. *Aliment Pharmacol Ther* 2004; **20:** 859–65.
6. Ingram JR, *et al.* A randomized trial of nicotine enemas for active ulcerative colitis. *Clin Gastroenterol Hepatol* 2005; **3:** 1107–14.
7. Green JT, *et al.* An oral formulation of nicotine for release and absorption in the colon: its development and pharmacokinetics. *Br J Clin Pharmacol* 1999; **48:** 485–93.

Dependence and Withdrawal

Nicotine dependence is most commonly associated with cigarette smoking. It is characterised by a strong desire to continue taking the agent, a physical and psychological need for it, and a characteristic abstinence syndrome on withdrawal. Common symptoms seen on nicotine withdrawal include irritability, anxiety, depression, restlessness, poor concentration, increased appetite, weight gain, and insomnia. The management of smoking cessation is discussed under Uses and Administration, p. 2570.2.

Mild withdrawal symptoms have been reported from nicotine replacement preparations used to aid smoking cessation.

References.

1. Hatsukami D, *et al.* Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology (Berl)* 1993; **111:** 449–56.
2. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *N Engl J Med* 1994; **331:** 123–5.
3. Keenan RM, *et al.* Pharmacodynamic effects of cotinine in abstinent cigarette smokers. *Clin Pharmacol Ther* 1994; **55:** 581–90.
4. Slade J, *et al.* Nicotine and addiction: the Brown and Williamson documents. *JAMA* 1995; **274:** 225–33.
5. Kessler DA. Nicotine addiction in young people. *N Engl J Med* 1995; **333:** 186–9.
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7. Benowitz NL. Nicotine addiction. *Prim Care* 1999; **26:** 611–31.
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10. West R, *et al.* A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)* 2000; **149:** 198–202.

Adverse Effects and Treatment

Nicotine is a highly toxic substance and in acute poisoning death may occur within 1 hour due to respiratory failure arising from paralysis of the muscles of respiration. The fatal oral dose of nicotine for an adult is from 40 to 60 mg.

Less severe poisoning causes initial stimulation followed by depression of the autonomic nervous system. Typical symptoms include burning of the mouth and throat, nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, weakness, hypertension followed by hypotension, mental confusion, headache, hearing and visual disturbances, dyspnoea, faintness, convulsions, sweating, and prostration. Transient cardiac standstill or paroxysmal atrial fibrillation may occur.

Nicotine is rapidly absorbed through the skin or by inhalation as well as by ingestion, and nicotine poisoning may occur due to careless handling when it is used as a horticultural insecticide.

Prompt treatment of nicotine poisoning is essential. If contact was with the skin, contaminated clothing should be removed and the skin washed thoroughly with cold water without rubbing. If the patient has swallowed nicotine, gastric lavage and activated charcoal may be beneficial. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

Apart from effects such as dizziness, headache, and gastrointestinal disturbances mentioned above, adverse effects associated with *nicotine replacement preparations* have also included cold and flu-like symptoms, palpitations, insomnia, vivid dreams, myalgia, chest pain, blood pressure changes, anxiety, irritability, somnolence, and dysmenorrhoea. Allergic reactions have been reported. Adverse effects associated with specific preparations include skin reactions with transdermal patches; nasal irritation, epistaxis, lachrymation, and sensations in the ear with the nasal spray; throat irritation with the spray, inhalator, sublingual tablets, lozenges, or chewing gum; aphthous ulceration with the inhalator, sublingual tablets, lozenges, or chewing gum; increased salivation and sometimes swelling of the tongue with chewing gum; cough, rhinitis, stomatitis, sinusitis, and dry mouth with the inhalator; and unpleasant taste with the sublingual tablets or lozenges. Excessive swallowing of nicotine released from oral replacement preparations may cause hiccups in the first few days of treatment.

References.

1. Greenland S, *et al.* A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998; **18:** 297–308.
2. Gourlay SG, *et al.* Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Safety* 1999; **20:** 545–55.

Adverse effects of tobacco products. Chronic use of tobacco is linked to a variety of diseases. By the mid-1960s, epidemiological data established tobacco smoking as a cause of lung cancer (p. 710.2). Smoking is also associated with cancers of the larynx, mouth, cervix, bladder, pancreas, oesophagus, stomach, and kidneys, and with leukaemia.[1] Smoking is a risk factor in cardiovascular, respiratory, and peripheral and cerebral vascular diseases.[1-4] Smoking also increases the risk of developing peptic ulcer disease and may affect other gastrointestinal disorders.[2] There is also evidence that smoking tobacco products increases the risk of developing age-related macular degeneration,[5] type 2 diabetes mellitus,[6] and adenomatous polyps.[7]

Maternal smoking in pregnancy is associated with low birth-weight infants and increased risk of abortion, stillbirth, and neonatal death (see also Pregnancy under Precautions, p. 2572.1).

Passive smoking refers to inhalation of secondhand tobacco smoke or environmental tobacco smoke. Risks to health from passive exposure are lower than those from active smoking. However, studies have established passive smoking as a cause of lung cancer;[8] passive smoking is also associated with increased risk of heart disease[9] and chronic respiratory disease.[10,11] Smokeless tobacco products also carry risks to health, for example the association of cancers of the head and neck (see p. 708.1) with the use of mixtures of tobacco and areca (p. 2446.3) and probably snuff or chewing tobacco.[12,13]

1. Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; **52:** 3–11.
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3. Teo KK, *et al.* INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; **368:** 647–58.
4. Patel RR, *et al.* Cigarette smoking and diffuse lung disease. *Drugs* 2008; **68:** 1511–27.
5. Tan JSL, *et al.* Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol* 2007; **125:** 1089–95.
6. Willi C, *et al.* Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007; **298:** 2654–64.
7. Botteri E, *et al.* Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008; **134:** 388–95.
8. Lam TH. Passive smoking in perspective. *Med Toxicol Adverse Drug Exp* 1989; **4:** 153–62.
9. Steenland K. Passive smoking and the risk of heart disease. *JAMA* 1992; **267:** 94–9.
10. Law MR, Hackshaw AK. Environmental tobacco smoke. *Br Med Bull* 1996; **52:** 22–34.
11. DiFranza JR, Lew RA. Mortality and morbidity in children associated with the use of tobacco products by other people. *Pediatrics* 1996; **97:** 560–8.
12. Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93:** 511–15.
13. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003; **58:** 435–43.

Effects on carbohydrate metabolism. Hyperinsulinaemia and insulin resistance have been associated with long-term use of nicotine gum.[1] Smoking tobacco products may increase the risk of developing type 2 diabetes mellitus (see above).

1. Eliasson B, *et al.* Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation* 1996; **94:** 878–81.

Effects on the cardiovascular system. As mentioned above, nicotine from tobacco products is associated with increased risk of cardiovascular disease. It would not be surprising, therefore, if nicotine replacement preparations were also associated with cardiovascular adverse effects, and there are anecdotal reports of cardiovascular events, including myocardial infarction,[1,2] stroke,[3,4] and cerebral haematoma,[5] associated with use of such products. However, a case-control study in the general population,[6] and both cohort studies[7] and short-term placebo-controlled studies[8,9] in patients with cardiovascular disease have failed to show any increased cardiovascular risk associated with transdermal nicotine. Results from a retrospective matched cohort study[10] of the use of nicotine replacement therapy (NRT) in patients immediately after coronary artery bypass graft (CABG) surgery showed an increase in mortality compared with CABG-patients who did not receive NRT. The authors suggest that NRT in critically ill patients should be restricted to use after patient discharge from hospital until data on inpatient usage are available from larger studies.

1. Warner JG, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994; **120:** 695.
2. Arnaot MR. Nicotine patches may not be safe. *BMJ* 1995; **310:** 663–4.
3. Pierce JR. Stroke following application of a nicotine patch. *Ann Pharmacother* 1994; **28:** 402.
4. Ang R, *et al.* Nicotine replacement therapy and ischaemic stroke. *Hosp Med* 2005; **66:** 366–7.
5. Riche G, *et al.* Intracerebral haematoma after application of nicotine patch. *Lancet* 1995; **346:** 777–8.
6. Kimmel SE, *et al.* Risk of acute first myocardial infarction and use of nicotine patches in a general population. *J Am Coll Cardiol* 2001; **37:** 1297–1302.
7. Meine TJ, *et al.* Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *Am J Cardiol* 2005; **95:** 976–8.
8. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994; **154:** 989–95.
9. Joseph AM, *et al.* The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996; **335:** 1792–8.
10. Paciullo CA, *et al.* Impact of nicotine replacement therapy on postoperative mortality following coronary artery bypass graft surgery. *Ann Pharmacother* 2009; **43:** 1197–1202.

Vasculitis. Vasculitis occurring in 2 patients was associated with transdermal nicotine patches.[1]

1. van der Klauw MM, *et al.* Vasculitis attributed to the nicotine patch (Nicotinell). *Br J Dermatol* 1996; **134:** 361–4.

Precautions

Nicotine preparations should not be used in patients who have had recent cerebrovascular accident. They should be used with caution in patients with cardiovascular disease. Use should preferably be avoided completely in severe cardiovascular disease, including during the immediate postmyocardial infarction period, and in patients with severe arrhythmias or unstable angina pectoris, although use under medical supervision may be considered if the patient is otherwise unable to stop smoking. They should be used with caution in those with peripheral vascular disease, in endocrine disorders including phaeochromocytoma, hyperthyroidism, and diabetes mellitus, in peptic ulcer disease, or renal or hepatic impairment. They should also be used with caution, and avoided if possible, during pregnancy or breast feeding (see p. 2572.1 and below, respectively).

Skin patches should not be used on broken skin.

Breast feeding. The American Academy of Pediatrics[1] notes that there have been reports of decreased milk production in breast-feeding mothers who smoke, and of decreased weight gain in the infant. There is, however, controversy regarding the effects of nicotine on infant size at 1 year of age. Although nicotine and its metabolite cotinine have been shown to be distributed into breast milk there are hundreds of compounds in tobacco smoke; nicotine is not necessarily the only component that might be detrimental to the breast-fed infant. Nicotine is present in breast milk in concentrations between 1.5 to 3 times the maternal plasma concentration, but there is no evidence documenting whether this amount of nicotine presents a health risk to the infant. Indeed, one study reported that the incidence of acute respiratory illness in infants whose mothers smoked was decreased in those who were breast fed when compared with those infants who were bottle fed.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/07/04)

Exercise. Physical exercise increased mean peak plasma concentrations of nicotine in 8 healthy subjects treated with a transdermal nicotine patch.[1] The effect was thought to be most likely due to increased skin perfusion resulting in increased uptake.

1. Klemsdal TO, *et al.* Physical exercise increases plasma concentrations of nicotine during treatment with a nicotine patch. *Br J Clin Pharmacol* 1995; **39:** 677–9.

Myasthenia gravis. A patient with myasthenia gravis noted worsening of his symptoms after application of transdermal nicotine patches, the effects being most severe about 1 hour after application, and resolving within 3 hours once the patch was removed.[1] Previous heavy smoking had not produced similar adverse effects, despite the fact that blood-nicotine concentrations are typically higher just after finishing a cigarette than when using the patch.[2]

1. Moreau T, *et al.* Nicotine-sensitive myasthenia gravis. *Lancet* 1994; **344:** 548–9.
2. Pethica D. Nicotine-sensitive myasthenia gravis. *Lancet* 1994; **344:** 961.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nicotine-contain-

ing products (used as aids for smoking cessation) as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 01/11/11)

Pregnancy. Cigarette smoking during pregnancy is associated with an increased risk of low birth-weight, spontaneous abortion, and perinatal mortality.[1] There is also some evidence of a possible association between smoking during pregnancy and the sudden infant death syndrome (SIDS).[2] In addition to nicotine, cigarette smoke contains many other chemicals, which are also fetal toxins, including carbon monoxide and lead.[3] Results from a study[4] in a large community sample showed that exposure to maternal smoking was associated with increased irritability and hypertonicity in neonates. Although smoking poses a far greater risk than pure nicotine, nicotine replacement therapy (NRT) is not without potential risks and should be reserved for mothers unable to quit with behavioural therapy alone.[3] It has been suggested that where NRT is required, the intermittent delivery formulations such as nicotine gum or inhalator, which expose the fetus to a lower total dose of nicotine, are preferable to continuous use formulations such as patches.[3]

1. British Medical Association. *Smoking and reproductive life: the impact of smoking on sexual, reproductive and child health*. London: British Medical Association, 2004. Available at: http://www.bma.org.uk/images/smoking_tcm41-21289.pdf (accessed 16/06/10)
2. Wisborg K, *et al*. A prospective study of smoking during pregnancy and SIDS. *Arch Dis Child* 2000; **83:** 203–6. Corrections. *ibid*. 2001; **84:** 93 and 187.
3. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001; **24:** 277–322.
4. Stroud LR, *et al*. Maternal smoking during pregnancy and neonatal behavior: a large-scale community study. Abstract: *Pediatrics* 2009; **123:** 1398–9. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/5/e842 (accessed 16/06/10)

Interactions

Tobacco smoking induces hepatic metabolic enzymes and the pharmacokinetics of many drugs are altered. Drugs such as methoxsalen which inhibit the cytochrome P450 isoenzyme CYP2A6 may decrease the metabolism of nicotine, resulting in increased plasma concentrations.

References.
1. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
2. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36:** 425–38.
3. Sellers EM, *et al*. Inhibition of cytochrome P450 2A6 increases nicotine's oral bioavailability and decreases smoking. *Clin Pharmacol Ther* 2000; **68:** 35–43.
4. Hukkanen J, *et al*. Effects of nicotine on cytochrome P450 2A6 and 2E1 activities. *Br J Clin Pharmacol* 2010; **69:** 152–9.

Interactions with tobacco smoking. For reports of possible interactions between tobacco smoking and some drugs, see:

- antipsychotics (see Chlorpromazine, p. 1053.2)
- atracurium, p. 2033.2
- benzodiazepines (see Diazepam, p. 1070.3)
- bupropion, see under Pharmacokinetics, p. 410.3
- corticosteroids, p. 1620.3
- fluvoxamine (see under Fluoxetine, p. 425.1)
- insulin, p. 486.2
- irinotecan, p. 814.2
- lidocaine, p. 1991.1
- melatonin, p. 2552.2
- pentazocine, p. 121.2
- quinine, p. 668.2
- theophylline, p. 1233.3
- tricyclic antidepressants (see Amitriptyline, p. 407.2)
- vecuronium, p. 2033.2

Nicotinic acid. As described on p. 2084.3, a possible interaction between nicotinic acid and nicotine from a transdermal patch has been reported.

Pharmacokinetics

Nicotine is readily absorbed through mucous membranes and the skin; bioavailability of oral nicotine is low due to extensive first-pass metabolism. Nicotine is widely distributed; it crosses the blood-brain barrier and the placenta and is found in breast milk. The elimination half-life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotinine and nicotine-*N*-oxide. Nicotine and its metabolites are excreted in the urine.

References.
1. Gorsline J, *et al*. Steady-state pharmacokinetics and dose relationship of nicotine delivered from Nicoderm (nicotine transdermal system). *J Clin Pharmacol* 1993; **33:** 161–8.
2. Gupta SK, *et al*. Bioavailability and absorption kinetics of nicotine following application of a transdermal system. *Br J Clin Pharmacol* 1993; **36:** 221–7.
3. Schneider NG, *et al*. Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokinet* 1996; **31:** 65–80.
4. Benowitz NL, *et al*. Sources of variability in nicotine and cotinine levels with the use of nicotine nasal spray, transdermal nicotine and cigarette smoking. *Br J Clin Pharmacol* 1997; **43:** 259–67.
5. Zins BJ, *et al*. Pharmacokinetics of nicotine tartrate after single-dose liquid enema, oral, and intravenous administration. *J Clin Pharmacol* 1997; **37:** 426–36.
6. Schneider NG, *et al*. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 2001; **40:** 661–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nicorette; Nicotinell TTS; NiQuitin; Niux; ***Austral.***: Nicabate; Nicorette; Nicotinell; QuitX; ***Austria***: Nicorette; Nicotinell; Nicotrol; NiQuitin; ***Belg.***: Nicopatch; Nicorette; Nicotinell; NiQuitin; ***Braz.***: Nicorette; Nicotinell TTS; NiQuitin; ***Canad.***: Habitrol; Nicoderm; Nicorette; Nicotrol†; Prostep†; Thrive; ***Chile***: Nicorette; Nicotinell; ***China***: Ao Fei Ni (奥菲尼); Nicorette (力克雷); Nicotinell (尼古泰); NiQuitin (力凯定); ***Cz.***: Nicopass†; Nicopatch†; Nicorette; Nicotinell†; NiQuitin; ***Denm.***: Nicodose; Nicorette; Nicotinell; Nicovel; Nikaloz; Zonnic; ***Fin.***: Nicopass; Nicopatch; Nicorette; Nicotinell; Nicotrol†; ***Fr.***: Nicogum†; Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; NiQuitinminis; ***Ger.***: Nicorette; Nicotinell†; nikofrenon; NiQuitin; ***Gr.***: Camryn; Exodus; Nicopass; Nicopatch; Nicorette; Nicotinell; ***Hong Kong***: Nicorette; Nicotinell; ***Hung.***: Nicopass†; Nicorette; Nicotinell; NiQuitin; ***India***: Nicotex-2; Nulife; ***Irl.***: Boots NicAssist; NCH; Nicopass; Nicorette; Nicotinell; NiQuitin; ***Israel***: Nicorette; Nicotinell; NiQuitin†; ***Ital.***: Nicorette; Nicotinell; NiQuitin; ***Malaysia***: Nicorette; Nicotinell; NiQuitin; ***Mex.***: Nicorette; NiQuitin; ***Neth.***: Exmo; Nicopass; Nicopatch†; Nicorette; Nicorol; Nicotinell; Niqero; NiQuitin; ***Norw.***: Nicorette; Nicotinell; Nicovel; ***NZ***: Habitrol; Nicabate†; Nicorette; Nicotinell; Nicotrol; ***Philipp.***: Nicorette; Nicotinell; ***Pol.***: Nicorette; Nicotinell†; NiQuitin; ***Port.***: Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***Rus.***: Nicorette (Никоретте); Nicotinell (Никотинелл); NiQuitin (НиКвитин); ***S.Afr.***: Nicorette; Quit; ***Singapore***: Nicorette; Nicotinell; Niquitin; ***Spain***: Nicorette; Nicotinell; NiQuitin; ***Swed.***: Nicorette; Nicotinell; Nikotugg†; NiQuitin; Zonnic; ***Switz.***: Nicorette; Nicotinell; ***Thai.***: Nicomild; Nicorette; Nicotinell; ***Turk.***: Nicotinell; ***UK***: Nicopass†; Nicopatch†; Nicorette; Nicotinell; NiQuitin; ***Ukr.***: Nicorette (Никоретте); ***USA***: Commit†; Habitrol; Nicoderm; NicoRelief; Nicorette; Nicotrol; Prostep; Thrive.

Homoeopathic Preparations. ***Canad.***: Nixotinex.

Pharmacopoeial Preparations
BP 2014: Nicotine Inhalation Cartridges; Nicotine Nasal Spray; Nicotine Resinate Medicated Chewing Gum; Nicotine Sublingual Tablets; Nicotine Transdermal Patches;
USP 36: Nicotine Polacrilex Gum; Nicotine Transdermal System.

Nitisinone *(USAN, rINN)*

Nitisinona; Nitisinonum; NTBC; SC-0735; Нитизинон.
2-(α,α,α-Trifluoro-2-nitro-*p*-toluoyl)-1,3-cyclohexanedione.
$C_{14}H_{10}F_3NO_5$=329.2
CAS — 104206-65-7.
ATC — A16AX04.
ATC Vet — QA16AX04.
UNII — K5BN214699.

Uses and Administration

Nitisinone is a 4-hydroxyphenylpyruvate dioxygenase inhibitor used in the management of hereditary tyrosinaemia type 1; dietary restriction of tyrosine and phenylalanine is also necessary. An initial daily dose of 1 mg/kg given orally is recommended; daily dosage should be given in 2 divided doses, which may be unequally split. Monitoring of urine succinylacetone and plasma alpha-fetoprotein, as well as liver function tests, must be carried out. If necessary, the daily dose may be increased to 1.5 mg/kg after one month; the maximum daily dose is 2 mg/kg. If satisfactory results are obtained from biochemical testing, doses should only be increased in line with body-weight gain.

Nitisinone is under investigation for the treatment of alkaptonuria, another hereditary metabolic disorder.

References.
1. Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). *J Inherit Metab Dis* 1998; **21:** 507–17.
2. Phornphutkul C, *et al*. Natural history of alkaptonuria. *N Engl J Med* 2002; **347:** 2111–21.
3. Gissen P, *et al*. Ophthalmic follow-up of patients with tyrosinaemia type I on NTBC. *J Inherit Metab Dis* 2003; **26:** 13–16.
4. Joshi SN, Venugopalan P. Experience with NTBC therapy in hereditary tyrosinaemia type I: an alternative to liver transplantation. *Ann Trop Paediatr* 2004; **24:** 259–65.
5. Suwannarat P, *et al*. Use of nitisinone in patients with alkaptonuria. *Metabolism* 2005; **54:** 719–28.
6. McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. *Drugs* 2006; **66:** 743–50.

Adverse Effects and Precautions

Adverse effects of nitisinone have included granulocytopenia, leucopenia, and thrombocytopenia; regular monitoring of platelet and white cell counts is recommended. Eye disorders may occur due to increases in plasma tyrosine; they include conjunctivitis, corneal opacity, keratitis, photophobia, and eye pain. Slit-lamp examination of the eyes is recommended before starting treatment; patients developing visual disturbances during treatment should be referred to an ophthalmologist immediately, and further dietary restrictions implemented if plasma tyrosine is too high. Although it is unknown if nitisinone is excreted into human milk, breast feeding is contra-indicated because of the potential effects on a suckling child.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Orfadin; Orfadin; ***Belg.***: Orfadin; ***Cz.***: Orfadin; ***Denm.***: Orfadin; ***Fin.***: Orfadin; ***Fr.***: Orfadin; ***Ger.***: Orfadin; ***Gr.***: Orfadin; ***Irl.***: Orfadin; ***Israel***: Orfadin; ***Neth.***: Orfadin; ***Norw.***: Orfadin; ***Pol.***: Orfadin; ***Port.***: Orfadin; ***Rus.***: Orfadin (Орфадин); ***Spain***: Orfadin; ***Swed.***: Orfadin; ***USA***: Orfadin.

Nitric Acid

Acide nitrique; Acidum Nitricum; Acidum Nitricum 70%; Aqua Fortis; Azotic Acid; Kwas azotowy; Kyselina dusičná 70%; Nit. Acid; Nitrato rūgštis; Nítrico, ácido; Salétromsav; Salpetersäure; Salpetersyra; Typpihappo.
HNO_3=63.01
CAS — 7697-37-2.
UNII — 411VRN1TV4.

Pharmacopoeias. In *Eur.* (see p. vii) (68 to 70%). Also in *USNF* (69 to 71%).

Ph. Eur. 8: (Nitric Acid). A clear, colourless to almost colourless liquid. Miscible with water. It contains 68.0 to 70.0% w/w of HNO_3. Protect from light.

USNF 31: (Nitric Acid). A highly corrosive fuming liquid, having a characteristic, highly irritating odour. It contains 69.0 to 71.0% w/w of HNO_3. Store in airtight containers.

Uses and Administration

Nitric acid has a powerful corrosive action and has been used to remove warts (p. 1689.3), but it should be applied with caution, and less corrosive substances are available. It has also been used for the removal of tattoos.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

There may be methaemoglobinaemia. Nitric acid stains the skin yellow.

Effects on the respiratory system. Respiratory failure due to pulmonary oedema occurred in a 56-year-old man after inhaling nitric acid which he had used as a metal cleaner.[1] The man died despite extensive ventilatory support.

1. Bur A, *et al*. Fatal pulmonary edema after nitric acid inhalation. *Resuscitation* 1997; **35:** 33–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***China***: Solcoderm (思可得); ***Ger.***: Solco-Derman; ***Hong Kong***: Solcoderm†; ***Pol.***: Solcogyn; ***Rus.***: Solcoderm (Солкодерм); Solcovagin (Солковагин); ***Switz.***: Solcoderm; Solcogyn; ***Ukr.***: Solcoderm (Солкодерм); Solcovagin (Солковагин).

Homoeopathic Preparations. ***Austria***: Argentum Med Complex; Erbiode Blasen und Nieren; ***Canad.***: Bioactiv H†; Cat Complex†; Detox L37; Echinacea L40†; Homeo-Form PMT†; PMS; Reneel†; Renelix; War Complex†; ***Chile***: Bioactiv H; ***Cz.***: Galium; Hormeel S; Lamioflur†; ***Fr.***: Cimicifuga Complexe No 21†; Echinacea Complexe No 40; Euphorbium Complexe No 88; Juniperus Complexe No 6; Mercurius Cyanatus Complexe No 43†; Rhododendron Complexe No 42†; Thuya Complexe No 37; Verrulia; ***Ger.***: Haemorrhoid-Gastreu N; Lowe-Komplex Nr 6; Onocalman; Regenaplex Haut W; Rufebran gastro†; Solidago Hevert Complex; Ulco-cyl L Ho-Len-Complex; ***Hung.***: Hormeel S; ***Neth.***: Akutur spag; Habifac; Opsonat; ***Rus.***: Helidonium-Plus (Хелидониум-Плюс); Hormeel SN (Гормель СН); Paeonia-Plus (Пеония-Плюс); ***Switz.***: Regenaplex Nr 28a; Regenaplex Nr 86a; Regenaplex Nr. 25b; Regenaplex Nr. 25c; Regenaplex Nr. 31a; Regenaplex Nr. 50b; Regenaplex Nr. 59b; Regenaplex Nr. 71b.

Pharmacopoeial Preparations
USP 36: Ferric Subsulfate Solution.

Nitrobenzene

Aceite de mirbana; Nitrobenceno; Nitrobenzen; Nitrobenzol; Oil of Mirbane.
$C_6H_5NO_2$=123.1

CAS — 98-95-3.
UNII — E57JCN6SSY.

Uses

Nitrobenzene is used in the manufacture of aniline, as a preservative in polishes, and in perfumery and soaps.

Adverse Effects

Nitrobenzene is highly toxic and the ingestion of 1 g may be fatal. Poisoning may occur from absorption through the skin, by inhalation, or by ingestion. Toxic effects are usually delayed for several hours and may include nausea, prostration, burning headache, methaemoglobinaemia with cyanosis, haemolytic anaemia, vomiting (with characteristic odour), convulsions, and coma, ending in death after a few hours.

Treatment of Adverse Effects

Although the benefit of gastric decontamination after ingestion of nitrobenzene is uncertain, gastric lavage or activated charcoal may be considered if given within 1 hour of ingestion. Methaemoglobinaemia may be treated with methylthioninium chloride. Oxygen should be given if cyanosis is severe.

If the skin or eyes are splashed with nitrobenzene, contaminated clothing should be removed immediately and the affected areas washed thoroughly with water at room temperature for at least 15 minutes.

Nix-0699

NOTE. The names Hemoxin, Nicosan, and Niprosan have been used as trade marks for nix-0699.

Profile

Nix-0699 is an extract of the leaf of *Sorghum bicolor* (sorghum), the stem of *Pterocarpus osun* (camwood), the seed of *Piper guineense* (Ashanti or Benin pepper), and the flower of *Syzygium aromaticum*; *Eugenia caryophyllus* (clove). It is being investigated in the treatment of sickle-cell disease.

Reviews.

1. Cordeiro NJV, Oniyangi O. Phytomedicines (medicines derived from plants) for sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 19/08/08).

Nucleic Acid

Acide Zymonucléique; Acidum Nucleicum; Nucleico, ácido; Nucleinic Acid; Нуклеиновая Кислота.

Profile

Nucleic acids, which are present in all cellular organisms and viruses, are composed of high molecular weight polynucleotides. A nucleotide is a phosphate ester of a nucleoside, which is made up of either a purine or pyrimidine nitrogenous base attached to a pentose sugar by an *N*-glycosidic linkage. Diester phosphate linkages between the sugar moieties produce a polynucleotide strand. Nucleic acids are of two types: deoxyribonucleic acid (DNA) (p. 2492.2) and ribonucleic acid (RNA) (p. 2604.1). Synthetic or recombinant nucleic acids are used in gene therapy (p. 2511.2).

Since the administration of nucleic acid gives rise to a marked temporary leucocytosis (usually preceded by a short period of leucopenia) it was formerly given in the treatment of a variety of bacterial infections in the hope of enhancing the natural defence mechanisms. Its therapeutic value, however, has never been established.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Nulip†.

Nutmeg

Muscade; Myristica; Noz Moscada; Nuez Moscada; Nux Moschata; Мускатный Орех.

*ATC Herb — HN02BG5009 (*Myristica fragrans*: seed); HA07XA5006 (*Myristica fragrans*: seed); HN05CM5016 (*Myristica fragrans*: seed); HA03AW5041 (*Myristica fragrans*: seed).*
UNII — AEE24M3MQ9.

Description. Nutmeg consists of the dried kernels of the seeds of *Myristica fragrans* (Myristicaceae), containing not less than 5% v/w of volatile oil; the powdered drug contains not less than 4% v/w. Mace (see Mace Oil, p. 2547.3) is the dried arillus of the seed of *M. fragrans*.

Pharmacopoeias. In *Chin.*

Uses and Administration

Nutmeg is the source of nutmeg oil (below). It is aromatic and carminative and is used as a flavour. Nutmeg has been reported to inhibit prostaglandin synthesis.

Homoeopathy

Nutmeg has been used in homoeopathic medicines under the following names: Myristica fragrans; Nux moschata; Nux mosch; Nux. mos.

References.

1. Barceloux DG. Nutmeg (*Myristica fragrans* Houtt.). *Dis Mon* 2009; **55:** 373–9.

Adverse Effects

Nutmeg, taken in large doses, may cause nausea and vomiting, flushing, dry mouth, tachycardia, stimulation of the CNS possibly with epileptiform convulsions, miosis or occasionally mydriasis, euphoria, and hallucinations. Myristicin and elimicin are thought to be the constituents responsible for the psychotic effects of nutmeg, possibly because of metabolism to amfetamine-like compounds.

Some references to the adverse effects of nutmeg.

1. Panayotopoulos DJ, Chisholm DD. Hallucinogenic effect of nutmeg. *BMJ* 1970; **1:** 754.
2. Brenner N, *et al.* Chronic nutmeg psychosis. *J R Soc Med* 1993; **86:** 179–80.
3. Sangalli BC, Chiang W. Toxicology of nutmeg abuse. *J Toxicol Clin Toxicol* 2000; **38:** 671–8.
4. Stein U, *et al.* Nutmeg (myristicin) poisoning—report on a fatal case and a series of cases recorded by a poison information centre. *Forensic Sci Int* 2001; **118:** 87–90.
5. Kelly BD, *et al.* Nutmeg and psychosis. *Schizophr Res* 2003; **60:** 95–6.
6. McKenna A, *et al.* Acute nutmeg poisoning. *Eur J Emerg Med* 2004; **11:** 240–1.
7. Demetriades AK, *et al.* Low cost, high risk: accidental nutmeg intoxication. *Emerg Med J* 2005; **22:** 223–5.
8. Forrester MB. Nutmeg intoxication in Texas, 1998-2004. *Hum Exp Toxicol* 2005; **24:** 563–6.
9. Pérez Valdivieso JR. Intoxicación aguda por nuez moscada. *Rev Esp Anestesiol Reanim* 2007; **54:** 633–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Klosterfrau Melissengeist; Mariazeller; Pervivo; ***Belg.***: Eau Des Carmes; ***Braz.***: Paratonico†; Vitonico; ***Cz.***: Dr Theiss Schwedenbitter†; Klosterfrau Melisana; Original Schwedenbitter; ***Ger.***: Klosterfrau Melissengeist; Melissengeist; ***Hung.***: Bano Svedkeseru; Bittner; Klosterfrau Melisana; ***India***: Diakof; Koflet; Laviril; Lukol; Mentat; Mustong; ***Pol.***: Melisana Klosterfrau; Pervivo; ***Rus.***: Doppelherz Melissa (Доппельгерц Мелисса); Fitovit (Фитовит); Himcolin (Химколин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Entressdruppels HM; Melissengeist†; Rooilavental; Spiritus Contra Tussim Drops†; ***Spain***: Agua del Carmen; ***UK***: Digestion Calming Drops; Melissa Comp.; ***Ukr.***: Bronchomed (Бронхомед); Fitovit (Фитовит); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trypsidan (Трипсидан)†.

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; Relax; ***Canad.***: Homeogene 46; Hylands Gas; ***Cz.***: Hepeel; Hormeel S; ***Fr.***: Eudyne†; Homeogene 46; ***Ger.***: Neuri-cyl N Ho-Len-Complex; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rowo Rytesthin Ro-Plex (Rowo-318); Rytesthin; Sedaphin†; Tamechol; ***Hung.***: Hepeel; Hormeel S; ***Neth.***: Speci-chol; ***Rus.***: Hormeel SN (Гормель СН); ***Switz.***: Hepeel; ***UK***: Cough Drops.

Nutmeg Oil

Ätherisches Muskatöl; Esencia de Nuez Moscada; Essence de Muscade; Essência de Moscada; Muskatų eterinis aliejus; Muskatöl; Muškátovníková silice; Muskotolja; Muskottiöljy; Myristica Oil; Myristicae Etheroleum; Myristicae Fragrantis Aetheroleum; Noix muscade, huile essentielle de; Nuez moscada, aceite esencial de; Oleum Myristicae; Szerecsendióolaj; Эфирное Масло Мускатного Ореха.

UNII — Z1CLM48948.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nutmeg Oil). The oil obtained by steam distillation of the dried and crushed kernels of *Myristica fragrans*. A colourless to pale yellow liquid with a spicy odour. Store in well-filled, airtight containers. Protect from light and heat.

Profile

Nutmeg oil is aromatic and carminative and is used as a flavour. Nutmeg oil and expressed nutmeg oil, a solid fat, are rubefacient. Nutmeg oil is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Vicks Vaporub; ***Austria***: Pe-Ce†; ***Belg.***: Vicks Vaporub; ***Braz.***: Vick Vaporub; ***Canad.***: Melisana†; Vaporizing Ointment†; ***Chile***: Agua Melisa Carminativa; ***Fr.***: Activox; Aromadetox†; Aromadigest†; Aromavital†; Vicks Vaporub; ***Ger.***: esto-gast; ***Gr.***: EKS; Revigel; ***Hung.***: Carmol; Kinder Luuf Balsam; ***NZ***: Vicks Vaporub; ***Pol.***: Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Wick Vaporub; ***Rus.***: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Doktor Mom (Доктор Мом); ***S.Afr.***: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Enterodyne†; Stuidruppels; Vicks Vaporub†; ***Spain***: Arkoresp†; ***Swed.***: Vicks Vaporub; ***Switz.***: Eucapinol; Vicks Vaporub N; ***Turk.***: Vicks Vaporub; ***UK***: Dragon Balm; No-Sor Vapour Rub; Nowax; ***Ukr.***: Doktor Mom (Доктор Мом); Rostiran (Розтиран); ***USA***: Vicks Vaporub.

Pharmacopoeial Preparations

BP 2014: Aromatic Ammonia Spirit.

Nux Vomica

Brechnuss; Noce Vomica; Noix Vomique; Nuez vómica; Strychni Semen; Чилибуха.

CAS — 357-57-3 (anhydrous brucine).
*ATC Herb — HA15WA5001 (*Strychnos nux-vomica*: seed); HA13AW5001 (*Strychnos nux-vomica*: seed).*
UNII — 269XH13919.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Nux vomica consists of the dried ripe seeds of *Strychnos nux-vomica* (Loganiaceae). It has the actions of strychnine (see p. 2623.2). As well as containing strychnine, nux vomica contains brucine which has similar properties.

Nux vomica is used in herbal medicine for several disorders including those of digestion or debility.

Homoeopathy

Nux vomica has been used in homoeopathic medicines under the following names: Nux vom.; Strychnos nux-vomica.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Mindac; Nervatona Calm; Nervatona Focus; ***Braz.***: Gotas Digestivas; ***Chile***: Fenokomp 39; ***India***: Arthrill; ***Mex.***: Bigenol†; ***Philipp.***: BSI Medicated Spray; ***Port.***: Cephyl†; ***Rus.***: Tentex (Тентекс); ***Spain***: Alofedina; ***Switz.***: Padma-Lax; Padmed Laxan; ***Thai.***: Corisul; Flataco; Flatulence†; Patarsul.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Childrens Sleep; Elimitona Slim & Detox; Elimitona; Hangover Relief; IBS Eze; Nervatona Calm; Nervatona Focus; Respatona Head Cold; Respatona Nasal Spray Decongestant; Snore Eze; Snorestop; Stomach Calm; Teething Relief; Travellers Relief; ***Austria***: Argentum Med Complex; Astomera; Gastricumeel; Katerex; Nux Med Complex; Nux Vomica-Homaccord; Schnarchex; Vomitusheel; ***Canad.***: Acne; Hylands Hemorrhoids; Hylands Motion Sickness; Hylands Upset Stomach; Kids Allergies; Passiflora Complex†; ***Chile***: Bioactiv S; Bioactiv V; ***Cz.***: Cocculine; Gastrocynesine; ***Fr.***: Abbe Chaupitre no 15†; Abbe Chaupitre no 18†; Abbe Chaupitre no 30†; Abbe Chaupitre no 82†; Abbe Chaupitre no 83†; Abbe Chaupitre no 88†; Aesculus Complexe No 103; Arnica Complexe no 1; Boripharm No 15†; Boripharm No 1†; Carominthe; Cholesterolum Complexe No 112†; Cocculine; Cocculus Complexe No 73; Crataegus Complexe No 15; Dolisedal†; Gastro-Drainol†; Gastrocynesine; Gelsemium Complexe No 70; Gentiana Complexe No 33†; Grindelia Complexe No 58; Homeogene 21†; L 107; L 114; Millefolium Complexe No 7†; Momordica Complexe No 109†; Nausetum; Nux Vomica Complexe No 49; Nux Vomica Compose; Oenanthe Crocata Complexe No 78; Polyrhinium; Rhododendron Complexe No 42†; Rhus Toxicodendron Complexe No 80; Soreal; Tabapass; Tamarindus Complexe No 95†; Tonique Vegetal; Veinosium†; Vinicard†; Yucca Complexe No 110; ***Ger.***: Arnica Oligoplex; Berberis N Oligoplex; Biodolor; Bomagall; Carminativum Hevert; Choanol N; Colintest-Gastreu; Femi-cyl L Ho-Len-Complex; gastri-loges N; Gastriseletct N; Gastro Magentabletten; Gastro-Pasc; Gelsemium Comp; Gripps; Haemorrhoid-Gastreu N; Hepa-Gastreu N R7; Heparanox H; Infi-China; Infifer N; Infinerval; Influvit; Jowidarmin; Jsostoma S; Leber Albin; Leber-Galletropfen; Lowe-Komplex Nr 6; Metaharonga; Mucosa compositum; Nervo-Plantin†; Nuvorell; Nux Vomica N Oligoplex; Nuxal comp; Nuxal H; Pflugerplex Gelsemium; Rheuma-Hevert; Rheuma-Hevert; Rheumaselect; Schwoneural N; Spasmo-Bomaleb†; Ventrigutt M; Vertigo-Hevert; ***Hung.***: Cocculine; ***Neth.***: Ambheel; Apo-STOM; Cocculine; Colintest-Gastreu R37; Collite; Cystilite; Gastricumeel; Gastrifleur; Gastrocynesine†; Gravifem†; Hepa-Gastreu R7; Hepeel H; Homeocare Digesto; Homeocare Vasco; Mucosa comp H; Nux Vomica-Homaccord; Rhodolith-Gastreu R46; Snurdim; Travelin; ***Port.***: Cocculine; Gastrocynesine; ***Rus.***: Berberis-Plus (Берберис-Плюс); Capsicum-Plus (Капсикум-Плюс); Cocculine (Коккулин); Helido-

nium-Plus (Хелидониум-Плюс); Nux Vom-Plus (Нукс Вом-Плюс); ***Switz.***: Cocculine; Gastricumeel; Gastronol; HerBalance; Lithiumeel; Nelsons Travella†; Polyrhinium; Regenaplex Nr. 12; Regenaplex Nr. 24c; Regenaplex Nr. 25a; Regenaplex Nr. 25b; Regenaplex Nr. 59b; Vomitusheel; ***UK***: Nausyn; Travella; ***USA***: Preferred Remedies Aches & Pains; Preferred Remedies Antacid; Preferred Remedies Detoxin.

Oak Bark

Chêne, écorce de; Common Oak; Corteza de roble; Dubová kůra; Durmast Oak; Écorce de Chêne; Eichenrinde; Ekbark; Kora dębowa; Quercus; Quercus cortex; Tammenkuori; Tölgyfakéreg; Ąžuolų žievė; Дубовая Кора.

*ATC Herb — HD03WA5008 (*Quercus robur*: bark); HA07XA5009 (*Quercus petraea*: bark); HD03WA5007 (*Quercus petraea*: bark); HA01WA5005 (*Quercus petraea*: bark); HA01WA5006 (*Quercus robur*: bark); HA07XA5010 (*Quercus robur*: bark).*

*UNII — 2JFK226947 (*Quercus robur *twig bark); ML644HED2V (*Quercus robur *flower); Q7MU1F4GLY (*Quercus robur *nut).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oak Bark). The cut and dried bark from the fresh young branches of *Quercus robur*, *Q. petraea*, and *Q. pubescens*. It contains a minimum of 3.0% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Oak bark contains quercitannic acid. It has astringent properties and is used in some herbal preparations. It was formerly used for haemorrhoids and as a gargle.

Homoeopathy

Oak bark has been used in homoeopathic medicines under the following names: Quercus; Quercus robur; Quercus rob.

The flowers of *Quercus robur* are used in homoeopathic medicines under the following names: Quercus robur, flos; Quercus rob, flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Urocalun (优克龙); ***Cz.***: Dubova Kura†; ***Hong Kong***: Urocalun†; ***Jpn***: Urocalun; ***Pol.***: Quecor; ***Singapore***: Urocalun; ***USA***: Amerigel.

Multi-ingredient Preparations. ***Austria***: Menodoron; ***Ger.***: Imupret; Menodoron; ***Hung.***: Gombarex; ***India***: Acneguard; ***Jpn***: Jidabokuippo; Jumihaidokuto; ***Pol.***: Arnisol; Dentosept A; Dentosept; Enterosol; Mucosit; Sanofil; Stomatosol; ***Rus.***: Polygemostat (Полигемостат); Stomatophit (Стоматофит); Tonsilgon N (Тонзилгон Н); ***S.Afr.***: Menodoron†; ***Switz.***: Kernosan Eau Dentifrice†; Kernosan Elixir; Menodoron; ***UK***: Peerless Composition Essence; ***Ukr.***: Imupret (Имупрет); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Tonsilgon N (Тонзилгон)†; ***USA***: Amerigel.

Homoeopathic Preparations. ***Canad.***: Homeodel 15†; ***Fr.***: Gentiana Complexe No 33†; Sels Calcaires Nutritifs; ***Ger.***: Lobelia comp; ***S.Afr.***: Aufbaukalk II†; ***UK***: Conchae comp..

Ocriplasmin *(USAN, rINN)*

Microplasmin; Ocriplasmina; Ocriplasmine; Ocriplasminum; Окриплазмин.

Truncated human plasmin: human plasmin heavy chain A-(543-561)-peptide (548-666;558-566)-bisdisulfide with human plasmin light chain B.

CAS — 1048016-09-6.

UNII — 7V6HE3DM5A.

Profile

Ocriplasmin is a recombinant proteolytic enzyme used in the treatment of symptomatic vitreomacular adhesion.

It is given by intravitreal injection into the affected eye in a single dose of 125 micrograms. Repeated injection of ocriplasmin in the same eye is not recommended. Treatment of the other eye, if required, is not recommended within 7 days of the initial injection, to allow monitoring for adverse effects in the injected eye.

Reported adverse effects include vitreous floaters, conjunctival haemorrhage, eye pain, photopsia, dyschromatopsia, and decreased visual acuity.

References.

1. Stalmans P, *et al.* MIVI-TRUST Study Group. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. *N Engl J Med* 2012; **367:** 606–15. Correction. *ibid.*; 2054.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Jetrea; ***USA***: Jetrea.

Octamylamine *(rINN)*

Octamilamina; Octamylaminum; Octisamyl hydrochloride (octamylamine hydrochloride); Октамиламин.

N-Isopentyl-1,5-dimethylhexylamine.

$C_{13}H_{29}N$=199.4

CAS — 502-59-0 (octamylamine); 5964-56-7 (octamylamine hydrochloride).

UNII — S0737084O9.

Profile

Octamylamine is a smooth muscle relaxant that has been used as an antispasmodic. The hydrochloride and mucate salts have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Octinum-D.

Octanoic Acid *(USAN, rINN)*

Acide caprylique; Acide Octanoïque; Ácido caprílico; Ácido octanoico; Ácido octílico; Ácido octoico; Acidum Caprylicum; Acidum Octanoicum; Caprylic Acid; Caprylsäure; Kaprilo rūgštis; Kaprilsav; Kaprylsyra; Kapryylihappo; Kwas kaprylowy; Kyselina oktanová; Octanoico, ácido; Octoic Acid; Octylic Acid; Октаноевая Кислота.

$CH_3.(CH_2)_6.CO_2H$=144.2

CAS — 124-07-2.

UNII — OBL58JN025.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Caprylic Acid; Octanoic Acid BP 2014). A clear, colourless or slightly yellowish, oily liquid. Very slightly soluble in water; very soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides.

USNF 31: (Caprylic Acid). A clear, colorless or slightly yellowish, oily liquid. Very slightly soluble in water; very soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

Sodium Octanoate *(rINNM)*

Caprilato sódico; Natrii Caprylas; Natrii Octanoas; Natrio kaprilatas; Natriumcaprylat; Nátrium-kaprilát; Natriumkaprylaatti; Natriumkaprylat; Natrium-oktanoát; Octanoate de Sodium; Octanoato de sodio; Octanoato sódico; Sodium Caprylate; Sodium, caprylate de; Натрия Октаноат.

$C_8H_{15}NaO_2$=166.2

CAS — 1984-06-1.

UNII — 9XTM81VK2B.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Caprylate). A white or almost white, crystalline powder. Very soluble or freely soluble in water; sparingly soluble in alcohol; freely soluble in acetic acid; practically insoluble in acetone. A 10% solution in water has a pH of 8.0 to 10.5.

USNF 31: (Sodium Caprylate). A white crystalline powder. Very soluble or freely soluble in water; sparingly soluble in alcohol; freely soluble in acetic acid; practically insoluble in acetone. A 10% solution in water has a pH of 8.0 to 10.5.

Profile

Octanoic acid and its salts have antifungal activity.

Sodium octanoate is used to stabilise albumin solution against the effects of heat. Octanoic acid labelled with carbon-13 has been used in a breath test to measure gastric emptying.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Caprilate†.

Olaquindox *(BAN, rINN)*

Bay-Va-9391; Olaquindoxum; Олахиндокс.

2-(2-Hydroxyethylcarbamoyl)-3-methylquinoxaline 1,4-dioxide.

$C_{12}H_{13}N_3O_4$=263.3

CAS — 23696-28-8.

ATC Vet — QJ01MQ01.

UNII — G3LAW9U88T.

Profile

Olaquindox is an antibacterial added to animal feedstuffs as a growth promotor. Photoallergic reactions in animal handlers have been reported on exposure to olaquindox.

Oleander

Adelfa; Baladre; Common Oleander; Espirradeira; Laurier Rose; Oleanderblätter; Oleandri Folium; Rose Bay; Олеандр.

*ATC Herb — HC01AX5003 (*Nerium oleander*: leaf); HC01AX5004 (*Nerium oleander*: root).*

*UNII — 7KV510R6H6 (*Nerium oleander *leaf); WO4WVF1WVM (*Nerium oleander *extract).*

Uses and Administration

The dried leaves of the oleander shrub, *Nerium oleander* (Apocynaceae), contain cardiac glycosides, including oleandrin. They have been used in the treatment of heart disorders. The flowers and bark have been used similarly.

Homoeopathy

Oleander has been used in homoeopathic medicines under the following names: Nerium oleander; Oleand.

Adverse Effects and Treatment

Oleander contains cardiac glycosides (see above) and toxicity, similar to that seen with digoxin, may occur after ingestion of any part of the plant; fatalities have been reported. Yellow oleander (*Thevetia peruviana*) also contains cardiac glycosides and has similar toxicity to oleander. Digoxin-specific antibody fragments may be used in the management of severe poisoning.

Treatment of adverse effects. References to the treatment of oleander poisoning or yellow oleander poisoning.

1. Shumaik GM, *et al.* Oleander poisoning: treatment with digoxin-specific Fab antibody fragments. *Ann Emerg Med* 1988; **17:** 732–5.
2. Safadi R, *et al.* Beneficial effect of digoxin-specific Fab antibody fragments in oleander intoxication. *Arch Intern Med* 1995; **155:** 2121–5.
3. Eddleston M, *et al.* Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial. *Lancet* 2000; **355:** 967–72.
4. Fonseka MM, *et al.* Yellow oleander poisoning in Sri Lanka: outcome in a secondary care hospital. *Hum Exp Toxicol* 2002; **21:** 293–5.
5. de Silva HA, *et al.* Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet* 2003; **361:** 1935–8.
6. Eddleston M, *et al.* Ox-Col Poisoning Study collaborators. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet* 2008; **371:** 579–87.
7. Peiris-John RJ, Wickremasinghe AR. Efficacy of activated charcoal in yellow oleander poisoning. *Ceylon Med J* 2008; **53:** 33–5.
8. Rajapakse S. Management of yellow oleander poisoning. *Clin Toxicol* 2009; **47:** 206–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Miroton†; ***Mex.***: Verisan Triplex.

Homoeopathic Preparations. ***Chile***: Bioactiv P; ***Fr.***: Boripharm No 23; Dermo-Drainol†; ***Ger.***: Arrhythmie-Gastreu N; Crataegus Herzcomplex; Hypotonie-Gastreu R44; ***Neth.***: Entero-Gastreu R4.

Olive

Oleae folium (olive leaf); Olivier, feuille d' (olive leaf); Маслина; Олива.

UNII — 6HD2W46UEG (green olive); 2M6QWV94OC (black olive).

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract.

Ph. Eur. 8: (Olive Leaf; Oleae Folium). The dried leaf of *Olea europaea*. It contains a minimum of 5.0% of oleuropein ($C_{25}H_{32}O_{13}$ = 540.5), calculated on the dried basis. Protect from light.

Profile

The fresh or dried leaf of the olive, *Olea europaea* (Oleaceae), is used in herbal medicine for its antihypertensive and diuretic actions.

Olive fruit is the source of olive oil, p. 2575.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Olivevital†; ***Ger.***: Olivysat†.

Multi-ingredient Preparations. ***Austral.***: Airborne Immunity; Bioage Peripheral†; Cats Claw-Echine; Cold & Flu Relief; Echinacea Royale; Olive Leaf Plus; ***Canad.***: Optomega; ***Fr.***: B.O.P.; Dida; Tavmet; Ultraselem; ***Ger.***: Antihypertonicum S; ***Switz.***:

Gouttes pour le coeur et les nerfs; ***Ukr.***: Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Cardiopress; Immunicare.

Olive Oil

Aceite de oliva; Alyvuogių aliejus; Azeite; Huile d'Olive; Olej z oliwek; Oliiviöljy; Olivae Oleum; Olivaolaj; Olive, huile d'; Olivenöl; Olivolja; Olivový olej; Оливковое Масло; Прованское Масло.

ATC Herb — HD02WB5006 (Olea europaea: oil).

UNII — 6UYK2W1W1E.

Pharmacopoeias. In *Jpn*. Also in *USNF*.

Eur. (see p. vii) includes monographs for virgin olive oil and refined olive oil.

Ph. Eur. 8: (Olive Oil, Virgin; Olivae Oleum Virginale). The fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea*. It is a clear, yellow or greenish-yellow, transparent liquid. When cooled it begins to become cloudy at 10 degrees and becomes a butter-like mass at 0 degrees. Practically insoluble in alcohol; miscible with petroleum spirit (50 degrees to 70 degrees). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

Ph. Eur. 8: (Olive Oil, Refined; Olivae Oleum Raffinatum). The fatty oil obtained by refining of crude olive oil. A suitable antoxidant may be added. It is a clear, colourless, or greenish-yellow, transparent liquid. When cooled it begins to become cloudy at 10 degrees and becomes a butter-like mass at about 0 degrees. Practically insoluble in alcohol; miscible with petroleum spirit (50 degrees to 70 degrees). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light. Store under an inert gas if intended for use in the manufacture of parenteral dosage forms.

USNF 31: (Olive Oil). The fixed oil obtained from the ripe fruits of *Olea europaea* (Oleaceae). It may contain suitable antoxidants. It is a pale yellow, or light greenish-yellow, oily liquid, having a slight characteristic odour. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store in airtight containers at a temperature not exceeding 40 degrees.

Profile

When taken internally, olive oil is nutrient, demulcent, and mildly laxative. It may also be given rectally (100 to 500 mL warmed to about 32 degrees) to soften impacted faeces (see Constipation, p. 1804.3).

Externally, olive oil is emollient and soothing to inflamed surfaces, and is used to soften the skin and crusts in eczema (p. 1684.1) and psoriasis (p. 1688.1), and as a lubricant for massage. It is used to soften ear wax (p. 1836.3).

Olive oil is used in the preparation of liniments, ointments, plasters, and soaps; it is also used as a vehicle for oily suspensions for injection.

Epidemiological evidence points to the cardiovascular benefits of olive oil in the diet. Olive leaf (p. 2574.3) is used in herbal medicine.

References.

1. Waterman E, Lockwood B. Active components and clinical applications of olive oil. *Altern Med Rev* 2007; **12:** 331–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Malaysia***: Olivenol livin' Begin†; Olivenol; ***Singapore***: Olivenol Livin' Active; Olivenol Livin' Begin; ***UK***: Arjun Ear Drops; ***Ukr.***: Vaxol (Ваксол).

Multi-ingredient Preparations. ***Arg.***: Clinoleic; ***Austral.***: Clinoleic; SMOFlipid; ***Austria***: Clinoleic; OliClinomel; PeriOlimel; SMOFlipid; ZentroOlimel; ***Belg.***: Clinoleic; OliClinomel; Olimel; PeriOlimel; ***Canad.***: Clinoleic; Olimel; PeriOlimel; Pure Gardens; ***Chile***: OliClinomel; ***Cz.***: Clinoleic; OliClinomel; Olimel; PeriOlimel; SMOFKabiven; SMOFlipid; ***Denm.***: Clinoleic; Numeta GE; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; ***Fin.***: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; ***Fr.***: Clinoleic; Maghora†; Menolistica; OliClinomel; Olimel; Olivalax; PeriOlimel; Phytosolaire†; SMOFKabiven; SMOFlipid; ***Ger.***: Clinoleic; Numeta GE; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; ***Gr.***: Clinoleic; Multimel; OliClinomel; SMOFKabiven; SMOFlipid; ***Hong Kong***: SMOFlipid; ***Hung.***: OliClinomel; SMOFlipid; ***India***: Efatop-PE; Elure; ***Irl.***: Clinoleic†; Numeta GE; OliClinomel; SMOFKabiven; SMOFlipid; Triomel; ***Israel***: Clinoleic; OliClinomel; SMOFKabiven; SMOFlipid; ***Ital.***: Acumel; Ad_3; Clinoleic; OliClinomel; Pasta Di Hoffmann; SMOFlipid; ***Malaysia***: Olivenol livin' Vigor†; Olivenol livin' Youthful†; ***Neth.***: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; ***Norw.***: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; ***NZ***: Clinoleic; OliClinomel; Snorenz; ***Pol.***: Clinoleic; SMOFKabiven; SMOFlipid; ***Port.***: Clinoleic; OliClinomel; SMOFKabiven; SMOFlipid; ***Rus.***: Oliclinomel (ОлиКлиномель); SMOFlipid (СМОФлипид); ***Singapore***: Clinoleic; Dhaxtra; Hepasil DTX†; Olivenol Livin' Vigor; Olivenol Livin' Youthful; Snoreeze; ***Spain***: Aceite Acalorico; Clinoleic; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; ***Swed.***: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; ***Switz.***: Clinoleic; Numeta; OliClinomel†; Olimel; PeriOlimel; SmofKabiven; SMOFlipid; ***Thai.***: Clinoleic; OliClinomel; SMOFlipid; ***Turk.***: Clinoleic; SMOFlipid; Snoreless; ***UK***: Clinoleic; OliClinomel; SMOFlipid; Snor-Away; ***Ukr.***: SMOFlipid (СМОФлипид); ***USA***: Clinolipid; Mimyx†.

Pharmacopoeial Preparations

BP 2014: Olive Oil Ear Drops.

Ololiuqui

CAS — 2889-26-1 (isoergine); 478-94-4 (ergine); 2390-99-0 (chanoclavine); 548-43-6 (elymoclavine); 602-85-7 (lysergol).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for 'morning glory' seeds:

Flying saucers; Glories; Heavenly blue; Pearly gates; Tlitlilzin; Yaxce'lil.

Profile

Ololiuqui consists of the seeds of *Rivea corymbosa* or *Ipomoea tricolor* (*I. violacea*) both convolvulaceous plants similar to the garden plant 'morning glory', *Ipomoea purpurea*. The brown seeds of *R. corymbosa* are known as 'badoh' and the black seeds of *I. tricolor* as 'badoh negro'.

Ololiuqui has hallucinogenic properties and is considered to be sacred by some Mexican Indians. Alkaloidal fractions contain at least 5 closely related individual components, namely D-isolysergic acid amide (isoergine), D-lysergic acid amide (ergine), chanoclavine, elymoclavine, and lysergol.

The name 'ololiuqui' has been erroneously applied to seeds of *Datura meteloides* (Solanaceae).

Omega-6 Fatty Acids

n-6 Fatty Acids; Omega 6 Acids; Omega 6 Fatty Acids.

UNII — 116Z6MZN1M.

Profile

Omega-6 fatty acids are long-chain polyunsaturated fatty acids similar to omega-3 fatty acids (p. 1460.1) but with the first double bond in the n-6 position. They include arachidonic acid (p. 2446.1), linoleic acid (p. 2509.2), and gamolenic acid (p. 2509.2). Mixtures of omega-6 fatty acids, for example from evening primrose oil (p. 2502.2), have been used in skin-care products and nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Exomega; ***Chile***: Exomega; ***Fr.***: Exomega; Nutrilarm; Omegacoeur; ***India***: Eriz; ***Indon.***: Curbexon; ***Ital.***: Eutears; Skinproject; ***Venez.***: Exomega.

Onion

Cebolla; Cipolla; Oignon; Zwiebel; Лук Репчатый.

ATC Herb — HC10AW5001 (Allium cepa: bulb).

UNII — 492225Q21H.

Profile

Onion is the bulb of *Allium cepa* (Liliaceae). It has been reported to reduce platelet aggregation, lower serum cholesterol, and to enhance fibrinolysis. It has been used in preparations for the treatment of urinary-tract disorders and in topical preparations for scars and contractures.

Homoeopathy

Onion has been used in homoeopathic medicines under the following names: Cepa; Allium cepa; All. cepa.

General references.

1. WHO. Bulbus Allii Cepae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/3.html (accessed 05/02/10)

Cardiovascular disease. A review of controlled studies purporting to show beneficial effects of garlic and/or onion on cardiovascular risk factors found those studies to have severe methodological failings.[1]

1. Kleijnen J, *et al*. Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol* 1989; **28**: 535–44.

Stings. An onion bulb was used to treat the wound caused by a blue-spotted stingray (*Dasyatis kuhlii*).[1] Pain relief occurred within 30 minutes.

1. Whiting SD, Guinea ML. Treating stingray wounds with onions. *Med J Aust* 1998; **168:** 584.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mederma†; ***Israel***: Mederma; ***Malaysia***: Mederma; ***Pol.***: Alcep; ***Rus.***: Allilchep (Аллилчеп); ***Singapore***: Mederma; ***USA***: Mederma.

Multi-ingredient Preparations. ***Arg.***: Contractubex; Integrum; ***Austral.***: Garlic Allium Complex; Gartech†; ***Austria***: Contractubex; ***Braz.***: Contractubex; ***China***: Contractubex (康瑞保); ***Cz.***: Contractubex; ***Fr.***: Amana Cellium; Androlistica; Pelvimag; ***Ger.***: Contractubex; ***Gr.***: Contractubex; ***Hong Kong***: Contractubex; ***Hung.***: Contractubex; ***India***: Contractubex; Hexilak; ***Indon.***: Mederma; ***Ital.***: Skarflex; ***Malaysia***: Palmer's Cocoa Butter Formula Scar Serum; ***Mex.***: Contractubex; Mederma; ***Philipp.***: Contractubex; Hiruscar; ***Pol.***: Alcepalan†; Cepan; Cepasmel; Cepastil; Contractubex; ***Rus.***: Contractubex (Контрактубекс); ***Singapore***: Androlistica; Erase; Hiruscar; Scar Esthetique; ***Switz.***: Contractubex; ***Turk.***: Contractubex; ***Ukr.***: Contractubex (Контрактубекс); Uronephron (Уронефрон).

Homoeopathic Preparations. ***Austral.***: Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Hay Fever; Respatona Head Cold; ***Austria***: Apozema Allium Cepa compositum; Cepa Med Complex; Famulan; Globuli gegen Heiserkeit; Globuli gegen Schnupfen Nr 1; Luffa Med Complex; ***Canad.***: Allergies; Allergy Relief†; Cold Tablets with Zinc†; Coryzalia; EnurAid; Hay Complex†; Hay Fever; Hayfever; Homeo-Form AL†; Homeo-Form SI†; Homeodel 15†; Homeodel 21†; Hylamine HF; Hylands Formula CZ; Hylands Formula E; Kids Allergies; Pollen Plus; Sabalia; Sinus; ***Chile***: Allium Compuesto; Rinoplex; ***Cz.***: Coryzalia; Rhinallergy; ***Fr.***: Allium Cepa Compose; Coryzalia; Dolistamine†; Polyrhinium; Rhinallergy; ***Ger.***: Muco-cyl L Ho-Len-Complex; Schleimhaut-Komplex L Ho-Fu-Complex; Sinapis nigra N Oligoplex; ***Hung.***: Coryzalia; ***Neth.***: Cold Care; Coryzalia; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Mercurialis zalf; Nisyspray; Sniffle Care; ***Port.***: Coryzalia; ***Rus.***: Coryzalia (Коризалия); Famulan (Фамулан); ***Switz.***: Alceprin-N; Coryzalia; Gouttes contre les rhumes des foins†; Nelsons Pollenna†; Polyrhinium; Rhinallergy; Spagyrhin; ***UK***: Pollenna; ***Ukr.***: Coryzalia (Коризалия); ***USA***: Preferred Remedies Allergy; Preferred Remedies Sinus.

Ononis

Arrête-Boeuf; Bugrane, racine de; Busktörnerot; Dirvenių šaknys; Gatuña; Hauhechelwurzel; Jehlicový kořen; Ononidis Radix; Piikkiorakonjuuri; Racine de Bugrane; Radix Ononidis; Restharrow Root; Spiny Restharrow; Tövisesiglice-gyökér; Стальник Колючий (*Ononis spinosa*).

ATC Herb — HG04BW5023 (Ononis spinosa: root).

UNII — RP8496915M (Ononis spinosa); FD2FMC53M1 (Ononis spinosa root).

Pharmacopoeias. In *Eur*. (see p. vii).

Ph. Eur. 8: (Restharrow Root). The whole or cut, dried root of *Ononis spinosa*.

Profile

Ononis has diuretic activity. It has been used in herbal preparations for the treatment of oedema, urinary-tract disorders, rheumatic disorders, and constipation.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Nierentee St Severin; Uropurat†; ***Canad.***: Entschlackungstee N†; ***Cz.***: Species Urologicae Planta; Urologicka Cajova Smes; ***Fr.***: Depuratum; Schoum; ***Ger.***: Alasenn; Aqualibra; Biofax†; Hevert-Blasen-Nieren-Tee N†; Nephroselect M; Renob Blasen- und Nierentee†; ***Ital.***: Slimmer Plus; Soluzione Schoum; ***Pol.***: Betasol; Diuronis; ***Rus.***: Herbion Urological Drops (Гербион Урологические Капли); ***Switz.***: Demonatur Dragees pour les reins et la vessie†; Herbaprosta-Caps N†; Nephrosolid; ***Ukr.***: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†.

Homoeopathic Preparations. ***Canad.***: Male +; ***Cz.***: Galium; ***Fr.***: Berberis Complexe No 83; L 8; ***Ger.***: Heweberberol; metasolidago S†; Pascodem.

Bitter Orange

Aurantii amari flos (bitter-orange flower); Aurantii Amari Pericarpium (bitter orange fruit); Bigaradier; Chéng Pí; Karčiavaisių citrinmedžių žiedai (bitter-orange flower); Keserű narancs virág (bitter-orange flower); Květ hořkého pomeranče (bitter-orange flower); Naranja Amarga; Naranja amarga, corteza de; Oranger amer, fleur d' (bitter-orange flower); Owocnia pomarańczy gorzkiej (bitter orange fruit); Pomeransblomma (bitter-orange flower); Pomeranssinkukka (bitter-orange flower); Pomeranze; Seville Orange; Померанец; Апельсин.

ATC Herb — HN05CM5002 (Citrus aurantium: *flower*); *HA03AW5013* (Citrus aurantium: *peel*); *HA09WA5008* (Citrus aurantium: *peel*).
UNII — 055456JHI7 (Citrus aurantium *fruit rind*); *DQD16J2B5O* (Citrus aurantium *fruit*); *O730ZX2Z83* (Citrus aurantium *flower*).

Pharmacopoeias. *Eur.* includes the dried peel and flowers. *Jpn* includes the peel.

Ph. Eur. 8: (Bitter-orange Epicarp and Mesocarp; Aurantii amari epicarpium et mesocarpium; Dried Bitter-orange Peel BP 2014). The dried epicarp and mesocarp of the ripe fruit of *Citrus aurantium*, partly freed from the white spongy tissue of the mesocarp and endocarp, containing a minimum of 2.0% v/w of essential oil, calculated with reference to the anhydrous drug. It has an aromatic odour and a spicy bitter taste.

Ph. Eur. 8: (Bitter-orange Flower; Aurantii amari flos). The whole, dried, unopened flower of *C. aurantium* subsp. *aurantium* containing a minimum of 8.0% of total flavonoids, expressed as naringin ($C_{27}H_{32}O_{14} = 580.5$), calculated with reference to the dried drug.

Profile

The dried peel of the bitter orange, *Citrus aurantium* subsp. *aurantium* (*Citrus aurantium* subsp. *amara*) (Rutaceae) is used as a flavour and for its bitter and carminative properties. Bitter-orange oil is an essential oil prepared from fresh bitter-orange peel that is similar to sweet orange oil (below). Both bitter-orange oil and petitgrain bigarade oil (prepared from the leaves and twigs) are used in aromatherapy.

The flowers are an ingredient of herbal remedies used for nervous and sleep disorders. Bitter-orange flower is the source of Neroli Oil (p. 2568.3).

The whole dried immature fruit is used similarly to the dried peel. In Chinese medicine, the dried immature fruits are known as zhi shi and zhi qiao. Extracts of bitter orange may have sympathomimetic properties (see below).

Photosensitivity is associated with citrus oils.

Action and use. *Citrus aurantium* was one of the most frequently used herbal remedies in Puerto Rico.[1] Indications included sleep disorders, gastrointestinal disorders, respiratory ailments, and raised blood pressure.

The volatile oil of dried bitter-orange peel has shown antifungal activity.[2]

Bitter-orange extract has been added to herbal weight loss remedies as it contains the sympathomimetic synephrine (a name that has been used for both phenylephrine and oxedrine), which is claimed to increase metabolism and promote thermogenesis, although efficacy is not proven. Variant angina[3] and ischaemic colitis[4] have been reported in patients taking dietary supplements containing bitter orange, and reports of serious cardiovascular adverse effects possibly associated with the synephrine content of bitter orange present in such preparations have been received in Canada.[5,6] Raised systolic and diastolic blood pressure and heart rate were seen after ingestion of a proprietary bitter orange preparation in one small randomised placebo-controlled crossover study.[7] However, in a similar study[8] comparing a single-ingredient bitter orange preparation with a combination preparation, adverse haemodynamic effects appeared to be related to the additional presence of other possible stimulants such as caffeine, rather than directly proportional to the dose of bitter orange alone.

1. Hernández L, *et al.* Use of medicinal plants by ambulatory patients in Puerto Rico. *Am J Hosp Pharm* 1984; **41:** 2060–4.
2. Ramadan W, *et al.* Oil of bitter orange: new topical antifungal agent. *Int J Dermatol* 1996; **35:** 448–9.
3. Gange CA, *et al.* Variant angina associated with bitter orange in a dietary supplement. *Mayo Clin Proc* 2006; **81:** 545–8.
4. Sultan S, *et al.* Ischemic colitis associated with use of a bitter orange-containing dietary weight-loss supplement. *Mayo Clin Proc* 2006; **81:** 1630–1.
5. Health Canada. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. *Can Adverse React News* 2004; **14** (4): 3–4. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 06/08/08)
6. Health Canada. Bitter orange or synephrine: update on cardiovascular adverse reactions. *Can Adverse React News* 2007; **17** (2): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 06/08/08)
7. Bui LT, *et al.* Blood pressure and heart rate effects following a single dose of bitter orange. *Ann Pharmacother* 2006; **40:** 53–7.
8. Haller CA, *et al.* Hemodynamic effects of ephedra-free weight-loss supplements in humans. *Am J Med* 2005; **118:** 998–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Calmtabs; ***Austral.***: Kick-Start Detox; Metabolift Fat Burner; ***Austria***: China-Eisenwein†; Eicebaer; Klosterfrau Melissengeist; Mariazeller; Montana; Pervivo; Sigman-Haustropfen; St Bonifatius-Tee†; Tussimont; ***Braz.***: A Saude da Mulher; ***Canad.***: Trim-Fit†; ***Chile***: Propolkit; ***Cz.***: Klosterfrau Melisana; ***Fr.***: Biofirm; Boribel Tisane No 8†; Calmotisan†; Diatisan†; Elixir Bonjean†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Quintonine†; Santane N9; Solaire; Vegetoserum†; ***Ger.***: Amara-Pascoe; Carminativum-Hetterich; Gallexier; Klosterfrau Melissengeist; Montana N; Sedovent†; ***Hung.***: Bittner; China; Klosterfrau Melisana; Montana; ***Indon.***: Jesscool†; ***Israel***: Passiflora; ***Ital.***: Altadrine; Gastro-Pepsin; Idren; ***Pol.***: Doppelherz Energovital Tonik†; Herbaton†; Krople Zoladkowe†; Krople Zoladkowe; Pervivo; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Melissa (Доппельгерц Мелисса); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.***: Versterkdruppels; ***Singapore***: Bio-Taches†; Chitosano; ***Spain***: Sedonat; ***Switz.***: DemoPectol; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; ***Turk.***: Nevrol Cemal; ***UK***: Vital Eyes; ***Ukr.***: Lipomin (Липомин); Liponorm (Липонорм).

Homoeopathic Preparations. ***Fr.***: Poconeol no 58.

Pharmacopoeial Preparations
BP 2014: Concentrated Compound Gentian Infusion; Concentrated Orange Peel Infusion; Orange Peel Infusion; Orange Syrup;
Ph. Eur.: Bitter-Orange-Epicarp and Mesocarp Tincture.

Sweet Orange

Naranja; Апельсин Сладкий.
ATC Herb — HA09WA5009 (Citrus aurantium: *unripe fruit*).

Pharmacopoeias. *Swiss* includes the ripe fresh fruit of *Citrus sinensis*.

Chin. includes under the name Immature Orange Fruit (Fructus Aurantii Immaturus; Zhishi) both the dried immature fruit of *Citrus aurantium* and its cultivated varieties or the dried young fruit of *C. sinensis*.

Profile

Sweet orange, *Citrus sinensis* (*Citrus aurantium* var. *dulcis*) (Rutaceae), is an ingredient of herbal remedies used for nervous and sleep disorders. The peel is the source of sweet orange oil (below). Citrus fruits are a source of vitamin C (p. 2110.3).

Photosensitivity is associated with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: GR² Control Appetite Reducer; Vitamin C - Threshold Controlled; ***Austria***: Magentee St Severin; Mariazeller; Pervivo; ***Canad.***: Floradix Kindervital†; Salusan†; ***Cz.***: Passedan†; ***Fr.***: Calmiflorine†; Santane V3†; ***Hung.***: Bittner; ***Pol.***: Pervivo; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***Switz.***: Femisan.

Pharmacopoeial Preparations
USNF 31: Orange Syrup; Sweet Orange Peel Tincture.

Sweet Orange Oil

Apelsininių citrinmedžių vaisių žievelių eterinis aliejus; Apelsinolja; Appelsiininkuoriöljy; Arancia Dolce Essenza; Aurantii Dulcis Aetheroleum; Aurantii Dulcis Pericarpii Etheroleum; Essence of Orange; Essence of Portugal; Essência de Laranja; Naranja, aceite esencial de; Orange douce, huile essentielle d'; Orange Oil; Silice oplodí sladkého pomeranče; Süssorangenschalenöl; Масло Сладкого Апельсина; Апельсиновое Масло, Сладкое.
ATC Herb — HN05CM5001 (Citrus aurantium: *essential oil*).
UNII — AKN3KSD11B.

NOTE. The oil from the flowers of *Citrus aurantium* var. *amara* is known as neroli oil or orange flower oil (p. 2568.3).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Sweet Orange Oil). An essential oil obtained without heating, by suitable mechanical treatment from the fresh peel of the fruit of *Citrus sinensis* (*Citrus aurantium* var. *dulcis*). A suitable antoxidant may be added. It contains 0.4 to 0.6% α-pinene, 0.02 to 0.3% β-pinene, 0.2 to 1.1% sabinene, 1.7 to 2.5% β-myrcene, 92.0 to 97.0% limonene, 0.1 to 0.4% octanal, 0.1 to 0.4% decanal, 0.2 to 0.7% linalol, 0.02 to 0.10% neral, 0.02 to 0.5% valencene, and 0.03 to 0.02% geranial.

A clear, pale yellow to orange, mobile liquid, which may become cloudy when chilled. It has a characteristic odour of fresh orange peel. Relative density 0.842 to 0.850. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Orange Oil). The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Rutaceae), containing not less than 1.2% w/v and not more than 2.5% w/v of aldehydes, calculated as decanal ($C_{10}H_{20}O = 156.3$). It may be California-type or Florida-type orange oil. Store in well-filled airtight containers.

Profile

Sweet orange oil is used as a flavour, in perfumery, and in aromatherapy. It is used in the preparation of terpeneless orange oil. Photosensitivity reactions have been reported with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; ***Canad.***: Melisana†; ***Cz.***: Coldastop; Pleumolysin; ***Fr.***: Aromadetox†; Aromazen†; Thermo Gomenol; ***Ger.***: GeloSitin; ***Hong Kong***: Magesto; ***Hung.***: Perskindol Classic; ***Malaysia***: Bio-Enhanced Fish Oil Plus; ***Switz.***: Perskindol Classic; Perskindol Classic; Sibrovita†; ***Turk.***: Myo-Oil; Nevrol Cemal.

Pharmacopoeial Preparations
USNF 31: Compound Orange Spirit.

Terpeneless Orange Oil

Naranja sin terpeno, aceite esencial de; Oleum Aurantii Deterpenatum; Апельсиновое Масло Бестерпеновое.

Pharmacopoeias. In *Br.*

BP 2014: (Terpeneless Orange Oil). A clear yellow or orange-yellow liquid, visibly free from water, with the odour and taste of orange, prepared by concentrating orange oil under reduced pressure until most of the terpenes have been removed, or by solvent partition. It contains not less than 18% w/w of aldehydes calculated as decanal ($C_{10}H_{20}O = 156.3$). Soluble 1 in 1 of alcohol (90%). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Terpeneless orange oil consists chiefly of the free alcohols (+)-linalol and (+)-terpineol. It is used as a flavour. It is stronger in flavour and more readily soluble than the natural oil. Photosensitivity is associated with citrus oils.

Preparations

Pharmacopoeial Preparations
BP 2014: Compound Orange Spirit.

Orazamide *(rINN)*

AICA Orotate; Orazamida; Orazamidum; Oroxamide; Оразамид.
5-Aminoimidazole-4-carboxamide orotate dihydrate.
$C_9H_{10}N_6O_5.2H_2O = 318.2$
CAS — 2574-78-9 (anhydrous orazamide); 60104-30-5 (orazamide dihydrate).
UNII — CLY9MRR8FV.

Profile

Orazamide has been given orally in the treatment of liver disorders.

Orchis Mascula

Early Purple Orchid; Ятрышник Мужской.
UNII — 4119KOT30J (Orchis mascula); *6H1JQK35LA* (Orchis mascula *flower*).

Profile

Orchis mascula, which is alleged to have aphrodisiac properties, has been used in herbal preparations for male sexual disorders.

Salep, a flour made from the dried ground tubers of *Orchis mascula* and various other species of orchid, contains a nutritious mucilage called bassorin; ice-cream made from salep is a great delicacy in Turkey.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Speman (Спеман); Speman Forte (Спеман Форте); Tentex (Тентекс); ***Ukr.***: Confido (Конфидо)†; Speman (Спеман); Trypsidan (Трипсидан)†.

Oregano

Dost; Dosteńkraut; Origan; Origani herba; Origani Vulgaris Herba; Wild Marjoram; Оригано.
CAS — 8007-11-2 (origanum oil).
UNII — 0E5AT8T16U (oregano); 38SNL0F81Z (Origanum vulgare *subsp.* hirtum); *39736Z7Q8W (origanum oil).*

NOTE. Distinguish from Marjoram, p. 2550.1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oregano). The dried leaves and flowers, separated from the stems, of *Origanum onites* or *O. vulgare* subsp. *hirtum*, or a mixture of both species. It contains a minimum of 2.5% v/w of essential oil, which contains a minimum of 60% of carvacrol and thymol, calculated with reference to the anhydrous drug. Protect from light.

Profile

The aerial parts of oregano, *Origanum onites* (Lamiaceae), or *O. vulgare* or its subspecies, are used as a culinary herb and in herbal preparations.

There is some confusion over the naming of origanum oils. Oil from *O. vulgare* has been used medicinally. Origanum Oil is the oil obtained from *Coridothymus capitatus* (*Thymus capitatus*) but oils from other related species may also be referred to as origanum oils, and Oil of Origanum was also given as a synonym for Thyme Oil in BPC 1949. Preparations listed in *Martindale* as containing origanum oil may contain an oil from any of these related species.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Austria***: Asthmatee EF-EM-ES; Baby Luuf; ***Canad.***: Defense; Para-Gone; Relax Plus; ***Cz.***: Bronchosan†; Fytokliman Planta; ***Fr.***: Dida; Santane D_5†; ***Hung.***: Baby Luuf; ***Pol.***: Herbolen D†; Herbolen†; ***Rus.***: Bronchosan (Бронхосан); Pectorales Species No 1 (Грудной Сбор 1); Sedativae Species No 3 (Седативный Сбор 3); Urocholesan (Урохолесан); Valoserdin (Валосердин); ***Spain***: Pazbronquial; ***Switz.***: Demonatur Capsules contre les refroidissements; ***Ukr.***: Bronchosan (Бронхосан)†; Klimased (Климасед); Urolesan (Уролесан).

Homoeopathic Preparations. ***Fr.***: Poconeol no 9.

Oregon Grape

Barberry; Holly Barberry; Mahonia; Mountain Grape; Sowberry; Магония Падуболистная (*Mahonia aquifolium*).

ATC Herb — HN02BW5004 (Mahonia aquifolium: *bark*); *HD05AX5002* (Mahonia aquifolium: *bark*).

UNII — J4WG1JVR05 (Mahonia aquifolium); *P119855ERN* (Mahonia aquifolium *fruiting top*); *746TB9VNDP* (Mahonia aquifolium *root*); *VZJ9F3C35B* (Mahonia aquifolium *root bark*).

NOTE. The names Barberry, Oregon Grape, and Sowberry have been applied to both Oregon Grape and European Barberry (see p. 2502.1).

Profile

The rhizome and root of the Oregon grape, *Berberis aquifolium* (*Mahonia aquifolium*) (Berberidaceae) is used orally in herbal medicine mainly for gastrointestinal disorders and topically for skin disorders.

Berberis aquifolium is a source of berberine (p. 2455.1).

Homoeopathy

Oregon grape has been used in homoeopathic medicines under the following names: Berberis aquifolium; Berber aqui; Berb. aq.

References.

1. Gulliver WP, Donsky HJ. A report on three recent clinical trials using Mahonia aquifolium 10% topical cream and a review of the worldwide clinical experience with Mahonia aquifolium for the treatment of plaque psoriasis. *Am J Ther* 2005; **12:** 398–406.
2. Bernstein S, *et al.* Treatment of mild to moderate psoriasis with Reliéva, a Mahonia aquifolium extract—a double-blind, placebo-controlled study. *Am J Ther* 2006; **13:** 121–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: DermaCo; ***Ukr.***: Hepahealth (Гепахелс).

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; ***Austria***: Rubisan; Sensicare; ***Canad.***: Endoteel†; ***Cz.***: Rubisan; ***Fr.***: Euphorbium Complexe No 88; ***Ger.***: Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Derma-Plantin†; Ekzevowen; Hewelymphon N†; Rubisan; ***Hung.***: Rubisan; ***Neth.***: Rubisan†; ***Rus.***: Psoriaten (Псориатен); ***Switz.***: Omida Rubiderm; ***Ukr.***: Psoriaten (Псориатен).

Orlistat *(BAN, USAN, rINN)*

Orlipastat; Orlistaatti; Orlistatum; Ro-18-0647; Ro-18-0647/002; Tetrahydrolipstatin; Орлистат.

N-Formyl-L-leucine, ester with (3*S*,4*S*)-3-hexyl-4-[(2*S*)-2-hydroxytridecyl]-2-oxetanone; (*S*)-1-[(2*S*,3*S*)-3-Hexyl-4-oxooxetan-2-ylmethyl]dodecyl *N*-formyl-L-leucinate.

$C_{29}H_{53}NO_5$=495.7

CAS — 96829-58-2.

ATC — A08AB01.

ATC Vet — QA08AB01.

UNII — 95M8R751W8.

Pharmacopoeias. In *US.*

USP 36: (Orlistat). A white to off-white fine powder or fine powder with lumps. Practically insoluble in water; very soluble in methyl alcohol and in alcohol; freely soluble in chloroform. Store at a temperature between 2 degrees and 8 degrees.

Uses and Administration

Orlistat is a gastric and pancreatic lipase inhibitor that limits the absorption of dietary fat. It is used together with dietary modification in the management of obesity (p. 2315.1), i.e. in patients with a BMI of 30 kg/m^2 or greater. It may also be used in overweight patients with a BMI of 27 kg/m^2 or more if there are associated risk factors. Orlistat is given orally in a usual dose of 120 mg three times daily, immediately before, during, or up to 1 hour after meals. The patient's diet should be reduced in calories and nutritionally balanced with 30% of calories obtained from fat, and the daily intake of the major nutrients spread over the 3 main meals. If a meal is missed or contains no fat, the dose should be omitted. Orlistat therapy should be stopped if the patient does not lose at least 5% of their body-weight during the first 12 weeks of therapy. Orlistat may also be given in a lower dose of 60 mg three times daily in patients with a BMI of 28 kg/m^2 or more irrespective of any risk factors.

References.

1. Lucas KH, Kaplan-Machlis B. Orlistat—a novel weight loss therapy. *Ann Pharmacother* 2001; **35:** 314–28.
2. Keating GM, Jarvis B. Orlistat: in the prevention and treatment of type 2 diabetes mellitus. *Drugs* 2001; **61:** 2107–21.
3. Snider LJ, Malone M. Orlistat use in type 2 diabetes. *Ann Pharmacother* 2002; **36:** 1210–18.
4. Henness S, Perry CM. Orlistat: a review of its use in the management of obesity. *Drugs* 2006; **66:** 1625–56.
5. Filippatos TD, *et al.* Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Safety* 2008; **31:** 53–65.
6. Anonymous. Over-the-counter weight loss with orlistat? *Drug Ther Bull* 2009; **47:** 125–7.

Adverse Effects

Gastrointestinal disturbances, including faecal urgency and incontinence, flatulence, and fatty stools or discharge, are the most frequently reported adverse effects during treatment with orlistat, especially when taken with a high-fat diet. Other reported effects have included headache, anxiety, fatigue, rectal bleeding, and menstrual irregularities. Severe liver damage with hepatocellular necrosis or acute hepatic failure have been reported rarely in patients taking orlistat, and some of these cases have resulted in liver transplant and death. There have been concerns about an increased risk of breast cancer and colon cancer in patients taking orlistat but the FDA considers that there is no evidence of a causal link.

Effects on the cardiovascular system. A report of hypertension associated with orlistat therapy.[1] Blood pressure decreased on stopping orlistat and increased again on rechallenge. The authors noted that 13 cases of hypertension associated with orlistat had been reported to the manufacturers.

1. Persson M, *et al.* Orlistat associated with hypertension. *BMJ* 2000; **321:** 87.

Effects on the skin. Lichenoid drug eruption affecting the vulva, feet, and axillae has been reported in a woman during orlistat treatment.[1] Symptoms resolved on stopping orlistat with only the vulval lesions requiring topical treatment with mometasone furoate 0.1%.

1. Sergeant A, *et al.* Lichenoid eruption associated with orlistat. *Br J Dermatol* 2006; **154:** 1020–21.

Precautions

Orlistat should not be given to patients with chronic malabsorption syndrome or cholestasis and should be given with caution to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis. Adjustments to dosage of hypoglycaemics may be necessary in patients with type II diabetes because of improved metabolic control after weight loss in these patients. Patients reporting severe and/or persistent rectal bleeding with orlistat should undergo further investigation. Supplements of fat-soluble vitamins may be necessary during long-term therapy, but they should be taken at least 2 hours before or after an orlistat dose or at bedtime. Hormonal contraceptive failure may occur in the event of severe diarrhoea with orlistat, and patients are advised to use an additional contraceptive method.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies orlistat as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Interactions

Orlistat may reduce the absorption of fat-soluble vitamins. In patients taking warfarin, international normalised ratio should be monitored during treatment with orlistat. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported in transplant recipients given orlistat (see p. 1953.2). Hypothyroidism has been described in a woman stabilised on levothyroxine sodium, within 2 weeks of starting orlistat (see p. 2342.1). Orlistat may decrease the absorption of antiepileptics and thereby increase the risk of seizures. Orlistat may also reduce the absorption of propafenone. For the possibility of hormonal contraceptive failure with orlistat see Precautions, above. Use of orlistat with acarbose should be avoided as the combination has not been studied.

Pharmacokinetics

Orlistat is minimally absorbed after oral doses. About 97% of a dose is excreted in the faeces, with 83% as unchanged orlistat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisplus; Fingras; Frugal; Liposol; Oleofin; Xenical; Xeniplus†; Xinplex; ***Austral.***: Xenical; ***Austria***: Alli; Xenical; ***Belg.***: Alli; Xenical; ***Braz.***: Lipiblock; Xenical; ***Canad.***: Xenical; ***Chile***: Adell; Liberat; Oradiet; Sagras; Symfona; Viplena; Xenical; ***China***: Xenical (赛尼可); ***Cz.***: Alli; Xenical; ***Denm.***: Alli†; Xenical; ***Fin.***: Xenical; ***Fr.***: Alli; Xenical; ***Ger.***: Alli; Xenical; ***Gr.***: Alli; Xenical; ***Hong Kong***: Alli; Xenical; ***Hung.***: Alli; Xenical; ***India***: Cobese; Lipocut; Lipophage; Obelit; Obiless; Obitrol; Olisat; Orlica; Orlimac; Orlitroy; ***Indon.***: Xenical; ***Irl.***: Alli; Xenical; ***Israel***: Alli; Xenical; ***Ital.***: Xenical; ***Malaysia***: Cuvarlix; Xenical; ***Mex.***: Amsafast; Leben-Celtics; Lindeza; Lysthin; Redustat; Vasdecom; Ventu; Xenical; ***Neth.***: Alli; Xenical; ***Norw.***: Alli†; Xenical; ***NZ***: Xenical; ***Philipp.***: Lesofat; Obestal; Xenical; ***Pol.***: Alli; Xenical; ***Port.***: Alli; Xenical; ***Rus.***: Alli (Алли); Orsoten (Орсотен); Xenical (Ксеникал); ***S.Afr.***: Xenical; ***Singapore***: Xenical; ***Spain***: Alli; Xenical; ***Swed.***: Alli; Xenical; ***Switz.***: Alli; Calobalin; Xenical; ***Thai.***: Xenical; ***Turk.***: Thincal; Xenical; ***UK***: Alli; Xenical; ***Ukr.***: Xenical (Ксенікал); ***USA***: Alli; Xenical; ***Venez.***: Xenical.

Pharmacopoeial Preparations

USP 36: Orlistat Capsules.

Ornipressin *(rINN)*

Ornipresina; Ornipressine; Ornipressinum; Орнипрессин.

[8-Ornithine]-vasopressin.

$C_{45}H_{63}N_{13}O_{12}S_2$=1042.2

CAS — 3397-23-7.

ATC — H01BA05.

ATC Vet — QH01BA05.

UNII — 1KTH6N080W.

Profile

Ornipressin is a synthetic derivative of vasopressin (p. 2642.3) with similar actions. It is reported to be a strong vasoconstrictor with only weak antidiuretic properties and is used to reduce bleeding during surgery. A solution containing up to 5 units in 20 to 60 mL of sodium chloride 0.9% is infiltrated into the area involved. Ornipressin has also been given by intravenous infusion for the treatment of bleeding oesophageal varices (under Monoethanolamine, p. 2563.1).

References.

1. Kam PC, Tay TM. The pharmacology of ornipressin (POR-8): a local vasoconstrictor used in surgery. *Eur J Anaesthesiol* 1998; **15:** 133–9.
2. De Kock M, *et al.* Ornipressin (Por 8): an efficient alternative to counteract hypotension during combined general/epidural anesthesia. *Anesth Analg* 2000; **90:** 1301–7.

Adverse effects. Acute pulmonary oedema occurred in a patient after infiltration of ornipressin (12 units in 40 mL isotonic saline) as a local vasoconstrictor during surgery.[1] It was suggested that no more than 100 milliunits/kg should be given in this manner.

1. Borgeat A, *et al.* Acute pulmonary oedema following administration of ornithine-8-vasopressin. *Br J Anaesth* 1990; **65:** 548–51.

Hepatorenal syndrome. Ornipressin has been found to be of benefit[1-4] in the hepatorenal syndrome, a form of renal insufficiency associated with cirrhosis of the liver, and thought to be due to severe renal vasoconstriction secondary to systemic arterial vasodilatation. However, caution

in its use has been urged[2] because of the risk of ischaemic complications.

1. Lenz K, *et al*. Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis: effects on renal hemodynamics and atrial natriuretic factor. *Gastroenterology* 1991; **101:** 1060–7.
2. Guevara M, *et al*. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998; **27:** 35–41.
3. Gülberg V, *et al*. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. *Hepatology* 1999; **30:** 870–5.
4. Restuccia T, *et al*. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome: a case-control study. *J Hepatol* 2004; **40:** 140–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: POR 8; ***NZ***: POR 8; ***S. Afr.***: POR 8.

Orotic Acid *(BAN, pINN)*

Acide Orotique; Ácido orótico; Acidum Oroticum; Animal Galactose Factor; Oroottihappo; Orótico, ácido; Orotsyra; Uracil-6-carboxylic Acid; Vitamin B_{13}; Vitamina B_{13}; Whey Factor; Оротовая Кислота.

1,2,3,6-Tetrahydro-2,6-dioxopyrimidine-4-carboxylic acid.

$C_5H_4N_2O_4$=156.1

CAS — 65-86-1 (anhydrous orotic acid); 50887-69-9 (orotic acid monohydrate).

UNII — 61H4T033E5 (orotic acid); 91532S02AO (orotic acid monohydrate).

Profile

Orotic acid, an intermediate in the biosynthesis of pyrimidine nucleotides, occurs naturally in the body and is also found in milk. Orotic acid and its calcium, carnitine, choline, lithium, lysine, and potassium salts have been used in liver disorders. Some of these salts, as well as chromium, cyproheptadine, deanol (p. 2319.1), magnesium, and zinc orotates have been given as tonics or dietary supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Orotate.

Multi-ingredient Preparations. ***Arg.***: Bil 13; Zimerol; ***Austral.***: Potasi; ***Hong Kong***: Hepatofalk†; Lipochol; ***Mex.***: Lipovitasi-Or; ***Philipp.***: Godex†; Godex; Inlex; Mitocore; Mitodex; Mitonerb; Mivex; Vita SL; ***Rus.***: Vitamax (Витамакс)†; ***S.Afr.***: Hepabionta†; ***Spain***: Hepadif; Pleon†; ***Thai.***: Lipochol; ***UK***: Sugar Bloc; ***Ukr.***: Energin (Энергин); Hepadif (Гепадиф); Hepadif (Гепадиф).

Homoeopathic Preparations. ***Ger.***: Hepar comp.

Orthodichlorobenzene

Ortodiclorobenceno; Орто-дихлорбензол.

1,2-Dichlorobenzene.

$C_6H_4Cl_2$=147.0

CAS — 95-50-1.

UNII — 6PJ93I88XL.

Profile

Orthodichlorobenzene has been used as an ingredient of solutions for dissolving ear wax. It has also been used as a wood and furniture preservative. Orthodichlorobenzene is an irritant volatile liquid; lens opacities have occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Cerumol; ***Switz.***: Cerumenol.

Oryzanol

Gamma orizanol; Gamma Oryzanol; Orizanol; γ-Oryzanol; γ-OZ; Гамма-оризанол.

Triacontanyl 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate.

$C_{40}H_{58}O_4$=603.0

CAS — 11042-64-1.

UNII — SST9XCL51M.

Profile

Oryzanol is a substance extracted from rice bran oil and rice embryo bud oil. It has been given orally in the treatment of hyperlipidaemias. It has also been used for its supposed effects on autonomic and endocrine function.

References.

1. Cicero AF, Gaddi A. Rice bran oil and gamma-oryzanol in the treatment of hyperlipoproteinaemias and other conditions. *Phytother Res* 2001; **15:** 277–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Luo Bei Jing (络倍静); ***Jpn***: Hi-Z.

Multi-ingredient Preparations. ***Ital.***: Anasterol; Lenirose; ***Jpn***: Q & P; Sin Q & P Gold†; ***Singapore***: Gin-Vita.

Otilonium Bromide *(BAN, rINN)*

Bromuro de otilonio; Octylonium Bromide; Otilonii Bromidum; Otilonio, bromuro de; Otilonium, Bromure d'; SP-63; Отилония Бромид.

Diethylmethyl{2-[4-(2-octyloxybenzamido)benzoyloxy]ethyl} ammonium bromide.

$C_{29}H_{43}BrN_2O_4$=563.6

CAS — 26095-59-0.

ATC — A03AB06.

ATC Vet — QA03AB06.

UNII — 21HN3N72PV.

Profile

Otilonium bromide is used in the symptomatic treatment of gastrointestinal disorders associated with smooth muscle spasms in oral doses up to 120 mg daily. It has also been given rectally and by nebuliser.

References.

1. Battaglia G, *et al*. Otilonium bromide in irritable bowel syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol Ther* 1998; **12:** 1003–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bromotil; Motid; Pasminox; Spasmoctyl; ***Belg.***: Spasmomen; ***Braz.***: Lonium; ***China***: Spasmomen (斯巴敏); ***Cz.***: Spasmomen; ***Gr.***: Doralin; Otilax; ***Hong Kong***: Spasmomen; ***Hung.***: Spasmomen; ***India***: Menoctyl; ***Indon.***: Spasmomen; ***Israel***: Spasmomen; ***Ital.***: Spasen; Spasmomen; ***Mex.***: Debromu; Omuro; ***Port.***: Spasmomen; ***Spain***: Spasmoctyl; ***Turk.***: Ekspaz; Spasmomen; ***Ukr.***: Spasmomen (Спазмомен).

Multi-ingredient Preparations. ***Arg.***: Pasminox Somatico; Spasmoctyl Somatico; ***Ital.***: Spasen Somatico; Spasmomen Somatico.

Oxaceprol *(rINN)*

Acetylhydroxyproline; C061; Oxacéprol; Oxaceprolum; Оксацепрол.

(-)-1-Acetyl-4-hydroxy-L-proline.

$C_7H_{11}NO_4$=173.2

CAS — 33996-33-7.

ATC — D11AX09; M01AX24.

ATC Vet — QD11AX09; QM01AX24.

UNII — Q0XV76B96L.

Profile

Oxaceprol is reported to affect connective tissue metabolism and has been used in dermatology, to promote wound healing, and in rheumatic disorders. Adverse effects have included gastric pain, nausea, diarrhoea, dizziness, headache, and rashes.

References.

1. Bauer HW, *et al*. Oxaceprol is as effective as diclofenac in the therapy of osteoarthritis of the knee and hip. *Clin Rheumatol* 1999; **18:** 4–9.
2. Herrmann G, *et al*. Oxaceprol is a well-tolerated therapy for osteoarthritis with efficacy equivalent to diclofenac. *Clin Rheumatol* 2000; **19:** 99–104.
3. Krüger K, *et al*. Oxaceprol—a randomised, placebo-controlled clinical study in osteoarthritis with a non-conventional non-steroidal anti-inflammatory drug. *Clin Exp Rheumatol* 2007; **25:** 29–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Joint; ***Fr.***: Flammaspray; Jonctum Cica; ***Ger.***: AHP 200; ***Spain***: Tejuntivo†.

Multi-ingredient Preparations. ***Spain***: Robervital†.

Oxalic Acid

Kwas szczawiowy; Oxálico, ácido.

$HO_2C,CO_2H,2H_2O$=126.1

CAS — 144-62-7 (anhydrous oxalic acid); 6153-56-6 (oxalic acid dihydrate).

ATC Vet — QP53AG03.

UNII — 9E7R5L6H31 (oxalic acid); 0K2L2IJ59O (oxalic acid dihydrate).

Uses

Oxalic acid has varied industrial uses and has been used in escharotic preparations. Oxalic acid salts have been given orally and the urinary excretion of oxalate used as a screening test for lipid malabsorption.

Diagnostic use. References.

1. Rampton DS, *et al*. Screening for steatorrhoea with an oxalate loading test. *BMJ* 1984; **288:** 1419. Correction. *ibid.*; 1728.
2. Sangaletti O, *et al*. Urinary oxalate recovery after oral oxalic acid load: an alternative method to the quantitative determination of stool fat for the diagnosis of lipid malabsorption. *J Int Med Res* 1989; **17:** 526–31.

Adverse Effects

On ingestion, severe gastroenteritis is produced by the corrosive action of oxalic acid and its soluble salts on the gastrointestinal tract. Burning of the mouth, throat, and oesophagus with ulceration may also occur. Hypoxia may occur in the presence of laryngeal oedema, and shock and hypotension may arise in severe cases. Oxalates can chelate body calcium following systemic absorption, and may produce symptoms of hypocalcaemia such as tetany, convulsions, and, in some cases, ventricular fibrillation. Oxalate crystals may be deposited in the blood vessels, brain, heart, liver, and lungs; deposition in the renal tubules leads to acute renal failure. The mean fatal dose of oxalates has been reported to be about 15 to 30 g, although death has occurred with much lower doses. Death may occur within a few hours of ingestion.

Fatalities have resulted from intravenous administration of sodium oxalate[1] or ingestion of oxalic acid.[2]

Crystals of calcium oxalate present in the sap of daffodils[3] or *Agave tequilana* plants[4] have been reported to contribute to the rash experienced by workers coming into contact with these plants.

1. Dvořáčková I. Tödliche Vergiftung nach intravenöser Verabreichung von Natriumoxalat. *Arch Toxikol* 1966; **22:** 63–7.
2. Farré M, *et al*. Fatal oxalic acid poisoning from sorrel soup. *Lancet* 1989; **ii:** 1524.
3. Julian CG, Bowers PW. The nature and distribution of daffodil pickers' rash. *Contact Dermatitis* 1997; **37:** 259–62.
4. Salinas ML, *et al*. Irritant contact dermatitis caused by needle-like calcium oxalate crystals, raphides, in Agave tequilana among workers in tequila distilleries and agave plantations. *Contact Dermatitis* 2001; **44:** 94–6.

Treatment of Adverse Effects

After ingestion of oxalic acid, a dilute solution of any soluble calcium salt should be given to precipitate the oxalate; alternatively milk may be given. Oral activated charcoal has also been suggested if ingestion has occurred within 1 hour. Gastric lavage is contra-indicated by some centres given the corrosive nature of oxalic acid. Calcium gluconate 10% should be given intravenously to prevent tetany. Acute renal failure should be anticipated in surviving patients and calls for careful fluid management. Haemodialysis or peritoneal dialysis have also been suggested for the removal of oxalate in primary oxalosis in an attempt to prevent acute renal failure and correct hypocalcaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***China***: Solcoderm (思可得); ***Ger.***: Solco-Derman; ***Hong Kong***: Solcoderm†; ***Pol.***: Solcogyn; ***Rus.***: Solcoderm (Солкодерм); Solcovagin (Солковагин); ***Switz.***: Solcoderm; Solcogyn; ***Ukr.***: Solcoderm (Солкодерм); Solcovagin (Солковагин).

Homoeopathic Preparations. ***Fr.***: Berberis Complexe No 83; ***Ger.***: Agnus castus comp†; ***Switz.***: Regenaplex Nr 28a.

Oxalacetic Acid

Àcid oxalacètic; Acid Oxalilacetic; Acide Oxaloacétique; Acido Ossalacetico; Ácido Oxaloacético; Ketosuccinic Acid; Kwas Szczawiooctowy; Kyselina Oxaloctová; Oksaloetikkahappo; Oxaalazijnzuur; Oxalättiksyra; Oxálecetsav; Oxalessigsäure; Oxaloacetic Acid; Oxosuccinic Acid; Skābeņetiķskābe; Щавелевоуксусная Кислота.

2-Oxobutanedioic Acid.

$C_4H_4O_5$=132.1

CAS — 328-42-7 (oxalacetic acid); 108-56-5 (diethyl oxalacetate); 40876-98-0 (diethyloxalacetate sodium).

UNII — 2F399MM81J.

Profile

Oxalacetic acid is an intermediate in the citric acid cycle and therefore has an important role in cellular respiration. It has been used in a stabilised form as a nutritional supplement.

Homoeopathy

Salts and esters of oxaloacetic acid have been used in homoeopathic medicines but the precise identity is not always clear. The following names have been used: Sodium diethyloxalacetate; Diethyloxalacetate de sodium; Natrium oxalaceticum; Natriumoxalacetat.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Zeel; Zeel.

Homoeopathic Preparations. ***Cz.***: Zeel Salbe†; ***Ger.***: Hepar comp; Mucosa compositum; Zitronensaurezyklus-Heel; ***Hung.***: Zeel; ***Rus.***: Zeel T (Цель Т).

Oxogluric Acid

Acide alpha-cétoglutarique; Acide Oxoglurique; Acide 2-oxoglutarique; Ácido alfacetoglutárico; Acido 2-chetoglutarico; Acido 2-ossoglutarico; Acidum alpha-ketoglutaricum; Alfa-ketoglutársav; Alfa-ketoglutarsyra; Alfa-ketoglutarsyre; α-Ketoglutaric Acid; α-Ketoglutarsäure; Kwas alfa-ketoglutarowy; 2-Oxoglutaric Acid; α-Oxoglutaric Acid; 2-Oxoglutarová kyselina; 2-Oxoglutarsäure; 2-Oxopentandisäure; α-Кетоглутаратная кислота.

2-Oxopentanedioic Acid.

$C_5H_6O_5$=146.1

CAS — 328-50-7.

UNII — 8ID597Z82X.

Profile

Oxogluric acid is an intermediate in the citric acid cycle. It has been used as a dietary supplement and has also been used in preparations for vaginal disorders. The calcium and magnesium salts have also been used.

Homoeopathy

Oxogluric acid has been used in homoeopathic medicines under the following names: Acidum alpha ketoglutaricum; Ketoglutaricum acidum; Ketoglutaric acid; 2-Oxoglutarsäure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cetoglutaran†.

Multi-ingredient Preparations. ***Ital.***: Gynegella P; Ipoazotal Complex.

Homoeopathic Preparations. ***Ger.***: Hepar comp; Zitronensaurezyklus-Heel.

Ozagrel *(rINN)*

OKY-046 (ozagrel hydrochloride); Ozagrelum; Озарел.

(*E*)-*p*-(Imidazol-1-ylmethyl)cinnamic acid.

$C_{13}H_{12}N_2O_2$=228.3

CAS — 82571-53-7.

UNII — L256JB984D.

Profile

Ozagrel is a thromboxane synthetase inhibitor that has been given orally as the hydrochloride for the treatment of asthma in doses of 200 mg twice daily. It has also been given as the sodium salt by intravenous infusion for the treatment of cerebrovascular disorders in a dose of 80 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Xin Kang (奥辛康); Ci He Ying (赐禾盈); Dan Lun (丹仑); Eryechang (二叶畅); Hong Bang (鸿邦); Hua Yi Mai (华益迈); Kang En (康恩); Kawin Di Ning (凯因迪宁); Qi Ming Lei Ao (齐铭雷奥); Qing Er (晴尔); Tai Ya Pu Xi (泰亚普昔); Zhou Bang (洲邦); ***Jpn***: Cataclot; Domenan; Vega; Xanbon.

Palifermin *(BAN, USAN, rINN)* ⊗

AMJ-9701; Palifermina; Palifermine; Paliferminum; rHu-KGF; Палифермин.

24-163 Fibroblast growth factor 7 (human).

CAS — 162394-19-6; 178254-26-7.

ATC — V03AF08.

ATC Vet — QV03AF08.

UNII — QMS40680K6.

Uses and Administration

Palifermin is a human recombinant keratinocyte growth factor (KGF) used to reduce the incidence and duration of severe oral mucositis (see below) in patients with haematological neoplasms who receive myelotoxic chemotherapy with radiotherapy, followed by haematopoietic stem cell transplantation. The recommended course of palifermin is 6 doses of 60 micrograms/kg, by intravenous bolus injection. A dose is given on each of 3 consecutive days before, and 3 consecutive days after, myelotoxic therapy. Palifermin should not be given during, or for 24 hours before or after, myelotoxic therapy. Thus, the third pre-chemotherapy dose of palifermin should be given 24 to 48 hours before myelotoxic therapy, and the first post-chemotherapy dose of palifermin should be given after, but on the same day as, the haematopoietic stem cell infusion, and at least 4 days after the third pre-myelotoxic dose.

Mucositis. Palifermin is a human recombinant keratinocyte growth factor (KGF) that binds to KGF receptors and repairs damaged epithelium by stimulating the proliferation, differentiation, and migration of epithelial cells.[1,2] Controlled studies have shown it to be effective in reducing the severity and duration of oral mucositis (p. 732.1) in patients receiving myelotoxic therapy for haematological neoplasms and requiring haematopoietic stem cell support.[3,4] It has also shown benefit compared with placebo in reducing the incidence of oral mucositis and diarrhoea in patients receiving fluorouracil and leucovorin for metastatic colorectal cancer.[5]

1. Siddiqui MAA, Wellington K. Palifermin: in myelotoxic therapy-induced oral mucositis. *Drugs* 2005; **65:** 2139–46.
2. McDonnell AM, Lenz KL. Palifermin: role in the prevention of chemotherapy- and radiation-induced mucositis. *Ann Pharmacother* 2007; **41:** 86–94.
3. Spielberger R, *et al.* Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004; **351:** 2590–8.
4. Stiff PJ, *et al.* Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. *J Clin Oncol* 2006; **24:** 5186–93.
5. Rosen LS, *et al.* Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *J Clin Oncol* 2006; **24:** 5194–5200.

Adverse Effects

Adverse reactions reported with palifermin therapy have included rash, erythema, oedema, pruritus, fever, perioral dysaesthesia, tongue discoloration and thickening, and altered taste. Skin hyperpigmentation and gastrointestinal and respiratory disturbances have also been reported. The safety and efficacy of palifermin in patients given treatment for non-haematological neoplasms has not been established; stimulation and growth of tumour cell lines have been found in *animal* and *in-vitro* models of non-haematopoietic human tumours.

Effects on the skin. Flexural hyperpigmentation has been reported in 5 white-skinned patients being treated with palifermin.[1] The lesions were described as ill-defined symmetrical hyperpigmented papillomatous plaques with slight erythema in the skin folds, especially affecting axillary and inguinal areas.

A papular eruption clinically resembling lichen planus or plane warts, with histologic features of verruca plana, and intertriginous erythema has been reported in a patient; the lesions resolved spontaneously without treatment.[2]

1. Sibelt LAG, *et al.* Palifermin-induced flexural hyperpigmentation: a clinical and histological study of five cases. *Br J Dermatol* 2008; **159:** 1200–3.
2. King B, *et al.* Palifermin-associated papular eruption. *Arch Dermatol* 2009; **145:** 179–82.

Interactions

In-vitro and *in-vivo* data suggest that palifermin binds to unfractionated as well as low-molecular-weight heparins, and licensed product information therefore recommends that such combinations should be used with care, although the clinical relevance is unclear.

Pharmacokinetics

The pharmacokinetics of palifermin were approximately dose-linear after a single intravenous dose in healthy subjects given larger than usual doses. The terminal elimination half-life is about 4.5 hours.

References.

1. Zia-Amirhosseini P, *et al.* Pharmacokinetics, pharmacodynamics, and safety assessment of palifermin (rHuKGF) in healthy volunteers. *Clin Pharmacol Ther* 2006; **79:** 558–69.
2. Gillespie B, *et al.* Effect of renal function on the pharmacokinetics of palifermin. *J Clin Pharmacol* 2006; **46:** 1460–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Kepivance; ***Austria***: Kepivance; ***Belg.***: Kepivance; ***Canad.***: Kepivance; ***Cz.***: Kepivance; ***Denm.***: Kepivance; ***Fin.***: Kepivance; ***Fr.***: Kepivance; ***Ger.***: Kepivance; ***Gr.***: Kepivance; ***Hung.***: Kepivance; ***Irl.***: Kepivance; ***Israel***: Kepivance; ***Ital.***: Kepivance; ***Neth.***: Kepivance; ***Norw.***: Kepivance; ***Pol.***: Kepivance; ***Port.***: Kepivance; ***Spain***: Kepivance; ***Swed.***: Kepivance; ***Switz.***: Kepivance; ***UK***: Kepivance; ***USA***: Kepivance.

Palladium

Paladij; Paladio; Paládio; Paladis; Paladiu; Paladium; Paladyum; Pallaadium; Pallad; Pallādijs; Palladín; Palladio; Pallādium; Палладий; Паладий.

Pd=106.42

CAS — 7440-05-3.

UNII — 5TWQ1V240M.

Profile

Palladium is a precious metal with similar properties and uses to platinum (p. 2593.1).

Homoeopathy

Palladium has been used in homoeopathic medicines under the following names: Palladium; Palladium metallicum.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Canad.***: Passiflora Complex†; ***Fr.***: Passiflora Compose.

Palmarosa Oil

Essência de Palma-rosa; Indian Geranium Oil; Turkish Geranium Oil.

CAS — 8014-19-5.

UNII — 0J3G3O53ST.

Profile

Palmarosa oil is derived from palmarosa (*Cymbopogon martini*, Poaceae) and is used in perfumery and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Singapore***: Teenstick; ***UK***: Teenstick.

Palmidrol *(rINN)*

Palmidrolum; Пальмидрол.

N-(2-Hydroxyethyl)palmitamide.

$C_{18}H_{37}NO_2$=299.5

CAS — 544-31-0.

UNII — 6R8T1UDM3V.

Profile

Palmidrol is a naturally occurring lipid compound that may be isolated from soybean lecithin, egg-yolk, or peanut meal. It has been used as an immunostimulant. It is given orally in doses of 1 g two or three times daily for the treatment of respiratory-tract infections.

Pancreatic Enzymes

Панкреатические Ферменты.

Pancreatin *(BAN)* ⊗

Haimajauhe (pancreas powder); Kasos milteliai (pancreas powder); Pancréas, poudre de (pancreas powder); Pancreatina; Pancreatinum; Pancreatis pulvis (pancreas powder); Pankreaspulver (pancreas powder); Pankreatiini; Pankreatin; Pankreáz-por (pancreas powder); Панкреатин.

CAS — 8049-47-6.

UNII — FQ3DRG0N5K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US* as pancreatin or another pancreatic exocrine extract or both.

Ph. Eur. 8: (Pancreas Powder; Pancreatis Pulvis; Pancreatic Extract BP 2014). It is prepared from the fresh or frozen pancreases of mammals. It contains various enzymes having proteolytic, lipolytic, and amylolytic activities. Each mg of pancreas powder contains not less than 1 Ph. Eur. unit of total proteolytic activity, not less than 15 Ph. Eur. units of lipolytic activity, and not less than 12 Ph. Eur. units of amylolytic activity. A slightly brown, amorphous powder. Partly soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP 2014: (Pancreatin). A preparation of mammalian pancreas containing enzymes having protease, lipase, and amylase activity. Each mg of pancreatin contains not less than 1.4 FIP units of free protease activity, not less than 20 FIP units of lipase activity, and not less than 24 FIP units of

amylase activity. It may contain sodium chloride. A white or buff amorphous powder, free from unpleasant odour. Soluble or partly soluble in water forming a slightly turbid solution; practically insoluble in alcohol and in ether. Store at a temperature not exceeding 15 degrees.

USP 36: (Pancreatin). A substance containing enzymes, mainly amylase, lipase, and protease, obtained from the pancreas of the hog or of the ox. It is a cream-coloured, amorphous powder, having a faint, characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action.

Pancreatin contains, in each mg, not less than 25 USP units of amylase activity, not less than 2 USP units of lipase activity, and not less than 25 USP units of protease activity. Pancreatin of a higher digestive power may be labelled as a whole-number multiple of the 3 minimum activities, or may be diluted with lactose, or with sucrose containing not more than 3.25% of starch, or with pancreatin of lower digestive power. Store in airtight containers at a temperature not exceeding 30 degrees.

Pancrelipase *(USAN)* ⊗

Pancrelipasa; Панкрелипаза.
CAS — 53608-75-6.
UNII — YOJ58O116E (pancrelipase amylase); 8MYC339320 (pancrelipase lipase); 3560D81V50 (pancrelipase protease).

Pharmacopoeias. In *US.*

USP 36: (Pancrelipase). A substance containing enzymes, mainly lipase, with amylase and protease, obtained from the pancreas of the hog. It is a cream-coloured, amorphous powder having a faint characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action. Pancrelipase contains, in each mg, not less than 24 USP units of lipase activity, not less than 100 USP units of amylase activity, and not less than 100 USP units of protease activity. Store in airtight containers preferably at a temperature not exceeding 25 degrees.

Units

The Ph. Eur. and USP units of protease activity depend upon the rate of hydrolysis of casein, those of lipase activity depend upon the rate of hydrolysis of olive oil, and those of amylase activity depend upon the rate of hydrolysis of starch. Because of differences in the assay conditions, the Ph. Eur. and USP units are not readily comparable.

FIP units of protease, lipase, and amylase activity are approximately equivalent to Ph. Eur. units.

Uses and Administration

Pancreatic enzymes (as pancreatin or pancrelipase) hydrolyse fats to glycerol and fatty acids, break down protein into peptides, proteoses and derived substances, and convert starch into dextrins and sugars. They are given orally in conditions of pancreatic exocrine deficiency such as pancreatitis and cystic fibrosis. They are available in the form of powder, capsules containing powder or enteric-coated granules (which may be opened before use and the contents sprinkled on soft food), enteric-coated tablets, or granules. If pancreatic enzymes are mixed with liquids or food the resulting mixture should not be allowed to stand for more than 1 hour before use. Histamine H_2-receptor antagonists, such as cimetidine or ranitidine, have been given an hour before a dose in an attempt to lessen destruction of the pancreatic enzymes by gastric acid, or proton pump inhibitors such as omeprazole may be used; alternatively, antacids may be given with the dose.

The dose of pancreatic enzymes is adjusted according to the needs of the individual patient and will also depend on the dosage form. In the UK, proprietary preparations generally provide about 5000 to 10 000 units of lipase activity per dose-unit and usual doses, given with each meal, range from about 5000 to 56 000 units of lipase activity (with varying proportions of protease and amylase activity, depending on the preparation). In the USA, doses providing up to 40 000 USP units of lipase activity may be given with each meal. So-called high-strength or high-potency preparations are available for those receiving high doses, and typically contain about 20 000 to 40 000 units of lipase activity per dose unit, but their use has been associated with the development of fibrosing colonopathy in children with cystic fibrosis (see Effects on the Gastrointestinal Tract, p. 2581.1). Such preparations are consequently not recommended for children in the UK and authorities there consider the total daily dose of pancreatic supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg.

Purified lipase preparations have also been used. A recombinant human bile-salt stimulated lipase is under investigation for the treatment of fat malabsorption in patients with exocrine pancreatic insufficiency and cystic fibrosis.

Pancreatin is also used to remove protein deposits from the surface of soft contact lenses (p. 1730.2).

Cystic fibrosis. Patients with cystic fibrosis (p. 177.2) suffer from pancreatic insufficiency and consequent malabsorption. Pancreatin or pancrelipase may therefore play a role in the management of the disorder, being taken before or with each meal or snack.

Generic substitution. Three patients with cystic fibrosis whose gastrointestinal symptoms had been well controlled with pancrelipase developed symptoms after substitution of generic pancrelipase for their previous brand.[1] The generic product had a different lipase content and was almost inactive at stomach pH *in vitro*, apparently because of a defective enteric coating. Different brands of pancrelipase may not be therapeutically equivalent and should not be routinely substituted.

1. Hendeles L, *et al.* Treatment failure after substitution of generic pancrelipase capsules: correlation with in vitro lipase activity. *JAMA* 1990; **263:** 2459–61.

Pancreatitis. Pancreatitis is an inflammatory process affecting the pancreas. Acute pancreatitis comprises necrosis of pancreatic tissue occurring in an otherwise healthy gland, whereas chronic pancreatitis is the manifestation of pathological processes resulting in inflammation and progressive fibrosis of pancreatic tissue. Acute disease may be superimposed on a background of chronic pancreatitis.[1]

Acute pancreatitis is frequently associated with either biliary-tract disorders (such as gallstones or cholecystitis) or the intake of large amounts of alcohol, or less frequently with abdominal surgery, pancreatic trauma, hyperparathyroidism, hyperlipidaemia, or infection,[1-10] or rarely the adverse effects of drugs.[11] Endoscopic retrograde cholangiopancreatography (ERCP) is followed by acute pancreatitis in anywhere between 3 and 40% of patients,[1] although it may also be used successfully to treat acute pancreatitis associated with gallstones.[12]

Symptoms of acute pancreatitis include pain, which ranges from mild to extremely severe and which typically persists for several days, nausea and vomiting, ileus, and hypovolaemic shock. In severe disease, pulmonary, renal, and hepatic failure, encephalopathy, and death may ensue. A mortality rate of about 10% has been reported.

The management of acute disease is essentially supportive.[1-10] Adequate analgesia for pain is important (see Pancreatic Pain, p. 10.2); in mild cases, analgesia, adequate hydration, and temporary interruption of oral intake of food to 'rest' the pancreas may be adequate. In more severe disease enteral or parenteral nutrition may be needed,[1,6] although some[4,5,7-10,13] advocate enteral over parenteral nutrition because of potential complications with the latter. Adding probiotics to enteral feeds for prophylaxis against infectious complications in patients with predicted severe acute pancreatitis was not found to be of any benefit and might be associated with an increased risk of mortality.[14] Since most patients suffer from hypoxaemia it has been recommended that they should receive additional humidified oxygen by mask, with mechanical ventilation if blood gases indicate the development of severe pulmonary failure. Shock should be managed with blood or plasma, and electrolyte solutions, while insulin may be required for disturbances of glucose homoeostasis.

The value of other interventions is mostly doubtful. As an extension of the concept of 'pancreatic rest', inhibitors of pancreatic secretion including somatostatin or octreotide have been tried but without significant effect, while protease inhibitors such as aprotinin or gabexate mesilate have also proven disappointing,[2] perhaps because activation of pancreatic proteases (thought to play a significant role in pathogenesis) has already taken place by the time therapy is begun.[2] A meta-analysis[15] of studies using aprotinin or gabexate mesilate suggested that these might reduce mortality in moderate to severe acute pancreatitis. However, this conclusion has been criticised[16] based on weaknesses in the original studies and the criteria used for severity grading. Gabexate and somatostatin may have roles in the prevention of acute pancreatitis after ERCP,[17] but it remains difficult to identify which patients should be offered prophylaxis, since not all will develop the condition.[1,2] Furthermore, it has been suggested[18] that with improved techniques, the use of prolonged infusions of pharmacological prophylaxis against severe pancreatitis after ERCP may no longer be justified. Preliminary studies of the platelet-activating factor antagonist lexipafant for treatment of pancreatitis were initially promising but were not supported by subsequent larger studies.[3]

Although prophylactic antibacterials are often given, there has been some uncertainty about their value (see p. 196.2).

The role of surgery continues to be somewhat controversial; it is accepted for complications or when a potential surgical emergency exists.[1,2,4-7] Surgery to remove the gallbladder is usually delayed in severe episodes of acute, gallstone-related pancreatitis to allow resolution of the inflammatory process and improvement in the patient's nutritional state.[1] Early ERCP to clear an obstructed bile duct may reduce complications in patients with predicted severe pancreatitis, but does not reduce mortality.[12]

Chronic pancreatitis is frequently associated with high alcohol-intake,[1,19] although a tropical form[1] associated with malnutrition also exists, and some cases are idiopathic[20] or auto-immune.[21,22] Symptoms include recurrent episodes of pain (often less excruciating and of shorter duration than in acute pancreatitis) which normally become less severe and frequent over the years with the inexorable progression of fibrosis. Loss of exocrine tissue eventually leads in many patients to pancreatic exocrine insufficiency, with maldigestion and steatorrhoea, and in some to diabetes mellitus due to islet cell loss. Other symptoms may include cholestatic jaundice, fatty degeneration of the liver, stenosis of the bile duct, and hepatic cirrhosis (although this may also be due to alcohol intake). It has been estimated that more than 50% of patients die within 20 years of diagnosis, with those who continue to drink alcohol being at greatest risk. In some patients, chronic pancreatitis, especially that of hereditary origin, is a premalignant disorder.[1,19]

Current methods for diagnosis of chronic pancreatitis are to first use imaging techniques such as ultrasound or computed tomography (CT), but if those are equivocal or negative, then ERCP may be considered. Pancreatic function tests have also been used in the diagnosis of chronic pancreatitis. The secretin hormone stimulation test is the most sensitive test of pancreatic function but it is time-consuming, requires duodenal intubation, and is not widely available; the cholecystokinin test is similar but enzyme rather than hormone secretion is stimulated. Secretin is used alone or with cholecystokinetic drugs such as ceruletide, pancreozymin, or sincalide. Indirect noninvasive tubeless tests of pancreatic function are much simpler and more convenient to perform, and include the pancreolauryl test using fluorescein dilaurate, and the bentiromide (PABA) test in which metabolites excreted in the urine are taken as a measure of the enzyme-secreting activity of the pancreas. However, these are considered to be less reliable than direct hormone or enzyme stimulation tests. Pancreatic function tests are generally only reliable in patients with severe exocrine pancreatic insufficiency causing steatorrhoea and therefore have limited clinical use and are not routinely performed in practice. However, they might be helpful in the diagnosis of suspected chronic pancreatitis in patients who have normal imaging scans. Other noninvasive tests that have been used to diagnose chronic pancreatitis include faecal fat determination, and faecal measurement of pancreatic enzymes such as elastase and chymotrypsin, although these are limited by difficulties in sample collection and lack of sensitivity in early disease.[1,19,23,24]

Adequate analgesia with NSAIDs and opioids is essential for patients with chronic pancreatitis (see Pancreatic Pain, p. 10.2).[1,19] Nerve blocks of the coeliac plexus with phenol or alcohol have generally proved disappointing, although coeliac plexus blocks using corticosteroids and local anaesthetic may be effective.[1] However, response to nerve ablation procedures is often limited and of short duration.[20] Patients should be advised to abstain from alcohol, which can exacerbate the frequency and severity of painful episodes.[1,19] A low-fat diet is also recommended, or for patients who cannot tolerate oral intake, parenteral or enteral nutrition.[1,19,20] Steatorrhoea requires replacement of pancreatic enzymes with preparations of pancreatin or pancrelipase.[1,19,20] Because pancreatic enzymes are inactivated by gastric acid they may be taken after inhibitors of acid secretion[1,19] or with a sodium-containing antacid such as sodium bicarbonate (magnesium-, calcium-, and possibly aluminium-containing antacids may further interfere with fat absorption). Alternatively, enteric-coated enzyme preparations may be used.[20] In some patients with mild disease pancreatic enzyme replacement may also improve pain, although for this purpose only non-enteric coated preparations are effective.[1,19,20] However, a systematic review[25] found no strong evidence for recommending treatment with pancreatic enzymes for pain control or reduction of steatorrhoea, and no beneficial effect on quality of life was shown. There was also no evidence to suggest any advantage of enteric-coated over non-enteric-coated preparations. The authors concluded that sufficiently powered, randomised clinical studies comparing pancreatic enzymes with placebo are required before firm recommendations can be made. Supplements of fat-soluble vitamins are not normally necessary, but may be given intravenously

if required. Diabetes should be managed appropriately once steatorrhoea is under control.

Surgery, up to and including total pancreatectomy, has an important role in the relief of intractable pain, and may also be necessary for the management of complications.[1,19,20] Endoscopic decompression using contrast media containing prednisolone and ulinastatin has been reported to produce beneficial responses.[26]

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Adverse Effects and Precautions

Pancreatic enzyme supplements commonly cause gastrointestinal adverse effects such as abdominal discomfort and nausea and vomiting. They may also cause buccal and perianal irritation, particularly in infants. Colonic strictures (fibrosing colonopathy) have occurred, mainly in children with cystic fibrosis receiving high doses of pancreatin preparations; the use of high doses in patients with cystic fibrosis should preferably be avoided (see Effects on the Gastrointestinal Tract, below). Adequate hydration should be maintained at all times in patients receiving higher strength preparations.

Hypersensitivity reactions have been reported; these may be sneezing, lachrymation, or skin rashes. Hyperuricaemia or hyperuricosuria have occurred with high doses. There have been occasional reports of the contamination of pancreatin preparations with *Salmonella* spp.

Effects on folic acid. Pancreatic extract significantly inhibited folate absorption in healthy subjects and in pancreatic insufficient patients.[1] Testing *in vitro* showed that pancreatic extract formed insoluble complexes with folate. It was suggested[1] that patients being treated for pancreatic insufficiency should be monitored for folate status or given folic acid supplementation, particularly if pancreatic enzymes and bicarbonate (or cimetidine) were being used together in the treatment regimen.

1. Russell RM, *et al*. Impairment of folic acid absorption by oral pancreatic extracts. *Dig Dis Sci* 1980; **25:** 369–73.

Effects on the gastrointestinal tract. *FIBROSING COLONOPATHY.* After the introduction of high-strength pancreatic enzyme preparations, there were reports[1-6] of colonic strictures in children with cystic fibrosis given these formulations, and the problem, now dubbed fibrosing colonopathy, was reviewed.[7,8] Fibrosing colonopathy has also been reported[9] in an adult who was not thought to have cystic fibrosis, but who had been taking high doses of pancreatic enzyme supplements, including 2 with methylacrylic acid copolymer (MAC) coatings, for 5 years after surgical removal of the pancreas.

The pathogenesis and aetiology of this condition still remain unclear. Dose-related thickening of the colon wall has been described,[10] and an inflammatory or immune-mediated mechanism has been suggested.[11,12] It has also been suggested that the type of preparation used may have a role. An analysis[13] of cases of fibrosing colonopathy occurring in the UK between 1984 and 1994 showed that there was a dose-related association between the high-strength preparations and this adverse effect although there was some criticism and debate surrounding the methodology of this particular analysis.[14-16] A subsequent case-control study[17] of patients in the US presenting between 1990 and 1994 concluded that there was a strong association between high daily doses of pancreatic enzymes, in any form, and the development of fibrosing colonopathy; no significant differences were seen between the various high- and low-strength preparations used. Re-analysis[18] of the UK data found a highly statistically significant association with the intake of preparations using MAC for enteric coating, but no evidence that a high intake of lipase in the absence of MAC was a risk factor for the disease. However, at least one case has been reported with a preparation that did not contain this material.[19]

As a result of these problems, high-strength preparations were withdrawn in the USA, while in the UK, the CSM recommended[20] that unless special reasons exist, patients with cystic fibrosis should not use high-strength pancreatin preparations, and that all patients treated with these products should be monitored carefully for gastrointestinal obstruction. The CSM later elaborated on these recommendations:[21] they advised that *Nutrizym 22*, *Pancrease HL*, and *Panzytrat 25 000* [now discontinued in the UK] should not be used in children with cystic fibrosis who were aged 15 years or less; that the total daily dose of pancreatic enzyme supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg; and that patients on any pancreatin preparation should be reviewed to exclude colonic damage if new abdominal symptoms or a change in symptoms occurred. Other risk factors identified were male sex, more severe cystic fibrosis, and the concomitant use of laxatives.[21] The US Cystic Fibrosis Foundation has made recommendations for the management of patients who do not respond adequately to moderate doses of pancreatic enzymes,[22] and similar recommendations have been made in the UK.[23]

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MOUTH ULCERATION. In 3 children taking preparations of pancreatic extracts (*Pancrex V powder*, *Pancrex V Forte*), severe mouth ulceration and angular stomatitis, causing dysphagia, loss of weight, and pyrexia, were attributed to digestion of the mucous membrane due to retention of the preparations in the mouth before swallowing.[1]

1. Darby CW. Pancreatic extracts. *BMJ* 1970; **2:** 299–300.

Hypersensitivity. A successful desensitisation regimen has been described[1] for a child with cystic fibrosis who vomited within 1 to 2 hours after ingestion of pancreatic enzymes, suggestive of a type I hypersensitivity reaction.

1. Chamarthy LM, *et al*. Desensitization to pancreatic enzyme intolerance in a child with cystic fibrosis. Abstract: *Pediatrics* 1998; **102:** 134–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/102/1/e13.pdf (accessed 14/07/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pancreatic enzymes as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Creon; Pancrecura; Pankreozym; Prolipase; Ultrase; ***Austral.***: Cotazym S Forte†; Creon; Panazyme†; Pancrease†; Panzytrat; ***Austria***: Kreon; Pancrin; Panzynorm; ***Belg.***: Creon; ***Braz.***: Cotazym†; Creon; Pancrease; Panzytrat; Polyzym; ***Canad.***: Bio-Zyme†; Cotazym; Creon; Pancrease; Ultrase; Viokase; ***Chile***: Creon; ***China***: Creon (得每通); ***Cz.***: Gastrix†; Kreon; Pancreolan; Pangrol; Panzynorm; Panzytrat; ***Denm.***: Creon; Kreon; Pancrease; ***Fin.***: Creon; ***Fr.***: Creon; ***Ger.***: Cotazym; Fermento duodenal†; Helopan; Kreon; Lipazym; Mezym F; Ozym; Pangrol; Pankreatan; Panpur; Panzynorm forte-N; Panzytrat; Unexym mono; ***Gr.***: Creon; Pancrease; Panzytrat; ***Hong Kong***: Creon; ***Hung.***: Kreon; Mezym Forte; Neo-Panpur; Pangrol; Panzytrat; ***India***: Biopank; Creon; Digeplex; Enzar-HS; Festal N; Panstal N; Panzynorm-N; ***Irl.***: Creon; Nutrizym†; ***Israel***: Creon; Pancrease; ***Ital.***: Creon; Pancrex; ***Jpn***: LipaCreon; ***Malaysia***: Creon; ***Mex.***: Creon; Kenyna†; Opti-Free Supra Clens; Opti-Free; Pancrease; Trepetan; ***Neth.***: Creon; Pancrease HL; Pancrease†; Panzytrat; ***Norw.***: Creon; Kreon; Pancrease†; ***NZ***: Cotazym†; Creon; Pancrease; Pancrex; Panzytrat; ***Philipp.***: Creon; ***Pol.***: Kreon; Lipancrea; Neo-Pancreatinum; Pangrol; Panzytrat; ***Port.***: Kreon; ***Rus.***: Enzystal (Энзистал); Ermytal (Эрмиталь); Festal (Фестал); Gastenorm (Гастенорм); Kreon (Креон); Mezym Forte (Мезим Форте); Mikrazym (Микразим); Normoenzym Forte (Нормоэнзим Форте); Panzim (Панзим); Panzynorm (Панзинорм); Panzytrat (Панцитрат); Penzital (Пензитал); ***S.Afr.***: Creon; Pankrease†; Polyzym†; Viokase†; ***Singapore***: Creon; Norzyme; ***Spain***: Kreon; Papine†; ***Swed.***: Creon; Pancrease†; ***Switz.***: Creon; Panzytrat; ***Thai.***: Creon; ***Turk.***: Festal N; Kreon; ***UK***: Clen-Zym; Creon; Nutrizym; Pancrease HL; Pancrex; ***Ukr.***: Enzibene (Энзибене); Kreasim (Креазим); Kreon (Креон); Mezym Forte (Мезим Форте); Micrazim (Микразим); Pancreasim (Панкреазим)†; Pangrol (Пангрол); Panzynorm (Панзинорм Форте-Н); ***USA***: Creon; Dygase; Enzymatic Cleaner†; Ku-Zyme HP†; Lapase; Lipram†; Opti-Zyme†; Palcaps†; PAN-2400†; Pancrease†; Pancreaze; Panocaps†; Pertzye; Tri-Pase; Ultrase†; Ultresa; Viokace; Viokase†; Vision Care Enzymatic Cleaner†; Zenpep; ***Venez.***: Orozim; Pankreon.

Multi-ingredient Preparations. ***Arg.***: Arnol; Bibol Leloup; Bil 13 Enzimatico; Biletan Enzimatico; Biluen Enzimatico; Carbogasol Digestivo; Digenorflat; Digesplen; Dom-Polienzim; Enzybar; Facilgest; Faradil Enzimatico†; Gastridin-E; Homocisteon Compuesto; Moperidona Enzimatica†; Mosar Enzimatico; Pakinase; Pankreoflat; Pankreon Total; Polienzim; Praxis; Pronto Digest; Tridigestivo Soubeiran; ***Austral.***: Digestaid; Enzyme; Vegie Digestaid; ***Austria***: Helopanflat; Helopanzym; Intestinol†; Pankreoflat; Rennie Digestif; Wobenzym; ***Belg.***: Digestomen; ***Braz.***: Dasc†; Digecap-Zimatico; Essen; Pankreoflat; Peptopancreasi†; Plasil Enzimatico; Primeral; Proteobil; Sintozima†; ***Canad.***: Digesdyn; Digest; Digesta; Digestolax; Dipan†; Hepaticol; Lipozyme†; Multi-Zyme†; Pancre Zyme†; Wobenzym; ***Chile***: Combizym Compositum†; Digenil; Flapex E; Hepabil; Neopankreoflat; Nutrizima; ***China***: Combizym (慷彼申); Dages (达吉); Mite (泌特); YiMei (怡美); ***Cz.***: Combizym Compositum†; Digestif Rennie†; Wobenzym; ***Ger.***: Chol-Arbuz NF; Enzym-Lefax; Meteozym; Pankreoflat†; Pascopankreat; Ventracid N†; Wobenzym N†; ***Hong Kong***: Appezym; Combizym; Digezym; Enzyme Co†; Enzyplex; ***Hung.***: Digestif Rennie†; Dipankrin; Pankreoflat; ***India***: Analiv; B-Zyme; Barozyme; Biohep; Digeplex-T; Dispeptal; Dizec; Enzar Forte; Enzolact; Enzovit; Farizym; Festal; Gaskit; Gesdyp; Hepa-Merz; Hepalon; Hepan-L; Hepasure; Hepator; Hepawin; Hiact-P; Kamozyme-EP; Kayliv; Laxzyme; Leno-EZ; Livtop; Medizyme; Merckenzyme†; Moret; Mumzyme; Orniliv; Ornipan; Pankreoflat; Panlipase; Papytazyme; ***Indon.***: Benozym; Berzymplex; Cotazym Forte; Elsazym; Elsazym; Enzymfort; Enzyplex; Excelase-E; Flazymec; Gasflat;

Librozym Plus†; Librozym†; Nutriflam; Pankreoflat; Pankreon Comp; Pankreon for Children; Primperan Compositum; Tripanzym; Vitazym; Xepazym; ***Israel***: Encypalmed; Pankreoflat†; ***Malaysia***: Biotase; Enzyme Digest; Enzyplex†; ***Mex.***: Difarben; Dixiflen; Espaven Enzimatico; Ochozim; Onoton; Pankreoflat; Plasil Enzimatico; Wobenzym; Zimeton; Zimotris; ***Neth.***: Combizym†; ***Norw.***: Combizym; ***Philipp.***: Pankreoflat; Spasmo-Canulase; ***Pol.***: Combizym; ***Port.***: Colerin-F†; Espasmo Canulase†; Fermetone Composto; Helopanflat; Pankreoflat; ***Rus.***: Biofestal (Биофесталь); Cholenzim (Холензим); Ipental (Ипентал)†; Pankreoflat (Панкреофлат); Pheresthal (Ферестал); Wobenzym (Вобэнзим); ***S.Afr.***: Pankreoflat; Spasmo-Canulase†; ***Singapore***: Biotase; Enzyplex; ***Spain***: Digestomen Complex; Nulacin Fermentos†; Pankreoflat; ***Swed.***: Combizym Compositum†; Combizym; ***Switz.***: Combizym Compositum; Combizym; Spasmo-Canulase; ***Thai.***: Combizym Compositum†; Combizym; Enzymet; Gaszym; Pepsitase; Polyenzyme-I†; Polyenzyme-N; Proctase-P; ***Turk.***: Fermento; Flaton; Hazmolin; Intestinol; Multanzim†; Pankreoflat; Pankreon Comp; Pankrodigest†; ***UK***: Enzyme Digest; Enzyme Plus; ***Ukr.***: Festal (Фестал); Wobenzym (Вобэнзим); ***USA***: Bio-Zyme; Digepepsin; Digex†; Enzyme; Hi-Vegi-Lip; Ku-Zyme†; Kutrase†; Pangestyme†; Panplex 2-Phase; Similase Jr; ***Venez.***: Combizym Forte; Festal Reformulado; Nutizym Compositum; Pankreon Compositum; Pankreosil; Stamyl; Wobenzym N.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Pancreatin Tablets; Pancreatin Granules;

USP 36: Pancreatin Tablets; Pancrelipase Capsules; Pancrelipase Delayed-release Capsules; Pancrelipase Tablets.

Pancreozymin *(BAN)*

CCK-PZ; Pancreocimina; Pankreotsymiini; Pankreozymin; Панкреозимин.

ATC — V04CK02.

ATC Vet — QV04CK02.

NOTE. The endogenous hormone is known as cholecystokinin (CCK).

Units

The potency of pancreozymin may be expressed as Crick-Harper-Raper units based on the pancreatic secretion in *cats* or as Ivy *dog* units based on the increase in gallbladder pressure. One Ivy dog unit is considered to be equivalent to about 1 Crick-Harper-Raper unit.

Profile

Pancreozymin is a polypeptide hormone prepared from the duodenal mucosa of *pigs*. When given by intravenous injection it causes an increase in the secretion of pancreatic enzymes and stimulates gallbladder contraction.

Pancreozymin has been used, usually with secretin, as a test for exocrine pancreatic function (see under Pancreatitis, p. 2580.2) and in the diagnosis of biliary-tract disorders; these tests generally involved duodenal intubation of the patient and examination of duodenal aspirate. Pancreozymin has also been used as an adjunct to cholecystography. Vasomotor reactions, abdominal discomfort, and hypersensitivity have been reported.

Biliary-tract disorders. It was concluded that cholecystokinin provocation testing was ineffective in predicting which patients with acalculous biliary pain would receive symptomatic relief from cholecystectomy in a study involving 58 patients.[1]

1. Smythe A, *et al.* A requiem for the cholecystokinin provocation test? *Gut* 1998; **43:** 571–4.

Pangamic Acid

Pangámico, ácido; Пангамовая Кислота.

UNII — MPQ53A9F5C.

Profile

The name pangamic acid has been applied variously to gluconic acid 6-[bis(diisopropylamino)acetate] ($C_{20}H_{40}N_2O_8$ = 436.5), gluconic acid, 6-ester with N,N-dimethylglycine ($C_{10}H_{19}NO_8$ = 281.3), gluconic acid, 6-ester with N,N-diisopropylglycine ($C_{14}H_{27}NO_8$ = 337.4), and a substance or mixture of substances isolated from apricot kernels and rice bran. It has also been known as 'vitamin B_{15}' although there is no evidence that pangamic acid is a vitamin. Preparations containing the vasoactive substance di-isopropylammonium dichloroacetate (p. 1359.1) have sometimes been described as pangamic acid or 'vitamin B_{15}'. There is much uncertainty about the identity of products sold in health food stores as 'vitamin B_{15}', pangamic acid, or sodium or calcium pangamate and different brands have been reported to have completely different compositions.

Claims for the activity of pangamic acid as a promotor of tissue oxygenation and its alleged value in many disorders have not been substantiated.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Desfatigan; Pulsor.

Multi-ingredient Preparations. ***Arg.***: Varicofem; ***Mex.***: B1-12-15; ***Spain***: Policolinosil.

Homoeopathic Preparations. ***Ger.***: Infi-Camphora.

Panthenol *(BAN, USAN, rINN)*

dl-Panthenol; Pantenol; Panthénol; Panthenolum; Пантенол; (±)-Pantothenyl Alcohol.

$C_9H_{19}NO_4$ = 205.3

CAS — 16485-10-2.

UNII — WV9CM0O67Z.

Pharmacopoeias. In *US*.

USP 36: (Panthenol). A racemic mixture of the dextrorotatory and laevorotatory isomers of panthenol. A white to creamy white, crystalline powder with a slight, characteristic odour. Freely soluble in water, in alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerol. Store in airtight containers.

Dexpanthenol *(BAN, USAN, rINN)*

Dekspantenoli; Dekspantenolis; Dexpantenol; Dexpanthénol; Dexpanthenolum; Dextro-Pantothenyl Alcohol; Pantothenol; Provitamin B_5; Декспантенол.

(*R*)-2,4-Dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethylbutyramide.

$C_9H_{19}NO_4$ = 205.3

CAS — 81-13-0.

ATC — A11HA30; D03AX03; S01XA12.

ATC Vet — QA11HA30; QD03AX03; QS01XA12.

UNII — 1O6C93RI7Z.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Dexpanthenol). A colourless or slightly yellowish, hygroscopic, viscous liquid, or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH not greater than 10.5. Store in airtight containers.

USP 36: (Dexpanthenol). A clear, viscous, somewhat hygroscopic liquid, having a slight characteristic odour. Some crystallisation may occur on standing. Freely soluble in water, in alcohol, in methyl alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerol. Store in airtight containers.

Uses and Administration

Dexpanthenol is the alcoholic analogue of D-pantothenic acid (p. 2085.2). It has been given intramuscularly in doses of 250 or 500 mg to prevent or control gastrointestinal atony but its value has not been established. It has also been given by slow intravenous infusion.

Dexpanthenol and the racemate panthenol have been used topically in strengths of 2 or 5% for the treatment of various minor skin disorders. They are also included in some vitamin preparations.

References.

1. Kehrl W, Sonnemann U. Verbesserung der Wundheilung nach Nasenoperationen durch kombinierte Anwendung von Xylometazolin und Dexpanthenol. *Laryngorhinootologie* 2000; **79:** 151–4.
2. Gehring W, Gloor M. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydration: results of a human in vivo study. *Arzneimittelforschung* 2000; **50:** 659–63.
3. Ebner F, *et al.* Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol* 2002; **3:** 427–33.
4. Biro K, *et al.* Efficacy of dexpanthenol in skin protection against irritation: a double-blind, placebo-controlled study. *Contact Dermatitis* 2003; **49:** 80–4.
5. Rockmann H, *et al.* Anaphylaxis after dexpanthenol exposure by multivitamin tablets. *Clin Exp Dermatol* 2005; **30:** 714–16.

Adverse Effects and Precautions

There have been a few reports of allergic reactions possibly associated with dexpanthenol. Dexpanthenol is contra-indicated in haemophiliacs and in patients with ileus due to mechanical obstruction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Recugel; ***Austral.***: Bepanthen; ***Austria***: Bepanthen; Corneregel†; Panto Liquid; Pantothen; ***Braz.***: Bepantol; Cicatenol; Dexpantol; Neopantol; Pantodex; ***Chile***: Bepantol; ***Cz.***: Bepanthen; Panthenol; ***Fin.***: Bepanthen; ***Fr.***: Bepanthen; Bepanthene; BepanthenSensicalm; ***Ger.***: Bepanthen; Corneregel; Marolderm†; NasenSpray Panthenol; Nasic-cur; Otriven mit Dexpanthenol†; Pan-Ophtal; Panthenol; ***Gr.***: Bepanthene; Corneregel; ***Hong Kong***: Corneregel; ***Hung.***: Bepanthen; Corneregel; Panthenol; ***Indon.***: Bepanthen; Pasquam; Tentalux; ***Israel***: Bepanthen; Dermacalm; Neocutan; ***Ital.***: Bepanten; ***Mex.***: Bepanthen; Corneregel; ***NZ***: Bepanthen; ***Philipp.***: Corneregel; ***Pol.***: Bepanthen; Corneregel; Dermopanten; ***Port.***: Bepanthene; ***Rus.***: Bepanthen (Бепантен); Corneregel (Корнерегель); Moreal-Plus (Мореаль-Плюс); Pantenol (Пантенол); Panthenol (Пантенол); Panthoderm (Пантодерм); ***S.Afr.***: Bepanthen†; ***Singapore***: Bepanthen; ***Spain***: Bepanthene; ***Switz.***: Bepanthen; Bepanthene; ***Thai.***: Bepanthen; ***Turk.***: Armathene; Bepanthene; Bepantol†; Pantebiol; Pantenol†; Pantomed; ***UAE***: Dexipan; ***UK***: Bepanthen; ***Ukr.***: Bepanthen (Бепантен); Corneregel (Корнерегель); Depantol (Депантол); Panthecream (Пантекрем); Panthenol (Пантенол Спрей); ***USA***: Ilopan; Panthoderm.

Multi-ingredient Preparations. ***Arg.***: Aftersun; Amplus; Dermocridin; Dermvien; Heduline; Hydratone; Lociherp Liposomas Vitaminado; Macbirs; Mucobase; Novofarma; Rain-LY; Sebulex; Talowin; ***Austral.***: Macro Natural Vitamin E Cream; Sebirinse; ***Austria***: Bepanthen Plus; Bepanthen†; Colda; Coldistan; Dolobene; Keratosis forte; Keratosis; Nasic; Oleovit; Siccaprotect; Sigman-Haustropfen; Venobene; ***Belg.***: Algi-Cool†; Purigel NF; ***Braz.***: Capel; Dolobene†; Esmalfort; Ferrocomplex; Fisioativ; Naridrin; Nariflux; Uvless; ***Chile***: Aftagel Bucal; Benutrex 1000†; Biopiel; Cicapost; Diencil; Eucerin Correctora Anti-Espinillas; Eucerin Micropigmentos; Eucerin Piel Grasa†; Panthoderm-A†; Pomada Vitaminica; Queratopil; Ureadin Facial Anti-arrugas; Ureadin Rx DB; Ureadin Rx RD; Urealeti; Vitis Encias Colutorio; Vitis Encias Pasta; ***China***: Dolobene (瑞乐平); Xin Le Dun (新乐敦); ***Cz.***: Bepanthen Plus; Dolobene; Nasic; Panlid†; Siccaprotect; ***Fin.***: Oftan A-Pant; Pantyson; Wicaran; Wicarba; ***Fr.***: Bebebiafine Anti-Rougeures; Calmobrul; Cicactive; Herpclair; ***Ger.***: Bepanthen Antiseptische; Bepanthen Augentropfen; Dispatenol; Dolobene†; GeloBacin; Hewekzem novo N; Hydro Cordes; Hylo-Care; InfectoGripp; Lipo Cordes; Nasic; PC 30 V; Remederm; Saseem; Siccaprotect; Siozwo San; ***Gr.***: Aquasol A; Nasosyn; Novaquasol-A; ***Hong Kong***: Dolobene†; Mar Plus; Pregnacare; Sebirinse; ***Hung.***: Alksebor; Antikeloid; Aurobin; Bepanthen Plus; Dolobene; Pelsano Med; Phlogosam; ***India***: Acmic-S; Alfariz; Alprovit DPS; Altone; Altrazyme; Alvit; Ampiro; Aneudox-12; Anvital DPS; Anzykair; Asiplex; Astyfer; Aviton; B-12; B-12; Cherrytone; Climdan; Climdan; Focobal Plus; Meconerv; Mego-XL; Mericobal; Nurokind Plus; Nutrared; Optineuron; Sioneuron; Vitneurin; ***Indon.***: Apecur; Bevita; Brainvit; Confortin; Romilar Expectorant; Skintex†; ***Israel***: Bepanthen Plus; Kamil Blue; Kamil Blue; Neocutan Silver; Panthisone†; Pedisol†; ***Ital.***: Alfa Acid; Biomineral 5-Alfa Shampoo; Biorag; Gastrotuss; Hylo-Care; Keto Z; Lenirose; Parogencyl; Recugel; Respifree Nasale; Rinopanteina; ***Malaysia***: Bepanthen Plus; Hairmonius; Mar Plus; Palmer's Cocoa Butter Formula Nappy Rash Ointment; Palmer's Cocoa Butter Formula Nursing Cream; pH Care; ***Mex.***: Aloemagnolia; Cetopic; Emolin Neo; Nutrem; Salilex; ***Neth.***: Prunacolon; Prunasine; ***NZ***: Sebirinse; ***Philipp.***: Ascovit-C†; Megavit; pH Care; Remederm†; Sebo Fluid†; Suplenex; ***Pol.***: Acodin; Alantan-Plus; Bepanthen Plus; Dolobene†; ***Port.***: Bepanthene Plus; Bepanthene†; Bexident; Cicapost; Efluvium Anti-seborreico†; Lactigriet; Nutraisdin; Nutraisdin; Ureadin 10 Plus; ***Rus.***: Aurobin (Ауробин); Bepanthen Plus (Бепантен Плюс); Depanthol (Депантол); Dolobene (Долобене); Hepatrombin (Гепатромбин); Hylozar-COMOD (Хилозар-КОМОД); Venolife (Венолайф); ***S.Afr.***: Broncol†; ***Singapore***: pH Care Intimate Wash; ***Switz.***: Alphastria; Assan rem; Bepanthen Plus; Bepanthene Plus; Carbamide + VAS; Dermacalm-d; Dolobene; Fluimare Plus; Gorgonium; Hylo-Care; Lyman; Nasic; Nasmer 3plus; Nasmer free; No Pic; Nose Fresh au D-panthenol; Osa Gel de dentition; Parapic†; PC 30 V; Pelsano; Pigmanorm; Rhinomer mini; Siccalix; Siccaprotect; Sportium; Sportusal Spray sine heparino; Sportusal; Stilex; Turexan Capilla†; Unathene†; Undex†; Venucreme; Venugel; ***Thai.***: Bepanthen First Aid; Mar Plus; Romilar; ***Turk.***: Bepanthene Plus; Numis; Pantenol Plus; Rinopanteina; Siccaprotect; Stilex; ***UK***: Allerclear; Hylo-Care; Oilatum Scalp Intensive; Uvistat Eye Drops; Vipsogal; ***Ukr.***: Aurobin (Ауробин); Bepanthen Plus (Бепантен Плюс); Dolobene (Долобене); Fitoval Shampoo (Фитовал шампунь); Hepathrombin (Гепатромбин); Panthestin (Пантестин); Panthevenol (Пантевенол); Phytobene (Фитобене); Rjativnik (Рятивныk); Venohepanol (Веногепанол); ***USA***: Aquaphor Healing Ointment; ***Venez.***: Cepin; Diadex; Pantonic.

Pharmacopoeial Preparations

USP 36: Dexpanthenol Preparation; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Water-soluble Vitamins Capsules; Water-soluble Vitamins with Minerals Capsules.

Papain ⊗

EC 3.4.22.2; Papaina; Papaína; Papayotin; Папаин.

CAS — 9001-73-4.

ATC Herb — HA09AA5002 (Carica papaya: extract).

UNII — A236A06Y32.

Pharmacopoeias. In *US*.

USP 36: (Papain). A purified proteolytic substance derived from *Carica papaya* (Caricaceae). It contains not less than 6000 USP units per mg. A white to light tan, amorphous powder. Soluble in water, the solution being colourless to light yellow and more or less opalescent; practically insoluble in alcohol, in chloroform, and in ether. pH of a 2% solution in water is between 4.8 and 6.2. Store in airtight

containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Units

USP 36 defines the USP unit of papain activity as the activity that releases the equivalent of 1 microgram of tyrosine from a specified casein substrate under the conditions of the assay, using the enzyme concentration that liberates 40 micrograms of tyrosine per mL of test solution.

One FIP unit of papain is defined as the enzyme activity which under specified conditions hydrolyses 1 micromol of *N*-benzoyl-L-arginine ethyl ester per minute.

The Warner-Chilcott unit, based on the quantity of enzyme required to clot 2.64 microlitre of milk substrate in 2 minutes at 40 degrees, under specified conditions, has also been used for papain.

Uses and Administration

Papain consists chiefly of a mixture of papain and chymopapain, proteolytic enzymes that hydrolyse polypeptides, amides, and esters, especially at bonds involving basic amino acids, or leucine or glycine, yielding peptides of lower molecular weight. It is used with urea as a topical debriding agent. It is also used for the removal of protein deposits from the surface of soft contact lenses (p. 1730.2).

Preparations of papain, alone or combined with antibacterial agents and/or other substances, have been taken orally for their supposed anti-inflammatory properties, and it has also been used as an ingredient of various mixtures claimed to aid digestion.

Papain is widely used as a meat tenderiser and in the clarification of beverages.

Malignant neoplasms. Papain has been included in proteolytic enzyme preparations used in oncology to reduce the adverse effects of chemotherapy and radiotherapy. Although the number of clinical studies on which to judge efficacy is limited, a review[1] of such studies suggested that systemic enzyme therapy might be beneficial. Clinical studies have used a preparation containing papain, trypsin, and chymotrypsin in a weight ratio of 5:2:2, and the beneficial effect seems to be based on its anti-inflammatory potential.

1. Leipner J, Saller R. Systemic enzyme therapy in oncology: effect and mode of action. *Drugs* 2000; **59:** 769–80.

Adverse Effects

Hypersensitivity reactions have occurred.

Effects on the eyes. Ocular and periorbital angioedema occurring within 4 hours of use of a contact lens cleansing solution containing papain has been reported.[1]

1. Bernstein DI, *et al*. Local ocular anaphylaxis to papain enzyme contained in a contact lens cleansing solution. *J Allergy Clin Immunol* 1984; **74:** 258–60.

Oesophageal perforation. Extensive destruction of the oesophageal wall, with perforation, resulted from the use of a papain suspension given to treat an obstruction caused by impacted meat.[1] The patient had been given 1.2 g of papain over a 12-hour period. Ten days after a thoracotomy, the descending thoracic aorta ruptured, and she died from haemorrhage.

1. Holsinger JW, *et al*. Esophageal perforation following meat impaction and papain ingestion. *JAMA* 1968; **204:** 734–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Stop Itch; ***Canad.***: Digest Aid†; Digestol; Solarcaine Stop Itch†; ***Chile***: Papenzima; ***Hong Kong***: Eurolase; ***Malaysia***: Beazyme; ***NZ***: Stop Itch; ***Rus.***: Caripazym (Карипазим); ***USA***: Allergan Enzymatic†; ProFree†.

Multi-ingredient Preparations. ***Arg.***: Bucal Tac Whitening Gel; Butimerin; Docechol; Homocisteon Compuesto; Opoenterol; Pankreon Total; Solustres; ***Austral.***: Betaine Digestive Aid; Bio-Disc†; Digestaid; Enzyme; Tresos B PluSe; Vegie Digestaid; ***Austria***: Rennie Digestif; Wobe-Mugos; Wobenzym; ***Belg.***: Digestomen; ***Canad.***: Digesdyn; Digest; Digestolax; Multi Enzyme†; Multi-Zyme†; Proteozyme Forte; Wobenzym; ***China***: Dages (达吉); ***Cz.***: Digestif Rennie†; Wobenzym; ***Ger.***: Wobenzym N†; ***Gr.***: Lysopaine; Sopain-Plus; ***Hong Kong***: Appezym; Caricose†; Digezym; Enzyme Co†; ***Hung.***: Digestif Rennie†; ***India***: Bestozyme P; Bestozyme; Bestozyme; Catalyd; Catazyme-P; Dipep; Eaze; Enzofast; Gastrozyme; Glozyme; Intrazyme; Jayzyme; Lac-B; Laxzyme; Merispas; Merozyme-C; Neopeptine; Neopeptine; Neopeptine; Nutrozyme; Nutrozyme; Papytazyme; Unienzyme; ***Indon.***: Papaven†; ***Malaysia***: Enzyme Digest; Pepfiz; ***Mex.***: Digenor Plus; Wobe-Mugos; Wobenzym; ***Pol.***: Caridentt; ***Rus.***: Pepfiz (Пепфиз); Unienzyme с MPS (Юниэнзим с МПС); Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); ***Singapore***: Stop-Itch Plus; ***Spain***: Digestomen Complex; Lizipaina; ***Switz.***: Lysopaine†; ***Thai.***: Pepfiz; Pepsitase; Polyenzyme-I†; ***UK***: Enzyme Digest; Herbal Indigestion Naturtabs; Indigestion and Flatulence; ***Ukr.***: Digestin (Дигестин); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); Wobe-Mugos E (Вобэ-Мугос Е)†; Wobenzym (Вобэнзим); ***USA***: Accuzyme†; AllanEnzyme†; AllanfillEnzyme†; Bio-Zyme; Gladase-C†; Gladase†; Kovia†; Panafil-White†; Panafil†; Papaya Enzyme; Papfyll; Ziox†; ***Venez.***: Wobenzym N.

Pharmacopoeial Preparations

USP 36: Papain Tablets for Topical Solution.

Paradichlorobenzene

Dichlorbenzol; Paradiclorobenceno; Пара-дихлорбензол.

1,4-Dichlorobenzene.

$C_6H_4Cl_2$=147.0

CAS — 106-46-7.

UNII — D149TYB5MK.

Profile

Paradichlorobenzene has general properties similar to those of orthodichlorobenzene (see p. 2578.1) but is considered to be less toxic. It is present in several preparations intended for the removal of ear wax (see p. 1836.3). It has been used as a furniture preservative and in mothballs and lavatory deodorant blocks. Abuse of preparations containing paradichlorobenzene has been reported.

Abuse. Neurocutaneous symptoms have been reported[1] in 2 18-year-old twin girls after abuse of mothballs by inhaling the fumes, and in one twin, also chewing the mothballs. Once they stopped, both sisters recovered completely within 3 to 6 months depending on their previous level of abuse. Intermittent nasal inhalation and ingestion of mothballs over many years led to toxic leukoencephalopathy in a 32-year-old woman.[2] Her symptoms improved when she had no access to mothballs but reappeared when abuse resumed. In another patient it was suggested that neurotoxicity after abuse of mothballs may have been due to a withdrawal syndrome rather than direct toxicity of paradichlorobenzene.[3] Haemolytic anaemia has also been associated with ingestion of mothballs.[4]

1. Feuillet L, *et al*. Twin girls with neurocutaneous symptoms caused by mothball intoxication. *N Engl J Med* 2006; **355:** 423–4.
2. Kumar N, *et al*. Mothball mayhem: relapsing toxic leukoencephalopathy due to *p*-dichlorobenzene neurotoxicity. *Ann Intern Med* 2009; **150:** 362–3.
3. Cheong R, *et al*. Mothball withdrawal encephalopathy: case report and review of paradichlorobenzene neurotoxicity. *Subst Abus* 2006; **27:** 63–7.
4. Sillery JJ, *et al*. Hemolytic anemia induced by ingestion of paradichlorobenzene mothballs. *Pediatr Emerg Care* 2009; **25:** 252–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Cerumol; ***Canad.***: Cerumol; ***India***: Ceruklin; Clearwax; Desol; Despol; Dewax; Fastwax; Nayawax; Nill-O-Wax; Otoclean; Otorex; Parabec; Waxolve†; ***Irl.***: Cerumol; ***Israel***: Cerumol; ***Malaysia***: Cerumol; ***Port.***: Otoceril; ***S.Afr.***: Cerumol; ***Singapore***: Cerumol; ***Switz.***: Cerumenol; ***UK***: Cerumol.

Paraphenylenediamine

Parafenilendiamina; Парафенилендиамин.

p-Phenylenediamine; 1,4-Benzenediamine.

$C_6H_4(NH_2)_2$=108.1

CAS — 106-50-3.

UNII — U770QIT64J.

NOTE. Commonly known in the hairdressing trade as *'para'*. 'PPD' is an abbreviation sometimes used for paraphenylenediamine, which should not be confused with tuberculin purified protein derivative (see Tuberculins, p. 2635.3), which is also referred to by the same abbreviation.

Profile

Paraphenylenediamine is widely used in permanent hair colour preparations. However it is a potent contact allergen and EU legislation restricts its concentration in the finished product to a maximum of 6% calculated as free base. Both type I and type II reactions occur and symptoms usually present as dermatitis on the face or hands. More severe reactions can lead to angioedema; anaphylaxis has also been reported. Systemic symptoms similar to those after ingestion (see below) may also occur following absorption through intact skin. For references to hypersensitivity after skin tattoos with henna that was mixed with paraphenylenediamine, see below.

Application of tints to the eyelashes or eyebrows may produce blepharoconjunctivitis, eye oedema, and eye pain, with progression to facial oedema and dermatitis, lachrymation, photophobia, uveitis, and keratitis in severe cases. Corneal necrosis has led to blindness. In some countries, use of paraphenylenediamine in eyelash or eyebrow tints is banned.

Early symptoms after ingestion of paraphenylenediamine are vomiting and abdominal pain. Severe oedema of the face and oropharynx can lead to life-threatening obstruction of the airways. Other symptoms may include hypotension or hypertension, tachycardia, hepatotoxicity, renal failure, metabolic acidosis, methaemoglobinaemia, rhabdomyolysis, tremor, convulsions, and coma; multisystem failure may be fatal.

Some studies have linked hair dyes with mutagenicity and carcinogenicity, although such findings have often been refuted. In the EU, legislation controls which substances may be used in hair dye products.

Paraphenylenediamine is also used in the textile and photographic industries.

Hypersensitivity. Paraphenylenediamine is added to natural henna (p. 2525.1) to darken it (known as black henna) for use in temporary skin tattoos. However, there have been reports of the paraphenylenediamine component producing hypersensitivity reactions,[1-9] permanent skin pigment changes,[6,9] and also cross-sensitisation to paraphenylenediamine-containing hair dyes[2,6-9] and textile dyes;[6,9] there is also the possibility of sensitisation to other allergens such as natural rubber latex.[9]

1. Brancaccio RR, *et al*. Identification and quantification of *para*-phenylenediamine in a temporary black henna tattoo. *Am J Contact Dermat* 2002; **13:** 15–18.
2. Marcoux D, *et al*. Sensitization to para-phenylenediamine from a streetside temporary tattoo. *Pediatr Dermatol* 2002; **19:** 498–502.
3. Neri I, *et al*. Childhood allergic contact dermatitis from henna tattoo. *Pediatr Dermatol* 2002; **19:** 503–5.
4. Bowling JCR, Groves R. An unexpected tattoo. *Lancet* 2002; **359:** 649.
5. Leggiadro RJ, *et al*. Temporary tattoo dermatitis. *J Pediatr* 2003; **142:** 586.
6. Matulich J, Sullivan J. A temporary henna tattoo causing hair and clothing dye allergy. *Contact Dermatitis* 2005; **53:** 33–6.
7. Sosted H, *et al*. Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006; **54:** 87–91.
8. Redlick F, DeKoven J. Allergic contact dermatitis to paraphenylendiamine in hair dye after sensitization from black henna tattoos: a report of 6 cases. *CMAJ* 2007; **176:** 445–6.
9. Sonnen G. Type IV hypersensitivity reaction to a temporary tattoo. *Proc (Bayl Univ Med Cent)* 2007; **20:** 36–8.

Poisoning. References.

1. Ashraf W, *et al*. Systemic paraphenylenediamine (PPD) poisoning: a case report and review. *Hum Exp Toxicol* 1994; **13:** 167–70.
2. Lifshits M, *et al*. Fatal paraphenylenediamine (hair dye) intoxication in a child resembling Ludwig's angina. *J Toxicol Clin Toxicol* 1993; **31:** 653–6.
3. Anuradha S, *et al*. Acute renal failure following para-phenylenediamine (PPD) poisoning: a case report and review. *Ren Fail* 2004; **26:** 329–32.
4. Kallel H, *et al*. Clinical manifestations of systemic paraphenylene diamine intoxication. *J Nephrol* 2005; **18:** 308–11.
5. Brahmi N, *et al*. Acute myocarditis and myocardial infarction induced by paraphenylenediamine poisoning. Interest of angiocoronarography. *Int J Cardiol* 2006; **113:** E93–E95.
6. Bhargava P, Matthew P. Hair dye poisoning. *J Assoc Physicians India* 2007; **55:** 871–2.
7. Abidi K, *et al*. Myocardial lysis in a fetus induced by maternal paraphenylenediamine poisoning following an intentional ingestion to induce abortion. *Hum Exp Toxicol* 2008; **27:** 435–8.
8. Soni SS, *et al*. Systemic toxicity of paraphenylenediamine. *Indian J Med Sci* 2009; **63:** 164–6.

Paratoluenediamine

Paratoluendiamina; Пара-толуолдиамин.

2-Methyl-1,4-phenylenediamine.

$C_7H_{10}N_2$=122.2

CAS — 95-70-5.

UNII — 24JO8Z0RJU.

Profile

Paratoluenediamine is used in hair colour preparations.

Like paraphenylenediamine, above, paratoluenediamine may be associated with sensitivity reactions.

Parsley

Perejil; Persil; Persil, racine de (parsley root); Petersilie; Petrželový kořen (parsley root); Petroselini Radix (parsley root); Petroselinum; Петрушка.

*ATC Herb — HA03AW5045 (*Petroselinum crispum*: root); HG02WB5006 (*Petroselinum crispum*: fruit); HG04BW5026 (*Petroselinum crispum*: fruit); HG04BW5027 (*Petroselinum crispum*: root).*

*UNII — 58FMD0Q0EV (*Petroselinum crispum *top); 1WZA4Y92EX (*Petroselinum crispum*); 030FN2959H (*Petroselinum crispum *root).*

Profile

Parsley (*Petroselinum crispum*, Umbelliferae) is used in herbal medicine, where it is mainly given as a diuretic. It is also used as a culinary herb and flavouring.

Parsley oil has been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Odo-fre.

Multi-ingredient Preparations. ***Arg.***: Daily Nutrilite; Parselenium E; ***Austral.***: Extralife Fluid-Care†; Hair Skin & Nails; Odourless Garlic; ***Canad.***: Cellutex; Diuretic Formula; Herbal Diretic; Herbal Diuretic†; Herbal Diuretic; Saw Palmetto Formula†; ***Cz.***: Species Urologicae Planta; Urologicka Cajova Smes; ***Fr.***: Alibi; Oropur; ***Ger.***: Asparagus-P; ***India***: Nutiva-Lyco; ***Rus.***: Herbion Urological Drops (Гербион Урологические Капли); ***UK***: AsPar-Aid; Athera; Fre-bre; Mixed Vegetable Tablets; Modern Herbals Menopause; ***Ukr.***: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Nephrocare (Нефрокеа); Tazalok (Тазалок); Urocran (Урокран); Uronephron (Уронефрон).

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Fr.***: Santalum Complexe No 30†; ***Ger.***: Cysto Hevert; Hewecyst Blasen-Nieren†; Pascorenal N; ***Neth.***: Cystilite; Homeocare Uro.

Parsley Piert

Alchémille des Champs; Alquimila arvense; Aphanes; Gewöhnlicher Acker-Frauenmantel; Невзрачница Полевая (*Aphanes arvensis*).

Profile

Parsley piert, the aerial parts of *Aphanes arvensis* (*Alchemilla arvensis*) (Rosaceae) has astringent, diuretic, and demulcent properties. It is used for urinary-tract disorders, including renal and urinary calculi.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Kontryhelova Nat.

Multi-ingredient Preparations. ***Cz.***: Fytokliman Planta; ***UK***: Backache Relief; Diuretabs; HRI Water Balance.

Passion Flower

Burucuyá; Flor de la pasión; Golgotavirág hajtásvég; Granadilla; Grenadille; Kärsimyskukka; Maracuyá; May-pop; Mučenková nať; Pasiflorų žolė; Pasiflora; Pasionari; Pasionaria; Passiflora; Passiflorae Herba; Passiflore; Passionsblomma; Passionsblumenkraut; Страстоцвет Мясо-красный.

CAS — 8057-62-3 (passion flower extract).

*ATC Herb — HN05CM5019 (*Passiflora incarnata*: herb).*

*UNII — CLF5YFS11O (*Passiflora incarnata *top); K8F3G29S6Z (*Passiflora incarnata *flower); SF2061I8G4P (*Passiflora incarnata *fruit); SY49TH8VUA (passion flower extract).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Passion Flower). The fragmented or cut, dried aerial parts of *Passiflora incarnata*; it may also contain flowers and/or fruits. It contains not less than 1.5% of total flavonoids expressed as vitexin ($C_{21}H_{20}O_{10}$=432.4), calculated with reference to the dried drug. Protect from light.

Profile

Passion flower is reputed to have antispasmodic and sedative properties and has been used as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture.

Homoeopathy

Passion flower has been used in homoeopathic medicines under the following names: Passiflora incarnata; Passiflora; Passi. in.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sedante Noche; ***Austria***: Pascoflair; Passiflorin; ***Belg.***: Sedanxio; Sedistress; ***Braz.***: Acalmil; Sintocalmy; Tensart; ***Ger.***: Hoggar Balance; Kytta-Sedativum fur den Tag; Pascoflair; Passidon; Passiflora Curarina; ***Hung.***: Naturest; ***Pol.***: Passiflor; ***Rus.***: Novo-Passit (Ново-Пассит); ***Spain***: Pasang; ***Switz.***: A Vogel Gouttes relaxantes; Dormodyn; Valverde Apaisement; ***Turk.***: Alora; Poliflorin; Sedaflora; ***UK***: DiaPassion; Modern Herbals Sleep Aid; Natracalm; Naturest; Nodoff; Pascoe Calm; Phytocalm; RelaxHerb; ***Ukr.***: Alora (Алора); ***Venez.***: Floral Pas.

Multi-ingredient Preparations. ***Arg.***: Armonil; Calmtabs; Nervocalm; Passacanthine; Phytocalm; SDN 200; Sedanat†; Sedante Dia; Serenil; Sigmasedan; Valeriana Compuesta; Yerba Diet; ***Austral.***: Advanced Restless Leg Care; Aloe Vera Plus; Calmo†; Euphorbia Complex†; Executive B Stress Formula; Executive B†; Executive Sleep Formula; Extralife Sleep-Care†; Herbal Rest & Relax; Humulus Compound; Natural Deep Sleep†; Nervatona Calm; Nervatona Focus; Passionflower Plus†; Sleep Easy; Sleep Naturally; Tranquil Night; Valerian Complex; ***Austria***: Alpinamed Passelyt; Nervenruh; Neurapas; Passedan; Sedogelat; Wechseltee St Severin; ***Belg.***: Sedinal; Seneuval; ***Braz.***: A Saude da Mulher; A Saude da Mulher; Bronquiogen†; Calman; Calmapax; Calmiplan; Floriny; Pasalix; Pasic; Passaneuro; Passaneuro; Passiflorine; Ritmoneuran; Sedantol; Serenus; Sominex; Vagostesyl; ***Canad.***: Calmane; Calmane; Detente†; Dormane Plus; Dormane Tisane; Dormane; Herbal Insomnia†; Myoplex†; Natural HRT Nightime; Nervinat; Phytocalm†; Relax Plus; Relaxant; Relaxol; Salusan†; Sleep Relax; ***Chile***: Armonyl Nocturno; Armonyl; Melipass; Recalm†; ***Cz.***: Novo-Passit; Passedan†; Passit; ***Fr.***: Biocarde; Boribel Tisane No 8†; Calmiflorine†; Calmotisan†; Euphytose; Fibromyalgine Fort; Fibromyalgine; Mediflor Tisane Calmante Troubles du Sommeil No 14; Natudor; Neuroflorine†; Neuropax†; Nocvalene†; Panxeol†; Passiflorine; Passinevryl†; Plenesia; Provencale No 4†; Santane N$_9$; Sedatif Tiber†; Sympavagol†; Tisane Provencale no 4†; ***Ger.***: Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee†; Kytta-Sedativum; Moradorm S; Neurapas; Passin; Phytonoctu; Seda-Plantina N; Tornix; Valeriana Beruhigungsdragees; Vivinox Day; ***Gr.***: Passiflorine; Passinevrol; Vivinox; ***Hung.***: Habstal-Nerv N; Sedogelat; ***Indon.***: Slip-iZZZ+; ***Irl.***: Avena Sativa Comp; Quiet Life; ***Israel***: Calmanervin; Calmanervin; Nerven-Dragees; Passiflora Compound†; Passiflora; ***Ital.***: Actenacol; Anevrasi; Biocalm; Calmason; Controller; Dormil; Fitosonno; No Gas Enzimi; Noctis; Parvisedil; Passiflorine; Saniquiet; Sedatol; Sedatol; Sedopuer F; Vagostabil Junior; ***Mex.***: Ifupasil; Pasinordin; ***Neth.***: Plantival; ***Philipp.***: Sleepasil; ***Pol.***: Nervendragees; Nerwonal; Passibil; Passispasmin; Passispasmol†; Psychotonisol†; Valused; ***S.Afr.***: Avena Sativa Comp†; Biral†; ***Spain***: Netisum; Neurapas; Passiflorine; Sedonat; Valdispert Complex; Valeriana Leo; Valrelax†; ***Switz.***: Circulan†; Dragees pour la detente nerveuse et le sommeil†; Dragees pour la detente nerveuse†; Dragees pour le coeur et les nerfs; Femisan; Gouttes pour le coeur et les nerfs; Passiflor; Relaxane; Relaxo; Strath Gouttes pour le nerfs et contre l'insomnie; Tisane antirhumatismale; Tisane calmante pour les enfants; Valverde Coeur; Valverde Detente dragees; ***UK***: Anased; Avena Sativa Comp; Bio-Strath Valerian Formula; Botanova; Chamomile Blend; Daily Tension & Strain Relief; DiaDay & Night; DiaNight Plus; DiaRelax; DiaSleep Plus; Gerard House Serenity; Goodnight; Herbal Pain Relief; HRI Night; Kalms Sleep; Modern Herbals Stress; Napiers Herbal Stress & Sleep Aid; Niteherb Plus; Nodoff; Nytol Herbal; PMT Formula; Quiet Life; Quiet Nite; Quiet Tyme; Relax B$^+$; Slumber; Sominex Herbal; SuNerven; Valerian Passiflora and Hops; ***Ukr.***: Central-B (Централ-Б); Herbastress (Гербастресс); Klimased (Климасед); Novo-Passit (Ново-Пассит); Persen Cardio (Персен Кардио); ***USA***: PowerSleep; ***Venez.***: Equaliv; Lupassin; Pasidor; Pasifluidina; Passiflorum; Rendetil; Sedival.

Homoeopathic Preparations. ***Austral.***: Calm; Nervatona Calm; Nervatona Focus; Sleep & Insomnia Relief; Smoke Eze; ***Austria***: Avena Rihom Komplex†; ***Canad.***: Calms Forte; Calsom†; Comp-Drops 1 Stress†; Comp-Drops 7 Sleepless†; Homeo-Form I†; Homeogene 46; Hylands Formula C; Hylands Formula CF; Insomnia Passiflora†; Insomnia; Passiflora Complex†; Quietude; Sedilor†; Spascupreel; ***Cz.***: Sedalia; Spascupreel S†; ***Fr.***: Boripharm No 3; Boripharm No 41; Calmodren; Homeogene 46; Passiflora Compose; Passiflora GHL; Quietude; Slipeol†; ***Ger.***: Alho-Sedosan; Avena sativa comp†; Calmvalera; Cefaneuro; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; Dormosyx; dysto-loges N; dysto-loges S; Infinerval; Nervo-Plantin†; Nervoid N; Nervoregin H; Nervoregin; Neurexan; Neuro-Ginsan N; Neuroselect; Pascolibrin; Passiflora Complex†; Seda-Do; Sedakatt; Spascupreel; Tondinel H; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Spascupreel; ***Neth.***: Homeocare Nervo; Hyperilite; Quietude†; Weleda Avena Valeriana; ***Rus.***: Nux Vom-Plus (Нукс Вом-Плюс); Passidorm (Пассидорм); Tabacum-Plus (Табакум-Плюс); Valeriana-Plus (Валериана-Плюс); ***Switz.***: Nelsons Nocturna†; Quietude; ***UK***: Noctura; ***USA***: Preferred Remedies Sleep.

Patchouli

Пачули.

Profile

Patchouli (*Pogostemon cablin*, Lamiaceae) is the source of patchouli oil, which is distilled from the dried leaves and young shoots. Patchouli oil is used in aromatherapy and perfumery.

In traditional Chinese medicine the dried aerial part is known as Guang Huo Xiang.

Homoeopathy

Patchouli oil has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Thai.***: Relief Mouth Ulcer.

Patent Blue V

Acid Blue 3; Azul Patente V; CI Food Blue 5; Colour Index No. 42051; E131; Патентованный Голубой V; Патентованный Синий V.

Calcium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclohexa-2,5-dienylidene)-5-hydroxytoluene-2,4-disulphonate.

$(C_{27}H_{31}N_2O_7S_2)_2Ca$=1159.4

CAS — 3536-49-0.

UNII — 8QE473DV1Z.

NOTE. The name Patent Blue V is also used as a synonym for Sulfan Blue (CI No. 42045) (see p. 2624.1).

Pharmacopoeias. In *Fr.*

Uses and Administration

Patent blue V is given by subcutaneous injection in a dose of 1 to 10 mL of a 2.5% solution to colour the lymph vessels so that they can be injected with a contrast medium; a local anaesthetic may also be given. Patent blue V is also given by intravascular injection, in a solution prepared with sodium chloride 0.9% and lidocaine 1%, to visualise the arterial bed before giving intra-arterial chemotherapy.

Patent blue V is used as a food colour.

Malignant neoplasms of the breast. Intradermal injection of patent blue V at the site of a primary breast tumour has been used to identify the associated lymph nodes,[1] but concern has been expressed regarding possible long-term staining of the skin.[2]

1. Borgstein PJ, *et al.* Intradermal blue dye to identify sentinel lymph-node in breast cancer. *Lancet* 1997; **349:** 1668–9.
2. Giuliano AE. Intradermal blue dye to identify sentinel lymph node in breast cancer. *Lancet* 1997; **350:** 958.

Adverse Effects and Precautions

Hypersensitivity reactions may occur immediately or a few minutes after injection of patent blue V; on rare occasions they may be severe and include shock, dyspnoea, laryngeal spasm, and oedema. Nausea, hypotension, and tremor have been reported.

Giving a small dose to test for hypersensitivity has been suggested.

References.

1. Jaffer U, *et al.* Skin necrosis following patent blue V injection for sentinel node detection during breast cancer excision: case report. *Breast J* 2008; **14:** 508–9.

Hypersensitivity. An urticarial rash occurred in a 5-year-old girl after use of tablets containing patent blue V to disclose the presence of dental plaque.[1] Severe anaphylactic reactions, including shock, have been reported.[2-6] Cross-sensitivity to sulfan blue has been reported.[7]

1. Chadwick BL, *et al.* Allergic reaction to the food dye patent blue. *Br Dent J* 1990; **168:** 386–7.
2. Woltsche-Kahr I, *et al.* Anaphylactic shock following peritumoral injection of patent blue in sentinel lymph node biopsy procedure. *Eur J Surg Oncol* 2000; **26:** 313–14.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Patent blue V and anaphylaxis. *Aust Adverse Drug React Bull* 2002; **21:** 10. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0208.pdf (accessed 02/07/04)
4. Wöhrl S, *et al.* Near-fatal anaphylaxis to patent blue V. *Br J Dermatol* 2004; **150:** 1037–8.
5. Dewachter P, *et al.* Anaphylactic reaction to patent blue V after sentinel lymph node biopsy. *Acta Anaesthesiol Scand* 2006; **50:** 245–7.
6. Bricou A, *et al.* Anaphylactic shock during the sentinel lymph node procedure for cervical cancer. *Gynecol Oncol* 2009; **114:** 375–6.
7. Scherer K, *et al.* Anaphylaxis to isosulfan blue and cross-reactivity to patent blue V: case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol* 2006; **96:** 497–500.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Blueron.

Pegademase *(rINN)*

EC 3.5.4.4 (adenosine deaminase); PEG-ADA; Pegademasa; Pégadémase; Pegademasum; PEG-Adenosine Deaminase; Пэгадемаза.

CAS — 9026-93-1 (adenosine deaminase).

ATC — L03AX04.

ATC Vet — QL03AX04.

UNII — HW3H7D91F6 (pegademase bovine).

NOTE. Pegademase Bovine is *USAN*.

Profile

Pegademase is a conjugate of adenosine deaminase, an endogenous enzyme that converts adenosine to inosine, with a macrogol (polyethylene glycol). Pegademase bovine is used in the treatment of severe combined immunodeficiency disease (SCID) associated with a deficiency of adenosine deaminase, in patients who are not suitable for bone marrow transplantation or in whom the transplantation has failed. It is given by intramuscular injection once every 7 days, in an initial dose of 10 units/kg; increments of 5 units/kg are then given weekly up to a usual weekly maintenance dose of 20 units/kg. A single dose of 30 units/kg should not be exceeded. Pegademase should be given with caution to patients with thrombocytopenia and avoided if the latter is severe.

References.
1. Lee CR, *et al.* Pegademase bovine: replacement therapy for severe combined immunodeficiency disease. *DICP Ann Pharmacother* 1991; **25:** 1092–5.
2. Hershfield MS. Adenosine deaminase deficiency: clinical expression, molecular basis, and therapy. *Semin Hematol* 1998; **35:** 291–8.
3. Gaspar HB, *et al.* How I treat ADA deficiency. *Blood* 2009; **114:** 3524–32.
4. Booth C, Gaspar HB. Pegademase bovine (PEG-ADA) for the treatment of infants and children with severe combined immunodeficiency (SCID). *Biologics* 2009; **3:** 349–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Adagen.

Pegaptanib Sodium *(BANM, USAN, rINNM)*

EYE-001; Natrii Pegaptanibum; NX-1838; Pegaptanib Octasodium; Pegaptanib sodico; Pégaptanib Sodique; Натрий Пегаптаниб.

CAS — 222716-86-1.
ATC — S01LA03.
ATC Vet — QS01LA03.
UNII — 3HP012Q0FH.

Uses and Administration

Pegaptanib is a pegylated modified oligonucleotide (aptamer) given as the sodium salt in the treatment of neovascular (wet) age-related macular degeneration. It is given by intravitreal injection into the affected eye in a dose of 300 micrograms once every 6 weeks. Stopping or withholding treatment should be considered if there has been no demonstrable benefit after 2 consecutive injections (i.e. at the 12-week visit).

Pegaptanib is also under investigation as an adjunct in the management of diabetic retinopathy.

Age-related macular degeneration. Pegaptanib is a pegylated modified oligonucleotide (aptamer) used in the treatment of age-related macular degeneration (AMD) (p. 880.2). It binds to and inhibits vascular endothelial growth factor (VEGF), which is a stimulant of angiogenesis thought to play a role in the neovascularisation and retinal changes associated with AMD. Pegaptanib is a selective antagonist of VEGF.[1,2]

Positive outcomes have been reported from two concurrent international multicentre prospective randomised controlled studies.[3] Vision loss was prevented and mean visual acuity improved in patients given 6-weekly injections of 300 micrograms, 1 mg, or 3 mg for 48 weeks compared with patients receiving sham injections. No dose-response relationship was found. In order to assess the effects of long-term therapy, patients who had been given pegaptanib in the first part of the study were then randomised at week 54 to receive either pegaptanib for a further 48 weeks or stop treatment, and patients who had been given sham injections were similarly re-randomised.[4] Results showed that patients given pegaptanib for a second year continued to derive additional benefit. A systematic review[5] of 5 randomised controlled studies found that pegaptanib was effective in reducing the risk of loss of visual acuity.

1. Siddiqui MAA, Keating GM. Pegaptanib: in exudative age-related macular degeneration. *Drugs* 2005; **65:** 1571–7.
2. Chapman JA, Beckey C. Pegaptanib: a novel approach to ocular neovascularization. *Ann Pharmacother* 2006; **40:** 1322–6.
3. Gragoudas ES, *et al.* Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; **351:** 2805–16.
4. Chakravarthy U, *et al.* VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113:** 1508–21.
5. Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 06/06/08).

Adverse Effects and Precautions

Endophthalmitis has been reported in patients given pegaptanib sodium and patients should be monitored for signs of infections for a week after the procedure. Retinal haemorrhage, retinal detachment, iatrogenic traumatic cataract, and raised intra-ocular pressure have also been reported. Immediate or delayed intravitreous haemorrhage may occur after injection. Common but less serious ocular adverse effects include eye pain, irritation, inflammation, blurred vision, visual disturbances, corneal oedema, punctate keratitis, and vitreous floaters.

Non-ocular adverse effects that have been reported include headache, rhinorrhoea, bronchitis, diarrhoea, dizziness, nausea, and urinary-tract infections.

Hypersensitivity reactions, including anaphylaxis or anaphylactoid reactions, and angioedema have been reported rarely within several hours of a dose.

Pegaptanib is contra-indicated in patients with active or suspected ocular or periocular infections.

Data from two concurrent international multicentre prospective randomised controlled studies[1] were analysed to assess the safety of pegaptanib after 2 years of treatment for neovascular (wet) age-related macular degeneration. The most common ocular adverse effects were attributed to the injection procedure and were transient and mild to moderate in intensity. Failure to follow the injection preparation protocol accounted for most cases of endophthalmitis. The incidence of adverse effects associated with systemic inhibition of vascular endothelial growth factor or severe ocular inflammation, cataract progression, or glaucoma was not higher in the pegaptanib-treated patients compared with patients receiving sham injections. Overall, the safety profile of pegaptanib was favourable in these studies.

1. D'Amico DJ, *et al.* VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006; **113:** 992–1001.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Macugen; ***Belg.***: Macugen; ***Braz.***: Macugen†; ***Canad.***: Macugen; ***Cz.***: Macugen; ***Denm.***: Macugen; ***Fr.***: Macugen; ***Ger.***: Macugen; ***Gr.***: Macugen; ***Hong Kong***: Macugen; ***Hung.***: Macugen; ***Irl.***: Macugen; ***Ital.***: Macugen; ***Neth.***: Macugen; ***Norw.***: Macugen†; ***Philipp.***: Macugen; ***Pol.***: Macugen; ***Port.***: Macugen; ***Singapore***: Macugen; ***Spain***: Macugen; ***Swed.***: Macugen†; ***Switz.***: Macugen; ***Thai.***: Macugen†; ***Turk.***: Macugen; ***UK***: Macugen; ***Ukr.***: Macugen (Макуген); ***USA***: Macugen.

Pelargonium Sidoides

Kalwerbossie; Kapland-Pelargonie; Rabassam; South African Geranium; Пеларгониум Сидоидес.

*UNII — 4FY2944729 (*Pelargonium sidoides*); H6J53HEX8E (*Pelargonium sidoides *root).*

Pharmacopoeias. *Eur.* (see p. vii) contains pelargonium root.

Ph. Eur. 8: (Pelargonium Root). Dried, usually fragmented, underground organs of *Pelargonium sidoides* and/or *Pelargonium reniforme*. It contains a minimum of 2.0% of tannins, expressed as pyrogallol calculated with reference to the dried drug.

Uses and Administration

An extract of the roots of *Pelargonium sidoides* (Geraniaceae) is used in preparations for the relief of symptoms of the common cold and other respiratory-tract disorders. *Pelargonium reniforme* is used similarly.

Reviews.
1. Agbabiaka TB, *et al. Pelargonium sidoides* for acute bronchitis: a systematic review and meta-analysis. *Phytomedicine* 2008; **15:** 378–85.
2. Brendler T, van Wyk BE. A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae). *J Ethnopharmacol* 2008; **119:** 420–33.
3. Timmer A, *et al.* Pelargonium sidoides extract for acute respiratory tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 05/02/10).

Adverse Effects

Hypersensitivity. Allergic reactions have been reported[1] with herbal preparations containing extracts of *Pelargonium sidoides* and *P. reniforme* used for respiratory-tract infections.

1. de Boer HJ, *et al.* Allergic reactions to medicines derived from Pelargonium species. *Drug Safety* 2007; **30:** 677–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kaloba; ***Belg.***: Kaloban; ***Braz.***: Kaloba; Umckan; ***Chile***: Kaloba; ***Cz.***: Kaloba; ***Ger.***: Umckaloabo; ***Hung.***: Kaloba; ***Indon.***: Kaloba; ***Malaysia***: Kaloba; ***Mex.***: Umckaloabo; ***Neth.***: Kaloba; Umkan; ***Philipp.***: Kaloba; ***Rus.***: Umckalor (Умкалор); ***Singapore***: Kaloba; ***Spain***: Kaloba; ***Swed.***: Kaloba; ***Switz.***: Kaloba; Umckaloabo; ***Turk.***: Umca; ***UK***: DiaCold; DiaPelargo; Kaloba; ***Venez.***: Kaloba.

Multi-ingredient Preparations. ***Ukr.***: Umckalor (Умкалор).

Penicilloyl-polylysine

Benzylpenicilloyl-polylysine; Peniciloil polilisina; PO-PLL; PPL.

CAS — 53608-77-8.

Description. Penicilloyl-polylysine is a polypeptide compound formed by the interaction of a penicillanic acid and polylysine of an average degree of polymerisation of 20 lysine residues per molecule.

Pharmacopoeias. *US* includes a concentrated form.

USP 36: (Benzylpenicilloyl Polylysine Concentrate). It has a molar concentration of benzylpenicilloyl moiety of not less than 0.0125 M and not more than 0.020 M. It contains one or more suitable buffers. It is not intended for direct administration. pH of the concentrate is between 6.5 and 8.5. Store in airtight containers.

Uses and Administration

Penicilloyl-polylysine is used to detect penicillin hypersensitivity. It is generally indicated only for adults with a history of penicillin hypersensitivity. After a preliminary scratch test it may then be given by intradermal injection. The development, usually within 5 to 15 minutes, of a wheal, erythema, and pruritus is generally judged a positive reaction. The incidence of penicillin hypersensitivity is stated to be less than 5% in patients showing a negative reaction. Penicilloyl-polylysine does not detect those liable to suffer late reactions or reactions due to minor antigen determinants; these reactions require other tests. False-positive reactions to penicilloyl-polylysine also occur.

Adverse Effects and Precautions

Severe hypersensitivity reactions have occasionally been reported after use of penicilloyl-polylysine; a scratch test is recommended before intradermal use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Pre-Pen†.

Pharmacopoeial Preparations
USP 36: Benzylpenicilloyl Polylysine Injection.

Pentagastrin *(BAN, USAN, rINN)*

AY-6608; ICI-50123; Pentagastriini; Pentagastrina; Pentagastrine; Pentagastrinum; Пентагастрин.

tert-Butyloxycarbonyl-[β-Ala[13]]gastrin-(13-17)-pentapeptide amide; Boc-β-Ala-Trp-Met-Asp-Phe—NH_2.

$C_{37}H_{49}N_7O_9S$=767.9

CAS — 5534-95-2.
ATC — V04CG04.
ATC Vet — QV04CG04.
UNII — EF0NX91490.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Pentagastrin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dimethylformamide and in 5M ammonia. Protect from light.

Uses and Administration

Pentagastrin is a synthetic pentapeptide that is not active when given orally but when given parenterally has effects similar to those of natural gastrin. Since it stimulates the secretion of gastric acid, pepsin, and intrinsic factor, it is used as a diagnostic agent to test the secretory action of the stomach. It has been used to diagnose disorders associated with increased or decreased gastric acid secretion and in the evaluation of gastric acid secretion following vagotomy or gastric resection. The usual dose is 6 micrograms/kg by subcutaneous or intramuscular injection. By intravenous infusion the dose is 600 nanograms/kg per hour, in sodium chloride 0.9%.

Pentagastrin stimulates the secretion of pancreatic enzymes and thus has been used as a test for pancreatic function. It has also been tried in the diagnosis of medullary carcinoma of the thyroid.

Adverse Effects

Pentagastrin may cause gastrointestinal effects including nausea and abdominal cramps. Cardiovascular effects including flushing of the skin, tachycardia, and hypotension have occasionally been reported. There may be headache, drowsiness, dizziness, and altered sensations in the extremities. Hypersensitivity reactions are rare.

Precautions

Pentagastrin should be given with care to patients with acute peptic ulceration or with active pancreatic, hepatic, or biliary-tract disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Peptavlon†.

Pharmacopoeial Preparations
BP 2014: Pentagastrin Injection.

Black Pepper

Pepper; Pimenta; Piper; Перец Чёрный.
CAS — 8006-82-4 (black pepper oil).
UNII — KM66971LVF.

Pharmacopoeias. In *Chin.*, which describes both black and white pepper, and *US*, which also describes the powdered and powdered extract forms.

USP 36: (Black Pepper). The dried fully developed unripe fruits of *Piper nigrum*. It contains not less than 2.5% of piperine, calculated with reference to the dried drug. Protect from light and moisture.

Profile

Black pepper is the dried unripe fruit of *Piper nigrum* (Piperaceae). It is used as a culinary spice and is included in some herbal remedies.

Pepper oil, obtained from black pepper, is used in aromatherapy.

White pepper is the ripe fruit with the outer part of the pericarp removed. It too is used as a culinary spice.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Cellasene Gold; ***Austria***: Klosterfrau Melissengeist; ***Cz.***: Klosterfrau Melisana; ***Fr.***: Doluperine; Trikatu; ***Hung.***: Herbadict; Klosterfrau Melisana; Munipyrin; ***India***: Aglotus; Aptivate OS; Happy'tizer†; Tummy Ease†; ***Philipp.***: Bo-D-Fense†; ***Pol.***: Melisana Klosterfrau; ***Rus.***: Maraslavin (Мараславин); Tentex (Тентекс); Travisil (Трависил); ***Singapore***: Septilin; ***Switz.***: Wala Elixir amer; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Maraslavin (Мараславин); Travisil (Трависил).

Homoeopathic Preparations. ***Fr.***: Poconeol no 22.

Pepsin ⊗

Pepsiini; Pepsiinijauhe; Pepsin práškový; Pepsin, pulver; Pepsina; Pepsine; Pepsini Pulvis; Pepsino milteliai; Pepsinum; Pepszin-por; Пепсин.
CAS — 9001-75-6.
ATC — A09AA03.
ATC Vet — QA09AA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Viet.* In *Jpn* as Saccharated Pepsin.

Ph. Eur. 8: (Pepsin Powder; Pepsin BP 2014). It is prepared from the gastric mucosa of pigs, cattle, or sheep. It contains gastric proteinases active in acid medium (pH 1 to 5). It has an activity of not less than 0.5 Ph. Eur. units/mg, calculated with reference to the dried substance. A hygroscopic, white or slightly yellow, crystalline or amorphous powder. Soluble in water; practically insoluble in alcohol. A solution in water may be slightly opalescent with a weak acidic reaction. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Uses and Administration

Pepsin contains proteolytic enzymes secreted by the stomach, which control the degradation of proteins into proteoses and peptones. It hydrolyses polypeptides including those with bonds adjacent to aromatic or dicarboxylic L-amino-acid residues.

Pepsin has been given with dilute hydrochloric acid, or with substances such as glutamic acid hydrochloride, or betaine hydrochloride, as an adjunct in the treatment of gastric hypochlorhydria, or to treat deficiencies of digestive enzyme secretion. It has also been given for its supposed benefit as an ingredient of mixtures for dyspepsia and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Fermentol; ***Pol.***: Mixtura Pepsini.

Multi-ingredient Preparations. ***Arg.***: Docechol; Gastridin-E; Opoenterol; Tridigestivo Soubeiran; ***Austral.***: Betaine Digestive Aid; Digestaid; Digestive Zyme†; Enzyme; ***Austria***: Helo-acid; Helopanzym; Oroacid†; ***Belg.***: Digestomen; ***Braz.***: Digeplus; Essen; Peptopancreasi†; Primeral; ***Canad.***: Digesdyn; Digest; Digestolax; Formula 17605 Diaplex; Lipozyme†; Multi-Zyme†; Pepsotol†; Proteozyme Forte; ***Chile***: Flapex E; ***China***: Dages (达吉); YiMei (怡美); ***Ger.***: Pepzitrat†; ***Hong Kong***: Bio-Tomosan†; Enzyme Co†; Uni-Paptase†; ***Hung.***: Betacid; ***India***: Afizyme; Aglozyme; Aglozyme; Alcezyme; Aldezyme; Altrazyme; Alzyme; Anzykair; Anzykair; Aristozyme; Arizyme; Arogyme; Asizyme; Astozyme; Atopep; Bactzyme; Biozyme; Canzyme; Cascazyme; Daffozyme; Dewzym; Digems-CT; Digeplex-T; Digeplex; Digeplex; Digitage; Dipep; Dipep; Disnizyme; Dorzy; Duozyme; E-Pep; Elfazyme; Endos; Entozyme; Entrozyme; Enzar; Enzofast; Enzytel; Estzyme; Extrazyme; Ferizyme; Fozyme; Fyzyme; Gaskit; Gastrofit; Genozyme; Genozyme; HG Zyme; Ifyzyme; Indozyme; Infazyme; Intazyme; Intazyme; Intrazyme Tonic; Intrazyme; Kairase; Kamozyme; KDZyme; Kingzyme; Lupizyme; Lyzyme; M-Zyme; Maprazyme; Martiz; NBGest; Nectozyme; Nifazyme; Novazyme Elachi; Nutrozyme; Onazyme; Optizyme; Panzyme; Unienzyme; ***Indon.***: Librozym Plus†; Librozym†; ***Israel***: Babyzim; ***Ital.***: Gastro-Pepsin; ***Mex.***: Ochozim; Zimotris; ***Philipp.***: Spasmo-Canulase; ***Pol.***: Citropepsin; ***Port.***: Espasmo Canulase†; Modulanzime; ***S.Afr.***: Sentinel Ulcer Mixture†; Spasmo-Canulase†; ***Spain***: Digestomen Complex; Troforex Pepsico†; ***Switz.***: Halipepsin†; Spasmo-Canulase; Stomacine; ***Thai.***: Pepsitase; ***Turk.***: Pepzan; ***UK***: Enzyme Plus; ***Ukr.***: Digestin (Дигестин); ***USA***: Digepepsin; Panplex 2-Phase.

Perflubron *(USAN, rINN)* ⊗

Perflubrón; Perflubronum; Perfluorooctylbromide; PFOB; Перфлуброн.
1-Bromoheptadecafluorooctane.
C_8BrF_{17}=499.0
CAS — 423-55-2.
ATC — V08CX01.
ATC Vet — QV08CX01.
UNII — Q1D0Q7R4D9.

Pharmacopoeias. In *US*.

USP 36: (Perflubron). A clear, colourless, practically odourless liquid. Store in airtight containers. Protect from light.

Profile

Perfluorocarbons can absorb, transport, and release oxygen and carbon dioxide. Perflubron is a perfluorocarbon tried as an alternative to red blood cell preparations to improve gaseous transport, in particular oxygen supply, to the tissues. It may also be instilled directly to the lungs for use in partial liquid ventilation as an adjunct to mechanical ventilation in patients with respiratory failure.

Perflubron is being studied for use as an intravenous contrast medium in computed tomography and ultrasound. It has also been given orally to enhance delineation of the bowel during magnetic resonance imaging.

Other perfluorocarbons have also been used. A mixture of perfluamine (perfluorotripropylamine) and perflunafene (below) has been used to prevent myocardial ischaemia during percutaneous transluminal coronary angioplasty.

Perfluorocarbons such as perflunafene and perfluorooctane (p. 2587.1) have been used in eye surgery.

Precautions. After liquid ventilation therapy perflubron is typically cleared from the lung within weeks but there have been isolated reports[1,2] of patients with residual perflubron in the lungs or other tissues years after treatment. No long-term clinical effects have been found but the bromine atom within perflubron renders perflubron radiodense and such patients may have residual radiographic opacities.[2]

1. Hagerty RD, *et al.* Radiographic detection of perflubron fluoromediastinum and fluororetroperitoneum 9 years after partial liquid ventilation. *Emerg Radiol* 2008; **15:** 71–5.
2. Servaes S, Epelman M. Perflubron residua: 12 years following therapy. *Pediatr Radiol* 2009; **39:** 393–5.

Uses. *BLOOD SUBSTITUTES.* References to the use of perflubron and other perfluorocarbons as oxygen carriers.

1. Garrelts JC. Fluosol: an oxygen-delivery fluid for use in percutaneous transluminal coronary angioplasty. *DICP Ann Pharmacother* 1990; **24:** 1105–12.
2. Ravis WR, *et al.* Perfluorochemical erythrocyte substitutes: disposition and effects on drug distribution and elimination. *Drug Metab Rev* 1991; **23:** 375–411.
3. Urbaniak SJ. Artificial blood. *BMJ* 1991; **303:** 1348–50.
4. Jones JA. Red blood cell substitutes: current status. *Br J Anaesth* 1995; **74:** 697–703.
5. Remy B, *et al.* Red blood cell substitutes: fluorocarbon emulsions and haemoglobin solutions. *Br Med Bull* 1999; **55:** 277–98.
6. Lowe KC. Perfluorinated blood substitutes and artificial oxygen carriers. *Blood Rev* 1999; **13:** 171–84.
7. Prowse CV. Alternatives to standard blood transfusion: availability and promise. *Transfus Med* 1999; **9:** 287–99.
8. Matsumoto S, Kuroda Y. Perfluorocarbon for organ preservation before transplantation. *Transplantation* 2002; **74:** 1804–9.
9. Jahr JS, *et al.* Blood substitutes and oxygen therapeutics: an overview and current status. *Am J Ther* 2002; **9:** 437–43.
10. Kim HW, Greenburg AG. Artificial oxygen carriers as red blood cell substitutes: a selected review and current status. *Artif Organs* 2004; **28:** 813–28.
11. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; **11:** 4099–4114.
12. Riess JG. Perfluorocarbon-based oxygen delivery. *Artif Cells Blood Substit Immobil Biotechnol* 2006; **34:** 567–80.

RESPIRATORY DISTRESS SYNDROME. References to the use of perfluorocarbons, including perflubron, for partial liquid ventilation in neonatal respiratory distress syndrome (p. 1608.3) and acute respiratory distress syndrome (p. 1599.3).

1. Hirschl RB, *et al.* Liquid ventilation in adults, children, and full-term neonates. *Lancet* 1995; **346:** 1201–2.
2. Leach CL, *et al.* Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 1996; **335:** 761–7.
3. Hirschl RB, *et al.* Initial experience with partial liquid ventilation in adult patients with acute respiratory distress syndrome. *JAMA* 1996; **275:** 383–9.
4. Wolfson MR, Shaffer TH. Liquid assisted ventilation update. *Eur J Pediatr* 1999; **158:** S27–S31.
5. Davies M. Liquid ventilation. *J Paediatr Child Health* 1999; **35:** 434–7.
6. Weis CM, Fox WW. Current status of liquid ventilation. *Curr Opin Pediatr* 1999; **11:** 126–32.
7. Kacmarek RM. Liquid ventilation. *Respir Care Clin N Am* 2002; **8:** 187–209.
8. Davies MW, Fraser JF. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 28/04/05).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Imagent GI; LiquiVent.

Perflunafene *(BAN, rINN)* ⊗

Perflunafène; Perflunafeno; Perflunafenum; Perfluorodecahydronaphthalene; Perfluorodecalin; Perfluorodekalin; Перфлунафен.
$C_{10}F_{18}$=462.1
CAS — 306-94-5.
UNII — 54A06VV62N.

Profile

Perflunafene is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injections of perflunafene, alone or with other perfluorocarbons, are used to provide temporary tamponade in ophthalmic procedures such as retinal re-attachment. Perflunafene and perfluamine have been used together for their oxygen-carrying properties in blood substitute preparations and to prevent myocardial ischaemia during percutaneous transluminal coronary angioplasty.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: F-Decalin; ***Neth.***: Eftiar Decalin; ***Turk.***: DK-Line†.

Multi-ingredient Preparations. ***Ger.***: F-Decalin Plus; ***Rus.***: Perftoran (Перфторан).

Perfluorohexylhexane ⊗

Перфторгексилгексан.
$C_{12}H_{13}F_{13}$=404.2

Profile

Perfluorohexylhexane is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injections of preparations containing perfluorohexylhexane, alone or with other perfluorocarbons, are used to provide temporary tamponade during ophthalmic procedures such as retinal re-attachment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Semifluoran F6H6†.

Multi-ingredient Preparations. ***Ger.***: F-Octane Light.

Perfluorohexyloctane ⊗

Перфторгексилоктан.
$C_{14}H_{17}F_{13}$=432.3

Profile

Perfluorohexyloctane is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injections of preparations containing perfluorohexyloctane, alone or with other perfluorocarbons or dimeticone, are used to provide temporary tamponade during ophthalmic procedures such as retinal re-attachment.

References.

1. Rizzo S, *et al.* The combined use of perfluorohexyloctane (F6H8) and silicone oil as an intraocular tamponade in the treatment of severe retinal detachment. *Graefes Arch Clin Exp Ophthalmol* 2006; **244:** 709–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: F6H8 Vitreous Substitute.

Multi-ingredient Preparations. ***Ger.***: Densiron 68; F-Decalin Plus; F-Octane Plus.

Perfluorooctane ⊗

Octadecafluorooctane; Perfluoro-octa; Perfluoro-*n*-octane; Октадекафтороктан.

C_8F_{18}=438.1

CAS — 307-34-6.

UNII — 6P60ZBK0QL.

Profile

Perfluorooctane is a perfluorocarbon with similar properties to perflubron (p. 2586.2). Intra-ocular injections of perfluorooctane, alone or with other perfluorocarbons, are used to provide temporary tamponade in ophthalmic procedures such as retinal re-attachment.

References.

1. Scott IU, *et al.* Outcomes of surgery for retinal detachment associated with proliferative vitreoretinopathy using perfluoro-n-octane: a multicenter study. *Am J Ophthalmol.* 2003; **136:** 454–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: F-Octane; ***Neth.***: Eftiar Octane; ***USA***: Perfluoron.

Multi-ingredient Preparations. ***Ger.***: F-Octane Light; F-Octane Plus.

Persic Oil

Melocotón, aceite de; Oleum Persicorum; Peach oil; Персиковое Масло (peach kernel oil); Абрикосовое Косточковое Масло (apricot kernel oil).

*ATC Herb — HD02WB5007 (*Prunus armeniaca*: oil); HD02WB5009 (*Prunus persica*: oil).*

UNII — 5M26W7T072.

Pharmacopoeias. *Chin.* and *Jpn* include Peach Kernel (Persicae Semen) and also Apricot Kernel (Armeniacae Semen).

Profile

Persic oil is the fixed oil expressed from the kernels of varieties of *Prunus persica* (peach) or *P. armeniaca* (apricot) (Rosaceae). It closely resembles almond oil (p. 2437.1) in its general characteristics and is used as an oily vehicle.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Audiclean.

Multi-ingredient Preparations. ***Fr.***: Audiclean; Saugella allaitment anti-crevasses; Saugella douceur Poligyn; ***Singapore***: Bio-Taches†; Disco.

Peru Balsam

Bals. Peruv.; Bálsamo del Perú; Balsamum Peruvianum; Baume du Pérou; Baume du San Salvador; Peru balzamas; Peruánský balzám; Perubalsam; Perui balzsm; Perunpalsami; Peruvian Balsam; Перуанский Бальзам.

CAS — 8007-00-9.

*ATC Herb — HC05AW5004 (*Myroxylon balsamum *var. pereirae: balsam); HD03WX5012 (*Myroxylon balsamum *var. pereirae: balsam).*

UNII — 8P5F881OCY.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Peru Balsam). The balsam obtained from the scorched and wounded trunk of *Myroxylon balsamum* var. *pereirae*. It contains not less than 45.0% w/w and not more than 70.0% w/w of esters, mainly benzyl benzoate and benzyl cinnamate.

A dark brown, viscous liquid which is not sticky, is non-drying, and does not form threads. It is transparent and yellowish-brown when viewed in a thin layer. Practically insoluble in water, freely soluble in dehydrated alcohol; not miscible with fatty oils except for castor oil. Protect from light.

Profile

Peru balsam has a very mild antiseptic action by virtue of its content of cinnamic and benzoic acids. Diluted with an equal part of castor oil, it has been used as an application to bedsores and chronic ulcers; it has also been used in topical preparations for the treatment of superficial skin lesions and pruritus. It is an ingredient of some rectal preparations used for the symptomatic relief of haemorrhoids (see p. 1808.1).

Peru balsam is an ingredient of some preparations used in the treatment of respiratory congestion. It is also used in aromatherapy.

Skin sensitisation has been reported.

References.

1. Pfützner W, *et al.* Systemic contact dermatitis elicited by oral intake of balsam of Peru. *Acta Derm Venereol* 2003; **83:** 294–5.
2. Avalos-Peralta P, *et al.* Sensitivity to *Myroxylon pereirae* resin (balsam of Peru). A study of 50 cases. *Contact Dermatitis* 2005; **52:** 304–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Baume des Pyrenees; ***Pol.***: Balsolan.

Multi-ingredient Preparations. ***Arg.***: Anusol Duo S; Anusol-A; Anusol-HC; Anusol†; Novobroncol; ***Austral.***: Anusol; Ayrton's Chilblain†; ***Austria***: Mamellin; Pudan-Lebertran-Zinksalbe; Rombay; Vulpuran; ***Belg.***: Perubore†; Rectovasol; ***Braz.***: Anusol-HC; Balmex; Calminex H; Claudemor; ***Fr.***: Agathol; Anaxeryl; Balsofumine; Brulex; Dermophil Indien; Dolirhume; Lelong Pommade; Oxyperol†; ***Hong Kong***: Anusol; Haemoral†; ***Hung.***: Pulmex Baby; Pulmex; ***Indon.***: Sapona†; ***Irl.***: Anugesic-HC; Anugesic-HC; Anusol-HC; Anusol; Anusol; ***Israel***: Hemo; Pulmex; ***Ital.***: Fomentil; ***Malaysia***: Anucare; Anusol†; ***NZ***: Anusol; ***Pol.***: Aromagel†; Aromatol Hot Gel; Depulol; Hemorectal; Pulmex Baby; Rectosec; ***Rus.***: Pulmex (Пульмекс)†; Pulmex Baby (Пульмекс Бэби); Theraflu Bro (Терафлю Бро); ***S.Afr.***: Anugesic†; Heilsalbe†; Ung Vernleigh; ***Singapore***: Anusol; Anusol; ***Spain***: Antigrietun; Cicatral; Grietalgen; Linitul; Vapores Pyt†; Vitamina F99 Topica†; ***Switz.***: Dermophil Indien; Haemolan†; HEC†; Peru Stick; Pommade au Baume; Pulmex Baby; Pulmex; Rapura; Wala Baume nasal doux; Wala Baume nasal; ***Thai.***: Anusol†; ***UK***: Anugesic-HC†; Anugesic-HC; Anusol-HC, Plus HC; Anusol; Anusol; Dragon Balm; ***USA***: Allanderm-T†; Anumed HC; Anumed; Balmex Baby; Boudreaux's All Natural Butt Paste; Boudreaux's Butt Paste; Dermuspray; Dr Dermi-Heal; Flanders Buttocks; Granulderm†; Granulex; GranuMed; Hemril; Mammol; Optase; Proderm; Saratoga; Vasolex; Venelex; Xenaderm.

Homoeopathic Preparations. ***Austria***: Tonsan chronisch; ***Canad.***: Formula MBC†; ***Ger.***: Weleda Heilsalbe; ***UK***: Balsamicum; Frost Cream.

Petroleum

Coal Oil; Oleum Petrae; Rock Oil; Steinöl.

UNII — 6ZAE7X688J.

Profile

Petroleum is a complex mixture consisting mainly of hydrocarbons that occurs naturally beneath the earth's surface; it is toxic by inhalation and by ingestion. It is used as a source for numerous compounds; those with pharmaceutical uses include hard paraffin (p. 2188.1), kerosene (p. 2191.1), liquid paraffin (p. 2191.2), petroleum spirit (p. 2201.2), and soft paraffin (p. 2211.3).

Homoeopathy

Petroleum, in both crude and refined forms, has been used in homoeopathic medicines under the following names: petroleum; petroleum rectificatum; oleum petrae.

Reviews of toxicity.

1. Seymour FK, Henry JA. Assessment and management of acute poisoning by petroleum products. *Hum Exp Toxicol* 2001; **20:** 551–62.
2. Aguilera F, *et al.* Review on the effects of exposure to spilled oils on human health. *J Appl Toxicol* 2010; **30:** 291–301.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Travellers Relief; ***Austria***: Erbiode Haarvital; Frostsalbe†; Nausyn; Vertigoheel; ***Canad.***: Cocculine; Eczema; Execalm†; Hylands Motion Sickness; ***Cz.***: Cocculine; Vertigoheel; ***Fr.***: Cocculine; Dermo-Drainol†; Dolitravel†; Euphorbium Complexe No 88; Tabacum Compose; ***Ger.***: Genu-cyl L Ho-Len-Complex; Vertigoheel; ***Hung.***: Cocculine; Vertigoheel; ***Neth.***: Cocculine; Dermafleur; Emvita 10; Gravifem†; Travelin; Vertigoheel; ***Port.***: Cocculine; ***Rus.***: Cocculine (Коккулин); ***S.Afr.***: Vertigoheel; ***Switz.***: Cocculine; Nelsons Travella†; Vertigoheel; ***UK***: Nausyn; Travella; ***USA***: Vertigoheel.

Pexelizumab *(BAN, USAN, rINN)*

h5G1.1 scFv; h5G1.1 scFv (CDR); Pexélizumab; Pexelizumabum; Пекселизумаб.

Immunoglobulin, anti-(human complement C5a-chain) (human-mouse monoclonal 5G1.1-SC chain).

CAS — 219685-93-5.

UNII — CHZ6OLQ3UU.

Profile

Pexelizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker (p. 2485.1) by inhibiting terminal complement activation at the C5 protein. It is under investigation for treatment of patients undergoing coronary artery reperfusion and revascularisation procedures.

References.

1. Mahaffey KW, *et al.* Effect of pexelizumab on mortality in patients with acute myocardial infarction or undergoing coronary artery bypass surgery: a systematic overview. *Am Heart J* 2006; **152:** 291–6.
2. Armstrong PW, *et al.* APEX AMI Investigators. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2007; **297:** 43–51.

Phaseolus Vulgaris

Bean; Böna; Chícharo; Feijão; Feijoeiro; Frijol; Gartenbohne; Habichuela; Haricot Commun; Navy Bean; Owocnia Fasoli (fruit); Phaseoli Pericarpium (fruit); Poroto; Tarhapapu; Trädgårdsböna.

*UNII — HC262P51WU (*Phaseolus vulgaris*); N9D69B2Q7Y (*Phaseolus vulgaris *immature fruit); M98C8416QO (*Phaseolus vulgaris *seed); G5A780J22X (*Phaseolus vulgaris *seed sprout).*

Pharmacopoeias. In *Pol.*

Profile

The pods of the beans of *Phaseolus vulgaris* (*P. nanus*) (Fabaceae) have a weak diuretic action and are used in herbal medicines for urinary disorders. Phaseolus vulgaris is a source of phaseolamin, an inhibitor of alpha amylase, and extracts of bean pods have been promoted as aids to weight loss and adjuncts in the management of diabetes mellitus. Phaseolus vulgaris is included in herbal preparations for constipation, probably as a source of fibre.

The entire bean pods and the seeds are widely used as foodstuffs. Some varieties (especially kidney beans) contain toxic concentrations of lectins that are degraded by heat and require thorough cooking at a high temperature before consumption.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Delgadol; Forma 2.

Multi-ingredient Preparations. ***Chile***: Delgadol Fibra; Delgadol Vita; ***Cz.***: Diabetan; Diabeticka Cajova Smes-Megadiabetin†; ***Fr.***: Anastase; ***Indon.***: F-Slim†; ***Pol.***: Betasol; Diabetofort; Diabetosol; Dyspepsin; Melisana Klosterfrau; Nefrol; Urosept; ***Rus.***: Arfazetin-E (Арфазетин-Э); ***Ukr.***: Lipomin (Липомин); Sadifit (Садифит).

Phencyclidine Hydrochloride

(BANM, USAN, rINNM)

CI-395; CN-25253-2; Fenciclidina, hidrocloruro de; GP-121; Hidrocloruro de fenciclidina; NSC-40902; PCP; Phencyclidine, Chlorhydrate de; Phencyclidini Hydrochloridum; Фенциклидина Гидрохлорид.

1-(1-Phenylcyclohexyl)piperidine hydrochloride.

$C_{17}H_{25}N,HCl$=279.9

CAS — 77-10-1 (phencyclidine); 956-90-1 (phencyclidine hydrochloride).

UNII — V1JZQ7GDTX.

NOTE. The name PCP has also been used as a synonym for pentachlorophenol (p. 2159.2).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phencyclidine:

Ace; AD; Aliamba; Amoeba; Amoebae; Amp; Angel; Angel dust; Angel hair; Angel mist; Angel poke; Animal trank; Animal tranq; Animal tranquilizer; Aurora borealis; Bad pizza; Belladonna; Black dust; Black whack; Blotter acid; Blud madman; Blue madman; Boat; Bohd; Bush; Busy bee; Butt naked; Buzy bee; Cadillac; Cannabinol; Cat tranquilizer; Christal; Cigarrode cristal; CJ; Cliffhanger; Cliqum; Columbo; Cozmo's; Crazy coke; Crazy Eddie; Cristal; Crystal; Crystal joint; Crystal T; Crystal TAC; Cycline; Cyclona; Cyclone; Cyclones; Cystal T; D; Detroit pink; Devil's dust; Dipper; Dips; Dirge; Disembalming Fluid; DMT; Do it Jack; DOA; Drink; Drinks; Dummy dust; Dust; Dust joint; Dust of angels; Dusted parsley; Elephant; Elephant trank; Elephant tranquilizer; Embalming fluid; Energizer; Engelenspul; Erth; Fake STP; Fake THC; Fake X; Flakes; Flying saucers; Formaldehyde; Fresh; Fry; Fuel; Good; Goon; Goon crystal; Goon dust; Gorilla biscuits; Gorilla pills; Gorilla tab; Green; Green double domes; Green leaves; Green tea; Green tear; Half track; Happy sticks; HCP; H.c.p.; Heaven & Hell; Heaven and Hell; Herms; High;

Hinkley; Hog; Horse franks; Horse tracks; Horse trank; Horse tranquilizer; Ice; Ill; Illies; Illy momo; Jet fuel; Juice; K; Kaps; Kay Jay; K-blast; Killer; Killer joints; Killer weed; KJ; Koller joints; Kools; Kools sherms; Krystal; Krystal joint; Krystal joints; KW; LBJ; Leak; Leakie; Leaky; Leaky bolla; Leaky leak; Lemon 714; Lenos; Lethal weapon; Little ones; Live ones; Log; Love boat; Loveboat; Lovely; Mad dog; Mad man; Madman; Magic; Magic dust; Magic mist; Mean green; Mesk; Mint leaf; Mint weed; Mintweed; Missile; Mist; Monkey dust; Monkey gland; Monkey tranquilizer; More; New acid; New magic; Niebla; Oil; OPP; O.P.P.; Orange crystal; Ozone; P; Parsley; Paz; PCP; PCPA; Peace; PeaCe Pill; Peace pill; Peace pills; Peace weed; Peep; Peter Pan; Pig killer; Pit; Pits; Po-de-anjo; Polvo; Polvo de angel; Polvo de estralos; Polvo de estrellas; Porker; Puffy; Purple rain; Red devil; Red devils; Rocket fuel; Rocketfuel; Rupture; Scaffle; Scuffle; Serenity Tranquility Peace; Sernyl; Sernylan; Shabu; Sheets; Sherm; Sherm sticks; Sherman Hemsley; Shermans; Sherms; Skuffle; Smoking; Snorts; Soma; Space rock; Speed boat; Spores; Star dust; Stardust; Stick; STP; Sugar; Super; Super grass; Super joint; Super kools; Super weed; Supergrass; Surfer; Synthetic cocaine; Synthetic THT; T; TAC; Tac et tic; Taking a cruise; T-buzz; Tea; THC; Tic; Tic tac; Tick; Tic-tac; TicTac; Tish; Titch; Trank; Tranks; Tranq; TT 1; TT 2; TT 3; Venom; Vredestro; Wack; Water; Wave; Weed; Wet; Wet daddies; Wetdaddy; Whack; White horizon; White powder; Wobble weed; Wolf; Woolies; Wooly blunts; Worm; Yellow fever; Zombie; Zombie weed; Zoom; Zoot.

Uses and Administration

Phencyclidine is related chemically to ketamine (see p. 1905.1) and is a potent analgesic and anaesthetic. It was formerly given intravenously to produce an amnesic trance-like state, with analgesia, but severe adverse effects, especially postoperative psychoses, precluded its use. It was formerly used in veterinary medicine as an immobilising agent. Phencyclidine is widely abused in some countries for its hallucinogenic effects and has been taken orally, sniffed, injected, or smoked.

Many analogues of phencyclidine have been similarly abused and include:

- PHP (rolicyclidine; 1-(1-phenylcyclohexyl)pyrrolidine)
- PCC (1-piperidinocyclohexanecarbonitrile)
- PCE (*N*-ethyl-1-phenylcyclohexylamine)
- TCP (1-[1-(2-thienyl)cyclohexyl]piperidine)

Adverse Effects, Treatment, and Precautions

Phencyclidine can induce a psychosis clinically indistinguishable from schizophrenia. Adverse effects reported include bizarre and violent behaviour, hallucinations, euphoria, agitation, catatonic rigidity, disorientation, incoordination, nystagmus, hypersalivation, vomiting, convulsions, numbness, hypertension, tachycardia, rhabdomyolysis leading to renal failure, acidosis, and, occasionally, malignant hyperthermia. Severe intoxication may result in respiratory depression, coma, and death.

In cases of phencyclidine overdose, activated charcoal should preferably be given within 1 hour of ingestion; multiple doses may be of benefit since phencyclidine is actively secreted into the gastrointestinal tract. Treatment of the adverse effects of phencyclidine is symptomatic; if agitated the patient should be kept quiet in a darkened room, and diazepam given if necessary. Butyrophenone antipsychotics such as haloperidol have been used for severe behavioural problems and psychoses, although they are associated with adverse effects and some suggest that they should generally be avoided. Phenothiazines may lower the seizure threshold and should also be avoided. Hyperthermia should be treated. Renal excretion should be promoted by hydration and use of diuretics if necessary. Acidification of the urine is no longer recommended since acidosis may be exacerbated and renal failure precipitated.

Breast feeding. The American Academy of Pediatrics[1] has stated that, when used as a drug of abuse by a breast-feeding mother, phencyclidine has caused hallucinogenic effects in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/07/04)

Phenolsulfonphthalein

Czerwień fenolowa; Fenolisulfoniftaleiini; Fenolsolfonftaleina; Fenolsulfonftalein; Fenolsulfonftaleína; Fenolsulfonftaleinas; Fenolszulfonftalein; Phenol Red; Phénolsulfonephtaléine; Phenolsulfonphthaleinum; Phenolsulphonphthalein (BAN); PSP; Фенолсульфонфталеин.

4,4′-(3*H*-2,1-Benzoxathiol-3-ylidene)diphenol *S,S*-dioxide.

$C_{19}H_{14}O_5S$=354.4

CAS — 143-74-8.
ATC — V04CH03.
ATC Vet — QV04CH03.
UNII — I6G9Y0J1OJ.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8 (Phenolsulfonphthalein; Phenolsulphonphthalein BP 2014). A bright to dark red, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol.

USNF 31: (Phenolsulfonphthalein). A bright-red to dark-red, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol.

Profile

Phenolsulfonphthalein has been used as a test of renal function by estimating the rate of urinary excretion after intravenous administration. It has also been given intramuscularly.

Alkaline urine is coloured red to violet.

Phenolsulfonphthalein has also been used as a drug ingestion indicator, a marker in drug absorption studies, and in a test of residual urine.

Hypersensitivity reactions to phenolsulfonphthalein may occasionally occur.

Phenylpropanol

Ethyl Phenyl Carbinol; Etilfenilcarbinol; Fenilpropanol; α-Hydroxypropylbenzene; SH-261; Фенилпропанол.

1-Phenylpropan-1-ol; α-Ethylbenzyl alcohol.

$C_9H_{12}O$=136.2

CAS — 93-54-9.

UNII — 0F897O3O4M.

Pharmacopoeias. In *Chin.*

Profile

Phenylpropanol is a choleretic used for the treatment of biliary-tract and gastrointestinal disorders.

Phloroglucinol *(BAN)*

Floroglucina; Floroglucinol; Floroglucynol; Floroglusinoli; Phloroglucin; Phloroglucinolum; Флороглуцинол.

Benzene-1,3,5-triol.

$C_6H_6O_3$=126.1

CAS — 108-73-6.

ATC — A03AX12.

ATC Vet — QA03AX12.

UNII — DHD7FFG6YS.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dihydrate.

Ph. Eur. 8: (Phloroglucinol, Anhydrous; Phloroglucinolum Anhydricum). A white or almost white powder. Sparingly soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in a mixture of alcohol and water has a pH of 4.0 to 6.0. Protect from light.

Ph. Eur. 8: (Phloroglucinol Dihydrate; Phloroglucinolum Dihydricum). A white or almost white powder. Sparingly soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in a mixture of alcohol and water has a pH of 4.0 to 6.0. Protect from light.

Profile

Phloroglucinol is an antispasmodic that has been given orally as the hydrate in a usual dose of 160 mg at the onset of symptoms, which may be repeated if necessary. It is also given orally in a preparation with trimethylphloroglucinol in daily doses of 480 mg; lower doses have been given by intravenous or intramuscular injection, and rectally.

Uses. Short-term treatment for one week with a combination of phloroglucinol and trimethylphloroglucinol has been reported[1] to provide fast relief of acute pain in patients with irritable bowel syndrome (p. 1810.3).

1. Chassany O, *et al.* Acute exacerbation of pain in irritable bowel syndrome: efficacy of phloroglucinol/trimethylphloroglucinol— a randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2007; **25:** 1115–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pasmovit; ***Fr.***: Solispasm; Spasfon-Lyoc; Spasmocalm; Spassirex†; ***Ital.***: Spasmex; ***Mex.***: Panclasa Fem; Panclasa.

Multi-ingredient Preparations. ***Arg.***: Nero; ***Belg.***: Spasfon; ***Fr.***: Meteoxane; Spasfon; ***Gr.***: Spasfon; ***Ital.***: Spasmex; ***Mex.***: Klonaza; Modipas; Morelax; Panclasa; Tilmetin.

Phosgene

Carbonic Dichloride; Carbonyl Chloride; Chloroformyl Chloride; Cloruro de carbonilo; Dicloruro carbónico; Fosgen; Fosgeno; Oxicloruro de carbono.

$COCl_2$=98.92

CAS — 75-44-5.

UNII — 117K140075.

Uses

Phosgene is used in the chemical industry. It has been used as a war gas.

References.

1. Borak J, Diller WF. Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med* 2001; **43:** 110–9.

Adverse Effects

Poisoning may occur from industrial use or from the generation of phosgene from chlorinated compounds such as dichloromethane, chloroform, or carbon tetrachloride in the presence of heat. Symptoms of poisoning, which may be delayed for up to 24 (rarely 72) hours, include burning of the eyes and throat, cough, dyspnoea, cyanosis, and pulmonary congestion and oedema. Death may result from anoxia. Exposure to 50 ppm may be rapidly fatal. Massive exposure may cause intravascular haemolysis, thrombus formation, and immediate death. Exertional dyspnoea may persist for months after exposure to high concentrations.

Treatment of Adverse Effects

After inhalation of phosgene or absorption from the skin, treatment consists of complete rest and inhalation of oxygen. The mouth, eyes, nose, and skin should be irrigated with copious amounts of water. Oral or parenteral corticosteroids have been used for bronchospasm but the role of inhaled corticosteroids is considered to be controversial. Antibacterials may reduce respiratory infections. Further treatment is symptomatic.

References.

1. Russell D, *et al.* Clinical management of casualties exposed to lung damaging agents: a critical review. *Emerg Med J* 2006; **23:** 421–4.

Phosphatidyl Choline

Fosfatidilcolina; Phosphatidylcholine; Фосфатидилхолин.

NOTE. The term phosphatidylcholine is sometimes used as a synonym for lecithin (p. 2542.2).

Profile

Phosphatidyl choline is a phospholipid and a constituent of lecithin (p. 2542.2). Phosphatidyl choline is an ingredient of preparations that have been promoted for liver disorders, peripheral vascular disorders, hyperlipidaemias, and fat emboli. Some injection preparations of phosphatidyl choline have been promoted for use in cosmetic surgery to remove subcutaneous fat deposits, but this use is not licensed in the UK.

Ulcerative colitis. Phosphatidyl choline is a component of mucus and plays a key role in mucosal defence. Since a disturbed mucosal barrier is believed to be a factor in the pathogenesis of ulcerative colitis, exogenous phosphatidyl choline has been investigated to improve the protective effects of colonic mucus. Controlled-release oral phosphatidyl choline was beneficial compared with placebo in patients with ulcerative colitis in 2 small short-term studies.[1,2]

1. Stremmel W, *et al.* Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. *Gut* 2005; **54:** 966–71.
2. Stremmel W, *et al.* Phosphatidylcholine for steroid-refractory chronic ulcerative colitis: a randomized trial. *Ann Intern Med* 2007; **147:** 603–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Essentiale N (易善复); ***S. Afr.***: Adco-Sociale; Cruciale; ***Singapore***: Hepakur; ***Ukr.***: L'Esfal (Л'Есфаль); Lipin (Ліпін); ***USA***: PhosChol.

Multi-ingredient Preparations. ***Arg.***: Ikx Gel Reductor†; ***Canad.***: Nervrite; ***Ger.***: Leferdivin†; Repithel; Silence; ***Indon.***: Liposerin†; ***Ital.***: Essaven; Linfonorm Cremagel; Mirtilux; Zeroac; ***Malaysia***: Lesichol; NeuroPlus; ***Philipp.***: Essentiale; Livolin; ***Singapore***: Lesichol; Silence; ***Switz.***: Silence†; Silence; ***Ukr.***: Detoxil (Детоксил).

Phosphatidyl Serine

Fosfatidilserina; Phosphatidylserine; Серинфосфатид; Фосфатидилсерин.

Profile

Phosphatidyl serine is a phospholipid that has been tried in the treatment of organic psychiatric syndromes and investigated as a cognition adjuvant. Phosphatidyl serine is a constituent of lecithin (p. 2542.2).

Phosphoserine, which lacks the lipid and glycerol groups of phosphatidyl serine, has been used similarly; both (+)-L-phosphoserine (dexfosfoserine) and the racemic form (DL-phosphoserine) have been used. Phosphoserine has sometimes been used as a synonym for phosphatidyl serine.

References.

1. Pepping J. Phosphatidylserine. *Am J Health-Syst Pharm* 1999; **56:** 2038, 2043–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Bros; ***Indon.***: Memoran; ***UK***: Cognito.

Multi-ingredient Preparations. ***Indon.***: Liposerin†; ***Ital.***: Acutil Fosforo; Fosfo Plus; Glutamin Fosforo; Memovit B12; Mirtilux; NeoBros 10; NeoBros C; NeoBros; ***Spain***: Agudil†; Nucleserina; ***Switz.***: Vitasprint B12; Vitasprint Complex†; ***UK***: Neurozan.

Phosphoric Acid

Acide phosphorique; Acido Fosfórico; Ácido ortofosfórico; Acidum phosphoricum; Concentrated Phosphoric Acid; E338; Fosfato rūgštis; Fosfórico, ácido; Fosforihappo; Fosforsyra; Foszforsav; Kwas fosforowy; Kyselina fosforečná; Orthophosphoric Acid; Phosph. Acid; Phosphorsäure.

H_3PO_4=97.99

CAS — 7664-38-2.

UNII — E4GA8884NN.

Pharmacopoeias. *Eur.* (see p. vii) includes various concentrations. Also in *USNF*.

Ph. Eur. 8: (Phosphoric Acid, Concentrated; Phosphoric Acid BP 2014). It contains 84 to 90% w/w of H_3PO_4. A clear, colourless, corrosive, syrupy liquid. When stored at a low temperature it may solidify, forming a mass of colourless crystals which do not melt until the temperature reaches 28 degrees. Miscible with water and with alcohol. Store in glass containers.

Ph. Eur. 8: (Phosphoric Acid, Dilute). It contains 9.5 to 10.5% w/w H_3PO_4 and is prepared by mixing phosphoric acid 115 g with water 885 g.

USNF 31: (Phosphoric Acid). It contains 85 to 88% w/w of H_3PO_4. A colourless, odourless liquid of syrupy consistency. Miscible with water and with alcohol. Store in airtight containers.

USNF 31: (Diluted Phosphoric Acid). It contains 9.5 to 10.5% w/v H_3PO_4 and may be prepared by mixing phosphoric acid 69 mL with purified water to 1000 mL. A clear, colourless, odourless liquid. Store in airtight containers.

Uses and Administration

Phosphoric acid has industrial uses. Dilute phosphoric acid has been used well diluted in preparations intended for the management of nausea and vomiting (p. 1811.3); it has also been included in preparations for vaginal infections. Phosphoric acid is used in dentistry to etch tooth enamel.

Homoeopathy

Phosphoric acid has been used in homoeopathic medicines under the following names: Acidum phosphoricum; Phosphoricum acidum; Phosphoricum ac; Ac. phos.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

Toxicity from mixing cleaning agents. For reference to the adverse effects of mixing phosphoric acid-based and hypochlorite-based cleaning agents see Sodium Hypochlorite, p. 1769.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Irontona†; Nervatona Calm; Nervatona Focus; Vitatona†; ***Braz.***: Paratonico†; Vitonico; ***Canad.***: Perfect Solutions 1-Minute†; ***Chile***: Vigofortal†; ***Fr.***: Biotone; Marinol; Phosphoneuros; Stimuplexe†; ***Gr.***: Dulox; Enter-Out; Fleelaxat; Fleet Phospho-Soda; Frubiose Calcium; Kathargon; Mineralin; Odrinol; Phospho-Laxat; Phosphoclean; Trifalac; ***India***: Neogadine; ***Israel***: Peptical; ***S.Afr.***: Emetrol; Emex; ***Spain***: Oximen; ***Thai.***: Quinradon-N†; ***USA***: Emetrol; Formula EM; Nausatrol; Nausetrol.

Homoeopathic Preparations. ***Austral.***: Hangover Relief; Nervatona Calm; Nervatona Focus; Vitatona Energy†; ***Austria***: Acidum phosphoricum Med Complex; Barium Med Complex; China Med Complex; Erbiode-Starkungstropfen; Nervoheel; Phosphorus Med Complex; Selenium Med Complex; Veratrum Med Complex; ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Bioactiv E†; Comp-Drops 1 Stress†; Cutisitum†; Fatigue; Homeo-Form F†; Homeo-Form M†; Hylagene; Ikoplex 5†; Indigestion; Mental Alertness; Passiflora Complex†; Sedilor†; Ton 2 Complex†; ***Chile***: Anacardio con Fosforo; Bioactiv E; Bioactiv P; ***Cz.***: Vita C-R15 forte†; Vita C-R15†; ***Fr.***: Abbe Chaupitre no 43†; Acidum Phosphoricum Complexe No 5; Acidum Phosphoricum Compose†; Passiflora Compose; Sativol†; ***Ger.***: Entero-Gastreu S R4; Infi-China; Infinerval; Manuia; Nervo-Plantin†; Nervoregin H; Nervoregin; Presselin Nervenkomplex; Presselin Nervennahrung N†; Rufebran regeno†; Tondinel H; Tondinel; Virilis-Gastreu S R41; ***Hung.***: Nervoheel; PSY-Stabil; ***Neth.***: Cephalite; Cerebrum comp; Entero-Gastreu R4; Nervoheel; PSY-stabil; Sativol†; ***Rus.***: Damiana-Plus (Дамиана-Плюс); ***Switz.***: Nervoheel; ***Ukr.***: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); ***USA***: Preferred Remedies Fatigue.

Pharmacopoeial Preparations

BP 2014: Phosphate Oral Solution;

USP 36: Sodium Fluoride and Phosphoric Acid Gel.

Phosphorus

Fósforo; Fósforo amarillo; Fósforo blanco; Phosphor; Phosphore; White Phosphorus; Yellow Phosphorus; Фосфор.

P=30.973762

CAS — 7723-14-0.

UNII — 27YLU75U4W.

Handling. Phosphorus has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Stability and storage. Phosphorus is unstable in air and should be stored under water.

Uses

Elemental phosphorus is no longer used in medicine. Inorganic phosphates are given in deficiency states and bone diseases (see Uses and Administration of Sodium Phosphate, p. 1791.3). Phosphorus has been used in the manufacture of rat and cockroach poisons.

Homoeopathy

Phosphorus has been used in homoeopathic medicines under the following names: Phos.

Adverse Effects

Acute poisoning by yellow (white) phosphorus, a general protoplasmic poison, occurs in three distinct stages. The first stage represents local gastrointestinal irritation with intense thirst, pain, nausea, vomiting, and diarrhoea. The vomitus and stool may smell of garlic and are luminescent. Shock, delirium, convulsions, coma, and death may occur. In patients who survive, a second asymptomatic stage may be present lasting for up to several days or even weeks. The third stage represents systemic toxicity characterised by hepatic and renal damage, cardiovascular collapse, and CNS involvement including confusion, convulsions, and coma. Death may occur during either the first or third stages.

The fatal dose is about 1 mg/kg.

Symptoms of chronic poisoning are associated with defective tissue repair, including necrosis of the mandible ('phossy jaw').

Externally, phosphorus causes severe burns to the skin. Phosphorus is absorbed after skin contamination and systemic symptoms may occur.

Treatment of Adverse Effects

Gastric lavage may be considered after ingestion of elemental yellow (white) phosphorus, although the risks versus potential benefits must be considered in order to prevent spontaneous combustion. Activated charcoal may be used, although there is no clear evidence of benefit. Induction of emesis is contra-indicated. Potassium permanganate solution 1 in 5000 has been instilled into the stomach in an attempt to convert elemental phosphorus to an oxide, but there is no sound clinical reason to recommend this.

Further treatment is symptomatic and supportive and may include fluid and electrolyte replacement, and management of convulsions and renal and hepatic dysfunctions.

Contaminated areas on skin should be immersed in water or irrigated with copious amounts of warm water. Solutions containing copper sulfate have also been suggested for dermal irrigation to convert elemental phosphorus to copper phosphate, although concerns have been raised due to its potential to cause lethal haemolysis through inhibition of G6PD. Eyes contaminated with phosphorus should be irrigated with copious amounts of tepid water for at least 15 minutes. Exposed areas should be covered with wet dressings or compresses to prevent spontaneous combustion. It is essential that all particles of unoxidised phosphorus are removed from the skin. Lipid or oil-based topical preparations may increase the absorption of phosphorus through the skin and should not be used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Sigmaflex; ***Austral.***: Nutribone; PM Kiddiecal; ***Canad.***: Cal Mag Phos Plus D†; Liquid Cal-Mag plus Vitamin D and Phosphorus; T-OS; ***Chile***: Chicovit Pharmaton; ***Cz.***: Biomin H; ***Hong Kong***: Dical-D†; ***India***: Abrovit-Cal; Bio-Milk; Calcimilk; Calcizin; Calriz; Calstat; Estovon; Familykair; Glucose-D; Gynacea; Hycal; Lactocal; Milky-Rich; Milky-Rich; Milkytab; Osex Forte; Osex; Ossofez; Ossopan Alfa; ***Indon.***: Calcidol; Obical; Phoscal; ***Malaysia***: Obical; Shine Fememino; ***Mex.***: Multi-Sanostol; ***Singapore***: Lacto Calcium; Obical; ***Thai.***: FB Fer†; ***Ukr.***: Kalcinova (Кальцинова); Univit (Юнивит); ***USA***: CalciCaps with iron; Dical†; Diostate; Pro-Cal.

Homoeopathic Preparations. ***Austral.***: Childrens Cough Relief; Respatona Chesty Cough & Nasal Congestion; Respatona Dry Cough & Nasal Congestion; ***Austria***: Acidum phosphoricum Med Complex; Ambra Med Complex; Cepa Med Complex; China Med Complex; Galstena; Gripp Heel; Infludo; Nisylen†; Notta; Phosphor-Homaccord; Phosphorus Med Complex; Pneumodoron Nr 2; Robinia Med Complex; Tonsan akut; ***Canad.***: Ateria-Heel†; Bryaconeel†; Cou Complex†; Detox L37; Diarrex; Echinacea Compositum; Endoteel†; Fatigue; Formula DE 226†; Formula FA 224†; Formula INF; Formula PC 223†; Hecocur†; Homeo-Form F†; Nareel†; Phosphor-Homaccord†; Rhinar†; Sinall Formula†; Spascupreel; ***Chile***: Ikoplex No 23; ***Cz.***: Galium; Gripp Heel; Hepeel; ***Fr.***: Hypericum Complexe No 26; Momordica Complexe No 109†; Myosotis Complexe No 63†; Pulmo-Drainol†; Thuya Complexe No 37; ***Ger.***: Agaricus comp Phosphorus; Delto-cyl Ho-Len-Complex; Feminon N; Gastro-Pasc; Gripp-Heel; Gripps; Infi-Echinacea; Infihepan; Infludo; Mucosa compositum; Nisylen; Nux Vomica N Oligoplex; Pancreas-Gastreu N; Pneumodoron 2; Roth's Rotacard; Thuja WA Oligoplex; Vertizin; Zincum Hevert N; ***Hung.***: Gripp-Heel; Hepeel; Naso-Heel S; ***Neth.***: Apo-Hepat; Chavita 5; Echilite; Emvita 15; Emvita 20; Emvita 6; Emvita 7; Gripp-Heel H; Infludo; Kind 0-6 Nisykind; Mucosa comp H; Neurovita; Nisyleen; Speci-chol; ***Rus.***: Briacon (Бриакон); Galstena (Галстена); Influcid (Инфлюцид); Notta (Нотта); Tonsan-Akut (Тонзан-акут); ***S. Afr.***: Gripp-Heel; Infludo†; Pneumodoron 2†; Sambucus Comp†; ***Switz.***: Gripp-Heel; Hepeel; Infludo; ***UK***: Infludo; ***Ukr.***: Galstena (Галстена); Influcid (Инфлюцид); Notta (Нотта).

Pharmacopoeial Preparations

USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Phosphorylcolamine

2-Aminoethanol Phosphate; 2-Aminoethyl Phosphate; Colamine Phosphate; Ethanolamine Phosphate; Fosfoetanolamina; Fosforylcholamine; Fosforylethanolamine; NSC-254167; Pe-104; *O*-Phosphocolamin; Phosphoethanolamin; Phosphoethanolamine; *O*-Phosphorylethanolamine; Phosphorylethanolamine.

2-Aminoethyl dihydrogen phosphate.

$C_2H_8NO_4P$=141.1

CAS — 1071-23-4.

Profile

Phosphorylcolamine, the phosphate ester of monoethanolamine, has been used as a tonic and dietary supplement. It has also been given as its calcium, magnesium, and potassium salts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Calcium-EAP; ***Irl.***: Fosfor†; ***UK***: Fosfor.

Multi-ingredient Preparations. ***Arg.***: Stimulnerv; ***Ger.***: Phosetamin†; ***Spain***: Vita Menal.

Phosphothreonine

O-Phospho-L-threonine; *O*-Phosphono-L-threonine; L-Threonine *O*-phosphate; L-Threonine Dihydrogen Phosphate; Threoninium Dihydrogen Phosphate.

(*S*)-2-Amino-3-hydroxybutanoic acid 3-phosphate.

$C_4H_{10}NO_6P$=199.1
CAS — 1114-81-4 (L-phosphothreonine); 27530-80-9 (DL-phosphothreonine).

Profile

Phosphothreonine, the phosphorylated form of threonine (p. 2098.2), has been used in tonic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Gr.***: Tonotil-N; ***Switz.***: Vitasprint Complex†.

Phyllanthus Amarus

Филлантус Обыкновенный (*Phyllanthus amarus*).
*UNII — 5578I1KA35 (*Phyllanthus amarus*); 7OG98361LN (*Phyllanthus amarus *fruit).*

Pharmacopoeias. In *US*, which also includes the powdered form.

USP 36: (Phyllanthus Amarus). The dried aerial parts of *Phyllanthus amarus* (Euphorbiaceae). It contains not less than 0.25% of lignans, calculated as the sum of phyllanthin and hypophyllanthin on the dried basis. Protect from light and moisture.

Phyllanthus Niruri

Chanca Piedra; Shatter Stone; Филлантус Нирури.
*UNII — NSN3MQO38G (*Phyllanthus niruri*); K4EM2N538T (*Phyllanthus niruri *top).*

Profile

Phyllanthus is a large genus (more than 600 species) of shrubs, trees, and herbs of the family Euphorbiaceae. Two species particularly, *P. amarus* and *P. niruri*, are closely related in appearance, phytochemical contents, and history, and this has sometimes caused problems in identification, with subsequent confusion as to which one is being referred to in the setting of medicinal herb usage. The name bhumyaamalaki appears to be commonly used in India for these two species.

Phyllanthus amarus has been used in Ayurvedic medicine as a diuretic as well as in liver disorders.

Phyllanthus niruri has been used worldwide as a traditional herbal remedy for a variety of disorders including kidney stones and other urinary-tract disorders and jaundice and other hepatic disorders.

Phyllanthus emblica is discussed separately under Indian Gooseberry, p. 2532.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Divens; Stimuno.

Multi-ingredient Preparations. ***Fr.***: Pilosuryl; ***Hung.***: Livfit; ***India***: Britesite; Hepaliv; Li-Verve; Livasa; Livasa; Livosil-H; Megacure-DS; Megacure-DS; ***Indon.***: Biofos†; Dibost; Erphacea; Formuno; Glimunos; Gramuno; Hepimun Plus; Hepimun; Imudator; Imulan; Imunal Plus; Imunogard; Kidimun; Picula; Reliv†; Tribost; ***Ital.***: Bionefrol; ***Port.***: Biureol†; ***Rus.***: Dipana (Дипана); ***Ukr.***: Imunin (Иммунин)†; ***Venez.***: Flucirac; Natrossil.

Physalis

Alkékenge; Alkekengi; Alquenque; Alquequenje; Amour en cage; Bladder Cherry; Blasenkirsche; Chinese Lantern; Coqueret; Ground Cherry; Judenkirsche; Lampionblume; Strawberry Tomato; Tomatillo inglés; Vejiga de perro; Winter Cherry; Песья Вишня; Физалис Обыкновенный.
*UNII — M71L0X809T (*Physalis alkekengi *fruiting top).*

NOTE. The name Winter Cherry has been applied to several plants including *Cardiospermum halicacabum* and *Withania somnifera* (see p. 2450.2) as well as *Physalis alkekengi*.

Pharmacopoeias. In *Chin.*

Profile

The berries of *Physalis alkekengi* (Solanaceae) are reputed to have diuretic properties.

Cape gooseberry is the edible fruit of *P. peruviana*.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Albo-Sang; ***Indon.***: Hyric.

Picibanil

OK-432; Пицибанил.
CAS — 39325-01-4.
UNII — 2F42BH7X2L.

Profile

Picibanil is a lyophilised preparation of a low-virulence strain of *Streptococcus pyogenes* inactivated by heating with benzylpenicillin; it is reported to act as an immunomodulator. It has been given by injection in the treatment of malignant neoplasms.

References.

1. Luzzatto C, *et al.* Sclerosing treatment of lymphangiomas with OK-432. *Arch Dis Child* 2000; **82:** 316–18.
2. Sakamoto J, *et al.* Meta-analysis of adjuvant immunochemotherapy using OK-432 in patients with resected non-small-cell lung cancer. *J Immunother* 2001; **24:** 250–6.
3. Laranne J, *et al.* OK-432 (Picibanil) therapy for lymphangiomas in children. *Eur Arch Otorhinolaryngol* 2002; **259:** 274–8.
4. Sakamoto J, *et al.* Efficacy of adjuvant immunochemotherapy with OK-432 for patients with curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials. *J Immunother* 2002; **25:** 405–12.
5. Giguere CM, *et al.* Treatment of lymphangiomas with OK-432 (Picibanil) sclerotherapy: a prospective multi-institutional trial. *Arch Otolaryngol Head Neck Surg* 2002; **128:** 1137–44.
6. Watanabe M, *et al.* Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil and uracil/tegafur. *Int J Clin Oncol* 2004; **9:** 98–106.
7. Sato Y, *et al.* A randomized controlled study of immunochemotherapy with OK-432 after curative surgery for gastric cancer. *J Immunother* 2004; 394–7.
8. Taniguchi T, *et al.* Clinical results of OK-432 injection therapy for ganglions. *J Dermatol* 2005; **32:** 262–5.
9. Kasahara K, *et al.* Randomized phase II trial of OK-432 in patients with malignant pleural effusion due to non-small cell lung cancer. *Anticancer Res* 2006; **26:** 1495–9.
10. Knipping S, *et al.* Sclerotherapy of cervical cysts with Picibanil (OK-432). *Eur Arch Otorhinolaryngol* 2007; **264:** 423–7.
11. Nygaard U, *et al.* New treatment of early fetal chylothorax. *Obstet Gynecol* 2007; **109:** 1088–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Picibanil.

Picrorhiza Kurroa

Kuru; Kutki; *Picrorhiza urrooa*; Picrolex.
*UNII — ZB5K2O2999 (*Picrorhiza kurroa *root).*

Profile

The dried and powdered rhizomes of *Picrorhiza kurroa* (Plantaginaceae) are used as an ingredient in herbal preparations for liver disorders and it has been tried as an adjunct to methoxsalen for the treatment of vitiligo. It has also been used in Ayurvedic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hung.***: Herbadict; Livfit; Munipyrin; ***Rus.***: Bonjigar (Бонджигар); Dipana (Дипана); Fitovit (Фитовит); ***Singapore***: Hemoglo; ***Ukr.***: Apitol (АПИТОЛ); Bonjigar (Бонджигар); Fitovit (Фитовит).

Pidotimod *(rINN)*

Pidotimodum; Пидотимод.
(*R*)-3-[(*S*)-5-Oxoprolyl]-4-thiazolidinecarboxylic acid.
$C_9H_{12}N_2O_4S$=244.3
CAS — 121808-62-6.
ATC — L03AX05.
ATC Vet — QL03AX05.
UNII — 785363R681.

Profile

Pidotimod is an immunostimulant used in patients with cell-mediated immunodepression during respiratory- and urinary-tract infections. It is given orally in usual doses of 800 mg twice daily.

References.

1. Riboldi P, *et al.* Pidotimod: a reappraisal. *Int J Immunopathol Pharmacol* 2009; **22:** 255–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: De Chang (得畅); Fuluyin (芙露饮); Li De (力德); Polimod (普利莫); Pu Le Yi (谱乐益); Wan Shi Ning (万适宁); WeiTian (唯田); ***Gr.***: Polimod; ***Ital.***: Axil; Onaka; Pigitil; Polimod; ***Mex.***: Adimod; ***Rus.***: Imunorix (Имунорикс); ***Ukr.***: Imunorix (Имунорикс).

Pilewort

Celidonia menor; Escrofularia menor; Ficaire; Ficaria Ranunculoides; Ficaria Verna; Lesser Celandine; Чистяк Весенний.
*UNII — YO2M043F0W (*Ranunculus ficaria*).*

Pharmacopoeias. In *Fr.*

Profile

Pilewort, the aerial parts of *Ranunculus ficaria* (Ranunculaceae), has astringent and demulcent properties and is used topically for the treatment of haemorrhoids.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Confortel; ***Cz.***: Avenoc†; ***Fr.***: Avenoc; ***UK***: Piletabs.

Homoeopathic Preparations. ***Canad.***: Avenoc†; ***Port.***: Avenoc†.

Pinaverium Bromide *(rINN)*

Bromuro de pinaverio; Pinaverii Bromidum; Pinaverio, bromuro de; Pinavérium, Bromure de; Pinaveriumbromid; Pinaveriumbromidi; Pinaveryum Bromür; Пинаверия Бромид.
4-(6-Bromoveratryl)-4-{2-[2-(6,6-dimethyl-2-norpinyl)ethoxy]ethyl}morpholinium bromide.
$C_{26}H_{41}Br_2NO_4$=591.4
CAS — 59995-65-2 (pinaverium); 53251-94-8 (pinaverium bromide).
ATC — A03AX04.
ATC Vet — QA03AX04.
UNII — 7SCF54H12J.

Profile

Pinaverium bromide is a calcium-channel blocker with some antimuscarinic-like effects. It is used for the relief of gastrointestinal spasm in usual doses of 50 mg orally three times daily at mealtimes, which may be increased if necessary up to a maximum of 100 mg three times daily.

Effects on the gastrointestinal tract. Two patients had heartburn and dysphagia after taking pinaverium bromide orally between meals; endoscopy revealed acute oesophageal ulceration, which healed on stopping treatment.[1] The manufacturer's recommendation to take pinaverium bromide during meals was emphasised.

1. André J-M, *et al.* Ulcères oesophagiens après prise de bromure de pinaverium. *Acta Endosc* 1980; **10:** 289–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dicetel; Nulite; ***Braz.***: Dicetel; Siilif; ***Canad.***: Dicetel; ***Chile***: Eldicet; ***China***: Dicetel (得舒特); ***Cz.***: Dicetel†; ***Fr.***: Dicetel; ***Gr.***: Dicetel; ***Hung.***: Dicetel; ***India***: Eldicet; ***Ital.***: Dicetel; ***Mex.***: Dicetel; Distental; Diver; Lutropen; Pakab; Zerpyco; ***Phil.***: Eldicet; ***Port.***: Dicetel; ***Rus.***: Dicetel (Дицетел); ***Spain***: Eldicet; ***Switz.***: Dicetel; ***Thai.***: Dicetel; ***Turk.***: Dicetel; ***Ukr.***: Dicetel (Дицетел); ***Venez.***: Dicetel.

Multi-ingredient Preparations. ***Mex.***: Alevian Duo.

Maritime Pine

Cluster Pine; Strandkiefer; Сосна Приморская.
CAS — 174882-69-0 (pycnogenol).
*UNII — J27867F361 (*Pinus pinaster*); 50JZ5Z98QY (*Pinus pinaster *bark); 0L1DQ35D6G (*Pinus pinaster *wood).*

Pharmacopoeias. In *USNF.*

USNF 31: (Maritime Pine). It consists of the bark of stems of *Pinus pinaster* (*Pinus maritima*) (Pinaceae). It contains not less than 8.0% and not more than 12.0% of procyanidins, calculated on the dried basis and is intended to be used in the preparation of extracts only and is not for direct human consumption. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from moisture.

Profile

The bark of the maritime pine, *Pinus pinaster* (*P. maritima*) (Pinaceae) is a source of flavonoid compounds (p. 2505.2). A mixture of procyanidins extracted from the bark is known as pycnogenol, although the term pycnogenols has also been applied to procyanidin flavonoids in general.

Preparations of such bark extracts are promoted for their antoxidant action.

Maritime pine is a source of pine needle oil (see Pine Oils, below). Pine needle oil from maritime pine (Pinus pinaster oil) is included in preparations for minor respiratory-tract disorders and in topical preparations for the relief of musculoskeletal, joint, and soft-tissue disorders. Turpentine oil (p. 2636.3) is distilled from the oleoresin.

Osteoarthritis. Extracts of maritime pine bark have been given as dietary supplements to patients with osteoarthritis; an evidence-based report[1] by the Arthritis Research Campaign in the UK considered that maritime pine was possibly effective in reducing pain and improving physical function.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aseptobron; ***Austral.***: Radiance; ***Ital.***: Algorex; Flebil Plus; Flogofort; Signum; ***Malaysia***: Evelle; Pynocarewhite; ***Philipp.***: Gloww; Glucontrol; Pynocare 40 Actisome; ***Singapore***: Evelle; Glow; Scar Esthetique; ***UK***: Zinopin; ***USA***: Pycnogenol Plus.

Pharmacopoeial Preparations
USP 36: Maritime Pine Extract.

Scots Pine

Pin Sylvestre; Pinus Sylvestris; Scotch pine; Сосна Обыкновенная (*Pinus sylvestris*).
ATC Herb — HM02AW5015 (Pinus sylvestris: *balsam*); *HM02AW5017* (Pinus sylvestris: *shoot tip*); *HR05WA5039* (Pinus sylvestris: *balsam*); *HR05WA5041* (Pinus sylvestris: *shoot tip*).
UNII — VP00HZL9IC (Pinus sylvestris); *M402HHT991* (Pinus sylvestris *bark*); *856B44M480* (Pinus sylvestris *cone*); *2HEM73YI9I* (Pinus sylvestris *flowering top*); *Q1RGP4UB73* (Pinus sylvestris *leafy twig*).

Pharmacopoeias. In *Fr.*

Profile

The sprouts of the Scots pine, *Pinus sylvestris* (Pinaceae), are used in herbal medicine for the treatment of catarrh and in topical preparations for mild muscular pain.

Scots pine is a source of Scots pine oil and pine needle oil (see Pine Oils, below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Olioseptil Gorge-Larynx; Pectoflorine†; ***Pol.***: DexaPini; Herbapini; Sirupus Pini Compositus; Sirupus Tussipini D; Sirupus Tussipini; Syrop Sosnowy Zlozony†; Syrop Sosnowy Zlozony.

Homoeopathic Preparations. ***Austria***: Lymphomyosot; ***Cz.***: Lymphomyosot; ***Ger.***: Asthmakhell N; Lymphomyosot N; Lymphomyosot; ***Hung.***: Lymphomyosot; ***Neth.***: Asakell; Asthmakhell†; Lymfelite; ***S.Afr.***: Lymphomyosot; ***Ukr.***: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pine Oils

Сосновые Масла.
ATC Herb — HM02AW5013 (Pinus nigra: *essential oil*).

Pumilio Pine Oil

Dwarf Mountain Pine Oil; Dwarf Pine Needle Oil; Dwarf Pine Oil; Essence de Pin de Montagne; Latschenkiefernöl; Latschenöl; Oleum Pini Pumilionis; Olio di Mugo; Pin de montagne, huile essentielle de; Pini pumilionis aetheroleum; Pino mugo, aceite esencial de; Масло Сосны Горной.
CAS — 8016-46-4.
ATC Herb — HM02AW5012 (Pinus mugo: *essential oil*); *HR05YA5017* (Pinus mugo: *essential oil*).
UNII — 6KF1RLN1CI.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dwarf Pine Oil). An essential oil obtained by steam distillation of the fresh leaves and twigs of *Pinus mugo*. A suitable antoxidant may be added. Relative density 0.857 to 0.868. A clear, colourless or pale yellow liquid. Store in inert, well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Scots Pine Oil

Borovicová silice; Fir-wool Oil; Kiefernnadelöl; Olejek sosny zwyczajnej; Oleum Pini Silvestris; Pin sylvestre, huile essentielle de; Pine Silvestris Oil; Pini silvestris aetheroleum; Pini Silvestris Etheroleum; Pini Sylvestris Aetheroleum; Scotch Pine Needle Oil; Scots Pine Needle Oil; Sylvestris Pine Oil; Масло Сосны Обыкнавенной.
ATC Herb — HR05WA5040 (Pinus sylvestris: *needle essential oil*); *HM02AW5016* (Pinus sylvestris: *essential oil*).
UNII — 5EXL5H740Y.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pine Sylvestris Oil). An essential oil obtained by steam distillation of the fresh leaves and branches of *Pinus sylvestris*. A suitable antoxidant may be added. A clear, colourless or pale yellow liquid with a characteristic odour. Relative density 0.855 to 0.875. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Pine oil from unspecified species of pine is included in preparations for the relief of coughs and cold symptoms and in topical preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Oils from fresh needles, tips, and boughs of *Pinus nigra*, *P. mugo* var. *pumilio*, *P. pinaster* (Maritime Pine, p. 2590.3), and *P. sylvestris* (Scots Pine, above) are all described as pine needle oil.

Pumilio pine oil is a volatile oil obtained by distillation from the fresh leaves of *Pinus mugo* var. *pumilio* (Pinaceae). It has been inhaled with steam, sometimes with other essential oils, to relieve cough and nasal congestion and has been applied externally as a rubefacient. It has also been used as a perfume.

Scots pine oil is obtained from the needles and tips of Scots pine (above). It is used for catarrh and related disorders of the respiratory tract, often with other volatile substances. It is applied externally for rheumatic disorders and is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ukr.***: Fitesten (Фитестен).

Multi-ingredient Preparations. ***Arg.***: Bayagel; Bronco Etersan; Inhalador Medex; Medex Rub; Medex Rub; Novobroncol; Pre Calent; ***Austral.***: Biosal Arthritis†; Goanna Heat Cream; Goanna Oil Liniment; Goanna Salve†; Vicks Inhaler; ***Austria***: Babix; Berggeist; Bronchostop†; Colda; Luuf Balsam; Nasanal; Opino; Piniment; Piniment; Piniment; ***Belg.***: Inopectol†; ***Braz.***: Peitoral Martel; ***Canad.***: Artriben†; ***Chile***: Hansaplast Descongestionante†; Mentholatum Inhalador; Menthose; ***Cz.***: Mucoplant Eukalyptovy; Pinosol†; Pinosol; Thrombocid; Transpulmin†; ***Fr.***: Aromasol; Bronchorectine au Citral; Febrectol†; Maghora†; Nazinette du Docteur Gilbert; Olioseptil Gorge-Larynx; Poudre du Marcheur†; Respirea†; ***Ger.***: Bronchoforton Kinderbalsam†; Dolo-cyl†; Erkaltungs Bad N†; Euflux; Franzbranntwein†; Grippostad Erkaltungsbalsam mild; Klosterfrau Franzbranntwein Latschenkiefer†; Pinimenthol Erkaltungsinhalat; Pinimenthol Erkaltungssalbe; polio-elan†; Poly-elan; Tetesept Erkaltungs Bad; Tetesept Rheuma Badekonzentrat; Thrombocid; Transpulmin Kinderbalsam S†; Tumarol Kinderbalsam; Weleda Bronchialbalsam; ***Gr.***: Opino; Pinimenthol; ***Hong Kong***: Sloan's Liniment†; ***Hung.***: Bronchovit; Hustagil Anticold Cream; Mentholatum Rub; Pasta Cool; Perskindol Classic; Pinosol; Pinosol; Rosarthron; ***Indon.***: Sloan's Liniment†; ***Irl.***: Karvol; ***Israel***: Karvol; Ment-O-Cap†; Mentholatum Balm; ***Ital.***: Abiostil; Altuss; Broncosedina; Calyptol; Narhinel Balsamico Bambini; Ozopulmin G; Ozopulmin; Pumilene Vapo; Sloan†; Vicks Inalante; ***Mex.***: Balsamo Ifusa; ***Mon.***: Bronchodermine; Bronchodermine; Calyptol; ***Neth.***: Luuf Verkoudheidsbalsem; ***NZ***: Karvol; Tixylix Chest Rub; Vicks Inhaler; ***Philipp.***: Kamillosan M; ***Pol.***: Analgol; Analgolan; Eukaliptiss; Herbolen D†; Herbolen†; Inhalol; Pinimentol; Pinosol†; Pulmonil; Reumatik; Reumosol; Rhin-Bac; ***Port.***: Thrombocid; ***Rus.***: Carmolis Fluid (Кармолис Жидкость); Eucabal S (Эвкабал С); Pinosol (Пиносол); Pinosol (Пиносол); Pinosol (Пиносол); Pinovitum (Пиновитум); Tussamag Balsam (Туссамаг Бальзам от Простуды)†; Urocholesan (Уроholесан); Urolesan (Уролесан); ***S. Afr.***: Karvol†; Oleum Salviae Comp†; Respisniffers†; Woodwards Inhalant; ***Singapore***: Karvol; ***Spain***: Genurat; Pulmofasa; Sinus Inhalaciones; Vapores Pyt†; ***Swed.***: Alpenkraft; ***Switz.***: Denosol; Eucapinol; Liberol Baby N; Liberol N; Marament-N; Nasmer free; Novital; Perskindol Classic; Perskindol Classic; Perskindol Dolo; Pulmex; Ziegella†; ***UK***: Dragon Balm; Karvol; Mentholatum Rub; Original Cabdrivers Expectorant; Pickles Smelling Salts; Potter's Catarrh Pastilles; Proctor's Pinelyptus; ***Ukr.***: Eucabal Balsam S (Эвкабал Бальзам С); Eucalyptus Cold Balm Dr Theiss (-Эвкалиптовый Бальзам От Др Тайсс)†; Flavia (Флавия); Kofanol (Кофанол)†; Phytolysin Plus (Фитолизин Плюс); Pinosol (Пиносол)†; Pinosol (Пиносол); Pinosol (Пиносол); Pinovit (Піновіт); Rostiran (Розтиран); Urolesan (Уролесан); Vipratox (Випратокс); ***Venez.***: Reugel.

Pinene

Пинен.
2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (α-pinene); 6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptane (β-pinene).
$C_{10}H_{16}$=136.2
CAS — 80-56-8 (α-pinene); 127-91-3 (β-pinene).

Profile

Pinene is a terpene constituent of turpentine oil (p. 2636.3) and many other essential oils and has been used in preparations for biliary-tract, urinary-tract, and other disorders. It exists as 2 isomers, α-pinene and β-pinene (nopinene, norpinene, terbenthene, terebenthene).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Anastim; Rowatinex; ***Austria***: Rowachol; Rowatinex; ***Chile***: Rowatinex; ***China***: Qie Nuo (切诺); ***Cz.***: Rowachol; Rowatinex; ***Fr.***: Pectoderme†; ***Ger.***: Rowachol; Rowatinex; ***Hong Kong***: Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.***: Rowachol; Rowatinex; ***Irl.***: Rowachol; Rowatinex; ***Israel***: Rowachol; Rowatinex; ***Malaysia***: Rowachol; Rowatinex; ***Mex.***: Cholex; ***Philipp.***: Rowachol; Rowatinex; ***Pol.***: Rowachol; Rowatinex; Terpichol; ***Rus.***: Rowatinex (Роватинекс); ***Spain***: Rowachol; Rowanefrin; ***Thai.***: Rowachol; Rowatinex; ***UK***: Rowachol; ***Venez.***: Rowachol; Rowatinex.

Pipoxolan *(BAN, pINN)*

Pipoxolán; Pipoxolanum; Пипоксолан.
5,5-Diphenyl-2-(2-piperidinoethyl)-1,3-dioxolan-4-one.
$C_{22}H_{25}NO_3$=351.4
CAS — 23744-24-3.
UNII — 493GZJ5T6I.

Pipoxolan Hydrochloride *(BANM, USAN, pINNM)*

Hidrocloruro de pipoxolán; Pipoxolan, Chlorhydrate de; Pipoxolán, hidrocloruro de; Pipoxolani Hydrochloridum; Пипоксолана Гидрохлорид.
$C_{22}H_{25}NO_3$,HCl=387.9
CAS — 18174-58-8.
UNII — VIA6WM647S.

Profile

Pipoxolan has been used as the base and the hydrochloride as a smooth muscle relaxant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Irl.***: Migranat†.

Pirenoxine Sodium *(rINNM)*

Catalin Sodium; Natrii Pirenoxinum; Pirenoxina sódica; Pirénoxine Sodique; Pirfenoxone Sodium; Натрий Пиреноксин.
Sodium 1-hydroxy-5-oxo-5*H*-pyrido[3,2-*a*]phenoxazine-3-carboxylate.
$C_{16}H_7N_2NaO_5$=330.2
CAS — 1043-21-6 (pirenoxine); 51410-30-1 (pirenoxine sodium).
ATC Vet — QS01XA91.
UNII — 95JU7URF64.

Pharmacopoeias. *Jpn* includes Pirenoxine.

Profile

Pirenoxine sodium is used in the treatment of cataracts, usually as 0.005% eye drops.

References.
1. Inui S, *et al.* Contact dermatitis due to pirfenoxone. *Contact Dermatitis* 2004; **50:** 375–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Clarvisol; ***China***: Catalin (卡他灵); Kary Uni (卡林优); ***Gr.***: Catalin; ***Hong Kong***: Catalin; Kary Uni; ***India***: Catalin; ***Indon.***: Catalin; Kary Uni; ***Ital.***: Clarvisan; Pirfalin; ***Jpn***: Catalin; ***Philipp.***: Catalin; Kary Uni; ***Pol.***: Catalin; ***Port.***: Clarvisan; ***Singapore***: Catalin; Kary Uni; ***Spain***: Clarvisan†; ***Thai.***: Catalin; Kary Uni.

Pirfenidone *(USAN, rINN)*

AMR-69; F-647; Pirfenidona; Pirfénidone; Pirfenidonum; Пирфенидон.

5-Methyl-1-phenyl-2(1*H*)-pyridone.

$C_{12}H_{11}NO$=185.2

CAS — 53179-13-8.

UNII — D7NLD2JX7U.

Uses and Administration

Pirfenidone is an antifibrotic drug used for the treatment of mild to moderate idiopathic pulmonary fibrosis (see under Interstitial Lung Disease, p. 1607.1).

Pirfenidone is given orally and should be taken with food. In the EU, where a product supplying unit doses of 267 mg is licensed, treatment is begun by titration of doses over a 2-week period to the maintenance dose as follows:

- 267 mg 3 times daily for the first 7 days of treatment
- 534 mg 3 times daily for the next 7 days of treatment
- 801 mg 3 times daily thereafter, which is the maximum dose and should not be exceeded

Slightly lower doses are given in Japan, where a product supplying unit doses of 200 mg is available.

If 14 or more consecutive days of treatment are missed, pirfenidone treatment should be restarted using the 2-week titration schedule described above. If the interruption in treatment is less than 14 days, treatment can be resumed at the previous daily dose without titration.

In patients with persistent gastrointestinal adverse effects, the dose may be reduced to 267 to 534 mg 2 or 3 times daily, and then raised again to the recommended daily dose as tolerated. If necessary, treatment may be interrupted for 1 to 2 weeks to allow symptoms to resolve.

In the event of mild to moderate hypersensitivity reactions or rash, the dose may be reduced to 267 mg 3 times daily. If the rash persists for more than 7 days, pirfenidone should be stopped for 15 days and then re-escalated to the recommended daily dose.

Pirfenidone is also under investigation in other disorders such as multiple sclerosis, familial adenomatous polyposis, and neurofibromatosis type 1.

References.

1. Nicod LP. Pirfenidone in idiopathic pulmonary fibrosis. *Lancet* 1999; **354:** 268–9.
2. Walker JE, Margolin SB. Pirfenidone for chronic progressive multiple sclerosis. *Multiple Sclerosis* 2001; **7:** 305–12.
3. Nagai S, *et al*. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. *Intern Med* 2002; **41:** 1118–23.
4. Bowen JD, *et al*. Open-label study of pirfenidone in patients with progressive forms of multiple sclerosis. *Multiple Sclerosis* 2003; **9:** 280–3.
5. Lindor NM, *et al*. Desmoid tumors in familial adenomatous polyposis: a pilot project evaluating efficacy of treatment with pirfenidone. *Am J Gastroenterol* 2003;**98:** 1868–74.
6. Azuma A, *et al*. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; **171:** 1040–7.
7. Walker JE, *et al*. A double-blind, randomized, controlled study of oral pirfenidone for treatment of secondary progressive multiple sclerosis. *Multiple Sclerosis* 2005; **11:** 149–58.
8. Babovic-Vuksanovic D, *et al*. Phase II trial of pirfenidone in adults with neurofibromatosis type 1. *Neurology* 2006; **67:** 1860–2.
9. Shi S, *et al*. Single- and multiple-dose pharmacokinetics of pirfenidone, an antifibrotic agent, in healthy Chinese volunteers. *J Clin Pharmacol* 2007; **47:** 1268–76.
10. Azuma A. Pirfenidone: antifibrotic agent for idiopathic pulmonary fibrosis. *Expert Rev Respir Med* 2010; **4:** 301–10.
11. Cho ME, Kopp JB. Pirfenidone: an anti-fibrotic therapy for progressive kidney disease. *Expert Opin Invest Drugs* 2010; **19:** 275–83.
12. Noble PW, *et al*. CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; **377:** 1760–9.

Adverse Effects and Precautions

Adverse effects most commonly reported with pirfenidone include nausea, diarrhoea, dyspepsia, fatigue, rash, and photosensitivity reactions; dizziness and weight loss have also occurred. Other more serious reactions include jaundice and hepatic failure, and blood dyscrasias such as agranulocytosis, leucopenia, and neutropenia.

Raised liver transaminases have been reported in patients receiving pirfenidone and liver function tests should be carried out before starting treatment, and at monthly intervals for the first 6 months of treatment, then every 3 months thereafter. Use of pirfenidone is contra-indicated in patients with severe hepatic impairment or end-stage liver disease, and in severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease requiring dialysis. Patients should be cautioned to avoid or minimise exposure to direct sunlight, and to apply sunblock daily during treatment. Care should be taken if driving or operating machinery.

Interactions

Fluvoxamine inhibits the metabolism of pirfenidone resulting in a significant increase in pirfenidone exposure, and therefore concomitant administration of these two drugs is contra-indicated.

Tobacco smoking has been reported to increase the clearance of, and therefore reduce the exposure to, pirfenidone by 50%.

Pharmacokinetics

Pirfenidone is absorbed after oral doses; taking doses with food reduces peak plasma concentrations by about 50% but has only moderate effects on exposure, resulting in a lower incidence of adverse effects. It is metabolised primarily by the cytochrome P450 isoenzyme CYP1A2, with some contribution by CYP2C9, CYP2C19, CYP2D6 and CYP2E1. The major metabolite is 5-carboxy-pirfenidone; about 80% of a dose is excreted in urine within 24 hours, less than 1% as unchanged drug. The terminal elimination half-life after single doses is reported to be about 2.4 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Esbriet; ***Ger.***: Esbriet; ***Irl.***: Esbriet; ***Jpn***: Pirespa; ***Neth.***: Esbriet; ***Norw.***: Esbriet; ***Swed.***: Esbriet; ***UK***: Esbriet.

Pirglutargine

Arginina, piroglutamato de; Arginine Pidolate; Arginine Pyroglutamate; Пидолат Аргинина.

L-Arginine DL-pyroglutamate.

$C_{11}H_{21}N_5O_5$=303.3

CAS — 64855-91-0.

UNII — 808T94CEU6.

Profile

Pirglutargine has been used for its reputed cerebral stimulant effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Port.***: Detoxergon.

Pirisudanol Maleate *(rINNM)*

Dimaleato de pirisuccideanol; Dimaleato de pirisudanol; Pirisudanol, dimaleato de; Pirisudanol, Maléate de; Pirisudanoli Maleas; Pyrisuccideanol Maleate; Пирисуданола Малеат.

2-Dimethylaminoethyl 5-hydroxy-4-hydroxymethyl-6-methyl-3-pyridylmethyl succinate maleate.

$C_{16}H_{24}N_2O_6.(C_4H_4O_4)_2$=572.5

CAS — 33605-94-6 (pirisudanol); 53659-00-0 (pirisudanol maleate).

ATC — N06BX08.

ATC Vet — QN06BX08.

Profile

Pirisudanol is the succinic acid ester of pyridoxine and of deanol. It has been given orally as the maleate in the management of impaired mental function in doses of up to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Nadexen; ***Port.***: Pridana; ***Spain***: Mentis.

Pitofenone Hydrochloride *(rINNM)*

Hidrocloruro de pitofenona; Pitofénone, Chlorhydrate de; Pitofenoni Hydrochloridum; Питофенона Гидрохлорид.

Methyl 2-[4-(2-piperidinoethoxy)benzoyl]benzoate hydrochloride.

$C_{22}H_{25}NO_4$,HCl=403.9

CAS — 54063-52-4 (pitofenone); 1248-42-6 (pitofenone hydrochloride).

UNII — HE1ZA4ZBEX.

Profile

Pitofenone hydrochloride has been used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Algifen Neo; Algifen; Analgin; Spasmopan; ***Fin.***: Litalgin; ***India***: Combispas; Nidi Spas; Nobel Spas; Novaspas; ***Pol.***: Spasmalgon; ***Rus.***: Bioralgin (Биоралгин); Bral (Брал); Bralangine (Бралангин); Maxigan (Максиган); Nebalgan (Небалган); Novigan (Новиган); Plenalgin (Пленалгин); Renalgan (Реналган); Revalgin (Ревалгин); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); ***Thai.***: Donagan; Kanegan†; ***Ukr.***: Baralginus (Баралгинус)†; Novigan (Новиган); Spasgan (Спазган); Spasmadol (Спазмадол)†; Spasmalgon (Спазмалгон); Spasmil-M (Спазмил-М); ***Venez.***: Flemibar.

Powdered Pituitary (Posterior Lobe) ⊗

Hipófisis pulverizada (neurohipófisis); Hypophysis Cerebri Pars Posterior; Hypophysis Sicca; Ipofisi Posteriore; Pituitarium Posterius Pulveratum; Pituitary; Posterior Pituitary.

NOTE. Pituitary Extract (Posterior) is *BAN*.

Pharmacopoeias. In *Chin.*

Profile

Powdered pituitary (posterior lobe) is a preparation from the posterior lobes of mammalian pituitary bodies. It has oxytocic, pressor, antidiuretic, and hyperglycaemic actions and has generally been replaced by compounds or preparations with more specific actions such as oxytocin (p. 2143.1) and desmopressin (p. 2355.1).

It has been included in preparations of combined tissue extracts promoted as tonics or for a variety of non-endocrine disorders. Hypersensitivity reactions, including anaphylaxis, have occasionally been reported.

Plantain

Llantén; Llantén mayor; Plantain grand; Подорожник Большой (*Plantago major*).

ATC Herb — HC05AW5005 (Plantago major: *leaf*).

UNII — W2469WNO6U.

Pharmacopoeias. *Chin.* and *Jpn.* include the herb and seeds from *Plantago asiatica*. *Chin* also permits *P. depressa*.

Profile

The seeds and leaves of the common or greater plantain (*Plantago major*) are reported to possess diuretic and antihaemorrhagic properties. They are used in herbal preparations.

The Asian plantain (*P. asiatica*) and the depressed plantain (*P. depressa*) are also used in herbal medicine. The seeds of some other species of *Plantago* are used as the bulk laxatives ispaghula and psyllium (see p. 1849.1).

The ribwort plantain (*P. lanceolata*) is described on p. 2604.2.

Homoeopathy

Plantain has been used in homoeopathic medicines under the following names: Plantago; Plantago major; Plant. m.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Ultrabalance-Herbulk†; ***Rus.***: Plantacid (Плантацид); Plantaglucid (Плантаглюцид).

Multi-ingredient Preparations. ***Canad.***: Natraway Sport 1 & 2†; Natraway Sport 3†; ***Chile***: Propolkit; Propolkit; ***Indon.***: Hyric; Renax; ***Port.***: Erpecalm; ***Rus.***: Evalar (Эвалар); Fitantis (Фитантис); Kliophyt (Клиофит); Pectorales Species No 2 (Грудной Сбор 2); ***Switz.***: DemoPectol; Kernosan Elixir; Pectoral N; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; ***Ukr.***: Pectoral (Пекторал); Stoptussin Fito (Стоптуссин).

Homoeopathic Preparations. ***Austral.***: Earache Relief†; ***Austria***: Echinacea-Cosmoplex; ***Canad.***: Viburcol; ***Chile***: Drosemiel; Gug/X†; Llanten†; TBR/X; ***Cz.***: Viburcol; ***Fr.***: Abbe Chaupitre no 66†; Millefolium Complexe No 7†; ***Ger.***: Entzundungstropfen; Enuroplant N; Viburcol N; ***Hung.***: Viburcol; ***Neth.***: Auriculite; Enulite; Homeocare keelspray; Oteel H; Ricura; Viburcol H; Vinceel H; ***Port.***: Homeodent†; ***Rus.***: Plantago-Plus (Плантаго-Плюс); Tabacum-Plus (Табакум-Плюс); ***S.Afr.***: Viburcol; ***Switz.***: Viburcol N.

Plastics

Plásticos.

Pharmacopoeias. Many pharmacopoeias include standards for plastic containers and closures.

Profile

Plastic materials have many uses in medicine and pharmacy, but may give rise to adverse effects, either by direct contact of the plastic with tissues or by indirect contact (for example, when a solution stored in a plastic container, such as a disposable syringe, is injected). Adverse

effects may also arise among workers through handling the materials or by inhaling fumes during manufacture.

Pure polymeric plastics appear to be of low toxicity, though carcinogenic effects have been produced by some on prolonged implantation. However, some monomers are toxic, as may be substances added during manufacture to impart specific physical properties. These additives include plasticisers added to reduce brittleness, ultraviolet-ray absorbers to prevent degradation by light, and antoxidants and lubricants which are sometimes needed for satisfactory processing. Monomer residues or additives can leach out from the finished plastic materials and have been the main causes of adverse effects. These may include haemolysis of blood cells, thrombosis, hypersensitivity reactions, precancerous changes, and local tissue necrosis. Silicone particles have been shed from dialysis tubing resulting in hypersplenism, pancytopenia, and occasionally in the production of a granulomatous hepatitis.

See also under Vinyl Chloride, p. 2645.3, Methylmethacrylate, p. 2558.2, and Polytef, p. 2594.2.

Platinum

Plaatina; Platí; Platin; Platină; Platina; Platine; Platino; Platīns; Platyna; Платина.

Pt=195.084

CAS — 7440-06-4.

UNII — 49DFR088MY.

Chloroplatinic Acid

Acide hexachloroplatinique; Acido cloroplatinico; Cloroplatínico, ácido; Heksakloroplatinahappo; Hexachloorplatinazuur; Hexachloridoplatinsäure; Hexakloro-platina(IV)-sav; Kloroplatinasyra; Kwas chloroplatynowy; Платинохлористоводородная Кислота.

Hexachloroplatinic acid hexahydrate.

$H_2PtCl_6.6H_2O$=517.9

CAS — 16941-12-1 (anhydrous chloroplatinic acid); 18497-13-7 (chloroplatinic acid hexahydrate).

UNII — Q65224GJ7F (chloroplatinic acid); 9W7LR29OOB (chloroplatinic acid hexahydrate).

NOTE. The names Platinic Chloride and Platinum Chloride have been applied to both chloroplatinic acid and platinum tetrachloride.

Platinum Tetrachloride

Platinum Chloride; Platinum (IV) Chloride; Tetrachloroplatinum.

$PtCl_4$=336.9

CAS — 13454-96-1.

Profile

Platinum is a noble metal used industrially for its catalytic properties. It is also used in jewellery, and platinum alloys have occasionally been used in dentistry. Platinum compounds such as chloroplatinic acid and platinum tetrachloride also have industrial uses. Aqueous solutions of platinum tetrachloride have been used in corneal tattooing procedures.

For the use of platinum compounds as antineoplastics, see Cisplatin, p. 766.1.

Homoeopathy

Platinum and its compounds have been used in homoeopathic medicines under the following names:

- Platinum metal: Platinum metallicum; Platina; Platin
- Chloroplatinic acid or platinum tetrachloride: Platinum muriaticum; Platinum Chloridum.

References.

1. Khan AO, Meyer D. Corneal tattooing for the treatment of debilitating glare in a child with traumatic iris loss. *Am J Ophthalmol* 2005; **139:** 920–1.

Adverse effects. Exposure to platinum compounds may result in irritation of the eyes, nose, and throat. Long-term exposure may lead to respiratory and skin sensitisation; contact allergy to platinum metal is very rare.

References.

1. Koch P, Baum HP. Contact stomatitis due to palladium and platinum in dental alloys. *Contact Dermatitis* 1996; **34:** 253–7.
2. Cristaudo A, *et al.* Occupational hypersensitivity to metal salts, including platinum, in the secondary industry. *Allergy* 2005; **60:** 159–64.
3. Fowler JF, *et al.* Positive patch-test reactions to platinum are rare. *Dermatitis* 2008; **19:** 146–7.
4. Wiseman CL, Zereini F. Airborne particulate matter, platinum group elements and human health: a review of recent evidence. *Sci Total Environ* 2009; **407:** 2493–500.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Cz.*: Lamioflur†; Platina; *Fr.*: Aurum Complexe No 38†; Ferrum Complexe No 29; *Ger.*: Bomaklim; Calmvalera; Cocculus Oligoplex; Thuja WA Oligoplex; Zincum Hevert N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Neth.*: Chavita 2; Emvita 4.

Pleurisy Root

Asclepia tuberosa; Butterfly Weed; Hierba de mariposa; Inmortal; Плевритный Корень.

UNII — 4X6S7KQ99Y (Asclepias tuberosa); Y62M9GTW4A (Asclepias tuberosa flowering top); 1ZL82U5D18 (Asclepias tuberosa root).

Profile

The root of *Asclepias tuberosa* (Asclepiadaceae) has traditionally been used for pleurisy and other respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Broncafect; *UK*: Antibron; Chest Mixture; Cough Soother Herbal Syrup; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Vegetable Cough Remover.

Homoeopathic Preparations. *Fr.*: Boripharm No 23; *Ger.*: Neuralgie-Injektopas SL.

Pokeroot

Espinaca de Indias; Fitolaca; Granilla; Hierba carmín; Hierba de la oblea; Mechoacan; Poke Root; Tintilla; Uva de América; Фитолакка Американская (*Phytolacca americana*).

Pharmacopoeias. In *Chin.*

Profile

Pokeroot, the root of *Phytolacca decandra* (*P. americana*) (Phytolaccaceae) has emetic, purgative, anti-inflammatory, and anti-infective actions. It has been used for rheumatic and arthritic disorders, and for respiratory-tract infections, but is highly toxic in large doses and is not generally recommended. It has also been used externally for skin disorders.

The related species, *P. dodecandra*, is the source of the molluscicide endod (p. 2154.2).

Homoeopathy

Pokeroot has been used in homoeopathic medicines under the following names: Phytolacca; Phytolacca americana; Phytolacca americana e baccis; Phytolacca e baccis; Phytolacca decandra; Phyto.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Echinacea Royale; *Fr.*: Homeoplasmine; *UK*: Napiers Oral Skin Soother Herbal Relief; Psorasolv.

Homoeopathic Preparations. *Austria*: Echinacea-Cosmoplex; Lymphdiaral; Vocara; *Canad.*: Angeel†; Calendula +; Calnor†; Echinacea Compositum; Echinacea L40†; Homeoplasmine; Hylands Sore Throat; Larydol†; Roxalia; Sore Throat; *Chile*: Fucus Especial; Lessfat; *Cz.*: Angin-Heel S; Homeogene 9; *Fr.*: Angipax; Boripharm No 10†; Camilia; Echinacea Complexe No 40; Homeogene 9; Phytogargarisme†; Pulviplasmine†; Scrofularia Compose; Thuya Complexe No 37; *Ger.*: Adenolin-Entoxin NN; Angina-Gastreu S R1; Bryorheum N; Entzundungstropfen; Febro-cyl L Ho-Len-Complex; G1-Injektopas; Homvioartrin; Lymphaden Complex; Lymphaden; Lymphdiaral; Lymphdiaral; Lymphozil H; Otofren; Rheuma-Pasc; Tonsipret; *Hung.*: Angin-Heel; Homeogene 9; *Neth.*: Belachin-Gastreu R1; Echinacea comp; Homeocare keelspray; Homeocare Revito; Homeocare Uro; Homeogene 9†; Lymfelite; Lymphdiaral; Mercurius-Heel; Spiroflor; Vinceel H; *Port.*: Homeogene 9; Homeoplasmine†; *Rus.*: Pharyngomed (Фарингомед); Phytolacca-Plus (Фитолакка-Плюс); Tonsipret (Тонзипрет); Vocara (Вокара); *Switz.*: Camilia; Homeogene 9; Homeoplasmine; Regenaplex Nr 28b; *Ukr.*: Tonsipret (Тонзипрет); Vocara (Вокара).

Poliglusam *(USAN, rINN)*

Chitosan; Poliglusamum; Полиглузам.

Poly-β-(1,4)-2-amino-2-deoxy-D-glucose.

CAS — 9012-76-4.

Pharmacopoeias. In *USNF.*

USNF 31: (Chitosan). An unbranched binary polysaccharide consisting of *N*-acetyl-D-glucosamine and D-glucosamine units linked in a (1→4) manner. It is obtained by partial deacetylation of chitin, which is extracted from the shells of edible shrimps and crabs suitable for human use. Its degree of deacetylation is 70.0 to 95.0%. A white or almost white powder or granules. Practically insoluble in water and in organic solvents; soluble in aqueous solutions of glycolic acid, of formic acid, of acetic acid, of hydrochloric acid, and of lactic acid. Store at a temperature below 30 degrees. Protect from light and moisture.

Poliglusam Hydrochloride *(rINNM)*

Chitosan Hydrochloride; Chitosane, chlorhydrate de; Chitosan-hydrochlorid; Chitosanhydrochlorid; Chitosani Hydrochloridum; Chitozano hidrochloridas; Hidrocloruro de poliglusam; Kitosaanihydrokloridi; Kitosanhydroklorid; Kitozán-hidroklorid; Poliglusam, Chlorhydrate de; Poliglusami Hydrochloridum; Полиглузама Гидрохлорид.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Chitosan Hydrochloride). The chloride salt of an unbranched binary heteropolysaccharide consisting of the two units *N*-acetyl-D-glucosamine and D-glucosamine, obtained by partial deacetylation of chitin, normally leading to a degree of deacetylation of 70.0 to 95.0%. Chitin is extracted from the shells of shrimp and crab. A white or almost white fine powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Poliglusam is a polysaccharide composed of polymers of glucosamine and *N*-acetylglucosamine produced by partial deacetylation of chitin. It is manufactured commercially by chemical treatment of crustacean shells. Poliglusam is under investigation as a pharmaceutical excipient for formulations including oral dosage forms and gene carrier systems. It has been used as a dietary supplement in preparations for obesity and hypercholesterolaemia.

References.

1. Ylitalo R, *et al.* Cholesterol-lowering properties and safety of chitosan. *Arzneimittelforschung* 2002; **52:** 1–7.
2. Jull AB, *et al.* Chitosan for overweight or obesity. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 16/09/09).

Interactions. For reference to the effect of poliglusam on warfarin, see Dietary Supplements under Interactions of Warfarin, p. 1533.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Chito-Lafarmen; *Braz.*: Magrix; *Ital.*: Chitoderm; Formoline L112; *Switz.*: Formoline L112; *UK*: Bio Slim Silueta; Formoline L112.

Multi-ingredient Preparations. *Arg.*: Redualgas; XLS; *Braz.*: Control†; *Chile*: Biopiel; *India*: Chitosyl; *Indon.*: Betaslim; Combes†; Kitoles†; Naturlesterol; Vitaslim; *Singapore*: Chitosano; *Ukr.*: Bodimarin (Бодимарин); Liponorm (Липонорм).

Pollen and Pollen Extracts

Profile

Preparations containing pollen and pollen extracts from various plant sources have been used as nutritional supplements and in preparations for urological disorders. They are also used for allergen immunotherapy (p. 2435.1).

Bee pollen, which is flower pollen mixed with secretions from the honey bee, *Apis mellifera* (p. 2445.2), has also been used.

Adverse effects. In common with other products derived from bees, products containing bee pollen may cause serious adverse reactions. Many plant pollens may contribute to bee pollen, including common allergens such as ragweed pollen. For reference to hypersensitivity reactions with bee products, including bee pollen, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cernilton; Polenat; *Austria*: Grazax; Oralair; Prostaflor; *Belg.*: Oralair; *Canad.*: Oralair; Pollinex-R; *Cz.*: Grazax; Oralair; Pollinex; *Denm.*: Grazax; *Fin.*: Grazax; *Fr.*: Grazax; Prostal; Sodilen; *Ger.*: Cernilton†; Clustoid; Depiquick; Depot-Hal; Grazax; Pollinex Quattro; Purethal; Roxoid; TA Baume; TA Graser; TA Krauter top; TA MIX†; *Gr.*: Grazax; *Irl.*: Grazax; *Ital.*: Grazax; *Jpn*: Cernilton; *Malaysia*: Femal; Sanaxeen; *Neth.*: Allergopharma; Allergovit; Grazax; Oralair; Pollinex; Purethal; *Norw.*: Alutard; Grazax; *Pol.*: Allergovit; Catalet; Grazax; Perosall; Pollinex; *Port.*: Grazax; *Rus.*: Cernilton (Цернилтон); Fostal (Фосталь); *S.Afr.*: Allpyral Special Grass†; *Spain*: Grazax; Oralair; *Swed.*: Cernitol; Femal Balans; Grazax; *Switz.*: ALK; Grazax; Oralair; Polvac; Prostaflor†; Staloral; *Turk.*: Allergovit; *UK*: Grazax; Pollinex; Soluprick SQ.

Multi-ingredient Preparations. *Arg.*: Novo Prostasan; Optimina Fem; Optimina Plus; PR21; Prostafit; *China*: Prostat (舍尼通); *Fr.*: Propargile; Prostabiol; *Ger.*: Pollstimol; Sublivac; Sulgen;

Hung.: Pollstimol; ***Ital.***: Api Baby; Apistress; Bio-200; Biotrefon Plus; Longevital; Neoplus; Ottovis; Pollingel Ginseng; Pollingel; Ristabil; Taingel; ***Mon.***: Serelys; ***Philipp.***: Jamieson Total Energy; Korgivit-E†; ***Rus.***: Prostopine (Простопин); ***Singapore***: Femal; Vitaton; ***UK***: Regina Royal Five; ***Ukr.***: Apiprost (Апипрост); Energin (Энергин); Rotavit Royal (Ротавит Ройял); ***USA***: PowerVites.

Homoeopathic Preparations. ***Canad.***: Pollen Plus.

Poly A.poly U

Poli (A). poli (U); Polyadenylic-polyuridylic Acid; Поли(А).поли(У).

$(C_{10}H_{14}N_5O_7P)x.(C_9H_{13}N_2O_8P)x$

CAS — 24936-38-7.

Profile

Poly A.poly U is a double-stranded polyribonucleotide comprising polyadenylic and polyuridylic acids, and is believed to be an immunostimulant. It has been studied as an adjuvant in the management of operable solid tumours and in the management of hepatitis B. A complex of potassium polyriboadenylate-potassium polyribouridylate is used in the treatment of viral eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Poludan (Полудан).

Poly I.poly C

Poli (I). poli (C); Polyinosinic-polycytidylic Acid; Поли(И).поли(Ц).

$(C_{10}H_{13}N_4O_8P)x.(C_9H_{14}N_3O_8P)x$

CAS — 24939-03-5.

ATC — L03AX07.

ATC Vet — QL03AX07.

Profile

Poly I.poly C is a synthetic double-stranded polyribonucleotide complex of equimolar concentrations of polyinosinic and polycytidylic acids, described as a mismatched double-strand RNA.

Poly I.poly C and the complex of poly I.poly C stabilised with poly-L-lysine in carmellose [poly(ICLC)] have been found to induce the production of interferon and have been investigated in the treatment of malignant neoplasms and viral infections. In the form of poly I.poly C12U (p. 1009.2) it has been investigated for the treatment of AIDS, SARS, avian influenza, chronic fatigue syndrome, renal cell carcinoma, and invasive metastatic melanoma; poly(ICLC) has been investigated for the treatment of primary brain tumours.

Polyacrylamide

Acrylamide Polymer; Poliacrilamida; Poliakrylamid; Polyacrylamid; Polyakrylamid; 2-Propenamide Homopolymer; Полиакриламид.

Poly(2-propenamide).

CAS — 9003-05-8.

Profile

Polyacrylamides are polymers of acrylamide (p. 2429.2) and are available in different molecular weights and with different degrees of cross-linking. They form soft gels when hydrated and also have thickening, suspending, and flocculating properties. They are used in cosmetics, soft contact lenses, and electrophoretic gels, and also have many industrial uses. Polyacrylamide copolymers are also used.

Polyacrylamides may contain free acrylamide, a known toxin, and this has led to concerns about their safety.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***NZ***: Aquamid.

Multi-ingredient Preparations. ***Singapore***: Bio-Taches Masque†; Bio-Taches†.

Polysaccharide-K

Polisacárido-K; PS-K; PSK; Полисахарид-К.

Profile

Polysaccharide-K is a beta-glucan protein complex isolated from a fungus, *Trametes versicolor* (*Coriolus versicolor*). It is claimed to have immunostimulant and antineoplastic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Krestin; ***Philipp.***: Kayken; ***Singapore***: Stimmune.

Polytef *(USAN)*

Politef (piNN); Politefo; Politefum; PTFE; Политеф.

Poly(tetrafluoroethylene).

$(C_2F_4)_n$

CAS — 9002-84-0.

Profile

Polytef has many industrial applications. As 'Teflon' it is used on 'non-stick' cooking utensils.

A paste of polytef has been used for a variety of purposes including the treatment of aphonia, for replacement grafts in vascular surgery, and in the correction of some forms of urinary incontinence (p. 2349.2). The main concern with these procedures is migration of polytef particles. It has also been applied to the skin as a barrier paste with perfluoroalkylpolyether to reduce exposure to chemical warfare agents.

Adverse effects. Brain injury in a child was possibly associated with migration of polytef particles from a periureteral injection performed 1 year earlier.[1] Three cases of polytef adenopathy and one case of giant granuloma have been reported[2] in children who had previously undergone subureteral polytef injection for the treatment of vesicoureteral reflux. Teflon-associated granulomas (teflonomas) may produce false-positive diagnoses of malignancy during PET scans.[3,4]

1. Borgatti R, *et al*. Brain injury in a healthy child one year after periureteral injection of Teflon. *Pediatrics* 1996; **98:** 290–1.
2. Aragona F, *et al*. Polytetrafluoroethylene giant granuloma and adenopathy: long-term complications following subureteral polytetrafluoroethylene injection for the treatment of vesicoureteral reflux in children. *J Urol (Baltimore)* 1997; **158:** 1539–42.
3. Chadwick JL, *et al*. Teflon granuloma results in a false-positive "second primary" on 18F-2-deoxyglucose positron emission tomography in a patient with a history of nasopharyngeal cancer. *Am J Otolaryngol* 2007; **28:** 251–3.
4. Ondik MP, *et al*. Teflon laryngeal granuloma presenting as laryngeal cancer on combined positron emission tomography and computed tomography scanning. *J Laryngol Otol* 2009; **123:** 575–8.

Uses. References.

1. Polley JW, *et al*. The use of Teflon in orbital floor reconstruction following blunt facial trauma: a 20-year experience. *Plast Reconstr Surg* 1987; **79:** 39–43.
2. Puri P. Endoscopic correction of primary vesicoureteric reflux by subureteric injection of polytetrafluoroethylene. *Lancet* 1990; **335:** 1320–2.
3. Maskell R, *et al*. Correction of vesicoureteric reflux by endoscopic injection. *Lancet* 1991; **338:** 1460–1.
4. Anonymous. Use of Teflon preparations for urinary incontinence and vesicoureteral reflux. *JAMA* 1993; **269:** 2975–80.
5. Duckett JRA. The use of periurethral injectables in the treatment of genuine stress incontinence. *Br J Obstet Gynaecol* 1998; **105:** 390–6.
6. Su TH, *et al*. Injection therapy for stress incontinence in women. *Int Urogynecol J* 1999; **10:** 200–6.
7. Chaffange P, *et al*. Traitement endoscopique du reflux vésico-rénal chez l'enfant: résultats à court et à long terme des injections de polytétrafluoroéthylene (Téflon). *Prog Urol* 2001; **11:** 546–51.
8. Meschia M, *et al*. Injection therapy for the treatment of stress urinary incontinence in women. *Gynecol Obstet Invest* 2002; **54:** 67–72.
9. Huber TS, *et al*. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. *J Vasc Surg* 2003; **38:** 1005–11.
10. Klinkert P, *et al*. Saphenous vein versus PTFE for above-knee femoropopliteal bypass: a review of the literature. *Eur J Vasc Endovasc Surg* 2004; **27:** 357–62.

Poplar Buds

Álamo, brotes de; Balm of Gilead; Balm of Gilead Buds; Brotes de chopo; Тополь (*Populus*).

NOTE. The name Balm of Gilead has also been applied to *Commiphora gileadensis*.

Pharmacopoeias. *Pol.* includes the leaves from *Populus nigra*.

Profile

The buds of various species of *Populus*, including *P. nigra*, *P. gileadensis*, and *P. tacamahacca* (*P. balsamifera*; *P. candicans*), have been used as an ingredient of herbal preparations for cough and topically for a variety of skin conditions and rheumatic disorders. Poplar buds contain salicin, volatile oil, resin, and other substances. The resin from poplar buds is one of the major sources of propolis (p. 2597.3). For the uses of the leaf and bark of other species of *Populus*, see Aspens, p. 2450.3.

Homoeopathy

Populus candicans has been used in homoeopathic medicines under the following names: Populus can.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Bronchial Cough; Mielocol†; ***UK***: Balm of Gilead†.

Homoeopathic Preparations. ***Hung.***: Gentos.

Poppy-seed Oil

Adormidera, aceite de semilla de; Amapola, aceite de semilla de; Huile d'Oeillette; Maw Oil; Oleum Papaveris; Oleum Papaveris Seminis; Маковое Масло.

UNII — 9G3Z76ES9J.

Profile

Poppy-seed oil is the fixed oil expressed from the ripe seeds of the opium poppy, *Papaver somniferum* (Papaveraceae). It is used as a substitute for olive oil for culinary and pharmaceutical purposes. It is also used in the preparation of Iodised Oil Fluid Injection (BP 2014). Commercial grades are used in making soaps, paints, and varnishes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Switz.***: Olbas.

Potassium Aminobenzoate

Aminobenzoate Potassium; Aminobenzoato potásico; Potassium Para-aminobenzoate; Аминобензоат Калия.

Potassium 4-aminobenzoate.

$C_7H_6KNO_2$=175.2

CAS — 138-84-1.

UNII — 41KZS5432U.

Pharmacopoeias. In *US*.

USP 36: (Aminobenzoate Potassium). A white crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 7, while a 5% solution has a pH of 8.0 to 9.0.

Uses and Administration

Potassium aminobenzoate has been used in the treatment of various disorders associated with excessive fibrosis, such as scleroderma (p. 1938.3) and Peyronie's disease, in usual oral doses of 12 g daily in 4 to 6 divided doses.

Peyronie's disease. Variable results have been reported with potassium aminobenzoate in the treatment of Peyronie's disease,[1-3] but evidence from well controlled studies is lacking. It has been suggested that a successful response is more likely if treatment is started in the acute stage.[2]

1. Gingell JC, Desai KM. Peyronie's disease. *BMJ* 1988; **298:** 1489–90.
2. Mohanty KC, Strachan RG. Peyronie's disease. *BMJ* 1989; **298:** 254.
3. Carson CC. Potassium para-aminobenzoate for the treatment of Peyronie's disease: is it effective? *Tech Urol* 1997; **3:** 135–9.

Adverse Effects and Precautions

Anorexia, nausea, fever, and rashes have been reported.

Potassium aminobenzoate should be given with caution to patients with renal impairment. Licensed product information recommends that treatment should be interrupted during periods of fasting, anorexia, or low food intake, to avoid the possible development of hypoglycaemia.

Effects on the liver. References.

1. Roy J, Carrier S. Acute hepatitis associated with treatment of Peyronie's disease with potassium para-aminobenzoate (Potaba). *J Sex Med* 2008; **5:** 2967–9.

Interactions

Potassium aminobenzoate can inactivate sulfonamides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Potaba; ***Canad.***: Potaba; ***Ger.***: Potaba; ***Gr.***: Potaba; ***UK***: Potaba; ***USA***: Potaba.

Pharmacopoeial Preparations

USP 36: Aminobenzoate Potassium Capsules; Aminobenzoate Potassium for Oral Solution; Aminobenzoate Potassium Tablets.

Potassium Arsenite

Arsenious Acid, Potassium Salt; Potassium Arsonate; Potassium Metaarsenite.

$KAsO_2.HAsO_2$ (approximate)=253.9
CAS — 10124-50-2; 13464-35-2; 1332-10-1 (potassium arsenite solution).
UNII — HQE48MPP30.

Profile

Potassium arsenite is a trivalent arsenic compound (see Arsenic Trioxide, p. 2448.1). It has been used as a pesticide, although such use is banned in the UK.

Homoeopathy

Potassium arsenite and potassium arsenite solution have been used in homoeopathic medicines under the following names: Arsénite de potassium; Kali arsenicosum; Kalium arsen; Kalium arsenicosum; Kaliumarsenit; Potassium arsenite.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Berberis Cosmoplex†; ***Canad.***: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Eczema; ***Ger.***: Drufusan N†.

Potassium Borotartrate

Borotartrato potásico; Borotartrato sódico y potásico; Potassium Sodium Borotartrate; Soluble Cream of Tartar; Tartraborato potásico; Калия Боротартрат.
CAS — 12001-68-2.

Profile

Potassium borotartrate is reported to have similar properties to those of bromides (p. 2460.3). It has been used in nervous disorders and has been used in photography as a retarder for alkaline developers. Chronic boron poisoning (see under Boric Acid, p. 2460.1) has been reported after the use of potassium borotartrate internally.

Potassium Bromate

924; Bromato potásico; Potasu bromian.
$KBrO_3$=167.0
CAS — 7758-01-2.
UNII — 04MB35W6ZA.

Uses

Potassium bromate is an oxidising agent. It has no therapeutic uses but it has been widely used as the 'neutraliser' of thioglycollate hair-waving lotions. It has been used in the preparation of barley malt for beer. It has also been used as a flour-maturing agent but such use is no longer considered appropriate and is prohibited in some countries.

Food additive. Potassium bromate is a genotoxic carcinogen and should not be present in foods when consumed. Its use for the treatment of flour for bread-making is not appropriate.[1]

1. FAO/WHO. Evaluation of certain food additives and contaminants: forty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 859* 1995. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_859.pdf (accessed 18/07/08)

Adverse Effects

Nausea, vomiting, severe abdominal pain, diarrhoea, and lethargy are common after ingestion of potassium bromate. Acute renal failure arising from tubular necrosis usually presents with oliguria or anuria within 1 to 3 days of significant ingestion, and is the most frequent cause of death. Ototoxicity may present as tinnitus or hearing loss within hours of ingestion, and can progress to sensorineural deafness in some patients. Ototoxicity and nephrotoxicity may be irreversible.

Potassium bromate poisoning can also produce hypotension, myocarditis, hepatitis, and encephalopathy characterised by agitation, delirium, convulsions, and coma. Microangiopathic anaemia has also been reported.

Potassium bromate is carcinogenic in *animals*.

Acute toxicity. Reports of bromate poisoning.

1. Lue JN, *et al*. Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; **7:** 66–70.
2. Lichtenberg R, *et al*. Bromate poisoning. *J Pediatr* 1989; **114:** 891–4.
3. De Vriese A, *et al*. Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.

Treatment of Adverse Effects

Gastric lavage should be considered if the patient presents within 1 hour of acute ingestion of potassium bromate; use of a 2 to 5% solution of sodium bicarbonate has been suggested to reduce bromate absorption and prevent hydrobromic acid production. Activated charcoal has also been recommended as an adsorbent. Attention to the patient's fluid, acid–base, and electrolyte status is important, particularly in the presence of acute renal failure. An intravenous infusion of 100 to 500 mL of a 1% sodium thiosulfate solution has sometimes been given. Oxygen may be indicated. The prompt use of haemodialysis or peritoneal dialysis has been suggested.

Thiosulfate. Although the use of intravenous sodium thiosulfate is an accepted practice in the treatment of bromate poisoning, convincing evidence that it reduces bromate to bromide is lacking.[1,2] Oral sodium thiosulfate solutions have also been used but are no longer recommended because hydrogen sulfide, itself a powerful irritant and toxic agent, may be evolved in the presence of hydrochloric acid.[2]

1. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 570–2.
2. De Vriese A, *et al*. Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.

Potassium Carbonate

Carbonat de potassi; Carbonate of Potash; Carbonato di potassio; E501 (potassium carbonates); Kalii Carbonas; Kālija karbonāts; Kalio karbonatas; Kalium Carbonicum; Kaliumcarbonaat; Kaliumcarbonat; Kaliumkarbonaatti; Kaliumkarbonat; Kálium-karbonát; Pearl Ash; Potassium, carbonate de; Potasu węglan; Salt of Tartar; Uhličitan draselný; Калиев карбонат.
K_2CO_3=138.2
CAS — 584-08-7 (anhydrous potassium carbonate); 6381-79-9 (potassium carbonate sesquihydrate).
UNII — BQN1B9B9HA.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Potassium Carbonate). A white or almost white, hygroscopic granular powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Potassium Carbonate).

Profile

Potassium carbonate is an inorganic alkali. It has similar properties to potassium bicarbonate (p. 1780.3) but tends to be more caustic and irritating. It is used as an alkalinising agent and potassium source in pharmaceuticals and the food industry; it also has many industrial uses.

Homoeopathy

Potassium carbonate has been used in homoeopathic medicines under the following names: Kali Carbonicum Kaliumcarbonat Kalium Carbonicum Kali-c Kali. Carb.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Chlorvescent; ***Spain***: Taponoto.

Multi-ingredient Preparations. ***S.Afr.***: Helmontskruie†; Wonderkroonessens; ***Switz.***: Silence†.

Homoeopathic Preparations. ***Austria***: Cactus compositum; Cralonin; Globuli gegen Kopfschmerzen; Pumpan; ***Canad.***: Ind Complex†; Lympatox; Menopause L122; ***Fr.***: Abbe Chaupitre no 90†; Dolisedal†; Gentiana Complexe No 33†; Hepatocynesine†; Lachesis Complexe No 122; Sepia Complexe No 20; Soludor; Staphysagria Complexe No 92†; Vespa Complexe No 46†; ***Ger.***: Aktivon; Conva-cyl Ho-Len-Complex; Cralonin; Hevert-Activon Kreislauftropen†; Infifer N; Pascodem; Strophanthus comp; ***Neth.***: Cralonin H; Cralonin; Gynaelite; Homeocare Cyclo; Lymphomyosot; ***Rus.***: Pumpan (Пумпан); ***Switz.***: Cralonin; ***Ukr.***: Pumpan (Пумпан).

Potassium Chlorate

Clorato potásico; Kalium Chloricum; Potassii Chloras; Potasu chloran.
$KClO_3$=122.5
CAS — 3811-04-9.
UNII — H35K568EE7.

Handling and storage. Potassium chlorate is unstable and, in contact with organic or readily oxidisable substances such as charcoal, phosphorus, or sulfur it is liable to explode especially if heated or subjected to friction or percussion. It should not be allowed to come into contact with matches or surfaces containing phosphorus compounds. Reasonable steps should be taken before supplying potassium chlorate to ensure that it will not be used for the illicit preparation of explosives or fireworks.

Profile

Potassium chlorate has been used as an astringent, usually as a mouthwash or gargle. Concentrated solutions are irritant.

Acute poisoning from ingestion requires prompt symptomatic treatment. Symptoms include nausea, vomiting, diarrhoea, abdominal pain, haemolytic anaemia, haemorrhage, methaemoglobinaemia, hyperkalaemia, and renal failure. There may be liver damage and central effects with convulsions and coma.

Gastric lavage should be considered within 1 hour of ingestion of potassium chlorate; activated charcoal is also recommended by some. If methaemoglobinaemia is severe, patients may require exchange transfusion with whole blood. Several authorities consider that methylthioninium chloride should be given intravenously if methaemoglobinaemia is greater than 30%, although some have advised against such use for fear of converting chlorate to the more toxic hypochlorite.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Fletchers Sore Mouth Medicine; ***Spain***: Edifaringen†; Faringenilo; Solurrinol.

Potassium Hydroxide

Ätzkali; Caustic Potash; E525; Hidróxido potásico; Hydroxid draselný; Kalii Hydroxidum; Kalii Hydroxydum; Kalio hidroksidas; Kalium Hydroxydatum; Kálium-hidroxid; Kalium-hydroksidi; Kaliumhydroxid; Potash Lye; Potassium Hydrate; Potassium, hydroxyde de; Potasu wodorotlenek.
KOH=56.11
CAS — 1310-58-3.
UNII — WZH3C48M4T.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. Also in *USNF*.

Ph. Eur. 8 (Potassium Hydroxide). White or almost white, crystalline, hard masses, supplied as sticks, pellets, or irregularly shaped pieces; it is deliquescent in air, hygroscopic, and absorbs carbon dioxide. Very soluble in water; freely soluble in alcohol. Store in airtight, nonmetallic containers.

USNF 31: (Potassium Hydroxide). It contains not less than 85% of total alkali, calculated as KOH, including not more than 3.5% of K_2CO_3. White or practically white, fused masses, or small pellets, or flakes, or sticks, or other forms. It is hard and brittle and shows a crystalline fracture. Exposed to air, it rapidly absorbs carbon dioxide and moisture, and deliquesces. Soluble 1 in 1 of water, 1 in 3 of alcohol, and 1 in 2.5 of glycerol; very soluble in boiling alcohol. Store in airtight containers.

Uses and Administration

Potassium hydroxide is a powerful caustic that has been used to remove warts. A 2.5% solution in glycerol has been used as a cuticle solvent. An escharotic preparation of potassium hydroxide and calcium hydroxide was known as Vienna paste. Potassium hydroxide is used to adjust the pH of solutions in pharmaceutical formulations.

Homoeopathy

Preparations of potassium hydroxide have been used in homoeopathy under the following names: Aetzstoff; Caustic Potash; Caust; Causticum; Causticum d'Hahnemann; Causticum, Hahnemann's; Causticum Hahnemanni; Kali Causticum; Kalium Causticum; Kalium Hydroxydatum; Kalium Hydroxidum; Hahnemann's Causticum; Potassic Hydrate; Tinctura Acris sine Kali

Adverse Effects and Treatment

As for Sodium Hydroxide, p. 2619.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Molutrex; Poxkare; ***Ger.***: InfectoDell; ***Spain***: Cerumenol.

Multi-ingredient Preparations. ***Austria***: Leberinfusion; ***China***: Piaojiamei (朴佳美); ***Ital.***: Sekudrill†.

Homoeopathic Preparations. ***Austral.***: Joint & Muscle Oral Spray†; ***Austria***: Proagil; Rheuma; ***Canad.***: Arthritic Pain; Artis-Heel†; Barijodeel†; Cou Complex†; Fibromyalgie; Homeo-Form AR†; Husteel†; Hylands Cough; Reneel†; War Complex†; ***Chile***: Arnica Compuesta; ***Cz.***: Husteel; ***Fr.***: Abbe Chaupitre no 48†; Abbe Chaupitre no 79†; Dermo-Drainol†; Millefolium Complexe No 7†; Rhus Toxicodendron Complexe No 80; ***Ger.***: Curare comp; Cysto-cyl L Ho-Len-Complex; Genu-cyl L Ho-Len-Complex; Grippe-Gastreu S R6; Hewecyst Blasen-Nieren†; Lumbago-Gastreu S R11; Rheuma-Pasc; Roth's RKT Tropfen; ***Hung.***: Husteel; ***Neth.***: Acidolite; Actelite; Chavita 2; Dulcar-

hus-Gastreu R11; Enulite; Grippe-Gastreu R6; Homeocare Allerlo; Husteel; Rhumeel; ***Switz.***: Regenaplex Nr. 25c; Rheuma-Heel.

Pharmacopoeial Preparations
BP 2014: Chloroxylenol Solution; Potassium Hydroxide Solution.

Pramiverine Hydrochloride *(BANM, rINNM)*

EMD-9806 (pramiverine); Hidrocloruro de pramiverina; HSP-2986 (pramiverine); Pramiverina, hidrocloruro de; Pramivérine, Chlorhydrate de; Pramiverini Hydrochloridum; Прамиверина Гидрохлорид.

N-Isopropyl-4,4-diphenylcyclohexylamine hydrochloride.

$C_{21}H_{27}N,HCl=329.9$

CAS — 14334-40-8 (pramiverine); 14334-41-9 (pramiverine hydrochloride).

Profile

Pramiverine hydrochloride has been used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: Systabon; ***Venez.***: Sistalcin.

Multi-ingredient Preparations. ***Venez.***: Sistalcin Compositum.

Pregnancy and Fertility Tests

Pruebas de embarazo y de fertilidad.

Profile

There are several types of kits available for simple pregnancy and fertility testing. A common method of detecting pregnancy is to use specific antibodies to measure the increase in chorionic gonadotrophin in the urine. The period of ovulation can be detected by measuring luteinising hormone excretion in similar ways.

These tests can give false results. Those carrying out the tests should be aware of this and of problems such as contaminated specimens, drug therapy, or other factors that could affect the result.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: After 10; Ahora Test; B-Quick; Biofem Test; Define; Discretest; Evanol; Evaplan; Evatest; Mater Test; Nueve Lunas; PG/53; Simple HCG; Tea Test; ***Austral.***: Clearview HCG†; Discover Onestep Pregnancy Planning Kit; Discover Onestep; OvuPlan; Predictor; Pregnosis; ***Braz.***: Baby Sure; Clearblue Easy; Clearblue; Detect Baby; Fertility Day; Maxtest; Predictor†; Unitest; ***Canad.***: Clearblue†; Confirm†; Fact Plus†; First Response†; ***Chile***: Clear Blue; ***Fr.***: Babycheck-Plus†; BB Test; Clearblue test d'ovulation; Clearblue test de grossesse; Predictor†; Primastick†; Revelatest†; ***Irl.***: Omega 1-step†; Testpack hCG-Urine†; Today Ovulation Test†; Uni-Gold hCG†; ***Israel***: Clearblue; Predictor; Pregnosticon; ***Ital.***: Clearblue; Clearplan†; Conferma 3 Plus; Confidelle Progress; Diagnosis; Gravitest; Illa; Predictor; ***Jpn***: Gonavislide†; ***Mex.***: Fertility Day; Inditest†; Pre-Baby; Quik-Check†; ***NZ***: Clearblue; Clearplan†; Crystal Clear; Discover One Step; MDS Quick†; ***Turk.***: Predictor; ***UK***: Calista; Check-Mate; Clearblue; Clearview HCG; Concept; Discover; Early Bird; Fertell; First Response; Maybe Baby; Ovuquick; Predictor; Quick N Easy; Reveal; Test Pack Plus; ***USA***: Advance; Answer; Clearblue Easy Ovulation; Clearblue Easy; Clearview HCG; Conceive Pregnancy; ept Stick Test; Fact Plus; First Response; Fortel; Nimbus; Pregnosis; QTest; QuickVue; RapidVue; TestPack Plus hCG-Urine; UCG-Slide; Unistep hCG.

Prenylamine *(BAN, USAN, rINN)* ⊗

B-436; Hoechst-12512; Prenilamina; Prenylamin; Prénylamine; Prenylaminum; Prenyyliamiini; Пренилами́н.

2-Benzhydrylethyl(α-methylphenethyl)amine.

$C_{24}H_{27}N=329.5$

CAS — 390-64-7.

ATC — C01DX02.

ATC Vet — QC01DX02.

UNII — K2OH82Z000.

Prenylamine Lactate *(BANM, rINNM)* ⊗

Lactato de prenilamina; Prenilamina, lactato de; Prénylamine, Lactate de; Prenylamini Lactas; Prenylaminii Lactas; Пренилами́на Лактат.

$C_{24}H_{27}N,C_3H_6O_3=419.6$

CAS — 69-43-2.

ATC — C01DX02.

ATC Vet — QC01DX02.

UNII — 6J3J6SX17V.

Profile

Prenylamine depletes myocardial catecholamine stores and has some calcium-channel blocking activity. It was formerly used in the treatment of angina pectoris but has been superseded by less toxic drugs. Use of prenylamine has been associated with the development of ventricular arrhythmias and ECG abnormalities. Tremor and extrapyramidal symptoms have also occurred.

Primula Root

Gullviverot; Kankalingyökér; Kevätesikonjuuri; Primavera; Primavera de jardines; Primelwurzel; Primevère, racine de; Prímula; Primulae radix; Prvosenkový kořen; Racine de Primevère; Raktažolių šaknys; Schlüsselblumenwurzel; Примула (*Primula*); Первоцвет (*Primula*).

ATC Herb — HR05WA5047 (Primula veris*: rhizome); HR05WA5046* (Primula veris*: flower).*

UNII — W6LFQ57E4M (Primula veris*); TA94NTR55X* (Primula veris *root).*

Pharmacopoeias. *Eur.* (see p. vii) includes Primula root.

Ph. Eur. 8: (Primula Root; Primulae Radix). Consists of the whole or cut, dried rhizome and root of *Primula veris* [cowslip] or *P. elatior*[oxlip].

Profile

Primula root has expectorant properties and is used for cough and other respiratory-tract disorders.

Cowslip, the flowers, leaves, and roots of *Primula veris* (*P. officinalis*) (Primulaceae), is widely used in herbal medicine. The flowers have sedative properties and are used for insomnia, hyperactivity, and anxiety disorders. The flowers and leaves have also been used similarly to primula root.

Oxlip flowers and root (*P. elatior*) and primrose root (*P. vulgaris*) have also been used.

Homoeopathy

Cowslip has been used in homoeopathic medicines under the following names: Primula veris; Primula ver.

Primula vulgaris has been used in homoeopathic medicines under the following names: Primula vulg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Keptan.

Multi-ingredient Preparations. ***Arg.***: Expectosan Hierbas y Miel; ***Austral.***: Sinupret; Throat-Clear; ***Austria***: Bronchithym†; Cardiodoron; Heumann's Bronchialtee; Sinupret; Solvopret†; ***Canad.***: Honey Herb Cough Drops†; Original Herb Cough Drops†; ***Cz.***: Biotussil; Bronchipret Tymian a Prvosenka; Sinupret; ***Ger.***: Bronchicum Elixir; Bronchicum; Bronchipret; Brust-und Hustentee†; Cardiodoron; Cimicifuga comp; Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee; Drosithym-N†; Equisil N†; Expectysat N; Heumann Bronchialtee Solubifix T; Kneipp Husten- und Bronchial-Tee†; Phytobronchin; Sinuforton†; Sinupret; ***Hong Kong***: Sinupret; ***Hung.***: Bronchicum; Bronchicum; Bronchipret; Sinupret; ***Indon.***: Bronchipret†; Silex; Sinupret†; ***Malaysia***: Sinupret; ***Mex.***: Bisolsinus; ***Neth.***: Bronchicum; ***Philipp.***: Bronchipret†; Sinupret; ***Pol.***: Bronchicum Eliksir†; Bronchosol; Herbapect; Sinupret; ***Rus.***: Bronchicum (Бронхикум)†; Bronchicum Husten (Бронхикум Сироп от Кашля)†; Bronchicum TP (Бронхикум ТП); Bronchipret TP (Бронхипрет ТП); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Sinupret (Синупрет); ***S.Afr.***: Cardiodoron†; ***Singapore***: Sinupret; ***Swed.***: Sinova; ***Switz.***: Bronchipret TP; Cardiodoron; DemoPectol; Kernosan Elixir; Pectoral N; Sinupret; Sirop pectoral contre la toux S; Sirop pectoral; Siropectan; Strath Gouttes contre la toux; Tisane pectorale pour les enfants; ***Thai.***: Sinupret†; Solvopret TP†; ***UK***: Bio-Strath Willow Formula; Onopordon Comp B; Sinueeze; Sinuherb; Spotner; ***Ukr.***: Bronchipret TP (Бронхипрет ТП); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Pectoral (Пекторал); Sinupret (Синупрет).

Homoeopathic Preparations. ***Canad.***: Formula C Doron†; Formula C Doroon†; ***Ger.***: Biodolor; Cordiodoron†; Crataegus comp; Pflugerplex Gelsemium; Roth's RKT Tropfen; Schwoneural N.

Proadifen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de proadifeno; NSC-39690; Proadifène, Chlorhydrate de; Proadifeni Hydrochloridum; Proadifeno, hidrocloruro de; Propyladiphenine Hydrochloride; RP-5171; SKF-525A; SKF-525-A; Проадифена Гидрохлорид.

2-Diethylaminoethyl 2,2-diphenylvalerate hydrochloride.

$C_{23}H_{31}NO_2,HCl=390.0$

CAS — 302-33-0 (proadifen); 62-68-0 (proadifen hydrochloride).

UNII — 30624AA6X2.

Profile

Proadifen is a cytochrome P450 inhibitor used in the study of drug metabolism.

Probiotics

Probiotics are defined as live micro-organisms used as dietary supplements to improve the health of the host when given in adequate amounts.

Composition and viability. Some preparations of probiotics have been found to contain smaller quantities or different species of organisms to those specified on the label.[1] An FAO/WHO working group[2] published some guidelines that should be followed in order to claim that a food has a probiotic effect. These include the genus, species, and strain of the organisms in the preparation to be stated on the product label using currently recognised systematic nomenclature, and a statement of the minimum number of viable organisms remaining at the end of the product shelf-life.

1. Hamilton-Miller JMT, *et al.* "Probiotic" remedies are not what they seem. *BMJ* 1996; **312:** 55–6.
2. FAO/WHO. *Guidelines for the evaluation of probiotics in food.* London Ontario, Canada: Food and Agriculture Organization of the United Nations, 2002. Also available at: http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (accessed 11/02/08)

Lactic-acid-producing Organisms

Láctico, organismos productores de ácido; МолочноКислые Бактерии.

ATC Vet — QA07FA01.

Uses and Administration

Lactic-acid-producing organisms were first introduced as potential therapeutic agents with the idea of acidifying the intestinal contents and thus preventing the growth of putrefactive organisms. *Lactobacillus bulgaricus* (*Lactobacillus delbrueckii* subsp. *bulgaricus*), which occurs in naturally soured milk, was the organism originally used but it can be difficult to obtain growth of this organism in the intestines. Natural yogurt (p. 2649.3) is a common source of lactic-acid-producing organisms.

It is now thought that the gastrointestinal tract may play a wider part in host defences and consequently there is increasing interest in the use of live non-pathogenic microbial cultures to optimise the enteric microbiota, including in neonates. These are referred to as probiotics and are generally commensal lactic-acid producing bacteria, although some yeasts are also used. Organisms currently being used in probiotic preparations include *Lactobacillus* spp. and *Bifidobacterium* spp. Other organisms that may be used are *Enterococcus* and *Streptococcus* spp., and the yeast *Saccharomyces boulardii*.

Probiotics are promoted to restore or maintain a healthy microbial flora, and are widely available as yogurts or other fermented milk products, as well as oral dosage forms such as tablets, capsules, and powders. They are being investigated in the management of several gastrointestinal disorders including diarrhoea and inflammatory bowel disorders. Probiotics are also being investigated in vaginal disorders and allergic disorders such as atopic eczema.

A vaccine produced from strains of lactobacillus found in women with trichomoniasis has been used in the prophylaxis of recurrent trichomoniasis (see p. 2422.2).

Allergic disorders. Oral ingestion of probiotic bacteria may play a role in the development of the adaptive immune system[1] and there has been some interest in their use in the management of allergic disorders such as atopic eczema.[2-5] Early reviews[6,7] of studies in allergic disorders concluded that although there appeared to be a reasonable theoretical basis for expecting benefit with probiotics, there were insufficient data to support their inclusion in routine treatment regimens for atopic eczema, perennial allergic rhinitis, or asthma. Subsequently a systematic review[8] has concluded that probiotics are not an effective treatment for eczema and carry a small risk of adverse events such as infections and bowel ischaemia.

1. Rinne M, *et al.* Effect of probiotics and breastfeeding on the *Bifidobacterium* and *Lactobacillus/Enterococcus* microbiota and humoral immune responses. *J Pediatr* 2005; **147:** 186–91.
2. Kalliomäki M, *et al.* Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003; **361:** 1869–71.
3. Rosenfeldt V, *et al.* Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; **145:** 612–16.
4. Weston S, *et al.* Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; **90:** 892–7.

5. Fölster-Holst R, *et al*. Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; **155:** 1256–61.
6. Anonymous. Probiotics for atopic diseases. *Drug Ther Bull* 2005; **43:** 6–8.
7. Prescott SL, Björkstén B. Probiotics for the prevention or treatment of allergic diseases. *J Allergy Clin Immunol* 2007; **120:** 255–62.
8. Boyle RJ, *et al*. Probiotics for treating eczema. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 10/08/10).

Gastrointestinal disorders. Oral probiotics are under investigation for several gastrointestinal disorders and although they appear to be of benefit in some conditions, further study is required to confirm these findings. It is probable that efficacy depends on the species and strain of the organism as well as on the condition being treated.[1,2]

Conclusions from a systematic review[3] suggest that probiotics might be a useful adjunct to oral rehydration therapy in the treatment of acute infectious *diarrhoea* in adults and children. A meta-analysis[4] of studies of *Lactobacillus* therapy in children reached a similar conclusion. However, it was not possible to draw up definitive treatment guidelines because of a lack of standardisation in probiotic regimens, patient groups, or definition of acute diarrhoea between the available studies.[3,4] Meta-analyses[5,6] and a systematic review[7] of studies investigating the use of probiotics in the prevention of antibiotic-associated diarrhoea in adults[5] and children[5-7] also suggest a beneficial effect, although again, further clinical confirmation is required before they can be routinely recommended.[5-7] A review[8] of studies that looked specifically at treatment or prevention of *Clostridium difficile*-associated diarrhoea with the probiotics *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* concluded that while these specific probiotics might be useful in patients at risk of recurrent *C. difficile* infection, the potential risks of bacteraemia or fungaemia in this particular patient group might outweigh any benefit.

Probiotics have been investigated to correct aberrant intestinal microflora associated with chronic *inflammatory bowel disease* and reviews of such studies suggest some benefit in the prevention and treatment of ulcerative colitis[9-11] and maintenance of remission in pouchitis,[10-12] although the data are not so clear for Crohn's disease.[10,13,14] Larger controlled clinical studies, again with standardised probiotic preparations and treatment regimens, are necessary to establish the place of probiotics in the management of inflammatory bowel disease.[9-13] A systematic review[15] concluded that although *Bifidobacterium infantis* appeared to be effective for the management of symptoms of *irritable bowel syndrome* there were inadequate data to comment on the efficacy of other probiotics. For reference to the use of probiotics in *pancreatitis*, see p. 2580.2.

Probiotics given to preterm neonates of very low birthweight reduced the incidence and severity of *necrotising enterocolitis* in 2 randomised controlled studies.[16,17] Systematic reviews[18,19] of these and other controlled studies reached the same conclusion, although the authors called for confirmation of these results by a larger study to strengthen the case for routine use of probiotics in preterm neonates. Similar results were obtained in a later multicentre prospective randomised controlled study[20] involving a total of 434 infants of gestational age less than 34 weeks and birth-weight less than 1500 g who were given probiotics enterally for 6 weeks, although it was difficult to interpret results for infants weighing less than 750 g due to an imbalance of infants in this lower weight range between the study and control groups.

Probiotics have also been tried in constipation[21] and infantile colic.[22]

1. Anonymous. Probiotics for gastrointestinal disorders. *Drug Ther Bull* 2004; **42:** 85–8.
2. Limdi JK, *et al*. Do probiotics have a therapeutic role in gastroenterology? *World J Gastroenterol* 2006; **12:** 5447–57.
3. Allen SJ, *et al*. Probiotics for treating infectious diarrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 11/02/08).
4. Van Niel CW, *et al*. *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; **109:** 678–84.
5. D'Souza AL, *et al*. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002; **324:** 1361–6.
6. Szajewska H, *et al*. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. *J Pediatr* 2006; **149:** 367–72.
7. Johnston BC, *et al*. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 11/02/08).
8. Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. *Ann Pharmacother* 2007; **41:** 1212–21.
9. Bai A-P, Ouyang Q. Probiotics and inflammatory bowel diseases. *Postgrad Med J* 2006; **82:** 376–82.
10. Ewaschuk JB, Dieleman LA. Probiotics and prebiotics in chronic inflammatory bowel diseases. *World J Gastroenterol* 2006; **12:** 5941–50.
11. Chapman TM, *et al*. VSL#3 probiotic mixture: a review of its use in chronic inflammatory bowel diseases. *Drugs* 2006; **66:** 1371–87.
12. Holubar SD, *et al*. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 16/08/10).
13. Rolfe VE, *et al*. Probiotics for maintenance of remission in Crohn's disease. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 11/02/08).
14. Butterworth AD, *et al*. Probiotics for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 19/03/10).
15. Brenner DM, *et al*. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol* 2009; **104:** 1033–49.
16. Bin-NunA, *et al*. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; **147:** 192–6.
17. Lin H-C, *et al*. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; **115:** 1–4.
18. Deshpande G, *et al*. Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. *Lancet* 2007; **369:** 1614–20.
19. Alfaleh KM, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/10).
20. Lin H-C, *et al*. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. *Pediatrics* 2008; **122:** 693–700.
21. Banaszkiewicz A, Szajewska H. Ineffectiveness of *Lactobacillus* GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr* 2005; **146:** 364–9.
22. Savino F, *et al*. *Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics* 2007; **119:** e124-e30. Available at: http://pediatrics.aappublications.org/cgi/reprint/119/1/e124.pdf (accessed 11/02/08)

Urogenital infections. Probiotic preparations given orally or intravaginally are under investigation for the prevention or treatment of vaginal infections. Reviews of studies in vulvovaginal candidiasis[1] and bacterial vaginosis[2] concluded that while there was some indication of benefit, larger controlled studies are required to confirm efficacy and the place of probiotics in therapy. Systematic reviews[3,4] have also found some evidence of benefit for the use of lactobacillus probiotics in the treatment of bacterial vaginosis, but did not find sufficient evidence that these probiotics were more effective than antibacterials or enhanced their efficacy.[4] Another systematic review[5] confirmed that probiotics may be of benefit in the prevention and treatment of bacterial vaginosis in pregnancy but due to insufficient data it was not possible to assess the effect that this might have in preventing preterm labour. A review[6] of studies investigating probiotics for the prevention of urinary-tract infections in women has suggested some benefit.

1. Falagas ME, *et al*. Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. *J Antimicrob Chemother* 2006; **58:** 266–72.
2. Falagas ME, *et al*. Probiotics for the treatment of women with bacterial vaginosis. *Clin Microbiol Infect* 2007; **13:** 657–64.
3. Oduyebo OO, *et al*. The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 24/02/10).
4. Senok AC, *et al*. Probiotics for the treatment of bacterial vaginosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 24/02/10).
5. Othman M, *et al*. Probiotics for preventing preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
6. Falagas ME, *et al*. Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. *Drugs* 2006; **66:** 1253–61.

Adverse effects

Metabolic acidosis has occurred after use of tablets containing *Lactobacillus acidophilus*.[1] Cases of infection associated with the use of lactic-acid-producing organisms seem to be very rare,[2] although fungaemia associated with the use of *Saccharomyces boulardii*,[3] and sepsis associated with *Lactobacillus* spp.[4] have been reported. Reviews[5,6] on the safety of probiotics concluded that their overall safety record is good. However, the authors recommend caution in certain patient groups such as the elderly and premature or immunocompromised neonates because of occasional reports of sepsis that have rarely occurred in previously healthy patients.[5] Use of enterococci and streptococci as probiotics give a theoretical cause for concern since these genera include pathogenic bacteria.[5] Properties of probiotics are specific to species and strain and therefore reports on safety for one probiotic cannot be generalised to others.[5]

1. Oh MS, *et al*. D-Lactic acidosis in a man with short-bowel syndrome. *N Engl J Med* 1979; **301:** 249–52.
2. Borriello SP, *et al*. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis* 2003; **36:** 775–80.
3. Piarroux R, *et al*. Are live saccharomyces yeasts harmful to patients? *Lancet* 1999; **353:** 1851–2.
4. Land MH, *et al*. Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005; **115:** 178–81.
5. Boyle RJ, *et al*. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006; **83:** 1256–64.
6. Hammerman C, *et al*. Safety of probiotics: comparison of two popular strains. *BMJ* 2006; **333:** 1006–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acidofilofago; Flevic; Floratil; Lactinex; Tropivag; ***Austral.***: Bioglan Acidophilus†; Digestive Bio Balance; Forbiotic†; ProTract; Superdophilus†; ***Austria***: Antibiophilus; Bioflorin; Doderlein; Reflor; Symbioflor Enterococcus; Yomogi; ***Belg.***: Enterol; Lacteol; ***Braz.***: Flomicin; Floratil; Floren; Florent; Lactipan; Leiba; Repoflor; ***Canad.***: Align; Bacid; BioGaia; Florastor; Lacidofil; TuZen; ***Chile***: Bio-Flora; BioGaia; Biolactus; Bion Transit; Econormotil†; Gastrofloral†; Lactil; Perenteryl; ***China***: Bioflor (亿活); Ding Jun Sheng (定君生); Ju Ke (聚克); Lacteol Fort (乐托尔); Yan Hua (延华); ***Cz.***: Enterol; ***Denm.***: Paraghurt; Vivag; ***Fin.***: Lactophilus; Precosa; ***Fr.***: Bacilor; BioGaia; Bion Transit; Bioprotus; Gyno-Control; Gynophilus; Lacteol; Lactibiane Candisis; Lactibiane Protect; Lyobifidus; Normafilus; Orogyn; Ultra-Levure; ***Ger.***: Doderlein Med†; Gynophilus; Hylak N†; Hylak Plus†; InfectoDiarrstop LGG Mono; Lacteol; Lyseen; Paidoflor; Perenterol; Symbioflor 1; Vagiflor; ***Gr.***: Ultra-Levure; ***Hong Kong***: Bioflor; Lacteol; Reuteri; ***Hung.***: Enterol; Gynevac; Ovulobact; Symbioflor 1; ***India***: Babylac; Baclac; Base; Benspore; Bio 4; Cefocef-LB; Comensal; Darolac-IBS; Econorm; Flora-L; GNorm; GSLB; Lac-M; Lactiflora; Lactobacil; Lactogenes; Lactolus; Lactospore; Lactra; Lactrol; Lacven; LBDix; Lexicom; Medalac; Myconip; Sporlac; ***Indon.***: BioGaia; Geebio; Lacbon; Rillus; ***Ital.***: Bactocin; Bioflorin; Codex; Dicoflor; Ecocillin; Ecoflorina; Eptavis; Giflorex; Inulac; Lacteol; Lactonorm; Probinul; Provag†; Regolact Plus; Reuflor; Softigyn; VSL 3; ***Mex.***: Biolactos; Floratil; Lacteol Fort; Lactipan; Lactocil†; Lactovita†; Liolactil; Neoflor; Sinuberase†; ***Norw.***: Precosa; ***NZ***: Blis K12 Throat Guard; ***Philipp.***: Floratil; Infloran; Pro-bio; ***Pol.***: EcoVag; Enterol; Lactovaginal; Lakcid; ***Port.***: Antibiophilus; Lacteol; UL 250; ***Rus.***: Bificol (Бификол); Bifidumbacterin (Бифидумбактерин); Bifinorm (Бифинорм); Ecofemin (Экофемин); Enterol (Энтерол); Gastropharm (Гастрофарм); IRS 19 (ИРС 19); Lactobacterin (Лактобактерин); Probifor (Пробифор); ***S.Afr.***: Actiflora†; Inteflora; ***Singapore***: BioGaia; DiarrStope; Lacteol; Pro-BIS; Protexin; Reutefene†; ***Spain***: Casenfilus; Lacteol; Lactofilus; Ultra-Levura; ***Swed.***: Precosa; Probiomax; Vivag; ***Switz.***: Bioflorin; Bioflorina; Florosan†; Lacteol; Lactoferment; Perenterol; Symbioflor 1; Ultra-Levure†; ***Thai.***: Bioflor; ***Turk.***: Perocur; Reflor; ***UK***: Bio Acidophilus; Biodophilus; Gum PerioBalance; Infacol Probiotic; ***Ukr.***: BioGaia (БиоГая); Bioselac (Биоселак); Enterol (Энтерол); Gynolakt (Гинолакт); Hylak (Хилак); Linbi (Линби); Normagut (Нормагут); Preema (Према); SolcoTrichovac (Солкотриховак)†; ***USA***: Acidophilus; Align Daily Probiotic Supplement; Bacid; BioGaia; Culturelle; Florastor; Gerber Soothe Colic Drops; Intestinex; Kala; Lactinex; Lacto-Key; MoreDophilus; Pro-Bionate; Superdophilus; ***Venez.***: Florcidin; Florestor; Lacteol; Lactobacilos; Liolactil; Proflor.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Promelase *(pINN)* ⊗

EC 3.4.21.63; Oryzin; Promelasa; Promélase; Promelasum; Seaprose S; Промелаза.
CAS — 9074-07-1.

Profile

Promelase is an alkaline protease derived from *Aspergillus melleus*. It has been taken orally in doses of 30 to 90 mg daily for its supposed benefit in oedema and inflammation associated with trauma, infection, and surgical procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Altan; Flaminase.

Pronase ⊗

Проназа.

Profile

Pronase is a mixture of proteinases obtained from *Streptomyces griseus*. It is used for inflammation associated with trauma, chronic sinusitis, and surgical procedures and as a mucolytic for tenacious sputum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Empynase.

Propolis

Bee Glue; Propóleo; Própolis; Прополис.
UNII — 6Y8XYV2NOF.

Profile

Propolis is a resinous substance collected by bees, mainly, at least in temperate climates, from poplar buds (see also p. 2594.2) and to a lesser extent from conifers. It is mixed with wax by bees and used in the construction and maintenance of their hives. Propolis is composed of resins, balsams, essential and aromatic oils, and pollen, although

the exact proportions of each varies from region to region, bee species, and local flora, therefore making standardisation of propolis for medicinal use difficult. Propolis has been reported to have anti-inflammatory and antimicrobial properties. It has been used as a nutritional supplement and in preparations for coughs, mouth disorders, and skin disorders. It has been used as an ointment for the relief of symptoms of herpes labialis. Propolis has also been used in cosmetics and varnishes.

Effects on the kidneys. Acute renal failure associated with 4 months of use of propolis in a homoeopathic product (exact form and dose not reported) developed in a 3-year-old boy with a history of gluten enteropathy.[1] Creatinine concentrations returned to normal after stopping propolis.

1. Health Canada. Propolis: suspected association with renal failure. *Can Adverse React News* 2009; **19**(1): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v19n1-eng.pdf (accessed 05/02/09)

Hypersensitivity. For reference to hypersensitivity reactions with bee products, including propolis, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Propoleos; Sweety; ***Chile***: Propolkit; ***Ger.***: Propolisept-Salbe†; ***Hung.***: Propur; ***Ital.***: Golapiol; Oral Spray†; Pro-Gola; Propociclina; Propolcream†; Propolgel; ***Pol.***: Apizel; Propolan†; Propolisan; Propolisol; ***Rus.***: Proposol (Пропосол); ***Swed.***: Herstat†; ***USA***: Probax.

Multi-ingredient Preparations. ***Arg.***: Farinop; ***Braz.***: Malvatricin Natural Organic†; ***Chile***: Propolis C; Propolkit; Propolkit; Timuss-Kit (sin azucar); Timuss-Kit; ***Fr.***: Alvityl Defenses; Duab; Olioseptil Gorge-Larynx; Olioseptil Gorge-Larynx; Propargile; ***Hong Kong***: Vita Coldycin Echinacea Plus†; ***Hung.***: Aranyer Elleni; ***Indon.***: Imumax; Neoboost Kids; Opinacea; Opinacea; ***Ital.***: Actires; Altuss; Apistress; Biogreen; Body Guard; Bron 6; Coryfin C senza Zucchero; Emoform Alifresh; Faringel; Fosfarsile Forte; Golapiol C; Immumil Plus†; Influpiol C; Influtux; Keratolip; Neo-Stomygen; Nepiros; Probigol; Promix 3; Propast; Valcap; Valda Propoli†; Valda Propoli; ***Pol.***: Scaldex; ***Rus.***: Proposol-N (Пропосол-Н); Prostopine (Простопин); ***Singapore***: Arkopharma Propolis Spray; ***Turk.***: Immuzinc; ***UK***: Sinose; ***Ukr.***: Apibact (Апибакт); Apiprost (Апипрост); Proalor (Проалор)†.

Homoeopathic Preparations. ***Ger.***: Propolisept Urtinktur.

Proteases

Peptidasas; Peptidasen; Peptidases; Peptidazės; Peptidbindungshydrolasen; Proteaasit; Proteaser; Protéases; Proteasi; Proteázok; Proteazy; Proteázy; Proteinases.

Profile

Proteases are enzymes that hydrolyse proteins. They are found in all living organisms and are involved in a wide range of biological and physiological processes. Proteases are an important constituent of pancreatic enzymes (p. 2579.3) and preparations containing proteases have been used in gastrointestinal disorders. Proteases such as collagenase (p. 2484.1) have been used for wound debridement. Proteases have also been used for instrument disinfection and contact lens care. Some proteases have been promoted for pain and inflammation and for auto-immune disorders, but such uses are not established.

Reviews.
1. Craik CS, *et al*. Proteases as therapeutics. *Biochem J* 2011; **435**: 1–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Flaviastase†; ***USA***: PAN-2400†.

Multi-ingredient Preparations. ***Arg.***: Dom-Polienzim; Polienzim; ***Canad.***: Multi-Zyme†; Synergy Defense; ***Cz.***: Iruxol Mono; ***Fin.***: Iruxol Mono; ***Fr.***: Aniosyme†; ***Hong Kong***: Enzyplex; ***Hung.***: Iruxol Mono†; ***India***: Digestomen-P; Farizym; Leno-EZ; ***Indon.***: Enzyplex; Excelase-E; Vitazym; Xepazym; ***Irl.***: Iruxol Mono; ***Malaysia***: Enzyplex†; Iruxol Mono; ***S.Afr.***: Iruxol Mono; ***Singapore***: Enzyplex; ***Spain***: Iruxol Mono; ***Thai.***: Enzyplex†; ***USA***: Digex†; Enzyme; Ku-Zyme†; Kutrase†; Pangestyme†; ***Venez.***: Festal Reformulado.

Prostaglandins

Простагландины.

Profile

The prostaglandins, along with thromboxanes and leukotrienes, are all derived from 20-carbon polyunsaturated fatty acids and are collectively termed *eicosanoids*. In man, the most common precursor is arachidonic acid (eicosatetraenoic acid; p. 2446.1) whereas eicosapentaenoic acid is a predominant precursor in fish and marine animals.

Arachidonic acid is released from cell-membrane phospholipids by the enzyme phospholipase A_2 and is then rapidly metabolised by several enzymes, the major ones being cyclo-oxygenase (prostaglandin synthetase) and lipoxygenase (see Figure 1, below). The prostaglandins, thromboxanes, and prostacyclin (sometimes collectively termed *prostanoids*) all contain ring structures and are products of arachidonic acid oxidation by cyclo-oxygenase, an enzyme with 2 isoforms (COX-1 or COX-2) widely distributed in cell membranes.

The leukotrienes are products of the lipoxygenase pathway; arachidonic acid is metabolised by lipoxygenases to hydroperoxyeicosatetraenoic acids, which are then further metabolised to leukotrienes.

The initial step in the cyclo-oxygenase pathway is the formation of cyclic endoperoxide prostaglandin G_2 (PGG_2), which is then reduced to the endoperoxide prostaglandin H_2 (PGH_2). Prostaglandin H_2 is then converted to the primary prostaglandins prostaglandin D_2, prostaglandin E_2, and prostaglandin $F_{2\alpha}$, to thromboxane A_2 (TXA_2) via the enzyme thromboxane synthetase, or to prostacyclin (PGI_2) via the enzyme prostacyclin synthetase. These products are further metabolised and rapidly inactivated in the body.

The secondary prostaglandins, prostaglandin A_2 (PGA_2), prostaglandin B_2 (PGB_2), and prostaglandin C_2 (PGC_2) are derived from prostaglandin E_2, but are formed during extraction and probably do not occur biologically.

The prostaglandins are all derivatives of the carbon skeleton 7-(2-octilcyclopentyl)heptanoic acid (also known as prostanoic acid). All natural prostaglandins have a double bond at position 1,2 and a hydroxyl group at position 3 of the octil side-chain. Depending on the substitutions on the cyclopentane ring, the main series of prostaglandins are distinguished by the letters A, B, C, D, E, and F; the members of each series are further subdivided by subscript numbers that indicate the degree of unsaturation in the side-chains—hence, those derived from eicosatrienoic acid (dihomo-γ-linolenic acid) have the subscript 1, those derived from arachidonic acid have the subscript 2, and those derived from eicosapentaenoic acid have the subscript 3. In man, only prostaglandins of the '2' series appear to be of physiological importance. Thromboxane A_2 has an oxane rather than a cyclopentane ring; it is chemically unstable and breaks down to thromboxane B_2. Prostacyclin has a double-ring structure and breaks down to 6-keto-prostaglandin $F_{1\alpha}$.

Endogenous prostaglandins are autacoids; they can be formed by virtually all tissues and cells in response to a variety of stimuli, have many **actions**, and are involved in the regulation of virtually all biological functions. Prostaglandins appear to act through various receptor-mediated mechanisms. Some of their effects are mediated within cells by activation or inhibition of adenylate cyclase and the regulation of cyclic adenosine monophosphate production. At one time prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were thought to be of paramount importance, but with the discovery of thromboxane A_2, prostacyclin, and the leukotrienes it was realised that these primary prostaglandins belong to a large family of physiologically active eicosanoids. Thromboxane A_2 induces platelet aggregation and constricts arterial smooth muscle whereas prostacyclin causes vasodilatation and prevents platelet aggregation; the balance between these opposing actions has an important role in the regulation of intravascular platelet aggregation and thrombus formation. The leukotrienes are important mediators of inflammation.

The pharmacological properties of prostaglandins are wide-ranging and include contraction or relaxation of smooth muscle in the blood vessels, bronchi, uterus, and gastrointestinal tract; inhibition of gastric acid secretion; and effects on platelet aggregation, the endocrine system, and metabolic processes.

Individual prostaglandins vary greatly in their activities and potencies; their actions also depend on the animal species, on the tissues in which they are acting, and on the concentration present, and entirely opposite actions may be elicited with very small structural changes in the molecule.

The diverse **clinical applications** of prostaglandins reflect their wide-ranging physiological and pharmacological properties. Synthetic analogues have been developed with the aim of obtaining compounds that are more stable, have a longer duration of action, and a more specific effect. Applications include:

- softening and dilating the cervix and for uterine stimulation, e.g. dinoprost (prostaglandin $F_{2\alpha}$) (p. 2133.3) and its analogue carboprost (p. 2133.1); dinoprostone (prostaglandin E_2) (p. 2134.1) and its analogue sulprostone (p. 2145.3); and gemeprost (p. 2137.2) and misoprostol (p. 2140.3), analogues of prostaglandin E_1
- vasodilators and inhibitors of platelet aggregation, e.g. alprostadil (prostaglandin E_1) (p. 2352.2) and its analogue limaprost (p. 1420.3); and epoprostenol (prostacyclin) (p. 1374.3) and its analogue iloprost (p. 1408.1)
- inhibition of gastric acid secretion and protection of the gastrointestinal mucosa, e.g. misoprostol (p. 2140.3)
- glaucoma treatment, e.g. bimatoprost (p. 2004.2), latanoprost (p. 2008.1), travoprost (p. 2012.1), and unoprostone (p. 2013.1)
- as luteolytics (causing regression of the corpus luteum in the ovary) in veterinary medicine, e.g. synthetic analogues of prostaglandin $F_{2\alpha}$.

References.

1. Moncada S, Vane JR. Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. *N Engl J Med* 1979; **300**: 1142–7.
2. Higgs GA, Vane JR. Inhibition of cyclo-oxygenase and lipoxygenase. *Br Med Bull* 1983; **39**: 265–70.
3. Halushka PV, *et al*. Thromboxane, prostaglandin and leukotriene receptors. *Annu Rev Pharmacol Toxicol* 1989; **29**: 213–39.
4. Smith WL, *et al*. Prostaglandin and thromboxane biosynthesis. *Pharmacol Ther* 1991; **49**: 153–79.
5. O'Neill C. The biochemistry of prostaglandins: a primer. *Aust N Z J Obstet Gynaecol* 1994; **34**: 332–7.
6. Wu KK. Molecular regulation and augmentation of prostacyclin biosynthesis. *Agents Actions Suppl* 1995; **45**: 11–17.

Figure 1. Prostaglandin biosynthesis.

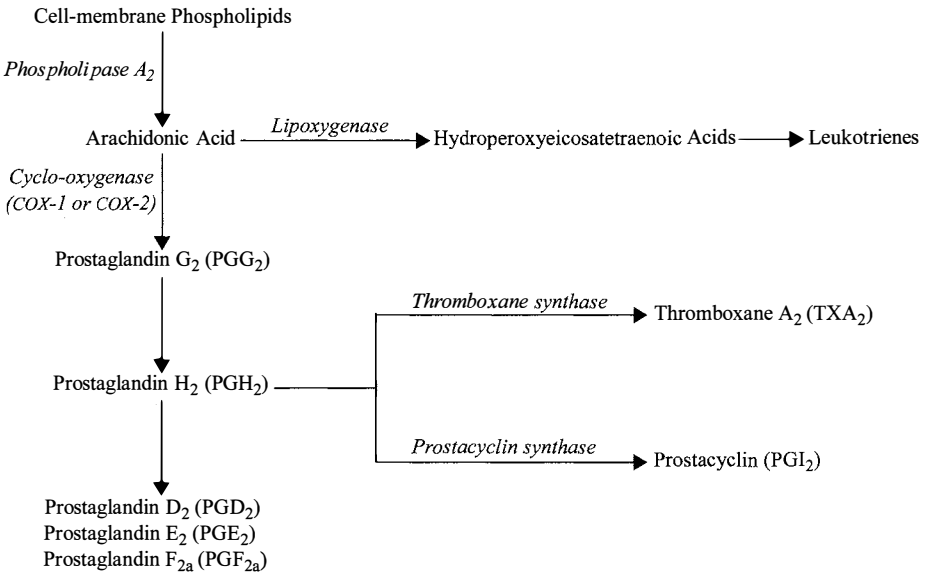

Protoporphyrin IX Disodium

Protoporfirina IX disódica; Protoporphyrin Disodium.
Disodium 7,12-diethenyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphine-2,18-dipropanoate.
$C_{34}H_{32}N_4Na_2O_4$=606.6
CAS — 50865-01-5 (protoporphyrin IX disodium); 553-12-8 (protoporphyrin IX).
UNII — 54N4UY1C7C.

Profile

Protoporphyrin IX disodium has been given orally for the treatment of impaired hepatic function associated with gallstones and cholecystitis.

Psilocin

4-Hydroxy-*NN*-dimethyltryptamine; Psilocina; Psilocyn.
3-(2-Dimethylaminoethyl)indol-4-ol.
$C_{12}H_{16}N_2O$=204.3
CAS — 520-53-6.
UNII — CMS88KUW0G.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of psilocin or mushrooms containing psilocin:

1UP's; Abhort; Aborts; Alice; Benzies; Blue Rimmers; Boom-Dads; Boomers; Caps; Crumb Tarts; Cubes; FireWorks; Fun Gus; Fun Guys; Fungus; God's flesh; Goombas; Gus; Jesus; Lalkas; Liberty caps; Little smoke; Magic mushroom; Magic Mushrooms; Marios; Mexican mushroom; Mexican mushrooms; Mucks; Muggers; Mush; Mushies; Mushrooms; Musk; Pizza Toppings; Shroomies; Shrooms; Silly putty; Simple Simon; Smurfhats; Toads; Umbrellas; Yellow Bentines; Zoomers; Zoomies.

Psilocybine *(BAN, rINN)*

CY-39; 4-Phosphoryloxy-*NN*-dimethyltryptamine; Psilocibina; Psilocybin; Psilocybinum; Psilosybiini; Псилоцибин.
3-(2-Dimethylaminoethyl)indol-4-yl dihydrogen phosphate.
$C_{12}H_{17}N_2O_4P$=284.3
CAS — 520-52-5.
UNII — 2RV7212BP0.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of psilocybine or mushrooms containing psilocybine:

1 UP's; Alice; Benzies; Blue caps; Blue Rimmers; Boom-Dads; Boomers; Booms; Buttons; Caps; Champ; Crumb Tarts; Cubes; FireWorks; Fun Gus; Fun Guys; Fungus; Funguys; God's flesh; Goombas; Gus; Hombrecitos; Jesus; Lalkas; Las mujercitas; Little smoke; Magic mushroom; Magic mushrooms; Marios; Mexican mushroom; Mexican mushrooms; Mucks; Muggers; Mush; Mushies; Mushroom soup; Mushroom tea; Mushrooms; Musk; Philosopher's Stones; Pizza toppings; Rooms; Sacre mushroom; Sacred mushroom; Sacred mushrooms; Shroomies; Shrooms; Silly putty; Simple Simon; Smurfhats; Teonanactl; Toads; Truffles; Umbrellas; Yellow Bentines; Zoomers; Zoomies.

Profile

Psilocin and psilocybine are indole alkaloids obtained from the sacred Mexican mushroom (teonanácatl), *Psilocybe mexicana* (Agaricaceae).

In the UK, psilocybine is present in the indigenous mushroom *Psilocybe semilanceata* (magic mushroom; liberty cap). Psilocybine is also present in other species of mushrooms including *Stropharia cubensis* and *Conocybe* spp.

Psilocybine has hallucinogenic and sympathomimetic properties similar to those of lysergide (p. 2547.1). It is less potent than lysergide and its hallucinogenic effects last for up to 6 hours. There is evidence to suggest that psilocybine is converted to the active form psilocin in the body. It has no therapeutic use.

Pulegium Oil

Aceite esencial de menta poleo; Aceite esencial de poleomenta; Pennyroyal Oil; Poleo, aceite esencial de; Масло Мяты Болотной.
UNII — AK85U7Y3MV.

Uses and Administration

Pulegium oil is a volatile oil distilled from pennyroyal herb, *Mentha pulegium* (Labiatae), containing pulegone ($C_{10}H_{16}O$ = 152.2). It was formerly used as an emmenagogue. Pulegium is reported to have insect repellent activity.

Adverse Effects

Severe toxic effects have followed use of pulegium oil as an abortifacient with convulsions, hepatotoxicity, and death.

Severe hepatotoxicity accompanied by seizures occurred in 2 infants each of whom had received herbal teas containing pulegium oil.[1] In one of the infants multiple organ failure developed, and fulminant hepatic failure with hepatocellular necrosis and cerebral oedema proved fatal. A further 4 cases of toxicity associated with ingestion of pulegium oil have been reported;[2] three of the cases were adult patients who had ingested either herbal teas to induce menses (2 cases) or a herbal extract as an abortifacient (1 fatality), and the fourth was a 22-month old child who had ingested the oil.

1. Bakerink JA, *et al.* Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. *Pediatrics* 1996; **98:** 944–7.
2. Anderson IB, *et al.* Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. *Ann Intern Med* 1996; **124:** 726–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Wunderbalsam.

Pulmonary Surfactants

Tensioactivos pulmonares; Лёгочные Сурфактанты.

Description. Pulmonary surfactants are mixtures consisting mainly of phospholipids and surfactant proteins that are used to replace deficient endogenous lung surfactants. Several preparations have been studied including:

- natural human surfactant obtained from amniotic fluid or biosynthetic material
- natural animal-derived surfactants, which are bovine or porcine lung extracts that may be modified by the addition of synthetic surfactants, as in the case of beractant, or unmodified, as in the case of bovactant and calfactant
- synthetic or semisynthetic preparations, which may contain the phospholipid colfosceril palmitate, a major constituent of natural lung surfactants, in combination with other substances that aid spreading and absorption such as the synthetic peptide sinapultide.

Beractant *(BAN, USAN)*

A-60386X; Берактант.
CAS — 108778-82-1.
UNII — S866O45PIG.

Description. Beractant is a modified bovine lung extract containing mostly phospholipids, modified by the addition of colfosceril palmitate, palmitic acid, and tripalmitin.

The term Surfactant TA has been applied to a modified bovine lung surfactant.

Bovactant *(BAN)*

SF-R11; SF-RI1.
CAS — 151437-98-8.

Description. Bovactant is an extract of bovine lung containing about 92% of phospholipids, 3.2% of cholesterol, 0.6% of surfactant-associated hydrophobic proteins, and 0.4% of free fatty acid.

Calfactant *(BAN, USAN)*

CAS — 183325-78-2.
UNII — Q4K217VGA9.

Description. Calfactant is an unmodified calf lung extract that includes mostly phospholipids and hydrophobic surfactant-specific proteins (SP-B and SP-C).

Colfosceril Palmitate *(BAN, USAN, rINN)*

129Y83; Colfoscéril, Palmitate de; Colfoscerili Palmitas; Colfoscerilo, palmitato de; Dipalmitoylphosphatidylcholine; DPPC; Palmitato de colfoscerilo; Колфосцерила Пальмитат.
1,2-Dipalmitoyl-*sn*-glycero(3)phosphocholine.
$C_{40}H_{80}NO_8P$=734.1
CAS — 63-89-8.
ATC — R07AA01.
ATC Vet — QR07AA01.
UNII — 319X2NFW0A (L-Dipalmitoylphosphatidylcholine); 2W15RT5V7V (DL-Dipalmitoylphosphatidylcholine).

Description. Colfosceril palmitate is a phospholipid which forms an important constituent of natural and many synthetic pulmonary surfactant compounds.

Lucinactant *(USAN)*

API-02; ATI-02; KL_4-surfactant.
CAS — 825600-90-6.

Description. Lucinactant is a mixture of sinapultide, colfosceril palmitate, sodium palmitoyloleaylphosphatidyl glycerol, and palmitic acid.

Poractant Alfa *(BAN)*

Порактант Альфа.
CAS — 129069-19-8.
UNII — KE3U2023NP.

Description. Poractant alfa is an extract of porcine lung containing not less than 90% of phospholipids, about 1% of hydrophobic proteins (SP-B and SP-C), and about 9% of other lipids.

Pumactant *(BAN)*

Artificial Lung Expanding Compound; Пумактант.
CAS — 258856-56-3.

Description. Pumactant is a mixture of colfosceril palmitate and phosphatidyl glycerol (2-oleoyl-1-palmitoyl-*sn*-glycero(3)phospho(1)-*sn*-glycerol) in the proportion 7:3.

Sinapultide *(USAN, rINN)*

ATI-01; KL-4 Peptide; Sinapultida; Sinapultidum; Синапультид.
CAS — 138531-07-4.
UNII — 040X3AX99T.

Description. Sinapultide is a synthetic peptide that mimics the actions of human surfactant protein B, an important constituent of natural pulmonary surfactant compounds.

Uses and Administration

Pulmonary surfactants are compounds with surface active properties similar to those natural substances in the lung that help to maintain the patency of the airways by reducing the surface tension of pulmonary fluids. Exogenous pulmonary surfactants are used in the treatment of neonatal respiratory distress syndrome (see p. 2600.1) in premature infants, and may also be given for prevention in infants considered to be at risk of developing the syndrome. Doses vary, but most pulmonary surfactants are given in recommended doses of 100 to 200 mg phospholipids per kg birth-weight; a suggested dose for colfosceril palmitate has been 67.5 mg/kg. For the treatment of overt neonatal respiratory distress syndrome, the initial dose is given as soon as possible after diagnosis, while for prevention it is given as soon as possible after birth. It is given as a suspension via an endotracheal tube to intubated neonates receiving mechanical ventilation. Manufacturers may recommend regimens with or without disconnection from the ventilator. Repeat doses may be given if necessary, although the number of doses and the dosage interval varies.

Pulmonary surfactants have also been tried in bronchopulmonary dysplasia in premature infants, meconium aspiration syndrome in newborn infants, and acute respiratory distress syndrome in adults.

Reviews.

1. Stevens TP, Sinkin RA. Surfactant replacement therapy. *Chest* 2007; **131:** 1577–82.
2. Sweet DG, Halliday HL. The use of surfactants in 2009. *Arch Dis Child Educ Pract Ed* 2009; **94:** 78–83.

Administration in children. Doses of pulmonary surfactants for the treatment of neonatal respiratory distress syndrome are given under Uses and Administration above.

Acute respiratory distress syndrome. Pulmonary surfactants have been investigated for acute respiratory distress syndrome (p. 1599.3). In adults, they have been given by intrabronchial instillation[1] or nebulisation[2-4] but results have been largely disappointing. Sequential bronchopulmonary segmental lavage with a synthetic surfactant has also been tried[5] and appeared to be well tolerated. Endotracheal poractant alfa moderately improved oxygenation in some children with severe acute respiratory distress syndrome secondary to pulmonary or systemic disease.[6] Pulmonary surfactants have also been used in two infants in the management of pneumonitis and acute respiratory distress syndrome after accidental hydrocarbon aspiration.[7,8]

1. Haslam PL, *et al.* Surfactant replacement therapy in late-stage adult respiratory distress syndrome. *Lancet* 1994; **343:** 1009–11.
2. do Campo JL, *et al.* Natural surfactant aerosolisation in adult respiratory distress syndrome. *Lancet* 1994; **344:** 413–14.
3. Weg JG, *et al.* Safety and potential efficacy of an aerosolized surfactant in human sepsis-induced adult respiratory distress syndrome. *JAMA* 1994; **272:** 1433–8.
4. Anzueto A, *et al.* Aerosolized surfactant in adults with sepsis-induced respiratory distress syndrome. *N Engl J Med* 1996; **334:** 1417–21.

5. Wiswell TE, *et al*. Bronchopulmonary segmental lavage with Surfaxin (KL_4-Surfactant) for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; **160:** 1188–95.
6. López-Herce J, *et al*. Surfactant treatment for acute respiratory distress syndrome. *Arch Dis Child* 1999; **80:** 248–52.
7. Horoz OO, *et al*. Surfactant therapy in acute respiratory distress syndrome due to hydrocarbon aspiration. *Singapore Med J* 2009; **50:** e130–2.
8. Mastropietro CW, Valentine K. Early administration of intratracheal surfactant (calfactant) after hydrocarbon aspiration. Abstract: *Pediatrics* 2011; **127:** 1170. Full version: http://pediatrics.aappublications.org/content/127/6/e1600.full.pdf (accessed 23/11/12)

Drowning. Reference to the use of colfosceril palmitate in the management of a 9-year-old rescued after near drowning.[1]

1. McBrien M, *et al*. Artificial surfactant in the treatment of near drowning. *Lancet* 1993; **342:** 1485–6.

Meconium aspiration syndrome. Meconium aspiration syndrome produces respiratory distress in infants born at term or later and is a consequence of airways obstruction, chemical pneumonitis, disturbances of pulmonary surfactant, and pulmonary hypertension. Bolus intratracheal doses of exogenous pulmonary surfactant may reduce the need for extracorporeal membrane oxygenation in infants with moderate to severe respiratory failure,[1] and promising results have been reported in studies involving bronchoalveolar lavage of the lungs with diluted surfactant.[2] However, there are few controlled studies of these treatments and further comparative investigations are needed.

1. El Shahed AI, *et al*. Surfactant for meconium aspiration syndrome in full term/near term infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 03/01/13).
2. Choi HJ, *et al*. Surfactant lavage therapy for meconium aspiration syndrome: a systematic review and meta-analysis. *Neonatology* 2012; **101:** 183–91.

Neonatal respiratory distress syndrome. Pulmonary surfactants improve the clinical outcome of premature infants with neonatal respiratory distress syndrome (p. 1608.3). A systematic review[1] of 9 randomised studies conducted in the 1990s concluded that intubation and prophylactic surfactant therapy in infants thought to be at risk of developing respiratory distress syndrome (RDS) has a greater effect on improvements in clinical outcome than intubation and surfactant given to infants with established RDS; prophylactic surfactant was shown to decrease the risk of pneumothorax, pulmonary interstitial emphysema, and mortality. Furthermore, multiple doses of surfactant for prophylaxis or treatment were shown to have greater benefits than a single dose in a systematic review[2] of 3 studies. Starting treatment when there were early signs of respiratory distress also reduced the risk of both short-term and longer-term lung injury.[3]

However, mechanical ventilation can contribute to lung injury in premature infants with RDS, and a systematic review[4] of 6 randomised studies concluded that giving early surfactant therapy with extubation to nasal continuous positive airway pressure (CPAP) was associated with less need for mechanical ventilation, a lower incidence of bronchopulmonary dysplasia, and fewer air leak syndromes compared with selectively giving surfactant later when RDS has worsened requiring mechanical ventilation. Later studies undertaken when maternal antenatal corticosteroid prophylaxis and CPAP had become routine found that early stabilisation on CPAP, with surfactant only given to infants needing intubation, was associated with a reduced risk of chronic lung disease or death when compared with prophylactic surfactant.[1] The administration of intratracheal surfactant through a temporary thin catheter to infants receiving CPAP has also been reported, and in a randomised study of 220 infants this method was associated with a reduced need for mechanical ventilation compared with CPAP alone.[5]

1. Rojas-Reyes MX, *et al*. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2012 (accessed 09/01/13).
2. Soll R, Özek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 09/01/13).
3. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 11. Chichester: John Wiley; 2012 (accessed 09/01/13).
4. Stevens TP, *et al*. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/01/13).
5. Göpel W, *et al*. German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet* 2011; **378:** 1627–34.

Adverse Effects and Precautions

Surfactant therapy may be associated with an increased risk of pulmonary haemorrhage, especially in more premature infants. Therapy should only be given where there are adequate facilities for ventilation and monitoring. Rapid chest expansion and improvement of oxygenation may follow successful treatment, and peak ventilatory pressure and inspired oxygen concentration may need to be reduced promptly to avoid the risk of pneumothorax and hyperoxaemia. A transient decrease in brain electrical activity has been reported in neonates given surfactant but its significance is unknown. Transient bradycardia and oxygen desaturation have also been reported. Giving surfactant has occasionally been associated with obstruction of the endotracheal tube by mucus.

While surfactant therapy is clearly associated with an increased risk of pulmonary haemorrhage,[1-4] meta-analysis suggests that the risk is small compared with the benefits.[1] However, neonates who do develop moderate or severe pulmonary haemorrhage after surfactant therapy are at increased risk of death or short-term morbidity.[5] Haemodynamic changes associated with surfactant therapy or consequent pulmonary haemorrhage may also predispose premature infants to intracranial (periventricular) haemorrhage.[5,6] Early preventive use of surfactant in very low birth-weight infants may be associated with a poorer neurodevelopmental outcome,[7] although a long-term follow-up study[8] of premature infants born in the surfactant era concluded that these children had similar neurodevelopmental outcomes to such children born before the introduction of surfactant therapy. Decreased brain electrical activity has been reported after surfactant treatment.[9]

The rate of instillation of surfactant may be significant: one study,[10] in which the apparatus was adapted so that mechanical ventilation could continue while giving surfactant, found that rapid instillation over a 5-minute period provoked a transient increase in cerebral blood flow velocity associated with an increase in carbon dioxide tension, compared with slow instillation over 15 minutes. Although the authors acknowledged that such changes were likely to be related to several factors, particularly the type of surfactant, they recommended that, until further data were available, instillation should take place slowly, over at least 15 to 20 minutes.

1. Raju TNK, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a metaanalysis. *J Pediatr* 1993; **123:** 603–10.
2. Majeed-Saidan MA, *et al*. Pulmonary haemorrhage in low-birthweight babies. *Lancet* 1993; **341:** 120.
3. Rogers D. Pulmonary haemorrhage, surfactant, and low-birthweight babies. *Lancet* 1993; **341:** 698.
4. Pappin A, *et al*. Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. *J Pediatr* 1994; **124:** 621–6.
5. Pandit PB, *et al*. Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. *Arch Dis Child Fetal Neonatal Ed* 1999; **81:** F40–F44.
6. Gunkel JH, Banks PLC. Surfactant therapy and intracranial hemorrhage: review of the literature and results of new analyses. *Pediatrics* 1993; **92:** 775–86.
7. Vaucher YE, *et al*. Outcome at twelve months of adjusted age in very low birthweight infants with lung immaturity: a randomized placebo-controlled trial of human surfactant. *J Pediatr* 1993; **122:** 126–32.
8. D'Angio CT, *et al*. Longitudinal, 15-year follow-up of children born at less than 29 weeks' gestation after introduction of surfactant therapy into a region: neurologic, cognitive, and educational outcomes. *Pediatrics* 2002; **110:** 1094–1102.
9. Hellström-Westas L, *et al*. Cerebroelectrical depression following surfactant treatment in preterm neonates. *Pediatrics* 1992; **89:** 643–7.
10. Saliba E, *et al*. Instillation rate effects of Exosurf on cerebral and cardiovascular haemodynamics in preterm neonates. *Arch Dis Child* 1994; **71:** F174–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Baby Fact B; Surfactante B; Survanta; ***Austral.***: Curosurf; Exosurf†; Survanta†; ***Austria***: Curosurf; ***Belg.***: Curosurf; Survanta; ***Braz.***: Alveofact; Curosurf; Survanta; ***Canad.***: BLES; Survanta; ***Chile***: Surfacur; Survanta; ***China***: Curosurf (固尔苏); Ke Li Su (珂立苏); ***Cz.***: Curosurf; Survanta†; ***Denm.***: Curosurf; ***Fin.***: Curosurf; ***Fr.***: Curosurf; Survanta†; ***Ger.***: Alveofact; Curosurf; Survanta†; ***Gr.***: Alvofact; Curosurf; Exosurf; Survanta; ***Hong Kong***: Survanta; ***Hung.***: Curosurf; Survanta; ***Indon.***: Survanta; ***Irl.***: Curosurf; ***Israel***: Curosurf; Infasurf; ***Ital.***: Curosurf; ***Jpn***: Surfacten; ***Malaysia***: Curosurf; Survanta; ***Mex.***: Exosurf†; Survanta; ***Neth.***: Curosurf; Survanta; ***Norw.***: Curosurf; ***NZ***: Curosurf; Survanta; ***Philipp.***: Newfactan; Survanta; ***Pol.***: Alveofact†; Curosurf; Survanta; ***Port.***: Curosurf; Survanta; ***Rus.***: Alveofact (Альвеофакт); Curosurf (Куросурф); Surfactant-BL (Сурфактант-БЛ); ***S.Afr.***: Curosurf†; Survanta†; ***Singapore***: Survanta; ***Spain***: Curosurf; Survanta; ***Swed.***: Curosurf; ***Switz.***: Curosurf; Survanta; ***Thai.***: Curosurf; Survanta; ***Turk.***: Alveofact; Curosurf; Survanta; ***UK***: Curosurf; Survanta; ***Ukr.***: Curosurf (Куросурф); Infasurf (Инфасурф); Suzacrin (Сузакрин); ***USA***: Curosurf; Infasurf; Surfaxin; Survanta; ***Venez.***: Survanta.

Pulsatilla

Anémona; Anémone pulsatille; Meadow Anemone; Pasque Flower; Пульсатилла.

CAS — 62887-80-3.

ATC Herb — HN05CM5023 (Pulsatilla vulgaris: herb); *HG01AW5001* (Pulsatilla vulgaris: herb); *HD08AW5003* (Pulsatilla vulgaris: herb); *HN05CM5022* (Pulsatilla pratensis: herb); *HA03WX5006* (Pulsatilla vulgaris: herb).

UNII — 176KB35JEV (Pulsatilla vulgaris).

Profile

Pulsatilla is the whole flowering plant of *Pulsatilla vulgaris* (*Anemone pulsatilla*) or *Pulsatilla pratensis* (Ranunculaceae). It has been used in herbal preparations for the treatment of conditions including nervous disorders, circulatory disorders, and gynaecological disorders and benign prostatic hyperplasia.

Homoeopathy

Pulsatilla has been used in homoeopathic medicines under the following names: Pulsatilla pratensis; Pulsatilla vulgaris; Pulsatilla nigricans; Puls.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Calmo†; Femi-Nan; ***Austria***: Hustensaft Weleda; ***Cz.***: Cicaderma; ***Fr.***: Hepatoum; Histo-Fluine P; ***Ger.***: Eviprostat N; Weleda Hustenelixier; ***Indon.***: Eviprostat; ***Jpn***: Eviprostat; ***Port.***: Cicaderma; Stodal; ***S.Afr.***: Cough Elixir†; ***Singapore***: Eviprostat; ***Switz.***: Elixir contre la toux†; ***UK***: Anased; Menopause Relief; Period Pain Relief; Prementaid.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Childrens Sleep; Earache Relief†; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Joint & Muscle Oral Spray†; Pain & Fever Relief; Respatona Chesty Cough & Nasal Congestion; Respatona Head Cold; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; Snore Eze; ***Austria***: Apozema Allium Cepa compositum; Cepa Med Complex; Delufen; Echinacea-Cosmoplex; Euphorbium Compositum; Gastricumeel; Globuli gegen Schlafstorungen; Lakrima; Otodolor; Pascofemin; Pulsatilla Med Complex; Rhododendroneel; Schnarchex; Vensa; ***Canad.***: Acne; Bioactiv E†; Calms Forte 4 Kids; Calnor†; Cat Complex†; Cicaderma†; Comp-Drops 9†; Coryzalia; Cough & Cold; Cruroheel S†; Detox L37; Earache; Echinacea Compositum; Euphorbium Compositum; Euphorbium Compositum; Homeo-Form G†; Homeo-Form R†; Homeodel 21†; Hylands Formula MC; Hylands Formula S; Hylands Menstrual Cramps†; Hylands Sinus†; Indigestion†; Infilex†; Kids Allergies; Men Complex†; Rhinar†; Roxalia; Sinus; Stodal; Travel Sickness; Viburcol; ***Chile***: Arnica Hamamelis Compuesta; Bioactiv A; Bioactiv E; Calcarea fluor Compuesta; Ikoplex No 18; ***Cz.***: Coryzalia; Euphorbium Compositum; Homeogene 9; Hormeel S; Stodal; Viburcol; Ypsiloheel; ***Fr.***: Abbe Chaupitre no 20†; Abbe Chaupitre no 30†; Abbe Chaupitre no 35†; Abbe Chaupitre no 64†; Abbe Chaupitre no 7; Abbe Chaupitre no 82†; Agnus Castus Complexe No 2†; Angipax; Arthro-Drainol; Berberis Complexe No 83; Cistus Canadensis Complexe No 86†; Cocculus Complexe No 73; Coryzalia; Drosera Complexe No 64; Formica Rufa Compose; Hamamelis Compose; Homeodose 20†; Homeogene 41†; Homeogene 9; Iodum Complexe No 118; Ipeca Compose; Millefolium Complexe No 7†; Myosotis Complexe No 63†; Nux Vomica Complexe No 49; Phytogargarisme†; Pulmo-Drainol†; Pulsatilla Complexe No 60†; Rhododendron Complexe No 42†; Sabal Serrulata Compose; Scrofularia Compose; Spirodrine; Staphysagria Complexe No 92†; Stodal; Stodal; Thuya Complexe No 37; Uva Ursi Complexe No 9; Vascodran; Veino-Drainol†; ***Ger.***: Agnus castus comp†; Agnus femin; Aletris N Oligoplex; Aletris Oligoplex†; Antimas†; Cephaloplant†; Entzundungstropfen; Enuroplant N; Euphorbium comp SN; Femi-cyl L Ho-Len-Complex; Feminon N; Gastro-Plantin N†; Hewelymphon N†; Infifer N; Mucosa compositum; Neuroselect; Otimed; Pascofemin spasmo; Pascofemin; Prostata-Gastreu N R25; Pulsatirell; Rheuma-Hevert†; Schleimhaut-Komplex L Ho-Fu-Complex; Schwoneural N; Schworosin; Urotruw N; Varicylum N; Venen-Komplex Ho-Fu-Complex; Venoselect N; Viburcol N; Ypsiloheel N; ***Hung.***: Coryzalia; Homeogene 9; Hormeel S; Stodal; Toxex; Viburcol; ***Neth.***: Akutur spag; Coryzalia; Echinacea comp; Euphorbium comp; Gastricumeel; Gynaelite; Homeocare Cyclo; Homeocare neusspray; Homeogene 9†; Hormeel H; Kind 0-3 Chamodent; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Mucosa comp H; Nervofleur; Nisyspray; Oteel H; Pulsatilla comp; Sinufleur; Stodal; Toxex; Viburcol H; ***Port.***: Coryzalia; Homeogene 9; ***Rus.***: Aphlubin-Naze (Афлубин-Назе); Cicaderma (Цикадерма); Coryzalia (Коризалия); Delufen (Делуфен); Dysmenorm (Дисменорм); Hormeel SN (Гормель СН); Ruta-Plus (Рута-Плюс); Stodal (Стодаль); Vensa (Венза); ***S.Afr.***: Euphorbium Compositum S†; Viburcol; ***Switz.***: Coryzalia; Gastricumeel; Homeogene 9; Menstruasan; Multiplex 1; Nelsons Sinusit†; Regenaplex Nr 86a; Regenaplex Nr. 31a; Regenaplex Nr. 31c; Regenaplex Nr. 49a; Regenaplex Nr. 71b; Stodal; Viburcol N; ***UK***: Cough Elixir; ***Ukr.***: Coryzalia (Коризалия); Delufen (Делуфен); Dentokind (Дентокинд); Dysmenorm (Дисменорм.); Incena (Инцена); Stodal (Стодаль); ***USA***: Yeast-Gard†.

Punarnava

Punarnaba; Пунарнава.

Profile

Punarnava is the fresh or dried plant *Boerhaavia diffusa* (*B. repens*) (Nyctaginaceae), containing an alkaloid, punarnavine. It has been used as a diuretic and for liver disorders, usually in the form of a liquid extract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Gecitral.

Multi-ingredient Preparations. ***Hung.***: Herbadict; ***India***: Abana; Agloliv; Arjin; Arjunin; Arthopack; Bonnisan; Calcury; Cystone; Cytozen; Diabecon; Distone; Distone; Evecare; Evecare; Flush; Flush; Geriforte; Gynoset; Hepaliv; Hipato-P; Imunocin; Li-Verve; Livasa; Livomyn; Livomyn; Livto; Liyurto; Lukol; Megacure-DS; Megacure-DS; Megacure-DS; Neeri; New-Livfit; Nobese; Obenyl; ***Malaysia***: Bonnisan; ***Rus.***: Bonjigar (Бонджигар); Dipana (Дипана); ***Ukr.***: Bonjigar (Бонджигар); Eve Care (Ив Кер)†; Imunin (Иммунин)†.

Homoeopathic Preparations. ***Fr.***: Poconeol no 23†.

Pyricarbate *(rINN)*

Piricarbato; Pyricarbatum; Pyridinolcarbamate; Пирикарбат.

2,6-Pyridinediyldimethylene bis(methylcarbamate).

$C_{11}H_{15}N_3O_4$=253.3

CAS — 1882-26-4.

UNII — 81R511UV73.

Profile

Pyricarbate has been given orally in the treatment of atherosclerosis and other vascular disorders, hyperlipidaemias, and thromboembolic disorders. Adverse effects have included gastrointestinal disturbances and liver damage.

Pyrogen

Pyrogenium.

Profile

Pyrogen is produced from a mixture of lean beef and water left to stand for several weeks.

Homoeopathy

Pyrogen has been used in homoeopathic medicines under the following names: Pyrogenium; Pyrexin; Sepsin; Putrescinum.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Echinacea-Cosmoplex; ***Canad.***: Kids' Earache; ***Cz.***: Galium; ***Ger.***: metabiarex; Pyrogenium.

Quassia

Bitter Wood; Casia de Surinam; Cuasia; Cuasia surinamense; Leño amargo; Leño de Cuasia; Palo amargo; Palo de Cuasia; Quassia amara; Quassia Wood; Quassiae Lignum; Quassiaholz; Quina de Cayena; Квассия.

CAS — 76-78-8 (quassin); 76-77-7 (neoquassin).

ATC — P03AX04.

ATC Vet — QP53AX03.

*ATC Herb — HP03AX5003 (*Quassia amara*: wood); HP03BX5005 (*Quassia amara*: wood); HP02WA5003 (*Picrasma excelsa*: wood); HP02WA5004 (*Quassia amara*: wood); HP03BX5004 (*Picrasma excelsa*: wood); HA09WA5020 (*Picrasma excelsa*: wood); HA09WA5021 (*Quassia amara*: wood); HP03AX5002 (*Picrasma excelsa*: wood).*

*UNII — O2G7GY29MO (*Quassia amara*); S5249Q85HW (*Quassia amara *wood).*

Profile

Quassia is the dried stem wood of Jamaica quassia, *Picrasma excelsa* (*Aeschrion excelsa; Picraena excelsa*) (Simaroubaceae), or of Surinam quassia, *Quassia amara* (Simaroubaceae). It has been used as a bitter. It was formerly given as an enema for the expulsion of threadworms and was applied for pediculosis. It may also be used as a flavour in food, drinks, and confectionery. Extracts of quassia or preparations containing its triterpenoid bitter principle quassin are used to denature alcohol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cuassicum Prevent; Life + Quality; Picutex.

Multi-ingredient Preparations. ***Arg.***: Aulo Repelente De Piojos; Cuassicum; Fuera Bicho†; Rep Locion Repelente; Uze Active; ***Braz.***: Camomila; ***Canad.***: Para-Gard; Para-Gone; ***Fr.***: Quintonine†; Skin Nail; Spevin†; ***Ital.***: Dekar 2†; ***S.Afr.***: Essens Amara of Groen Amara; Versterkdruppels; ***Switz.***: Stomacine; ***UK***: Sanderson's Throat Specific.

Homoeopathic Preparations. ***Fr.***: Gentiana Complexe No 33†; ***Ger.***: Bomagall; Choanol N; Cholo 2-injektopas; Hepa-Loges N; Hepar-Hevert N; Leber Albin; Pankreaticum; Pankreaticum; Spasmo-Bomaleb†; ***Switz.***: metaheptachol.

Quebracho

Quebracho Blanco; White Quebracho; Квебрахо Белое.

*ATC Herb — HR03WA5001 (*Aspidosperma quebracho-blanco*: bark); HN02BW5001 (*Aspidosperma quebracho-blanco*: bark); HA09WA5003 (*Aspidosperma quebracho-blanco*: bark).*

UNII — 52B1340190.

NOTE. Do not confuse with trees belonging to the genus *Schinopsis* that may also be referred to as quebracho.

Profile

The bark of white quebracho, *Aspidosperma quebracho-blanco* (Apocynaceae) is used in herbal medicine for the treatment of respiratory disorders. It has also been used to reduce fever, as an antihypertensive, and as a flavouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Afrodor†; ***Hung.***: Bronchicum; Bronchicum; ***Pol.***: Bronchicum Eliksir†; ***Rus.***: Afrodor (Афродор)†; Bronchicum (Бронхикум)†.

Homoeopathic Preparations. ***Austria***: Tartephedreel; ***Chile***: Similibus; ***Switz.***: Regenaplex Nr. 24c.

Quinagolide Hydrochloride *(BANM, rINNM)*

CV-205-502 (quinagolide); Hidrocloruro de quinagolida; Quinagolida, hidrocloruro de; Quinagolide, Chlorhydrate de; Quinagolidi Hydrochloridum; SD2-CV-205-502 (quinagolide); Хинаголида Гидрохлорид.

(±)-*N,N*-Diethyl-*N*′-[(3*R**,4a*R**,10a*S**)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[*g*]quinolin-3-yl]sulfamide hydrochloride.

$C_{20}H_{33}N_3O_3S,HCl$=432.0

CAS — 87056-78-8 (quinagolide); 94424-50-7 (quinagolide hydrochloride).

ATC — G02CB04.

ATC Vet — QG02CB04.

UNII — 33474X943Y.

Uses and Administration

Quinagolide is a non-ergot dopamine D_2-agonist that has actions and uses similar to those of bromocriptine (p. 895.3). It is used in the treatment of disorders associated with hyperprolactinaemia (p. 2252.2).

Quinagolide is given as the hydrochloride, but doses are described in terms of the base; 27.3 micrograms of quinagolide hydrochloride is equivalent to about 25 micrograms of quinagolide. The initial dose, given orally once daily with food at bedtime, is 25 micrograms daily for 3 days. Doses are increased thereafter at 3-day intervals in steps of 25 micrograms until the optimal response is achieved, which is usually within the range of 75 to 150 micrograms daily. If doses greater than 300 micrograms daily are required, the daily dosage may be increased in steps of 75 to 150 micrograms at intervals of not less than 4 weeks.

Hyperprolactinaemia and prolactinomas. References.

1. Rohmer V, *et al.* Efficacy of quinagolide in resistance to dopamine agonists: results of a multicenter study. *Ann Endocrinol (Paris)* 2000; **61:** 411–17.
2. Schultz PN, *et al.* Quinagolide in the management of prolactinoma. *Pituitary* 2000; **3:** 239–49.
3. Barlier A, Jaquet P. Quinagolide—a valuable treatment option for hyperprolactinaemia. *Eur J Endocrinol* 2006; **154:** 187–95.

Lactation inhibition. The routine use of dopamine agonists such as quinagolide is not recommended for the suppression of physiological lactation (see p. 2130.1).

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3, although it is not an ergot derivative and does not seem to be associated with fibrotic reactions or vasoconstriction. Licensed product information contra-indicates the use of quinagolide in patients with hepatic or renal impairment; however, this is based on a lack of data in such patients.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including quinagolide, see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinagolide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Quinagolide is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism to the *N*-desethyl analogue which is biologically active and the *N,N*-didesethyl analogue. Roughly equal amounts of a dose appear in the urine and the faeces; it is excreted in the urine as sulfate or glucuronide conjugates of quinagolide and its metabolites and in the faeces as the unconjugated forms. Protein binding has been reported to be about 90%. The elimination half-life of quinagolide at steady state is about 17 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Norprolac; ***Austria***: Norprolac; ***Belg.***: Norprolac; ***Canad.***: Norprolac; ***Cz.***: Norprolac; ***Denm.***: Norprolac; ***Fin.***: Norprolac; ***Fr.***: Norprolac; ***Ger.***: Norprolac; ***Gr.***: Norprolac; ***Hong Kong***: Norprolac; ***Hung.***: Norprolac; ***Israel***: Norprolac; ***Mex.***: Norprolac; ***Neth.***: Norprolac; ***Norw.***: Norprolac; ***NZ***: Norprolac; ***Pol.***: Norprolac; ***Port.***: Norprolac; ***Rus.***: Norprolac (Норпролак); ***S.Afr.***: Norprolac; ***Singapore***: Norprolac; ***Spain***: Norprolac; ***Swed.***: Norprolac; ***Switz.***: Norprolac; ***Turk.***: Norprolac; ***UK***: Norprolac; ***Ukr.***: Norprolac (Норпролак).

Quinine and Urea Hydrochloride

Carbamidated Quinine Dihydrochloride; Chininum Dihydrochloricum Carbamidatum; Quinina y urea, hidrocloruro de; Urea-Quinine.

$C_{20}H_{24}N_2O_2,CH_4N_2O,2HCl,5H_2O$=547.5

CAS — 549-52-0 (anhydrous quinine and urea hydrochloride).

Profile

Quinine and urea hydrochloride has been used for the treatment of haemorrhoidal bleeding and anal fissure. It was formerly used as a local anaesthetic and for the therapeutic actions of quinine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Kinurea H.

Quinine Arsenite

Tris[(8α)-6′-methoxycinchonan-9(*R*)-ol] arsenite.

$(C_{20}H_{24}N_2O_2)_3AsH_3O_3$=1099.2

CAS — 94138-87-1.

UNII — 42QO5P0NLM.

Profile

Quinine arsenite is a trivalent arsenic compound (see Arsenic Trioxide, p. 2448.1) and may also show toxicity related to its quinine component (p. 665.1).

Homoeopathy

Quinine arsenite has been used in homoeopathic medicines under the following names: Arsénite de quinine; Chininum arsenicosum.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Ger.***: Cefasinu; Dolo-Injektopas; Lycoaktin; Schworocor A; ***Switz.***: Sinfrontal.

Quinine Ascorbate *(USAN)*

Quinina, ascorbato de; Quinine Biascorbate; Аскорбиново-кислый Хинин.

$C_{20}H_{24}N_2O_2.2C_6H_8O_6$=676.7

CAS — 146-40-7.

UNII — KAU4V10S2I.

Profile

Quinine ascorbate is a compound (2 : 1) of ascorbic acid with quinine. It has been used as an ingredient of preparations promoted as smoking deterrents.

Ramatroban *(BAN, rINN)*

BAY-U-3405; EN-137774; Ramatrobán; Ramatrobanum; Раматробан.

(*R*)-3-[3-(4-Fluorophenylsulphonylamino)-1,2,3,4-tetrahydrocarbazol-9-yl]propionic acid.

$C_{21}H_{21}FN_2O_4S$=416.5

CAS — 116649-85-5.

UNII — P1ALI72U6C.

Profile

Ramatroban is a thromboxane A_2 inhibitor that has been used for the treatment of allergic rhinitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Baynas.

Ranibizumab *(BAN, USAN, rINN)*

Ranibizumabum; Ранибицумаб.

Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFAB V2 γ1-chain), disulfide with human-mouse monoclonal rhuFAB V2 κ-chain.

CAS — 347396-82-1.

ATC — S01LA04.

ATC Vet — QS01LA04.

UNII — ZL1R02VT79.

Uses and Administration

Ranibizumab is a recombinant humanised monoclonal antibody fragment related to bevacizumab (p. 747.1). It binds to vascular endothelial growth factor A (VEGF-A), which prevents VEGF-A binding to the receptors VEGFR-1 and VEGFR-2, thereby reducing endothelial cell proliferation, new blood vessel formation (neovascularisation) and vascular leakage. Ranibizumab is used in the treatment of (wet) age-related macular degeneration (AMD) (below), diabetic macular oedema and macular oedema secondary to retinal vein occlusion (see Macular Oedema, below), and pathologic myopia (below)

In AMD and macular oedema secondary to retinal vein occlusion, ranibizumab is given by intravitreal injection into the affected eye in a dose of 500 micrograms once a month. For diabetic macular oedema, UK licensed product information recommends a monthly intravitreal dose of 500 micrograms, but US product information suggests 300 micrograms once a month, stating that the higher dose provides no additional benefit.

For all indications, US product information recommends ongoing monthly treatment. However, for patients with AMD, ranibizumab therapy may be reduced to 1 injection every 3 months after the first 4 injections if monthly treatment is not feasible, although this is not as effective. In contrast, UK product information recommends that treatment should continue only until visual acuity is stable for 3 consecutive monthly assessments. However, treatment should not continue if there has been no improvement of visual acuity over the course of the first 3 injections in patients with macular oedema. After stabilisation, monitoring should continue monthly until loss of visual acuity due to AMD or macular oedema recurs. Monthly ranibizumab treatment should then be restarted and continued until visual acuity is again stable for 3 consecutive monthly assessments. UK information also recommends that the interval between injections should be at least 1 month.

When given with laser photocoagulation for diabetic macular oedema or macular oedema secondary to branch retinal vein occlusion, ranibizumab should be given at least 30 minutes after the photocoagulation.

In pathologic myopia a single intravitreal injection of ranibizumab 500 micrograms is given into the affected eye. If subsequent monitoring shows disease activity, further injections can be given at intervals of no less than one month. Many patients will need only one or two injections in the first year, but some will need more frequent treatment and therefore monitoring should be monthly for the first 2 months and at least every 3 months thereafter during the first year.

Antimicrobial eye drops should be used for 3 days before and 3 days after each injection of ranibizumab.

Age-related macular degeneration. Ranibizumab is given by intravitreal injection in the treatment of (wet) age-related macular degeneration (AMD) (p. 880.2). Vision loss was prevented and mean visual acuity improved in patients given ranibizumab monthly for 2 years compared with patients receiving sham injections.[1] Ranibizumab was also shown to be superior to verteporfin photodynamic therapy after 1 year[2] and 2 years of therapy.[3,4] Open-label extensions of these studies showed that ranibizumab was well tolerated over at least 4 years of treatment.[5] The use of both ranibizumab and photodynamic therapy over 2 years has been reported to be more effective than photodynamic therapy alone.[6,7]

Monthly injection during maintenance therapy has produced the best results for visual acuity in clinical studies. Regular monitoring with flexible but less frequent dosing may be used when a monthly regimen is not possible, but is likely to be less effective.[8]

For results of a comparative study of the use of ranibizumab and bevacizumab in this disease, see Age-related Macular Degeneration, under Bevacizumab, p. 747.2.

1. Rosenfeld PJ, *et al.* for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1419–31.
2. Brown DM, *et al.* for the ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1432–44.
3. Brown DM, *et al.* ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 2009; **116:** 57–65.
4. Bressler NM, *et al.* for the ANCHOR Research Group. Improved vision-related function after ranibizumab vs photodynamic therapy: a randomized clinical trial. *Arch Ophthalmol* 2009; **127:** 13–21.
5. Singer MA, *et al.* HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2012; **119:** 1175–83.
6. Heier JS, *et al.* FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol* 2006; **124:** 1532–42. Correction. *ibid.* 2007; **125:** 138.
7. Antoszyk AN, *et al.* FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. *Am J Ophthalmol* 2008; **145:** 862–74.
8. Mitchell P, *et al.* Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. *Br J Ophthalmol* 2010; **94:** 2–13.

Myopia. Intravitreal injection of ranibizumab has been reported to improve visual acuity in patients with choroidal neovascularisation secondary to pathologic myopia followed up for one[1,2] to 3 years;[3,4] retreatment was performed if monitoring showed persistent or new disease activity.

1. Vadalà M, *et al.* Is ranibizumab effective in stopping the loss of vision for choroidal neovascularisation in pathologic myopia? A long-term follow-up study. *Br J Ophthalmol* 2011; **95:** 657–61.
2. Lorenzo D, *et al.* Intravitreal ranibizumab for choroidal neovascularization secondary to pathological myopia: 12-month follow-up. *Ophthalmologica* 2011; **226:** 103–9.
3. Franqueira N, *et al.* Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. *Ophthalmologica* 2012; **227:** 39–44.
4. Hefner L, *et al.* Three years follow-up results of ranibizumab treatment for choroidal neovascularization secondary to pathologic myopia. *Klin Monbl Augenheilkd* 2013; **230:** 401–4.

Macular oedema. Intravitreal ranibizumab may be used in the treatment of diabetic macular oedema (see Diabetic Eye Disease, p. 464.2). It can improve visual acuity and reduce macular oedema, and retinopathy is less likely to worsen and more likely to improve. The need for laser procedures may also be reduced.[1,2] Monthly doses of 300 and 500 micrograms have produced similar results, but these studies comparing ranibizumab treatment with sham injections for 2 years were not designed to compare the two doses.[1] Ranibizumab appeared to be more effective than laser photocoagulation, but the combination may be no better than ranibizumab alone; follow-up studies are ongoing.[2]

Improved visual acuity and reduced macular oedema were also found in studies of intravitreal ranibizumab given for 6 months to treat macular oedema caused by branch or central retinal vein occlusion.[3-5] Ranibizumab also accelerated the clearance of retinal haemorrhage. However, recurrent or persistent disease was common during subsequent observation, necessitating repeat treatment as required to maintain benefit.[3,4,6]

1. Nguyen QD, *et al.* RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; **119:** 789–801.
2. Frampton JE. Ranibizumab: in diabetic macular oedema. *Drugs* 2012; **72:** 509–23.
3. Brown DM, *et al.* Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology* 2011; **118:** 1594–1602.
4. Campochiaro PA, *et al.* Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology* 2011; **118:** 2041–9.
5. Garnock-Jones KP. Ranibizumab: in macular oedema following retinal vein occlusion. *Drugs* 2011; **71:** 455–63.
6. Heier JS, *et al.* Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology* 2012; **119:** 802–9.

Adverse Effects and Precautions

Ranibizumab is contra-indicated in patients with active or suspected ocular or periocular infections, or active severe intra-ocular inflammation.

Adverse effects relating to the injection procedure include intra-ocular inflammation, endophthalmitis, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Raised intra-ocular pressure has been reported within 60 minutes of injection and patients should be monitored and managed appropriately. Patients should also be monitored for signs of infections for a week after the procedure. Common but less serious ocular adverse effects include red eye, conjunctival or retinal haemorrhage, dry eye, blepharitis, eye pruritus, eye pain, vitreous floaters, eye irritation, increased lachrymation, and the sensation of a foreign body in the eye. Temporary visual disturbances have also been reported and patients should be advised not to drive or operate machinery until these have subsided.

Non-ocular adverse effects that have been reported include headache, nausea, arthralgia, nasopharyngitis, cough, bronchitis, and anaemia. Arterial thromboembolic events are a theoretical possibility following intravitreal use of vascular endothelial growth factor inhibitors. Ranibizumab should not be given concurrently with other inhibitors of vascular endothelial growth factor A (VEGF-A).

References.

1. Schmucker C, *et al.* Intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) for the treatment of age-related macular degeneration: a safety review. *Br J Ophthalmol* 2011; **95:** 308–17.

Effects on the cardiovascular system. Arterial thromboembolic events are a theoretical possibility following intravitreal use of vascular endothelial growth factor inhibitors.

Retrospective cohort studies[1-3] found no association between intravitreal ranibizumab and cardiovascular events such as stroke, myocardial infarction, venous thromboembolism, and congestive heart failure. However, an analysis[4] of data pooled from 5 controlled studies in patients with neovascular (wet) age-related macular degeneration showed trends suggesting an increased risk of cerebrovascular accident in patients given ranibizumab compared with controls. Although the rates of events were small and may have been confounded by other risk factors in this population, the authors concluded that continued monitoring of this risk is warranted.

1. Curtis LH, *et al.* Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol* 2010; **128:** 1273–9. Correction. *ibid.*; 1623.
2. Campbell RJ, *et al.* Stroke rates after introduction of vascular endothelial growth factor inhibitors for macular degeneration: a time series analysis. *Ophthalmology* 2012; **119:** 1604–8.
3. Campbell RJ, *et al.* Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. *BMJ* 2012; **345:** e4203.
4. Bressler NM, *et al.* Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina* 2012; **32:** 1821–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lucentis; ***Austral.***: Lucentis; ***Austria***: Lucentis; ***Belg.***: Lucentis; ***Braz.***: Lucentis; ***Canad.***: Lucentis; ***Chile***: Lucentis; ***Cz.***: Lucentis; ***Denm.***: Lucentis; ***Fr.***: Lucentis; ***Ger.***: Lucentis; ***Gr.***: Lucentis; ***Hong Kong***: Lucentis; ***Indon.***: Lucentis; ***Irl.***: Lucentis; ***Israel***: Lucentis; ***Ital.***: Lucentis; ***Jpn***: Lucentis; ***Malaysia***: Lucentis; ***Neth.***: Lucentis; ***Norw.***: Lucentis; ***NZ***: Lucentis; ***Philipp.***: Lucentis; ***Pol.***: Lucentis; ***Port.***: Lucentis; ***Rus.***: Lucentis (Луцентис); ***S.Afr.***: Lucentis; ***Singapore***: Lucentis; ***Spain***: Lucentis; ***Swed.***: Lucentis; ***Switz.***: Lucentis; ***Thai.***: Lucentis; ***Turk.***: Lucentis; ***UK***: Lucentis; ***Ukr.***: Lucentis (Луцентис); ***USA***: Lucentis.

Rapeseed Oil

Aceite de nabina o navilla; Aceite de semilla de colza; Colza, aceite de; Colza, huile de; Colza Oil; Olej rzepakowy; Oleum Rapae; Rapae oleum; Rape Oil; Rapsų aliejus; Rapsolja; Repceolaj; Rypsiöljy; Řepkový olej; Рапсовое Масло; Сурепное Масло.

UNII — N4G8379626 (rapeseed oil); K168T6Y0YU (fully hydrogenated rapeseed oil).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. *USNF* includes fully hydrogenated rapeseed oil and superglycerinated fully hydrogenated rapeseed oil.

Ph. Eur. 8: (Rapeseed Oil, Refined). The fatty oil obtained from the seeds of *Brassica napus* and *Brassica campestris* by mechanical expression or extraction and then refined. A suitable antoxidant may be added. It contains not more than 2% of erucic acid. A clear light yellow liquid. Practically insoluble in water and in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Protect from light.

USNF 31: (Fully Hydrogenated Rapeseed Oil). A mixture of triglycerides in which the fatty acid composition is a mixture of saturated fatty acids. It is obtained by refining and hydrogenating oil obtained from the seeds of *Brassica napus* and *Brassica campestris*. It contains not more than 1% of erucic acid. A white, waxy solid. Insoluble in water and in alcohol. Store in airtight containers. Protect from light.

USNF 31: (Superglycerinated Fully Hydrogenated Rapeseed Oil). A mixture of mono-, di-, and triglycerides, with triglycerides as a minor component. It is obtained by refining, hydrogenating, and glycerinating oil obtained from the seeds of *Brassica napus* and *Brassica campestris*. It contains not more than 1% of erucic acid. A white solid. Insoluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Rapeseed oil has been used in liniments in place of olive oil. It is used in some countries as an edible oil but the erucic acid ($C_{22}H_{42}O_2$ = 338.6) content of the oil has been implicated in muscle damage. The erucic acid content of oils and fats intended for human consumption and of foodstuffs containing oil or fat is subject to legal control. Contaminated rapeseed oil was the cause of the toxic oil syndrome that affected thousands of Spanish citizens in early 1981; it was associated with rapeseed oil denatured with 2% aniline, although the exact causative agent was never discovered. Refined rapeseed oil with a lower erucic acid content is known as canola oil (see p. 2469.2). Rapeseed oil is also used in industrial manufacturing.

There has been some debate whether the frequency of allergic respiratory symptoms in sensitive individuals is increased in areas in which oilseed rape is cultivated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Gr.***: Fissan-Pate.

Raspberry Leaf

Frambuesa, hoja de; Rubi Idaei Folium; Малиновый Лист.
UNII — 8O2V33JG64.

Profile

Raspberry leaf consists of the dried leaflets of *Rubus idaeus* (Rosaceae). It contains a principle, readily extracted with hot water, which relaxes the smooth muscle of the uterus and intestine of some *animals*.

Raspberry 'tea' has been a traditional remedy for painful and profuse menstruation and for use before and during labour. The infusion has also been used as an astringent gargle.

References.

1. Simpson M, *et al*. Raspberry leaf in pregnancy: its safety and efficacy in labor. *J Midwifery Womens Health* 2001; **46:** 51–9.
2. Holst L, *et al*. Raspberry leaf—should it be recommended to pregnant women? *Complement Ther Clin Pract* 2009; **15:** 204–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Cramplex; ***Cz.***: Detsky Caj s Hermankem; Diabetan; Hypotonicka†; Species Cholagogae Planta†; ***Philipp.***: Completia†.

Red Yeast Rice

Red Rice Yeast; Красный Ферментированный Рис.

Profile

Red yeast rice is the product of fermentation of rice with the red yeast *Monascus purpureus*. It has a long history of use in China as a red food colorant and flavour, and has also been used in traditional Chinese medicine. Red yeast rice contains HMG-CoA reductase inhibitors (mainly lovastatin) and is used as a dietary supplement for hyperlipidaemias. There have been some reports of hepatotoxicity and rhabdomyolysis associated with its use.

References

1. Prasad GV, *et al*. Rhabdomyolysis due to red yeast rice (Monascus purpureus) in a renal transplant recipient. *Transplantation* 2002; **74:** 1200–1.
2. Smith DJ, Olive KE. Chinese red rice-induced myopathy. *South Med J* 2003; **96:** 1265–7.
3. Anonymous. *Monascus purpureus* (red yeast rice). *Altern Med Rev* 2004; **9:** 208–10.
4. Liu J, *et al*. Chinese red yeast rice (*Monascus purpureus*) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. *Chin Med* 2006; **1**: 4. Available at: http://www.cmjournal.org/content/pdf/1749-8546-1-4.pdf (accessed 11/05/09)
5. Mueller PS. Symptomatic myopathy due to red yeast rice. *Ann Intern Med* 2006; **145:** 474–5.
6. Roselle H, *et al*. Symptomatic hepatitis associated with the use of herbal red yeast rice. *Ann Intern Med* 2008; **149:** 516–7.
7. Lapi F, *et al*. Myopathies associated with red yeast rice and liquorice: spontaneous reports from the Italian Surveillance System of Natural Health Products. *Br J Clin Pharmacol* 2008; **66:** 572–4.
8. Becker DJ, *et al*. Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. *Ann Intern Med* 2009; **150:** 830–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Monaless; ***Fr.***: Arterin; Temperol; ***Indon.***: Redaxin†; ***Malaysia***: Hypocol; Lipascor; ***Singapore***: HypoCol; Lipascor.

Multi-ingredient Preparations. ***Fr.***: Arterin Plus.

Relaxin

Relaxina; Релаксин.
CAS — 9002-69-1.

Profile

Relaxin is a polypeptide hormone that has been extracted from the corpus luteum of the ovaries of pregnant sows, although a human recombinant form is also now available. It is reported to be related structurally to insulin and has a molecular weight of about 6000.

Relaxin is secreted by the human corpus luteum during pregnancy and is thought to interact with other reproductive hormones. It acts on connective tissue, including collagen, and causes relaxation of the pubic symphysis and softening of the uterine cervix. In many *animal* species relaxin appears to play a major part in cervical ripening before parturition; significant species difference is shown. It has been studied for cervical ripening in humans. Recombinant human relaxin has also been investigated in infertility, cardiovascular disorders, and scleroderma (p. 1938.3).

References.

1. Seibold JR, *et al*. Safety and pharmacokinetics of recombinant human relaxin in systemic sclerosis. *J Rheumatol* 1998; **25:** 302–7.
2. Seibold JR, *et al*. Recombinant human relaxin in the treatment of scleroderma: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **132:** 871–9.
3. Kelly AJ, *et al*. Relaxin for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester; John Wiley; 2001 (accessed 28/04/06).

Resveratrol

NSC-327430; Ресвератрол; 3,4′,5-Stilbenetriol; 3,4′,5-Trihydroxystilbene.
(E)-5-[2-(4-Hydroxyphenyl)ethenyl]-1,3-benzenediol.
$C_{14}H_{12}O_3$=228.2
CAS — 501-36-0.
UNII — Q369O8926L.

Profile

Resveratrol is a phytoalexin present in a range of plant sources including species of *Arachis*, *Pinus*, *Polygonum*, *Veratrum*, and *Vitis*. It is thought to be one of the compounds responsible for the cardioprotective action of wine (see Grape, p. 2521.3, and Flavonoid Compounds, p. 2505.2).

Resveratrol used in commercial preparations is often derived from the root of Japanese knotweed, *Fallopia japonica* (*Polygonum cuspidatum*; *Reynoutria japonica*) (Polygonaceae) often as the racemate although the *trans*-isomer is also promoted.

Resveratrol is promoted as an antoxidant for the prevention of atherosclerosis. It also has mixed agonist/antagonist activity at oestrogen receptors and some anti-inflammatory and antiproliferative activity, and is under investigation in the prevention and treatment of malignancy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Ultraselem; ***Indon.***: Lecitrol; ***Ital.***: Biogel Resv; Linfoflu; Res Vin†; Resvelife Sole; Resvelife; Sametrix; Skinproject; ***USA***: Alive Mens Energy; Alive Once Daily Womens 50+ Ultra Potency; Alive Womens 50+; ***Venez.***: Uvagen.

Rhamnose

Ramnosa; Ramnoza; L-Rhamnose; Рамноза.
6-Deoxy-L-mannose.
$C_6H_{12}O_5$=164.2
CAS — 3615-41-6.
UNII — QN34XC755A.

Profile

Rhamnose is a monosaccharide used to assess intestinal permeability.

For reference to the use of rhamnose in the differential sugar absorption test, see Diagnosis and Testing under Lactulose, p. 1851.1.

References.

1. van Nieuwenhoven MA, *et al*. The sensitivity of the lactulose/rhamnose gut permeability test. *Eur J Clin Invest* 1999; **29:** 160–5.
2. Haase AM, *et al*. Dual sugar permeability testing in diarrheal disease. *J Pediatr* 2000; **136:** 232–7.
3. van Nieuwenhoven MA, *et al*. Effects of pre- and post-absorptive factors on the lactulose/rhamnose gut permeability test. *Clin Sci* 2000; **98:** 349–53.

Rhatany Root

Krameria; Krameria Root; Ratanhia, racine de; Ratanhiae Radix; Ratanhiagyökér; Ratanhiawurzel; Ratanhový kořen; Ratania, raíz de; Ratanianjuuri; Ratanirot; Ratanijų šaknys; Корень Ратании.
UNII — P29ZH1A35Z.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rhatany Root). The dried, usually fragmented, underground organs of *Krameria triandra*. It contains not less than 5% of tannins, expressed as pyrogallol, calculated with reference to the dried drug. It is known as Peruvian rhatany. Protect from light.

Profile

Rhatany root has astringent properties and is used in herbal preparations for a variety of disorders, including oropharyngeal inflammation.

Homoeopathy

Rhatany root has been used in homoeopathic medicines under the following names: Ratanhia; Krameria triandra; Ratanhiae radix; Ratania peruviana; Ratan.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Parodontax.

Multi-ingredient Preparations. ***Arg.***: Esculeol P; Parodontax Fluor; ***Austria***: Parodontax†; ***Braz.***: Malvatricin Natural Organic†; Parodontax†; ***Ger.***: Ratanhia comp†; Repha-Os†; ***Switz.***: Kernosan Eau Dentifrice†; Prosal N; Sanogencive.

Homoeopathic Preparations. ***Austral.***: Snore Eze; ***Austria***: Haemex; ***Canad.***: Avenoc†; Hylands Hemorrhoids; ***Fr.***: Avenoc; ***Port.***: Avenoc; ***Rus.***: Paeonia-Plus (Пеония-Плюс); ***UK***: Medicinal Gargle.

Pharmacopoeial Preparations
Ph. Eur.: Rhatany Tincture.

Rhus

Sumach Berries; Сумах (*Rhus*); Zumaque.
UNII — RHH784E0K6 (Rhus glabra).

Pharmacopoeias. *Br.* includes Toxicodendron Quercifolium for Homoeopathic Preparations.

BP 2014: (Toxicodendron Quercifolium for Homoeopathic Preparations). Fresh, young, not yet lignified shoots, with leaves, of *Toxicodendron quercifolium*. The shoots contain a yellowish-white milky sap that is a strong cutaneous irritant and darkens the skin. Contact with the skin and mucous membranes is to be avoided.

Profile

Rhus consists of the dried fruits of the smooth or Pennsylvanian sumach, *Rhus glabra* (Anacardiaceae). It has astringent and reputed diuretic properties. *R. aromatica* has been used similarly to *R. glabra*.

Poison ivy (*R. radicans*) and poison oak (*R. toxicodendron*; *Toxicodendron quercifolium*; *T. pubescens*), species growing in the USA, contain irritant poisons, such as urushiol, that produce severe contact dermatitis. Extracts of poison ivy and poison oak have been used for the prophylaxis of poison ivy dermatitis but their efficacy has not been proved. The spice sumac is prepared from the berries of *R. coriaria*.

Homoeopathy

Some *Rhus* spp. have been used in homoeopathic medicines under the following names: Toxicodendron

quercifolium; Rhus toxicodendron; Rhus. tox.; Rhus glabra; Rhus glab; Rhus aromatica; Rhus arom.

References.
1. Gladman AC. *Toxicodendron* dermatitis: poison ivy, oak, and sumac. *Wilderness Environ Med* 2006; **17:** 120–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Hernidisc; Joint & Muscle Cream; ***Canad.***: Cystoforce†; ***Chile***: Rhus Opodeldoc; ***Ger.***: Granu Fink Femina; Rhus-Rheuma-Gel N; ***S.Afr.***: Zeel; Zeel.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Arthritis Relief; Childrens Cold and Flu Relief; Echine†; Homoderma; Joint & Muscle Oral Spray†; Sports Ice Joint & Muscle; ***Austria***: Apozema Allium Cepa compositum; Apozema Apis compositum; Echinacea-Cosmoplex; Globuli gegen Hautausschlage; Ledum Med Complex; Rheuma; Rhus Med Complex; Wirbelsaule- und Gelenkstropfen Nr 2†; ***Canad.***: Arnica-Heel Comp†; Arthritis Pain Formula; Bed Wetting†; Bioactiv E†; Bladder Irritation; Calnor†; Capsicum + Arthri-Cream; Echinacea Compositum; EnurAid; Fibromyalgie; Herpes Soothing Cream; Hyalgesic LBP†; Hylagesic APF; Hylands Formula E; Hylands Kinder-BW; Hylands LCQ; Hylands Leg Cramps; Ivernax; Leg Cramps with Quinine; Poison Ivy/Oak; Rudistrol†; SK Complex†; Zeel Comp; ***Chile***: Apis Compuesto; Arnica Compuesta; Bioactiv E; ***Cz.***: Gelsemium-Homaccord; Zeel Compositum; Zeel Salbe†; ***Fr.***: Abbe Chaupitre no 1†; Abbe Chaupitre no 23†; Abbe Chaupitre no 25†; Abbe Chaupitre no 59†; Abbe Chaupitre no 6; Abbe Chaupitre no 82†; Arthro-Drainol; Boripharm No 1†; Boripharm No 22†; Boripharm No 23; Euphorbium Complexe No 88; Gelsemium Complexe No 70; Homeogene 41†; Hypericum Complexe No 26; Rhus Toxicodendron Complexe No 80; Rhus Toxicodendron Compose; Rudistrol†; ***Ger.***: Alho-Arthrosan N; Araniforce arthro; Arthrorell N; Bomarthros Harpagophytum Complex; Bryorheum N; Cefadolor Arnica Komplex†; Dularell N; Entzundungstropfen; Gelsemium Comp; Gelsemium Comp; Gnaphalium Injektopas SL; Herpes-Gastreu R68; Hewerheum N†; Infi-Symphytum; Intercostal-Gastreu; Lumbago-Gastreu S R11; Lymphaden Complex; Lymphaden; Mato; Neuri-cyl N Ho-Len-Complex; Pyrogenium; Regenaplex Haut G; rheumaloges; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; Rheumeda; Rhus toxicodendron N Oligoplex; Rhustoxicorell; Ruta-Gastreu N R55; Schwoneural N; Trauma SL; Traumakatt; Vertizin; Zeel comp; ***Hung.***: Gelsemium-Homaccord; Zeel; ***Neth.***: Arnilite; Artifleur; Bronchilite; Dulcarhus-Gastreu R11; Entero-Gastreu R4; Enulite; Head Care; Homeocare Exercito; Muscle Care; Prurilite; Red Skin; Restructa H; Rhumeel; Rudistrol†; Skin Care; Spiroflor; Spiroflor; Strain care; Zeel comp N; ***Rus.***: Briacon (Бриакон); Psorilom (Псорилом); Rewma-Gel (Ревма-Гель); Rhus-Plus (Рус-Плюс); Zeel T (Цель Т); ***Switz.***: Lithiumeel; Nelsons Traumatica†; Omida Gel Antirhumatismal; Regenaplex Nr. 31a; Rheuma-Heel; ***UK***: Rheumatica; ***Ukr.***: Reuma-Gel (Ревма-Гель); ***USA***: Preferred Remedies Aches & Pains; Preferred Remedies Fatigue.

Ribonuclease

Ribonucleasa; RNase; Рибонуклеаза.
CAS — 9001-99-4.

Profile

Ribonuclease is an enzyme present in most mammalian tissue, and it is involved in the catalytic cleavage of ribonucleic acid. It has been applied, alone or with other drugs, for its supposed anti-inflammatory properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Cro 50.

Multi-ingredient Preparations. ***Mex.***: Ofzim; Ridasa.

Ribonucleic Acid

ARN; Plant Nucleic Acid; Ribonucleico, ácido; Ribose Nucleic Acid; RNA; Yeast Nucleic Acid; Рибонуклеиновая Кислота.

Profile

Ribonucleic acid (RNA) is a nucleic acid (p. 2573.1) in which the pentose sugar moiety of the nucleotides is ribose, the purine bases are adenine (p. 2430.2) and guanine, and the pyrimidine bases are cytosine and uracil (p. 2637.3). RNA exists as a single polynucleotide strand that replicates using DNA as a template during which process the pairing of bases between the complementary strands of RNA and DNA is always the same: adenine with uracil and cytosine with guanine. RNA is present in cell nuclei and cytoplasm and is directly involved in protein synthesis; it also plays a part in encoding genetic information. RNA also carries the genetic material of RNA viruses. Gene suppression by RNA interference (RNAi), using specific double-stranded ribonucleic acid sequences, is under investigation. For the role of RNA as a tool in gene therapy, see p. 2511.2.

Proprietary preparations containing RNA are marketed in some countries for a variety of asthenic and convalescent conditions. RNA has also been tried in the treatment of mental retardation and to improve memory in senile dementia. It may also have a role in enteral feeds under some circumstances.

Immune RNA (extracted from the spleens and lymph nodes of immunised animals) has been tried in the immunotherapy of hepatitis and cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: AU 4 Regeneresen†; Osteochondrin S†; Regeneresen†; RN13 Regeneresen†; ***Ukr.***: Nucleinas (Нуклеинат).

Multi-ingredient Preparations. ***Arg.***: RNA DNA; ***India***: Placentrex; ***Spain***: Dertrase; Nucleserina; Policolinosil.

Ribwort Plantain

Heinäratamonlehti; Jitrocelový list; Liść babki lancetowatej; Plantaginis Folium; Plantaginis Lanceolatae; Plantaginis Lanceolatae Folium; Plantain Herb; Plantain lancéolé; Siauralapių gysločių lapai; Spitzwegerich; Spitzwegerichblätter; Spitzwegerichkraut; Svartkämparblad.
*ATC Herb — HD02WX5004 (*Plantago lanceolata*: herb); HR05YA5018 (*Plantago lanceolata*: herb); HA01WB5004 (*Plantago lanceolata*: leaf).*
UNII — 2YWL9J7EE8.

Pharmacopoeias. *Eur.* (see p. vii) includes the leaf.

Ph. Eur. 8: (Ribwort Plantain; Plantaginis Lanceolatae Folium). The whole or fragmented, dried leaf and scape of *Plantago lanceolata*. It contains not less than 1.5% of total *ortho*-dihydroxycinnamic acid derivatives expressed as acteoside ($C_{29}H_{36}O_{15}$ = 624.6) with reference to the dried drug. Protect from light.

Profile

Ribwort plantain is an ingredient in herbal remedies used for catarrh and inflammation of the upper respiratory tract. Plantain (*P. major*, *P. asiatica*, or *P. depressa*) is described on p. 2592.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Jitrocelovy; ***Fr.***: Sensivision au plantain; ***Ger.***: Broncho-Sern; Tetesept Husten Saft; Tetesept Husten Tropfen; ***Pol.***: Lancetan; Lanceticum; Plantagen.

Multi-ingredient Preparations. ***Austria***: Brust- und Hustentee St Severin; Grippetee St Severin; Pneumopan†; Scottopect; ***Canad.***: Honey Herb Cough Drops†; Original Herb Cough Drops†; ***Cz.***: Biotussil; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Mucoplant Jitrocelovy; Pruduskova; Pulmoran; Species Pectorales Planta; Thymomel; ***Ger.***: Equisil N†; Kneipp Husten- und Bronchial-Tee†; ***Hung.***: Gombarex; ***Pol.***: Babicum; Bronchial†; Echinasal; Flegatussin†; Gwajatussin; Padma 28; Pectobonisol; Plantifort; Saponarex; ***Rus.***: Eucabal (Эвкабал); Herbion Plantain Syrup (Гербион Сироп Подорожника); Stoptussin-Fito (Стоптуссин-фито); ***Switz.***: Arteria-vita; Nican†; Pastilles bronchiques S; Siropectan; Wala Baume pectoral au plantain; Wala Pulmonium suc contre la toux; ***UK***: Padma Circosan; ***Ukr.***: Eucabal Syrup (Эвкабал Сироп); Herbion Plantaginis Syrup (Гербион Сироп Подорожника); Tussavit (Тусавит).

Ricin

Ricino.
CAS — 9009-86-3.

NOTE. The title ricin is used for the castor seed in *Chin.* and *Fr.*

Profile

Ricin is a lectin present in castor seeds, the seeds of *Ricinus communis* (Euphorbiaceae). It is extremely toxic when given parenterally and the fatal dose by injection has been reported to be around 1 microgram/kg. The toxicity of orally ingested beans depends on how thoroughly they are chewed since the hard seed coat prevents absorption. Ingestion of as few as 3 castor seeds by a child and 4 by an adult may be fatal. Ricin may also be absorbed through abraded skin. It has potential use in aerosol form as an agent of chemical warfare. Toxic effects may be delayed for several days after exposure by any route. Early symptoms include severe gastrointestinal irritation, haemorrhage, vomiting, and diarrhoea, which may result in circulatory collapse. Abnormal liver function tests and pulmonary oedema have been reported. Ophthalmological disturbances ranging from irritation and conjunctivitis to optic nerve damage may occur; miosis and mydriasis have also been reported. Proteinuria, haematuria, and renal impairment may develop and serum creatinine levels may be raised. In severe cases haemolysis of the red blood cells with subsequent acute renal failure may occur. Fatalities due to multi-organ failure have occurred. If the patient presents within 1 hour of ingestion any seeds may be removed by gastric lavage and activated charcoal given. Treatment thereafter is symptomatic.

After expression of the oil from castor seeds (see p. 2472.1), the ricin remaining in the seed cake or 'pomace' is destroyed by steam treatment. The detoxified pomace is used as a fertiliser.

Ricin conjugated with monoclonal or polyclonal antibodies is being studied in the treatment of cancers; zolimomab aritox is an example of such a conjugate. Some of these conjugates have been investigated for various malignancies, particularly leukaemias and lymphomas.

Toxicity. A report of ricin toxicity after partial chewing and ingestion of 10 to 15 castor oil seeds,[1] and reviews[2-4] of ricin toxicity, including its potential as an agent of chemical warfare.

1. Aplin PJ, Eliseo T. Ingestion of castor oil plant seeds. *Med J Aust* 1997; **167:** 260–1.
2. Bradberry SM, *et al.* Ricin poisoning. *Toxicol Rev* 2003; **22:** 65–70.
3. Lord MJ, *et al.* Ricin: mechanisms of cytotoxicity. *Toxicol Rev* 2003; **22:** 53–64.
4. Audi J, *et al.* Ricin poisoning: a comprehensive review. *JAMA* 2005; **294:** 2342–51.

Uses. References to the use of ricin conjugates with monoclonal antibodies in the treatment of cancer.

1. Byers VS, *et al.* Phase I study of monoclonal antibody-ricin A chain immunotoxin XomaZyme-791 in patients with metastatic colon cancer. *Cancer Res* 1989; **49:** 6153–60.
2. Oratz R, *et al.* Antimelanoma monoclonal antibody-ricin A chain immunoconjugate (XMMME-001-RTA) plus cyclophosphamide in the treatment of metastatic malignant melanoma: results of a phase II trial. *J Biol Response Mod* 1990; **9:** 345–54.
3. Anonymous. Application considered for immunotoxin in treatment of graft-vs-host disease. *JAMA* 1991; **265:** 2041–2.
4. Amlot PL, *et al.* A phase I study of an anti-CD22-deglycosylated ricin A chain immunotoxin in the treatment of B-cell lymphomas resistant to conventional therapy. *Blood* 1993; **82:** 2624–33.
5. Senderowicz AM, *et al.* Complete sustained response of a refractory, post-transplantation, large B-cell lymphoma to an anti-CD22 immunotoxin. *Ann Intern Med* 1997; **126:** 882–5.
6. Multani PS, *et al.* Phase II clinical trial of bolus infusion anti-B4 blocked ricin immunoconjugate in patients with relapsed B-cell non-Hodgkin's lymphoma. *Clin Cancer Res* 1998; **4:** 2599–2604.
7. Dinndorf P, *et al.* Phase I trial of anti-B4-blocked ricin in pediatric patients with leukemia and lymphoma. *J Immunother* 2001; **24:** 511–16.
8. Schnell R, *et al.* Clinical evaluation of ricin A-chain immunotoxins in patients with Hodgkin's lymphoma. *Ann Oncol* 2003; **14:** 729–36.
9. Tsimberidou AM, *et al.* Anti-B4 blocked ricin post chemotherapy in patients with chronic lymphocytic leukemia—long-term follow-up of a monoclonal antibody-based approach to residual disease. *Leuk Lymphoma* 2003; **44:** 1719–25.

Ricinoleic Acid

Kwas rycynolowy; Ricinoleico, ácido; Рициноленовая Кислота.
CAS — 141-22-0.
UNII — I2D0F69854.

Profile

Ricinoleic acid is a mixture of fatty acids obtained by the hydrolysis of castor oil. It is an ingredient of some proprietary vaginal jellies used to maintain or restore normal vaginal acidity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Israel***: Glovan; ***USA***: Acid Jelly†.

Rilonacept *(USAN, rINN)*

IL-1 Trap; Interleukin-1 Receptor; Interleukin-1 Trap; Rilonaceptum; Рильонацепт.
CAS — 501081-76-1.
ATC — L04AC04.
ATC Vet — QL04AC04.
UNII — 8K80YB5GMG.

Uses and Administration

Rilonacept is an interleukin-1 blocker used in the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders. Rilonacept is a soluble decoy interleukin-1 receptor that binds interleukin-1β (p. 2533.3) and blocks its actions at cell surfaces.

Rilonacept is given by subcutaneous injection. The solution, when prepared according to the manufacturer's

directions, contains 160 mg per 2 mL and this is the maximum amount that should be given as a single injection or at a single site; if a larger dose is required (as at loading) two separate injections should be given on the same day at two different sites.

The loading dose is 320 mg (as two separate injections). A single injection of 160 mg is then given once weekly. The loading dose for children aged 12 to 17 years is 4.4 mg/kg up to a maximum of 320 mg (given as one or two injections with a maximum single-injection volume of 2 mL). A single injection of 2.2 mg/kg up to a maximum of 160 mg is then given once weekly.

Rilonacept is also under investigation for the treatment of gout.

References.

1. Goldbach-Mansky R, *et al.* A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. *Arthritis Rheum* 2008; **58:** 2432–42.
2. Hoffman HM, *et al.* Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum* 2008; **58:** 2443–52.
3. Terkeltaub R, *et al.* The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. *Ann Rheum Dis* 2009; **68:** 1613–17.

Administration in children. For doses in children aged 12 to 17 years, see p. 2604.3.

Adverse Effects and Precautions

The adverse effects that have been reported most commonly with rilonacept are injection site reactions, headache, sinusitis, and respiratory-tract infections.

Rilonacept has been associated with an increased incidence of serious infections and it should therefore not be given to patients with active or chronic infections. It should be given with caution to patients with a history of recurring infections, or underlying conditions that may predispose them to developing infections. Rilonacept treatment should be stopped in patients who develop severe infections. Patients should be screened for active and latent tuberculosis infection before starting rilonacept treatment. Patients should be up to date with appropriate immunisation schedules, including pneumococcal vaccine and inactivated influenza, before starting treatment with rilonacept. Live vaccines should not be given at the same time as rilonacept unless the benefits clearly outweigh the risks. Giving other interleukin-1 inhibitors or tumour necrosis factor inhibitors at the same time as rilonacept may increase the risk of serious infections. Treatment with immunosuppressants at the same time as rilonacept could theoretically increase the risk of malignancies.

Treatment with rilonacept should not be started in patients with neutropenia, and it is recommended that neutrophil counts should be taken before starting treatment, 1 to 2 months later, and periodically thereafter. Lipid profiles should be monitored in patients taking rilonacept for the treatment of CAPS.

Development of antibodies directed against the receptor domains of rilonacept have been detected in 35% of patients, although it is not clear what effect this might have on efficacy or safety.

Vertigo has been reported with rilonacept treatment, and patients should be advised to avoid driving or operating machinery if this occurs.

Interactions

During inflammation the expression of cytochrome P450 isoenzymes is suppressed by cytokines such as interleukin-1, and cytochrome P450 expression may therefore be normalised when treatment with an interleukin-1 inhibitor such as rilonacept is started. This becomes clinically significant for cytochrome P450 isoenzyme substrates that have narrow therapeutic ratios where the dose has to be individually adjusted (e.g. warfarin). Therefore when starting or stopping therapy with rilonacept, patients being treated with such drugs should be monitored as doses of these drugs may need to be adjusted.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Rilonacept Regeneron†; ***USA***: Arcalyst.

Riluzole *(BAN, USAN, rINN)*

PK-26124; Rilutsoli; Riluzol; Riluzolum; RP-54274; Рилузол.

2-Amino-6-(trifluoromethoxy) benzothiazole; 6-Trifluoromethoxy-1,3-benzothiazol-2-ylamine.

$C_8H_5F_3N_2OS$=234.2

CAS — 1744-22-5.

ATC — N07XX02.

ATC Vet — QN07XX02.

UNII — 7LJ087RS6F.

Pharmacopoeias. In *US.*

USP 36: (Riluzole). A white to slightly yellow powder or crystalline powder. Very slightly soluble in water; freely soluble in alcohol, in acetonitrile, and in dichloromethane; slightly soluble in hexane.

Uses and Administration

Riluzole is a glutamate antagonist used in the management of amyotrophic lateral sclerosis, a form of motor neurone disease. Riluzole is indicated to slow progression of early disease but efficacy has not been shown in its late stages. The precise mechanism of action is unknown but it may inhibit presynaptic glutamate release and interfere with its postsynaptic effects. The usual adult dose of riluzole is 50 mg twice daily given orally on an empty stomach.

Motor neurone disease. Motor neurone disease (motoneuron disease) represents a group of fatal progressive degenerative disorders that affect upper and/or lower motor neurones in the brain and spinal cord. The most common form of motor neurone disease is amyotrophic lateral sclerosis (known in the USA as Lou Gehrig's disease), which involves both upper and lower motor neurones. It produces muscular atrophy and weakness and symptoms of progressive bulbar palsy such as slowness of movement and speech disturbances. Most patients die within 2 to 5 years of disease onset, usually from respiratory failure. There is no completely effective treatment and management remains largely supportive with appropriate symptomatic management of spasticity (p. 2014.2), pain (p. 10.1), and sialorrhoea. Tricyclic antidepressants are widely used for their multiple beneficial effects. Occupational and speech therapy also play a crucial role in maximising function. Pathological crying or laughing (pseudobulbar affect) may occur in as many as 50% of patients and has been treated with amitriptyline or fluvoxamine. Dysphagia may eventually compromise food and fluid intake necessitating enteral nutrition as an alternative or supplemental route for oral nutrition. Respiratory support will ultimately be necessary, initially with non-invasive ventilation but progressing eventually to tracheostomy.

Although the pathogenesis of motor neurone disease is still uncertain, it is thought that accumulation of the excitatory neurotransmitter glutamate in the CNS may be involved. Clinical studies have shown riluzole, a glutamate antagonist, to be modestly effective in prolonging survival by an average of 3 months and delaying the time to use of tracheostomy. However, there are still insufficient data to be able to assess which patients would derive greatest benefit. Additionally, questions have been raised about the clinical usefulness of riluzole in terms of cost-benefit, and there are concerns about adverse effects, notably hepatotoxicity.

Also under study for the treatment of motor neurone disease are somatomedins, in particular mecasermin (insulin-like growth factor I). Neurotrophic factors have been investigated including brain-derived neurotrophic factor (BDNF) and recombinant ciliary neurotrophic factor (CNTF), but results have been generally inconclusive. Glial-cell-derived neurotrophic factor (GDNF) and xaliproden are under investigation.

There has been some interest in the antiepileptic drug gabapentin, which may inhibit glutamate formation in the CNS from branched-chain amino acids. Lamotrigine and topiramate have also been tried but with disappointing results. ONO-2506 is an enantiomeric homologue of valproate that is also under investigation. Dextromethorphan has been studied in amyotrophic lateral sclerosis. Minocycline has shown neuroprotective effects in *animal* studies and is therefore also being studied in this condition; ceftriaxone is also under investigation. Immunoglobulins have been tried in some forms of motor neurone disease such as multifocal motor neuropathy.

Antoxidants, including vitamins C and E, are commonly used by patients in the belief that one mechanism for neuronal death is free radical accumulation resulting from oxidative stress. However, despite substantial literature on the subject and widespread use of antoxidants, significant evidence to support their benefit in motor neurone disease is lacking. Creatine supplements have been tried in a bid to preserve motor function and motor neurones, although benefit has not been shown in controlled studies.

A small percentage of patients with familial amyotrophic lateral sclerosis has been shown to have a mutation in the gene encoding for the enzyme copper-zinc superoxide dismutase but there has been no consensus as to whether patients with this mutation should be given superoxide dismutase supplements.

References.

1. Ludolph AC, Riepe MW. Do the benefits of currently available treatments justify early diagnosis and treatment of amyotrophic lateral sclerosis? — Arguments against. *Neurology* 1999; **53** (suppl 5): S46–S49.
2. Cashman NR. Do the benefits of currently available treatments justify early diagnosis and announcement? — Arguments for. *Neurology* 1999; **53** (suppl 5): S50–S52.
3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; **344:** 1688–1700.
4. Dib M. Amyotrophic lateral sclerosis: progress and prospects for treatment. *Drugs* 2003; **63:** 289–310.
5. Leigh PN, *et al.* The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* 2003; **74** (suppl 4): iv32–iv47.
6. Ashworth NL, *et al.* Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 28/04/06).
7. Choudry RB, Cudkowicz ME. Clinical trials in amyotrophic lateral sclerosis: the tenuous past and the promising future. *J Clin Pharmacol* 2005; **45:** 1334–44.
8. Traynor BJ, *et al.* Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; **67:** 20–7.
9. Miller RG, *et al.* Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
10. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis or motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
11. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet* 2007; **369:** 2031–41.
12. Mitsumoto H, Rabkin JG. Palliative care for patients with amyotrophic lateral sclerosis: prepare for the worst and hope for the best. *JAMA* 2007; **298:** 207–16.
13. McDermott CJ, Shaw PJ. Diagnosis and management of motor neurone disease. *BMJ* 2008; **336:** 658–62.
14. Corcia P, Meininger V. Management of amyotrophic lateral sclerosis. *Drugs* 2008; **68:** 1037–48.
15. Miller RG, *et al.* The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; **73:** 1218–26.
16. Miller RG, *et al.* The care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; **73:** 1227–33.

Movement disorders. Beneficial results have been obtained with riluzole in small studies of patients with Huntington's chorea.[1,2] Riluzole has been tried in a small number of patients with early Parkinson's disease but no evidence of benefit was seen.[3] It has also been tried in levodopa-induced dyskinesias in advanced Parkinson's disease with conflicting reports of benefit[4] or no benefit.[5] Riluzole has shown promise as potential symptomatic therapy for cerebellar ataxia in an 8-week study in a small number of patients.[6]

1. Rosas HD, *et al.* Riluzole therapy in Huntington's disease (HD). *Mov Disord* 1999; **14:** 326–30.
2. Huntington Study Group. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. *Neurology* 2003; **61:** 1551–6.
3. Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* 2002; **8:** 271–6.
4. Merims D, *et al.* Riluzole for levodopa-induced dyskinesias in advanced Parkinson's disease. *Lancet* 1999; **353:** 1764–5.
5. Braz CA, *et al.* Effect of riluzole on dyskinesia and duration of the ON state in Parkinson disease patients: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol* 2004; **27:** 25–9.
6. Ristori G, *et al.* Riluzole in cerebellar ataxia: a randomized, double-blind, placebo-controlled pilot trial. *Neurology* 2010; **74:** 839–45.

Psychiatric disorders. Glutamate is implicated in the aetiology of various psychiatric disorders and consequently riluzole has been suggested as a potential treatment in view of its glutamate-modulating properties.

Reviews.

1. Pittenger C, *et al.* Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs* 2008; **22:** 761–86.
2. Zarate CA, Manji HK. Riluzole in psychiatry: a systematic review of the literature. *Expert Opin Drug Metab Toxicol* 2008; **4:** 1223–34.

Adverse Effects and Treatment

Adverse effects associated most commonly with riluzole are asthenia, nausea, elevations in liver enzyme values, headache, and abdominal pain. Other gastrointestinal effects may include diarrhoea or constipation, anorexia, and vomiting. There may be tachycardia, dizziness, vertigo, or somnolence. Circumoral paraesthesia and rhinitis may occur. Lung function may be decreased and cases of interstitial lung disease, sometimes severe, have been reported. Anaphylactoid reactions, angioedema, pancreatitis, and neutropenia have all been reported rarely.

Effects on the blood. Severe neutropenia has been reported[1] in a 71-year old patient with amyotrophic lateral sclerosis receiving standard doses of riluzole. The neutrophil count returned to normal on cessation of riluzole.

See also under Overdosage, p. 2606.1.

1. Weber G, Bitterman H. Riluzole-induced neutropenia. *Neurology* 2004; **62:** 1648.

Effects on the kidneys. A 44-year-old patient developed renal tubular impairment 3 months after starting riluzole

for amyotrophic lateral sclerosis.[1] Tubular function recovered 1 month after stopping riluzole.

1. Poloni TE, *et al.* Renal tubular impairment during riluzole therapy. *Neurology* 1999; **52:** 670.

Effects on the liver. Icteric toxic hepatitis, with jaundice and elevated liver enzyme values, has been reported[1] in an elderly woman receiving riluzole for amyotrophic lateral sclerosis (ALS). Acute hepatitis developed in 2 patients several weeks after starting therapy with riluzole for ALS.[2] Liver histology showed hepatocellular damage with inflammatory infiltration and microvesicular steatosis without fibrosis. Hepatotoxicity was reversed in all these cases when riluzole was stopped.

1. Castells LI, *et al.* Icteric toxic hepatitis associated with riluzole. *Lancet* 1998; **351:** 648.
2. Remy A-J, *et al.* Acute hepatitis after riluzole administration. *J Hepatol* 1999; **30:** 527–30.

Effects on the pancreas. Riluzole was cited[1] as the most likely cause of severe pancreatitis that developed in a 77-year-old woman 6 months after starting therapy for sporadic amyotrophic lateral sclerosis; pancreatic symptoms improved when riluzole was stopped.

1. Drory VE, *et al.* Riluzole-induced pancreatitis. *Neurology* 1999; **52:** 892–3.

Hypersensitivity. A severe life-threatening systemic inflammatory reaction occurred in a patient 2 weeks after starting treatment with riluzole for amyotrophic lateral sclerosis.[1] Symptoms resolved spontaneously on stopping riluzole.

1. Sorenson EJ. An acute, life-threatening, hypersensitivity reaction to riluzole. *Neurology* 2006; **67:** 2260–1.

Overdosage. Severe neutropenia developed in a 63-year-old woman receiving riluzole for amyotrophic lateral sclerosis 10 days after inadvertent dose increase to 200 mg daily (twice the standard recommended dose).[1]

Methaemoglobinaemia has been reported[2] in a 43-year-old patient with amyotrophic lateral sclerosis after intentional overdose with 2.8 g of riluzole. The patient was treated with gastric lavage followed by activated charcoal; intravenous methylthioninium chloride successfully reversed the methaemoglobinaemia. However, the patient died of respiratory failure related to her underlying disease 7 days after the overdose.

An amnesic syndrome that persisted for over a year developed in a woman 4 days after ingestion of 3 g of riluzole.[3]

1. North WA, *et al.* Reversible granulocytopenia in association with riluzole therapy. *Ann Pharmacother* 2000; **34:** 322–4.
2. Viallon A, *et al.* Methemoglobinemia due to riluzole. *N Engl J Med* 2000; **343:** 665–6.
3. Haaxma CA, *et al.* Delayed amnesic syndrome after riluzole autointoxication in Huntington disease. *Neurology* 2006; **66:** 1123–4.

Precautions

Riluzole is contra-indicated in patients with hepatic disease or markedly raised liver enzyme values. Liver function tests should be performed before and throughout treatment with riluzole. In the UK, riluzole is not recommended in patients with renal impairment although US licensed product information states that the pharmacokinetics are not significantly different in renal impairment. Caution should be exercised in those with a history of liver disorders. Patients or their carers should be told how to recognise signs of neutropenia and should be advised to seek immediate medical attention if symptoms such as fever develop; white blood cell counts should be determined in febrile illness and riluzole stopped if neutropenia occurs. Patients who develop respiratory symptoms such as dyspnoea or dry cough should have chest radiography, and in cases suggestive of interstitial lung disease, riluzole should be discontinued immediately. Riluzole may cause dizziness or vertigo and patients should be warned not to drive or operate machinery if these symptoms occur.

Riluzole has been reported to impair fertility in *animals*.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies riluzole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Riluzole is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur in 1 to 1½ hours. The rate and extent of absorption are decreased when riluzole is given with a high-fat meal. Riluzole is widely distributed throughout the body and is about 97% bound to plasma proteins. It crosses the blood-brain barrier. Riluzole is extensively metabolised to several metabolites in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2, and subsequent glucuronidation. Riluzole is excreted mainly in the urine, mainly as glucuronides, with an elimination half-life of about 9 to 15 hours. About 2% is excreted unchanged in the urine. Small amounts are excreted in faeces. There is some evidence that clearance of riluzole is reduced in Japanese patients.

References.

1. Le Liboux A, *et al.* Single- and multiple-dose pharmacokinetics of riluzole in white subjects. *J Clin Pharmacol* 1997; **37:** 820–7.
2. Le Liboux A, *et al.* A comparison of the pharmacokinetics and tolerability of riluzole after repeat dose administration in healthy elderly and young volunteers. *J Clin Pharmacol* 1999; **39:** 480–6.
3. Groeneveld GJ, *et al.* Riluzole serum concentrations in patients with ALS: associations with side effects and symptoms. *Neurology* 2003; **61:** 1141–3.
4. van Kan HJ, *et al.* Association between CYP1A2 activity and riluzole clearance in patients with amyotrophic lateral sclerosis. *Br J Clin Pharmacol* 2005; **59:** 310–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rilasat; Rilutek; Rizol; ***Austral.***: Rilutek; ***Austria***: Rilutek; ***Belg.***: Rilutek; ***Braz.***: Rilutek; ***Canad.***: Rilutek; ***Chile***: Rilutek; ***China***: Rilutek; Xie Yi Li (协一力); ***Cz.***: Rilutek; Sclefic; ***Denm.***: Lizolorol†; Rilutek; ***Fin.***: Rilutek; ***Fr.***: Rilutek; ***Ger.***: Rilutek; ***Gr.***: Rilutek; ***Hong Kong***: Rilutek; ***Hung.***: Rilutek; ***Irl.***: Rilutek; ***Israel***: Rilutek; ***Ital.***: Rilutek; ***Jpn***: Rilutek; ***Mex.***: Rilutek; ***Neth.***: Glentek; Lizorolol; Rilutek; ***Norw.***: Rilutek; ***NZ***: Rilutek; ***Pol.***: Rilutek; ***Port.***: Rilutek; ***S.Afr.***: Rilutek†; ***Singapore***: Rilutek; ***Spain***: Rilutek; ***Swed.***: Rilutek; ***Switz.***: Rilutek; ***Thai.***: Rilutek; ***Turk.***: Rilutek; ***UK***: Rilutek; ***Ukr.***: Borizol (Боризол); Rilutek (Рілутек); ***USA***: Rilutek; ***Venez.***: Rilutek.

Pharmacopoeial Preparations

USP 36: Riluzole Tablets.

Rimonabant *(USAN, rINN)*

Rimocaban; Rimonabantum; SR-141716; Римонабант.

5-(*p*-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide.

$C_{22}H_{21}Cl_3N_4O$=463.8

CAS — 168273-06-1 (rimonabant); 158681-13-1 (rimonabant hydrochloride).

ATC — A08AX01.

ATC Vet — QA08AX01.

UNII — RML78EN3XE.

Profile

Rimonabant is a selective cannabinoid type-1 receptor antagonist that has been used as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m^2), and also for overweight patients (BMI > 27 kg/m^2) who have associated risk factors such as type 2 diabetes mellitus or dyslipidaemia. Oral doses of 20 mg daily before breakfast have been used. However, after concern about psychiatric reactions marketing of rimonabant was withdrawn in Europe in January 2009.

Nausea, anxiety, and dizziness occur commonly with rimonabant. Depressive symptoms have also occurred and rimonabant should not be given to patients with major depression or to those being treated with antidepressants; it is also not recommended in patients with other uncontrolled serious psychiatric disorders. Since rimonabant is metabolised by the liver, caution is advised in patients with moderate hepatic impairment. Licensed product information does not recommend its use in patients with severe hepatic or renal impairment because of lack of data in these patient groups. Plasma concentrations of rimonabant are increased when given with ketoconazole; other CYP3A4 inhibitors might have the same effect.

Rimonabant has also been investigated as an aid for smoking cessation.

The action and potential uses of rimonabant have been reviewed.[1-5] Rimonabant is a selective cannabinoid type-1 receptor antagonist that reduces the overactivity of the endocannabinoid (endogenous cannabinoid) system. Studies of rimonabant *in vitro* and in *animals* have shown that it inhibits the proliferation and maturation of adipocytes, improves lipid and glucose metabolism, and regulates food intake and energy balance.[1,3,4]

Four large multicentre randomised controlled studies have been carried out to examine the effects of rimonabant in obesity (RIO) used with a mildly hypocalorific diet (deficit of about 600 kcal/day),[6-9] and all studies showed that rimonabant was of benefit when given at a dose of 20 mg daily. A significant decrease in body-weight and waist circumference was reported from the RIO-Europe study[6] over 1 year, although results from the RIO-North America study[7] conducted over 2 years were more modest; both studies also showed improvement in cardiovascular risk factors. The RIO-Lipids study[8] examined the effects of rimonabant over 1 year in overweight or obese patients with untreated dyslipidaemias and noted improvement in several metabolic risk factors as well as weight loss. Similar results including improvement in plasma-glucose concentrations (as indicated by glycosylated haemoglobin measurements) were obtained in overweight or obese patients with type 2 diabetes mellitus given rimonabant over 1 year in the RIO-Diabetes study.[9] Meta-analysis[10] and systematic review[11] of the 4 studies in the RIO-programme agreed that rimonabant produced statistically greater weight loss than placebo, although some problems with methodology were noted. Since no follow-up data were reported, no conclusion could be reached about weight regain.[10] Of particular concern was the increase in incidence of psychiatric adverse effects such as depression and anxiety in the treatment group, and postmarketing experience in this respect eventually led to withdrawal of marketing authorisation in the EU because it was considered that the risks outweigh the benefits (see above).[10]

Two cases of atrial fibrillation associated with the use of rimonabant in overweight patients have recently been reported.[12]

Rimonabant has also been studied as an aid to smoking cessation but a systematic review[13] of randomised controlled studies concluded that although rimonabant 20 mg daily may be of benefit in stopping smoking, the evidence in maintaining abstinence is inconclusive.

1. Boyd ST, Fremming BA. Rimonabant—a selective CB1 antagonist. *Ann Pharmacother* 2005; **39:** 684–90.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acomplia; Resibant; ***Austria***: Acomplia†; ***Belg.***: Acomplia†; ***Cz.***: Acomplia†; Zimulti†; ***Denm.***: Acomplia†; ***Fr.***: Acomplia†; ***Gr.***: Acomplia†; ***Hong Kong***: Acomplia†; ***Israel***: Acomplia†; ***Ital.***: Acomplia†; ***Neth.***: Zimulti†; ***Norw.***: Acomplia†; ***Port.***: Zimulti†; ***Rus.***: Zimulti (Зимулти); ***Swed.***: Acomplia†; ***Switz.***: Acomplia†; ***UK***: Acomplia†.

Rociverine *(rINN)*

LG-30158; Rociverina; Rocivérine; Rociverinum; Роциверин.

2-Diethylamino-1-methylethyl *cis*-1-hydroxy(bicyclohexyl)-2-carboxylate.

$C_{20}H_{37}NO_3$=339.5

CAS — 53716-44-2.

ATC — A03AA06.

ATC Vet — QA03AA06.

UNII — VI08KS44V0.

Profile

Rociverine is an antispasmodic that has been given orally in doses of 30 to 40 mg or rectally in doses of 50 to 75 mg daily. It has also been given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Rilaten (里拉通); ***Ital.***: Rilaten.

Rose Bengal Sodium

CI Acid Red 94; Colour Index No. 45440; Rosa de bengala sódico; Rose Bengal; Sodium Rose Bengal; Бенгальский Розовый.

The disodium salt of 4,5,6,7-tetrachloro-2′,4′,5′,7′-tetraiodofluorescein .

$C_{20}H_2Cl_4I_4Na_2O_5$=1017.6

CAS — 11121-48-5 (rose bengal); 632-69-9 (rose bengal disodium).

ATC — S01JA02.

ATC Vet — QS01JA02.

UNII — 956575SN5L.

NOTE. The name Rose Bengale has been applied to the substance described in this monograph as well as to dichlorotetraiodofluorescein (CI Acid Red 93; Ext. D & C Reds Nos. 5 and 6; Colour Index No. 45435), a compound used as its disodium or dipotassium salt as a colouring agent.

ROS is a code approved by the BP 2014 for use on single unit doses of eye drops containing rose bengal sodium where the individual container may be too small to bear all the appropriate labelling information.

Profile

Rose bengal sodium stains devitalised conjunctival and corneal epithelial cells as well as mucus and is used as an aid in the diagnosis of dry eye. It is used to detect or assess ocular damage resulting from Sjögren's syndrome or from ill-fitting contact lenses, and for keratitis, squamous cell carcinomas, and detection of foreign bodies. Rose bengal sodium is applied as 1% eye drops or as sterile papers impregnated with the dye.

Instillation of this dye may be painful, especially in dry eyes. Rose bengal sodium can stain skin, clothing, and soft contact lenses. Rose bengal sodium should not be used before taking swabs as it possesses some antiviral activity.

Rose bengal sodium is taken up by the liver and excreted in the bile; the iodine-131-labelled compound (p. 2226.1) has been used as a diagnostic aid in the determination of hepato-biliary function.

Reviews.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Ak-Rose; ***USA***: Rosets†.

Rose Fruit

Brier Fruit; Csipkerózsa áltermés; Cynorrhodon; Cynosbati Fructus; Cynosbati Pseudofructus; Dog Rose Fruits; Églantier; Erškėčių vaisiai; Escaramujo; Escarbaculo; Hips; Hypanthium Rosae; Nypon; Rosae Fructus; Rosae Pseudo-fructus; Rosal montés; Rose Hips; Ruusunmarja; Šípek; Tapaculo; Плод Шиповника.

ATC Herb — HA11WA5004 (Rosa canina: pseudofruit); HR05YA5020 (Rosa canina: pseudofruit); HM01AW5016 (Rosa canina: fruit); HG04BW5029 (Rosa canina: fruit).

UNII — 3TNW8D08V3 (Rosa canina fruit).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Dog Rose). The rose hips made up by the receptacle and the remains of the dried sepals of *Rosa canina, R. pendulina*, and other *Rosa* spp., with the achenes removed. It contains not less than 0.3% of ascorbic acid, calculated with reference to the dried drug. Protect from light.

Profile

The fruits of various *Rosa* species, in particular the dog rose, *R. canina*, are used as a source of vitamin C (p. 2110.3). Rose fruit is included in herbal preparations for constipation and urinary-tract disorders. It has also been tried in osteoarthritis and rheumatoid arthritis.

Osteoarthritis. An evidence-based report[1] by the Arthritis Research Campaign in the UK considered that rose fruit was safe and possibly effective in improving some of the symptoms associated with osteoarthritis of the knee or hip. Others[2] have also noted benefit. GOPO((2*S*)-1,2-di-*O*-[(9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienoyl]-3-*O*-β-D-galactopyranosyl glycerol), a galactolipid isolated from rose fruit, is claimed by one manufacturer to be the active anti-inflammatory agent.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: I-Flex; ***Rus.***: Cholemax (Холемакс); Cholos (Холос); Cholosas (Холосас); ***UK***: LitoZin; ***Ukr.***: Cholosas (Холосас).

Multi-ingredient Preparations. ***Arg.***: Vitamina C-Complex; ***Austral.***: Bio C; Calporo†; Flavons†; Hair Skin & Nails; Mega C†; Neo C; Super Cal C†; Sustained Release C; Tresos B PluSe; ***Austria***: Aktivanad; Amersan; ***Canad.***: Floradix Kindervital†; Floradix Tab†; Rose Hips C; ***Chile***: Calcio 520; Natursel-C; Propolkit; Reduc-Te; Romox-ARL; ***Cz.***: Amersan; Pruduskova; ***Fr.***: Hydracur; ***Hung.***: Kilo-Nit; ***India***: Britesite; Marc Free; Ophthacare; ***Ital.***: Angiorex Complex; Cistefi; Gemiol Plus; Golapiol C; Longevital; Nepiros; ***Malaysia***: Nat-C†; ***Philipp.***: Delrosa; ***Pol.***: Cholesol; Diabetofort; Diges-Tonic; Echinasal; Sedomix; Tiliros; ***Rus.***: Arfazetin-E (Арфазетин-Э); Bronchicum Husten (Бронхикум Сироп от Кашля)†; Brusniver (Бруснивер); Evalar (Эвалар); Kliophyt (Клиофит); Phyto Novo-Sed (Фито Ново-Седа); ***Singapore***: Nat-C; Silence; ***Switz.***: Silence; Tisane contre les refroidissements; ***Thai.***: Blackmores Bio C; Blackmores Naturetime Buffered C; Nat C; ***UK***: GlucOsamax; Top C; ***USA***: Amino-Opti-C; C Factors "1000" Plus; Ester-C Plus Multi-Mineral; Ester-C Plus; ***Venez.***: Ro-C-Var.

Rose Oil

Attar of Rose; Esencia de Rosa; Oleum Rosae; Otto of Rose; Rosa, aceite esencial de; Розовое Масло.

UNII — WUB68Y35M7 (rose oil); FF1Y064QVO (Rosa alba flower oil); H32V31VMWY (Rosa centifolia flower oil); 18920M3T13 (Rosa damascena flower oil); B3Y66352HF (Rosa gallica flower oil).

Pharmacopoeias. In *USNF*.

USNF 31: (Rose Oil). A volatile oil distilled with steam from the fresh flowers of *Rosa gallica, R. damascena, R. alba, R. centifolia*, and varieties of these species (Rosaceae). It is a colourless or yellow liquid, having the characteristic odour of rose. At 25 degrees it is a viscous liquid. On gradual cooling, it changes to a translucent, crystalline mass, easily liquefied by warming. Miscible with an equal volume of chloroform. Store in well-filled airtight containers.

Profile

Rose oil is largely employed in perfumery and toilet preparations and has been used as a flavour. It is also used in aromatherapy. It contains citronellol. Hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Estri-Atlas; ***Chile***: Cicapost; Estri-Atlas; ***India***: Artrex; ***Port.***: Cicapost.

Homoeopathic Preparations. ***Ger.***: Aurum/Lavandula comp..

Pharmacopoeial Preparations
USNF 31: Stronger Rose Water;
USP 36: Rose Water Ointment.

Rosemary

Romarin; Romarin (rosemary leaf); Roris Marini; Rosmariininlehti (rosemary leaf); Rosmarin; Rosmarinblad (rosemary leaf); Rosmarini folium (rosemary leaf); Rozmarinų lapai (rosemary leaf); Rozmaringlevél (rosemary leaf); Rozmarýnový list (rosemary leaf); Розмарин.

ATC Herb — HP03BX5006 (Rosmarinus officinalis: leaf); HA03AW5052 (Rosmarinus officinalis: leaf); HA05AW5015 (Rosmarinus officinalis: leaf); HG04BW5030 (Rosmarinus officinalis: leaf); HN05CM5024 (Rosmarinus officinalis: leaf); HD03WX5015 (Rosmarinus officinalis: leaf).

UNII — IJ67X351P9.

NOTE. The name Wild Rosemary has been applied to the unrelated plant, Marsh Tea (p. 2550.1).

Pharmacopoeias. *Eur.* (see p. vii) includes the dried leaf.

Ph. Eur. 8: (Rosemary Leaf; Rosmarini Folium). The whole, dried leaf of *Rosmarinus officinalis*. It contains not less than 1.2% v/w of essential oil and not less than 3% of total hydroxycinnamic derivatives, expressed as rosmarinic acid ($C_{18}H_{16}O_8$ = 360.3) both with reference to the anhydrous drug.

Profile

Rosemary (*Rosmarinus officinalis*, Lamiaceae) has rubefacient and mild analgesic activity when applied topically, and is included in external preparations for rheumatic and circulatory disorders. It is also reported to have carminative, spasmolytic, and diuretic effects and is included in herbal preparations for gastrointestinal, cardiovascular, and urinary-tract disorders.

Rosemary is a source of rosemary oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Alrinte.

Multi-ingredient Preparations. ***Arg.***: Acnetrol; Acnetrol; Albion; Sequals G; ***Austral.***: Avena Complex†; Bacopa & Ginkgo Compound; Garlic Allium Complex; LivCo; Vitanox; ***Austria***: Euka; ***Belg.***: Cynactil; ***Canad.***: Optomega; Phyto-Marinex; Salusan†; ***Chile***: Rhus Opodeldoc; Romox-ARL; ***Fr.***: Aromadetox†; Boldoflorine; Boldoflorine; Boribel Tisane No 7†; Boribel Tisane No 9; Calmiflorine†; Depuratum; Hepato-Solutines†; Hepatoflorine†; Kotor Articulations; Mediflor Contre la Constipation Passagere No 7; Mediflor Digestive No 3; Mediflor Hepatique No 5; Romarene†; Santane F_{10}†; Santane O1; Santane R_8†; ***Ger.***: Canephron N; Melissengeist; ***Mex.***: Norex; ***Mon.***: Romarinex Chrome; Romarinex; ***Pol.***: Cardiactiv; Doppelherz Energovital Tonik K; ***Rus.***: Canephron N (Канефрон Н); ***Spain***: Linimento Naion; Resolutivo Regium†; ***Switz.***: Metabol; ***UK***: Cystipret; Outlook; ***Ukr.***: Canephron N (Канефрон Н); Fitoval Shampoo Anti-Hair Loss (Фитовал шампунь против выпадения волос); Memory Booster (Мемори Бустер); Vitrum Beauty Elite (Витрум Бьюти Элит); ***Venez.***: Flocadep.

Homoeopathic Preparations. ***Ger.***: Levisticum S; ***Rus.***: Dysmenorm (Дисменорм); ***Ukr.***: Dysmenorm (Дисменорм.).

Rosemary Oil

Esencia de Romero; Essence de Romarin; Essência de Alecrim; Oleum Roris Marini; Oleum Rosmarini; Romarin, huile essentielle de; Romero, aceite esencial de; Rosmariiniöljy; Rosmarini aetheroleum; Rosmarini Etheroleum; Rosmariniöl; Rosmarinolja; Rozmarinų eterinis aliejus; Rozmaringolaj; Rozmarýnová silice; Розмариновое Масло.

ATC Herb — HA03AW5051 (Rosmarinus officinalis: essential oil); HM02AW5018 (Rosmarinus officinalis: essential oil).

UNII — 8LGU7VM393.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rosemary Oil). The essential oil obtained by steam distillation from the flowering aerial parts of *Rosmarinus officinalis*. It is available as Spanish type rosemary oil and Moroccan and Tunisian type rosemary oil. Spanish type rosemary oil contains 2.0 to 4.5% borneol, 0.5 to 2.5% bornyl acetate, 8.0 to 12.0% camphene, 13.0 to 21.0% camphor, 16.0 to 25.0% cineole, 1.0 to 2.2% *p*-cymene, 2.5 to 5.0% limonene, 1.5 to 5.0% β-myrcene, 18 to 26% α-pinene, 2.0 to 6.0% β-pinene, 1.0 to 3.5% α-terpineol, and 0.7 to 2.5% verbenone. Moroccan and Tunisian type rosemary oil contains 1.5 to 5.0% borneol, 0.1 to 1.5% bornyl acetate, 2.5 to 6.0% camphene, 5.0 to 15.0% camphor, 38.0 to 55.0% cineole, 0.8 to 2.5% *p*-cymene, 1.5 to 4.0% limonene, 1.0 to 2.0% β-myrcene, 9.0 to 14.0% α-pinene, 4.0 to 9.0% β-pinene, 1.0 to 2.6% α-terpineol, and a maximum of 0.4% verbenone.

A clear, mobile, colourless to pale yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Rosemary oil is carminative and mildly irritant. It is used in perfumery and as a flavour and has been employed in hair lotions, inhalations, and liniments. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Rosapinol†.

Multi-ingredient Preparations. ***Austral.***: Accelerex painEASE; Accelerex painEASE; Bacopa Complex; Bio-Oil; Bosisto's Vaporising Ointment†; Euky Bearub; Vicks Baby Balsam; ***Austria***: Berggeist; Carl Baders Divinal; Opino; Rheuma; Rowalind; ***Belg.***: Perubore†; Pulmex Baby; Pulmex†; ***Braz.***: Aliviol; Benegel; Gelflex; Nevrol†; ***Canad.***: Restorativ Glucosamine Muscle and Joint; ***Chile***: Agua del Carmen; Agua Melisa Carminativa; Lefkaflam; ***Cz.***: Thrombocid; ***Fr.***: Aromadetox†; Aromadigest†; Aromasol; Esculape†; Maghora†; Olioseptil Nez-Gorge; Perubore; Veino Gomenol; ***Ger.***: Cor-Vel; Dolo-cyl†; Hingfong-Essenz Hofmanns; polio-elan†; Poly-elan; Retterspitz Ausserlich; Retterspitz Quick Muskel; Rheuma Bad†; Rheuma- und Schmerzsalbe; Thrombocid; Weleda Bronchialbalsam; Weleda-Rheumasalbe M†; ***Gr.***: Ilon; Opino; ***Hung.***: Inno Rheuma Forte; Inno Rheuma; Inno Rheuma; Pasta Cool; Pulmex Baby; Pulmex; Rosarthron; ***Indon.***: Opino†; ***Irl.***: Massage Balm with Arnica; ***Ital.***: Calyptol; Cinarepa; Neuralta Migren; Valda Propoli†; ***Malaysia***: Bio-Oil; ***Mon.***: Calyptol; ***NZ***: Electric Blue Headlice; Tixylix Chest Rub; Vicks Baby Balsam; ***Pol.***: Argol Rheuma; Aromagel†; Aromatol Hot Gel; Depulol; Doppelherz Energovital Tonik†; Pulmex Baby; ***Port.***: Thrombocid; ***Rus.***: Carmolis Fluid (Кармолис Жидкость); Doppelherz Energotonik (Доппельгерц Энерготоник); Pulmex (Пульмекс)†; Pulmex Baby (Пульмекс Бэби); Theraflu Bro (Терафлю Бро); ***S.Afr.***: Arnica

Massage Oil; Balsem Vita GEEL†; Balsem Vita ROOI†; Entressdruppels HM; Oleum Salviae Comp†; Rooilavental; Stuidruppels; ***Spain***: Beta Romero; Dolokey†; Masagil†; Tonimax; ***Switz.***: DUL-X Cool; DUL-X Sport; DUL-X warm; DUL-X; DUL-X; Echinarom; Nasobol Inhalo; Novital; Perskindol Classic; Perskindol Classic; Pulmex Baby; Pulmex; Pulmex; Spagyrom; Ziegella†; ***UK***: Adiantine; Arnica Massage Balm; Medicated Extract of Rosemary; Puncto Rub; Soothol; Tradimed Vapour & Muscle Rub; ***Ukr.***: Alflutop (Алфлутоп Гель)†.

Homoeopathic Preparations. ***Ger.***: Aconitum Nicotiana comp†; Arnica comp/Apis†; Arnica/Symphytum comp; ***UK***: Frost Cream; Rheumadoron.

Roxarsone *(BAN, USAN, rINN)*

NSC-2101; Roxarsona; Roxarsonum; Роксарсон.
4-Hydroxy-3-nitrophenylarsonic acid.
$C_6H_6AsNO_6$=263.0
CAS — 121-19-7.
UNII — H5GU9YQL7L.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Roxarsone). A pale yellow, crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in dehydrated alcohol, in acetic acid, in acetone, in methyl alcohol, and in alkalis; insoluble in ether and in ethyl acetate; sparingly soluble in dilute mineral acids. It puffs up and deflagrates on heating.

Profile

Roxarsone has been used as a growth promotor in animal feeds.

Royal Jelly

Apilak; Jalea real; Queen Bee Jelly; Маточное Молочко.
CAS — 8031-67-2.
UNII — L497I37F0C.

Profile

Royal jelly is a milky-white viscid secretion from the salivary glands of the worker honey bee, *Apis mellifera* (Apidae); it is essential for the development of queen bees. Royal jelly has been used as a nutritional supplement, but of the many and diverse claims made for its therapeutic value, none has been substantiated.

Royal jelly is also included in some cosmetic preparations for its supposed beneficial effect on skin tissue.

Hypersensitivity. For reference to hypersensitivity reactions with bee products, including royal jelly, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Apiserum; ***Ital.***: Alvear; Biogel; Biovital†; Clinvit; Pa-Real; Ritmogel; Roburvit; Telergon II†; Theogel; Trofomed; ***Rus.***: Apilac (Апилак); ***UK***: Biobees; Regina Royal One Hundred; Rojema; ***Ukr.***: Apilac (Апилак).

Multi-ingredient Preparations. ***Arg.***: Energizante Vital con ginseng; Energizante; ***Fr.***: Arkoroyal; Aromavital†; Fibromyalgine; Phytozac; ***Hung.***: Aktivit; Klimovit; Sam-Ginseng Royal; ***Indon.***: Armovit; Hemaviton Energy Drink; Hemaviton Jreng; Neo Hormoviton Greng; Neo Hormoviton; Neo Hormoviton; ***Ital.***: Almavigor; Alvear con Ginseng; Apergan; Api Baby; Apiserum con Telergon 1†; Apistress; Bebimix†; Bidro; Bio-200; Biogel Resv; Bioton; Biotrefon Plus; Eavit Plus; Eavit; Eurogel; Fosfarsile Forte†; Fosfarsile Forte; Fosfarsile Junior; Granvit; Longevital; Neoplus; Nerex; Nutrigel; Ottovis; Plusvit; Pollingel; Provitamin A-E; Ribovir; Ristabil; Royal E; Taingel; Vigogel; ***Malaysia***: Dermaheal Post Laser Cream; ***Mex.***: Hepafol-F; Maxivit; Supravital; ***Philipp.***: Jamieson Total Energy; Memovit-E†; Revicon Max; Rogin-E; Vita SL; ***Rus.***: Multimax for Eyes (Мультимакс Для Глаз); Prostopine (Простопин); Vitamax (Витамакс)†; ***Singapore***: Vitaton; ***Spain***: Vitestable; ***Thai.***: Multilim RG; ***UK***: Regina Royal Concorde; Regina Royal Five; ***Ukr.***: Energin (Энергин); Gold Ray (Голд Рей); Rotavit Royal (Ротавит Ройял).

Rubber

Borracha; Caoutchouc; Caucciù; Caucho; Gummi; India-Rubber; Kumi; Каучук.
UNII — 2LQ0UUW8IN.

Profile

Rubber consists of the prepared latex of *Hevea brasiliensis* and other species of *Hevea* (Euphorbiaceae). It is used as a component of many medical devices such as catheters, syringes, enema tips, ostomy bags, balloons, and surgical gloves. Hypersensitivity reactions have occurred after direct contact of skin and mucous membranes with rubber components of such products and also after indirect contact with preparations stored in or given by them; deaths have been reported. Reactions have been attributed either to protein components of the rubber or to additives such as preservatives or vulcanisation accelerators. For references to glove starch powder as a possible risk factor in the development of rubber latex allergy, see Glove Powder under Adverse Effects of Starch, p. 2096.2. Cross-sensitivity between rubber proteins and those of certain fruits, including bananas and chestnuts, has been reported.

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Rubidium Iodide

Rubidio, ioduro de; Yoduro de rubidio; Рубидия Йодид.
RbI=212.4
CAS — 7790-29-6.
UNII — 18CYW0VL2X.

Profile

Rubidium iodide has the actions of iodine and the iodides (see p. 2336.3). It is an ingredient of several proprietary ophthalmic preparations promoted for the treatment of eye disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Facovit; Jodo Calcio Vitaminico; Polijodurato; Rubjovit.

Rue Oil

Oleum Rutae; Ruda, aceite esencial de; Рутовое Масло.
UNII — VDI0O08XRA.

Profile

Rue oil is a volatile oil obtained from rue, *Ruta graveolens* (Rutaceae). Rue oil and infusions of rue were formerly used as antispasmodics and emmenagogues and are reported to have abortifacient properties. Rue is a photosensitiser and the oil is a powerful local irritant.

Homoeopathy

Rue has been used in homoeopathic medicines under the following names: Ruta; Ruta gra.; Ruta grav.; Ruta graveolens.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aulo Repelente De Piojos; Max Repel; Max Repel; Rep Locion Repelente; ***Austral.***: Hernidisc; Joint & Muscle Cream.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Austria***: Apozema Apis compositum; Arnica Komplex†; Repisan; Tropfen bei Verletzungen; Wirbelsaule-und Gelenkstropfen Nr 2†; ***Canad.***: Aches & Pains; Arnicaid; Bumps and Bruises; Headache & Migraine L77; Rudistrol†; ***Fr.***: Arnica Complexe no 1; Calendula Complexe No 89; Homeofortil†; Homeogene 41†; Phapax; Poconeol no 54; Ranunculus Complexe No 79; Rudistrol†; ***Ger.***: Cranio-cyl Ho-Len-Complex; Flenin; Gelenk Albin; Infiossan; Rheucostan R; Rheuma-Pasc; Rheumeda; Ruta-Gastreu N R55; Steirocall S†; Symphytum Rowo†; Venokatt; ***Neth.***: Gletar; Muscle Care; Rudistrol†; Strain care; ***Rus.***: Repisan (Реписан); Ruta-Plus (Рута-Плюс); ***Switz.***: Nelsons Traumatica†; Regenaplex Nr. 25c; Regenaplex Nr. 3; ***UK***: Strains Cream; ***Ukr.***: Homvio-Reuman (Хомвио-Ревман).

Ruscogenin

Ruscogenina; Ruskojenin; Рускогенин.
(25*R*)-Spirost-5-ene-1β,3β-diol.
$C_{27}H_{42}O_4$=430.6
CAS — 472-11-7.
UNII — BXI92R2VUJ.

Profile

Ruscogenin is a sapogenin obtained from butcher's broom, *Ruscus aculeatus* (Liliaceae). It is reported to have anti-inflammatory and antithrombotic actions and has been applied in the local treatment of haemorrhoids as rectal ointment or suppositories. It has also been tried in peripheral vascular disorders.

References.

1. Anonymous. *Ruscus aculeatus* (butcher's broom). *Altern Med Rev* 2001; **6:** 608–12.
2. Ramírez-Hernández M, *et al.* Allergic contact dermatitis to ruscogenins. *Contact Dermatitis* 2006; **54:** 60.
3. Gonzalo-Garijo MA, *et al.* Compound allergy to an antihemorrhoidal ointment demonstrated by the repeated open application test. *J Investig Allergol Clin Immunol* 2009; **19:** 414–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flebodolor.

Multi-ingredient Preparations. ***Arg.***: Miopropan Proctologico; Procto Venart; ***Fr.***: Proctolog; ***Gr.***: Ibuprocт; ***Ital.***: Perfluxi Cremagel; Ruscoroid; ***Pol.***: Ruskorex; ***Port.***: Proctolog; ***Singapore***: Proctolog; ***Spain***: Abrasone Rectal; Proctolog; Ruscus; Venacol†; ***Turk.***: Proctolog; Progtolog.

Sacrosidase *(USAN)*

EC 3.2.1.26; β-Fructofuranosidase; Glucosucrase; Invertase; Saccharase; Sacrosidasa; Сакрозидаза.
β-D-Fructofuranoside fructohydrolase.
CAS — 85897-35-4.
ATC — A16AB06.
ATC Vet — QA16AB06.
UNII — 8A7F670F2Y.

Profile

Sacrosidase is a therapeutic enzyme used for sucrase replacement therapy in congenital sucrase-isomaltase deficiency. It is given with each meal or snack in usual doses of 8 500 international units for patients up to 15 kg, or 17 000 international units for patients over 15 kg.

Sacrosidase may cause hypersensitivity reactions. The commercial product may contain yeast, yeast products, glycerol, and papain and is contra-indicated in patients known to be hypersensitive to these substances.

References.

1. Treem WR, *et al.* Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1999; **28:** 137–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Sucraid.

Multi-ingredient Preparations. ***Canad.***: Synergy Defense.

Sage

Feuilles de Sauge; Hármaslevelű zsálya levél (sage leaf, three-lobed); Krūminių šalavijų lapai (sage leaf, three-lobed); List šalvěje lékařské (sage leaf); List šalvěje trojlaločné (sage leaf, three-lobed); Liść szałwii (sage leaf); Orvosizsálya-levél (sage leaf); Salbeiblätter; Salvia; Salviablad (sage leaf); Salviablad, treflikat (sage leaf, three-lobed); Salviae Folium (sage leaf); Salviae Officinalis Folium (sage leaf); Salviae trilobae folium (sage leaf, three-lobed); Salvianlehti, kolmiliuskainen (sage leaf, three-lobed); Salvianlehti (sage leaf); Sauge officinale, feuille de (sage leaf); Sauge trilobée, feuille de (sage leaf, three-lobed); Vaistinių šalavijų lapai (sage leaf); Шалфей.
*ATC Herb — HD11AA5001 (*Salvia officinalis*: leaf); HA01WC5004 (*Salvia officinalis*: leaf).*
*UNII — M9C36LC10E (*Salvia officinalis*); 065C5D077J (*Salvia officinalis *leaf); 48JCS720FN (*Salvia officinalis *flowering top); 236QY0A1BL (*Salvia officinalis *root).*

NOTE. The term Red Sage has been used for both *Salvia officinalis* and *Salvia miltiorrhiza* (Danshen, p. 2491.3).

Pharmacopoeias. *Eur.* (see p. vii) includes separate monographs for the leaf of the common or garden sage (*Salvia officinalis*) and the leaf of Greek or three-lobed sage (*Salvia fruticosa*).

Ph. Eur. 8: (Sage Leaf (Salvia officinalis); Salviae Officinalis Folium). The whole or cut dried leaves of *Salvia officinalis*. The whole drug contains not less than 1.5% v/w and the cut drug not less than 1.0% v/w of essential oil, both calculated with reference to the anhydrous drug. Sage leaf oil is rich in thujone. Protect from light.

Ph. Eur. 8: (Sage Leaf, Three-lobed; Salviae Trilobae Folium). The whole or cut, dried leaves of *Salvia* (*S. triloba*). The whole drug contains not less than 1.8% v/w of essential oil, and the cut drug not less than 1.2% v/w of essential oil, both calculated with reference to the anhydrous drug. It has a spicy odour when ground, similar to eucalyptus oil. Protect from light.

Profile

Plants in several genera are commonly referred to as sage but if the term is used without further qualification it is usually understood to mean the common or garden sage (*Salvia officinalis*). Sage leaf has carminative, antispasmodic, antiseptic, and astringent properties and is used as a flavour. It is used in preparations for many purposes, including respiratory-tract disorders, gastrointestinal disorders, and in mouthwashes and gargles for disorders of the mouth and throat. The leaf of the Greek or three-lobed sage (*Salvia fruticosa*) is also used in herbal medicine and it is sometimes found as an adulterant of sage.

Sage is the source of sage oil (see below).

Homoeopathy

Sage has been used in homoeopathic medicines under the following names: Salvia; Salvia officinalis; Salvia officinalis e foliis siccatis; Sal. off.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nosweat; Salvysat†; ***Cz.***: Caj ze Salveje; Florsalmin; Nat Salveje Lekarske†; Salvej Lekarske List†; Salvejova Nat; ***Ger.***: Aperisan; Salbei Curarina; Salvysat; Sweatosan N†; ***Hung.***: Aperisan; ***Ital.***: Saugella Dermoliquido; ***Norw.***: Nosweat†; ***Pol.***: Aperisan; ***Rus.***: Salbei (Шалфей); Salvin (Сальвин); ***Switz.***: MenoMed; Valverde bucopharynge; ***Turk.***: Parodontax; ***UK***: Menoforce Sage; Salvian.

Multi-ingredient Preparations. ***Arg.***: Acnetrol; Parodontax Fluor; Sigmafem Free; Sigmafem; Sigmaflavon Plus; Tereonsit; ***Austral.***: Femi-Nan; Feminine Herbal Complex; Herbal Throat Spray; Olf†; PM Meno-Care; Wild Yam Complex; ***Austria***: Cional; Dynexan; Phytovir; ***Braz.***: Parodontax†; ***Canad.***: Depuratif des Trappistes; Herbanat†; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; ***Chile***: Eciclean; ***Cz.***: Diabetan; Diabeticka Cajova Smes-Megadiabetin†; Herbadent; Pulmoran; Tormentan; ***Fr.***: Bolcitol†; Dexsil Peau; Fibromyalgine Fort; Gonaxine; NurAiD; Santane D_5†; Santane F_{10}†; Saugella Antiseptic; Saugella Antiseptic; Saugella Dermoliquide; Saugella HydraSerum; Tisane D'Ars†; Tisane Hepatique de Hoerdt†; ***Ger.***: Amara-Tropfen; InfectoGingi; Melissengeist; Parodontal; ***Hung.***: Uroherb; ***Israel***: Baby Paste + Chamomile†; Kamilotract; ***Ital.***: Donalg; Fito Stomygen†; Saugella Attiva; Saugella Dermolatte; Saugella Fitothym; Saugella Salviettine; Saugella Solido ph 3.5; ***Neth.***: Bioforce; ***Pol.***: Dentosept A; Dentosept; Enterosol; Herbogastrin; Mucosit; Salumin†; Salviasept; Sanofil; Septosan†; Tymsal; ***Rus.***: Elecasol (Элекасол); Fitantis (Фитантис); Inhaphytol No 1 (Ингафитол 1); Pectorales Species No 3 (Грудной Сбор 3); Salvarom (Сальваром); Stomatophit (Стоматофит); ***S.Afr.***: Amara†; Dynexan; Fragador†; ***Singapore***: Nu-Derm Toner; Purifying Gel; Stop Snoring; ***Switz.***: A Vogel Spray pour la gorge; Gouttes Amara; Kernosan Eau Dentifrice†; Mucosan†; Parsenn Creme pour herpes; Phytovir; Prosal N; Strath Gouttes pour les muqueuses; Tisane pectorale et antitussive; Wala Echinacea; ***UK***: Echinaforce Sore Throat Spray; Red Sage Catarrh Remedy; ***Ukr.***: Ambovit (Амбовит); Elecasol (Элткасол); Fitoval Shampoo (Фитовал шампунь); Klimased (Климасед); Sage Extract with Vitamin C Dr Theiss (Экстракт Шалфея с Витамином С Др Тайсс); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Vitokan (Витокан).

Homoeopathic Preparations. ***Austria***: Vocara; ***Canad.***: Amaratopfen†; ***Chile***: Matico Compuesto; ***Fr.***: Mercurius Cyanatus Complexe No 43†; Poconeol no 66; ***Ger.***: Flenin; ***Neth.***: Vinceel H; ***Rus.***: Vocara (Вокара); ***UK***: Fragador; ***Ukr.***: Vocara (Вокара).

Pharmacopoeial Preparations
Ph. Eur.: Sage Tincture.

Sage Oil

Kvapiųjų šalavijų eterinis aliejus (clary sage oil); Muskatellisalviaõljy (clary sage oil); Muskatellsalviaolja (clary sage oil); Salviae sclareae aetheroleum (clary sage oil); Salviae Sclareae Etheroleum (clary sage oil); Sauge sclarée, huile essentielle de (clary sage oil); Silice šalvěje muškátové (clary sage oil); Шалфейное Масло.
CAS — 8016-63-5 (clary sage oil).
ATC Herb — HA01WC5003 (Salvia officinalis: *essential oil).*
UNII — U27K0H1H2O.

Pharmacopoeias. *Swiss* includes, Salbeiöl (Salviae aetheroleum), oil from the common or garden sage (*Salvia officinalis*). *Eur.* (see p. vii) includes separate monographs for the oil from the clary sage (*Salvia sclarea*) and from Spanish sage (*Salvia lavandulifolia*).

Ph. Eur. 8: (Clary Sage Oil). Colourless to brownish-yellow liquid, usually pale yellow, with a characteristic odour. It is obtained by steam distillation from the fresh or dried flowering stems of *Salvia sclarea*. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Ph. Eur. 8: (Spanish Sage Oil). A clear, colourless or pale yellow, mobile liquid with a camphor-like odour. It is obtained by steam distillation from the aerial parts of *Salvia lavandulifolia* collected at the flowering stage. Store at a temperature not exceeding 25 degrees.

Profile

Clary sage oil (from *Salvia sclarea*) and Spanish sage oil (from *S. lavandulifolia*) are used in perfumery and aromatherapy. Sage oil from the common or garden sage (*Salvia officinalis*) (see p. 2608.3) is also used in perfumery but it is not recommended for use in aromatherapy because of its skin irritant properties, nor is it recommended for ingestion due to its thujone content.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Chiacaps; ***Fr.***: Node G†.

Multi-ingredient Preparations. ***Arg.***: Dermomega; ***Austral.***: Advanced Menopause Care; ***Austria***: Colda; Coldistan; Parodontax†; Piniment; ***Ger.***: Salviathymol N; Trauma-cyl†; Varicylum-S†; Weleda Bronchialbalsam; ***Hung.***: Carmol; Szent Lukacs; ***Indon.***: Transpulmin Balsam; ***Ital.***: Venalta; ***Philipp.***: Kamillosan M; Transpulmin Balsam†; ***Pol.***: Carmolis; Doppelherz Energovital Tonik†; Salviasept; ***Rus.***: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Doppelherz Energotonik (Доппельгерц Энерготоник); Parodontocide (Пародонтоцид); ***S. Afr.***: Oleum Salviae Comp†; ***Switz.***: Bismorectal†; Denosol; Wiewohl†; Ziegella†; ***Ukr.***: Phytolysin Plus (Фитолизин Плюс); Sage Extract with Vitamin C Dr Theiss (Экстракт Шалфея с Витамином С Др Тайсс).

Homoeopathic Preparations. ***UK***: Medicinal Gargle.

Salicyl Alcohol *(USAN)*

Salicain; Saligenin; Saligenol; Салициловый Спирт.
2-Hydroxybenzyl alcohol.
$C_7H_8O_2$=124.1
CAS — 90-01-7.
UNII — FA1N0842KB.

NOTE. The name salicain has also been used as a proprietary name for hydroxytetracaine.

Profile

Salicyl alcohol is reported to have local anaesthetic and analgesic properties and has been used in various topical preparations. It is present in the bark of some trees and has been associated with contact sensitivity; it is also a metabolite of salicin (salicyl alcohol glucoside—see Salix, p. 129.2).

Salverine Hydrochloride *(rINNM)*

Hidrocloruro de salverina; M-811 (salverine); Salverina, hidrocloruro de; Salvérine, Chlorhydrate de; Salverini Hydrochloridum; Сальверина Гидрохлорид.
2-[2-(Diethylamino)ethoxy]-benzanilide hydrochloride.
$C_{19}H_{24}N_2O_2$,HCl=348.9
CAS — 6376-26-7 (salverine).

Profile

Salverine hydrochloride has been used as an antispasmodic in combination preparations for the treatment of biliary-tract disorders, respiratory-tract disorders, and pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Cynarix comp; Montamed; Novipec†.

Salvia Divinorum

Diviner's Sage; Divining Sage; Hierba de María; *Salvia divinorum*; ska María Pastora.
CAS — 83729-01-5 (salvinorin A).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of Salvia divinorum:

Big Sal; heirba Maria; hojas de la Pastora; hojas de Maria; la Maria; La Pastora; LSD Lite; Magic mint; Maria Pastora; Sally D; Salvia; Ska; ska Maria; ska Pastora; The Shepherdess.

Profile

Salvia divinorum has been traditionally used in Mexican Indian culture to induce hallucinations and is now a substance of abuse. Salvinorin A (divinorin A) is the main active constituent.

References.
1. Prisinzano TE. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*. *Life Sci* 2005; **78:** 527–31.
2. Singh S. Adolescent salvia substance abuse. *Addiction* 2007; **102:** 823–4.
3. Paulzen M, Gründer G. Toxicpsychosis after intake of the hallucinogen salvinorin A. *J Clin Psychiatry* 2008; **69:** 1501–2.

Sambucus

Bodzavirág; Elder Flower; Fläderblomma; Holunderblüten; Juoduogių šeivamedžių žiedai; Květ bezu černého; Kwiat bzu czarnego; Mustaseljankukka; Sabugueiro; Sambuc.; Sambuci flos; Sambuci Nigrae Flos; Saúco; Sureau, fleur de; Бузина.
ATC Herb — HA06AX5009 (Sambucus nigra: *fruit); HR05YA5021* (Sambucus nigra: *flower); HG04BW5031* (Sambucus nigra: *flower).*
UNII — 07V4DX094T (Sambucus nigra *flower); CT03BSA18U* (Sambucus nigra *flowering top).*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Elder Flower). The dried flowers of *Sambucus nigra*. It contains not less than 0.8% of flavonoids, calculated as isoquercitroside with reference to the dried drug. Protect from light.

Profile

Sambucus, in the form of flowers of the elder, *Sambucus nigra* (Black Elder; European Elderberry; European Black Elderberry), has astringent, diaphoretic, and anticatarrhal properties and is used in herbal preparations for a variety of disorders, particularly respiratory-tract disorders. Elder-flower water has been used as a vehicle for eye and skin lotions. Elder-flower ointment has been used as a basis for pomades and cosmetic ointments.

Homoeopathy

Sambucus has been used in homoeopathic medicines under the following names: Sambucus nigra; Sambucus nig; Samb. nig.

General references.
1. WHO. Flos Sambuci. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/26.html (accessed 05/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Caj z Kvetu Bezu Cerneho; ***Rus.***: Novo-Passit (Ново-Пассит).

Multi-ingredient Preparations. ***Arg.***: Gripofit; Yuyo; ***Austral.***: DiaCo; HRF; Immune Boost with Andrographis; Nyal Cold + Flu Fighter Day + Night; Nyal Cold + Flu Fighter; Nyal Sinus Relief Day + Night; Nyal Sinus Relief; Olive Leaf Plus; Sinupret; ***Austria***: Entschlackender Abfuhrtee EF-EM-ES; Grippetee St Severin; Laxalpin†; Sinupret; Solvopret†; Tuscalman; ***Canad.***: Honey Herb Cough Drops†; Natraway Sport 1 & 2†; Natraway Sport 3†; Original Herb Cough Drops†; Swiss Herb Cough Drops; ***Cz.***: Biotussil; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Novo-Passit; Pulmoran; Reduktan; Sinupret; Species Urologicae Planta; Urcyston Planta; ***Fr.***: Hydrastart; Pharyndol; Pharyndol; Santane R_8†; ***Ger.***: Sinupret; ***Hong Kong***: Sinupret; ***Hung.***: Sinupret; Tamarinlax; ***Indon.***: Dibost; Elanos Kids; Elanos; Formuno; Glimunos; Idesar Plus; Imboost Force; Imforce Plus; Imforce; Imox; Imufor; Imunogard; Imunvit Plus; Sinupret†; StarMuno; ***Ital.***: Atlantis; ETDR; Rinotrofina C; ***Malaysia***: Sinupret; ***Mex.***: Bisolsinus; Bronkitose Mielimon; ***Philipp.***: Sinupret; ***Pol.***: Betasol; Infektoten†; Normosan†; Pyrosal; Sinupret; Termasil; ***Rus.***: Sinupret (Синупрет); ***Singapore***: Sinupret; ***Swed.***: Sinova; ***Switz.***: Sinupret; Tisane contre les refroidissements; ***Thai.***: Sinupret†; ***Turk.***: Immuzinc; ***UK***: Cleansing Herbs; EP&C Essence; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Herb and Honey Cough Elixir; Life Drops; Lion Cleansing Herbs; Lustys Herbalene; Modern Herbals Cold & Catarrh; Sinotar; Sinueeze; Sinuherb; Tabritis; ***Ukr.***: Novo-Passit (Ново-Пассит); Sinupret (Синупрет); Urochol (Урохол)†; ***Venez.***: Dromil Sauco.

Homoeopathic Preparations. ***Austria***: Otovowen; ***Canad.***: Aches & Pains; Breathe More; Eczema L87; Homeodel 15†; Sinall Formula†; Snore No More; ***Chile***: Similibus; ***Fr.***: Allium Cepa Compose; Arnica Complexe no 1; Santaherba; Scabiosa Complexe No 87; Spirodrine; ***Ger.***: Lowe-Komplex Nr 13; Otovowen; ***Neth.***: Nectadyn H; ***Rus.***: Atma (Атма); Sambucus-Plus (Самбукус-Плюс); ***S.Afr.***: Sambucus Comp†; ***Switz.***: Alceprin-N; Spagyrhin; ***Ukr.***: Atma (Атма).

Sandalwood

East Indian Sandalwood; White Sandalwood; Сантал Белый (*Santalum album*).
*ATC Herb — HJ01WB5013 (*Santalum album: *wood).*
UNII — 3641YW25N2.

Pharmacopoeias. In *Chin.*

Profile

The wood of white sandalwood, *Santalum album* (Santalaceae), has antibacterial and antispasmodic activity and is used in herbal medicine as an adjunct in the treatment of infections of the lower urinary tract. Sandalwood and its preparations contain essential oil.

Sandalwood oil is used in aromatherapy and in perfumery.

References.

1. Burdock GA, Carabin IG. Safety assessment of sandalwood oil (Santalum album L.). *Food Chem Toxicol* 2008; **46:** 421–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Brady's-Magentropfen; ***Switz.***: Kernosan Eau Dentifrice†; ***Ukr.***: Eve Care (Ив Кер)†; Imunin (Иммунин)†.

Homoeopathic Preparations. ***Fr.***: Santalum Complexe No 30†.

Sanguinaria

Bloodroot; Red Puccoon; Sanguinaria canadensis; Sanguinaris canadensis; Tetterwort; Волчья Стопа Канадская (*Sanguinaria canadensis*).
*UNII — B3XJA0OV6T (*Sanguinaria canadensis*); N9288CD508 (*Sanguinaria canadensis *root).*

NOTE. The name Tetterwort has also been used for Greater Celandine (p. 2522.2).

Profile

Sanguinaria consists of the dried rhizome of *Sanguinaria canadensis* (Papaveraceae). Sanguinarine, an alkaloid extracted from sanguinaria, has been used as an antiplaque agent in toothpaste and mouthwash preparations. Sanguinaria was formerly used as an expectorant but fell into disuse because of its toxicity. Sanguinaria has also been classified by the FDA as a herb that is unsafe for use in foods, beverages, or drugs.

Homoeopathy

Sanguinaria has been used in homoeopathic medicines under the following names: Sanguinaria canadensis; Sang. ca.

Sanguinarium nitrate has been used in homoeopathic medicines under the following names: Sanguinarinum Nitricum; Sang. nit.

Reviews.

1. Karlowsky JA. Bloodroot: Sanguinaria canadensis L. *Can Pharm J* 1991; **124:** 260, 262–3, 267.
2. Grenby TH. The use of sanguinarine in mouthwashes and toothpaste compared with some other antimicrobial agents. *Br Dent J* 1995; **178:** 254–8.
3. Tenenbaum H, *et al.* Effectiveness of a sanguinarine regimen after scaling and root planing. *J Periodontol* 1999; **70:** 307–11.
4. Mackraj I, *et al.* Sanguinarine. *Cardiovasc Ther* 2008; **26:** 75–83.
5. Vlachojannis C, *et al.* Rise and fall of oral health products with Canadian bloodroot extract. *Phytother Res* 2012. Available at: doi:10.1002/ptr.4606

Malignant neoplasms of the skin. Self-treatment of basal cell carcinoma on the nasal tip by a 51-year-old man using a topical caustic preparation containing *Sanguinaria canadensis* has been reported.[1] Although a similar caustic paste was originally used in the 1930s as part of Mohs' micrographic surgery (MMS) for some types of skin cancer, the MMS technique in use today is more refined, and self-administration of caustic pastes containing sanguinaria for skin lesions is not recommended. However, such use has continued to be reported and has caused serious skin damage in some patients.[2,3] The Therapeutic Goods Administration[4] in Australia has advised against the use of these preparations which are also marketed as black or red salves.

1. Affleck AG, Varma S. A case of do-it-yourself Mohs' surgery using bloodroot obtained from the internet. *Br J Dermatol* 2007; **157:** 1078–9.
2. Saltzberg F, *et al.* Deforming self-treatment with herbal "black salve". *Dermatol Surg* 2009; **35:** 1152–4.
3. Cienki JJ, Zaret L. An internet misadventure: bloodroot salve toxicity. *J Altern Complement Med* 2010; **16:** 1125–7.
4. Australian Government Department of Health and Ageing: Therapeutic Goods Administration. Black and red salves in treating cancer (issued 19th March, 2012). Available at: http://www.tga.gov.au/safety/alerts-medicine-black-salve-120203.htm (accessed 17/04/12)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Bronchial Cough; Mielocol†; ***Ital.***: Emoform Alifresh; ***S.Afr.***: Zeel; Zeel; ***Switz.***: Kernosan Eau Dentifrice†.

Homoeopathic Preparations. ***Austral.***: Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Respatona Dry Cough & Nasal Congestion; ***Austria***: Klimaktoplant; Lymphdiaral; Otovowen; Remens; ***Canad.***: Bronchial Cough; Echinacea Compositum; Formula DM 210†; Hea Complex†; Headache & Migraine L77; Homeo-Form ME†; Hylaquell BC; Menopause; Sinusalia; Zeel Comp; ***Cz.***: Zeel Compositum; Zeel Salbe†; ***Fr.***: Actheane; Phapax; Pulmo-Drainol†; Sepia Compose; ***Ger.***: Biodolor; Cefakliman N†; Cefakliman S; Cephaloplant†; Cranio-cyl Ho-Len-Complex; Delto-cyl Ho-Len-Complex; Dolfin; Drosera-Weliplex†; Dularell N; Elana†; Gripps; Klimaktoplant N; Klimax-Gastreu S R10; Lymphdiaral; Meno-cyl L Ho-Len-Complex; Migrane-Gastreu R16; Otovowen; Pflugerplex Gelsemium; Pflugerplex Lemna; Rephalgin N; Zeel comp; ***Hung.***: Klimakt-Heel; Zeel; ***Neth.***: Cephalite; Homeocare Allerlo; Homeocare neusspray; Homeocare siroop; Klimaktolan; Klimax-Gastreu R10; Lymphdiaral; Zeel comp N; ***Rus.***: Klimaktoplan (Климактоплан); Remens (Ременс); Zeel T (Цель Т); ***Switz.***: Menosan†; Multiplex 1; Regenaplex Nr. 21e; ***Ukr.***: Capadol (Кападол); Klimaktoplan N (Климактоплан Н); Remens (Ременс).

Saponins

Sapogenin Glycosides; Saponinai; Saponinas; Saponine; Saponinen; Saponiner; Saponines; Saponiny; Saponosidi; Сапонины.
CAS — 8047-15-2.

Profile

Saponins are a diverse group of plant glycosides that share the property of foaming strongly when shaken with water. They are amphiphilic molecules, consisting of a lipophilic polycyclic aglycone with a hydrophilic sugar side-chain. The aglycone is referred to as a sapogenin and may have either a triterpenoid or steroid structure.

Saponins are found in many plants but common sources include quillaia (p. 2207.1), soapwort (p. 2617.2), yucca (p. 2649.3) and gypsophila (*Gypsophila paniculata* and related species). They are used for their surfactant properties as emulsifying agents (see p. 2164.1) in foods and pharmaceuticals, and have also been used medicinally in preparations for respiratory-tract and other disorders. Saponins and sapogenins with specific pharmacological actions include digoxin (p. 1353.3) and ruscogenin (p. 2608.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Cz.***: Pleumolysin; Tussilen†; ***Neth.***: Bronchicum.

Sapropterin Hydrochloride *(rINNM)*

Dapropterin Hydrochloride; Hidrocloruro de sapropterina; Sapropterin Dihydrochloride (USAN); Sapropterin Dihydrochloride (BANM); Sapropterina, hidrocloruro de; Saproptérine, Chlorhydrate de; Sapropterini Hydrochloridum; SUN-0588 (sapropterin or sapropterin hydrochloride); T-1401; (6*R*)-5,6,7,8-Tetrahydrobiopterin Hydrochloride; Сапроптерина Гидрохлорид.
(-)-(6*R*)-2-Amino-6-[(1*R*,2*S*)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(3*H*)-pteridinone dihydrochloride.
$C_9H_{15}N_5O_3,2HCl=314.2$
CAS — 62989-33-7 (sapropterin); 69056-38-8 (sapropterin hydrochloride).
ATC — A16AX07.
ATC Vet — QA16AX07.
UNII — RG277LF5B3.

Profile

Sapropterin is the synthetic form of tetrahydrobiopterin (BH_4), an endogenous cofactor for phenylalanine hydroxylase. It is used for the treatment of hyperphenylalaninaemia due to phenylketonuria (p. 2042.2) or tetrahydrobiopterin deficiency.

Sapropterin is given orally as the hydrochloride in a single daily dose with food, preferably in the morning. The initial daily dose in patients 4 years of age and above with *phenylketonuria* is 10 mg/kg adjusted until adequate phenylalanine concentrations have been achieved; usual maintenance daily doses are 5 to 20 mg/kg. The initial daily dose in patients 4 years of age and above with *tetrahydrobiopterin deficiency* is 2 to 5 mg/kg, adjusted up to 20 mg/kg daily as required; it may be necessary to distribute the dose over the day as 2 or 3 divided doses.

References.

1. Opladen T, *et al.* Severe mucitis after sublingual administration of tetrahydrobiopterin in a patient with tetrahydrobiopterin-responsive phenylketonuria. *Eur J Pediatr* 2005; **164:** 395–6.
2. Feillet F, *et al.* Pharmacokinetics of sapropterin in patients with phenylketonuria. *Clin Pharmacokinet* 2008; **47:** 817–25.
3. Sanford M, Keating GM. Sapropterin: a review of its use in the treatment of primary hyperphenylalaninaemia. *Drugs* 2009; **69:** 461–76.
4. Trefz FK, *et al.* Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomized, double-blind, placebo-controlled study. *J Pediatr* 2009; **154:** 700–7.
5. Hegge KA, *et al.* Sapropterin: a new therapeutic agent for phenylketonuria. *Ann Pharmacother* 2009; **43:** 1466–73.
6. Somaraju UR, Merrin M. Sapropterin dihydrochloride for phenylketonuria. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 06/08/10).

Administration in children. For doses in children 4 years of age and over, see above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Kuvan; ***Austria***: Kuvan; ***Belg.***: Kuvan; ***Canad.***: Kuvan; ***China***: Kuvan (科望); ***Cz.***: Kuvan; ***Denm.***: Kuvan; ***Fr.***: Kuvan; ***Ger.***: Kuvan; ***Gr.***: Kuvan; ***Hung.***: Kuvan; ***Irl.***: Kuvan; ***Israel***: Kuvan; ***Jpn***: Biopten; ***Neth.***: Kuvan; ***Norw.***: Kuvan; ***NZ***: Kuvan; ***Pol.***: Kuvan; ***Port.***: Kuvan; ***Spain***: Kuvan; ***Swed.***: Kuvan; ***Switz.***: Kuvan; ***UK***: Kuvan; ***USA***: Kuvan.

Sarsaparilla

Raíz de zarzaparrilla; Salsaparilha; Salsepareille; Sarsa; Sarsaparilla Root; Smilacis Rhizoma; Zarzaparrilla; Сассапарель.
*UNII — H51N91QNEB (*Smilax glabra*); PES3YXA3LR (*Smilax glabra *tuber).*

Pharmacopoeias. In *Chin.* and *Jpn.*, which specify *Smilax glabra.*

Profile

Sarsaparilla is the dried root of various species of *Smilax* (Liliaceae). It has been used, usually in the form of a decoction or extract, as a vehicle and flavour for medicaments. It is also an ingredient of herbal preparations.

Homoeopathy

Sarsaparilla has been used in homoeopathic medicines under the following names: Smilax; Sarsap.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Urinefrol; ***Austral.***: Derma-Co; ***Braz.***: Galenogal; ***Canad.***: Depuratif des Trappistes; Eliminex; Herbanat†; ***Indon.***: Instink†; Provigor†; ***Ital.***: Tisana Kelemata; ***UK***: Gerard House Reumalex; HRI Clear Complexion; Jamaican Sarsaparilla; Napiers Oral Skin Soother Herbal Relief; Skin Eruptions Mixture; ***USA***: Detox.

Homoeopathic Preparations. ***Austria***: Erbiode Blasen und Nieren; ***Canad.***: Common Mallow Combination†; Yellow Dock Combination†; ***Cz.***: Lymphomyosot; ***Fr.***: Calendula Complexe No 89; Formica Rufa Compose; Pareira Brava Compose; Saponaria Compose; ***Ger.***: Derivatio H; Derivatio; Haut-Gastreu R60; Jsostoma S; Lymphomyosot N; Lymphomyosot; Pascorenal N; uro-loges; Uroselect; Urotruw N; ***Hung.***: Pro-Aller; ***Neth.***: Restructa H; ***S.Afr.***: Lymphomyosot; ***Ukr.***: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Sassafras Oil

Oleum Sassafras; Sasafrás, aceite esencial de; Сассафрасовое Масло.
*ATC Herb — HA03AW5053 (*Sassafras albidum: *essential oil); HM02AW5019 (*Sassafras albidum: *essential oil); HP03AX5004 (*Sassafras albidum: *essential oil).*
UNII — 78ZX2PFG2Z.

Uses and Administration

Sassafras oil is a volatile oil distilled from the root or root bark of *Sassafras albidum* (Lauraceae), or from the wood of certain species of *Ocotea* (Lauraceae). It contains safrole.

Sassafras oil has rubefacient properties and was formerly used as a pediculicide.

Adverse Effects

Neither sassafras nor the oil should be taken internally; the use of herb teas of sassafras may lead to a large dose of safrole. The use of safrole in foods has been banned because of carcinogenic and hepatotoxic risks. The use of safrole in toilet preparations is also controlled.

Poisoning. A 47-year-old woman experienced 'shakiness', vomiting, anxiety, tachycardia, and raised blood pressure after ingestion of a potentially fatal dose of sassafras oil (5 mL). She was given activated charcoal and symptomatic management.[1]

1. Grande GA, Dannewitz SR. Symptomatic sassafras oil ingestion. *Vet Hum Toxicol* 1987; **29:** 447.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Inhalador Medex; ***Cz.***: Stopangin; Stopangin; ***Hong Kong***: Sloan's Liniment†; ***Indon.***: Thymcal; ***Rus.***: Stopangin (Стопангин); ***S.Afr.***: Moultons Pain Paint†; Zam-Buk; ***Ukr.***: Stopangin (Стопангин); Stopangin (Стопангин).

Satavaptan (rINN) ⊗

Satavaptán; Satavaptanum; SR-121463 (satavaptan); SR-121463B (satavaptan phosphate); Сатаваптан.

N-tert-Butyl-4-({cis-5′-ethoxy-4-[2-(morpholin-4-yl)ethoxy]-2′-oxo-1′,2′-dihydrospiro[cyclohexane-1:3′-indole]-1′-yl}sulfonyl)-3-methoxybenzamide.

$C_{33}H_{45}N_3O_8S$=643.8

CAS — 185913-78-4 (satavaptan); 308145-17-7 (satavaptan phosphate).

UNII — AJS8S3P31H.

Profile

Satavaptan is a selective vasopressin V_2-receptor antagonist that has been investigated for the treatment of hyponatraemia in the syndrome of inappropriate antidiuretic hormone secretion.

References.

1. Soupart A, *et al*. Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V_2-receptor antagonist. *Clin J Am Soc Nephrol* 2006; **1:** 1154–60.

Saxitoxin

Saxitoxina.

CAS — 35523-89-8.

Profile

Saxitoxin is a neurotoxin associated with paralytic shellfish poisoning. It is an endotoxin produced by species of dinoflagellate plankton present in infected molluscs.

References.

1. Halstead BW, Schantz EJ. *Paralytic shellfish poisoning*. Geneva: WHO, 1984.
2. WHO. Aquatic (marine and freshwater) biotoxins. *Environmental Health Criteria 37*. Geneva: WHO,1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc37.htm (accessed 24/07/08)
3. Hartigan-Go K, Bateman DN. Redtide in the Philippines. *Hum Exp Toxicol* 1994; **13:** 824–30.
4. Gessner BD, *et al*. Hypertension and identification of toxin in human urine and serum following a cluster of mussel-associated paralytic shellfish poisoning outbreaks. *Toxicon* 1997; **35:** 711–22.
5. de Carvalho M, *et al*. Paralytic shellfish poisoning: clinical and electrophysiological observations. *J Neurol* 1998; **245:** 551–4.
6. Lehane L. Paralytic shellfish poisoning: a potential public health problem. *Med J Aust* 2001; **175:** 29–31.
7. Garcia C, *et al*. Paralytic shellfish poisoning: post-mortem analysis of tissue and body fluid samples from human victims in the Patagonia fjords. *Toxicon* 2004; **43:** 149–58.
8. Llewellyn LE. Saxitoxin, a toxic marine natural product that targets a multitude of receptors. *Nat Prod Rep* 2006; **23:** 200–22.

Schick Test

Prueba de Schick; Реакция Шика.

Pharmacopoeias. *Br.* include standards for Schick test toxin and control.

BP 2014: (Schick Test Toxin). It is prepared from a toxigenic strain of *Corynebacterium diphtheriae*. It contains a suitable antimicrobial preservative. Store at 2 degrees to 8 degrees.

BP 2014: (Schick Control). It is Schick Test Toxin that has been heated at a temperature not lower than 70 degrees and not higher than 85 degrees for not less than 5 minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is to be used. Store at 2 degrees to 8 degrees.

Profile

Intradermal injection of Schick test toxin has been used for the diagnosis of susceptibility to diphtheria and, more importantly, to detect patients who might have an adverse reaction to diphtheria vaccines. Children up to the age of about 8 to 10 years rarely suffer from such reactions and therefore the Schick test is not usually performed in this age group. In older children and adults a Schick test was formerly used before the use of standard diphtheria vaccines. However, diphtheria vaccines for use in adults and adolescents (p. 2382.3) are now formulated with lesser amounts of toxoid so Schick testing is unnecessary.

Schisandra

Schizandra; Лимонник; Шизандра.

Pharmacopoeias. *Chin.* includes the dried ripe fruit of *Schisandra chinensis* (Fructus Schisandrae Chinensis) and *S. sphenanthera* (Fructus Schisandra Sphenanthera)

Eur. (see p. vii) and *Jpn* include the fruit of *S. chinensis*.

Ph. Eur. 8: (Schisandra Fruit). The whole, dried, or steamed and dried, ripe fruit of *Schisandra chinensis*. It contains a minimum of 0.40% schisandrin ($C_{24}H_{32}O_7$=432.5) calculated with reference to the dried drug. Protect from light.

Profile

The dried ripe fruit of *Schisandra chinensis* or *S. sphenanthera*, sometimes referred to as schizandrae fructus, are known in Chinese medicine as wuweizi and nanwuweizi respectively. Schisandra is used in a variety of disorders and contains lignans claimed to have protective effects on the liver. The oil is also used.

The derivative bifendate has been reported to interact with ciclosporin (see p. 1953.2). SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin, is reported to be an inhibitor of cytochrome P450 isoenzymes of the CYP3A subfamily, and has been reported to increase maximum blood concentrations of tacrolimus (see p. 1973.3).

References.

1. Panossian A, Wikman G. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. *J Ethnopharmacol* 2008; **118:** 183–212.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Bacopa Complex; Echinacea Royale; Herbal Rest & Relax; LivCo; Liver Detox; Liver Tonic Complex; Mindac; Nevaton; PM Syrin; ***Indon.***: Bio-Curliv; Curliv Plus; Curliv Plus; Curliv; Hepa-Q; Hepacell†; Hepamax; Naturliver; Sanoliv; ***Jpn***: Ryokankyomishingeninto; Seihaito; Seishoekkito; ***Pol.***: Penigra; ***Rus.***: Carmolis (Кармолис); Theravit Tonic (Теравит Тоник); ***Swed.***: Chisan; Chisandra; ***Ukr.***: PM Sirin (ПМ Сирин); Theravit Tonic (Теравит Тоник)†; ***USA***: Adrenoid.

Schoenocaulon Officinale

Caustic Barley; Cevadilla; Cévadille; Sabadilla; Sabadillgermer.

*UNII — QLC7BUA4V8 (*Schoenocaulon officinale*); 6NAF1689IO (*Schoenocaulon officinale *seed).*

Profile

The dried seeds of *Schoenocaulon officinale* (*Veratrum officinale*) (Melanthiaceae) contain a number of alkaloids and are a source of veratrine (see p. 2644.2). They were formerly used as a topical insecticide. Preparations of the seeds have also been given internally as an anthelmintic and for rheumatism, but were generally considered to be too toxic for medicinal use either topically or systemically. Overdose has been fatal. Schoenocaulon has also been used in veterinary medicine and as an environmental insecticide.

Homoeopathy

Schoenocaulon officinale has been used in homoeopathy.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Hay Fever; ***Austria***: Apozema Apis compositum; Erbiode Heuschnupfen; Famulan; Ferrum Phosphoricum comp; Infludo; ***Canad.***: Adrisin†; Allergies; Allergy Relief†; Comp-Drops 5 Expectorant†; Coryzalia; Formula INF; Hay Complex†; Hay Fever; Hayfever; Homeo-Form AL†; Homeodel 15†; Hylamine HF; Kids Allergies; Sabalia; Sinus Ease; Sinuspax†; ***Chile***: Allium Compuesto; Rinoplex; ***Cz.***: Coryzalia; Rhinallergy; ***Fr.***: Coryzalia; Dolistamine†; Infludo; Phytogargarisme†; Rhinallergy; Sinuspax; ***Ger.***: Allergokatt; Ferrum phosphoricum comp; Gripps; Infludo; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Psychoneuroticum (Rowo-578)†; Sinapis nigra N Oligoplex; Vertizin; ***Hung.***: Coryzalia; PSY-Stabil; ***Neth.***: Coryzalia; Grippe-Gastreu R6; Infludo; PSY-stabil; ***Port.***: Coryzalia; ***Rus.***: Coryzalia (Коризалия); Famulan (Фамулан); ***S.Afr.***: Ferrum Phos Comp†; Infludo†; ***Switz.***: Coryzalia; Gouttes contre les rhumes des foins†; Infludo; Nelsons Pollenna†; Rhinallergy; Sinuspax†; ***UK***: Infludo; Pollenna; ***Ukr.***: Coryzalia (Коризалия); ***USA***: Preferred Remedies Allergy.

Scoparium

Broom Tops; Genêt; Genêt à Balai; Planta Genista; Retama negra; Scoparii Cacumina; Жарновец Метельчатый (*Sarothamnus scoparius*).

*ATC Herb — HC01EB5014 (*Cytisus scoparius*: herb); HG04BW5008 (*Cytisus scoparius*: herb).*

*UNII — XZC6H8R666 (*Cytisus scoparius *flowering top).*

Pharmacopoeias. In *Fr.*

Profile

Scoparium is the dried tops of broom, *Sarothamnus scoparius* (*Cytisus scoparius*) (Leguminosae). It is a mild diuretic, haemostatic, and vasoconstrictor and has been given as a decoction or alcoholic extract. It has oxytocic properties and should be avoided in pregnancy. It contains sparteine (p. 2621.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Spartiol†.

Multi-ingredient Preparations. ***Fr.***: Rap Phyto; ***Pol.***: Fitoven.

Homoeopathic Preparations. ***Austria***: Aurumheel; Rytmopasc; ***Canad.***: Tyglan†; ***Ger.***: Arrhythmie-Gastreu N; Derivatio H; Derivatio; Hypotonie-Gastreu R44; Rytmopasc; Spartiol Cardio; ***Hung.***: Aurumheel; ***Neth.***: Cralonin H.

Scopolia

Belladonna Scopola; Dårört; European Scopolia; Glockenbilsenkraut; Krainer Tollkraut; Russian Belladonna; Scopola; Scopolia Rhizome; Scopoliae Rhizoma; Tollkraut.

*UNII — D5E3O48XGC (*Scopolia carniolica *root); 04AC8ASX63 (*Scopolia japonica*); R2649T20OV (*Scopolia parviflora*).*

NOTE. Distinguish from Belladonna, p. 2453.3. The name Japanese belladonna has been applied to *Scopolia carniolica* but is more correctly applied to *S. japonica*.

Pharmacopoeias. In *Jpn.*, which defines scopolia as the rhizome and root of *Scopolia japonica*, *Scopolia carniolica*, or *Scopolia parviflora*.

Profile

The root of *Scopolia carniolica* (Solanaceae) contains alkaloids with antimuscarinic activity, mainly hyoscyamine, and has actions similar to those of belladonna (see p. 2453.3). Alkaloids are also present in the leaves.

It is included in herbal preparations for gastrointestinal, biliary, and urinary-tract spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Magesto; ***Jpn***: Cabagin S New; ***Thai.***: Diasgest; Digestin; Magesto; Mesto-Of.

Sea Buckthorn

Argousier; Sallowthorn; Sea-buckthorn; Облепиха Крушиновидная.

NOTE. Distinguish from Alder Buckthorn Bark (see Frangula Bark, p. 1843.3) and from Buckthorn (p. 1824.2).

Profile

Sea buckthorn (*Hippophae rhamnoides*, Eleagnaceae) is used in traditional medicine and is the source of sea buckthorn oil, p. 2612.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Hiporhamin (Гипорамин); ***Ukr.***: Erebra (Эребра).

Multi-ingredient Preparations. ***Rus.***: Hyporolam (Гипоролам); Sodecor (Содекор).

Sea Buckthorn Oil

Облепиховое Масло.

Profile

Sea buckthorn oil is extracted from the seeds and berries of sea buckthorn (p. 2611.3) and has been taken orally for skin and mucous membrane disorders and as a tonic. It has also been investigated in liver fibrosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Omega 7.

Multi-ingredient Preparations. ***Fr.***: Alphalarm; Hydromega; ***Rus.***: Olasol (Олазоль); Olestesin (Олестезин).

Sea Water

Aqua marina.

Sea Salt

UNII — 87GE52P74G.

Profile

Sea water is water obtained from a sea or ocean. It contains sodium chloride (p. 1795.1) and other essential minerals and trace elements; the sodium chloride content is about 3.5%, although this varies depending on the source. Processed sea water has been used as a dietary mineral supplement and as a solution for nasal irrigation, either undiluted or as an isotonic solution.

Sea salt is obtained by evaporation of sea water and contains sodium chloride and other minerals. It has been used similarly to sea water in preparations for nasal disorders. It also has widespread culinary uses.

Homoeopathy

Sea water has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Demazin Saline; Otrivin Sea Water; Sinoclear; ***Belg.***: Lyomer Plus; ***Canad.***: Hydrasense; Rhinaris Sinomarin; ***Chile***: Fisiomar; Sinomarin; Sterimar†; ***Fr.***: Audi Baby; Audiclean; Audispray; Docuspray; Fanomer; Marimer†; Physiomer; Plasma du Dr Quinton†; Proceane Hypertonique†; Quies auriculaire†; Selgine; Sinomarin†; Sterimar; Thalamag; ***Ger.***: Rhinomer†; Rhinospray Atlantik†; Rinupret; ***Gr.***: Physiomer; ***Hong Kong***: Sinomarin; Sterimar; ***Hung.***: Solimar; Sterimar; ***Irl.***: Sterimar†; ***Israel***: Drossanose†; Rhinomer; Sterimar; ***Ital.***: Physiomer; Sterimar; ***Malaysia***: Sterimar; ***Mex.***: Allemar Nasalmer; Sterimar; ***Philipp.***: Physiomer; ***Rus.***: Aqua Maris (Аква Марис); Fluimarin (Флуимарин); Marimer (Маример); Morenazal (Мореназал); Physiomer (Физиомер); ***Singapore***: Sinomarin; Sterimar; ***Switz.***: Drossa-Nose; Fluimare; Nose Fresh; Otrivin Mer; Rhinomer; Siccoral; Sinomarin; Triomer; ***Turk.***: Lyomer†; Rhinomer; Sinomarin; Sterimar; Tonimer; ***UK***: Sterimar; ***Ukr.***: Aqua Maris (Аква Марис); Humer (Хьюмер); Marimer (Маример); Quixx (Квікс).

Multi-ingredient Preparations. ***Austral.***: Otrivin Saline Plus; ***Fr.***: Marinol; Thalamag fer B_9; ***Ger.***: Aliamare; Siozwo San; Weleda-Rheumasalbe M†; ***Hong Kong***: Mar Plus; ***Hung.***: Yam; ***Ital.***: Kamillosan Ocean; Respifree; Sterimar Cu; Sterimar Mn; ***Malaysia***: Mar Plus; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); ***Switz.***: Fluimare Plus; Narifresh; Nasmer 3plus; Nasmer free; Nose Fresh au D-panthenol; Nose Fresh; Rhinomer mini; Siccalix; ***Thai.***: Mar Plus; Marimer; ***UK***: Allerclear.

Seaweeds, Kelps, and Wracks

UNII — 477TV3P5UX (seaweed).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Kelp; Fucus vel Ascophyllum). The fragmented dried thallus of *Fucus vesiculosus* or *F. serratus* or *Ascophyllum nodosum*. It contains not less than 0.03% and not more than 0.2% of total iodine, calculated with reference to the dried drug. It has a salty and mucilaginous taste, and an unpleasant marine odour. Protect from light.

The Ph. Eur. title was formerly Bladderwrack and the BP 2014 gives Bladderwrack and Fucus as approved synonyms.

Uses and Administration

Dried seaweeds of various species are used in herbal preparations.

The terms kelps and wracks have been used indiscriminately for each other and other brown seaweeds. For example, Kelp (Ph. Eur. 8) refers to a preparation of various species of wrack and was formerly titled Bladderwrack.

Bladder wrack (*Fucus vesiculosus*), toothed wrack (*F. serratus*), or knotted wrack (*Ascophyllum nodosum*) are included in preparations given for various disorders including obesity, constipation, and iodine deficiency.

Kelps refer properly to species of *Laminaria* and *Macrocystis*. They are present as an ingredient of several dietary supplements and herbal preparations, including for use in obesity; they have also been used as a source of iodine. Laminaria stalks (p. 2540.1) are used for dilation of cavities or the cervix.

Fucoidan (p. 2508.1) is a sulfated polysaccharide extracted from brown seaweeds. Carrageenan (p. 2176.3) may be extracted from red seaweeds.

Homoeopathy

Fucus vesiculosus has been used in homoeopathic medicines under the following names: Fucus; Fucus v.

Adverse Effects and Precautions

Kelp can concentrate various heavy metals; auto-immune thrombocytopenic purpura and disordered erythropoiesis in a patient who had been taking kelp tablets for 6 weeks was attributed to the arsenic content of the preparation.[1]

Clinical hyperthyroidism has also been reported in patients taking kelp-containing preparations as part of a slimming regimen[2] or a dietary supplement.[3]

The FDA has advised that preparations containing compounds such as kelp, which may be taken orally in bulk laxatives or weight-control preparations, should be taken with a full glass of water or, if the patient has difficulty in swallowing, they should be avoided. Such compounds swell into masses that may obstruct the oesophagus if not taken with sufficient water.

1. Pye KG, *et al.* Severe dyserythropoiesis and autoimmune thrombocytopenia associated with ingestion of kelp supplements. *Lancet* 1992; **339:** 1540.
2. de Smet PA, *et al.* Hyperthyreoidie tijdens het gebruik van kelp tabletten. *Ned Tijdschr Geneeskd* 1990; **134:** 1058–9.
3. Eliason BC. Transient hyperthyroidism in a patient taking dietary supplements containing kelp. *J Am Board Fam Pract* 1998; **11:** 478–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sual; ***Braz.***: Redufat†; ***Canad.***: Thyodyn; ***Fr.***: Algues†; Dictyolone; ***UK***: Adios Max.

Multi-ingredient Preparations. ***Arg.***: Adelgacin; Arceligasol; Cellasene Gold; Cellasene†; Celu-Atlas; Centella Queen Complex; Centellase de Centella Queen; Centellase Gel; Dermasolutions†; Desgras Complex; Desgras; Herbaccion Celfin; Herbaccion Diet; KLB6 Fruit Diet; Natural Diet; Nio Marine; Redualgas; Silueta Plus†; Varisedan Gel; Yerba Diet; ***Austral.***: Daily Plus Max†; PMT-Eze†; Zellulean with Escin†; ***Canad.***: Floradix Tab†; Kyolic 101†; Saw Palmetto Formula†; Trim-Fit†; ***Chile***: Cellenergy; Celltech; Celu-Atlas; ***Cz.***: Reduktan; ***Fr.***: Boribel Tisane No 9; Cyclotelia; Dellova†; Dragees Fuca; Duo Reparation; Elusanes Algues brunes/aloes†; Marinol; Mediflor no 1; Menolistica; Neurovitol; Obeflorine†; Provencale No 2†; Tisane Provencale no 2†; ***Hong Kong***: Slimming Aid†; ***Hung.***: Metabol; ***Indon.***: DFM; ***Ital.***: Altadrine Firming†; Fave di Fuca; Skarflex; ***Pol.***: Herbaton†; ***S.Afr.***: Activex 40 Plus†; ***Singapore***: Scar Esthetique; Vitaton; ***Spain***: Lipograsil†; ***UK***: Adios; Aquella; Boldex; Gerard House Water Relief Tablets; HealthAid Boldo-Plus; Kelp Plus 3; Pure Plan; Water Naturtabs; Weight Loss Aid; ***Ukr.***: Mammoleptin (Маммолептин); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Adrenoid; KLB6; ***Venez.***: Demerung; Fugras; Lecivar Plus.

Homoeopathic Preparations. ***Austria***: Gracil; ***Canad.***: Formula Homeo QR 209†; Fucus L111†; Homeo-Form S†; Lympatox; Weight Control; Weight Loss Kit†; ***Chile***: Fucus Especial; ***Fr.***: Fucus Complexe No 111; ***Ger.***: Adiporell; Fucus-Gastreu S R59; Thyreo-Pasc; ***Switz.***: Regenaplex Nr. 71b; ***Venez.***: Strumeel T.

Secretin *(BAN, USAN, rINN)*

Secretina; Sécrétine; Secretinum; Sekretiini; Sekretin; Секретин.

CAS — 17034-35-4 (porcine); 108153-74-8 (human).
ATC — V04CK01.
ATC Vet — QV04CK01.
UNII — 88C55N56UU (scretin); A0426J905J (secretin human).

Units

The potency of secretin may be expressed as Crick-Harper-Raper (CHR) units based on the pancreatic secretion in *cats* or as clinical units, the value of which was amended in the 1960s. One clinical unit is considered to be equivalent to about 4 CHR units. One clinical unit is equivalent to 200 nanograms of a purified synthetic preparation of secretin.

Uses and Administration

Secretin is a polypeptide hormone involved in the regulation of gastric function. It may be prepared from the duodenal mucosa of *pigs*; synthetic human and porcine versions are also available. On intravenous injection it causes an increase in the secretion by the pancreas of water and bicarbonate into the duodenum.

Secretin is used as a diagnostic agent in various disorders of the pancreas. Patients should be given an initial intravenous test dose of 1 or 2 clinical units (200 or 400 nanograms); if no hypersensitivity reaction is noted after 1 minute, the diagnostic dose may be given.

Secretin is used alone, or with pancreozymin (p. 2582.1) or other cholecystokinetic agents such as ceruletide (p. 2473.3) or sincalide (p. 2616.3), as a test for exocrine pancreatic function (see under Pancreatitis, p. 2580.2). The test usually involves duodenal intubation of the patient and examination of duodenal aspirate. The diagnostic dose of secretin used has varied but common doses have been 1 clinical unit/kg (200 nanograms/kg) given by slow intravenous injection.

Patients with the Zollinger-Ellison syndrome (p. 1814.3) show an increase in gastrin when given secretin; this is in contrast to a small change or no effect in subjects without the disorder. The usual dose of secretin for the diagnosis of Zollinger-Ellison syndrome is 2 clinical units/kg (400 nanograms/kg) by slow intravenous injection. Serum-gastrin concentrations are measured for up to 30 minutes following the diagnostic dose.

Secretin is also used in a dose of 1 clinical unit/kg (200 nanograms/kg) by slow intravenous injection as an aid in the identification of the pancreatic ducts in patients undergoing endoscopic retrograde cholangiopancreatography.

Autism. There have been anecdotal reports of improvement in behaviour in autistic children given porcine secretin. However, a double-blind placebo-controlled study[1] involving 60 children with autism or pervasive developmental disorder noted no benefit over 4 weeks after a single infusion of 400 nanograms/kg of synthetic human secretin. A randomised, placebo-controlled study[2] in 64 children with autism has similarly found no evidence of efficacy from 2 repeated doses of porcine secretin. Further controlled studies have likewise failed to show efficacy.[3,4]

1. Sandler AD, *et al.* Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. *N Engl J Med* 1999; **341:** 1801–6.
2. Roberts W, *et al.* Repeated doses of porcine secretin in the treatment of autism: a randomized, placebo-controlled trial. Abstract: *Pediatrics* 2001; **107:** e71. Full version: http://pediatrics.aappublications.org/cgi/reprint/107/5/e71.pdf (accessed 16/08/10)
3. Levy SE, *et al.* Children with autistic spectrum disorders. I: comparison of placebo and single dose of human synthetic secretin. *Arch Dis Child* 2003; **88:** 731–6.
4. Coplan J, *et al.* Children with autistic spectrum disorders. II: parents are unable to distinguish secretin from placebo under double-blind conditions. *Arch Dis Child* 2003; **88:** 737–9.

Adverse Effects

Adverse effects reported with secretin include flushing, nausea, vomiting, and abdominal pain. There is the potential for hypersensitivity reactions to occur.

Precautions

The secretin test should be avoided in patients with acute pancreatitis. Patients should receive an intravenous test dose because of the risk of hypersensitivity reactions. Results of the secretin test should be interpreted with caution in patients who have had a vagotomy, who have inflammatory bowel disease, or who are receiving anticholinergics at the time of the test because they may be hyporesponsive to secretin stimulation. Conversely, patients with alcoholic or other hepatic impairment occasionally show a greater than normal response to secretin stimulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Secrelux; ***Gr.***: Secrelux; ***USA***: ChiRhoStim.

Senecio

Крестовник Якова (*Senecio jacobaea*); Крестовник Золотистый (*Senecio aureus*).

*ATC Herb — HG04BW5036 (*Senecio aureus*: herb); HG02WA5003 (*Senecio aureus*: herb).*
*UNII — 5WS1632J8W (*Senecio aureus*).*

NOTE. The common name tansy ragwort has also been used for *Senecio jacobaea* and should not be confused with tansy, which is *Tanacetum vulgare* (see p. 2625.3).

Profile

The ragwort, *Senecio jacobaea*, and, in the USA, the golden ragwort (golden senecio; liferoot; squaw weed), *S. aureus* (Compositae), have been used in the form of extracts as emmenagogues but are of doubtful value. Ragwort, in the form of a decoction or ointment, has also been applied externally to aid wound healing and in the treatment of peripheral vascular disorders.

Many species of the genus *Senecio*, which includes the ragworts and groundsels, are poisonous. They have been found to contain pyrrolizidine alkaloids, which produce hepatic necrosis. The ragwort, *S. jacobaea*, which is abundant throughout the British Isles, is poisonous to livestock when eaten in quantity. Poisoning has also been reported in humans after ingestion of herbal teas containing pyrrolizidine alkaloids. In the UK, the sale, supply, or importation of unlicensed medicinal products containing *Senecio* spp. for internal use is prohibited.

Homoeopathy

Golden ragwort has been used in homoeopathic medicines under the following names: Senecio aur.; Senecio aureus; Sen. aur..

Ragwort has been used in homoeopathic medicines under the following names: Senecio jacobaea; Senecio jac.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Pascofemin; ***Canad.***: Motherwort Combination 1†; ***Cz.***: Hormeel S; ***Fr.***: L 25; Sclerocalcine; ***Ger.***: Pascofemin; ***Hung.***: Hormeel S; ***USA***: Succus Cineraria Maritima†.

Senicapoc *(USAN, rINN)*

17043; ICA-17043; Sénicapoc; Senicapocum; Сеникапок.
2,2-bis (4-Fluorophenyl)-2-phenylacetamide.
$C_{20}H_{15}F_2NO$=323.3
CAS — 289656-45-7.
UNII — TS6G201A6Q.

Profile

Senicapoc is an inhibitor of the Gardos calcium-activated potassium channel that is under investigation as an oral treatment for asthma. It has also been investigated to prevent the dehydration of red cells in sickle-cell anaemia.

References.

1. Ataga KI, *et al.* Efficacy and safety of the Gardos channel blocker, senicapoc (ICA-17043), in patients with sickle cell anemia. *Blood* 2008; **111:** 3991–7.
2. Ataga KI, Stocker J. Senicapoc (ICA-17043): a potential therapy for the prevention and treatment of hemolysis-associated complications in sickle cell anemia. *Expert Opin Invest Drugs* 2009; **18:** 231–9.

Senlizumab *(BAN)*

Bay-10-3356; Bay-w-3356; CDP-571; Сенлизумаб.
CAS — 336128-48-4.

NOTE. The name Humicade has been used as a trade mark for senlizumab.

Profile

Senlizumab is a humanised monoclonal antibody to tumour necrosis factor. It has been investigated in the treatment of Crohn's disease, ulcerative colitis, and rheumatoid arthritis.

References.

1. Rankin EC, *et al.* The therapeutic effects of an engineered human anti-tumour necrosis factor alpha antibody (CDP571) in rheumatoid arthritis. *Br J Rheumatol* 1995; **34:** 334–42.
2. Evans RC, *et al.* Treatment of ulcerative colitis with an engineered human anti-TNF alpha antibody CDP571. *Aliment Pharmacol Ther* 1997; **11:** 1031–5.
3. Stack WA, *et al.* Randomised controlled trial of CDP571 antibody to tumour necrosis factor-α in Crohn's disease. *Lancet* 1997; **349:** 521–4.
4. Anonymous. CDP 571: anti-TNF monoclonal antibody, BAY 103356, BAY W 3356, Humicade. *Drugs R D* 2003; **4:** 174–8.
5. Sandborn WJ, *et al.* CDP571, a humanised monoclonal antibody to tumour necrosis factor α, for moderate to severe Crohn's disease: a randomised, double blind, placebo controlled trial. *Gut* 2004; **53:** 1485–93.
6. Mamula P, *et al.* CDP571, a humanized anti-tumor necrosis factor-alpha monoclonal antibody in pediatric Crohn's disease. *Inflamm Bowel Dis* 2004; **10:** 723–30.
7. Feagan BG, *et al.* A randomized, double-blind, placebo-controlled trial of CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, in patients with corticosteroid-dependent Crohn's disease. *Aliment Pharmacol Ther* 2005; **21:** 373–84.
8. Feagan BG, *et al.* CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006; **23:** 617–28.

Sepia

UNII — QDL83WN8C2.

Profile

Sepia is the dried inky secretion of the cuttle fish.

Homoeopathy

Sepia has been used in homoeopathic medicines under the following names: Sepia officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Femi-Nan; Nervatona Calm; Nervatona Focus; ***Thai.***: Venium.

Homoeopathic Preparations. ***Austral.***: Homoderma; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Nervatona Calm; Nervatona Focus; Respatona Nasal Spray Decongestant; Travellers Relief; ***Austria***: Haemex; Klimaktoplant; Mefem; Nervoheel; Orgafem; Remens; Sulfur Med Complex; ***Canad.***: Eczema; Formula CA 205†; Men Complex†; ***Chile***: Lachess; ***Cz.***: Hormeel S; Vita C-R15 forte†; Vita C-R15†; ***Fr.***: Abbe Chaupitre no 23†; Abbe Chaupitre no 30†; Abbe Chaupitre no 59†; Helonias Compose; Sepia Complexe No 20; Sepia Compose; ***Ger.***: Ambrax; Cefakliman S; Cefaklimant†; Dermi-cyl L Ho-Len-Complex; HanoFemin; Infi-China; Infi-Symphytum; Infifer N; Klimaktoplant N; Meno-cyl L Ho-Len-Complex; Sepia comp; ***Hung.***: Hormeel S; Klimakt-Heel; Nervoheel; ***Neth.***: Homeocare Cyclo; Homeocare Nervo; Hormeel H; Klimaktolan; Mulimen H; Nervofleur; Nervoheel; ***Rus.***: Hormeel SN (Гормель СН); Klimaktoplan (Климактоплан); Remens (Ременс); ***Switz.***: Menosan†; Nervoheel; ***Ukr.***: Homvio-Nervin (Хомвио-Нервин); Klimaktoplan N (Климактоплан Н); Remens (Ременс); ***USA***: Estrex.

Serotonin

Enteramina; Enteramine; 5-Hidroxitriptamina; 5-HT; 5-Hydroxytryptamine; Serotonina; Серотонин.
3-(2-Aminoethyl)-1*H*-indol-5-ol.
$C_{10}H_{12}N_2O$=176.2
CAS — 50-67-9.
UNII — 333DO1RDJY.

Profile

Serotonin, which is synthesised in the body from the essential amino acid tryptophan, is found in the brain, blood platelets, and throughout the gastrointestinal tract. It acts as a biochemical mediator and its roles include involvement in CNS neurotransmission, haemostasis, vascular spasm, and gastrointestinal motility. Abnormalities within the serotonin system are associated with a variety of disorders and many drugs have been developed to manipulate serotonin concentrations.

Serotonin itself may be of value in the treatment of posthypoxic myoclonus (p. 511.3). Concentrations of endogenous serotonin may be increased through synthesis and serotonin precursors have been given for the treatment of depression (see Oxitriptan, p. 440.3 and Tryptophan, p. 453.2).

Some antidepressants increase serotonin concentrations by inhibiting the metabolism of monoamine oxidase type A, the enzyme that deaminates serotonin. Examples include the older non-selective irreversible inhibitors of monoamine oxidase types A and B (MAOIs) such as phenelzine (p. 442.1), and the newer selective reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (p. 437.2).

Drugs that inhibit the neuronal reuptake of serotonin after release (and thus potentiate its action) are also used in the treatment of depression. They include tricyclic antidepressants such as amitriptyline (p. 401.1), the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (p. 417.1), and selective serotonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine (p. 454.2). Some SSRIs and SNRIs are also used in the management of anxiety disorders, and SSRIs have been tried in the management of premature ejaculation. Sibutramine (p. 2330.2) is an SNRI used in the management of obesity.

Serotonin receptors, a major site of drug action, are classified by structure and function into seven families: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 with each family having further subtypes. Consequently, drugs acting on serotonin receptors have widely differing chemical structures and diverse pharmacological activities depending on which receptor subtype they act on and whether they act as agonists or antagonists. Serotonin receptor activity is complex and it is possible for the same disorder to be treated by both serotonin agonists or antagonists. For example, serotonin antagonists used in the treatment of migraine include the older ergot-derived compounds such as methysergide (p. 677.1) and metergoline (p. 2557.2) whereas the newer triptans such as sumatriptan (p. 679.2) are selective 5-HT_1 agonists. Buspirone (p. 1042.1) is a 5-HT_{1A} partial agonist used in the treatment of anxiety disorders. Cisapride (p. 1831.3) is a 5-HT_4 agonist used for gastrointestinal disorders. 5-HT_{2C} agonists are under investigation for obesity.

Many different drugs act as serotonin antagonists. They include sedating antihistamines such as carbinoxamine (p. 619.1), cyproheptadine (p. 624.1), methdilazine (p. 635.3), and promethazine (p. 638.2) used for allergic conditions. Some antiserotonergic antihistamines such as cyproheptadine, oxetorone (p. 678.1), and pizotifen (p. 678.2) are also used in the management of migraine. Antagonists specific for the 5-$HT_{2A/2C}$ receptor include the antihypertensive ketanserin (p. 1415.3), the antipsychotic risperidone (p. 1103.2), and the antidepressant trazodone (p. 451.1). The antipsychotic clozapine (p. 1057.3) also has antiserotonergic activity at the 5-$HT_{2A/2C}$ receptor in addition to its other properties. Ondansetron (p. 1872.1) is a 5-HT_3 antagonist used for chemotherapy-induced emesis and postoperative nausea and vomiting.

Drugs with other mechanisms of action involving serotonin systems include fenclonine, an inhibitor of serotonin synthesis that has been used in the treatment of carcinoid syndrome. Reserpine (p. 1485.3) depletes serotonin stores in the brain, heart, and many other organs and has been used in hypertension and psychoses. Fenfluramine (p. 2322.3) and its isomer dexfenfluramine (p. 2320.3) appear to stimulate the release of serotonin and selectively inhibit its reuptake resulting in increased CNS serotonin concentrations; both were formerly used in the treatment of obesity.

Some hallucinogenic drugs of abuse such as bufotenine (p. 2462.2) and lysergide (p. 2547.1) have serotonergic properties.

Serotonin also occurs in stinging nettles (*Urtica dioica*) (p. 2639.3), bananas, and other fruit, and in the stings of wasps and scorpions.

References.

1. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. *Br J Anaesth* 1994; **73:** 395–407.
2. Hoyer D, *et al.* International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 1994; **46:** 157–203.

Serrapeptase *(rINN)* ⊗

Serrapeptasa; Serrapeptasum; Serrapeptidase; Serratia Extracellular Proteinase; Serratiopeptidasa; Serratiopeptidase; Серрапептаза.
CAS — 37312-62-2; 95077-02-4.

Pharmacopoeias. In *Jpn.*

Profile

Serrapeptase is a proteolytic enzyme derived from *Serratia* spp. It has been taken orally for its supposed action in relieving inflammation and oedema associated with conditions such as trauma, infection, respiratory-tract congestion, or chronic venous insufficiency, in usual doses of 5 to 10 mg (10 000 to 20 000 units) up to three times daily.

References.

1. Tachibana M, *et al.* A multi-centre, double-blind study of serrapeptase versus placebo in post-antrotomy buccal swelling. *Pharmatherapeutica* 1984; **3:** 526–30.
2. Shimizu H, *et al.* A case of serratiopeptidase-induced subepidermal bullous dermatosis. *Br J Dermatol* 1999; **141:** 1139–40.
3. Nakamura S, *et al.* Effect of the proteolytic enzyme serrapeptase in patients with chronic airway disease. *Respirology* 2003; **8:** 316–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Danzen; ***Chile***: Damizen; ***China***: Dasen (达先); Qu Tan (曲坦); Seradase (释瑞达); ***Fr.***: Dazen†; ***Ger.***: Aniflazym; ***Gr.***: Brasan; Enziflur; Eze; Lergan; Retazymon; Revicam; Salavira; Smaritass; Tsoncel; Verolin; ***Hong Kong***: Danzen; Unizen; ***India***: Adpep; Aldase; Amidase; Asidase; Aslera; Avisera; Bidanzen; Biodase; Biosera; Biosuganril; Bradyhist; C-Serra; Cipzen; Copres-M; Cuzen; CYS; Dacnis; Daze; Dazen; Dazina-Forte; Densera; Emanzen; Ensera; Erasan; Eudase; Everser; Flanzen; Flaser Forte; Forses; GS; Infladase Forte; Infladase; Inflazen; Intase; Kineto; Kinex; Lupict; Lyser; Maxilase; Microdase; Optase; Seraim; Serato-M; ***Ital.***: Danzen; ***Jpn***: Dasen†; ***Malaysia***: Danzen; Serrin; Unizen; ***Mex.***: Danzen; ***Port.***: Aniflazime; ***Singapore***: Danzen; Serrazyme; Sinsia†; Tolpa; Unizen; ***Thai.***: Dailat; Danzen; Danzinin; Danzyme; Denzo; Fazen; Medizyme; Rodase; Seramed†; Serdas; Serradase; Serrano; Serrao; Serrapep; Serrason; Serrin; Serti-O; Sumidin; Tanza; Unizen; ***Ukr.***: Movinaza (Мовиназа); Serox (Серокс).

Multi-ingredient Preparations. ***India***: Abdal-SP; AC Sera; ACB-S; Accept-SP; Acec Plus; Aceclo-Sera; Acecloren; Acedase; Acefen-SP; Aceforce-SP; Acelofan-SP; Acelom-SP; Acemove Plus; Acemove; Acent-SD; Acepara-S; Acetal-SP; Acetuff-SP; Acicloflex-SF; Acimol-S; Aciz-SP; Aclocta-P; Aclodase; Aclog-SD; Aclomp-SP; Aclonac-SN; Acloson-SP; Acota-3; Actimol-S; Adifax-SP; Adpep-D; Afesan-SP; Agile-S; Alco-PS; Aldase-D; Aldidase-P; Aldidase; Aleron; Alnase-SP; Alostar-SP; Alto-3D; Amclox-LBS; Amiclox Plus; Amidase-D; Amidase-DP; Amidase-N; Amoxydase; Arflur-3D; Armdic SP; Aroff-EZ; Arrestin-SP; Arsulide-S;

Artidin; Artirox-SP; Asflam; Aslera-D; Aslera-DP; Asonac-SR Plus; Asonac-SR; Atodase-D; Avidox-SP; Aviflox-ST; Avirox-ST; Avisera Plus; Avisera-MR; Axcel-LS; Bclomox; Bilin-CS; Biodase-D; Bionac-Forte; Biopep-D; Biozobid-N; Biozobid; Biplox-SL; C-Serra-D; C-Tri EM; Cadmoxin-CS; Cadpo-D; Cadpo-N; Canmet-SN; Capilac XP; Ceco-SP; Ceflame-K; Ceflame; Celfast Plus; Cep-DP; Cipzen D; Cipzen N; Claridase; Clobee-SP; Clofen-SP; Clonac-SP; Cluster; Cobacta-S; Copres-M-20; Cuga Plus; Cuga; Cure; Cuzen-DP; Cuzen-NM; Cynac-S; Cynac-SP; Cynox; CYS-D; Cytodec Forte; Cytodec; Dacpar-S; Daze-D; Daze-DP; Daze-MX; Dazina-DP; Delaxin; Delnim-SP; Demo-S; Demo-SP; Denim Plus; Densera-D; Densera-N; Devona-S; Dicin; Diciosis; Dicloflam SP; Diclom-SP; Diclopep Plus; Diclopep; Diclosar-P; Dicnacx-S; Dicnacx-SP; Dicol-S; Dicoliv-S; Difin-S; Dikul SP; Dil SE; Dilona-SP; Dilophen-SP; Diplofen 3D; Diser; Divon-S; Dixer-S; Dixfree-SP; Dizer-N; Dofec-S; Dol; Dolocrat; Dolokind-AA; Doloral; Doloroff-ASP; Dolowin Forte; Dordase-D; Dordase-DP; Dox-M ST; DS-15 Plus; DS-15; DSP; Dublace-SP; Ebility; Edase-D; Edase-N; Edilox-S; Emanzen-D; Emanzen-DP; Emanzen-N; Enzoflam; Enzovexx; Erase-D; Essmol-3 Plus; Eudase-D; Eudase-DP; Eudase-MX; Everser-D; Fenbest Plus; Fico-SP; Filco-S; Flago; Flamace-S; Flamace-SP; Flamese; Flanzen-D; Flanzen-DP; Flanzen-MX; Flanzen-RX; Flaser-D; Flaxinac-SP; Flexigesic-S; Floxzen-ST; Flozen Plus; Flozen-AA; Flozen-NS; Flupara-SN; Fonim-S; Forgesic-SP; Fornac-SP; Freedom Forte; Freedom; Genac-SP; Gesnim-S; Gic-SR; Glymox-Plus; Glymox; Godic-S; Gramol-SP; Healpil; Hidiclo Plus; Hidiclodase; Hifenac-D; Himox-LS; Hydase-D; Icobit-S; Inflahit-SP; Inflakod; Inloxy-SLB; Insider; Intase DF; Kevrox-S; Kevrox-SA; Kineto DP; Kineto-D; Kinser-DP; Klick; Klonac-XS; Kurdase Plus; Kurdase-D; Lebec-D; Leemoxin-CS; Leofenac-SP; Litonac-SP; Lyser-A Plus; Lyser-D; Lyser-DP; Mahanac Pro; Mardase-K; Maxiflam-SP; Maxoflam; MDace-SP; Megadase-D; Microdase-D; Microdase-DP; Minipar-SP; Mobinorm-S; Morcet Plus; Movinim-S; Moviz-3D; Moxtid-CS; Moxyplus-SL; Mydic-S; N-S-Plus; Naclomol-S; Nacser D; Neet-S; Nelsid-S; Neomol-XP; Niclofen-S; Niclopar-S; Nifen Plus; Nile-S; Nile-SP; Nimacesp; Nimdase-P; Nimkul SP; Nimley-S; Nimpain PS; Nimpep; Nimpure-PS; Nimsaid-S; Nimsol Plus; Nimulase-D; Nimulid SP; Nimustar-S; Nimven-S; Nimvon-S; Niser; Nismol-S; Nizapas-SP; Novodase; Novolid-S; Nucoxia-SP; Nugesia-SP; Nusaid-SP; Optase-D; Optizen-D; Orra-D; Orthobid Plus; Oxin Plus; Pacinac; Panama-SP; Panum-SP; Paratel-DS; ***Indon.***: Dansera; Flavin; Nutriflam.

Sesame Oil

Aceite de Ajonjoli; Aceite de sésamo refinado; Benne Oil; Gingelly Oil; Oleum Sesami; Refined Sesame Oil; Seesamiöljy; Sésame, huile de; Sesami oleum; Sésamo, aceite de; Sesamolja; Sezamų aliejus; Sezamový olej; Szezámolaj; Teel Oil; Кунжутное Масло; Сезамовое Масло.

CAS — B00B-74-0.

UNII — QX10HYY4QV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Sesame Oil, Refined; Sesami Oleum Raffinatum). The fatty oil obtained from the ripe seeds of *Sesamum indicum* by expression or extraction and subsequent refining. It may contain a suitable antoxidant. It is a clear, light yellow, almost colourless liquid. It solidifies to a soft mass at about -4 degrees. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled, airtight containers. Protect from light. Refined sesame oil for use in the manufacture of parenteral dosage forms should be stored under an inert gas in airtight containers.

USNF 31: (Sesame Oil). The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* (Pedaliaceae). It may contain suitable antoxidants. A pale yellow, practically odourless, oily liquid. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, with ether, and with petroleum spirit. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps, as well as for culinary purposes. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been seen.

Adverse effects. References to hypersensitivity reactions[1-7] associated with sesame, and subcutaneous nodules[8] after injection of the oil.

1. Kanny G, *et al.* Sesame seed and sesame seed oil contain masked allergens of growing importance. *Allergy* 1996; **51:** 952–7.
2. Stern A, Wuthrich B. Non-IgE-mediated anaphylaxis to sesame. *Allergy* 1998; **53:** 325–6.
3. Pecquet C, *et al.* Immediate hypersensitivity to sesame in foods and cosmetics. *Contact Dermatitis* 1998; **39:** 313.
4. Asero R, *et al.* A case of sesame seed-induced anaphylaxis. *Allergy* 1999; **54:** 526–7.
5. Dalal I, *et al.* The pattern of sesame sensitivity among infants and children. *Pediatr Allergy Immunol* 2003; **14:** 312–16.
6. Agne PS, *et al.* Sesame seed allergy in children. *Allerg Immunol (Paris)* 2004; **36:** 300–305.
7. Gangur V, *et al.* Sesame allergy: a growing food allergy of global proportions? *Ann Allergy Asthma Immunol* 2005; **95:** 4–11.
8. Darsow U, *et al.* Subcutaneous oleomas induced by self-injection of sesame seed oil for muscle augmentation. *J Am Acad Dermatol* 2000; **42:** 292–4.

Uses. References.

1. Ji ZL, *et al.* Therapeutic value of sesame oil in the treatment of adhesive small bowel obstruction. *Am J Surg* 2010; **199:** 160–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Rhinaris Nozoil; ***India***: Keratex; ***Switz.***: Nose Fresh; ***UK***: Noseeze.

Multi-ingredient Preparations. ***Austral.***: Nozoil; ***Canad.***: Pure Gardens; ***Ger.***: GeloSitin; ***India***: Aloederm-G; Aloederm; ***Jpn***: Shiunko; ***NZ***: Snorenz; ***Singapore***: Snoreeze; ***Switz.***: Prevalin; ***Turk.***: Snoreless; ***UK***: Goodnight StopSnore; Snor-Away.

Shark-liver Oil

Жир Печени Акулы.

UNII — 4B24275HEU.

Profile

Shark-liver oil is the fixed oil extracted from the liver of various species of shark and is used in preparations for anorectal disorders. It has been used as a source of vitamin A.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sperti Preparacion H; ***Hung.***: Alkymer; ***Pol.***: Ecomer; Selamer†; ***Rus.***: Relief Advance (Релиф Адванс); ***UK***: Immutone.

Multi-ingredient Preparations. ***Arg.***: Sperti PH; ***Austria***: Sperti Praparation H; ***Canad.***: Preparation H; ***Chile***: Sperti Preparation H; ***Cz.***: Preparation H; ***Gr.***: Preparation H; ***Hong Kong***: Preparation H; ***Hung.***: Sperti Preparation H; ***India***: Medithane; ***Irl.***: Preparation H†; ***Israel***: Preparation H; ***Ital.***: Preparazione H; ***Malaysia***: Palmer's Cocoa Butter Formula Scar Serum; ***Mex.***: Cartibon; Preparation H; ***Neth.***: Sperti Preparation H; ***Port.***: Sperti Preparacao H; ***Rus.***: Preparation H (Препарейшн Эйч)†; Relief (Релиф); Relief Ultra (Релиф Ультра); ***S.Afr.***: Preparation H†; ***Singapore***: Preparation H; ***Spain***: Preparacion H†; ***Switz.***: Sperti Preparation H†; ***Thai.***: Preparation H†; ***UK***: Preparation H; ***Ukr.***: Relief (Релиф); Relief Advance (Релиф Адванс); Relief Ultra (Релиф Ультра); ***USA***: Hem-Prep; Preparation H; Rectacaine; Rectagene Medicated Balm; Wyanoids Relief Factor.

Shatavari

Satavar; Satmuli; Wild Asparagus; Шатавари.

NOTE. Distinguish from garden asparagus which is covered in Asparagus, p. 2450.2.

Profile

The root of shatavari, *Asparagus racemosus* (Asparagaceae), is used in Ayurvedic medicine for a range of disorders. There is some interest in its antidiabetic and oestrogenic properties.

The related species *A. adscendens* is used in Ayurvedic medicine as a tonic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Aspamom; Lukure.

Multi-ingredient Preparations. ***Hung.***: Munipyrin; ***India***: Abana; Addyzoa; Aswal Plus; Cephagraine; Cystone; Diabecon; Eugynin; Evecare; Geriforte; Geriforte; Glowone; Good Time; Gynoset; Happy'tizer†; Herr; Himplasia; Lactacrat; Lactare; Lactare; Lactonic; Lima; Lukol; Memtone; Menosan; Mentofer; ***Singapore***: Imunomet; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Eve Care (Ив Кер)†; Fitovit (Фитовит); Imunin (Иммунин)†.

Shepherd's Purse

Bolsa de pastor; Bourse à pasteur; Capsella; Herba Bursae Pastoris; Jaramago; Paniquesillo; Shepherds Burse Herb; Zurrón de pastor; Пастушья Сумка Обыкновенная.

ATC Herb — HG02WC5001 (Capsella bursa-pastoris: herb).

UNII — W0X9457M59 (Capsella bursa-pastoris).

Pharmacopoeias. In *Fr.*

Profile

Shepherd's purse, the aerial parts of *Capsella bursa-pastoris* (*Thlaspi bursa-pastoris*) (Cruciferae) has antihaemorrhagic and astringent properties. It is used to prevent or arrest bleeding, and has been specifically used for menorrhagia. It is also used for urinary-tract disorders and diarrhoea.

Homoeopathy

Shepherd's purse has been used in homoeopathic medicines under the following names: Capsella bursa-pastoris; Thlaspi bursa pastoris; Thlaspi; Capsella; Thal. b. p.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Styptysat.

Multi-ingredient Preparations. ***Austral.***: Capsella Complex; Femi-Nan; ***Austria***: Menodoron; ***Fr.***: Histo-Fluine P; Tisane Provencale no 3†; ***Ger.***: Menodoron; ***Pol.***: Klimax; Prostapol; Uroprost; ***S.Afr.***: Menodoron†; ***Switz.***: Menodoron; ***UK***: Antitis; Sciargo.

Homoeopathic Preparations. ***Canad.***: Renelix; ***Chile***: Variplex; ***Cz.***: Hormeel S; ***Fr.***: Boripharm No 15†; Sabal Serrulata Compose; Urodren; ***Hung.***: Hormeel S; ***UK***: Menodoron.

Siam Benzoin

Benjoin du Laos; Benjuí de Siam; Bensoe, Siam; Bentsoe, Siam; Benzoe Tonkinensis; Benzoino derva; Benzoová pryskyřice siamská; Сиамский Бензоин.

CAS — 9000-72-0.

ATC Herb — HD02WX5007 (Styrax tonkinensis: resin); HR05WA5054 (Styrax tonkinensis: resin).

UNII — QB299X2IBD.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in some pharmacopoeias under the title benzoin and should not be confused with Sumatra benzoin. *Jpn* and *US* allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

Ph. Eur. 8: (Benzoin, Siam). The resin obtained by incising the trunk of *Styrax tonkinensis*. It has a characteristic odour of vanillin and contains 45.0 to 55.0% of total acids, calculated as benzoic acid, and with reference to the dried drug. Protect from light.

USP 36: (Benzoin). A balsamic resin from *Styrax tonkinensis*, or other species of the *Anthostyrax* section of the genus *Styrax* (Styracaceae). It yields not less than 90% of alcohol-soluble extractive. It occurs as pebble-like tears of variable size and shape, compressed, yellowish-brown to rusty brown externally, milky white on fracture, separate or very slightly agglutinated, hard and brittle at ordinary temperatures but softened by heat. It has an agreeable, balsamic, vanilla-like odour.

Profile

Siam benzoin has been used similarly to Sumatra benzoin (p. 2624.3). It has also been used as a preservative and was formerly used in the preparation of benzoinated lard.

Preparations of Siam benzoin are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Balsolene; Borostyrol; Euvanol; Homeoplasmine; Inotyol; ***Israel***: Inotyol.

Homoeopathic Preparations. ***Canad.***: Homeoplasmine; ***Port.***: Homeoplasmine†; ***Switz.***: Homeoplasmine.

Pharmacopoeial Preparations

USP 36: Compound Benzoin Tincture; Podophyllum Resin Topical Solution.

Siberian Ginseng

Ciwujia; Eleuterokokų šaknys (eleuthero-coccus); Eleuterokokový kořen (eleutherococcus); Eleuthero; Eleutherococci Radix (eleutherococcus); Éleuthérocoque (eleutherococcus); Korzeń eleuterokoka (eleutherococcus); Rysk rot (eleutherococcus); Tajgagyökér (eleutherococcus); Venäjänjuuri (eleutherococcus); Элеутерококк; Сибирский Женьшень.

ATC Herb — HN06WA5001 (Eleutherococcus senticosus: root).

UNII — ZX5Z2LW23O (Eleutherococcus senticosus); ZQH6VH092Z (Eleutherococcus senticosus root); 0DAFB7OMMD (Eleutherococcus senticosus root water).

NOTE. The name Russian Ginseng has been applied to *Eleutherococcus senticosus*.

The name Ginseng usually refers to *Panax ginseng* and related species (see p. 2513.3).

Some material supplied as Siberian ginseng may be *Periploca sepium* (Asclepiadaceae), a plant unrelated to *Eleutherococcus senticosus*, due to the similarity of the Chinese names for these plants.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *US* also includes a powdered form and a powdered extract.

Ph. Eur. 8: (Eleutherococcus; Eleutherococci Radix). The dried, whole or cut underground organs of *Eleutherococcus senticosus*. It contains not less than 0.08% for the sum of eleutheroside B and eleutheroside E.

USP 36: (Eleuthero). The dried rhizome with roots of *Eleutherococcus senticosus* (Araliaceae) (*Acanthopanax senticosus*) (Araliaceae). It contains not less than 0.08% of the sum of eleutheroside B and eleutheroside E, calculated on the dried basis. Protect from light.

Uses and Administration

Siberian ginseng is reported to enhance natural resistance and to improve performance under stress. It is used similarly to ginseng (*Panax ginseng*) (see p. 2513.3) although the constituents of the two herbs are different. It is also used in traditional Chinese medicine.

Reviews.

1. Davydov M, Krikorian AD. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol* 2000; **72:** 345–93.
2. WHO. Radix Eleutherococci. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/10.html (accessed 04/02/10)

Adverse Effects

Stroke. Thalamic infarction occurred in a 26-year-old man who had taken oral high-energy dietary supplements containing Siberian ginseng daily for about a year during a vigorous training programme for a marathon.[1] He had taken about 1.5 to 2 g of Siberian ginseng daily; small amounts of caffeine were also contained in the preparations. In the absence of other aetiological factors, it was proposed that prolonged daily use of Siberian ginseng and caffeine with vigorous exercise was responsible for the stroke.

1. Polenakovik S. Dietary supplements and stroke. *Mayo Clin Proc* 2005; **80:** 1240–1.

Interactions

For a report of raised serum-digoxin concentrations in a patient taking *digoxin* and Siberian ginseng, see Interference with Digoxin Assays, p. 1355.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Russisk Rod; ***Ger.***: Eleu-Kokk; Eleu; Konstitutin; ***Pol.***: Immunostim†; Syberian; ***Switz.***: Vigor; ***UK***: Elagen.

Multi-ingredient Preparations. ***Arg.***: Sigmafem; Vitalsex; ***Austral.***: Aloe Vera Plus; Astragalus Complex; Bacopa Complex; Enhance for Men; For Women Active Woman Formula†; Ginsynergy plus Rhodiola; Mens Dual-Action Multi; Tribulus & Epimedium Compound; Withania Compound; Women's Vitality Multi; Womens Multi; ***Fr.***: Ginvit; ***Indon.***: Reximax; Tripote†; ***Ital.***: Almavigor; Atlantis; Energeia; Fon Wan Memory; Lactovit; Ristabil; Taingel; Vitalmix Fos; ***Philipp.***: Immuvit; Jamieson Total Energy; Leginsol-E; ***Pol.***: Tripoten; ***Rus.***: Arfazetin-E (Арфазетин-Э); Evalar (Эвалар); Kliophyt (Клиофит); Phytonefrol (Фитонефрол); ***Spain***: Tonimax; ***Swed.***: Chisan; Chisandra; Kan Jang; ***Ukr.***: Alfagin (Алфагин); Herbastress (Гербастресс); Immuno-Ton (Іммуно-Тон); Liponorm (Липонорм).

Homoeopathic Preparations. ***Canad.***: Alfalfa Tonic; Alfalfa Tonic.

Sigetin

Sygethin; Сигетин.
Dipotassium *meso*-3,4-Bis(*p*-sulfophenyl)hexane.
$C_{18}H_{20}O_6S_2K_2$=474.7
CAS — 13517-49-2.

Profile

Sigetin is an analogue of hexestrol (p. 2283.3) but is reported to have no oestrogenic activity. It is used in the management of menopausal symptoms in a usual oral daily dose of 100 to 200 mg.

Sigetin is also reported to enhance the action of oxytocin and to improve placental blood flow and has been given intravenously or intramuscularly in the active management of labour and for threatened intra-uterine fetal asphyxia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Sagenit (Сагенит).

Silver

Argent; Argentum; E174; Plata; Silber; Серебро.
Ag=107.8682
CAS — 7440-22-4.
ATC — D08AL30.
ATC Vet — QD08AL30.
UNII — 3M4G523W1G.

Profile

Silver is a pure white, malleable and ductile metal. It possesses antibacterial properties and is used topically either as the metal or as silver salts. It is not absorbed to any great extent and the main problem associated with the metal is argyria, a grey discoloration of the tissues (see below). Silver is also present as the core in some copper-wound plastic intra-uterine contraceptive devices. Silver is used as a colouring agent for some types of confectionery.

Salts or compounds of silver that have been used therapeutically include silver acetate (below), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (below), silver-nylon polymers, silver protein (p. 2616.2), and sulfadiazine silver (p. 362.3).

Homoeopathy

Silver has been used in homoeopathic medicines under the following names: Argentum metallicum; Arg. met.

Silver chloride has been used in homoeopathic medicines under the following names: Argentum muriaticum; Arg. mur.

Silver cyanide has been used in homoeopathic compounds under the following names: Argentum cynatum; Argentum cyanatum; Arg cyanat;Arg. cy.

Silver iodide has been used in homoeopathic medicines under the following names: Argentum iodatum; Arg. iod.

Silver oxide has been used in homoeopathic medicines under the following names: Argentum oxydatum; Arg oxyd.

Silver phosphate has been used in homoeopathic medicines under the following names: Argentum phosphoricum; Arg phos.

Reviews.

1. Lansdown AB. Silver in health care: antimicrobial effects and safety in use. *Curr Probl Dermatol* 2006; **33:** 17–34.

Argyria. Argyria (generalised argyrosis), characterised by a slate, blue-grey discoloration of the skin, sclera, mucosal surfaces, and nails, developed in a patient who had used vasoconstrictor nasal drops containing silver protein for 4 years. The colour changes were most obvious in skin exposed to the sun. Argyria is irreversible and withdrawal of the nasal drops and use of other measures such as use of sun block and chemical peeling had little effect in this patient.[1]

1. Tomi NS, *et al.* A silver man. *Lancet* 2004; **363:** 532.

Catheter care. The benefits of silver coated or impregnated catheters in preventing or reducing urinary-tract infection are uncertain, and studies have provided conflicting evidence. A meta-analysis[1] involving 8 studies with a total of 2355 patients concluded, despite some concerns about the quality and heterogeneity of the studies, that there was a benefit, but that silver alloy coated catheters were significantly more effective in preventing urinary-tract infections than were those coated with silver oxide. A later, slightly larger, meta-analysis[2] also concluded that silver alloy catheters reduced the risk of infection, but considered that a cost-effective analysis was needed.

1. Saint S, *et al.* The efficacy of silver alloy-coated urinary catheters in preventing urinary tract infection: a meta-analysis. *Am J Med* 1998; **105:** 236–41.
2. Schumm K, Lam TBL. Types of urethral catheters for management of short-term voiding problems in hospitalised adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 30/06/09).

Wound healing. Silver is incorporated into topical dressings for wound care although a systematic review[1] of 3 randomised controlled studies found insufficient evidence to support the use of silver-containing dressings or other formulations for the treatment of infected or contaminated wounds. Another review[2] concluded that there was insufficient evidence from high-quality studies to justify the routine use of silver dressings in the treatment of uncomplicated leg ulcers or acute wounds, and although there is a slightly better case for use in infected burns, the evidence base is still weak. Bacterial resistance to silver can occur, but this risk can be minimised by choosing dressings that release high levels of silver ions and have a rapid bactericidal action.[3]

The mechanism of bactericidal action of silver in dressings is that silver atoms are oxidised and slowly released as positively charged silver cations when in contact with fluid. The silver ions bind to and disrupt bacterial cell walls as well as binding to bacterial enzymes and DNA. A nanocrystalline silver coating to the dressing increases the surface area of exposure and facilitates release of silver ions. Silver can also be incorporated as complex silver molecules in various different topical formulations that regulate the speed of delivery.[1] Proposed mechanisms of silver resistance have been plasmid acquisition and gene mutation.[3]

1. Vermeulen H, *et al.* Topical silver for treating infected wounds. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/06/08).
2. Anonymous. Silver dressings—do they work? *Drug Ther Bull* 2010; **48:** 38–42.
3. Chopra I. The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern? *J Antimicrob Chemother* 2007; **59:** 587–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Acticoat; ***Belg.***: Contreet†; ***Fr.***: Atrauman Ag; Urgocell Ag; ***Ger.***: Biatain Ag; Contreet†; ***Ital.***: Acticoat; Katomed; ***Singapore***: Acticoat Flex; Acticoat; ***UK***: Acticoat; Avance; Contreet; ***USA***: Elta SilverGel; Silverseal; SilvrStat.

Multi-ingredient Preparations. ***Arg.***: Actisorb Plus; Efodil; Nova-T; ***Belg.***: Aquacel-Ag; Biatain-Ag; ***Canad.***: Nova-T; ***China***: Nova T (新体); ***Fr.***: Actisorb Ag+; Aquacel Ag; Biatain Ag; Micropur Forte DCCNa; Oligorhine; Release Ag†; ***Ger.***: Iscador c Arg; Nova-T; SeaSorb-Ag; UrgoCell Silver; Urgosorb Silver; Urgotul Silver; ***Hong Kong***: Nova-T†; ***Indon.***: Nova-T; ***Irl.***: Actisorb Silver; ***Israel***: Neocutan Silver; Nova-T; ***Ital.***: Actisorb; Aquacel Ag; Katoxyn; Nova-T; Promogran Prisma; Rino Get; Silvercel; Silverdres; Vulnopur; ***Malaysia***: Nova-T; ***Mex.***: Nova-T; ***NZ***: Nova-T†; ***S.Afr.***: Nova-T; ***Singapore***: Acticoat Absorbent; Nova-T; ***Switz.***: Creme vulneraire; Nova-T; ***Turk.***: Nova-T†; ***UK***: Actisorb Silver; Aquacel Ag; Nova-T; ***Venez.***: Nova-T.

Homoeopathic Preparations. ***Canad.***: Formula FA 224†; ***Cz.***: Galium; ***Fr.***: Abbe Chaupitre no 1†; Abbe Chaupitre no 90†; Silicea Complexe No 11; ***Ger.***: Agaricus comp Phosphorus; Derivatio H; Derivatio; Weleda Fieber- und Zahnungszapfchen; ***Neth.***: Chavita 2.

Silver Acetate

Argenti Acetas; Plata, acetato de; Ацетат Серебра; Уксуснокислое Серебро.
$C_2H_3AgO_2$=166.9
CAS — 563-63-3.
UNII — 19PPS85F9H.

Profile

Silver acetate has been used similarly to silver nitrate as an antiseptic. It has also been used in antismoking preparations.

Smoking cessation. Silver acetate produces an unpleasant taste when combined with cigarettes but a systematic review[1] concluded that there was little evidence that it had any specific effect in promoting smoking cessation. It was considered likely that any effect would be smaller than that produced by nicotine replacement therapy.

1. Lancaster T, Stead LF. Silver acetate for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 12/04/06).

Silver Nitrate

Argent, nitrate d'; Argenti nitras; Dusičnan stříbrný; Ezüstnitrát; Gümüş Nitrat; Hopeanitraatti; Nitrato de Plata; Nitrato de Prata; Plata, nitrato de; Sidabro nitratas; Silbernitrat; Silvernitrat; Srebra azotan; Нитрат Серебра; Азотнокислое Серебро.
$AgNO_3$=169.9
CAS — 7761-88-8.
ATC — D08AL01.
ATC Vet — QD08AL01.
UNII — 95IT3W8JZE.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Silver Nitrate). A white or almost white, crystalline powder or transparent colourless crystals. Very soluble in water; soluble in alcohol. Store in nonmetallic containers. Protect from light.

USP 36: (Silver Nitrate). Colourless or white crystals. On exposure to light in the presence of organic matter, it becomes grey or greyish-black. Soluble 1 in 0.4 of water, 1 in 0.1 of boiling water, 1 in 30 of alcohol, and 1 in 6.5 of boiling alcohol; slightly soluble in ether. Its solutions in water have a pH of about 5.5. Store in airtight containers. Protect from light.

Incompatibility. Silver nitrate is incompatible with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose

from the reaction of the silver nitrate with alkali released from the glass bottle, which appeared to be soda-glass.[1]

1. *PSGB Lab Report P/80/6* 1980.

Uses and Administration

Silver nitrate possesses antiseptic properties and is used in many countries as 1% eye drops for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p. 193.2). However, as it can cause irritation, other drugs are often used.

In stick form it has been used as a caustic to destroy warts (p. 1689.3) and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical antiseptics and astringents in other conditions. Instillation of silver nitrate solution has been investigated for pleurodesis in the management of malignant effusions.

Silver nitrate has been used in cosmetics to dye eyebrows and eyelashes.

Homoeopathy

Silver nitrate has been used in homoeopathic medicines under the following names: Argent. Nit.; Argenti nitras; Argentum nitricum; Arg. nit.

References.
1. van Hasselt P, Gudde H. Randomized controlled trial on the treatment of otitis externa with one per cent silver nitrate gel. *J Laryngol Otol* 2004; **118:** 93–6.
2. Dalela D, *et al.* Silver nitrate sclerotherapy for 'clinically significant' chyluria: a prospective evaluation of duration of therapy. *Urol Int* 2004; **72:** 335–40.
3. da Silveira Paschoalini M, *et al.* Prospective randomized trial of silver nitrate vs talc slurry in pleurodesis for symptomatic malignant pleural effusions. *Chest* 2005; **128:** 684–9.
4. Alidaee MR, *et al.* Silver nitrate cautery in aphthous stomatitis: a randomized controlled trial. *Br J Dermatol* 2005; **153:** 521–5.
5. Amin M, *et al.* Silver nitrate cauterisation, does concentration matter? *Clin Otolaryngol* 2007; **32:** 197–9.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, abdominal pain, diarrhoea, vomiting, coma, and convulsions.

Short-term mild conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness. Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria (see Silver, p. 2615.2), which though difficult to treat is mainly a cosmetic hazard.

Although silver nitrate is not readily absorbed, absorption of nitrite after reduction of nitrate may cause methaemoglobinaemia. There is also a risk of electrolyte disturbances.

Effects on the eyes. Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.[1] After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibacterials and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; **231:** 245.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xin Na Xing (欣纳星); ***Pol.***: Mova Nitrat; ***Spain***: Argenpal.

Multi-ingredient Preparations. ***Austral.***: Nervatona Focus; ***Ger.***: Ratanhia comp†; ***Neth.***: Diarrheel S; ***Switz.***: Wala Echinacea; ***UK***: Avoca; ***USA***: Grafco.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; IBS Eze; Nervatona Focus; ***Austria***: Argentum Med Complex; Astomera; Barium Med Complex; Berberis Cosmoplex†; Dalektro; Echinacea-Cosmoplex; Euphorbium Compositum; Gastricumeel; Lakrima; Phosphor-Homaccord; Rhododendroneel; ***Canad.***: Arum Triphyllum Plex†; Bladder Irritation; Calnor†; Calsom†; Echinacea Compositum; Endoteel†; Euphorbium Compositum; Euphorbium Compositum; Formula ES 211; Headache & Migraine L77; Headache & Migraine; Homeo-Form CO†; Homeo-Form MI†; Homeo-Form ST†; Infilex†; Kids Calm; Nixotinex; Phosphor-Homaccord†; Stress; Toxex; Travel Sickness; ***Chile***: Anacardio con Fosforo; Bioactiv I; Bioactiv V; ***Fr.***: Acidum Phosphoricum Compose†; Anxietum; Arum Triphyllum Compose; Boripharm No 10†; Boripharm No 15†; Cocculus Complexe No 73; Conium Complexe No 36†; Gastro-Drainol†; Nux Vomica Compose; Phapax; ***Ger.***: EAP-61; Entzundungstropfen; Euphorbium comp SN; Gastro-Pasc; metakaveron; Mucosa compositum; Rufebran gastro†; ***Hung.***: Toxex; ***Neth.***: Coconium-Gastreu; Euphorbium comp; Gastricumeel; Infragil; Toxex; ***Rus.***: Capsicum-Plus (Капсикум-Плюс); ***S.Afr.***: Euphorbium Compositum S†; ***Switz.***: Akutur; Diarrheel S; Gastricumeel; Gastronol; metaneuron N; Regenaplex Nr. 24b; Regenaplex Nr. 88b; ***UK***: Medicinal Gargle; ***USA***: Preferred Remedies Antacid.

Pharmacopoeial Preparations

BP 2014: Silver Nitrate Solution; Sterile Silver Nitrate Solution; **USP 36:** Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Silver Protein

Albumosesilber; Argent colloïdal (colloidal); Argent Colloïdal par Voie Chimique (colloidal); Argent, protéinate d'; Argentoproteinum; Argentoproteinum Mite (mild); Argentum Colloidale (colloidal); Argentum proteicum; Argentum Proteinicum; Argentum Vitellinicum (mild); Collargol (colloidal); Colloidal Silver (colloidal); Hopea, kolloidinen (colloidal); Hopeaproteiini; Kolloides Silber (colloidal); Mild Protargin (mild); Mild Silver Protein (mild); Mild Silver Proteinate (mild); Plata coloidal (colloidal); Plata, proteína de; Prata Coloidal (colloidal); Protargolum; Proteína de plata fuerte; Proteína de plata ligera (mild); Proteinato de Plata; Proteinato de Prata; Silver, kolloidalt (colloidal); Silver Nucleinate (mild); Silver Proteinate; Silver Vitellin (mild); Silverprotein; Srebra proteinicum; Srebro koloidalne (colloidal); Stříbro koloidní (colloidal); Strong Protargin; Strong Protein Silver; Strong Silver Protein; Vitelinato de Plata (mild); Vitelinato de Prata (mild); Протаргол.

CAS — 9007-35-6 (colloidal silver); 9015-51-4 (silver protein).

Pharmacopoeias. In *It.*, *Jpn*, and *Viet.*

Eur. (see p. vii) includes Silver, Colloidal, for External Use.

Ph. Eur. 8: (Silver, Colloidal, for External Use; Argentum Colloidale ad Usum Externum). It is colloidal metallic silver, containing protein. It contains 70.0 to 80.0% of Ag, calculated with reference to the dried substance. Green or bluish-black, metallic, hygroscopic, shiny flakes or powder. Freely soluble or soluble in water; practically insoluble in alcohol and in dichloromethane. Store in airtight containers.

Profile

Silver protein solutions have antibacterial properties, due to the presence of the silver, and have been used as eye drops and topically. Various types have been used: the form referred to as silver protein, also sometimes called strong silver protein, contains about 8% silver. Although the mild form contains more silver (about 20%) it is considered to be less active but also less irritating. Colloidal forms of silver protein have a much smaller particle size of silver and may contain up to about 80% silver.

Homoeopathy

Silver protein has been used in homoeopathic medicines under the following names: Argentum colloidale.

Adverse effects. Irreversible neurotoxicity associated with the daily ingestion of a home-made colloidal silver drink for 4 months developed in an elderly patient.[1] He presented with myoclonic status epilepticus, then entered into a prolonged coma, and eventually died of pneumonia some months later. On admission, high levels of silver were found in the plasma, erythrocytes, and CSF, and at autopsy there was evidence of selective silver accumulation in the brain. As of October 2007, four reports of silver toxicity in patients ingesting home-made products, likewise prepared using a colloidal silver generator, had also been received by the Australian Adverse Drug Reactions Advisory Committee;[2] one patient also applied it topically after shaving. All patients had high plasma-silver concentrations and developed skin discoloration; some also had systemic symptoms including hepatotoxicity, cardiomyopathy, amnesia, and incoherent speech.

For argyria after prolonged use of nasal drops containing silver protein see under Silver, p. 2615.2.

1. Mirsattari SM, *et al.* Myoclonic status epilepticus following repeated oral ingestion of colloidal silver. *Neurology* 2004; **62:** 1408–10.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Dangers associated with chronic ingestion of colloidal silver. *Aust Adverse Drug React Bull* 2007; **26:** 19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0710.pdf (accessed 24/06/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Argirol; ***Ger.***: Rhinoguttae Argenti diacetylotannici proteinici†; Rhinoguttae pro Infantibus N†; ***USA***: RevitaDERM Wound Care.

Multi-ingredient Preparations. ***Austria***: Coldargan; ***Belg.***: Argyrophedrine†; ***Ger.***: Gastrarctin N; ***Hung.***: Coldargan†; ***Ital.***: Argisone; Argotone Rino; Arscolloid; Bioarscolloid; Corti-Arscolloid; Hyalosilver.

Homoeopathic Preparations. ***Fr.***: Argentum Complexe no 98; Kalmia Complexe No 18; Uva Ursi Complexe No 9; ***Ger.***: Chirofossat.

Sincalide *(BAN, USAN, rINN)*

CCK-OP; Sincalida; Sincalidum; Sinkalid; Sinkalidi; SQ-19844; Синкалид.

De-1-(5-oxo-L-proline)-de-2-L-glutamine-5-methionine-caerulein.

$C_{49}H_{62}N_{10}O_{16}S_3$=1143.3

CAS — 25126-32-3.

ATC — V04CC03.

ATC Vet — QV04CC03.

UNII — M03GIQ7Z6P.

Pharmacopoeias. *US* includes Sincalide for Injection.

Uses and Administration

Sincalide is the synthetic C-terminal octapeptide of cholecystokinin (see pancreozymin, p. 2582.1) and when given by intravenous injection it stimulates gallbladder contraction; it also stimulates intestinal muscle.

Sincalide is used for testing gallbladder function and as an adjunct to cholecystography. It is usually given in doses of 20 nanograms/kg by intravenous injection over 30 to 60 seconds. It is also used as a diagnostic agent, often with secretin (p. 2612.2), for testing the functional capacity of the pancreas; this test generally requires duodenal intubation of the patient and examination of duodenal aspirate. A suggested procedure is to give a 1-hour intravenous infusion of secretin, and 30 minutes after starting this infusion, to start a separate infusion of sincalide 20 nanograms/kg over a 30-minute period. A dose of 40 nanograms/kg may be given to accelerate the transit time of a barium meal through the small bowel; it should be given after the barium meal has passed the proximal jejunum.

Reviews.
1. Prescott WA, Btaiche IF. Sincalide in patients with parenteral nutrition-associated gallbladder disease. *Ann Pharmacother* 2004; **38:** 1942–5.

Adverse Effects

Sincalide stimulates gallbladder contraction and gastrointestinal muscle and may give rise to abdominal discomfort. Dizziness, nausea, and flushing may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Kinevac; ***USA***: Kinevac.

Sivelestat *(USAN, rINN)*

EI-546; LY-544349; ONO-5046; Sivélestat; Sivelestatum; Сивелестат.

o-(*p*-Hydroxybenzenesulfonamido)hippuric acid pivalate.

$C_{20}H_{22}N_2O_7S$=434.5

CAS — 127373-66-4.

UNII — DWI62G0P59.

Sivelestat Sodium *(USAN, rINNM)*

Natrii Sivelestatum; Sivelestat sódico; Sivélestat Sodique; Натрий Сивелестат.

$C_{20}H_{21}N_2NaO_7S,4H_2O$=528.5

CAS — 201677-61-4.

UNII — 737RR8Y409.

Profile

Sivelestat is an elastase inhibitor that mainly inhibits neutrophil elastase. It is given by intravenous infusion as the sodium salt in the treatment of acute lung injury associated with systemic inflammatory response syndrome. However, a large study in patients with acute lung injury did not find it of benefit.

References.
1. Zeiher BG, *et al.* Neutrophil elastase and acute lung injury: prospects for sivelestat and other neutrophil elastase inhibitors as therapeutics. *Crit Care Med* 2002; **30** (suppl): S281–S287.
2. Zeiher BG, *et al.* Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. *Crit Care Med* 2004; **32:** 1695–1702.
3. Hayakawa M, *et al.* Sivelestat (selective neutrophil elastase inhibitor) improves the mortality rate of sepsis associated with both acute respiratory distress syndrome and disseminated intravascular coagulation patients. *Shock* 2010; **33:** 14–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Elaspol.

Skullcap

Escutelaria; Scullcap; Scutellaria; Шлёмник Широколистный.
ATC Herb — HG04BW5035 (Scutellaria lateriflora: herb); HN02BG5013 (Scutellaria lateriflora: herb); HA09WA5022 (Scutellaria lateriflora: herb); HN05CM5025 (Scutellaria lateriflora: herb); HG02WX5004 (Scutellaria lateriflora: herb).
UNII — 7BP4DH5PDC (Scutellaria lateriflora); C6CNB75R61 (scutellaria).

Pharmacopoeias. *Chin.* includes Herba Scutellariae Barbatae (Barbated Skullcap Herb; *Scutellaria barbata*) and Radix Scutellariae (Baical Skullcap Root; *S. baicalensis*).

Eur. (see p. vii) includes Baical Skullcap Root (*S. baicalensis*).

Jpn includes Scutellaria Root (*S. baicalensis*).

Ph. Eur. 8: (Baical Skullcap Root; Scutellariae Baicalensis Radix). The dried, peeled, usually fragmented root of *Scutellaria baicalensis* without rootlets. It is collected in spring or autumn. It contains not less than 9.0% of baicalin ($C_{21}H_{18}O_{11}$ = 446.4) (dried drug). Protect from moisture.

Profile

Skullcap, the aerial parts of *Scutellaria lateriflora* (Labiatae) and other *Scutellaria* spp., has sedative and antispasmodic properties. It is used as a nerve tonic, and for insomnia and menstrual disorders.

Baical skullcap (*S. baicalensis*) is used in Chinese herbal medicine.

References.
1. Wolfson P, Hoffmann DL. An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers. *Altern Ther Health Med* 2003; **9:** 74–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.***: MEBO; ***Pol.***: Baikadent.

Multi-ingredient Preparations. ***Austral.***: Albizia Complex; Andrographis Compound; Calmo†; Euphrasia Compound; Feminine Herbal Complex; Herbal Rest & Relax; Masculine Herbal Complex; Nevaton; Nyal Allergy + Hayfever Relief; Nyal Sinus Relief Day + Night; Passionflower Plus†; PulmaCo; Withania Complex; ***Canad.***: Calm-Aid†; Herbal Nerve†; Nervrite; Sleep Relax; ***Jpn***: Bofutsushosan; Daisaikoto; Gorinsan; Hangeshashinto; Junchoto; Keigairengyoto; Nijutsuto; Nyoshinsan; Orengedokuto; Otsujito; Ryutanshakanto; Saibokuto; Saikanto; Saikokaryukotsuboreito; Saikokeishikankyoto; Saikokeishito; Saikoseikanto; Saireito; Sammotsuogonto; San'oshashinto; Seihaito; Seijobofuto; Seishinrenshiin; Shin'iseihaito; Shosaikoto; Shosaikotokakikyosekko; Unseiin; ***Philipp.***: Sleepasil; ***Pol.***: Baikaderm; ***Singapore***: Bio-Taches Masque†; Bio-Taches†; Disco; ***UK***: Herbal Indigestion Naturtabs; HRI Calm Life; Napiers Herbal Stress & Sleep Aid; Neurotone; Newrelax; Nodoff; Quiet Days; Quiet Tyme; Scullcap & Gentian Tablets; St Johnswort Compound; Stressless; Valerian Passiflora and Hops; Vegetable Cough Remover; Wellwoman.

Homoeopathic Preparations. ***Austria***: Relax.

Skunk Cabbage

Col apestosa; Dragón fétido; Skunkweed; Симплокарпус Вонючий.
UNII — 5760ZQ4B6S (Symplocarpus foetidus); R88254608W (Symplocarpus foetidus root).

Profile

Skunk cabbage, the root and rhizome of *Symplocarpus foetidus* (*Dracontium foetidum*) (Araceae), has expectorant properties and is used in respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***UK***: Cough Soother Herbal Syrup; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Vegetable Cough Remover.

Slippery Elm

Elm Bark; Olmo americano; Olmo resbaladizo; Olmo rojo americano; Slippery Elm Bark; Ulmus; Вяз Ржавый.
ATC Herb — HA02WB5002 (Ulmus rubra: bark).
UNII — 91QY4PXU8Q (Ulmus rubra bark); 63POE2M46Y (Ulmus rubra inner bark).

Pharmacopoeias. In *US.*

USP 36: (Elm). The dried inner bark of *Ulmus rubra* (*U. fulva*) (Ulmaceae). Store in a dry place at a temperature of 8 degrees to 15 degrees.

Profile

Slippery elm contains a considerable amount of mucilage and has been used as a demulcent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Burdock Complex; Cal Alkyline†; Psylli-Mucil Plus†; ***Hong Kong***: Vita Coldycin Echinacea Plus†; ***UK***: Modern Herbals Pile; Pileabs; Slippery Elm Stomach Tablets.

Homoeopathic Preparations. ***Canad.***: Essigen†.

Soapwort

Bouncing Bet; Fuller's Herb; Red Soapwort; Saponaire; Мыльнянка Лекарственная; Мыльная Трава.
ATC Herb — HR05WA5051 (Saponaria officinalis: root).
UNII — 4V1PP5J0HJ (Saponaria officinalis); 3988313MM7 (Saponaria officinalis leaf); RI2K1BMA8B (Saponaria officinalis root).

NOTE. Distinguish from White Soapwort, *Gypsophila paniculata* (Caryophyllaceae)

Pharmacopoeias. In *Fr.*

Profile

The root of red soapwort, *Saponaria officinalis* (Caryophyllaceae), contains saponins and is included in herbal preparations for catarrh and other respiratory-tract disorders and for skin disorders. It has been used as a foaming agent. The aerial parts of the herb have also been used.

Homoeopathy

Soapwort has been used in homoeopathic medicines under the following names: Saponaria; Saponaria officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Depuratif Parnel†; ***Ger.***: Cefabronchin; ***Pol.***: Pectosol; Reumosol; Saponarex; ***Port.***: Erpecalm; ***Ukr.***: Pectolvan Phyto (Пектолван Фито).

Homoeopathic Preparations. ***Cz.***: Galium; ***Fr.***: Saponaria Compose.

Soda Lime

Cal Sodada; Calcaria absorbens; Calcaria Compositio; Calx Sodica; Chaux Sodée; Натронная Известь.
CAS — 8006-28-8.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Soda Lime). A mixture of sodium hydroxide, or sodium hydroxide and potassium hydroxide, with calcium hydroxide. White or greyish-white granules, or it may be coloured with an indicator to show when its absorptive capacity is exhausted. It absorbs about 20% of its weight of carbon dioxide. Partially soluble in water; almost completely soluble in 1M acetic acid. A suspension in water is strongly alkaline to litmus.

USNF 31: (Soda Lime). A mixture of calcium hydroxide and sodium or potassium hydroxide or both. It may contain an indicator that is inert and that changes colour when the soda lime can no longer absorb carbon dioxide. White or greyish-white granules. May have a colour if an indicator is added.

Incompatibility. Soda lime is incompatible with trichloroethylene.

Profile

Soda lime is used to absorb carbon dioxide, for instance in closed-circuit anaesthetic apparatus, and in the determination of the basal metabolic rate. Limits are specified for particle size, and particles should be free from dust.

Soda lime must not be used with trichloroethylene, since this is decomposed by warm alkali to produce a toxic end product that gives rise to lesions of the nervous system.

Soda lime is irritating and corrosive to skin, mucous membranes, and eyes.

Sodium Aminobenzoate

Aminobenzoate Sodium; Sodium Para-aminobenzoate; Аминобензоат Натрия.
Sodium 4-aminobenzoate.
$C_7H_6NNaO_2$=159.1
UNII — 75UI7QUZ5J.

Pharmacopoeias. In *US.*

USP 36: (Aminobenzoate Sodium). pH of a 5% solution in water is between 8.0 and 9.0.

Profile

Sodium aminobenzoate has been used in analgesic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Fotofil; Neo-Ustiol; ***Spain***: Tri Hachemina†.

Sodium Arsenate

Arseniato de sodio; Dibasic Sodium Arsenate; Disodium Arsenate; Natrium Arsenicicum; Sodium Arseniate; Мышьяковокислый Натрий; Арсенат Натрия.
$Na_2HAsO_4.7H_2O$=312.0
CAS — 7778-43-0 (anhydrous sodium arsenate); 10048-95-0 (sodium arsenate heptahydrate).
UNII — ANU034TUJ4 (anhydrous sodium arsenate).

Profile

Sodium arsenate was formerly used in the treatment of chronic skin diseases, in parasitic diseases of the blood, and in some forms of anaemia. It has the adverse effects of Arsenic Trioxide, p. 2448.3.

Sodium Camsilate

Sodium Camphorsulphonate; Натрий Камсилат.
Sodium (+)-camphor-10-sulfonate.
$C_{10}H_{15}NaO_4S$=254.3
CAS — 21791-94-6; 34850-66-3.

Pharmacopoeias. In *Viet.*

Profile

Sodium camsilate has been used as a respiratory and cardiac stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Algice; Gripsay; Ozonyl Aquoso; Ozonyl Expectorante; Tetrapulmo†; ***Chile***: Gruben; ***Ukr.***: Bronchobru (Бронхобрю).

Sodium Carbonate

Sodu węglan.
UNII — 45P3261C7T.

Sodium Carbonate Anhydrous

Carbonato de sodio anhidro; Cenizas de Soda; Cenizas de sosa; E500; Exsiccated Sodium Carbonate; Natrii Carbonas; Natrii Carbonas Anhydricus; Natrio karbonatas, bevandenis; Natrium Carbonicum Calcinatum; Natrium Carbonicum Siccatum; Natriumkarbonaatti, vedetön; Natriumkarbonat, vattenfritt; Sodium (carbonate de) anhydre; Uhličitan sodný; Uhličitan sodný bezvodý; Vízmentes nátrium-karbonát; Безводный Карбонат Натрия.
Na_2CO_3=106.0
CAS — 497-19-8.
UNII — 45P3261C7T.

NOTE. Soda ash is a synonym for the technical grade of sodium carbonate anhydrous.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn. USNF* allows the anhydrous substance or the monohydrate.

Ph. Eur. 8: (Sodium Carbonate, Anhydrous). A white or almost white, slightly granular, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

USNF 31: (Sodium Carbonate). Colourless crystals, or white, crystalline powder or granules. Soluble 1 in 3 of water and 1 in 1.8 of boiling water.

Sodium Carbonate Decahydrate

Carbonato de sodio decahidratado; Cristales de Sosa; E500; Natrii Carbonas; Natrii Carbonas Decahydricus; Natrio karbonatas dekahidratas; Natrium Carbonicum Crystal-

lisatum; Natriumcarbonat-Decahydrat; Natriumkarbonaattidekahydraatti; Nátrium-karbonát-dekahidrát; Natriumkarbonatdekahydrat; Sodium (carbonate de) décahydraté; Sosa de lavado; Uhličitan sodný dekahydrát; Карбонат Натрия Декагидрат.

$Na_2CO_3,10H_2O$=286.1

CAS — 6132-02-1.

UNII — L5505BG22I.

NOTE. Washing soda is a synonym for the technical grade of sodium carbonate decahydrate.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Sodium Carbonate Decahydrate). Colourless, efflorescent, transparent crystals or a white or almost white crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

Sodium Carbonate Monohydrate

Carbonato de sodio monohidratado; E500; Natrii Carbonas Monohydricus; Natrio karbonatas monohidratas; Natriumcarbonat-Monohydrat; Natriumkarbonaattimonohydraatti; Nátrium-karbonát-monohidrát; Natriumkarbonatmonohydrat; Sodium (carbonate de) monohydraté; Sodu węglan jednowodny; Uhličitan sodný monohydrát; Карбонат Натрия Моногидрат.

Na_2CO_3,H_2O=124.0

CAS — 5968-11-6.

UNII — 2A1Q1Q3557.

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* allows the anhydrous substance or the monohydrate.

Ph. Eur. 8: (Sodium Carbonate Monohydrate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

USNF 31: (Sodium Carbonate). Colourless crystals, or white, crystalline powder or granules. When exposed to dry air above 50 degrees, it effloresces and at 100 degrees it becomes anhydrous. Soluble 1 in 3 of water and 1 in 1.8 of boiling water.

Profile

Sodium carbonate is used in antacid preparations. Anhydrous sodium carbonate and the monohydrate are also used as reagents. The decahydrate has been used in alkaline baths. Sodium carbonate in its anhydrous or hydrated form is also used as a water softener.

Sodium carbonate may be irritating or mildly corrosive to skin, mucous membranes, and eyes.

Homoeopathy

Sodium carbonate has been used in homoeopathic medicines under the following names: Natrum carbonicum; Natrii carbonas; Natrium carbonicum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Urologic G.

Multi-ingredient Preparations. ***Arg.***: Alikal; Cerosporin; Otocalmia Biotic; Otocerol; Otoclean Gotas Oticas; Sal de Fruta Eno; Sincerum; Uvasal; Yasta; ***Austral.***: Eno; ***Austria***: Blanel; ***Braz.***: Digestbem; Estomazil; Sal de Fruta Eno; Sonrisal; ***Canad.***: Lithines du Dr Gustin†; ***China***: Shi Wei (仕卫); ***Denm.***: Samarin; ***Fr.***: Bactident†; Hydralin Classic; ***Hong Kong***: Eno†; Hydralin; ***Hung.***: Samarin; ***India***: Cephagraine; ***Irl.***: Cymalon; Resolve†; ***Israel***: Urikal; ***Ital.***: Gastrotuss; ***Port.***: Eno†; Gastropensant†; ***S.Afr.***: Fragador†; ***Spain***: Sal de Fruta Eno; ***Swed.***: Samarin; Samarin; ***UK***: Cymalon; Eno; Resolve; ***Venez.***: Eno.

Homoeopathic Preparations. ***Austria***: Echinacea-Cosmoplex; Spigelon; ***Canad.***: Arthritic Pain; Homeo-Form AR†; Spigelon†; ***Cz.***: Lamioflur†; ***Fr.***: Billerol; Natrum Carbonicum Complexe No 10†; Selenium Complexe No 99; Tamarindus Complexe No 95†; ***Ger.***: Entzundungstropfen; ***Hung.***: Spigelon; ***Switz.***: Lithiumeel; Spigelon; ***UK***: Fragador.

Pharmacopoeial Preparations

BPC 1973: Surgical Chlorinated Soda Solution;
USP 36: Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation.

Sodium Chlorate

Clorato de potasio; Natrium Chloricum; Sodii Chloras.

$NaClO_3$=106.4

CAS — 7775-09-9.

UNII — T95DR77GMR.

Profile

Sodium chlorate closely resembles potassium chlorate (p. 2595.2) in its properties and has been used as an astringent. Its main use is as a weedkiller and it is therefore a common household chemical. Poor storage conditions can lead to explosions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Spain***: Co Bucal.

Sodium Dichloroacetate *(USAN)*

CPC-211; DCA; Dicloroacetato de sodio; Натрий Дихлорацетат.

$C_2HCl_2NaO_2$=150.9

CAS — 2156-56-1 (sodium dichloroacetate); 79-43-6 (dichloroacetic acid).

UNII — 42932X67B5.

NOTE. The name Ceresine has been used as a trade mark for sodium dichloroacetate.

Profile

Dichloroacetic acid activates pyruvate dehydrogenase, a mitochondrial enzyme that catalyses metabolism of pyruvate and lactate, and it inhibits glycolysis. It also stimulates myocardial contractility. Sodium dichloroacetate has been used for the treatment of congenital lactic acidosis, lactic acidosis in patients with severe malaria, homozygous familial hypercholesterolaemia, and for severe brain injury. It is also under investigation for stroke. Doses of sodium dichloroacetate for acquired and congenital lactic acidosis are given under Use in Metabolic Acidosis, below.

Administration in children. Doses of sodium dichloroacetate in children are given under Use in Metabolic Acidosis, below.

Adverse effects. Adverse effects reported with sodium dichloroacetate have mainly involved the central and peripheral nervous systems.[1] Anxiolytic or sedative effects are common. Reversible polyneuropathy has been reported after chronic use, as has asymptomatic elevation of serum transaminases. Reduced urate clearance and elevated serum urate levels have been reported in patients with type 2 diabetes mellitus. See also under Use in Metabolic Acidosis, below for references to long-term treatment with sodium dichloroacetate and to early termination of a study due to development of peripheral neuropathy.

1. Stacpoole PW, *et al.* Pharmacokinetics, metabolism, and toxicology of dichloroacetate. *Drug Metab Rev* 1998; **30:** 499–539.

Pharmacokinetics. References.

1. Henderson GN, *et al.* Pharmacokinetics of dichloroacetate in adult patients with lactic acidosis. *J Clin Pharmacol* 1997; **37:** 416–25.
2. Shangraw RE, Fisher DM. Pharmacokinetics and pharmacodynamics of dichloroacetate in patients with cirrhosis. *Clin Pharmacol Ther* 1999**66:** 380–90.

Use in metabolic acidosis. In a study[1] in 29 patients with lactic acidosis (p. 1775.2), sodium dichloroacetate 50 mg/kg given by intravenous infusion over 30 minutes, followed by a second dose 2 hours after beginning the first infusion, produced a metabolic response in 23 patients with a short-term increase in survival. However, a subsequent study[2] found that, while dichloroacetate infusion did reduce blood-lactate concentrations, it did not alter haemodynamics or survival in patients with severe lactic acidosis. A review[3] of these and other controlled studies in the treatment of acquired and congenital lactic acidosis concluded that the maximum lactate-lowering effect is dose-dependent but independent of time after dosing. Whether lowering lactate levels contributes to reducing morbidity and mortality in hyperlactataemia remains controversial, although data from recent studies suggest that treatment in mild cases may reduce the risk of death. A review[4] of the treatment of children with dichloroacetate for congenital lactic acidosis hypothesised that it might improve quality of life by reducing the frequency of acid–base decompensations, improving neurological function, and stimulating linear growth. A randomised controlled study[5] of dichloroacetate for the treatment of congenital lactic acidosis in 43 patients ranging in age from 3 months to 18 years found that dichloroacetate for 6 months was well tolerated and reduced blood-lactate response to a carbohydrate challenge but had no effect on basal-lactate concentrations nor did it improve neurologic or other measures of clinical outcome. Follow-up[6] of 36 of these children for up to 10 years showed that sodium dichloroacetate is generally well tolerated although it may precipitate or worsen underlying peripheral neuropathy in some cases. In another randomised controlled study[7] of the effects of dichloroacetate in the treatment of the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), 13 of 15 patients given the study medication developed peripheral neuropathy, displaying either clinical signs and symptoms or electrophysiological evidence. The study was therefore stopped early, and on this basis, the authors concluded that dichloroacetate could not be recommended for the treatment of MELAS.

In a randomised, double-blind, placebo-controlled study[8] in 124 West African children with severe *Plasmodium falciparum* malaria, a single intravenous infusion of sodium dichloroacetate in a dose of 50 mg/kg given at the same time as quinine increased the rate and magnitude of fall in blood-lactate levels without compromising the plasma kinetics of quinine.

In the UK, the *BNFC* includes the following doses for neonates and children with pyruvate dehydrogenase defects: 12.5 mg/kg 4 times daily orally, adjusted according to response up to 200 mg/kg daily.

Sodium dichloroacetate has also been studied[9] in patients with traumatic brain injury for its lactate-lowering effect in cerebrospinal fluid.

1. Stacpoole PW, *et al.* Dichloroacetate in the treatment of lactic acidosis. *Ann Intern Med* 1988; **108**: 58–63.
2. Stacpoole PW, *et al.* A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. *N Engl J Med* 1992; **327:** 1564–9.
3. Stacpoole PW, *et al.* Efficacy of dichloroacetate as a lactate-lowering drug. *J Clin Pharmacol* 2003; **43:** 683–91.
4. Stacpoole PW, *et al.* Treatment of congenital lactic acidosis with dichloroacetate. *Arch Dis Child* 1997; **77:** 535–41.
5. Stacpoole PW, *et al.* Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. *Pediatrics* 2006; **117:** 1519–31.
6. Stacpoole PW, *et al.* Evaluation of long-term treatment of children with congenital lactic acidosis with dichloroacetate. Abstract: *Pediatrics* 2008; **121:** 1024–5. Full version available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/e1223.pdf (accessed 25/06/09)
7. Kaufmann P, *et al.* Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. *Neurology* 2006; **66:** 324–30.
8. Agbenyega T, *et al.* Population kinetics, efficacy, and safety of dichloroacetate for lactic acidosis due to severe malaria in children. *J Clin Pharmacol* 2003; **43:** 386–96.
9. Williams PJ, Dichloroacetate: population pharmacokinetics with a pharmacodynamic sequential link model. *J Clin Pharmacol* 2001; **41:** 259–67.

Sodium Dithionite

Ditionito de sodio; Hidrosulfito de sodio; Natrii Dithionis; Sodium Hydrosulfite; Sodium Hydrosulphite; Sodium Sulphoxylate; Sodu ditionian; Sodu podsiarczyn; Дитионит Натрия.

$Na_2S_2O_4$=174.1

CAS — 7775-14-6.

UNII — 2K5B8F6ES1.

NOTE. The name sodium hydrosulfite is also applied to $NaHSO_2$ = 88.06.

Pharmacopoeias. In *Pol.*

Profile

Sodium dithionite is used as a reducing agent. It may be used in the form of a simple urine test in the detection of paraquat poisoning. A 0.25% solution has been used to remove phenazopyridine stains from fabric. It is irritant to the skin.

Sodium Gluconate

E576; Gluconato de sodio; Глюконат Натрия.

Monosodium D-gluconate.

$C_6H_{11}NaO_7$=218.1

CAS — 527-07-1.

UNII — R6Q3791S76.

Pharmacopoeias. In *US.*

Profile

Sodium gluconate is a food additive.

Gluconates act as acceptors of hydrogen ions produced by metabolic processes and are an indirect source of bicarbonate ions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ke Rui Te (克瑞特).

Multi-ingredient Preparations. ***China***: Er Qi (尔祺); ***Ital.***: Altaflora with electrolytes.

Sodium Humate

Гумат Натрий.

CAS — 1415-93-6 (humic acids); 68131-04-4 (sodium humates).

Profile

Humic acids are mixtures of complex macromolecules derived from the decomposition of organic material and are

found in soils and peats. They have been used topically, usually as sodium humate, for musculoskeletal and joint disorders. They also have industrial applications.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Humal; Salhumin; ***Ger.***: Salhumin Rheuma-Bad; ***Hung.***: Humet-R.

Sodium Hydrogen Sulfate

Sodium Acid Sulphate; Sodium Bisulfate; Sodium Bisulphate.
$NaHSO_4,H_2O$=138.1
CAS — 7681-38-1 (anhydrous sodium hydrogen sulfate); 10034-88-5 (sodium hydrogen sulfate monohydrate).
UNII — BU8V88OWIQ.

Profile

Sodium hydrogen sulfate may be found in preparations used as a buffering agent in gastrointestinal disorders. It has also been used for preparing effervescing baths.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Optacid.

Sodium Hydroxide

Ätznatron; Caustic Soda; Cáustica blanca; E524; Hidrato de sodio; Hidróxido de Sódio; Hidróxido de sodio; Hydroxid sodný; Natrii hydroxidum; Natrio hidroksidas; Natrium Hydricum; Natrium Hydroxydatum; Nátrium-hidroxid; Natriumhydroksidi; Natriumhydroxid; Soda Lye; Sodium, hydroxyde de; Sodu wodorotlenek; Sosa cáustica.
NaOH=40.00
CAS — 1310-73-2.
UNII — 55X04QC32I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Sodium Hydroxide). White or almost white, crystalline masses supplied as pellets, sticks, or slabs. It is deliquescent and readily absorbs carbon dioxide. Very soluble in water; freely soluble in alcohol. A 0.01% solution in water has a pH of not less than 11.0. Store in airtight, nonmetallic containers.

USNF 31: (Sodium Hydroxide). White or practically white fused masses, small pellets, flakes, sticks, or other forms. It is hard and brittle and shows a crystalline fracture. When exposed to air it rapidly absorbs moisture and carbon dioxide. Soluble 1 in 1 of water; freely soluble in alcohol. Store in airtight containers.

Uses and Administration

Sodium hydroxide is a powerful caustic. A 2.5% solution in glycerol has been used as a cuticle solvent. An escharotic preparation of sodium hydroxide and calcium oxide was known as London paste. Sodium hydroxide is also used for adjusting the pH of solutions.

Disinfection. For reference to the possible use of sodium hydroxide for the disinfection of material contaminated by the agent causing Creutzfeldt-Jakob disease, see p. 1730.3.

Adverse Effects

Sodium hydroxide is strongly alkaline and corrosive, and rapidly destroys organic tissues.

The ingestion of caustic alkalis causes immediate burning pain in the mouth, throat, substernal region, and epigastrium, and the lining membranes become swollen and detached. There is dysphagia, hypersalivation, vomiting with the vomitus becoming blood-stained, diarrhoea, and shock. In severe cases, abdominal pain, asphyxia due to oedema of the glottis, circulatory failure, oesophageal or gastric perforation, peritonitis, or pneumonia may occur. Stricture of the oesophagus can develop weeks or months later.

Caustic alkalis on contact with the skin can produce full thickness burns leading to extensive damage. Alkali burns to the eyes cause conjunctival oedema and corneal destruction; damage may be irreversible.

Treatment of Adverse Effects

Ingestion should not be treated by lavage or emesis. Dilution with water or milk is generally considered controversial for management of corrosive ingestion. However, early dilution therapy of alkalis may reduce oesophageal injury; large volumes of fluid should be avoided. Neutralisation of alkalis is contra-indicated. The airway should be maintained and shock and pain alleviated.

In cases of skin contamination, clothing should be removed immediately and the skin flooded with copious amounts of water for at least 15 minutes. Excision or skin grafting of burnt areas may be necessary in severe cases. Contaminated eyes should be irrigated thoroughly with water or 0.9% sodium chloride until the conjunctival sac pH is normal, which may require irrigation for up to an hour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Leberinfusion.

Sodium Methylarsinate

Metilarsinato de sodio; Natrium Methylarsonicum; Sodium Metharsinite; Метиларсинат Натрия.
Disodium monomethylarsonate hexahydrate.
$CH_3AsNa_2O_3,6H_2O$=292.0
CAS — 5967-62-4 (sodium methylarsinate); 124-58-3 (methylarsinic acid).

Profile

Sodium methylarsinate is an organic arsenic compound with adverse effects similar to those of arsenic trioxide (p. 2448.3). It was formerly included in some vitamin and mineral preparations. It has also been used as a herbicide.

Sodium Morrhuate *(rINN)*

Morrhuate de Sodium; Morrhuate Sodium; Morruato de sodio; Natrii Morrhuas; Natriummorruaatti; Natriummorruat; Натрия Морруат.
CAS — 8031-09-2.
UNII — 652U49DZTP.

Pharmacopoeias. *Chin.* and *US* include the injection.

Profile

Sodium morrhuate consists of the sodium salts of the fatty acids of cod-liver oil. It is a sclerosant that has been used in the treatment of varicose veins (p. 2564.1). Usual doses are 50 to 100 mg for small or medium veins or 150 to 250 mg for large veins given as a 5% solution by intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Scleromate.

Pharmacopoeial Preparations
USP 36: Morrhuate Sodium Injection.

Sodium Phenylacetate *(USAN)*

Fenilacetato de sodio; Фенилацетат Натрия.
$C_8H_7NaO_2$=158.1
CAS — 114-70-5.
UNII — 48N6U1781G.

Profile

Sodium phenylacetate is used as adjunctive treatment for acute hyperammonaemia (p. 2049.3) and associated encephalopathy in patients with enzymatic deficiencies in the urea cycle. It is given with sodium benzoate (p. 1738.2) as a combined preparation for intravenous infusion in which 1 mL contains 100 mg of each component. The preparation is diluted in sterile glucose injection 10% at ≥25 mL/kg before infusion. Other similar therapies (e.g. oral sodium phenylbutyrate or glycerol phenylbutyrate, see p. 2518.3) should be stopped before starting the infusion. A loading dose is infused over 90 to 120 minutes followed by an equivalent maintenance dose infused over 24 hours. Doses of sodium phenylacetate (given with the same amount of sodium benzoate) are 250 mg/kg for patients weighing 20 kg or less, and 5.5 g/m² for those over 20 kg. Maintenance infusions are continued until plasma ammonia concentrations are normal or oral nutrition and therapy can be tolerated. Sodium phenylacetate has also been given orally.

References.
1. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl 1): S1–S5.
2. Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr* 2001; **138** (suppl 1): S30–S39.
3. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl 1): S46–S55. Correction. *ibid.* 2002; **140:** 490.
4. MacArthur RB, *et al.* Pharmacokinetics of sodium phenylacetate and sodium benzoate following intravenous administration as both a bolus and continuous infusion to healthy adult volunteers. *Mol Genet Metab* 2004; **81** (suppl 1): S67–S73.
5. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356:** 2282–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***USA***: Ammonul; Ucephan†.

Sodium Polymetaphosphate

E452 (sodium polyphosphates); Polimetafosfato de sodio; Полифосфат Натрия (sodium polyphosphate).
CAS — 50813-16-6.
UNII — P1BM4ZH95L.

NOTE. Although Sodium hexametaphosphate has been used as a synonym for the polymetaphosphate, the latter also exists in much higher degrees of polymerisation.

Profile

Sodium polymetaphosphate has been used as a 5% dusting powder in hyperhidrosis and bromhidrosis, and as a prophylactic against athlete's foot.

Sodium polymetaphosphate combines with calcium and magnesium ions to form complex soluble compounds and is used as a water softener.

Sodium Pyrophosphate *(USAN)*

Sodu pirofosforan; Tetrasodium Pyrophosphate; TSPP; Пирофосфат Натрия.
$Na_4P_2O_7$=265.9
CAS — 7722-88-5.
UNII — O352864B8Z.

Profile

Sodium pyrophosphate acts as a calcium chelator and is used in products for dental care to reduce tartar formation. It is also used as a food additive, and as a water softener in detergents and for industrial applications. Potassium pyrophosphate (tetrapotassium pyrophosphate) and sodium acid pyrophosphate (disodium pyrophosphate) are used similarly.

Sodium pyrophosphate is also used in kits for the preparation of technetium-99m pyrophosphate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Malvatricin Antitartaro†.

Multi-ingredient Preparations. ***Arg.***: Esmedent Dientes Sens Blanq + Ctrol Sarro; Fluordent PX; Sensodyne Antisarro; ***Braz.***: Emoform AT; Malvatricin Antiplaca†; Malvatricin Dentes Sensiveis†; ***Chile***: FKD; ***Fr.***: Fluocaril blancheur†; ***Ital.***: AZ Tartar Control; Emoform-Tat; ***USA***: Plax.

Sodium Pyruvate

Acetilformiato de sodio; Pirorracemato de sodio; Piruvato de sodio; Пируват Натрия.
Sodium α-ketopropionate; sodium 2-oxopropanoate.
$C_3H_4NaO_3$=111.1
CAS — 127-17-3 (pyruvic acid); 113-24-6 (sodium pyruvate).
UNII — POD38AIF08.

Profile

Sodium pyruvate has been given intravenously in the diagnosis of disorders of pyruvate metabolism.

Relative serum concentrations of lactate and pyruvate after a 10-minute intravenous infusion of sodium pyruvate 500 mg/kg have been used as an aid to the diagnosis of disorders of pyruvate metabolism.[1] Death shortly after pyruvate loading in a 9-year-old child with restrictive cardiomyopathy suggests that the test should not be performed when cardiac function is decreased.[2]

1. Dijkstra U, *et al.* Friedreich's ataxia: intravenous pyruvate load to demonstrate a defect in pyruvate metabolism. *Neurology* 1984; **34:** 1493–7.
2. Matthys D, *et al.* Fatal outcome of pyruvate loading test in child with restrictive cardiomyopathy. *Lancet* 1991; **338:** 1020–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Ger.***: Zitronensaurezyklus-Heel.

Sodium Silicate

Aqua Silicata; Silicato de sodio; Soluble Glass; Vidrio soluble; Water Glass; Натриевосиликатные; Силикат Натрия.

CAS — 1344-09-8.
UNII — UF18F77L3.

Profile

In dry form the most commonly available sodium silicates are Na_2SiO_3, $Na_6Si_2O_7$, and $Na_2Si_3O_7$, with varying amounts of water. Concentrated aqueous solutions of sodium silicate are commercially available and have many industrial uses. The solutions vary in composition, viscosity, and density; the greater the ratio of Na_2O to SiO_2 the more tacky and alkaline the solution.

Sodium Succinate

Succinato de sodio; Янтарнокислый Натрий.
$C_4H_4Na_2O_4.6H_2O$=270.1
CAS — 150-90-3 (anhydrous sodium succinate); 6106-21-4 (sodium succinate hexahydrate).
UNII — V8ZGC8ISR3 (anhydrous sodium succinate); U16QOD6C4E (sodium succinate hexahydrate).

Profile

Sodium succinate, the sodium salt of succinic acid (p. 2214.3), is an ingredient of topical preparations tried for the treatment of cataract. It is also used as a food additive.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Gr.***: Collyre Vitaphakol.

Sodium Tetradecyl Sulfate *(rINN)*

Natrii Tetradecylis Sulfas; Natriumtetradecylsulfat; Natriumtetradekyylisulfaatti; Sodium Tetradecyl Sulphate; Tetradecilsulfato de sodio; Tétradécyl Sulfate de Sodium; Натрия Тетрадецил Сульфат.
Sodium 4-ethyl-1-isobutyloctyl sulfate.
$C_{14}H_{29}NaO_4S$=316.4
CAS — 139-88-8.
ATC — C05BB04.
ATC Vet — QC05BB04.
UNII — Q1SUG5KBD6.

Pharmacopoeias. *Br.* includes as a concentrated form.

BP 2014: (Sodium Tetradecyl Sulfate Concentrate). A clear, colourless gel. Store at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Sodium tetradecyl sulfate is an alkyl sulfate anionic surfactant (p. 2164.1). It has sclerosing properties and is used in the treatment of varicose veins (p. 2564.1). It has also been given in the management of bleeding oesophageal varices (p. 2563.1), and tried in endoscopic injection therapy for nonvariceal bleeding associated with peptic ulcer disease (p. 1813.2).

For sclerotherapy of varicose veins a solution of sodium tetradecyl sulfate is injected slowly into the lumen of an isolated segment of an emptied superficial vein, followed by compression. Solutions are available in a variety of strengths (0.2 to 3%); doses depend on the site and condition being treated. A test dose is advisable in patients with a history of allergy. Facilities for treating anaphylaxis should be available.

Adverse Effects and Precautions

The complications of injection sclerotherapy with sclerosants such as sodium tetradecyl sulfate are discussed under Monoethanolamine Oleate, p. 2564.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fibro-Vein; ***Austral.***: Fibro-Vein; ***Canad.***: Tromboject; ***Fr.***: Trombovar; ***Hung.***: Fibro-Vein; ***Irl.***: Fibro-Vein; ***Israel***: STS†; ***Ital.***: Fibro-Vein; Trombovar†; ***Neth.***: Trombovar; ***NZ***: Fibro-Vein; ***Rus.***: Fibro-Vein (Фибро-Вейн); Trombovar (Тромбовар)†; ***S.Afr.***: Fibrovein†; STD†; ***Singapore***: Trombovar†; ***UK***: Fibrovein; ***USA***: Sotradecol.

Pharmacopoeial Preparations
BP 2014: Sodium Tetradecyl Sulphate Injection.

Solidago

Aranyvesszűfű (solidaginis herba); Echtes Goldrutenkraut (*S. virgaurea*); European Goldenrod (*S. virgaurea*); Golden Rod; Goldrutenkraut (*S. gigantea* or *S. canadensis*); Gullris, europeisk (solidaginis virgaureae herba); Gullris (solidaginis herba); Herba Virgaureae (*S. virgaurea*); Kultapiisku, eurooppalainen (solidaginis virgaureae herba); Kultapiisku (solidaginis herba); Nať zlatobýlu obecného (solidaginis virgaureae herba); Paprastųjų rykštenių žolė (solidaginis virgaureae herba); Rykštenių žolė (solidaginis herba); Solidage; Solidage Verge d'Or (*S. virgaurea*); Solidaginis Herba (*S. gigantea* or *S. canadensis*); Solidaginis Virgaureae Herba (*S. virgaurea*); Solidago Virga Aurea (*S. virgaurea*); Verge d'Or; Ziele nawłoci pospolitej (*S. virgaurea*); Ziele nawłoci (*S. virgaurea*); Zlatobýlová nať (solidaginis herba); Золотарник.
*ATC Herb — HJ01WB5014 (*Solidago virgaurea*: herb).*
*UNII — ZHL562L3PR (*Solidago canadensis*).*

NOTE. The name Aaron's Rod has been applied to several plants including *Solidago* spp., *Verbascum* spp., and *Sempervivum tectorum.*

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Goldenrod, European; Solidaginis virgaureae herba). The whole or fragmented dried, flowering aerial parts of *Solidago virgaurea*. It contains not less than 0.5% and not more than 1.5% flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) with reference to the dried drug.

Ph. Eur. 8: (Goldenrod; Solidaginis herba). The whole or cut dried, flowering aerial parts of *Solidago gigantea* or *S. canadensis*. It contains not less than 2.5% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) with reference to the dried drug.

Profile

Solidago virgaurea (Asteraceae) has diuretic and anti-inflammatory activity. It is mainly used in inflammatory disorders of the bladder and kidneys and for the treatment of renal stones. It is also included in herbal preparations used for a variety of disorders.

S. gigantea (Early golden-rod) and *S. canadensis* were once considered to be adulterants of *S. virgaurea* but are now recognised as having similar activity.

Homoeopathy

Solidago has been used in homoeopathic medicines under the following names: Solidago virgaurea; Sol. vir.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Zlatobylova Nat†; ***Ger.***: Cystinol Long; Cystium Solidago†; Nephrisol mono†; Nieral; Polbax novo; Solidacur; Solidagoren Mono; Solidagoren mono; Stromic†; Urol; ***Hung.***: Stromic.

Multi-ingredient Preparations. ***Austral.***: Cranbiotic Super†; Euphrasia Complex; Euphrasia Compound; Extralife Fluid-Care†; Phytodolor; ***Austria***: Heumann's Blasen- und Nierentee; Phytodolor; Solubitrat†; Urelium Neu; ***Canad.***: Entschlackungstee N†; ***Cz.***: Antirevmaticky Caj†; Epilobin; Phytodolor†; Urcyston Planta; ***Fr.***: Solution Stago Diluee; Tisane de Sante†; ***Ger.***: Aqualibra; BioCyst†; Cefasabal†; Cystinol N; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee†; Harntee 400 N; Harntee-Steiner†; Heumann Blasen- und Nierentee Solubitrat uro; Nephroselect M; Phytodolor; Prostamed; Renob Blasen- und Nierentee†; Solidagoren; ***Hung.***: Herpesil; Prostazyn; Vesevedo; Worishofener; ***Ital.***: Flavion; ***Malaysia***: Cefasabal; ***Pol.***: Diuronis; Fitoven; Nefrobonisol; Nefrol; Nefrosept; NeoFitolizyna†; Prostapol; Reumacor; Urofort; Uromix†; Uroprost; ***Rus.***: Prostanorm (Простанорм); ***Switz.***: Demonatur Dragees pour les reins et la vessie†; Dragees S pour les reins et la vessie; Impuls dragees pour la vessie et les reins; Impuls pastilles pour les bronches; Nephrosolid; Sabrinin dragees pour les reins et la vessie; Urinex; ***Ukr.***: Prostamed (Простамед); Uronephron (Уронефрон).

Homoeopathic Preparations. ***Austral.***: Echine†; ***Austria***: Berberis Cosmoplex†; ***Canad.***: Allergy Relief†; Breathe More; Chelidonium Plex†; Common Mallow Combination†; Drosera Complex; Drosera Plex†; Formula CI 207†; Formula FV 213; Formula Homeo QR 209†; Goldenrod Combination†; Homeoknop Ikoplex 13†; Lympatox; Male +; Renelix; Sabalia; ***Chile***: Ikoplex No 13; ***Cz.***: Drosetux; Rhinallergy; ***Fr.***: Boripharm No 1†; Boripharm No 41; Chelidonium Compose; Drosera Compose; Drosetux; Formica Rufa Compose; Homeofortil†; Kalium Iodatum Complexe No 84†; L 8; Nux Vomica Compose; Pareira Brava Compose; Rhinallergy; Santaherba; Scrofularia Compose; Thlascose†; Urodren; ***Ger.***: Chol-Do; Cysto Hevert; Heparanox H; Hevertnier Complex N†; Heweberberol; Hewecyst Blasen-Nieren†; Josskleran; Lowe-Komplex Nr 13; metasolidago S†; Nephroplex; Nierentropfen Cosmochema; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Renorell; Solidago Hevert Complex; Solidagosan N; Uro Albin; uro-loges; ***Hung.***: Drosetux; ***Neth.***: Akutur spag; Homeocare Uro; Phonix Solidago comp; Reneel H; Restructa H; ***Rus.***: Psorilom (Псорилом); ***Switz.***: Akutur; Drosetux; Rhinallergy; Silacten; ***Ukr.***: Homviocorin-N (Хомвиокорин-N); ***USA***: Preferred Remedies Antacid; Preferred Remedies Detoxin.

Sorrel

Acedera Común; Azeda-Brava; Garden Sorrel; Herba Rumicis Acetosae; Oseille; Sorrel Dock; Sour Dock; Vinagrera; Wiesensauerampfer; Щавель Обыкновенный (*Rumex acetosa*); Щавель Кислый (*Rumex acetosa*).

NOTE. The name sour dock has also been used for yellow dock (p. 2649.3).

Profile

Sorrel (*Rumex acetosa,* Polygonaceae) has been used for respiratory-tract disorders. It is also used as a culinary herb.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Sinupret; ***Austria***: Sinupret; Solvopret†; ***Cz.***: Sinupret; ***Ger.***: Sinupret; ***Hong Kong***: Sinupret; ***Hung.***: Sinupret; ***Indon.***: Sinupret†; ***Malaysia***: Sinupret; ***Mex.***: Bisolsinus; ***Philipp.***: Sinupret; ***Pol.***: Sinupret; ***Rus.***: Sinupret (Синупрет); ***Singapore***: Sinupret; ***Swed.***: Sinova; ***Switz.***: Sinupret; ***Thai.***: Sinupret†; ***UK***: Sinueeze; Sinuherb; ***Ukr.***: Sinupret (Синупрет).

Homoeopathic Preparations. ***Canad.***: Essigen†.

Soya Isoflavones

Соевые Изофлавоны.

Pharmacopoeias. In *US.*

USP 36: (Powdered Soy Isoflavones Extract). It is prepared from the seeds of *Glycine max* (Fabaceae) by extraction with water or hydroalcoholic mixtures. Its content is calculated on the dried basis as the sum of daidzin, glycitin, genistin, and one or more of the following isoflavones: malonyl daidzin, malonyl glycitin, malonyl genistin, acetyl daidzin, acetyl glycitin, acetyl genistin, daidzein, glycitein, and genistein. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Daidzein

Даидзеин.
4′,7-Dihydroxyisoflavone; 7-Hydroxy-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.
$C_{15}H_{10}O_4$=254.2
CAS — 486-66-8.
UNII — 6287WC5J2L.

Genistein

CI-75610; Genisteol; Prunetol; Генистеин.
4′,5,7-Trihydroxyisoflavone; 5,7-Dihydroxy-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.
$C_{15}H_{10}O_5$=270.2
CAS — 446-72-0.
UNII — DH2M523P0H.

Profile

Genistein and daidzein are soya isoflavones. Genistein, a tyrosine kinase inhibitor, is a phytoestrogen that is used for the relief of menopausal symptoms. It is also being investigated for its beneficial effect on blood lipids and for its proposed tumour-suppressing activity. Daidzein has been used similarly. Daidzein, mainly in the form of its glycoside daidzin, is a component of some herbal medicines traditionally used in the management of alcohol abuse.

DT56a, a phytoestrogen derived from soya, is also used for the relief of symptoms associated with menopausal disorders.

Effects on the endocrine system. For a suggestion that isoflavones in soya-based formulas may exert biological effects, see p. 2093.3.

Hyperlipidaemias. For a discussion of possible beneficial effects of soya isoflavones on blood lipids, see p. 2093.2.

Menopausal disorders. Soya contains phytoestrogens in the form of isoflavones, in particular daidzein (above) and genistein (above), which have been investigated for their oestrogen-modulating effects in the treatment of menopausal symptoms (p. 2245.1).[1] It is thought that genistein may exert oestrogenic effects in the presence of low oestrogen concentrations, but that it may be anti-oestrogenic when concentrations of oestrogen are high.[2]

A small reduction in the incidence of hot flushes has been noted with soya isoflavone extract.[3] A systematic review,[4] however, concluded that phytoestrogens available as soya foods, soya extracts, or red clover extracts (p. 2482.1) do not improve hot flushes or other menopausal symptoms.

Isoflavones may have a beneficial effect on cholesterol and lipid concentrations (see Hyperlipidaemias, p. 2093.2). Some epidemiological studies and *animal* data suggest that they may also provide protection against breast cancer.[1,2,5] However, phytoestrogens could also stimulate breast tumour growth due to oestrogenic activity.[6] These stimulating and inhibitory effects may be concentration-dependent; soya products contain only small amounts of phytoestrogens and it may be difficult to consume enough soy to have any beneficial effect on breast cancer growth.[7] A meta-analysis[8] concluded that soya intake may be associated with a small reduction in breast cancer risk, but that this result should be interpreted with caution due to confounding factors and a lack of dose response. Given the possibility of adverse effects, recommendations for high-dose soya isoflavone supplementation to prevent breast cancer or its recurrence are premature.

A few small studies have shown that soya isoflavones can decrease bone turnover, leading to speculation that they could be used to prevent osteoporosis (p. 1168.1).[1] The effects of these isoflavones should be investigated in larger studies before they can be recommended as alternatives to conventional HRT.[3-7] (For the view that they may lack cardiovascular benefits see Hyperlipidaemias, p. 2093.2.) In a study to investigate effects on cognitive function, bone mineral density, and plasma lipids in postmenopausal women, no differences were noted between soya protein containing isoflavones, and placebo.[9]

1. Vincent A, Fitzpatrick LA. Soy isoflavones: are they useful in menopause? *Mayo Clin Proc* 2000; **75:** 1174–84.
2. Goldwyn S, *et al.* Promotion of health by soy isoflavones: efficacy, benefit and safety concerns. *Drug Metabol Drug Interact* 2000; **17:** 261–89.
3. Upmalis DH, *et al.* Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2000; **7:** 236–42. Correction. *ibid.;* 422.
4. Krebs EE, *et al.* Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstet Gynecol* 2004; **104:** 824–36.
5. Sirtori CR. Risks and benefits of soy phytoestrogens in cardiovascular diseases, cancer, climacteric symptoms and osteoporosis. *Drug Safety* 2001; **24:** 665–82.
6. Mason P. Isoflavones. *Pharm J* 2001; **266:** 16–19.
7. de Lemos ML. Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. *Ann Pharmacother* 2001; **35:** 1118–21.
8. Trock BJ, *et al.* Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst* 2006; **98:** 459–71.
9. Kreijkamp-Kaspers S, *et al.* Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 2004; **292:** 65–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Isolife; Melinda; Sojadiol; Sojar Men; Tanvimil Isoflavonas; ***Belg.***: Elugyn; ***Braz.***: Buona; Flavonil†; Isoflavine; Menop; Soy 50; Soyfemme; ***Chile***: Fitoflavona; Phyto Soya; ***Fr.***: Gydrelle Phyto; Inoclim; ***Hong Kong***: Phyto Soya; Phyto-Care; ***India***: Isoflav; Menoflav; ***Indon.***: Calvonin; Promensil; ***Ital.***: Genivis; Soymen Gel; ***S.Afr.***: Phytopause†; ***Singapore***: Isoflav; Isovon; Phyto Soya; ***Spain***: Flavosul; ***Swed.***: Menosoy; ***Thai.***: Flamina; ***Turk.***: Gynogen; Isoflavin; ***Venez.***: Climasoy.

Multi-ingredient Preparations. ***Arg.***: Equilibrol Fem; Fem Plus 50; Fitogenos; Isaflavon; La Edad De Oro; Melinda Plus; Selder; Sigmafem Free; Sigmaflavon Plus; Snella D + E; Sojar Plus-Calcio; Tanvimil Gel; Tanvimil Isoflavonas Calcio D3; Tanvimil Isoflavonas; Upsala; ***Austral.***: In-Control; Meno Support Plus; ***Canad.***: Natural HRT; Phytoestrin; ***Chile***: Dennov; ***Fin.***: Femarelle; ***Fr.***: Anacaps†; Estrofort†; Imedeen Prime Renewal†; Menoceane†; ***Gr.***: Femarelle; ***Hong Kong***: Caltrate + Soy†; Femarelle; Palmetto Plus†; Phyto-Ease; Phytoestrin†; ***India***: Alfaflavon; Calciflavone; Cavit-PM; Ease-PMS; Estovon-XT; Estovon; Evepearl-MP; Femarelle; Gynacea; Isovon; Melaglow; Menoease; Menopace Iso; Menosoft; Menosoy; Moxafav; Osteo-G; ***Indon.***: Biocal-95; Bonilav; Cal-95; Calosbon; Calplex; Femosa; Hi-Bone; Isofem†; Isomenopace; Naturliver; Opus; Ossovit Plus; ***Israel***: Femarelle†; ***Ital.***: Apogeo; Biolastic T5; Climil Complex; Climil Gel; Climil-80; Evestrel; Fitogenase; Ginepausil; Rinnova; ***Malaysia***: Isoflav; Shine Fememino; ***Mex.***: Caflovan; Tofupill; ***Norw.***: Femarelle; ***S.Afr.***: Phytopause BSF†; ***Singapore***: Caltrate + Soy†; Femarelle; Palmetto Plus†; Phytoestrin†; ***Spain***: Femarelle; ***Swed.***: Femarelle; ***UK***: Aria; Estroven Nighttime; Estroven; Femarelle; SoyPlus; ***USA***: Better Cholesterol; Femarelle; Fosteum; ***Venez.***: Calcibon D Soya.

Pharmacopoeial Preparations
USP 36: Soy Isoflavones Capsules; Soy Isoflavones Tablets.

Sparteine Sulfate *(USAN, rINNM)*

Esparteína, sulfato de; Spart. Sulph.; Spartéine, Sulfate de; *l*-Sparteine Sulphate; Sparteine Sulphate; (-)-Sparteine Sulphate; Sparteini Sulfas; Sparteinum Sulfuricum; Sulfato de esparteína; Спартеина Сульфат.

Dodecahydro-7,14-methano-2*H*,6*H*-dipyrido[1,2-*a*:1′,2′-*e*][1,5]diazocine sulphate pentahydrate.

$C_{15}H_{26}N_2,H_2SO_4,5H_2O$=422.5

CAS — 90-39-1 (sparteine); 299-39-8 (anhydrous sparteine sulfate); 6160-12-9 (sparteine sulfate pentahydrate).

ATC — C01BA04.
ATC Vet — QC01BA04.
UNII — GQ3J2TLZ7E.

Pharmacopoeias. In *Fr.* and *Viet.*

Profile

Sparteine sulfate is a salt of the dibasic alkaloid, sparteine, which is obtained from scoparium (p. 2611.3). Sparteine sulfate has been reported to lessen the irritability and conductivity of cardiac muscle and has been used in the treatment of cardiac arrhythmias. Small doses stimulate and large doses paralyse the autonomic ganglia. Peripherally, it has a fairly strong curare-like action, arresting respiration by paralysing the phrenic endings.

The metabolic oxidation of sparteine exhibits genetic polymorphism and this property has been exploited in *in-vitro* screening tests to identify other drugs that may be subject to similar genetic variations in their metabolism.

Precautions. Sparteine present in a herbal slimming preparation might cause adverse effects in slow metabolisers if excessive doses were ingested; pregnant women might be particularly at risk.[1]

1. Galloway JH, *et al.* Potentially hazardous compound in a herbal slimming remedy. *Lancet* 1992; **340:** 179.

Spearmint

Asanda; Grüne Minze; Hierba buena; Menta; Menta crespa; Menta romana; Menta verde; Mentastro verde; Mentha Viridis; Menthae Crispae Folium; Menthe douce; Menthe verte; Mint; Sándalo de jardín; Speer-Minze; Мята Колосистая (*Mentha spicata*); Yerba buena; Yerba santa; Yerbabuena.

UNII — J7I2T6IV1N (spearmint); FV98Z8GITP (mint); O2H83I4PUN (Mentha spicata).

Profile

Spearmint consists of the dried leaves and flowering tops of common spearmint, *Mentha spicata* (*M. viridis*) or of scotch spearmint (*M. cardiaca*) (Labiatae). Spearmint is the source of spearmint oil (below). It has carminative properties and is used as a flavour.

References.

1. Akdoğan M, *et al.* Effect of spearmint (*Mentha spicata* Labiatae) teas on androgen levels in women with hirsutism. *Phytother Res* 2007; **21:** 444–7.
2. Grant P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. *Phytother Res* 2010; **24:** 186–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Giamebil.

Multi-ingredient Preparations. ***Canad.***: Calmane; ***Chile***: Te Laxante†; ***Fr.***: Detoxifiance; Tisane Provencale no 4†; ***Indon.***: Fitajoint; ***Switz.***: Kernosan Eau Dentifrice†; Tisane antirhumatismale; Tisane pour l'estomac; Tisane pour le coeur et la circulation; Tisane pour le sommeil et les nerfs; ***Ukr.***: Florised (Флорисед).

Spearmint Oil

Huile Essentielle de Menthe Crépue; Menta, aceite esencial de; Oleum Menthae Crispae; Oleum Menthae Viridis; Мятное Масло.

UNII — C3M81465G5.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Spearmint Oil). It is obtained by distillation from fresh flowering plants of *Mentha spicata* or *Mentha* X *cardiaca*. A clear colourless, pale yellow or greenish-yellow liquid when freshly distilled, visibly free from water and with the odour of spearmint. It becomes darker and viscous on keeping. It contains not less than 55% w/w of carvone. Soluble 1 in 1 of alcohol (80%) at 20 degrees; the solution may become cloudy when diluted. Store at a temperature not exceeding 25 degrees in well-filled containers. Protect from light.

Uses and Administration

Spearmint oil has similar properties to peppermint oil (p. 1877.1) and is used as a carminative and as a flavour. It is also used in aromatherapy.

Adverse Effects

Hypersensitivity. Allergic contact cheilitis in a patient has been attributed to the spearmint oil present in tooth paste.[1] Other cases of sensitivity reactions have been reported.[2,3]

1. Skrebova N, *et al.* Allergic contact cheilitis from spearmint oil. *Contact Dermatitis* 1998; **39:** 35.
2. Bonamonte D, *et al.* Allergic contact dermatitis from Mentha spicata (spearmint). *Contact Dermatitis* 2001; **45:** 298.
3. Clayton R, Orton D. Contact allergy to spearmint oil in a patient with oral lichen planus. *Contact Dermatitis* 2004; **51:** 314–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pervinox Extra Mint; ***Austria***: Euka; ***Chile***: Polvos Alcalinos; ***Hung.***: Pudin Haran; ***India***: Aglotus; ***Indon.***: Listerine Coolmint†; ***Ital.***: Dentosan Azione Intensiva; Dentosan Mese; ***Philipp.***: CleanEars; Listerine Coolmint; Medisnore; ***Switz.***: Alvogyl; ***UK***: Fre-bre; Profelan; ***USA***: Nostrilla Conditioning Double Moisture.

Spigelia Anthelmia

Demerara Pinkroot; Erva-lombrigueira; Pink Root of Demerara; West Indian Pinkroot; West Indian-pink; Wormbush.

UNII — WYT05213GE.

NOTE. The names Indian Pink, Pink Root (or Pinkroot), and Worm Grass (or Wormgrass) have been applied to both Spigelia Anthelmia and Spigelia Marilandica.

Spigelia Marilandica

American Wormgrass; American-wormroot; Carolina Pink; Carolina Wormroot; Maryland Pink; Maryland Pinkroot; Maryland Wormroot; Maryland-Wormroot; Star Bloom; Starbloom; Woodland Pinkroot; Spigelia.

UNII — FI1A4U61CP (Spigelia marilandica)*; 467D26HS0B* (Spigelia marilandica *root).*

Profile

The dried roots and rhizomes of *Spigelia anthelmia* and *S. marilandica* (*Lonicera marilandica*), (Loganiaceae) have historically been used in herbal and traditional medicine for the treatment of intestinal helminth infections and for cardiac disorders. The entire plant has also been used. Adverse effects, which are reportedly less frequent if given with a purgative, include dizziness, visual disturbances, and muscle spasms. High doses may result in cardiotoxicity, convulsions, and respiratory depression; fatalities have occurred. *S. anthelmia* may be more potent and more toxic than *S. marilandica.*

Homoeopathy
Spigelia has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Port.***: Cephyl†.

Homoeopathic Preparations. ***Austria***: Cactus compositum; Cora; Cralonin; Spigelon; ***Canad.***: Formula DM 210†; Sinusalia; Spigelon†; ***Fr.***: Abbe Chaupitre no 20†; Amanita Complexe No 75; Boripharm No 31; Cina Compose; Neurocynesine†; Sclero-Drainol†; ***Ger.***: Cardioselect N; Confludin N; Cralonin; Craniocyl Ho-Len-Complex; DolorA; Habstal-Cor N; HanoCor N; Migrane Hevert†; Migrane-Gastreu R16; Myonasan; Pectapas CPL; Pectapas SL; Pectapas; Rephalgin N; Strophanthus comp; ***Hung.***: Spigelon; ***Neth.***: Cephalite; Cralonin H; Cralonin; Neurocynesine†; ***Switz.***: Cralonin; Spigelon.

Spike Lavender

Lavande aspic; Лаванда Широколистная.

Profile

Spike lavender, *Lavandula latifolia* (Lamiaceae), is used similarly to lavender (p. 2541.1) as a sedative and for biliary disorders. It is the source of spike lavender oil (below).

Spike Lavender Oil

Alhucema, aceite esencial de; Huile Essentielle d'Aspic; Ol. Lavand. Spic.; Oleum Lavandulae Spicatae; Speiköl; Spicae Aetheroleum; Spike Oil; Спиковое Лавандовое Масло.

UNII — 7S2HYV1VJQ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Spike Lavender Oil; Spicae Aetheroleum). The essential oil obtained by steam distillation of the flowering tops of *Lavandula latifolia.* A clear, mobile, light yellow or greenish-yellow liquid with an odour reminiscent of cineole

and camphor. Store at a temperature not exceeding 25 degrees.

Profile

Spike lavender oil is the volatile oil from *Lavandula latifolia* (Labiatae). It resembles lavender oil (p. 2541.1) in its properties and is mainly used in perfumery. It is also used in aromatherapy. Hypersensitivity reactions may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Tavipec; ***Thai.***: Tavipec.

Multi-ingredient Preparations. ***Austria***: Novipec†; Tussamag; ***Rus.***: Carmolis (Кармолис); ***S.Afr.***: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Stuidruppels; ***Switz.***: Baume du Chalet; Fortalis.

Spirulina

Espirulina; Спирулина.

Profile

Spirulina is a species of blue-green algae that has been promoted as an anorectic, but there is no convincing evidence that it is safe or effective for this indication.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Eufit; Fitness; Novalina; Nuclina; ***Indon.***: Spirumate†; ***Rus.***: Radahlorin (Радахлорин); ***UK***: Biolina; Immulina.

Multi-ingredient Preparations. ***Arg.***: Adel; Centella Asiatica Spir; Doctor 10 Body; No-Gras; Spiruvita; ***Austral.***: Cal Alkyline†; NutriMulti; ***Chile***: Natur-Zin; Natursel-C; Perfect Body; Reducform-F; ***Fr.***: Biofirm; Cicatendon; Proselem; Ultraselem; ***India***: Actima; Ampiro; Antex; Antoxyl; Becose; Bethadoxin-XL; Candor; Fezys-SM; MSA; Neuroage Plus; Newvit-S; Optifit; Oximino; Vitexid; ***Ital.***: Lactovit; Salovit; ***Philipp.***: Spigrow for Boys; Spigrow for Girls; ***USA***: Alive Once Daily Womens 50+ Ultra Potency.

Star Anise

Anís Estrellado; Anis Étoilé; Anisi Stellati Fructus; Anisum Badium; Anisum Stellatum; Badiana; Badiane; Badiane de Chine; Badyáníkový plod; Chinese Star Anise; Csillagánizs; Owoc anyżu gwiaździstego; Star Anise Fruit; Sternanis; Stjärnanis; Tähtianis; Žvaigždanyžių vaisiai; Анис Звёздчатый.
*UNII — XKC1657P78 (*Illicium verum *seed); CK15HA8438 (*Illicium verum *fruit).*

NOTE. Distinguish from Japanese star anise.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Star Anise; Anisi Stellati Fructus). The dried composite fruit of *Illicium verum*, containing not less than 7% v/w of essential oil with reference to the anhydrous drug and a minimum 86.0% of *trans*-anethole in the essential oil. Protect from light.

Uses and Administration

The fruit of star anise, *Illicium verum* (Illiciaceae), is used as an expectorant for catarrh and as a gastrointestinal antispasmodic. It is used with thyme (p. 2630.2) in herbal preparations for colds and upper respiratory-tract disorders. It is also used as a culinary spice.

Star anise is the source of star anise oil (below). It is also the source of shikimic acid, which is used in the production of the anti-influenza drug oseltamivir (p. 1006.2).

Adulteration of star anise with Japanese star anise (shikimi fruits; *I. anisatum*) has been responsible for cases of neurotoxicity (see below). Import restrictions have been implemented in the EU. The problem is further complicated because the name *I. anisatum* has been applied to *I. verum*.

Adverse Effects

Effects on the nervous system. Neurotoxicity has been associated with the use of star anise infusions in infants.[1-4] The toxicity is attributed to adulteration or contamination of Chinese star anise (*Illicium verum*) with Japanese star anise (*I. anisatum*), which contains toxic sesquiterpene lactones such as anisatin.

1. Garzo Fernandez C, *et al.* Casos de enfermedad de sintomatología neurológica asociados al consumo de anís estrellado empleado como carminativo. *An Esp Pediatr* 2002; **57:** 290–4.
2. Minodier P, *et al.* Intoxication aiguë par la badiane chez Le nourrisson. *Arch Pediatr* 2003; **10:** 619–21.
3. Ize-Ludlow D, *et al.* Neurotoxicities in infants seen with the consumption of star anise tea. Abstract: *Pediatrics* 2004; **114:** 1330. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/5/e653.pdf (accessed 16/08/10)
4. de la Rubia Fernández L, *et al.* Intoxicación por anís estrellado. *An Pediatr (Barc)* 2009; **71:** 581–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Wunderbalsam; ***Austria***: Pervivo; ***Braz.***: Ductoveran; ***Ger.***: Cefabronchin; ***Hung.***: Bittner; ***Ital.***: Relaxcol; ***Pol.***: Pervivo; ***Switz.***: Kernosan Eau Dentifrice†; Tisane laxative; Tisane pectorale et antitussive; ***Venez.***: Atrobel; Ervossil.

Homoeopathic Preparations. ***Austria***: Tartephedreel.

Star Anise Oil

Anisi Stellati Aetheroleum; Anisi Stellati Etheroleum; Badiane, huile essentielle de; Badyáníková silice; Oleum Badianae; Sternanisöl; Stjärnanisolja; Tähtianisöljy; Žvaigždanyžių eterinis aliejus; Бадьяновое Масло.
UNII — 6RXP35EIRE.

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* includes star anise oil under the title Anise Oil.

Ph. Eur. 8: (Star Anise Oil; Anisi Stellati Aetheroleum). An essential oil obtained by steam distillation from the dry ripe fruits of *Illicium verum*. It contains 0.2 to 2.5% linalol, 0.5 to 6.0% estragole, less than 0.3% α-terpineol, 0.1 to 0.5% *cis*-anethole, 86 to 93% *trans*-anethole, 0.1 to 0.5% anisaldehyde, and 0.1 to 3.0% foeniculin. A clear, colourless or pale yellow liquid. Relative density 0.979 to 0.985. F.p. 15 degrees to 19 degrees. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Anise Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* (Apiaceae) or from the dried ripe fruit of *Illicium verum* (Illiaceae). Congealing temperature not lower than 15 degrees. Soluble 1 in 3 of alcohol (90%). Store in well-filled airtight containers. If solid material has separated, carefully warm the oil until it is completely liquefied, and mix before using.

Profile

Star anise oil is included in preparations for the treatment of coughs and cold symptoms. It is used in the pharmaceutical and food industries as an alternative to anise oil (see p. 2444.3). It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Zap.

Multi-ingredient Preparations. ***Cz.***: Biotussil; ***Ger.***: Makatussin Tropfen; ***Swed.***: Alpenkraft; Multipretten; ***Switz.***: DUL-X warm; DUL-X; Liberol Baby N; Odontal; ***Turk.***: Sandolin†.

Pharmacopoeial Preparations
BP 2014: Camphorated Opium Tincture; Compound Orange Spirit; Concentrated Anise Water; Concentrated Camphorated Opium Tincture.

Stone Root

Collinsonia; Collinsonia del Canadá; Hardhack; Heal-all; Knob Root; Коллинсония Канадская (*Collinsonia canadensis*).
*UNII — J9BTD5377V (collinsonia); O2630F3XDR (*Collinsonia canadensis *root).*

Profile

Stone root, the root and rhizome of *Collinsonia canadensis* (Labiatae), has diuretic and litholytic properties and is used in the treatment of renal and urinary calculi. It is also used as an astringent for gastrointestinal disorders. It has also been included in herbal preparations for haemorrhoids.

Homoeopathy

Stone root has been used in homoeopathic medicines under the following names: Collinsonia; Collinsonia canadensis; Collin. c.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Diuretic Tablets; ***UK***: Piletabs.

Homoeopathic Preparations. ***Canad.***: Hae 2 Complex†; ***Fr.***: Aesculus Complexe No 103; Carominthe; Sepia Compose; ***Ger.***: Haemorrhoid-Gastreu N; ***Neth.***: Collite; ***Switz.***: Hemolingual.

Storax

Balsamum Styrax Liquidus; Estoraque; Estoraque Líquido; Liquid Storax; Styrax; Стиракс.
*ATC Herb — HD03WX5010 (*Liquidambar styraciflua*: balsam); HR05WA5025 (*Liquidambar styraciflua*: balsam); HD03WX5009 (*Liquidambar orientalis*: balsam); HR05WA5024 (*Liquidambar orientalis*: balsam).*
UNII — 63V91G4W93.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Storax). The balsam obtained from the trunk of *Liquidambar orientalis* (Levant storax) or *L. styraciflua* (American storax) (Hamamelidaceae). It is a semiliquid greyish to greyish-brown, sticky, opaque mass depositing on standing a heavy dark brown layer (Levant storax), or semisolid, sometimes a solid mass, softened by gently heating (American storax). It is transparent in thin layers, has a characteristic odour, and is more dense than water.

Insoluble in water; soluble, usually incompletely, in an equal weight of warm alcohol; soluble in acetone, in carbon disulfide, and in ether, some insoluble residue usually remaining.

Profile

Storax has actions similar to those of Peru balsam (p. 2587.1). Purified storax or prepared storax was formerly applied as an ointment in the treatment of parasitic skin diseases. Storax has a mild antiseptic action and is an ingredient of some preparations for upper respiratory-tract disorders and for application to skin and mucous membranes. Skin sensitisation has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Friar's Balsam; ***NZ***: Frador†; ***S.Afr.***: Turulington Tincture†; ***UK***: Frador; Friars Balsam.

Pharmacopoeial Preparations
BP 2014: Benzoin Inhalation; Compound Benzoin Tincture;
BPC 1954: Compound Iodoform Paint;
USP 36: Compound Benzoin Tincture.

Stramonium

Datura; Durmanový list (stramonium leaf); Durnaropių lapai (stramonium leaf); Estramonio; Hulluruohonlehti (stramonium leaf); Inferno; Jamestown Weed; Jimson Weed; Maszlaglevél (stramonium leaf); Stechapfel; Stramoine; Stramoine, feuille de (stramonium leaf); Stramonii folium (stramonium leaf); Stramoniumblad (stramonium leaf); Thornapple; Дурман Обыкновенный (*Datura stramonium*).
ATC Vet — QR03BB03.
*ATC Herb — HA03YA5003 (*Datura stramonium*: leaf); HR03BB5001 (*Datum stramonium*: leaf).*
*UNII — G6W4F0V8Z3 (*Datura stramonium*); WQ9QD9P2XV (*Datura stramonium *leaf).*

NOTE. The terms Datura, Datura Herb, and Datura Leaf have been applied to preparations of various species of the genus Datura including *Datura metel*.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of stramonium:

Devil's weed; Loco weed.

Pharmacopoeias. *Eur.* (see p. vii) includes a monograph for Stramonium Leaf and Prepared Stramonium.

Ph. Eur. 8: (Stramonium Leaf; Stramonii Folium). It consists of the dried leaf or the dried leaf, flowering tops and occasionally fruit-bearing tops of *Datura stramonium* and its varieties. It contains not less than 0.25% of total alkaloids, calculated as hyoscyamine. The alkaloids consist mainly of hyoscyamine with varying proportions of hyoscine. It has an unpleasant odour. Protect from light and moisture.

The BP 2014 directs that when stramonium leaf or powdered stramonium leaf is prescribed, prepared stramonium shall be dispensed.

Ph. Eur. 8: (Stramonium, Prepared; Stramonii Pulvis Normatus). It is stramonium leaf powder adjusted to contain 0.23 to 0.27% of total alkaloids, calculated as hyoscyamine. Store in airtight containers. Protect from light.

Uses and Administration

Stramonium has the actions of atropine (p. 1312.1). It has been given with other drugs in oral and rectal dosage forms for respiratory-tract disorders. It has also been smoked in cigarettes or burnt in powders and the fumes inhaled but the irritation produced by the fumes may aggravate bronchitis.

Homoeopathy

Stramonium has been used in homoeopathic medicines under the following names: Datura stramonium; Stram.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Abuse. Some reports of poisoning mostly associated with abuse of *Datura stramonium* or its preparations.

1. Gowdy JM. Stramonium intoxication: review of symptomatology in 212 cases. *JAMA* 1972; **221:** 585–7.
2. Shervette RE, *et al*. Jimson "Loco" weed abuse in adolescents. *Pediatrics* 1979; **63:** 520–3.
3. Anonymous. Jimson weed poisoning—Texas, New York, and California, 1994. *MMWR* 1995; **44:** 41–4.
4. Salen P, *et al*. Effect of physostigmine and gastric lavage in a Datura stramonium-induced anticholinergic poisoning epidemic. *Am J Emerg Med* 2003; **21:** 316–17.
5. Boumba VA, *et al*. Fatal poisoning from ingestion of Datura stramonium seeds. *Vet Hum Toxicol* 2004; **46:** 81–2.
6. Forrester MB. Jimsonweed (Datura stramonium) exposures in Texas, 1998-2004. *J Toxicol Environ Health A* 2006; **69:** 1757–62.
7. Marc B, *et al*. Intoxications aiguës à Datura stramonium aux urgences. *Presse Med* 2007; **36:** 1399–1403.
8. Spina SP, Taddei A. Teenagers with Jimson weed (Datura stramonium) poisoning. *CJEM* 2007; **9:** 467–8.
9. Wiebe TH, *et al*. Angel's trumpet (Datura stramonium) poisoning and delirium in adolescents in Winnipeg, Manitoba: Summer 2006. *Paediatr Child Health* 2008; **13:** 193–6.
10. Suk SH, Kwak YT. Toxic encephalopathy after taking dried seeds of Datura stramonium in two elderly subjects. *Geriatr Gerontol Int* 2009; **9:** 326–8.
11. CDC. Jimsonweed poisoning associated with a homemade stew—Maryland, 2008. *MMWR* 2010; **59:** 102–4.

Effects on the eyes. Anisocoria (unequal dilatation of the pupils) developed after accidental entry of a piece of jimson weed *(Datura stramonium)* into a patient's eye while gardening.[1]

1. Savitt DL, *et al*. Anisocoria from Jimsonweed. *JAMA* 1986; **255:** 1439–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austria***: Mygale compositum†; ***Canad.***: Barijodeel†; Breathe More; Homeogene 46; Kids Calm; Quietude; ***Cz.***: Sedalia; ***Fr.***: Abbe Chaupitre no 67†; Abbe Chaupitre no 6; Boripharm No 12†; Homeogene 46; Lobelia Complexe No 74†; Noctium; Oenanthe Crocata Complexe No 78; Quietude; Santaherba; Somnidoron; Tarentula Complexe No 71; Zincum Cyanidum Complexe No 101†; ***Ger.***: A-Bomin; Asthmavowen-N†; ***Neth.***: Quietude†; ***Switz.***: Quietude; Sleepium; ***USA***: Preferred Remedies Stress.

Streptodornase *(BAN, rINN)*

Estreptodornasa; Streptococcal Deoxyribonuclease; Streptodornaasi; Streptodornas; Streptodornasum; Стрептодорназа.

CAS — 37340-82-2.

UNII — DV8J2R3544.

Profile

Streptodornase is an enzyme obtained from cultures of various strains of *Streptococcus haemolyticus*. It catalyses the depolymerisation of polymerised deoxyribonucleoproteins. It liquefies the viscous nucleoprotein of dead cells; it has no effect on living cells. It is used with streptokinase in the topical treatment of lesions, wounds, and other conditions that require the removal of clots or purulent matter; the combination may also be used to dissolve clots in the bladder or in urinary catheters.

It has also been given orally with streptokinase and sometimes with antibacterials, for its supposed benefit in reducing oedema and inflammation associated with trauma and infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Varidase; ***Fin.***: Varidase†; ***Ger.***: Varidase; ***Mex.***: Varidasa; ***Norw.***: Varidase†; ***Pol.***: Biostreptaza; Distreptaza; ***Spain***: Ernodasa; Varidasa; ***Ukr.***: Biostrepta (Биострепта); Distreptaza (Дистрептаза).

Strontium Chloride

Estroncio, cloruro de; Stronsiyum Klorür; Strontii Chloridum; Strontiumklorid; Strontiumkloridi; Хлорид Стронция.

$SrCl_2,6H_2O$=266.6

CAS — 10476-85-4 (anhydrous strontium chloride).

UNII — EKE8PS9J6Z (strontium chloride); O09USB7Z44 (strontium chloride hexahydrate).

Profile

Strontium chloride is used as a 10% toothpaste for the relief of dental hypersensitivity. Strontium acetate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sensodyne Original; ***Austria***: Sensodyne med†; ***Braz.***: Sensodyne Formula Original; ***Canad.***: Sensodyne†; Zarosen†; ***Chile***: Dentoxil†; ***India***: Bentoform; Denex-S; ***Turk.***: Sensodyne Mint; ***UK***: Sensodyne Mint; Sensodyne Original; ***USA***: Sensodyne-SC; ***Venez.***: Sencia.

Multi-ingredient Preparations. ***Arg.***: Esme Topico; Sensodyne Rapido Alivio; ***Austral.***: Macleans Sensitive; ***Ital.***: Pitiren; ***Singapore***: 2Sensitive.

Homoeopathic Preparations. ***Fr.***: Sepia Complexe No 20.

Strychnine ⊗

Estricnina; Strychnina.

Strychnidin-10-one.

$C_{21}H_{22}N_2O_2$=334.4

CAS — 57-24-9.

Description. Strychnine is an alkaloid obtained from the seeds of nux vomica (p. 2573.3) and other species of *Strychnos*.

Strychnine Hydrochloride ⊗

Estricnina, hidrocloruro de; Strych. Hydrochlor.; Strychninae Hydrochloridum.

$C_{21}H_{22}N_2O_2$,HCl,$2H_2O$=406.9

CAS — 1421-86-9 (anhydrous strychnine hydrochloride); 6101-04-8 (strychnine hydrochloride dihydrate).

Strychnine Nitrate ⊗

Azotato de Estricnina; Estricnina, nitrato de; Nitrato de Estricnina; Strychninae Nitras; Strychnini Nitras; Strychninum Nitricum; Strykniininitratti; Strykninnitrat.

$C_{21}H_{22}N_2O_2$,HNO_3=397.4

CAS — 66-32-0.

UNII — O642E96711.

Pharmacopoeias. In *Chin.*

Strychnine Sulfate ⊗

Estricnina, sulfato de; Strychninae Sulphas; Strychnine Sulphate; Strychninum Sulfuricum; Sulfato de Estricnina.

$(C_{21}H_{22}N_2O_2)_2$,H_2SO_4,$5H_2O$=857.0

CAS — 60-41-3 (anhydrous strychnine sulfate); 60491-10-3 (strychnine sulfate pentahydrate).

UNII — FA486DV76S.

Pharmacopoeias. In *Fr.* and *Viet.*

Uses and Administration

Strychnine competes with glycine, which is an inhibitory neurotransmitter; it thus exerts a central stimulant effect by blocking an inhibitory activity.

Strychnine was formerly used as a bitter and analeptic but is now mainly used under strict control as a rodenticide. It has also been used as a mole poison, although this use is banned in some countries including the UK. Strychnine has been used in multi-ingredient preparations for the treatment of ophthalmic and urinary-tract disorders. It has also been tried in the treatment of nonketotic hyperglycinaemia.

Homoeopathy

Strychnine and its salts have been used in homoeopathic medicines under the following names:

- Strychnine: strychninum; strychninum purum; stry.
- Strychnine nitrate: strychninum nitricum; stry-n.
- Strychnine phosphate: strychninae phosphas; strychninum phosphoricum; strychnia phosphorica; stry-p.

Nonketotic hyperglycinaemia. Nonketotic hyperglycinaemia (also known as glycine encephalopathy) is an inborn defect in the enzyme system responsible for the metabolism of glycine. It is characterised by raised concentrations of glycine in plasma, CSF, and urine. Symptoms of glycine accumulation include respiratory distress, muscular hypotonia, seizures, vomiting, and extreme lethargy. Mental retardation and early infant death are common.

Sodium benzoate can reduce plasma-glycine concentrations to near normal[1] but is relatively ineffective in reducing CSF levels or in preventing mental retardation.[2] Strychnine, a glycine antagonist, has been of some benefit in counteracting its CNS effects.[3-5] However, even treatment with both drugs may be ineffective in severe cases[6] and may ultimately have little effect on the course of the disease.[7] Glycine is reported to stimulate *N*-methyl-D-aspartate (NMDA) receptors in the CNS and the combination of strychnine and ketamine (an NMDA receptor antagonist) was of some benefit in a newborn infant with severe nonketotic hyperglycinaemia.[8] Addition of low-dose dextromethorphan (an NMDA receptor antagonist) to treatment with sodium benzoate, arginine, carnitine, diazepam, and phenobarbital in an infant with nonketotic hyperglycinaemia[9] was associated with resolution of nystagmus and improvement in eye contact and interactive behaviour, without altering serum- or CSF-glycine concentrations. Dextromethorphan with sodium benzoate alone may also be helpful, although the combination is not uniformly effective.[10] Treatment with sodium benzoate and dextromethorphan was beneficial in a 6-month-old child with mild atypical nonketotic hyperglycinaemia,[11] although it was later shown that it was sodium benzoate that had the greatest effect on EEG and behavioural changes. A partial response to low-protein diet and sodium benzoate occurred in a patient with late-onset nonketotic hyperglycinaemia; there was a more dramatic response when imipramine was added to therapy.[12]

1. Van Hove JLK,*et al*. Benzoate treatment and the glycine index in nonketotic hyperglycinaemia. *J Inherit Metab Dis* 2005; **28:** 651–63.
2. Krieger I, *et al*. Cerebrospinal fluid glycine in nonketotic hyperglycinemia: effect of treatment with sodium benzoate and a ventricular shunt. *Metabolism* 1977; **26:** 517–24.
3. Ch'ien LT, *et al*. Glycine encephalopathy. *N Engl J Med* 1978; **298:** 687.
4. Gitzelmann R, *et al*. Strychnine for the treatment of nonketotic hyperglycinaemia. *N Engl J Med* 1978; **298:** 1424.
5. Arneson D, *et al*. Strychnine therapy in nonketotic hyperglycinemia. *Pediatrics* 1979; **63:** 369–73.
6. Sankaran K, *et al*. Glycine encephalopathy in a neonate. *Clin Pediatr (Phila)* 1982; **21:** 636–7.
7. MacDermot KD, *et al*. Attempts at use of strychnine sulfate in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1980; **65:** 61–4.
8. Tegtmeyer-Metzdorf H, *et al*. Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154:** 649–53.
9. Alemzadeh R, *et al*. Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97:** 924–6.
10. Hamosh A, *et al*. Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132:** 709–13.
11. Neuberger JM, *et al*. Effect of sodium benzoate in the treatment of atypical nonketotic hyperglycinaemia. *J Inherit Metab Dis* 2000; **23:** 22–6.
12. Wiltshire EJ, *et al*. Treatment of late-onset nonketotic hyperglycinaemia: effectiveness of imipramine and benzoate. *J Inherit Metab Dis* 2000; **23:** 15–21.

Adverse Effects

The symptoms of strychnine poisoning are mainly those arising from stimulation of the CNS. Early signs occurring within 15 to 30 minutes of ingestion include tremors, slight twitching, and stiffness of the face and limbs. Painful convulsions develop and may be triggered by minor sensory stimuli; since consciousness is not impaired patients may be extremely distressed. All forms of sensation are heightened. The body becomes arched backwards in hyperextension with the head retracted, arms and legs extended, fists clenched, and the feet turned inward. The jaw is rigidly clamped and contraction of the facial muscles produces a characteristic grinning expression known as 'risus sardonicus'. The convulsions may recur repeatedly and are interspersed with periods of relaxation. If not treated adequately, few patients survive more than 5 episodes of convulsions, death usually occurring due to respiratory and cardiac arrest. Fatalities in adults have occurred with doses as little as 16 mg.

Secondary effects arising from the severe spasms include lactic acidosis, rhabdomyolysis, renal failure, hyperthermia, hyperkalaemia, and dehydration.

Poisoning. References.

1. O'Callaghan WG, *et al*. Unusual strychnine poisoning and its treatment: report of eight cases. *BMJ* 1982; **285:** 478.
2. Blain PG, *et al*. Strychnine poisoning: abnormal eye movements. *J Toxicol Clin Toxicol* 1982; **19:** 215–17.
3. Boyd RE, *et al*. Strychnine poisoning: recovery from profound lactic acidosis, hyperthermia, and rhabdomyolysis. *Am J Med* 1983; **74:** 507–12.
4. Burn DJ, *et al*. Strychnine poisoning as an unusual cause of convulsions. *Postgrad Med J* 1989; **65:** 563–4.
5. Yamarick W, *et al*. Strychnine poisoning in an adolescent. *J Toxicol Clin Toxicol* 1992; **30:** 141–8.
6. Heiser JM, *et al*. Massive strychnine intoxication: serial blood levels in a fatal case. *J Toxicol Clin Toxicol* 1992; **30:** 269–83.
7. Nishiyama T, Nagase M. Strychnine poisoning: natural course of a nonfatal case. *Am J Emerg Med* 1995; **13:** 172–3.
8. Katz J, *et al*. Strychnine poisoning from a Cambodian traditional remedy. *Am J Emerg Med* 1996; **14:** 475–7.
9. Hernandez AF, *et al*. Acute chemical pancreatitis associated with nonfatal strychnine poisoning. *J Toxicol Clin Toxicol* 1998; **36:** 67–71.
10. Greene R, Meatherall R. Dermal exposure to strychnine. *J Anal Toxicol* 2001; **25:** 344–7.
11. Wood D, *et al*. Case report: survival after deliberate strychnine self-poisoning, with toxicokinetic data. *Crit Care* 2002; **6:** 456–9.
12. Scheffold N, *et al*. Strychninvergiftung. *Dtsch Med Wochenschr* 2004; **129:** 2236–8.
13. Shadnia S, *et al*. A case of acute strychnine poisoning. *Vet Hum Toxicol* 2004; **46:** 76–9.

Treatment of Adverse Effects

The main aim of therapy in strychnine poisoning is the prompt prevention or control of convulsions and asphyxia. Activated charcoal should be given if the patient presents within 1 hour of ingestion. Convulsions should be

controlled or prevented by diazepam or lorazepam. Intubation and assisted respiration may be required. Should benzodiazepines fail then phenytoin or phenobarbital may be tried. All unnecessary external stimuli should be avoided and if possible the patient should be kept at rest in a quiet darkened room. Patients should be monitored for any secondary effects such as metabolic acidosis so that appropriate symptomatic treatment can be given.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Vigofortal†; ***Pol.***: Cardiamid-Coffein†; ***Thai.***: Hemo-Cyto-Serum†.

Homoeopathic Preparations. ***Fr.***: Conium Complexe No 36†; Diabene; Sativol†; ***Neth.***: Sativol†.

Suanzaorentang

Ziziphus Soup.

Profile

Suanzaorentang is a traditional Chinese remedy for anxiety and insomnia. It contains five herbs: suanzaoren (*Zizyphus spinosus*, Rhamnaceae), fuling (*Poria cocos*, Polyporaceae), gancao (*Glycyrrhiza uralensis*, Leguminosae), zhimu (*Anemarrhena asphodeloides*, Liliaceae), and chuanxiong (*Ligusticum chuanxiong*, Umbelliferae).

Subtilisin A ⊗

EC 3.4.21.62; Subtilisin Carlsberg; Subtilopeptidase A; Субтилизин А.

CAS — 9014-01-1 (subtilisin).

Profile

Subtilisins are a class of serine proteases isolated initially from *Bacillus subtilis* but which are also excreted by other *Bacillus* species. They are widely used in the manufacture of enzymatic detergents. Hypersensitivity reactions have been reported.

Subtilisin A, which is obtained from *Bacillus licheniformis*, is used as an enzymatic cleanser for contact lenses.

References.

1. Lemiere C, *et al.* Isolated late asthmatic reaction after exposure to a high-molecular-weight occupational agent, subtilisin. *Chest* 1996; **110:** 823–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Naclens; Ultrazyme; ***Austral.***: Complete Protein Remover†; Ultrazyme; ***Canad.***: Ultrazyme†; Unizyme†; ***NZ***: Ultrazyme; ***Turk.***: Unizyme; ***USA***: Renu Enzymatic Cleaner†; Soft Mate Enzyme Plus Cleaner; Ultrazyme.

Succinic Dinitrile

Butanedinitrile; Cyanure d'éthylène; Ethylene Cyanide; Ethylene Dicyanide; Succinic Acid Dinitrile; Succinonitrile; Sukkinonitriili.

1,2-Dicyanoethane.

$C_4H_4N_2$=80.09

CAS — 110-61-2.

UNII — 1R479O92DO.

Profile

Succinic dinitrile is a cyanide compound and shares their toxicity (see Adverse Effects under Hydrocyanic Acid, p. 2156.2). It has industrial uses and has also been used in preparations for nervous disorders and in tonics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Enervit; ***Venez.***: Dinitrile-Vit; Dinitro-B.

Sulfan Blue *(BAN)*

Azul sulfán; Błękit sulfanowy; Blue VRS; Isosulfan Blue (USAN); P-1888; P-4125; Sulphan Blue.

Sodium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclohexa-2,5-dienylidene)toluene-2,5-disulfonate.

$C_{27}H_{31}N_2NaO_6S_2$=566.7

CAS — 68238-36-8 (2,5-disulfonate isomer); 129-17-9 (2,4-disulfonate isomer).

UNII — FH1929ICIT (sulfan blue); 39N9K8S2A4 (isosulfan blue).

NOTE. Sulfan blue was formerly described in *BPC 1954* as the 2,4-disulfonate isomer and the following synonyms have been applied to this 2,4-isomer: Acid Blue 1; Alphazurine 2G; Colour Index No. 42045; Patent Blue V; Sulphanum Caeruleum. The name Patent Blue V, however, is mainly used for CI No. 42051 (p. 2584.2).

Profile

Sulfan blue 1% solution is injected subcutaneously to outline the lymph vessels as an adjunct to lymphography. It was formerly given intravenously as a visual test of the circulation in normal and damaged tissue.

Sulfan blue is reported to be incompatible with local anaesthetics, such as lidocaine.

Urine may be coloured blue for 24 hours, and transient or long-term blue coloration of the skin can occur after subcutaneous use. Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, pruritus, and asthma attacks have been reported. Cross-sensitivity with patent blue V has been reported (see p. 2584.3). Sulfan blue has also been reported to interfere with blood tests for protein and iron. It may also cause falsely low measurements of oxygen saturation in peripheral blood by pulse oximetry and falsely elevated readings of methaemoglobin by arterial blood gas analyser.

References.

1. Kaufman G, *et al.* A cautionary tale: anaphylaxis to isosulfan blue dye after 12 years and 3339 cases of lymphatic mapping. *Am Surg* 2008; **74:** 152–5.
2. Bézu C, *et al.* Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surg Oncol* 2011; **20:** e55–9.
3. Gur I, *et al.* Sudden false oxygen desaturation and factitious methemoglobinemia after subcutaneous injection of isosulfan blue (Lymphazurin). *Am Surg* 2011; **77:** 383–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Lymphazurin†; ***Gr.***: Lymphazurin; ***USA***: Lymphazurin.

Sulfobromophthalein Sodium *(BANM)*

Bromsulfophthalein Sodium; Bromsulphthalein Sodium; BSP; SBP; Sodium Sulfobromophthalein; Sulfobromoftaleína sódica; Sulphobromophthalein Sodium; Сульфобромфталеин Натрия.

Disodium 4,5,6,7-tetrabromophenolphthalein-3′,3″-disulphonate; Disodium 5,5′-(4,5,6,7-tetrabromophthalidylidene) bis(2-hydroxybenzenesulphonate).

$C_{20}H_8Br_4Na_2O_{10}S_2$=838.0

CAS — 297-83-6 (sulfobromophthalein); 71-67-0 (sulfobromophthalein sodium).

ATC — V04CE02.

ATC Vet — QV04CE02.

UNII — 62E5JU30OV.

Pharmacopoeias. In *Chin.*, *It.*, and *Jpn.*

Profile

In patients with normal hepatic function sulfobromophthalein sodium is rapidly extracted, conjugated, and excreted in bile. It was formerly used intravenously as a diagnostic agent for testing the functional capacity of the liver but may cause severe hypersensitivity reactions.

Sulfur Iodide

Iodosulfane; Sulphur Iodide.

CAS — 1312-15-8.

UNII — L6L8KA2AA0.

Profile

Sulfur iodide is obtained by fusing sulfur (p. 1721.1) with iodine (p. 2336.3).

Homoeopathy

Sulfur iodide has been used in homoeopathic medicines under the following names: Sulfur iodatum; Iodure de soufre.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Canad.***: Acne; ClearAc†; Hylands Formula CA; Phyto-Cal; ***Fr.***: Boripharm No 22†; Osteocynesine; ***Ger.***: Pascoleucyn; Steiroderm; ***Neth.***: Kind 0-6 Caltrivat; Osteocynesine†; ***Port.***: Osteocynesine; ***Switz.***: Exsepta; Regenaplex Nr. 31b; ***Ukr.***: Immunokind (Иммунокинд).

Sulfuric Acid

Acid. Sulph.; Acid. Sulph. Dil.; Acide sulfurique; Acidum sulfuricum; E513; Kénsav; Kwas siarkowy; Kyselina sírová; Oil of Vitriol; Rikkihappo; Schwefelsäure; Sulfato rūgštis; Sulfúrico, ácido; Sulphuric Acid; Svavelsyra; Verdünnte Schwefelsäure (dilute sulfuric acid).

H_2SO_4=98.07

CAS — 7664-93-9.

UNII — O40UQP6WCF.

NOTE. Concentrated oil of vitriol of commerce, 'COV', contains about 95 to 98% w/w, and brown oil of vitriol, 'BOV', contains 75 to 85% w/w of H_2SO_4.

Nordhausen or fuming sulfuric acid, 'Oleum', is sulfuric acid containing SO_3.

Battery or accumulator acid is sulfuric acid diluted with distilled water to a specific gravity of 1.2 to 1.26.

Pharmacopoeias. *Br.* and *Eur.* (see p. vii) include various concentrations. Also in *USNF*.

BP 2014: (Dilute Sulfuric Acid). It contains 9.5 to 10.5% w/w of H_2SO_4 and is prepared by adding 104 g of sulfuric acid to 896 g of water, with constant stirring and cooling.

Ph. Eur. 8: (Sulfuric Acid). It contains 95.0 to 100.5% w/w of H_2SO_4. A colourless, very hygroscopic, oily liquid. Miscible with water and with alcohol producing intense heat. Store in airtight containers.

USNF 31: (Sulfuric Acid). It contains 95.0 to 98.0% w/w of H_2SO_4. A clear, colourless, oily liquid. Is very caustic and corrosive. Miscible with water and with alcohol with the generation of much heat. Store in airtight containers.

Dilution. When sulfuric acid is mixed with other liquids, it should always be added slowly, with constant stirring, to the diluent.

Uses and Administration

Sulfuric acid has various industrial uses. Dilute sulfuric acid has been used as an astringent in diarrhoea and it has occasionally been prescribed in mixtures with vegetable bitters to stimulate appetite.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Oralmedic; ***UK***: Oralmedic; ***USA***: Debacterol.

Homoeopathic Preparations. ***Canad.***: Adrisin†; Bioactiv H†; ***Chile***: Bioactiv H; ***Fr.***: Aftosium; Gentiana Complexe No 33†; Homeoaftyl; ***Ger.***: Lowe-Komplex Nr 6; Panalgan; Secale-Gastreu; ***Neth.***: Opsonat; ***Rus.***: Nux Vom-Plus (Нукс Вом-Плюс); ***Switz.***: Regenaplex Nr. 51c.

Pharmacopoeial Preparations

USP 36: Ferric Subsulfate Solution.

Sumatra Benzoin

Benjoim; Benjoin; Benjoin de sumatra; Benjuí, bálsamo de; Benzoë; Benzoe, Sumatra-; Benzoe sumatranus; Benzoin; Benzoina; Gum Benjamin; Gum Benzoin; Styrax tonkinensis et Styrax benzoin; Суматранский Бензоин.

CAS — 9000-05-9.

*ATC Herb — HR05WA5053 (*Styrax paraleloneurum*: resin); HR05WA5052 (*Styrax benzoin*: resin); HD02WX5005 (*Styrax benzoin*: resin); HD02WX5006 (*Styrax paraleloneurum*: resin).*

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

US allows both Siam benzoin and Sumatra benzoin under the title Benzoin.

Ph. Eur. 8: (Sumatra Benzoin). A resin obtained by incising the trunk of *Styrax benzoin*. It contains 25 to 50% of total acids, calculated as benzoic acid (dried drug).

Creamy white, rounded to ovoid tears, which may be embedded in a dull, greyish-brown or reddish-brown matrix. It is hard and brittle and the fractured surface is dull and uneven.

USP 36: (Benzoin). A balsamic resin from *Styrax paralleloneurus* or *S. benzoin* (Styracaceae). It yields not less than 75% of alcohol-soluble extractive. It occurs as blocks or lumps of variable size made up of tears, compacted together, with a reddish-brown, reddish-grey, or greyish-brown resinous mass. The tears are externally yellowish or rusty brown, milky white on fresh fracture, hard and brittle at ordinary temperatures but softened by heat. It has an aromatic and balsamic odour. When heated it does not emit a pinaceous odour. When digested with boiling water, the odour suggests cinnamates or storax.

Profile

Sumatra benzoin is an ingredient of inhalations that are used in the treatment of catarrh of the upper respiratory

tract. Sumatra benzoin is also used in topical preparations for its antiseptic and protective properties. Skin sensitisation has been reported.

Preparations of Sumatra benzoin are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Benzoinspray.

Multi-ingredient Preparations. ***Belg.***: Borostyrol; ***Braz.***: Inhalante Yatropan; ***Canad.***: Cold Sore Lotion; Skin-E-Dip; ***Fr.***: Balsofumine; Dolirhume; ***Israel***: Kank-A; ***Ital.***: Citrosil Nubesan; Fomentil; ***NZ***: Cold Sore†; ***Port.***: Vaporil; ***S.Afr.***: Turulington Tincture†; ***Switz.***: Baume Zeller; Pommade au Baume; ***Turk.***: Buguseptil; Rinolar; ***UK***: Allens Dry Tickly Cough; Frador; Friars Balsam; Kilkof; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Snowfire; Throaties Pastilles; ***USA***: Pfeiffer's Cold Sore; ***Venez.***: Aftil.

Pharmacopoeial Preparations
BP 2014: Benzoin Inhalation; Compound Benzoin Tincture;
BPC 1954: Compound Iodoform Paint;
Ph. Eur.: Benzoin Tincture, Sumatra;
USP 36: Compound Benzoin Tincture; Podophyllum Resin Topical Solution.

Summer Savory

Bohnenkraut; Sarriette; Savory; Чабёр Садовый.
UNII — RU34139IYL.

Profile

Summer savory (*Satureja hortensis*, Lamiaceae) is included in herbal preparations and is used as a culinary herb.

It is the source of savory oil which is included in herbal preparations, mainly for the relief of cold symptoms. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Fr.***: Resistim; ***Rus.***: Maraslavin (Мараславин); ***Spain***: Tonimax; ***Switz.***: Demonatur Capsules contre les refroidissements; Echinarom; Spagyrom.

Surgibone *(USAN)*

Profile

Surgibone is sterile, specially processed mature bovine bone, that has been used for grafting procedures in orthopaedic and reconstructive surgery.

Sweet Chestnut

Aito Kastanja; Äkta Kastanj; Castanheiro-comum; Castaño; Castaño Común; Châtaignier; Châtaignier Commun; Chestnut; Edelkastanie; Esskastanie; European Chestnut; Jalokastanja; Kastanie; Marone; Spanish Chestnut.
*ATC Herb — HR05DB5004 (*Castanea sativa*: leaf); HD03WA5002 (*Castanea sativa*: leaf).*
*UNII — DK55N3C1AK (*Castanea sativa*); PK19Q4Q3Y4 (*Castanea sativa *bark); YHZ719F7M3 (*Castanea sativa *flower); IV3S2HH53G (*Castanea sativa *leaf); 2MT5XMR2YW (*Castanea sativa *nut); F71O639GCL (*Castanea sativa *shell).*

NOTE. The name Spanish Chestnut has been applied both to Sweet Chestnut and to Aesculus (p. 2431.2).

Profile

The leaves of sweet chestnut, *Castanea sativa* (*C. vesca*; *C. vulgaris*) (Fagaceae) have traditionally been included in herbal medicines for cough and other respiratory disorders. They have also been used for circulatory disorders.

The fruits are used as a foodstuff, usually roasted.

The American chestnut, *C. dentata* has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: LF 100.

Multi-ingredient Preparations. ***Austria***: Brust- und Hustentee St Severin; Tussamag; ***Fr.***: Calmiflorine†; ***Ger.***: Equisil N†; ***Ital.***: Broncosed; Tussamag; ***Switz.***: Siropectan; ***Venez.***: T-Samag.

Tafamidis *(USAN, rINN)*

FX-1006; Tafamidisum; Тафамидис.
2-(3,5-Dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid.
$C_{14}H_7Cl_2NO_3$=308.1
CAS — 594839-88-0.
UNII — 8FG9H9D31J.

Tafamidis Meglumine *(USAN, rINNM)*

FX-1006A; Meglumini Tafamidisum; Tafamidis meglumina; Tafamidis Méglumine; Тафамидис Меглюмин.
D-*gluco*-2,3,4,5,6-Pentahydroxy-*N*-methylhexan-1-aminium 2-(3,5-dichlorophenyl)benzoxazole-6-carboxylate.
$C_{14}H_7Cl_2NO_3,C_7H_{17}NO_5$=503.3
CAS — 951395-08-7.
UNII — ZU7CF08A1A.

Profile

Tafamidis stabilises transthyretin thereby inhibiting amyloid formation in the hereditary disease familial ATTR amyloidosis (transthyretin amyloidosis; familial amyloid polyneuropathy; see Amyloidosis, p. 819.3) with the potential to delay peripheral neurological impairment. It is used for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy. Tafamidis is given as the meglumine, but doses are expressed in terms of the base; tafamidis meglumine 32.7 mg is equivalent to about 20 mg of tafamidis. The usual oral dose is equivalent to 20 mg of tafamidis once daily. Commonly reported adverse effects include gastrointestinal complaints and urinary-tract or vaginal infections.

References.
1. Said G, *et al.* Tafamidis. *Nat Rev Drug Discov* 2012; **11:** 185–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Vyndaqel; ***Denm.***: Vyndaqel; ***Fr.***: Vyndaqel; ***Irl.***: Vyndaqel; ***Neth.***: Vyndaqel; ***Swed.***: Vyndaqel; ***UK***: Vyndaqel.

Taltirelin *(rINN)*

TA-0910; Taltirelina; Taltiréline; Taltirelinum; Тальтирелин.
(-)-*N*-{[(*S*)-Hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl]carbonyl}-L-histidyl-L-prolinamide.
$C_{17}H_{23}N_7O_5$=405.4
CAS — 103300-74-9.
UNII — DOZ62MV6A5.

Profile

Taltirelin is an analogue of protirelin (p. 2344.2) and is claimed to have beneficial effects on CNS function. It is used in the treatment of spinocerebellar degeneration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Ceredist.

Tannic Acid

Acide tannique; Acidum Tannicum; Gallotannic Acid; Garvsyra; Gerbstoff; Kwas taninowy; Tánico, ácido; Tanin; Tanina; Taninas; Tann. Acid; Tanniini (Parkkihappo); Tannin; Tanninum; Дубильная Кислота.
CAS — 1401-55-4.
UNII — 28F9E0DJY6 (tannic acid); P4J831S9H6 (tannic acid from Caealpinia spinosa *seed); 2711I21VE5 (tannic acid from* Quercus infectoria *nutgall); 5PG9M8BASQ (tannic acid from* Quercus *spp. nutgall); 54OM1T1DZQ (tannic acid from* Rhus *spp. leaf); 41F04WC310 (tannic acid from* Rhus *spp. nutgall).*

NOTE. In pharmaceutical literature, the name digallic acid is frequently confused with tannic acid.

Commercial grades of tannic acid may contain gallic acid and being less soluble are not suitable for medicinal use.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tannic Acid). A mixture of esters of glucose with gallic acid and 3-galloylgallic acid. A yellowish-white or slightly brown amorphous light powder or shiny plates. Very soluble in water; freely soluble in alcohol, in acetone, and in glycerol (85%); practically insoluble in dichloromethane. Protect from light.

USP 36: (Tannic Acid). A tannin usually obtained from nutgalls (see Gall, p. 2508.3), the excrescences produced on the young twigs of *Quercus infectoria* and allied species of *Quercus*, from the seed pods of tara (*Caesalpinia spinosa*), or from the nutgalls or leaves of sumac (any of genus *Rhus*). Amorphous powder, glistening scales, or spongy masses, varying in colour from yellowish-white to light brown. Is odourless or has a faint, characteristic odour. Very soluble in water, in alcohol, and in acetone; freely soluble in diluted alcohol; slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ether, in petroleum spirit, and in benzene; soluble 1 in about 1 of warm glycerol. Store in airtight containers. Protect from light.

Profile

Tannic acid has been used as an astringent for the mucous membranes of the mouth and throat, and in suppositories for the treatment of haemorrhoids. It is an ingredient in several dermatological preparations.

Former uses of tannic acid include application to burns, addition to barium sulfate enemas to improve the quality of radiological pictures of the colon, and as an ingredient of 'Universal Antidote'. However, tannic acid has been associated with liver toxicity, sometimes fatal.

Tattoo removal. Although tannic acid may be used by plastic surgeons and dermatologists to produce a controlled partial-thickness burn in tattoo removal[1] it has been pointed out that in unskilled or amateur hands this procedure has resulted in full thickness burns requiring skin grafting to obtain satisfactory healing.[2]

1. Mercer NSG, Davies DM. Tattoos. *BMJ* 1991; **303:** 380.
2. Scott M, Ridings P. Tattoos. *BMJ* 1991; **303:** 720.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Tanagel Polvo; ***Switz.***: Tanno-Hermal.

Multi-ingredient Preparations. ***Austral.***: SM-33; ***Austria***: Haemanal; ***Belg.***: Hemorhinol†; ***Braz.***: Anapyon; Lacto Vagin; ***Canad.***: Tanac; ***Chile***: Paralymphine; ***Fr.***: HEC; ***Ger.***: Eulatin NH; Eulatin NH; ***Gr.***: Oulogram; ***India***: Arofil; Clenora; Clenorush; Cureg; Dentakind; Dordent; Icee; Klinit; Me-Fresh Gum Paint; O2-Fresh-GP; Ora-G; Orex; ***Irl.***: Phytex†; ***Israel***: Rectozorin; ***Ital.***: Blefarolin; Neo Emocicatrol; ***Philipp.***: Zilactin; ***Pol.***: Acifungin; Salumin†; ***Rus.***: Contraceptin T (Контрацептин Т); Neo-Anusol (Нео-анузол); ***Spain***: Antihemorroidal; Depurativo Richelet†; Dextricea†; Tanagel; ***Switz.***: Eau Precieuse; HEC†; Tanno-Hermal; ***Turk.***: Deriseptol; ***UK***: Colsor; Phytex; TCP; ***USA***: Dermasept Antifungal; Orasept†; Outgro; Tanac Dual Core; Tanac.

Tansy

Atanasia; Barbotine; Hierba lombriguera; Rainfarn; Tanaceto; Tanaisie; Пижма.
UNII — D52957JQ8M.

NOTE. Distinguish from tansy ragwort which is *Senecio jacobaea* (see Senecio p. 2612.3), a different plant and a common cause of livestock poisoning.

Profile

Tansy, the flowering tops of *Tanacetum vulgare* (*Chrysanthemum vulgare*) (Compositae), has been used as an anthelmintic and to stimulate menstruation. The oil is highly toxic and use of tansy is generally not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Calmo†; ***Pol.***: Artemisol.

Taraxacum

Dandelion Root; Diente de León; Korzeń mniszka (root); Löwenzahnwurzel; Pissenlit; Taraxaci Herba; Taraxaci Radix (root); Taraxacum officinalis; Taraxacum Root; Одуванчик Лекарственный (*Taraxacum officinale*); Ziele mniszka.
*ATC Herb — HA05AW5017 (*Taraxacum officinale sensu auct.: *root); HA05AW5016 (*Taraxacum officinale sensu auct.: *leaf); HA06AX5011 (*Taraxacum officinale sensu auct.: *root); HA09WA5025 (*Taraxacum officinale sensu auct.: *root); HA06AX5010 (*Taraxacum officinale sensu auct.: *leaf).*
*UNII — 39981FM375 (*Taraxacum officinale*); DQS85W46HV (*Taraxacum officinale *flowering top); 0022LFJ74Y (*Taraxacum officinale *leaf); 9DE5YCO0RU (*Taraxacum officinale *root).*

Pharmacopoeias. In *Eur.* (see p. vii).

Chin. specifies Taraxacum Herb from other species of *Taraxacum*.

Ph. Eur. 8: (Dandelion Herb with Root; Taraxaci Officinalis Herba cum Radice). A mixture of the whole or fragmented, dried aerial and underground parts of *Taraxacum officinale*. It has a bitter taste.

Ph. Eur. 8: (Dandelion Root); Taraxaci Officinalis Radix. A mixture of the whole or cut, dried underground parts of *Taraxacum officinale*. It has a bitter taste.

Profile

Taraxacum is the fresh or dried root of the common dandelion, *Taraxacum officinale* (Compositae). It has been used as a bitter, as a diuretic, and as a mild laxative.

Homoeopathy

Taraxacum has been used in homoeopathic medicines under the following names: Taraxacum officinale; Taraxacum officinale, radix; Taraxacum, rad; Tarax.

References.

1. Houghton P. Bearberry, dandelion and celery. *Pharm J* 1995; **255:** 272–3.
2. Sweeney B, *et al.* Evidence-based systematic review of dandelion (*Taraxacum officinale*) by Natural Standard Research Collaboration. *J Herb Pharmacother* 2005; **5:** 79–93.
3. Goksu E, *et al.* First report of hypoglycemia secondary to dandelion (Taraxacum officinale) ingestion. *Am J Emerg Med* 2010; **28:** 111.e1–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Paverysat L; ***Pol.***: Talion.

Multi-ingredient Preparations. ***Arg.***: Desgras Complex; Quelodin F; ***Austral.***: Berberis Complex†; Colax†; Colax; Cranbiotic Super†; Detox Program; DiGest; Digestive Bitters; Extralife Fluid-Care†; Extralife Liva-Care†; Feminine Herbal Complex; GR² Control Thermogenic Enhancer; Liver Detox; Liver Tonic Complex; Livton Complex; St Mary's Thistle Plus†; Toxicol; Vegie Digestaid; ***Austria***: Gallen- und Lebertee St Severin; Gallesyn neu; Gallesyn neu; Magentee St Severin; Montana; Urelium Neu; ***Canad.***: Anti Dyspepsia Digestive Aid†; Biliherb; Cellutex; Depuratif des Trappistes; Diuretic Formula; Duo-Bil; Gallexier†; Hepatol; Herbanat†; Intestinal Bulking Agent II†; Metab Herbs No 1†; Metab Herbs†; Milk Thistle Extract Formula; Phyto-Marinex; Special Formula Bulking Agent†; Traditional Herbal Laxative†; ***Cz.***: Diabetan; Diabeticka Cajova Smes-Megadiabetin†; Original Schwedenbitter; The Salvat; ***Fr.***: Aromadigest†; Biofirm; Drainuryl; Expuryl; Gastrotisane†; Hepatoflorine†; Hydracur; Romarene†; ***Ger.***: Alasenn; Amara-Tropfen; Carmol Magen-Galle-Darm†; Gallemolan forte†; Gallexier; Gallexier; Hevert Stoffwechsel-Tee N†; Imupret; ***Hong Kong***: Hepatofalk†; ***Hung.***: Diabess; Gallexier; Majvedo es Detoxikalo; Montana; Vensaxa; Zeatax; ***Indon.***: DFM; Proliva; ***Ital.***: Cinarepa; Idren; Linfoguard†; ***Mon.***: Romarinex Chrome; ***Philipp.***: Completia†; Hepamin; ***Pol.***: Artecholin†; Artecholwex†; Cholavisol; Cholesol; Cholitol; Diabetosol; Dyspepsin; Gastrobonisol; Nefrobonisol; Nefrol; Tabletki Przeciw Niestrawnosci; ***Rus.***: Sodecor (Содекор); Tonsilgon N (Тонзилгон Н); ***S.Afr.***: Amara†; ***Spain***: Diurette†; ***Swed.***: Cynaramin; ***Switz.***: Boldocynara; Gastrosan; Gouttes Amara; Kernosan 24; Kernosan 26; Strath Gouttes pour les reins et la vessie; Tisane hepatique et biliaire; ***UK***: Adios; Aqualette; Aquella; Backache; Boldex; Cassilax; Digestisan; HealthAid Boldo-Plus; Herbulax; HRI Water Balance; Lowater; Milk Thistle Complex; Natravene; Natural Herb Tablets; Out-of-Sorts; Pure Plan; Rheumatic Pain; Senokot Dual Relief; Stomach Mixture; Uvacin; Weight Loss Aid; Wind & Dyspepsia Relief; ***Ukr.***: Detoxil (Детоксил); Imupret (Имупрет); Mammoleptin (Маммолептин); Tonsilgon N (Тонзилгон)†; ***USA***: Clinical Nutrients Prenatal Formula; ***Venez.***: Celyth's; Flocadep; Rheu-Tarx 1.

Homoeopathic Preparations. ***Austria***: Galstena; Lymphdiaral; Taraxacum Med Complex; ***Canad.***: Amaratopfen†; Carduus Plex†; Chelidonium Plex†; Common Mallow Combination†; Cynara Complex†; Dandelion Combination†; Formula FV 213; Hecocur†; Hepar Compositum; Lympatox; Pollen Plus; Yellow Dock Combination†; ***Chile***: Cynara Compuesta; Digherbal; ***Fr.***: Chelidonium Compose; Diabene; Diacure; Digeodren; Hepatopan†; Homeogene 22†; Yucca Complexe No 110; ***Ger.***: Bomagall; Chelidonium comp; Chol-Do; Chole-cyl L Ho-Len-Complex; Cholo 2-injektopas; Derivatio H; Derivatio; Galloselect; HanoHepan; Hepa-Loges N; Hepar comp; Hepar-Hevert N; Hepar-Hevert; Hepar-Hevert; Heparanox H; Hepatorell H Leber-Spezifikum; Homviohepan; Leber-Galletropfen; Lymphdiaral; Metaharonga; Pankreaticum; Pankreaticum; Taraxan; ***Hung.***: Pro-Aller; ***Neth.***: Apo-Hepat; Apo-Rheum†; Dolilite; Hepalite; Hepeel H; Lymphdiaral; Reudol; ***Rus.***: Berberis-Plus (Берберис-Плюс); Galstena (Галстена); ***Switz.***: Regenaplex Nr. 79; Regenaplex Nr. 80aN; ***Ukr.***: Galstena (Галстена); ***USA***: Preferred Remedies Detoxin.

Tartaric Acid

Acide tartrique; Acidum Tartaricum; Borkősav; E334; E353 (metatartaric acid); Kwas winowy; Kyselina vinná; Tart. Acid; Tartárico, ácido; Tartarik Asit; Tartrique (Acide); Viinihappo; Vinsyra; Vyno rūgštis; Weinsäure; Виннокаменная Кислота; Винная Кислота.

(+)-L-Tartaric acid; (2*R*,3*R*)-2,3-Dihydroxybutane-1,4-dioic acid.

$C_4H_6O_6$=150.1

CAS — 87-69-4; 526-83-0.

UNII — W4888I119H.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Tartaric Acid). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol.

USNF 31: (Tartaric Acid). Colourless or translucent crystals or a white, fine to granular, crystalline powder. Is odourless. Soluble 1 in 0.8 of water, 1 in 0.5 of boiling water, 1 in 3 of alcohol, 1 in 250 of ether, and 1 in 1.7 of methyl alcohol.

Uses and Administration

Tartaric acid is used in the preparation of effervescent powders, granules, and tablets, as an ingredient of cooling drinks, and as a saline purgative. If not neutralised, it must be taken well diluted. Tartaric acid or metatartaric acid are used in wine-making as de-acidifying agents to assist in the removal of excess malic acid by forming an insoluble double salt with calcium carbonate.

Adverse Effects

Strong solutions of tartaric acid are mildly irritant and if ingested undiluted may cause violent vomiting and diarrhoea, abdominal pain, and thirst. Cardiovascular collapse or acute renal failure may follow.

Pharmacokinetics

Tartaric acid is absorbed from the gastrointestinal tract but up to 80% of an ingested dose is probably destroyed by micro-organisms in the lumen of the intestine before absorption occurs. Absorbed tartaric acid is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Yasta; ***Austral.***: Citralite†; Citravescent; Dexsal†; Salvital; Ural; ***Austria***: Duplotrast Weinsaure; Helo-acid; ***Canad.***: Baros†; Lithines du Dr Gustin†; ***Chile***: Frunalia†; Frutasal Knop; Uroknop; ***Denm.***: Samarin; ***Fr.***: Dermacide; Zeniac LP Fort; ***Ger.***: Eubiolac; Retterspitz Ausserlich; Retterspitz Innerlich; ***Gr.***: Coup-Lax Compose; Dermacide; Eno; ***Hong Kong***: Baros†; ***Hung.***: Samarin; ***India***: Citro-Soda; Urisoda; ***Ital.***: Antimicotica Solforata†; Geffer; Magnesia Effervescente Sella; ***Malaysia***: Ezee; U-Lite; Ural; Urisoda; ***NZ***: Ural; ***Philipp.***: Ural; ***Port.***: Safrux†; ***S.Afr.***: Adco-Sodasol; Alkafizz; Citro-Soda; Quatro-Soda; Uri-Alk; ***Singapore***: Citravescent; Uricalm; ***Spain***: Citinoides†; Hectonona; Salcedol; Sales Fruta Mag Viviar†; Salmagne; ***Swed.***: Samarin; ***Switz.***: Siesta-1; ***Thai.***: TAP†; ***Turk.***: Enhos; Purgyl; Radyobarit-Double Contrast; ***UK***: Jaaps Health Salt; ***USA***: Baros†.

Taurine *(BAN, rINN)*

Taurina; Taurinum; Таурин.

2-Aminoethanesulphonic acid.

$C_2H_7NO_3S$=125.1

CAS — 107-35-7.

UNII — 1EQV5MLY3D.

Pharmacopoeias. In *Chin., Jpn,* and *US.*

USP 36: (Taurine). White crystals or crystalline powder. Soluble in water.

Profile

Taurine is an amino acid known to be involved in bile acid conjugation as well as other physiological functions. It has been included in preparations for parenteral nutrition of low-birth-weight infants and in infant formulas but its role as an essential nutrient has not been established.

Taurine is included in some preparations for cardiovascular and metabolic disorders.

References.

1. Redmond HP, *et al.* Immunonutrition: the role of taurine. *Nutrition* 1998; **14:** 599–604.
2. Militante JD, Lombardini JB. Treatment of hypertension with oral taurine: experimental and clinical studies. *Amino Acids* 2002; **23:** 381–93.
3. Bidri M, Choay P. La taurine: un aminoacide particulier aux fonctions multiples. *Ann Pharm Fr* 2003; **61:** 385–91.
4. Kingston R, *et al.* The therapeutic role of taurine in ischaemia-reperfusion injury. *Curr Pharm Des* 2004; **10:** 2401–10.
5. Franconi F, *et al.* Taurine supplementation and diabetes mellitus. *Curr Opin Clin Nutr Metab Care* 2006; **9:** 32–6.
6. Verner AM, *et al.* Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tairuining (泰瑞宁); Xiao Le Dun (小乐敦); ***Ital.***: O-Due; ***Philipp.***: Taurex; ***Rus.***: Dibicor (Дибикор); Taufon (Тауфон).

Multi-ingredient Preparations. ***Arg.***: Synapsys; ***Austral.***: Liver Detox; Liver Tonic Complex; PM Syrin; ***Belg.***: Ostrin Q10; ***China***: Run Jie (润洁); Zhongxin (中鑫); ***Fr.***: D-Stress; Formag; Phytozac; ***India***: Diapill; Nefrosave; ***Indon.***: Asten; Biofos†; Fitkom; Growee; Hemaviton Energy Drink; Hemaviton Jreng; Lanavision Plus; nutrivision; Proview; Regresor; Sangobion ActiFe; Vidoran Smart Plus; Vidoran Smart; Vipro-G; Vipro-G; Xanda; ***Ital.***: Magen-700; Novostatin; Taurovit; ***Malaysia***: Appeton; ***Philipp.***: Biomix; Ceegeefer†; Celermin†; Chlorvytol†; Crevytin†; Dreamvite; Ener A Plus; Enersel; Enouvim; EZ-Grow; Flexivit; Folanerve; Healthy Kidz; Hi-Smart Teens; Hi-Smart; Kiddie Estamin; Kiddirel; Lexivit; Lysadam Plus; Lysmix; Memorx IQ Plus; Multigrow; Natalsure; Natalwiz; Nerveplex; Nerveplex; Neurosmart; Nutrazinc; Nutri 10; Nutricaire; Nutrigrow Plus; Nutrigrow†; Nutrigrow; Nutrilin; Nutrotal; OB Max; OB Smart SG; Onevit; Optigrow; Pediafortan Forte-GE; Pediafortan Forte; Propan TLC; Pryce-Kidz; Regeron Vita with Chlorella; Regeron Vita with Chlorella; Rejuvon; Restor-F; Restor; Strevit; Supranutrol; Syplex; TLC Vita; Tropicee Plus; Ultravit-TL; United American Tiki Tiki Star; Vigorvit; Vita SL Plus; Vitakids; Vitaplex; Vitazinc; ***Port.***: Detoxergon; ***Rus.***: Genferon (Генферон); Genferon Light (Генферон Лайт); ***Singapore***: Growee†; Nutrivision†; ***UK***: Boost; ***Ukr.***: Cratal (Кратал); Oko-Health (Око-хелс); PM Sirin (ПМ Сирин); ***USA***: Diabetiks.

Teriflunomide *(USAN, rINN)*

A-771726; HMR-1726; RS-61980; SU-0020; Teriflunomida; Tériflunomide; Teriflunomidum; Терифлуномид.

(*Z*)-2-Cyano-α′α′α-trifluoro-3-hydroxy-*p*-crotonotoluidide.

$C_{12}H_9F_3N_2O_2$=270.2

CAS — 108605-62-5; 163451-81-8.

UNII — 1C058IKG3B.

Uses and Administration

Teriflunomide is a pyrimidine synthesis inhibitor that acts as an immunomodulator with anti-inflammatory and immunosuppressant properties. It is used in the treatment of relapsing forms of multiple sclerosis (p. 996.3). An oral dose of 7 or 14 mg is given once daily.

Teriflunomide is the major active metabolite of leflunomide (p. 81.3).

References.

1. O'Connor PW, *et al.* Teriflunomide Multiple Sclerosis Trial Group. University of British Columbia MS/MRI Research Group. A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology* 2006; **66:** 894–900.
2. O'Connor P, *et al.* TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011; **365:** 1293–1303.
3. Confavreux C, *et al.* Teriflunomide Multiple Sclerosis Trial Group. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. *Multiple Sclerosis* 2012; **18:** 1278–89.
4. Miller AE, *et al.* Teriflunomide Multiple Sclerosis Trial Group. Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. *Multiple Sclerosis* 2012; **18:** 1625–32.
5. Freedman MS, *et al.* Teriflunomide Multiple Sclerosis Trial Group and the MRI Analysis Center. Teriflunomide added to interferon-β in relapsing multiple sclerosis: a randomized phase II trial. *Neurology* 2012; **78:** 1877–85.

Adverse Effects and Precautions

As for Leflunomide, p. 82.1. Hyperkalaemia has also been reported in patients given teriflunomide.

Interactions

Interactions for teriflunomide are expected to be similar to those for leflunomide (see p. 82.3). Studies have also suggested that teriflunomide may be an inhibitor of the cytochrome P450 isoenzyme CYP2C8 and a weak inducer of CYP1A2.

For reference to the effect of teriflunomide on warfarin, see Immunosuppressants, under Warfarin, p. 1534.2.

Pharmacokinetics

Teriflunomide is absorbed from the gastrointestinal tract and peak plasma concentrations are reached between 1 and 4 hours after an oral dose. It is mainly distributed in plasma and is more than 99% bound to plasma proteins. Teriflunomide is mostly eliminated as unchanged drug in the bile and as metabolites in the urine. It is thought to undergo enterohepatic recycling and has an elimination half-life of about 18 to 19 days after repeated oral doses; it takes about 3 months to reach steady-state concentrations.

Teriflunomide is distributed into the milk of *rats.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Aubagio.

Terlipressin *(BAN, USAN, rINN)* ⊗

Terlipresina; Terlipressine; Terlipressinum; Triglycyl-lysine-vasopressin; Терлипрессин.

N-[*N*-(*N*-Glycylglycyl)glycyl]lypressin; Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2 cyclic (4→9) disulphide.

$C_{52}H_{74}N_{16}O_{15}S_2$=1227.4
CAS — 14636-12-5.
ATC — H01BA04.
ATC Vet — QH01BA04.
UNII — 7Z5X49W53P.

Terlipressin Acetate *(BANM, rINNM)* ⊗

Acetato de terlipresina; Terlipresin Asetat; Terlipresina, acetato de; Terlipressiiniasetaatti; Terlipressin Diacetate; Terlipressinacetat; Terlipressine, Acétate de; Terlipressini Acetas; Терлипрессина Ацетат.
$C_{52}H_{74}N_{16}O_{15}S_2,2C_2H_4O_2,5H_2O$=1437.6
ATC — H01BA04.
ATC Vet — QH01BA04.
UNII — 4U092XZF0K.

Uses and Administration

Terlipressin is an inactive prodrug that is slowly converted in the body to lypressin, and has the general physiological actions of vasopressin (p. 2643.1). It is given as the acetate although doses may be expressed as the base; 1 mg of terlipressin acetate is equivalent to about 0.85 mg of terlipressin.

Terlipressin acetate is used to control bleeding oesophageal varices and is given by intravenous injection in doses of 1 to 2 mg, followed by 1 to 2 mg every 4 to 6 hours if necessary, until bleeding is controlled, for up to 72 hours.

In the treatment of hepatorenal syndrome type 1 (see below) the recommended starting dose is the equivalent of 0.85 mg of terlipressin every 6 hours by slow intravenous bolus injection. If, after 3 days, serum creatinine has not decreased by at least 30% from its baseline value, the dose can be increased to 1.7 mg every 6 hours; however, such increases are not advised in patients with severe pre-existing cardiovascular disease or an ongoing significant adverse effect such as pulmonary oedema or ischaemia. Treatment should be continued until about 2 days after the patient achieves a reversal of hepatorenal syndrome, as indicated by a serum creatinine concentration of ≤132.6 micromoles/litre. The initial course of treatment may be continued for up to 2 weeks.

Terlipressin is under investigation in the treatment of shock.

Hepatorenal syndrome. Terlipressin given intravenously is used in the treatment of hepatorenal syndrome, a form of renal impairment associated with cirrhosis of the liver. A literature review[1] of clinical studies and meta-analyses found evidence to suggest that renal function was improved in patients with hepatorenal syndrome when treated with terlipressin; a reduction in mortality was also shown in some but not all studies. However, relapse was noted in one study after terlipressin was stopped and adverse effects have occurred. In particular, systemic ischaemic effects can be a problem even in patients without a known risk of cardiovascular disease. The authors considered that terlipressin was a reasonable option for improving renal function before liver transplantation; however, definitive recommendations could not be given.

1. Mazur JE, *et al.* Terlipressin in hepatorenal syndrome. *Ann Pharmacother* 2011; **45:** 380–7.

Shock. Terlipressin has vasopressor effects and has been tried[1,2] in the management of septic shock (p. 1279.3). In a group of 8 patients who could not be adequately managed with conventional vasopressor therapy, an intravenous bolus of terlipressin 1 to 2 mg produced a progressive increase in mean arterial pressure over 10 to 20 minutes that was sustained for at least 5 hours, allowing reduction or cessation of noradrenaline.[3] Similar beneficial results have also been reported by others.[4,5] The use of a continuous infusion of terlipressin (500 micrograms/hour for 6 hours followed by half this dose for a further 12 hours) has been described in one case and appeared to be effective.[6] There are also reports[7,8] of a total of 20 children treated with bolus doses of 20 micrograms/kg every 4 hours for up to 72 hours. Terlipressin has also been used with some success as rescue therapy in doses of 7 to 20 micrograms/kg in children with extremely low cardiac output following open-heart surgery.[9]

1. Delmas A, *et al.* Clinical review: vasopressin and terlipressin in septic shock patients. *Crit Care* 2005; **9:** 212–22.
2. Pesaturo AB, *et al.* Terlipressin: vasopressin analog and novel drug for septic shock. *Ann Pharmacother* 2006; **40:** 2170–7.
3. O'Brien A, *et al.* Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002; **359:** 1209–10.
4. Morelli A, *et al.* Effects of terlipressin on systemic and regional haemodynamics in catecholamine-treated hyperkinetic septic shock. *Intensive Care Med* 2004; **30:** 597–604.
5. Leone M, *et al.* Terlipressin in catecholamine-resistant septic shock patients. *Shock* 2004; **22:** 314–19.
6. Jolley DH, *et al.* Terlipressin infusion in catecholamine-resistant shock. *Anaesth Intensive Care* 2003; **31:** 560–4.
7. Rodríguez-Núñez A, *et al.* Terlipressin for catecholamine-resistant septic shock in children. *Intensive Care Med* 2004; **30:** 477–80.
8. Rodríguez-Núñez A, *et al.* Rescue treatment with terlipressin in children with refractory septic shock: a clinical study. *Crit Care* 2006; **10:** R20. Available at: http://ccforum.com/content/10/1/R20 (accessed 28/05/09)
9. Matok I, *et al.* Terlipressin for children with extremely low cardiac output after open heart surgery. *Ann Pharmacother* 2009; **43:** 423–9.

Variceal haemorrhage. Systematic review has indicated[1] that terlipressin is effective in the management of acute oesophageal variceal haemorrhage (see under Monoethanolamine, p. 2563.1), and reduces the relative risk of mortality by about one-third. Differences in efficacy from other therapies could not be conclusively shown. Comparison of a regimen of terlipressin given by intravenous bolus injection, plus glyceryl trinitrate given sublingually, with balloon tamponade in variceal bleeding has suggested similar efficacy.[2] However, tamponade was successful in all patients that were previously unresponsive to terlipressin plus glyceryl trinitrate whereas this drug combination failed in all patients previously unresponsive to tamponade. A comparison of terlipressin and endoscopic injection sclerotherapy found them to be equally effective for the control of acute variceal bleeding.[3]

1. Ioannou GN, *et al.* Terlipressin for acute esophageal variceal hemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
2. Fort E, *et al.* A randomized trial of terlipressin plus nitroglycerin vs balloon tamponade in the control of acute variceal hemorrhage. *Hepatology* 1990; **11:** 678–81.
3. Escorsell À, *et al.* Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology* 2000; **32:** 471–6.

Adverse Effects, Treatment, and Precautions

As for Vasopressin, p. 2643.3.

The pressor and antidiuretic effects of terlipressin are reported to be less marked than those of vasopressin.

Effects on electrolytes. A report of hypokalaemia in a patient receiving terlipressin.[1]

1. Stéphan F, Paillard F. Terlipressin-exacerbated hypokalaemia. *Lancet* 1998; **351:** 1249–50.

Effects on the skin. Ischaemic skin necrosis developed in 3 patients several days after starting terlipressin treatment.[1] Skin lesions developed on the abdomen and lower limbs, which are not typical areas for ischaemia related to vasoconstrictors, and the authors concluded that obesity and venous insufficiency in these patients put them at particular risk.

1. Donnellan F, *et al.* Ischaemic complications of Glypressin in liver disease: a case series. *Br J Clin Pharmacol* 2007; **64:** 550–2.

Interactions

As for Vasopressin, p. 2644.2.

Pharmacokinetics

Following intravenous injection, terlipressin shows a biphasic decline in plasma concentrations, with distribution and elimination half-lives of between about 8 to 12 minutes and 50 to 80 minutes, respectively. Terlipressin is metabolised by tissue peptidases resulting in the slow release of lypressin; maximum plasma concentrations are reached after about 2 hours. Terlipressin is almost completely metabolised in the kidneys and liver, with less than 1% of terlipressin and less than 0.1% of lypressin excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Glypressin; ***Austral.:*** Lucassin; ***Austria:*** Glycylpressin; Haemopressin; ***Belg.:*** Glypressin; Variquel; ***China:*** Glypressin (可利新); Remestyp (安立亭); ***Cz.:*** Glypressin; Remestyp; ***Denm.:*** Glypressin; Glypressine; Variquel; ***Fin.:*** Glypressin; Stemflova; ***Fr.:*** Glypressine; Haemopressin; ***Ger.:*** Glycylpressin; Haemopressin; ***Gr.:*** Glypressin; ***Hong Kong:*** Glypressin; ***Hung.:*** Glypressin; ***Irl.:*** Glypressin; Haemopressin; ***Israel:*** Glypressin; ***Ital.:*** Glipressina; ***Malaysia:*** Glypressin; ***Mex.:*** Glyverase; ***Neth.:*** Glypressin; Haemopressin; ***Norw.:*** Glypressin; Stemflova; ***NZ:*** Glypressin; ***Philipp.:*** Glypressin; ***Pol.:*** Glypressin; Remestyp; ***Port.:*** Glypressine; ***Rus.:*** Remestyp (Реместип); ***Singapore:*** Glypressin; ***Spain:*** Glypressin; Variquel; ***Swed.:*** Glypressin; Variquel; ***Switz.:*** Glypressine; Haemopressin; ***Thai.:*** Glypressin; ***Turk.:*** Glypressin; ***UK:*** Glypressin; Variquel; ***Ukr.:*** Glypressin (Глипрессин); Remestip (Реместип).

Terpineol

Терпинеол.
$C_{10}H_{18}O$=154.3
CAS — 8000-41-7 (terpineol); 98-55-5 (α-terpineol).
UNII — R53Q4ZWC99 (terpineol); 21334LVV8W (α-terpineol); 21M14KDA67 (l-α-terpineol); 5PH9U7XEWS (gamma-terpineol).

Pharmacopoeias. In *Br.*

BP 2014: (Terpineol). A mixture of structural isomers in which α-terpineol predominates. It is a colourless, slightly viscous liquid which may deposit crystals; it has a pleasant characteristic odour. Very slightly soluble in water; freely soluble in alcohol (70%); soluble in ether.

Profile

Terpineol has disinfectant and solvent properties. It is used with other volatile agents in preparations for respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.:*** Atomo Desinflamante Familiar; Atomo Desinflamante G; Atomo Desinflamante; Bronco Etersan; Di-Neumobron; Previnfec; ***Braz.:*** Bromil Grip†; Bromil; Bromil; Penetro; ***Cz.:*** Coldastop; ***Fr.:*** Nazinette du Docteur Gilbert; Pectoderme†; Valda†; ***India:*** Aerway; Coriminic-Vaporise; Dettol Obstetric; Dettol; Easi Breathe; Fairgenol; Genvol Plus; Karvol Plus; Kolq Inhalant; Sinarest Vapocaps; ***Irl.:*** Karvol; ***Israel:*** Gargol; Karvol; Rexitol†; ***Ital.:*** Calyptol; Rikospray; Skab 2†; ***Mon.:*** Calyptol; ***NZ:*** Tixylix Chest Rub; ***S.Afr.:*** AF; Karvol†; ***Singapore:*** Karvol; ***Spain:*** Caltoson Balsamico†; Eupnol; ***Switz.:*** Perskindol Classic; ***UK:*** Chymol; Jacksons Mentholated Balm; Karvol; Nowax.

Pharmacopoeial Preparations
BP 2014: Chloroxylenol Solution.

Tesmilifene Hydrochloride *(USAN, rINNM)*

BMS-217380-01; BMY-33419; DPPE; Hidrocloruro de tesmilifeno; Tesmilifène, Chlorhydrate de; Tesmilifeni Hydrochloridum; Tesmilifeno, hidrocloruro de; Тезмилифена Гидрохлорид.
2-[(α-Phenyl-*p*-tolyl)oxy]triethylamine hydrochloride; *N,N*-Diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine hydrochloride.
$C_{19}H_{25}NO,HCl$=319.9
CAS — 98774-23-3 (tesmilifene); 92981-78-7 (tesmilifene hydrochloride).
UNII — 1U4B477260.

Profile

Tesmilifene hydrochloride is an intracellular histamine antagonist that appears to augment the antineoplastic activity of drugs such as the anthracyclines and taxanes. It is under investigation for the treatment of various cancers, including hormone-refractory cancer of the prostate and gastric and hepatic cancers.

References.

1. Reyno L, *et al.* Phase III study of N,N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine (BMS-217380-01) combined with doxorubicin versus doxorubicin alone in metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA19. *J Clin Oncol* 2004; **22:** 269–76.
2. Raghavan D, *et al.* Phase II trial of tesmilifene plus mitoxantrone and prednisone for hormone refractory prostate cancer: high subjective and objective response in patients with symptomatic metastases. *J Urol (Baltimore)* 2005; **174:** 1808–13.

Tetrabenazine *(BAN, rINN)*

Ro-1-9569; Tetrabenatsiini; Tetrabenazin; Tetrabenazina; Tétrabénazine; Tetrabenazinum; Тетрабеназин.
1,3,4,6,7,11b-Hexahydro-3-isobutyl-9,10-dimethoxybenzo-[*a*] quinolizin-2-one.
$C_{19}H_{27}NO_3$=317.4
CAS — 58-46-8.
ATC — N07XX06.
ATC Vet — QN07XX06.
UNII — Z9O08YRN8O.

Uses and Administration

Tetrabenazine is used in the management of movement disorders including chorea (p. 1029.3), ballism (p. 1029.3), dystonias (p. 903.3), tardive dyskinesia (see under Extrapyramidal Disorders, p. 1049.2), and similar symptoms of CNS dysfunction.

For the treatment of chorea, ballism, and other organic CNS movement disorders, a starting oral dose of 12.5 to 25 mg up to three times daily has been recommended. The dose may be gradually increased by 12.5 to 25 mg every 3 or 4 days according to response up to a maximum of 200 mg daily. If the patient does not respond within 7 days of receiving the maximum dose further treatment with tetrabenazine is unlikely to be of benefit.

In the USA, the following doses are recommended for Huntington's chorea. A starting dose of 12.5 mg daily given in the morning is recommended, which may be increased after one week to 25 mg daily given in 2 divided doses. The dose may then be gradually increased by 12.5 mg daily at weekly intervals according to response. Daily doses greater than 37.5 to 50 mg should be given in 3 divided doses with a maximum single dose of 25 mg. Patients who appear to need doses above 50 mg daily should be genotyped for the cytochrome P450 isoenzyme CYP2D6: doses in extensive or intermediate CYP2D6 metabolisers may be increased by 12.5 mg daily at weekly intervals according to response up to a maximum daily dose of 100 mg given in 3 divided doses with a maximum single dose of 37.5 mg; in poor CYP2D6 metabolisers, the maximum daily dose is 50 mg given in 3 divided doses with a maximum single dose of 25 mg.

For moderate to severe tardive dyskinesia, a dose of 12.5 mg daily is recommended initially, subsequently titrated according to response.

For doses in hepatic impairment, see below.

Reviews.
1. Fasano A, Bentivoglio AR. Tetrabenazine. *Expert Opin Pharmacother* 2009; **10:** 2883–96.

Administration in hepatic impairment. UK licensed product information for tetrabenazine recommends that an initial oral dose of 6.25 mg up to three times daily, and a slower increase in dose, should be used in patients with mild to moderate hepatic impairment. Information is lacking about use in patients with severe impairment and so caution is advised.

Extrapyramidal disorders. In a long-term study[1] of the use of tetrabenazine in 400 patients with movement disorders, the best responses seemed to be in tardive dyskinesia, tardive dystonia, and Huntington's disease but benefit was also obtained in some patients with idiopathic dystonia, segmental myoclonus, and Tourette's syndrome. Others have commented that in severe dystonia unresponsive to other drugs a combination of tetrabenazine with trihexyphenidyl and pimozide is sometimes effective.[2] Tetrabenazine significantly reduced chorea in ambulatory patients with Huntington's disease in a small 12-week randomised placebo-controlled study.[3] It was well tolerated, although there was a significant increase in reports of drowsiness and insomnia, which generally resolved with adjustment of doses.

1. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 1997; **48:** 358–62.
2. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.
3. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* 2006; **66:** 366–72.

Adverse Effects

Drowsiness is the most frequent adverse effect of tetrabenazine. Orthostatic hypotension, symptoms of extrapyramidal dysfunction, gastrointestinal disturbances, and depression may also occur. Neuroleptic malignant syndrome and parkinsonism have been reported rarely. Overdosage has produced sedation, sweating, hypotension, and hypothermia.

Effects on mental function. Depression is well documented as an adverse effect of tetrabenazine, and occurs in about 15% of patients; it has been reported to respond to reboxetine.[1] Florid psychiatric symptoms such as panic attacks and obsessive-compulsive symptoms may be precipitated or exacerbated by tetrabenazine.[2]

1. Schreiber W, *et al.* Reversal of tetrabenazine induced depression by selective noradrenaline (norepinephrine) reuptake inhibition. *J Neurol Neurosurg Psychiatry* 1999; **67:** 550.
2. Bruneau MA, *et al.* Catastrophic reactions induced by tetrabenazine. *Can J Psychiatry* 2002; **47:** 683.

Extrapyramidal disorders. Dysphagia and choking were associated with tetrabenazine in the treatment of Huntington's chorea.[1] Fatal pneumonia, probably as a consequence of aspiration, had also been reported.

1. Snaith RP, Warren H de B. Treatment of Huntington's chorea with tetrabenazine. *Lancet* 1974; **i:** 413–14.

Overdosage. A patient who swallowed about 1 g (40 tablets) of tetrabenazine became drowsy 2 hours later and marked sweating occurred.[1] Her state of consciousness improved after 24 hours and she talked rationally and gained full control of micturition after 72 hours.

1. Kidd DW, McLellan DL. Self-poisoning with tetrabenazine. *Br J Clin Pract* 1972; **26:** 179–80.

Precautions

Tetrabenazine is contra-indicated in actively suicidal patients or in cases of untreated or inadequately treated depression. It should be given with caution to patients with hepatic impairment. Tetrabenazine may exacerbate the symptoms of parkinsonism. It may cause drowsiness; affected patients should not drive or operate machinery.

Interactions

Tetrabenazine may diminish the effects of levodopa and exacerbate the symptoms of parkinsonism. Tetrabenazine should not be started until at least 20 days after stopping reserpine in order to avoid major depletion of serotonin and noradrenaline in the CNS. Use of tetrabenazine immediately after a course of an MAOI may lead to confusion, restlessness, and disorientation; tetrabenazine should not be given with, or within 14 days of stopping, such therapy.

Pharmacokinetics

Absorption of tetrabenazine is poor and erratic after oral doses. It appears to be extensively metabolised by first-pass metabolism; the cytochrome P450 isoenzyme CYP2D6 has a significant role in the metabolism of tetrabenazine and this may affect doses (see Uses and Administration, p. 2627.3). The major metabolite of tetrabenazine, hydroxytetrabenazine, which is formed by reduction, is reported to be as active as the parent compound. Tetrabenazine is excreted in the urine mainly in the form of metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Nitoman; ***Cz.***: Tetmodis; ***Denm.***: Nitoman; Tetmodis; ***Fin.***: Tetmodis; ***Fr.***: Xenazine; ***Ger.***: Nitoman; Tetmodis; ***Gr.***: Xenazine; ***India***: Revocon; ***Irl.***: Nitoman; Tetmodis; ***Israel***: Xenazine; ***Ital.***: Xenazina; ***Jpn***: Choreazine; ***Neth.***: Tetmodis; Xenazine; ***NZ***: Xenazine; ***Port.***: Nitoman; Revocon; ***Spain***: Nitoman; ***Swed.***: Tetmodis; Xenazine; ***Switz.***: Xenazine; ***UK***: Revocon; Tetmodis; Xenazine; ***USA***: Xenazine.

Tetrachlorodecaoxide

TCDO; Tetrachlorodecaoxygen Anion Complex; Tetraclorodecaóxido; WF-10.
Cl_4O_{10}=301.8
CAS — 92047-76-2.

Profile

Tetrachlorodecaoxide is a water-soluble anion complex containing oxygen in a chlorite matrix. Active oxygen is only released in the presence of biological material. It has been applied as a solution for the stimulation of wound healing, and has been tried in the management of mucositis.

Mucositis. Benefit has been reported from the use of tetrachlorodecaoxide in the management of mucositis induced by chemotherapy[1] or radiotherapy,[2] although it appears to be minor.[1] Benefit has also been reported in reducing recurrence of radiation-induced haemorrhagic cystitis.[3]

1. Malik IA, *et al.* A double-blind, placebo-controlled, randomized trial to evaluate the role of tetrachlorodecaoxide in the management of chemotherapy-induced oral mucositis. *J Pain Symptom Manage* 1997; **14:** 82–7.
2. Penpattanagul S. Reduced incidence and severity of acute radiation mucositis by WF10 (IMMUNOKINE) as adjunct to standard of cure in the management of head & neck cancer patients. *J Med Assoc Thai* 2007; **90:** 1590–600.
3. Veerasarn V, *et al.* Reduced recurrence of late hemorrhagic radiation cystitis by WF10 therapy in cervical cancer patients: a multicenter, randomized, two-arm, open-label trial. *Radiother Oncol* 2004; **73:** 179–85.

Wounds. Tetrachlorodecaoxide was reported to promote wound healing compared with saline in a double-blind study of 271 patients,[1] but a smaller study failed to show any benefit over glycerol.[2]

1. Hinz J, *et al.* Rationale for and results from a randomised, double-blind trial of tetrachlorodecaoxygen anion complex in wound healing. *Lancet* 1986; **i:** 825–8.
2. Hughes LE, *et al.* Failure of tetrachlorodecaoxygen anion complex to assist wound healing. *Lancet* 1989; **ii:** 1271.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Oxoferin; ***Indon.***: Oxoferin; ***Port.***: Oxoferin; ***Thai.***: Immunokine; Oxoferin; ***Venez.***: Oxoferin.

Tetramethylammonium Iodide

Tetrametilamonio, ioduro de; Иодид Тетраметиламмония.
$C_4H_{12}IN$=201.1
CAS — 75-58-1.

Profile

Tetramethylammonium iodide is a quaternary ammonium compound that has been used for the emergency disinfection of drinking water. It has also been used for its ganglion-blocking properties.

Thallium Acetate

Talio, acetato de; Thallous Acetate.
$C_2H_3O_2Tl$=263.4
CAS — 7440-28-0 (thallium); 563-68-8 (thallium acetate); 7446-18-6 (thallium sulfate).

Uses and Administration

Thallium acetate was formerly used orally for depilation in ringworm and as an ingredient of depilatory creams but both systemic and local treatments have caused deaths, and it is no longer used for such purposes. It has also been used as a rodenticide and insecticide; thallium sulfate has been used similarly. The use of thallium salts is strictly regulated in many countries. However, use in industry could still constitute a hazard. Cases of malicious poisoning still occur occasionally.

Adverse Effects

Thallium salts are toxic when inhaled, ingested, or absorbed through the skin. Symptoms of poisoning may appear within 12 to 24 hours of a single toxic dose and include severe abdominal pain, nausea and vomiting, diarrhoea, gastrointestinal haemorrhage, salivation, metallic taste, paralytic ileus, pancreatic damage, and in severe cases cardiovascular collapse, tremors, delirium, convulsions, paralysis, and coma, leading to death in 1 to 2 days. However, the acute reaction may subside, to be followed within about 10 days by the development of neurological effects including paraesthesia, myalgia, myopathy, motor neuropathy, and visual disturbances due to optic neuropathy, psychosis, delirium, convulsions, and other signs of encephalopathy, tachycardia, hypertension, skin eruptions, and hepatorenal injury. Recovery from neurological damage is slow and may be incomplete. Alopecia occurs within 15 to 20 days; stomatitis may also develop. Death may result from respiratory failure; patients are also predisposed for several weeks to cardiac arrhythmias and sudden death. Fatalities have occurred after ingestion of 3 to 10 g of thallium compounds by adults and 85 to 89 mg/kg by children.

Smaller repeated doses are also toxic, with symptoms appearing over several weeks. Constipation is a common feature of less severe poisoning.

Poisoning. References.
1. Moeschlin S. Thallium poisoning. *Clin Toxicol* 1980; **17:** 133–46.
2. Heyl T, Barlow RJ. Thallium poisoning: a dermatological perspective. *Br J Dermatol* 1989; **121:** 787–92.
3. Luckit J, *et al.* Thrombocytopenia associated with thallium poisoning. *Hum Exp Toxicol* 1990; **9:** 47–8.
4. Moore D, *et al.* Thallium poisoning. *BMJ* 1993; **306:** 1527–9.
5. Tabandeh H, Thompson GM. Visual function in thallium toxicity. *BMJ* 1993; **307:** 324.
6. Questel F, *et al.* Thallium-contaminated heroin. *Ann Intern Med* 1996; **124:** 616.
7. Tromme I, *et al.* Skin signs in the diagnosis of thallium poisoning. *Br J Dermatol* 1998; **138:** 321–5.
8. Hoffman RS. Thallium poisoning during pregnancy: a case report and comprehensive literature review. *J Toxicol Clin Toxicol* 2000; **38:** 767–75.
9. Misra UK, *et al.* Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. *Postgrad Med J* 2003; **79:** 103–5.
10. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22:** 29–40.
11. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; **38:** 1509–14.
12. Kuo H-C, *et al.* Acute painful neuropathy in thallium poisoning. *Neurology* 2005; **65:** 302–4.
13. CDC. Thallium poisoning from eating contaminated cake—Iraq, 2008. *MMWR* 2008; **57:** 1015–18.

Treatment of Adverse Effects

Gastric lavage should be considered if the patient presents within 1 hour of acute ingestion. Intensive supportive therapy is necessary.

Attempts have been made to increase the faecal and urinary excretion of thallium. A suspension of activated charcoal has been given to reduce intestinal absorption and enteric recycling. Prussian blue (p. 1572.3) given orally or via a nasogastric tube is also used routinely. A purgative such as mannitol may be required with either activated charcoal or Prussian blue as constipation is common in severe thallium toxicity. Giving potassium chloride orally may mobilise thallium from the tissues but is hazardous, especially if given during the early stage as signs of poisoning may be aggravated. Traditional chelation therapy is not generally recommended for thallium poisoning.

Haemoperfusion, haemodialysis, or peritoneal dialysis have been reported to be effective in eliminating absorbed thallium, although clinical benefit is doubtful.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Ger.***: Hautfunktionstabletten N; Hautfunktionstropfen N; ***Neth.***: Cutis comp.

Theodrenaline Hydrochloride

(BANM, rINNM) ⊗

H-8352; Hidrocloruro de teodrenalina; Noradrenaline Theophylline Hydrochloride; Teodrenalina, hidrocloruro de; Théodrénaline, Chlorhydrate de; Theodrenalini Hydrochloridum; Теодреналина Гидрохлорид.

7-[2-(3,4,β-Trihydroxyphenethylamino)ethyl]theophylline hydrochloride.

$C_{17}H_{21}N_5O_5$,HCl=411.8

CAS — 13460-98-5 (theodrenaline); 2572-61-4 (theodrenaline hydrochloride).

ATC — C01CA23.

ATC Vet — QC01CA23.

Profile

Theodrenaline is mainly used as the hydrochloride in preparations with cafedrine promoted for the treatment of hypotension. This preparation has been subject to abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Akrinor†; ***Fr.***: Praxinor; ***Ger.***: Akrinor; ***Indon.***: Akrinor; ***S.Afr.***: Akrinor.

Thioctic Acid

Acide thioctique; Ácido α-lipoico; Acidum thiocticum; Alpha Lipoic Acid; Kwas tioktynowy; Kyselina thioktová; Lipoic Acid; α-Liponic Acid; Thioctsäure; Tióctico, ácido; Тиоктовая Кислота.

5-(1,2-Dithiolan-3-yl)valeric acid.

$C_8H_{14}O_2S_2$=206.3

CAS — 62-46-4.

ATC — A16AX01.

ATC Vet — QA16AX01.

UNII — 73Y7P0K73Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Thioctic Acid). A yellow, crystalline powder. M. p. about 61 degrees. Very slightly soluble in water; very soluble in dimethylformamide; freely soluble in methyl alcohol. Protect from light.

USP 36: (Alpha Lipoic Acid). M.p. 60.0 degrees to 62.0 degrees.

Profile

Thioctic acid is used for its antoxidant effects in the treatment of diabetic neuropathy. It has been tried in the treatment of liver dysfunction, subacute necrotising encephalopathy, and pain. Beneficial results have been claimed in amanitin poisoning after ingestion of the mushroom *Amanita phalloides*, but such use is controversial (see Amanita Phalloides under Poisonous Mushrooms or Toadstools, p. 2565.3). Ethylenediamine thioctate, sodium thioctate, thioctic acid amide (thioctamide), and trometamol thioctate have been used similarly.

Adverse effects. Severe cholestatic hepatitis has been reported[1] in a patient who was taking thioctic acid for the symptomatic treatment of diabetic neuropathy; symptoms resolved when the drug was stopped and recurred on rechallenge.

Insulin auto-immune syndrome has been associated with the use of thioctic acid as a dietary supplement.[2]

1. Ridruejo E, *et al.* Thioctic acid-induced acute cholestatic hepatitis. *Ann Pharmacother* 2011; **45:** e43.
2. Bresciani E, *et al.* Insulin autoimmune syndrome induced by α -lipoic acid in a Caucasian woman: case report. *Diabetes Care* 201 l; **34:** e146.

Pharmacokinetics. References.

1. Teichert J, *et al.* Pharmacokinetics of alpha-lipoic acid in subjects with severe kidney damage and end-stage renal disease. *J Clin Pharmacol* 2005; **45:** 313–28.

Use in diabetic neuropathy. A review[1] and meta-analysis[2] of randomised controlled studies concluded that thioctic acid 600 mg daily given intravenously for 3 weeks reduced the symptoms of diabetic neuropathy (p. 465.2); however, the clinical relevance of improvements seen after oral dosage of 600 mg daily for up to 5 weeks is unclear.[2]

1. McIlduff CE, Rutkove SB. Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. *Ther Clin Risk Manag* 2011; **7:** 377–85.
2. Mijnhout GS, *et al.* Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol* 2012; **2012:** 456279.

Use in pain. Thioctic acid has been tried in the treatment of pain (see Choice of Analgesic, p. 4.2) of various causes including sciatic pain following herniated disc,[1] back pain,[2] and burning mouth syndrome.[3]

1. Memeo A, Loiero M. Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study. *Clin Drug Investig* 2008; **28:** 495–500.
2. Ranieri M, *et al.* The use of alpha-lipoic acid (ALA), gamma linolenic acid (GLA) and rehabilitation in the treatment of back pain: effect on health-related quality of life. *Int J Immunopathol Pharmacol* 2009; **22** (suppl): 45–50.
3. López-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of burning mouth syndrome: a randomized, double-blind, placebo controlled trial. *Med Oral Patol Oral Cir Bucal* 2011; **16:** e635–e640.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biletan; Ciagen; Neurotioct; Neutracol; Sigmus; Tioctan; Tioctic; Tiodrix; Tioneurol; ***Austria***: Thioctacid; Tioctan; ***Braz.***: Thioctacid; ***China***: Alpha-Lipon (奥力宝); Ao Tian Li (奥天利); ***Cz.***: Thioctacid; Thiogamma; ***Ger.***: Alpha-Lipogamma; Alpha-Lipon†; alpha-Vibolex; Biomolipon†; Neurium†; Pleomix-Alpha; Thioctacid; Thiogamma; Tromlipon; Verla-Lipon†; Vitatrans†; ***Hong Kong***: Thiogamma; ***Hung.***: Thioctacid; Thiogamma; ***India***: Ala; Aladin; Cobal Forte; Lipocid; ***Indon.***: Alanox; Mecola Forte; ***Ital.***: Patiox; Tiobec Crema; ***Mex.***: Thioctacid; ***Pol.***: Neurex†; Neurolipon; Thiogamma; ***Port.***: Thioctacid; ***Rus.***: Berlithion (Берлитион); Espa-Lipon (Эспа-липон); Lipothioxon (Липотиоксон); Octolipen (Октолипен); Thioctacid (Тиоктацид); Thiogamma (Тиогамма); Thiolepta (Тиолепта); Thiolipon (Тиолипон); ***Thai.***: Lipoicin; ***Ukr.***: Alfa-Lipon (Альфа-Липон); Berlithion (Берлитион); Dialipon (Диалипон); Espa-Lipon (Эспа-Липон); Thioctacid (Тиоктацид); Thiogamma (Тиогамма).

Multi-ingredient Preparations. ***Arg.***: Biletan Enzimatico; Carbogasol Digestivo; Cellasene Gold; Cistidac; Co-Tioctan; Nervomax TB12; ***Austral.***: Gluco Support; Tresos B PluSe; Womens Multi; ***Canad.***: Trim-Fit†; ***Fr.***: Glycontrol; ***Hong Kong***: Lipochol; ***India***: Acmic-Alpha; Ala-Plus; Alcrin-M; Alcrin; Alfariz; Almecol-B; Almecol; Alnacob-OD; Alpha Cad; Alphaneuron; Aluno-A; Ameco Plus; Ancob; Armet Plus; Barovit; Basix-AL; Beminal Forte; Bencoba; Benerv Forte; Benfage Forte; Benfo Forte; Berocin-CZ; Bigvin Plus; Cally Plus; Canbol Plus; Canmik; Catalyst; Cobaday-AV; Cobalip; Cobals Plus; Cobalvit Forte; Cobalvit Plus; Cobanerve Plus; Cobanerve; Cobasoft; Cobaver-OD; Coblona Plus; Colaba-B; Compicare-XL; Cumee-A; Dianerve; Dianuron; Diapill; Diavit; Doravit Forte; Ebiza-L; EC; Ecobal-Plus; Ecobal; Efcoba Forte; Efcoben; Elmecob Plus; Elneuro; Encentin-AM; Escobal; Eucobal; Exerge; Exox; Felicita-OD; Folirich-B; Fotia Plus; GCobal; GMab Plus; Hicobal; Hosit Plus; Humax-Alpha-R; Incobal Plus; Inerve; Keeneuron; Kefive Plus; L-Nit; Lameco Plus; Levineuro; Logic; Maconeuron-OD; Macraberin-M; Maddox-AL; Malzix; Marinol Alpha; Matilda; MCF-Max; Me Plus; Me-Plus; Mebal-Plus; Mecatin; Mecoba Alpha; Mecobal Plus; Mecobil-OD; Mecobion-OD; Mecobion; Mecoblend; Mecobyte; Mecocas; Mecoday Plus; Mecofol-A; Mecolife Plus; Mecompy-Forte; Meconerv Forte; Mecopil; Mecoriv Plus; Mecosa-OD; Mecovon; Medhamin Forte; Meganeuron; Mego-XL; Melcovit; Melvit; Memi; Menol-Plus; Met-Neurobion; Methico-AL; Methygard-OD; Mewin Forte; Mexivit; Mezen; Miko-OD; Mixovim; Moblo-AF; Moblo-Plus; MSA; Mycotop; Mycovit; N-Care Forte; Necob Plus; Nerjuwin; Nerve-O-Fitt; Nervic; Nervicin; Nervijen-D; Nervijen; Nervimax Plus; Nervion; Nervonic; Nervup Forte; Nervup-OD; Nervup-PG; Nervup; Nervz-B; Nervz; Nerwin-MD; Neucobal-Forte; Neuractin Forte; Neuroage; Neurocap-OD; Neurochek; Neuroforte; Neuroglow-B; Neuroglow; Neurokair; Neurolax-OD; Neuromed; Neurontin; Neuropill; Neurosoz-MC; Neurotop Plus; Neurozen; Neuvesca; Nexcob Plus; Nocad; Numeth; Nuro-M Plus; Nuro-M; Nurobest; Nuroclad-Plus; Nurokind Plus; Nuromax-OD; Nuromin; Nurosenz; Nurovir; Nurovole Plus; Nurozac-OD; Nuthyl-AL; Nutricobal Plus; Onerve; Oscob Forte; ***Indon.***: Aldovas; Alicron; Aptivium Liver Support†; Canergy†; Cinula; Covitala; Fres Diab; Kapset; Mecola; Neofer; nu Qten Com; Proliva; Reliv†; Seloxy AA; Tiola; Univoxy; Vitala; ***Ital.***: Alceclar†; Alfa Lip; Angiovein; Biophase Complex†; Biotad; Blunorm; Byodinoral; Depatox; Deproctol; Endoepatox; Lipoacid Combi; Neuralfa; Neuroptic; Osteolip Crema; Osteolip; Reumil; Rischiaril; Semel; Thiospot; Tiobec; Tiofort; Traumaven; Ulceclar; Vasobrain Plus; Visu-len; ***Malaysia***: Olivenol livin' Youthful†; ***Philipp.***: ALAnerv; Diamaxin; Illumina; ***Port.***: Lipoacid Combi; Lipoacid; Thiospot; ***Rus.***: Corylip (Корилип); Neurokomplit (Нейрокомплит); Selmevit (Селмевит); ***S.Afr.***: Zeel; Zeel; ***Singapore***: Essentials†; Olivenol Livin' Youthful; ***Spain***: Policolinosil; ***Thai.***: Lipochol; ***UK***: Lacrima; Selene-Activ; ***Ukr.***: Livonorm (Ливонорм); Oko-Health (Око-хелс); ***USA***: Blood Sugar Balance; Cardio Tone; Corvita; Corvite Free; Daily Betic; Diabetiks.

Homoeopathic Preparations. ***Canad.***: Hepar Compositum; Ubicoenzyme; ***Cz.***: Zeel Salbe†; ***Ger.***: Hepar comp; ***Hung.***: Zeel; ***Rus.***: Zeel T (Цель Т).

Pharmacopoeial Preparations

USP 36: Alpha Lipoic Acid Capsules; Alpha Lipoic Acid Tablets.

Thiomucase

C-84-04; Chondroitinsulphatase; Condroitinsulfatasa; EC 3.1.6.14; Tiomucasa; Тиомуказа.

Profile

Thiomucase is a mucopolysaccharidase with general properties similar to those of hyaluronidase, p. 2527.2, but which also depolymerises chondroitin sulfate. It has been given to assist the diffusion of local anaesthetic injections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Thiocase†.

Multi-ingredient Preparations. ***Braz.***: Thiomucase.

Thiotriazoline

Tiotriazolin; Тиотриазолин.

Morpholine 5-methyl-1,2,4-triazoline-5-thioacetate.

Profile

Thiotriazoline is reported to have anti-ischaemic, membrane stabilising, and antoxidant actions. It is used as a hepatoprotectant in various liver disorders and as a protectant in cardiovascular and cerebrovascular disorders. It is also used locally as an anti-inflammatory for wounds and lesions of the skin and mucous membranes and for vaginal or rectal inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ukr.***: Dalmaxin (Далмаксин).

Multi-ingredient Preparations. ***Ukr.***: Tiocetam (Тиоцетам); Tiodaron (Тиодарон).

Thiram *(USAN, rINN)*

NSC-1771; SQ-1489; Thirame; Thiramum; Tiram; Tiramo; TMT; TMTD; Тирам.

Tetramethylthiuram disulphide.

$C_6H_{12}N_2S_4$=240.4

CAS — 137-26-8.

ATC — P03AA05.

UNII — 0D771IS0FH.

Profile

Thiram, the methyl analogue of disulfiram (p. 2495.3), has antibacterial and antifungal activity. It has been applied topically as an aerosol in the treatment of wounds and other skin disorders. It has been used as a fungicide in agriculture, and in industry as a rubber accelerator. Occupational exposure to thiram may cause irritation of mucous membranes and skin.

Thorium Dioxide

Óxido de torio; Thorium Oxide; Torio, dióxido de; Диоксид Тория; Двуокись Тория.

ThO_2=264.0

CAS — 1314-20-1.

UNII — 9XA7X17UQC.

Profile

Colloidal solutions of thorium dioxide were formerly used as X-ray contrast media for examination of the liver and spleen, for arteriography, and occasionally for outlining the cerebral ventricles. Its elimination is very slow and incomplete. It accumulates in the reticuloendothelial system, especially in the liver and spleen. As it is radioactive (half-life: 1.41×10^{10} years), this accumulation is dangerous and there is strong evidence that the ensuing prolonged exposure to its radiation is a contributing factor in the development of malignant diseases and blood disorders often 20 to 30 years after its use.

Thuja

Tuya; White Cedar; Туя Западная (*Thuja occidentalis*).

ATC Herb — HD11AF5001 (Thuja occidentalis: *herb*).

UNII — 5HBV6WCE3N (Thuja occidentalis); *19RAD88E6O* (Thuja occidentalis *bark*); *0T0DQN8786* (Thuja occidentalis *leaf*); *1NT28V9397* (Thuja occidentalis *leafy twig*); *12958C0BR3* (Thuja occidentalis *root*).

Profile

Thuja consists of the fresh leaves and twigs of *Thuja occidentalis* (Cupressaceae). It is included in some topical preparations for warts and in herbal antiseptic preparations. It is also used in herbal preparations for respiratory-tract disorders.

The oil distilled from the leaves and twigs is known as thuja oil or cedar leaf oil. It has been included in preparations for inhalation for the relief of respiratory-tract symptoms and for external use but is generally considered to be too toxic for internal use. Cedar leaf oil should be distinguished from cedar wood oil, obtained from *Juniperus virginiana* (see p. 2472.3).

Homoeopathy

Thuja has been used in homoeopathic medicines under the following names: Thuja occidentalis; Thuja occ.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Thujaderm.

Multi-ingredient Preparations. ***Austral.***: Esberitox N; Vicks Vaporub; ***Austria***: Colda; Esberitox; Pe-Ce†; ***Belg.***: Aporil; Vicks Vaporub; ***Braz.***: Vick Vaporub; ***China***: Esberitox (施保利通); ***Fr.***: Nitrol†; Verrupan; Vicks Vaporub; ***Ger.***: Esberitox; ***Malaysia***: Esberitox N; ***Pol.***: Esberitox N; ***Port.***: Alpha Cade; Alphacedre; Erpecalm; ***S.Afr.***: Vicks Vaporub†; ***Spain***: Arkorespt†; Nitroina; ***Swed.***: Esberitox; ***Switz.***: Esberitop; Vicks Vaporub N; ***Turk.***: Kataljin; Vicks Vaporub; ***UK***: Fuerte; ***Ukr.***: Esberitox (Эсберитокс); ***USA***: Vicks Vaporub.

Homoeopathic Preparations. ***Austral.***: Echine†; ***Austria***: Echinacea-Cosmoplex; Gracil; Mandragora Med Complex; Sensicare; Spigelon; Thuja Med Complex; ***Canad.***: Acne; Adrisin†; Calnor†; Candida Yeast Relief; Cutisitum†; Detox L37; Earache; Echinacea Compositum; Formula CA 205†; Homeo-Form C†; Homeo-Form CA†; Homeo-Form SI†; Homeo-Form T†; Lympatox; Nixotinex; Rhinar†; Sinus Ease; Sinus; Sinuspax†; Sorinoheel; Spigelon†; Ubicoenzyme; War Complex†; ***Chile***: Allium Compuesto; Bioactiv Q; Formula II Especial; Fucus Especial; ***Cz.***: Galium; Ypsiloheel; ***Fr.***: Juniperus Complexe No 6; Pulviplasmine†; Rhododendron Complexe No 42†; Sabal Serrulata Compose; Santalum Complexe No 30†; Sinuspax; Thuya Complexe No 37; Urtica Complexe No 82†; Verrulia; ***Ger.***: Antimast TN†; Colchicum Complex; Entzundungstropfen; HanoFemin; Hanotoxin M; Hautfunktionstabletten N; Hautfunktionstropfen N; Hevertotox; Hewelymphon N†; Hewesoor N†; ISO-Augentropfen C; Jowidarmin; Juv 110; Lowe-Komplex Nr 5 Echinacea; Lymphaden; Muco-cyl L Ho-Len-Complex; Otofren; Pascoleucyn N; Pascoleucyn; Pflugerplex Lemna; Phonix Thuja-Lachesis spag; Prostata-Komplex N Ho-Fu-Complex†; Rapako comp; rheuma-loges; Rheuma-Pasc; Schleimhaut-Komplex L Ho-Fu-Complex; Sinuselect N; Sinusyx; Thuja N Oligoplex†; Thuja WA Oligoplex; Thujarell; Tondinel; Ulco-cyl L Ho-Len-Complex; Ypsiloheel N; ***Hung.***: Spigelon; ***Neth.***: Chavita 2; Chavita 5; Cutis comp; Habifac; Ricura; Thuyalite; ***Rus.***: Berberis Comp (Барбарис Комп); Mastopol (Мастопол); Phytolacca-Plus (Фитолакка-Плюс); Ruta-Plus (Рута-Плюс); ***Switz.***: Nelsons Sinusit†; Regenaplex Nr 28a; Regenaplex Nr. 31c; Spigelon.

Thymalfasin *(USAN, rINN)*

Thymalfasine; Thymalfasinum; Thymosin α1; Timalfasina; Тимальфазин.

CAS — 62304-98-7; 69521-94-4.

UNII — W0B22ISQ1C.

Profile

Thymalfasin is a thymus hormone (p. 2631.1) found in thymosin fraction 5 (a crude thymus gland extract) but now produced by synthesis. Thymalfasin is used alone or with interferon as an immunomodulator for the treatment of chronic hepatitis B and is given by subcutaneous injection in a dose of 1.6 mg twice weekly for 6 to 12 months. The dose in patients who weigh less than 40 kg is 40 micrograms/kg. It is used with interferon for hepatitis C (p. 952.1). Thymalfasin is also used for chemotherapy-induced immunosuppression, and to enhance the efficacy of influenza vaccines in immunocompromised or elderly patients and of influenza and hepatitis B vaccines in chronic haemodialysis patients.

Thymalfasin is under investigation for hepatitis D and HIV infection and AIDS.

References.

1. Garaci E, *et al.* Sequential chemoimmunotherapy for advanced non-small cell lung cancer using cisplatin, etoposide, thymosin-α 1 and interferon-α 2a. *Eur J Cancer* 1995; **31A:** 2403–5.
2. Rasi G, *et al.* Combination thymosin α_1 and lymphoblastoid interferon treatment in chronic hepatitis C. *Gut* 1996; **39:** 679–83.
3. Zavaglia C, *et al.* A pilot study of thymosin-α 1 therapy for chronic hepatitis D. *J Clin Gastroenterol* 1996; **23:** 162–3.
4. Andreone P, *et al.* A randomized controlled trial of thymosin-α_1 versus interferon alfa treatment in patients with hepatitis B e antigen antibody- and hepatitis B virus DNA-positive chronic hepatitis B. *Hepatology* 1996; **24:** 774–7.
5. Sherman KE, *et al.* Combination therapy with thymosin α 1 and interferon for the treatment of chronic hepatitis C infection: a randomized, placebo-controlled double-blind trial. *Hepatology* 1998; **27:** 1128–35.
6. Chien R-N, *et al.* Efficacy of thymosin α 1 in patients with chronic hepatitis B: a randomized, controlled trial. *Hepatology* 1998; **27:** 1383–7.
7. Rasi G, *et al.* Combined treatment with thymosin-α 1 and low dose interferon-α after dacarbazine in advanced melanoma. *Melanoma Res* 2000; **10:** 189–92.
8. Ancell CD, *et al.* Thymosin alpha-1. *Am J Health-Syst Pharm* 2001; **58:** 879–85.
9. Andreone P, *et al.* Thymosin-alpha 1 plus interferon-alpha for naive patients with chronic hepatitis C: results of a randomized controlled pilot trial. *J Viral Hepatitis* 2004; **11:** 69–73.
10. Sjogren MH. Thymalfasin: an immune system enhancer for the treatment of liver disease. *J Gastroenterol Hepatol* 2004; **19:** S69–S72.
11. Rustgi V. Combination therapy of thymalfasin (thymosin-alpha 1) and peginterferon alfa-2a in patients with chronic hepatitis C virus infection who are non-responders to standard treatment. *J Gastroenterol Hepatol* 2004; **19:** S76–S78.
12. Iino S, *et al.* The efficacy and safety of thymosin alpha-1 in Japanese patients with chronic hepatitis B; results from a randomized clinical trial. *J Viral Hepatitis* 2005; **12:** 300–306.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Zadaxin; ***China***: He Ri (和日); Ji Tai (基泰); Wan Yuan (万原); Xin Fu Tai (新状泰); Zadaxin (日达仙); ***Hong Kong***: Zadaxin; ***Indon.***: Zadaxin; ***Ital.***: Zadaxin; ***Malaysia***: Zadaxin; ***Mex.***: Zadaxin; ***Philipp.***: Zadaxin; ***Rus.***: Zadaxin (Задаксин); ***Singapore***: Zadaxin; ***Thai.***: Zadaxin.

Thyme

Common Thyme; Estremoncillo; French Thyme; Garden Thyme; Kakukkfű; Rubbed Thyme; Thym; Thymi Herba; Thymian; Timjami; Timjan; Timo; Tomello; Tomillo; Tremoncillo; Tymiánová vňať; Vaistinių čiobrelių žolė; Тимьян Обыкновенный (*Thymus vulgaris*); Ziele tymianku.

*ATC Herb — HR05WA5059 (*Thymus vulgaris*: herb); HA03AW5060 (*Thymus vulgaris*: herb); HA01WC5007 (*Thymus vulgaris*: herb).*

UNII — CW657OBU4N.

NOTE. Distinguish from Wild Thyme, p. 2648.1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Thyme). The whole leaves and flowers separated from the previously dried stems of *Thymus vulgaris*, or *T. zygis*, or a mixture of both species. It contains not less than 12 mL/kg of essential oil, of which a minimum of 40% is thymol and carvacrol, both calculated with reference to the anhydrous drug. It has a strong aromatic odour reminiscent of thymol.

Profile

Thyme is the source of thyme oil (below). It has carminative, antiseptic, antitussive, and expectorant properties and is used chiefly in preparations for respiratory-tract disorders and as a flavour.

General references.

1. WHO. Herba Thymi. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/28.html (accessed 05/02/10)
2. Basch E, *et al.* Thyme (*Thymus vulgaris* L.), thymol. *J Herb Pharmacother* 2004; **4:** 49–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Toularynx Thym; ***Ger.***: Aspecton; Biotuss†; Bronchipret; Expectysat T; Gelobronchial; Hustagil Thymian-Hustensaft; Hustagil Thymiantropfen; Isephca S†; Melrosum Hustensirup; Nimopect; Pertussin; Soledum Hustensaft; Soledum Hustentropfen; Tetesept Erkaltungs; Thymipin N†; Thymiverlan; Tussamag Hustenlosung†; Tussamag Hustensaft N†; Tussiflorin Thymian; ***Hung.***: Hustagil Cough; ***Israel***: Thymi Syrup; ***Pol.***: Bronchicum N; Bronchicum T; ***Rus.***: Bronchicum Husten (Бронхикум Пастилки от Кашля)†; Bronchicum S (Бронхикум С); Tussamag (Туссамаг); ***Switz.***: Thymusin N†; ***Ukr.***: Bronchostop (Бронхостоп).

Multi-ingredient Preparations. ***Arg.***: Cellskinlab Phyto Spot; Expectosan Hierbas y Miel; ***Austral.***: Broncafect; Euphorbia Complex†; HRF; ***Austria***: Bronchipret; Bronchithym†; Bronchostop; Brust- und Hustentee St Severin; Codelum†; Eicebaer; Hustensaft Weleda; Luuf-Hustentee; Pilka Forte; Pilka; Pneumopan†; Scottopect; Tussamag; Tussimont; ***Belg.***: Thymoseptine; ***Canad.***: Clear Capsules†; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; ***Chile***: Pectokast; Phyto Corrective Gel†; Phyto Spot; Rhus Opodeldoc; Timuss-Kit (sin azucar); Timuss-Kit; ***Cz.***: Biotussil; Bronchipret Tymian a Brect'an; Bronchipret Tymian a Prvosenka; Pleumolysin; Pulmoran; Thymomel; Urcyston Planta; ***Fin.***: Katapekt; ***Fr.***: Biofirm; Depuratum; Dida; Hepato-Solutines†; Mediflor Pectorale d'Alsace no 8†; Pectoflorine†; Santane O1; Saugella Antiseptic; Saugella Antiseptic; Saugella Antiseptic; Saugella Poligyn; Tisane Provencale no 5†; Tussidoron; ***Ger.***: Bronchicum Elixir; Bronchicum; Bronchipret; Bronchipret; Broncholitan; Brust- und Hustentee†; Cefabronchin; Cefadrin†; Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee; Drosithym-N†; Ephepect-Pastillen N; Equisil N†; Expectysat N; Kneipp Husten- und Bronchial-Tee†; Makatussin Tropfen; Melissengeist; Phytobronchin; Sinuforton†; Weleda Hustenelixier; ***Hung.***: Bronchicum; Bronchicum; Bronchicum; Bronchipret; Bronchipret; Gombarex; Herbalakt; Herpesil; ***Indon.***: Bronchipret†; Codipront cum Expectorant; Jesscool†; Pectum; Silex; Thymcal; ***Israel***: Pilka; ***Ital.***: Bron 6; Broncosed; Broncosedina; Broncosedina; Enatus; Immumil Plus†; Piodermina; Saugella Attiva; Saugella Fitothym; Saugella Poligyn; Tussol; ***Neth.***: Balsoclase Compositum†; Bronchicum; Verzachtende Hoestsiroop met tijm; ***Norw.***: Bronchosan†; ***Philipp.***: Bronchipret†; ***Pol.***: ApiHelix†; Bobodent; Bronchicum Eliksir†; Bronchosol; Dentosept A; Dentosept; Echinasal; Enterosol; Hedelicum; Herbapect; Mucosit; Neoazarina; Pectobonisol; Pectosol; PiniHelix; Salviasept; Saponarex; Septosan†; Tussipect; Tymsal; ***Rus.***: Bronchicum (Бронхикум)†; Bronchicum Husten (Бронхикум Сироп от Кашля)†; Bronchicum TP (Бронхикум ТП); Bronchipret (Бронхипрет); Bronchipret TP (Бронхипрет ТП); Codelac Broncho with Thymus Serpyllum (Коделак Бронхо с Чабрецом Обусловлено); Codelac Phyto (Коделак Фито); Eucabal (Эвкабал); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Passifit (Пассифит); Stomatophit (Стоматофит); Stoptussin-Fito (Стоптуссин-фито); ***S.Afr.***: Cough Elixir†; ***Singapore***: Arkopharma Propolis Spray; Stop Snoring; ***Spain***: Pilka; ***Swed.***: Alpenkraft; ***Switz.***: Bronchipret TP; Bronchosan; DemoPectol; Demo-Pectol; Elixir contre la toux†; Kernosan 26; Liberol Dragees contre la toux†; Liberol Pastilles contre la toux†; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Nican†; Pectoral N; Pilka; Sanotussin; Sirop pectoral; Strath Gouttes contre la toux; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; ***Thai.***: Solvopret TP†; Solvopret†; ***UK***: Bronchoforce Chesty Cough Ivy Complex; Herb and Honey Cough Elixir; ***Ukr.***: Bronchipret (Бронхипрет); Bronchipret TP (Бронхипрет ТП); Bronchostop (Бронхостоп); Bronchostop (Бронхостоп); Eucabal Syrup (Эвкабал Сироп); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Maraslavin (Мараславин); Pectolvan Phyto (Пектолван Фито); Pectoral (Пекторал); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Stoptussin Fito (Стоптуссин); Tussavit (Тусавит); ***Venez.***: Codebromil; Mixagel; T-Samag.

Homoeopathic Preparations. ***Austria***: Tonsan chronisch; ***Fr.***: Drosera Complexe No 64; ***UK***: Cough Elixir.

Thyme Oil

Esencia de Tomillo; Essência de Tomilho; Kakukkfűolaj; Kekik Yağı; Ol. Thym.; Olejek tymiankowy; Oleum Thymi; Thym, huile essentielle de; Thymi aetheroleum; Thymi Etheroleum; Thymianöl; Timjamiöljy; Timjanolja; Tomillo, aceite esencial de; Tymiánová silice; Vaistinių čiobrelių eterinis aliejus; Тимьяновое Масло.

*ATC Herb — HR05WA5058 (*Thymus vulgaris: *essential oil); HA03AW5059 (*Thymus vulgaris: *essential oil).*

UNII — 2UK410MY6B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8 (Thyme Oil, Thymol Type). The essential oil obtained by steam distillation from the fresh flowering aerial parts of *Thymus vulgaris, T. zygis*, or a mixture of both species. A clear, yellow or very dark reddish-brown, mobile liquid with an odour reminiscent of thymol. Miscible with dehydrated alcohol and with petroleum spirit. It contains between 36 and 55% of thymol. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Thyme oil is used similarly to thyme (above). It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Penaten; Thymian Erkaltungs-Bad.

Multi-ingredient Preparations. ***Arg.***: Cuassicum; ***Austral.***: Olive Leaf Plus; Throat-Clear; ***Austria***: Baby Luuf atherische Ole; Bronchostop†; Heumann's Bronchialtee; Luuf-Hustentee; Nasenol; Scottopect; ***Belg.***: Perubore†; ***Cz.***: Tussilen†; ***Fr.***: Balsofumine; Biogaze; Dolirhume; Gouttes aux Essences; Nazinette du Docteur Gilbert; Otylol; Perubore; ***Ger.***: Enelbin-Paste†; Erkaltungs Bad N†; Heumann Bronchialtee Solubifix T; Nasulind†; Pulmotin; Retterspitz Innerlich; Schnupfencreme; Tetesept Erkaltungs Bad; Weleda Nasenol; ***Gr.***: Ilon; Snufflebabe; ***Hung.***: Bronchovit; Carmol; Hustagil Anticold Cream; Pulminetta; ***Israel***: Gargol; ***Ital.***: Altuss; Calyptol; Fomentil; Naturocil; Valda Timo e Limone; Vegetallumina; ***Mon.***: Calyptol; ***NZ***: Efalex; Tixylix Chest Rub; ***Pol.***: Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Carmolis; Inhalol; Salviasept; ***Port.***: Erpecalm; Vaporil; ***Rus.***: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); ***S.Afr.***: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Oleum Rhinale Nasal Oil†; Zam-Buk; ***Spain***: H Tussan†; Termosan; ***Swed.***: Efalex; ***Switz.***: Demonatur Capsules contre les refroidissements; DUL-X warm; Echinarom; Eucapinol; Liberol N; Nasmer free; Nasobol Inhalo; Pulmex; Spagyrom; Wala Baume pectoral au plantain; ***Thai.***: St Luke's Oil; ***Turk.***: Algo-Wax; Mentoseptol; ***UK***: Efalex; Nine Rubbing Oils; Snowfire; Snufflebabe; ***USA***: Flexall; Maximum Strength Flexall 454; Unguentine.

Homoeopathic Preparations. ***UK***: Catarrh Cream.

Thymidine

NSC-21548; Thymine 2-Desoxyriboside; Timidina; Tymidyna; Тимидин.

1-(2-Deoxy-β-D-ribofuranosyl)-5-methyluracil; 1-(2-Deoxy-β-D-ribofuranosyl)-1,2,3,4-tetrahydro-5-methylpyrimidine-2,4-dione.

$C_{10}H_{14}N_2O_5$=242.2

CAS — 50-89-5.

UNII — VC2W18DGKR.

Profile

Thymidine is an endogenous thymine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). It was formerly given by intravenous infusion to modulate the toxicity of methotrexate but is not considered to be a substitute for calcium folinate; it may also have an antineoplastic action of its own.

Thymidine is given topically with other nucleosides in preparations for the treatment of corneal damage.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Vitacic†; ***Mon.***: Vitacic.

Thymus Hormones

Timo, hormonas del.

CAS — 69558-55-0 (thymopentin); 60529-76-2 (thymopoietin); 63340-72-7 (thymic humoral factor).

Profile

The thymus gland controls the development of T-lymphocytes and thereby plays a central role in cell-mediated immunity and the regulation of immune responses. Several polypeptides characterised in the thymus or serum are able to induce lymphocyte differentiation *in vitro* and *in vivo*. They include: thymosin fraction 5, a crude thymus gland extract; thymalfasin (p. 2630.1); thymosin beta 4; thymic humoral factor (THF), isolated from crude thymic extract dialysate; nonathymulin (thymulin, serum thymic factor, Facteur Thymique Serique, FTS), a synthetic nonapeptide; thymomodulin, a partially purified extract from calf thymus; thymogene A, extracted from calf thymus; thymopoietin, a polypeptide of known amino acid sequence; thymopentin (thymopoietin pentapeptide, TP-5), a fragment of thymopoietin with 5 amino acids; and thymostimulin (TP-1), extracted from calf thymus.

Various preparations, including crude extracts from calf thymus gland, thymomodulin, thymopentin, and thymostimulin have been tried as immunomodulators in many conditions including rheumatoid arthritis, diabetes mellitus, immunodeficiency disorders, skin disorders, malignant neoplasms, and some infections.

References.

1. Huff T, *et al.* β-Thymosins, small acidic peptides with multiple functions. *Int J Biochem Cell Biol* 2001; **33:** 205–20.
2. Hannappel E, Huff T. The thymosins—prothymosin alpha, parathymosin, and beta-thymosins: structure and function. *Vitam Horm* 2003; **66:** 257–96.
3. Goldstein AL, Badamchian M. Thymosins: chemistry and biological properties in health and disease. *Expert Opin Biol Ther* 2004; **4:** 559–73.
4. Chen C, *et al.* Roles of thymosins in cancers and other organ systems. *World J Surg* 2005; **29:** 264–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Leucotrofina; ***Austral.***: Thymunes†; ***Braz.***: Leucogen; ***China***: An Fa Bu (安珐布); HeXin (和信); Ou Ning (欧宁); Qimoxin (奇莫欣); Ti Bo Ding (替波定); Xin Luo Wei (欣洛维); ***Ger.***: Thym-Uvocal†; Thymoject†; Thymophysin†; ***Pol.***: TFX; ***Rus.***: Tactivin (Тактивин); Thymalin (Тималин).

Multi-ingredient Preparations. ***Austria***: Wobe-Mugos; ***Ger.***: Fega-Coren; NeyDesib Nr 78; ***Indon.***: Idesar Plus; ***Rus.***: Cytovir (Цитовир).

Homoeopathic Preparations. ***Ger.***: AntiFocal Nr 69-Sol L†; Conisan B†; Conjunctisan-BN†; Glandulae-F-Gastreu R20; Hepar comp; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; NeyChon Nr 68; NeyChondrin Nr 68-Sol†; NeyDil Nr 66†; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A; NeyIm Nr 73 pro injectione; NeyImmun Nr 73-Sol†; NeyLing Nr 66; NeyNormin Nr 65; NeySol L 66†; Neythymun†; NeyTroph Nr 96 oral†; NeyTroph Nr 96 pro injectione; NeyTroph Nr96-Sol†; Thymorell; ***Neth.***: Emvita 15.

Tiaprost Trometamol *(BANM, rINNM)*

Tiaprost Trométamol; Tiaprostum Trometamolum; Тиапрост Трометамол.

Trometamol salt of (±)-(*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*RS*)-3-hydroxy-4-(3-thienyloxy)but-1-enyl]cyclopentyl}hept-5-enoic acid.

$C_{20}H_{28}O_6S.C_4H_{11}NO_3$=517.6

CAS — 71116-82-0 (tiaprost).

Profile

Tiaprost trometamol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Tibezonium Iodide *(rINN)*

Ioduro de tibezonio; Rec-15/0691; Tibezonii Iodidum; Tibezonio, ioduro de; Tibézonium, Iodure de; Тибезония Йодид.

Diethylmethyl{2-[4-(4-phenylthiophenyl)-3*H*-1,5-benzodiazepin-2-ylthio]ethyl}ammonium iodide.

$C_{28}H_{32}IN_3S_2$=601.6

CAS — 54663-47-7.

ATC — A01AB15.

ATC Vet — QA01AB15.

UNII — E9P274AJEW.

Profile

Tibezonium iodide has been used in the treatment of infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Riposon; ***Ital.***: Antoral; ***Mex.***: Maxoral†; ***Port.***: Maxius.

Tilactase *(rINN)*

EC 3.2.1.23; β-D-Galactosidase; β-Galactosidase; β-D-Galactoside Galactohydrolase; Lactase; Tilactasa; Tilactasum; Тилактаза.

CAS — 9031-11-2.

ATC — A09AA04.

ATC Vet — QA09AA04.

Pharmacopoeias. In *Jpn* (from *Aspergillus oryzae* or *Penicillium multicolor*) and *US* (from *Aspergillus oryzae*).

USP 36: (Lactase). A hydrolytic enzyme derived from *Aspergillus oryzae*. Each g contains not less than 30 000 USP units. Store in airtight containers at room temperature.

Profile

Tilactase hydrolyses lactose into glucose and galactose. It has been added to milk and milk products, or taken orally with a meal containing dairy products, in order to prevent the symptoms of lactose intolerance (p. 2079.1) in persons deficient in the endogenous enzyme.

References.

1. Portincasa P, *et al.* Beneficial effects of oral tilactase on patients with hypolactasia. *Eur J Clin Invest* 2008; **38:** 835–44.
2. Ojetti V, *et al.* The effect of oral supplementation with *Lactobacillus reuteri* or tilactase in lactose intolerant patients: randomized trial. *Eur Rev Med Pharmacol Sci* 2010; **14:** 163–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lac-Tas; ***Canad.***: Dairy Free†; Dairyaid; Lactaid; Lacteeze; LactoMax; Lactrase†; Prolactase; Regular Strength Lactaid; ***Chile***: Diolasa; ***China***: Lactrase (力德士); ***Fr.***: Alvityl Digest; ***Ger.***: TilactaMed; ***India***: Galazyme-Pro; Lactes; ***Irl.***: Colief†; ***Ital.***: Lacdigest; Silact; ***Jpn***: Galantase; ***Mex.***: Enzylac Ultra; ***Philipp.***: Lactezeze; ***Pol.***: Lactosanol†; ***Port.***: Lisolac; ***Switz.***: Lacdigest; ***Turk.***: Lacdigest; ***UK***: Colief; ***Ukr.***: Mamalak (Мамалак); ***USA***: Dairy Ease; Lac-Dose; Lactaid; Lactrase; SureLac.

Multi-ingredient Preparations. ***Austral.***: Vegie Digestaid; ***Canad.***: Digesta; Synergy Defense; ***Chile***: Lactomol-D; ***India***: Leno-EZ; ***Ital.***: No Gas Enzimi; ***Malaysia***: Lacto Care; ***Singapore***: Dairy Care; ***USA***: Similase Jr.

Tilarginine *(rINN)*

546C88; BW-546C88; L-NMMA; Targinina; Targinine (BAN); Targininum; Tilarginina; Tilargininum; Таргинин.

N^{ω}-Methyl-L-arginine.

$C_7H_{16}N_4O_2$=188.2

CAS — 17035-90-4.

UNII — 27JT06E6GR.

Profile

Tilarginine is a nitric oxide synthase inhibitor under investigation in the treatment of cardiogenic shock, although results have been disappointing. It has also been tried in septic shock but appears to have been associated with increased mortality. It has also been investigated in migraine.

References.

1. Lassen LH, *et al.* The effect of nitric oxide synthase inhibition on histamine induced headache and arterial dilatation in migraineurs. *Cephalalgia* 2003; **23:** 877–86.
2. Bakker J, *et al.* Administration of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit Care Med* 2004; **32:** 1–12.
3. Watson D, *et al.* Cardiovascular effects of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) in patients with septic shock: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit Care Med* 2004; **32:** 13–20.
4. Lopez A, *et al.* Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; **32:** 21–30.
5. Alexander JH, *et al.* TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA* 2007; **297:** 1657–66.
6. Howes LG, Brillante DG. Expert opinion on tilarginine in the treatment of shock. *Expert Opin Invest Drugs* 2008; **17:** 1573–80.

Tilia

Hársfavirág; Kwiatostan lipy; Lehmuksenkukka; Liepų žiedai; Lime Flower; Lindblomma; Linden; Lipový květ; Tiliae Flos; Tilleul; Tilleul, fleur de; Tilo; Липовый Цвет.

*ATC Herb — HR05YA5027 (*Tilia cordata*: flower); HN02CW5007 (*Tilia platyphyllos*: flower); HN02CW5006 (*Tilia cordata*: flower); HR05YA5028 (*Tilia platyphyllos*: flower).*

*UNII — CFN6G1F6YK (*Tilia cordata *flower); 1R02M833TN (*Tilia platyphyllos *flower).*

Pharmacopoeias. *Eur.* (see p. vii) includes the flowers.

Fr. also includes the bark.

Ph. Eur. 8: (Lime Flower). The whole dried inflorescences of *Tilia cordata, Tilia platyphyllos, Tilia X vulgaris* (=[*Tilia X europaea*]), or a mixture of these species. It has a faint aromatic odour. Protect from light.

Profile

Tilia is mildly astringent and is reputed to have antispasmodic and diaphoretic properties. Lime-flower 'tea' is a traditional domestic remedy.

Various species of tilia are used in herbal preparations for a variety of disorders.

Homoeopathy

Tilia has been used in homoeopathic medicines under the following names: Tilia europaea; Til. euro.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Vibtil; ***Cz.***: Lipovy; ***Mon.***: Vibtil; ***Pol.***: Lipomal.

Multi-ingredient Preparations. ***Arg.***: Armonil; Incaico Serenidad; Maprosol Gel; Nervocalm; Phytocalm; Sedanat†; Sedante Dia; Serenil; Valeriana Compuesta; ***Austral.***: Aloe Vera Gel; DiaCo; ***Austria***: Grippetee St Severin; St Bonifatius-Tee†; ***Belg.***: Natudor; ***Canad.***: Calmane; Calmane; Detente†; Formula T13 Tea†; Nervinat; Relax Plus; Relaxant; Relaxol; Swiss Herb Cough Drops; ***Chile***: Bebe Son; Calmatol; Nature Complex Reduct-Te; Recalm†; Reduc-Te; ***Cz.***: Cajova Smes pri Nachlazeni; Pruduskova; ***Fr.***: Aromazen†; Azema†; Boribel Tisane No 8†; Lenicalm†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Provencale No 4†; Santane N_o; Tisane Provencale no 4†; Vigilia†; ***Israel***: Jungborn†; ***Ital.***: Alkagin; Ginepausil; Lenicalm; Saniquiet; Tussol; ***Pol.***: Bronchial†; DexaCaps; Fitoven; Melisal; Melissed; Pectobonisol; Pyrosal; Termasil; Tiliros; ***Port.***: Alkagin; Alkagin; Alkagin; ***Spain***: Agua del Carmen; ***Swed.***: Alpenkraft; ***Switz.***: Tisane contre les refroidissements; Tisane pour nourissons et enfants; ***Turk.***: Alkagin; ***UK***: Menopause Relief; Wellwoman; ***Ukr.***: Klimased (Климасед).

Homoeopathic Preparations. ***Chile***: Melinerv; TBR/X; ***Fr.***: Poconeol no 35.

Timonacic *(rINN)*

ATC; NSC-25855; Thioproline; Timonácico; Timonacicum; Тимонацик.

Thiazolidine-4-carboxylic acid.

$C_4H_7NO_2S$=133.2

CAS — 444-27-9.

UNII — E5913T3IBL.

NOTE. The name ATC has also been used for a combination of paracetamol and trichloroethanol (4-acetamidophenyl 2,2,2-trichloroethyl carbonate).

Profile

Timonacic is used as an adjuvant in the treatment of acute and chronic hepatic disorders.

Timonacic methyl hydrochloride (carbolidine hydrochloride) has been used as a mucolytic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Hepacom†; Heparegen.

Tin

Cyna; Estaño; Étain; Stannum; Zinn; Олово.
Sn=118.71
CAS — 7440-31-5.
UNII — 387GMG9FH5 (tin); QI30938BMS (tin ion).

Profile

Tin is a silver-white, lustrous, malleable, ductile metal. Owing to their low solubility, tin and tin oxide are very poorly absorbed from the gastrointestinal tract and have low toxicity. Chronic inhalation causes a benign form of pneumoconiosis.

Organic compounds of tin are highly toxic and may cause liver and kidney damage as well as severe neurological damage associated with oedema of the white matter of the brain. Treatment has been symptomatic. Contamination of the skin with organic tin compounds can cause severe burning; suitable precautions should be taken to prevent absorption of organic tin compounds through the skin.

Tin and tin oxide have been given in the treatment of boils, but there is little evidence of efficacy; they were also formerly used in some countries for the treatment of tapeworm. Organic tin compounds, especially tributyltin oxide (TBTO), are used as molluscicides.

Tin in food. Excess amounts of inorganic tin in food tend to arise from tin-coated cans, especially unlacquered ones, and may produce gastric irritation. Concentrations as low as 150 mg/kg in canned beverages and 250 mg/kg in other canned foods have produced adverse effects in certain individuals, but some foods containing up to 700 mg/kg have not produced any detectable effects. Consumers should be advised not to store foods in opened tinplated cans.[1]

A recommended acceptable daily intake for chronic exposure to tin has been suggested as a provisional tolerable weekly intake of 14 mg/kg, although it was subsequently noted that this value may have been derived from intakes associated with acute effects, and it was concluded that the toxicokinetics and effects of inorganic tin after long-term exposure to dietary doses at concentrations that did not elicit acute effects should be re-assessed.[1] It was also concluded that it was inappropriate to establish an acute reference dose for inorganic tin, since development of gastric irritation depends on the concentration and nature of tin in the food product rather than on the dose ingested on a body-weight basis.[1] In the EU regulations limit the maximum amount of tin in foods sold in member states to wet weights of 200 mg/kg in canned foods other than beverages, 100 mg/kg in canned beverages including fruit and vegetable juices, and 50 mg/kg in various canned foods for infants.[2]

1. FAO/WHO. Evaluation of certain food contaminants: sixty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 930* 2006. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_930_eng.pdf (accessed 22/07/08)
2. The Commission of the European Communities. Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. *Off J EU* 2006; **49:** L364/5–24. Also available at: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_364/l_36420061220en00050024.pdf (accessed 22/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***S.Afr.***: Metinox†.

Homoeopathic Preparations. ***Austral.***: Hangover Relief; Respatona Chesty Cough & Nasal Congestion; ***Canad.***: Kids Cough & Cold Phytux; Phytotux H; ***Fr.***: Abbe Chaupitre no 1†; Kreosotum Complexe No 62; Pulmo-Drainol†; ***Ger.***: Derivatio H; Derivatio; Rufebran heparo†; ***Hung.***: Klimakt-Heel; ***Switz.***: metaossylen N.

Pharmacopoeial Preparations
USP 36: Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets.

Tin-protoporphyrin

Protoporfirina-Estaño; (Sn)-protoporphyrin; Олово-протопорфирин.

Profile

Tin-protoporphyrin and the related compound tin-mesoporphyrin are metalloporphyrins which inhibit haem oxygenase, an enzyme involved in the breakdown of haem to bile pigments. They have been investigated as inhibitors of bilirubin production in hyperbilirubinaemia of various causes, and have been tried in porphyria (p. 1556.1).

References.

1. Valaes T, *et al.* Control of hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns using an inhibitor of bilirubin production, Sn-mesoporphyrin. Abstract: *Pediatrics* 1998; **101:** 915. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/5/e1 (accessed 09/07/04)
2. Martinez JC, *et al.* Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Pediatrics* 1999; **103:** 1–5.
3. Kappas A, *et al.* A single dose of Sn-mesoporphyrin prevents development of severe hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns. *Pediatrics* 2001; **108:** 25–30.
4. Kappas A, *et al.* Sn-mesoporphyrin interdiction of severe hyperbilirubinemia in Jehovah's Witness newborns as an alternative to exchange transfusion. *Pediatrics* 2001; **108:** 1374–7.
5. Kappas A. A method for interdicting the development of severe jaundice in newborns by inhibiting the production of bilirubin. *Pediatrics* 2004; **113:** 119–23.
6. Drummond GS, Kappas A. Chemoprevention of severe neonatal hyperbilirubinemia. *Semin Perinatol* 2004; **28:** 365–8.
7. Dennery PA. Metalloporphyrins for the treatment of neonatal jaundice. *Curr Opin Pediatr* 2005; **17:** 167–9.

Tiropramide Hydrochloride *(rINNM)*

Hidrocloruro de tiropramida; Tiropramida, hidrocloruro de; Tiropramide, Chlorhydrate de; Tiropramidi Hydrochloridum; Тиропрамида Гидрохлорид.
DL-α-Benzamido-*p*-[2-(diethylamino)ethoxy]-*N*,*N*-dipropylhydrocinnamamide hydrochloride.
$C_{28}H_{41}N_3O_3$,HCl=504.1
CAS — 55837-29-1 (tiropramide); 57227-16-4 (tiropramide hydrochloride).
ATC — A03AC05.
ATC Vet — QA03AC05.
UNII — 9523013Y6R.

Profile

Tiropramide hydrochloride is used as an antispasmodic. Doses of 100 mg 2 or 3 times daily or 200 mg twice daily have been given orally. It has also been given rectally and parenterally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Alfospas; Maiorad†; ***Philipp.***: Triopan; ***Port.***: Maiorad; ***Thai.***: Maiorad.

Titanium

Titan; Titane; Titanio; Титан; Титан.
Ti=47.867
CAS — 7440-32-6.
UNII — D1JT611TNE.

Profile

Titanium has been used in the repair of skull damage and for implantation in dental surgery.

References.

1. Brown D. All you wanted to know about titanium, but were afraid to ask. *Br Dent J* 1997; **182:** 393–4.
2. Williams D. The golden anniversary of titanium biomaterials. *Med Device Technol* 2001; **12:** 8–11.
3. Sicilia A, *et al.* Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin Oral Implants Res* 2008; **19:** 823–35.
4. Ohkubo C, *et al.* Present status of titanium removable dentures—a review of the literature. *J Oral Rehabil* 2008; **35:** 706–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Minesol.

Tobacco

Cultivated Tobacco; Nicotiane; Tabac; Tabac Commun; Tabaco; Tabacum; Tabak; Tobak; Virginiantupakka; Virginiatobak; Virginischer Tabak; Virginsk Tobak; Yan Cao; Табак; Тютюн.
UNII — 6DI1HBV20R (Nicotiana tabacum); 6YR2608RSU (Nicotiana tabacum leaf).

Profile

Tobacco is the prepared and cured leaves of *Nicotiana tabacum* (Solanaceae) and related species. Tobacco was formerly used medicinally, but now is most commonly used as a recreational drug, typically by smoking, chewing, or as snuff. Although tar and other products of combustion contribute to the adverse effects of smoking, the physiological and addictive properties of tobacco products derive from the content of the alkaloid nicotine; for discussion of the effects of tobacco use, see under Nicotine, p. 2569.3.

Homoeopathy

Tobacco is also used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Austral.***: Smoke Eze; Travellers Relief; ***Austria***: Katerex; Travelex; ***Canad.***: Ateria-Heel†; Cocculine; Formula TA 220†; Homeo-Form T†; Hylands Motion Sickness; Nixotinex; ***Cz.***: Cocculine; ***Fr.***: Cocculine; Dolitravel†; Homeogene 21†; Nausetum; Tabacum Compose; Tabapass; ***Ger.***: Aconitum Nicotiana comp†; Arte-cyl Ho-Len-Complex; metabiarex; metaginkgo†; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Procordal vertigo; Tabarell; Vasa-Gastreu N R63; Vertigo Hevert SL; ***Hung.***: Cocculine; ***Neth.***: Cocculine; Gletar; Gravifem†; Travelin; ***Port.***: Cocculine; ***Rus.***: Cocculine (Коккулин); Tabacum-Plus (Табакум-Плюс); Tonginal (Тонгинал); ***Switz.***: Cocculine; metaginkgo; Nelsons Travella†; ***UK***: Travella; ***Ukr.***: Tonginal (Тонгинал).

Tolonium Chloride *(rINN)*

CI Basic Blue 17; Cloruro de tolonio; Colour Index No. 52040; Tolonii Chloridum; Tolonio, cloruro de; Tolonium, Chlorure de; Toluidine Blue O; Толония Хлорид.
3-Amino-7-dimethylamino-2-methylphenazathionium chloride.
$C_{15}H_{16}ClN_3S$=305.8
CAS — 92-31-9.
UNII — 15XUH0X66N.

NOTE. Distinguish from Toluidine Blue, Colour Index No. 63340.

Profile

Tolonium chloride is a thiazine dye chemically related to methylthioninium chloride (p. 1559.1). It has been used to stain oral and gastric neoplasms and was given intravenously to stain the parathyroid glands. Other uses have included the treatment of menstrual disorders and methaemoglobinaemia.

Tolonium chloride should be avoided in patients with G6PD deficiency as haemolysis may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Toluidinblau; ***Ger.***: Toluidinblau; ***Gr.***: Orascreen; OraTest; ***Neth.***: OraTest†; ***NZ***: Orascreen; ***Port.***: OraTest.

Tolvaptan *(BAN, USAN, rINN)* ⊗

OPC-41061; Tolvaptán; Tolvaptanum; Толваптан.
(±)-4′-[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-*o*-tolu-*m*-toluidide.
$C_{26}H_{25}ClN_2O_3$=448.9
CAS — 150683-30-0.
ATC — C03XA01.
ATC Vet — QC03XA01.
UNII — 21G72T1950.

Uses and Administration

Tolvaptan is a selective vasopressin V_2-receptor antagonist used to treat euvolaemic and hypervolaemic hyponatraemia (p. 1778.1) including that in heart failure and syndrome of inappropriate antidiuretic hormone secretion. Tolvaptan therapy should be started in hospital.

Tolvaptan is given orally in a single daily dose of 15 mg, which may be increased after at least 24 hours to 30 mg. The dose should be adjusted up to a maximum of 60 mg once daily to achieve the desired serum-sodium concentrations. US licensed product information recommends that treatment should be continued for no longer than 30 days (see Adverse Effects and Precautions, p. 2633.1). Patients should be monitored for changes in serum electrolytes and volume during the initiation and titration phase especially those at high risk of demyelination syndromes such as patients with hypoxia, alcoholism, malnutrition, or a very low serum sodium at baseline. Fluid restriction should be avoided during the first 24 hours of therapy, and patients should be instructed to drink fluids in response to thirst. If a rapid rise in serum-sodium occurs (more than 12 mmol/litre

in 24 hours) tolvaptan should be stopped, and serum-sodium and neurological status should be carefully monitored because of the risk of osmotic demyelination syndrome; hypotonic fluid should be considered in patients whose serum-sodium rises too rapidly. If hypovolaemia develops, tolvaptan therapy should be interrupted or stopped and volume status and vital signs monitored with supportive care as required. At the end of tolvaptan therapy, patients should resume fluid restriction and be monitored for changes in serum-sodium and volume status.

Adjustment of tolvaptan doses or monitoring of potassium concentrations may be required when tolvaptan is given with some other drugs—see Interactions below.

References.
1. Plosker GL. Tolvaptan. *Drugs* 2010; **70:** 443–54.
2. Cyr PL, *et al.* Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure. *Am J Health-Syst Pharm* 2011; **68:** 328–33.
3. Amin A, Meeran K. New drugs for hyponatraemia: evidence is lacking that they are better than cheaper standard treatment. *BMJ* 2011; **342:** 559–60.
4. Peri A. The use of vaptans in clinical endocrinology. *J Clin Endocrinol Metab* 2013; **98:** 1321–32.

Cystinuria. Tolvaptan 15 mg orally, once daily for 5 days substantially increased urine output in 2 patients with homozygous cystinuria.[1] This resulted in urinary cystine concentrations below the level at which cystine stone formation could occur, suggesting that tolvaptan may be useful to prevent formation of new stones and help to dissolve existing ones.

1. de Boer H, *et al.* Antidiuretic hormone antagonist to reduce cystine stone formation. *Ann Intern Med* 2012; **157:** 459–60.

Polycystic kidney disease. In a study in patients with autosomal dominant polycystic kidney disease treatment with tolvaptan slowed the rate of increase in kidney volume and the decline in renal function compared with placebo over a 3-year period.[1]

1. Torres VE, *et al.* TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367:** 2407–18.

Adverse Effects and Precautions

The most common adverse effects of tolvaptan are thirst, dry mouth, asthenia, nausea, constipation, hyperglycaemia, and pollakiuria or polyuria. Water loss may be excessive and dehydration and hypovolaemia can occur.

Tolvaptan is contra-indicated in hypovolaemic hyponatraemia, in patients who require a rapid increase in serum-sodium concentrations, and in those who cannot sense or who respond inappropriately to thirst. Rapid correction of serum-sodium concentrations with tolvaptan could increase the risk of osmotic demyelination syndrome. Tolvaptan is ineffective and therefore inappropriate to use in anuric patients. Tolvaptan can cause serious and potentially fatal liver injury and it should be stopped if symptoms suggesting liver injury occur. US licensed product information recommends that treatment with tolvaptan is limited to a maximum of 30 days to reduce the risk of liver injury; it also states that tolvaptan should be avoided in patients with underlying liver disease including cirrhosis.

Interactions

As a substrate of the cytochrome P450 isoenzyme CYP3A4, concentrations of tolvaptan can be increased by CYP3A4 inhibitors. The use of tolvaptan with potent CYP3A4 inhibitors such as clarithromycin, ketoconazole, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin is contra-indicated. Use of tolvaptan with moderate CYP3A4 inhibitors such as aprepitant, diltiazem, erythromycin, fluconazole, and verapamil should also be avoided on theoretical grounds that an increase in tolvaptan concentrations would also be expected.

Rifampicin is a CYP3A4 inducer and significantly reduces tolvaptan concentrations. It is expected that other CYP3A4 inducers such as rifabutin, rifapentine, barbiturates, carbamazepine, phenytoin, and St John's Wort would have the same effect. Therefore concomitant use of tolvaptan with CYP3A4 inducers should be avoided where possible.

Ciclosporin or grapefruit juice may increase tolvaptan concentrations.

For the effect of tolvaptan on digoxin, see p. 1358.1.

Hyperkalaemia has been reported in patients taking tolvaptan at the same time as angiotensin II receptor antagonists, ACE inhibitors, or potassium sparing diuretics. Monitoring of potassium concentrations is recommended when any of these drugs are given with tolvaptan.

Pharmacokinetics

Peak concentrations of tolvaptan occur about 2 to 4 hours after oral doses. It is metabolised mainly, if not exclusively, by the cytochrome P450 isoenzyme CYP3A4, and is highly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Samsca; ***Cz.***: Samsca; ***Denm.***: Samsca; ***Ger.***: Samsca; ***Irl.***: Samsca; ***Jpn***: Samsca; ***Neth.***: Samsca; ***Norw.***: Samsca; ***Pol.***: Samsca; ***Port.***: Samsca; ***Spain***: Samsca; ***Swed.***: Samsca; ***UK***: Samsca; ***USA***: Samsca.

Tormentil

Blodrot; Consolda Vermelha; Consuelda roja; Erect Cinquefoil; Miškinių sidabražolių šakniastiebiai; Nátržníkový oddenek; Rätvänänjuurakko; Sietenrama; Tormentilla; Tormentillae rhizoma; Tormentille; Tormentillwurzelstock; Véronfűgyökértörzs; Калган (*Potentilla erecta*); Лапчатка Прямостоячая (*Potentilla erecta*).

UNII — BI896CKT6B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tormentil). The whole or cut, dried rhizome, freed from the roots, of *Potentilla erecta* (*P. tormentilla*). It contains not less than 7% of tannins expressed as pyrogallol, calculated with reference to the dried drug. Protect from light.

Profile

Tormentil has astringent properties and is used in herbal preparations for diarrhoea and other indications. Gastrointestinal irritation and vomiting have occasionally occurred.

References.
1. Subbotina MD, *et al.* Effect of oral administration of tormentil root extract (Potentilla tormentilla) on rotavirus diarrhea in children: a randomized, double blind, controlled trial. *Pediatr Infect Dis J* 2003; **22:** 706–11.
2. Huber R, *et al.* Tormentil for active ulcerative colitis: a n open-label, dose-escalating study. *J Clin Gastroenterol* 2007; **41:** 834–8.
3. Tomczyk M, Latté KP. Potentilla—a review of its phytochemical and pharmacological profile. *J Ethnopharmacol* 2009; **122:** 184–204.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Switz.***: Tormentasan†.

Multi-ingredient Preparations. ***Cz.***: Dr Theiss Schwedenbitter†; Herbadent; Original Schwedenbitter; Tormentan; ***Ger.***: Repha-Os†; ***Hung.***: Bano Svedkeseru; Travelon; ***Pol.***: Hemorol; Neo-Tormentil; Stomatosol; Tobacoff; Tormentile Forte; Tormentiol; ***Rus.***: Fitantis (Фитантис); Linkus (Линкас); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***Switz.***: Baume Zeller; Pommade au Baume; ***Ukr.***: Linkus (Линкас); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Homoeopathic Preparations. ***Switz.***: Diarrheel S.

Pharmacopoeial Preparations
Ph. Eur.: Tormentil Tincture.

Transfer Factor

Transferencia, factor de; Трансферный Фактор.

Profile

Transfer factor is a peptide constituent of dialysable leucocyte extracts prepared from the leucocytes of a sensitised donor, that can passively transfer cell-mediated immunity to a non-sensitised recipient.

Transfer factor has been suggested for use in infections due to bacteria, fungi, and viruses, inflammatory disorders, skin disorders such as eczema, nervous system disorders, immunodeficiency diseases, and malignancies, although the response when it has been tried in some of these conditions has not always been satisfactory.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Gan Sheng Su (肝生素); JinGanTai (金甘泰); Oligotide (奥肝肽); Tai Lai Tai (泰来肽); YiKangNing (亿康宁); ***Cz.***: Imunor.

Transforming Growth Factor Antibodies

Антитела к Трансформирующему Фактору Роста.

Profile

A human monoclonal antibody specific for transforming growth factor β1 is under investigation for the treatment of systemic sclerosis.

Lerdelimumab (p. 2544.1) is a human monoclonal antibody specific for transforming growth factor β2.

Trepibutone *(rINN)*

AA-149; Trepibutona; Trépibutone; Trepibutonum; Trepionate; Трепибутон.

3-(2,4,5-Triethoxybenzoyl)propionic acid.

$C_{16}H_{22}O_6$=310.3

CAS — 41826-92-0.

ATC — A03AX09.

ATC Vet — QA03AX09.

UNII — H1187LU49Q.

Pharmacopoeias. In *Jpn.*

Profile

Trepibutone has been reported to have spasmolytic and choleretic activity and has been used in biliary-tract disorders and pancreatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Choliatron.

Tribenoside *(BAN, USAN, rINN)*

21401-Ba; Ba-21401; Tribenosid; Tribénoside; Tribenosidi; Tribenósido; Tribenosidum; Tribenozid; Tribenozidas; Трибенозид.

Ethyl 3,5,6-tri-*O*-benzyl-D-glucofuranoside.

$C_{29}H_{34}O_6$=478.6

CAS — 10310-32-4.

ATC — C05AX05; C05CX01.

ATC Vet — QC05AX05; QC05CX01.

UNII — Z7N0Y673NU.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tribenoside). A yellowish to pale yellow, clear, viscous liquid. Practically insoluble in water; very soluble in acetone, in dichloromethane, and in methyl alcohol. Store under nitrogen in airtight containers.

Profile

Tribenoside has been used in inflammatory and varicose disorders of the veins, including haemorrhoids (p. 1808.1). It has been given orally in usual doses of 800 mg daily. It has also been given rectally and topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Glyvenol; ***Cz.***: Glyvenol; ***Gr.***: Glyvenol; ***Mex.***: Glyvenol; ***Philipp.***: Glyvenol; ***Rus.***: Glyvenol (Гливенол); ***Venez.***: Glyvenol.

Multi-ingredient Preparations. ***Arg.***: Procto-Glyvenol; ***Braz.***: Procto-Glyvenol; ***Chile***: Euproct; Procto-Glyvenol; Proctogel; ***Cz.***: Procto-Glyvenol; ***Gr.***: Procto-Glyvenol; ***Israel***: Procto-Glyvenol; ***Mex.***: Procto-Glyvenol; ***Philipp.***: Procto-Glyvenol; ***Pol.***: Procto-Glyvenol; Procto-Hemolan; Venozel; ***Port.***: Procto-Glyvenol; ***Rus.***: Procto-Glyvenol (Прокто-Гливенол); ***Switz.***: Procto-Glyvenol; ***Turk.***: Procto-Glyvenol; ***UAE***: Haemoproct; ***Ukr.***: Procto-Glyvenol (Прокто-Гливенол); ***Venez.***: Bargonil; Procto-Glyvenol.

Tribulus Terrestris ⊗

Caltrp.; Gokhru; Jili; Puncture Vine; Punctureviné; Tribulus; Якорцы Стелющиеся (*Tribulus terrestris*).

*UNII — 4X4HLN92OT (*Tribulus terrestris*); 8JMX062MNR (*Tribulus terrestris *flower); QNL076V6EQ (*Tribulus terrestris *fruit); 6WY8ROM74K (*Tribulus terrestris *root).*

Pharmacopoeias. In *Chin.* and *Jpn*, which specify the fruit.

Profile

The fruit, flowers, and root of *Tribulus terrestris* (Zygophyllaceae) are used in herbal medicine for many different purposes, including the treatment of urinary stones and other urinary disorders, for digestive disorders, for male sexual disorders, and as a diuretic and an aphrodisiac.

The fruit is also used in Ayurvedic and traditional Chinese medicine.

It is included in dietary supplements and tonics, and has been taken by athletes for its reported anabolic effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Androsten; ***Indon.***: Tribestan; ***Rus.***: Tribestan (Трибестан); ***Singapore***: Tribestan; ***Ukr.***: Tribestan (Трибестан).

Multi-ingredient Preparations. ***Austral.***: Enhance for Men; Femi-Nan; Mens Performance Multi; The Blue One†; Tribulus & Epi-

medium Compound; ***Canad.***: Libeeda for Men; Libeeda for Women; ***Hung.***: Munipyrin; ***India***: Addyzoa; Alka; Benprost-B; Bonnisan; Calcury; Confido; Cystone; Diabecon; Distone; Femi Forte; Femiplex; Flush; Flush; Galakol; Geriforte; Gynodex; Gynoset; Himplasia; Kof-Rid; Lactare; Laforte; Manix; Manoll; Mustong; Neeri; Nefid; Pallrywyn Forte; ***Indon.***: Bioretin†; Instink†; Maxirex; Reximax; Sirec; Tetris; Tristan†; ***Ital.***: Cistefi; ***Jpn***: Tokiinshi; ***Malaysia***: Bonnisan; Rumalaya; ***Philipp.***: Cogent db+; ***Rus.***: Fitovit (Фитовит); Speman (Спеман); Speman Forte (Спеман Форте); Verona (Верона); ***Singapore***: Andromet; Cystone; Tentex Royal; ***Ukr.***: Andropower (Андропауэр); Bon-Apetit (Бон-Аппетит); Confido (Конфидо)†; Fitovit (Фитовит); Imunin (Иммунин)†; Speman (Спеман); Verona (Верона).

Trichophyton Antigen

Trichophytin.

Profile

Preparations containing antigens extracted from *Trichophyton* spp. (a cause of fungal skin infections) have been used to assess cell-mediated immunity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Multitest CMI†; ***Gr.***: Multitest.

Trilostane *(BAN, USAN, pINN)*

Trilostaani; Trilostan; Trilostano; Trilostanum; Win-24540; Трилостан.

4α,5α-Epoxy-17β-hydroxy-3-oxoandrostane-2α-carbonitrile.

$C_{20}H_{27}NO_3$=329.4

CAS — 13647-35-3.

ATC — H02CA01.

ATC Vet — QH02CA01.

UNII — L0FPV48Q5R.

Uses and Administration

Trilostane is an adrenocortical suppressant that inhibits the enzyme system essential for the production of glucocorticoids and mineralocorticoids. It is used for the treatment of adrenal cortical hyperfunction such as Cushing's syndrome and primary hyperaldosteronism. It is also used in postmenopausal breast cancer that has relapsed after oestrogen antagonist therapy.

The usual daily dose in adrenal cortical hyperfunction is 240 mg orally in divided doses for at least 3 days and then adjusted, according to response, within the range of 120 to 480 mg daily. Doses of 960 mg daily have been given.

In postmenopausal breast cancer an initial daily dose of 240 mg is given orally in divided doses, with glucocorticoid replacement therapy. This is increased in steps of 240 mg every 3 days up to a maintenance dose of 960 mg daily; this may be reduced to 720 mg daily if adverse effects are intolerable.

Adverse Effects

Adverse effects associated with trilostane have included flushing, nausea, vomiting, diarrhoea, rhinorrhoea, and tingling and swelling of the mouth. Rashes may occur and, rarely, granulocytopenia in immunocompromised patients.

Precautions

Trilostane is contra-indicated in pregnancy and should be used with caution in patients with renal or hepatic impairment. Circulating corticosteroids and blood electrolytes should be monitored. In some patients, supplementation with corticosteroids may be necessary.

Interactions

Trilostane may interfere with the activity of oral contraceptives. Hyperkalaemia may occur if trilostane is given with potassium-sparing diuretics or aldosterone antagonists.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Desopan; ***UK***: Modrenal†.

Trimebutine Maleate *(BANM, rINNM)*

Maleato de trimebutina; Trimebutin Maleat; Trimebutina, maleato de; Trimébutine, maléate de; Trimebutini Maleas; Тримебутина Малеат.

2-Dimethylamino-2-phenylbutyl 3,4,5-trimethoxybenzoate hydrogen maleate.

$C_{22}H_{29}NO_5.C_4H_4O_4$=503.5

CAS — 39133-31-8 (trimebutine); 34140-59-5 (trimebutine maleate).

ATC — A03AA05.

ATC Vet — QA03AA05.

UNII — 2A051GM4YM.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Trimebutine Maleate). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in acetone; soluble in acetonitrile.

Profile

Trimebutine maleate has been used as an antispasmodic in gastrointestinal disorders in oral doses of up to 600 mg daily in divided doses. It has also been given by injection and rectally. Trimebutine base has also been used.

Irritable bowel syndrome. Trimebutine has been reported[1-3] to be effective in the treatment of irritable bowel syndrome (p. 1810.3) although a considerable placebo response has been seen.[1] Its action is thought to be mediated both via gastrointestinal opioid receptors and modulation of the release of gastrointestinal peptides.[4]

1. Ghidini O, *et al.* Single drug treatment for irritable colon: rociverine versus trimebutine maleate. *Curr Ther Res* 1986; **39:** 541–8.
2. Schaffstein W, *et al.* Comparative safety and efficacy of trimebutine versus mebeverine in the treatment of irritable bowel syndrome. *Curr Ther Res* 1990; **47:** 136–45.
3. Kountouras J, *et al.* Efficacy of trimebutine therapy in patients with gastroesophageal reflux disease and irritable bowel syndrome. *Hepatogastroenterology* 2002; **49:** 193–7.
4. Delvaux M, Wingate D. Trimebutine: mechanism of action, effects on gastrointestinal function and clinical results. *J Int Med Res* 1997; **25:** 225–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Altrip; Biorgan; Colixane; Debridat; Eumotil; Fenatrop; Miopropan; Plidex T; Plidex; Tributina†; ***Braz.***: Digedrat; ***Canad.***: Modulon; ***Chile***: Debridat; Dolpic Forte; Tidomel; Trim; ***China***: Cerekinon (舒丽启能); Diway (诺为); Ni Wei Fu (尼为孚); Rui Jian (瑞健); Shuang Di (双迪); Yuan Sheng Li Wei (援生力维); ***Fr.***: Debricalm; Debridat; Modulon†; Transacalm; ***Gr.***: Garapepsin; Ibutin; Trienter; ***Hong Kong***: Cerekinon; ***Ital.***: Debridat; Digerent; ***Jpn***: Cerekinon; ***Malaysia***: Cerekinon; Trima†; ***Mex.***: Cineprac; Crismotil; Debridat; Dolbutin; Espabion; Farbutin†; Krisxon; Libertrim; Muttifen; Prescol; Scitin; ***Pol.***: Debretin; Debridat; Tribux; ***Port.***: Debridat; ***Rus.***: Trimedat (Тримедат); ***Singapore***: Cerekinon; Debridat; ***Spain***: Polibutin; ***Switz.***: Debridat; ***Thai.***: Cerekinon; ***Turk.***: Debridat; Gismotal; Tribudat; ***Ukr.***: Tribudat (Трибудат); ***Venez.***: Bumetin; Colypan.

Multi-ingredient Preparations. ***Arg.***: Biorgan B; Colixane B; Debridat B; Eumotil-T; Fenatrop-A†; Miopropan Proctologico; Miopropan S; Miopropan-T; ***Fr.***: Proctolog; ***Gr.***: Ibuproct; ***Ital.***: Debrum; ***Mex.***: Libertrim SDP; Libertrim SII; ***Port.***: Proctolog; ***Singapore***: Proctolog; ***Spain***: Proctolog; ***Turk.***: Proctolog; Progtolog.

Trinitrophenol

Ácido pícrico; Carbazotic Acid; Kwas pikrynowy; Picric Acid; Picrinic Acid; TNP; Trinitrofenol; Тринитрофенол.

2,4,6-Trinitrophenol.

$C_6H_3N_3O_7$=229.1

CAS — 88-89-1.

UNII — A49O50F91S.

Pharmacopoeias. In *Fr.*

Storage and hazards. Trinitrophenol burns readily and explodes when heated rapidly or when subjected to percussion.

For safety in handling, trinitrophenol is usually supplied mixed with not less than half its weight of water. It should be stored in a cool place. It must not be stored in glass-stoppered bottles.

Trinitrophenol combines with metals to form salts, some of which are very explosive.

Profile

Trinitrophenol has disinfectant properties and was formerly used in the treatment of burns. It is now chiefly used in manufacturing and as a laboratory reagent.

Dermatitis, skin eruptions, severe itching, and yellow staining of the skin may occur after contact with trinitrophenol. Systemic toxicity may follow ingestion or absorption through the skin or lungs; symptoms may include vomiting, pain, and diarrhoea, progressing to haemolysis, hepatitis, anuria, convulsions, unconsciousness, and death. The metabolic rate is increased, causing pyrexia.

Homoeopathy

Trinitrophenol and its salts have been used in homoeopathic medicines under the following names:

- Trinitrophenol: Picricum acidum; Picricum ac
- Calcium picrate: Calcarea picrata; Cal. pic.; Calc pic.
- Iron picrate: Ferri picras; Ferric picrate; Ferrum picricum; Ferr-pic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Agua Sulfatada Picrica†; ***Spain***: Oftalmol Ocular.

Homoeopathic Preparations. ***Austral.***: Hangover Relief; Vitatona Energy†; ***Austria***: Acidum picrinicum Med Complex†; Asarum Med Complex; Erbiode Akne; Gentos; Phosphorus Med Complex; Valerianaheel; ***Canad.***: Acne; Homeo-Form M†; Mental Alertness; Valerianaheel Comp†; ***Fr.***: Acidum Phosphoricum Complexe No 5; Sabal Serrulata Compose; ***Ger.***: Evisco Misteltropfen N; Neuro-Ginsan N; Presselin Nervenkomplex; Presselin Nervennahrung N†; Prostata-Gastreu N R25; Prostata-Komplex L Ho-Fu-Complex; Prostata-Komplex N Ho-Fu-Complex†; Sedacalman; Viragil; ***Hung.***: Gentos; ***Rus.***: Gentos (Гентос); ***Ukr.***: Gentos (Гентос); ***USA***: Preferred Remedies Fatigue.

Trolamine *(pINN)*

TEA; Trietanolamina; Trietanoloamina; Triethanolamine; Trolamiini; Trolamin; Trolamina; Trolaminas; Trolaminum; Троламин.

CAS — 102-71-6.

UNII — 9O3K93S3TK.

Description. Trolamine is a variable mixture of bases containing mainly 2,2′,2″-nitrilotriethanol (trolamine $(CH_2OH.CH_2)_3N$), with 2,2′-iminobisethanol (diolamine) and smaller amounts of 2-aminoethanol (monoethanolamine).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8 (Trolamine; Triethanolamine BP 2014). A clear, viscous, colourless or slightly yellow, very hygroscopic liquid. Miscible with water and with alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Trolamine). A mixture of alkanolamines consisting largely of trolamine containing some diolamine and monoethanolamine. A colourless to pale yellow, viscous, hygroscopic liquid having a slight ammoniacal odour. Miscible with water and with alcohol; soluble in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Trolamine is used with fatty acids such as stearic and oleic acids as an emulsifier and as an alkalinising agent. It has also been used to reduce dithranol-induced staining of the skin.

Ear drops containing trolamine polypeptide oleate-condensate 10% are used for the removal of impacted ear wax (p. 1836.3).

Trolamine salicylate (p. 141.2) has also been used.

Reviews.

1. Del Rosso JQ, Bikowski J. Trolamine-containing topical emulsion: clinical applications in dermatology. *Cutis* 2008; **81:** 209–14.

Radiotherapy. An emulsion of trolamine has been widely used in the treatment and prevention of radiation-induced dermatitis in patients undergoing radiotherapy. However, several studies have suggested that it is of little or no benefit.[1-3]

1. Fisher J, *et al.* Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys* 2000; **48:** 1307–10.
2. Szumacher E, *et al.* Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *Int J Radiat Oncol Biol Phys* 2001; **51:** 81–6.
3. Elliott EA, *et al.* Phase III trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99-13. *J Clin Oncol* 2006; **24:** 2092–7.

Adverse Effects

Trolamine salts may be irritating to the skin and mucous membranes. Contact dermatitis has been reported after the use of ear drops containing trolamine polypeptide oleate-condensate.

Carcinogenicity. Because of concern about the possible production of carcinogenic nitrosamines in the stomach, the Swiss authorities restricted the use of trolamine to preparations for external use.[1]

1. Anonymous. Trolamine: concerns regarding potential carcinogenicity. *WHO Drug Inf* 1991; **5:** 9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biafine; Reumosan Flex; Solucer; ***Belg.***: Lamiderm; Xerumenex; ***Canad.***: Cerumenex†; ***Chile***: Biafine; ***China***: Biafine (比亚芬); ***Fr.***: Biafine; Biafineact; Lamiderm; ***Ger.***: Cerumenex N; ***Israel***: Biafine; ***Mex.***: Orlawax; ***Port.***: Biafine; ***Singapore***: Biafine; ***Switz.***: Biafine; Cerumenex; ***USA***: Biafine; ***Venez.***: Biafine.

Multi-ingredient Preparations. ***Arg.***: Tereonsit; ***Braz.***: Cerumin; Paraqueimol; ***Canad.***: Soropon†; ***Ital.***: Dopo Pik; ***Turk.***: Sac-Bi-Toks; ***USA***: Maxilube; Neosalus; Sonafine.

Trometamol *(BAN, rINN)* ⊗

NSC-6365; THAM; Trihydroxymethylaminomethane; TRIS; Tris (hydroksymetylo)aminometan; Tris(hydroxymethyl)aminomethane; Trometamina; Trométamol; Trometamoli; Trometamolis; Trometamolum; Tromethamine (USAN); Трометамол.

2-Amino-2-(hydroxymethyl)propane-1,3-diol.

$C_4H_{11}NO_3$=121.1

CAS — 77-86-1.

ATC — B05BB03; B05XX02.

ATC Vet — QB05BB03; QB05XX02.

UNII — 023C2WHX2V.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Trometamol). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol; very slightly soluble in ethyl acetate. A 5% solution in water has a pH of 10.0 to 11.5.

USP 36: (Tromethamine). A white, crystalline powder having a slight characteristic odour. Soluble 1 in 1.8 of water and 1 in 45.5 of alcohol; freely soluble in low-molecular-weight aliphatic alcohols; practically insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 5% solution in water is between 10.0 and 11.5. Store in airtight containers.

Incompatibility. There is evidence to suggest that fluorouracil degrades to cardiotoxic compounds in formulations buffered with trometamol.[1]

1. Lukaschek J, *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; **22:** 5022–5.

Uses and Administration

Trometamol is an organic amine proton acceptor used as an alkalinising agent in the treatment of metabolic acidosis (p. 1775.2). It also acts as a weak osmotic diuretic. Trometamol is mainly used during cardiac bypass surgery and during cardiac arrest. It may also be used to reduce the acidity of citrated blood for use in bypass surgery.

The dose used should be the minimum required to increase the pH of the blood to within normal limits and is based on the body-weight and the base deficit. Trometamol is given by slow intravenous infusion as a 0.3M solution; it should not be given for longer than a day except in life-threatening emergencies.

Trometamol citrate is given orally for the management of urinary calculi and acidosis. Trometamol acefyllinate has also been used for acidosis.

References.

1. Nahas GG, *et al.* Guidelines for the treatment of acidaemia with THAM. *Drugs* 1998; **55:** 191–224.

Adverse Effects and Precautions

Great care must be taken to avoid extravasation at the injection site as solutions may cause tissue damage. Local irritation, venospasm and phlebitis have occurred.

Respiratory depression can occur and mechanical ventilation may be required. Hypoglycaemia may also occur. Trometamol is contra-indicated in anuria and uraemia, and should be used cautiously in patients with renal impairment as hyperkalaemia has been reported in such patients. Trometamol is not recommended for use in patients with respiratory acidosis alone. If it is used in patients with respiratory acidosis accompanying metabolic acidosis, ventilation should be maintained mechanically. Trometamol is contra-indicated in chronic respiratory acidosis.

Blood concentrations of bicarbonate, glucose, and electrolytes, partial pressure of carbon dioxide, and blood pH should be monitored during infusion of trometamol.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trometamol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tham†; ***Canad.***: Tham; ***Ger.***: Tham; Tris; ***Gr.***: Tham; ***Ital.***: Thamesol; ***Singapore***: Tham; ***Swed.***: Addex-THAM.

Multi-ingredient Preparations. ***Austral.***: Blink-N-Clean; ***Fr.***: Alcaphor; ***Malaysia***: Cationorm; ***Norw.***: Tribonat; ***Spain***: Cardi-Braun; ***Swed.***: Tribonat.

Pharmacopoeial Preparations

USP 36: Tromethamine for Injection.

Trypan Blue

CI Direct Blue 14; Colour Index No. 23850; Trypanum Caeruleum; Трипановый Синий.

Tetrasodium 3,3′-[(3,3′-dimethylbiphenyl-4,4′-diyl)bisazo]bis [5-amino-4-hydroxynaphthalene-2,7-disulphonate].

$C_{34}H_{24}N_6Na_4O_{14}S_4$=960.8

CAS — 72-57-1.

UNII — I2ZWO3LS3M.

Profile

Trypan blue solutions are used as stains in microscopy and for visualisation of various tissues as an aid to ophthalmic surgery.

References.

1. Werner L, *et al.* Permanent blue discoloration of a hydrogel intraocular lens by intraoperative trypan blue. *J Cataract Refract Surg* 2002; **28:** 1279–86.
2. Haritoglou C, *et al.* Functional outcome after trypan blue-assisted vitrectomy for macular pucker: a prospective, randomized, comparative trial. *Am J Ophthalmol* 2004; **138:** 1–5.
3. Gouws P, *et al.* Cystoid macular oedema with trypan blue use. *Br J Ophthalmol* 2004; **88:** 1348–9.
4. Lee KL, *et al.* A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; **89:** 420–4.
5. Healey PR, Crowston JG. Trypan blue identifies antimetabolite treatment area in trabeculectomy. *Br J Ophthalmol* 2005; **89:** 1152–6.
6. Roos JC, Kerr Muir MG. Use of trypan blue for penetrating keratoplasty. *J Cataract Refract Surg* 2005; **31:** 1867–9.
7. Dick HB, *et al.* Effect of trypan blue on the elasticity of the human anterior lens capsule. *J Cataract Refract Surg* 2008; **34:** 1367–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Oftalblu†; ***Neth.***: MembraneBlue†; VisionBlue; ***USA***: MembraneBlue; VisionBlue.

Trypsin *(BAN)* ⊗

EC 3.4.21.4; Thrypsinum; Tripsina; Tripsinas; Tripszin; Trypsiini; Trypsine; Trypsinum; Trypsyna; Трипсин.

CAS — 9002-07-7.

ATC — B06AA07; D03BA01.

ATC Vet — QB06AA07; QD03BA01.

UNII — GV54A213NN (trypsin); 57I8NCH27R (bovine trypsin); V6GZ69J3FW (porcine trypsin).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Trypsin). A proteolytic enzyme obtained by the activation of trypsinogen extracted from mammalian pancreas. It has an activity of not less than 0.5 microkatals/mg, calculated with reference to the dried substance. A white or almost white, crystalline or amorphous powder; the amorphous form is hygroscopic. Sparingly soluble in water. A 1% solution in water has a pH of 3.0 to 6.0. Solutions have a maximum stability at pH 3 and a maximum activity at pH 8. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Crystallized Trypsin). A proteolytic enzyme crystallised from an extract of the pancreas of healthy bovine or porcine animals, or both. It contains not less than 2500 USP units in each mg, calculated on the dried basis. A white to yellowish-white, odourless, crystalline or amorphous powder. Store in airtight containers at temperature not exceeding 40 degrees.

Profile

Trypsin is a proteolytic enzyme that has been applied for the debridement of wounds. It has also been taken orally, usually with chymotrypsin (p. 2477.3), and sometimes with antibacterial or other drugs, for its supposed benefit in relieving oedema and inflammation associated with infection or trauma. Trypsin solutions have been inhaled for the liquefaction of viscous sputum, and trypsin is also an ingredient of mixtures intended to relieve various gastrointestinal disorders. Trypsin has been used in oncology in a combination preparation with chymotrypsin and papain (see under Uses and Administration of Papain, p. 2583.1).

Hypersensitivity reactions may occasionally occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Leukase†; Phlogenzym; Rutozym; Traumazym; Wobenzym; ***Braz.***: Parenzyme Analgesico; Parenzyme†; ***Canad.***: Wobenzym; ***China***: YiMei (怡美); ***Cz.***: Phlogenzym; Wobenzym; ***Ger.***: Phlogenzym†; Wobenzym plus; ***Gr.***: Chymoral; Itastab; Tricuval; ***Hung.***: Phlogenzym; ***India***: Alfapsin; Ceze; Chymase; Chymin; Chymobel Plus; Chymobel; Chymoral; Chymosoz-D; Chymotas; Chymotrip; Chymutrip; Disperzyme; Enractin; Ficlo-Forte; Flamotryp; K-Trip Plus; K-Trip; Kymovil Plus; Omotrip; Optase-DC; Orthal Forte; Orthotime; Soluzyme; ***Jpn***: Kimotab†; ***Mex.***: Ochozim; Phlogenzym; Quimotrip†; Ribotripsin; Wobe-Mugos; Wobenzym; Zimotris; ***Port.***: Anginova; Chimar; ***Rus.***: Phlogenzym (Флогэнзим); Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); ***Spain***: Dertrase; Dosil Enzimatico; Doxiten Enzimatico; Kanapomada†; Naso Pekamin†; Quimodril; ***Ukr.***: Phlogenzym (Флогэнзим); Wobe-Mugos E (Вобэ-Мугос Е)†; Wobenzym (Вобэнзим); ***USA***: Allanderm-T†; Bio-Zyme; Dermuspray; Granulderm†; Granulex; GranuMed; Optase; Vasolex; Xenaderm; ***Venez.***: Phlogenzym; Wobenzym N.

Tuberculins

Tuberculinas; Туберкулины.

ATC — V04CF01.

ATC Vet — QV04CF01.

NOTE. 'PPD' is an abbreviation sometimes used for tuberculin purified protein derivative which should not be confused with paraphenylenediamine (p. 2583.2), which is also referred to by the same abbreviation.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tuberculin for Human Use, Old). It consists of a filtrate, concentrated by heating, containing the soluble products of the culture and lysis of one or more strains of *Mycobacterium tuberculosis* and/or *M. bovis*. It contains a suitable preservative that does not give rise to false-positive reactions. In concentrated form, it is a transparent, viscous, yellow or brown liquid. Protect from light.

Ph. Eur. 8: (Tuberculin Purified Protein Derivative for Human Use). A preparation obtained by precipitation from the heated products of the culture and lysis of *Mycobacterium tuberculosis* and/or *M. bovis*. It contains a suitable preservative that does not give rise to false-positive reactions. It is a colourless or pale yellow liquid; the diluted preparation may be a freeze-dried powder which upon dissolution gives a colourless or pale yellow liquid. Protect from light.

Uses and Administration

Tuberculin skin tests are used to detect tuberculoprotein hypersensitivity when BCG vaccination is being considered or as an aid to diagnosis of tuberculosis. A person showing a specific sensitivity to tuberculin is considered to have been infected with the tubercle bacillus, though the infection may be inactive. Tuberculin for sensitivity testing is given by intradermal injection as in the Mantoux test. Multiple-puncture devices such as the Heaf test or tine tests have also been used, although they are no longer available in the UK.

In the UK, it is recommended that tuberculin testing should always be performed when BCG vaccination is being considered, and the **Mantoux** test is recommended. For a routine Mantoux test, a diluted solution (2TU/0.1 mL) of tuberculin purified protein derivative (PPD) is given by intradermal injection and the reaction, which is graded by the transverse diameter of the area of induration, read 48 to 72 hours later. A retest with a stronger solution (10TU/0.1 mL) of PPD may be considered if the results of the initial test are unclear.

Individuals with a negative reaction (induration of less than 6 mm) who have not previously been given BCG vaccines may be offered BCG vaccination. Patients with a reaction (induration of 6 mm or greater) are considered to be positive (hypersensitive) to tuberculoprotein and should not be vaccinated. Investigation for the presence of active tuberculosis is generally only indicated for patients showing a strongly positive reaction (induration 15 mm and above) to a tuberculin skin test. However, there are many factors that should be considered when interpreting the results; in addition to those listed under Precautions (see p. 2636.2), there are the effects of previous BCG vaccination, repeated tuberculin testing, and age. In some areas, a positive reaction may be a result of cross-sensitivity of the test to non-tuberculous mycobacteria (see p. 2636.1).

For the **Heaf** test, a solution of PPD is applied to the forearm using a multiple-puncture gun (Heaf gun), and the reaction evaluated about a week later.

The term **tine** test is generally used for disposable multiple-puncture devices coated with dried old tuberculin or PPD. However, some consider tine tests to be unreliable.

In some other countries, the population tested, the procedures used, and grading of reactions may differ slightly from that outlined above.

Tuberculins have also been used with other antigens for anergy testing to assess the status of cell-mediated immunity.

Latent tuberculosis. Full eradication of tuberculosis from developed countries requires identification of latent as well as active cases.[1] Tuberculin testing has been in use for over 100 years and, while still considered a useful diagnostic agent for tuberculosis, the problems of false-positive reactions or reduced sensitivity to the test are well recognised.[1] Use of the test to identify latent disease has evolved with experience.[2] Previous BCG vaccination is one factor that significantly increases the likelihood of a false-positive reaction to tuberculin testing, which makes the diagnosis of latent tuberculosis particularly difficult.[3] Interpretation of the skin test should therefore be made by considering the induration size in the context of the individual clinical profile, including other risk factors for infection.[2,3] Three different approaches to assess the annual risk of tuberculous infection using tuberculin testing gave different results in a study of schoolchildren who had been given BCG vaccinations early in life.[4] This led the authors to conclude that the effect of previous BCG vaccination on tuberculin reactivity may be more complex than assumed, and that the tuberculin test is a poor indicator of latent infection. It has been suggested[2] that it is not necessary for low-risk persons in the general population of the USA to receive routine tuberculin testing for tuberculosis; high-risk groups of adults and children for whom screening might be warranted have been defined, and consensus recommendations made.

1. Lee E, Holzman RS. Evolution and current use of the tuberculin test. *Clin Infect Dis* 2002; **34:** 365–70.
2. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. 1999. Available at: http://www.thoracic.org/statements/resources/mtpi/latenttb1-27.pdf (accessed 16/08/10)
3. Wang L, *et al*. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax* 2002; **57:** 804–9. Correction: *ibid.* 2003; **58:** 188.
4. Leung CC, *et al*. Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. *Thorax* 2005; **60:** 124–9.

Malignant disease. Benefit has been reported[1] in 2 patients with adult T-cell leukaemia/lymphoma mainly involving the skin after local treatment with tuberculin purified protein derivative.

1. Kanekura T, *et al*. Purified protein derivative treatment for skin lesions of adult T-cell leukaemia/lymphoma. *Br J Dermatol* 1999; **140:** 767–8.

Non-tuberculous mycobacterial infection. The tuberculin skin test is not specific for *Mycobacterium tuberculosis*, but can also represent a cross-reaction caused by antigens on other non-tuberculous mycobacteria. Re-examination[1] of results from children with non-tuberculous mycobacterial infection concluded that the avian Mantoux test (avian tuberculin purified protein derivative (PPD) prepared from *M. avium*) was more sensitive than the human Mantoux test (tuberculin PPD prepared from *M. tuberculosis*) in the detection of non-tuberculous mycobacteria in regions with a low incidence of tuberculosis, and may be a useful aid to differential diagnosis in areas where tuberculosis is prevalent.

1. Daley AJ, Isaacs D. Differential avian and human tuberculin skin testing in non-tuberculous mycobacterial infection. *Arch Dis Child* 1999; **80:** 377–9.

Adverse Effects

Pain and pruritus may occur at the injection site, occasionally with vesiculation, ulceration, or necrosis in highly sensitive persons. Granuloma has been reported.

Nausea, headache, dizziness, malaise, rash, urticaria, oedema, and pyrexia have been reported occasionally; immediate systemic hypersensitivity, including anaphylaxis, has been reported rarely. There have also been rare reports of lymphangitis.

Hypersensitivity. There are rare reports[1-4] of severe anaphylactic or anaphylactoid reactions, occasionally fatal,[1] to tuberculin.

1. DiMaio VJM, Froede RC. Allergic reactions to the tine test. *JAMA* 1975; **233:** 769.
2. Spiteri MA, *et al*. Life threatening reaction to tuberculin testing. *BMJ* 1986; **293:** 243–4.
3. Wright DN, *et al*. Systemic and local allergic reactions to the tine test purified protein derivative. *JAMA* 1989; **262:** 2999–3000.
4. Sanofi Pasteur, Canada. Risk of serious allergic reactions following TUBERSOL [Tuberculin Purified Protein Derivative (Mantoux)] administration (issued 19th May 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/tubersol_hpc-cps-eng.pdf (accessed 08/08/08)

Lymphangitis. Lymphangitis has been reported on 5 occasions after the Mantoux test and on 7 occasions after the Heaf test.[1] However, it was noted that a tuberculin test may have been inappropriate in some of these patients, particularly older subjects and those with evidence of healed tuberculous lesions.[2]

1. Morrison JB. Lymphangitis after tuberculin tests. *BMJ* 1984; **289:** 413.
2. Festenstein F. Lymphangitis after tuberculin tests. *BMJ* 1984; **289:** 625–6.

Precautions

Tuberculin should be given with caution to patients who have, or are suspected of having, active tuberculosis; although severe local reactions may occur in patients with active tuberculosis, sensitivity may be diminished if it is particularly severe. Sensitivity to tuberculin may also be diminished in the following conditions: viral or severe bacterial infection including HIV infection and infectious mononucleosis; neoplastic disease particularly lymphoma; sarcoidosis; corticosteroid or immunosuppressive therapy; recent use of live virus vaccines; ultraviolet light treatment; chronic renal failure; dehydration; and malnutrition.

Tuberculins may be adsorbed onto the surface of syringes and should therefore be given immediately.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tuberculin PPD as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Tubersol; ***Fr.***: Tubertest; ***Gr.***: Imotest Tuberculin; ***India***: Monotest; ***Israel***: Tubersol; ***Ital.***: Biocine Test PPD†; ***NZ***: Tubersol; ***S.Afr.***: Biocine Test†; Japan Freeze-Dried Tuberculin†; ***USA***: Aplisol; Tubersol.

Multi-ingredient Preparations. ***Austral.***: Multitest CMI†; ***Gr.***: Multitest.

Homoeopathic Preparations. ***Ger.***: metabiarex.

Pharmacopoeial Preparations

Ph. Eur.: Old Tuberculin for Human Use; Tuberculin Purified Protein Derivative for Human Use.

Tucaresol *(BAN, rINN)* ⊗

589C; 589C80; BW-589C; Tucarésol; Tucaresolum; Тукарезол.

α-(2-Formyl-3-hydroxyphenoxy)-*p*-toluic acid.

$C_{15}H_{12}O_5$=272.3

CAS — 84290-27-7.

UNII — JH368G5B9M.

Profile

Tucaresol is reported to interact with haemoglobin to increase oxygen affinity. It has been investigated as an oral drug for the treatment of sickle-cell disease (p. 1123.2). Tucaresol is also reported to have immunostimulant properties and is under investigation in HIV infection and hepatitis B. Hypersensitivity reactions have occurred.

References.

1. Rolan PE, *et al*. The pharmacokinetics, tolerability and pharmacodynamics of tucaresol (589C80; 4[2-formyl-3-hydroxyphenoxymethyl] benzoic acid), a potential anti-sickling agent, following oral administration to healthy subjects. *Br J Clin Pharmacol* 1993; **35:** 419–25.
2. Arya R, *et al*. Tucaresol increases oxygen affinity and reduces haemolysis in subjects with sickle cell anaemia. *Br J Haematol* 1996; **93:** 817–21.
3. Peck RW, *et al*. Effect of food and gender on the pharmacokinetics of tucaresol in healthy volunteers. *Br J Clin Pharmacol* 1998; **46:** 83–6.
4. Gori A, *et al*. Immunomodulation induced by tucaresol in HIV infection: results of a 16 week pilot Phase I/II trial. *Antivir Ther* 2004; **9:** 603–14.

Javanese Turmeric

Curcuma Zanthorrhiza; Curcumae Javanicae; Curcumae xanthorrhizae rhizoma; Geltonšaknių ciberžolių šakniastiebiai; Gurkmeja, javanesisk; Jaavan kurkuma; Jávai-kurkuma gyökértörzs; Oddenek kurkumy žlutokořenné; Temoe lawacq; Temoe Lawak; Témoé-lawaq; Куркума Явансная.

*ATC Herb — HA03AW5021 (*Curcuma zanthorrhiza*: rhizome); HA05AW5006 (*Curcuma zanthorrhiza*: rhizome).*

UNII — SD3M9OA214.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Turmeric, Javanese). It consists of the dried rhizome, cut in slices, of *Curcuma xanthorrhiza*. It contains not less than 5% v/w of essential oil and not less than 1% of dicinnamoyl methane derivatives expressed as curcumin, both calculated with reference to the anhydrous drug. It has an aromatic odour. Protect from light.

Profile

Javanese turmeric is an ingredient of preparations indicated for biliary and gastrointestinal disorders. It is a close relative of the spice turmeric (p. 2218.1), which has been used similarly.

Irritable bowel syndrome. For reference to the ineffectiveness of Javanese turmeric in patients with irritable bowel syndrome see under Fumitory, p. 2508.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Curcu-Truw; Pankreaplex mono.

Multi-ingredient Preparations. ***Austria***: Choleodoron; ***Canad.***: Gallexier†; ***Fr.***: Hepaclem†; Kotor Articulations; ***Ger.***: Bilisan Duo†; Enzym-Harongan; Gallexier; Gallexier; Hevert Stoffwechsel-Tee N†; Infi-tract V; ***Hong Kong***: Hepatofalk Planta†; Hepatofalk†; ***Indon.***: Curbexon; Curliv Plus; Curliv Plus; Curliv; Cursil; Curson†; Gramuno; Hepa-Q; Hepacell†; Heparsitin; Hepatofalk Planta†; Hepimun Plus; Hepimun; Librozym†; Norflam; Nutrijoint; Picula; Verona; ***S.Afr.***: Choleodoron†; ***Singapore***: Hepatofalk Planta†; ***Switz.***: Choleodoron.

Homoeopathic Preparations. ***Canad.***: Choleodoron†; ***Fr.***: Choleodoron; ***Ger.***: Choleodoron†; ***Neth.***: Choleodoron; ***UK***: Choleodoron.

Turpentine Oil

Aetheroleum Terebinthinae; Esencia de Trementina; Essence de Térébenthine; Oleum Terebinthinae; Oleum Terebinthinae Depuratum; Rectified Turpentine Oil; Spirits of Turpentine; Térébenthine, huile essentielle de; Terebentin Yağı; Terebinthini aetheroleum; Terebintin Esansı; Trementina, aceite esencial de; Скипидар; Терпентинное Масло.

*ATC Herb — HM02AW5014 (*Pinus pinaster*: essential oil).*

UNII — C5H0QJ6V7F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8 (Turpentine Oil, Pinus Pinaster Type; Terebinthini Aetheroleum ab Pinum Pinastrum). An essential oil obtained by steam distillation, followed by rectification at a temperature below 180 degrees, from the oleoresin obtained by tapping *Pinus pinaster*. A suitable antoxidant may be added. It contains 70.0 to 85.0% α-pinene, 0.5 to 1.5% camphene, 11.0 to 20.0% β-pinene, maximum 1% car-3-ene, 0.4 to 1.5% β-myrcene, 1.0 to 7.0% limonene, 0.2 to 2.5% longifolene, 0.1 to 3.0% β-caryophyllene, and maximum 1.0% caryophyllene oxide.

A clear, colourless or pale yellow liquid with a characteristic odour. Relative density 0.856 to 0.872. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Turpentine oil is widely used as a solvent. It is applied topically as a rubefacient. It is an ingredient of many preparations used in respiratory-tract disorders, but is now judged to be neither safe nor effective.

Adverse Effects

In poisoning with turpentine oil there may be local burning and gastrointestinal upset, coughing and choking, pulmonary oedema, excitement, coma, fever, tachycardia, liver damage, haematuria, and albuminuria. Fatalities have occurred.

The application to the skin of liniments containing turpentine oil may cause irritation and absorption of large amounts may cause some of the effects listed above. Hypersensitivity reactions and local irritation have been reported.

References.

1. Khan AJ, *et al*. Turpentine oil inhalation leading to lung necrosis and empyema in a toddler. *Pediatr Emerg Care* 2006; **22:** 355–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ozothine; ***Port.***: Vicks Vaporub.

Multi-ingredient Preparations. ***Arg.***: Adhesol; Atomo Desinflamante C; Bronco Etersan; Cerax; Fluido Spineda; Notoxin; Novobroncol; Otocalmia; Rati Salil Crema; ***Austral.***: Goanna Heat Cream; Goanna Oil Liniment; Goanna Salve†; Vicks Vaporub; ***Austria***: Acimont; Baby Luuf atherische Ole; Baby Luuf; Bronchostop†; Carl Baders Divinal; Ilon Abszess; Kinder Luuf; Luuf Balsam; Pe-Ce†; Piniment; Piniment; Piniment; Rubriment; Scottopect; Trauma-Salbe warmend; Tussamag; Vulpuran; Wick Vaporub; ***Belg.***: Algis-Spray; Reflexspray; Vicks Vaporub; ***Braz.***: A Curitybina; Aliviol; Angino-Rub; Benegel; Frixopel; Gelflex; Gelo-Bio; Gelofrix; Massageol; Nevrol†; Prati-

gel; Traumac†; Traumagel; Vick Vaporub; ***Canad.***: Cal Mo Dol†; Cerumol; Hot Stuff†; ***Chile***: Calorub Nueva Formula; Hansaplast Descongestionante†; Mentobalsam†; ***China***: Zheng Tong Gao (正通高); ***Cz.***: Ilon Abszess; ***Fin.***: Vicks Vaporub; ***Fr.***: Activox; Lumbalgine; Ozothine a la Diprophylline; Ozothine†; Respirea†; Vicks Vaporub; ***Ger.***: Erkaltungs Bad N†; Grippostad Erkaltungsbalsam; Ilon Abszess; Kneipp Rheumabad Spezial†; tactu-mobil; Tetesept Erkaltungs Bad; Wick Vaporub; ***Gr.***: Deep Heat; EKS; Faragel-Forte; Ilon; Pinimenthol; Revigel; Santoux; Vicks Vaporub; ***Hung.***: Baby Luuf; Deep Heat Rub; Kinder Luuf Balsam; ***India***: Artrex; Ceruklin; Clearwax; Desol; Despol; Dewax; Diclowin; Fastwax; Flexi-muv†; Lima; Nayawax; Neurophen; Nill-O-Wax; Otoclean; Otorex; Parabec; Systaflam; Waxolve†; ***Indon.***: Opino†; Sloan's Liniment†; ***Irl.***: Deep Heat; Menthol & Wintergreen; Vicks Vaporub; ***Israel***: Deep Heat Rub; Ment-O-Cap†; ***Ital.***: Capsolin; Vicks Vaporub; ***Malaysia***: Thermorub†; ***Neth.***: Luuf Verkoudheidsbalsem (voor baby's); Luuf Verkoudheidsbalsem (voor kinderen); Luuf Verkoudheidsbalsem; Vicks Vaporub; ***NZ***: Vicks Vaporub; ***Pol.***: Analgol; Analgolan; Capsigel N; Derhotill; Dip Hot; Herbolen†; Inhalol; Neo-Capsiderm; Pulmonil; Reumatik; Rub-Arom; Wick Vaporub; ***Port.***: Balsamo Analgesico Basi; Balsamo Analgesico Labesfal; Calicida Indiano; ***Rus.***: Alvipsal (Алвипсал); Capsicam (Капсикам); Carmolis Fluid (Кармолис Жидкость); Deep Heat (Дип Хит); Doktor Mom (Доктор Мом); Mentholatum (Ментолатум); Moov (Мув); Nigvisal B (Нижвисал В); Salvisar (Салвисар); Suprima-Plus (Суприма-Плюс); Viprosal B (Випросал В); ***S.Afr.***: Balsem Sulphuris; Deep Heat Rub†; Haarlemensis; Puma Balm; Respisniffers†; Sloan's Liniment Rub†; Vicks Vaporub†; Woodwards Inhalant; ***Singapore***: Woodward's Baby Chest Rub; ***Spain***: Arkoresp†; Embrocacion Gras†; Masagil†; Otocerum; Reflex; Termosan; ***Swed.***: Vicks Vaporub; ***Switz.***: Baume du Chalet; Cerumenol; Eucapinol; Knobel Huile N†; PO-HO bleu; Pommade au Baume; Vicks Vaporub N; ***Thai.***: Stoke'Liniment Sahakarn; Stopain; U-Gesic Balm; ***Turk.***: Algo-Wax; Antidot; Bugumentol; Buguseptil; Capsalgine; Gelocaps; Kataljin; Vicks Vaporub; ***UK***: Deep Heat Rub; Dragon Balm; Ellimans; Goddards Embrocation; Gonne Balm; Modern Herbals Muscular Pain; Nasciodine; Nine Rubbing Oils; Vicks Vaporub; ***Ukr.***: Capsicam (Капсикам); Deep Heat (Дип Хит); Doktor Mom (Доктор Мом); Helpex Effect (Хелпекс Эффект); Ilon (Илон); Viprosal B (Випросал В); ***USA***: Vicks Vaporub.

Homoeopathic Preparations. ***Ger.***: Cysto-cyl L Ho-Len-Complex; uro-loges; ***Neth.***: Enulite; ***Rus.***: Helidonium-Plus (Хелидониум-Плюс).

Pharmacopoeial Preparations
BP 2014: White Liniment.

Tyramine Hydrochloride ⊗

Tiramina, hidrocloruro de; *p*-Tyramine Hydrochloride; Tyrosamine Hydrochloride; Тирамина Гидрохлорид.
4-Hydroxyphenethylamine hydrochloride; 4-(2-Aminoethyl) phenol hydrochloride.
$C_8H_{11}NO,HCl$=173.6
CAS — 51-67-2 (tyramine); 60-19-5 (tyramine hydrochloride).
UNII — Z5KDH3H147.

Profile

Tyramine hydrochloride is a sympathomimetic with indirect effects on adrenergic receptors. It has been given orally or by injection in the tyramine pressor test for the investigation of monoamine oxidase inhibitory activity or amine uptake blocking activity. It has also been used in studies of physiological and disease states, and in the diagnosis of migraine and phaeochromocytoma.

The hazards of consuming foods rich in tyramine while taking MAOIs are described under Phenelzine, p. 444.3.

The bioavailability of oral tyramine is significantly reduced by the presence of food, which could have implications when used in tyramine pressor tests.[1]

1. VanDenBerg CM, *et al.* Tyramine pharmacokinetics and reduced bioavailability with food. *J Clin Pharmacol* 2003; **43:** 604–9.

Ubidecarenone *(BAN, rINN)*

Coenzima Q-10; Coenzyme Q10; Ubidecarenon; Ubidecarenona; Ubidécarénone; Ubidecarenonum; Ubidekarenon; Ubidekarenonas; Ubidekarenoni; Ubiquinona-10; Ubiquinone-10; Убидекаренон.
2-Deca(3-methylbut-2-enylene)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.
$C_{59}H_{90}O_4$=863.4
CAS — 303-98-0.
ATC — C01EB09.
ATC Vet — QC01EB09.
UNII — EJ27X76M46.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ubidecarenone). A yellow or orange crystalline powder. It gradually decomposes and darkens on exposure to light. M.p. about 48 degrees. Practically insoluble in water; very slightly soluble in dehydrated alcohol; soluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Ubidecarenone). A yellow to orange, crystalline powder. M.p. about 48 degrees. Practically insoluble in water; very slightly soluble in dehydrated alcohol; soluble in ether. Protect from light.

Profile

Ubidecarenone is a naturally occurring coenzyme involved in electron transport in the mitochondria. It is claimed to be a free radical scavenger and to have antoxidant and membrane stabilising properties. It has been given orally as an adjunct in cardiovascular disorders, including mild or moderate heart failure. It has also been tried in other conditions associated with coenzyme deficiency, and is promoted as a dietary supplement. Ubidecarenone is under investigation for the management of cancer, Huntington's chorea (p. 1029.3) and parkinsonism.

For a discussion of the use of ubidecarenone in statin-induced muscle disorders, see Effects on Skeletal Muscle, under Simvastatin, p. 1493.2.

References.
1. Greenberg S, Frishman WH. Co-enzyme Q_{10}: a new drug for cardiovascular disease. *J Clin Pharmacol* 1990; **30:** 596–608.
2. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; **344:** 1372–3.
3. Garcia Silva MT, *et al.* Improvement of refractory sideroblastic anaemia with ubidecarenone. *Lancet* 1994; **343:** 1039.
4. Gattermann N, *et al.* No improvement of refractory sideroblastic anaemia with ubidecarenone. *Lancet* 1995; **345:** 1121–2.
5. Nagao T, *et al.* Treatment of warfarin-induced hair loss with ubidecarenone. *Lancet* 1995; **346:** 1104–5.
6. Pepping J. Coenzyme Q_{10}. *Am J Health-Syst Pharm* 1999; **56:** 519–21.
7. Khatta M, *et al.* The effect of coenzyme Q_{10} in patients with congestive heart failure. *Ann Intern Med* 2000; **132:** 636–40.
8. Tran MT, *et al.* Role of coenzyme Q10 in chronic heart failure, angina, and hypertension. *Pharmacotherapy* 2001; **21:** 797–806.
9. Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 2001; **57:** 397–404.
10. Rahman S, *et al.* Neonatal presentation of coenzyme Q10 deficiency. *J Pediatr* 2001; **139:** 456–8.
11. Roffe L, *et al.* Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: a systematic review. *J Clin Oncol* 2004; **22:** 4418–24.
12. Sándor PS, *et al.* Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005; **64:** 713–15.
13. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q_{10} during statin therapy. *Ann Pharmacother* 2006; **40:** 290–4.
14. The NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q_{10} and GPI-1485 in early Parkinson disease. *Neurology* 2007; **68:** 20–8.
15. Rosenfeldt FL, *et al.* Coenzyme Q_{10} in the treatment of hypertension: a meta-analysis of the clinical trials. *J Hum Hypertens* 2007; **21:** 297–306.
16. Ho MJ, *et al.* Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 15/07/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: QX 100; ***Braz.***: Vinocard Q10; ***Canad.***: CoQuinone; Ultra COQ10†; ***China***: Fu Xin (辅辛); He Fu (合夫); Neuquinon (能气朗); ***Fr.***: Q10; ***Hong Kong***: CoQuinone†; Eiquinon; ***Hung.***: Myoqinon; Q-Gel; ***India***: Atp; Co.Q.Care; Coq; Coten; Miraqule; ***Indon.***: Co-En Q; Coten; Enzimten; Nuzym; Q-Ten; Qubi; Ubi-Q; VQ; ***Ital.***: Decafar†; Decorenone; Oropigma Gel; Tricoxen; Ubicor; Ubidenone†; Ubidex†; Ubimaior; ***Jpn***: Neuquinon; ***Malaysia***: Alerten; Bio-Quinone; Eurobio BioQ-10; Neuquinon; ***Mex.***: CoQuinone; ***Philipp.***: Addlife; Alerten; EssenVida; Neuquinon; ***Pol.***: Envit Q_{10}†; Vita Care Q_{10}; ***Port.***: Q 10; Ubenzima; ***Rus.***: Qudesan (Кудесан); ***Singapore***: Alerten; CoQuinone†; Ubi-Q; Vita Co-Enzyme Q10; ***Thai.***: Alerten; Bio Q10 VQ50; Bio-Quinone; Decaquinon; VQ†; ***UK***: Bio-Quinone; ***USA***: CoQuinone.

Multi-ingredient Preparations. ***Arg.***: Cardiobiotral; Desgras Piel Naranja; Marathon Antioxidante; Marathon; QX 10; ***Austral.***: CardiWell Omega Q10; Homme-F; Proactive Multi for 50+; Radiance; ***Belg.***: Ostrin Q10; ***Canad.***: Clear Q†; Mega AO; Protect†; Support Formula†; ***Chile***: Eucerin Q10 Active; Infor Q10; Logical; Marathon; Trivitana Q10; Ubiten; Ultrac Q10; Ureadin Facial Antiarrugas; ***Fr.***: Arterin Plus; Microbiane Q10; ***Hong Kong***: Cardiozen; ***Hung.***: Q_{10}; ***India***: Bio-10; Cardi-NRG; Cardio-Pro; Co-Q-Dent; Coq Forte; Ecozyme; Enhance; Hairstim-HGF; Hepa; Hi-Q Plus; Hi-Q; Hyrase; I-10; I-Vit Plus; Imunolife; Jivak; Jstat; Liveril; Maxoza; ***Indon.***: Baliin Q10; Bioquinone; Canergy†; Car-Q; Carnon; Co-Q-10; Co-vitala; Combes†; Cor-Q; Corsel; Enercore; Galten; Life 10; Liproqy; Lycoq†; Metsel; nu Qten Com; Qutan-10; RG-Q; ***Ital.***: Anasten Plus; Berart; Coqun; Diaberet; Linfolipase; Ocustress; Phototrop; Salovit; Selemix; Visu Q10; VisuQ10; Vitalmix Complex; Vitalmix Fos; ***Malaysia***: Hovid Q-10 SupraBio + L-Carnitine; Hovid Q10 Plus†; ***Mex.***: Avitil; ***Philipp.***: Havitall; Immuvit; Nutrotal; Polynerv-E with lecithin; SafeStat; ***Singapore***: Cardio-Essentials; Co3E + CoQ10; Enerbolis; Espanone; Essentials†; RejuvaSkin Anti-Aging Serum; Scar Esthetique; ***UK***: Neurozan; NutriScience; Red Kooga Co-Q-10 and Ginseng; ***Ukr.***: Perfectil Plus (Перфектил Плюс); Vitrum Beauty Q10 (Витрум Бьюти Q10)†; ***USA***: AquADEKS; Cardio Tone; Corvite Free; Diabetiks; PreQue 10; ProtectNatal; Triveen-Ten; ***Venez.***: Uvagen.

Pharmacopoeial Preparations
USP 36: Ubidecarenone Capsules; Ubidecarenone Tablets.

Ulinastatin *(rINN)*

Ulinastatina; Ulinastatine; Ulinastatinum; Urinastatin; Улинастатин.
CAS — 80449-31-6; 80449-32-7.

Pharmacopoeias. In *Jpn*.

Profile

Ulinastatin is a glycoprotein proteolytic enzyme inhibitor isolated from human urine. It has been given by slow intravenous injection or by intravenous infusion in acute pancreatitis (p. 2580.2) and in acute circulatory insufficiency.

References.
1. Ohwada M, *et al.* New endoscopic treatment for chronic pancreatitis, using contrast media containing ulinastatin and prednisolone. *J Gastroenterol* 1997; **32:** 216–21.
2. Sugita T, *et al.* Effect of a human urinary protease inhibitor (Ulinastatin) on respiratory function in pediatric patients undergoing cardiopulmonary bypass. *J Cardiovasc Surg* 2002; **43:** 437–40.
3. Tsujino T, *et al.* Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 2005; **3:** 376–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Luo An (洛安); ***Jpn***: Miraclid.

Uracil *(USAN)*

BMS-205603-01; Sq-6201; Sq-7726; Sq-8493; Урацил.
2,4(1*H*,3*H*)-pyrimidinedione.
$C_4H_4N_2O_2$=112.1
CAS — 66-22-8.
UNII — 56HH86ZVCT.

Profile

Uracil is a pyrimidine base and one of the components of uridine nucleotides that form ribonucleic acid (p. 2604.1). It inhibits dihydropyrimidine dehydrogenase and reduces the metabolism of fluorouracil; it is given orally with tegafur (p. 864.2), an oral fluorouracil prodrug, to increase the bioavailability of fluorouracil.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Asofurtal; Fimer; UFT; ***Austria***: UFT; ***Belg.***: UFT; ***Braz.***: UFT; ***Cz.***: UFT†; ***Denm.***: UFT; Uftoral†; ***Fr.***: UFT; ***Ger.***: UFT; ***Gr.***: UFT; ***Hong Kong***: UFT†; ***Hung.***: UFT†; ***Irl.***: UFT†; ***Israel***: UFT; ***Ital.***: UFT; ***Jpn***: UFT; ***Malaysia***: UFT; ***Mex.***: UFT; ***Neth.***: UFT; ***Norw.***: UFT†; ***Philipp.***: Tefudex; UFT; ***Pol.***: UFT; ***Port.***: UFT; ***Rus.***: UFT (УФТ); ***S.Afr.***: UFT; ***Singapore***: UFT; ***Spain***: UFT†; ***Swed.***: UFT†; ***Thai.***: UFT†; UFUR; ***Turk.***: UFT; ***UK***: Uftoral†.

Urazamide

5-Aminoimidazole-4-carboxamide ureidosuccinate.
$C_9H_{14}N_6O_6$=302.2
CAS — 34879-34-0.
UNII — 671534JBYI.

Profile

Urazamide has been given orally in the treatment of hepatic disorders. It has also been given by intramuscular and intravenous injection.

Uridine

Uracil Riboside; Uridina; Urydyna; Уридин.
1-β-D-Ribofuranosyluracil; 1-β-D-Ribofuranosylpyrimidine-2,4(1*H*,3*H*)-dione.
$C_9H_{12}N_2O_6$=244.2
CAS — 58-96-8.
UNII — WHI7HQ7H85.

Profile

Uridine is an endogenous uracil nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). Uridine is used in preparations containing other nucleosides in the treatment of corneal damage. It has been included in preparations for peripheral and cerebral vascular disorders and myopathies; it has also been used for liver disorders, anaemias, and as a tonic. Uridine has been tried in patients with hereditary orotic aciduria.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Vitacic†; ***Ital.***: Centrum; ***Mon.***: Vitacic.

Uridine Triphosphate

Ins-316; Trifosfato de uridina; Uridina trifosfato; Uridine Triphosphoric Acid; UTP; Уридин Трифосфат.

Uridine 5′-(tetrahydrogen triphosphate).

$C_9H_{15}N_2O_{15}P_3$=484.1

CAS — 63-39-8.

Profile

Uridine triphosphate is an endogenous uracil nucleotide involved in many biological processes. It has been claimed to be of value in muscular atrophy and muscular weakness, and has been included in preparations for neuralgia, neuritis, and muscular disorders; the disodium and trisodium salts have also been used.

Uridine triphosphate has been reported to have beneficial effects on mucociliary clearance in chronic respiratory disease such as cystic fibrosis, asthma, and chronic bronchitis, although it may not be suitable for such therapy because it is rapidly degraded by enzymatic activity within sputum and by airway epithelial cells.[1,2] It may, however, have a role as a method of producing deep-lung sputum specimens for cytological evaluation and is being investigated as an aid to the diagnosis of for example, lung cancer[1,2] or airway inflammation in asthma.[3]

1. Bennett WD, *et al*. Effect of aerosolized uridine 5′-triphosphate on mucociliary clearance in mild chronic bronchitis. *Am J Respir Crit Care Med* 2001; **164:** 302–6.
2. Johnson FL, *et al*. Improved sputum expectoration following a single dose of INS316 in patients with chronic bronchitis. *Chest* 2002; **122:** 2021–9.
3. Tamaoki J, *et al*. Validity and safety of sputum induction by inhaled uridine 5′-triphosphate. *Am J Respir Crit Care Med* 2001; **164:** 378–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Uteplex.

Multi-ingredient Preparations. ***Braz.***: Etna; Nucleo CMP; ***Chile***: Citoneuron; ***Mex.***: Nucleo CMP; ***Spain***: Nucleo CMP; ***Ukr.***: Keltican (Келтикан); Nucleo CMF Forte (Нуклео ЦМФ Форте).

Ursodeoxycholic Acid *(BAN, rINN)*

Acide Ursodéoxycholique; Acide ursodésoxycholique; Ácido ursodeoxicólico; Ácido ursodesoxicólico; Acidum ursodeoxycholicum; Kyselina ursodeoxycholová; UDCA; Ursodeoksicholio rūgštis; Ursodeoksikolik Asit; Ursodeoksikoolihappo; Ursodeoxicholsyra; Ursodeoxicólico, ácido; Ursodesoxycholic Acid; Ursodesoxycholsäure; Ursodiol (USAN); Urzodezoxikólsav; Урсодезоксихолевая Кислота.

3α,7β-Dihydroxy-5β-cholan-24-oic acid.

$C_{24}H_{40}O_4$=392.6

CAS — 128-13-2.

ATC — A05AA02.

ATC Vet — QA05AA02.

UNII — 724L30Y2QR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ursodeoxycholic Acid). A white or almost white powder. Practically insoluble in water and in dichloromethane; freely soluble in alcohol; slightly soluble in acetone.

USP 36: (Ursodiol). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether. Store in airtight containers.

Stability. References.

1. Mallett MS, *et al*. Stability of ursodiol 25 mg/mL in an extemporaneously prepared oral liquid. *Am J Health-Syst Pharm* 1997; **54:** 1401–4.
2. Johnson CE, Streetman DD. Stability of oral suspensions of ursodiol made from tablets. *Am J Health-Syst Pharm* 2002; **59:** 361–3.

Uses and Administration

Ursodeoxycholic acid is a naturally occurring bile acid (see p. 2457.2) present in small quantities in human bile. Ursodeoxycholic acid suppresses the synthesis and secretion of cholesterol by the liver and inhibits intestinal absorption of cholesterol. It is given orally for the dissolution of cholesterol-rich **gallstones** in patients with functioning gallbladders (see p. 2639.1). The usual dose is 6 to 12 mg/kg daily as a single bedtime dose or in 2 or 3 divided doses; obese patients may require up to 15 mg/kg daily. The daily dose may be divided unequally and the larger dose given before bedtime to counteract the increase in biliary cholesterol concentration seen overnight. The time required for dissolution of gallstones is likely to be between 6 and 24 months depending on stone size and composition. Treatment should be continued for 3 to 4 months after radiological disappearance of the stones. A dose of 300 mg twice daily may be used for the *prevention* of gallstones in patients undergoing rapid weight loss. Ursodeoxycholic acid has also been given in reduced doses in combination with chenodeoxycholic acid (p. 2475.1).

Ursodeoxycholic acid is also used in **primary biliary cirrhosis** (see below). The usual dose is 10 to 16 mg/kg daily in 2 to 4 divided doses. After the first 3 months of treatment the dose may be taken once daily in the evening.

The more hydrophilic derivative, tauroursodeoxycholic acid, has also been used.

Administration in children. For the use of ursodeoxycholic acid in children, see Chronic Liver Disease, below.

Chronic liver disease. The use of ursodeoxycholic acid in chronic liver diseases has been summarised.[1-5] There have been differing opinions of its value in primary biliary cirrhosis (below). Response has been reported in obstetric cholestasis of pregnancy,[6-10] primary sclerosing cholangitis,[11] chronic active hepatitis,[12] and viral hepatitis.[13,14] Although ursodeoxycholic acid is widely used in the treatment of obstetric cholestasis, data on its safety and efficacy in this indication are lacking, and its possible role therefore remains unclear until further larger studies have been done.[15] See also Adverse Effects and Precautions, p. 2639.2.

Ursodeoxycholic acid appears to be of benefit in liver disease associated with cystic fibrosis[16-18] and in the UK the *BNFC* recommends an oral dose of 10 to 15 mg/kg twice daily in children from 1 month to 18 years of age with this condition; alternatively the total daily dose may be given in 3 divided doses.

Ursodeoxycholic acid had initially shown some promise in the treatment of nonalcoholic steatohepatitis,[19] but a randomised, controlled study[20] failed to confirm this. There has also been some interest in the use of ursodeoxycholic acid to treat refractory graft-versus-host disease of the liver in transplant patients,[21] and possibly as an adjuvant to immunosuppressant therapy[22-24] after orthotopic liver transplantation (p. 1936.3). It may also be of benefit in the prevention of hepatic complications following allogeneic bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1).[25,26]

Ursodeoxycholic acid has shortened the clinical course of parenteral nutrition-associated cholestasis in very-low-birth-weight infants,[27] and benefit has also been reported[28] in children and adults, although the optimal timing and duration of therapy remains to be evaluated. The *BNFC* recommends an oral dose of 10 mg/kg three times daily for neonates and all children up to 18 years of age for cholestasis associated with total parenteral nutrition.

Ursodeoxycholic acid has also been associated with a lower incidence of colonic dysplasia in patients with ulcerative colitis and primary sclerosing cholangitis.[29,30] For sclerosing cholangitis in children from 1 month to 18 years of age, the *BNFC* recommends an oral dose of 5 to 10 mg/kg 2 or 3 times daily up to a maximum of 15 mg/kg 3 times daily depending on response.

In children with cholestatic conditions such as familial intrahepatic cholestasis and biliary atresia, ursodeoxycholic acid may be used to improve bile flow. The *BNFC* recommends an oral dose of 5 mg/kg three times daily in neonates and children up to 2 years of age, the dose and frequency adjusted according to response up to a maximum of 10 mg/kg three times daily. Ursodeoxycholic acid has also been shown to improve liver function for several years when given to children after successful surgery for biliary atresia.[31]

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PRIMARY BILIARY CIRRHOSIS. Primary biliary cirrhosis (PBC) is a chronic liver disease of unknown aetiology that develops due to progressive destruction of small and intermediate bile ducts within the liver, subsequently evolving to fibrosis and cirrhosis. Over 90% of patients are female, usually aged between 40 and 60 years. The disease is thought to be auto-immune in nature. Most patients develop antimitochondrial antibodies that may be evident even before disease is clinically apparent.[1,2] Genetic factors and hormonal stimulation may play a role in precipitating PBC.[1,2] Infectious agents such as *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*)[2] or retroviruses[3] may be involved in the pathogenesis.

Clinical manifestations include pruritus, fatigue, jaundice, hepatomegaly, and hypercholesterolaemia leading to xanthoma formation. In late disease portal hypertension, bleeding oesophageal varices and liver failure may develop. Impaired calcium and vitamin D absorption may result in osteomalacia or osteoporosis, and fat-soluble vitamin deficiencies may occur. There may be accumulation of copper in the liver.[4] Other disorders including rheumatoid arthritis, scleroderma, thyroiditis, and Sjögren's syndrome may be associated with PBC.[1,5]

The disease is slowly progressive, with a mean survival of 8 years for symptomatic patients, and 16 years for asymptomatic individuals.[1,6] Despite its presumed autoimmune aetiology, few immunosuppressive drugs have shown any benefit,[5,7] although newer drugs such as mycophenolate mofetil, sirolimus, and tacrolimus have yet to be fully evaluated.[7]

The best-studied treatment for PBC is ursodeoxycholic acid, which is thought to replace toxic endogenous bile acids, stimulate bile acid secretion, and exert local immunosuppressive and cytoprotective effects.[1,4,5,7-9] The value of ursodeoxycholic acid is controversial: its reported therapeutic benefits in terms of delaying disease progression and the need for liver transplantation[5,10] have not been confirmed by meta-analysis[11] or systematic review,[12] although the former was, however, criticised[13,14] on the grounds that most of the studies included had follow-up periods of only 2 years. In consequence, some do not recommend its use,[11,12,15] but others still believe it to be the treatment of choice.[1,7,13,14,16] Its advocates consider that it appears to be efficacious for about 10 years and improves long-term survival by delaying the progression of hepatic fibrosis, development of oesophageal varices, and the need

for liver transplantation. However, it is not effective in the presence of extensive fibrosis or cirrhosis in advanced disease.[13,14,16]

Both penicillamine and azathioprine have been used in PBC, but studies have failed to show any benefit from treatment[5-7] and their use has declined. A systematic review[17] identified a significant increase in the occurrence of adverse effects with penicillamine and concluded that its use could not be supported for patients with PBC. Corticosteroids, colchicine, ciclosporin, and chlorambucil have also been tried, but toxicity has restricted their use.[5,7] They may be of benefit[2,4,6,7] when used with ursodeoxycholic acid, although some guidelines[5] do not recommend their use. A systematic review[18] of studies with methotrexate concluded that it had no effect on mortality or the need for liver transplantation and should not therefore be used in patients with PBC outside clinical studies. Budesonide[7] and bezafibrate[1,7] have also been tried.

Symptomatic treatment includes the use of bile acid sequestrants, such as colestyramine, to treat both pruritus and hypercholesterolaemia. Ursodeoxycholic acid may also improve pruritus in up to 40% of patients, and rifampicin, phenobarbital, and opioid antagonists are used as second-line therapies.[1,4,5,8] Vitamin D and calcium supplementation will prevent osteomalacia; supplementation with vitamins A, E, and K may also be necessary.[1,4,5,8] Liver transplantation is recommended for liver failure, although PBC can recur in the allograft.[5,13,14,16]

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Gallstones. Gallstones (cholelithiasis) occur when mechanisms for the solubilisation of cholesterol or bilirubin fail or are overcome. They may be divided into those formed of pure cholesterol, which are usually solitary; pigment stones, largely made up of bilirubin or its derivatives; and mixed stones of cholesterol, bile pigment, and calcium salts, which form the great majority of cases seen in the West.

Gallstones are generally more common in women than in men. The prevalence also increases with age and obesity, although rapid weight loss as a result of dieting or surgery is associated with an increased risk.

As many as two-thirds of patients with gallstones are asymptomatic. Symptoms usually relate to the site of the stone although biliary colic is often present regardless of whether the stone is in the gallbladder or biliary tract. If the stone blocks the exit from the gallbladder, inflammation and bacterial infection may follow (acute cholecystitis), sometimes leading to perforation and subsequent peritonitis. Less commonly, obstruction of the common bile duct by gallstones (choledocholithiasis) may lead to cholestasis and jaundice; infection of the bile ducts and septicaemia may follow. Pancreatitis may also be associated with gallstone disease, and there may be an increased risk of developing malignant neoplasms of the gallbladder.

Treatment. Asymptomatic gallstones discovered during other investigations should not be treated, and even mildly symptomatic patients may be managed with analgesics and subsequent observation. Potent analgesics such as morphine may be needed in more severe cases (see Biliary and Renal Colic, p. 6.3). In symptomatic patients the preferred treatment for gallstones is surgical removal of the gallbladder by laparoscopic cholecystectomy which has largely replaced open surgery. Endoscopic retrograde cholangiopancreatography is also widely used to extract gallstones.

In patients unsuited to, or unwilling to undergo, surgery for gallbladder stones, drug therapy, alone or with lithotripsy, may be considered.

Exogenous bile acids have been tried in an attempt to dissolve the cholesterol component of gallstones. Ursodeoxycholic acid is more effective and is associated with fewer adverse effects than chenodeoxycholic acid. Combination therapy has also been tried but this is no more effective than ursodeoxycholic acid alone. Dissolution of gallstones is slow but can be achieved in about one-third of cases with the best results seen with small stones. However, about half of all successfully treated patients will develop further gallstones within 10 years. Studies of prophylactic bile acid therapy have mostly yielded disappointing results, although such therapy may be of benefit in patients on very-low-calorie diets, after surgery for weight loss, and in those receiving treatment with octreotide.

Somewhat larger stones may respond to extracorporeal shock-wave lithotripsy, mechanical lithotripsy, intracorporeal electrohydraulic lithotripsy, or fluoroscopically guided laser lithotripsy. Oral bile acids should then be given to dissolve the stone fragments.

Another method that has been used is the direct instillation of a solvent such as methyl *tert*-butyl ether or monooctanoin into the gallbladder, which dissolves stones in some patients. However, this form of treatment is no longer recommended given the frequency and seriousness of complications associated with the technique.

Patients with **stones in the common bile duct** or **acute cholecystitis** require prompt therapy because of the risk of serious complications; endoscopic sphincterotomy and physical retrieval of the stones with a basket or balloon catheter appears to be the preferred treatment, with open surgery as an alternative. A biliary stent to allow bile flow around the stone has been used as a temporary measure in patients with stones too large to remove by endoscopic sphincterotomy.

In patients who develop cholecystitis or cholangitis antibacterial therapy may be required (see Biliary-tract Infections, p. 174.2).

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Adverse Effects and Precautions

Ursodeoxycholic acid may cause nausea, vomiting, and other gastrointestinal disturbances; diarrhoea is reported to occur less frequently than with chenodeoxycholic acid. Pruritus may occur. Calcification of gallstones and deterioration in liver function have been reported rarely.

Ursodeoxycholic acid should not be given to patients with intestinal and hepatic disorders that interfere with entero-hepatic circulation of bile salts (but see Chronic Liver Disease p. 2638.2). It is ineffective for the dissolution of calcified and radio-opaque gallstones and is of no value in patients without a patent and functioning gallbladder. Liver enzymes and bilirubin levels should be monitored every 4 weeks during the first 3 months of treatment and every 3 to 6 months thereafter. Licensed product information recommends that its use should be avoided in pregnancy.

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1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Ursodeoxycholic acid should not be used with drugs that increase bile cholesterol such as oestrogenic hormones and cholesterol-lowering drugs such as clofibrate. Use with bile-acid binding drugs including antacids, charcoal, and colestyramine should be avoided since this may reduce the efficacy of therapy with ursodeoxycholic acid.

For references to the possible effects of ursodeoxycholic acid on ciclosporin, see p. 1955.1.

Pharmacokinetics

Ursodeoxycholic acid is absorbed from the gastrointestinal tract and undergoes enterohepatic recycling. It is partly conjugated in the liver before being excreted into the bile. Under the influence of intestinal bacteria the free and conjugated forms undergo 7α-dehydroxylation to lithocholic acid, some of which is excreted directly in the faeces and the rest absorbed and mainly conjugated and sulfated by the liver before excretion in the faeces. However, in comparison with chenodeoxycholic acid, less ursodeoxycholic acid undergoes such bacterial degradation.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Audecol; Dexo; Solutrat; UDCA; UR 03; Ursidesox; Ursofalk; Ursomax; Urzac; ***Austral.***: Urso; Ursofalk; ***Austria***: Ursofalk; ***Belg.***: Ursochol; Ursofalk; ***Braz.***: Ursacol; ***Canad.***: Urso; ***Chile***: Solvobil; Ursofalk; ***China***: Taurolite (滔罗特); Ursofalk (优思弗); ***Cz.***: Ursochol; Ursofalk; Ursosan; ***Fin.***: Adursal; ***Fr.***: Delursan; Ursolvan; ***Ger.***: Cholit-Ursan†; Cholofalk†; UDC†; Ursochol; Ursofalk; ***Gr.***: Ursofalk; ***Hong Kong***: Urso; Ursofalk; Ursosan†; ***Hung.***: Ursofalk; ***India***: Actibile; Golbi; Intraliv-UD; Livokind; Udiliv; ***Indon.***: Estazor; Lofibra; Pramur†; Urdafalk; Urdahex; Ursochol; Ursolic; ***Irl.***: Ursofalk; ***Israel***: Ursofalk; Ursolit; ***Ital.***: Biliepar; Desoxil; Deursil; Dissolursil; Fraurs; Litoff; Litursol; Tauro; Tudcabil†; Urdes; Ursacol; Ursilon; Ursobil; Ursodamor†; Ursoflor; Ursolisin; ***Jpn***: Urso; ***Malaysia***: Ursofalk; ***Mex.***: Ursofalk; ***Neth.***: Ursochol; Ursofalk; ***Norw.***: Ursofalk; ***NZ***: Actigall; Ursofalk; ***Philipp.***: Ursofalk; ***Pol.***: Proursan; Ursocam; Ursofalk; Ursopol; ***Port.***: Destolit; Ursofalk; ***Rus.***: Urdoxa (Урдокса); Ursodex (Урсодекс); Ursofalk (Урсофальк); Ursoliv (Урсолив); Ursorom (Урсором); Ursosan (Урсосан); ***S.Afr.***: Ursotan; ***Singapore***: Ursofalk; ***Spain***: Bilifalk; Ursobilane; Ursochol; ***Swed.***: Ursofalk; Ursosan; ***Switz.***: De-ursil; Ursochol; Ursofalk; ***Thai.***: Udihep†; URSA; Ursofalk; Ursolin; ***Turk.***: Taurolite; Ursofalk; ***UK***: Destolit; Urdox; Ursofalk; Ursogal; ***Ukr.***: Choludexan (Холудексан); Ursochol (Урсохол); Ursofalk (Урсофальк); Ursosan (Урсосан); ***USA***: Actigall; Urso.

Multi-ingredient Preparations. ***China***: Dages (达吉); ***Ger.***: Lithofalk†; ***Gr.***: Lithofalk; ***Ital.***: Bilenor; ***Jpn***: Cabe 2†; Eki Cabe S.

Pharmacopoeial Preparations
BP 2014: Ursodeoxycholic Acid Capsules; Ursodeoxycholic Acid Tablets;
USP 36: Ursodiol Capsules; Ursodiol Oral Suspension.

Urtica

Brännässleblad (nettle leaf); Brennessel; Dilgėlių lapai (nettle leaf); Kopřivový list (nettle leaf); Liść pokrzywy (nettle leaf); Nokkosenlehti (nettle leaf); Ortie; Ortie dioïque; Ortie, feuille d' (nettle leaf); Ortiga; Ortiga mayor; Pokrzywa zwyczajna; Stinging Nettle; Urtica dioica; Urticae folium (nettle leaf); Крапива Двудомная (*Urtica dioica*).

ATC Herb — HG04CW5009 (Urtica dioica: *herb); HA05AW5018* (Urtica dioica: *fruit); HG04CW5010* (Urtica dioica: *root); HA07XA5014* (Urtica dioica: *fruit); HG04BW5041* (Urtica dioica: *herb); HG04BW5042* (Urtica dioica: *root); HM02AX5005* (Urtica dioica: *fruit); HM01AW5024* (Urtica dioica: *herb).*

UNII — 710FLW4U46 (Urtica dioica); *IHN2NQ5OF9* (Urtica urens); *0DCW2P163M* (Urtica urens *leaf).*

Pharmacopoeias. In *Ger.* and *US* (both specify the root and rhizome of *Urtica dioica*).

Eur. (see p. vii) includes the leaf of *Urtica* spp. and also a form of *Urtica dioica* for homoeopathic preparations.

Br. includes a form of *Urtica urens* for homoeopathic preparations.

Ph. Eur. 8: (Nettle Leaf; Urticae Folium). The whole or cut dried leaves of *Urtica dioica*, *Urtica urens*, or a mixture of the 2 species. It contains a minimum of 0.3% for the sum of caffeoylmalic acid and chlorogenic acid expressed as

chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated on the dried basis.

Ph. Eur. 8: (Common Stinging Nettle for Homoeopathic Preparations). The whole, fresh, flowering plant of *Urtica dioica*. Protect from light.

BP 2014: (Urtica Urens Herb for Homoeopathic Preparations). Fresh leaves and flowers of *Urtica urens*. The plant produces an itchy, burning sensation.

USP 36: (Stinging Nettle). The dried roots and rhizomes of *Urtica dioica* (Urticaceae), and may contain *Urtica urens*, known in commerce as dwarf nettle, as a minor component. It contains not less than 0.8% of total amino acids, not less than 0.05% of sitosterol, and not less than 0.003% scopoletin ($C_{10}H_8O_4$ = 192.2), calculated on the dried basis. Store in airtight containers. Protect from light.

Profile

Urtica (*Urtica dioica*) has been used in herbal medicine, mainly for urinary-tract and rheumatic disorders. *Urtica urens* has been used similarly.

Homoeopathy

Urtica has been used in homoeopathic medicines under the following names: Common stinging nettle; Urtica dioica; Urtica di.

Urtica urens has been used in homoeopathic medicines under the following names: Urtica ur; Urt. u.

References.

1. WHO. Radix Urticae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/31.html (accessed 04/02/10)
2. Safarinejad MR. *Urtica dioica* for treatment of benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled, crossover study. *J Herb Pharmacother* 2005; **5:** 1–11.
3. Alford L. The use of nettle stings for pain. *Altern Ther Health Med* 2007; **13:** 58.
4. Anonymous. *Urtica dioica; Urtica urens* (nettle). *Altern Med Rev* 2007; **12:** 280–4.
5. Sahin M, *et al*. Gynaecomastia in a man and hyperoestrogenism in a woman due to ingestion of nettle (Urtica dioica). *N Z Med J* 2007; **120:** U2803.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Uro-POS†; ***Cz.***: Koprivovy Caj, Koprivova Nat; ***Ger.***: Bazoton; Hox Alpha; Natu-lind; Natu-prosta; Prosta-Truw; Prostafortont; Prostaherb N; Prostamed Urtica; Prostata†; Rheuma-Hek; Rheuma-Kapseln†; Selenk; Uro-POS†; Urol pros; Urtivit†; utk; ***Pol.***: Prostaherb N; Urtix; ***Rus.***: Prostaherb N (Простагерб Н); ***Singapore***: Prostakan; ***Switz.***: Valverde Prostate capsules; ***UK***: DiaUrtica; Nettle Leaf Capsules; ***Ukr.***: Allocholum (Аллохол).

Multi-ingredient Preparations. ***Arg.***: Cistidac; Novo Prostasan; Prostafit; Troxac; ***Austral.***: Bio Iron; Extralife Flow-Care†; Fe-Max; Haemo-Red; HRF; Irontona†; Prosta Balance; ProstaCo; Prostate Care; Prostate Health Formula; Vitatona†; ***Austria***: Anaemodoron; Berggeist; Menodoron; Prostagutt; Urogutt; ***Belg.***: Prostalane†; Prostatonin†; ***Braz.***: Prostem Plus; ***Canad.***: Floradix Kindervital†; Floradix Tab†; Rheuma Heilkrauter Tee†; Ultra Quercitin†; ***Cz.***: Calmonal†; Diabeticka Cajova Smes-Megadiabetin†; Prostakan Forte; Pulmoran; Species Urologicae Planta; ***Fr.***: Alpharegul Femme; Alpharegul Homme; Arthroflorine†; Biofirm; Cledist; Phytalgic; ProstaSecurA; Silibiol; Sun Vue; ***Ger.***: Combudoron; Menodoron; Prostagutt forte; Vollmers praparierter gruner N; ***Hong Kong***: Calmiderm; ***Hung.***: Diabess; Herbalakt; Kilo-Nit; Majvedo es Detoxikalo; Prostatonin; Prostazyn; Telma; Urogin; Uroherb; Vensaxa; Vesevedo; Zeatax; ***Irl.***: Combudoron†; ***Ital.***: Bioestril Valeriana; Biothymus DS; Dren'it; Lignamid; Pluvio; Prostaplant; ***Mex.***: Prosgutt; ***Philipp.***: Lungcaire Plus; ***Pol.***: Alliofil; Herbaton†; Immunofort; Naturapia Prostata†; Nefrobonisol; Seboren; Urofort; ***Rus.***: Herbion Urtica (Гербион Уртика); Laxantis Species No 1 (Слабительный Сбор 1); Polygemostat (Полигемостат); Prostagutt Forte (Простагут Форте); ***S.Afr.***: Combudoron†; Enzian Anaemodoron Drops†; Fragador†; Menodoron†; ***Singapore***: Hair and Nails; ***Switz.***: Combudoron; Kernosan 26; Menodoron; Prostagutt-F; Prostatonin; The d'avoine verte Vollmers†; Tisane Diuretique; Tisane pour les problemes de prostate; ***UK***: Sinose; ***Ukr.***: Fitoval Shampoo (Фитовал шампунь); Pravenor (Правенор); Prostaplant Forte (Простаплант Форте); Vitrum Beauty Elite (Витрум Бьюти Элит).

Homoeopathic Preparations. ***Austral.***: Allergy Relief; ***Austria***: Berberis Cosmoplex†; Sonnenbrandspray; ***Canad.***: Common Mallow Combination†; Cutisitum†; Execalm†; Hives; Ursical Formula†; Urticalcin; ***Chile***: Apis Compuesto; Arnica Compuesta; Bioactiv L; Similibus; ***Cz.***: Galium; ***Fr.***: Formica Rufa Compose; Rhus Toxicodendron Compose; Urocalm; Urtica Complexe No 82†; ***Ger.***: Araniforce arthro; Chelidonium comp; Cysto Hevert; Heweurat N; Levisticum S; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Rheuma-Hevert†; Solidagosan N; ***Neth.***: Actelite; Chavita 1; Combudoron; Itch Care; Phonix Solidago comp; Prrrikweg; Prurilite; Red Skin; Skin Care; Urtizon complex; ***Rus.***: Urtica-Plus (Уртика-Плюс); ***Switz.***: Silacten; Urticalcin; ***UK***: Burns Cream; Combudoron; Fragador; Menodoron.

Usnea Barbata

Barba de capuchino; Barba de Fraile; Уснея Бородатая.
CAS — 125-46-2 (usnic acid).
UNII — D6DVA9TCAP.

NOTE. The name Barba de Fraile has also been used for *Fimbristylis littoralis*.

Profile

Usnea barbata is a lichen. It contains usnic acid, which is reported to have antimicrobial activity. *Usnea barbata* extract, usnic acid, and copper usnate have been used in topical preparations.

Adverse effects. Severe hepatotoxicity was believed to be associated with usnic acid contained in a multi-ingredient herbal preparation promoted for weight loss; one patient required emergency liver transplantation.[1] The toxicity of usnea barbata extracts and usnic acid has been reviewed.[2]

1. Sanchez W, *et al*. Severe hepatotoxicity associated with use of a dietary supplement containing usnic acid. *Mayo Clin Proc* 2006; **81:** 541–4.
2. Guo L, *et al*. Review of usnic acid and Usnea barbata toxicity. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2008; **26:** 317–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Vidermina; Zeta N†.

Multi-ingredient Preparations. ***Indon.***: Scabicid; ***Ital.***: Foot Zeta; Micofoot; Sideck Shampoo Antiforfora; Steril Zeta; Steril Zeta.

Homoeopathic Preparations. ***Fr.***: Neurocynesine†; ***Ger.***: Usneabasan; ***Neth.***: Neurocynesine†.

Valepotriates

Valepotriatos; Валепотриаты.

Acevaltrate *(rINN)*

Acévaltrate; Acevaltrato; Acevaltratum; Ацевалтрат.
4-Acetoxymethyl-(1 or 6)-3-(acetoxy-3-methylbutyryloxy)-1,6,7,7a-tetrahydro-(6 or 1)-isovaleryloxycyclopenta[*c*]pyran-7-spiro-2′-oxiran.
$C_{24}H_{32}O_{10}$=480.5
CAS — 25161-41-5.
UNII — S9MFK45GY9.

Didrovaltrate *(rINN)*

Didrovaltrato; Didrovaltratum; Дидровальтрат.
6-Acetoxy-1,4a,5,6,7,7a-hexahydro-1-isovaleryloxy-4-isovaleryloxymethylcyclopenta[*c*]pyran-7-spiro-2′-oxiran.
$C_{22}H_{32}O_8$=424.5
CAS — 18296-45-2.
UNII — KEN63D125F.

Valtrate *(pINN)*

Valtrato; Valtratum; Вальтрат.
4-Acetoxymethyl-1,6-di-isovaleryloxy-1,6,7,7a-tetrahydrocyclopenta[*c*]pyran-7-spiro-2′-oxiran.
$C_{22}H_{30}O_8$=422.5
CAS — 18296-44-1.
UNII — L3JQ035X9B.

Profile

Valepotriates are epoxy-iridoid esters, isolated from valerian (see below). They include acevaltrate, didrovaltrate, and valtrate. On prolonged storage and drying they are hydrolysed to yield isovaleric acid.

A mixture stated to contain acevaltrate, didrovaltrate, and valtrate has been used as a sedative and as an anxiolytic. Concern has been expressed over the potential toxicity of valepotriates which have been reported to have cytotoxic properties *in vitro*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Valmane; ***Gr.***: Valmane.

Multi-ingredient Preparations. ***Arg.***: SDN 200.

Valerian

Baldrianwurzel; Korzeń kozłka; Kozlíkový kořen; Macskagyökér; Raíz de valeriana; Rizoma de valeriana; Valer; Valeriaananjuuri; Valerian Rhizome; Valerian Root; Valeriana; Valerianae Radix; Valerianarot; Valériane, racine de; Valerijonų šaknys; Валериана.
CAS — 8057-49-6 (valerian extract).
ATC — N05CM09.
ATC Vet — QN05CM09.
ATC Herb — HA03AW5061 (Valeriana officinalis: root); HN05CM5027 (Valeriana officinalis: root).
UNII — JWF5YAW3QW (Valeriana officinalis root).

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Eur.* also includes cut valerian root, valerian dry aqueous extract, dry hydroalcoholic extract, and tincture. *US.* includes the powdered form.

Jpn has Japanese Valerian from *V. fauriei*.

Ph. Eur. 8: (Valerian Root; Valerian BP 2014). The yellowish-grey to pale brownish-grey whole underground parts of *Valeriana officinalis*, including the rhizome surrounded by the roots and stolons, or by fragments of these parts. It contains not less than 0.4% v/w of essential oil for the whole drug and not less then 0.3% v/w for the cut drug, both calculated with reference to the dried drug. Protect from light.

USP 36: (Valerian). The subterranean parts of *Valeriana officinalis* (Valerianaceae), including the rhizome, roots, and stolons. It contains not less than 0.5% of volatile oil, not less than 0.05% of valerenic acid, and not less than 0.17% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid, on the dried basis. Store in airtight containers. Protect from light.

Uses and Administration

Valerian has sedative properties and is used as an extract, infusion, or tincture, or occasionally as the dried root, in preparations for anxiety states. It has also been used as a carminative. Valerian oil is used in aromatherapy. The odour of valerian may be removed from the skin and from hard surfaces with sodium bicarbonate.

References.

1. WHO. Radix Valerianae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/29.html (accessed 04/02/10)
2. Houghton PJ. The scientific basis for the reputed activity of valerian. *J Pharm Pharmacol* 1999; **51:** 505–12.
3. Plushner SL. Valerian: valeriana officinalis. *Am J Health-Syst Pharm* 2000; **57:** 328–35.
4. Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. *Sleep Med* 2000; **1:** 91–9.
5. Bent S, *et al*. Valerian for sleep: a systematic review and meta-analysis. *Am J Med* 2006; **119:** 1005–12.
6. Taibi DM, *et al*. A systematic review of valerian as a sleep aid: safe but not effective. *Sleep Med Rev* 2007; **11:** 209–30.

Adverse Effects and Precautions

Chronic ingestion of valerian has been associated with headache, insomnia, agitation, and hepatotoxicity. Cardiac complications and delirium have been reported following abrupt withdrawal. Symptoms of overdose have included fatigue, lightheadedness, abdominal pain, tremor, hypotension, and mydriasis.

References.

1. MacGregor FB, *et al*. Hepatotoxicity of herbal remedies. *BMJ* 1989; **299:** 1156–7.
2. Garges HP, *et al*. Cardiac complications and delirium associated with valerian root withdrawal. *JAMA* 1998; **280:** 1566–7.
3. Health Canada. Natural health products and adverse reactions: update. *Can Adverse React News* 2009; **19** (1): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v19n1-eng.pdf (accessed 16/08/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valerian as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nervisatis; ***Austral.***: Dozile Natural; ***Belg.***: Dormiplant Mono; Dormiplant†; Relaxine; Valerial; ***Braz.***: Ansival; Noctaval; Recalm; Sonoripan; Sonotabs†; Traminer†; Valdorm; Valeriane; Valerimed; Valerin†; Valerix; Valezen; Valmane; ***Canad.***: Nytol Natural Source; ***Chile***: Sominex; ***Cz.***: Kozlik; ***Denm.***: Valerina Forte; ***Fin.***: Dormiplant; Sedonium; ***Ger.***: Baldorm†; Baldrivit; Baldurat†; Cefan†; Dolestan†; Euvegal Balance; Ivel mono†; Kytta-Sedativum†; Luvased mono†; Pascosedon Baldrian†; Sedonium; ***India***: Naturbotic; ***Irl.***: Valdrian; ***Israel***: Relaxine; Valeton; ***Ital.***: Noctaval; Ticalma; ***Mex.***: Neolaikan; ***Neth.***: Dormiplant; Nerviplant†; Sedonium†; Valdispert; ***Norw.***: Sobal Forte†; Valerina Forte; ***Pol.***: Cirkused; Relana Forte; Valerin; ***Port.***: Livetan; Valdispert; Valditas†; ***Rus.***: Cirkulin (Циркулин); Novo-Passit (Ново-Пассит); Phytorelax (Фиторелакс); Valdispert (Валдисперт); ***S.Afr.***: Calmettes†; ***Spain***: Ansiokey; Coenrelax; Normoval; Ratiomir†; Tauval†; Valdispert; Valeriana Orto†; Valsedan†; Verdeval†; ***Swed.***: Baldrian-Dispert; Dormiplant; Neurol; Neval; Valerecen; Valerina; ***Switz.***: Baldriparan pour la

nuit; Natu-Seda; Plantival Mono; ReDormin†; Sanadorm; Sedasol eco natura†; Sedonium; Valdispert†; ***Thai.***: Valian-x; ***Turk.***: Cirkulin Valerian; ***UK***: DiaMood; DiaNight; DiaSleep; Kalms Night; Kira Restful Sleep; Niteherb; Phytorelax; Relaxisleep; Sedonium; SleepAid; SleepEezy; Valdrian; ValRelax; ***Venez.***: Floral Pas.

Multi-ingredient Preparations. ***Arg.***: Armonil; Calmtabs; Dioxicolagol; Incaico Serenidad; Nervocalm; Phytocalm; SDN 200; Sedanat†; Sedante Dia; Serenil; Sigmasedan; Valeriana Compuesta; Valeriana Diates†; Valeriana Oligoplex; Valeriana Relax Diates†; Valeriana; ***Austral.***: Advanced Restless Leg Care; Calmo†; Coleus Complex†; Dan Shen Compound; Executive B†; Extralife Sleep-Care†; Humulus Compound; Lavandula Compound; Lemsip First Signs Cold & Flu Day + Night; Natural Deep Sleep†; Nervatona Focus; Nyal Cold + Flu Fighter Day + Night; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Nyal Sleep Aid; Passionflower Plus†; PM Dreamtime; ReDormin; Sleep Easy; Sleep Sound Formula; Valerian Complex; ***Austria***: Baldracin; Baldrian comp; Hova; Nervenruh; Nerventee St Severin; Neurapas; Schlaf- und Beruhigungsdragees; Sedogelat; Wechseltee St Severin; ***Belg.***: Calmiplant; Natudor; Seneuval; Songha†; ***Braz.***: Remilev; Sedantol; Sominex; Sonhare; ***Canad.***: Calm-Aid†; Calmane; Detente†; Dormane Plus; Dormane Tisane; Dormane; Herbal Insomnia†; Herbal Nerve†; Myoplex†; Nervinat; Nervrite; Painease; Phytocalm†; Relaxant; Relaxol; Salusan†; Sleep Relax; ***Chile***: Armonyl Nocturno; Armonyl; Recalm†; Valupass; ***Cz.***: Baldracin†; Doppelherz Energie-Tonikum†; Dr Theiss Schwedenbitter†; Euvekan†; Hova; Nervova Cajova Smes; Novo-Passit; Passit; Persen; Sanason†; Species Nervinae Planta; Valofyt Neo†; ***Denm.***: Relana†; ***Fr.***: Biocarde; Boribel Tisane No 8†; Calmiflorine†; Calmotisan†; Euphytose; Fibromyalgine Fort; Mediflor Tisane Calmante Troubles du Sommeil No 14; Neuroflorine†; Passinevryl†; Phytozac; Sedalozia†; Spasmine; Tranquital; ***Ger.***: Alluna Nacht†; Allunapret; Ardeysedon; Avedorm duo†; Baldrian-Dispert Nacht†; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee†; Dreierlei; Einschlaf-Kapsein extra†; Euvegal Entspannungs- und Einschlaftropfen; Euvegal; Heumann Beruhigungstee Tenerval; Hingfong-Essenz Hofmanns; Hyperesa†; Kneipp Gute Nacht†; Kytta-Sedativum; Moradorm S; Nervenkapseln; Neurapas; Oxacant-sedativ; Pascosedon; Phytonoctu; Plantival forte; Plantival novo; Psychotonin-sed†; Sandrin; Schwedentrunk Elixier; Seda-Plantina N; Sedacur; Sedariston Konzentrat†; Sedariston plus†; Sedaselect D; Selon; Tornix; Valeriana Beruhigungsdragees; Vivinox Day; ***Gr.***: Passinevrol; Vivinox; ***Hung.***: Cirkulin Valeriana; Doppelherz Energie Tonikum N; Euvekan†; Habstal-Nerv N; Hova; Kalms; Kardalept; ReDormin; Sedacur; Sedogelat; Worishofener; ***India***: Gynedol; Neo-Cordial; Nicy Days; ***Indon.***: Slip-iZZZ†; ***Irl.***: Avena Sativa Comp; Quiet Life; ***Israel***: Calmanervin; Calmanervin; Nerven-Dragees; Passiflora Compound†; Passiflora; Redormin Night; Songha Night; ***Ital.***: Anevrasi; Biocalm; Bioestril Valeriana; Calmason; Dormiplant; Fitosonno; Florelax; Glicero-Valerovit; Noctis; Parvisedil; Pineal Notte; Sedatol; Sedopuer F; ***Mex.***: Ivel†; Nervinetas; Pasinordin; Plantival; ***Neth.***: Plantival; ***Norw.***: Euvekan†; Sobal†; Songha Natt; Valerina Natt; ***Philipp.***: Sleepasil; ***Pol.***: Calmina; Cardiol C; Cardiotonic; Cholitol; Doppelherz Energovital Tonik K; Doppelherz Energovital Tonik†; Dormiplant; Fortestomachicae; Guttae Stomachicae; Hova; Kalms; Krople Zoladkowe†; Krople Zoladkowe; Krople Zoladkowe; Lekosen†; Lumewal; Lunapret; Neocardina; Neospasmina; Neospasmol†; Nervendragees; Nervomag; Nervomix; Nervosan†; Nervosol; Nerwobonisol; Padma 28; Passispasmin; Passispasmol†; Persen; Prostapol; Relana†; Sedomix; Somnoten†; Tabletki Uspokajajace; Uroprost; Vallup†; Valuherb; Valused; ***Port.***: Antispasmina Colica†; ***Rus.***: Bromenval (Броменвал); Cardiovalen (Кардиовален); Dentaguttal (Дентагуттал); Dentaplus (Дентаплюс); Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Dormiplant (Дормиплант); Gastroguttal (Гастроготтал); Herbion Drops for the Heart (Гербион Сердечные Капли)†; Insti (Инсти); Passifit (Пассифит); Persen (Персен); Sanason (Санасон); Sedativae Species No 2 (Седативный Сбор 2); Sedativae Species No 3 (Седативный Сбор 3); Valemidin (Валемидин); Valocormid (Валокормид); Zelenin (Зеленин); ***S.Afr.***: Avena Sativa Comp†; Biral†; Entressdruppels HM; Helmontskruie†; Krampdruppels; Restin†; Stuidruppels; Wonderkroonessens; ***Spain***: Dormiplant†; Melival; Nervikan; Netisum; Neurapas; Relana†; Sedonat; Tranquigor; Valdispert Complex; Valeriana Leo; Valrelax†; ***Swed.***: Dormeasan; Sedacur; ***Switz.***: Arteria-vita; Baldriparan; Cardiophyt A; Dormeasan; Dormiplant; Dragees pour la detente nerveuse et le sommeil†; Dragees pour la detente nerveuse†; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Femisan; Hova; Metabol; Nervinetten; Padma 28; Padmed Circosan; ReDormin; Relaxane; Relaxo; Songha Night; Strath Gouttes pour le nerfs et contre l'insomnie; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; Valverde Coeur; Valverde Detente dragees; Valverde Sommeil; Zeller Sommeil; ***Turk.***: Nervikan; Nevrol Cemal; ***UK***: Avena Sativa Comp; Bio-Strath Valerian Formula; Botanova; Chamomile Blend; Daily Tension & Strain Relief; DiaCalm; DiaDay & Night; DiaNight Plus; DiaRelax; DiaSleep Plus; Digestive; Dornneasan; Gerard House Serenity; Gerard House Somnus; Goodnight; Herbal Indigestion Naturtabs; Herbal Pain Relief; HRI Calm Life; HRI Golden Seal Digestive; HRI Night; Indigestion and Flatulence; Kalms Day; Kalms Sleep; Kalms; Laxative Tablets; Menopause Relief; Modern Herbals Stress; Natrasleep; Natural Herb Tablets; Neurotone; Newrelax; Niteherb Plus; Nodoff; Nytol Herbal; Padma 28; Padma Circosan; Period Pain Relief; PMT Formula; Prementaid; Puncto SleepTight; Quiet Days; Quiet Life; Quiet Nite; Quiet Tyme; Relax B+; Scullcap & Gentian Tablets; Sominex Herbal; Stressless; SuNerven; Sure-Lax (Herbal); Tranquil; Unwind Herbal Nytol; Valerian Passiflora and Hops; Valerina Day Time; Valerina Night-Time; Vegetable Cough Remover; Wellwoman; Wind & Dyspepsia Relief; ***Ukr.***: Central-B (Централ-Б); Dormiplant (Дормиплант); Florised (Флорисед); Gastropin (Гастропин); Herbion Drops for Heart (Гербион Сердечные Капли)†; Herbion Sedative Drops (Гербион Успокаивающие Капли)†; Insti (Інсті); Menovalen (Меновален); Novo-Passit (Ново-Пассит); Persen (Персен); Relaxil (Релаксил); Sanason (Санасон)†; Sedafiton (Седафитон); Sedasen (Седасен); Sedavit (Седавит); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trivalumen (Тривалумен); Trypsidan (Трипсидан)†; ***USA***: PowerSleep; ***Venez.***: Equaliv; Euvekan; Femendol; Insocaps; Lupassin; Nervinetas; Pasidor; Pasifluidina; Rendetil; Sedival.

Homoeopathic Preparations. ***Austral.***: Nervatona Focus; Sleep & Insomnia Relief; ***Austria***: Aurumheel; Pasconal; Valerianaheel; ***Canad.***: Amphosca†; Aurumheel†; Calsom†; Homeo-Form I†; Homeo-Form M†; Homeo-Form ST†; Insomnia Passiflora†; Insomnia; Kids Calm; Mental Alertness; Soludor†; Stress L72†; Stress; Travel Sickness; Valerianaheel Comp†; ***Fr.***: Acidum Phosphoricum Complexe No 5; Amphosca Orchitine; Amphosca Ovarine; Boripharm No 3; Calmodren; Dolirelax†; L 72; Passiflora GHL; Poconeol no 32†; Soludor; Somnidoron; Strophantus Compose; Vespa Complexe No 46†; ***Ger.***: Alho-Sedosan; Angioton S†; Avena sativa comp†; Calmvalera; Corselect N; Crataegus Herzcomplex; Diacard; Dormi-Gastreu S R14; Dormosyx; dysto-loges N; Hyperforat Nervo; Liquidorm N; Nervoid N; Nervoject F; Nervoregin comp; Neuro-Ginsan N; Pasconal Nerventropfen; Passiflora Complex†; Pectapas; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rowo Rytesthin Ro-Plex (Rowo-318); Rytesthin; Sedacalman; Sedaphin†; Sedaselect; Sedativa-Injektopas; Tondinel H; Zappelin N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Aurumheel; ***Neth.***: Homeocare Nervo; Hyperilite; Weleda Avena Valeriana; ***Rus.***: Valeriana-Plus (Валериана-Плюс); ***Switz.***: Gouttes d'Or; Nelsons Noctura†; ***UK***: Noctura; ***Ukr.***: Kindinorm (Киндинорм).

Pharmacopoeial Preparations

Ph. Eur.: Valerian Dry Hydroalcoholic Extract; Valerian Tincture; **USP 36:** Valerian Tablets; Valerian Tincture.

Valeric Acid

Acide pentanoïque; Ácido Valérico; Baldriansäure; Baldriānskābe; Kwas walerianowy; Kyselina Pentanová; Kyselina Valerová; Pentaanzuur; Pentanoic Acid; Pentansäure; Pentansyra; Propylacetic Acid; Valeriaanahappo; Valeriaanzuur; Valerianic Acid; Valeriansäure; Valeriánsav; Valeriansyra; *n*-Valeric Acid; Валериановая Кислота; Валериановa Киселина.

1-Butanecarboxylic acid.

$C_5H_{10}O_2$=102.1

CAS — 109-52-4.

UNII — GZK92PJM7B.

NOTE. The name valeric acid has been used for a mixture of valeric acid and isovaleric acid.

Isovaleric Acid

Acide Isovalérianique; Ácido Isovalérico; Delphinic Acid; Isopentanoic Acid; Isopentansyra; Isopropylacetic Acid; Isovaleriaanzuur; Isovalerianic Acid; Isovaleriansäure; Isovaleriansyra; Kwas Izowalerianowy; 3-Methylbutaanzuur; 3-Methylbuttersäure.

3-Methylbutanoic acid.

$C_5H_{10}O_2$=102.1

CAS — 503-74-2.

UNII — 1BR7X184L5.

Profile

Valeric acid and isovaleric acid have been used in the treatment of nervous conditions. Some of their salts have been used similarly. Esters of valeric acid and isovaleric acid are used as flavourings and in perfumery.

Homoeopathy

Salts of valeric acid and isovaleric acid have been used in homoeopathic medicines. Zinc valerate has been used under the following names: zincum valerianicum; zincum isovalerianicum; zinkvalerianat; zinkisovalerianat

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Neurol.

Homoeopathic Preparations. ***Austria***: Avena Rihom Komplex†; Globuli gegen Schlafstorungen; Nervoheel; Notta; ***Canad.***: Ervopax†; ***Fr.***: Cocculus Complexe No 73; Nervopax; Tarentula Complexe No 71; ***Ger.***: Agnus castus comp†; Agnus femin; Alho-Sedosan; Calmvalera; Curare comp; Dormi-Gastreu S R14; Nervoregin comp; Neurexan; Presselin Nervenkomplex; Presselin Nervennahrung N†; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Sedakatt; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Nervoheel; ***Neth.***: Kind 0-6 Kindival; Myamolite; Nervival; Nervoheel; ***Rus.***: Notta (Нотта); Uspokoi (Успокой); Valeriana-Plus (Валериана-Плюс); ***Switz.***: Nervoheel; ***Ukr.***: Dormikind (Дормикинд); Notta (Нотта).

Valspodar *(BAN, USAN, rINN)*

PSC-833; SDZ-PSC-833; Valspodarum; Вальсподар.

Cyclo{[(2*S*,4*R*,6*E*)-4-methyl-2-(methylamino)-3-oxo-6-octenoyl]-L-valyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl}.

$C_{63}H_{111}N_{11}O_{12}$=1214.6

CAS — 121584-18-7.

UNII — Q7ZP55KF3X.

NOTE. The name Amdray has been used as a trade mark for valspodar.

Profile

Valspodar is an analogue of ciclosporin (p. 1945.2). It inhibits P-glycoprotein, which is associated with multidrug resistance. Valspodar is being investigated in various neoplasms to restore sensitivity of resistant tumour cells to anticancer drugs, but results have been disappointing.

Valspodar inhibits the cytochrome P450 isoenzyme CYP3A4, and may reduce the metabolism and clearance of other drugs.

References.

1. Advani, R, *et al.* Treatment of poor prognosis AML patients using PSC833 (valspodar) plus mitoxantrone, etoposide, and cytarabine (PSC-MEC). *Adv Exp Med Biol* 1999; **457:** 47–56.
2. Sparreboom A, Nooter K. Does P-glycoprotein play a role in anticancer drug pharmacokinetics? *Drug Resist Updat* 2000; **3:** 357–63.
3. Kang MH, *et al.* The P-glycoprotein antagonist PSC 833 increases the plasma concentrations of 6α -hydroxypaclitaxel, a major metabolite of paclitaxel. *Clin Cancer Res* 2001; **7:** 1610–17.
4. Fracasso PM, *et al.* Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: a gynecologic oncology group study. *J Clin Oncol* 2001; **19:** 2975–82.
5. Baekelandt M, *et al.* Phase I/II trial of the multidrug-resistance modulator valspodar combined with cisplatin and doxorubicin in refractory ovarian cancer. *J Clin Oncol* 2001; **19:** 2983–93.
6. Baer MR, *et al.* Phase 3 study of the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age and older with acute myeloid leukemia: Cancer and Leukemia Group B Study 9720. *Blood* 2002; **100:** 1224–32.
7. Ma MK, *et al.* Pharmacokinetic study of infusional valspodar. *J Clin Pharmacol* 2002; **42:** 412–18.
8. Greenberg PL, *et al.* Mitoxantrone, etoposide, and cytarabine with or without valspodar in patients with relapsed or refractory acute myeloid leukemia and high-risk myelodysplastic syndrome: a phase III trial (E2995). *J Clin Oncol* 2004; **22:** 1078–86. Correction. *ibid.*; 2747.
9. van der Holt B, *et al.* The value of the MDR1 reversal agent PSC-833 in addition to daunorubicin and cytarabine in the treatment of elderly patients with previously untreated acute myeloid leukemia (AML), in relation to MDR1 status at diagnosis. *Blood* 2005; **106:** 2646–54.
10. Friedenberg WR, *et al.* Phase III study of PSC-833 (valspodar) in combination with vincristine, doxorubicin, and dexamethasone (valspodar/VAD) versus VAD alone in patients with recurring or refractory multiple myeloma (E1A95): a trial of the Eastern Cooperative Oncology Group. *Cancer* 2006; **106:** 830–8.

Varenicline *(BAN, rINN)*

Vareniclene; Vareniclin; Vareniclina; Varénicline; Vareniclinum; Vareniklīni; Vareniklin; Wareniklina; Варениклин.

7,8,9,10-Tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline.

$C_{13}H_{13}N_3$=211.3

CAS — 249296-44-4.

ATC — N07BA03.

ATC Vet — QN07BA03.

UNII — W6HS99O8ZO.

Varenicline Tartrate *(BANM, USAN, rINNM)*

CP-526555-18; Tartrato de vareniclina; Vareniclina, tartrato de; Varénicline, Tartrate de; Vareniclini Tartras; Варениклина Тартрат.

$C_{13}H_{13}N_3$,$C_4H_6O_6$=361.4

CAS — 375815-87-5.

ATC — N07BA03.

ATC Vet — QN07BA03.

UNII — 82269ASB48.

Uses and Administration

Varenicline is a selective nicotinic receptor partial agonist that is used as an aid for smoking cessation.

Varenicline is given orally as the tartrate with doses expressed in terms of the equivalent amount of varenicline; 1.71 mg of varenicline tartrate is equivalent to about 1 mg of varenicline. An initial dose equivalent to 500 micrograms varenicline is given once daily for the first 3 days, increasing to 500 micrograms twice daily for the next 4 days. The dose from the eighth day for the remainder of the course is 1 mg

twice daily. The dose may be reduced to 500 micrograms twice daily if adverse effects are intolerable. Patients are advised to set a date to stop smoking and start varenicline 1 to 2 weeks before. Alternatively, the patient may stop smoking between 8 and 35 days after starting varenicline. Treatment is normally given for 12 weeks; in patients who successfully stop smoking, a further 12 weeks of treatment has been recommended to reduce the risk of relapse. In those who do not succeed in the first 12 weeks or who relapse after treatment, a second course of varenicline may be tried after factors contributing to the initial failure have been addressed. For doses in renal impairment, see below.

Reviews.

1. Zierler-Brown SL, Kyle JA. Oral varenicline for smoking cessation. *Ann Pharmacother* 2007; **41:** 95–9.
2. Potts LA, Garwood CL. Varenicline: the newest agent for smoking cessation. *Am J Health-Syst Pharm* 2007; **64:** 1381–4.
3. Hays JT, *et al.* Efficacy and safety of varenicline for smoking cessation. *Am J Med* 2008; **121** (suppl 1): S32–S42.
4. Anonymous. Varenicline for smoking cessation. *Drug Ther Bull* 2008; **46:** 33–6.
5. Hays JT, Ebbert JO. Varenicline for tobacco dependence. *N Engl J Med* 2008; **359:** 2018–24.
6. Cahill K, *et al.* A preliminary benefit-risk assessment of varenicline in smoking cessation. *Drug Safety* 2009; **32:** 119–35.
7. Jiménez-Ruiz C, *et al.* Varenicline: a novel pharmacotherapy for smoking cessation. *Drugs* 2009; **69:** 1319–38.

Administration in renal impairment. In patients with severe renal impairment (creatinine clearance less than 30 mL/minute) licensed product information for varenicline recommends a starting dose of 500 micrograms daily given orally, increased after 3 days to a maximum dose of 500 micrograms twice daily (in the USA) or 1 mg once daily (in the UK). In patients with end-stage renal disease undergoing haemodialysis, a maximum dose of 500 micrograms once daily may be given provided that this is well tolerated. No dosage adjustment is considered to be needed in patients with lesser degrees of impairment, although in patients with moderate renal impairment (creatinine clearance between 30 mL/minute and 50 mL/minute), dosing may be reduced to 1 mg daily in patients who have intolerable adverse effects. For reference to acute renal failure associated with varenicline in patients who had pre-existing moderate renal impairment, see Effects on the Kidneys, below.

Smoking cessation. Varenicline is an α4β2 nicotinic acetylcholine receptor partial agonist that is used as an aid for smoking cessation (p. 2570.2). Results from 2 randomised controlled studies[1,2] show greater efficacy than placebo as well as favourable results compared with bupropion, a standard treatment for smoking cessation. However, these studies also showed that nausea was reported in almost 30% of participants in the varenicline group; abnormal dreams were also a problem. A further 12 weeks of treatment with varenicline improved abstinence at 24 weeks in patients who stopped smoking in the first 12 weeks of treatment; after stopping all treatment, the reduced relapse rate was maintained in this group up to 28 weeks later (i.e. 1 year from the start of treatment).[3] Higher abstinence rates were achieved with varenicline than transdermal nicotine replacement therapy in a randomised open-label study.[4] Additionally, there was a greater reduction in craving, withdrawal, and smoking satisfaction at the end of varenicline therapy.

1. Gonzales D, *et al.* Varenicline, an α 4 β 2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006; **296:** 47–55.
2. Jorenby DE, *et al.* Efficacy of varenicline, an α 4 β 2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006; **296:** 56–63. Correction. *ibid.*; 1355.
3. Tonstad S, *et al.* Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006; **296:** 64–71.
4. Aubin H-J, *et al.* Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* 2008; **63:** 717–24.

Adverse Effects and Precautions

The most common adverse effect of varenicline is nausea; other adverse effects also commonly reported are headache, dizziness, somnolence, fatigue, sleep disturbances including abnormal dreams and insomnia, bad taste in the mouth, increased appetite, and gastrointestinal disturbances including vomiting, constipation, and flatulence. There have been reports of neuropsychiatric symptoms as well as exacerbation of pre-existing psychiatric illness in patients who have taken varenicline. Patients should be monitored for such symptoms, including suicidal ideation or behaviour, agitation, depression, or other changes in behaviour or thinking. Hypersensitivity reactions including angioedema have occurred, and severe cutaneous reactions such as Stevens-Johnson syndrome and erythema multiforme have been reported rarely. Varenicline has been reported to be associated with a small increased risk of cardiovascular events in patients with pre-existing cardiovascular disease.

Varenicline should be given with caution to patients with renal impairment—see Effects on the Kidneys, below.

Dizziness, somnolence, loss of consciousness, and difficulty in concentrating have been reported, and patients should be warned to avoid potentially hazardous activities including driving or operating machinery.

Effects on the kidneys. Acute renal failure has been associated with varenicline in 2 men who had pre-existing moderate renal impairment;[1,2] acute interstitial nephritis was diagnosed in the second case.[2]

Licensed product information states that in patients with moderate renal impairment (creatinine clearance between 30 mL/minute and 50 mL/minute) varenicline exposure increased 1.5-fold compared with subjects with normal renal function, while in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) varenicline exposure increased 2.1-fold. Therefore reduction in dosage may be necessary when giving varenicline to patients with renal impairment—see Administration in Renal Impairment above for further details.

1. Bird ML, Vesta KS. Varenicline-associated acute renal failure. *Ann Pharmacother* 2008; **42:** 1908–11.
2. Selby MG, *et al.* Does varenicline induce acute interstitial nephritis? *Mayo Clin Proc* 2009; **84:** 560–1.

Effects on mental state. A retrospective cohort study[1] using data from the UK General Practice Research Database provided no clear evidence of an increased risk of self-harm, suicidal thoughts, or depression in patients given varenicline compared with other smoking cessation products, although it was acknowledged that the study power was limited and there may have been confounding factors not controlled for. Given the limitations of these data, it has been recommended that prescribers remain cautious when prescribing varenicline for smoking cessation.[2] A pooled analysis[3] of data from 10 randomised, double-blind, placebo-controlled studies found no significant increase in overall psychiatric disorders apart from disturbances in sleep; however, the subjects of this analysis were smokers with no current psychiatric problems and results from studies of varenicline in psychiatric patients are awaited.

1. Gunnell D, *et al.* Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. Abstract: *BMJ* 2009; **339:** 1072. Full version: http://www.bmj.com/cgi/reprint/339/oct01_1/b3805 (accessed 01/07/10)
2. Lavigne JE. Smoking cessation agents and suicide. *BMJ* 2009; **339:** 1042–3.
3. Tonstad S, *et al.* Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. *Drug Safety* 2010; **33:** 289–301.

Effects on the skin. Varenicline has been temporally associated with development of maculopapular exanthema in a 71-year-old woman 7 days after she started treatment.[1] Varenicline was stopped and she was treated with diphenhydramine; all her symptoms gradually resolved over 8 days.

1. Song W, Miller WA. Diffuse exanthema in a patient receiving varenicline. *Am J Health-Syst Pharm* 2008; **65:** 1239–41.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies varenicline as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Varenicline is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 3 to 4 hours; bioavailability is high. Steady state concentrations are reached within 4 days of multiple oral dosing. Metabolism is minimal and about 92% of a dose is excreted unchanged in the urine; the elimination half-life is about 24 hours.

References.

1. Faessel HM, *et al.* Single-dose pharmacokinetics of varenicline, a selective nicotinic receptor partial agonist, in healthy smokers and nonsmokers. *J Clin Pharmacol* 2006; **46:** 991–8.
2. Burstein AH, *et al.* Pharmacokinetics, safety, and tolerability after single and multiple oral doses of varenicline in elderly smokers. *J Clin Pharmacol* 2006; **46:** 1234–40.
3. Faessel HM, *et al.* Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. *J Clin Pharmacol* 2006; **46:** 1439–48.
4. Ravva P, *et al.* Population pharmacokinetic analysis of varenicline in adult smokers. *Br J Clin Pharmacol* 2009; **68:** 669–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Champix; ***Austral.***: Champix; ***Austria***: Champix; ***Belg.***: Champix; ***Braz.***: Champix; ***Canad.***: Champix; ***Chile***: Champix; ***China***: Champix (畅沛); ***Cz.***: Champix; ***Denm.***: Champix; ***Fr.***: Champix; ***Ger.***: Champix; ***Gr.***: Champix; ***Hong Kong***: Champix; ***Hung.***: Champix; ***India***: Champix; ***Indon.***: Champix; ***Irl.***: Champix; ***Israel***: Champix; ***Ital.***: Champix; ***Jpn***: Champix; ***Malaysia***: Champix; ***Mex.***: Champix; ***Neth.***: Champix; ***Norw.***: Champix; ***NZ***: Champix; ***Philipp.***: Champix; ***Pol.***: Champix; ***Port.***: Champix; ***Rus.***: Champix (Чампикс); ***Singapore***: Champix; ***Spain***: Champix; ***Swed.***: Champix; ***Switz.***: Champix; ***Thai.***: Champix; ***Turk.***: Champix; ***UK***: Champix; ***Ukr.***: Champix (Чемпикс); ***USA***: Chantix.

Vascular Endothelial Growth Factor ⊗

Сосудистого Эндотелиального Фактора Роста; Factor de Crecimiento Endotelial Vascular; Фактор Роста Эндотелия Сосудов.

Profile

Vascular endothelial growth factor is a family of structurally related proteins involved in angiogenesis and vasculogenesis. VEGF-A, the first member of the family to be discovered and still often referred to as simply VEGF, is thought to provide most of the angiogenic effect of this family. Other members described to date include: VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor.

A gene therapy product supplying the gene for vascular endothelial growth factor D via an adenoviral vector is under investigation for the prevention of stenosis in synthetic grafts used in haemodialysis.

Vasoactive Intestinal Peptide

Péptido vasoactivo intestinal; PIV; Vasoactive Intestinal Polypeptide; VIP; Вазоактивный Пептид Кишечника.

CAS — 37221-79-7.

Aviptadil *(BAN, rINN)*

Aviptadilum; Vasoactive Intestinal Octacosapeptide (Swine); Авиптадил.

$C_{147}H_{238}N_{44}O_{42}S$=3325.8

CAS — 40077-57-4.

UNII — A67JUW790C.

Profile

Vasoactive intestinal peptide acts as a hormone and neurotransmitter in various parts of the body; it is a potent relaxant of smooth muscle and has vasodilator and bronchodilator properties as well as stimulating the gastrointestinal tract to increased secretion. It is available as a synthetic analogue, aviptadil. It has been tried in the management of acute oesophageal food impaction, and for the treatment of acute respiratory distress syndrome, pulmonary arterial hypertension, acute lung injury, and chronic thromboembolic pulmonary hypertension. Aviptadil has been tried as a combination product with phentolamine for erectile dysfunction (p. 2348.2).

Vasoactive intestinal peptide has potential therapeutic applications in immunological disorders since it appears to inhibit inflammatory responses; it modulates the function of inflammatory cells via specific receptors affecting both innate and adaptive immunity.[1] It also appears to have endogenous neuroprotective properties within the CNS, possibly through influencing the expression and secretion of glial-cell derived neuroprotective factors. Consequently, it may have therapeutic potential in neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and stroke.[2]

1. Delgado M, *et al.* The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev* 2004; **56:** 249–90.
2. Dejda A, *et al.* Neuroprotective potential of three neuropeptides PACAP, VIP and PHI. *Pharmacol Rep* 2005; **57:** 307–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***NZ***: Invicorp.

Multi-ingredient Preparations. ***Denm.***: Invicorp.

Vasopressin *(rINNM)* ⊗

ADH; Antidiuretic Hormone; Beta-Hypophamine; Vasopresina; Vasopressiini; Vasopressine; Vasopressinum; Vazopresin; Вазопрессин.

CAS — 11000-17-2 (vasopressin injection).

ATC — H01BA01.

ATC Vet — QH01BA01.

UNII — Y87Y826H08.

NOTE. Vasopressin Injection is *rINN*.

Pharmacopoeias. In *US*, which includes both argipressin and lypressin in this title.

An injection is included in *Jpn*.

USP 36: (Vasopressin). A polypeptide hormone having the properties of causing the contraction of vascular and other

smooth muscles, and of antidiuresis. It is prepared by synthesis. Store in airtight containers at 2 degrees to 8 degrees.

Argipressin *(BAN, rINN)* ⊗

Argipresina; Argipressine; Argipressinum; AVP; [8-Arginine] vasopressin; Аргипрессин.

Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2 cyclic (1→6) disulphide.

$C_{46}H_{65}N_{15}O_{12}S_2$=1084.2

CAS — 113-79-1.

ATC — H01BA06.

ATC Vet — QH01BA06.

UNII — Y4907O6MFD.

Description. Argipressin is a form of vasopressin obtained from most mammals including man but excluding pig. It is usually prepared synthetically. Lypressin (see below) is vasopressin from pig.

Argipressin Tannate *(BANM, USAN, rINNM)* ⊗

8-L-Arginine-vasopressin Tannate; Argipressine, Tannate d'; Argipressini Tannatum; CI-107; Tanato de argipresina; Аргипрессина Таннат.

Tannins compound with argipressin.

ATC — H01BA06.

ATC Vet — QH01BA06.

Units

8.2 units of argipressin for bioassay are contained in about 20 micrograms of synthetic peptide acetate (with human albumin 5 mg and citric acid) in one ampoule of the first International Standard (1978).

Lypressin *(BAN, USAN, rINN)* ⊗

L-8; Lipresina; Lipressina; Lipresszin; LVP; Lypressiini; Lypressine; Lypressinum; Липрессин.

[8-Lysine]vasopressin; Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2 cyclic (1→6) disulphide.

$C_{46}H_{65}N_{13}O_{12}S_2$=1056.2

CAS — 50-57-7.

ATC — H01BA03.

ATC Vet — QH01BA03.

UNII — 7CZF3L922Y.

Description. Lypressin is the form of vasopressin present in the posterior pituitary of pigs.

Pharmacopoeias. *US* includes Lypressin Nasal Solution.

Incompatibility. Vasopressin was shown to be physically compatible (when injected at the Y-site in an intravenous tubing set) when tested in intravenous fluids with other drugs commonly used in cardiac arrest.[1] However, tests of vasopressin with drugs commonly used in septic shock showed physical incompatibility with phenytoin (when mixed in infusion bags).[2] Precipitation has also been reported[3] with vasopressin and furosemide together in intravenous fluids (tested at the Y-site).

1. Feddema S, *et al.* Physical compatibility of vasopressin with medications commonly used in cardiac arrest. *Am J Health-Syst Pharm* 2003; **60:** 1271–2.
2. Barker B, *et al.* Visual compatibility of vasopressin with other injectable drugs. *Am J Health-Syst Pharm* 2005; **62:** 1969, 1975–6.
3. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; **63:** 906–8.

Units

7.7 units of lypressin are contained in about 23.4 micrograms of synthetic peptide (with albumin 5 mg and citric acid) in one ampoule of the first International Standard (1978).

Uses and Administration

Vasopressin is secreted by the hypothalamus and stored in the posterior lobe of the pituitary gland. It may be prepared from the gland of mammals or by synthesis. Vasopressin has a direct antidiuretic action on the kidney, increasing tubular reabsorption of water. It also constricts peripheral blood vessels and causes contraction of the smooth muscle of the intestine, gallbladder, and urinary bladder. It has practically no oxytocic activity.

Vasopressin, which is usually given parenterally or intranasally in the synthetic forms of argipressin or lypressin, is used in the treatment of cranial diabetes insipidus due to a deficiency in antidiuretic hormone. It is ineffective in nephrogenic diabetes insipidus. Argipressin has also been used in the prevention and treatment of postoperative abdominal distension, and was formerly given to remove gas in abdominal visualisation procedures. Argipressin or lypressin are used in the treatment of bleeding oesophageal varices. Argipressin may have a role in cardiopulmonary resuscitation and shock due to vasodilatation.

In the treatment of cranial diabetes insipidus to control polyuria, argipressin may be given subcutaneously or intramuscularly; the dose in the UK is 5 to 20 units every 4 hours. In the USA, 5 to 10 units given 2 to 4 times daily has been used. Alternatively, argipressin or lypressin has been given as a nasal spray; dosage should be individually adjusted as required. A long-acting oily suspension of vasopressin tannate was formerly used by intramuscular injection in diabetes insipidus.

In the initial control of variceal bleeding argipressin is given in an initial dose of 20 units in 100 mL of glucose 5% infused intravenously over 15 minutes. Lypressin has also been given for bleeding oesophageal varices. Doses for children are given under Administration in Children, below.

Vasopressin has also been used as a vasoconstrictor in local anaesthetic injections.

Administration. Results[1] suggesting that although intravenous argipressin produced much higher plasma concentrations than intranasal, the latter evoked a greater CNS response.

1. Pietrowsky R, *et al.* Brain potential changes after intranasal vs intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. *Biol Psychiatry* 1996; **39:** 332–40.

Administration in children. Although not licensed in the UK for use in children, the *BNFC* includes a dose of argipressin for adjunctive treatment of acute massive haemorrhage of the gastrointestinal tract or oesophageal varices in patients aged from 1 month to 18 years. An initial dose of 0.3 units/kg (up to 20 units) is given intravenously over 20 to 30 minutes, followed by a continuous infusion of 0.3 units/kg per hour adjusted according to response to a maximum of 1 unit/kg per hour. If the bleeding stops the infusion is continued at the same dose for 12 hours, then gradually withdrawn over 24 to 48 hours; the maximum duration of treatment should be 72 hours.

Vasopressin given by continuous intravenous infusion in an average dose of 9 milliunits/kg per hour was safe and effective in 5 children who had diabetes insipidus as a manifestation of severe brain injury.[1] A dose of 1.5 to 3 milliunits/kg per hour has also been used safely for postoperative diabetes insipidus in 2 children aged 3 years and under.[2] Similar initial doses of argipressin were used in 3 comatose children with cranial diabetes insipidus,[3] while a published algorithm for the management of acute cranial diabetes insipidus has recommended an initial dose of vasopressin of 0.25 to 1 milliunits/kg per hour, subsequently titrated to achieve an appropriate output and specific gravity of urine, and a serum sodium value of between 140 and 145 mmol/litre.[4]

1. Ralston C, Butt W. Continuous vasopressin replacement in diabetes insipidus. *Arch Dis Child* 1990; **65:** 896–7.
2. McDonald JA, *et al.* Treatment of the young child with postoperative central diabetes insipidus. *Am J Dis Child* 1989; **143:** 201–4.
3. Lee Y-J, *et al.* Continuous infusion of vasopressin in comatose children with neurogenic diabetes insipidus. *J Pediatr Endocrinol Metab* 1995; **8:** 257–62.
4. Lugo N, *et al.* Diagnosis and management algorithm of acute onset of central diabetes insipidus in critically ill children. *J Pediatr Endocrinol Metab* 1997; **10:** 633–9.

Advanced cardiac life support. Vasopressin (as argipressin) may be used as an alternative to adrenaline in cardiopulmonary resuscitation (see Cardiac Arrest, p. 1268.3). In a preliminary study argipressin 40 units by intravenous injection appeared to be of value in the treatment of cardiac arrest due to ventricular fibrillation.[1] Spontaneous circulation returned in 16 of 20 patients so treated; 14 were successfully resuscitated on arrival in hospital and 8 survived to be discharged. In comparison, of 20 patients treated with 1 mg of adrenaline intravenously only 7 were resuscitated and 3 survived till discharge. However, a larger study[2] found no difference between vasopressin and adrenaline in the rates of survival to hospital admission for patients with ventricular fibrillation or pulseless electrical activity, although vasopressin was associated with a higher rate of hospital admission and discharge among patients with asystole. It also found that two doses of vasopressin followed by a single dose of adrenaline resulted in a better survival rate than three doses of adrenaline. Another large study[3] of patients who had a cardiac arrest while in hospital and were treated with either vasopressin 40 units or adrenaline 1 mg, found no difference in survival to discharge from hospital. A systematic review[4] of 5 studies, including these 3, found no clear advantage for the use of vasopressin over adrenaline in the treatment of cardiac arrest. Further studies using a combination of vasopressin and adrenaline have had mixed results. No improvement in outcome was found when both vasopressin and adrenaline were used in out-of-hospital cardiac arrest,[5] but an in-hospital study[6] using vasopressin, adrenaline, and corticosteroids found that survival was improved.

1. Lindner KH, *et al.* Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997; **349:** 535–7.
2. Wenzel V, *et al.* A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004; **350:** 105–13.
3. Stiell IG, *et al.* Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet* 2001; **358:** 105–9.
4. Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med* 2005; **165:** 17–24.
5. Gueugniaud P-Y, *et al.* Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008; **359:** 21–30.
6. Mentzelopoulos SD, *et al.* Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009; **169:** 15–24.

Diabetes insipidus. For a discussion of diabetes insipidus and its management, including reference to the use of vasopressin analogues (particularly desmopressin), see p. 2348.2.

Haemorrhagic disorders. There are reports of vasopressin being used in the management of various haemorrhagic disorders including blood loss in abortion and caesarean section[1,2] and haemoptysis.[3,4] Infusion of vasopressin into the superior or inferior mesenteric artery has been used in the management of lower gastrointestinal bleeding, but modern embolisation techniques may be associated with fewer complications.[5] For the use of vasopressin in upper gastrointestinal variceal haemorrhage, see below.

1. Schulz KF, *et al.* Vasopressin reduces blood loss from second-trimester dilatation and evacuation abortion. *Lancet* 1985; **ii:** 353–6.
2. Lurie S, *et al.* Subendometrial vasopressin to control intractable placental bleeding. *Lancet* 1997; **349:** 698.
3. Noseworthy TW, Anderson BJ. Massive hemoptysis. *Can Med Assoc J* 1986; **135:** 1097–9.
4. Bilton D, *et al.* Life threatening haemoptysis in cystic fibrosis: an alternative therapeutic approach. *Thorax* 1990; **45:** 975–6. Correction. *ibid.* 1991; **46:** 274.
5. Darcy M. Treatment of lower gastrointestinal bleeding: vasopressin infusion versus embolization. *J Vasc Interv Radiol* 2003; **14:** 535–43.

Nocturnal enuresis. For references to the use of the vasopressin analogue, desmopressin, in nocturnal enuresis, see p. 2356.1.

Shock. Argipressin has been reported to have beneficial vasopressor effects in the management of shock (p. 1279.3) due to vasodilatation. It has been given by continuous intravenous infusion at a dose of about 2 to 6 units/hour as supplemental therapy in patients who could not be adequately managed with conventional vasopressor therapy.[1,2] In a retrospective study[3] vasopressin given with or without catecholamines for haemodynamic support of shock did not increase the incidence of venous thromboembolism compared with catecholamines given alone. Further reports[4,5] of the benefit of vasopressin in septic shock suggest that it may be of value in reducing doses of catecholamine vasopressors.

1. Dünser MW, *et al.* Management of vasodilatory shock: defining the role of arginine vasopressin. *Drugs* 2003; **63:** 237–56.
2. Dünser MW, *et al.* Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation* 2003; **107:** 2313–19.
3. Doepker BA, *et al.* Thromboembolic events during continuous vasopressin infusions: a retrospective evaluation. *Ann Pharmacother* 2007; **41:** 1383–9.
4. Obritsch MD, *et al.* Effects of continuous vasopressin infusion in patients with septic shock. *Ann Pharmacother* 2004; **38:** 1117–22.
5. Szumita PM, *et al.* Vasopressin for vasopressor-dependent septic shock. *Am J Health-Syst Pharm* 2005; **62:** 1931–6.

Variceal haemorrhage. Vasopressin has been widely used to control bleeding from oesophageal varices, as discussed under Monoethanolamine, on p. 2563.1. However, terlipressin, and more recently octreotide, have been found to have some advantages over vasopressin, including bolus dosage and fewer adverse effects, and octreotide is increasingly preferred for this purpose. Glyceryl trinitrate has been given with the aim of counteracting the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure.[1-4]

1. Stump DL, Hardin TC. The use of vasopressin in the treatment of upper gastrointestinal haemorrhage. *Drugs* 1990; **39:** 38–53.
2. Williams SGJ, Westaby D. Management of variceal haemorrhage. *BMJ* 1994; **308:** 1213–17.
3. Sung JJY. Non-surgical treatment of variceal haemorrhage. *Br J Hosp Med* 1997; **57:** 162–6.
4. McCormack G, McCormack PA. A practical guide to the management of oesophageal varices. *Drugs* 1999; **57:** 327–35.

Adverse Effects

Large parenteral doses of vasopressin may give rise to marked pallor, pounding headache, vertigo, sweating, tremor, nausea, vomiting, diarrhoea, eructation, cramp, and a desire to defaecate; some of these effects may also occur after large intranasal doses of lypressin. In women, vasopressin may cause uterine cramps of a menstrual character. Hyponatraemia with water retention and signs of water intoxication can occur.

Hypersensitivity reactions have occurred and include urticaria and bronchoconstriction. Anaphylactic shock and cardiac arrest have been reported.

Vasopressin may constrict coronary arteries. Chest pain, myocardial ischaemia, and infarction have occurred following injection, and fatalities have been reported. Other cardiovascular effects include occasional reports of arrhythmias and bradycardia, as well as hypertension. Peripheral vasoconstriction has resulted in gangrene, and thrombosis as well as local irritation at the injection site may occur.

Nasal congestion, irritation, and ulceration have been reported occasionally after intranasal use, usually as lypressin; systemic effects at usual intranasal doses are mostly reported to be mild.

Effects on the heart. Arrhythmias, including ventricular tachycardia and fibrillation,[1] torsade de pointes,[2-4] and asystole[5] are among the adverse effects of vasopressin. Paradoxical bradycardia and hypotension have also been reported.[6]

1. Kelly KJ, *et al*. Vasopressin provocation of ventricular dysrhythmia. *Ann Intern Med* 1980; **92:** 205–6.
2. Eden E, *et al*. Ventricular arrhythmia induced by vasopressin: torsade de pointes related to vasopressin-induced bradycardia. *Mt Sinai J Med* 1983; **50:** 49–51.
3. Stein LB, *et al*. Fatal torsade de pointes occurring in a patient receiving intravenous vasopressin and nitroglycerin. *J Clin Gastroenterol* 1992; **15:** 171–4.
4. Faigel DO, *et al*. Torsade de pointes complicating the treatment of bleeding esophageal varices: association with neuroleptics, vasopressin, and electrolyte imbalance. *Am J Gastroenterol* 1995; **90:** 822–4.
5. Fitz JD. Vasopressin induction of ventricular ectopy. *Arch Intern Med* 1982; **142:** 644.
6. Kraft W, *et al*. Paradoxical hypotension and bradycardia after intravenous arginine vasopressin. *J Clin Pharmacol* 1998; **38:** 283–6.

Ischaemia. Myocardial ischaemia and infarction have occurred with vasopressin but there have also been reports of non-cardiac ischaemia and infarction.[1-10]

1. Greenwald RA, *et al*. Local gangrene: a complication of peripheral Pitressin therapy for bleeding esophageal varices. *Gastroenterology* 1978; **74:** 744–6.
2. Colombani P. Upper extremity gangrene secondary to superior mesenteric artery infusion of vasopressin. *Dig Dis Sci* 1982; **27:** 367–9.
3. Lambert M, *et al*. Reversible ischemic colitis after intravenous vasopressin therapy. *JAMA* 1982; **247:** 666–7.
4. Anderson JR, Johnston GW. Development of cutaneous gangrene during continuous peripheral infusion of vasopressin. *BMJ* 1983; **287:** 1657–8.
5. Reddy KR, *et al*. Bilateral nipple necrosis after intravenous vasopressin therapy. *Arch Intern Med* 1984; **144:** 835–6.
6. Brearly S, *et al*. A lethal complication of peripheral vein vasopressin infusion. *Hepatogastroenterology* 1985; **32:** 224–5.
7. Sweren BS, Bohlman ME. Gastric and splenic infarction: a complication of intraarterial vasopressin infusion. *Cardiovasc Intervent Radiol* 1989; **12:** 207–9.
8. Maceyko RF, *et al*. Vasopressin-associated cutaneous infarcts, alopecia, and neuropathy. *J Am Acad Dermatol* 1994; **31:** 111–13.
9. Lin RY, *et al*. Vasopressin-induced amber-like skin necrosis. *Dermatology* 1997; **195:** 271–3.
10. Dunser MW, *et al*. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med* 2003; **31:** 1394–8.

Treatment of Adverse Effects

The antidiuretic effects on water retention and sodium imbalance may be treated by water restriction and a temporary withdrawal of vasopressin. Severe cases may require osmotic diuresis alone or with furosemide.

Extravasation. Localised intravenous and intra-arterial guanethidine was used in the treatment of a patient with extravasation of vasopressin.[1] The intra-arterial use of guanethidine was considered to have helped to avoid necrotic changes.

1. Crocker MC. Intravascular guanethidine in the treatment of extravasated vasopressin. *N Engl J Med* 1981; **304:** 1430.

Precautions

Vasopressin should not be used in patients with chronic nephritis with nitrogen retention. It should be avoided or given only with extreme care, and in small doses, to patients with vascular disease, especially of the coronary arteries.

It should be given with care to patients with conditions which might be aggravated by water retention including asthma, epilepsy, migraine, and heart failure. Fluid intake should be adjusted to avoid hyponatraemia and water intoxication. Care is also required in hypertension or other conditions that may be exacerbated by a rise in blood pressure. Nasal absorption of vasopressin may be impaired in patients with rhinitis.

Abuse. Vasopressin or its analogues have been abused as so-called 'smart drugs' for their supposed effect on memory recall and cognition.

Resistance. Antibodies to vasopressin were detected in 6 of 28 patients being treated for diabetes insipidus, all of whom had a decrease in antidiuretic effect with previously effective argipressin or lypressin therapy;[1] desmopressin and chlorpropamide remained effective in these patients. There have been reports of patients with diabetes insipidus of pregnancy unresponsive to argipressin but responsive to desmopressin.[2] This was probably due to excessive placental production of vasopressinase, an enzyme which degrades argipressin.

1. Vokes TJ, *et al*. Antibodies to vasopressin in patients with diabetes insipidus: implications for diagnosis and therapy. *Ann Intern Med* 1988; **108:** 190–5.
2. Shah SV, Thakur V. Vasopressinase and diabetes insipidus of pregnancy. *Ann Intern Med* 1988; **109:** 435–6.

Interactions

The antidiuretic effects of vasopressins might be expected to be enhanced in some patients receiving chlorpropamide, clofibrate, carbamazepine, fludrocortisone, urea, or tricyclic antidepressants. Lithium, heparin, demeclocycline, noradrenaline, and alcohol may decrease the antidiuretic effect. Ganglion-blocking drugs may increase sensitivity to the pressor effects of vasopressins.

Cimetidine. A report of severe bradycardia and heart block leading to asystole in a patient given combined vasopressin and cimetidine therapy.[1]

1. Nikolic G, Singh JB. Cimetidine, vasopressin and chronotropic incompetence. *Med J Aust* 1982; **2:** 435–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Novopressina-V; ***Austral.***: Pitressin; ***Braz.***: Encrise; ***Canad.***: Pressyn; ***Gr.***: Pitressin; ***India***: CPressin; ***Irl.***: Pitressin; ***NZ***: Pitressin; ***UK***: Pitressin†; ***USA***: Pitressin Synthetic.

Multi-ingredient Preparations.

Used as an adjunct in:. ***Gr.***: Neo-Lidocaton.

Pharmacopoeial Preparations
USP 36: Lypressin Nasal Solution; Vasopressin Injection.

Veratrine

Veratriini; Veratrin; Veratrina; Veratrinum.
CAS — 8051-02-3 (veratrine mixture); 71-62-5 (veratrine amorphous); 62-59-9 (veratrine crystallised, cevadine).

Description. Veratrine is a mixture of alkaloids from the dried ripe seeds of *Schoenocaulon officinale* (Melanthiaceae) (see p. 2611.2). Veratrine should be distinguished from protoveratrines obtained from *Veratrum* spp.

Uses and Administration

Veratrine should not be used internally. It was formerly applied externally for its analgesic properties and as a parasiticide, especially for head lice, but even when used in this way there is danger of systemic poisoning from absorption.

Adverse Effects, Treatment, and Precautions

Veratrine resembles aconite (p. 2428.3) in its action on the peripheral nerve endings and poisoning should be treated similarly. It is an intense local irritant and has a powerful direct stimulating action on all muscle tissues. It has a violent irritant action on mucous membranes, even in minute doses, and must be handled with great care. When ingested it causes violent vomiting, purging, an intense burning sensation in the mouth and throat, and general muscular weakness.

Veratrol

Catechol Dimethyl Ether; *O*-Dimethoxybenzene; 2-Methoxyanisole; Pyrocatechol Dimethyl Ether; Veratrole.
1,2-Dimethoxybenzene.
$C_8H_{10}O_2$=138.2
CAS — 91-16-7.
UNII — 61WJZ2Q41I.

Profile

Veratrol is a phenolic compound that has been used topically in preparations for musculoskeletal, skin, and mouth disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Bain de Bouche Lipha†; Synthol.

Green Veratrum

American Hellebore; American Veratrum; Ballestera Verde; Eléboro verde; Green Hellebore; Green Hellebore Rhizome; Veratro americano; Veratro Verde; Veratrum Viride; Чемерица Зелёная.
CAS — 65072-04-0.
ATC — C02KA01.
ATC Vet — QC02KA01.
ATC Herb — HC02KA5002 (Veratrum viride: rhizome).
UNII — 36K54AW5KX (Veratrum viride); 197B3Q7T5Q (Veratrum viride root).

Description. Green veratrum consists of the dried rhizome and roots of *Veratrum viride* (Liliaceae) from which are derived the alkaloidal mixtures alkavervir and cryptenamine.

White Veratrum

Ballestera Blanca; Eléboro blanco; Eléboro europeo; European Hellebore; Vedegambre; Veratrum Album; White Hellebore; White Hellebore Rhizome; Чемерица Белая.
ATC — C02KA01.
ATC Vet — QC02KA01.
ATC Herb — HC02KA5001 (Veratrum album: rhizome).
UNII — 7DEL4FSK0E (Veratrum album); QNS6W5US1Z (Veratrum album root).

Description. White veratrum consists of the dried rhizome and roots of *Veratrum album* (Liliaceae) from which are derived the alkaloids protoveratrine A and B.

Uses and Administration

White and green veratrum contain several pharmacologically active alkaloids that produce centrally mediated peripheral vasodilatation and bradycardia. They have been used in the treatment of hypertension but are generally considered to produce an unacceptably high incidence of adverse effects and have largely been replaced by less toxic antihypertensives.

Both green and white veratrum have also been used as insecticides.

Homoeopathy

White Veratrum has been used in homoeopathic medicines under the following names: Veratrum album; Veratrum alb; Ver. alb.

Green Veratrum has been used in homoeopathic medicines under the following names: Veratrum viride; Veratrum vir.

Adverse Effects

Veratrum alkaloids may cause nausea and vomiting at conventional therapeutic doses. Other adverse effects include epigastric and substernal burning, sweating, mental confusion, bradycardia or cardiac arrhythmias, dizziness, and hiccup. Profound hypotension and respiratory depression can occur at high doses.

References.

1. Schep LJ, *et al*. *Veratrum* poisoning. *Toxicol Rev* 2006; **25:** 73–8.

Sneezing powder. Various symptoms of intoxication occurred in 7 patients due to the use of a sneezing powder containing white veratrum alkaloids.[1]

1. Fogh A, *et al*. Veratrum alkaloids in sneezing-powder: a potential danger. *J Toxicol Clin Toxicol* 1983; **20:** 175–9.

Treatment of Adverse Effects

Activated charcoal may be considered within 1 hour of ingestion. Symptomatic bradycardia or cardiac arrhythmias can be treated with atropine. The patient should be placed in a supine position with the feet raised; more severe hypotension may require the use of inotropes such as dopamine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Neth.***: Diarrheel S.

Homoeopathic Preparations. ***Austral.***: Vitatona Energy†; ***Austria***: Daram; Metavirulent; Pertudoron†; Rytmopasc; Veratrum Med Complex; ***Canad.***: Pertudoron 1†; ***Cz.***: Hepeel; Spascupreel S†; ***Fr.***: Abbe Chaupitre no 19†; Apomorphinum Complexe No 97†; Drosera Complexe No 64; Geranium Complexe No 108†; Pertudoron; Vinicard†; ***Ger.***: Arnica Oligoplex; Corvipas SL; Entero-Gastreu S R4; HanoCor N; Infi-Camphora; Infi-Echinacea; Infihepan; metavirulent; Myonasan; Pertudoron 1; Rytmopasc; Viscum album H†; ***Hung.***: Hepeel; Spascupreel; ***Neth.***: Collite; Entero-Gastreu R4; Homeocare Digesto; Kind 0-6 Kindigest; Okugest; ***Rus.***: Avia-Mor (Авиа-Море); Tonginal (Тонгинал); ***S.Afr.***: Pertudoron Drops†; ***Switz.***: Diarrheel S; Hepeel; metavirulent; Regenaplex Nr. 21c; Regenaplex Nr. 31a; ***Ukr.***: Gastrokind (Гастрокинд); Tonginal (Тонгинал).

Verbascum

Aaron's Rod (*Verbascum thapsus*); Bouillon Blanc; Bouillon blanc, fleur de (mullein flower); Diviznový květ (mullein flower); Great Mullein (*Verbascum thapsus*); Kungsljusblomma (mullein flower); Mullein; Ökörfarkkoró virág (mullein flower); Orange Mullein (*Verbascum phlomoides*); Tūbių žiedai (mullein flower); Ukontulikukankukka (mullein flower); Verbasci flos (mullein flower); Wollblumen; Коровяк Обыкновенный (*Verbascum thapsus*).

*ATC Herb — HR05WA5063 (*Verbascum densiflorum*: flower).*

*UNII — C9TD27U172 (*Verbascum thapsus*); CZI843G1J8 (*Verbascum phlomoides *flower).*

NOTE. The name Aaron's Rod has been applied to several plants including *V. densiflorum*, *Solidago* spp., and *Sempervivum tectorum*.

Pharmacopoeias. *Eur.* (see p. vii) includes the dried flowers.

Ph. Eur. 8: (Mullein Flower; Verbasci flos). The dried flowers, reduced to the corolla and the androecium, of *Verbascum thapsus*, *V. densiflorum*, and *V. phlomoides*. Store in airtight containers.

Profile

Verbascum flower is an ingredient of herbal remedies for cough and cold symptoms. The dried leaves and stems have also been used.

References.

1. Turker AU, Gurel E. Common mullein (*Verbascum thapsus* L.): recent advances in research. *Phytother Res* 2005; **19:** 733–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Noverban.

Multi-ingredient Preparations. ***Austral.***: ResCo; ***Austria***: Brust- und Hustentee St Severin; Pervivo; ***Canad.***: Echinamide Cold and Cough†; Honey Blend Herbal Cough Syrup; ***Cz.***: Species Pectorales Planta; ***Fr.***: Pectoflorine†; ***Ger.***: Equisil N†; ***Hung.***: Antipoll; Bittner; ***Mex.***: Bronkitose Mielimon; ***Philipp.***: Lungcaire Plus; ***Pol.***: Flegatussin†; Gwajatussin; Pervivo; Termasil; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера).

Homoeopathic Preparations. ***Austria***: Globuli gegen Heiserkeit; Metasinusit; ***Fr.***: Aesculus Complexe No 103; ***Ger.***: Dolo-Injektopas; Hewallergia Complex; Neuralgie-Gastreu R70; Pulmo Bronchialcomplex; ***Switz.***: metasinusit; Regenaplex Nr. 71b.

Verbenone

Werbenon; Вербенон.

2-Pinen-4-one; 4,6,6-Trimethylbicyclo[3.1.1]hept-3-en-2-one.

$C_{10}H_{14}O$=150.2

CAS — 80-57-9 (verbenone); 18309-32-5 (d-verbenone); 1196-01-6 (l-verbenone).

ATC Vet — QR05CA11 (L-verbenone).

UNII — 99S17893UW (d-verbenone); IFV46DXC6U (dl-verbenone).

Profile

Verbenone is a terpene found in lemon-verbena oil, rosemary oil (p. 2607.3) and some other essential oils. It has been used, sometimes with pine oil, for respiratory disorders.

Verbenone has also been used as an insect repellent in forestry.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Ozopulmin G†; Ozopulmin.

Multi-ingredient Preparations. ***Ital.***: Ozopulmin G; Ozopulmin G; Ozopulmin.

Vervain

Herba Columbariae; Herba Verbenae; Shop Vervain Wort; Verbena; Verveine Officinale; Вербена Лекарственная (*Verbena officinalis*).

*ATC Herb — HN05CM5028 (*Verbena officinalis*: herb); HR05YA5029 (*Verbena officinalis*: herb); HG02WD5001 (*Verbena officinalis*: herb); HA01WD5001 (*Verbena officinalis*: herb).*

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Verbena Herb). The whole or fragmented, dried aerial parts of *Verbena officinalis* collected during flowering. It contains a minimum of 15% of verbenalin ($C_{17}H_{24}O_{10}$ = 388.4) calculated with reference to the dried drug.

Profile

Vervain, the aerial parts of *Verbena officinalis* (Verbenaceae), has been used for many disorders. It is a bitter and has been used for digestive disorders. It also has sedative properties and has been used for anxiety disorders and as a tonic during convalescence from chronic illness.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Avena Complex†; Calmo†; Herbal Rest & Relax; Sinupret; ***Austria***: Sinupret; ***Canad.***: Calmane; ***Cz.***: Sinupret; ***Fr.***: Aromadigest†; Aromazen†; Santane A_4†; Tisane Provencale no 4†; Vigilia†; ***Ger.***: Sinupret; ***Hong Kong***: Sinupret; ***Hung.***: Antipoll; Sinupret; ***Indon.***: Sinupret†; ***Ital.***: Neoderma 47; ***Malaysia***: Sinupret; ***Mex.***: Bisolsinus; ***Philipp.***: Sinupret; ***Pol.***: Sinupret; ***Rus.***: Sinupret (Синупрет); ***Singapore***: Sinupret; ***Swed.***: Sinova; ***Switz.***: Sinupret; Tisane pour nourissons et enfants; ***Thai.***: Sinupret†; ***UK***: Athera; Goodnight; HRI Night; Kalms Sleep; Modern Herbals Menopause; Modern Herbals Stress; Napiers Herbal Stress & Sleep Aid; Newrelax; Period Pain Relief; Prementaid; Scullcap & Gentian Tablets; Sinueeze; Sinuherb; Stressless; SuNerven; ***Ukr.***: Sinupret (Синупрет).

Homoeopathic Preparations. ***Fr.***: Poconeol no 48; ***Ger.***: Phonix Thuja-Lachesis spag.

Vetrabutine Hydrochloride *(BANM, rINNM)*

Dimophebumine Hydrochloride; Hidrocloruro de vetrabutina; Sp-281; Vetrabutina, hidrocloruro de; Vétrabutine, Chlorhydrate de; Vetrabutini Hydrochloridum; Ветрабутина Гидрохлорид.

N,N-Dimethyl-α-(3-phenylpropyl)veratrylamine hydrochloride.

$C_{20}H_{27}NO_2$,HCl=349.9

CAS — 3735-45-3 (vetrabutine); 5974-09-4 (vetrabutine hydrochloride).

Profile

Vetrabutine hydrochloride is used as a uterine relaxant in veterinary medicine.

Vinburnine *(rINN)*

CH-846; 3α,16α-Eburnamonine; (-)-Eburnamonine; Vinburnina; Vinburninum; Vincamone; Винбурнин.

(3α,16α)-Eburnamenin-14(15*H*)-one.

$C_{19}H_{22}N_2O$=294.4

CAS — 4880-88-0.

ATC — C04AX17.

ATC Vet — QC04AX17.

UNII — G54D0HMY25.

Profile

Vinburnine is an alkaloid related to vincamine (below) and has been used in conditions associated with cerebral circulatory insufficiency.

Vinburnine phosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cervoxan; ***Port.***: Cervoxan; ***Spain***: Cervoxan.

Vincamine *(BAN, rINN)*

Vincamina; Vincaminum; Винкамин.

Methyl (3α,16α)-14,15-dihydro-14β-hydroxyeburnamenine-14-carboxylate.

$C_{21}H_{26}N_2O_3$=354.4

CAS — 1617-90-9.

ATC — C04AX07.

ATC Vet — QC04AX07.

UNII — 996XVD0JHT.

Pharmacopoeias. In *Fr.*

Profile

Vincamine is an alkaloid obtained from *Vinca minor* (Apocynaceae). It is claimed to increase cerebral circulation and utilisation of oxygen and has been used in a variety of cerebral disorders. Vincamine may have adverse effects on the cardiovascular system and care should be taken in patients with hypertension or cardiac dysfunction.

Vincamine salts including vincamine hydrochloride, oxoglurate, teprosilate, and hydrogen tartrate have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vinkhum; ***China***: Ao Bo Lan (奥勃兰); ***Gr.***: Etuamol; Livenza; Neuro-Kranit; Sozinalin; Vencano; Verolinex; Vincaminor; ***Ital.***: Vinca-Treis; ***Mex.***: Vincapan; ***Port.***: Arteriovinca; Cervinca; ***Spain***: Tefavinca; Vincacen†; ***Switz.***: Oxygeron†; ***Ukr.***: Oxybral (Оксибрал); Vinoxin (Виноксин).

Multi-ingredient Preparations. ***Arg.***: Ribex; ***Fr.***: Rheobral†; ***Mon.***: Vincarutine; ***Port.***: Anacervix; ***Spain***: Anacervix; Devincal†.

Homoeopathic Preparations. ***Hung.***: Naso-Heel S.

Vinpocetine *(BAN, USAN, rINN)*

Apovincaminato de etilo; AY-27255; Ethyl Apovincaminate; Ethyl Apovincaminoate; RGH-4405; Vinpocetin; Vinpocetina; Vinpocétine; Vinpocetinum; Vinposetiini; Винпоцетин.

Ethyl (3α,16α)-eburnamenine-14-carboxylate.

$C_{22}H_{26}N_2O_2$=350.5

CAS — 42971-09-5.

ATC — N06BX18.

ATC Vet — QN06BX18.

UNII — 543512OBTC.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Vinpocetine). A white or slightly yellow, crystalline powder. Practically insoluble in water; soluble in dichloromethane; slightly soluble in anhydrous alcohol.

USP 36: (Vinpocetine). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Vinpocetine is a derivative of vincamine (above) that has been given orally in cerebrovascular disorders and dementia. Good evidence to support its use in cognitive impairment is lacking.

References.

1. Grandt R, *et al.* Vinpocetine pharmacokinetics in elderly subjects. *Arzneimittelforschung* 1989; **39:** 1599–1602.
2. Blaha L, *et al.* Clinical evidence of the effectiveness of vinpocetine in the treatment of organic psychosyndrome. *Hum Psychopharmacol Clin Exp* 1989; **4:** 103–11.
3. Bereczki D, Fekete I. A systematic review of vinpocetine therapy in acute ischaemic stroke. *Eur J Clin Pharmacol* 1999; **55:** 349–52.
4. Szatmári SZ, Whitehouse P. Vinpocetine for cognitive impairment and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 31/03/06).
5. Kemény V, *et al.* Acute and chronic effects of vinpocetine on cerebral hemodynamics and neuropsychological performance in multi-infarct patients. *J Clin Pharmacol* 2005; **45:** 1048–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Vicog; ***China***: Bai Rui De (百锐得); Bang Chuan Nai Xin (邦川乃新); Bo Jian (博健); Cavinton (开文通); Chang Gui Qing (长贵青); Ding Na (丁那); Duolikang (多力康); Hua Mai Tong (华迈通); Jie Li Shu (杰力纾); Li Nuo Sheng (丽诺生); LiHuan (立环); Ning Xu Xin (宁绪欣); Qing He (青禾); Run He Er (润荷尔); Run Tan (润坦); Shu Lin (枢霖); Tailiping (泰力平); Tong Ming (同铭); Wei Li Ming (维力明); Yi Qi Xian (易齐先); Yuan Tuo (元妥); Zui Xing (最醒); ***Cz.***: Cavinton; Vicebrol; ***Hung.***: Cavinton; ***India***: Neurovin; ***Pol.***: Cavinton; Vicebrol; Vinpoton; ***Port.***: Cavinton; DC Vin†; Ultra-Vinca; Vipocem; ***Rus.***: Bravintone (Бравинтон); Cavinton (Кавинтон); Telectol (Телектол); Vincetin (Винцетин)†; Vinpoton (Винпотон)†; ***Singapore***: Cavinton; ***Thai.***: Cavinton; Vinpocen; Vinpotin; ***Ukr.***: Cavinton (Кавинтон).

Multi-ingredient Preparations. ***Rus.***: Vinpotropile (Винпотропил).

Vinyl Chloride

Cloruro de vinilo; VCM; Vinilo, cloruro de; Vinyl Chloride Monomer; Winylu chlorek.

Chloroethylene.

C_2H_3Cl=62.50

CAS — 75-01-4.

UNII — WD06X94M2D.

Profile

Vinyl chloride is used in the manufacture of polyvinyl chloride (PVC) and other vinyl polymers. Occupational exposure to vinyl chloride in polymerisation plants has been associated with acro-osteolysis, especially in the terminal phalanges of the fingers, a condition resembling Raynaud's phenomenon, and sclerodermatous skin changes. Liver damage and hepatic angiosarcoma, splenomegaly, thrombocytopenia, impaired respiratory function, and chromosomal abnormalities have also occurred.

References.

1. Infante PF, *et al.* Genetic risks of vinyl chloride. *Lancet* 1976; **i:** 734–5.
2. Black CM, *et al.* Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. *Lancet* 1983; **i:** 53–5.

3. Piratsu R, *et al.* La mortalità dei produttori di cloruro di vinile in Italia. *Med Lav* 1991; **82:** 388–423.
4. Riordan SM, *et al.* Vinyl chloride related hepatic angiosarcoma in a polyvinyl chloride autoclave cleaner in Australia. *Med J Aust* 1991; **155:** 125–8.
5. Mur JM, *et al.* Spontaneous abortion and exposure to vinyl chloride. *Lancet* 1992; **339:** 127–8.
6. McLaughlin JK, Lipworth L. A critical review of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. *J Epidemiol Biostat* 1999; **4:** 253–75.
7. Bolt HM. Vinyl chloride—a classical industrial toxicant of new interest. *Crit Rev Toxicol* 2005; **35:** 307–23.
8. Sherman M. Vinyl chloride and the liver. *J Hepatol* 2009; **51:** 1074–81.

Visnadine *(BAN, rINN)*

Visnadina; Visnadinum; Виснадин.

10-Acetoxy-9,10-dihydro-8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[2,3-*f*]chromen-9-yl 2-methylbutyrate.

$C_{21}H_{24}O_7$=388.4

CAS — 477-32-7.

ATC — C04AX24.

ATC Vet — QC04AX24.

UNII — 0RL4V0K263.

Profile

Visnadine is a vasodilator obtained from *Ammi visnaga* fruit (p. 2441.2) or by synthesis. It has been used in coronary, cerebral, and peripheral vascular disorders.

Volatile Mustard Oil

Allylsenföl; Essence of Mustard; Mostaza, aceite esencial de; Oleum Sinapis Volatile; Эфирное Горчичное Масло.

ATC Herb — HM02AW5002 (Brassica nigra: essential oil).

Profile

Volatile mustard oil, prepared from black mustard seeds (p. 2566.1), is largely composed of allyl isothiocyanate (p. 2436.3). It is an extremely powerful irritant that has been used as a counter-irritant and rubefacient. Expressed mustard oil contains a smaller proportion of volatile oil and has been used as a less powerful counter-irritant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Aliviol; Benegel; Gelflex; Nevrol†; ***Canad.***: External Anti-Pain Oil†; Penetrating Rub†; ***Cz.***: Apisarthron†; ***Rus.***: Apisarthron (Апизартрон); Efcamon (Эфкамон); ***Spain***: Dolokey†; ***Switz.***: DUL-X warm; Knobel Huile N†; ***UK***: Nine Rubbing Oils; Radian-B Red Oils; Red Oil; ***USA***: Dermolin; Musterole Extra.

Black Walnut

American Black Walnut; Black Walnut Nut; Carya; Nogal Americano; Nogal Negro; Nogueira-preta; Noyer Noir; Noyer Noir d'Amérique; Noyer Noir d'Amérique du Nord; Schwarze Walnuss; Schwarznuss; Schwarznuss Baum.

UNII — 02WM57RXZJ (black walnut); J7DAA933PR (black walnut extract); 3M3MMX2NG2 (black walnut bark); I2OQ2W1NI2 (black walnut leaves).

NOTE. The name Black Walnut has also been applied to the English Walnut, *Juglans regia* (see below). Some sources do not distinguish between Black Walnut and English Walnut. The name Walnut may refer to either species, and other common names for English Walnut have also been applied (erroneously) to Black Walnut.

Distinguish from Butternut (White Walnut), p. 2463.2.

Profile

The fruit hulls and other parts of the black walnut, *Juglans nigra* (*Wallia nigra*), Juglandaceae, are sometimes used in herbal medicine, although the English walnut (see below) is more commonly used. Black walnut has been used in the traditional medicine of some North American native tribes.

The fruit is used as a foodstuff and the tree is a source of brown dye.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Wormwood Complex.

English Walnut

Carpathian Walnut; Common Walnut; Echte Walnuss; Hetaoren (seed); Hu Tao; Hu Tao Ren (seed); Juglandis Folium (leaf); Madeira Walnut; Nogal; Nogal Común; Nogal Europeo; Nogal Inglés; Nogueira-comum; Noyer Commun; Noyer Royal; Persian Walnut; Semen Juglandis (seed); Valnöt; Walnussblätter (leaf).

ATC Herb — HD03WA5005 (Juglans regia: leaf); HD10AW5001 (Juglans regia: leaf).

UNII — 1V3SHR7QB7 (Juglans regia nut); 3BA2N709NG (Juglans regia flowering top); 85HKB87105 (Juglans regia leaf).

NOTE. The name Black Walnut has been applied to the English Walnut, *Juglans regia*, but is more commonly used for *J. nigra* (see above). Some sources do not distinguish between Black Walnut and English Walnut. The name Walnut may refer to either species, and other common names for English Walnut have also been applied (erroneously) to Black Walnut.

The name Juglans is applied to both English Walnut and Butternut (see p. 2463.2).

Pharmacopoeias. In *Chin.* and *Fr.*

Profile

Various parts of the English walnut, *Juglans regia* (*J. ducloux uiana*; *J. fallax*; *J. kamaonica*; *J. kamaonia*; *J. orientis*; *J. sinensis*) (Juglandaceae), are used in herbal medicine preparations.

The leaf is used for gastrointestinal disorders. The leaf is also used externally for superficial inflammation and as an antiperspirant.

The hull of the fruit (pericarp) has traditionally been used in preparations for a variety of conditions including disorders of the gastrointestinal tract and skin.

Unspecified parts are used in preparations for constipation and other gastrointestinal disorders and for disorders of the upper respiratory tract.

Walnut kernels are used in traditional Chinese medicine.

The kernel is used as a foodstuff and has been promoted as having a beneficial effect on blood lipids when included in the diet.

Homoeopathy

English walnut has been used in homoeopathic medicines under the following names: Juglans regia; Juglans reg.

The flowers of *Juglans regia* are also used in homoeopathic medicines under the following names: Juglans regia, flos; Juglans reg, flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Juglanex (Юглланэкс).

Multi-ingredient Preparations. ***Cz.***: Original Schwedenbitter; ***Ger.***: Imupret; ***Hung.***: Gombarex; ***Rus.***: Tonsilgon N (Тонзилгон Н); ***Ukr.***: Imupret (Имупрет); Tonsilgon N (Тонзилгон)†.

Homoeopathic Preparations. ***Austria***: Lymphomyosot; ***Canad.***: Itires; Minerals+; Rexorubia†; ***Cz.***: Lymphomyosot; ***Fr.***: Diacure; Hepatodrainol; Poconeol no 37; Rexorubia; Uranium Compose†; ***Ger.***: Haut-Gastreu R60; Lymphomyosot; Regenaplex Haut G; Tumoglin†; ***Hung.***: Lymphomyosot; Pro-Aller; PSY-Stabil; ***Neth.***: Acidolite; Hepatodrainol†; Lymfelite; ***Port.***: Hepatodrainol; ***Ukr.***: Lymphomyosot (Лімфоміозот).

Water

Acqua; Agua; Agua potable; Aqua; Aqua Communis; Aqua Fontana; Aqua Potabilis; Eau Potable; Vand; Vann; Vatten; Vesi; Víz; Wasser; Woda; Вода.

H_2O=18.02

CAS — 7732-18-5.

Purified Water

Agua purificada; Aqua Purificata; Eau purifiée; Išgrynintas vanduo; Puhdistettu vesi; Tisztított víz; Vatten, renat; Voda čištěná; Woda oczyszczona; Очищенная Вода (purified water); Дистиллированная Вода (distilled water).

UNII — 059QF0KO0R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Eur. also includes Highly Purified Water. *US* also includes Sterile Purified Water.

Some pharmacopoeias only include distilled water or have additional monographs for demineralised water or distilled water.

Ph. Eur. 8: (Water, Purified; Aqua Purificata). It is water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised. It is prepared from suitable potable water either by distillation, by ion exchange, by reverse osmosis, or by any other suitable method. Store in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. Sub-monographs cover Purified Water in Bulk and Purified Water in Containers.

Ph. Eur. 8: (Water, Highly Purified; Aqua Valde Purificata). It is water intended for the preparation of medicinal products where water of high biological quality is needed, except where Water for Injections is required.

USP 36: (Purified Water). It is prepared from potable water by a suitable process.

Preparation. *DEIONISATION.* By passing potable water through columns of anionic and cationic ion-exchange resins, ionisable substances can be removed, producing a water of high specific resistance. Colloidal and non-ionisable impurities such as pyrogens may not be removed by this process.

DISTILLATION. In this process water is separated as vapour from non-volatile impurities and is subsequently condensed. In practice, non-volatile impurities may be carried into the distillate by entrainment unless a suitable baffle is fitted to the still.

Water for Injections

Agua para inyecciones; Agua para inyectables; Aq. pro Inj.; Aqua ad iniectabilia; Aqua ad Injectionem; Aqua Injectabilis; Aqua pro Iniectione; Aqua pro Injectione; Aqua pro Injectionibus; Eau pour préparations injectables; Injekcinis vanduo; Injektionesteisiin käytettävä vesi; Vatten för injektionsvätskor; Víz parenterális célra; Voda na injekci; Wasser für Injektionszwecke; Water for Injection; Woda do wstrzykiwań; Вода Для Инъекций.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes Sterile Water for Injection, Sterile Water for Inhalation, Sterile Water for Irrigation, and Bacteriostatic Water for Injection.

Ph. Eur. 8: (Water for Injections). It is water for the preparation of medicines for parenteral administration when water is used as the vehicle, and for dissolving or diluting substances or preparations for parenteral administration. It is prepared by distillation of potable water or purified water from a neutral glass, quartz, or suitable metal still fitted with an effective device for preventing the entrainment of droplets; the first portion of the distillate is discarded and the remainder collected. Store in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. Sub-monographs cover Water for Injections in Bulk and Sterilised Water for Injections.

USP 36: (Water for Injection). It is purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and micro-organisms. When used for the preparation of parenteral solutions it should be sterilised first or the final preparation should be sterilised after preparation. Sterile Water for Injection, Inhalation, or Irrigation and Bacteriostatic Water for Injection are the subjects of separate monographs.

Profile

There are international standards for the quality of water intended for human consumption. Toxic substances such as arsenic, barium, cadmium, chromium, copper, cyanide, lead, and selenium may constitute a danger to health if present in drinking water in excess of the recommended concentrations. Water-borne infections are also a hazard.

Fluoride is regarded as an essential constituent of drinking water but may endanger health if present in excess—see Sodium Fluoride, p. 2090.1. Ingestion of water containing large quantities of nitrates may cause methaemoglobinaemia in infants; many countries have standards for nitrates in water.

The use of tap water containing metal ions (such as aluminium, copper, and lead), fluoride, or tosylchloramide sodium, for dialysis may be hazardous.

Hard water contains soluble calcium and magnesium salts, which form scale and sludge in boilers, water pipes, and autoclaves; they also cause the precipitation of soap and prevent its lathering. Temporary hardness in water is due to the presence of bicarbonates which are converted to insoluble carbonates on heating. Permanent hardness is due to dissolved chlorides, nitrates, and sulfates, which do not form a precipitate on heating. The presence or absence of such salts can play a part in cardiovascular health.

Without further purification, potable water may be unsuitable for certain pharmaceutical purposes. In such instances, purified water should always be used. Most pharmacopoeias include monographs on various preparations of water, such as water suitable for injections. Potable water should not be used when such preparations of water are specified.

Excessive ingestion of water can lead to water intoxication with disturbances of the electrolyte balance.

References.

1. Manz F, *et al.* The most essential nutrient: defining the adequate intake of water. *J Pediatr* 2002; **141:** 587–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Humaqua; Rins-Aqua; ***Turk.***: Ser-Fiz; ***UK***: Aquasol; Uriflex W; ***USA***: Fleet Bagenema.

Multi-ingredient Preparations. ***Philipp.***: BioSil†.

Homoeopathic Preparations. ***Fr.***: Urarthone.

Pharmacopoeial Preparations
BPC 1973: Surgical Chlorinated Soda Solution;
USP 36: Cascara Sagrada Fluidextract.

Wheat

Blé; Froment; Frumento; Grano; Trigo; Weizen; Пшеница Мягкая.
UNII — 4J2I0SN84Y.

NOTE. Distinguish from Triticum, a synonym for Couch-grass (see p. 2487.2).

Profile

Wheat (*Triticum* spp., Poaceae) is a grass cultivated worldwide as a cereal crop. Common wheat (*Triticum aestivum*, (*T. vulgare*)) is the source of wheat germ and wheat-germ oil (below). Malted grain of wheat is used in the preparation of malt extract (p. 2080.2). Wheat is also used as a source of bran (p. 1823.3) and starch (p. 2095.1).

Wheat germ is used in preparations for lesions of the skin and mucous membranes and as nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Dermocrem†; Vagitrene; ***Canad.***: Dermatix Fitocream†; ***Ger.***: Vulnostimulin; ***Hong Kong***: Benefiber; ***India***: Benefiber; ***Ital.***: Fitostimoline; Step 2; ***Singapore***: Benefiber; ***Turk.***: Fito; ***USA***: Benefiber; ***Venez.***: Derain; Gynoderain.

Multi-ingredient Preparations. ***Arg.***: Amenite Plus; Cicatul; Microlift; ***Canad.***: Floradix Kindervital†; ***Cz.***: Revalid; ***Hung.***: Revalid; ***Ital.***: Decon Ovuli; Fitostimoline; Sclerovis H Plus; Solecin†; ***Mex.***: Fitoestimulina; Italdermol; ***Port.***: Fitocreme; ***Singapore***: Pro-4; ***Spain***: Dextricea†; ***Switz.***: Revalid†; ***UK***: S.P. H.P.; ***Ukr.***: Revalid (Ревалид); ***Venez.***: Multivit Natura.

Homoeopathic Preparations. ***UK***: Fragador.

Wheat-germ Oil

Búzacsíraolaj; Germes de blé, huile de; Huile de Germe de Blé; Kviečių gemalų aliejus; Oleum Tritici Germinis; Pšeničný olej; Tritici aestivi oleum; Tritici Oleum; Vehnänalkioöljy; Vetegroddolja; Масло Пшеничных Зародышей.
CAS — 8006-95-9.
ATC Herb — HA11YA5001 (Triticum aestivum: germ oil).
UNII — 14C97E680P.

Pharmacopoeias. *Eur.* (see p. vii) includes Wheat-germ Oil, Refined, and Wheat-germ Oil, Virgin.

Ph. Eur. 8: (Wheat-germ Oil, Refined; Tritici Aestivi Oleum Raffinatum). The fatty oil obtained from the germ of the grain of *Triticum aestivum* by cold expression or by other suitable mechanical means and/or by extraction. It is then refined. A suitable antoxidant may be added. A clear, light yellow liquid. Practically insoluble in water and in alcohol; miscible with light petroleum at 40 degrees to 60 degrees. Relative density about 0.925. Store in an airtight container. Protect from light.

Ph. Eur. 8: (Wheat-germ Oil, Virgin; Tritici Aestivi Oleum Virginale). The fatty oil obtained from the germ of the grain of *Triticum aestivum* by cold expression or other suitable mechanical means. A clear, light yellow or golden-yellow liquid. Practically insoluble in water and in alcohol; miscible with light petroleum at 40 degrees to 60 degrees. Relative density about 0.925. Store in an airtight container. Protect from light.

Profile

Wheat-germ oil is a rich source of vitamin E (p. 2119.1). It is included in dietary supplements and in preparations for lesions of the skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Tre-en-en; Vitamin E Complex; ***Braz.***: Gamaline-V; Primoris†; ***Canad.***: Salusan†; ***Fr.***: Actymine†; Bio-Selenium†; Omegaline Solaire; Phytophanere†; ***Hung.***: Aktivit; ***India***: Climdan; E-Cod Omega; E-Cod Plus; Evaren; Evox; Hartivit; Humidus; Korisma; Lycogold; Lycostar-CM; Marc Free; Moiste; ***Indon.***: Eviprostat; ***Ital.***: Babigoz Crema Protettiva; Babysteril; Eavit Plus; Eavit; Eu-Visus; Granvit; Ottovis; Vitalux; ***Jpn***: Eviprostat; ***Pol.***: Klosterfrau Aktiv; ***Port.***: Rilastil Dermo Solar; ***Rus.***: Vitamax (Витамакс)†; ***Singapore***: Eviprostat; ***Switz.***: Priorin N; ***Turk.***: Priorin; ***UK***: No-Sor Nose Balm; Skin Perfecting Oil; ***Ukr.***: Energin (Энергин); Gold Ray (Голд Рей); Reytoil (Рейтоил).

Wild Carrot

Dauci Herba; Daucus; Queen Anne's Lace; Zanahoria silvestre; Морковь Дикая.

NOTE. The name Queen Anne's lace has also been used for cow parsley (*Anthriscus sylvestris*), another umbellifer. The name Wild Carrot has also been applied to Hemlock, p. 2524.3.

Pharmacopoeias. In *Chin.*

Profile

The fruits of the wild carrot, *Daucus carota* (Umbelliferae) have been used as a diuretic and anthelmintic, and are included in herbal preparations for various indications. Other parts of the plant have been used in folk medicine. Carrot seed oil is used in aromatherapy. The root of the cultivated form, *D. carota* subsp. *sativus*, is a culinary item and a source of carotenoids in the diet.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Chofitol Plus; Daily Nutrilite; Fegalgina; Hepatalgina; Hepatalgina; Metiogen; Palatrobil; ***Chile***: Natur-Zin; Natursel-C; ***India***: Lunarex; Oxitard; ***Ital.***: Evamilk; ***Rus.***: Urocholesan (Урохолесан); Urolesan (Уролесан); ***UK***: Sciargo; Watershed; ***Ukr.***: Urochol (Урохол)†; Urolesan (Уролесан).

Wild Cherry Bark

Corteza de cerezo silvestre; Prunus Serotina; Virginian Prune; Virginian Prune Bark; Wild Black Cherry Bark; Wild Cherry; Черёмуха Поздняя (*Prunus serotina*).
UNII — P3XAO4115F (Prunus serotina); 5D48E975HA (Prunus serotina bark); A77056YJ4K (Prunus serotina fruit); XNO4R623ZD (Prunus serotina juice).

Profile

Wild cherry bark is the dried bark of the wild or black cherry, *Prunus serotina* (Rosaceae), known in commerce as Thin Natural Wild Cherry Bark, containing not less than 10% of water-soluble extractive. It has a slight odour and an astringent, aromatic, bitter taste, recalling that of bitter almonds. It contains (+)-mandelonitrile glucoside (prunasin) and an enzyme system, which interact in the presence of water yielding benzaldehyde, hydrocyanic acid, and glucose.

Wild cherry bark, in the form of the syrup, has been used in the treatment of cough but it has little therapeutic value. It has also been used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Bronchial Cough; Echinamide Cold and Cough†; Herbal Cough Syrup†; Honey Blend Herbal Cough Syrup; Mielocol†; ***Venez.***: Cerylana.

Wild Indigo

American Indigo; Baptisia; False Indigo; Horsefly Weed; Horseflyweed; Indigo; Indigo Broom; Indigo Sauvage; Indigo Weed; Rattlebush; Rattleweed; Wilder Indigo; Yellow Broom; Yellow Indigo; Yellow Wild Indigo.
ATC Herb — HJ01WB5004 (Baptisia tinctoria: root); HL03AW5002 (Baptisia tinctoria: root); HJ01WA5002 (Baptisia tinctoria: root).
UNII — 5K1UO2888Y (Baptisia tinctoria); 7BC6Z38NXU (Baptisia tinctoria leaf); 5EF0HWI5WU (Baptisia tinctoria root).

NOTE. The name Baptisia may also apply to other species of *Baptisia*. The name Indigo is usually applied to the dye traditionally obtained from various species of *Indigofera* (Fabaceae).

Profile

The root of wild indigo, *Baptisia tinctoria* (*Sophora tinctoria*) (Fabaceae), is used for its possible antimicrobial and immunostimulant activity in herbal medicines for respiratory-tract infections and cold symptoms, commonly with Echinacea (p. 2498.1) and Thuja (p. 2629.3). It is also used in topical preparations for skin disorders. Wild indigo has been used in traditional North American native medicine. In large doses it can cause vomiting and diarrhoea.

Wild indigo yields a blue dye that has been used as a substitute for indigo.

Homoeopathy

Wild indigo is also used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Esberitox N; ***Austria***: Esberitox; ***China***: Esberitox (施保利通); ***Ger.***: Esberitox; ***Malaysia***: Esberitox N; ***Pol.***: Esberitox N; ***Swed.***: Esberitox; ***Switz.***: Esberitop; ***UK***: Echinacea; Fuerte; Napiers Elixir of Echinacea Complex; Potters Elixir of Echinacea Plus; ***Ukr.***: Esberitox (Эсберитокс).

Homoeopathic Preparations. ***Austria***: Tonsillopas; toxi-loges; ***Canad.***: Arnica-Heel Comp†; Calnor†; Candida Yeast Relief; Cold Sores & Fever Blisters; Echinacea Compositum; Homeo-Form C†; Hylavir FB†; ***Fr.***: Boripharm No 22†; ***Ger.***: Anovin; Echinacin akut; Hevertotox; Lowe-Komplex Nr 5 Echinacea; Pascoleucyn N; Pascoleucyn; Schworotox; Sinusitis Hevert SL; Tonsillopas; toxi-loges; toxi-loges; toxi-loges; ***Neth.***: Febrilite; Grippe-Gastreu R6; Habifac; Nectadyn H; ***Switz.***: Influaforce†; Regenaplex Nr 28b; Regenaplex Nr 41a; ***Ukr.***: Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†.

Wild Lettuce

Herba Lactucae Virosae; Laitue Vireuse; Lechuga Montés; Lechuga silvestre; Lechuga Virosa; Poison Lettuce; Латук Дикий.
ATC Herb — HR05DB5006 (Lactuca virosa: leaf); HR05DB5005 (Lactuca virosa: herb); HN05CM5008 (Lactuca virosa: dry latex); HN05CM5010 (Lactuca virosa: leaf); HN05CM5009 (Lactuca virosa: herb).

Profile

The wild lettuce, *Lactuca virosa* (Compositae), has been given in herbal medicine as a sedative and antitussive. The dried latex extract (lactucarium; lettuce opium) is also used.

Abuse. A 23-year-old man had sensory distortion, euphoria, and analgesia after ingesting a concentrated aqueous extract of wild lettuce leaves.[1] The authors of the report noted that there had been a report in the literature of a 22-year-old Moroccan woman who died after ingesting wild lettuce stems with 'tilfaf' (*Sonchus* spp). Toxicity has also been associated with intravenous injection of aqueous extracts of wild lettuce.[2]

1. Spadari M, *et al.* Abus de laitue vireuse. *Presse Med* 2003; **32:** 702–3.
2. Mullins ME, Horowitz BZ. The case of the salad shooters: intravenous injection of wild lettuce extract. *Vet Hum Toxicol* 1998; **40:** 290–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Herbal Insomnia†; Sirop Cocillana Codeine; ***Indon.***: Diasulin; ***S.Afr.***: Choats Extract of Lettuce Cough Mixture†; ***UK***: Anased; Antibron; Gerard House Somnus; Goodnight; HRI Night; Kalms Sleep; Quiet Life; Quiet Nite; Slumber; Unwind Herbal Nytol; Valerian Passiflora and Hops; ***Venez.***: Cerylana; Diamel.

Wild Pansy

European Field Pansy (*Viola arvensis*); European Wild Pansy (*Viola arvensis* or *V. tricolor*); Field Pansy (*Viola arvensis* or *V. tricolor*); Heart's Ease; Heartsease (*Viola tricolor*); Johnny-jump-up (*Viola tricolor*); Keto-orvokki; Love-in-idleness (*Viola tricolor*); Pansy (*Viola tricolor*); Pensée sauvage; Viol; Violae Herba; Violae Tricoloris Herba (viola tricolor); Фиалка Трёхцветная (*Viola tricolor*); Ziele fiołka trójbarwnego (viola tricolor).
ATC Herb — HD11AX5009 (Viola tricolor: herb).
UNII — 9Q24RAI43V (Viola tricolor).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Wild Pansy (Flowering Aerial Parts); Viola Herba cum Flore). The dried flowering aerial parts of *Viola arvensis* and/or *V. tricolor*. It contains a minimum of 1.5% of flavonoids, expressed as violanthin ($C_{27}H_{30}O_{14}$ = 578.5), calculated with reference to the dried drug. Protect from light.

Profile

Wild pansy, *Viola tricolor* or *V. arvensis* (Violaceae) is used in herbal medicine in topical preparations for minor skin disorders, in particular for seborrhoeic skin diseases. Wild pansy is also included in oral preparations for gastrointestinal and respiratory-tract disorders.

Homoeopathy

Wild Pansy has been used in homoeopathic medicines under the following names: Viola tricolor; Violo tric.

Adverse effects. Haemolysis was reported in a 9-month-old infant with G6PD deficiency given an extract of wild pansy orally.[1]

1. Behmanesh Y, Abdollahi M. Haemolysis after consumption of Viola tricolor. *WHO Drug Inf* 2002; **16:** 15–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Bioage Peripheral†; ***Cz.***: Antirevmaticky Caj†; ***Fr.***: Boribel Tisane No 6†; Colitisane†; Depuratif Parnel†; Evacrine; ***Hung.***: Zeatax; ***Ital.***: Neoderma 47; ***Switz.***: Antidry; Viola; ***UK***: Gerard House Skin; Pure Plan.

Homoeopathic Preparations. ***Canad.***: Acne; Eczema L87; ***Cz.***: Lamioflur†; ***Fr.***: Cistus Canadensis Complexe No 86†; Homeodose 24†; Saponaria Compose; Scabiosa Complexe No 87; Staphysagria Complexe No 92†; ***Ger.***: Derma-Plantin†; Ekzevowen; Regenaplex Haut G; ***Neth.***: Chavita 5.

Wild Thyme

Backtimjan; Creeping Thyme; Kangasajuruoho; Mateřídoušková nať (Nať mateřídoušky); Mother of Thyme; Paprastųjų čiobrelių žolė; Quendel; Quendelkraut; Serpolet; Serpylli herba; Тимьян Ползучий.

ATC Herb — HD08AW5004 (Thymus serpyllum: herb); HN05CM5026 (Thymus serpyllum: herb); HA03AW5058 (Thymus serpyllum: herb); HR05WA5057 (Thymus serpyllum: herb); HR05WA5056 (Thymus serpyllum: essential oil); HA03AW5057 (Thymus serpyllum: essential oil).

UNII — 86H4S6K51N (Thymus serpyllum); KXK6I80R8W (wild thyme).

NOTE. Distinguish from Thyme, p. 2630.2.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Wild Thyme; Serpylli Herba). The whole or cut, dried, flowering aerial parts of *Thymus serpyllum* containing a minimum of 0.3% v/w of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Wild thyme (*Thymus serpyllum*, Lamiaceae) is included in herbal medicines for disorders of the upper respiratory tract. Its actions are similar to, but weaker than, those of thyme (p. 2630.2). Commercially, *T. pulegioides* and *T. praecox* subsp. *arcticus* are also offered as *T. serpyllum*.

Wild thyme oil is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Austria***: Hustensaft Weleda; Scottopect; ***Belg.***: Thymoseptine; ***Canad.***: Swiss Herb Cough Drops; ***Cz.***: Detsky Caj s Hermankem; Pruduskova; Thymomel; ***Fr.***: Aromasol; Bronchorectine au Citral; Dinacode avec codeine; Nazinette du Docteur Gilbert; ***Ger.***: Weleda Hustenelixier; ***Indon.***: Silex; ***Ital.***: Stenobronchial; Tussamag Complex; Tussamag; ***Rus.***: Pertussin (Пертуссин); Sedativae Species No 3 (Седативный Сбор 3); Stoptussin-Fito (Стоптуссин-фито); ***Switz.***: Tisane contre les refroidissements; ***Ukr.***: Stoptussin Fito (Стоптуссин).

Wild Yam

Atlantic Yam; Colic Root; Rheumatism Root; Дикий Ямс.

ATC Herb — HR05YA5005 (Dioscorea villosa: root with rhizome); HG02WB5002 (Dioscorea villosa: root with rhizome); HM01AW5008 (Dioscorea villosa: root with rhizome).

UNII — IWY3IWX2G8 (Dioscorea villosa root).

Profile

The root of the wild yam, *Dioscorea villosa* (Dioscoreaceae), is included in herbal remedies for menopausal disorders and rheumatoid arthritis. Wild yam root contains diosgenin, which has been used as a precursor for the chemical synthesis of human steroidal hormones. Some preparations containing wild yam have been promoted as "natural DHEA" but there is little evidence that diosgenin acts as a precursor to hormone synthesis in the human body. Other species of *Dioscorea* are used as food sources and for medicinal purposes.

Homoeopathy

Wild yam has been used in homoeopathic medicines under the following names: Dioscorea villosa; Igname Sauvage; Zottige Yamswurzel.

References.

1. Komesaroff PA *et al.* Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. *Climacteric* 2001; **4:** 144–50.
2. Final report of the amended safety assessment of Dioscorea Villosa (Wild Yam) root extract. *Int J Toxicol* 2004; **23:** 49–54.
3. Wojcikowski K, *et al.* Dioscorea villosa (wild yam) induces chronic kidney injury via pro-fibrotic pathways. *Food Chem Toxicol* 2008; **46:** 3122–31.
4. Wojcikowski K, *et al.* An in vitro investigation of herbs traditionally used for kidney and urinary system disorders: potential therapeutic and toxic effects. *Nephrology (Carlton)* 2009; **14:** 70–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Advanced Menopause Care; Cimicifuga Compound; Cramplex; Dyzco†; Femi-Nan; Feminine Herbal Complex; Soy Power Plus†; Wild Yam Complex; ***Canad.***: Herbal Laxative†; Libeeda for Women; Milk Thistle Extract Formula; Natural HRT; Painease; ***Fr.***: Androlistica; Biopause; Menolistica; ***Ital.***: Ri-Donna; ***Singapore***: Androlistica; ***Ukr.***: Lifemin (Лайфемин).

Homoeopathic Preparations. ***Canad.***: Colic; Hylands Kinder-CL†; Kid's Colic; Motherwort Combination 1†; ***Fr.***: Aloe Compose; Conium Complexe No 36†; ***Ger.***: Dolo-Injektopas; Homviohepan; Phytocortal; ***Switz.***: Regenaplex Nr. 80aN; ***USA***: Estrex.

Xanthine-containing Beverages

Xantina, bebidas con; Ксантинсодержащие Напитки.

Uses and Administration

Xanthine-containing beverages including chocolate, coffee, cocoa, cola, maté, and tea are widely consumed and have a mild stimulant effect on the CNS. The primary xanthine constituent is caffeine (p. 1203.3) but other xanthine derivatives such as theobromine (p. 1229.2) and theophylline (p. 1229.3) may also be present; cocoa and chocolate contain significant amounts of theobromine.

Coffee is the kernel of the dried ripe seeds of *Coffea arabica*, *C. liberica*, *C. canephora* (robusta coffee), and other species of *Coffea* (Rubiaceae), roasted until it acquires a deep brown colour and a pleasant characteristic aroma. It contains about 1 to 2% of caffeine. Coffee has been used in the form of an infusion or decoction as a stimulant and as a flavour in some pharmaceutical preparations. A decoction is used as a beverage containing up to about 100 mg of caffeine per 100 mL. Preparations of instant coffee may contain up to 40% less caffeine while decaffeinated preparations may contain only up to about 3 mg per 100 mL.

Kola (cola, cola seeds, kola nuts) is the dried cotyledons of *Cola nitida* and *C. acuminata* (Sterculiaceae), containing up to about 2.5% of caffeine and traces of theobromine. Kola is used in the preparation of cola drinks which may contain up to 20 mg of caffeine per 100 mL.

Maté (Paraguay Tea) is the dried leaves of *Ilex paraguensis* (Aquifoliaceae), containing 0.2 to 2% of caffeine and traces of theobromine. Maté is less astringent than tea and is extensively used as a beverage in South America.

Tea (thea, chá, thé, tee) is the prepared young leaves and leaf-buds of *Camellia sinensis* (=*C. thea*) (Theaceae). It contains 1 to 5% of caffeine, up to 24% of tannin, and small amounts of theobromine and theophylline. Tea is used in an infusion as a beverage containing up to about 60 mg of caffeine per 100 mL.

Guarana consists of the crushed seeds of *Paullinia cupana* var *sorbilis* (Sapindaceae). Caffeine appears to be its major active ingredient which was once termed guaranine. Herbal preparations include a beverage or liquid extract and may contain 5% caffeine.

Homoeopathy

Coffee has been used in homoeopathic medicines under the following names: Coffea arabica; Coffea; Coffea cruda; Coff. cr.; Coffea tosta.

Kola has been used in homoeopathic medicines under the following names: Cola; Sterculia acuminata; Sterculia acum.

Maté has been used in homoeopathic medicines under the following names: Ilex paraguayensis; Ile. para.; Ilex paraguariensis; Ilex parag.

Guarana has been used in homoeopathic medicines.

Diabetes mellitus. Regular coffee consumption has been reported[1-6] to reduce the risk of developing type 2 diabetes mellitus, although it is not clear whether this effect is due to caffeine or some other constituent in coffee.

1. Salazar-Martinez E, *et al.* Coffee consumption and risk for type 2 diabetes mellitus. *Ann Intern Med* 2004; **140:** 1–8.
2. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA* 2005; **294:** 97–104.
3. van Dam RM, *et al.* Coffee, caffeine, and risk of type 2 diabetes: a prospective cohort study in younger and middle-aged U.S. women. *Diabetes Care* 2006; **29:** 398–403.
4. Iso H, *et al.* The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. *Ann Intern Med* 2006; **144:** 554–62.
5. Pereira MA, *et al.* Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28812 postmenopausal women. *Arch Intern Med* 2006; **166:** 1311–16.
6. Smith B, *et al.* Does coffee consumption reduce the risk of type 2 diabetes in individuals with impaired glucose? *Diabetes Care* 2006; **29:** 2385–90.

Adverse Effects

The adverse effects of xanthine-containing beverages are largely due to their caffeine (p. 1203.3), theophylline (p. 1229.3), and theobromine (p. 1229.2) content. Common adverse effects are sleeplessness, anxiety, tremor, palpitations, and withdrawal headache.

Breast feeding. For references to the effects of caffeinated beverages in breast feeding, see under Caffeine, p. 1205.2.

Effects on the heart. A meta-analysis of published studies found no evidence of an association between coffee consumption and the development of coronary heart disease,[1] and a large cohort study in men followed up for 14 years and women for up to 20 years also found no evidence of a link.[2] Expert opinion in the UK[3] has been that the evidence that caffeine or coffee consumption contributes to coronary heart disease development is inconsistent. Coffee prepared by boiling, as is the practice in Scandinavia for example, does raise serum cholesterol concentrations due to the presence of the diterpenes cafestol and kahweol, and coffee made in a cafetière (French press) has a similar effect, but filtered coffee does not, as the hypercholesterolaemic fraction does not pass a paper filter.[4] A case-control study has suggested a relationship between consumption of boiled, but not filtered, coffee and incidence of a first non-fatal myocardial infarction.[5] Others have raised concern that the potential pressor effect of caffeine itself may be a cardiovascular risk factor,[6] but as mentioned above there is little evidence for this. A large prospective cohort study[7] found no association between dietary caffeine and risk of atrial fibrillation or flutter.

Tea drinking has not been associated with increased cardiovascular risk[3]—indeed, its polyphenol content has been suggested to have beneficial antoxidant effects.[8,9]

1. Myers MG, Basinski A. Coffee and coronary heart disease. *Arch Intern Med* 1992; **152:** 1767–72.
2. Lopez-Garcia E, *et al.* Coffee consumption and coronary heart disease in men and women: a prospective cohort study. *Circulation* 2006; **113:** 2045–53.
3. DoH. Nutritional aspects of cardiovascular disease. Report of the cardiovascular review group committee on medical aspects of food policy. Report on health and social subjects no. 46. London: HMSO, 1994.
4. Urgert R, *et al.* Comparison of effect of cafetière and filtered coffee on serum concentrations of liver aminotransferases and lipids: six month randomised controlled trial. *BMJ* 1996; **313:** 1362–6.
5. Hammar N, *et al.* Association of boiled and filtered coffee with incidence of first nonfatal myocardial infarction: the SHEEP and the VHEEP study. *J Intern Med* 2003; **253:** 653–9.
6. James JE. Is habitual caffeine use a preventable cardiovascular risk factor? *Lancet* 1997; **349:** 279–81.
7. Frost L, Vestergaard P. Caffeine and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005; **81:** 578–82.
8. Luo M, *et al.* Inhibition of LDL oxidation by green tea extract. *Lancet* 1997; **349:** 360–1.
9. Geleijnse JM, *et al.* Tea flavonoids may protect against atherosclerosis: the Rotterdam study. *Arch Intern Med* 1999; **159:** 2170–4.

Effects on the muscles. Severe myositis in an elderly man who drank around 14 litres of tea daily was attributed to hypokalaemia produced by the xanthine content of the beverage.[1] The patient improved after intravenous potassium replacement and subsequently remained well with a reduction in tea intake.

1. Trewby PN, *et al.* Teapot myositis. *Lancet* 1998; **351:** 1248.

Malignant neoplasms. A review of available data did not suggest a clinically significant association between the regular use of coffee and the development of cancer of the lower urinary tract in men or women.[1]

1. Viscoli CM, *et al.* Bladder cancer and coffee drinking: a summary of case-control research. *Lancet* 1993; **341:** 1432–7.

Interactions

The possibility of synergistic effects in patients receiving xanthines who consume large amounts of xanthine-containing beverages should be borne in mind.

Antipsychotics. Xanthine-containing beverages have been reported to precipitate some antipsychotic drugs from solution *in vitro*, but do not appear to alter antipsychotic concentrations *in vivo*. For references, see p. 1053.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ollantay; Radite; ***Austria***: Veregen; ***Braz.***: Guarafort†; ***Chile***: Revaleskin; ***Fr.***: Camiline; ***Ger.***: Carbo Konigsfeld; Veregen; ***Ital.***: Categ; ***Neth.***: Veregen; ***Spain***: Veregen; ***Switz.***: Veregen; ***UK***: Yariba; ***USA***: Tegreen.

Multi-ingredient Preparations. ***Arg.***: Adelgazar; ADX; Centella Incaico; Cesagrip; Delgacin; Desgras Complex; Energizante Vital con ginseng; Energizante; Energy Plus; Ginkgo Biloba Memo Diates†; Guarana Diates†; Guaranup; Ikx Gel Reductor†; Radite Plus; Supervitaminico†; Vitalfort Antioxidante; Vitalsex; Yerba Diet; Zinc Antioxidante + Guarana; ***Austral.***: 3B Beer Belly Buster†; Avena Complex†; Femme-F; Flavonoid Complex; GR² Control Thermogenic Enhancer; Hairy Lemon; Irontona†; Liver

Detox; Metabolift Fat Burner; PM Joint-Care; ViG; Vitanox; Vitatona†; ***Braz.***: Gero Forte†; ***Canad.***: Super Energex Plus†; Trim-Fit†; ***Chile***: Cellenergy; Draineur; ***Fr.***: Alibi; Alpharegul Femme; Amana Cellium; Anti-oxydant F4; Biotone; Drainuryl; Dynabiane; Elusanes Starphyt†; Expuryl; Filigel†; Gerimax adultes†; Guaramate†; Hydrastart; Imedeen Prime Renewal†; Mediflor no 1; Mincifit†; Photoderm; Quintonine†; Santane O1; Sun Vue; Tavmet; Tealine†; Teaslim†; Tonactil†; Uromil; Vitrecor; YSE†; ***Ger.***: Myrrhinil-Intest; Repursan†; ***Hong Kong***: Mega-Antioxidant†; Sessofort†; Wari-Procomil†; Wellman†; ***Hung.***: Antifront; Antifront; Menofit; Sam-Ginseng Royal; Vensaxa; ***India***: Absolut; Dayvital; Gardian; Gen-One; Lycogreen; Lyconet Green; Morvit; Multivite Gold; Multivite Woman; Nislutin; Nutiva-Lyco; Obedeuce; ***Indon.***: Antox; F-Slim†; Lycoq†; Naturlesterol; Oncoxin; Oxan; Radiblock; ***Irl.***: Avena Sativa Comp; Biofreeze†; ***Israel***: Biolax Protect; Coltect†; ***Ital.***: Almavigor; Altadrine Firming†; Biomineral 5-Alfa Shampoo; Biomineral 5-Alfa; Calmason; Dam; Idren; Linfolipase; Snell Cell†; Valcap; Vitalmix Complex; Vitalmix Fast; ***Jpn***: Senkyu-chachosan; ***Malaysia***: Glow; ***Mex.***: Noxivid†; Zumba; ***Philipp.***: Fit-N-Trim; Fitrum; Gloww; Jamieson Total Energy; Lungcaire Plus; Memory DD†; Nutrafit; ***Pol.***: Cardiol C; Penigra; Tobacoff; ***Rus.***: Insti (Инсти); ***S.Afr.***: Avena Sativa Comp†; ***Singapore***: Berocca Boost; Bio-Taches†; Glow; Hepasil DTX†; Mincifit Body Shaper; ***Spain***: Enofosforina Vigor†; Exodren; Fitosvelt†; Rimagrip†; Tealine; ***Switz.***: Enuton†; Tonique D liquide†; ***Turk.***: Keten; ***UK***: Avena Sativa Comp; Biofreeze; Chlorophyll; Cleansing Herbs; Daily Fatigue Relief; Damiana and Kola Tablets; Glykola; Lion Cleansing Herbs; Pure Plan; S.P.H.P.; Strength; Zotrim; ***Ukr.***: Antifront (Антифронт); Antifront (Антифронт); Grinvitals Cereloba Plus (Гринвитал Церелоба Плюс); Insti (Інсті); Lipomin (Липомин); Liponorm (Липонорм); Sadifit (Садифит); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Cardio Tone; Cardiopress; Diabetiks; Immunicare; Macu-Trition; PowerMate; ***Venez.***: Demerung; Ocoxin.

Homoeopathic Preparations. ***Austral.***: Childrens Sleep; Elimitona; Sleep & Insomnia Relief; ***Austria***: Ambra Med Complex; Iris Med Complex; Notta; Nux Med Complex; ***Canad.***: Calsom†; Comp-Drops 7 Sleepless†; Den 141†; Homeo-Form CA†; Homeoknop Bioactiv O Weight Loss Aid†; Hylands Kinder-T†; Nervita; Passiflora Complex†; Sedilor†; Tee Complex†; Teething; ***Chile***: Bioactiv Z; ***Fr.***: Eudyne†; Noctium; Passiflora Compose; Poconeol no 75; Sativol†; Selenium Complexe No 99; Somnidoron; Tonique Vegetal; ***Ger.***: Aktivon; Avena sativa comp†; Biodolor; Cranio-cyl Ho-Len-Complex; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; dysto-loges N; dysto-loges S; Hevert-Activon Kreislauftropen†; Infinerval; Liquidorm N; Lycoaktin; Nervo-Plantin†; Neurexan; Pflugerplex Gelsemium; Psychoneuroticum (Rowo-578)†; Seda-Do; Sedakatt; ***Neth.***: Kruidvat Homeopathie Nachtrust†; Nervival; Sativol†; Weleda Avena Valeriana; ***Rus.***: Notta (Нотта); ***Switz.***: Nelsons Nocturna†; Sleepium; ***UK***: Noctura; ***Ukr.***: Notta (Нотта); ***USA***: Preferred Remedies Sleep.

Xanthopterin

Ксантоптерин.
2-Amino-4,6-dihydroxypteridine.
$C_6H_5N_5O_2$=179.1
CAS — 119-44-8.
UNII — V66551EU1R.

Profile

Xanthopterin is a natural pigment that has been used topically in the management of eye disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Xantervit Antibiotico; Xantervit Eparina; Xantervit.

Xylazine *(BAN, rINN)*

Ksylatsiini; Xilazina; Xylazin; Xylazinum; Ксилазин.
N-(5,6-Dihydro-4*H*-1,3-thiazin-2-yl)-2,6-xylidine.
$C_{12}H_{16}N_2S$=220.3
CAS — 7361-61-7.
ATC Vet — QN05CM92.
UNII — 2KFG9TP5V8.

Pharmacopoeias. In *US*.

USP 36: (Xylazine). Colourless to white crystals. Sparingly soluble in acetone, in chloroform, and in dilute acid; insoluble in dilute alkali. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Xylazine Hydrochloride *(BANM, USAN, rINNM)*

Bay-Va-1470; Hidrocloruro de xilazina; Ksylatsiinihydrokloridi; Xilazina, hidrocloruro de; Xilazin-hidroklorid; Xylazine, chlorhydrate de; Xylazin-hydrochlorid; Xylazinhydroklorid; Xylazini Hydrochloridum; Ксилазина Гидрохлорид.
$C_{12}H_{16}N_2S$, HCl=256.8
CAS — 23076-35-9.
UNII — NGC3S0882S.

Pharmacopoeias. In *US*.

Eur. (see p. vii) includes for veterinary use only.

Ph. Eur. 8: (Xylazine Hydrochloride for Veterinary Use; Xylazine Hydrochloride BP(Vet) 2014). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in dichloromethane; very soluble in methyl alcohol. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Xylazine Hydrochloride). Colourless to white crystals. Sparingly soluble in acetone, in methyl alcohol, and in dilute acid; insoluble in dilute alkali. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Xylazine is a sedative, analgesic, and muscle relaxant used in veterinary medicine. The hydrochloride is used similarly. Abuse has been reported.

Adverse effects. Reports[1-7] of toxicity and abuse associated with xylazine. Bradycardia, hypotension, and coma were associated with the self-administration of 200 mg of xylazine. Treatment was supportive.[1] Systemic toxicity has been reported after accidental ocular exposure.[6]

1. Samanta A, *et al*. Accidental self administration of xylazine in a veterinary nurse. *Postgrad Med J* 1990; **66:** 244–5.
2. Mittleman RE, *et al*. Xylazine toxicity—literature review and report of two cases. *J Forensic Sci* 1998; **43:** 400–2.
3. Hoffmann U, *et al*. Severe intoxication with the veterinary tranquilizer xylazine in humans. *J Anal Toxicol* 2001; **25:** 245–9.
4. Capraro AJ, *et al*. Severe intoxication from xylazine inhalation. *Pediatr Emerg Care* 2001; **17:** 447–8.
5. Elejalde JI, *et al*. Drug abuse with inhalated xylazine. *Eur J Emerg Med* 2003; **10:** 252–3.
6. Velez LI, *et al*. Systemic toxicity after an ocular exposure to xylazine hydrochloride. *J Emerg Med* 2006; **30:** 407–10.
7. Liu CM, *et al*. Xylazine abuse: a rare cause of syncope. *Clin Toxicol* 2007; **45:** 309–11.

Xylose

Azúcar de la madera; Ksilozė; Ksyloosi; Ksyloza; Wood Sugar; Ксилоза; Древесный Сахар; D-xilosa; Xilosa; Xilóz; Xylos; Xylosa; D-Xylose; Xylosum.
α-D-Xylopyranose.
$C_5H_{10}O_5$=150.1
CAS — 58-86-6; 6763-34-4.
UNII — A1TA934AKO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Xylose). A white or almost white crystalline powder or colourless needles. Freely soluble in water; soluble in hot alcohol.

USP 36: (Xylose). Odourless, colourless needles or white crystalline powder. Very soluble in water; slightly soluble in alcohol. Store in airtight containers at a temperature of 15 degrees to 30 degrees.

Profile

Xylose has been used for the investigation of absorption from the gastrointestinal tract. In the absence of malabsorption, about 35% of a 5-g oral dose and about 25% of a 25-g oral dose are reported to be excreted in the urine within 5 hours. It has been given orally, usually in a dose of either 5 or 25 g, with up to 700 mL of water. The amount recovered in the urine is estimated and used to assess any malabsorption. Adjustment may have to be made for renal impairment. Xylose may cause some gastrointestinal discomfort with large doses. Other drugs may affect the absorption of xylose and interfere with the xylose test.

The test has been adapted to measure blood-xylose concentrations.

References.

1. CraigRM, Ehrenpreis ED. D-xylose testing. *J Clin Gastroenterol* 1999; **29:** 143–50.

Precautions. Preparations that contain, or are metabolised to, xylose may interfere with the results from glucose tests (p. 2516.3). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 16/08/10)

Yellow Dock

Curly Dock; Eviloriva; Lengua de vaca; Sour Dock; Щавель Курчавый (*Rumex crispus*).
UNII — S9T422Q956 (Rumex crispus); 9N1RM2S62C (Rumex crispus root).

NOTE. The name sour dock has also been used for sorrel (p. 2620.3).

Profile

Yellow dock, the root of *Rumex crispus* (Polygonaceae) has laxative and choleretic properties. It is used for constipation, jaundice, and chronic skin disorders.

Homoeopathy

Yellow Dock has been used in homoeopathic medicines under the following names: Rumex; Rumex crispus; Rumex crisp; Rumex c.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Arctium & Zinc Compound; Colax†; Colax; DermaCo; Haemo-Red; ***Canad.***: Herbanat†; Kalenite†; ***Port.***: Stodal; ***Swed.***: Sinova; ***UK***: Skin Eruptions Mixture.

Homoeopathic Preparations. ***Austral.***: Respatona Dry Cough & Nasal Congestion; ***Canad.***: Arum Triphyllum Plex†; Brocosin; Bronchial Cough; Hylaquell BC; Yellow Dock Combination†; ***Chile***: Pertussin; ***Cz.***: Stodal; ***Fr.***: Arum Triphyllum Compose; Spirodrine; Stodal; Stodal; ***Hung.***: Stodal; ***Neth.***: Nectadyn H; Stodal; ***Rus.***: Stodal (Стодаль); ***Switz.***: Stodal; ***UK***: Pyrethrum Spray; ***Ukr.***: Stodal (Стодаль).

Ylang Ylang Oil

Cananga Oil; Ylang-ylang Oil.

Profile

Ylang ylang oil from the flowers of ylang ylang (*Cananga odorata*, Annonoceae), is used in perfumery, as a flavouring agent, and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Paranix; ***Fr.***: Arthro; ***Ger.***: Paranix; ***Singapore***: Teenstick; ***Switz.***: Paranix; ***UK***: Teenstick.

Yogurt

Iaurt; Iogurt; Joghurt; Jogurt; Jogurtas; Jogurtti; Yaourt; Yoghourt; Yoghurt; Yogur; Yoğurt; Кисело Мляко; Йогурт.

Profile

Yogurt is produced by bacterial fermentation of milk and is a source of protein, calcium, and vitamins. It has been used in preparations for gastrointestinal disorders and in nutritional supplements. It may also be used as a source of lactic-acid producing organisms (see p. 2596.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Herbal Laxative plus Yogurt†; ***Fr.***: Benetransit†; ***Ital.***: Lactivis.

Yucca

Yuca; Юкка.

Profile

Various species of *Yucca* (Liliaceae), including Mohave yucca (*Y. schidigera*; *Y. mohavensis*), the Joshua tree (*Y. brevifolia*; *Y. arborescens*), and bear grass (*Y. filamentosa*) have been used in herbal medicine and as foods.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: Bronquiogen†.

Homoeopathic Preparations. ***Fr.***: Yucca Complexe No 110; ***Ger.***: Heparanox H; Leber Albin.

Zanthoxylum Fruit

Prickly Ash Berries; Sichuan Pepper; Szechuan Pepper; Зантоксилум Перечный (*Zanthoxylum piperitum*); Zanthoxylum, fruto de.

*UNII — Y8IKP41338 (*Zanthoxylum piperitum*); 7PFC2VA251 (*Zanthoxylum piperitum *fruit pulp*); 728JDI7G4M (*Zanthoxylum piperitum *fruit rind*).*

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Zanthoxylum fruit is the pericarp of the ripe fruit of *Zanthoxylum piperitum* (*Xanthoxylum piperitum*) (Rutaceae) or other species of *Zanthoxylum*. It contains about 3.3% v/w of essential oil.

Zanthoxylum (BPC 1934) (Toothache Bark; Xanthoxylum) is the dried bark of the northern prickly ash, *Z. americanum*, or the southern prickly ash, *Z. clavaherculis*. Both varieties contain a complex mixture of components, including benzophenanthridine alkaloids; northern prickly ash also contains coumarins.

Zanthoxylum fruit has carminative properties and has been used for rheumatic disorders and as a culinary spice. Zanthoxylum bark has been used similarly, but there is some concern about the potential toxicity of the benzophenanthridine alkaloids which it contains, and some authorities consider that it should not be recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: For Peripheral Circulation Herbal Plus Formula 5†; ***Fr.***: Node K; Phytheol Force†; ***Jpn***: Daikenchuto; Tokito; ***UK***: Daily Overwork & Mental Fatigue Relief; Peerless Composition Essence; Tabritis.

Zilpaterol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de zilpaterol; RU-42173 (base or hydrochloride); Zilpatérol, Chlorhydrate de; Zilpateroli Hydrochloridum; Зилпатерола Гидрохлорид.

(±)-*trans*-4,5,6,7-Tetrahydro-7-hydroxy-6-(isopropylamino) imidazo[4,5,1-*jk*][1]benzazepin-2(1*H*)-one hydrochloride.

$C_{14}H_{19}N_3O_2$,HCl=297.8

CAS — 117827-79-9 (zilpaterol); 119520-05-7 (zilpaterol); 119520-06-8 (zilpaterol hydrochloride).

UNII — EX8IEP25JU.

Profile

Zilpaterol hydrochloride is a beta$_2$-agonist. It is employed in the USA and some other countries as an animal-feed additive to promote weight gain but such use is not permitted in the EU. It has anabolic properties and may be subject to abuse in sport.

Zinc Nitrate

Azotan Cynku; Nitrate de zinc; Zinc Dinitrate; Zinknitraat; Zinknitrat; Цинков Динитрат.

$Zn(NO_3)_2$=189.4

CAS — 7779-88-6 (zinc nitrate); 10196-18-6 (zinc nitrate hexahydrate).

UNII — EDO66F5U49.

Profile

Zinc nitrate has oxidising and corrosive properties. It has various industrial uses, including electro-galvanizing and as a mordant in dyeing. It has also been used as the hexahydrate in preparations for the treatment of benign vaginal lesions.

For more information on zinc and its salts, see p. 2126.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Pol.***: Solcogyn; ***Rus.***: Solcovagin (Солковагин); ***Switz.***: Solcogyn; ***Ukr.***: Solcovagin (Солковагин).

Zinc Ricinoleate

Рицинолеат Цинка.

$(C_{18}H_{33}O_3)_2Zn$=660.3

CAS — 13040-19-2.

UNII — BOH1Z111J2.

Profile

Zinc ricinoleate is used in preparations to combat body odour including underarm, colostomy, and ileostomy deodorant products. It is also used as a deodoriser in laundry products.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Antio.

Multi-ingredient Preparations. ***Austral.***: Banish II.

Zirconium

Circonio; Zirconio; Zirkonium; Цирконий.

Zr=91.224

CAS — 7440-67-7 (zirconium); 1314-23-4 (zirconium dioxide); 60676-90-6 (zirconium lactate); 7699-43-6 (zirconium oxychloride).

UNII — C6V6S92N3C.

Profile

Zirconium and its compounds e.g. zirconium dioxide, zirconium lactate, and zirconium oxychloride, have been used in deodorant preparations; the dioxide is also used in dentistry. There have been reports of hypersensitivity reactions with granulomas. Zirconium dioxide has also been used as a contrast medium.

Adverse effects. A report[1] of pulmonary fibrosis associated with inhalation of a polishing agent containing mainly zirconium dioxide with quartz.

1. Bartter T, *et al*. Zirconium compound-induced pulmonary fibrosis. *Arch Intern Med* 1991; **151:** 1197–1201.

Index

Index entries for this volume may be found in the General and Cyrillic indices in Volume B, p. 4110.

Preparations
Manufacturers
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General Index
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Preparations

This part of Martindale contains brief details of proprietary preparations available in a number of countries and includes those supplied on prescription as well as those sold directly to the public. They are provided to help the reader identify preparations and to suggest their uses. Inclusion is not an endorsement of the activity of any ingredient, nor of the preparation's indications.

For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, the United Arab Emirates, UK, USA, and Venezuela. Generally, each entry consists of the proprietary name, the manufacturer or distributor and country, the active ingredients, and a summary of the indications as given by the manufacturer. Where possible, entries from different countries but with the same name and active ingredients have been amalgamated for clarity. Instances where a preparation name has been used for preparations with significantly different ingredients have been highlighted. Such names may be for actively marketed preparations or for preparations that have been withdrawn from the market.

An entry may cover a range of dosage forms and strengths. Dosage forms are only specified when different forms have the same proprietary name but different active ingredients. Furthermore, this section is not intended as a guide to prescribing; where a preparation is to be supplied the dose should be appropriate for that preparation and that particular patient, and authoritative local sources should be consulted.

With the exception of homoeopathic preparations the names of the ingredients have been translated into English. Almost all the ingredients listed are described in the monographs in Drugs and Ancillary Substances, and readers are directed to an appropriate monograph by the page number provided after the ingredient.

Preparations that have been withdrawn from the market in the last few years or are no longer being actively marketed may be identified by the symbol †. These preparations are retained in Martindale since they may still be in circulation or their names may still be referred to in the literature and in practice. Readers should be aware that since this section was prepared other preparations are likely to have been withdrawn or introduced; also ingredients may change, as may indications.

The manufacturer's full name and contact details can be found in the Directory of Manufacturers.

Each preparation title is listed in the General Index. Where thought helpful, preparation titles have been listed at the end of the relevant monograph. However, it should be noted that the absence of such a list at the end of a monograph is no indication as to the availability of a substance as many drugs are marketed as generic or unbranded preparations.

50:50 *BCM, UK.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry skin.

123 *Frisian Flag, Indon.*
Preparation for enteral nutrition.
Nutritional supplement.

222 *Johnson & Johnson, Canad.*
Aspirin (p. 22·2); caffeine citrate (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever; inflammation.

282 *Pendopharm, Canad.†*
Aspirin (p. 22·2); caffeine citrate (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever; inflammation.

292 *Pendopharm, Canad.*
Aspirin (p. 22·2); caffeine citrate (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever; inflammation.

456 *Frisian Flag, Indon.*
Preparation for enteral nutrition.
Nutritional supplement.

642 *Pendopharm, Canad.†*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

A-125 *Adventure Life Science, India.*
Paracetamol (p. 115·1).
Pain; fever.

A 313 *Pharmadeveloppement, Fr.*
Capsules: Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Pharmadeveloppement, Fr.
Ointment: Vitamin A (p. 2098·3).
Dermatitis.

A Acido *Dominguez, Arg.*
Tretinoin (p. 1725·2).

A Bei Sai *Nuo De, China.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

A Curitybina *Uniao Quimica, Braz.*
Paste: Salicylic acid (p. 1719·1).
Keratinisation disorders.

Uniao Quimica, Braz.
Topical liquid: Salicylic acid (p. 1719·1); glacial acetic acid (p. 2426·3); turpentine oil (p. 2636·3).
Keratinisation disorders.

A & D *Twin Laboratories, Canad.†*
Vitamin A acetate (p. 2098·3); colecalciferol (p. 2113·1).

A & D Ointment
Note: this name may be used for preparations of different composition.
Schering-Plough, Canad.
Wool fat (p. 2219·3); yellow soft paraffin (p. 2212·1).

A Di Xian *United Lab, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

A Duo Ting *Pu Kang, China.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

A Fa Duo Xin *Duoburuifei, China.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension.

A Gan Ding *Guang Sheng Tang, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

A Grin *Grin, Mex.†*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

A Le Xian *United Lab, China.*
Ticarcillin sodium (p. 378·2); potassium clavulanate (p. 268·3).
Bacterial infections.

A Li Wei *Lv Zhou, China.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; pancreatic dysfunction; dyspepsia.

A Lin Xin *CSPC, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

A Lun *Bosen, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

A Mai Xin *Ke Lun, China.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

A Nuo Lei Te *Shaji, China.*
Gatifloxacin hydrochloride.
Bacterial infections.

3A Ofteno *Volta, Chile; Sophia, Mex.; Elmor, Venez.*
Diclofenac sodium (p. 48·3).
Pain and inflammation associated with eye surgery; prevention of cystoid macular oedema; prevention of miosis during cataract surgery; uveitis.

A Rui *Zhong Xiang Kang Shen, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

A Rui Si *Ark, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

A Sai Qi *Yiqiao, China.*
Azithromycin hydrochloride (p. 221·2).
Bacterial infections.

A Sai Song *Tian Yao, China.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

A Saúde da Mulher *EMS, Braz.*
Tablets: Sodium salicylate (p. 132·2); plumeria lancifolia; passion flower (p. 2584·1).
Dysmenorrhoea.

EMS, Braz.
Oral solution: Sodium salicylate (p. 132·2); plumeria lancifolia; passion flower (p. 2584·1); bitter orange peel (p. 2575·3).
Dysmenorrhoea.

A Shen Nuo Qi *Duoburuifei, China.*
Diprophylline (p. 1207·3).
Obstructive airways disease.

A Si Ka *Xudong Haipu, China.*
Calcium aspartate (p. 1783·1).

A Si Ke Ding *Duoburuifei, China.*
Dopamine hydrochloride (p. 1367·2).
Heart failure.

A Si Pan *Rui Feng, China.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).
Stroke prophylaxis.

A Tai Ning *Eastsea, China.*
Clostridium butyricum.
Diarrhoea.

A Te Mi An *Gui Long, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

A Tuo Mo Lan *Yaoyou, China.*
Glutathione (p. 1555·2).

A Vogel Comprimés en cas de rhumatisme *Bioforce, Switz.*
Devil's claw (p. 42·3).
Musculoskeletal and joint disorders.

A Vogel Gel en cas de rhumatisme *Bioforce, Switz.*
Arnica (p. 2447·2).
Musculoskeletal and joint disorders.

A Vogel Gouttes relaxantes *Bioforce, Switz.*
Passion flower (p. 2584·1).
Nervous disorders; sleep disorders.

A Vogel pour les sinus *Bioforce, Switz.*
Cinnabaris (p. 2555·3); hydrastis canadensis (p. 2528·1); kalium bichromicum (p. 2476·3); lemna minor; luffa operculata (p. 2545·3).
Homoeopathic preparation.

A Vogel Spray contre le rhume des foins *Bioforce, Switz.*
Ammi visnaga (p. 2441·2); aralia racemosa; cardiospermum halicacabum; larrea mexicana (p. 2474·3); luffa operculata (p. 2545·3); okoubaka aubrevillei; thryallis glauca.
Homoeopathic preparation.

A Vogel Spray pour la gorge *Bioforce, Switz.*
Echinacea (p. 2498·1); sage (p. 2608·3).
Throat disorders.

A Xi Le *Sanjing, China.*
Aspirin (p. 22·2); vitamin C (p. 2110·3).

A Xi Ya *Wu Zhou Tong, China.*
⊗Furosemide (p. 1387·1).
Oedema; renal failure.

A to Z *Alkem, India.*
Vitamins; minerals.

A1A *Grandix, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

AAA *Manx, UK.*
Benzocaine (p. 1980·2).
Sore throat.

Aablaquin *Piramal, India.*
Bulaquine.
Malaria.

AABP *Brookstone, USA.*
Acetic acid (p. 2426·3); phenazone (p. 124·1); benzocaine (p. 1980·2); polycosanol.

Aacidexam *Organon, Belg.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Aacifemine *Organon, Belg.*
Estriol (p. 2274·3).
Oestrogen deficiency.

Aafact *Sanquin, Neth.*
A factor VIII preparation (p. 1148·1).
Haemophilia A.

Aamin *Medisys, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Aamin-A *Medisys, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Aamin-L *Medisys, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Aansoo *Nitro Organics, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

aar gamma N *aar, Ger.*
Cynara (p. 2490·3).
Dyspepsia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

aar os *aar, Ger.*
Putamen ovi.
Bone and teeth disorders; calcium deficiency.

aar vir *aar, Ger.*
Echinacea pallida (p. 2498·1).
Influenza.

Aarane N *Sanofi-Aventis, Ger.*
⊗Sodium cromoglicate (p. 1225·3); reproterol hydrochloride (p. 1219·2).
Obstructive airways disease.

Aartee *Sienna, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

AAS *Sanofi-Aventis, Braz.; GSK Consumer, Port.; Sanofi-Aventis, Spain.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis; inflammation.

AB *Saval, Chile.*
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disorders.

AB 300 *Finderm, Ital.*
Boric acid (p. 2459·3).
Gynaecological hygiene.

AB Antitusivo *Saval, Chile.*
Chlorhexidine hydrochloride (p. 1743·3); noscapine (p. 1670·3).
Cough.

AB Ausbiobone *Aus Biopharm, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1); manganese gluconate (p. 2081·2).
Osteoarthritis; rheumatoid arthritis.

AB Carsa Giox *Max Biocare, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1); ginger (p. 1844·1); phellodendron amurense.
Osteoarthritis; rheumatoid arthritis; gout.

AB Extra Bone-Care + *Max Biocare, Austral.*
Calcium amino acid chelate (p. 2048·3); calcium phosphate (p. 1784·2); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); magnesium phosphate (p. 1787·3); zinc amino acid chelate (p. 2048·3); manganese amino acid chelate (p. 2048·3); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1); folic acid (p. 2063·1).
Calcium deficiency; osteoporosis.

AB Oriostin *Aus Biopharm, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); manganese amino acid chelate (p. 2048·3); ginger (p. 1844·1).
Osteoarthritis; rheumatoid arthritis.

A-B Vask *Lapi, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

ABA *Intra-Labs, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

ABA-AT *Intra-Labs, India.*
Artesunate (p. 648·2).
Malaria.

Abact *Sarabhai Piramal, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Abacten *Andromaco, Chile.*
Azithromycin (p. 221·2).
Bacterial infections.

Abacus
Note: this name may be used for preparations of different composition.
Emcure, India.
Acarbose (p. 466·2).
Diabetes mellitus.
Pharmaland, Thai.
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; hypersensitivity reactions; anxiety; tension.

Abadasol *Zekides, Gr.†*
Salicylic acid (p. 1719·1).

Abaglin *Teva Tuteur, Arg.*
Gabapentin (p. 523·3).
Epilepsy; postherpetic neuralgia.

Abajos *Nufarindo, Indon.*
Paracetamol (p. 115·1); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia.

Abaktal *Lek, Cz.; Lek, Hung.†; Sandoz, Pol.; Lek, Rus.; Lek, Ukr.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Abalgin
Note: this name may be used for preparations of different composition.
DLF, Denm.; Alternova, Fin.†
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.
Laboratorios Chile, Chile.
Oral drops: Adiphenine hydrochloride (p. 2431·1); phenobarbital (p. 535·2).
Muscle spasm; pain.
Laboratorios Chile, Chile.
Suppositories: Propyphenazone (p. 127·3); adiphenine hydrochloride (p. 2431·1).
Muscle spasm; pain.

Abamune *Cipla, India.*
Abacavir sulfate (p. 963·1).
HIV infection.

Abana *Himalaya Herbal, India.*
Aparagus racemosus (p. 2614·2); punarnava (p. 2601·1); centella (p. 1698·3); cinnamomum cassia (p. 2471·3); crocus sativus (p. 2208·2); cyperus rotundus; cardamom (p. 2471·1); fennel (p. 2503·2); liquorice (p. 1853·2); ocimum sanctum; piper longum; clove (p. 2481·2); chebulic myrobalan (p. 2474·3); tinospora cordifolia; ashwagandha (p. 2450·2); ginger (p. 1844·1).

Abanifan *Biospray, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Abanta *Columbia, Arg.*
Ointment: Zinc oxide (p. 1729·1); allantoin (p. 1693·1); cod-liver oil (p. 2056·3).
Skin disorders.
Columbia, Arg.
Skin cleanser: Vitamin E (p. 2119·1); aloe vera (p. 1693·2).
Soap substitute.

Abanxl *XL, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

AB-AT *Zee, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Abate *Genesis, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Abate-CZ *Genesis, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Abatem *Wermar, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Abate-SR *Genesis, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Abavil *Atral, Port.*
Irbesartan (p. 1411·1).
Hypertension.

Abaxon *Roemmers, Venez.*
Alprazolam (p. 1035·2).
Anxiety.

Abba
Note: this name may be used for preparations of different composition.
Farmellas, Gr.
Ketoconazole (p. 585·3).
Fungal scalp infections.
Fidia, Ital.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Abbé Chaupitre Hivernum No 5 *Arkopharma, Fr.†*
Aconitum (p. 2428·3); belladonna (p. 2453·3); bryonia (p. 2461·3); drosera (p. 2497·2); ipecacuanha (p. 1667·2); silphium; hepar sulfuris (p. 1721·3).
Homoeopathic preparation.

Abbé Chaupitre no 1 *Arkopharma, Fr.†*
⊗Aconitum (p. 2428·3); belladonna (p. 2453·3); bryonia (p. 2461·3); drosera (p. 2497·2); ipeca (p. 1667·2); rhus toxicodendron (p. 2603·3); argentum follium (p. 2615·1); aurum (p. 2521·1); calcarea phosphorica (p. 1784·2); hepar sulfuris (p. 1721·3); kalium bromatum (p. 2461·1); kalium nitricum (p. 1766·2); spongia; stannum (p. 2632·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 6 *Arkopharma, Fr.*
Aconitum (p. 2428·3); anacardium (p. 2471·3); belladonna (p. 2453·3); berberis (p. 2502·1); bryonia (p. 2461·3); cicuta virosa; crocus (p. 2208·2); rhus toxicodendron (p. 2603·3); stramonium (p. 2622·3); calcarea phosphorica (p. 1784·2).
Homoeopathic preparation.

Abbé Chaupitre no 7 *Arkopharma, Fr.*
Chamomilla (p. 2474·1); hyoscyamus niger (p. 2530·2); pulsatilla (p. 2600·2); helleborus; ignatia (p. 2532·1).
Homoeopathic preparation.

Abbé Chaupitre no 10 *Arkopharma, Fr.†*
Arnica (p. 2447·2); alumina (p. 2439·2); aurum (p. 2521·1); antimonium crudum (p. 2445·1); staphysagria.
Homoeopathic preparation.

Abbé Chaupitre no 13 *Arkopharma, Fr.*
Arnica montana (p. 2447·2); ledum palustre (p. 2550·1); belladonna (p. 2453·3).
Homoeopathic preparation.

Abbé Chaupitre no 15 *Arkopharma, Fr.†*
Arnica (p. 2447·2); hamamelis (p. 2523·3); nux vomica (p. 2573·3); aesculus (p. 2431·2).
Homoeopathic preparation.

Abbé Chaupitre no 18 *Arkopharma, Fr.†*
Nux vomica (p. 2573·3); mercurius corrosivus (p. 2555·2); aconitum (p. 2428·3); china (p. 2478·3); chamomilla (p. 2474·1); dulcamara (p. 2497·3).
Homoeopathic preparation.

Abbé Chaupitre no 19 *Arkopharma, Fr.†*
Veratrum album (p. 2644·3); opium (p. 111·3); arsenicum album (p. 2448·1); plumbum (p. 2541·3); cuprum (p. 2057·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 20 *Arkopharma, Fr.†*
Arsenicum album (p. 2448·1); digitalis (p. 1352·3); kalmia latifolia (p. 2537·2); cactus grandiflorus (p. 2473·2); spigelia (p. 2621·3); hamamelis (p. 2523·3); asparagus (p. 2450·2); pulsatilla (p. 2600·2); aconitum (p. 2428·3).
Homoeopathic preparation.

Abbé Chaupitre no 22 *Arkopharma, Fr.†*
Graphites (p. 2522·1); alumina (p. 2439·2); belladonna (p. 2453·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 23 *Arkopharma, Fr.†*
Belladonna (p. 2453·3); ledum palustre (p. 2550·1); rhus toxicodendron (p. 2603·3); sepia officinalis (p. 2613·1); graphites (p. 2522·1); silicea (p. 2208·3); zincum (p. 2126·1).
Homoeopathic preparation.

Abbé Chaupitre no 25 *Arkopharma, Fr.†*
Rhus toxicodendron (p. 2603·3); belladonna (p. 2453·3); bryonia (p. 2461·3); aconitum (p. 2428·3); arnica (p. 2447·2).
Homoeopathic preparation.

Abbé Chaupitre no 30 *Arkopharma, Fr.†*
Arnica montana (p. 2447·2); chamomilla (p. 2474·1); nux vomica (p. 2573·3); anemone pulsatilla (p. 2600·2); sepia officinal (p. 2613·1); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Abbé Chaupitre no 35 *Arkopharma, Fr.†*
Chelidonium (p. 2522·2); pulsatilla (p. 2600·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 43 *Arkopharma, Fr.†*
Chamomilla (p. 2474·1); acide phosphoricum (p. 2589·1); cuprum (p. 2057·1); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Abbé Chaupitre no 44 *Arkopharma, Fr.†*
Viola odorata; calcarea carbonica (p. 1824·3); carbo vegetabilis (p. 1537·3).
Homoeopathic preparation.

Abbé Chaupitre no 48 *Arkopharma, Fr.†*
Iodum (p. 2336·3); silicea (p. 2208·3); causticum (p. 2595·3); hepar sulfuris (p. 1721·3); calcarea carbonica (p. 1824·3).
Homoeopathic preparation.

Abbé Chaupitre no 59 *Arkopharma, Fr.†*
Sepia (p. 2613·1); arsenicum album (p. 2448·1); rhus toxicodendron (p. 2603·3); lycopodium (p. 2546·3).
Homoeopathic preparation.

Abbé Chaupitre no 64 *Arkopharma, Fr.†*
Hamamelis (p. 2523·3); arsenicum album (p. 2448·1); aesculus (p. 2431·2); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Abbé Chaupitre no 66 *Arkopharma, Fr.†*
Euphrasia (p. 2502·1); plantago major (p. 2592·3); aconitum (p. 2428·3); atropa belladonna (p. 2453·3).
Homoeopathic preparation.

Abbé Chaupitre no 67 *Arkopharma, Fr.†*
Stramonium (p. 2622·3); ipeca (p. 1667·2); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Abbé Chaupitre no 79 *Arkopharma, Fr.†*
Causticum (p. 2595·3); lycopodium (p. 2546·3); silicea (p. 2208·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 82 *Arkopharma, Fr.†*
China (p. 2478·3); digitalis (p. 1352·3); nux vomica (p. 2573·3); pulsatilla (p. 2600·2); rhus toxicodendron (p. 2603·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 83 *Arkopharma, Fr.†*
Chamomilla (p. 2474·1); arsenicum album (p. 2448·1); nux vomica (p. 2573·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 88 *Arkopharma, Fr.†*
Belladonna (p. 2453·3); bryonia (p. 2461·3); china (p. 2478·3); nux vomica (p. 2573·3); arsenicum album (p. 2448·1); mercurius dulcis (p. 2555·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Abbé Chaupitre no 90 *Arkopharma, Fr.†*
Asa foetida (p. 2449·3); argentum follium (p. 2615·1); arsenicum album (p. 2448·1); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Abbé Chaupitre no 91 *Arkopharma, Fr.†*
Aconitum (p. 2428·3); belladonna (p. 2453·3); ipeca (p. 1667·2); calcarea phosphorica (p. 1784·2); hepar sulfuris (p. 1721·3); kalium bromatum (p. 2461·1); iodum (p. 2336·3); spongia; sulfur (p. 1721·1).
Homoeopathic preparation.

Abbocalcijex *Abbott, Gr.*
Calcitriol (p. 2113·1).
Vitamin D deficiency; renal osteodystrophy.

Abbocillin-V *Sigma, Austral.*
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Abbocillin-VK *Sigma, Austral.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Abbocurium *Abbott, Pol.†*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Abbodop *Hospira, Denm.†; Hospira, Fin.†; Hospira, Norw.†; Electra-Box, Swed.†*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure.

Abbofol *Abbott, Pol.†*
Propofol (p. 1909·3).
General anaesthesia; sedation in intensive care patients.

Abbokinase *Abbott, Gr.; Abbott, Israel†; Abbott, Singapore.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Abboplegisol *Hospira, Spain.†*
Electrolytes (p. 1775·1).
Adjunct to open-heart surgery.

Abbosynagis *Abbott, Israel.*
Palivizumab (p. 2415·2).
Respiratory syncytial virus infections.

Abbotic *Abbott, Indon.*
Clarithromycin (p. 266·2).
Bacterial infections.

Abboticin *Amdipharm, Denm.; Amdipharm, Fin.; Amdipharm, Norw.; Amdipharm, Swed.*
Erythromycin ethyl succinate (p. 291·2), erythromycin lactobionate (p. 291·3), or erythromycin stearate (p. 291·3).
Bacterial infections.

Abboticine *CSP, Fr.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Abbott Grow *Abbott, Philipp.*
Nutritional supplement for children.

Abbottracurium *Abbott, Braz.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Abbovir *Abbott, Pol.†*
Aciclovir sodium (p. 964·1).
Herpesvirus infections.

ABC
Note: this name may be used for preparations of different composition.
Hertz, Braz.
Clotrimazole (p. 576·2).
Fungal skin infections.
Offenbach, Mex.†
Vitamins; minerals.

ABC-9 *Rass, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

ABC Baby *Arbonne, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

ABC Derm *Emcure, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); clioquinol (p. 273·1); tolnaftate (p. 596·1).
Infected skin disorders.

ABC Hydrogel-Warmepflaster *Beiersdorf, Austria.†*
Nonivamide (p. 102·3).
Muscle pain.

ABC to Z *Nature's Bounty, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

AB-CEF *Bestochem, India.*
Cefixime (p. 240·3).
Bacterial infections.

Abcet *Procure, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Abcid *Arbro, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Abcid-D *Arbro, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux.

Abcler *Airela, Braz.*
Choline citrate (p. 2055·2); methionine (p. 1558·2); betaine (p. 2456·1).

ABClox *Centaur, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Abcof *Shinto, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); guaifenesin (p. 1666·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Abcof-DM *Shinto, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Abcool-D *Xieon, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux.

ABD *Intas, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Abdal *Madhav, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Abdal Plus *Madhav, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Abdal-SP *Madhav, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Abdec *Pfizer, India; Pfizer, Indon.†*
Vitamins.

Abdec Forte *Pfizer, India.*
Vitamins; zinc (p. 2126·1).

Abdelyn *Coronet, Indon.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin D (p. 2112·3); lysine hydrochloride (p. 2079·3).
Vitamin supplement.

Abdiflam *Tunggal Idaman, Indon.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Abdimox *Tunggal Idaman, Indon.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Abdine Cold Relief *Bell, UK.*
Paracetamol (p. 115·1).
Cold and influenza symptoms.

Abdogyl-N *GSK, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).
Diarrhoea; dysentery.

Abdomilon N *Caesaro, Austria; Cesra, Ger.*
Absinthium (p. 2426·1); angelica (p. 2443·3); calamus (p. 2464·2); gentian (p. 2512·1); melissa (p. 2552·3).
Dyspepsia; gastrointestinal disorders.

Abdominol *Medea, Spain.†*
Atropine methobromide (p. 1310·2); caffeine (p. 1203·3); propyphenazone (p. 127·3).
Pain due to smooth muscle spasm.

Abdoscan *Nycomed, Gr.*
Ferristene (p. 1584·1).
Contrast medium for magnetic resonance imaging.

Abdowin *Shinto, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Abdrot *Captab, India.*
Drotaverine (p. 2497·3).

Abduce *Iasis, Gr.*
Aciclovir (p. 964·1).
Labial and genital herpes simplex infections.

Abec *Emcure, India.*
Abacavir (p. 962·3).
HIV infection.

Abecidin A C D *Pasteur, Chile.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); vitamin C (p. 2110·3).
Vitamin supplement.

Abefen *Pisa, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Abeita *Tasly, China.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Abel *Lupin, India.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Abelcet *Bioprofarma, Arg.; Orphan, Austral.; Cephalon, Austria; Cephalon, Belg.; Bago, Braz.; Sigma-Tau, Canad.; Cephalon, Cz.; Cephalon, Denm.; Teva, Fin.; Cephalon, Fr.; Cephalon, Ger.†; Teva, Gr.; Cephalon, Hung.; Cephalon, Irl.; Cephalon, Ital.; Armstrong, Mex.; Teva, Neth.; Cephalon, Norw.; Healthcare Logistics, NZ; Cephalon, Pol.; Cephalon, Port.; Elan, Singapore; Teva, Spain; Teva, Swed.; Onko, Turk.; Cephalon, UK; Enzon, USA.*
Amphotericin B phospholipid complex (p. 569·2).
Fungal infections; leishmaniasis.

Abelitan *SM, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.

Abella *VS, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Abelonelle *Alternova, Swed.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Abenol *Pendopharm, Canad.*
Paracetamol (p. 115·1).
Pain; fever.

Abentel *Atlantic, China; Atlantic, Thai.†*
Albendazole (p. 149·1).
Worm infections.

Abenz *Affy, India.*
Benzoyl peroxide (p. 1696·1).
Acne.

ABE-Plyn *Inco Veritas, Pol.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Corns.

Aberela *Janssen-Cilag, Norw.; Janssen-Cilag, Swed.*
Tretinoin (p. 1725·2).
Acne; photoageing of the skin.

Aberten *Menarini, Gr.*
Theophylline (p. 1229·3).
Asthma; obstructive airways disease; neonatal apnoea and bradycardia.

Abesart *Genepharm, Ital.; Genepharm, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Abesyl *Medochemie, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Abetathen *Remedina, Gr.*
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Abflex *Cipla, S.Afr.*
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain with tension.

Abführtee St Severin *Smetana, Austria.*
Achillea (p. 2427·3); peppermint leaf (p. 1877·1); senna (p. 1885·1).
Constipation.

Abhayrab *Indian Immunologicals, Philipp.; Human, Thai.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Abide *Laborate, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Abidec *IFET (ΙΦΕΤ), Gr.; Chefaro, Irl.; Teofarma, Ital.; Chefaro, UK.*
Vitamins.
Vitamin supplement.

Abilify *BMS, Austral.; Otsuka, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; Otsuka, China; Otsuka, Cz.; Otsuka, Denm.; Otsuka, Fin.; Otsuka, Fr.; BMS, Ger.; Otsuka, Ger.; Otsuka, Gr.; Otsuka, Hong Kong; Otsuka, Hung.; Otsuka, Indon.; BMS, Irl.; BMS, Israel; BMS, Ital.; Otsuka, Jpn; BMS, Malaysia; BMS, Mex.; Otsuka, Neth.; Otsuka, Norw.; BMS, NZ; Otsuka, Philipp.; Otsuka, Pol.; Otsuka, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; Otsuka, Spain; BMS, Swed.; BMS, Switz.; Otsuka, Thai.; BMS, Turk.; Otsuka, UK; BMS, USA; Otsuka, USA; BMS, Venez.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder; mania; depression; behaviour disorders in autistic disorder.

Abimono *Finderm, Ital.*
Isoconazole nitrate (p. 583·2).
Vulvovaginal infections.

Abine *Dosa, Arg.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Abingem *Miracalus, India.*
Gemcitabine hydrochloride (p. 801·2).
Non-small cell lung cancer; pancreatic cancer; bladder cancer; breast cancer; ovarian cancer.

Abinol *Lafi, Chile.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; childhood behaviour disorders.

Abiolex *Andromaco, Chile.*
Amoxicillin (p. 216·2).
Bacterial infections.

Abiostil *Deca, Ital.*
Neomycin sulfate (p. 330·1); cineole (p. 2479·1); Scots pine oil (p. 2591·2); camphor (p. 2466·2); menthol (p. 2553·2).
Nasopharyngeal infections.

Abiotyl *Biocrom, Arg.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Abiphos *Shinto, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3); zinc (p. 2126·1).

Abiplatin *Pharmachemie, Israel; Teva, S.Afr.; Pharmachemie, Singapore; Abic-Teva, Thai.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Abis *AGIPS, Ital.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Abitaxel *Teva, Rus.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer.

A-Bite *Hoe, Malaysia.*
Crotamiton (p. 1699·2).
Insect bites and stings.

Abitren *Abic, Israel.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Abitrexate *Pharmachemie, Israel; Teva, S.Afr.; Pharmachemie, Singapore; Abic-Teva, Thai.*
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis; Crohn's disease.

Abitrol *Intermed, Gr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Abivax *Gap, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Abix *Triton, India.*
Pyridoxine (p. 2105·3).
Vitamin B_6 deficiency; sideroblastic anaemia.

Abixa *Lundbeck, Philipp.; Lundbeck, Ukr.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Abizol *Nobel, Turk.*
Aripiprazole (p. 1038·3).

ABKI *Quimica y Farmacia, Mex.*
Ibuprofen (p. 68·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Abkwik *Misha, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Ablavar *TMC, Austria; Lantheus, Canad.; TMC, Cz.; Bayer, Ger.†; Bayer Schering, Gr.†; Bayer Schering, Neth.†; Bayer Schering, Norw.†; TMC, Port.; Bayer, Spain†; TMC, Swed.†; TMC, UK; Lantheus, USA.*
Gadofosveset trisodium (p. 1585·3).
Formerly known as Vasovist.
Contrast medium for magnetic resonance angiography.

Ablaze-IM *Zenon, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Ableed *Greenco, India.*
Butyl alcohol (p. 2172·2); citric acid (p. 2480·3).

Ablok *Biolab Sanus, Braz.*
⊗Atenolol (p. 1308·2).
Hypertension.

Ablok Plus *Biolab Sanus, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Abloom *Duncan, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Abluent *Tolmann, Philipp.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with excessive mucus.

Abnobaviscum *Abnoba, Ger.*
Mistletoe (p. 2560·2).
Malignant neoplasms.

Abo Pill *CureQuick, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour following intra-uterine fetal death; postcoital oral contraceptive.

Abodars *Teva, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Abodine *Abbott, Indon.†*
Povidone-iodine (p. 1767·1).
Antiseptic.

Abof *Constant, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Abof-NZ *Constant, India.*
Ofloxacin (p. 334·3); nitazoxanide (p. 942·2).

Abof-OZ *Constant, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Abolibe *Sideforma, Port.*
Ginkgo biloba (p. 2512·3).
Mental function disorders; vascular disorders.

A-Bomin
Note: this name may be used for preparations of different composition.
Pfluger, Ger.
Ammi visnaga (p. 2441·2); cephaelis ipecacuanha; cetraria islandica (p. 2531·2);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

chamomilla recutita (p. 2474·1); datura stramonium (p. 2622·3); drosera (p. 2497·2); echinacea angustifolia (p. 2498·1); eriodictyon californicum (p. 1665·2); euspongia officinalis; gelsemium sempervirens (p. 2511·2); natrium sulfuricum (p. 1888·1); blatta orientalis; grindelia robusta (p. 2522·3); selenicereus grandiflorus (p. 2473·2).
Homoeopathic preparation.

Abomin
Note: this name may be used for preparations of different composition.
Binnofarm, Rus.
Proteases.
Digestive disorders.

Abonic *Shinto, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Aboprost *Cure Quick, India.*
Misoprostol (p. 2140·3).
Peptic ulcer; termination of pregnancy.

Aborcin *Samarth, India.*
Ethacridine lactate (p. 1732·3).
Termination of pregnancy.

Abortil *Troikaa, India.*
Ethacridine lactate (p. 1732·3).
Termination of pregnancy.

Abortom *Neiss, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour following intra-uterine fetal death; postcoital contraceptive.

Abound *Abbott, Hong Kong; Abbott Nutrition, Singapore.*
Preparation for enteral nutrition.
Nutritional supplement.
Abbott, Ital.
Amino acids.
Enteral nutrition.

Abovis *Taisho, Jpn.*
Aclatonium napadisilate (p. 1815·1).
Nausea; vomiting; reduced appetite; abdominal distension.

Ab-Phylline *Sun, India.*
Ambroxol acefyllinate (p. 1201·2).

Abra *Positif, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Abra-D *Positif, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Abralux *Valuge, Arg.*
Polyethylene granules (p. 1690·3).
Abrasive skin wash.

Abramox *Vitarum, Arg.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Abrasone *Anotaciones, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); framycetin sulfate (p. 301·2).
Infected skin disorders.

Abrasone Rectal *Anotaciones, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); hexetidine (p. 1755·1); ruscogenin (p. 2608·3).
Anorectal disorders.

Abraxane *Abraxis, Austral.; Celgene, Canad.; Celgene, Cz.; Celgene, Denm.; Celgene, Fr.; Celgene, Ger.; Celgene, Gr.; IFET (ΙΦΕΤ), Gr.; Biocon, India; Celgene, Irl.; Celgene, Neth.; Celgene, Norw.; Healthcare Logistics, NZ; Abraxis, Pol.; Abraxis, Port.; Celgene, Spain; Celgene, Swed.; Celgene, UK; Celgene, USA.*
Paclitaxel albumin-bound particles (p. 839·3).
Breast cancer; non-small cell lung cancer; pancreatic adenocarcinoma.

Abraxil *Gynopharm, Chile.*
Doxycycline (p. 288·1).
Bacterial infections.

Abretia *Pharma Invesi, Chile.*
Atomoxetine hydrochloride (p. 2316·3).
Attention deficit hyperactivity disorder.

Abreva *GSK Consumer, Canad.; SmithKline Beecham Consumer, USA.*
Docosanol (p. 974·3).
Herpes labialis.

Abrilar
Note: this name may be used for preparations of different composition.
Farmoquimica, Braz.; Engelhard, Singapore; Diafarm, Spain.†
Ivy (p. 2536·2).
Cough; respiratory-tract disorders with increased mucus.
Pharma Investi, Chile.
Alpha-hederin.
Respiratory-tract congestion; cough.

Abrion *Centrum, Spain.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Abrixone *Eurodrug, Mex.*
Metadoxine (p. 2105·3).
Alcoholism; steatohepatitis.

Abrobion *Help, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Abrodil *Bayer, Gr.*
Azlocillin sodium (p. 223·2).
The name Abrodil has also been used for a contrast medium containing methiodal sodium.
Bacterial infections.

Abroflor *VSM, Neth.*
Abrotanum.
Homoeopathic preparation.

Abrol *Rekah, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Abrolen *Alet, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Abrolet *Rekah, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Abrovit-Cal *Arbro, India.*
Calcium (p. 1783·1); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); phosphorus (p. 2589·2); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

A-Bruzzy *Hoe, Malaysia; Hoe, Singapore.*
Arnica (p. 2447·2); calendula (p. 2465·2); aloe vera (p. 1693·2).
Bruising.

Abseamed *Medice, Austria; Medice, Cz.; Medice, Ger.; Medice, Gr.; Medice, Irl.; Fidia, Ital.; EuroCept, Neth.; Medice, Pol.; Medice, Port.; Salmon, Switz.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion; reduction of blood transfusion following orthopaedic surgery.

Absenor *Orion, Cz.; Orion, Fin.; Orion, Pol.; Orion, Swed.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder; mania.

Absolue *Lancome, Canad.*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Absolut *Pharmed, India.*
Capsules: Vitamins; minerals; trace elements; citrus bioflavonoids (p. 2505·2); green tea (p. 2648·2); *Lactobacillus sporogenes* (p. 2596·3); lutein (p. 2079·2).
Pharmed, India.
Oral syrup: Vitamins; minerals; lysine (p. 2079·3).

Absorbase *Carolina, USA.*
Vehicle for topical preparations.

Absorbine Arthritis *Young, Canad.†*
Menthol (p. 2553·2); capsicum (p. 2469·3).

Absorbine Jr *Young, Canad.; Young, USA.*
Menthol (p. 2553·2).
Muscluloskeletal, joint, and soft-tissue pain; neuralgia.

Absorbine Jr Antifungal *Young, Canad.*
Tolnaftate (p. 596·1).
Tinea pedis.

Absorbine Jr Roll-on Ice *Young, Canad.†*
Menthol (p. 2553·2).

Absorbine Junior Patch *Young, Canad.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).

Absorbine Power Gel *Young, Canad.*
Menthol (p. 2553·2).

Absorcol *MSD, Spain.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Absorica *Ranbaxy, USA.*
Isotretinoin (p. 1706·2).
Acne.

Absorlent *Esteve, Spain.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Absorlent Plus *Esteve, Spain.†*
Patch A, estradiol (p. 2271·1); patch B, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Absten S *Medley, Braz.†*
⊗Mazindol (p. 2324·1).
Obesity.

Abstensyl *Sintesina, Arg.*
Disulfiram (p. 2495·3).
Alcoholism.

Abstral *ProStrakan, Belg.; Paladin, Canad.; ProStrakan, Denm.; ProStrakan, Fin.; ProStrakan, Fr.; ProStrakan, Ger.; ProStrakan, Gr.; ProStrakan, Irl.; Neopharm, Israel; ProStrakan, Neth.; ProStrakan, Norw.; ProStrakan, Spain; ProStrakan, Swed.; Pro Concepta, Switz.; ProStrakan, UK; Galena, USA.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Abter *Zytras, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Ab-Ther *Laksun, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Abufen-C *Shinto, India.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); ibuprofen (p. 68·2).
Pain.

Abufene *Bouchara, Singapore; Bouchara-Recordati, Ukr.*
Beta-alanine (p. 2048·3).
Menopausal disorders.

Abufène *Bouchara-Recordati, Fr.*
Beta-alanine (p. 2048·3).
Menopausal disorders.

Abuglib *Pharmacos Abug, Mex.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Abutiroi *Pharmacos Abug, Mex.†*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Abutol *Schwarz, Pol.†*
⊗Acebutolol hydrochloride (p. 1289·2).
Hypertension; angina pectoris; arrhythmias.

Abvitos *Gache, Venez.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Vitamin A, C, and D deficiency.

ABZ *Indoco, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

ABZ Plus *Indoco, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Abzole *Euphoric, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

AC
Note: this name may be used for preparations of different composition.
MMC, India.
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.
Vilco, India.
Ear drops: Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

AC2 *Procure, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

AC & C *Pharmascience, Canad.*
Aspirin (p. 22·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever; inflammation.

AC Lan *Lanpharm, Arg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

AC Nex *MPSI, Philipp.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1) phenylpropanolamine hydrochloride (p. 1674·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

AC Para *MMC, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

AC Sera *MMC, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

AC Vascular *Biotenk, Arg.*
Nimodipine (p. 1455·2).
Cerebrovascular disorders.

Aca *Atlantic, Malaysia; Atlantic, Thai.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Acabel *Nycomed, Port.; Grunenthal, Spain; Grunenthal, Venez.*
Lornoxicam (p. 83·2).
Pain; musculoskeletal and joint disorders; inflammation.

Acacin *Ivax, Mex.†*
Cefalexin (p. 234·1).
Bacterial infections.

Academ *Marching, Hong Kong.†*
Benzyl benzoate (p. 2149·1).
Scabies.

Acadimox *Farmochimica, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Acadione *Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.*
Tiopronin (p. 1578·1).
Rheumatoid arthritis; cystinuric lithiasis.

Acal *Helios, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

A-Calcid *Biomedica, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Acalix *Roemmers, Arg.; Vargas, Venez.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; ischaemic heart disease; myocardial infarction; arrhythmias.

Acalka *Silesia, Chile†; Patriot, Philipp.; Ferrer, Port.; Robert, Spain; Ferrer, Thai.*
Potassium citrate (p. 1780·3).
Alkalinisation of urine; renal calculi.

Acalmil *Multilab, Braz.*
Passion flower (p. 2584·1).

ACAM2000 *Acambis, USA.*
A smallpox vaccine (p. 2418·2).
Active immunisation.

Acamed *Medifive, Thai.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Acamol *Volta, Chile; Teva, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Acamol Compuesto *Volta, Chile.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Acamol Focus *Teva, Israel.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Acamol Night *Teva, Israel.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Fever; pain; insomnia.

Acamol Orange *Teva, Israel.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Acamol Tsinun Day *Teva, Israel.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Acamol Tsinun Night *Teva, Israel.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Acamol Tsinun & Shapa'at Day *Teva, Israel.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; cough.

Acamol Tsinun & Shapa'at Night *Teva, Israel.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine

hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Acamoli *Teva, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Acamoli Cold *Teva, Israel.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Acamprol *Sun, India.*
Acamprosate calcium (p. 1034·2).

Acandix *Italfarmaco, Spain.*
Fluconazole (p. 578·2).
Fungal infections.

Acanol *Sanofi-Aventis, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Acantex *Roche, Arg.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Roche, Chile.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Acanya *Valeant, USA.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Acarb *Orchid, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Acarbay *Cipla, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Acarbixin *Sons, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Acard *Polfa Warszawa, Pol.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Acarden *Errekappa, Ital.*
⊗Carvedilol (p. 1333·1).

Acardi *Boehringer Ingelheim, Jpn.*
Pimobendan (p. 1470·1).
Heart failure.

Acardust *Scot, Israel.*
Esdepallethrine (p. 2154·3); piperonyl butoxide (p. 2160·2).
Eradication of house dust mite.

Omega, Fr.†
Sumithrine.
House dust mite allergies (adjuvant).

Acarex
Note: this name may be used for preparations of different composition.
Invision, India.
Acarbose (p. 466·2).
Diabetes mellitus.

Acaril *Allergo, Turk.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Acarilbial *Bial, Port.*
Benzyl benzoate (p. 2149·1).
Scabies.

Acaris *Ali, Turk.*
Acarbose (p. 466·2).

Acaroid *Allergopharma, Ger.*
Mite allergen extract (p. 2434·3).
Allergen immunotherapy.

Acarosan *Allergo, Turk.*
House-dust mite allergen extracts (p. 2434·3).
Allergen immunotherapy.

Acarsan *Biosintetica, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Acarwin *Intra-Labs, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Acasmul *Pharma Investi, Chile.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; ischaemic heart disease.

Acatar
Note: this name may be used for preparations of different composition.
SMB, Belg.
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

US Pharmacia, Pol.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Acatar Acti-Tabs *US Pharmacia, Pol.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Rhinitis.

Acatar Zatoki *US Pharmacia, Pol.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

ACB
Note: this name may be used for preparations of different composition.
Pacific, Singapore.
⊗Acebutolol (p. 1289·1).
Hypertension; angina pectoris; arrhythmias.

Vensat, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Pacific, NZ.†
⊗Acebutolol hydrochloride (p. 1289·2).
Angina pectoris; arrhythmias; hypertension.

ACB Plus *Vensat, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

ACB-S *Vensat, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

ACC *Sandoz, Arg.; Hexal, Austria; Hexal, Cz.; Hexal, Ger.†; Sandoz, Hung.; Sandoz, Mex.; Hexal, Pol.; Hexal, Rus.; Sandoz, S.Afr.; Salutas, Singapore; Sandoz, Switz.; Sandoz, Ukr.*
Acetylcysteine (p. 1652·2) or acetylcysteine sodium.
Respiratory-tract congestion; paracetamol poisoning.

Accelerex *Bioglan, Austral.*
Glucosamine hydrochloride (p. 2515·3); amino acids; colecalciferol (p. 2113·1); boron (p. 2052·3); manganese sulfate (p. 2081·2); salix (p. 129·2).
Osteoarthritis.

Accelerex painEASE *Bioglan, Austral.*
Cream: Australian sandalwood oil; emu oil; rosemary oil (p. 2607·3); arnica (p. 2447·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bioglan, Austral.
Topical spray: Eucalyptus oil (p. 2501·2); arnica (p. 2447·2); rosemary oil (p. 2607·3).
Musculoskeletal, joint, and soft-tissue disorders.

Accent *Zee, India.*
⊗Potassium nitrate (p. 1766·2).

Accept *Vivid, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Vivid, India.
Topical gel: Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); linoleic acid (p. 2509·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Accept-P *Vivid, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Accept-SP *Vivid, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Accesum *Roux-Ocefa, Arg.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Accetiz-P *Geno, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine hydrochloride (p. 2026·2).

Accocit *Accord, Mex.*
Cisplatin (p. 766·1).
Malignant neoplasms.

A.C.Cod *Pharmachemie, Neth.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Accogard *Accord, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Accolate *AstraZeneca, Arg.; AstraZeneca, Austral.†; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Fin.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Mex.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore†; AstraZeneca, Spain; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Zafirlukast (p. 1239·3).
Asthma.

Accoleit *AstraZeneca, Ital.*
Zafirlukast (p. 1239·3).
Asthma.

Accomin *Wyeth Consumer, Austral.†*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3); iron (p. 2073·1).

Accoodryl *Ankom, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Accrete D3 *Internis, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Accu-Chek *Roche, Arg.; Roche Diagnostics, Austral.; Roche Diagnostics, Braz.; Roche Diagnostics, Canad.†; Roche, Chile; Roche Diagnostics, Fr.; Roche Diagnostics, Irl.; Roche Diagnostics, Ital.; Roche Diagnostics, Mex.; Roche Diagnostics, NZ.*
Test for glucose in blood (p. 2516·3).

Accu-Chek Advantage *Boehringer Mannheim, USA.*
Test for glucose in blood (p. 2516·3).

Accu-Chek Dextrose OGT *Roche, Ger.*
Glucose (p. 2068·3).
Oral glucose tolerance test.

Accuhist *Tiber, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Formerly contained pseudoephedrine hydrochloride and brompheniramine maleate.

Accuhist DM Pediatric *Pediamed, USA.*
Syrup: ⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Accuhist PDX *Tiber, USA.*
Oral drops: Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Formerly contained pseudoephedrine hydrochloride, brompheniramine maleate, and dextromethorphan hydrobromide.
Upper respiratory-tract disorders.

Pediamed, USA.†
Syrup: Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Accu lol *Ashford, Singapore.*
⊗Betaxolol (p. 1322·3).
Glaucoma.

Accumax *Pfizer, S.Afr.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Accumax Co *Pharmacia, S.Afr.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Accuneb *Dey, USA.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma.

Accupaque *GE Healthcare, Austria; GE Healthcare, Ger.; Farmazak, Gr.; GE Healthcare, Switz.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Accupep *Sherwood, USA.*
Preparation for enteral nutrition.
Gastrointestinal disorders.

Accupril *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Parke, Davis, USA; Pfizer, Venez.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Accuprin *Pfizer, Ital.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Accupro *Pfizer, Austria; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK; Pfizer, Ukr.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Accupro Comp *Pfizer, Fin.; Pfizer, Swed.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Accupron *Pfizer, Gr.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure; myocardial infarction.

Accuran *Nexus, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Accurbron *Marion Merrell Dow, USA.*
Theophylline (p. 1229·3).
Asthma; bronchospasm.

Accure *Alphapharm, Austral.†*
Isotretinoin (p. 1706·2).
Acne.

Accuretic *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, NZ; Pfizer, S.Afr.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Parke, Davis, USA; Pfizer, Venez.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Accusol *Baxter, Cz.; Baxter, Denm.; Baxter, Fr.; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.†*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); with or without potassium chloride (p. 1793·2) and glucose (p. 2068·3) (p. 1778·2).
Haemofiltration; haemodialysis; haemodiafiltration.

Accutane *Roche, Canad.; Roche, USA.†*
Isotretinoin (p. 1706·2).
Acne.

Accutin *Sandoz, Denm.*
Isotretinoin (p. 1706·2).
Acne.

Accutrend *Roche Diagnostics, Braz.†*
Tests for cholesterol, triglycerides or glucose (p. 2516·3) in blood.

Accutrend Cholesterol *Roche Diagnostics, Ital.; Roche Diagnostics, Mex.†; Roche Diagnostics, UK.*
Test for cholesterol in blood.

Accutrend Colesterol *Roche, Arg.; Roche, Chile.†*
Test for cholesterol in blood.

Accutrend Glucosa *Roche, Arg.; Roche, Chile.†*
Test for glucose in blood (p. 2516·3).

Accutrend Glucose *Roche Diagnostics, Ital.; Roche Diagnostics, Mex.†*
Test for glucose in blood (p. 2516·3).

Accutrend Plus *Roche, Chile.*
Tests for cholesterol, glucose, lactate, or triglycerides in blood.

Accutrend Triglicéridos *Roche, Chile.†*
Test for triglycerides in blood.

Accuvit *Ache, Braz.*
Vitamins; minerals; bioflavonoids (p. 2505·2); acetylcysteine (p. 1652·2); levoglutathione.

Accuzide *Pfizer, Austria; Pfizer, Cz.; Pfizer, Ger.; Pfizer, Hung.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, Turk.; Pfizer, Ukr.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Accuzyme *Healthpoint, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3).
Debridement of necrotic tissue.

ACD *Gobbi, Arg.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

ACD3 *Berko, Turk.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).
Dietary supplement for infants.

Ac-De *Teva, Mex.†*
Dactinomycin (p. 776·3).
Malignant neoplasms.

ACE plus Selenyum *Kocak, Turk.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3).

Acea *Ferndale, UK.*
Metronidazole (p. 936·1).
Rosacea.

Aceact *Active, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aceact-P *Active, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acebitor
Note: this name may be used for preparations of different composition.
GSK, India.
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Unison, Philipp.
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Ace-Bloc
Note: this name may be used for preparations of different composition.
Panion, Philipp.
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy.

Acebloc
Note: this name may be used for preparations of different composition.
Biochem, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acebloc-P *Biochem, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acebron *Drugtech, Chile.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Acec *Intra-Labs, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acec Plus *Intra-Labs, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acecap *Kocak, Turk.*
Betacarotene (p. 2051·1).

Acecardin *Phytopharm, Ukr.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Acecardol *Sintez, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Acecat *Tiedra, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Acecgen *Generics, Hung.*
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Aceclo *Aristo, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Aceclo Plus *Aristo, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aceclofar *Julphar, UAE.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders; pain.

Aceclo-MR *Aristo, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Aceclonac *Verisfield, Gr.*
Aceclofenac (p. 16·2).
Inflammation.

Acecloren *Indoco, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acecloren-P *Indoco, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aceclo-Sera *Aristo, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acecol *Daiichi Sankyo, Jpn.*
Temocapril hydrochloride (p. 1510·2).
Hypertension.

Acecomb *AstraZeneca, Austria.*
⊗Hydrochlorothiazide (p. 1403·2); lisinopril (p. 1420·3).
Hypertension.

Acecor
Note: this name may be used for preparations of different composition.
SPA, Cz.
⊗Acebutolol hydrochloride (p. 1289·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Acecor Cardio *Microkhim, Ukr.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Acecovyl *Alpharma, Mex.†*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Vitamin A, C, and D deficiency.

Acec-P *Intra-Labs, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acedase *Candor, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Acedase-P *Candor, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acedicone *Boehringer Ingelheim, Belg.†*
Thebacon hydrochloride (p. 1679·1).
Cough.

Acedip *RPG, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Acediur
Note: this name may be used for preparations of different composition.
Menarini, Ital.
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sigma-Tau, Spain.
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acedril *Intra-Labs, India.*
Ambroxol acefyllinate (p. 1201·2).

A-Cee *Ace, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ace-Ex *Excare, India.*
Vitamins; minerals.

Acef *KG, Ital.*
Cefazolin sodium (p. 237·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Acefen *Salud, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acefen-P *Salud, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acefen-SP *Salud, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Aceflo *Ashford, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Otitis externa.

Aceflow-P *BL, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aceforce *Akums, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aceforce-MR *Akums, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Aceforce-P *Akums, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aceforce-SP *Akums, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

ACE-Hemmer *RAN, Ger.; Ratiopharm, Ger.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

ACE-Hemmer comp *Ratiopharm, Ger.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Aceína *Hipolabor, Braz.*
Ascorbic acid (p. 2110·3).

Aceite Acalorico *Ordesa, Spain.*
Olive oil (p. 2575·1); betacarotene (p. 2051·1); liquid paraffin (p. 2191·2).
Obesity; constipation.

Aceite Esmeralda Moone *Gordon, Arg.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); phenol (p. 1763·3).
Musculoskeletal and joint disorders.

Aceite Geve Concentrado *Teoforma, Spain.*
Cod-liver oil (p. 2056·3).
Deficiency of vitamins A and D.

Acekapton *Strallhofer, Austria.†*
Aspirin (p. 22·2).
Pain; fever.

Aceler *Senosiain, Mex.*
Fusidic acid (p. 302·1).

Aceler-Co *Senosiain, Mex.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).

Acelisino comp *Lannacher, Austria.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acellulair *GSK, Neth.†*
An acellular pertussis vaccine (p. 2408·2).
Active immunisation.

Acelluvax DTP *Chiron, Israel; Berk, Turk.†*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Acelofan *Acto, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acelofan Plus *Acto, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acelofan-SP *Acto, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Acelom *Om Biotec, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acelom-P *Om Biotec, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acelom-SP *Om Biotec, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acelopram *Ferakon, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Acelysin *Arterium, Ukr.*
Lysine aspirin (p. 84·3).
Pain; fever; thrombosis prophylaxis.

Acem *Emcure, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Acema *Hos & Ins, India.*
Tramadol (p. 139·2).
Pain.

Acemag-P *Magnus, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acema-P *Hos & Ins, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Acemedrox *Bunker, Braz.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogenic.

Acemet *Synmosa, Malaysia.*
Acemetacin (p. 16·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Acemetadoc *Docpharm, Ger.†*
Acemetacin (p. 16·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders.

Acemin *AstraZeneca, Austria.*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acemit *Medphano, Ger.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Acemiz *Lupin, India.*
Astemizole (p. 616·1).
Hypersensitivity reactions.

Acemiz-MR *Lupin, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Acemove *Sanat, India.*
Injection: Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Sanat, India.
Tablets: ⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Acemove Plus *Sanat, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acemove-MR *Sanat, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Acemove-SR *Sanat, India.*
Aceclofenac (p. 16·2).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Acemove-XT *Sanat, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acemuc *Betapharm, Ger.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucus.

Acemucol *Streuli, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with excess or viscous mucus.

Acemuk *Investi, Arg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Acemuk Biotic *Investi, Arg.*
Amoxicillin trihydrate (p. 216·2); acetylcysteine (p. 1652·2).
Respiratory-tract infections.

Acemuk L *Investi, Arg.*
Acetylcysteine (p. 1652·2); tyrothricin (p. 384·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Acemycin *Elpen (Ελπεν), Gr.*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Acenac *Medley, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acenac-P *Medley, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acenam *Smaller, Spain.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Acenec *Elfin, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acenez *Wintech, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acenez-P *Wintech, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acenil *Tocogino, Mex.*
⊗Fluocinolone (p. 1636·1); nystatin (p. 590·3); metronidazole (p. 936·1).
Vaginal infections.

Acenol *Galena, Pol.*
Paracetamol (p. 115·1).
Fever; pain.

Acenor-M *BMS, Indon.†*
Fosinopril sodium (p. 1386·2).
Hypertension.

Acenorm *Alphapharm, Austral.*
Captopril (p. 1331·2).
Hypertension; myocardial infarction; heart failure; diabetic nephropathy.

Acenotromb *Prieto, Arg.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Acenox *Pasteur, Chile.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Acent *Intra-Labs, India.*
Injection; tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Intra-Labs, India.
Topical gel: Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Acenterine *Nycomed, Belg.*
Aspirin (p. 22·2).
Pain; fever.

Acent-MR *Intra-Labs, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Acent-P *Intra-Labs, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acent-SD *Intra-Labs, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Acent-TZ *Intra-Labs, India.*
Aceclofenac (p. 16·2); tizanidine (p. 2026·2).

Aceo *American Taiwan, Thai.*
Acemetacin (p. 16·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis; gout.

Aceomel *PannonPharma, Hung.; Clonmel, Irl.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Aceon *Xoma, USA.*
Perindopril erbumine (p. 1467·1).
Hypertension; cardiovascular risk reduction.

Aceoto *Zambon, Spain.*
Ciprofloxacin (p. 261·1).
Otitis externa.

Aceoto Plus *Zambon, Spain.*
⊗Ciprofloxacin hydrochloride (p. 261·2); fluocinolone acetonide (p. 1636·1).
Otitis externa.

Acepar *Allenge, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acepara *Auspi, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acepara-S *Auspi, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acepar-MR *Allenge, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Aceper *3a, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Acephen *G & W, USA.*
Paracetamol (p. 115·1).
Pain.

Acepil-P *Biosync, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aceplus
Note: this name may be used for preparations of different composition.
BMS, Ital.
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acepramin *PannonPharma, Hung.*
Aminocaproic acid (p. 1131·3).
Fibrinolysis.

Acepran *Andromaco, Chile.*
Clonazepam (p. 519·1).
Epilepsy; panic attacks.

Acepress *Bernofarm, Indon.; BMS, Ital.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Acepril
Note: this name may be used for preparations of different composition.
BMS, UK.
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

CCM, Malaysia.
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Sain, India; Ultra, India.
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Teva, Hung.; Spirig, Switz.†
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Acepril PlusZ *Vera, Hung.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acepril-A *Ultra, India.*
Ramipril (p. 1483·3); amlodipine (p. 1304·1).

Aceprin *Hovid, Malaysia; Hovid, Philipp.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aceprix *Ali, Turk.*
Cilazapril (p. 1336·2).

Aceprix Plus *Ali, Turk.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).

Ace-Proxyvon *Wockhardt, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); rabeprazole sodium (p. 1881·1).

Aceptik *Piramal, India.*
Cetrimide (p. 1742·1).
Wound disinfection.

Aceptik-HC *Piramal, India.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).

Aceptik-LA *Piramal, India.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).

Aceptin *Metro, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acepurin *ACE, Neth.*
Allopurinol sodium (p. 600·2).
Hyperuricaemia; gout.

Ace-Q-Para *Q Check, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acequide *Recordati, Ital.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acequin *Recordati, Ital.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Acer
Note: this name may be used for preparations of different composition.
Arika, India.
Diacerein (p. 45·3).
Osteoarthritis.

Ratiopharm, Pol.†
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Acera *Ipca, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Acerap *Rapross, India.*
Aceclofenac betadex (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acerap-P *Rapross, India.*
Aceclofenac betadex (p. 16·2) paracetamol (p. 115·1).
Pain; inflammation.

Aceratum *Delta, Braz.*
Urea hydrogen peroxide (p. 1774·2).
Cleansing of external ear.

Acerbin *Montavit, Ukr.*
Malic acid (p. 2549·2); benzoic acid (p. 1738·2); salicylic acid (p. 1719·1).
Burns; wounds; skin ulcers; anal fissure.

Acerbine *Montavit, Austria.*
Benzoic acid (p. 1738·2); malic acid (p. 2549·2); salicylic acid (p. 1719·1).
Burns; sunburn; wounds; ulcers; bruises.

Acerbiol *Urgo, Spain.†*
Benzyl alcohol (p. 1739·3); benzoic acid (p. 1738·2); malic acid (p. 2549·2); propylene glycol malate (p. 2205·2); propylene glycol (p. 2205·2); salicylic acid (p. 1719·1).
Burns; skin ulcers; wounds.

Acerbon *AstraZeneca, Ger.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Acercomp *AstraZeneca, Ger.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acerdil *Recalcine, Chile.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Acerdil-D *Recalcine, Chile.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Aceret *Glenmark, India.*
Acitretin (p. 1690·3).
Psoriasis; ichthyosis; lichen planus.

Aceril *Dexcel, Israel.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acerilin *Sandoz, Turk.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Acerin *Scan-Anida, Pol.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Corns; calluses.

Aceroc-P *Wockhardt, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acerogrip C *Luper, Braz.*
Ascorbic acid (p. 2110·3).

Acerpes *Investi, Arg.; Riemser, Ger.†*
Aciclovir (p. 964·1).
Herpesvirus infections; herpes labialis.

Acertil *Servier, China; Servier, Fin.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease.

Servier, Hong Kong.
Perindopril (p. 1466·3) or perindopril arginine (p. 1466·3).
Heart failure; hypertension.

Acertil Comp *Servier, Fin.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Acertil Plus *Servier, Hong Kong.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Acertol *Lacer, Spain.†*
Paracetamol (p. 115·1).
Pain; fever.

A-Cerumen *Batteur, Malaysia.*
TEA-cocoyl hydrolysed collagen; coco-betaine; PEG-120 methyl glucose dioleate.
Ear wax removal.

Gilbert, Hong Kong; Gilbert, Ukr.
Trolamine-cocoyl hydrolysed collagen; coco-betaine; PEG 120 methyl glucose dioleate.
Ear wax removal.

Acerycal *Servier, Irl.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension; coronary artery disease.

Aces *Carlson, USA.*
Betacarotene (p. 2051·1); calcium ascorbate (p. 2111·1); *d*-alpha tocoferol; selenomethionine (p. 2087·1).
Nutritional supplement.

Acesal *Takeda, Ger.*
Aspirin (p. 22·2).
Pain; fever; thrombosis prophylaxis.

Acesan *Sun-Farm, Pol.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Acescap *Kocak, Turk.*
Vitamins.

Acesial *Adamed, Cz.*
Ramipril (p. 1483·3).
Hypertension; myocardial infarction; diabetic nephropathy.

Acesistem *Sigma-Tau, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acespargin *Filofarm, Pol.*
Potassium N-acetylhydroaspartate.
Potassium deficiency.

Acestad *Stada, Ukr.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Acestrol *Almirall, Port.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; prostatic cancer; cachexia associated with malignant neoplasms.

Acesyl
Note: this name may be used for preparations of different composition.
Akacia, S.Afr.
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Citopharma, Braz.
Thiamine hydrochloride (p. 2103·1).

Acesyl Co *Thebe, S.Afr.*
⊗Perindopril (p. 1466·3); indapamide (p. 1409·2).

A-Cet
Note: this name may be used for preparations of different composition.
Acto, India.
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Acet
Note: this name may be used for preparations of different composition.
Pharmascience, Canad.; Euro-Med, Philipp.; Pharmascience, Singapore.
Paracetamol (p. 115·1).
Fever; pain.

Acet-2, Acet-3 *Pharmascience, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain; fever.

Acet Codeine *Pharmascience, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Aceta *Suphong, Thai.; Century, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Aceta with Codeine *Century, USA.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Acetabs *Krewel, Ger.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucus.

Acetacol *PP Lab, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; nasal congestion; hay fever.

Acetacol-P *PP Lab, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Aceta-Diazol *Grin, Mex.†*
⊗Acetazolamide (p. 2001·1).
Oedema; glaucoma; epilepsy.

Acetadol *Medi-Rx, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Acetadote *Phebra, Austral.; AFT, NZ; Cumberland, USA.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Acetafen *Rayere, Mex.; Infinity, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Aceta-Gesic *Rugby, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Formerly contained phenyltoloxamine citrate and paracetamol.
Upper respiratory-tract symptoms.

Acetal C *Zdorovje, Ukr.*
Acetylcysteine (p. 1652·2).
Respiratory tract congestion; paracetamol poisoning.

Acetalgin *Streuli, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Acetalis *Proula, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Acetal-SP *Zytras, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Acetamide *Micro, India.*
⊗Acetazolamide (p. 2001·1).
Diuresis; glaucoma; epilepsy; high-altitude disorders.

Acetamil *Ducto, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Acetamin *Time, India.*
⊗Acetazolamide (p. 2001·1).
Diuresis; glaucoma; epilepsy; high-altitude disorders.

Acetaminophen with Codeine *Pharmascience, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever; cough.

Acetaminophen PM *Plus Pharma, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Acetamol *Vickmans, Hong Kong†; Abiogen, Ital.*
Paracetamol (p. 115·1).
Fever; pain.

Acetan *Kwizda, Austria.*
Lisinopril (p. 1420·3).
Diabetic nephropathy; hypertension; heart failure; myocardial infarction.

Aceta-P *PP Lab, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

AcetaPhos *Salmon, Switz.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Acetapyrin-C *PP Lab, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; hay fever.

Acetar
Note: this name may be used for preparations of different composition.
Labesfal, Port.
Piracetam (p. 393·3).
Cerebrovascular disorders; chronic alcoholism; mental function impairment; Raynaud's syndrome.

Thai Otsuka, Thai.
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Acetariv *East African, India.*
⊗Acetazolamide (p. 2001·1).
Diuresis; glaucoma; epilepsy; high-altitude disorders.

Acetasil *Silom, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Acetasol *Actavis, USA.*
Acetic acid (p. 2426·3); propylene glycol acetate (p. 2206·2); benzethonium chloride (p. 1738·1).
Ear infection.

Acetasol HC *Actavis, USA.*
⊗Hydrocortisone (p. 1640·1); acetic acid (p. 2426·3); propylene glycol diacetate (p. 2206·2); benzethonium chloride (p. 1738·1).
Ear infection.

Acetate *Pond's, Thai.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Acetazone Forte *Teva, Canad.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Pain; skeletal muscle spasm.

Acetazone Forte C8 *Teva, Canad.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; skeletal muscle spasm.

Acetec
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Biolab, Malaysia.
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left ventricular dysfunction.

Reddy, India.
Acitretin (p. 1690·3).
Psoriasis; ichthyosis; lichen planus.

Acetech-P *Pharma-Tech, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aceten *Wockhardt, India; Wockhardt, Rus.†; Biotech, S. Afr.†*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Acetensa *Fahrenheit, Indon.*
Losartan potassium (p. 1422·2).
Hypertension.

Acetensil *Aristo, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Acetensil Plus *Aristo, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acetest *Bayer Diagnostics, Mex.*
Test for ketones in urine, blood, serum and plasma.

Bayer Diagnostics, UK.
Test for ketones in urine, plasma, or serum.
In the UK these are described in the Drug Tariff as Nitroprusside Reagent Tablets (Rothera's Tablets).

Bayer Diagnostics, Irl.†
Test for ketones in urine, plasma, and serum.

Aceticil *Cazi, Braz.*
Aspirin (p. 22·2).
Fever; inflammation; pain; thromboembolism prophylaxis.

Acetif *Novag, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Acetil-A *Precimex, Mex.*
Aspirin (p. 22·2).
Fever; inflammation; pain; thromboembolic disorders.

Acetin
Note: this name may be used for preparations of different composition.
LBS, Malaysia; LBS, Thai.
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus; paracetamol poisoning.

IQFA, Mex.†
Aspirin (p. 22·2).
Fever; inflammation; pain.

Acetoben *Ronava, Venez.*
Ammonium acetate (p. 1655·3); ammonium carbonate (p. 1656·1); sodium benzoate (p. 1738·2); camacho; polygala (p. 1677·2).
Cough.

Acétocaustine *Meda, Switz.*
Monochloroacetic acid (p. 1714·3).
Warts.

Acetofen *Medley, Braz.*
Paracetamol (p. 115·1).
Pain; fever.

Acetoflux *EMS, Braz.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogenic.

Acetol *Psychotropics, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Acetolit *Mertens, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Acetolyt *Medicopharm, Austria; Protina, Ger.*
Calcium-sodium-hydrogencitrate.
Acidosis.

Acetonac *Acto, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Acetonal *Brady, Austria.†*
Aluminium acetotartrate (p. 2440·1); trichlorisobutyl salicylate.
Anorectal disorders.

Acetopt *Sigma, Austral.†; Healthcare Logistics, NZ; Sigma, Philipp.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Acetosal *Rekah, Israel.*
Aspirin (p. 22·2).
Pain; fever; inflammation.

Acetoxyl *Valeo, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Acetrop *Elfin, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acetuber *Teofarma, Spain.*
Suppositories: Cocarboxylase (p. 2103·1); dimenhydrinate (p. 625·2); glucose (p. 2068·3); pyridoxine (p. 2105·3); potassium chloride (p. 1793·2).
Acetonaemia; vomiting in pregnancy.

Acetuff *Servocare, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acetuff-MR *Servocare, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Acetuff-SP *Servocare, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acetyratio *Ratiopharm, Norw.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Acetyst *Ritsert, Ger.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Aceval *Valmor, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Acevit *Recalcine, Chile.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3).
Vitamin supplement.

Acevor *Help, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Acewin *Arrowin, India; Blossoms, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acewin-SR *Arrowin, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Ace-X
Note: this name may be used for preparations of different composition.
Elfin, India.
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acex
Note: this name may be used for preparations of different composition.
Orion, India.
Azithromycin (p. 221·2).
Bacterial infections.

Acezide *Wockhardt, India; BMS, UK.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
These ingredients can be described by the British Approved Name Co-zidocapt.
Hypertension; heart failure.

AC-FA *Pharmasant, Thai.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Ac-Fast *Hormona, Mex.†*
Paracetamol (p. 115·1).
Pain.

Acfol *ITF, Port.; Italfarmaco, Spain.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy; megaloblastic anaemia.

Acgel *Rapross, India.*
Clarithromycin (p. 266·2).
Acne.

Acheflan *Ache, Braz.*
Cordia verbenacea oil.
Inflammatory disorders.

Aches & Pains *Homeocan, Canad.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); belladonna (p. 2453·3); bryonia alba (p. 2461·3); cinchona officinalis (p. 2478·3); hypericum perforatum (p. 449·1); ruta graveolens (p. 2608·2); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Achilite *Holland Pharma, Neth.*
Hypericum perforatum (p. 449·1); aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); millefolium (p. 2427·3).
Homoeopathic preparation.

Achillea Comp *Weleda, S.Afr.†*
Aesculus (p. 2431·2); antimonit (p. 2445·1); gentiana lutea (p. 2512·1); hamamelis (p. 2523·3); achillea millefolium (p. 2427·3).
Homoeopathic preparation.

Achpilori *Misha, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Achpilori-D *Misha, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Achromide *Adcock Ingram, S.Afr.*
Merbromin (p. 1760·1); acriflavinium chloride (p. 1732·3); sulfanilamide (p. 368·1); zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Wounds; burns; ulcers.

Achromycin *Aspen, Austral.; Wyeth, India; Wyeth, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections; amoebiasis.

Achtung *California Scientific, Arg.*
Test for glucose (p. 2516·3).

Aciana-P *Aronex, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aciban
Note: this name may be used for preparations of different composition.
Be-Tabs, S.Afr.
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Cadila, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aciban-DSR *Cadila, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Acic *Hexal, Austria; Hexal, Ger.†; Rowex, Irl.; Sandoz, Ukr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acicare *Unique, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acichek *Sanofi-Aventis, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Aciclin *Fidia, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aciclinlabiale *Fidia, Ital.*
Aciclovir (p. 964·1).
Herpes labialis.

Aciclo *Ahimsa, Arg.; CT, Ger.†*
Aciclovir (p. 964·1).
Herpes labialis.

Aciclobene *Ratiopharm, Austria.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Aciclobeta *Betapharm, Ger.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aciclodan *Pharmacodane, Denm.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aciclofar *Belfar, Braz.*
Aciclovir (p. 964·1).

Acicloflex *Grandix, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acicloflex-MR *Grandix, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Acicloflex-SF *Grandix, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Aciclomed *Ranbaxy, Belg.; Cimed, Braz.*
Aciclovir (p. 964·1).
Herpesvirus skin infections.

Aciclor *Hertz, Braz.; Megat, Venez.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aciclosina *Atral, Port.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aciclostad *Stada, Austria; Stada, Ger.; VP, Spain.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aciclotex *Sertex, Arg.*
Aciclovir (p. 964·1).
Herpes simplex infections of the face and lips.

Aciclovax *Labesfal, Port.*
Aciclovir sodium (p. 964·1).
Herpesvirus infections.

Aciclovivax *Ivax, Fr.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acicon *Bactolac, India.*
Vitamin C (p. 2110·3).
Vitamin C supplement.

Acic-Ophtal *Winzer, Ger.*
Aciclovir (p. 964·1).
Herpes simplex eye infections.

Acicot *Skymax, India.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer; gastrointestinal haemorrhage.

Acicot-O *Skymax, India.*
Sucralfate (p. 1889·1); oxetacaine (p. 1993·1).

Acicral-O *Talent, India.*
Sucralfate (p. 1889·1); oxetacaine (p. 1993·1).

Acicutan *Dermapharm, Switz.*
Acitretin (p. 1690·3).
Keratinisation disorders; psoriasis.

Acid A Vit *Pierre Fabre, Neth.*
Tretinoin (p. 1725·2).
Acne.

Acid Concentrate *Baxter, Canad.*
Acetic acid (p. 2426·3); calcium chloride (p. 1783·1); glucose (p. 2068·3); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); with or without potassium chloride (p. 1793·2) (p. 1778·2).
A range of haemodialysis solutions.

Acid Control *Novopharm, Canad.; Pendopharm, Canad.; Stanley, Canad.*
Famotidine (p. 1842·1).
Gastric hyperacidity.

Acid Gone *Major, USA.*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Antacid.

Acid Jelly *Hope, USA.†*
Hydroxyquinoline sulfate (p. 2530·1); ricinoleic acid (p. 2604·3); acetic acid (p. 2426·3).
Maintenance of vaginal acidity.

Acid Mantle
Note: this name may be used for preparations of different composition.
Bayer, Venez.
Aluminium acetate (p. 2440·1).

Darier, Mex.†
Emollient.
Skin irritation.

Acid Reducer *Mylan, Canad.; Pharmascience, Canad.; Vita Health, Canad.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity.

Acidal *New Life, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Acidan *Ace, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Acidanon *Zentiva, Cz.†*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Aciderm *Sanval, Braz.†*
Ketoconazole (p. 585·3).
Fungal infections.

Acidex *Ivax, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pinewood, Irl.; Pinewood, UK.
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; heartburn; hiatus hernia; flatulence.

Adcock Ingram, S.Afr.†
Aluminium hydroxide (p. 1817·2).
Heartburn; dyspepsia.

Acidin *East India Pharma, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; flatulence; peptic ulcer.

Acidina *Vitapan, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Acidix *Solfran, Mex.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Acid-Lac *Remexa, Mex.*
Lactic acid (p. 2539·1).
Maintenance of normal skin pH.

Acidof *Chemo-Drugs, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Acidofilofago *Roux-Ocefa, Arg.*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea; enterocolitis.

Acidolac *Polpharma, Ukr.*
Lactobacillus acidophilus (p. 2596·3); Bifidobacterium (p. 2596·3).
Restoration of gastrointestinal flora; diarrhoea.

Acidolite *Holland Pharma, Neth.*
Aesculus hippocastanum (p. 2431·2); ambra grisea (p. 2440·3); berberis vulgaris (p. 2502·1); carduus marianus (p. 1561·1); causticum (p. 2595·3); juglans regia (p. 2646·1); lycopodium clavatum (p. 2547·1).
Homoeopathic preparation.

Acidol-P *Armour, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acidom *Siesta, India.*
Domperidone (p. 1838·1); ranitidine (p. 1882·1).

Acidom-O *Siesta, India.*
Ranitidine (p. 1882·1); ondansetron (p. 1872·1).

Acidopent *Medihealth, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acidopent-DSR *Medihealth, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Acidophilus *Mason, USA; Nature's Bounty, USA.*
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement.

Acidophilus Bifidus *Blackmores, Austral.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium animalis* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Acidophilus with Bifidus *Mason, USA; Nature's Bounty, USA.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus bifidus* (p. 2596·3).
Dietary supplement.

Acidophilus with Citrus Pectin *Rugby, USA.*
Lactobacillus acidophilus (p. 2596·3); calcium (p. 1783·1); citrus pectin (p. 2200·3).

Acidophilus Pearls *Enzymatic Therapy, USA.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Maintenance of gastro-intestinal flora.

Acidophilus Plus *GNLD, Austral.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Digestive disorders.

Quest, UK.
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Acidosis *Potter's, UK.*
Oral liquid: Meadowsweet (p. 2550·2); compound gentian infusion (p. 2512·1); euonymus (p. 1842·1).
Dyspepsia; flatulence; heartburn.

Potter's, UK.
Tablets: Meadowsweet (p. 2550·2); vegetable charcoal (p. 1537·3); rhubarb (p. 1884·2).
Dyspepsia; gastric hyperacidity; heartburn.

Acidown *Pharma-Q, S.Afr.*
Cimetidine (p. 1827·1).
Gastrointestinal disorders.

Acidrine *Teofarma, Austria; Teofarma, Fr.; Solvay, Indon.; Teofarma, Ital.; Frik, Turk.*
Aluminium glycinate (p. 1817·2); galactan sulfate (p. 2508·3); myrtecaine laurilsulfate (p. 1993·1).
Gastrointestinal disorders.

Acidum Phosphoricum Complexe No 5 *Lehning, Fr.*
Acidum phosphoricum (p. 2589·1); zincum muriaticum (p. 2126·1); acidum picricum (p. 2634·2); gelsemium (p. 2511·2); valeriana (p. 2640·2).
Homoeopathic preparation.

Acidum Phosphoricum Compose *Boiron, Fr.†*
Acide phosphoricum (p. 2589·1); kalium phosphoricum (p. 1790·3); anacardium orientale (p. 2471·3); arnica montana (p. 2447·2); gelsemium sempervirens (p. 2511·2); selenium metallicum (p. 2086·3); argentum nitricum (p. 2615·3); avena sativa (p. 2451·1).
Homoeopathic preparation.

Acidum phosphoricum Med Complex *Dynamit, Austria.*
Acidum phosphoricum (p. 2589·1); avena sativa (p. 2451·1); china (p. 2478·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Acidum picrinicum Med Complex *Dynamit, Austria.†*
Acidum picrinicum (p. 2634·2); berberis (p. 2502·1); graphites (p. 2522·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Acid-X *BDI, USA.*
Paracetamol (p. 115·1); calcium carbonate (p. 1824·3).
Gastrointestinal disorders.

Acifact *Medico, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acifact-P *Medico, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acifar *Ifars, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acifein *Herbacos, Cz.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Acifix *Morepen, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); sodium alginate (p. 2167·3) or alginic acid (p. 2167·2).

Acifol
Note: this name may be used for preparations of different composition.
Dominguez, Arg.
Folic acid (p. 2063·1).
Megaloblastic anaemia; folic acid deficiency; prevention of neural tube defects in pregnancy.

Acifol-B12 *Dominguez, Arg.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Folic acid and vitamin B_{12} deficiency.

Acifolik *Hasco-Lek, Pol.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Acifon *Zenon, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acifre *GX, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acifungin *Unia, Pol.*
Boric acid (p. 2459·3); methyl salicylate (p. 92·1); salicylic acid (p. 1719·1); gallic acid; acetic acid (p. 2426·3); tannic acid (p. 2625·2).
Fungal skin, scalp, and nail infections.

Acifur *Teva, Mex.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acifusin *Andromaco, Arg.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections; burns; wounds.

Acifusin B *Andromaco, Arg.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Skin disorders with bacterial infection.

Acigon *Sanofi-Aventis, India.*
Alginic acid (p. 2167·2) or sodium alginate (p. 2167·3); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Heartburn; gastro-oesophageal reflux.

Acigone *Sarthak, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Acigone-D *Sarthak, India.*
Domperidone (p. 1838·1); simeticone (p. 1886·2); magaldrate (p. 1856·1).

Acihalt *Sipra, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aciherpin *Agio, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acihexal *Sandoz, Austral.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acihit *Sanat, India.*
Alginic acid (p. 2167·2); magaldrate (p. 1856·1); simeticone (p. 1886·2).

Acikair *PDC, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Acikure *Orifarm, Denm.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux.

Acil *DR Johns, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Acilac
Note: this name may be used for preparations of different composition.
Bioceutica, Arg.
⊗Lactic acid (p. 2539·1); vitamin E (p. 2119·1); urea (p. 1727·3).
Dry skin.

Acilanz *Themis, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Acilax *Jean-Marie, Hong Kong.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acilex *Lexus, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acilex-P *Lexus, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acilin *Berman, Mex.*
Charcoal (p. 1537·3); iodochloride; papaverine (p. 2362·2).
Gastrointestinal astringent.

Acilmed *Bajamed, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Acilo *Wanbury, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Aciloc
Note: this name may be used for preparations of different composition.
Cadila, India; Cadila, Philipp.; Cadila, Rus.; Cadila, Singapore; Cadila, Thai.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; pathological hypersecretory disorders; acid aspiration; Zollinger-Ellison syndrome.

Aciloc RD *Cadila, India.*
Ranitidine hydrochloride (p. 1882·1); domperidone (p. 1838·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Acimax *AstraZeneca, Austral.*
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aci-Med
Note: this name may be used for preparations of different composition.
Triomed, S.Afr.†
Cimetidine (p. 1827·1).
Dyspepsia; gastric hyperacidity; heartburn.

Acimed
Note: this name may be used for preparations of different composition.
Sanitas, Arg.
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acimethin *Madaus, Austria; Gry, Ger.†; Vifor, Switz.*
Methionine (p. 1558·2).
Urinary-tract disorders; paracetamol overdosage; renal calculi; adjunct in antibiotic therapy.

Acimol *Pfleger, Ger.*
Methionine (p. 1558·2).
Urine acidification; renal calculi; adjunct in antibacterial therapy.

Acimol-S *Plus, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acimont *Pharmonta, Austria.*
Formic acid (p. 2507·1); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders.

Acimox *Diba, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Acimox AC *Diba, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Acimox-Ex *Diba, Mex.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Aci-MR *Plus, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Acinat *Natufarma, Arg.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Dietary supplement; gastric hyperacidity.

Acinic
Note: this name may be used for preparations of different composition.
Adelco, Gr.
Mefenamic acid (p. 85·3).
Pain; inflammation.
Biolab Sanus, Braz.
Nicotinic acid (p. 2083·1).

Acinil
Note: this name may be used for preparations of different composition.
Citadel, India.
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Acinil-O *Citadel, India.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Acinopril *Sanofi-Aventis, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Acio *Bennet, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Aciom *Osmed, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Acipax *Wyeth, India.*
Astemizole (p. 616·1).
Hypersensitivity reactions.

Acipen *Astellas, Neth.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Acipep *Kramer, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Aciphen *Wagner, Hung.*
Diethylamine salicylate (p. 51·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Aciphex *Janssen-Cilag, Spain; Eisai, USA.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acipol *Lekko, Rus.*
Lactobacillus acidophilus (p. 2596·3); kefir.
Regulation of intestinal flora.

Acipoun *Medipharma, Arg.*
Chlorhexidine (p. 1743·2).

Acipres *OEP, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Aciran *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Acirex *Worth, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Acirufan *Laetitia, Ger.*
Acid. formicicum (p. 2507·1); aurum chloratum natronatum (p. 2521·2).
Homoeopathic preparation.

Aci-SR *Plus, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acistal *Unichem, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Acistal-D *Unichem, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Acit *Savoy, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Acitab *Cipla-Medpro, S.Afr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Mavi, Mex.
Aspirin (p. 22·2).
Fever; pain.

Acitec *Symbiosis, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Acitec-D *Symbiosis, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Aci-Tip *Investi, Arg.*
Oral suspension: Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; hiatus hernia; peptic ulcer; gastro-oesophageal reflux.

Investi, Arg.
Chewable tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; hiatus hernia; peptic ulcer; gastro-oesophageal reflux.

Acitop *Cipla-Medpro, S.Afr.*
Aciclovir (p. 964·1).
Herpes labialis.

Acitral *Interbat, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis; dyspepsia; flatulence; hiatus hernia.

Acitrin *Ipca, India.*
Acitretin (p. 1690·3).
Ichthyosis; psoriasis; lichen planus.

Acitrom *Piramal, India.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Aciv *Zee, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acival *Geminis, Arg.*
Nimodipine (p. 1455·2).
Cerebrovascular disorders.

Aciveral *Bunker, Braz.*
Aciclovir (p. 964·1).

Acivir *Cipla, Austral.; Pharmacodane, Denm.; Cipla, India; Cipla, Israel; Spirig, Switz.; Norton, Ukr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Actavis, Ger.†
Aciclovir sodium (p. 964·1).
Herpes simplex infections.

Acivirax *Cifarma, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

AciVision *OmniVision, Ger.*
Aciclovir (p. 964·1).
Herpes simplex eye infection.

Acix
Note: this name may be used for preparations of different composition.
Sandoz, Pol.
Aciclovir (p. 964·1).
Herpesvirus infections.

Zentiva, Cz.
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Acixx *Glenmark, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Aciz *Ritz, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aciz Plus *Ritz, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aciz-SP *Ritz, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acks *BPL, India.†*
Ibuprofen (p. 68·2); mephenesin (p. 2025·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

ACL *Sysmed, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Aclacinon *Astellas, Jpn.*
Aclarubicin hydrochloride (p. 735·3).
Malignant neoplasms.

Aclam *Lapi, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Aclarex *Pfizer, Gr.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Aclaro *JSJ, USA.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Aclasta *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Dipa, Indon.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.*
Zoledronic acid (p. 1192·3).
Paget's disease of bone; osteoporosis; hypercalcaemia of malignancy.

Aclav *Glenmark, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Columbia, Arg.†
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Aclear *Hanall, Hong Kong.*
Adapalene (p. 1692·1).
Acne.

Aclene *Cipla, India.*
Adapalene (p. 1692·1).
Acne.

Acler *Pharmatrix, Arg.*
Fluorouracil (p. 795·2).
Actinic keratoses; basal cell carcinoma.

Aclimafel *Carnot, Mex.*
Veralipride (p. 1114·2).
Menopausal disorders.

Aclin
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Alphapharm, Hong Kong.
Sulindac (p. 134·2).
Gout; musculoskeletal and joint disorders; pain; inflammation.

Candor, India.
Clindamycin (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Aclipak *Actavis, Singapore.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Aclixel *Armstrong, Mex.†*
Paclitaxel (p. 839·3).
Non-small cell lung cancer; ovarian cancer; Kaposi's sarcoma; breast cancer.

Aclo *Cure Quick, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aclocen *Centrum, Spain.*
Aceclofenac (p. 16·2).
Gout; musculoskeletal and joint disorders; pain.

Aclocta *Notco, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aclocta-P *Natco, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Aclodase *Cure Quick, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Aclofen *Ind-Swift, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aclofen Plus *Ind-Swift, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aclog *Dallas, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aclog-CX *Dallas, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Aclog-SD *Dallas, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Aclomax *Admac, India.*
Diclofenac sodium (p. 48·3).
Pain.

Aclomp-P *Kaizen, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aclomp-SP *Kaizen, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Aclonac *Pharos, Indon.*
Diclofenac potassium (p. 48·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; pain.

Aclonac-P *Candor, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aclonac-SN *Candor, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Aclonac-SR *Candor, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aclophen *Nutripharm, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Aclor *Aspen, Austral.*
Cefaclor (p. 232·3).
Bacterial infections.

Acloral *Liomont, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Aclosan *Gobbi, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Acloson-P *Dr Alson, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acloson-SP *Dr Alson, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Aclotad *Dolorgiet, Fin.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Aclotil *Bal, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Aclotin *Valeant, Hung.; ICN, Pol.; ICN, Ukr.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Aclotine *Lab Francais du Fractionnement, Fr.*
Antithrombin III (human) (p. 1132·3).
Thromboembolic disorders.

Aclovate *PharmaDerm, USA.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Aclovir *Ratiopharm, Fin.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aclovirax *Marching, Hong Kong.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Adox *Osper, India.*
Cloxacillin (p. 274·3).
Benzylpenicillin-resistant staphylococcal infection.

Adozox *Cure Quick, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Aclusin *Casasco, Arg.*
Cilostazol (p. 1337·1).
Occlusive arterial disease.

ACM 20 *ACM, Fr.†*
Vitamins; minerals; amino acids.

Acmic *Adley, India.*
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Adley, India.
Tablets: Mecobalamin (p. 2108·1); folic acid (p. 2063·1); nicotinamide (p. 2083·1); pantothenic acid (p. 2085·2); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Acmic-Alpha *Adley, India.*
Biotin (p. 2052·2); folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Acmic-S *Adley, India.*
Mecobalamin (p. 2108·1); dexpanthenol (p. 2582·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); lysine hydrochloride (p. 2079·3).

Acnacyl *Pfizer Consumer, Singapore.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Acnaid *Stiefel, Chile.*
Soap: Sulphonated rice bran oil; sulfonated mustard oil; liquid paraffin (p. 2191·2).
Acne.

Stiefel, Mex.
Soap substitute.
Acne.

Acnase *Zurita, Braz.*
Cream: Benzoyl peroxide (p. 1696·1); sulfur (p. 1721·1).
Acne.

Zurita, Braz.
Topical gel: Benzoyl peroxide (p. 1696·1).
Acne.

Acnaveen
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Ital.
Avena (p. 2451·1); salicylic acid (p. 1719·1).
Seborrhoea; acne.

Acne *Homeocan, Canad.*
Antimonium tartaricum (p. 151·2); calcarea picrata (p. 2634·2); echinacea (p. 2498·1); kalium bromatum (p. 2461·1); pulsatilla (p. 2600·2); selenium metallicum (p. 2086·3); sulphur iodatum (p. 2624·2); thuja occidentalis (p. 2629·3); viola tricolor (p. 2647·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Acne Clear
Note: this name may be used for preparations of different composition.
Altaire, USA.
Benzoyl peroxide (p. 1696·1).
Acne.

ICM, Singapore.
Sulfur (p. 1721·1); zinc oxide (p. 1729·1); resorcinol (p. 1718·3); calamine (p. 1697·2).
Acne.

Acné Crème *Widmer, Switz.*
Salicylic acid (p. 1719·1); colloidal sulfur (p. 1721·1); colloidal silicon dioxide (p. 2209·1); triclosan (p. 1773·2).
Acne.

Acné Crème Plus *Widmer, Switz.*
Benzoyl peroxide (p. 1696·1); miconazole nitrate (p. 589·1).
Acne.

Acne Derm *Fischer, Israel.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acne Feldin *Galenium, Indon.*
Sulfur (p. 1721·1).
Acne.

Acné Gel *Widmer, Switz.*
⊗Colloidal sulfur (p. 1721·1); pyridoxine hydrochloride (p. 2105·3); triclosan (p. 1773·2); urea (p. 1727·3).
Acne.

Acne Hermal *Olvos, Gr.*
Erythromycin (p. 291·2).
Acne.

Acné Lotion *Widmer, Switz.*
Salicylic acid (p. 1719·1); triclosan (p. 1773·2); zinc sulfate (p. 2126·2); magnesium sulfate (p. 1787·3).
Acne.

Acne Lotion 10 *C & M, USA.*
Sulfur (p. 1721·1).
Acne.

Acne Medication *Rugby, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acne Plus *Widmer, Austria; Widmer, Ger.; Widmer, Philipp.†*
Miconazole nitrate (p. 589·1); benzoyl peroxide (p. 1696·1).
Acne.

Acne Solutions *Clinique, Canad.*
Lotion: Benzoyl peroxide (p. 1696·1).
Acne.

Acne Sulf *RiC, Pol.†*
Sulfur (p. 1721·1); camphor (p. 2466·2); lime water (p. 2465·1).
Acne; seborrhoea; rosacea.

Acne Vanishing Treatment *Mentholatum, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acne-Aid
Note: this name may be used for preparations of different composition.
GSK, Arg.; Stiefel, Austral.†; Stiefel, Canad.; Stiefel, Hong Kong; Stiefel, S.Afr.†
Bar: Soap.
Acne; cleansing of oily skin.

Stiefel, Braz.; Stiefel, India; Stiefel, Israel; Stiefel, Philipp.; Stiefel, Singapore.
Soap substitute.
Acne.

Stiefel, Hong Kong.
Topical liquid: Liquid skin cleanser.
Acne.

Stiefel, Malaysia; Stiefel, Singapore; Stiefel, Thai.†
Bar; liquid cleanser: Skin cleanser.
Acne.

Stiefel, Hong Kong†; Stiefel, Malaysia†; Stiefel, Singapore.†
Cream: Sulfur (p. 1721·1); resorcinol (p. 1718·3); chloroxylenol (p. 1748·2).
Acne.

Acneban *Nutrimmune, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acnebenz *Sarabhai Piramal, India.*
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

AcneCare
Note: this name may be used for preparations of different composition.
Hoe, Malaysia.
⊗Triclosan (p. 1773·2); glycerol (p. 2517·2).
Acne; seborrhoea.

Acnecare
Note: this name may be used for preparations of different composition.
Widmer, Neth.
Benzoyl peroxide (p. 1696·1); miconazole nitrate (p. 589·1).
Acne.

Acnecide *Galderma, Irl.; Galderma, UK.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acneclear
Note: this name may be used for preparations of different composition.
Janpharm, S.Afr.†
Cleansing bar: Triclosan (p. 1773·2).
Acne.

Janssen-Cilag, S.Afr.†
Cream: Miconazole nitrate (p. 589·1); benzoyl peroxide (p. 1696·1).
Acne.

Acneclin
Note: this name may be used for preparations of different composition.
Investi, Arg.
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Themis, India.
Clindamycin (p. 269·3).
Acne.

Acnecolor *Spirig, Switz.*
Clotrimazole (p. 576·2).
Acne.

Acne-Derm
Note: this name may be used for preparations of different composition.
Unia, Pol.
Azelaic acid (p. 1695·1).
Acne; melasma.

Acnederm
Note: this name may be used for preparations of different composition.
Ego, Hong Kong; Ego, Singapore.
Lotion: ⊗Azelaic acid (p. 1695·1); glycerol (p. 2517·2).
Acne.

Ego, NZ.
Lotion: Azelaic acid (p. 1695·1); phenoxyethanol (p. 1764·3).
Acne.

Pharmacia Upjohn, India.
Erythromycin (p. 291·2).
Acne.

Acnederm Foaming Wash
Note: this name may be used for preparations of different composition.
Ego, Malaysia; Ego, NZ†; Ego, Singapore.
⊗Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3); glycerol (p. 2517·2).
Acne.

Ego, Austral.†
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Acne.

Acnederm Lotion *Ego, Malaysia.*
Azelaic acid (p. 1695·1).
Acne.

Acnederm Wash
Note: this name may be used for preparations of different composition.
Ego, Hong Kong.
⊗Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3); glycerol (p. 2517·2).
Acne.

Acnederma
Note: this name may be used for preparations of different composition.
Psychotropics, India.
Allantoin (p. 1693·1); vitamin E (p. 2119·1).
Acne.

Confar, Port.†
Sulfur (p. 1721·1).
Acne.

Acnedox-LB *Shinto, India.*
Lactobacillus (p. 2596·3); doxycycline (p. 288·1).

Acnedur *Adeka, Turk.*
Tetracycline hydrochloride (p. 373·2).

Acnéfuge *Spirig, Switz.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acnegon *Zyg, Thai.*
Clindamycin phosphate (p. 269·3).
Acne.

Acneguard *Psychotropics, India.*
Allantoin (p. 1693·1); menthol (p. 2553·2); oak bark (p. 2574·1); melaleuca oil (p. 2551·1); vitamin E (p. 2119·1); jojoba oil.
Acne.

Acnelak *Shalaks, India.*
Soap: Triclosan (p. 1773·2); zinc oxide (p. 1729·1).
Acne.

Shalaks, India.
Topical gel: Erythromycin (p. 291·2).
Acne.

Acnelak-Z *Shalaks, India.*
Erythromycin (p. 291·2); zinc acetate (p. 2126·1).
Acne.

Acnelyse *Abdi, Turk.*
Tretinoin (p. 1725·2).
Acne.

Acnemask *Pivot, Gr.†*
Hexachlorophene (p. 1754·1).

Acnemin *Vinas, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Acneout *HLB, Arg.*
Tretinoin (p. 1725·2); erythromycin (p. 291·2).
Acne.

Acnepas *Atlas, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acnepas E *Atlas, Arg.*
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

Acneplus *Widmer, Belg.*
Benzoyl peroxide (p. 1696·1); miconazole nitrate (p. 589·1).
Acne.

Acneral *Laboratorios Chile, Chile.*
Isotretinoin (p. 1706·2).
Acne.

Acneris *Psyco Remedies, India.*
Clindamycin (p. 269·3).
Acne.

Acneris-AD *Psyco Remedies, India.*
Adapalene (p. 1692·1); clindamycin phosphate (p. 269·3).
Acne.

Acneryne *Galderma, Belg.*
Erythromycin (p. 291·2).
Acne.

Acnesan
Note: this name may be used for preparations of different composition.
Ingens, Arg.
Benzoyl peroxide (p. 1696·1).
Acne.

Novogaleno, Ital.
Sulfur (p. 1721·1); zinc sulfate (p. 2126·2); glycolic acid (p. 1704·3); enoxolone (p. 54·2).
Seborrhoea.

Acnesoap *Stiefel, Braz.*
Soap substitute.
Acne.

Acnesol
Note: this name may be used for preparations of different composition.
Systopic, India.
Erythromycin (p. 291·2).
Acne.

Deltapharm, Hong Kong.†
Benzoyl peroxide (p. 1696·1); chlorocresol (p. 1748·1).
Acne.

Acnesol-CL *Systopic, India.*
Clarithromycin (p. 266·2).
Acne.

Acnesone *Systopic, India.*
Dapsone (p. 281·2).
Acne.

Acnestal *Biomedica, India.*
Allantoin (p. 1693·1); aloe vera (p. 1693·2); melaleuca oil (p. 2551·1).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Acnestop
Note: this name may be used for preparations of different composition.
Arterium, Ukr.
Azelaic acid (p. 1695·1).
Acne; skin pigmentation disorders.

Bioceutica, Arg.
Clindamycin phosphate (p. 269·3).
Acne.

Acnet *Amideep, India.*
Erythromycin (p. 291·2).
Acne.

Acnetane *Adcock Ingram, S.Afr.*
Isotretinoin (p. 1706·2).
Acne.

Acnetin *Jadran, Ukr.*
Isotretinoin (p. 1706·2).
Acne.

Acnetrex *Mega Lifesciences, Philipp.*
Isotretinoin (p. 1706·2).
Acne.

Acnetrim *Trima, Israel.*
Erythromycin (p. 291·2).
Acne.

Acnetrol *Lagos, Arg.*
Lotion: Mallow (p. 2549·2); calendula (p. 2465·2); rosemary (p. 2607·2); enebro (p. 1723·2).
Skin disorders.

Lagos, Arg.
Topical gel: Chamomile (p. 2474·1); trepadora; sage (p. 2608·3); rosemary (p. 2607·2).
Skin disorders.

Acnex
Note: this name may be used for preparations of different composition.
Konsuma, Venez.
Benzoyl peroxide (p. 1696·1).
Acne.

Unichem, India.
Capsules: Isotretinoin (p. 1706·2).
Acne.

Unichem, India.
Soap: Soap substitute.
Acne.

Acnexyl *Pharmasant, Thai.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acnezil *Cimed, Braz.*
Benzoyl peroxide (p. 1696·1).
Acne.

Acniben *Isdin, Arg.*
A soap substitute and moisturiser.
Acne.

Acniben Gel Limpiador *Isdin, Chile.*
Skin cleanser.
Acne.

Acniben Gel-Crema Equilibrante *Isdin, Chile.*
Emollient in acne.

Acniben Rx Balsamo Reparador *Isdin, Chile.*
Emollient for lips.
Protection for lips from anti-acne preparations.

Acniben Rx Hidratante *Isdin, Chile.*
Emollient.
Acne.

Acniben Rx Limpiadora *Isdin, Chile.*
Soap substitute.
Acne.

Acniben Toallitas *Isdin, Chile.*
Salicylic acid (p. 1719·1); triclosan (p. 1773·2); aloe vera (p. 1693·2).
Skin cleanser for oily skin.

Acnidazil
Note: this name may be used for preparations of different composition.
Ariston, Arg.
Adapalene (p. 1692·1).
Acne.

Italchimici, Ital.; Janssen-Cilag, S.Afr.†
Miconazole nitrate (p. 589·1); benzoyl peroxide (p. 1696·1).
Acne.

Acnil
Note: this name may be used for preparations of different composition.
Glenmark, India.
Aluminium sodium silicate (p. 1818·3); sulfur (p. 1721·1).
Acne.

IQFA, Mex.
Tretinoin (p. 1725·2).
Acne.

Mediphar, Venez.
Gel; liquid soap; lotion: Salicylic acid (p. 1719·1).
Acne.

Cristalia, Braz.†
Isotretinoin (p. 1706·2).
Acne.

Acnisal *Alliance, Irl.; Alliance, UK.*
Salicylic acid (p. 1719·1).
Acne.

Acno
Note: this name may be used for preparations of different composition.
Ajanta, India.
Isotretinoin (p. 1706·2).
Acne.

Baker Cummins, USA.
Sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Acne.

Acno Cleanser *Baker Cummins, USA.*
Skin cleanser.

Acnocin
Note: this name may be used for preparations of different composition.
Community Pharmacy, Thai.
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Sandoz, UK.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.

Acnogen *Genepharm, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Acnoil Free *Dermoteca, Port.†*
Magnesium silicate (p. 2195·3); aluminium silicate (p. 1818·3).
Acne.

Acnomel *Numark, Canad.†; Darier, Mex.*
Resorcinol (p. 1718·3); sulfur (p. 1721·1).
Acne.

Numark, USA.
Resorcinol (p. 1718·3); sulfur (p. 1721·1); titanium dioxide (p. 1725·1).
Acne.

Acnopur *Biotherm, Canad.†*
Cream; lotion: Salicylic acid (p. 1719·1).
Acne.

Biotherm, Canad.†
Mousse: Triclosan (p. 1773·2).

Acnotan *Farmaten, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Acnotex *C & M, USA.*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1); methylbenzethonium chloride (p. 1760·3).
Acne.

Acnotin *Bago, Chile; Mega Lifesciences, Hong Kong; Mega Lifesciences, Malaysia; Mega Lifesciences, Singapore; Mega Lifesciences, Thai.*
Isotretinoin (p. 1706·2).
Acne.

A-Cnotren *Pharmathen, Gr.; Pharmathen, Thai.*
Isotretinoin (p. 1706·2).
Acne.

A1cNOW *Metrika, USA.*
Test for glycosylated haemoglobin in blood.

Acnoxin *Andromaco, Arg.*
Salicylic acid (p. 1719·1); resorcinol monoacetate (p. 1718·3); chloramphenicol (p. 257·1).
Acne.

Acnoxyl Abrasivo *Mepro, Chile.†*
Essential fatty acids; melaleuca oil (p. 2551·1).
Acne.

Acnoxyl Acondicionador *Koni-Cofarm, Chile.*
Melaleuca oil (p. 2551·1).
Seborrhoea.

Acnoxyl Gel Humectante *Koni-Cofarm, Chile.*
Melaleuca oil (p. 2551·1); collagen (p. 2483·2).
Acne.

Acnoxyl Jabon Liquido *Mepro, Chile.†*
⊗Melaleuca oil (p. 2551·1); alfa hydroxy acids; glycerol (p. 2517·2).
Acne.

Acnoxyl Locion Tonica *Koni-Cofarm, Chile.*
⊗Melaleuca oil (p. 2551·1); alfa hydroxy acids; alcohol (p. 1733·1); menthol (p. 2553·2).
Acne.

ACNU *Baxter Oncology, Ger.†*
Nimustine hydrochloride (p. 836·3).
Malignant neoplasms.

Acocarb *Accord, Mex.*
Dacarbazine (p. 776·1).
Malignant melanoma; soft-tissue sarcoma; Hodgkin's lymphoma.

Acocontin *Modi-Mundipharma, India.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Acodin *Sanofi-Aventis, Pol.*
Syrup: Dextromethorphan hydrobromide (p. 1660·1); dexpanthenol (p. 2582·2).
Cough.

Sanofi-Aventis, Pol.
Tablets: Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Acoexcel *Accord, Mex.*
Paclitaxel (p. 839·3).
Breast cancer; non-small cell lung cancer; ovarian cancer.

A-Cof *Aust Ind, India.*
Chloramphenicol palmitate (p. 257·1); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Acofide *Zeria, Jpn.*
Acotiamide hydrochloride (p. 1815·1).
Functional dyspepsia.

Acoflut *Accord, Mex.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Acoin *Combustin, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Acolate *Gujarat Terce, India.*
Oral drops: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Gujarat Terce, India.
Tablets: ⊗Levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Acolate DPS *Gujarat Terce, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Acolate Plus *Gujarat Terce, India.*
⊗Ambroxol hydrochloride (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Acolate-P *Gujarat Terce, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

A'Cold *Arika, India.*
Drops: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Arika, India.
Oral suspension; tablets: ⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Allergic rhinitis.

A-Colest *K2 Health & Wellness, Chile.*
Phytosterols (p. 1471·2).
Hypercholesterolaemia.

A-Colest TG *K2 Health & Wellness, Chile.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Acolic *Asiapharm, Singapore.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Acolyt *Modi-Mundipharma, India.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Acomexol *Armstrong, Mex.*
Crotamiton (p. 1699·2).
Pruritus; scabies; pediculosis.

Acomicil *Adamed, Spain.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Acomir con hierro *Medipharm, Chile.†*
Ferrous sulfate (p. 2062·2); vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3).
Iron and vitamin deficiency.

Acomplex P *Hoch Wertig, Arg.*
Calcium carbonate (p. 1824·3).
Dietary supplement.

Acomplia *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austria†; Sanofi-Aventis, Belg.†; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fr.†; Sanofi-Aventis, Gr.†; Sanofi-Aventis, Hong Kong†; Sanofi-Aventis, Israel†; Sanofi-Aventis, Ital.†; Sanofi-Aventis, Norw.†; Sanofi-Aventis, Swed.†; Sanofi-Aventis, Switz.†; Sanofi-Aventis, UK.†*
Rimonabant (p. 2606·2).
Obesity.

Acon
Note: this name may be used for preparations of different composition.
Roemmers, Venez.
Pyritinol (p. 394·3).
Mental function disorders.

Aconeuba *Accord, Mex.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Aconex *Agepha, Austria.*
⊗Naphazoline hydrochloride (p. 1669·3).
Conjunctivitis.

Aconitum Composé *Boiron, Fr.†*
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); apis mellifica (p. 2445·2); mercurius dulcis (p. 2555·3); arnica montana (p. 2447·2).
Homoeopathic preparation.

Aconitum Med Complex *Dynamit, Austria.*
Aconitum (p. 2428·3); belladonna (p. 2453·3); bryonia (p. 2461·3); gelsemium (p. 2511·2).
Homoeopathic preparation.

Aconitum Nicotiana comp *Weleda, Ger.†*
Aconitum napellus (p. 2428·3); tabacum (p. 2632·2); ol. rosmarini (p. 2607·3).
Homoeopathic preparation.

Acoplasic *Accord, Mex.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Acord *Invision, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Acord-A *Invision, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Acord-L *Invision, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Acortral *Accord, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Acorvio Plus *Ferndale, UK.*
⊗Miconazole nitrate (p. 589·1); fluprednidene acetate (p. 1637·3).
Skin disorders with fungal infection.

Acota *Cadila, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Acota-3 *Cadila, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Acota-MR *Cadila, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Acotral *Phoenix, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Acotril *Pharma Nutria, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Acovil *Sanofi-Aventis, Spain.*
Ramipril (p. 1483·3).
Hypertension; heart failure following myocardial infarction; diabetic nephropathy; myocardial infarction prevention.

Acoxxel *MSD, Irl.; MSD, Spain.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; gout; pain.

Acpan *Gray, Arg.*
Glycopyrronium bromide (p. 2519·3).

Acpio *Aspen, Austral.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

AC-Plus *Laksun, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Acpulsif *Dexa, Indon.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Acqta *Rayere, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Acqua Sirmione *Nycomed, Ital.*
Sulfurous thermal water (p. 1721·1).
Catarrh; rhinitis; sinusitis; cold symptoms.

Acqua Virginiana *Kelemata, Ital.*
Hamamelis (p. 2523·3).
Skin irritation; hand wash.

Acquin *Arrow, Austral.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Acquire *Shreshtha, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Acral *Acto, India.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer; gastrointestinal haemorrhage.

Acral-O *Acto, India.*
Sucralfate (p. 1889·1); oxetacaine (p. 1993·1).

Acran *Sanbe, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Acrea *Aulo Gelio, Arg.*
Arginine (p. 2049·1); menthol (p. 2553·2); jojoba oil.
Vaginal lubricant.

Acredin *Sarabhai Piramal, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger Ellison syndrome; dyspepsia.

Acrel *Warner Chilcott, Spain.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Acresil *Pasteur, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Acrexon *Shin Poong, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Acridilole *Akrikhin, Rus.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Acridin *Legrand, Braz.*
Acriflavinium chloride (p. 1732·3); methenamine (p. 322·3); methylthioninium chloride (p. 1559·1); belladonna (p. 2453·3).
Urinary-tract infections.

Acriflex *Thornton & Ross, UK.*
Chlorhexidine gluconate (p. 1743·3).
Wounds; burns; scalds.

Acrilans *Akrikhin, Rus.†*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Acrilo *Pasteur, Philipp.*
Famotidine (p. 1842·1).
Dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer.

Acris
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Risedronate sodium (p. 1189·3).
Osteoporosis.

Gland, India.
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Acroken *Kendrick, Mex.*
Octreotide (p. 1924·1).
Acromegaly.

Acromax
Note: this name may be used for preparations of different composition.
Agepha, Austria.†
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Acromicina *Wyeth, Mex.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Acromon *Biosynthesis, Gr.*
Omeprazole (p. 1867·2).

Acronitol *Farmanic, Gr.*
Potassium chloride (p. 1793·2).

Acrose *Rafa, Israel.*
Acarbose (p. 466·2).
Diabetes mellitus.

Acroser *Farmanic, Gr.*
Potassium gluconate (p. 1793·2).

Acroxil *Sons, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Acroxil-C *Sons, Mex.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Acrub *Psychotropics, India.*
Lotion: Erythromycin (p. 291·2); zinc acetate (p. 2126·1).
Acne.

Psychotropics, India.
Topical gel: Clindamycin (p. 269·3); zinc acetate (p. 2126·1).
Acne.

Acrylarm *Poen, Arg.; Poen Vision, Mex.; Roemmers, Venez.*
Carbomer 940 (p. 2173·3).
Dry eyes.

Acsacea *Remek, Gr.*
Metronidazole (p. 936·1).
Rosacea.

Ac-Sal *Isdin, Chile.†*
Salicylic acid (p. 1719·1); triclosan (p. 1773·2); aloe vera (p. 1693·2).
Acne.

Acsolve-C *Ind-Swift, India.*
Clindamycin (p. 269·3); tretinoin (p. 1725·2).
Acne.

Acsolve-H *Ind-Swift, India.*
⊗Hydrocortisone (p. 1640·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).

ACT
Note: this name may be used for preparations of different composition.
Johnson & Johnson Medical, USA.
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Act
Note: this name may be used for preparations of different composition.
Adeka, Turk.
Acetylcysteine (p. 1652·2).

ACT-3 *Whitehall Consumer, Austral.†; Wyeth Consumer, NZ.*
Ibuprofen (p. 68·2).
Fever; pain; inflammation; musculoskeletal and joint disorders.

Acta *Jean-Marie, Hong Kong.*
Tretinoin (p. 1725·2).
Acne.

Actacef *Actavis, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Actacel *Sanofi Pasteur, Arg.; Sanofi Pasteur, Chile; Sanofi Pasteur, Israel; Aventis, S.Afr.†; Sanofi Pasteur, Singapore†; Sanofi Pasteur, Thai.†*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Actacode *Aspen, Austral.*
Codeine phosphate (p. 40·2).
Cough.

Actadomp *Actavis, Neth.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; epigastric discomfort; gastro-oesophageal reflux.

Actadon *Acdhon, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; agitation.

Actagen *Goldline, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Actagen-C Cough *Goldline, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); triprolidine hydrochloride (p. 642·3).
Coughs and cold symptoms.

Actal
Note: this name may be used for preparations of different composition.
Adley, India.
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Invida, Hong Kong; ICN, Malaysia†; Invida, Singapore; Invida, Thai.†; Merck Consumer, UK.
Alexitol sodium (p. 1815·1).
Gastric hyperacidity; heartburn; peptic ulcer; dyspepsia.

Transfarma, Indon.; Valeant, Indon.
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; peptic ulcer; gastritis; dyspepsia; flatulence.

Actal Plus
Note: this name may be used for preparations of different composition.
Invida, Hong Kong; Transfarma, Indon.; Valeant, Indon.; Invida, Singapore.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; heartburn; peptic ulcer; dyspepsia; gastritis; flatulence.

ICN, Malaysia.†
Alexitol sodium (p. 1815·1); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; heartburn; peptic ulcer.

Actalide *Errekappa, Ital.*
Nimesulide (p. 101·3).

Actalipid *Actavis, Port.†; Actavis, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Actamax *Pharma Dynamics, S.Afr.*
Risedronate sodium (p. 1189·3).

Actamol *Teva, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Actan *Saval, Chile.*
Fluoxetine (p. 417·1).
Depression; obsessive-compulsive disorder.

Actaparoxetine *Actavis, Rus.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Actapin *Actavis, Hong Kong; Actavis, Indon.; Actavis, Singapore.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Actapront *Purissimus, Arg.*
Isothipendyl hydrochloride (p. 631·2).
Pruritus; insect bites.

Actapulgite *Ipsen, Belg.; Ipsen, Fr.; Beaufour, Switz.†*
Attapulgite (p. 1820·1).
Diarrhoea; meteorism; gastrointestinal disorders.

Actastav *Actavis, Rus.*
Stavudine (p. 1015·3).
HIV infection.

Actasulid *Zdravlje, Rus.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Actazolam *Actavis, Indon.*
Alprazolam (p. 1035·2).
Anxiety.

Actebral *Recalcine, Chile.*
Dedietilaminoetil-p-aminobenzoato hydrochloride; gamma-aminobutyric acid (p. 2509·2); haematoporphyrin hydrochloride (p. 2523·3).
Mental function impairment.

Actelite *Holland Pharma, Neth.*
Bryonia cretica; causticum (p. 2595·3); chelidonium majus (p. 2522·2); urtica urens (p. 2639·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Actelsar *Actavis, Irl.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Actemra *Roche, Arg.; Roche, Austral.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Hong Kong; Roche, Israel; Chugai, Jpn; Roche, NZ; Roche, Philipp.; Roche, Rus.; Roche, Switz.; Roche, Thai.; Roche, Ukr.; Genentech, USA.*
Tocilizumab (p. 77·3).
Castleman's disease; rheumatoid arthritis; juvenile idiopathic arthritis.

Actenacol *Dicofarm, Ital.*
Fennel (p. 2503·2); passion flower (p. 2584·1); melissa (p. 2552·3).
Gastrointestinal disorders.

Acter *Active, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Acthar *Questcor, USA.*
⊗Corticotropin (p. 1628·3).
Diagnostic testing of adrenocortical function; corticosteroid release stimulant.

Acthéane *Boiron, Fr.*
Cimicifuga racemosa (p. 2478·1); arnica montana (p. 2447·2); glonoinum (p. 1391·2); sanguinaria canadensis (p. 2610·1); lachesis mutus (p. 2538·3).
Formerly known as Menocynesine.
Homoeopathic preparation.

Acthelea *Elea, Arg.*
⊗Corticotropin (p. 1628·3).
Corticosteroid release stimulant; diagnostic testing of adrenocortical function.

Act-HIB *Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, China; Aventis Pasteur, Cz.†; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Biological E, India; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.†; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Aventis, S.Afr.†; Sanofi Pasteur, Singapore†; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.; Sanofi Pasteur, USA.*
A haemophilus influenzae conjugate vaccine (p. 2387·2).
Active immunisation.

Acthrel *Ferring, USA.*
⊗Corticorelin triflutate (p. 1628·2).
Determination of ACTH production in Cushing's syndrome.

Acti 5 *Pierre Fabre Sante, Fr.*
Oral liquid: ⊗Deanol pidolate (p. 2319·1); sodium ascorbate (p. 2111·1); magnesium aminobenzoate.
Tonic.

Acti Talc *Tree of Life, Israel.*
Zinc undecenoate (p. 596·3); zinc stearate (p. 2221·2); magnesium stearate (p. 2195·3); menthol (p. 2553·2); undecenoic acid (p. 596·3); melaleuca oil (p. 2551·1).
Skin irritation.

Acti-B_{12} *Sandoz, Canad.†*
Hydroxocobalamin (p. 2107·3); amino acids.
Anaemia.

ActiBath *Jergens, USA.*
Avena (p. 2451·1).
Dry skin; pruritus.

Actiben *Advik, India.*
Benzoyl peroxide (p. 1696·1).
Acne.

Actibil *Arkomedika, Fr.†*
Cynara (p. 2490·3); fumitory (p. 2508·2).
Gastrointestinal and urinary-tract disorders.

Actibile *David, India.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; primary biliary cirrhosis.

Actiblok-IPR *Biocon, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

ActiCal *Yacca, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).

Actical *Usana, Mex.*
Colecalciferol (p. 2113·1); minerals.
Dietary supplement.

ActiCal Plus *Yacca, India.*
Colecalciferol (p. 2113·1); minerals.

Acticalcin *TRB, Braz.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; bone pain due to malignancy; sympathetic pain syndromes.

Acticarbine *Elerte, Fr.*
Papaverine hydrochloride (p. 2362·3); activated charcoal (p. 1537·3).
Gastrointestinal disorders.

Acticard *Active, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Acticef *Active, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Acticef-SB *Active, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Actichlor *Adams, Hong Kong.*
Troclosene sodium (p. 1774·1).
Disinfection of surfaces and equipment.

Acticillin *British Dispensary, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Acticin
Note: this name may be used for preparations of different composition.
Alpharma, USA; Penederm, USA.
Permethrin (p. 2159·3).
Scabies.

Acticlav *Active, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Acticlor *Active, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Acticoat *Smith & Nephew, Austral.; Smith & Nephew, Ital.; Smith & Nephew, Singapore; Smith & Nephew, UK.*
Nanocrystalline silver (p. 2615·1).
Medicated dressing; wounds; ulcers; burns.

Acticoat Absorbent *Smith & Nephew, Singapore.*
Nanocrystalline silver (p. 2615·1); alginate (p. 2167·2).
Medicated dressing; wounds; ulcers; burns.

Acticoat Flex *Smith & Nephew, Singapore.*
Nanocrytalline silver (p. 2615·1).
Medicated dressing.

Acticold *Pharmed, India.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Cold symptoms; cough.

Acticort
Note: this name may be used for preparations of different composition.
Baker Cummins, USA.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Overseas, India.
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Acticuf *Pharmed, India.*
Ammonium chloride (p. 1656·1); menthol (p. 2553·2); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).

Actide *Samarth, India.*
Octreotide (p. 1924·1).
Acromegaly; variceal haemorrhage; prevention of complications following pancreatic surgery; HIV-associated diarrhoea; gastrointestinal endocrine tumours.

Actidem *GSK, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Respiratory-tract congestion.

Actidol-DP *Obsurge, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Actidose with Sorbitol *Paddock, USA.*
Activated charcoal (p. 1537·3); sorbitol (p. 2092·1).
Emergency treatment of poisoning.

Actidose-Aqua *Paddock, USA.*
Activated charcoal (p. 1537·3).
Emergency treatment of poisoning.

Actidose-Aqua Advance *Alliance, UK.*
Activated charcoal (p. 1537·3).
Emergency treatment of poisoning.

Actidox *Saninter, Port.*
Doxycycline (p. 288·1).
Bacterial infections.

Actidrox *Active, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Actidue *Johnson & Johnson, Ital.*
⊗White tablets (daytime), paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); blue tablets (night-time) paracetamol; diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Actifed
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Austral.†; GSK, Belg.†; McNeil Consumer, Canad.; GSK, India; GSK, Indon.; McNeil Healthcare, Irl.; Johnson & Johnson, Ital.; GSK, Malaysia; Johnson & Johnson Consumer, Mex.†; Johnson & Johnson, NZ†; Johnson & Johnson, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Thai.†; GSK, Turk.; GSK, Ukr.†; Wellcome, USA.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion; cold and influenza symptoms; rhinitis; allergic rhinitis; sinusitis; upper respiratory-tract congestion; nasal congestion; upper respiratory-tract disorders; cold symptoms; catarrh; otitis media.

Johnson & Johnson, Fr.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract congestion; cold symptoms.

McNeil, Pol.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Actifed Advance *Johnson & Johnson Consumer, Mex.*
Phenylephrine hydrochloride (p. 1672·3).

Actifed Allergie *Johnson & Johnson, Fr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Actifed Allergy *Wellcome, USA.*
⊗White daytime caplets, pseudoephedrine (p. 1676·1); blue night time caplets, pseudoephedrine; diphenhydramine hydrochloride (p. 626·2).

Actifed CC Chesty *Johnson & Johnson, Austral.†*
Guaifenesin (p. 1666·2).
Cough.

Actifed CC Dry *Johnson & Johnson, Austral.†*
Pholcodine (p. 1675·1).
Cough.

Actifed CC Junior *Pfizer Consumer, Austral.†*
Dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract disorders.

Actifed Chesty *Pfizer Consumer, Austral.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; respiratory-tract congestion.

Actifed Cold & Allergy *Warner-Lambert, USA.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Actifed Cold & Fever *GSK, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Actifed Cold & Sinus *Warner-Lambert, USA.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms.

Actifed Composto *Johnson & Johnson, Ital.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; respiratory-tract congestion.

Actifed Compound
Note: this name may be used for preparations of different composition.
GSK, Hong Kong; GSK, Singapore.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough; nasal congestion.

Actifed Dia *Johnson & Johnson Consumer, Mex.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Actifed Dia Advance *Johnson & Johnson Consumer, Mex.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Actifed DM
Note: this name may be used for preparations of different composition.
GSK, India.
Triprolidine hydrochloride (p. 642·3); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract congestion.

GSK, Malaysia; Johnson & Johnson Consumer, Mex.†; GSK, Singapore; GSK, Thai.†
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms; allergic rhinitis; nasal congestion.

Actifed Dry *Pfizer Consumer, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Actifed Dry Cough Regular *GSK, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Actifed Dry Cough Sugar Free *GSK, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Actifed États Grippaux *Johnson & Johnson, Fr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Actifed Expectorant
Note: this name may be used for preparations of different composition.
GSK, Malaysia; GSK, Singapore; GSK, Ukr.†
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Actifed Nasale *Johnson & Johnson, Ital.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Actifed New *GSK, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Actifed Noche *Johnson & Johnson Consumer, Mex.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2).
Cold symptoms; rhinitis.

Actifed Noche Advance *Johnson & Johnson Consumer, Mex.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Actifed PE *Johnson & Johnson, Austral.†*
Phenylephrine hydrochloride (p. 1672·3).

Actifed Plus
Note: this name may be used for preparations of different composition.
GSK, India.
Triprolidine hydrochloride (p. 642·3); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1).
Respiratory-tract congestion associated with pain or fever.

McNeil Consumer, Canad.; Wellcome, USA.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms; sinusitis; allergic respiratory-tract disorders.

Actifed Plus Cough Suppressant *GSK, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Allergic rhinitis; cough.

Actifed Plus Expectorant *GSK, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Allergic rhinitis; cold symptoms; cough.

Actifed Rhinite Allergique *Johnson & Johnson, Fr.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Formerly known as Actifedduo.
Allergic rhinitis.

Actifed Rhume jour et nuit *Johnson & Johnson, Fr.*
⊗12, White tablets (daytime), paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); 4, blue tablets (night), paracetamol; diphenhydramine hydrochloride (p. 626·2).
Cold symptoms.

Actifed Sinus Daytime *Wellcome, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Actifed Sinus Nighttime *Wellcome, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Actifed Wet Cough Non Drowsy *GSK, S.Afr.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Actifedon *GSK, Gr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).

Actifedrin
Note: this name may be used for preparations of different composition.
Investi, Arg.; Farmoquimica, Braz.; GSK, Chile.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms; rhinitis; upper respiratory-tract congestion.

Investi, Arg.†
Lozenges: Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Actifedrin Antitusivo *GSK, Chile.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Actifedrin Nasal *Investi, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Actifedsign *Johnson & Johnson, Fr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold symptoms.

Actiflex *Pendopharm, Canad.†*
Trolamine salicylate (p. 141·2).

Actiflora *Brovar, S.Afr.†*
Lactobacillus acidophilus (p. 2596·3).
Restoration of a normal gastrointestinal flora.

Actiflox
Note: this name may be used for preparations of different composition.
Saga, India.
Sparfloxacin (p. 357·3).
Bacterial infections.

Actiflox-400
Note: this name may be used for preparations of different composition.
Alicon, India.
Norfloxacin (p. 333·3).
Bacterial infections.

Actiflox-T *Alicon, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Actiflu *Cipla, India.*
Triprolidine hydrochloride (p. 642·3); phenylpropanolamine (p. 1674·1).

ActiFlu Extra C *US Pharmacia, Pol.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Actiflu Plus *Cipla, India.*
Triprolidine hydrochloride (p. 642·3); phenylpropanolamine (p. 1674·1); paracetamol (p. 115·1).

Actifluor *Polifarma Benessere, Ital.*
Sodium fluoride (p. 2089·2); stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

ActiFreeze *Passion for Life, UK.*
Dimethyl ether (p. 1798·3).
Verrucas; warts.

Actigall *Novartis, NZ; Watson, USA.*
Ursodeoxycholic acid (p. 2638·1).
Primary biliary cirrhosis; primary sclerosing cholangitis; gallstones.

Actigeron *Bago, Chile.*
Acetylcarnitine hydrochloride (p. 2053·2).
Dementia.

Actigesic *GSK, Indon.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms; sinusitis; nasopharyngitis.

Actigess *Schwarz, Fr.†*
Ornithine hydrochloride (p. 2085·2); betaine (p. 2456·1); sorbitol (p. 2092·1); citric acid (p. 2480·3); magnesium carbonate (p. 1856·2).
Digestive disorders.

Actigrip *Johnson & Johnson, Ital.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Respiratory-tract congestion; influenza symptoms.

Actihaemyl *Stulln, Ger.*
Protein-free bovine blood extract (p. 2444·1).
Wounds; eye disorders.

Actihist *Hovid, Malaysia†; Hovid, Singapore.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Actihist Expectorant *Hovid, Malaysia.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough and cold symptoms.

Actihist-Co *Hovid, Malaysia.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough; nasal congestion.

Actikerall *Almirall Hermal, Ger.; Almirall, Switz.; Almirall, UK.*
Fluorouracil (p. 795·2); salicylic acid (p. 1719·1).
Actinic keratosis.

Actil *Masa, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Actilac *Embiotic, India.*
Lactobacillus (p. 2596·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Actilam *Sofex, Port.*
⊗Hesperidin (p. 2505·2); deanol acetamidobenzoate (p. 2319·1); magnesium glycerophosphate (p. 1787·2).
Mental function disorders; vascular disorders.

Actilax
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Medic, Denm.
Sodium picosulfate (p. 1887·2).
Constipation.

Actilife
Note: this name may be used for preparations of different composition.
Apex, India.
Vitamins; minerals; trace elements.

Acti-Life Protein Plus *Blackmores, Austral.*
Preparation for enteral nutrition.

Actilis *Laphi, Fr.†*
Barrier cream.

Actilop *Active, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Actilop-H *Active, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Actilyse *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, Venez.*
Alteplase (p. 1296·3).
Myocardial infarction; pulmonary embolism; ischaemic stroke; maintenance of central venous catheter patency.

Actima *Seagull, India.*
Betacarotene (p. 2051·1); manganese (p. 2081·2); selenium (p. 2086·3); spirulina (p. 2622·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Actimag *Faes, Spain.*
Magnesium pidolate (p. 1787·3).
Magnesium depletion.

Actimagon *Nycomed, Switz.†*
Magnesium lactate (p. 1787·2); magnesium citrate (p. 1857·1).
Magnesium deficiency; skeletal muscle spasm.

Actiman *Bioforma, Mex.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); ascorbic acid (p. 2110·3); manganese sulfate (p. 2081·2).
Osteoarthritis.

Actimax
Note: this name may be used for preparations of different composition.
Investi, Arg.
Alendronate sodium (p. 1171·3).
Osteoporosis.

PSA, Philipp.
Cefixime (p. 240·3).
Bacterial infections.

Actiment *Tecnonat, Arg.*
Nutritional supplement.

Actimin *CCM, Malaysia.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms; rhinitis.

Actimmune
Note: this name may be used for preparations of different composition.
Pharos, Indon.
Echinacea (p. 2498·1); vitamins; herbs.
Cold symptoms; immunostimulant.

Vidara, USA.
Interferon gamma-1b (p. 999·1).
Infections in chronic granulomatous disease; osteopetrosis.

Actimol *Pharmed, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Actimol-F *Pharmed, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; inflammation.

Actimol-S *Pharmed, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Actimox *Active, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Actimycin *Venus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Actin *The Forty-Two, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Actinac *Peckforton, UK.†*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1); nicoboxil (p. 101·1); allantoin (p. 1693·1); precipitated sulfur (p. 1721·1).
Acne.

Actine *Darrow, Braz.*
Liquid soap: Salicylic acid (p. 1719·1); aloe vera (p. 1693·2).
Acne; seborrhoea.

Darrow, Braz.
Soap: Salicylic acid (p. 1719·1); sulfur (p. 1721·1); aloe vera (p. 1693·2).
Acne; seborrhoea.

Actinerval *Bago, Arg.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia.

Actinim *Active, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Actinium *Armstrong, Mex.*
Oxcarbazepine (p. 533·2).
Epilepsy; neuropathic pain.

Actinoma *Orva, Turk.*
Diclofenac sodium (p. 48·3).
Actinic keratosis; musculoskeletal and joint pain.

Actinor-MZ *Active, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Actinor-TZ *Active, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Actins *Taiyang, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Action Chewable *Bayer Consumer, Austral.†*
Chlorphenamine maleate (p. 620·3); phenylephrine tartrate (p. 1672·3).
Cold symptoms; hay fever.

Action Cold & Flu *Bayer Consumer, Austral.†*
Chlorphenamine maleate (p. 620·3); phenylephrine acid tartrate (p. 1672·3); aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Action O G *Le Naturiste, Canad.†*
Chromium (yeast) (p. 2125·2).

Actioner *Nexus, India.*
Capsules: Vitamins; minerals; lycopene (p. 2546·2).

Nexus, India.
Oral liquid: Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Actioner-DX *Nexus, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1).

Actipiril *Confar, Port.*
Aspirin (p. 22·2).
Fever; pain.

Actiplex *Umeda, Thai.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms; nasal congestion.

Actipol *Diafarm, Rus.; Infamed, Ukr.*
Aminobenzoic acid (p. 1694·2).
Viral eye infections.

Actipram *Laboratorios Chile, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression.

Acti-Prex *Glenmark, S.Afr.*
Perindopril (p. 1466·3).

Actipro *Active, India.*
Vitamins; minerals; proteins.

Actiprofen *GSK Consumer, Austral.†; Sanofi-Aventis, Braz.; GSK Consumer, Irl.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation; musculoskeletal and joint disorders.

Actipur Anti-imperfections *Noreva, Fr.*
Nicotinamide (p. 2083·1); phytosphingosine; ceramides (p. 1699·1).
Acne.

Actipur 3 en 1 *Noreva, Fr.*
Keratozine A; nicotinamide (p. 2083·1); phytosphingosine; ceramides (p. 1699·1).
Acne.

Actipur Stop *Noreva, Fr.*
Nicotinamide (p. 2083·1); phytosphingosine.
Skin blemishes.

Actiq *Orphan, Austral.; Cephalon, Austria; Cephalon, Denm.; Cephalon, Fin.†; Cephalon, Fr.; Cephalon, Ger.; Alapis, Gr.; Cephalon, Irl.; Cephalon, Israel; Dompe, Ital.; Cephalon, Neth.; Cephalon, Norw.†; Cephalon, Port.; Teva, Spain; Swedish Orphan, Swed.; Teva, Switz.; Genesis, Turk.; Cephalon, UK; Cephalon, USA.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Actiquim *Quimica y Farmacia, Mex.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Actira *Bayer, Austria; Sigma-Tau, Ital.; Bayer, Spain.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Actiran *Active, India.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Actiran-D *Active, India.*
Ranitidine (p. 1882·1); domperidone (p. 1838·1).

Actirelax *Northia, Arg.*
Suxamethonium (p. 2037·1).
Depolarising neuromuscular blocker.

Actires *Dicofarm, Ital.*
Propolis (p. 2597·3); boswellia (p. 2507·3).
Respiratory-tract disorders.

Actiribex *Johnson & Johnson, Ital.*
Dropropizine (p. 1662·2).
Cough.

Actiribexen *Johnson & Johnson, Ital.*
Dropropizine (p. 1662·2); guaifenesin (p. 1666·2).
Cough.

Actirox *Active, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Actisac *Polipharm, Thai.*
Fluoxetine (p. 417·1).
Depression.

Actisens *Polifarma Benessere, Ital.*
⊗Sodium fluoride (p. 2089·2); potassium nitrate (p. 1766·2).
Gum hypersensitivity.

Actiseptic *Johnson & Johnson, Ital.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Actiser *Unimarck, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; premenstrual dysphoric disorder.

Actiser-T *Silesia, Chile.*
⊗Testosterone (p. 2305·1).
Hypogonadism.

Actiskenan *BMS, Fr.*
⊗Morphine sulfate (p. 92·3).
Pain.

Actison *Buxton, Arg.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; levodopa-induced dyskinesias.

Actisorb *Systagenix, Ital.*
Activated charcoal (p. 1537·3); silver (p. 2615·1).
Infected or malodorous wounds.

Actisorb Ag *Ethicon, Fr.*
Activated charcoal (p. 1537·3); silver (p. 2615·1).
Infected wounds.

Actisorb Plus *Johnson & Johnson Medical, Arg.*
Activated charcoal (p. 1537·3); silver (p. 2615·1).
Infected wounds.

Actisorb Silver *Systagenix, Irl.; Johnson & Johnson Medical, UK.*
Activated charcoal (p. 1537·3); silver (p. 2615·1).
Formerly known as Actisorb Plus.
Infected or malodorous wounds.

Actisoufre *Grimberg, Fr.*
Sodium sulfate (p. 1888·1); dried yeast (p. 2125·2).
Upper respiratory-tract inflammation; rhinitis.

Actispas Plus *Shinto, India.*
Paracetamol (p. 115·1); dicycloverine (p. 1834·2).

Actispas-R *Shinto, India.*
Dicycloverine (p. 1834·2); ranitidine (p. 1882·1).

Actistav *Biofarm, Pol.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Actisuny *Pharmanel, Gr.*
Diclofenac sodium (p. 48·3).
Joint disorders.

Actit *Kowa, Jpn.*
Electrolytes (p. 1775·1); maltose (p. 2081·1).
Fluid and electrolyte disorders.

Actitherapy *Johnson & Johnson, Ital.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2); camphor (p. 2466·2).
Respiratory congestion.

Actithiol *Almirall, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Actithiol Antihist *Almirall, Spain.*
Carbocisteine (p. 1658·1); promethazine hydrochloride (p. 638·2).
Respiratory-tract disorders.

Actitop *Khandelwal, India.*
Etoposide (p. 790·2).
Testicular cancer; small cell lung cancer.

Actitrin *Hasco-Lek, Pol.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold and influenza symptoms; cough.

Activ Dopo Puntura *Bouty, Ital.†*
Ammonia (p. 2441·2); almond oil (p. 2437·1).
Insect bites.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Activa Balance *Europe Cosmetiques, Canad.*
Vitamins; minerals.

Activa Bio *Europe Cosmetiques, Canad.*
Ascorbic acid (p. 2110·3).

Activa C *Europe Cosmetiques, Canad.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).

Activacin *Kyowa, Jpn.*
Alteplase (p. 1296·3).
Myocardial infarction; acute ischaemic stroke.

Activadone *Thea, Spain.*
Eye drops: Chromocarb diethylamine (p. 2477·1).
Conjunctival capillary fragility; adjunct in eye surgery.

Actival *Beres, Ukr.*
Vitamins; minerals.

Activase *Roche, Canad.; Genentech, USA.*
Alteplase (p. 1296·3).
Myocardial infarction; pulmonary embolism; stroke; maintenance of central venous catheter patency.

Active 4 *Vivier, Canad.*
Hydroquinone (p. 1705·1).

Active C *Roche-Posay, Braz.; Roche-Posay, Mex.; Roche-Posay, Singapore.*
Ascorbic acid (p. 2110·3).
Wrinkles; skin ageing.

Active Calcium *Usana, Canad.; Usana, Singapore.†*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); silicon (p. 2088·3).
Dietary supplement.

Usana, Hong Kong.†
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); magnesium citrate (p. 1857·1); magnesium oxide (p. 1857·3); colecalciferol (p. 2113·1); silicon (p. 2088·3).
Calcium and magnesium supplement.

Active Control *Matrix, Canad.†*
Pyrithione zinc (p. 1718·1).

Active Cough Syrup *Marching, Hong Kong.†*
Ammonium chloride (p. 1656·1); pentoxyverine (p. 1672·1); chlorphenamine (p. 620·3); phenylephrine (p. 1672·2).

Active Duty *Apex, NZ.*
Diethyltoluamide (p. 2153·1); permethrin (p. 2159·3).
Formerly known as Safehold Active Duty.
Insect repellent.

Active Duty with Sunscreen *Apex, NZ.*
SPF 23+: Diethyltoluamide (p. 2153·1); ethyl butylacetylaminopropionate (p. 2154·3); permethrin (p. 2159·3); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Formerly known as Safehold Active Duty with Sunscreen.
Insect repellent.

Active Duty Sunscreen *Apex, NZ.*
SPF 30: Titanium dioxide (p. 1725·1).
Formerly known as Safehold Active Duty Sunscreen.
Sunscreen.

Active FE *GM, USA.*
Minerals; vitamins.
Dietary supplement.

Active OB *GM, USA.*
Minerals; vitamins; docosahexaenoic acid (p. 1460·1).

Activella *Novo Nordisk, USA.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Activelle *Novo Nordisk, Arg.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Novo Nordisk, Canad.; Silesia, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Procter & Gamble, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Isdin, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; hormone replacement therapy.

Activent *More, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Activex 40 Plus *Adcock Ingram, S.Afr.†*
Ginseng (p. 2513·3); muira-puama; vitamins; minerals; kelp (p. 2612·1); lysine hydrochloride (p. 2079·3).
Tonic.

Activil *Casasco, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Activir *GSK, Austria; GSK, Fr.; GSK, S.Afr.*
Aciclovir (p. 964·1).
Herpes labialis.

Activis *Osmed, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Activon *Meda, Hung.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Activox
Note: this name may be used for preparations of different composition.
Arkopharma, Fr.
Pastilles: Erysimum (p. 2524·2); chamomile (p. 2474·1).
Mouth and throat disorders.

Arkopharma, Fr.
Ointment: Camphor (p. 2466·2); turpentine oil (p. 2636·3); levomenthol (p. 2553·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar oil (p. 2472·3); thymol (p. 1772·2).
Respiratory-tract disorders.

World Foods, UK.
Ivy (p. 2536·2).
Cough.

Activox Expectorant *Arkopharma, Fr.†*
Ivy (p. 2536·2).
Cough.

Activox Lierre *Arkopharma, Fr.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Actizid *Overseas, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Actizide-M *Active, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Actizobid *Active, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Actizox *Intas, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Actnovate *TP, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected inflammatory skin disorders.

ActoCalD *Warner Chilcott, Neth.†*
Orange tablets, risedronate sodium (p. 1189·3) (Actonel); white tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Actocortina *Takeda, Spain.*
⊗Hydrocortisone sodium phosphate (p. 1640·2).
Corticosteroid.

Actokit *Warner Chilcott, Neth.*
Blue tablets, calcium carbonate (p. 1824·3); orange tablets, risedronate sodium (p. 1189·3).
Osteoporosis.

Actokit D *Warner Chilcott, Neth.*
Tablets, risedronate sodium (p. 1189·3); granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Actomite *Ceuta, UK.*
Bioallethrin (p. 2149·2).
Elimination of house dust mite.

Acton Prolongatum *Ferring, India.*
⊗Corticotropin (p. 1628·3).
Corticosteroid release stimulant.

Actonaze *OEP, Philipp.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Actonel *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Procter & Gamble, Belg.; Sanofi-Aventis, Braz.; Warner Chilcott, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.†; Warner Chilcott, Fr.; Warner Chilcott, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Warner Chilcott, Irl.; Sanofi-Aventis, Israel; Procter & Gamble, Ital.; Ajinomoto, Jpn; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Warner Chilcott, Neth.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Procter & Gamble, Rus.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Aventis, UK; Procter & Gamble, UK; Warner Chilcott, USA; Sanofi-Aventis, Venez.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Actonel with Calcium *Warner Chilcott, USA.†*
4 Tablets, risedronate sodium (p. 1189·3); 24 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Actonel Combi *Procter & Gamble, UK.*
Tablets, risedronate sodium (p. 1189·3); effervescent granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Sanofi-Aventis, Austral.; Sanofi-Aventis, Irl.; Warner Chilcott, Irl.
Tablets, risedronate sodium (p. 1189·3); tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Actonel Combi D *Sanofi-Aventis, Austral.; Warner Chilcott, Belg.*
Tablets, risedronate sodium (p. 1189·3); effervescent granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Actonel Plus Ca & D *Warner Chilcott, Irl.*
Tablets, risedronate sodium (p. 1189·3); effervescent granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Actonel plus Calcium *Warner Chilcott, Canad.†; Warner Chilcott, Ger.; Tap Pharma, Neth.†*
4 Tablets, risedronate sodium (p. 1189·3); 24 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Actonel plus Calcium D *Sanofi-Aventis, Hong Kong.*
Tablets, risedronate sodium (p. 1189·3); effervescent granules, calcium carbonate (p. 1824·3) colecalciferol (p. 2113·1).
Osteoporosis.

Warner Chilcott, Ger.
4 Tablets, risedronate sodium (p. 1189·3); 24 effervescent granule sachets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Actonel Trio *Sanofi-Aventis, Hung.; Sanofi-Aventis, Mex.*
4 Tablets, risedronate sodium (p. 1189·3) (Actonel); 60 tablets, colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Osteoporosis.

Actonelcombi *Warner Chilcott, Fr.*
Tablets, risedronate sodium (p. 1189·3); effervescent granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Actonorm *Wallace Mfg Chem., UK.*
Oral gel: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; dyspepsia.

Wallace Mfg Chem., UK.
Oral powder: Magnesium carbonate (p. 1856·2); aluminium hydroxide (p. 1817·2); atropine sulfate (p. 1310·2); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1); peppermint oil (p. 1877·1).
Gastric hyperacidity; flatulence; dyspepsia.

Actophlem *Adcock Ingram, S.Afr.*
Theophylline (p. 1229·3); etofylline (p. 1208·2); diphenylpyraline hydrochloride (p. 627·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Actoplatin *Actavis, Indon.*
Carboplatin (p. 759·1).
Ovarian cancer; small-cell lung cancer.

Actoplus Met *Takeda, USA.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Acto-Pred *Ferring, India.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Actorin *Hua, Thai.†*
Aspirin (p. 22·2).
Pain.

Actos *Abbott, Arg.; Lilly, Austral.; Takeda, Austria; Lilly, Belg.; Abbott, Braz.; Takeda, Canad.; Abbott, Chile; Takeda, China; Takeda, Cz.; Takeda, Denm.; Takeda, Fin.; Takeda, Fr.†; Takeda, Ger.; Takeda, Gr.; Takeda, Hong Kong; Takeda, Hung.; Takeda, Indon.; Takeda, Irl.; Takeda, Ital.; Takeda, Jpn; Takeda, Malaysia; Lilly, Neth.; Takeda, Norw.; Lilly, NZ; Takeda, Philipp.; Takeda, Pol.; Takeda, Port.; Lilly, Rus.; Lilly, S.Afr.; Takeda, Singapore; Takeda, Spain; Takeda, Swed.; Takeda, Switz.; Takeda, Thai.; Lilly, Turk.; Takeda, UK; Lilly, USA; Takeda, USA; Abbott, Venez.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Actos Met *Abbott, Chile.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Actosmet *Takeda, Hong Kong; Takeda, Philipp.; Takeda, Thai.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Actosolv *Eumedica, Belg.; Eumedica, Fr.*
Urokinase (p. 1520·3).
Thromboembolic disorders; venous catheter occlusion.

Actospect *Adcock Ingram, S.Afr.*
Guaifenesin (p. 1666·2).
Cough.

Actovegin *Nycomed, Austria; Nycomed, China; Nycomed, Ger.†; Nycomed, Gr.; Nycomed, Hong Kong; Nycomed, Hung.†; Nycomed, Rus.; Nycomed, Ukr.*
Protein-free bovine blood extract (p. 2444·1).
Wounds; burns; scalds; skin grafts; radiation-induced skin and mucous membrane damage; cerebral circulatory and metabolic disorders; peripheral vascular disorders; ulcers; corneal disorders; eye disorders.

Actovit *Acto, India.*
Vitamin B substances (p. 2102·3); glutamic acid (p. 2070·2); zinc acetate (p. 2126·1).

Actparin *Bergamo, Braz.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Actraphane *Novo Nordisk, Irl.*
⊗Mixture of neutral insulin injection (human, emp) 30% and isophane insulin injection (human, emp) 70% (p. 475·3).
Diabetes mellitus.

Actraphane 10, 20, 30, 40, 50 *Novo Nordisk, Neth.; Novo Nordisk, Pol.; Novo Nordisk, Port.*
⊗Mixtures of insulin injection (human) 10%, 20%, 30%, 40%, or 50% and isophane insulin injection (human) 90%, 80%, 70%, 60%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Actraphane 30 *Novo Nordisk, Gr.*
⊗A mixture of insulin injection (human, recombinant) 30% and isophane insulin (human, recombinant) 70% (p. 475·3).
Diabetes mellitus.

Actraphane 30, 40, 50 *Novo Nordisk, Cz.*
⊗Mixtures of insulin injection (human) 30%, 40%, or 50% and isophane insulin (human) 70%, 60%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Actraphane 30, 50 *Novo Nordisk, Ger.; Novo Nordisk, Ital.*
⊗Mixtures of insulin injection (human) 30% or 50% and isophane insulin injection (human) 70% or 50%, respectively (p. 475·3).
Diabetes mellitus.

Actraphane HM *Novo Nordisk, S.Afr.*
⊗Mixture of soluble insulin injection (human, biosynthetic) 30% and isophane insulin injection (human, biosynthetic) 70% (p. 475·3).
Diabetes mellitus.

Actrapid *Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hung.; Novo Nordisk, India†; Novo Nordisk, Indon.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Turk.; Novo Nordisk, UK.*
⊗Neutral insulin injection (human, pyr, monocomponent) (p. 475·3).
Diabetes mellitus.

Actrapid HM *Novo Nordisk, Arg.; Novo Nordisk, Chile; Novo Nordisk, Hong Kong; Novo Nordisk, India; Novo*

Nordisk, Malaysia; Novo Nordisk, Philipp.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Switz.; Novo Nordisk, Thai.
⊗Neutral insulin injection (human, monocomponent) (p. 475·3).
Formerly known as Human Actrapid.
Diabetes mellitus.

Actrapid MC *Novo Nordisk, Rus.†*
⊗Insulin (porcine) (p. 475·3).
Diabetes mellitus.

Actretin *Bio-Gen, Turk.*
Isotretinoin (p. 1706·2).

Actril *Minntech, Canad.*
Hydrogen peroxide (p. 1755·2); peracetic acid (p. 1763·1).
Disinfection of instruments.

Actrim *Medicine Products, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Actrol *Matrix, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Actron
Note: this name may be used for preparations of different composition.
Bayer Consumer, Arg.; Bayer, Chile; Bayer, Mex.
Ibuprofen (p. 68·2).
Pain; fever; inflammation; musculoskeletal and joint disorders.
Bayer, Fr.
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Actron Compuesto *Bayer, Spain.*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Actron Plus *Bayer, Mex.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain; fever.

Actual *Bago, Arg.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Dyspepsia; heartburn.

Actualene *Pfizer, Ital.*
Cabergoline (p. 899·3).
Lactation suppression; hyperprolactinaemia; prolactinoma.

Actum *Alicon, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Actyferil *Codifra, Fr.*
Vitamin B substances (p. 2102·3); iron (p. 2073·1); copper (p. 2057·1).
Iron supplement.

Actyfilus *Codifra, Fr.*
Lactobacillus lactis (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); Lactobacillus acidophilus NCFM (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); inulin (p. 2534·3).
Digestive disorders.

Actyl *Acdhon, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Actymine *Codifra, Fr.†*
Vitamins; minerals; borage oil (p. 2459·2); wheat-germ oil (p. 2647·1); lycopene (p. 2546·2).
Dry skin; sun-induced skin damage.

Actyn-Myosyn *Hoch Wertig, Arg.*
Glutamine (p. 2070·3).
Dietary supplement.

Actypral *Codifra, Fr.†*
Flavonoids (p. 2505·2); vitamins; minerals; lycopene (p. 2546·2).
Skin ageing.

Acuaderm *Bajer, Arg.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); aloe vera (p. 1693·2).
Pruritus.

Acuafil Ofteno *Sophia, Mex.; Elmor, Venez.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes; eye irritation.

Acuafil Ungena *Sophia, Mex.*
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2).
Dry eyes.

Acuaiss *Visiontec, Arg.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Acuatim *Otsuka, Indon.; Otsuka, Jpn.*
Nadifloxacin (p. 328·1).
Acne.

Acubiron *ProStrakan, Spain.†*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Acucal *Sun, India.*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).

Acucil *Apotex, S.Afr.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Acuco *Apotex, S.Afr.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Acudex *Teva, Pol.†*
Dextranomer (p. 1699·3).
Ulcers; wounds.

Acudor *Ferring, Port.†*
Etodolac (p. 57·1).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Acudrin *Sun, India.*
⊗Paracetamol (p. 115·1); dichloralphenazone (p. 1071·3); isometheptene mucate (p. 2535·1).

Acudrox *Macleods, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Acudryl *Acuition, India.*
Ammonium chloride (p. 1656·1); menthol (p. 2553·2); diphenhydramine (p. 626·1); sodium citrate (p. 1781·2).

ACU-dyne *Acme, USA.*
Povidone-iodine (p. 1767·1).
Skin disinfection; vaginal disorders.

Acu-Erylate S *Apotex, S.Afr.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Acufer *Acuition, India.*
Vitamin B substances (p. 2102·3); calcium gluconate (p. 1783·3); ferric ammonium citrate (p. 2060·1); zinc sulfate (p. 2126·2); protein.

Acuflam *Unison, Philipp.*
Diclofenac potassium (p. 48·3).
Musculoskeletal and joint disorders; pain; fever; gout; actinic keratoses.

Acuflex *Acupharm, S.Afr.†*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Acuflu *Acuition, India.*
Oral syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).
Acuition, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Acuflu P *Aspen, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Acuflu Plus *Acuition, India.*
Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2); sodium citrate (p. 1781·2).

Acugel *Acupharm, S.Afr.†*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Acugesic *CCM, Malaysia; Duopharma, Singapore.*
Tramadol hydrochloride (p. 139·2).
Pain.

Acugest *Acupharm, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Acugest Co *Acupharm, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Acugest DM *Apotex, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Acugest Expect *Acupharm, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Acugrain *CCM, Malaysia.*
Pizotifen maleate.
Vascular headache including migraine; cluster headache.

Acuilfem *Gezzi, Arg.*
Ibuprofen (p. 68·2).
Pain.

Acuilix *Pfizer, Fr.*
⊗Hydrochlorothiazide (p. 1403·2); quinapril hydrochloride (p. 1480·2).
Hypertension.

Acuitel *Pfizer, Fr.; Pfizer, Turk.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Acular *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, China; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, Hong Kong; Allergan, India; Allergan, Irl.; Allergan, Ital.; Allergan, Malaysia; Allergan, Neth.; Allergan, NZ; Allergan, Philipp.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Gervasi, Spain; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.*
Ketorolac trometamol (p. 80·2).
Cystoid macular oedema; allergic eye disorders; inflammation, pain, and photophobia following eye surgery.

Aculare *Allergan, Belg.*
Ketorolac trometamol (p. 80·2).
Eye inflammation following cataract surgery; allergic conjunctivitis.

Acularen *Allergan, Mex.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; postoperative ocular inflammation.

Aculax *Watson, S.Afr.*
Lactulose (p. 1850·3).

Aculoid *Pharmascript, S.Afr.*
Cyclizine hydrochloride (p. 623·2).
Nausea; vomiting; vestibular disorders; motion sickness.

Acumel *Baxter, Ital.*
Lipids (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); amino acids; glucose (p. 2068·3).
Contains egg lecithin.
Parenteral nutrition.

Acumerck *Generics, Hung.†*
Quinapril hydrochloride (p. 1480·2).
Heart failure; hypertension.

Acumet *Acupharm, S.Afr.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Acunaso *Watson, S.Afr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Acuode *Lafi, Chile.*
Colecalciferol (p. 2113·1).
Hypoparathyroidism; osteomalacia; rickets; hypocalcaemic tetany; vitamin D deficiency.

Acuolens *Alcon Cusi, Spain.*
Hypromellose (p. 2189·2).
Dry eyes.

Acu-Oxytet *Apotex, S.Afr.†*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Acupan *Meda, Belg.; Biocodex, Fr.; Meda, Irl.; iNova, NZ; 3M, UK; Biocodex, Ukr.*
Nefopam hydrochloride (p. 100·2).
Pain.

Acuphlem *Acupharm, S.Afr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess mucus.

Acupil *Pfizer, India.*
Quinapril hydrochloride (p. 1480·2).

Acupil-H *Pfizer, India.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).

Acupillin *Apotex, S.Afr.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Acuprel *Parke, Davis, Spain.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Acupril *Pfizer, Mex.; Pfizer, Neth.; Pfizer, Port.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Acura *Nordic, Swed.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Acurate *Pharmascript, S.Afr.*
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain with tension.

Acurenal *ICN, Pol.*
Quinapril (p. 1480·2).
Hypertension; heart failure.

Valeant, Ukr.†
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Acuretic *Pfizer, Port.; Binesa, Spain.†*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acurmil *Lisapharma, Ital.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Acus *Roemmers, Chile.*
Meropenem (p. 321·3).
Bacterial infections.

Acuspar *Themis, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Acusprain *Apotex, S.Afr.†*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Acustat *Transpen, UK.*
Skin patch.
Musculoskeletal, joint, and soft-tissue injury.

Acustop *Apotex, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Acustop Cataplasma *Sang-A, Malaysia; Sang-A, Singapore.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Acutears *Poen Vision, Mex.*
Carmellose sodium (p. 2175·2).
Dry eyes.

AcuTect *Diatide, USA.*
Technetium-99m apcitide (p. 2228·1).
Scintigraphic imaging of acute venous thrombosis.

Acuten *Farma, Venez.*
Paracetamol (p. 115·1); codeine (p. 40·2).
Fever; pain.

Acutil *Angelini, Ital.*
Vitamins.

Acutil Fosforo *Angelini, Ital.*
Aceglutamide (p. 2426·2) or glutamine (p. 2070·3); L-asparagine (p. 2050·3); DL-phosphoserine (p. 2589·1); pyridoxine (p. 2105·3) or pyridoxine hydrochloride (p. 2105·3).
Tonic.

Acutral *Grunenthal, Pol.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Acutret *Ipca, India.*
Isotretinoin (p. 1706·2).
Acne.

Acutrex *Medica Korea, Philipp.*
Isotretinoin (p. 1706·2).
Acne.

Acutussive *Pharmascript, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Acuvail *Allergan, Canad.; Allergan, USA.*
Ketorolac trometamol (p. 80·2).
Inflammation and pain following cataract surgery.

Acuver *Cyathus, Fin.; Cyathus, Hung.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders; Ménière's disease; vertigo.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Acuvin *Piramal, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Acuzide *Pfizer, Neth.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Acuzole *Pharmascript, S.Afr.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Acuzyrt *Watson, S.Afr.*
Cetirizine hydrochloride (p. 619·2).

ACV *Geo, India; Greater Pharma, Thai.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Acvirall *Finecure, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acviscin *Actavis, Pol.*
Vancomycin (p. 384·2).
Bacterial infections.

Acvit *Unimarck, India.*
Injection: Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.
Unimarck, India.
Tablets: Vitamin B substances (p. 2102·3).

ACWY Vax *GSK, UK.*
A meningococcal vaccine (groups A, C, W_{135}, and Y) (p. 2401·3).
Active immunisation.

Acxion *IFA, Mex.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

ACY *Farmigea, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acyclostad *Stada, Cz.; Stada, Fin.; Stada, Hung.; Stada, Neth.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acyclo-V *Alphapharm, Austral.; CTS, Israel.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acyclovenir *Bioavenir, Israel.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acydex *Temapharm, Cz.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Acydona *Arafarma, Spain.*
Povidone-iodine (p. 1767·1).
Disinfection of burns, skin, and wounds.

Acyflox *Arafarma, Spain.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Acyhex *Hexal, Philipp.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acyl *Biofarma, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acylcoffin *Zentiva, Cz.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Acylete *Kireen, Malaysia.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Acylpyrin *Herbacos, Cz.*
Aspirin (p. 22·2).
Fever; pain.

Acylpyrin + C *Herbacos, Cz.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Acyprin *Collins, Mex.†*
Allopurinol (p. 600·2).
Hyperuricaemia.

Acyprost *Merck Medication Familiale, Fr.*
Betasitosterols (p. 1471·2); pomegranate fruit (p. 164·1); cranberry (p. 2488·1); cucurbita oil (p. 2489·2); tomato.
Dietary supplement for prostatic health.

Acyrax *Orion, Fin.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Acyvir *Glaxo Allen, Ital.†; Pharmasant, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aczebri *Shin Poong, Philipp.†*
Cefaclor (p. 232·3).
Bacterial infections.

Aczee *Zee, Thai.*
Benzoyl peroxide (p. 1696·1).
Acne.

Aczone *Valeant, Canad.; Allergan, USA.*
Dapsone (p. 281·2).
Acne.

Ad *Hetero, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Ad_3 *Baif, Ital.*
Olive oil (p. 2575·1); carrot extract; octacosanol (p. 1472·1); vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); *dl*-alpha tocoferil acetate (p. 2119·2).
Dietary supplement.

Ad Baby *Zimalaya, India.*
Ashwagandha (p. 2450·2).

AD Mycin *ADP, Philipp.; Boryung, Thai.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

AD Pabyrn *LPB, Ital.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1).
Vitamin A and D deficiency.

A-D Plex *Kolbe, Indon.*
Vitamin A (p. 2098·3); vitamin B substances (p. 2102·3); vitamin D (p. 2112·3).
Nutritional supplement.

AD Shock *Mertens, Arg.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Rickets; hypocalcaemia; hypoparathyroidism; osteoarthritis; osteomalacia; renal osteodystrophy; tetanus.

A+D Zinc Oxide Cream *Schering-Plough, USA.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Nappy rash.

ADA *Estedi, Spain.†*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinus congestion.

Adacai
Note: this name may be used for preparations of different composition.
MSD, Port.
Ezetimibe (p. 1379·2).
Hypercholesterolaemia.
Schering-Plough, Chile; Schering-Plough, Venez.
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia.

Adacel *Sanofi Pasteur, Arg.; Sanofi Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Israel; Sanofi Pasteur, Malaysia; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Thai.; Aventis Pasteur, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Adacel Polio *Sanofi Pasteur, Austral.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Israel.; Sanofi-Aventis, NZ; Sanofi Pasteur, Thai.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Adacel-Polio *Sanofi Pasteur, Canad.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Adacin *Ajanta, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Adacne *Glenmark, Braz.*
Adapalene (p. 1692·1).
Acne.

Adacne Clin *Glenmark, Braz.*
Adapalene (p. 1692·1); clindamycin phosphate (p. 269·3).
Acne.

Adaderm *Vargas, Venez.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).
Skin disorders.

Adafen *Biofarma, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Adaferin *Galderma, Gr.; Galderma, India; Galderma, Israel; Galderma, Mex.*
Adapalene (p. 1692·1).
Acne.

Adage Plus *Mystico, India.*
Vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Adagen *Enzon, USA.*
Pegademase bovine (p. 2584·3).
Adenosine deaminase deficiency.

Adalat *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.†; Bayer, Denm.; Bayer, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer, India; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer, Jpn; Bayer, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.†; Centrofarma, Port.; Bayer, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, Ukr.; Bayer, USA; Schering, USA; Bayer, Venez.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome; coronary spasm.

Adalat XL Plus *Bayer, Canad.*
Rose tablets, nifedipine (p. 1447·2); blue tablets, aspirin (p. 22·2).
Angina pectoris; cardiovascular risk reduction.

Adalate *Bayer, Fr.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

Adalgur
Note: this name may be used for preparations of different composition.
Teofarma, Spain.
Paracetamol (p. 115·1); thiocolchicoside (p. 2026·2).
Pain; skeletal muscle spasm.

Adalgur N *Angelini, Port.*
Paracetamol (p. 115·1); thiocolchicoside (p. 2026·2).
Musculoskeletal and joint pain.

Adalken *Kendrick, Mex.*
Penicillamine (p. 1567·1).
Wilson's disease; heavy metal poisoning; cystinuria.

Adamed *Labomed, Chile.*
Adapalene (p. 1692·1).
Acne.

Adamin-G *Nutricia, Cz.; Scientific Hospital Supplies, Irl.†*
Glutamine (p. 2070·3).
Nutritional supplement.

Adamon
Note: this name may be used for preparations of different composition.
Medo, Austria; Meda, Hung.; Zydus, India; Meda, Ital.; Meda, Pol.
Tramadol hydrochloride (p. 139·2).
Pain.

Adams Delite *Ind-Swift, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Adana *Sandoz, Arg.*
Irbesartan (p. 1411·1).
Hypertension.

Adana Plus *Sandoz, Arg.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Adancor *Merck Serono, Fr.*
Nicorandil (p. 1446·2).
Angina pectoris.

Adant *Daiichi Sankyo, Fr.; Meiji, Indon.; Tedec Meiji, Israel†; Meiji, Malaysia; Meiji, Thai.; Er-Kim, Turk.*
Sodium hyaluronate (p. 2526·2).
Joint disorders; osteoarthritis of the knee; shoulder pain.

Adapel *Medley, Braz.*
Adapalene (p. 1692·1).
Acne.

Adapen *Intas, India.*
Adapalene (p. 1692·1).
Acne.

Adapettes *Alcon, Mex.*
Disodium edetate (p. 1550·3); sorbic acid (p. 1770·2).
Wetting solution for contact lenses.
Alcon, USA.
Range of solutions for contact lenses.

Adaphen *Aspen, S.Afr.†*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Adaple *Wallace, India.*
Adapalene (p. 1692·1).
Acne.

Adapne *Cinetic, Arg.*
Adapalene (p. 1692·1).
Acne.

Adapta *Hero, Switz.†*
Preparation for enteral nutrition.

AdaptaCide PAA-C *Johnson & Johnson, Ger.*
Peracetic acid (p. 1763·1); hydrogen peroxide (p. 1755·2); acetic acid (p. 2426·3).
Instrument disinfection.

Adaptic *Systagenix, Ital.*
White soft paraffin (p. 2211·3).
Burns; wounds.

Adaptol *Olainfarm, Rus.; Olainfarm, Ukr.*
Mebikar.
Anxiety; cardialgia; smoking withdrawal; neuroses; adjunct to antipsychotics and tranquillisers.

Adaptoplast *Vican, Gr.*
Salicylic acid (p. 1719·1).
Calluses.

Adaret *Cosme, India.*
Adapalene (p. 1692·1).
Acne.

Adartrel *GSK, Cz.; GSK, Denm.; GSK, Fin.†; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Irl.†; GSK, Ital.†; GSK, Neth.; GSK, Norw.; GSK, Pol.; Beecham, Port.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Ropinirole hydrochloride (p. 913·2).
Restless legs syndrome.

Adasept *Odan, Canad.*
Cleanser: Triclosan (p. 1773·2).
Skin cleanser.
Odan, Canad.
Topical gel: Triclosan (p. 1773·2); salicylic acid (p. 1719·1); sodium thiosulfate (p. 1576·1).
Acne.

Adasept BP *Odan, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Adaspor *IMS, Ital.†*
Adazone; peracetic acid (p. 1763·1).
Instrument disinfection.

Adasuve *Alexza, USA.*
Loxapine (p. 1082·2).
Acute agitation associated with bipolar disorder or schizophrenia.

Adavin *Sandoz, Pol.*
Nicergoline (p. 2569·1).
Vascular disorders; pulmonary hypertension; migraine and vascular headache.

Adavite *Hudson, USA.*
Vitamins.

Adax *Saval, Chile.*
Alprazolam (p. 1035·2).
Anxiety; panic attacks; mixed anxiety depressive states.

Adaxil *Nycomed, Arg.*
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Adaxil Forte *Nycomed, Arg.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate (p. 2515·3).
Joint disorders.

Adaxil Plus *Nycomed, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Adazol *Makers, Philipp.*
Albendazole (p. 149·1).
Cysticercosis; echinococcosis.

Adbeta *Zuventus, India.*
⊗Esatenolol (p. 1377·2).
Hypertension; angina pectoris; migraine.

Adbeta-H *Zuventus, India.*
⊗Esatenolol (p. 1377·2); hydrochlorothiazide (p. 1403·2).

A-D-C
Note: this name may be used for preparations of different composition.
Mertens, Arg.
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin C (p. 2110·3).
Vitamin A, D, and C supplement.

ADC
Note: this name may be used for preparations of different composition.
Rass, India.
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

ADC Fluor *Mertens, Arg.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin C (p. 2110·3); sodium fluoride (p. 2089·2).
Vitamin and fluoride deficiency.

Ad-C Plus *Gruppo Medica, Philipp.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Vitamin C deficiency; dietary supplement.

Adcal
Note: this name may be used for preparations of different composition.
Admac, India.
Oral syrup: Calcium (p. 1783·1); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).
Admac, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1).
ProStrakan, UK.
Calcium carbonate (p. 1824·3).
Calcium supplement; hyperphosphataemia; osteoporosis.

Adcal-D_3 *ProStrakan, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Adcapone *Sun, India.*
Entacapone (p. 901·2).
Parkinsonism.

Adcef *Torrent, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Adcetris *Takeda, Belg.; Takeda, Switz.; Takeda, UK; Seattle Genetics, USA.*
Brentuximab vedotin (p. 754·1).
Hodgkin's lymphoma; anaplastic large cell lymphoma.

Adcip *Admac, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Adcip-TZ *Admac, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Adcirca *Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Cz.; Lilly, Denm.; Lilly, Fr; Lilly, Ger.; Lilly, Neth.; Lilly, Norw.; Lilly, Port.; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, USA.*
Tadalafil (p. 2368·1).
Pulmonary hypertension.

Adclav *Admac, India.*
Amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Adco Emtevir *Adcock Ingram, S.Afr.*
Tenofovir disoproxil fumarate (p. 1018·1); emtricitabine (p. 976·3).

Adco-Alcophyllin *Adcock Ingram, S.Afr.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Adco-Allergin Expectorant *Adcock Ingram, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Adco-Alzam *Adcock Ingram, S.Afr.*
Alprazolam (p. 1035·2).
Formerly known as Alzam.
Anxiety; panic disorder.

Adco-Amoclav *Adcock Ingram, S.Afr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Adco-Bencole *Adcock Ingram, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Adco-Biohist *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1); calamine (p. 1697·2); phenol (p. 1763·3).
Skin disorders.

Adco-Biskapect *Adcock Ingram, S.Afr.†*
Light kaolin (p. 1850·1); apple pectin (p. 2200·3); bismuth subcarbonate (p. 1822·1).
Diarrhoea.

Adco-Bisocor *Adcock Ingram, S.Afr.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Adco-Captomax *Adcock Ingram, S.Afr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Adco-Ciprin *Adcock Ingram, S.Afr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Adco-Clofelam *Adcock Ingram, S.Afr.*
Diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Adco-Cocillana Co *Adcock Ingram, S.Afr.*
Cocillana (p. 1659·2); squill (p. 1677·3); menthol (p. 2553·2).
Cough.

Adco-Combineb *Adcock Ingram Critical Care, S.Afr.*
⊗Ipratropium bromide (p. 1211·3); salbutamol (p. 1220·2).
Obstructive airways disease.

Adco-Contromet *Adcock Ingram, S.Afr.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Adco-Dapamax *Adcock Ingram, S.Afr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Adco-Dermed *Adcock Ingram, S.Afr.*
Ketoconazole (p. 585·3).
Pityriasis versicolor; pityriasis capitis; seborrhoeic dermatitis.

Adco-Dol *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); doxylamine succinate (p. 627·3).
Pain.

Adco-Fem *Adcock Ingram, S.Afr.*
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgen dependent acne, alopecia androgenetica, and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Adco-Flupain *Adcock Ingram, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Adco-Glucomed *Adcock Ingram, S.Afr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Adco-Indogel *Adcock Ingram, S.Afr.*
Indometacin (p. 71·2).
Musculoskeletal and joint pain.

Adco-Kiddipayne *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Fever; pain.

Adcold-BR *Adley, India.*
⊗Ammonium chloride (p. 1656·1); bromhexine (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Adcold-G *Adley, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); guaifenesin (p. 1666·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Adcold-SBG *Adley, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Adcold-T *Adley, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Adco-Linctopent *Adcock Ingram, S.Afr.*
⊗Bromhexine hydrochloride (p. 1656·3); orciprenaline sulfate (p. 1217·3).
Cough associated with bronchospasm and excess mucus.

Adco-Liquilax *Adcock Ingram, S.Afr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Adco-Loten *Adcock Ingram, S.Afr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Adcomag Trisil *Adco, S.Afr.†*
Magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity; flatulence.

Adco-Mayogel *Adcock Ingram, S.Afr.*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Dyspepsia; gastric hyperacidity; peptic ulcer.

Adco-Medigel *Adcock Ingram, S.Afr.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3); simeticone (p. 1886·2).
Gastrointestinal disorders.

Adco-Metaxol *Adcock Ingram, S.Afr.*
Theophylline (p. 1229·3); codeine phosphate (p. 40·2); mepyramine maleate (p. 635·1).
Cough.

Adco-Metrostat *Adcock Ingram, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Adco-Mirteron *Adcock Ingram, S.Afr.*
Mirtazapine (p. 436·1).
Depression.

Adco-Muco Expect *Adcock Ingram Generics, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Adcon *Admac, India.*
Fluconazole (p. 578·2).
Fungal infections.

Adco-Nasdro *Adcock Ingram, S.Afr.†*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline nitrate (p. 1669·3).
Nasal congestion.

Adco-Neofed *Adcock Ingram, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Adco-Neutragel D *Adcock Ingram, S.Afr.*
Aluminium hydroxide (p. 1817·2); dicycloverine hydrochloride (p. 1834·2); light magnesium oxide (p. 1857·3).

Adco-Otised *Adcock Ingram, S.Afr.*
Phenazone (p. 124·1); benzocaine (p. 1980·2).
Ear infections.

Adco-Otophen *Adcock Ingram, S.Afr.*
Phenazone (p. 124·1).
Otitis; earache.

Adco-Oxypan *Adcock Ingram, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Adco-Payne *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain with tension.

Adco-Phenobarbitone Vitalet *Adcock Ingram, S. Afr.*
Phenobarbital (p. 535·2); vitamin B substances (p. 2102·3).
Insomnia; sedative; epilepsy.

Adco-Quinaretic *Adcock Ingram, S.Afr.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Adco-Retic *Adcock Ingram, S.Afr.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Adcorone *Adcock Ingram, S.Afr.*
Amiodarone (p. 1300·1).

Adco-Roxy *Adcock Ingram, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Adco-Roznal *Adcock Ingram, S.Afr.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; dyspepsia.

Adcort *Amideep, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).
Infected eye disorders.

Adcortyl *BMS, Irl.; BMS, UK.*
⊗Triamcinolone acetonide (p. 1649·1).
Musculoskeletal, joint, and peri-articular disorders; skin disorders.

Adcortyl in Orabase *BMS, Irl.†; BMS, UK.†*
⊗Triamcinolone acetonide (p. 1649·1).
Inflammatory disorders of the mouth.

Adco-Salterpyn *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Adco-Sinal Co *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); phenyltoloxamine citrate (p. 638·1); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Adco-Sinal NS *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Formerly contained paracetamol, caffeine, and phenylephrine hydrochloride.
Cold and influenza symptoms.

Adco-Sociale *Adcock Ingram, S.Afr.*
Phosphatidyl choline (p. 2588·3).

Adco-Sodasol *Adcock Ingram, S.Afr.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1); anhydrous citric acid (p. 2480·3); tartaric acid (p. 2626·1).
Gastric hyperacidity; urinary alkalinisation; adjunct to sulfonamide therapy.

Adco-Sporozole *Adcock Ingram, S.Afr.*
Itraconazole (p. 583·3).
Fungal infections.

Adco-Sufedrin *Adcock Ingram, S.Afr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Adco-Symptofed *Adcock Ingram, S.Afr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Adco-Synaleve *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); mepробamate (p. 1083·3).
Pain and associated tension.

Adco-Talomil *Adcock Ingram, S.Afr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Adco-Tussend *Adcock Ingram, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Adco-Vascard *Adcock Ingram, S.Afr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Adco-Wormex *Adcock Ingram, S.Afr.*
Mebendazole (p. 158·3).
Worm infections.

Adco-Zertra *Adcock Ingram, S.Afr.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Adco-Zetofen *Adcock Ingram, S.Afr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; allergic skin disorders.

Adco-Zetomax *Adcock Ingram, S.Afr.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Adco-Zetomax Co *Adcock Ingram, S.Afr.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Adco-Zildem *Adcock Ingram, S.Afr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Adco-Zopimed *Adcock Ingram, S.Afr.*
Zopiclone (p. 1118·1).
Insomnia.

Add App *Cadila, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and vascular headache.

Add Tears *Ciplo, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Addamel *Fresenius Kabi, Rus.; Fresenius Kabi, Spain.*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

Addamel N *SSPC, China; Fresenius Kabi, Cz.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong.; Fresenius Kabi, Hung.; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

Addel N *Baxter, Ger.*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

Addera D3 *Farmasa, Braz.*
Colecalciferol (p. 2113·1).
Vitamin D supplement; osteoporosis; rickets.

Addera Plus *Nestle, Denm.*
Preparation for enteral nutrition.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Adderall *Shire, Canad.; Shire, USA.*
⊗Dexamfetamine sulfate (p. 2319·1); dexamfetamine saccharate (p. 2319·1); amfetamine sulfate (p. 2316·2); amfetamine aspartate (p. 2316·1).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Addex
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.
Electrolytes (p. 1775·1).

Korea United, Philipp.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Addex-THAM *Fresenius Kabi, Swed.*
⊗Trometamol (p. 2635·1).
Acute metabolic acidosis; acute respiratory acidosis.

Addiflu *Sanofi Pasteur, Irl.†*
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Addigrip *Aventis Pasteur, Austria†; Sanofi Pasteur, Ger.†; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Port.†*
An influenza vaccine (p. 2393·3).
Active immunisation.

Addi-K *Leo, Thai.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Add-Ins *Nutricia, Cz.; SHS, Irl.; SHS, UK.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Addiphos *Fresenius Kabi, Denm.; Fresenius Kabi, Irl.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, UK.*
Electrolytes (p. 1775·1).
Phosphate supplement in parenteral nutrition.

Additiva
Note: this name may be used for preparations of different composition.
Scheffler, Cz.
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Scheffler, Ger.†
Simeticone (p. 1886·2).
Flatulence; aid in gastrointestinal investigation.

Additiva Calcium *Natur Produkt, Pol.†*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis.

Additiva Ferrum *Natur Produkt, Pol.†*
Ferrous gluconate (p. 2061·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Additiva Magnesium *Natur Produkt, Pol.†*
Magnesium carbonate (p. 1856·2).
Magnesium deficiency.

Additiva Multiwitamina *Natur Produkt, Pol.†*
Vitamins; minerals.

Additrace *Fresenius Kabi, Irl.; Fresenius Kabi, S.Afr.; Fresenius Kabi, UK.*
Trace elements.
Parenteral nutrition.

Addivit *Medice, Ger.†*
Vitamins.

Addivita *Scheffler, Ital.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Addlife *Pascual, Philipp.*
Ubidecarenone (p. 2637·1).
Dietary supplement.

Addnok *Rusan, India.*
⊗Buprenorphine (p. 30·2).
Pain.

Addofix *Epifarma, Ital.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Addos *Aspen, Austral.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Ad-DT *Hetero, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Addtrim *Medicine Products, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Addwize *Sun, India.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Narcolepsy; hyperactivity disorders in children.

Addyzoa *Charak, India.*
⊗Shatavari (p. 2614·2); tinospora cordifolia; tribulus terrestris (p. 2633·3); ashwagandha (p. 2450·2).
Erectile dysfunction.

ADE 2 (Adedois) *Prodotti, Braz.†*
Vitamin A acetate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

Adebion *Berlico Mulia, Indon.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin D (p. 2112·3); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Adebit *Zentiva, Hung.*
Buformin hydrochloride (p. 469·2).
Diabetes mellitus.

Adec *Savoy, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Adecal
Note: this name may be used for preparations of different composition.
Bio-Kem, Turk.†
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); calcium gluconate (p. 1783·3); calcium phosphate (p. 1784·2).

Teuto, Braz.†
Vitamin A acetate (p. 2098·3); colecalciferol (p. 2113·1).

Adecaps *Gelcaps, Mex.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Pharmaselect, Austria.†
Cod-liver oil (p. 2056·3).
Vitamin A and D deficiency.

Adecco *Pharos, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Adecon *Swiss Biotech, India.*
Fluconazole (p. 578·2).
Fungal infections.

Adeconce *Lafedar, Arg.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Dietary supplement.

Adecur *Asofarma, Mex.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Tecnofarma, Chile; Nolver, Venez.
Terazosin (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Adecut *Takeda, Jpn.*
Delapril hydrochloride (p. 1350·2).
Hypertension.

Adederme *EMS, Braz.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); zinc oxide (p. 1729·1).
Skin disorders.

Adee *Admac, India.*
Injection: Vitamin B substances (p. 2102·3).

Admac, India.
Tablets: Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Adefin *Alphapharm, Austral.; Mylan, NZ.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Adeflox-O *Swiss Biotech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Adeforte *Gross, Braz.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); tocoferil acetate (p. 2119·2).
Vitamin supplement.

Adehl *Kayaku, Jpn.*
Colforsin daropate hydrochloride (p. 2483·2).
Heart failure.

Adekals *Offenbach, Mex.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

Adekin
Note: this name may be used for preparations of different composition.
Erfar, Gr.
Cyproheptadine hydrochloride (p. 624·1).

Adekon *Concordia, Mex.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

Adekon C *Concordia, Mex.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3).
Vitamin A, D, and C deficiency.

Adeks *Axcan, Canad.; Axcan, USA.†*
Vitamins; zinc (p. 2126·1).

Scandipharm, Arg.
Vitamins; minerals.

Adel
Note: this name may be used for preparations of different composition.
New Life, Arg.
Garcinia cambogia (p. 2510·2); pyridoxine (p. 2105·3); spirulina (p. 2622·1).
Dietary supplement.

Senosiain, Mex.
Clarithromycin (p. 266·2).
Bacterial infections.

Adelan *Alacan, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Adelcopen *Adelco, Gr.*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Adelcort *Adelco, Gr.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Adele *Stragen, Cz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Adeleks *Nevzat, Turk.*
Thiocolchicoside (p. 2026·2).

Ad-Element *Darrow, Braz.†*
Trace elements.
Parenteral nutrition.

Adelgacin *Higate, Arg.*
Fibre (p. 1823·3); glucomannan (p. 2515·2); kelp (p. 2612·1).
Dietary supplement.

Adelgazar *AM, Arg.*
Green tea (p. 2648·2); hyssop (p. 2530·3); fucus vesiculosus; centella (p. 1698·3); equisetum (p. 2500·1); fennel (p. 2503·2); cynara (p. 2490·3); peppermint (p. 1877·1); psyllium (p. 1849·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).
Dietary supplement; slimming aid.

Adelheid-Jodquelle, Tolzer *Jodquellen, Ger.*
Sodium iodide (p. 2337·1); potassium (p. 1793·1); sodium (p. 1795·1); ammonium; calcium (p. 1783·1); magnesium (p. 1786·3); iron (p. 2073·1); chloride; sodium bromide (p. 2461·1); bicarbonate (p. 1780·3).
Iodine-deficiency disorders.

Adell *Silesia, Chile.*
Orlistat (p. 2577·1).
Obesity.

Adelone *Cooper (Κοπερ), Gr.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Inflammatory eye disorders.

Adelphan *Novartis, Turk.†*
Reserpine (p. 1485·3); dihydralazine sulfate (p. 1358·3).
Hypertension.

Adelphane *Novartis, India.*
Reserpine (p. 1485·3); dihydralazine sulfate (p. 1358·3).
Hypertension.

Adelphane-Esidrex *Novartis, India; Sandoz, Rus.; Novartis, Ukr.*
⊗Reserpine (p. 1485·3); dihydralazine sulfate (p. 1358·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Adelphan-Esidrex *Novartis, Turk.†*
⊗Reserpine (p. 1485·3); dihydralazine sulfate (p. 1358·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Adelseril *Serral, Mex.*
⊗Sibutramine (p. 2330·2).
Obesity.

Adelvag *Novag, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Adelysin *Prafa, Indon.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin D (p. 2112·3); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Ademina *Etifar, Venez.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); zinc oxide (p. 1729·1); boric acid (p. 2459·3).
Skin irritation.

Adempas *Bayer, USA.*
Riociguat (p. 1487·2).
Pulmonary hypertension.

Adenamin *Farmamust, Gr.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; arrhythmias; myocardial infarction.

Adenar *Proula, Venez.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Vitamin deficiency; rickets.

Adenil *Lamsa, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Adenim *Swiss Biotech, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Adenim Plus *Swiss Biotech, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Adenim-MR *Swiss Biotech, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Adenocard *Libbs, Braz.; Astellas, Canad.; Fujisawa, USA.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Adenocor *Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Torrent, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.†; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Thai.; Sanofi Synthelabo, UK.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias; acute intermittent porphyria.

Adenocynesine *Boiron, Fr.†*
Chelidonium (p. 2522·2); cinchona (p. 2478·3); conium maculatum (p. 2524·3); crataegus oxyacantha (p. 2488·1); hydrastis (p. 2528·1).
Homoeopathic preparation.

Adenofer *Fourrts, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc ascorbate (p. 2110·3).

Adenoject *Sun, India.*
Adenosine (p. 1291·1).
Coronary vasodilator in diagnostic procedures; paroxysmal supraventricular tachycardia.

Adenolin-Entoxin NN *Meckel, Ger.*
Clematis recta; phytolacca americana (p. 2593·2); scrophularia nodosa.
Homoeopathic preparation.

Adenomin *Ordain, India.*
Cobamamide (p. 2107·2).
Vitamin B_{12} supplement.

Adenoplex *EG, Ital.*
Cocarboxylase (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis.

Adenorm *KVZ, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Adenosan *Iasis, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Adenoscan *Sanofi-Aventis, Austral.; Fujisawa, Canad.†; Sanofi-Aventis, Fin.†; Sanofi-Aventis, Ger.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Ital.; Daiichi Sankyo, Jpn; Sanofi-Aventis, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi Synthelabo, UK; Fujisawa, USA.*
Adenosine (p. 1291·1).
Coronary vasodilator during radionuclide myocardial perfusion imaging.

Adénoscan *Sanofi-Aventis, Fr.*
Adenosine (p. 1291·1).
Coronary vasodilator during radionuclide myocardial perfusion imaging.

Adenosterid *Zdorovje, Ukr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Adenuric *Menarini, Belg.; Menarini, Cz.; Menarini, Fr.; Berlin-Chemie, Ger.; Menarini, Gr.; Ipsen, Irl.; Menarini, Ital.; Menarini, Neth.; Menarini, Port.; Menarini, Spain; Menarini, UK.*
Febuxostat (p. 607·1).
Hyperuricaemia.

Adényl *H2 Pharma, Fr.*
Adenosine phosphate (p. 2430·2).
Haemorrhoids; venous insufficiency.

Adep *XL, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Depression; premenstrual dysphoric disorder; anxiety; obsessive-compulsive disorder; post-traumatic stress disorder; panic disorder; social phobia; bulimia nervosa.

Adepal *Codepharma, Fr.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Adepend *Orpha-Devel, Cz.; Orpha-Devel, Denm.; Desitin, Ger.; AOP Orphan, UK.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol withdrawal syndrome; opioid dependence; cholestatic pruritus.

Adepiron *Abbott, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Adepos *Optaderm, Philipp.*
Adenosine triphosphate (p. 2430·3).
Cataract.

Adeprenal *Adelco, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Adepress *Veropharm, Rus.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

A-Depress-Therapy *AG Therapy, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Adepril
Note: this name may be used for preparations of different composition.
Teofarma, Ital.
Amitriptyline hydrochloride (p. 401·1).
Depression.

Adepsique *Psicoforma, Mex.*
Amitriptyline hydrochloride (p. 401·1); diazepam (p. 1063·2); perphenazine (p. 1095·3).
Mixed anxiety depressive states; insomnia.

Adepssir *Ferrer, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Adept *Baxter, Arg.; Shire, UK.*
Icodextrin (p. 2059·2).
Prevention of surgical adhesions.

Aderan *Roemmers, Arg.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

A-Derma Lait Solaire *Ducray, Fr.†*
SPF 25: Avena (p. 2451·1); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Adermicina *Sanofi-Aventis, Arg.*
Neomycin sulfate (p. 330·1); vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); zinc oxide (p. 1729·1); benzocaine (p. 1980·2).
Infected skin disorders.

Adermicina A *Sanofi-Aventis, Arg.*
Vitamin A (p. 2098·3); zinc oxide (p. 1729·1); benzocaine (p. 1980·2).
Skin disorders; wounds; burns.

Adermicina A Mama *Sanofi-Aventis, Arg.*
Vitamin A palmitate (p. 2098·3).
Stretch marks; sore nipples; barrier preparation.

Adermicina A Post Solar *Sanofi-Aventis, Arg.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); allantoin (p. 1693·1).
Sun-induced skin damage.

Adermicina A Solar *Sanofi-Aventis, Arg.*
A range of sunscreen preparations.

Adermina *Koni-Cofarm, Chile.*
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Aderogil D3 *Sanofi-Aventis, Braz.*
Colecalciferol (p. 2113·1); vitamin A acetate (p. 2098·3).
Vitamin deficiencies.

Aderogyl *Millet-Franklin, Arg.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); acetomenaphthone (p. 2122·1).
Vitamin A, D, and K supplement.

Aderosol *Medical, Arg.*
Ergocalciferol (p. 2113·3).
Vitamin D_2 supplement.

Aderplus spezial Dr Hagedorn *Naturarzneimittel, Ger.†*
Secale cornutum (p. 2137·1); arnica montana (p. 2447·2); crocus sativus (p. 2208·2).
Homoeopathic preparation.

Aderta *Shinto, India.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Adesera *Cipla, India.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Adesial *Vitarum, Arg.†*
Ranitidine (p. 1882·1).

Adesitrin *Pfizer, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Adesna *Mintlab, Chile.*
Mefenamic acid (p. 85·3).
Pain.

Adesul *Dr Kumars, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Adetphos *Kowa, Jpn.*
Adenosine triphosphate, disodium salt (p. 2430·3).
Heart failure; gastritis; vertigo.

Adevitan G *Kener, Mex.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Adex *Dexcel, Israel.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Adexim *Admac, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Adexolin *GSK, India.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).

Adexone *Rekah, Israel.†*
⊗Dexamethasone (p. 1630·3); salicylic acid (p. 1719·1).
Skin disorders.

Adexor *Egis, Cz.†; Egis, Hung.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders.

Adezan *Adelco, Gr.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Adezio *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Adfe *Adroit, India.*
Ferrous fumarate (p. 2060·3) or ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Adfe-C *Adroit, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Adfen
Note: this name may be used for preparations of different composition.
Meditab, Thai.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.
Adcock Ingram Self Medication, S.Afr.†
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; inflammation.

Adfer *Fahrenheit, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Adflox *Adley, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Adfovir *Sun, India.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Adgat *Admac, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Adgel *Adley, India.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; osteoarthritis.

Adgel-O *Adley, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Adgelon *Endo, Rus.*
Bovine glycoprotein.
Osteoarthritis.

Adgem *Medihealth, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Adheb *Ranbaxy, India.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Adhesol *Biol, Arg.*
Colophony (p. 2484·2); turpentine oil (p. 2636·3).

Adiamil *Mediderm, Chile.*
Adapalene (p. 1692·1).
Acne.

Adiantine *Potter's, UK.*
Hamamelis (p. 2523·3); rosemary oil (p. 2607·3); bay oil (p. 2453·1).
Scalp disorders.

Adiaril *ABC, Fr.*
Glucose (p. 2068·3); sucrose (p. 2096·3); potassium gluconate (p. 1793·2); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Adiatin *Novag, Mex.*
Famotidine (p. 1842·1).
Peptic ulcer.

Adiazine *Bouchara-Recordati, Fr.; IFET (ΙΦΕΤ), Gr.†*
Sulfadiazine (p. 361·3).
Toxoplasmosis; nocardiosis; bacterial infections.

Adibal *Diba, Mex.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

Adical *Themis, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).

Adicanil *Pharmathen, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Adiclair *Ardeypharm, Ger.*
Nystatin (p. 590·3).
Fungal infections.

Adicure *Savoy, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Adiecal *Francia, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Adifax-P *Scoshia, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Adifax-SP *Scoshia, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Adifen
Note: this name may be used for preparations of different composition.
Medicamerc, Gr.
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.
Pharmaniaga, Malaysia.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Adifer-Z *Stalwart, India.*
Syrup: Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3).
Stalwart, India.
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Adiff *Ipca, India.*
Adapalene (p. 1692·1).
Acne.

Adiflam *Leben, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Adiflam Compound *Leben, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Adiflam Plus *Leben, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Adiflox *Intas, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

Adilin *Lincoln, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

Adilox *David, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Adimet *Ratiopharm, Cz.; Ratiopharm, Hung.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Adimod *Armstrong, Mex.*
Pidotimod (p. 2590·2).
Immunostimulant.

Adin *Ferring, Israel.†*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis.

Adine *Laboratorios Chile, Chile.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Adinir *Vensat, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Adinol *Teva, Israel.†*
Zinc oxide (p. 1729·1); Burrow's solution; wool alcohols (p. 2219·2); silicon dioxide (p. 2208·3).
Barrier preparation; eczema; nappy rash; skin irritation.

Adinsulin-S *SJA, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Adiod *Teofarma, Spain.*
Colecalciferol (p. 2113·1); vitamin A (p. 2098·3); iodine (p. 2336·3).
Deficiency of vitamins A and D.

Adios *Diomed, UK.*
Bladderwrack (*Fucus* spp.) (p. 2612·1); boldo (p. 2458·3); butternut (p. 2463·2); taraxacum (p. 2625·3).
Obesity.

Adios Max *Diomed, UK.*
Bladderwrack (*Fucus* spp.) (p. 2612·1).
Obesity.

Adipex *Gerot, Cz.*
⊗Phentermine resinate (p. 2329·2).
Obesity.
Gerot, Malaysia.
⊗Phentermine (as an ion-exchange resin complex) (p. 2329·2).
Obesity.

Adipex-P *Gate, USA.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Adipin *Sain, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Adipine
Note: this name may be used for preparations of different composition.
ICN, Pol.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.
Patar, Thai.; Trinity, UK.
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Adiporell *Sanorell, Ger.*
Fucus vesiculosus (p. 2612·1).
Homoeopathic preparation.

Adiporetic *Frandiet, Fr.*
Nutritional supplement.

Adiprost *Adipharm (Αδηφαρμ), Gr.†*
Flutamide (p. 798·2).
Prostatic cancer.

Adiro *Bayer, Spain.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Adisar *Roemmers, Chile.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Adisterolo *Abiogen, Ital.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).
Vitamin A and D deficiency.

Adital *Gobbi, Arg.*
Macrogol (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Aditasin *Vilco, Gr.*
⊗Reserpine (p. 1485·3); hydrochlorothiazide (p. 1403·2).

Adiugrip *Sanofi Pasteur, Ital.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Adiupressin *Ameda, Ukr.*
⊗Desmopressin (p. 2355·1).
Diabetes insipidus; test for renal-concentrating capacity.

Adiuretin *Ferring, Neth.†*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; polyuria; polydipsia; nocturnal enuresis.

Adiuvan *Lazar, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Adivaz *Fariberica, Port.†*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Adivit *Tripharma, Rus.†*
Vitamins.

Adivon *Ederka, Mex.†*
Ibuprofen (p. 68·2).
Inflammation; pain.

Adixone *Genopharm, Fr.*
⊗Fludrocortisone (p. 1634·3).
Adrenocortical insufficiency.

Adizem *Mundipharma, Irl.; Rafa, Israel; Napp, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Adjuvin *Lannacher, Austria; Lannacher, Cz.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia.

Adkalizer *Admac, India.*
Sodium acid citrate (p. 1781·1).

A-D-Kan *Sons, Mex.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

Adle *Adley, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Adlene-AD *Psyco Remedies, India.*
Adapalene (p. 1692·1).
Acne.

Adlin *David, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Adlox *Adley, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Adlube *Cipla, India.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry eyes.

Adlynx *Aldril, Philipp.*
Lincomycin hydrochloride (p. 317·1).
Staphylococcal infections.

Admadol *Admac, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Admag *TP, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity.

Admag-M *TP, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; gastritis; peptic ulcer.

Admax *Zuventus, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Admenta *Sun, India.*
Memantine hydrochloride (p. 393·1).

Admine *Adley, India.*
Calcium pantothenate (p. 2085·2); glucosamine sulfate (p. 2515·3); colecalciferol (p. 2113·1); vitamin E (p. 2119·1).

Admiral *SJA, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Admon *Esteve, Spain.†*
Nimodipine (p. 1455·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Ad-Muc *Biolab Sanus, Braz.*
Chamomile (p. 2474·1).

Merz, Hong Kong.
Chamomile (p. 2474·1); myrrh (p. 2566·1).
Inflammation of gums and oral mucosa.

Admycin-L *Adley, India.*
Lincomycin (p. 317·1).
Anaerobic bacterial infections.

ADN
Note: this name may be used for preparations of different composition.
Braun, Arg.
Preparation for enteral nutrition with or without fibre.

Sigma, Arg.†
Deoxyribonucleic acid (p. 2492·2).
Tonic.

ADN Nutricomp *Behrens, Venez.*
A range of preparations for enteral nutrition.

Adnac-MR *Admac, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1); diclofenac potassium (p. 48·3).

Adnemic-F *TNP, Thai.*
Vitamins; minerals; ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; vitamin deficiency.

Adnim-P *Adventure Life Science, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Adocomp *TAD, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Adocor *TAD, Ger.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Adofen *Brainpharma, Spain.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; mixed anxiety depressive states; obsessive-compulsive disorder.

Adol *Julphar, UAE.*
Paracetamol (p. 115·1).
Pain; fever.

Adol Allergy Sinus *Julphar, UAE.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; hay fever.

Adol Cold *Julphar, UAE.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Adol Compound *Julphar, UAE.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Adol Extra *Julphar, UAE.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Adol PM *Julphar, UAE.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Pain with insomnia.

Adol Sinus *Julphar, UAE.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinus headache.

Adolan *Teva, Israel.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal syndrome; pain.

Adolcas *Casasco, Arg.*
Monofluoride phosphate (p. 2091·3); calcium carbonate (p. 1824·3).
Osteoporosis.

Adolef *Biomed, Ital.*
Paracetamol (p. 115·1).
Pain.

Adolen *Konsuma, Venez.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Headache.

Adoless *Farmoquimica, Braz.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Adolex *Medipharm, Chile.*
Cetylpyridinium chloride (p. 1743·1); allantoin (p. 1693·1).
Mouth and throat disorders.

Adolonta *Grunenthal, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.

Adolor
Note: this name may be used for preparations of different composition.
Obolenskoe, Rus.
Ketorolac trometamol (p. 80·2).
Pain.

Stada, Cz.
⊗Fentanyl (p. 60·1).
Pain.

Adolorin *Kwizda, Austria.*
Propyphenazone (p. 127·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Adolorin Ibuforte *Kwizda, Austria.*
Ibuprofen (p. 68·2).
Pain.

Adolphs Salt Substitute *Adolphs, USA.*
Potassium chloride (p. 1793·2).
Sodium-free dietary salt substitute.

Adolquir *Fermon, Spain.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Adomet *Medicine Products, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Adom-O *Admac, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Adona
Note: this name may be used for preparations of different composition.
Tanabe, Hong Kong†; Tanabe, Indon.; SIT, Ital.; Tanabe, Jpn.
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Silesia, Chile.†
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Fever; inflammation; pain.

Adonep *Stada, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Adonix *Umedica, Philipp.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Adoplan *Esan, Chile.*
Clonixin lysine (p. 40·1).
Pain.

Adoport *Sandoz, Spain; Sandoz, UK.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Adormix *Sanofi-Aventis, Chile.†*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Adovia *Medochemie, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Adoxa
Note: this name may be used for preparations of different composition.
Doak, USA.†
Doxycycline (p. 288·1).
Bacterial infections.

Adozole *Plus Pharma, Cz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

ADP *Caplet, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Adpace *Sun, India.*
Losartan potassium (p. 1422·2); perindopril (p. 1466·3).
Hypertension.

Adpax *Adley, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Adpep *Admac, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Adpep-D *Admac, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

ADPHO *Advanced Remedies, Thai.†*
Amphotericin B (p. 569·2).
Fungal infections.

Adpime *Admac, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Adpine-AT *Purewin, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Adplatt *Grandix, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndromes.

Adprazole *Admac, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Adprazole-D *Admac, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Adprin-B *Pfeiffer, USA.*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3), magnesium carbonate (p. 1856·2), and magnesium oxide (p. 1857·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Adrecort *Allen, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Tai Yu, Philipp.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Asthma; allergic rhinitis; cerebral oedema.

Adreject *Merck, Chile; ALK, Spain.†*
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Adrekar *Sanofi-Aventis, Ger.*
Adenosine (p. 1291·1).
Tachycardia.

Adrena
Note: this name may be used for preparations of different composition.
Geo, India.
⊗Adrenaline acid tartrate (p. 1292·2).
Cardiac arrest; anaphylactic shock; asthma.

Teva, Philipp.
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Adrenaclick *Amedra, USA.*
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Adrenal Complex *Mediherb, Austral.*
Liquorice (p. 1853·2); rehmannia rhizome.
Dietary supplement for maintenance of adrenal function.

Adrenin *Oboi, Philipp.*
⊗Adrenaline hydrochloride (p. 1292·2).
Shock; haemorrhage; urticaria; ad junct in infiltration anaesthesia.

Adrenoid *MedChem, USA.*
Vitamin B_{12} (p. 2107·2); minerals; ashwagandha (p. 2450·2); bladderwrack (p. 2612·1); cayenne pepper (p. 2469·3); schisandra (p. 2611·2); tyrosine (p. 2098·3).
Dietary supplement.

Adrenol *Fabra, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Adrenor *Samarth, India.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Adrenotone *Mylan, S.Afr.*
⊗Adrenaline acid tartrate (p. 1292·2).
Bronchospasm; anaphylaxis cardiac arrest.

Adrenoxil *Sanofi-Aventis, Port.†*
Carbazochrome (p. 1137·1).
Haemorrhagic disorders.

Adrenyl *UCI, Braz.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

AdreView *GE Healthcare, Belg.†; GE Healthcare, Fr.; GE Healthcare, Neth.; GE Healthcare, Spain; GE Healthcare, Switz.; GE Healthcare, UK; GE Healthcare, USA.*
Iodine-123 iobenguane sulfate (p. 2225·1).
Radionuclide imaging.

Adriacin *Kyowa, Jpn.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adriaderm *Terapeutico, Ital.*
Barrier preparation.

Adrianol *Zdravlje, Rus.*
⊗Phenylephrine hydrochloride (p. 1672·3); tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Adriblastin *Pfizer, Austria; Pharmacia, Ger.†; Pfizer, Switz.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adriblastina *Pfizer, Arg.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile†; Pfizer, Cz.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Carlo Erba, Turk.; Deva, Turk.; Pfizer, Ukr.†; Pfizer, Venez.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adriblastine *Pfizer, Fr.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adricin *Novell, Indon.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adride *Grandix, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Adride-M *Grandix, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Adride-P *Grandix, India.*
Glimepiride (p. 473·2); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Adrigyl *Crinex, Fr.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; vitamin D supplement.

Adrim *Biogalenic, Venez.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adrimedac *Medac, Ger.; Medac, Pol.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Adrisin *Biological Homeopathic Industries, Canad.†*
Antimony trisulfide (p. 2445·1); arnica montana (p. 2447·2); burdock (p. 2540·1); formic acid (p. 2507·1); graphite (p. 2522·1); histamine (p. 2525·2); ledum palustre (p. 2550·1); lycopodium clavatum (p. 2547·1); pine tar (p. 1723·3); sabadilla (p. 2611·2); selenium (p. 2086·3); sodium chloride (p. 1795·1); sulfur (p. 1721·1); sulfuric acid (p. 2624·2); tellurium metallicum; thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Adriz *Birz, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Adrome *Landson, Indon.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Adromux *Gador, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Adronat *Alphapharm, Austral.; Neopharmed, Ital.; Tecnifar, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Adronat Plus *Alphapharm, Austral.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Adronat Plus D-Cal *Alphapharm, Austral.*
4 Tablets, alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1)(Adronat Plus); 48 tablets, calcium carbonate (BoneCal) (p. 1824·3).
Osteoporosis.

Adronis *Neiss, India.*
⊗Noradrenaline (p. 1458·2).
Gastrointestinal haemorrhage; hypotension; shock.

Adrosal *Naprod, Philipp.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

VHB, India.
Doxorubicin (p. 782·3).
Malignant neoplasms.

Adrotan *Elpen (Ελπεν), Gr.*
Gemfibrozil (p. 1390·3).

Adrovance *MSD, Cz.; MSD-Chibret, Fr.; MSD, Gr.; MSD, Irl.; Sigma-Tau, Ital.; MSD, Neth.; MSD, Pol.; MSD, Port.; Ferrer, Spain.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Adrovit *Adley, India.*
Capsules: Alpha tocoferil acetate (p. 2119·2); lycopene (p. 2546·2); selenium dioxide (p. 2087·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).
Adley, India.
Syrup: Vitamin B substances (p. 2102·3); lysine (p. 2079·3); vitamin A (p. 2098·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Adrovit-LB *Adley, India.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); *Lactobacillus sporogenes* (p. 2596·3).

Adrovit-Z *Adley, India.*
Zinc (p. 2126·1).

Adroxef *Laboratorios Chile, Chile.*
Cefadroxil (p. 233·2).
Bacterial infections.

Adroyd *Pfizer, India.*
⊗Oxymetholone (p. 2298·3).
Aplastic anaemia.

Adrucil *Teva, USA.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Adrusen *SIFI, Ital.*
Lycopene (p. 2546·2); vitamins; minerals.

Ad-Sachet *Hetero, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Adsal *Advanced Remedies, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Adsal Plus *Advanced Remedies, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ad-Sorb *Key, Austral.†*
Activated charcoal (p. 1537·3).
Flatulence.

Adsorba *Gambro, Canad.*
Activated charcoal (p. 1537·3).
Cartridge for haemoperfusion containing cellulose-coated activated charcoal.
Acute poisoning; drug overdosage.

Adsorba C *Gambro, Fin.; Gambro, Ger.; Gambro, UK.*
Activated charcoal (p. 1537·3).
Cartridge for haemoperfusion containing cellulose-coated activated charcoal.
Acute poisoning; drug overdosage.

Adsorbed DT Vaccine *Bio Farma, Malaysia; Bio Farma, Thai.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Adsorbocarpine *Alcon, USA.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Adsorbonac *Alcon, Ger.†; Alcon, Ital.†; Alcon, Singapore†; Alcon, USA.†*
Sodium chloride (p. 1795·1).
Corneal oedema; eye irritation.

ADT
Note: this name may be used for preparations of different composition.
CSL Biotherapies, Austral.; CSL, NZ; CSL, Singapore.
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Wynn, Port.
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Adtendyl *Christo, Hong Kong.†*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Adthec *Adley, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

AD-Til *Nycomed, Braz.*
Colecalciferol (p. 2113·1); vitamin A acetate (p. 2098·3).
Vitamin deficiency.

Aduar *Vannier, Arg.*
Mebendazole (p. 158·3); tinidazole (p. 949·2).

Adulax *Casen Fleet, Spain; Casen Fleet, Ukr.*
⊗Glycerol (p. 2517·2).
Constipation.

Adulfed *TP, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; cold symptoms.

Adulfen Lysine *Reckitt Benckiser, Belg.†*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Adult Chesty Cough *Numark, UK.*
Diphenhydramine (p. 626·1).
Coughs.

Adult Chesty Cough Non Drowsy *Numark, UK.*
Guaifenesin (p. 1666·2).
Coughs.

Adult Citrex *Pharmaniaga, Malaysia.*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Adult Citrex Cal-Mag-D3 *Pharmaniaga, Malaysia.†*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3).
Vitamin D and mineral supplement.

Adult Citrex Multivitamin + Ginseng + Omega 3 *Pharmaniaga, Malaysia.*
Vitamins; ginseng (p. 2513·3); omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Adult Dry Cough *Numark, UK.*
Dextromethorphan (p. 1660·1).
Coughs.

Adult Formula 50+ *WN, Canad.†*
Vitamins; minerals.

Adult Meltus for Chesty Coughs & Catarrh *SSL, UK.*
Guaifenesin (p. 1666·2); cetylpyridinium chloride (p. 1743·1); honey (p. 2072·1).
Coughs; catarrh.

Adumbran *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Gr.*
Oxazepam (p. 1092·2).
Sleep disorders; anxiety disorders.

Adursal *Leiras, Fin.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders; gallstones; chronic active hepatitis.

Advabase *Intendis, Ital.*
Emollient.

Advaferon *IFET (ΙΦΕΤ), Gr.*
Interferon alfacon-1 (p. 989·2).
Hypertension; diabetic nephropathy; heart failure; reduction of stroke risk in left ventricular hypertrophy.

Advagraf *Astellas, Austria; Astellas, Belg.; Astellas, Canad.; Astellas, China; Astellas, Cz.; Astellas, Denm.; Astellas, Fr.; Astellas, Ger.; Astellas, Gr.; Astellas, Hong Kong; Astellas, Hung.; Astellas, Irl.; Astellas, Ital.; Astellas, Neth.; Astellas, Norw.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Astellas, Thai.; Astellas, UK.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Advair *GSK, Canad.; GSK, USA.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease; asthma.

Advance
Note: this name may be used for preparations of different composition.
Advanced Care, USA.
Pregnancy test (p. 2596·1).

Future, Canad.
A range of vitamin and mineral preparations.

Advance 12A *Advance, Canad.*
Sodium hypochlorite (p. 1768·3).
Disinfectant.

Advance Formance *Abbott, Mex.*
Preparation for enteral nutrition.

Advance Quat *Advance, Canad.*
Alkyldimethylethylbenzyl ammonium chloride (p. 1736·2); benzalkonium chloride (p. 1737·1).
Surface disinfection.

Advanced Bladder Care *Advacare, Austral.*
Equisetum (p. 2500·1); crataeva nurvala; silicon (p. 2088·3); calcium hydrogen phosphate (p. 1783·3); magnesium phosphate (p. 1787·3).
Bladder hyperactivity.

Advanced D *Mason, USA.*
Vitamin D (p. 2112·3).
Dietary supplement.

Advanced Ear Health Formula *Mason, USA.*
Bioflavonoids (p. 2505·2); calcium (p. 1783·1); choline (p. 2055·2); inositol (p. 2533·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Advanced Eye Relief *Bausch & Lomb, USA.*
Propylene glycol (p. 2205·2).
Dry eyes.

Advanced Eye Relief Redness *Bausch & Lomb, USA.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Advanced Formula Cerovite *Rugby, USA.*
Vitamins; minerals.
Dietary supplement.

Advanced Formula Di-Gel *Schering-Plough, USA.*
Magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Hyperacidity.

Advanced Formula Zenate *Solvay, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Nutritional supplement in pregnancy and lactation.

Advanced Menopause Care *Advacare, Austral.*
Wild yam (p. 2648·1); linseed oil (p. 2544·2); geranium oil (p. 2512·2); sage oil (p. 2609·1); *d*-alpha tocoferil acetate (p. 2119·1).
Menopausal disorders.

Advanced Prostate Care *Advacare, Austral.*
Equisetum (p. 2500·1); crataeva nurvala; saw palmetto (p. 2363·3); lycopene (p. 2546·2); zinc (p. 2126·1); selenium (p. 2086·3).
Prostate disorders.

Advanced Relief Visine *Pfizer Consumer, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3); macrogol 400 (p. 2547·3); povidone (p. 2204·3); dextran 70 (p. 1138·3).
Eye irritation; dry eyes.

Advanced Restless Leg Care *Advacare, Austral.*
Valerian (p. 2640·2); passion flower (p. 2584·1); magnesium (p. 1786·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Restless legs syndrome.

Advanced Urinary Tract Care *Advacare, Austral.*
Equisetum (p. 2500·1); crataeva nurvala; cranberry (p. 2488·1); ascorbic acid (p. 2110·3); magnesium phosphate (p. 1787·3).
Cystitis.

Advanced-RF Natal Care *Ethex, USA.†*
Vitamins; minerals.

Advanpro *Accord, Mex.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Advantage 24 *Lake, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Advantan *Bayer, Arg.; CSL, Austral.; Intendis, Austria; Bayer, Belg.; Intendis, Braz.; Intendis, Cz.; Intendis, Fin.; Jenapharm, Ger.; Intendis, Gr.; Intendis, Hong Kong; Unicorp, Hung.; Transfarma, Indon.; Intendis, Irl.; Intendis, Ital.; Intendis, Mex.; CSL, NZ; Intendis, Philipp.; Intendis, Philipp.; Intendis, Pol.; Bayer, Port.; Intendis, Rus.; Bayer*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Schering, S.Afr.; Bayer, Switz.; Schering, Turk.; Intendis, Ukr.; Schering, Venez.
⊗Methylprednisolone aceponate (p. 1642·2).
Skin disorders.

Advate *Baxter, Arg.; Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Irl.; Baxter, Ital.; Baxter, Jpn; Baxter, Malaysia; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK; Baxter, USA.*
Octocog alfa (p. 1148·2).
Haemophilia A ; haemorrhagic disorders.

Advel *Hexal, Ger.†*
Tablets: Ibuprofen (p. 68·2).
Fever; pain.

Hexal, Ger.†
Cream: Cayenne pepper (p. 2469·3).
Musculoskeletal and joint disorders.

Hexal, Ger.†
Gel: Ketoprofen (p. 79·1).
Musculoskeletal and soft-tissue pain and inflammation.

Advent *Cipla, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Adventan *Intendis, Spain.*
⊗Methylprednisolone aceponate (p. 1642·2).
Skin disorders.

Advera *Abbott, Braz.; Abbott, Mex.; Ross, USA.*
Preparation for enteral nutrition.
Dietary management in HIV infection or AIDS.

Adversuten *AWD, Ger.†*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Advicor *Sepracor, Canad.†; AbbVie, USA.*
Nicotinic acid (p. 2083·1); lovastatin (p. 1425·2).
Hypercholesterolaemia.

Advil *Wyeth Consumer, Austral.; Wyeth Consumer, Braz.; Pfizer Consumer, Canad.; Pfizer, China; Pfizer, Cz.; Pfizer Sante, Fr.; Pfizer, Gr.; Pfizer, Hung.; Pfizer Consumer, Irl.; Neopharm, Israel; Wyeth Consumer, Mex.; Pfizer, Neth.; Wyeth, Philipp.; Pfizer Consumer, S.Afr.; Wyeth, Spain†; Wyeth, Turk.; Wyeth Consumer, UK; Whitehall, USA; Wyeth-Ayerst, USA; Wyeth Consumer, Venez.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Advil Allergy Sinus *Pfizer Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); ibuprofen (p. 68·2).
Upper respiratory-tract disorders.

Advil Cold *Wyeth, Cz.†; Wyeth, Hung.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Advil Cold & Flu *Pfizer Consumer, Irl.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Advil Cold & Sinus *Pfizer Consumer, Canad.; Neopharm, Israel; Whitehall, USA.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Advil Cold & Sinus Nighttime *Pfizer Consumer, Canad.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic symptoms; sinusitis.

Advil Cold & Sinus Plus *Pfizer Consumer, Canad.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic symptoms; sinusitis.

Advil CS *Wyeth Consumer, S.Afr.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Advil Migraine *Wyeth, USA.*
Ibuprofen (p. 68·2); ibuprofen potassium (p. 68·2).
Migraine.

Advil Mono *PSI, Belg.†*
Ibuprofen (p. 68·2).
Pain; fever.

Advil Nighttime *Pfizer Consumer, Canad.*
Ibuprofen (p. 68·2); diphenhydramine hydrochloride (p. 626·2).
Pain with insomnia.

Advil PM *Wyeth Consumer, USA.*
Diphenhydramine citrate (p. 626·2); ibuprofen (p. 68·2).

Advilcaps *Pfizer Sante, Fr.*
Ibuprofen (p. 68·2).
Fever; pain.

AdvilEff *Pfizer Sante, Fr.*
Ibuprofen (p. 68·2).
Fever; pain.

Adviltab *Pfizer Sante, Fr.*
Ibuprofen (p. 68·2).
Fever; pain.

Adviltab Rhume *Wyeth Sante, Fr.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Formerly known as Anadvil Rhume.
Cold symptoms.

Advin-NC *Anglo-French Drugs, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

A-D-Vit *Meyer, Venez.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); calcium phosphate (p. 1784·2).
Osteoporosis; rickets.

Advit *Admac, India.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); colecalciferol (p. 2113·1); zinc (p. 2126·1); iron (p. 2073·1).

Advit Plus *Admac, India.*
Vitamins; minerals.

Advit-A *Natco, India.*
Copper (p. 2057·1); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

AD-vitamin *ACO, Swed.†*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1).
Vitamin supplement.

Advit-C *Orchid, India.*
Folic acid (p. 2063·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Advit-DR *Admac, India.*
Vitamins.

Advnasal *Advfarma, Braz.†*
Sodium chloride (p. 1795·1).

Advocard *FarKoS, Ukr.*
Adenosine-5′-triphosphategluconate-magnesium (ii) trisodium salt; molsidomine (p. 1441·1); folic acid (p. 2063·1).
Ischaemic heart disease; angina pectoris.

ADX *Sigma, Arg.*
Ginseng (p. 2513·3); catuaba; guarana (p. 2648·2); damiana (p. 2491·3); saw palmetto (p. 2363·3); ginkgo biloba (p. 2512·3); arginine (p. 2049·1); zinc (p. 2126·1); bovine testicle hydrolysate; pollen; vitamin E (p. 2119·1).
Dietary supplement.

Adytenn *Ultra, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Adzole *Adley, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Adzole-DM *Adley, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Adzopip *Admac, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Aecoras *CCM, Malaysia.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections.

Aedolac *Rottapharm, Ital.*
Emollient.

Aedon *GL Pharma, Cz.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Sanofi-Aventis, India.
Clobazam (p. 518·2).
Anxiety; epilepsy.

Aegis *Benedetti, Ital.*
Bacillus subtilis.
Restoration of gastrointestinal flora.

AEgte Venustorn *Natur-Drogeriet, Denm.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders; reduced appetite; dyspepsia.

Aeknil *Therapeutic, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Aelxim *Allenge, India.*
Cefixime (p. 240·3).
Bacterial infections.

Aelxim-CL *Allenge, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Aequamen *Takeda, Ger.*
Betahistine mesilate (p. 2455·3).
Vestibular disorders; Ménière's syndrome.

Aequifusine *Braun, Switz.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

A-E-R *Birchwood, USA.*
Hamamelis (p. 2523·3).
Anorectal disorders; vaginal irritation.

Aerflu *Boniscontro & Gazzone, Ital.*
⊗Flunisolide (p. 1635·3).
Respiratory-tract hypersensitivity; rhinitis.

Aerinaze *Schering-Plough, Belg.; Schering-Plough, Cz.; MSD, Gr.; MSD, Irl.; MSD, Israel; MSD, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.*
⊗Desloratadine (p. 625·1); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; nasal congestion.

Aerius *Schering-Plough, Arg.; Schering-Plough, Austral.; Schering-Plough, Austria; MSD, Belg.; Schering-Plough, Canad.; Schering-Plough, Chile; MSD, China; Schering-Plough, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; MSD, Irl.; MSD, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; MSD, Neth.; MSD, Norw.; Schering-Plough, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, Ukr.; Schering-Plough, Venez.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria; allergic conjunctivitis; pruritus.

Aerius D-12 *MSD, Singapore.*
⊗Desloratadine (p. 625·1); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Aerius Dual Action 12 Hour *Schering-Plough, Canad.*
⊗Desloratadine (p. 625·1); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Aero Itan *Saval, Chile.*
Dimeticone (p. 2209·3); metoclopramide (p. 1862·2); chlordiazepoxide (p. 1044·2).
Dyspepsia; flatulence; gastrointestinal motility disorders; meteorism.

Aero Red *Uriach, Spain.*
Dimeticone (p. 1886·2).
Flatulence.

Aero Red Antiacido *Uriach, Spain.†*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).
Flatulence; gastric hyperacidity.

Aero Red Complex *Uriach, Spain.†*
Dimeticone (p. 1886·2); lipolytic enzymes; amylolytic enzymes; proteolytic enzymes; cellulolytic enzymes.
Digestive system disorders.

Aeroaid *Graham-Field, USA†; Health & Medical, USA.†*
Thiomersal (p. 1771·3).
Skin disinfection; wounds.

AeroBec *Teva, Denm.; Teva, Fin.; Ivax, Ger.†; Teva, Norw.; Teva, Swed.; 3M, UK.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

AeroBid *Roche, USA.*
⊗Flunisolide (p. 1635·3).
Asthma.

Aerobin *Farmasan, Ger.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Aero-Bud *Andromaco, Chile.*
⊗Budesonide (p. 1625·1).
Asthma.

Aerocef *Astellas, Austria.*
Cefixime (p. 240·3).
Bacterial infections.

Aerocort *Cipla, India; Cipla, Venez.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

Cipla, Malaysia.
⊗Salbutamol sulfate (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Aerocort S *Glenmark, Braz.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).

Aerocortin *Fujisawa, Austria.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Aerodan *Medipharm, Chile.†*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; allergic skin disorders.

Aeroderma *Pharmanik (Φαρμανικ), Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Aerodesin *Lysoform, Ger.*
⊗Propyl alcohol (p. 1768·1); alcohol (p. 1733·1); glutaral (p. 1753·2).
Surface disinfection.

Aerodini *Teuto, Braz.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Aerodiol *Servier, Arg.; Servier, Austral.†; Servier, Belg.†; Servier, Braz.; Servier, Gr.; Servier, Irl.†; Servier, Neth.; Servier, NZ†; Servier, Turk.; Servier, Venez.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Aeroduol *Aerocare, Thai.*
⊗Ipratropium bromide (p. 1211·3); fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Aerodur *AstraZeneca, Ger.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Aerofillin *ABC, Ukr.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Aeroflat *Rottapharm, Spain.*
Metoclopramide (p. 1862·2); dimeticone (p. 1886·2).
Aerophagia; delayed gastric emptying.

Aeroflux
Note: this name may be used for preparations of different composition.
GSK, Braz.
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Obstructive airways disease.

GSK, Mex.; GSK, Venez.
⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Asthma; bronchitis; respiratory-tract disorders with increased mucus.

Aerofreeze *Graham-Field, USA.†*
Dichlorodifluoromethane (p. 1798·2); trichlorofluoromethane (p. 1798·2).
Topical anaesthesia.

Aerogal *Galien, Arg.*
Silicone oil (p. 2209·3).
Barrier preparation.

Aerogastrol *Medipharm, Chile.*
Metoclopramide (p. 1862·2); simeticone (p. 1886·2); chlordiazepoxide (p. 1044·2).
Dyspepsia; flatulence; gastrointestinal motility disorders; meteorism.

Aerogold *Glenmark, Braz.*
⊗Salbutamol sulfate (p. 1220·2).

Aerogreen *Greenpharma, Braz.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

AeroHist Plus *Aero, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Aerojet *Chiesi, Braz.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

AeroKid *Aero, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Aerolate *Fleming, USA.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Aerolid *Piam, Ital.*
⊗Flunisolide (p. 1635·3).
Respiratory-tract hypersensitivity; rhinitis.

Aerolin *GSK, Braz.; GSK, Gr.; Norton Waterford, Irl.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; asthma; chronic respiratory failure.

GSK, Chile.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour.

Aeromax
Note: this name may be used for preparations of different composition.
Medinfar, Port.
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.
GSK, Ger.†
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Aeromed *Medipharm, Chile.*
Ivy (p. 2536·2).
Cough.

Aerometrol Plus *Andromaco, Chile.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Asthma.

Aeromist *Ranbaxy, India.*
⊗Ipratropium bromide (p. 1211·3); salbutamol (p. 1220·2).

Aeromol *Aerocare, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Aeromox *Aglowmed, India.*
Amoxicillin (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Aeromuc *Astellas, Austria.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders.

Aeron *Aspen, Austral.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Aeronide *Aerocare, Thai.*
⊗Budesonide (p. 1625·1).
Asthma.

Aeronix *AstraZeneca, Spain.*
Zafirlukast (p. 1239·3).
Asthma.

Aero-Om *OM, Neth.; OM, Port.; OM, Switz.*
Simeticone (p. 1886·2).
Flatulence; meteorism; diarrhoea; reduction of gastrointestinal gas.

AeroOM *OM, Cz.*
Simeticone (p. 1886·2).
Flatulence; meteorism.

Aeropax *Orion, Denm.; Sandoz, Neth.*
Dimeticone (p. 1886·2).
Aid in radiography and gastroscopy; infant colic; meteorism; flatulence.

Aero-Plus *Andromaco, Chile.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Aeroseb *Panalab, Arg.*
Shampoo: Pyrithione zinc (p. 1718·1); cade oil (p. 1723·2).
Scalp disorders.
Panalab, Arg.
Soap: Pyrithione zinc (p. 1718·1).
Seborrhoea.

Aeroseb-Dex *Allergan Herbert, USA.*
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Aerosial *Ivax, Mex.†*
⊗Budesonide (p. 1625·1).
Asthma; bronchitis.

Aerosil *Degussa, UK.*
Colloidal silicon dioxide (p. 2208·3).
Pharmaceutical formulation aid.

Aerosoma *Etex, Chile.†*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Aeroson *Soho, Indon.†*
Dimeticone (p. 1886·2).
Flatulence; meteorism; abdominal distension; dyspepsia.

Aerosonit *GSK, Pol.*
Isosorbide dinitrate (p. 1412·2).
Ischaemic heart disease; myocardial infarction.

AeroSpan *Forest Laboratories, USA.*
⊗Flunisolide (p. 1635·3).
Asthma.

Aerosporin *GSK, India.*
Polymyxin B (p. 342·3).
Gram-negative infections.
GSK, Philipp.
Polymyxin B sulfate (p. 342·3).
Bacterial ear infections.

Aerotaz *Sun, India.*
⊗Salbutamol (p. 1220·2).
Bronchospasm; asthma.

Aerotide *GSK, Braz.; Sun, India.*
⊗Beclometasone dipropionate (p. 1621·2); salbutamol (p. 1220·2).
Asthma.

Aerotina *Raffo, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Aerotrat *Cazi, Braz.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Aerotrop *Cassara, Arg.; D & M, Chile.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

AeroTuss 12 *Aero, USA.*
Dextromethorphan tannate (p. 1660·1).
Cough.

Aerovac G *Casasco, Arg.*
Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae; Moraxella catarrhalis; Micrococcus.
Respiratory-tract infections.

Aero-Vent *Cipla, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; bronchospasm.

Aerovent
Note: this name may be used for preparations of different composition.
Cassara, Arg.
⊗Budesonide (p. 1625·1).
Cipla, India.
⊗Beclometasone dipropionate (p. 1621·2); salbutamol sulfate (p. 1220·2).
Asthma.
Teva, Israel.
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Aerovial *Atlas, Arg.; Recalcine, Chile.*
⊗Budesonide (p. 1625·1).
Asthma.

Aerovial Aqua *Recalcine, Chile.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Aerovit *Ufavita, Rus.*
Vitamins; rutoside (p. 2505·3).

Aerox *Torrex Chiesi, Hung.*
⊗Budesonide (p. 1625·1).
Asthma.

Aeroxina *Elea, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Aerozoin *Graham-Field, USA.*
Compound benzoin tincture.
Barrier preparation.

AErran *Baxter, Rus.*
Isoflurane (p. 1903·2).
General anaesthesia.

AErrane *Baxter, Austral.; Baxter, Canad.; Baxter, China; Baxter, Cz.; Baxter, Fr.; Baxter, Hong Kong†; Baxter, Hung.; Baxter, India; Kalbe, Indon.; Baxter, Irl.; Baxter, Israel; Baxter, Ital.; Baxter, Neth.†; Baxter, NZ; Baxter, Philipp.; Baxter, Pol.; AstraZeneca, S.Afr.†; AstraZeneca, Singapore; Baxter, Spain; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter Anaesthesia, UK.*
Isoflurane (p. 1903·2).
General anaesthesia.

Aeruginox *Shenzhen, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Aeruxim *Shenzhen, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Aerway *Merck, India.*
Camphor (p. 2466·2); chlorothymol (p. 1748·2); cineole (p. 2479·1); menthol (p. 2553·2); terpineol (p. 2627·2).

Aescorin Forte *Steigerwald, Ger.*
Aesculus (p. 2431·2).
Venous insufficiency; soft-tissue injury.

Aesculaforce *Aponova, Austria; Bioforce, Switz.*
Aesculus (p. 2431·2).
Venous insufficiency.

AesculaMed *Bioforce, Switz.*
Aesculus (p. 2431·2).
Venous insufficiency.

Aesculan *Herbapol Poznan, Pol.*
Esculoside (p. 2431·2); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Aesculo Gel L *Medice, Ger.*
Coconut oil (p. 2179·3).
Pediculosis.

Aesculus Comp *Heel, Neth.*
Aesculus hippocastanum (p. 2431·2); secale cornutum (p. 2137·1); vipera berus; lycopodium clavatum (p. 2547·1); melilotus officinalis (p. 2552·3); sulfur (p. 1721·1); hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Aesculus Complexe No 103 *Lehning, Fr.*
Aesculus (p. 2431·2); hamamelis (p. 2523·3); boldo (p. 2458·3); verbascum (p. 2645·1); nux vomica (p. 2573·3); paeonia officinal; collinsonia (p. 2622·2); teucrium scordium; natrum nitricum (p. 1769·3); sulfur (p. 1721·1); aloe (p. 1816·1).
Homoeopathic preparation.

Aesculus Compose *Boiron, Fr.*
Aesculus hippocastanum (p. 2431·2); hamamelis virginiana (p. 2523·3); hydrastis canadensis (p. 2528·1); viburnum prunifolium (p. 2458·1).
Homoeopathic preparation.

Aesculus & Ruscus Compound *Phytomedicine, Austral.*
Aesculus (p. 2431·2); ginkgo biloba (p. 2512·3); centella (p. 1698·3); butcher's broom (p. 2463·1); rutoside (p. 2505·3); magnesium oxide.
Varicose veins; capillary disorders.

Aescusan *Mibe, Ger.; Mibe, Ukr.*
Delayed-release tablets; tablets: Aesculus (p. 2431·2).
Venous insufficiency.
Pharma Wernigerode, Rus.
Aescin (p. 2431·2); thiamine hydrochloride (p. 2103·1).
Venous insufficiency; haemorrhoids.
Wernigerode, Ukr.
Oral drops: Aesculus (p. 2431·2); thiamine hydrochloride (p. 2103·1).
Venous insufficiency; haemorrhoids.
Riemser, Ger.†
Cream: Aesculus (p. 2431·2); hamamelis (p. 2523·3).
Venous insufficiency; soft-tissue inflammation.

Aescuven *Cesra, Ger.; Cesra, Pol.*
Aesculus (p. 2431·2).
Venous insufficiency; soft-tissue inflammation; oedema.

Aesim *Lamsa, Arg.*
Simeticone (p. 1886·2).
Flatulence.

Aesplant *KVZ, Ukr.*
Aesculus (p. 2431·2).
Venous insufficiency.

Aet *Craveri, Arg.*
Lauromacrogol 400 (p. 2194·1).
Varices.

Aethoxysklerol *BSN, Austral.; Nycomed, Austria; MPCA, Belg.; Kreussler, Cz.; Kreussler, Denm.; Kreussler, Fin.; Kreussler, Ger.; IFET [ΙΦΕΤ], Gr.; Kreussler, Hung.; Sigma-Tau, Neth.; Kreussler, Pol.; Inverdia, Swed.; Pro Concepta, Switz.; Kreussler, Thai.; Cem, Turk.*
Lauromacrogol 400 (p. 2194·1).
Varices; haemorrhoids; dilated cutaneous veins.

Aetoxisclérol *Kreussler, Fr.*
Lauromacrogol 400 (p. 2194·1).
Varices.

Aetoxysklerol *Dominguez, Arg.*
Lauromacrogol 400 (p. 2194·1).
Varices.

AEvit *KVZ, Ukr.*
Vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Vitamin A and E supplement.

AF
Note: this name may be used for preparations of different composition.
Aspen Consumer, S.Afr.
Zinc undecenoate (p. 596·3); undecenoic acid (p. 596·3); terpineol (p. 2627·2).
Fungal skin infections.
Systopic, India.
Fluconazole (p. 578·2).
Fungal infections.
Valdecasas, Mex.
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects.

Afacort *Anfarm, Gr.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Bacterial eye infections with inflammation; skin disorders.

Afalpi *CTS, Israel.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Afardin *Anfarm, Gr.*
Indometacin (p. 71·2).

Afax *Baldacci, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia.

Afaxin *Sanofi-Aventis, Philipp.*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Afazol *Grin, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Afazol Z *Grin, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Eye disorders.

AFB3 *Lark, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

AFB4 *Lark, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

AFBM *Sigma, Braz.*
Vitamin A palmitate (p. 2098·3); pyridoxine hydrochloride (p. 2105·3); tocoferil acetate (p. 2119·2).

Afcal *Alcure, India.*
Vitamin D (p. 2112·3); calcium carbonate (p. 1824·3).

Af-Care *Vitamed, Israel.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Afcin *Alpha Aromatic, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Afdec *Alpha Aromatic, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Afdicomplex *Anglo-French Drugs, India.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Afdiex *Cadila, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

AFD-Multivitamin *Anglo-French Drugs, India.*
Vitamins; minerals.

Afdura *Sun, India.*
Alfuzosin hydrochloride (p. 2351·3); dutasteride (p. 2357·2).

Afebril *Bago, Arg.*
Ibuprofen (p. 68·2).
Fever; pain; musculoskeletal and joint disorders.

Afebrin
Note: this name may be used for preparations of different composition.
Konimex, Indon.†
Paracetamol (p. 115·1).
Fever; pain.

Afebryl *SMB, Belg.; SMB, Fr.†; Azevedos, Port.; Cem, Turk.*
Aspirin (p. 22·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; inflammation; fever.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Afecton *Help, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

A-fed *Patar, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Afeditab *Watson, USA.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Afema *Novartis, Jpn.*
⊗Fadrozole hydrochloride (p. 793·1).

Afeme *Cetus, Arg.*
Dexchlorpheniramine (p. 620·3).
Hypersensitivity reactions.

Afenexil *Temis, Arg.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Afenil
Note: this name may be used for preparations of different composition.
Abbott, Gr.
Trandolapril (p. 1517·2).
Hypertension; left ventricular dysfunction following myocardial infarction.
Piam, Ital.
Food for special diets.
Phenylketonuria.

Afenoxin *Faran, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Afen-P *Psychotropics, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

A-ferin *Husnu Arsan, Turk.*
Capsules: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Cold and influenza symptoms.
Husnu Arsan, Turk.
Forte tablets: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.
Husnu Arsan, Turk.
Sachets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.
Husnu Arsan, Turk.
Sinus tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold and influenza symptoms.

A-ferin Plus *Bilim, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; sinusitis; allergic rhinitis.

Afesan *Sanify, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Afesan-CZ *Sanify, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Afesan-P *Sanify, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Afesan-SP *Sanify, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Afexdine *Adley, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Afexil *Zentiva, Cz.†*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

AFF *Q Check, India.*
Atorvastatin calcium (p. 1309·2); fenofibrate (p. 1381·1); folic acid (p. 2063·1).
Hyperlipidaemias.

Affex *Astellas, Irl.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Affirab *Pharmaffiliates, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Affirab-D *Pharmaffiliates, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Affusine *Will-Pharma, Belg.; Will-Pharma, Neth.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Afiancen *Buxton, Arg.*
Leflunomide (p. 81·3).

AFI-D_2 *Nycomed, Norw.*
Ergocalciferol (p. 2113·3).
Hypoparathyroid tetany.

Afid Plus *Fresenius Kabi, Ger.†*
Didecyloxethylmethylammoniumpropionate; cocospropylenediamineguanidinium diacetate.
Instrument disinfection.

Afidil *Ranbaxy, Singapore.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

A-Fil *PharmaDerm, USA.*
Meradimate (p. 1711·2); titanium dioxide (p. 1725·1).
Sunscreen.

Afilan *Quesada, Arg.*
⊗Mazindol (p. 2324·1).
Obesity.

Afilon *Liconsa, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Afinitor *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; IFET (ΙΦΕΤ), Gr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Irl.; Novartis, Israel; Novartis, Jpn; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.*
Everolimus (p. 1957·3).
Renal cell carcinoma; pancreatic neuroendocrine tumours; giant cell astrocytoma; breast cancer; tuberous sclerosis; renal angiomyolipoma.

Afipran *Nycomed, Norw.*
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal investigations; migraine.

Afiten *Medochemie, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Afixim *Acto, India.*
Cefixime (p. 240·3).
Bacterial infections.

Afixim Clav *Acto, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Afizyme *Alcure, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1); protein hydrolysate.

Af-Kid *Rekah, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

AF-Kit *Systopic, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, ornidazole (p. 943·1).
Vaginal infections.

Aflacin *Ashford, Singapore.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Aflamid *Anchor, Mex.*
Meloxicam (p. 86·3).
Ear, nose, and throat inflammation.

Aflamin
Note: this name may be used for preparations of different composition.
Gedeon Richter, Hung.
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders; pain.
Hexal, S.Afr.†
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Aflarex *Alcon, Chile; Alcon, Venez.*
⊗Fluorometholone acetate (p. 1637·2).
Inflammatory eye disorders.

Aflat *Omega, Arg.*
Simeticone (p. 1886·2).
Flatulence; infant colic.

Aflavic *Polfarmex, Pol.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Aflazin *Pro-Pharma, Ukr.*
Hibiscus (p. 2525·2).
Urinary-tract infections; renal calculi.

Aflegan *ICN, Pol.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Aflem *Jumont, Philipp.*
Carbocisteine (p. 1658·1).
Cough; respiratory-tract congestion.

Aflen *Galenica, Gr.*
Triflusal (p. 1519·3).
Thrombosis prophylaxis.

Aflevo *Positif, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Aflex *Pharmaland, Thai.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Afligec *Filadams, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Aflobax *Temapharm, Cz.; Temapharm, Pol.*
Levofloxacin (p. 315·3).
Bacterial infections.

Afloben *Pliva, Ital.†*
Benzydamine hydrochloride (p. 29·2).
Vaginitis; puerperal vaginal hygiene.

Afloderm *Belupo, Cz.; Belupo, Pol.; Belupo, Rus.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Aflogen *Faran, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Aflogol *Sanitas, Chile.*
Calcium aminosalicylate (p. 215·2).
Skin and hair disorders.

Aflorix *Sanofi-Aventis, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

A-Flox *Adventure Life Science, India.*
Ofloxacin (p. 334·3); *Lactobacillus sporogenes* (p. 2596·3).

Aflox *Psyco Remedies, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

A-Flox M *Adventure Life Science, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Afloxan *Rottapharm, Hong Kong; Rotta, Philipp.; Rottapharm, Thai.*
Proglumetacin maleate (p. 127·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation.

A-Flox-OZ *Adventure Life Science, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Aflox-OZ *Psyco Remedies, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

AFlox-TZ *Psyco Remedies, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Afloyan
Note: this name may be used for preparations of different composition.
Alter, Spain.
Mirtazapine (p. 436·1).
Depression.

Aflubin *Bittner, Austria; Bittner, Hung.; Bittner, Rus.; Bittner, Ukr.*
Gentiana (p. 2512·1); aconitum (p. 2428·3); bryonia (p. 2461·3); ferrum phosphoricum (p. 2077·1); acidum sarcolacticum (p. 2539·1).
Homoeopathic preparation.

Afluditen *Biotika, Cz.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Afluhist *Duncan, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Afluhist Plus *Duncan, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); prednisolone sodium phosphate (p. 1645·3).
Rhinitis.

Aflukin C *IPS, Neth.†*
Quinine sulfate (p. 665·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Aflumicort *Cafar, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Aflumycin *Perrigo, Israel.*
⊗Prednisolone (p. 1645·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Aflunov *Novartis Vaccines, Cz.; Novartis Vaccines, Irl.; Novartis Vaccines, Neth.; Novartis Vaccines, Pol.; Novartis Vaccines, Port.*
An influenza vaccine (H5 N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Afluon *Meda, Gr.; Meda, Spain.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis; allergic conjunctivitis.

Afluria *CSL Biotherapies, Ger.; CSL Biotherapies, Neth.; CSL Biotherapies, Swed.; CSL Biotherapies, USA.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Aflusil *Loeffler, Mex.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Afobam *Anpharm, Pol.; Egis, Pol.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Afocid *Candor, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Afoklin *Roemmers-Klinos, Venez.*
Folic acid (p. 2063·1).
Antidote to folic acid antagonists; folic acid deficiency; prevention of neural tube defects in pregnancy.

Afol *Lincoln, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folic acid supplement; prevention of neural tube defects in pregnancy.

Afomix *Nufarindo, Indon.*
Folic acid (p. 2063·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); ginger (p. 1844·1); docosahexaenoic acid (p. 1460·1); amino acids.
Dietary supplement in pregnancy; vomiting in pregnancy.

Afon MD *Genesis, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Afongan *Lavipharm, Gr.; Galderma, Mex.†*
Omoconazole nitrate (p. 591·3).
Fungal infections of the skin and mucous membranes.

Afonilum *Abbott, Cz.; Abbott, Ger.†; Abbott, Pol.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Afonisan *Purissimus, Arg.*
Sulfadiazine (p. 361·3); allantoin (p. 1693·1).
Mouth and throat disorders.

Afopic *Teuto, Braz.*
Folic acid (p. 2063·1).

Aforbes *Merck, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Afordel *Merck, Philipp.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Aforglim *Merck, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Aforvir *Xeno, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

afpred-DEXA *Riemser, Ger.†*
⊗Dexamethasone sodium metasulfobenzoate (p. 1631·1).
Obstructive airways disease.

afpred-THEO *Riemser, Ger.†*
Theophylline (p. 1229·3).
Obstructive airways disease; cor pulmonale; neonatal apnoea.

Afra *Homme de Fer, Fr.†*
Senna (p. 1885·1); boldo (p. 2458·3); chamomile (p. 2474·1); fennel (p. 2503·2); cinnamon (p. 2479·2); achillea (p. 2427·3).
Constipation.

Afra-Z *Hos & Ins, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Afrazine *Schering-Plough, UK.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

A'Fresh *Arika, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Afresho *Zee, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Afrin
Note: this name may be used for preparations of different composition.
Mantecorp, Braz.; Schering-Plough, Canad.†; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Mex.†; MSD, Neth.; Schering-Plough, Pol.; MSD, Singapore; Schering-Plough, USA; Schering-Plough, Venez.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Ocular congestion; nasal congestion; middle ear infections; aid in intranasal examination; nasopharyngeal congestion.

Schering-Plough, USA.
Tablets: ⊗Pseudoephedrine sulfate (p. 1676·1).
Nasal congestion.

Afrin Extra Moisturizing *Schering-Plough, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Afrin Natural *Mantecorp, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Afrin Sinus *Schering-Plough, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Afrinex *Schering-Plough, Mex.†*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Nasal congestion.

Afrinex Infantil *Schering-Plough, Mex.†*
Aspirin (p. 22·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Nasal congestion; allergic rhinitis; pain; fever.

Afrixon *MJ Biopharm, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Afro *Casel, Turk.*
⊗Methyltestosterone (p. 2291·3).
Male hypogonadism; male infertility; cryptorchidism; mastalgia; breast cancer in women.

Afrodita *Duncan, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Afrodor
Note: this name may be used for preparations of different composition.
Iasis, Gr.
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Farco, Cz.†
Acecarbromal (p. 1035·1); quebracho (p. 2601·2); alpha tocopheril acetate.
Tonic.

Farco, Rus.†
Acecarbromal (p. 1035·1); quebracho (p. 2601·2); tocoferil acetate (p. 2119·2).
Tonic.

Afronis *Elanda, Pol.*
Boric acid (p. 2459·3); menthol (p. 2553·2); resorcinol (p. 1718·3); thymol (p. 1772·2).
Skin disorders.

Aftab *Rottapharm, Fin.; Madaus, Ger.; Rottapharm, Ger.; Rottapharm, Ital.*
⊗Triamcinolone acetonide (p. 1649·1).
Aphthous ulcer; stomatitis; gingivitis.

Aftach *Teijin, Hong Kong; Teijin, Jpn; Angelini, Port.*
⊗Triamcinolone acetonide (p. 1649·1).
Aphthous ulcer.

Aftagel *Cooperation Pharmaceutique, Fr.*
Lidocaine hydrochloride (p. 1988·2); zinc sulfate (p. 2126·2).
Inflammatory mouth disorders.

Aftagel Bucal *Medipharm, Chile.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1); dexpanthenol (p. 2582·2).
Mouth lesions and infections.

Aftaid *Isdin, Port.*
Amlexanox (p. 1202·2).
Aphthous ulcer.

Aftajuventus *Ern, Spain.*
⊗Benzalkonium chloride (p. 1737·1); hydrocortisone hydrogen succinate (p. 1640·2).
Stomatitis.

Aftamed *Pharmaniaga, Malaysia.*
Sodium hyaluronate (p. 2526·2).
Mouth ulcers.

Sunstar, Fr.
Hyaluronic acid (p. 2526·2).
Aphthous ulcers; oral lesions.

Aftasol *Meda, Fin.†*
Amlexanox (p. 1202·2).
Aphthous ulcers.

Aftasone *Vinas, Spain.*
⊗Hydrocortisone hydrogen succinate (p. 1640·2).
Mouth ulcers.

Aftasone B C *Vinas, Spain.†*
⊗Ascorbic acid (p. 2110·3); hydrocortisone hydrogen succinate (p. 1640·2); pyridoxine (p. 2105·3); riboflavin (p. 2104·3).
Mouth ulcers.

Aftate *Schering-Plough, USA.†*
Tolnaftate (p. 596·1).
Fungal skin infections.

Aftee DPS *Ind-Swift, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

After 10 *Step, Arg.*
Pregnancy test (p. 2596·1).

After Bite *Tender, Canad.†; Ardern, Irl.; Esteve, Spain; Meda, Switz.; Ardern, UK.*
Ammonia (p. 2441·2).
Insect bites; stings.

After Burn *Medimpex, Hung.*
Lidocaine hydrochloride (p. 1988·2); aloe vera (p. 1693·2).
Sunburn.

Tender, Israel.
Lidocaine (p. 1988·1).
Pain and minor skin irritation.

After Sport *Kinesys, Canad.*
Triclosan (p. 1773·2).

After Sun *Dermoteca, Port.*
Moisturiser.

Kinesys, Canad.
Lidocaine (p. 1988·1).

Afterbite *Tender, Israel.*
Ammonia (p. 2441·2).
Bites and stings.

Afterburn *Tender, Canad.*
Lidocaine hydrochloride (p. 1988·2).

Afterday *Trima, Israel.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Aftersun *Isdin, Arg.*
⊗Glycerol (p. 2517·2); aloe vera (p. 1693·2); centella (p. 1698·3); panthenol (p. 2582·2); levomenol (p. 2544·1); vitamin E (p. 2119·1).
Sunburn.

Aftil *Elmor, Venez.*
Salicylic acid (p. 1719·1); benzoin resin (p. 2624·3); cinnamon (p. 2479·2).
Aphthous ulcers; herpes labialis.

Aftine *Cifarma, Braz.*
Neomycin sulfate (p. 330·1); bismuth sodium tartrate (p. 1821·3); menthol (p. 2553·2); procaine hydrochloride (p. 1994·3).
Mouth and throat disorders.

Af-Tipa *Perrigo, Israel.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Af-Tiponet *Floris, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Aftir Gel *Biochimici, Ital.*
Malathion (p. 2157·2).
Pediculosis.

Aftir Shampoo *Rottapharm, Ital.*
Hydroxyquinoline sulfate (p. 2530·1).
Pediculosis; for use after Aftir Gel.

Aftogel *Orva, Turk.*
⊗Diclofenac sodium (p. 48·3); triamcinolone acetonide (p. 1649·1).

Aftosium *Ferrier, Fr.*
Borax (p. 2459·2); magnesia carbonica (p. 1856·2); mercurius cyanatus (p. 2555·3); sulfuricum acidum (p. 2624·2).
Homoeopathic preparation.

Afucid *Ferron, Indon.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Infected skin disorders.

Afugin *Sandoz, Pol.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Afumix *Senosiain, Mex.*
Fluconazole (p. 578·2); tinidazole (p. 949·2).
Vaginal infections.

Afungil *Senosiain, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Afunginal *ACME, Philipp.*
Nystatin (p. 590·3).
Oral candidiasis.

Afymox-CL *Sanify, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Afymox-Clav *Sanify, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Afymox-DT *Sanify, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).

Afzid *Alpha Aromatic, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Afzone *Admac, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Afzone-S *Admac, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Afzot *Pfizer, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Agacel *Teva Tuteur, Arg.*
Imatinib (p. 807·3).

Agaffin *Merck, Austria.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Against Cough *Marching, Hong Kong.†*
⊗Pentoxyverine (p. 1672·1); ephedrine (p. 1663·1); promethazine (p. 638·2).
Cough.

Agalates *Teva, Rus.*
Cabergoline (p. 899·3).
Lactation inhibition; hyperprolactinaemia; pituitary adenoma.

Agapurin *Zentiva, Cz.; Medphano, Ger.†; Zentiva, Pol.; Zentiva, Rus.; Slovakofarma, Thai.†; Roemmers, Venez.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular disorders of the eye and ear.

Agaricus comp Phosphorus *Weleda, Ger.*
Agaricus; argentum metallicum (p. 2615·1); aspidium filix-mas (p. 158·3); conchae (p. 1824·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Agarol
Note: this name may be used for preparations of different composition.
Elea, Arg.; Johnson & Johnson, Braz.
Liquid paraffin (p. 2191·2); sodium picosulfate (p. 1887·2); agar (p. 2167·2).
Constipation; bowel evacuation.

Interbelle, Arg.
Chewing gum; gelcaps: Sodium picosulfate (p. 1887·2).
Constipation.

Johnson & Johnson, Austral.; Pfizer, India; Pfizer, Thai.†
Liquid paraffin (p. 2191·2).
Constipation.

Johnson & Johnson, Chile.
Sodium picosulfate (p. 1887·2); liquid paraffin (p. 2191·2).
Constipation; bowel evacuation.

Pfizer, Chile.†
⊗Liquid paraffin (p. 2191·2); phenolphthalein (p. 1877·3); agar (p. 2167·2); glycerol (p. 2517·2).
Constipation.

Agarol Extra *Numark, Canad.†*
Senna (p. 1885·1).
Constipation.

Agarol Plain *Johnson & Johnson, Gr.*
Liquid paraffin (p. 2191·2).
Constipation.

Numark, Canad.
⊗Liquid paraffin (p. 2191·2); glycerol (p. 2517·2).
Constipation.

Agarol with Sennosides *Numark, Canad.†*
Senna (p. 1885·1).
Constipation.

Agarol Soft *Janssen-Cilag, Switz.†*
Fig (p. 1843·2); sorbitol (p. 2092·1).
Constipation.

Agasten *Novartis, Braz.*
Clemastine fumarate (p. 622·3).
Hypersensitivity.

Agastin *Temapharm, Pol.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Agathol *D&A Pharma, Fr.*
Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); peru balsam (p. 2587·1).
Burns.

AGB *Cassara, Arg.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Agcomen *Alkem, Philipp.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Age Fitness *Biotherm, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Age Shield *Johnson & Johnson, Canad.*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Agein *Fourrts, India.*
Benfotiamine (p. 2102·3); pyridoxal phosphate (p. 2105·3).
Neuropathy.

A-Gel
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Austral.
Lubricant gel.

Agelan *Antigen, Irl.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Agelmin *Kleva, Gr.; Kleva, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria.

Agen
Note: this name may be used for preparations of different composition.
Embil, Turk.
Polysaccharide polysulfuric acid ester; nonoxinol (p. 2199·1).
Contraceptive.

Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

A-gen 53
Note: this name may be used for preparations of different composition.
Riemser, Austria.†
Polysaccharide polysulfuric acid ester.
Contraceptive.

Riemser, Ger.†
Cellulose poly(sulfuric acid ester), trisodium salt; nonoxinol 9 (p. 2199·1).
Contraceptive.

Agenerase *GSK, Arg.; GSK, Austral.; GSK, Austriat; GSK, Braz.; GSK, Chile†; GSK, Cz.†; GSK, Fin.†; GSK, Ger.†; GSK, Gr.; IFET, Gr.; GSK, Irl.†; GSK, Israel; GSK, Mex.†; GSK, Neth.†; GSK, NZ; GSK, Pol.†; GSK, Port.†; GSK, Rus.; GSK, Spain†; GSK, Switz.†; GSK, Turk.†; GSK, Venez.*
Amprenavir (p. 967·3).
HIV infection.

Agentam *Sinochem, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Agepin *Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Agerdex *Gerard, Irl.*
⊗Anastrozole (p. 742·1).
Breast cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ageroplas *Angelini, Spain.†*
Ditazole (p. 1365·3).
Thromboembolism prophylaxis.

Agglad *Sophia, Mex.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Agglad Ofteno *Volta, Chile; Elmor, Venez.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Aggovask *Proton, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Aggramed *Zydus, India.*
Tirofiban (p. 1515·1).
Acute coronary syndrome.

Aggrastat *Aspen, Austral.; Iroko, Austria; Iroko, Belg.; Iroko, Canad.; NovaMed, China; Orion, China; MSD, Cz.†; Orion, Fin.; Iroko, Ger.; Vianex (Βιανεξ), Gr.; Iroko, Hung.; MSD, India; MSD, Irl.; Baxter, Israel; MSD, Ital.; MSD, Malaysia†; Iroko, Neth.; Iroko, Norw.†; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; Aspen, Singapore; Orion, Swed.; Orion, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Medicure, USA.*
Tirofiban hydrochloride (p. 1515·1).
Myocardial infarction; unstable angina; prevention of ischaemic cardiac complications during percutaneous coronary intervention.

Aggrastet *MSD, S.Afr.*
Tirofiban hydrochloride (p. 1515·1).
Prevention of cardiac ischaemia in percutaneous coronary intervention; myocardial infarction; unstable angina.

Aggravan *Ferron, Indon.; Dexa, Philipp.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders; arterial occlusion; intermittent claudication.

Aggrenox *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Cz.; Paranova, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Rafa, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, USA.*
Dipyridamole (p. 1362·2); aspirin (p. 22·2).
Thromboembolic disorders; cerebral ischaemia; transient ischaemic attacks; stroke prophylaxis.

Aggribloc *Nicholas Piramal, India.*
Tirofiban hydrochloride (p. 1515·1).
Unstable angina; myocardial infarction.

Aggritor *Torrent, India.*
Tirofiban (p. 1515·1).
Acute coronary syndrome.

Aggs *Bharat, India.*
A gas-gangrene antitoxin (p. 2387·1).

Agilam *Elmor, Venez.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Agilan *Astellas, Austria.*
⊗Dihydroergotamine mesilate (p. 672·2); etilefrine hydrochloride (p. 1379·1).
Hypotension.

Agile *Ind-Swift, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Ind-Swift, India.
Tablets: Paracetamol (p. 115·1); diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Ind-Swift, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3).

Agile-K *Ind-Swift, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Agile-MR *Ind-Swift, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Agile-S *Ind-Swift, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Agilev *Konpharma, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Agilex *Mertens, Arg.*
Indometacin (p. 71·2).
Fever; inflammation; pain.

Agilisin *Sankyo, Braz.*
Indometacin (p. 71·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Agin *Nordin, Mex.*
Aspirin (p. 22·2); sulfadiazine (p. 361·3).

Aginax *CAG, Fr.*
Soap substitute.
Anogenital hygiene.

Seventy BG, Ital.
Barrier preparation.

Agiobita *SJA, Gr.*
Dihydroergocristine (p. 390·1).
Peripheral vascular disorders.

Agiobulk *Nycomed, S.Afr.*
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome; diverticulitis.

Agiocur *Madaus, Austria; Madaus, Fin.; Madaus, Ger.; Rottapharm, Ger.; Madaus, Hong Kong; Madaus, Israel; Madaus, Port.; Madaus, Thai.*
Ispaghula (p. 1849·1).
Constipation; stool softener; inflammatory bowel disease; diarrhoea; irritable bowel disease; colostomy management; diverticular disease; regulation of faecal consistency.

Agiofibe *Flordis, Austral.; Zuoz, Venez.*
Ispaghula (p. 1849·1).
Dietary fibre supplement; constipation.

Agiofibra *Nycomed, Braz.; Nycomed, Mex.; Neo-Farmaceutica, Port.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; dietary fibre supplement.

Agiofibras *Phoenix, Arg.*
Ispaghula (p. 1849·1).
Constipation; inflammatory bowel disease; irritable bowel syndrome; hypercholesterolaemia.

Agiofibre *Madaus, Ital.*
Ispaghula (p. 1849·1).
Dietary fibre supplement.

Agiolax *Phoenix, Arg.; Flordis, Austral.; Madaus, Austria; Madaus, Belg.; Nycomed, Braz.; Madaus, China; Madaus, Cz.†; Madaus, Fin.; Madaus, Fr.; Madaus, Ger.; Rottapharm, Ger.; Remek, Gr.; Rottapharm, Gr.; Madaus, Hong Kong; Madaus, Hung.; Madaus, Irl.; Madaus, Israel; Rottapharm, Ital.; Madaus, Malaysia; Nycomed, Mex.; Madaus, Neth.; Madaus, Norw.†; Madaus, Pol.; Neo-Farmaceutica, Port.; Nycomed, S.Afr.; Rottapharm, Spain; Meda, Swed.†; Madaus, Switz.; Madaus, Thai.; Zuoz, Venez.*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation; stool softener; bowel evacuation; irritable bowel.

Agiolax mite *Madaus, Switz.*
Ispaghula (p. 1849·1).
Constipation; stool softener; irritable bowel syndrome.

Agiolax Pico *Madaus, Cz.†; Madaus, Ger.; Rottapharm, Ger.; Madaus, Irl.†; Madaus, Ukr.†*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Agiopic *Madaus, Austria.†*
Sodium picosulfate (p. 1887·2).
Bowel evacuation; constipation.

Agioslim *Madaus, Ital.*
Ispaghula (p. 1849·1); glucomannan (p. 2515·2).
Slimming aid.

Agioten *Biomedica, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Agirax *Montpellier, Arg.*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo; Ménière's disease; vestibular disorders.

Agiserc *Perrigo, Israel.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Agispor *Perrigo, Israel.*
Bifonazole (p. 573·3).
Fungal skin infections; seborrhoeic dermatitis.

Agispor Onychoset *Perrigo, Israel.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Agistam *Stirol, Ukr.†*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin reactions.

Agisten *Perrigo, Israel.*
Clotrimazole (p. 576·2).
Fungal skin infections; vaginal infections.

Agisten 1 *Perrigo, Israel.*
Clotrimazole (p. 576·2); lactic acid (p. 2539·1).
Vaginal infections.

Agisten with Aloe Vera *Perrigo, Israel.*
Clotrimazole (p. 576·2); aloe vera (p. 1693·2).
Fungal skin infections.

Agit *Sanol, Ger.†*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; migraine and other vascular headaches; varices.

Aglan *Zentiva, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Aglandin *Lannacher, Austria.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Aglio *Veresne, Arg.†*
Garlic (p. 2510·3); acetic acid (p. 2426·3).
Pediculosis.

Aglitil *Sigma, Braz.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Aglocet *Aglowmed, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Aglocid *Aglowmed, India.*
Oral gel: Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Aglowmed, India.
Tablets: Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); aluminium magnesium silicate (p. 2168·2).

Aglocon *Aglowmed, India.*
Fluconazole (p. 578·2).
Fungal infections.

Aglodepin *Aglowmed, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Aglodepin-AT *Aglowmed, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Aglodine *Aglowmed, India.*
Povidone-iodine (p. 1767·1).

Aglodom *Aglowmed, India.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Aglofit *Aglowmed, India.*
Preparation for enteral nutrition.
Dietary supplement.

Agloliv *Aglowmed, India.*
Capsules: Andrographis (p. 2443·2); celery (p. 2472·3).

Aglowmed, India.
Syrup: Andrographis (p. 2443·2); punarnava (p. 2601·1); rhubarb (p. 1884·2).

Aglomycetin *Aglowmed, India.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Aglon *Keshav, India.*
Vitamins; ferrous fumarate (p. 2060·3).

Aglonim *Aglowmed, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Aglopam *Aglowmed, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Agloscab *Aglowmed, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).

Agloten *Aglowmed, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Agloton *Aglowmed, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).

Aglotus *Aglowmed, India.*
Malabar nut (p. 2549·1); ammonium chloride (p. 1656·1); turmeric (p. 2218·1); ocimum sanctum; black pepper (p. 2586·1); spearmint oil (p. 2621·2); ginger (p. 1844·1).

Aglozyme *Aglowmed, India.*
Capsules; oral liquid: ⊗Pepsin (p. 2586·1); amylase (p. 2442·1).

Aglowmed, India.
Oral drops: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1); nicotinamide (p. 2083·1); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_2 (p. 2104·3).

Aglucide *Beta, Arg.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Aglucil *Elofar, Braz.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Aglucose *Sigma, Braz.*
Acarbose (p. 466·2).
Diabetes mellitus.

Aglumet *Probiomed, Mex.*
Metformin (p. 489·1).
Diabetes mellitus.

Aglutin *Target, Gr.*
Amphotericin B (p. 569·2).
Fungal infections.

Agnicin *Parggon, Mex.*
Amikacin (p. 214·1).
Bacterial infections.

Agnofem *Madaus, Austria.*
⊗Agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Agnolyt *Madaus, Ger.; Rottapharm, Ger.*
⊗Vitex agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Agnu Gyne *Medikon, Indon.†*
⊗Agnus castus (p. 2432·2).
Menstrual disorders; mastalgia; female infertility.

Agnucaston *Sanova, Austria; Bionorica, Cz.; Bionorica, Ger.; Bionorica, Hung.; Bionorica, Indon.†; Darya-Varia, Indon.†; Bionorica, Rus.; Biomeks, Turk.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders; mastalgia; female infertility.

Agnukliman *Gebro, Austria.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Agnumens *Gebro, Austria.†*
⊗Agnus castus (p. 2432·2).
Menstrual disorders; premenstrual syndrome.

Agnurell *Sanorell, Ger.*
⊗Vitex agnus castus (p. 2432·2).
Homoeopathic preparation.

Agnus *Sanol, Ger.; UCB, Ger.*
⊗Agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Agnus castus comp *Hevert, Ger.†*
⊗Acid. oxalicum (p. 2578·2); agnus castus (p. 2432·2); cimicifuga (p. 2478·1); hamamelis (p. 2523·3); pulsatilla (p. 2600·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Agnus Castus Complexe No 2 *Lehning, Fr.†*
⊗Agnus castus (p. 2432·2); glonoinum (p. 1391·2); phytolacca; spongia tosta; apis mellifica (p. 2445·2); anemone pulsatilla (p. 2600·2); mercurius corrosivus (p. 2555·2); atropa belladonna (p. 2453·3); arsenicum album (p. 2448·1); juglans (p. 2463·2).
Homoeopathic preparation.

Agnus femin *Hevert, Ger.*
⊗Agnus castus (p. 2432·2); cimicifuga (p. 2478·1); pulsatilla (p. 2600·2); zincum val. (p. 2641·2).
Homoeopathic preparation.

Agobilina *Biol, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Agofell *Janssen-Cilag, S.Afr.†*
Diisopromine hydrochloride (p. 1835·3); sorbitol (p. 2092·1).
Biliary-tract disorders.

Agofollin *Biotika, Cz.*
Estradiol benzoate (p. 2271·1) or estradiol dipropionate (p. 2271·2).
Menopausal disorders; menstrual disorders.

Agolutin *Biotika, Cz.*
Progesterone (p. 2300·2).
Menstrual disorders.

Agopton *Takeda, Austria; Takeda, Ger.; Takeda, Switz.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Agoral *Warner-Lambert, USA.*
Liquid paraffin (p. 2191·2); phenolphthalein (p. 1877·3); agar (p. 2167·2).
Constipation.

Agovirin *Biotika, Cz.*
⊗Testosterone isobutyrate (p. 2305·1).
Male hypogonadism; osteoporosis; aplastic anaemia.

Agpen *Emcure, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

A/G-Pro *Miller, USA.*
Vitamins; minerals; amino acids.

Agrastat *MSD, Arg.; Aspen, Braz.; MSD, Chile; MSD-Chibret, Fr.; MSD, Mex.; Iroko, Spain; MSD, Venez.*
Tirofiban hydrochloride (p. 1515·1).
Myocardial infarction; prevention of ischaemic cardiac complications during angioplasty or atherectomy; unstable angina.

Agreal *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile.†*
Veralipride (p. 1114·2).
Menopausal disorders.

Agre-Calvit *Solvay, Philipp.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement.

Agregal *Nizhpharm, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Myocardial infarction; stroke; peripheral arterial disease; unstable angina.

Agregex *Actavis, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Agre-Gola *Vemedia, Neth.†*
Cetylpyridinium chloride (p. 1743·1); phenol (p. 1763·3); menthol (p. 2553·2).
Sore throat.

Agrelan *Alacan, Spain.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Agrelex *Galex, Cz.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Agrelid *Ariston, Arg.*
Anagrelide hydrochloride (p. 2442·2).
Thrombocythaemia.

Agremol *Eurodrug, Thai.*
Dipyridamole (p. 1362·2).
Ischaemic heart disease; thromboembolism prophylaxis; angina pectoris.

Agrenox *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Ukr.*
Dipyridamole (p. 1362·2); aspirin (p. 22·2).
Cerebrovascular ischaemia; stroke prophylaxis.

Agreplat *Sanitas, Chile.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Agretik *Sandoz, Turk.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Agrezol *Meprofarm, Indon.†*
Cilostazol (p. 1337·1).
Arterial occlusion; intermittent claudication.

Agrifen *Pisa, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; fever.

Agrifen T *Pisa, Mex.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Agriflu *Novartis, Canad.; Novartis, USA.†*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Agrilin *Volta, Chile.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Agrip *Plata, Arg.*
Paracetamol (p. 115·1); bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Agripan *Temis, Arg.*
Oseltamivir (p. 1006·2).

Agrippal *Novartis, Arg.; Novartis, Belg.†; Novartis, Braz.†; Novartis, China; Novartis, Denm.; Novartis Vaccines, Fin.; Novartis Vaccines, Fr.; Novartis Vaccines, Gr.; Novartis Vaccines, Hong Kong; Novartis Vaccines, Hung.; Combiphar, Indon.; Novartis Vaccines, Indon.; Novartis, Irl.; Novartis, Israel; Novartis Vaccines, Ital.; Novartis, Malaysia; Ivax, Mex.†; Novartis Vaccines, Neth.; Novartis, Philipp.; Novartis, Rus.; Biovac, S.Afr.; Novartis Vaccines, Singapore; Novartis, Switz.; Novartis Vaccines, Thai.; Berk, Turk.†; Wyeth, UK.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Agrippin *Bernofarm, Indon.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold symptoms.

Agrisen *Alpharma, Mex.†*
Ranitidine (p. 1882·1).
Peptic ulcer.

Agroflox *Argon, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Agrophyllin *Argon, India.*
Etofylline (p. 1208·2); theophylline (p. 1229·3).
Bronchospasm.

Agrulex *Pisa, Mex.†*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; constipation.

Agrus *Profic Organic, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine (p. 1672·2).

Agrus-NS *Profic Organic, India.*
Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine (p. 1672·2).

Agruvit *Sanofi-Aventis, Ital.*
Ascorbic acid (p. 2110·3); calcium ascorbate (p. 2111·1).
Vitamin C deficiency; vitamin C supplement.

Agrylin *Orphan, Austral.; Shire, Canad.; IFET (ΙΦΕΤ), Gr.†; Shire, Hong Kong; Fahrenheit, Indon.; Medison, Israel; Shire, Philipp.; Tema, S.Afr.; IDS, Singapore†; Shire, Thai.; Shire, USA.*
Anagrelide hydrochloride (p. 2442·2).
Essential thrombocythaemia.

Agsulfa *Charoon Bhesaj, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections; paracoccidioidomycosis; mycetoma.

Agua del Carmen *Fardi, Spain.*
Coriander seeds (p. 2486·3); matricaria (p. 2474·1); melissa (p. 2552·3); tilia (p. 2631·3); lemon verbena (p. 2543·2); cinnamon (p. 2479·2); angelica (p. 2443·3); nutmeg (p. 2573·1); hyssop (p. 2530·3).
Nervous disorders; menstrual disorders.

Pasteur, Chile.
Melissa oil (p. 2553·2); lemon oil (p. 2543·1); rosemary oil (p. 2607·3); peppermint oil (p. 1877·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3).
Insomnia; nervous disorders.

Agua D'Alibour *Zasu, Arg.*
Copper (p. 2057·1); zinc (p. 2126·1).

Água Inglesa *Catarinense, Braz.†*
Broom; cinchona (p. 2478·3); pear.
Reduced appetite.

Agua Melisa Carminativa *Sanitas, Chile.*
Melissa oil (p. 2553·2); lemon oil (p. 2543·1); clove oil (p. 2481·3); nutmeg oil (p. 2573·2); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); neroli oil (p. 2568·3); cinnamon oil (p. 2479·3).
Anxiety; dyspepsia; excess gastrointestinal gas.

Agua Sulfatada Picrica *Valma, Chile.†*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); camphorated alcohol; trinitrophenol (p. 2634·2).

Aguala *Royal, Chile.*
Sodium picosulfate (p. 1887·2).
Bowel evacuation; constipation.

Agucort *LKM, Arg.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Aguder *Royal, Chile.*
Tazarotene (p. 1724·2).
Psoriasis; acne.

Agudil *Sigma-Tau, Spain.†*
Glutamine (p. 2070·3); asparagine (p. 2050·3); pyridoxine hydrochloride (p. 2105·3); phosphoserine (p. 2589·1).
Tonic.

Agufam *ST, Thai.†*
Famotidine (p. 1842·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Agufem *Biofarm, Pol.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Aguipental *Solfran, Mex.*
Benzylpenicillin (p. 228·1); streptomycin (p. 359·1).

Agulan *Darya-Varia, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Agurin
Note: this name may be used for preparations of different composition.
Nolver, Venez.
Paracetamol (p. 115·1).
Fever; pain.

AG-X *Karnataka, India.*
Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).

Agyrax *Pierre Fabre Sante, Belg.; UCB, Fr.*
Meclozine hydrochloride (p. 634·3).
Vertigo; nausea; vomiting; motion sickness.

AH-1 *Obsurge, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

AH 3 N *UCB, Ger.*
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; urticaria.

AHb-15 *Bestochem, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1).
Anaemias.

AH-chew *Dexo, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract symptoms.

AH-chew D *WE, USA.*
Phenylephrine hydrochloride (p. 1672·3) or phenylephrine tannate (p. 1672·2).
Nasal congestion.

AHD 2000 *Lysoform, Ger.; Sonix, Philipp.†*
⊗Alcohol (p. 1733·1).
Hand disinfection; skin disinfection.

AHF *CSL, NZ.†*
A factor VIII preparation (p. 1148·1).
Factor VIII deficiency.

Ahist *Magna, USA.*
Chlorcyclizine hydrochloride (p. 620·2).
Upper respiratory-tract allergies.

Ahiston *Teva, Israel.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions; rhinitis; allergic conjunctivitis; urticaria; angioedema.

Ahiston Compound *Teva, Israel.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Hypersensitivity reactions.

Ahora Test *Step, Arg.*
Pregnancy test (p. 2596·1).

AHP 200 *Rosen, Ger.*
Oxaceprol (p. 2578·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

A-Hydrocort *Hospira, USA.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Ai Di *Huang Long, China.*
Metronidazole benzoate (p. 936·1).

Ai Bang *Lukang Chenxin, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

Ai Bei *Qilu, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Ai Bei Qing *Kang Yuan, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ai Ben *HeBei, China.*
Ibandronate sodium (p. 1184·2).
Hypercalcaemia of malignancy; bone metastases; osteoporosis.

Ai Bo Ding *Hisun, China.*
Cladribine (p. 769·1).
Hairy-cell leukaemia; chronic lymphocytic leukaemia; chronic myeloid leukaemia.

Ai Da *Yangtze River, China.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Ai Da Sheng *Hisun, China.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Ai Duo *Guang Da, China.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Ai Di Er *FangDa, China.*
Povidone-iodine (p. 1767·1).

Ai Er Bei *Xi Cheng, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ai Er Jia *KeLun, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Ai Er Xin *Sine, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ai Er Xing *Shi Dai, China.*
Paracetamol (p. 115·1).
Fever; pain.

Ai Fei Le *Xinhua, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Ai Fen
Note: this name may be used for preparations of different composition.
Jin Si Li, China.
Injection: Etamsylate (p. 1145·2).

Ji Bei Er, China.†
Enteric-coated tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ai Feng *Hengrui, China.*
Doxifluridine (p. 782·3).

Ai Fu Bi *Jincheng Haisi, China.*
Ammonium glycyrrhizate (p. 2520·3).

Ai Fu Ding *Wuhan Wujing, China.*
Stavudine (p. 1015·3).
HIV infection.

Ai Fu Ji Fu *WanXing, China.*
Recombinant human acidic fibroblast growth factor.

Ai Ge *HuangLong, China.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; renal failure.

Ai Hao *NEGPF, China.*
Indinavir sulfate (p. 986·1).
HIV infection.

Ai He Fu *Sanjing Aifuxi, China.*
Ligustrazine phosphate.

Ai Heng *Hengrui, China.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Ai Hong *San Ai, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Ai Ji *Huahai, China.*
Nevirapine (p. 1005·1).
HIV infection.

Ai Jia *Shuai Ke, China.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1).

Ai Jia Xin *A La Bin Du Tong Ling, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Ai Jia Xing *Yi Kang, China.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Ai Jian *Neptunus, China.*
Zidovudine (p. 1024·2).
HIV infection.

Ai Jie Kang *Hua Lu, China.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; folate-deficient megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Ai Kai Ping *Healthcare Pharma, China.*
⊗Guaifenesin (p. 1666·2); methylephedrine hydrochloride (p. 1669·2); chlorphenamine maleate (p. 620·3).
Cough.

Ai Ke An *Ou Yi, China.*
Ramosetron hydrochloride (p. 1881·3).

Ai Ke Bao *Si Huan, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Ai Ke Bo Kang *Neptunus, China.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ai Ke Ning *Pude, China.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; cervical cancer; breast cancer; ovarian cancer.

Ai Ke Ting *Jin Yuan, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; pathological gastric hypersecretory disorders; acid aspiration.

Ai Ke Wei *Li Jie Xun, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological gastric hypersecretory disorders; acid aspiration; dyspepsia.

Ai Ke Xin *Shenyang First, China.*
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

Ai Ke Zhi *Li Jie Xun, China.*
Ethylenediamine diaceturate.

Ai Lang *Hengrui, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Ai Li *Hengrui, China.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Ai Li Da *Ruiying, China.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Ai Li Ke *Sanjing, China.*
Norfloxacin (p. 333·3).
Bacterial skin infections.

Ai Li Su *Shouhe Jinhai, China.*
Aceglutamide (p. 2426·2).

Ai Li Ya *Lv Yin, China.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Ai Lin Tai *Sanjing Aifuxi, China.*
Oxymatrine.

Ai Lin Wei *Jiu An, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Ai Lu Na *Shi Xin, China.*
Aceglutamide (p. 2426·2).

Ai Lue *Huahai, China.*
Didanosine (p. 972·3).
HIV infection.

Ai Luo Di *Gai Pu, China.*
Ampicillin (p. 218·2).
Probenecid (p. 607·3) is included in this preparation to reduce renal tubular excretion of ampicillin.
Bacterial infections.

Ai Luo *Qilu, China.*
⊗Esmolol hydrochloride (p. 1377·3).
Tachycardia; hypertension.

Ai Luo Xin *Hua Shen, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ai Lv Shuang *Shyndec, China.*
Nonoxinol (p. 2199·1).
Vaginal contraceptive.

Ai Mai Shu *Changzheng, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ai Mei Xing *Changzheng-Xinkai, China.*
Glucosamine hydrochloride (p. 2515·3); indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Ai Mi Qi *Mei Luo, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ai Mi Si *Hua Lu, China.*
Ethylenediamine diaceturate.

Ai Mi Te *JinYao, China.*
Amino acids.
Parenteral nutrition.

Ai Mu *Kang Yuan, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ai Na Duo *Otsuka, China.*
Sodium chloride (p. 1795·1).
Dry eyes.

Ai Nao Xing *Changzheng-Xinkai, China.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment.

Ai Neng *Hengrui, China.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Ai Ni *Ya Bao, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ai Ni Ya *Yong An, China.*
Povidone-iodine (p. 1767·1).

Ai Nuo Ji *Bei Da Gao Ke Hua Tai, China.*
Adenosine triphosphate, disodium (p. 2430·3); magnesium chloride (p. 1787·1).

Ai Nuo Ke *De Tian, China.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; cachexia associated with AIDS or cancer.

Ai Nuo Ning *Hisun, China.*
Idarubicin hydrochloride (p. 805·2).
Breast cancer; acute leukaemias.

Ai Nuo Tian Jian *Hencer, China.*
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene; mouth infections.

Ai Ping *Johnson & Johnson, China.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Ai Pu Kang *Dikang, China.*
Boanmycin hydrochloride.

Ai Pu Sheng *Tian Yuan, China.*
A Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Ai Di Qing *Hayao, China.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Ai Qing *Johnson & Johnson, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Ai Ru Xi *Tian Yu, China.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; folate-deficient megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Ai Rui De An *Wei Lun, China.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Ai Sen *Dinghengsheng, China.*
Paracetamol (p. 115·1).
Fever; pain.

Ai Sen Ao *Meng Sheng, China.*
Aceglutamide (p. 2426·2).

Ai Shi Lie *Conba, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Ai Si Jie *Da Zhong, China.*
Isotretinoin (p. 1706·2).
Acne.

Ai Si Mo *BSPC, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ai Si Ti Er *Jiu Tai, China.*
Ethylenediamine diaceturate.

Ai Su *Hengrui, China.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Ai Tai *Huahai, China.*
Nevirapine (p. 1005·1).
HIV infection.

Ai Le Ting *Qilu, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; ischaemic heart disease.

Ai Tong *HeBei, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ai Tuo *Hengrui, China.*
Topotecan hydrochloride (p. 872·3).
Malignant neoplasms.

Ai Wei Ning *Bang Yu, China.*
Nevirapine (p. 1005·1).
HIV infection.

Ai Wen *Guang Da, China.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Ai Xi *Yi Hua, China.*
Bismuth salicylate (p. 1821·3).
Diarrhoea.

Ai Xin *Guo Yao, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ai De Xin *Livzon, China.*
Vindesine sulfate (p. 884·2).
Malignant neoplasms.

Ai Xin Bao *Ba Da, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Ai Xin Mo Er *Hengrui, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ai Xin Wei *Wei Men, China.*
Lysine hydrochloride (p. 2079·3).

Ai Xin Yi Le *GuoRui, China.*
Pemirolast potassium (p. 1218·2).
Asthma; allergic rhinitis.

Ai Xing *Aike, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Ai Xing Dan *San Ai, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders; cerebral trauma.

Ai Yi *Aike, China.*
Etimicin sulfate (p. 298·2).
Bacterial infections.

Ai Zhu Kang *Wansheng, China.*
Sodium demethylcantharidate.

Aibrex *Allergan, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Aicadryl *Marching, Hong Kong.†*
Calamine (p. 1697·2); camphor (p. 2466·2); diphenhydramine (p. 626·1); menthol (p. 2553·2); zinc oxide (p. 1729·1).

Aida
Note: this name may be used for preparations of different composition.
Aida, China.
Etimicin sulfate (p. 298·2).
Bacterial infections.

Jenapharm, Ger.
Ethinylestradiol betadex clathrate (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Aidex *Ovelle, Irl.†*
Aminoacridine hydrochloride (p. 1732·3); benzocaine (p. 1980·2); phenoxyethanol (p. 1764·3).
Wounds; scalds.

Aidia *Biomedica, India.*
Lactobacillus (p. 2596·3); racecadotril (p. 1881·3).
Diarrhoea.

Aidite *Xinhua, China.*
Etofesalamide.
Neurodermatitis; eczema.

Aidol *Iasis, Gr.*
Mefenamic acid (p. 85·3).
Pain; inflammation; musculoskeletal and joint disorders.

AiFen *Ji Bei Er, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Aifude *KeRui, China.*
Prulifloxacin (p. 345·1).
Bacterial infections.

AiKe *Nhwa, China.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; cachexia associated with AIDS or cancer.

Aikeer *Xincat, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ailax *Galen, Irl.†*
Dantron (p. 1833·3); poloxamer 188 (p. 2202·1).
Constipation.

Ailgeno spag *Pekana, Neth.*
Agaricus muscarius; arsenicum album (p. 2448·1); carduus marianus (p. 1561·1); ceanothus americanus; china officinalis (p. 2478·3); glechoma hederacea (p. 2523·1); grindelia robusta (p. 2522·3); natrium muriaticum (p. 1795·1).
Homoeopathic preparation.

AiLiKe
Note: this name may be used for preparations of different composition.
Yong An, China.
Topical solution: Povidone-iodine (p. 1767·1).

Ailike
Note: this name may be used for preparations of different composition.
Liang Fu, China.
Tablets: Tretinoin (p. 1725·2).
Acne.

Ailuwei *Changzheng-Xinkai, China.*
Adefovir dipivoxil (p. 967·1).
Hepatitis B.

Ailyn *Bial, Spain.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ailzid *Candor, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Aimafix *Kedrion, Arg.; Biosano, Chile; Kedrion, Ital.; Kedrion, Port.; Kedrion, Rus.; Kedrion, Thai.; Onko, Turk.*
Factor IX (p. 1149·3).
Haemorrhagic disorders; haemophilia B.

Aimix *Dainippon, Jpn.*
Irbesartan (p. 1411·1); amlodipine besilate (p. 1304·1).
Hypertension.

Aimpart *Zentiva, UK.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Ainedif *Penn, Arg.*
Diclofenac (p. 48·3).
Inflammation.

Ainelac *Hexal, Mex.†*
Ketorolac trometamol (p. 80·2).
Pain.

Ainex
Note: this name may be used for preparations of different composition.
Schering-Plough, Chile†; Schering-Plough, Venez.
Nimesulide (p. 101·3).
Fever; pain; musculoskeletal and joint disorders; inflammation.

Sandoz, Mex.†
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Aiphagan *Senju, Jpn.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Air Bus *Sanify, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Air Salonpas
Note: this name may be used for preparations of different composition.
Vianex (Βιανεξ), Gr.; Veximp, Hung.
Benzyl nicotinate (p. 29·3); camphor (p. 2466·2); glycol salicylate (p. 66·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue injury.

DKSH, Hong Kong.†
Camphor (p. 2466·2); glycol salicylate (p. 66·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Hisamitsu, USA.†
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Airacof *Centurion, USA.*
Codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Airapy *Linde Gas, Belg.; AGA, Denm.; AGA, Fin.; Linde Gas, Neth.*
Oxygen (p. 1799·3); nitrogen (p. 1799·3).
Hypoxia.

Airathon *MSD, Fin.; MSD, Neth.; MSD, Pol.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Airbeclosona *Northia, Arg.†*
⊗Beclometasone (p. 1621·2).
Asthma.

Airborne Immunity *Bioglan, Austral.*
Garlic (p. 2510·3); ginger (p. 1844·1); echinacea (p. 2498·1); cayenne pepper (p. 2469·3); olive leaf (p. 2574·3); withania; citrus bioflavonoids (p. 2505·2); vitamins; minerals.
Common cold.

Airbude *Northia, Arg.†*
⊗Budesonide (p. 1625·1).

Airclin *Ache, Braz.*
⊗Triamcinolone acetonide (p. 1649·1).
Nasal disorders.

Aircort *Italchimici, Ital.*
⊗Budesonide (p. 1625·1).
Asthma; croup; nasal polyps; rhinitis.

Aircosalm *Atlas, Arg.*
⊗Salbutamol (p. 1220·2).

Aires *Euroforma, Braz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Airex *Medhaus, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Airfen *Cofasa, Venez.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Airitis *Piramal, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Airitis Plus *Piramal, India.*
Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3).

Airlast *Bioforma, Turk.*
Montelukast sodium (p. 1214·3).

Airol *Pierre Fabre Dermatologie, Cz.†; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Roche, Gr.; Piramal, India; Pierre Fabre, Israel†; Pierre Fabre, Ital.; Pierre Fabre, Philipp.†; Pharmaco, S.Afr.; Pierre Fabre, Switz.*
Tretinoin (p. 1725·2).
Acne; hyperpigmentation; photodamaged skin.

Airomet *Masa, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Airomir *iNova, Austral.; UCB, Belg.; Graceway, Canad.; Teva, Denm.; Teva, Fin.; Teva, Fr.; Norton Waterford, Irl.†; 3M, Malaysia†; Teva, Neth.; 3M, NZ; iNova, Philipp.; AMPDR, Port.; Teva, Swed.; Ivax, UK.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

3M, Chile†; Teva, Norw.; 3M, S.Afr.†
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Airomol *Zydus, India.*
⊗Choline theophyllinate (p. 1207·1); salbutamol (p. 1220·2).
Obstructive airways disease.

Airon *Oftalmi, Venez.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Airrox *Millimed, Thai.†*
Simeticone (p. 1886·2).
Aid to gastroscopy and X-ray examination; excess gastrointestinal gas.

Airsalbu *Northia, Arg.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Airtab *Millimed, Thai.†*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; peptic ulcer; gastritis; heartburn.

Air-Tal *Almirall, Belg.*
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Airtal *Almirall, Ital.; Almirall, Port.; Gedeon Richter, Rus.; Almirall, Spain; Gedeon Richter, Ukr.*
Aceclofenac (p. 16·2).
Gout; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Airtal Difucrem *Almirall, Spain.*
Aceclofenac (p. 16·2).
Peri-articular and soft-tissue disorders.

Airtis *Piramal, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Airtis Plus *Piramal, India.*
Ambroxol (p. 1654·3); cetirizine hydrochloride (p. 619·2).

Airum *Recalcine, Chile.*
⊗Clenbuterol (p. 1207·2).
Bronchospasm.

Airuohua *Changzheng-Xinkai, China.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Airway *Intra-Labs, India.*
Montelukast (p. 1214·3).
Asthma; allergic rhinitis.

Airway-L *Intra-Labs, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Air-X *RX, Hong Kong; RX, Thai.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; aid to gastroscopy; aid to gastroscopy and X-ray examination; flatulence.

Airyfen *Panacea, India.*
Ketotifen (p. 631·3).
Hypersensitivity reactions; asthma.

Aisike *Sandoz, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aisiwan *Taiho, China.†*
Tegafur (p. 864·2).
Malignant neoplasms.

Aisoskin *Fidia, Ital.*
Isotretinoin (p. 1706·2).
Acne.

Aiti *Samjin, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Aitornet *Bajamed, Mex.*
Ketorolac (p. 80·2).
Pain.

Aiyiling *Changzheng-Xinkai, China.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo; tinnitus.

Aizea *Marlborough Pharmaceuticals, UK.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Aizole *Zim, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Ajatin *Proforma, Cz.*
Benzododecinium bromide (p. 1739·2).
Disinfection of skin and wounds.

Ajo 1000 + C *Garden House, Arg.*
Garlic (p. 2510·3); ascorbic acid (p. 2110·3).
Dietary supplement.

Ajo Forte *Proveforma, Arg.†*
Garlic (p. 2510·3); ascorbic acid (p. 2110·3); acerola.
Dietary supplement.

Ajo Mas Vitamina C *Lafarmen, Arg.*
Garlic (p. 2510·3); ascorbic acid (p. 2110·3).

Ajo Vital *AM, Arg.*
Garlic (p. 2510·3).
Dietary supplement.

Ajolip *Natuforma, Arg.*
Garlic (p. 2510·3); bearberry (p. 2453·2).
Dietary supplement.

Ajomast *Monserrat, Arg.*
Garlic (p. 2510·3).
Hyperlipidaemia.

AK-60 *Bactolac, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ak Lip Balm *Aloe Care, Canad.†*
Camphor (p. 2466·2); phenol (p. 1763·3).

Ak Mycin *Akorn, Canad.*
Erythromycin (p. 291·2).
Bacterial eye infections.

Ak Spor *Akorn, Canad.*
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Ak Trol *Akorn, Canad.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Ak Vernacon *Akorn, Canad.*
Pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Akabar *Carnot, Mex.*
Nifuroxazide (p. 331·3).
Bacterial infections of the gastrointestinal tract.

Akacin *Diba, Mex.; Atlantic, Thai.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Akaderm N *Gepepharm, Ger.†*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Skin disorders.

Akamin *Alphapharm, Austral.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Akamon *Medochemie, Hong Kong; Medochemie, Malaysia.*
Bromazepam (p. 1041·2).
Anxiety.

Akarin *Nycomed, Denm.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Akarpine *Akorn, Canad.; Akorn, USA.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Akatinol *Phoenix, Arg.; Merz, Mex.; Merz, Rus.*
Memantine hydrochloride (p. 393·1).
Dementia; mental function impairment; spasticity; Alzheimer's disease; movement disorders.

Ak-Beta *Akorn, USA.*
⊗Levobunolol hydrochloride (p. 2008·3).
Glaucoma; ocular hypertension.

Ak-Chlor *Akorn, Canad.*
Chloramphenicol (p. 257·1).
Eye infections.

Ak-Cide *Akorn, Canad.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Ak-Con *Akorn, Canad.; Akorn, USA.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Ak-Dex *Akorn, Canad.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Ak-Dilate *Akorn, Canad.; Akorn, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis; uveitis; open-angle glaucoma; refraction without cycloplegia.

AKE *Fresenius Kabi, Ger.*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Fresenius Kabi, Neth.; Fresenius Kabi, Turk.†
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

AKEDamins *Macoven, USA.*
Vitamins; zinc (p. 2126·1).

Akelin *Neptunus, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Aken *Kendrick, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Akeprul *Loeffler, Mex.*
Benzoyl peroxide (p. 1696·1).
Acne.

Akérat *Avene, Fr.*
⊗Urea (p. 1727·3); salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Dry skin; keratinisation disorders.

Akerat *Pierre Fabre Dermo-Cosmetique, Arg.; Medifarm Avene, Venez.*
⊗Urea (p. 1727·3); salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Skin disorders.

Silesia, Chile.
⊗Urea (p. 1727·3); salicylic acid (p. 1719·1); lactic acid (p. 2539·1); almond oil (p. 2437·1).
Skin disorders.

Aketon *Yoo Young, Philipp.*
Biperiden hydrochloride (p. 895·1).
Parkinsonism; drug-induced extrapyramidal syndrome.

Akevir *Kener, Mex.*
Aciclovir (p. 964·1).

Akezol *Kener, Mex.*
⊗Acetazolamide (p. 2001·1).

AK-Fluor *IFET (ΙΦΕΤ), Gr.*
Fluorescein sodium (p. 2506·2).

Ak-Fluor *Akorn, Canad.; Akorn, USA.*
Fluorescein sodium (p. 2506·2).
Ophthalmic diagnostic agent.

Akicin *General Drugs, Thai.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Akidin *MedChoice, Philipp.*
Biperiden hydrochloride (p. 895·1).
Parkinsonism; drug-induced extrapyramidal disorders.

Akildia *Asepta, Mon.*
Centella (p. 1698·3); karite.
Foot care in diabetes.

Akileïne *Asepta, Mon.*
A range of preparatations for foot disorders.

Akilen
Note: this name may be used for preparations of different composition.
Sanbe, Indon.; Sanbe, Singapore.
Ofloxacin (p. 334·3).
Bacterial infections.

Medochemie, Malaysia.†
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; heart failure; hypertension.

Akineton *Abbott, Arg.; Abbott, Austral.; Desma, Austria; Pharmacobel, Belg.; Abbott, Braz.; SIT, Cz.; SIT, Denm.; SIT, Fin.; DB, Fr.; Desma, Ger.; Desma, Gr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; CT, Hung.; SIT, Irl.; SIT, Ital.; Abbott, Mex.; Abbott, Neth.; SIT, Norw.; Desma, Pol.; Desma, Port.; Desma, Rus.; Pharmaco, S.Afr.; SIT, Spain; SIT, Swed.; Desma, Switz.; Abbott, Turk.; AbbVie, USA; Abbott, Venez.*
Biperiden hydrochloride (p. 895·1) or biperiden lactate (p. 895·1).
Drug-induced extrapyramidal disorders; parkinsonism; spasticity; extrapyramidal disorders; nicotine poisoning; phosphorus poisoning; head injury; trigeminal neuralgia; bronchospasm; nocturnal cramps.

Abbott, Chile†; Abbott, Philipp.
Biperiden (p. 895·1).
Parkinsonism; drug-induced movement disorders.

Akinspray *Urgo, Belg.†*
Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Akipic *Asepta, Mon.*
Ethyl butylacetylaminopropionate (p. 2154·3) citronella oil (p. 2481·1).
Insect repellent.

Akistin *Pharmaselect, Austria.*
Diethylamine salamidacetate (p. 129·2).
Musculoskeletal and joint disorders; neuralgias.

Akitropio *Kilab, Arg.*
Ipratropium bromide (p. 1211·3).

AKK *Yuri, Ukr.*
Aminocaproic acid (p. 1131·3).
Respiratory viral infections.

Aklav *Konpharma, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Aklovir *Sandoz, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ak-NaCl *Akorn, USA.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Akne Cordes *Ichthyol, Austria.†*
Erythromycin (p. 291·2).
Acne.

Aknecolor *Spirig, Cz.; Spirig, Switz.*
Clotrimazole (p. 576·2).
Acne.

Aknederm Ery *Gepepharm, Ger.†*
Erythromycin (p. 291·2).
Acne.

Aknederm Neu *Gepepharm, Ger.†*
Ictasol (p. 1706·1); zinc oxide (p. 1729·1).
Skin disorders.

Aknefug BP *Abbott, Turk.*
Benzoyl peroxide (p. 1696·1).
Acne.

Aknefug Doxy *Wolff, Ger.†*
Doxycycline hyclate (p. 288·2).
Acne.

Aknefug Iso *Wolff, Ger.*
Isotretinoin (p. 1706·2).
Acne.

Aknefug Mino *Wolff, Ger.†*
Minocycline hydrochloride (p. 325·1).
Acne.

Aknefug-EL *Wolff, Cz.†; Wolff, Ger.; Wolff, Hung.*
Erythromycin (p. 291·2).
Acne.

Aknefug-liquid *Wolff, Ger.*
Salicylic acid (p. 1719·1).
Acne.

Aknefug-oxid *Wolff, Ger.; Wolff, Hung.*
Benzoyl peroxide (p. 1696·1).
Acne.

Aknemin *Surtech, Irl.; Merck, Neth.; Crookes Healthcare, UK.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Akne-Mycin *Almirall, Port.; Almirall, Singapore; iNova, Singapore; Almirall, Switz.; Valeant, USA.*
Erythromycin (p. 291·2).
Acne.

Almirall, Switz.†
Topical emulsion: Erythromycin (p. 291·2); ichthammol (p. 1705·3).
Acne.

Aknemycin *Reckitt Benckiser, Belg.; Almirall Hermal, Cz.; Almirall Hermal, Ger.; iNova, Hong Kong; Almirall, Hung.; Hermal, Israel; Hermal, Malaysia†; Hermal, Neth.†; Herrmann, Pol.*
Erythromycin (p. 291·2).
Acne.

Almirall Hermal, Ger.†; Hermal, Israel.
Topical emulsion: Erythromycin (p. 291·2); ichthammol (p. 1705·3).
Acne.

Aknemycin compositum *Hermal, Austria.*
Erythromycin (p. 291·2); light ammonium bituminosulfonate (p. 1705·3).
Acne.

Aknemycin Plus *Almirall Hermal, Cz.; Almirall Hermal, Ger.; iNova, Hong Kong; Boots Piramal, India; Hermal, Israel; Almirall, Malaysia; Herrmann, Pol.; Almirall, Singapore; iNova, Singapore; Crookes Healthcare, UK.*
Erythromycin (p. 291·2); tretinoin (p. 1725·2).
Acne.

Aknenormin *Almirall Hermal, Cz.; Almirall Hermal, Ger.; Almirall, Hung.; Herrmann, Pol.*
Isotretinoin (p. 1706·2).
Acne.

Ak-Neo-Dex *Akorn, USA.*
⊗Neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Eye inflammation with bacterial infection.

Akneroxid *Hermal, Austria; Reckitt Benckiser, Belg.; Almirall Hermal, Cz.; Almirall Hermal, Ger.; iNova, Hong Kong; Almirall, Hung.; Boots Piramal, India; Almirall, Malaysia; Hermal, Neth.†; Herrmann, Pol.; Almirall, Singapore; iNova, Singapore; Almirall, Switz.*
Benzoyl peroxide (p. 1696·1).
Acne.

Aknesil *Iasis, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Aknesol *Naturprodukt, Hung.*
Benzoic acid (p. 1738·2); methenamine (p. 322·3).
Acne.

Aknetrent *Frik, Turk.*
Isotretinoin (p. 1706·2).

Aknex *Gebro, Switz.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Aknex Cleaning *Gebro, Switz.†*
Cetrimonium bromide (p. 1742·3).
Acne; skin cleansing.

Aknicare *Dermoteca, Port.*
Pyruvic acid; triclosan (p. 1773·2).
Soap substitute for acne-prone skin.

Aknicare Cleanser *General Topics, Ital.*
Pyruvic acid; triclosan (p. 1773·2).
Acne.

Aknichthol *Ichthyol, Austria.*
Ictasol (p. 1706·1); salicylic acid (p. 1719·1); colloidal sulfur (p. 1721·1).
Acne.

Ichthyol, Ger.
Cream: Ictasol (p. 1706·1).
Acne.

Ichthyol, Ger.
Lotion: Ictasol (p. 1706·1); salicylic acid (p. 1719·1).
Acne.

Medinova, Switz.
Sodium bituminosulfonate (p. 1706·1); salicylic acid (p. 1719·1).
Acne.

Aknil *Sunthi Sepuri, Indon.†*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Aknilox *Drossapharm, Switz.; Assos, Turk.*
Erythromycin (p. 291·2).
Acne.

Aknin-N *Sanofi, Switz.†*
Minocycline hydrochloride (p. 325·1).
Acne.

Aknoral *IBSA, Switz.†*
Minocycline hydrochloride (p. 325·1).
Acne.

Aknoren *Herbacos, Cz.*
Azelaic acid (p. 1695·1).
Acne.

Aknosan *Almirall Hermal, Ger.*
Minocycline hydrochloride (p. 325·1).
Acne.

Akorazol *Collins, Mex.†*
Ketoconazole (p. 585·3).
Fungal infections.

Akoset *CCM, Malaysia.*
⊗Furosemide (p. 1387·1).
Oedema.

Akotid *Bright Future, Hong Kong.†*
Tetracycline (p. 373·1).
Bacterial infections.

Ak-Pentolate *Akorn, Canad.; Akorn, USA.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Akpod *Akesiss, India.*
Cefpodoxime.
Bacterial infections.

Ak-Poly-Bac *Akorn, USA.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Eye infections.

AkPro *Akorn, USA.†*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Akratol *Rafarm, Gr.*
Nabumetone (p. 97·1).
Pain; inflammation; musculoskeletal and joint disorders.

Akriderm *Akrikhin, Rus.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Akriderm CK *Akrikhin, Rus.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Akriderm Genta *Akrikhin, Rus.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Akriderm GK *Akrikhin, Rus.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Akridipin *Marvel, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Akrinor *Meda, Austria†; Ratiopharm, Ger.; Transfarma, Indon.; Adcock Ingram, S.Afr.*
⊗Cafedrine hydrochloride (p. 1330·1); theodrenaline hydrochloride (p. 2629·1).
Hypotension; circulatory disorders.

Ak-Rinse *Akorn, USA.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Akripamide *Akrikhin, Rus.*
⊗Indapamide (p. 1409·2).
Hypertension.

Akrofen *Nufarindo, Indon.*
Phenylbutazone (p. 125·1).
Musculoskeletal, joint, and peri-articular disorders; thrombophlebitis.

Akrofolline *Biofarma, Turk.*
Estradiol propionate (p. 2271·2).
Menopausal disorders.

Ak-Rose *Akorn, Canad.*
Rose bengal sodium (p. 2607·1).
Ophthalmic diagnostic agent.

Aksef *Nobel, Turk.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Nobel, Ukr.
Cefuroxime (p. 255·2).
Bacterial infections.

Aksil *Embil, Turk.*
Benzoyl peroxide (p. 1696·1).
Acne.

Aksoderm *Gemi, Pol.*
Vitamin A (p. 2098·3).
Skin disorders.

Ak-Spore *Akorn, USA.†*
Eye ointment: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Eye infections.

Ak-Sulf *Akorn, Canad.; Akorn, USA.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Akt-2 *Lupin, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Akt-3 *Lupin, India.*
1 Capsule, rifampicin (p. 350·3); 1 tablet, ethambutol (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Akt-4 *Lupin, India.*
1 Capsule, rifampicin (p. 350·3); 2 tablets, pyrazinamide (p. 345·2); 1 tablet, ethambutol (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Akta *Nicholas, Indon.*
Vitamins.

Aktace *Nicholas, Indon.*
Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3).
Vitamin B and C deficiency.

Ak-Taine *Akorn, Canad.; Akorn, USA.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

Akten *IFET (ΙΦΕΤ), Gr.; Akorn, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Akt-FD *Lupin, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Aktibol *Nevzat, Turk.*
Cobamamide (p. 2107·2).
Megaloblastic anaemia.

Aktiferrin *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Rus.; Mepha, Switz.; Ratiopharm, Ukr.*
Ferrous sulfate (p. 2062·2).
DL-Serine (p. 2088·2) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Aktiferrin Compositum *Ratiopharm, Austria; Merckle, Rus.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
DL-Serine (p. 2088·2) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron and folic acid deficiency.

Ratiopharm, Cz.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
DL-Serine (p. 2088·2) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Aktiferrin N *Merckle, Ger.†*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Aktiferrin-F *Mepha, Israel; Mepha, Malaysia†; Mepha, Singapore†; Mepha, Switz.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
DL-Serine (p. 2088·2) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.

Aktil *Gedeon Richter, Hung.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Aktivanad *Pharmonta, Austria.*
Oral liquid: Liver extract (p. 2444·1); yeast (p. 2125·2); rose fruit (p. 2607·1); caffeine (p. 1203·3).
Tonic.

Aktivanad-N *Medice, Ger.*
Oral liquid: Liver extract (p. 2444·1); yeast extract (p. 2125·2); caffeine (p. 1203·3).
Tonic.

Aktivin *Michallik, Ger.*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Aktivit *Gradiens, Hung.*
Royal jelly (p. 2608·1); wheat-germ oil (p. 2647·1).
Tonic.

Aktivon *Hevert, Ger.*
Camphora (p. 2466·2); cola (p. 2648·2); crataegus (p. 2488·1); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

AkTob *Akorn, USA.*
Tobramycin (p. 380·1).

Akton *Nycomed, Belg.*
Cloxazolam (p. 1057·2).
Anxiety; sleep disorders; premedication.

Aktren *Bayer, Austria; Bayer, Ger.*
Ibuprofen (p. 68·2).
Pain; fever.

Aktufoam *Darier, Mex.*
Clindamycin phosphate (p. 269·3).
Acne.

Akudol *Wassermann, Ital.*
Naproxen (p. 98·2).
Pain; musculoskeletal and joint disorders; fever.

AKuriT *Lupin, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Akurit *Lupin, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Akurit-3 *Lupin, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

AKuriT-4 *Lupin, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Akurit-4 *Lupin, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Akurit-Z *Lupin, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Akutol *Aveflor, Pol.*
Acrylic copolymer aerosol.
Wounds.

Akutur *Ebi, Switz.*
Acidum benzoicum e resina (p. 1738·2); apis mellifica (p. 2445·2); argenti nitras (p. 2615·3); berberis vulgaris (p. 2502·1); echinacea angustifolia (p. 2498·1); lytta vesicatoria; solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Akutur spag *Pekana, Neth.*
Benzoicum acidum (p. 1738·2); nitricum acidum (p. 2572·3); apis mellifica (p. 2445·2); cantharis vesicatoria; populus tremuloides spag (p. 2450·3); pulsatilla pratensis (p. 2600·2); zingiber officinale; solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Akwa Tears *Akorn, Canad.*
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2); yellow soft paraffin (p. 2212·1).
Dry eyes.

Akorn, USA.
Eye drops: Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Akorn, USA.†
Eye ointment: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

AL
Note: this name may be used for preparations of different composition.
Lejal, Philipp.
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Al
Note: this name may be used for preparations of different composition.
Radicura, India.
Albendazole (p. 149·1).
Worm infections; giardiasis.

al12 *JSJ, USA.*
Ammonium lactate (p. 1694·3).
Emollient.

al 110 *Nestle, Hong Kong; Nestle, Philipp.*
Infant feed.
Lactose intolerance; diarrhoea.

Nestle, Braz.†; Nestle, Indon.; Nestle, Ital.
Food for special diets.
Lactose intolerance.

ALA
Note: this name may be used for preparations of different composition.
FDZJ, China.
Aminolevulinic acid hydrochloride (p. 740·1).
Anogenital warts.

Ala
Note: this name may be used for preparations of different composition.
Alembic, India.
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

ala seb *Del-Ray, USA.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).

Ala seb T *Del-Ray, USA.*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Seborrhoeic dermatitis.

Alabel *Nobel, Jpn.*
Aminolevulinic acid hydrochloride (p. 740·1).
Visualisation of malignant tissue during surgery for glioma.

Alacapsin *Bama, Spain.*
Capsicum oleoresin (p. 2469·3).
Diabetic neuropathy.

Alacare *Intendis, Irl.*
5-Aminolevulinic acid (p. 740·1).
Actinic keratosis.

Alacetan NNA *Asconex, Ger.†*
Naproxen sodium (p. 98·2).
Pain; fever.

Alacol DM *Ballay, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Ala-Cort *Del-Ray, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Alacramyn *Bioclon, Mex.*
Scorpion venom antisera (p. 2418·1).
Scorpion stings.

Alacre *Neo-Farmaceutica, Port.*
St John's wort (p. 449·1).
Depression.

Alactin *Teva, Ukr.*
Cabergoline (p. 899·3).
Inhibition of lactation; hyperprolactinaemia; prolactin-secreting pituitary adenoma.

Aladin
Note: this name may be used for preparations of different composition.
Farmak, Ukr.
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Reddy, India.
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Alador *Alboran, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Alager *Denver, Arg.*
Azelastine hydrochloride (p. 617·1).
Allergic eye disorders.

Alagesic LQ *Poly, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3); caffeine (p. 1203·3).
Pain.

Alaglio *SBI, Jpn.*
Aminolevulinic acid hydrochloride (p. 740·1).
Visualisation of malignant tissue during surgery for glioma.

Alahist AC *Poly, USA.*
Codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alahist DHC *Poly, USA.*
Dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alahist DM *Poly, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alahist IR *Poly, USA.*
Dexbrompheniramine maleate (p. 618·1).
Respiratory-tract allergies.

Alahist LQ *Poly, USA.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alairgix *Cooperation Pharmaceutique, Fr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Alamag *Goldline, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Hyperacidity.

Alamag Plus *Goldline, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Alamast *Vistakon, USA.*
Pemirolast potassium (p. 1218·2).
Allergic conjunctivitis.

Alamflu *Sanify, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Alamin *David, India.*
Amino acids.
Parenteral nutrition.

Alamin Forte *David, India.*
Amino acids; vitamins.
Dietary supplement.

Alamin-Fez *David, India.*
Vitamin B substances (p. 2102·3); ferrous fumarate (p. 2060·3); amino acids; zinc sulfate (p. 2126·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Alampen *Spefar, Venez.*
Ampicillin (p. 218·2).
Bacterial infections.

Alanase *Mylan, NZ.*
⊗Beclometasone dipropionate (p. 1621·2).
Nasal polyps; rhinitis.

ALAnerv *Wassermann, Philipp.*
Thioctic acid (p. 2629·1); fatty acids; vitamin E (p. 2119·1) vitamin B substances (p. 2102·3); selenium (p. 2086·3); methionine (p. 1558·2).
Dietary supplement.

Alangel *Systopic, India.*
Adapalene (p. 1692·1).
Acne.

Alanox *Darya-Varia, Indon.*
Thioctic acid (p. 2629·1).
Nutritional supplement in diabetes mellitus.

Alantamida *Meyer, Venez.*
Dequalinium chloride (p. 1749·3); allantoin (p. 1693·1).

Alantan *Unia, Pol.*
Allantoin (p. 1693·1).
Skin disorders; burns; wounds.

Alantan-Plus *Unia, Pol.*
Allantoin (p. 1693·1); dexpanthenol (p. 2582·2).
Skin disorders; burns; wounds.

Alantavit *Coel, Pol.*
Allantoin (p. 1693·1); vitamin A (p. 2098·3); colecalciferol (p. 2113·1).
Skin disorders; wounds; burns; ulcers.

Alap *Aurobindo, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alapanzol *Alacan, Spain.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ala-Plus *Alembic, India.*
Thioctic acid (p. 2629·1); betacarotene (p. 2051·1); vitamin B substances (p. 2102·3).

Alapren *Ranbaxy, S.Afr.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Alapril
Note: this name may be used for preparations of different composition.
Mediolanum, Ital.
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

S Med, Austria.
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Alapryl *Menarini, Spain.*
Halazepam (p. 1077·1).
Anxiety.

Alarimed *Medis, Denm.*
Ramipril (p. 1483·3).
Hypertension; nephropathy; heart failure; myocardial infarction.

Alarin *Biofarma, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Alased *Elpen (Ελπεν), Gr.*
Haloperidol (p. 1077·1).
Psychoses; mania; aggression; movement disorders; nausea; vomiting; intractable hiccup.

Alasenn *Schwarer, Ger.*
Senna (p. 1885·1); ononis (p. 2575·3); achillea (p. 2427·3); taraxacum (p. 2625·3).
Constipation.

Alaspan *Fulford, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alastina *Alacan, Spain.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Alasulf *Major, USA.*
Sulfanilamide (p. 368·1); aminoacridine hydrochloride (p. 1732·3); allantoin (p. 1693·1).
Vaginal infections.

Alateris *Ransom, UK.*
Glucosamine (p. 2515·3).
Knee osteoarthritis.

Alatopran *Actavis, Denm.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Alatrol *Square, Malaysia.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Alavert *Wyeth-Ayerst, USA.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alavert Allergy & Sinus D *Wyeth Consumer, USA.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Alaway *Bausch & Lomb, USA.*
Ketotifen fumarate (p. 631·3).
Eye irritation.

Alax *Herbapol Poznan, Pol.*
Aloes (p. 1816·1); belladonna (p. 2453·3); frangula bark (p. 1843·3); liquorice (p. 1853·2).
Constipation.

Alaxa *Angelini, Ital.*
Bisacodyl (p. 1821·1).
Constipation.

Alaxan
Note: this name may be used for preparations of different composition.
United Laboratories, Philipp.
Capsules; tablets: Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Fever; pain.

Great Eastern, Thai.†; Therapharma, Thai.†
Carisoprodol (p. 2021·3); phenylbutazone calcium (p. 125·1).
Musculoskeletal and joint disorders.

United Laboratories, Philipp.†
Topical gel: Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Alaxan PI *Great Eastern, Thai.†*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal pain.

Alba
Note: this name may be used for preparations of different composition.
Life Medicare, India; Biem, Turk.
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoalbuminaemia; hypovolaemic shock; hypoproteinaemia.

Alba-3
Note: this name may be used for preparations of different composition.
IQB, Braz.
Albendazole (p. 149·1).
Worm infections.

Albacos *Symbiosis, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albacos-IR *Symbiosis, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Albactin *Meridian, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Albafort *Baroli, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); desiccated liver (p. 2444·1); vitamin C (p. 2110·3).

Albalon
Note: this name may be used for preparations of different composition.
Allergan, Austral.; Allergan, Canad.; Allergan, Hong Kong; Allergan, Irl.†; Allergan, Malaysia†; Allergan, Neth.†; Allergan, Thai.; Allergan, USA.†
⊗Naphazoline hydrochloride (p. 1669·3).
Ocular congestion; eye irritation.

Allergan, India.
Ketotifen (p. 631·3).
Allergic conjunctivitis.

Albalon Relief *Allergan, Austral.; Allergan, NZ.*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Albalon-A *Allergan, Austral.; Allergan, Canad.*
⊗Naphazoline hydrochloride (p. 1669·3); antazoline phosphate (p. 615·3).
Eye disorders.

Albamaa *Lifeon, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albapure *CSL, Indon.; Dexa, Indon.*
⊗Albumin (p. 1130·2).
Hypoproteinaemia; shock; burns.

Albarel *Egis, Rus.*
Rilmenidine (p. 1487·1).
Hypertension.

Egis, Cz.†
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Albasym *Symbiosis, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albatel *TO-Chemicals, Thai.*
Albendazole (p. 149·1).
Worm infections.

Albatin *Exsymol, Mon.*
Aminoethylphosphinic acid.
Skin lightener.

Albatussin *Baroli, USA.*
Capsules: Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Bart, USA.
Oral liquid: Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Cold symptoms; cough.

Albaxin *Pharmacia Upjohn, Gr.*
Bacampicillin hydrochloride (p. 225·2).

Albay *Thomson, Austral.†; Bayer, S.Afr.†; Miles, USA.†*
Bee venom (p. 2434·3), wasp venom, hornet venom, yellow jacket venom, or mixed vespids venom (p. 2434·3).
Allergen immunotherapy; diagnosis of hypersensitivity to insect stings.

Albazole *Wings, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albec *Psicofarma, Mex.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Albekon *Briskon, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albel *Geolab, Braz.*
Albendazole (p. 149·1).
Worm infections.

Albemed *Medicpharma, Thai.*
Albendazole (p. 149·1).
Worm infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alben *Biolab, Thai.*
Albendazole (p. 149·1).
Worm infections.

Albenda *Milano, Thai.; Julphar, UAE.*
Albendazole (p. 149·1).
Worm infections.

Albendol *Vianex (Βιανεξ), Gr.; Micro, India; Eurodrug, Malaysia†; Micro, Singapore.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albendrox *Royton, Braz.*
Albendazole (p. 149·1).
Worm infections.

Albendy *Hertz, Braz.*
Albendazole (p. 149·1).
Worm infections.

Alben-Hero *Heromycin, Thai.*
Albendazole (p. 149·1).
Worm infections.

Albensil *Arlex, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Albent *Acto, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albentel *Teuto, Braz.*
Albendazole (p. 149·1).
Worm infections.

Alben-VC *Vesco, Thai.*
Albendazole (p. 149·1).
Worm infections.

Albenz *The Forty-Two, Thai.*
Albendazole (p. 149·1).
Worm infections.

Albenza *Amedra, USA.*
Albendazole (p. 149·1).
Cysticercosis; echinococcosis.

Albenzole *Glories, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albenzonil *Ducto, Braz.*
Albendazole (p. 149·1).
Worm infections.

Albeoler *Andromaco, Chile.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Albepir *Albephar, Venez.*
Pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

Alber T *Unison, Thai.*
Tolnaftate (p. 596·1); triacetin (p. 596·2).
Fungal skin infections.

Albera *Alde Medi Impex, Ind'ia.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Albercilin *Sanofi-Aventis, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Albesan *Sanify, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albesin *Biotech, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Albesine Biotic *Indeco, Arg.*
Amoxicillin (p. 216·2); diclofenac (p. 48·3).

Albest *Nestor, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albestar *Minova, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albetol *Leiras, Fin.*
⊗Labetalol hydrochloride (p. 1416·2).
Angina pectoris; hypertension; hypotension in anaesthesia.

Albetor *Valenta, Rus.*
Proxodolol hydrochloride.
Hypertension; angina pectoris; heart failure.

Albex *Saga, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albey *Stallergenes, Fr.; Ebos, NZ; Medi Challenge, S. Afr.†*
Bee venom (p. 2434·3), wasp venom (p. 2434·3), or yellow jacket venom (p. 2434·3).
Diagnosis of hypersensitivity to insect stings; allergen immunotherapy.

Albezin *Brasterapica, Braz.*
Albendazole (p. 149·1).
Worm infections.

Albezol *Union Drug, Thai.; SM, Venez.*
Albendazole (p. 149·1).
Worm infections.

Albezole *Khandelwal, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albicansan *Sanum-Kehlbeck, Ger.*
Candida albicans.
Homoeopathic preparation.

Albicar
Note: this name may be used for preparations of different composition.
Casasco, Arg.
Levocarnitine (p. 2053·2).
Carnitine deficiency; disorders of muscle metabolism.
Elmor, Venez.
Albendazole (p. 149·1).
Worm infections.

Albicon *Chiesi, Braz.*
Potassium chloride (p. 1793·2); benzocaine (p. 1980·2); sodium bicarbonate (p. 1781·1).
Local disinfection and anaesthesia.

Albicort *Sanofi-Aventis, Belg.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Albiomin *Biotest, Ger.; Biotest, Gr.; Kamada, Israel; Biotest, Port.; Biotest, Spain; Biotest, Thai.*
⊗Albumin (p. 1130·2).
Plasma volume expansion.

Albion *LKM, Arg.*
Cinchona (p. 2478·3); juniper (p. 2537·1); calendula (p. 2465·2); rosemary (p. 2607·2).

Albios *Giuliani, Ital.*
Dietary fibre; minerals.

Albiotin *Kalbe, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Albistin *Cazi, Braz.*
Nystatin (p. 590·3).
Fungal infections.

Albital
Note: this name may be used for preparations of different composition.
Kedrion, Ital.
⊗Albumin (p. 1130·2).
Hypoalbuminaemia.

Albizia Complex *Mediherb, Austral.*
Albizia; skullcap (p. 2617·1); feverfew (p. 676·1).
Tonic.

Albocresil *Nycomed, Arg.; Nycomed, Braz.*
Policresulen (p. 1160·2).
Gynaecological disorders; wounds; burns; ulcers; vaginal infections; haemorrhage; mucous membrane inflammation in the mouth.

Albol *East West, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albolene *DSE, USA.*
Liquid paraffin (p. 2191·2); soft paraffin (p. 2211·3).
Soap substitute.

Albonate *Elfin, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alboral *Silanes, Mex.*
Diazepam (p. 1063·2).
Anxiety disorders; insomnia; tetany; epilepsy; alcohol withdrawal syndrome; skeletal muscle spasm; premedication.

Albosan *Mepha, Port.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Albo-Sang *J & J DeChane, India.*
Calcium lactate (p. 1784·1); calcium hydrogen phosphate (p. 1783·3); magnesium phosphate (p. 1787·3); physalis (p. 2590·1).
Dietary supplement.

Albosym *Symbiosis, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albosym-IR *Symbiosis, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Albothyl *Nycomed, China; Takeda, Ger.; Nycomed, Hong Kong; Pharos, Indon.; Nycomed, Malaysia; Nycomed, Mex.; Nycomed, Philipp.; Nycomed, Pol.; Takeda, Singapore.*
Policresulen (p. 1160·2).
Cervical and vaginal disorders; burns; ulcers; mouth lesions and inflammation; anogenital warts; skin infections; wounds; haemorrhage.

Albotyl *Help, Gr.*
Nicergoline (p. 2569·1).
Vasodilator.

Alboven *Vencare, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Alboz *Collins, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia.

Albrinol *Alvartis, Mex.*
Calcitriol (p. 2113·1).
Hypocalcaemia; hypoparathyroidism; renal osteodystrophy.

Albrodo *Shalaks, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Albucid *Allergan, India; Nicholas, Indon.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye and ear infections; eye infections.

Albudac *Zydus, India.*
⊗Albumin (p. 1130·2).
Hypovolaemic shock; hypoproteinaemia; neonatal hyperbilirubinaemia.

Albulair *Cassara, Arg.*
⊗Levosalbutamol sulfate (p. 1213·3).
Obstructive airways disease.

Albuman *Sanquin, Fin.; Faran, Gr.; Sanquin, Neth.; Berna, Turk.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoalbuminaemia.

Albumarc *American Red Cross, USA.*
⊗Albumin (p. 1130·2).

Albumax *Green Cross, Philipp.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; burns; neonatal hyperbilirubinaemia.

Albumed *Medispan, India.*
⊗Albumin (p. 1130·2).
Hypovolaemic shock; hypoproteinaemia; neonatal hyperbilirubinaemia.

Albumeon *Zydus, India.*
⊗Albumin (p. 1130·2).
Hypovolaemic shock; hypoproteinaemia; neonatal hyperbilirubinaemia.

Albumex *CSL, Austral.; CSL Biotherapies, Hong Kong; CSL, NZ.*
⊗Albumin (p. 1130·2).
Hypovolaemia; hypoalbuminaemia; adult respiratory distress syndrome; haemodialysis; plasma exchange; cardiopulmonary bypass surgery; hypoproteinaemia; shock; burns; plasma volume expansion.

Albuminar *CSL, Arg.; CSL, Braz.; CSL, China; Gerolymatos, Gr.; CSL, Indon.; Dexa, Indon.; CSL, Philipp.; Farma-Tek, Turk.; CSL, USA.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; shock; hypovolaemia; hypoproteinaemia; hypoalbuminaemia.

Albuminativ *Octapharma, Denm.†; Octapharma, Fin.; Octapharma, Gr.; Octapharma, Irl.†; Octapharma, Israel; Octapharma, Norw.†; Octapharma, Port.†; Octapharma, Swed.*
⊗Albumin (p. 1130·2).
Hypovolaemia; plasma volume expansion.

Albunate *CSL, Mex.*
⊗Albumin (p. 1130·2).
Hypovolaemia.

Albunorm *Octapharma, Austria; Octapharma, Belg.; Octapharma, Cz.; Octapharma, Fin.; Octapharma, Fr.; Octapharma, Ger.; Octapharma, Irl.; Octapharma, Neth.; Octapharma, Port.; Octapharma, Spain; Octapharma, Swed.; Octapharma, UK.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypovolaemia.

Alburaas *Combiphar, Indon.; Shanghai RAAS, Thai.*
⊗Albumin (p. 1130·2).
Hypovolaemia; hypoproteinaemia; plasma volume expansion.

Alburel *Reliance, India; Reliance, Philipp.*
⊗Albumin (p. 1130·2).
Hypovolaemic shock; hypoproteinaemia; neonatal hyperbilirubinaemia; plasma volume expansion.

Alburex *CSL, Belg.; CSL, Braz.; CSL, Canad.; CSL, Cz.; CSL, Ger.; Demo, Gr.; CSL, Ital.; CSL, Neth.; CSL, Port.; CSL, Spain; CSL, UK.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; burns; hypoproteinaemia; hypovolaemic shock; hypovolaemia.

AlbuRx *CSL, China; CSL, USA.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoalbuminaemia; hypovolaemia; neonatal hyperbilirubinaemia.

Albusol *NBI, S.Afr.*
⊗Albumin (p. 1130·2).
Hypovolaemia; hypoproteinaemia; plasma volume expansion.

Albustix *Siemens, Fr.†; Bayer Diagnostics, Irl.†; Siemens, Ital.; Bayer, NZ; Bayer Diagnostics, UK; Siemens, USA.*
Test for protein in urine.

Albutamol *Centaur, India.*
⊗Etofylline (p. 1208·2); salbutamol (p. 1220·2); bromhexine (p. 1656·3).
Obstructive airways disease.

Albutein *Grifols, Canad.; Grifols, China; Grifols, Hong Kong; Grifols, India; Grifols, Indon.; Tempo Scan Pacific, Indon.; Alpha Therapeutic, Ital.; Grifols, Malaysia; Grifols, Philipp.; Grifols, Singapore; Grifols, Spain; Grifols, Thai.; Grifols, UK; Grifols, USA.*
⊗Albumin (p. 1130·2).
Hypovolaemia; hypoalbuminaemia; dialysis; hyperbilirubinaemia; cardiopulmonary bypass; plasma volume expansion; hypovolaemic shock; hypoproteinaemia; burns.

Albutol *Alkem, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Albyl minor *Recip, Swed.*
Aspirin (p. 22·2).
Pain; fever.

Albyl-E *Nycomed, Norw.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Alcabase *Homeocan, Canad.*
Minerals.

Alca-C *Melisana, Switz.; Novartis, Turk.*
Carbasalate calcium (p. 36·2); ascorbic acid (p. 2110·3).
Cold symptoms; pain; fever; inflammation.

Alcachofa Plus *Tecnonat, Arg.*
Cynara (p. 2490·3); boldo (p. 2458·3); cedron (p. 2552·3); carqueja (p. 2471·2); vitamin B_6 (p. 2105·3).
Digestive disorders.

Alcachofrax *Catarinense, Braz.*
Cynara (p. 2490·3).
Lipid disorders.

Alcacyl *Hanseler, Switz.*
Tablets: Carbasalate calcium (p. 36·2). Aluminium hydroxide (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever.

Alcacyl instantanee *Novartis Consumer, Switz.*
Lysine aspirin (p. 84·3).
Pain; fever.

Alcagest *Airela, Braz.*
Cynara (p. 2490·3).

Alcain *Alcon, Ukr.*
Proxymetacaine (p. 1995·3).
Local anaesthesia.

Alcaine
Note: this name may be used for preparations of different composition.
Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, China; Alcon, Gr.; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Mex.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.†; Alcon, Singapore†; Alcon, Switz.; Alcon, Turk.; Alcon, USA; Alcon, Venez.
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.
Sun, India.
Magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Alcal *Indkus, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alcalci *Adley, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Alcalci-D *Adley, India.*
Alfacalcidol (p. 2112·3); calcium citrate (p. 1783·2); copper sulfate (p. 2057·2); magnesium sulfate (p. 1787·3); zinc sulfate (p. 2126·2).

Alcalergin *Herbarium, Braz.†*
Liquorice (p. 1853·2).
Cough.

Alcalone Plus *Bunker, Braz.*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Alcalosio *SIT, Ital.*
Anhydrous glucose (p. 2069·1); potassium citrate (p. 1780·3); pyridoxine hydrochloride (p. 2105·3); sodium bicarbonate (p. 1781·1); sodium citrate (p. 1781·2).
Hypokalaemia.

Alcals Plus *Shreshtha, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alca-Luftal *BMS, Braz.*
Simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; flatulence.

Alcamex *Remek, Gr.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Alcamex-Mg *Remek, Gr.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).

Alcaphor *Pharmadeveloppement, Fr.*
⊗Trometamol citrate (p. 2635·1); sodium acid citrate (p. 1781·1); dipotassium citrate (p. 1780·3).
Renal calculi; metabolic acidosis.

Alcare
Note: this name may be used for preparations of different composition.
Steris, Canad.†; Calgon Vestal, USA.
⊗Alcohol (p. 1733·1).
Antiseptic.
Haledew, India.
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alcare-CC *Haledew, India.*
⊗Levocetirizine (p. 632·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Alcare-L *Haledew, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alcasedine *Will-Pharma, Neth.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Dyspepsia; heartburn.

Alcasol *Meda, Belg.*
Sodium bicarbonate (p. 1781·1); borax (p. 2459·2); sodium chloride (p. 1795·1).
Conjunctivitis; dry eyes.

Alcavixin *Korea United, Philipp.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Alceclar *Amnol, Ital.†*
Thioctic acid (p. 2629·1); unsaturated fatty acids; levomenol (p. 2544·1); zinc oxide (p. 1729·1).
Skin disorders.

Alcee *Zee, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Alcelam *Pharmasant, Thai.*
Alprazolam (p. 1035·2).
Anxiety; insomnia; mixed anxiety depressive states.

Alcep *Hasco-Lek, Pol.*
Onion (p. 2575·2).
Upper respiratory-tract infections.

Alcepalan *Herbapol Poznan, Pol.†*
Onion (p. 2575·2); heparin sodium (p. 1396·3).
Scars; keloids.

Alcephin *Alembic, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Alcephin-LA *Alembic, India.*
⊗Cefalexin (p. 234·1); probenecid (p. 607·3).
Bacterial infections.

Alceprin-N *Boiron, Switz.*
Allium cepa (p. 2575·2); atropa belladonna (p. 2453·3); euphrasia officinalis (p. 2502·1); hydrargyri subchloridum (p. 2555·3); hydrastis canadensis (p. 2528·1); kalii dichromas (p. 2476·3); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Alcerelief *Mac, Gr.*
Omeprazole sodium (p. 1867·2).
Gastro-oesophageal reflux; acid aspiration; peptic ulcer.

Alcet *Osper, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alcetam *Alkem, India.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Alcetamol *Sunward, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Alcetra *Servocare, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Alcetra Plus *Servocare, India.*
⊗Ambroxol (p. 1654·3); levocetirizine (p. 632·3); pseudoephedrine (p. 1676·1).

Alcevit *Dr Alson, India.*
Oral powder: Vitamins; minerals; carbohydrate; milk protein; lysine hydrochloride (p. 2079·3).
Dietary supplement.
Dr Alson, India.
Syrup: Vitamin B substances (p. 2102·3); protein; minerals.

Alce-Z *Dr Alson, India.*
Minerals; carbohydrate; ascorbic acid (p. 2110·3); lactobacillus (p. 2596·3).
Dietary supplement.

Alcezyme *Dr Alson, India.*
⊗Vitamin B substances (p. 2102·3); pepsin (p. 2586·1); protein hydrolysate (p. 2086·2); iron choline citrate (p. 2060·2).

Alchemed *Alchemed, Canad.†*
A range of homoeopathic preparations.
Homoeopathic preparation.

Alchera *Aspen, S.Afr.*
Zopiclone (p. 1118·1).
Insomnia.

Alchinal *Gemi, Pol.*
Garlic (p. 2510·3); echinacea purpurea (p. 2498·1).
Respiratory-tract disorders.

Alci *Bombay Tablet, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alcidol *Medley, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alcidolin *Sanopharm, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alcilox *Acto, India.*
Ampicillin trihydrate (p. 218·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Alcinal New *Rekah, Israel.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Alcinin *Pharmathen, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alcip *Allenge, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Alcipro *Alkem, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.
Alkem, Philipp.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Alciprocin *Mac, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Alcipro-TN *Alkem, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Alcip-TZ *Allenge, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Alcirid-O *Candor, India.*
Ondansetron (p. 1872·1); ranitidine (p. 1882·1).

Alciriz *Ritz, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alcis *Chiesi, Spain.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Alciton *Kleva, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Alclos-GM *Candor, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Alclox
Note: this name may be used for preparations of different composition.
Lancer, India.
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Alclox-D *Lancer, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Alco *Interbat, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Alco Plus *Interbat, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Nasal congestion.

Alco Plus DMP *Interbat, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Nasal congestion; cough.

Alco-Aloe *Ansell, Fr.†*
⊗Alcohol (p. 1733·1); aloes (p. 1816·1); chlorhexidine gluconate (p. 1743·3); phenoxyethanol (p. 1764·3).
Hand disinfection.

Alcobal *Obsurge, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Alcobuse *TO-Chemicals, Thai.†*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Alcocid *Zytras, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Alcocin *Alicon, India.*
Paracetamol (p. 115·1).
Pain; fever.

Alcoderm
Note: this name may be used for preparations of different composition.
Alicon, India.
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); clioquinol (p. 273·1); tolnaftate (p. 596·1).
Infected skin disorders.
Bajer, Arg.
Coal tar (p. 1723·2).
Skin disorders.

Alcofen *Alicon, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Alcohep *Grandix, India.*
Metadoxine (p. 2105·3); ornithine aspartate (p. 2085·2); silymarin (p. 1561·2); thiamine (p. 2102·3).

Alcohocel *Perez Gimenez, Spain.†*
⊗Alcohol (p. 1733·1); cetylpyridinium chloride (p. 1743·1).
Skin disinfection.

Alcohol Benzalconio *Viviar, Spain.*
⊗Alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1).
Skin, wound, and surface disinfection.

Alcohol CL Benz *Betamadrileno, Spain.†*
⊗Alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1).
Skin, wound, and surface disinfection.

Alcohol Hand Rub *Rhema, Singapore.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Hand disinfection.

Alcohol Potenciado *Maxfarma, Spain.*
⊗Alcohol (p. 1733·1); benzethonium chloride (p. 1738·1).
Skin, wound, and surface disinfection.
Viviar, Spain.
⊗Alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1).
Skin, wound, and surface disinfection.

Alcohol Sahakarn *United Drug, Thai.*
Isopropyl alcohol (p. 1758·3).

Alcohol-free Spray Sunscreen *Kinesys, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Alcold *Biological E, India.*
⊗Cetirizine (p. 619·2); pseudoephedrine (p. 1676·1).
Allergic rhinitis.

Alcolex *Labomed, Chile.†*
⊗Benzoxonium chloride (p. 1739·2); alcohol (p. 1733·1).
Disinfection of instruments, skin, and wounds.

Alcoliv *Sun, India.*
Metadoxine (p. 2105·3).
Liver disorders; alcohol intoxication.

Alcon Adequad *Alcon, Belg.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Alcon AE *Alcon, Arg.*
Vitamin A palmitate (p. 2098·3); vitamin E acetate (p. 2119·2).
Dietary supplement.

Alcon Eye Gel *Alcon, Belg.*
Carbomer (p. 2173·3).
Dry eyes.

Alcon Lagrimas *Alcon, Arg.*
Eye drops: ⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes; eye irritation.
Alcon, Arg.
Eye ointment: Liquid paraffin (p. 2191·2); wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Dry eyes.

Alcona *Alde Medi Impex, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Alconmide *Alcon, Philipp.†*
Lodoxamide trometamol (p. 2545·1).
Allergic eye disorders.

Alco-P *Sterkem, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Alcophyllex *Adcock Ingram, S.Afr.*
Theophylline (p. 1229·3); etofylline (p. 1208·2); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Bronchospasm.

Alco-PS *Sterkem, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Alcored *Admac, India.*
Vitamins; selenium dioxide (p. 2087·1); zinc (p. 2126·1); lycopene (p. 2546·2).

Alcorim-F *David, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Alcortin A *Primus, USA.*
⊗Hydrocortisone acetate (p. 1640·1); diiodohydroxyquinoline (p. 931·1).
Skin disorders.

Alcos-Anal *Meda, Norw.*
Lauromacrogol 400 (p. 2194·1); chlorocarvacrol (p. 1747·3); sodium oleate (p. 2211·2).
Anorectal disorders.
Meda, Swed.
Sodium oleate (p. 2211·2); 2-hydroxy-5-chlorothymol.
Anorectal disorders.

Alcoscrub *Erie, Canad.†*
⊗Alcohol (p. 1733·1).
Antiseptic.

Alcosept *Floris, Israel.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Skin disinfection.

Alcosin *Vir, Spain.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Alcotint *Vitamed, Israel.*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Alcough *Union, Singapore.*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alcover *GL Pharma, Austria; CT, Ital.*
Sodium oxybate (p. 1914·1).
Alcohol withdrawal syndrome.

Alcowipe *SSL, UK.*
Isopropyl alcohol (p. 1758·3).
Hard surface disinfection.

Alcoxib *Alkem, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Alcoxidine *Vitamed, Israel.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Skin disinfection.

Alcrin *Anglo-French Drugs, India.*
Chromium (p. 2055·3); inositol (p. 2533·2); thioctic acid (p. 2629·1).

Alcrin-M *Anglo-French Drugs, India.*
Thioctic acid (p. 2629·1); chromium polynicotinate (p. 2055·3); inositol (p. 2533·2); mecobalamin (p. 2108·1).
Peripheral neuropathy.

Alcrist *Alkem, India.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Alcusal *Alcusal, Austral.†*
Copper salicylate.
Musculoskeletal and joint disorders; sports injuries.

Alcytam *Torrent, Braz.*
Citalopram (p. 411·1).
Depression; alcohol withdrawal syndrome.

Alda *TNP, Thai.*
Albendazole (p. 149·1).
Worm infections.

Aldactacine *Pfizer, Spain.*
⊗Altizide (p. 1298·2); spironolactone (p. 1499·3).
Ascites; hypertension; oedema.

Aldactazida *Pfizer, Venez.*
⊗Spironolactone (p. 1499·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Aldactazide *Pfizer, Canad.; IFET (ΙΦΕΤ), Gr.; SPA, Ital.; Ali, Turk.; Pfizer, USA.*
⊗Spironolactone (p. 1499·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure; liver cirrhosis with oedema or ascites; nephrotic syndrome.

Aldactazine *Continental Pharma, Belg.; Pfizer, Fr.; Vianex (Βιανεξ), Gr.; Pfizer, Port.*
⊗Altizide (p. 1298·2); spironolactone (p. 1499·3).
Hypertension; oedema; ascites; nephrotic syndrome.

Aldactide *RPG, India; Pfizer, Irl.†; Pfizer, UK.*
⊗Spironolactone (p. 1499·3); hydroflumethiazide (p. 1406·3).
These ingredients can be described by the British Approved Name Co-flumactone.
Heart failure; hypertension.

Aldactone *Pfizer, Arg.; Pfizer, Austral.; Cheplapharm, Austria; Continental Pharma, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Fr.; Riemser, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; RPG, India; Soho, Indon.; Pfizer, Irl.; Pfizer, Israel; Lepetit, Ital.; Pfizer, Mex.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Ali, Turk.; Pharmacia, UK; Searle, USA; Pfizer, Venez.*
Capsules; tablets: ⊗Spironolactone (p. 1499·3).
Liver cirrhosis with ascites or oedema; nephrotic syndrome; heart failure; hyperaldosteronism; cor pulmonale; hypertension; oedema; hypokalaemia; myasthenia gravis; malignant ascites; hypomagnesaemia; hirsutism in women.
Riemser, Austria; Riemser, Cz.; Riemser, Ger.; Riemser, Pol.
Injection: ⊗Potassium canrenoate (p. 1472·2).
Hyperaldosteronism; heart failure; liver cirrhosis with ascites or oedema; nephrotic syndrome; oedema.

Aldactone EP *Pfizer, Arg.*
⊗Eplerenone (p. 1374·2).
Heart failure following myocardial infarction.

Aldactone HCT *Pfizer, Arg.*
⊗Spironolactone (p. 1499·3); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; oedema; ascites; nephrotic syndrome; hyperaldosteronism.

Aldactone Saltucin *Cheplapharm, Austria.*
⊗Spironolactone (p. 1499·3); butizide (p. 1329·3).
Liver cirrhosis with ascites and oedema; heart failure; cor pulmonale; nephrotic syndrome; hypertension.

Aldactone-D *Pfizer, Arg.*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Heart failure; oedema; liver cirrhosis with ascites; nephrotic syndrome; hyperaldosteronism.

Aldalix *Pfizer, Fr.*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Heart failure.

Aldamin *Unipharm, Mex.*
Albendazole (p. 149·1).
Worm infections.

Aldan *Polfarmex, Pol.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Aldara *Sidus, Arg.; iNova, Austral.; Meda, Austria; Meda, Belg.; Intendis, Braz.; Graceway, Canad.; 3M, Chile†; 3M, China; Meda, Cz.; Meda, Denm.; Meda, Fin.; Meda, Fr.; Meda, Ger.; Meda, Gr.; iNova, Hong Kong; Meda, Hung.; 3M, Irl.; 3M, Israel; Meda, Ital.; iNova, Malaysia; Graceway, Mex.; Meda, Neth.; Meda, Norw.; iNova, NZ; iNova, Philipp.; Meda, Pol.; Meda, Port.; iNova, S.Afr.; iNova, Singapore; Meda, Spain; Meda, Swed.; Meda, Switz.; iNova, Thai.; Eczacibasi, Turk.; 3M, UK; Meda, Ukr.; Valeant, USA.*
Imiquimod (p. 985·2).
Anogenital warts; basal cell carcinoma; actinic keratosis.

Aldarone *Zydus, India; Cadila, Thai.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Aldase *Lincoln, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Aldase-D *Lincoln, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Aldazida *Pfizer, Arg.; Pfizer, Braz.*
⊗Spironolactone (p. 1499·3); hydrochlorothiazide (p. 1403·2).
Heart failure; hyperaldosteronism; hypertension; liver cirrhosis with ascites and oedema; nephrotic syndrome; oedema.
Pfizer, Mex.
⊗Spironolactone (p. 1499·3); butizide (p. 1329·3).
Hypertension; oedema; ascites; hepatic cirrhosis.

Aldazide *Soho, Indon.; Pfizer, Philipp.; Pfizer, S.Afr.*
⊗Spironolactone (p. 1499·3); butizide (p. 1329·3).
Hypertension; oedema; heart failure; liver cirrhosis; nephrotic syndrome.

Aldazine *Alphapharm, Austral.†; Pacific, NZ.†*
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia; agitation; alcohol withdrawal syndrome; anxiety; behaviour disorders in children and the elderly; psychoses.

Aldazole *Utopian, Thai.; KVZ, Ukr.*
Albendazole (p. 149·1).
Worm infections.

Aldecin *Schering-Plough, Cz.†; Schering-Plough, Rus.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease; rhinitis; nasal polyps.

Aldee-P *Aust Ind, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Aldepraz-D *Alde Medi Impex, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Aldesonit *Help, Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders; allergic rhinitis.

Aldevit *Alde Medi Impex, India.*
Protein; vitamins; minerals.

Aldex AN *Zyber, USA.*
Doxylamine succinate (p. 627·3).

Aldex GS DM *Pernix, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Aldex-CT *Zyber, USA.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Aldezol-DF *David, India.*
Diloxanide furoate (p. 931·2); metronidazole (p. 936·1).

Aldezole *David, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; Helicobacter pylori eradication.

Aldezyme *Alde Medi Impex, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Aldiab *Merck, Indon.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Aldiagram *Alkem, India.*
Metronidazole benzoate (p. 936·1); nalidixic acid (p. 328·3).

Aldiamycin *Alkem, India.*
Belladonna (p. 2453·3); furazolidone (p. 933·3); metronidazole (p. 936·1).

Aldidase *Candor, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Aldidase-P *Candor, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3); paracetamol (p. 115·1).

Aldifex *Serral, Mex.*
Fexofenadine (p. 629·1).

Aldin *Merck, Indon.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Aldine *Piramal, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Aldine-D *Piramal, India.*
⊗Ambroxol (p. 1654·3); levocetirizine (p. 632·3); pseudoephedrine (p. 1676·1).

Aldinir *Alembic, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Aldireca *Liconsa, Neth.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Aldirek *Actavis, Fr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Aldisa *Sanbe, Indon.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Aldivina *Farcoral, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Aldo Asma *Aldo, Spain.†*
⊗Phenylephrine hydrochloride (p. 1672·3); isoprenaline hydrochloride (p. 1411·3).
Obstructive airways disease.

Aldobronquial *Aldo, Spain.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Aldoclor *Merck, USA.*
⊗Methyldopa (p. 1431·1); chlorothiazide (p. 1334·3).
Hypertension.

Aldocumar *Aldo, Spain.*
Warfarin sodium (p. 1527·1).
Thrombosis prophylaxis; thromboembolic disorders.

Aldoderma *Aldo, Spain.*
⊗Framycetin sulfate (p. 301·2); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Aldofen *Tocogino, Mex.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Aldolan *Liba, Turk.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Aldoleo *Teofarma, Spain.*
⊗Chlortalidone (p. 1335·2); spironolactone (p. 1499·3).
Oedema; hypertension.

Aldolor *CTI, Israel.†*
Paracetamol (p. 115·1).
Fever; pain.

Aldom *Dr Alson, India.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Aldomer *Mersifarma, Indon.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Aldomet *Biotoscana, Arg.; Aspen, Austral.; Cophana, Belg.; MSD, Braz.; MSD, Denm.†; HAC, Fr.; Vianex (Βιανεξ), Gr.; Iroko, Irl.; Alloga, Ital.; MSD, Mex.; MSD, Neth.†; MSD, Norw.†; MSD, Philipp.; Pharmalink, Philipp.; Iroko, Port.; MSD, S.Afr.†; MSD, Singapore; Iroko, Spain; MSD, Swed.†; Future Health, Switz.; M & H, Thai.; MSD, UK; MSD, Venez.*
Methyldopa (p. 1431·1).
Hypertension.

Aldometil *Iroko, Austria.*
Methyldopa (p. 1431·1).
Hypertension.

Aldomin *MSD, Israel.*
Methyldopa (p. 1431·1).
Hypertension.

Aldomine *Utopian, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Aldonar *Upsifarma, Port.†*
⊗Spironolactone (p. 1499·3).
Hypertension.

Aldopam *Samarth, India.*
Pralidoxime (p. 1571·1).
Organophosphorus poisoning.

Aldoron *Ivax, Arg.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders.

Aldoron Flex *Ivax, Arg.*
Meloxicam (p. 86·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint, and peri-articular disorders.

Aldoron M *Ivax, Arg.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders; inflammation.

Aldoron NF *Ivax, Arg.*
Diclofenac sodium (p. 48·3).
Pain; musculoskeletal and joint disorders.

Aldosion *Alapis, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Aldosomnil *Aldo, Spain.*
Lormetazepam (p. 1082·1).
Insomnia; premedication.

Aldospirone *Teva, Israel.†*
⊗Spironolactone (p. 1499·3).
Heart failure; hyperaldosteronism; hypertension; hypokalaemia; liver cirrhosis.

Aldospray *Aldo-Union, Rus.*
Mabuprofen (p. 68·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Aldospray Analgesico *Aldo, Spain.*
Mabuprofen (p. 68·2).
Peri-articular and soft-tissue disorders.

Aldostix *Bal, India.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Hypertension; oedema; ascites.

Aldotensin *Teuto, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Aldovas *Dexa, Indon.*
Thioctic acid (p. 2629·1); biotin (p. 2052·2); chromium picolinate (p. 2056·1).
Dietary supplement in diabetes mellitus.

Aldozone *Pfizer, Switz.†*
⊗Spironolactone (p. 1499·3); butizide (p. 1329·3).
Heart failure; liver cirrhosis with ascites; hypertension; nephrotic syndrome; oedema.

Al-Drem *Cubit, India.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Aldren *Zydus, S.Afr.; Zydus Cadila, Thai.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aldribid *Aldril, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Aldricin *Aldril, Philipp.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Aldrion *Orion, Cz.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aldromax *Gap, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aldronac *Roemmers, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Aldrox
Note: this name may be used for preparations of different composition.
Pasteur, Chile.
Alendronate sodium (p. 1171·3).
Osteoporosis.
Vargas, Venez.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Aldrox-D *Pasteur, Chile.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Aldry *Curatio, India.*
Aluminium chlorohydrate (p. 1694·1).

Aldurasim *Genzyme, Ukr.†*
Laronidase (p. 2540·2).
Mucopolysaccharidosis I.

Aldurazyme *Genzyme, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Braz.; Genzyme, Canad.; Genzyme, Chile; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Israel; Genzyme, Ital.; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Norw.; Healthcare Logistics, NZ; Genzyme, Pol.; Genzyme, Port.; Genzyme, Spain; Genzyme, Swed.; Sanofi-Aventis, Switz.; Genzyme, Thai.; Sanofi-Aventis, Thai.; Genzyme, Turk.; Genzyme, UK; Genzyme, USA.*
Laronidase (p. 2540·2).
Mucopolysaccharidosis I.

Aldyzine *Zizine, Fr.*
⊗Dexamethasone acetate (p. 1631·1); phenol (p. 1763·3); guaiacol (p. 1666·1).
Root canal infections.

Ale *Jialin, China.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.
Zee, India.
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

Alea *Berlin-Chemie, Denm.; Menarini, Denm.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Aledrolet *Alet, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aledron *IQFA, Mex.*
Oxolamine citrate (p. 1671·2).
Cough.

Aleez *Alde Medi Impex, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alefen *Allenge, India.*
Diclofenac sodium (p. 48·3).
Pain.

Aleflox *Alna, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Aleflox-OZ *Allenge, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Alefos *Santa, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alegi *Lapi, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Alegysal *Santen, China; Ferron, Indon.; Santen, Indon.; Mitsubishi, Jpn; Santen, Philipp.*
Pemirolast potassium (p. 1218·2).
Asthma; allergic rhinitis; allergic conjunctivitis.

Alehelm *Vitalion, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alektra *Zytras, India.*
Sulfacetamide (p. 361·1).
Bacterial eye infections.

Aleli *Bernabo, Arg.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Alemaks *Deva, Turk.*
Alendronate sodium (p. 1171·3).

Alembicol D *Alembic, UK.*
Fractionated coconut oil (p. 2082·2).
Food for special diets; malabsorption syndromes.

Alenat *Arrow, Swed.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alenato *Investi, Arg.; ICN, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Alenbit *Chrispa (Χρισπα), Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Alenca D3 *Takeda, Neth.*
4 Tablets, alendronate sodium (p. 1171·3); 24 chewable tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1) (Calci-Chew).
Osteoporosis.

Alencast *Armedica, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Alenda *Prompt Cure, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Alendil *Farmoquimica, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendil Calcio D *Farmoquimica, Braz.*
Tablets, alendronate sodium (p. 1171·3); tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; hypocalcaemia.

Alendis *Generics, Hung.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendo *Polychronus, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendosseo *EMS, Braz.*
Alendronate sodium (p. 1171·3).

Alendral *Biospray, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendran *Ranbaxy, Pol.*
Alendronic acid (p. 1171·3).
Osteoporosis.

Alendratol *Ranbaxy, Neth.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendris *Tiefenbacher, Neth.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendro *Aspen, Austral.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Alendrobell *Bellwether, Austral.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendrocare *Cantabria, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendrofarm *Farmalider, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendrogen *Generics, Cz.; Billev, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendrogyn *Sintexline, Spain.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

AlendroLEK *Sandoz, Pol.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendromax *Arrow, Hung.; Arrow, Irl.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendromed *Mibe, Ger.*
Alendronate sodium (p. 1171·3).
Osteoporosis.
Takeda, Neth.
1 Tablet, alendronate sodium (p. 1171·3); 6 chewable tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Alendron *Betapharm, Ger.; Sandoz, Hung.; Mepha, Switz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendronax *Will-Pharma, Neth.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendronorm *Genericon, Neth.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendronstad *Stada, Austria.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendro-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendros *Abiogen, Ital.; Zentiva, Ukr.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alendrovenir *Bioavenir, Israel.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alene
Note: this name may be used for preparations of different composition.
Cadila, India.
Adapalene (p. 1692·1).
Acne.

Alenia *Biosintetica, Braz.*
⊗Formoterol fumarate (p. 1209·2); budesonide (p. 1625·1).
Asthma.

Alenic *Epifarma, Ital.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alenic Alka *Rugby, USA.*
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Hyperacidity.
Rugby, USA.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Hyperacidity.

A-Lennon *Pharmacare, S.Afr.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Alenost *Macleods, India.*
Alendronic acid (p. 1171·3).
Osteopetrosis; osteoporosis; Paget's disease of bone.

Alenstran *Chrispa (Χρισπα), Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Alental *Chobet, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; eating disorders.

Alenthus *Medley, Braz.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety disorders; social phobia; panic disorder.

Alentol *Farmo Quimica, Chile.*
Fluoxetine (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder; mixed anxiety depressive states.

Alenvir *Vir, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alenwin *Arrow, Cz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alenys *GSK, Arg.; Etex, Chile.*
⊗Fluticasone furoate (p. 1638·1).
Allergic rhinitis.

Alenzantyl *Chrispa (Χρισπα), Gr.*
Azelaic acid (p. 1695·1).
Acne.

Aleostito *Green Avet, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alep *DR Johns, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alepa *Duopharm, Ger.†*
Milk thistle (p. 1561·1).
Liver disorders.

Alepafort *Salus, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Alepam
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.
Scoshia, India.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Alepet *Eurolab, S.Afr.*
Ondansetron (p. 1872·1).

Alepram *Alet, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Aleprozil *Diba, Mex.*
Omeprazole (p. 1867·2).
Aspiration syndrome; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Alepsal
Note: this name may be used for preparations of different composition.
Genevrier, Fr.
Phenobarbital (p. 535·2); caffeine (p. 1203·3).
Epilepsy.
Spedrog, Arg.; Sanofi-Aventis, Mex.
Phenobarbital (p. 535·2).
Epilepsy; sedative.

Alepsal Compuesto *Sanofi-Aventis, Mex.*
Phenobarbital (p. 535·2); phenytoin sodium (p. 538·2).
Epilepsy.

Aleptan *Lannacher, Austria.*
Risperidone (p. 1103·2).
Schizophrenia; aggression; bipolar disorder.

Aleptiz *Apotex, Philipp.*
Valproic acid (p. 553·1).
Bipolar disorder; migraine; epilepsy.

Alerace *Ace, Philipp.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic disorders; nausea; vomiting; motion sickness; parkinsonism; cough and cold symptoms; insomnia.

Aleradina *Germed, Braz.*
Desloratadine (p. 625·1).

Alerbak *Pfizer, Chile.†*
Sodium spaglumate (p. 2535·2).
Allergic conjunctivitis.

Alerbloc *Karnataka, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alercas *Casasco, Arg.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Alercas D *Casasco, Arg.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Alerchek *Indoco, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Alercina *Cinfa, Spain.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Alercrom *Grin, Mex.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Alerdain *Ordain, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Alerdaune *Confar, Port.*
Loratadine (p. 633·2).

Alerdex *Armoxindo, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Alerdil *Diba, Mex.*
Chlorphenamine (p. 620·3).
Hypersensitivity.

Alerdina *Cafar, Venez.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Aler-Dryl *Reese, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Alerest *Community Pharmacy, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; rhinitis; urticaria.

Alerfan *Anpharm, Pol.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Alerfed *Guardian, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; sinusitis; allergic disorders; nasal congestion.

Alerfedine *Lazar, Arg.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Alerfedine D *Lazar, Arg.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Alerfin
Note: this name may be used for preparations of different composition.
Chiesi, Braz.
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Liferpal, Mex.
Loratadine (p. 633·2).
Hypersensitivity.

Alerfin Ex *Liferpal, Mex.*
Loratadine (p. 633·2); ambroxol (p. 1654·3).

Alerfix *Andromaco, Chile.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Alerfrin *Allergan, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Ocular congestion and irritation.

Alerfur *Ivax, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Alergaliv *Legrand, Braz.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alergaliv D *Legrand, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).

Alergan *Chemopharma, Chile.*
Loratadine (p. 633·2).
Allergic eye disorders; allergic skin disorders; allergic rhinitis; urticaria.

Alergi *Raymos, Arg.*
⊗Dexamethasone (p. 1630·3); chlorphenamine (p. 620·3).
Hypersensitivity reactions.

Alergiano *Northia, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alergibon *Galderma, Mex.*
Soap.
Skin disorders.

Alergical *Faes, Spain.*
Cream: ⊗Betamethasone valerate (p. 1624·1); fluocinolone acetonide (p. 1636·1).
Skin disorders.

Uorente, Spain.
Syrup: ⊗Chlorphenamine maleate (p. 620·3); prednisolone metasulfobenzoate sodium (p. 1645·3).
Hypersensitivity reactions; skin disorders.

Alergical Expectorante *Uorente, Spain.*
Chlorphenamine maleate (p. 620·3); diprophylline (p. 1207·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Cold symptoms.

Alergiderm *Prodotti, Braz.†*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions.

Alergidex *Neo Quimica, Braz.*
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).

Alergidryl *Klonal, Arg.*
Chlorphenamine (p. 620·3).
Hypersensitivity reactions.

Alergiftalmina *Davi, Port.*
⊗Antazoline phosphate (p. 615·3); naphazoline hydrochloride (p. 1669·3).
Conjunctivitis; blepharospasm.

Alergin *Cipla, India.*
⊗Ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3); phenobarbital (p. 535·2).
Asthma; bronchospasm.

Alergipan *Benitol, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Alergitanil *Prodotti, Braz.†*
Mepyramine maleate (p. 635·1).
Hypersensitivity reactions.

Alergitrat *Fecofar, Arg.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Alergitrat L *Fecofar, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alergo Filinal *Eurofarma, Braz.*
Diphenhydramine hydrochloride (p. 626·2); aminophylline (p. 1201·2); guaifenesin (p. 1666·2); pyridoxine hydrochloride (p. 2105·3).
Respiratory-tract disorders.

Alergocrom *Aldo, Spain.†*
Sodium cromoglicate (p. 1225·3).
Asthma; bronchospasm.

Alergoftal *Alcon Cusi, Malaysia†; M4, Spain; Alcon, Turk.*
⊗Antazoline phosphate (p. 615·3); naphazoline hydrochloride (p. 1669·3).
Allergic or inflammatory eye disorders.

Alergoliber *Biohorm, Spain.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

Alergolon *Biolab Sanus, Braz.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Alergonase *Montrose, Cz.†*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Alergonil *Ducto, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Alergoral *Darrow, Braz.*
Allergen preparation (p. 2434·3).
Allergen immunotherapy.

Alergot
Note: this name may be used for preparations of different composition.
Charoon Bhesaj, Thai.
Codergocrine mesilate (p. 389·2).
Mental function impairment; migraine and other vascular headaches; peripheral vascular disorders; hypertension.

Oftalmi, Venez.
Azelastine (p. 617·1).
Allergic conjunctivitis.

Alergoxal *Bros, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Alergyo *Sanval, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Aleric *US Pharmacia, Pol.; US Pharmacia, Ukr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Alerid *Cipla, Cz.; Neopharma, Hung.†; Cipla, India.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria; allergic skin disorders.

Alerid Cold *Cipla, India.*
Cetirizine hydrochloride (p. 619·2); phenylpropanolamine (p. 1674·1); paracetamol (p. 115·1).
Rhinitis; cold symptoms; sinusitis.

Alerid D *Cipla, India.*
Cetirizine hydrochloride (p. 619·2); phenylpropanolamine hydrochloride (p. 1674·1).
Allergic rhinitis.

Alerion
Note: this name may be used for preparations of different composition.
Filaxis, Arg.†
Clonazepam (p. 519·1).
Panic disorder; epilepsy.

Alerjon *Edol, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye irritation.

Alerken *Kener, Mex.*
Astemizole (p. 616·1).
Hypersensitivity.

Alerlisin *Menarini, Spain.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Alermed *Lek-Am, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Alermi *Offenbach, Mex.*
Astemizole (p. 616·1).
Hypersensitivity.

Alermina *Lafedar, Arg.†*
Diphenhydramine (p. 626·1).
Hypersensitivity reactions.

Alermine *Royton, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Alermuc *Elisium, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alernex *Dabur, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Alernitis *Ikapharmindo, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Alernix *Elea, Arg.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Alernyl-B *Svizera, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Alernyl-DC *Svizera, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Alero *Sandoz, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Aleron
Note: this name may be used for preparations of different composition.
Actavis, Ukr.
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria; allergic skin reactions.

Cosme, India.
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Alerpect *Themis, India.*
Bromhexine hydrochloride (p. 1656·3); dexchlorpheniramine maleate (p. 621·1); dextromethorphan (p. 1660·1).

Alerpriv *Montpellier, Arg.; Montpellier, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; hypersensitivity reactions.

Alerpriv D *Montpellier, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Cold symptoms; allergic rhinitis.

Alerstin *Mount Mettur, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Alert *Alkem, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Alert Aid *Sun Labs, Canad.†*
Caffeine (p. 1203·3).

Alertec *Shire, Canad.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; obstructive sleep apnoea; shift-work sleep disorder.

Alerten *Mega Lifesciences, Malaysia; Mega Lifesciences, Philipp.; Mega Lifesciences, Singapore; Mega Lifesciences, Thai.*
Ubidecarenone (p. 2637·1).
Dietary supplement; cardiovascular disorders.

Alertex *Saval, Chile.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Alerton *Sun-Farm, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Alertonic *Odan, Canad.*
Pipradrol hydrochloride (p. 2329·3); vitamin B substances (p. 2102·3).
Tonic.

Adcock Ingram, S.Afr.†
Pipradrol hydrochloride (p. 2329·3); vitamin B substances (p. 2102·3); minerals.
Tonic.

Alertop *Laboratorios Chile, Chile.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alertop-D *Laboratorios Chile, Chile.†*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Alertrin *Plough, Port.*
Loratadine (p. 633·2).
Allergic rhinitis; eye irritation; urticaria.

Alertriz *Cadila, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Alertyne *PP Lab, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alervin *Ultramark, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alervo *Arvincare, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alerxem *Kleva, Gr.*
⊗Fluticasone propionate (p. 1638·1).

Alerza *Ipca, Rus.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alerzin *Egis, Ukr.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Alerzina *Lek-Am, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Alerzole *Themis Medicare, India.*
Astemizole (p. 616·1).
Hypersensitivity reactions.

Alerzona *Silesia, Chile.†*
⊗Mepyramine maleate (p. 635·1); prednisone acetate (p. 1647·2).
Skin disorders.

Alesa *Glenmark, India.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Alesal *Zuoz, Venez.*
Diethylamine salicylate (p. 51·3).
Musculoskeletal and joint disorders.

Alese *Zee, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Alesion *Boehringer Ingelheim, China; Boehringer Ingelheim, Jpn.*
Epinastine hydrochloride (p. 628·3).
Asthma; allergic rhinitis; pruritus.

Alesone *Ultra, Mex.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Alespan *Intermed, Gr.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Alesse *Pfizer, Canad.; Wyeth, Neth.†; Wyeth-Ayerst, USA.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; acne.

Wyeth, Chile†; Wyeth, Mex.; Wyeth, Venez.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive; androgen-associated acne in women.

Alestopor *Kleva, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Aletir *Bunker, Braz.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Aletor *XL, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Aletris N Oligoplex *Madaus, Ger.*
Aletris farinosa; helonias dioica (p. 2524·3); lilium tigrinum; pulsatilla (p. 2600·2).
Homoeopathic preparation.

Aletris Oligoplex *Madaus, Ger.†*
Aletris farinosa; china (p. 2478·3); helonias dioica (p. 2524·3); hydrastis (p. 2528·1); kreosotum (p. 1659·3); lilium tigrinum; pulsatilla (p. 2600·2); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Aletro *Noventis, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Aleudrina *Reig Jofre, Spain.*
⊗Isoprenaline sulfate (p. 1411·3).
Cardiac disorders; shock.

Aleva
Note: this name may be used for preparations of different composition.
Aronex, India.
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

OEP, Philipp.
Ebastine (p. 628·1).
Allergic rhinitis; urticaria.

Aleval *Sun, Mex.; Sun, Rus.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Alevarin *Bioforma, Mex.*
Aesculus (p. 2431·2).
Venous insufficiency.

Aleve *Bayer, Austria; Bayer, Belg.; Roche, Belg.; Bayer Consumer, Canad.; Bayer, Cz.; Bayer, Ger.; Bayer, Hung.; Bayer, Ital.; Bayer, Neth.; Bayer, Pol.; Bayer Consumer, S. Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Switz.; Abdi, Turk.; Procter & Gamble, USA.*
Naproxen sodium (p. 98·2).
Gout; pain; inflammation; fever; musculoskeletal, joint, and soft-tissue disorders.

Bayer Consumer, Arg.
Naproxen (p. 98·2).
Fever; pain.

Alevetabs *Bayer Sante, Fr.*
Naproxen sodium (p. 98·2).
Pain; fever.

Alevian Duo *Nycomed, Mex.*
Pinaverium bromide (p. 2590·3); simeticone (p. 1886·2).
Irritable bowel syndrome; meteorism; gastrointestinal motility disorders.

Aleviate *CSL Biotherapies, Hong Kong; CSL, Malaysia.*
A factor VIII preparation (p. 1148·1).
Haemophilia A.

Aleviatin *Dainippon, Jpn.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Alevior *Aurora, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Alevo *Alkem, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Alex
Note: this name may be used for preparations of different composition.
Glenmark, India.
Dextromethorphan hydrobromide (p. 1660·1).
Formerly known as Alex Cough.
Cough; sore throat; pharyngitis.

Savoy, India.
Gatifloxacin (p. 303·2).
Bacterial infections.

Glenmark, India.†
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cough; cold symptoms.

Alex Cough *Glenmark, India.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, chlorphenamine maleate, and guaifenesin.
Cough.

Alex Paediatric *Glenmark, India.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Formerly contained phenylpropanolamine hydrochloride and chlorphenamine maleate.
Nasal congestion; rhinitis.

Alex Plus *Glenmark, Rus.; Glenmark, Ukr.†*
Dextromethorphan hydrobromide (p. 1660·1); terpin hydrate (p. 1678·2); levomenthol (p. 2553·2).
Cough.

Alex Sugar Free *Glenmark, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine (p. 1672·2).

Alexa *Sigma, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Alexan *Ebewe, Austria; Pfizer, Chile†; Pfizer, China; Ebewe, Cz.; Ebewe, Ger.†; Neocorp, Ger.†; Sandoz, Hong Kong; Ebewe, Hung.; Ferron, Indon.; Ebewe, Israel; EuroCept, Neth.†; Ebewe, Pol.; Ebewe, Rus.; Pharmafrica, S.Afr.†; Ebewe, Thai.; Eczacibasi, Turk.*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphomas.

Alexfix *Eris, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alexia *Saval, Chile.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; allergic skin disorders.

Alexia D *Saval, Chile.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Alexin
Note: this name may be used for preparations of different composition.
Dabur, India.
Cefalexin (p. 234·1).
Bacterial infections.

Farmoz, Port.
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Alexing *Farcoral, Mex.*
Ambroxol (p. 1654·3); dextromethorphan (p. 1660·1).
Cough; respiratory-tract congestion.

Alexis *Zytras, India.*
Ketorolac (p. 80·2).
Allergic conjunctivitis; inflammation, pain, and photophobia following eye surgery; cystoid macular oedema.

Alexonal *Sandoz, Indon.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Alex-P *Glenmark, India.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, chlorphenamine maleate, and paracetamol.
Cough; cold symptoms.

Aleztem *Rayere, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity reactions.

Alfa
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Spain.†
⊗Naphazoline nitrate (p. 1669·3).
Eye irritation.

Alfa Acid *Merz, Ital.*
Ammonium lactate (p. 1694·3); salicylic acid (p. 1719·1); dexpanthenol (p. 2582·2).
Scalp disorders.

Alfa Bergamon *Chefaro, Ital.*
Didecyldimethylammonium chloride (p. 1750·3).
Disinfection of burns, mucous membranes, and wounds.

Alfa C *Bracco, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye irritation.

Alfa Calcinol *Raptakos, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3); calcium citrate (p. 1783·2); calcium phosphate (p. 1784·2); magnesium hydroxide (p. 1857·2).

Alfa Caps *Glenmark, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Alfa Caps Plus *Glenmark, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Alfa Kappa *Kedrion, Ital.†*
Amino acids.
Nutritional supplement in renal failure.

Alfa Lip *NCSN, Ital.*
Thioctic acid (p. 2629·1); vitamins.
Nutritional supplement.

Alfa Normix *Alfa Wassermann, Rus.*
Rifaximin (p. 355·2).
Gastrointestinal bacterial infections.

Alfa Ostebon *Aristo, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).
Osteoporosis; osteomalacia; rickets; hypoparathyroidism; renal osteodystrophy.

Alfa Surecal *Pure Health, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alfa Tab *Vensat, India.*
Fluconazole (p. 578·2).
Fungal infections.

Alfabase *Cassaro, Arg.*
Emollient.

Alfabase 8 *Cassaro, Arg.*
Glycolic acid (p. 1704·3).
Photoageing of skin.

Alfabet *Invision, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Alfabol *Meridian, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Alfacaina *Dentsply, Ital.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Alfacal *Macleods, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Alfacal Plus *Macleods, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Alfacalcil *Zwitter, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alfacan *Simcere, China.*
Alfacalcidol (p. 2112·3).
Osteoporosis; rickets; osteomalacia; renal osteodystrophy; hypoparathyroidism.

Alfacare *Cure Quick, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Alfaciclina *Vargas, Venez.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Alfacillin *Vista, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Alfacip *Cipla, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Alfacip Plus *Cipla, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alfacolin *Catalysis, Arg.*
Colistin (p. 275·3).
Bacterial infections.

Alfacort *Cassara, Arg.; Julphar, UAE.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Inflammatory eye disorders; skin disorders.

Alfacortone *Spirig, Switz.*
⊗Hydrocortisone acetate (p. 1640·1).
Burns; insect stings; skin disorders.

Alfacrist *Chrispa (Χρισπα), Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Alfad *Nycomed, Mex.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; osteoporosis; hyperparathyroidism; hypoparathyroidism; osteomalacia; rickets.

Alfadel *Polychronus, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alfadil *Pfizer, Philipp.; Pfizer, Swed.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Alfadiman *Lazar, Arg.*
Allopurinol (p. 600·2).
Hyperuricaemia; renal calculi.

Alfadina *Bausch & Lomb, Spain.*
Brimonidine tartrate (p. 2004·3).
Ocular hypertension; glaucoma.

Alfadiol *GSK, Pol.*
Alfacalcidol (p. 2112·3).
Osteoporosis; hypocalcaemia; rickets; osteomalacia; hypoparathyroidism; nephrotic syndrome; renal osteodystrophy.

Alfadoxin *Laboratorios Chile, Chile.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Alfadrops *Cipla, India.*
Apraclonidine hydrochloride (p. 2003·3).
Glaucoma.

Alfaferone *Alfa Wassermann, Cz.†; Wassermann, Ital.; Alfa Wassermann, Pol.; Alfa Wassermann, Rus.*
Interferon alfa (p. 989·2).
Malignant neoplasms; chronic hepatitis B; chronic hepatitis C; anogenital warts.

Alfaflavon *Indo French, India.*
Vitamins; minerals; betacarotene (p. 2051·1); isoflavone (p. 2620·3).

Alfaflor *INTES, Ital.*
⊗Bottle A, betamethasone sodium phosphate (p. 1623·3); naphazoline nitrate (p. 1669·3); bottle B, tetracycline hydrochloride (p. 373·2).
Inflammatory eye disorders.

Alfagin *Herbion, Ukr.*
Ginseng (p. 2513·3); siberian ginseng (p. 2614·3); alfalfa (p. 2433·1); Indian gooseberry (p. 2532·2); fenugreek (p. 2504·1).
Asthenia; neurasthenia.

Alfaken *Kendrick, Mex.*
Lisinopril (p. 1420·3).
Hypertension.

Alfalastin *LFB, Fr.*
Alpha$_1$-proteinase inhibitor (p. 2438·1).
Alpha$_1$ antitrypsin deficiency.

Alfalfa Tonic
Note: this name may be used for preparations of different composition.
Boiron, Canad.
Alfalfa (p. 2433·1); avena sativa (p. 2451·1); cyclamen europaeum (p. 2490·2); eleutherococcus (p. 2614·3); ginseng (p. 2513·3); kalium phosphoricum (p. 1790·3); menyanthes trifoliata (p. 2554·2).
Homoeopathic preparation.

Homeocan, Canad.
⊗Agnus castus (p. 2432·2); alfalfa (p. 2433·1); avena sativa (p. 2451·1); cinnamomum (p. 2479·2); eleutherococcus (p. 2614·3); phosphoricum acidum (p. 2589·1); selenium metallicum (p. 2086·3); kali arsenicosum (p. 2594·3).
Homoeopathic preparation.

Alfalfa Tonic with Ginseng *Homeocan, Canad.†*
⊗Alfalfa (p. 2433·1); cinnamomum (p. 2479·2); avena sativa (p. 2451·1); ginseng (p. 2513·3); phosphoricum acidum (p. 2589·1); selenium metallicum (p. 2086·3); agnus castus (p. 2432·2); kali arsenicosum (p. 2594·3).
Homoeopathic preparation.

Alfa-Lipon *KVZ, Ukr.*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy; liver disorders; heavy-metal poisoning; mushroom poisoning.

Alfam *David, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Alfamatic *Medichrom, Gr.*
Tretinoin (p. 1725·2).

Alfa-Maxical *Mankind, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alfamedin *Kade, Ger.†*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia.

Alfamet *Eczacibasi, Turk.*
Methyldopa (p. 1431·1).
Hypertension.

Alfa-Mon *Biotech, Venez.*
Vitamin A (p. 2098·3).

Alfamox *Teofarma, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Alfan *Alpharma, Mex.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2).
Nasal congestion; cough.

Alfaprost *Biomed, Spain.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Alfapsin *Hetero, India.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Inflammation; oedema; respiratory-tract congestion; adjunct in antibacterial therapy; thrombophlebitis.

Alfapsin D *Hetero, India.*
⊗Chymotrypsin (p. 2477·3); diclofenac potassium (p. 48·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alfare *Nestle, Braz.; Nestle, Ital.; Nestle, Mex.; Nestle, Venez.*
Preparation for enteral nutrition.
Diarrhoea; malabsorption disorders; cows' milk intolerance; soy protein intolerance.

Nestle, Austral.†; Nestle, Philipp.
Infant feed.
Diarrhoea; hypersensitivity; malabsorption disorders.

Alfaré *Nestle, Fr.*
Infant feed.
Cows' milk allergy; diarrhoea; malabsorption.

Alfarich *Cipla, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Alfariz *Ritz, India.*
Injection: Dexpanthenol (p. 2582·2); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Ritz, India.
Tablets: Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); vitamins.

Alfarol
Note: this name may be used for preparations of different composition.
Chugai, Jpn.
Alfacalcidol (p. 2112·3).
Hypoparathyroidism; osteomalacia; osteoporosis; renal failure; rickets.

Soylu, Turk.
Phenylpropanolamine (p. 1674·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Alfarona *Pharmaclon, Rus.*
Interferon alfa-2b (p. 989·2).
Hepatitis B; chronic hepatitis C; malignant neoplasms.

Alfaset *Orchid, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Alfasid *Fako, Turk.; Yavuz, Turk.*
Injection: Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Lidocaine hydrochloride (p. 1988·2) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

Fako, Turk.; Yavuz, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1) or sultamicillin tosilate (p. 369·1).
Bacterial infections.

Alfasilin *Fako, Turk.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Alfasin *Abbott, Braz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Alfason *Astellas, Ger.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Alfast *Cristalia, Braz.*
⊗Alfentanil hydrochloride (p. 18·2).
Pain.

Alfasurecal *Pure Health, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alfatam *Zydus, India.*
Tamsulosin (p. 2369·1).
Benign prostatic hyperplasia.

Alfate *Stadmed, India.†*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Alfatec-C *Technica, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Alfater
Note: this name may be used for preparations of different composition.
ABC, Ukr.
Terazosin (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Alfatil *Dexo, Fr.*
Cefaclor (p. 232·3).
Bacterial infections.

Alfaton *Angelini, Gr.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis.

Alfatoz *ATOZ, India.*
Alfacalcidol (p. 2112·3); betacarotene (p. 2051·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Alfavit-Eoxi *Gelcaps, Mex.†*
Alpha tocopherol (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Alfavitil *DNR, Arg.*
Pronalen.
Cellulitis.

Alfaxin *Bago, Arg.*
Venlafaxine (p. 454·2).
Depression.

Alfazic *Trumac, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alfazina
Note: this name may be used for preparations of different composition.
Alvartis, Mex.
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Alfazol *IQFA, Mex.*
Albendazole (p. 149·1).
Worm infections.

Alfazosin *Aurobindo, India.*
Doxazosin (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Alfe *Candor, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Alfem *Nucitec, Mex.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3).
Calcium, vitamin D, and magnesium supplement; osteoporosis; rickets; osteomalacia; tetany.

Alfener *Farmamust, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Alfenta *Akorn, USA.*
⊗Alfentanil hydrochloride (p. 18·2).
Analgesia during anaesthesia; induction of anaesthesia.

Alfer *Alde Medi Impex, India.*
Sodium feredetate (p. 2088·3).

Alferon *Zydus, India; Cryopharma, Mex.*
Interferon alfa-2a (recombinant) (p. 989·2).
Malignant neoplasms; chronic hepatitis B; chronic hepatitis C.

Alferon N *HemispheRx, USA.†*
Interferon alfa-n3 (p. 989·2).
Genital warts.

Alfetim *Sanofi-Aventis, Hung.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfex *Zee, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alfex-BT *Zee, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3); betacarotene (p. 2051·1).

Alfexo *Ind-Swift, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Alficetin *Nova Argentia, Arg.*
Colistimethate sodium (p. 275·3).
Bacterial infections.

Alfi-CV *Anvik, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).

Alfin *Sanitas, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Alfin Combo *Sanofi-Aventis, Hung.*
Tablets, alfuzosin hydrochloride (p. 2351·3) (Alfetim Uno); tablets, finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Alfinal *Valenta, Rus.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Alfinor *Medochemie, Hong Kong; Medochemie, Malaysia.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Alfiral *Silanes, Mex.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and leprosy; meningitis prophylaxis.

Alfiron *Arterium, Ukr.*
Interferon alfa-2b (p. 989·2).
Viral bacterial infections; laryngeal papillomatosis; multiple sclerosis; malignant neoplasms.

Alfirum *Ranbaxy, Irl.†*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfitar *Sesderma, Spain.*
Coal tar (p. 1723·2).
Psoriasis; seborrhoeic dermatitis.

Alflam *Mugi, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Alflox *Alkem, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Alflutop *Biotehnos, Rus.*
Defatted and deproteinised sea fish extract.
Musculoskeletal and joint disorders.

Biotehnos, Ukr.
Injection: Extract marine organisms.
Musculoskeletal and joint disorders.

Biotehnos, Ukr.†
Gel: Extract marine organisms; rosemary oil (p. 2607·3).
Musculoskeletal and joint disorders.

Alfoo *Reddy, India.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfospas *Rottapharm, Ital.*
Tiropramide hydrochloride (p. 2632·2).
Gastrointestinal spasm.

Alfoxan *Remedica, Singapore.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Alfoxil *Fako, Turk.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Alfron *Sigma, Braz.*
Alprazolam (p. 1035·2).
Anxiety; alcohol withdrawal syndrome; panic disorder.

Alfu *Rowex, Irl.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfuca *Kenyaku, Thai.*
Albendazole (p. 149·1).
Worm infections.

Alfucoz *Alembic, India.*
Fluconazole (p. 578·2).
Fungal infections.

Alfugen *Generics, Hung.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfu-Kal *Perrigo, Israel.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hypertrophy.

AlfuLEK *Sandoz, Pol.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfumet *David, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Alfunar *Apogepha, Ger.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfuprost *Farmedia, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfural *Rafarm, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfusin *TAD, Ger.†; Cipla, India.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfuzin *Biomedica, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alfuzina *Bunker, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Alfuzostad *Stada, Cz.; Stada, Hung.; Steigerwald, Pol.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alga Maris *Laboratoires de Biarritz, Fr.*
SPF 10; SPF 20; SPF 30; SPF 50: Titanium dioxide (p. 1725·1); gelidium sesquipedale.
Sunscreen.

Alganax *Guardian, Indon.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder.

Alganex *Meda, Swed.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; dysmenorrhoea; postoperative pain.

Algat *Alkem, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Algedol *Pfizer, Arg.*
⊗Morphine sulfate (p. 92·3).
Pain.

Algedrox *De Mayo, Braz.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Algefit *Pharmaselect, Austria.*
Diclofenac sodium (p. 48·3).
Soft-tissue and peri-articular disorders.

Algesal
Note: this name may be used for preparations of different composition.
Vemedia, Belg.†; Solvay, Fin.†; Famar, Gr.; Solvay, Neth.†; Nycomed, Norw.; Abbott, Swed.; Frik, Turk.; Zeroderma, UK.
Diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Raffo, Arg.; Pharmaselect, Austria; Pharmaselect, Cz.; Biokanol, Ger.†; Pharmaselect, Hung.; CS, Port.; Stada, Spain.
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Algésal *Pharmadeveloppement, Fr.*
Diethylamine salicylate (p. 51·3).
Musculoskeletal and peri-articular pain.

Algesal Forte *Solvay, Neth.†*
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Muscle and joint pain.

Algesal Superactive *Solvay, Indon.*
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Algesal Suractive *Pharmaselect, Gr.; Frik, Turk.*
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Musculoskeletal and joint pain.

Algésal Suractivé *Pharmadeveloppement, Fr.*
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Musculoskeletal and peri-articular pain.

Algesia *Biomedis, Philipp.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Algest *Cadila, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Alges-X *Axapharm, Switz.*
Ibuprofen (p. 68·2).
Fever; pain.

Algetuss *Diapit, Gr.†*
Amino acids.
Dietary supplement.

Algex
Note: this name may be used for preparations of different composition.
Farmo Quimica, Chile.
Mefenamic acid (p. 85·3).
Pain.

Algexin *Cimed, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Algezir *Obolenskoe, Rus.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain; inflammation.

Algi *Mabo, Spain.*
Metamizole magnesium (p. 53·3).
Fever; pain.

Algiafin *Interpharma, Chile.*
Paracetamol (p. 115·1).
Pain; fever.

Algiasdin *Isdin, Spain.*
Ibuprofen (p. 68·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Algibon *Galderma, Venez.*
Skin cleanser.

Algibra *Cosme, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Algibron *Pharmathen, Gr.*
Indometacin (p. 71·2).

Algical Kalzarevet *Femi Agran, Israel.*
Calcium carbonate (p. 1824·3); sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Algicalm *Grunenthal, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Algicê *Cazi, Braz.*
Green tablets, dipyrone (p. 53·3); sodium camsilate (p. 2617·3); cineole (p. 2479·1); guaifenesin (p. 1666·2); niaouli oil (p. 2569·1); yellow tablets, vitamin C (p. 2110·3).
Cold and influenza symptoms.

Algicler *Monserrat, Arg.*
Tablets: Diclofenac (p. 48·3); paracetamol (p. 115·1).

Monserrat, Arg.
Topical gel: Diclofenac diethylamine (p. 48·3).

Algicon *Sanofi-Aventis, Neth.*
Oral suspension: Magnesium alginate (p. 2167·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium carbonate (p. 1856·2); potassium bicarbonate (p. 1780·3); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; heartburn.

Sanofi-Aventis, Neth.
Tablets: Magnesium alginate (p. 2167·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium carbonate (p. 1856·2); potassium bicarbonate (p. 1780·3).
Gastro-oesophageal reflux; heartburn.

Algi-Cool *Qualiphar, Belg.†*
Menthol (p. 2553·2); dexpanthenol (p. 2582·2); chamomile (p. 2474·1); arnica (p. 2447·2); devil's claw (p. 42·3); camphor (p. 2466·2).
Musculoskeletal and joint disorders.

Algicote *Sanofi-Aventis, Chile.†*
Chewable tablets: Magnesium alginate (p. 2167·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium carbonate (p. 1856·2); potassium bicarbonate (p. 1780·3).
Gastro-oesophageal reflux.

Sanofi-Aventis, Chile.†
Oral suspension: Magnesium alginate (p. 2167·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium carbonate (p. 1856·2); calcium carbonate (p. 1824·3); potassium bicarbonate (p. 1780·3).
Gastro-oesophageal reflux.

Algicuivre *Dissolvurol, Mon.*
Tablets: Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); meadowsweet (p. 2550·2); copper (p. 2057·1).
Osteoarthritis.

Dissolvurol, Mon.
Transdermal patch: Copper (p. 2057·1).
Musculoskeletal and joint pain.

Algicum *Azevedos, Port.†*
Diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, and soft-tissue disorders.

Algiderm *Finadiet, Arg.*
Erythromycin ethyl succinate (p. 291·2).
Acne.

Algiderma *Davi, Port.†*
Diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, and soft-tissue disorders.

Algidol
Note: this name may be used for preparations of different composition.
Almirall, Spain.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); ascorbic acid (p. 2110·3).
Fever; pain.

Vitae, Mex.
Ibuprofen (p. 68·2).
Pain.

Algidrin *Fardi, Spain.*
Ibuprofen lysine (p. 68·3).
Inflammation; pain.

Algifast *Fardi, Spain.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Algifemin *Sanitas, Chile.*
Mefenamic acid (p. 85·3).
Pain.

Algifen
Note: this name may be used for preparations of different composition.
Ulagay, Turk.
Ibuprofen (p. 68·2).
Pain; fever.

Zentiva, Cz.
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Painful smooth muscle spasm.

Algifen Neo *Teva, Cz.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Painful smooth muscle spasm.

Algifene
Note: this name may be used for preparations of different composition.
Ferraz, Lynce, Port.
Tablets: Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Pain.

Algiflamanil *Neo Quimica, Braz.†*
Oxyphenbutazone (p. 114·3); paracetamol (p. 115·1).
Fever; inflammation; pain.

Algiflex
Note: this name may be used for preparations of different composition.
EMS, Braz.
Ibuprofen (p. 68·2).

Algifor *Vifor, Switz.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Pain; fever; juvenile idiopathic arthritis.

Algifort *GPC, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Algik *Azevedos, Port.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Algikey *Inkeysa, Spain.†*
Ketorolac trometamol (p. 80·2).
Pain.

Algimate *Jaba Recordati, Port.*
Clonixin lysine (p. 40·1).
Pain.

Algimesil *Francia, Ital.*
Nimesulide (p. 101·3).
Pain.

Algina
Note: this name may be used for preparations of different composition.
Confar, Port.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); guaiacol (p. 1666·1).
Musculoskeletal, joint, and soft-tissue disorders.

Geno, India.
Paracetamol (p. 115·1).
Pain; fever.

Alginac *Merck, Braz.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2); diclofenac sodium (p. 48·3).

Alginatol *Nizhpharm, Rus.*
Sodium alginate (p. 2167·3).
Anorectal disorders.

Algine *Adelco, Gr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Alginor *Boehringer Ingelheim, Ital.*
Cimetropium bromide (p. 1831·3).
Gastrointestinal disorders; adjunct in gastrointestinal examinations and surgical procedures.

Algin-P *Gujarat Terce, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Algin-Vek *Faran, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Algio Nervomax *TRB, Arg.*
Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ampoule 2, diclofenac sodium (p. 48·3).
Peri-articular and soft-tissue disorders; pain.

Algio Nervomax Fuerte *TRB, Arg.*
⊗Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ampoule 2, diclofenac sodium (p. 48·3); betamethasone sodium phosphate (p. 1623·3).
Musculoskeletal and joint disorders.

Algio-Bladuril *Casasco, Arg.*
Flavoxate hydrochloride (p. 2360·1); propyphenazone (p. 127·3).
Bladder disorders; female genital-tract spasm.

Algiodent *Ronnet, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2); hexylresorcinol (p. 1755·1); cresol (p. 1749·1).
Mouth and throat infections.

Algion *Saval, Chile.†*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Algiospray *Galenica, Gr.*
Picolamine salicylate (p. 125·3).

Algioxib *Dupomar, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation.

Algipan
Note: this name may be used for preparations of different composition.
Qualiphar, Belg.
Methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2); mephenesin (p. 2025·2).
Musculoskeletal pain; skeletal muscle spasm.

Wyeth, India.
Methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2); capsicum oleoresin (p. 2469·3); histamine hydrochloride (p. 2525·2).
Muscle and joint pain; neuralgia.

Pierre Fabre Sante, Fr.†
Methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2); histamine hydrochloride (p. 2525·2); mephenesin (p. 2025·2).
Muscle pain.

Algipatch *Angelini, Spain.*
Diclofenac sodium (p. 48·3).
Soft-tissue trauma.

Algirem *Olifen, Rus.†*
Rimantadine hydrochloride (p. 1012·2).
Influenza.

Algi-Reumatril *Hertz, Braz.*
Ibuprofen (p. 68·2).
Pain; inflammation.

Algirona *Bunker, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Algiseda *Sanitas, Arg.*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Musculoskeletal, joint, and peri-articular disorders.

Algiseda Plus *Sanitas, Arg.*
⊗Carisoprodol (p. 2021·3); paracetamol (p. 115·1); dexamethasone (p. 1630·3).

Algisedal *Meda, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Algisite M *Smith & Nephew, Austral.; Smith & Nephew, Belg.*
Calcium alginate (p. 1136·3).
Wounds.

Algispray *Casasco, Arg.*
Dichlorodifluoromethane (p. 1798·2); trichlorofluoromethane (p. 1798·2).
Local anaesthesia; pain.

Algis-Spray *Qualiphar, Belg.*
Turpentine oil (p. 2636·3); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Algistop *ISA, Arg.†*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Algi-Tanderil *Glenmark, Braz.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); carisoprodol (p. 2021·3); caffeine (p. 1203·3).
Inflammation; pain.

Algitrin *Schering-Plough, Mex.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Algix *Gentili, Ital.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Alglid *Candor, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Alglid-M *Candor, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Alglutamin *Rivero, Arg.*
L-Alanyl-L-glutamine (p. 2070·2).
Glutamine supplement for parenteral nutrition.

Algo *Lokman, Turk.†*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Algo Bebe *Lokman, Turk.*
Aspirin (p. 22·2).
Pain; fever.

Algocit *Demo, Gr.*
Paracetamol (p. 115·1).
Fever; pain.

Algocod *SMB, Belg.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Algocor *Teofarma, Ital.*
Gallopamil hydrochloride (p. 1390·3).
Angina pectoris; myocardial infarction.

Algodol *Pharmastra, Fr.*
Paracetamol (p. 115·1).
Fever; pain.

Algodol Cafeine *Pharmastra, Fr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Algofen *SIT, Ital.*
Ibuprofen (p. 68·2).
Pain.

Algofetin *Obolenskoe, Rus.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain; fever.

Algofina *Sanamed, Austria.†*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Fever; pain.

Algoflex *Sanofi-Aventis, Hung.*
Tablets: Ibuprofen (p. 68·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Sanofi-Aventis, Hung.
Topical gel: Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue disorders.

Algoflex-M *Sanofi-Aventis, Hung.*
Round tablets, ibuprofen (p. 68·2); oblong tablets, drotaverine hydrochloride (p. 2497·3).
Dysmenorrhoea.

Algofren *Intermed, Gr.*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal and joint disorders.

Algogen *Nakornpatana, Thai.*
Paracetamol (p. 115·1).
Pain.

Algolider *Siar, Ital.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Algolysin *Teva, Israel.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Fever; pain.

Algomax *Teva, Ukr.*
Sumatriptan (p. 679·2).
Migraine.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Algon *Minerva, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

Algophene *SMB, Belg.†*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Algopirina *Pielle, Ital.*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Cold and influenza symptoms; pain.

Algoplaque *Urgo, Belg.; Urgo, Fr.†*
A hydrocolloid dressing.
Wounds; burns; ulcers.

Urgo, Ger.
Carmellose sodium (p. 2175·2).
Ulcers; wounds.

Algopress *Intermed, Gr.*
Mefenamic acid (p. 85·3).

Algopyrin *Sanofi-Aventis, Hung.*
Dipyrone (p. 53·3).
Fever; pain.

Algopyrin Complex *Sanofi-Aventis, Hung.*
Dipyrone (p. 53·3); caffeine (p. 1203·3); drotaverine hydrochloride (p. 2497·3).
Headache; migraine.

Algoren *Ronava, Venez.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; arrhythmias; hypertension; migraine.

Algorex *Amnol, Ital.*
⊗Maritime pine (p. 2590·3); aesculus (p. 2431·2); bromelains (p. 2460·3); vitamin B substances (p. 2102·3).
Inflammation; oedema.

Algosenac *Senese, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; painful smooth muscle spasm.

Algosfar *Medifarma, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Algostase *SMB, Belg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Algostase Mono *SMB, Belg.*
Paracetamol (p. 115·1).
Fever; pain.

Algostéril *Brothier, Fr.*
Calcium alginate (p. 1136·3).
Haemostatic dressing.

Algosteril *Johnson & Johnson Consumer, Belg.; Systagenix, Ital.; Smith & Nephew, UK.*
Calcium alginate (p. 1136·3).
Wounds; haemostatic dressing.

Algosulid *Med-One, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Algotropyl *Biocodex, Fr.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2).
Cold symptoms.

Algover *Iapharm, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Algo-Wax *Lokman, Turk.*
Menthol (p. 2553·2); camphor (p. 2466·2); capsicum oleoresin (p. 2469·3); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3); turpentine oil (p. 2636·3); lavender oil (p. 2541·1).
Musculoskeletal and joint pain.

Algozone *Labormed, Hung.*
Dipyrone (p. 53·3).
Fever; pain.

Algues *Boiron, Fr.†*
Fucus (p. 2612·1).
Obesity.

Algun *Diba, Mex.*
Latanoprost (p. 2008·1).
Ocular hypertension.

Algut *Merck, Indon.†*
Allopurinol (p. 600·2).
Gout.

Algybrex *Northia, Arg.†*
Celecoxib (p. 36·3).

Algycon *American Taiwan, Philipp.; America n Taiwan, Thai.*
Alginic acid (p. 2167·2); magnesium carbonate (p. 1856·2); aluminium hydroxide (p. 1817·2).
Gastro-oesophageal reflux; antacid; hiatus hernia; heartburn; dyspepsia.

Algyfree *Galpha, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alho-Arthrosan N *Wiedemann, Ger.*
Calcium phosphoricum (p. 1784·2); berberis vulgaris (p. 2502·1); bryonia cretica; colchicum autumnale (p. 607·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Alho-Sedosan *Wiedemann, Ger.*
Humulus lupulus (p. 2546·1); zincum valerianicum (p. 2641·2); passiflora incarnata (p. 2584·1); avena sativa (p. 2451·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Alhydrate *Nestle, Ital.*
Oral rehydration solution (p. 1780·1).
Diarrhoea.

Nestle, Fr.†
Maltodextrin (p. 2080·3); sucrose (p. 2096·3); sodium chloride (p. 1795·1); citric acid (p. 2480·3); potassium citrate (p. 1780·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Ali Veg *GSK Consumer, Spain.†*
Cimetidine (p. 1827·1).
Acid aspiration; gastrointestinal haemorrhage; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; short-bowel syndrome; Zollinger-Ellison syndrome.

Aliamare *IBSA, Ger.*
Sodium hyaluronate (p. 2526·2); sea water (p. 2612·1).
Nasal disorders.

Aliane *Bayer, Austria; Bayer, Pol.; Lusal, Port.*
Ethinylestradiol betadex clathrate (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Alibi *Pierre Fabre, Fr.*
Green tea (p. 2648·2); parsley oil (p. 2583·3).
Oral hygiene.

Alicalm *SHS, UK.*
Food for special diets.
Crohn's disease.

Alice *Ind-Swift, India.*
Paracetamol (p. 115·1).
Pain; fever.

Alice-D *Ind-Swift, India.*
Paracetamol (p. 115·1); domperidone (p. 1838·1).
Migraine.

A-Lices *Hoe, Hong Kong; Hoe, Malaysia; AFT, NZ; Hoe, Philipp.; Hoe, Singapore; Hoe, Thai.*
Malathion (p. 2157·2).
Pediculosis; scabies.

Alici-A *Mallix, Philipp.*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Alicin *Allenge, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Alicitonin *Rafarm, Gr.*
Calcitonin (salmon) (p. 1178·1).

Alicold *Alicon, India.*
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1).

Alicon *Adley, India.*
Fluconazole (p. 578·2).
Fungal infections.

Alicron *Ferron, Indon.*
Thioctic acid (p. 2629·1); biotin (p. 2052·2); chromium polynicotinate (p. 2055·3).
Supplement in diabetes mellitus.

Alicura *Catarinense, Braz.†*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain; inflammation.

Alidase *Bernabo, Arg.*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Alidec *Allenge, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Aliderma *Candor, India.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Alidex *Peseri, Fin.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Alidial *Filaxis, Arg.*
Gabapentin (p. 523·3).
Epilepsy; postherpetic neuralgia.

Alidil *Psychotropics, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alidol *Syntex, Mex.†*
Ketorolac trometamol (p. 80·2).
Pain.

Alifate *Candor, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastrointestinal haemorrhage.

Ali-Flex
Note: this name may be used for preparations of different composition.
Lalema, Canad.
Sodium hypochlorite (p. 1768·3).
Disinfection.

Aliflex
Note: this name may be used for preparations of different composition.
Medinova, Thai.
Sweet birch oil (p. 92·1); menthol (p. 2553·2).
Musculoskeletal pain.

Aliflus *Orifarm, Denm.†; Menarini, Ital.; Medcor, Neth.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease; asthma.

Align *Procter & Gamble, Canad.*
Bifidobacterium longum (p. 2596·3).
Probiotic supplement.

Align Daily Probiotic Supplement *Procter & Gamble, USA.*
Bifidobacterium infantis (p. 2596·3).

Aligout *Finecure, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Alikal *GSK, Arg.*
Aspirin (p. 22·2); caffeine (p. 1203·3); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); sodium carbonate (p. 2617·3).
Dyspepsia; headache.

Alikal Dolor *GSK, Arg.*
Paracetamol (p. 115·1).
Pain; fever.

Alimax *Cristalia, Braz.*
Heparin sodium (p. 1396·3).
Burns.

Alimentum *Abbott, Canad.; Abbott, Malaysia; Ross, USA.*
Protein hydrolysate (p. 2086·2) infant feed.
Protein intolerance; food allergy; fat malabsorption.

Alimix *Janssen-Cilag, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Alimta *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, India; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, Ukr.; Lilly, USA.*
Pemetrexed disodium (p. 844·3).
Malignant pleural mesothelioma; non-small cell lung cancer.

Alin
Note: this name may be used for preparations of different composition.
Biofarma, Turk.
Phenolphthalein (p. 1877·3).
Constipation; bowel evacuation.

Chinoin, Mex.
⊗Dexamethasone (p. 1630·3), dexamethasone isonicotinate (p. 1631·1), or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Lazar, Arg.
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Millet Roux, Braz.
Albendazole (p. 149·1).
Worm infections.

Alin Nasal *Chinoin, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Rhinitis; sinusitis.

Alin Oftalmico *Chinoin, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Eye disorders.

Alinamin *Takeda, Indon.*
Fursultiamine (p. 2103·1) with or without vitamin B_2 (p. 2104·3).
Vitamin B deficiency.

Alinamin B12 *Takeda, Thai.*
Fursultiamine hydrochloride (p. 2102·3); vitamin B_{12} (p. 2107·2).
Macrocytic anaemia; megaloblastic anaemia; neuritis.

Alinamin-F *Takeda, Jpn; Takeda, Thai.*
Injection: Fursultiamine hydrochloride (p. 2102·3).
Vitamin B_1 deficiency; vitamin B_1 supplement; neuralgia; myalgia; arthralgia; neuritis.

Takeda, Singapore.
Fursultiamine (p. 2103·1); riboflavin (p. 2104·3).
Vitamin B_1 deficiency; neuralgia; myalgia; arthralgia; neuritis.

Takeda, Thai.
Tablets: Fursultiamine hydrochloride (p. 2102·3); riboflavin (p. 2104·3).
Vitamin B_1 deficiency; neuralgia; myalgia; arthralgia; neuritis.

Alindrin *Recip, Swed.*
Ibuprofen (p. 68·2).
Fever; pain.

Alinia *Romark, USA.*
Nitazoxanide (p. 942·2).
Cryptosporidiosis; giardiasis.

Alinol *Pharmasant, Thai.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Alinor *VHB, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Alinvit *Collins, Mex.†*
Vitamins.

Alio *Osmed, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Alione *Coloplast, Ger.*
Carmellose (p. 2175·1).
Wounds; burns; ulcers.

Aliot *Biotech, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aliovital *Agropharm, Pol.†*
Garlic (p. 2510·3).
Hyperlipidaemias; atherosclerosis.

Alip *Talent, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Alip-AM *Talent, India.*
Amlodipine (p. 1304·1); atorvastatin (p. 1309·2).

Alipas *Bernaba, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Alipas Duo *Bernabo, Arg.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia.

Aliplex *Candor, India.*
Vitamins.

Alipride *Centaur, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; delayed gastric emptying.

Alipride MPS *Centaur, India.*
Cisapride (p. 1831·3); simeticone (p. 1886·2).

Alipza *Kowa, Irl.; Esteve, Spain.*
Pitavastatin calcium (p. 1471·1).
Hypercholesterolaemia.

Alirose *Candor, India.*
Vitamins; minerals; protein.

Alis *Panjon, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Alisade *GSK, Cz.; GSK, Pol.*
⊗Fluticasone furoate (p. 1638·1).
Allergic rhinitis.

Alis-AT *Panjon, India.*
Levamlodipine; ramipril (p. 1483·3).

Alisazim *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Aliserin *Farmakopea, Ital.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Alisia *Zytras, India.*
Vitamin B substances (p. 2102·3); silymarin (p. 1561·2).

Alis-Plus *Lincoln, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Alis-R *Panjon, India.*
Levamlodipine; ramipril (p. 1483·3).

Alisrythm *Sawai, Jpn.*
Pilsicainide hydrochloride (p. 1470·1).
Arrhythmias.

Alista *Novell, Indon.*
Cilostazol (p. 1337·1).
Arterial occlusion.

Alister *Rafarm, Gr.*
Amlodipine besilate (p. 1304·1).

Alistine *TP, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucous.

Alisyd *Darier, Mex.*
⊗Prednicarbate (p. 1645·1).
Skin disorders.

Alitax *Candor, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Alitax-S *Candor, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Aliterol *Piam, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

A-Lith *Pfizer, India.*
Lithium.
Bipolar disorder; depression.

Alither *Allenge, India.*
Injection: Alpha-beta arteether (p. 648·1).
Malaria.

Allenge, India.
Tablets: Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Alitol *KRKA, Pol.*
Garlic oil (p. 2510·3).
Atherosclerosis.

Alitraq *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Mex.†; Abbott, NZ; Abbott, Philipp.; Abbott, Turk.; Abbott, Venez.*
Preparation for enteral nutrition.

Alivate *Daffohils, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Alivate-E *Daffohils, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Alivax *Vivax, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Alivbaby *Cazi, Braz.*
Nystatin (p. 590·3); zinc (p. 2126·1).

Alive *Uniao Quimica, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Alive Mens Energy *Natures Way, USA.*
Vitamins; minerals; Garden Veggies Blend; lutein (p. 2079·2); lycopene (p. 2546·2); Orchard Fruits Blend; resveratrol (p. 2603·2); saw palmetto (p. 2363·3).
Dietary supplement.

Alive Once Daily Womens 50+ Ultra Potency *Natures Way, USA.*
Vitamins; minerals; Cardiovascular Blend with resveratrol (p. 2603·2); choline (p. 2055·2); Citrus Bioflavonoid Complex (p. 2505·2); CranRx; Digestive Enzyme Blend; Flax Lignan Blend; Garden Veggies Blend; Green Food/Spirulina Blend (p. 2622·1); inositol (p. 2533·2); lutein (p. 2079·2); Mind & Body Energy Blend; Orchard Fruits Blend; Organic Mushroom Defense Blend; rutoside (p. 2505·3).
Dietary supplement.

Alive Womens 50+ *Natures Way, USA.*
Vitamins; minerals; Garden Veggies Blend; lutein (p. 2079·2); Orchard Fruits Blend; resveratrol (p. 2603·2).
Dietary supplement.

Alivet *Leti, Venez.*
Paracetamol (p. 115·1); chlorphenamine (p. 620·3) or chlorphenamine maleate (p. 620·3).
Cold symptoms.

Alivet Dia *Leti, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms.

Alivetforte *Leti, Venez.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Alivetnoc *Leti, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Alivetos *Leti, Venez.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Alivetos Pediatrico *Leti, Venez.*
Guaifenesin (p. 1666·2).
Cough.

Aliviagrip *Denver, Arg.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Alivialux *Denver, Arg.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Alivian
Note: this name may be used for preparations of different composition.
Cazi, Braz.
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders.

Vitarum, Arg.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Aliviapres *Denver, Arg.*
⊗Dorzolamide (p. 2006·3); timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Aliviatos *Denver, Arg.*
Loratadine (p. 633·2); ambroxol (p. 1654·3).

Alivin Plus *Grossman, Mex.*
Clemizole penicillin (p. 269·2); sodium ascorbate (p. 2111·1); dipyrone (p. 53·3).
Bacterial infections associated with colds and influenza.

Aliviodol *Centrum, Spain.*
Meloxicam (p. 86·3).
Osteoarthrosis; rheumatoid arthritis; ankylosing spondylitis.

Aliviol *Cifarma, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); turpentine oil (p. 2636·3); mustard oil (p. 2646·1); rosemary oil (p. 2607·3); lavender oil (p. 2541·1).
Pain.

Aliviomas *Alacan, Spain.†*
Naproxen (p. 98·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Aliviosin *Alacan, Spain.*
Indometacin (p. 71·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Alivium *Mantecorp, Braz.*
Ibuprofen (p. 68·2).
Pain; fever.

Alizar *Gynopharm, Chile.*
⊗Spironolactone (p. 1499·3).
Oedema; hypertension; hyperaldosteronism; hypokalaemia.

Alizil *Decomed, Port.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's dementia.

Alizole-DSR *Allenge, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Aljil *Yeni, Turk.*
Caffeine (p. 1203·3); propyphenazone (p. 127·3); paracetamol (p. 115·1).
Fever; pain.

ALK *ALK, Denm.; ALK Abello, Ger.*
A range of allergen extracts (p. 2434·3).
Allergen immunotherapy; diagnosis of hypersensitivity.

ALK, Switz.
A range of grass and tree pollen allergen extracts (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

Alka
Note: this name may be used for preparations of different composition.
Bayer Consumer, UK.
Aspirin (p. 22·2).
Fever; pain.

Charak, India.
⊗Coriander (p. 2486·3); cuminum cyminum; tribulus terrestris (p. 2633·3).

Alkabel *Cypress, USA.*
Phenobarbital (p. 535·2); hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3).
Irritable bowel syndrome; enterocolitis.

Alka-C *Interchemex, Philipp.*
Sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Alkaceff *Dr Alson, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Alkaceff-S *Dr Alson, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Alkacel *Celon, India.*
Melphalan (p. 819·1).
Malignant neoplasms; polycythaemia vera.

Alkacool *Kaizen, India.*
Sodium acid citrate (p. 1781·1).

Alkacos *Symbiosis, India.*
Citric acid (p. 2480·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Alka-Coup *Coup, Gr.*
Sodium tartrate (p. 1888·2).

Alkafizz *First Pharm, S.Afr.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1); anhydrous citric acid (p. 2480·3); tartaric acid (p. 2626·1).
Gastric hyperacidity; urinary alkalinisation.

Alkagel *EMS, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Alkagel Complex *Quimica y Farmacia, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Alkagel IS *Quimica y Farmacia, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Alkagin
Note: this name may be used for preparations of different composition.
Berko, Turk.
Topical powder: Starch (p. 2095·1); zinc (p. 2126·1).
Personal hygiene.

Berko, Turk.
Topical solution: Triclosan (p. 1773·2); calendula (p. 2465·2); tilia (p. 2631·3).
Personal hygiene.

Dermoteca, Port.
Topical gel: Calendula (p. 2465·2); mallow (p. 2549·2); tilia (p. 2631·3); aloe (p. 1693·2); chlorhexidine gluconate (p. 1743·3).
Personal hygiene.

Dermoteca, Port.
Topical solution: Calendula (p. 2465·2); mallow (p. 2549·2); tilia (p. 2631·3); triclosan (p. 1773·2).
Personal hygiene.

Dermoteca, Port.
Wipes: Calendula (p. 2465·2); mallow (p. 2549·2); tilia (p. 2631·3); dipotassium glycyrrhizate (p. 2520·3); tocoferil acetate (p. 2119·2).
Personal hygiene.

Ganassini, Ital.
Calendula (p. 2465·2); mallow (p. 2549·2); tilia (p. 2631·3).
Personal hygiene.

Alkala N *Sanum-Kehlbeck, Ger.*
Sodium citrate (p. 1781·2); potassium bicarbonate (p. 1780·3); sodium bicarbonate (p. 1781·1).
Gastrointestinal hyperacidity.

Alkala T *Sanum-Kehlbeck, Ger.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis.

Alkaligen *Teva, Hung.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis; barbiturate and salicylate poisoning.

Alkaline Citrate *Citadel, India.*
Sodium acid citrate (p. 1781·1).

Alkalite D *Garec, S.Afr.†*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Alkalith *Alkem, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression.

Alkamax *Overseas, India.*
Citric acid monohydrate (p. 2480·3); potassium citrate (p. 1780·3).

Alkamax-MB6 *Overseas, India.*
Magnesium citrate (p. 1857·1); potassium citrate (p. 1780·3); vitamin B_6 (p. 2105·3).

Alkamine *ANB, Thai.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); kaolin (p. 1850·1); atropine sulfate (p. 1310·2).
Gastric hyperacidity; peptic ulcer.

Alka-Mints *Bayer, USA.*
Calcium carbonate (p. 1824·3).
Hyperacidity.

Alkanil *Inga, India.*
Sodium acid citrate (p. 1781·1).
Metabolic acidosis; urinary alkalinisation.

Alkanit *Dr Alson, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Alkanorm *Ultramark, India.*
Sodium acid citrate (p. 1781·1).

Alka-Prim *Polpharma, Pol.; Polpharma, Rus.; Polpharma, Ukr.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Alkarex-PD *Symbiosis, India.*
⊗Ambroxol hydrochloride (p. 1654·3); choline theophyllinate (p. 1207·1); salbutamol sulfate (p. 1220·2).

Al-Karish *Concept, Israel.†*
Sodium citrate (p. 1781·2) anticoagulant solution.

Alkaryl *Cadila, India.*
Sodium acid citrate (p. 1781·1).

Alka-Seltzer *Bayer Consumer, Austral.; Bayer, Austria; Bayer, Braz.; Bayer Consumer, Canad.; Bayer, Cz.; Bayer, Fin.†; Bayer Sante, Fr.; Bayer, Ger.; Bayer, Hong Kong†; Bayer, Hung.; Bayer, Irl.; Bayer, Ital.; Bayer Consumer, Malaysia; Bayer, Neth.; Bayer, NZ; Bayer, Philipp.†; Bayer Consumer, Rus.; Bayer, Singapore; Bayer, Swed.†; Bayer, Switz.; Bayer Consumer, Thai.; Bayer, Turk.; Bayer Consumer, UK; Bayer, Ukr.; Miles, USA; Bayer, Venez.*
Aspirin (p. 22·2); citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).
Pain; fever; headache with dyspepsia; heartburn.

Bayer, Belg.; Bayer, Israel†; Bayer, Pol.
Aspirin (p. 22·2).
Pain; fever; musculoskeletal and joint disorders; thrombosis prophylaxis.

Bayer, Port.
Sodium bicarbonate (p. 1781·1).

Alka-Seltzer Antacid *Miles Consumer Healthcare, USA.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); potassium bicarbonate (p. 1780·3).
Gastrointestinal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alka-Seltzer with Aspirin *Miles Consumer Healthcare, USA.*
Aspirin (p. 22·2); citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).
Arthritis; pain; fever; gastrointestinal disorders; myocardial infarction.

Alka-Seltzer Doble Accion *Bayer Consumer, Arg.*
Aspirin (p. 22·2); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Gastrointestinal disorders; pain.

Alka-Seltzer Heartburn Relief *Bayer Consumer, USA.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).
Antacid.

Alka-Seltzer N *Bayer, Gr.*
Aspirin (p. 22·2).

Alka-Seltzer New Formula *Bayer, Spain.*
Sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Alka-Seltzer Plus Cold *Bayer Consumer, USA.*
Effervescent tablets: Chlorphenamine maleate (p. 620·3); aspirin (p. 22·2); phenylephrine acid tartrate (p. 1672·3).
Nasal congestion; cold symptoms.

Miles Consumer Healthcare, USA.
Capsules: ⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Alka-Seltzer Plus Cold & Cough *Miles Consumer Healthcare, USA.*
Capsules: ⊗Dextromethorphan (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Bayer Consumer, USA.†
Oral liquid: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Alka-Seltzer Plus Day Cold *Bayer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cough; cold symptoms.

Alka-Seltzer Plus Day & Night Cold *Bayer Consumer, USA.*
Capsules: Day capsules, paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); night capsules, paracetamol; dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cold symptoms; cough.

Bayer Consumer, USA.
Effervescent tablets: Day tablets, paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); night tablets, paracetamol; dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); doxylamine succinate (p. 627·3).
Cold symptoms; cough.

Alka-Seltzer Plus Day Non-Drowsy Cold *Bayer Consumer, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Fast Crystal Packs *Bayer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Flu *Bayer Consumer, USA.*
Aspirin (p. 22·2); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Alka-Seltzer Plus Mucus & Congestion *Bayer Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Night Cold *Bayer Consumer, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Alka-Seltzer Plus Night-Time Cold *Miles Consumer Healthcare, USA.*
Capsules: ⊗Doxylamine succinate (p. 627·3); dextromethorphan (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Alka-Seltzer Plus Nose & Throat *Bayer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Original Cold Formula *Bayer Consumer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Regular Seltzer Multi-Symptom Cold Relief *Bayer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Severe Sinus Congestion Allergy & Cough *Bayer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Alka-Seltzer Plus Sinus *Bayer Consumer, USA.*
Capsules: ⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Formerly known as Alka-Seltzer Plus Cold & Sinus.
Cold symptoms; nasal congestion.

Alka-Seltzer PM *Bayer, USA.*
Aspirin (p. 22·2); diphenhydramine citrate (p. 626·2).
Insomnia.

Alka-Seltzer Wake-Up Call *Bayer, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Alka-Seltzer XS *Bayer Consumer, UK.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).
Pain; gastric discomfort.

Alkasid *Julphar, UAE.*
Aluminium magnesium silicate (p. 2168·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Alkasol *Stadmed, India.*
Sodium acid citrate (p. 1781·1).
Metabolic acidosis; fever; dysuria; adjunct to sulfonamide therapy.

Alkasol-P *Stadmed, India.*
Sodium acid citrate (p. 1781·1); paracetamol (p. 115·1); sorbitol (p. 2092·1).
Alkali depletion; fever; cold symptoms; pain.

Alkasolve *Sam-On, Israel.*
Potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Urinary alkalinisation.

Alkastom *Panvifarm, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; acid aspiration.

Alkasym *Symbiosis, India.*
Citric acid (p. 2480·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Alkavite *Vitality, USA.*
Vitamins; minerals.

Alkazol *Legrand, Braz.†*
Lansoprazole (p. 1851·3).

Alkcema *Valeant, Hung.*
⊗Triamcinolone acetonide (p. 1649·1); chlorhexidine hydrochloride (p. 1743·3).
Infected skin disorders.

Alkeran *Aspen, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; Aspen, Fin.; Aspen, Ger.; GSK, Gr.; IFET (ΙΦΕΤ), Gr.; Aspen, Hong Kong; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; Aspen, Neth.; Aspen, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; Pro Concepta, Switz.; Aspen, Thai.; GSK, Turk.; GSK, UK; Apo, USA.*
Melphalan (p. 819·1) or melphalan hydrochloride (p. 819·1).
Malignant neoplasms; polycythaemia vera.

Alkéran *Genopharm, Fr.*
Melphalan (p. 819·1).
Malignant neoplasms.

Alkerana *GSK, Arg.*
Melphalan (p. 819·1).
Malignant neoplasms.

Alket *SF, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; phlebitis.

Poen, Arg.
Epinastine hydrochloride (p. 628·3).
Allergic conjunctivitis.

Alkimus *Atral, Port.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alkocortenbioform *Genopharm, Fr.†*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Infected skin disorders.

Alkonatrem *Genopharm, Fr.*
Demeclocycline hydrochloride (p. 285·2).
Syndrome of inappropriate ADH secretion.

Alkos *Hos & Ins, India.*
Sodium acid citrate (p. 1781·1).

Alkosalen *Genopharm, Fr.†*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Alkotar *Genopharm, Fr.†*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Eczema; psoriasis.

Alksebor *Valeant, Hung.*
Chlorhexidine hydrochloride (p. 1743·3); vitamin A (p. 2098·3); tocoferil acetate (p. 2119·2); dexpanthenol (p. 2582·2).
Skin and scalp disorders.

Alkyloxan *Choongwae, Singapore; Kocsel, Turk.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Alkymer *Naturprodukt, Hung.*
Shark-liver oil (p. 2614·2).
Dietary supplement.

All Clear *Bausch & Lomb, Hong Kong; Bausch & Lomb, USA.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

All Day Allergy *Major, USA.*
Cetirizine hydrochloride (p. 619·2).

All Day Allergy-D *Major, USA.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

All in One *Teka, Turk.*
A cleansing, rinsing, disinfecting, and storage solution for contact lens care.

Allam *HK Pharm, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Allanderm-T *Allan, USA.†*
⊗Trypsin (p. 2635·2); Peru balsam (p. 2587·1); castor oil (p. 2472·1).

AllanEnzyme *Allan, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3); with or without chlorophyllin copper complex sodium (p. 2178·3).
Ulcers; wounds.

AllanfillEnzyme *Allan, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3); chlorophyllin copper complex (p. 2178·3).

Allapinin *Vilar, Rus.*
Lappaconitine hydrobromide (p. 1418·1).
Arrhythmias.

Allard *Ikon, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Allavin Expectorant *CCM, Malaysia.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; allergic symptoms of upper respiratory-tract disorders.

Allavin Plus Expectorant *CCM, Malaysia.*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Allbee *Inverness, USA.*
Vitamins.

Allcet-DC *Laksun, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Allcitra *Lincoln, India.*
Sodium acid citrate (p. 1781·1).

Alleal *Pierre Fabre, Ital.†*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis.

Allecet *Cipla-Medpro, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alledine *Arrow, Austral.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Alledryl *Prater, Chile.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Alledryl D *Prater, Chile.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; nasal congestion.

Allefast *Sterling, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Allegix *Intas, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Allegra *Sanofi-Aventis, Arg.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Swed.; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Sanofi-Aventis, Braz.
Fexofenadine (p. 629·1) or fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Allegra-D *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Chattem, USA; Sanofi-Aventis, Venez.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Sanofi-Aventis, Mex.
Fexofenadine hydrochloride (p. 629·1); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Allegro *Trima, Israel.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Berlin-Chemie, Ger.
Frovatriptan succinate (p. 676·2).
Migraine.

Allegron *Aspen, Austral.; King, UK.*
Nortriptyline hydrochloride (p. 439·3).
Depression; nocturnal enuresis.

Allelock *Kirin, China; Kyowa, Jpn.*
Olopatadine hydrochloride (p. 636·2).
Allergic rhinitis; urticaria; pruritus.

Allemar Nasalmer *Sanofi-Aventis, Mex.*
Hypertonic sea water (p. 2612·1).
Nasal cleansing and irrigation; nasal congestion.

Allenik *Galen, Turk.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; motion sickness; vertigo.

Allenopar *Gerot, Austria.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic attacks; anxiety; post-traumatic stress disorder.

Allens Chesty Cough *Allens, UK.*
Ammonium chloride (p. 1656·1); tolu tincture (p. 1679·2); squill tincture (p. 1677·3); menthol (p. 2553·2); marrubium (p. 1668·3).
Coughs.

Allens Dry Tickly Cough *Allens, UK.*
Benzoin tincture (p. 2624·3); ipecacuanha tincture (p. 1667·2); capsicum tincture (p. 2469·3); cetylpyridinium chloride (p. 1743·1).
Coughs.

Allens Junior Cough *Allens, UK.*
⊗Glycerol (p. 2517·2); anhydrous citric acid (p. 2480·3).
Coughs; sore throat.

Allens Pine & Honey *Thornton & Ross, UK.*
Ipecacuanha (p. 1667·2); liquorice (p. 1853·2); Indian squill (p. 1677·3).
Respiratory-tract congestion in coughs and colds.

Allent *Ascher, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Allentop *Hanall, Hong Kong.*
Alendronic acid (p. 1171·3).
Osteoporosis.

Alleoftal *Sanofi-Aventis, Mex.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

AllePak *Everton, USA.*
⊗Day tablets, pseudoephedrine hydrochloride (p. 1676·1); hyoscine methonitrate (p. 1846·1); night tablets, chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Aller-Aide *Rougier, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Allerax *Bangkok Lab & Cosmetic, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; allergic skin reactions; sedative.

Allerban *Saga, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Allercalm
Note: this name may be used for preparations of different composition.
Actavis, UK.
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allercet *Micro, India; Micro, Singapore; Micro, Thai.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; allergic rhinitis; urticaria; allergic conjunctivitis.

Allercet-DC *Micro, India.*
Cetirizine hydrochloride (p. 619·2); phenylephrine hydrochloride (p. 1672·3).
Rhinitis.

Aller-Chlor *Rugby, USA.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allerclear *Potter's, UK.*
Eye drops: Euphrasia (p. 2502·1).
Eye irritation; dry eyes.

Potter's, UK.
Nasal spray: Dead Sea salt (p. 2612·1); dexpanthenol (p. 2582·2).
Nasal congestion; nasal dryness.

Potter's, UK.
Tablets: Garlic (p. 2510·3); garlic oil (p. 2510·3); echinacea (p. 2498·1).
Rhinitis; nasal congestion; catarrh.

Allercon *Parmed, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Allercrom *FDC, India.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Allerdine *LBS, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Allerdrug *Med-One, Gr.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Allerdryl
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Allergic skin disorders; skin irritation.

Valeant, Canad.
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity.

Allerede *East West, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Allerest Allergy & Sinus Relief *Heritage Consumer, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Allerest Headache Strength *Ciba, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Allerest 12 Hour Nasal *Ciba Consumer, USA.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Allerest Maximum Strength *Ciba, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Allerest Sinus Pain Formula *Ciba, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Aller-Eze
Note: this name may be used for preparations of different composition.
Novartis Consumer, UK.
Eye drops; nasal spray: Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis; allergic rhinitis.

AllerEze
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Allerfex *North Star, Rus.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Allerfexo *Ascent, Austral.*
Fexofenadine hydrochloride (p. 629·1).
Urticaria; allergic rhinitis.

Allerfre *Reckitt Benckiser, Neth.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Allerfrim *Rugby, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Allerfrim with Codeine *Rugby, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); triprolidine hydrochloride (p. 642·3).
Coughs and cold symptoms.

Allerg-Abak *Thea, Neth.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Allergan *Bouty, Ital.*
Diphenhydramine hydrochloride (p. 626·2).
Pruritus; sunburn; insect bites.

Allergan Enzymatic *Allergan, USA.†*
⊗Papain (p. 2582·3).
Cleansing solution for soft contact lenses.

Allergefon *SERP, Mon.†*
Carbinoxamine maleate (p. 619·1).
Hypersensitivity reactions.

Allergen
Note: this name may be used for preparations of different composition.
Goldline, USA.
⊗Benzocaine (p. 1980·2); phenazone (p. 124·1); glycerol (p. 2517·2).
Ear pain.

T Man, Thai.
Dexchlorpheniramine (p. 620·3).
Hypersensitivity.

Allergesic *Meridian, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Allergex *Adcock Ingram, S.Afr.*
Eye drops: ⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye congestion.

Adcock Ingram, S.Afr.
Oral liquid; tablets: Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allergie-Injektopas *Pascoe, Ger.*
Acid. formicium (p. 2507·1); arsenicum album (p. 2448·1); cuprum (p. 2057·1).
Homoeopathic preparation.

Allergies *Homeocan, Canad.*
Allium cepa (p. 2575·2); aralia racemosa; collubrina; cuprum metallicum (p. 2057·1); euphrasia (p. 2502·1); metallum album (p. 2448·1); sabadilla (p. 2611·2); sticta pulmonaria (p. 2546·1).
Homoeopathic preparation.

Allergiflash *Chauvin, Fr.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis.

Allergin *PP Lab, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity.

Allergis *TNP, Thai.*
⊗Antazoline hydrochloride (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Allergic eye disorders.

Aller-Go *TC Pharma-Chem, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis; urticaria.

Allergo Rhinathiol *Sanofi-Aventis, Belg.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Allergo-COMOD *Croma, Austria; Ursapharm, Cz.; Horus, Fr.; Ursapharm, Ger.; Ursapharm, Neth.; Ursapharm, Pol.; Ursapharm, Switz.; Biem, Turk.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Allergocrom *Ursapharm, Cz.; Ursapharm, Ger.; Ursapharm, Malaysia; Ursapharm, Pol.; Ursapharm, Singapore; Biem, Turk.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis; keratoconjunctivitis.

Allergocrom Kombi *Ursapharm, Cz.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Allergodil *Pharmadorf, Arg.; Meda, Austria; Meda, Belg.; Meda, Cz.; Meda, Denm.; Meda, Fr.; Meda, Ger.; Meda, Hung.; Meda, Ital.; Meda, Neth.; Meda, Pol.; Meda, Port.; Meda, Rus.; Meda, Switz.; Gen, Turk.; Meda, Ukr.; Zuoz, Venez.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis; allergic conjunctivitis.

Allergodip *Allergo, Turk.*
A range of allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.

Allergofact *Doctum, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Allergojovis *Biomedica, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Allergokatt *Kattwiga, Ger.*
Cardiospermum; galphimia glauca; luffa operculata (p. 2545·3); sabadilla (p. 2611·2).
Homoeopathic preparation.

Allergo-Loges *Loges, Ger.*
Acid. formicicum (p. 2507·1); apis mellifica (p. 2445·2); cardiospermum; galphimia glauca; hydrocotyle asiatica (p. 1698·3); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Allergone *Perrigo, Israel.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Allergopen *Allergo, Turk.*
Allergen extracts (p. 2434·3).
Diagnosis of penicillin allergy.

Allergopharm *Doctum, Gr.*
A range of allergen extracts (p. 2434·3).

Allergopharma *Allergopharma, Neth.*
A range of allergen extracts from pollen (p. 2593·3) and house dust mite (p. 2434·3).
Diagnosis of hypersensitivity.

Allergopos N *Ursapharm, Ger.†*
⊗Antazoline phosphate (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Allergospasmin *Meda, Ger.*
⊗Sodium cromoglicate (p. 1225·3); reproterol hydrochloride (p. 1219·2).
Obstructive airways disease.

Allergospray *Meda, Austria.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Allergostop
Note: this name may be used for preparations of different composition.
Faran, Gr.
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Phytopharm, Ukr.
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Allergotin *Cooper (Κοπερ), Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Allergoval *Kohler-Pharma, Ger.*
Sodium cromoglicate (p. 1225·3).
Hypersensitivity reactions.

Allergovit *Allergopharma, Neth.; Allergopharma, Pol.; Allergo, Turk.*
Pollen allergens (p. 2593·3) (p. 2434·3).
Allergen immunotherapy; hyposensitisation.

Allergopharma, Ger.; Allergopharma, Switz.
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Allergy
Note: this name may be used for preparations of different composition.
Accudial, Canad.
Diphenhydramine hydrochloride (p. 626·2).

Parmed, USA.
Chlorphenamine maleate (p. 620·3).

Allergy Cream *G & W, Canad.†*
Diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1).

Allergy Defence *Thornton & Ross, UK.*
Cellulose (p. 2177·2).
Formerly known as Nasaleze.
Allergic rhinitis.

Allergy Drops *Bausch & Lomb, Canad.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Allergy Elixir *Tanta, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Allergy Eye Drops *Arrow, Canad.*
⊗Tetryzoline hydrochloride (p. 1678·3); zinc sulfate (p. 2126·2).
Eye disorders.

Allergy Formula *Perrigo, Canad.; Pharmetics, Canad.; Vita Health, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Allergy & Hayfever Relief *Cenovis, Austral.*
Perilla frutescens leaf; ascorbic acid (p. 2110·3); citrus bioflavonoids (p. 2505·2).
Allergic disorders.

Allergy Relief
Note: this name may be used for preparations of different composition.
Apotex, Canad.
Cetirizine hydrochloride (p. 619·2).

Boots, UK; Zee, USA.
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Brauer, Austral.
Antim. tart. (p. 151·2); argent. nit. (p. 2615·3); bryonia (p. 2461·3); calc. carb. (p. 1824·3); chamomilla (p. 2474·1); histaminum mur. (p. 2525·2); nat. mur. (p. 1795·1); nux vomica (p. 2573·3); pulsatilla (p. 2600·2); rhus tox. (p. 2603·3); urtica urens (p. 2639·3).
Homoeopathic preparation.

Beaumont, Canad.†
Goldenrod (p. 2620·1); lac caninum; onion (p. 2575·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Allergy Relief & Nasal Decongestant *Ohm, USA.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract disorders.

Allergy Sinus *Vita Health, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Allergy Sinus Headache *Tanta, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Allergy Sinus Nighttime Relief *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Allergy + Sinus Relief *Phanmetics, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).

Allergy Tablets *Tanta, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Allergy-Care *Trima, Israel.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Allergy-Time *Time-Cap, USA.*
Chlorphenamine maleate (p. 620·3).

Allergyx *Teva, Israel.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Allerhist
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.†
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allerief *Orbis Consumer, UK.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allerin
Note: this name may be used for preparations of different composition.
Medifarma, Indon.
⊗Guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); diphenhydramine hydrochloride (p. 626·2); phenylpropanolamine hydrochloride (p. 1674·1); alcohol (p. 1733·1).
Cough.

Great Eastern, Thai.†; United American, Thai.†
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough and cold symptoms.

Allerin AH *United Laboratories, Philipp.*
Diphenhydramine hydrochloride (p. 626·2).
Cough; rhinitis; motion sickness.

Allerin Reformulated *United Laboratories, Philipp.*
Diphenhydramine hydrochloride (p. 626·2); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Allerjin *Gunsa, Turk.†*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; motion sickness; vertigo.

Allerket *Pulitzer, Ital.*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis; asthma; atopic eczema.

Allerkid *Pediatrica, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; pruritus; allergic rhinitis; allergic conjunctivitis.

Allerlux *Mediwhite, Ital.*
Liquorice (p. 1853·2); calendula (p. 2465·2); lappa (p. 2540·1); helichrysum italicum.
Allergic disorders.

AllerMax
Note: this name may be used for preparations of different composition.
Pfeiffer, USA.
Diphenhydramine hydrochloride (p. 626·2).
Motion sickness; parkinsonism; insomnia.

Allermed
Note: this name may be used for preparations of different composition.
EuroHealth, Philipp.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Murdock, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Allermin *Synco, Singapore.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allermin Expectorant *Synco, Hong Kong.†*
Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); sodium citrate (p. 1781·2).
Cough.

Allermine *Mylan, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

AllerNaze *Collegium, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Formerly known as Tri-Nasal.
Allergic rhinitis.

Allernix *Teva, Canad.*
Diphenhydramine hydrochloride (p. 626·2).
Antihistamine.

Allernon *Lannacher, Austria.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Allerphed *Great Southern, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Allerpid *China Chem & Pharma, Malaysia.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Allersan *Europharm, Hong Kong.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Allerset
Note: this name may be used for preparations of different composition.
Santa, Turk.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Allersil *Silom, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; hay fever; allergic skin disorders.

Allersin *Sunward, Singapore.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allersine *CCM, Malaysia.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Allersol
Note: this name may be used for preparations of different composition.
Sanovel, Turk.
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Allersoothe *AFT, NZ.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; premedication; sedative.

Allerta *United Laboratories, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Aller-Tab *Silom, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; hay fever; allergic skin disorders.

Allertec *Polfa Warszawa, Pol.; Warsaw-Polfa, Rus.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

AllerTek *Ratiopharm, UK.*
Cetirizine (p. 619·2).
Allergic rhinitis; urticaria.

Allertek *Polfa Warsaw, Ukr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Allertyn *DHA, Hong Kong; DHA, Singapore.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

AlleRx *Adams, USA.†*
Tablets: ⊗AM Tablets, pseudoephedrine hydrochloride (p. 1676·1); hyoscine methonitrate (p. 1846·1); PM tablets, chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Cold symptoms; rhinitis; sinusitis.

Cornerstone, USA.†
Suspension: Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

AlleRx DF *Cornerstone, USA.*
Tablets AM, chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); tablets PM, chlorphenamine maleate; hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Alleryl *Idaman, Singapore.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Allerzine *Jenburkt, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Allestra *Ache, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Allevyn *Smith & Nephew, Austral.; Smith & Nephew, Belg.; Smith & Nephew, Fr.; Smith & Nephew, Ger.; Smith & Nephew, Irl.; Smith & Nephew, Ital.; Smith & Nephew, UK.*
Hydrophilic polyurethane dressing (p. 1718·1).
Ulcers; wounds.

Allevyn Ag *Smith & Nephew, Austral.*
Sulfadiazine silver (p. 362·3).
Medicated dressing; wounds.

Allexofedrin *EMS, Braz.*
Fexofenadine (p. 629·1).

Allfen CDX *MCR, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Allfen-DM *MCR, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

All-G *Intra-Labs, India.*
Lactobacillus (p. 2596·3); pantothenic acid (p. 2085·2); vitamin C (p. 2110·3).

Allgoric *Kamron, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Alli *GSK, Austria; GSK Consumer, Belg.; GSK, Cz.; GSK Consumer, Denm.†; GSK Sante, Fr.; GSK Consumer, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK Consumer, Neth.; GSK, Norw.†; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK Consumer, Spain; GSK Consumer, Swed.; GSK Consumer, Switz.; GSK, UK; GSK, USA.*
Orlistat (p. 2577·1).
Obesity.

Allice *Teva, Hung.*
Soya oil (p. 2092·3); onion oil.
Respiratory-tract infections; hay fever.

Allidex *Pharmafontana, Hung.*
Garlic oil (p. 2510·3).
Atherosclerosis.

Allilchep *Pskovskaya, Rus.*
Onion (p. 2575·2).
Gastrointestinal disorders; skin disorders; atherosclerosis.

All-in-One *Roche, Hong Kong.†*
Vitamins; minerals.

Alliocaps *Madaus, Arg.*
Garlic (p. 2510·3).

Alliofil *Herbapol Poznan, Pol.*
Garlic (p. 2510·3); urtica (p. 2639·3).
Gastrointestinal, urinary-tract, and respiratory-tract disorders; atherosclerosis.

Alliorut *Herbapol Poznan, Pol.†*
Garlic (p. 2510·3); crataegus (p. 2488·1); troxerutin (p. 2505·3).
Peripheral vascular disorders; hyperlipidaemias.

Allithera *Teva, Hung.*
Garlic (p. 2510·3); evening primrose oil (p. 2502·2).
Cardiovascular disorders; multiple sclerosis; tonic.

Allium Cepa Compose *Boiron, Fr.*
Allium cepa (p. 2575·2); belladonna (p. 2453·3); euphrasia officinalis (p. 2502·1); mercurius dulcis (p. 2555·3); hydrastis canadensis (p. 2528·1); kalium bichromicum (p. 2476·3); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Allium Compuesto *Ximena Polanco, Chile.*
Allium cepa (p. 2575·2); belladonna (p. 2453·3); gelsemium (p. 2511·2); sabadilla (p. 2611·2); thuja (p. 2629·3).
Homoeopathic preparation.

Allium Plus *Zeller, Switz.†*
Ginkgo biloba (p. 2512·3); garlic (p. 2510·3).
Cerebrovascular disease.

Al-Live *Alcure, India.*
Sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Allixon *Leti, Venez.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Vitamin A and D deficiency.

Allmox *Austell, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Lincoln, India.
Amoxicillin (p. 216·2).
Bacterial infections.

Allnet *Gentech, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

All-Nite Cold Formula *Major, USA.*
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, doxylamine succinate, and paracetamol.
Coughs and cold symptoms.

Allo *CT, Ger.†; YSP, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Allo Comp *Ratiopharm, China.*
Allopurinol (p. 600·2); benzbromarone (p. 603·3).
Gout; hyperuricaemia.

Allobenz *Arcana, Austria.*
Allopurinol (p. 600·2); benzbromarone (p. 603·3).
Hyperuricaemia; gout; renal calculi.

Allobeta *Betapharm, Ger.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Allocholum *Borshchagovskii, Ukr.*
Bile (p. 2457·2); garlic (p. 2510·3); urtica (p. 2639·3); activated charcoal (p. 1537·3).
Cholecystitis; cholelithiasis; biliary-tract disorders; constipation.

Allochrysine *Genopharm, Fr.*
Aurotioprol (p. 28·2).
Rheumatoid arthritis.

Allo.comp. *Ratiopharm, Ger.†*
Allopurinol (p. 600·2); benzbromarone (p. 603·3).
Hyperuricaemia; gout.

Allocor *Lloyd, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Alloferin *Valeant, Ger.†; Pharmaco, S.Afr.; Valeant, Ukr.†*
Alcuronium chloride (p. 2029·3).
Competitive neuromuscular blocker.

Allofex *Wockhardt, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Allogut *Atabay, Turk.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Allohex *Kalbe, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Allohexal *Sandoz, Austral.†; Hexal, NZ†; Sandoz, Ukr.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Allokin-Alpha *Ecofarm, Ukr.*
Alloferon.
Herpes infections; hepatitis B.

Allomaron *Natrapharm, Philipp.; Sanofi-Aventis, Thai.*
Allopurinol (p. 600·2); benzbromarone (p. 603·3).
Gout; hyperuricaemia.

Allomycin *Proel, Gr.*
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Allonol *Ratiopharm, Fin.; Utopian, Thai.*
Allopurinol (p. 600·2).
Gout; uric acid nephropathy; hyperuricaemia.

Allopin *T-Boma, Hong Kong†; General Drugs, Thai.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Alloprin *Valeant, Canad.*
Allopurinol (p. 600·2).
Gout; uric acid nephropathy; hyperuricaemia; renal calculi.

Alloptrex *Pierre Fabre, Fr.†*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Allopur *Nycomed, Norw.; Sandoz, Switz.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Alloric *TO-Chemicals, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Alloril *Dexcel, Israel.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Allorin *Douglas, NZ.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Alloris *Sanbe, Indon.; Sanbe, Singapore.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Allosig *Fawns & McAllan, Austral.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Allostad *Stada, Austria.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi; uric acid nephropathy.

Allo-Ürik *Sanli, Turk.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Alloxygen *Gruppo Medica, Philipp.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Allpyral *Thomson, Austral.†; Miles, USA.*
Range of allergen extracts (p. 2434·3).
Allergen immunotherapy.

Allpyral Pure Mite *Bayer, S.Afr.†*
D. pteronyssinus extracts (p. 2434·3).
Hyposensitisation.

Allpyral Special Grass *Bayer, S.Afr.†*
Grass pollen extracts (p. 2593·3) (p. 2434·3).
Hyposensitisation.

Allres DS Tannate *Allegis, USA.†*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Allres Pd *Allegis, USA.†*
⊗Pentoxyverine citrate (p. 1672·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Allrite *Zydus, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Allrite-D *Zydus, India.*
⊗Levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Allsafe *Lincoln, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Allsan *Biomed, Switz.*
Vitamins; with or without minerals.

Allset *Medex, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Allstam *Biostam (Βιοστα), Gr.*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Alltop *Ind-Swift, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alltop-P *Ind-Swift, India.*
⊗Alprazolam (p. 1035·2); propranolol hydrochloride (p. 1479·1).

Alltop-S *Ind-Swift, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Alltrex *Miracalus, India; Naprod, Philipp.; Naprod, Thai.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Allumag M *Clinifood, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Allumag MPS *Clinifood, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Alluna Nacht *GSK Consumer, Ger.†*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Allunapret *Bionorica, Ger.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Sleep disorders.

All-Up *Adcock Ingram, S.Afr.†*
Vitamins; minerals.

Allupol *Richter, Pol.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Allurase *Terramedic, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Allurene *Bayer, Irl.†; Bayer, Neth.†; Lusal, Port.*
Estradiol (p. 2271·1); drospirenone (p. 2269·1).
Menopausal disorders; osteoporosis.

Alluric *Kalbe, Indon.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Allurit *Teofarma, Ital.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Allvoran *TAD, Ger.†*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Allynat *Pascoe, Spain.*
Devil's claw root (p. 42·3).
Musculoskeletal pain.

Allynol *VHB, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Allytry *Intra-Labs, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Alma
Note: this name may be used for preparations of different composition.
Akdeniz, Turk.
Aluminium glycinate (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastritis; peptic ulcer; heartburn.
Gifrer Barbezat, Fr.
Terpin (p. 1678·2).
Respiratory-tract disorders.
Millimed, Thai.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Adcock Ingram, S.Afr.†
Peppermint oil (p. 1877·1); cardamom (p. 2471·1).
Carminative.

Almacarb
Note: this name may be used for preparations of different composition.
GSK, India.
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); liquorice (p. 1853·2); light magnesium carbonate (p. 1856·2).

Almacon *Pyridam, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; gastritis; dyspepsia; flatulence.

Almacone *Rugby, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Almadin *Aspen, S.Afr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Almag
Note: this name may be used for preparations of different composition.
Alde Medi Impex, India.
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Hua, Thai.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Almagel
Note: this name may be used for preparations of different composition.
Actavis, Hung.†; Balkanpharma, Rus.
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2).
Peptic ulcer; gastritis; gastro-oesophageal reflux; dyspepsia.
Indian Drugs, India.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Almagel A *Actavis, Hung.†; Balkanpharma, Rus.*
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2); benzocaine (p. 1980·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Almagel Neo *Balkanpharma, Rus.; Actavis, Ukr.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastro-oesophageal reflux; peptic ulcer; flatulence; gastritis; dyspepsia.

Almagel Plus *Atlas, Canad.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Almagel T *Actavis, Ukr.*
Magaldrate (p. 1856·1).
Gastro-oesophageal reflux; peptic ulcer.

Almal-Z *Emar, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Almarion *Chew, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Almarl *Sumitomo, China; Sumitomo, Jpn.*
⊗Arotinolol hydrochloride (p. 1308·1).
Hypertension; angina pectoris; arrhythmias; tremor.

Almarytm *Meda, Ital.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Almasal *Chew, Thai.*
⊗Theophylline (p. 1229·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Almavigor *Amnol, Ital.*
Royal jelly (p. 2608·1); guarana (p. 2648·2); Siberian ginseng (p. 2614·3); amino acids; vitamins.
Tonic.

Almax *Almirall, Mex.; Almirall, Spain.*
Almagate (p. 1815·3).
Dyspepsia; gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; hiatus hernia.

Almaximo *Fabop, Arg.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Almay Clear Complexion *Revlon, Canad.†*
Salicylic acid (p. 1719·1).

Almay Hydracolor Lipstick *Revlon, Canad.†*
Octinoxate (p. 1715·1).
Sunscreen.

Almay Ideal Lip *Revlon, Canad.†*
SPF 17: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Almay Nearly Naked *Revlon, Canad.†*
SPF 12: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.
Revlon, Canad.†
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Almay TLC Truly Lasting *Revlon, Canad.†*
Octinoxate (p. 1715·1).
Sunscreen.

Almay Wake-Up *Revlon, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Almazine *Psyco Remedies, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

Almebex Plus B_{12} *Propharma, USA.*
Vitamin B substances (p. 2102·3).

Almecol *Unichem, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Almecol-B *Unichem, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Almeida *Savio, Ital.*
⊗Salbutamol (p. 1220·2); ipratropium bromide (p. 1211·3).
Asthma.

Almer *Actavis, Ukr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Almetec *Schering-Plough, Mex.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Almetec-Co *Schering-Plough, Mex.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Almevax *Chiron Vaccines, UK.*
A rubella vaccine (Wistar RA 27/3 strain) (p. 2417·1).
Active immunisation.

Almex *Square, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Almic *TS, Ital.*
Fish oil (p. 1460·1).
Nutritional supplement.

Almide *Alcon, Fr.*
Lodoxamide trometamol (p. 2545·1).
Allergic eye disorders.

Almidis *Epifarma, Ital.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Almigástrico *Labesfal, Port.*
Aluminium hydroxide (p. 1817·2).
Antacid.

Almigripe *Jaba, Port.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Almin
Note: this name may be used for preparations of different composition.
Candor, India.
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

Alminox *Nycomed, Denm.*
Aluminium glycinate (p. 1817·2); magnesium oxide (p. 1857·3).
Gastro-oesophageal reflux.

Alminth *Torrent, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Almiral *Medochemie, Cz.; Medochemie, Malaysia; Medochemie, Rus.†; Medochemie, Singapore.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain; renal and biliary colic.
Medochemie, Hong Kong.
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders.

Almirid *Polichem, Cz.†; Desitin, Ger.†; Beacon, Irl.†; Poli, Pol.*
Dihydroergocryptine mesilate (p. 390·2).
Parkinsonism; migraine; hyperprolactinaemia; lactation inhibition.

Almiron Pepti *Nutricia, Fin.†*
Infant feed.
Cow's milk and soya protein allergy.

Almito *Alkem, India.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Almocef *Gujarat Terce, India.*
Cefixime (p. 240·3).
Bacterial infections.

Almodin *Nordin, Mex.*
Aesculus (p. 2431·2); hamamelis (p. 2523·3).
Haemorrhoids; varices.

Almogran *Almirall, Austria†; Almirall, Belg.; Almirall, Denm.; Almirall, Fin.; Almirall, Fr.; Almirall Hermal, Ger.; Almirall, Gr.; Almirall, Irl.; Almirall, Ital.; Almirall, Neth.; Almirall, Norw.; Almirall, Port.; Almirall, Spain; Gervasi, Spain; Meda, Swed.; Merz, Switz.; Organon, UK.*
Almotriptan malate (p. 672·1).
Migraine.

Almora
Note: this name may be used for preparations of different composition.
Elpen (Ελπεν), Gr.
Potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration solution.

Almorsan *TRB, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Almotrex *Solvay, Ital.*
Almotriptan malate (p. 672·1).
Migraine.

Almyrol *Lysoform, Ger.*
Polihexanide (p. 1766·1); laurylamine dipropylenediamine (p. 1759·2); didecyldimethylammonium chloride (p. 1750·3).
Instrument disinfection.

Alna *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Alnacef *Alna, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Alnacef-S *Alna, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Alnacef-T *Alna, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Alnacer *Alna, India.*
Paracetamol (p. 115·1); DL-methionine (p. 1558·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alnacet *Alna, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alnacet-AL *Alna, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Alnacet-M *Alna, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Alnaclox *Alna, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Alnacob *Alna, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Alnacob-G *Alna, India.*
Mecobalamin (p. 2108·1); gabapentin (p. 523·3).

Alnacob-OD *Alna, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Alnacob-P *Alna, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Alnacort *Alna, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Alnaferon *Alna, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Alnagon *Zentiva, Cz.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); phenobarbital (p. 535·2); codeine phosphate (p. 40·2).
Pain.

Alnalive *Alna, India.*
Ornithine aspartate (p. 2085·2).

Alnamax *Alna, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Alnamax-G *Alna, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Alnamet *Alna, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Alnamet-G *Alna, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Alnamet-GSR *Alna, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Alnamik *Alna, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Alnase
Note: this name may be used for preparations of different composition.
Alna, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.
Taro, Israel.
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline hydrochloride (p. 1669·3); mepyramine maleate (p. 635·1).
Cold symptoms; rhinitis; sinusitis.

Alnase-P *Alna, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Alnase-SP *Alna, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Alnather *Alna, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Alnavas *Alna, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Alnavas-A *Alna, India.*
Atorvastatin (p. 1309·2); amlodipine (p. 1304·1).
Hypertension; angina pectoris; hyperlipidaemias; cardiovascular risk reduction.

Alnavas-EZ *Alna, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Alnax *Masa, Thai.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Alnex *Pisa, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Alnix *Westmont, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Alnok *Sandoz, Denm.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic rhinitis; allergic conjunctivitis.

Alnorcon *Alapis, Gr.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Alnox *Air Liquide, Canad.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).

Aloat NC *Shalaks, India.*
Aloe vera (p. 1693·2); theobroma oil (p. 2216·1); jojoba oil.
Emollient.

Aloax *Ativus, Braz.*
Aloe vera (p. 1693·2).

Alocapil *Spirig, Switz.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Alocare *Cantabria, Spain.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Aloce *Miklich, Port.†*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Alocin
Note: this name may be used for preparations of different composition.
Candor, India.
Oral suspension: Ofloxacin (p. 334·3).
Bacterial infections.
Candor, India.
Tablets: Lactobacillus sporogenes (p. 2596·3); ofloxacin (p. 334·3).
Conba, China.
Azlocillin sodium (p. 223·2).
Bacterial infections.

Alocin-OZ *Candor, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Alockin *Zydus, India.*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

Aloclair
Note: this name may be used for preparations of different composition.
Butler, Ger.†; Forest Laboratories, UK.
Povidone (p. 2204·3).
Mouth pain.
Kalbe, Indon.
Povidone (p. 2204·3); sodium hyaluronate (p. 2526·2); enoxolone (p. 54·2).
Mouth ulcers; mouth lesions.
Sinclair, Malaysia.
Povidone (p. 2204·3); sodium hyaluronate (p. 2526·2).
Mouth ulcers; mouth lesions.

Alocril *Allergan, Canad.; Allergan, USA.*
Nedocromil sodium (p. 1216·2).
Allergic conjunctivitis.

Alodan *Gerot, Austria.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Alodip *Zytras, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Alodip-AT *Zytras, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Alodont *Tonipharm, Fr.*
Cetylpyridinium chloride (p. 1743·1); chlorobutanol (p. 1747·2); eugenol (p. 2501·2).
Mouth and throat infections.

Alodorm *Alphapharm, Austral.; LCH, Hong Kong.†*
Nitrazepam (p. 1089·1).
Insomnia.

Alodox *Ocusoft, USA.*
Doxycycline (p. 288·1).
Bacterial infections.

Alo-E *Maneesh, India.*
Aloe vera (p. 1693·2); vitamin E acetate (p. 2119·2).

Aloe Compose *Boiron, Fr.*
Aloe socotrina (p. 1816·1); colocynthis (p. 1833·3); podophyllum peltatum (p. 1717·1); bryonia (p. 2461·3); belladonna (p. 2453·3); arsenicum album (p. 2448·1); dioscorea villosa (p. 2648·1); magnesia phosphorica (p. 1787·3).
Homoeopathic preparation.

Aloe Grande *Gordon, USA.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); aloe vera (p. 1693·2).
Skin disorders.

Aloe Kote *Aloe Care, Canad.*
SPF 25: Homosalate (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Aloe Vera Gel *GNLD, Austral.*
Aloe vera (p. 1693·2); calendula (p. 2465·2); chamomile (p. 2474·1); centaurea cyanus; St John's wort (p. 449·1); tilia (p. 2631·3).
Skin irritation.

Aloe Vera Plus *GNLD, Austral.*
Aloe vera (p. 1693·2); ascorbic acid (p. 2110·3); chamomile (p. 2474·1); Siberian ginseng (p. 2614·3); ginseng (p. 2513·3); passion flower (p. 2584·1).
Tonic.

Aloe Vesta *Convatec, USA.*
Ointment: Miconazole nitrate (p. 589·1).
Fungal skin infections.
Convatec, USA.
Topical wipe: Emollient.

Aloebel *Fortbenton, Arg.*
⊗Aloe vera (p. 1693·2); urea (p. 1727·3).

Aloedent *Odontofarma, Arg.†*
Aloe vera (p. 1693·2).

Aloederm *Fem Care, India.*
Aloes (p. 1816·1); nicotinamide (p. 2083·1); sesame oil (p. 2614·1); vitamin E acetate (p. 2119·2).

Aloederm-B *Fem Care, India.*
Allantoin (p. 1693·1); aloes (p. 1816·1); chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3); sodium pidolate (p. 1720·3); vitamin E acetate (p. 2119·2).

Aloederm-G *Fem Care, India.*
Aloes (p. 1816·1); gentamicin sulfate (p. 304·2); sesame oil (p. 2614·1); vitamin E acetate (p. 2119·2).

Aloekin *Zydus, India.*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

Aloelax *Knop, Chile.*
Cape aloes (p. 1816·1); linseed (p. 2544·2).
Constipation.

Aloemagnolia *Nordin, Mex.*
Aloe vera (p. 1693·2); calendula (p. 2465·2); panthenol (p. 2582·2).

Aloepure *Aloette, Canad.*
Sulfur (p. 1721·1).
Acne.

Alof *Admac, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Alofedina *Tecsolpar, Spain.*
Aloes (p. 1816·1); belladonna (p. 2453·3); ipecacuanha (p. 1667·2); nux vomica (p. 2573·3); podophyllum (p. 1717·1).
Constipation.

Aloferal *Bailleul, Fr.*
Ferrous fumarate (p. 2060·3).
Iron supplement.

Alofin *Kocak, Turk.*
Finasteride (p. 2358·3).

Alof-T *Admac, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Alogard *Mars, India.*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

Alogesia *Fardi, Spain.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Alo-Haar *Dedousis, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Aloha-XT *Indoco, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Aloha-XT DPS *Indoco, India.*
Ferrous ascorbate (p. 2060·3).

Aloid *Janssen-Cilag, Mex.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Alois *Apsen, Braz.*
Memantine hydrochloride (p. 393·1).
Parkinsonism; Alzheimer's disease.

Alomid *Alcon, Ukr.*
Lodoxamide (p. 2544·3).
Allergic conjunctivitis.

Alomide *Alcon, Arg.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile†; Alcon, China; Alcon, Cz.†; Alcon, Denm.; Alcon, Fin.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Norw.†; Alcon, Pol.; Alcon, Port.†; Alcon, Rus.†; Alcon, S. Afr.; Alcon, Singapore†; Alcon Cusi, Spain; Alcon, Thai.†; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Lodoxamide trometamol (p. 2545·1).
Allergic conjunctivitis; keratitis; keratoconjunctivitis.

Alonet *Pharmachemie, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction.

Aloo *Bestochem, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aloo-SR *Bestochem, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Alopam *Actavis, Denm.; Actavis, Norw.*
Oxazepam (p. 1092·2).
Anxiety; agitation; insomnia.

Alopate *Kela, Belg.*
Zinc oxide (p. 1729·1); titanium oxide (p. 1725·1); kaolin (p. 1850·1).
Skin disorders.

Alopek *Royal, Chile.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Aloperidin *Janssen-Cilag, Gr.*
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Psychoses; Huntington's chorea; tics.

Alopexy *Pierre Fabre, Belg.; Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Israel; Pierre Fabre, Neth.†; Pierre Fabre, Spain; Pierre Fabre, Switz.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Alophen
Note: this name may be used for preparations of different composition.
Numark, Canad.†; Numark, USA.
Bisacodyl (p. 1821·1).
Constipation.

Aloplastine *Kela, Belg.†; Johnson & Johnson, Fr.*
⊗Zinc oxide (p. 1729·1); glycerol (p. 2517·2); purified talc (p. 1722·2).
Skin irritation; napkin rash; skin disorders.

Aloprim *Bioniche, USA.*
Allopurinol sodium (p. 600·2).
Hyperuricaemia during cancer chemotherapy.

Alopros *Pharmacore, Indon.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Alopur *Rowex, Irl.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Aloquin
Note: this name may be used for preparations of different composition.
Primus, USA.
Diiodohydroxyquinoline (p. 931·1).

Alor *Atley, USA.†*
Hydrocodone tartrate (p. 67·2); aspirin (p. 22·2).
Pain.

Alora
Note: this name may be used for preparations of different composition.
Actavis, USA.
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency.
Medizone, India.
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.
Nobel, Turk.; Nobel, Ukr.
Passion flower (p. 2584·1).
Anxiety; sleep disorders; neurasthenia; depression.

Pharos, Indon.
Vitamins; minerals.
Pre- and postnatal supplement.

Alorex *Maneesh, India.*
Allantoin (p. 1693·1); aloes (p. 1816·1); chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).

Aloric *Intas, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Aloriv *East African, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Alorom *Vifiteh, Rus.*
Aloes (p. 1816·1); calendula (p. 2465·2); levomenthol (p. 2553·2); chamomile (p. 2474·1); eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Alosen *Baif, Ital.†*
Senna (p. 1885·1); frangula bark (p. 1843·3); cascara (p. 1826·1); rhubarb (p. 1884·2); california poppy (p. 2466·1).
Constipation.

Alosfar *Esfar, Port.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Alosol
Note: this name may be used for preparations of different composition.
Poen, Arg.
⊗Oxymetazoline hydrochloride (p. 1671·3); sodium hyaluronate (p. 2526·2).
Eye irritation.
Sanofi-Aventis, Mex.
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat infections.

Alospray *Paracelsia, Port.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Alostar-SP *Sanify, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Alostil
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Fr.
Minoxidil (p. 1438·3).
Alopecia androgenetica.
Pharos, Indon.
Amikacin sulfate (p. 214·2).
Bacterial infections.

Alostin *Apotex, Rus.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis; hypercalcaemia.

Alotac *Candor, India.*
Ondansetron (p. 1872·1); ranitidine hydrochloride (p. 1882·1).

Alotec *Boehringer Ingelheim, Jpn.†*
⊗Orciprenaline sulfate (p. 1217·3).

Aloten *Terramedic, Philipp.*
⊗Atenolol (p. 1308·2).
Hypertension.

Alotendin *Egis, Ukr.*
⊗Bisoprolol fumarate (p. 1325·3); amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Alovell *Novell, Indon.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aloven *Vensat, India.*
Aloe vera (p. 1693·2).

Alovent *Boehringer Ingelheim, Venez.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Alovir *Adley, India; Caber, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Alovit *Micro, India.*
Aloe (p. 1693·2); vitamin E (p. 2119·1).

Alovit-AF *Micro, India.*
Aloe (p. 1693·2); lactic acid (p. 2539·1); sunflower oil (p. 2098·1); vitamin E (p. 2119·1).

Alox
Note: this name may be used for preparations of different composition.
Aust Ind, India.
Ofloxacin (p. 334·3).
Bacterial infections.
Marching, Hong Kong.†
Allantoin (p. 1693·1); enoxolone (p. 54·2); lidocaine (p. 1988·1); mepyramine (p. 635·1); tolnaftate (p. 596·1).

Aloxan Derma *Resinag, Israel.†*
Aluminium chlorohydrate (p. 1694·1).
Burns; skin disorders; skin ulceration; wounds.

Aloxi *Helsinn Birex, Austria; Vifor, Belg.; Helsinn Birex, Cz.; Helsinn Birex, Denm.; Riemser, Ger.; Helsinn Birex, Gr.; Helsinn Birex, Hung.; Helsinn Birex, Irl.; Italfarmaco, Ital.; Taiho, Jpn; Helsinn Birex, Neth.; Helsinn Birex, Norw.; Helsinn Birex, Pol.; Helsinn Birex, Port.; Mundipharma, Singapore; Helsinn, Spain; Biovitrum, Swed.; Vifor, Switz.; Helsinn, Thai.; Onko, Turk.; Sinclair, UK; Eisai, USA.*
Palonosetron hydrochloride (p. 1875·1).
Nausea and vomiting associated with cancer chemotherapy.

Aloxid *Interbat, Indon.*
Minoxidil (p. 1438·3).
Alopecia.

Aloxidil *IDI, Ital.; Vinas, Spain.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Alox-OD *Aust Ind, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Alozex *PharOS, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Alozof *Savio, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Alozur *Labormed, Cz.; Labormed, Hung.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Alp *Casca, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpagelle *CAG, Fr.*
Miristalkonium chloride (p. 1761·3).
Contraceptive.

Alpam *Saga, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpara *Molex Ayus, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Influenza symptoms; cough.

Alparazole *Laborate, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpaz *Royal, Chile.*
Zopiclone (p. 1118·1).
Insomnia.

Alpazam *TNP, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic attacks.

Alpenaso *Soho, Indon.†*
Terfenadine (p. 640·3).
Allergic rhinitis; allergic skin disorders.

Alpenkraft *MaxMedica, Swed.*
Pumilio pine oil (p. 2591·1); lemon oil (p. 2543·1); star anise oil (p. 2622·2); fennel oil (p. 2503·3); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); thyme (p. 2630·2); tilia (p. 2631·3); aniseed (p. 2444·2); caraway (p. 2470·2); fennel (p. 2503·2); knotgrass (p. 2538·2).
Cold symptoms; cough.

Alpentin *Actavis, Indon.*
Gabapentin (p. 523·3).
Epilepsy.

Alperol *Pharmasant, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; angina pectoris; hypertension; tremor.

Alpertan *Raffo, Arg.*
Valsartan (p. 1521·2).
Hypertension.

Alpertan D *Raffo, Arg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Alpet E3 *Avmor, Canad.*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Alp-FT *Casca, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Alp-FTD *Casca, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride.

1-Alpha *Leo, Belg.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; osteoporosis; rickets.

Alpha B-Cal *Osper, India.*
Alfacalcidol (p. 2112·3); betacarotene (p. 2051·1); calcium carbonate (p. 1824·3).

Alpha Cad
Note: this name may be used for preparations of different composition.
Shrishti, India.
Vitamins; minerals; thioctic acid (p. 2629·1).

Alpha Cade *Dermoteca, Port.*
Salicylic acid (p. 1719·1); cade oil (p. 1723·2); cedar oil (p. 2629·3).
Seborrhoeic dermatitis; psoriasis.

Alpha D3 *Sidus, Arg.; Teva, Cz.; Gerolymatos, Gr.; Teva, Hong Kong; Teva, Hung.; GSK, Indiat; Teva, Israel; Teva, Ital.; TPW, Malaysia; Teva, Philipp.; Teva, Rus.; Teva, Singapore; Teva, Thai.; Med, Turk.; Teva, Ukr.; Vivax Gynopharm, Venez.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency; hyperparathyroidism; osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia; neonatal hypocalcaemia; pseudohypoparathyroidism; Fanconi syndrome; renal acidosis; hypophosphataemia; hypocalcaemia.

Alpha Hydrox *Neoteric, Canad.†*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Alpha Keri *Mentholatum, Austral.; BMS, NZ; BMS, UK; Novartis, USA.*
Liquid paraffin (p. 2191·2); oil-soluble dewaxed lanolin fraction (p. 2219·3).
Dry skin disorders; pruritus.
BMS, USA.
Cleansing bar: Skin cleanser.

Alpha Renol *Phytofrance, Fr.*
Equisetum (p. 2500·1); maize (p. 2487·1); juniper (p. 2537·1); couch-grass (p. 2487·2).
Herbal preparation.

Alpha Septol *Dermoteca, Port.*
Pyrithione zinc (p. 1718·1); piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1).
Seborrhoeic dermatitis.

Alpha Toothache Essence *Adco, S.Afr.†*
Phenol (p. 1763·3); clove oil (p. 2481·3).
Toothache.

Alpha-Amoxi *Apotex, NZ.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Alpha-Amoxyclav *Alpha, NZ.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Alphabetas *Shreshtha, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Alphabikal *Demo, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alphabrin *Geolab, Braz.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Alphacad
Note: this name may be used for preparations of different composition.
Admac, India.
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alphacaïne *Dentsply, Fr.; Heck, Switz.*
Articaine hydrochloride (p. 1980·1).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Alphacaine *Simaport, Port.†; Dentsply, Rus.*
Articaine hydrochloride (p. 1980·1).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Alphacal *Energon, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alphacèdre *Dermoteca, Port.*
Vitamin B substances (p. 2102·3); chlorhexidine gluconate (p. 1743·3); cedar oil (p. 2629·3).
Scalp disorders.

Alphacin *Alphapharm, Austral.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Alpha-D3 *Teva, China.*
Alfacalcidol (p. 2112·3).
Osteoporosis; hyperparathyroidism; rickets; osteomalacia; hypoparathyroidism.

Alphaderm *Alliance, Irl.; Alliance, UK.*
⊗Hydrocortisone (p. 1640·1); urea (p. 1727·3).
Skin disorders.

Alphadinal *Alpharma, Mex.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Alphadine
Note: this name may be used for preparations of different composition.
Minerva (Μινερβα), Gr.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.
Piramal, India.
Povidone-iodine (p. 1767·1).
Bacterial and fungal infections of the skin and mucous membranes; skin disinfection.

Alphadol *Panacea, India; Panacea, Thai.†*
Alfacalcidol (p. 2112·3).
Osteoporosis; hyperparathyroidism; hypoparathyroidism; renal osteodystrophy; rickets; osteomalacia.

Alphadol-C *Panacea, India; Panacea, Thai.†*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).
Osteoporosis; renal osteodystrophy; hyperparathyroidism; rickets; osteomalacia.

Alphadol-Ca *Panacea, Rus.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).
Osteoporosis; calcium and vitamin D_3 supplement.

Alphadopa *Wockhardt, India.*
Methyldopa (p. 1431·1).
Hypertension.

Alpha-Due *Phoinix Pharm (Φοινιξ Φαρμ), Gr.†*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alphagan *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, China; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Allergan, Malaysia; Allergan, Mex.; Allergan, Neth.; Allergan, Norw.; Allergan, NZ; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, Ukr.; Allergan, USA; Allergan, Venez.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension; raised intra-ocular pressure.
Allergan, India.
Brimonidine tartrate (p. 2004·3); polyvinyl alcohol (p. 2204·2).
Glaucoma.

Alphagram Otic *Pascual, Philipp.*
Chloramphenicol (p. 257·1).
Ear infections.

Alphahist *Apex, Indon.†*
Cyproheptadine hydrochloride (p. 624·1).
Allergic skin disorders; reduced appetite.

Alphalan *Natco, India.*
Melphalan (p. 819·1).
Malignant neoplasms.

Alphalarm *Densmore, Fr.*
Sea buckthorn oil (p. 2612·1); borage oil (p. 2459·2); fish oil (p. 1460·1); ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alpha-Lipogamma *Worwag, Ger.*
Thioctic acid (p. 2629·1), meglumine thioctate (p. 2629·1) or ethylenediamine thioctate (p. 2629·1).
Diabetic polyneuropathy.

Alpha-Lipon *Stada, China; Aliud, Ger.†; Stada, Ger.†*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Alphalox-D *Alpharma, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dicycloverine hydrochloride (p. 1834·2).
Gastric hyperacidity; dyspepsia.

Alphamid *Actavis, Indon.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Alphamix *Q Check, India.*
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.
Q Check, India.
Tablets: Linolenic acid (p. 1460·2); chromium tripicolinate (p. 2056·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); sodium selenite (p. 2087·1).

Alphamix-BT *Q Check, India.*
Linolenic acid (p. 1460·2); benfotiamine (p. 2102·3); chromium tripicolinate (p. 2056·1); folic acid (p. 2063·1); inositol (p. 2533·2); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Alphamol *Molex Ayus, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Alphamox *Alphapharm, Austral.; Mylan, NZ.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Alphanate *Grifols, Hong Kong; Alpha Therapeutic, Ital.; Grifols, Malaysia; Grifols, Neth.; Grifols, Philipp.; Grifols, Singapore; Grifols, Thai.; Grifols, UK; Grifols, USA.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; factor VIII deficiency; von Willebrand's disease.

Alphaneuron *Pulse, India.*
Cobamamide (p. 2107·2); thioctic acid (p. 2629·1); gamolenic acid (p. 2509·2); mecobalamin (p. 2108·1).

Alphanine *Grifols, Ger.; Grifols, Hong Kong; Alpha Therapeutic, Ital.†; Grifols, Malaysia; Grifols, Neth.; Grifols, Philipp.†; Grifols, Singapore; Grifols, Thai.; Grifols, UK; Grifols, USA.*
A factor IX preparation (p. 1149·3).
Haemophilia B; factor IX deficiency.

Alphapen *Unipharm, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Alpha-Plus *Genepharm, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alphapress *Alphapharm, Austral.; LCH, Hong Kong.†*
Hydralazine hydrochloride (p. 1401·2).
Hypertension.

Alphapril *Alphapharm, Austral.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Alpharégul Femme *Arlor, Fr.*
Day capsules, cucurbita oil (p. 2489·2); urtica (p. 2639·3); borage oil (p. 2459·2); zinc oxide (p. 1729·1); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3); night capsules, amino acids; ferrous gluconate (p. 2061·2); green tea (p. 2648·2); selenium yeast (p. 2125·2); copper gluconate (p. 2057·2); vitamins.
Hair loss.

Alpharégul Homme *Arlor, Fr.*
Day capsules, cucurbita oil (p. 2489·2); urtica (p. 2639·3); borage oil (p. 2459·2); zinc oxide (p. 1729·1); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3); night capsules, linseed (p. 2544·2); urtica; soya (p. 2092·3); zinc oxide; vitamin B_6.
Hair loss.

Alpharekin *Pro-Pharma, Ukr.*
Interferon alfa-2b (p. 989·2).
Viral and bacterial infections; urogenital chlamydiosis; neuropathic pain; laryngeal papillomatosis; multiple sclerosis; malignant neoplasms.

Alpharexin *Alpharma, Mex.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); ferrous sulfate (p. 2062·2); zinc sulfate (p. 2126·2).

Alphasidol *AG Therapy, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alphastad *Stada, Denm.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Alphastria *Zambon, Switz.*
Sodium hyaluronate (p. 2526·2); vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2); dexpanthenol (p. 2582·2); allantoin (p. 1693·1); camphor (p. 2466·2); menthol (p. 2553·2).
Prevention of skin striae.

Alphate *Marching, Hong Kong.†*
Allantoin (p. 1693·1); lidocaine (p. 1988·1); mepyramine (p. 635·1); tolnaftate (p. 596·1); zinc oxide (p. 1729·1).

alpha-Vibolex *CNP, Ger.*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy.

Alpha-Zedex *Wockhardt, India.*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Alphazol *Vocate, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Alpheus *Boniscontro & Gazzone, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Alphosyl *Stafford-Miller, Austral.†; Elder, India; GSK, S. Afr.†; GSK Consumer, Spain.†*
Allantoin (p. 1693·1); coal tar (p. 1723·2).
Psoriasis; seborrhoeic dermatitis.
Stafford-Miller, Austral.†; GSK, S.Afr.†; GSK Consumer, Spain.†
Shampoo: Coal tar (p. 1723·2).
Scalp disorders; skin and scalp disorders.

Alphosyl 2 in 1 *Perrigo, Israel; GSK Consumer, UK.*
Coal tar (p. 1723·2).
Scalp disorders.

Alphosyl HC *GSK Consumer, UK.†*
⊗Allantoin (p. 1693·1); coal tar (p. 1723·2); hydrocortisone (p. 1640·1).
Psoriasis.

Alpicort
Note: this name may be used for preparations of different composition.
Wolff, Cz.; Wolff, Ger.; Wolff, Hung.; Wolff, Pol.
⊗Prednisolone (p. 1645·2); salicylic acid (p. 1719·1).
Scalp disorders; psoriasis; eczema; alopecia areata.

Alpicort E *Wolff, Pol.*
⊗Prednisolone (p. 1645·2); salicylic acid (p. 1719·1); estradiol benzoate (p. 2271·1).
Alopecia.

Alpicort F *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.; Alcina, Switz.*
⊗Prednisolone (p. 1645·2); salicylic acid (p. 1719·1); estradiol benzoate (p. 2271·1).
Scalp disorders; alopecia; hair loss.

Alpider *Velka, Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Alpidol *Syntro, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Alpin *Arlex, Mex.*
Hyoscine butylbromide (p. 1845·3).

Alpinamed *Gebro, Austria.*
Ivy (p. 2536·2).
Cough.

Alpinamed Passelyt *Gebro, Austria.*
Passion flower (p. 2584·1).
Anxiety disorders; sleep disorders.

Alpirex *Berman, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Alpkair *PDC, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alplax *Gador, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alplax Digest *Gador, Arg.*
Alprazolam (p. 1035·2); sulpiride (p. 1107·3).
Somatic disorders.

Alplax Net *Gador, Arg.*
Alprazolam (p. 1035·2); domperidone (p. 1838·1); simeticone (p. 1886·2).
Anxiety with gastrointestinal disorders.

Alpose *Osper, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpostin *Samarth, India.*
Alprostadil (p. 2352·2).

Alpovex *Rivero, Arg.*
Ampicillin (p. 218·2).
Bacterial infections.

Alpoxen *Actavis, Fin.; Actavis, Swed.†*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; fever; inflammation.

Alpra *Avalanche, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpradol-MD *Skymax, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpralan *Olan-Kemed, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpralid *CTS, Israel.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder; mixed anxiety depressive states.

Alpraline *Taiwan Biotech, Malaysia.*
Alprazolam (p. 1035·2).
Anxiety.

Alpram *Valmor, Venez.*
Alprazolam (p. 1035·2).
Anxiety; depression; panic disorder.

Alpramed *LSP, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alpranax *YSP, Malaysia.*
Alprazolam (p. 1035·2).
Anxiety; depression; panic disorder.

Alpraquil *Lupin, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alprastad *Stada, Austria.*
Alprazolam (p. 1035·2).
Anxiety.

Alpravecs *Marvecs, Ital.*
Alprazolam (p. 1035·2).
Anxiety disorders; panic disorders.

Alprax *Aspen, Austral.; Arrow, Hong Kong; Torrent, India; Torrent, Thai.†*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder.

Alprax Forte *Torrent, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Alprax Plus *Torrent, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Alprax Z *Torrent, India.*
Alprazolam (p. 1035·2); melatonin (p. 2551·3).

Alpraz *SMB, Belg.*
Alprazolam (p. 1035·2).
Anxiety; depression; panic disorder.

Alprazig *Baldacci, Ital.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alprazol *Casasco, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alprazomed *Ranbaxy, Belg.*
Alprazolam (p. 1035·2).
Anxiety disorders.

Alprazomerck *Generics, Pol.*
Alprazolam (p. 1035·2).
Anxiety.

Alpreg *Almet, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Alpress *Pfizer, Fr.*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Alprestil *Gebro, Cz.; Gebro, Hung.*
Alprostadil (p. 2352·2).
Peripheral vascular disorders.

Alprida *Altius, Arg.†*
Mosapride (p. 1865·2).

Alprim *Alphapharm, Austral.; Alphapharm, Malaysia†; Alphapharm, Singapore.*
Trimethoprim (p. 381·2).
Bacterial infections of the urinary tract.

Alprine Plus *Sunshine, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Alprine-H *Sunshine, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Alprocontin *Modi-Mundipharma, India.†*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Alprol *Rowex, Irl.*
Alprazolam (p. 1035·2).
Anxiety.

Alpron *Aldril, Philipp.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Alprose *Pharma Synth, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alprostan *Zentiva, Cz.; Zentiva, Rus.*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus; peripheral vascular disorders.

Alprostapint *Gebro, Austria; Pint, Austria; Pint, Cz.; Pint, Hung.†; Pint, Israel.†*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus; heart failure; peripheral vascular disorders; peripheral arterial occlusion.

Alprostar *Recordati, Ital.*
Alprostadil alfadex (p. 2352·2).
Thromboangiitis obliterans.

Alprosym *Symbiosis, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alprotec *Empifarma, Port.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Alprovit *Alkem, India.*
Vitamins; minerals; protein hydrolysate.
Tonic; dietary supplement.

Alprovit DPS *Alkem, India.*
Dexpanthenol (p. 2582·2); vitamin B substances (p. 2102·3).
Infant vitamin supplement.

Alprox *Orion, Denm.; Orion, Fin.; Orion, Irl.†; Rafa, Israel; Orion, Pol.*
Alprazolam (p. 1035·2).
Anxiety; alcohol withdrawal syndrome; panic disorder; depression associated with pain; mixed anxiety depressive states.

Alproxen *Alkem, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Alps *Lincoln, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Alpurase *Biolink, Philipp.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Alpuric *Socobom, Belg.†*
Allopurinol (p. 600·2).
Gout; renal calculi.

Alpyrin *Lincoln, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Alquen *GSK, Spain.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Alquimid *Sanfer, Mex.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Alquin
Note: this name may be used for preparations of different composition.
Grandix, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Alquinn
Note: this name may be used for preparations of different composition.
The Forty-Two, Thai.
Quinine sulfate (p. 665·2).
Malaria.

Alquit *Yacca, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Alquit-L *Yacca, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alres *Elmor, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); dexchlorpheniramine maleate (p. 621·1).
Cold and influenza symptoms.

Alrex *Bausch & Lomb, Arg.; Bausch & Lomb, Braz.; Bausch & Lomb, Canad.; Bausch & Lomb, Hong Kong; Bausch & Lomb, USA.*
⊗Loteprednol etabonate (p. 1642·1).
Allergic conjunctivitis.

Alrheumun *Teofarma, Ger.*
Ketoprofen (p. 79·1).
Inflammation; musculoskeletal and joint disorders; gout.

Alrif *Intra-Labs, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alrin *Teva, Israel.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Alrin Baby *Teva, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Alrin-B *Admac, India.*
Capsules: Silymarin (p. 1561·2).
Liver disorders.

Admac, India.
Syrup: Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).
Liver disorders.

Alrinte *Ativus, Braz.*
Rosemary (p. 2607·2).
Dyspepsia; liver and biliary-tract disorders.

Alrubicin *Alkem, India.*
Epirubicin (p. 787·1).
Malignant neoplasms.

Alsan *Gulf Drug, S.Afr.*
Mepyramine maleate (p. 635·1).

Alsarex *Charak, India.*
Achyranthes aspera; cuminum cyminum; liquorice (p. 1853·2).
Peptic ulcer; dyspepsia.

Alsart *Meyer Alian, Venez.*
Valsartan (p. 1521·2).
Hypertension.

Alsartan
Note: this name may be used for preparations of different composition.
Aristo, India.
Losartan potassium (p. 1422·2).
Hypertension.

Crinos, Ital.
Valsartan (p. 1521·2).
Hypertension.

Alsartan-AM *Aristo, India.*
Losartan potassium (p. 1422·2); amlodipine besilate (p. 1304·1).
Hypertension.

Alsartan-H *Aristo, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Alsepa *Teva, Israel.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement; hyperlipidaemias.

Alsepa Focus *Teva, Israel.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement.

Alsepa 9 Months *Teva, Israel.*
Omega-3 triglycerides (p. 1460·1); folic acid (p. 2063·1).
Dietary supplement in pregnancy.

Alsepa Super *Teva, Israel.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement; hyperlipidaemias.

Alserine *Union Drug, Thai.*
Cimetidine hydrochloride (p. 1827·1).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Alsflu *Candor, India.*
Fluconazole (p. 578·2).
Fungal infections.

Alsidexten *Lemery, Mex.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Alsidol *Savio, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Alsigra *Alembic, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Alsine *Apex, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Alsol
Note: this name may be used for preparations of different composition.
Athenstaedt, Ger.; Egis, Hung.
Basic aluminium acetotartrate (p. 2440·1).
Superficial wounds; skin disorders.

Alsolide Plus *Dr Alson, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Pain.

Alsolide-MR *Dr Alson, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Alsoy *Nestle, Braz.†*
Soya preparation.
Nutritional supplement.

Nestle, Canad.†
Soya infant feed.
Cows' milk intolerance; lactose intolerance.

Alspas Forte *Allenge, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Alstat *David, India.*
Etamsylate (p. 1145·2).
Haemorrhage; menorrhagia.

Alsteride *Alapis, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Alsucral *Orion, Fin.; Orion, Malaysia†; Orion, Singapore.†*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis.

Alsucril *Pentafarma, Port.*
Acarbose (p. 466·2).
Diabetes mellitus.

Alsylax *Boehringer Ingelheim, Chile.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Altabax *GSK, USA.*
Retapamulin (p. 348·1).
Impetigo.

Altabor *Borshchagovskii, Ukr.*
Alder.
Influenza and SARS prevention.

Altace *Sanofi-Aventis, Canad.; King, USA; Sanofi-Aventis, Venez.*
Ramipril (p. 1483·3).
Hypertension; heart failure following myocardial infarction; cardiovascular risk reduction; diabetic nephropathy; heart failure.

Altace HCT *Sanofi-Aventis, Canad.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Altace Plus *Sanofi-Aventis, Venez.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Altace Plus Felodipine *Sanofi-Aventis, Canad.*
Ramipril (p. 1483·3); felodipine (p. 1380·3).
Hypertension.

Altacef *Glenmark, India.*
Cefuroxime (p. 255·2), cefuroxime axetil (p. 255·2), or cefuroxime sodium (p. 255·3).
Bacterial infections.

Glenmark, Malaysia; Glenmark, Philipp.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Altacet
Note: this name may be used for preparations of different composition.
Sandoz, Pol.
Aluminium acetotartrate (p. 2440·1).
Oedema.

Altacid *Bosnalijek, Rus.*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Dyspepsia; gastritis; peptic ulcer; gastro-oesophageal reflux.

Bosnalijek, Ukr.†
Aluminium oxide (p. 1690·3); magnesium hydroxide (p. 1857·2) or magnesium oxide (p. 1857·3).
Dyspepsia; gastritis; peptic ulcer; gastro-oesophageal reflux.

Altacite *Roussel, S.Afr.†*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity.

Altacite Plus *Peckforton, UK.*
Hydrotalcite (p. 1845·2); simeticone (p. 1886·2).
These ingredients can be described by the British Approved Name Co-simalcite.
Gastrointestinal disorders.

Altaclor *CT, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Altacura Ipragocce *Alta Care, Ital.*
Chamomile (p. 2474·1); hamamelis (p. 2523·3); euphrasia (p. 2502·1).
Eye irritation.

Altadrine *Alta Care, Ital.*
Garcinia cambogia (p. 2510·2); caffeine (p. 1203·3); simmondsia chinensis; aesculus (p. 2431·2); capsicum (p. 2469·3); bitter orange (p. 2575·3).
Cellulite.

Altadrine Firming *Alta Care, Ital.†*
Fucus vesiculosus (p. 2612·1); guarana (p. 2648·2); kola (p. 2648·2); theophylline (p. 1229·3); caffeine (p. 1203·3); simmondsia chinensis; melissa oil (p. 2553·2); peppermint oil (p. 1877·1); lupulus (p. 2546·1).
Slimming-aid.

Altafed *Altaire, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract disorders.

Altaflora with electrolytes *Alta Care, Ital.*
Lactobacillus rhamnosus (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); sodium gluconate (p. 2618·3); potassium gluconate (p. 1793·2); magnesium gluconate (p. 1787·2).
Restoration of gastrointestinal flora.

Altalin *Panjon, India.*
Alprazolam (p. 1035·2); sertraline hydrochloride (p. 448·1).

Altamet *Alembic, India.*
Cefetamet pivoxil (p. 240·2).
Bacterial infections.

Altan *Rottapharm, Ital.*
⊗Promelase (p. 2597·3).
Respiratory-system disorders; oedema; haematomas; inflammation.

Altanum *Borshchagovskii, Ukr.*
Alnus glutinosa fruit.
Gastritis; dyspepsia; gastroduodenitis; peptic ulcer; colitis; enterocolitis.

Altargo *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, UK.*
Retapamulin (p. 348·1).
Impetigo; infected wounds; bacterial skin infections.

Altaryl Childrens Allergy *Altaire, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Altase *Apotex, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Altat *Teikoku, Jpn.*
Roxatidine acetate hydrochloride (p. 1884·3).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastritis; gastrointestinal haemorrhage; premedication.

Altavera *Sandoz, USA.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Altaxa *Alapis, Gr.*
Sumatriptan succinate (p. 679·2).
Migraine.

Altaxel *Alkem, India.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Altaziaja *Ziaja, Pol.*
Aluminium acetotartrate (p. 2440·1).
Inflammation.

Altazinc *Saval, Chile.*
Zinc sulfate (p. 2126·2).
Zinc deficiency; adjuvant in hypogonadism and hypothyroidism.

Alteana *Sevapharma, Cz.*
A tetanus vaccine (p. 2421·1).
Active immunisation.

Altec
Note: this name may be used for preparations of different composition.
Hetero, India.
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Zee, India.
Albendazole (p. 149·1).
Worm infections; giardiasis.

Altec Cough Formula *Hetero, India.*
Chlorphenamine maleate (p. 620·3); codeine (p. 40·2); phenylpropanolamine (p. 1674·1).

Altec-P *Hetero, India.*
Chlorphenamine maleate (p. 620·3); codeine (p. 40·2); phenylpropanolamine (p. 1674·1); paracetamol (p. 115·1).
Colds and influenza symptoms.

Alteis *Menarini, Fr.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Alteisduo *Menarini, Fr.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Altellus *Meda, Spain.*
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Alten *Medochemie, Malaysia†; Medochemie, Singapore.†*
Tretinoin (p. 1725·2).
Acne.

Altenal *Rayere, Mex.†*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis; trichomoniasis; balanitis.

Alterfast *Alternova, Denm.; Docpharma, Fin.†*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Alterflex *IBSA, Denm.*
Diclofenac epolamine (p. 48·3).
Epicondylitis; sprains.

Altergen *IBSA, Ital.*
Sodium hyaluronate (p. 2526·2); sulfadiazine silver (p. 362·3).
Burns; ulcers; wounds.

Altermicron *Alternova, Denm.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Altermon *Faran, Gr.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

Alterna
Note: this name may be used for preparations of different composition.
Abbott, Arg.
Preparation for enteral nutrition.

Grisi, Mex.
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

ALternaGEL *J&J-Merck, USA.*
Dried aluminium hydroxide gel (p. 1817·2).
Hyperacidity symptoms.

Alternus *Recalcine, Chile.*
Haloperidol (p. 1077·1).

Altersol *IBSA, Ital.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Altesse *Silesia, Chile.*
Estradiol (p. 2271·1); drospirenone (p. 2269·1).
Menopausal disorders; osteoporosis.

Altevir *Farmapark, Rus.*
Interferon alfa-2b (p. 989·2).
Chronic hepatitis B; chronic hepatitis C; anogenital warts; malignant neoplasms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alteyka *Arterium, Ukr.*
Althaea (p. 2438·3).
Respiratory-tract disorders; oesophagitis; gastritis; peptic ulcer; enterocolitis.

Altezerod *Altius, Arg.*
Tegaserod maleate (p. 1893·1).

Altezym *Alter, Spain.†*
Azithromycin (p. 221·2).
Bacterial infections.

Althaea Complex *Blackmores, Austral.†*
Maize (p. 2487·1); althaea (p. 2438·3); buchu (p. 2461·3); bearberry (p. 2453·2); *d*-alpha tocoferil acid succinate (p. 2119·2); vitamin A acetate (p. 2098·3).
Urinary-tract disorders.

Althagem *Gemi, Pol.*
Althaea (p. 2438·3).
Respiratory-tract disorders.

Althamel *Gemi, Pol.*
Althaea (p. 2438·3).
Respiratory-tract disorders.

Althea *Pond's, Philipp.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; acne and hirsutism; menstrual disorders.

Althemix *Zdorovje, Ukr.†*
Althaea (p. 2438·3).
Respiratory-tract disorders.

Althéra *Nestle, Denm.*
Infant feed.
Cows' milk allergy; soya protein allergy.

Althera *Nestle, Mex.*
Infant feed.
Cows' milk allergy; soya protein allergy.

Althocin *Erfar, Gr.*
Ethambutol (p. 296·1).
Tuberculosis.

Althrocin *Alembic, India.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Althromicin *Mac, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Altiazem *Menarini, Hong Kong; Lusofarmaco, Ital.; Lusofarmaco, Rus.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; myocardial infarction; arrhythmias.

Alticon *KB, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Alticort *Silesia, Chile.†*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Altifex *Oriform, Denm.; Orifarm, Norw.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Altigmin *Deva, Turk.*
Rivastigmine hydrogen tartrate (p. 395·1).

Altim *Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.*
⊗Cortivazol (p. 1629·3).
Corticosteroid.

Altin *Zee, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Altinate *Allenge, India.*
Artesunate (p. 648·2).
Falciparum malaria.

Altin-LE *Sysmed, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Altisben *Alter, Spain.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder.

Altissum *O2, China.*
Ribavirin (p. 1010·2).
Viral infections.

Altiva *Ranbaxy, Braz.; Ranbaxy, Hung.; Ranbaxy, India; Ranbaxy, Ukr.*
Fexofenadine hydrochloride (p. 629·1).
Hypersensitivity reactions; allergic rhinitis; urticaria.

Altiva-D *Ranbaxy, India.*
⊗Fexofenadine (p. 629·1); pseudoephedrine (p. 1676·1).
Ranbaxy, Malaysia.
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Altiver *Maver, Mex.*
Captopril (p. 1331·2).
Hypertension.

Altix *Herba Studio, Pol.*
Aluminium acetotartrate (p. 2440·1).
Musculoskeletal, joint, and soft-tissue injury; skin disorders.

Altizem *Nobel, Turk.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Alto *Pharmatech, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.
Pharmatech, India.
Topical gel: Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Alto P *Pharmatech, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Altocel *Sanofi-Aventis, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Altocerin *Acto, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Altocerin-GM *Acto, India.*
Diacerein (p. 45·3); glucosamine sulfate potassium chloride (p. 2515·3); dimethyl sulfone (p. 2493·3).

Alto-3D *Pharmatech, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Altofen *Sanbe, Indon.*
Ketoprofen (p. 79·1).
Rheumatoid arthritis; ankylosing spondylitis; gout; osteoarthritis.

Altone
Note: this name may be used for preparations of different composition.
David, India.
Vitamin B substances (p. 2102·3); minerals; dexpanthenol (p. 2582·2); peptone (p. 2086·2).
Pharmasant, Thai.
⊗Spironolactone (p. 1499·3).
Liver cirrhosis with ascites; heart failure; oedema.

Altopou *Arkomedika, Fr.†*
Piperonyl butoxide (p. 2160·2); methoprene (p. 2158·1); permethrin (p. 2159·3).
Pediculosis.

Altoprev *Sciele, USA.*
Lovastatin (p. 1425·2).
Formerly known as Altocor.
Hyperlipidaemias.

Altoram *Med-One, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Altosec *Aspen, S.Afr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Altosone *Essex, Ital.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Altovas *Servocare, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Altovas-EZ *Servocare, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Altovast *Foramen, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Altozef *Manix, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Altra *Herbapol Poznan, Pol.*
Frangula bark (p. 1843·3).
Constipation.

Altraflam *Ranbaxy, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Altraflam-P *Ranbaxy, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Altramet *Lek, Pol.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome acid aspiration; gastrointestinal haemorrhage.

Altraz *Alkem, India.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Altrazyme *Ultramark, India.*
⊗Dexpanthenol (p. 2582·2); nicotinamide (p. 2083·1); pepsin (p. 2586·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); thiamine hydrochloride (p. 2103·1).

Altreet Ag *Coloplast, Fr.*
Sulfadiazine silver (p. 362·3); carmellose sodium (p. 2175·2).
Infected burns and wounds.

Altriabak *Thea, Belg.; Thea, Neth.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Altrical *Pisa, Mex.†*
Calcitriol (p. 2113·1).
Osteoporosis; hypocalcaemia; hypoparathyroidism; rickets.

Altrip *Larco, Arg.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders; gastrointestinal radiography and endoscopy.

Altrol
Note: this name may be used for preparations of different composition.
Gelcaps, Mex.
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.
Taj, India.
⊗Anastrozole (p. 742·1).
Breast cancer.

Altrox *Torrent, Braz.; Torrent, Philipp.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder.

Altruline *Pfizer, Chile; Pfizer, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; mixed anxiety depressive states; social phobia; premenstrual dysphoric disorder.

Altum *Dr Alson, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Altus
Note: this name may be used for preparations of different composition.
Fortbenton, Arg.
⊗Hydrocortisone (p. 1640·1); neomycin (p. 329·3).

Altuss
Note: this name may be used for preparations of different composition.
SIFFRA, Ital.
Senega (p. 1677·2); althaea (p. 2438·3); red-poppy (p. 2207·3); marrubium (p. 1668·3); pinus montana (p. 2591·1); eucalyptus leaf (p. 2501·1); propolis (p. 2597·3); carpinus betulus; thyme oil (p. 2630·3).
Cough.

Altuzan *Roche, Turk.*
Bevacizumab (p. 747·1).
Colorectal cancer.

Alubar *Christo, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); amobarbital (p. 1037·2); atropine sulfate (p. 1310·2).

Alubifar *Rottapharm, Spain.†*
Almasilate (p. 1815·3).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Alu-Cap *IFET (ΙΦΕΤ), Gr.; 3M, UK.*
Aluminium hydroxide (p. 1817·2).
Antacid; hyperphosphataemia.

Alucid
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence; heartburn.
Labima, Belg.
Aluminium glycinate (p. 1817·2); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Dyspepsia; flatulence; gastric hyperacidity.

Alucinol *Franco-Indian, India.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; dyspepsia; heartburn; peptic ulcer.

Alucol
Note: this name may be used for preparations of different composition.
Sanova, Austria†; Melisana, Switz.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastro-oesophageal reflux; gastric irritation; peptic ulcer.

Aluctyl *Astellas, Ital.†*
Aluminium lactate (p. 2440·2).
Mouth and throat disorders.

Aludal *Teva Tuteur, Arg.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Aludix *Sons, Mex.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Aludon *Acdhon, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Aludonna *Armoxindo, Indon.*
Oral suspension: Aluminium oxide (p. 1690·3); magnesium oxide (p. 1857·3); hyoscyamine hydrobromide (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3).
Peptic ulcer; gastritis; heartburn; gastric hyperacidity.
Armoxindo, Indon.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); calcium carbonate (p. 1824·3); caffeine (p. 1203·3); amylase (p. 2442·1); chlorphenamine maleate (p. 620·3); hyoscine hydrobromide (p. 1845·3).
Peptic ulcer; gastritis; heartburn; gastric hyperacidity.

Aludonna D *Armoxindo, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; heartburn; gastro-oesophageal reflux; flatulence.

Aludrox
Note: this name may be used for preparations of different composition.
Pfizer, Gr.
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Antacid.
Pfizer, Gr.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Antacid.
Riemser, Ger.†; Wyeth, India; Pfizer Consumer, Irl.†
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; peptic ulcer; dyspepsia; heartburn; hyperphosphataemia.
Wyeth-Ayerst, USA.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Aludrox II *Omicron, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Aludrox MH *Wyeth, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer.

Aludroxil *Sanval, Braz.*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Alugastrin *Polfa Lodz, Pol.*
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Gastric hyperacidity; peptic ulcer.

Alugel *Chefaro, Spain.†*
Aluminium hydroxide (p. 1817·2).
Dyspepsia; gastritis; gastric hyperacidity; gastro-oesophageal reflux; hyperphosphataemia.

Alugel MPS *Bactolac, India.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Alugen *Generics, Pol.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Alujel *Deva, Turk.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence; gastro-oesophageal reflux.

Alukon *Acupharm, S.Afr.†*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Alum *Utopian, Thai.; Utopian, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Alumag
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Dyspepsia; peptic ulcer; gastritis; gastro-oesophageal reflux.

Trianon, Canad.†; Novag, Mex.; Richter, Pol.; Gedeon Richter, Ukr.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastro-oesophageal reflux; dyspepsia; gastritis; peptic ulcer; gastric hyperacidity.

TC Pharma-Chem, Thai.
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); kaolin (p. 1850·1); atropine sulfate (p. 1310·2).
Gastric hyperacidity; peptic ulcer.

Alumag D *MDI, S.Afr.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Alumag Plus *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Abdominal retention; flatulence.

Alumbra *Gynopharm, Chile.*
Misoprostol (p. 2140·3).

Alumed *Medicpharma, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Alumina-Magnesia *GPO, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Antacid.

Alumino Nippas Calcium *Mitsubishi Tanabe, Jpn.*
Calcium aluminium aminosalicylate.
Tuberculosis.

Alumite D *Xixia, S.Afr.†*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Alumpak *Investi, Arg.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Aluno-A *Salud, India.*
Allopurinol (p. 600·2); thioctic acid (p. 2629·1).

Alupectin *Bio-Drug, India.*
Aluminium hydroxide (p. 1817·2); carmellose sodium (p. 2175·2); aluminium magnesium silicate (p. 2168·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1).

Alupectin DGL *Bio-Drug, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); carmellose sodium (p. 2175·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); liquorice (p. 1853·2).

Alupent *Boehringer Ingelheim, Austria†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Ital.†; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, UK†; Boehringer Ingelheim, USA.†*
⊗Orciprenaline sulfate (p. 1217·3).
Obstructive airways disease; bronchospasm; premature labour; threatened miscarriage; digitalis intoxication; beta blocker overdosage; arrhythmias; Stokes-Adams attacks.

Alupent Expectorant *Boehringer Ingelheim, Irl.†*
⊗Orciprenaline sulfate (p. 1217·3); bromhexine hydrochloride (p. 1656·3).
Obstructive airways disease.

Alupep *Sriprasit, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); kaolin (p. 1850·1); atropine sulfate (p. 1310·2).
Gastric hyperacidity; peptic ulcer.

Aluprex *Collins, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Alupro *Medicine Products, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Alur *Alna, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Alurid *Evershine, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Aluron *Ronava, Venez.*
Allopurinol (p. 600·2).
Gout; renal calculi; hyperuricaemia.

Alusal *Richter, Pol.*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; peptic ulcer; hyperphosphataemia.

Alusil *Adcock Ingram, S.Afr.†*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Aluspastyl *Adcock Ingram, S.Afr.†*
Dicycloverine hydrochloride (p. 1834·2); dried aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastrointestinal disorders.

Alustal *Stallergenes, Ger.; Stallergenes, Hung.; Stallergenes, Ital.†; Ebos, NZ; Trimedal, Switz.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy; hyposensitisation.

Alusulin *Teva, Hung.*
Sucralfate (p. 1889·1).
Gastro-oesophageal reflux; peptic ulcer.

Alu-Tab *3M, Austral.†; iNova, Hong Kong; iNova, Malaysia; 3M, NZ; iNova, Philipp.; iNova, Singapore.†*
Aluminium hydroxide gel (p. 1817·2).
Gastric hyperacidity; peptic ulcer; hyperphosphataemia.

Alutacid *ICM, Singapore.*
Aluminium hydroxide (p. 1817·2).
Antacid; hyperphosphataemia.

Alutal *Synco, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); amobarbital (p. 1037·2); atropine sulfate (p. 1310·2).

Alutard *ALK, Neth.*
A range of allergen extracts (p. 2434·3).
Hyposensitisation.

ALK, Norw.
Allergen extracts from timothy (*Phleum pratense*) (p. 2593·3) or birch (*Betula verrucosa*) (p. 2434·3).
Allergen immunotherapy.

Alutard SQ *ALK, China.*
House-dust mite allergens (p. 2434·3).
Allergen immunotherapy.

ALK, Cz.; ALK, Denm.; ALK, Fin.; ALK, Pol.; ALK, Swed.; ALK, Switz.
Allergen extracts (p. 2434·3).
Hyposensitisation; allergen immunotherapy.

Alutop *General Drugs, Thai.*
Oral gel: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; meteorism; peptic ulcer.

General Drugs, Thai.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer.

Aluvea *Merz, USA.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders.

Aluvia *Abbott, China; Abbott, S.Afr.; Abbott, Thai.*
Lopinavir (p. 1002·1); ritonavir (p. 1013·1).
HIV infection.

Aluvit-U *Frankin, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2); magnesium trisilicate (p. 1858·1); oxyphencyclimine (p. 1875·1); methylmethionine sulfate.

Alv *Laborate, India.*
⊗Aloe vera (p. 1693·2); glycerol (p. 2517·2); vitamin E (p. 2119·1).

Alvace *Sarabhai Piramal, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Alvalin *Riemser, Ger.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Alvand *Reddy, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Alvastin *Ali, Turk.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Alvastran *Zentiva, Hung.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Alvastran HCT *Zentiva, Hung.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Alvavitaros *Sandoz, Ital.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastro-oesophageal reflux.

Alvear *SIT, Ital.*
Royal jelly (p. 2608·1).
Nutritional supplement.

Alvear con Ginseng *SIT, Ital.*
Ginseng (p. 2513·3); honey (p. 2072·1); royal jelly (p. 2608·1); myrtillus (p. 2566·2).
Nutritional supplement.

Alvect *Trumac, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Alvedon *Multicare, Philipp.; GSK Consumer, Swed.; AstraZeneca, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Alvedrin *Offenbach, Mex.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Alvein *Alapis, Gr.*
Irbesartan (p. 1411·1).

Alven *Wassermann, Ital.†*
Diosmin (p. 2505·2).
Peripheral vascular disorders.

Alvena *Diba, Mex.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract disorders.

Alvenex *Wassermann, Ital.*
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility.

Alvenor *Servier, China.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Chronic venous insufficiency; haemorrhoids.

Alvent *Farmalab, Braz.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Alventa *KRKA, Pol.; KRKA, Rus.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Alveofact *Boehringer Ingelheim, Braz.; Lyomark, Ger.; Boehringer Ingelheim, Pol.†; BAG, Rus.; Boehringer Ingelheim, Turk.*
Bovine lung phospholipids (p. 2599·2).
Neonatal respiratory distress syndrome.

Alveofen *Prieto, Arg.*
⊗Fenoterol (p. 1208·2).
Obstructive airways disease.

Alveoten *IBI, Ital.*
Neltenexine (p. 1670·2).
Respiratory-tract disorders.

Alveoterol *Tetraform, Arg.*
Tobramycin (p. 380·1).
Bacterial infections.

Alveritin *Alvartis, Mex.*
⊗Epoetin alfa (p. 1141·1).
Anaemia of chronic renal failure.

Alvesco *Nycomed, Arg.; Nycomed, Austral.; Nycomed, Austria; Takeda, Belg.; Nycomed, Braz.; Nycomed, Canad.; Grunenthal, Chile†; Nycomed, Cz.; Nycomed, Denm.; Takeda, Fin.; Nycomed, Fr.; Takeda, Ger.; Nycomed, Gr.; Nycomed, Hong Kong; Nycomed, Hung.; Nycomed, Irl.; Nycomed, Israel; Teijin, Jpn; Nycomed, Malaysia; Nycomed, Mex.; Nycomed, Neth.; Nycomed, Norw.; Nycomed, Pol.; Nycomed, Port.; Nycomed, S.Afr.; Takeda, Singapore; Nycomed, Spain; Nycomed, Swed.; Takeda, Switz.; Nobel, Turk.; Nycomed, UK; Sunovion, USA; Grunenthal, Venez.*
⊗Ciclesonide (p. 1626·3).
Asthma; obstructive airways disease.

Alvesin *Berlin-Chemie, Ger.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Alvi *Alna, India.*
Clotrimazole (p. 576·2); lactobacillus (p. 2596·3); tinidazole (p. 949·2).

Alvicet *Sigman, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Alvipsal *Altayvitamin, Rus.*
Camphor (p. 2466·2); salicylic acid (p. 1719·1); turpentine oil (p. 2636·3); adder venom.
Musculoskeletal pain; neuralgia.

Alvisan Neo *Leros, Cz.*
Mistletoe (p. 2560·2); St John's wort (p. 449·1); equisetum (p. 2500·1); crataegus (p. 2488·1); peppermint leaf (p. 1877·1); melissa (p. 2552·3); chamomile (p. 2474·1).
Hypertension; pre-sclerotic states.

Alvit *Plus, India.*
Cyanocobalamin (p. 2107·2); dexpanthenol (p. 2582·2); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Alvi-Tec *Tecnofarma, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Alvityl *Urgo, Fr.; Solvay, Rus.; Solvay, Ukr.†*
Vitamins.
Vitamin deficiency; tonic.

Alvityl A *Urgo, Fr.*
Vitamins; minerals; trace elements.
Dietary supplement.

Alvityl Défenses *Urgo, Fr.*
Echinacea angustifolia (p. 2498·1); echinacea purpurea; propolis (p. 2597·3); vitamin C (p. 2110·3).
Immunostimulant.

Alvityl Digest *Urgo, Fr.*
Tilactase (p. 2631·2).
Lactose intolerance.

Alvityl Plus *Urgo, Fr.*
Vitamins; minerals; trace elements.
Dietary supplement.

Alvityl Tonus *Urgo, Fr.*
Vitamins; minerals; trace elements; ginseng (p. 2513·3); caffeine (p. 1203·3).
Tonic.

Alviz *Pharos, Indon.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder.

Alvo *Taisho, Jpn.*
Oxaprozin (p. 112·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Alvo Nasal *Lafedar, Arg.*
⊗Diphenhydramine hydrochloride (p. 626·2); naphazoline hydrochloride (p. 1669·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Alvofact *Boehringer Ingelheim, Gr.*
Bovactant (p. 2599·2).
Neonatal respiratory distress syndrome.

Alvofer *Specifar (Σπεσιφαρ), Gr.*
Iron sucrose (p. 2078·1).

Alvogil *Septodont, Spain.†*
Butyl aminobenzoate (p. 1982·3); eugenol (p. 2501·2); iodoform (p. 1758·2).
Maxillary alveolitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alvogyl
Note: this name may be used for preparations of different composition.
Septodont, Cz.; Septodont, Fr.; Septodont, Israel.
Lidocaine (p. 1988·1); eugenol (p. 2501·2).
Dental disorders; alveolitis.
Wild, Switz.
Butyl aminobenzoate (p. 1982·3); iodoform (p. 1758·2); eugenol (p. 2501·2); spearmint oil (p. 2621·2); penghawar djambi fibra.
Alveolitis; pain following tooth extraction.

Alvonal *Pfizer, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Alvox *Bombay Tablet, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Alwel *Zuventus, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Alworm
Note: this name may be used for preparations of different composition.
Medopharm, India.
Albendazole (p. 149·1).
Worm infections; giardiasis.
The Forty-Two, Thai.
Mebendazole (p. 158·3).
Worm infections.

Alxil *Bernofarm, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Alxis *Farmaceutica H, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Aly *The Forty-Two, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions; anaphylaxis.

Alyacen 1/35 *Glenmark, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Combined oral contraceptive.

Alyacen 7/7/7 *Glenmark, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Triphasic oral contraceptive.

Alynol *Pharos, Indon.*
Allylestrenol (p. 2255·2).
Threatened or recurrent miscarriage.

Alyostal *Stallergenes, Belg.*
Venoms of bee (p. 2434·3) and wasp (p. 2434·3).
Allergen immunotherapy.
Stallergenes, Cz.; Stallergenes, Fr.; Tracymed, Gr.; Stallergenes, Hung.; Stallergenes, Pol.; Trimedal, Switz.†
A range of allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity; hyposensitisation; allergen immunotherapy.

Alyrane *Baxter, China; Zeneca, Israel†; AstraZeneca, Philipp.†*
Enflurane (p. 1899·3).
General anaesthesia.

Alzad *Wockhardt, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Alzaimax *Rontag, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzam *Psicofarma, Mex.*
Alprazolam (p. 1035·2).
Anxiety disorders; alcohol withdrawal syndrome.

Alzancer *Nobel, Turk.*
Donepezil hydrochloride (p. 390·2).

Alzant *Bilim, Turk.*
Memantine hydrochloride (p. 393·1).

Alzaten *Ariston, Arg.*
Phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Hypotension.

Alzdone *Unia, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzel *Zee, Philipp.*
Albendazole (p. 149·1).
Worm infections.

Alzen *Orifarm, Denm.; Tecnifar, Port.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; mania.

Alzene *Alphapharm, Austral.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Alzental *Shin Poong, Singapore.*
Albendazole (p. 149·1).
Worm infections.

Alzepam *Psyco Remedies, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; skeletal muscle spasm; seizures; alcohol withdrawal syndrome.

Alzepezil *Egis, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzepil *Egis, Ukr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzepinol *Medley, Braz.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Alzero *Ind-Chemie, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Alzex
Note: this name may be used for preparations of different composition.
Ativus, Braz.
Vitamins.
Psychotropics, India.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzex Forte *Psychotropics, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Alzex Plus *Psychotropics, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Alzhedon *Teva, Cz.†*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzil *Glenmark, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzim *Fahrenheit, Indon.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Alzmeran *Ranbaxy, Irl.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostate hyperplasia.

Alzmex *Kocak, Turk.*
Memantine (p. 393·1).

ALZ-NAC *Macoven, USA.*
Mecobalamin (p. 2108·1); calcium methylfolate (p. 2053·1); acetylcysteine (p. 1652·2).

Alzoact *Active, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzocum *Taj, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzokam *Baroda, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzol *Bal, India; Pharmasant, Thai.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Alzolam *Sun, India; Sun, Rus.; Sun, Singapore.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzolid *Alembic, India.*
Linezolid (p. 317·3).
Bacterial infections.

Alzomax *Kamron, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzopax *La Pharmaceuticals, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzoprim *IQFA, Mex.*
Allopurinol (p. 600·2).
Gout.

Alzor *Ajanta, Philipp.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Alzor CCB *Ajanta, Philipp.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Alzor HCT *Ajanta, Philipp.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Alzot *Pfizer, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzy *Zee, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Alzyme *Candor, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Alzyr *Actavis, Fin.; Actavis, Norw.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Alzytec *Samchully, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria.

Am
Note: this name may be used for preparations of different composition.
Orchid, India.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Ama *Atlantic, Thai.*
Chlorpromazine hydrochloride (p. 1045·2); amobarbital (p. 1037·2).
Anxiety; tension.

Amace *Systopic, India.*
Amlodipine (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Amace-BP *Systopic, India.*
Amlodipine besilate (p. 1304·1); benazepril (p. 1314·3).
Hypertension.

Amacin *Asian Pharm, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amacone *Hua, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Meteorism; gastric hyperacidity; peptic ulcer.

Amaday *Ajanta, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amadiab *Lapi, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amadol *Meda, Ger.†; TAD, Ger.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Amagen *Generics, Hung.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amagesan *Ritsert, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amalar *Micro, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Amalset *Biomax, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Amalvia *Pliva, Rus.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Am-An
Note: this name may be used for preparations of different composition.
Berman, Mex.
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amana Cellium *Legacy, Fr.*
Cellium GC (onion (p. 2575·2); lemon (p. 2542·3); paullinia cupana seed (p. 2648·2); theobroma seed (p. 2216·1)).
Hair loss.

Amanda *Unison, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Amanita Complexe No 75 *Lehning, Fr.*
Cinchona succirubra (p. 2478·3); chelidonium (p. 2522·2); solanum dulcamara (p. 2497·3); amanita muscaria; spigelia (p. 2621·3); secale cornutum (p. 2137·1); cicuta virosa; cuprum aceticum (p. 2486·2); cantharis (p. 2469·2); echinacea (p. 2498·1).
Homoeopathic preparation.

Amantadol *Hexal, Cz.†*
Amantadine sulfate (p. 890·3).
Parkinsonism; influenza.

Amantagamma *Worwag, Ger.†*
Amantadine hydrochloride (p. 890·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Amantan *Nycomed, Belg.†*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza A.

Amantix *Merz, Pol.*
Amantadine sulfate (p. 890·3).
Parkinsonism.

AMantle *PharmaDerm, USA.*
An ointment base.

Amantrel *Cipla, India.*
Amantadine (p. 890·3).
Parkinsonism.

Amaphen with Codeine *Trimen, USA.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain.

Amapirid *Teva, Ukr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amapirida *Teuto, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amara *Weleda, S.Afr.†*
Absinthium (p. 2426·1); achillea (p. 2427·3); chicory (p. 2475·2); centaury (p. 2473·2); gentian (p. 2512·1); imperatoria ostruthium; juniper (p. 2537·1); sage (p. 2608·3); taraxacum (p. 2625·3).
Gastrointestinal disorders.

Amarance *Codepharma, Fr.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Triphasic oral contraceptive.

Amara-Pascoe *Pascoe, Ger.*
Gentian (p. 2512·1); cinchona bark (p. 2478·3); bitter orange peel (p. 2575·3); cinnamon bark (p. 2479·2).
Gastrointestinal disorders.

Amaratopfen *Weleda, Canad.†*
Absinthinum (p. 2426·1); achillea millefolium (p. 2427·3); centaurium umbellatum (p. 2473·2); cichorium intybus (p. 2475·2); gentiana lutea (p. 2512·1); juniper berries (p. 2537·1); masterwort; salvia (p. 2608·3); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Amara-Tropfen *Weleda, Ger.*
Absinthium (p. 2426·1); chicory (p. 2475·2); centaury (p. 2473·2); gentian (p. 2512·1); imperatoria; juniper (p. 2537·1); achillea (p. 2427·3); sage (p. 2608·3); taraxacum (p. 2625·3).
Gastrointestinal disorders.

Amarel *Sanofi-Aventis, Fr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amargine *IFET (ΙΦΕΤ), Gr.*
Arginine hydrochloride (p. 2049·1).

Amargozin *Pascual, Philipp.*
Karela.
Food supplement for blood sugar management.

Amarkor *SF, Ital.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Amaro Medicinale *Giuliani, Ital.*
Rhubarb (p. 1884·2); cascara (p. 1826·1); gentian (p. 2512·1); boldo (p. 2458·3).
Appetite loss; constipation; digestive disorders.

Amaropo Plus *Phapros, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); lycopene (p. 2546·2).
Dietary supplement.

Amarosal *Herbapol Wroclaw, Pol.*
Achillea (p. 2427·3); fennel (p. 2503·2); melissa (p. 2552·3); marrubium (p. 1668·3).
Reduced appetite; meteorism; dyspepsia.

Amarwin *Winthrop, Cz.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amaryl
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis,

Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Aventis, NZ†; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.
Glimepiride (p. 473·2).
Diabetes mellitus.

Amaryl Flex *Sanofi-Aventis, Braz.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Amaryl M *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile; Sanofi-Aventis, Indon.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Thai.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sanofi-Aventis, Ukr.
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Amaryll
Note: this name may be used for preparations of different composition.
Gland, Philipp.
Tramadol hydrochloride (p. 139·2).
Pain.

Amarylle *Sanofi-Aventis, Belg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amaryl-M *Sanofi-Aventis, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Amasulin *Takeda, Jpn.*
Carumonam sodium (p. 232·2).
Mepivacaine hydrochloride (p. 1992·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Amat *Piramal, India.*
Amlodipine (p. 1304·1); atorvastatin (p. 1309·2).

Amatine *Shire, Canad.†*
⊗Midodrine hydrochloride (p. 1437·3).
Orthostatic hypotension.

Amato *Eurofarma, Braz.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Amatol *Liferpal, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Amavio *Nycomed, Gr.*
⊗Ciclesonide (p. 1626·3).
Asthma.

AMB *Croesus, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambacitam *Pan-Ject, Philipp.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Vitroforma, Thai.
Sultamicillin (p. 369·1).
Bacterial infections.

Ambamida *Sintesina, Arg.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Ambcet *Fourrts, India.*
Ambroxol hydrochloride (p. 1654·3); cetirizine hydrochloride (p. 619·2).

Ambe 12 *Recordati, Ger.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Amben *Medochemie, Hong Kong.*
Cefadroxil (p. 233·2).
Bacterial infections.

Ambenat *Ratiopharm, Austria.†*
Glycol salicylate (p. 66·2); benzyl nicotinate (p. 29·3); heparin sodium (p. 1396·3).
Muscle, nerve, and joint pain.

Ambene
Note: this name may be used for preparations of different composition.
Merckle, Rus.
⊗Solution A: phenylbutazone sodium (p. 125·1); sodium salamidacetate (p. 129·2); dexamethasone (p. 1630·3); Solution B: cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to reduce the pain of injection.
Gout; musculoskeletal and joint disorders; neuritis; neuralgia.

Recordati, Ger.
Phenylbutazone (p. 125·1) or phenylbutazone sodium (p. 125·1).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Ankylosing spondylitis; gout; rheumatoid arthritis.

Ambene N *Ratiopharm, Austria.†*
Suppositories: Phenylbutazone (p. 125·1); cyanocobalamin (p. 2107·2).
Musculoskeletal, joint, soft-tissue, and peri-articular disorders; neuritis; gout; superficial thrombophlebitis.

Ambenyl Cough Syrup *Forest Pharmaceuticals, USA.†*
Codeine phosphate (p. 40·2); bromazine hydrochloride (p. 617·3).
Coughs and cold symptoms; allergic upper respiratory symptoms.

Ambenyl-D *Forest Pharmaceuticals, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Nasal congestion; coughs.

Amber *Pond's, Philipp.*
Lynestrenol (p. 2287·3).
Progestogen only oral contraceptive.

Ambes *Twilight Litaka, Philipp.; GPO, Thai.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ambese *Biotech, Venez.*
Secnidazole (p. 947·3).
Protozoal infections.

Ambesyl *Sandoz, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ambeven *Medikon, Indon.†*
Graptophyllum pictum; sophora japonica; rubia cordifolia; coleus atropurpureus; burnet (p. 2462·3); kaempferia angustifolia; curcuma heyneana.
Haemorrhoids.

Ambeven Plus *Medikon, Indon.†*
Graptophyllum pictum; troxerutin (p. 2505·3).
Haemorrhoids.

Ambex *Walmark, Cz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambezetal *Cimed, Braz.*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Ambheel *Heel, Neth.*
Aesculus hippocastanum (p. 2431·2); hamamelis virginiana (p. 2523·3); paeonia officinalis; lycopodium clavatum (p. 2547·1); nux vomica (p. 2573·3).
Homoeopathic preparation.

AMBI 60/580 *AMBI, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

AMBI 60/580/30 *AMBI, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs; respiratory-tract congestion.

AMBI 1000/5 *AMBI, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

AMBI 1000/55 *AMBI, USA.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

AMBI DM/CPM *AMBI, USA.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

AMBI PEH/CPM *AMBI, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

AMBI PEH/CPM/DM *AMBI, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

AMBI PEH/GFN *AMBI, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

AMBI PEH/GFN/DM *AMBI, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

AMBI PSE/CPM *AMBI, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

AMBI PSE/CPM/DM *AMBI, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

AMBI PSE/GFN *AMBI, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

AMBI PSE/GFN/DM *AMBI, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Ambicet *Ind-Swift, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Ambidrin *Collins, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Ambien *Sanofi-Aventis, Arg.; Sanofi-Aventis, Hung.†; Sanofi-Aventis, Israel; Sanofi, USA.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Ambifed *MCR, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ambifed CD *American Pharmaceutical, USA; MCR, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ambifed CDX *American Pharmaceutical, USA; MCR, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ambifed-G *MCR, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ambifed-G DM *MCR, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Ambiform *GSK, India.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis; giardiasis.

Ambigra *Suhitas, Philipp.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Ambilan *Laboratorios Chile, Chile.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ambilan Bid *Laboratorios Chile, Chile.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ambiopi *Mersifarma, Indon.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ambiosol *Solfran, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Ambirix *GSK, Cz.; GSK, Denm.; GSK, Irl.; GSK, Neth.; GSK, Pol.; GSK, Port.; GSK, Swed.; GSK, UK.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p. 2391·3).
Active immunisation.

AmBisome *Gador, Arg.; Gilead, Austral.; Gilead, Austria; UCB, Belg.; United Medical, Braz.; Astellas, Canad.; Gilead, Denm.; Gilead, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hong Kong; Piramal, India; Gilead, Irl.; Gilead, Israel; Gilead, Ital.; Dainippon, Jpn; Gilead, Neth.; Gilead, Norw.; Gilead, NZ; Gilead, Pol.; Gilead, Port.; Gilead, Rus.†; Key Oncologics, S.Afr.; Gilead, Singapore; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; Gilead, Thai.; Er-Kim, Turk.; Gilead, UK; Astellas, USA.*
Liposomal amphotericin B (p. 569·2).
Fungal infections; leishmaniasis; visceral leishmaniasis; cryptococcosis; febrile neutropenia.

Gilead, Hung.
Liposomal amphotericin B (p. 569·2).
Fungal infections.

Ambistryn-S *Piramal, India.*
Streptomycin sulfate (p. 359·1).
Tuberculosis.

Ambitus *Siomond, India.*
Ammonium chloride (p. 1656·1); bromhexine (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Ambixime *Suhitas, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ambixol *United Drug, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambiz *Unichem, India.†*
Zolpidem (p. 1116·2).
Insomnia.

Ambloc *Unison, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ambodil-C *Arlex, Mex.*
⊗Ambroxol (p. 1654·3); clenbuterol (p. 1207·2).
Cough.

Amboneural *Arcana, Austria.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Amboral *Alapis, Gr.; Remek, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Amborex-GS *Curex, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Ambotetra *Janssen-Cilag, Mex.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Ambovit *Fitapharm, Ukr.*
White birch (p. 2457·3); populus nigra; strawberry timber; sage (p. 2608·3); aloe vera (p. 1693·2); knotgrass (p. 2538·2); St John's wort (p. 449·1); achillea (p. 2427·3); sandy immortelle flowers; hazelnut leaf.
Urinary-tract disorders.

Ambra Med Complex *Dynamit, Austria.*
Ambra (p. 2440·3); coffea (p. 2648·2); phosphorus (p. 2589·2).
Homoeopathic preparation.

Ambra Oligoplex *Madaus, Arg.*
Minerals.

Ambral *Aquila, S.Afr.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Ambramicina *Scharper, Ital.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Ambra-Sinto T *Medley, Braz.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Ambrax *Homviora, Ger.*
Sepia (p. 2613·1); ambra (p. 2440·3); hyoscyamus (p. 2530·2); ignatia (p. 2532·1).
Homoeopathic preparation.

Ambre Solaire *Garnier, UK.*
Avobenzone (p. 1695·1); enzacamene (p. 1703·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ambreks *Nobel, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambrex *Grandix, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2); menthol (p. 2553·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ambrexin *Teva, Mex.†*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Ambril *Merck Serono, Arg.; Svizera, India; Merck, Indon.; Merck, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambril-S *Svizera, India.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2).

Ambril-SG *Svizera, India.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2); guaifenesin (p. 1666·2).

Ambrix *GSK, UK.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p. 2391·3).
Active immunisation.

Ambri-Xil *Medarte, Gr.*
Ambroxol hydrochloride (p. 1654·3).

Ambro *1A, Pol.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambro PD *Grandix, India.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol (p. 1220·2).

Ambro S *Grandix, India.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol (p. 1220·2).

Ambro TS *Grandix, India.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol (p. 1220·2); theophylline (p. 1229·3).

Ambrobene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Rus.; Ratiopharm, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion; respiratory-tract disorders with viscous mucus.

Ambrobeta *Betapharm, Ger.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Ambrocin *Medicpharma, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambroclar *Schering-Plough, Venez.*
Loratadine (p. 633·2); ambroxol (p. 1654·3).

Ambrocol *Hanmi, China.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Cough; respiratory-tract congestion.

Ambroday *Metz, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambrodex *Emar, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); phenylpropanolamine hydrochloride (p. 1674·1).

Ambrodil
Note: this name may be used for preparations of different composition.
Aristo, India.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Farmoz, Port.†
Zidovudine (p. 1024·2).
HIV infection.

Ambrodil Plus *Aristo, India.*
Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2).
Rhinitis; bronchitis; sinusitis; cold symptoms.

Ambrodil-S *Aristo, India.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol (p. 1220·2).
Asthma; smokers' cough.

Ambrodoxy *Hexal, Ger.†*
Doxycycline hyclate (p. 288·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections with increased or viscous mucus.

Ambrofluid *Farmakopea, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambroflux *Luper, Braz.*
Ambroxol (p. 1654·3).

Ambrofur *Teva, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Ambrogen-S *Sterling, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Ambrohexal *Hexal, Austria; Sandoz, China; Hexal, Ger.†; Sandoz, Hung.†; Sandoz, Pol.; Hexal, Rus.; Sandoz, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambroksol *Nycomed, Pol.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambrol *Brasterapica, Braz.; Deva, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambrol Plus *Glenmark, India.*
⊗Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Ambrol-AM *Adley, India.*
Ambroxol hydrochloride (p. 1654·3); ammonium chloride (p. 1656·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Ambrolax *Helax, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Ambrolax-PD *Helax, India.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2); theophylline (p. 1229·3).

Ambrol-C *Adley, India.*
Ambroxol hydrochloride (p. 1654·3); cetirizine (p. 619·2).

Ambrolex *GSK, Philipp.; GSK, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus; cough.

Ambrol-GPC *Adley, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); phenylpropanolamine hydrochloride (p. 1674·1).
CIMS class.

Ambrolite *Tablets, India.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambrolite-D *Tablets, India.*
⊗Cetirizine (p. 619·2); dextromethorphan (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Ambrolite-S *Tablets, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Ambrolite-2S *Tablets, India.*
Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2).

Ambrolite-ST *Piramal, India.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol (p. 1220·2); theophylline (p. 1229·3).

Ambrolitic *Chiesi, Spain.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Ambrol-TG *Adley, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Ambrolytic *Union Drug, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion mucus.

Ambromax *Huons, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambromucil *Malesci, Ital.*
Ambroxol acefyllinate (p. 1201·2).
Obstructive airways disease.

Ambromuco *Cafar, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambromuco Compositum *Cafar, Venez.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Ambromyc *Farmedia, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Ambrosan *ProMed, Cz.; ProMed, Pol.; Promed, Rus.; ProMed, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus; respiratory-tract congestion.

Ambros-GM *Indkus, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Ambrosin-T *Lexus, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Ambrosol
Note: this name may be used for preparations of different composition.
Klar Sehen, India.
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Pliva Krakow, Pol.
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Pliva, Rus.†
Ambroxol hydrochloride (p. 1654·3).

Ambrospray *Cyathus, Cz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambrotard *Borshchagovskii, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambroten *Marjan, Braz.†*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Ambroter *Indo Pacific, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Ambrotos *Lafi, Chile.*
Ambroxol hydrochloride (p. 1654·3); ammonium citrate (p. 2441·3).
Respiratory-tract disorders.

Ambrotus *Epifarma, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Ambrowin *Wintech, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Ambrowin-DX *Wintech, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Ambrox *TNP, Thai.; SM, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion; respiratory-tract disorders associated with increased or viscous mucus.

Ambroxan *M & H, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ambroxit *Ranbaxy, India.*
Ambroxol (p. 1654·3); roxithromycin (p. 356·2).
Respiratory-tract infections.

Ambroxmel *Cimed, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ambroxol AL comp *Aliud, Ger.†*
Ambroxol hydrochloride (p. 1654·3); doxycycline hyclate (p. 288·2).
Respiratory-tract infections.

Ambroxol comp *Ratiopharm, Ger.*
Ambroxol hydrochloride (p. 1654·3); doxycycline hyclate (p. 288·2).
Respiratory-tract infections.

Ambufen *Macrophar, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Ambulase *Grunenthal, Pol.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Ambulax *Unimarck, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Ambulax-AD *Unimarck, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Ambulax-FM *Unimarck, India.*
Flupentixol hydrochloride (p. 1074·2); melitracen hydrochloride (p. 434·2).
Depression.

Ambulax-HD *Unimarck, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Ambulax-M *Unimarck, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Ambulax-Z *Unimarck, India.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Ambutyrate *IFET (ΙΦΕΤ), Gr.*
Sodium phenylbutyrate (p. 2518·3).

Amcal *OEP, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amcard *Systopic, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amcard-AT *Systopic, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Amcardia *Unique, Thai.*
Amlodipine besilate (p. 1304·1).
Hypertension; myocardial ischaemia; angina pectoris.

Amcard-LP *Systopic, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Amcare *Vensat, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Amcef *Amrit, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Antibioticos, Mex.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Amceft *Health Biotech, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Amceft-S *Health Biotech, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Amchafibrin *Rottapharm, Spain.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Amchek *Indoco, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amchek AT *Indoco, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Amchek L *Indoco, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amchek-Z *Indoco, India.*
Amlodipine (p. 1304·1); losartan (p. 1422·2).
Hypertension.

Amci-Clox *Wings, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Amciderm *Almirall Hermal, Ger.; Pharmasant, Thai.†*
⊗Amcinonide (p. 1621·1).
Skin disorders.

Amcidil *Macrophar, Thai.†*
Dicloxacillin (p. 286·1).
Gram-positive bacterial infections.

Amcillin *Actavis, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amcin *Cadila, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amcinafal *Relyo, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Amclaid *Indoco, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amclo *Piramal, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Amclominus *Almet, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); Lactobacillus (p. 2596·3).
Bacterial infections.

Amclosym *Symbiosis, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amclox *Bushnell, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Amclox DL *Active, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amcloxin *Universal Drug, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Amclox-LB *Active, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Amclox-LBS *Active, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Amco *Polipharm, Thai.*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Amcof *Cipla, India.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol (p. 1220·2); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Amcold *Cipla, India.*
Cetirizine hydrochloride (p. 619·2); ambroxol hydrochloride (p. 1654·3).
Cold symptoms.

Amcopan *Macrophar, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Amcopan Plus *Macrophar, Thai.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm and pain.

Amcor *Merck, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

AMD *NBF, Ital.*
Lutein (p. 2079·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); nicotinic acid (p. 2083·1); licophene; carrot.
Macular degeneration in the elderly.

Seroyal, Canad.†
Trace elements; vitamin C (p. 2110·3).

Amdarone *Berlin Pharm, Thai.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amdepin *Cadila, India.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Hexal, Denm.†
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amdepin Duo *Cadila, India.*
Amlodipine (p. 1304·1); atorvastatin (p. 1309·2).

Amdepin-AT *Cadila, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Amdepin-L *Cadila, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amdiclox *Trumac, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amdin *Hexal, Denm.†*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amdip *Dallas, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amdip-AT *Dallas, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amdipin *Labomed, Chile.*
Amlodipine besilate (p. 1304·1).
Ischaemic heart disease; hypertension.

Amdixal *Sandoz, Indon.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amdocin *Innovata, S.Afr.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Amdol *APT, Hong Kong.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amdonex-AT *Aronex, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amdory *Wermar, Mex.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Amdrec *Amrit, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Amebamagma *Wyeth, India.*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis; trichomoniasis.

Ameban *Parggon, Mex.*
Oral suspension: Diiodohydroxyquinoline (p. 931·1); kaolin (p. 1850·1); pectin (p. 2200·3).
Amoebiasis.

Parggon, Mex.
Tablets: Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Amebis Forte *Zydus, India.*
Diloxanide furoate (p. 931·2); tinidazole (p. 949·2).

Ameblin *Degorts, Mex.*
Metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis; anaerobic bacterial infections.

Amebyl *Offenbach, Mex.*
Metronidazole (p. 936·1); diiodohydroxyquinoline (p. 931·1).
Amoebiasis; bacterial infections; giardiasis.

Amebysol *Rayere, Mex.†*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis; trichomoniasis.

Ameciron *Am-Europharma, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron and folic acid supplement.

Amecladin *Am-Europharma, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Ameclina *Offenbach, Mex.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ameco *Aamorb, India.*
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Aamorb, India.
Tablets: Calcium pantothenate (p. 2085·2); glutamic acid (p. 2070·2); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Ameco Plus *Aamorb, India.*
Biotin (p. 2052·2); folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Amedin *Medreich, Hong Kong.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amedran *Farmedia, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Amefin *Pfizer, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Amefur *Ivax, Mex.†*
Quinfamide (p. 947·1).
Amoebiasis.

Ameinon *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Nabumetone (p. 97·1).

Ameket *SM, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Amekrin *NordMedica, Swed.*
Amsacrine (p. 741·3).
Acute leukaemias.

Amelior *Menarini, Austria.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Amelotex *Sotex, Rus.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Amelox *Square, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ameluz *Biofrontera, Denm.; Bipharma, Neth.; Biofrontera, Norw.; Spirit, UK.*
Aminolevulinic acid hydrochloride (p. 740·1).
Actinic keratosis.

Amender *Serral, Mex.*
Methyldopa (p. 1431·1).
Hypertension.

Amenicil *Phoenix, Arg.*
St John's wort (p. 449·1).
Depression.

Amenite A *Amenite, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Amenite Cap *Amenite, Arg.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Amenite E *Amenite, Arg.*
Collagen (p. 2483·2); elastin (p. 2483·2).
Skin disorders.

Amenite Plus *Amenite, Arg.*
Wheat germ (p. 2647·1); collagen (p. 2483·2).
Hair disorders.

Amenite Vera *Amenite, Arg.*
Aloe vera (p. 1693·2).

Amenopam *Barrenne, Braz.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Amenova *Bol, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; progestogen-only oral contraceptive; menopausal disorders; premenstrual syndrome; breast cancer.

Amenox *Sanofi-Aventis, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Ament *Ethix, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amenur *GP, Spain.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Ameparomo *Pfizer, Jpn.*
Paromomycin sulfate (p. 943·3).
Intestinal amoebiasis.

Amerge *GSK, Canad.; Glaxo Wellcome, USA.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

America *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); brompheniramine (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Americaine *Insight, USA.*
Benzocaine (p. 1980·2).
Anorectal disorders.

Americaine First Aid *Insight, USA.*
Benzocaine (p. 1980·2).
Local anaesthesia.

American Crew Classic *Colomer, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Americet *MCR, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain.

Ameride
Note: this name may be used for preparations of different composition.
Frosst, Spain.
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis with ascites.

Pharmaniaga, Malaysia.
Glimepiride (p. 473·2).
Diabetes mellitus.

Amerifed *AMBI, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Amerigel *Amerx, USA.*
Lotion: Oak (p. 2574·1).
Nappy rash.

Amerx, USA.
Ointment: Oak bark (p. 2574·1); meadowsweet (p. 2550·2); zinc acetate (p. 2126·1).
Skin disorders.

Amerituss AD *AMBI, USA.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

AmeriWash *Ameriderm, USA.*
Triclosan (p. 1773·2).
Skin cleanser.

Amermycin *Unison, Hong Kong; Unison, Thai.*
Doxycycline (p. 288·1).
Bacterial infections.

Amerol *Tempo Scan Pacific, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Ameropem *Adley, India.*
Meropenem (p. 321·3).
Bacterial infections.

Amersan *Austroplant, Austria.*
Agrimony herb (p. 2432·3); achillea (p. 2427·3); peppermint oil (p. 1877·1); rose fruit (p. 2607·1); berberis (p. 2502·1); black currant (p. 2458·1); myrtillus (p. 2566·2).
Liver and biliary tract disorders.

Austroplant, Cz.
Agrimony (p. 2432·3) achillea (p. 2427·3); peppermint oil (p. 1877·1); rose fruit (p. 2607·1); berberis (p. 2502·1); black currant (p. 2458·1); myrtillus (p. 2566·2).
Biliary-tract disorders; digestive disorders.

Amerscan DMSA *Nycomed Amersham, UK.*
Technetium-99m succimer (p. 2228·1).
Radionuclide imaging of the kidney.

Amerscan Etain Stanneux *GE Healthcare, Fr.†*
Technetium-99m (p. 2228·1) stannous medronate.

Amerscan Hepatate *GE Healthcare, Cz.†; GE Healthcare, Fin.†; GE Healthcare, Fr.†; GE Healthcare, Neth.†; Nycomed Amersham, UK.*
Technetium-99m colloidal tin (p. 2228·1).
Radionuclide imaging of the liver and spleen.

Amerscan Medronate *GE Healthcare, Belg.†; GE Healthcare, Cz.; GE Healthcare, Fin.†; GE Healthcare, Fr.†; GE Healthcare, Irl.; GE Healthcare, UK.*
Technetium-99m (p. 2228·1) medronate.
Bone scintigraphy.

GE Healthcare, Denm.†
Medronate disodium (p. 1186·1).
For radiolabelling with technetium-99m to produce technetium-99m medronate.
Bone scintigraphy.

Amerscan Pentetate *GE Healthcare, Fr.†; Nycomed Amersham, UK.*
Technetium-99m pentetate (p. 2228·1).
Assessment of renal function; radionuclide imaging of the brain and lungs; studies of gastro-oesophageal reflux and gastric emptying.

Amerscan Pulmonate *Nycomed Amersham, UK.*
Technetium-99m (p. 2228·1) labelled albumin aggregates.
Scintigraphic imaging of the lung.

Amerscan Stannous *GE Healthcare, Cz.†; GE Healthcare, Fin.; GE Healthcare, Irl.†; GE Healthcare, Neth.†; Nycomed Amersham, UK.*
Technetium-99m (p. 2228·1) stannous medronate.
Red blood cell labelling for blood pool scintigraphy.

GE Healthcare, Denm.†
Stannous fluoride (p. 2094·3); medronate disodium (p. 1186·1).
Red blood cell labelling for blood pool scintigraphy.

Amertec *Nycomed Amersham, UK.*
Technetium-99m (p. 2228·1) as sodium pertechnetate.
Radionuclide imaging.

Amertil *Biofarm, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Ameryl *Medi-Rx, Philipp.*
Metronidazole (p. 936·1).
Amoebiasis; giardiasis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Amesos *Gedeon Richter, Cz.*
Lisinopril (p. 1420·3); amlodipine besilate (p. 1304·1).
Hypertension.

Amet *IFA, Mex.†*
Desiccated thyroid (p. 2345·3).
Hypothyroidism.

A-Methapred *Hospira, USA.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Amethia *Watson, USA.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, ethinylestradiol.
Biphasic oral contraceptive.

Ametik *Kurtsan, Turk.*
Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Ametop *Smith & Nephew, Canad.; Smith & Nephew, Irl.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Smith & Nephew Healthcare, UK.
Tetracaine (p. 1996·3).
Local anaesthesia.

Ametricid *Medix, Mex.*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis; trichomoniasis.

Amétycine *Sanofi-Aventis, Fr.; Biosyn, Ger.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Ameu *Cassella-med, Ger.*
Marine fish oil (p. 1460·3).
Hyperlipidaemias.

Ameustyn *Am-Europharma, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with excess mucus.

Amevive *Raffo, Arg.†; Astellas, Canad.†; Astellas, Israel; Biogen Dompe, Switz.†; Astellas, USA.*
Alefacept (p. 1692·3).
Psoriasis.

Amexel *Piramal, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amexine *Pharmacia Upjohn, India.*
Amoxicillin (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Amfast-AT *Overseas, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Amfidor *Egis, Cz.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Amfobase *Herba Studio, Pol.†*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Skin disorders; barrier preparation.

Amfocan *Dabur, India.*
Amphotericin B (p. 569·2).
Fungal infections.

Amfos *VHB, India.*
Amifostine (p. 1539·2).
Reduction of toxicity due to cytotoxic therapy; radiotherapy-associated xerostomia.

Amfostat *BMS, Mex.*
Amphotericin B (p. 569·2).
Fungal infections.

Amfotex *Alkem, India.*
Amphotericin B (p. 569·2).
Fungal infections.

Amgat *Ind-Swift, India.*
Ambroxol (p. 1654·3); gatifloxacin (p. 303·2).
Respiratory-tract infections.

Amgenal Cough *Goldline, USA.†*
Bromazine hydrochloride (p. 617·3); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Amgrace *La Pharmaceuticals, India.*
Amisulpride (p. 1036·3).
Psychoses.

Amgrip *Collins, Mex.†*
Caffeine (p. 1203·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3); moroxydine hydrochloride (p. 1004·1).
Cold and influenza symptoms.

Amiact *Active, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amiada *Jenapharm, Ger.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Amiaid *Nitto Denko, China.*
⊗Tulobuterol (p. 1239·2).

Amias *2care4, Denm.; Orifarm, Denm.; EU, Neth.†; Farmagon, Norw.; Orifarm, Norw.; Takeda, UK.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Amibex *Ind-Swift, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Amibex-NA *Ind-Swift, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Amibex-TZ *Ind-Swift, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Amibiotic *Neon, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amic *JK Biochem, India; Jaba Recordati, Port.*
Amikacin sulfate (p. 214·2).
Bacterial infections; Gram-negative bacterial infections.

Amicaba *Acto, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amicagel *Med-One, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial skin infections.

Amicaliq *Tanabe, Jpn.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Amicar *Xanodyne, USA.*
Aminocaproic acid (p. 1131·3).
Fibrinolysis.

Amicasil *Phoinix Pharm (Φοινιξ Φαρμ), Gr.; Pharmatex, Ital.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amicets *Elmor, Venez.*
Benzydamine hydrochloride (p. 29·2); menthol (p. 2553·2); thymol (p. 1772·2).
Mouth and throat disorders.

Amichlor *Orchid, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Amicil
Note: this name may be used for preparations of different composition.
Arterium, Ukr.
Amikacin sulfate (p. 214·2).
Bacterial infections.

Unipharm, Mex.
Amoxicillin (p. 216·2).
Bacterial infections.

Amicilin *Inpac, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amicilon *Ariston, Braz.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amicin *Biochem, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amicina *Kener, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amicip *Cipla, India.*
Amikacin (p. 214·1).
Bacterial infections.

Amicla *Erfa, Belg.*
⊗Amcinonide (p. 1621·1).
Skin disorders.

Amiclair *Abatron, UK.*
Enzymatic contact lens cleanser.

Amiclaran *Zentiva, Cz.†*
⊗Amiloride hydrochloride (p. 1299·1).
Oedema; liver cirrhosis with ascites; hypertension.

Amicline *Franco-Indian, India.*
Diloxanide furoate (p. 931·2).

Amicline Plus *Franco-Indian, India.*
Dicycloverine hydrochloride (p. 1834·2); diloxanide furoate (p. 931·2); tinidazole (p. 949·2).

Amicloton *Zentiva, Cz.*
⊗Amiloride hydrochloride (p. 1299·1); chlortalidone (p. 1335·2).
Hypertension.

Amiclox Plus *Cure Quick, India.*
⊗Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Amico
Note: this name may be used for preparations of different composition.
TO-Chemicals, Thai.
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; peptic ulcer.

SIT, Ital.†
Amino acids; cobamamide (p. 2107·2).
Tonic.

Amicof *Union Drug, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Amico-L
Note: this name may be used for preparations of different composition.
TO-Chemicals, Thai.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Amicom *Comed, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amicor *Samarth, India.*
Amrinone lactate (p. 1305·1).
Heart failure.

Amicozol *Aspen, Braz.*
Miconazole (p. 588·3).

Amicrobin *Quimifar, Spain.*
Norfloxacin (p. 333·3).
Genito-urinary tract infections.

Amida *Euphoric, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Amidalin *Sandoz, Braz.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Amidaron *KVZ, Ukr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amidarone 200 *TO-Chemicals, Thai.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amidase *Adley, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Amidase-D *Adley, India.*
⊗Serrapeptase (p. 2613·3); diclofenac sodium (p. 48·3).

Amidase-DP *Adley, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Amidase-N *Adley, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Amidate *Hospira, USA.*
Etomidate (p. 1901·1).
General anaesthesia.

Amident *Leksredstva, Rus.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of mucous membranes, skin, surfaces and wounds.

Amidex *Clonmel, Irl.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Amidiaz *Richmond, Arg.*
⊗Morphine (p. 92·3).
Pain.

Amidolite *Braun, Ital.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Hypovolaemia; shock.

Amidrin *Fardi, Spain.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinus congestion.

Amidrox *Crinos, Ital.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolytic metastases in breast cancer; multiple myeloma.

Amielect *Braun, Ital.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Amifarin *Wandel, Mex.†*
Dicloxacillin (p. 286·1).
Bacterial infections.

Amifen *Meyer, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Amifru *Elder, India.*
⊗Amiloride hydrochloride (p. 1299·1); furosemide (p. 1387·1).
Hypertension; oedema.

Amifru-S *Elder, India.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Hypertension; ascites; oedema.

Amifull *Bionova, India.*
Amino acids.
Dietary supplement.

Amigdagen *Prodotti, Braz.†*
Neomycin sulfate (p. 330·1); tyrothricin (p. 384·1); benzocaine (p. 1980·2); menthol (p. 2553·2).
Mouth and throat disorders.

Amigdalin *Farmanic, Gr.*
Methenamine mandelate (p. 323·1).

Amigdalol *Delta, Braz.*
Tyrothricin (p. 384·1); cetrimonium bromide (p. 1742·3); vitamin C (p. 2110·3); lidocaine (p. 1988·1).
Mouth and throat disorders.

Amigdobis *Chinoin, Mex.*
Bismuth ethylhexanoate.
Sore throat.

Amigesic *Amide, USA.*
Salsalate (p. 130·1).
Pain; fever; inflammation.

Amignul *Almirall, Gr.†; Almirall, Port.†; Almirall, Spain.*
Almotriptan malate (p. 672·1).
Migraine.

Amigold *Lupin, India.*
Amisulpride (p. 1036·3).
Psychoses.

Amigrenex *Temapharm, Pol.*
Sumatriptan succinate (p. 679·2).
Migraine.

Amigrenin *Veropharm, Rus.*
Sumatriptan succinate (p. 679·2).
Migraine.

Ami-Hydrotride *CCM, Malaysia.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Amijeksin *Tum, Turk.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amijet *Hanburys, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amik *Farmigea, Ital.†*
Amikacin sulfate (p. 214·2).
Skin infections.

Amikable *Nitro Organics, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amikacide *United American, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amikafur *Teva, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amikalem *Lemery, Mex.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amikan *Anfarm, Gr.; SoSe, Ital.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amikas *Chandra Bhagat, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amikasons *Sons, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amikater *Gujarat Terce, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amikavax *Vivax, Venez.*
Amikacin (p. 214·1).
Bacterial infections.

Amikavel *Biosync, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amikavi *Mavi, Mex.*
Amikacin (p. 214·1).
Bacterial infections.

Amikayect *Grossman, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amikcin *Vista, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amikef *Lupin, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amiketem *Ulagay, Turk.†*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amikin *BMS, Austral.†; BMS, Cz.; BMS, Hong Kong; BMS, Hung.†; BMS, Indon.†; BMS, Irl.; BMS, Mex.; BMS, NZ†; BMS, Philipp.†; BMS, Pol.; BMS, S.Afr.; BMS, Switz.; BMS, Thai.†; BMS, UK; Apothecon, USA.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

PC India, India.
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amiklin *BMS, Fr.†; BMS, Turk.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amikozit *Eczacibasi, Rus.†; Eczacibasi, Turk.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amilab *Laborate, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amilamont *Rosemont, UK.*
⊗Amiloride hydrochloride (p. 1299·1).
Hypertension; heart failure; hepatic cirrhosis with ascites.

Amilate *Plus, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage following surgery.

Amil-Co *Ivax, UK.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
These ingredients can be described by the British Approved Name Co-amilozide.
Heart failure; hypertension; hepatic cirrhosis; ascites.

Amilco *OBA, Denm.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Amilene *Tecnofarma, Chile.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Amilia *ProMed, Cz.*
Amisulpride (p. 1036·3).
Schizophrenia.

Amilin *Hua, Thai.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amilitrap *Dosa, Arg.*
Lamivudine (p. 1000·2).

Amilochlor *Finecure, India.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amilocomp beta *Betapharm, Ger.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Amiloferm *Nordic, Swed.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; liver cirrhosis with ascites.

Amilonosar *Biochimic, Rus.*
Sodium nicotinyl-gamma-aminobutyrate.
Mental function disorders; cerebrovascular disorders; alcoholism.

Amilopid *Med-One, Gr.*
Amlodipine besilate (p. 1304·1).

Amilopil *Cifarma, Braz.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amiloretic *Aspen, S.Afr.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Amiloretik *Hexal, Austria; Hexal, Ger.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; liver cirrhosis with ascites.

Amilorid *Neo Quimica, Braz.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Amilorid Comp *Walmark, Hung.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; liver cirrhosis; oedema.

Amilorid comp *Genericon, Austria; Ratiopharm, Ger.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure; liver cirrhosis with ascites.

Amiloride/HCT *Helvepharm, Switz.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; liver cirrhosis with ascites.

Amilorid/HCT *Aliud, Cz.; Aliud, Ger.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Amilostad *Stada, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amilostad HCT *Stada, Austria.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; liver cirrhosis with ascites.

Amilozid-B *Teva, Hung.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; liver cirrhosis with ascites; oedema.

Amilozide *TO-Chemicals, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hepatic cirrhosis with ascites; hypertension.

Amimac *Ikon, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amimax *Innovative, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amimide *GSK, India.*
⊗Amiloride (p. 1299·1); furosemide (p. 1387·1).
Hypertension; oedema.

Amimox *Meda, Swed.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections; peptic ulcer associated with Helicobacter pylori.

Amin 21 K *Italfarmacia, Ital.*
Amino acids; potassium (p. 1793·1).
Nutritional supplement.

Aminabel *Faran, Gr.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).

Amin-Aid *R&D, USA.*
Preparation for enteral nutrition in renal failure.

Aminalon *Akrikhin, Rus.; KVZ, Ukr.*
Gamma-aminobutyric acid (p. 2509·2).
Cerebrovascular disorders; mental function impairment; motion sickness.

Aminazin *Arterium, Ukr.*
Chlorpromazine (p. 1045·2).
Psychoses; alcohol withdrawal; pain.

Valenta, Rus.
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; bipolar disorder; chronic pain; vomiting.

Aminefron *Dexa, Indon.*
Amino acids.
Dietary supplement in renal failure.

Aminess *Recip, Gr.; Recip, Norw.; Recip, Swed.; Abdi, Turk.; Sandoz, Turk.; Baxter, USA.†*
Amino acids.
Nutritional supplement in renal impairment; parenteral nutrition in renal impairment.

Aminess-N *Recip, Fin.; United Biotech, India; Meda, Neth.*
Amino acids.
Dietary supplement.

Amineurin *Hexal, Ger.†*
Amitriptyline hydrochloride (p. 401·1).
Depression; pain.

Aminic *Mitsubishi, China.*
Amino acids.
Parenteral nutrition.

Amino
Note: this name may be used for preparations of different composition.
Empresa de Nutricion, Arg.; Gentech, Arg.; Teingro, Arg.
Amino acids.
Dietary supplement.

Patar, Thai.
Aminophylline (p. 1201·2).
Bronchospasm.

Amino8 *Protan, Arg.*
Protein; vitamins; minerals.
Gluten-free dietary supplement.

Amino 3 *Fiori, Ital.*
Amino acids.

Aminobrain *More, Philipp.*
Vitamins; amino acids; minerals.
Dietary supplement.

Aminocal *Tablets, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3); magnesium (p. 1786·3); pyridoxine hydrochloride (p. 2105·3); zinc (p. 2126·1).

Aminocal 500 *Tablets, India.*
Arginine hydrochloride (p. 2049·1); ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3); pyridoxine hydrochloride (p. 2105·3).

Aminocardol *Novartis, Turk.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Aminocer *Verisfield, Gr.*
Levocarnitine (p. 2053·2) or levocarnitine tartrate (p. 2053·2).

Amino-Cerv *Cooper, USA.*
⊗Cystine (p. 2059·1); inositol (p. 2533·2); methionine (p. 1558·2); sodium propionate (p. 593·1); urea (p. 1727·3).
Cervicitis; postpartum cervical tears; post cauterisation; post cryosurgery; post conisation.

Aminocin *Meridian, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Aminocont *Mundipharma, Fin.*
Aminophylline hydrate (p. 1201·3).
Obstructive airways disease.

Aminocore 5-S Plus *Claris, India.*
Amino acids; electrolytes (p. 1775·1); sorbitol (p. 2092·1).
Parenteral nutrition.

Aminocrat *Cratus, India.*
Preparation for enteral nutrition.

Aminodrip *Wockhardt, India.*
Amino acids.
Parenteral nutrition.

Aminoefedrison *Rhein, Mex.*
Theophylline (p. 1229·3); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Aminofit *Universal Medicare, India.*
Amino acids minerals.
Dietary supplement.

Aminoflex *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Aminofluid *Otsuka, Indon.; Otsuka, Jpn.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Aminofusin *Pharmacia Upjohn, Gr.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Aminofusin Hepar *Baxter, Ger.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition in liver disorders.

Kalbe, Indon.
Amino acids.
Parenteral nutrition in liver disease.

Aminofusin L *Kalbe, Indon.*
Amino acids; sorbitol (p. 2092·1); xylitol (p. 2220·3); vitamins; electrolytes (p. 1775·1).
Parenteral nutrition.

Aminofusin Paed *Kalbe, Indon.*
Amino acids; vitamins; electrolytes (p. 1775·1).
Parenteral nutrition in neonates and infants.

Aminofusion *Tablets, India.*
Amino acids; sorbitol (p. 2092·1).
Parenteral nutrition.

Aminogen-S *Taiwan Biotech, Philipp.*
Amino acids.
Parenteral nutrition.

Aminogran *UCB, Austral.†; UCB, Irl.†; Euromed, Ital.†; Pharmabroker, NZ†; UCB, Swed.†*
Food for special diets.
Phenylketonuria.

Aminogran Mineral Mixture *UCB, Austral.†*
Minerals.
Mineral supplement; phenylketonuria (in conjunction with Aminogran).

Aminoima *IMA, Braz.†*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Aminokrovin *Microgen, Rus.*
Amino acids; glucose (p. 2068·3).
Parenteral nutrition.

Aminol *Demo, Gr.*
L-Alanyl-L-glutamine (p. 2070·2).

Yuriya-Farm, Ukr.
Amino acids.
Parenteral nutrition.

Aminoleban *Otsuka, Hong Kong; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Philipp.; Thai Otsuka, Thai.*
Amino acids.
Hepatic encephalopathy; hepatic insufficiency.

Aminoleban EN *Otsuka, Hong Kong.*
Preparation for enteral nutrition.
Hepatic encephalopathy; liver failure.

Otsuka, Jpn.
Nutritional supplement.
Hepatic encephalopathy.

Aminoleban Oral *Otsuka, Indon.; Thai Otsuka, Thai.*
Preparation for enteral nutrition.
Hepatic encephalopathy; liver failure.

Otsuka, Philipp.
Nutritional supplement.
Liver disease.

Aminolight *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Aminoliv *Teuto, Braz.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Aminomal *Malesci, Ital.*
Delayed-release tablets; injection; suppositories:
Aminophylline (p. 1201·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection; lidocaine (p. 1988·1) is also included in the suppositories.
Obstructive airways disease.

Malesci, Ital.
Elixir: Theophylline (p. 1229·3).
Obstructive airways disease.

Aminomel *Baxter, Pol.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Amino-Mel G *Fresenius Kabi, Austria.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3).
Parenteral nutrition.

Amino-Mel Nephro *Fresenius Kabi, Austria.*
Amino acids.
Parenteral nutrition in renal disease.

Aminomel nephro *Baxter, Ger.*
Amino acids.
Parenteral nutrition in renal failure.

Amino-Min-D *Tyson, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3); minerals.
Calcium deficiency; dietary supplement.

Aminomix *Fresenius Kabi, Austria; Fresenius Kabi, India; Fresenius Kabi, Spain†; Fresenius Kabi, Switz.*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Fresenius Kabi, Fr.
Amino acids; carbohydrate; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr; Fresenius Kabi, Hung.; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Turk.
Amino acids; with or without electrolytes (p. 1775·1); glucose (p. 2068·3).
Parenteral nutrition.

Aminomux *Gador, Arg.; Pasteur, Chile†; Leti, Venez.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; osteoporosis; Paget's disease of bone.

Amino-Opti-C *Tyson, USA.*
Lemon bioflavonoids (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2); vitamin C (p. 2110·3); rose hips (p. 2607·1).
Capillary bleeding.

Aminopäd *Baxter, Ger.*
Amino acids.
Parenteral nutrition.

Aminopad *Fresenius Kabi, Austria.†*
Amino acids.
Parenteral nutrition.

Aminoplasmal *Braun, Arg.; Braun, Belg.; Braun, Chile.; Braun, Cz.; Braun, Denm.; Braun, Ger.; Bioser (Βιοσερ), Gr.; Papaellinas (Παπαελληνας), Gr.; Braun, Hong Kong; Braun, Hung.; Braun, India; Braun, Indon.†; Braun, Irl.†; Braun, Israel; Braun, Ital.; Braun, Pol.; Braun, Port.; Braun, Rus.; Braun, Singapore; Braun, Spain; Braun, Turk.; Braun, UK; Braun, Ukr.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Braun, Austria; Braun, Fin.; Braun, Fr.; Braun, Neth.; Braun, Thai.
Amino acids.
Parenteral nutrition.

Aminoplasmal Hepa *Braun, China.*
Amino acids.
Parenteral nutrition in liver disorders.

Aminopro *Euro-Med, Philipp.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Aminopt *Sigma, Austral.†*
Aminoacridine hydrochloride (p. 1732·3).
Eye infections.

Aminoral *Soho, Indon.*
Amino acids.
Nutritional supplement in renal failure.

Aminoram *Fresenius Kabi, Ital.*
Food for special diets.
Liver disorders.

Aminorich *Stedman, India.*
Amino acids; cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); pyridoxine (p. 2105·3); riboflavin (p. 2104·3); thiamine (p. 2102·3).
Dietary supplement.

Aminos *Intra-Labs, India.*
Protein hydrolysate; sodium selenite (p. 2087·1); glutamine (p. 2070·3).

Aminosam *Szama, Arg.*
Biotin (p. 2052·2).
Alopecia; disorders of biotin metabolism.

Aminosol *Hemofarm, Rus.*
Amino acids; sorbitol (p. 2092·1); electrolytes (p. 1775·1); vitamins.
Parenteral nutrition.

Abbott, Mex.†; Thai Otsuka, Thai.
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Aminosol Neo *Hemofarm, Rus.; Hemofarm, Ukr.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Aminosport *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Aminostar *Intra-Labs, India.*
Amino acids; vitamins; zinc sulfate (p. 2126·2).

Aminosteril *Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Mex.; Fresenius Kabi, Singapore; Fresenius Kabi, Thai.†*
Amino acids.
Parenteral nutrition.

Fresenius Kabi, Ger.; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Spain; Fresenius Kabi, Switz.; Novartis, Turk.; Fresenius Kabi, Ukr.
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Aminosteril Hepa *Fresenius Kabi, Port.*
Amino acids.
Parenteral nutrition.

Aminosteril N Hepa *Fresenius Kabi, Cz.; Fresenius Kabi, India; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.*
Amino acids.
Parenteral nutrition in liver disease.

Aminosyn *Hospira, Canad.*
A range of amino-acid infusions with or without glucose (p. 2068·3) and electrolytes (p. 1775·1).
Parenteral nutrition.

Hospira, USA.
Amino acids; with or without glucose (p. 2068·3) and electrolytes (p. 1775·1).
Parenteral nutrition.

Aminoterapia *Raymos, Arg.*
Oral powder; tablets: ⊗Cystine (p. 2059·1); gelatin (p. 1154·1).
Skin, hair, and nail disorders.

Raymos, Arg.†
Cream: Vitamin A (p. 2098·3); vitamin E acetate (p. 2119·2); ceramide (p. 1699·1); amino acids.
Nail disorders.

Aminoterapia Capilar *Raymos, Arg.*
Cystine (p. 2059·1); hydrolysed animal protein; hydrolysed hair keratin; tocopheryl acetate (p. 2119·2); ascorbyl palmitate (p. 1737·1).
Hair disorders.

Aminotool *Volchem, Ital.*
Amino acids.

Aminotripa *Otsuka, Jpn.*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Aminotroph *Bioethic, Fr.*
Amino acids; vitamin B substances (p. 2102·3).
Dietary supplement in sarcopenia.

Aminotrophylle-88 *Proel, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Aminovac *Nikkho, Braz.*
Allergen preparation (p. 2434·3).
Allergen immunotherapy.

Aminoveinte *Madariaga, Spain.†*
Vitamins; amino acids.
Tonic.

Aminovel *Otsuka, Indon.*
Amino acids; sorbitol (p. 2092·1); electrolytes (p. 1775·1); vitamins.
Parenteral nutrition.

Aminoven *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Fr.; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Ital.; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK; Fresenius Kabi, Ukr.*
Amino acids.
Parenteral nutrition; parenteral nutrition in infants.

Fresenius Kabi, Austria; Fresenius Kabi, Fin.†; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Irl.; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Turk.
Amino acids; with or without glucose (p. 2068·3) and electrolytes (p. 1775·1).
Parenteral nutrition.

Aminovenoes N Paed *Fresenius Kabi, Cz.*
Amino acids.
Parenteral nutrition in neonates.

Aminovenos *Fresenius Kabi, Neth.; Fresenius Kabi, Turk.†*
Amino acids.
Parenteral nutrition.

AminoVita *More, Philipp.*
Vitamins; amino acids.

Aminovital *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Aminoxidin Sulbactam *Fada, Arg.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Aminoyodarsencal *Italmex, Mex.*
Calcium formate (p. 2507·1); calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); lysine hydrochloride (p. 2079·3); orthoiodine; tryptophan (p. 453·2).
Dietary supplement; calcium deficiency.

Aminozyme *Stadmed, India.*
Protein hydrolysate (p. 2086·2); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).
Enzyme deficiency; nutritional supplement; hypoproteinaemia; burns.

Aminut *Invision, India.*
Glutamine (p. 2070·3); protein hydrolysate; sodium selenite (p. 2087·1).

Amio *Salutas, Philipp.*
Amiodarone hydrochloride (p. 1300·1).
Supraventricular tachycardia.

Amiobal *Baldacci, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiocar *Klonal, Arg.*
Amiodarone (p. 1300·1).
Arrhythmias.

Amiocor *Taro, Israel.*
Amiodarone hydrochloride (p. 1300·1).
Ventricular arrhythmias; coronary insufficiency.

Amiodacore *CTS, Israel; Sanofi-Aventis, Israel.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; heart failure.

Amiodar *Micro, India.*
Amiodarone (p. 1300·1).
Arrhythmias.

Paranova, Denm.†; Sigma-Tau, Ital.; Sandoz, Switz.
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; angina pectoris.

Amiodarex *Sanofi Synthelabo, Ger.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiodon *Neon, India.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiogamma *Worwag, Ger.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiohexal *Hexal, Cz.; Hexal, Ger.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiokordin *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiopia *Medical, Spain.†*
Vitamins; minerals; amino acids; isoniazid (p. 311·2).
Eye disorders.

Amiorel *Boehringer Ingelheim, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Amiorel Compuesto *Boehringer Ingelheim, Arg.*
⊗Bromhexine hydrochloride (p. 1656·3); diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract disorders.

Amioron *Geolab, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amiotach *Aspen, S.Afr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amioxid *Neuraxpharm, Ger.*
Amitriptylinoxide (p. 401·1).
Depression.

Amiparen *Otsuka, Indon.; Otsuka, Jpn; Thai Otsuka, Thai.*
Amino acids.
Parenteral nutrition.

Amiphos *Dabur, India.*
Amifostine (p. 1539·2).
Reduction of neutropenia due to cyclophosphamide and cisplatin therapy for ovarian cancer; reduction of nephrotoxicity due to cisplatin; radiation-associated xerostomia.

Amiprid *Actavis, Hung.*
Amisulpride (p. 1036·3).
Psychoses.

Amipride *Aspen, Austral.*
Amisulpride (p. 1036·3).
Schizophrenia.

Amira *Alphapharm, Austral.*
Moclobemide (p. 437·2).
Depression.

Amirel *Medipharm, Chile.*
Mirtazapine (p. 436·1).
Depression; bipolar disorder.

Amiretic *Biolab Sanus, Braz.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amiridine *Central European Pharmaceutical, Rus.*
Ipidacrine (p. 687·1).
Central and peripheral nervous system disorders; Alzheimer's disease; demyelinating disease; myasthenia gravis.

Amirol *AFT, NZ.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Amiron *Kamron, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amirone *Julphar, UAE.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Amisan
Note: this name may be used for preparations of different composition.
PraMed, Pol.
Amisulpride (p. 1036·3).
Schizophrenia.

Sandoz, Austria.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Amisol *Medica Korea, Singapore.*
⊗Clobetasone butyrate (p. 1627·3).
Skin disorders.

Amistar *Cadila, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amister *Sterfil, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amisul *Cubit, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Amisulf *Samarth, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amisulid *Temmler, Ger.†*
Amisulpride (p. 1036·3).
Schizophrenia.

Amit *Orchid, India.*
Amitriptyline (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Amitab *Wockhardt, India.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis; giardiasis.

Amitax *Alkem, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Alkem, Philipp.
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amitec *Utopian, Thai.*
Amitriptyline hydrochloride (p. 401·1).
Depression; neuropathic pain; migraine.

Amiten *Sanbe, Indon.*
Amino acids.
Parenteral nutrition.

Amithiazide *Jean-Marie, Hong Kong.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Amitiza *Sucampo, Jpn; Sucampo, Switz.; Sucampo, UK; Takeda, USA.*
Lubiprostone (p. 1856·1).
Chronic constipation; irritable bowel syndrome.

Amiton *Christo, Hong Kong.†*
⊗Aminophylline (p. 1201·2); amobarbital (p. 1037·2); ephedrine hydrochloride (p. 1663·2).

Amitone
Note: this name may be used for preparations of different composition.
Intas, India.
Amitriptyline (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Unison, Hong Kong; Unison, Singapore.
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Amitor *Torrent, India.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Amitrex *Orifarm, Denm.†; Sanofi-Aventis, Hung.; Sanofi-Aventis, Port.*
Amisulpride (p. 1036·3).
Schizophrenia.

Amitrexyl *BMS, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amitrid *Leiras, Fin.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; oedema.

Amitrip *East West, India; Mylan, NZ.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Amitron *Torlan, Spain.*
Amoxicillin sodium (p. 216·2).
Bacterial infection.

Amitrox *Farmaten, Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Amitryn *T Man, Thai.*
Amitriptyline (p. 401·1).
Depression; neuropathic pain; migraine.

Amivir *East African, India.*
Arnikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amix
Note: this name may be used for preparations of different composition.
PDMS, UK.†
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amixal *Braun, Ital.*
Amino acids.
Parenteral nutrition.

Amixen *Bernabo, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amixen Clavulanico *Bernabo, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amixen Duo *Bernabo, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amixen Plus *Bernabo, Arg.*
Amoxicillin trihydrate (p. 216·2); diclofenac potassium (p. 48·3).
Bacterial infections with inflammation.

Amixide *Sun, Rus.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Anxiety; depression.

Amixide H *Sun, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states.

Amixin *Farmstandart, Rus.; Interchem, Ukr.*
Tilorone (p. 1019·2).
Viral infections; chlamydia.

Amixx
Note: this name may be used for preparations of different composition.
Krewel, Ger.
Amantadine hydrochloride (p. 890·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Amiyec *IQFA, Mex.*
Arnikacin sulfate (p. 214·2).
Bacterial infections.

Amiyu *Ajinomoto, Thai.; Biotek, Turk.†*
Amino acids.
Renal failure; nutritional supplement.

Amiz *Ritz, India.*
Arnikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amiza *Trumac, India.*
Arnikacin (p. 214·1).
Gram-negative bacterial infections.

Amizal *Atral, Port.*
Idebenone (p. 392·3).
Mental impairment associated with cerebrovascular disorders.

Amize *Hi-Tec, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Amizep *La Pharmaceuticals, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states.

Amizepin *Polpharma, Pol.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia; bipolar disorder; alcohol withdrawal syndrome.

Amizet XB *Terumo, Jpn.*
Amino acids; xylitol (p. 2220·3).
Parenteral nutrition.

Amizide *Alphapharm, Austral.; Alphapharm, Malaysia†; Pacific, NZ.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis with ascites.

Amizin *Giempi, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Amizon *Farmak, Ukr.*
Amizon.
Viral and bacterial infections; pain.

Amizonchik *Farmak, Ukr.*
Enisamium iodide.
Respiratory-tract viral infections.

Amizox *JK Biochem, India.*
Diclofenac diethylamine (p. 48·3); diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

AMK
Note: this name may be used for preparations of different composition.
Kee, India.
Amikacin (p. 214·1).
Gram-negative bacterial infections.
Pisa, Mex.
Amikacin sulfate (p. 214·2).
Bacterial infections.
RX, Thai.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amklok *Laksun, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amlace *USV, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlactin *Upsher-Smith, USA.*
Ammonium lactate (p. 1694·3).
Dry skin.

AmLactin AP *Upsher-Smith, USA.†*
Pramocaine hydrochloride (p. 1993·3); lactic acid (p. 2539·1).

Amlan *VHB, India.*
Amlodipine (p. 1304·1) or levamlodipine.
Hypertension; angina pectoris.

Am-Laqer *Sun, India.*
Amorolfine (p. 569·1).
Fungal nail infections.

Amlarrow *Arrow, Swed.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlat *Essweil, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Amlate *Reddy, S.Afr.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlee-P *Indkus, India.*
⊗Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Amlibon *Novartis, India; Sandoz, Venez.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris; heart failure.
Sandoz, Mex.
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.
Sandoz, Gr.; Sandoz, Malaysia.
Amlodipine besilate (p. 1304·1) or amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlibon B *Sandoz, Venez.*
Amlodipine (p. 1304·1); benazepril (p. 1314·3).
Hypertension.

Amlibon Bes *Sandoz, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlid *Pinewood, Irl.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlidual *Sandoz, Mex.*
Amlodipine mesilate (Amlibon) (p. 1304·1); simvastatin (Simplaqor) (p. 1489·2).

Amlin *Lincoln, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlinc *Amrit, India.*
Lincomycin (p. 317·1).
Anaerobic bacterial infections.

Amlip *Cipla, India; SM, Venez.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlip Beta *Cipla, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Amlipin *Teva, Hung.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlipril *Sandoz, Mex.†*
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Amlist *Gerard, Irl.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlix
Note: this name may be used for preparations of different composition.
Pasteur, Philipp.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.
Pharmout, Port.†
Topiramate (p. 550·3).
Epilepsy.

Amlo *Spirit, Austral.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amlo CB *Shrrishti, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlo eco *Sandoz, Switz.†*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlo Tad *TAD, Ger.†*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amloact *Active, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amloact-AT *Active, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlo-AT *Orchid, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlo-B *Orchid, India.*
Amlodipine (p. 1304·1); benazepril (p. 1314·3).
Hypertension.

Amlober *KRKA, Neth.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlobes *Verheilen, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlobesilat *Sandoz, Ger.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlobesyl *Pharmacodane, Denm.; Valeant, Hung.; Stada, Swed.†*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlobet *Sun, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlobeta *Betapharm, Ger.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amloc *Bago, Chile; Pfizer, Singapore.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.
Pfizer, Arg.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.
Pharma Dynamics, S.Afr.
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amlocal-AT *Acto, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlocan *Candor, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlocan-TN *Candor, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlocard *AWD, Ger.†*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Amlocard Forte *Intra-Labs, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlocard-S *Intra-Labs, India.*
Levamlodipine.
Hypertension.

Amloclair *Hennig, Ger.*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlocom *Comed, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlocom-AT *Comed, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlocor *Torrent, Braz.; Torrent, India; Torrent, Philipp.; Atral, Port.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlod *Unison, Hong Kong; Unison, Thai.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodac *Zydus, India; Cadila, Malaysia; Zydus Cadila, Philipp.; Cadila, Rus.; Simayla, S.Afr.; Zydus Cadila, Thai.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodac-AT *Zydus, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlodac-L *Zydus, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlode *Rowex, Irl.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodep *Extractum, Hung.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodibene *Ratiopharm, Austria.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodicord *Geminis, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodigamma *Worwag, Cz.†; Worwag, Ger.; Worwag, Hong Kong; Worwag, Hung.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodil *Vitapan, Braz.; Bosnalijek, Ukr.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.
Gap, Gr.; Bosnalijek, Rus.†
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodilan *GL Pharma, Austria.*
Amlodipine mesilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodin *Kleva, Gr.; Sumitomo, Jpn.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodine *Quesada, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Westfield, Philipp.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodinova *KRKA, Austria.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlodipress *1A, Hung.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlodis *Eczacibasi, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodno *KRKA, Neth.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlodoc *Docpharm, Ger.†*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlodowin *Sanofi-Aventis, Hung.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amlogal *SMB, Belg.*
Amlodipine maleate.
Angina pectoris; hypertension.

Amlogard *Pfizer, India.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlogen *Alkem, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlogen-AT *Alkem, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlogen-EL *Alkem, India.*
Amlodipine (p. 1304·1); enalapril (p. 1371·1).
Hypertension.

Amlohex *Sandoz, Turk.*
Amlodipine maleate (p. 1304·1).

Amlohexal *Hexal, Denm.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlohyp *Hexal, Austria.†*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amlo-Isis *Actavis, Ger.†*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlokamman *Hexal, Denm.†*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amlokard *Sanovel, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlokath *Life Medicare, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlokath-A *Life Medicare, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlokath-L *Life Medicare, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlokind *Mankind, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlokind-AT *Mankind, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2),.
Hypertension; angina pectoris.

Amlokind-H *Mankind, India.*
⊗Amlodipine (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amlokind-L *Mankind, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Amlokos *Raptakos, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlokos L *Raptakos, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Amlokos-AT *Raptakos, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlokos-R *Raptakos, India.*
Amlodipine (p. 1304·1); ramipril (p. 1483·3).

Amlo-L *Orchid, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlol *Themis Medicare, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

AmloLich *Winthrop, Ger.†*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlomas *1A, Denm.†*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlonex *Taiwan Biotech, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlong *Eurodrug, Hong Kong; Micro, India; Eurodrug, Malaysia; Eurodrug, Philipp.; Micro, Rus.; Eurodrug, Singapore; Micro Labs, Ukr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension; heart failure; ischaemic heart disease.

Amlong-A *Micro, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlong-H *Micro, India.*
⊗Amlodipine (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amlonol *Khandelwal, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlonor *Polfa Pabianice, Pol.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlonorm *Adipharm, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlonova *Haledew, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlopen *Elpen (Ελπεν), Gr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlophar *Julphar, UAE.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlopharm *Stada, Denm.*
Amlodipine mesilate (p. 1304·1).
Hypertension; angina pectoris.

Amlopin *Sandoz, Pol.; Farma, Venez.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Deltapharm, Hong Kong†; USV, India.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Spirig, Switz.†
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlopin Plus *USV, India.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).

Amlopin-AT *USV, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlopine *Domesco, Philipp.; Berlin Pharm, Thai.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlopol *Polifarma, Ital.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlopp *Cipla, Cz.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlopres *Cipla, Hong Kong; Cipla, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlopres AT *Cipla, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension.

Amlopres L *Cipla, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlopres Z *Cipla, India.*
Amlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Amlopres-NB *Cipla, India.*
⊗Amlodipine (p. 1304·1); nebivolol (p. 1444·2).

Amlopress *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlopril
Note: this name may be used for preparations of different composition.
Darnitsa, Ukr.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Pfizer, Arg.
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Amlo-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlo-R *Orchid, India.*
Amlodipine (p. 1304·1); ramipril (p. 1483·3).

Amlor *Pfizer, Belg.; Pfizer, Fr.; Binesa, Spain.†*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amloratio *Ratiopharm, Cz.; Ratiopharm, Fin.; Ratiopharm, Pol.; Ratiopharm, Swed.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amloretin *Biomedica, Gr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlorus *Sintez, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlosafe *Otsira, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlosafe-AT *Otsira, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).

Amlosafe-LS *Otsira, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlosandoz *Sandoz, Ukr.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlosilat *AG Therapy, Gr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlostad *Stada, Neth.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amlostat *Biochem, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlostat-AT *Biochem, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlostin *Schein, UK.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amlosun *Sun, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlosyl *KRKA, Neth.†; Intas, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Sarabhai Piramal, India.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlosyn *Aspen, S.Afr.*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlot *Trumac, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlotab *Cure Quick, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlotal *Symbiosis, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlotal-AT *Symbiosis, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlotan *Athlone, Irl.*
Amlodipine mesilate (p. 1304·1).
Hypertension; angina pectoris.

Amlot-AT *Trumac, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlotec-AT *Technica, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amloten *Grandix, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlotens *Klonal, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Specifar, Gr.; Specifar, Singapore.
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlotenz *Belupo, Cz.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlotin *Orchid, India.*
Amlodipine besilate (p. 1304·1); losartan (p. 1422·2).
Hypertension.

Amlot-L *Trumac, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlotop *Makiz-Pharma, Rus.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlotrac *Intra-Labs, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amlotrust *Centaur, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlotyrol *Sandoz, Austria.†*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlovas *Drogsan, Hong Kong; Macleods, India; Unique, Rus.; Drogsan, Turk.; Megat, Venez.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension; heart failure.

Amlovas-AT *Macleods, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlovasc *Hexal, Braz.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Streuli, Switz.
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Amlovas-L *Macleods, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amlovas-M *Macleods, India.*
⊗Amlodipine (p. 1304·1); metoprolol (p. 1434·3).

Amlovas-SN *Macleods, India.*
⊗Levamlodipine; nebivolol (p. 1444·2).
Hypertension.

Amlovin *East West, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amlow *Trima, Israel.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Amloz *Shreya, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amloz AT *Shreya, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amlozaar *Micro, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Amlozek *Adamed, Cz.; Adamed, Hung.; Adamed, Pol.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amlozen *Dawnrays, Hong Kong.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ammeltz *Kobayashi, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); nonivamide (p. 102·3).
Musculoskeletal pain; soft-tissue disorders.

Ammidene *Macrophar, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Ammiformin *Macrophar, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ammifurin *Vilar, Rus.*
Ammi majus (p. 2441·2).
Skin disorders.

Ammi-Indocin *Macrophar, Thai.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Ammilazo *Macrophar, Thai.†*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Amminac *Macrophar, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation; pain.

Ammirox *Macrophar, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ammitram *Macrophar, Thai.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Ammi-Votara *Macrophar, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ammonaps *Swedish Orphan, Austria; Swedish Orphan, Belg.; Swedish Orphan, Cz.; Swedish Orphan, Denm.; Swedish Orphan, Fr.; Swedish Orphan, Ger.; Swedish Orphan, Irl.; Orphan, Ital.; Orphan, Neth.; Swedish Orphan, Norw.; Orphan, Pol.; Swedish Orphan, Port.; Orphan, Spain; Swedish Orphan, Swed.; Swedish Orphan, UK.*
Sodium phenylbutyrate (p. 2518·3).
Urea cycle disorders.

Ammonul *Ucyclyd, USA.*
Sodium phenylacetate (p. 2619·2); sodium benzoate (p. 1738·2).
Hyperammonaemia.

Amnesteem *Mylan, USA.*
Isotretinoin (p. 1706·2).
Acne.

Amniolina *Reig Jofre, Spain.*
Talc (p. 1722·2); zinc oxide (p. 1729·1).
Nappy rash.

Amnique *Unique, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amnolake *Shinyaku, Jpn.*
Tamibarotene (p. 860·2).
Acute promyelocytic leukaemia.

Amnopra *AMN Life Science, Thai.*
Omeprazole sodium (p. 1867·2).

Amnorel *Sanbe, Indon.*
Amino acids; sorbitol (p. 2092·1); electrolytes (p. 1775·1); vitamins.
Parenteral nutrition.

AMO Endosol *Advanced Medical Optics, Austral.†; AMO, Canad.*
Electrolytes (p. 1775·1).
Eye irrigation during surgery.

AMO Vitrax *Advanced Medical Optics, Austral.†; Genop, S.Afr.†; Allergan, USA.†*
Sodium hyaluronate (p. 2526·2).
Aid in ophthalmic surgery.

Amobay *Bayer, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amobay CL *Bayer, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amobiotic *Bernofarm, Indon.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Laboratorios Chile, Chile.
Amoxicillin (p. 216·2).
Bacterial infections.

Amobronc *Ist. Chim. Inter., Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-system disorders.

Amo-C Plus *H & Care, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amocas *Be-Tabs, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amocasin *Northia, Arg.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Amocetin *Remedina, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Amocid *Lysoform, Ger.*
Orthophenylphenol (p. 1762·3).
Surface disinfection.

Amocillin *Caps, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amocla *Penmix, Singapore.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Kuhnil, Thai.†
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclabene *Ratiopharm, Cz.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclan *Arrow, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Katwijk, Neth.†; Hikma, Pol.; Hexal, Rus.†
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Westward, USA.
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclane *Eurogenerics, Belg.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

AmoclanHexal *Hexal, Austria.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclav *Biomedis, Philipp.; Pediatrica, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Casasco, Arg.; Hexal, Ger.†; 1A, Hung.; Rowex, Irl.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclav Duo *Casasco, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclavam *BA Farma, Port.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclave *Bial, Spain.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoclavs *Shreshtha, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amoclavs-LB *Shreshtha, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Amoclen *Zentiva, Cz.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoclox-D *Merion, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amocol *Offenbach, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Amocomb *Bernofarm, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amodep *FDC, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amodep-AT *FDC, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amodex
Note: this name may be used for preparations of different composition.
Bouchara-Recordati, Fr.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amodion *Schering-Plough, Venez.*
Syrup (child): ⊗Ammonium acetate (p. 1655·3); sodium benzoate (p. 1738·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Amodipan *Santa, Gr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Amodivyr *Copernico, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Amodormin *Omicron, Arg.*
Diphenhydramine (p. 626·1).
Insomnia.

Amoebriz *Janssen-Cilag, Mex.*
Mebendazole (p. 158·3); quinfamide (p. 947·1).
Amoebiasis; worm infections.

Amofar *Cafar, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amofarma *Continentales, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Amofen *Lafi, Chile.*
Diclofenac (p. 48·3).
Pain; inflammation; fever.

Amofil *Sanquin, Fin.*
A factor VIII preparation (p. 1148·1).
Haemophilia A; factor VIII deficiency.

Amofilin *Pisa, Mex.†*
Aminophylline (p. 1201·2).

Amofin *Galen, Ger.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Amoflux *Bergamo, Braz.†; Lampugnani, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amofur *Ivax, Mex.†*
Quinfamide (p. 947·1).
Amoebiasis.

Amogin *Millimed, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; dyspepsia; flatulence.

Amohexal *Hexal, Austral.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoka *Orion, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amoklavin *Deva, Turk.*
Amoxicillin (p. 216·2), amoxicillin trihydrate (p. 216·2), or amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoksiklav *Sandoz, China; GPO, Thai.; Sandoz, Thai.; Sandoz, Ukr.*
Amoxicillin (p. 216·2), amoxicillin sodium (p. 216·2), or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3) or clavulanic acid (p. 268·3).
Bacterial infections.

Lek, Cz.; Sandoz, Pol.; Lek, Rus.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sandoz, Hong Kong.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoksilav *Sandoz, Turk.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoksilin *Nobel, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoksina *Nevzat, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

A-Mol
Note: this name may be used for preparations of different composition.
Siam Bheasach, Thai.
Paracetamol (p. 115·1).
Fever; pain.

Amol
Note: this name may be used for preparations of different composition.
Altana, Hung.; Nycomed, Pol.
Peppermint oil (p. 1877·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); lavender oil (p. 2541·1); lemon oil (p. 2543·1); melissa oil (p. 2553·2); menthol (p. 2553·2).
Cold symptoms; digestive disorders; anxiety; skin disorders; nervous disorders; musculoskeletal and joint disorders; neuralgia; headache; toothache; insect bites; oral hygiene.

Nycomed, Cz.
Peppermint oil (p. 1877·1); citronella oil (p. 2481·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); lavender oil (p. 2541·1); lemon oil (p. 2543·1); menthol (p. 2553·2).
Digestive disorders; cough; sore throat; cold symptoms; musculoskeletal pain.

Amol, Canad.†
Cinnamon oil (p. 2479·3); clove oil (p. 2481·3); lavender oil (p. 2541·1); peppermint oil (p. 1877·1).

Amol Heilkräutergeist N *Takeda, Ger.*
Melissa oil (p. 2553·2); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); lemon oil (p. 2543·1); peppermint oil (p. 1877·1); lavender oil (p. 2541·1); menthol (p. 2553·2).
Gastrointestinal disorders; capillary disorders.

A-Mol Plus *Siam Bheasach, Thai.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms.

Amolac *Alicon, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Amolac Plus *Alicon, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Amolac Plus DT *Alicon, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Amolex *Andromaco, Chile.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amolgen *Solfran, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Amoli *Tiancifu, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amolife *La Pharmaceuticals, India.*
Amoxapine (p. 407·3).
Depression.

Am-O-Lin
Note: this name may be used for preparations of different composition.
Bayer, NZ.†
Almond oil (p. 2437·1); calamine (p. 1697·2); salicylic acid (p. 1719·1); zinc oxide (p. 1729·1).
Nappy rash; skin irritation.

Amolin
Note: this name may be used for preparations of different composition.
Stada, Irl.
⊗Atenolol (p. 1308·2).
Arrhythmias; hypertension; angina pectoris; myocardial infarction.

Amoling *Bright Future, China.†*
Amoxicillin (p. 216·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Amoltex *Aldril, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour.

Amon *Vickmans, Hong Kong.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Amo-Nate *Sanify, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Amonate *Dafra, Belg.†*
White tablets, artesunate (p. 648·2); yellow tablets, amodiaquine (p. 647·2).
Malaria.

Amone *Talent, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amone-AT *Talent, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amonit Plus *Nitro Organics, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amopin *Finecure, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amoram *LPC, UK.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amorion *Orion, Fin.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amorion Comp *Orion, Fin.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amosan
Note: this name may be used for preparations of different composition.
Procter & Gamble, Canad.; Oral-B, USA.
Sodium perborate (p. 1770·1).
Oral lesions; oral disinfection.

Oral-B, Austral.†
Sodium perborate (p. 1770·1); sodium bitartrate (p. 1888·2).
Inflammatory mouth disorders.

Amosept *Lysoform, Ger.*
Didecyldimethylammonium chloride (p. 1750·3).
Hand disinfection.

Amosin *Sintez, Rus.; Sanli, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amosine *Mugi, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amosol *SoSe, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amospes *Specifar, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amosym *Symbiosis, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amosyt *Bioglan, Swed.*
Dimenhydrinate (p. 625·2).
Vertigo; Ménière's syndrome; nausea; motion sickness.

Amotaks *Polfa Tarchomin, Pol.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amotein *Chiesi, Spain.†*
Metronidazole (p. 936·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Amoval *Saval, Chile.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoval Duo *Saval, Chile.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amovin *Cofasa, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Amox *EMS, Braz.; Jaapharm, Canad.; Vickmans, Hong Kong†; Cure Quick, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

KG, Ital.; SM, Thai.; Utopian, Thai.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxa *Atlantic, Singapore; Atlantic, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxadene *Cifarma, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxal *GSK, Venez.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxapen *Remedica, Hong Kong; Remedica, Singapore.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amox-AR *Cure Quick, India.*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Amoxaren *Areu, Spain.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxcillin *Greater Pharma, Thai.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxclav *Sandoz, Ger.†*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amox-G *Klonal, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amox-G Bronquial *Klonal, Arg.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Bacterial infections.

Amoxi *1A, Ger.†; CT, Ger.†; Sandoz, Ger.†; Generics, Israel; Pharmachemie, Neth.†; Apotex, NZ; TO-Chemicals, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mar, Arg.
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxi Duo *Mar, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi Gobens *Normon, Spain.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi Plus *Mar, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxian *United Lab, China.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxibeta *Betapharm, Ger.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxibiot *Investi, Arg.†*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxibron
Note: this name may be used for preparations of different composition.
GSK, Mex.
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Kinder, Braz.†
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxicap *Gulf Drug, S.Afr.; Hovid, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxicillin comp *Ratiopharm, Ger.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxicina *Oriental, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxiclav *Apotex, Belg.; Mylan, Belg.; Sandoz, Belg.; Teva, Belg.; Betapharm, Ger.; Teva, Israel; Pisa, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxi-Clavulan *Aliud, Ger.†; Stada, Ger.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

AmoxiClavulan *1A, Austria.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxicler *Monserrat, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxiclide *Rimsa, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3); nimesulide (p. 101·3).
Respiratory-tract infections.

Amoxico *Sel-J, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxicomb *Aringa, Ukr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amoxicomp *Genericon, Austria.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxidal *Roemmers, Arg.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxidal Duo *Roemmers, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxidal Respiratorio *Roemmers, Arg.*
Oral suspension; tablets: Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Roemmers, Arg.
Injection: Amoxicillin sodium (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Amoxidal Respiratorio Duo *Roemmers, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Amoxident *LPC, UK.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxidil *Cifarma, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi-Diolan *Meda, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxidoc *Docpharm, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxidon *Acdhon, Thai.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxiduo *Roemmers, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxifar *Zambon, Braz.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxifur *Teva, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxiga *Elter, Venez.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxigran *Hovid, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxigrand *Ahimsa, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxigrand Bronquial *Ahimsa, Arg.*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Amoxigrand Compuesto *Fada, Arg.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amoxi-Hefa *Riemser, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxihexal *Hexal, Austria; Hexal, Cz.; Hexal, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxil *GSK, Singapore; Arterium, Ukr.*
Amoxicillin (p. 216·2).
Bacterial infections.

GSK, Braz.; Zydus, India; GSK, Indon.; GSK, NZ; GSK, Philipp.; Aspen, S.Afr.; GSK, Thai.; Reddy, USA.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

GSK, Austral.; GSK, Gr.; GSK, Irl.; GSK, Mex.; Labesfal, Port.; GSK, UK.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxilan *Lannacher, Austria; Meyer, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxilin *Baiyunshan, China; Livzon, China; Sine, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxil-K *Arterium, Ukr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amoxillin *Benedetti, Ital.†; Actavis, Norw.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pharos, Indon.
Amoxicillin (p. 216·2).
Bacterial infections.

Amoximed *Cimed, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxi-Mepha *Mepha, Switz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoximycin *Medichrom, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxin *Ratiopharm, Fin.; Inpac, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxin Comp *Ratiopharm, Fin.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxina *Aesculapius, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hexal, Braz.
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxinga *Inga, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxinovag *Novag, Mex.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi-Ped *Stiefel, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxipen *PC India, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxipenil *Montpellier, Arg.; Bago, Chile.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxipenil Bronquial *Montpellier, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Amoxiplus *Ratiopharm, Austria.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxipoten *Del Bel, Arg.†*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi-saar *MIP, Ger.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi-saar plus *MIP, Ger.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxisol *Rimsa, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxistad *Stada, Austria.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxistad plus *Stada, Austria.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amoxi-Tablinen *Winthrop, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxitan *Bunker, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxitenk *Biotenk, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxitenk Plus *Biotenk, Arg.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amoxival *Valmor, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxivan *Khandelwal, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxivet *Valeant, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxi-Wolff *Wolff, Ger.†*
Oral liquid; tablets: Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amox-LB *Cure Quick, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Amoxlin *Utopian, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxol *Cassara, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxol Duo *Cassara, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxon *Vickmans, Hong Kong.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxsan *Caprifarmindo, Indon.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxy *United Lab, China; Christo, Hong Kong†; M & H, Thai.; Osoth, Thai.; PP Lab, Thai.; RX, Thai.; T Man, Thai.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxybid *GSK, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxydase *Chemech, India.*
⊗Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3) or *Lactobacillus acidophilus* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Amoxyfizz *Schwulst, S.Afr.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxylin *Biomedis, Thai.†; Great Eastern, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxyn *Saga, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amoxypac *Inpac, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxypen *Invision, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Socobom, Belg.; Grunenthal, Ger.†
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amoxytek *Arunabh, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Amoxytek D *Arunabh, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amozen-AT *Zenon, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Ampac *Inpac, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampakine *Rontag, Arg.*
Amantadine (p. 890·3).
Influenza; parkinsonism; drug-induced extrapyramidal disorders.

Ampamet *Menarini, Ital.*
Aniracetam (p. 389·1).
Mental function impairment.

Amparax *Wyeth, Chile.*
Lorazepam (p. 1080·3).
Anxiety; premedication; nausea and vomiting.

Amparo *Mibe, Ger.*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Ampavit *ANB, Thai.*
Vitamin B_{12} (p. 2107·2).
Pernicious anaemia.

Ampcoxin *T Man, Thai.*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Ampecyclal *Erempharma, Fr.*
⊗Heptaminol adenosine phosphate (p. 2525·1).
Haemorrhoids; venous insufficiency; metrorrhagia.

Ampen
Note: this name may be used for preparations of different composition.
Amrit, India; Health Biotech, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ampenina *Behrens, Venez.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampex *Exakta, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amphadase *Amphastar, USA.*
Hyaluronidase (p. 2527·2).
Adjuvant to increase the absorption and dispersion of injected drugs; hypodermoclysis; adjunct in subcutaneous urography.

Amphiprol *Proel, Gr.*
Amphotericin B (p. 569·2).
Fungal infections.

Amphochol *Herbapol Lodz, Pol.†*
Fumitory (p. 2508·2).
Biliary-tract disorders.

Amphocil *Mayne, Austral.†; Torrex, Austria; Zodiac, Braz.; Torrex, Cz.; Three Rivers, Denm.; Samaritan, Irl.†; Sequus, Israel†; Speciality European Pharma, Ital.; Teva, Mex.; Alkopharma, Neth.; Torrex Chiesi, Pol.; Farmoz, Port.; Intermune, Singapore; Farmatec, Spain; Vitaflo, Swed.†; Hospira, Thai.†; AstraZeneca, Turk.; Beacon, UK.†*
Amphotericin B-sodium cholesteryl sulfate complex (p. 569·2).
Fungal infections; aspergillosis; leishmaniasis.

Smart Intermed, Gr.; Torrex, Hung.; Three Rivers, Malaysia.
Amphotericin B-sodium cholesteryl sulfate complex (p. 569·2).
Fungal infections.

Amphodyn *Astellas, Austria.†*
⊗Etilefrine hydrochloride (p. 1379·1); aescin (p. 2431·2).
Hypotension; circulatory disorders.

Amphoglucamin *Sintez, Rus.†*
Amphotericin B (p. 569·2).
Fungal infections.

Amphojel *Aurium, Canad.; Aspen Consumer, S.Afr.; Wyeth-Ayerst, USA.*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; dyspepsia; gastritis; heartburn.

Ampholin *Mediorals, Thai.*
Amphotericin B (p. 569·2).
Fungal infections.

Ampholip *Bharat, India; Xeno, Philipp.*
Amphotericin B (p. 569·2).
Fungal infections.

Ampho-Moronal *Dermapharm, Austria; Dermapharm, Ger.; Dermapharm, Switz.*
Amphotericin B (p. 569·2).
Fungal infections.

Amphosca *Homeocan, Canad.†*
⊗Agnus castus (p. 2432·2); ambra grisea (p. 2440·3); lycopodium clavatum (p. 2547·1); selenium metallicum (p. 2086·3); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Amphosca Orchitine *Lehning, Fr.*
⊗Agnus castus (p. 2432·2); valeriana (p. 2640·2); ambra (p. 2440·3); damiana (p. 2491·3); selenium (p. 2086·3); lycopodium (p. 2546·3); orchitinum (p. 2304·3).
Homoeopathic preparation.

Amphosca Ovarine *Lehning, Fr.*
⊗Agnus castus (p. 2432·2); valeriana (p. 2640·2); ambra (p. 2440·3); damiana (p. 2491·3); selenium (p. 2086·3); lycopodium (p. 2546·3); ovarinum (p. 2298·2).
Homoeopathic preparation.

Amphotec *Raffo, Arg.; Ben Venue, China; Bioavenir, Israel†; Biomeks, Turk.; Sequus, USA; Nolver, Venez.*
Liposomal amphotericin B (p. 569·2).
Fungal infections; aspergillosis.

Three Rivers, Canad.
Amphotericin B-sodium cholesteryl sulfate complex (p. 569·2).
Aspergillosis.

Amphotin *United Biotech, India.*
Amphotericin B (p. 569·2).
Fungal infections.

Amphotin-Lip *United Biotech, India.*
Liposomal amphotericin B (p. 569·2).
Fungal infections.

Amphotret *Bharat, India; Xeno, Philipp.; Bharat, Thai.*
Amphotericin B (p. 569·2).
Fungal infections.

Amphy *Profic Organic, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Ampi *Interbat, Indon.; T Man, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Prodotti, Braz.†
Ampicillin (p. 218·2).
Bacterial infections.

Ampi Frx *United Drug, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampibactan *Behrens, Venez.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Ampi-Bis *Northia, Arg.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampi-Bis Plus *Northia, Arg.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Ampicap *Hovid, Singapore.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampiciflan *Bunker, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampicil *Medley, Braz.†*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Ampicilab *Multilab, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampicilase *Teuto, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampicilil *Greenpharma, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampicillin comp *Hexal, Ger.†*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Ampicilon *Delta, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampicin *The Forty-Two, Thai.*
Ampicillin (p. 218·2).
Bacterial infections.

Westmont, Philipp.
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampicipen *Elpen (Ελπεν), Gr.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampicler *Monserrat, Arg.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampiclin *Taisheng, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampiclox *GSK, S.Afr.†*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

GSK, Thai.†
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Ampicloxa *PC India, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Ampiclox-D *GSK, Mex.†*
Ampicillin trihydrate (p. 218·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Ampico *Sel-J, Philipp.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampicyn *Aspen, Austral.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Siam Bheasach, Thai.†
Ampicillin (p. 218·2).
Bacterial infections.

Ampifort *Panjon, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ampigen *Fabra, Arg.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampigen SB *Fabra, Arg.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Fabra, Arg.
Tablets: Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Ampigran *Legrand, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampigrand *Ahimsa, Arg.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampigrin *Collins, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Ampihof *Pharmahof, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampijet *Pharmed, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampikyy *Vitabalans, Fin.*
⊗Hydrocortisone (p. 1640·1).
Snake bites; wasp and bee stings.

Ampilan *Meyer, Venez.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampilevel *Ern, Spain.†*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Ampilin *Hetero, India; Atlantic, Malaysia; Atlantic, Singapore.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Utopian, Thai.
Ampicillin (p. 218·2).
Bacterial infections.

Ampillin *PP Lab, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampilong
Note: this name may be used for preparations of different composition.
American Remedies, India.
⊗Ampicillin trihydrate (p. 218·2); probenecid (p. 607·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ampilox *Biochem, India.*
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2); cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1).
Bacterial infections.

Ampilox-LB *Biochem, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ampilozin *Ducto, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampilux *Tubilux, Ital.*
Ampicillin sodium (p. 218·2).
Eye infections.

Ampimax
Note: this name may be used for preparations of different composition.
Keun Wha, Philipp.
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Hexal, S.Afr.†
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampimex *Arlex, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampimycin *Acdhon, Thai.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampina *Penn, Arg.†*
Nimodipine (p. 1455·2).
Cerebrovascular disorders.

Ampine *Biomedica, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Sunij, India.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Ampine-AT *Sunij, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Ampine-RL *Sunij, India.*
Amlodipine (p. 1304·1); ramipril (p. 1483·3).

Ampinex *Medopharm, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampinox *Lamsa, Arg.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampi-Oral *Utopian, Thai.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampipac *Inpac, Thai.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampipen *Caps, S.Afr.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Wyeth, India.
Ampicillin (p. 218·2).
Bacterial infections.

Ampiplus Simplex *Menarini, Ital.†*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampip-T *Health Biotech, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Ampi-Quim *Quimica y Farmacia, Mex.*
Ampicillin (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampiro *Medizone, India.*
Oral powder: Vitamins; minerals; trace elements; carbohydrate; amino acids; spirulina (p. 2622·1).

Medizone, India.
Syrup: Vitamin B substances (p. 2102·3); dexpanthenol (p. 2582·2); calcium gluconate (p. 1783·3); ferrous gluconate (p. 2061·2); zinc sulfate (p. 2126·2); protein hydrolysate.

Ampirovix *Farmedia, Gr.*
Tenoxicam (p. 136·2).
Inflammatory disorders.

Ampisalt *Adcock Ingram, S.Afr.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampisan *Syncom, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampisid *Nevzat, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Nevzat, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Nevzat, Ukr.
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Ampisina *Nevzat, Turk.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampisodex *Leontik, Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Ampisul *Taisheng, Philipp.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Universal, Hong Kong.†
Ampicillin (p. 218·2).
Bacterial infections.

Ampisulbin *Arterium, Ukr.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Ampisyn *Cipla, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampitam *Great Eastern, Thai.†*
Sultamicillin (p. 369·1).
Bacterial infections.

Ampitasol *Pharmex (Φαρμεξ), Gr.*
Triclosan (p. 1773·2).
Disinfection.

Ampi-Tecno *Tecnofarma, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampitenk *Biotenk, Arg.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampitrex *Harbin, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ampitum *FDC, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Ampixen *Oriental, Arg.†*
Ampicillin (p. 218·2).
Bacterial infections.

Ampizef *Sel-J, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Amplacilina *Eurofarma, Braz.*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Amplacin *Cifarma, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Amplamox *Tecnifar, Port.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amplamox AC *Uniao Quimica, Braz.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amplamox Plus *Tecnifar, Port.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amplavit *Cimed, Braz.*
Vitamins.

Ample *Mission Happiness, India.*
Sodium acid citrate (p. 1781·1).

Ampliactil *Sanofi-Aventis, Arg.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; agitation; nausea and vomiting; behaviour disorders in children; pain; pruritus.

Ampliar *Casasco, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Ampliar Duo *Casasco, Arg.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Ampliar Plus *Casasco, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Amplibac
Note: this name may be used for preparations of different composition.
Bergamo, Braz.†
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Amplibenzatin Bronquial *Ivax, Arg.*
1 Ampoule, ampicillin sodium (p. 218·2); ampicillin benzathine (p. 218·2); 1 ampoule, clonixin lysine (p. 40·1); chlorphenamine maleate (p. 620·3); bromhexine hydrochloride (p. 1656·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection
Respiratory-tract infections.

Amplictil *Sanofi-Aventis, Braz.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; nausea and vomiting; tetanus.

Amplifar *Tecnifar, Port.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampligen
Note: this name may be used for preparations of different composition.
HemispheRx, USA.
Poly I.poly C12U (p. 1009·2).
AIDS and HIV infection; renal cell carcinoma; chronic fatigue syndrome; invasive metastatic melanoma.

Ampliron *Rhein, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ampliron Duo *Rhein, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amplital *Pfizer, Ital.*
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ampliton *Makiz-Pharma, Rus.*
Tablets, amlodipine besilate (p. 1304·1); tablets, cilazapril (p. 1336·2).
Hypertension.

Amplium
Note: this name may be used for preparations of different composition.
Farmasa, Braz.
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Sigma-Tau, Ital.
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Amplium-G *Farmasa, Braz.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Amplizer *OFF, Ital.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amplobac *Bergamo, Braz.†*
Vancomycin hydrochloride (p. 384·2).

Amplotal *Medley, Braz.†*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Amplus
Note: this name may be used for preparations of different composition.
Jagsonpal, India.
Capsules; tablets: Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Jagsonpal, India.
Injection: Ampicillin sodium (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Szama, Arg.
Salicylic acid (p. 1719·1); pilocarpine hydrochloride (p. 2010·3); dexpanthenol (p. 2582·2); vitamin B_6 (p. 2105·3).
Scalp disorders.

AM-PM Junior *Elder, India.*
Sodium benzoate (p. 1738·2); sodium fluoride (p. 2089·2); triclosan (p. 1773·2).

AM-PM Plus *Elder, India.*
⊗Alcohol (p. 1733·1); sodium benzoate (p. 1738·2); triclosan (p. 1773·2).

AM-PM Special *Elder, India.*
⊗Alcohol (p. 1733·1); eucalyptus oil (p. 2501·2); sodium benzoate (p. 1738·2); sodium fluoride (p. 2089·2); thymol (p. 1772·2); triclosan (p. 1773·2).

Ampol *Asian Pharm, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Ampoxin *Unichem, India; Goldex, S.Afr.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Ampoxin Plus *Unichem, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Ampoxin-LB *Unichem, India.*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1); lactic-acid-producing organisms (p. 2596·3).
Bacterial infections.

Ampra *M & H, Thai.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amprace *MSD, Austral.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left ventricular dysfunction.

Ampres *Amdipharm, UK.*
Chloroprocaine hydrochloride (p. 1983·1).
Local anaesthesia.

Amprexyl *Unison, Hong Kong.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Unison, Thai.
Ampicillin (p. 218·2).
Bacterial infections.

Amprexyn *Liferpal, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Ampril *KRKA, Pol.; KRKA, Ukr.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction; nephropathy.

Ampril HD *KRKA, Pol.; KRKA, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ampril HL *KRKA, Pol.; KRKA, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amprilan *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction; diabetic nephropathy.

Amprilan H *KRKA, Cz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amprilan HD *KRKA, Hung.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amprilan HL *KRKA, Hung.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amprilan ND *KRKA, Rus.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Amprilan NL *KRKA, Rus.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ampromed *Millimed, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ampty *Glenmark, India.*
Itopride hydrochloride (p. 1850·1).

Ampucare *Venus, India.*
Beeswax; European barberry (p. 2502·1); capsicum abbreviata; copper sulfate (p. 2057·2); curcuma longa; liquorice (p. 1853·2); saussurea lappa; chebulic myrobalan (p. 2474·3).

Ampy *Global, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Ampy C *Global, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Ampy S *Global, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Ampylox *Global, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Ampyra *Acorda, USA.*
Fampridine (p. 686·2).
Multiple sclerosis.

Ampysul *Global, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Amrap *Rapross, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amrap-AT *Rapross, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amrea *Cinerea, India.*
Amitriptyline (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Amrea-C *Cinerea, India.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).

Amricin *Amrit, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Amrisol *SG, India.*
Amrinone (p. 1305·1).
Heart failure.

Amritacicl *Chemica, Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Amritam *Health Biotech, India.*
Piracetam (p. 393·3).
Mental function impairment.

Amrix *Teva, USA.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Amrixal *PharmaSwiss, Israel.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm and pain.

Amriz *Ritz, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Amrolite 2S *Tablets, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Amropenem *Health Biotech, India.*
Meropenem (p. 321·3).
Bacterial infections.

Amsa PD *Erfa, Canad.*
Amsacrine (p. 741·3).
Acute leukaemias.

Amsach *Sarabhai Piramal, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amsafast *Antibioticos, Mex.*
Orlistat (p. 2577·1).
Obesity.

Amsalyo *ProStrakan, Fr.*
Amsacrine (p. 741·3).
Acute leukaemias.

Amsapen *Antibioticos, Mex.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Amsat *Vensat, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Amsati *Antibioticos, Mex.†*
Azithromycin (p. 221·2).
Bacterial infections.

Amsaxilina *Antibioticos, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amset *Pulse, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amset-XT *Pulse, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amsidine *Pfizer, Belg.†; Warner-Lambert, Gr.; Goldshield, Irl.; NordMedica, Neth.; Mercury, UK.†*
Amsacrine (p. 741·3).
Acute leukaemias.

Amsidyl *Pfizer, Austral.†; NordMedica, Ger.; IFET (ΙΦΕΤ), Gr.; Pro Concepta, Switz.*
Amsacrine (p. 741·3).
Acute leukaemias.

Amsler *Antibioticos, Mex.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Amsol *Kopran, India.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Amstar-Clav *Sanify, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Amsten *Stadmed, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amsubac *Kapl, Thai.*
Sultamicillin (p. 369·1).
Bacterial infections.

Amsyn *Synmedic, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amtadol *Amrit, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Amtas *Intas, India; Accord, S.Afr.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Intas, Singapore.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Amtas-AT *Intas, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amtas-E *Intas, India.*
Amlodipine (p. 1304·1); enalapril (p. 1371·1).
Hypertension.

Amtas-LP *Intas, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Amtaxime *Amrit, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Amtenol *Orchid, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Amtersol *Yaroslavl, Rus.*
Ammonium chloride (p. 1656·1); potassium bromide (p. 2461·1); sodium benzoate (p. 1738·2); liquorice (p. 1853·2); thermopsis.
Respiratory-tract disorders.

Amtev *Teva, Mex.*
Amlodipine maleate (p. 1304·1).
Angina pectoris.

Amther *Scoshia, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Amtocort *Pharos, Indon.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Amtop *Ind-Swift, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amtor *Alembic, India.*
Amlodipine besilate (p. 1304·1); atorvastatin (p. 1309·2).

Amtuss *Unison, Malaysia; Unison, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Amuchina *Aphth, Gr.*
Sodium chloride (p. 1795·1); sodium hypochlorite (p. 1768·3).

Amucin *Multicare, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Motion sickness; nausea; vomiting; premedication; production of cycloplegia and mydriasis.

Amuclan *Wolff, Neth.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Amuco *Austell, S.Afr.*
Acetylcysteine (p. 1652·2).

Amukin *BMS, Belg.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Amukina *Regen, Switz.*
Sodium chloride (p. 1795·1); sodium hypochlorite (p. 1768·3).
Burn, mucous membrane, skin, and wound disinfection.

Amukine *Gifrer Barbezat, Fr.*
Sodium hypochlorite (p. 1768·3); sodium chloride (p. 1795·1).
Skin, mucous membrane and wound cleansing.

Amukine Med *Amuchina, Ital.*
Sodium hypochlorite (p. 1768·3).
Disinfection of burns, skin, wounds, and mucous membranes.

Amulsin *Sanitas, Chile.*
Olanzapine (p. 1089·3).
Psychoses.

Amusa *Icon, Philipp.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Amvar *Simex, Indon.*
Citrus bioflavonoids (p. 2505·2); diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; phlebitis; haemorrhoids.

Amvas *Millimed, Thai.*
Amlodipine besilate (p. 1304·1).
Hypertension; myocardial ischaemia.

Amvasc *Therapharma, Philipp.*
Amlodipine besilate (p. 1304·1) or amlodipine camsilate (p. 1304·1).
Hypertension; angina pectoris.

Amvastan *Rottapharm, Ukr.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Amvax *Amson, Philipp.*
A recombinant hepatitis B vaccine (p. 2389·3).
Active immunisation.

Amvaz *Reddy, Malaysia.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Amven-C *Vensat, India.*
Ambroxol (p. 1654·3); cetirizine (p. 619·2).

Amvisc *Chiron, Fr.†; Bio-Fizik, Turk.; Bausch & Lomb, USA.*
Sodium hyaluronate (p. 2526·2).
Aid in ophthalmic surgery.

AMX *Croesus, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amxol *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Amy *Ind-Swift, India.*
Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); loratadine (p. 633·2).

Amyben *Lexon, UK.*
Amiodarone hydrochloride (p. 1300·1).
Tachyarrhythmias.

Amyclon *Nizpharm, Rus.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Amyclox *Ind-Swift, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Amyclox-LB *Ind-Swift, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Amycor *Merck Serono, Fr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Amycor Onychoset *Merck Serono, Fr.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Amydramine *Julphar, UAE.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Amydramine II *Julphar, UAE.*
Diphenhydramine hydrochloride (p. 626·2).
Cough; cold symptoms; hypersensitivity reactions.

Amydramine Paediatric *Julphar, Malaysia; Julphar, UAE.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; respiratory-tract congestion.

Amygdorectol *Actipharm, Switz.*
Bismuth camphocarbonate (p. 1821·3).
Mouth and throat disorders.

Amykal *Pelpharma, Austria.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Amylin *Roemmers Rowe, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Amylodiastase *SERP, Mon.*
Amylase (p. 2442·1).
Digestive disorders.

Amyn *Kopran, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Amypres *Psyco Remedies, India.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Amypres-C *Psyco Remedies, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Amyrcl *Candor, India.*
Ambroxol (p. 1654·3); amoxicillin (p. 216·2).
Respiratory-tract infections.

Amytal *IFET (ΙΦΕΤ), Gr.; Lilly, Thai.; Flynn, UK; Marathon, USA.†*
Amobarbital sodium (p. 1037·3).
Insomnia; status epilepticus; sedative.

Amytril *Cristalia, Braz.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Amyvid *Lilly, UK; Lilly, USA.*
Fluorine-18 florbetapir (p. 2224·1).
Radioactive diagnostic agent for investigation of cognitive impairment.

Amyx *Zentiva, Cz.; Zentiva, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Amyzol *Lek, Rus.†*
Amitriptyline hydrochloride (p. 401·1).

Amze *Penn, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Amzel *Zee, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Amzel-EL *Zee, India.*
Amlodipine (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Amziax *Chobet, Arg.*
Alprazolam (p. 1035·2).
Anxiety; delirium tremens; alcoholism.

Amzo *Arlak, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Amzoate *IFET (ΙΦΕΤ), Gr.*
Sodium benzoate (p. 1738·2).

Amzole *Innovata, S.Afr.*
Metronidazole (p. 936·1).

Amzuvag *Novag, Mex.*
Tamsulosin (p. 2369·1).
Benign prostatic hyperplasia.

An Bei Te *Ji Sheng, China.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold symptoms.

An Ben *Chen Pai, China.*
Aminomethylbenzoic acid (p. 1132·2).

An Bu *Yu Heng, China.*
Bromhexine (p. 1656·3); cefaclor (p. 232·3).
Respiratory-tract infections.

An Da *Il-Yang, China.*
Hydrotalcite (p. 1845·2).
Dyspepsia.

An Da Fen *Anke, China.*
Interferon alfa-2b (p. 989·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

An Duo Mei *TianAn, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

An Duo Ming *TianAn, China.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

An Er Ke *JinYao, China.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

An Fa Bu *Jiang Shi, China.*
Thymosin (p. 2631·1).

An Fan Zheng *Kang Ji Er, China.*
Levofloxacin lactate.
Bacterial infections.

An Fei Lin *Sine, China.*
Theophylline (p. 1229·3).
Bronchospasm.

An Du Fen *Tuo Bin, China.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

An Fu Le *Lai En, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

An Fu Ding *Ge Dian Ren Fu, China.*
Amifostine (p. 1539·2).
Reduction of toxicity associated with cancer chemotherapy; radiotherapy-induced xerostomia.

An Fu Kang *Man Xiu Lei Dun, China.*
Crotamiton (p. 1699·2).
Scabies; pruritus.

An Fu Long *HuaLiDa, China.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; chronic hepatitis; herpes zoster infections; genital warts.

An He *Chia Tai, China.*
Amlexanox (p. 1202·2).

An Ji Er Le *Yang An, China.*
Kitasamycin acetate (p. 315·2).
Bacterial infections.

An Ji Er Ning *Yong An, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

An Ji Er Shu *Yang An, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

An Ji Xin
Note: this name may be used for preparations of different composition.
Haini, China.
Capsules: Zaleplon (p. 1114·3).
Insomnia.
Suzhong Haixin, China.†
Tablets: Actarit (p. 17·1).

An Jie Di Lin *Topsun, China.*
Inosine (p. 2533·1).

An Jie Suo *An Jie, China.*
Interleukin-2 (recombinant) (p. 810·1).

An Jie De Xin *Topsun, China.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental impairment.

An Jie Xing *C & O, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

An Ka *Xinhua, China.*
Irisquinone.

An Kai Shu *Yaoyau, China.*
Glutamine (p. 2070·3).
Burns; nutritional supplement.

An Kang *Yi Sheng, China.*
A Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

An Ke *Jiangxi, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

An Ke Rui *Sanwei, China.*
Adenovirus type 5 (human, recombinant) (p. 2376·1).

An Ke Tuo *Dikang, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

An Di Ke Tuo *Tai Sheng, China.*
Cefixime (p. 240·3).
Bacterial infections.

An Di Ke Wei *Tai Sheng, China.*
Cefixime (p. 240·3).
Bacterial infections.

An Lai *Huahai, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

An Lan Shu *Jin Lan, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

An Li *Bayer, China.*
Naproxen sodium (p. 98·2).
Pain.

An Li Bo *Yuan He, China.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

An Li Kang *Tong He, China.*
Artenimol (p. 648·2); piperaquine phosphate (p. 659·3); trimethoprim (p. 381·2).

An Li Lai *Jiangxi, China.*
Levofloxacin (p. 315·3).
Bacterial infections.

An Li Nuo Er *Topsun, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

An Li Qing *Simcere, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

An De Lin *Open, China.*
⊗Midodrine hydrochloride (p. 1437·3).
Hypotension; urinary incontinence.

An Long *Xiang Yang, China.*
⊗Salicylic acid (p. 1719·1); triamcinolone acetonide (p. 1649·1).
Skin disorders.

An Long Ping *HuaXia, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

An Luo *Kang Yuan, China.*
Aminobutyric acid (p. 2509·2).
Mental function impairment; hypertension.

An Lv Fan *Otsuka, China.†*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

An Mei Lin *Welman, China.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections; streptococcal infections.

An Mei Qin *ZhenYuan, China.*
Azithromycin lactobionate.
Bacterial infections.

An Nei Zhen *Dawnrays, China.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

An Ni Ping *Jing Yi Tang, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

An Ni Tuo *Zheng An, China.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

An Nuo Xin Mei *Duoburuifei, China.*
Isosorbide dinitrate (p. 1412·2).
Heart failure; unstable angina.

An Di Pian *TaiYuan, China.*
Cetirizine hydrochloride (p. 619·2).

An Pu Luo *Yi Tian, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

An Pu Nuo Xin *SanJiu, China.*
Chondroitin sulfate (p. 2476·1).

An Qi *Simcere, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

An Qi Mi Rui *Duoburuifei, China.*
Inosine (p. 2533·1).

An Rui Ke *Hayao, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

An Ruo Ning *Nanjing, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

An Sai Ma *Fu He Hua Xing, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

An Shi *Simcere, China.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; heart failure.

An Shi Li *An Shi, China.*
Levofloxacin mesilate.
Bacterial infections.

An Shi Tong *Shi Xin, China.*
Azasetron hydrochloride (p. 1820·2).

An Si Fei *Dikang, China.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; pathological gastric hypersecretory disorders; peptic ulcer.

An Si Nuo Kang *HongQi, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

An Si Ping *Hisun, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

An Si Tuo Li *Tong Ji Xian Dai, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

An Si Xin *Topsun, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

An Su Mei *ZhenYuan, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

An Su Meng *Anke, China.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; AIDS-associated cachexia; short bowel syndrome.

An Di Tai *Bo Kang, China.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

An Tai Da *Rundu Mintong, China.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

An Tai Lin *Guo Jing, China.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

An Te Bo *Hiteck Bio, China.*
Levofloxacin mesilate.
Bacterial infections.

An Te Fan *Lai Mei, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

An Te Fu *Neptunus, China.*
Interferon alfa-2b (p. 989·2).

An Te Wei Luo *Tai An, China.*
Potassium sodium dehydroandroandrographolide succinate.

An Ti *Rui Nian Qian Jin, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

An Ti Fen *Sine, China.*
Ipriflavone (p. 1185·3).
Osteoporosis.

An Ti Shu *Mao Xiang, China.*
Chloroxoquinoline.

An Ti Wei Le *Nuo Jin, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

An Tian *Rui Yang, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

An Ting
Note: this name may be used for preparations of different composition.
San Lian, China.
Injection: Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.
Shenyang First, China.
Tablets: Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

An Di Tong *Ke Lun, China.*
Potassium sodium dehydroandrographolide succinate.

An Wan Tong *Tai Sheng, China.*
Lysine hydrochloride (p. 2079·3).
Dietary supplement.

An Wei De *Si Bao, China.*
Zaleplon (p. 1114·3).
Insomnia.

An Wei Te *Hua Lu, China.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

An Di Xi Si *Zhi Jun, China.*
Cetirizine hydrochloride (p. 619·2).

An Xian *San Jin, China.*
Lamotrigine (p. 527·2).
Epilepsy.

An Di Xin *Topsun, China.*
Etamsylate (p. 1145·2).

An Xin Da *ZhenYuan, China.*
Puerarin.
Coronary heart disease; angina pectoris; myocardial infarction; retinal vein occlusion; sudden deafness.

An Xin Fu Ning *Hong Yuan, China.*
Diammonium glycyrrhizate (p. 2520·3).

An Ya *Xinglin Baima, China.*
Telmisartan (p. 1509·3).
Hypertension.

An Yi *Yangtze River, China.*
Zinc acexamate (p. 2427·3).

An Yi Ning *Dawnrays, China.*
Telmisartan (p. 1509·3).
Hypertension.

An Yun *Sanmenxia Sinoway, China.*
Zaleplon (p. 1114·3).
Insomnia.

Anabact *Cambridge Healthcare, UK.*
Metronidazole (p. 936·1).
Malodorous fungating tumours; malodorous skin ulcers.

Anabar
Note: this name may be used for preparations of different composition.
Edas, Rus.
Semecarpus anacardium (p. 2471·3); ferrum phosphoricum (p. 2077·1); barium carbonicum (p. 2452·2); arnica montana (p. 2447·2); echinacea purpurea (p. 2498·1).
Homoeopathic preparation.
Lunsco, USA†
Paracetamol (p. 115·1); salicylamide (p. 129·2); phenyltoloxamine citrate (p. 638·1).

Anabion *Berlico Mulia, Indon.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Anabion Plus DHA *Berlico Mulia, Indon.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3); docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Anabix *Helm, Port.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Anablock
Note: this name may be used for preparations of different composition.
Pfleger, Ger.
⊗Anastrozole (p. 742·1).
Breast cancer.

Anabol
Note: this name may be used for preparations of different composition.
British Dispensary, Thai.
⊗Methandienone (p. 2291·3).
Anabolic.
Zota, India.
Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Anaboline Depot *Adelco, Gr.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic.

anabol-loges *Loges, Ger.†*
Alpha tocoferil acetate (p. 2119·2); magnesium hydrogen phosphate (p. 1786·3); terra silicea (p. 2208·3); St John's wort (p. 449·1).
Tonic.

Anabrest *Synthon, Cz.†; Egis, Hung.; Uriach, Spain.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anabrez *Sun, India.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anabron *Millet Roux, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Anacal
Note: this name may be used for preparations of different composition.
Ciclum, Port.
⊗A heparinoid (p. 1401·1); lauromacrogol 400 (p. 2194·1); prednisolone (p. 1645·2); hexachlorophene (p. 1754·1).
Anorectal disorders.

Genus, UK.
A heparinoid (p. 1401·1); lauromacrogol 400 (p. 2194·1).
Anorectal disorders.

Anacaps *Ducray, Fr.†*
Soya isoflavones (p. 2620·3); cystine (p. 2059·1); methionine (p. 1558·2); vitamins; evening primrose oil (p. 2502·2); zinc sulfate (p. 2126·2).
Hair and scalp disorders.

Anacaps tri-Activ *Ducray, Fr.*
Evening primrose oil (p. 2502·2); vitamins; cystine (p. 2059·1); methionine (p. 1558·2); iron (p. 2073·1).
Hair and nail disorders.

Anacardio con Fosforo *Ximena Polanco, Chile.*
Acidum phosphor. (p. 2589·1); anacardium (p. 2471·3); argentum nitric. (p. 2615·3); arnica montana (p. 2447·2); kalium phosph. (p. 1790·3); natrium muriaticum (p. 1795·1).
Homoeopathic preparation.

Anacervix *Angelini, Port.; Angelini, Spain.*
Piracetam (p. 393·3); vincamine (p. 2645·2).
Cerebrovascular disorders; cerebral trauma.

Anacetine *Berlico Mulia, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms; cough.

Anacid
Note: this name may be used for preparations of different composition.
Ind-Swift, India.
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Teva, Cz.; Teva, Hung.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; gastritis.

Anacid S *Ivax, Cz.†*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Anacidol
Note: this name may be used for preparations of different composition.
Menarini, Ital.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2); milk powder.
Gastrointestinal disorders.

Anacin *Paladin, Canad.; Pfizer Consumer, Chile; Insight, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever; inflammation.

Anacin Advanced Headache *Insight, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Anacin Max *Pfizer Consumer, Chile.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Anaclosil *IFET (ΙΦΕΤ), Gr.; Reig Jofre, Spain.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Anacold *Darou Pakhsh, Rus.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; upper respiratory-tract disorders.

Anacrodyne *Rekah, Israel.*
Vitamin B_6 (p. 2105·3).
Vitamin B_6 deficiency.

Anact C *Teijin, Jpn.*
Protein C (p. 1161·1).
Thromboembolic disorders in congenital protein C deficiency.

Anacuf *Zytras, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Anacyne *Remedica, Port.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anadar *Liptis, USA.*
Ibuprofen (p. 68·2).

Anadar Cold & Flu *Liptis, USA.*
⊗Ibuprofen (p. 68·2); pseudoephedrine (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Anadekin *Collins, Mex.†*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin K (p. 2122·1).

Anadent *Taro, Israel.*
Topical gel: Benzocaine (p. 1980·2).
Mouth disorders.

Anadex
Note: this name may be used for preparations of different composition.
Interbat, Indon.
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; cough.
Medac, Ger.
⊗Anastrozole (p. 742·1).
Breast cancer.

Anadil *Liferpal, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Fever; pain; muscle spasm.

Anadin
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Irl.
Aspirin (p. 22·2); caffeine (p. 1203·3); quinine sulfate (p. 665·2).
Pain; cold symptoms.
SA Druggists Self Med, S.Afr.†; Wyeth Consumer, UK.
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.
Wyeth, Gr.
Paracetamol (p. 115·1).
Pain, fever.

Anadin-3 *SA Druggists Self Med, S.Afr.†*
Paracetamol (p. 115·1).
Fever; pain.

Anadin Extra *Pfizer Consumer, Irl.; Wyeth Consumer, UK.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; cold and influenza symptoms; fever.
Wyeth, Gr.
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine citrate (p. 1203·3).
Fever, pain.

Anadin Ibuprofen *Pfizer Consumer, UK.*
Ibuprofen (p. 68·2).
Pain; fever.

Anadin Joint Pain *Wyeth Consumer, UK.*
Ibuprofen (p. 68·2).
Joint pain.

Anadin LiquiFast *Pfizer Consumer, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Anadin Maximum Strength *Pfizer Consumer, Irl.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; cold and influenza symptoms.

Anadin Paracetamol *Wyeth, Irl.†; Wyeth Consumer, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Anadin Ultra *Pfizer Consumer, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Anadir *Ist. Chim. Inter., Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Anadium *Guardian, Indon.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Anadol *TO-Chemicals, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Anador
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Braz.
Dipyrone (p. 53·3).
Fever; pain.

Anador PRT *Boehringer Ingelheim, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Anadrol *Alaven, USA.*
⊗Oxymetholone (p. 2298·3).
Anaemias.

Anadurin *Elvipe, Gr.*
⊗Nandrolone hexyloxyphenylpropionate (p. 2293·1).

Anadvil *Wyeth Sante, Fr.†; Pfizer, Port.*
Ibuprofen (p. 68·2).
Pain; fever.

Anaemodoron *Weleda, Austria.*
Fragaria vesca; urtica dioica (p. 2639·3).
Iron-deficiency anaemia.

Anaerid-F *Mount Mettur, India.*
Metronidazole (p. 936·1); furazolidone (p. 933·3).

Anaerid-S *Mount Mettur, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Anaerobex *GL Pharma, Austria.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; Helicobacter pylori *infections.*

Anaerobyl *MDI, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Anaerocef *Abolmed, Rus.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Anaerocid *Sigma, Braz.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginal infections.

Anaestalgin *Streuli, Switz.†*
Procaine hydrochloride (p. 1994·3); caffeine (p. 1203·3).
Pain.

Anaesthecomp N *Ritsert, Ger.†*
Lidocaine hydrochloride (p. 1988·2); diphenhydramine hydrochloride (p. 626·2).
Allergic rashes; insect stings; sunburn.

Anaestherit *Ritsert, Austria.*
Benzocaine (p. 1980·2).
Skin disorders; anorectal disorders.

Anaesthesin *Ritsert, Ger.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Anaesthesin akut *Ritsert, Ger.†*
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Anaesthesin N *Ritsert, Ger.†*
Benzocaine (p. 1980·2).
Local anaesthesia.

Anaesthesol *Nizpharm, Rus.*
Benzocaine (p. 1980·2); bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1); menthol (p. 2553·2).
Anorectal disorders.

Anaesthesulf *Infectopharm, Ger.*
Lauromacrogol 400 (p. 2194·1).
Pruritic skin disorders.

Anaesthetic Ear Drops *Vitamed, Israel.*
Tetracaine hydrochloride (p. 1996·3); phenazone (p. 124·1).
Otitis.

Anaesthetica *Pharmachemie, Neth.†*
Bismuth subgallate (p. 1822·1); lidocaine (p. 1988·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anafebrin *Themis, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Anafen
Note: this name may be used for preparations of different composition.
Bernofarm, Indon.
Ibuprofen (p. 68·2).
Fever; pain.

Anaferon *Materia Medica, Rus.*
Interferon gamma antibodies.
Infections.

Anafertin *Armstrong, Mex.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Menstrual disorders; injectable contraceptive.

Anaflam *David, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; musculoskeletal and joint disorders; pain; fever.

Ana-Flex
Note: this name may be used for preparations of different composition.
Gunther, Braz.
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).

Anaflex
Note: this name may be used for preparations of different composition.
Bago, Arg.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.
Dekaz, Gr.; Geistlich, Singapore; Geistlich, UK.
Polynoxylin (p. 1766·1).
Skin infections.

Anafortan *Khandelwal, India.*
Injection; oral drops: Camylofin hydrochloride (p. 2467·1).
Smooth muscle spasm.
Khandelwal, India.
Syrup; tablets: Camylofin hydrochloride (p. 2467·1); paracetamol (p. 115·1).
Smooth muscle spasm.

Anafortan-N *Khandelwal, India.*
Camylofin hydrochloride (p. 2467·1); nimesulide (p. 101·3).

Anafranil *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Defiante, Belg.; Novartis, Braz.; Sunovion, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Sigma-Tau, Fr.; Dolorgiet, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Biofutura, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Teva, Pol.; Defiante, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Defiante, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; phobias; panic disorder; narcoleptic syndrome; nocturnal enuresis; chronic pain; neurogenic pain; social phobia; neuropathic pain.

Anagan *Burapha, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Anagastra *Nycomed, Spain.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Anagen
Note: this name may be used for preparations of different composition.
Cassara, Arg.
Minoxidil (p. 1438·3).
Alopecia.

Anagic *T Man, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Anagraine *Aspen, Austral.*
Metoclopramide hydrochloride (p. 1862·2); paracetamol (p. 115·1).
Migraine.

Anagrid *Rafa, Israel.*
Anagrelide hydrochloride (p. 2442·2).
Essential thrombocythaemia.

Ana-Guard *Bayer, S.Afr.†*
⊗Adrenaline hydrochloride (p. 1292·2).
Anaphylaxis.

Anahelp *Stallergenes, Fr.†*
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Anahis *Unison, Thai.†*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Cold symptoms.

Anaida *Reddy, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Anaketon *Dicofarm, Ital.*
Vitamins; minerals; amino acids.

Ana-Kit *Bayer, USA.*
Combination pack: ⊗Injection, adrenaline hydrochloride (p. 1292·2); 4 chewable tablets, chlorphenamine maleate (p. 620·3).
Anaphylaxis.

Anakonidin *Konimex, Indon.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough.

Analab *Biolab, Malaysia; Biolab, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Analcam *CCM, Malaysia; Duopharma, Singapore.*
Tenoxicam (p. 136·2).
Osteoarthritis; rheumatoid arthritis; musculoskeletal and joint disorders.

Analcid *Terramedic, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Analem *EuroHealth, Philipp.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; sinusitis.

Analept *Faran, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Analerg *Rontag, Arg.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Analergin *Teva, Cz.; Ivax, Rus.†; Teva, Ukr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; pruritus; allergic skin disorders.

Analeric *Vianex (Βιανεξ), Gr.*
Diflunisal (p. 51·3).
Pain; inflammation.

Analfin *Tecnofarma, Mex.*
⊗Morphine sulfate (p. 92·3).
Pain.

Analgen
Note: this name may be used for preparations of different composition.
ANH, Thai.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); thymol (p. 1772·2).
Musculoskeletal and joint pain.

Liomont, Mex.
Naproxen (p. 98·2).
Inflammation; pain.

Aventis, S.Afr.†
Tablets: Aspirin (p. 22·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain; fever.

Analgen Forte *Liomont, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Inflammation; pain.

Analgesia Creme *Rugby, USA.*
Trolamine salicylate (p. 141·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Analgesic Balm
Note: this name may be used for preparations of different composition.
Watkins, Canad.†; Geritrex, USA; Goldline, USA; Major, USA; URL, USA.
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Muscle, joint, and soft-tissue pain; neuralgia.

GPO, Thai.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eugenol (p. 2501·2); eucalyptus oil (p. 2501·2).
Muscle and joint pain.

Analgesic Cream *Pharmascience, Canad.*
Trolamine salicylate (p. 141·2).

Analgesic Creme *Major, USA.*
Trolamine salicylate (p. 141·2).

Analgesic and Muscle Relaxant Caplets *Teva, Canad.*
Ibuprofen (p. 68·2); methocarbamol (p. 2025·3).
Pain; skeletal muscle spasm.

Analgesic Sport *Kinesys, Canad.†*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).

Analgesic/Calmative *Sandoz, Austral.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain.

Analgesico Dental *Hofmann, Chile.*
Eugenol (p. 2501·2).
Toothache.

Analgesil *Kinder, Braz.†*
Dipyrone (p. 53·3).
Pain.

Analgesin *Teuto, Braz.*
Aspirin (p. 22·2).
Fever; inflammation; pain.

Analget *Polfa Grodzisk, Pol.†*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Fever; pain.

Analgex Sap *Recalcine, Chile.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Analgil *Azevedos, Port.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint disorders.

Analgilasa *Faes, Spain.*
Tablets: Caffeine (p. 1203·3); codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Analgin
Note: this name may be used for preparations of different composition.
Medphano, Ger.; Indian Drugs, India; Armavir, Rus.; Dalkhimfarm, Rus.; Pharmachim, Rus.; Samson-Med, Rus.; Tatkhimfarm, Rus.
Dipyrone (p. 53·3).
Fever; pain.

BB, Cz.
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Smooth muscle spasm.

Analgin Akut *Medphano, Ger.*
Ibuprofen (p. 68·2).
Pain; fever.

Analgin C-R *EMS, Braz.*
Green tablets, dipyrone (p. 53·3); chlorphenamine maleate (p. 620·3); orange tablets, vitamin C (p. 2110·3).
Cold and influenza symptoms.

Analgina *Lafedar, Arg.*
Dipyrone (p. 53·3).
Fever; pain.

Analgin-Chinin *Sopharma, Rus.*
Dipyrone (p. 53·3); quinine hydrochloride (p. 665·2).
Pain; fever.

Analgine *Pharmacobel, Belg.*
Dipyrone (p. 53·3).
Pain; fever.

Analgiplus *Faes, Spain.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Analgisen *TKS, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Analgol *Profarm, Pol.*
Camphor (p. 2466·2); juniper oil (p. 2537·2); menthol (p. 2553·2); pine oil (p. 2591·1); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain; neuralgia; catarrh.

Analgolan *Profarm, Pol.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); pine oil (p. 2591·1); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain; neuralgia.

Analipin *Intermed, Gr.*
Pravastatin sodium (p. 1473·1).

Analiv *Systopic, India.*
Injections; tablets: Ornithine aspartate (p. 2085·2).

Systopic, India.
Tablets: ⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Analmin *Flamingo, Philipp.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Analmorph *Gray, Arg.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Analog RVHB *Scientific Hospital Supplies, UK.*
Food for special diets.
Homocystinuria; hypermethioninaemia.

Analpan *CCM, Malaysia; Duopharma, Singapore.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Analphen *Randall, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Analpram E *Sebela, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).

Analpram-HC *Sebela, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Analsik *Sanbe, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Analspec *Metiska, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Anamai *TNP, Thai.*
21 Tablets, norethisterone (p. 2294·2); mestranol (p. 2291·1); 7 tablets, inert.
Combined oral contraceptive.

AnaMantle HC *Kenwood, USA.†*
⊗Hydrocortisone acetate (p. 1640·1); lidocaine hydrochloride (p. 1988·2).

Anamataz *Teva, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anamika *Meridian, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Anamix *Nutricia, Cz.; Nutricia, Ital.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Anamix PKU *Nutricia, Fr.; SHS, Irl.*
Food for special diets.
Phenylketonuria.

Anamol *Bliss, India.*
Paracetamol (p. 115·1).
Pain; fever.

Anamorph *Fawns & McAllan, Austral.*
⊗Morphine sulfate (p. 92·3).
Pain.

Ananase *Rottapharm, Ital.; Delta, Port.; Vargas, Venez.*
⊗Bromelains (p. 2460·3).
Soft-tissue inflammation and oedema.

Ananase Forte *Sanofi-Aventis, Chile.*
⊗Bromelains (p. 2460·3).
Inflammation; episiotomy.

Anandron *Sanofi-Aventis, Austral.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Port.*
Nilutamide (p. 836·2).
Prostatic cancer.

Anangor *Biosintetica, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ananty *Plusandex, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Anapen
Note: this name may be used for preparations of different composition.
Link, Austral.; Lincoln Medical, Austria; Lincoln, Canad.; Lincoln, Cz.; Bioprojet, Fr.; Beckmann, Ger.; Allertec, Gr.; Lincoln, Hung.; Lincoln Medical, Irl.; Lincoln Medical, Neth.; Link, NZ; Lincoln Medical, Pol.; Lincoln Medical, Port.; Lincoln, Singapore; Nigaard, Swed.; AllergyCare, Switz.; Allergy Therapeutics, UK.
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Anapenil *Grossman, Mex.*
Injection: Clemizole penicillin (p. 269·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Grossman, Mex.
Oral solution; tablets: Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Anaphase *Ducray, Fr.*
Tocoferil nicotinate (p. 1516·1); ruscus (p. 2463·1); vitamin B substances (p. 2102·3).
Hair disorders.

Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Mediform Ducray, Venez.
Tocoferil nicotinate (p. 1516·1); vitamin B substances (p. 2102·3).
Hair disorders.

Anaplas *Intermed, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Anaplex DM *ECR, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Anaplex HD *ECR, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Coughs and cold symptoms.

Anapolon *Abdi, Turk.*
⊗Oxymetholone (p. 2298·3).
Anaemias.

Anapran *Polfa Pabianice, Pol.*
Naproxen sodium (p. 98·2).
Fever; inflammation; pain.

Anapres *Lemery, Mex.†*
Prazosin (p. 1473·3).
Hypertension.

Anaprex *Noventis, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anapril *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Anaprilin *Biosintez, Rus.; Valenta, Rus.*
⊗Propranolol (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; tremor; migraine; alcohol withdrawal syndrome; anxiety; phaeochromocytoma; hyperthyroidism.

Anaproct *Ind-Swift, India.*
Capsules: Liquorice (p. 1853·2).

Ind-Swift, India.
Ointment: ⊗Allantoin (p. 1693·1); hydrocortisone acetate (p. 1640·1); lidocaine (p. 1988·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anaprol *Provit, Mex.†*
Dipyrone (p. 53·3).
Pain; fever; inflammation.

Anaprolina *Andromaco, Chile.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis.

Anaprotab *Sanli, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Anaprox *Roche, Austral.; Roche, Canad.; Minerva (Μινερβα), Gr.; Roche, USA.*
Naproxen sodium (p. 98·2).
Pain; inflammation; gout; musculoskeletal, joint, and peri-articular disorders.

Anapsique *Psicofarma, Mex.*
Amitriptyline hydrochloride (p. 401·1).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; insomnia; smoking withdrawal; nocturnal enuresis; bulimia; pain.

Anapsyl *Novag, Mex.†*
Naproxen sodium (p. 98·2).
Inflammation; musculoskeletal and joint disorders; pain.

Anaptivan *Help, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Anapyon *DM, Braz.*
Tyrothricin (p. 384·1); chlorophyll (p. 2178·3); tannic acid (p. 2625·2).
Mouth and throat infections.

Anapyrol *Maypo, Mex.†*
Dipyrone (p. 53·3).

Ana-Q *Ariston, Arg.*
Tramadol hydrochloride (p. 139·2).
Pain.

Anara *Chinoin, Mex.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Anarex *CCM, Malaysia; Beacons, Singapore.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle spasm and pain; dysmenorrhoea; tension headache.

Anargil *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Thai.*
⊗Danazol (p. 2263·2).
Endometriosis; female infertility; benign breast disorders; precocious puberty; menorrhagia; gynaecomastia; hereditary angioedema.

Anaribes Plus *Farmachimici, Ital.*
Black currant (p. 2458·1); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Anaromat *Actavis, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anartan *Ratiopharm, Pol.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Anartan Comp *Actavis, Denm.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Anartan HCT *Ratiopharm, Pol.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Anarthril *Minerva (Μινερβα), Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Anartrit
Note: this name may be used for preparations of different composition.
Garden House, Arg.
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis.
Hexal, Braz.
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; gout; dysmenorrhoea.

Anascorp *Accredo, USA.*
Scorpion immune Fab (equine) (p. 2418·1).
Scorpion bites.

Anased *Potter's, UK.*
Lupulus (p. 2546·1); Jamaica dogwood (p. 2536·3); wild lettuce (p. 2647·3); passion flower (p. 2584·1); pulsatilla (p. 2600·2).
Pain; tension.

Anaseptil *Farmasa, Braz.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); zinc peroxide (p. 1774·3).
Bacterial skin infections.

Anaseran *Medhaus, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Anasic *Polipharm, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Anasilpiel *Euroexim, Spain.†*
⊗Neomycin undecenoate (p. 330·1); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Anaskebir *Aspen, Arg.*
⊗Anastrozole (p. 742·1).

Anasma *GSK, Spain.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Anasmol *Roemmers Rowe, Venez.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Anasolde *Gedeon Richter, Cz.†*
⊗Anastrozole (p. 742·1).

Anaspas *Khandelwal, India.*
Camylofin hydrochloride (p. 2467·1); diclofenac (p. 48·3) or diclofenac potassium (p. 48·3).
Smooth muscle spasm and pain.

Anaspaz *Ascher, USA.†*
Hyoscyamine sulfate (p. 1848·1).
Smooth muscle spasm.

Anassa *TO-Chemicals, Thai.*
Aspirin (p. 22·2).
Inflammation; pain; fever.

Anastar *Ardez, Cz.*
⊗Anastrozole (p. 742·1).
The name Anastar has been used in some countries for a preparation of prasterone.
Breast cancer.

Anastarrow *Arrow, Irl.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastase *Motima, Fr.*
Phaseolus vulgaris (p. 2587·3); cyprus; hamamelis (p. 2523·3); rorippa nasturtium-aquaticum; lemon (p. 2542·3); pineapple.

Anastelb *Pharmacodane, Denm.; Pharmacodane, Swed.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anasten Plus *Errekappa, Ital.*
Arginine (p. 2049·1); magnesium (p. 1786·3); potassium (p. 1793·1); creatine (p. 2488·3); levocarnitine (p. 2053·2); ubidecarenone (p. 2637·1); vitamin C (p. 2110·3).
Nutritional supplement.

Anastera *Tuteur, Rus.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anasterol *Terapeutico, Ital.*
Cyclanthera pedata; lespedeza capitata; oryzanol (p. 2578·1); vitamins.
Hypercholesterolaemia.

Anastim
Note: this name may be used for preparations of different composition.
Silesia, Chile; Medifarm Ducray, Venez.
Butcher's broom (p. 2463·1); piroctone olamine (p. 1716·3); tocoferil nicotinate (p. 1516·1); biotin (p. 2052·2).
Hair disorders; alopecia.
Pierre Fabre Dermo-Cosmetique, Arg.
RTH extract; α-pinene (p. 2591·3); saw palmetto (p. 2363·3); crotamiton (p. 1699·2); enoxolone (p. 54·2).
Scalp disorders.

Anastol *Remedina, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Anastrad *Stada, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastralan *ICN, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastraze *Sandoz, Arg.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastro *CellPharm, Ger.*
⊗Anastrozole (p. 742·1).
Breast cancer.

AnastroGen *Synthon, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastrogen *Biogen, Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastrol *Aspen, Austral.; Perrigo, Israel.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastrolan *Lannacher, Austria.*
⊗Anastrozole (p. 742·1).
Breast cancer.

AnastroLek *Sandoz, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastromin *Cancernova, Ger.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anastrose *Taro, Israel.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anatac *Arafarma, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Anaten *Eurofarma, Braz.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Anatensol *Piramal, India; BMS, Neth.; BMS, Port.*
Fluphenazine decanoate (p. 1075·1).
Psychoses; mania; agitation; schizophrenia; anxiety.
BMS, Indon.†; BMS, NZ·
Fluphenazine hydrochloride (p. 1075·1).
Psychoses.

Anatera *Alcon, Irl.; Alcon, Norw.*
Fluorescein sodium (p. 2506·2).
Diagnostic aid in eye examinations.

Anatetall *Novartis Vaccines, Ital.; Novartis Vaccines, Philipp.; Novartis Vaccines, Thai.; Berk, Turk.†*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Anatoxal Di Te Berna *Faran, Gr.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Anatoxal Te Di *Berna, Spain.†*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation of children and adults.

Anatoxal Di Te Per *Faran, Gr.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Anatoxal Tedi *Crucell, Spain.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Anatoxal-Te-Berna *Faran, Gr.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Anatram *Hiral, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Anatram-P *Hiral, India.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Anatrast *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Anatyl
Note: this name may be used for preparations of different composition.
Medizone, India.
Simeticone (p. 1886·2); magaldrate (p. 1856·1).
Sanval, Braz.
Paracetamol (p. 115·1).
Fever; pain.

Anatyl-D *Medizone, India.*
Simeticone (p. 1886·2); magaldrate (p. 1856·1); domperidone (p. 1838·1).

Anauran *Zambon, Ital.; Zambon, Rus.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
External ear disorders; infected ear disorders.

Anaus *Beta, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Anausin *Meda, Fr.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Anavan *Fuji, Jpn.*
Diclofenac sodium (p. 48·3).
Pain; fever; inflammation.

Anavenol *Zentiva, Cz.; Zentiva, Pol.†; Zentiva, Rus.*
Dihydroergocristine mesilate (p. 390·1); esculoside (p. 2431·2); rutoside (p. 2505·3).
Venous insufficiency; thrombophlebitis; leg ulcers; intermittent claudication; cerebrovascular disorders; migraine.

Anavit *Nufarindo, Indon.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin D (p. 2112·3).
Nutritional supplement.

Anavix *Demo, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Anawin *Neon, India.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Anax
Note: this name may be used for preparations of different composition.
Cachet, India; Millimed, Thai.†
Alprazolam (p. 1035·2).
Anxiety; panic disorder; mixed anxiety depressive states.

Anaxéryl *Bailly, Fr.*
Dithranol (p. 1701·2); ichthammol (p. 1705·3); salicylic acid (p. 1719·1); resorcinol (p. 1718·3); peru balsam (p. 2587·1).
Psoriasis.

Anaya *Heaton, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anazo *Medicine Products, Thai.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain; dysuria.

Anazol *Avansor, Fin.*
⊗Anastrozole (p. 742·1).
Breast cancer.

ANB 100 Complex *ANB, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; dietary supplement in pregnancy and lactation.

Anbacim *Sanbe, Indon.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Anbesol
Note: this name may be used for preparations of different composition.
SSL, Irl.; SA Druggists SelfMed, S.Afr.†; Alliance, UK.
Lidocaine hydrochloride (p. 1988·2); chlorocresol (p. 1748·1); cetylpyridinium chloride (p. 1743·1).
Denture irritation; mouth ulcers; teething; aphthous stomatitis; cold sores; sore gums.
Paladin, Canad.; Wyeth Consumer, Chile.†
Benzocaine (p. 1980·2).
Mouth pain; minor skin abrasions.
Wyeth Consumer, USA.
Topical gel: Benzocaine (p. 1980·2); phenol (p. 1763·3).
Oral lesions.
Wyeth Consumer, USA.
Topical liquid: Benzocaine (p. 1980·2); phenol (p. 1763·3); menthol (p. 2553·2); camphor (p. 2466·2); povidone-iodine (p. 1767·1).
Mouth and throat disorders.

Anbesol Baby *Paladin, Canad.*
Benzocaine (p. 1980·2).
Teething.

Anbesol Cold Sore Therapy *Wyeth Consumer, USA.*
Benzocaine (p. 1980·2); allantoin (p. 1693·1); camphor (p. 2466·2).
Herpes labialis.

Anbesol Extra Strength *Paladin, Canad.*
Benzocaine (p. 1980·2).
Mouth pain.

Anbesol Jr *Wyeth Consumer, USA.*
Benzocaine (p. 1980·2).

Anbicyn *China Chem & Pharma, Philipp.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.
China Chem & Pharma, Thai.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Anbifen *ANB, Thai.†*
Ibuprofen (p. 68·2).
Pain; fever.

Anbikan *ANB, Thai.†*
Kanamycin (p. 314·3).
Gram-negative bacterial infections.

Anbikin *ANB, Thai.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Anbin *Dem, Turk.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Anbinex *Grifols, Arg.; Grifols, Cz.; Grifols, Ger.; Grifols, Israel; Grifols, Ital.; Grifols, Port.; Grifols, Singapore; Grifols, Spain.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency; thromboembolic disorders.

Anbiolid *Meprofarm, Indon.*
Roxithromycin (p. 356·2).
Bacterial infections.

Anbiotop *Andromaco, Chile.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial skin infections.

Anbixian *United Lab, China.*
Ampicillin (p. 218·2).
Bacterial infections.

Anbrol *Adley, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Anbrol-A *Adley, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Anbutol *Psyco Remedies, India.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Ancamin *PP Lab, Thai.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); chlorphenamine maleate (p. 620·3).
Pruritus; skin irritation; insect bites.

Ancaron *Sanofi-Aventis, Jpn.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Ance *Zee, India.*
Diacerein (p. 45·3).
Osteoarthritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ancea *Unicure, Philipp.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Combined oral contraceptive; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Ancef
Note: this name may be used for preparations of different composition.
Norma (Νορμα), Gr.
Dihydroergocristine mesilate (p. 390·1).
Mental function impairment in the elderly.

Ancefa *Meprofarm, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Ancet *C & M, USA.*
Skin cleanser.

Ancetev *Teva, Mex.†*
Cefalexin (p. 234·1).
Bacterial infections.

Anchang *Zheng An, China.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Anchocalm *Integris, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Anchusan *Tsumura, Jpn.*
Cinnamon (p. 2479·2); corydalis tuber; oyster shell; fennel (p. 2503·2); liquorice (p. 1853·2); amomum seed; alpinia officinarum rhizome.
Traditional Kampo medicine.

Ancid
Note: this name may be used for preparations of different composition.
Duckbill, India.
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1).
Hexal, Ger.†
Hydrotalcite (p. 1845·2).
Gastric hyperacidity; heartburn; peptic ulcer.

Ancine *Arlex, Mex.†*
Clindamycin (p. 269·3).
Bacterial infections.

Ancivin *Padro, Spain.†*
Famciclovir (p. 979·1).
Herpesvirus infections.

Ancla *Meprofarm, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Anclomax *Blausiegel, Braz.*
Aciclovir (p. 964·1).

Ancloric *Vitapan, Braz.*
⊗Amiloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Anco *Sandoz, Ger.†*
Ibuprofen (p. 68·2).
Inflammation; musculoskeletal and joint disorders; pain.

Ancob *Ankom, India.*
Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Ancob Plus *Ankom, India.*
Bitamin B_6 (p. 2105·3).

Ancobon *Invida, Hong Kong; ICN, USA.*
Flucytosine (p. 581·1).
Candidiasis; cryptococcosis.

Ancolin *DHA, Singapore.*
⊗Ephedrine (p. 1663·1); guaifenesin (p. 1666·2).
Cough.

Anconevron *Pharmanik (Φαρμανικ), Gr.*
Bromazepam (p. 1041·2).
Anxiety disorders.

Ancopir *Grossmann, Switz.*
Vitamin B substances (p. 2102·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Neuritis; neuralgia; sciatica; lumbago; vitamin B deficiency; alcoholism; adjuvant in radiation therapy.

Ancoron *Libbs, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Ancotil *Valeant, Arg.†; Valeant, Austral.; Meda, Austria; Meda, Denm.; Meda, Fr.; Meda, Ger.; IFET (ΙΦΕΤ), Gr.; Inovail, Hong Kong†; Meda, Irl.; Valeant, Ital.; Meda, Neth.; ICN, NZ†; ICN, Pol.; Valeant, Singapore†; Meda, Swed.; Meda, Switz.; ICN, UK.*
Flucytosine (p. 581·1).
Fungal infections.

Ancotyl *ICN, Rus.*
Flucytosine (p. 581·1).
Fungal infections.

Ancozan *Sandoz, Denm.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; left-ventricular dysfunction.

Andalpha *Actavis, Indon.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Andante
Note: this name may be used for preparations of different composition.
Gedeon Richter, Rus.; Gedeon Richter, Ukr.
Zaleplon (p. 1114·3).
Sleep disorders.

Sanovel, Turk.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Eisai, Ger.†
Bunazosin hydrochloride (p. 1329·3).
Hypertension.

Andantol *Ache, Braz.; Transforma, Indon.; Sanfer, Mex.*
Isothipendyl hydrochloride (p. 631·2).
Burns; skin irritation; allergic skin disorders.

Andantol Jalea *Zuoz, Venez.*
Camphor (p. 2466·2); menthol (p. 2553·2); chamomile (p. 2474·1); arnica (p. 2447·2); calendula (p. 2465·2); aloe vera (p. 1693·2).
Pruritus; insect bites and stings; burns; sunburn.

Andapsin *Orion, Swed.*
Sucralfate (p. 1889·1).
Gastrointestinal haemorrhage; peptic ulcer.

Andaxin *Egis, Hung.†*
Meprobamate (p. 1083·3).
Alcoholism; anxiety disorders; spasticity.

Andazol *Biofarma, Turk.*
Albendazole (p. 149·1).
Hydatid disease; strongyloidiasis.

Andelux *Novartis, Braz.*
Cyproterone acetate (p. 2261·2).

Andep *Medikon, Indon.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Andepin *Synteza, Pol.*
Fluoxetine (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Andever *Gedeon Richter, Hung.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis.

Andial *Citadel, India.*
Loperamide (p. 1854·2).
Diarrhoea.

Andikap *Supra Ferbindo, Indon.†*
Activated attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Andiogan *Interbat, Philipp.*
Domperidone (p. 1838·1).
Dyspepsia; nausea; vomiting.

Andipal *North Star, Rus.*
Bendazol hydrochloride (p. 2454·3); dipyrone (p. 53·3); papaverine hydrochloride (p. 2362·3); phenobarbital (p. 535·2).
Smooth muscle spasm and pain.

Andissa *Sanofi-Aventis, Port.*
Glimepiride (p. 473·2).
Diabetes mellitus.

A-N-Dix *Provit, Mex.†*
Nalidixic acid (p. 328·3).
Bacterial infections of the urinary tract.

Andocit *Medicine Products, Thai.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Andofin *Gerot, Hung.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Andolba *Eurofarma, Braz.*
Benzocaine (p. 1980·2); benzethonium chloride (p. 1738·1); menthol (p. 2553·2); hydroxyquinoline benzoate (p. 2530·1).
Gynaecological disorders.

Andolex *Meda, Denm.; iNova, S.Afr.; Meda, Swed.*
Benzydamine hydrochloride (p. 29·2).
Painful inflammation of the mouth and throat.

Andolex-C *iNova, S.Afr.*
Lozenges; oral gel: Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Inflammation and infection of the mouth and throat.

iNova, S.Afr.
Mouthwash: Benzydamine hydrochloride (p. 29·2); chlorhexidine gluconate (p. 1743·3).
Inflammation and infection of the mouth and throat.

Andolor
Note: this name may be used for preparations of different composition.
Biofarma, Turk.
Dipyrone (p. 53·3).
Fever; pain.

Krewel, Ger.†
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Andonex *Meprofarm, Indon.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); ipecacuanha (p. 1667·2).
Cough.

Andoprim *Andromaco, Mex.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Andosept *Aspen, S.Afr.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Andosept-Co *Aspen, S.Afr.*
Benzydamine hydrochloride (p. 29·2); chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Andox *Atlantis, Mex.†*
Paracetamol (p. 115·1).
Pain; fever.

Andractim *Besins, Belg.; Besins, Fr.; Besins, Singapore.*
⊗Androstanolone (p. 2255·3).
Male hypogonadism; gynaecomastia; lichen sclerosus.

Andraxan *Medicom, Cz.†; PH&T, Gr.; Mayne, Thai.; Onko, Turk.*
Flutamide (p. 798·2).
Prostatic cancer.

Andre *Intas, India.*
⊗Boric acid (p. 2459·3); chlorphenamine maleate (p. 620·3); sodium chloride (p. 1795·1); zinc sulfate (p. 2126·2); chlorobutanol (p. 1747·2); naphazoline hydrochloride (p. 1669·3).
Conjunctivitis.

Andre Carpine *Intas, India.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Andreafol *Andreabal, Switz.*
Folic acid (p. 2063·1).
Neural tube defect prophylaxis.

Andreamag *Andreabal, Switz.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency.

Andreavit *Andreabal, Switz.*
Vitamins; minerals; trace elements.
Dietary supplement.

Andrecin *Intas, India.*
Chloramphenicol (p. 257·1).
Eye infections.

Andregen *Andre, India.†*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Andre-I-Kul *Andre, India.†*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline hydrochloride (p. 1669·3); menthol (p. 2553·2); camphor (p. 2466·2).
Eye irritation.

Andremide *Intas, India.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Andrews *GSK Consumer, Irl.; GSK Consumer, UK.*
Citric acid (p. 2480·3); magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1).
Constipation; dyspepsia.

Andrews Antacid
Note: this name may be used for preparations of different composition.
GSK Consumer, Irl.†; GSK Consumer, UK.
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Dyspepsia; gastric hyperacidity; heartburn.

SmithKline Beecham, Gr.
Sodium bicarbonate (p. 1781·1); magnesium carbonate (p. 1856·2).

Andrews Tums *Aspen, Austral.*
Calcium carbonate (p. 1824·3).
Heartburn; dyspepsia.

Andrin *Casasco, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Andrioderma *Andromaco, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Andriodermol *Uniao Quimica, Braz.*
Topical powder: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); calcium propionate (p. 592·3); hexylresorcinol (p. 1755·1).
Fungal skin infections.

Uniao Quimica, Braz.
Topical liquid: Undecenoic acid (p. 596·3); sodium undecenoate (p. 596·3); propionic acid (p. 592·3); sodium propionate (p. 593·1); hexylresorcinol (p. 1755·1).
Fungal skin infections.

Andriol *Schering-Plough, Austral.; Organon, Austria; Merck, Canad.; MSD, China; Organon, Denm.; MSD, Ger.; MSD, Hong Kong; Organon, Hung.; Organon, India; Schering-Plough, Indon.; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Philipp.; Organon, Port.; Organon, Rus.; MSD, Singapore; MSD, Switz.; MSD, Thai.; Organon, Ukr.; Organon, Venez.*
⊗Testosterone undecylate (p. 2305·2).
Testosterone deficiency; male hypogonadism; female gender transformation; osteoporosis; male infertility; hypopituitarism; masculinisation in transexuals.

Androbas *Stragen, Switz.†*
Cyproterone acetate (p. 2261·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; male sexual deviation; prostatic cancer.

Androbloc *Lannacher, Austria.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Androcal *Apogepha, Ger.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Androcortil *Teuto, Braz.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Androcur *Gobbi, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Schering, Braz.; Bayer, Canad.; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ†; Bayer, Philipp.; Bayer Schering, Pol.; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Schering, Venez.*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; sexual deviation and hypersexuality in males; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; precocious puberty.

Androderm *Hospira, Austral.; Watson, Canad.; IFET (ΙΦΕΤ), Gr.; Hospira, NZ; Watson, USA.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency.

Andro-Diane *Bayer, Austria.*
Cyproterone acetate (p. 2261·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Androfarm *Farmak, Ukr.*
Cyproterone (p. 2261·2).
Prostatic cancer; sexual deviation in men; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Andro-Feme *Lawley, Austral.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency in women.

Androfil *Cipla, India.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Androfin *GL Pharma, Austria; Lannacher, Cz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Androfloxin *Teuto, Braz.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

AndroGel *Besins, Belg.; Abbott, Canad.; Besins, Cz.; Besins, Fr.; Besins, Hong Kong; Besins, Hung.; Besins, Irl.; Besins, Israel; Solvay, Ital.; Besins, Neth.; Besins, Port.; Besins, Rus.; Besins, Singapore; Besins, Ukr.; AbbVie, USA; Biopas, Venez.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency; male hypogonadism.

Andrographis Complex *Mediherb, Austral.*
Andrographis (p. 2443·2); echinacea (p. 2498·1); ocimum sanctum.
Respiratory-tract disorders; liver disorders; tonic.

Andrographis Compound *Phytomedicine, Austral.*
Andrographis (p. 2443·2); echinacea purpurea (p. 2498·1); skullcap (p. 2617·1).
Cold symptoms.

Android *Valeant, USA.*
⊗Methyltestosterone (p. 2291·3).
Cryptorchidism; male hypogonadism; breast cancer.

Androlic *British Dispensary, Thai.*
⊗Oxymetholone (p. 2298·3).
Cachexia; anaemias; anabolic.

Androlip *Teuto, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Androlistica *Holistica, Fr.*
Cucurbita oil (p. 2489·2); palm-nut oil (p. 2200·2); onion (p. 2575·2); omega-3 marine triglycerides (p. 1460·3); borage oil (p. 2459·2); yam extract (p. 2648·1); ulva lactuca.
Male menopause.

Holistica, Singapore.
⊗Fish gelatin (p. 1154·1); cucurbita oil (p. 2489·2); palm-nut oil (p. 2200·2); onion (p. 2575·2); fish oil (p. 1460·1); borage oil (p. 2459·2); yam (p. 2648·1); ulva lactuca; carotene (p. 2051·1); vitamin E (p. 2119·1).
Health supplement for men.

Androlon *Meprofarm, Indon.†*
⊗Mesterolone (p. 2291·1).
Androgen deficiency; male infertility.

Androlone *Beta, Arg.*
⊗Testosterone (p. 2305·1).
Hypogonadism.

Androlone-D *Keene, USA.*
⊗Nandrolone decanoate (p. 2293·1).
Anaemia in renal disease.

Andromet *Matxin, Singapore.*
⊗Chlorophytum borivilianum; anacyclus pyrethrum; tribulus terrestris (p. 2633·3); hygrophila auriculata; acacia arabica.
Health supplement for men.

Androneo *Neo Quimica, Braz.*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; hypersexuality in males; androgen-dependent disorders in females.

Andropatch *IFET (ΙΦΕΤ), Gr.; GSK, Irl.†; GSK, UK.†*
⊗Testosterone (p. 2305·1).
Testosterone deficiency; hypogonadism.

Andropel *Fortbenton, Arg.*
Finasteride (p. 2358·3).
Alopecia.

Andropower *Plethico, Ukr.*
⊗Dolichos pruriens; asparagus (p. 2450·2); withania somnifera; anacyclus pyrethrum; tribulus terrestris (p. 2633·3); hygrophilia spinosa.
Tonic for men.

Andros *Biomedis, Philipp.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Androskat *Nycomed, Austria; Takeda, Neth.*
Papaverine hydrochloride (p. 2362·3); phentolamine mesilate (p. 1468·3).
Erectile dysfunction.

Androstat
Note: this name may be used for preparations of different composition.
Bioprofarma, Arg.
Cyproterone acetate (p. 2261·2).
Prostatic cancer.

Orion, Irl.†
Flutamide (p. 798·2).
Prostatic cancer.

Androsten *Herbarium, Braz.*
⊗Tribulus terrestris (p. 2633·3).

Androsteron *Bergamo, Braz.*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in females; sexual deviation in males.

Androtag *Rontag, Arg.*
⊗Testosterone (p. 2305·1).
Male hypogonadism.

Androtardyl *Bayer, Fr.*
⊗Testosterone enantate (p. 2305·1).
Male hypogonadism.

Androtin *Andromaco, Mex.†*
Famotidine (p. 1842·1).
Dyspepsia.

Androtop *Besins, Ger.; Kade, Ger.; Besins, Pol.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency.

Androvit *Chemech, India.*
Calcium (p. 1783·1); protein; selenious acid (p. 2087·1); vitamin B_6 (p. 2105·3); colecalciferol (p. 2113·1); vitamin E acetate (p. 2119·2).

Androvite *Optimox, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Androxicam *Andromaco, Mex.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint and peri-articular disorders; pain.

Androxon *Schering-Plough, Braz.; Organon, Israel; Adcock Ingram, S.Afr.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Androxy *Upsher-Smith, USA.*
⊗Fluoxymesterone (p. 2278·1).
Hypogonadism; delayed puberty; breast cancer.

Androxyl *CCM, Malaysia; Duopharma, Singapore.*
Cefadroxil (p. 233·2).
Bacterial infections.

Androz *Torrent, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Andursil *Novartis, Braz.; Welti, Switz.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence; gastro-oesophageal reflux; gastritis; peptic ulcer.

Andysan *Sanify, India.*
⊗Nandrolone decanoate (p. 2293·1).
Osteoporosis; breast cancer; anaemias; anabolic.

Anebol *Gador, Arg.; Pasteur, Chile.*
⊗Anastrozole (p. 742·1).
Breast cancer.

AneCream *Focus, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Anectine *GSK, Irl.; GSK, Mex.†; GSK, Spain; GSK, UK; Glaxo Wellcome, USA.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Anefol *Laboratorios Chile, Chile.*
Propofol (p. 1909·3).
General anaesthesia; sedation.

Anekain *Pliva, Rus.†*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Anekcin *Harson, Philipp.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Aneket *Neon, India.*
Ketamine (p. 1905·1).
Induction of anaesthesia.

Anekron *EMS, Braz.*
Choline citrate (p. 2055·2); betaine hydrochloride (p. 2456·1); methionine (p. 1558·2); adenosine (p. 1291·1); vitamin B_6 (p. 2105·3); sorbitol (p. 2092·1).
Liver disorders.

Anektil *Oboi, Philipp.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Anelat *Ifars, Indon.*
Folic acid (p. 2063·1).
Anaemias; nutritional supplement in pregnancy.

Anemet *Sanofi-Aventis, Ger.†*
Dolasetron mesilate (p. 1837·2).
Nausea and vomiting.

Anemicon Plus *San Marino, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron and folic acid deficiency; anaemia in pregnancy.

Anemidox *Merck, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Vitamin C (p. 2110·3) is included to increase the absorption and availability of iron.
Anaemias.

Merck Serono, Arg.
Folic acid (p. 2063·1); thiamine (p. 2102·3); riboflavin (p. 2104·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1).
Anaemias; vitamin B deficiency.

Anemidox Folico *Merck Serono, Arg.*
Folic acid (p. 2063·1).
Prevention of neural tubes defects; megaloblastic anaemia.

Anemidox Ultra *Merck Serono, Arg.*
Ferrous glycinate chelate (p. 2061·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias; iron, folic acid and vitamin B_{12} supplement.

Anemidox-Ferrum *Merck Serono, Arg.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Anemidox-Solutab *Merck Serono, Arg.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron and folic acid deficiency; vitamin B_{12} deficiency.

Anemifer *Pharma Line, Gr.*
Iron sucrose (p. 2078·1).
Anaemia.

Anepol *Hana, Thai.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Anepro *Neon, Ukr.†*
⊗Metoprolol tartrate (p. 1434·3).
Ischaemic heart disease; myocardial infarction; arrhythmias.

Aneprosil *Verisfield, Gr.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Aneptir *Helm, Port.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Anerex *Carnot, Mex.*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).
Tonic; anaemias.

Anergy *Arika, India.*
Protein.

Anerobia *Pfizer, Philipp.†*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; anaerobic bacterial infections.

Anerobizol *Marck Biosciences, Philipp.*
Metronidazole (p. 936·1).
Protozoal infections.

Anerocid *Ferron, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Anerocin *Aldril, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Anervan *Recip, Swed.*
Ergotamine tartrate (p. 674·1); chlorcyclizine hydrochloride (p. 620·2); caffeine (p. 1203·3).
Migraine.

Recip, Fin.†; Recip, Norw.†
Ergotamine tartrate (p. 674·1); chlorcyclizine hydrochloride (p. 620·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Migraine; cluster headache.

Anerzol *Liferpal, Mex.†*
Astemizole (p. 616·1).

Anesderm *Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Switz.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Anesevo *Biochimico, Braz.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Anesfar *Fahrenheit, Indon.*
Midazolam (p. 1085·1).
Sedative; premedication; induction of anaesthesia.

Anesject *Danpac, Indon.*
Ketamine hydrochloride (p. 1905·1).
Anaesthesia; analgesia in obstetrics.

Anesolin *Neon, India.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Anespas *Rudefsa, Mex.†*
Prifinium bromide (p. 1879·3).
Pain; muscle spasm.

Anespin *Oriental, Philipp.*
Atropine sulfate (p. 1310·2).
Premedication; counteracts muscarinic effects of anticholinesterases; bradycardia; antidote to organophosphates and cholinomimetics.

Anespro *Behrens, Venez.*
Propofol (p. 1909·3).
General anaesthesia.

Anestacon *PolyMedica, USA.*
Lidocaine hydrochloride (p. 1988·2).
Urethral pain.

Anestafoam *Onset, USA.†*
Lidocaine (p. 1988·1).
Local anaesthesia.

Anestalcon *Alcon, Arg.; Alcon, Braz.; Alcon, Chile.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

Anestefarin *Farline, Spain.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Anesteloc *Adamed, Pol.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia; peptic ulcer; Zollinger-Ellison syndrome.

Anestesia Local Braun S/A *Braun, Spain.*
Cinchocaine hydrochloride (p. 1983·2); procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Anestesia Topi Braun C/A *Braun, Spain.†*
Tetracaine hydrochloride (p. 1996·3).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Anestesia Topi Braun S/A *Braun, Spain.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Anestesico *Allergan, Braz.; Alcon Cusi, Spain.*
Tetracaine hydrochloride (p. 1996·3).
Naphazoline hydrochloride (p. 1669·3) or phenylephrine hydrochloride (p. 1672·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Anestesico Doble *Alcon Cusi, Spain.*
Oxybuprocaine hydrochloride (p. 1993·2); tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Anesthal *Jagsonpal, India.*
Thiopental sodium (p. 1915·1).
General anaesthesia; status epilepticus.

Anestocil *Edol, Port.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Anestol *Sandoz, Turk.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Anesvan *Chi Sheng, Thai.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Anethaine *Sanofi-Aventis, S.Afr.; Torbet Laboratories, UK.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Aneubion *Universal, Hong Kong.†*
Thiamine (p. 2102·3).

Aneudox-12 *P & B, India.*
Injection: Dexpanthenol (p. 2582·2); nicotinamide (p. 2083·1); vitamin B_1

(p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3).

P & B, India.
Tablets: Glutamic acid (p. 2070·2); nicotinamide (p. 2083·1); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Aneurol
Note: this name may be used for preparations of different composition.
Lacer, Spain.
Diazepam (p. 1063·2).
Contains pyridoxine hydrochloride.
Anxiety; insomnia; epilepsy; skeletal muscle spasm; alcohol withdrawal syndrome.

Anevrasi *Donini, Ital.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); valerian (p. 2640·2).
Insomnia.

Anew Alternative *Avon, Canad.†*
SPF 25 cream: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Anew Rejuvenate *Avon, Canad.*
SPF 25 eye cream: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Avon, Canad.†
SPF 15 cream: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Anew Reversalist *Avon, Canad.*
SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Anew Youth-Awakening *Avon, Canad.*
SPF 15 stick: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Anewway *Hiteck Bio, China.*
Mouse nerve growth factor.
n-Hexane induced peripheral neuropathy.

Anexa *Microsules, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Anexat *Roche, Rus.*
Flumazenil (p. 1551·3).
Reversal of benzodiazepine-induced sedation; benzodiazepine overdosage.

Anexate *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Canad.†; Roche, China; Roche, Cz.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.†; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK.†*
Flumazenil (p. 1551·3).
Benzodiazepine overdosage; reversal of benzodiazepine and ethanol induced sedation.

Anexin *Sanbe, Indon.*
Sertraline hydrochloride (p. 448·1).
Depression.

Anexopen *Coup, Gr.*
Naproxen (p. 98·2).

Anexsia *Mallinckrodt, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Anfadox *Anfarm, Gr.†*
Doxycycline hyclate (p. 288·2).

Anfagladin *Alapis, Gr.; Anfarm, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Anfen Ka Pilin *Lisheng, China.*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Anfer *Anfarm, Gr.*
Nabumetone (p. 97·1).
Inflammatory disorders; pain.

Anfertil *Wyeth, Braz.*
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Anfibol *Drugtech, Chile.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Anfix *Mahakam Beta, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Anflene *Teuto, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; dysmenorrhoea.

Anflu *Sinovac, China.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Anfogen *Richmond, Arg.†*
Liposomal amphotericin B (p. 569·2).
Fungal infections.

Anfokali *Bano, Austria.*
Guajacum (p. 2523·1); cistus canadensis; lobaria pulmonaria (p. 2546·1).
Homoeopathic preparation.

Dronania, Hung.
Guaiacum (p. 2523·1); helianthemum canadense; lobaria pulmonaria (p. 2546·1).
Homoeopathic preparation.

Anfolic *TRB, Arg.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folic acid deficiency; prevention of neural tube defects in pregnancy.

Anfomilan *Proel, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Anforicin B *Cristalia, Braz.*
Amphotericin B (p. 569·2).
Fungal infections.

Anfoterin *Teuto, Braz.*
Tetracycline hydrochloride (p. 373·2); amphotericin B (p. 569·2).
Vaginal infections.

Anfozan *Proel, Gr.*
Etidronate disodium (p. 1182·3).
Osteoporosis.

Anfree *Aristopharma, Hong Kong.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Anxiety; depression.

Anfugine *Blausiegel, Braz.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Trichomoniasis; vaginal candidiasis.

Anfugitarin *Blausiegel, Braz.*
Miconazole nitrate (p. 589·1).
Perianal and vulvovaginal candidiasis.

Anfuhex *Hexpharm, Indon.†*
Ketoconazole (p. 585·3).
Fungal infections.

Ang Ke *Gaoxin, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ang Si *KangNing, China.*
Sodium ferulate.

Ang Te *Hisun, China.*
Tosufloxacin tosilate (p. 381·2).
Bacterial infections.

Angass *Medice, Ger.†*
Bismuth subnitrate (p. 1822·1); bismuth aluminate (p. 1821·3).
Peptic ulcer.

Ange *Aska, Jpn.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Angeel *Heel, Canad.†*
Apis mellifica (p. 2445·2); arnica montana (p. 2447·2); belladonna (p. 2453·3); calcium sulfide crude (p. 1721·3); dulcamara (p. 2497·3); echinacea purpurea (p. 2498·1); phytolacca decandra (p. 2593·2).
Homoeopathic preparation.

Angela *T Man, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Angeliq *Bayer, Arg.; Schering, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, Philipp.; Bayer Schering, Pol.; Berlex, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Bayer, UK; Bayer, Ukr.; Bayer, USA.*
Estradiol (p. 2271·1); drospirenone (p. 2269·1).
Menopausal disorders; osteoporosis.

Angemin *Bayer, Denm.; Bayer, Swed.*
Drospirenone (p. 2269·1); estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Angenovag *Novag, Mex.*
⊗Dequalinium chloride (p. 1749·3); enoxolone (p. 54·2); hydrocortisone acetate (p. 1640·1); tyrothricin (p. 384·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Angettes *BMS, UK.†*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Angeze *Opus, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Anghostan *Biostam (Βιοσταμ), Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Angi Sept Dr Theiss *Naturwaren, Ukr.*
Dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2); anethole (p. 2443·3); peppermint oil (p. 1877·1).
Mouth and throat disorders.

Angi Truw N *Truw, Ger.*
Echinacea ang. (p. 2498·1); chamomilla recutita (p. 2474·1); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Angiben *Amavita, Switz.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2); levomenthol (p. 2553·2).
Mouth and throat disorders.

Angiblock *Alkem, India.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

Angicam, *Blue Cross, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Angicam-Beta *Blue Cross, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Angicam-LT *Blue Cross, India.*
Amlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Angicon *Royal, Chile.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Angicor
Note: this name may be used for preparations of different composition.
Novartis, India.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Sanofi-Aventis, Denm.
Nicorandil (p. 1446·2).
Angina pectoris.

Angidine *Vifor, Switz.†*
Gramicidin (p. 308·3); benzethonium chloride (p. 1738·1); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Angie *Serral, Mex.*
Cyproterone (p. 2261·2); ethinylestradiol (p. 2275·3).

Angiguard *Ind-Swift, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Angil *Sanval, Braz.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Angileptol *Sigma-Tau, Spain.*
Enoxolone (p. 54·2); benzocaine (p. 1980·2); chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disorders.

Angiless *Pharlab, Braz.*
⊗Atenolol (p. 1308·2).

Angilex *Zdorovje, Ukr.*
Hexetidine (p. 1755·1); choline salicylate (p. 39·2); chlorobutanol (p. 1747·2).
Mouth and throat disorders.

Angilo *Nitro Organics, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Angilo-AM *Nitro Organics, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Angilo-H *Nitro Organics, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Angilol *Douglas, NZ; DDSA Pharmaceuticals, UK.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; hyperthyroidism; obstructive cardiomyopathy; tremor; phaeochromocytoma.

Angilos *Talent, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Angilos-H *Talent, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Angimax *YSS, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Angimet
Note: this name may be used for preparations of different composition.
Interhealthcare, Philipp.
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Bergamo, Braz.†
Methyldopa (p. 1431·1).
Hypertension.

Angina MCC *Streuli, Switz.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2).
Mouth and throat disorders.

Angina-Gastreu S R1 *Reckeweg, Ger.*
Apis (p. 2445·2); belladonna (p. 2453·3); calcium iodatum (p. 1658·1); kalium bichromicum (p. 2476·3); marum verum; mercurius sublimatus corrosivus (p. 2555·2); phytolacca (p. 2593·2).
Homoeopathic preparation.

Anginamide *Medgenix, Belg.*
Sulfacetamide sodium (p. 361·1).
Infections of the mouth and throat.

Anginazol *Intermedica, Switz.*
Dichlorobenzyl alcohol (p. 1750·2); cetylpyridinium chloride (p. 1743·1); chlorquinaldol (p. 260·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat infections.

Anginex *Wyeth, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Angin-Heel *Peithner, Hung.*
Hydrargyrum bicyanatum (p. 2555·3); phytolacca americana (p. 2593·2); apis mellifica (p. 2445·2); arnica montana (p. 2447·2); hepar sulfuris (p. 1721·3); solanum dulcamara (p. 2497·3); atropa belladonna (p. 2453·3).
Homoeopathic preparation.

Angin-Heel S *Heel, Cz.*
Hydrargi cyanidum (p. 2555·3); phytolacca decandra (p. 2593·2); apis mellifica (p. 2445·2); arnica montana (p. 2447·2); calcii sulfidum (p. 1721·3); solanum dulcamara (p. 2497·3); belladonna (p. 2453·3).
Homoeopathic preparation.

Anginine *Sigma, Austral.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Anginocum *Novag, Spain.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Anginol
Note: this name may be used for preparations of different composition.
Labima, Belg.
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Anginol-Lidocaine *Labima, Belg.*
Dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Angino-Rub *Eurofarma, Braz.*
Benzydamine hydrochloride (p. 29·2); cineole (p. 2479·1); turpentine oil (p. 2636·3); camphor (p. 2466·2); thymol (p. 1772·2); menthol (p. 2553·2).
Mouth and throat disorders.

Anginotrat *Purissimus, Arg.*
Gentamicin embonate (p. 304·2); sulfadiazine (p. 361·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Anginotricin *Sanval, Braz.*
Neomycin sulfate (p. 330·1); tyrothricin (p. 384·1); benzocaine (p. 1980·2); sodium perborate (p. 1770·1).
Mouth and throat disorders.

Anginova *Confar, Port.*
⊗Dequalinium chloride (p. 1749·3); benzocaine (p. 1980·2); trypsin (p. 2635·2).
Mouth and throat disorders.

Medinova, Switz.
Dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Anginovag *Novag, Spain; Ferrer, Ukr.*
⊗Dequalinium chloride (p. 1749·3); tyrothricin (p. 384·1); enoxolone (p. 54·2); hydrocortisone acetate (p. 1640·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Angin-San *Nycomed, Belg.*
Dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Angio II *Medley, Braz.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Angiobloc *Medic+Aid, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; heart failure; hyperthyroidism; migraine.

Angiocine *Kela, Belg.*
Lidocaine hydrochloride (p. 1988·2); chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disorders.

Angiocis *CIS, Fin.; CIS, Fr.; CIS, Port.; CIS, Spain; Schering, UK.*
Technetium-99m (p. 2228·1) stannous pyrophosphate.
Red blood cell labelling.

Angiodarona *Cazi, Braz.*
Amiodarone (p. 1300·1).
Arrhythmias.

Angiodel *Organon, Turk.*
Bencyclane fumarate (p. 1315·1).
Cerebral and peripheral vascular disorders.

Angiodrop *Densmore, Fr.*
Mallow (p. 2549·2); chamomile (p. 2474·1).
Dry eyes.

Angiodrox *Abbott, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Angiofilina *Fabra, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Angioflux *Aesculapius, Ital.; Farmamos, Rus.*
Sulodexide (p. 1507·3).
Thrombosis prophylaxis.

Angiografin *Bayer, China; Zydus, India.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Angiografina *Bayer, Arg.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Angiolingual *Royal, Chile.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Angiolong
Note: this name may be used for preparations of different composition.
Chiesi, Braz.
Diltiazem hydrochloride (p. 1359·2).
Arrhythmias; angina pectoris; hypertension.

Ethypharm, China.
Isosorbide dinitrate (p. 1412·2).
Prevention and treatment of angina pectoris due to coronary artery disease.

Angiolot *Neo Quimica, Braz.*
Coumarin (p. 2487·2); troxerutin (p. 2505·3).

Angiomax *Bago, Arg.; Sunovion, Canad.; CSL, NZ; Medicines Company, USA.*
Bivalirudin trifluoroacetate (p. 1326·2).
Thromboembolism prophylaxis in patients undergoing percutaneous coronary interventions.

CSL, Austral.; Mastercare, Chile; Medison, Israel.
Bivalirudin (p. 1326·2).
Thromboembolism prophylaxis in patients undergoing percutaneous coronary intervention.

Angionorm
Note: this name may be used for preparations of different composition.
Sydenham, Philipp.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; heart failure; myocardial infarction; hyperthyroidism; migraine.

Farmasan, Ger.†
Dihydroergotamine mesilate (p. 672·2).
Circulation disorders; hypotension; migraine.

Angiopohl *Pisa, Mex.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; heart failure; controlled hypotension; coronary spasm; hypertension during cardiac surgery; uterine relaxant for manual extraction of retained placenta.

Angiopril
Note: this name may be used for preparations of different composition.
Torrent, Rus.
Captopril (p. 1331·2).
Hypertension; heart failure; left ventricular dysfunction following myocardial infarction; diabetic nephropathy.

Angiopril-DU *Torrent, India.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Angioretic *Medarte, Gr.*
Amlodipine besilate (p. 1304·1).

Angiorex Complex *Lampugnani, Ital.*
Rose fruit (p. 2607·1); myrtillus (p. 2566·2); butcher's broom (p. 2463·1); centella (p. 1698·3).
Venous insufficiency.

Angioten *Kalbe, Indon.*
Losartan potassium (p. 1422·2).
Hypertension.

Angioton
Note: this name may be used for preparations of different composition.
GD, Ital.
Cream: Ginkgo biloba (p. 2512·3); centella (p. 1698·3); menthol (p. 2553·2); bioflavonoids (p. 2505·2).
Peripheral vascular disorders.

GD, Ital.
Tablets: Centella (p. 1698·3); myrtillus (p. 2566·2); rutoside (p. 2505·3); vitamins.
Venous disorders.

Angioton H *DHU, Ger.*
⊗Crataegus (p. 2488·1); convallaria majalis (p. 2486·2); adonis vernalis (p. 2431·1); cactus (p. 2473·2); lobelia inflata (p. 2323·2); aether (p. 1900·3).
Homoeopathic preparation.

Angioton S
Note: this name may be used for preparations of different composition.
DHU, Ger.†
⊗Crataegus (p. 2488·1); convallaria majalis (p. 2486·2); adonis vernalis (p. 2431·1); valeriana (p. 2640·2); cactus (p. 2473·2); lobelia inflata (p. 2323·2); aether (p. 1900·3).
Homoeopathic preparation.

Angiotrofin *Armstrong, Mex.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris; anal fissure.

Angioval *Galenica, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Angiovan *Giempi, Venez.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension; heart failure.

Angiovein *Piam, Ital.*
Thioctic acid (p. 2629·1); grape (p. 2521·3); centella (p. 1698·3); aesculus (p. 2431·2); andrographis (p. 2443·2); ginkgo biloba (p. 2512·3); garlic (p. 2510·3); vitamin B substances (p. 2102·3).
Circulatory disorders.

Angiovist *Bayer, Chile.†*
Sodium amidotrizoate (p. 1581·3); meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Angiovit *Altayvitamin, Rus.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Circulatory disorders; hyperhomocysteinaemia.

Angiox *Medicines Company, Austria; Medicines Company, Belg.; Medicines Company, Cz.; Medicines Company, Denm.; Medicines Company, Fin.; Medicines Company, Fr.; Medicines Company, Ger.; Medicines Company, Gr.; Medicines Company, Hung.; Medicines Company, Irl.; Nycomed, Ital.; Medicines Company, Neth.; Medicines Company, Norw.; Medicines Company, Pol.; Medicines Company, Port.; Ferrer, Spain; Medicines Company, Swed.; Medicines Company, UK.*
Bivalirudin (p. 1326·2).
Acute coronary syndromes; thromboembolism prophylaxis in percutaneous coronary intervention.

Medicines Company, Switz.; Nycomed, Ukr.†
Bivalirudin trifluoroacetate (p. 1326·2).
Thrombosis prophylaxis in percutaneous coronary intervention.

Angiozem *Littman, Philipp.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Angiozil *Sotex, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vascular eye disorders; vestibular disorders.

Angipax *Lehning, Fr.*
Apis mellifica (p. 2445·2); belladonna (p. 2453·3); mercurius corrosivus (p. 2555·2); phytolacca decandra (p. 2593·2); anemone pulsatilla (p. 2600·2).
Homoeopathic preparation.

Angipec *Lamsa, Arg.*
Amlodipine besilate (p. 1304·1).

Angipina *Azevedos, Port.*
Nifedipine (p. 1447·2).
Angina pectoris.

Angipress
Note: this name may be used for preparations of different composition.
Biosintetica, Braz.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Angipress CD *Biosintetica, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Angirel *Unison, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; Ménière's disease.

Angisan
Note: this name may be used for preparations of different composition.
Amavita, Switz.
Cetylpyridinium chloride (p. 1743·1); dichlorobenzyl alcohol (p. 1750·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Angisartan *Sel-J, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Angised *GSK, Hong Kong; GSK, India; Aspen, S.Afr.; GSK, Singapore.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; pulmonary oedema.

Angispan-TR *USV, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Angi-Spray
Note: this name may be used for preparations of different composition.
Akromed, S.Afr.†
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction.

Angispray
Note: this name may be used for preparations of different composition.
Merck Medication Familiale, Fr.
Hexetidine (p. 1755·1); propionic acid (p. 592·3); chlorobutanol (p. 1747·2).
Mouth and throat disorders.

Angistad *Stada, Philipp.*
Isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease; angina pectoris; pulmonary hypertension; heart failure.

Angitab *ICI, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Angitak *Boston Healthcare, UK.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Angital *Shchelkovskii, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic eye disorders; ischaemic vestibular disorders.

Angitil *Trinity, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Angitol Plus *Ind-Swift, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Angitrate *Akromed, S.Afr.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Angitrit *Ranbaxy, Thai.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Angizaar *Micro, India; Brown & Burk, Philipp.†; Micro, Singapore; Micro Labs, Ukr.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; stroke prophylaxis; heart failure; myocardial infarction.

Angizaar Plus *Micro Labs, Ukr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Angizaar-AT *Micro, India.*
⊗Losartan potassium (p. 1422·2); atenolol (p. 1308·2).
Hypertension.

Angizaar-H *Micro, India; Brown & Burk, Philipp.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Angizem *Sun, India; Sanofi-Aventis, Ital.; Sun, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Anglix *Novartis, Mex.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Anglopen *Liomont, Mex.†*
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Anglotex *Arlex, Mex.†*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Anglucid *Collins, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Angocin Anti-Infekt N *Repha, Ger.*
Tropaeolum majus (p. 2454·3); horseradish (p. 2526·1).
Urinary-tract infections; respiratory-tract infections.

Angocin Bronchialtropfen *Repha, Ger.*
Marrubium vulgare (p. 1668·3).
Catarrh.

Angoron *Paranova, Denm.; Sanofi-Aventis, Gr.; BB, Ital.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; Wolff-Parkinson-White syndrome.

Angoten *Microsules, Arg.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; heart failure; angina pectoris.

Angrip *Giempi, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms.

Angrip Noche *Giempi, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Angsobide *CCM, Malaysia; Duopharma, Singapore.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Angstrom Corpo *Chefaro, Ital.*
Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Angstrom Viso *Chefaro, Ital.*
Cream: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); vitamin E acetate (p. 2119·2); dimeticone (p. 2209·3); betacarotene (p. 2051·1); allantoin (p. 1693·1); sodium pidolate (p. 1720·3); triclosan (p. 1773·2).
Sunscreen; barrier preparation.

Chefaro, Ital.
Stick: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); vitamin E acetate (p. 2119·2); betacarotene (p. 2051·1).
Sunscreen; barrier preparation.

Angtaifen *Angtai, China.*
Nabumetone (p. 97·1).
Rheumatoid arthritis; osteoarthritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Angular
Note: this name may be used for preparations of different composition.
Fada, Arg.†
Diltiazem (p. 1359·2).

Angyton *Royton, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

ANH Mat *ANH, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); atropine sulfate (p. 1310·2).

AnHe *ZhenYuan, China.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Anhigot *Grin, Mex.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Anhissen *Sunthi Sepuri, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Anhista *Sriprasit, Thai.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Anhiten-A *Ultra, Mex.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Anhydrol Forte *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Aniall *Pfizer Consumer, Irl.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Cold and influenza symptoms; pain.

Aniduv *LKM, Arg.*
Nimodipine (p. 1455·2).
Cerebrovascular disorders.

Anifen *Soldan, Canad.†*
Fennel oil (p. 2503·3); menthol (p. 2553·2); anise oil (p. 2444·3).

Aniflazime *Lusomedicamenta, Port.*
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion.

Aniflazym *Takeda, Ger.*
⊗Serrapeptase (p. 2613·3).
Inflammation.

Aniflox *Sanify, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Anikef *CCM, Malaysia.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Anilar *LKM, Arg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Anilid *Kener, Mex.*
⊗Chlortalidone (p. 1335·2).

Anim *Daffohils, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Animal Shapes *Major, USA.*
Vitamins.

Animal Shapes + Iron *Major, USA.*
Vitamins; iron (p. 2073·1).

Animex-On *Bernabo, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia.

Animi-3 *PBM, USA.*
Omega-3 triglycerides (p. 1460·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Dietary supplement.

Animi-3 with Vitamin D *PBM, USA.*
Omega-3 fatty acids (p. 1460·1); vitamin D (p. 2112·3); vitamin B substances (p. 2102·3); phytosterols (p. 1471·2).

Animic *Vinas, Spain.†*
St John's wort (p. 449·1).
Sleep disorders; tonic.

Animine
Note: this name may be used for preparations of different composition.
McGloin, Austral.
Lotion: Lidocaine hydrochloride (p. 1988·2); benzalkonium chloride (p. 1737·1); calamine (p. 1697·2).
Stings; bites; pruritus.

McGloin, Austral.†
Cream: Benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1).
Stings; bites; pruritus.

Anim-P *Daffohils, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Pain.

Anin *Ind-Swift, India.*
Injection: Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Ind-Swift, India.
Tablets: Allylestrenol (p. 2255·2).
Threatened miscarriage.

Aninegalem *Alvartis, Mex.*
Placenta extract (Melagenin) (p. 2444·1).
Vitiligo.

Anionen-Spurenelement *Fresenius Kabi, Austria.*
Electrolytes (p. 1775·1).
Parenteral nutrition.

Anios DD *Anios, Fr.†*
Quaternary ammonium compound; guanidinium acetate; propyl alcohol (p. 1768·1).
Cleaning and disinfection of surfaces and instruments.

Aniospray 29 *Anios, Fr.†*
⊗Didecyldimethylammonium chloride (p. 1750·3); polihexanide (p. 1766·1); alcohol PE (p. 1733·1); glycolic acid (p. 1704·3).
Instrument and surface disinfection.

Aniosyme *Anios, Fr.†*
Didecyldimethylammonium chloride (p. 1750·3); chelators; proteases (p. 2598·1); lipases; amylases.
Instrument disinfection.

Anioxyde *Anios, Fr.†*
Peracetic acid (p. 1763·1); hydrogen peroxide (p. 1755·2).
Instrument disinfection.

Anipen *Choongwae, Philipp.; Unimex, Philipp.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Aniran *Rontag, Arg.*
Aniracetam (p. 389·1).
Mental function disorders.

Anisimol *Medipharm, Chile.*
Fluoxetine (p. 417·1).
Bulimia; depression.

Anistal *Silanes, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Anitid *Bernofarm, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hypersecretory disorders; duodenal ulcer.

Anitrim *Italmex, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Aniup *Raam, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; premenstrual dysphoric disorder; obsessive-compulsive disorder.

Anival *Errekappa, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Aniwel DPS *Ind-Swift, India.*
Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1).

Anixon *Kramer, Philipp.*
Vitamin B substances (p. 2102·3); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; nutritional supplement.

Anji *Docan, China.*
Foscarnet sodium (p. 981·1).

Anjielishu *Topsun, China.*
Nimesulide (p. 101·3).
Pain.

Anjiesha *Topsun, China.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Anjioflux *Bio-Gen, Turk.*
Sulodexide (p. 1507·3).

Ankare *Anvik, India.*
Aceclofenac (p. 16·2); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Ankarma *Biomedica, Ital.*
⊗Anastrozole (p. 742·1).

Anksen *Sanovel, Turk.*
Dipotassium clorazepate (p. 1056·3).
Anxiety.

Anksilon *Orion, Fin.*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders.

Anlene *Fonterra, Malaysia.*
High calcium food supplements.
Nutritional supplement.

Fonterra, Philipp.
A range of high calcium food supplements.
Calcium supplement.

Fonterra, Indon.†
Nutritional supplements.

Anli *Qianjiang, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Anlina *Deltapharm, Hong Kong.†*
Chloramphenicol (p. 257·1); diiodohydroxyquinoline (p. 931·1); nystatin (p. 590·3).
Vaginal disorders.

Anlo *Sigma, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Anlodibal *Baldacci, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Anlodil *Vitapan, Braz.†*
Amlodipine (p. 1304·1).

Anlodin *YSP, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Anlos *Sandoz, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Anlostin *Biovena, Pol.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Anlun *Winsunny, China.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Anmerob *Medikon, Indon.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; trichomoniasis; amoebiasis; giardiasis.

Anmiejun *NCPC, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Anm-P *Armour, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Pain.

Anmum *Fonterra, Indon.*
Nutritional supplements.
For infants, children, and for pregnancy and breast feeding.

Fonterra, Malaysia.
A range of preparations for enteral nutrition.
Nutritional supplement.

Fonterra, Philipp.
A range of nutritional milk products with vitamins and minerals.
Nutritional supplement for pregnant and breast-feeding women.

Anna *TNP, Thai.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Annadine *Unison, Thai.†*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Annantah *Leon, Neth.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Annie *Pharmahof, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Oral contraceptive in women with androgenic symptoms.

Annita *Farmoquimica, Braz.*
Nitazoxanide (p. 942·2).
Worm infections.

Annoxen *Siam Bheasach, Thai.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Annylyn *TNP, Thai.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-day packs also contain 7 inert tablets.
Combined oral contraceptive.

Anocream *Pharma Synth, India.*
⊗Beclometasone dipropionate (p. 1621·2); lidocaine (p. 1988·1); phenylephrine hydrochloride (p. 1672·3); zinc oxide (p. 1729·1).
Anorectal disorders.

Anodan-HC *Odan, Canad.*
⊗Hydrocortisone acetate (p. 1640·1); zinc sulfate (p. 2126·2).
Anorectal disorders.

Anodesyn *Thornton & Ross, UK.*
Lidocaine hydrochloride (p. 1988·2); allantoin (p. 1693·1).
Anorectal disorders.

Anodyne-P *Aqualife, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Anofer *Sun, India.*
Copper (p. 2057·1); iodine (p. 2336·3); iron (p. 2073·1); zinc (p. 2126·1); vitamins.
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Anoflam *Pharma Nutria, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Anoion *GX, Philipp.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Anol *Psyco Remedies, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Anol-AD *Psyco Remedies, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Anolor *Blansett, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).

Anol-Plus *Lincoln, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Anomex *Bliss, India.*
⊗Allantoin (p. 1693·1); hydrocortisone acetate (p. 1640·1); lidocaine (p. 1988·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anopyrin *Zentiva, Cz.*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Anore *Kalbe, Indon.*
Norethisterone (p. 2294·2).
Premenstrual syndrome; postponement of menstruation; endometriosis; dysfunctional bleeding.

Anore rheumat *Schwarzwalder, Ger.*
Colchicinum (p. 604·1); ledum palustre (p. 2550·1); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Anorex
Note: this name may be used for preparations of different composition.
Scoshia, India.
Cefuroxime (p. 255·2).
Bacterial infections.

Anorexin Plus *Strassenburg, India.*
Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Anorsia *Asian Pharm, Thai.*
Pizotifen malate (p. 678·2).
Anorexia; vascular headache.

102 Años *ISA, Arg.*
A range of dietary supplements.

Anosoglobin *Neiadas (Νειάδας), Gr.*
A normal immunoglobulin (p. 2403·3).

Anovate *USV, India.*
⊗Betamethasone valerate (p. 1624·1); phenylephrine hydrochloride (p. 1672·3); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Anovin *Pfluger, Ger.*
Aconitum napellus (p. 2428·3); baptisia (p. 2647·2); cephaelis ipecacuanha; eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens

(p. 2511·2); mercurius solubilis (p. 2555·3); natrium sulfuricum (p. 1888·1); solanum lycopersicum.
Homoeopathic preparation.

Anovis *Unipharma, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Anovulatorio Micro-Dosis *Andromaco, Chile; Laboratorios Chile, Chile; Mintlab, Chile.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Anovulatorios *Laboratorios Chile, Chile.*
Lynestrenol (p. 2287·3); mestranol (p. 2291·1).
Combined oral contraceptive; menstrual disorders.

A-Nox *Aroma, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Anoxant *Eagle, Austral.†*
Vitamins; minerals; amino acids; herbs.
Antoxidant preparation.

Anoxen *Roemmers, Venez.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states.

Anoxid *Volchem, Ital.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Anoxidil *Italchimici, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anoxolan *Neo Quimica, Braz.*
Cloxazolam (p. 1057·2).
Anxiety.

Anpec *Alphapharm, Austral.; LCH, Hong Kong.†*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Anpeval *Vir, Spain.†*
Triflusal (p. 1519·3).
Thromboembolic disorders.

Anpheclor *Medhaus, Philipp.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Anphexin *Acto, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Anpiride *Sanbe, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Anplag *Mitsubishi, China; Mitsubishi, Jpn.*
Sarpogrelate hydrochloride (p. 1489·1).
Occlusive arterial disease.

Anpo *Biotech, China.*
⊗Ritodrine hydrochloride (p. 2145·1).
Premature labour.

Anposel *Medipharm, Chile.*
Meloxicam (p. 86·3).
Osteoarthritis; pain; rheumatoid arthritis.

Anpre *Wermar, Mex.*
Meloxicam (p. 86·3).
Dysmenorrhoea; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Anpress *Condrugs, Thai.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Anpro
Note: this name may be used for preparations of different composition.
Ankom, India.
Protein; vitamins; minerals.
The Forty-Two, Thai.
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Anpu Laishi *RAAS, China.*
⊗Albumin (p. 1130·2).
Plasma volume expansion.

Anpuzz *TNP, Thai.*
Mefenamic acid (p. 85·3); dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm; pain; musculoskeletal and joint pain.

Anquil *Archimedes, UK.*
Benperidol (p. 1041·1).
Deviant sexual behaviour.

Anquin *Hetero, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Anremed *Bajamed, Mex.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Anrushan *Ethypharm, China.†*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder.

Ansaid *Pfizer, Canad.; Pfizer, Chile; Pfizer, Mex.; Pfizer, Turk.; Upjohn, USA.†*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; gout.

Ansaiding *NEGPF, China.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Ansailong *NEGPF, China.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ansaitamei *NEGPF, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Ansal *Novartis, Denm.†*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis.

Ansar *Bioclon, Mex.†*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Ansatipin *Pfizer, Fin.; IFET (ΙΦΕΤ), Gr.; Binesa, Spain; Pfizer, Swed.*
Rifabutin (p. 348·3).
Tuberculosis; nontuberculous mycobacterial infections.

Ansatipine *SERB, Fr.*
Rifabutin (p. 348·3).
Mycobacterial infections; tuberculosis.

Ansecare *Evershine, India.*
Ondansetron (p. 1872·1).
Nausea; vomiting.

Anselol *Douglas, Austral.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Ansentron *Biosintetica, Braz.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Anseren *Novartis, Ital.*
Ketazolam (p. 1079·2).
Anxiety disorders.

Anset *Bennet, India.*
Ondansetron (p. 1872·1).
Nausea; vomiting.

Ansi *Bernofarm, Indon.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Ansial *Rontag, Arg.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Ansielix *Craveri, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Ansielix Digest *Craveri, Arg.*
Alprazolam (p. 1035·2); domperidone (p. 1838·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Ansieten *Ivax, Arg.*
Ketazolam (p. 1079·2).
Anxiety.

Ansietil *Tecnofarma, Chile.*
Ketazolam (p. 1079·2).
Anxiety.

Ansilan
Note: this name may be used for preparations of different composition.
Cosmopharm, Gr.
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.
Giempi, Venez.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.
Iek, Cz.
Medazepam (p. 1083·2).
Anxiety; nervous disorders; alcohol withdrawal syndrome; insomnia.

Ansilive *Libbs, Braz.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Ansilor *Sofex, Port.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; epilepsy.

Ansimar *ABC, Ital.; OEP, Philipp.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Ansiokey *Inkeysa, Spain.*
Valerian (p. 2640·2).
Insomnia; nervous disorders.

Ansiolin *Almirall, Ital.*
Diazepam (p. 1063·2).
Anxiety; insomnia; epilepsy; premedication.

Ansiopax *Hebron, Braz.*
Kava (p. 2537·3).
Sedative.

Ansiotex *Cimed, Braz.*
Pimethixene (p. 638·1).
Hypersensitivity reactions.

Ansioval *Maver, Chile.*
Diazepam (p. 1063·2); chlormezanone (p. 1045·1).
Anxiety; tension; skeletal muscle spasm.

Ansirax *Teuto, Braz.*
Lorazepam (p. 1080·3).

Ansitec *Libbs, Braz.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Ansiten *Azevedos, Port.*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders.

Ansium *Qualigen, Spain.*
Diazepam (p. 1063·2); sulpiride (p. 1107·3).
Anxiety; insomnia.

Ansival *Ativus, Braz.*
Valerian (p. 2640·2).

Anso *Lacer, Hong Kong.*
⊗Hexetidine (p. 1755·1); lidocaine hydrochloride (p. 1988·2); triamcinolone acetonide (p. 1649·1); pentosan polysulfate (p. 1465·1).
Anorectal disorders.
Lacer, Spain.
⊗Lidocaine hydrochloride (p. 1988·2); triamcinolone acetonide (p. 1649·1); pentosan polysulfate sodium (p. 1465·1).
Anorectal disorders.

Ansolar *GSK, Arg.*
A range of sunscreen preparations.
Stiefel, Chile.
SPF 30: Octocrilene (p. 1715·2); bemotrizinol (p. 1695·3); amiloxate (p. 1694·1); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Sunscreen.
Stiefel, Chile.
SPF 60: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octil triazone (p. 1715·1); bisoctrizole (p. 1697·1).
Sunscreen.

Anson *Heromycin, Thai.*
Niclosamide (p. 161·2); phenolphthalein (p. 1877·3).
Worm infections.

Anstrep *Solas, Indon.*
Psidium guajava; curcuma longa; betel pepper; cimicifuga (p. 2478·1).
Diarrhoea.

Ansures *Siu Guan, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Answell *Cadila, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever.

Answer *Carter-Wallace, USA.*
Fertility test or pregnancy test (p. 2596·1).

Ansyn *Actavis, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anta *Pharmasant, Thai.*
Lorazepam (p. 1080·3).
Anxiety; epilepsy; insomnia; muscle relaxation.

Anta-al *T Man, Thai.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Antabenz *CCM, Malaysia.*
Flumazenil (p. 1551·3).
Reversal of benzodiazepine-induced sedation.

Antabus *Actavis, Austria; Farmo Quimica, Chile; Actavis, Cz.; Actavis, Denm.; Actavis, Fin.; Nycomed, Ger.†; Actavis, Neth.; Actavis, Norw.; Actavis, Rus.; Bohm, Spain; Actavis, Swed.; Actavis, Switz.; Nobel, Turk.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Antabuse *Orphan, Austral.; Sanofi-Aventis, Belg.; Actavis, Irl.; Actavis, Ital.; CSL, NZ; Aspen, S.Afr.; Alpharma, Singapore†; Alpharma, UK; Barr, USA; Duramed, USA.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Antacaine *Quality, Hong Kong.*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2) or magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).
Dyspepsia; gastritis; heartburn; reflux oesophagitis; peptic ulcer.

Antacal *Errekappa, Ital.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Antacia *The Forty-Two, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Antacia-SM *The Forty-Two, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Antacid *Geneva, USA.*
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Hyperacidity.
Goldline, USA.
Tablets: Calcium carbonate (p. 1824·3).
Hyperacidity.

Antacid 2 *Advertising Unlimited, Canad.†*
Calcium carbonate (p. 1824·3); glycine (p. 2071·2).
Gastric hyperacidity.

Antacid Chewable Tablets *Vitelle, Austral.†*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Dyspepsia; gastro-oesophageal reflux; heartburn.

Antacid Plus *Supplements Aromatik, Canad.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Antacid Regular with Anti-Gas *Supplements Aromatik, Canad.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Antacid Suspension *Pharmel, Canad.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Antacidum *Pfizer, Austria.†*
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Hyperacidity; peptic ulcer; dyspepsia.

Antacil *TNP, Thai.*
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; peptic ulcer.

Antacimin *Universal, Hong Kong.†*
Sodium bicarbonate (p. 1781·1).

Antacin-D *Quality, Hong Kong.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; gastritis; hiatus hernia; heartburn; oesophagitis; peptic ulcer.

Antacsal *Alpharma, Mex.*
Aspirin (p. 22·2).
Pain; fever.

Antadar *Basi, Port.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Antaderm *Darier, Mex.*
Allantoin (p. 1693·1); coal tar (p. 1723·2).
Psoriasis; seborrhoeic dermatitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Antadex-H *Continentales, Mex.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Antadys *Theramex, Mon.*
Flurbiprofen (p. 65·2).
Pain; musculoskeletal and joint disorders.

Antaethyl *Sanofi-Aventis, Hung.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Antafit *Polipharm, Thai.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Antag *MedGen, Philipp.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; gastro-intestinal haemorrhage; short-bowel syndrome.

Antagel *PannonPharma, Hung.*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Pharmachemie, Neth.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders associated with hyperacidity.

Antagel M *PannonPharma, Hung.*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Antagit *Leben, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Antagon
Note: this name may be used for preparations of different composition.
Ativus, Braz.
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Antagon 1
Note: this name may be used for preparations of different composition.
Liomont, Mex.†
Astemizole (p. 616·1).
Hypersensitivity.

Antagonil *Astellas, Ger.†*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension.

Antak *GSK, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Antalfebal *Johnson & Johnson, Ital.*
Ibuprofen (p. 68·2).
Pain; fever.

Antalfort *Johnson & Johnson, Ital.*
Ibuprofen lysine (p. 68·3).
Pain; fever.

Antalgic *Caps, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Antalgil *Johnson & Johnson, Ital.*
Ibuprofen (p. 68·2).
Pain.

Antalgin
Note: this name may be used for preparations of different composition.
Berlico Mulia, Indon.; Corsa, Indon.
Dipyrone (p. 53·3).
Fever; pain.

Medix, Mex.
Indometacin (p. 71·2).
Gout; musculoskeletal, joint and peri-articular disorders; pain; inflammation.

Roche, Spain.
Naproxen sodium (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Antalin *Saval, Chile.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states.

Antalisin *Johnson & Johnson, Ital.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Antalnox *Pierre Fabre, Fr.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; dysmenorrhoea.

Antalor *Errekappa, Ital.*
Nimesulide (p. 101·3).

Antalyre *Europhta, Mon.*
Salicylic acid (p. 1719·1).
Conjunctival irritation.

Antamebin *Raptakos, India.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Antamin
Note: this name may be used for preparations of different composition.
Pascual, Philipp.; Pharex, Philipp.; Xepa-Soul Pattinson, Singapore.
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Tack Fung, Hong Kong.†
Chlorphenamine (p. 620·3).

Yik Kwan, Hong Kong.†
Chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1); salicylamide (p. 129·2).

Antanax *Novartis, Gr.*
Alprazolam (p. 1035·2).
Anxiety disorders.

Antanazol *Shin Poong, Singapore.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Antangping *United Lab, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Antapiril *Exakta, Mex.†*
Aspirin (p. 22·2); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Influenza symptoms.

Antara *Reliant, USA.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Antarène *Elerte, Fr.*
Ibuprofen (p. 68·2).
Fever; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Antarène Codéine *Elerte, Fr.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Antasida Plus Famotidine *Soho, Indon.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Antasol *Sol, Fr.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Analgesia in anaesthesia and painful procedures.

Antasone *Shin Poong, Singapore.*
⊗Betamethasone (p. 1623·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Antasten *Cetus, Arg.†*
Captopril (p. 1331·2).
Hypertension.

Antasten-Privin *Novartis Ophthalmics, Swed.†*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis; eye irritation.

Antaxon *Zambon, Hung.*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal.

Antaxone *Zambon, Ital.; Zambon, Port.; Zambon, Rus.; Pharmazam, Spain; Zambon, Ukr.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol withdrawal syndrome; opioid withdrawal syndrome.

Antazallerge *Siam Bheasach, Thai.*
⊗Antazoline hydrochloride (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Conjunctivitis.

Antazoline-V *Rugby, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); antazoline phosphate (p. 615·3).
Eye irritation.

Antebe *Rafarm, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Antebor *Kela, Belg.*
Sulfacetamide sodium (p. 361·1).
Skin infections.

Antébor *Johnson & Johnson, Fr.†*
Sulfacetamide sodium (p. 361·1).
Acne.

Antébor N *Sanofi, Switz.†*
Chlorhexidine (p. 1743·2); triclosan (p. 1773·2).
Acne; seborrhoea.

Antemin compositum *Streuli, Switz.*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting.

Antemine *Streuli, Switz.†*
Dimenhydrinate (p. 625·2).
Nausea and vomiting.

Anten *Mylan, NZ.*
Doxepin hydrochloride (p. 414·2).
Depression.

Antenac *GPO, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Antenex *Alphapharm, Austral.; LCH, Hong Kong.†*
Diazepam (p. 1063·2).
Anxiety disorders; alcohol withdrawal syndrome; skeletal muscle spasm; spasticity.

Anteovin *Gedeon Richter, Hung.†; Richter, Pol.†; Gedeon Richter, Rus.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Antepan *Sanofi-Aventis, Austria; Henning, Ger.†; Sanofi-Aventis, Ger.†*
Protirelin (p. 2344·2).
Assessment of pituitary and thyroid function.

Antepsin *Boehringer Ingelheim, Arg.; Orion, Denm.; Orion, Fin.; Chugai, Irl.; Baldacci, Ital.; Orion, Norw.; Bilim, Turk.†; Chugai, UK; Merck, UK.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage.

Antergan *TNP, Thai.*
⊗Hydrocortisone acetate (p. 1640·1); mepyramine maleate (p. 635·1).
Pruritus; skin irritation.

Antesvel *Martel Hammer, India.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Antex *Zee, India.*
Vitamins; spirulina (p. 2622·1).

Antheda *Osoth, Thai.†*
Albendazole (p. 149·1).
Worm infections.

Anthel
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Pyrantel embonate (p. 165·3).
Worm infections.

Lincoln, India.
Albendazole (p. 149·1).
Worm infections; giardiasis.

Anthelios *Roche-Posay, Arg.; Roche-Posay, Irl.†*
SPF 30; SPF 40; SPF 50; SPF 60+: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen; polymorphous light eruption.

Roche-Posay, Canad.
Lotion, SPF 45: Avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); drometrizole trisiloxane (p. 1702·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2).
Sunscreen.

Roche-Posay, Fr.
SPF 30; SPF 50+: Octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); bemotrizinol (p. 1695·3); octil triazone (p. 1715·1).
Sunscreen.

Roche-Posay, Fr.
SPF 30; SPF 50+: Octisalate (p. 1715·2); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); bemotrizinol (p. 1695·3); octil triazone (p. 1715·1).
Sunscreen.

Roche-Posay, Fr.
SPF 20; SPF 30; SPF 50+: Octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); octil triazone (p. 1715·1).
Sunscreen.

Roche-Posay, Irl.
SPF 40: Octocrilene (p. 1715·2); avobenzone (p. 1695·1); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Roche-Posay, Canad.†
Cream, SPF 30: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Roche-Posay, Canad.†
Topical spray, SPF 30: Avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2); octisalate (p. 1715·2).
Sunscreen.

Anthelios 40 *Roche-Posay, USA.*
Avobenzone (p. 1695·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios AC *Roche-Posay, Chile.*
Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios AE *Roche-Posay, Chile.*
Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios Dermo-Pediatrics *Roche-Posay, Chile.*
Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios Extremo *Roche-Posay, Chile.*
SPF 30: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios Helioblock *Roche-Posay, Braz.*
SPF 20; SPF 30; SPF 60: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios Helioblock Dermopediatrics *Roche-Posay, Braz.*
SPF 40: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios Helioblock Spray *Roche-Posay, Braz.*
SPF 20: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1).
Sunscreen.

Anthelios Helioblock W30 *Roche-Posay, Braz.*
SPF 30: Ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1).
Sunscreen.

Anthelios Helioblock W40 *Roche-Posay, Braz.*
SPF 40: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios Spray *Roche-Posay, Chile.*
Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios SX *Roche-Posay, USA.*
SPF 15: Avobenzone (p. 1695·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2).
Sunscreen.

Anthelios W *Roche-Posay, Chile.*
SPF 30: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Anthelios XL *Roche-Posay, Canad.; Roche-Posay, Chile.*
SPF 60 cream: lotion; stick: Avobenzone (p. 1695·1); drometrizole trisiloxane

(p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Roche-Posay, Canad.; Roche-Posay, Chile.
SPF 60: Lotion SPF 50+: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Roche-Posay, UK.
SPF 50+: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); octocrilene (p. 1715·2); octil triazone (p. 1715·1).
Sunscreen.

Anthelios XL Extreme *Roche-Posay, Singapore.*
Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1).
Sunscreen.

Anthel-UP *Lincoln, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Antherpos
Note: this name may be used for preparations of different composition.
Roche-Posay, Arg.; Roche-Posay, Braz.; Roche-Posay, Canad.†; Roche-Posay, Fr.†
Ecamsule (p. 1702·1); avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Roche-Posay, Irl.†
Enzacamene (p. 1703·2); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Lip protectant; sunscreen.

Anthical *Elder, India.*
Mepyramine maleate (p. 635·1); zinc oxide (p. 1729·1).

Anthisan *Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, UK.*
Mepyramine maleate (p. 635·1).
Allergic skin disorders; insect bites and stings; pruritus; nettle rash.

Anthisan Plus *Aventis, UK.*
Mepyramine maleate (p. 635·1); benzocaine (p. 1980·2).
Bites and stings.

Anthogenol *Phytologic, Austral.*
Grape (p. 2521·3); ascorbic acid (p. 2110·3).
Antioxidant.

Anthol *Anthiea, India.*
Paracetamol (p. 115·1).
Pain; fever.

Anthoxin *Anthiea, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Anthozym *Petrasch, Austria.†*
Beta vulgaris; lactic acid (p. 2539·1); ferrous lactate (p. 2062·1); ascorbic acid (p. 2110·3); calcium lactate (p. 1784·1); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1); black currant juice.
Tonic.

Anthracin *Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.†*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Anthracord *Accord, Mex.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Anthraforte *Medican, Canad.*
Dithranol (p. 1701·2).
Psoriasis.

Anthramed *Surya Dermato, Indon.*
Dithranol (p. 1701·2).
Psoriasis.

Anthranol *Medican, Canad.; Stiefel, S.Afr.†*
Dithranol (p. 1701·2).
Psoriasis.

Anthrascalp *Medican, Canad.*
Dithranol (p. 1701·2).
Psoriasis.

Anthraxiton *Chrispa (Χρισπα), Gr.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Anthro *Profic Organic, India.*
Paracetamol (p. 115·1); aceclofenac (p. 16·2).
Pain; inflammation.

Anthrom *Yung Shin, Philipp.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Anthylline *Lesourd, Fr.†*
Hamamelis (p. 2523·3); melilot (p. 2552·3); red vine (p. 2521·3).
Venous insufficiency; haemorrhoids.

Anti *Antula, Swed.*
Aciclovir (p. 964·1).
Herpes labialis.

Anti Dysp *Curewell, India.*
Indian gooseberry (p. 2532·2); fennel (p. 2503·2).

Anti Dyspepsia Digestive Aid *Labofarm, Canad.†*
Caraway (p. 2470·2); peppermint (p. 1877·1); taraxacum (p. 2625·3).

Anti Leg Cramps *Naveh, Israel.*
Magnesium hydroxide (p. 1857·2); vitamin E (p. 2119·1).
Nocturnal leg cramps.

Antiac *Salcura, UK.*
Aloe vera (p. 1693·2); manuka (p. 2550·1).
Acne.

Antiacid
Note: this name may be used for preparations of different composition.
Garden House, Arg.
Magnesium carbonate (p. 1856·2); menthol (p. 2553·2); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).
Antacid; dietary supplement.

Lemax, Arg.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Antacid.

Antiacido *GC, Venez.*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Anti-Acne
Note: this name may be used for preparations of different composition.
MDM, Ital.
Sublimed sulfur (p. 1721·1); meclocycline sulfosalicylate (p. 321·2); nicoboxil (p. 101·1).
Acne.

Antiadipositum *Riemser, Ger.*
Phenylpropanolamine hydrochloride (p. 1674·1); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); ascorbic acid (p. 2110·3).
Obesity.

Antiadipositum X-112 T *Riemser, Ger.†*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Antiadiposo *Teofarma, Ital.*
Iodocasein (p. 2336·3); thiamine nitrate (p. 2103·2).
Metabolic activator.

Anti-Age Energy *Argenfarma, Arg.*
Vitamins; minerals.

Anti-Aging *Kamins, Canad.; La Prairie, Canad.*
SPF 15 lotion; SPF 15 cream: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

La Prairie, Canad.
SPF 30 lotion: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Anti-Aging Follow-Up *Vichy, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Anti-Aging Foundation *La Prairie, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Anti-Aging Moisturizing *Apollo, Canad.†*
Avobenzone (p. 1695·1); ensulizole (p. 1703·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Antiamox *Epicaris, Arg.†*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Antianem *Verisfield, Gr.*
Iron polymaltose (p. 2077·2).
Anaemia.

Anti-Angin *Natur Produkt, Rus.*
Ascorbic acid (p. 2110·3); chlorhexidine acetate (p. 1743·2); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Anti-Anorex Triple *Qualigen, Spain.*
⊗Cyproheptadine hydrochloride (p. 624·1); deanol aceglumate (p. 2319·1); metoclopramide hydrochloride (p. 1862·2).
Reduced appetite.

Antiaril *Kleva, Gr.*
Mexiletine hydrochloride (p. 1436·2).

Anti-Asidoz *Assos, Turk.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis; urinary alkalinisation; dyspepsia.

Anti-Asmático *CPH, Port.†*
⊗Aminophylline (p. 1201·2); phenobarbital (p. 535·2); ephedrine hydrochloride (p. 1663·2).
Asthma.

Antiax *Saval, Chile.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Antib *Biogam, Arg.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Anti-Bac *Bentfield, Canad.*
Triclosan (p. 1773·2).

Antibacin *Elpen (Ελπεν), Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Elpen, Singapore.
Ceftriaxone (p. 253·3).
Bacterial infections.

Antibacter Forte *Bayer, Gr.*
Triclocarban (p. 1773·2).
Disinfection.

Antibacterial *ABC, Canad.*
Chloroxylenol (p. 1748·2).

Anti-Bacterial Deep Cleansing *Bath & Body Works, Canad.*
⊗Alcohol (p. 1733·1); triclosan (p. 1773·2).

Antibacterial Honey Barrier *Medihoney, Austral.†*
Honey (p. 2072·1).
Wounds; burns.

Anti-Bacterial Moisturizing *Bath & Body Works, Canad.*
Triclosan (p. 1773·2).

Anti-Bacterial Waterless *Bath & Body Works, Canad.†*
⊗Alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1).

Antiban *Blue Cross, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Antiban-ASP *Blue Cross, India.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Thromboembolism prophylaxis.

Antibeksin *Fako, Turk.*
⊗Ephedrine hydrochloride (p. 1663·2); sodium citrate (p. 1781·2); sulfogaiacol (p. 1678·1); pheniramine maleate (p. 637·2).
Respiratory-tract congestion.

Antiben *Liferpal, Mex.*
Dicloxacillin (p. 286·1).
Bacterial infections.

Antibic-DF *Strassenburg, India.*
Diloxanide furoate (p. 931·2); tetracycline hydrochloride (p. 373·2); tinidazole (p. 949·2).

Antibin *Medispan, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Anti-Bio *Leon, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Antibiocort *Biosintex, Arg.*
⊗Hydrocortisone (p. 1640·1); naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Infected eye disorders.

Antibiophilus *Germania, Austria; Azevedos, Port.*
Lactobacillus casei var *rhamnosus* (p. 2596·3).
Diarrhoea.

Antibioptal
Note: this name may be used for preparations of different composition.
Farmila, Ital.
Chloramphenicol (p. 257·1); neomycin sulfate (p. 330·1).
Bacterial eye infections.

Poen, Arg.
Tobramycin (p. 380·1); phenylephrine hydrochloride (p. 1672·3).
Bacterial eye infections.

Antibio-Synalar *Jolly-Jatel, Fr.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Otitis externa.

Antibi-Otic
Note: this name may be used for preparations of different composition.
Seng, Thai.
Chloramphenicol (p. 257·1).
Bacterial ear infections.

Antibiotic Cold Sore Ointment *Columbia, Canad.†*
Polymyxin B sulfate (p. 342·3); tyrothricin (p. 384·1); camphor (p. 2466·2); menthol (p. 2553·2); benzocaine (p. 1980·2).
Herpes labialis.

Antibiotic Cream
Note: this name may be used for preparations of different composition.
Taro, Canad.
Gramicidin (p. 308·3); lidocaine hydrochloride (p. 1988·2); polymyxin B sulfate (p. 342·3).

Antibiotic Ointment *Canadian Custom Packaging, Canad.; Jamp, Canad.; Pharmascience, Canad.; Pharmetics, Canad.; Taro, Canad.*
Bacitracin (p. 225·3) or bacitracin zinc (p. 225·3); polymyxin B sulfate (p. 342·3).

Antibiotic Plus *Taro, Canad.*
Gramicidin (p. 308·3); lidocaine hydrochloride (p. 1988·2); polymyxin B sulfate (p. 342·3).

Antibiotic Simplex *Howmedica, NZ.*
Erythromycin gluceptate (p. 291·3); colistimethate sodium (p. 275·3); polymethylmethacrylate/methylmethacrylate copolymer (p. 2558·2).
Bone cement for orthopaedic surgery.

Antibiotique Onguent *Prodemdis, Canad.†*
Bacitracin (p. 225·3); polymyxin B sulfate (p. 342·3).

Antibiotrex *GSK, Fr.*
Isotretinoin (p. 1706·2); erythromycin (p. 291·2).
Acne.

Antibioxim *Atral, Rus.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Antibioxime *Atral, Port.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Anti-Bit *Eczacibasi, Rus.†; Eczacibasi, Turk.*
Phenothrin (p. 2160·1).
Pediculosis.

Antibloc *Craveri, Arg.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; hypertension.

Antiblut *Genepharm, Gr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Antibron *Potter's, UK.*
⊗Lobelia (p. 2323·2); wild lettuce (p. 2647·3); coltsfoot (p. 1659·2); euphorbia (p. 2501·3); pleurisy root (p. 2593·2); senega (p. 1677·2).
Coughs.

Antican
Note: this name may be used for preparations of different composition.
Elpen (Ελπεν), Gr.
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Baroda, India.
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Antican-O *Baroda, India.*
Fluconazole (p. 578·2).
Fungal infections.

Anticataral *Sperko, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Anticatarral *Edigen, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Anti-CC *Embiotic, India.*
Syrup: ⊗Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); sodium citrate (p. 1781·2).

Embiotic, India.
Tablets: ⊗Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Anticepim *Verisfield, Gr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Anticerumen *SIT, Spain.*
Sodium laurilsulfate (p. 2210·3).
Removal of ear wax.

Antichol *Help, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Anticholium *Kohler, Austria; Kohler, Cz.; Kohler, Ger.; IFET (ΙΦΕΤ), Gr.*
Physostigmine salicylate (p. 2009·3).
Antimuscarinic poisoning; central anticholinergic syndrome; alcohol withdrawal syndrome.

Anticina *Ivax, Mex.†*
Ranitidine (p. 1882·1).
Gastric hyperacidity.

Anticol
Note: this name may be used for preparations of different composition.
Polfa Warszawa, Pol.
Disulfiram (p. 2495·3).
Alcoholism.

Vickmans, Hong Kong.†
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1); salicylamide (p. 129·2).
Cough; cold symptoms.

Anticold
Note: this name may be used for preparations of different composition.
Christo, Hong Kong.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Colds; influenza.

Pharmed, India.
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Cough; cold symptoms.

Andromaco, Chile.†
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine sulfate (p. 1676·1).
Cold and influenza symptoms.

Anticongestiva *Sanofi-Aventis, Spain.*
Zinc oxide (p. 1729·1).
Skin irritation.

Anticor *Pharmadevelappement, Fr.†*
Salicylic acid (p. 1719·1); acetic acid (p. 2426·3).
Corn; callouses; verrucas.

Anticors Diable Vert *Colin, Belg.†*
Salicylic acid (p. 1719·1).
Warts.

Anticude *Arafarma, Spain.*
Edrophonium bromide (p. 686·1).
Reversal of competitive neuromuscular blockade; diagnosis of myasthenia gravis.

IFET (ΙΦΕΤ), Gr.
Edrophonium chloride (p. 686·1).
Myasthenia gravis.

Anti-D
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Zydus, India.
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Antidep *Torrent, India.*
Imipramine hydrochloride (p. 426·2).
Depression; narcoleptic syndrome; nocturnal enuresis.

Antideprimal *Jelfa, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Antiderm *Marching, Hong Kong.†*
⊗Neomycin (p. 329·3); triamcinolone (p. 1648·3).
Infected skin disorders.

Anti-Dessèchement *Lierac, Fr.†*
⊗Urea (p. 1727·3).
Dry skin.

Antidia
Note: this name may be used for preparations of different composition.
Bernofarm, Indon.†
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Antidiab *KRKA, Pol.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Antidiarrhoeals for children *Srichand, Thai.*
Bismuth subnitrate (p. 1822·1); chalk (p. 1826·3).

Antidifar *Alpharma, Mex.*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Antidin *Teuto, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Antidine *Kimia, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Antidol
Note: this name may be used for preparations of different composition.
Quimica y Farmacia, Mex.; Cinfa, Spain.
Paracetamol (p. 115·1).
Pain; fever.

Sandoz, Pol.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Antidot *Sistas, Turk.*
Eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Minor cuts and abrasions.

Antidotum Thallii-Heyl *Heyl, Ger.*
Prussian blue (p. 1572·3).
Thallium poisoning.

Antidral *Teva, Pol.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Antidrasi *Visufarma, Ital.†*
⊗Diclofenamide (p. 2006·3) or diclofenamide sodium (p. 2006·3).
Glaucoma; control of intra-ocular pressure during eye surgery.

Anti-Dry *Maccabi Care, Israel.†*
Oral rehydration solution (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Antidry *Merz, Switz.*
Ointment: Pansy (p. 2647·3); zinc oxide (p. 1729·1); almond oil (p. 2437·1).
Skin disorders.

Merz, Switz.
Bath oil: Liquid paraffin (p. 2191·2); almond oil (p. 2437·1).
Skin disorders.

Merz, Switz.
Shower oil: Liquid paraffin (p. 2191·2); soya oil (p. 2092·3); levomenol (p. 2544·1).
Skin disorders.

Merz, Switz.
Topical lotion: Sodium lactate (p. 1781·2); almond oil (p. 2437·1).
Skin disorders.

Antiedema *Alcon Cusi, Spain.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Anti-Em *Eczacibasi, Turk.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; motion sickness; vertigo; vestibular disorders.

Antiemorroidali *AFOM, Ital.†*
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1); belladonna (p. 2453·3).
Haemorrhoids.

Antiespasmodico *Veinfar, Arg.*
Homatropine methylbromide (p. 2007·3).
Smooth muscle spasm.

Antiestrias *Isdin, Port.*
Centella (p. 1698·3); borage oil (p. 2459·2); *dl*-alpha tocoferil acetate (p. 2119·2); jojoba oil.
Firming cream.

Antietanol *Sanofi-Aventis, Braz.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Antifebrin *Royton, Braz.*
Aspirin (p. 22·2).
Fever; inflammation; pain.

Antifect
Note: this name may be used for preparations of different composition.
Potter's, UK.
Garlic (p. 2510·3); garlic oil (p. 2510·3); echinacea (p. 2498·1).
Nasal congestion; rhinitis; catarrh.

Antiflam
Note: this name may be used for preparations of different composition.
Prem, India.
Diclofenac (p. 48·3).
Pain.

Antiflat *Lannacher, Austria; Tripharma, Turk.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; aid in gastrointestinal radiography; detergent poisoning; flatulence.

Antiflog *FIRMA, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Antiflogol *Poen, Arg.*
⊗Betamethasone (p. 1623·2); tetryzoline hydrochloride (p. 1678·3); chloramphenicol (p. 257·1).
Infected eye disorders.

Antiflu
Note: this name may be used for preparations of different composition.
Sagmel, Rus.
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Antiflu-Des *Chinoin, Mex.*
Amantadine hydrochloride (p. 890·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Influenza symptoms.

AntiFocal Nr 69-Sol L *Vitorgan, Ger.†*
Diencephalon (p. 2444·1); cerebellum (p. 2444·1); cort. cerebri; cerebrum fet.; medulla spinal (p. 2444·1); hepar. (p. 2444·1); pancreas (p. 2444·1); lien (p. 2444·1); thyreoidea (p. 2345·3); thymus juv. (p. 2631·1); placenta (p. 2444·1); mucosa misc. (p. 2444·1).
Homoeopathic preparation.

Antifom *Vargas, Venez.*
Simeticone (p. 1886·2).
Flatulence.

Antifort *Christo, Hong Kong.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; upper respiratory-tract congestion.

Anti-Fosfat Al *Assos, Turk.*
Aluminium chlorohydrate (p. 1694·1).

Anti-Fosfat Ca *Assos, Turk.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Anti-Fosfat Cc *Assos, Turk.*
Calcium carbonate (p. 1824·3).
Hyperphosphataemia.

Antifront *Beres, Hung.; Beres, Ukr.*
Maté (p. 2648·2); ginger (p. 1844·1); liquorice (p. 1853·2); melissa (p. 2552·3); curcuma (p. 2218·1).
Malaise associated with weather conditions; motion sickness.

Antifungal
Note: this name may be used for preparations of different composition.
Fortbenton, Arg.
Sulconazole nitrate (p. 593·3).
Fungal skin infections.

YSP, Malaysia; Yung Shin, Singapore.
Miconazole nitrate (p. 589·1).
Fungal skin and vulvovaginal infections.

Antifungol *Hexal, Ger.†*
Paste: Clotrimazole (p. 576·2); zinc oxide (p. 1729·1).
Fungal skin infections.

Hexal, Ger.†; Hexal, Rus.†
Clotrimazole (p. 576·2).
Fungal infections of the skin and genito-urinary tract; fungal skin and vaginal infections.

Antifungal Extra *Hexal, Ger.†*
Bifonazole (p. 573·3).
Fungal skin infections.

Antigeron *Farmasa, Braz.*
Cinnarizine (p. 622·1).
Vestibular disorders.

Antiglan *Potter's, UK.*
Saw palmetto (p. 2363·3); equisetum (p. 2500·1); hydrangea (p. 2528·1).
Bladder discomfort.

Antigram *Armstrong, Mex.*
Lysine aspirin (p. 84·3); metoclopramide (p. 1862·2).
Migraine; vascular headache.

Antigreg *Piam, Ital.; Vecchi, Malaysia; Vecchi, Singapore.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Antigrietun *Casen Fleet, Spain.*
⊗Allantoin (p. 1693·1); aminoacridine (p. 1732·3); peru balsam (p. 2587·1); prednisolone (p. 1645·2).
Allergic skin disorders; cracked nipples; mastitis; superficial burns.

Antigrilin *Samarth, India.*
Eptifibatide (p. 1376·3).
Unstable angina; adjunct in coronary angioplasty.

Antigripal Compuesto *Vent-3, Arg.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Anti-Gripe Asclepius *Plough, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Antigriphine *GSK Consumer, Belg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Antigrippin *Natur Produkt, Rus.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Rhinitis; influenza symptoms.

Antigrippin-ANVI *Antiviral, Rus.*
Green capsules: aspirin (p. 22·2); ascorbic acid (p. 2110·3); rutoside (p. 2505·3); white capsules: dipyrone (p. 53·3); diphenhydramine (p. 626·1); calcium gluconate (p. 1783·3).
Cold and influenza symptoms.

Antigrippine
Note: this name may be used for preparations of different composition.
GSK Consumer, Neth.
Paracetamol (p. 115·1); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Pain; fever.

GSK Consumer, Port.
Paracetamol (p. 115·1); mepyramine (p. 635·1); caffeine (p. 1203·3).
Pain; fever.

Antigrippine à l'Aspirine *GSK Sante, Fr.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); caffeine hydrate (p. 1203·3).
Pain; fever.

Antigrippin-Maximum *Antiviral, Rus.*
Paracetamol (p. 115·1); rimantadine hydrochloride (p. 1012·2); loratadine (p. 633·2); ascorbic acid (p. 2110·3); rutoside (p. 2505·3); calcium gluconate (p. 1783·3).
Viral respiratory-tract infections.

Antihemorroidal
Note: this name may be used for preparations of different composition.
Cinfa, Spain.
⊗Benzocaine (p. 1980·2); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); tannic acid (p. 2625·2).
Anorectal disorders.

Denver, Arg.
⊗Lidocaine hydrochloride (p. 1988·2); betamethasone valerate (p. 1624·1); phenylephrine hydrochloride (p. 1672·3).
Haemorrhoids.

Sertex, Arg.
Zinc oxide (p. 1729·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Antihep *Microgen, Rus.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Antihist
Note: this name may be used for preparations of different composition.
Vickmans, Hong Kong†; Mylan, S.Afr.†
Mepyramine maleate (p. 635·1).
Hypersensitivity reactions; pruritus.

Vickmans, Hong Kong.†
Syrup; tablets: Chlorphenamine (p. 620·3).

Antihist EC Expectorant *Vickmans, Hong Kong.†*
⊗Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); codeine (p. 40·2); ephedrine (p. 1663·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Antihist Expectorant *Vickmans, Hong Kong.†*
Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3).
Cough; cold symptoms.

Antihistaminico *Llorens, Spain.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions of the eye.

Anti-Homocysteine Factor *Eagle, Austral.†*
Amino acids; vitamin B substances (p. 2102·3); minerals.
Elevated homocysteine levels.

Antihus *GPH, Singapore.*
Ivy (p. 2536·2).
Cough.

Antihydral *Robugen, Ger.; Robugen, Hong Kong.*
Methenamine (p. 322·3).
Hyperhidrosis.

Antihypertonicum N *Hevert, Ger.†*
Aurum colloidale (p. 2521·1); barium jodat. (p. 2452·2); rauwolfia (p. 1485·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Antihypertonicum S *Schuck, Ger.*
Betula (p. 2457·3); crataegus (p. 2488·1); mistletoe (p. 2560·2); olive (p. 2574·3); rhododendron leaf; rutoside (p. 2505·3); proxyphylline (p. 1219·2).
Hypertension; atherosclerosis.

Antihypertonicum-Tropfen N *Schuck, Ger.†*
Barium carbonicum (p. 2452·2); crataegus (p. 2488·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Anti-Itch
Note: this name may be used for preparations of different composition.
Taro, Canad.
Diphenhydramine hydrochloride (p. 626·2).

Taro, USA.
Diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1).
Pruritus.

Anti-Kalium Na *Medice, Ger.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Antikataraktikum N *Ursapharm, Ger.†*
Disodium inosinate (p. 2495·2).
Visual disturbances.

Antikatarata Plus *Novartis, Arg.*
Potassium iodide (p. 2336·3); sodium iodide (p. 2337·1).
Cataracts.

Antikeloid *In Vitro, Hung.*
Leech (p. 1418·1); vitamin A (p. 2098·3); rutoside (p. 2505·3); dexpanthenol (p. 2582·2); vitamin E (p. 2119·1); salicylic acid (p. 1719·1).
Scars.

Antikun *Interbat, Indon.*
Piracetam (p. 393·3).
Cerebral infarction.

Antilep *Psyco Remedies, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Antilerg *Raymos, Arg.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Antilergal *Medix, Mex.*
Loratadine (p. 633·2).
Hypersensitivity reactions; rhinitis.

Antilerg-F *Demo, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Bacterial eye and ear infections with inflammation.

Antilipholine *Russian Institute of Gerontology, Rus.*
Antilymphocyte immunoglobulin (p. 1939·2).
Transplant rejection; aplastic anaemia.

Antilipid *Kleva, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Antilirium *Forest, Singapore.*
Physostigmine salicylate (p. 2009·3).
Reversal of drug-induced CNS antimuscarinic effects; postoperative intestinal atony.

Antimais Séptico *Hertz, Braz.*
Benzethonium chloride (p. 1738·1); lidocaine (p. 1988·1).

Antimas *Asconex, Ger.†*
⊗Condurango (p. 2485·3); agnus castus (p. 2432·2); hydrastis (p. 2528·1); pulsatilla (p. 2600·2); lilium tigrinum.
Homoeopathic preparation.

Antimast TN *Asconex, Ger.†*
⊗Vitex agnus castus (p. 2432·2); cyclamen purpurascens (p. 2490·2); strychnos ignatii (p. 2532·1); lilium lancifolium; thuja occidentalis (p. 2629·3); lupulinum (p. 2546·1).
Homoeopathic preparation.

Antimax *Orva, Turk.*
Doxepin hydrochloride (p. 414·2).

Antimed *Bajamed, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Antimeningococica A+C *Sanofi Pasteur, Arg.*
A meningococcal vaccine (group A and C) (p. 2401·3).
Active immunisation.

Antimet
Note: this name may be used for preparations of different composition.
Antigen, Irl.†
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Antimic *Chew, Thai.*
Isoniazid (p. 311·2).
Tuberculosis.

Antimicon
Note: this name may be used for preparations of different composition.
Casasco, Arg.
Fluconazole (p. 578·2).
Fungal infections.

Antimicotica Solforata *AFOM, Ital.†*
Sodium thiosulfate (p. 1576·1); tartaric acid (p. 2626·1).
Fungal skin infections.

Antimicotico *Savoma, Ital.*
Cream: Clotrimazole (p. 576·2).
Fungal skin infections; erythrasma; candidal balanitis.

Antimicotico Martel *Hertz, Braz.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Anti-Microbe *Atoms, Canad.*
Benzalkonium chloride (p. 1737·1).

Anti-Microbial *Skin Care, Canad.*
Triclosan (p. 1773·2).

Antimigren
Note: this name may be used for preparations of different composition.
Pascoe, Ger.
Iris (p. 2534·3); gelsemium (p. 2511·2); cyclamen (p. 2490·2); paris quadrifolia.
Homoeopathic preparation.

Zdorovje, Ukr.
Sumatriptan succinate (p. 679·2).
Migraine.

Antimigrin *Gebro, Austria.†*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Antimine Expectorant *Christo, Hong Kong.†*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Antiminth
Note: this name may be used for preparations of different composition.
Costec, Arg.
Shampoo: Pyrithione zinc (p. 1718·1).
Scalp disorders.

Costec, Arg.
Soap: Chlorhexidine gluconate (p. 1743·3).
Skin cleanser.

Anti-Mosquito *Premio, UK.*
Menthoglycol.
Insect repellent.

Antimox *East West, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Antimycotic *Biospray, Gr.*
⊗Miconazole nitrate (p. 589·1); fluprednidene acetate (p. 1637·3).
Infected skin disorders.

Antin *Kern, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Antinag *Allenge, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Antinaus *Mylan, NZ.*
Prochlorperazine maleate (p. 1098·3).
Anxiety; Ménière's disease; nausea and vomiting; psychoses; vertigo.

LCH, Hong Kong.†
Prochlorperazine (p. 1098·2).

Anti-Nauseant *Vita Health, Canad.*
Dimenhydrinate (p. 625·2).
Nausea.

Anti-Nausee *Confab, Canad.†*
Dimenhydrinate (p. 625·2).

Antinelle *Kern, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Antinerveux Lesourd *Lesourd, Fr.†*
Lotus petal; melilot (p. 2552·3).
Insomnia; irritability.

Antineuralgica
Note: this name may be used for preparations of different composition.
Egis, Hung.
Caffeine (p. 1203·3); aminophenazone (p. 21·1); phenacetin (p. 124·1).
Fever; pain.

Actavis, Norw.†
Caffeine (p. 1203·3); phenazone (p. 124·1).
Pain.

Antineurina *Tedec Meiji, Spain.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Neuritis; vitamin B deficiency.

AnTing *Zuo Li, China.*
Phentolamine mesilate (p. 1468·3).

Antinicoticum mono *Asconex, Ger.†*
⊗Lobelia inflata (p. 2323·2).
Homoeopathic preparation.

Antinol *Charoen, Thai.†*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Antio *Pentamedical, Ital.*
Zinc ricinoleate (p. 2650·2).
Body odour.

Antion *Landson, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin supplement.

Antiopiaz *Richmond, Arg.†*
Naloxone hydrochloride (p. 1562·3).
Opioid intoxication; reversal of post-anaesthetic respiratory depression.

Antiox
Note: this name may be used for preparations of different composition.
Janssen, Philipp.
Mebendazole (p. 158·3).
Worm infections.

Antioxidans E *Hevert, Ger.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Antioxidant Formula *Nutrifarma, Turk.*
Vitamins; minerals.

Rugby, USA.
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Antioxidant Forte Tablets *Vitelle, Austral.†*
Betacarotene (p. 2051·1); riboflavin (p. 2104·3); ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); *d*-alpha tocoferil acid succinate (p. 2119·2); zinc amino acid chelate (p. 2048·3); folic acid (p. 2063·1); milk thistle (p. 1561·1); grape (p. 2521·3).
Antoxidant; vitamin A, C, E, and B_2, folic acid, and zinc deficiencies.

Antioxidant Tablets *Cenovis, Austral.†; Vitelle, Austral.†*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); betacarotene (p. 2051·1); *d*-alpha tocoferil acid succinate (p. 2119·2); zinc amino acid chelate (p. 2048·3); riboflavin (p. 2104·3).
Antoxidant; vitamin A, C, E, B_2, and zinc deficiencies.

Antioxidant Vita Tech *Vita Green, Hong Kong.†*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Antioxidante Natural *Framingham, Arg.†*
d-Alpha tocopherol (p. 2119·1).
Vitamin E supplement.

Antioxidante Plus *ISA, Arg.*
Vitamins; selenium (p. 2086·3).

Antioxidante Vital *AM, Arg.*
Vitamins; minerals.
Dietary supplement.

Antioxycaps *Minskinterkaps, Rus.*
Ascorbic acid (p. 2110·3); alpha tocoferil acetate (p. 2119·2); betacarotene (p. 2051·1).
Vitamin supplement.

Antioxycaps with Iodine *Minskinterkaps, Rus.*
Betacarotene (p. 2051·1); alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); potassium iodide (p. 2336·3).
Vitamin and iodine supplement.

Antioxycaps with Selenium *Minskinterkaps, Rus.*
Ascorbic acid (p. 2110·3); alpha tocoferil acetate (p. 2119·2); betacarotene (p. 2051·1); selenium yeast (p. 2125·2).
Vitamin and selenium deficiency.

Antioxycaps with Zincum *Minskinterkaps, Rus.*
Betacarotene (p. 2051·1); alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); zinc oxide (p. 1729·1).
Vitamin and zinc supplement.

Anti-oxydant 200 *Synergia, Fr.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); lycopene (p. 2546·2); lutein (p. 2079·2); selenium (p. 2086·3).
Antoxidant preparation.

Anti-oxydant F4 *Synergia, Fr.*
Vitamin C (p. 2110·3); citroflavonoids; green tea (p. 2648·2); myrtillus (p. 2566·2); grape extract (p. 2521·3); vitamin E (p. 2119·1); carotenoids; lycopene (p. 2546·2); selenium (p. 2086·3).
Antoxidant preparation.

Antipain *Nida, Singapore.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal disorders.

Antipar *Novag, Mex.*
Botulinum A toxin (p. 2017·1).
Blepharospasm; hemifacial spasm; strabismus; spasmodic torticollis.

Antiparkin *Meda, Ger.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Antipasmol *Monserrat, Arg.*
Belladonna (p. 2453·3); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Antipect *Frankin, Hong Kong.†*
⊗Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); codeine (p. 40·2); ephedrine (p. 1663·1); menthol (p. 2553·2).
Cough; cold symptoms.

Antipen
Note: this name may be used for preparations of different composition.
Sun, India.
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Antipen-T *Sun, India.*
Nimesulide betadex (p. 101·3); tizanidine (p. 2026·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Antipeol *Medico-Biological Laboratories, UK.*
⊗Zinc oxide (p. 1729·1); ichthammol (p. 1705·3); salicylic acid (p. 1719·1); urea (p. 1727·3).
Skin disorders.

Restan, S.Afr.
Zinc oxide (p. 1729·1); ichthammol (p. 1705·3); salicylic acid (p. 1719·1).
Skin disorders.

Anti-phlegm *Sunward, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); sodium citrate (p. 1781·2).
Cough and cold symptoms.

Antiphlogistine
Note: this name may be used for preparations of different composition.
Doetsch, Grether, Switz.
Salicylic acid (p. 1719·1); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1).
Pain; inflammation.

Anti-Phosphat *Brady, Austria.*
Aluminium hydroxide (p. 1817·2).
Hyperphosphataemia.

Antiphosphat *Teva, Ger.*
Algeldrate (p. 1817·2).
Hyperphosphataemia.

Anti-phosphate *Bichsel, Switz.†*
Dried aluminium hydroxide (p. 1817·2).
Hyperphosphataemia.

Antipiol *Denolin, Belg.†*
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1).
Skin disorders.

Antiplaq *Penn, Arg.*
Clopidogrel bisulfate (p. 1342·3).

Antiplar *Emcure, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Emcure, Philipp.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Antiplat *Dexa, Indon.*
Cilostazol (p. 1337·1).
Cerebral and peripheral vascular disorders.

Antipoll *Biropharma, Hung.*
Angelica (p. 2443·3); juniper (p. 2537·1); melissa (p. 2552·3); crataegus (p. 2488·1); marjoram (p. 2550·1); marrubium (p. 1668·3); verbascum (p. 2645·1); elecampane (p. 1662·3); vervain (p. 2645·1).
Upper respiratory-tract disorders.

Anti-potasium *Assos, Turk.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Antipres
Note: this name may be used for preparations of different composition.
Giempi, Venez.
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Jelfa, Pol.
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; heart failure.

Psyco Remedies, India.
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Sandoz, Indon.
Sertraline (p. 448·1).
Depression.

Antipressan *Berk, UK.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Antiprestin *Pharos, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Antiprex *Elpen (Ελπεν), Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Antipros *Medicamerc, Gr.*
Flutamide (p. 798·2).
Prostatic cancer.

Antiprost *Orion, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Antiprotin *Julphar, UAE.*
Bromocriptine mesilate (p. 895·3).
Acromegaly; benign breast disorders; female infertility; hyperprolactinaemia; menstrual disorders; parkinsonism; prolactinoma.

Antipru *BJ Benjaosoth, Thai.*
Lotion: Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Pruritus.

BJ Benjaosoth, Thai.
Syrup; tablets: Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Antipsichos *Proel, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Antipyn Forte *Garec, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain associated with tension.

Antireumina *Teofarma, Ital.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Antirevmatický Čaj *Leros, Cz.†*
Meadowsweet (p. 2550·2); equisetum (p. 2500·1); pansy (p. 2647·3); devil's claw root (p. 42·3); salix (p. 129·2); solidaginis (p. 2620·1); calluna.
Rheumatism; influenza symptoms.

Antirrinum *Reig Jofre, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Anti-rugas C *Dermoteca, Port.†*
Ascorbic acid (p. 2110·3).
Sun-induced skin damage.

Antis *Exelixis, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Anti-Scab
Note: this name may be used for preparations of different composition.
Eczacibasi, Turk.
Permethrin (p. 2159·3).
Scabies.

Antiscab
Note: this name may be used for preparations of different composition.
Mandar, India.
Cetrimide (p. 1742·1); lindane (p. 2157·1).
Scabies.

Universal, Hong Kong.†
Benzyl benzoate (p. 2149·1).
Scabies.

Antiscabbia CM *Candioli, Ital.*
Benzyl benzoate (p. 2149·1); benzocaine (p. 1980·2); permethrin (p. 2159·3).
Scabies.

Antiscabio *Marching, Hong Kong.†*
Benzyl benzoate (p. 2149·1).
Scabies.

Antiscabiosum *Strathmann, Ger.*
Benzyl benzoate (p. 2149·1).
Scabies.

Antisept
Note: this name may be used for preparations of different composition.
Cadila, India.†
Bergenia ligulata; leptadenia reticulata; kamala; rubia cordifolia; Indian barberry (p. 2532·1); shorea robusta.
Wounds; burns; skin infections.

Antiseptic Plus *Florida, Arg.†*
Benzalkonium chloride (p. 1737·1); chlorhexidine (p. 1743·2).
Disinfection.

Antiseptic Cleanser *Niagara, Canad.; Sage, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Antiseptic First Aid *Wasip, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Antiseptic Hand Soap *Alcare, Canad.; Inland, Canad.*
Triclosan (p. 1773·2).

Dustbane, Canad.
Bronopol (p. 1740·3); triclosan (p. 1773·2).

Antiseptic Lotion *Alcare, Canad.†; Inland, Canad.†*
Chloroxylenol (p. 1748·2); phenoxyisopropanol (p. 1765·1).

Antiseptic Mouthwash *Sutton, Canad.; Trillium, Canad.*
Cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2).

Thornton & Ross, UK.
Sodium salicylate (p. 132·2); thymol (p. 1772·2); menthol (p. 2553·2).
Mouth disorders.

Antiseptic Oral Rinse *Vi-Jon, Canad.*
Cetylpyridinium chloride (p. 1743·1).

Antiseptic Salve *Golden Pride, Canad.†; Rawleigh, Canad.†*
Phenol (p. 1763·3).

Antiseptic Skin Cleanser *Canadian Custom Packaging, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Antiseptic Swabs *Zee, Canad.*
Benzalkonium chloride (p. 1737·1).

Antiseptic Throat Drops *Boots Healthcare, Irl.†*
Amylmetacresol (p. 1736·3).
Sore throat.

Antiseptic Throat Lozenges
Note: this name may be used for preparations of different composition.
Boots Healthcare, Irl.; Unichem, UK.
Amylmetacresol (p. 1736·3).
Sore throat.

Sutton, Canad.
Hexylresorcinol (p. 1755·1).

Antiseptic Wound & Skin Cleanser *MPM, USA.*
Benzethonium chloride (p. 1738·1).
Disinfection of skin and wounds.

Antiseptico *Fidex, Arg.*
Povidone-iodine (p. 1767·1).

Antiseptico Hertz *Hertz, Braz.†*
Lidocaine (p. 1988·1); benzethonium (p. 1738·1).

Antiseptin *Sanitas, Chile.*
Triclosan (p. 1773·2).
Disinfection of hands; skin infection.

Antiseptique Pastilles *Prodemdis, Canad.†*
Domiphen bromide (p. 1751·1).

Antisettico Astringente Sedativo *Bruschettini, Ital.*
⊗Zinc phenolsulfonate (p. 1729·3); sulfacetamide sodium (p. 361·1); naphazoline hydrochloride (p. 1669·3); lidocaine hydrochloride (p. 1988·2).
Conjunctivitis.

Antisklerin *Pro Vita, Hung.*
Garlic oil (p. 2510·3); soya lecithin (p. 2542·2); vitamin E (p. 2119·1).
Atherosclerosis.

Antismoke *Pro Vita, Hung.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2); calcium ascorbate (p. 2111·1); cysteine hydrochloride (p. 2058·3).
Dietary supplement for smokers.

Antisnake Venom *Bharat, India; Haffkine, India; Serum Institute, India.*
Snake venom antiserum (polyvalent) (p. 2419·1).
Snake bite.

Antispa *TP, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Antispa Plus *TP, Thai.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Antispas
Note: this name may be used for preparations of different composition.
Keene, USA.
Dicycloverine hydrochloride (p. 1834·2).
Functional bowel syndrome; irritable bowel syndrome.

Antispasmina *Hexa, Arg.*
Dipyrone (p. 53·3); papaverine hydrochloride (p. 2362·3); homatropine methylbromide (p. 2007·3).
Pain; smooth muscle spasm.

Antispasmina Colica
Note: this name may be used for preparations of different composition.
Recordati, Ital.
Papaverine hydrochloride (p. 2362·3); belladonna (p. 2453·3).
Gastrointestinal spasm.

Angelini, Port.†
Papaverine (p. 2362·2); belladonna (p. 2453·3); valerian (p. 2640·2).
Smooth muscle spasm.

Antispasmina Compuesto *Fada, Arg.*
Pargeverine (p. 1877·1); clonixin lysine (p. 40·1).

Antispasmodic Elixir *Morton Grove, USA.*
Phenobarbital (p. 535·2); hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3).

Antistax *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Fher, Ital.; Pharmaton, Rus.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK.*
Red vine (p. 2521·3).
Venous insufficiency.

Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Mex.
Grape (p. 2521·3).
Venous insufficiency.

Antisten *Ozone, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic vestibular disorders; ischaemic eye disorders.

Antisterin *Intermed, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Antistina-Privin *Novartis, Denm.*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis.

Antistine-Privine *Novartis, Austral.*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Eye irritation; allergic conjunctivitis.

Antistin-Privin *Novartis, Ger.†; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.†*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis.

Antistin-Privina *Novartis, Ital.*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis.

Anti-Stress Hi B Plus C *Roche, Hong Kong.†*
Choline (p. 2055·2); folic acid (p. 2063·1); inositol (p. 2533·2); vitamins.

Antistrumin *Darnitsa, Ukr.*
Potassium iodide (p. 2336·3).
Iodine-deficiency disorders; goitre.

Antitensin *Teuto, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension.

Antitet *Sinochem, Philipp.*
A tetanus antitoxin (p. 2420·2).
Passive immunisation.

Anti-Tet (ATS) *VHB, India.*
A tetanus vaccine (p. 2420·2).
Active immunisation.

Anti-Thyrox *Macleods, India; Sel-J, Philipp.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Antitis *Potter's, UK.*
Buchu leaf (p. 2461·3); clivers (p. 2481·2); couch-grass (p. 2487·2); equisetum (p. 2500·1); shepherd's purse (p. 2614·2); bearberry (p. 2453·2).
Urinary or bladder discomfort; cystitis.

Antitoss *Kleva, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Antitrom *Lazar, Arg.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Antitusivo *Labsa, Arg.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Antitusivo L *Labsa, Arg.*
Ambroxol (p. 1654·3); loratadine (p. 633·2).

Anti-Uron *Pliva Krakow, Pol.*
Mesna (p. 1557·2).
Prevention of urotoxicity associated with cyclophosphamide, ifosfamide, or trofosfamide.

Antiverrugas *Isdin, Spain.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Antivert *Pfizer, USA.*
Meclozine hydrochloride (p. 634·3).
Motion sickness; vertigo.

Anti-Ves *Novartis, Ital.*
Soya oil (p. 2092·3); vitamins.
Nutritional supplement.

Antivipmyn *Bioclon, Mex.*
Polyvalent crotalidae antiserum (p. 2419·1).
Snake envenomation.

Antivir
Note: this name may be used for preparations of different composition.
GPO, Thai.
Zidovudine (p. 1024·2).
HIV infection.

Sanofi-Aventis, Pol.
Aciclovir (p. 964·1).
Herpesvirus infections.

Antivirax *EMS, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Antivix *Elvipe, Gr.*
Oxeladin citrate (p. 1671·2).

Antivom
Note: this name may be used for preparations of different composition.
Teva, Hung.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Unipharma, Gr.
Betahistine hydrochloride (p. 2455·3).
Vertigo; Ménière's disease.

Anti-Vomit *Deva, Turk.*
Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Anti-White Spot *Beacons, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Anti-Worm *Leidapharm, Neth.†; Patar, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Antiworm *Hi-Tec, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Anti-Wrinkle *Johnson & Johnson, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Antix *Meda, Fin.; Meda, Norw.*
Aciclovir (p. 964·1).
Herpes labialis.

Antiza *Coronet, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Fever; cough; cold symptoms.

Antizid *Lilly, S.Afr.†*
Nizatidine (p. 1866·1).
Hyperacidity; heartburn.

Antizide *Medispan, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Antizine *Pharmasant, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; sedative.

Antizol *Paladin, Canad.; Orphan Medical, Israel; IDIS, UK; Medisource, UK; Paladin, USA.*
Fomepizole (p. 1553·1).
Ethylene glycol poisoning; methanol poisoning.

Antizolid *Verisfield, Gr.*
Linezolid (p. 317·3).
Gram-positive bacterial infections.

Antodox *Juta, Ger.†; Q-Pharm, Ger.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Antomol *Medicine Products, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; bronchitis.

Antong *Actavis, China.*
Guaifenesin (p. 1666·2); theophylline (p. 1229·3).
Bronchitis; asthma.

Antoral *Recordati, Ital.*
Tibezonium iodide (p. 2631·2).
Mouth and throat disinfection.

Antorcin *Elpen (Ελπεν), Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Antoril *Teva Tuteur, Arg.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Antotalgin *Farmina, Pol.*
Phenazone (p. 124·1).
Earache.

Antox
Note: this name may be used for preparations of different composition.
Interbat, Indon.
Lycopene (p. 2546·2); grape seed extract (p. 2521·3); green tea extract (p. 2648·2); betacarotene (p. 2051·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Nutritional supplement.

Pharma Nord, Irl.; Pharma Nord, UK.
Methionine (p. 1558·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3).
Dietary supplement for chronic pancreatitis.

Antoxid *Reddy, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).
Dietary supplement.

Antoxyl *Tablets, India.*
Vitamins; amino acids; minerals; spirulina (p. 2622·1).

Antra *AstraZeneca, Ger.; Bayer, Ger.*
Omeprazole magnesium (p. 1867·2) or omeprazole sodium (p. 1867·2).
Heartburn; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

AstraZeneca, Ital.
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

AstraZeneca, Switz.†
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Antrain *Interbat, Indon.*
Dipyrone (p. 53·3).
Pain.

Antral *Farmak, Ukr.*
Mefenamate aluminium.
Hepatitis; liver cirrhosis.

Antramups *AstraZeneca, Switz.*
Omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

AntraPro *Bayer, Switz.*
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux.

Antrazine *More, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Antrend *Labormed, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Antrenyl *Novartis, India.*
Oxyphenonium bromide (p. 1875·1).
Peptic ulcer; gastritis; gastrointestinal hyperacidity; gastrointestinal hypermotility; adjunct in diarrhoea.

Antrex *Orion, China; Orion, Fin.; Atafarm, Turk.†*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Antrima *Piramal, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Antrizine *Major, USA.*
Meclozine hydrochloride (p. 634·3).
Motion sickness; vertigo.

Antrolin *NewFaDem, Ital.*
Nifedipine (p. 1447·2); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Antroquoril *MSD, Austral.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Antuc *Neiss, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Antuc DSR *Neiss, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Antuc-IT *Neiss, India.*
Rabeprazole (p. 1881·1); itopride.
Gastro-oesophageal reflux.

Antunes *SoSe, Ital.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Antup *Teijin, Jpn.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction; ischaemic heart disease.

Anturan *Amdipharm, UK.†*
Sulfinpyrazone (p. 608·3).
Gout; hyperuricaemia.

Anturane *Novartis, USA.†*
Sulfinpyrazone (p. 608·3).
Gouty arthritis.

Anturol *Watson, USA.†*
Oxybutynin (p. 2361·2).
Bladder hyperactivity.

Antus *New York Chemical, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Antuss *Johnson & Johnson, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Nasal congestion; cough; cold symptoms.

Antuss Cough *Johnson & Johnson, China.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cough; respiratory-tract congestion.

Antussia *Asian Pharm, Thai.*
Capsules; tablets: ⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2).
Cough and cold symptoms.

Asian Pharm, Thai.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2).
Cough.

Antust *Medicine Products, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2).
Cough.

Antux *Ache, Braz.; Leti, Venez.*
Levodropropizine (p. 1662·3).
Cough.

Antygrypin *Natur Produkt, Pol.*
Aspirin (p. 22·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Pain; fever.

Antypot *Farko, Pol.*
Boric acid (p. 2459·3); salicylic acid (p. 1719·1).
Hyperhidrosis.

Anuar
Note: this name may be used for preparations of different composition.
Farmasierra, Spain.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Nova Argentia, Arg.
Levofloxacin (p. 315·3).
Bacterial infections.

Pfizer, Arg.
Injection: Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Tecnofarma, Chile.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-induced acne, alopecia, and hirsutism in women.

Anubis *Investi, Arg.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Anucare *YSP, Malaysia.*
Benzyl benzoate (p. 2149·1); peru balsam (p. 2587·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anucet *Sanobia, Port.*
Ointment: ⊗Hydrocortisone acetate (p. 1640·1); phenylephrine hydrochloride (p. 1672·3); lidocaine hydrochloride (p. 1988·2); tetracaine hydrochloride (p. 1996·3).
Anorectal disorders.

Anucort-HC *G & W, USA.*
⊗Hydrocortisone acetate (p. 1640·1).

Anufen *Medicine Products, Thai.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Anugesic *Johnson & Johnson, S.Afr.*
Ointment: Pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Pfizer Consumer, S.Afr.†
Suppositories: Bismuth subgallate (p. 1822·1); bismuth oxide (p. 1821·3); resorcinol (p. 1718·3); bismuth oxyiodide (p. 1821·3); peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1); zinc oxide (p. 1729·1); boric acid (p. 2459·3); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Anugesic-HC *McNeil Consumer, Canad.*
⊗Pramocaine hydrochloride (p. 1993·3); hydrocortisone acetate (p. 1640·1); zinc sulfate (p. 2126·2).
Anorectal disorders.

Pfizer, Irl.; Pfizer, UK.
Cream: ⊗Pramocaine hydrochloride (p. 1993·3); hydrocortisone acetate (p. 1640·1); zinc oxide (p. 1729·1); peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1); bismuth oxide (p. 1821·3).
Anorectal disorders.

Pfizer, Irl.; Pfizer, UK.†
Suppositories: ⊗Pramocaine hydrochloride (p. 1993·3); hydrocortisone acetate (p. 1640·1); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1); peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1); bismuth oxide (p. 1821·3).
Anorectal disorders.

Anulcer *Andromaco, Chile.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Anulette *Silesia, Chile.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Anu-Med
Note: this name may be used for preparations of different composition.
Major, USA.
Phenylephrine hydrochloride (p. 1672·3).
Anorectal disorders.

Anumed
Note: this name may be used for preparations of different composition.
Major, USA.
Bismuth subgallate (p. 1822·1); bismuth resorcinol compound (p. 1821·3); benzyl benzoate (p. 2149·1); zinc oxide (p. 1729·1); peru balsam (p. 2587·1).
Anorectal disorders.

Anumed HC *Major, USA.*
⊗Hydrocortisone acetate (p. 1640·1); bismuth subgallate (p. 1822·1); bismuth resorcinol compound (p. 1821·3); benzyl benzoate (p. 2149·1); peru balsam (p. 2587·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anusol
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Austral.; Pfizer, Malaysia†; Pfizer, NZ; Johnson & Johnson, Singapore
Ointment; suppositories: Zinc oxide (p. 1729·1); peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1).
Anorectal disorders.

Johnson & Johnson, Hong Kong; McNeil Healthcare, Irl.; Pfizer Consumer, UK.
Ointment; suppositories: Peru balsam (p. 2587·1); bismuth oxide (p. 1821·3); bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1).
Anorectal disorders.

McNeil, Fr.†; Johnson & Johnson, S.Afr.
Bismuth subgallate (p. 1822·1); bismuth oxide (p. 1821·3); zinc oxide (p. 1729·1).
Anorectal disorders.

McNeil, Belg.
Lidocaine hydrochloride (p. 1988·2); zinc oxide (p. 1729·1).
Haemorrhoids.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

McNeil Consumer, Canad.
Zinc sulfate (p. 2126·2).
Anorectal disorders.

McNeil Healthcare, Irl.; Pfizer Consumer, UK.
Cream: Zinc oxide (p. 1729·1); bismuth oxide (p. 1821·3); peru balsam (p. 2587·1).
Anorectal disorders.

Biosintez, Rus.; Nizhpharm, Rus.
Belladonna (p. 2453·3); zinc sulfate (p. 2126·2); bismuth tribromphenate (p. 1821·3).
Anorectal disorders.

Warner-Lambert, USA.
Ointment: Zinc oxide (p. 1729·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Elea, Arg.†
Bismuth resorcinol compound (p. 1821·3); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1); peru balsam (p. 2587·1); bismuth oxyiodide (p. 1821·3); boric acid (p. 2459·3).
Haemorrhoids.

Pfizer Consumer, Austral.†
Wipes: ⊗Hamamelis water (p. 2523·3); glycerol (p. 2517·2).
Anorectal irritation.

Pfizer, Indon.†
Bismuth subgallate (p. 1822·1); bismuth resorcinol compound (p. 1821·3); bismuth oxyiodide (p. 1821·3); zinc oxide (p. 1729·1).
Haemorrhoids; anal fissures.

Pfizer, Thai.†
Peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1); bismuth oxide (p. 1821·3); bismuth subgallate (p. 1822·1); resorcinol (p. 1718·3); zinc oxide (p. 1729·1).
Haemorrhoids; pruritus ani.

Anusol Duo *Elea, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Anusol Duo S *Elea, Arg.*
⊗Pramocaine hydrochloride (p. 1993·3); hydrocortisone acetate (p. 1640·1); benzyl benzoate (p. 2149·1); bismuth oxide (p. 1821·3); bismuth subgallate (p. 1822·1); peru balsam (p. 2587·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anusol Plus *McNeil Consumer, Canad.*
Pramocaine hydrochloride (p. 1993·3); zinc sulfate (p. 2126·2).
Anorectal disorders.

Anusol-A *Elea, Arg.*
Pramocaine hydrochloride (p. 1993·3); zinc oxide (p. 1729·1); peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1); kaolin (p. 1850·1); calcium phosphate (p. 1784·2).
Haemorrhoids.

Anusol-HC
Note: this name may be used for preparations of different composition.
Elea, Arg.
Cream: ⊗Hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Elea, Arg.
Suppositories: ⊗Hydrocortisone acetate (p. 1640·1); bismuth resorcinol compound (p. 1821·3); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1); peru balsam (p. 2587·1); boric acid (p. 2459·3); bismuth oxyiodide (p. 1821·3).
Anorectal disorders.

McNeil Consumer, Canad.
⊗Zinc sulfate (p. 2126·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

McNeil Healthcare, Irl.
⊗Hydrocortisone acetate (p. 1640·1); benzyl benzoate (p. 2149·1); bismuth subgallate (p. 1822·1); bismuth oxide (p. 1821·3); peru balsam (p. 2587·1); zinc oxide (p. 1729·1); resorcinol (p. 1718·3).
Anorectal disorders.

Pfizer, Braz.
⊗Hydrocortisone acetate (p. 1640·1); bismuth resorcinol compound (p. 1821·3); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1); peru balsam (p. 2587·1); benzyl benzoate (p. 2149·1).
Anorectal disorders.

Pfizer, Indon.†
⊗Hydrocortisone acetate (p. 1640·1); bismuth subgallate (p. 1822·1); bismuth resorcinol compound (p. 1821·3); bismuth oxyiodide (p. 1821·3); zinc oxide (p. 1729·1).
Haemorrhoids; anal pruritus.

Anusol-HC, Plus HC *Pfizer Consumer, UK.*
⊗Bismuth subgallate (p. 1822·1); bismuth oxide (p. 1821·3); peru balsam (p. 2587·1); zinc oxide (p. 1729·1); hydrocortisone acetate (p. 1640·1); benzyl benzoate (p. 2149·1).
Anorectal disorders.

Anuzinc
Note: this name may be used for preparations of different composition.
Sandoz, Canad.†; Technilab, Hong Kong.†
Zinc sulfate (p. 2126·2).
Anorectal disorders.

Technilab, Hong Kong.†
Suppositories: Bismuth oxide (p. 1821·3); bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Anuzinc HC *Sandoz, Canad.*
⊗Zinc sulfate (p. 2126·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Anuzinc HC Plus *Sabex, Canad.*
⊗Zinc sulfate (p. 2126·2); hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Anuzinc Plus *Sandoz, Canad.*
Pramocaine hydrochloride (p. 1993·3); zinc sulfate (p. 2126·2).
Anorectal disorders.

Anvelin *Tack Fung, Hong Kong.†*
⊗Terbutaline (p. 1228·1).

Anvifen *Anvi, Rus.*
Aminophenylbutyric acid hydrochloride.
Anxiety; stuttering; tics; insomnia; vestibular disorders; alcohol withdrawal syndrome.

Anviro *Zydus, S.Afr.*
Valaciclovir (p. 1021·1).

Anvistat *Antiviral, Rus.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Anvital *Dr Alson, India.*
Capsules: Vitamins; minerals; ginseng (p. 2513·3); *Lactobacillus sporogenes* (p. 2596·3).

Dr Alson, India.
Syrup: Vitamins; zinc sulfate (p. 2126·2).

Anvital DPS *Dr Alson, India.*
Vitamins; minerals; dexpanthenol (p. 2582·2); lysine hydrochloride (p. 2079·3).

Anvomer B6 *Dexa, Indon.*
Parathiazine teoclate (p. 637·1); vitamin B_6 (p. 2105·3).
Vomiting; motion sickness.

Anvomin *Christo, Hong Kong.*
Promethazine teoclate (p. 638·2).
Nausea; vertigo; vestibular disorders; motion sickness.

Anxene *Utopian, Thai.*
Dipotassium clorazepate (p. 1056·3).

Anxibloc *Dexa, Indon.*
Clobazam (p. 518·2).
Anxiety.

Anxicalm
Note: this name may be used for preparations of different composition.
Clonmel, Irl.
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; spasticity; insomnia; tetanus; premedication; epilepsy.

Lupin, India.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anxico *Aglowmed, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anxielax *Macrophar, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Anxietum *Ferrier, Fr.*
Anacardium orientale (p. 2471·3); argentum nitricum (p. 2615·3); gelsemium (p. 2511·2); ignatia amara (p. 2532·1).
Homoeopathic preparation.

Anxila *KRKA, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Anxiol *Tai Yu, Philipp.*
Diazepam (p. 1063·2).
Anxiety; premedication; status epilepticus; febrile convulsions; skeletal muscle spasm; alcohol withdrawal symptoms.

Anxiolan *Medochemie, Thai.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Anxiolit *GL Pharma, Austria; Vifor, Switz.*
Oxazepam (p. 1092·2).
Anxiety; insomnia.

Anxiolit plus *GL Pharma, Austria.*
Oxazepam (p. 1092·2); methylbenactyzium bromide (p. 1861·3).
Anxiety disorders.

Anxipose *Psychotropics, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting associated with cancer chemotherapy.

Anxira *Condrugs, Thai.*
Lorazepam (p. 1080·3).
Anxiety disorders.

Anxiron *Valeant, Hung.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Anxit *Micro, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anxit Forte *Micro, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Anxit Plus *Micro, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Anxitab *Psyco Remedies, India.*
Chlordiazepoxide (p. 1044·2); imipramine hydrochloride (p. 426·2).
Depression.

Anxium *Knop, Chile.*
St John's wort (p. 449·1).
Depression.

Anxizide *Psychotropics, India.*
Chlordiazepoxide (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; insomnia.

Anxol *Svizera, India.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; insomnia; skeletal muscle spasm; seizures; tetanus.

Anxorel *Life Medicare, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anxrea *Cinerea, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Anxut *Eisai, Ger.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Anxyl *Waves, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anxyrex *Sanofi-Aventis, Fr.†*
Bromazepam (p. 1041·2).
Anxiety; alcohol withdrawal syndrome.

Any *Homme de Fer, Fr.*
Mequinol (p. 1711·1).
Hyperpigmentation.

AnYi *Baiyunshan, China.*
Paracetamol (p. 115·1).
Fever; pain.

Anzac *T-Boma, Hong Kong†; Bangkok Lab & Cosmetic, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states; obsessive-compulsive disorder; depression.

Anzacor *Neo Quimica, Braz.*
Losartan (p. 1422·2).

Anzal *Gentech, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anzapine *CCM, Malaysia.*
Clozapine (p. 1057·3).
Schizophrenia.

AnzaPlus *Xeno, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Anzar *Xeno, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Anzatax *Hospira, Austral.; Hospira, China; Hospira, Cz.; Hospira, Hong Kong; Tempo Scan Pacific, Indon.; Hospira, Ital.; Hospira, Malaysia; Hospira, NZ; Pharmaplan, S.Afr.; Hospira, Singapore; Hospira, Thai.; Orna, Turk.*
Paclitaxel (p. 839·3).
Breast cancer; non-small cell lung cancer; ovarian cancer; Kaposi's sarcoma.

Anze *Zee, India.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Anzemet *Sanofi-Aventis, Austral.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Switz.†; Amdipharm, UK†; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Dolasetron mesilate (p. 1837·2).
Nausea and vomiting.

Anzi *Azine, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Anzibel *Nobel, Ukr.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2); enoxolone (p. 54·2).
Mouth and throat disorders.

Anzidin *Stadmed, India.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Anzilum *Cadila, India.*
Alprazolam (p. 1035·2).
Anxiety.

Anzi-P *Azine, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Anzitel *Essweil, India.*
Telmisartan (p. 1509·3).
Hypertension.

Anzitel-H *Essweil, India.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Anzol *Naprod, Philipp.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Anzolden *Denver, Arg.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia; premenstrual dysphoric disorder.

Anzolid *Claris, India.*
Linezolid (p. 317·3).
Bacterial infections.

Anzop *Hos & Ins, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Anzop-D *Hos & Ins, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Anzorin *Orion, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia.

Anzykair *PDC, India.*
Capsules; oral drops: ⊗Vitamin B substances (p. 2102·3); amylase (p. 2442·1); pepsin (p. 2586·1).

PDC, India.
Oral liquid: ⊗Vitamin B substances (p. 2102·3); dexpanthenol (p. 2582·2); amylase (p. 2442·1); pepsin (p. 2586·1); peptone (p. 2086·2).

Ao Di *Jiu Xu, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Ao-7 *Piramal, India.*
Vitamins; minerals.

Ao Bei Li *Aosaikang, China.*
Levocarnitine (p. 2053·2).

Ao Bi Xin *Yuan Rui, China.*
Candesartan cilexetil (p. 1330·2).
Heart failure; hypertension.

Ao Bo Lan *Lu Yin, China.*
Vincamine (p. 2645·2).
Cerebrovascular insufficiency; Ménière's disease.

Ao Bo Lin *Bai Li, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Ao Cheng *Huasen, China; Luye, China.*
Oxymatrine.

Ao Ding Ni *Southwest Synthetic, China.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

Ao Duo Li *Lianhuan, China.*
⊗Bambuterol hydrochloride (p. 1203·1).

Ao Er Fei *Shanghai Pharma, China.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Ao Er Man *Aosaikang, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Ao Fei Ni *Jiashidaheng, China.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Ao Fu *Nhwa, China.*
Ligustrazine hydrochloride.

Ao Fu An *C & O, China.*
Clarithromycin (p. 266·2).
Bacterial infections.

Ao Di Fu Kang *Huakang, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ao Ge Er *Kang Yuan, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders; cerebral trauma.

Ao Ge Men Ding *Welman, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ao Ge Shen *Jian Fa, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ao Gu Li *Aosaikang, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ao Guang Su *Yang Zhou, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Ao Guang Xian *Yang Zhou, China.*
Gatifloxacin mesilate.
Bacterial infections.

Ao Gui Ren *Yang Zhou, China.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Ao Hui Feng *Lianhuan, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Ao Jia *Di Ao Jiu Hong, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Ao Jia Xi *Yang Zhou, China.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Ao De Jin *Ao Hong, China.*
Deproteinised calf blood (p. 2444·1).

Ao Kang Xin *A o Dong Yan Bian, China.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Ao Ke *C & O, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ao Ke An *Grand, China.*
Metronidazole (p. 936·1).
Mouth infections.

Ao Ke Qing *Tong Ji Xian Dai, China.*
Oxaprozin (p. 112·3).
Musculoskeletal and joint disorders; gout; pain.

Ao Lai Ke *Di Ao, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Ao Li De *Yang Zhou, China.*
Ligustrazine phosphate.

Ao Li Ao *Yang Zhou, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Ao Li Bao Ke *Ao Li Da Nai De, China.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebrovascular disorders; vertigo; vestibular disorders.

Ao Li Ning *Si Huan Ke Bao, China.*
Ethylenediamine diaceturate.

Ao Li Ping *Aoya, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ao Li Tuo *Wan Long, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Ao Li Xi *Si Huan Ke Bao, China.*
Aceglutamide (p. 2426·2).

Ao Li Xian *Aosaikang, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Ao Li Ya *Actavis, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ao Luo Hua *Yellow River, China.*
Rosiglitazone hydrochloride (p. 496·3).
Diabetes mellitus.

Ao Mai Bi Li *Ao Li Da Nai De, China.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Ao Di Mai Er *Ao Li Da Nai De, China.*
Verapamil hydrochloride (p. 1522·1).
Supraventricular arrhythmias; angina pectoris; hypertension.

Ao Mai Lun *ZhongXi, China.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Ao Mei Xin *Yi Ao, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Ao Mi Xin *Jida, China.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Ao Ming Run *Aosaikang, China.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Ao Na Xin *TaiYuan, China.*
Meglumine adenosine cyclophosphate.

Ao Le Ni *C & O, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Ao Ni Jie *SanJiu, China.*
Mizolastine (p. 636·1).
Hypersensitivity reactions.

Ao Ni Ya *Lianhuan, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ao De Ning *Hai Shan, China.*
Cefixime (p. 240·3).
Bacterial infections.

Ao Ning
Note: this name may be used for preparations of different composition.
Qian Jin Xiang Jiang, China.
Tablets: Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity.

Rui Yang, China.
Injection: Oxymatrine.

Ao Nuo Hong *Aosaikang, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Ao Nuo Sheng *Yang Zhou, China.*
Oxymatrine.

Ao Nuo Xian *Aosaikang, China.*
Dexrazoxane (p. 1548·1).

Ao Nuo Ya *Aosaikang, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Ao Pai *ZhongXi, China.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Ao Pu Li *Di Ao, China.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Ao Pu Xin *FuDong, China.*
Oxaprozin (p. 112·3).
Osteoarthritis; rheumatoid arthritis.

Ao Qi *C & O, China.*
⊗Exemestane (p. 792·2).
Breast cancer.

Ao Qun *Jiu Xu, China.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Ao Rou La *Jinyu, China.*
Potassium sodium dehydroandroandrographolide succinate.

Ao Rui Ai *Si Huan Ke Bao, China.*
Aminomethylbenzoic acid (p. 1132·2).

Ao Rui Xin *Meng Xin, China.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Ao Sai Jing *Yi Ao, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Ao Sai Tuo Xing *Mei Ka, China.*
Oxytocin (p. 2143·1).
Promotion of lactation.

Ao Shu *Weiao, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Ao Shu Jie *C & O, China.*
Levocarnitine (p. 2053·2).

Ao Shu Zhi *C & O, China.*
Liranaftate (p. 588·1).

Ao Si Hui *Xing Qun, China.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; hypoparathyroidism; hypophosphataemia; renal osteodystrophy; rickets; osteomalacia.

Ao Si Ling *Dong Fang, China.*
⊗Chlorphenamine maleate (p. 620·3); pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Ao Si Ping *ZhongXi, China.*
Duloxetine hydrochloride (p. 415·1).
Stress urinary incontinence in women.

Ao Si Tan *Tuo Bin, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ao Te Min *Bu Chang, China.*
Tranilast (p. 1239·1).

Ao Tian Li *Aosaikang, China.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Ao Tian Yu *Zhong Bao, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Ao Tian Yuan *Yang Zhou, China.*
Ethylenediamine diaceturate.

Ao Wan Ji *Lianhuan, China.*
Gatifloxacin mesilate.
Bacterial infections.

Ao Wan Lu *Lianhuan, China.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Ao Wan Yuan *Yang Zhou, China.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Ao Wei Kang *Sanjiu Aidefu, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ao Wei Li *Yang Zhou, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Ao Wei Mei *Aosaikang, China.*
Gatifloxacin mesilate.
Bacterial infections.

Ao Wei Te *ZhongTian, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ao Wei Xian
Note: this name may be used for preparations of different composition.
Hengrui, China.
Tablets: Itopride hydrochloride (p. 1850·1).
Nausea and vomiting; gastrointestinal motility disorders.

Aosaikang, China.†
Injection: Levofloxacin lactate.
Bacterial infections.

Ao Xi Tong *Yi Ao, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Ao Xian *Bright Future, China.†*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ao Xian Da *Aosaikang, China.*
Nedaplatin (p. 834·3).

Ao Xian Ning *C & O, China.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Ao Le Xin *Wu Zhou Tong, China.*
Asarone.

Ao Xin Kang *ShiJiaZhuang No 4, China.*
Ozagrel (p. 2579·1).

Ao Di Ya *Aosaikang, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ao Yi Ding *Guo Ao, China.*
Moxonidine hydrochloride.
Hypertension.

Ao Yi Ning *Yang Zhou, China.*
Aceglutamide (p. 2426·2).

Ao Yi Xin *Aosaikang, China.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; peri-operative hypertension.

Ao De Zhen *Guo Yao, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Ao Zheng Nan *Aosaikang, China.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

A-OD *Elisa, India.*
Azithromycin (p. 221·2).
Bacterial infections.

AO-Encap *Thorne, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc citrate (p. 2126·2).

Aofen
Note: this name may be used for preparations of different composition.
C & O, China.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Medicine Products, Thai.
Griseofulvin (p. 582·2).
Fungal infections of skin, hair, and nails.

Aofolin *Bright Future, China.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Aofuqing *Bright Future, China.*
Calcipotriol (p. 1697·2).
Psoriasis.

Aofuxing *Double-Crane, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Aokelu *Lianhuan, China.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Aoluona *Aosaikang, China.*
Topotecan hydrochloride (p. 872·3).
Small-cell lung cancer; ovarian cancer.

Aomeizhen *Shanghai No 1, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Aoneng *Bright Future, China.*
⊗Halometasone (p. 1639·3).
Skin disorders.

AoNing *Ai Sheng, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Aoqi *Rotam Reddy, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Aoricet *Medicine Products, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Aorinyl *Medicine Products, Thai.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1); phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion; allergic respiratory-tract disorders.

Aorten *Brasterapica, Braz.*
Captopril (p. 1331·2).
Hypertension.

Aosept *Ciba Vision, Austral.; Ciba Vision, Canad.; Ciba Vision, NZ; Ciba Vision, USA.*
Hydrogen peroxide (p. 1755·2).
Disinfection and storage of contact lenses.

Aosept Plus *Ciba Vision, Arg.*
Hydrogen peroxide (p. 1755·2).
Disinfecting solution for contact lenses.

AoShu *C & O, China.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

AoShuDa *Bright Future, China.*
Erythromycin (p. 291·2).
Bacterial infections.

AoShuXin *Bright Future, China.*
Erythromycin (p. 291·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

A-Ostin-D3 *Farmedia, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Aotal *Merck Serono, Fr.*
Acamprosate calcium (p. 1034·2).
Alcoholism.

Aotong *Treeful, China.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Aova *Velka, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Aamorb, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Aova-EZ *Aamorb, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Aova-F *Aamorb, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Aoweishu *C & O, China.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); methiosulfonium chloride (p. 2558·1); belladonna (p. 2453·3).
Gastric pain caused by hyperacidity or gastritis.

Aoxikang *Aosaikang, China; Lianhuan, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Aoyimai *Aosaikang, China.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

AP *Steigerwald, Ger.*
A range of homoeopathic preparations.
Homoeopathic preparation.

AP-2 *Kyorin, Jpn.*
Simetride; caffeine (p. 1203·3).
Inflammation; pain.

AP Methylpred *Aspen, S.Afr.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

APA *Lannacher, Austria.†*
Tablets: Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Apacet *Parmed, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Apadex *Egis, Hung.*
⊗Indapamide (p. 1409·2).
Hypertension.

Apagen *Stomygen, Ital.*
Hydroxyapatite (p. 2529·3).
Dental disorders.

Apaisance *Lierac, Fr.†*
Cream: Tilia (p. 2631·3); mallow (p. 2549·2); avena (p. 2451·1); ashwagandha (p. 2450·2); inca inchi oil.
Skin disorders.

Apaisyl *Merck Medication Familiale, Fr.†*
Isothipendyl hydrochloride (p. 631·2).
Hypersensitivity.

Apaisylgel *Merck Medication Familiale, Fr.*
Isothipendyl hydrochloride (p. 631·2).
Insect bites and stings.

Apalin *CCM, Malaysia.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Apamox *Euroespes, Spain; Pliva, Spain.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Apanta *Alpic, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Apap *Medique, Canad.; US Pharmacia, Pol.; US Pharmacia, Rus.; Cypress, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Apap C Plus *US Pharmacia, Pol.; US Pharmacia, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; pain; fever.

Apap Extra *US Pharmacia, Pol.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Apap Noc *US Pharmacia, Pol.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Pain with insomnia.

Apap Przeziebienie Extra Plus *US Pharmacia, Pol.*
⊗Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; cough.

A-Par *Omega, Fr.*
Tetramethrin (p. 2162·2); phenothrin (p. 2160·1).
Destruction of scabies mite, fleas and lice in textiles and adjunct to treatment.

Aparoxal *Pierre Fabre, Fr.*
Phenobarbital (p. 535·2).
Epilepsy.

Apasmo *Sidus, Arg.*
Camylofin hydrochloride (p. 2467·1); dipyrone (p. 53·3).
Smooth muscle pain and spasm.

Apasmo Compuesto *Sidus, Arg.*
Pargeverine (p. 1877·1); dipyrone (p. 53·3).
Smooth muscle pain and spasm.

Apatinac *Herbapol Wroclaw, Pol.*
St John's wort (p. 449·1).
Depression.

Apatite *Weleda, UK.*
Apatite; cucurbita flowers (p. 2489·2).
Homoeopathic preparation.

Apaurin *KRKA, Cz.; KRKA, Rus.*
Diazepam (p. 1063·2).
Anxiety disorders; alcohol withdrawal syndrome; epilepsy; tetanus; skeletal muscle spasm; premedication; eclampsia; sleep disorders; status epilepticus.

Apazol *Dexa, Indon.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

APC *Apotex, Neth.; Sameko, Neth.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Apcal Forte *Ajanta, India.*
Vitamins; minerals.

Apdil *Ajanta, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Apdrops *Ajanta, India.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Apecitab *Dosa, Arg.*
Capecitabine (p. 757·3).
Malignant neoplasms.

Apecur *Simex, Indon.*
Vitamins; curcuminoid (p. 2489·3); dexpanthenol (p. 2582·2); calcium pidolate (p. 1784·3); fructo-oligosaccharides (p. 2508·1).
Dietary supplement.

Apedin *Medizone, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Apel *Lancer, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Apel-G *Lancer, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

A-Pen
Note: this name may be used for preparations of different composition.
Orion, Fin.
Ampicillin sodium (p. 218·2).
Bacterial infections.

Apen
Note: this name may be used for preparations of different composition.
Mylan, S.Afr.
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Apenic *Candor, India.*
Cyproheptadine (p. 624·1); dried yeast (p. 2125·2).

Apenorm *Cipla, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity disorders; migraine and other vascular headaches.

Apentin *Biomedica, Ital.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Apentral *Arlak, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Apentral-D *Arlak, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Apeplus
Note: this name may be used for preparations of different composition.
Lafedar, Arg.
Cyproheptadine hydrochloride (p. 624·1); cyanocobalamin (p. 2107·2); calcium phosphate (p. 1784·2).
Reduced appetite.

Radicura, India.
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

A-Per *Aroma, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Apercap *Auden McKenzie, UK.*
Peppermint oil (p. 1877·1).
Gastrointestinal spasm; flatulence.

Apergan *Panzera, Ital.*
Royal jelly (p. 2608·1); glucose (p. 2068·3); ginseng (p. 2513·3).
Nutritional supplement.

Aperisan *Dentinox, Ger.; Penta, Hung.; Dentinox, Pol.*
Sage (p. 2608·3).
Mouth and throat inflammation.

Aperixon *Temapharm, Cz.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Aperomid *Masterlek, Rus.*
Pipecuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Apertum-Ox *Rayere, Mex.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Apetamin *Tablets, India.*
Cyproheptadine hydrochloride (p. 624·1).
Reduced appetite.

Apetil
Note: this name may be used for preparations of different composition.
Bunker, Braz.
Buclizine hydrochloride (p. 618·3); amino acids; vitamin B substances (p. 2102·3).
Tonic; reduced appetite.

Apetitol Forte *Mertens, Arg.*
Cyproheptadine hydrochloride (p. 624·1); vitamins.
Reduced appetite.

Apetivit BC *Cifarma, Braz.*
Cyproheptadine hydrochloride (p. 624·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Reduced appetite; vitamin deficiency.

Apetiviton BC *Cifarma, Braz.*
Cyproheptadine hydrochloride (p. 624·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Reduced appetite.

Apeton *IPI, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic skin disorders; rhinitis.

Apetrol *Medipharm, Chile.*
Cyproheptadine hydrochloride (p. 624·1); vitamins.
Reduced appetite.

Apevinat BC *Airela, Braz.*
Cyproheptadine (p. 624·1); thiamine (p. 2102·3); riboflavin (p. 2104·3); pyridoxine (p. 2105·3); ascorbic acid (p. 2110·3).

Apevitin BC *EMS, Braz.*
Cyproheptadine hydrochloride (p. 624·1); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Tonic; reduced appetite.

Apex
Note: this name may be used for preparations of different composition.
Biokem, Turk.
Codeine phosphate (p. 40·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms; sinusitis; rhinitis.

Gerolymatos, Gr.
Bicalutamide (p. 749·1).
Prostatic cancer.

Apex Repel *Skin Shield, Austral.*
Pump spray: Diethyltoluamide (p. 2153·1); ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Skin Shield, Austral.
Roll-on: Diethyltoluamide (p. 2153·1).
Insect repellent.

Apex Repel Junior *Apex, NZ.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Apex Repel Natural *Skin Shield, Austral.*
Lavender oil (p. 2541·1); melaleuca oil (p. 2551·1); eucalyptus oil (p. 2501·2); lemon grass oil (p. 2543·2); citronella oil (p. 2481·1).
Insect repellent.

Apex Repel New Era *Skin Shield, Austral.; Apex, NZ.*
Icaridin (p. 2156·3).
Insect repellent.

Apex Repel with Sunscreen *Skin Shield, Austral.*
SPF 23+: Diethyltoluamide (p. 2153·1); ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent; sunscreen.

Apex Repel Super *Apex, NZ.*
Topical spray: Diethyltoluamide (p. 2153·1).
Insect repellent.

Apex, Austral.†
Diethyltoluamide (p. 2153·1); 1,3-di(4-imidazolino-2-methoxyphenoxy)propane.
Insect repellent.

Apex, NZ.†
Lotion: Diethyltoluamide (p. 2153·1); ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Apex Repel Super with Sunscreen *Apex, NZ.*
Topical spray: Diethyltoluamide (p. 2153·1).
Insect repellent.

Apex Repel Ultra *Skin Shield, Austral.; Apex, NZ.*
Diethyltoluamide (p. 2153·1); ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Apex-Clavutin *Austell, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

ApexiCon *Sandoz, USA.*
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Apextatin *Kanonfarma, Rus.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Apgel *H & H, India.*
Adapalene (p. 1692·1).
Acne.

Aphen *MedChem, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Aphénylbarbit *Streuli, Switz.*
Phenobarbital (p. 535·2).
Epilepsy; sedative; febrile convulsions.

Aphilan *Pierre Fabre, Fr.*
Cream: ⊗Hydrocortisone acetate (p. 1640·1).
Bites; stings; sunburn.

A-phine *Daewon, Hong Kong.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

A-P-Histallin *Medichem, Philipp.†*
Phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1).
Cold symptoms.

Aphloïne P *DB, Fr.*
Aphloia; hamamelis (p. 2523·3); viburnum (p. 2458·1); esculoside (p. 2431·2).
Peripheral vascular insufficiency; haemorrhoids.

Aphlubin-Naze *Bittner, Rus.*
Sinapis nigra (p. 2566·1); euphorbium resiniferous; pulsatilla (p. 2600·2); luffa (p. 2545·3); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Aphrenil *Euro-Med, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Aphrodyne *Star, USA.*
Yohimbine hydrochloride (p. 2372·3).

Aphrofem *Liptis, USA.*
Lyophilised fish roe; ginkgo biloba (p. 2512·3).

Aphtagone *Trima, Israel.†*
Aloe vera (p. 1693·2); benzalkonium chloride (p. 1737·1); enoxolone (p. 54·2); sodium hyaluronate (p. 2526·2); povidone (p. 2204·3).
Oral lesions.

Aphthasol *Discus, USA.†*
Amlexanox (p. 1202·2).
Aphthous ulcers.

Aphtheal *Meda, Irl.*
Amlexanox (p. 1202·2).
Aphthous ulcer.

Aphtin *Aflofarm, Pol.; Coel, Pol.; Farmina, Pol.; Galenowe Olsztyn, Pol.; Microfarm, Pol.; Prolab, Pol.*
Borax (p. 2459·2).
Mouth infections.

Aphtoral *Pierre Fabre, Fr.*
Chlorhexidine gluconate (p. 1743·3); tetracaine hydrochloride (p. 1996·3); ascorbic acid (p. 2110·3).
Mouth and throat disorders.

Api Baby *Sanitalia, Ital.*
Pollen (p. 2593·3); royal jelly (p. 2608·1); fructose (p. 2068·2); myrtillus (p. 2566·2).
Nutritional supplement.

Apialys *Lapi, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Apibact *Prolisok, Ukr.*
Bifidobacteria; lactobacillus propionic acid bacteria; lactococci; streptococci; acetobacters; propolis (p. 2597·3).
Maintenance of normal gastrointestinal flora.

Apidin *Indian Drugs, India.*
Aspirin (p. 22·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Apidox *Alicon, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Apidra *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Aventis Pasteur, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi Pasteur, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.†; Aventis, USA.*
⊗Insulin glulisine (p. 475·3).
Diabetes mellitus.

ApiHelix *Apipol, Pol.†*
Ivy (p. 2536·2); liquorice (p. 1853·2); thyme (p. 2630·2).
Respiratory-tract inflammation.

Apihepar *Meda, Austria.*
Milk thistle (p. 1561·1).
Liver disorders.

Apihist *Bombay Tablet, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Apikobal *Santa, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Apilac *Grindex, Rus.; Grindeks, Ukr.*
Royal jelly (p. 2608·1).
Tonic; skin disorders.

Apilaxe *Cooperation Pharmaceutique, Fr.*
Sorbitol (p. 2092·1); althaea leaf (p. 2438·3).
Constipation.

Apilep *Sanovel, Turk.*
Oxcarbazepine (p. 533·2).

Apilepsin *KRKA, Rus.†*
Sodium valproate (p. 553·1).
Epilepsy; spasticity; bipolar disorder; febrile convulsions.

Apimore *Cosme, India.*
Cuminum cyminum; cyperus rotundus; fennel (p. 2503·2); piper longum; tinospora cordifolia; trachyspermum ammi.

Apimox *Alicon, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Apinorm *Apipol, Pol.†*
Aloes (p. 1816·1); caraway (p. 2470·2); aniseed (p. 2444·2).
Constipation; bowel evacuation.

AP-Inyect *Fresenius Kabi, Spain.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Apiprost *Zdorovje, Ukr.*
Propolis (p. 2597·3); flower pollen (p. 2593·3).
Prostatitis; chronic pelvic pain.

Apipulmol *Apipol, Pol.*
Ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1).
Cough.

Apiracohl *Kyowa, Jpn.†*
Todralazine hydrochloride (p. 1516·1).
Hypertension.

Apiredol *Ionfarma, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Apiret *Oftalmi, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Apiretal *Ern, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Apiretal Codeina *Ern, Spain.†*
Paracetamol (p. 115·1); codeine (p. 40·2).
Pain.

Apirich *USP, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Apirofeno *Ern, Spain.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Apirol
Note: this name may be used for preparations of different composition.
Koutsoumani, Gr.
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.
MSD, Israel.†
Norfloxacin (p. 333·3).
Bacterial infections.

Apiron *Delta, Braz.*
Dipyrone (p. 53·3).
Pain; fever.

Apiroserum Clorurado *Fresenius Kabi, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Apiroserum Glucosado *Fresenius Kabi, Spain.*
Glucose (p. 2068·3).
Fluid and electrolyte disorders; parenteral nutrition.

Apiroserum Glucosalino *Fresenius Kabi, Spain.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Apiroserum Normaion Restaurador *Fresenius Kabi, Spain.*
Glucose (p. 2068·3); electrolytes (p. 1775·1).

Apiroserum Ringer *Fresenius Kabi, Spain.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Apiroserum Ringer Lactato *Fresenius Kabi, Spain.*
Electrolytes (p. 1775·1); sodium lactate (p. 1781·2).
Fluid and electrolyte disorders.

Apis Compuesto *Ximena Polanco, Chile.*
Apis (p. 2445·2); histaminum (p. 2525·2); rhus toxicodendron (p. 2603·3); urtica urens (p. 2639·3).
Homoeopathic preparation.

Apisarthron *Esparma, Hung.; Esparma, Ukr.*
Bee venom (p. 2445·2); methyl salicylate (p. 92·1); allyl isothiocyanate (p. 2436·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis; sciatica; radiculitis; peripheral vascular disorders.
Esparma, Cz.†; Esparma, Rus.
Bee venom (p. 2445·2); methyl salicylate (p. 92·1); volatile mustard oil (p. 2646·1).
Musculoskeletal, peri-articular, and soft-tissue disorders; neuralgia; neuritis.

Apisate *Sunthi Sepuri, Indon.†; Wyeth, Indon.†*
⊗Diethylpropion hydrochloride (p. 2321·1); vitamin B substances (p. 2102·3).
Obesity.

Apiserum *DB, Fr.*
Royal jelly (p. 2608·1).
Tonic.

Apiserum con Telergon 1 *Medicalfarm, Ital.†*
Wine; acacia honey (p. 2072·1); royal jelly (p. 2608·1).
Nutritional supplement.

Apistress *Sanitalia, Ital.*
Royal jelly (p. 2608·1); pollen (p. 2593·3); propolis (p. 2597·3).
Nutritional supplement.

Apitol *Lupin, Ukr.*
Picrorhiza kurroa (p. 2590·2); fennel (p. 2503·2); cuminum cyminum; trachyspermum ammi; piper longum; ginger (p. 1844·1).
Reduced appetite.

Apitussic *Apipol, Pol.*
Sulfogaiacol (p. 1678·1).
Respiratory-tract disorders.

Apitus-TC *Lexus, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Apizel *Apipol, Pol.*
Propolis (p. 2597·3).
Skin disorders; burns; insect bites.

APL *Akromed, S.Afr.†*
⊗Chorionic gonadotrophin (p. 2258·1).
Infertility; cryptorchidism; male hypogonadism.

Aplacaina *Richmond, Arg.†*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Aplacasse *Menarini, Arg.*
Lorazepam (p. 1080·3).
Anxiety.

Aplace *Kyorin, Jpn.*
Troxipide (p. 1894·3).
Peptic ulcer; gastritis.

Aplacid *ITF, Chile.*
Sulpiride (p. 1107·3).
Depression.

Aplactin *FIRMA, Ital.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; atherosclerosis.

Aplaket *Rottapharm, Hong Kong; Rottapharm, Ital.; Rotta, Malaysia; Delta, Port.; Rottapharm, Singapore; Rotta, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis; maintenance of extracorporeal circulation.
Elder, India.
Ticlopidine (p. 1512·1).
Stroke prophylaxis; ischaemic heart disease; intermittent claudication; thromboembolism prophylaxis during stent placement.

Aplatic *Ratiopharm, Hung.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Aplatin *Saga, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Aplause *Marjan, Braz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Aplenzin *Valeant, USA.*
Bupropion hydrobromide (p. 408·2).
Depression; seasonal-affective disorder.

Aplicav *Libbs, Braz.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Apligraf *Novartis, USA.*
Bioengineered human skin equivalent (p. 1720·2).
Diabetic foot ulcers; venous leg ulcers.

Aplisol *JHP, USA.*
Tuberculin purified protein derivative (p. 2635·3).
Diagnosis of tuberculosis.

Aplom *Valmor, Venez.*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aplona *Athenstaedt, Ger.*
Apple powder; colloidal silicon dioxide (p. 2209·1).
Diarrhoea.

Aplonit *Unipharma, Gr.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension.

Aplosyn *Pascual, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.
Yik Kwan, Hong Kong.†
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Aplosyn C *Pascual, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Aplosyn N *Pascual, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Aplosyn-C *Yik Kwan, Hong Kong.†*
⊗Fluocinolone (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Aplosyn-N *Yik Kwan, Hong Kong.†*
⊗Fluocinolone (p. 1636·1); neomycin (p. 329·3).
Infected skin disorders.

Aplosyn-Otic *Pascual, Hong Kong; Pascual, Philipp.*
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); fluocinolone acetonide (p. 1636·1).
Otitis externa; otitis media; infected ear disorders.

Apmed *Cimed, Braz.*
Cyproheptadine hydrochloride (p. 624·1); vitamins.
Reduced appetite.

Apnol *Pharmaland, Thai.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Apo *Demo, Gr.*
Zidovudine (p. 1024·2).
HIV infection.

Apo-Acebutol *Apotex, Cz.*
⊗Acebutolol hydrochloride (p. 1289·2).
Hypertension; arrhythmias; angina pectoris; myocardial infarction.

Apo-Alpraz *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Alprazolam (p. 1035·2).
Anxiety; sedative.

Apo-Amilzide *Apotex, Canad.; Apotex, Cz.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis with ascites.

Apo-Amlo *Apotex, Cz.; Apotex, Pol.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Apo-Amoxi *Apotex, Canad.; Apotex, NZ; Apotex, Pol.†; Apotex, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Apo-Amoxi Clav *Apotex, Canad.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Apo-Ampi *Apotex, Canad.; Hind Wing, Hong Kong.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Apo-Asa *Apotex, Canad.*
Aspirin (p. 22·2).

Apo-Atenidone *Apotex, Canad.; Apotex, Malaysia.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Apo-Atenol *Apotex, Canad.; Apotex, Cz.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Apo-Atorva *Apotex, Pol.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Apobacyn *Gerolymatos, Gr.*
Neomycin (p. 329·3); bacitracin zinc (p. 225·3).
Bacterial skin infections.

Apobase *Actavis, Fin.*
Emollient.

Apo-Benztropine *Apotex, Cz.†*
Benzatropine mesilate (p. 894·3).
Parkinsonism; dystonia.

Apo-C *Apotex, Canad.†*
Ascorbic acid (p. 2110·3).
Vitamin supplement.

Apo-Cal *Apotex, Canad.; Apotex, Hong Kong; Apotex, Singapore.*
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency.

Apo-Capto *Apotex, Canad.; Apotex, Rus.†; Apotex, Singapore.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Apocard *Meda, Belg.; Meda, Port.; Meda, Spain.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Apo-Carve *Apotex, Cz.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; hypertension.

Apo-Cephalex *Apotex, Canad.; Apotex, Hong Kong†; Apotex, Singapore.*
Cefalexin (p. 234·1).
Bacterial infections.

Apo-Chlorax *Apotex, Canad.; Apotex, Singapore.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal disorders with associated anxiety.

Apochralen *Chrispa (Χρισπα), Gr.*
Ambroxol hydrochloride (p. 1654·3).

Apocillin *Actavis, Norw.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Apocin *Apotex, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Apo-Ciproflox *Apotex, Canad.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Apocit *Apogepha, Ger.*
Potassium sodium hydrogen citrate (p. 1780·3).
Renal calculi.

Apo-Cital *Apotex, Cz.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Apoclavox *Apotex, Mex.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Apo-Clodin *Apotex, Pol.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis.

Apo-Cloxi *Apotex, Canad.; Apotex, Hong Kong; Apotex, Singapore.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Apo-Combilos *Apotex, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Apo-Conest *Apotex, Canad.†*
Conjugated oestrogens (p. 2260·1).

Apocort *Actavis, Fin.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Apo-Cromolyn *Apotex, Canad.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis; asthma.

Apocyclin *Actavis, Fin.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Apodefil *Apotex, Mex.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Apodepi *Apotex, Hung.*
Paroxetine (p. 440·3).
Anxiety; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia.

Apodespan *Accord, UK.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Apo-Diclo *Apotex, Canad.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Apotex, China; Apotex, Cz.; Apotex, NZ; Apotex, Rus.†
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; inflammation; pain.

Apotex, Hong Kong; Apotex, Pol.†; Apotex, Singapore.
Diclofenac (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Apo-Diltiaz *Apotex, Canad.; Apotex, Hong Kong.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Apo-Doperil *Apotex, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's dementia.

Apodorm *Alpharma, Denm.; Actavis, Norw.; Actavis, Swed.†*
Nitrazepam (p. 1089·1).
Insomnia; absence seizures; epilepsy; infantile spasm.

Apodox *Uniroyal, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Apo-Doxan *Apotex, Pol.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Apo-Doxy *Apotex, Canad.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Apotex, Singapore.
Doxycycline (p. 288·1).
Bacterial infections.

Apodrolen *Apotex, Mex.*
Alendronic acid (p. 1171·3).
Osteoporosis.

Apodrot *Apotex, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Apodruff *Apotex, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Apo-Erythro *Apotex, Canad.*
Erythromycin (p. 291·2), erythromycin ethyl succinate (p. 291·2), or erythromycin stearate (p. 291·3).
Bacterial infections.

Apofarm *Gezzi, Arg.*
Aciclovir (p. 964·1).
Herpes infections of the face and lips.

Apo-Feno *Apotex, Canad.; Apotex, Cz.; Apotex, Hong Kong; Apotex, Pol.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Apo-Feno-Micro *Apotex, Malaysia; Apotex, Singapore.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Apo-Fide *Apotex, Mex.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Apofin *Chiesi, Ital.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Apo-Fina *Apotex, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Apo-Finas *Apotex, Cz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Apoflox
Note: this name may be used for preparations of different composition.
Apotex, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Apotex, Mex.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Apo-Fluoxetine *Apotex, Rus.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Apo-Flutam *Apotex, Pol.*
Flutamide (p. 798·2).
Prostatic cancer.

Apoflux *Santa, Gr.*
Sodium fluoride (p. 2089·2).
Prophylaxis of dental caries.

Apo-Fosinop *Apotex, Cz.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Apo-Gab *Apotex, Cz.*
Gabapentin (p. 523·3).
Epilepsy; peripheral neuropathy.

Apo-Gain *Apotex, Canad.; Apotex, Malaysia.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Apo-Galant *Apotex, Cz.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Apogeo *Progen, Ital.*
Soya isoflavones (p. 2620·3); vitamin E (p. 2119·1).
Nutritional supplement for the menopause.

Apo-Glim *Apotex, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Apo-Glimep *Apotex, Cz.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Apogly *Apotex, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

APO-go *Cephalon, Austria; ITF, Chile; Medeva, Cz.; NordicInfu Care, Denm.; Britannia Pharmaceuticals, Fin.; Licher, Ger.; ITF, Gr.; Stada, Hong Kong; Genus, Irl.; Teva, Israel; Britannia Pharmaceuticals, Neth.; Hospira, NZ†; Britannia Pharmaceuticals, Port.; Britannia Pharmaceuticals, Spain; NordicInfu Care, Swed.; Stada, Thai.; Gen, Turk.; Britannia Pharmaceuticals, UK.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Apogrip *Apotex, Spain.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Apo-Hepat *Pekana, Neth.*
Boldo fragrans (p. 2458·3); chionanthus virginica; cynara scolymos (p. 2490·3); iberis amara; lycopodium clavatum (p. 2547·1); mandragora officinarum; phosphorus (p. 2589·2); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Apo-Hexa *Apotex, Canad.†*
Vitamins.

Apo-Hydro *Apotex, Canad.; Hind Wing, Hong Kong†; Apotex, Malaysia; Apotex, Singapore.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Apo-Hydroxyquine *Apotex, Canad.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; malaria.

Apo-Indap *Apotex, Pol.*
⊗Indapamide (p. 1409·2).
Hypertension.

Apo-Ipravent *Apotex, Canad.; Apotex, NZ.*
Ipratropium bromide (p. 1211·3).
Bronchodilator; obstructive airways disease; rhinitis.

Apo-ISDN *Apotex, Canad.; Apotex, Hong Kong; Apotex, Singapore.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Apo-ISMN *Apotex, Canad.; Apotex, Hong Kong.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Apo-K *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
Potassium chloride (p. 1793·2).
Potassium depletion; hypokalaemia; digitalis intoxication.

Apo-Keto *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Ketoprofen (p. 79·1).
Pain; inflammation; musculoskeletal and joint disorders.

Apo-Keto-E *Apotex, Hong Kong.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders.

Apokinon *Buxton, Arg.; Aguettant, Fr.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Apokyn *Kyowa Hakko Kirin, Jpn; US Worldmeds, USA.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Apol *Etifar, Venez.*
Vitamins; minerals.
Dietary supplement.

Apolar *Actavis, Fin.; Actavis, Indon.; Actavis, Norw.*
⊗Desonide (p. 1630·1).
Skin disorders; anogenital pruritus.

Apolar med dekvalin *Actavis, Norw.*
⊗Desonide (p. 1630·1); dequalinium chloride (p. 1749·3).
Infected skin disorders.

Apolar-N *Actavis, Indon.*
⊗Desonide (p. 1630·1); neomycin sulfate (p. 330·1).
Infected skin disorders; anogenital pruritus; otitis externa.

Apo-Lato *Apotex, Mex.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Apo-Letro *Apotex, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Apolets *Apotex, Thai.*
Clopidogrel bisulfate (p. 1342·3).
Myocardial infarction; stroke; unstable angina; peripheral arterial disease.

Apo-Levocarb *Apotex, Canad.; Apotex, Cz.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, NZ.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Apolide *Apotex, Mex.*
Nimesulide (p. 101·3).
Inflammation; pain.

Apoliz *Apotex, Mex.*
Cetirizine (p. 619·2).
Hypersensitivity.

Apollo *Philusa, Philipp.*
Soft paraffin (p. 2211·3).
Barrier preparation.

Apollonset *Farmanic, Gr.*
Diazepam (p. 1063·2).
Anxiety disorders; sleep disorders; status epilepticus; alcohol withdrawal syndrome; skeletal muscle spasm; tetanus; premedication.

Apo-Lova *Apotex, Pol.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Apo-Lozart *Apotex, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure.

Apomastina *Apotex, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Apo-Medroxy *Apotex, Canad.; Apotex, Hong Kong.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogenic; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer; breast cancer; hormone replacement therapy.

Apometglu *Apotex, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Apo-Methazide *Apotex, Canad.*
⊗Methyldopa (p. 1431·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Apo-Methoprazine *Apotex, Canad.*
Levomepromazine maleate (p. 1079·3).

Apo-Metoclop *Apotex, Canad.; Apotex, Rus.†; Apotex, Singapore.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Apometoclor *Apotex, Mex.*
Metformin (p. 489·1); chlorpropamide (p. 470·1).
Diabetes mellitus.

Apomiclin *Apotex, Mex.*
Clindamycin (p. 269·3).
Bacterial infections.

Apo-Mina *Apotex, Mex.*
Dimenhydrinate (p. 625·2).
Nausea; vertigo.

Apomine *Hospira, Austral.; Hospira, NZ.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Apo-Moclob *Apotex, Cz.*
Moclobemide (p. 437·2).
Depression; social phobia.

Apomorphinum Complexe No 97 *Lehning, Fr.†*
Apomorphinum muriaticum (p. 892·3); atropinum sulfuricum (p. 1310·2); cocculus (p. 2483·1); veratrum album (p. 2644·3).
Homoeopathic preparation.

Apomuxol *Apotex, Mex.*
⊗Salbutamol (p. 1220·2); ambroxol (p. 1654·3).

Apo-Nadol *Apotex, Canad.*
⊗Nadolol (p. 1442·3).
Angina pectoris; hypertension.

Aponal *Cheplapharm, Ger.*
Doxepin hydrochloride (p. 414·2).
Depression; anxiety; insomnia; withdrawal syndromes.

Apo-Napro *Apotex, Pol.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Apo-Napro-Na *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Naproxen sodium (p. 98·2).
Pain; inflammation.

Apo-Nastrol *Apotex, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Apo-Nifed *Apotex, Canad.; Apotex, Singapore.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome; heart failure.

Aponil *Glaxo Allen, Ital.*
Lacidipine (p. 1417·3).
Hypertension.

Medochemie, Rus.
Nimesulide (p. 101·3).
Pain; fever; musculoskeletal, joint, and peri-articular disorders.

Aponistan *Apotex, Mex.*
Nystatin (p. 590·3).
Fungal infections.

Apo-Norflox *Apotex, Canad.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Apo-Oflox *Apotex, Canad.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Apo-Ome *Apotex, Cz.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; acid aspiration.

Apo-Oxpar *Apotex, Mex.*
Paroxetine (p. 440·3).
Depression.

Apo-Panto *Apotex, Cz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Apo-Parox *Apotex, Cz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Apo-Pentox *Apotex, Pol.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Apo-Pen-VK *Apotex, Canad.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Apo-Pera *Apotex, Mex.*
Loperamide (p. 1854·2).

Apo-Peram *Apotex, Canad.†*
Amitriptyline hydrochloride (p. 401·1); perphenazine (p. 1095·3).

Apo-Perindo *Apotex, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiac ischaemia.

Apo-Perindox *Apotex, Pol.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; ischaemic heart disease.

Apo-Pindol *Apotex, Canad.*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris.

Apo-Prava *Apotex, Pol.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Apopraza *Apotex, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Apo-Prazo *Apotex, Canad.; Apotex, Hong Kong; Apotex, NZ; Apotex, Singapore.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; benign prostatic hyperplasia; heart failure; Raynaud's disease.

Apo-Prochlorazine *Apotex, Canad.*
Prochlorperazine maleate (p. 1098·3).

Apoprod *Apotex, Mex.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Apo-Pyl *Apotex, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Apo-Quin-G *Apotex, Canad.†*
Quinidine gluconate (p. 1481·2).

A-Por *Aspen Consumer, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal fungal infections.

Apo-Rami *Apotex, Pol.*
Ramipril (p. 1483·3).
Hypertension; myocardial infarction; heart failure; nephropathy; cardiovascular risk reduction.

Aporex *Actavis, Norw.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Apo-Rheum *Pekana, Neth.†*
Arnica montana spag (p. 2447·2); bryonia cretica spag; colchicum autumnale (p. 607·1); dulcamara (p. 2497·3); gnaphalium polycephalum; guajacum officinale (p. 2523·1); lachnanthes tinctoria; taraxacum officinale spag (p. 2625·3).
Homoeopathic preparation.

Aporil *Qualiphar, Belg.*
Salicylic acid (p. 1719·1); acetic acid (p. 2426·3); lactic acid (p. 2539·1); thuja (p. 2629·3); greater celandine (p. 2522·2).
Warts.

Apo-Risper *Apotex, Cz.*
Risperidone (p. 1103·2).
Schizophrenia; mania.

Apo-Risperid *Apotex, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; aggression in Alzheimer's disease; behaviour disorders in children and adolescents.

Aposada *Apotex, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Apo-Salvent *Apotex, Canad.; Apotex, Mex.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease; asthma.

Apotex, NZ†; Apotex, Singapore.
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm; status asthmaticus.

Apo-Seleg *Apotex, Cz.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism; Alzheimer's disease.

Apo-Selin *Apotex, Pol.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Apo-Sertral *Apotex, Cz.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Apo-Simva *Apotex, Cz.; Apotex, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Apo-Spirozide *Apotex, Canad.†*
⊗Hydrochlorothiazide (p. 1403·2); spironolactone (p. 1499·3).

Apo-STOM *Pekana, Neth.*
Antimonum crudum (p. 2445·1); belladonna spag (p. 2453·3); colchicum autumnale (p. 607·1); colocynthis (p. 1833·3); millefolium (p. 2427·3); natrium phosphoricum (p. 1791·2); nux vomica (p. 2573·3); robinia pseudacacia spag.
Homoeopathic preparation.

Apo-Sulfatrim *Apotex, Canad.; Apotex, NZ†; Apotex, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Apo-Sulin *Apotex, Canad.; Apotex, Singapore.*
Sulindac (p. 134·2).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Apo-Tamis *Apotex, Cz.; Apotex, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Apo-Tamox *Apotex, Canad.; Apotex, Hong Kong; Apotex, Singapore.†*
⊗Tamoxifen citrate (p. 860·2).
Anovulatory infertility; breast cancer; endometrial cancer.

Apotel *Unipharma, Gr.*
Paracetamol (p. 115·1).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Pain; fever.

Apotel C-500 *Uniphanna, Gr.*
Paracetamol (p. 115·1); vitamin C (p. 2110·3).
Pain; fever.

Apotel Extra *Unipharma, Gr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Apo-Tetra *Apotex, Canad.; Apotex, Singapore.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Apo-Theo *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Theophylline (p. 1229·3).
Bronchospasm; obstructive airways disease.

Apo-Tic *Apotex, Cz.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Apo-Timol *Apotex, Canad.; Apotex, NZ*
⊗Timolol maleate (p. 1513·2).
Hypertension; angina pectoris; arrhythmias; migraine; myocardial infarction.

Apo-Timop *Apotex, Canad.; Apotex, NZ*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Apotoke *Apotex, Mex.*
Ketorolac (p. 80·2).
Inflammation; pain.

Apo-Triazide *Apotex, Canad.; Apotex, Hong Kong; Apotex, Rus.; Apotex, Singapore.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Oedema; hypertension.

Apo-Triazo *Apotex, Canad.*
Triazolam (p. 1112·3).
Insomnia.

Apo-Trihex *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Trihexyphenidyl hydrochloride (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Apo-Trimip *Apotex, Canad.*
Trimipramine maleate (p. 453·1).
Depression.

Apotex, Singapore.
Trimipramine hydrochloride (p. 453·1).
Depression.

Apo-Trina *Apotex, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Apo-Trinelax *Apotex, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Apoven *Douglas, Austral.†*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Apovent *Luxembourg, Israel.†*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Apo-Verap *Apotex, Canad.; Apotex, Hong Kong.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Apo-Vir *Apotex, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Apozema *Apomedica, Austria.†*
Turmeric oil (p. 2218·1); *p,α*-dimethylbenzyl alcohol (p. 2493·3); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); camphor (p. 2466·2); menthol (p. 2553·2).
Gastrointestinal disorders; digestive disorders.

Apozema Allium Cepa compositum *Apomedica, Austria.*
Allium cepa (p. 2575·2); acidum formicicum (p. 2507·1); aconitum (p. 2428·3); apis (p. 2445·2); arsenicum album (p. 2448·1); euphrasia (p. 2502·1); pulsatilla (p. 2600·2); rhus toxicodendron jeweils (p. 2603·3).
Homoeopathic preparation.

Apozema Apis compositum *Apomedica, Austria.*
Apis (p. 2445·2); belladonna (p. 2453·3); euphrasia (p. 2502·1); euphorbium; mercuris solubilis (p. 2555·3); rhus toxicodendron (p. 2603·3); ruta graveolens (p. 2608·2); sabadilla jeweils (p. 2611·2).
Homoeopathic preparation.

Apozemia *Apotex, Mex.*
Metformin (p. 489·1).
Diabetes mellitus.

Apozepam *Actavis, Denm.*
Diazepam (p. 1063·2).
Anxiety; spasticity; alcohol withdrawal syndrome.

Apo-Zolpin *Apotex, Pol.*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Apozone-S *Apotex, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Appearex *Merz, USA.*
Biotin (p. 2052·2).
Nail disorders.

Appebon *United Laboratories, Philipp.*
Syrup: Buclizine hydrochloride (p. 618·3); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Appetite stimulant.

United Laboratories, Philipp.
Tablets: Buclizine hydrochloride (p. 618·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Appetite stimulant.

Appebon with Iron *United Laboratories, Philipp.*
Capsules: Buclizine hydrochloride (p. 618·3); vitamin B substances (p. 2102·3); ferrous fumarate (p. 2060·3).
Appetite stimulant.

United Laboratories, Philipp.
Syrup: Buclizine hydrochloride (p. 618·3); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3); ferrous sulfate (p. 2062·2).
Appetite stimulant.

Appe-Care *Invision, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Appelin-B12 *Savoy, Singapore.*
Lysine (p. 2079·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).
Tonic.

Appese *Aspen, Austral.*
Ropinirole hydrochloride (p. 913·2).
Restless legs syndrome.

Appet *Finecure, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Appetason *Ad-Drugstel, Philipp.*
Capsules: Vitamin B substances (p. 2102·3); ferrous sulfate (p. 2062·2); buclizine hydrochloride (p. 618·3).
Reduced appetite.

Ad-Drugstel, Philipp.
Syrup: Vitamin B substances (p. 2102·3); ferrous sulfate (p. 2062·2); lysine hydrochloride (p. 2079·3).
Reduced appetite.

Appetens *Novartis, Philipp.*
Pizotifen (p. 678·2) or pizotifen malate (p. 678·2); vitamin B substances (p. 2102·3).
Reduced appetite.

Appetidin *Om Biotec, India.*
Syrup: Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Om Biotec, India.
Tablets: Cyproheptadine (p. 624·1).

Appetin *Christo, Hong Kong.†*
Cyproheptadine (p. 624·1).
Reduced appetite.

Appetiser Mixture *Potter's, UK.*
Chamomile (p. 2474·1); calumba (p. 2466·1); compound gentian infusion (p. 2512·1).
Tonic; flatulence.

Appetite with Iron *MPSI, Philipp.*
Buclizine hydrochloride (p. 618·3); ferrous sulfate (p. 2062·2); vitamins; lysine hydrochloride (p. 2079·3).
Reduced appetite; iron-deficiency anaemia; tonic.

Appetite OB *MPSI, Philipp.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement; tonic; iron-deficiency anaemia.

Appetite Plus *MPSI, Philipp.*
Buclizine hydrochloride (p. 618·3); vitamins; lysine hydrochloride (p. 2079·3).
Reduced appetite; tonic.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Appeton *Kotra, Malaysia.*
Vitamins; with or without minerals, ginseng (p. 2513·3), lysine (p. 2079·3), or taurine (p. 2626·2).

Appeton Teengrow *Hind Wing, Hong Kong.†*
Vitamins; minerals.

Appezym *Jean-Marie, Hong Kong.*
⊗Pancreatin (p. 2579·3); amylase (p. 2442·1); papain (p. 2582·3) lysine hydrochloride (p. 2079·3); vitamin B_1 (p. 2102·3).
Digestive disorders.

Applaud *Zep, Canad.*
Triclosan (p. 1773·2).

Apple Cider Vinegar Diet *Beacons, Singapore.*
Vitamin B_6 (p. 2105·3); chromium (p. 2055·3); apple cider vinegar; apple pectin (p. 2200·3); gymnema silvestre.
Slimming aid.

Applicaine *Carter, Austral.†*
Oral gel: Choline salicylate (p. 39·2).
Teething; oral pain.

Carter, Austral.†
Topical liquid: Benzocaine (p. 1980·2).
Teething; mouth ulcers; oral pain.

App-Up *Intas, India.*
Syrup: Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Intas, India.
Tablets: Cyproheptadine hydrochloride (p. 624·1).

Apra *Altaire, USA.†*
Paracetamol (p. 115·1).
Fever; pain.

Apracur
Note: this name may be used for preparations of different composition.
Gemardi, Thai.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); clemizole hydrochloride (p. 623·1); salicylamide (p. 129·2).
Cold symptoms.

HMA, Arg.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); clemizole (p. 623·1).
Cold and influenza symptoms.

Apracur Antifebril *Higate, Arg.†*
Paracetamol (p. 115·1).
Fever; pain.

Apracur Antigripal *HMA, Arg.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); butetamate (p. 1658·1); caffeine (p. 1203·3).
Influenza symptoms.

Apracur Expectorante *HMA, Arg.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Apracur Nasal *HMA, Arg.*
⊗Oxymetazoline (p. 1671·3).
Nasal congestion.

Apracur PC *United Drug, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Apracur Te Antifebril *HMA, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Apracur Te Descongestivo *HMA, Arg.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2).
Cold symptoms.

Apradil *Proton, Gr.*
Lansoprazole (p. 1851·3).

Apraljin *Deva, Turk.†*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Apranax *Roche, Belg.; Valeant, Hung.; Roche, Switz.; Abdi, Turk.*
Naproxen sodium (p. 98·2).
Gout; pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Roche, Fr.
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Pain; inflammatory disorders; musculoskeletal, joint, and peri-articular disorders.

Apraz *Mantecorp, Braz.*
Alprazolam (p. 1035·2).
Anxiety; alcohol withdrawal syndrome; panic disorder.

Aprazol *Abbott, Turk.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aprecap *Glenmark, India.*
Aprepitant (p. 1819·2).

Aprednislon *Merck, Austria.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Apresia *Teva, Pol.†*
Sertraline (p. 448·1).
Depression.

Apresol *Ordain, India.*
Dihydralazine sulfate (p. 1358·3).
Hypertension.

Apresolin *Amdipharm, Norw.; Amdipharm, Swed.*
Hydralazine hydrochloride (p. 1401·2).
Heart failure; hypertension.

Apresolina *Novartis, Braz.; Novartis, Mex.*
Hydralazine hydrochloride (p. 1401·2).
Hypertension; heart failure.

Apresoline *Novartis, Austral.; SteriMax, Canad.; Novartis, Irl.; AFT, NZ; Novartis, Philipp.; Novartis, S.Afr.†; Novartis, Singapore; Amdipharm, Thai.; Amdipharm, UK; Novartis, USA.†*
Hydralazine hydrochloride (p. 1401·2).
Hypertensive crisis; heart failure; hypertension.

Apress *Gerolimatos (Γερολυματος), Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Aprezin *Oriental, Philipp.*
Hydralazine hydrochloride (p. 1401·2).
Hypertension; heart failure.

Apri *Apotex, Canad.; Duramed, USA.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Aprical
Note: this name may be used for preparations of different composition.
Amdipharm, Ger.
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

April *Gador, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

AprilGen *Generics, Pol.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Aprinol
Note: this name may be used for preparations of different composition.
Anfarm, Gr.
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Mintlab, Chile.
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Aprinox *Abbott, Austral.†; IFET (ΙΦΕΤ), Gr.; Sovereign, UK.*
⊗Bendroflumethiazide (p. 1315·2).
Oedema; hypertension; suppression of lactation.

Aprior *OEP, Philipp.*
Nicorandil (p. 1446·2).
Angina pectoris.

Apriso *Salix, USA.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Aprocin *Aristopharma, Hong Kong.*
Ciprofloxacin (p. 261·1).
Bacterial conjunctivitis.

Aprodent *Farmoral, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout.

Aprodine *Major, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Aprodine with Codeine *Major, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); triprolidine hydrochloride (p. 642·3).
Cough; cold symptoms.

Aprofen *Polfarmex, Pol.; Medicine Products, Thai.*
Ibuprofen (p. 68·2).
Fever; pain.

Aprogen *Alkem, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Aprokam *Thea, Fin.; Thea, Neth.; Spectrum, UK.*
Cefuroxime sodium (p. 255·3).
Endophthalmitis following cataract surgery; bacterial eye infections following cataract surgery.

Aprol *Bilim, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Aprolat *Jelfa, Ukr.*
⊗Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3); hydrocortisone acetate (p. 1640·1).
Bacterial eye infections; otitis externa.

Apromed *Kocak, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Apronin *Chandra Bhagat, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Apronol *Medicine Products, Thai.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Aprost *Polfarmex, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Aprostal *Solvay, Philipp.†*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Aprostat *Samarth, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Aprotec *United Biotech, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Aproten *Diet Erba, NZ†; Ultrapharm, UK.*
Low-protein, gluten-free foods for special diets.

Aprotex *Veropharm, Rus.*
Aprotinin (p. 1133·2).
Pancreatic disorders; haemorrhage; shock.

Aprotilin *Kleva, Gr.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Aprotin *VHB, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Aprovel *Sanofi-Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi, Denm.; BMS, Fin.†; BMS, Fr.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; BMS, Hung.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; BMS, Irl.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; BMS, Neth.; Sanofi, Neth.; Sanofi BMS, Norw.; Sanofi-Aventis, Philipp.; BMS, Pol.; Sanofi-Aventis, Pol.; BMS, Port.; Sanofi-Aventis, Port.; Sanofi Winthrop, Rus.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Singapore; BMS, Spain; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; BMS, Switz.; Sanofi, Switz.; Sanofi-Aventis, Thai.; Sanofi, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, Venez.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy; heart failure.

Aprowell *Ali, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Aproxal *Elpen (Ελπεν), Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Aprozide *Sanofi-Aventis, Braz.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Apsi *Say, Turk.*
Allergen extracts (p. 2434·3).

Apsico *LKM, Arg.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Apsoderm *Rafarm, Gr.*
Salicylic acid (p. 1719·1).
Skin disorders.

Apsolox
Note: this name may be used for preparations of different composition.
Scoshia, India.
Ketorolac trometamol (p. 80·2).
Inflammation, pain, or photophobia following eye surgery; macular oedema.

Apsomol *Farmasan, Ger.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Apsor
Note: this name may be used for preparations of different composition.
Merck Serono, Fr.
Tacalcitol (p. 1722·1).
Psoriasis.

Aptamil 1 *Support, Braz.*
Infant feed.
Constipation; colic.

Aptamil AR *Nutricia, Austral.; Support, Braz.; Milupa, Ital.; Milupa, Port.*
Infant feed.
Regurgitation; gastro-oesophageal reflux.

Aptamil De-Lact *Nutricia, Austral.*
Infant feed.
Lactose intolerance.

Aptamil Feed Thickener *Nutricia, Austral.*
Pregelatinised maize starch (p. 2095·1).
Formerly known as Karicare Food Thickener.
Gastro-oesophageal reflux in infants; dysphagia in children and adults.

Aptamil HA *Mellin, Ital.; Milupa, Ital.; Milupa, Port.†*
Infant feed.
Food intolerance; milk intolerance.

Aptamil HA 2 *Milupa, Ital.*
Infant feed.
Cow's milk intolerance.

Aptamil HN 25 *Milupa, Ital.*
Food for special diets.
Diarrhoea.

Aptamil Pepti *Milupa, UK.*
Hydrolysed whey infant feed.
Cows' milk protein allergy.

Aptamil Pregomin SP *Milupa, Ital.*
Infant feed.
Cows' milk allergy; malabsorption.

Aptamil Soja *Support, Braz.*
Infant feed.
Lactose intolerance.

Aptamil Soya *Milupa, Ital.*
Infant feed.
Lactose intolerance.

Aptase-DSR HG *Akums, India.*
Domperidone maleate (p. 1838·1); rabeprazole (p. 1881·1).

Aptaur *Taurus, India.*
Cyproheptadine (p. 624·1).

Apteor *Solvay, Austria; Solvay, Port.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Aptha-X *CTI, Israel.†*
Aloe vera (p. 1693·2); benzalkonium chloride (p. 1737·1); enoxolone (p. 54·2); povidone (p. 2204·3); sodium hyaluronate (p. 2526·2).
Oral lesions.

Aptiom *Sunovion, USA.*
Eslicarbazepine acetate (p. 520·3).
Epilepsy.

Aptivate *Lupin, India.*
Cuminum cyminum; cyperus scariosus; piper longum.

Aptivate OS *Lupin, India.*
Cuminum cyminum; cyperus scariosus; fennel (p. 2503·2); piper longum; black pepper (p. 2586·1); trachyspermum ammi.

Aptivium Liver Support *Cynergen, Indon.†*
Silymarin (p. 1561·2); turmeric (p. 2218·1); thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); vitamin E (p. 2119·1).
Liver disorders.

Aptivium Optimum Joint Formula *Cynergen, Indon.†*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3).
Osteoarthritis; rheumatoid arthritis.

Aptivus *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.†; Boehringer Ingelheim, Fr.;*

Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.†; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.
Tipranavir (p. 1019·3).
HIV infection.

Aptizooom *Charak, India.*
Celery (p. 2472·3); cinnamon (p. 2479·2); piper longum; ashwagandha (p. 2450·2); ginger (p. 1844·1).
Reduced appetite.

Aptodin Plus *GD, Ital.*
Vitamins; minerals; amino acids.

Aptogrel *Aurobindo, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Apton *Delta, Port.*
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux.

Aptor *Nicholas, Indon.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Apuldon *Aristopharma, Hong Kong.*
Domperidone (p. 1838·1).
Dyspepsia; nausea; vomiting.

Apurin *Sandoz, Fin.*
Allopurinol (p. 600·2).
Gout; renal calculi; hyperuricaemia.

Apurol *Siegfried, Thai.†*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Apurone *Gerda, Fr.*
Flumequine (p. 300·2).
Bacterial infections of the urinary tract.

Apuzin *YSP, Malaysia.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Apydan *Desitin, Denm.; Algol, Fin.; Desitin, Ger.; Desitin, Hung.†; Desitin, Pol.†; Desitin, Switz.*
Oxcarbazepine (p. 533·2).
Epilepsy; trigeminal neuralgia.

Apyr *Gerolymatos, Gr.*
Aspirin (p. 22·2).

Apyrene *Vincenti, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Apzet *Tripharma, Turk.*
Olanzapine (p. 1089·3).

Aqium *Ego, Austral.*
⊗Alcohol (p. 1733·1).
Hand sanitiser.

Aqsia *Farmex, Gr.†; Abdi, Turk.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Aqua Ban *Lane, UK; Thompson, USA.*
Ammonium chloride (p. 1656·1); caffeine (p. 1203·3).
Premenstrual water retention.

Aqua Ban Herbal *Lane, UK.*
Lappa (p. 2540·1); bearberry (p. 2453·2); clivers (p. 2481·2).
Water retention.

Aqua Ban Plus *Thompson, USA.*
Ammonium chloride (p. 1656·1); caffeine (p. 1203·3); ferrous sulfate (p. 2062·2).
Premenstrual water retention.

Aqua Care
Note: this name may be used for preparations of different composition.
Frezyderm, Malaysia.
⊗Hyaluronic acid (p. 2526·2); glycerol (p. 2517·2); hydrogenated palm glycerides; sodium pidolate (p. 1720·3).
Vaginal dryness.

Aqua Cream *CCM, Malaysia.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); emulsifying wax (p. 2184·1).
Emollient for irritating skin conditions.

Aqua Dermis *Bio-Pharmaceuticals, Malaysia.*
Soap substitute.

Aqua Ear *Wyeth Consumer, Austral.*
Glacial acetic acid (p. 2426·3); isopropyl alcohol (p. 1758·3).
Prevention of otitis externa.

Aqua Emoform *Polifarma Benessere, Ital.*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Oral hygiene; gingival inflammation.

Aqua Fusion *Lancome, Canad.†*
SPF 15 cream: Octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Lancome, Canad.†
SPF 15 lotion: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Aqua Fusion Teinte *Lancome, Canad.†*
Octinoxate (p. 1715·1).
Sunscreen.

Aqua Lent Colirio *Inmunolab, Arg.*
⊗Ephedrine (p. 1663·1); phenazone (p. 124·1).
Eye disorders.

Aqua Lent Limpia Cristales *Inmunolab, Arg.*
Sodium chloride (p. 1795·1).
Contact lens care.

Aqua Lent Lubricante *Inmunolab, Arg.*
Carmellose sodium (p. 2175·2).
Eye irritation; dry eyes.

Aqua Maris *Jadran, Rus.; Jadran, Ukr.*
Sea water (p. 2612·1) with natural salts and trace elements.
Nasal disorders; throat disorders.

Aqua Soleil *Occy, Canad.*
SPF 30: Ensulizole (p. 1703·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.

Occy, Canad.
SPF 35: Ensulizole (p. 1703·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Aquabase *Avene, Fr.†; Paddock, USA.*
Vehicle for topical preparations.

Aquablock *Pfizer, NZ.†*
SPF 30+: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Aquacare *Allergan, Austral.; Allergan, NZ†; Numark, USA.*
⊗Urea (p. 1727·3).
Eczema; dry skin; keratinisation disorders.

Aquacel *Werfen, Arg.; Convatec, Belg.; Convatec, Canad.; Convatec, Fr.; BMS, S.Afr.†; Convatec, UK.*
Carmellose sodium (p. 2175·2).
Wounds; burns; ulcers.

Aquacel Ag *Convatec, Fr.; Convatec, Ital.; Convatec, UK.*
Silver (p. 2615·1); carmellose sodium (p. 2175·2).
Burns; ulcers; wounds; infected wounds and lesions.

Aquacel-Ag *Convatec, Belg.*
Carmellose sodium (p. 2175·2); silver (p. 2615·1).
Infected wounds and burns.

Aquachloral *PolyMedica, USA.†*
Cloral hydrate (p. 1055·2).
Sedative.

Aquacitramon *Agrophytopharm, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

AquADEKS *Yasoo, USA.*
Vitamins; ubidecarenone (p. 2637·1); selenium (p. 2086·3); zinc (p. 2126·1).

Aquadent-K *Intra-Labs, India.*
⊗Potassium nitrate (p. 1766·2).

Aquaderm *Baker Cummins, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Pendopharm, Canad.
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Aquadetrim *Medana, Rus.; Polpharma, Ukr.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; rickets; osteomalacia; tetany; hypoparathyroidism; osteoporosis; vitamin D supplement.

Aquadil-P *Gufic, India.*
Amylase (p. 2442·1); caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); peppermint oil (p. 1877·1); simeticone (p. 1886·2).

Aquadon *Rekah, Israel.†*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema; liver cirrhosis.

Aquadrate *Alliance, Irl.; Alliance, UK.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Aqua-E
Note: this name may be used for preparations of different composition.
Troikaa, India.
Eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).

Yasoo, USA.
Vitamin E (p. 2119·1).

Aquae *Hamilton, Austral.*
Carmellose sodium (p. 2175·2); sorbitol (p. 2092·1); electrolytes (p. 1775·1).
Artificial saliva; dry mouth.

Aquaform *Aspen Medical, UK.*
Hydrogel dressing.
Wounds; ulcers.

Aquafresh *GSK Consumer, Venez.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Aquafresh Sensitive *GSK, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth; dental caries prophylaxis.

Aquafresh Triple Proteccion *GSK, Arg.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Aquafresh Ultimate White *GSK, Arg.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Aquagel *Adams, Hong Kong.*
Lubricating jelly.

Aquagen SQ *ALK, Denm.; ALK, Fin.; ALK, Swed.*
Allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity; allergen immunotherapy.

Aqualane *Roux-Ocefa, Arg.*
Beeswax (p. 2170·2); liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Emollient.

Aqualette *Lichtwer, UK.*
Taraxacum (p. 2625·3); equisetum (p. 2500·1).

Aqualia *Vichy, Canad.*
Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1).
Sunscreen.

Aqualibra *Medice, Ger.*
Ononis (p. 2575·3); java tea (p. 2536·3); solidago (p. 2620·1).
Urinary-tract disorders.

Aqualip *Aqualife, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Aquamaster *Evalar, Rus.*
Sodium chloride (p. 1795·1).
Nasal disorders.

Aquamax *Dermato Logical, UK.*
Emollient.
Dry skin disorders.

Aquamet *Sun, India.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis; nasal polyps.

Aquamid *Mondeal, NZ.*
Polyacrylamide gel (p. 2594·1).
Soft-tissue contour deformities of the face.

Aquamide *Sun, India.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Hypertension; ascites; oedema.

Aquamol *Thornton & Ross, UK.*
Emollient.
Dry skin.

Aquanil
Note: this name may be used for preparations of different composition.
Darier, Mex.
Sodium laurilsulfate (p. 2210·3).
Skin disorders.

Person & Covey, USA.
Emollient and moisturiser.

Dispolab, Chile.†
Soap-free skin cleanser.

OmniVision, Denm.†
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Aquanil HC *Dispolab, Chile†; Darier, Mex.; Person & Covey, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Aquapask *Valenta, Rus.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Aquaphar *Albephar, Venez.*
⊗Urea (p. 1727·3).

Aquaphilic *Medco, USA.*
Vehicle for topical preparations.

Aquaphor
Note: this name may be used for preparations of different composition.
Cheplapharm, Ger.
⊗Xipamide (p. 1536·1).
Oedema; hypertension.

Beiersdorf, USA.†
Yellow soft paraffin (p. 2212·1); liquid paraffin (p. 2191·2); mineral wax; wool wax alcohol.
Ointment base; barrier ointment.

Aquaphor Healing Ointment *BSN, USA.*
Soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); ceresin; wool alcohols (p. 2219·2); panthenol (p. 2582·2); bisabolol.
Dry skin disorders.

Aquaphoril *Meda, Austria.*
⊗Xipamide (p. 1536·1).
Hypertension; oedema.

Aquaplus *JB Chemicals, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Aquapred
Note: this name may be used for preparations of different composition.
Micro, India.
⊗Prednisolone sodium phosphate (p. 1645·3).
Inflammatory eye disorders.

Winzer, Ger.†
Eye drops: ⊗Chloramphenicol (p. 257·1); prednisolone sodium phosphate (p. 1645·3).
Inflammatory disorders and infections of the eye.

Aquaradiance *Biotherm, Canad.†*
Octinoxate (p. 1715·1).
Sunscreen.

Aquarest *Chauvin, Fr.*
Carbomer (p. 2173·3).
Dry eyes.

Aquarid
Note: this name may be used for preparations of different composition.
Thebe, S.Afr.
⊗Furosemide (p. 1387·1).
Oedema.

Aquarius *Demo, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Aquasec *Micro, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Aquasept *Medlock Medical, UK.†*
Triclosan (p. 1773·2).
Skin disinfection.

Aquasmooth *Procter & Gamble, Canad.†*
Titanium dioxide (p. 1725·1).
Sunscreen.

Aqua-Soap *Remexa, Mex.*
Soap substitute.

Aquasoft *Ajanta, India.*
Isopropyl myristate (p. 2190·3); light liquid paraffin (p. 2191·2).

Aquasol *SSL, UK.*
Purified water (p. 2646·2).

Aquasol A *Hospira, USA.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

Minerva (Μινερβα), Gr.
Vitamin A (p. 2098·3); panthenol (p. 2582·2).

Aquasol ACD *Interpharma, Chile.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); ergocalciferol (p. 2113·3).
Vitamin A, C, and D deficiency.

Aquasol AD *Grossman, Mex.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Aquasol A+D *Minerva (Μινερβα), Gr.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D deficiency.

Aquasol C *Lifeon, India.*
Vitamin C (p. 2110·3).

Aquasol Ceezed *Lifeon, India.*
Vitamin C (p. 2110·3); zinc (p. 2126·1).

Aquasol E *Columbia, Canad.†; Hospira, USA.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; vitamin supplement.

Aquasource *Biotherm, Canad.*
SPF 8: Octinoxate (p. 1715·1).
Sunscreen.

Biotherm, Canad.
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Aquasun *Pfizer, NZ.*
SPF 30+ lotion; SPF 30+ cream: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Sunscreen.

Pfizer, NZ.†
Lotion SPF 18: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); octocrilene (p. 1715·2).
Sunscreen.

Aquatab C *Deston, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Aquatab D *Adams, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Aquatab DM *Adams, USA.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Aquatabs *Dermatech, Austral.; Sovedis, Fr.*
Troclosene sodium (p. 1774·1).
Water disinfection.

AquaTears
Note: this name may be used for preparations of different composition.
Novartis, Austria.
Carbomer 974P (p. 2173·3).
Dry eyes.

Aquatears
Note: this name may be used for preparations of different composition.
Cipla, India.
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Formerly contained polyvinyl alcohol.
Dry eyes.

Aquaviron *Piramal, India.*
⊗Testosterone (p. 2305·1).
Hypogonadotrophic hypogonadism; delayed puberty; breast cancer in women.

Aquavit-E *Cypress, USA.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Aquazan *Iodine Technologies, Rus.*
Povidone-iodine (p. 1767·1).
Skin disinfection; skin infections.

Aquazide *Sun, India.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Aquella *Lifeplan, UK.*
Boldo (p. 2458·3); kelp (p. 2612·1); cider vinegar; lappa (p. 2540·1); taraxacum (p. 2625·3).
Herbal supplement.

Aqueous Charcodote *Pharmascience, Singapore.*
Activated charcoal (p. 1537·3).
Emergency treatment of poisoning.

Aquex *Gry, Ger.†*
⊗Xipamide (p. 1536·1).
Hypertension; oedema.

Aquiflav *Uriach Aquilea OTC, Spain.†*
Soya (p. 2092·3).
Menopausal disorders.

Aquify *Ciba Vision, Arg.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Aquimicix *Uriach Aquilea OTC, Spain.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Aquimod *Taro, Israel.*
Imiquimod (p. 985·2).
Anogenital warts; actinic keratosis; superficial basal cell carcinoma.

Aquinafil *Pfizer, Austral.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Aquitos *Uriach Aquilea OTC, Spain.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Aquoral *Sinclair, UK.*
Oxidised glycerol triester.
Dry mouth.

Aquo-Trinitrosan *Merck, Ger.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; controlled hypotension; heart failure; hypertension; myocardial infarction.

Aqupla *Shionogi, Jpn.*
Nedaplatin (p. 834·3).
Malignant neoplasms.

Aqurea *ICM, Singapore.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Aqwet *Cipla, India.*
Carmellose sodium (p. 2175·2); sorbitol (p. 2092·1); electrolytes (p. 1775·1).

ARA *PSA, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Ara *Haledew, India.*
Tablets: Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Haledew, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Arabine *Hospira, Denm.; Mayne, Fin.†; Hospira, Swed.*
Cytarabine (p. 774·1).
Malignant neoplasms; acute leukaemias.

Arabloc *Sanofi-Aventis, Austral.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Arablocktans *Liconsa, Neth.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Aracaf *TNP, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms; nasal congestion.

Aracalm *Arafarma, Spain.*
Amisulpride (p. 1036·3).
Schizophrenia.

Arace *Cyclos, Gr.*
Cytarabine (p. 774·1).

ARA-cell *Stada, Austria†; Cell Pharm, Ger.; Stada, Port.; Assos, Turk.*
Cytarabine (p. 774·1).
Acute leukaemias; non-Hodgkins lymphoma.

Aracenac *Arafarma, Spain.*
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders.

Arachitol *Solvay, India.*
Colecalciferol (p. 2113·1).
Rickets, osteomalacia; hypoparathyroidism.

Aracidina *Raga, Spain.†*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Araclof *Armoxindo, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Aracmyn *Bioclon, Mex.*
Spider venom antiserum (p. 2419·3).
*Spider bites (*Latrodectus mactans, Loxosceles*).*

Aracytin *Pfizer, Braz.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Ital.*
Cytarabine (p. 774·1).
Lymphomas; myelodysplastic syndrome; acute leukaemias.

Aracytine *Pfizer, Fr.*
Cytarabine (p. 774·1).
Leukaemias; myelodysplasia.

Aradix *Drugtech, Chile.*
⊗Methylphenidate (p. 2326·1).
Attention-deficit hyperactivity disorder; narcolepsy.

Aradois *Biolab Sanus, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Aradois H *Biolab Sanus, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Arafarmadol *Arafarma, Spain.†*
Capsaicin (p. 35·1).
Neuropathic pain; myalgia.

Arafaxina *Arafarma, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Arafisio *Arafarma, Spain.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Arafriol *Arafarma, Spain.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Aragam *Oxbridge, UK.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone-marrow transplantation.

Aragel *Arafarma, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Arahormo *Arafarma, Spain.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Arainno *Arafarma, Spain.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Aralast *Baxter, Arg.; IFET (ΙΦΕΤ), Gr.; Baxter, USA.*
Alpha$_1$-proteinase inhibitor (p. 2438·1).
Alpha$_1$- proteinase deficiency.

Aralen *Sanofi-Aventis, Mex.; Sanofi Synthelabo, Philipp.†; Sanofi-Aventis, USA.*
Chloroquine phosphate (p. 650·1).
Malaria; amoebiasis.

Aralevo *Arafarma, Spain.*
Levocetirizine hydrochloride (p. 632·3).
Urticaria.

Aralis *Pfluger, Ger.*
⊗Cephaëlis ipecacuanha; grindelia robusta (p. 2522·3); hyoscyamus niger (p. 2530·2); lobelia inflata (p. 2323·2).
Homoeopathic preparation.

Aralter *Arafarma, Spain.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Aralter Plus *Arafarma, Spain.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Aram *Candor, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Aramef *Opus Materia, Gr.*
⊗Letrozole (p. 817·1).

Aramin *Cristalia, Braz.*
⊗Metaraminol tartrate (p. 1430·1).
Hypotension.

Aramine *MSD, Austral.†; MSD, NZ†; MSD, Singapore; MSD, Thai.; Merck, USA.†*
⊗Metaraminol tartrate (p. 1430·1).
Hypotension; shock.

Aramix *Elea, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; panic disorder; social phobia.

Aranelle *Barr, USA.*
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Aranesp *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Amgen, Gr.; Amgen, Hong Kong; Amgen, Hung.; Amgen, Irl.; Amgen, Israel; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, NZ; Amgen, Pol.; Amgen, Port.; Amgen, Rus.; Amgen, Singapore†; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Eczacibasi, Turk.; Amgen, UK; Amgen, USA.*
⊗Darbepoetin alfa (p. 1137·1).
Anaemia in renal failure; anaemia associated with cancer chemotherapy.

Araniforce arthro *Weber & Weber, Ger.*
Acid. arsenicosum (p. 2448·1); berberis vulgaris (p. 2502·1); colocynthis (p. 1833·3); toxicodendron quercifolium (p. 2603·3); urtica urens e planta tota rec flor (p. 2639·3).
Homoeopathic preparation.

Araniforce rheuma *Weber & Weber, Ger.†*
Alchemilla vulgaris; acidum silicum (p. 2208·3); calcium carbonicum (p. 1824·3); calcium phosphoricum (p. 1784·2); equisetum arvense (p. 2500·1); ilex aquifolium; symphytum officinale (p. 2484·2).
Homoeopathic preparation.

Aranka *Gedeon Richter, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Arankelle *Gedeon Richter, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Aranox *APT, Hong Kong.*
Itraconazole (p. 583·3).
Fungal infections.

Aranyér Elleni *Tradenet, Hung.*
Aesculus (p. 2431·2); calendula (p. 2465·2); chamomile (p. 2474·1); propolis (p. 2597·3).
Anorectal disorders; phlebitis.

Arapamin *Arafarma, Spain.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Arapaxel *Arafarma, Spain.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Arapride *Arafarma, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Arasena-A *Mochida, Jpn.*
Vidarabine (p. 1023·1).
Herpesvirus infections.

Arasid *Intas, India.*
Cytarabine (p. 774·1).
Acute leukaemias; lymphomatous meningitis.

Aratac *Alphapharm, Austral.; LCH, Hong Kong†; Alphapharm, Malaysia†; Mylan, NZ; Alphapharm, Singapore; Merck, Singapore; Merck, Thai.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Aratan *Andromaco, Chile.*
Losartan potassium (p. 1422·2).
Hypertension.

Aratan D *Andromaco, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Aratis *Farbio, Port.*
Losartan potassium (p. 1422·2).
Hypertension; cardiovascular risk reduction; diabetic nephropathy.

Aratro *Arafarma, Spain.*
Azithromycin (p. 221·2).
Bacterial infections.

Arava *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis Pasteur, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Arax *Vitabalans, Denm.*
Paracetamol (p. 115·1).
Pain; fever.

Arax Extra *Vitabalans, Denm.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Araxacina *Arafarma, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Arazid *BioSaude, Port.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Arbartan *Teva, Hung.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular hypertrophy; diabetic nephropathy.

Arbid
Note: this name may be used for preparations of different composition.
Hetero, India.
Roxithromycin (p. 356·2).
Bacterial infections.
Vifor, Switz.†
⊗Buphenine hydrochloride (p. 2462·3); diphenylpyraline hydrochloride (p. 627·2).
Rhinitis; sinusitis.

Arbid N
Note: this name may be used for preparations of different composition.
Vifor, Switz.
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

Arbid-A *Hetero, India.*
Roxithromycin (p. 356·2); ambroxol (p. 1654·3).
Respiratory-tract infections; urogenital infections.

Arbidol *Farmstandart, Rus.; Farmstandart, Ukr.*
6-Bromo-5-hydroxy-1-methyl-4-dimethylaminomethyl-2-phenylthiomethylindole-3 carboxylic acid hydrochloride ethyl ester monohydrate.
Viral infections.

Arbid-S *Damvergis, Gr.†*
Diphenylpyraline hydrochloride (p. 627·2).

Arbid-top *Vifor, Switz.*
Phenylephrine hydrochloride (p. 1672·3); dequalinium chloride (p. 1749·3); muramidase hydrochloride (p. 2565·1).
Nasal congestion.

Arbil *Ranbaxy, UK.*
Carbamazepine (p. 512·2).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Arbinoxa *Hawthorn, USA.*
Carbinoxamine maleate (p. 619·1).
Rhinitis; allergic conjunctivitis; hypersensitivity reactions.

Arbistin *Nycomed, Mex.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Arbitel *Micro, India.*
Telmisartan (p. 1509·3).
Hypertension.

Arbitel-H *Micro, India.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Arbixil *Meyer, Venez.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol (p. 1207·2) or clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Arbloc *YSS, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Arblos *Aqualife, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Arblos-H *Aqualife, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Arbonid *Intermed, Gr.*
Azelaic acid (p. 1695·1).

Arbos *Eczacibasi, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Arbum *Jaldes, Fr.*
Lappa (p. 2540·1); zinc (p. 2126·1); selenium (p. 2086·3); vitamins.
Seborrhoea.

ARC *Xttrium, USA.*
Soft paraffin (p. 2211·3); zinc oxide (p. 1729·1).
Emollient.

Arca-Be *Arcana, Austria.*
Thiamine disulfide (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia.

Arcalen *Herbapol Poznan, Pol.*
Arnica (p. 2447·2); calendula (p. 2465·2); esculoside (p. 2431·2).
Soft-tissue injury.

Arcalion *Servier, Braz.; Grunenthal, Chile; Servier, Fr.; Servier, Gr.; Servier, Hong Kong; Serdia, India; Servier, Indon.; Servier, Malaysia; Servier, Mex.; Servier, Philipp.; Servier, Port.; Servier, Singapore; Lestral, Spain; Servier, Switz.; Servier, Thai.†; Servier, Turk.; Servier, Venez.*
Sulbutiamine (p. 2103·1).
Tonic; vitamin B_1 deficiency; asthenia.

Arcalyst *Regeneron, USA.*
Rilonacept (p. 2604·3).
Cryopyrin-associated periodic syndromes.

Arcamox *Armoxindo, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Arcanafenac *Merck, S.Afr.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Arcapec *Meprofarm, Indon.*
Attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Arcapta *Novartis, USA.*
⊗Indacaterol maleate (p. 1211·2).
Obstructive airways disease.

Arcasin
Note: this name may be used for preparations of different composition.
Meda, Ger.
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Arcavit A/E *Arcana, Austria.†*
Vitamin A palmitate (p. 2098·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Vitamin A and E deficiency.

Arc-Chlor *United Drug, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions; anaphylaxis.

Arcef *Armour, India.*
Cefixime (p. 240·3).
Bacterial infections.

Arcefal *Arlex, Mex.*
Cefaclor (p. 232·3).
Bacterial infections.

Arceligasol *Gezzi, Arg.*
Hyssop (p. 2530·3); bladderwrack (p. 2612·1); fennel (p. 2503·2); coltsfoot (p. 1659·2); cynara (p. 2490·3); equisetum (p. 2500·1); peppermint (p. 1877·1).

Arcental *Milo, Spain.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Arcet
Note: this name may be used for preparations of different composition.
Armour, India.
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Archidex *TP, Thai.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin (p. 329·3).
Infected eye or ear disorders.

Archifen *Archifar, Thai.*
Ear drops: Chloramphenicol (p. 257·1); lidocaine hydrochloride (p. 1988·2).
Bacterial ear infections.
Archifar, Thai.
Eye drops: Chloramphenicol (p. 257·1).
Bacterial eye infections.

Archimol *TP, Thai.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Architol *DIL, India.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Arcid *Diafarm, Spain.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration; gastric hyperacidity; Zollinger-Ellison syndrome.

Arcin *Chemech, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Arclav *Aronex, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Arclonac *Condrugs, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Arclone *Galderma, India.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Arcobee with C *Nature's Bounty, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Arcocilin *Biofarma, Venez.*
Ampicillin (p. 218·2).
Bacterial infections.

Arcocillin *Armoxindo, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Arcodryl *Armoxindo, Indon.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic disorders.

Arcolan *Galderma, Braz.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Arcolane *Galderma, Chile; Galderma, India; Galderma, Venez.*
Ketoconazole (p. 585·3).
Pityriasis versicolor; seborrhoeic dermatitis; scalp disorders.

Arcold *Armour, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Arcored *Armoxindo, Indon.*
Vitamin B_{12} (p. 2107·2).
Anaemias; nutritional supplement.

Arcosal *Meda, Denm.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Arcostrong *Eadriex, Philipp.†*
Vitamins; minerals; ginseng (p. 2513·3); choline (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2).
Tonic.

Arcoxia *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, UK; MSD, Ukr.; MSD, Venez.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout; pain; ankylosing spondylitis; dysmenorrhoea.

Arc-Soda *United Drug, Thai.*
Sodium bicarbonate (p. 1781·1).
Alkalinisation of urine; metabolic acidosis; dyspepsia.

Arctium & Zinc Compound *Phytomedicine, Austral.*
Vitamin A acetate (p. 2098·3); pyridoxine hydrochloride (p. 2105·3); echinacea (p. 2498·1); yellow dock (p. 2649·3); calendula (p. 2465·2); arctium lappa (p. 2540·1); zinc sulfate (p. 2126·2).
Eczema.

Arctuvan *Klinge, Ger.*
Bearberry leaves (p. 2453·2).
Urinary-tract infections.

Arcuf Plus *Armour, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Arcure *NuLife, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ardbeg *Crinos, Ital.*
Ketoprofen (p. 79·1).

Ardeaelytosol *Ardeapharma, Cz.*
Electrolytes (p. 1775·1).

Ardeanutrisol G *Ardeapharma, Cz.*
Anhydrous glucose (p. 2069·1).
Hypoglycaemia; ketoacidosis; parenteral nutrition.

Ardeaosmosol MA *Ardeapharma, Cz.*
⊗Mannitol (p. 1427·3).
Acute renal failure; intracranial hypertension; intra-ocular hypertension; forced diuresis.

Ardent *Deutsche, Philipp.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Ardey-aktiv *Ardeypharm, Ger.*
Ginseng (p. 2513·3).
Tonic.

Ardeycholan *Ardeypharm, Ger.*
Cynara (p. 2490·3).
Dyspepsia; biliary-tract disorders.

Ardeycordal mono *Ardeypharm, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Ardeydorm *Ardeyphann, Ger.*
Tryptophan (p. 453·2).
Sleep disorders.

Ardeyhepan *Ardeypharm, Austria; Ardeypharm, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Ardeynephron *Ardeypharm, Ger.*
Java tea (p. 2536·3).
Urinary-tract disorders.

Ardeysedon *Ardeypharm, Ger.*
Valerian root (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Ardeytropin *Ardeypharm, Ger.*
Tryptophan (p. 453·2).
Depression; sleep disorders.

Ardicat *Sandoz, Port.*
⊗Fentanyl (p. 60·1).
Pain.

Ardin *Korea Pharma, Singapore.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Ardinel *Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Ardinex *Abbott, Fin.; Abbott, Pol.†; Mundipharma, Swed.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Ardium *Servier, Indon.*
Flavonoids (hesperidin (p. 2505·2), diosmin (p. 2505·2)).
Venous insufficiency; phlebitis; haemorrhoids.

Ardivit *Novell, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Ardoral *Cinfa, Spain.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity.

Ardosons *Sons, Mex.*
⊗Indometacin (p. 71·2); betamethasone (p. 1623·2); methocarbamol (p. 2025·3).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis; gout; peri-articular disorders.

Arduan *Gedeon Richter, China; Gedeon Richter, Cz.; Biotechnologia, Gr.; Gedeon Richter, Hung.; Themis Medicare, India; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Pipecuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Arecamin *Northia, Arg.*
Cefalotin (p. 235·1).
Bacterial infections.

Arechin *Polfa Pabianice, Pol.*
Chloroquine phosphate (p. 650·1).
Malaria; amoebiasis; lambliasis; lupus erythematosus; rheumatoid arthritis.

Arecid *Allertec, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Areclok *Grindeks, Ukr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Arecolex *Arlex, Mex.*
Econazole (p. 577·2).
Fungal skin infections.

Aredia *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Cz.†; Novartis, Denm.†; Novartis, Fin.†; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.†; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Philipp.; Novartis, Pol.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.†; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; Paget's disease of bone; osteoporosis; osteolytic bone metastases; osteogenesis imperfecta; fibrous dysplasia of bone.
Novartis, India.
Pamidronic acid (p. 1186·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone.

Arédia *Novartis, Fr.†; Novartis, Switz.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolytic lesions in multiple myeloma and in bone metastases

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

associated with breast cancer; Paget's disease of bone.

Aredronet *Sun, India.*
Pamidronic acid (p. 1186·3).
Hypercalcaemia of malignancy; osteolytic lesions and bone pain in multiple myeloma and in bone metastases associated with breast cancer; Paget's disease of bone.

Arefarin *Fuji, Jpn.*
Warfarin potassium (p. 1526·3).
Thromboembolic disorders.

Aregen *Novartis, Gr.; Normal, Port.*
Pimecrolimus (p. 1716·1).
Atopic eczema.

Arelix *Sanofi-Aventis, Braz.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Irl.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Switz.*
⊗Piretanide (p. 1470·3).
Oedema; hypertension; heart failure; renal failure.

Arelix ACE *Sanofi-Aventis, Ger.†*
⊗Piretanide (p. 1470·3); ramipril (p. 1483·3).
Hypertension.

Areloger *Gerard, Irl.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Arem *Aspen, S.Afr.*
Nitrazepam (p. 1089·1).
Insomnia.

Aremed *AFT, NZ; Remedica, Singapore; Remedica, Thai.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Aremedan *EirGen, Denm.*
⊗Exemestane (p. 792·2).
Breast cancer.

Aremin *Morgan, Ital.*
Suleparoid (p. 1507·2).
Soft-tissue injury; haemorrhoids.

Aremis *Esteve, Spain.*
Sertraline hydrochloride (p. 448·1).
Depression; anxiety; obsessive-compulsive disorder; post-traumatic stress disorder.

Arena *Talent, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arenbil *Qualigen, Spain.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Arendal *Ivax, Arg.; Pharma Invesli, Chile.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Arendal D3 *PharmaInvesti, Chile.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Arentopres *Torrent, Rus.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Arepanrix *ID Biomedical, Canad.; GSK, Neth.†; GSK, Pol.*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Areplex *Adamed, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thrombosis prophylaxis.

Adamed, Ukr.†
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Ares *Uniao Quimica, Braz.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Arestal *Janssen-Cilag, Fr.; Janssen-Cilag, Neth.*
Loperamide oxide (p. 1854·2).
Diarrhoea.

Arestin *Johnson & Johnson, Canad.; H&A, Israel; OraPharma, Port.; OraPharma, Swed.†; OraPharma, USA.*
Minocycline hydrochloride (p. 325·1).
Periodontitis.

A-Ret *Shalaks, India.*
Tretinoin (p. 1725·2).
Acne.

A-Ret HC *Shalaks, India.*
⊗Tretinoin (p. 1725·2); hydrocortisone (p. 1640·1); hydroquinone (p. 1705·1).
Acne.

A-Ret TZ *Shalaks, India.*
Tazarotene (p. 1724·2).
Acne; psoriasis; photoaging.

Areta *IFA, Mex.*
Vitamins; minerals.
Dietary supplement.

Areuma *Ecobi, Ital.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Areuzolin *Areu, Spain.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Arfagel *Advik, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); sodium alginate (p. 2167·3).

Arfam *Arrow, Austral.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Arfarel *Pharmanik (Фармэник), Gr.*
Clindamycin phosphate (p. 269·3).
Acne.

Arfazetin-E *Krasnogorskleksredstva, Rus.*
St John's wort (p. 449·1); chamomile (p. 2474·1); kidney bean (p. 2587·3); equisetum (p. 2500·1); blueberry; rose fruit (p. 2607·1); Siberian ginseng (p. 2614·3).
Adjunct in diabetes mellitus.

Arfen
Note: this name may be used for preparations of different composition.
Lisapharma, Ital.
Ibuprofen lysine (p. 68·3).
Musculoskeletal and joint disorders; radiculitis; gynaecological inflammatory disorders.

Solas, Indon.; Medinfar, Port.
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; fever.

Medochemie, Malaysia.
Paracetamol (p. 115·1).
Fever; pain.

Arfen Plus *Medochemie, Hong Kong.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Arficin *Belupo, Cz.*
Rifampicin (p. 350·3).
Tuberculosis and other mycobacterial infections.

Arfine *Biomedica, Gr.*
Nimodipine (p. 1455·2).

Arflex *Diffucap, Braz.*
Nimesulide (p. 101·3).

Arfloxina *Arlex, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Arflur *FDC, India.*
Tablets: Flurbiprofen (p. 65·2).
Musculoskeletal and joint disorders; pain.

FDC, India.
Injection: Aceclofenac (p. 16·2).

FDC, India.
Topical gel: Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Arflur-100 *FDC, India.*
Aceclofenac betadex (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Arflur-3D *FDC, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Arflur-MR *FDC, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Arflur-P *FDC, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Arg-9 *Nouveau, India.*
Arginine (p. 2049·1); proanthocyanidins.

Arganova *LFB, Fr.; Mitsubishi, Neth.*
Argatroban (p. 1307·2).
Heparin-induced thrombocytopenia.

Argaron *Nichi-Iko, Jpn.*
Argatroban (p. 1307·2).
Thromboembolic disorders.

Argatra *Mitsubishi, Austria; Mitsubishi, Ger.*
Argatroban (p. 1307·2).
Heparin-induced thrombocytopenia.

Argeal
Note: this name may be used for preparations of different composition.
Pierre Fabre, Arg.; Silesia, Chile; Ducray, Fr.
Kaolin (p. 1850·1); saw palmetto (p. 2363·3).
Seborrhoeic dermatitis.

Medifarm Ducray, Venez.
Saw palmetto (p. 2363·3); cucurbita (p. 2489·2); kaolin (p. 1850·1).
Seborrhoeic dermatitis of the scalp.

Argedin *Bosnalijek, Ukr.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers, and wounds.

Argeflox *Nova Argentia, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Argemol *Loeffler, Mex.*
Sulfadiazine silver (p. 362·3).
Burns.

Argenpal *Braun, Spain.*
Silver nitrate (p. 2615·3).
Granulomas; verrucas; epistaxis; mouth ulcers.

Argentafil *Valeant, Mex.*
Sulfadiazine silver (p. 362·3).
Skin disorders; ulcers; burns; wounds.

Argental *Liferpal, Mex.*
Sulfadiazine silver (p. 362·3).
Infected skin disorders.

Argent-Eze *Lennon, S.Afr.†*
Sulfadiazine silver (p. 362·3).
Burns.

Argentum Complexe no 98 *Lehning, Fr.*
Argentum colloidale (p. 2616·2); bismuthum subgallicum (p. 1822·1); atropinum sulfuricum (p. 1310·2).
Homoeopathic preparation.

Argentum Med Complex *Dynamit, Austria.*
Acidum nitricum (p. 2572·3); argentum nitricum (p. 2615·3); mandragora; nux vomica (p. 2573·3).
Homoeopathic preparation.

Argesic
Note: this name may be used for preparations of different composition.
Centaur, India.
Diclofenac sodium (p. 48·3).
Pain.

Argesic Plus *Centaur, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Argesic-SA *Econo Med, USA.*
Salsalate (p. 130·1).
Pain; fever; inflammation.

Argidam *Terapeutico, Ital.*
L-Arginine (p. 2049·1); damiana (p. 2491·3); muira-puama; zinc gluconate (p. 2126·2); vitamin E (p. 2119·1).
Nutritional supplement.

Argin *Volchem, Ital.*
Protein supplement.
Arginine deficiency.

Arginaid Extra *Novartis Nutrition, USA.*
Preparation for enteral nutrition.

Arginax *Therapeutic Foods, Canad.†*
Vitamin A (p. 2098·3).

Arginitric *Medreich, India; Saimirra, Malaysia.*
Arginine (p. 2049·1).
Dietary supplement.

Arginotri-B *Bouchara-Recordati, Fr.*
Arginine hydrochloride (p. 2049·1); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Tonic.

Argirol *Allergan, Braz.*
Mild silver protein (p. 2616·2).
Eye infections.

Argisept *Centaur, India.*
Sulfadiazine silver (p. 362·3); chlorhexidine gluconate (p. 1743·3).
Burns; wounds.

Argisone *Teofarma, Ital.*
⊗Hydrocortisone acetate (p. 1640·1); mild silver protein (p. 2616·2).
Bacterial eye infections.

Argivit *Aesculapius, Ital.*
Amino acids; vitamins; minerals.
Nutritional supplement.

Argocian *Biol, Arg.*
⊗Hexoprenaline sulfate (p. 1211·1).
Premature labour.

Argofan *Zentiva, Cz.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Argol Essenza Balsamica *Alba Thyment, Pol.*
Cinnamon oil (p. 2479·3); melissa oil (p. 2553·2); mint oil (p. 2560·1); clove oil (p. 2481·3); thyme oil (p. 2630·3); lemon oil (p. 2543·1); nutmeg oil (p. 2573·2); coriander oil (p. 2487·1); menthol (p. 2553·2).
Respiratory-tract disorders; motion sickness; musculoskeletal and joint pain; digestive disorders; pruritus; insect bites.

Argol Grip *Alba Thyment, Pol.*
Melissa oil (p. 2553·2); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); nutmeg oil (p. 2573·2); thyme oil (p. 2630·3); lemon oil (p. 2543·1); coriander oil (p. 2487·1); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); niaouli oil (p. 2569·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint disorders; respiratory-tract disorders.

Argol Rheuma *Alba Thyment, Pol.*
Melissa oil (p. 2553·2); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); nutmeg oil (p. 2573·2); thyme oil (p. 2630·3); lemon oil (p. 2543·1); coriander oil (p. 2487·1); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); cajuput oil (p. 2464·1); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Argosulfan *Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.*
Sulfathiazole silver (p. 368·3).
Burns; ulcers; wounds; infected skin disorders.

Argosulphan *Jelfa, Ukr.*
Sulfathiazole silver (p. 368·3).
Infected burns, ulcers, and wounds; infected skin disorders.

Argotone Dec *Bracco, Ital.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Argotone Rino *Bracco, Ital.*
⊗Ephedrine hydrochloride (p. 1663·2); mild silver protein (p. 2616·2).
Nasal congestion.

Argyrophedrine *Merck, Belg.†*
⊗Ephedrine levulinate (p. 1663·1); mild silver protein (p. 2616·2).
Respiratory-tract congestion.

Arh *Lincoln, India.*
Injection: Alpha-beta arteether (p. 648·1).
Malaria.

Lincoln, India.
Tablets: Artesunate (p. 648·2).
Malaria.

Arh Plus *Lincoln, India.*
Artesunate (p. 648·2).
Malaria.

Arhémapectine Antihémorragique *H2 Pharma, Fr.†*
Pectin (p. 2200·3).
Haemorrhage.

Arheumacare *Health Perception, UK.*
Tablets, glucosamine sulfate (p. 2515·3); turmeric (p. 2218·1); ginger (p. 1844·1); capsules, cod-liver oil (p. 2056·3); borage oil (p. 2459·2).
Joint disorders.

Arh-L *Lincoln, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Aria
Note: this name may be used for preparations of different composition.
Lichtwer, UK.
Soya isoflavones (p. 2620·3); calcium (p. 1783·1); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); selenium (p. 2086·3).
Nutritional supplement.

Linde, Ital.
Oxygen (p. 1799·3).

Piramal, India.
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arial
Note: this name may be used for preparations of different composition.
Constant, India.
Alpha-beta arteether (p. 648·1).
Malaria.

Dompe, Ital.
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Arianit *Help, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Arianna *Bayer, Ital.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ariban *Arika, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Ariban Plus *Arika, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Aribzol *Arika, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Aribzol-D *Arika, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Arical *Arika, India.*
Calcium carbonate (p. 1824·3); lysine (p. 2079·3); colecalciferol (p. 2113·1).

Arical Forte *Arika, India.*
Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Aricef *Arika, India.*
Cefixime (p. 240·3).
Bacterial infections.

Aricep *Eisai, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Aricept *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Eisai, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Eisai, Fr.; Eisai, Ger.; Pfizer, Ger.; Pfizer, Gr.; Eisai, Hong Kong; Pfizer, Hung.; Eisai, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Eisai, Jpn; Eisai, Malaysia; Pfizer, Norw.; Pfizer, NZ; Eisai, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Eisai, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Eisai, Thai.; Pfizer, Turk.; Eisai, UK; Pfizer, USA.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease; vascular dementia.

Aricilina *Ariston, Braz.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Aricip *Arika, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Aricip-TZ *Arika, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ariclaim *Lilly, Cz.; Lilly, Ger.; Lilly, Gr.; Lilly, Irl.; Lilly, Neth.; Lilly, Pol.; Lilly, Port.; Lilly, Swed.*
Duloxetine hydrochloride (p. 415·1).
Diabetic peripheral neuropathy; stress urinary incontinence in women.

Ariclav *Arika, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Ariclopin *Ariston, Arg.*
Clopidogrel (p. 1342·3).

Aricodiltosse *Menarini, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Aricort M *Arika, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Arid *Sienna, India.*
⊗Ambroxol (p. 1654·3); cetirizine (p. 619·2); pseudoephedrine (p. 1676·1).

Arid Plus *Sienna, India.*
Cetirizine (p. 619·2); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Arid-D *Sienna, India.*
Ambroxol (p. 1654·3); cetirizine (p. 619·2); dextromethorphan (p. 1660·1).

Arident *Arika, India.*
⊗Potassium nitrate (p. 1766·2).

Aridex *Gentex, USA.*
Phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1); pentoxyverine citrate (p. 1672·1).
Upper respiratory-tract disorders.

Aridil *CP Pharmaceuticals, UK.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
These ingredients can be described by the British Approved Name Co-amilofruse.
Oedema; ascites.

Aridine *VS, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Aridol *Pharmaxis, Austral.; Pharmaxis, Fin.; Novex, Fr.; Pharmaxis, Ger.; Allertec, Gr.; Pharmaxis, Norw.; Pharmaxis, Port.; Nigaard, Swed.; Stallergenes, Switz.; Pharmaxis, USA.*
⊗Mannitol (p. 1427·3).
Assessment of bronchial hyperresponsiveness.

Aridom-C *Arvincare, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Aridron *Arika, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Aridus *Zydus, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Ariel *Caleb, Hong Kong.*
Hyoscine (p. 1845·3).
Motion sickness.

Arifenicol *Ariston, Braz.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Arifil *Apocare, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Ariflam *Ultra, Mex.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Ariflam Forte *Ultra, Mex.*
Diclofenac sodium (p. 48·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuropathy; neuralgia; musculoskeletal pain.

Ariflox *Arika, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ariflox-OZ *Arika, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Arifnac *Arika, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Arifnac-P *Arika, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Arifon *Socofar, Port.†; Servier, Rus.; Servier, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Arifzon-SB *Arika, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Arigat *Arika, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Arigest *Arika, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Arigoline *Watson, S.Afr.*
Cabergoline (p. 899·3).

Ariknow *Ranbaxy, S.Afr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Arikof-D *Arika, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).

Arikof-P *Arika, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Arilan *Micro, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arilex
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Aripiprazole (p. 1038·3).
Schizophrenia.
Eczacibasi, Turk.
Risedronate sodium (p. 1189·3).

Arilif-OZ *Ind-Swift, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Arilin *Wolff, Ger.; Wolff, Pol.; Alcina, Switz.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; trichomoniasis; bacterial vaginitis.

Ariline *Wolff, Austria.*
Metronidazole (p. 936·1).
Trichomoniasis; bacterial vaginosis.

Arilla *Mensana, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Arilvax *Novartis Vaccines, Fin.†; Evans Medical, Israel†; Chiron Vaccines, Neth.†; Medpro, S.Afr.†; Chiron Vaccines, UK.*
A yellow fever vaccine (17D strain) (p. 2424·3).
Active immunisation.

Arima
Note: this name may be used for preparations of different composition.
Scoshia, India.
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).
Alphapharm, Austral.†
Moclobemide (p. 437·2).
Depression.

Arimed *Promed, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Arimic *Arika, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Arimidex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; AstraZeneca, USA; AstraZeneca, Venez.*
⊗Anastrozole (p. 742·1).
Breast cancer; prostatic cancer.

Arimox-D *Arika, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Arinate *Dafra, Belg.†*
Artesunate (p. 648·2).
Malaria.

Arindap *Polpharma, Rus.*
⊗Indapamide (p. 1409·2).
Hypertension.

Arinel *US Pharmacia, Pol.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Arinox Plus *Arika, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Arinox-MD *Arika, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Arintapin *Sandoz, Denm.*
Mirtazapine (p. 436·1).
Depression.

Arion *Arika, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1); mecobalamin (p. 2108·1).

Arion Cronos *Visiontec, Arg.*
Solution, hydrogen peroxide (p. 1755·2); tablets, catalase (p. 2472·2).
Disinfection of soft contact lenses.

Arion Forte *Arika, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Arionecs *Liconsa, Cz.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Arionex *Glenmark, Cz.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; stroke prophylaxis.

Arionex Combi *Glenmark, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Aripan *Arika, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aripan-D *Arika, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux.

Aripat-MD *Gentech, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Aripax *Erfar, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Aripdox *Arika, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Aripez *Teva, Irl.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Aripezil *Specifar, Gr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Aripil *Gerard, Irl.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Ariply *Unipharm, Israel.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arip-MT *Torrent, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Aripnem *Arika, India.*
Meropenem (p. 321·3).
Bacterial infections.

Aripra-MT *Ranbaxy, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arisafe *Arika, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

Ariscorten *Ariston, Braz.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Arisfolic *Ariston, Arg.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects.

Aristaloe *Neo Dermos, Arg.*
Cream; topical emulsion: Aloe vera (p. 1693·2); elastin (p. 2483·2).
Emollient.
Neo Dermos, Arg.
Topical gel: Aloe vera (p. 1693·2); avena (p. 2451·1); calendula (p. 2465·2); mallow (p. 2549·2).
Emollient.

Aristamid *Nordmark, Thai.*
Sulfisomidine (p. 369·1).

Aristen *Aristopharma, Hong Kong.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Aristin-C *Anfarm, Gr.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Aristo
Note: this name may be used for preparations of different composition.
Aristopharma, Hong Kong.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Aristobet-N *Aristopharma, Hong Kong.*
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected or inflammatory eye, ear, or nose disorders.

Aristochol Gallekapsein *Steiner, Ger.†*
Cynara (p. 2490·3).
Gallbladder disorders.

Aristocillin *Aristo, India.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Aristocor *Meda, Austria.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Aristocort *Aspen, Austral.; Valeo, Canad.; Healthcare Logistics, NZ; Pfizer, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Aristogyl *Aristo, India.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis.

Aristogyl Plus *Aristo, India.*
Metronidazole (p. 936·1); diloxanide furoate (p. 931·2); simeticone (p. 1886·2).
Amoebiasis.

Aristogyl-F *Aristo, India.*
Oral suspension: Metronidazole benzoate (p. 936·1); furazolidone (p. 933·3).
Bacterial and protozoal gastrointestinal infections.

Aristo, India.
Tablets: Metronidazole (p. 936·1); furazolidone (p. 933·3); simeticone (p. 1886·2).
Bacterial and protozoal gastrointestinal infections.

Aristomox *Aristo, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Aristomycin *Farmanic, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Aristoneurol *Aristo, India.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Aristophen *Aristopharma, Hong Kong.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Aristopiron *Ariston, Arg.†*
Buspirone (p. 1042·1).

Aristopramida *Ariston, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Aristopyrin *Aristo, India.*
Paracetamol (p. 115·1); phenylbutazone (p. 125·1); propyphenazone (p. 127·3).

Aristospan *Valeo, Canad.; Fujisawa, USA.*
⊗Triamcinolone hexacetonide (p. 1649·2).
Corticosteroid; musculoskeletal, joint, and periarticular disorders.

Aristozyme *Aristo, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
The capsules and oral drops formerly contained amylase, pepsin, and simeticone.
Digestive disorders.

Aristrol *Aristo, India.*
Calcitriol (p. 2113·1).

Aristrol Forte *Aristo, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Aritaz *Arika, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Aritel *Kanonfarma, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Aritel Plus *Kanonfarma, Rus.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Arither *Arika, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Aritmal *Biosel, Turk.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias; local anaesthesia.

Aritmil *Borshchagovskii, Ukr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Aritom-L *Arika, India.*
Vitamins; lycopene (p. 2546·2); selenium dioxide (p. 2087·1); zinc (p. 2126·1).

Aritomycin *Cadila, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Arive *Alkem, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arixen *Valeant, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Arixime *Arika, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Arixind *Indeco, Arg.*
Aripiprazole (p. 1038·3).
Psychoses.

Arixon *Arika, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Arixon-SB *Arika, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Arixon-TZB *Arika, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Arixtra *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA.*
Fondaparinux sodium (p. 1385·3).
Thromboembolic disorders; thromboembolism prophylaxis following surgery or immobilisation; acute coronary syndrome.

Arizime *Niche, Irl.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Arizin-L *Arika, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Arizith *Arika, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Arizyme *Arika, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Arjet *Zydus, India.*
Benzyl nicotinate (p. 29·3); camphor (p. 2466·2); glycol salicylate (p. 66·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); squalane (p. 2213·3).

Arjin *Alarsin, India.*
Achyranthes aspera; malabar nut (p. 2549·1); punarnava (p. 2601·1); curcuma longa; rauwolfia serpentina (p. 1485·1).

Arjun Cream *Arjun, UK.*
Levomenthol (p. 2553·2) in aqueous cream.
Emollient; urticaria.

Arjun Ear Drops *Arjun, UK.*
Olive oil (p. 2575·1).
Ear wax removal.

Arjunin *Charak, India.*
Punarnava (p. 2601·1); elettaria cardamomum; pistacia lentiscus.
Cardiac disorders.

Ark *Apex, India.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Arkadin *Pharmex (Φαρμεξ), Gr.*
Riboflavin (p. 2104·3); adenosine phosphate (p. 2430·2).

Arkamin *Unichem, India.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Arkamin-H *Unichem, India.*
⊗Clonidine hydrochloride (p. 1339·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Arket *Ethypharm, China; Lemery, Mex.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Arketin *Qualigen, Spain.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders in children; autism; dementia.

Arketis *Medochemie, Cz.; Vipharm, Pol.; Medartuum, Swed.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Arkine *Pyridam, Indon.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Arkocaps Bourdaine *Arko Diffusion, Switz.*
Frangula bark (p. 1843·3).
Constipation.

Arkocapsulas Carbon Vegetal *Arkopharma, Spain.*
Activated charcoal (p. 1537·3).
Diarrhoea; flatulence.

Arkocapsulas Hiperico *Arkopharma, Spain.*
St John's wort (p. 449·1).
Tonic.

Arkocapsulas Rusco *Arkopharma, Spain.*
Butcher's broom (p. 2463·1).
Peripheral vascular disorders.

Arkocapsulas Sen *Arkopharma, Spain.*
Senna (p. 1885·1).
Constipation.

Arkogélules *Arkopharma, Fr.*
A range of herbal preparations.

Arkolamyl *Generics, Cz.; Mylan, Denm.; Mylan, Fr.; Gerard, Irl.; Mylan, Ital.; Mylan, Neth.; Generics, Pol.; Mylan, Swed.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Arkolevure *Arkopharma, Fr.*
Saccharomyces boulardii (p. 2596·3); inulin (p. 2534·3).
Maintenance of intestinal flora.

Arkopharma Propolis Spray *Arkopharma, Singapore.*
⊗Pine buds; eucalyptus (p. 2501·1); chamomile (p. 2474·1); thyme (p. 2630·2); mallow (p. 2549·2); propolis (p. 2597·3); maltitol (p. 2080·3); honey (p. 2072·1); glycerol (p. 2517·2); larch extract.

Arkophytum *Arkomedika, Fr.†*
Devil's claw root (p. 42·3); black currant (p. 2458·1); salix (p. 129·2).
Painful joint disorders.

Arkoresp *Arkochim, Spain.†*
Camphor (p. 2466·2); turpentine oil (p. 2636·3); levomenthol (p. 2553·2); eucalyptus oil (p. 2501·2); cedar leaf oil (p. 2629·3); nutmeg oil (p. 2573·2); thymol (p. 1772·2).
Respiratory-tract disorders.

Arkoroyal *Arkopharma, Fr.*
Royal jelly (p. 2608·1); larch; *Bifidobacterium lactis* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); *Bacillus coagulans.*
Dietary supplement.

Arkotux *Arkopharma, Spain.*
Ivy (p. 2536·2).
Respiratory-tract congestion.

Arlan *Armour, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Arlec *Ali, Turk.*
⊗Carvedilol (p. 1333·1).

Arlecyn-K *Ultra, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Arlemide *AstraZeneca, Arg.*
Aripiprazole (p. 1038·3).
Schizophrenia; mania; bipolar disorder; depression.

Arlet *Synthesis, Rus.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Arlette *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Arlevert *Hennig, Cz.; Hennig, Fin.; Hennig, Ger.; Henning, Hung.; Hennig, Irl.; Hennig, Neth.; Hennig, Swed.; Zambon, Switz.; Ashbourne, UK.*
Cinnarizine (p. 622·1); dimenhydrinate (p. 625·2).
Vertigo; vestibular disorders.

Arlevertan *Kela, Belg.; Polifarma, Ital.*
Cinnarizine (p. 622·1); dimenhydrinate (p. 625·2).
Vertigo.

Arlevid *Arlex, Mex.*
Zalcitabine (p. 1023·2).
HIV infection.

Arlexen *Arlex, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Arlexen B *Arlex, Mex.*
Cefalexin (p. 234·1); bromhexine (p. 1656·3).
Respiratory-tract infections.

Arlexicam *Arlex, Mex.*
Piroxicam (p. 125·3).
Fever; inflammation; rheumatism.

Arlidin *Erfa, Canad.; USV, India; Grossman, Mex.*
⊗Buphenine hydrochloride (p. 2462·3).
Organic mental disorders; cerebral and peripheral vascular disorders.

Arlina *Rafarm, Gr.*
Aceclofenac (p. 16·2).
Inflammatory disorders.

Arliv *Merck, Chile.*
Ivy (p. 2536·2).
Cough.

Arloc *DR Johns, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Arloc-D *DR Johns, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Arlufe *Neiss, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Arluy *Asofarma, Mex.*
Mebeverine (p. 1858·3).
Gastrointestinal spasm.

Armadin *Microkhim, Ukr.*
Emoxypine succinate (p. 1371·1).
Cardiovascular disorders; alcohol withdrawal syndrome; pancreatitis; peritonitis; cerebrovascular disorders; anxiety.

Armak *Ethical, Philipp.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Armament *Faran, Gr.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma.

Armanaks *Arma, Turk.*
Naproxen sodium (p. 98·2).
Pain; inflammation.

Armanor *Servier, Pol.†; Servier, Rus.*
Almitrine dimesilate (p. 2315·3).
Respiratory failure with hypoxaemia.

Armarrok *Sandoz, Neth.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Armaseft *Arma, Turk.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Armathene *Arma, Turk.*
Dexpanthenol (p. 2582·2).

Armaya *Centrum, Spain.*
Polypodium leucotomos.
Psoriasis; eczema.

Armbid OZ *Armour, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Armcid D *Armour, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Armdic *Armour, India.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Armdic MR *Armour, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Armdic Plus *Armour, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Armdic SP *Armour, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Armer *Plus, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Armet G *Armour, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Armet Plus *Armour, India.*
Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2).

Armflox *Armour, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Armilla *Abiogen, Ital.*
Alpha tocoferol (p. 2119·1).
Vitamin E deficiency.

Arminol *Krewel, Ger.†*
Sulpiride (p. 1107·3).
Schizophrenia.

Armisetin *Gunsa, Turk.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Armistor *Servier, Mex.†*
Estradiol (p. 2271·1).
Menopausal disorders.

Armix
Note: this name may be used for preparations of different composition.
BPL, India.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Servier, Hung.
Perindopril arginine (p. 1466·3) or perindopril erbumine (p. 1467·1).
Hypertension; heart failure; myocardial infarction.

Armix Komb *Servier, Hung.*
⊗Indapamide (p. 1409·2); perindopril erbumine (p. 1467·1).
Hypertension.

Armix Prekomb *Servier, Hung.*
⊗Indapamide (p. 1409·2); perindopril erbumine (p. 1467·1).
Hypertension.

Armoglobulina *ZLB, Braz.†*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; passive immunisation; immune thrombocytopenia.

Armolev *Armoxindo, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Armonia *Nathura, Ital.*
Melatonin (p. 2551·3).

Armonil
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Tilia (p. 2631·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Insomnia.

Recordati, Ital.
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Armonil Noche *Ivax, Arg.*
Melatonin (p. 2551·3).
Jet-lag symptoms.

Armonyl *Maver, Chile.*
Valerian (p. 2640·2); passion flower (p. 2584·1); crataegus (p. 2488·1).
Insomnia.

Armonyl Nocturno *Maver, Chile.*
Valerian (p. 2640·2); passion flower (p. 2584·1); chamomile (p. 2474·1).
Insomnia.

Armotraz *Cipla, Cz.; Cipla, India.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Armovit *Armoxindo, Indon.*
Royal jelly (p. 2608·1); ginseng (p. 2513·3); vitamins; minerals; rutoside (p. 2505·3).
Tonic; nutritional supplement.

Armoxin *Arlex, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Armunia *Sandoz, Neth.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Arnaril *Farmanic, Gr.*
Enalapril maleate (p. 1371·1).

Arnela *Andromaco, Chile.*
Clotrimazole (p. 576·2).
Fungal vulvovaginal infections.

Arnet *Zytras, India.*
Artesunate (p. 648·2).
Malaria.

Arnetin *Medochemie, Malaysia.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastrointestinal haemorrhage.

Arnica Comp *DHU, Ger.; DHU, Malaysia.*
Arnica (p. 2447·2); calendula (p. 2465·2).
Homoeopathic preparation.

Arnica comp/Apis *Weleda, Ger.†*
Aconitum napellus (p. 2428·3); arnica mont. (p. 2447·2); fol. betulae (p. 2457·3); mandragora; apis mellifica (p. 2445·2); ol. rosmarini (p. 2607·3).
Homoeopathic preparation.

Arnica Complexe no 1 *Lehning, Fr.*
Arnica (p. 2447·2); aconitum (p. 2428·3); belladonna (p. 2453·3); bryonia alba; china rubra (p. 2478·3); nux vomica (p. 2573·3); ruta graveolens (p. 2608·2); hypericum (p. 449·1); achillea millefolium (p. 2427·3); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Arnica Compuesta *Ximena Polanco, Chile.*
Acidum benzoicum (p. 1738·2); arnica (p. 2447·2); causticum (p. 2595·3); colchicum (p. 607·1); rhus toxicodendron (p. 2603·3); urtica urens (p. 2639·3).
Homoeopathic preparation.

Arnica Cream *Seroyal, Canad.†*
Arnica montana (p. 2447·2); calendula (p. 2465·2).
Homoeopathic preparation.

Arnica Hamamelis Compuesta *Knop, Chile.*
Arnica (p. 2447·2); clematis; hamamelis (p. 2523·3); lycopodium (p. 2546·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Arnica Komplex *Richter, Austria.†*
Arnica montana (p. 2447·2); ruta graveolens (p. 2608·2); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Arnica Massage Balm *Weleda, UK.*
Arnica flower oil (p. 2447·2); birch leaf oil (p. 92·1); lavender oil (p. 2541·1); rosemary oil (p. 2607·3).
Rheumatic and muscular pain.

Arnica Massage Oil *Weleda, S.Afr.*
Arnica flower oil (p. 2447·2); birch leaf oil (p. 2457·3); rosemary oil (p. 2607·3); lavender oil (p. 2541·1); lavandine oil.
Muscle and joint pain.

Arnica Med Complex *Dynamit, Austria.*
Arnica (p. 2447·2); barium chloratum (p. 2452·3); crataegus (p. 2488·1).
Homoeopathic preparation.

Arnica Ointment *Pure-Li, Canad.†*
Arnica montana (p. 2447·2); methyl salicylate (p. 92·1).

Arnica Oligoplex *Madaus, Ger.*
Arnica (p. 2447·2); aconitum (p. 2428·3); belladonna (p. 2453·3); china (p. 2478·3); eucalyptus (p. 2501·1); nux vomica (p. 2573·3); veratrum album (p. 2644·3).
Homoeopathic preparation.

Arnica + Pain Relief *Homeocan, Canad.*
Arnica montana (p. 2447·2); hypericum perforatum (p. 449·1); symphytum officinalis (p. 2484·2).
Homoeopathic preparation.

Arnica/Betula comp *Weleda, Ger.*
Arnica planta (p. 2447·2); betula cortex (p. 2457·3); plumbum mellitum (p. 2541·3).
Homoeopathic preparation.

Arnicadol *Phytomedica, Fr.†*
Arnica (p. 2447·2); menthol (p. 2553·2); clove oil (p. 2481·3).
Soft-tissue injury.

Arnicagel *Weleda, Fr.*
Arnica (p. 2447·2).
Bruising.

Arnica-Heel Comp *Heel, Canad.†*
Apis mellifica (p. 2445·2); arnica montana (p. 2447·2); baptisia tinctoria (p. 2647·2); benzoic acid (p. 1738·2); bryonia (p. 2461·3); colchicum (p. 607·1); dog's mercury; dulcamara (p. 2497·3); echinacea angustifolia (p. 2498·1); eucalyptus (p. 2501·1); eupatorium cannabinum; poison oak (p. 2603·3); solanum nigrum (p. 2458·2); tomato.
Homoeopathic preparation.

Arnicaid *Hylands, Canad.*
Arnica montana (p. 2447·2); hypericum perfoliatum (p. 449·1); ruta graveolens (p. 2608·2); ledum palustre (p. 2550·1); bellis perennis (p. 2454·2).
Homoeopathic preparation.

ArnicaMed *Flor de Loto, Spain.*
Arnica (p. 2447·2).
Soft-tissue disorders.

Arnican *Melisana, Belg.; Cooperation Pharmaceutique, Fr.*
Arnica (p. 2447·2).
Soft-tissue disorders.

Arnicare *Nelson, UK.*
Arnica (p. 2447·2).
Bruising.

Arnicarell *Sanorell, Ger.*
Arnica montana (p. 2447·2).
Homoeopathic preparation.

Arnica/Symphytum comp *Weleda, Ger.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); betulae folium (p. 2457·3); mandragora; symphytum officinale (p. 2484·2); ol. rosmarini (p. 2607·3); resina laricis.
Homoeopathic preparation.

Arnicet *Metochem, Austria.†*
Arnica (p. 2447·2); hamamelis (p. 2523·3).
Skin irritation; muscle pain; soft-tissue disorders.

Arnid *Pharos, Indon.†*
Nimesulide (p. 101·3).
Osteoarthritis; rheumatoid arthritis; pain.

Arnident *Grisi, Mex.*
Arnica (p. 2447·2); sodium fluoride (p. 2089·2).
Toothpaste; gum irritation.

Arnidol *Harras-Curarina, Cz.*
Glycol salicylate (p. 66·2); arnica (p. 2447·2).
Musculoskeletal, joint, and soft-tissue disorders.

Arniflor *VSM, Neth.*
Arnica (p. 2447·2).
Homoeopathic preparation.

Arnigel *Boiron, Fr.; Boiron, Neth.†; Boiron, Port.; Boiron, Switz.*
Arnica (p. 2447·2).
Soft-tissue injury; muscle pain.

Arnikaderm *Knop, Chile.*
Arnica (p. 2447·2).
Inflammation; oedema.

Arnikatinktur *Hofmann & Sommer, Ger.; Teofarma, Ger.*
Arnica (p. 2447·2).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Arnilite *Holland Pharma, Neth.*
Aconitum napellus (p. 2428·3); apis mellifica (p. 2445·2); arnica montana (p. 2447·2); hypericum perforatum (p. 449·1); rhus toxicodendron (p. 2603·3); gelsemium sempervirens (p. 2511·2); symphytum officinale (p. 2484·2); ledum palustre (p. 2550·1).
Homoeopathic preparation.

Arnim-P *McNeil & Argus, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Arnisol *Profarm, Pol.*
Aesculus (p. 2431·2); arnica (p. 2447·2); oak (p. 2574·1).
Soft-tissue injury.

Arnol
Note: this name may be used for preparations of different composition.
Cetus, Arg.
⊗Pancreatin (p. 2579·3); dehydrocholic acid (p. 2492·1); cellulase (p. 2473·1); diazepam (p. 1063·2).
Nervous digestive disorders.

Vickmans, Hong Kong.†
Allopurinol (p. 600·2).
Gout.

Arocal *Aronex, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Arocap *Psychotropics, India.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1).

Arocef *Arrowin, India.*
Cefpodoxime.
Bacterial infections.

Arodox *Aronex, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Arofek *Avefarm, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Aroff *Unichem, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Aroff BCD *Unichem, India.*
Aceclofenac betadex (p. 16·2).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Aroff Plus *Unichem, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Aroff-EZ *Unichem, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Arofil *Symbiosis, India.*
Gum paint: Camphor (p. 2466·2); iodine (p. 2336·3); menthol (p. 2553·2); potassium iodide (p. 2336·3); tannic acid (p. 2625·2); thymol (p. 1772·2).

Symbiosis, India.
Mouthwash: Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Arofuto *Mitsubishi Tanabe, Jpn.*
Afloqualone (p. 2014·3).
Skeletal muscle spasm; spasticity.

Aroglim-M2 *Arrowin, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Aroglycem *MSD, Jpn.*
Diazoxide (p. 1351·3).
Hypoglycaemia.

Arogyme *Argil, India.*
⊗Lysine hydrochloride (p. 2079·3); pepsin (p. 2586·1); vitamin B substances (p. 2102·3).

Arokan *Sanovel, Turk.*
Acarbose (p. 466·2).
Diabetes mellitus.

Arokast *Aronex, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Arola Rosebalm *Pharmaceutical Enterprises, S.Afr.†*
Bismuth subnitrate (p. 1822·1); dimeticone (p. 2209·3); allantoin (p. 1693·1); zinc oxide (p. 1729·1).
Skin disorders.

Arolac *Lisapharm, Fr.*
Lisuride maleate (p. 908·2).
Hyperprolactinaemia; lactation inhibition; erectile dysfunction; gynaecomastia in males.

Arolin-XN *Haledew, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Aroltex *LKM, Arg.*
Pergolide mesilate (p. 910·2).
Parkinsonism.

Aromadetox *Omega, Fr.†*
Honey (p. 2072·1); black radish; rosemary (p. 2607·2); cynara (p. 2490·3); lemon oil (p. 2543·1); rosemary oil (p. 2607·3); basil oil (p. 2453·1); dill oil (p. 2493·2); peppermint oil (p. 1877·1); anise oil (p. 2444·3); wild carrot oil; orange oil (p. 2576·2); bay oil (p. 2453·1); nutmeg oil (p. 2573·2); almond oil (p. 2437·1).
Aid to detoxification.

Aromadigest *Omega, Fr.†*
Vervain (p. 2645·1); taragon; taraxacum (p. 2625·3); lemon oil (p. 2543·1); basil oil (p. 2453·1); dill oil (p. 2493·2); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); anise oil (p. 2444·3); cardamom oil (p. 2471·1); ginger oil (p. 1844·1); bay oil (p. 2453·1); nutmeg oil (p. 2573·2); juniper oil (p. 2537·2).
Digestive disorders.

Aromag *ICM, Singapore.*
Light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Heartburn; dyspepsia; gastric hyperacidity.

Aromagel *Hasco-Lek, Pol.†*
Camphor (p. 2466·2); Peru balsam (p. 2587·1); rosemary oil (p. 2607·3); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders; rheumatism.

Aromasil *Pfizer, Spain.*
⊗Exemestane (p. 792·2).
Breast cancer.

Aromasin *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pharmacia, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pharmacia Upjohn, USA; Pfizer, Venez.*
⊗Exemestane (p. 792·2).
Breast cancer; prostatic cancer.

Aromasine *Pfizer, Fr.*
⊗Exemestane (p. 792·2).
Breast cancer.

Aromasol *Pierre Fabre, Fr.*
Clove oil (p. 2481·3); peppermint oil (p. 1877·1); pine oil (p. 2591·1); lavender oil (p. 2541·1); cinnamon oil (p. 2479·3); rosemary oil (p. 2607·3); wild thyme oil (p. 2648·1).
Respiratory-tract congestion.

Aromatol *Hasco-Lek, Pol.*
Melissa (p. 2552·3); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); lemon oil (p. 2543·1); peppermint oil (p. 1877·1); lavender oil (p. 2541·1); menthol (p. 2553·2).
Gastrointestinal disorders; circulatory disorders; insomnia; headache; rheumatism; neuralgia; cold symptoms.

Aromatol Hot Gel *Hasco-Lek, Pol.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); peru balsam (p. 2587·1); rosemary oil (p. 2607·3).
Respiratory-tract disorders; musculoskeletal and joint disorders.

Aromavital *Omega, Fr.†*
Fruit juice; honey (p. 2072·1); royal jelly (p. 2608·1); acerola; ginseng (p. 2513·3); cinnamon oil (p. 2479·3); turmeric oil (p. 2218·1); ginger oil (p. 1844·1); lemon grass oil (p. 2543·2); clove oil (p. 2481·3); nutmeg oil (p. 2573·2); peppermint oil (p. 1877·1); cumin oil.
Tonic.

Aromazen *Omega, Fr.†*
Melissa (p. 2552·3); honey (p. 2072·1); tilia (p. 2631·3); orange; vervain (p. 2645·1); basil oil (p. 2453·1); dill oil (p. 2493·2); orange oil (p. 2576·2); chamomile oil (p. 2474·1); santalum album oil; lemon verbena oil.
Sleep disorders.

Aromed *Proton, Gr.*
⊗Letrozole (p. 817·1).

Aromek *Celon, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Aromenal *Panalab, Arg.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Arômes *Nutricia, Fr.*
Amino acids.
Enteral nutrition.

Aromeston *Veropharm, Rus.*
⊗Exemestane (p. 792·2).
Breast cancer.

Aronal Forte *Teva, Israel.*
Vitamin A (p. 2098·3); guaiazulene (p. 2523·1); aluminium lactate (p. 2440·2); aldioxa (p. 1692·2).
Sensitive gums; toothpaste.

Aronamin Gold *Ildong, Philipp.*
Vitamin E (p. 2119·1); vitamin B substances (p. 2102·3); vitamin c (p. 2110·3).
Dietary supplement.

Aroniae+C *Vifiteh, Rus.*
Ascorbic acid (p. 2110·3); aronia.
Tonic.

Aronomag *Herbapol Wroclaw, Pol.†*
Aronia melanocarpa; dibasic magnesium citrate (p. 1857·1).
Magnesium deficiency.

Aropax *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Braz.; Novartis, Mex.; GSK, NZ; GSK, S.Afr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Aropilo *Vipharm, Cz.; Vipharm, Hung.; Vipharm, Pol.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Aropix *Temapharm, Cz.; Temapharm, Pol.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Aroselin *Leovan, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Arosi *Arvincare, India.*
Injection: Ornithine aspartate (p. 2085·2).

Arvincare, India.
Tablets: Ornithine aspartate (p. 2085·2); silymarin (p. 1561·2).

Arotin
Note: this name may be used for preparations of different composition.
Arrowin, India.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Sandoz, Braz.
Paroxetine hydrochloride (p. 440·3).

Arovit *Bayer Consumer, Arg.; Bayer, Braz.; Bayer, Ital.; Bayer, S.Afr.†; Bayer, Swed.†*
Vitamin A acetate (p. 2098·3) or vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Bio-Sante, Canad.†; Roche, India.
Vitamin A (p. 2098·3).

Arowash *Cadila, India.†*
Black catechu (p. 2457·3); liquorice (p. 1853·2); clove oil (p. 2481·3).
Mouth ulcers; halitosis; toothache.

Aroxat *GSK, Chile.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic attacks; social phobia.

Aroxim *Aronex, India.*
Cefixime (p. 240·3).
Bacterial infections.

Aroxin *DHA, Hong Kong; DHA, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Arpa *Osmed, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Arpadol *Apsen, Braz.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Arpezol *Proge, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Arphos *Fournier, Fr.*
Calcium glycerophosphate (p. 1783·3); magnesium gluconate (p. 1787·2).
Tonic.

Arpicin *Cinerea, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arpicolin *Rosemont, UK.*
Procyclidine hydrochloride (p. 912·2).
Parkinsonism; drug-induced extrapyramidal disorders.

Arpimune *Pascual, Philipp.*
Ciclosporin (p. 1945·2).
Transplant rejection; bone-marrow transplantation; rheumatoid arthritis; psoriasis; atopic dermatitis; nephrotic syndrome.

Arpisen *Arlex, Mex.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Arpisine *PP Lab, Thai.*
Aspirin (p. 22·2).
Fever; pain.

Arpitor *RPG, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Arpizol *Sun, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arpolax *Incepta, Hong Kong.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Arranon *GSK, Jpn; GSK, USA.*
Nelarabine (p. 834·3).
Acute lymphoblastic leukaemia; lymphoblastic lymphoma; lymphoblastic leukaemia.

Arreno *Intas, India.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).
Stroke prophylaxis.

Arrestadol *Misha, India.*
Tramadol (p. 139·2).
Pain.

Arrestadol-P *Misha, India.*
Tramadol (p. 139·2); paracetamol (p. 115·1).
Pain.

Arresten *Shinyaku, Jpn.*
⊗Meticrane (p. 1433·1).
Hypertension.

Arrestin
Note: this name may be used for preparations of different composition.
Svizera, India.
Aceclofenac (p. 16·2).
Pain; inflammation.

Arrestin-P *Svizera, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Arrestin-SP *Svizera, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Arret *McNeil Healthcare, Irl.; Johnson & Johnson MSD Consumer, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Arretin *Valeant, Mex.; ICN, Pol.†*
Tretinoin (p. 1725·2).
Acne; photoageing of the skin; hyperkeratosis.

Arrhythmie-Gastreu N *Reckeweg, Ger.*
Iberis amara; leonurus cardiaca (p. 2564·2); oleander (p. 2574·3); spartium scoparium (p. 2611·3); sumbulus moschatus.
Homoeopathic preparation.

Arrif *Eurofarma, Braz.*
Rifamycin sodium (p. 354·3).
Bacterial skin infections.

Arrolina *Arrowblue, Port.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Arrosertra *Arrowblue, Port.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Arrox *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Arrythgo *Euro Generics, Philipp.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Arscolloid *SIT, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); silver protein (p. 2616·2).
Oral disinfection.

Arsen *Arlex, Mex.†*
Senna (p. 1885·1).
Constipation.

Arsenal *IQFA, Mex.*
Naproxen (p. 98·2).
Inflammation.

Arsenal Compuesto *IQFA, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Inflammation; pain; fever.

Arsenic Comp Iov-Diabet *Talion-A, Ukr.*
Acidum arsenicosum (p. 2448·1); secale cornutum (p. 2137·1); iodum (p. 2336·3); acidum phosphoricum (p. 2589·1); lycopodium clavatum (p. 2547·1).
Homoeopathic preparation.

Arsenox *Intas, India.*
Arsenic trioxide (p. 2448·1).

Arsicort *Arsmedendi, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Arsikem *Alkem, India.*
Arsenic trioxide (p. 2448·1).

Arsinal *Meprofarm, Indon.*
Dipyrone (p. 53·3); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); tocoferil acetate (p. 2119·2).
Pain.

Arsipor *Arsmedendi, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Arsitam *Meprofarm, Indon.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Arsitec *Arsmedendi, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Arsol *Adelco, Gr.*
Allopurinol (p. 600·2).

Arsorb *Arrow, Austral.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Arstatin *Arsmedendi, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Arsuamoon *Guilin, Gr.*
Artesunate (p. 648·2); amodiaquine hydrochloride (p. 647·2).

Arsulide *Sterkem, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Arsulide-D *Sterkem, India.*
Nimesulide (p. 101·3); dicycloverine (p. 1834·2).

Arsulide-P *Sterkem, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Arsulide-S *Sterkem, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Arsumet-L *Aronex, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Art *Negma, Fr.; Rafa, Israel.*
Diacerein (p. 45·3).
Osteoarthritis.

Art Complex *Thompsons, Canad.†*
Arnica (p. 2447·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Artacil *Neon, India.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Artagen *Ranbaxy, India.*
Naproxen (p. 98·2).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Artager
Note: this name may be used for preparations of different composition.
Gerot, Hung.†
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure.

Lannacher, Cz.†
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Artal *Pharmia, Fin.†*
Pentoxifylline (p. 1465·3).
Peripheral and cerebral vascular disorders; vascular eye disorders.

Artamin *Sandoz, Austria; Chandra Bhagat, India; VHB, India; Sandoz, Malaysia.*
Penicillamine (p. 1567·1).
Wilson's disease; cystine calculi; cystinuria; heavy metal poisoning; rheumatoid arthritis; chronic active hepatitis; primary biliary cirrhosis; scleroderma; benign purpura hyperglobulinaemia; juvenile idiopathic arthritis.

Artane *Wyeth, Arg.; Aspen, Austral.; Teofarma, Belg.; Apsen, Braz.; Sanofi-Aventis, Fr.; Teofarma, Ger.; IFET, Gr.; Wyeth, Gr.; Lederle, Indon.†; Teofarma, Ital.; Teofarma, Neth.; Teofarma, Port.; Wyeth, S.Afr.†; Teofarma, Spain; Wyeth, Thai.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Artaxan *Malesci, Ital.*
Nabumetone (p. 97·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artaxol *Loeffler, Mex.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Arte Plus *Zydus, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Artears *Yik Kwan, Hong Kong†; Optaderm, Philipp.*
Hypromellose (p. 2189·2).
Dry eyes.

Artecef *Artecef, Neth.*
Artemotil (p. 648·2).
Malaria.

Artechol *Anglo-French Laboratories, Canad.†*
Cynara (p. 2490·3); sodium oleate (p. 2211·2); decholesterinised bile (p. 2457·2); heavy magnesium oxide (p. 1857·3).
Choleretic; cholagogue.

Artecholin *Phytofarm Kleka, Pol.†*
Artemisia abrotanum; milk thistle (p. 1561·1); peppermint leaf (p. 1877·1); cnicus benedictus (p. 2482·2); greater celandine (p. 2522·2); achillea (p. 2427·3); taraxacum (p. 2625·3).
Biliary-tract disorders.

Artecholwex *Herbapol Lodz, Pol.†*
Artemisia abrotanum; milk thistle (p. 1561·1); cnicus benedictus (p. 2482·2); achillea (p. 2427·3); peppermint leaf (p. 1877·1); taraxacum (p. 2625·3); greater celandine (p. 2522·2).
Biliary-tract disorders.

Arte-cyl Ho-Len-Complex *Liebermann, Ger.*
Abrotanum; cactus (p. 2473·2); cuprum arsenic.; glonoinum (p. 1391·2); kalium jod.

(p. 2336·3); kreosotum (p. 1659·3); secale (p. 2137·1); tabacum (p. 2632·2).
Homoeopathic preparation.

Artedil
Note: this name may be used for preparations of different composition.
Chiesi, Spain.
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Artedin *GD, Ital.*
Garlic (p. 2510·3); ginkgo biloba (p. 2512·3); curcubita; policosanol (p. 1472·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Artelac *Bausch & Lomb, Arg.; Riel, Austria; Tramedico, Belg.; Bausch & Lomb, Braz.; Santen, Denm.; Santen, Fin.; Chauvin, Fr.; Mann, Ger.; Bausch & Lomb, Irl.; Teva, Israel; Bausch & Lomb, Mex.; Bausch & Lomb, Neth.; Santen, Norw.; Bausch & Lomb, Philipp.; Mann, Pol.; Angelini, Port.; Mann, Singapore; Santen, Swed.; Bausch & Lomb, UK; Bausch & Lomb, Ukr.*
Hypromellose (p. 2189·2).
Dry eyes; corneal burns, ulcers, and wounds; eye examination.

Artelac Advanced *Bausch & Lomb, Hong Kong.*
Hyaluronic acid (p. 2526·2).
Dry eyes.

Bausch & Lomb, Ital.
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Artelac Nighttime *Bausch & Lomb, UK.*
Carbomer (p. 2173·3).
Dry eyes.

Artelac Rebalance *Bausch & Lomb, UK.*
Sodium hyaluronate (p. 2526·2); macrogol 8000 (p. 2547·3).
Dry eyes.

Artelac Splash *Mann, Ger.*
Hyaluronic acid (p. 2526·2).
Formerly known as Artelac Advanced.
Dry eyes.

Artelife *Diba, Mex.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; circulatory disorders of the eyes and ears.

Artem *Multi Mitra, Indon.*
Artemether (p. 648·1).
Malaria.

Artem E *Panjon, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Artemax *Gap, Gr.†*
Artenimol (p. 648·2).

Artemidis *Sigma, Braz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in women; combined oral contraceptive.

Artemisol *Herbapol Krakow, Pol.*
Absinthium (p. 2426·1); tansy (p. 2625·3).
Pediculosis.

Artemodi *Holley-Cotec, China.*
Artesunate (p. 648·2); amodiaquine (p. 647·2).
Malaria.

Artemotial *Taj, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Artenol *Yik Kwan, Hong Kong.†*
⊗Atenolol (p. 1308·2).

Arteolol *Lacer, Spain.†*
⊗Carteolol hydrochloride (p. 1332·3).
Angina pectoris; arrhythmias; hypertension.

Arteopilo *Bausch & Lomb, Switz.†*
⊗Carteolol hydrochloride (p. 1332·3); pilocarpine hydrochloride (p. 2010·3).
Ocular hypertension; glaucoma.

Arteoptic *Bausch & Lomb, Belg.; Novartis, Cz.; Thea, Ger.; Otsuka, Hong Kong; Chauvin, Neth.†; Thea, Pol.; OM, Port.; Bausch & Lomb, Spain; Chauvin, Spain; Bausch & Lomb, Switz.; Otsuka, Thai.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Arteparon *Farmalex, Gr.†*
A heparinoid (p. 1401·1).

Artepid *Pharos, Indon.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; unstable angina.

Artérase *Clement, Fr.*
Equisetum (p. 2500·1); garlic (p. 2510·3); cypress (p. 2491·1); aesculus (p. 2431·2).
Venous insufficiency; capillary fragility.

Arterenol *Sanofi-Aventis, Ger.*
⊗Noradrenaline hydrochloride (p. 1458·2).
Shock.

Arteria-vita *Permamed, Switz.*
Aegle sepiar fructus; aquilegia vulgaris; calcium sulfate (p. 2173·1); calendula (p. 2465·2); camphor (p. 2466·2); cardamom (p. 2471·1); clove (p. 2481·2); kaempferiae galangae; lactucae sativae; Iceland moss (p. 2531·2); liquorice (p. 1853·2); meliae tousend; myrobalan fruit; pepper; plantago lanceolata (p. 2604·2); knotgrass (p. 2538·2); potentilla aureae; santali rubri lignum; sidae cordifoliae; aconite (p. 2428·3); valerian (p. 2640·2).
Circulatory disorders.

Arterin *Vegemedica, Fr.*
Red yeast rice (p. 2603·1).
Hyperlipidaemias.

Arterin Plus *Vegemedica, Fr.*
Red yeast rice (p. 2603·1); ubidecarenone (p. 2637·1).
Hyperlipidaemias.

Arteriol *Gador, Arg.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders; Raynaud's syndrome.

Arteriosan *Bernabo, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Arteriosan Plus *Bernabo, Arg.*
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Arteriotrat *Purissimus, Arg.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Folate and vitamin B deficiency.

Arteriovinca *Angelini, Port.*
Vincamine (p. 2645·2).
Mental function impairment.

Arterodiet *Yves Ponroy, Singapore.†*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); vitamin E (p. 2119·1); polyphenols.
Tonic.

Arteron *Ariston, Braz.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Artérosan Plus *Doetsch, Grether, Switz.†*
Crataegus (p. 2488·1); melissa (p. 2552·3); garlic oil (p. 2510·3); ginkgo biloba (p. 2512·3).
Cerebrovascular disorders.

Arterosol *Minerva (Μινερβα), Gr.*
Piracetam (p. 393·3).
Central nervous system disorders.

Artesa *Orion, India.*
Artesunate (p. 648·2).
Malaria.

Artesiane *Dafra, Belg.*
Artemether (p. 648·1).
Malaria.

Artesol *Drugtech, Chile.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Artestar *Invision, India.*
Artesunate (p. 648·2).
Malaria.

Artevil *Drugtech, Chile.*
Clopidogrel (p. 1342·3).
Atherosclerosis.

Artex *Servier, Fr.; Servier, Neth.; Servier, Port.*
⊗Tertatolol hydrochloride (p. 1511·2).
Hypertension.

Artexal *Servier, Gr.†; Servier, Irl.†*
⊗Tertatolol hydrochloride (p. 1511·2).
Hypertension.

Artezine *Valenta, Rus.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Artfin *Zee, India.*
Artesunate (p. 648·2).
Malaria.

Artflex *Ivax, Arg.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee; shoulder pain.

Arth
Note: this name may be used for preparations of different composition.
Plus, India.
Injection: Artesunate (p. 648·2).
Malaria.

Zuventus, India.
Capsules: Chondroitin sulfate (p. 2476·1); glucosamine (p. 2515·3).

Artha-G *Williams, USA.*
Salsalate (p. 130·1).
Pain; fever; inflammation.

Arthar *Admac, India.*
Glucosamine sulfate (p. 2515·3); vitamins.

Artharen *T-Boma, Hong Kong.†*
Diclofenac (p. 48·3).

Artheal *Medihealth, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Arthflex *Homeocan, Canad.*
Colchicum autumnale (p. 607·1); bryonia alba (p. 2461·3); dulcamara (p. 2497·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Arthocare *Gland, India.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine (p. 2515·3).

Arthocare DS *Gland, India.*
Chondroitin sulfate (p. 2476·1); glucosamine hydrochloride (p. 2515·3).

Arthocerin *Pulse, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Arthocerin-A *Pulse, India.*
Diacerein (p. 45·3); aceclofenac (p. 16·2).

Arthocerin-G *Pulse, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Arthodia-G *Aronex, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Arthopack *Dalmia, India.*
Capsules: Malabar nut (p. 2549·1); punarnava (p. 2601·1).

Dalmia, India.
Oil: Acacia arabica; achyranthes aspera; malabar nut (p. 2549·1); curcuma longa; piper longum; piper nigrum; syzygium aromaticum; syzygium aromaticum oil; ginger (p. 1844·1).

Arthorid *DR Johns, India.*
Oral suspension: Nimesulide (p. 101·3); paracetamol (p. 115·1).

DR Johns, India.
Tablets: Nimesulide (p. 101·3).
Osteoarthritis; pain.

Arthotec *Pharmacia, Ger.*
Diclofenac sodium (p. 48·3). Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Arthralgon *Lavipharm, Gr.*
Capsaicin (p. 35·1).
Postherpetic neuralgia; diabetic peripheral neuropathy.

Arthramina *Pharma Nord, Port.†*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Arthran *Su-Heung, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Arthrease *Biotechnology, Israel; DePuy, UK.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Arthrella *Charak, India.*
Camphor (p. 2466·2); ashwagandha (p. 2450·2).

Arthrex
Note: this name may be used for preparations of different composition.
1A, Ger.†
Diclofenac sodium (p. 48·3).
Soft-tissue injury.

Arthrexin *Alphapharm, Austral.; LCH, Hong Kong†; Mylan, NZ; Aspen, S.Afr.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain; fever.

Arthri Plus *Bioglan, Austral.†*
Celery seed oil (p. 2472·3); evening primrose oil (p. 2502·2); fish oil (p. 1460·3); devil's claw root (p. 42·3); salix (p. 129·2).
Arthritis; rheumatism; sports injuries.

Arthriaid *FMC Pharma, Irl.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

ArthriCare *MD, Singapore.*
Glucosamine hydrochloride (p. 2515·3) or glucosamine sulfate (p. 2515·3).
Dietary supplement; joint disorders.

Arthrid *TTK, Philipp.*
Boswellia serrata (p. 2507·3); piper longum.
Joint pain.

Arthrifen *Armoxindo, Indon.*
Ibuprofen (p. 68·2).
Osteoarthritis; rheumatoid arthritis; fever; pain.

Arthrifen Plus *Armoxindo, Indon.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Arthriforte *Blackmores, Austral.†*
Fish oil (p. 1460·3); eicosapentaenoic acid (p. 1460·2); vitamin A (p. 2098·3); turmeric (p. 2218·1); devil's claw root (p. 42·3); celery seed oil (p. 2472·3); vitamin E (p. 2119·1).
Arthritis; inflammation; rheumatism.

Arthril *Sons, Mex.*
Ketoprofen (p. 79·1).
Inflammation.

Arthrill *Ind-Swift, India.*
Garlic (p. 2510·3); camphor (p. 2466·2); capsaicin (p. 35·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); nux vomica (p. 2573·3); sweet birch oil (p. 92·1); ashwagandha (p. 2450·2).

Arthrill Forte *Ind-Swift, India.*
Boswellia serrata (p. 2507·3); curcuma longa; zingiber officinale.

Arthrimel *Clonmel, Irl.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Stada, Fin.
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Arthriplex *Steierl, Ger.*
Apis mellifica (p. 2445·2); bryonia cretica; ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Arthriselect *Dreluso, Ger.*
Berberis (p. 2502·1); lithium carbonicum (p. 427·3).
Homoeopathic preparation.

Arthrisone *Biodica, Fr.†*
⊗Hydrocortisone acetate (p. 1640·1); framycetin sulfate (p. 301·2).
Root canal infections.

Arthritic Pain *Homeocan, Canad.*
Apis mellifica (p. 2445·2); arnica montana (p. 2447·2); benzoicum acidum (p. 1738·2); causticum (p. 2595·3); colchicum autumnale; natrum carbonicum (p. 2617·3).
Homoeopathic preparation.

Arthritic Pain Herbal Formula 1 *Vitelle, Austral.†*
Celery (p. 2472·3); juniper (p. 2537·1); devil's claw root (p. 42·3); salix alba.
Arthritis; rheumatism.

Arthritil *Marching, Hong Kong.†*
Glucosamine hydrochloride (p. 2515·3).
Joint disorders.

Arthritil Plus *Marching, Hong Kong.†*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Arthritis Free *Young Again Products, USA.*
Vitamins; minerals; glucosamine (p. 2515·3); boswellic acid.

Arthritis Hot Creme *Thompson, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Arthritis Pain *Vita Health, Canad.*
Paracetamol (p. 115·1).
Pain.

Arthritis Pain Formula *Hylands, Canad.*
Arnica montana (p. 2447·2); bryonia; cimicifuga racemosa (p. 2478·1); guaicacum (p. 2523·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Whitehall, USA.
Aspirin (p. 22·2).
Aluminium hydroxide (p. 1817·2) and magnesium hydroxide (p. 1857·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Arthritis; pain; fever.

Arthritis Pain Formula Aspirin Free *Whitehall, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Arthritis Relief *Brauer, Austral.*
Cream: Arnica montana (p. 2447·2); bellis perennis (p. 2454·2); ledum palustre (p. 2550·1); apis mellifica (p. 2445·2); belladonna (p. 2453·3); bryonia alba (p. 2461·3); camphora (p. 2466·2); hypericum perforatum (p. 449·1); kalmia latifolia (p. 2537·2); ranunculus bulbosus; rhus toxicodendron (p. 2603·3); ruta graveolens (p. 2608·2); symphytum (p. 2484·2); strontium carbonicum.
Homoeopathic preparation.

Arthritisane *Lesourd, Fr.†*
Meadowsweet (p. 2550·2); salix (p. 129·2); ash (p. 2450·1); black currant (p. 2458·1).
Joint pain.

Arthro *Gomenol, Fr.*
Niaouli oil (p. 2569·1); lavender oil (p. 2541·1); sweet birch oil (p. 92·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); ylang ylang oil (p. 2649·3); rock rose oil; immortelle oil; boswellia (p. 2507·3).
Joint disorders.

Arthrobiane *Pileje, Fr.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); galanga.
Joint disorders.

Arthrocalman *Schwarzwalder, Ger.*
Viscum album (p. 2560·2).
Homoeopathic preparation.

Arthrocare *Coral, Rus.*
Diacerein (p. 45·3).
Osteoarthritis.

Arthrocine *Gerda, Fr.*
Sulindac (p. 134·2).
Musculoskeletal, joint, and peri-articular disorders.

Arthrocox *Simayla, S.Afr.*
Meloxicam (p. 86·3).
Osteoarthritis; ankylosing spondylitis; rheumatoid arthritis; sciatica.

Arthrodex *Vickmans, Hong Kong.†*
⊗Dexamethasone (p. 1630·3); paracetamol (p. 115·1); vitamin B substances (p. 2102·3).

Arthrodont *Pierre Fabre, Fr.; Dupricz, Hung.; Pierre Fabre, S.Afr.†; Pierre Fabre Sante, Singapore.*
Enoxolone (p. 54·2).
Gum disorders.

Arthro-Drainol *Boiron, Fr.*
Arnica montana (p. 2447·2); bryonia dioica (p. 2461·3); solanum dulcamara (p. 2497·3); anemone pulsatilla (p. 2600·2); chamomilla (p. 2474·1); kalium iodatum (p. 2336·3); rhododendron ferrugineum; acide benzoicum (p. 1738·2); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Arthro-Eze *Golden Glow, Austral.*
Celery seed (p. 2472·3); ginger (p. 1844·1); grape seed (p. 2521·3); centella (p. 1698·3); glucosamine hydrochloride (p. 2515·3); fish oil (p. 1460·3); evening primrose oil (p. 2502·2); cod-liver oil (p. 2056·3).
Musculoskeletal and joint disorders.

Arthrofar *Vocate, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Arthrofen *Ashbourne, UK.*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal and joint disorders.

Arthro-Flex *Biotech, Singapore.*
Glucosamine sulfate (p. 2515·3); manganese amino acid chelate (p. 2048·3).
Musculoskeletal and joint disorders.

Arthroflorine *Lehning, Fr.†*
Salix (p. 129·2); urtica (p. 2639·3); ash (p. 2450·1); meadowsweet (p. 2550·2); black currant (p. 2458·1).
Joint pain.

Arthrofluor *Teva, Hung.†*
Sodium fluoride (p. 2089·2).
Musculoskeletal and joint disorders.

Arthrofon *Materia Medica, Rus.*
Tumour necrosis factor-α antibodies.
Homoeopathic preparation.

Arthrokatt *Kattwiga, Ger.*
Ledum palustre (p. 2550·1); bryonia (p. 2461·3); apis mellifica (p. 2445·2); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Arthroloc *Balu, Gr.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Arthrolur *Drossapharm, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Arthromuv *Aristo, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Arthron Chondrex *Unipharm, Ukr.*
Chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Arthron Complex *Unipharm, Ukr.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Joint disorders.

Arthron Flex *Unipharm, Ukr.*
Glucosamine hydrochloride (p. 2515·3).
Joint disorders.

Arthron-Triactive *Unipharm, Ukr.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine hydrochloride (p. 2515·3); dimethyl sulfone (p. 2493·3).
Joint disorders.

Arthroplus *Target, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Arthrorein *Aurora, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Arthrorell N *Sanorell, Ger.*
Acid benzoicum e resina (p. 1738·2); colchicum autumnale (p. 607·1); ledum palustre (p. 2550·1); toxicodendron quercifolium (p. 2603·3); acidum silicicum (p. 2208·3).
Homoeopathic preparation.

Arthro-S *Pharmahof, Thai.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Arthrosenex N *Riemser, Ger.*
Arnica (p. 2447·2).
Musculoskeletal and joint disorders.

Arthrotabs *Salus, Ger.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Arthrotec *Pfizer, Austral.; Pfizer, Austria; Continental Pharma, Belg.; Pfizer, Canad.; Pfizer, China; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Irl.; Pfizer, Israel; Pfizer, Neth.; Pfizer, Norw.; Pharmacia, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Ali, Turk.; Pfizer, UK; Searle, USA; Pfizer, Venez.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis; inflammation.

Arthrovit Plus *Lifestyle, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Arthrox *Pharmanel, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Arthroxen *CP Pharmaceuticals, UK.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Arthru-Derm *Meyer Zall, S.Afr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint pain.

Arthrum H *LCA, Fr.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Arthryal *Meditron, Gr.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Arthryl *Rottapharm, Fin.; Rafa, Israel; Rottapharm, Pol.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; degenerative knee disorders.

Artibesan *Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Artic Ice *Scott, Canad.†*
Menthol (p. 2553·2).

Artica *Ind-Swift, India.*
Glucosamine sulfate (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Articadent *Dentsply, Fr.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Articalm
Note: this name may be used for preparations of different composition.
Cadila, India.
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Korhispana, Spain.
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Articho-Nat *Naturatec, Canad.*
Cynara (p. 2490·3); deoxycholic acid (p. 2457·2); bile extract (p. 2457·2); magnesium oxide (p. 1857·3).

Articlor *Icarus, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Articlox *Unipharma, Gr.*
Hydroxocobalamin acetate (p. 2107·3).
Megaloblastic anaemia; vitamin B12 deficiency.

Articolase (w/glucosamine) *SIRC, Singapore.*
Collagen (p. 2483·2); glucosamine sulfate (p. 2515·3).
Joint disorders.

Articulaire Sérocytol *Serolab, Switz.*
An immunoglobulin (equine).
Musculoskeletal and joint disorders.

Articulan *Pentafarma, Port.†*
Etodolac (p. 57·1).
Musculoskeletal and joint disorders; gout; pain.

Articurell *Sanorell, Ger.*
Bryonia cretica.
Homoeopathic preparation.

Artidin *Hindustan Antibiotic, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Artifar *Unipharma, Gr.*
Carisoprodol (p. 2021·3).

Artifen *Aglowmed, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Artifen Plus *Aglowmed, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Artifen-D *Aglowmed, India.*
Diclofenac (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Artifene *Northia, Arg.*
Dextropropoxyphene (p. 43·2); dipyrone (p. 53·3).
Pain.

Artific *Angelini, Spain.*
Hypromellose (p. 2189·2).
Dry eyes.

Artificial Tears
Note: this name may be used for preparations of different composition.
Bausch & Lomb, USA.
Hypromellose (p. 2189·2).
Dry eyes.

Ivax, Canad.; Pharmascience, Canad.
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Ivax, Canad.†
⊗Dextran (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Artificial Tears Extra *Pharmascience, Canad.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Artificial Tears Plus *Ivax, Canad.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Artifit *FDC, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Artifix *Emar, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Artifleur *Bloem Beheer, Neth.*
Colchicum autumnale; rhus toxicodendron (p. 2603·3); bryonia alba; arnica montana (p. 2447·2); chamomilla (p. 2474·1).
Homoeopathic preparation.

Artiflex
Note: this name may be used for preparations of different composition.
Gelcaps, Mex.
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Synergen, Philipp.
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Zdorovje, Ukr.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Artifrin *Zdorovje, Rus.; Zdorovje, Ukr.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1) or adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Artigesic *Glenmark, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Artigesic-MR *Glenmark, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Artihol *KVZ, Ukr.*
Cynara scolymus (p. 2490·3).
Hepatobiliary disorders; renal disorders.

Artikamine *Adipharm, Gr.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Artilog *Pfizer, Ital.; Esteve, Spain.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Artilov *UniOrange, India.*
Tablets: Diclofenac sodium (p. 48·3).
Inflammation; pain.

UniOrange, India.
Topical gel: Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Artimal *Indi, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Artin *Sanova, Austria.†*
Aloes (p. 1816·1); frangula bark (p. 1843·3).
Constipation; stool softener.

Artinibsa *CSP, Fr.; Inibsa, Port.; Inibsa, Spain.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Artinizona *Teuto, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Artinostrum *Nostrum, Port.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Artirem *Guerbet, Austria; Codali, Belg.; Guerbet, Fr.; Guerbet, Ger.; Guerbet, Neth.; Guerbet, Switz.*
Meglumine gadoterate (p. 1587·1).
Contrast medium for magnetic resonance imaging.

Artirox *Panjon, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Artirox-SP *Panjon, India.*
⊗Roxithromycin (p. 356·2); serrapeptase (p. 2613·3).
Bacterial infections.

Artis-Heel *Heel, Canad.†*
Arnica montana (p. 2447·2); bryonia (p. 2461·3); ferrum phosphoricum (p. 2077·1); hahnemann's causticum (p. 2595·3); poison ivy.
Homoeopathic preparation.

Artisial *Biocodex, Fr.*
Electrolytes (p. 1775·1); carmellose sodium (p. 2175·2); sorbitol (p. 2092·1).
Saliva substitute.

Artisid *Sun, India.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Artisin *Symbiosis, India.*
Artesunate (p. 648·2).
Malaria.

Artispar *RPG, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Artiss *Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Irl.; Baxter, Neth.; Baxter, Norw.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, USA.*
Component 1, fibrinogen (p. 1151·3); aprotinin (p. 1133·2); component 2, calcium chloride (p. 1783·1); thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; tissue glue; wounds; skin-graft adhesion.

Artistry Blemish Control *Access, Canad.†*
Salicylic acid (p. 1719·1).
Skin disorders.

Artistry Essential *Amway, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Artival
Note: this name may be used for preparations of different composition.
Geno, India.
Valdecoxib betadex.
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Artiz *Ritz, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Artizia *Zentiva, Cz.; Zentiva, Pol.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Artodarin *Chemedica, Rus.*
Diacerein (p. 45·3).
Osteoarthritis.

Artofen *Teva, Israel; Vifor, Switz.†*
Ibuprofen (p. 68·2).
Pain; fever; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artoglico *Sigma, Braz.*
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Artonil *Sandoz, Swed.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Artosin *Roche, Mex.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Artosolv *Rottapharm, Fin.†*
Chondroitin sulfate (p. 2476·1).
Osteoarthritis of the knee.

Artotec *Pfizer, Fr.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Artovit *Cardinal, Indon.; Pharos, Indon.*
Vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); zinc (p. 2126·1); betacarotene (p. 2051·1); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); selenium (p. 2086·3); lecithin (p. 2542·2).
Dietary supplement.

Artra *Unipharm, Rus.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Artra Chondroitin *Unipharm, Rus.*
Chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis; osteochondrosis.

Artrait *TRB, Arg.*
Methotrexate (p. 822·2) or methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Artren *Merck, Braz.; Merck, Venez.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Merck, Chile.
Diclofenac (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Artrenac *Merck, Mex.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Artrenac Pro *Merck, Mex.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Rheumatoid arthritis; osteoarthritis.

Artrene
Note: this name may be used for preparations of different composition.
Merck, Mex.
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Rheumatoid arthritis; osteoarthritis.

Artrex
Note: this name may be used for preparations of different composition.
Bio-Ved, Singapore.
Ashwagandha (p. 2450·2); boswellia serrata (p. 2507·3); turmeric (p. 2218·1); ginger (p. 1844·1).
Musculoskeletal, joint, and soft-tissue disorders.

Pharmalink, India.
Capsules: Boswellia serrata (p. 2507·3); curcuma longa; ashwagandha (p. 2450·2); zingiber officinale.

Pharmalink, India.
Cream: Camphor (p. 2466·2); cinnamon oil (p. 2479·3); eucalyptus oil (p. 2501·2); ginger oil (p. 1844·1); lemon grass oil (p. 2543·2); peppermint oil (p. 1877·1); rose oil (p. 2607·2); thymol (p. 1772·2); turpentine oil (p. 2636·3); sweet birch oil (p. 92·1).

Spedrog, Arg.
Allopurinol (p. 600·2); colchicine (p. 604·1).
Gout; hyperuricaemia.

Artri *Medical, Spain.†*
Adenosine phosphate (p. 2430·2); indometacin (p. 71·2).
Pain; fever; inflammation.

Artriben *Benarth, Canad.†*
Fir oil; cedar oil (p. 2472·3); pine oil (p. 2591·1).
Musculoskeletal and joint pain.

Artricol *Medosan, Ital.*
Amtolmetin guacil (p. 21·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artricom *Combiphar, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Artriden *Degorts, Mex.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Artridol
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Rimsa, Mex.
Capsules: ⊗Indometacin (p. 71·2); betamethasone (p. 1623·2); methocarbamol (p. 2025·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rimsa, Mex.
Topical gel: ⊗Betamethasone dipropionate (p. 1623·3); indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Merck, Port.†
Hydroxymethoxy ethyl benzoate; phenylpropyl salicylate.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artridol Duo *Laboratorios Chile, Chile.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Artrifar *Farcoral, Mex.*
Glucosamine (p. 2515·3); ascorbic acid (p. 2110·3).
Joint disorders.

Artrifenil *Teuto, Braz.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders.

Artril
Note: this name may be used for preparations of different composition.
Advance, Malaysia; Advance, Singapore.†
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Farmasa, Braz.; Eczacibasi, Turk.
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Artril C *Advance, Singapore.†*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Artrilab *Labomed, Chile.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Artrilan *Offenbach, Mex.†*
⊗Prednisolone (p. 1645·2); salicylamide (p. 129·2); meprobamate (p. 1083·3).
Musculoskeletal and joint disorders.

Artrilase *Bago, Arg.; Bago, Singapore.*
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders; joint disorders.

Bago, Singapore.
Tablets: Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Artrilase Complex *Bago, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Arthroses.

Artrilom *ProMed, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Artrilox *Combiphar, Indon.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Artriman *Biofarma, Mex.*
Glucosamine (p. 2515·3).
Osteoarthritis.

Artrimax *Prater, Chile.*
Collagen UC-II (type 2, denatured) (p. 2483·2).
Osteoarthritis; rheumatoid arthritis.

Artrimod *Labomed, Chile.†*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Artrinid *Uniao Quimica, Braz.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Artrinol-On *Alvartis, Mex.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Artrinovo *Llorens, Spain.*
Indometacin (p. 71·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Artriox *Medikon, Indon.†*
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); zinc (p. 2126·1).
Osteoarthritis.

Artritapsin *Maver, Chile.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Fever; inflammation; pain.

Artritin *Teguhsindo, Indon.*
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis; nutritional supplement.

Artritol *Bio-Sante, Canad.*
Capsules: Paracetamol (p. 115·1).

Bio-Sante, Canad.†
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Artritosamin *Healthyway, Ukr.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin E (p. 2119·1); boswellia (p. 2507·3); turmeric (p. 2218·1); grape seed extract (p. 2521·3).
Musculoskeletal and joint disorders.

Artrizan *Negma, Spain.*
Diacerein (p. 45·3).
Osteoarthritis.

Artrizona *Silesia, Chile.*
Diacerein (p. 45·3).
Degenerative joint disorders.

Artro *Ikapharmindo, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); zinc (p. 2126·1); manganese (p. 2081·2); magnesium (p. 1786·3).
Joint disorders.

Artro Plus *Ikapharmindo, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); selenium (p. 2086·3); vitamin C (p. 2110·3); zinc (p. 2126·1); manganese (p. 2081·2).
Joint disorders.

Artroben *Mavi, Mex.*
Benzydamine hydrochloride (p. 29·2).
Inflammation; pain.

Artrobiotral *Bionutre, Arg.*
Amino acids; minerals; vitamin B substances (p. 2102·3).
Dietary supplement for prevention of osteoporosis.

ArtroCam *Kamelia, Rus.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Artrocaptin
Note: this name may be used for preparations of different composition.
Spedrog, Arg.
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Estedi, Spain.†
Tolmetin sodium (p. 139·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artrocel *Biotecnoquimica, Venez.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Artrodar *TRB, Arg.; TRB, Braz.; Jida, China; TRB, Cz.; Chemedica, Hong Kong; Elder, India; Combiphar, Indon.; Chemedica, Malaysia; Chemedica, Thai.; Bio-Gen, Turk.; Leti, Venez.*
Diacerein (p. 45·3).
Osteoarthritis; degenerative joint disorders.

Artrodesmol Extra *Nupel, Spain.*
⊗Dimethyl sulfoxide (p. 2182·2); phenylbutazone (p. 125·1); fluocinolone acetonide (p. 1636·1); methyl salicylate (p. 92·1).
Peri-articular and soft-tissue disorders.

Artrodue *MDM, Ital.*
Collagen (p. 2483·2); mucopolysaccharides; vitamins; copper (p. 2057·1).
Joint disorders.

Artrofort Complex *Rotta, Thai.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis.

Artroject *DJO, Ger.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Artroksin *Terra, Turk.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders; gout.

Artrolin-F *Marching, Hong Kong.†*
⊗Dexamethasone (p. 1630·3); indometacin (p. 71·2); vitamin B substances (p. 2102·3). Magnesium trisilicate (p. 1858·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Artrolive *Ache, Braz.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Artrolyt *Chemedica, Austria; Neo-Farmaceutica, Port.*
Diacerein (p. 45·3).
Osteoarthritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Artromed *Medosan, Ital.*
Amtolmetin guacil (p. 21·1).
Musculoskeletal and joint disorders; pain.

Artronil *Eurodrug, Malaysia; Eurodrug, Singapore†; Eurodrug, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; degenerative joint disorders.

Artropan *Kocak, Turk.*
⊗Triamcinolone hexacetonide (p. 1649·2).
Corticosteroid.

Artrophytum *Arkomedika, Fr.†*
Devil's claw root (p. 42·3).
Joint pain.

Artroplex *Knop, Chile.*
Acidum benzoicum (p. 1738·2); colchicum (p. 607·1); guajacum (p. 2523·1); ledum palustre (p. 2550·1); lithium carbonicum (p. 427·3); lycopodium clav. (p. 2547·1).
Homoeopathic preparation.

Artrosamin *Lapreven, Venez.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); collagen (p. 2483·2).
Arthroses.

Artrosil *Ache, Braz.*
Ketoprofen lysine (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artrosilen *Dompe, Rus.*
Ketoprofen lysine (p. 79·1).
Pain; inflammation.

Artrosilene *Dompe, Ital.*
Ketoprofen lysine (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Artrosulfur *Laborest, Ital.*
Dimethyl sulfone (Lignisul) (p. 2493·3); zinc (p. 2126·1); copper (p. 2057·1); boswellia; vitamin B substances (p. 2102·3).
Musculoskeletal pain.

Artrotec *Pfizer, Ital.; Pfizer, Mex.; Pfizer, Spain.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders; pain; inflammation.

Artrox *Pfizer, Swed.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Artroxicam
Note: this name may be used for preparations of different composition.
Medichrom, Gr.
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.
SoSe, Ital.
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artrozan *Farmstandart, Rus.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Artrum *Biosintez, Rus.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; phlebitis.

ARTU *Artu, Neth.*
A range of allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.

Artu *Terra, Turk.*
⊗Promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Respiratory-tract congestion.

Artuvac *Artu, Neth.*
Dermatophagoides pteronyssinus extracts (p. 2434·3).
Allergen immunotherapy.

Artyflam *Rayere, Mex.*
Piroxicam (p. 125·3).
Inflammation; musculoskeletal and joint disorders.

ARTZ *Seikagaku, China.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee; peri-arthritis of the shoulder.

Artz *Nordic Drugs, Denm.; MDM, Ital.; Daiichi Sankyo, Port.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Artzal *Sankyo, Austria; Nordic Drugs, Fin.; AstraZeneca, Swed.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Arucal *Avalanche, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Aruclonin *Chauvin Ankerpharm, Cz.; Chauvin Ankerpharm, Hung.†*
Clonidine hydrochloride (p. 1339·1).
Glaucoma; ocular hypertension.

Arudel *Alter, Spain.†*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Arufil *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.†; Chauvin Ankerpharm, Hung.†*
Povidone (p. 2204·3).
Dry eyes.

Arufil C *Chauvin ankerpharm, Ger.†*
Carbomer (p. 2173·3).
Dry eyes.

Arular *Arlex, Mex.†*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Arulatan *Mann, Cz.; Mann, Neth.†; Bausch & Lomb, Spain.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Arum Triphyllum Compose *Boiron, Fr.*
Arum triphyllum; aconitum napellus (p. 2428·3); rumex crispus (p. 2649·3); drosera rotundifolia (p. 2497·2); spongia tosta; argentum nitricum (p. 2615·3); grindelia robusta (p. 2522·3).
Homoeopathic preparation.

Arum Triphyllum Plex *Seroyal, Canad.†*
Aconite (p. 2428·3); arum triphyllum; drosera rotundifolia (p. 2497·2); gumweed (p. 2522·3); silver nitrate (p. 2615·3); spongia tosta; yellow dock (p. 2649·3).
Homoeopathic preparation.

Arutimol *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.; Chauvin, Rus.; Bausch & Lomb, Ukr.; Chauvin Ankerpharm, Ukr.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Aruzilina *Megat, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Arvastatil *Pharmanel, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Arvekap *Ipsen, Gr.*
⊗Triptorelin (p. 2310·3) or triptorelin embonate (p. 2311·1).
Endometriosis; uterine fibroids; female infertility; prostatic cancer.

Arveles *Ulagay, Turk.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Arvenum *Sermedica, Port.; Sermedica, Port.†*
Bioflavonoids (p. 2505·2).
Stroder, Ital.
Diosmin (p. 2505·2).
Peripheral vascular disorders.

Arvicin *Obolenskoe, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Arvifax *Arriani, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Arviflox *Arvincare, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Arviflox-OZ *Arvincare, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Arviron *Masterlek, Rus.†*
Ribavirin (p. 1010·2).
Respiratory syncytial virus infections; chronic hepatitis C; haemorrhagic fever with renal syndrome.

Arvisone *Arvincare, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Arvo *Elea, Arg.*
Travoprost (p. 2012·1).
Glaucoma; ocular hypertension.

Arxen *Arlex, Mex.*
Naproxen (p. 98·2).
Inflammation; rheumatism.

Arxen Compositum *Arlex, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Inflammation; rheumatism.

Arya *GX, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Arycor *Sanofi-Aventis, S.Afr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Aryl *Active, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Aryl Plus *Active, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).

Arypez *Biofarma, Turk.*
Donepezil hydrochloride (p. 390·2).

Arythmol *Abbott, Irl.; Abbott, Port.; Abbott, UK.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Arz *Willow, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Arza *Orchid, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Arzade *David, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Arzedyn *Leovan, Gr.*
Cetirizine hydrochloride (p. 619·2).

Arzep *Zydus, India.*
Azelastine hydrochloride (p. 617·1).
Rhinitis.

Arzepam *Solfran, Mex.*
Diazepam (p. 1063·2).
Anxiety; sedative.

Arzerra *GSK, Austria; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Irl.; GSK, Israel; GSK, Jpn; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Spain†; GSK, Swed.; GSK, Switz.; GSK, UK; GSK, USA.*
Ofatumumab (p. 837·2).
Chronic lymphocytic leukaemia.

Arzi *Miracalus, India.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Arzide *David, India.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Arzimol
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Fusidic acid (p. 302·1).
Skin infections.

Arzimol B *Lazar, Arg.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Skin disorders with bacterial infection.

Arzip *Winthrop, UK.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Arzomeba *Pisa, Mex.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Arzomicin *Nycomed, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Arzomidol *Dollder, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Arzu *Lupin, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

AS Cor *Sanfer, Mex.*
⊗Norfenefrine hydrochloride (p. 1459·1).
Hypotension.

AS Saliva Orthana *A.S., UK.*
Oral spray: Mucin (p. 2186·1); xylitol (p. 2220·3); sodium fluoride (p. 2089·2).
Saliva substitute.
A.S., UK.
Lozenges: Mucin (p. 2186·1); xylitol (p. 2220·3).
Saliva substitute.

ASA *Novopharm, Canad.; Pendopharm, Canad.; Pharmascience, Canad.; Sorres, Canad.; Vita Health, Canad.; Zydus, India; Liomont, Mex.; Curtis, Pol.†; Streuli, Switz.; SSP, Thai.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Asa Right Powder *Eagle, Austral.†*
Vitamins; minerals; equisetum (p. 2500·1); ginger (p. 1844·1).
Respiratory congestion.

Asa Tones *Eagle, Austral.†*
Grindelia (p. 2522·3); iodine (p. 2336·3); crataegus (p. 2488·1); euphorbia (p. 2501·3); liquorice (p. 1853·2); polygala (p. 1677·2); drosera (p. 2497·2).
Upper respiratory-tract symptoms.

Asabium *Otto, Indon.*
Clobazam (p. 518·2).
Anxiety.

Asabon *Merck, Mex.†*
Piroxicam (p. 125·3).
Inflammation.

Asabrin *Biokem, Turk.*
Aspirin (p. 22·2).
Fever; pain; inflammation.

Asacard *Flamel, Irl.; Flamel, Neth.; Flamel, Port.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Asa-Cardio *Medisorb, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Asacol *Warner Chilcott, Canad.; Tillotts, Cz.; Tillotts, Denm.; Tillotts, Fin.; Meduna, Ger.†; Angelini, Gr.; Tillotts, Hong Kong; Keri, Hung.†; Win-Medicare, India; Tillotts, Israel; Giuliani, Ital.; Nycomed, Mex.; Takeda, Neth.; Tillotts, Norw.; Baxter, NZ; Vitoria, Port.; Lek, Rus.; Pharmaplan, S.Afr.; Tillotts, Singapore; Tillotts, Swed.; Sanofi-Aventis, Switz.; Biofarma, Turk.; Warner Chilcott, UK; Warner Chilcott, USA.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Asacolitin *Meduna, Ger.†*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Asacolon *Tillotts, Irl.*
Mesalazine (p. 1859·2).
Proctitis; Crohn's disease; ulcerative colitis; proctosigmoiditis.

ASAD *Stallergenes, Fr.†*
A range of allergen extracts (p. 2434·3).
Allergen immunotherapy.

Asadin *American Taiwan, Thai.†*
Arsenic trioxide (p. 2448·1).
Acute promyelocytic leukaemia.

Asadol *Pendopharm, Canad.†*
Aspirin (p. 22·2).

Asafen
Note: this name may be used for preparations of different composition.
Sanofi Synthelabo, Mex.†
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Pain.

Asaflow *Takeda, Belg.*
Aspirin (p. 22·2).
Cardiovascular and cerebrovascular disorders.

Asakell *Steigerwald, Neth.*
Ammi visnaga (p. 2441·2); grindelia robusta (p. 2522·3); lycopodium clavatum (p. 2547·1); pinus silvestris (p. 2591·1); sulfur (p. 1721·1); urginea maritima var rubra (p. 2161·2).
Homoeopathic preparation.

Asalazin *Medichrom, Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Asalen *Adcock Ingram, S.Afr.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Asalex *Chiesi, Ital.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Asalid *Gabriel, Gr.*
Salicylic acid (p. 1719·1).

Asalit *Merck, Braz.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Asalt *Mars, India.*
Rabeprazole (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Asalt-D *Mars, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Asaltec *Polfa Warszawa, Pol.*
Aspirin (p. 22·2).
Fever; pain.

Asam *Landson, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Asamax *Astellas, Ital.; Astellas, Neth.†; CSL, NZ; Astellas, Pol.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Asamnex *Metiska, Indon.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Asaphen *Pharmascience, Canad.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Asapiuci *Mylan, Ital.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Asaprim *Primera, Philipp.*
Aspirin (p. 22·2).
Thrombosis prophylaxis; pain; fever; juvenile rheumatoid arthritis.

Asaprol *Leti Gentek, Venez.*
Aspirin (p. 22·2).
Fever; pain.

Asarum Med Complex *Dynamit, Austria.*
Acidum picrinicum (p. 2634·2); ambra (p. 2440·3); asarum europaeum (p. 2449·3); lycopus virginicus (p. 2462·2).
Homoeopathic preparation.

Asasantin *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, UK.*
Dipyridamole (p. 1362·2); aspirin (p. 22·2).
Stroke prophylaxis; thromboembolism prophylaxis; transient ischaemic attacks.

Asasantine *Orifarm, Denm.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Switz.*
Dipyridamole (p. 1362·2); aspirin (p. 22·2).
Stroke prophylaxis; thromboembolic disorders.

Asatab *Odan, Canad.; TO-Chemicals, Thai.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Asavixin *Rottapharm, Ital.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Asax *Pasteur, Chile.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Asazine *Tillotts, Switz.*
Mesalazine (p. 1859·2).
Ulcerative colitis; ulcerative proctitis; haemorrhoids.

Asbunyl *IAE, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asbunyl Plus *IAE, Philipp.*
⊗Salbutamol (p. 1220·2); guaifenesin (p. 1666·2).
Cough.

ASC *Geritrex, USA.*
Triclosan (p. 1773·2).
Skin cleanser.

Ascabiol
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Austral.; Aspen Consumer, S.Afr.; Sanofi-Aventis, UK.†
Benzyl benzoate (p. 2149·1).
Scabies; pediculosis.

Piramal, India.
Lindane (p. 2157·1).
Scabies; pediculosis.

Zambon, Fr.
Benzyl benzoate (p. 2149·1); sulfiram (p. 2161·3).
Scabies.

A-Scabs *Hoe, Hong Kong; Hoe, Malaysia.*
Permethrin (p. 2159·3).
Scabies.

Ascad *Micro, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Ascafer-Z *Pulse, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Ascafyl *Meyer, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Ascain *Dexa, Philipp.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Ascal *Meda, Irl.; Meda, Neth.; Meda, Port.*
Carbasalate calcium (p. 36·2).
Thromboembolism prophylaxis; fever; pain.

Ascalan *GL Pharma, Austria.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Ascalcin *Polfa Lodz, Pol.*
Aspirin (p. 22·2); calcium lactate gluconate (p. 1784·2).
Fever; pain.

Ascalcin Plus *Polfa Lodz, Pol.*
Aspirin (p. 22·2); calcium lactate gluconate (p. 1784·2); ascorbic acid (p. 2110·3).
Fever; pain.

Ascapar-P *Akums, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Ascapil A *Piramal, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Ascardia *Pharos, Indon.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Ascarical *Farmoquimica, Braz.*
Pyrantel embonate (p. 165·3).
Worm infections.

Ascaridil *Janssen-Cilag, Braz.*
Levamisole hydrochloride (p. 157·2).
Ascariasis.

Ascazin *Apex, India.*
Zinc sulfate (p. 2126·2).
Zinc supplement.

Ascee 500 *Hua, Thai.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Ascencia *Bayer, Chile.*
Test system for measuring glucose in blood (p. 2516·3).

Ascensia *Bayer, Arg.; Bayer, Austral.†; Bayer Diabetes Care, Fr.; BB, Ital.*
Test for glucose in blood (p. 2516·3).

Ascensia Elite *Bayer, Canad.*
Test for glucose in blood (p. 2516·3).

Ascensia Glucodisc *Bayer Diagnostics, UK.*
Test for glucose in blood (p. 2516·3).

Asche Basis *Asche Chiesi, Ger.†*
Emollient.
Skin disorders.

Asclera *BioForm, USA.*
Lauromacrogol 400 (p. 2194·1).
Varicose veins.

Asco-Caps *Key, USA.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Ascochrom *Medichrom, Gr.*
⊗Halcinonide (p. 1639·3).

Ascocid
Note: this name may be used for preparations of different composition.
Key, USA.
Calcium ascorbate (p. 2111·1).
Vitamin C supplement.

Volchem, Ital.
Peptides; lipids; carbohydrate; vitamin C (p. 2110·3).
Nutritional supplement.

Ascodan *Polpharma, Pol.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Fever; pain.

Ascodex Plus *Glenmark, India.*
Ammonium chloride (p. 1656·1); bromhexine (p. 1656·3); diphenhydramine (p. 626·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Ascodryl *Taj, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Ascof *Pascual, Philipp.*
Vitex negundo.
Cough; obstructive airways disease.

Ascofer *Espefa, Pol.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Gerda, Fr.
Ferrous ascorbate (p. 2060·3).
Iron-deficiency anaemias.

Ascofit *Intra-Labs, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Ascofol *Altayvitamin, Rus.*
Ascorbic acid (p. 2110·3); folic acid (p. 2063·1).

Ascoliza *Candor, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Ascomp with Codeine *Breckenridge, USA.*
Codeine phosphate (p. 40·2); aspirin (p. 22·2); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain.

Asconvita *Medic+Aid, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; scurvy.

Ascopen *Vendiz, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Ascophen *Darnitsa, Ukr.*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Ascophen-P *Organika, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Ascoplex *Actavis, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Ascor *McGuff, USA.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Ascorbin *Montavit, Austria; Orion, Fin.†; Orion, Malaysia†; Taisheng, Philipp.; Orion, Singapore.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Ascorbine *Elvipe, Gr.*
Vitamin C (p. 2110·3).

Ascorbisal *Lannacher, Austria.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever; musculoskeletal and joint disorders.

Ascorbplex *Douglas, Canad.*
Ascorbic acid (p. 2110·3).

Ascorcee *Virgo, Philipp.*
Ascorbic acid (p. 2110·3).
Scurvy; wound healing; methaemoglobinaemia.

Ascorell *Sanorell, Ger.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ascorgem *Gemi, Pol.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Ascoril *Glenmark, India.*
⊗Bromhexine (p. 1656·3); terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Formerly known as Ascoril +.
Cough.

Ascoril Expectorant *Glenmark, India.*
⊗Bromhexine (p. 1656·3); terbutaline sulfate (p. 1228·1) guaifenesin (p. 1666·2); menthol (p. 2553·2).
Formerly known as Ascoril +.
Cough.

Glenmark, Rus.; Glenmark, Ukr.†
⊗Salbutamol sulfate (p. 1220·2); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Respiratory-tract disorders.

Ascoril-C *Glenmark, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.

Ascoril-D *Glenmark, India.*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); triprolidine hydrochloride (p. 642·3); menthol (p. 2553·2).
Cough.

Ascorutical *Jelfa, Pol.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); calcium hydrogen phosphate (p. 1783·3); rutoside (p. 2505·3).
Cold and influenza symptoms; capillary fragility; hypersensitivity reactions.

Jelfa, Rus.
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3); calcium carbonate (p. 1824·3).
Vitamin deficiency; vascular disorders.

Ascorutical Forte *Jelfa, Ukr.†*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3); calcium carbonate (p. 1824·3).
Infections; glomerulonephritis, arachnoiditis; venous and capillary permeability disorders; hypersensitivity reactions.

Ascorutin *Zentiva, Cz.; Biopharma, Rus.; KVZ, Ukr.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Capillary fragility; tonic; haemorrhage.

Ascorvit *Mibe, Ger.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ascorvita *Natur Produkt, Pol.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Ascosal *Grossmann, Switz.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold symptoms.

Ascot *Polipharm, Thai.*
Aspirin (p. 22·2).
Inflammation; pain; thromboembolic disorders.

Ascotodin *Bruschettini, Ital.*
Mebechinium metilsulfate; thonzylamine hydrochloride (p. 642·1).
Eye disorders.

AscoTop *AstraZeneca, Ger.*
Zolmitriptan (p. 682·2).
Migraine.

Ascovit *Natur Produkt, Rus.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ascovit-C *China Chem & Pharma, Philipp.†*
Glucose (p. 2068·3); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); dexpanthenol (p. 2582·2).
Parenteral nutrition.

Ascoxal *AstraZeneca, Austral.†; AstraZeneca, Mex.†*
Ascorbic acid (p. 2110·3); sodium percarbonate (p. 1770·1); copper sulfate (p. 2057·2).
Mouth and throat inflammation and infection; oral hygiene.

Ascriptin *Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.; Novartis, USA; Vargas, Venez.*
Aspirin (p. 22·2).
Aluminium hydroxide (p. 1817·2), calcium carbonate (p. 1824·3), and magnesium hydroxide (p. 1857·2) or aluminium hydroxide (p. 1817·2) and magnesium hydroxide (p. 1857·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever; inflammation; thrombosis prophylaxis.

Asdron *Marjan, Braz.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic conjunctivitis; allergic rhinitis; urticaria.

Asedas *Pyridam, Indon.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1); curcuma; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Aselan *Marching, Hong Kong.†*
Allantoin (p. 1693·1); lidocaine (p. 1988·1); mepyramine (p. 635·1); tolnaftate (p. 596·1); zinc oxide (p. 1729·1).

Aselli *Weifa, Norw.†*
Cream: Cetylpyridinium chloride (p. 1743·1); zinc tannate.
Minor skin disorders; sunburn; skin disinfection.

Asendin *Lederle, Indon.†*
Amoxapine (p. 407·3).
Depression.

Asenlix *Sanofi-Aventis, Mex.*
⊗Clobenzorex hydrochloride (p. 2318·3).
Obesity.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Asenta *Perrigo, Israel.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Asentra *KRKA, Cz.; KRKA, Hung.; KRKA, Neth.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; anxiety.

Asenza Plus *Ajanta, Philipp.*
Pioglitazone hydrochloride (p. 493·1); glimepiride (p. 473·2).
Diabetes mellitus.

ASEP *Galen, UK.*
Glutaral (p. 1753·2).
Instrument disinfection.

Asepar *Gunsa, Turk.†*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Asepsan *Zambon, Ital.*
Povidone-iodine (p. 1767·1).
Disinfection of vaginal mucosa.

Asept *Avmor, Canad.*
Triclosan (p. 1773·2).

Asepta *Konimex, Indon.†*
Povidone-iodine (p. 1767·1).
Disinfection.

A-Septic AS *Hoe, Malaysia.*
Triclosan (p. 1773·2).
Minor wounds; burns.

Aseptiderm *Pharmacobel, Belg.*
Cetrimide (p. 1742·1).
Disinfection of skin and instruments.

Aseptobron *Temis, Arg.*
Inhalation: Menthol (p. 2553·2); cineole (p. 2479·1); niaouli oil (p. 2569·1); camphor (p. 2466·2); terpinol (p. 1678·2); pinus pinaster oil (p. 2590·3).
Respiratory-tract disorders.

Temis, Arg.
Injection: Cineole (p. 2479·1); niaouli oil (p. 2569·1); guaiacol (p. 1666·1); iodoform (p. 1758·2).
Respiratory-tract disorders.

Temis, Arg.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders.

Aseptobron Antigripal *Temis, Arg.*
Levophenylephrine hydrochloride (p. 1672·2); paracetamol (p. 115·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Aseptobron Bromexina *Temis, Arg.*
Oxeladin citrate (p. 1671·2); bromhexine hydrochloride (p. 1656·3).
Cough.

Aseptobron C *Temis, Arg.*
Oxeladin citrate (p. 1671·2); carbinoxamine maleate (p. 619·1).

Aseptobron Caramelos *Temis, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Aseptobron Descongestivo *Temis, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Aseptobron Expectorante *Temis, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Aseptobron N *Temis, Arg.*
Mouth and throat spray: Benzocaine (p. 1980·2); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Mouth and throat disorders.

Temis, Arg.
Pastilles: Benzocaine (p. 1980·2); gramicidin (p. 308·3); neomycin sulfate (p. 330·1); cineole (p. 2479·1); menthol (p. 2553·2).
Mouth and throat disorders.

Aseptobron Respiratorio *Temis, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Aseptobron Unicap *Temis, Arg.*
Hydrocodone resinate; chlorphenamine resinate (p. 620·3).

Asepto-Glutaral *Preston, Arg.*
Glutaral (p. 1753·2).
Disinfection.

Aseptol *Akdeniz, Turk.†*
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Aseptolin *Institute of Medicine, Rus.*
Glitseritan.
Antiseptic.

Aseptone *CCM, Malaysia.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal syndrome.

Aseptone 1 *Riva, Canad.*
Clorophene sodium (p. 1748·3); sodium *o*-phenylphenol (p. 1762·3).
Surface disinfection for clean surfaces.

Aseptone 2 *Riva, Canad.*
Clorophene sodium (p. 1748·3); sodium *o*-phenylphenol (p. 1762·3); sodium lauril ether sulfate (p. 2210·3).
Surface disinfection.

Aseptone 5 *Riva, Canad.*
Clorophene sodium (p. 1748·3); sodium *o*-phenylphenol (p. 1762·3); sodium alkyl-polyether sulfate.
Surface disinfection.

Aseptone Quat *Riva, Canad.*
Benzalkonium chloride (p. 1737·1); *n*-alkyldimethylethylbenzylammonium chlorides; octoxinols (p. 2199·3).
Surface disinfection.

Asepzona *Diba, Mex.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Aseranox *Janssen-Cilag, Gr.*
Ketanserin tartrate (p. 1415·3).

Aserbine *Pharmaco, S.Afr.*
Benzoic acid (p. 1738·2); malic acid (p. 2549·2); salicylic acid (p. 1719·1); propylene glycol (p. 2205·2).
Burns; skin ulcers; wounds.

Aserin *Vir, Port.; Vir, Spain.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Asering *Otsuka, Indon.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid replacement; carbohydrate source.

Aserta *Pentafarma, Port.*
Sertraline hydrochloride (p. 448·1).
Depression.

Asertin *Biofarm, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder; panic disorder.

Asestor *Spedrog, Arg.*
Simeticone (p. 1886·2); homatropine methylbromide (p. 2007·3).
Flatulence; gastrointestinal spasm.

Asey *Centrum, Spain.*
Levofloxacin (p. 315·3).
Bacterial infections.

Asflam *Panjon, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3); tizanidine (p. 2026·2).

Asfrenon *Terramedic, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Asfrenon GF *Terramedic, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Cough.

Ashaninka *Ashaninka, Hung.*
Uncaria tomentosa.
Musculoskeletal and joint pain.

Ashton & Parsons Infants Powders *Group, S. Afr.†; Alliance, UK.*
Chamomile (p. 2474·1).
Teething; gastrointestinal disorders.

Ashwita *Newtramax, India.*
Capsules: Vitamins; minerals; ginseng (p. 2513·3); *Lactobacillus sporogenes* (p. 2596·3).

Newtramax, India.
Oral powder: Vitamins; minerals; trace elements; protein hydrolysate.

Asiabron *Asian Pharm, Thai.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Asialax *Asian Pharm, Thai.†*
Carisoprodol (p. 2021·3); phenylbutazone (p. 125·1).
Musculoskeletal and joint disorders.

Asialum *Asian Pharm, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer; dyspepsia.

Asiamox *Asian Pharm, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Asiatapp *Asian Pharm, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Asthma; cold symptoms; nasal congestion.

Asiazole *Asian Pharm, Thai.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis.

Asiazole-TN *Asian Pharm, Thai.*
Tinidazole (p. 949·2).
Trichomoniasis; giardiasis; amoebiasis.

Asibend *Willow, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Asic
Note: this name may be used for preparations of different composition.
Pharmaceutical Enterprises, S.Afr.
Dicycloverine hydrochloride (p. 1834·2); doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Asical *Willow, India.*
Calcium carbonate (p. 1824·3) or calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Asicef *Willow, India.*
Cefixime (p. 240·3).
Bacterial infections.

Asicet *Willow, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Asiclo *Willow, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Asicold *Willow, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Asicold Relief *Willow, India.*
Chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Asicom *Comed, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Asicom Plus *Comed, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Asicot *Laboratorios Chile, Chile.*
Quetiapine fumarate (p. 1101·1).
Psychoses.

Asidal *Eczacibasi, Turk.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Heartburn; dyspepsia; excess gastrointestinal gas.

Asidase *Willow, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Asidik *Biosel, Turk.*
Haemodialysis solution (p. 1778·2).

Asidopan Plus *Wyeth, Turk.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Dyspepsia.

Asidrat *Pharos, Indon.†*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer.

Asi-Dryl *Willow, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Asiflox *Willow, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Asiflox-OZ *Willow, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Asig *Sigma, Austral.†*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Asi-Kuff *Willow, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

Asilar *Gedeon Richter, Cz.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Asilax *Willow, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).

Asilax Plus *Willow, India.*
Sodium picosulfate (p. 1887·2).

Asile *United Lab, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Asilid *Willow, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Asilid Relief *Willow, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Asi-Liv *Willow, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Asilon *Wyeth, Turk.*
Pipenzolate bromide (p. 1878·1); simeticone (p. 1886·2).
Aerophagia; dyspepsia.

Asilone *Seton, Irl.†; Thornton & Ross, UK.*
Tablets: Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastritis; peptic ulcer; hiatus hernia; gastro-oesophageal reflux; heartburn.

Daudt, Braz.†
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; flatulence.

Seton, Irl.†; Thornton & Ross, UK.†
Oral gel; oral suspension: Dried aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastritis; heartburn; peptic ulcer; hiatus hernia; gastro-oesophageal reflux.

Asimat *Mersifarma, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Asi-Min MV *Willow, India.*
Vitamins; trace elements; lycopene (p. 2546·2).

Asimol *Willow, India.*
Paracetamol (p. 115·1).
Pain; fever.

Asimol-AC *Willow, India.*
Paracetamol (p. 115·1); aceclofenac (p. 16·2).
Pain; inflammation.

Asimol-DC *Willow, India.*
Paracetamol (p. 115·1); dicycloverine (p. 1834·2).

Asinac *Medley, Rus.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders.

Asinis *Bittner, Austria; Bittner, Rus.; Bittner, Ukr.*
Armoracia (p. 2526·1); kalium bichromicum (p. 2476·3); hydrastis (p. 2528·1); calcium sulfuricum (p. 2173·1); cinnabaris (p. 2555·3).
Homoeopathic preparation.

Asinpirine *Ulagay, Turk.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Asipan *Willow, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Asipan-D *Willow, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Asiplex *Willow, India.*
Dexpanthenol (p. 2582·2); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).

Asipress *Willow, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Asipress-H *Willow, India.*
⊗Losartan (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Asirab *Willow, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Asirab-D *Willow, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Asi-Ril *Willow, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Asisneez *Willow, India.*
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Asist *Husnu Arsan, Turk.*
Acetylcysteine (p. 1652·2).
Respiratory disorders with increased mucus; paracetamol poisoning.

Asiviral *Terra, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Asixintai *Minsheng, China.*
Acetylcysteine (p. 1652·2).
Liver failure.

Asizyme *Willow, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Askamex *Konimex, Indon.†*
Levamisole hydrochloride (p. 157·2).
Ascariasis; ancylostoma.

Askaripar *Eras, Turk.*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Askey *Brown & Burk, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Askina
Note: this name may be used for preparations of different composition.
Braun, UK.
Sodium chloride (p. 1795·1).
Wound cleansing and irrigation.

Askina Biofilm *Braun, Belg.*
Hydrocolloid dressing.
Wounds.

Askina Gel *Braun, Belg.*
Hydrogel dressing.
Wounds.

Askina Sorb *Braun, Belg.*
Calcium alginate (p. 1136·3).
Wounds.

Askina Transorbent *Braun, Belg.†*
Polyurethane dressing (p. 1718·1).
Wounds.

Askit *Askit, UK.†*
Aspirin (p. 22·2); aloxiprin (p. 20·3); caffeine citrate (p. 1203·3).
Pain; fever.

Asklerol *Samarth, India.*
Lauromacrogol 400 (p. 2194·1).
Varices.

Asko *Pasifik, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Askonova *KVZ, Ukr.*
Vitamins; minerals.
Dietary supplement.

Askorbin *Kimia, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; capillary bleeding.

Aslera *Genesis, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Aslera-D *Genesis, India.*
⊗Serrapeptase (p. 2613·3); diclofenac potassium (p. 48·3).

Aslera-DP *Genesis, India.*
⊗Serrapeptase (p. 2613·3); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Asmabec *Sciencex, Fr.; UCB, Irl.; Focus, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Asmacaire *Aldo-Union, Philipp.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Asmacare *Kimia, Indon.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Asmacortone *NCSN, Ital.†*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Asma-Dec *Medicine Products, Thai.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).

Asmadex *Dexa, Indon.*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2).
Asthma; bronchitis.

Asmadon *Acdhon, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Asmafen *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Pacific, NZ†; Xepa-Soul Pattinson, Singapore.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic bronchitis; hypersensitivity disorders; allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Asmafilin *Casel, Turk.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Asmafin *Cazi, Braz.*
Aminophylline hydrate (p. 1201·3).
Obstructive airways disease.

Asmaflu *Max Farma, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic disorders of the respiratory tract.

Asmafort *Julphar, UAE.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis; allergic rhinitis; asthma; urticaria.

Asmag *Farmapol, Pol.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Asmag B *Farmapol, Pol.*
Magnesium aspartate (p. 1787·1); pyridoxine (p. 2105·3).
Magnesium deficiency.

Asmakil *Elofar, Braz.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Asmalergin *Merck, Braz.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Asmalia *Umeda, Thai.†*
Aminophylline (p. 1201·2).
Asthma; heart failure.

Asmalin
Note: this name may be used for preparations of different composition.
Pediatrica, Philipp.; United American, Philipp.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.
Sunward, Singapore.
⊗Terbutaline sulfate (p. 1228·1).
Bronchospasm.

Asmalin Broncho *Pediatrica, Philipp.; United American, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Cough; bronchospasm.

Asmaline *Polipharm, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Asmaline Expectorant *Polipharm, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Asmaliv *Legrand, Braz.; Tack Fung, Hong Kong.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asmalix *Century, USA.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Asmalon *Poly, China.*
Theophylline (p. 1229·3).
Obstructive airways disease.

AsmalPred Plus *Tiber, USA.*
⊗Prednisolone (p. 1645·2).

Asmanex *Aesca, Austria; Merck, Canad.; Schering-Plough, Cz.; Schering-Plough, Denm.; MSD, Fin.; MSD, Ger.; MSD, Gr.; MSD, Irl.; MSD, Neth.; MSD, Norw.; Schering-Plough, NZ†; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; Schering-Plough, Turk.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
⊗Mometasone furoate (p. 1644·1).
Asthma; obstructive airways disease.

Asmanil *Inga, India.*
⊗Salbutamol (p. 1220·2).
Bronchospasm.

Asmano *Corsa, Indon.*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2).
Obstructive airways disease.

Asmanon *Cazi, Braz.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Asmapax *Piramal, India.*
⊗Ephedrine (p. 1663·1); theophylline (p. 1229·3); phenobarbital (p. 535·2).
Obstructive airways disease.

Asmapen *Neo Quimica, Braz.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Asmaral-K *Serral, Mex.*
Ketotifen (p. 631·3).
Asthma.

Asmaril *DWD, India.*
⊗Terbutaline (p. 1228·1).
Bronchospasm.

Asmasal *Sciencex, Fr.; UCB, Irl.; Focus, UK.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.
Silom, Thai.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Asmasolon
Note: this name may be used for preparations of different composition.
Westmont, Philipp.; Great Eastern, Thai.
Theophylline (p. 1229·3).
Obstructive airways disease.
Probus, Indon.
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2).
Obstructive airways disease.

Asmatec *UCB, Port.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Asmaten *CCM, Malaysia; Duopharma, Singapore.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Asmatide-BR *Systopic, India.*
⊗Salbutamol sulfate (p. 1220·2); bromhexine hydrochloride (p. 1656·3); theophylline (p. 1229·3).
Obstructive airways disease.

Asmatil *Alter, Port.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Asmatol *Roux-Ocefa, Arg.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asmavent
Note: this name may be used for preparations of different composition.
Mintlab, Chile.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.
United American, Philipp.
⊗Budesonide (p. 1625·1).
Asthma.

Asmavent-B *Mintlab, Chile.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Asmax *Ativus, Braz.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Asma-ZED *Mission Happiness, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Asmelor *Meda, Fr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Asmen *Chiesi, Braz.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Asmenol *Polpharma, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Asmeren *Labomed, Chile.*
⊗Clenbuterol (p. 1207·2).
Obstructive airways disease.

Asmetic *AVI, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Asmeton *Daiichi Sankyo, China.*
⊗Methoxyphenamine hydrochloride (p. 1669·1); noscapine (p. 1670·3); aminophylline (p. 1201·2); chlorphenamine (p. 620·3).
Respiratory-tract disorders.
Sankyo, Hong Kong.
⊗Methoxyphenamine hydrochloride (p. 1669·1); aminophylline (p. 1201·2); chlorphenamine maleate (p. 620·3); noscapine (p. 1670·3).
Asthma; bronchitis; cough.

Asmifen *Bunker, Braz.*
Ketotifen fumarate (p. 631·3).
Hypersensitivity reactions.

Asmigen *Pacific, NZ·†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asmodrin *Sanval, Braz.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Asmofen *Teuto, Braz.*
Ketotifen fumarate (p. 631·3).
Asthma.

Asmol *Alphapharm, Austral.; LCH, Hong Kong†; Suphong, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.
Sunward, Singapore.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Asmol Expectorant *Suphong, Thai.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Asmo-Lavi *Vitoria, Port.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Asmopul
Note: this name may be used for preparations of different composition.
Asmopul, Arg.
⊗Atropine sulfate (p. 1310·2); adrenaline (p. 1292·1).
Asthma.
Cassara, Arg.
⊗Fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Asmoquinol *Ducto, Braz.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Asmotone Plus *East India Pharma, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Asnea *Valeant, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Asniton *Vertex, Rus.*
Betahistine hydrochloride (p. 2455·3).
Vertigo; Ménière's disease.

Asocol *Biofarma, Turk.*
Mesalazine (p. 1859·2).

Asodal *Nycomed, Belg.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); tiemonium iodide (p. 1893·3).
Muscle spasm and pain; colic.

Asodocel *Asofarma, Arg.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Asoflon *Asofarma, Mex.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Asoflut *Raffo, Arg.*
Flutamide (p. 798·2).

Asofurtal *Raffo, Arg.*
Tegafur (p. 864·2); uracil (p. 2637·3).
Malignant neoplasms.

Asoglutan *Raffo, Arg.*
Glucosamine sulfate (p. 2515·3).
Arthroses.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Asolan *CCM, Malaysia.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Asolfena *KRKA, Cz.*
Solifenacin succinate (p. 2367·3).
Bladder hyperactivity.

Asolmicina.dox *Raymos, Arg.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Asolt *Profic Organic, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Asolt-AT *Profic Organic, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1); methocarbamol (p. 2025·3).

Asomal *Casel, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Asomex *Emcure, Philipp.; Actavis, Ukr.*
Levamlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Emcure, India.
Levamlodipine.
Hypertension.

Asomex H *Actavis, Ukr.*
⊗Levamlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Asomex-AT *Emcure, India.*
⊗Levamlodipine; atenolol (p. 1308·2).
Hypertension; angina pectoris.

Asomex-D *Emcure, India.*
⊗Levamlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Asomex-LT *Emcure, India.*
Levamlodipine; losartan potassium (p. 1422·2).
Hypertension.

Asomex-R *Emcure, India.*
Levamlodipine; ramipril (p. 1483·3).
Hypertension.

Asomutan *Raffo, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Asonac *Zee, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Asonac Forte *Zee, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Asonac Plus *Zee, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Asonac-SR *Zee, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Asonac-SR Plus *Zee, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Asonor *TannerMedico, Hong Kong; Pharma-Export, UK.*
⊗Sodium chloride (p. 1795·1); glycerol (p. 2517·2); polysorbate 80 (p. 2203·3).
Snoring.

Asoride *AS, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Asotax *Raffo, Arg.; Asofarma, Mex.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Asotecan *Raffo, Arg.*
Topotecan (p. 872·3).
Malignant neoplasms.

Asoten *Actavis, Ukr.†*
⊗Esatenolol (p. 1377·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Asoteron *Nolver, Venez.*
Cyproterone acetate (p. 2261·2).
Precocious puberty; prostatic cancer; female androgenisation.

Raffo, Arg.
Cyproterone (p. 2261·2).
Prostatic cancer.

Asotrex *Raffo, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Musculoskeletal and joint disorders.

Asovon *Medicine Products, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Asovorin *Raffo, Arg.*
Calcium levofolinate (p. 2067·1).
Malignant neoplasms; antidote to folic acid antagonists; anaemias.

ASP *Medinfar, Port.*
Aspirin (p. 22·2).
Fever; pain.

Aspa *Chemech, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Aspa Plus *Chemech, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1); diclofenac sodium (p. 48·3).

Aspaco *Burapha, Thai.*
Aspirin (p. 22·2).
Fever; pain.

Aspafar *Farmapol, Pol.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium and potassium deficiency.

Aspagin *Proel, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Aspalgin *Aspen, Austral.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; fever.

Aspamol *Pharmahof, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Aspamom *Bionova, India.*
Asparagus racemosus (p. 2614·2).

Aspapirine *ICE, Turk.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Aspar
Note: this name may be used for preparations of different composition.
Admac, India.
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Espefa, Pol.
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium and potassium deficiency.

Tanabe, Indon.
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1); bisbentiamine (p. 2103·1); vitamin B_6 (p. 2105·3).
Nutritional supplement; tonic.

Asparagus-P *Grunwalder, Ger.*
Asparagus (p. 2450·2); parsley (p. 2583·3).
Oedema; renal calculi.

AsParAid *PlantaPhile, UK.*
Asparagus (p. 2450·2); parsley (p. 2583·3).
Urinary-tract disorders.

Asparcam *Microgen, Rus.; Arterium, Ukr.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Arrhythmias.

Aspargin *Espefa, Pol.; Farmapol, Pol.; Filofarm, Pol.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium deficiency.

Aspar-K *Tanabe, Indon.*
Potassium aspartate (p. 1793·1).
Potassium supplement.

Aspartatol *Eagle, Austral.†*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1); glutamine (p. 2070·3).
Tonic.

Asparten *Grunenthal, Port.*
Arginine aspartate (p. 2049·1).
Asthenia.

Aspartil *Munir, Turk.*
Aspartame (p. 2169·2).
Sugar substitute.

Aspartina *Bouty, Ital.*
Aspartame (p. 2169·2).
Sugar substitute.

Aspasweet *Intas, India.*
Aspartame (p. 2169·2).
Sugar substitute.

Aspav *Alpharma, UK.†*
Aspirin (p. 22·2); papaveretum (p. 112·2).
Pain.

Aspavor *Pfizer, S.Afr.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Aspaxa *AstraZeneca, Belg.*
Aspirin (p. 22·2).
Esomeprazole magnesium (p. 1841·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Aspec *PSM, NZ; Pharmaspec, Philipp.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; fever; inflammation; pain.

Aspecard *Stirol, Ukr.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspecton *Krewel, Ger.*
Thyme (p. 2630·2).
Respiratory-tract congestion.

Aspecton Eukaps *Krewel, Ger.*
Eucalyptus oil (p. 2501·2).
Respiratory-tract congestion.

Aspegic *Sanofi-Aventis, Belg.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Ital.†; Sanofi-Aventis, Neth.; Sanofi-Aventis, Port.; Sanofi Synthelabo, Turk.*
Lysine aspirin (p. 84·3).
Pain; fever; inflammation; rheumatism; gout; musculoskeletal and joint disorders; neuralgia; thrombosis prophylaxis.

Aspégic *Sanofi-Aventis, Fr.; Sanofi-Aventis, Switz.*
Lysine aspirin (p. 84·3).
Pain; fever; rheumatism.

Aspégic Codéine *Sanofi-Aventis OTC, Fr.†*
Lysine aspirin (p. 84·3); codeine phosphate (p. 40·2).
Pain.

Aspelone *Aspen, S.Afr.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Aspen *EuroHealthcare, Philipp.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspen Hand Soap *Zep, Canad.*
Triclosan (p. 1773·2).

Aspendos *Medochemie, Neth.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Aspent *Ranbaxy, India; Ranbaxy, Thai.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; pain; fever; osteoarthritis; rheumatoid arthritis.

Aspercreme
Note: this name may be used for preparations of different composition.
Chattem, Canad.; Thompson, USA.
Trolamine salicylate (p. 141·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Aspercreme Max *Chattem, USA.*
Menthol (p. 2553·2); capsaicin (p. 35·1).

Aspergum *Heritage, Canad.; Schering-Plough, USA.†*
Aspirin (p. 22·2).
Pain; fever; inflammation; transient ischaemic attacks; myocardial infarction.

Asperivo *Rivopharm, Switz.*
Aspirin (p. 22·2).
Pain; fever.

Aspeter *Stirol, Ukr.†*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Aspex *Rekah, Israel.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Aspicalm *Medichrom, Gr.*
Lysine aspirin (p. 84·3).
Pain; fever.

Aspicam *Biofarm, Pol.*
Meloxicam (p. 86·3).
Degenerative joint disorders; osteoarthritis.

Aspicot *Concept, India.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspidon *Torrent, Philipp.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Aspiglicina *Antonetto, Ital.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Neuralgia.

Aspikor *Vertex, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspil *Fahrenheit, Indon.*
Cefotiam (p. 246·1).
Bacterial infections.

Aspilets *United American, Hong Kong; Medifarma, Indon.; Imperial, Philipp.; Great Eastern, Thai.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; pregnancy-induced hypertension; fever; pain.

Aspimag *Espefa, Pol.*
Aspirin (p. 22·2).
Magnesium oxide (p. 1857·3) is included in this preparation in an to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Aspimirin *Er-Em, Turk.*
Aspirin (p. 22·2).
Pain; fever.

Aspin *Cipla, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Aspinal *Munir, Turk.*
Aspirin (p. 22·2).
Fever; pain; inflammation.

Aspinat *Valenta, Rus.*
Aspirin (p. 22·2).
Pain; fever.

Aspinat C *Valenta, Rus.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Aspinat Cardio *Valenta, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspinat Plus *Valenta, Rus.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Aspipac *Inpac, Thai.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Aspirin Activ *Bayer, Pol.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Aspirin C *Bayer, Cz.; Bayer, Fin.; Bayer, Gr.; Bayer, Israel; Bayer, Pol.; Bayer, Rus.; Bayer, Ukr.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Aspirin + C *Bayer, Austria.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Aspirin Cardio *Bayer, Fin.; Bayer, Israel; Bayer Schering, Malaysia; Bayer, Rus.; Bayer, Ukr.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspirin Complex
Note: this name may be used for preparations of different composition.
Bayer, Austria; Bayer, Cz.; Bayer, Ger.; Bayer, Pol.
⊗Aspirin (p. 22·2); pseudoephedrine hydrochloride (p. 1676·1).
Pain; fever; nasal congestion; cold and influenza symptoms.

Bayer, Rus.; Bayer Consumer, Ukr.
Aspirin (p. 22·2); phenylephrine acid tartrate (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Aspirin Complexoral
Note: this name may be used for preparations of different composition.
Bayer, Turk.
⊗Aspirin (p. 22·2); pseudoephedrine hydrochloride (p. 1676·1).

Aspirin Extra *Bayer, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Aspirin Forte *Bayer, Ger.†; Bayer, Turk.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain; inflammation.

Aspirin Free Anacin *Robins, USA.*
Paracetamol (p. 115·1).
Formerly known as Anacin-3.

Aspirin Free Anacin PM *Whitehall, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia; pain.

Aspirin Free Excedrin *BMS, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Aspirin Free Pain Relief *Hudson, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Aspirin Night-Time *Bayer Consumer, Canad.†*
Aspirin (p. 22·2); methocarbamol (p. 2025·3).

Aspirin plus C *Bayer, Ger.; Bayer, Hung.; Bayer, Turk.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever; cold symptoms; inflammation.

Aspirin Protect *Bayer, Austria; Bayer Schering, Hung.; Bayer, Pol.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspirin with Stomach Guard *Bayer Consumer, Canad.*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3), magnesium carbonate (p. 1856·2), and magnesium oxide (p. 1857·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; inflammation; fever.

Aspirin Zipp *Bayer, Fin.*
Aspirin (p. 22·2).
Pain; fever.

Aspirina *Bayer Consumer, Arg.; Benitol, Arg.; Fecofar, Arg.; Gezzi, Arg.; Klonal, Arg.; Richet, Arg.; Vent-3, Arg.; Bayer, Braz.; Bayer, Chile; Bayer, Ital.; Bayer, Port.; Bayer, Spain; Gervasi, Spain.*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3) and magnesium oxide (p. 1857·3) are included in some preparations in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain; thromboembolism prophylaxis.

Aspirina 03 *Bayer, Ital.*
Tablets: Aspirin (p. 22·2).
Magnesium hydroxide (p. 1857·2) and aluminium glycinate (p. 1817·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever.

Aspirina C *Bayer, Braz.; Bayer, Chile†; Bayer, Ital.; Bayer, Port.; Bayer, Spain.*
Aspirin (p. 22·2); vitamin C (p. 2110·3).
Fever; pain; musculoskeletal disorders.

Aspirina Complex *Bayer, Spain.*
Aspirin (p. 22·2); phenylephrine acid tartrate (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Aspirina Forte *Bayer, Braz.†*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Aspirina Plus *Bayer, Spain.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Aspirina Protect *Bayer, Mex.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Aspirine *Bayer, Belg.; Bayer, Fr.; SSP, Thai.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Aspirine C *Bayer, Belg.; Bayer, Neth.; Bayer, Switz.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Aspirine Cafeine *Bayer, Belg.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Aspirine Cardio *Bayer, Switz.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Aspirine Complex *Bayer, Switz.*
⊗Aspirin (p. 22·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms.

Aspirine pH8 *Meda, Fr.*
Aspirin (p. 22·2).
Fever; pain.

Aspirine Protect *Bayer, Neth.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Aspirine vitamine C *UPSA, Fr.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Aspirinetas *Bayer Consumer, Arg.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Aspirinetta *Bayer, Ital.; BB, Ital.*
Aspirin (p. 22·2).
Pain; fever.

Aspirin-Free Bayer Select Allergy Sinus *Sterling Health, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Aspirin-Free Bayer Select Head & Chest Cold *Sterling Health, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).

Aspirisucre *Arkomedika, Fr.†*
Aspirin (p. 22·2).
Fever; pain.

AspirLow *Major, USA.*
Aspirin (p. 22·2).

Aspisol *Shreya, India.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis; pain; fever.

Aspisport *Bayer, Braz.*
Etofenamate (p. 57·2).

Aspitopic *Bayer, Spain.*
Etofenamate (p. 57·2).
Pain; inflammation.

Aspitrate *Aristo, India.*
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).
Angina pectoris; myocardial infarction prophylaxis.

Aspitrom *Interbat, Indon.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Asprito *Intas, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Aspro *Bayer Consumer, Austral.; Klosterfrau, Austria; Bayer Sante, Fr.; Bayer, Irl.†; Bayer, Ital.; Bayer, Neth.; Bayer, NZ; Bayer, Singapore†; Bayer, Switz.; Roche Consumer, UK.*
Aspirin (p. 22·2).
Fever; inflammation; pain; cold and influenza symptoms.

Aspro C *Bayer, Hung.; Bayer, Ital.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; fever; inflammation; pain.

Aspro mit Vitamin C *Klosterfrau, Austria.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Aspro Protect *Bayer, Austral.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Aspro vitamine C *Bayer Sante, Fr.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Asproaccel *Bayer Sante, Fr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Asprocard *Arrow, Pol.†*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thrombosis prophylaxis.

Asprocol *ICN, Pol.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Asquam *Pierre Fabre Dermatologie, Cz.†; Pierre Fabre, Ital.*
Ketoconazole (p. 585·3).
Scalp disorders; seborrhoeic dermatitis.

Asrina *Pharmasant, Thai.*
Aspirin (p. 22·2).
Pain; inflammation; rheumatism.

ASS *Genericon, Austria; Hexal, Austria; Ratiopharm, Austria; Ratiopharm, Ger.; TAD, Ger.; Worwag, Ger.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thrombosis prophylaxis; rheumatism.

ASS + C *1A, Austria; Ratiopharm, Ger.; BMS, Hung.†; Sandoz, Switz.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever; cold symptoms; inflammation.

ASS Cardio *Spirig, Switz.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

ASS plus Vit C *1A, Austria.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Assal *Salus, Mex.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).

Assalix *Bionorica, Ger.; Biomed, Switz.; Bionorica, Ukr.*
Salix (p. 129·2).
Rheumatism; fever; pain.

Assan *Permamed, Switz.*
Flufenamic acid (p. 65·1); glycol salicylate (p. 66·2); heparin sodium (p. 1396·3).
Musculoskeletal and joint pain; soft-tissue injury; peripheral vascular disease.

Assan rem *Permamed, Switz.*
Lauromacrogol 400 (p. 2194·1); dimethyl sulfoxide (p. 2182·2); glycol salicylate (p. 66·2); dexpanthenol (p. 2582·2); levomenthol (p. 2553·2); dextrocamphor (p. 2466·2).
Soft-tissue injury.

Assan thermo *Permamed, Switz.*
Flufenamic acid (p. 65·1); glycol salicylate (p. 66·2); benzyl nicotinate (p. 29·3); heparin sodium (p. 1396·3).
Musculoskeletal and joint disorders.

Assepium *Gross, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Assepium Balsamico *Gross, Braz.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Respiratory-tract infections.

Asseptcare *Neo Quimica, Braz.*
Chlorhexidine gluconate (p. 1743·3).

Asseptic *Neo Quimica, Braz.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Assert *Eurofarma, Braz.*
Sertraline hydrochloride (p. 448·1).
Depression.

Assieme *Orifarm, Denm.; Simesa, Ital.; AstraZeneca, Neth.; Tecnifar, Port.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Obstructive airways disease; asthma.

Assiememite *Simesa, Ital.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Asthma.

Assist *GD, Ital.*
Soya oil (p. 2092·3); lutein (p. 2079·2); zinc (p. 2126·1).
Nutritional supplement.

Assival *Teva, Israel.*
Diazepam (p. 1063·2).
Anxiety; concussions; skeletal muscle spasm; alcohol withdrawal syndrome; status epilepticus; premedication.

Assocals *SJA, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Assocort *BMS, Ital.†*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Infected skin disorders.

Assolid *Konpharma, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic respiratory-tract disorders.

Assoprol *SJA, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Assoral *Savio, Ital.*
Roxithromycin (p. 356·2).
Bacterial infections.

Assosept-S *SJA, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Assy Crema de Enjuague *Assistance, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Assy Espuma *Assistance, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Assy Max *Assistance, Arg.*
Cyclopentasiloxane (p. 2209·2); dimeticone (p. 2209·3).
Pediculosis.

Assy Tratamiento Integral *Assistance, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Astacor *Soho, Indon.*
Astaxanthin (p. 2170·1); omega-3 fatty acids (p. 1460·1).
Antoxidant.

Astadiab *Soho, Indon.*
Astaxanthin (p. 2170·1); cinnamon (p. 2479·2).
Antoxidant.

Astafen *Sandoz, Turk.*
Ketotifen fumarate (p. 631·3).
Asthma.

Astagen *Genesis, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Astagraf *Astellas, USA.*
Tacrolimus (p. 1968·3).
Renal transplant rejection.

Astar *INTES, Ital.*
Fish oil (p. 1460·1); zinc (p. 2126·1); copper (p. 2057·1); lutein (p. 2079·2); mesozeaxanthin; zeaxanthin (p. 2125·3).
Dietary supplement.

Astat
Note: this name may be used for preparations of different composition.
Maruho, Jpn.
Lanoconazole (p. 587·3).
Fungal skin infections.

Astaz-P *Sandoz, Thai.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Astebron *Integrated Pharmaceutical, Philipp.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Astecon *Avansor, Fin.*
Montelukast sodium (p. 1214·3).
Asthma.

Astefor *Farmasierra, Spain.*
Codeine phosphate (p. 40·2); ibuprofen (p. 68·2).
Pain.

Astelin *Sanfer, Mex.; Wallace, USA.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Astelong *Torrent, India.*
Astemizole (p. 616·1).
Hypersensitivity reactions.

Astemil *Anpharm (Ανφαρμ), Gr.*
Salicylic acid (p. 1719·1).

Astemina *Diba, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Asten *Solas, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1); taurine (p. 2626·2); betacarotene (p. 2051·1); arginine (p. 2049·1); glutamic acid (p. 2070·2); magnesium aspartate (p. 1787·1).
Vitamin B deficiency; peripheral neuritis; anaemias.

Astende *Lazar, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Astenolit *Ern, Spain.*
Vitamins; minerals; amino acids.
Tonic.

Astepro *Meda, USA.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Astergina *Flupal, Venez.*
Codergocrine (p. 389·2).
Cerebral and peripheral vascular disorders; hypertension; mental function impairment in the elderly.

Asterilon *IWA, Denm.†; Pharmathen, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; mania; bipolar disorder.

Astesen *Senosiain, Mex.*
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Ast-Ex *Sresan, India.*
⊗Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2); sodium citrate (p. 1781·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Astexana *Vipharm, Cz.*
⊗Exemestane (p. 792·2).
Breast cancer.

Astha *Dalmia, India.*
Capsules: Malabar nut (p. 2549·1); curcuma longa; piper longum; piper nigrum; syzygium aromaticum; syzygium aromaticum oil; zingiber officinale.
Asthma.

Dalmia, India.
Syrup: Achyranthes aspera; malabar nut (p. 2549·1); curcuma longa; elettaria cardamomum; piper longum; piper nigrum; syzygium aromaticum; syzygium aromaticum oil; zingiber officinale.
Asthma.

Asthacrom *Cipla, India.†*
⊗Salbutamol (p. 1220·2); sodium cromoglicate (p. 1225·3).
Asthma.

Asthafen *Torrent, India.*
Ketotifen (p. 631·3).
Hypersensitivity reactions; asthma.

Asthafree *Zuventus, India.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Asthakind *Mankind, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Asthalin *Cipla, Hong Kong; Cipla, India; Cipla, Malaysia; Cipla, Venez.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Rex, NZ; Cipla, Rus.; Cipla, Thai.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asthalin AX *Cipla, India.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Asthalin Expectorant *Cipla, India.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Astham *FDC, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Asthamol *Okasa, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asthavent *Cansin, Turk.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Cipla-Medpro, S.Afr.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asthavent-BR *Ultramark, India.*
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol sulfate (p. 1220·2).

Astherin *Pyridam, Indon.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Asthesia *Unichem, India.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Asthin *Soho, Indon.*
Astaxanthin (p. 2170·1).
Antoxidant.

Asthin B-OND *Soho, Indon.*
Astaxanthin (p. 2170·1); cucumis melo (Extramel).
Antoxidant.

Asthma
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
⊗Ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3).
Bronchial asthma; chronic bronchitis.

Asthma & Catarrh Relief *Herbal Concepts, UK.*
⊗Ipecacuanha (p. 1667·2); lobelia (p. 2323·2); marrubium (p. 1668·3); liquorice (p. 1853·2).
Asthma; catarrh.

Asthma Formula *ICM, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Asthma Soho *Soho, Indon.*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2).
Asthma.

AsthmaHaler Mist *Numark, USA.*
⊗Adrenaline acid tartrate (p. 1292·2).
Bronchospasm.

Asthmakhell *Steigerwald, Neth.†*
Ammi visnaga (p. 2441·2); grindelia robusta (p. 2522·3); lycopodium clavatum (p. 2547·1); pinus silvestris (p. 2591·1); squilla maritima (p. 1677·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Asthmakhell N *Steigerwald, Ger.*
Ammi visnaga (p. 2441·2); grindelia robusta (p. 2522·3); pinus silvestris (p. 2591·1); lycopodium clavat. (p. 2547·1); sulfur (p. 1721·1); urginea maritima var. rubra (p. 2161·2).
Homoeopathic preparation.

AsthmaNefrin *Nephron, USA.*
⊗Racepinefrine hydrochloride (p. 1292·1).
Obstructive airways disease.

Asthmasian *Asian Pharm, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Asthmatee EF-EM-ES *Smetana, Austria.*
Enulae root; marrubium vulgare (p. 1668·3); origanum (p. 2576·3); aniseed (p. 2444·2); arnica (p. 2447·2); cacao husk (p. 2216·1).
Obstructive airways disease.

Asthmavowen-N *Weber & Weber, Ger.†*
⊗Aconitum nap. (p. 2428·3); convalaria maj. (p. 2486·2); drosera (p. 2497·2); kalium jod. (p. 2336·3); lobelia infl. (p. 2323·2); datura stram. (p. 2622·3).
Homoeopathic preparation.

Asthmaxine *Synco, Singapore.*
Bromhexine hydrochloride (p. 1656·3).
Cough associated with excess mucus.

Asthmic *T Man, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Asthmolin *Pharmasant, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Asthmont *Specifar, Denm.†; Specifar, Ital.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Asthmotrat *Intermed, Gr.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; chronic respiratory failure.

Asthnyl *Osoth, Thai.*
⊗Terbutaline (p. 1228·1); guaifenesin (p. 1666·2).
Bronchospasm.

Asthos *Osmed, India.*
⊗Bromhexine hydrochloride (p. 1656·3); etofylline (p. 1208·2); salbutamol sulfate (p. 1220·2).

Asthromed *Medhaus, Philipp.*
Aspirin (p. 22·2).
Pain; fever; thrombosis prophylaxis.

Astic *Grandix, India.*
Aspirin (p. 22·2); ticlopidine (p. 1512·1).

Astifen *Christo, Hong Kong; Hexpharm, Indon.†*
Ketotifen fumarate (p. 631·3).
Asthma; allergic bronchitis; hypersensitivity disorders; allergic rhinitis; allergic conjunctivitis.

Astika *Ikapharmindo, Indon.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Astin
Note: this name may be used for preparations of different composition.
Medic+Aid, Philipp.
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Micro, India; Micro Labs, Ukr.
Atorvastatin (p. 1309·2).
Hyperlipidaemias; hypercholesterolaemia; cardiovascular risk reduction.

Probiomed, Mex.
Pravastatin sodium (p. 1473·1).
Atherosclerosis; hypercholesterolaemia.

Astinon *Samarth, Philipp.*
Pyridostigmine bromide (p. 689·2).
Gastrointestinal atony; myasthenia gravis; tachycardia.

Astizole *Cadila, India.†*
Astemizole (p. 616·1).

Astmadin *Ilacsan, Turk.*
Diprophylline (p. 1207·3).
Obstructive airways disease.

Astmerole *Fako, Turk.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Astmirex *Temapharm, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Astmopent *Polfa Warszawa, Pol.†; GSK, Rus.†*
⊗Orciprenaline sulfate (p. 1217·3).
Arrhythmias; asthma; premature labour.

Asto-Chol *SM, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Astomera *Bittner, Austria.*
Glycyrrhiza glabra (p. 1853·2); anacardium (p. 2471·3); nux vomica (p. 2573·3); argentum nitricum (p. 2615·3); bismutum subnitricum (p. 1822·1).
Homoeopathic preparation.

Astomin *Astellas, Jpn.*
Dimemorfan phosphate (p. 1661·3).
Cough.

Aston
Note: this name may be used for preparations of different composition.
Fako, Turk.
Losartan potassium (p. 1422·2).

Yik Kwan, Hong Kong.†
Diclofenac (p. 48·3).

Aston Plus *Fako, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Astonin *Merck, Spain.*
⊗Fludrocortisone (p. 1634·3).
Hypotension; adrenocortical insufficiency.

Astonin H *Merck, Austria; Merck Serono, Ger.; Merck, Hung.*
⊗Fludrocortisone (p. 1634·3).
Adrenocortical insufficiency; congenital adrenal hyperplasia; hypotension.

Astoz *AMPDR, Port.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Astozyme *Laborate, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Astracaine *Dentsply, Canad.†*
Articaine hydrochloride (p. 1980·1). Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Astragalus Complex *Mediherb, Austral.*
Astragalus; echinacea purpurea (p. 2498·1); Siberian ginseng (p. 2614·3).
Tonic.

Astramorph *Astra, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Astrasept *Transatlantic, Rus.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2).
Sore throat.

Astrazol *Santa, Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Astrexine *Pierre Fabre Sante, Belg.*
Chlorhexidine hydrochloride (p. 1743·3).
Wound and skin disinfection.

Astrijesan *FarmoQuimica, Chile.*
Mint oil (p. 2560·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); myrrh (p. 2566·1); eugenol (p. 2501·2); zinc chloride (p. 2126·1).
Mouth disorders.

Astriluge *Valuge, Arg.*
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3); hamamelis (p. 2523·3).

Astrix *Mayne, Austral.; Hospira, Hong Kong†; Teva, Hung.; Mayne, Philipp.; Faulding, Singapore.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Astro *Eurofarma, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Astrocast *Chrispa (Χριπα), Gr.*
⊗Budesonide (p. 1625·1).
Topical corticosteroid.

Astrofen *Liferpal, Mex.†*
Phenylbutazone (p. 125·1).
Inflammation; rheumatism.

Astrogin *Candor, India.*
Vitamins; minerals.

Astroglide *Biofilm, USA.*
⊗Glycerol (p. 2517·2); propylene glycol (p. 2205·2); polyquaternium-5.
Vaginal lubricant.

Astrozone *Leksredstva, Rus.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Astucor *Almirall, Spain.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).
Cardiovascular risk reduction.

Astudal *Almirall, Spain.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Astute *Kamakshi, India.*
Cefixime (p. 240·3).
Bacterial infections.

Astute-CV *Kamakshi, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Astyfer *Tablets, India.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); glycine (p. 2071·2); histidine (p. 2072·1); lysine (p. 2079·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Tablets, India.
Oral liquid: Dexpanthenol (p. 2582·2); ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); histidine (p. 2072·1); lysine (p. 2079·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Astyfer-Z *Tablets, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); glycine (p. 2071·2); histidine (p. 2072·1); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Astymin *Tablets, India.*
Amino acids; vitamins.
Tonic.

Astymin-3 *Tablets, India.*
Amino acids.
Parenteral nutrition.

Astymin-C *Tablets, India.*
Amino acids; vitamin C (p. 2110·3).
Nutritional supplement.

Astymin-M Forte *Tablets, India.*
Amino acids; vitamins; minerals.

Astymin-SN *Tablets, India.*
Amino-acid infusion.
Parenteral nutrition.

Astymin-Z Forte *Tablets, India.*
Amino acids; vitamins; zinc sulfate (p. 2126·2).

Astyvit *Tablets, India.*
Amino acids vitamins.
Dietary supplement.

Asubtela *Temapharm, Pol.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Asucrose *Wockhardt, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Asugrin *Unipharma, Gr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Asulblan *Fada, Arg.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; angina pectoris.

Asulpan *Vera, Hung.*
Amisulpride (p. 1036·3).
Psychoses.

Asumalife *YSP, Malaysia; Yung Shin, Singapore.*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis; allergic skin disorders; asthma; pruritus; urticaria; dermatitis.

Asumate *Velvian, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Asumol *Asian Union, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Asunate *Adley, India.*
Artesunate (p. 648·2).
Malaria.

Asvasin *AS, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Asventol *Laboratorios Chile, Chile.*
Montelukast sodium (p. 1214·3).
Asthma.

Asverin *Primal, Hong Kong†; Tanabe, Jpn.*
Tipepidine hibenzate (p. 1679·1).
Cough.

Asvex *Tanabe, Indon.*
Tipepidine hibenzate (p. 1679·1).
Cough; upper respiratory-tract congestion.

Asvimol *Virgo, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

ASVS *Serum Institute, India.*
Snake venom antisera (p. 2419·1).
Poisonous snake bites.

Aswal Plus *Gufic, India.*
Asparagus racemosus (p. 2614·2); piper longum; tinospora cordifolia; ashwagandha (p. 2450·2).
Stress.

Asyntilsan *Sandoz, Denm.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

AT III *Baxter, Ger.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

AT 10 *Merck, Austria†; Bayer, Ger.; Intrapharm, Irl.; Merck, Rus.; Bayer, S.Afr.†; Bayer, Switz.†; Intrapharm, UK.*
Dihydrotachysterol (p. 2113·2).
Hypoparathyroidism; pseudohypoparathyroidism; rickets; tetany; renal osteodystrophy.

Atabex EC Prenatal *Advanced Medical Enterprises, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1).
Dietary supplement.

Atac *K2 Health & Wellness, Chile.*
Naproxen sodium (p. 98·2).
Pain; inflammation; fever.

Atacand *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Turk.; AstraZeneca, Ukr.; Astra, USA; AstraZeneca, Venez.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure; left-ventricular dysfunction.

Atacand Comb *AstraZeneca, Braz.*
Tablets, candesartan cilexetil (p. 1330·2); tablets, felodipine (p. 1380·3).

Atacand D *AstraZeneca, Arg.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Atacand Duo *AstraZeneca, Arg.*
Tablets, candesartan cilexetil (Atacand) (p. 1330·2); tablets felodipine (Plendil) (p. 1380·3).
Hypertension; heart failure; angina pectoris.

Atacand HCT *AstraZeneca, Braz.; AstraZeneca, USA.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Atacand Plus *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.†; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Rus.; AstraZeneca, S. Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Turk.; AstraZeneca, Ukr.; AstraZeneca, Venez.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Atacand Zid *AstraZeneca, Denm.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Formerly known as Atacand Plus.
Hypertension.

Atacor *Actavis, Hong Kong.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atadar *Shin Poong, Philipp.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Atafloks *Atabay, Turk.*
Moxifloxacin (p. 326·3).

Atalak *Sons, Mex.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Ataline *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore.†*
⊗Terbutaline sulfate (p. 1228·1).
Asthma; obstructive airways disease.

Atalog *Chinta, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Atam *ATOZ, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Atamel *Pfizer, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Atamel Plus *Pfizer, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Atamelco *Pfizer, Venez.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Atamet *Athena Neurosciences, USA.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Atamir *Sandoz, Denm.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; heavy metal poisoning; Wilson's disease; cystinuria.

Atamo *Finecure, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atano *Milano, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety disorders; pruritus; hypersensitivity reactions.

Atanol *Remedina, Gr.*
Trimetazidine hydrochloride (p. 1520·1).

Atapryl *Athena Neurosciences, USA.*
⊗Selegiline hydrochloride (p. 914·2).

Ataralgin *Glenmark, Cz.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); caffeine (p. 1203·3).
Influenza symptoms; pain.

Atarax
Note: this name may be used for preparations of different composition.
UCB, Austria; UCB, Belg.; Erfa, Canad.; UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; UCB, Gr.; GSK, Hong Kong; UCB, Hung.; UCB, India; UCB, Ital.; GSK, Malaysia; UCB, Mex.; UCB, Neth.†; UCB, Norw.; UCB, Pol.; UCB, Port.; UCB, Rus.; GSK, Singapore; UCB, Spain; UCB, Swed.; UCB, Switz.; GSK, Thai.; UCB, Turk.; Alliance, UK.
Hydroxyzine hydrochloride (p. 630·3).
Anxiety disorders; premedication; pruritus; insomnia; nausea and vomiting; alcohol withdrawal syndrome; allergic skin reactions; urticaria; hypersensitivity reactions.
Mersifarma, Indon.
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.
UCB, Ukr.
Hydroxyzine (p. 630·3).
Anxiety; premedication; pruritus.

Ataraxone *Lazar, Arg.*
Hydroxyzine hydrochloride (p. 630·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; anxiety.

Atarin *Leiras, Fin.†*
Amantadine hydrochloride (p. 890·3).
Influenza A; parkinsonism.

Ataroc *Novell, Indon.*
⊗Procaterol hydrochloride (p. 1219·1).
Dyspnoea.

Atarva *Duncan, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atarviton *Erfar, Gr.*
Diazepam (p. 1063·2).
Anxiety disorders; sleep disorders; status epilepticus; alcohol withdrawal syndrome; skeletal muscle spasm; tetanus; premedication.

Atasol
Note: this name may be used for preparations of different composition.
Church & Dwight, Canad.
Paracetamol (p. 115·1).
Pain; fever.
Scoshia, India.
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2); ofloxacin (p. 334·3).
Ear disorders.

Atasol-8, -15, -30 *Church & Dwight, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine citrate (p. 1203·3).
Pain; fever.

Ataspin *Atabay, Turk.*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Atassol *Solfran, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Atazid *AstraZeneca, Denm.†*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Atazor *Emcure, India.*
Atazanavir (p. 968·1).

ATB *BJ Benjaosoth, Thai.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Atba *Aronex, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atbend *ATOZ, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Atbeta *Shrrishti, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atcal *ATOZ, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Atcal Forte *ATOZ, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); calcium hydrogen phosphate (p. 1783·3); magnesium (p. 1786·3); zinc sulfate (p. 2126·2).

Atcard *Utopian, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Atcardil *Sun, India.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; migraine.

Atcet-LV *ATOZ, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Atcet-MD *ATOZ, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Atchol *Aristo, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atchol Asp *Aristo, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Atchol-F *Aristo, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atcold *ATOZ, India.*
Oral suspension: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
ATOZ, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Atcom *Comed, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atcurium *Chandra Bhagat, India.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atcuron *Sun, India.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atd
Note: this name may be used for preparations of different composition.
H & Care, India.
Drotaverine (p. 2497·3).

Atderm *ATOZ, India.*
⊗Fluocinolone (p. 1636·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Atdol *ATOZ, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Atdol Plus *ATOZ, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Ate
Note: this name may be used for preparations of different composition.
Rishab, India.
Artesunate (p. 648·2).
Malaria.

Ate Lich *Winthrop, Ger.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ate Lich comp *Winthrop, Ger.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atébémyxine *Chauvin, Fr.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Atebeta *Betapharm, Ger.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Atecard *Cazi, Braz.; Dabur, India.*
⊗Atenolol (p. 1308·2).
Arrhythmias; hypertension; angina pectoris.

Atecard-AM *Dabur, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atecard-D *Dabur, India.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atecilina *Gramon, Arg.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Atecor *Rowex, Irl.*
⊗Atenolol (p. 1308·2).
Arrhythmias; myocardial infarction; angina pectoris; hypertension.

Atecor CT *Rowex, Irl.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atecortin *Jelfa, Pol.*
⊗Hydrocortisone acetate (p. 1640·1); oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Infected ear or eye disorders.

Atédurex *Sandoz, Switz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Ateez *East African, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Ateez-F *East African, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Atege *Fresenius Biotech, Spain.*
Antithymocyte immunoglobulin (rabbit) (p. 1939·2).
Transplant rejection.

Atehexal *Sandoz, Austral.†; Hexal, Austria; Hexal, Cz.; Hexal, Ger.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Atehexal comp *Hexal, Ger.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Atehexal Compositum *Sandoz, Rus.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atekind *Mankind, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atel
Note: this name may be used for preparations of different composition.
Betapharm, Ger.†
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.
Investi, Arg.†
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; heart failure; hypertension; myocardial infarction.

Atelan *Lanpharm, Arg.†*
⊗Atenolol (p. 1308·2).

Atelec *Mochida, Jpn.*
Cilnidipine (p. 1337·1).
Hypertension.

Atelidona *Teuto, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).

Atelol *Themis, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atelol-D *Themis, India.*
⊗Atenolol (p. 1308·2); indapamide (p. 1409·2).
Hypertension.

Atelvia *Warner Chilcott, USA.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Atem *Promedica, Ital.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Atembin *Temapharm, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Atemos *Genesis, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Atemos-AT *Genesis, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Atemperator
Note: this name may be used for preparations of different composition.
Drugtech, Chile; Armstrong, Mex.
Magnesium valproate (p. 553·1).
Epilepsy; migraine; bipolar disorder.
Ivax, Arg.
Bromazepam (p. 1041·2).
Anxiety; delirium tremens.

Atemur *GSK, Ger.†*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Aten *Zydus, India; Zydus Cadila, Philipp.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine.

Aten-AM *Zydus, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atenase *UCI, Braz.*
Niclosamide (p. 161·2).
Cestode infections.

Atenativ *Octapharma, Austria; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Gr.; Octapharma, Hung.; Octapharma, Ital.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Port.; Octapharma, Spain; Octapharma, Swed.; Octapharma, Switz.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency; thromboembolic disorders.

Atenblock *Mylan, Fin.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; myocardial infarction; migraine.

Aten-D *Zydus, India.*
⊗Atenolol (p. 1308·2); indapamide (p. 1409·2).

Atend *CSL, Mex.*
An antithrombin III preparation (p. 1132·3).
Antithrombin III deficiency.

Atenegran *Legrand, Braz.*
⊗Atenolol (p. 1308·2).
Hypertension.

Atenemeal *Hing Ah, Hong Kong.†*
⊗Atenolol (p. 1308·2).

Ateneo *Neo Quimica, Braz.*
⊗Atenolol (p. 1308·2).
Arrhythmias; hypertension.

Atenet *Nycomed, Denm.†*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; myocardial infarction; angina pectoris.

Atenetic *Gerard, Irl.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Ateneum *Neo Quimica, Braz.*
⊗Atenolol (p. 1308·2).

Atenex *Zydus, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atenex-AM *Zydus, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atenfar *Medipharm, Chile.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Aten-H *Cadila, India.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2).

Ateni *Gerard, Irl.*
⊗Atenolol (p. 1308·2).
Arrhythmias; myocardial infarction; hypertension; angina pectoris.

AteNif beta *Betapharm, Ger.†*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension.

Atenigron *Mitim, Ital.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenij *Sunij, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Aténil *Sandoz, Switz.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Atenix
Note: this name may be used for preparations of different composition.
Raffo, Arg.
Sertraline (p. 448·1).
Depression.
Tecnofarma, Chile.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.
Ashbourne, UK.†
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

AtenixCo *Ashbourne, UK.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
These ingredients can be described by the British Approved Name Cotenidone.
Hypertension.

Ateno *Actavis, Ger.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Ateno comp *Actavis, Ger.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenobal *Baldacci, Braz.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenobene *Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Ukr.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenoblock *Klonal, Arg.*
⊗Atenolol (p. 1308·2).
Hypertension.

Atenoblok *Triomed, S.Afr.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

Atenodan *Pharmacodane, Denm.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenodip *Admac, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atenogamma *Worwag, Ger.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Atenogamma comp *Worwag, Ger.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenogen *Antigen, Irl.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Atenokin *Kinder, Braz.†*
⊗Atenolol (p. 1308·2).
Hypertension.

Atenol *AstraZeneca, Braz.; CT, Ital.; Merck, Mex.†; TO-Chemicals, Thai.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenolab *Multilab, Braz.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenolan *Lannacher, Austria; Lannacher, Rus.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Atenolan comp *GL Pharma, Austria.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenolol comp *Genericon, Austria; Ratiopharm, Ger.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenolol Compositum *Sandoz, Rus.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenomel *PannonPharma, Hung.; Clonmel, Irl.*
⊗Atenolol (p. 1308·2).
Arrhythmias; angina pectoris; hypertension; myocardial infarction.

Atenopharma *Fada, Arg.*
⊗Atenolol (p. 1308·2).

Atenopress *Hexal, Braz.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Atenor *Sandoz, Denm.†*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; myocardial infarction; angina pectoris.

Atenorese *Hexal, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).

Atenoric *Neo Quimica, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atenorm *Cifarma, Braz.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; migraine.

Atenoton *Royton, Braz.*
⊗Atenolol (p. 1308·2).

Atenotop *Topgen, Belg.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Atenova *Lupin, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atenova H *Lupin, India.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2).

Atenova-SA *Lupin, India.*
⊗Levamlodipine; atenolol (p. 1308·2).

Atenovit *Vitarum, Arg.*
⊗Atenolol (p. 1308·2).
Arrhythmias; hypertension.

Atens *Farmasa, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Atens H *Farmasa, Braz.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Atensec *Neo Quimica, Braz.*
Ramipril (p. 1483·3).
Hypertension.

Atenses *Novag, Mex.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Atensia *Willow, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atensia-AM *Willow, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atensil *Biomedica, Ital.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Atensina *Boehringer Ingelheim, Braz.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Atensiol *Globo, Braz.*
⊗Atenolol (p. 1308·2).

Atenual *Tecnofarma, Chile.*
Clomipramine (p. 412·1).
Depression; narcoleptic syndrome; nocturnal enuresis; obsessive-compulsive disorder; pain.

Atenuol *Greenpharma, Braz.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenuol CRT *Greenpharma, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Atépadène *Mayoly-Spindler, Fr.†*
Adenosine triphosphate disodium (p. 2430·3).
Muscle pain.

Atepodin *Medix, Spain.*
Adenosine triphosphate sodium (p. 2430·3).
Muscular dystrophies; arrhythmias; prevention of anoxia.

Atepres *Micro, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atepress *Teuto, Braz.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atepros *Biomedis, Philipp.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Aterax *AHN, S.Afr.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; premedication; pruritus.

Ateria-Heel *Heel, Canad.†*
Arnica (p. 2447·2); baryta iodata (p. 2452·2); mistletoe (p. 2560·2); phosphorus (p. 2589·2); solanum nigrum (p. 2458·2); tobacco (p. 2632·2).
Homoeopathic preparation.

Aterina *Tedec Meiji, Spain.*
Sulodexide (p. 1507·3).
Atherosclerosis; thromboembolic disorders; hyperlipidaemias.

Aterkey *Pharminicio, Spain.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Atermin *Magis, Ital.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Aterocard *KVZ, Ukr.*
Clopidogrel (p. 1342·3).
Atherosclerosis; myocardial infarction; unstable angina; peripheral arterial disease.

Ateroclar
Note: this name may be used for preparations of different composition.
Beta, Arg.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.
Lafi, Chile.
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.
Medibase, Ital.†
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Ateroclar Combi *Beta, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Ateroclar Duo *Beta, Arg.*
Ezetimibe tablets (p. 1379·2); atorvastatin calcium tablets (p. 1309·2).
Hypercholesterolaemia.

Ateroid *Cornelli, Ital.*
A heparinoid (p. 1401·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Thrombosis prophylaxis.

Ateronon *Cambridge Theranostics, UK.*
Lycopene (p. 2546·2).
Antioxidant.

Aterostat *Leksir, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Ateroz *Bilim, Turk.*
Atorvastatin calcium (p. 1309·2).

Atervix *Biofarma, Turk.*
Clopidogrel bisulfate (p. 1342·3).

Atestad *Stada, Philipp.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Atevan *Apotex, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atexal *Sandoz, Turk.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).

At-Eze *Douglas, NZ.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Atezys *Zytras, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atformin *Active, India.*
Metformin (p. 489·1).
Diabetes mellitus.

ATG *Fresenius, Belg.; Fresenius Kabi, China; Fresenius Biotech, Cz.; Fresenius Biotech, Gr.; IFET (ΙΦΕΤ), Gr.; Fresenius, Hong Kong; Fresenius Medical, Hung.; Fresenius Biotech, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Neth.; Fresenius Medical, Pol.; Fresenius Biotech, Rus.; Fresenius Hemocare, Singapore; Fresenius Medical, Swed.; Fresenius Medical, Switz.; Fresenius Biotech, Thai.; Fresenius Kabi, Turk.*
An antithymocyte immunoglobulin (rabbit) (p. 1939·2).
Transplant rejection; graft-versus-host disease; aplastic anaemia.

Atgam *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Hong Kong; Pharmacia Upjohn, India; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Rus.; Pfizer, S.Afr.†; Pfizer, Singapore; Pfizer, Ukr.†; Upjohn, USA; Pfizer, Venez.*
Antithymocyte immunoglobulin (horse) (p. 1939·2).
Renal transplant rejection; immunosuppressant; aplastic anaemia.

Atheart *Franco-Indian, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atheart-EZ *Franco-Indian, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Athera *Lane, UK.*
Parsley (p. 2583·3); vervain (p. 2645·1); senna leaf (p. 1885·1); clivers (p. 2481·2).
Menopausal symptoms.

Atherochek *Indoco, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atherochek-5 *Indoco, India.*
Atorvastatin (p. 1309·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Atherochek-10 *Indoco, India.*
Atorvastatin (p. 1309·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Atheros *Apotex, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Atherotwo *Grandix, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atherovit *Beres, Hung.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; vitamin B supplement.

Athimil *Schering-Plough, Chile.*
Mianserin hydrochloride (p. 434·2).
Depression.

Athlete *Muscle Marketing, Canad.†*
Cyanocobalamin (p. 2107·2).

Athletes Foot *SSL, Israel.*
Tolnaftate (p. 596·1).
Tinea pedis.

Athlete's Foot *Schering-Plough, Canad.*
Tolnaftate (p. 596·1).
Tinea pedis.

Athos
Note: this name may be used for preparations of different composition.
Medix, Mex.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.
Roemmers, Arg.
Ivy (p. 2536·2).
Respiratory-tract disorders.

Athos-B *Roemmers, Arg.*
Ivy (p. 2536·2); benzocaine (p. 1980·2).
Mouth and throat inflammation.

Athril *TO-Chemicals, Thai.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Athymil *Schering-Plough, Fr.†*
Mianserin hydrochloride (p. 434·2).
Depression.

Atibax C *Fabop, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Atifan *KRKA, Cz.†; KRKA, Neth.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Atifin *KRKA, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Atiflan *Ederka, Mex.†*
Naproxen (p. 98·2).
Inflammation; pain.

Atiglauc *Biosintex, Arg.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension.

Atimos *Torrex, Cz.; Chiesi, Fr.; Torrex Chiesi, Hung.; Chiesi, Ital.; Chiesi, Neth.; Torrex Chiesi, Pol.; Chiesi, Port.; Chiesi, Rus.; Chiesi, Turk.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease; asthma.

Atimos Modulite *Trinity, UK.*
⊗Formoterol fumarate (p. 1209·2).
Asthma.

Atinorm
Note: this name may be used for preparations of different composition.
Chrispa (Χρισπα), Gr.
Citalopram hydrochloride (p. 411·1).
Depression.

Atipam *Ind-Swift, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; nausea and vomiting associated with cytotoxic therapy; premedication.

Atipina *LKM, Arg.*
Quetiapine fumarate (p. 1101·1).
Bipolar disorder; schizophrenia.

Atisuril
Note: this name may be used for preparations of different composition.
Italmex, Mex.
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Atiten *Bayer, Ital.*
Dihydrotachysterol (p. 2113·2).
Hypoparathyroidism; pseudohypoparathyroidism.

Ativan *Aspen, Austral.; Pfizer, Canad.; IFET (ΙΦΕΤ), Gr.; Wyeth, India; Sunthi Sepuri, Indon.†; Wyeth, Indon.†; Pfizer, Irl.; Wyeth, Malaysia†; Wyeth, Mex.; Healthcare Logistics, NZ; Aspen, S.Afr.; Wyeth, Singapore†; Wyeth, Turk.; Pfizer, UK; Valeant, USA; Westward, USA; Wyeth, Venez.*
Lorazepam (p. 1080·3).
Anxiety; premedication; status epilepticus; insomnia; mania; mixed anxiety depressive states; alcohol withdrawal syndrome; nausea and vomiting.

Ativol *Teva, Spain.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Atix *Invision, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atix-EZ *Invision, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atizor *Medipharm, Chile.*
Azithromycin (p. 221·2).
Bacterial infections.

Atkinson & Barker's Gripe Mixture *Torbet Laboratories, UK.*
Sodium bicarbonate (p. 1781·1); caraway oil (p. 2470·3); dill oil (p. 2493·2).
Infant colic.

Atlabiclo *Tetrafarma, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Atlacne *Atlas, Arg.*
Isotretinoin (p. 1706·2).
Acne.

Atlamicin *Atlas, Arg.*
Erythromycin (p. 291·2).
Acne.

Atlansil *Roemmers, Arg.; Sanofi-Aventis, Braz.; Pharma Investi, Chile.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; angina pectoris.

Atlantis *Piam, Ital.*
Sambucus (p. 2609·3); Siberian ginseng (p. 2614·3); carnitine (p. 2053·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Tonic.

ATLC *Grin, Mex.*
⊗Triamcinolone acetonide (p. 1649·1).
Macular oedema; macular degeneration; chronic uveitis; diabetic retinopathy; neovascular glaucoma; ad junct in vitrectomy.

Atloma *Q Check, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atm *Indoco, India.*
Azithromycin (p. 221·2).
Bacterial infections.

ATM 101 *Lafedar, Arg.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Atma *Bittner, Rus.; Bittner, Ukr.*
Sambucus nigra (p. 2609·3); natrium sulfuricum (p. 1888·1); dulcamara (p. 2497·3); arsenicum album (p. 2448·1); tartarus emeticus (p. 151·2).
Homoeopathic preparation.

Atmadisc *Sanol, Ger.; UCB, Ger.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Atmika *ATOZ, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Atmocol *Adams, UK.*
A deodorant spray for use with colostomies and ileostomies.

Atmos
Note: this name may be used for preparations of different composition.
Eurofarma, Braz.
Amlodipine besilate (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.
AstraZeneca, Norw.†; AstraZeneca, Swed.†
⊗Testosterone (p. 2305·1).
Hypogonadism.

Atmose *Morishita, Philipp.*
Mefenamic acid (p. 85·3).
Osteoarthritis; pain; rheumatoid arthritis.

Atmox *ATOZ, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Atmox-CL *ATOZ, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Atnuron *ATOZ, India.*
Injection: Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.
Tablets: Mecobalamin (p. 2108·1); folic acid (p. 2063·1); pyridoxine (p. 2105·3).

Ato *Skymax, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Ato Quat *Atoms, Canad.*
Benzalkonium chloride (p. 1737·1).
Disinfectant.

Atocef *ATOZ, India.*
Cefixime (p. 240·3).
Bacterial infections.

Atocid *ATOZ, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Atocip *ATOZ, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Atocip-TZ *ATOZ, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Atock *Astellas, China; Astellas, Jpn; Astellas, Philipp.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Atocor *Reddy, India; Reddy, Ukr.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias; hypercholesterolaemia.

Atodase-D *ATOZ, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Atodel *Remedica, Malaysia; Remedica, Singapore; Remedica, Thai.*
Prazosin hydrochloride (p. 1473·3).
Heart failure; hypertension; benign prostatic hyperplasia; Raynaud's syndrome.

Atoderm
Note: this name may be used for preparations of different composition.
Bioderma, Ital.
Emollient.
Dry skin disorders.
Bioderma, Venez.
A soap substitute and a moisturiser.
Dry skin disorders.

Atoderm crème *Bioderma, Fr.*
Emollient.
Dry skin disorders.

Atoderm moussant *Bioderma, Fr.*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Cleansing of dry skin.

Atodine-M *ATOZ, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Atofar *Fahrenheit, Indon.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atofast *Intra-Labs, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atofast-EZ *Intra-Labs, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atofast-F *Intra-Labs, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atofast-M *Intra-Labs, India.*
Atorvastatin (p. 1309·2); mecobalamin (p. 2108·1).

Atofen *ATOZ, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Atofen Plus *ATOZ, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Atofloc *Sandoz, Neth.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atoflox *ATOZ, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Atoflox-OZ *ATOZ, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Atogal *Ingers, Cz.†*
Atorvastatin (p. 1309·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Atoken *Kendrick, Mex.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Atoksilin *Atabay, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Atol *East West, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atol-AM *East West, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atolant *Hisamitsu, Jpn.*
Neticonazole hydrochloride (p. 590·3).
Fungal skin infections.

Atolip *Cipla-Medpro, S.Afr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atolone *Major, USA.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Atolteva *Med, Turk.*
⊗Atenolol (p. 1308·2).

Atolux *Sandoz, Neth.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atom *Yacca, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Atomase *Douglas, NZ; Douglas, Thai.†; TTN, Thai.†*
⊗Beclometasone dipropionate (p. 1621·2).
Nasal polyps; rhinitis.

Atomax *Makiz-Pharma, Rus.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atomex *Andromaco, Chile.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Atomo Desinflamante *Imvi, Arg.*
Amyl salicylate (p. 21·2); camphor (p. 2466·2); menthol (p. 2553·2); terpineol (p. 2627·2); cineole (p. 2479·1); guaiacol (p. 1666·1).
Musculoskeletal, joint, and peri-articular disorders.

Atomo Desinflamante C *Imvi, Arg.*
Amyl salicylate (p. 21·2); camphor (p. 2466·2); turpentine oil (p. 2636·3); salicylic acid (p. 1719·1); capsaicin (p. 35·1).
Musculoskeletal and joint disorders; neuralgia.

Atomo Desinflamante Depor *Imvi, Arg.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Atomo Desinflamante Familiar *Imvi, Arg.*
Camphor (p. 2466·2); menthol (p. 2553·2); amyl salicylate (p. 21·2); cineole (p. 2479·1); terpineol (p. 2627·2); guaiacol (p. 1666·1).
Musculoskeletal, joint, and soft-tissue disorders.

Atomo Desinflamante G *Imvi, Arg.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); cineole (p. 2479·1); terpineol (p. 2627·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Atomo Desinflamante Geldic *Imvi, Arg.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Atomo Desinflamante Ibu *Imvi, Arg.*
Ibuprofen (p. 68·2).
Fever; pain.

Atomo Ordeñador *Imvi, Arg.*
Aloe vera (p. 1693·2); vitamin A (p. 2098·3); vitamin F (p. 2509·2); nicotinamide (p. 2083·1).
Skin disorders.

Atomoderma A *Imvi, Arg.*
Vitamin A (p. 2098·3).
Skin irritation.

Atomoderma A-D *Imvi, Arg.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); cod-liver oil (p. 2056·3).
Skin disorders; burns; ulcers.

Atomoderma A-E *Imvi, Arg.*
Vitamin A palmitate (p. 2098·3); tocoferil acetate (p. 2119·2); allantoin (p. 1693·1).
Skin disorders.

Atomoderma Plus *Imvi, Arg.*
⊗Hydrocortisone (p. 1640·1); fish-liver oil; cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin disorders; anorectal disorders.

Atone *Ethix, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atop *Finecure, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atopalm Light Touch Stretch Care *NeoPharm, Singapore.*
Emollient.
Emollient; stretch marks.

Atopalm MLE Comfort Stretch Care *NeoPharm, Singapore.*
Emollient.
Emollient; stretch marks.

Atopalm MLE Derma Rash *NeoPharm, Singapore.*
Emollient.
Skin irritation.

Atopep *ATOZ, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Atopiclair *Sinclair, Israel; Invida, Singapore; Sinclair, UK; Medicis, USA.*
Enoxolone (p. 54·2); piroctone olamine (p. 1716·3); grape (p. 2521·3); telmesteine (p. 1678·2); allantoin (p. 1693·1); sodium hyaluronate (p. 2526·2).
Skin irritation; dry skin; atopic eczema.

Kalbe, Indon.
Enoxolone (p. 54·2); proanthocyanidin (p. 2521·3); telmesteine (p. 1678·2); allantoin (p. 1693·1); hyaluronic acid (p. 2526·2).
Pruritus; skin disorders.

Sinclair, Austral.†
Enoxolone (p. 54·2); grape (p. 2521·3); hyaluronic acid (p. 2526·2); telmesteine (p. 1678·2).
Atopic eczema.

Atopitar *Geofman, Philipp.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atopix *Cassara, Arg.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Atoplus *Triton, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Atopran *Bilim, Turk.*
Citalopram (p. 411·1).

Ator *InnoGen, Philipp.; Sanovel, Turk.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

AtoraB *Basics, Neth.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorbest *Cadila, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorbir *Sandoz, Swed.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Ator-Chol *Farmedia, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atordin *Meridian, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorec *Emcure, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorem *MSN, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atorem-F *MSN, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atorfen *Zuventus, India.*
Atorvastatin calcium (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atorfit *Ajanta, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atorgamma *Worwag, Cz.; Worwag, Hung.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Worwag, Pol.
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Atorgon *Proel, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atoril
Note: this name may be used for preparations of different composition.
ATOZ, India.
Syrup: ⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Aurobindo, India.
Tablets: Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorin *Medley, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Ranbaxy, Denm.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorin-EZ *Medley, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atorin-F *Medley, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atoris *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.; KRKA, Spain; KRKA, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

KRKA, Pol.
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Atoriv *East African, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorless *Germed, Braz.*
Atorvastatin (p. 1309·2).

Atorlip *Pharmavita, Chile; Lyofin, Gr.; Cipla, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; hypercholesterolaemia.

Atorlip-EZ *Cipla, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atorlip-F *Cipla, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atorlonga *Lamda (Λαμδα), Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atormac *Macleods, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atormac-TG *Macleods, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atormax *Geminis, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atormin *PC India, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atornet *Akesiss, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atornet-F *Akesiss, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atornil *Ferrer, Spain.†*
Risperidone (p. 1103·2).
Psychoses; dementia; bipolar disorder; autism; behaviour disorders in children.

Atoroll *VHB, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atoroll-EZ *VHB, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atorpharm *Medis, Cz.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atorsan *Sandoz, Indon.; Lek, Thai.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Atorsi *Sidhbali, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorstad *Pharmacodane, Swed.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorstat *Specifar, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atortin *Panjon, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atortus *Cratus, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atortus-EZ *Cratus, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atorva *Teva, Hung.; Zydus, India; Pfizer, Switz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Atorvacor *Farmak, Ukr.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Atorval *Bennett, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atorvalet *Alet, Gr.*
Atorvastatin calcium (p. 1309·2).

Atorvan *Alter, Port.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorvanox *Verisfield, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atorvaratio *Teva, Fin.*
Atorvastatin calcium (p. 1309·2).
Formerly known as Atoveta.
Hypercholesterolaemia; cardiovascular risk reduction.

Atorvas *Rowex, Irl.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorvasia *Willow, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorvastan *Biotenk, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; atherosclerosis.

Atorvasterol *Polpharma, Pol.; Polpharma, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorva-TG *Zydus, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atorvep *Extractum, Hung.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atorvik *Anvik, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atorvik-EZ *Anvik, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Atorvin *Aurora, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atorvox *Gedeon Richter, Hung.; Farmacom, Pol.; Pliva, Rus.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atosa *Skymax, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Atosar *Sarabhai Piramal, India; Sarthak, India.*
Atorvastatin (p. 1309·2) or atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atosener *Sandoz, Ital.*
Atorvastatin (p. 1309·2).

Atoseptal *Actipharm, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Atosil *Bayer, Ger.*
Injection; oral solution; tablets: Promethazine hydrochloride (p. 638·2).
Agitation; restlessness; hypersensitivity reactions; nausea and vomiting; insomnia.

Atospar *ATOZ, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Atossa *Anpharm, Pol.; Egis, Pol.; ICN, Pol.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Atossion *Elofar, Braz.*
Dropropizine (p. 1662·2).
Cough.

Atossisclerol *IFET [ΙΦΕΤ], Gr.; Gloria, Ital.*
Lauromacrogol 400 (p. 2194·1).
Sclerotherapy of varices.

Atostan *Pharmathen, Gr.*
Somatostatin (p. 1930·3).

Atouxx *Schwarz, Fr.†*
Isomyrtol; pholcodine (p. 1675·1).
Cough.

Atouxx Toux Seche *Schwarz, Fr.†*
Pholcodine (p. 1675·1).
Cough.

Atovarol *Vivax, Venez.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Atover
Note: this name may be used for preparations of different composition.
Evershine, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atovit *ATOZ, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3).

Atovit-Z *ATOZ, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Atoxitom *Landsteiner, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Atozide *Essweil, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atozide-F *Essweil, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Atozol *ATOZ, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Atozol-D *ATOZ, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Atozon-S *ATOZ, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Atp
Note: this name may be used for preparations of different composition.
Biomiicron, India.
Atropine sulfate (p. 1310·2).
Bradycardia; premedication; organophosphorus poisoning; antimuscarinic.
Vanguard, India.
Ubidecarenone (p. 2637·1).

ATP Daiichi *Daiichi Sankyo, Hong Kong.*
Adenosine triphosphate, disodium salt (p. 2430·3).
Cardiovascular disorders; eye disorders; vestibular disorders.

Atpark *Pfizer, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

ATP-Long *Borshchagovskii, Ukr.*
Adenosine-5′-triphosphatehistidine-magnesium(ii) tripotassium salt octahydrate.
Ischaemic heart disease; arrhythmias.

Atpro *ATOZ, India.*
Iron choline citrate (p. 2060·2); nicotinamide (p. 2083·1); protein hydrolysate; vitamin B_1 (p. 2102·3); vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3).

Atpure *Emcure, India.*
⊗Esatenolol (p. 1377·2).
Hypertension; angina pectoris; migraine.

Atra *Hana, Thai.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atracade *Baxter, India.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atracor *Hana, Philipp.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atractil *Trenker, Hong Kong; Trenker, Thai.†*
⊗Diethylpropion (p. 2321·1).
Obesity.

Atractin *Medis, Pol.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atractylon *Leontik, Gr.*
Magaldrate (p. 1856·1).

Atrakt *Gland, India.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atralcilina *Atral, Port.†*
Benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Atralex *CCM, Malaysia.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atralidon *Atral, Port.*
Paracetamol (p. 115·1).
Pain; fever.

Atralin *Coria, USA.*
Tretinoin (p. 1725·2).
Acne.

Atralxitina *Atral, Port.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Atram *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Atranac *Corsa, Indon.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Atrauman Ag *Hartmann, Fr.*
Silver (p. 2615·1).
Wound dressing.

Atraven *Glenmark, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Atrederm *Teva, Pol.*
Tretinoin (p. 1725·2).
Acne.

Atrelax *Piramal, India.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Atren *Ilacsan, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue injuries; gout; pain.

Atrest *Centaur, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Atrexel *Schering-Plough, Mex.*
Methotrexate (p. 822·2).
Rheumatoid arthritis.

Atria *Orion, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atriance *GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Nelarabine (p. 834·3).
Acute lymphoblastic leukaemia; lymphoblastic lymphoma.

Atric Plus *Admac, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Atrican *Innotech, Fr.; Innotech, Rus.; Innotech, Ukr.*
Tenonitrozole (p. 949·1).
Urogenital trichomoniasis.

Atridox *Sidus, Arg.†; Pharmascience, Canad.; Tolmar, Fin.†; Tolmar, Gr.; Tolmar, Irl.†; Tolmar, Ital.; Atrix, Neth.†; Tolmar, Port.†; Tolmar, Spain†; Meda, Swed.†; Oraldent, UK; Tolmar, USA.*
Doxycycline hyclate (p. 288·2).
Bacterial mouth infections; periodontal disease.

Atrimon
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Combined injectable contraceptive.
Nolver, Venez.
Zolpidem tartrate (p. 1116·2).
Insomnia.

Atripla *Gilead, Austral.; BMS, Austria; Gilead, Austria; Gilead, Belg.; Gilead, Canad.; BMS, Cz.; Gilead, Denm.; Gilead, Fr.; BMS, Ger.; Gilead, Ger.; BMS, Gr.; Gilead, Hong Kong; Gilead, Irl.; Neopharm, Israel; Gilead, Ital.; Gilead, Neth.; Gilead, Norw.; Gilead, NZ; BMS, Pol.; Gilead, Pol.; BMS, Port.; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; Gilead, Thai.; Gilead, UK; Gilead, USA.*
Efavirenz (p. 975·1); emtricitabine (p. 976·3); tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Atriscal *Lacer, Spain.*
Dexibuprofen (p. 43·1).
Osteoarthritis; dysmenorrhoea; pain.

Atriser *Serral, Mex.*
Sulindac (p. 134·2).
Inflammation.

Atrisol *Quimica y Farmacia, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Atrisolon *Intas, India.*
⊗Atropine sulfate (p. 1310·2); prednisolone (p. 1645·2).
Inflammatory eye disorders.

Atrivex *Multicare, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with abnormal mucus; upper respiratory-tract inflammation.

Atro *Prem, India.*
Atropine sulfate (p. 1310·2).
Bradycardia; premedication; organophosphorus poisoning; antimuscarinic.

Atro Grin *Grin, Mex.*
Atropine sulfate (p. 1310·2).
Production of mydriasis.

Atro Ofteno *Sophia, Mex.*
Atropine sulfate (p. 1310·2).
Production of mydriasis and cycloplegia.

Atroact *XL, Philipp.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atroaldo *Aldo, Spain.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Atrobel
Note: this name may be used for preparations of different composition.
Ronava, Venez.
Papaverine hydrochloride (p. 2362·3); belladonna (p. 2453·3); hyoscyamus (p. 2530·2); paregoric (p. 111·3); star anise (p. 2622·1).
Smooth muscle spasm.

Atrocin *Syntho, India.*
Atropine sulfate (p. 1310·2); tetracycline (p. 373·1).

Atrodual *Boehringer Ingelheim, Fin.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Atrogel *Bioforce, Irl.; Bioforce, UK.*
Arnica (p. 2447·2).
Muscle pain; bruises.

Atrogrel *Borshchagovskii, Ukr.*
Clopidogrel (p. 1342·3).
Atherosclerosis; cardiovascular risk reduction.

Atroil *Rafarm, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Atrolar *Lark, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atrombin
Note: this name may be used for preparations of different composition.
Gedeon Richter, Hung.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

AtroMed *Bioforce, Switz.*
Arnica (p. 2447·2).
Musculoskeletal and joint pain and inflammation.

Atromicin *Teuto, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Atromid-S *Cana, Gr.*
Clofibrate (p. 1338·3).

Atromizin *Cofar, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Atronase *Boehringer Ingelheim, Belg.*
Ipratropium bromide (p. 1211·3).
Rhinitis.

Atropair *Teva, Switz.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

AtroPen *Meridian, USA.*
Atropine sulfate (p. 1310·2).
Organophosphorus or carbamate pesticide poisoning.

Atropion *Ariston, Braz.*
Atropine sulfate (p. 1310·2).
Arrhythmias.

Atropisa *Pisa, Mex.†*
Atropine (p. 1310·2).

Atropocil *Edol, Port.*
Atropine sulfate (p. 1310·2).
Production of mydriasis and cycloplegia.

Atropol *Duopharma, Philipp.*
Atropine sulfate (p. 1310·2).
Premedication; bradycardia; smooth muscle spasm; organophosphate and muscarinic poisoning.

Atropt *Aspen, Austral.; Healthcare Logistics, NZ.*
Atropine sulfate (p. 1310·2).
Production of cycloplegia and mydriasis.

Atropulm *Julphar, UAE.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Atroren-P *Indoco, India; Indoco, Thai.*
Atropine sulfate (p. 1310·2).
Production of cycloplegia and mydriasis; uveitis.

Atrosan *Bioforce, Irl.; Bioforce, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Atrosept *Geneva, USA.*
Methenamine (p. 322·3); salol (p. 129·3); atropine sulfate (p. 1310·2); hyoscyamine sulfate (p. 1848·1); benzoic acid (p. 1738·2); methylthioninium chloride (p. 1559·1).
Urinary-tract infections.

Atrosol *Ashford, Singapore; Sanovel, Turk.*
Atropine sulfate (p. 1310·2).
Production of mydriasis and cycloplegia.

Atrospan *Fischer, Israel.*
Atropine sulfate (p. 1310·2).
Production of cycloplegia and mydriasis.

Atrost *Gap, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atrostat *Themis, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atrosterol *Kleva, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atrosun *Sunways, India.*
Atropine sulfate (p. 1310·2).
Production of cycloplegia and mydriasis.

Atrovent *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Teijin, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.†; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.
Ipratropium bromide (p. 1211·3).
Obstructive airways disease; rhinitis; rhinorrhoea; asthma.

Atrovent Beta *Boehringer Ingelheim, S.Afr.*
⊗Ipratropium bromide (p. 1211·3); fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Atrovent Comp *Boehringer Ingelheim, Fin.*
⊗Ipratropium bromide (p. 1211·3); fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Atroveran
Note: this name may be used for preparations of different composition.
Vargas, Venez.
Papaverine (p. 2362·2); belladonna (p. 2453·3); hyoscyamus (p. 2530·2).
Smooth muscle spasm.

Atroveran Plus *DM, Braz.*
Paracetamol (p. 115·1); hyoscine (p. 1845·3).

Atrovin *Admac, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Atrovita *Proton, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Atrox
Note: this name may be used for preparations of different composition.
ATOZ, India.
Roxithromycin (p. 356·2).
Bacterial infections.

Biofarm, Pol.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Atrozol *Vipharm, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

ATryn *GTC, Cz.; Leo, Denm.†; Leo, Neth.; Leo, Pol.; GTC, Port.; Leo, Swed.†; Leo, UK; Lundbeck, USA.*
Antithrombin alfa (p. 1132·3).
Antithrombin III deficiency; thromboembolism prophylaxis in surgical patients with antithrombin III deficiency.

Atryn *Leo, Gr.*
Antithrombin alfa (p. 1132·3).
Thromboembolism prophylaxis during surgery in congenital antithrombin III deficiency.

ATS
Note: this name may be used for preparations of different composition.
Hoechst Marion Roussel, USA.
Erythromycin (p. 291·2).
Acne.

Atstat *Ind-Swift, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Attain *Sherwood, USA.*
Lactose-free preparation for enteral nutrition.

Attempta *Ratiopharm, Ger.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Attenta *Alphapharm, Austral.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Attentio *Dalmia, India.*
Centella (p. 1698·3); liquorice (p. 1853·2); ashwagandha (p. 2450·2).

Attentrol *Sun, India.*
Atomoxetine hydrochloride (p. 2316·3).

Attenuvax *Merck, USA.†*
A live measles vaccine (more attenuated Enders' Edmonston strain) (p. 2398·3).
Active immunisation.

Attor *Biochem, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Attozette *Gedeon Richter, Cz.*
⊗Letrozole (p. 817·1).

Aturgyl
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinopharyngeal congestion.

Atus *Metapharma, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Atus-D *ATOZ, India.*
Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Atusil *Recalcine, Chile.*
Promolate (p. 1676·1).
Cough.

Atuss DM *Atley, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Coughs and associated respiratory-tract disorders.

Atuss-12 DM *Atley, USA.†*
⊗Pseudoephedrine polistirex (p. 1676·1); chlorphenamine polistirex (p. 620·3); dextromethorphan polistirex (p. 1660·1).
Upper respiratory-tract disorders.

Atuss DS *Atley, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1) or dextromethorphan tannate (p. 1660·1); chlorphenamine maleate (p. 620·3) or chlorphenamine tannate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1) or pseudoepehdrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Atuss-12 DX *Atley, USA.†*
Dextromethorphan polistirex (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Atuss G *Atley, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs and associated respiratory-tract disorders.

Atuss HC *Atley, USA.†*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Atuss HD *Atley, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

Atuss HS *Atley, USA.†*
⊗Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Atuss HX *Atley, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

A-Tussin *Osoth, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Atussin *Stirol, Ukr.†*
Dextromethorphan hydrobromide (p. 1660·1); ascorbic acid (p. 2110·3).
Cough.

Atuxane *Merck Medication Familiale, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Atv *Zee, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atvas *Cadila, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Atywia *Temapharm, Pol.*
Ethinylestradiol (p. 2275·3); dienogest (p. 2267·2).
Combined oral contraceptive; acne.

Atzee *Zee, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Atzee-AM *Zee, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Atzirut X *CTS, Israel.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

AU 4 Regeneresen *Dyckerhoff, Ger.†*
Ribonucleic acid (p. 2604·1).
Ear disorders.

Aubagio *Genzyme, USA.*
Teriflunomide (p. 2626·3).
Multiple sclerosis.

Aubeline *Arkopharma, Belg.*
Crataegus (p. 2488·1).

Aubéline *Arkopharma, Fr.†*
Crataegus (p. 2488·1).
Nervous disorders; cardiac disorders.

Aubrex *Corbridge, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; adenomatous polyposis.

Aubril *Novartis, India.*
Trimethoprim (p. 381·2); sulfadiazine (p. 361·3).
Respiratory-tract infections; urinary-tract infections.

Aucee *Auspi, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Aucic *Poen, Arg.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Aucusik *Andromaco, Chile.*
Benzocaine (p. 1980·2); benzethonium chloride (p. 1738·1); benzyl alcohol (p. 1739·3); menthol (p. 2553·2).
Pruritus.

Audax *SSL, Irl.*
Choline salicylate (p. 39·2).
Earache; ear wax removal.

Audazol *Lesvi, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Audecol *Ariston, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones.

Audi Baby *Diepharmex, Fr.*
Sea water (p. 2612·1).
External ear hygiene.

Audiclean *De la Mer, Fr.*
Ear drops: Apricot kernel oil (p. 2587·1); eucalyptus oil (p. 2501·2).
Ear wax removal.

De la Mer, Fr.
Topical spray: Sea water (p. 2612·1).
Ear wax removal.

Omega, Austral.
Apricot kernel oil (p. 2587·1).
Ear wax removal.

Audifluor *Diba, Mex.*
Sodium fluoride (p. 2089·2).
Otosclerosis.

Audione *Serra Pamies, Spain.†*
Vitamins; potassium iodide (p. 2336·3).
Ear disorders; eye disorders.

Audispray *Diepharmex, Fr.*
Sea water (p. 2612·1).
External ear hygiene.

Audmonal *Auden McKenzie, UK.*
Alverine citrate (p. 1819·1).
Gastrointestinal spasm.

Aufbaukalk I *Weleda, S.Afr.†*
Apatit; cucurbita (p. 2489·2).
Homoeopathic preparation.

Aufbaukalk II *Weleda, S.Afr.†*
Conchae (p. 1824·3); quercus cortex (p. 2574·1).
Homoeopathic preparation.

Augclav
Note: this name may be used for preparations of different composition.
Pharmahof, Thai.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

VHB, India.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Augenschutz NA *Salushaus, Ger.*
Vitamin A palmitate (p. 2098·3).
Night-blindness.

Augentonicum *Medserve, Switz.*
Digitalis (p. 1352·3); esculoside (p. 2431·2).
Eye disorders.

Augentropfen Mucokehl D5 *Sanum-Kehlbeck, Ger.†*
Mucor racemosus.
Homoeopathic preparation.

Augentropfen Stulln *Stulln, Austria.†*
Digitalis (p. 1352·3); esculoside (p. 2431·2).

Augentropfen Stulln Mono *Stulln, Ger.*
Digitalis leaf (p. 1352·3); esculoside (p. 2431·2).
Eyestrain.

Augex *Poen Vision, Mex.*
Tropicamide (p. 2012·2); phenylephrine (p. 1672·2).
Mydriasis.

AugMaxcil *Aspen, S.Afr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Augment Bone Graft *Joint Solutions, Canad.*
⊗Becaplermin (p. 1695·2); calcium phosphate (p. 1784·2).
Bone graft substitute.

Augmentan *GSK, Ger.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Augmentin *GSK, Austral.; GSK, Chile; GSK, Fin.; GSK, Israel; GSK, NZ; Reddy, USA.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
These ingredients can be described by the British Approved Name Co-amoxiclav.
Bacterial infections.

GSK, China; GSK, India; GSK, Indon.
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

GSK, Ukr.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Augmentin Bid *GSK, Chile.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Augmentin Duo *GSK, Cz.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Augmentin-Duo *GSK, Hung.; GSK, UK.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
These ingredients can be described by the British Approved Name Co-amoxiclav.
Bacterial infections.

Augmentine *GSK, Spain.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Augmentin-Extra *GSK, Hung.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Augmex *Korea United, Philipp.†; Pharmatrix, Philipp.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Augmexx *VHB, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Augnic *Siomond, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Augpen *Zuventus, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Emcure, Thai.†
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Augpen-LB *Zuventus, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Augpod *Elder, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Augtax *Zuventus, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Augtaz *Zuventus, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Augurcin *Aldril, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Augxil-G *Pharmahof, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Aulanic *Genesis, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Aulcer *Alacan, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Aulin *CSC, Austria†; Medicom, Cz.; Lavipharm, Gr.; Helsinn Birex, Indon.†; Helsinn Birex, Irl.; Roche, Ital.; Essex, Philipp.†; Medicom, Pol.; Angelini, Port.; Vifor, Switz.; Schering-Plough, Venez.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Aulis *Aulo Gelio, Arg.*
Cranberry (p. 2488·1); ginkgo biloba (p. 2512·3).
Tired legs.

Aulo Gelio Pie *Aulo Gelio, Arg.*
Camphor (p. 2466·2); vitamin A (p. 2098·3).
Foot disorders.

Aulo Gelio Repelente *Aulo Gelio, Arg.*
Citronella oil (p. 2481·1).
Insect repellent.

Aulo Gelio Toallitas *Aulo Gelio, Arg.*
Citronella oil (p. 2481·1).
Insect repellent.

Aulo Repelente De Piojos *Aulo Gelio, Arg.*
Citronella oil (p. 2481·1); rue (p. 2608·2); quassia (p. 2601·1); eucalyptus citriodora oil.
Pediculosis.

Aulzadin *Fortune, Hong Kong.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux.

Aunativ *Octapharma, Gr.; Pfizer, Gr.; Pharmacia Upjohn, India.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Aura *Daffohils, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Auradol *Lusofarmaco, Ital.*
Frovatriptan succinate (p. 676·2).
Migraine.

Auralgan
Note: this name may be used for preparations of different composition.
Paladin, Canad.; Whitehall, NZ; Deston, USA.
⊗Benzocaine (p. 1980·2); phenazone (p. 124·1); glycerol (p. 2517·2).
Acute otitis media; ear wax removal; pain and inflammation of the ear.

Pfizer Consumer, Austral.; Wyeth, Philipp.; Wyeth, Thai.
Benzocaine (p. 1980·2); phenazone (p. 124·1).
Earache; ear wax removal; otitis media.

Auralyt
Note: this name may be used for preparations of different composition.
Wyeth Consumer, Mex.
Benzocaine (p. 1980·2).
SA Druggists Self Med, S.Afr.†
⊗Glycerol (p. 2517·2); phenazone (p. 124·1); benzocaine (p. 1980·2).
Otitis media; ear wax removal.

Auram *Ache, Braz.*
Oxcarbazepine (p. 533·2).
Epilepsy; trigeminal neuralgia.

Auramin *Valeant, Austria.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Aurantin *Pfizer, Ital.*
Phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias.

Auraphene-B *Reese, USA.*
Urea hydrogen peroxide (p. 1774·2).

Aurasept *Adcock Ingram, S.Afr.*
Benzocaine (p. 1980·2); phenazone (p. 124·1).
Otitis.

Aurax *Acella, USA.*
⊗Phenazone (p. 124·1); benzocaine (p. 1980·2); glycerol (p. 2517·2); hydroxyquinoline sulfate (p. 2530·1).
Otitis media; ear wax removal.

Aureciclina *Sanval, Braz.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Aurene *Ivax, Arg.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Aureocort *Dermapharm, Austria; Teofarma, Ital.; Goldshield, UK.*
⊗Chlortetracycline hydrochloride (p. 260·2); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Aureocrem *Puebla, Arg.*
Polysaccharides of *Pseudomonas aeruginosa.*

Aureomicina *Meda, Ital.; Alcon, Spain.*
Chlortetracycline hydrochloride (p. 260·2).
Bacterial eye infections; bacterial infections.

Aureomix *SIT, Ital.*
Chlortetracycline hydrochloride (p. 260·2); sulfacetamide sodium (p. 361·1).
Ear, nose, and eye infections.

Aureomycin *Erfa, Belg.; Riemser, Ger.; Wyeth, Gr.; US Summit, Thai.†*
Chlortetracycline hydrochloride (p. 260·2).
Bacterial infections.

Auréomycine *DB, Fr.; Merck Medication Familiale, Fr.*
Chlortetracycline hydrochloride (p. 260·2).
Eye and skin infections.

Aureomycine *Meda, Belg.†*
Chlortetracycline hydrochloride (p. 260·2).
Eye infections.

Aurex *Sandoz, Pol.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Auricam *Collins, Mex.†*
Meloxicam (p. 86·3).
Inflammation.

Auricularum *Grimberg, Fr.; Lilly, Gr.*
⊗Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3); dexamethasone sodium phosphate (p. 1631·2); nystatin (p. 590·3).
Ear infections.

Auriculite *Holland Pharma, Neth.*
Arnica montana (p. 2447·2); belladonna (p. 2453·3); calcarea carbonica ostrearum (p. 1824·3); chamomilla (p. 2474·1); ferrum phosphoricum (p. 2077·1); plantago major (p. 2592·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Aurid *Pharmathen, Gr.*
⊗Budesonide (p. 1625·1).

Auriderm *Auriga, Hong Kong.†*
Vitamin K (p. 2122·2).
Purpura; haematomas; erythema; pre- and post-sclerotherapy; pre- and post- injection of wrinkle-filling product.

Auriderm K2 *Medstyle, Chile.†*
Vitamin K (p. 2122·1).
Skin discoloration.

Aurigoutte *Merck Medication Familiale, Fr.*
Hexamidine isetionate (p. 1754·3); lidocaine hydrochloride (p. 1988·2).
Otitis externa.

Auritricin *Delta, Braz.*
Tyrothricin (p. 384·1); etyl metaborate; chlorobutanol (p. 1747·2).
Ear infections.

Aurituss *Pharmabiotics, Chile; Recalcine, Chile.*
⊗Salmeterol (p. 1224·1); fluticasone (p. 1638·1).
Asthma.

Aurnida *Globus, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Auro *Del, USA.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Auro-Amoxiclav *Aurobindo, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Aurobin *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
⊗Prednisolone caproate (p. 1645·3); lidocaine hydrochloride (p. 1988·2); dexpanthenol (p. 2582·2); triclosan (p. 1773·2).
Anorectal disorders.

Gedeon Richter, Ukr.
⊗Prednisolone caproate (p. 1645·3); lidocaine (p. 1988·1); panthenol (p. 2582·2); triclosan (p. 1773·2).
Anorectal disorders.

Aurocalcin *AVI, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Aurocard *DHU, Ukr.*
Crataegus (p. 2488·1); aurum chloratum (p. 2521·1); convallaria majalis (p. 2486·2); ignatia (p. 2532·1); arnica (p. 2447·2).
Homoeopathic preparation.

Aurochobet *Chobet, Arg.*
Calcium gold keratinate (p. 66·3).
Rheumatoid arthritis.

Aurocris *Samarth, India.*
Sodium aurothiomalate (p. 130·2).

Aurodipine *Aurora, Gr.*
Nimodipine (p. 1455·2).
Ischaemic nervous system disorders.

Aurodren *Aurora, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Auro-Dri *Insight, Canad.; Del, USA.*
Isopropyl alcohol (p. 1758·3).
Ear disorders; water in the ear.

Aurofox *Salus, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Auroguard Otic *SDA, USA.*
Benzocaine (p. 1980·2); phenazone (p. 124·1); hydroxyquinoline sulfate (p. 2530·1).
Ear disorders.

Auroken *Kendrick, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive disorders.

Aurolate *Pasadena, USA.†*
Sodium aurothiomalate (p. 130·2).

Auromelid *Farmilia, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Auronal *Egis, Cz.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Aurone *Aspen Consumer, S.Afr.*
Phenazone (p. 124·1).
Earache.

Aurone Forte *Aspen Consumer, S.Afr.†*
Phenazone (p. 124·1); benzocaine (p. 1980·2); chlorobutanol (p. 1747·2).
Inflammatory ear disorders with infection.

Auronim *Aurobindo, India; Aurobindo, Rus.*
Nimesulide (p. 101·3).
Pain; musculoskeletal and joint disorders; inflammation.

Auropan *KRKA, Rus.†*
Auranofin (p. 27·3).
Rheumatoid arthritis.

Auropennz *Biosano, Chile.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Auroprozil *Actor, S.Afr.*
Cefprozil (p. 248·2).
Bacterial infections.

Aurorex *Roche, Mex.*
Moclobemide (p. 437·2).
Depression; social phobia.

Aurorix *Meda Valeant, Austral.; Meda, Austria; Meda, Belg.; Roche, Braz.; HLB, Chile; Roche, Cz.; Meda, Denm.; Meda, Fin.; Meda, Ger.; Roche, Gr.; Roche, Hong Kong†; Meda, Hung.; Roche, Indon.†; Roche, Malaysia; Meda, Neth.; Meda, Norw.; Valeant, NZ; Roche, Philipp.†; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.†; Roche, Singapore; Meda, Swed.; Meda, Switz.; Roche, Thai.†; Roche, Turk.*
Moclobemide (p. 437·2).
Depression; social phobia; bipolar disorder.

Aurostatin *Aurora, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Aurotaz-P *Biosano, Chile.*
Tazobactam (p. 369·3); piperacillin (p. 340·1).
Bacterial infections.

Aurox 50 *Aurobindo, India.*
Roxithromycin (p. 356·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Aurox 150 *Aurobindo, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Auroxicam *Aurora, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Auroxidol *Aurora, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Auroxime *Aurobindo, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Auroxizine *Aurora, Gr.*
Cetirizine hydrochloride (p. 619·2).

Aurox-Kid *Aurobindo, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Auroxol *Aurora, Gr.*
Ambroxol hydrochloride (p. 1654·3).

Auroxone *SMHP, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Aurstat *Onset, USA.*
Sodium magnesium fluorosilicate.
Skin irritation; wounds; burns 406 Also contains sodium phosphate, sodium chloride, hypochlorous acid, and sodium hypochlorite.

Aurum Complexe No 38 *Lehning, Fr.†*
Secale cornutum (p. 2137·1); ferrum iodatum (p. 2061·3); cerium oxalicum (p. 1826·2); arsenicum iodatum (p. 2448·1); platina muriatica (p. 2593·1); aurum muriaticum natronatum (p. 2521·2).
Homoeopathic preparation.

Aurum Plus *Doctor H, Rus.*
Anamirta cocculus (p. 2483·1); arnica montana (p. 2447·2); aurum iodatum (p. 2521·2); barium iodatum (p. 2452·2); barium chloratum (p. 2452·3); gelsemium sempervirens (p. 2511·2).
Homoeopathic preparation.

Aurumarell Kreislauf-Spezifikum *Sanorell, Ger.*
Aurum metallicum (p. 2521·1).
Homoeopathic preparation.

Aurum-Gastreu S R2 *Reckeweg, Ger.*
Aconitum (p. 2428·3); arnica (p. 2447·2); aurum chlor. (p. 2521·1); cactus (p. 2473·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Aurumheel *Heel, Austria; Peithner, Hung.*
Natrium tetrachloroauratum (p. 2521·2); valeriana officinalis (p. 2640·2); cytisus scoparius (p. 2611·3); convallaria majalis (p. 2486·2); arnica montana (p. 2447·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Heel, Canad.†
Arnica (p. 2447·2); convallaria majalis (p. 2486·2); hawthorn (p. 2488·1); sodium tetrachloroaurate (p. 2521·2); sparteine; valerian (p. 2640·2).
Homoeopathic preparation.

Aurum/Lavandula comp. *Weleda, Ger.*
Aurum metallicum (p. 2521·1); ol. lavandulae (p. 2541·1); aetheroleum rosae damascenae et centifoliae (p. 2607·2).
Homoeopathic preparation.

Auscap *Aspen, Austral.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Ausentron *Laboratorios Chile, Chile.*
Clomipramine (p. 412·1).
Depression; nocturnal enuresis; obsessive-compulsive disorder; premature ejaculation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ausfam *Aspen, Austral.; Arrow, Hong Kong.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ausgem *Aspen, Austral.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Auspilic *Pharos, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Auspril *Aspen, Austral.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Ausran *Aspen, Austral.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Aussamin *Pharmaction, Hong Kong.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Joint disorders.

Aussie Tan *Or-Dov, Austral.†*
SPF 7: SPF 15 Lotion: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3).
Sunscreen.

Or-Dov, Austral.†
SPF 15 Topical gel: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Aussie Tan Pre-Tan *Or-Dov, Austral.†*
Tyrosine (p. 2098·3); tyrosinase.
To accelerate tanning.

Aussie Tan Skin Moisturiser *Or-Dov, Austral.†*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).

Aussie Tan Sunstick *Or-Dov, Austral.†*
Salol (p. 129·3).
Sunscreen.

Austac *Austell, S.Afr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; heartburn; gastric hyperacidity.

Austrapen *Lennon, Austral.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Autan *SC Johnson, UK.*
Diethyltoluamide (p. 2153·1); icaridin (p. 2156·3).
Insect repellent.

Autdol *Laboratorios Chile, Chile.*
Diclofenac sodium (p. 48·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Autidine *Aurobindo, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger Ellison syndrome; dyspepsia.

Auto *Patar, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Autoderm Extra *Ecolab, Ger.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3); benzyl alcohol (p. 1739·3).
Skin disinfection.

Autogene *UniVaccin, Ger.†*
An inactivated bacterial preparation.
Bacterial infections.

Autohaler *Cipla, India.*
⊗Isoprenaline sulfate (p. 1411·3).
Obstructive airways disease.

Autohelios *Roche-Posay, Braz.; Roche-Posay, Fr.*
Dihydroxyacetone (p. 1700·1).
Tanning aid.

Autohélios Bronze *Roche-Posay, Arg.*
Dihydroxyacetone (p. 1700·1).
Tanning aid.

Autoplasme Vaillant *SERP, Mon.*
Black mustard (p. 2566·1).
Respiratory-tract congestion.

Autrin
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Wyeth, India.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Aspen, S.Afr.†
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); intrinsic factor (p. 2534·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Autritis *Pentafarma, Port.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Auvi-Q *Sanofi-Aventis, USA.*
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Auxib *MSD, Austria†; MSD, Neth.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gouty arthritis; ankylosing spondylitis; gout.

Auxina A + E *Chiesi, Spain.*
Vitamin A palmitate (p. 2098·3); tocoferil acetate (p. 2119·2).
Deficiency of vitamins A and E; skin disorders; eye disorders; recurrent miscarriage; infertility.

Auxina A Masiva *Chiesi, Spain.*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Auxina E *Chiesi, Spain.*
Tocoferil acetate (p. 2119·2).
Cystic fibrosis; hypoproteinaemia; vitamin E deficiency; biliary-tract disorders.

Auxinol *Expanscience, Fr.*
Delmopinol hydrochloride (p. 2492·2).
Oral hygiene; gingivitis; periodontitis.

Auxitrans *Aerocid, Fr.*
Pentaerythritol (p. 1877·1).
Constipation.

Auxofer *Magis, Ital.†*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Auxxil *Laboratorios Chile, Chile.*
Levofloxacin (p. 315·3).
Bacterial infections.

Auz *Unikid, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Av Cort *Keshav, India.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Avaden *Bayer, Braz.; Schering, Chile†; Bayer, Mex.; Schering, Venez.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; gestodene (p. 2279·3).
Menopausal disorders; osteoporosis.

Avadène *Bayer, Fr.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; gestodene (p. 2279·3).
Menopausal disorders; osteoporosis.

Avadene *Bayer, Port.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; gestodene (p. 2279·3).
Menopausal disorders; osteoporosis.

Avadol *Advance, Malaysia.*
Paracetamol (p. 115·1).
Fever; pain.

Avafontan *Alpharma, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Avagard CHG *3M, Canad.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).

Avage *Allergan, Singapore; Allergan, USA.*
Tazarotene (p. 1724·2).
Skin pigmentation disorders; facial wrinkles.

Avaglim *GSK, Austria†; GSK, Cz.†; GSK, Denm.†; GSK, Ger.†; GSK, Gr.†; GSK, Hung.†; GSK, Irl.†; GSK, Ital.†; GSK, Neth.†; GSK, Norw.†; GSK, Port.†; GSK, Spain†; GSK, Swed.†*
Rosiglitazone maleate (p. 496·3); glimepiride (p. 473·2).
Diabetes mellitus.

Avail *Menley & James, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Avala *Farmasa, Mex.; DHU, Spain.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Avalide *Sanofi-Aventis, Canad.; BMS, Mex.; Sanofi-Aventis, USA.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Avalon *Difa, Ital.*
Avena (p. 2451·1).
Emollient skin cleanser.

Avalox *Bayer, Braz.; Bayer, Ger.; Bayer, Ital.; Bayer, Switz.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Avalsan *Iasis, Gr.*
Valsartan (p. 1521·2).
Heart failure; myocardial infarction.

Avamax *Therapharma, Philipp.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Avamigran
Note: this name may be used for preparations of different composition.
Invida, Thai.
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and related vascular headaches.

Meda, Austria.
Ergotamine tartrate (p. 674·1); mecloxamine citrate (p. 1859·1); camylofin hydrochloride (p. 2467·1); caffeine (p. 1203·3); propyphenazone (p. 127·3).
Migraine; cluster headache.

Transfarma, Philipp.
Ergotamine tartrate (p. 674·1).
Vascular headache.

Avamina *Bioton, Pol.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Avamis *GSK, Ukr.*
⊗Fluticasone furoate (p. 1638·1).
Allergic rhinitis.

Avamys *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S. Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK.*
⊗Fluticasone furoate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Avance *Medlock Medical, UK.*
Hydropolymer wound dressing containing silver (p. 2615·1).
Exudating wounds.

Avancel
Note: this name may be used for preparations of different composition.
Bago, Arg.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Oral contraceptive in women with androgenic symptoms.

Avancort *Intendis, Ital.†*
⊗Methylprednisolone aceponate (p. 1642·2).
Skin disorders.

Avandaglim *GSK, Rus.*
Glimepiride (p. 473·2); rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Avandamet *GSK, Arg.; GSK, Austral.; GSK, Austria†; GSK, Belg.†; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, China†; GSK, Cz.†; GSK, Denm.†; GSK, Fin.†; GSK, Fr.†; GSK, Ger.†; GSK, Gr.†; GSK, Hong Kong; GSK, Hung.†; GSK, Indon.; GSK, Irl.†; GSK, Israel; GSK, Ital.†; GSK, Malaysia; GSK, Mex.; GSK, Neth.†; GSK, Norw.†; GSK, Philipp.†; GSK, Pol.†; GSK, Port.†; GSK, Rus.; GSK, Singapore; GSK, Spain†; GSK, Swed.†; GSK, Switz.†; GSK, Thai.†; GSK, Turk.; GSK, UK†; GSK, Ukr.†; GSK, USA; GSK, Venez.*
Rosiglitazone maleate (p. 496·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Avandaryl *GSK, Arg.; GSK, Canad.†; GSK, Chile; GSK, Indon.; GSK, Philipp.†; GSK, Thai.†; GSK, USA.*
Rosiglitazone maleate (p. 496·3); glimepiride (p. 473·2).
Diabetes mellitus.

Avandia *GSK, Arg.; GSK, Austral.; GSK, Austria†; GSK, Belg.†; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, China†; GSK, Cz.†; GSK, Denm.†; GSK, Fin.†; GSK, Fr.†; GSK, Ger.†; GSK, Gr.†; GSK, Hong Kong; GSK, Hung.†; GSK, Indon.; GSK, Irl.†; GSK, Israel; GSK, Ital.†; GSK, Malaysia; GSK, Mex.; GSK, Neth.†; GSK, Norw.†; GSK, NZ; GSK, Philipp.†; GSK, Pol.†; GSK, Port.†; GSK, Rus.; GSK, S.Afr.†; GSK, Singapore; GSK, Spain†; GSK, Swed.†; GSK, Switz.†; GSK, Thai.†; GSK, Turk.; GSK, UK†; SmithKline Beecham, USA; GSK, Venez.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Avanz *ALK Abello, Ger.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Avanza *MSD, Austral.; MSD, NZ.*
Mirtazapine (p. 436·1).
Depression.

Avapena *Sandoz, Mex.*
Chloropyramine hydrochloride (p. 620·3).
Hypersensitivity.

Avapro *BMS, Arg.; BMS, Austral.; BMS, Braz.; BMS, Canad.; Sanofi-Aventis, Canad.; BMS, Mex.; BMS, USA; Sanofi Winthrop, USA.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Avapro HCT *BMS, Arg.; BMS, Austral.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Avar *Mission Pharmacal, USA.*
Sulfur (p. 1721·1); sulfacetamide sodium (p. 361·1).
Acne.

Avarin *Mega Lifesciences, Thai.*
Simeticone (p. 1886·2); alverine citrate (p. 1819·1).
Gastrointestinal disorders; dysmenorrhoea.

Avaron *Bioton, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Avarte *Ratiopharm, Port.*
Atorvastatin calcium (p. 1309·2).

Avas *Micro, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Avas AM *Micro, India.*
Amlodipine (p. 1304·1); atorvastatin (p. 1309·2).

Avas EZ *Micro, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Avas Plus *Micro, India.*
Atorvastatin (p. 1309·2); nicotinic acid (p. 2083·1).

Avascare *Q Check, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Avascare-EZ *Q Check, India.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Avastar *Vianex (Βιανεξ), Gr.*
Tirofiban hydrochloride (p. 1515·1).

Avastat *Metrolink, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Avastin
Note: this name may be used for preparations of different composition.
Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Roche, Ukr.; Genentech, USA.
Bevacizumab (p. 747·1).
Colorectal cancer; breast cancer; non-small cell lung cancer; renal cell carcinoma; ovarian cancer; malignant glioma.

Orchid, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Avastinee *APT, Hong Kong.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Avastoph *Medic+Aid, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Avatratin *Iator, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Avaxim *Sanofi Pasteur, Arg.; Sanofi-Aventis, Austral.; Aventis Pasteur, Austria; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, China; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.†; Sanofi Pasteur, Fr.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Aventis Pasteur, India; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Mex.; Sanofi Pasteur, Neth.; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Rus.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.; Aventis Pasteur, UK.*
An inactivated hepatitis A vaccine (p. 2388·3).
Separate preparations are available for children and for adolescents and adults.
Active immunisation.

Avazinc *Rekah, Israel.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Avbet *Arvincare, India.*
Artesunate (p. 648·2).
Malaria.

Avcamol *SLE, Israel.*
Paracetamol (p. 115·1).
Pain; fever.

Avcamoli *SLE, Israel.*
Paracetamol (p. 115·1).
Pain; fever.

Avcef *Arvincare, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Avcef-S *Arvincare, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Avcef-TZ *Arvincare, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Avcet *Arvincare, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Avcif *Positif, India.*
Cefixime (p. 240·3).
Bacterial infections.

Avcip *Positif, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Avclav *Arvincare, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Av-Cor *Grandix, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

Avcort *Arvincare, India.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Avdol *Arvincare, India.*
Tramadol (p. 139·2).
Pain.

Avdol-P *Arvincare, India.*
Tramadol (p. 139·2); paracetamol (p. 115·1).
Pain.

Avebact *Ranbaxy, S.Afr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Avecyde *Galderma, Mex.†*
Lactic acid (p. 2539·1).
Skin cleansing.

Aveda Balancing *Aveda, Canad.*
Salicylic acid (p. 1719·1).
Acne.

Aveda Daily Light Guard *Aveda, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Aveda Lip Saver *Aveda, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Aveda Lip Tint *Aveda, Canad.†*
SPF 15: Octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Aveda Tourmaline *Aveda, Canad.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Avedol *Polpharma, Pol.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Avedorm duo *Eberth, Ger.†*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Agitation; sleep disorders.

Avedox-FC *Continentales, Mex.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Aveendix *Darier, Mex.*
Avena (p. 2451·1); borage (p. 2459·1); lactyl glutamate; vitamin E acetate (p. 2119·2); levomenol (p. 2544·1).
Dry skin; skin irritation.

Aveeno *Johnson & Johnson, USA.*
Soap-free skin cleanser; emollient and moisturiser.

Aveeno Active Naturals Hydrocortisone *Johnson & Johnson, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Aveeno Active Naturals Sunscreen *Johnson & Johnson, Canad.; Johnson & Johnson, Canad.*
SPF 60: SPF 30; SPF 45; SPF 55: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Aveeno Anti-Itch *Johnson & Johnson, Canad.; Johnson & Johnson, USA.†*
Calamine (p. 1697·2); pramocaine hydrochloride (p. 1993·3).
Skin disorders; minor skin irritation.

Aveeno Baby *Johnson & Johnson, Canad.*
SPF 55: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Aveeno Cleansing Bar *Rydelle, USA.†*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1); colloidal oatmeal (p. 2451·1).
Acne.

Aveeno Diaper Rash *Johnson & Johnson, Canad.†*
Zinc oxide (p. 1729·1).
Nappy rash.

Aveeno Preparations *Johnson & Johnson, Austral.; Johnson & Johnson, Canad.; Johnson & Johnson, Fr.; Johnson & Johnson, Ital.; Johnson & Johnson, Port.†; Johnson & Johnson, UK.*
A range of preparations containing avena (p. 2451·1).
Dry skin; skin irritation; skin cleansing; emollient.

Avegesic *Avex, Malaysia.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Aveggio *AGIPS, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Avegon *Menarini, Gr.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1).

Avelon *Bayer Schering, S.Afr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Avelox *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Jpn; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.; BayHealth, Port.; Bayer, Rus.; Bayer, Singapore; Bayer, Swed.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, Ukr.; Schering-Plough, USA; Bayer, Venez.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Avemar *Er-Kim, Turk.†*
Preparation for enteral nutrition.

Avena Complex *Blackmores, Austral.†*
Rosemary (p. 2607·2); avena (p. 2451·1); vervain (p. 2645·1); kola (p. 2648·2); vitamin B substances (p. 2102·3).
Tonic.

Avena Med Complex *Dynamit, Austria.*
Ambra (p. 2440·3); avena sativa (p. 2451·1); chamomilla (p. 2474·1).
Homoeopathic preparation.

Avena Rihom Komplex *Richter, Austria.†*
Avena sativa (p. 2451·1); passiflora incarnata (p. 2584·1); zincum isovalerianicum (p. 2641·2).
Homoeopathic preparation.

Avena Sativa Comp *Weleda, Irl.; Weleda, S.Afr.†; Weleda, UK.*
Avena (p. 2451·1); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2); coffea arabica (p. 2648·2).
Restlessness; insomnia; to aid relaxation; sedative.

Avena sativa comp *Weleda, Ger.†*
Avena sativa (p. 2451·1); humulus lupulus (p. 2546·1); passiflora incarnata (p. 2584·1); valeriana (p. 2640·2); coffea (p. 2648·2).
Homoeopathic preparation.

Avene *Pierre Fabre Dermo-Cosmetique, Arg.*
A range of moisturisers, skin cleansers, and sunscreen preparations.

Avène Antirougeurs *Avene, Fr.*
Butcher's broom (p. 2463·1); dextran sulfate (p. 2492·2); hesperidin methyl chalcone (p. 2505·2); OMC; bisoctrizole (p. 1697·1).
Skin redness.

Avene 50 Proteccion Extrema *Silesia, Chile.*
SPF 50: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Avene 20 Proteccion Total *Silesia, Chile.*
Cream SPF 20: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); cinnamate (p. 1699·2).
Sunscreen.

Silesia, Chile.
Stick SPF 20: Titanium dioxide (p. 1725·1); cinnamate (p. 1699·2).
Sunscreen.

Avene Spray 50+ *Silesia, Chile.*
Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3).
Sunscreen.

Aveno *Andromaco, Arg.*
A range of emollients, soap substitutes and shampoos.

Galderma, Braz.
Barrier preparation; skin cleanser.

Avenoc *Boiron, Cz.†; Boiron, Fr.; Boiron, Port.†*
Ointment: ⊗Ficaria verna (p. 2590·3); paeonia officinalis; adrenalinum (p. 1292·1); amylocaine hydrochloride (p. 1979·3).
Haemorrhoids; anorectal disorders; homoeopathic preparation.

Boiron, Canad.†
Ointment: ⊗Adrenalinum (p. 1292·1); amyleine hydrochloridum (p. 1979·3); ficaria verna (p. 2590·3); paeonia.
Homoeopathic preparation.

Boiron, Fr.
Suppositories: Paeonia officinalis; krameria triandra (p. 2603·3); aesculus hippocastanum (p. 2431·2); hamamelis viginiana (p. 2523·3).
Homoeopathic preparation.

Boiron, Canad.†; Boiron, Port.
Suppositories: Paeonia; ratanhia (p. 2603·3); aesculus (p. 2431·2); hamamelis (p. 2523·3).
Homoeopathic preparation.

Avensyl *Elmor, Venez.*
Ispaghula (p. 1849·1); avena (p. 2451·1).
Constipation.

Aventyl *Pendopharm, Canad.; Ranbaxy, USA.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Aveptol *Aledicine, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Avertex *Beta, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Avertin *Avefarm, Cz.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Avertyn *Umut, Turk.*
Escitalopram (p. 416·2).

Avessa
Note: this name may be used for preparations of different composition.
Ranbaxy, India.
⊗Fluticasone propionate (p. 1638·1); formoterol fumarate (p. 1209·2).

GSK, Belg.†
Ondansetron (p. 1872·1).
Nausea and vomiting.

Avessaron *GSK, Belg.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Avestra *Sanofi-Aventis, Ital.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Aveten *Avex, Malaysia.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Avevasc *Avex, Malaysia; Aegis, Singapore.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Avexa *Great Eastern, Thai.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Avexus *Xepa-Soul Pattinson, Malaysia.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Avezol *Avex, Malaysia.*
Fluconazole (p. 578·2).
Fungal infections.

Avia-Mor *Materia Medica, Rus.*
Anamirtua cocculus (p. 2483·1); sodium tetraboracicum (p. 2459·2); veratrum album (p. 2644·3).
Homoeopathic preparation.

Aviane *Apotex, Canad.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Aviane 28 also contains 7 inert tablets.
Combined oral contraceptive; acne.

Duramed, USA.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Aviant *Schering-Plough, Mex.*
Desloratadine (p. 625·1).
Allergic rhinitis; allergic skin disorders.

Aviband *Avalanche, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Avibon *Sanofi-Aventis, Fr.*
Vitamin A palmitate (p. 2098·3).
Skin disorders.

Avical *Alde Medi Impex, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Avicap *Kocak, Turk.*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Avicef *Admac, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Avicef-O *Admac, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Avicef-S *Admac, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Avicid *Avalanche, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Avicis *Galderma, Braz.*
Estradiol (p. 2271·1).
Alopecia.

Avicof *Avalanche, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Avid Plus *Avalanche, India.*
Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Avidart *Orifarm, Denm.; GSK, Spain.*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Avidazine *Bell, India.†*
Cinnarizine (p. 622·1).
Vertigo; tinnitus; Ménière's disease.

Avidox-LB *Avalanche, India.*
Doxycycline (p. 288·1); lactobacillus (p. 2596·3).
Bacterial infections.

Avidox-OZ *Avalanche, India.*
Doxycycline (p. 288·1); ornidazole (p. 943·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Avidox-SP *Avalanche, India.*
⊗Doxycycline (p. 288·1); serrapeptase (p. 2613·3).
Bacterial infections.

Avidoxy *Avidas, USA.*
Doxycycline (p. 288·1).
Bacterial infections.

Avidoxy DK *Avidas, USA.*
Tablets, doxycycline (p. 288·1); lotion SPF 30+ (Defence Solare), octinoxate (p. 1715·1); zinc oxide (p. 1729·1); skin wash (Defence Acne), salicylic acid (p. 1719·1).

Avielid *Libytec, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Avifem *Avalanche, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Avifem-MR *Avalanche, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Aviflox *Avalanche, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Aviflox-M *Avalanche, India.*
Ofloxacin (p. 334·3); metronidazole (p. 936·1).

Aviflox-OZ *Avalanche, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Aviflox-ST *Avalanche, India.*
⊗Ofloxacin (p. 334·3); serrapeptase (p. 2613·3).
Bacterial infections.

Aviflox-TZ *Avalanche, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Aviflu *Avalanche, India.*
Fluconazole (p. 578·2).
Fungal infections.

Aviflucox *Pantafarm, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Avigat *Avalanche, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Avigen *Eras, Turk.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

Avigilen
Note: this name may be used for preparations of different composition.
Sanova, Austria.
Alpha tocoferil acetate (p. 2119·2).
Muscle and connective tissue disorders; intermittent claudication.

Aviglen *Avinash, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Aviglen-Forte *Avinash, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Aviglen-MF *Avinash, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Aviglic *Avinash, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Aviglic-MF *Avinash, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Avigra *Pfizer, NZ.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Pharmacia, S.Afr.
Sildenafil (p. 2364·1).

Avikacin *Admac, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Avil *Sanofi-Aventis, Austral.; Sanofi-Aventis, Indon.; Sandoz, Turk.*
Pheniramine maleate (p. 637·2).
Hypersensitivity reactions; pruritus; rhinitis; motion sickness; vestibular disorders; allergic disorders.

Sanofi-Aventis, India.
Pheniramine (p. 637·2) or pheniramine maleate (p. 637·2).
Cold symptoms; hypersensitivity reactions.

Avil Decongestant *Aventis, Austral.†*
Pheniramine maleate (p. 637·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough; bronchial and nasal congestion.

Avil Expectorant *Sanofi-Aventis, India.*
Pheniramine maleate (p. 637·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Bronchitis; cough; respiratory-tract hypersensitivity.

Avilac *Perrigo, Israel.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Avilact-B *Avalanche, India.*
Vitamin B substances (p. 2102·3); lactic acid bacillus (p. 2596·3).

Avillin *Admac, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Avilox *Avalanche, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Avilox-M *Avalanche, India.*
Ciprofloxacin (p. 261·1); metronidazole (p. 936·1).

Avilox-TZ *Avalanche, India.*
Ciprofloxacin hydrochloride (p. 261·2); tinidazole (p. 949·2).

Avimet
Note: this name may be used for preparations of different composition.
Avinash, India.
Metformin (p. 489·1).
Diabetes mellitus.

Moraceae, India.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; Helicobacter pylori eradication; leg ulcers; pressure sores.

A-Vin *Bestochem, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

A-Vin-AS *Bestochem, India.*
Atorvastatin (p. 1309·2); aspirin (p. 22·2).

Avineuron *Admac, India.*
Vitamin B substances (p. 2102·3).

Avinim *Avalanche, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Avinim Plus *Avalanche, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Avinim-MR *Avalanche, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3).

Avintac *Mavi, Mex.*
Ranitidine (p. 1882·1).

Avinza *King, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Aviomarin *Pliva Krakow, Pol.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting.

Aviоplant *Phytopharm, Rus.; Phytopharm, Ukr.†*
Ginger (p. 1844·1).
Motion sickness; post-operative nausea and vomiting; flatulence; digestive disorders.

Avipro *Avinash, India.*
Protein preparation.
Dietary supplement.

Avipur *Taro, Israel.†*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Avir
Note: this name may be used for preparations of different composition.
East African, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Roemmers-Klinos, Venez.
Aciclovir (p. 964·1).
Herpesvirus infections.

Aviral
Note: this name may be used for preparations of different composition.
Medley, Braz.; Mepha, Switz.; Pliva, UK.†
Aciclovir (p. 964·1).
Herpesvirus infections.

Aviran *Ranbaxy, Mex.†*
Indinavir sulfate (p. 986·1).
HIV infection.

Avirase *Lampugnani, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Avirex-T *Tecnofarma, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Aviron *Arvincare, India.*
Iron sucrose (p. 2078·1).

Avirostat *Varifarma, Arg.*
Interferon alfa-2a (p. 989·2).
Anogenital warts; hepatitis; malignant neoplasms.

Avirox
Note: this name may be used for preparations of different composition.
Avalanche, India.
Roxithromycin (p. 356·2).
Bacterial infections.

Sandoz, Denm.
Aciclovir (p. 964·1).
Herpesvirus infections.

Avirox-AM *Avalanche, India.*
Roxithromycin (p. 356·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Avirox-ST *Avalanche, India.*
⊗Roxithromycin (p. 356·2); serrapeptase (p. 2613·3).
Bacterial infections.

Avisan *Novag, Mex.*
Nitazoxanide (p. 942·2).
Amoebiasis; giardiasis; worm infections; trichomoniasis.

Vifiteh, Rus.
Ammi visnaga (p. 2441·2).
Urinary-tract disorders.

Avisera *Avalanche, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Avisera Plus *Avalanche, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Avisera-MR *Avalanche, India.*
⊗Diclofenac potassium (p. 48·3); tizanidine (p. 2026·2); serrapeptase (p. 2613·3).

Avishot *Schering, Jpn.†*
Naftopidil (p. 2361·1).
Benign prostatic hyperplasia.

Avispas *Avalanche, India.*
Dicycloverine hydrochloride (p. 1834·2); ranitidine hydrochloride (p. 1882·1); simeticone (p. 1886·2).

Avistar *Wermar, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Avistatin *Avinash, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

A-Vita
Note: this name may be used for preparations of different composition.
Leiras, Fin.
Vitamin A palmitate (p. 2098·3); menthol (p. 2553·2).
Nasal dryness.

Avita
Note: this name may be used for preparations of different composition.
Mylan, USA.
Tretinoin (p. 1725·2).
Acne.

A-vitamin *Medic, Denm.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

Avitan *Elvipe, Gr.*
Vitamin A acetate (p. 2098·3).

Avitana *Pfizer, Chile.†*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Avitaz Plus *Reliance, India.*
Copper (p. 2057·1); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Metabolic disorders.

Avitcid *Orion, Fin.*
Tretinoin (p. 1725·2).
Acne; keratinisation disorders.

A-Vite *Neves, Port.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

A-Vitel *Medipharma, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

A-Vitel E *Medipharma, Arg.*
Vitamin A (p. 2098·3); alpha tocopherol (p. 2119·1).
Skin disorders.

Avitene *Shionogi, USA.†*
Collagen (p. 2483·2).
Haemostasis in surgery.

Aviter *Interbat, Indon.*
Malic acid (p. 2549·2); glucosamine hydrochloride (p. 2515·3); arginine hydrochloride (p. 2049·1); glycine (p. 2071·2); glycyrrhizic acid (p. 2520·2); zinc sulfate (p. 2126·2); calcium pantothenate (p. 2085·2); pyridoxine (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pink rock rose.
Tonic.

Avitil *Medihealth, Mex.*
Superoxide dismutase (p. 135·2); catalase (p. 2472·2); ubidecarenone (p. 2637·1); glutathione (p. 1555·2).
Vitiligo.

Pharma Investi, Chile; Roemmers Medihe, Venez.
Microencapsulated melon juice (Extramel).
Vitiligo; pigmentation disorders.

Aviton *Avalanche, India.*
Capsules: Copper sulfate (p. 2057·2); cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); manganese sulfate (p. 2081·2); zinc sulfate (p. 2126·2).

Avalanche, India.
Syrup: Calcium lactate (p. 1784·1); dexpanthenol (p. 2582·2); iron (p. 2073·1); vitamin B substances (p. 2102·3); protein hydrolysate.

Avitorel *Munir, Turk.*
Atorvastatin calcium (p. 1309·2).

Avix *Ibirn, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Avixis *Galderma, Arg.; Galderma, Mex.*
Alfatradiol (p. 2255·2).
Alopecia androgenetica.

Avizin *Avalanche, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Avizine *Taj, India.*
Piperazine (p. 163·1).
Ascariasis; enterobiasis.

Avizol *Avalanche, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Avizol-D *Avalanche, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Avizole *Adley, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Avlocardyl *AstraZeneca, Fr.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction; obstructive cardiomyopathy; migraine; tremor; oesophageal varices.

Avloclor *AstraZeneca, Indon.†; AstraZeneca, Irl.†; AstraZeneca, UK.*
Chloroquine phosphate (p. 650·1).
Malaria; hepatic amoebiasis; lupus erythematosus; rheumatoid arthritis.

Avm *Sienna, India.*
Syrup: Vitamins; minerals; fat; protein; carbohydrate.

Sienna, India.
Tablets: Vitamins; minerals; lysine (p. 2079·3).

Avmigran *Sandoz, Turk.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); mecloxamine citrate (p. 1859·1); paracetamol (p. 115·1).
Migraine.

Avmik *Positif, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Avoca *Bray, UK.*
⊗Silver nitrate (p. 2615·3); potassium nitrate (p. 1766·2).
Warts; verrucas.

Avocal *Wintech, India.*
Oral suspension: Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Wintech, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Avodart *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.†; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA.*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Avogin *Lapi, Indon.*
Ginger (p. 1844·1); vitamin B_6 (p. 2105·3).
Nausea and vomiting.

Avolve *GSK, Austria†; Alenfarma, Port.†*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Avomine *Sanofi-Aventis, Austral.; Piramal, India; Aventis, NZ; Aspen Consumer, S.Afr.; Manx, UK.*
Promethazine teoclate (p. 638·2).
Motion sickness; nausea and vomiting.

Avomit-M *VS, Thai.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Avon *Zee, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia.

Avon Anew *Avon, Canad.†*
SPF 15 cream; SPF 15 lotion: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

Avon, Canad.†
SPF 15 eye cream: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Avon Anew Force Extra *Avon, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Avon Anew Luminosity *Avon, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Avon Anew Retroactive *Avon, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Avon Antiperspirant Deodorant *Avon, Canad.†*
Aluminium chlorohydrate (p. 1694·1).

Avon Beyond *Avon, Canad.*
SPF 15 stick: Octinoxate (p. 1715·1).
Sunscreen.

Avon, Canad.†
SPF 15 cream: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Avon Clearskin Invigorating Cleansing *Avon, Canad.†*
Benzethonium chloride (p. 1738·1).
Skin cleansing.

Avon Clearskin Invisible Blemish Corrector *Avon, Canad.†*
Salicylic acid (p. 1719·1).
Skin disorders.

Avon Clearskin Purifying Gel Cleanser *Avon, Canad.†*
Salicylic acid (p. 1719·1).
Skin disorders.

Avon On Duty *Avon, Canad.†*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Avon Footworks *Avon, Canad.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Avon Footworks Cracked Heel *Avon, Canad.†*
Benzalkonium chloride (p. 1737·1); lidocaine (p. 1988·1).
Skin disorders.

Avon Moisture *Avon, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Avon Perfect *Avon, Canad.†*
SPF 12: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Avon Personal *Avon, Canad.†*
SPF 10: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Avon Solutions *Avon, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Avon Sun *Avon, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Avon, Canad.
SPF 30; SPF 40: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Avon Sun Self-Tanning *Avon, Canad.†*
SPF 6: Octinoxate (p. 1715·1).
Sunscreen.

Avon Vitadvance *Avon, Canad.*
Vitamins; minerals.

Avonex *Abbott, Arg.; Biogen, Austral.; Biogen, Austria; Biogen, Belg.; Abbott, Braz.; Biogen, Canad.; Abbott, Chile; Biogen, Cz.; Biogen, Denm.; Biogen, Fin.; Biogen, Fr.; Biogen, Ger.; Biogen, Gr.; Biogen, Hung.; Biogen, Irl.; Biogen, Israel; Biogen Dompe, Ital.; Abbott, Mex.; Biogen, Neth.; Biogen, Norw.; Healthcare Logistics, NZ; Biogen, Pol.; Biogen, Port.; Gedeon Richter, Rus.; Pharmaplan, S. Afr.; Biogen, Spain; Biogen, Swed.; Biogen Dompe, Switz.; Gen, Turk.; Biogen, UK; Nycomed, Ukr.; Biogen, USA; Abbott, Venez.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

Avopan *Wintech, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Avopan-D *Wintech, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Avorax *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Avosil *Avocet, USA.*
Sodium salicylate (p. 132·2).
Scars.

Avotrin *Intermed, Gr.*
Hyoscine butylbromide (p. 1845·3).

Avpred *Arvincare, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Avpro *Positif, India.*
Capsules: Copper sulfate (p. 2057·2); ferrous fumarate (p. 2060·3); manganese sulfate (p. 2081·2); protein; zinc sulfate (p. 2126·2).

Positif, India.
Oral powder: Protein preparation.

Positif, India.
Syrup: Carbohydrate; iron choline citrate (p. 2060·2); lysine hydrochloride (p. 2079·3); magnesium chloride (p. 1787·1); manganese chloride (p. 2081·2); nicotinamide (p. 2083·1); protein hydrolysate; zinc sulfate (p. 2126·2).

Avpro-XP *Positif, India.*
Protein; mecobalamin (p. 2108·1).

Avramin *Intermed, Gr.*
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).

Avrazor *Zentiva, Cz.†*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Avril *Teofarma, Spain.*
Cod-liver oil (p. 2056·3); aluminium acetotartrate (p. 2440·1); benzalkonium chloride (p. 1737·1); zinc oxide (p. 1729·1).
Wounds; burns.

Avural *LKM, Arg.*
Indinavir sulfate (p. 986·1).
HIV infection.

Avuxilan *Arlex, Mex.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Avva *Intas, India.*
⊗Acetazolamide (p. 2001·1).
Diuresis; glaucoma; epilepsy; high-altitude disorders.

Avyclor *Farma 1, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Avyplus *Epifarma, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Avzeth *Positif, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Awadik *Verisfield, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Away-P *Stalwart, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Awestatin *AWD, Hung.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Awirol *ICN, Pol.†*
Aciclovir (p. 964·1).
Herpesvirus skin infections.

Axacef *Medreich, Hong Kong; Medreich, India; Helm, Port.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Axagon *Simesa, Ital.*
Esomeprazole magnesium (p. 1841·1) or esomeprazole sodium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Axal
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
⊗Benfluorex hydrochloride (p. 1315·3).
Hyperlipidaemias; diabetes mellitus.

Axalan *Medifarma, Indon.†*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; pain.

Axalin *Cipla, India.*
⊗Salbutamol sulfate (p. 1220·2); ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Axalin Expectorant *Cipla, India.*
Ambroxol (p. 1654·3); guaifenesin (p. 1666·2).

Axalin-AX *Cipla, India.†*
⊗Salbutamol (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Obstructive airways disease.

Axamin
Note: this name may be used for preparations of different composition.
Bangkok Lab & Cosmetic, Thai.
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Axamon *Pik, Rus.*
Ipidacrine (p. 687·1).
CNS and peripheral nervous system disorders; Alzheimer's disease; demyelinating disease; myasthenia; gastrointestinal atony.

Axane *Medley, India.*
Camphor (p. 2466·2); capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Axant *Mintlab, Chile.*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

A-Xanthin *Alna, India.*
Ambroxol acefyllinate (p. 1201·2).

Axanthin *Ethica, Indon.*
Astaxanthin (p. 2170·1).
Tonic.

Axanum *AstraZeneca, Cz.; AstraZeneca, Ger.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Switz.*
Aspirin (p. 22·2).
Esomeprazole magnesium (p. 1841·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Axasol *Andromaco, Chile.*
Clotrimazole (p. 576·2).
Fungal vaginal infections; balanitis.

Axastrol *Grindex, Hung.; Grindeks, Ukr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Axcel *Candor, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Axcel Dextrozine *Kotra, Malaysia.*
Dextromethorphan hydrobromide (p. 1660·1); promethazine hydrochloride (p. 638·2).
Cough; respiratory-tract congestion; allergic rhinitis.

Axcel Eviline Forte *Kotra, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Axcel Fungicort *Kotra, Singapore.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).

Deltapharm, Hong Kong.†
⊗Hydrocortisone (p. 1640·1); miconazole (p. 588·3).

Axcel Fusi-Corte *Kotra, Malaysia.†*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Axcel Kaopec *Kotra, Singapore.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Axcel Tridine *Kotra, Malaysia.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion; cold symptoms; sinusitis; rhinitis.

Axcel-L *Candor, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Axcel-LS *Candor, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Axcin *Laksun, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Axe Armour *Unilever, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Axe Freeze *Unilever, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Axed *Grin, Mex.†*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and E deficiency.

Axeen *Galenica, Gr.*
Proxibarbal (p. 1100·2).

Axel *Grisi, Mex.*
Cream: Sulfur (p. 1721·1); triclosan (p. 1773·2); resorcinol (p. 1718·3).
Acne.

Grisi, Mex.
Lotion: Sulfur (p. 1721·1); sulfacetamide (p. 361·1).
Acne.

Grisi, Mex.
Soap: Triclosan (p. 1773·2).
Acne.

Axelabron *Ferakon, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Axelan *Farmazak, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Axelanol *Ferakon, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Axeler *Menarini, Fr.*
Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2).
Hypertension.

Axelorax *Proel, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Axelovert *Pharmex (Φαρμεξ), Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Axelvin *Proel, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Axépim *BMS, Fr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Axepta *Intas, India.*
Atomoxetine hydrochloride (p. 2316·3).

Axeptil *Emar, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Axera *Westmont, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Axeris *Symbiosis, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Axerophthol *Biotika, Cz.*
Vitamin A acetate (p. 2098·3).
Vitamin A deficiency.

Axert *McNeil Consumer, Canad.; Janssen, USA.*
Almotriptan malate (p. 672·1).
Migraine.

Axet *Xeno, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Axetam *Medihealth, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Axetef *Domesco, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Axetim *Indu, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Axetine *Medochemie, Cz.; AFT, NZ; Medochemie, Rus.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Medochemie, China.
Cefuroxime (p. 255·2).
Bacterial infections.

Axiago *Beta, Spain.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Axibin *Korea United, Philipp.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Axicarb *axios, Ger.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Axid *Farmoquimica, Braz.; Pendopharm, Canad.; Lilly, China; Lilly, Gr.; Lilly, Indon.†; Flynn, Irl.; Lilly, Mex.†; Lilly, Neth.; Norgine, Neth.; GSK, Philipp.†; Lilly, Thai.; Lilly, Turk.; Flynn, UK†; Braintree, USA; GSK, USA†; Wyeth Consumer, USA.*
Nizatidine (p. 1866·1).
Dyspepsia; heartburn; gastro-oesophageal reflux; peptic ulcer; gastritis.

Axidexa *Apocare, Ger.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Axidoxo *axios, Ger.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Axidronat *axios, Ger.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Axifolin *Apocare, Ger.*
Calcium folinate (p. 2066·3).
Adjunct to fluorouracil therapy; reduction of methotrexate toxicity.

Axigem *axios, Ger.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Axigran *axios, Ger.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting induced by chemotherapy or radiotherapy.

Axil *Polichem, Ital.*
Pidotimod (p. 2590·2).
Immunostimulant.

Axilin *Ivax, Mex.†*
Flunarizine (p. 629·3).
Migraine.

Axilium *Boniscontro & Gazzone, Ital.*
Lormetazepam (p. 1082·1).
Insomnia.

Axim
Note: this name may be used for preparations of different composition.
Aristopharma, Hong Kong.
Cefuroxime (p. 255·2).
Bacterial infections.

Kee, India.
Cefixime (p. 240·3).
Bacterial infections.

Aximad *Boniscontro & Gazzone, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Axineuron *Medihealth, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Axinim *Medihealth, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Axin-LA *Allenge, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Axinotecan *axios, Ger.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Axiom *Panjon, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Axiomat *Beta, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder.

Axiom-OR *Panjon, India.*
Cefixime (p. 240·3).
Bacterial infections.

Axiplatin *Apocare, Ger.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Axiron *Lilly, USA.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency.

Axirubicin-e *axios, Ger.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Axisetron *Apocare, Ger.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Axistal *Asian Pharm, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Axit *Alphapharm, Austral.*
Mirtazapine (p. 436·1).
Depression.

Axitaxel *axios, Ger.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Axitof *Caplin, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Axl *Indoco, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Axmaxolv *Jewim, Philipp.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Axmel *Myrex Ethica, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Axobat *Lisapharma, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Axobion *Grandix, India.*
Vitamins trace elements.

Axocare *Evershine, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Axocare-S *Evershine, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Axocare-T *Evershine, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Axofin *Eurodrug, Mex.†*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Axofor *Sanofi-Aventis, Mex.*
Hydroxocobalamin acetate (p. 2107·3).
Anaemias; neuralgias; neuritis; vitamin B_{12} deficiency; neuropathies.

Axokine
Note: this name may be used for preparations of different composition.
Rontag, Arg.
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus.

Axol
Note: this name may be used for preparations of different composition.
YSP, Malaysia; Bayer, Mex.; Yung Shin, Singapore.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Axol Plus *Cubit, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Axol-XL *Active, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Axona *Accera, USA.*
Tricaprylin (p. 2098·2).
Alzheimer's disease.

Axone
Note: this name may be used for preparations of different composition.
Cadila, India; Ajanta, Rus.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Volta, Chile.
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety.

Axone-SB *Cadila, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Axon-SB *Blossoms, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Axoplan *Mac, Gr.*
Oxaliplatin (p. 838·1).

Axoptic *CCM, Malaysia.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Axorid *Meda, UK.*
Ketoprofen (p. 79·1).
Omeprazole (p. 1867·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Axotide *GSK, Switz.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Axotret *Axxon, Pol.*
Isotretinoin (p. 1706·2).
Acne.

Axovir *Samarth, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Axsain *Cephalon, Irl.; Cephalon, UK; Rodlen, USA.*
Capsaicin (p. 35·1).
Diabetic neuropathy; postherpetic neuralgia.

Axsol SR *Sigman, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Axsol-P *Sigman, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Axtan *Solas, Indon.*
Astaxanthin (p. 2170·1).
Antoxidant.

Axtar *Unipharm, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Axtil *Adamed, Pol.*
Ramipril (p. 1483·3).
Heart failure; hypertension; myocardial infarction; non-diabetic glomerulonephropathy; cardiovascular risk reduction.

Axtin *Mavi, Mex.*
Fluoxetine (p. 417·1).
Depression.

Axtl *Aurobindo, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Axtrim *Unipharm, Mex.*
Piroxicam (p. 125·3).
Inflammation.

Axtrum *Positif, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Axtrum-S *Positif, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Axual *Ivax, Arg.*
Pregabalin (p. 545·3).
Anxiety; neuropathic pain; epilepsy; fibromyalgia.

Axura *Merz, Austria; Merz, Cz.; Merz, Denm.; Merz, Ger.; Merz, Irl.; Merz, Neth.; Merz, Pol.; Merz, Port.; Merz, Spain; Merz, Swed.; Merz, Switz.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Axurocef *China Chem & Pharma, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

China Chem & Pharma, Thai.†
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Axyplot *Iamatica, Gr.*
Amlodipine besilate (p. 1304·1).

Axyven *Temapharm, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder.

Ayendi *Wockhardt, UK.*
⊗Diamorphine hydrochloride (p. 46·1).
Pain.

Aygestin *Barr, USA.*
Norethisterone acetate (p. 2294·3).
Secondary amenorrhoea; endometriosis; abnormal uterine bleeding.

Aylide *Alphapharm, Austral.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ayr-5 *SMB, Chile.*
⊗Urea (p. 1727·3).
Skin disorders.

Ayr Saline *Hind Wing, Hong Kong†; Ascher, USA.*
Sodium chloride (p. 1795·1).
Nasal irritation.

Ayr con urea *SMB, Chile.*
⊗Urea (p. 1727·3).
Dry skin; hyperkeratosis.

Ayra *Sanovel, Turk.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Ayra Plus *Sanovel, Turk.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ayrementol *SMB, Chile.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Dry skin; skin irritation.

Ayrtons Antiseptic *McGloin, Austral.*
Zinc oxide (p. 1729·1); dichlorobenzyl alcohol (p. 1750·2).
Burns; skin irritation; wounds.

Ayrton's Chilblain *McGloin, Austral.†*
Camphor (p. 2466·2); benzocaine (p. 1980·2); peru balsam (p. 2587·1); phenol (p. 1763·3).
Chilblains.

Ayton *Maigal, Arg.*
Vegetable oils; soya lecithin (p. 2542·2).
Skin disorders.

AZ *Elmor, Venez.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Az-1 *Kopran, India.*
Azithromycin (p. 221·2).
Bacterial infections.

A2-Z *ATOZ, India.*
Glucose (p. 2068·3); sucrose (p. 2096·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

AZ 15 *Procter & Gamble, Ital.*
Sodium chloride (p. 1795·1); benzalkonium chloride (p. 1737·1); azulene (p. 2452·1).
Oral hygiene; gum protection.

AZ Combination *Nipro, Jpn.*
Sodium gualenate (p. 1887·1); sodium bicarbonate (p. 1781·1).
Mouth and throat disorders.

AZ Ofteno *Valta, Chile; Sophia, Mex.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

AZ Protezione Gengive *Procter & Gamble, Ital.*
Triclosan (p. 1773·2); pyrophosphate; sodium fluoride (p. 2089·2).
Gum disorders.

AZ Tartar Control *Procter & Gamble, Ital.*
Sodium fluoride (p. 2089·2); potassium and sodium pyrophosphates (p. 2619·3).
Dental tartar; dental caries prophylaxis.

AZ Verde *Procter & Gamble, Ital.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Aza 20 *Pharmacore, Indon.*
Azelaic acid (p. 1695·1).
Acne.

Aza Cap *Moraceae, India.*
Vitamins; selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2); lycopene (p. 2546·2).

Azacard *Oftalmi, Venez.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Azacid *Fako, Turk.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azacleus *Nucleus, Neth.†*
Azithromycin ethanolate (p. 221·2).
Bacterial infections.

Azacortid *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Azacortine *Omega, Belg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Azactam *BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Chile†; BMS, China; BMS, Cz.†; BMS, Denm.; BMS, Fin.; Sanofi-Aventis, Fr.; BMS, Ger.†; BMS, Gr.; BMS, India; BMS, Irl.; BMS, Ital.†; Eisai, Jpn; BMS, Norw.; BMS, NZ; BMS, Philipp.†; BMS, Pol.†; BMS, Port.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, UK; BMS, USA; BMS, Venez.*
Aztreonam (p. 224·1).
Gram-negative bacterial infections.

Azadose *Pfizer, Fr.*
Azithromycin (p. 221·2).
Tuberculosis prophylaxis in immunocompromised patients with HIV.

Azadus *Zydus Cadila, Thai.*
Azathioprine (p. 1940·3).
Transplant rejection; rheumatoid arthritis.

Azafalk *Falk, Ger.; Falk, Neth.*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.

Azafor *Sofar, Ital.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azafrine *Korea United, Singapore.*
Azathioprine (p. 1940·3).
Rheumatoid arthritis; transplant rejection.

Azaglax *GSK, Austria.†*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azahexal *Sandoz, Austral.†*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.

Azaimun *Mibe, Ger.; Dermapharm, Switz.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azaleptin *Organika, Rus.*
Clozapine (p. 1057·3).
Schizophrenia; bipolar disorder; behaviour disorders.

Azalia *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Spain.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Azalide *Bunker, Braz.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azamedac *Medac, Ger.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azamun *Ascent, Austral.; Leiras, Fin.; Douglas, Malaysia; Douglas, NZ; Pharmaplan, S.Afr.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders; immunosuppressant.

Azanem *Biochimico, Braz.*
Aztreonam (p. 224·1).

Azanplus *GSK, Mex.†*
Ranitidine bismuth citrate (p. 1883·3).
Peptic ulcer.

Azantac *GSK, Fr.; GSK, Mex.; PCO, Neth.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; dyspepsia; gastrointestinal haemorrhage; gastritis.

Azap *Chandra Bhagat, India.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azaphen *Makiz-Pharma, Rus.*
Pipofezine (p. 446·2) or pipofezine hydrochloride (p. 446·2).
Depression.

Azapin
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.
KVZ, Ukr.
Clozapine (p. 1057·3).
Schizophrenia.
Pharmathen, Gr.
Mirtazapine (p. 436·1).
Depression.

Azapress *Cooper (Κοπερ), Gr.; Aspen, S.Afr.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azaprin *Nolver, Venez.*
Azathioprine (p. 1940·3).
Transplant rejection.

Azaprine *Teva, Cz.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders; immune thrombocytopenia.

Aza-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.

Azaran *Hemofarm, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Azard *Pharma-Tech, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azarek *Sandoz, Switz.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azarga *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hung.; Alcon, Irl.; Alcon, Ital.; Alcon, Malaysia; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, Singapore; Alcon, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK.*
⊗Brinzolamide (p. 2005·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Azaro *Dexter, India.*
Vitamins; minerals.

Azaron
Note: this name may be used for preparations of different composition.
Cinetic, Arg.; Sanova, Austria; Chefaro, Ger.; Omega, Neth.; Omega, Spain.
Tripelennamine hydrochloride (p. 642·3).
Bites and stings; urticaria; hypersensitivity reactions.
Omega, Belg.
Diphenhydramine hydrochloride (p. 626·2).
Pruritus; skin irritation.

Azaro-Z *Dexter, India.*
Vitamins; zinc (p. 2126·1).

Azasan *Salix, USA.*
Azathioprine (p. 1940·3).
Rheumatoid arthritis; transplant rejection.

AzaSite *Inspire, USA.*
Azithromycin (p. 221·2).
Bacterial conjunctivitis.

Azathiodura *Mylan, Denm.*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.

Azathioregio *Heumann, Denm.*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.

Azatill *Prodotti, Braz.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azatrilem *Teva, Mex.*
Azathioprine (p. 1940·3).
Immunosuppressant.

Azatrim *Tabuk, Neth.†*
Mirtazapine (p. 436·1).
Depression.

Azatyl *Remedina, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Azauk *Aamorb, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azax *Nobel, Turk.; Nobel, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azbir *Birz, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azclear *Ego, Austral.*
Azelaic acid (p. 1695·1).
Acne.

Aze *Tai Guk, Singapore.*
Zinc oxide (p. 1729·1); aloe vera (p. 1693·2); vitamin E (p. 2119·1).
Nappy rash; skin irritation.

Azecar *Bago, Arg.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Azectol *Help, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Azed *Sigman, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Azedose *Alapis, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Azee *Cipla, Hong Kong; Cipla, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azeflo *Lupin, India.*
⊗Azelastine hydrochloride (p. 617·1); fluticasone propionate (p. 1638·1).

Azegud *Biosync, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azela *Siu Guan, Philipp.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Azelac *Med-One, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Azelan *Intendis, Braz.*
Azelaic acid (p. 1695·1).
Acne.

Azelast *Sun, India.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis; allergic rhinitis.

Azelaxine *Velka, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Azelderm *Kleva, Gr.; Abbott, Turk.*
Azelaic acid (p. 1695·1).
Acne.

Azelex *Allergan, USA.*
Azelaic acid (p. 1695·1).
Acne.

Azeloc *Symbiotic, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azelone *Korea United, Philipp.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis; allergic skin disorders; urticaria.

Azeltin *Biofarma, Turk.*
Azithromycin (p. 221·2).
Bacterial infections.

Azelvin *Novartis, Norw.†; Novartis, Swed.†*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Azema *Homme de Fer, Fr.†*
Boldo (p. 2458·3); peppermint (p. 1877·1); melissa (p. 2552·3); kinkeliba (p. 2538·2); coriander (p. 2486·3); ash (p. 2450·1); tilia (p. 2631·3); fumitory (p. 2508·2).
Digestive disorders.

Azenam *Med-One, Gr.; Aristo, India.*
Aztreonam (p. 224·1).
Gram-negative bacterial infections.

Azenil *Pfizer, Israel.*
Azithromycin (p. 221·2).
Bacterial infections.

Azep *iNova, Austral.; Health Vision, China; Meda, Hong Kong; Zydus, India; Transfarma, Philipp.; Meda, Port.; Asta Medica, Singapore.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Azepam *Macrophar, Thai.†*
Diazepam (p. 1063·2).
Anxiety; musculoskeletal spasm; psychoneurotic disorders; autonomic disorders.

Azepezil *Ranbaxy, Swed.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Azeptin *Eisai, Jpn.*
Azelastine hydrochloride (p. 617·1).
Asthma; allergic rhinitis; pruritus.

A-Zerax *Asian Pharm, Thai.*
Diazepam (p. 1063·2).

Azet Plus *Moraceae, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Azetavir *Tecnofarma, Mex.*
Zidovudine (p. 1024·2).
Viral infections.

Azforin *Unichem, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azi *Sigma, Braz.; Sandoz, Hung.; InnoGen, Philipp.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziatop *Elea, Arg.*
Omeprazole (p. 1867·2).
Heartburn.

Azi-Ator *Ananta, Ukr.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Azibact *Ipca, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azibactron *Proton, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azibest *Blue Cross, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azi-Big *Bestochem, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azibiot *KRKA, Cz.; KRKA, Hung.; Mavi, Mex.; KRKA, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Azibiotic *Baliarda, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Azicid *Generics, Hung.†; Zentiva, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Azicin *Darnitsa, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azicine *Stada, Hong Kong.*
Azithromycin (p. 221·2).
Bacterial infections.

Azicip *Cipla, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziclav *Spirig, Switz.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Azicos *Symbiosis, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azicure *Radicura, India.*
Azithromycin (p. 221·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Azid
Note: this name may be used for preparations of different composition.
Admac, India.
Injection: Ceftazidime (p. 250·2).
Bacterial infections.
Indi, India.
Oral liquid; syrup; tablets: Azithromycin (p. 221·2).
Bacterial infections.

Azidac Plus *Eurolab, Arg.*
Amino acids; vitamins; minerals; ubidecarenone.
Dietary supplement.

Aziderm *Micro, India.*
Azelaic acid (p. 1695·1).
Acne.

Azidex *Sandoz, Austria.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Azidral *Silanes, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Azidraw *Q Check, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azifarm *Mediapharm, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azifast *Ipca, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azifem *Fem Care, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azifine *Glenmark, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azigram *United Lifecare, India; Vivax, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Azikab *Lancer, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azikare *Anglo-French Drugs, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azikil *Maxo, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azileb *Leben, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azilect *Teva, Austria; Lundbeck, Belg.; Teva, Canad.; Teva, Cz.; Teva, Denm.; Teva, Fin.; Lundbeck, Fr.; Teva, Ger.; Teva, Gr.; Teva, Hung.; Lundbeck, Irl.; Teva, Israel; Lundbeck, Ital.; Teva, Mex.; Teva, Neth.; Teva, Norw.; Teva, Pol.; Teva, Port.; Teva, Rus.; Lundbeck, S.Afr.; Lundbeck, Spain; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.; Lundbeck, UK; Teva, USA.*
Rasagiline mesilate (p. 912·3).
Parkinsonism.

Azilide *Micro, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azilife *Aqualife, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azilin *Lincoln, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziliv *Delta, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Azilline *Spirig, Switz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Azilup *Lupin, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azilva *Takeda, Jpn.*
Azilsartan (p. 1313·2).
Hypertension.

Azim *BL, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azimac *Mandar, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azimakrol *Roemmers-Klinos, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Azimax
Note: this name may be used for preparations of different composition.
Cipla, India; Pfizer, Port.†; Arrow, S.Afr.
Azithromycin (p. 221·2).
Bacterial infections.

Azimed *Cimed, Braz.; Daquimed, Port.; Arterium, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azimef *Yung Shin, Philipp.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Azimit *Interpharma, Chile.*
Azithromycin (p. 221·2).
Bacterial infections.

Azimix *Ativus, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azimune *Sun, India.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azimycin *Polfa Tarchomin, Pol.; Micro, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Azin *Indo Pacific, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azina *Zota, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azinc *Arkopharma, Fr.; Arkopharma, UK.*
Vitamins; minerals.
A range of dietary supplements.

Azinex *Aronex, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azinix *Khandelwal, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azinorm *Azine, India.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Azinorm C *Azine, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).

Azinorm O *Azine, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Azinort *Norton, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azinostil *EMS, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azinova *Bombay Tablet, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azinox *Ekohimteh, Rus.*
Praziquantel (p. 164·1).
Worm infections.

Azintra *Intra-Labs, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azintra-3 *Intra-Labs, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Azintra-AX *Intra-Labs, India.*
Ambroxol hydrochloride (p. 1654·3); azithromycin (p. 221·2).
Respiratory-tract infections.

Aziom *Zenon, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azipar *Molekule, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziphar *Alpharma, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Azipokyn *Misha, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azipos *Aglowmed, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziral *Hiral, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziram *Uniao Quimica, Braz.*
Aluminium hydroxide (p. 1817·2).
Antacid.

Azirid *Armour, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziriv *East African, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azirock *Ankom, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azirox *Pharmanel, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azirutec *Zwitter, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azis *Taurus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azisafe *UniOrange, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azisara *Sarabhai Piramal, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziset *Active, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azisia *Willow, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azison *Dr Alson, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azistar *Sanify, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azisym *Symbiosis, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitas *Intas, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziter *Gujarat Terce, India.*
Azithromycin (p. 221·2).
Bacterial infections.

AziTeva *Teva, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziteva *Teva, Mex.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azith *Aspen, Austral.; Zee, India; Siam Bheasach, Thai.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithom *Om Biotec, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithral *Verisfield, Gr.; Alembic, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithral Jun *Alembic, India.*
Ambroxol (p. 1654·3); azithromycin (p. 221·2).
Respiratory-tract infections.

Azithral XP *Alembic, India.*
Azithromycin (p. 221·2); fluconazole (p. 578·2); secnidazole (p. 947·3).
Vaginal infections.

Azithrin *Alet, Gr.; TO-Chemicals, Thai.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithro *Meda, Ger.†; Ind-Swift, India; M & H, Thai.; Sandoz, Ukr.; Sandoz, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithrobeta *Betapharm, Ger.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithrox *Farmstandart, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Azithrus *Sintez, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziton *Labesfal, Port.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azitone *Keshav, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitoz *ATOZ, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrac *Invision, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitral *Sanitas, Arg.; Shreya, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrin *Delta, Braz.; Pharmatech, India; Genexo, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrix *Pentafarma, Port.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitro *Acino, Switz.; Deva, Turk.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrocin *Pfizer, Ital.; Pfizer, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrogal *Sant Gall, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrogran *Legrand, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrohexal *Sandoz, Mex.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrolab *Multilab, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrolabsa *Labsa, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrolan *Lanpharm, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

AzitroLEK *Sandoz, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrolid *Minerva (Μινερβα), Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrom *Laboratorios Chile, Chile; SM, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitromax *Pfizer, Norw.; Pfizer, Swed.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitro-Mepha *Mepha, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitromicil *Greenpharma, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitromin *Farma, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitron *Cifarma, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrona *Klonal, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrop *Elfin, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrophar *Pharlab, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrosol *Luper, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitrotek *Deva, Turk.*
Azithromycin (p. 221·2).
Sexually transmitted infections.

Azitrox *Lamsa, Arg.; Zentiva, Cz.; Zentiva, Pol.; Zentiva, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitroxil *De Mayo, Braz.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azitsa *Akesiss, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azitus *Zuventus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azivar *Zota, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azivirus *Verisfield, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziwin *Bal, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aziwok *Wockhardt, India; Wockhardt, Rus.; Wockhardt, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azix *Alicon, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azixratio *Ratiopharm, Port.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azla *Candor, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azlaire *Schering-Plough, Mex.; Schering-Plough, Venez.*
Pranlukast (p. 1218·3).
Asthma; allergic rhinitis.

Azmacon *Armoxindo, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Azmacort *Sanofi-Aventis, Braz.†; Abbott, USA.†*
⊗Triamcinolone acetonide (p. 1649·1).
Asthma.

Azmag *Magnus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azmasol *Beximco, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Azmic *Emar, India.*
Azithromycin (p. 221·2).
Bacterial infections.

AZmycin *Invent, Singapore.*
Azithromycin (p. 221·2).
Bacterial infections.

Aznam *Jodas, Rus.*
Aztreonam (p. 224·1).
Bacterial infections.

Azo *Tulip, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azo Gantrisin *Roche, Turk.*
Sulfafurazole (p. 364·1); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Azobac *Medinova, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azodac *Eurolab, Arg.*
Levocarnitine fumarate (p. 2053·2); fructose (p. 2068·2); acetylcarnitine (p. 2053·2); vitamin E (p. 2119·1); citric acid (p. 2480·3); vitamin C (p. 2110·3).
Dietary supplement.

Azo-F *Allenge, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Azofen *Lark, India.*
Ketotifen (p. 631·3).
Hypersensitivity reactions; asthma.

Azofen-T *Lark, India.*
Ketotifen (p. 631·3); theophylline (p. 1229·3).

Azoflu *Vianex (Βιανεξ), Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Azoflune *Tecnimede, Port.†*
Fluconazole (p. 578·2).
Fungal infections.

Azofur *Ivax, Mex.†*
Phenazopyridine (p. 124·3).
Urinary-tract pain.

Azogel *Phytopharm, Ukr.*
Azelaic acid (p. 1695·1).
Acne; rosacea.

Azogen *Degorts, Mex.*
Phenazopyridine hydrochloride (p. 124·3); nalidixic acid (p. 328·3).
Bacterial infections of the urinary tract.

Azol
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; LCH, Hong Kong†; Merck, Indon.; Alphapharm, Malaysia†; Mylan, NZ; Alphapharm, Singapore.†
⊗Danazol (p. 2263·2).
Benign breast disorders; endometriosis; menorrhagia; hereditary angioedema; gynaecomastia; pre-operative endometrial thinning.
DR Johns, India.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.
Kern, Spain.
Topical powder: Sulfanilamide (p. 368·1).
Skin infections.

Azolac Folico *Nycomed, Arg.*
Folic acid (p. 2063·1).
Anaemias; folic acid supplement.

Azolen *Stratus, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Azolid *Scoshia, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azolife *Dexter, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azolin *Biochem, India.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Azoline *Fischer, Israel.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Azolmen *Menarini, Ital.*
Bifonazole (p. 573·3).
Fungal skin infections.

Azom
Note: this name may be used for preparations of different composition.
Finecure, India.
Syrup; tablets: Azithromycin (p. 221·2).
Bacterial infections.
United Biotech, India.
Injection: Aztreonam (p. 224·1).
Bacterial infections.

Azo-Mandelamine *Pfizer, Venez.*
Methenamine mandelate (p. 323·1); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Azo-Max *Unipharm, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Azomax *Max, India; Kocak, Turk.*
Azithromycin (p. 221·2).
Bacterial infections.

Azomid *Restan, S.Afr.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Azomir *Sanofi Synthelabo, Philipp.†*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain and irritation.

Azomycin *Royale, Philipp.; Julphar, UAE.*
Azithromycin (p. 221·2).
Bacterial infections.

Azomyr *Schering-Plough, Cz.; MSD, Gr.; MSD, Irl.; Essex, Ital.; Schering-Plough, Mex.; MSD, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.; Menarini, Spain.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria; allergic skin disorders.

Azona
Note: this name may be used for preparations of different composition.
Keton, Mex.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.
Orion, Fin.
Trazodone hydrochloride (p. 451·1).
Psychoses; depression; insomnia.
Torrent, India.
Ziprasidone hydrochloride (p. 1115·2).
Schizophrenia; mania.

Azone *NB, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azonutril *Sanofi-Aventis, Gr.*
Amino acids.
Parenteral nutrition.

Azo-O *Allenge, India.*
Alprazolam (p. 1035·2); omeprazole (p. 1867·2).

Azopet *Vista, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azopi *Generics, Israel.*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection; rheumatoid arthritis.

Azoprine *VHB, India.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Azopt *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, Ukr.; Alcon, USA; Alcon, Venez.*
⊗Brinzolamide (p. 2005·1).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Azoptic *Alcon, S.Afr.*
⊗Brinzolamide (p. 2005·1).
Glaucoma; ocular hypertension.

Azor *Aspen, S.Afr.*
Alprazolam (p. 1035·2).
Anxiety.
Daiichi Sankyo, USA.
Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2).
Hypertension.

Azoran *RPG, India.*
Azathioprine (p. 1940·3).
Organ transplantation; auto-immune disorders.
Columbia, Mex.†
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Azoren *Pfizer, Hong Kong; Pfizer, Singapore.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Azo-S *Allenge, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Azosilin *Fako, Turk.*
Ampicillin trihydrate (p. 218·2); phenazopyridine hydrochloride (p. 124·3).
Bacterial infections.

Azo-Standard *Amerifit, USA.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Azostar *Gentech, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azostat *Ranbaxy, India.*
1 Capsule, fluconazole (p. 578·2); 2 tablets, tinidazole (p. 949·2).
Vaginal infections.

Azostix *Bayer, Austral.†; Bayer Diagnostics, UK; Bayer, USA.*
Test for urea in blood.

Azotesin *Santen, Jpn.*
Sodium gualenate (p. 1887·1).
Conjunctivitis; keratitis; blepharitis; scleritis.

Azotum *Venus, India.*
Aztreonam (p. 224·1).
Bacterial infections.

Azo-Uronalin *Vitae, Mex.*
Nalidixic acid (p. 328·3); phenazopyridine (p. 124·3).
Urinary-tract infections.

Azovox *TP, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Azovir
Note: this name may be used for preparations of different composition.
ICN, Pol.†
Zidovudine (p. 1024·2).
HIV infection.
Medikon, Indon.†
Aciclovir (p. 964·1).
Herpesvirus infections.

Azo-Wintomylon *Sanofi-Aventis, Mex.*
Nalidixic acid (p. 328·3); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Azoxina *Unipharma, Gr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Azpencil *Degorts, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Azras *Rass, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azrea *Cinerea, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azro *Piramal, India; Eczacibasi, Turk.; Eczacibasi, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Azro AM *Piramal, India.*
Ambroxol (p. 1654·3); azithromycin (p. 221·2).
Respiratory-tract infections.

Azrol *Natco, India.*
⊗Salmeterol (p. 1224·1).
Obstructive airways disease.

Azromax *Gerard, Irl.*
Azithromycin (p. 221·2).
Bacterial infections.

Aztatin *Sun, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Aztec *Ind-Swift, India.*
Ranitidine (p. 1882·1) or ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Aztec-D *Ind-Swift, India.*
Ranitidine hydrochloride (p. 1882·1); domperidone (p. 1838·1).

Aztemin *Apotex, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Aztil *Offenbach, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Aztin *Laksun, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Aztor *Sun, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Aztor Asp *Sun, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Aztor EZ *Sun, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Aztram *Shanxi, Philipp.*
Aztreonam (p. 224·1).
Bacterial infections.

Aztreo *Zydus, India.*
Aztreonam (p. 224·1).
Bacterial infections.

Aztreobol *Abolmed, Rus.*
Aztreonam (p. 224·1).
Bacterial infections.

Aztreotic *Kleva, Gr.*
Aztreonam (p. 224·1).
Bacterial infections.

Aztrin *Pharos, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Aztrolen *Degorts, Mex.*
Astemizole (p. 616·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Aztus *Emcure, India.*
Azithromycin (p. 221·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Azucalen *Herbapol Wroclaw, Pol.*
Calendula (p. 2465·2); chamomile (p. 2474·1).
Vulvovaginal disorders.

Azucort *Collins, Mex.†*
⊗Triamcinolone (p. 1648·3).
Skin disorders.

Azufracid *Bajer, Arg.*
Sulfur (p. 1721·1); sodium thiosulfate (p. 1576·1).
Soap substitute.

Azugaguru *Sawai, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Azukon *Torrent, Braz.; Torrent, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Azukon M *Torrent, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Azul *Pond's, Philipp.*
21 tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive; menstrual disorders.

Azulan *Herbapol Pruszkow, Pol.; Herbapol Wroclaw, Pol.; Phytofarm Kleka, Pol.*
Chamomile (p. 2474·1).
Skin and mucous membrane inflammation; gastrointestinal spasm.

Azulavine *Nitten, Jpn.*
Sodium gualenate (p. 1887·1).
Conjunctivitis; keratitis; blepharitis; scleritis.

Azulemic *Ono, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Azulemin *Nipro, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Azulenal *Agepha, Austria.*
Guaiazulene (p. 2523·1).
Hypersensitivity disorders; skin disorders; mucus membrane inflammation.

Azulene *Teva Kowa, Jpn; Wakamoto, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders; conjunctivitis; keratitis; blepharitis; scleritis.

Azulène *Gifrer Barbezat, Fr.†*
Guaiazulene (p. 2523·1).
Conjunctival irritation.

Azulene.Glutamine *Eisai, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Azulenol *Teva, Hung.*
Guaiazulene (p. 2523·1).
Skin disorders.

Azuleone *Isei, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Azulfidina *Pfizer, Mex.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; rheumatoid arthritis.

Azulfidine *Pfizer, Arg.; Pfizer, Chile; Pfizer, Ger.; Santen, Jpn; Pharmacia Upjohn, USA; Pfizer, Venez.*
Sulfasalazine (p. 1890·1).
Rheumatoid arthritis; inflammatory bowel disease.

Azulfin *Apsen, Braz.*
Sulfasalazine (p. 1890·1).
Rheumatoid arthritis; ulcerative colitis; Crohn's disease; ankylosing spondylitis.

Azulina *Llorens, Spain.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Azulix *Torrent, Braz.; Torrent, India; Torrent, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Azulix MF *Torrent, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Azulon
Note: this name may be used for preparations of different composition.
Szama, Arg.
Guaiazulene (p. 2523·1).
Scalp disorders.

Azuloxa *Kotobuki, Jpn.*
Egualen sodium (p. 1840·3).
Gastric ulcer.

Azulsix *Farmalider, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Azunol *Shinyaku, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders; gastric ulcer; gastritis.

Azuprostat *Sandoz, Ger.†*
Sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Azur
Note: this name may be used for preparations of different composition.
Biores, Ital.
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.
Steiner, Ger.†
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Azur compositum *Steiner, Ger.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain.

Azurette *Watson, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 tablets, inert.
Sequential oral contraceptive.

Azurex *Teva, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Azuril *Pharmanel, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Azurinse *Tsuruhara, Jpn.†*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Azuron *Liferpal, Mex.*
Nalidixic acid (p. 328·3); phenazopyridine (p. 124·3).
Urinary-tract infections.

Azuseptol *Hasco-Lek, Pol.*
Chamomile (p. 2474·1).
Gastrointestinal spasm; skin and mucous membrane inflammation.

Azutan *Arex, Venez.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat inflammation.

Azuthidrona *Lafedar, Arg.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Azvig *Madhav, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azvit *Ikapharmindo, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Vitamin and mineral supplement.

Azy *Uniroyal, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azycin
Note: this name may be used for preparations of different composition.
GPO, Thai.
Azithromycin (p. 221·2).
Bacterial infections.
TP, Thai.†
Aciclovir (p. 964·1).
Herpesvirus infections.

Azycyna *Polfa Pabianice, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Azydrop *Thea, Spain.*
Azithromycin (p. 221·2).
Bacterial eye infections.

Azylin *Zota, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azymol *Drugtech, Chile.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Azyr *SIFI, Ital.*
Vitamins; minerals.

Azyrol *Sons, Mex.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Azysafe *Overseas, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azystate *Haledew, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azytan *Medilat, Gr.†*
Azithromycin (p. 221·2).
Bacterial infections.

Azyter *Thea, Austria; Thea, Denm.; Thea, Fin.; Thea, Fr.; Thea, Ger.; Thea, Irl.; Thea, Neth.; Thea, Norw.; Thea, Pol.; Thea, Port.; Thea, Swed.; Thea, Thai.; Spectrum, UK.*
Azithromycin (p. 221·2).
Bacterial infections.

Azyth *Sandoz, Philipp.*
Azithromycin (p. 221·2).
Bacterial infections.

Azyxin *Centaur, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azyxin Plus *Centaur, India.*
Ambroxol hydrochloride (p. 1654·3); azithromycin (p. 221·2).
Respiratory-tract infections.

Azza *Wintech, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Azzalure *AB-Consult, Austria; Galderma, Belg.; Ipsen, Denm.; Ipsen, Fin.; Galderma, Fr.; Galderma, Ger.; Ipsen, Irl.; Ipsen, Neth.; Galderma, Norw.; Ipsen, Port.; Ipsen, Spain; Galderma, Swed.; Galderma, UK.*
Botulinum A toxin (p. 2017·1).
Glabellar lines.

Azzol-S *SJA, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

B Com *Siomond, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

B1-6-12 *Chinta, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

B1-12-15 *Italmex, Mex.*
Pangamic acid (p. 2582·1); cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2).
Anaemias; neuralgia; neuritis.

B_2-400 *Bio-Tech, USA.*
Vitamin B_2 (p. 2104·3).

3B *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Anaemias; neural disorders.

B-6 *Pharmasant, Thai.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

B6-50 *Utopian, Thai.*
Pyridoxine (p. 2105·3).
Vitamin B_6 supplement.

B-9 *Juggat, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

B-12
Note: this name may be used for preparations of different composition.
Biological E, India.
Injection: Dexpanthenol (p. 2582·2); nicotinamide (p. 2083·1); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Biological E, India.
Syrup: Dexpanthenol (p. 2582·2); lysine hydrochloride (p. 2079·3); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Mason Natural, USA.
Vitamin B_{12} (p. 2107·2).
Vitamin B_{12} deficiency.
21st Century, USA.
Vitamin B_{12} (p. 2107·2); calcium (p. 1783·1).

B_{12} Ankermann *Worwag, Ger.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

B1 B6 B12 *Utopian, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

3B Beer Belly Buster *Bioglan, Austral.†*
Garcinia (p. 2510·2); chromium trichloride (p. 2055·3); pectin (p. 2200·3); methylcellulose (p. 2197·3); guarana (p. 2648·2); St John's wort (p. 449·1).
Obesity.

B Chabre *Sopharm, Fr.†*
Vitamin B substances (p. 2102·3).
Tonic.

B Complex *GNLD, Canad.; Natures Sunshine, Canad.; Pharmetics, Canad.; CCM, Malaysia; Vesco, Thai.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

B-100 Complex *TP, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3); nicotinamide (p. 2083·1).
Vitamin B deficiency; peripheral neuritis.

B Complex 50 *Jamieson, Hong Kong.*
Vitamin B substances (p. 2102·3); choline (p. 2055·2); inositol (p. 2533·2).
Dietary supplement.

B Complex 100 *Bioglan, Austral.†*
Vitamin B (p. 2102·3).
Dietary supplement.

B Complex C *Adams, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B Complex P *PP Lab, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

B Complex plus C *Pharmetics, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B Complex with Vitamin C *Jamieson, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B Compound *Gahler, Canad.†; Swiss Herbal, Canad.†*
Vitamin B substances (p. 2102·3).

B Compound with C *Viva, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B Compound with Vitamin C *Cherish, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B_{12} Depot-Hevert *Hevert, Ger.†*
Hydroxocobalamin acetate (p. 2107·3).
Vitamin B_{12} deficiency.

B12 Depot-Rotexmedica *Rotexmedica, Ger.*
Hydroxocobalamin acetate (p. 2107·3).
Vitamin B_{12} deficiency.

B Dexol *Pharmasant, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

B-12 Dots *Twinlab, USA.*
Vitamin B_{12} (p. 2107·2).
Vitamin B_{12} deficiency.

B Feron *Greater Pharma, Thai.*
Vitamins; minerals.

B & O Supprettes No. 15A *Amerifit, USA.*
Prepared opium (p. 111·3); powdered belladonna extract (p. 2453·3).
Ureteral spasm pain.

B & O Supprettes No. 16A *Amerifit, USA.*
Prepared opium (p. 111·3); powdered belladonna extract (p. 2453·3).
Ureteral spasm pain.

B7 Plus *Genesis, India.*
Biotin (p. 2052·2); cupric oxide; manganese sulfate (p. 2081·2); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

B-9 Plus *Juggat, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

B plus C *Novapharm, Canad.†; Vita Health, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B12 Rotexmedica *Rotexmedica, Ger.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

B Six P *PP Lab, Thai.*
Pyridoxine hydrochloride (p. 2105·3).
Dietary supplement.

B-12 SL *Carlson, USA.*
Vitamin B_{12} (p. 2107·2).
Vitamin B_{12} deficiency.

B12 Steigerwald *Steigerwald, Ger.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

B-9 Tetra *Juggat, India.*
Biotin (p. 2052·2); carbohydrates; glucose; folic acid (p. 2063·1); vitamin C (p. 2110·3).
Nutritional supplement.

B Twelve P *PP Lab, Thai.*
Cyanocobalamin (p. 2107·2).
Anaemias.

B_6 Vicotrat *Heyl, Ger.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

B_6 Vigen *Aksu, Turk.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency; isoniazid neuropathy; idiopathic sideroblastic anaemia; premenstrual syndrome.

Ba Le *Yong He, China.*
Matrine.

Ba Hong *Bei Te, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Ba Ping Te Jia *Duoburuifei, China.*
Verapamil hydrochloride (p. 1522·1).
Supraventricular arrhythmias.

Ba Qi *Da Heng, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ba Qu Ting *Bei Da Gao Ke Hua Tai, China.*
Haemocoagulase atrox.

Ba Quan *Bei Te, China.*
Inosine (p. 2533·1).

Ba Sha *Bei Te, China.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Ba Tai *Bei Te, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ba Ti *Bei Te, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Ba Xin *Bei Te, China.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Ba Yang Pu Rui *Rui Yang, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Babee *Pfeiffer, USA.*
Benzocaine (p. 1980·2); cetalkonium chloride (p. 1741·3); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1).
Oral lesions.

Babic *Teva, Israel.†*
Sodium bicarbonate (p. 1781·1).
Infant colic.

Babicum *Natur Produkt, Pol.*
Ribwort plantain (p. 2604·2); honey (p. 2072·1).
Cough; catarrh.

Babigoz Crema Protettiva *Guigoz, Ital.*
Zinc oxide (p. 1729·1); chamomile (p. 2474·1); wheat-germ oil (p. 2647·1).
Nappy rash.

Babi-Lyte *SEA Pharm, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Babinoks *Sistas, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Babix
Note: this name may be used for preparations of different composition.
GSK, Arg.
Liquid paraffin (p. 2191·2).
Skin cleansing.

Madaus, Austria.
Cajuput oil (p. 2464·1); pumilio pine oil (p. 2591·1); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders.

Babix-Inhalat N *Mickan, Ger.*
Eucalyptus oil (p. 2501·2); Norway spruce oil.
Respiratory-tract disorders.

Baby A + D *Vitamed, Israel.†*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).
Vitamin A and D supplement.

Baby AF *Sam-On, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Baby Anbesol *Pfizer, USA.*
Benzocaine (p. 1980·2).
Teething pain.

Baby Brand Antacid *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).

Baby Cough with Antihistamine *Atlantic, Hong Kong†; Atlantic, Thai.*
⊗Acetic acid (p. 2426·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); glycerol (p. 2517·2); tolu syrup (p. 1679·2); chlorphenamine maleate (p. 620·3).
Cough.

Baby Cough Syrup Atlantic
Note: this name may be used for preparations of different composition.
Atlantic, Thai.
⊗Acetic acid (p. 2426·3); ammonium chloride (p. 1656·1); glycerol (p. 2517·2); sodium citrate (p. 1781·2); tolu syrup (p. 1679·2).
Cough.

Baby Cough Syrup Greater
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Baby Drops *Carlson, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Baby Faces *Energizer, Canad.†*
SPF 50: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Baby Fact B *Gemepe, Arg.*
Colfosceril palmitate (p. 2599·2).
Neonatal respiratory distress syndrome.

Baby Gas-X *Novartis Consumer, USA.*
Simeticone (p. 1886·2).
Infant colic.

Baby Gel *Mediline, Israel.*
Benzocaine (p. 1980·2).
Teething pain.

Baby Gripe *TO-Chemicals, Thai.†*
Dill oil (p. 2493·2); sodium bicarbonate (p. 1781·1).
Infant bloating; flatulence.

Baby Gum *Rafa, Israel.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Mouth pain.

Baby Luuf *Apomedica, Austria; Volmix, Hung.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); majoram oil (p. 2576·3).
Respiratory-tract disorders; cough; cold symptoms; respiratory-tract congestion.

Baby Luuf ätherische Öle *Apomedica, Austria.*
Eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); thyme oil (p. 2630·3).
Respiratory-tract disorders.

Baby Orajel *Church & Dwight, Canad.; Hand-Prod, Pol.†; Del, USA.*
Benzocaine (p. 1980·2).
Teething pain.

Baby Orajel Tooth and Gum Cleanser *Del, USA.*
Poloxamer 407 (p. 2202·1); simeticone (p. 1886·2).
Dental hygiene.

Baby Paste *Vitamed, Israel.†*
Zinc oxide (p. 1729·1); starch (p. 2095·1).
Nappy rash; skin irritation.

Baby Paste + Chamomile *Vitamed, Israel.†*
Chamomile (p. 2474·1); sage (p. 2608·3); calamine (p. 1697·2); zinc oxide (p. 1729·1).
Skin disorders.

Baby Saline *Rekah, Israel.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

Baby Sebamed *Bayer, Mex.*
A range of skin cleansers and emollients.

Sebapharma, Thai.
A range of skin cleansers, emollients, and shampoos.

Baby Shield Medicated Cleanser *Hoe, Malaysia.*
Tar (p. 1723·3).
Pruritus; inflammatory skin disorders.

Baby Shield Plus *Hoe, Malaysia; Hoe, Singapore.*
Chlorhexidine gluconate (p. 1743·3).
Nappy rash.

Baby Sunscreen *Energizer, Canad.†*
SPF 50: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Baby Sure *Uniao Quimica, Braz.*
Pregnancy test (p. 2596·1).

Baby Tear Free *Energizer, Canad.*
SPF 50 lotion; SPF 60 lotion: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Energizer, Canad.
SPF 60 spray: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Baby Zanzara *Bouty, Ital.†*
Ammonia (p. 2441·2); almond oil (p. 2437·1).
Bites.

BabyBIG *California Department of Health, USA.*
Botulism immunoglobulin (p. 2380·2).
Botulism in infants.

Babycheck-Plus *Veda, Fr.†*
Pregnancy test (p. 2596·1).

Babycold *Pharmasant, Thai.†*
Brompheniramine maleate (p. 618·1).
Allergic rhinitis; hypersensitivity reactions.

Babydent *Stada, Cz.†; Stada, Hung.†; Stada, Ukr.†*
Benzocaine (p. 1980·2).
Teething pain.

Baby-Drax *Uniao Quimica, Braz.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Diarrhoea; oral rehydration.

Babyfen *Qualiphar, Belg.†*
Fennel oil (p. 2503·3).
Infant colic.

Babygella *Rottapharm, Fr.*
Cream; paste: Zinc oxide (p. 1729·1).
Emollient; nappy rash.

Rottapharm, Ital.
Cream: Calendula (p. 2465·2); chamomile (p. 2474·1); zinc oxide (p. 1729·1).
Barrier preparation.

Rottapharm, Ital.
Topical paste: Squalane (p. 2213·3); sweet almond oil (p. 2437·1); lactic acid (p. 2539·1); zinc oxide (p. 1729·1).
Barrier preparation.

Babygencal *Qualiphar, Belg.†*
Chamomile (p. 2474·1).
Teething pain.

Babygesic *Meyer, India.*
Paracetamol (p. 115·1).
Pain; fever.

Babylac *Bactolac, India.*
Lactobacillus (p. 2596·3).

Babylax *Infectopharm, Ger.; Kite (Κιτε), Gr.; Bausch & Lomb, Irl.; Fleet, Philipp.*
⊗Glycerol (p. 2517·2).
Constipation; bowel evacuation.

Babymed *Cimed, Braz.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); zinc (p. 2126·1).
Nappy rash.

Babyneo *Neo Quimica, Braz.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).

Babynos *Penta, Hung.; Dentinox, Rus.*
Coriander (p. 2486·3); chamomile (p. 2474·1); fennel (p. 2503·2).
Infant colic; flatulence; gastrointestinal disorders.

Babynose *Cooper (Κοπερ), Gr.*
Sodium chloride (p. 1795·1).

Babypasmil *Lafedar, Arg.*
Dicycloverine hydrochloride (p. 1834·2).

Babyprin *Pfizer, Turk.*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Babyrhinol *Aventis, Turk.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders; sinusitis.

Babyrinolo *Bruno, Ital.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Respiratory-tract disorders.

Babyrinolo Feb Dol *Bruno, Ital.*
Paracetamol (p. 115·1).
Fever; pain.

Babys Own Cough Syrup *Mentholatum, S.Afr.†*
Ammonium chloride (p. 1656·1); camphor (p. 2466·2).
Cough.

Babys Own Tummy Tablets *Hyde, S.Afr.†*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; constipation.

Babysan Powder *Szama, Arg.*
Alcloxa (p. 1692·2).
Hyperhidrosis; skin disorders.

Babysiton *Faes, Spain.†*
Cetylpyridinium chloride (p. 1743·1); zinc oxide (p. 1729·1).
Skin disorders.

Babyskin *Albephar, Venez.*
Barrier preparation.

Babysteril *Eurospital, Ital.*
Zinc oxide (p. 1729·1); almond oil (p. 2437·1); wheat-germ oil (p. 2647·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Napkin rash.

Baby-Tex *Sertex, Arg.*
Vitamin A (p. 2098·3); zinc oxide (p. 1729·1); boric acid (p. 2459·3).
Skin disorders.

Babytrim *TO-Chemicals, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Babyzim *Sam-On, Israel.*
⊗Pepsin (p. 2586·1); sodium glycerophosphate (p. 2519·2); nicotinic acid (p. 2083·1).
Constipation; flatulence.

Bac Liq *Lepine, Canad.*
Benzalkonium chloride (p. 1737·1).

Bacacil *Rottapharm, Ital.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Bacagen *Boniscontro & Gazzone, Ital.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Bacal *Nakornpatana, Thai.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Bacamcillin *CCM, Malaysia.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Bacamine *Marching, Hong Kong.†*
Calamine (p. 1697·2); camphor (p. 2466·2); diphenhydramine (p. 626·1); menthol (p. 2553·2); zinc oxide (p. 1729·1).

Bacard *Chew, Thai.†*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin and wound disinfection.

Bacard Antiseptic *Chew, Thai.*
Chlorhexidine gluconate (p. 1743·3).
Skin, hand, and wound disinfection.

Bacasint *Piam, Ital.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

bacbutINH *Armoxindo, Indon.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Bacbutol *Armoxindo, Indon.*
Ethambutol (p. 296·1).
Tuberculosis.

Baccidal *Kyorin, Jpn.*
Norfloxacin (p. 333·3).
Bacterial infections.

Bacda-B *Millimed, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Inflammatory fungal skin infections.

Bacfar *Elofar, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bacfuron *Bernabo, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Bach Rescue Remedy *Bach, UK.*
Helianthemum nummularium; clematis vitalba; impatiens glandulifera; prunus cerasifera; ornithogalum umbellatum.

Bacibact *Orion, Fin.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Baciclox *Alembic, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Bacicoline *CSP, Fr.*
⊗Bacitracin (p. 225·3); colistimethate sodium (p. 275·3); hydrocortisone acetate (p. 1640·1).
Eye disorders.

Bacicoline-B *Daleco, Neth.*
⊗Colistimethate sodium (p. 275·3); bacitracin (p. 225·3); hydrocortisone acetate (p. 1640·1).
Inflammatory ear infections.

Bacid
Note: this name may be used for preparations of different composition.
Erfa, Canad.; Insight, USA.
Lactobacillus rhamnosus (p. 2596·3).
Stomatitis; diarrhoea; dietary supplement.

Bacidal
Note: this name may be used for preparations of different composition.
Charoon Bhesaj, Thai.
Mupirocin (p. 327·2).
Gram-positive bacterial skin infections.

Medichem, Philipp.
Co-trimoxazole (p. 277·3).
Bacterial infections.

Baciderm *SM, Venez.*
Bacitracin (p. 225·3).
Skin infections.

Baciderma *Confar, Port.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial skin infections.

Bacidermina *Greenpharma, Braz.*
Neomycin (p. 329·3); bacitracin (p. 225·3).
Skin infections.

Bacidin *Tack Fung, Hong Kong.†*
Chlorhexidine (p. 1743·2).

Bacifim *Medipharma, Arg.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Bacigen *Cazi, Braz.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Skin infections.

Bacigyl *Aristo, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Baci-IM *X-Gen, USA.*
Bacitracin (p. 225 3).
Bacterial infections.

Bacıject *SteriMax, Canad.*
Bacitracin (p. 225·3).
Bacterial infections.

Bacilexin *Danlex, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Bacillin *New Research, Ital.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Bacillol *Bode, Ger.†*
⊗Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1); 1,6-dihydroxy-2,5-dioxahexane (p. 1750·3); mecetronium etilsulfate (p. 1760·1).
Surface disinfection.

Bacillol AF *Bode, Ger.*
⊗Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1).
Surface disinfection.

Bacillol Foam *Bode, Ger.*
⊗Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1); N-alkylaminopropylglycine.
Surface disinfection.

Bacillol plus *Bode, Ger.*
Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); glutaral (p. 1753·2).
Surface disinfection.

Bacillol Tissues *Bode, Ger.*
⊗Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1).
Surface disinfection.

Bacillol Wipes *Bode, Ger.*
⊗Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1).
Surface disinfection.

Bacilor *Alfa Wassermann, Fr.*
Lactobacillus casei var *rhamnosus* (p. 2596·3).
Diarrhoea.

Bacimex
Note: this name may be used for preparations of different composition.
Claris, Philipp.; Claris, Rus.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; amoebiasis; protozoal infections.

Bacimox *Alembic, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Bacimycin
Note: this name may be used for preparations of different composition.
Actavis, Norw.
Bacitracin zinc (p. 225·3); chlorhexidine acetate (p. 1743·2).
Infected skin disorders.

Bacimyxin *Pharmascience, Canad.; Hind Wing, Hong Kong.†*
Polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3).
Bacterial skin infections.

Bacin *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bacina *Belfar, Braz.*
Bacitracin (p. 225·3); neomycin (p. 329·3).

Bacipen *Alembic, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Bacipro *Claris, Philipp.; Biogalenic, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Bacirom *Aristo, India.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Bacisporin *Alcala, Spain.†*
⊗Bacitracin zinc (p. 225·3); hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected skin disorders.

Bacitin *Pharmascience, Canad.*
Bacitracin (p. 225·3).
Bacterial skin infections.

Bacitopic Compuesto *Laboratorios Chile, Chile.†*
⊗Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); antazoline phosphate (p. 615·3); xylometazoline hydrochloride (p. 1680·1).
Cold symptoms; rhinitis; sinusitis.

Bacitracina Zimaia *Wynn, Port.*
Bacitracin (p. 225·3); vitamin A (p. 2098·3).
Bacterial skin infections.

Bacitracin-N *YSP, Malaysia.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected burns; infected wounds.

Bacitraycin Plus *First Aid Research, USA.*
Bacitracin zinc (p. 225·3); pramocaine hydrochloride (p. 1993·3).
Minor wounds.

Back Pain-Off *Medique, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); magnesium salicylate (p. 85·2).
Pain.

Backache *Potter's, UK.*
Oral mixture: Bearberry (p. 2453·2); juniper (p. 2537·1); clivers (p. 2481·2); taraxacum (p. 2625·3); lappa (p. 2540·1).
Backache.

Potter's, UK.
Tablets: Gravel root (p. 2522·1); hydrangea root (p. 2528·1); buchu (p. 2461·3); bearberry (p. 2453·2).
Backache.

Backache with Arnica *Hylands, Canad.†*
Arnica montana (p. 2447·2); benzoicum acidum (p. 1738·2); colchicum autumnale; sulfur (p. 1721·1).
Homoeopathic preparation.

Backache Maximum Strength Relief *BMS, USA.*
Magnesium salicylate (p. 85·2).

Backache Relief *Herbal Concepts, UK.*
Buchu (p. 2461·3); bearberry (p. 2453·2); parsley piert (p. 2584·1).
Backache.

Back-Aid *Rougier, Canad.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Bac-Killer *GK Chemical, Canad.*
Benzalkonium chloride (p. 1737·1).

Back2Norm *Biomiicron, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

BackOsamine *Health Perception, UK.*
⊗Glucosamine (p. 2515·3); chondroitin (p. 2476·1); bromelains (p. 2460·3); turmeric (p. 2218·1).
Back disorders.

Baclac *Raproos, India.*
Lactobacillus (p. 2596·3).

Baclan *Medi Globe, India.*
Baclofen (p. 2014·3).
Spasticity.

Baclasia-CG *Willow, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Baclasia-CN *Willow, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).
Infected skin disorders.

Baclecin *XL, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Baclin *Biomax, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Baclo *Douglas, Austral.†*
Baclofen (p. 2014·3).
Skeletal muscle spasm.

Baclodox *Indeco, Arg.†*
Baclofen (p. 2014·3).
Skeletal muscle spasm or spasticity.

Baclon *Uniao Quimica, Braz.*
Baclofen (p. 2014·3).
Skeletal muscle spasm.

Baclopar *Gerard, Irl.*
Baclofen (p. 2014·3).
Spasticity.

Baclosal *Unipharm, Israel; M & H, Thai.*
Baclofen (p. 2014·3).
Spasticity.

Baclosan *Polpharma, Rus.*
Baclofen (p. 2014·3).
Skeletal muscle spasm.

Bacmax *Biomax, India.*
Baclofen (p. 2014·3).
Spasticity.

Bacmin *Marnel, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Bacnorm *Bactolac, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; gastro-oesophageal reflux; premedication.

Bacnutri *Grisi, Mex.*
Cod-liver oil (p. 2056·3).
Vitamin A and D supplement.

Bacopa Complex *Mediherb, Austral.*
Bacopa (p. 2452·1); schisandra (p. 2611·2); Siberian ginseng (p. 2614·3); rosemary oil (p. 2607·3).
Anxiety; tonic.

Bacopa & Ginkgo Compound *Phytomedicine, Austral.*
Bacopa (p. 2452·1); ginkgo biloba (p. 2512·3); rosemary (p. 2607·2).
Mental function impairment.

Bacotan *TO-Chemicals, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Bacperazone *Gepach, Rus.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Bacpiryl *Parggon, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bacproin *Best, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bacprotin *Prodotti, Braz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bacqure *Nanxin, China; Ranbaxy, Malaysia.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Ranbaxy, Thai.
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Bacrocin *Valeant, Braz.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Bacskin *Serral, Mex.*
Mupirocin (p. 327·2).

Bac-Sulfitrin *Ducto, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactacin *Osoth, Thai.*
Nitrofurazone (p. 333·1).
Burns; wounds; skin ulcers.

Bactalin *Genepharm, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Bactaz *PSA, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Bactazon *Graha, Indon.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Bactedene *Macrophar, Thai.*
Povidone-iodine (p. 1767·1).
Disinfection of skin, wounds, burns, and umbilicus.

Bactelan *Quimica y Farmacia, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bacter *Cubit, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bacteracin *Teuto, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Bacteric *Sandoz, Mex.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bacterix *Gifrer Barbezat, Fr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Bacter-M *Cubit, India.*
Ofloxacin (p. 334·3); metronidazole (p. 936·1).

Bacternil *Maffioli, Ital.*
Sulfadiazine silver (p. 362·3).
Burns; ulcers; wounds.

Bacter-NZ *Cubit, India.*
Ofloxacin (p. 334·3); nitazoxanide (p. 942·2).

Bacterol *Recalcine, Chile.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bacter-OZ *Cubit, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Bacter-TZ *Cubit, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Bactesyn *Kalbe, Indon.*
Sultamicillin (p. 369·1).
Bacterial infections.

Bacteval *Valmor, Venez.*
Sulfamethizole (p. 365·1); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Bactex *Union Drug, Thai.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Bactezoa-LB *Stedman, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1); *Lactobacillus sporogenes* (p. 2596·3).

Bacticef
Note: this name may be used for preparations of different composition.
Mitim, Ital.
Cefaclor (p. 232·3).
Bacterial infections.

Neon, India.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Bacticel *Bago, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bacticep *M & H, Thai.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Bacticid-CS *Tablets, India.*
Cefoperazone (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Bacticide *Euro-Med, Philipp.*
Povidone-iodine (p. 1767·1).
Wounds; skin cleanser; skin disinfection; vaginal cleansing.

Bacti-Cleanse *Pedinol, USA.*
Benzalkonium chloride (p. 1737·1).
Skin cleanser.

Bacticlor *Ranbaxy, UK.*
Cefaclor (p. 232·3).
Bacterial infections.

Bacticort
Note: this name may be used for preparations of different composition.
Montpellier, Arg.
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Bacticort Complex *Montpellier, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); nystatin (p. 590·3).
Infected skin disorders.

Bactide *Collins, Mex.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactident *UPSA Conseil, Fr.†*
Sodium perborate (p. 1770·1); sodium carbonate (p. 2617·3); sodium phosphate (p. 1791·2); sodium laurilsulfate (p. 2210·3).
False teeth hygiene.

Bactidol *Johnson & Johnson, Hong Kong; Pfizer, Indon.†; Johnson & Johnson, Philipp.; Johnson & Johnson, Singapore.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Bactidox *Unison, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Bactiflox *Mepha, Malaysia; Mepha, Ukr.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bacti-Foam *Ecolab, Canad.*
Triclosan (p. 1773·2).

Bactifree *BioFemme, Philipp.*
Mupirocin (p. 327·2).
Skin infections.

Bactifren *Montpellier, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Bactigen *FDC, India.*
Gentamicin (p. 304·2).
Bacterial eye infections.

Bactigent *Filadams, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bactigram *Magis, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Bactigras *Smith & Nephew, Austral.; Smith & Nephew, Canad.†; Smith & Nephew, Ger.; Smith & Nephew, Ital.; Smith & Nephew, Malaysia; Smith & Nephew, Philipp.; Smith & Nephew, S.Afr.; Smith & Nephew, Thai.; Smith & Nephew, UK.*
Chlorhexidine acetate (p. 1743·2).
Wounds; burns; ulcers; scalds.

Bactigyn *CCD, Fr.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3); sodium hyaluronate (p. 2526·2); *Lactobacillus crispatus; Lactobacillus reuteri* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Maintenance of vaginal pH.

Bactil *Omega, Spain.*
Ebastine (p. 628·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Bactilen *Cryopharma, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactilene *Casen Fleet, Ital.†*
Dimethyldidecylammonium chloride; enoxolone (p. 54·2).
Genital irritation.

Bactilina *Richmond, Arg.*
Ampicillin (p. 218·2).
Bacterial infections.

Bactille *More, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactimed
Note: this name may be used for preparations of different composition.
3DDD, Belg.
Amoxicillin (p. 216·2).
Bacterial infections.

MedGen, Philipp.†
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Bactimox *Taurus, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Bactimox Plus *Taurus, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Bactin *Siam Medicare, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactine
Note: this name may be used for preparations of different composition.
Bayer Consumer, Canad.
Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).
Wound cleansing; skin disorders.

Miles, USA.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Bactine Antiseptic *Miles, USA.*
Lidocaine (p. 1988·1); benzalkonium chloride (p. 1737·1).
Skin disorders.

Bactine Pain Relieving Cleansing *Bayer, USA.*
Topical spray: Lidocaine (p. 1988·1); benzalkonium chloride (p. 1737·1).

Bactio Rhin *Nycomed, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Bactio Rhin Prednisolona *Nycomed, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); prednisolone (p. 1645·2).
Allergic rhinitis; sinusitis.

Bactipoz *Renata, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Bactiprox *Erlimpex, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bactirom *Sanbe, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Bactisan *Bentfield, Canad.†*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Bactisona
Note: this name may be used for preparations of different composition.
LDA, Arg.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Lafedar, Arg.†
⊗Ketoconazole (p. 585·3); hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2).
Skin infections.

Bactisone *Yash, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).

Bactisporin *Immunopreparat, Rus.*
Bacillus subtilis.
Gastrointestinal infections; bacterial vaginosis.

Bacti-Stat *Ecolab, Canad.*
Triclosan (p. 1773·2).

Bactisubtil *Sanofi-Aventis, Rus.*
Bacillus cereus IP 5832.
Gastrointestinal disorders.

Bacti-Uril *Bago, Arg.*
Co-trimoxazole (p. 277·3); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Bactiv *YSS, Philipp.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bactiver *Maver, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bactizef *LBS, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Bactizon *Sanbe, Philipp.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Bactob *Solitaire, India.*
Tobramycin (p. 380·1).
Bacterial infections.

Bactocef
Note: this name may be used for preparations of different composition.
Siomond, India.
Cefuroxime (p. 255·2); sulbactam (p. 360·1).
Bacterial infections.

Bactocep *Bactolac, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Bactocide *Larose, Canad.*
Benzalkonium chloride (p. 1737·1).
Disinfection.

Bactocilina *Lazar, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Bactocin
Note: this name may be used for preparations of different composition.
Bunker, Braz.
Mupirocin (p. 327·2).
Bacterial skin infections.

Hormona, Mex.
Ofloxacin (p. 334·3).
Bacterial infections.

Scharper, Ital.
Lactobacillus plantarum (p. 2596·3).
Vulvovaginitis.

Bactoclav *Micro, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

OEP, Philipp.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bactoderm
Note: this name may be used for preparations of different composition.
Hertz, Braz.
Neomycin (p. 329·3); bacitracin (p. 225·3).
Skin infections.

Ikapharmindo, Indon.
Mupirocin (p. 327·2).
Bacterial skin infections.

Innotech, Rus.
Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3).
Skin and mucous membrane disinfection.

Bactof *Svizera, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bactofen *Teleflex, Ital.*
Benzoxonium chloride (p. 1739·2).
Disinfection of skin, mucous membranes, and instruments.

Bactoff *3a, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bactoff-OZ *3a, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Bactoflox
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
Ofloxacin (p. 334·3).
Bacterial infections.

Bactogard *Indaco, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Bactoil *Plurisystem, Ital.*
Emollient soap substitute.
Dry skin disorders.

Bactokil *Chinta, Thai.*
Mupirocin (p. 327·2).
Bacterial skin infections; burns; wounds.

Bactokina *Mavi, Mex.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Bactoklav *Micro Labs, Ukr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Bactol *Avmor, Canad.*
Benzalkonium chloride (p. 1737·1).

Bactolyte *Bactolac, India.*
Calcium lactate (p. 1784·1); lactobacillus (p. 2596·3); glucose (p. 2068·3); magnesium sulfate (p. 1787·3); potassium chloride (p. 1793·2); monobasic sodium phosphate (p. 1791·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Bactomax *Cristalia, Braz.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Bactomet *Win-Medicare, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Bactonis *Neiss, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Bactopen
Note: this name may be used for preparations of different composition.
EMS, Braz.
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Bactophase *Ecofarm, Ital.*
Soap substitute.

Bactoprim *Charoen, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactoprim Combi *Combiphar, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactopumon *Cinfa, Spain.*
Tolu balsam (p. 1679·2); bromhexine hydrochloride (p. 1656·3); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Bactoquin *Otsira, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bactorus *Icarus, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Bactoscrub *Vitamed, Israel.†*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Bactosept *Vitamed, Israel.†*
Chlorhexidine gluconate (p. 1743·3).
Burn cleansing; disinfection of instruments and skin; wound cleansing.

BactoShield *Amsco, USA.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Bactosul *Pharma-Tech, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Bactox
Note: this name may be used for preparations of different composition.
Innotech, Fr.
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Bactpar *Bactolac, India.*
Paracetamol (p. 115·1).
Pain; fever.

Bactpar Plus *Bactolac, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold symptoms.

Bactracid *Apogepha, Ger.†*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Bactral *Bactolac, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Bactramin *Chugai, Jpn.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bactrazine *Smith & Nephew, S.Afr.*
Sulfadiazine silver (p. 362·3).
Infected ulcers and burns.

Bactrias *Wockhardt, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bactricid *Soho, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactricide *Medicpharma, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Wounds.

Bactrim *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Fr.; Piramal, India; Roche, Indon.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, Ukr.; Roche, USA.*
Co-trimoxazole (p. 277·3).
Pneumocystis pneumonia; toxoplasmosis; bacterial infections; protozoal infections; paracoccidioidomycosis; actinomycosis; nocardiosis.

Bactrim Balsamico *Roche, Arg.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Bactrim Compositum *Roche, Mex.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Bactrimel *Roche, Chile; Roche, Gr.; Roche, Neth.; Roche, Venez.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; nocardiosis; blastomycosis; toxoplasmosis.

Bactrinol *Nestor, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis; nocardiosis.

Bactrisan *Sanval, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bactrizol
Note: this name may be used for preparations of different composition.
Behrens, Venez.
Metronidazole (p. 936·1).
IMA, Braz.†; Corsa, Indon.
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bactroban *GSK, Fr.; GSK, Hong Kong; GSK, Jpn; Beecham, Port.*
Mupirocin calcium (p. 327·2).
Elimination of nasal staphylococci; bacterial skin infections.
GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; SKF, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Gr.; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; Stiefel, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; SmithKline Beecham, USA; GSK, Venez.
Mupirocin (p. 327·2) or mupirocin calcium (p. 327·2).
Bacterial skin infections; elimination of nasal staphylococci; infected burns and wounds.

Bactrocin
Note: this name may be used for preparations of different composition.
LBS, Thai.
Netilmicin sulfate (p. 331·1).
Bacterial infections.
Zyg, Philipp.
Mupirocin (p. 327·2).
Bacterial skin infections.

Bactrocine *Help, Gr.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Bactroneo *Neo Quimica, Braz.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Bactropin *Cimed, Braz.; Sons, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bactzyme *Bactolac, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Baculamyl *Mylan, Swed.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bacup *Keshav, India.*
Liquorice (p. 1853·2).

Bacxal *Pharmacare, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Baczole *San Marino, Philipp.†; Nakornpatana, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Baderol *Specifar (Σπεσιφαρ), Gr.*
Dimenhydrinate (p. 625·2).

Badiaga Complexe No 47 *Lehning, Fr.*
Badiaga; spongia tosta; baryta carbonica (p. 2452·2); lycopus virginicus (p. 2462·2); kalium iodatum (p. 2336·3); cerium oxalicum (p. 1826·2).
Homoeopathic preparation.

Badyket
Note: this name may be used for preparations of different composition.
Menarini, Arg.
Bemiparin (p. 1314·2).
Thromboembolic disorders.

BAF *Medicine Products, Thai.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

BAF-2 *Medicine Products, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B_1, B_6, and B_{12} deficiency.

Bafen *Indeco, Arg.*
Baclofen (p. 2014·3).
Spasticity.

Baflox *Galeno, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Bafucin *McNeil, Fin.; McNeil, Swed.*
Benzocaine (p. 1980·2); gramicidin (p. 308·3); cetylpyridinium chloride (p. 1743·1); dichlorobenzyl alcohol (p. 1750·2).
Mouth and throat disorders.

Bages *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Bago B1 B6 B12 *Bago, Arg.*
Cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Dietary supplement.

Bago B6 B12 Folic *Bago, Arg.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Vitamin B deficiency.

Bagociletas *Bago, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Bagociletas con Anestesia *Bago, Arg.†*
Nitrofurantoin (p. 332·1); tetracaine dibudinate (p. 1996·3).
Mouth and throat disorders.

Bagoco *Pefanic, Gr.†*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Bagoderm *Bago, Arg.*
Sodium acexamate (p. 2427·3); cetrimonium bromide (p. 1742·3).
Burns; cracked nipples; nappy rash; ulcers; wounds.

Bagodilol *Bago, Rus.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Bagohepat *Bago, Arg.; Armstrong, Mex.†*
Cynara (p. 2490·3); dehydrocholic acid (p. 2492·1).
Liver disorders; digestive disorders.

Bagomet *Montpellier, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bagomet Plus *Montpellier, Rus.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bagomicina *Bago, Chile.*
Minocycline (p. 324·3).
Bacterial infections.

Bagomigral *Bago, Chile.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Bagomol *Armstrong, Mex.†*
Molgramostim (p. 1156·2).
Neutropenia.

Bagopril *Bago, Rus.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Bagopront *Armstrong, Mex.†*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; sexual deviation; precocious puberty; androgen-associated acne, alopecia, hirsutism, and seborrhoea in women.

Bagotam *Armstrong, Mex.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Bagotanilo *Armstrong, Mex.†*
Carboplatin (p. 759·1).
Ovarian cancer.

Bagothyrox *Montpellier, Rus.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer.

Bagovir *Armstrong, Mex.†*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Bagovit A *Bago, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Bago, Chile.
Vitamin A palmitate (p. 2098·3).
Skin disorders.

Bagovit A Plus *Bago, Arg.*
⊗Vitamin A palmitate (p. 2098·3); triamcinolone acetonide (p. 1649·1).
Skin disorders.

Bagovit Avant *Bago, Arg.*
Vitamin A (p. 2098·3); methylsilanol manuronate (p. 2088·3); dimethylsilanol hyaluronate (p. 2088·3).
Skin disorders.

Bagovit Solar *Bago, Arg.*
A range of sunscreen preparations.

Bagren *Serono, Braz.†*
Bromocriptine mesilate (p. 895·3).
Lactation inhibition; parkinsonism; menstrual disorders; female infertility; acromegaly; prolactinomas; benign breast disorders; polycystic ovary.

Bagton *Loeffler, Mex.*
Clioquinol (p. 273·1).
Skin infections; burns.

Bahutcef-SL *Sipra, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Bai De *Global, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Bai Ao *Bai Ao, China.*
Lumbrokinase.

Bai Chang *Tongyong, China.*
⊗Bumetanide (p. 1329·1).
Oedema.

Bai Da Tu *Otsuka, China.*
⊗Procaterol hydrochloride (p. 1219·1).
Bronchospasm.

Bai Ding *Rui Yang, China.*
Piperacillin sodium (p. 340·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Bai Duo Rui *Jiang Shi, China.*
Amino acids.

Bai Er Luo *Sine, China.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris.

Bai Fu Li *Wu Zhou Tong, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Bai Fu Long *Tian Fu, China.*
Sodium ferulate.

Bai Hong *Lukang Chenxin, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Bai Jia Hei *Bayer, China.†*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Bai Jie Min *Mei Luo, China.*
Zaleplon (p. 1114·3).
Insomnia.

Bai Jie Yi *A Hua, China.*
Interleukin-2 (p. 810·1).

Bai Jin Shi Er Kang *BMS, China.*
Vitamins; minerals.

Bai Kang *Simcere, China.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bai Ke Di *Tiancheng, China.*
Potassium dehydroandrographolide succinate.

Bai Ke Kang Di *Bai Ke, China.*
Propylene glycol alginate sodium.

Bai Ke Luo Wei *Bai Ke, China.*
Ligustrazine phosphate.

Bai Ke De Rui *Bai Ke, China.*
Azithromycin lactobionate.
Bacterial infections.

Bai Ke Sha *Bai Ke, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Bai Ling *Xia Du, China.*
Adenosine cyclophosphate.
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Bai Ni Duo *WuJi, China.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Bai Rui De *San Lian, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Bai Rui *Yuan Heng, China.*
Ethylenediamine diaceturate.

Bai Sai Nuo *Beijing Union, China.*
Bicyclol (p. 2457·1).
Chronic hepatitis.

Bai Shi Xin *Pu Luo Kang Yu, China.*
Ubenimex (p. 878·2).

Bai Si Ping *Ao Hua, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bai Te Xi *Kexing, China.*
Recombinant human granulocyte colony stimulating factor.

Bai Tong *Qing Yu Tang, China.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Bai Wei Le *Wan Te, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Bai Wei Qing *Wan Te, China.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Cold symptoms; allergic rhinitis.

Bai Ye Xing *Wei Kang, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Bai Yue *Zhong Sheng, China.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Baietta *Lilly, Mex.*
Exenatide (p. 471·1).
Diabetes mellitus.

Baihongyou *Xinhua, China.*
Clarithromycin (p. 266·2).
Bacterial infections.

Baikadent *Herbapol Wrodaw, Pol.*
Skullcap (p. 2617·1).
Mouth disorders.

Baikaderm *Herbapol Wroclaw, Pol.*
Allantoin (p. 1693·1); skullcap (p. 2617·1).
Skin irritation.

Baimoting *Gedeon Richter, China.†*
Bromocriptine mesilate (p. 895·3).
Menstrual disorders; female infertility; hyperprolactinaemia; acromegaly; lactation inhibition; benign breast disorders; parkinsonism.

Bain de Bouche Lipha *Merck Medication Familiale, Fr.†*
Veratrol (p. 2644·2); menthol (p. 2553·2); resorcinol (p. 1718·3).
Mouthwash.

Bain extra-doux *Widmer, Switz.*
Ichthammol (p. 1705·3); chamomile (p. 2474·1); guaiazulene (p. 2523·1).
Skin disorders.

Bain de Soleil *Procter & Gamble, USA.*
SPF 4: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Bain de Soleil All Day *Procter & Gamble, USA.*
SPF 4; SPF 8: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Procter & Gamble, USA.
SPF 15; SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Bain de Soleil Color *Procter & Gamble, USA.*
SPF 8+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Procter & Gamble, USA.
SPF 15+; SPF 30+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Bainto *TP, Thai.*
Gamma-aminobutyric acid (p. 2509·2).
Mental function impairment; amnesia; speech disorders; palsy; hypertension.

Bajaten *Merck Serono, Arg.*
⊗Indapamide (p. 1409·2).
Hypertension.

Sanitas, Chile.
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Bajaten D *Sanitas, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension.

Bajoffin *Dallas, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).

Bakamol *Medicpharma, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Bakamsilin *Kocak, Turk.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Baknil *Psychotropics, India.*
⊗Bromelains (p. 2460·3); glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3); turmeric (p. 2218·1); vitamin C (p. 2110·3).

Bakol *Arkopharma, Fr.*
Phytosterols (p. 1471·2); polycosanols.
Hypercholesterolaemia.

Baktar *Shionogi, Jpn.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Baktisef *Sanovel, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Baktocillin *CNP, Ger.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bakton *Sandoz, Turk.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Bakumondoto *Tsumura, Jpn.*
Ophiopogon tuber; pinellia tuber; jujube; liquorice (p. 1853·2); ginseng (p. 2513·3); brown rice.
Traditional Kampo medicine.

Balacall DM *Centurion, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Balacet *Cornerstone, USA.†*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Balacol *Torrent, India.*
Balsalazide disodium (p. 1820·2).

Baladex *Demo, Gr.; Aflofarm, Pol.*
Guaifenesin (p. 1666·2); theophylline (p. 1229·3).
Obstructive airways disease.

Balafen *Adeka, Turk.*
Ibuprofen (p. 68·2).

Balamine *Umeda, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Balamol *Fada, Arg.†*
Bromazepam (p. 1041·2).

Balanca *Grunenthal, Austria; Gedeon Richter, Ger.†*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Balance
Note: this name may be used for preparations of different composition.
Douglas, Canad.
A range of vitamin and mineral preparations.

Fresenius Kabi, Turk.
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); sodium lactate (p. 1781·2); magnesium chloride (p. 1778·2); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Fresenius Medical, Canad.; Fresenius Medical, Ital.; Fresenius Medical, Port.
Calcium chloride (p. 1783·1); glucose (p. 2068·3); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemodialysis; peritoneal dialysis.

Fresenius Medical, Cz.; Fresenius Medical, Fin.; Fresenius Medical, Hung.; Fresenius Medical, Neth.; Fresenius Medical, Norw.; Fresenius Medical, Swed.
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose monohydrate (p. 2069·1) (p. 1778·2).
Peritoneal dialysis.

Fresenius Medical, Irl.†
A range of peritoneal dialysis solutions (p. 1778·2).

Ocean Nutrition, Canad.†
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Balance Activ RX *BBI, UK.*
Lactic acid (p. 2539·1); glycogen (p. 2519·2).
Bacterial vaginosis.

Balance Elastin E *Bio-Pharmaceuticals, Malaysia.*
Elastin (p. 2483·2); vitamin E (p. 2119·1).
Dry skin disorders.

Balance Glucosa Calcio *Fresenius Medical, Spain.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

balance glucose calcium *Fresenius Medical, Denm.*
Glucose (p. 2068·3); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2) (p. 1778·2).
Peritoneal dialysis.

Balance Sunblock *Bio-Pharmaceuticals, Malaysia.*
SPF 35: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Balanced B *Pharmetics, Canad.; Vitality, Canad.*
Vitamin B substances (p. 2102·3).

Balanced Cal-Mag *Quest, UK.*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3).

Balanced Irrigating Salt Solution *Teva, Israel.*
Electrolytes (p. 1775·1).
Irrigation of eyes, ears, nose, and throat.

Balanced Salt Solution *Hospira, Canad.; Euro-Med, Philipp.; Abbott, USA; Akorn, USA; Bausch & Lomb, USA.*
Electrolytes (p. 1775·1).
Eye irrigation.

Balancid Novum *Meda, Denm.; Meda, Fin.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastro-oesophageal reflux; heartburn.

Balans *Labomed, Chile.†*
Betacarotene (p. 2051·1); alpha tocopherol (p. 2119·1); ascorbic acid (p. 2110·3).
Vitamin supplement.

Balanse *Cadila, India.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Balansol *Teva, Hung.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium acetate (p. 1781·1); sodium malate; sorbitol (p. 2092·1).
Fluid and electrolyte disorders.

Balarm *SF, Ital.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Balarpan *Ergofarm, Rus.*
A heparinoid (p. 1401·1).
Eye disorders.

Balbek *Provit, Mex.†*
Dextromethorphan (p. 1660·1).
Cough.

Balcobal *Samarth, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Balcor *Baldacci, Braz.*
Diltiazem hydrochloride (p. 1359·2).
Arrhythmias; angina pectoris; hypertension.

Balderm *Bal, India.*
⊗Betamethasone valerate (p. 1624·1); chlorocresol (p. 1748·1); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1).
Infected skin disorders.

Baldmin *Mintlab, Chile.*
Pipenzolate bromide (p. 1878·1); phenobarbital (p. 535·2).

Baldorm *Klein, Ger.†*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Baldracin *Austroplant, Austria; Austroplant, Cz.†*
Valerian (p. 2640·2); peppermint leaf (p. 1877·1); melissa (p. 2552·3); lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Baldrian comp *Sanova, Austria.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders.

Baldrian-Dispert *Abcur, Swed.*
Valerian (p. 2640·2).
Anxiety; sleep disorders.

Baldrian-Dispert Nacht *Solvay, Ger.†*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Insomnia.

Baldriparan *Pfizer, Switz.*
Valerian (p. 2640·2); melissa (p. 2552·3); lupulus (p. 2546·1).
Nervous disorders.

Baldriparan pour la nuit *Pfizer, Switz.*
Valerian (p. 2640·2).
Sleep disorders.

Baldrivit *Rodisma, Ger.*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Baldurat *Pohl, Ger.†*
Valerian (p. 2640·2).
Sleep disorders; nervous tension.

Baléa *Norwood, Canad.†*
SPF 15: Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Norwood, Canad.†
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Balepton *Leovan, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Balfibro *Buxton, Arg.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain; fibromyalgia; anxiety.

Balgyl *Bal, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; Helicobacter pylori eradication.

Balianca *Faes, Spain.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Baliartrin *Baliarda, Arg.*
Glucosamine sulfate (p. 2515·3).
Musculoskeletal and joint disorders.

Baliartrin Duo *Baliarda, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Baliartrin Potasico *Baliarda, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Joint disorders.

Balidon *Lafi, Chile.*
Triazolam (p. 1112·3).
Sleep disorders.

Baligluc *Baliarda, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Baliin Q10 *Fortune Star, Indon.*
Ubidecarenone (p. 2637·1); safflower oil (p. 2086·3); fish oil (p. 1460·3); vitamin E (p. 2119·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); nicotinamide (p. 2083·1); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Balin *Atlantic, Malaysia; Atlantic, Singapore.*
Sulfadiazine (p. 361·3); trimethoprim (p. 381·2).
Bacterial infections.

Baling *Baiyunshan, China.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Balisa *Riemser, Ger.*
⊗Urea (p. 1727·3).
Keratinisation disorders.

Balisa VAS *Riemser, Ger.*
⊗Urea (p. 1727·3); tretinoin (p. 1725·2).
Keratinisation disorders.

Balivent *Baliarda, Arg.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Balkis *Dolorgiet, Ger.†*
Nasal drops; nasal spray: ⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Bal-Lanz *Bal, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Balleo *Bal, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Balm of Gilead *Potter's, UK.†*
Oral mixture: ⊗Balm of Gilead (p. 2594·2); squill (p. 1677·3); lobelia (p. 2323·2); lungwort.
Coughs.

Balmandol *Abbott, Turk.*
Almond oil (p. 2437·1); liquid paraffin (p. 2191·2).
Eczema; seborrhoeic dermatitis; psoriasis.

Mastelli, Ital.
Emollient.
Dry skin disorders.

Spirig, Cz.; Spirig, Switz.
Almond oil (p. 2437·1); light liquid paraffin (p. 2191·2).
Skin disorders.

Balmed Hermal *Almirall, Switz.*
Soya oil (p. 2092·3).
Bath additive; skin disorders.

Balmed Hermal F *Almirall, Switz.*
Arachis oil (p. 2446·1); liquid paraffin (p. 2191·2).
Bath additive; skin disorders.

Balmed Hermal Plus *Almirall, Switz.*
Soya oil (p. 2092·3); lauromacrogol 400 (p. 2194·1).
Bath additive; skin disorders.

Balmex
Note: this name may be used for preparations of different composition.
GSK, Braz.
Zinc oxide (p. 1729·1); liquid paraffin (p. 2191·2); beeswax (p. 2170·2); silicone (p. 2209·2); peru balsam (p. 2587·1).
Skin disorders.

Balmex Baby *Macsil, USA.*
Zinc oxide (p. 1729·1); peru balsam (p. 2587·1); corn starch (p. 2095·1); calcium carbonate (p. 1824·3).
Nappy rash.

Balmex Diaper Rash *Chattem, USA.*
Zinc oxide (p. 1729·1).
Nappy rash.

Balmex Emollient *Chattem, USA.*
Emollient and moisturiser.

Balmikel *Minorock Mandiri, Indon.†*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1).
Muscle and joint pain.

Balminil Codeine Night-Time+Expectorant *Rougier, Canad.*
Codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; respiratory-tract congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Balminil Codeine+Decongestant+Expectorant *Rougier, Canad.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Balminil Cough & Flu *Rougier, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Cough; congestion.

Balminil Decongest *Rougier, Canad.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Balminil DM *Rougier, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Balminil DM+Decongestant *Rougier, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; congestion.

Balminil DM+Decongestant+Expectorant *Rougier, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; congestion.

Balminil DM+Expectorant *Rougier, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Balminil Expectorant *Rougier, Canad.*
Guaifenesin (p. 1666·2).
Cough.

Balminil Nasal Decongestant *Rougier, Canad.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Balminil Night-Time *Rougier, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; congestion.

Balmosa *Forest Laboratories, UK.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); capsicum oleoresin (p. 2469·3).
Musculoskeletal, joint, and soft-tissue pain.

Balmox *Beecham, Port.; Meda, Switz.*
Nabumetone (p. 97·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Balmusa *Symbiotic, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Balmusa Plus *Symbiotic, India.*
⊗Alprazolam (p. 1035·2); propranolol hydrochloride (p. 1479·1).

Balneoconzen N *S & K, Ger.*
Soya oil (p. 2092·3).
Skin disorders.

Balneol *Alaven, USA.*
Perianal and vaginal cleanser.
Anal or vaginal irritation.

Balneovit *Mavena, Ger.*
Soya oil (p. 2092·3).
Bath additive; skin disorders.

Balnetar *Westwood-Squibb, Canad.†; Westwood-Squibb, USA.*
Coal tar (p. 1723·2).
Dermatitis; psoriasis; skin disorders.

Balneum
Note: this name may be used for preparations of different composition.
Hermal, Austria; Almirall Hermal, Ger.; Hermal, Hung.; Boots Healthcare, Irl.†; Neopharm, Israel; Almirall, UK.
Bath oil: Soya oil (p. 2092·3).
Dry skin disorders.

Hermal, Malaysia†; Almirall, Singapore; iNova, Singapore.
Cream; lotion: White soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry skin disorders.

Almirall, UK.
Cream: ⊗Urea (p. 1727·3); ceramide 3 (p. 1699·1).
Dry skin.

Hermal, Malaysia†; Hermal, Singapore.†
Bath oil: Light liquid paraffin (p. 2191·2).
Pruritus; dry skin; skin irritation.

Balneum F *Hermal, Austria; Almirall Hermal, Ger.; Neopharm, Israel.*
Arachis oil (p. 2446·1); light liquid paraffin (p. 2191·2).
Bath additive; skin disorders.

Balneum Hermal *Almirall Hermal, Cz.; Almirall, Ital.; Herrmann, Pol.†*
Soya oil (p. 2092·3).
Bath additive; dry skin disorders; pruritus.

Balneum Hermal F *Almirall Hermal, Cz.; Hermal, Hung.; Herrmann, Pol.†*
Arachis oil (p. 2446·1); liquid paraffin (p. 2191·2).
Bath additive; dry skin disorders; pruritus.

Balneum Hermal Forte *Almirall, Ital.*
Arachis oil (p. 2446·1); liquid paraffin (p. 2191·2).
Bath additive; skin disorders.

Balneum Hermal Plus *Almirall Hermal, Cz.; Hermal, Hung.; Herrmann, Pol.†*
Soya oil (p. 2092·3); lauromacrogol 400 (p. 2194·1).
Bath additive; dry skin disorders; pruritus.

Balneum Intensiv *Almirall, Malaysia.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Almirall, Singapore; iNova, Singapore.
Cream; lotion; wash: ⊗Urea (p. 1727·3); ceramide (p. 1699·1); physiological lipids.
Dry skin.

Hermal, Singapore.†
Shower gel: Soap substitute.

Balneum Intensiv Plus *Almirall, Malaysia; Almirall, Singapore; iNova, Singapore.*
⊗Lauromacrogol 400 (p. 2194·1); urea (p. 1727·3).
Dry skin disorders; pruritus.

Balneum Plus *Hermal, Austria; Almirall Hermal, Ger.; Neopharm, Israel.*
Soya oil (p. 2092·3); lauromacrogol 400 (p. 2194·1).
Bath additive; skin disorders; pruritus.

Boots Healthcare, Irl.†; Almirall, UK.
Bath additive: Soya oil (p. 2092·3); macrogol lauril ethers (p. 2193·3).
Pruritus; dry skin.

Almirall, UK.
Cream: ⊗Macrogol lauril ethers (p. 2193·3); urea (p. 1727·3).
Skin disorders.

Balnox *Guidotti, Gr.*
Lacidipine (p. 1417·3).
Hypertension.

Balofer *Bal, India.*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2).

Balpril *Baldacci, Port.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Bal-Riactin *Bal, India.*
Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Balsabit *Esteve, Spain.†*
Pramocaine hydrochloride (p. 1993·3).
Burns; insect bites; pruritus.

Balsam Mentholi compositum *Chema-Elektromet, Pol.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders; neuralgia.

Balsam Sakti *Konimex, Indon.†*
Menthol (p. 2553·2); camphor (p. 2466·2); clove oil (p. 2481·3); peppermint oil (p. 1877·1); cajuput oil (p. 2464·1).
Pain; nasal congestion.

Balsam Szostakowskiego (Vinilinum) *ICN, Pol.†*
Polyvinox.
Peptic ulcer; gastric hyperacidity; ulcers; wounds; chilblains; burns.

Balsamex *Konimex, Indon.†*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Muscle and joint pain.

Balsamico *Sella, Ital.*
Cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2).
Cold symptoms.

Balsamicum *Weleda, UK.*
Calendula (p. 2465·2); mercurialis perennis; peru balsam (p. 2587·1); stibium metallicum praeparatum (p. 2445·1).
Homoeopathic preparation.

Balsamina *Ahimsa, Arg.*
Hexylresorcinol (p. 1755·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Balsamina Kroner *Ceccarelli, Ital.*
Sulfogaiacol (p. 1678·1); mepyramine maleate (p. 635·1); hedera (p. 2536·2); cherry laurel (p. 2475·2).
Cough; catarrh.

Balsamo Alesida *Pfizer, Venez.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Muscle and joint pain.

Bálsamo Analgésico *Gestafarma, Port.*
Salicylic acid (p. 1719·1); benzyl nicotinate (p. 29·3); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Labesfal, Port.
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders.

Upsifarma, Port.
Methyl salicylate (p. 92·1); salicylic acid (p. 1719·1); menthol (p. 2553·2); capsicum oleoresin (p. 2469·3).
Formerly contained methyl salicylate, salicylic acid, menthol, and belladonna.
Musculoskeletal and joint pain.

Balsamo Analgesico
Note: this name may be used for preparations of different composition.
Pasteur, Chile.
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Bálsamo Analgésico Basi *Basi, Port.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders.

Balsamo Analgesico con Fenilbutazona *Sanitas, Chile.*
Phenylbutazone (p. 125·1); dimeticones (p. 2209·3); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and peri-articular pain.

Bálsamo Bengué *EMS, Braz.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Bálsamo Branco *Catarinense, Braz.*
Lavender (p. 2541·1); melissa (p. 2552·3); caraway (p. 2470·2); aniseed (p. 2444·2); cinnamon (p. 2479·2); clove (p. 2481·2); lemon (p. 2542·3); fennel (p. 2503·2).
Dyspepsia.

Balsamo Ifusa *Ifusa, Mex.*
Methyl salicylate (p. 92·1); pine oil (p. 2591·1); peppermint oil (p. 1877·1).
Musculoskeletal and joint pain.

Balsamo Italstadium *Falqui, Ital.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Balsamo Nordin *Nordin, Mex.*
Arnica (p. 2447·2); chamomile (p. 2474·1); methyl salicylate (p. 92·1).
Soft-tissue disorders.

Balsamo Nordin Unguento *Nordin, Mex.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Bálsamo Nostrum *Nostrum, Port.†*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2).

Balsamo Primi Denti *Sanofi-Aventis, Ital.*
Milk serum (p. 2125·2).
Teething pain.

Balsamo Sifcamina *Teofarma, Ital.*
Methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2).
Musculoskeletal disorders.

Balsamorhinol *Pierre Fabre, Fr.*
Chlorobutanol (p. 1747·2); menthol (p. 2553·2).
Nasal disorders.

Balsan
Note: this name may be used for preparations of different composition.
Pharma Investi, Chile.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Balsasulf *Fabra, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Balsedrina *IQFA, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Balsem Kopiva *Aspen Consumer, S.Afr.*
Balsam copaiba.
Bladder and kidney disorders.

Balsem Sulphuris *Aspen Consumer, S.Afr.*
Turpentine oil (p. 2636·3); precipitated sulfur (balsem sulfuris) (p. 1721·1).
Constipation.

Balsem Vita GEEL *Lennon, S.Afr.†*
Spike lavender oil (p. 2621·3); rosemary oil (p. 2607·3); clove oil (p. 2481·3); cassia oil (p. 2471·3); nutmeg oil (p. 2573·2); lemon oil (p. 2543·1); thyme oil (p. 2630·3).
Colic; flatulence.

Balsem Vita ROOI *Lennon, S.Afr.†*
Spike lavender oil (p. 2621·3); clove oil (p. 2481·3); cassia oil (p. 2471·3); nutmeg oil (p. 2573·2); lemon oil (p. 2543·1); rosemary oil (p. 2607·3); thyme oil (p. 2630·3).
Colic; flatulence.

Balsem Vita Wit *Aspen Consumer, S.Afr.*
Cassia oil (p. 2471·3); spike lavender oil (p. 2621·3); clove oil (p. 2481·3); nutmeg oil (p. 2573·2); thyme oil (p. 2630·3).
Colic; flatulence.

Balsibron *Liferpal, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Balsibron-C *Liferpal, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders with viscous mucus.

Balsoclase *UCB, Neth.†*
Pentoxyverine citrate (p. 1672·1).
Cough.

Balsoclase Antitussivum *Pierre Fabre Sante, Belg.*
Pentoxyverine (p. 1672·1), pentoxyverine citrate (p. 1672·1), or pentoxyverine hydrochloride (p. 1672·2).
Cough.

Balsoclase Compositum *UCB, Neth.†*
Pentoxyverine citrate (p. 1672·1); cineole (p. 2479·1); sodium citrate (p. 1781·2); terpin hydrate (p. 1678·2); thyme (p. 2630·2).
Cough.

Balsoclase Dextromethorphan *Pierre Fabre Sante, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Balsoclase Mucolyticum *Pierre Fabre Sante, Belg.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Balsoclase-E *Pierre Fabre, Neth.†*
Pentoxyverine (p. 1672·1); cineole (p. 2479·1).
Cough.

Balsofumine *Sanofi-Aventis, Fr.*
Peru balsam (p. 2587·1); sumatra benzoin (p. 2624·3); eucalyptus (p. 2501·1); lavender oil (p. 2541·1); thyme oil (p. 2630·3).
Respiratory-tract congestion.

Balsolan *Gemi, Pol.*
Peru balsam (p. 2587·1).
Ulcers; burns; chilblains.

Balsolène *Cooperation Pharmaceutique, Fr.*
Eucalyptus oil (p. 2501·2); niaouli oil (p. 2569·1); menthol (p. 2553·2); siam benzoin (p. 2614·3).
Respiratory-tract congestion.

Balsoprim *Desma, Spain.*
Bromhexine hydrochloride (p. 1656·3); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Bal-Spar *Bal, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Bals-Sulphur *Sulphur Zdroj, Pol.*
Sodium chloride (p. 1795·1); bromide; iodide; borate; sulfur (p. 1721·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Balticin *Metiska, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Balto Foot Balm *Lane, UK.*
Camphor (p. 2466·2); menthol (p. 2553·2); zinc oxide (p. 1729·1); precipitated sulfur (p. 1721·1).
Aching feet; excessive perspiration; hard skin.

Baludol *Balu, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Balurol *Baldacci, Braz.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Balvidine *Bal, India.*
Povidone-iodine (p. 1767·1).
Skin infections; wounds.

Balvidine-M *Bal, India.*
Povidone-iodine (p. 1767·1); metronidazole (p. 936·1).

Balya *Sanofi Synthelabo, Turk.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).

Balyfen *Qualiphar, Belg.†*
Caraway oil (p. 2470·3).
Flatulence; bloating; digestive aid.

Balzak *Menarini, Spain.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Balzak Plus *Menarini, Spain.*
⊗Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Balzide *Malesci, Ital.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Balziva *Barr, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Combined oral contraceptive.

Balzoprem *Uquifa, Port.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Balzox *Bal, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Bamalite *Tecnobio, Spain.†*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Bambair *Mantecorp, Braz.*
⊗Bambuterol (p. 1203·1).

Bambec *AstraZeneca, Austria; AstraZeneca, Braz.; AstraZeneca, China; AstraZeneca, Denm.; AstraZeneca, Ger.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Thai.; AstraZeneca, UK.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease; asthma.

Bambiti Kid *Dey's, India.*
Paracetamol (p. 115·1).
Pain; fever.

Bambudil *Cipla, India.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Bambutec *Taiwan Biotech, Philipp.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Bamgetol *Mersifarma, Indon.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia.

Bamifix *Chiesi, Braz.; Chiesi, Ital.*
Bamifylline hydrochloride (p. 1203·2).
Obstructive airways disease.

Bamyl *AstraZeneca, China; Meda, Swed.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis; inflammation; musculoskeletal and joint disorders.

Bamyl koffein *Meda, Swed.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Bamyxin *Rekah, Israel.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Ban Ning *Haixin, China.*
Sodium demethylcantharidate.

Ban Pain *Aspen Consumer, S.Afr.*
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Pharmacare, S.Afr.†
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain with tension.

Ban Su *Yangtze River, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Banadoz *Sandoz, Indon.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Banadroxin *Pharmanik (Φαρμανικ), Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Banadyne-3 *Norstar, USA.*
⊗Lidocaine (p. 1988·1); menthol (p. 2553·2); alcohol (p. 1733·1).
Herpes labialis.

Banalg *Forest Pharmaceuticals, USA.†*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Banan *Daiichi Sankyo, China; Sankyo, Hong Kong; Sandoz, Indon.†; Daiichi Sankyo, Jpn; Pharmalink, Philipp.†; Sankyo, Philipp.†; Sankyo, Thai.†*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Banana Boat Active Kids *Banana Boat, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Banana Boat Aloe Vera Lip Balm Sunblock *Playtex, Canad.†*
SPF 30: Padimate O (p. 1716·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); homosalate (p. 1705·1).
Sunscreen.

Banana Boat Baby Sunblock *Playtex, Canad.†*
SPF 50: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Banana Boat Dark Tanning *Playtex, Canad.†*
Oil SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Playtex, Canad.†
Lotion SPF 4: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Formerly contained padimate O.
Sunscreen.

Playtex, Canad.†
Oil SPF 4: Padimate O (p. 1716·1); octinoxate (p. 1715·1).
Sunscreen.

Banana Boat Everyday Glow *Playtex, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Banana Boat Kids Sunblock *Banana Boat, Canad.†*
Stick SPF 30: Homosalate (p. 1705·1); octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Playtex, Canad.†
Cream SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Playtex, Canad.†
SPF 50: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Banana Boat Protective *Playtex, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Banana Boat Quik Blok Kids *Playtex, Canad.†*
SPF 25: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Banana Boat Sooth-A-Caine
Note: this name may be used for preparations of different composition.
Playtex, Canad.†
Menthol (p. 2553·2); lidocaine (p. 1988·1).

Banana Boat Soothacaine
Note: this name may be used for preparations of different composition.
Playtex, Canad.†
Lidocaine (p. 1988·1).

Banana Boat Sport *Banana Boat, Canad.†; Playtex, Canad.†*
Cream SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Playtex, Canad.†
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Playtex, Canad.†
Lip balm SPF 30: Stick SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Banana Boat Sunblock *Playtex, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Banana Boat Sunscreen *Energizer, Canad.*
SPF 4: Octinoxate (p. 1715·1); padimate O (p. 1716·1).
Sunscreen.

Energizer, Canad.
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Banana Boat Suntanicals *Playtex, Canad.†*
SPF 8: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Banana Boat Ultra *Banana Boat, Canad.†; Playtex, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Banana Boat Ultra Plus *Playtex, Canad.†*
Lotion SPF 50: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); octocrilene (p. 1715·2).
Sunscreen.

Banana Boat Ultra Plus Ecran *Playtex, Canad.†*
SPF 50: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Banatin *Remedina, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Banbact *T Man, Thai.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Band *Vensat, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Band-Aid Antibiotic Adhesive Bandages plus Antibiotic *Johnson & Johnson, Canad.*
Bacitracin zinc (p. 225·3); polymyxin B sulfate (p. 342·3).

Band-Aid Anti-Itch *Johnson & Johnson, Canad.†*
Camphor (p. 2466·2).
Skin disorders.

Band-Aid Antiseptic *Johnson & Johnson, Canad.*
Lidocaine hydrochloride (p. 1988·2).

Bandax *Lloyd, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Bandi *Tapwin, Canad.†*
⊗Glycerol (p. 2517·2).
Constipation.

Bandrobon *Gobbi, Arg.*
Ibandronate sodium (p. 1184·2).
Hypercalcaemia of malignancy; osteoporosis; osteolysis of malignancy.

Bandrone *Natco, India.*
Ibandronic acid (p. 1184·2).

Bandy *Mankind, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Bandy Plus *Mankind, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Banedif *Bago, Chile.†*
Ointment: Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); zinc oxide (p. 1729·1).
Bacterial skin infections.

Bago, Chile.†
Topical powder: Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); aluminium hydroxide (p. 1817·2).
Bacterial skin infections.

Maxfarma, Spain.†
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); zinc oxide (p. 1729·1).
Infected skin disorders.

Banedif Oftalmico *Bago, Chile.†*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial eye infections.

Banedif Oftalmico con Prednisolona *Bago, Chile.†*
⊗Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); prednisolone (p. 1645·2).
Infected eye disorders with inflammation.

Banedif ZN *Bago, Chile.*
Bacitracin (p. 225·3); neomycin (p. 329·3).

Baneocin *Sandoz, Austria.*
Bacitracin (p. 225·3) or bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial infections.

Sandoz, Hung.; Sandoz, Malaysia; Sandoz, Pol.; Sandoz, Rus.; Sandoz, Singapore; Sandoz, Ukr.
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial infections of skin and mucous membranes.

Banéopol *Streuli, Switz.†*
Bacitracin (p. 225·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Infected eye and skin disorders.

Banflex *Forest Pharmaceuticals, USA.*
Orphenadrine citrate (p. 909·2).
Musculoskeletal pain.

Bang Ao Shu *De Tian, China.*
⊗Carbocisteine (p. 1658·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Bang Chuan Nai Xin *Run Bang, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Bang Da *Qilu, China.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Bang Jia Fen Ning *Run Bang, China.*
Gatifloxacin mesilate.
Bacterial infections.

Bang Jie Qing *Rui Feng, China.*
Ticlopidine hydrochloride (p. 1512·1).
Intermittent claudication; ischaemic heart disease; stroke prophylaxis; thromboembolism prophylaxis following stent implantation.

Bang Lai *Double-Crane, China.*
Teniposide (p. 867·1).

Bang Lai Li Xin *Run Bang, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Bang Lin *Tai Fu, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bang De Mei *Duoburuifei, China.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Bang Neng *Hui Ren, China.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Bang Nuo *Shuang Jing, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Bang Ping *Wan Bang, China.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Bang Qi *Xin Bang, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bang Qing *Haiyan, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Bang Rui De *Lian He, China.*
Calcitonin (salmon) (p. 1178·1).

Bang Sai *Run Bang, China.*
Gatifloxacin mesilate.
Bacterial infections.

Bang Tan *Wan Bang, China.*
Telmisartan (p. 1509·3).
Hypertension.

Bang Te Lin *Ju Le, China.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Bang Ting *Ao Hong, China; Xin Ma, China.*
Haemocoagulase (p. 1135·1).

Bang Tuo *Kang Ji Er, China.*
Sodium ferulate.

Bang Wei Lin Xin *Run Bang, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Bang Yi *Shenyang First, China.*
Rifaximin (p. 355·2).

Bang Zhi Lin Xin *Run Bang, China.*
Ethylenediamine diaceturate.

Bang-Aid *Johnson & Johnson, China.*
Benzalkonium chloride (p. 1737·1).

BangLin *Qi Li, China.*
Ethylenediamine diaceturate.

Bangna *Xincat, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

BangNi *Ling Tai, China.*
Nimesulide (p. 101·3).
Pain.

Bangning ShaJi *NingguoBangning, China.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

BangShun *Shuang Jing, China.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Banholeum *Sofex, Port.*
Soya oil (p. 2092·3).
Skin disorders.

Banholeum Composto *Sofex, Port.*
Soya oil (p. 2092·3); coal tar (p. 1723·2).
Bath additive; skin disorders.

Banholeum Gele *Sofex, Port.*
Soya oil (p. 2092·3); liquid paraffin (p. 2191·2).
Skin disorders.

Banimed *Bajamed, Mex.*
Minocycline (p. 324·3).
Bacterial infections.

Banin *Uni-Sankyo, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Banish II *Smith & Nephew, Austral.*
Zinc ricinoleate (p. 2650·2); dipropylene glycol.
Colostomy and ileostomy odour.

Banishing Cream Skin Tone *Avon, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Banlice *Johnson & Johnson, Austral.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Banner Protein *Osotspa, Thai.*
Amino acids.
Dietary supplement.

Bano *Meditop, Hung.*
Calcium citrate (p. 1783·2).
Calcium deficiency; calcium supplement; osteoporosis.

Baño Coloide *Arlex, Mex.; Serral, Mex.*
Soya bean (p. 2092·3); povidone-iodine (p. 1767·1).
Skin disorders.

Baño Ocular *Poen, Arg.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Baño Ocular Agrand *Ahimsa, Arg.†*
⊗Naphazoline (p. 1669·3).
Eye disorders.

Báno Svédkeserü *Fahrvitex, Hung.*
Aloes (p. 1816·1); castor (p. 2472·1); mace (p. 2547·3); therion opii; myrrh (p. 2566·1); saffron (p. 2208·2); senna (p. 1885·1); angelica (p. 2443·3); calamus (p. 2464·2); gentian (p. 2512·1); rhubarb (p. 1884·2); tormentil (p. 2633·2); zedoary; nutmeg (p. 2573·1); dictamnus; camphor (p. 2466·2).
Gastrointestinal disorders.

Banocide *GSK, India.*
Diethylcarbamazine citrate (p. 153·1).
Worm infections.

Banocin *Nakornpatana, Thai.*
Ointment: Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Wounds; burns; ulcers.

Nakornpatana, Thai.
Topical powder: Clioquinol (p. 273·1); bacitracin (p. 225·3); neomycin sulfate (p. 330·1); zinc stearate (p. 2221·2).
Wounds; burns; ulcers.

Banoclus *Lamsa, Arg.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Fever; inflammation; pain.

Bañoftal *Alcon, Spain.†*
Boric acid (p. 2459·3); calendula (p. 2465·2); hamamelis (p. 2523·3); borax (p. 2459·2).
Eye disorders.

Banophen Allergy *Major, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; motion sickness; insomnia.

Banophen Decongestant *Major, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Hypersensitivity reactions; motion sickness; insomnia.

Ban-Sol *Remexa, Mex.*
SPF 50; SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Bantel *TNP, Thai.*
Pyrantel embonate (p. 165·3).
Worm infections.

Banthel *Candor, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Bantif Child *Capriformindo, Indon.; Sanbe, Indon.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Bantix *Mediderm, Chile.*
Mupirocin calcium (p. 327·2).
Skin infections; elimination of nasal staphylococci.

Bantizol *Blue Sky, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bantuc *Baliarda, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Banyass *Pharmacross, Chile.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Banzel *Eisai, Canad.; Novartis, USA.*
Rufinamide (p. 548·3).
Lennox-Gastaut syndrome.

Bao Le *Jialin, China.*
Magnesium gluconate (p. 1787·2).

Bao Le An *Eastsea, China.*
Clostridium butyricum.
Diarrhoea and dyspepsia associated with disorders of gut flora.

Bao Da *Shu Tai Bao, China.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Bao Jia Wei *RenFu, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Bao Jie Li *Tong Ren, China.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Bao Li An *Meirui, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Bao Lin *Double-Crane, China.*
Lysine hydrochloride (p. 2079·3).

Bao Nuo *Rundu Mintong, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Bao Yi Tian *ShiKangTe, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Bao Zhen Kang *Wufeng, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Baolijin *Ronsen, China.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Baolongkang *Bao Long, China.*
⊗Clobetasol propionate (p. 1627·1); ketoconazole (p. 585·3).
Fungal skin infections.

Bapex *Probiomed, Mex.*
Gabapentin (p. 523·3).
Epilepsy.

Bapixied *Bajamed, Mex.*
Piroxicam (p. 125·3).
Inflammation; pain.

Baquinor *Sanbe, Indon.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Baraclude *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, China; BMS, Cz.; BMS, Denm.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, India; Taisho, Indon.; BMS, Irl.; BMS, Israel; BMS, Ital.; BMS, Malaysia; BMS, Neth.; BMS, Norw.; BMS, NZ; BMS, Philipp.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS, USA.*
Entecavir (p. 977·3).
Chronic hepatitis B.

Baralgan-D *Sanofi-Aventis, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Baralgan-DM *Sanofi-Aventis, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Baralgan-M *Sanofi-Aventis, India.*
Dipyrone (p. 53·3).
Pain.

Baralgin *GSK, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Baralgin M *Sanofi-Aventis, Rus.; Pharmagen, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Baralgina M *Sanofi-Aventis, Chile.*
Dipyrone (p. 53·3).
Fever; pain.

Baralginus *Norton, Ukr.†*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Painful smooth muscle spasm.

Baratol *Akromed, S.Afr.†; Amdipharm, UK.†*
Indoramin hydrochloride (p. 1410·2).
Hypertension.

Barazan *Teofarma, Ger.*
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract.

Barbee *Ind-Swift, India.*
Phenobarbital (p. 535·2).
Epilepsy; sedative; insomnia.

Barbitoin *Medopharm, India.*
Phenobarbital (p. 535·2); phenytoin sodium (p. 538·2).
Epilepsy.

Barbitron *Sanval, Braz.*
Phenobarbital (p. 535·2).
Convulsions.

Barbloc *Alphapharm, Austral.; LCH, Hong Kong.†*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris; arrhythmias.

Barboval *Farmak, Rus.; Farmak, Ukr.*
Phenobarbital (p. 535·2); ethyl alpha-bromoisovalerate (p. 1073·1); menthyl isovalerate (p. 2554·1).
Nervous disorders; colic; flatulence; angina pectoris; hypertension; tachycardia; neuroses; insomnia; hysteria; gastrointestinal spasm; meteorism.

Bareon *Abbott, Jpn.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Barex *Dominguez, Arg.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Barexal *Ipsen, Belg.*
Smectite (p. 1887·1); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Diarrhoea.

Bargonil *Roemmers Rowe, Venez.*
Tribenoside (p. 2633·3); a heparinoid (p. 1401·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Baricat *Bracco, Irl.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal computerised tomography.

Bariclor *Degorts, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Baricol *Bracco, Neth.*
Barium sulfate (p. 1583·2).
Radiography of the gastrointestinal tract.

Baricon *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Baridium *Pfeiffer, USA.*
Phenazopyridine hydrochloride (p. 124·3).
Irritation of the lower urinary tract.

Bariederm *Uriage, Fr.*
Barrier preparations.

Bariésun *Uriage, Fr.*
SPF 50+: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Barigesic *Degorts, Mex.†*
⊗Aspirin (p. 22·2); prednisone (p. 1647·2).
Inflammation; pain.

Barigraf *Justesa Imagen, Arg.; Juste, Spain.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Barijodeel *Heel, Canad.†*
Aconite (p. 2428·3); anacardium orientale (p. 2471·3); arnica montana (p. 2447·2); barium carbonate (p. 2452·2); calcium iodide (p. 1658·1); hahneman's causticum (p. 2595·3); potassium phosphate dibasic (p. 1791·1); stramonium (p. 2622·3).
Homoeopathic preparation.

Barilux *Sanochemia, Ger.; IFET (ΙΦΕΤ), Gr.; Iberoinvesa, Spain.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Barin *Roemmers Osmoph, Venez.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Bario *GP, Arg.; Temis, Arg.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Bario Dif *Rovi, Spain.†*
Barium sulfate (p. 1583·2).
Dimeticone (p. 1886·2) is included in this preparation to eliminate gas from the gastrointestinal tract before radiography.
Contrast medium for gastrointestinal radiography.

Bariofarma *Varifarma, Arg.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Bariogel *Cristalia, Braz.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Bariplex *Degorts, Mex.*
Vitamins.

Baripril *Qualigen, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Baripril Diu *Qualigen, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Baritop *Sanochemia, UK.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal tract radiography.

Barium Jodatum Oligoplex *Madaus, Arg.*
Barium iodide (p. 2452·2); crataegus (p. 2488·1).

Barium Med Complex *Dynamit, Austria.*
Acidum phosphoricum (p. 2589·1); argentum nitricum (p. 2615·3); barium carbonicum (p. 2452·2); strophantus (p. 1507·2).
Homoeopathic preparation.

Bari-Vit *Somapharm, Canad.†*
Vitamins; minerals.

Barkeit *Uni-Sankyo, India.*
Guaifenesin (p. 1666·2).
Cough.

Barlem *Juggat, India.*
Preparation for enteral nutrition.

Barlodin *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).

Barmicil Compuesto *Sons, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Barnascan *Barnatron, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide agent for positron emission tomography.

Barnetil *Synthelabo Lavipharm, Gr.*
Sultopride hydrochloride (p. 1108·3).

Barnix *Bial, Spain.*
Barnidipine hydrochloride (p. 1314·1).
Hypertension.

Barobag *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Baroc *Bayer, Port.*
Ibuprofen (p. 68·2).
Fever; pain.

Bayer, Cz.†
Ibuprofen sodium (p. 68·2).
Fever; pain.

Barocal *Baroda, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Barocal Forte *Baroda, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Baro-cat *Mallinckrodt, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Barocat *Tyco, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Barocef *Baroda, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Barochem *Baroda, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Barohem *Baroda, India.*
Syrup: Sodium feredetate (p. 2088·3).

Baroda, India.
Tablets: Sodium feredetate (p. 2088·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Barohexy *Baroda, India.*
Trihexyphenidyl (p. 917·3).
Extrapyramidal disorders; parkinsonism.

Barohist AC *Baroda, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Barohist-D *Baroda, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Barol *Mega Lifesciences, Ukr.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; gastritis.

Barominic *Am-Europharma, Philipp.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Baron *Medicine Products, Thai.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Baronite *Baroda, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Baropyrine *Am-Europharma, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Baros
Note: this name may be used for preparations of different composition.
Tyco, Canad.†; Eisai, Hong Kong.†
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Adjunct on radiography.

Mallinckrodt, USA.†
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); simeticone (p. 1886·2).
Adjunct in gastrointestinal radiography.

Barosperse *Mallinckrodt, Arg.†; Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Barostatin *Baroda, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Barovit *Baroda, India.*
Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Baroxal *Alapis, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Baroxime *Baroda, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Barozac *Baroda, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Barozyme *Baroda, India.*
⊗Bile; dimeticone (p. 1886·2); pancreatin (p. 2579·3).
Digestive disorders.

Barriere *Wellspring, Canad.*
Dimeticone (p. 2209·3).
Nappy rash; skin irritation.

Barriere-HC *Pendopharm, Canad.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Barrocutina *Esme, Arg.*
Aloe vera (p. 1693·2).

Barrycidal *Manfred Sauer, Ital.*
Alkylbenzyldimethylammonium chloride (p. 1737·1); benzethonium chloride (p. 1738·1); diisobutylcresoxyethoxyethyl benzyldimethylammonium chloride.
Instrument disinfection.

Barstra *Synthon, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Bart *SoSe, Ital.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders.

Bartil *Medarte, Gr.*
Butamirate citrate (p. 1657·3).

Bartolium *Nufarindo, Indon.*
Flunarizine (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Baruden *Anpharm (Ανφαρμ), Gr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Bar-VIPS *Vips-Med, Rus.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Bar-X-Ray *Dermanci, Turk.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Barzepin *Novell, Indon.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Basalflex *Braun, Ital.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Basalin *Gan & Lee, Thai.*
⊗Insulin glargine (p. 475·3).
Diabetes mellitus.

Basdène *Bouchara-Recordati, Fr.*
Benzylthiouracil (p. 2334·3).
Hyperthyroidism.

Bas-Dextrano *Braun, Port.†*
⊗Dextran 40 (p. 1138·1) in glucose or sodium chloride.
Plasma volume expansion; thromboembolic disorders.

Base
Note: this name may be used for preparations of different composition.
Bestochem, India.
Saccharomyces boulardii (p. 2596·3).

Lero, Fr.
Fish oil (p. 1460·1); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); vitamins; minerals.
Tonic.

Baséal *Pierre Fabre Dermatologie, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Baseflox OZ *Arunabh, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).
Bacterial infections.

Baselide *Ultramark, India.*
Paracetamol (p. 115·1); nimesulide (p. 101·3).

Basen *Takeda, China; Takeda, Jpn; Takeda, Philipp.; Takeda, Thai.*
Voglibose (p. 505·3).
Diabetes mellitus.

Basic
Note: this name may be used for preparations of different composition.
Lark, India.
⊗Betamethasone (p. 1623·2); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); urea (p. 1727·3).

Basic 12 *Basic, Canad.†*
Sodium hypochlorite (p. 1768·3).
Disinfectant.

Basic Prenatal *Thorne, Canad.*
Vitamins; minerals.

Basicaina *Senese, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Basifen *Basi, Port.*
Fenbufen (p. 59·1).
Musculoskeletal, joint, and peri-articular disorders.

Basiflux *Basi, Port.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with increased mucus.

Basikol *Arkopharma, Hong Kong; Arkopharma, Singapore.*
Phytosterols (p. 1471·2); vitamin E (p. 2119·1).
Hypercholesterolaemia; hyperlipidaemias.

Basilicum Complexe No 96 *Lehning, Fr.*
Basilicum (p. 2453·1); vinca minor; asa foetida (p. 2449·3); podophyllinum (p. 1717·1); china (p. 2478·3); chamomilla (p. 2474·1); sulfur (p. 1721·1); lycopodium (p. 2546·3); colchicum (p. 607·1); belladonna (p. 2453·3).
Homoeopathic preparation.

Basina *T Man, Thai.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Basinal *Basi, Port.*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal syndrome; alcohol withdrawal syndrome.

Basiron *Galderma, Denm.; Galderma, Fin.; Galderma, Norw.; Galderma, Rus.; Galderma, Swed.*
Benzoyl peroxide (p. 1696·1).
Acne.

Basiron AC *Galderma, Cz.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Basiscreme *Genesis, Turk.*
Emollient.

Basiton *Sarabhai Piramal, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); folic acid (p. 2063·1).
Vitamin B and C deficiency.

Basix *Plus, India.*
Vitamin B substances (p. 2102·3).

Basix Neutral *Avmor, Canad.*
Didecyldimethylammonium chloride (p. 1750·3).
Disinfection.

Basix-AL *Plus, India.*
Vitamins; minerals; thioctic acid (p. 2629·1).

Basix-LB *Plus, India.*
Vitamin B substances (p. 2102·3); vitamin A (p. 2098·3); protein; lycopene (p. 2546·2); zinc sulfate (p. 2126·2).

Basix-OD *Plus, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

B1-ASmedic *Dyckerhoff, Ger.*
Thiamine nitrate (p. 2103·2).
Vitamin B_1 deficiency.

B2-ASmedic *Dyckerhoff, Ger.*
Riboflavin (p. 2104·3).
Riboflavin deficiency.

B6-ASmedic *Dyckerhoff, Ger.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

B_{12}-ASmedic *Dyckerhoff, Ger.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Basocef *Actavis, Ger.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Basocin *Galderma, Ger.*
Clindamycin phosphate (p. 269·3).
Acne.

Basodexan *Almirall Hermal, Ger.*
⊗Urea (p. 1727·3).
Skin disorders.

Basofortina *Novartis, Arg.*
Methylergometrine maleate (p. 2137·3).
Postpartum atony; postpartum haemorrhage; uterine subinvolution.

Basol *Cadila, India.*
Electrolytes (p. 1775·1).

Basol Plus *Cadila, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3); oxiglutatione (p. 1555·2).

Basoplex *Riemser, Ger.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Basoquin *Pfizer, India.†*
Amodiaquine (p. 647·2).
Malaria.

B-Aspirin *Osoth, Thai.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Bassado *Pfizer, Ital.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Basta *Krolton, Arg.*
Cyclomethicone 5; dimeticone (p. 2209·3).
Pediculosis.

Basti-Mag *Bastian, Ger.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Bat
Note: this name may be used for preparations of different composition.
Madhav, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Zeta, Ital.
Cetylpyridinium chloride (p. 1743·1).
Disinfection of wounds and burns.

Batafil *Proel, Gr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Bateral *Allen, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bath E45 *Crookes Healthcare, UK.*
Bath additive.
Dry skin.

Batif *Epifarma, Ital.*
Azithromycin (p. 221·2).
Bacterial infections.

Batiflox *Indoco, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Batinel *Teva Tuteur, Arg.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Batiodin *Oro, Turk.*
Povidone-iodine (p. 1767·1).
Minor cuts and abrasions; skin disinfection.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Batixim *SoSe, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Batmen *Menarini, Spain.*
⊗Prednicarbate (p. 1645·1).
Skin disorders.

Batrafan *Sanofi-Aventis, India.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Batrafen *Sanofi-Aventis, Austria; Sanofi-Aventis, Chile; Dermik, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.†; Sanofi-Aventis, Rus.; Abbott, Switz.†; Sanofi-Aventis, Venez.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Seborrhoeic dermatitis; fungal skin, nail and vaginal infections.

Batramycin *Geistlich, Singapore; Geistlich, Switz.†*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial skin infections; infected wounds or burns.

Batrevac *Solvay, Austria†; Abbott, Neth.; Solvay, Port.†*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Batrizol *Medimport, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Batrox *Bergamo, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Batticon *Genesis, Turk.*
Povidone-iodine (p. 1767·1).
Oral hygiene; skin disorders; skin disinfection.

Battizer *SF, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Batugin *Kimia, Indon.*
Strobilanthes crispus; sonchus arvensis.
Renal colic.

Batzeta *Zeta, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Disinfection of burns, ulcers, and wounds.

Baudry *Boiron, Fr.*
Aconitum napellus (p. 2428·3); atropa belladonna (p. 2453·3); drosera (p. 2497·2); bryonia dioica (p. 2461·3); coccus cacti (p. 2179·2); ipecac (p. 1667·2).
Homoeopathic preparation.

Baume Analgesique *Superco, Canad.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2).

Baume Analgesique Medicamente *Prodemdis, Canad.†*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).

Baume Aroma *Mayoly-Spindler, Fr.*
Clove oil (p. 2481·3); capsicum oil; methyl salicylate (p. 92·1).
Muscle and joint pain.

Baume Bengué *Ipsen, Fr.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Muscle and joint pain.

Baume du Chalet *Plan, Switz.*
Lavender oil (p. 2541·1); citronella oil (p. 2481·1); spike lavender oil (p. 2621·3); terebinthin (p. 2636·3).
Wounds; skin disorders.

Baume Dalet
Note: this name may be used for preparations of different composition.
Uhlmann-Eyraud, Switz.
Lidocaine (p. 1988·1); camphor (p. 2466·2); chlorobutanol (p. 1747·2); hamamelis (p. 2523·3); levomenthol (p. 2553·2); aluminium hydroxide (p. 1817·2); aluminium chloride (p. 1693·3); allantoin (p. 1693·1).
Bunions.

Baume Esco *Streuli, Switz.*
Salicylic acid (p. 1719·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Baume Esco Forte *Streuli, Switz.†*
Salicylic acid (p. 1719·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); ethyl nicotinate (p. 56·3).
Musculoskeletal and joint pain.

Baume Levres *Ombrelle, Canad.*
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Baume Pulmonaire *Kela, Belg.*
Ethylmorphine hydrochloride (p. 56·3); guaifenesin (p. 1666·2).
Cough.

Baume des Pyrenees *Pierre Fabre, Fr.*
Peru balsam (p. 2587·1).
Skin irritation.

Baume Saint-Bernard *Merck Medication Familiale, Fr.*
Amyl salicylate (p. 21·2); menthol (p. 2553·2); camphor (p. 2466·2); capsicum oleoresin (p. 2469·3).
Muscle and joint pain.

Baume du Tigre blanc *Doetsch, Grether, Switz.*
Menthol (p. 2553·2); camphor (p. 2466·2); mint oil (p. 2560·1); clove oil (p. 2481·3); cajuput oil (p. 2464·1).
Musculoskeletal, joint, and soft-tissue disorders; cold symptoms; headache.

Baume du Tigre huile *Doetsch, Grether, Switz.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue disorders; cold symptoms.

Baume du Tigre rouge *Doetsch, Grether, Switz.*
Menthol (p. 2553·2); camphor (p. 2466·2); mint oil (p. 2560·1); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); cajuput oil (p. 2464·1).
Musculoskeletal, joint, and soft-tissue disorders; cold symptoms.

Baume Zeller *Zeller, Switz.*
Achillea (p. 2427·3); absinthium (p. 2426·1); poppy flowers (p. 2207·3); guaiacum wood; tormentil root (p. 2633·2); cinnamon bark (p. 2479·2); benzoin (p. 2624·3); myrrh (p. 2566·1); tolu balsam (p. 1679·2).
Gastrointestinal disorders; cold symptoms.

Bausch & Lomb Computer Eye Drops *Bausch & Lomb, Austral.†*
⊗Glycerol (p. 2517·2).
Dry eyes; eye irritation.

Bausch & Lomb Concentrated Cleaner *Bausch & Lomb, Austral.†*
Cleansing solution for gas permeable and hard contact lenses.

Bausch & Lomb Conditioning Solution *Bausch & Lomb, Austral.†*
Disinfecting and storage solution for gas permeable and hard contact lenses.

Bausch & Lomb, S.Afr.†
Storage solution for contact lenses.

Bausch & Lomb Daily Cleaner *Bausch & Lomb, S. Afr.†*
Cleaning solution for soft contact lenses.

Bausch & Lomb Lens Lubricant *Bausch & Lomb, S. Afr.†*
Rewetting solution for hard and soft contact lenses.

Bausch & Lomb Moisture Eyes *Bausch & Lomb, Canad.*
⊗Glycerol (p. 2517·2); propylene glycol (p. 2205·2).
Dry eyes.

Bauxol *Mintlab, Chile.*
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1).
Cough.

Bavilon *Medhel, Gr.*
Indometacin (p. 71·2).

Bavitam *Candor, India.*
Syrup: Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Candor, India.
Tablets: Vitamin B substances (p. 2102·3); glutamic acid (p. 2070·2).

Baxamed *Bajamed, Mex.*
Norfloxacin (p. 333·3).
Bacterial infections.

Baxan *BMS, UK.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Baxcarbas *Asta Oncologia, Braz.†*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Baxedin *Omega, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection and antisepsis.

Omega, Hong Kong.
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Baxedin 2% - 70% *Omega, Canad.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Disinfection.

Baxemin *Andromaco, Chile.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Baxidin *Sanitas, Ital.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Disinfection of wounds and burns.

Baxidyme *Bosch, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Baxil *Erfa, Belg.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Baxima *Sandoz, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Baxin *Hetero, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Baxin-D *Hetero, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Baxin-D-LB *Hetero, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Baxin-D-LB+ *Hetero, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Baxin-LB *Hetero, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Baxmicin *Asta Oncologia, Braz.†*
Mitomycin (p. 830·3).
Malignant neoplasms.

Baxmune *Ranbaxy, India.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Baxo *Taisho Toyama, Jpn.*
Piroxicam (p. 125·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Baxogar *Pharmathen, Cz.; Pharmathen, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Baxolyn *Bosch, Philipp.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Baxytax *Ranbaxy, Mex.†*
Cefotaxime (p. 244·1).
Bacterial infections.

Bayagel *Bayer Consumer, Arg.*
Etofenamate (p. 57·2); pine oil (p. 2591·1); eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, and soft-tissue pain.

Bayer, Chile.†
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bayaspirin Protect *Bayer Schering, China.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Bayaspirina *Bayer Consumer, Arg.*
Aspirin (p. 22·2).
Fever; inflammation; pain; thromboembolism prophylaxis.

Bayaspirina C *Bayer Consumer, Arg.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold symptoms; fever; pain.

Baycadron *Wockhardt, USA.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

BayCal *Bayer Consumer, Thai.*
Calcium carbonate (p. 1824·3).

Baycillin *Bayer, Ger.†*
Propicillin potassium (p. 344·3).
Bacterial infections.

Baycip *Bayer, Chile; Bayer, India; Bayer, Spain.*
Ciprofloxacin (p. 261·1), ciprofloxacin hydrochloride (p. 261·2), or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Baycip-TZ *Bayer, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Bayclear Plus *Bayer, China.*
Bifonazole (p. 573·3).
Fungal skin infections.

Baycuten
Note: this name may be used for preparations of different composition.
Bayer, Braz.; Bayer, Chile; Bayer, Cz.†; Bayer, Mex.; Bayer, Philipp.
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1).
Infected skin disorders.

Bayer, Port.
⊗Clotrimazole (p. 576·2); dexamethasone (p. 1630·3).
Fungal skin infections with inflammation.

Baycuten HC *Bayer, Ger.*
⊗Clotrimazole (p. 576·2); hydrocortisone (p. 1640·1).
Infected skin disorders.

Baycuten N
Note: this name may be used for preparations of different composition.
Bayer, Mex.; Bayer, Venez.
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bayer Schering, Malaysia.†
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1).
Fungal skin infections.

Baycuten-N *Bayer Schering, Indon.*
⊗Dexamethasone acetate (p. 1631·1); clotrimazole (p. 576·2).
Infected skin disorders.

Bayer Extra Strength Back & Body Pain *Bayer, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Bayer Low Adult Strength *Sterling Health, USA.*
Aspirin (p. 22·2).

Bayer Migraine Formula *Bayer, USA.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Migraine.

Bayer Quick Release Crystals *Bayer Consumer, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Bayer Select Chest Cold *Sterling Health, USA.*
Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Bayer Select Flu Relief *Sterling Health, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Bayer Select Head Cold *Sterling Health, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Bayer Select Maximum Strength Backache *Sterling Health, USA.*
Magnesium salicylate (p. 85·2).

Bayer Select Maximum Strength Night Time Pain Relief *Sterling Health, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia; pain.

Bayer Select Maximum Strength Sinus Pain Relief *Sterling Health, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; pain.

Bayer Select Night Time Cold *Sterling Health, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3).

Bayer Womens Aspirin Plus Calcium *Bayer, USA.*
Aspirin (p. 22·2); calcium (p. 1783·1).
Pain.

Bayers Tonic *Bayer, India.*
⊗Liver extract (p. 2444·1); yeast extract; alcohol (p. 1733·1).
Formerly contained sodium acid phosphate, liver extract, yeast extract, and alcohol.
Tonic.

Bayflex *Blue Bio, Cz.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Baygam *LCH, Hong Kong.†*
A normal immunoglobulin (p. 2403·3).

Baygon *Skills, Ital.*
Propoxur (p. 2160·3); tetramethrin (p. 2162·2); piperonyl butoxide (p. 2160·2).
Insecticide.

BayHep B *Bayer, Philipp.; GenAsia, Philipp.; Biem, Turk.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Baylotensin *Mitsubishi Tanabe, Jpn.*
Nitrendipine (p. 1456·3).
Hypertension; angina pectoris.

Baymycard *Bayer, Ger.; Bayer Schering, Hung.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Baynas *Shinyaku, Jpn.*
Ramatroban (p. 2602·1).
Allergic rhinitis.

Bayolin *Bayer, Gr.*
A heparinoid (p. 1401·1); glycol salicylate (p. 66·2); benzyl nicotinate (p. 29·3).
Topical relief of rheumatic pain.

Bayotensin *Bayer, Ger.*
Nitrendipine (p. 1456·3).
Hypertension.

Baypen *Bayer, Austria; Bayer, China; Bayer, Fr.†; Bayer, Ger.†; Bayer, Ital.*
Mezlocillin sodium (p. 324·1).
Bacterial infections.

Baypresol *Baysalud, Spain.*
Nitrendipine (p. 1456·3).
Angina pectoris; hypertension; Raynaud's syndrome.

Baypress *Bayer, Austria; Bayer, Belg.; Bayer Schering, Cz.; Bayer, Denm.; Bayer, Fr.; Bayer, Gr.; Bayer, Hong Kong†; Bayer Schering, Hung.; Bayer, Ital.; Bayer, Neth.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, Venez.*
Nitrendipine (p. 1456·3).
Hypertension.

Baypril *Bayer, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; unstable angina.

Bayprin *Bayer, Philipp.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

BayRab *Bayer, Philipp.; GenAsia, Philipp.; Biem, Turk.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

BayRho-D *Bayer, Israel†; Biem, Turk.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Bayro *Bayer, Braz.; Bayer, Mex.*
Etofenamate (p. 57·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Bayro Termo *Bayer, Mex.*
Etofenamate (p. 57·2); benzyl nicotinate (p. 29·3).
Musculoskeletal, joint, and peri-articular disorders.

BayTet *Bayer, Philipp.†; GenAsia, Philipp.†; Biem, Turk.; Bayer, USA.†*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Baywood Fizz *Baywood, Canad.†*
Vitamins; minerals.

Bayzolam *Bayer, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Baza Antifungal *Coloplast, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Bazetham *Pliva Krakow, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Pliva, UK.†
Tamsulosin (p. 2369·1).

Bazoton *Abbott, Ger.*
Urtica root (p. 2639·3).
Benign prostatic hyperplasia.

Bazuctril *Chrispa (Χρισπα), Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bazuka *Dendron, UK.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; verrucas; corns; calluses.

Bazzy *Glenmark, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

B3B *Morishita, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

BB Test *Innotech, Fr.*
Pregnancy test (p. 2596·1).

B-Banc *Vanguard, India.*
Vitamins; minerals; glutamic acid (p. 2070·2).

BBdent Gel Topico *Maver, Chile.*
Benzocaine (p. 1980·2).

B-Beta *Ferron, Indon.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

BB-K8 *BMS, Ital.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

B-Bloc *Mandar, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

B-Block *Be-Tabs, S.Afr.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

BC 300 *Micro, India.*
Vitamins; trace elements.

BC Allergy Sinus Headache *GSK Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

BC Fast Pain Relief *GSK Consumer, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Formerly contained aspirin, caffeine, and salicylamide.
Pain.

BCAA *Baxter, Canad.†*
Amino acids.

BCAD *Mead Johnson, Fr.*
Food for special diets.
Maple syrup urine disease.

BCAD 1 *Mead Johnson, Hong Kong.*
Food for special diets.
Maple syrup urine disease.

BCAD 2 *Mead Johnson Nutritionals, USA.*
Food for special diets.
Maple syrup urine disease.

B-Cal
Note: this name may be used for preparations of different composition.
Brawn, India.
Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Georen, S.Afr.
Calcium carbonate (p. 1824·3).

B-Caroteno *AM, Arg.*
Betacarotene (p. 2051·1).
Skin pigmentation.

BCC *Biocell, Singapore.*
Chondroitin sulfate (p. 2476·1); hyaluronic acid (p. 2526·2); hydrolysed collagen type II (p. 2483·2).
Maintenance of healthy joints.

Bclomox *Briskon, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

B-Cobal *Advance, Malaysia.*
Mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).
Neuritis; neuralgia; neuropathy; vitamin B deficiency; megaloblastic anaemia.

Bcolen *Galpha, India.*
Vitamins.

B-Com Nerve *Blue Sky, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Bcom Plus *Global, India.*
Vitamins; trace elements.

B-Combin *Amgros, Denm.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Bcom-L *Plus, India.*
Glutamic acid (p. 2070·2); lysine (p. 2079·3); protein; vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

B-Compleet *Carlson, USA.*
Vitamin B substances (p. 2102·3).

B-Complex *BMS, China.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

B-Complex Multi-Tabs *Ferrosan, Ukr.†*
Thiamine (p. 2102·3); riboflavin (p. 2104·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); pantothenic acid (p. 2085·2); folic acid (p. 2063·1).
Vitamin B deficiency disorders.

B-Complex Threshold Controlled *GNLD, Austral.*
Vitamin B substances (p. 2102·3); rutoside (p. 2505·3).
Vitamin B deficiencies.

B-Cool *Julphar, UAE.*
Oxybuprocaine hydrochloride (p. 1993·2); cetylpyridinium chloride (p. 1743·1); tyrothricin (p. 384·1).
Throat disorders.

BC-Vit *Bactolac, India.*
Vitamins.
Nutritional supplement.

BC-Zole *Helax, India.*
Ear drops: ⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2); lidocaine (p. 1988·1).

Helax, India.
Ointment: ⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).
Infected skin disorders.

Bd-GARD *Mahakam Beta, Indon.*
Lactoferrin (p. 2539·3); bovine colostrum (p. 2380·3); echinacea angustifolia (p. 2498·1); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1).
Immunostimulant; tonic for patients with cancer.

Bdm *Laborate, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc sulfate (p. 2126·2).
Skin disorders.

B-Dol *Be-Tabs, S.Afr.*
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain with tension.

Bd-Rox *Panacea, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Beacodyl *Beacons, Singapore.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Allergic rhinitis; urticaria; cough.

Beacolytic *CCM, Malaysia.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with viscous mucus.

Beacon K *CCM, Malaysia.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Beacons *Beacons, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Beacons Cough *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2).
Cough.

Beacons DQ *Beacons, Singapore.*
Dequalinium chloride (p. 1749·3).
Sore throat.

Beactafed *Beacons, Singapore.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; urticaria; nasal congestion.

Beactafed Co *Beacons, Singapore.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Nasal congestion; cough.

Beadalet *Beacons, Singapore.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Beafemic *CCM, Malaysia; Beacons, Singapore.*
Mefenamic acid (p. 85·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Beaflu-Plus *Beacons, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Hypersensitivity reactions; cold symptoms.

Beafort *Beacons, Singapore.*
Thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); calcium pantothenate (p. 2085·2).
Vitamin B supplement.

Beagarol *Beacons, Singapore.*
Liquid paraffin (p. 2191·2); phenolphthalein (p. 1877·3).
Constipation.

Beagenta *CCM, Malaysia.*
Gentamicin sulfate (p. 304·2).
Bacterial skin, eye, and ear infections.

Beaglobe *CCM, Malaysia.*
Sulfadiazine (p. 361·3); trimethoprim (p. 381·2).
Bacterial infections.

Béagyne *Effik, Fr.*
Fluconazole (p. 578·2).
Vaginal and perineal candidiasis.

Beahexol *Beacons, Singapore.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Beakopectin *Beacons, Singapore.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Beamodium *CCM, Malaysia.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Beamotil *CCM, Malaysia; Beacons, Singapore.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea; colostomy and ileostomy management.

Beamoxy *CCM, Malaysia.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Be-Ampicil *Be-Tabs, S.Afr.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Beanamine Expectorant *Beacons, Singapore.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Allergic rhinitis; urticaria; cough.

Beano *GSK Consumer, Canad.; Stafford-Miller, UK; Prestige, USA.*
Alpha galactosidase A (p. 2437·2).
Flatulence arising from ingestion of complex carbohydrates.

Beapen *CCM, Malaysia.*
Phenoxymethylpenicillin potassium (p. 338·3).
Gram-positive bacterial infections; rheumatic fever.

Beaphenicol *CCM, Malaysia; Beacons, Singapore.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Beapizide *Beacons, Singapore.*
Glipizide (p. 474·1).
Diabetes mellitus.

Beaplen *Temis, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Beaplex *Beacons, Singapore.*
Thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); folic acid (p. 2063·1).
Vitamin B supplement.

Beaptin *Beacons, Singapore.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; arrhythmias.

Bearantel *Beacons, Singapore.*
Pyrantel embonate (p. 165·3).
Worm infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

BeaRAX *Beacons, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Bearcef *Daewoong, Singapore.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Bear-E-Yum *Mallinckrodt, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Beatac *Beacons, Singapore.*
Ranitidine (p. 1882·1).
Dyspepsia; peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Beatacycline *Beacons, Singapore.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

CCM, Malaysia.
Tetracycline (p. 373·1).
Bacterial infections.

Beatafed *CCM, Malaysia.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis; upper respiratory-tract congestion; sinusitis.

Beathorphan *Beacons, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Beathricin *Beacons, Singapore.*
Lidocaine hydrochloride (p. 1988·2); tyrothricin (p. 384·1).
Mouth and throat pain.

Beatifen *Beacons, Singapore.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; allergic conjunctivitis.

Beatizem *Beacons, Singapore.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Beatoconazole *Beacons, Singapore.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Beatolin *CCM, Malaysia.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Beats *Biological E, India.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Beauté Initiale *Chanel, Canad.†*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Beavate *CCM, Malaysia.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Beavate N *CCM, Malaysia.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Beazyme *CCM, Malaysia.*
⊗Papain (p. 2582·3).
Inflammatory disorders; oedema.

Bebe Dep *Pasteur, Chile.*
Glucose monohydrate (p. 2069·1); tamarind (p. 1892·2); plum; kiwi fruit.
Constipation.

Bebe Flat *Pasteur, Chile.*
Glucose monohydrate (p. 2069·1); chamomile (p. 2474·1); fennel (p. 2503·2).
Digestive disorders.

Bebe Son *Pasteur, Chile.*
Glucose monohydrate (p. 2069·1); tilia (p. 2631·3); chamomile (p. 2474·1); melissa (p. 2552·3).
Sleep disorders.

Bebebiafine Anti-Rougeures *Johnson & Johnson, Fr.*
Zinc oxide (p. 1729·1); panthenol (p. 2582·2).
Nappy rash.

Bebederm *Lafedar, Arg.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); zinc oxide (p. 1729·1); benzocaine (p. 1980·2).
Skin disorders.

Bebedermis Pomada *HMA, Arg.*
Zinc oxide (p. 1729·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Skin disorders.

Bebedol *VHB, India.*
⊗Bisoprolol (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bébégel *Meda, Fr.*
⊗Glycerol (p. 2517·2).
Constipation; bowel evacuation.

Bebegel *Meda, Port.*
⊗Glycerol (p. 2517·2).
Constipation; bowel evacuation.

Bebegesic *Medipharm, Chile.*
Lidocaine hydrochloride (p. 1988·2).
Teething pain; stomatitis; pharyngitis.

Bebektin *Janssen-Cilag, Mex.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Infected skin disorders.

Bebelac EC *Global Eramas, Indon.; Lyempf, Indon.; Tempo Scan Pacific, Indon.; Dumex, Malaysia.†*
Infant feed.
Gastrointestinal disorders.

Bebelac FL *Nutricia, Indon.*
Lactose-free infant feed.
Lactose intolerance.

Dumex, Malaysia.†
Infant feed.
Lactose intolerance.

Beben *Johnson & Johnson, Ital.*
⊗Betamethasone benzoate (p. 1623·3).
Skin disorders.

Beben Clorossina *Johnson & Johnson, Ital.*
⊗Betamethasone benzoate (p. 1623·3); chloroxine (p. 260·1).
Infected skin disorders.

Bebex ADE *Geolab, Braz.*
Zinc oxide (p. 1729·1); colecalciferol (p. 2113·1); vitamin A (p. 2098·3).

Bebex N *Geolab, Braz.*
Nystatin (p. 590·3).

Bebex Previne *Geolab, Braz.*
Zinc oxide (p. 1729·1).

Bebexin *Demo, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Bebidol *TNP, Thai.*
Dill oil (p. 2493·2); sodium bicarbonate (p. 1781·1).
Infant bloating; flatulence.

Bebilon Amino *Nutricia, Pol.†*
Infant feed.
Food allergy; colic.

Bebilon BMF *Nutricia, Pol.†*
Vitamins; minerals.
For low-birth weight infants.

Bebilon Neocate *SHS, Pol.*
Infant feed.
Cows milk allergy; protein intolerance; gastro-oesophageal reflux; short-bowel syndrome; colitis.

Bebilon Pepti *Nutricia, Pol.*
A range of infant feeds.
Food allergy; diarrhoea; colic.

Bebilon Sojowy *Nutricia, Pol.*
Soy-based infant feed.
Lactose and sucrose intolerance; galactosaemia; fructosaemia; cows milk intolerance.

Bebimix *Sella, Ital.†*
Honey (p. 2072·1); royal jelly (p. 2608·1); myrtillus (p. 2566·2).
Nutritional supplement.

Bebol *Wyeth, Turk.†*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Bebulin VH *Immuno, USA.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Bec *Nichi-Iko, Jpn.*
Aranidipine (p. 1307·1).
Hypertension.

Becadex *GSK, India.*
Oral drops: Vitamins.

GSK, India.
Tablets: Vitamins; calcium hydrogen phosphate (p. 1783·3).

Becadexamine *GSK, India.*
Vitamins; minerals.

Became *Yung Shin, Hong Kong; YSP, Malaysia; Yung Shin, Singapore.*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Becantex
Note: this name may be used for preparations of different composition.
Pharos, Indon.
Rebamipide (p. 1884·1).
Gastric ulcer; gastritis.

Sanofi-Aventis, Port.
Sodium dibunate (p. 1677·3).
Cough.

Becap-CZ *Gujarat Terce, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Becarbon
Note: this name may be used for preparations of different composition.
Shchelkovskii, Rus.
Belladonna (p. 2453·3); sodium bicarbonate (p. 1781·1).
Gastrointestinal disorders.

Becarin *CCM, Malaysia.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Becarve *Medley, Braz.*
⊗Carvedilol (p. 1333·1).

Becderm *Cipla, India.*
⊗Beclometasone (p. 1621·2).
Skin disorders.

Becderm-N *Cipla, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bêcê *Codilab, Port.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin supplement.

Becebuen Compuesto *Monserrat, Arg.*
Pargeverine hydrochloride (p. 1877·1); clonixin lysine (p. 40·1).
Smooth muscle pain and spasm.

Becebuen Gotas *Monserrat, Arg.*
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm.

Bececar *Interbat, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin supplement.

BECeco *Sandoz, Switz.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Becede *Vannier, Arg.*
Alprazolam (p. 1035·2).
Anxiety.

Becedyn *Bayer, Philipp.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C deficiency.

Becef *Alkem, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Becefort *Phapros, Indon.*
Vitamins.
Dietary supplement.

Becelac *Reddy, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); *Lactobacillus acidophilus* (p. 2596·3).

Becelac Forte *Reddy, India.*
Vitamin B substances (p. 2102·3); *Lactobacillus acidophilus* (p. 2596·3).

Becelac PB *Reddy, India.*
Bacillus mesentericus; *Clostridium butyricum*; *Lactobacillus sporogenes* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).

Becenun *BMS, Braz.*
Carmustine (p. 761·2).
Malignant neoplasms.

Becetamol *Gebro, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Becetamol C *Gebro, Switz.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Beceton *Elpen (Ελπεν), Gr.*
Vitamins; minerals; lysine (p. 2079·3).

Beceze *Biotech, S.Afr.; Ivax, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; allergic rhinitis.

Bechilar *Montefarmaco, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bechlomin *Jean-Marie, Hong Kong.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; inflammatory eye disorders.

Bécilan *DB, Fr.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Becilan *IFET (ΙΦΕΤ), Gr.*
Pyridoxine hydrochloride (p. 2105·3).

Beciosal *Candor, India.*
⊗Beclometasone dipropionate (p. 1621·2); salicylic acid (p. 1719·1).

Beclase *De Mayo, Braz.†*
⊗Sodium dibunate (p. 1677·3); mepyramine maleate (p. 635·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Beclasma *Raffo, Arg.*
⊗Beclometasone dipropionate (p. 1621·2); salbutamol (p. 1220·2).
Asthma.

Beclasone *Emcure, India.*
⊗Beclometasone (p. 1621·2).
Skin disorders.

Beclasone-C *Emcure, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).

Beclasone-GM *Emcure, India.*
⊗Beclometasone dipropionate (p. 1621·2); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Beclate *Cipla, Hong Kong; Cipla, India; Cipla, Malaysia; Cipla, Rus.; Cipla-Medpro, S.Afr.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; nasal polyps; skin disorders; allergic rhinitis.

Beclate-C *Cipla, India.*
⊗Beclometasone dipropionate (p. 1621·2); clioquinol (p. 273·1).
Infected skin disorders.

Beclate-N *Cipla, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Beclazide *Berlin Pharm, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Beclazone *Ivax, Hong Kong; Teva, Hong Kong; Norton Waterford, Irl.; Ivax, Malaysia; Ivax, Mex.†; Airflow, NZ; Teva, Rus.; Teva, UK†; Teva, Ukr.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

Beclex-GM *Lexus, India.*
⊗Betamethasone dipropionate (p. 1623·3); chlorocresol (p. 1748·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Beclo *Sandoz, Ger.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclo Asma *Aldo-Union, Singapore; Aldo, Spain.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclo Rino *Aldo, Spain.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis; nasal polyps.

Becloair *Biodeal, India.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Beclocid *Intermed, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).

Beclocid-G *Intermed, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Beclocin-O *Haledew, India.*
⊗Beclometasone (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).

Beclocip *Medispray, Thai.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclocort-N *Sun, India.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin (p. 329·3).
Infected skin disorders.

Becloderm *Intermed, India.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Becloderm-C *Intermed, India.*
⊗Beclometasone dipropionate (p. 1621·2); clioquinol (p. 273·1).

Becloderm-N *Intermed, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Beclodin *Chiesi, Neth.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Becloenema *Farmalider, Spain.*
⊗Beclometasone dipropionate (p. 1621·2).
Ulcerative colitis.

Becloforte *GSK, Cz.; GSK, Neth.†; GSK, Rus.†; GSK, S. Afr.†; GSK, Spain; GSK, Turk.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclofortil *Medifarm, Venez.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclogen
Note: this name may be used for preparations of different composition.
Generics, UK.
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Tocogino, Mex.
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Beclohale *Julphar, UAE.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclohexal *Hexal, Ger.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclojet *Chiesi, Fr.; Chiesi, Rus.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclolab-CG *Laborate, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Beclolab-NC *Laborate, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).
Infected skin disorders.

Beclomet *Lannacher, Austria; Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Ger.; Farmaten, Gr.; Actavis, Indon.†; Orion, Malaysia; Orion, Norw.; Orion, Singapore; Orion, Swed.; Orion, Thai.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; nasal polyps; allergic rhinitis.

Beclometatop *Topgen, Belg.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Beclomin
Note: this name may be used for preparations of different composition.
Jean-Marie, Hong Kong.
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; inflammatory eye disorders.

Leben, India.
Lotion: ⊗Beclometasone dipropionate (p. 1621·2); miconazole nitrate (p. 589·1).

Leben, India.
Ointment: ⊗Beclometasone dipropionate (p. 1621·2); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Beclomycin *Medichrom, Gr.*
⊗Nystatin (p. 590·3); beclometasone dipropionate (p. 1621·2).
Infected skin disorders.

Beclonarin *Rappai, Switz.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis; polyps.

Beclonasal *Orion, Fin.; Orion, Hung.; Orion, Pol.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis; nasal polyps.

Beclonato *Ducto, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Beclone *Leurquin, Fr.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Becloneb *Chiesi, Gr.; Chiesi, Irl.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclophar *Sandoz, Belg.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclo-Rhino *Meda, Fr.; Goldshield, Irl.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis; sinusitis.

Beclorhinol *Chiesi, Ger.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis; nasal polyps.

Beclorino *Medifarm, Venez.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis; nasal polyps.

Beclort *Glenmark, Braz.*
⊗Beclometasone dipropionate (p. 1621·2).

Beclosal *Medispray, Thai.; Biogalenic, Venez.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease; asthma.

Beclosema *Etex, Chile.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclosil *Medifarm, Venez.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Beclosol *GSK, Braz.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; rhinitis; nasal polyps.

Beclosona *Spyfarma, Spain.†*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Beclospin *Chiesi, Fr.; Chiesi, Gr.; Chiesi, Irl.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclospir *Pharmaceutical Factory of St Petersburg, Rus.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclospray *Chiesi, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclotaide *Alenfarma, Port.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclotis-C *Cadila, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).
Infected skin disorders.

Beclotis-CG *Cadila, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Beclotrin *Arlex, Mex.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Beclov *Sanbe, Indon.*
Citicoline (p. 2480·1).
Head injury; ischaemic stroke; hemiplegia.

Beclovent *Glaxo Wellcome, USA.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beclozen *Haledew, India.*
⊗Beclometasone (p. 1621·2); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Becmet-CG *Ind-Swift, India.*
Cream: ⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Ind-Swift, India.
Ear drops: ⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2); lidocaine hydrochloride (p. 1988·2).

Becmet-G *Ind-Swift, India.*
⊗Beclometasone dipropionate (p. 1621·2); gentamicin (p. 304·2).
Infected skin disorders.

Becmet-GM *Ind-Swift, India.*
⊗Beclometasone dipropionate (p. 1621·2); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Becmet-N *Ind-Swift, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Becmet-S *Ind-Swift, India.*
⊗Beclometasone dipropionate (p. 1621·2); salicylic acid (p. 1719·1).
Hyperkeratotic skin disorders; dry skin disorders.

Becobol *Ultramark, India.*
Vitamin B substances (p. 2102·3).

Becoderm *GSK Consumer, Austral.†*
⊗Glycerol (p. 2517·2).
Dry skin; pruritus.

Becoderm-C *GSK Consumer, Austral.†; GSK, NZ.†*
⊗Clobetasone butyrate (p. 1627·3).
Eczema; skin disorders.

Becodisk *GSK, Pol.†; GSK, Rus.†; GSK, Switz.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Becodisks *GSK, Cz.†; GSK, Turk.; Allen & Hanburys, UK.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Becodryl *JK Biochem, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Becof *Caps, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Becoff *Caps, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).

Becofine *Finecure, India.*
Vitamin B substances (p. 2102·3).

Becolex *Chiesi, Gr.*
⊗Beclometasone dipropionate (p. 1621·2).
Corticosteroid.

Becolim *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Becom *Global, India; British Dispensary, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Becom Plus *Global, India.*
Vitamins; minerals.

Becombion *Merck, Indon.; Merck Serono, Malaysia.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Becombion Extra Lysine *Merck, Indon.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Becombion Grow Syrup *Merck Consumer, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); inulin (p. 2534·3); calcium phosphate (p. 1784·2).
Dietary supplement.

Becom-C *Sanbe, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Becompex *Christo, Hong Kong.†*
Vitamins; with or without zinc (p. 2126·1).

Becomplina Fuerte *Labomed, Chile.†*
Thiamine (p. 2102·3); riboflavin (p. 2104·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); calcium pantothenate (p. 2085·2).
Vitamin B supplement.

Bêcomvite *Azevedos, Port.†*
Vitamin B substances (p. 2102·3).

Becom-Zet *Sanbe, Indon.*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Beconac *Plus, India.*
Diclofenac sodium (p. 48·3).
Pain.

Beconase *GSK Consumer, Austral.†; GSK, Belg.†; GSK, China; GSK, Cz.†; GSK, Denm.; GSK, Fin.; GSK, Hong Kong; GSK, Indon.†; GSK, Irl.; GSK, Malaysia; GSK, Mex.; GSK Consumer, Port.; GSK, Rus.†; GSK, S.Afr.; Allen, Spain; GSK, Switz.; GSK, Thai.; GSK Consumer, UK; Glaxo Wellcome, USA; GSK, Venez.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis; allergic rhinitis; nasal polyps.

Béconase *GSK, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Beconase Allergy & Hayfever 12 Hour *GSK Consumer, Austral.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Beconase Aquosum *GSK, Ger.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis; nasal polyps.

Beconase Hayfever *GSK Consumer, Irl.; GSK, NZ.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Beconasol *GSK, Switz.†*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis; nasal polyps.

Becoplex Ido *Biotech, S.Afr.*
Vitamin B substances (p. 2102·3).

Becoplus *Uni-Sankyo, India.*
Lactobacillus; vitamin B substances (p. 2102·3).

Becoplus Z *Uni-Sankyo, India.*
Lactobacillus; vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Beco-Red-12 *Invision, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Becored-TR *Invision, India.*
Lactobacillus; vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Becoride *GSK, India.*
⊗Beclometasone (p. 1621·2).
Asthma.

Becortem *Bergamo, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Becortin *Purissimus, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin embonate (p. 304·2); clotrimazole (p. 576·2).
Infected skin and mucous membrane disorders.

Becoryl *Aglowmed, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Becoscosh *Scoshia, India.*
Vitamins.

Becose *Medizone, India.*
Vitamins; trace elements; spirulina (p. 2622·1).

Becosules *Pfizer, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Becotac *Plus, India.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Bécotal *Streuli, Switz.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; neuropathies.

Becotide *GSK, Austral.†; GSK, Austria; GSK, China; GSK, Cz.†; GSK, Gr.; GSK, Indon.†; GSK, Irl.; Lusofarmaco, Ital.; GSK, Mex.†; GSK, Norw.†; GSK, Rus.; GSK, S.Afr.†; GSK, Spain; GSK, Swed.; GSK, Turk.†*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease; asthma; rhinitis; nasal polyps.

Bécotide *GSK, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Becovigen *Eras, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Becovit *Julphar, UAE.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Becovit Forte *Cipla, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Becovital *Kocak, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Becovital-C *Kocak, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Becowel Forte *Akums, India.*
Vitamins; minerals.

Becox Forte Kit *Panjon, India.*
1 Tablet, ethambutol (p. 296·1); isoniazid (p. 311·2); 2 tablets, pyrazinamide (p. 345·2); rifampicin (p. 350·3); pyridoxine hydrochloride (p. 2105·3).
Tuberculosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Becox RH *Panjon, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Becozinc *Reddy, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc gluconate (p. 2126·2) or zinc sulfate (p. 2126·2).

Becozym *Bayer Consumer, Arg.; Piramal, India; Roche, Israel; Bayer, Ital.; Bayer, Swed.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; alcoholism; neuralgia; neuropathies; vitamin B supplement.

Becozym C Forte *Piramal, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Becozyme *Roche, Gr.; Bayer, Port.; Bayer, Switz.; Abbott, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; neuritis; nausea and vomiting in pregnancy; liver disorders; alcoholism; neuralgia.

Bayer, Belg.
Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3); minerals.

Bécozyme *Bayer Sante, Fr.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; tonic.

Becozyme C *Bayer, Port.; Abbott, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Becozyme C Forte *Bayer, Spain.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Becozyme-S *Bayer, Gr.; IFET (ΙΦΕΤ), Gr.*
Vitamins.
Vitamin B deficiency.

Bectam *Labomed, Chile.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Bectop *Cosme, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).

Bectosan *Liferpal, Mex.*
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Bectozid *Cadila, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Becze-N *Zee, India.*
⊗Beclometasone (p. 1621·2); neomycin (p. 329·3).
Infected skin disorders.

Bed Wetting *Hylands, Canad.†*
Belladonna (p. 2453·3); equisetum hyemale; rhus aromatica (p. 2603·3).
Homoeopathic preparation.

Bedelix *Ipsen, Fr.*
Montmorillonite beidellitique.
Irritable bowel syndrome.

Bedena *SM, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Bediatil *Pasteur, Chile.*
Ibuprofen (p. 68·2).
Fever; pain.

Bedice *Genepharm, Gr.*
Flurbiprofen (p. 65·2).
Inflammatory disorders; pain.

Bedicort G *Jelfa, Pol.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Bedin *Pharmasant, Thai.*
⊗Dihydroergocristine mesilate (p. 390·1); clopamide (p. 1342·3); reserpine (p. 1485·3).
Hypertension.

Bedix *Bernabo, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Bedix-D *Bernabo, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Bedoc *IFET (ΙΦΕΤ), Gr.*
Cyanocobalamin (p. 2107·2).

Bedoce-Cal *Sanofi-Aventis, Mex.*
Calcium phosphate (p. 1784·2); cyanocobalamin (p. 2107·2).
Anaemias; calcium supplement.

Bedodeka *Teva, Israel.*
Cyanocobalamin (p. 2107·2).
Anaemias; vitamin B_{12} deficiency.

Bedol *Resource Medical, UK.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Bedoral *Be-Tabs, S.Afr.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Bedovit Compuesto *Inquifave, Venez.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).
Neurological disorders resulting from vitamin deficiency.

Bedovit Pharmaton *Boehringer Ingelheim, Chile.*
⊗Ginseng (p. 2513·3); deanol tartrate (p. 2319·1); vitamins; rutoside (p. 2505·3); minerals; soya lecithin (p. 2542·2).
Tonic.

Bedovit Simple *Inquifave, Venez.*
Cyanocobalamin (p. 2107·2).
Anorexia; vitamin B_{12} deficiency.

Bedoxin *Plus, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Bedoxinal *Ilacsan, Turk.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Vitamin B deficiency.

Bedoxine *Therabel, Belg.†*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Bedoyecta
Note: this name may be used for preparations of different composition.
Farma, Venez.
Hydroxocobalamin (p. 2107·3); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Neuritis; neuralgia.

Grossman, Mex.
Calcium ascorbate (p. 2111·1); vitamin B substances (p. 2102·3); inositol (p. 2533·2); rutoside (p. 2505·3).

Bedoyecta Ped *Grossman, Mex.*
Vitamin B substances (p. 2102·3).

Bedoyecta Tri *Grossman, Mex.*
Vitamin B substances (p. 2102·3).

Bedozil *Bunker, Braz.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} supplement; megaloblastic anaemia.

Bedranol *Sandoz, UK.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; migraine; tremor; anxiety; hyperthyroidism; upper gastrointestinal bleeding.

Bee three *Medicine Products, Thai.*
Thiamine nitrate (p. 2103·2); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).

Beecham Lemon *GSK Consumer, Spain.†*
Ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Beechams Active Cold Relief *GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Beechams All-In-One *GSK Consumer, UK.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Beechams Cold & Flu *GSK Consumer, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Beechams Cold Relief *GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Beechams Decongestant Plus with Paracetamol *GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Beechams Flu-Plus *GSK Consumer, UK.*
Tablets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

GSK Consumer, UK.
Oral liquid: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); vitamin C (p. 2110·3).
Cold and influenza symptoms.

GSK Consumer, Irl.†
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Beechams Hot Lemon *GSK, Hong Kong.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Beechams Max Strength Sore Throat Relief *GSK Consumer, UK.*
Hexylresorcinol (p. 1755·1); benzalkonium chloride (p. 1737·1).
Sore throat.

Beechams for Natural Defence *GSK Consumer, UK.*
Ascorbic acid (p. 2110·3) with zinc.

Beechams Powders *GSK Consumer, UK.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Cold and influenza symptoms; pain.

Beechams Powders Capsules *GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Beechams Throat-Plus *GSK Consumer, UK.*
Benzalkonium chloride (p. 1737·1); hexylresorcinol (p. 1755·1).
Sore throat.

Beedec *Alpic, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Beefolic *Sriprasit, Thai.*
Vitamin B substances (p. 2102·3); folic acid (p. 2063·1).
Vitamin B deficiency, neuritis.

Beehive Balsam *Ayrton, UK.*
⊗Purified honey (p. 2072·1); glycerol (p. 2517·2); ipecacuanha (p. 1667·2).
Coughs.

Beelith *Beach, USA.*
Pyridoxine hydrochloride (p. 2105·3); magnesium oxide (p. 1857·3).
Dietary supplement.

Beemine *Biomiicron, India.*
Neostigmine metilsulfate (p. 687·2).
Myasthenia gravis; reversal of competitive neuromuscular blockade; paralytic ileus; urinary retention.

Beenos *Mithra, Belg.*
Alendronic acid (p. 1171·3).
Osteoporosis.

Beesix *SA Druggists Self Med, S.Afr.†*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Beespan *Aspen, S.Afr.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiencies.

Beetab *Littman, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Vitamin B and E deficiency.

Beetal *Intas, India.*
Vitamin B substances (p. 2102·3); phenobarbital (p. 535·2).
Epilepsy; sedative.

Beetone *Yacca, India.*
Capsules: Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Yacca, India.
Syrup: Vitamin B substances (p. 2102·3); ferrous gluconate (p. 2061·2).

Beetrion *Franco-Indian, India.*
Vitamins; minerals.
Dietary supplement.

Bee-Zee *Rugby, USA.*
Vitamins; minerals.

Befact *SMB, Belg.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; neuritis; alcoholism.

Befar *Nexmed, Hong Kong.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Befarin *Berlin Pharm, Thai.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Beferon *Cristalia, Braz.†*
Interferon alfa (p. 989·2).

Beferron *Gache, Venez.*
Ferric ammonium citrate (p. 2060·1); vitamin B_{12} (p. 2107·2).
Anaemias.

Befibrat *Hennig, Ger.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Befimat *Biomedica, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Befitec *Tecnofarma, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Béfizal *Actavis, Fr.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Béflavine *Bayer Sante, Fr.*
Riboflavin (p. 2104·3).
Vitamin B deficiency.

Be-Flex Plus *Larken, USA.†*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1); salicylamide (p. 129·2).
Pain.

Befol
Note: this name may be used for preparations of different composition.
Biotenk, Arg.
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Farma, Venez.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Hyperhomocysteinaemia.

Madhav, India.
Iron carbonyl (p. 2073·1); vitamin E (p. 2119·1); zinc (p. 2126·1).

Befol Plus *Biotenk, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; inflammation; pain.

Be-Force *JK Biochem, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Beforplex *Eumedica, Belg.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Befosfin *Cafar, Venez.*
Cocarboxylase (p. 2103·1); vitamin B_{12} (p. 2107·2); riboflavin phosphate.
Neuritis; vitamin B deficiency.

Befozi *Soho, Indon.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Anaemias; dietary supplement in pregnancy and lactation.

Befucil *Biomedica, Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Befungin *Tatkhimfarm, Rus.*
Birch fungus.
Gastrointestinal disorders.

Begadon *Berman, Mex.*
Vitamin B substances (p. 2102·3).

Begalin *Pfizer, Gr.*
Sultamicillin (p. 369·1) or sultamicillin tosilate (p. 369·1).
Bacterial infections.

Begalin-P *Pfizer, Gr.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Begesic
Note: this name may be used for preparations of different composition.
Berlin Pharm, Singapore; Berlin Pharm, Thai.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint disorders.

Littman, Philipp.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); cajuput oil (p. 2464·1).
Pain; musculoskeletal, joint, and soft-tissue disorders; insect bites.

Begincalm *Genepharm, Gr.*
Indometacin (p. 71·2).
Inflammatory disorders.

Beglan *GSK, Spain.*
⊗Salmeterol xinafoate (p. 1224·1).
Asthma; bronchitis.

Beglaryl *Cosmopharm, Gr.*
Amlodipine mesilate (p. 1304·1).

Begrivac *Novartis, Arg.; Grunenthal, Austria†; Novartis, Chile; Novartis Vaccines, Cz.; Novartis, Denm.; Novartis Vaccines, Fin.†; Novartis Behring, Ger.†; Novartis, Hung.; Novartis Vaccines, Irl.; Novartis, Norw.†; Chiron Behring, Pol.; Novartis Vaccines, Rus.; Novartis Vaccines, Thai.†; Wyeth, UK.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Behepan *Pfizer, Swed.*
Tablets: Cyanocobalamin (p. 2107·2).
Megaloblastic anaemia; sprue; vitamin B_{12} deficiency.

Pfizer, Swed.
Injection: Hydroxocobalamin acetate (p. 2107·3).
Megaloblastic anaemia; sprue; vitamin B_{12} deficiency; schilling test.

Beheptal *Biosel, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Behistin *Pharmasant, Thai.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Behkacin *Behrens, Venez.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Behoedmiddel vir Kinders *Aspen Consumer, S.Afr.*
Magnesium carbonate (p. 1856·2); chalk (p. 1826·3).
Gastric hyperacidity.

Behrifil *Sanofi-Aventis, Ital.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Behyd *Kyorin, Jpn.*
⊗Benzylhydrochlorothiazide (p. 1316·2).
Hypertension; oedema.

Behyd-RA *Kyorin, Jpn.*
⊗Benzylhydrochlorothiazide (p. 1316·2); reserpine (p. 1485·3); carbazochrome (p. 1137·1).
Hypertension.

Bei Bang *Hengrui, China.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Bei Da Ruo Tong *NCPC, China.*
Levofloxacin mesilate.
Bacterial infections.

Bei Dun *Hailisheng, China.*
Cefalexin (p. 234·1).
Bacterial infections.

Bei En *Pharmachemie, China.*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms.

Bei Er Fen *Xindazhou, China.*
Interferon alfa-2a (human, recombinant) (p. 989·2).

Bei Er Ping *Haiyan, China.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension.

Bei De Fen *CSPC, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Bei Fen *Yi Hua, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Bei Fu Xin *Essex, China.*
Recombinant bovine basic fibroblast growth factor.

Bei He *Tianhedi Sainuo, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Bei He Jian *GuoRui, China.*
⊗Bambuterol hydrochloride (p. 1203·1).

Bei Jia *Chia Tai, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Bei Ka Ming *Jimin Kexin Shanhe, China.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Bei Ke *Aoda, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bei Ke Er *Minsheng, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bei Lai *Hengrui, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bei Lan De *Bei Shi, China.*
Famotidine (p. 1842·1).
Dyspepsia; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Bei Li De *Bei Shi, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bei Li *Deyer, China.*
Naproxen sodium (p. 98·2).
Pain.

Bei Li Ning *Lunan, China.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension.

Bei Li Si *Zhi Yuan Guang He, China.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Bei Luo *De Zhou, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Bei Luo Na *Kanghong, China.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Bei Luo Te *TianJin, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Bei Luo Xin *Dongbao, China.*
Diltiazem hydrochloride (p. 1359·2).

Bei Di Ning *Baiyunshan, China.*
Telmisartan (p. 1509·3).
Hypertension.

Bei Pin *Xinhua, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Bei Qing Xing *Shi Xin, China.*
Oxiracetam (p. 393·3).
Mental function impairment.

Bei Rui Ning *Lai Mei, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Bei Sha *Hui Pu Sen, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bei Shi Li *Tiantaishan, China.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Bei Shu *Di Ao, China.*
⊗Benorilate (p. 29·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Bei Shu Lin *Beiyuan, China.*
Amoxicillin sodium (p. 216·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Bei Shun *Hengrui, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bei Le Si *An Te, China.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Bei Si Qing *Kanghong, China.*
Flavoxate hydrochloride (p. 2360·1).
Urinary tract disorders.

Bei Si Te *Minsheng, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bei Su *Yangtze River, China.*
Moclobemide (p. 437·2).
Depression; social phobia.

Bei Su Qing *Topsun, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Bei Tai *Simcere, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bei Te Ling *Hailisheng, China.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Bei Xi Di *Sine, China.*
Betacarotene (p. 2051·1).
Dietary supplement.

Bei Xi Yi *Jiu Fu, China.*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); vitamin C (p. 2110·3).
Dietary supplement.

Bei Le Xin *Hengrui, China.*
Paracetamol (p. 115·1).
Fever; pain.

Bei Xin *Qian Long, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Bei Xing *Jin Yuan, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Bei Ying *Jinshi, China.*
Barium sulfate (p. 1583·2).

Bei Yu *Xin Gang Union, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Bei Zong *Daqing, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Beibeisha *Southwest, China.*
Josamycin propionate (p. 314·2).
Bacterial infections.

BeiFen *Lunan, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Beifuji *Essex, China.*
Recombinant bovine basic fibroblast growth factor.
Wounds; ulcers; burns.

Beifushu *Essex, China.*
Recombinant bovine basic fibroblast growth factor.
Corneal disorders.

Beigesi *Zhi Yuan Guang He, China.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Beikang *United Lab, China.*
Miconazole nitrate (p. 589·1).
Fungal infections of skin and nails; fungal and Gram-positive vaginal infections.

BeiKe *Dikang, China.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Beikele *Tianping, China.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Beikeli *Minsheng, China; Sanofi, China.*
Metildigoxin (p. 1433·1).
Heart failure; arrhythmias.

Beiklin *Scherer, Singapore.*
Vitamins; minerals.

Beilande *HPP, Hong Kong.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

BeiLiDe *Aoda, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Beilijin *Bangmin, China.*
Benorilate (p. 29·1).
Fever; pain.

BeiLong *Shide, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Beining *Zhi Jun, China.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Beinuoke *Baker Norton, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Beiqi *Chia Tai, China.*
Azelnidipine (p. 1313·2).

Beisong *United Lab, China.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Beitangning *Baoguang, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Beixi *Baoguang, China.*
Acarbose (p. 466·2).
Diabetes mellitus.

BeiXin *United Lab, China.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Beiyuan *LuoXin, China.*
Lysine hydrochloride (p. 2079·3).

Bekacin *Ultramark, India.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Bekamin C *Kimia, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; capillary bleeding.

Bekarbon *Kimia, Indon.*
Activated charcoal (p. 1537·3).
Diarrhoea; flatulence.

Bekaycin *Sanofi-Aventis, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Bekesina *Ultra, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Bekesina-S *Ultra, Mex.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bekfan-C *Arlex, Mex.†*
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Bekidiba *Diba, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Bekidiba Dex *Diba, Mex.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bekker *Positif, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bekker-M *Positif, India.*
Ofloxacin (p. 334·3); metronidazole (p. 936·1).

Bekker-OZ *Positif, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Beklamet *Tems, Turk.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Beklazon *Bilim, Turk.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Beknol *Kener, Mex.*
Benzonatate (p. 1656·2).
Cough.

Beko *Orion, Fin.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Bekunis
Note: this name may be used for preparations of different composition.
Roha, Canad.†; Roha, Port.; Abdi, Turk.
Tablets: Bisacodyl (p. 1821·1); senna (p. 1885·1).
Constipation.

Schulke & Mayr, Austria; Roha, Canad.; Novadental, Gr.; Roha, Israel; Farmasa, Mex.; Roha, Pol.; Roha, Port.; Roha, Singapore; Roha, Spain; Ars Vitae, Switz.
Senna (p. 1885·1).
Constipation; bowel evacuation.

Bekunis Bisacodyl *Roha, Ger.*
Bisacodyl (p. 1821·1).
Constipation.

Bekunis Complex *Roha, Spain.*
Bisacodyl (p. 1821·1); senna (p. 1885·1).
Constipation; bowel evacuation.

Bekunis Dragées *Ars Vitae, Switz.*
Bisacodyl (p. 1821·1).
Constipation.

Bekunis Instant *Roha, Ger.*
Senna (p. 1885·1).
Constipation.

Bekunis Laxante Bisacodil *Roha, Port.*
Bisacodyl (p. 1821·1).
Constipation.

Bekunis Laxante Natural *Roha, Port.*
Senna (p. 1885·1).
Constipation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bekunis Plantaardig *Roha, Neth.†*
Senna (p. 1885·1).
Constipation.

Bekunis Senna *Roha, Neth.†*
Senna (p. 1885·1).
Constipation.

Bekunis Tea *Thursday, Austral.†*
Senna (p. 1885·1).
Constipation.

Bekunis-Kräutertee N *Roha, Ger.*
Senna (p. 1885·1).
Constipation.

BeL *Winthrop, Ger.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease secondary prophylaxis.

Bel Labial *Nycomed, Spain.†*
Aciclovir (p. 964·1).
Herpes simplex infections.

Belachin-Gastreu R1 *Reckeweg, Neth.*
Apis mellifica (p. 2445·2); belladonna (p. 2453·3); kalium bichromicum (p. 2476·3); mercurius corrosivus (p. 2555·2); phytolacca decandra (p. 2593·2); teucrium marum verum.
Homoeopathic preparation.

Belacid *Nakornpatana, Thai.*
Charcoal (p. 1537·3); magnesium hydroxide (p. 1857·2); belladonna (p. 2453·3); peppermint oil (p. 1877·1).
Gastric hyperacidity; flatulence.

Belagin *IMA, Braz.†*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); aluminium (p. 2439·2); menthol (p. 2553·2); benzalkonium chloride (p. 1737·1).
Gynaecological infections.

Belanette *Bayer Schering, Cz.; Bayer, Fr.*
Ethinylestradiol betadex clathrate (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Bayer, Neth.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Belar *Comed, India.*
Cream: ⊗Beclometasone (p. 1621·2).
Skin disorders.

Comed, India.
Tablets: ⊗Betamethasone (p. 1623·2).
Corticosteroid.

Belara *Grunenthal, Austria; Janssen-Cilag, Braz.; Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Fr.; Gedeon Richter, Ger.; Grunenthal, Hung.; Tec-O-Pharm, Israel; Formenti, Ital.; Grunenthal, Mex.; Grunenthal, Port.; Grunenthal, Rus.; Gedeon Richter, Spain; Gedeon Richter, Switz.; Grunenthal, Switz.; Abbott, Thai.; Organon, Turk.; Grunenthal, Ukr.; Grunenthal, Venez.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; androgenisation in women.

Belar-G *Comed, India.*
⊗Beclometasone dipropionate (p. 1621·2); gentamicin (p. 304·2).
Infected skin disorders.

Belarina *Gedeon Richter, Switz.; Grunenthal, Switz.*
24 Tablets, ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3); 4 tablets, inert.
Combined oral contraceptive.

Belasperdal-S *SJA, Gr.*
Risperidone (p. 1103·2).

Be-Lax *Be-Tabs, S.Afr.*
Magnesium sulfate (p. 1787·3); magnesium carbonate (p. 1856·2).
Constipation.

Belax *Synmosa, Malaysia.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Belbar *Luar, Arg.*
⊗Neomycin (p. 329·3); polymyxin B (p. 342·3); dexamethasone (p. 1630·3).
Infected eye disorders.

Belbarmicina *Luar, Arg.*
Tobramycin (p. 380·1).

Belcid *Biolab, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; dyspepsia; flatulence.

Belcomplex *Belfar, Braz.*
Vitamin B substances (p. 2102·3).

Belen *New Life, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Belenzok *Norpharm, Cz.†*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; heart failure; arrhythmias; myocardial infarction; migraine.

Belestar *Biol, Arg.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Belex *Gulf Drug, S.Afr.*
Cefalexin (p. 234·1).
Bacterial infections.

Belexa *Farmasa, Braz.*
Vitamin B substances (p. 2102·3).

Belfactrim F *Belfar, Braz.*
Co-trimoxazole (p. 277·3).

Belfaren *Belfar, Braz.*
Diclofenac sodium (p. 48·3).

Belfedane *Novo Pharm, Philipp.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Belfix *Blubell, India.*
Cefixime (p. 240·3).
Bacterial infections.

Belfix-CV *Blubell, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Belfor *Menarini, Neth.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Belfor HCT *Menarini, Neth.*
⊗Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Belgabin *Alapis, Gr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Belgest *Blubell, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea.

Beliam *Abbott, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Belief *Symbiosis, India.*
Aluminium hydroxide (p. 1817·2); oxetacaine (p. 1993·1).

Belifax *Pharmathen, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori in combination with antimicrobials; reflux oesophagitis; Zollinger-Ellison syndrome; acid aspiration.

Belisina *CPH, Port.†*
Lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Tonic.

Belivon *JC Healthcare, Ital.; Janssen-Cilag, Neth.†*
Risperidone (p. 1103·2).
Schizophrenia; mania; aggressive behaviour in dementia.

Bell Diono Resolvent *Bell, India.†*
⊗Ethylmorphine (p. 56·3); allylthiourea; hydrocortisone (p. 1640·1); yellow mercuric oxide (p. 2555·2).
Corneal scars, ulcers, and opacities.

Bell Pentolate *Bell, India.†*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Bell Pino-Atrin *Bell, India.†*
Atropine sulfate (p. 1310·2).
Uveitis; production of mydriasis and cycloplegia.

Bell Resolvent *Bell, India.†*
⊗Ethylmorphine (p. 56·3); allylthiourea; hydrocortisone (p. 1640·1); yellow mercuric oxide (p. 2555·2).
Corneal scars, ulcers, and opacities.

Bella *Hexal, Ger.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Acne and hirsutism in women.

Bellacane *Treiner, USA.*
Hyoscyamine sulfate (p. 1848·1); phenobarbital (p. 535·2).
Gastrointestinal disorders.

Bellacehol *Vilar, Rus.*
Belladonna (p. 2453·3).
Gastrointestinal disorders.

Bellacid *Soho, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Belladonna-Plus *Doctor H, Rus.*
Atropa belladonna (p. 2453·3); aconitum napellus (p. 2428·3); bryonia (p. 2461·3); hepar sulfuris (p. 1721·3); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Belladonnysat Burger *Ysatfabrik, Ger.†*
Belladonna (p. 2453·3).
Smooth muscle spasm.

Bellafit N *Streuli, Switz.*
Atropine sulfate (p. 1310·2).
Sialorrhoea; hyperhidrosis; colic.

Bellagen *Deutsche, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Bellahist-D *Cypress, USA.*
Phenylephrine hydrochloride (p. 1672·3); hyoscyamine sulfate (p. 1848·1); hyoscine hydrobromide (p. 1845·3); chlorphenamine maleate (p. 620·3); atropine sulfate (p. 1310·2).
Upper respiratory-tract disorders.

Bellalgin *Borshchagovskii, Ukr.*
Belladonna (p. 2453·3); benzocaine (p. 1980·2); dipyrone (p. 53·3); sodium bicarbonate (p. 1781·1).
Gastrointestinal disorders.

Bellamine *Major, USA.†*
Levorotatory alkaloids of belladonna (p. 2453·3); phenobarbital (p. 535·2); ergotamine tartrate (p. 674·1).
Gastrointestinal disorders.

Bellamox *Soho, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bellanorm *Rosch & Handel, Austria.*
Belladonna (p. 2453·3).
Gastrointestinal disorders; bronchospasm; motion sickness; night sweats.

Bellapan *Farmapol, Pol.*
Belladonna (p. 2453·3).
Smooth muscle spasm; hyperhidrosis; dystonia; motion sickness; migraine; Ménière's disease.

Bellapheen *Soho, Indon.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Autonomic disorders; hypermenorrhoea; gastrointestinal disorders; menopausal disorders.

Bellasthesin *Biopharma, Rus.; Borshchagovskii, Ukr.*
Belladonna (p. 2453·3); benzocaine (p. 1980·2).
Gastritis; colic; smooth muscle spasm.

Bellatal *Richwood, USA.*
Phenobarbital (p. 535·2); hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3).
Sedative; hypnotic.

Bellataminal *Vilar, Rus.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Nervous disorders; insomnia.

Bellatotal *Cetus, Arg.*
Homatropine (p. 2007·3); dipyrone (p. 53·3).
Pain; smooth muscle spasm.

Bellatram *Soho, Indon.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Bellcalcid *Bellpharma, Irl.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Bellcital *Ranbaxy, Irl.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Bellergal *Triton, Canad.; Novartis, Turk.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Menopausal disorders; hyperthyroidism; palpitations; extrasystoles; nervous system disorders; gastrointestinal disorders.

Bellergal-S *Novartis, USA.*
Laevorotatory alkaloids of belladonna (Bellafoline) (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Menopausal disorders; cardiovascular disorders; gastrointestinal disorders; recurrent throbbing headache.

Bellergot *Herbapol Wroclaw, Pol.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Neuroses; vascular headache; dysmenorrhoea; menopausal disorders.

Bellformin *Bellpharma, Irl.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bellgyn *Ratiopharm, Austria.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-associated acne, alopecia, and hirsutism in women.

Bellimcor *Ranbaxy, Irl.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Bellisin *Ranbaxy, Irl.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Bellissima *Madaus, Ger.; Rottapharm, Ger.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Bellmentin *Ranbaxy, Irl.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Belloid
Note: this name may be used for preparations of different composition.
Inga, India.
Hyoscine butylbromide (p. 1845·3).
Nausea and vomiting; premedication; smooth muscle spasm; motion sickness.

Bellozal *Menarini, Belg.*
Bilastine (p. 617·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Bellprav *Ranbaxy, Irl.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Bellramil *Ranbaxy, Irl.*
Ramipril (p. 1483·3).
Cardiovascular risk reduction; hypertension; heart failure.

Bellran *Ranbaxy, Irl.†*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; heartburn.

Bells Muscle Rub *Bell, UK.*
Sweet birch oil (p. 92·1); cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal disorders.

Bellune *Teva, Cz.; Pliva, Rus.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Bellvirax *Ranbaxy, Irl.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Bellymed *Pharno-Wedropharm, Ger.*
Macrogol 3350 (p. 2547·3).
Constipation.

Bellzac *Ranbaxy, Irl.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Belmacina *Liconsa, Spain.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Belmalax *Teva, Spain.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Belmalen *Cetus, Arg.*
Diclofenac sodium (p. 48·3); orphenadrine hydrochloride (p. 909·3).

Belmalen Plus *Cetus, Arg.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Belmalip *Teva, Spain.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Belmazol
Note: this name may be used for preparations of different composition.
Daquimed, Port.; Teva, Spain.
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Verisfield, Gr.
Citalopram hydrochloride (p. 411·1).

Belmirax *Belfar, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Belmural *Fariberica, Port.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Belmycetin-C *Bell, India.†*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected eye disorders.

Belnarl *Asahi, Jpn.*
Beraprost sodium (p. 1316·2).
Occlusive arterial disease; pulmonary hypertension.

Belnif *Mibe, Ger.*
⊗Metoprolol tartrate (p. 1434·3); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Beloc
Note: this name may be used for preparations of different composition.
AstraZeneca, Austria; AstraZeneca, Ger.; AstraZeneca, Switz.
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias; myocardial infarction; angina pectoris; hypertension; migraine; hyperthyroidism; heart failure.

AstraZeneca, Turk.
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; migraine; myocardial infarction; heart failure.

Lafi, Chile.
⊗Acebutolol (p. 1289·1).
Angina pectoris; arrhythmias; hypertension.

Meyer Alian, Venez.
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Beloc comp *Sanova, Austria.†*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Beloc-Zok *AstraZeneca, Ger.; AstraZeneca, Switz.*
⊗Metoprolol succinate (p. 1434·3).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction; angina pectoris; heart failure.

Beloc-Zok comp *Pfizer, Ger.*
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Beloderm *Belupo, Cz.; Belupo, Pol.; Belupo, Rus.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Belogen *Genesis, India.*
Lactobacillus; vitamins.

Belogent *Belupo, Cz.; Belupo, Pol.; Belupo, Rus.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Farma-Tek, Turk.
⊗Beclometasone dipropionate (p. 1621·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Beloken *AstraZeneca, Spain.*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction; migraine.

Belomet *Recalcine, Chile.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Asthma.

Belosalic *Belupo, Cz.; Belupo, Pol.; Belupo, Rus.; Farma-Tek, Turk.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Belozok *AstraZeneca, Arg.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; heart failure; myocardial infarction; arrhythmias; migraine.

Bel-Phen-Ergot S *Goldline, USA.†*
Phenobarbital (p. 535·2); ergotamine tartrate (p. 674·1); belladonna (p. 2453·3).

Belpidex *Belfar, Braz.*
Docusate sodium (p. 1836·2); bisacodyl (p. 1821·1).

Belprel *Teva, Spain.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Belpro *Blubell, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Belrin-D *Globus, India.*
Syrup: ⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Globus, India.
Tablets: Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Belrin-LZ *Globus, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Belsar
Note: this name may be used for preparations of different composition.
Menarini, Belg.
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Belsar Plus *Menarini, Belg.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Belscopan *Belfar, Braz.*
Hyoscine (p. 1845·3).

Belsone *J K Biochem, India.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Belspan *Belfar, Braz.*
Hyoscine (p. 1845·3); dipyrone (p. 53·3).

Beltrax Uno *Baliarda, Arg.*
Saw palmetto (p. 2363·3).

Beluron *Neo-Farmaceutica, Port.†*
Paracetamol (p. 115·1).
Fever; pain.

Belusha *Gedeon Richter, Cz.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Belustine *ProStrakan, Fr.; ProStrakan, Neth.*
Lomustine (p. 818·1).
Malignant neoplasms.

Belvea Liquid Health Calcium *Capsule, Singapore.*
Colecalciferol (p. 2113·1); minerals; lysine (p. 2079·3).
Calcium supplement.

Belvea Pregnancy & Breastfeeding Formula *Capsule, Singapore.*
Fish oil (p. 1460·3); vitamin E (p. 2119·1).
Fatty acid supplement in pregnancy.

Belviq *Eisai, USA.*
Lorcaserin hydrochloride (p. 2323·3).
Obesity.

Bemag *Altana, Pol.†*
Magnesium lactogluconate; magnesium aspartate (p. 1787·1); vitamin B_6 (p. 2105·3).
Magnesium deficiency.

Bemase *Okasa, Thai.; TTN, Thai.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Bemasive *Gynea, Spain.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Combined oral contraceptive.

Bemaz *Laboratorios Chile, Chile.†*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Bemecor *Lek, Pol.*
Metildigoxin (p. 1433·1).
Heart failure; arrhythmias.

Bemedrex *CSP, Fr.; Orion, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

Bemetrazole *Be-Tabs, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Bemetson *Orion, Fin.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Bemetson-K *Orion, Fin.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Bemez-D *Argil, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Bemicin *Northia, Arg.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Bemiks *Eczacibasi, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Bemiks C *Eczacibasi, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Bemilon *Nizhpharm, Rus.*
⊗Chlorhexidine gluconate (p. 1743·3); betamethasone valerate (p. 1624·1).
Skin disorders.

Beminal *Eurofarma, Braz.; Akromed, S.Afr.†; Whitehall, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin deficiencies.

Overseas, India.
Syrup: Vitamins; minerals.
Nutritional supplement.

Overseas, India.
Capsules: Vitamins; minerals; ginseng (p. 2513·3); DL-methionine (p. 1558·2).
Dietary supplement.

Beminal Forte *Overseas, India.*
Vitamins; minerals; thioctic acid (p. 2629·1).
Dietary supplement.

Beminal Plus *Eurofarma, Braz.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); minerals.

Beminex *Sons, Mex.*
⊗Dexamethasone phosphate (p. 1631·1).
Eye disorders.

Bemlo *Emcure, India.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Bemocin *Fresenius Kabi, Philipp.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bemolan *Takeda, Spain.*
Magaldrate (p. 1856·1).
Gastric hyperacidity.

Bemon *Riemser, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Bemonalcool *Sanitas, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Disinfection of skin and wounds.

Bemplas *Casasco, Arg.*
⊗Clonidine hydrochloride (p. 1339·1); chlortalidone (p. 1335·2).
Hypertension.

Ben *Plus, India.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Ben Li *XinShiDai, China.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Ben Yue *BSPC, China; BSPC, China.*
Nicotinic acid (p. 2083·1).
Hyperlipidaemias.

Bena
Note: this name may be used for preparations of different composition.
Philusa, Philipp.
Guaifenesin (p. 1666·2).
Cough.

Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia.
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).
Cough; respiratory-tract congestion.

Benace *Novartis, India.*
Benazepril hydrochloride (p. 1314·3).
Heart failure; hypertension.

Benacid *Chew, Thai.*
⊗Probenecid (p. 607·3).
Gout; gouty arthritis.

Benacilina *Ivax, Mex.†*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benacof *Taj, India.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Benacol DTM *Kalbe, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Benacol Expectorant *Kalbe, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; nasal congestion; cold symptoms; sinusitis; bronchial congestion.

Benacort *Pulmomed, Rus.*
⊗Budesonide (p. 1625·1).
Asthma.

Benactiv *Reckitt Benckiser, Ital.*
Flurbiprofen (p. 65·2).
Mouth and throat pain and inflammation.

Benaday *McNeil, Denm.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic rhinitis.

Benaderma *Confar, Port.*
Diphenhydramine hydrochloride (p. 626·2).
Skin disorders.

Benaderma com Calamina *Confar, Port.*
Calamine (p. 1697·2); camphor (p. 2466·2); diphenhydramine hydrochloride (p. 626·2).
Skin disorders.

Benadon *Bayer Consumer, Arg.; Roche, Gr.; Bayer, Ital.; Bayer, Port.; Bayer, Spain; Bayer, Swed.†*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency; neuritis; anaemias; nausea and vomiting; alcoholism.

Piramal, India.
Vitamin B_6 (p. 2105·3).

Bénadon *Bayer, Switz.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Benadrex *Johnson & Johnson Consumer, Mex.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Benadryl *Johnson & Johnson, Malaysia.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough and cold symptoms.

Elea, Arg.; McNeil Consumer, Canad.; IFET (ΙΦΕΤ), Gr.; Johnson & Johnson, Gr.; Pfizer, Indon.†; Johnson & Johnson Consumer, Mex.; Pfizer, Singapore; McNeil, Spain†; Johnson & Johnson, Thai.; Pfizer, Turk.; Parke, Davis, USA; Warner-Lambert, USA; Pfizer, Venez.
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; cough; motion sickness; allergic skin disorders; allergic rhinitis; parkinsonism; minor skin irritation; insomnia; nausea and vomiting; sedative.

McNeil, Denm.; McNeil, Fin.
Acrivastine (p. 614·3).
Urticaria; allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

McNeil Healthcare, Irl.
Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Allergic skin disorders; skin irritation.

Pfizer, Austria†; Pfizer, Braz.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; cold and influenza symptoms.

Pfizer, India.
Diphenhydramine (p. 626·1) or diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Benadryl 24 *Elea, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Benadryl Allergy
Note: this name may be used for preparations of different composition.
McNeil, UK.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pfizer, USA.
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Benadryl Allergy Plus Sinus Headache *McNeil Consumer, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Formerly known as Benadryl Allergy & Sinus Headache.

Benadryl Allergy Relief *McNeil, UK.*
Acrivastine (p. 614·3).
Allergic rhinitis; urticaria.

Benadryl Allergy/Cold *Warner-Lambert, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Benadryl Allergy/Congestion *Warner-Lambert, USA.†*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Benadryl Allergy/Sinus Headache *McNeil Consumer, Canad.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders; eye irritation; headache.

Benadryl Antihistamine *Johnson & Johnson, Philipp.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Benadryl Antitusivo *Elea, Arg.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough.

Benadryl Bug Bite Relief *McNeil Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1).
Formerly Benadryl Itch Relief.

Benadryl CD *Pfizer, Thai.*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Benadryl Chesty Cough & Nasal Congestion *Johnson & Johnson, Austral.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Benadryl Chesty Cough and Nasal Congestion *Johnson & Johnson, NZ.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Benadryl Chesty Forte *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Benadryl Childrens Allergy *Pfizer, USA.*
Diphenhydramine citrate (p. 626·2).
Hypersensitivity reactions.

Benadryl Children's Anti-Itch *Johnson & Johnson, USA.*
Camphor (p. 2466·2).

Benadryl Children's Itch Cooling *Johnson & Johnson, USA.*
Camphor (p. 2466·2).

Benadryl CM *Pfizer, Indon.†*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2); alcohol (p. 1733·1).
Cough.

Benadryl Cold Nighttime Formula *Parke, Davis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Benadryl Cough *Pfizer, India; Johnson & Johnson, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; nasal congestion.

Johnson & Johnson, Singapore.†
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; cold symptoms.

Benadryl 24 D *Elea, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; allergic rhinitis.

Benadryl Day & Night
Note: this name may be used for preparations of different composition.
Elea, Arg.
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); night tablets, paracetamol; diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Benadryl Decongestant *Johnson & Johnson, Thai.†; Parke, Davis, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms; nasal congestion; cough.

Benadryl Descongestivo *Elea, Arg.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Benadryl D M Compuesto *Elea, Arg.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1).
Cough.

Benadryl DMP
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Thai.
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; respiratory-tract congestion.

Pfizer, Indon.†
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough and cold symptoms.

Benadryl DMP Child *Pfizer, Indon.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Benadryl Dry Cough & Nasal Congestion *Johnson & Johnson, Austral.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Benadryl Dry Cough and Nasal Congestion *Johnson & Johnson, NZ.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Benadryl Dry Forte *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Benadryl Dry Tickly Cough *Johnson & Johnson, NZ.*
Pholcodine (p. 1675·1).
Cough.

Benadryl E *Johnson & Johnson Consumer, Mex.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2).
Cough.

Benadryl Expectorant *Johnson & Johnson, Philipp.*
Guaifenesin (p. 1666·2).
Chest congestion.

Benadryl Itch *Warner-Lambert, USA.*
Cream; topical spray; topical stick:
Diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1).
Hypersensitivity reactions.

Warner-Lambert, USA.
Topical gel: Diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Benadryl Mucus Relief plus Decongestant *Johnson & Johnson, NZ.*
Guaifenesin (p. 1666·2); phenylephrine Hydrochloride (p. 1672·3).
Cough; nasal congestion.

Benadryl Nightime *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.†*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Cough; cold symptoms; cough and cold symptoms.

Benadryl One A Day *McNeil, UK.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Benadryl Original *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Benadryl Plus
Note: this name may be used for preparations of different composition.
McNeil, UK.
⊗Acrivastine (p. 614·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Benadryl Skin Allergy Relief *McNeil, UK.*
Diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2); zinc oxide (p. 1729·1).
Allergic skin disorders; skin irritation.

Benadryl Spray *McNeil Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1).

Benadryl Total/Allergy *McNeil Consumer, Canad.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders; eye irritation; headache.

Benafed *Pfizer, Turk.*
⊗Diphenhydramine hydrochloride (p. 626·2); levomenthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; rhinitis; respiratory-tract congestion.

Benagol *Reckitt Benckiser, Ital.; Reckitt Benckiser, Port.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Oral hygiene; mouth and throat disorders.

Benagol Mentolo-Eucaliptolo *Reckitt Benckiser, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Oral hygiene.

Benagol Vitamina C *Reckitt Benckiser, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); sodium ascorbate (p. 2111·1); ascorbic acid (p. 2110·3).
Oral hygiene; adjunct in cold symptoms.

Benakof *Aaron, India.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2); terpin hydrate (p. 1678·2).

Benal *Berman, Mex.*
Thiamine (p. 2102·3).
Vitamin B_1 deficiency.

Benalapril *Berlin-Chemie, China; Berlin-Chemie, Ger.; Berlin-Chemie, Pol.; Menarini, Pol.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Benalapril Plus *Berlin-Chemie, Ger.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Benalcon *Sanitas, Ital.*
Benzalkonium chloride (p. 1737·1).
Disinfection of wounds.

Benalet *Johnson & Johnson, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Upper respiratory-tract disorders.

Benalgin *Actavis, Rus.*
Dipyrone (p. 53·3); thiamine hydrochloride (p. 2103·1); caffeine (p. 1203·3).
Fever; pain.

Benalgis *Franco-Indian, India.*
Prosultiamine (p. 2103·1).
Neuritis; myalgia; radiculitis.

Benaliv *McNeil, Denm.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis; allergic rhinitis.

Benapen *Biolab Sanus, Braz.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Benaprost *Bago, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Benarin *Pulmomed, Rus.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Benarone *Sriprasit, Thai.*
Benzbromarone (p. 603·3).
Gout.

Benatex *Nizpharm, Rus.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Benatux *Cifarma, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Benaxil *Yoo Young, Philipp.*
Diphenhydramine hydrochloride (p. 626·2).
Urticaria; angioedema; rhinitis; conjunctivitis; pruritus.

Benaxima *Teva, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Benaxona *Teva, Mex.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Benazeplus *Aliud, Ger.†; Stada, Ger.†*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Benazepril comp *Betapharm, Ger.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bencard Priktestoplossing *Allergy Therapeutics, Neth.*
A range of allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.

Bencard Skin Testing Solutions *Allergy Therapeutics, UK.*
Allergen extracts (single and mixed) (p. 2434·3).
Diagnosis of hypersensitivity.

Bencef
Note: this name may be used for preparations of different composition.
Innovative, India.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Bencelin *Antibioticos, Mex.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Bencelin Combinado *Antibioticos, Mex.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Bencet-L *Bionet, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Bencid *Geno, India; Pharmaland, Thai.*
⊗Probenecid (p. 607·3).
Gout; gouty arthritis.

Benciefredil *Novag, Mex.*
Guaifenesin (p. 1666·2); dextromethorphan (p. 1660·1).
Cough.

Bencifem *Prieto, Arg.*
Benzydamine hydrochloride (p. 29·2).

Bencil Scab *Fabra, Arg.*
Permethrin (p. 2159·3); benzyl benzoate (p. 2149·1).
Pediculosis.

Benclamet *RPG, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Benclamid *Craveri, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Benclamin *Cazi, Braz.; Polipharm, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Bencoba *Triton, India.*
Vitamin B substances (p. 2102·3); thioctic acid (p. 2629·1).

Bencoçan *Teuto, Braz.*
Benzyl benzoate (p. 2149·1).
Scabies.

Bencort *Rivers Edge, USA.*
⊗Benzoyl peroxide (p. 1696·1); hydrocortisone (p. 1640·1).
Acne.

Benda
Note: this name may be used for preparations of different composition.
Bendalis, Ger.
Fluorouracil (p. 795·2).
Colorectal cancer; pancreatic cancer; breast cancer.
Neon, India.
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1).
Infected skin disorders.
TNP, Thai.
Mebendazole (p. 158·3).
Worm infections.

Bendacitabin *Bendalis, Ger.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Bendacor *Corsalud, Venez.*
Mebendazole (p. 158·3).
Worm infections.

Bendadocel *Bendalis, Ger.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Bendaepi *Bendalis, Ger.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Bendafolin *Bendalis, Ger.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; adjunct to fluorouracil in colorectal cancer.

Bendalina *Faran, Gr.; Angelini, Ital.; Angelini, Philipp.; Angelini, Port.; Elmor, Venez.*
Bendazac lysine (p. 29·1).
Cataracts.

Bendamen *Meyer, Venez.*
Mebendazole (p. 158·3).
Worm infections.

Bendapar *Ivax, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Bendaplatin *Bendalis, Ger.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Bendarabin *Bendalis, Ger.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Bendarelbin *Bendalis, Ger.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Bendatax *Bendalis, Ger.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Bendatreotid *Bendalis, Ger.†*
Octreotide acetate (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; complications following pancreatic surgery.

Bendatrexat *Bendalis, Ger.†*
Methotrexate (p. 822·2).
Malignant neoplasms.

Bendazole *Utopian, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Bendex *Cipla, India; Cipla-Medpro, S.Afr.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Bendix *Pasteur, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Bendol
Note: this name may be used for preparations of different composition.
Christo, Hong Kong.
Diphenhydramine hydrochloride (p. 626·2).
Urticaria; rhinitis; oedema.
Plus, India.
Albendazole (p. 149·1).
Worm infections; giardiasis.

Bendrol *Synco, Singapore.*
Diphenhydramine hydrochloride (p. 626·2).
Motion sickness; hypersensitivity reactions.
Synco, Hong Kong.†
Diphenhydramine (p. 626·1).

Bendrol Compound *Synco, Hong Kong.†*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); sodium citrate (p. 1781·2).

Bendzon *Dzwon, India.†*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Benecid *Valdecasas, Mex.; Chew, Thai.*
⊗Probenecid (p. 607·3).
Gout; adjunct to beta-lactam antibacterials.

Benectrin *Legrand, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Benectrin Balsamico *Legrand, Braz.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Bacterial infections.

Benedorm
Note: this name may be used for preparations of different composition.
Valeant, Mex.
Melatonin (p. 2551·3).
Sleep disorders.
Ariston, Arg.†
Bromazepam (p. 1041·2).
Alcohol withdrawal syndrome; anxiety.

Benefect *Sensible Life, Canad.†*
Thymol (p. 1772·2).
Disinfection.

Benefiber *Novartis Consumer, Hong Kong; Novartis, India; Novartis, Singapore; Novartis Consumer, USA.*
Wheat dextrin (p. 2647·1) (p. 2059·1).
Formerly contained guar gum.
Constipation; dietary fibre supplement.

Benefibra *Novartis, Chile; Novartis, Cz.; Novartis Consumer, Ital.*
Guar gum (p. 475·1).
Dietary fibre supplement; irritable bowel.

Benefix *Wyeth, Arg.; Pfizer, Austral.; Wyeth Lederle, Austria; Pfizer, Belg.; Pfizer, Canad.; Wyeth, Cz.; Wyeth, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, Hung.; Pfizer, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK; Pfizer, Ukr.*
Nonacog alfa (p. 1150·1).
Haemophilia B; factor IX deficiency; haemorrhagic disorders.
Wyeth, USA.
A factor IX preparation (recombinant DNA) (p. 1149·3).
Factor IX deficiency.

Beneflora *Cedar Health, UK.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium* spp; *Streptococcus thermophilus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); pea fibres.
Maintenance of normal gastrointestinal flora.

Beneflur *Bayer, Mex.; Genzyme, Spain.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Benegel *Legrand, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); rosemary oil (p. 2607·3); lavender oil (p. 2541·1); turpentine oil (p. 2636·3); mustard oil (p. 2646·1).
Musculoskeletal and joint disorders.

Benemicin *Palfa, Cz.; Tarchomin, Rus.†*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Benemid *IFET (ΙΦΕΤ), Gr.†; MSD, Thai.; Merck, USA.†*
⊗Probenecid (p. 607·3).
Gout; gouty arthritis; adjunct to beta-lactam antibacterials; hyperuricaemia.

Bénémide *Bouchara-Recordati, Fr.*
⊗Probenecid (p. 607·3).
Hyperuricaemia; gout; adjunct to beta-lactam antibacterials.

Benemox *SynPenn, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Benepax *Apsen, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression; mixed anxiety-depressive states; obsessive-compulsive disorder; panic disorder; social phobia.

Beneprav *Daiichi Sankyo, Irl.*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Benera *TO-Chemicals, Thai.†*
Belladonna alkaloids (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Menopausal disorders; neurocirculatory asthenia; psychosomatic disorders; migraine.

Benergina *Merck, Port.*
Diphenhydramine hydrochloride (p. 626·2).
Skin disorders.

Beneroc *Bayer, Braz.*
Vitamin B (p. 2102·3).

Benerv Forte *Intra-Labs, India.*
Benfotiamine (p. 2102·3); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3); thioctic acid (p. 2629·1).

Benerva *Bayer, Belg.; Bayer, Braz.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Bayer, Ital.; Bayer Consumer, Mex.; Bayer, Spain; Bayer, Swed.†; Bayer, Switz.; Bayer, UK.*
Thiamine hydrochloride (p. 2103·1).
Alcoholism; beri-beri; neuritis; vitamin B_1 deficiency; Wernicke's encephalopathy; neuropathies.

Bénerva *Bayer Sante, Fr.*
Thiamine hydrochloride (p. 2103·1).
Beri-beri; vitamin B deficiency; neuritis.

Benestan
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Port.; Sanofi-Aventis, Spain.
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Benestare *Medley, Braz.*
Polycarbophil calcium (p. 1879·2).
Constipation.

Benet *Takeda, Jpn.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Benetor *Menarini, Denm.; Menarini, Fin.; Daiichi Sankyo, Irl.*
Olmesartan medoxomil (p. 1459·2).
Hypertension; heart failure; diabetic nephropathy.

Benetor Comp *Menarini, Denm.; Menarini, Fin.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Benetor Plus *Daiichi Sankyo, Irl.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Benetransit *Kalisterra, Fr.†*
Cassia pulp (p. 1826·2); cynara (p. 2490·3); fennel (p. 2503·2); yogurt (p. 2649·3).
Digestive disorders.

Benetussin *Johnson & Johnson, Port.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).
Cough.

Beneum *Teuto, Braz.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 supplement.

Beneuran *Nycomed, Austria.†*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Beneuran compositum *Nycomed, Austria.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Neuralgia; neuritis; cervical syndrome; herpes zoster infection; funicular myelosis; nervous exhaustion; pregnancy induced vomiting.

Beneuron Forte *Franco-Indian, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Benevat *Teuto, Braz.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Benevran *Legrand, Braz.*
Diclofenac diethylamine (p. 48·3) or diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Benexol *Bayer, Turk.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Vitamin B deficiency.

Benexol B12 *Bayer, Ital.; Bayer Consumer, Mex.; Bayer, Switz.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiencies; neuritis; megaloblastic and sideroblastic anaemias; neuropathies; alcoholism.

Bayer, Ital.
Injection: Cocarboxylase (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin (p. 2107·3).
Neuropathies; vitamin B_1, B_6, and B_{12} deficiency.
Bayer, Turk.
Thiamine (p. 2102·3); pyridoxine (p. 2105·3); vitamin B_{12} (p. 2107·2).

Benexol B1 B6 B12 *Bayer, Spain.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Vitamin B deficiency.

Benfage *Orchid, India.*
Benfotiamine (p. 2102·3).
Neuropathy.

Benfage Forte *Orchid, India.*
Vitamin B substances (p. 2102·3); thioctic acid (p. 2629·1).

Benfage Plus *Orchid, India.*
Benfotiamine (p. 2102·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Benfinuron Forte *Fourrts, India.*
Vitamin B substances (p. 2102·3).

Benflogin
Note: this name may be used for preparations of different composition.
Ache, Braz.
Benzydamine hydrochloride (p. 29·2).
Fever; inflammation; pain.

Benflux *Atral, Port.; Polinac, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Benfo Forte *Orchid, India.*
Vitamin B substances (p. 2102·3); thioctic acid (p. 2629·1).

Benfo Plus *Orchid, India.*
Vitamin B substances (p. 2102·3).

Benfogamma *Worwag, Cz.; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.; Worwag, Ukr.*
Benfotiamine (p. 2102·3).
Vitamin B_1 deficiency; vitamin B deficiency; polyneuropathy.

Benfol *Andromaco, Mex.†*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Benfolipen *Farmstandart, Rus.*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; neuropathy.

Benfomet *Sun, India.*
Vitamin B substances (p. 2102·3).

Benformin *Orchid, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Benfree *Glenmark, India.*
Benfotiamine (p. 2102·3); mecobalamin (p. 2108·1).
Peripheral neuropathy.

Benfu *TO-Chemicals, Thai.†*
Mebendazole (p. 158·3).
Worm infections.

Ben-Gay *Pfizer, Cz.†; Pfizer, Hung.; Johnson & Johnson, Israel; McNeil, Pol.; Johnson & Johnson, Rus.; Pfizer, Turk.; Janssen-Cilag, Ukr.; Pfizer, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Bengay *Johnson & Johnson, Hong Kong†; Pfizer, Indon.†; Johnson & Johnson, Singapore; Ponce, Venez.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain; sports injuries; soft-tissue injury.

Bengay Arthritis *Johnson & Johnson, Canad.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Bengay Greaseless *Johnson & Johnson, Philipp.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Muscle pain.

Bengay Muscle Pain No Odor *Johnson & Johnson, Canad.*
Trolamine salicylate (p. 141·2).
Muscle and joint pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bengay Muscle Pain Regular (Original) *Johnson & Johnson, Canad.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Muscle and joint pain.

Bengay Muscle Pain Ultra *Johnson & Johnson, Canad.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Muscle and joint pain.

Ben-Gay Patch *Pfizer, USA.*
Menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Bengay Patch *Johnson & Johnson, Hong Kong; Johnson & Johnson, Singapore.*
Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Bengay Plus *Pfizer, Indon.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal pain; soft-tissue injury.

Ben-Gay Ultra *Pfizer, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Bengay Ultra *Johnson & Johnson, Hong Kong; Johnson & Johnson, Philipp.; Johnson & Johnson, Singapore.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain; sports injuries.

Ben-Gay Ultrastrength *Johnson & Johnson, Israel.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Ben-Gay Vanishing *Pfizer, USA.*
Menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Bengay Vanishing *Johnson & Johnson, Singapore.*
Menthol (p. 2553·2).
Musculoskeletal and joint pain.

Benglau *CSC, Austria.†*
Dapiprazole hydrochloride (p. 2006·2).
Reversal of mydriasis.

Benglycon *Lloyd, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Benhex *PSM, NZ.*
Lindane (p. 2157·1).
Scabies.

Benical *Bayer, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Bénical *Bayer, Switz.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough.

Benical Cold *Bayer, Turk.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Benicar *Sankyo, Braz.; Sankyo, USA; Sankyo, Venez.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Benicar HCT *Sankyo, Braz.; Sankyo, USA.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Benice-DT *Bionet, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Benicort *P & B, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Benicort-N *P & B, India.*
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).

Beniflant *Loeffler, Mex.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat inflammation.

Beniflex *Berksam, Turk.*
Benzydamine hydrochloride (p. 29·2).

Beniforte *Pharmatechnica, Philipp.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2).
Anaemias.

Benil
Note: this name may be used for preparations of different composition.
Bayer, Turk.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Respiratory-tract congestion.

Sunward, Singapore.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Vianex (Βιανεξ), Gr.
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Benilin *Medikon, Indon.†*
Dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1); diphenhydramine (p. 626·1).
Upper respiratory-tract disorders.

Benim *JK Biochem, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Benim-P *JK Biochem, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Beniod *Chiesi, Spain.*
Delapril hydrochloride (p. 1350·2).
Hypertension.

Beniprosin *Ranbaxy, S.Afr.*
Tamsulosin hydrochloride (p. 2369·1).

Benisan *Fabra, Arg.*
Piroxicam (p. 125·3).
Inflammation; pain.

Benison *Tems, Turk.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; motion sickness; vertigo.

Benitol *Benitol, Arg.*
Bismuth salicylate (p. 1821·3); sodium bicarbonate (p. 1781·1); magnesium oxide (p. 1857·3); magnesium carbonate (p. 1856·2); calcium carbonate (p. 1824·3); belladonna (p. 2453·3).
Antacid.

Benitrom *Ivax, Mex.†*
Erythromycin (p. 291·2).
Bacterial infections.

Benituss *Sarabhai Piramal, India.*
⊗Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Benketol *Benedetti, Ital.*
Ketorolac trometamol (p. 80·2).
Musculoskeletal and joint disorders.

Benlexin *Lloyd, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Benlysta *GSK, Belg.; GSK, Canad.; GSK, Denm.; GSK, Ger.; GSK, Israel; GSK, Neth.; GSK, Norw.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK; Human Genome, USA.*
Belimumab (p. 1945·1).
Systemic lupus erythematosus.

Bennaston *Intact, Malaysia.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal syndrome.

Bennatuss *Hoe, Malaysia; Hoe, Singapore.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2).
Cough; nasal congestion.

Bennetts Colic Mixture *Bennetts, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); belladonna (p. 2453·3).
Infant colic.

Benocetam *Bernofarm, Indon.*
Piracetam (p. 393·3).
Cerebrovascular disorders.

Benocten *Medinova, Switz.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Benodent *IMS, Ital.*
Mouthwash: Sodium fluoride (p. 2089·2); chlorhexidine (p. 1743·2).
Dental caries prophylaxis; dental hygiene.

Benodent CLX *IMS, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Dental disorders.

Benofomin *Bernofarm, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Benol *Eras, Turk.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Vitamin B deficiency.

Benolaxe *Landsteiner, Mex.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Benoquin
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Balsalazide (p. 1820·2).
Ulcerative colitis.

Valeant, Canad.; Mac, India; Valeant, USA.†
Monobenzone (p. 1714·2).
Post-inflammatory melasma; skin hyperpigmentation; final depigmentation in extensive vitiligo.

Benoral
Note: this name may be used for preparations of different composition.
BioSaude, Port.
Dichlorobenzyl alcohol (p. 1750·2); benzydamine hydrochloride (p. 29·2).
Mouth disorders.

Reig Jofre, Spain.
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Santa, Turk.
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Benormal *Cristalia, Braz.*
Vitamin B substances (p. 2102·3).
Nutritional supplement.

Benoson *Bernofarm, Indon.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Benoson V *Bernofarm, Indon.†*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Benoson G *Bernofarm, Indon.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Benoson M *Bernofarm, Indon.*
⊗Betamethasone valerate (p. 1624·1); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Benoson N *Bernofarm, Indon.†*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Skin disorders.

Benosone *Hoe, Malaysia.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Benosone-N *Hoe, Malaysia.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Skin disorders with infection.

Benostan *Bernofarm, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Benovit C *Bernofarm, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C supplement.

Benovit M *Bernofarm, Indon.*
Vitamins; minerals.

Benoxi *Unimed, Cz.; Unimed, Rus.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Benoxil *Santen, China.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Benoxinat *Agepha, Austria.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Benoxinate *Liba, Turk.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Benoxuric *Bernofarm, Indon.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Benoxygel *Stiefel, Port.; Stiefel, Spain.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Benoxyl *Stiefel, Canad.†; Stiefel, Mex.; Stiefel, Philipp.†; Stiefel, S.Afr.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Benozil *Kyowa, Jpn.*
Flurazepam hydrochloride (p. 1076·1).
Insomnia; premedication.

Benozym *Bernofarm, Indon.*
⊗Pancreatin (p. 2579·3); bromelains (p. 2460·3); ox bile extract (p. 2457·2).
Digestive enzyme and pancreatic deficiencies.

Benpen *CSL, Austral.; CSL, NZ.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Benph *Gerard, Irl.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Benpine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Alcohol withdrawal syndrome; anxiety; skeletal muscle spasm.

Benprost-B *Ind-Swift, India.*
⊗Piper nigrum; tribulus terrestris (p. 2633·3).

Ben-Q-Met *Q Check, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Benrod *Invision, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Benrod-I *Invision, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Bens *Ardern, UK.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Bens Natural *Ardern, UK.*
Menthoglycol.
Insect repellent.

Bensal HP *7 Oaks, USA.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1).
Fungal skin infections.

Bensolmin *Continentales, Mex.*
Mebendazole (p. 158·3).
Amoebiasis; worm infections.

Bensolmin Complex *Continentales, Mex.*
Quinfamide (p. 947·1); mebendazole (p. 158·3).

Bensons Bottom *Bensons Bottom, USA.*
Zinc oxide (p. 1729·1).
Nappy rash.

Benspar *Zydus, India.*
Benserazide (p. 894·1); levodopa (p. 902·2).
Parkinsonism.

Benspore *Vanguard, India.*
Lactobacillus sporogenes (p. 2596·3).
Restoration of intestinal flora; diarrhoea.

Benstatin *Kinder, Braz.*
Tiabendazole (p. 166·3).

Bensulf *Fada, Arg.*
Thiopental sodium (p. 1915·1).

Bensulfoid *ECR, USA.*
Cream: Colloidal sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne.

Ben-Tann *Midlothian, USA.†*
Diphenhydramine tannate (p. 626·1).
Hypersensitivity reactions.

Bentapen *Umedica, Philipp.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

BenTe *Jida, China.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Bentelan *Biofutura, Ital.*
Effervescent tablets; injection: ⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Bentifen *Novartis, Ital.; Novartis, Neth.†; Novartis, Port.; Thea, Spain.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Bentix *Sons, Mex.*
⊗Clioquinol (p. 273·1); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Bentoform *JK Biochem, India.*
Strontium chloride (p. 2623·1).

Bentome *Medana, Irl.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Bentophyto *Panalab, Arg.*
Soap: Undecenoic acid diethanolamide (p. 596·3).
Fungal skin infections.

Panalab, Arg.
Topical powder: Undecenoic acid diethanolamide (p. 596·3); triclosan (p. 1773·2); salicylic acid (p. 1719·1); boric acid (p. 2459·3); alum (p. 2439·1); precipitated sulfur (p. 1721·1).
Fungal skin infections.

Bentos *Kaken, Jpn.*
⊗Befunolol hydrochloride (p. 2004·2).
Ocular hypertension; glaucoma.

Bentyl *Medley, Braz.; Sanofi-Aventis, Mex.; Duncan, Philipp.; Axcan, USA.*
Dicycloverine hydrochloride (p. 1834·2).
Functional bowel syndrome; irritable bowel syndrome; smooth muscle spasm.

Bentylol *Aptalis, Canad.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Benur
Note: this name may be used for preparations of different composition.
Bioindustria, Ital.
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia.

Raymos, Arg.
Levofloxacin (p. 315·3).
Bacterial infections.

Ben-u-ron *Sigmapharm, Austria; Bene, China; Bene, Cz.; Bene, Ger.; Bene-Chemie, Hong Kong; Bene, Hung.; Neo-Farmaceutica, Port.; Nutrimedis, Switz.*
Paracetamol (p. 115·1).
Fever; pain.

Benuryl *Valeant, Canad.*
⊗Probenecid (p. 607·3).
Hyperuricaemia.

Benutrex *Organon, Venez.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Benutrex 1000 *Organon, Chile.†*
Thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); nicotinamide (p. 2083·1); dexpanthenol (p. 2582·2); cyanocobalamin (p. 2107·2); hydroxocobalamin (p. 2107·3).
Neuralgia; neuritis; vitamin B deficiency.

Benutrex B12 *Organon, Venez.*
Vitamin B substances (p. 2102·3).

Benutrex C *Organon, Philipp.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Benutrion *Sanbe, Indon.*
Amino acids; electrolytes (p. 1775·1); vitamin B substances (p. 2102·3).
Parenteral nutrition.

Benuvit-C *Tai Yu, Philipp.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); glucose (p. 2068·3).
Parenteral nutrition.

Benyad *Inpac, Thai.*
Albendazole (p. 149·1).
Worm infections.

Benyl *Medicine Products, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).

Benyl Expectorant *Synco, Singapore.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough and cold symptoms.

Synco, Hong Kong.†
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); sodium citrate (p. 1781·2).

Benylan *McNeil, Denm.*
Diphenhydramine hydrochloride (p. 626·2).
Cough; hypersensitivity.

Benylin *McNeil Healthcare, Irl.; Johnson & Johnson, Port.*
Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Cough.

Johnson & Johnson, Chile†; Pfizer, Turk.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Respiratory-tract congestion; cough.

Benylin a la codeine N *Janssen-Cilag, Switz.*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2).
Cough.

Benylin All-in-One Cold & Flu Night *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Benylin All-In-One Cold and Flu Night PE *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Benylin Bronchospect *Johnson & Johnson, S.Afr.†*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Cough associated with bronchospasm.

Benylin CD *Olic, Thai.*
Codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).

Benylin Chest Congestion *McNeil Consumer, Canad.*
Guaifenesin (p. 1666·2).
Cough.

Benylin Chesty *Johnson & Johnson, S.Afr.*
⊗Orciprenaline sulfate (p. 1217·3); bromhexine hydrochloride (p. 1656·3).
Cough associated with bronchospasm and congestion.

Benylin Chesty Coughs Non-Drowsy *Pfizer Consumer, UK.*
Guaifenesin (p. 1666·2); menthol (p. 2553·2).
Coughs.

Benylin Chesty Coughs Original *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Coughs.

Benylin for Children All-In-One Cold & Fever *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; fever.

Benylin for Children All-In-One Cold & Fever Nightime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Cold symptoms; fever.

Benylin Childrens Apple Flavour Cough Syrup *McNeil, UK.*
⊗Glycerol (p. 2517·2).
Cough.

Benylin Childrens Chesty Cough *McNeil Healthcare, Irl.*
Guaifenesin (p. 1666·2).
Cough.

Benylin Childrens Chesty Coughs *McNeil, UK.*
Guaifenesin (p. 1666·2).
Cough.

Benylin Childrens Cough and Cold *McNeil Healthcare, Irl.*
Dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3).
Cough; cold symptoms.

Benylin Childrens Coughs & Colds *Pfizer Consumer, UK.*
Dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3).
Coughs and cold symptoms.

Benylin Childrens Dry Cough *McNeil Healthcare, Irl.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Benylin Childrens Dry Coughs *McNeil, UK.*
Pholcodine (p. 1675·1).
Cough.

Benylin Childrens Night Coughs *McNeil, UK.*
Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Cough; hypersensitivity symptoms of the respiratory tract.

Benylin with Codeine *Johnson & Johnson, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1).
Cough.

McNeil Healthcare, Irl.†
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); menthol (p. 2553·2).
Cough.

Benylin Cold & Flu *Pfizer Consumer, UK.*
Capsules: Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Pfizer Consumer, UK.
Sachets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Benylin 1 Cold and Flu *McNeil Consumer, Canad.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Cough and cold symptoms.

Benylin 2 Cold and Flu with Codeine *McNeil Consumer, Canad.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; nasal congestion.

Benylin 1 Cold and Flu Day Night *Pfizer Consumer, Canad.†*
⊗Day caplets, paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); night caplets, paracetamol; pseudoephedrine hydrochloride; diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Benylin 1 Cold and Flu Nightime *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Benylin Cold & Sinus *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Benylin Cold & Sinus Night *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Benylin Cold & Sinus Plus *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Benylin For Colds *Johnson & Johnson, S.Afr.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Benylin Compuesto *Pfizer, Venez.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Benylin Cough
Note: this name may be used for preparations of different composition.
Pfizer, India.
⊗Dextromethorphan (p. 1660·1); pseudoephedrine (p. 1676·1).
Cough.

Benylin Cough and Chest Congestion *McNeil Consumer, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Benylin Cough, Cold & Congestion *McNeil Consumer, Canad.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Benylin Cough & Cold with Extra Strength Acetaminophen *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Benylin Cough & Congestion *McNeil Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Pfizer Consumer, UK.
⊗Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Benylin D *Pfizer Consumer, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Benylin Day & Night *McNeil Healthcare, Irl.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Pfizer Consumer, UK.
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Cold and influenza symptoms.

Benylin Descongestivo *McNeil, Spain.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Benylin DM *McNeil Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1) or dextromethorphan polistirex (p. 1660·1).
Cough.

Benylin DM-D *McNeil Consumer, Canad.; Pfizer Consumer, S.Afr.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Benylin DM-D-E *McNeil Consumer, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; nasal congestion.

Benylin DM-D-E Cough & Cold *McNeil Consumer, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Benylin DM-D-E with Menthactin *McNeil Consumer, Canad.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cold and influenza symptoms; cough.

Benylin DM-D-E-A Cold and Sinus *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Benylin DM-E *McNeil Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Benylin DM-E with Menthactin *McNeil Consumer, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough; sore throat.

Benylin DM-E Menthol Cough & Congestion *McNeil Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Benylin Dry Cough
Note: this name may be used for preparations of different composition.
Johnson & Johnson, S.Afr.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

McNeil Healthcare, Irl.
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Benylin Dry Coughs Non-Drowsy *Pfizer Consumer, UK.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Benylin Dry Coughs Original *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).
Coughs.

Benylin Dual Action Chesty *McNeil Healthcare, Irl.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; upper respiratory-tract congestion.

Benylin Dual Action Dry *McNeil Healthcare, Irl.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3).
Cough; cold and influenza symptoms.

Benylin E
Note: this name may be used for preparations of different composition.
Pfizer, India.
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).
Pfizer Consumer, Canad.†
Guaifenesin (p. 1666·2).
Cough.

Benylin E with Menthactin *McNeil Consumer, Canad.†*
Guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Benylin 4 Flu *McNeil Healthcare, Irl.; Pfizer Consumer, UK.*
⊗Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Benylin Four Flu
Note: this name may be used for preparations of different composition.
Johnson & Johnson, S.Afr.†
⊗Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Benylin Mucous and Phlegm Relief *McNeil Consumer, Canad.*
Guaifenesin (p. 1666·2); menthol (p. 2553·2).

Benylin Mucous and Phlegm Relief plus Cough Control *McNeil Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Benylin Mucus Cough *McNeil, UK.*
Guaifenesin (p. 1666·2); levomenthol (p. 2553·2).
Cough.

Benylin Mucus Cough & Cold All in One Relief *McNeil, UK.*
Guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Benylin Mucus Cough Honey & Lemon *McNeil, UK.*
Guaifenesin (p. 1666·2).
Cough.

Benylin Mucus Cough Menthol *McNeil, UK.*
Guaifenesin (p. 1666·2); levomenthol (p. 2553·2).
Cough.

Benylin Mucus Cough Night *McNeil, UK.*
Guaifenesin (p. 1666·2); diphenhydramine (p. 626·1); levomenthol (p. 2553·2).
Cough.

Benylin Mucus Cough plus Decongestant *McNeil, UK.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine (p. 1676·1).
Cough.

Benylin Mucus Relief *McNeil Healthcare, Irl.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Benylin Night Cough *McNeil Consumer, Canad.†*
Diphenhydramine hydrochloride (p. 626·2).
Cough.

Benylin Non-Drowsy Chesty Cough *McNeil Healthcare, Irl.*
Guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Benylin Non-Drowsy Dry Cough *McNeil Healthcare, Irl.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Benylin Original *Johnson & Johnson, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Benylin Tickly Coughs *McNeil, UK.*
⊗Glycerol (p. 2517·2).
Cough.

Benylin Tickly Throat Cough *McNeil Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Benylin Wet Cough *Johnson & Johnson, S.Afr.*
Guaifenesin (p. 1666·2).
Cough.

Benz *Lupin, India.*
Benzonatate (p. 1656·2).

Benz Application *Christo, Hong Kong.†*
Benzyl benzoate (p. 2149·1).
Scabies.

Benza *Century, USA.*
Benzalkonium chloride (p. 1737·1).
Skin, mucous membrane, and wound disinfection; eye, bladder, urethra, and body cavity irrigation; vaginal douching.

Benzac *Galderma, Austral.; Galderma, Belg.; Galderma, Braz.; Galderma, Canad.; Galderma, Chile; Galderma, Israel; Galderma, Ital.; Galderma, Neth.; Galderma, NZ; Galderma, Port.; Galderma, Singapore; Galderma, Switz.; Galderma, Thai.; Galderma, USA.*
Benzoyl peroxide (p. 1696·1).
Acne; skin disinfection.

Benzac AC *Galderma, Braz.; Galderma, Hong Kong; Galderma, India; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, S.Afr.; Liba, Turk.; Galderma, Venez.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzac Plus *Galderma, Chile; Galderma, Mex.†*
Benzoyl peroxide (p. 1696·1); erythromycin estolate (p. 291·2).
Acne.

Benzaclin *Valeant, Canad.; Dermik, Israel†; Darier, Mex.†; Farma-Tek, Turk.*
Clindamycin phosphate (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

Valeant, USA.
Clindamycin (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

Benzacne *Nycomed, Pol.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzac-W *Galderma, Gr.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzaderm *Remexa, Mex.*
Soap.
Skin cleansing.

Remexa, Mex.
Topical gel: Benzoyl peroxide (p. 1696·1).
Acne.

Benzadermine *Trenker, Belg.*
Erythromycin (p. 291·2); benzoyl peroxide (p. 1696·1).
Acne.

Benzafur *Ivax, Mex.†*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzagel *Columbia, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzaknen *Galderma, Austria; Galderma, Ger.; Galderma, Switz.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzalcor *Corsalud, Venez.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Benzalcrem *Gezzi, Arg.*
Zinc oxide (p. 1729·1); white soft paraffin (p. 2211·3).
Nappy rash.

Benzamycin *Trenker, Belg.†; Sanofi-Aventis, Canad.; Dermik, China; Papaellinas (Παπαελλήνας), Gr.; Schwarz, Irl.†; Dermik, Israel; Darier, Mex.†; Dermik, Singapore†; Farma-Tek, Turk.; Dermik, USA.*
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

Benzanil Compuesto *Roche, Mex.†*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Benzanil Simple *Roche, Mex.†*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzantine H *Rekah, Israel.*
⊗Diphenhydramine hydrochloride (p. 626·2); hydrocortisone (p. 1640·1).
Insect bites; stings; skin irritation.

Benzapen *Tum, Turk.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzapen 6.3.3 *Tum, Turk.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Benzapen G *Teuto, Braz.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Benzapur *Herbapol Poznan, Pol.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzatec *Caps, S.Afr.†*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Benzatron *Ariston, Braz.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzecilin *Teuto, Braz.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Benzedrex *Ascher, USA.*
⊗Propylhexedrine (p. 2330·1).
Nasal congestion.

BenzEFoam *Onset, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzemul *McGloin, Austral.*
Benzyl benzoate (p. 2149·1).
Scabies; pediculosis.

Benzenil *Biochimico, Braz.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Benzetacil *Wyeth, Arg.; Eurofarma, Braz.; Sandoz, Mex.; Reig Jofre, Spain.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzetacil 3-3 *Sandoz, Venez.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2); benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzetacil 6-3-3 *Sandoz, Venez.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Benzetacil Combinado *Sandoz, Mex.*
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Benzetacil Compuesta *Reig Jofre, Spain.*
Benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2); benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzetacil L-A *Sandoz, Venez.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzevit *Elofar, Braz.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Skin infections.

Benzevit Prevent *Elofar, Braz.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); zinc oxide (p. 1729·1).

Benzidan *Deva, Turk.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and inflammation; soft-tissue pain and inflammation.

Benzidrol *Prati-Donaduzzi, Braz.*
Benzydamine (p. 29·2).

Benziflex *EMS, Braz.*
Benzydamine hydrochloride (p. 29·2).
Fever; inflammation; pain.

Benzihex *Galderma, Arg.; Galderma, China.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzin
Note: this name may be used for preparations of different composition.
Vida, Port.†
Lisinopril (p. 1420·3).

Benziq *Graceway, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzitrat *Uniao Quimica, Braz.*
Benzydamine hydrochloride (p. 29·2).
Inflammation; pain.

Benzo *Greater Pharma, Thai.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); zinc oxide (p. 1729·1).

Benzoax *Ducto, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Benzo-Bencil *Vita, Venez.*
Benzyl benzoate (p. 2149·1).
Scabies; pediculosis.

Benzocaine PD *Produits Dentaires, Switz.*
Benzocaine (p. 1980·2); hydroxyquinoline sulfate (p. 2530·1); eugenol (p. 2501·2).
Dental pain.

Benzoclav *Medreich, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Benzodent *Procter & Gamble, USA.*
Benzocaine (p. 1980·2).
Oral lesions.

Benzodiazol *Meyer, Venez.*
Dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Benzogal *Rafarm, Gr.*
Benzyl benzoate (p. 2149·1).
Lice infestations.

Benzo-Ginestryl *Sanofi-Aventis, Mex.*
Estradiol benzoate (p. 2271·1).
Menopausal disorders; osteoporosis; menstrual disorders.

Benzo-Ginoestril *Sanofi-Aventis, Braz.*
Estradiol hexahydrobenzoate (p. 2271·2).
Menopausal disorders; osteoporosis.

Benzoinspray *Pharmascience, Canad.*
Benzoin (p. 2624·3).
Skin disorders.

Benzol
Note: this name may be used for preparations of different composition.
Bennett, Gr.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Greenpharma, Braz.; Mercury, Philipp.
Albendazole (p. 149·1).
Worm infections.

Solitaire, India.
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; gynaecomastia; hereditary angioedema; endometrial thinning; menorrhagia.

Benzolac *Surya Dermato, Indon.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzolac Cl *Surya, Hong Kong; Surya Dermato, Indon.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Benzolait *RCA, Ital.*
A range of preparations containing benzoyl peroxide (p. 1696·1).
Acne; oily skin.

Benzole *Flamingo, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Benzoleks *Sanofi Synthelabo, Turk.†*
Phenyltoloxamine citrate (p. 638·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1).
Respiratory-tract congestion.

Benzomid *Surya Dermato, Indon.*
Benzocaine (p. 1980·2); cetrimide (p. 1742·1).
Sunburn; burns; minor wounds; skin irritation; insect bites.

Benzonac *Stedman, India.*
Benzocaine (p. 1980·2); diclofenac (p. 48·3).

Benzonal *Cryopharma, Mex.*
Benzonatate (p. 1656·2).
Cough.

Benzopin *Schwulst, S.Afr.†*
Diazepam (p. 1063·2).
Anxiety; premedication; alcohol withdrawal syndrome.

Benzosed *Troikaa, India; Troika, Venez.*
Midazolam (p. 1085·1).
General anaesthesia; premedication; sedative.

Benz-O-Sthetic *Geritrex, USA.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Benzotal *Cifarma, Braz.*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Benzotisan *Sanval, Braz.*
Benzyl benzoate (p. 2149·1).
Scabies.

Benzotripen *Sons, Mex.*
Procaine benzylpenicillin (p. 344·2).
Respiratory-tract infections.

Benzoyt *Riemser, Ger.*
Benzoyl peroxide (p. 1696·1).
Acne.

Benzperox *Medphano, Ger.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Benztrop *Phebra, Austral.; AFT, NZ.*
Benzatropine mesilate (p. 894·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Benzycillin 1 *Krasfarma, Rus.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Benzycillin 3 *Krasfarma, Rus.*
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Benzycillin 5 *Krasfarma, Rus.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Benzydol-P *La Pharmaceuticals, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; hiccup; restlessness; confusion.

Benzyme *Collins, Mex.†*
Diazepam (p. 1063·2).

Benzys *Zytras, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Benzyzine *La Pharmaceuticals, India.*
Trihexyphenidyl hydrochloride (p. 917·3); trifluoperazine (p. 1113·2).
Psychoses.

Beof *Saval, Chile.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Beofenac *Almirall Hermal, Ger.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Be-Oxytet *Be-Tabs, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Bepamol *Biological E, India.*
Paracetamol (p. 115·1).
Pain; fever.

Bepanten *Bayer, Ital.*
Dexpanthenol (p. 2582·2).
Intestinal atony.

Bepanthen
Note: this name may be used for preparations of different composition.
Bayer Consumer, Austral.; Bayer, Austria; Bayer, Cz.; Bayer, Fin.; Bayer Sante, Fr.; Bayer, Ger.; Bayer, Hung.; Bayer Consumer, Indon.; Bayer Consumer, Israel; Bayer Consumer, Mex.; Bayer, Pol.; Bayer Consumer, Rus.; Bayer Consumer, S.Afr.†; Bayer, Singapore; Bayer, Switz.; Bayer Consumer, Thai.; Bayer, UK; Bayer Consumer, Ukr.
Dexpanthenol (p. 2582·2).
Wounds; minor skin lesions; nappy rash; dry skin; sunburn; skin irritation; sore or cracked nipples; burns; skin ulcers; anal fissures; eye disorders; gastrointestinal disorders; nasal dryness and inflammation.
Roche, NZ.
Panthenol (p. 2582·2).
Burns; skin lesions; skin irritation.
Bayer, Austria.†
Solution: Dexpanthenol (p. 2582·2); domiphen bromide (p. 1751·1).
Skin damage; mouth and throat disorders; nasal disorders; respiratory tract disorders; gastrointestinal disorders.

Bepanthen Antiseptische *Bayer, Ger.*
Dexpanthenol (p. 2582·2); chlorhexidine gluconate (p. 1743·3).
Wounds.

Bepanthen Augentropfen *Bayer, Ger.*
Sodium hyaluronate (p. 2526·2); dexpanthenol (p. 2582·2).
Dry eyes; eye irritation.

Bepanthen First Aid *Bayer Consumer, Thai.*
Dexpanthenol (p. 2582·2); chlorhexidine hydrochloride (p. 1743·3).

Bepanthen Plus *Bayer, Austria.*
Dexpanthenol (p. 2582·2); chlorhexidine gluconate (p. 1743·3) or chlorhexidine hydrochloride (p. 1743·3).
Wounds.
Bayer, Cz.; Bayer, Hung.; Bayer Consumer, Israel; Bayer Consumer, Malaysia; Bayer, Pol.; Bayer Consumer, Rus.; Bayer, Switz.; Bayer Consumer, Ukr.
Dexpanthenol (p. 2582·2); chlorhexidine hydrochloride (p. 1743·3).
Wounds; burns; ulcers; skin infections; cracked nipples.

Bepanthene *Roche, Gr.; Bayer, Port.; Bayer, Spain; Bayer, Turk.*
Dexpanthenol (p. 2582·2).
Skin disorders; wounds; gastrointestinal disorders; respiratory-tract disorders; oral lesions.
Bayer, Port.†
Lotion: Dexpanthenol (p. 2582·2); chlorhexidine hydrochloride (p. 1743·3).
Skin disorders; wounds.

Bépanthène *Bayer Sante, Fr.; Bayer, Switz.*
Dexpanthenol (p. 2582·2).
Alopecia; skin disorders; gastrointestinal disorders; respiratory-tract disorders; nasal disorders; mouth and throat disorders.

Bepanthene Plus *Bayer, Port.; Bayer, Turk.*
Dexpanthenol (p. 2582·2); chlorhexidine hydrochloride (p. 1743·3).
Wounds; skin disorders.
Bayer, Switz.
Dexpanthenol (p. 2582·2); chlorhexidine gluconate (p. 1743·3) or chlorhexidine hydrochloride (p. 1743·3).
Skin disorders; ulcers; wounds.

BepanthenSensicalm *Bayer Sante, Fr.*
Panthenol (p. 2582·2).
Skin irritation.

Bepantol *Bayer, Braz.; Roche, Braz.; Bayer, Chile; Merkez, Turk.†*
Dexpanthenol (p. 2582·2).
Skin disorders; burns; wounds.

Beparine *Biological E, India.*
Cream: Heparin sodium (p. 1396·3); benzyl nicotinate (p. 29·3).
Superficial thrombophlebitis; varicose veins; bed sores; sprains; bruises; haematomas; tenosinovitis; carbuncles; furuncles.
Biological E, India.
Injection; topical gel: Heparin sodium (p. 1396·3).
Thromboembolic disorders; superficial thrombophlebitis; varicose veins; bed sores; sprains; bruises; haematomas; tenosinovitis; carbuncles; furuncles.

Bepeben *Teuto, Braz.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Bepeno *Milano, Thai.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Respiratory-tract disorders; nasal congestion.

Bepeno-G *Milano, Thai.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1); guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Beplarid *Choseido, Jpn.†*
Beraprost sodium (p. 1316·2).
Occlusive arterial disease.

Beplex *Anglo-French Drugs, India.*
Vitamin B substances (p. 2102·3); with or without vitamin C (p. 2110·3).
Vitamin B deficiency.
Synco, Hong Kong†; Darou Pakhsh, Rus.†
Vitamin B substances (p. 2102·3).

Beplexaron *Ariston, Braz.*
Vitamin B substances (p. 2102·3).

Beplex-Zee *Anglo-French Drugs, India.†*
Vitamins; zinc (p. 2126·1).

Beplus *Cazi, Braz.*
Vitamin B substances (p. 2102·3).
Plusandex, Venez.
Thiamine (p. 2102·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; neuritis; neuralgia.

Beposid *Biological E, India.*
Etoposide (p. 790·2).
Small-cell lung cancer; testicular cancer.

Bepreve *Ista, USA.*
Bepotastine besilate (p. 617·3).
Allergic conjunctivitis.

Bepricor *MSD, Jpn.*
Bepridil hydrochloride (p. 1316·2).
Arrhythmias.

Bepride *Avinash, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Bepride-MF *Avinash, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Bepride-SF *Avinash, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Beprin *Taj, India.*
Heparin (p. 1396·3).
Thromboembolic disorders.

Bepro *Wallace Mfg Chem., UK.*
Codeine phosphate (p. 40·2).
Coughs.

Beprogel *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Beprogent *Hoe, Malaysia; Hoe, Singapore.; Hoe, Thai.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Beprogenta *Chew, Thai.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected inflammatory skin disorders.

Beprolic *Hoe, Thai.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Bepronate *Pharmasant, Thai.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Beprosalic *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Beprosone *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore; Chew, Thai.; Hoe, Thai.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Beprospen *Biotech, Venez.*
⊗Betamethasone phosphate (p. 1623·2); betamethasone dipropionate (p. 1623·3).
Corticosteroid.

Bepsar *Nabiqasim, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Beptazine *MM, India.†*
⊗Propranolol hydrochloride (p. 1479·1); dihydralazine sulfate (p. 1358·3).
Hypertension.

Beptazine-H *MM, India.†*
⊗Propranolol hydrochloride (p. 1479·1); dihydralazine sulfate (p. 1358·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bequidril *Teuto, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Bequium *Saval, Chile.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); codeine (p. 40·2).
Cough; nasal congestion.

Beradorlin *Daiichi Sankyo, Jpn.*
Beraprost sodium (p. 1316·2).
Occlusive arterial disease; pulmonary hypertension.

Beramicina *Berman, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Beramikin *Berman, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Berart *Baif, Ital.*
Indian barberry (p. 2532·1); milk thistle (p. 1561·1); monacolina; ubidecarenone (p. 2637·1); folic acid (p. 2063·1); lutein (p. 2079·2); policosanol (p. 1472·1).
Hyperlipidaemias.

Berastolin *Taisho, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Berasus *Kaken, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension.

Beratex *Chew, Thai.*
Thiamine hydrochloride (p. 2103·1).
Dietary supplement; thiamine deficiency.

Berber CO *Frankin, Hong Kong.†*
Berberine (p. 2455·1); dicycloverine (p. 1834·2); furazolidone (p. 933·3).

Berberell *Sanorell, Ger.*
Berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Berberil *Mann, Pol.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation; conjunctivitis.

Berberil Dry Eye *Mann, Ger.*
Hypromellose (p. 2189·2).
Dry eyes.

Berberil N *Mann, Ger.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Berberis Comp *Talion-A, Rus.*
Berberis vulgaris (p. 2502·1); eupatorium perfoliatum (p. 2459·1); iodum (p. 2336·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Berberis Complex *Blackmores, Austral.†*
European barberry (p. 2502·1); taraxacum (p. 2625·3); greater celandine (p. 2522·2); boldo (p. 2458·3); lecithin (p. 2542·2); methionine (p. 1558·2); thiamine hydrochloride (p. 2103·1).
Liver disorders; dyspepsia; constipation.

Berberis Complexe No 83 *Lehning, Fr.*
Berberis vulgaris (p. 2502·1); acidum oxalicum (p. 2578·2); colchicum (p. 607·1); colocynthis (p. 1833·3); betula folia (p. 2457·3); ononis spinosa (p. 2575·3); natrum sulfuricum (p. 1888·1); gnaphalium polycephalum; pulsatilla (p. 2600·2); terebinthina.
Homoeopathic preparation.

Berberis Cosmoplex *Heel, Austria.†*
Berberis vulgaris (p. 2502·1); solidago virgaurea (p. 2620·1); apocynum cannabinum; myristica fragrans (p. 2573·1); lytta vesicatoria; herniaria glabra (p. 2525·1); citrullus colocynthis; barosma (p. 2461·3); chondodendron tomentosum; serenoa repens (p. 2363·3); urginea maritima var rubra (p. 2161·2); populus tremuloides (p. 2450·3); petroselinum crispum (p. 2583·3); chimaphila umbellata; equisetum hyemale; juniperus communis; terebinthina laricina; urtica urens (p. 2639·3); hydrargyrum bichloratum (p. 2555·2); kalium arsenicosum (p. 2594·3); strychnos ignatii (p. 2532·1); plumbum aceticum (p. 2541·3); apisinum (p. 2434·3); argentum nitricum (p. 2615·3); ren suis

(p. 2444·1); vesica urinaria suis (p. 2444·1); capsicum annuum (p. 2469·3).
Homoeopathic preparation.

Berberis N Oligoplex *Madaus, Ger.*
Berberis (p. 2502·1); abrotanum; colchicum (p. 607·1); gnaphalium polycephalum; ledum (p. 2550·1); nux vomica (p. 2573·3).
Homoeopathic preparation.

Berberis/Cantharis Comp *Weleda, S.Afr.†*
Hypericum (p. 449·1); cantharis (p. 2469·2); berberis; apis (p. 2445·2).
Homoeopathic preparation.

Berberis-Homaccord *Heel, Canad.†*
Barberry root (p. 2502·1); citrullus colocynthis (p. 1833·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Berberis-Plus *Doctor H, Rus.*
Berberis vulgaris (p. 2502·1); podophyluum peltatum (p. 1717·1); strychnos nux-vomica (p. 2573·3); taraxacum officinale (p. 2625·3); calcium carbonicum (p. 1824·3); chelidonium majus (p. 2522·2).
Homoeopathic preparation.

Bercetina *Bernabo, Arg.*
Flunarizine hydrochloride (p. 629·3).

Berciclina *Berman, Mex.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Berciclina Enzimatica *Berman, Mex.*
Tetracycline (p. 373·1) with enzymes.
Bacterial infections.

Berclomine *Polipharm, Thai.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Gastrointestinal colic and spasm; irritable bowel syndrome.

Berea *Zenith, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Beres *Beres, Hung.*
Trace elements.
Nutritional supplement.

Beres B1 *Beres, Hung.*
Thiamine nitrate (p. 2103·2).
Vitamin B_1 deficiency.

Beres B6 *Beres, Hung.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Beres C *Beres, Hung.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Béres Calcium *Beres, Hung.*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis; allergic disorders.

Beres Calcium Plus D3 *Beres, Ukr.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; osteomalacia; calcium and vitamin D deficiency.

Beres Drops Plus *Beres, Rus.; Beres, Ukr.*
Minerals; trace elements.

Beres Magnesium Plus B6 *Beres, Ukr.*
Pyridoxine (p. 2105·3); magnesium (p. 1786·3).
Magnesium deficiency; magnesium supplement.

Béres Magnézium + B_6 *Beres, Hung.*
Magnesium oxide (p. 1857·3); magnesium citrate (p. 1857·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency; magnesium supplement.

Berest *Anvik, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Berex *Leiras, Fin.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Bergacid *Casen Fleet, Ital.†*
Boric acid (p. 2459·3); bergamot oil (p. 2455·1).
Fungal skin and vaginal infections.

Bergagyn *Chefaro, Ital.*
Benzalkonium chloride (p. 1737·1).
Vaginal disinfection.

Bergal *KRKA, Neth.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Bergamol *Medichrom, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Bergamon In *Chefaro, Ital.*
Didecyldimethylammonium chloride (p. 1750·3).
Vaginal infections; vaginal hygiene.

Berggeist *Kur und Stadtapotheke, Austria.*
Arnica tincture (p. 2447·2); urtica tincture (p. 2639·3); formic acid (p. 2507·1); menthol (p. 2553·2); methyl nicotinate (p. 91·3); juniper oil (p. 2537·2); lavender oil (p. 2541·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3); pumilio pine oil (p. 2591·1).
Musculoskeletal and joint disorders; neuralgia; bruising.

Bergoline *Aspen, Austral.*
Cabergoline (p. 899·3).
Parkinsonism.

Beriate *CSL, Austria; CSL, Ger.; GSK, Rus.; CSL, Switz.*
A factor VIII preparation (p. 1148·1).
Factor VIII deficiency; haemophilia A; haemorrhagic disorders.

Beriate P *CSL, Arg.; ZLB, Braz.†; CSL, Hung.; CSL, Ital.; CSL, Mex.; CSL, Port.; CSL, Spain; Farma-Tek, Turk.; Aventis Behring, UK.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; factor VIII deficiency.

Beribumin *CSL, Braz.*
⊗Albumin (p. 1130·2).
Plasma volume expansion.

Bericard *Sigmapharm, Austria.*
Crataegus (p. 2488·1).
Cardiovascular disorders.

Berifen *Mepha, Indon.†; Sunthi Sepuri, Indon.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout.

Beriglobin *CSL, Austria; CSL, Denm.; CSL, Ger.; Gerolymatos, Gr.; Mirren, S.Afr.; CSL, Swed.; CSL, Switz.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; mucositis.

Beriglobin P *CSL, Israel.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; passive immunisation; primary immunodeficiency.

Beriglobina *CSL, Arg.; CSL, Braz.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia.

Beriglobina P *Sanofi Pasteur, Chile†; CSL, Mex.; CSL, Spain.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; passive immunisation.

Berin *GSK, India.*
Vitamin B_1 (p. 2102·3).

Berinert *CSL Biotherapies, Austral.; CSL, Austria; CSL, Belg.; CSL, Canad.; CSL, Cz.; CSL, Denm.; CSL, Fin.; CSL, Fr.; CSL, Ger.; CSL, Gr.; IFET (ΙΦΕΤ), Gr.; CSL, Israel; CSL, Neth.; CSL, Norw.; CSL, Port.; CSL, Spain; CSL, Swed.; CSL, Switz.; CSL, UK; CSL, USA.*
Complement C1 esterase inhibitor (p. 2485·1).
Hereditary angioedema.

Berinert P *CSL, Arg.; CSL, Hung.*
Complement C1 esterase inhibitor (p. 2485·1).
Hereditary angioedema.

Berinin *ZLB, Braz.†; CSL, Ger.; CSL, Switz.*
A factor IX preparation (p. 1149·3).
Haemophilia B; factor IX deficiency.

Berinin P *CSL, Arg.; CSL, Hung.; CSL, Mex.; CSL, Spain; Farma-Tek, Turk.*
A factor IX preparation (p. 1149·3).
Haemophilia B; factor IX deficiency.

Beriplast *CSL, Austria; Nycomed, Fr.; CSL, Ger.; Takeda, Ger.; CSL, Gr.; Gerolymatos, Gr.; Aventis Behring, Israel†; CSL, Ital.; Centeon, Pol.*
1 Vial, fibrinogen (p. 1151·3); factor XIII (p. 1150·3); 1 vial, aprotinin (p. 1133·2); 1 vial, thrombin (p. 1163·2); 1 vial, calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

CSL, Indon.; Dexa, Indon.
Fibrinogen (p. 1151·3); factor XIII (p. 1150·3); aprotinin (p. 1133·2); kininogen inactivator; thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Beriplast P *CSL, Arg.; CSL, Braz.; Sanofi Pasteur, Chile†; CSL Biotherapies, Hong Kong; CSL, Hung.; CSL, Mex.; CSL, Neth.; CSL, Switz.; Farma-Tek, Turk.*
1 Ampoule, fibrinogen (p. 1151·3); factor XIII (p. 1150·3); 1 ampoule, aprotinin (p. 1133·2); 1 ampoule, thrombin (p. 1163·2); 1 ampoule, calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Beriplast P Combi *CSL, Spain.*
1 Vial, fibrinogen (p. 1151·3); factor XIII (p. 1150·3); 1 vial, aprotinin (p. 1133·2); 1 vial thrombin (p. 1163·2); 1 vial, calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Beriplex *CSL, Israel; CSL, Port.; CSL, Spain; CSL, Switz.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders; anticoagulant overdose.

Beriplex PN *CSL, Arg.; CSL, Austria; CSL, Braz.; CSL, Canad.; CSL, Ger.; CSL, Gr.; CSL, Hung.; CSL, Neth.; CSL, UK.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders; factor II, VII, IX, and X deficiency; anticoagulant overdose.

Berirab *CSL, Austria; CSL, Ger.; CSL Biotherapies, Hong Kong; CSL, Israel; CSL, Switz.; CSL, Thai.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Berirab-P *Zydus, India; CSL, Mex.; CSL, Philipp.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Berirap *IFET (ΙΦΕΤ), Gr.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Berivine *Therabel, Belg.*
Riboflavin (p. 2104·3).
Vitamin B_2 deficiency.

Berizar *KRKA, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Berkofen *Berko, Turk.*
Ibuprofen arginine (p. 68·2).

Berko-Fiz *Berko, Turk.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Berkolin *Berko, Turk.*
⊗Xylometazoline hydrochloride (p. 1680·1).

Berk-Oral *Berko, Turk.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Berko-Setamol *Abbott, Turk.; Berko, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Berlamin Modular *Berlin-Chemie, Rus.†*
Preparation for enteral nutrition.

Berlex *Duncan, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Berlicort
Note: this name may be used for preparations of different composition.
Berlico Mulia, Indon.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.
Berlin-Chemie, Rus.†
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Berlifed *Berlico Mulia, Indon.*
⊗Promethazine hydrochloride (p. 638·2); pseudoephedrine hydrochloride (p. 1676·1); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1); alcohol (p. 1733·1).
Cough; influenza symptoms.

Berlinsulin H 30/70 *Berlin-Chemie, Ger.*
⊗Mixture of insulin injection (human, prb) and isophane insulin injection (human, prb) respectively in the proportions indicated (p. 475·3).
Diabetes mellitus.

Berlinsulin H Basal *Berlin-Chemie, Ger.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Berlinsulin H Normal *Berlin-Chemie, Ger.*
⊗Insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Berlipril *Berlin-Chemie, Cz.; Berlin-Chemie, Hung.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

Berlipril Plus *Berlin-Chemie, Ukr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Berlison *Berlico Mulia, Indon.*
Phenylbutazone (p. 125·1).
Musculoskeletal and joint disorders; gout.

Intendis, Braz.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Berlithion *Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy; alcoholic polyneuropathy.

Berlocid *Berlin-Chemie, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Berlofen *Elea, Arg.*
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Berlosid *Berlico Mulia, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; gastritis.

Berlosin *Berlin-Chemie, Ger.*
Dipyrone (p. 53·3).
Pain; fever.

Berloson-N *Berlico Mulia, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Berlthyrox *Berlin-Chemie, Ger.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Bernacin *Am-Europharma, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Bernafolic *Bernabo, Arg.*
Folic acid (p. 2063·1).
Anaemias; prevention of neural tube defects in pregnancy.

Bernesten *Berlico Mulia, Indon.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Bernoflox *Bernofarm, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Berocca *Bayer Consumer, Arg.; Bayer, Gr.; Bayer, Hung.; Roche Consumer, UK.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3).
Dietary supplement.

Bayer Consumer, Austral.; Bayer, Fin.; Bayer, Norw.; Bayer Consumer, Thai.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement; vitamin B deficiency; vitamin C deficiency.

Bayer Sante, Fr.; Bayer Consumer, Mex.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals.

Bayer, NZ.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Nutritional supplement.

Bayer, Philipp.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1).
Vitamin deficiency.

Roche, USA.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); folic acid (p. 2063·1).

Berocca Boost *Bayer, Singapore.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); guarana (p. 2648·2).
Dietary supplement.

Berocca Calcio e Magnesio *Bayer, Port.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3).
Vitamin deficiency.

Berocca Calcium & Magnesium *Bayer Consumer, Rus.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3).
Vitamin and mineral deficiency; vitamin and mineral supplement.

Bayer, Ukr.
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); magnesium (p. 1786·3).
Vitamin and mineral supplement.

Berocca calcium, magnesium + zinc *Bayer, Switz.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Vitamin deficiency; alcoholism.

Berocca CalMag *Bayer Consumer, S.Afr.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3).

Berocca Performance *Bayer Consumer, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals; ginseng (p. 2513·3).
Dietary supplement; tonic.

Bayer, Singapore.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Vitamin B and C deficiency; tonic.

Berocca Plus
Note: this name may be used for preparations of different composition.
Bayer, Chile.
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); zinc citrate (p. 2126·2).

Bayer Consumer, Arg.; Bayer Consumer, Rus.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement.

Roche, USA.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

Berocca plus Zink *Bayer, Austria.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); magnesium salts (p. 1786·3); calcium salts; zinc citrate (p. 2126·2).
Vitamin B and C deficiency; zinc deficiency.

Berocca Vit *Bayer, Chile.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Tonic.

Beroccal *Bayer, Braz.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Berocin C *Micro, India.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Berocin-CZ *Micro, India.*
Vitamin B substances (p. 2102·3); thioctic acid (p. 2629·1).

Berodual *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.†; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, Venez.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease; asthma.

Berodualin *Boehringer Ingelheim, Austria.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Berofin *Sanofi-Aventis, Arg.*
Biperiden hydrochloride (p. 895·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Berolat *New Life, Arg.*
Vitamins; minerals.
Dietary supplement.

Beromin *Condrugs, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuritis.

Beromun *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, UK.*
Tasonermin (p. 878·1).
Soft-tissue sarcoma; adjunct in surgery to prevent or delay amputation.

Beron *Ranbaxy, S.Afr.*
Mirtazapine (p. 436·1).
Depression.

Berosolvon *Boehringer Ingelheim Promeco, Mex.*
⊗Fenoterol hydrobromide (p. 1208·2); bromhexine hydrochloride (p. 1656·3).
Obstructive airways disease.

Berotec *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.†; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Neth.†; Boehringer Ingelheim, Philipp.†; Boehringer Ingelheim, Pol.; Unilfarma, Port.†; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.†; Boehringer Ingelheim, Ukr.*
⊗Fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease; dyspnoea; premature labour; uterine hypertonia.

Berovent *Boehringer Ingelheim, Gr.*
⊗Salbutamol sulfate (p. 1220·2); ipratropium bromide (p. 1211·3).
Asthma; obstructive airways disease.

Berri-Freez *Geritrex, USA.*
Menthol (p. 2553·2); camphor (p. 2466·2).

Berroca Plus
Note: this name may be used for preparations of different composition.
Roche, Ukr.†
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Vitamin and mineral supplement.

Berry Vision *Sanbe, Indon.*
Myrtillus (p. 2566·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Dietary supplement for eye health.

Bersen *Pasteur, Chile.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Bersin *Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Bersol *Bernofarm, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Bertanel *Ebewe, Spain.*
Methotrexate sodium (p. 822·2).
Rheumatoid arthritis; idiopathic juvenile arthritis; psoriasis.

Berthyco *Bernofarm, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Bertocil *Edol, Port.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Beruler *Ohara, Jpn.*
Beraprost sodium (p. 1316·2).
Occlusive arterial disease; pulmonary hypertension.

Beryx *KRKA, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Berzymplex *Bernofarm, Indon.*
⊗Pancreatin (p. 2579·3); ox bile extract (p. 2457·2); dimeticone (p. 1886·2); vitamin B substances (p. 2102·3).
Pancreatic enzyme deficiency; vitamin B deficiency; flatulence.

Besalol *Tatkhimfarm, Rus.*
Belladonna (p. 2453·3); salol (p. 129·3).
Digestive disorders.

Besartan
Note: this name may be used for preparations of different composition.
Kleva, Gr.
Irbesartan (p. 1411·1).

Unique, Philipp.
Losartan potassium (p. 1422·2).
Hypertension.

Besasin *SSP, Thai.*
Thiamine hydrochloride (p. 2103·1).
Dietary supplement; thiamine deficiency.

Besavar *Winthrop, UK.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Bescal *Trigenesis, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); zinc picolinate (p. 2126·1).

Bescal-P *Trigenesis, India.*
Colecalciferol (p. 2113·1); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Beselna *Mochida, Jpn.*
Imiquimod (p. 985·2).
Anogenital warts; actinic keratosis.

Besemax *Adcock Ingram, S.Afr.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Pain; skeletal muscle spasm.

Besenol *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Musculoskeletal spasm; pain.

Beserol *Sanofi-Aventis, Braz.*
Diclofenac sodium (p. 48·3); carisoprodol (p. 2021·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Inflammation; musculoskeletal and joint disorders.

Beseroldos *Sanofi-Aventis, Venez.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Skeletal muscle spasm; pain.

Beserol-S *Sanofi-Aventis, Chile.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Musculoskeletal spasm and pain.

Besflox *Labesfal, Port.*
Norfloxacin (p. 333·3).
Bacterial infections.

Besidin *Coup, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Besilapin *Geolab, Braz.*
Amlodipine besilate (p. 1304·1).

Besitrac *Biochimico, Braz.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Besitran *Pfizer, Spain.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; anxiety post-traumatic stress disorder.

Besivance *Bausch & Lomb, Canad.; Bausch & Lomb, Singapore; Bausch & Lomb, USA.*
Besifloxacin hydrochloride (p. 230·3).
Bacterial eye infections.

Besix *Alapis, Gr.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B6 deficiency; hyperoxaluria; sideroplastic anaemia.

Charoon Bhesaj, Thai.
Pyridoxine (p. 2105·3).
Vitamin B_6 deficiency.

Beslodipin *Stada, Fin.†*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Besmal *Sriprasit, Thai.*
Bismuth salicylate (p. 1821·3).
Peptic ulcer; abdominal cramps; nausea; dyspepsia; diarrhoea.

Besobrial *Merck, S.Afr.*
Acamprosate calcium (p. 1034·2).
Chronic alcoholism.

Besodin *Belfar, Braz.*
⊗Isometheptene (p. 2535·1); caffeine (p. 1203·3); dipyrone (p. 53·3).

Besone *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Besone-N *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Besonin *Synmosa, Malaysia; Synmosa, Thai.*
⊗Budesonide (p. 1625·1).
Rhinitis.

Bespar *BMS, Ger.†; Vianex (Βιανεξ), Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Bespres *Teva, Pol.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Besquil *Ranbaxy, India; Ranbaxy, Malaysia.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder; depression; mixed anxiety depressive states.

Bessasone *Pharmaland, Thai.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Best
Note: this name may be used for preparations of different composition.
Konsuma, Venez.
dl-Alpha tocoferil acetate (p. 2119·2).
Antoxidant.

Unipharma, Gr.
Glucosamine sulfate (p. 2515·3).

Best Balm *Minorock Mandiri, Indon.†*
Camphor (p. 2466·2); peppermint oil (p. 1877·1).
Muscle pain; insect bites.

Bestafen *Best, Mex.*
Ibuprofen (p. 68·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Bestalen *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bestalin *Lapi, Indon.*
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; anxiety.

Bestatin
Note: this name may be used for preparations of different composition.
Berlin Pharm, Thai.
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Kayaku, Jpn.
Ubenimex (p. 878·2).
Acute non-lymphocytic leukaemia.

Bestax *Biological E, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

BestBreast *Milte, Ital.*
Vitamins; minerals.

Bestcall *Takeda, China.*
Cefmenoxime.
Bacterial infections.

Takeda, Jpn.
Cefmenoxime hydrochloride (p. 241·2). Mepivacaine hydrochloride (p. 1992·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bestcilina-A *Best, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Bestec *Symbiosis, India.*
Ear drops: ⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Symbiosis, India.
Tablets: Chlorphenamine maleate (p. 620·3); diclofenac sodium (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Bestelar *Best, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Bester Complex *Salvat, Spain.*
Thiamine hydrochloride (p. 2103·1); hydroxocobalamin acetate (p. 2107·3); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Bestin *Cyathus, Austria; Cyathus, Cz.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Bestinem *Ranbaxy, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Best-M *Madhav, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Bestocalm *Help, Gr.*
⊗Reserpine (p. 1485·3); chlortalidone (p. 1335·2).
Hypertension.

Bestocef *Symbiosis, India.*
Cefixime (p. 240·3).
Bacterial infections.

Bestocef-LB *Symbiosis, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Bestocid *Symbiosis, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Bestocid-O *Symbiosis, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2); oxetacaine (p. 1993·1).

Bestocin *Best, Mex.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Bestocol *Tanabe, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms.

Bestodek *Bestochem, India.*
Diclofenac potassium (p. 48·3).
Pain.

Bestodin *Symbiosis, India.*
Povidone-iodine (p. 1767·1).

Bestodin-M *Symbiosis, India.*
Povidone-iodine (p. 1767·1); metronidazole (p. 936·1).

Bestodol *Bestochem, India.*
Tramadol (p. 139·2).
Pain.

Bestofen *Biological E, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Bestoflame *Symbiosis, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Bestoflox *Bestochem, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bestoflox N *Bestochem, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Bestofyline *Bestochem, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Bestofyline-A *Bestochem, India.*
Ambroxol acefyllinate (p. 1201·2).
Asthma.

Bestogesic *Bestochem, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Bestogesic MR *Bestochem, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Bestomax *Bestochem, India.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Bestomax 375 *Bestochem, India.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Beston *Tanabe, Indon.*
Bisbentiamine (p. 2103·1).
Vitamin B_1 deficiency disorders.

Bestonim *Alicon, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Bestonim C *Alicon, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bestonim N *Alicon, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bestonim P *Alicon, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Bestopic *Systopic, India.*
⊗Beclometasone dipropionate (p. 1621·2); econazole nitrate (p. 577·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Bestopic-N *Systopic, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bestor *Biocon, India.*
Rosuvastatin (p. 1488·2).
Hyperlipidaemias.

Bestorner *Alfresa, Jpn.†*
Beraprost sodium (p. 1316·2).
Occlusive arterial disease.

Bestozyme *Biological E, India.*
Capsules; syrup: ⊗Amylase (p. 2442·1); papain (p. 2582·3).
Capsules formerly contained amylase, papain, and simeticone.
Dyspepsia; colic.

Biological E, India.
Oral drops: ⊗Amylase (p. 2442·1); papain (p. 2582·3); anise oil (p. 2444·3); caraway oil (p. 2470·3); dill oil (p. 2493·2).
Dyspepsia; colic.

Bestozyme P *Biological E, India.*
⊗Amylase (p. 2442·1); papain (p. 2582·3); anise oil (p. 2444·3); caraway oil (p. 2470·3); cinnamon oil (p. 2479·3); dill oil (p. 2493·2).
Dyspepsia; colic.

Bestpirin *Teva, Pol.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Bestrol *Cetus, Arg.*
Alprazolam (p. 1035·2).
Anxiety; depression.

Bestron *Senju, Jpn.*
Cefmenoxime hydrochloride (p. 241·2).
Bacterial eye infections.

Bestum *Wockhardt, Rus.*
Ceftazidime (p. 250·2).
Bacterial infections.

Besvital *Silanes, Mex.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia.

Besylon *Medhaus, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Beta
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory eye and ear disorders.

Mylan, NZ; Jean-Marie, Philipp.; Chew, Thai.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders; skin and scalp disorders.

Stadmed, India.
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Beta 21 *IDI, Ital.*
⊗Betamethasone valero-acetate (p. 1623·2).
Skin disorders.

Beta A-C *Eagle, Austral.*
Tablets: Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); calcium ascorbate (p. 2111·1); *d*-alpha tocoferil acid succinate (p. 2119·2); rutoside (p. 2505·3); zinc amino acid chelate (p. 2048·3); betacarotene (p. 2051·1); bioflavonoids (p. 2505·2).
Dietary supplement.

Eagle, Austral.
Oral powder: Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); calcium ascorbate (p. 2111·1); *d*-alpha tocoferil acetate (p. 2119·1); rutoside (p. 2505·3); zinc amino acid chelate (p. 2048·3); betacarotene (p. 2051·1).
Dietary supplement.

Beta Alcanforado *Betamadrileno, Spain.†*
⊗Camphor (p. 2466·2); alcohol (p. 1733·1).
Musculoskeletal, joint, and soft-tissue pain.

Beta Amlol *Themis Medicare, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Beta Long *Uniao Quimica, Braz.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Beta Micoter *Teofarma, Spain.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections.

Beta Nicardia *Unique, Singapore.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Beta Nicip *Cipla, India.*
Nimesulide betadex (p. 101·3).

Beta Opthiole *Kite (Κιτε), Gr.*
⊗Metipranolol hydrochloride (p. 2009·2); benzalkonium chloride (p. 1737·1).
Glaucoma.

Beta Plus *Plus, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Beta Romero *Betamadrileno, Spain.*
⊗Alcohol (p. 1733·1); rosemary oil (p. 2607·3).
Musculoskeletal pain and fatigue.

Beta XMA *Beta, USA.*
Emollient.

Beta-Adalat *Bayer, Austria; Bayer, Irl.; Bayer, Switz.; Bayer, UK.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Beta-Adalate *Bayer, Fr.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension.

Betabare *Egis, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Beta-Biduret *GSK, India.*
⊗Amiloride hydrochloride (p. 1299·1); atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Betabion
Note: this name may be used for preparations of different composition.
Bioton, Pol.†
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Merck Serono, Ger.†; Merck, Swed.†
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Betabioptal *Farmila, Ital.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3); chloramphenicol (p. 257·1).
Infected eye disorders.

Betabiot *Serral, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Betabloc *USV, India.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; angina pectoris; hypertension.

Betablok *Hexpharm, Indon.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Betabolin *Bestochem, India.*
⊗Nandrolone (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Betabronze *Lafarmen, Arg.*
Betacarotene (p. 2051·1); vitamin A (p. 2098·3); alpha tocopherol (p. 2119·1).
Tanning aid.

Be-Tabs Antacid *Be-Tabs, S.Afr.†*
Magnesium trisilicate (p. 1858·1); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Gastrointestinal disorders associated with hyperacidity.

Betabus *Globus, India.*
⊗Propranolol (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor.

Beta-C
Note: this name may be used for preparations of different composition.
Chew, Thai.
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Body Wise, Canad.†
Betacarotene (p. 2051·1); vitamin C (p. 2110·3).

Betac *Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; angina pectoris; myocardial infarction; hypertrophic cardiomyopathy; arrhythmias.

Betacade *Dermoteca, Port.*
Salicylic acid (p. 1719·1); cade oil (p. 1723·2); cedar oil (p. 2472·3); liquid paraffin (p. 2191·2).
Psoriasis.

Betacaine *Canderm, Canad.; Theraderm, Israel†; Darier, Mex.†*
Lidocaine (p. 1988·1).
Local anaesthesia.

Betacap
Note: this name may be used for preparations of different composition.
Dermal Laboratories, Irl.; Trupharm, Israel; Dermal Laboratories, UK.
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders.

Sun, India.
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor.

Betacar
Note: this name may be used for preparations of different composition.
Mega Lifesciences, Thai.
Betacarotene (p. 2051·1).
Vitamin A deficiency.

Sanofi-Aventis, Chile.
⊗Atenolol (p. 1308·2).
Hypertension.

Betacard
Note: this name may be used for preparations of different composition.
GX, Philipp.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Torrent, India; Torrent, Rus.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine; arrhythmias; myocardial infarction; tremor; hypertrophic obstructive cardiomyopathy; phaeochromocytoma; hyperthyroidism.

Betacard H *Torrent, India.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2).

Betacard Plus *Torrent, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).

Betacard-AM *Torrent, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Beta-Cardone *Focus, UK.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Betacarpin *Agepha, Austria.*
⊗Pilocarpine hydrochloride (p. 2010·3); metipranolol hydrochloride (p. 2009·2).
Glaucoma.

Beta-CE *Otto, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Dietary supplement.

Betacentrine *Jadran, Rus.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betachek *California Scientific, Arg.; National Diagnostic, Austral.*
Test for glucose in blood (p. 2516·3).

Betacid *Meditop, Hung.*
⊗Pepsin (p. 2586·1); betaine hydrochloride (p. 2456·1).
Hypochlorhydria.

Betacillin
Note: this name may be used for preparations of different composition.
Vista, India.
Amoxicillin (p. 216·2).
Bacterial infections.

Betacin
Note: this name may be used for preparations of different composition.
Be-Tabs, S.Afr.
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

CCM, Malaysia.
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Betaclar *Angelini, Ital.†*
⊗Befunolol hydrochloride (p. 2004·2).
Glaucoma.

Betaclav *Ranbaxy, Braz.†; Corsa, Indon.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Betaclomin *Be-Tabs, S.Afr.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Betaclopramide *Be-Tabs, S.Afr.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Betaclox *Ajanta, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Betacomplesso *Medosan, Ital.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; tonic.

Betacon *Concertina, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Betacor *KVZ, Ukr.*
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; angina pectoris.

Betacort
Note: this name may be used for preparations of different composition.
Biospray, Gr.
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Skin disorders.

Cassara, Arg.
Cream: ⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Cassara, Arg.
Injection: ⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cassara, Arg.; SM, Venez.
⊗Betamethasone (p. 1623·2).
Corticosteroid; skin disorders.

Utopian, Thai.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betacort Plus *Cassara, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betacortazol *Belfar, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone (p. 1623·2); neomycin (p. 329·3).

Betacorten *Trima, Israel; Trima, Singapore†; Unipharm, Singapore.†*
⊗Betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

Betacorten-G *Trima, Israel.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betacort-N *Utopian, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betacorton *Abbott, Turk.*
⊗Halcinonide (p. 1639·3); urea (p. 1727·3).
Skin disorders.

Spirig, Cz.†
⊗Halcinonide (p. 1639·3).
Skin disorders.

Betacorton S *Spirig, Cz.†*
⊗Halcinonide (p. 1639·3); salicylic acid (p. 1719·1).
Skin disorders.

Betacorton U *Spirig, Cz.†*
⊗Halcinonide (p. 1639·3); urea (p. 1727·3).
Skin disorders.

Bétacortone *Spirig, Switz.*
Cream: ⊗Halcinonide (p. 1639·3); urea (p. 1727·3).
Skin disorders.

Spirig, Switz.
Topical solution: ⊗Halcinonide (p. 1639·3).
Skin disorders.

Bétacortone S *Spirig, Switz.*
⊗Halcinonide (p. 1639·3); salicylic acid (p. 1719·1).
Skin disorders.

Betacortril *Pfizer, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betacream *Epifarma, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

BetaCreme *Winthrop, Ger.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Beta-D *Agio, Philipp.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Betadac-DC *Scoshia, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Betaday *Sun, India.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Vesco, Thai.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Betadecabolin *Bestochem, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Betaderm
Note: this name may be used for preparations of different composition.
Stiefel, Braz.; Taro, Canad.; Eadriex, Philipp.; Biotech, Venez.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders; scalp disorders.

Jelfa, Rus.; Jelfa, Ukr.
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Beta, Ital.†
Salicylic acid (p. 1719·1); aluminium acetate (p. 2440·1); zinc oxide (p. 1729·1).
Skin disinfection.

Betaderm con Gentamicina *Biotech, Venez.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betaderm N *Stiefel, Braz.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betadermic *Galen, Ger.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Betadex *Vickmans, Hong Kong.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine (p. 620·3).

Betadex-12 *Ikon, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Betadex Forte *Ikon, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Betadine *Faulding Consumer, Austral.; Purdue, Canad.; Egis, Cz.; Leiras, Fin.; Meda, Fr.; Lavipharm, Gr.; Mundipharma, Hong Kong; Egis, Hung.; Win-Medicare, India; Mahakam Beta, Indon.; Mundipharma, Indon.; Medlock Medical, Irl.; Meda, Ital.; Mundipharma, Malaysia; Meda, Neth.; Faulding, NZ; Mundipharma, Philipp.; Pascual, Philipp.; Egis, Pol.; Meda, Port.; Egis, Rus.; Adcock Ingram, S.Afr.; Mundipharma, Singapore; Meda, Spain; Mundipharma, Switz.; Mundipharma, Thai.; Molnlycke, UK; Egis, Ukr.; Purdue Frederick, USA; Novapharm, Venez.*
Povidone-iodine (p. 1767·1).
Skin infections; vaginal infections; mouth and throat infections; ulcers; burns; herpes labialis; oral hygiene; lubricant in catheterisation; seborrhoeic dermatitis; disinfection of skin, hands, wounds, and mucous membranes.

Betadine-AD *Win-Medicare, India.*
Povidone-iodine (p. 1767·1).
Scalp disorders.

Beta-Dipo *TNP, Thai.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betadona *Mundipharma, Austria.*
Povidone-iodine (p. 1767·1).
Infected wounds and burns.

Betadorm D *Recordati, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Betadox *Apotex, India.*
Vitamins.

Betadrenol
Note: this name may be used for preparations of different composition.
Unipharma, Gr.
⊗Propranolol hydrochloride (p. 1479·1).

Desma, Ger.†
⊗Bupranolol hydrochloride (p. 1329·3).
Hypertension; ischaemic heart disease; myocardial infarction.

Betadrin *Polfa Warszawa, Pol.; Polfa, Rus.*
⊗Diphenhydramine hydrochloride (p. 626·2); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis; eye irritation; allergic rhinitis.

Betadure *Micro, Mex.*
⊗Atenolol (p. 1308·2).

Betaeffe Complex *Mavi, Ital.*
Carotenoids; vitamin E (p. 2119·1); vitamin C (p. 2110·3); grape (p. 2521·3).
Nutritional supplement.

Betaeffe Plus *Mavi, Ital.*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); selenium (p. 2086·3).
Nutritional supplement.

Betafact *LFB, Fr.; Vianex (Βιανεξ), Gr.; Omrix, Israel; Lab Francais du Fractionnement, Neth.; LFB, Port.; Er-Kim, Turk.*
A factor IX preparation (p. 1149·3).
Haemophilia B; haemorrhagic disorders; factor IX deficiency.

Betafed *Be-Tabs, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Betaferon *Bayer, Arg.; Bayer, Austral.; Bayer Schering, Austria; Bayer, Belg.; Schering, Braz.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer Schering, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; German Remedies, India†; Bayer Schering, Indon.; Schering, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer Schering, Pol.; Bayer Schering, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer Schering, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Bayer, UK.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Betafloroto *INTES, Ital.*
⊗Betamethasone sodium phosphate (p. 1623·3); tetracycline hydrochloride (p. 373·2).
Ear infections; rhinitis.

Betafoam *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1).
Asthma; skin disorders.

Betafoam-S *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1); salicylic acid (p. 1719·1).

Betafort *Phapros, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); betacarotene (p. 2051·1).
Dietary supplement.

Betafusin *Pharmex (Φαρμεξ), Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Betagalen *Galen, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betagan *Allergan, Arg.; Allergan, Austral.†; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, China; Allergan, Hong Kong; Allergan, India; Allergan, Irl.; Allergan, Malaysia; Allergan, Mex.; Allergan, Neth.; Allergan, NZ; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.†*
⊗Levobunolol hydrochloride (p. 2008·3).
Glaucoma; ocular hypertension.

Bétagan *Allergan, Fr.*
⊗Levobunolol hydrochloride (p. 2008·3).
Ocular hypertension; glaucoma.

Betagan Forte *Apotex, India.*
Vitamins; minerals; lycopene (p. 2546·2).

BetaGard *GNLD, Austral.*
Vitamins; minerals; amino acids.

Betagard *Golden Neo-Life, Canad.*
Vitamins minerals; methionine (p. 1558·2).

Betagel *Micro, India.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Betagel-G *Micro, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin (p. 304·2).
Infected skin disorders.

Betagel-N *Micro, India.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betagel-S *Micro, India.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Psoriasis; seborrhoeic dermatitis.

Betagen
Note: this name may be used for preparations of different composition.
Allergan, Chile.
⊗Levobunolol hydrochloride (p. 2008·3).
Glaucoma; ocular hypertension.

Biotech, Venez.
⊗Betamethasone (p. 1623·2).
Corticosteroid.

CCM, Malaysia.
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected eye and ear disorders.

Generics, Hung.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

TNP, Thai.
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betagen Solspen *Biotech, Venez.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Betagenot *Lekko, Rus.*
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected ear and eye disorders.

Beta-Genta *Vickmans, Hong Kong.†*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2).
Infected skin disorders.

Betagentam *Sanbe, Indon.*
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Betagesic *Adcock Ingram, S.Afr.*
Ibuprofen (p. 68·2).
Pain; fever.

Betagis *Pharma Start, Ukr.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Betaglid *Pliva Krakow, Pol.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Betaglim *Panacea, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Betaglim M *Panacea, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Betagram *Chinta, Thai.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betagranulos *Medihealth, Mex.; Roemmers Medihe, Venez.*
Polyethylene granules (p. 1690·3).
Acne.

Betagrim-M *Panacea, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Betahecon *Abbott, Irl.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betahis *Farmaline, Thai.*
Betahistine mesilate (p. 2455·3).
Vertigo; Ménière's disease.

Betahist *Geno, India.*
Betahistine hydrochloride (p. 2455·3) in betadex.
Ménière's disease; vertigo.

Betahist-B *Farmaline, Thai.†*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Betahistop *Topgen, Belg.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Betaimune *Pharmadass, UK.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Antoxidant preparation.

Betaine Digestive Aid *GNLD, Austral.*
⊗Betaine hydrochloride (p. 2456·1); pepsin (p. 2586·1); papain (p. 2582·3); pectin (p. 2200·3); natural dried beet; rhubarb (p. 1884·2); liquorice (p. 1853·2).
Digestive disorders.

Betaisodona *Mundipharma, Austria; Mundipharma, Ger.*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane disinfection; vaginal infections; wounds; burns; mouth and throat infections; skin infections; skin ulcers.

Betaject *Sandoz, Canad.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Betakele *Labormed, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betakile *Biofarm, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betakind *Mankind, India.*
Povidone-iodine (p. 1767·1).
Oral hygiene; oral candidiasis.

Betaklav *KRKA, Cz.†; KRKA, Ukr.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Betakole *US Pharmacia, Neth.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betakon *Aroma, Turk.*
Povidone-iodine (p. 1767·1).
Oral hygiene; skin disinfection.

Betaksim *Nevzat, Turk.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Betakule *Jelfa, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betalan *Polfarmex, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betalane
Note: this name may be used for preparations of different composition.
DDSA, Neth.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Bétalane *Diepharmex, Fr.*
Beta-alanine (p. 2048·3).
Dietary supplement.

Betalans *Mahakam Beta, Indon.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Betalar *Lark, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betalase *Biogened, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betalbee *Wellhealth, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Betalene *Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betalese *Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betaleukin *Gosnii, Rus.*
Interleukin-1 (p. 2533·3).
Leucopenia; secondary immunodeficiency.

Betalgon *Nizpharm, Rus.*
Nicoboxil (p. 101·1); nonivamide (p. 102·3).
Neuralgia; musculoskeletal, joint, peri-articular and soft-tissue disorders; peripheral circulatory disorders.

Betalic *Psyco Remedies, India.*
⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1).

Betalin
Note: this name may be used for preparations of different composition.
Beta, Arg.
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Be-Tabs, S.Afr.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Betalin Lenta *Beta, Arg.†*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Betalin Mix *Beta, Arg.*
⊗A mixture of soluble insulin (human) 30% and isophane insulin (human) 70% (p. 475·3).
Diabetes mellitus.

Betalin NPH *Beta, Arg.†*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Betaline *Disphar, Neth.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betalix *Be-Tabs, S.Afr.†*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Betalmic *Unimed, Cz.; Unimed, Rus.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Betalobin *Bestochem, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Betaloc *AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, India; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Philipp.; AstraZeneca, Singapore†; AstraZeneca, UK.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; migraine; arrhythmias; myocardial infarction; hyperthyroidism.

AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; Egis, Hung.; AstraZeneca, NZ; AstraZeneca, Pol.; AstraZeneca, Rus.; AstraZeneca, Thai.; AstraZeneca, Ukr.
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; arrhythmias; hyperthyroidism; heart failure; hypertension; migraine; left ventricular dysfunction.

Betaloc H *AstraZeneca, India.*
⊗Hydrochlorothiazide (p. 1403·2); metoprolol (p. 1434·3).
Hypertension.

Betaloc Zok *AstraZeneca, Chile; Abacus, Denm.†*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; migraine; myocardial infarction; hyperthyroidism; heart failure.

Betalol *Berlin Pharm, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; tremor; anxiety disorders.

Betalor *Biosintetica, Braz.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Betalose *Glenmark, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

BetaLotio *Winthrop, Ger.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betalune *Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betaluse *Jelfa, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betama *Union Drug, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betama-EN *Union Drug, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betamann *Mann, Ger.; Mann, Pol.*
⊗Metipranolol hydrochloride (p. 2009·2).
Glaucoma; ocular hypertension.

Betamatic *Medichrom, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betamax *Grindex, Rus.; Grindeks, Ukr.*
Sulpiride (p. 1107·3).
Psychoses; schizophrenia; delirium; depression; neuroses; vestibular disorders; peptic ulcer; irritable bowel syndrome.

Betamaz *Farmasierra, Spain.*
Sulbactam sodium (p. 360·1).
Bacterial infections.

Betamed
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.
Povidone-iodine (p. 1767·1).
Skin disinfection.

Medochemie, Cz.
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; angina pectoris.

Wabosan, Austria.
⊗Bupranolol hydrochloride (p. 1329·3); diazepam (p. 1063·2).
Anxiety disorders.

Betamesol *Proge, Ital.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Betamet *CCM, Malaysia.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory eye and ear disorders.

Betametagen *Kinder, Braz.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betametasona B12 *Roux-Ocefa, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3); hydroxocobalamin (p. 2107·3). Procaine hydrochloride (p. 1994·3) is included in this preparation to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Betameth *Osoth, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betamethason comp *Hexal, Ger.†*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Betamethasone Clo *Pharmaniaga, Malaysia.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections.

Betamethasone G *Pharmaniaga, Malaysia.*
⊗Betamethasone (p. 1623·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betamethasone N *Pharmaniaga, Malaysia.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betamethasone SA *Pharmaniaga, Malaysia.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Betameth-N *Osoth, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betamican *GSK, Spain.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Beta-Micoter *Leo, Port.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections.

Betamil *Merck, India.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Betamil-GM *Merck, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betamil-M *Merck, India.*
⊗Betamethasone dipropionate (p. 1623·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betamil-N *Merck, India.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betamin *Sanofi-Aventis, Austral.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Betamine
Note: this name may be used for preparations of different composition.
Kela, Belg.
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency; Wernicke's encephalopathy.

Unimarck, India.
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betam-Ophtal *Sanbe, Indon.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory eye disorders.

Betamore *Osper, India.*
Carotenoids; mecobalamin (p. 2108·1); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2).

Betamotil *Ipca, India.*
Artemotil (p. 648·2).
Malaria.

Betamox
Note: this name may be used for preparations of different composition.
Atral, Port.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

CCM, Malaysia; Be-Tabs, S.Afr.; Duopharma, Singapore.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Betamp *Torrent, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Betamycin *Be-Tabs, S.Afr.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Beta-N *Chew, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betanase *Zydus, India; Cadila, Rus.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Betanate *Cosme, India.*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Betanate G *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betanate GM *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betanate M *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Betaneuron OD *Speciality Meditech, India.*
Vitamin B substances (p. 2102·3); glutamic acid (p. 2070·2).

Beta-Nicardia *JB Chemicals, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Betanicomylon *Nizhpharm, Rus.*
Nicoboxil (p. 101·1); nonivamide (p. 102·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; peripheral vascular disorders.

Betanif *Unichem, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Beta-Nifedipine *Piramal, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Betanil *Biofarm, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betanis *Astellas, Jpn.*
Mirabegron (p. 2360·3).
Overactive bladder.

Betannorm
Note: this name may be used for preparations of different composition.
North Star, Rus.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betanoid *Aspen, S.Afr.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Bétanol *Europhta, Mon.*
⊗Metipranolol (p. 2009·2).
Ocular hypertension; glaucoma.

Betanorm *Ali, Turk.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Phytopharm, Ukr.
Betahistine (p. 2455·3).
Ménière's disease; vertigo.

Beta-One *Hexpharm, Indon.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Betaone *Reddy, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Beta-Ophtiole *Bausch & Lomb, Austria; Tramedico, Belg.; Bausch & Lomb, Braz.; Tramedico, Neth.; Bausch & Lomb, Philipp.; Angelini, Port.†; Bausch & Lomb, S.Afr.; Mann, Singapore.*
⊗Metipranolol hydrochloride (p. 2009·2).
Glaucoma; ocular hypertension.

Betapace *Bayer, USA.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Betapam *Be-Tabs, S.Afr.*
Diazepam (p. 1063·2).
Anxiety; premedication; alcohol withdrawal syndrome; skeletal muscle spasm.

Betapect *Be-Tabs, S.Afr.*
Light kaolin (p. 1850·1); apple pectin (p. 2200·3).
Diarrhoea.

Betapen *Be-Tabs, S.Afr.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Betaperamide *Adcock Ingram, S.Afr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Betaphlem *Be-Tabs, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased mucous.

Betapirox *Medihealth, Mex.; Roemmers Medihe, Venez.*
Piroctone olamine (p. 1716·3).
Dandruff; seborrhoeic dermatitis.

Betaplex *Drugtech, Chile.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Betapred *Defiante, Fin.; Swedish Orphan, Swed.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Betapres *Polpharma, Cz.*
⊗Aspirin (p. 22·2); bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Betapress *Polipharm, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; tremor.

Betapressin *Actavis, Ger.*
⊗Penbutolol sulfate (p. 1464·3).
Arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Betapride *Avinash, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Betaprofen *Be-Tabs, S.Afr.*
Ibuprofen (p. 68·2).
Pain; inflammation.

Beta-Prograne *Tillomed, Irl.; Tillomed, UK.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; migraine; essential tremor; anxiety; hyperthyroidism; variceal bleeding.

Betaprospan *Uniao Quimica, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Betapyn *Adcock Ingram, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3); caffeine (p. 1203·3).
Pain.

Betapyr *Kela, Belg.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B_1 and/or B_6 deficiency; prophylaxis during isoniazid therapy; alcoholic polyneuritis.

Betarave *Farma-Projekt, Neth.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betared *Invision, India.*
Vitamins; trace elements.

Betarelix *Actavis, Ger.*
⊗Penbutolol sulfate (p. 1464·3); piretanide (p. 1470·3).
Hypertension.

Betarem *Remek, Gr.*
Povidone-iodine (p. 1767·1).

Betaren *Dexcel, Israel.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Betarene *Darya-Varia, Indon.†*
Carotenoids (p. 2176·2).
Antoxidant.

Betaretic *Be-Tabs, S.Afr.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Betarevin *Sager, Hung.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betareze *Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betarhin *Mahakam Beta, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Betaris *Ali, Turk.*
Betahistine hydrochloride (p. 2455·3).

Betariv *East African, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betarive *Medana, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betarove *Pliva, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betaroxime *Be-Tabs, S.Afr.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Betarretin *Roemmers Medihe, Venez.*
Tretinoin (p. 1725·2).
Acne.

Betaruve *Tabuk, Neth.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betaryx *Integrated Pharmaceutical, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension; hyperthyroidism; migraine; tachycardia.

Beta-S *Chew, Thai.*
⊗Betamethasone valerate (p. 1624·1); salicylic acid (p. 1719·1).
Skin disorders.

BetaSalbe *Winthrop, Ger.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betasalic *Andromaco, Arg.; Cipla, India; Arterium, Ukr.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders; psoriasis.

Beta-Sclerobion *Merck, India.*
Betacarotene (p. 2051·1); carotenoids; chromium tripicolinate (p. 2056·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Betasel
Note: this name may be used for preparations of different composition.
Alcon, Arg.
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Zota, India.
Vitamins; trace elements.

Bétasélen *Arkopharma, Fr.*
Vitamins; minerals.
Tonic.

Betasemid *Actavis, Ger.*
⊗Penbutolol sulfate (p. 1464·3); furosemide (p. 1387·1).
Hypertension.

Betasept
Note: this name may be used for preparations of different composition.
Purdue Frederick, USA.
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Betaseptic
Note: this name may be used for preparations of different composition.
Mundipharma, Austria; Meda, Ital.
Povidone-iodine (p. 1767·1).
Medicated dressing; skin disinfection.

Mundipharma, Ger.; Mundipharma, Switz.
⊗Povidone-iodine (p. 1767·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1).
Skin disinfection.

Bétaseptic *Meda, Fr.†*
Povidone-iodine (p. 1767·1).
Vaginal infections.

Betaserc *Raffo, Arg.; Solvay, Austria; Solvay, Belg.; Abbott, Braz.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Solvay, Gr.; Solvay, Hong Kong; Abbott, Hung.; Solvay, Indon.; BB, Ital.; Solvay, Malaysia; Abbott, Neth.; Solvay, Pol.; Abbott, Port.; Solvay, Rus.; Abbott, Singapore; Abbott, Switz.; Solvay, Turk.; Abbott, Ukr.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vestibular disorders; nausea and vomiting; vertigo; tinnitus.

Betaseron *Bayer, Canad.; Bayer, USA.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Betasid *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Betasin *Otto, Indon.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Betasint *Beta, Arg.*
⊗Insulin injection (bovine or porcine) (p. 475·3).
Diabetes mellitus.

Betasleep *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Betaslim *GMP, Indon.*
Poliglusam (p. 2593·2); garcinia cambogia (p. 2510·2); levocarnitine (p. 2053·2); chromium tripicolinate (p. 2056·1); vitamin C (p. 2110·3).
Weight reduction.

Betasol
Note: this name may be used for preparations of different composition.
Chew, Thai.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Herbapol Pruszkow, Pol.
Phaseolus (p. 2587·3); lappa (p. 2540·1); ononis (p. 2575·3); rhubarb (p. 1884·2); equisetum (p. 2500·1); buckwheat (p. 2462·1); sambucus (p. 2609·3); birch leaf (p. 2457·3).
Urinary-tract inflammation.

Betasolde *PharmaSwiss, Cz.†*
⊗Anastrozole (p. 742·1).

Betason *Kimia, Indon.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betasone *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore; Julphar, UAE.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Julphar, UAE.
Tablets: ⊗Betamethasone (p. 1623·2).
Corticosteroid.

Lekko, Rus.
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory eye disorders; otitis externa.

Betasone D *Christo, Hong Kong.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).

Betasone N *Laborate, India.*
⊗Betamethasone (p. 1623·2); neomycin (p. 329·3).
Infected eye or ear disorders.

Betasone-G *Klonal, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3) or betamethasone valerate (p. 1624·1).
Corticosteroid.

Betasone-G Compuesto *Klonal, Arg.*
⊗Betamethasone (p. 1623·2); neomycin (p. 329·3).
Infected skin disorders.

Betasone-G 12 Horas *Klonal, Arg.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Betason-N *Kimia, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Skin disorders.

Betaspan
Note: this name may be used for preparations of different composition.
Delta, Braz.
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Farmak, Ukr.
⊗Betamethasone (p. 1623·2).
Corticosteroid.

GSK, India.†
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; hypertension; migraine; anxiety; tremor; hyperthyroidism.

Betaspasm Forte *Vilco, India.*
Diclofenac sodium (p. 48·3); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Betaspi-GM *Auspi, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1); zinc sulfate (p. 2126·2).
Infected skin disorders.

Betaspore *Aristo, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Betasporina *Atral, Port.; Atral, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Betasym *Symbiosis, India.*
Povidone-iodine (p. 1767·1).

Beta-Synto *Coda I Synto, Hong Kong.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betasys *Systacare, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Beta-Tablinen *Winthrop, Ger.†*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias; angina pectoris; anxiety; essential tremor; migraine; hyperthyroidism.

Betatape *Faran, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

BetaTemp *Beta, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Betateva *Med, Turk.*
Betahistine hydrochloride (p. 2455·3).

Betatop *Alfa Wassermann, Fr.*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; angina pectoris; myocardial infarction.

Betatopic *Andromaco, Arg.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Betatrinta *Eurofarma, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Betatrop *Sun, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Betatul *Meda, Spain.*
Povidone-iodine (p. 1767·1).
Infected skin disorders; skin disinfection.

Beta-Turfa *Worwag, Ger.†*
⊗Propranolol hydrochloride (p. 1479·1); triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Beta-Val *Lemmon, USA.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

BetaVent *WraSer, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Betaver *Veropharm, Rus.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Betavert *Farmasyn, Gr.; Sun, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Hennig, Ger.
Betahistine hydrochloride (p. 2455·3) or betahistine mesilate (p. 2455·3).
Vestibular disorders.

Betavit *Cipla, India†; Terramedic, Philipp.*
Vitamins.

Betavite *Piramal, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Betavix *Genepharm, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Betawin
Note: this name may be used for preparations of different composition.
Bestochem, India.
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

CCM, Malaysia.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; migraine.

Betaxa *Zentiva, Cz.*
⊗Betaxolol hydrochloride (p. 1322·3).
Angina pectoris; hypertension.

Betaxel *Biological E, India.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Betaxin *Hospira, Canad.*
Thiamine hydrochloride (p. 2103·1).

Betaxol *Oftalmi, Venez.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Betazela *Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Betazide *AstraZeneca, Philipp.†*
⊗Hydrochlorothiazide (p. 1403·2); metoprolol tartrate (p. 1434·3).
Hypertension.

Betazidim *Lapreven, Venez.*
Ceftazidime (p. 250·2).
Bacterial infections.

Betazok *AstraZeneca, Philipp.*
⊗Metoprolol succinate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Betazol Cort *Delta, Braz.†*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betcef *Umedica, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Betek *Be-Tabs, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders.

Beten *Svizera, India; CCM, Malaysia.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; hypertrophic subaortic stenosis; tremor; myocardial infarction; hyperthyroidism; prolapsed mitral valve.

Beten-AM *Svizera, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Betesil *IBSA, Cz.; Genevrier, Fr.; IBSA, Hung.; IBSA, Ital.; Genus, UK.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betex *United Drug, Thai.*
Thiamine hydrochloride (p. 2103·1) or thiamine disulfide (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Betfu *Medimar, Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Bethacil *Bioindustria, Ital.*
Injection: Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bethacin *Aurum, India.*
Vitamins; minerals.

Bethacol *Shree Ganesh, India.*
Bethanechol chloride (p. 2456·2).
Urinary retention.

Bethadoxin-12 *Biological E, India.*
Injection: Vitamin B substances (p. 2102·3).
Vitamin B supplement.

Biological E, India.
Syrup: Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Vitamin B supplement.

Bethadoxin-P *Biological E, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3); zinc gluconate (p. 2126·2).
Dietary supplement.

Bethadoxin-XL *Biological E, India.*
Vitamins; trace elements; electrolytes (p. 1775·1); spirulina (p. 2622·1).

Bethasone *Greater Pharma, Thai.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Bethasone-N *Greater Pharma, Thai.*
⊗Betamethasone (p. 1623·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bethiol *Nizhpharm, Rus.*
Belladonna (p. 2453·3); ichthammol (p. 1705·3).
Haemorrhoids; anal fissure.

Bethkis *Cornerstone, USA.*
Tobramycin (p. 380·1).
Pseudomonal infections in cystic fibrosis.

Beth-P *Biological E, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3); protein hydrolysate; zinc gluconate (p. 2126·2).

Betiga *Solas, Indon.†*
Aluminium chlorohydrate (p. 1694·1); menthol (p. 2553·2); salicylic acid (p. 1719·1); triclosan (p. 1773·2); zinc oxide (p. 1729·1).
Hyperhidrosis.

Betim *Leo, Gr.; ICN, UK.*
⊗Timolol maleate (p. 1513·2).
Angina pectoris; hypertension; myocardial infarction; migraine.

Betimol *Santen, Fin.†; Novartis Ophthalmics, USA.*
⊗Timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Betip *Daffohils, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Betiral *Roche, Gr.*
Ornidazole (p. 943·1).
Protozoal infections; anaerobic bacterial infections.

Betistine *Rafa, Israel.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Betitotal *Adcock Ingram, S.Afr.*
Vitamin B substances (p. 2102·3); minerals.

Betji-Cort *2M, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Betlife *Grunenthal, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Betmiga *Astellas, UK.*
Mirabegron (p. 2360·3).
Overactive bladder.

Betmox *UniOrange, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Betmox-CV *UniOrange, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Betnecip *Cipla, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betnecort *Cipla, India.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Betnederm *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnederm C *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Betnederm GM *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betnederm N *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betnelan *Farmoquimica, Braz.; GSK, India; UCB, Irl.†; GSK, Philipp.; Focus, UK.†*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

GSK, Neth.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnelan-V *GSK, Belg.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnesalic *GSK, Fr.†*
⊗Betamethasone valerate (p. 1624·1); salicylic acid (p. 1719·1).
Skin disorders.

Betnesalic mono *Meda, Ger.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnesol *Defiante, Austria; Defiante, Belg.; Paladin, Canad.; Sigma-Tau, Fr.; Sigma-Tau, Ger.; GSK, Gr.; IFET (ΙΦΕΤ), Gr.; GSK, India; UCB, Irl.; Defiante, Neth.; GSK, NZ; Aspen, S.Afr.; Sigma-Tau, Switz.; Focus, UK.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid; inflammatory bowel disease; inflammatory disorders of the eye, ear, or nose.

Devries, Israel.
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betnesol Aqueous *GSK, NZ.*
⊗Betamethasone sodium phosphate (p. 1623·3); naphazoline nitrate (p. 1669·3).
Nasal congestion and inflammation.

Betnesol-N *Defiante, Austria; GSK, India; UCB, Irl.; Devries, Israel†; Aspen, S.Afr.; Focus, UK.*
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).
Inflammatory eye, ear, or nose disorders.

Betnesol-N Nasal *GSK, India.†*
⊗Betamethasone sodium phosphate (p. 1623·3); naphazoline nitrate (p. 1669·3); neomycin sulfate (p. 330·1).
Nasal disorders.

Betnesol-V *GSK, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betneton *GSK, Philipp.*
⊗Betamethasone (p. 1623·2); chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Betneval *GSK, Fr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betni *Intas, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Betnoderm *ACO Hud, Swed.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnolon *Cifarma, Braz.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnor *Indoco, India.†*
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).
Inflammatory eye and ear disorders.

Betnosone *Hoe, Malaysia.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnosone N *Hoe, Malaysia.†*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betnovat *GSK, Denm.; GSK, Fin.; GSK, Norw.; GSK, Swed.*
⊗Betamethasone valerate (p. 1624·1).
Skin and scalp disorders; otitis externa.

Betnovat med Chinoform *GSK, Denm.; GSK, Norw.; GSK, Swed.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Betnovat med Neomycin *GSK, Swed.†*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betnovat-C *GSK, Fin.†*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Betnovate *GSK, Arg.; Aspen, Austral.; GSK, Austria; GSK, Braz.; GSK, Cz.; 2care4, Denm.; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Indon.†; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Philipp.; GSK, Port.; Sekpharma, S.Afr.; GSK, Singapore; Cantabria, Spain; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
⊗Betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

Betnovate Capilar *GSK, Arg.*
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders.

Betnovate RD (Ready Diluted) *GSK, UK.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betnovate-C *GSK, Arg.; GSK, Austria†; GSK, Gr.; GSK, India; GSK, Irl.; GSK, Israel†; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.†; GSK, Switz.; GSK, Thai.†; GSK, Turk.; Chemidex, UK.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Betnovate-GM *GSK, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betnovate-M *GSK, India.*
⊗Betamethasone valerate (p. 1624·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betnovate-N *GSK, Arg.; GSK, Austria; GSK, Braz.; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel†; GSK, Malaysia; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.†; GSK, Switz.†; GSK, Thai.; Chemidex, UK.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Betnovate-Q *GSK, Braz.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Betnovate-S *GSK, India.*
⊗Betamethasone valerate (p. 1624·1); salicylic acid (p. 1719·1).
Psoriasis.

Beto *Sandoz, Pol.*
⊗Metoprolol succinate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; migraine.

Betoderm *Mugi, Indon.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betoftan *Rompharm, Rus.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Betogenta *Geolab, Braz.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2).

Betol *Tocogino, Mex.*
Vitamins.

Betolvex *Actavis, Denm.; Actavis, Fin.; Actavis, Swed.*
Cyanocobalamin (p. 2107·2) or cyanocobalamin tannate (p. 2107·2).
Megaloblastic anaemia; vitamin B_{12} deficiency.

Actavis, Norw.; Actavis, Switz.; Assos, Turk.
Cyanocobalamin tannate (p. 2107·2).
Vitamin B_{12} deficiency; megaloblastic anaemia.

Betolvidon *Abigo, Swed.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Betonin *Knoll, India.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Betonin-AST *Abbott, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3); zinc sulfate (p. 2126·2).
Vitamin B supplement; tonic.

Betonin-CZ *Abbott, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); chromium (p. 2055·3).
Vitamin B and C supplement.

Betonin-XT *Abbott, India.*
Vitamin B substances (p. 2102·3); trace elements; lycopene (p. 2546·2).

Betopic *Armoxindo, Indon.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betoptic *Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, Ukr.; Alcon, USA; Alcon, Venez.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Betoptima *Alcon, Ger.; Alcon, Indon.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Betoquin *Ioquin, Austral.*
⊗Betaxolol hydrochloride (p. 1322·3).
Ocular hypertension; glaucoma.

Betosalic *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
⊗Betamethasone valerate (p. 1624·1); salicylic acid (p. 1719·1).
Inflammatory skin disorders; keratinisation disorders.

Betosone *TO-Chemicals, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betosone-CE *TO-Chemicals, Thai.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Betosone-EN *TO-Chemicals, Thai.*
⊗Betamethasone (p. 1623·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Be-Total *Pfizer Consumer, Ital.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Be-Total Plus *Johnson & Johnson, Ital.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Betowel *Bright Future, Hong Kong.†*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Betoxid *Briskon, India.*
Vitamins; trace elements.

Betozone *De Mayo, Braz.†*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3).
Anaemias.

De Mayo, Braz.†
Oral liquid: Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Anaemias.

Betpher-1a *Biopharma, Ukr.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

Betpher-1b *Biopharma, Ukr.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Betrat B *Ativus, Braz.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betres AP *Offenbach, Mex.†*
Vitamin B substances (p. 2102·3).

Betricort *Geolab, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).

Betrigen *IQFA, Mex.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Betrimine *Help, Gr.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Betrion *Otto, Indon.*
Thiamine disulfide (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; rheumatism; vitamin B deficiency.

Betris *Siam Bheasach, Thai.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Betrix *Mahakam Beta, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Betrospam *Legrand, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Betrox *Serral, Mex.*
Hydroxocobalamin acetate (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency; neuralgias; neuropathies; metabolic disorders.

Betsol Z *Zafiro, Mex.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis.

Betsona *Neo Quimica, Braz.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Betsone *Medopharm, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Bett *Biological E, India.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Bettamousse *Recipharm, Denm.; RPH, Fin.; UCB, Irl.; UCB, Irl.; Evans Medical, Israel; Sandoz, Ital.; RPH, Norw.; UCB, Spain; Vitaflo, Swed.; Focus, UK.*
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders; skin disorders.

Better Cholesterol *Young Again Products, USA.*
Sitosterol (p. 1471·2); beta-glucan (p. 2455·2); soya isoflavones (p. 2620·3).

Bettermood *Herbal Research, UK.*
St John's wort (p. 449·1).
Anxiety; low mood.

Bettrix *Umedica, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Betulacur *Rodisma, Ger.†*
Birch leaf (p. 2457·3).
Urinary-tract disorders.

Betuline *Ferndale, USA.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Betzee *Apex, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc sulfate (p. 2126·2).

Betzee-G *Apex, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc sulfate (p. 2126·2); gentamicin (p. 304·2).
Infected skin disorders.

Betzee-GM *Apex, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc sulfate (p. 2126·2); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Betzee-M *Apex, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc sulfate (p. 2126·2); miconazole nitrate (p. 589·1).

Betzee-S *Apex, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc oxide (p. 1729·1); salicylic acid (p. 1719·1).

Beum *Eurofarma, Braz.*
Thiamine hydrochloride (p. 2103·1).
Neuritis; Wernicke-Korsakoff syndrome; vitamin B_1 deficiency.

Beuresis *Be-Tabs, S.Afr.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Beurises *Be-Tabs, S.Afr.*
⊗Furosemide (p. 1387·1).
Oedema; hypercalcaemia; hypertension.

Bevac *Biological E, India.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Bevalex *Molex Ayus, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bevent *Kopran, India.*
⊗Betamethasone (p. 1623·2).
Asthma.

Bevi Dam *Vincenti, Venez.*
Benzydamine hydrochloride (p. 29·2).
Musculoskeletal, joint, and soft-tissue inflammation.

Bevidox *Pharmacia Upjohn, India.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Bevigen *Aksu, Turk.; Eras, Turk.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B deficiency.

Bevindazol *Vincenti, Venez.*
Albendazole (p. 149·1).
Worm infections.

Beviplex *Galenika, Rus.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Beviplex Comp *Abigo, Swed.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Beviplex forte *Abigo, Swed.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; alcoholism; neuropathies.

Bevispas *Aspen, S.Afr.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Bevit *Synco, Hong Kong.†*
Thiamine (p. 2102·3).

Bevit Forte *Hexal, Ger.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous system disorders.

Bevita *Gracia, Indon.*
Vitamin B substances (p. 2102·3); dexpanthenol (p. 2582·2); betacarotene (p. 2051·1); calcium gluconate (p. 1783·3); curcuminoid (p. 2489·3).
Vitamin B supplement; appetite stimulant.

Bevitab *Kocak, Turk.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Bevitamel *Westlake, USA.*
Melatonin (p. 2551·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Sleep disorders; aid in homocysteine metabolism.

Bevitecê *Azevedos, Port.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Bevitex
Note: this name may be used for preparations of different composition.
Manon, Israel.
Vitamin B_{12} (p. 2107·2).
Vitamin supplement.

Prater, Chile.
Pargeverine hydrochloride (p. 1877·1).
Aid in endoscopy or colonoscopy; nausea and vomiting; smooth muscle spasm.

Bevitin *Abbott, Ital.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Bevitin-C *Abfar, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Bévitine *DB, Fr.*
Thiamine hydrochloride (p. 2103·1).
Beri beri; vitamin B deficiency; neuritis.

Bevitol *Lannacher, Austria.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Munir, Turk.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Bevitotal comp *Recip, Swed.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency; alcoholism; neuropathies.

Bevitplus *Plus, India.*
Amino acids; vitamins; minerals; trace elements; evening primrose oil (p. 2502·2).

Bevitran *Landson, Indon.*
Vitamins.

Bevizil *Sanbe, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Bevon *Zuventus, India.*
Vitamins; minerals; with or without lysine (p. 2079·3).

Bevonazole *Bevo, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Bevoren *Almirall, Belg.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Bevostatin *Bevo, Gr.; Desant, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

BeWell *Aus Biomed, Austral.†*
Lactoferrin (p. 2539·3).
Immunomodulator; restoration of gastrointestinal flora.

Bex
Note: this name may be used for preparations of different composition.
Purewin, India.
Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Bexacal *Sandoz, Mex.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Bexalcor *Sandoz, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bexalov *Sandoz, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Bexarid *Shalaks, India.*
Lindane (p. 2157·1).
Scabies; pediculosis.

Bexatus *Bexal, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bex-C *Triton, India.*
Vitamin C (p. 2110·3).

Bexce *Tempo Scan Pacific, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Nutritional supplement.

Bexce Plus *Tempo Scan Pacific, Indon.*
Vitamins.
Nutritional supplement.

Bexeton *Geolab, Braz.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Bexicom *Nufarindo, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Dietary supplement.

Bexicom Fit *Nufarindo, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); levocarnitine tartrate (p. 2053·2).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bexicom-Z *Nufarindo, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Dietary supplement.

Bexicortil *Isdin, Spain.†*
⊗Fluorometholone (p. 1637·2); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Bexident *Isdin, Port.*
Dental gel; dental spray; mouthwash: Chlorhexidine (p. 1743·2).
Gingivitis.

Isdin, Port.
Paediatric dental gel: Dipotassium glycyrrhizate (p. 2520·3); dexpanthenol (p. 2582·2).
Gum protection.

Isdin, Port.
Toothpaste: Triclosan (p. 1773·2); sodium fluoride (p. 2089·2).
Gingivitis.

Bexidermil *Isdin, Spain.*
Trolamine salicylate (p. 141·2).
Peri-articular disorders; soft-tissue disorders.

Bexilon *Plusandex, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bexine
Note: this name may be used for preparations of different composition.
Spirig, Switz.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Collins, Mex.†
Nasal drops: ⊗Dexamethasone (p. 1630·3); phenylephrine (p. 1672·2); neomycin (p. 329·3).

Collins, Mex.†
Injection: ⊗Dexamethasone (p. 1630·3).

Bexinor *Beacons, Singapore.*
Norfloxacin (p. 333·3).
Bacterial infections.

Bexistar *Barcino, Spain.†*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Bexivit *IFET (ΙΦΕΤ), Gr.*
Pyridoxine hydrochloride (p. 2105·3).

Bexmirt *Ergha, Irl.†*
Mirtazapine (p. 436·1).
Depression.

Bexol
Note: this name may be used for preparations of different composition.
Intas, India.
Trihexyphenidyl hydrochloride (p. 917·3).
Extrapyramidal disorders; parkinsonism.

Bexomed *Spirig, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bexon *Gobbi, Arg.*
Pessaries: ⊗Metronidazole (p. 936·1); nystatin (p. 590·3); hydrocortisone (p. 1640·1).
Vaginal infections.

Gobbi, Arg.
Tablets: Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Bexsero *Novartis Vaccines, UK.*
A recombinant meningococcal group B vaccine (p. 2401·3).
Active immunisation.

Bextra IM/IV *Pfizer, Braz.*
Parecoxib sodium (p. 119·3).
Postoperative pain.

Bexxam *Unison, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Bexxar *GSK, Canad.; Corixa, USA; GSK, USA.*
Iodine-131 tositumomab (p. 2225·3) (see also Tositumomab (p. 874·2)).
Non-Hodgkin's lymphoma.

BexZis *Ergha, Irl.†*
Mirtazapine (p. 436·1).
Depression.

Beyacin *Conba, China.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Beyaz *Bayer, USA.*
Pink tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); calcium levomefolate (p. 2053·1); orange tablets, calcium levomefolate.
Combined oral contraceptive; premenstrual dysphoric disorder; acne in women.

Beysonit *Leovan, Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Beytina *Panagiotis, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Beza *Otsira, India.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezabeta *Betapharm, Ger.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezachol *Kleva, Gr.*
Bezafibrate (p. 1323·2).

Bezachole *Aspen, S.Afr.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezacur *Investi, Arg.; Hexal, Austria.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezadoc *Docpharm, Ger.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezafisal *Cryopharma, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezagamma *Worwag, Ger.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezagen *Generics, UK.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezalex *Pharmacos Abug, Mex.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezalip *Roche, Arg.; Actavis, Austria; Actavis, Canad.; Actavis, Fin.; Roche, Gr.; Actavis, Hong Kong; Actavis, Hung.; Piramal, India; Actavis, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.†; Actavis, Neth.; Healthcare Logistics, NZ; Actavis, Port.; Akacia, S.Afr.; Roche, Singapore; Actavis, Swed.; Actavis, Thai.; Actavis, UK; Roche, Venez.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezalip Mono *Actavis, UK.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezam *Littman, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Bezamidin *Pliva Krakow, Pol.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezamil *Milano, Thai.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezanin *Iasis, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Bezart *Intas, Philipp.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Bezastad *Stada, Austria; Stada, Philipp.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bezit *Plus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Bezornil *Dao-Pharm, Ukr.*
Musk (p. 2198·2); pearl; bezoar; amber (p. 2440·3); borneol (p. 2460·2); zinc carbonate (p. 1728·3).
Anorectal disorders; burns; wounds; insect bites.

Bezpa *Wockhardt, Rus.†*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

BF-2-4-2 *Bright Future, Hong Kong.†*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Keratinisation disorders; psoriasis.

B-Fact *Indo French, India.*
Vitamins; trace elements.

BF-Analgesic Balm *Bright Future, Hong Kong.†*
Cajuput oil (p. 2464·1); cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

BF-Diphenhydramine Compound Linctus *Bright Future, Hong Kong.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).

BF-Horloten *Bright Future, Hong Kong.†*
Hyoscine (p. 1845·3).

BF-Hycort *Bright Future, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

BFI *Numark, USA.*
Bismuth-formic-iodide (p. 1821·3); zinc phenolsulfonate (p. 1729·3); alum (p. 2439·1); bismuth subgallate (p. 1822·1); boric acid (p. 2459·3); menthol (p. 2553·2); cineole (p. 2479·1); thymol (p. 1772·2).
Antiseptic.

B-Flox *Bactolac, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

BF-Maschew *Bright Future, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

BF-Micozo *Bright Future, Hong Kong.†*
Miconazole (p. 588·3).
Fungal skin infections.

B-Fol *Plus, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy; dietary supplement.

BF-Paradac *Bright Future, Hong Kong.†*
Paracetamol (p. 115·1).
Fever; pain.

BG Prot *Wockhardt, India.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Bglau *Edol, Port.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Bgramin *Ascent, Austral.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

B-Grup *Sanli, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

BGT *Sunij, India.*
⊗Terbutaline (p. 1228·1).
Bronchospasm.

Bharglob *Bharat, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

B-Hex *Xepa-Soul Pattinson, Singapore.*
Trihexyphenidyl hydrochloride (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Bi Ai *Ji Sheng, China.*
⊗Terbutaline sulfate (p. 1228·1).
Bronchospasm.

Bi Ai Di *Siping Aimo, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bi An Lai *Haibin, China.*
Ceftezole sodium (p. 252·2).
Bacterial infections.

Bi C *New Life, Arg.*
Vitamins.
Dietary supplement.

Bi Cai Ni *Xinshitong, China.*
Enoxacin (p. 290·2).
Bacterial infections.

Bi Chuan *Double-Crane, China.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Bi Cun *Simcere, China.*
Edaravone (p. 1370·2).
Cerebral infarction.

Bi Da Shu *Sanofi, China.*
⊗Amiloride hydrochloride (p. 1299·1).
Oedema.

Bi Fa Er *Nikemei, China.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Bi Fen *Huayi, China.*
Ethacridine lactate (p. 1732·3).

Bi Fu *Huabang, China.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bi Jia Si *Lianshui, China.*
Itopride hydrochloride (p. 1850·1).
Nausea and vomiting; gastrointestinal motility disorders.

Bi Jie *Nanyue, China.*
Metronidazole (p. 936·1); chlorhexidine (p. 1743·2).

Bi Li *Hisun, China.*
Cefaclor (p. 232·3); bromhexine (p. 1656·3).
Respiratory-tract infections.

Bi Li Kang *Huataitang, China.*
Paracetamol (p. 115·1); amantadine hydrochloride (p. 890·3).
Cold symptoms.

Bi Li Shu *Hexin, China.*
Cefmetazole sodium (p. 241·3).
Bacterial infections.

Bi Liang *Huabang, China.*
Naftifine hydrochloride (p. 590·1); ketoconazole (p. 585·3).
Fungal skin infections.

Bi Lin *Yafeng, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bi Luo Ka *Xinzhongzheng, China.*
Matrine.

Bi Missilor *Pierre Fabre, Fr.*
Spiramycin (p. 358·3); metronidazole (p. 936·1).
Oral and dental infections.

Bi Moxal *Nycomed, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bi Moxal Duo *Nycomed, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bi Na Wei *Dina, China.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Bi Ning *Taiyang, China.*
Benzoyl peroxide (p. 1696·1).
Acne.

Bi Nuo *Guo Yao, China.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Bi Predonium *Servier, Port.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Bi Preterax *Servier, Belg.†; Servier, Port.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Bi Qi *Simcere, China.*
Smectite (p. 1887·1).
Diarrhoea; gastrointestinal disorders.

Bi Qi Er *Jiante, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bi Qing Su *Xianqiang, China.*
Sodium houttuyfonate.

Bi Sai Ning *Jing Xin, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Bi Shi *Nuo De, China.*
Tinidazole (p. 949·2).
Vaginal infections.

Bi Si Fu *Mianyang, China; Tiancheng, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Bi Si Ling *Zhongguan, China.*
Aniracetam (p. 389·1).
Alzheimer's disease.

Bi Suo *Neptunus, China.*
Propylene glycol sodium alginate.

Bi Tan *Conba, China.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Bi Te Li *Hengrui, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Bi Ting *Bu Chang, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Bi Xi *Double-Crane, China.*
Sodium ferulate.

Bi Yan Tong *Kechuang, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Bi Yun *RenFu, China.*
Mifepristone (p. 2138·1).

Bi Zheng *Double-Crane, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Bi Zhi *Xiuzheng, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Bi Zhi Ke *Tairong, China.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); lactic acid (p. 2539·1); boric acid (p. 2459·3).
Tinea pedis.

Biablan *Fada, Arg.*
Losartan (p. 1422·2).
Hypertension.

Biablan D *Fada, Arg.*
⊗Losartan (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Biacna *Valeant, Canad.*
Clindamycin phosphate (p. 269·3); tretinoin (p. 1725·2).
Acne.

Biactol Liquid *Crookes Healthcare, UK.*
Phenoxypropanol (p. 1764·3).
Acne.

Biafine
Note: this name may be used for preparations of different composition.
Craveri, Arg.; Swedpharm, Chile; Xian-Janssen, China; Johnson & Johnson, Fr.; Janssen-Cilag, Israel; Johnson & Johnson, Port.; Medix, Singapore; Janssen-Cilag, Switz.; Valeant, USA; Medifarm, Venez.
Trolamine (p. 2634·3).
Burns; ulcers; wounds; sunburn; erythema following radiotherapy.

Biafineact *Johnson & Johnson, Fr.*
Trolamine (p. 2634·3).
Burns; wounds.

Bi-Aglut *Novartis Consumer, UK.*
Gluten-free foods.
Gluten intolerance.

Plada, Ital.
A range of gluten-free and lactose-reduced foods.
Gluten and lactose intolerance.

Bialcol *Novartis, Chile; Novartis Consumer, Ital.; Teleflex, Ital.*
Benzoxonium chloride (p. 1739·2).
Disinfection of instruments; disinfection of burns, skin, wounds and surfaces.

Bialerge *Elofar, Braz.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Nasal congestion.

Bialfer *Bial, Spain.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Bialfoli *Bial, Spain.*
Folic acid (p. 2063·1).
Folic acid deficiency; folic acid supplement; prevention of neural tube defects in pregnancy.

Bialminal *Bial, Port.*
Phenobarbital (p. 535·2).
Epilepsy; sedative; alcohol withdrawal syndrome.

Bialzepam *Medibial, Port.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; epilepsy; premedication; alcohol withdrawal syndrome.

Biamotil *Allergan, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Biamotil-D *Allergan, Braz.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Biancort *Germed, Braz.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Biarison *Novartis, Turk.*
Proquazone (p. 128·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Biascor *Biol, Arg.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Biasquin F *Best, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Biasten *Pulmomed, Rus.*
⊗Salbutamol hemisuccinate (p. 1220·2); budesonide (p. 1625·1).
Asthma.

Biatain *Coloplast, Belg.; Coloplast, Ger.*
Polyurethane dressing (p. 1718·1).
Wounds; ulcers.

Coloplast, Fr.
Carmellose sodium (p. 2175·2).
Wounds; ulcers.

Biatain Ag *Coloplast, Fr.*
Silver (p. 2615·1); carmellose sodium (p. 2175·2).
Burns; wounds; ulcers.

Coloplast, Ger.
Silver (p. 2615·1); polyurethane foam (p. 1718·1).
Wounds; ulcers.

Biatain-Ag *Coloplast, Belg.*
Polyurethane dressing with silver (p. 2615·1).
Infected wounds.

Biatain-Ibu *Coloplast, Fr.; Coloplast, UK.*
Ibuprofen (p. 68·2).
Burns; ulcers; wounds; pain in chronic wounds.

Coloplast, Ger.
Ibuprofen (p. 68·2); polyurethane foam (p. 1718·1).
Wounds; ulcers.

Biatós *Cimed, Braz.*
Ketotifen (p. 631·3).
Asthma.

Biatrix *Baliarda, Arg.*
Quetiapine fumarate (p. 1101·1).
Bipolar disorder; schizophrenia.

Biatron *Pharos, Indon.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; anaerobic bacterial infections; giardiasis.

Biavax II *MSD, USA.†*
A rubella and mumps vaccine (Wistar RA 27/3 and Jeryl Lynn (B level) strains respectively) (p. 2417·3).
Active immunisation.

Biaxin
Note: this name may be used for preparations of different composition.
Abbott, Canad.; Abbott, Ger.†; Abbott, Neth.†; AbbVie, USA.
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori infections.

Biaxsig *Sanofi-Aventis, Austral.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bibag *Fresenius Medical, Fr.†*
Sodium bicarbonate (p. 1781·1).
Solution for haemodialysis.

Biberfrutta *Mellin, Ital.*
Carbohydrate; amino acids; lipid; vitamin C (p. 2110·3); iron (p. 2073·1).
Nutritional supplement.

Bibidip *RPG, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Bibien *BI, Gr.†*
Citalopram (p. 411·1).
Depression.

Bibix *Lemery, Mex.†*
Ketoprofen (p. 79·1).
Inflammation; pain; musculoskeletal, joint, and peri-articular disorders.

Bibol Leloup *Fada, Arg.*
⊗Silymarin (p. 1561·2); dehydrocholic acid (p. 2492·1); pancreatin (p. 2579·3); bile salts (p. 2457·2); homatropine methylbromide (p. 2007·3).
Liver disorders.

Bibora *Berko, Turk.*
Borax (p. 2459·2).

Bicadex *Peseri, Fin.†; TAD, Ger.; Santa, Gr.; Sandoz, Philipp.; Cipla-Medpro, S.Afr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicafar *CCM, Malaysia.*
Cefoperazone (p. 243·1).
Bacterial infections.

Bicain *Orion, Fin.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Bicalaccord *Arrow, NZ.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalem *Teva, Mex.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalinn *Helsinn Birex, Irl.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalox *Douglas, NZ; Pharmaplan, S.Afr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

BicaluPel *Pelpharma, Austria.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicaluplex *Ingers, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalustad *Stada, Denm.; Stada, Swed.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalut *Nexus, Gr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalutagen *Generics, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalutanorm *Plus Pharma, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalutatam *Generics, Cz.; Mylan, Denm.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicalutin *Pfleger, Ger.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicamal *Cipla, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicamed *Dermapharm, Austria; Mibe, Ger.; Dermapharm, Switz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicamedica *Ranbaxy, Neth.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicamid *Vipharm, Fin.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicamide *Genepharm, Gr.; Taro, Israel.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicamylan *Mylan, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

bicaNorm *Fresenius Medical, Ger.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis.

BicaNova *Fresenius Medical, Switz.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3); sodium bicarbonate (p. 1781·1) (p. 1778·2).
Peritoneal dialysis.

bicaNova *Fresenius Medical, Cz.; Fresenius Medical, Fin.; Fresenius Medical, Spain; Fresenius Medical, Swed.†*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3) (p. 1778·2).
A range of peritoneal dialysis solutions.

Bicaprol *Proel, Gr.*
Bicalutamide (p. 749·1).

Bicarbex *Inibsa, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicard *Aspen, Austral.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bicardef *Hasco-Lek, Pol.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Bicarnat *Pisa, Mex.†*
Sodium bicarbonate (p. 1781·1).
Electrolyte disorders.

Bicarnesine *Sanofi-Aventis, Gr.*
Levocarnitine (p. 2053·2).

Bicarsim *Kramer, USA.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas.

Bicart *Gambro, Canad.*
Sodium bicarbonate (p. 1781·1).

Bicasan *Pharminicio, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bicasil *Farmaprojects, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicastad *Genthon, Port.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicatin *Pharmanel, Gr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicatlon *Medico Uno, Hung.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicavan *Avansor, Fin.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicavera *Fresenius Medical, Cz.; Fresenius Medical, Fr.; Fresenius Medical, Irl.†; Fresenius Medical, Israel; Fresenius Medical, Port.; Fresenius Medical, Switz.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3) (p. 1778·2).
A range of peritoneal dialysis solutions.

Fresenius Medical, Fin.; Fresenius Medical, Neth.; Fresenius Medical, Norw.; Fresenius Medical, Swed.
Glucose monohydrate (p. 2069·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
A range of peritoneal dialysis solutions.

Fresenius Medical, Ital.
A range of peritoneal dialysis solutions (p. 1778·2).
Peritoneal dialysis.

Bicavera Glucosa *Fresenius Medical, Spain.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Bicavera Glucose *Fresenius Medical, Denm.*
Glucose (p. 2068·3); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1) (p. 1778·2).
Peritoneal dialysis.

Bicavine *Cazi, Braz.*
Dipyrone (p. 53·3); thiamine (p. 2102·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).
Pain; neuritis.

Bicef *Micro, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Bicetil *Menarini, Spain.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bicholate *Sabex, Canad.†*
Bile salts (p. 2457·2); cascara (p. 1826·1); aloin (p. 1816·2); bisacodyl (p. 1821·1).
Constipation.

Bicidal Plus *Kee, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Bicide *Fischer, Israel.†*
Lindane (p. 2157·1).
Scabies.

Bicil *Mars, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Bicillin-1 *Sintez, Rus.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bicillin-3 *Arterium, Ukr.*
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin (p. 228·1); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Sintez, Rus.
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin sodium (p. 228·2) or benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections; leishmaniasis.

Bicillin-5 *Sintez, Rus.; Arterium, Ukr.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Bicillin C-R *Monarch, USA.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Bicillin L-A *Aspen, Austral.; King, Canad.; Healthcare Logistics, NZ; Akromed, S.Afr.†; Monarch, USA.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Bicil-P *Mars, India.*
Syrup: Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Mars, India.
Tablets: Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Bicipro *Kee, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Bicirkan *Pierre Fabre, Fr.*
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Venous insufficiency.

Biciron *Alcon, Ger.*
⊗Tramazoline hydrochloride (p. 1679·3).
Eye disorders.

Bicitra *Alza, USA.†*
Sodium citrate (p. 1781·2); citric acid monohydrate (p. 2480·3).
Urine alkalinising agent; chronic metabolic acidosis.

Bi-Citrol *Delbert, Fr.*
Monosodium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Dyspepsia.

Bicitron *Medichem, Indon.†; Medifarma, Indon.†*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Anaemias; neuropathy; neuritis; vitamin B supplement.

Biclar *Abbott, Belg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Biclav *Duncan, Thai.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Biclin *BMS, Mex.; BMS, Port.†; BMS, Spain.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Biclomet *Biomedis, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; adjunct in intestinal intubation.

Biclopen *P & B, India.*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Biclora *Hawthorn, USA.*
Chlorcyclizine hydrochloride (p. 620·2); clofedanol hydrochloride (p. 1659·1).
Cough; cold symptoms; allergic rhinitis.

Biclora-D *Hawthorn, USA.*
⊗Chlorcyclizine hydrochloride (p. 620·2); clofedanol hydrochloride (p. 1659·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms; allergic rhinitis.

BiCNU *Merck Serono, Arg.; BMS, Austral.; BMS, Canad.; Masters, Chile; BMS, Cz.; BMS, Fr.; BMS, Gr.; IFET [IMET], Gr.; BMS, Hung.; BMS, Irl.†; BMS, Mex.; BMS, NZ; BMS, Philipp.†; BMS, S.Afr.†; BMS, Singapore; Heritage, USA; Masters, Venez.*
Carmustine (p. 761·2).
Malignant neoplasms.

Bicobon *PP Lab, Thai.*
Sodium bicarbonate (p. 1781·1); activated charcoal (p. 1537·3); peppermint oil (p. 1877·1).
Gastrointestinal disorders; flatulence; diarrhoea.

Bicofen *Iapharm, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bicolax *Synco, Hong Kong†; Armoxindo, Indon.; Synco, Singapore.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Bicomplex *ABC, Ital.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Bicompo *Bernofarm, Indon.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Biconcor *Merck, Braz.; Merck, Mex.; Merck, Venez.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bicor *Alphapharm, Austral.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bicosym *Symbiosis, India.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Bicox *Overseas, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Bicox Kid *Overseas, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3). Pyridoxine (p. 2105·3) or pyridoxine hydrochloride (p. 2105·3) may be included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Bicox-E *Overseas, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Bicozene *Novartis, USA.†*
Benzocaine (p. 1980·2); resorcinol (p. 1718·3).
Local anaesthesia.

Bicrinol *HLB, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections.

Bicrolid *Sanbe, Indon.; Sanbe, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections.

Bicromil *Cetus, Arg.*
Sertraline (p. 448·1).
Depression.

Bicronux *Nafar, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Bictamid *Arrow, Denm.; Arrow, Swed.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bicusan *Synthon, Fin.; Actavis, Hung.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bid *Kopran, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Bidanil *Vianex, Fin.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bidanzen *GSK, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; pain; hyphaema; respiratory-tract congestion; breast engorgement; pericoronitis; alveolar abscess.

Bidecar *Baliarda, Arg.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; myocardial infarction.

Bideon *Fecofar, Arg.*
⊗Phenazone (p. 124·1); naphazoline hydrochloride (p. 1669·3); lidocaine hydrochloride (p. 1988·2).
Eye disorders.

Bideon Biotic *Fecofar, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Bideon Biotic Plus *Fecofar, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Bideon Free *Fecofar, Arg.*
⊗Ephedrine (p. 1663·1); phenazone (p. 124·1).
Eye disorders.

Bideren *Novopharm, Philipp.; Pascual, Philipp.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Biderit *Merck, Mex.†*
Isosorbide dinitrate (p. 1412·2).

Bidex *SJ Pharm, USA.*
Guaifenesin (p. 1666·2).
Cough.

Bidex-A *Stewart Jackson, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Bidex-DMI *Stewart Jackson, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Bidhist *Cypress, USA.†*
Brompheniramine maleate (p. 618·1).
Rhinitis.

Bidiabe *Sanofi-Aventis, Ital.*
Chlorpropamide (p. 470·1); phenformin hydrochloride (p. 493·1).
Diabetes mellitus.

Bidiam *Menarini, Port.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Bidicef *Medikon, Indon.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Bidiclin *Chiesi, Gr.; Chiesi, Spain.*
⊗Beclometasone dipropionate (p. 1621·2).
Corticosteroid; ulcerative colitis.

Bidien *IDI, Ital.*
⊗Budesonide (p. 1625·1).
Skin disorders.

BiDil *Arbor, USA.*
Isosorbide dinitrate (p. 1412·2); hydralazine hydrochloride (p. 1401·2).
Heart failure in black patients.

Bidiprox *Medikon, Indon.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Biditin *Medikon, Indon.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Bi-Dizalon *Rayere, Mex.†*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Bidlax *GSK, India.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Bidnac *GSK, India.*
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

GSK, India.
Topical gel: Diclofenac (p. 48·3).
Pain; inflammation.

Bidocef
Note: this name may be used for preparations of different composition.
Cofasa, Venez.
Cefalexin (p. 234·1).
Bacterial infections.

Bidocsol *Doctors, Philipp.*
Bromhexine (p. 1656·3).
Cough.

Bidoflox *Kee, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bidogrel *Med-One, Gr.*
Clopidogrel (p. 1342·3).

Bidop *Gedeon Richter, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bidopal *GSK, India.*
Levodopa (p. 902·2).
Parkinsonism.

Bidor *Weleda, UK.*
Ferrous sulfate (p. 2062·2); silica.
Homoeopathic preparation.

Bidox-DT *Ajanta, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Bidro *Wellcome, Ital.*
A range of dietary supplement containing royal jelly (p. 2608·1).

Bidrolar *Spyfarma, Spain.†*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Bidrostat *Bioprofarma, Arg.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bidroxil *Symbiosis, India.*
Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

Bidroxyl *BMS, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Bidrozil *Collins, Mex.†*
⊗Nystatin (p. 590·3); triamcinolone (p. 1648·3).
Skin disorders.

Bidryl Expectorant *Hexpharm, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Biduret *GSK, India.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; hepatic cirrhosis with ascites.

Biduten *GSK, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Bienfait Multi-vital *Lancome, Canad.*
SPF 30: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Lancome, Canad.†
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Bienfait Multi-Vital Teinte *Lancome, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Bienol
Note: this name may be used for preparations of different composition.
Tripharma, Turk.
Vitamin B substances (p. 2102·3).

Bienterico *Caldeira & Marques, Port.†*
Streptomycin sulfate (p. 359·1); neomycin sulfate (p. 330·1).
Diarrhoea; bowel sterilisation; hepatic coma.

Bi-Euglucon *Roche, Venez.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bi-Euglucon M *Roche, Chile; Roche, Ital.; Roche, Mex.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bifardol *Liferpal, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Pain; fever.

Bifaren *Biomep, Mex.*
Bezafibrate (p. 1323·2).
Hypercholesterolaemia.

Bifazol *Bayer, Ital.†*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifebral *Sanofi-Aventis, Mex.*
Ketoprofen sodium (p. 79·1); paracetamol (p. 115·1).
Pain; fever.

Bifen *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Bifena *Panalab, Arg.*
Lotion 1, salicylic acid (p. 1719·1); undecenoic acid amide (p. 596·3); resorcinol monoacetate (p. 1718·3); sulfur (p. 1721·1); capsicum tincture (p. 2469·3); lotion 2, pantothenic acid (p. 2085·2); inositol (p. 2533·2); yeast (p. 2125·2); cinchona (p. 2478·3).
Hair disorders.

BiferaRx *Meda, USA.*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).

Biferce *Sanbe, Indon.; Sanbe, Singapore.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Bificol *Biomed, Rus.*
Bifidobacterium bifidum (p. 2596·3).
Restoration of normal gastrointestinal flora.

Biopharma, Ukr.
Bifidobacterium bifidum (p. 2596·3); *Escherichia coli.*

Bifidosa *Nutricia-Bago, Arg.*
Lactulose (p. 1850·3); ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Restoration of normal gastrointestinal flora.

Bifidumbacterin *Partner, Rus.*
Bifidobacterium bifidum (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Bifiform *Ferrosan, Rus.; Ferrosan, Ukr.*
Bifidobacterium longum (p. 2596·3); *Enterococcus faecium* (p. 2596·3).
Restoration of normal gastrointestinal flora; maintenance and restoration of intestinal flora.

Bifilac *Tablets, India.*
Enterococcus faecalis (p. 2596·3); *Clostridium butyricum; Bacillus mesentericus; Lactobacillus sporogenes* (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Bifilact *Fidia, Ital.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); vitamin B substances (p. 2102·3).
Maintenance of normal gastrointestinal flora.

Bifilis *Firma Ferment, Rus.*
Bifidobacterium bifidum (p. 2596·3); muramidase hydrochloride (p. 2565·1).

Bifinorm *St Petersburg Institute of Vaccines & Sera, Rus.*
Bifidobacterium bifidum (p. 2596·3).
Restoration of normal gastrointestinal flora.

Bifinorma *Merckle, Ger.†*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Bifiteral *Solvay, Austria†; Solvay, Belg.; Abbott, Ger.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; hepatic coma; stool softener.

Bifix
Note: this name may be used for preparations of different composition.
United American, Philipp.
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Bayer Sante, Fr.†
Nifuroxazide (p. 331·3).
Diarrhoea.

Bifized *Farmanic, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifluorid *Voco, Denm.; Voco, Fr.; Voco, Pol.; Meda, Swed.*
Sodium fluoride (p. 2089·2); calcium fluoride (p. 2053·1).
Dental caries prophylaxis.

Bifoal Semanal *Alter, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bifokey *Pharminicio, Spain.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifolac *Vitaflo, Swed.*
Lactobacillus rhamnosus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Restoration of gastrointestinal flora.

Bifomyk *Riemser, Ger.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifon *Dermapharm, Ger.; Genepharm, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifonal *Zdorovje, Ukr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifort
Note: this name may be used for preparations of different composition.
Finadiet, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Bifosa *Troikaa, India.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bifosal *Alter, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bifosin *Sintez, Rus.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bifotik *Sanbe, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Bifren *Pharma Start, Ukr.*
Phenibut.
Anxiety; alcohol withdrawal syndrome; vestibular disorders; mental function impairment.

Bifril *Menarini, Austria; Silesia, Chile†; Menarini, Fin.†; Lusofarmaco, Ital.; Menarini, Singapore.*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

Bifril Comp *Menarini, Fin.†*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bifril Plus *Menarini, Austria.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bifrizide *Lusofarmaco, Ital.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

BiFu *Double-Crane, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Big Friends *Natural Factors, Canad.*
Vitamins; minerals.

Big Mox *AstraZeneca, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Bigaflon *Yuriya-Farm, Ukr.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Bigan *Sresan, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bigan-GC *Sresan, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bigan-GM *Sresan, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetic mellitus.

Bigan-GP *Sresan, India.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bigan-P *Sresan, India.*
Metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Big-Ben *Greater Pharma, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Bigcef *Bestochem, India.*
Cefuroxime (p. 255·2), cefuroxime axetil (p. 255·2), or cefuroxime sodium (p. 255·3).
Bacterial infections.

Bigenol *Grisi, Mex.†*
⊗Methyltestosterone (p. 2291·3); calcium glycerophosphate (p. 1783·3); calcium anhydroxymethylenediphosphate; magnesium anhydroxymethylenediphosphate; glutamic acid (p. 2070·2); thiamine hydrochloride (p. 2103·1); nux vomica (p. 2573·3).
Anabolic.

Biger *Heremco, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Bigetric *Casasco, Arg.*
Domperidone (p. 1838·1); simeticone (p. 1886·2).
Dyspepsia; flatulence; nausea and vomiting.

Bigjoint *Bestochem, India.*
Calcium (p. 1783·1); glucosamine hydriodide (p. 2515·3); mecobalamin (p. 2108·1).
Osteoarthritis; rheumatoid arthritis.

Bigomet *Otsira, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus; polycystic ovary syndrome.

Bigonist *Sanofi-Aventis, Fr.*
⊗Buserelin acetate (p. 2256·2).
Prostatic cancer.

Bigonyl *Indoco, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bigsens *Zydus, India; Zydus, S.Afr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Big-Tum *Bestochem, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Biguanex *Denver, Arg.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Bigvin *Bestochem, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Bigvin Forte *Bestochem, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Bigvin Plus *Bestochem, India.*
Capsules: Vitamins trace elements; thioctic acid (p. 2629·1).

Bestochem, India.
Injection: Vitamin B substances (p. 2102·3).

Bigvin-F *Bestochem, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Biherpan *ICN, Pol.†*
Heparin sodium (p. 1396·3); zinc sulfate (p. 2126·2).
Herpes infections of the skin and mucous membranes.

Bikalard *Ardez, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bikalen *Elpen (Ελπεν), Gr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bikalex *Merck, Fin.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bikalm *Sanofi-Aventis, Ger.†*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Bikauk *Genthon, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Biken *Sanofi Pasteur, Chile.*
A live attenuated varicella-zoster vaccine (OKA strain) (p. 2423·3).
Formerly known as Varicela Biken.
Active immunisation.

Bikipen *Ivax, Mex.†*
Biperiden (p. 895·1).
Parkinsonism.

Biklin *BMS, Arg.†; BMS, Austria; BMS, Fin.; BMS, Ger.†; BMS, Swed.; BMS, Venez.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Bil 13 *Bago, Arg.*
Choline orotate (p. 2578·1); dehydrocholic acid (p. 2492·1); deoxycholic acid (p. 2457·2); casanthranol (p. 1826·1); boldine (p. 2458·3).
Constipation; liver and biliary-tract disorders.

Bil 13 Enzimatico *Bago, Arg.*
⊗Metoclopramide hydrochloride (p. 1862·2); dehydrocholic acid (p. 2492·1); pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive disorders; flatulence.

Bilactam *Cosme, India.*
Syrup; capsules; injection: Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Cosme, India.
Tablets: Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Bilactam-XL *Cosme, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Bilagol Antigas *Lazar, Arg.*
Bile salts (p. 2457·2); dehydrocholic acid (p. 2492·1); domperidone (p. 1838·1); simeticone (p. 1886·2).
Digestive disorders; dyspepsia.

Bilamide *Ethnor, India.†*
Hydroxymethylnicotinamide (p. 2530·1).
Anorexia; flatulence; dyspepsia; constipation.

Bilanz *Rontag, Arg.*
Mirtazapine (p. 436·1).
Depression.

Bilaska *Menarini, Fr.*
Bilastine (p. 617·3).
Allergic rhinitis; urticaria.

Bilaten *Medipharm, Chile.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Bilaten-D *Medipharm, Chile.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bilaxil *Bayer, Chile.*
Ispaghula husk (p. 1849·1); senna (p. 1885·1).
Bowel evacuation; constipation.

Bilaxten *Vitoria, Port.; Faes, Spain; Menarini, Switz.*
Bilastine (p. 617·3).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Bil-B *Bionova, India.*
Ginkgo biloba (p. 2512·3); vitamin B substances (p. 2102·3).

Bilberin *Hasco-Lek, Pol.†*
Myrtillus (p. 2566·2).
Circulatory eye disorders.

Bilberry Plus *Eagle, Austral.†*
Myrtillus (p. 2566·2); euphrasia (p. 2502·1); fenugreek (p. 2504·1); hydrastis (p. 2528·1).
Eye fatigue.

Bilberry Plus Eye Health *Cenovis, Austral.†*
Myrtillus (p. 2566·2); ginkgo biloba (p. 2512·3); big marigold; riboflavin (p. 2104·3); *dl*-alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); zinc gluconate (p. 2126·2); betacarotene (p. 2051·1).
Eye fatigue; eye irritation.

Bilduretic *Bangkok Lab & Cosmetic, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; hepatic cirrhosis with ascites.

Bileco *Ivax, Arg.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bilem *Teva, Mex.*
⊗Tamoxifen (p. 860·2).
Breast cancer; endometrial cancer; anovulatory infertility.

Teva, Thai.
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Bilenor *UCB, Ital.*
Magnesium trihydrate salt of chenodeoxycholic and ursodeoxycholic acids (p. 2475·1) (p. 2638·1).
Gallstones; biliary dyspepsia.

Bilenzima *Elofar, Braz.†*
Bromopride (p. 1824·2).
Gastrointestinal disorders.

Biletan *Gador, Arg.*
Thioctic acid (p. 2629·1).
Liver disorders.

Biletan Enzimatico *Gador, Arg.*
⊗Thioctic acid (p. 2629·1); pancreatin (p. 2579·3); cellulase (p. 2473·1); simeticone (p. 1886·2).
Digestive disorders.

BiLi *Yangtze River, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Bilicur *Sandoz, Ukr.*
Cynara (p. 2490·3).
Dyspepsia; hepatobiliary disorders.

Bilidren *Lanpharm, Arg.*
Cascara (p. 1826·1); cynara (p. 2490·3); bile salts (p. 2457·2).
Biliary-tract disorders.

Biliepar *Ibirn, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; biliary dyspepsia.

Bilifalk *Falk, Spain.*
Ursodeoxycholic acid (p. 2638·1).
Biliary cirrhosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bilifuge *Plan, Switz.*
Cynara (p. 2490·3); European barberry (p. 2502·1); java tea (p. 2536·3); kinkeliba (p. 2538·2).
Digestive disorders.

Biliherb *WR Enterprises, Canad.*
Berberry root (p. 2502·1); radish; taraxacum (p. 2625·3).

Bilin Plus *Winsome, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bilina *Esteve, Spain.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis; allergic rhinitis.

Bilin-CS *Winsome, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Bilin-LB *Winsome, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Bilinum Complexe No 113 *Lehning, Fr.*
Bilinum (p. 2457·2); atropinum sulfuricum (p. 1310·2); cholesterinum (p. 2179·1); magnesia phosphorica (p. 1787·3); podophyllum peltatum (p. 1717·1); apomorphinum muriaticum (p. 892·3).
Homoeopathic preparation.

Bilip *Penn, Arg.*
Rosuvastatin (p. 1488·2).
Hypercholesterolaemia.

Biliranin *Pharmathen, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Bilisan Duo *Repha, Ger.†*
Milk thistle (p. 1561·1); Javanese turmeric (p. 2636·2).
Biliary-tract disorders; dyspepsia; liver disorders.

Biliscopin *Bayer, Austral.; Bayer, Austria; Bayer, Ger.†; IFET (ΙΦΕΤ), Gr.; Schering, NZ†; Bayer, Switz.†; Bayer, UK.*
Meglumine iotroxate (p. 1593·1).
Contrast medium for biliary-tract radiography.

Bilive *Sinovac, China.*
An inactivated hepatitis A and hepatitis B (surface antigen) vaccine (p. 2391·3).
Active immunisation.

Billerol *Lehning, Fr.*
Atropinum sulfuricum (p. 1310·2); natrum carbonicum (p. 2617·3); acidum salicylicum (p. 1719·1); natrum muriaticum (p. 1795·1); natrum phosphoricum (p. 1791·2); anethum (p. 2493·1); podophyllum peltatum (p. 1717·1); curcuma (p. 2218·1).
Homoeopathic preparation.

Biloban *Atral, Port.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Bilobene *Ratiopharm, Austria; Merckle, Ger.†; Ratiopharm, Hung.*
Fumitory (p. 2508·2).
Biliary-tract disorders.

Bilobil *Teva, Hung.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function impairment.

Bilobil Duo *KRKA, Cz.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Mental function disorders; vertigo.

Bilocor *Pharma Dynamics, S.Afr.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Biloina *Andromaco, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Bilokan *Berksam, Turk.; Santa, Turk.*
Ginkgolides (p. 2513·3).
Dementia; peripheral vascular disorders; vertigo; vestibular disorders.

Bilol *Sandoz, Switz.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; hyperkinetic heart syndrome; heart failure.

Bilol comp. *Sandoz, Switz.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bilonat *Naturatec, Canad.*
Frangula (p. 1843·3); althaea (p. 2438·3); berberry root (p. 2502·1); cascara (p. 1826·1); mallow (p. 2549·2); melissa (p. 2552·3).

Biloptin *Bayer, Gr.*
Sodium iopodate (p. 1591·3).
Contrast medium for biliary-tract radiography.

Bilotec *Ethica, Indon.*
Bacopa (p. 2452·1); ginkgo biloba (p. 2512·3); vitamin E (p. 2119·1).
Circulatory disorders.

Bilovas *Zydus, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Bilozen *Klonal, Arg.*
Ketotifen (p. 631·3).
Eye disorders.

Bilron *Aspen, S.Afr.†*
Iron bile salts (p. 2457·2).
Bile salt deficiency; biliary-tract disorders.

Biltricid *Bayer Schering, Rus.; Bayer, Ukr.*
Praziquantel (p. 164·1).
Worm infections.

Biltricide *Bayer, Austral.; Bayer, Canad.; Bayer, Fr.; Bayer, Ger.; IFET (ΙΦΕΤ), Gr.; Bayer, Hong Kong; Bayer, Israel†; Bayer, Neth.; Bayer Schering, S.Afr.†; Schering, USA.*
Praziquantel (p. 164·1).
Schistosomiasis; trematode infections; fluke infections; worm infections.

Biluen Enzimatico *Nycomed, Arg.*
⊗Azintamide (p. 2451·3); pancreatin (p. 2579·3); cellulase (p. 2473·1); simeticone (p. 1886·2).
Liver and biliary-tract disorders.

Bilugen *Roche Diagnostics, Austral.†*
Test for urobilinogen and bilirubin in urine.

Bilumid *Veropharm, Rus.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bilumide *Kleva, Gr.; Kleva, Neth.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Biluron *Genthon, Neth.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Biluta *Rowex, Irl.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bilutamid *Vera, Hung.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bimade *Chiesi, Spain.*
Delapril hydrochloride (p. 1350·2); manidipine hydrochloride (p. 1427·2).
Hypertension.

Bimanol *Polfa Pabianice, Pol.†*
⊗Deanol (p. 2319·1).
Tonic; reduced concentration in children; atherosclerotic encephalopathy; depression; schizophrenia; faecal incontinence; nocturia.

Bimetdad *Bajamed, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Bimicot *Euroderm, Arg.*
Bifonazole (p. 573·3).
Fungal skin infections.

Bimidal *Bajamed, Mex.*
Losartan (p. 1422·2).
Hypertension.

Bi-Miotic *Bell, India.†*
Pilocarpine nitrate (p. 2010·3); physostigmine salicylate (p. 2009·3).
Glaucoma.

Bimixin *Sanofi-Aventis, Ital.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Enteric infections.

Bimode *Emcure, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Bimode-M *Nucron, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Bimoxal *Faran, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bimoxan *Hexal, Mex.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bin Fen *Binhu Shuanghe, China.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Bin Ke *Binhu Shuanghe, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Bin Li *Binhu Shuanghe, China.*
Fluconazole (p. 578·2).
Fungal infections.

Bin Qi *Qi Li, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Bin Shu *Binhu Shuanghe, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders.

Bin Xin *Binhu Shuanghe, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Bin Yu *Binhu Shuanghe, China.*
Ligustrazine phosphate.

Binabic *Oncogenerika, Cz.; Oncogenerika, Hung.; Oncogenerika, Pol.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Binafex *Serral, Mex.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Binafin *Shreya, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Binaldan *Vifor, Switz.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Binanidda *Ratiopharm, Neth.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Binapro *Puspa, Indon.*
Amino acids.
Dietary supplement.

Binarin *Pisa, Mex.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Binazin *Polfa Pabianice, Pol.†*
Todralazine hydrochloride (p. 1516·1).
Hypertension.

Bincet-L *Bionet, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Bincough *Bionet, India.*
Ammonium chloride (p. 1656·1); menthol (p. 2553·2); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).

Bindace *Novagen, S.Afr.*
Perindopril (p. 1466·3).

Bindazac *Norma (Νορμα), Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Bindoclav *Actor, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

BindRen *Mitsubishi, UK.*
Colestilan (p. 1345·2).
Hyperphosphataemia in dialysis patients.

Binea *Misha, India.*
Flurbiprofen (p. 65·2); hypromellose (p. 2189·2).

Binelol *Belupo, Rus.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; angina pectoris; heart failure.

Bi-Nerisona *Intendis, Braz.; Schering, Chile†; Intendis, Mex.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Binerisona *Schering, Venez.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Binex *Biological E, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3). Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Binex DT *Biological E, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Binex E *Biological E, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Binex Kid *Biological E, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Binex Z *Biological E, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Binex ZE *Biological E, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Binfolipase *Amnol, Ital.*
Aescin (p. 2431·2); melilot (p. 2552·3); phosphatylcholine; levocarnitine (p. 2053·2); hydroiodide; caffeine (p. 1203·3); theophylline (p. 1229·3); ivy (p. 2536·2); menthol (p. 2553·2).
Cellulite.

Binfonorm *Amnol, Ital.†*
Aescin (p. 2431·2); melilot (p. 2552·3) phosphatylcholine; caffeine (p. 1203·3); ivy (p. 2536·2); menthol (p. 2553·2).
Lymphoedema.

Bing Ke *Wanglintang, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Bing Ning *Xinhua, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Bingsaiyou *Zhaohui, China.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Binitab *Ultra, Mex.*
Cinitapride acid tartrate (p. 1831·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Binko *Hexal, Braz.*
Ginkgo biloba (p. 2512·3).

Binoclar *Sandoz, Hong Kong; Sandoz, Rus.; Sandoz, Venez.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication; peptic ulcer.

Binocrit *Sandoz, Austria; Sandoz, Belg.; Sandoz, Cz.; Sandoz, Fr.; Sandoz, Ger.†; Sandoz, Gr.; Sandoz, Hung.; Sandoz, Irl.; Novartis, Israel; Sandoz, Ital.; Sandoz, Neth.; Sandoz, Pol.; Sandoz, Port.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Switz.; Sandoz, UK.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion; reduction of allogeneic transfusion requirements in surgery.

Binocular *Sandoz, Malaysia.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication in peptic ulcer.

Binodian *Bayer, Mex.*
⊗Estradiol valerate (p. 2271·2); prasterone enantate (p. 2299·2).
Menopausal disorders; osteoporosis.

Binoklar *Sandoz, Indon.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Binospan *Cazi, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Pain; fever.

Binotal *Bayer, Braz.; Grunenthal, Ger.†; Bayer, Mex.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Bayer Schering, Indon.
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Binovum *Janssen-Cilag, UK.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Binozyt *Sandoz, Gr.; Sandoz, Indon.; Sandoz, Malaysia; Simayla, S.Afr.; Sandoz, Singapore; Sandoz, Thai.; Sandoz, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Binpain *Bionet, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Binprós *Vir, Port.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

BinQi *Binhu Shuanghe, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Bintamox *Hexpharm, Indon.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bintrax *Bionet, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Binvex *Ivax, Arg.*
Pargeverine hydrochloride (p. 1877·1); dihydroxydibutylether (p. 2493·1).
Liver and biliary-tract disorders.

Binzid *Bionet, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Bio-10 *Biomax, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); L-arginine (p. 2049·1); selenium (p. 2086·3); ubidecarenone (p. 2637·1).

Bio-200 *Dermofarma, Ital.*
Royal jelly (p. 2608·1); pollen (p. 2593·3).
Nutritional supplement.

Bio-8888 *American Remedies, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Bio 4 *Tablets, India.*
Lactobacillus (p. 2596·3).

Bio ACE *Blackmores, Austral.*
Betacarotene (p. 2051·1); ascorbic acid (p. 2110·3); *d*-alpha tocoferil acid succinate (p. 2119·2); vitamin B_1 (p. 2103·1) calcium pantothenate (p. 2085·2); vitamin B_6 (p. 2105·3); zinc amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Antoxidant preparation.

Bio ACE Excell *Blackmores, Austral.*
Grape (p. 2521·3); milk thistle (p. 1561·1); selenium (p. 2086·3); betacarotene (p. 2051·1); vitamin C (p. 2110·3); *d*-alpha tocopherol (p. 2119·1); vitamin B_1 (p. 2103·1); calcium pantothenate (p. 2085·2); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); zinc amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Antoxidant preparation.

Bio Acidophilus *Bioceuticals, UK.*
Lactobacillus acidophilus (p. 2596·3).

Bio Act *Bio-Drug, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Bio C *Blackmores, Austral.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); calcium ascorbate (p. 2111·1); bioflavonoids (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2); rose fruit (p. 2607·1); acerola.
Vitamin C supplement.

Bio C Plus *Nutrilite, Arg.*
Ascorbic acid (p. 2110·3); acerola; citrus flavonoids (p. 2505·2).
Vitamin C supplement.

Bio Cal-D *Bio-Drug, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Bio Cipron *Bio-Drug, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Bio Coll *Bio-Collagen, Malaysia.*
Collagen (p. 2483·2).
Wounds; ulcers.

Bio Cyp *McNeil & Argus, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Bio E *Uniao Quimica, Braz.*
Vitamin E (p. 2119·1).

Bio Fibralax Bi-Attivo *Giuliani, Ital.†*
Dietary fibre; *Lactobacillus acidophilus* (p. 2596·3).
Dietary supplement.

Bio Flexic *Bio-Drug, India.*
Chlorzoxazone (p. 2022·2).
Skeletal muscle spasm.

Bio Flo *Bio-Drug, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bio Glo *White, Canad.*
Fluorescein sodium (p. 2506·2).

Bio Glob *Hub, USA.*
Fluorescein sodium (p. 2506·2).
Aid in eye examination.

Bio Grip 4 *Gramon, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); butetamate citrate (p. 1658·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Bio Grip C *Sanofi-Aventis, Arg.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Bio Grip Classic *Sanofi-Aventis, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders; influenza symptoms.

Bio Grip Plus *Sanofi-Aventis, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); pentoxyverine citrate (p. 1672·1); ascorbic acid (p. 2110·3); thiamine (p. 2102·3).
Cold and influenza symptoms.

Bio Grip-T *Sanofi-Aventis, Arg.*
Paracetamol (p. 115·1).
Pain; fever.

Bio Grip-T Descongestivo *Sanofi-Aventis, Arg.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; influenza symptoms.

Bio Iron *Blackmores, Austral.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); urtica (p. 2639·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; nutritional supplement.

Bio Klean *GFR, Canad.*
Benzalkonium chloride (p. 1737·1); didecyldimethylammonium chloride (p. 1750·3).
Disinfection.

Bio Magnesium *Blackmores, Austral.*
Magnesium oxide (p. 1857·3); magnesium phosphate (p. 1787·3); calcium ascorbate (p. 2111·1); pyridoxine hydrochloride (p. 2105·3); colecalciferol (p. 2113·1); manganese amino acid chelate (p. 2048·3).
Muscle cramps; premenstrual disorders.

Bio Max *Valenta, Rus.*
Vitamins; minerals; rutoside (p. 2505·3).

Bio Q10 VQ50 *Daewoong, Thai.*
Ubidecarenone (p. 2637·1).
Dietary supplement.

Bio Renal *Bio-Sante, Canad.†*
Betula pendula (p. 2457·3); buchu (p. 2461·3); couch-grass (p. 2487·2); bearberry (p. 2453·2).

Bio Slim Silueta *Natrahealth, UK.*
Poliglusam (p. 2593·2).
Slimming aid.

Bio Statol *Bio-Sante, Canad.*
Zinc gluconate (p. 2126·2).

Bio T Pres *Advanced Generic, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).

Bio Tarbun *Duncan, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Bio Tears *Biotech, Arg.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Bio Zinc *Blackmores, Austral.*
Vitamin A acetate (p. 2098·3); pyridoxine hydrochloride (p. 2105·3); magnesium phosphate (p. 1787·3); manganese amino acid chelate (p. 2048·3); zinc amino acid chelate (p. 2048·3).
Skin disorders.

Bio Zolam *Bio-Drug, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Bioacne
Note: this name may be used for preparations of different composition.
Ikapharmindo, Indon.
Cetrimide (p. 1742·1); resorcinol (p. 1718·3); sulfur (p. 1721·1).
Acne.

Sanofi-Aventis, Gr.
Benzoyl peroxide (p. 1696·1).
Acne.

Bioactiv I *Knop, Chile.*
Argentum nitricum (p. 2615·3); caladium seguinum; lycopodium clavatum (p. 2547·1); selenium (p. 2086·3).
Homoeopathic preparation.

Bioactiv V *Knop, Chile.*
Argentum nitricum (p. 2615·3); bryonia (p. 2461·3); cocculus ind. (p. 2483·1); conium mac. (p. 2524·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Bioactiv A *Knop, Chile.*
Cinchona officinalis (p. 2478·3); gentiana lutea (p. 2512·1); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Bioactiv D *Knop, Chile.*
Calcium carbonicum (p. 1824·3); silicea (p. 2208·3); calcium phosphoricum (p. 1784·2).
Homoeopathic preparation.

Bioactiv E *Knop, Chile.*
Acidum phosphoricum (p. 2589·1); arnica montana (p. 2447·2); calcium carbonicum (p. 1824·3); cinchona officinalis (p. 2478·3); kalium phosphoricum (p. 1790·3); pulsatilla (p. 2600·2); rhus toxicodendrum (p. 2603·3).
Homoeopathic preparation.

Knop, Canad.†
Arnica (p. 2447·2); calcium carbonate (p. 1824·3); cinchona officinalis (p. 2478·3); phosphoric acid (p. 2589·1); poison oak (p. 2603·3); potassium phosphate dibasic (p. 1791·1); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Bioactiv F *Knop, Chile.*
Graphites (p. 2522·1); conium maculatum (p. 2524·3); onosmodium virginiana; lycopodium clavatum (p. 2547·1); caladium seguinum; kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Bioactiv H *Knop, Chile.*
Arsenicum album (p. 2448·1); borax (p. 2459·2); mercurius solubilis (p. 2555·3); acidum nitricum (p. 2572·3); acidum sulfuricum (p. 2624·2).
Homoeopathic preparation.

Knop, Canad.†
Nitric acid (p. 2572·3); potassium dichromate (p. 2476·3); sodium borate (p. 2459·2); sulfuric acid (p. 2624·2).
Homoeopathic preparation.

Bioactiv L *Knop, Chile.*
Urtica urens (p. 2639·3); cinchona officinalis (p. 2478·3); phellandrium aquatum.
Homoeopathic preparation.

Bioactiv M *Knop, Chile.*
Natrium muriaticum (p. 1795·1); kalium phosp. (p. 1790·3); anacardium orient. (p. 2471·3); barium carb. (p. 2452·2).
Homoeopathic preparation.

Bioactiv N *Knop, Chile.*
Belladonna (p. 2453·3); carbon vegetal (p. 1537·3); gelsemium semper (p. 2511·2); iris versicolor (p. 2534·3); natrium sulfuricum (p. 1888·1).
Homoeopathic preparation.

Knop, Canad.†
Belladonna (p. 2453·3); charcoal activated (p. 1537·3); gelsemium sempervirens (p. 2511·2); iris versicolor (p. 2534·3); sodium sulfate (p. 1888·1).
Homoeopathic preparation.

Bioactiv O *Knop, Chile.*
Antimonium crudum (p. 2445·1); ignatia amara (p. 2532·1); natrium muriaticum (p. 1795·1).
Homoeopathic preparation.

Bioactiv P *Knop, Chile.*
Acidum phosphoricum (p. 2589·1); acidum fluorhidricum (p. 2529·1); oleander (p. 2574·3); silicea (p. 2208·3); natrium muriaticum (p. 1795·1).
Homoeopathic preparation.

Bioactiv Q *Knop, Chile.*
Graphites (p. 2522·1); thuja (p. 2629·3).
Homoeopathic preparation.

Bioactiv R *Knop, Canad.†; Knop, Chile.*
Arnica (p. 2447·2); belladonna (p. 2453·3); berberis (p. 2502·1); calcium carbonicum (p. 1824·3); lycopodium (p. 2546·3); pareira brava.
Homoeopathic preparation.

Bioactiv S *Knop, Chile.*
Nux vomica (p. 2573·3); lycopodium (p. 2546·3).
Homoeopathic preparation.

Knop, Canad.†
Lycopodium (p. 2546·3); potassium phosphate dibasic (p. 1791·1).
Homoeopathic preparation.

Bioactiv Z *Knop, Chile.*
Aconitum nap. (p. 2428·3); hypericum perforatum (p. 449·1); mezereum; kalmia latif (p. 2537·2); coffea (p. 2648·2); belladonna (p. 2453·3).
Homoeopathic preparation.

Bioage Peripheral *Bioglan, Austral.†*
Wild pansy (p. 2647·3); crataegus (p. 2488·1); olive (p. 2574·3); magnesium orotate (p. 1786·3); *d*-alpha tocoferil acid succinate (p. 2119·2).
Peripheral circulatory disorders.

Bio-Amoksiclav *Biotech, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Bio-Amoksiklav *Biotech, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Bioarginina *Damor, Ital.*
Arginine (p. 2049·1) or arginine hydrochloride (p. 2049·1).
Hyperammonaemia; asthenia.

Bioarginol-C *Bioresearch, Mex.*
Sulfadiazine (p. 361·3).
Bacterial skin infections.

Bioaron C *Evroplant, Ukr.*
Aloes (p. 1816·1); mountain ash; ascorbic acid (p. 2110·3).
Tonic.

Phytofarm Kleka, Pol.
Aloes (p. 1816·1); aronia melanocarpa; vitamin C (p. 2110·3).
Infection prophylaxis; reduced appetite.

Phytopharm, Rus.
Aloes (p. 1816·1); ascorbic acid (p. 2110·3); aronia.
Respiratory-tract infection prophylaxis.

Bioarscolloid *SIT, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); silver protein (p. 2616·2); tyrothricin (p. 384·1).
Bacterial mouth infections.

Bioart *Biocin, India.*
Artesunate (p. 648·2).
Malaria.

Bio-ATP *Phapros, Indon.*
Adenosine triphosphate (p. 2430·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Asthenia; fatigue.

Bio-AZ *Biomax, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Biobase *Odan, Canad.*
⊗Alcohol (p. 1733·1).
Antiseptic vehicle for topical preparations.

Biobase-G *Odan, Canad.*
⊗Alcohol (p. 1733·1); glycolic acid (p. 1704·3).
Antiseptic vehicle for topical preparations.

Biobeclasona *Biogalenic, Venez.*
⊗Beclometasone (p. 1621·2).
Allergic rhinitis.

Biobeclod *Biogalenic, Venez.*
⊗Beclometasone (p. 1621·2).
Obstructive airways disease.

Biobees *Bioceuticals, UK.*
A range of preparations containing royal jelly (p. 2608·1).

Biobet *JK Biochem, India.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Biobica *Abamed, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bio-Biloba *Pharma Nord, Norw.; Pharma Hus, Swed.*
Ginkgo biloba (p. 2512·3).
Mental function impairment in the elderly; tonic; peripheral vascular disorders.

Biobin *Biochem, India.*
Cytarabine (p. 774·1).
Malignant neoplasms.

Biobran *Ferron, Indon.*
Arabinoxylan derivatives.
Dietary fibre supplement.

Biobron *Advanced Generic, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Bio-C *Uniao Quimica, Braz.; Naturo Aid, Canad.; Unicity, Canad.*
Vitamin C (p. 2110·3).

Pharma Nord, Denm.; Pharma Nord, Norw.; Pharma Nord, Thai.
Calcium ascorbate (p. 2111·1).
Vitamin C supplement; vitamin C deficiency.

Bio-C Complex *Blackmores, Austral.†*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); calcium ascorbate (p. 2111·1); lemon bioflavonoids (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2); acerola.
Vitamin C preparation.

Biocadmio *Uriach, Spain.†*
Cadmium sulfide (p. 2463·3).
Skin and scalp disorders.

Bio-Cal *YSP, Malaysia.*
Boron (p. 2052·3); calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); iodine (p. 2336·3); selenium (p. 2086·3).
Dietary supplement.

Biocal-95 *Simex, Indon.*
Coral calcium (p. 1783·1); soya isoflavone (p. 2620·3); colecalciferol (p. 2113·1); vitamin K_1 (p. 2122·2); magnesium (p. 1786·3); zinc (p. 2126·1); boron (p. 2052·3).
Osteoporosis; calcium supplement.

Biocalcin *United Biotech, India; Bio-Gen, Turk.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia; bone pain due to malignancy.

Biocalcit *DAST, Gr.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).

Biocalcium *Bioprogress, Ital.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Biocalcium D3 *Krugher, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Bio-Calcium + D_3 *Pharma Nord, Irl.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Calcium deficiency.

Bio-Calcium + D_3 + K *Pharma Nord, Irl.†; Pharma Nord, Thai.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); vitamin K (p. 2122·1).
Calcium supplement; osteoporosis.

Biocalm
Note: this name may be used for preparations of different composition.
Biolab, Thai.
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasticity and spasm; parkinsonism; obliterative vascular diseases.

Lizofarm, Ital.
Valerian (p. 2640·2); passion flower (p. 2584·1); peppermint leaf (p. 1877·1).
Insomnia.

Biocalron *Great Eastern, Thai.*
Calcium lactate (p. 1784·1); ferrous fumarate (p. 2060·3); vitamin C (p. 2110·3); rutoside (p. 2505·3).
Calcium and iron supplement.

BioCalth *BioCalth, UK.*
Calcium L-threonate (p. 1783·1).
Calcium supplement.

Biocalyptol *Zambon, Fr.*
Pholcodine (p. 1675·1).
Cough.

Biocanol *Fako, Turk.†*
Fluconazole (p. 578·2).
Fungal infections.

Bio-Caps *Bio-Health, UK.*
Vitamins; minerals.

Biocaps *Biotech Naturis, Venez.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Dietary supplement.

Biocarb *Biochem, India.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Biocarbo *Biosintetica, Braz.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Biocarbon *Trenka, Malaysia.*
Activated charcoal (p. 1537·3).
Diarrhoea; flatulence.

Biocard *Niche, Irl.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension.

Fako, Turk.†
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Biocarde *Lehning, Fr.*
Crataegus (p. 2488·1); passion flower (p. 2584·1); avena (p. 2451·1); valerian (p. 2640·2); melissa (p. 2552·3); motherwort (p. 2564·2).
Nervous disorders; insomnia.

BioCardine *Scandinavian Laboratories, Pol.†*
Fish oil (p. 1460·3).
Cardiovascular disorders; hyperlipidaemias.

Biocarn *Medice, Ger.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Biocarotine *Bioceuticals, UK.*
Betacarotene (p. 2051·1).

Biocef
Note: this name may be used for preparations of different composition.
Otto, Indon.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Pharmpartners, Philipp.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Plus, India.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Sandoz, Austria.
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Zambon, Spain.†
Ceftibuten (p. 252·2).
Bacterial infections.

Biocefazon *Bioton, Pol.†*
Cefoperazone sodium (p. 243·1).
Gram-negative bacterial infections.

Biocefra *Laquifa, Port.*
Cefradine (p. 249·1).
Bacterial infections.

Bioceftrax *Biogalenic, Venez.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Biocell *Madaus, Arg.*
Centella (p. 1698·3); caffeine (p. 1203·3); levocarnitine (p. 2053·2); salicylic acid (p. 1719·1).
Cellulite.

Biocellfax *Strathmann, Ger.†*
Milk thistle (p. 1561·1).
Liver disorders.

Biocepime *Otto, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Biocerulin *Biopharma, Ukr.*
Caeruloplasmin.
Immunostimulant.

Biocetamol *Biospray, Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Biochemic Phosphates *Hylands, Canad.*
Calcium phosphate (p. 1784·2); ferrous phosphate (p. 2077·1); magnesium phosphate dibasic (p. 1786·3); potassium phosphate dibasic (p. 1791·1); sodium phosphate dibasic (p. 1791·2).
Homoeopathic preparation.

Biochetasi *Sigma-Tau, Ital.*
Vitamin B substances (p. 2102·3); electrolytes (p. 1775·1).
Fluid and electrolyte disorders; liver disorders.

Biocholes *Medikon, Indon.†*
Cynara (p. 2490·3); vitamin C (p. 2110·3); nicotinamide (p. 2083·1); vitamin E (p. 2119·1); chromium tripicolinate (p. 2056·1).
Hyperlipidaemias.

Bio-Ci *Ceccarelli, Ital.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Biociclin *Francia, Ital.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Biocid *Biochem, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Biocidan *Menarini, Fr.*
Eye drops: Cethexonium bromide (p. 1742·1).
Minor eye infections.

Menarini, Fr.
Nasal spray: Cethexonium bromide (p. 1742·1); phenyltoloxamine citrate (p. 638·1).
Rhinitis.

Biocil
Note: this name may be used for preparations of different composition.
Formula, NZ.†
Povidone-iodine (p. 1767·1).
Skin disinfection; minor cuts and burns; herpes labialis.

Biocilin *Biochem, India.*
Ampicillin (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Biocilina *Biogalenic, Venez.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Bio-Cillin *Biotech, S.Afr.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Biocine Test *Biovac, S.Afr.†*
Tuberculin (p. 2635·3).
Diagnosis of tuberculosis.

Biocine Test PPD *Novartis Vaccines, Ital.†*
Tuberculin purified protein derivative (p. 2635·3).
Test for hypersensitivity to tubercle bacillus.

Biocip *Biochem, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ranbaxy, S.Afr.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Biocipro *Biospray, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Biocip-TZ *Biochem, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Bio-Citral *Intra-Labs, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Bioclar *Biochem, India.*
Clarithromycin (p. 266·2).
Bacterial infections.

Bioclate *CSL, Neth.†*
A factor VIII preparation (recombinant) (p. 1148·1).

Bioclav *Gamot, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Bioclavid *Sandoz, Arg.; Sandoz, Denm.; Sandoz, Fin.; Sandoz, Gr.; Sandoz, Neth.; Sandoz, Philipp.; Sandoz, Swed.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bioclenz *Rochester, Canad.†*
Triclosan (p. 1773·2).
Skin cleansing.

Bioclin Sebo Care *Dermoteca, Port.*
Capsules: Borage oil (p. 2459·2); Iceland moss (p. 2531·2); copper (p. 2057·1); zinc (p. 2126·1); cucurbita oil (p. 2489·2).
Seborrhoea.

Dermoteca, Port.†
Topical gel: Glycolic acid (p. 1704·3); piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Acne.

Bioclindax *Biogalenic, Venez.*
Clindamycin (p. 269·3).
Bacterial infections.

Bioclot
Note: this name may be used for preparations of different composition.
Elfin, India.
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Bioclox *Biochem, India.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Bioclusive *Systagenix, Ital.*
Polyurethane dressing (p. 1718·1).
Wounds.

Biocobal
Note: this name may be used for preparations of different composition.
Orchid, India.
Mecobalamin (p. 2108·1).

Lemery, Mex.†
Hydroxocobalamin (p. 2107·3).
Anaemias; neuritis.

Biocobal Forte *Orchid, India.*
Vitamin B substances (p. 2102·3).

Biocobal Plus *Orchid, India.*
Vitamin B substances (p. 2102·3).

Biocolchid *Biogalenic, Venez.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Bio-Cold *Indkus, India.*
⊗Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Biocombin *Meprofarm, Indon.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; neuritis; anaemias.

Biocord
Note: this name may be used for preparations of different composition.
Medipharm, Chile.
Vitamins; minerals; ginseng (p. 2513·3); soya lecithin (p. 2542·2); procaine hydrochloride (p. 1994·3); rutoside (p. 2505·3).
Tonic; skin, hair, and nail disorders.

Biocord Active *Medipharm, Chile.*
Vitamins; minerals.
Dietary supplement.

Biocord-E *Medipharm, Chile.*
Vitamins; minerals; rutoside (p. 2505·3); ginseng (p. 2513·3); soya lecithin (p. 2542·2); procaine hydrochloride (p. 1994·3).
Dietary supplement.

Biocort
Note: this name may be used for preparations of different composition.
Akacia, S.Afr.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Biosintex, Arg.
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

EuroHealthcare, Philipp.
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Medikon, Indon.†
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Biocoryl *IFET (ΙΦΕΤ), Gr.; Vifor, Spain.*
Procainamide hydrochloride (p. 1475·3).
Arrhythmias.

Biocos *APS, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Biocream *Merck, Indon.*
Moisturiser.

Biocrinal *Sofex, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Biocristin *Biochem, India.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Biocur *Mertens, Arg.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Biocure Pronatal *Qualiphar, Belg.*
Vitamins; minerals.
Dietary supplement in pregnancy.

Bio-Curkem *Soho, Indon.*
Curcuma longa.
Dietary supplement for cancer patients.

Bio-Curlam *Soho, Indon.*
Curcuma longa; fish oil (p. 1460·3).
Dietary supplement.

Bio-Curliv *Soho, Indon.*
Curcuma longa; silymarin (p. 1561·2); schisandra (p. 2611·2); liquorice (p. 1853·2); choline bitartrate (p. 2055·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Bio-C-Vitamin *Pharma Nord, Fin.†*
Calcium ascorbate (p. 2111·1).
Vitamin C deficiency; vitamin C supplement.

BioCyst *Holsten, Ger.†*
Birch leaf (p. 2457·3); solidago virgaurea (p. 2620·1); java tea (p. 2536·3).
Urinary-tract disorders.

Bio-D3 *Macleods, India.*
Calcitriol (p. 2113·1).
Hyperparathyroidism; hypoparathyroidism; pseudohypoparathyroidism; rickets; hypocalcaemia.

Bio-Dac *Bioresearch, Mex.*
Sulindac (p. 134·2).
Inflammation; rheumatism.

Biodaclin *Rayere, Mex.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Biodacyna *Bioton, Pol.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Biodalgic *Biocodex, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Biodan *Biomedis, Thai.; Great Eastern, Thai.*
Sulfaguanidine (p. 364·3); activated charcoal (p. 1537·3); bismuth subcarbonate (p. 1822·1); pectin (p. 2200·3); dicycloverine hydrochloride (p. 1834·2).
Diarrhoea.

Bioresearch, Mex.
Phenytoin sodium (p. 538·2).
Epilepsy.

Biodantyl-C *Bioresearch, Mex.*
Miconazole (p. 588·3).
Fungal skin infections.

Biodaron *Biodeal, India.*
Amiodarone hydrochloride (p. 1300·1).
Ventricular arrhythmias.

Biodase *Biomedica, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Biodase-D *Biomedica, India.*
⊗Serrapeptase (p. 2613·3); diclofenac potassium (p. 48·3).

Biodasin *Promed, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Biodel *Bioresearch, Mex.*
Bromocriptine (p. 895·3).

Bio-Delta Cortilen *SIFI, Ital.*
⊗Prednisolone acetate (p. 1645·2); neomycin sulfate (p. 330·1).
Eye infections.

Bioderm
Note: this name may be used for preparations of different composition.
Farmalex, Gr.
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Odan, Canad.
Polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3).
Bacterial skin infections.

Galenium, Indon.†
Gentamicin sulfate (p. 304·2).
Skin infections.

Biodermatin *Sinclair, Ital.*
Biotin (p. 2052·2).
Biotin deficiency.

Bio-Dermis *Sidus, Arg.*
Aloe arborescens.
Skin disorders.

Biodexan *Sophia, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); phenylephrine hydrochloride (p. 1672·3).
Infected eye disorders.

Biodezil *Bioresearch, Mex.*
Captopril (p. 1331·2).
Hypertension.

Biodiar *Sandoz, Indon.*
Activated attapulgite (p. 1820·1).
Diarrhoea.

Biodicaine *Biodica, Fr.†*
Injection: Lidocaine hydrochloride (p. 1988·2). Adrenaline acid tartrate (p. 1292·2) or noradrenaline acid tartrate (p. 1458·2) is included in some of the preparations as a vasoconstrictor to diminish absorption and localise the effects of the local anaesthetic.
Local anaesthesia.

Biodica, Fr.†
Topical solution: Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Surface anaesthesia for dental use.

Biodif *Bago, Chile.†*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); vitamin C (p. 2110·3); minerals.

Biodin *Bioresearch, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Biodinam *Roux-Ocefa, Arg.*
Vitamins; trace elements.

Biodine *Major, USA.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Bio-Disc *Blackmores, Austral.†*
⊗Minerals; vitamins; silicon dioxide (p. 2208·3); bromelains (p. 2460·3); papain (p. 2582·3).
Delayed bone healing; muscular and joint pain.

Biodol
Note: this name may be used for preparations of different composition.
Niche, Irl.
Tramadol hydrochloride (p. 139·2).
Pain.

Biodolor *Pfluger, Ger.*
Cyclamen purpurascens (p. 2490·2); gelsemium sempervirans (p. 2511·2); melilotus officinalis (p. 2552·3); primula veris (p. 2596·2); sanguinaria canadensis (p. 2610·1); strychnos nux vomica (p. 2573·3); thea chinensis (p. 2648·2).
Homoeopathic preparation.

Biodone *Biomed, Austral.; Biomed, NZ.*
⊗Methadone hydrochloride (p. 88·3).
Opioid dependence; opioid withdrawal syndrome.

Biodophilus *Bioceuticals, UK.*
Lactobacillus acidophilus (p. 2596·3).

Biodoron *Weleda, Neth.*
Ferrum/quarz (p. 2073·1).
Homoeopathic preparation.

Biodoxan *Biogalenic, Venez.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Biodoxi *Biochem, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Biodramina *Uriach, Spain.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Biodramina Cafeina *Uriach, Spain.*
Caffeine (p. 1203·3); dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Motion sickness; vertigo.

Biodribin *IBA, Pol.*
Cladribine (p. 769·1).
Leukaemias; lymphoma.

Biodrox
Note: this name may be used for preparations of different composition.
Brussels, India.
Cefadroxil (p. 233·2).
Bacterial infections.

Biodroxil *Sandoz, Cz.; IFET [ΦΕΤ], Gr.; Sandoz, Indon.; Sandoz, Israel; Sandoz, Pol.*
Cefadroxil (p. 233·2).
Bacterial infections.

Biodruff *Farmamust, Gr.*
Tenoxicam (p. 136·2).
Inflammatory disorders.

Bio-E *Reddy, India; Pharma Nord, Norw.; Pharma Nord, Thai.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Teguhsindo, Indon.
Vitamin E (p. 2119·1).
Antioxidant; vitamin E deficiency.

Bioelementa *Dekaz, Gr.*
⊗Mometasone furoate (p. 1644·1).
Inflammatory skin disorders.

Bioenergex *Medirex, Port.*
Arginine aspartate (p. 2049·1).
Asthenia.

Bio-Energol Plus *Medirex, Port.*
Arginine aspartate (p. 2049·1).
Tonic.

Bio-Enhanced Calcium Plus *Abbott, Malaysia.*
Calcium (p. 1783·1); ergocalciferol (p. 2113·3).
Dietary supplement.

Abbott, Philipp.
Calcium carbonate (p. 1824·3); ergocalciferol (p. 2113·3).
Dietary supplement.

Bio-Enhanced Evening Primrose Oil *Abbott, Malaysia.*
Evening primrose oil (p. 2502·2).
Dietary supplement.

Bio-Enhanced Fish Oil Plus *Abbott, Malaysia.*
Fish oil (p. 1460·3); vitamin E (p. 2119·1); orange oil (p. 2576·2).
Dietary supplement.

Bioentérine *DB, Fr.*
Nutritional supplement.
Maintenance of gastrointestinal flora.

Bioepicyna *IBA, Pol.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

BIO-EPL *Medikon, Indon.†*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); methionine (p. 1558·2).
Liver disorders.

Bioequiseto *Cabassi, Ital.†*
Equisetum (p. 2500·1).
Nutritional supplement.

Bioesse Plus *Mavi, Ital.*
Amino acids; biotin (p. 2052·2); selenium (p. 2086·3); saw palmetto (p. 2363·3).
Nutritional supplement.

Bioestril Ginseng *Meda, Ital.*
⊗Crataegus (p. 2488·1); red clover (p. 2482·1); soya (p. 2092·3); ginseng (p. 2513·3); agnus castus (p. 2432·2); vitamin E (p. 2119·1).
Dietary supplement; menopausal symptoms.

Bioestril Valeriana *Meda, Ital.*
⊗Valerian (p. 2640·2); red clover (p. 2482·1); soya (p. 2092·3); urtica (p. 2639·3); agnus castus (p. 2432·2); alpha tocoferil acetate (p. 2119·2).
Dietary supplement; menopausal symptoms.

Bio-E-Vitamin *Pharma Nord, Fin.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Biofair *Intra-Labs, India.*
Biotin (p. 2052·2); vitamin E (p. 2119·1).

Biofanal *Pfleger, Ger.*
Nystatin (p. 590·3).
Candidiasis.

Biofast *Solitaire, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Biofast-OZ *Solitaire, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Biofax *Maver, Chile.†*
Vitamin E (p. 2119·1); betacarotene (p. 2051·1); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc gluconate (p. 2126·2).

Strathmann, Ger.†
Birch leaf (p. 2457·3); ononis (p. 2575·3); seed-free garden bean pods.
Fluid retention.

Biofazolin *Polpharma, Pol.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Biofem
Note: this name may be used for preparations of different composition.
Biotenk, Arg.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Hexal, Ger.†; Ilsan, Turk.†
⊗Agnus castus (p. 2432·2).
Menstrual disorders; mastalgia.

Biofem 35 *Biotenk, Arg.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Biofem Test *Biotenk, Arg.*
Pregnancy test (p. 2596·1).

Biofenac
Note: this name may be used for preparations of different composition.
Ache, Braz.
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Almirall, Belg.; Galenica, Gr.; Almirall, Neth.; Almirall, Port.; Biomeks, Turk.
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Biofenor *Bioresearch, Mex.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Biofent *Biochimico, Braz.*
⊗Fentanyl (p. 60·1).
Pain.

Bio-Fer
Note: this name may be used for preparations of different composition.
Herbaxt, Fr.†
Iron pidolate; folic acid (p. 2063·1). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement.

Biofer
Note: this name may be used for preparations of different composition.
Bioresearch, Mex.
Paracetamol (p. 115·1).
Fever; pain.

Micro, India.
Syrup: Iron (p. 2073·1).

Micro, India; Micro, Rus.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).
Iron deficiency anaemia.

Bioferal *Bioprogress, Ital.*
Ferrous gluconate (p. 2061·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Bioferina *Bioresearch, Mex.*
Phenazopyridine (p. 124·3).
Urinary-tract infections.

Bioferon *Sidus, Arg.; Bio Sidus, Thai.*
Interferon alfa-2b (p. 989·2).
Hepatitis; anogenital warts; malignant neoplasms.

Bioferon Hepakit *Sidus, Arg.*
Capsules, ribavirin (p. 1010·2); injection, interferon alfa-2b (recombinant) (p. 989·2).
Chronic hepatitis C.

Bioferro *Prospa, Port.*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Bioferron *Ikapharmindo, Indon.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Nutritional supplement.

Bioferum Forte *Bio-Drug, India.*
Vitamin B substances (p. 2102·3); minerals; casein (p. 2055·2); lysine hydrochloride (p. 2079·3); sorbitol (p. 2092·1).

Biofestal *Biopharma, Rus.*
⊗Pancreatin (p. 2579·3); hemicellulase (p. 2473·1); ox bile extract (p. 2457·2).
Digestive disorders; pancreatic insufficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bioff *Biochem, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bioffin *Bio-Drug, India.*
Carmellose (p. 2175·1); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2); sorbitol (p. 2092·1).

Biofilen *Degorts, Mex.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Biofilgran *Landsteiner, Mex.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Biofilm *Braun, UK.*
Hydrocolloid dressing.
Wounds; ulcers.

Biofiloderm *Farmalex, Gr.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Biofiltrazione *NovaSelect, Ital.*
Preparations for haemofiltration (p. 1778·2).
Haemofiltration.

Biofirm *Vitalco, Fr.*
Chicory root inulin (p. 2475·2); bitter orange peel (p. 2575·3); taraxacum (p. 2625·3); fruit and vegetable fibre; cynara (p. 2490·3); spirulina (p. 2622·1); urtica (p. 2639·3); celery seed (p. 2472·3); asparagus (p. 2450·2); thyme (p. 2630·2).
Dietary supplement.

Bioflac *Cristalia, Braz.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis.

Bioflam *Rider, Chile.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bioflavin *Herbarium, Braz.†*
Ginkgo biloba (p. 2512·3).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders.

Biofleks *Osel, Turk.*
A range of electrolyte and/or carbohydrate infusions (p. 1775·1).
Fluid and electrolyte disorders.

Bioflevin *Biomedica, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Bioflex
Note: this name may be used for preparations of different composition.
Advanced Generic, USA.
Citrus bioflavonoids (p. 2505·2); crataegus (p. 2488·1); hesperidin complex; aesculus (p. 2431·2); rutoside (p. 2505·3); vitamin C (p. 2110·3); hamamelis (p. 2523·3).

Bio Macro, Braz.
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).

Elfin, India.
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1).

Aus Biomed, Austral.†
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1); ginger (p. 1844·1); phellodendron amurense.
Osteoarthritis; rheumatoid arthritis.

Rottapharm, Chile.†
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Degenerative joint disorders.

Bioflogil *Spedrog, Arg.*
Chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis; osteoporosis.

Bioflor *Biocodex, China; Biocodex, Hong Kong; Biocodex, Thai.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; irritable bowel syndrome.

Bio-Flora *Biodelta, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins; minerals.
Gastrointestinal disorders.

Maver, Chile.
Saccharomyces boulardii (p. 2596·3).
Diarrhoea.

Bioflora *Sidus, Arg.*
Lactobacillus casei (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3); *Bifidobacterium brevis* (p. 2596·3).
Restoration of gastrointestinal flora.

Bioflorax *Zdorovje, Ukr.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; intestinal dysbiosis; salmonellosis.

Bioflorin *Sanofi-Aventis, Ital.; Sanofi-Aventis, Switz.*
Lactic-acid-producing enterococci (p. 2596·3).
Gastrointestinal disorders; restoration of gastrointestinal flora.

Sanova, Austria.
Live *Enterococcus faecium* (p. 2596·3).
Gastrointestinal disorders.

Bioflorina *Sanofi-Aventis, Switz.*
Lactic-acid-producing enterococci (p. 2596·3).
Restoration of gastrointestinal flora.

Bioflox *Bioresearch, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Bioflоxcin *Niche, Irl.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Biofloxin *Biochem, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Bioflox-TZ *Biochem, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Bacterial infections.

Bio-Flu *Biosano, Chile.*
An inactivated influenza vaccine (split virion, H1N1) (p. 2393·3).
Active immunisation.

Bioflu *United Laboratories, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Formerly contained phenylpropanolamine hydrochloride, chlorphenamine maleate, and paracetamol.
Allergic rhinitis; cold and influenza symptoms; sinusitis.

Bioflusin *Bioresearch, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Hay fever.

Bioflutin *Sudmedica, Ger.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Bioforce *Biohorma, Neth.*
Arnica (p. 2447·2); calendula (p. 2465·2); hamamelis (p. 2523·3); St John's wort (p. 449·1); sage (p. 2608·3); sanicula; sunflower.

Bioform
Note: this name may be used for preparations of different composition.
Medley, India.
Bifidobacterium longum (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

Biofos
Note: this name may be used for preparations of different composition.
Meprofarm, Indon.†
Echinacea (p. 2498·1); curcuminoid (p. 2489·3); fructo-oligosaccharides (p. 2508·1); taurine (p. 2626·2); phyllanthus niruri (p. 2590·1).
Immunostimulant; reduced appetite; digestive disorders.

Biofreeze
Note: this name may be used for preparations of different composition.
Lane, UK.
Menthol (p. 2553·2); maté (p. 2648·2).
Musculoskeletal and joint pain.

Performance Health, USA.
Menthol (p. 2553·2).

Shield, Irl.†
Isopropyl alcohol (p. 1758·3); maté (p. 2648·2); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Performance Health, Canad.†
Camphor (p. 2466·2); menthol (p. 2553·2).

Biofrin *Sophia, Mex.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Biofructose *Bunker, Braz.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); fructose (p. 2068·2).

Bioftal *Lafedar, Arg.*
Chloramphenicol (p. 257·1); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).

Biofucid *Bausch & Lomb, Arg.*
Fusidic acid (p. 302·1).
Bacterial eye infections.

Biofurin *Bioresearch, Mex.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Biofuroksym *Polpharma, Pol.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Bioton, Ukr.†
Cefuroxime (p. 255·2).
Bacterial infections.

Biofuroso *Bioresearch, Mex.*
Ferrous fumarate (p. 2060·3).
Iron deficiency anaemia.

BioGaia *Ferring, Canad.; Recalcine, Chile; Bioethic, Fr.; Kalbe, Indon.; Age D'or, Singapore; BioGaia, Ukr.; Everidis, USA.*
Lactobacillus reuteri protectis (p. 2596·3).
Maintenance of gastrointestinal flora; diarrhoea; infant colic; maintenance of oral health; gastrointestinal disorders.

Biogaia Protectis ORS *Age D'or, Singapore.*
Lactobacillus reuteri protectis (p. 2596·3); salts; zinc (p. 2126·1).
Diarrhoea; vomiting.

Biogamma *Asubio, Jpn.†*
Interferon gamma-1a (p. 999·1).
Skin lymphoma.

Biogaracin *Biochem, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Bio-Gast *Bioresearch, Mex.*
Ranitidine (p. 1882·1).

Biogastron *Bernofarm, Indon.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); dimeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis; dyspepsia; flatulence.

Biogat *Biochem, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Biogaze
Note: this name may be used for preparations of different composition.
Dexo, Fr.
Niaouli oil (p. 2569·1); thyme oil (p. 2630·3).
Burns.

Novum, Belg.
Dodeclonium bromide (p. 1750·3); lidocaine hydrochloride (p. 1988·2).
Skin disorders.

Biogel
Note: this name may be used for preparations of different composition.
Ghimas, Ital.
Royal jelly (p. 2608·1).

Prater, Chile.
Ketoconazole (p. 585·3).
Fungal scalp infections.

Biogel Resv *Ghimas, Ital.*
Royal jelly (p. 2608·1); resveratrol (p. 2603·2).
Dietary supplement.

Biogem *United Biotech, India.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Biogena Dermo *Valetudo, Ital.*
Soap substitute.

Biogenol
Note: this name may be used for preparations of different composition.
Chemopharma, Chile.
Vitamin A palmitate (p. 2098·3); calcium ascorbate (p. 2111·1); alpha tocoferil acetate (p. 2119·2); selenium yeast (p. 2125·2); zinc gluconate (p. 2126·2); copper gluconate (p. 2057·2).
Nutritional supplement.

Hakay, Turk.
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Biogesic *Biomedis, Hong Kong; Biomedis, Indon.; Probus, Indon.; Biomedis, Malaysia†; United Laboratories, Philipp.; Biomedis, Singapore; Biomedis, Thai.†; Great Eastern, Thai.†*
Paracetamol (p. 115·1).
Fever; pain; influenza symptoms.

Bio-GI *Fahrenheit, Indon.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium animalis* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Maintenance of gastrointestinal flora.

Biogil *Advanced Generic, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Bioginal *SoSe, Ital.*
Ciclopirox olamine (p. 575·3).
Vulvovaginal candidiasis.

BioGinkgo *Pharmanex, USA.*
Ginkgo biloba (p. 2512·3).
Nutritional supplement.

Bioginko *Indofarma, Pol.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Mental function impairment; tonic.

Bioglan Acidophilus *Bioglan, Austral.†*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Bioglan Zinc Chelate *Bioglan, Austral.†*
Zinc amino acid chelate (p. 2048·3).
Zinc deficiency.

Bioglandin *United Biotech, India.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Bioglic *Biolab Sanus, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Bioglobina *Vargas, Venez.*
Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).
Iron and vitamin B deficiency; dietary supplement.

Bioglobin-U *Biolek, Ukr.*
Bioglobin (polypeptides 3,5-7%, amino acids 50-60%, aminosaccharides 4-5%, hexuronic acids 8-9%).
Osteoarthritis; rheumatoid arthritis.

Bio-Glucosamine *Pharma Nord, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Bioglufer *Euro-Pharma, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Biogold *Indkus, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Biograstim *CT, Cz.; CT, Ger.†; CT, Irl.; CT, Neth.; CT, Pol.; CT, Port.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Biogreen *Euro-Pharma, Ital.*
Sodium monofluorophosphate (p. 2091·3); propolis (p. 2597·3); tabebuia; plant extracts.
Mouth disorders.

Biogrip Forte *Sanitas, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Biogripe *Uniao Quimica, Braz.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

BioGtuss *Advanced Generic, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).

Biogyl *Biolab, Thai.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Bio-Gyn *Thorne, Canad.†*
Magnesium citrate (p. 1857·1); pyridoxal-5-phosphate (p. 2105·3); zinc citrate (p. 2126·2).

Biohep *Kee, India.*
Tablets: ⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).
Liver disorders.

Kee, India.
Injection: Ornithine aspartate (p. 2085·2).
Liver disorders.

Biohepax *Ducto, Braz.†*
Adenosine (p. 1291·1); methionine (p. 1558·2); betaine (p. 2456·1); choline citrate (p. 2055·2); pyridoxine hydrochloride (p. 2105·3).
Biliary-tract disorders.

Biohes *Biosel, Turk.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion.

Biohist-LA *Ivax, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Formerly contained carbinoxamine maleate and pseudoephedrine hydrochloride.
Cold symptoms.

Bio-H-Tin *Bio-H-Tin, Austria; Bio-H-Tin, Ger.; e+b, Hung.†; Gebro, Switz.*
Biotin (p. 2052·2).
Biotin deficiency; hair and nail disorders.

Biohulin C *Novo Nordisk, Arg.*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Biohulin N *Novo Nordisk, Arg.*
⊗Protamine zinc insulin (human) (p. 475·3).
Diabetes mellitus.

Biohulin NPH *Biobras, Braz.†*
⊗Isophane insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Biohulin Regular *Biobras, Braz.†*
⊗Insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Bioinsugen-30/70 *Biosano, Chile.*
⊗A mixture of insulin injection (human recombinant) 30% and isophane insulin (human, recombinant) 70% (p. 475·3).
Diabetes mellitus.

Bioinsugen-N *Biosano, Chile.*
⊗Isophane insulin (human, recombinant) (p. 475·3).
Diabetes mellitus.

Bioinsugen-R *Biosano, Chile.*
⊗Insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

Bioiodine *Bioceuticals, UK.*
Potassium iodate (p. 2336·3).

Biojara *Bioresearch, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Biojoint *Elfin, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Bio-K+ *Bio-K Plus, Canad.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3).
Maintenance of gastrointestinal flora.

Biokacin *Rayere, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Biokadin *Biokan, Turk.*
Povidone-iodine (p. 1767·1).
Oral hygiene; skin disinfection; vaginal infections.

Biokid *Medikon, Indon.†*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

BioKlot
Note: this name may be used for preparations of different composition.
Biopharma, Ukr.
A factor VIII preparation (p. 1148·1).
Factor VIII deficiency; von Willebrand's disease.

Bioklysm *Biospray, Gr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Biokonik *Apotex, Mex.*
Vitamins; minerals.

Bioksil *Gunsa, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bio-Kult Candea *Probiotics, Hong Kong; Probiotics, Singapore.*
Grapefruit seed; garlic (p. 2510·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Bifidobacterium breve* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Dietary supplement; maintenance of gastrointestinal flora.

Biol *Lek, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Biol Preo *Biol, Arg.*
Escherichia coli; Staphylococcus aureus; alpha haemolytic streptococcus; *Streptococcus pyogenes;* non-haemolytic streptococcus; *Enterococcus faecalis* (p. 2596·3); *Streptococcus pneumoniae; Klebsiella pneumoniae; Moraxella catarrhalis; Pseudomonas aeruginosa.*
Respiratory-tract infections.

Biolactine *Sella, Ital.*
Vitamin B substances (p. 2102·3); lactic-acid-producing organisms (p. 2596·3); myrtillus (p. 2566·2).
Nutritional supplement.

Biolactona *Bioresearch, Mex.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema.

Biolactos *Gelcaps, Mex.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of gastrointestinal flora.

Biolactus *Rider, Chile.*
Lactobacillus rhamnosus (p. 2596·3).
Diarrhoea.

Biolactyl *DB, Fr.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* var *rhamnosus* (p. 2596·3).
Maintenance of gastrointestinal flora.

Biolage Scalptherapie *Matrix, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Biolaif *Medix, Mex.*
⊗Prasterone (p. 2299·2).
Tonic.

Biolan *Santen, Ger.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Biolane *Prater, Chile.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Biolanz *Biogalenic, Venez.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Biolastic T5 *Dermofarma, Ital.*
Trealosio; hyaluronic acid (p. 2526·2); soya isoflavones (p. 2620·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1); filagrinol; amminoefaderma; enoxolone (p. 54·2); salicylic acid (p. 1719·1); allantoin (p. 1693·1); sunscreens.
Emollient.

Biolastin *Ikapharmindo, Indon.*
Collagen (p. 2483·2); hydrolastan.
Aid in maintaining skin elasticity.

Biolax
Note: this name may be used for preparations of different composition.
Beacons, Singapore; Chatfield Laboratories, UK.
Bisacodyl (p. 1821·1).
Constipation.

SupHerb, Israel.†
Ispaghula (p. 1849·1); sorbitol (p. 2092·1); fructo-oligosaccharides (p. 2508·1).
Constipation.

Biolax Protect *SupHerb, Israel.*
Ispaghula (p. 1849·1); sorbitol (p. 2092·1); fructo-oligosaccharides (p. 2508·1); thea sinensis (p. 2648·2).
Constipation.

Biolectra Magnesium *Genesis, Turk.*
Magnesium oxide (p. 1857·3).

Biolectra Magnesium 240 *Hermes, Ger.*
Magnesium oxide (p. 1857·3).
Muscular disorders associated with magnesium deficiency.

Biolectra Magnesium 365 *Hermes, Ger.*
Magnesium carbonate (p. 1856·2); magnesium oxide (p. 1857·3).
Magnesium deficiency.

Biolectro Zink *Hermes, Ger.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Biolergy *Konimex, Indon.†*
Mebhydrolin napadisilate (p. 634·2).
Allergic disorders; rhinitis; insect bites; urticaria.

Bioleukin *Arterium, Ukr.*
Interleukin-2 (p. 810·1).
Sepsis; tuberculosis; renal cell carcinoma.

Biolev *Ind Biosciences, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Rider, Chile.
Bicalutamide (p. 749·1).
Prostatic cancer.

Biolex *Cubit, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Biolfalic *Biol, Arg.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects.

Biolid *Bioresearch, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Rovi, Spain.
Ispaghula (p. 1849·1).
Constipation; diarrhoea.

Biolina *Bioceuticals, UK.*
Spirulina (p. 2622·1).

Biolincom *Otto, Indon.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Biolipe *BioSaude, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Biolite *Biosciences Pharmakon, India.*
Cyclomethicone (p. 2209·2); kojic acid (p. 1710·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Biolix *Bioresearch, Mex.*
Domperidone (p. 1838·1).
Dyspepsia.

Bio-Loba *Intra-Labs, India.*
Ginkgo biloba (p. 2512·3); vitamin E (p. 2119·1).

Bio-Logos *Sigma-Tau, Switz.*
Hydroxocobalamin (p. 2107·3); amino acids.
Tonic.

Biolon *Laboratorios Chile, Chile; Stulln, Ger.†; Pharmanel, Gr.; Biotechnology, Israel; Cryopharma, Mex.; Pharmafrica, S.Afr.†; Abdi, Turk.*
Sodium hyaluronate (p. 2526·2).
Aid in ophthalmic surgery.

Biolone
Note: this name may be used for preparations of different composition.
Ind Biosciences, India.
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Pharmafrica, S.Afr.
Sodium hyaluronate (p. 2526·2).
Aid in eye surgery.

Biolorat *Technobio, Mex.; Biogalenic, Venez.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; hypersensitivity.

Biolutam *Biotenk, Arg.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Biolyse *Key Oncologics, S.Afr.*
Paclitaxel (p. 839·3).
Breast cancer; non-small cell lung cancer; ovarian cancer.

Biolysin *Bernofarm, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3).
Vitamin supplement.

Biolysin Smart *Bernofarm, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3); arachidonic acid (p. 2446·1); docosahexaenoic acid (p. 1460·1).
Vitamin supplement for children.

Biolytan *Bioresearch, Mex.*
Disopyramide (p. 1363·2).

Bio-Lyte ORS *Intra-Labs, India.*
Ascorbic acid (p. 2110·3); calcium lactate (p. 1784·1); glucose (p. 2068·3); *Lactobacillus acidophilus* (p. 2596·3); magnesium sulfate (p. 1787·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Biomab EGFR *Biocon, India.*
Nimotuzumab (p. 836·3).

Biomac *Genesis, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Biomac-D *Genesis, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Biomag
Note: this name may be used for preparations of different composition.
Ache, Braz.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Baliarda, Arg.
Magnesium pidolate (p. 1787·3).
Magnesium supplement.

Boniscontro & Gazzone, Ital.
Cimetidine (p. 1827·1).
Gastrointestinal hyperacidity; oesophagitis; peptic ulcer; Zollinger-Ellison syndrome.

Lehning, Fr.
Magnesia muriatica (p. 1787·1); magnesia bromata (p. 1786·3); magnesia phosphorica (p. 1787·3); plumbum metallicum (p. 2541·3); kalium phosphoricum (p. 1790·3); ambra grisea (p. 2440·3).
Homoeopathic preparation.

Lehning, Canad.†
Ambra grisea (p. 2440·3); kalium phosphoricum (p. 1791·1); magnesii chloras (p. 1787·1); magnesii phosphas (p. 1787·3); magnesii stearate (p. 2195·3); plumbum metallicum (p. 2541·3).
Homoeopathic preparation.

Sanofi-Aventis, Pol.†
Magnesium lactate (p. 1787·2).
Magnesium deficiency.

Biomag Vital *Baliarda, Arg.*
Levocarnitine (p. 2053·2); magnesium pidolate (p. 1787·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Tonic.

Biomagnesin *Madaus, Ger.*
Dibasic magnesium phosphate (p. 1786·3); dibasic magnesium citrate (p. 1857·1).
Magnesium deficiency.

Bioman *T Man, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Bio-Maple *Kamins, Canad.†*
Cream SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Kamins, Canad.†
Lotion SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Bio-Maple Sunbar *Kamins, Canad.†*
SPF 15: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kamins, Canad.†
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Biomaterna *Biogalenic, Venez.*
Vitamins; minerals.
Dietary supplement in pregnancy.

Biomax Kid *Biofarma, Mex.*
Vitamins; echinacea (p. 2498·1).

BiOmega
Note: this name may be used for preparations of different composition.
Usana, Malaysia.†
Fish oil (p. 1460·1); natural tocopherols.
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Biomega
Note: this name may be used for preparations of different composition.
Usana, Mex.
Fish oil (p. 1460·3).
Usana, Singapore.†
Fish oil (p. 1460·1); colecalciferol (p. 2113·1).
Dietary supplement.
Graha, Indon.†
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis.

Biomega-3
Note: this name may be used for preparations of different composition.
Usana, Hong Kong.†
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); omega-3 triglycerides (p. 1460·1).
Fatty acid supplement.

Bio-Melatonin *Pharma Nord, Hung.*
Melatonin (p. 2551·3).
Regulation of sleep-wake cycle.

Biomelox *Biogalenic, Venez.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Bioment *Fako, Turk.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Biomers *Micrylium, Canad.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Disinfection.

Biomesina *Biomep, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Biomesina Compuesta *Biomep, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm and pain.

Biomet *Merck, Thai.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2).
Bone cement for orthopaedic surgery.

Biomet Bone Cement R *Biomet, Ger.*
Methylmethacrylate/methacrylate copolymer (p. 2558·2).
Bone cement for orthopaedic surgery.

Biomet Plus Bone Cement *Biomet, Ger.†*
Methylmethacrylate/methacrylate copolymer (p. 2558·2).
Bone cement for orthopaedic surgery.

Biometacin *Bioresearch, Mex.*
Indometacin (p. 71·2).
Rheumatism.

Biometrix *Schering-Plough, Mex.†*
Vitamins; minerals; ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).

Biometrox *Biosintetica, Braz.*
Methotrexate sodium (p. 822·2).
Malignant neoplasms.

Biomex *Actavis, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; vomiting of pregnancy; anaemias; neuralgia; liver disorders.

Biomic *Dr Kumars, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Biomicin *Pasteur, Chile.*
Clindamycin (p. 269·3).
Bacterial vaginal infections.

Bio-Milk *Intra-Labs, India.*
Oral powder: Preparation for enteral nutrition.
Intra-Labs, India.
Tablets: Calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).

Biomin H *Biomin, Cz.*
Calcium (p. 1783·1); magnesium (p. 1786·3); phosphorus (p. 2589·2); trace elements.
Mineral supplement.

Biomineral *Biochimici, Ital.*
Minerals; cystine (p. 2059·1).
Nutritional supplement.

Biomineral 5-Alfa *Biochimici, Ital.*
Cucurbita oil (p. 2489·2); soya oil (p. 2092·3); evening primrose oil (p. 2502·2); zinc-rich yeast (p. 2125·2); green tea (p. 2648·2); biotin (p. 2052·2).
Nutritional supplement; seborrhoea; thinning hair.

Biomineral 5-Alfa Shampoo *Biochimici, Ital.*
Green tea (p. 2648·2); biotin (p. 2052·2); pyridoxine (p. 2105·3); keratin (p. 2538·1); collagen (p. 2483·2); panthenol (p. 2582·2).
Seborrhoeic scalp disorders.

Biomineral Donna *Rottapharm, Ital.†*
Amino acids; minerals; vitamins; millet; cimicifuga (p. 2478·1); Steromax (palm oil phytosterol).
Nutritional supplement for menopausal women.

Bio-Mineral Formula *Blackmores, Austral.†*
Minerals.

Biomineral One *Biochimici, Ital.*
Vitamins; minerals; cystine (p. 2059·1); methionine (p. 1558·2).

Biomineral Plus *Biochimici, Ital.*
Vitamins; minerals; cystine (p. 2059·1); methionine (p. 1558·2).
Nutritional supplement.

Biomineral Unghie *Biochimici, Ital.*
Amino acids; vitamins; minerals.
Nail disorders.

Biominol *Alter, Spain.*
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Biominol A D *Alter, Spain.†*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Deficiency of vitamins A and D.

Biomira *Ingens, Arg.†*
Ketotifen (p. 631·3).
Allergic eye disorders.

Biomisen *Bioresearch, Mex.*
⊗Furosemide (p. 1387·1).

Biomist *Biodeal, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Biomitin *Bioresearch, Mex.*
Difenidol (p. 1835·1).
Nausea and vomiting; vertigo.

Biomix *Oriental, Philipp.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3); histidine hydrochloride (p. 2072·1); methionine (p. 1558·2); taurine (p. 2626·2); glucose (p. 2068·3).
Nutritional supplement.

Biomoist *Ikapharmindo, Indon.*
Moisturiser.

Biomo-lipon *Biomo, Ger.†*
Thioctic acid (p. 2629·1) or ethylenediamine thioctate (p. 2629·1).
Diabetic polyneuropathy.

Biomona *Bioresearch, Mex.*
Metronidazole (p. 936·1).
Vaginitis.

Biomoxil *Biochem, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Biomoxil-LB *Biochem, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Biomunil *Lusofarmaco, Ital.*
Klebsiella pneumoniae ribosomes and membrane fraction; *Streptococcus pneumoniae* ribosomes; *Streptococcus pyogenes* ribosomes; *Haemophilus influenzae* ribosomes.
Immunostimulant.

Biomunyl uno *Pierre Fabre, Ger.†*
Ribosomal fraction from *Klebsiella pneumoniae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Haemophilus influenzae*; membrane fraction from *Klebsiella pneumoniae.*
Respiratory-tract infections.

Biomycetin
Note: this name may be used for preparations of different composition.
JRalph, Philipp.
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.
Juggat, India.
Benzocaine (p. 1980·2); chloramphenicol (p. 257·1).
Bacterial ear infections.

Bion 3 *Merck, Chile.*
Lactobacillus gasseri (p. 2596·3); *Bifidobacterium bifidum*; *Bifidobacterium longum* (p. 2596·3); vitamins; minerals.
Dietary supplement.
Merck, Indon.; Merck Consumer, Singapore.†
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); vitamins; minerals; trace elements.
Dietary supplement.

Bion 3 Adultes *Merck Medication Familiale, Fr.*
Vitamins; minerals; *Lactobacillus gasseri* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Tonic.

Bion 3 Kid *Merck, Ukr.*
Vitamins; minerals; *Lactobacillus gasseri* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Dietary supplement.

Bion Restore *Merck Medication Familiale, Fr.*
Lactobacillus gasseri (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); vitamin C (p. 2110·3); zinc (p. 2126·1); histidine (p. 2072·1).
Tonic.

Bion 3 Seniors *Merck Medication Familiale, Fr.*
Vitamins; minerals; *Lactobacillus gasseri* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); ginseng (p. 2513·3); lutein (p. 2079·2); myrtillus (p. 2566·2).
Tonic.

Bion Tears *Alcon, Austral.; Alcon, Canad.; Alcon, China; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Singapore; Alcon, Swed.; Alcon, Thai.†; Alcon, USA.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Bion Transit *Merck, Chile; Merck Medication Familiale, Fr.*
Lactobacillus plantarum (p. 2596·3).
Maintenance of gastrointestinal flora; irritable bowel syndrome; digestive disorders.

Bionac *Ultramark, India.*
Diclofenac sodium (p. 48·3).
Pain.

Bionac-Forte *Ultramark, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Bionafil *Bioresearch, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Bionagre plus E *Bio-Sante, Canad.†*
Linoleic acid (p. 2509·2); linolenic acid (p. 1460·2); vitamin E (p. 2119·1).

Bionam *Ethica, Indon.*
Shorea robusta; azadirachta (p. 2451·2); pongamia pinnata; senna tora; ficus infectoria; liquorice (p. 1853·2); jasad bhasma; celastrus paniculatus.
Minor wounds.

Bionaryl *Bioresearch, Mex.*
Diphenhydramine (p. 626·1).
Hypersensitivity.

Bionasole *Bionasole, Ger.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); zinc acetate (p. 2126·1).
Nasal congestion.

Bionder-C *Bioresearch, Mex.*
Clioquinol (p. 273·1).
Skin infections.

Bioneb *Taiwan, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Bionect *Combiphar, Indon.; Fidia, Indon.*
Hyaluronic acid (p. 2526·2).
Skin irritation; wounds; barrier preparation; burns; ulcers.
CSC, Austria; Innocutis, USA.
Sodium hyaluronate (p. 2526·2).
Wounds; burns; facial wrinkles and folds.

Bionefrol *Amnol, Ital.*
Potassium citrate (p. 1780·3); magnesium citrate (p. 1857·1); niruri (p. 2590·1); bearberry (p. 2453·2).
Renal calculi.

Bionel *Advanced Generic, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Bionemi *Gracia, Indon.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemia during pregnancy and lactation.

Bioness *Bioresearch, Mex.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Bionet *Church & Dwight, Canad.*
Benzocaine (p. 1980·2); cetalkonium chloride (p. 1741·3).
Mouth and throat disorders.

Bioneuril *Bioresearch, Mex.*
Carbamazepine (p. 512·2).
Epilepsy.

Bioneuron *Phapros, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Neurological disorders; joint disorders; vitamin B deficiency; vomiting of pregnancy.

Bionicard *Rottapharm, Ital.*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension.

Bionike *ICIM, Singapore.†*
Skin cleanser.

Bio-Nim *Bio-Drug, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Bionit *Technobio, Mex.*
Nitazoxanide (p. 942·2).
Amoebiasis; trichomoniasis; lambliasis; worm infections.

Bionobal *Bioresearch, Mex.*
Hydralazine (p. 1401·2).
Hypertension; oedema.

Bionokaltran *Bioresearch, Mex.*
Calcium (p. 1783·1).
Calcium deficiency.

Bionol *Bioresearch, Mex.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Bionolip *Bioresearch, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bionolyte *Fresenius Kabi, Fr.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Bionorm
Note: this name may be used for preparations of different composition.
KVZ, Ukr.
Dietary fibre.
Gastrointestinal disorders.

Bionovium *Chrispa (Χρισπα), Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Bionoxol *Bioresearch, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract disorders.

Bionutrin *Great Eastern, Thai.†*
Vitamins; minerals.

Bionutrion *Mugi, Indon.*
Vitamin B substances (p. 2102·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1); calcium hypophosphite (p. 2530·3); lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Bio-Oil *Aspen, Austral.*
PurCellin Oil (Vitamin A (p. 2098·3); vitamin E (p. 2119·1); calendula oil (p. 2465·2); lavender oil (p. 2541·1); rosemary oil (p. 2607·3); chamomile oil (p. 2474·1)).
Scars; stretch marks; dry skin.
Union-Swiss, Malaysia.
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); calendula oil (p. 2465·2); lavender oil (p. 2541·1); rosemary oil (p. 2607·3); chamomile (p. 2474·1); cetearyl octanoate (PurCellin oil).
Scars; stretch marks; uneven skin tone.

Biopafen *Bioresearch, Mex.*
Propafenone (p. 1477·3).
Arrhythmias.

Biopain *Nestor, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Biopank *Kee, India.*
⊗Pancreatin (p. 2579·3).
Digestive disorders.

Biopar *Biomax, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Bioparox *Servier, Cz.; Servier, Hung.; Servier, Pol.; Egis-Servier, Rus.; Servier, Ukr.*
Fusafungine (p. 302·1).
Respiratory-tract infections.

Biopatch *Johnson & Johnson, Ital.*
Hydrophilic polyurethane dressing (p. 1718·1); chlorhexidine gluconate (p. 1743·3).
Wounds.

Johnson & Johnson Medical, USA.
Chlorhexidine gluconate (p. 1743·3).
Wound dressing.

Biopause *Monin, Fr.*
Soya bean (p. 2092·3); magnesium lactate (p. 1787·2); yam (p. 2648·1).
Menopausal disorders.

Biopaxel *Biosintetica, Braz.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Biopeg *Fresenius Kabi, Fr.*
Macrogol (p. 2547·3) in electrolytes.
Bowel evacuation.

Bio-Pen *Biotech, S.Afr.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Biopensyn *Biomedis, Indon.†; Medifarma, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Biopental *OM, Port.*
Lysates of *Streptococcus pneumoniae; Moraxella catarrhalis; Staphylococcus aureus; Klebsiella pneumoniae; Haemophilus influenzae; Streptococcus pyogenes.*
Respiratory-tract infections.

Biopep-D *Bionet, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Bioperazone *Biopharma, Ital.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Biophase *Ecofarm, Ital.*
Soap substitute.

Biophase Complex *Ecofarm, Ital.†*
Cysteine (p. 2058·3); ascorbic acid (p. 2110·3); methionine (p. 1558·2); troxerutin (p. 2505·3); *dl*-alpha tocoferil acetate (p. 2119·2); thioctic acid (p. 2629·1); borage oil (p. 2459·2).
Dietary supplement.

Biophase Shampoo *Ecofarm, Ital.*
Piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); cinnamon (p. 2479·2); clove (p. 2481·2); gaultheria procumbens.
Seborrhoeic scalp disorders.

Biophase Zinco Amidata *Ecofarm, Ital.†*
Barrier preparation.

Biophen *Biokem, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Biophenicol *Biochem, India.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Biophenox *United Biotech, India.*
Phenoxybenzamine (p. 1468·1).
Shock.

Biopiel *Mediderm, Chile.*
Poliglusam (p. 2593·2); portulaca oleracea; panthenol (p. 2582·2); lactic acid (p. 2539·1); polyaminopropyl biguanide (p. 1766·1).
Burns; dermal abrasion; skin irritation.

Biopime *Biochem, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Biopin *Biopin, Rus.*
Pine resin (p. 2484·2).
Burns; ulcers; skin disorders; wounds; musculoskeletal, joint, and soft-tissue disorders.

Bioplacenton *Kalbe, Indon.*
Neomycin sulfate (p. 330·1); placenta extract (p. 2444·1).
Burns; ulcers; wounds; skin infections.

Bioplacenton Tulle *Kalbe, Indon.*
Calcium alginate (p. 1136·3).
Wounds.

Bioplak *Ern, Spain.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Bioplasma FDP *NBI, S.Afr.*
⊗Plasma protein fraction (p. 1159·2).
Fluid depletion; haemorrhagic disorders.

Bioplatinex *Biogalenic, Venez.*
Carboplatin (p. 759·1).
Ovarian cancer; small cell lung cancer; head and neck cancer.

Bioplazma *Biosel, Turk.†*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion.

Bioplex
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Ital.†
Amino acids.
Parenteral nutrition.

Bioplus
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Caffeine (p. 1203·3); vitamins; calcium (p. 1783·1).
Tonic.

Hertz, Braz.
Ginseng (p. 2513·3).

Biopoin *Teva, Cz.; Teva, Ger.; CT, Irl.; Teva, Neth.; CT, Pol.; CT, Port.*
⊗Epoetin theta (p. 1141·2).
Anaemias.

Bioposide *Biochem, India.*
Etoposide (p. 790·2).
Malignant neoplasms.

Biopram *Bioresearch, Mex.*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Bioprazol *Biofarm, Pol.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Bioprexum *Servier, Indon.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; cardiovascular risk reduction.

Bioprexum Plus *Servier, Indon.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Biopril *Biochem, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Biopril AM *Biochem, India.*
Lisinopril (p. 1420·3); amlodipine besilate (p. 1304·1).
Hypertension.

Bioprim *Norma (Νορμα), Gr.; Bioresearch, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Biopro *Morepen, India.*
Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

Bioprol *Bioresearch, Mex.*
⊗Metoprolol (p. 1434·3).
Hypertension.

Bioprom *Otto, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Bioprost *Indofarma, Pol.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Intelpharm, Rus.
Cucurbita oil (p. 2489·2); thymol (p. 1772·2).
Prostatitis; benign prostatic hyperplasia.

Bio-Prot *Hoch Wertig, Arg.*
Whey protein (p. 2125·2).
Dietary supplement.

Bioprotect *Grossman, Mex.*
Vitamins; minerals.

Bio-Protection *Lise Watier, Canad.†*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Bioprotus *Carrare, Fr.*
Lactic-acid-producing organisms (p. 2596·3).
Maintenance of gastrointestinal flora.

Bioproxe *Biocin, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Biopsol *Drugtech, Chile.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Bioptan *Biofarma, Turk.†*
Propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain.

Biopten *Daiichi Sankyo, Jpn.*
Sapropterin hydrochloride (p. 2610·2).
Hyperphenylalaninaemia.

Bioptic *Bausch & Lomb, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Bioptic DX *Bausch & Lomb, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Bioptimum *Boiron, Port.†*
Amino acids.

Biopulmin *Grunenthal, Chile.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Bioquel *Biotecnoquimica, Venez.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Bioquidan *Bioresearch, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Bioquil *Atral, Port.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bioquin
Note: this name may be used for preparations of different composition.
Ikapharmindo, Indon.
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Lafi, Chile.
Erythromycin ethyl succinate (p. 291·2); sulfafurazole (p. 364·1).
Bacterial infections.

Bio-Quinone *Pharma Nord, Malaysia; Pharma Nord, Thai.; Pharma Nord, UK.*
Ubidecarenone (p. 2637·1).
Cardiovascular disorders; co-enzyme Q_{10} deficiency.

Bioquinone *Puspa, Indon.*
Ubidecarenone (p. 2637·1); levocarnitine (p. 2053·2); vitamin E (p. 2119·1).
Dietary supplement.

Bioracef *Polpharma, Pol.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Biorag *Ecofarm, Ital.*
Beta-glucan (p. 2455·2); dipotassium glycyrrhizate (p. 2520·3); panthenol (p. 2582·2).
Cracked nipples.

Bioral *Smith & Nephew, Austral.†*
Carbenoxolone sodium (p. 1825·3).
Mouth ulcers.

Bioralgin *Biopharma, Rus.*
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Smooth muscle spasm; pain.

Bioralin *Bioresearch, Mex.*
⊗Chlortalidone (p. 1335·2).
Heart failure; hypertension.

Bioran
Note: this name may be used for preparations of different composition.
Bioresearch, Mex.
Methenamine (p. 322·3).
Urinary-tract infections.

Rusan, India; Rusan, Rus.
Diclofenac sodium (p. 48·3).
Inflammation; pain; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Biorazon *Otto, Indon.*
Cefoperazone (p. 243·1).
Bacterial infections.

Biordyn *Bioresearch, Mex.*
Isosorbide dinitrate (p. 1412·2).

Biore Nourish *Kao, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Biorenyn *Bioresearch, Mex.*
⊗Salbutamol (p. 1220·2).
Asthma.

Bioretic *Jinling, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Bioretin *Medikon, Indon.†*
⊗Betacarotene (p. 2051·1); myrtillus (p. 2566·2); tribulus terrestris (p. 2633·3).
Dietary supplement for eye health.

Biorevit Gel *DNR, Arg.*
Aloe vera (p. 1693·2).
Skin disorders.

Biorevit Labial *DNR, Arg.*
Oxybenzone (p. 1715·3).

Biorevit Solar 15 *DNR, Arg.*
Titanium dioxide (p. 1725·1); aminobenzoic acid (p. 1694·2).
Sunscreen.

Biorex *JK Biochem, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Biorgan
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Biorgan B *Ivax, Arg.*
Trimebutine maleate (p. 2634·1); bromazepam (p. 1041·2).
Gastrointestinal disorders.

Biorganic Geri *Gisand, Switz.*
Vitamins; minerals; amino acids; ginseng (p. 2513·3).
Dietary supplement; tonic.

Biorganic Omega-3 *Gisand, Switz.*
Omega-3 marine triglycerides (p. 1460·3).
Hyperlipidaemia; dietary supplement.

Biorgasept *Biorga, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin and wounds; skin infections.

Biorinil *Farmila, Ital.*
⊗Betamethasone (p. 1623·2); tetryzoline hydrochloride (p. 1678·3).
Rhinitis; sinusitis; rhinopharyngitis.

Biorisan *Vocate, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Biorostan *Arterium, Ukr.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure.

Biorox *Biochem, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Biorphen *Alliance, UK.*
Orphenadrine hydrochloride (p. 909·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Biorrub *Biosintetica, Braz.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Biortan *Biogalenic, Venez.*
Losartan potassium (p. 1422·2).
Heart failure; hypertension.

BiOrto Al-C *Bioforce, Denm.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Dietary supplement.

BiOrto B1 *Bioforce, Denm.*
Thiamine nitrate (p. 2103·2).
Thiamine deficiency.

BiOrto B6 *Bioforce, Denm.*
Pyridoxine hydrochloride (p. 2105·3).
Pyridoxine deficiency.

BiOrto Pantothensyre *Bioforce, Denm.*
Calcium pantothenate (p. 2085·2).
Pantothenic acid deficiency.

BiOrto Total B *Bioforce, Denm.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

BiOrto Zink *Bioforce, Denm.*
Zinc gluconate (p. 2126·2); zinc picolinate (p. 2126·1).
Zinc deficiency.

Biorubina *IBA, Pol.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Bios Life *Unicity, Singapore.*
Guar gum (p. 475·1); acacia (p. 2166·1); ceratonia (p. 2178·1); pectin (p. 2200·3); oat fibre; vitamins; phytosterols (p. 1471·2); calcium carbonate (p. 1824·3); beta-glucan (p. 2455·2); chrysanthemum morifolium; policosanol (p. 1472·1); zinc gluconate (p. 2126·2); selenium yeast (p. 2125·2); chromium yeast (p. 2125·2).
Dietary supplement.

Bio-Safe *Biotech Transfer, Canad.*
Triclosan (p. 1773·2).

Biosal Arthritis *Yauyip, Austral.†*
Thurfyl salicylate (p. 137·1); methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1).
Arthritis.

Bio-San *West Penetone, Canad.*
Didecyldimethylammonium chloride (p. 1750·3).
Disinfection.

Biosanbe *Sanbe, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); intrinsic factor (p. 2534·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Bioscal *Chemica, Gr.*
Acetylcysteine (p. 1652·2).

Bioscalin *Giuliani, Ital.*
Vitamins; minerals.
Hair and nail disorders.

Bioselac *Rottapharm, Ukr.*
Lactobacillus rhamnosus (p. 2596·3).
Vaginal disorders.

Bio-Sélénium *Boiron, Fr.†*
Selenium (p. 2086·3) from *Saccharomyces cerevisiae*; alpha tocoferil acetate (p. 2119·2); wheat-germ oil (p. 2647·1).
Skin disorders; muscular disorders.

Bioselenium
Note: this name may be used for preparations of different composition.
Uriach, Spain.
Selenium sulfide (p. 1719·3).
Skin and scalp disorders.

Bio-Selenium Zinc *Pharma Nord, Thai.*
Vitamins; selenium (p. 2086·3); zinc (p. 2126·1).
Selenium and zinc deficiencies.

Biosemida *Biogalenic, Venez.*
⊗Furosemide (p. 1387·1).

Biosept *Biospray, Gr.†*
Hydrogen peroxide (3 per cent) (p. 1755·2).

Biosera *Panjon, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Biosetron *Medicus, Gr.*
Ondansetron hydrochloride (p. 1872·1).

BioSil *Bio Minerals, Philipp.†*
⊗Silicon dioxide (p. 2208·3); choline (p. 2055·2); glycerol (p. 2517·2); water (p. 2646·2).
Silicon supplement.

Biosim *Biochem, India.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Biosin *Indkus, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Biosint *Liomont, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Bioskin *Biomedica, India.*
Aloe vera (p. 1693·2); chlorhexidine hydrochloride (p. 1743·3); vitamin E (p. 2119·1).

Bioson *Micrylium, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection.

Biosone *Foramen, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Biosonida *Biogalenic, Venez.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease; rhinitis.

Biosonide *Help, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps; skin disorders; asthma.

Bio-Sorb *Johnson & Johnson, India.*
Starch (p. 2095·1).

Biosorb *Nutricia, Turk.†*
A range of preparations for enteral nutrition.

Biosotal *Sanofi-Aventis, Pol.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Biosoviran *Bioprogress, Ital.†*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Biospasmil *Biomed Lublin, Pol.†*
Papaverine hydrochloride (p. 2362·3); belladonna (p. 2453·3).
Smooth muscle spasm.

Biospec DMX *Deliz, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Biospirin *Biochem, India.*
Glycine (p. 2071·2); lysine aspirin (p. 84·3).
Pain; fever.

Biospore *Biosciences Pharmakon, India.*
Itraconazole (p. 583·3).
Fungal infections.

Biosporin *CRI, Rus.; Biopharma, Ukr.*
Bacillus subtilis; Bacillus licheniformis.
Restoration of intestinal flora; gastrointestinal infections; vulvovaginal infections; restoration of gastrointestinal flora.

Biospot *Hydrachem, Singapore.*
Troclosene sodium (p. 1774·1).

Biostan *Bioresearch, Mex.*
Astemizole (p. 616·1).

Bio-Star *Novag, Spain.†*
Ginseng (p. 2513·3).
Tonic.

Biostar *Micro, India.*
Vitamin B substances (p. 2102·3); zinc (p. 2126·1); ginseng (p. 2513·3).
Tonic.

Bio-Stat
Note: this name may be used for preparations of different composition.
Invision, India.
Tranexamic acid (p. 1164·2).
Haemorrhage.

Biostat
Note: this name may be used for preparations of different composition.
Biodeal, India.
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Biostate *CSL, Austral.; CSL Biotherapies, Hong Kong; CSL, NZ; CSL, Singapore.*
A factor VIII preparation (p. 1148·1).
Von Willebrand disease; haemophilia A.

Biostatik *Pharos, Indon.*
Roxithromycin (p. 356·2).
Bacterial infections.

Bio-Stat-MF *Invision, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Bi-Ostéo *Synergia, Fr.*
Omega-3 marine triglycerides (p. 1460·3); vitamins; minerals.
Dietary supplement.

Bioster *Terramedic, Philipp.†*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Biosteron *Lek-Am, Pol.*
⊗Prasterone (p. 2299·2).
Prasterone deficiency.

Biostim *Sanofi-Aventis, Braz.; Aventis, Cz.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Mex.*
Klebsiella pneumoniae glycoprotein (p. 2538·2).
Prophylaxis of respiratory-tract infection; ulcers; wounds; burns; adjunct to antibacterial therapy.

Biostimol *Zambon, Switz.*
Citrulline malate (p. 2056·3).
Asthenia.

Biostin
Note: this name may be used for preparations of different composition.
Bioresearch, Mex.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Teva, Hung.†
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Bio-Strath
Note: this name may be used for preparations of different composition.
Bio-Strath, Hung.; Indo Sehat, Indon.
Yeast (p. 2125·2).
Tonic.

CedarHealth, UK.
Saccharomyces cerevisiae (p. 2125·2).

Indo Sehat, Indon.
Liquid: Yeast (p. 2125·2); malt extract (p. 2080·2); honey (p. 2072·1); orange juice.
Tonic.

Bio-Strath Artichoke Formula *CedarHealth, UK.*
Cynara (p. 2490·3); thistle seeds (p. 2482·2); peppermint leaf (p. 1877·1); yeast plasmolysate (p. 2125·2).
Dyspepsia.

Bio-Strath Valerian Formula *CedarHealth, UK.*
Valerian (p. 2640·2); passion flower (p. 2584·1); peppermint leaf (p. 1877·1); yeast plasmolysate (p. 2125·2).
Tension; irritability; insomnia.

Bio-Strath Willow Formula *Cedar Health, UK.*
Salix (p. 129·2); primula root (p. 2596·2); yeast plasmolysate (p. 2125·2).
Musculoskeletal and joint pain.

Bio-Strep *Biotech, S.Afr.*
Streptomycin sulfate (p. 359·1).
Bacterial infections.

Biostrepta *Biomed, Ukr.*
Streptokinase (p. 1503·1); streptodornase (p. 2623·1).
Pelvic inflammation; endometriosis; haemorrhoids; rectal abscess and fistula.

Biostreptaza *Biomed Warszawa, Pol.*
Streptodornase (p. 2623·1); streptokinase (p. 1503·1).
Anorectal disorders; mouth and throat injury and inflammation.

Biostrogen *Biogalenic, Venez.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Biostrol *Polpharma, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Biostrum *Lapi, Indon.*
Bovine colostrum (p. 2380·3); docosahexaenoic acid (p. 1460·1); cod-liver oil (p. 2056·3); lysine hydrochloride (p. 2079·3); vitamins; zinc picolinate (p. 2126·1).
Nutritional supplement.

BioStym Balance *Aflofarm, Pol.*
⊗Prasterone (p. 2299·2).
Prasterone deficiency.

Biostymina *Phytofarm Kleka, Pol.*
Aloes (p. 1816·1).
Respiratory-tract infections; immunostimulant.

Biosufenil *Biochimico, Braz.*
⊗Sufentanil (p. 132·3).

Biosuganril *Piramal, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Biosulidd L *Biopharm, Philipp.*
⊗An insulin zinc injection (human) (p. 475·3).
Diabetes mellitus.

Biosulin 30/70 *Cipla-Medpro, S.Afr.*
⊗A mixture of soluble insulin injection (human, biosynthetic) 30% and isophane insulin injection (human, biosynthetic) 70% (p. 475·3).
Diabetes mellitus.

Biosulin L *Cipla-Medpro, S.Afr.*
⊗Insulin zinc suspension (human, biosynthetic) (p. 475·3).
Diabetes mellitus.

Biosulin N *Ufavita, Rus.; Cipla-Medpro, S.Afr.*
⊗Isophane insulin injection (human, biosynthetic) (p. 475·3).
Diabetes mellitus.

Biosulin R *Ufavita, Rus.; Cipla-Medpro, S.Afr.*
⊗Soluble insulin injection (human, biosynthetic) (p. 475·3).
Diabetes mellitus.

Biosure *Gentech, India.*
Biotin (p. 2052·2).

Biosurf *Micrylium, Canad.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Disinfection.

Bio-Taches *Sinclair, Singapore.†*
Azelaic acid (p. 1695·1); butylene glycol (p. 2172·2); hydrogenated coconut oil (p. 2179·3); apricot kernel oil (p. 2587·1); titanium dioxide (p. 1725·1); polyacrylamide (p. 2594·1) bitter orange (p. 2575·3); potassium azeloyl diglycinate; lactic acid (p. 2539·1); citric acid (p. 2480·3); malic acid (p. 2549·2); camellia sinensis (p. 2648·2); saxifraga sarmentosa; grape (p. 2521·3); morus bombycis; skullcap (p. 2617·1).
Melasma.

Bio-Taches Masque *Sinclair, Singapore.†*
⊗Polyvinyl alcohol (p. 2204·2); glycerol (p. 2517·2); kaolin (p. 1850·1); aluminium starch octenylsuccinate; polyacrylamide (p. 2594·1); C13-14 isoparaffin; butylene glycol (p. 2172·2); saxifraga sarmentosa; grape (p. 2521·3); morus bombycis; skullcap (p. 2617·1); levomenol (p. 2544·1); citrus nobilis oil; limonene; farnesol.
Melasma.

Biotad *Biomedica, Ital.*
Vitamin C (p. 2110·3); glutathione (p. 1555·2); thioctic acid (p. 2629·1); vitamin E (p. 2119·1).
Dietary supplement.

Biotaer an Caramelos *Investi, Arg.*
Bacitracin (p. 225·3); neomycin (p. 329·3); tyrothricin (p. 384·1).
Mouth and throat infections.

Biotaer Nasal *Investi, Arg.†*
⊗Framycetin sulfate (p. 301·2); gramicidin (p. 308·3); triamcinolone hexacetonide (p. 1649·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); naphazoline nitrate (p. 1669·3).
Nasal congestion.

Biotaer Nebulizable *Investi, Arg.*
⊗Nystatin (p. 590·3); beclometasone dipropionate (p. 1621·2); neomycin (p. 329·3); bacitracin (p. 225·3); tyrothricin (p. 384·1); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract disorders.

Biotaksym *Bioton, Pol.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Biotamoxal *Hexa, Arg.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Biota-P *Genesis, India.*
Amylase (p. 2442·1); fructo-oligosaccharides (p. 2508·1).
Digestive disorders.

Biotarson N *Ifusa, Mex.†*
⊗Hydrocortisone acetate (p. 1640·1); gramicidin (p. 308·3); neomycin (p. 329·3).
Bacterial nose infections.

Biotarson O *Ifusa, Mex.†*
⊗Naphazoline (p. 1669·3); gramicidin (p. 308·3); neomycin (p. 329·3).
Bacterial eye infections.

Biotase *YSP, Malaysia; Yung Shin, Singapore.*
Biodiastase (mixed digestive enzymes) (p. 2442·1); lipase (p. 2579·3); newlase.
Digestive disorders.

Biotassina *Teofarma, Ital.*
Amino acids; vitamin B substances (p. 2102·3); calcium gluconate (p. 1783·3). Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Asthenia.

Biotax *Biochem, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Tzamal, Israel.†
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small-cell lung cancer; Kaposi's sarcoma.

Biotaxel *Medicus, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Biotaxil *Mavi, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Biotax-O *Biochem, India.*
Cefixime (p. 240·3).
Bacterial infections.

Biotazol *Bioresearch, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis.

Biotebal *Polfa Warszawa, Pol.*
Biotin (p. 2052·2).
Biotin deficiency.

Biotecan *Biotenk, Arg.; Biosintetica, Braz.; Medicus, Gr.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Biotect Plus *Advanced Generic, USA.*
Minerals; vitamins; inositol (p. 2533·2); lysine (p. 2079·3).

Biotene *GSK, Singapore.*
Toothpaste: Glucose oxidase (p. 2516·3); lactoperoxidase (p. 2539·3); lactoferrin (p. 2539·3); muramidase (p. 2565·1); sodium monofluorophosphate (p. 2091·3).
Mouth disorders.

GSK, Singapore.
Mouthwash; dental gel; oral liquid: Glucose oxidase (p. 2516·3); lactoperoxidase (p. 2539·3); muramidase (p. 2565·1); lactoferrin (p. 2539·3).
Mouth disorders.

Laclede, Singapore.†
Chewing gum: Glucose oxidase (p. 2516·3); lactoperoxidase (p. 2539·3).
Mouth disorders.

Biotene with Calcium *Laclede, USA.*
Propylene glycol (p. 2205·2); hyetellose (p. 2188·3); aloe vera (p. 1693·2); zinc gluconate (p. 2126·2); calcium lactate (p. 1784·1); lactoferrin (p. 2539·3); muramidase (p. 2565·1); lactoperoxidase (p. 2539·3); glucose oxidase (p. 2516·3).
Dry mouth.

Biotene Dry Mouth *GSK, UK.*
Lactoperoxidase (p. 2539·3); glucose oxidase (p. 2516·3); lactoferrin (p. 2539·3); muramidase (p. 2565·1).
Dry mouth.

GSK, USA.
Sodium monofluorophosphate (p. 2091·3).

Biotene Oralbalance *GSK, UK.*
Lactoperoxidase (p. 2539·3); glucose oxidase (p. 2516·3); xylitol (p. 2220·3).
Dry mouth.

Bioteral *Northia, Arg.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Biotermin AS *Terramedic, Philipp.*
Vitamins; buclizine hydrochloride (p. 618·3).
Appetite stimulant; nutritional supplement.

Bio-Termin Plus with Lecithin *Terramedic, Philipp.*
Vitamins; lecithin (p. 2542·2); lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Biotest *Kansuk, Turk.*
⊗Albumin (p. 1130·2).

Biotext *Micrylium, Canad.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Disinfection.

Biotherm *Biotherm, Canad.†*
SPF 15; SPF 25; SPF 30: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Bio-Therm Pain Relieving Lotion *Weeks & Leo, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Biothicol *Sanbe, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Biothrax *Bioport, USA.*
An adsorbed anthrax vaccine (p. 2376·3).
Active immunisation.

Bio-Three *Jiuhui, China.*
Clostridium butyricum; Bacillus mesentericus; Enterococcus faecalis (p. 2596·3).
Restoration of gastrointestinal flora.

Bio-Throx *Bio-Drug, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Biothymus DS *Biochimici, Ital.*
Face wash: Levomenol (p. 2544·1); enoxolone (p. 54·2); piroctone olamine (p. 1716·3); salix (p. 129·2).
Seborrhoeic dermatitis.

Biochimici, Ital.
Scalp lotion: Piroctone olamine (p. 1716·3); urtica (p. 2639·3); salix (p. 129·2); salicylic acid (p. 1719·1); menthol (p. 2553·2).
Seborrhoeic dermatitis.

Biochimici, Ital.
Shampoo: Pyrithione zinc (p. 1718·1); dipotassium glycyrrhizate (p. 2520·3).
Seborrhoeic dermatitis.

Biothymus F *Biochimici, Ital.*
Paeonia suffruticosa.
Prevention of hair loss.

Biothymus M *Biochimici, Ital.*
Paeonia suffruticosa; saw palmetto (p. 2363·3).
Prevention of hair loss.

Biotic *TRB, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bioticaps *Richet, Arg.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Bioticic *PS, Ital.†*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Biotifen *Bioresearch, Mex.*
Ketotifen (p. 631·3).
Hypersensitivity; asthma.

Biotine *ICM, Singapore.*
Tetracycline hydrochloride (p. 373·2).
Skin infections.

Biotisan *Hubner, Fin.*
Biotin (p. 2052·2).
Biotin deficiency.

Bio-Tomosan *Hing Ah, Hong Kong.†*
⊗Amylase (p. 2442·1); lactobacillus (p. 2596·3); pepsin (p. 2586·1).
Digestive disorders.

Bioton
Note: this name may be used for preparations of different composition.
Mega Lifesciences, Thai.
Vitamins; minerals.
Vitamin and mineral deficiency.

Sella, Ital.
Honey (p. 2072·1); ginseng (p. 2513·3); royal jelly (p. 2608·1).
Nutritional supplement.

Biotone *Zambon, Fr.*
Kola (p. 2648·2); phosphoric acid (p. 2589·1); manganese glycerophosphate (p. 2519·2).
Tonic.

Biotone-TD *Ethix, India.*
Vitamins; ginseng (p. 2513·3).

Biotonus *Lafi, Chile.*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); ascorbic acid (p. 2110·3); minerals.

Biotrakson *Polpharma, Pol.; Bioton, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Biotrap *Aesculapius, Ital.*
Saccharomyces boulardii (p. 2596·3); white clay.
Diarrhoea; meteorism; restoration of gastrointestinal flora.

Biotrat *Biodeal, Thai.*
Zinc sulfate (p. 2126·2); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); chromium tripicolinate (p. 2056·1).
Vitamin and mineral supplement.

Biotredin
Note: this name may be used for preparations of different composition.
Biotiki, Rus.
Pyridoxine (p. 2105·3); threonine (p. 2098·2).
Mental function disorders; alcohol withdrawal syndrome.

Biotredine *Biomedica, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Biotrefon L *Italmex, Mex.*
Cobamamide (p. 2107·2).
Tonic.

Biotrefon Plus *Wyeth Consumer, Ital.*
Pollen (p. 2593·3); royal jelly (p. 2608·1); liver extract (p. 2444·1).

Biotrexate *Biochem, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Biotriamin *Sophia, Mex.†*
⊗Triamcinolone (p. 1648·3); polymyxin B (p. 342·3).
Skin disorders.

Biotriax *Sandoz, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Biotricina *Bioresearch, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Biotril *Bioresearch, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Biotril-s *Biolab, Thai.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Biotrivin *Bioresearch, Mex.*
Vitamin B substances (p. 2102·3).
Neuritis; vitamin B supplement.

BioTrombina *Biomed Lublin, Pol.*
Thrombin (p. 1163·2).
Haemorrhage.

Biotron *Adcock Ingram, S.Afr.*
Vitamins; minerals.

Biotropil *Biofarm, Pol.*
Piracetam (p. 393·3).
Mental function disorders; myoclonus.

Bio-Tropin *Biotechnology, Israel.*
⊗Somatropin (p. 1919·3).
Growth disorders in renal failure; growth hormone deficiency; Turner' syndrome.

Biotropin *Ivax, Arg.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome.

Biotrue Multi-purpose *Bausch & Lomb, USA.*
Solution for contact lens care.

Bio-TT *Bio Farma, Thai.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Biotum *Polpharma, Pol.; Bioton, Ukr.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Biotuss *Spitzner, Ger.†*
Thyme (p. 2630·2).
Respiratory-tract congestion.

Bio-Tussi *Advanced Generic, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Biotussil *Biomedica, Cz.*
Gentian (p. 2512·1); cowslip (p. 2596·2); plantaginis (p. 2604·2); sambucus (p. 2609·3); thyme (p. 2630·2); liquorice (p. 1853·2); fennel oil (p. 2503·3); star anise oil (p. 2622·2).
Respiratory-tract disorders.

Biovac *Micrylium, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection.

Biovac HB *Caif, Arg.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Biovac Typhoid *Wockhardt, India.*
A typhoid vaccine (Vi capsular polysaccharide) (p. 2422·2).
Active immunisation.

Biovac-A *Wockhardt, India.*
A hepatitis A vaccine (p. 2388·3).
Active immunisation.

Biovac-B *Wockhardt, India; Wockhardt, Rus.†*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Bio-Vagin *Elofar, Braz.*
Metronidazole benzoate (p. 936·1); nystatin (p. 590·3).
Gynaecological infections.

Bioval *Biochem, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Bioval-P *Biochem, India.*
Parecoxib (p. 119·3).
Postoperative pain.

Biovectrol Famille *Katadyn, Fr.*
Repellent 35/35 (p. 2154·3).
Insect repellent.

Biovectrol Naturel *Katadyn, Fr.*
Eucalyptus citriodora oil.
Insect repellent.

Biovectrol Tissu *Katadyn, Fr.*
Permethrin (p. 2159·3).
Insect repellent for fabrics.

Biovectrol Tropique *Katadyn, Fr.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Bioven Mono *Biopharma, Ukr.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; immune thrombocytopenia; Guillain-Barré syndrome; chronic inflammatory demyelinating neuropathy; myopathy; Wegener's granulomatosis; dermatomyositis; systemic connective tissue diseases; Kawasaki syndrome.

Bio-Venaphyt *Lyron, Switz.†*
Aesculus (p. 2431·2).
Venous insufficiency.

Biovent *Biomedis, Thai.†; Great Eastern, Thai.†*
⊗Salbutamol (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease; cough.

Biovicam *Bioresearch, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Biovicam Ex *Bioresearch, Mex.*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Biovigor
Note: this name may be used for preparations of different composition.
IBSA, Switz.
Hydroxocobalamin chloride (p. 2107·3); amino acids.
Tonic.

Biovinate *Biomedis, Philipp.*
Carboplatin (p. 759·1).
Ovarian cancer.

Biovir
Note: this name may be used for preparations of different composition.
GSK, Braz.
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Ivax, Arg.
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Bioviraz *Bioresearch, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Bio-Vis *Cielle, Ital.*
Carnitine (p. 2053·2).

Biovisc *Chauvin, Fr.†*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Biovision *Indofarma, Pol.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin B_2 (p. 2104·3); procyanidin (p. 2505·2).
Vascular eye disorders.

Biovit
Note: this name may be used for preparations of different composition.
Biospray, Gr.
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Biovit B2 *Union Drug, Thai.*
Riboflavin (p. 2104·3).
Vitamin B_2 deficiency.

Biovit B6 *Union Drug, Thai.*
Pyridoxine (p. 2105·3).
Vitamin B_6 deficiency.

Biovit-A *Bioceuticals, UK.*
Vitamin A (p. 2098·3).

Biovital
Note: this name may be used for preparations of different composition.
Bayer Consumer, Rus.
Vitamins; ferrous sulfate (p. 2062·2); crataegus (p. 2488·1); motherwort (p. 2564·2).
Vitamin and iron deficiency.

EMS, Braz.
Vitamins; minerals.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Micro, India.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc (p. 2126·1); ginseng (p. 2513·3).

Bayer, Pol.†
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); iron (p. 2073·1); manganese (p. 2081·2).
Tonic.

Famac, Ital.†
Royal jelly (p. 2608·1).
Nutritional supplement.

Biovital Ginseng *Bayer, Switz.*
Ginseng (p. 2513·3); caffeine (p. 1203·3); lecithin (p. 2542·2); rutoside sodium sulfate (p. 2505·2); vitamins; minerals.
Tonic.

Biovital N *Bayer, Pol.†*
Crataegus (p. 2488·1); motherwort (p. 2564·2); iron (p. 2073·1); vitamins.
Tonic.

Biovital Pro Q10 *Biotenk, Arg.*
Wine; ginkgo biloba (p. 2512·3).
Dietary supplement.

Biovite *Marching, Hong Kong.†*
Calcium (p. 1783·1); lysine (p. 2079·3); vitamins.

Biovitol-C *Bioresearch, Mex.*
Tretinoin (p. 1725·2).
Skin disorders.

Biovorin *Biochem, India.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Biowhey *Biomax, India.*
Preparation for enteral nutrition.

Bioxalyt *Bioresearch, Mex.*
Digoxin (p. 1353·3).

Bioxan *Bioresearch, Mex.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; inflammation.

Bioxel *Bioresearch, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Bioxetin *Sanofi-Aventis, Pol.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Bioxidol *Pharmathen, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation.

Bioxifeno *Biosintetica, Braz.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Bioxil *Biomep, Mex.*
Captopril (p. 1331·2).
Hypertension.

Bioxilina *Northia, Arg.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bioxilina Duo *Northia, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bioxilina Plus *Northia, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Bioximicina *Bioresearch, Mex.*
Doxycycline (p. 288·1).
Bacterial infections.

Bioximil *Bioresearch, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; inflammation.

Bioxine *Picco, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bioxon *Otto, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

BioXtra Programme *Pamex, Irl.*
Artificial saliva, toothpaste, and mouthrinse.
Dry mouth.

Bioxyllin *Biomedis, Indon.†; Medifarma, Indon.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Bioxyol *Richard, Fr.*
Zinc oxide (p. 1729·1); zinc peroxide (p. 1774·3); titanium dioxide (p. 1725·1).
Ulcers.

Bioyetin *Probiomed, Mex.*
⊗Erythropoietin (p. 1141·1).
Anaemias.

Bioz *Biocin, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Biozaar *Biological E, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Biozaar-AM *Biological E, India.*
Losartan potassium (p. 1422·2); amlodipine (p. 1304·1).
Hypertension.

Biozac *Niche, Irl.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Biozendi *Roemmers Osmoph, Venez.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders; inflammation.

Biozidima *Biogalenic, Venez.*
Ceftazidime (p. 250·2).
Bacterial infections.

Biozim *Otto, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Biozin *Biomedica, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Bio-Zinc *Herbaxt, Fr.†*
Zinc pidolate (p. 1720·3); vitamin A (p. 2098·3); vitamin B_6 (p. 2105·3).
Nutritional supplement.

Biozine *JK Biochem, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Biozirox *Aurora, Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Biozitra *BioSaude, Port.†*
Azithromycin (p. 221·2).
Bacterial infections.

Biozobid *Piramal, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Biozobid-N *Piramal, India.*
⊗Serrapeptase (p. 2613·3); nimesulide (p. 101·3).

Biozole *Biolab, Malaysia; Biolab, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Biozolin *Novartis, Gr.; Sandoz, Indon.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Biozoral *Bioresearch, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Bio-Zyme *Integrative, USA.*
⊗Trypsin (p. 2635·2); papain (p. 2582·3); bromelain (p. 2460·3); amylase (p. 2442·1); lipase (p. 2579·3); muramidase (p. 2565·1); chymotrypsin (p. 2477·3).
Digestive disorders.

Metagenics, Canad.†
⊗Pancreatin (p. 2579·3).

Biozyme *Indkus, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders.

BIP *Orion, Austral.*
Bismuth subnitrate (p. 1822·1); iodoform (p. 1758·2).
Wounds.

Bipasmin *Anchor, Mex.*
Tablets: Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm.

Anchor, Mex.
Oral drops: Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Bipasmin Compuesto *Anchor, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle pain and spasm.

Bipectinol *Adcock Ingram, S.Afr.†*
Kaolin (p. 1850·1); pectin (p. 2200·3); electrolytes (p. 1775·1).
Diarrhoea.

Bi-PegLyte *Pendopharm, Canad.*
Powder for oral solution, macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1); tablets, bisacodyl (p. 1821·1).
Bowel evacuation.

Bipéridys *Pierre Fabre, Fr.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastrointestinal discomfort; gastro-oesophageal reflux.

Bipgel *Bionet, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Biphasil *Aspen, S.Afr.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Biphasic oral contraceptive; menstrual disorders.

Biphenox *MedChem, USA.*
Paracetamol (p. 115·1); phenyltoloxamine citrate (p. 638·1).
Pain.

Biphentin *Purdue, Canad.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder.

Biplox-SL *Bionet, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Bipomax *Janssen-Cilag, Spain.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Bi-Pradia *Liferpal, Mex.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Biprel *Servier, China.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Bi-Prestarium *Servier, Ukr.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Bi-Preterax *Servier, Philipp.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Bipreterax *Servier, Fr.; Servier, Ger.; Abdi, Turk.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Servier, Arg.†; Servier, Irl.; Servier, S.Afr.†; Servier, Spain; Servier, Venez.
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Biprin *Vivax, Venez.*
Pyridoxine (p. 2105·3).
Vomiting; vitamin B_6 deficiency; neuritis; premenstrual syndrome.

Bipro
Note: this name may be used for preparations of different composition.
Fahrenheit, Indon.
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Kenyaku, Thai.†
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Bi-Profenid *Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Pol.; Eczacibasi, Turk.*
Ketoprofen (p. 79·1).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Bi-Profénid *Sanofi-Aventis, Fr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint and peri-articular disorders.

Biprokam *LKM, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Biprol *Makiz-Pharma, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Biprolol *Borshchagovskii, Ukr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; ischaemic heart disease; heart failure.

Biprosta *Alkem, India.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Biquinate *Aventis, Austral.†*
Quinine bisulfate (p. 665·1).
Muscle cramps; myotonia congenita; diagnosis of myasthenia gravis; malaria.

Bi-Qui-Nol *Merck Medication Familiale, Fr.*
Cineole (p. 2479·1); guaiacol (p. 1666·1); camphor (p. 2466·2); bismuth succinate (p. 1821·3).
Mouth and throat disorders.

Biral *Nycomed, S.Afr.†*
Valerian (p. 2640·2); passion flower (p. 2584·1).
Minor nervous disorders; anxiety.

Biravid *Helsinn Birex, Irl.*
Ofloxacin (p. 334·3).
Bacterial infections.

Biriklopi *Alchemia, Denm.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Birkenkohle comp *Weleda, Austria; Weleda, Ger.*
Antimonit (p. 2445·1); carbo betulae; chamomilla recutita (p. 2474·1).
Homoeopathic preparation.

Birley's *Torbet Laboratories, UK.*
Dried aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); light magnesium carbonate (p. 1856·2).
Gastric hyperacidity; dyspepsia; flatulence; heartburn.

Birnival *Birz, India.*
Vitamins; minerals.

Birodogyl *Sanofi-Aventis, Fr.*
Spiramycin (p. 358·3); metronidazole (p. 936·1).
Bacterial mouth infections.

Bi-Rofenid *Sanofi-Aventis, Belg.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; oedema.

Biron *Douglas, NZ.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Birvine *Birz, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Biryth *Emcure, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Bisacod *Medicine Products, Thai.*
Bisacodyl (p. 1821·1).
Constipation.

Bisacodylcoated *T Man, Thai.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Bisacolax *Valeant, Canad.*
Bisacodyl (p. 1821·1).
Constipation.

Bisakol *Yeni, Turk.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Bisa-Lax *Bergen Brunswig, USA.*
Bisacodyl (p. 1821·1).
Constipation.

Bisalax *Aspen, Austral.; Uniao Quimica, Braz.; Cipla, Philipp.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Bisariv *EastAfrican, India.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Bisatum *Teva, Cz.†*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Bisbeta *Shrrishti, India.*
⊗Bisoprolol (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bisco-Magaldrat *Biscova, Ger.†*
Magaldrate (p. 1856·1).
Gastric hyperacidity.

Biscor *Dexa, Indon.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Bisco-Zitron *Biscova, Ger.*
Bisacodyl (p. 1821·1).
Constipation.

Bisdiur *Austral, Arg.*
⊗Amiloride hydrochloride (p. 1299·1).
Hypertension; oedema; liver cirrhosis with ascites.

Bisectron *Corsalud, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Bisedyl *Christo, Hong Kong.†*
Bisacodyl (p. 1821·1).
Constipation.

Biseko
Note: this name may be used for preparations of different composition.
Biotest, Austria; Biotest, Ger.; Biotest, Hung.; Biotest, Thai.†; Kansuk, Turk.
⊗A plasma protein fraction (p. 1159·2).
Hypoproteinaemia; hypovolaemia; passive immunisation; plasma volume expansion; haemodilution; hypoalbuminaemia; hypogammaglobulinaemia.
Biotest, Hong Kong; Paviour, India; Biotest, Pol.
⊗Albumin (p. 1130·2).
Hypoproteinaemia; hypogammaglobulinaemia; hypoalbuminaemia; passive immunisation; plasma volume expansion.

Biselect *Intas, India.*
⊗Bisoprolol (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Biseptine *Bayer Sante, Fr.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1); benzyl alcohol (p. 1739·3).
Skin and wound disinfection; bacterial skin infections.

Biseptol *Polfa, Cz.; Medana, Pol.; Polfa Pabianice, Pol.; Polfa Warszawa, Pol.; Medana, Rus.; Pabianice, Rus.; Pabianice, Ukr.; Polpharma, Ukr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis; nocardiosis.

Biserol-Potassium *Bichsel, Switz.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Bisidim *Best, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

BI-Sifrol *Boehringer Ingelheim, Jpn.*
Pramipexole (p. 911·2).
Parkinsonism; restless legs syndrome.

Bisil *Sriprasit, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Bisincof *Loeffler, Mex.*
Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2).
Cough; respiratory-tract congestion.

Bislan *YSP, Malaysia; Yung Shin, Singapore.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Bismag *Wyeth Consumer, Singapore.†*
Heavy magnesium carbonate (p. 1856·2); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Dyspepsia; gastric hyperacidity.

Bisman *Radyum, Turk.*
Sodium bicarbonate (p. 1781·1); magnesium carbonate (p. 1856·2); aluminium hydroxide (p. 1817·2).
Gastrointestinal disorders.

Bisma-Rex
Note: this name may be used for preparations of different composition.
3M, UK.
Bismuth subcarbonate (p. 1822·1); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1); magnesium carbonate (p. 1856·2); peppermint oil (p. 1877·1).
Dyspepsia; flatulence.

Bismatrol *Major, USA.*
Bismuth salicylate (p. 1821·3).
Diarrhoea; dyspepsia; nausea.

Bismed *Quimica y Farmacia, Mex.*
Bismuth salicylate (p. 1821·3).
Diarrhoea; dyspepsia.

Bismocane *Chinta, Thai.*
Oxyphencyclimine hydrochloride (p. 1875·1); bismuth subnitrate (p. 1822·1); calcium carbonate (p. 1824·3).
Gastrointestinal disorders.

Bismofarma *Farmasa, Mex.*
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer.

Bismolan H Corti *Bittermedizin, Ger.*
⊗Prednisolone acetate (p. 1645·2); bismuth oxychloride (p. 1821·3); zinc oxide (p. 1729·1).
Anorectal disorders.

Bismomagnesie *Yeni, Turk.*
Granules: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.
Yeni, Turk.†
Chewable tablets: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Bismoral *Zentiva, Cz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Bismorectal *Vifor, Switz.†*
Bismuth succinate (p. 1821·3); bismuth hydroxyquinoline (p. 1821·3); eucalyptus oil (p. 2501·2); sage oil (p. 2609·1).
Mouth and throat disorders.

Bismu-Jet *Legrand, Braz.*
Neomycin sulfate (p. 330·1); bismuth sodium tartrate (p. 1821·3); menthol (p. 2553·2); procaine hydrochloride (p. 1994·3).
Mouth and throat disorders.

Bismultin *Rafarm, Gr.*
Econazole nitrate (p. 577·3).
Fungal skin and vaginal infections.

Bismutal *Rougier, Canad.*
Bismuth camphocarbonate (p. 1821·3); guaifenesin (p. 1666·2).
Sore throat.

Bismuth + Antacid *Perrigo, Canad.*
Bismuth salicylate (p. 1821·3); calcium carbonate (p. 1824·3).

Biso comp *AbZ, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Biso Lich *Winthrop, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisoact *Actavis, Denm.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bisobeta *Betapharm, Ger.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisobeta comp *Betapharm, Ger.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoblock *Extractum, Cz.†; Actavis, Hung.; Galex, Neth.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisocar HT *Rusan, India.*
⊗Bisoprolol (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bisocard *ICN, Cz.; Valeant, Hung.; ICN, Pol.; ICN, Rus.; Actavis, Swed.; ICN, Ukr.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure; angina pectoris; hypertension; ischaemic heart disease.

Bisoce *Mylan, Fr.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bisocombin *Kwizda, Austria.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisocor *Kwizda, Austria; Actavis, Denm.†; Niche, Irl.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; heart failure.

Bisod *Medreich, India.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bisodol *Forest, Irl.; Forest Laboratories, Port.†; SA Druggists Self Med, S.Afr.†; Forest Laboratories, UK.*
Tablets: Calcium carbonate (p. 1824·3); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Dyspepsia; heartburn; flatulence; gastric hyperacidity; gastro-oesophageal reflux.
Forest, Irl.†; SA Druggists Self Med, S.Afr.†; Forest Laboratories, UK.
Oral powder: Heavy magnesium carbonate (p. 1856·2); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Flatulence; dyspepsia; gastric hyperacidity; heartburn; gastro-oesophageal reflux.

Bisodol Extra *Forest Laboratories, UK.*
Magaldrate (p. 1856·1); alginic acid (p. 2167·2); sodium bicarbonate (p. 1781·1).
Antacid.

Bisodol Extra Strong Mint Tablets *Forest, Irl.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Dyspepsia; heartburn; flatulence.

Bisodol Heartburn Relief *Forest Laboratories, UK.*
Alginic acid (p. 2167·2); magaldrate (p. 1856·1); sodium bicarbonate (p. 1781·1).
Heartburn; dyspepsia.

Bisodol Wind Relief *Forest Laboratories, UK.*
Calcium carbonate (p. 1824·3); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); simeticone (p. 1886·2).
Flatulence; dyspepsia; gastric hyperacidity; heartburn.

Bisofan *Quality, Hong Kong.*
Bromhexine (p. 1656·3).
Cough.

Bisogamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisogen *Generics, Cz.; Merck, Hung.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Biso-Hennig *Hennig, Ger.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisohexal *Hexal, Ger.†; Sandoz, Pol.; Hexal, S.Afr.; Salutas, Singapore.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; heart failure; ischaemic heart disease.

Bisohexal plus *Hexal, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisolangin *Boehringer Ingelheim, Neth.*
Ambroxol hydrochloride (p. 1654·3).
Sore throat.

Bisolax
Note: this name may be used for preparations of different composition.
Neocare, Belg.
Bisacodyl (p. 1821·1).
Seng, Thai.
Bisacodyl (p. 1821·1); docusate sodium (p. 1836·2); carmellose sodium (p. 2175·2).
Constipation.

Bisolbruis *Boehringer Ingelheim, Neth.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased mucus.

Bisolgrip
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Spain.
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Catarrh; cold and influenza symptoms.
Unilfarma, Port.†
Paracetamol (p. 115·1).
Fever; pain.

Bisolgrip T *Unilfarma, Port.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; inflammation; fever.

BisoLich comp *Winthrop, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisolmed *Boehringer Ingelheim, Spain.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Bisolnasal *Boehringer Ingelheim, Neth.*
⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Bisolol *Rafa, Israel.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisolpent *Boehringer Ingelheim, Philipp.*
⊗Bromhexine hydrochloride (p. 1656·3); orciprenaline sulfate (p. 1217·3).
Asthma; bronchospasm.

Bisolpent Ex *Boehringer Ingelheim Promeco, Mex.*
⊗Bromhexine hydrochloride (p. 1656·3); orciprenaline sulfate (p. 1217·3).
Respiratory-tract disorders.

Bisolphar *Pharlab, Braz.*
Bromhexine (p. 1656·3).

Bisolsinus *Boehringer Ingelheim Promeco, Mex.*
Gentian (p. 2512·1); primula flower (p. 2596·2); sorrel (p. 2620·3); sambucus (p. 2609·3); vervain (p. 2645·1).
Respiratory-tract disorders.

Bisolspray *Boehringer Ingelheim, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Upper respiratory-tract congestion and inflammation.

Bisoltab *Macrophar, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Bisoltus *Boehringer Ingelheim, Spain.*
Codeine hydrochloride (p. 40·2).
Cough.

Bisoltussin *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Port.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bisolvex
Note: this name may be used for preparations of different composition.
Duopharma, Philipp.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bisolvon *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore†; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion; Sjögren's syndrome; cough.

Bisolvon A *Boehringer Ingelheim Promeco, Mex.*
Ampicillin trihydrate (p. 218·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Bisolvon Ambroxol *Boehringer Ingelheim, Switz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with excess mucus.

Bisolvon Antitusivo *Boehringer Ingelheim, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bisolvon Antitusivo Compositum *Boehringer Ingelheim, Spain.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Cough.

Bisolvon Chesty *Boehringer Ingelheim, Austral.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bisolvon Compositum *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Spain.†*
⊗Bromhexine hydrochloride (p. 1656·3); codeine hydrochloride (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract disorders.

Bisolvon Compositum NF *Boehringer Ingelheim, Arg.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Cough.

Bisolvon Dry *Boehringer Ingelheim, Austral.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bisolvon E *Boehringer Ingelheim Promeco, Mex.*
Bromhexine hydrochloride (p. 1656·3); erythromycin ethyl succinate (p. 291·2).
Respiratory-tract infections.

Bisolvon EX *Boehringer Ingelheim, Thai.*
Bromhexine hydrochloride (p. 1656·3); sulfogaiacol (p. 1678·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Bisolvon Extra *Boehringer Ingelheim, Indon.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Bisolvon Flu *Boehringer Ingelheim, Indon.*
Bromhexine hydrochloride (p. 1656·3); paracetamol (p. 115·1); chlorphenamine

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms; cough.

Bisolvon Linctus DA *Boehringer Ingelheim, S.Afr.*
⊗Bromhexine hydrochloride (p. 1656·3); orciprenaline sulfate (p. 1217·3).
Cough associated with bronchospasm.

Bisolvon Sinus *Boehringer Ingelheim, Austral.†*
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; respiratory-tract congestion.

Bisolvon Tosse Sed *Boehringer Ingelheim, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bisomerck *Merck, Fin.†; Merck, Swed.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisomyl *Mylan, Fin.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bison *Juggat, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Bisono *Toa Eiyo, Jpn.*
⊗Bisoprolol (p. 1325·3).
Hypertension.

Bisop *Rowex, Irl.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure; angina pectoris; hypertension.

Bisopine *Niche, Irl.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bisoplus *Aliud, Ger.†; Stada, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoproact *Actavis, Fin.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bisoprol *Farmak, Ukr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bisoprolol Comp *Ratiopharm, Austria; Ratiopharm, Fin.; Sandoz, Fin.; Synthon, Fin.; Ratiopharm, Ger.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoprolol HCT *Sandoz, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoprolol HCTad *TAD, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoprolol Plus *1A, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoprolol-HCT *1A, Austria; Arcana, Austria; Sandoz, Austria.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisopromerck *Merck, Pol.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; ischaemic heart disease.

Bisoprotop *Topgen, Belg.†*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Biso-Puren *Actavis, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Biso-Puren comp *Actavis, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisoral *Intermed, Gr.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).

Bisoratio *Ratiopharm, Pol.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; ischaemic heart disease; angina pectoris.

Bisosandoz *Sandoz, Belg.†*
⊗Bisoprolol (p. 1325·3).

Bisostad *Stada, Austria; Stada, Swed.; Stada, Ukr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure; ischaemic heart disease.

Stada, Fin.†
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bisostad plus *Stada, Austria.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bispec *Reddy, India.*
Solifenacin succinate (p. 2367·3).

Bispect *UCI, Braz.*
Bromhexine hydrochloride (p. 1656·3).

Bisphonal *Astellas, Jpn†; Astellas, Philipp.; Astellas, Thai.*
Incadronate disodium (p. 1185·3).
Hypercalcaemia of malignancy.

Bispro *Alphapharm, Austral.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Bisprotin *Vitabalans, Cz.; Vitabalans, Denm.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bissel 12 *Keton, Mex.*
Vitamin B_{12} (p. 2107·2).

Bistatin *Bioresearch, Mex.*
Nystatin (p. 590·3).
Fungal vaginal infections.

Biston *Zentiva, Cz.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia; bipolar disorder; diabetic neuropathy; alcohol withdrawal syndrome; diabetes insipidus.

Bistrepen *Alembic, India.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Bisultrim *Biomep, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Bisuran *EMS, Braz.*
Bromhexine (p. 1656·3).

Bisval *Valdecasas, Mex.†*
Bismuth salicylate (p. 1821·3).
Gastric hyperacidity; diarrhoea.

Bitagen *Taiwan Biotech, Philipp.*
Vitamins; glucose (p. 2068·3).
Nutritional supplement.

Bitakebir *Aspen, Arg.*
Bicalutamide (p. 749·1).

Bital *Solas, Indon.*
Anise oil (p. 2444·3); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Nasal congestion; cold and influenza symptoms; headache; insect bites.

Bitammon *Biotika, Cz.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Bitamox *Bombay Tablet, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Bitaquine *Bombay Tablet, India.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; amoebiasis; rheumatoid arthritis.

Bitazol *Ulagay, Turk.*
Ornidazole (p. 943·1).

Bite & Itch Lotion *Reese, USA.*
Diphenhydramine hydrochloride (p. 626·2); pramocaine hydrochloride (p. 1993·3).

Bite Rx *International Lab Tech, USA.*
Aluminium acetate (p. 2440·1).
Insect bites.

Bitecain AA *Cetus, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Bitensil *Q Pharma, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Bitensil Diu *Q Pharma, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Biteral *Roche, Turk.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Bite-X *Doetsch, Grether, Switz.*
Sucrose octa-acetate (p. 2215·1).
Prevention of nail biting.

Bithiol *Qualiphar, Belg.*
Ichthammol (p. 1705·3).
Skin disorders.

Bi-Tildiem *Sanofi-Aventis, Fr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Bitiron *Abdi, Turk.†*
Levothyroxine sodium (p. 2339·1); liothyronine sodium (p. 2342·3).
Hypothyroidism.

Bitis *Faran, Gr.*
Vitamins.

Bitnal *Nanbei, China.*
Colloidal bismuth tartrate.

BITNI X *CTS, Israel.*
Bismuth salicylate (p. 1821·3).
Diarrhoea; nausea; flatulence; upset stomach.

Bitobionil *SJA, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Bitoline *Caldern, India.*
Tricholine citrate (p. 2055·2).

Bitorva *USV, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Bitroxetan *Medinova (Μεντινοβα), Gr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Bittle *Europharm, Hong Kong.*
Clindamycin hydrochloride (p. 269·3).
Acne.

Bittner *Bittner, Hung.*
Cnicus benedictus (p. 2482·2); carlina; gentian (p. 2512·1); liquorice (p. 1853·2); nutmeg (p. 2573·1); treacle (p. 2096·3); menyanthes (p. 2554·2); star anise (p. 2622·1); sweet orange (p. 2576·2); clove (p. 2481·2); bitter orange peel (p. 2575·3); centaury (p. 2473·2); cubeb (p. 2489·2); verbascum (p. 2645·1); ginger (p. 1844·1); manna (p. 1858·2); zedoary; angelica (p. 2443·3); myrrh (p. 2566·1); elecampane (p. 1662·3); iris; calamus (p. 2464·2); aurantia curaca peel; absinthium (p. 2426·1); camphor (p. 2466·2) galanga; ivae moschatae.
Indigestion.

Bitumol *Streuli, Switz.*
Ichthammol (p. 1705·3).
Skin disorders.

Biureol *Plurilab, Port.†*
Piperazine hydrate (p. 163·1); avocado (p. 2451·2); phyllanthus niruri (p. 2590·1).
Urinary-tract disorders.

Bivacyn *Teva, Hung.†; Lek, Pol.†*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Infected skin disorders; bacterial eye infections; wounds; ulcers; otitis externa; otitis media.

Bivaflo *Sun, India.*
Bivalirudin (p. 1326·2).
Thrombosis prophylaxis in percutaneous coronary intervention.

Bivalos *Servier, Rus.; Servier, Ukr.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Bivate *Douglas, NZ.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Bivaxol *Ivax, Cz.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bivien *BI, Gr.*
Citalopram hydrobromide (p. 411·1).

Bivigam *Biotest, USA.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency.

Biviol *MSD, Ger.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Bivol *Specifar (Σπεσιφαρ), Gr.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Bivorilan *Medinova (Μεντινοβα), Gr.; Pharmanel, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Biwind *Valeas, Ital.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Biwom *Zydus, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Bixen *Biomep, Mex.*
Naproxen (p. 98·2).
Pain.

Bixianshu *Baiyunshan, China.*
Ampicillin (p. 218·2).
Bacterial infections.

Bixigard *Biomax, India.*
Cefixime (p. 240·3).
Bacterial infections.

Bixigard-C *Biomax, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

BiXin *Antai, China.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Bixon *Biores, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

BiYu *Yungong, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bizalip *Nicholas Piramal, India.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Bizo *Hos & Ins, India.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Bizo-D *Hos & Ins, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Bizo-IT *Hos & Ins, India.*
Rabeprazole (p. 1881·1); itopride hydrochloride (p. 1850·1).
Gastro-oesophageal reflux.

B-Jen *Lafedar, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

B-Joy *Concertina, India.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer combination with antimicrobials.

B-Joy Plus *Concertina, India.*
Rabeprazole sodium (p. 1881·1); domperidone (p. 1838·1).

BK *3M, NZ.*
Lotion: Liquid paraffin (p. 2191·2); oil-soluble dewaxed lanolin fraction (p. 2219·3).
Dry skin disorders; pruritus.

BK HC *3M, NZ.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

B-kombin *ACO, Swed.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

B-Komplex *Zentiva, Cz.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

B-Komplex forte *Hevert, Ger.†*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

B-Laboterol *Labomed, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections with inflammation.

Black Forest *Novartis Consumer, S.Afr.†*
Senna (p. 1885·1).
Constipation; bowel evacuation.

Black Snake Antivenom *CSL, Austral.*
A king brown snake venom antiserum (p. 2419·1).
King brown (mulga) or black snake bites.

Black-Draught *Lee, USA.*
Syrup: Casanthranol (p. 1826·1); senna (p. 1885·1); rhubarb (p. 1884·2).
Constipation.

Lee, USA.†
Tablets: Senna (p. 1885·1).
Constipation.

Blackmores B + C *Blackmores, Thai.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B deficiency; vitamin C deficiency.

Blackmores Bio *Blackmores, Thai.*
Vitamins; with or without minerals.

Blackmores Bio C *Blackmores, Thai.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); calcium ascorbate (p. 2111·1); bioflavonoids (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2); rose fruit (p. 2607·1); acerola.
Vitamin C deficiency.

Blackmores Bio E *Blackmores, Thai.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Blackmores Exec B's *Blackmores, Thai.*
Vitamins; minerals.
Dietary supplement; tonic.

Blackmores Multi B *Blackmores, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; tonic.

Blackmores Naturetime Buffered C *Blackmores, Thai.*
Calcium ascorbate (p. 2111·1); ascorbic acid (p. 2110·3); bioflavonoids (p. 2505·2); rutin (p. 2505·3); hesperidin (p. 2505·2); rose fruit (p. 2607·1).
Vitamin C deficiency.

Blackmores Proseren *Blackmores, Thai.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Blackoïds du Docteur Meur *SERP, Mon.*
Levomenthol (p. 2553·2); liquorice (p. 1853·2).
Throat irritation.

Blacor *LKM, Arg.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Bladder 2.2 *Theralogix, USA.*
Vitamins; minerals; trace elements; lycopene (p. 2546·2).
Dietary supplement.

Bladder Irritation *Hylands, Canad.*
Argentum nitricum (p. 2615·3); benzoicum acidum (p. 1738·2); cantharis (p. 2469·2); equisetum hyemale; rhus aromatica (p. 2603·3).
Homoeopathic preparation.

Bladderon *Shinyaku, Jpn.*
Flavoxate hydrochloride (p. 2360·1).
Pollakisuria.

Bladiron *Anfarm, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Bladuril *Cosasco, Arg.; Tecnofarma, Chile; Sanofi-Aventis, Mex.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders; bladder function disorders; genital-tract spasm in women.

B-Lady *DKT, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen dependent acne, alopecia, and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Blairex Lens Lubricant *Blairex, USA.†*
Range of solutions for soft contact lenses.

B-Laktam *Nevzat, Turk.*
Sulbactam sodium (p. 360·1).
Bacterial infections.

Blamy *Duncan, Arg.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Blanc Dient *Bernabo, Arg.*
Urea hydrogen peroxide (p. 1774·2).
Dental whitener.

Blancaler *Galdermo, Mex.*
Cream: Titanium dioxide (p. 1725·1).
Skin hyperpigmentation.

Galdermo, Mex.
Topical gel: Achillea (p. 2427·3).
Skin hyperpigmentation.

Blanel *Pfleger, Austria.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3); sodium bicarbonate (p. 1781·1); sodium carbonate (p. 2617·3).
Renal calculi.

Pfleger, Ger.
Potassium sodium hydrogen citrate (p. 1780·3).
Renal calculi.

Blanoxan *BMS, Mex.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Blasentee St Severin *Gall-Reidlinger, Austria.*
Birch leaf (p. 2457·3); herniaria (p. 2525·1); equisetum (p. 2500·1); calluna vulgaris.
Kidney and bladder disorders.

Blast *Madhav, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1).

Blastivin *Pharmachemie, Neth.†*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Blastocarb *Lemery, India; Teva, Mex.; Lemery, Rus.; Lemery, Thai.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Blastoestimulina *Almirall, Spain.*
Topical powder: Centella (p. 1698·3).
Burns; ulcers; wounds.

Almirall, Spain.
Ointment: Centella (p. 1698·3); neomycin sulfate (p. 330·1).
Wounds; burns; ulcers; skin infections.

Almirall, Spain.
Pessaries: Centella (p. 1698·3); miconazole nitrate (p. 589·1); metronidazole (p. 936·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Vulvovaginal infections.

Almirall, Spain.†
Topical aerosol: Centella (p. 1698·3); tetracaine (p. 1996·3).
Wounds; burns; ulcers.

Blastofen *Chandra Bhagat, India.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility.

Blastoferon *Sidus, Arg.; Pentafarma, Chile.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

Blastolem *Laboratorios Chile, Chile; Elder, India; Teva, Mex.; Lemery, Rus.†; Lemery, Thai.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Blastomat *Alvogen, Neth.*
Temozolomide (p. 865·2).
Malignant glioma.

Blastomunil *Enzifarm, Ukr.*
Blastolen.
Immunodeficiency; leucopenia; immunostimulant.

Blaston *Lacer, Spain.*
Cinitapride acid tartrate (p. 1831·3).
Gastroparesis; gastro-oesophageal reflux.

Blastop *TRB, Arg.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Hyperhomocysteinaemia; dietary supplement.

Blastop Prevent *TRB, Arg.*
Red tablets, folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); white tablets, aspirin (p. 22·2).
Hyperhomocystinaemia; cerebrovascular disorders; cardiovascular risk reduction.

Blastoplatin *Chandra Bhagat, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Blastovin *Teva Tuteur, Arg.; Teva, Israel.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Blaubimax *Blausiegel, Braz.*
⊗Albumin (p. 1130·2).
Plasma volume expansion.

Blauferon *Blausiegel, Braz.*
Interferon alfa-2b (p. 989·2).
Chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Blavin *Baliardo, Arg.*
Terazosin (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Blaxezan *Leontik, Gr.*
Co-trimoxazole (p. 277·3).

Blazter *Reddy, Ukr.*
Zoledronic acid (p. 1192·3).
Osteolysis; hypercalcaemia of malignancy.

Blaztere *Reddy, Braz.; Reddy, India; Reddy, Rus.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone; osteoporosis.

Blecidex *Sanbe, Indon.*
⊗Framycetin sulfate (p. 301·2); gramicidin (p. 308·3); dexamethasone sodium metasulfobenzoate (p. 1631·1).
Otitis externa; infected eye disorders.

Blédilait HA *Bledina, Fr.*
Infant feeds.
Cows' milk allergy.

Bledmax *Max, India.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Bledstop *Caprifarmindo, Indon.*
Methylergometrine maleate (p. 2137·3).
Uterine haemorrhage; management of third-stage labour.

Blederan *Alapis, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Blef-10 *Allergan, Mex.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Blefamide *Allergan, Arg.; Allergan, Chile.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Infected eye disorders; eye disorders.

Allergan, Chile†; Allergan, Mex.
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Eye disorders.

Blefamide-F *Allergan, Mex.*
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1); phenylephrine hydrochloride (p. 1672·3).
Infected eye disorders.

Blefarida *Alcon Cusi, Spain.†*
⊗Chloramphenicol (p. 257·1); cortisone acetate (p. 1629·2).
Infected eye disorders.

Blefarolin *Bruschettini, Ital.*
Tannic acid (p. 2625·2); resorcinol (p. 1718·3); menthol (p. 2553·2).
Eye disorders.

Blefarosan *Lersan, Arg.†*
Sulfathiazole sodium (p. 368·3).
Bacterial eye infections.

Blefaskin *Atlas, Arg.*
Eyelid cleanser.

Mediderm, Chile.
Hydroxyprolisilane C; cafeisilane C.
Blepharitis; dry eyes.

Blemaren *Esparma, Rus.; Esparma, Ukr.*
Citric acid (p. 2480·3); sodium citrate (p. 1781·2); potassium bicarbonate (p. 1780·3).
Urinary alkalinisation; renal calculi; porphyria cutanea tarda; hyperuricaemia.

Blemaren N *Esparma, Cz.; Aristo, Ger.; Esparma, Hung.*
Citric acid (p. 2480·3); anhydrous sodium citrate (p. 1781·2); potassium bicarbonate (p. 1780·3).
Renal calculi; hyperuricaemia; porphyria cutanea tarda.

Bleminol *Gepepharm, Ger.†*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Blemish Control *Kay, Canad.*
Salicylic acid (p. 1719·1).
Acne.

Blenamax *Aspen, Austral.; Combiphor, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Teva, Rus.; Pharmachemie, S.Afr.; Pharmachemie, Singapore.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Blendera *Otsuka, Thai.*
Preparation for enteral nutrition.

Blendox *Degorts, Mex.†*
Chlorphenamine (p. 620·3).

B-lene *Pator, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Blenoxane *BMS, Austral.†; BMS, Braz.; Bristol, Conod.†; BMS, NZ; BMS, Philipp.†; BMS, S.Afr.; BMS Oncology, USA.†*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleo *Koyaku, Jpn.*
Bleomycin hydrochloride (p. 749·3) or bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Kyowa, UK.
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleo-cell *Cell Pharm, Ger.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleochem *Biochem, India.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleocin *Kayaku, Malaysia; Euro Nippon Kayaku, Pol.†; Delta, Port.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Kayaku, Cz.†; Vianex (Βιανεξ), Gr.; Kayaku, Hong Kong; Kayaku, Hung.†; Khandelwal, India; Kolbe, Indon.; Kayaku, Indon.; Kayaku, Jpn†; Kayaku, Rus.; Kayaku, Singapore; Kayaku, Thai.; Onko, Turk.
Bleomycin hydrochloride (p. 749·3).
Malignant neoplasms.

Bleocip *Cipla, India.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Bleocris *LKM, Arg.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Bleolem *Lemery, India; Teva, Mex.; Teva, S.Afr.; Teva, Thai.; Atafarm, Turk.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleomax *Cryopharma, Mex.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleomedac *Medac, Cz.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Medac, Ger.; Medac, Neth.
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleomin *Teva, Belg.†*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleonco *VHB, India.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Bleo-S *Kayaku, Thai.†*
Bleomycin sulfate (p. 749·3).
Skin cancer.

Bleostar-S *Chandra Bhagat, India.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bleotex *Alkem, India.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Bleph *Allergan, India.*
Sulfacetamide (p. 361·1).

Bleph-10 *Allergan, Austral.; Allergan, Canad.†; Allergan, Irl.†; Allergan, NZ; Allergan, Thai.; Allergan, USA.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Blephaclean *Thea, Fr.; Spectrum, UK.*
Eyelid cleanser.

Blephagel *Pfizer, Arg.; Allergan, Braz.; Thea, Fr.; Allergan, Mex.; Thea, Philipp.; Pfizer, Singapore; Spectrum, UK; Pfizer, Venez.*
Eyelid cleanser.

Blephamide *Alvia (Αλβια), Gr.; Allergan, NZ†; Allergan, Singapore†; Abdi, Turk.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Infected eye disorders; conjunctivitis; blepharitis.

Allergan, Canad.; Allergan, Ger.; Allergan, Israel; Allergan, Switz.; Allergan, USA.
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Conjunctivitis; blepharitis; eye inflammation with bacterial infection.

Blephasol *Spectrum, UK.*
Eyelid cleanser.

Blerone *Zentiva, UK.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

BLES *Bles, Canad.*
Bovine lipid extract surfactant (p. 2599·2).
Neonatal respiratory distress syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Blesifen *Caprifarmindo, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Bless *Briskon, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Blessin *Egis, Cz.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Blessin Plus H *Egis, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blexit *Laboratorios Chile, Chile.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Blexon *Faran, Gr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; nocardiosis; toxoplasmosis.

Blezamont *Farmanic, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Blikonol *Pharmathen, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Blikosan *Pharmathen, Gr.*
⊗Prednisolone sodium phosphate (p. 1645·3); neomycin sulfate (p. 330·1).

Blindafe *Nucitec, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Blink *Advanced Medical Optics, UK.*
Polyvinyl alcohol (p. 2204·2); sodium chloride (p. 1795·1).
Dry eyes in contact lens wearers.

Blink Contacts *AMO, Arg.; Visiontec, Arg.; AMO, Austral.*
Sodium hyaluronate (p. 2526·2); OcuPure.
Dry eyes; lubricating drops for contact lenses.

Blink Gel Tears *Abbott, USA.*
Macrogol 400 (p. 2547·3).
Dry eyes.

Blink Intensive Tears *AMO, Malaysia; AMO, Singapore.*
Macrogol 400 (p. 2547·3).
Dry eyes.

AMO, UK.
Macrogol 400 (p. 2547·3); sodium hyaluronate (p. 2526·2).
Dry eyes.

Blink-N-Clean *AMO, Austral.*
⊗Hypromellose (p. 2189·2); tyloxapol (p. 2218·2); trometamol (p. 2635·1).
Cleansing and lubrication of contact lenses.

AMO, Arg.†; Visiontec, Arg.†
Cleansing drops for contact lenses.

Blinx *Pilkington Barnes-Hind, USA.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Blis K12 Throat Guard *Blis, NZ.*
Streptococcus thermophilus (p. 2596·3).
Restoration of normal throat bacterial flora.

Bliscal *Bliss, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Bliscal-ZM *Bliss, India.*
Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Bliskof *Bliss, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough.

Blismox *Bliss, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Blisprotex *Rider, Chile.*
Zinc oxide (p. 1729·1); dimeticone (p. 2209·3).
Nappy rash.

BlisterGard *Medtech, USA.*
Topical barrier preparation.

Blistex *Blistex, USA.*
Camphor (p. 2466·2); phenol (p. 1763·3); allantoin (p. 1693·1).
Oral lesions.

Pharmaceutical Enterprises, S.Afr.
Allantoin (p. 1693·1); phenol (p. 1763·3); camphor (p. 2466·2); menthol (p. 2553·2).
Dry lips; herpes labialis.

Rider, Chile.
Phenol (p. 1763·3); camphor (p. 2466·2).
Chapped lips.

Blistex Antiviral *Key, Austral.*
Aciclovir (p. 964·1).
Herpes labialis.

Blistex Clear Advance *Blistex, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Blistex Cold Sore Cream *DDD, UK.*
Docosanol (p. 974·3).
Herpes labialis.

Blistex Complete Moisture *Key, Austral.; Blistex, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen; dry lips.

Blistex DCT Lip Balm *Blistex, Canad.†*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); menthol (p. 2553·2); phenol (p. 1763·3); camphor (p. 2466·2).
Sunscreen; chapped lips.

Blistex Five Star Lip Protection *Blistex, USA.*
Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Blistex Fruit Smoothies *Rider, Chile.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Blistex Fruit Smoothies Lip Balm *Blistex, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen; chapped lips.

Blistex Herbal Answer *Blistex, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Blistex Herbal Lip Protector *Key, Austral.†*
SPF 16: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Blistex Lip Balm *Blistex, Canad.*
SPF 10: Padimate O (p. 1716·1); oxybenzone (p. 1715·3); dimeticone (p. 2209·3).
Sunscreen; chapped lips.

Blistex, USA.
SPF 10: Camphor (p. 2466·2); phenol (p. 1763·3); allantoin (p. 1693·1); dimethicone (p. 2209·3); padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen; chapped lips.

Key, Austral.
SPF 16: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Dry lips; sunscreen.

Blistex Lip Conditioner *Key, Austral.*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Blistex Lip Conditioning Balm *Key, Austral.*
SPF 20: Octinoxate (p. 1715·1).
Sunscreen; dry lips.

Blistex Lip Infusion Balm *Blistex, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen; chapped lips.

Blistex Lip Medex *Blistex, Canad.†*
Menthol (p. 2553·2); camphor (p. 2466·2); phenol (p. 1763·3).
Cold sores; chapped lips.

Blistex Lip Ointment
Note: this name may be used for preparations of different composition.
Key, Austral.
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3); camphor (p. 2466·2).
Dry lips; sunscreen.

Blistex Lip Revitalizer *Key, Austral.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Dry lips; sunscreen.

Blistex Lip Tone *Key, Austral.†*
SPF 18: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Dry lips; sunscreen.

Blistex Medicated Lip Conditioner *Key, Austral.†*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Dry lips; sunscreen.

Blistex Medicated Lip Ointment *Blistex, Canad.†*
Allantoin (p. 1693·1); camphor (p. 2466·2); phenol (p. 1763·3).
Herpes labialis; chapped lips.

Key, Austral.†
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3); allantoin (p. 1693·1); camphor (p. 2466·2).
Dry lips; sunscreen.

Blistex Relief *DDD, Irl.; DDD, UK.*
Strong ammonia solution (p. 2441·2); ammonia solution aromatic; phenol (p. 1763·3).
Chapped and cracked lips; herpes labialis.

Blistex Silk and Shine *Key, Austral.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen; dry lips.

Blistex Silk and Shine Lip Balm *Blistex, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen; chapped lips.

Blistex Soothe & Smooth *Key, Austral.*
SPF 30+: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen; dry lips.

Blistex Ultra Lip Balm *Key, Austral.*
SPF 30+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); meradimate (p. 1711·2); homosalate (p. 1705·1).
Dry lips; sunscreen.

Blistex Ultra Protection *Blistex, USA.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); meradimate (p. 1711·2); homosalate (p. 1705·1).
Sunscreen.

Blistex Ultra Protection Lip Balm *Blistex, Canad.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); meradimate (p. 1711·2); homosalate (p. 1705·1); dimeticone (p. 2209·3).
Sunscreen; chapped lips.

Blistik *Rider, Chile.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Blisto *Biocon, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Blisto-MF *Biocon, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Blis-To-Sol *Oakhurst, USA.*
Topical liquid: Tolnaftate (p. 596·1).
Fungal skin infections.

Oakhurst, USA.
Topical powder: Zinc undecenoate (p. 596·3).
Fungal skin infections.

Blistra *Pharos, Indon.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension.

Blisulide *Bliss, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Bliz *Grisi, Mex.†*
Boldo (p. 2458·3).
Constipation.

Bliz MD *Grandix, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Bloc *Finecure, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Blocacid
Note: this name may be used for preparations of different composition.
Ipca, India.
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Collins, Mex.†
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Inflammation; pain.

Blocadol *Ivax, Arg.*
Ketorolac trometamol (p. 80·2).
Pain.

Blocadren *SIT, Ital.; MSD, Mex.; MSD, Norw.; MSD, Swed.; Merck, USA.*
⊗Timolol maleate (p. 1513·2).
Hypertension; migraine; myocardial infarction; ocular hypertension; glaucoma; angina pectoris; heart failure.

Blocalcin *Pliva, Cz.†; Teva, Hung.; Pliva Lachema, Pol.†; Teva, Rus.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Blocamicina *Gador, Arg.*
Bleomycin hydrochloride (p. 749·3).
Malignant neoplasms.

Blocamine *Lafedar, Arg.*
⊗Labetalol hydrochloride (p. 1416·2).

Blocan
Note: this name may be used for preparations of different composition.
Atlantic, Port.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Blocanol *MSD, Fin.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Blocar *Bago, Chile.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension.

Blocatens *Unipharma, Gr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Blocatril *Tecnofarma, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

BloccoC *Soteks, Rus.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Blocin *Blossoms, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Block Up Oil Free *Fruit of the Earth, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 45: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Blockasol *Shree Ganesh, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Blocksol *Albephar, Venez.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); oxybenzone (p. 1715·3).
Sunscreen.

Bloc-Med *Ad-Drugstel, Philipp.*
Captopril (p. 1331·2).
Hypertension; myocardial infarction; heart failure; diabetic nephropathy.

Blocordil *KRKA, Rus.*
Captopril (p. 1331·2).
Hypertension; myocardial infarction; diabetic nephropathy; heart failure.

Blocotenol *Sandoz, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Bloctran *Farmstandart, Rus.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Bloculcer *Labesfal, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Bloflex *Blooming Fields, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Blogofort *Amnol, Ital.†*
Isodecyl salicylate; 18-beta glycyrrhetic acid (p. 54·2); unsaturated fatty acids; aescin (p. 2431·2); menthol (p. 2553·2); menthyl lactate (p. 2554·1).
Emollient.

Bloicin-S *Korea United, Philipp.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Blokace *Fako, Turk.*
Ramipril (p. 1483·3).

Blokace Plus *Fako, Turk.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).

Blokat *Atral, Port.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Bloken *Degorts, Mex.*
Phenylbutazone (p. 125·1).
Inflammation; pain.

Bloketangil *Liconsa, Neth.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blokium
Note: this name may be used for preparations of different composition.
Prodes, Hung.†; Almirall, Spain; Gentek, Venez.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Casasco, Arg.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Blokium B12 *Casasco, Arg.*
⊗Diclofenac potassium (p. 48·3); betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Musculoskeletal and joint disorders.

Blokium Diu *Almirall, Hung.; Almirall, Spain.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Blokium Flex *Casasco, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Blokium Gesic *Casasco, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Inflammation; pain.

Blokium Prost *Casasco, Arg.†*
Diclofenac sodium (p. 48·3). Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Rheumatoid arthritis; osteoarthritis.

Blokiuret *Gentek, Venez.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Blok-L *Nevzat, Turk.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Blomison *Cosmopharm, Gr.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Blonax *Mintlab, Chile.*
Clonixin lysine (p. 40·1).
Pain.

B-Long *Elder, India.*
Vitamin B_6 (p. 2105·3).

B-Long F *Elder, India.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

Blood Builder *Nutrifarma, Turk.*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).

Blood Sugar Balance *Mason, USA.*
Biotin (p. 2052·2); karela; chromium (p. 2055·3); ginkgo (p. 2512·3); gymnema; thioctic acid (p. 2629·1); magnesium (p. 1786·3); quercetin (p. 2505·3); vanadium; zinc (p. 2126·1).

Bloonis *Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Bloprazol *Fresenius Kabi, Port.†*
Omeprazole sodium (p. 1867·2).

Blopresid *Takeda, Ital.; Euro Registratie, Neth.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blopress *Takeda, Austria; Abbott, Braz.; Abbott, Chile; Takeda, China; Takeda, Ger.; Takeda, Hong Kong; Takeda, Indon.; Takeda, Irl.; Takeda, Ital.; Takeda, Jpn; Takeda, Malaysia; Abbott, Mex.; Euro Registratie, Neth.; Takeda, Philipp.; Lusomedicamenta, Port.; Takeda, Spain; Takeda, Switz.; Takeda, Thai.; Abbott, Venez.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure; left-ventricular dysfunction.

Blopress Comp *Lusomedicamenta, Port.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blopress D *Abbott, Chile.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blopress Forte *Takeda, Spain.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blopress Plus *Takeda, Austria; Takeda, Ger.; Takeda, Hong Kong; Takeda, Indon.; Takeda, Irl.; Abbott, Mex.; Takeda, Philipp.; Takeda, Spain; Takeda, Switz.; Takeda, Thai.; Abbott, Venez.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bloqadre *Micro, Mex.*
⊗Carvedilol (p. 1333·1).

Blorec *Fahrenheit, Indon.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Blosar *Siomond, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Blossom *Kanghong, China.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety.

Blosyn *Gufic, India.*
Syrup: Ferric ammonium citrate (p. 2060·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Formerly contained haemoglobin, ferric ammonium citrate, vitamin B_6, vitamin B_{12}, and folic acid.
Anaemias.

Gufic, India.
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Blotamax *Elder, India.*
Alpha galactosidase A (p. 2437·2); dimeticone (p. 1886·2).
Dyspepsia; flatulence.

Blotex *Sandoz, Mex.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

Blothin *Indi, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Blow-X *T Man, Thai.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas.

Blox *Saval, Chile.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Bloxang *Chauvin, Fr.†*
⊗Gelatin (porcine) (p. 1154·1).
Haemostatic.

Blox-D *Saval, Chile.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Blox-DC *Blubell, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Bloxiverz *Eclat, USA.*
Neostigmine metilsulfate (p. 687·2).
Reversal of competitive neuromuscular blockers.

Bluantina *Arrowblue, Port.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Blucef *Blue Cross, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Bluclox *Global, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Bluco *Hua, Thai.*
⊗Codeine phosphate (p. 40·2); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Bludrox *Blue Cross, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Blue *Ambix, USA; Moore, USA.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Blue Berry *Vitalco, Fr.*
Myrtillus (p. 2566·2); marigold (p. 2465·2); lutein (p. 2079·2); grape seed (p. 2521·3).
Dietary supplement for eye health.

Blue Cap *Tobbest Busindo, Indon.*
Cream: Pyrithione zinc (p. 1718·1).
Psoriasis; eczema.

Tobbest Busindo, Indon.
Shampoo: Pyrithione zinc (p. 1718·1); menthol (p. 2553·2).
Dandruff; seborrhoeic dermatitis.

Tobbest Busindo, Indon.
Topical spray: Pyrithione zinc (p. 1718·1); isopropyl myristate (p. 2190·3).
Psoriasis; eczema.

Blue Caps *SM, Venez.*
Pyrithione zinc (p. 1718·1).
Skin disorders.

Blue Collyrium *Sandoz, Canad.*
⊗Methylthioninium chloride (p. 1559·1); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Blue Ice Gel *Geritrex, USA.*
Menthol (p. 2553·2); isopropyl alcohol (p. 1758·3).

Blue Ice Rub *Delon, Canad.*
Menthol (p. 2553·2).

Bluecose *Bluepharma, Port.*
Acarbose (p. 466·2).
Diabetes mellitus.

Blue-Emu *NFI, USA.*
Menthol (p. 2553·2).

Bluegel *Medinova, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Bluegel-O *Medinova, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2); oxetacaine (p. 1993·1).

Bluegel-SF *Novaduo, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Blueron *Fluoron, Ger.*
Patent blue V (p. 2584·2).
Ophthalmic stain.

Bluesteril *IMS, Ital.†*
Benzalkonium chloride (p. 1737·1).
Instrument disinfection.

Bluetus *Novaduo, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Blueye *Sam Chun Dang, Hong Kong.*
Hypromellose (p. 2189·2).
Dry eyes.

Blugat *Landsteiner, Mex.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Blum *Ahimsa, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Blumet *Blue Cross, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Blumol *Farmanic, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Blumox *Blue Cross, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Blumox-CA *Blue Cross, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Blumox-DXL *Blue Cross, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Blumox-LB *Blue Cross, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Blumox-XL *Blue Cross, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Bluna *Faes, Spain.†*
Soya (p. 2092·3).
Menopausal disorders.

Blunorm
Note: this name may be used for preparations of different composition.
Laborest, Ital.
Thioctic acid (p. 2629·1); ginkgo biloba (p. 2512·3); leucoselect phytosome (oligomeric polyphenols prepared from *Vitis vinifera* (p. 2521·3)); vitamin B substances (p. 2102·3); selenium (p. 2086·3).
Dietary supplement.

Blush
Note: this name may be used for preparations of different composition.
Centaur, India.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Anaemias.

Pond's, Philipp.
21 tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive; menstrual disorders.

Bluspar *Blue Cross, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Blustark *Savio, Ital.†*
Ferrous gluconate (p. 2061·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Bluval *Sandoz, Port.*
Acetylcysteine (p. 1652·2).
Respiratory-tract infections with increased mucus.

BM Lactato *Roche, Arg.*
Test for lactic acid in blood.

BM-Accutest *Roche Diagnostics, Irl.†; Roche Diagnostics, UK.*
Test for glucose in blood (p. 2516·3).
For use with Accutrend blood glucose meters.

B-MIX *Patar, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

B-Mouthwash *Medicpharma, Thai.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

BM-Test 1-44 *Roche Diagnostics, UK.*
Test for glucose in blood (p. 2516·3).

BM-Test BG *Roche Diagnostics, Austral.†*
Test for glucose in blood (p. 2516·3).

BM-Test Glycemie 20-800 *Roche Diagnostics, Austral.†*
Test for glucose in blood (p. 2516·3).

BM-Test GP *Roche Diagnostics, Austral.†*
Test for glucose and protein in urine.

Bm-Vita *Arlak, India.*
Betacarotene (p. 2051·1); mecobalamin (p. 2108·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

B-Mycin *YSP, Malaysia.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

BN dolo *Staufen, Ger.†*
Arsenicum album (p. 2448·1); formica rufa; sulfur (p. 1721·1).
Homoeopathic preparation.

B-Nac *Elfin, India.*
Diclofenac (p. 48·3).
Pain.

B-natal *Ferring, Canad.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

B-N-C *Aglowmed, India.*
Capsules: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc (p. 2126·1).
Aglowmed, India.
Injection: Vitamin B substances (p. 2102·3).
Aglowmed, India.
Syrup: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

B-Nexa *Upsher-Smith, USA.*
Folic acid (p. 2063·1); calcium (p. 1783·1); vitamin B_6 (p. 2105·3); ginger (p. 1844·1).

BNIL *Millimed, Thai.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

BNP Ointment *Vendiz, Philipp.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected skin disorders.

Bo Le *Bei Da Gao Ke Hua Tai, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Bo De *Star, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Bo Bang Lin *Chase Sun, China.*
Aniracetam (p. 389·1).
Alzheimer's disease.

BO Cal
Note: this name may be used for preparations of different composition.
Newcharoen, Thai.
Calcium citrate (p. 1783·2).
Dietary supplement.

Bo En *Yangtze River, China.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; small-cell lung cancer; cervical cancer.

Bo Er Tai Li *Bo Er Tai Li, China.*
Oxymatrine.

Bo Ji *Yung Shin, China.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Bo Di Jia *Zizhu, China.*
Live *Bacillus subtilis.*
Diarrhoea.

Bo Jian *Star, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Bo Jing *Star, China.*
Ropivacaine mesilate.
Local anaesthesia.

Bo Ka Lai *Ke Lun, China.*
Oxymatrine.

Bo Kang *Star, China.*
Azithromycin aspartate.
Bacterial infections.

Bo La Kang Wei *San Ai, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Bo Ke *Wanhui Shuanghe, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bo Ke Bao *Star, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Bo Ke Le Wei *Yanshen, China.*
A furunculosis vaccine (p. 2420·2).
Active immunisation.

Bo Kun Li *Ke Lun, China.*
Hydroxycamptothecin.

Bo Lai Ning *Neptunus, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; osteolytic bone metastases.

Bo Lai Tong *Zhuoyikangna, China.*
Sodium alginate (p. 2167·3).

Bo Lang *Hong Yi, China.*
Di-isopropylammonium dichloroacetate (p. 1359·1).

Bo Lang Rui Ning *Qinba, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders.

Bo Li Gao *Yongning, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Bo Luo Ke *Jiangzhong, China.*
Lumbrokinase.

Bo Luo Ni *Zaozhuang, China.*
S ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Bo Man Xin *KeRui, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Bo Na Tong *Guo Yao, China.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Bo Ping *Rui Yang, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Bo Pu *Ke Lun, China.*
Potassium chloride (p. 1793·2); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Bo Rui *Zhengda Haier, China.*
Etoposide (p. 790·2).
Malignant neoplasms.

Bo Rui Te *NCPC, China.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Bo Shi Duo An *Li Neng Kang Tai, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Bo Shi Duo Bang *Li Neng Kang Tai, China.*
Enoxacin gluconate.
Bacterial infections.

Bo Shi Duo Ning *Li Neng Kang Tai, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency.

Bo Shi Duo Qing *Li Neng Kang Tai, China.*
Asarone.

Bo Shi Duo Ta *Li Neng Kang Tai, China; Star, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Bo Shi Duo Wei *Li Neng Kang Tai, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Bo Shu *Jiheng, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine (p. 1676·1).
Cold symptoms.

Bo Shu Te *Ji Sheng, China.*
Pentoxifylline (p. 1465·3).

Bo Shuai *Star, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Bo Si Te *Bosen, China.*
Lappaconitine hydrobromide (p. 1418·1).

Bo Su *Si Huan, China.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Bo Di Tong *Rui Er, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Bo Wei *Tian Zi Fu, China.*
Papaverine hydrochloride (p. 2362·3).

Bo Wei He *Xinhua, China.*
Fosfructose trisodium (p. 2507·2).
Hypophosphataemia.

Bo Wo Xin *Gutian, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Bo Xin *Boya, China.*
A normal immunoglobulin (p. 2403·3).

Bo Xin Shu *Jing Xin, China.*
Telmisartan (p. 1509·3).
Hypertension.

Bo Ying *Shi Xin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Bo Ying Kang *Guo Ao, China.*
Ligustrazine phosphate.

Bo Zhan Tong *Chase Sun, China.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease.

Bo Zhi *Shengfan, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Bobcef *Elder, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Bobei *Qilu, China.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Bobinum *Pharmathen, Gr.*
Dihydroergotamine mesilate (p. 672·2).

Bobodent *Hasco-Lek, Pol.*
Chamomile (p. 2474·1); thyme (p. 2630·2); lidocaine hydrochloride (p. 1988·2).
Mouth disorders.

Bobofen *Herbapol Lublin, Pol.†*
Chamomile (p. 2474·1); fennel (p. 2503·2); melissa (p. 2552·3).
Gastrointestinal disorders.

Bobothic *Polpharma, Ukr.*
Simeticone (p. 1886·2).
Colic in infants; flatulence; preparation for gastrointestinal procedures.

Bobotic *Medana, Pol.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; preparation for gastrointestinal procedures.

Bobotik *Medana, Rus.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; preparation for gastrointestinal procedures.

Bocacort-S *SJA, Gr.*
⊗Fluticasone propionate (p. 1638·1).

Bocasan *Oral-B, Irl.†; Gillette, Neth.†*
Sodium perborate (p. 1770·1).
Mouth disorders; gingivitis; oral hygiene.

Bocatriol *Leo, Austria†; DKSH, Hong Kong.†*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Bocouture *Merz, Fin.; Merz, Ger.; Merz, Neth.; Merz, Spain; Orion, Swed.; Merz, UK.*
Botulinum A toxin (p. 2017·1).
Glabellar lines.

Bocytin *Asian Pharm, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Boda *Yangtze River, China.*
Doxapram hydrochloride (p. 2321·2).
Respiratory failure.

Bo-D-Fense *Green Leaf, Philipp.†*
Andrographis (p. 2443·2); ginger (p. 1844·1); black pepper (p. 2586·1); vitamin C (p. 2110·3); zinc gluconate (p. 2126·2).
Upper respiratory-tract disorders.

Bodi Care Lotion *Geritrex, USA.*
Liquid paraffin (p. 2191·2); soft paraffin (p. 2211·3).
Dry skin.

Bodi Kleen *Geritrex, USA.*
Trolamine laurilsulfate (p. 2210·3); phenoxyethanol (p. 1764·3); hexylene glycol (p. 2188·3); aloe vera (p. 1693·2).

Bodi Line Action *Geritrex, USA.*
⊗Alcohol (p. 1733·1).
Hand cleanser.

Bodi Oil *Geritrex, USA.*
Liquid paraffin (p. 2191·2); lanolin oil (p. 2219·3); aloe vera oil (p. 1693·2).
Dry skin.

Bodi Protect *Geritrex, USA.*
Barrier ointment.

Bodimarin *Jadran, Ukr.*
Combination pack: 120 tablets, poliglusam (p. 2593·2); vitamin C (p. 2110·3); 30 tablets, omega-3 fatty acids (p. 1460·1); vitamin E (p. 2119·1); vitamin A (p. 2098·3); vitamin D (p. 2113·1).
Obesity; atherosclerosis; hypercholesterolaemia.

Bodimox-CV *Maxo, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Bodinet *Ecupharma, Ital.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Bodivitin *Hua, Thai.*
Vitamins; calcium (p. 1783·1).

Bodix *Errekappa, Ital.*
⊗Budesonide (p. 1625·1).
Asthma; croup.

Bodrex *Bode, Indon.; Tempo Scan Pacific, Indon.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

Bodrex Extra *Bode, Indon.; Tempo Scan Pacific, Indon.*
Caffeine (p. 1203·3); ibuprofen (p. 68·2); paracetamol (p. 115·1).
Headache.

Bodrex Flu & Batuk *Bode, Indon.; Tempo Scan Pacific, Indon.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Influenza symptoms; cough.

Bodrex Flu & Batuk Berdahak *Bode, Indon.; Tempo Scan Pacific, Indon.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Influenza symptoms; cough.

Bodrex Forte *Tempo Scan Pacific, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Bodrex Migra *Bode, Indon.; Tempo Scan Pacific, Indon.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Migraine.

Bodrexin *Bode, Indon.; Tempo Scan Pacific, Indon.*
Tablets: Aspirin (p. 22·2).
Fever; pain.

Bode, Indon.; Tempo Scan Pacific, Indon.
Syrup: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough; cold and influenza symptoms.

Bodrexin Demam *Bode, Indon.; Tempo Scan Pacific, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Bodrexin Flu & Batuk *Bode, Indon.; Tempo Scan Pacific, Indon.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Influenza symptoms; cough.

Bodrexin Pilek Alergi *Bode, Indon.; Tempo Scan Pacific, Indon.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Body Fort Hair *Natufarma, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Body Guard *Sanitalia, Ital.*
Echinacea (p. 2498·1); salix (p. 129·2); devil's claw root (p. 42·3); propolis (p. 2597·3).
Nutritional supplement.

Body Mist *Vital Science, Canad.*
SPF 70: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Bodycal *Medihealth, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Body-Calcin *Unipharma, Gr.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Boestrol *Antigen, Irl.†*
Diethylstilbestrol (p. 2267·3).
Breast cancer; prostatic cancer.

Bofen *Borshchagovskii, Ukr.*
Ibuprofen (p. 68·2).
Pain; fever.

Boflam *Neon, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Boflavin *Milano, Thai.*
Riboflavin (p. 2104·3).
Vitamin B_2 deficiency.

Bofutsushosan *Tsumura, Jpn.*
⊗Skullcap root (p. 2617·1); liquorice (p. 1853·2); platycodon root; gypsum; atractylodes rhizome; rhubarb (p. 1884·2); schizonepeta tenuifolia; gardenia fruit; peony root; cnidium rhizome; angelica acutiloba root (p. 2443·3); mentha; saposhnikovia root; ephedra (p. 1663·1); forsythia fruit; ginger (p. 1844·1); talc (p. 1722·2); mirabilitum.
Traditional Kampo medicine.

Boie Carminative (Carminasen) *Boie, Philipp.*
Liquorice (p. 1853·2); rhubarb (p. 1884·2); senna (p. 1885·1).
Colic; flatulence; indigestion; gastrointestinal spasm.

Boi-K *Merck, Spain.*
Potassium ascorbate (p. 1793·1).
Potassium depletion.

Boi-K Aspartico *Merck, Spain.*
Potassium ascorbate (p. 1793·1).
Potassium depletion.

Boil Ease *Commerce, USA; Del, USA.*
Benzocaine (p. 1980·2); ichthammol (p. 1705·3); sulfur (p. 1721·1); cade oil (p. 1723·2); camphor (p. 2466·2); phenol (p. 1763·3); zinc oxide (p. 1729·1); thymol (p. 1772·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Boils.

Boiogito *Tsumura, Jpn.*
Astragalus root (p. 2451·1); sinomenium stem; atractylodes lancea rhizome; jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Bokaiqing *Deyuan, China.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bokey *Yung Shin, Hong Kong; Yung Shin, Singapore.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Bolamyn *Teva, UK.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bo-Lax *Cipla, India.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Bolax *Brawn, India.*
Ispaghula (p. 1849·1); senna (p. 1885·1).

Bolcitol *Lesourd, Fr.†*
Fumitory (p. 2508·2); boldo (p. 2458·3); sage (p. 2608·3); fennel (p. 2503·2).
Gastrointestinal disorders; biliary disorders; kidney disorders.

Boldaloin *Herbapol Wrodaw, Pol.*
Aloes (p. 1816·1); boldine (p. 2458·3).
Liver and biliary-tract disorders; constipation; digestive disorders.

Boldex *Potter's, UK.*
Taraxacum (p. 2625·3); butternut bark (p. 2463·2); boldo (p. 2458·3); bladderwrack (p. 2612·1).
Slimming aid.

Boldina *Plata, Arg.*
Boldo (p. 2458·3); carqueja (p. 2471·2); cynara (p. 2490·3).
Liver disorders.

Boldina He *Teofarma, Ital.*
Boldine (p. 2458·3); aloin (p. 1816·2).
Constipation.

Boldocynara *Bioforce, Switz.*
Cynara (p. 2490·3); taraxacum (p. 2625·3); boldo (p. 2458·3); peppermint leaf (p. 1877·1).
Digestive disorders.

Boldoflorine *Dietetique et Sante, Fr.*
Tea: Boldo (p. 2458·3); senna (p. 1885·1); frangula bark (p. 1843·3); rosemary (p. 2607·2).
Constipation.

Dietetique et Sante, Fr.
Tablets: Boldine (p. 2458·3); senna (p. 1885·1); rosemary (p. 2607·2).
Constipation.

Boldovera *Aflofarm, Pol.*
Aloes (p. 1816·1); fumitory (p. 2508·2); boldine (p. 2458·3).
Digestive disorders; gastrointestinal spasm; constipation.

Bolesi *Yaoyau, China.*
Alprostadil (p. 2352·2).
Thrombophlebitis; chronic arterial occlusive disease; myocardial infarction; heart failure; central retinal vein thrombosis.

Bolheal *Astellas, Jpn.*
Fibrinogen (p. 1151·3); factor XIII (p. 1150·3); aprotinin (p. 1133·2); thrombin (p. 1163·2); calcium chloride (p. 1783·1).
Tissue sealant.

Bolinan *SERP, Mon.*
Povidone (p. 2204·3).
Gastrointestinal disorders.

Bolinet *BMS, Pol.†*
Ibuprofen (p. 68·2).
Fever; pain.

Bolisegna *Rafarm, Gr.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory disorders associated with viscous mucus.

Bollinol *Viofar, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Bolodol *Ultramark, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Bolovit *Ultramark, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Boloxen *Kato, Pol.†*
Naproxen sodium (p. 98·2).
Fever; pain.

Bol-Ran *Scan Biotech, Ukr.†*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; gout; pain; fever.

Boltin *MSD, Spain.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Bolus Adstringens *Egis, Hung.*
Albumin tannate (p. 1815·1); bismuth subgallate (p. 1822·1); kaolin (p. 1850·1).
Gastrointestinal disorders.

Bolus Eucalypti Comp *Weleda, Austria.*
Apis mellifica (p. 2445·2); belladonna (p. 2453·3); eucalyptus (p. 2501·1).
Homoeopathic preparation.

Weleda, S.Afr.†; Weleda, UK.
Apis mellifera (p. 2445·2); belladonna (p. 2453·3); eucalyptus (p. 2501·1); light kaolin (p. 1850·1).
Homoeopathic preparation.

Bolus Laxans *Egis, Hung.*
Rhubarb (p. 1884·2); sulfur (p. 1721·1); senna (p. 1885·1); kaolin (p. 1850·1).
Constipation; flatulence; meteorism; dyspepsia.

Boma *Ogna, Ital.*
Borax (p. 2459·2); benzocaine (p. 1980·2).
Oral hygiene; suppression of vomiting stimulus during dental procedures.

Bomacorin *Hevert, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Bomagall *Hevert, Ger.*
Carduus marianus (p. 1561·1); lycopodium (p. 2546·3); nux vomica (p. 2573·3); quassia amara (p. 2601·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Bomaklim *Hevert, Ger.*
⊗Agnus castus (p. 2432·2); cimicifuga (p. 2478·1); lilium tigrinum; platinum metallicum (p. 2593·1).
Homoeopathic preparation.

Bomapect N *Hevert, Ger.*
Hyoscyamus (p. 2530·2); coccus cacti (p. 2179·2); cuprum aceticum (p. 2486·2); drosera (p. 2497·2).
Homoeopathic preparation.

Bomarthros *Hevert, Ger.†*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Bomarthros Harpagophytum Complex *Hevert, Ger.*
Harpagophytum (p. 42·3); ledum (p. 2550·1); rhus tox. (p. 2603·3); tartarus stib. (p. 151·2).
Homoeopathic preparation.

Bomcin *Newcharoen, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Bomex *YSP, Malaysia; Yung Shin, Singapore.*
Brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

Bomexin *Pond's, Thai.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Bomine
Note: this name may be used for preparations of different composition.
Mayo, Mex.
Dimenhydrinate (p. 625·2); pyridoxine (p. 2105·3).
Nausea and vomiting.

Pharmasant, Thai.
Brompheniramine maleate (p. 618·1).
Allergic rhinitis.

Bomix *Bode, Ger.†*
Clorophene (p. 1748·3); orthophenylphenol (p. 1762·3); chlorocresol (p. 1748·1).
Instrument disinfection.

Bomix Plus *Bode, Ger.*
N,N-Didecyl-N-methyl-poly(oxyethyl) ammoniumpropionate.
Instrument disinfection.

Bomox *Millimed, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bompar *Newcharoen, Thai.*
Piperazine citrate (p. 163·1).
Worm infections.

Bomvital *Diamond, Philipp.*
Vitamins; lysine (p. 2079·3); omega 3-fatty acids; Chlorella growth factor (p. 2475·3).
Nutritional supplement.

Bonacal *Orion, Singapore.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Bonacal D3 *Orion, Singapore.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Bonacton *Fako, Turk.*
Alendronate sodium (p. 1171·3).

Bonadine CD *Pharmasant, Thai.*
Codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).

Bonadoxina *Pfizer, Mex.; Pfizer, Venez.*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3). Lidocaine (p. 1988·1) is included in the injection to alleviate the pain of injection.
Nausea and vomiting; vertigo; vomiting.

Bonair *Midas Care, Malaysia.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma.

Solara, Mex.†
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Bonal *Nutrifarma, Turk.*
Emollient.
Stretch marks.

Bonalen
Note: this name may be used for preparations of different composition.
Uniao Quimica, Braz.; Ingers, Cz.†
Alendronate sodium (p. 1171·3).
Osteoporosis.

Vitae, Mex.
Meclozine (p. 634·3); pyridoxine (p. 2105·3).
Nausea and vomiting.

Bonalet-Cee *Am-Europharma, Philipp.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Bonalfa *Schering-Plough, Chile†; Teijin, China; Teijin, Jpn; Schering-Plough, Mex.†; Isdin, Port.; Isdin, Spain.*
Tacalcitol (p. 1722·1).
Psoriasis; ichthyosis.

Bonalon *Teijin, Jpn.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bonamina *Johnson & Johnson, Chile.†*
Meclozine hydrochloride (p. 634·3).
Nausea and vomiting; vertigo.

Bonamine *McNeil Consumer, Canad.†; Johnson & Johnson, Philipp.*
Meclozine hydrochloride (p. 634·3).
Nausea; vestibular disorders; vomiting; vertigo.

Bonanoti *Novag, Mex.*
Diphenhydramine (p. 626·1).
Insomnia.

Bonapam *Alkem, India.*
Pamidronic acid (p. 1186·3).
Bone metastases; hypercalcaemia of malignancy; Paget's disease of bone.

Bon-Apetit *Norton, Ukr.*
⊗Grape (p. 2521·3); aloe vera (p. 1693·2); aegle marmelos; remna mucronata; oroxylum indicum; gmelina arborea; stereospermum suaveolens; desmodium gangeticum; uraria picta; solanum indicum; solanum xanthocarpum; tribulus terrestris (p. 2633·3); withania somnifera shoots (p. 2450·2); asparagus racemosus (p. 2614·2); terminalia chebula (p. 2474·3); terminalia bellirica (p. 2453·2); Indian gooseberry (p. 2532·2); tinospora cordifolia; liquorice (p. 1853·2); piper longum; ginger (p. 1844·1); black pepper (p. 2586·1); arjuna (p. 2447·2); symplocos racemosa; rubia cordifolia seed; caraway seed (p. 2470·2); coriander (p. 2486·3); turmeric (p. 2218·1); hedychium spicatum root; cuminum cyminum fruit; syzygium aromaticum.
Appetite stimulant.

Bonaplatin *Baxter, Philipp.†*
Carboplatin (p. 759·1).
Malignant neoplasms.

Bonar *Biosintetica, Braz.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Bonasanit *Biokanol, Ger.†*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Bonasol *Xeolas, Denm.; Xeolas, Fin.; Xeolas, Irl.; Xeolas, Ital.; Xeolas, Neth.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bonat *Roche, Israel.*
Ibandronic acid (p. 1184·2).
Prevention of skeletal events associated with breast cancer and bone metastases.

Bonatol *Coup, Gr.*
Indometacin (p. 71·2).

Bonatol-R *Coup, Gr.*
Flurbiprofen (p. 65·2).
Pain; inflammation; musculoskeletal and joint disorders.

Bonaven *Medihealth, Mex.*
Avena (p. 2451·1); sodium cocoyl isetionate (p. 2210·3).
Skin cleanser.

Roemmers Medihe, Venez.
Soap substitute with avena (p. 2451·1).

Bonazin *Collins, Mex.†*
Pyridoxine (p. 2105·3); meclozine (p. 634·3).
Nausea and vomiting.

Boncol *Sojar, Arg.*
Phytosterols.
Hypercholesterolaemia.

Boncordin *Sandoz, Arg.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Bondapen *Elpen (Ελπεν), Gr.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Bondenza *Roche, Cz.†; Roche, Neth.†; Roche, Pol.†; Roche, Port.†; Roche, Spain.†*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Roche, Irl.†
Ibandronic acid (p. 1184·2).
Osteoporosis.

Bondi *Ethica, Indon.*
Diacerein (p. 45·3).
Osteoarthritis.

Bondil *Meda, Norw.; Meda, Swed.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Bondiol *Brady, Austria; Teva, Ger.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; osteomalacia; hypoparathyroidism; rickets; osteoporosis.

Bondormin *Rafa, Israel.*
Brotizolam (p. 1042·1).
Insomnia.

Bondronat *Hospira, Austral.; Roche, Austria; Roche, Belg.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Syntex, Mex.†; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.†; Roche, Turk.; Roche, UK; Roche, Ukr.*
Ibandronate sodium (p. 1184·2).
Metastatic bone disease; hypercalcaemia of malignancy; osteolysis of malignancy.

Roche, India; Roche, S.Afr.
Ibandronic acid (p. 1184·2).
Hypercalcaemia of malignancy; metastatic bone disease.

Bone Builder *Bioglan, Austral.*
Calcium carbonate (p. 1824·3); hydroxyapatite (p. 2529·3); calcium citrate (p. 1783·2); calcium hydrogen phosphate (p. 1783·3); magnesium oxide (p. 1857·3); boron (p. 2052·3); zinc oxide (p. 1729·1); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); vitamins.
Calcium supplement for bone health.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bone Complex *Mediherb, Austral.*
Epimedium sagittatum; red clover (p. 2482·1); pueraria lobata root; cimicifuga (p. 2478·1).
Dietary supplement for bone health.

Bone Matrix Support *Eagle, Austral.*
Minerals; colecalciferol (p. 2113·1); phytomenadione (p. 2122·2).
Dietary supplement for bone health.

Boneact *Vera, Hung.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Bone-C Plus *Molekule, India.*
Calcitriol (p. 2113·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3); calcium (p. 1783·1).

Bo-Ne-Ca *ST, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Bonecal *Kevin, India.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1).

BoneCare *MD, Singapore.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Dietary supplement.

Bonecit-DE *Sriprasit, Thai.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement; osteoporosis; rickets.

Bonedron *Minerva (Μινερβα), Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bonefos *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, China; Bayer, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, Philipp.; Bayer Schering, Pol.; Lusalfarma, Port.; Bayer Schering, Rus.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Er-Kim, Turk.; Bayer, UK.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; metastatic bone disease; Paget's disease of bone.

Bonefurbit *Liconsa, Irl.; Liconsa, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Bonemax *Dincsa, Turk.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Bonendro *Will-Pharma, Neth.*
Tablets, alendronate sodium (p. 1171·3) (Alendronax); effervescent granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1) (CalD).
Osteoporosis.

Bonenza-D3 *Elisa, India.*
Minerals; colecalciferol (p. 2113·1).

Bonephos *Bayer Schering, S.Afr.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Bonesil D *Italfarmaco, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Bonesoy Optima *Nature's Way, Philipp.†*
Calcium citrate (p. 1783·2); soy isoflavones; vitamins; minerals.
Nutritional supplement.

Bonestat *Ind-Chemie, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).
Osteoporosis; renal osteodystrophy; hyperparathyroidism.

Bonetec *Sinensix, Thai.*
Calcium carbonate (p. 1824·3).
Dietary supplement.

Bonflox *Bestochem, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Bonforte *Flamingo, India.*
Capsules: Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1).

Flamingo, India.
Oral suspension: Calcium citrate (p. 1783·2); lysine hydrochloride (p. 2079·3); magnesium sulfate (p. 1787·3); colecalciferol (p. 2113·1).

Bonglixan *Landsteiner, Mex.*
⊗Insulin glargine (p. 475·3).
Diabetes mellitus.

Bonic *Ethica, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamins; minerals.
Osteoarthritis.

Bonic Plus *Ethica, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3).
Joint disorders.

Bonical-E *East West, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); vitamin E acetate (p. 2119·2).
Calcium and vitamin D supplement.

Bonidon *Mepha, Switz.†*
Indometacin (p. 71·2).
Aluminium glycinate (p. 1817·2) is included in the tablets in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Bonifen
Note: this name may be used for preparations of different composition.
Merck, Venez.
Pyritinol hydrochloride (p. 394·3).
Mental function disorders.

KRKA, Rus.
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; fever.

Bonil *Lafi, Chile.*
Ketoprofen (p. 79·1).
Pain; fever.

Bonilav *Ethica, Indon.*
Glucosamine hydrochloride (p. 2515·3); isoflavone (p. 2620·3).
Menopausal disorders.

Bonine *Pfizer, Rus.†; Insight, USA.*
Meclozine hydrochloride (p. 634·3).
Motion sickness; vertigo.

Bonine for Kids *Insight, USA.*
Cyclizine hydrochloride (p. 623·2).
Nausea and vomiting; motion sickness.

Boning *Neptunus, China.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Boniran *Specpharm, S.Afr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Bonit *Nortech, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Bonit Join *Nortech, India.*
Chondroitin sulfate (p. 2476·1); glucosamine (p. 2515·3).

Bonit Plus *Nortech, India.*
Minerals; colecalciferol (p. 2113·1).

Bonitrop *Cofasa, Venez.*
Pyritinol hydrochloride (p. 394·3).
Fatigue; developmental brain disorders; sleep disorders; mental function disorders.

Bonium *Centaur, India.*
Calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).
Calcium and vitamin D deficiency.

Boniva *Roche, USA.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Bonjedex *Loyal Advance, Hong Kong.*
⊗Betamethasone sodium phosphate (p. 1623·3); chlorphenamine maleate (p. 620·3); oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Bonjela
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Austral.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel†; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Mouth pain and irritation; infant teething; herpes labialis.

Bonjela Cool Mint *Reckitt Benckiser, UK.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Oral pain and irritation; cold sores.

Bonjela Junior *Reckitt Benckiser, UK.*
Lidocaine hydrochloride (p. 1988·2); cetylpyridinium chloride (p. 1743·1).
Mouth pain and irritation; teething pain.

Bonjela Teething Gel *Reckitt Benckiser, UK.*
Lidocaine hydrochloride (p. 1988·2); cetalkonium chloride (p. 1741·3).
Infant teething.

Bonjigar *Herbion, Ukr.*
Eclipta alba; picrorhiza kurroa (p. 2590·2); black nightshade (p. 2458·2); chicory (p. 2475·2); glycyrrhiza glabra (p. 1853·2); tamarix gallica; raphanus sativus; Indian barberry (p. 2532·1); sphaeranthus indicus; punarnava (p. 2601·1).
Hepatitis.

Herbion, Rus.
Eclipta alba; picrorhiza kurroa (p. 2590·2); black nightshade (p. 2458·2); chicory (p. 2475·2); glycyrrhiza glabra (p. 1853·2); tamarix dioica; raphanus sativus; Indian barberry (p. 2532·1); milk thistle (p. 1561·1); sphaeranthus indicus; punarnava (p. 2601·1).
Liver disorders.

Bonjo Aid *Winsome, India.*
Glucosamine sulfate potassium (p. 2515·3); dimethyl sulfone (p. 2493·3); boron (p. 2052·3); manganese (p. 2081·2); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Bonky *Yuyu, Malaysia.*
Calcitriol (p. 2113·1).
Osteoporosis; rickets; osteomalacia; hypoparathyroidism; renal osteodystrophy; hypocalcaemia.

Bonlax
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Ital.
⊗Glycerol (p. 2517·2).
Constipation.

Bonlutin *Max Biocare, Austral.*
Fish oil (p. 1460·3); glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis; rheumatoid arthritis.

Bonmate *Aurora, Gr.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Bonmax
Note: this name may be used for preparations of different composition.
Apatex, Thai.
Alendronic acid (p. 1171·3).
Osteoporosis.

Zydus, India.
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Bonmin
Note: this name may be used for preparations of different composition.
Aksu, Turk.
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Micro, India.
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Bonningtons Irish Moss
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Carrageenan (p. 2176·3); camphor (p. 2466·2); menthol (p. 2553·2).
Cough; sore throat.

GSK, NZ.
Carrageenan (p. 2176·3); camphor (p. 2466·2); menthol (p. 2553·2); liquorice (p. 1853·2).
Cough.

Bonnisan *Himalaya Herbal, India.*
⊗Achillea (p. 2427·3); punarnava (p. 2601·1); capparis spinosa; elettaria cardamomum; piper longum; chebulic myrobalan (p. 2474·3); tinospora cordifolia; tribulus terrestris (p. 2633·3).
Tonic; digestive disorders.

Himalaya Herbal, Malaysia.
⊗Dill oil (p. 2493·2); tinospora cordifolia; capparis spinosa; piper longum; Indian gooseberry (p. 2532·2); chicory (p. 2475·2); cassia occidentalis; chebulic myrobalan (p. 2474·3); cardamom (p. 2471·1); achillea (p. 2427·3); tamarix gallica; tribulus terrestris (p. 2633·3); punarnava (p. 2601·1).
Tonic.

Bonnispaz *Himalaya Herbal, India.*
Caraway (p. 2470·2); zingiber officinale.

Bonobol *Ultramark, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Bonocef *Medilusa, Port.†*
Cefixime (p. 240·3).
Bacterial infections.

Bonodec *Ultramark, India.*
⊗Nandrolone (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Bonogren *Vipharm, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Bon-One *Teijin, China; Teijin, Hong Kong; Dipa, Indon.; Teijin, Indon.; Teijin, Malaysia; Teijin, Philipp.†; Teijin, Singapore; Teijin, Thai.*
Alfacalcidol (p. 2112·3).
Osteoporosis; chronic renal failure; hypoparathyroidism; rickets; osteomalacia; renal osteodystrophy; hyperparathyroidism; malabsorption of calcium.

Bonoteo *Astellas, Jpn.*
Minodronic acid (p. 1186·2).
Osteoporosis.

Bonox *Welti, Switz.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Bonrich-CT *Invision, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Bonrich-Z *Invision, India.*
Syrup: Calcium gluconate (p. 1783·3); cyanocobalamin (p. 2107·2); vitamin B_3; zinc sulfate (p. 2126·2).

Invision, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Bonserin *Rafa, Israel.*
Mianserin hydrochloride (p. 434·2).
Depression.

Bontact *Cadila, India.*
⊗Raloxifene (p. 2303·1).
Osteoporosis.

Bontal *Continentales, Mex.*
Diiodohydroxyquinoline (p. 931·1); phthalylsulfathiazole (p. 339·3); homatropine (p. 2007·3).
Diarrhoea.

Bontil *Probiomed, Mex.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Bontril *Valeant, USA.*
⊗Phendimetrazine tartrate (p. 2328·3).
Obesity.

Bonviva *Roche, Arg.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Ukr.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Nycomed, Hong Kong; Elder, India; Nycomed, Malaysia; Takeda, Singapore; Roche, Thai.; Roche, Turk.; Roche, UK.
Ibandronic acid (p. 1184·2).
Osteoporosis.

Bonycal *Taj, India.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; hyperphosphataemia in renal failure.

Bonyl *Orion, Denm.*
Naproxen (p. 98·2).
Inflammation; musculoskeletal and joint disorders; pain.

Bonzela *Genesis, India.*
Benzalkonium chloride (p. 1737·1); choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).

Bonzol
Note: this name may be used for preparations of different composition.
Bajamed, Mex.
Lansoprazole (p. 1851·3).
Peptic ulcer.

Mitsubishi, Jpn.
⊗Danazol (p. 2263·2).
Endometriosis.

Bonzplus *Plus, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Bookey *Skymax, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Bookey Plus *Skymax, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

Boost *Nestle, Canad.; Nestle, USA.*
A range of preparations for enteral nutrition.

Seven Seas, UK.
Caffeine (p. 1203·3); glucose (p. 2068·3); vitamin B substances (p. 2102·3); taurine (p. 2626·2).
Fatigue.

Booster-Gynatren *Strathmann, Ger.*
A trichomonal vaccine (p. 2422·2).
Vaginal disorders.

Booster-StroVac *Strathmann, Ger.*
Escherichia coli; *Morganella morganii* ; *Proteus mirabilis*; *Klebsiella pneumoniae*; *Enterococcus faecalis* (p. 2596·3).
Urinary-tract infections.

Boostim *Svizera, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Boostim-LB *Svizera, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Boostrix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia†; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Ukr.; GSK, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Boostrix IPV *GSK, Austral.; GSK, Irl.; GSK, NZ.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Boostrix Polio *GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Israel; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Thai.*
A diphtheria, tetanus, acellular pertussis and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Boostrixtetra *GSK, Fr.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Boots Athlete's Foot Cream *Boots, UK.*
Terbinafine hydrochloride (p. 593·3).
Tinea pedis; tinea cruris.

Boots Bite & Sting Relief Antihistamine *Boots Healthcare, Irl.*
Mepyramine maleate (p. 635·1).
Bites and stings.

Boots Chesty Cough Syrup 6 Years Plus *Boots, UK.*
Guaifenesin (p. 1666·2).
Cough.

Boots Cold & Flu Relief *Boots, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3) caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Boots Cold & Flu Relief Hot Lemon *Boots, UK.*
Paracetamol (p. 115·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Boots Constipation Relief *Boots, UK.*
Tablets: Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Boots, UK.
Suppositories: ⊗Glycerol (p. 2517·2).
Constipation.

Boots Cough & Decongestant Syrup 2 Years Plus *Boots, UK.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Boots Cough Syrup 3 Months Plus *Boots, UK.*
⊗Glycerol (p. 2517·2).
Coughs.

Boots Decongestant Capsules *Boots, UK.*
Phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Boots Decongestant Tablets *Boots, UK.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Boots Diarrhoea Relief *Boots, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Boots Dry Cough Syrup 1 Year Plus *Boots, UK.*
Pholcodine (p. 1675·1).
Coughs.

Boots Gripe Mixture 1 Month Plus *Boots, UK.*
Sodium bicarbonate (p. 1781·1).
Dyspepsia.

Boots Maximum Strength Cold & Flu Relief *Boots, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Boots Mouth Ulcer Pastilles *Boots, UK.*
Benzalkonium chloride (p. 1737·1); Compound Benzoin Tincture BP.
Mouth ulcers; sore gums.

Boots NicAssist *Novartis Consumer, Irl.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Boots Nightime Cough Syrup 1 Year Plus *Boots, UK.*
Diphenhydramine hydrochloride (p. 626·2); pholcodine (p. 1675·1).
Coughs.

Boots Pain Relief Heat Rub *Thornton & Ross, UK.*
Ethyl nicotinate (p. 56·3); hexyl nicotinate (p. 67·1); thurfyl salicylate (p. 137·1).
Musculoskeletal and joint pain; sprains; strains.

Boots Pain Relief Heat Spray *Boots, UK.*
Ethyl nicotinate (p. 56·3); methyl salicylate (p. 92·1); camphor (p. 2466·2).
Musculoskeletal and joint pain; sprains; lumbago; fibrositis; sciatica; strains; stiffness.

Boots Pain Relief Suspension 6 Years Plus *Boots, UK.*
Paracetamol (p. 115·1).
Fever; pain.

Boots Skin Allergy Relief *Boots, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic skin disorders.

Boots Threadworm Tablets 2 Years Plus *Boots, UK.*
Mebendazole (p. 158·3).
Threadworm.

Boots Ultra Cold & Flu Relief All in One *Boots, UK.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; cough.

Boots Water Relief *Lane, UK.*
Bearberry (p. 2453·2); clivers (p. 2481·2); lappa (p. 2540·1).
Water retention.

Boots Wind Relief *Boots, UK.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia.

B.O.P. *PPDH, Fr.*
Olive leaf (p. 2574·3); birch leaf (p. 2457·3).
Oedema.

Boplatex *Pisa, Mex.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Bopuqing *Chase Sun, China.*
Low-molecular-weight calcium heparin (p. 1426·1).
Thromboembolic disorders.

Boracap *Sriprasit, Thai.*
Vitamins; ferrous fumarate (p. 2060·3); calcium phosphate (p. 1784·2).

Boracough *Sriprasit, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Boradrine *Thea, Belg.†*
Borax (p. 2459·2); boric acid (p. 2459·3); phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Thea, Neth.†
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Borafen *Sriprasit, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Borag *Ativus, Braz.*
Fish oil (p. 1460·3); borage oil (p. 2459·2); soya oil (p. 2092·3).
Dietary supplement.

Borakid *Sriprasit, Thai.†*
Ibuprofen (p. 68·2).
Fever; pain; inflammation.

Boraline *McNeil, Spain.†*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Boramycin *Sriprasit, Thai.†*
Tetracycline phosphate complex (p. 373·2).
Bacterial infections.

Borasol *Prolab, Pol.*
Boric acid (p. 2459·3).
Skin disorders; burns; oedema.

Borbalan *Spyfarma, Spain.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Borbin *Gedeon Richter, Hung.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Bordersin *Cosmopharm, Gr.†*
Codergocrine mesilate (p. 389·2).

Borea *Rottapharm, Spain; Onko, Turk.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; anorexia and cachexia associated with cancer.

Boreade R *Expanscience, Fr.*
Emollient.
Dry and irritated skin and lips.

Borealist *Probiomed, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Boribel Tisane No 6 *Dietetique et Sante, Fr.†*
Chamomile (p. 2474·1); wild pansy (p. 2647·3); althaea (p. 2438·3); melissa (p. 2552·3); angelica (p. 2443·3).
Digestive disorders.

Boribel Tisane No 7 *Dietetique et Sante, Fr.†*
Angelica (p. 2443·3); boldo (p. 2458·3); fumitory (p. 2508·2); rosemary (p. 2607·2).
Biliary-tract disorders.

Boribel Tisane No 8 *Dietetique et Sante, Fr.†*
Asperula; passion flower (p. 2584·1); bitter orange (p. 2575·3); tilia (p. 2631·3); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Boribel Tisane No 9 *Dietetique et Sante, Fr.*
Ash (p. 2450·1); rosemary (p. 2607·2); fucus (p. 2612·1).
Slimming aid.

Boribel Tisane No 13 *Dietetique et Sante, Fr.†*
Frangula (p. 1843·3); senna (p. 1885·1); althaea (p. 2438·3); mallow (p. 2549·2).
Constipation.

Boribel Tisane No 17 *Dietetique et Sante, Fr.†*
Bearberry (p. 2453·2); ash (p. 2450·1).
Urinary-tract disorders.

Boripharm No 1 *Boiron, Fr.†*
Solidago virga aurea (p. 2620·1); belladonna (p. 2453·3); aconitum napellus (p. 2428·3); china (p. 2478·3); ferrum phosphoricum (p. 2077·1); arnica montana (p. 2447·2); rhus toxicodendron (p. 2603·3); nux vomica (p. 2573·3); carduus marianus (p. 1561·1); berberis vulgaris (p. 2502·1); hydrocotyle asiatica (p. 1698·3); aesculus hippocastanum (p. 2431·2).
Homoeopathic preparation.

Boripharm No 3 *Boiron, Fr.*
⊗Valeriana officinalis (p. 2640·2); gelsemium sempervirens (p. 2511·2); hyoscyamus niger (p. 2530·2); sumbul; passiflora (p. 2584·1); lobelia inflata (p. 2323·2); ignatia (p. 2532·1); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Boripharm No 10 *Boiron, Fr.†*
Belladonna (p. 2453·3); apis mellifica (p. 2445·2); hepar sulfuris calcareum (p. 1721·3); phytolacca decandra (p. 2593·2); spongia tosta; arum triphyllum; argentum nitricum (p. 2615·3); borax veneta (p. 2459·2); kalium chloratum (p. 1793·2); kalium sulfuricum (p. 1793·2).
Homoeopathic preparation.

Boripharm No 11 *Boiron, Fr.†*
Coccus cacti (p. 2179·2); drosera rotundifolia (p. 2497·2); bryonia alba; spongia tosta; aconitum napellus (p. 2428·3); eupatorium perfoliatum (p. 2459·1); magnesia phosphorica (p. 1787·3); kreosotum (p. 1659·3); senega (p. 1677·2); yerba santa (p. 1665·2).
Homoeopathic preparation.

Boripharm No 12 *Boiron, Fr.†*
⊗Kermes mineralis; tartarus emeticus (p. 151·2); ipecacuanha cephoelis; belladonna (p. 2453·3); lobelia inflata (p. 2323·2); arsenicum album (p. 2448·1); stramonium (p. 2622·3); magnesia phosphorica (p. 1787·3); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Boripharm No 15 *Boiron, Fr.†*
Ipeca (p. 1667·2); lycopodium (p. 2546·3); china (p. 2478·3); natrum phosphoricum (p. 1791·2); argentum nitricum (p. 2615·3); nux vomica (p. 2573·3); camphora (p. 2466·2); chelidonium majus (p. 2522·2); carduus marianus (p. 1561·1); thlaspi bursa pastoris (p. 2614·2).
Homoeopathic preparation.

Boripharm No 22 *Boiron, Fr.†*
Berberis vulgaris (p. 2502·1); hepar sulfuris (p. 1721·3); silicea (p. 2208·3); sulfur iodatum (p. 2624·2); belladonna (p. 2453·3); hydrocotyle asiatica (p. 1698·3); rhus toxicodendron (p. 2603·3); kalium sulfuricum (p. 1793·2); baptisia tinctoria (p. 2647·2).
Homoeopathic preparation.

Boripharm No 23 *Boiron, Fr.*
Benzoicum acidum (p. 1738·2); bryonia (p. 2461·3); lithium iodatum; colchicum automnale; kalmia latifolia (p. 2537·2); digitalis purpurea (p. 1352·3); asclepias tuberosa (p. 2593·2); apocynum cannabinum; oleander (p. 2574·3); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Boripharm No 31 *Boiron, Fr.*
⊗Kali phosphoricum (p. 1790·3); belladonna (p. 2453·3); agnus castus (p. 2432·2); chininum arsenicicum; iodum (p. 2336·3); digitalis purpura (p. 1352·3); laurocerasus (p. 2475·2); spigelia anthelmia (p. 2621·3); gelsemium sempervirens (p. 2511·2).
Homoeopathic preparation.

Boripharm No 41 *Boiron, Fr.*
Ballota; passiflora (p. 2584·1); crataegus oxyacantha (p. 2488·1); solidago virga aurea (p. 2620·1); origanum majorana (p. 2550·1).
Homoeopathic preparation.

Borizol *Borshchagovskii, Ukr.*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Born *Riemser, Ger.†*
Crataegus (p. 2488·1).
Cardiac disorders.

Borneral *Sandoz, Turk.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Bornilene *Abiogen, Ital.*
Xibornol (p. 387·3).
Mouth and throat infections.

Borocaina Gola *Wassermann, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disinfection.

Borocanfor *Vita, Venez.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1) zinc stearate (p. 2221·2); menthol (p. 2553·2); salicylic acid (p. 1719·1); boric acid (p. 2459·3); camphor (p. 2466·2).
Fungal foot infections.

Borocell *Neutron Technology, USA.*
Sodium monomercaptoundecahydro-closo-dodecaborate.
Glioblastoma multiforme.

Boroclarine *Europhta, Mon.†*
Borax (p. 2459·2); boric acid (p. 2459·3); phenylephrine hydrochloride (p. 1672·3).
Conjunctivitis.

Borofair Otic *Major, USA.†*
Acetic acid (p. 2426·3); aluminium acetate (p. 2440·1).

Borofax *Warner-Wellcome, USA.*
Zinc oxide (p. 1729·1).
Skin irritation.

Borogin *Roemmers Osmoph, Venez.*
Cetylpyridinium chloride (p. 1743·1); hydroxyquinoline sulfate (p. 2530·1); boric acid (p. 2459·3); alum (p. 2439·1).
Vaginal infections.

Boronex *Remedina, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Boropak *Glenwood, Canad.†*
Aluminium sulfate (p. 2440·2); calcium acetate (p. 1783·1).
Skin disorders.

Borophen *Dekaz, Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Boro-Scopol *Winzer, Ger.*
Hyoscine hydrobromide (p. 1845·3).
Eye disorders; production of mydriasis and cycloplegia.

Borostyrol *ACP, Belg.*
Topical solution: Thymol (p. 1772·2); salol (p. 129·3); menthol (p. 2553·2); boric acid (p. 2459·3); benzoin (p. 2624·3).
Mouth disorders.

Mayoly-Spindler, Fr.
Thymol (p. 1772·2); salol (p. 129·3); levomenthol (p. 2553·2); boric acid (p. 2459·3); siam benzoin (p. 2614·3).
Minor skin and mouth disorders; insect stings.

Boroswift *Ind-Swift, India.*
Boric acid (p. 2459·3); zinc oxide (p. 1729·1).

Borox *Biomax, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Borox-L *Biomax, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Borozin *Klar Sehen, India.*
Boric acid (p. 2459·3); chlorobutanol (p. 1747·2); phenethyl alcohol (p. 1763·2); borax (p. 2459·2); zinc sulfate (p. 2126·2).
Eye infections.

Borraginol-N *Takeda, Hong Kong†; Takeda, Indon.*
Benzocaine (p. 1980·2); cinchocaine hydrochloride (p. 1983·2); diphenhydramine hydrochloride (p. 626·2); cetrimide (p. 1742·1); radix lithospermi.
Anorectal disorders.

Borraginol-S *Takeda, Indon.*
⊗Prednisolone (p. 1645·2); lidocaine (p. 1988·1); benzocaine (p. 1980·2); cetrimide (p. 1742·1); radix lithospermi.
Anorectal disorders.

Borsdruppels *Aspen Consumer, S.Afr.*
Liquorice (p. 1853·2); fennel oil (p. 2503·3); anise oil (p. 2444·3).
Cough; croup; bronchitis.

Borstol Cold and Flu Powders with Vitamin C *Group, S.Afr.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Borstol Cough Remedy *Group, S.Afr.†*
Ammonium chloride (p. 1656·1); senega root (p. 1677·2); buchu (p. 2461·3); camphor (p. 2466·2); cinchona (p. 2478·3); aristolochia (p. 2447·1); balsam sulphuris; turpentine gum.
Cough.

Borstol Linctus *Group, S.Afr.†*
Guaifenesin (p. 1666·2).
Cough.

Bortenat *Natco, India.*
Bortezomib (p. 752·1).

Borymycin *YSP, Malaysia; Yung Shin, Singapore.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

BOS *Newcharoen, Thai.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis; rheumatic disorders.

Bosconar *Teva Tuteur, Arg.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bosisto's Antiseptic Spray *Felton, Austral.*
Eucalyptus oil (p. 2501·2); melaleuca oil (p. 2551·1); lavender oil (p. 2541·1).
Wounds; insect bites; skin disorders.

Bosisto's Eucalyptus Inhalant *Felton, Austral.*
Eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); sweet birch oil (p. 92·1); lavender oil (p. 2541·1).
Respiratory-tract congestion.

Bosisto's Eucalyptus Rub *Felton, Austral.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Muscular aches and pains.

Bosisto's Eucalyptus Spray *Felton, Austral.*
Eucalyptus oil (p. 2501·2).
Muscular aches and pains; insect stings; skin irritation.

Bosisto's EucoSteam Inhalant *Felton, Austral.*
Eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); lavender oil (p. 2541·1); sweet birch oil (p. 92·1).
Respiratory-tract congestion.

Bosisto's Nasal Inhaler *Felton, Austral.*
Eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); sweet birch oil (p. 92·1); peppermint oil (p. 1877·1).
Nasal congestion; cold symptoms.

Bosisto's Nasal Spray *Felton, Austral.*
Eucalyptus oil (p. 2501·2); sodium chloride (p. 1795·1).
Nasal congestion; nasal irritation; nasal dryness.

Bosisto's Vaporising Ointment *Felton, Austral.†*
Eucalyptus oil (p. 2501·2); cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2); rosemary oil (p. 2607·3).
Cold symptoms.

Bosnum *Unison, Hong Kong.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Unison, Thai.
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Bosporon *Nycomed, Port.; Grunenthal, Spain.*
Lornoxicam (p. 83·2).
Musculoskeletal and joint disorders; pain; inflammation.

Boston *Bausch & Lomb, Austral.; Bausch & Lomb, Canad.*
A range of solutions for gas permeable contact lenses.

Bausch & Lomb, USA.
Range of solutions for contact lenses.

Bosulif *Pfizer, UK; Pfizer, USA.*
Bosutinib (p. 753·2).
Chronic myeloid leukaemia.

Boswellia Complex *Mediherb, Austral.*
Indian frankincense (p. 2507·3); celery (p. 2472·3); ginger (p. 1844·1); turmeric (p. 2218·1).
Musculoskeletal and joint disorders.

Boswellia Compound *Phytomedicine, Austral.*
Indian frankincense (p. 2507·3); devil's claw root (p. 42·3); ginger (p. 1844·1); guaiacum resin (p. 2523·1).
Arthritis.

Botaderm *Biospray, Gr.; DAST, Gr.; Zekides, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Botafex *Pharmex (Φαρμεξ), Gr.*
Minoxidil (p. 1438·3).

Botam *Boniscontro & Gazzone, Ital.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Botamiral *Biospray, Gr.†; Zekides, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Botamycin-N *Biospray, Gr.; DAST, Gr.*
Clindamycin phosphate (p. 269·3).
Acne.

Botanica Hayfever *Botanica, NZ.*
Chamomile (p. 2474·1); lavender (p. 2541·1); melissa (p. 2552·3); quercetin (p. 2505·3); vitamin C (p. 2110·3).
Prevention of minor allergic reactions in the upper respiratory tract.

Botanica Sunscreen *Botanica, NZ.*
SPF 30+: Zinc oxide (p. 1729·1); octinoxate (p. 1715·1).
Sunscreen.

Botanics Daily Hand Therapy *Boots Healthcare, Canad.†*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Botanics Face Firming *Boots Healthcare, Canad.†*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Botanics Face Renewal *Boots Healthcare, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Botanova *Pascoe, UK.*
St John's wort (p. 449·1); valerian (p. 2640·2); passion flower (p. 2584·1).
Anxiety; low mood; sleep disorders.

Botastin *DAST, Gr.; Zekides, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Botidine *Patar, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Botinit *Anotaciones, Spain.*
Nitrofurazone (p. 333·1).
Burns; skin infections.

Botox *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, China; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Alvia (Αλβια), Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, India; Allergan, Indon.; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; GSK, Jpn; Allergan, Malaysia; Allergan, Mex.; Allergan, Neth.; Allergan, Norw.; Allergan, NZ; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, Rus.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, Ukr.; Allergan, USA; Allergan, Venez.*
Botulinum A toxin (p. 2017·1).
It is also described as containing onabotulinumtoxinA.
Foot spasticity associated with paediatric cerebral palsy; blepharospasm; hemifacial spasm; spasmodic torticollis; hyperhidrosis; glabellar lines; upper-limb spasticity following stroke; chronic migraine; strabismus; spasmodic dysphonia; neurogenic bladder; urinary incontinence associated with spinal cord injury or multiple sclerosis; bruxism; anal fissures; achalasia.

Botroclot *Juggat, India.*
Haemocoagulase (p. 1135·1).

Botropase *Juggat, India.*
Haemocoagulase (p. 1135·1).

Botrostat *Juggat, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Bottom Better *InnoVisions, USA.†*
Yellow soft paraffin (p. 2212·1); wool fat (p. 2219·3).
Nappy rash.

Botulax *Hugel, Thai.*
Botulinum A toxin (p. 2017·1).
Blepharospasm.

Botulift *Bergamo, Braz.*
Botulinum A toxin (p. 2017·1).

Boucren *Bouzen, Arg.*
Cetrimide (p. 1742·1).
Skin infections.

Boudreaux's All Natural Butt Paste *Fleet, USA.*
Zinc oxide (p. 1729·1); beeswax (p. 2170·2); Peru balsam (p. 2587·1); aloe (p. 1693·2); wax; castor oil (p. 2472·1).
Nappy rash.

Boudreaux's Butt Paste *Fleet, USA.*
Zinc oxide (p. 1729·1); castor oil (p. 2472·1); liquid paraffin (p. 2191·2); Peru balsam (p. 2587·1); soft paraffin (p. 2211·3).
Nappy rash.

Bouillet *Dietetique et Sante, Fr.*
Potassium chloride (p. 1793·2); calcium glutamate; adipic acid (p. 2431·1); glutamic acid (p. 2070·2); magnesium carbonate (p. 1856·2).
Dietary salt substitute.

Bounty Bears *Nature's Bounty, USA.*
Vitamins.

Boutavixal *Novendia, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Bovine Fastact *USV, India.*
⊗Insulin injection (bovine, purified) (p. 475·3).
Diabetes mellitus.

Bovine Longact *USV, India.*
⊗Insulin injection (bovine, purified) (p. 475·3).
Diabetes mellitus.

Bovine-Mixact *USV, India.*
⊗Insulin injection (bovine, purified) (p. 475·3).
Diabetes mellitus.

Bovisan *Sanum-Kehlbeck, Ger.*
Mycobacterium bovis.
Homoeopathic preparation.

Bowa *TNP, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence.

BoWei *Shuang Cheng, China.*
Levocarnitine (p. 2053·2).

Bowelac *Durga, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Bowlease *Lark, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Boxazin plus C *Boehringer Ingelheim, Ger.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

BoXin *Bai Ke, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Boxogetten S *Cheplapharm, Ger.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Obesity.

Boxolam *Mayo, Mex.†*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Boxter *Innovative, India.*
Piperacillin (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Boyol Salve *Pfeiffer, USA.*
Ichthammol (p. 1705·3); benzocaine (p. 1980·2).
Skin disorders.

Bozaktral *Chrispa (Χρισπα), Gr.*
Cisapride (p. 1831·3).
Diabetic gastroparesis resistant to other therapy.

Bozo *T Man, Thai.*
Pizotifen (p. 678·2).
Migraine; cluster headache.

BP *Brookstone, USA.*
⊗Urea (p. 1727·3).
Dry skin.

BP Allergy Junior *Brookstone, USA.†*
Chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

BP Cleansing Wash *Brookstone, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

BP 8 Cough *Macoven, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

BP Gel *Cintex, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

BP New Allergy DM *Brookstone, USA.†*
Brompheniramine tannate (p. 618·1); dextromethorphan tannate (p. 1660·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Bp Norm *Medley, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

BP Poly-650 *Brookstone, USA.*
Paracetamol (p. 115·1); phenyltoloxamine citrate (p. 638·1).
Pain.

BP Wash *Rivers Edge, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Bp-Act *Active, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Bp-Cure-AT *PromptCure, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Bpgard *Finecure, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

B-Platin *Blausiegel, Braz.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Bp-Loride *Elder, India.*
⊗Amiloride hydrochloride (p. 1299·1); atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

BPM PE DM *Boca, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Bp-Mide *Elder, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Bp-Mide Plus *Elder, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Bp-Nol *Elder, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

BPNorm *Westmont, Philipp.*
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

B-Potent *EuroHealth, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; lumbago; neuropathy; alcoholism; joint pain.

B.P.P. *Vickmans, Hong Kong.†*
Brompheniramine (p. 618·1); phenylephrine (p. 1672·2); phenylpropanolamine (p. 1674·1).

BPP Cough Syrup *Vickmans, Hong Kong.†*
Brompheniramine (p. 618·1); phenylephrine (p. 1672·2); phenylpropanolamine (p. 1674·1).

B-Prime *Primera, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

B-Prime Plus *Primera, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); calcium pantothenate (p. 2085·2).
Vitamin B deficiency; anaemia associated with folic acid deficiency.

B-Protin *British Biologicals, India.*
Preparation for enteral nutrition.

B-Prox *Elfin, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

BPzide *Stadmed, India.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

BQL *Zydus, India.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

B-Quick *Brassora, Arg.*
Pregnancy test (p. 2596·1).

Brachy *Positif, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Bradelmin *Degorts, Mex.*
Albendazole (p. 149·1).
Worm infections.

Bradex-Vioform *Novartis, India.*
Domiphen bromide (p. 1751·1); tripelennamine hydrochloride (p. 642·3).

Bradia *Biocon, India.*
Ivabradine (p. 1415·1).

Bradimox *Dompe, Ital.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bradoral *Novartis Consumer, Ital.*
Domiphen bromide (p. 1751·1).
Mouth and throat disinfection.

Bradosol
Note: this name may be used for preparations of different composition.
Columbia, Canad.
Hexylresorcinol (p. 1755·1).
Sore throat.
Novartis Consumer, Austria.
Domiphen bromide (p. 1751·1); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); anise oil (p. 2444·3).
Sore throat.
Novartis Consumer, UK.
Benzalkonium chloride (p. 1737·1).
Sore throat.

Bradoxil *Pharmawealth, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bradyhist *Misha, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Brady's-Magentropfen *Brady, Austria.*
Cinchona bark (p. 2478·3); cinnamon (p. 2479·2); aniseed (p. 2444·2); coriander (p. 2486·3); fennel (p. 2503·2); myrrh (p. 2566·1); santalum album (p. 2610·1); gentian (p. 2512·1); zedoary.
Gastrointestinal disorders.

Bragg's Medicinal Charcoal *Bragg, UK.*
Activated charcoal (p. 1537·3).
Dyspepsia; flatulence; heartburn.

Brahmi Super Learning Complex *Golden Glow, Austral.*
Bacopa (p. 2452·1); centella (p. 1698·3).
Dietary supplement.

Brainact *Kalbe, Indon.*
Citicoline (p. 2480·1).
Mental function impairment in the elderly.

Brainal *Aristo, Spain.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Brainolin *Dexa, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebral infarction; cerebral trauma; hemiplegia.

Brainox *Grunenthal, Port.*
Nimodipine (p. 1455·2).
Cerebral ischaemia after subarachnoid haemorrhage.

Brain-Rest *Ind-Swift, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; hiccup; restlessness; confusion.

Brain-Spect *Medi-Radiopharma, Cz.*
Technetium-99m (p. 2228·1) exametazime.
Radionuclide imaging of the CNS.

Brainstrong Prenatal Multivitamin plus DHA *i-Health, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1).

Braintop *Nycomed, Belg.*
Piracetam (p. 393·3).
Mental function impairment.

Brainvit *Mahakam Beta, Indon.*
Bovine colostrum (p. 2380·3); docosahexaenoic acid (p. 1460·1); arachidonic acid (p. 2446·1); betacarotene (p. 2051·1); vitamin B substances (p. 2102·3); vitamin D (p. 2112·3); dexpanthenol (p. 2582·2); calcium citrate (p. 1783·2).
Dietary supplement.

Braito *Konimex, Indon.†*
⊗Tetryzoline hydrochloride (p. 1678·3).
Allergic eye disorders; eye irritation.

Brakhor *Alpharma, Mex.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; atherosclerosis; cardiovascular risk reduction.

Brakke *Franco-Indian, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Bral
Note: this name may be used for preparations of different composition.
Biotech, Venez.
Dipyrone (p. 53·3).
Fever; pain.
Micro, India.
Diclofenac potassium (p. 48·3); dicycloverine hydrochloride (p. 1834·2).
Micro, Rus.
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Pain; smooth muscle spasm.

Bralangine *Bryntsalov, Rus.*
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Pain; smooth muscle spasm.

Bralifex *Sanbe, Indon.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Bralifex Plus *Sanbe, Indon.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Bralin *Bernofarm, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebral infarction; hemiplegia.

Bramadol *Biocin, India.*
Tramadol (p. 139·2).
Pain.

Bramadol-P *Biocin, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Bramedil *Roemmers, Chile.*
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm; nausea and vomiting.

Bramedil Compuesto *Roemmers, Chile.*
Pargeverine hydrochloride (p. 1877·1); metamizole magnesium (p. 53·3).
Smooth muscle pain and spasm; nausea and vomiting.

Brameston *Remedica, Singapore.*
Bromocriptine (p. 895·3).
Parkinsonism; galactorrhoea; infertility; acromegaly; lactation suppression; benign breast disorders; hypogonadism.

Bramicil *Fisiopharma, Ital.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Bramin *Degorts, Mex.†*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).
Influenza symptoms.

Bramino *Taft, Denm.*
Branched chain amino acids.
Nutritional supplement in hepatic encephalopathy.

Bramitob *Torrex Chiesi, Austria; Chiesi, Braz.; Torrex Chiesi, Cz.; Chiesi, Ger; Chiesi, Gr; Torrex Chiesi, Hung.; Chiesi, Irl.; Chiesi, Israel; Chiesi, Ital.; Promedica, Neth.; Torrex Chiesi, Pol.; Angelini, Port.; Chiesi, Spain; Vifor, Switz.; Trinity, UK.*
Tobramycin (p. 380·1).
Pseudomonal lung infection in cystic fibrosis.

Chiesi, Rus.
Tobramycin sulfate (p. 380·2).

BranchAmin *Baxter, USA.†*
Amino acids.
Parenteral nutrition in hepatic encephalopathy.

Brand- u. Wundgel-Medice *Medice, Ger.*
⊗Benzethonium chloride (p. 1738·1); lauromacrogol 400 (p. 2194·1); urea (p. 1727·3).
Burns; insect stings; skin disorders; wounds.

Brandiazin *Medphano, Ger.†; IFET (ΙΦΕΤ), Gr.*
Sulfadiazine silver (p. 362·3).
Burns.

Brand's *Cerebos, Hong Kong.*
Nutritional supplements.

Branigen *Sigma-Tau, Ital.*
Acetylcarnitine hydrochloride (p. 2053·2).
Peripheral nerve disorders.

Branitil *OFF, Ital.†*
Acetylcarnitine hydrochloride (p. 2053·2).
Peripheral nerve disorders; cerebrovascular disorders.

Branta *Torrent, Braz.*
Amlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).

Branzol *Fecofar, Arg.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Brasan *Vianex (Βιανεξ), Gr.*
⊗Serrapeptase (p. 2613·3).
Inflammatory disorders.

Brasart *Sigma, Braz.*
Valsartan (p. 1521·2).

Brasivol *Stiefel, Austral.†; Stiefel, Fr.; Stiefel, Irl.†; Stiefel, S.Afr.†; Stiefel, UK; GSK, USA.*
Aluminium oxide (p. 1690·3).
Abrasive skin cleanser; acne.

Brasmatic *Darya-Varia, Indon.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Brassel *Marvecs, Ital.*
Citicoline sodium (p. 2480·2).
Parkinsonism.

Bratofil *Inquifave, Venez.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Bratofil c Neomicina *Inquifave, Venez.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Braunoderm
Note: this name may be used for preparations of different composition.
Braun, Belg.; Braun, Ger.; Braun, Irl.†; Braun, Ital.; Braun, Port.†; Braun, Switz.
Povidone-iodine (p. 1767·1); isopropyl alcohol (p. 1758·3).
Skin disinfection; wounds.

Braunodine *Braun, Belg.†*
Povidone-iodine (p. 1767·1).

Braunol *Braun, Austria; Braun, Belg.; Braun, Cz.; Braun, Ger.; Ratiopharm, Ger.; Braun, Irl.†; Braun, Ital.; Braun, Neth.; Braun, Port.; Braun, Switz.*
Povidone-iodine (p. 1767·1).
Disinfection of mucous membranes, skin, ulcers, and wounds; skin infections; burns.

Braunosan *Braun, Irl.†; Braun, Switz.†*
Povidone-iodine (p. 1767·1).
Skin disinfection; hand disinfection.

Braunosan H Plus *Braun, Switz.†*
Povidone-iodine (p. 1767·1).
Hand and skin disinfection.

Braunovidon *Braun, Austria; Braun, Cz.; Braun, Ger.; Braun, Hung.; Braun, Irl.†; Braun, Pol.; Braun, Switz.*
Povidone-iodine (p. 1767·1).
Burns; infected skin disorders; wounds; ulcers; skin disinfection.

Bravelle *Ferring, Austria; Ferring, Braz.; Ferring, Canad.; Ferring, Cz.; Ferring, Denm.; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Irl.; Ferring, Israel; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Port.; Ferring, Spain; Ferring, Swed.; Ferring, Ukr.; Ferring, USA.*
Urofollitropin (p. 2312·2).
Male and female infertility.

Bravintone *Bryntsalov, Rus.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; vestibular disorders; vascular eye disorders.

Bravoderm-N *Bufa, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Brax *Biomep, Mex.*
Paracetamol (p. 115·1); naproxen (p. 98·2).
Pain.

Braxan *Armstrong, Mex.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; angina pectoris.

Braxidin *Sanbe, Indon.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal disorders; smooth muscle spasm; anxiety.

Brazaves *Actelion, Jpn.*
Miglustat (p. 2559·3).
Niemann-Pick disease type C.

Brazepam *Aspen, S.Afr.*
Bromazepam (p. 1041·2).
Anxiety.

Brazo *Kamakshi, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Brazo-D *Kamakshi, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).

Brazo-IT *Kamakshi, India.*
Rabeprazole (p. 1881·1); itopride.
Gastro-oesophageal reflux.

Bre-A-Col
Note: this name may be used for preparations of different composition.
Grossman, Mex.
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Breacol
Note: this name may be used for preparations of different composition.
Invida, Hong Kong; Invida, Singapore.
Guaifenesin (p. 1666·2).
Cough; sore throat.

Breaflu *Grossman, Mex.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders; rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Breakyl *Meda, Denm.; Meda, Fin.; Meda, Irl.; Meda, Neth.; Meda, UK.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Breast Enhancer *Homeocan, Canad.*
Folliculinum; mammary glands; sabal serrulata (p. 2363·3); connective tissue.
Homoeopathic preparation.

Breathe Free *Thompson, USA.*
Sodium chloride (p. 1795·1).
Inflammation and dryness of nasal membranes.

Breathe More *Homeocan, Canad.*
⊗Adrenalinum (p. 1292·1); belladonna (p. 2453·3); ipecacuanha (p. 1667·2); lobelia inflata (p. 2323·2); sambucus niger (p. 2609·3); solidago virgaurea (p. 2620·1); stramonium (p. 2622·3); yerba santa (p. 1665·2).
Homoeopathic preparation.

Breathezy *MSN, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Breathezy-L *MSN, India.*
Montelukast (p. 1214·3); levocetirizine (p. 632·3).

Breathline *Gerolymatos, Gr.*
⊗Beclometasone dipropionate (p. 1621·2).

Breathquality-UBT *AB, Ital.*
Carbon-13 labelled urea (p. 2470·3).
Test for gastroduodenal Helicobacter pylori *infection.*

Breathy *Novell, Indon.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal dryness.

Brecare *Maple, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Brecila *Accord, Braz.*
Epirubicin (p. 787·1).

Brecolin *Malaysia Chemist, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).

Brecolin BM *Malaysia Chemist, Singapore.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Bredelin *Senosiain, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Bredinin *Asahi, China; Asahi, Jpn.*
Mizoribine (p. 1960·1).
Transplant rejection; rheumatoid arthritis; nephrotic syndrome; lupus nephritis.

Bredon *Organon, Mex.*
Oxolamine citrate (p. 1671·2).
Cough.

Bree-C *Bionova, India.*
⊗Bromelains (p. 2460·3); omega-3 fatty acids (p. 1460·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Breeze 2 *Bayer, UK.*
Test for glucose in blood (p. 2516·3).

Breezee Mist Foot Powder *Pedinol, USA.*
Aluminium chlorohydrate (p. 1694·1); menthol (p. 2553·2); undecenoic acid (p. 596·3).
Formerly known as Breezee Mist Antifungal.
Fungal skin infections.

Brefar *Farcoral, Mex.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Brefit *Ipca, Port.*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction; diabetic nephropathy; heart failure; myocardial infarction.

Bregamin *Continentales, Mex.*
Oral solution; tablets: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Allergic conjunctivitis; rhinitis; respiratory-tract congestion.

Continentales, Mex.
Syrup: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Allergic conjunctivitis; rhinitis; respiratory-tract congestion.

Bregamin FC *Continentales, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Breinox *Farma, Venez.*
Piracetam (p. 393·3).
Mental function impairment; fatigue.

Brek *TRB, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Brelcip *Micro, Philipp.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Brellercet *Brown & Burk, Philipp.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Brelomax *Abbott, Ger.†*
⊗Tulobuterol hydrochloride (p. 1239·2).
Obstructive airways disease.

Brelox *Brel, Philipp.†*
Cefaclor (p. 232·3).
Bacterial infections.

Bremagan Flu *Boehringer Ingelheim Promeco, Mex.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Allergic rhinitis; hay fever.

Bremax *Abbott, Mex.†; Abbott, Philipp.†*
⊗Tulobuterol hydrochloride (p. 1239·2).
Obstructive airways disease.

Bremecina *Collins, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Breminal *Gobbi, Arg.*
Tolterodine (p. 2370·2).
Bladder instability.

Bremol *Alpharma, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).

Bremon *Esteve, Spain.*
Clarithromycin (p. 266·2).
Bacterial infections.

Bremoxiral *Serral, Mex.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).

Bren *Kopran, India; Pharmachem, S.Afr.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Bren Plus *Kopran, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Brenaris *Metiska, Indon.*
Piracetam (p. 393·3).
Mental function disorders; alcoholism; behaviour disorders in children.

Brenax *Sandoz, Indon.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Brenda-35 ED *Alphapharm, Austral.*
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 inert tablets.
Androgenisation in females; combined oral contraceptive.

Brenea *Valeant, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Brenfed *Kopran, India.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Brenlax *Kopran, India.*
Chlorzoxazone (p. 2022·2); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Brenoxil *Tecnofarma, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Brentacort *Janssen-Cilag, Denm.*
⊗Hydrocortisone (p. 1640·1); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Brentan
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Indon.; Distriquimica, Spain.
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

McNeil, Denm.
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections.

Brentor *Zee, India.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Breo Ellipta *GSK, USA.*
⊗Fluticasone furoate (p. 1638·1); vilanterol trifenatate (p. 1239·3).
Obstructive airways disease.

Bresal *Berman, Mex.*
Phenylbutazone (p. 125·1).
Inflammation; musculoskeletal and joint disorders.

Bresben *Sandoz, Ger.†*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension.

Bresec *Vocate, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Brestazol *Tabuk, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Bretaris *Almirall, Spain.*
Aclidinium bromide (p. 1201·1).

Brethal *Fako, Turk.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Brethine *aai, USA.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Brethmol *Idaman, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Bretol *Flupal, Venez.*
⊗Tulobuterol hydrochloride (p. 1239·2).
Obstructive airways disease.

Bretylate *GSK, Singapore.*
Bretylium tosilate (p. 1328·2).
Ventricular arrhythmias.

Breva *Valeas, Ital.*
⊗Salbutamol (p. 1220·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Brevactid *Ferring, Ger.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility.

Brevafen *Janssen-Cilag, Arg.*
⊗Alfentanil hydrochloride (p. 18·2).
Analgesia in anaesthesia.

Brevex *Bago, Chile.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Muscle spasm; pain.

Brevibloc *Phebra, Austral.; Baxter, Austria; Baxter, Belg.; Cristalia, Braz.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; AFT, NZ; Baxter, Port.; Sanofi Synthelabo, S.Afr.†; BMS, Singapore; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK; Baxter, USA.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension; angina pectoris; myocardial infarction.

Breviblok *Baxter, Rus.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension.

Brevicon *Pfizer, Canad.; Searle, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Brevil *Meditrina, Gr.*
Clarithromycin (p. 266·2).

Brevinaze *Intramed, S.Afr.†*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia; analgesia in painful procedures.

Brevinor *Pfizer, Austral.; Pfizer, Irl.†; Pfizer, NZ; Pfizer, UK.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Brevital *JHP, USA.*
Methohexital sodium (p. 1906·3).
General anaesthesia.

Brevitax *Teva, Cz.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Brevoxyl *Stiefel, Austral.; GSK, Austria; Stiefel, Belg.; GSK, Fin.; GSK, Fr.; GSK Consumer, Ger.; Stiefel, Ger.; GSK, Gr.; Stiefel, Hong Kong; Stiefel, India; GSK, Irl.; Stiefel, Malaysia; Stiefel, Norw.†; Stiefel, NZ; Stiefel, Philipp.†; Stiefel, Pol.; GSK, S.Afr.; GSK, Singapore; Stiefel, Swed.; Stiefel, Thai.; Stiefel, UK; GSK, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Brewers Yeast *Greater Pharma, Thai.*
Dried yeast (p. 2125·2).
Vitamin B deficiency.

Nature's Bounty, USA.
Vitamin B substances (p. 2102·3).

Seven Seas, UK.
Yeast (p. 2125·2); vitamin B substances (p. 2102·3).

Brex *Shalaks, India.*
Syrup: ⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1).

Shalaks, India.
Tablets: Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Brexecam *Adcock Ingram, S.Afr.*
Piroxicam betadex (p. 126·1).
Musculoskeletal and joint disorders; gout.

Brexel *Kalbe, Indon.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer; ovarian cancer.

Brexelant *Zee, India.*
Vitamins; minerals.

Brexell Plus *TRB, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Brexic *Wockhardt, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Brexicam *Pierre Fabre, Mex.*
Piroxicam betadex (p. 126·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Brexidol *Leiras, Fin.†; Asche Chiesi, Ger.†; Nycomed, Norw.; Nycomed, Swed.; Chiesi, UK.*
Piroxicam betadex (p. 126·1).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Promedica, Ital.
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Brexin
Note: this name may be used for preparations of different composition.
Torrex, Austria; Gross, Braz.; Pierre Fabre, Fr.; Chiesi, Gr.; Torrex Chiesi, Hung.; Chiesi, Israel; Promedica, Ital.; Chiesi, Malaysia; Chiesi, Port.; Chiesi, Thai.
Piroxicam betadex (p. 126·1).
Pain; inflammation; gout; musculoskeletal, joint, and peri-articular disorders.

Cofasa, Venez.
Paracetamol (p. 115·1).
Fever; pain.

Brexine *Chiesi, Belg.; Chiesi, Neth.†*
Piroxicam betadex (p. 126·1).
Gout; pain; musculoskeletal, joint, and peri-articular disorders.

Brexinil *Chiesi, Spain.†*
Piroxicam betadex (p. 126·1).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

Brexivel *Promedica, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Brexodin *Quimica y Farmacia, Mex.*
Piroxicam (p. 125·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Brexonase *Etex, Chile.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Brexotide *Etex, Chile.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Brexovent *Etex, Chile.†*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Brex-S *Shalaks, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Brezal *Novartis, Ital.*
Choline alfoscerate (p. 389·2).
Mental function impairment in the elderly.

Briacon *Edas, Rus.*
Gelsemium sempervirens (p. 2511·2); phosphorus (p. 2589·2); aconitum napellus (p. 2428·3); bryonia dioica (p. 2461·3); drosera (p. 2497·2); toxicodendron quercifolium (p. 2603·3).
Homoeopathic preparation.

Briazide *Pierre Fabre, Fr.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Brical *Briskon, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Bricalin *Teva, Israel; LBS, Philipp.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease; premature labour.

Brical-ZM *Briskon, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Bricanyl *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, China; 3M, Cz.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.†; AstraZeneca, Turk.; AstraZeneca, UK.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease; premature labour.

Bricanyl Composto *AstraZeneca, Braz.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Bricanyl EX *AstraZeneca, Mex.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Bricanyl Expectorant *AstraZeneca, Irl.†; AstraZeneca, Philipp.; AstraZeneca, Thai.†*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Cough; obstructive airways disease.

Bricanyl Expektoran *AstraZeneca, Turk.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Respiratory-tract disorders with bronchospasm.

Bricarex *AstraZeneca, India.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Asthma; cough.

Bricarex A *AstraZeneca, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Bricasma *AstraZeneca, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bricasma Expectorant *AstraZeneca, Indon.†*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Bricasol *AstraZeneca, China.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Brick *Briskon, India.*
Oral suspension: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Briskon, India.
Tablets: Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Briclofar *Caldeira & Metelo, Port.*
Aciclovir (p. 964·1).
Herpes labialis.

Bricof *Cipla, India.*
⊗Guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Bridan *Organon, Rus.*
Sugammadex sodium (p. 1577·2).
Reversal of competitive neuromuscular blockade.

Bridatec *GE Healthcare, Fin.; GE Healthcare, Neth.; GE Healthcare, Port.†; GE Healthcare, Spain.*
Technetium-99m mebrofenin (p. 2228·1).
Radionuclide imaging of the biliary tract and liver.

Bridic *Menarini, Port.*
Brivudine (p. 970·1).
Herpes zoster infections.

Bridion *Schering-Plough, Austral.; Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; Organon, Cz.; Organon, Denm.; MSD-Chibret, Fr.; MSD, Ger.; Organon, Gr.; Organon, Hung.; Schering-Plough, Hung.; Organon, Irl.; Organon, Israel; Schering-Plough, Malaysia; Organon, Neth.; Organon, Norw.; Schering-Plough, NZ; Organon, Pol.; Organon, Port.; Organon, Spain; MSD, Swed.; MSD, Switz.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.*
Sugammadex sodium (p. 1577·2).
Reversal of competitive neuromuscular blockade.

Briellyn *Glenmark, USA.*
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Briem *Pierre Fabre, Fr.*
Benazepril hydrochloride (p. 1314·3).
Hypertension.

Brietal *Lilly, Austral.†; Hikma, Austria; Hikma, Neth.; Lilly, Pol.†; Lilly, Rus.*
Methohexital sodium (p. 1906·3).
General anaesthesia; hypnotic.

Brifeseptol *Bryntsalov, Rus.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis; malaria.

Briflam *Briskon, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); magnesium trisilicate (p. 1858·1).

Briform *CCPC, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Brighser *Solvang, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3).

Brighten Up *Dermalogica, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Briglau *Medana, Neth.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Briklin *BMS, Gr.; Vianex (Βιανεξ), Gr.*
Amikacin (p. 214·1).
Bacterial infections.

Bril *Ipca, Port.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Brilevo *Briskon, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Brilian *Gerolymatos, Gr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Brilinta *AstraZeneca, Braz.; AstraZeneca, Israel; AstraZeneca, Singapore; AstraZeneca, Thai.; AstraZeneca, USA.*
Ticagrelor (p. 1511·3).
Thromboembolism prophylaxis in acute coronary syndrome.

Brilique *AstraZeneca, Belg.; AstraZeneca, Denm.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Irl.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK.*
Ticagrelor (p. 1511·3).
Thromboembolism prophylaxis in acute coronary syndrome.

Brilizid *CCPC, Philipp.*
Glipizide (p. 474·1).
Diabetes mellitus.

Brillex *Lepine, Canad.*
Alkyldimethylethylbenzyl ammonium chloride (p. 1736·2); benzalkonium chloride (p. 1737·1).
Disinfection.

Brilliant Peel *Fluoron, Ger.*
Brilliant blue G (p. 2171·3).
Ophthalmic stain.

Brilocaine *Bryntsalov, Rus.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Brimex *Biomep, Mex.*
Aciclovir (p. 964·1).
Viral infections.

Brimo Ophtal *Winzer, Ger.*
Brimonidine tartrate (p. 2004·3).
Ocular hypertension; glaucoma.

Brimochek *Indoco, India.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brimochek-T *Indoco, India.*
⊗Brimonidine tartrate (p. 2004·3); timolol maleate (p. 1513·2).
Glaucoma.

Brimocom *Cipla, India.*
⊗Brimonidine tartrate (p. 2004·3); timolol maleate (p. 1513·2).
Glaucoma.

Brimocon *Alcon, China.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brimodin *Cipla, India.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brimodine *Alapis, Gr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brimoftal *Teuto, Braz.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brimogan *Cooper (Κοπερ), Gr.*
Brimonidine tartrate (p. 2004·3).
Ocular hypertension; glaucoma.

Brimo-Klonal *Klonal, Arg.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brimolol *Sun, India.*
⊗Brimonidine tartrate (p. 2004·3); timolol maleate (p. 1513·2).
Glaucoma.

Brimon *Rowex, Irl.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brimontal *Rafarm, Gr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brimopress *Poen, Arg.; Poen, Chile; Centaur, India.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brimoratio *Ratiopharm, Denm.; Ratiopharm, Norw.; Ratiopharm, Swed.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brimosun *Sun, India.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brimoteva *Teva, Pol.*
Brimonidine tartrate (p. 2004·3).
Ocular hypertension; glaucoma.

Brimox *Briskon, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Brimozept *Mibe, Ger.*
Brimonidine tartrate (p. 2004·3).
Ocular hypertension; glaucoma.

Brinal *Biomedica, Gr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brinaldix *Egis, Hung.; Novartis, India.*
⊗Clopamide (p. 1342·3).
Hypertension; oedema.

Brinavess *MSD, Belg.; MSD, Cz.; MSD, Denm.; MSD, Ger.; MSD, Gr.; MSD, Irl.; MSD, Israel; MSD, Neth.; MSD, Norw.; MSD, Pol.; MSD, Port.; MSD, Spain; MSD, Swed.; MSD, Switz.*
Vernakalant hydrochloride (p. 1526·2).
Atrial fibrillation.

Brinerdin *Novartis, Austria; KRKA, Rus.; Novartis, S.Afr.; Novartis, Thai.*
⊗Clopamide (p. 1342·3); dihydroergocristine mesilate (p. 390·1); reserpine (p. 1485·3).
Hypertension.

Brinerdina *Teofarma, Ital.*
⊗Clopamide (p. 1342·3); dihydroergocristine mesilate (p. 390·1); reserpine (p. 1485·3).
Hypertension.

Brinerdine *Novartis, Switz.*
⊗Clopamide (p. 1342·3); dihydroergocristine mesilate (p. 390·1); reserpine (p. 1485·3).
Hypertension.

Brinidin *Pharmanel, Gr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma.

Brinimo *Briskon, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Brintellix *Takeda, USA.*
Vortioxetine hydrobromide (p. 457·3).
Depression.

Brintenal *Beta, Arg.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Briofil *Teofarma, Ital.*
Bamifylline hydrochloride (p. 1203·2).
Obstructive airways disease.

Briomet *Farma, Venez.*
Cobamamide (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuropathy; myalgia; myopathy.

Brionot *Casasco, Arg.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Briop *Poen Vision, Mex.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Brioplus *Piam, Ital.*
Tryptophan (p. 453·2); griffonia simplicifolia (p. 2522·3); vitamin B substances (p. 2102·3).
Low mood.

Briovitan *Montefarmaco, Ital.*
Vitamins; minerals; flavonoids (p. 2505·2).
Nutritional supplement.

Briovitase *Montefarmaco, Ital.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium and potassium deficiency.

Briovitase Sostegno *Montefarmaco, Ital.*
Vitamins; minerals; carnitine (p. 2053·2); papaya.

Briptin *Bushnell, India.*
Bromocriptine (p. 895·3).
Parkinsonism; hypogonadism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Brisair *Euro Registratie, Neth.†; GSK, Spain.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease; asthma.

Briscocough *Quatromed, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Briscopyn *Quatromed, S.Afr.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); mepробamate (p. 1083·3); codeine phosphate (p. 40·2).
Pain with tension.

Briscotin *TO-Chemicals, Thai.†*
⊗Dihydroergocristine (p. 390·1); clopamide (p. 1342·3); reserpine (p. 1485·3).
Hypertension.

Brisdelle *Noven, USA.*
Paroxetine mesilate (p. 440·3).
Menopausal disorders.

Briserin N *Novartis, Ger.*
⊗Clopamide (p. 1342·3); reserpine (p. 1485·3).
Hypertension.

Brisking *Kanghong, China.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Brismucol *BMS, Braz.†; BMS, Mex.*
Ambroxol acefyllinate (p. 1201·2).
Respiratory-tract disorders.

Brisofer *Brymar, Philipp.*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Brisomax *Bialfar, Port.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Brisoral *BMS, Spain.†*
Cefprozil (p. 248·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Brisovent *Bialfar, Port.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Brispen *Hormona, Mex.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Bristacol *Juste, Spain.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Bristacycline *Bristol, USA.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Bristaflam *Almirall, Mex.; Elmor, Venez.*
Aceclofenac (p. 16·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Bristamox *BMS, Fr.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

BrisTaxol *BMS, Mex.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Bristopen *BMS, Fr.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Britagal *MD-Pharm, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Britaject *Britannia Pharmaceuticals, Norw.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Britaline *CCM, Malaysia.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Britamox *Reig Jofre, Spain.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Britapen *Reig Jofre, Spain.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Britapons *MD-Pharm, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Britaxol *BMS, Chile.*
Paclitaxel (p. 839·3).
Kaposi's sarcoma; ovarian cancer; breast cancer; non-small cell lung cancer.

Brite *Wallace, India.*
Lisadimate (p. 1710·3); hydroquinone (p. 1705·1).
Chloasma; melasma.

Britesite *Centaur, India.*
Indian barberry (p. 2532·1); coriander (p. 2486·3); curcuma longa; liquorice (p. 1853·2); honey (p. 2072·1); ocimum sanctum; phyllanthus niruri (p. 2590·1); piper longum; rose fruit (p. 2607·1).
Eye disorders.

Britlofex *Britannia Pharmaceuticals, UK.*
Lofexidine hydrochloride (p. 1556·3).
Opioid withdrawal symptoms.

Britomar *Ferrer, Ukr.*
⊗Torasemide (p. 1516·3).
Oedema; hypertension.

Brivex *Menarini, Switz.*
Brivudine (p. 970·1).
Varicella-zoster *infections.*

Brivir *Menarini, Gr.*
Brivudine (p. 970·1).
Herpes zoster infections.

Brivirac *Menarini, Ital.*
Brivudine (p. 970·1).
Herpes zoster infections.

Brixia *Poen, Arg.; Poen, Chile; Roemmers Poen, Venez.*
Azelastine hydrochloride (p. 617·1).
Allergic eye disorders; allergic conjunctivitis.

Brixilon
Note: this name may be used for preparations of different composition.
Leti, Venez.
Ambroxol acefyllinate (p. 1201·2).
Asthma.

Brixopan *Epifarma, Ital.*
Bromazepam (p. 1041·2).
Anxiety disorders; tension; psychosomatic disorders.

Brixoral *Biospray, Gr.; Zekides, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Broacil *Indian Drugs, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Broadced *Kalbe, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Broadcef *Sanjivani, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Broadcef-S *Sanjivani, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Broadcef-T *Sanjivani, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Broadcure *Sanjivani, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Broadicilin *Alkem, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Broadiclox *Alkem, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Broadiclox-LB *Alkem, India.*
Ampicillin (p. 218·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Bro-Am *T Man, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Brocaden *Pharmasant, Thai.†*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; parkinsonism.

Brocalcio D3 *Roemmers, Venez.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement.

Brocantol *Cofasa, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Brochlor *Sanofi-Aventis, UK.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Brocid *Briskon, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Brocil *Berman, Mex.*
Chloramphenicol succinate (p. 257·1).
Bacterial infections.

Brocin *Candor, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Brocof *Vamsler, Philipp.*
Ambroxol (p. 1654·3).
Respiratory-tract disorders with abnormal mucus.

Brocofrin *Diapit, Gr.*
⊗Salbutamol (p. 1220·2).

Brocolan *Berman, Mex.*
Dextromethorphan (p. 1660·1).

Brocosin *Heel, Canad.*
Antimonium tartaricum (p. 151·2); cuprum sulphuricum (p. 2057·2); drosera rotundifolia (p. 2497·2); ipecacuanha (p. 1667·2); spongia tosta; rumex crispus (p. 2649·3).
Homoeopathic preparation.

Brocoter *Dexter, India.*
⊗Guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Brocoter-A *Dexter, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Brodacid *Inco Veritas, Pol.*
Dimethyl sulfoxide (p. 2182·2); lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Brodifac *Mintlab, Chile.*
Ketorolac trometamol (p. 80·2).
Inflammation; pain.

Brodil
Note: this name may be used for preparations of different composition.
Sanovel, Turk.
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Vanguard, India.
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Brodilan *Zuoz, Venez.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Bronchospasm.

Brodil-D *Vanguard, India.*
Dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); triprolidine hydrochloride (p. 642·3).

Brodilin *Zuoz, Venez.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Bronchospasm.

Brodisym *Symbiosis, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Broend *Parggon, Mex.*
Guaifenesin (p. 1666·2); sodium dibunate (p. 1677·3).
Cough.

Brofed
Note: this name may be used for preparations of different composition.
Marnel, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Pharmaland, Thai.†
Bromperidol (p. 1041·3).
Psychoses.

Brofentol *Duckbill, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); sorbitol (p. 2092·1).

Brofentol Plus *Duckbill, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Broflex
Note: this name may be used for preparations of different composition.
Scoshia, India.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rosemont, UK.†
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Broflox *Briskon, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Broflox Plus *Briskon, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Brogal *Rayere, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Brogal Compositum *Rayere, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Brogalas *Galex, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Brogal-T *Rayere, Mex.*
Ambroxol hydrochloride (p. 1654·3); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract congestion; cough.

Brogamax *Rayere, Mex.*
Co-trimoxazole (p. 277·3); ambroxol (p. 1654·3).
Bacterial infections of the respiratory tract.

Brohist D *Allegis, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Broi *Vannier, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Broksin *Abdi, Turk.*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2); potassium iodide (p. 2336·3); diprophylline (p. 1207·3).
Respiratory-tract disorders.

Brolamina *Teva, Mex.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Brolene *Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Genop, S.Afr.; Aventis, UK.*
Dibrompropamidine isetionate (p. 1750·1) or propamidine isetionate (p. 1767·3).
Eye infections.

Sanofi-Aventis, Austral.; IFET [ΙΦΕΤ], Gr.
Propamidine isetionate (p. 1767·3).
Eye infections.

Brolene Cool Eyes *Aventis, UK.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Brolexan *Medifarma, Indon.†; UAP, Indon.†*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Brolin
Note: this name may be used for preparations of different composition.
Pharma Investi, Chile.
Cysteine (p. 2058·3); zinc (p. 2126·1); pyridoxine (p. 2105·3); biotin (p. 2052·2).
Hair and nail disorders.

Brolin Forte *Pharma Investi, Chile.*
Cysteine (p. 2058·3); vitamins; minerals.
Hair and nail disorders.

Brom *Inga, India.*
Bromocriptine mesilate (p. 895·3).
Parkinsonism; hypogonadism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Bromace *Ace, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with abnormal mucus.

Bromacef *Ad-Drugstel, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with abnormal mucus.

Bromadine-DM *Cypress, USA.*
Brompheniramine hydrochloride (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Bromalex *Sandoz, Braz.; Vitoria, Port.*
Bromazepam (p. 1041·2).
Anxiety.

Bromaline *Rugby, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Bromaline DM *Rugby, USA.†*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Bromam *Sandoz, Denm.*
Bromazepam (p. 1041·2).
Anxiety.

Bromarest DX *Warner Chilcott, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Bromatan Plus *Cypress, USA.*
⊗Pseudoephedrine tannate (p. 1676·1); dextromethorphan tannate (p. 1660·1); dexchlorpheniramine tannate (p. 620·3).
Cold symptoms; cough; sinusitis; allergic rhinitis.

Bromatan-DM *Cypress, USA.†*
Brompheniramine tannate (p. 618·1); phenylephrine tannate (p. 1672·2); dextromethorphan tannate (p. 1660·1).
Coughs; nasal congestion.

Bromatane DX *Goldline, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Bromatanil *Investi, Arg.†*
Bromazepam (p. 1041·2).
Anxiety.

Bromatop *Apotex, Belg.*
Bromazepam (p. 1041·2).
Anxiety; sleep disorders.

Bromavon *Hua, Thai.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; respiratory-tract disorders.

Bromax *Pentafarma, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bromazanil *Hexal, Ger.†*
Bromazepam (p. 1041·2).
Anxiety; tension.

Bromaze *Hexal, S.Afr.*
Bromazepam (p. 1041·2).
Anxiety.

Bromazep *CT, Ger.†*
Bromazepam (p. 1041·2).
Anxiety; insomnia.

Bromazolo *Baldacci, Ital.*
Thiamazole (p. 2345·2); dibromotyrosine (p. 2336·3).
Hyperthyroidism.

Bromceryl *Suphong, Thai.*
Guaifenesin (p. 1666·2); brompheniramine maleate (p. 618·1); phenylephrine (p. 1672·2).
Cold symptoms.

Bromcolex *Osoth, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromcolin *Synco, HongKong.†*
Bromhexine (p. 1656·3); codeine (p. 40·2).
Cough.

Bromcough *Hi-Tec, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Bromday *Ista, USA.*
Bromfenac sodium (p. 30·1).
Eye inflammation and pain following cataract surgery.

Bromdex D *Breckenridge, USA.*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Bromedrina *Sankyo, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromek *Kocak, Turk.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromeksin *Oro, Turk.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromel *Antibioticos, Mex.†*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Bromelip *Maver, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Bromenval *Omsk, Rus.*
Crataegus (p. 2488·1); valerian (p. 2640·2); menthol (p. 2553·2); sodium bromide (p. 2461·1).
Nervous disorders.

Bromergon *Sandoz, Hong Kong; Sandoz, Pol.; Lek, Rus.; Sandoz, Thai.*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; menstrual disorders; female infertility; prolactinoma; lactation inhibition; parkinsonism; benign breast disorders; galactorrhoea; acromegaly; amenorrhoea.

Bromesep Elixir *Siam Bheasach, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Bromesep Expectorant *Siam Bheasach, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Allergic rhinitis; cough; nasal congestion.

Bromesep Syrup *Siam Bheasach, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Bromex *Qualiphar, Belg.; Cipla, India; PP Lab, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion; obstructive bronchopneumonopathies; bronchiectasis; sinusitis; Sjögren's syndrome.

Bromexidril *Klonal, Arg.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Bromexol *Galeno, Venez.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Bromfed *Verum, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Bromfed-DM *Wockhardt, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Allergic rhinitis; coughs; vasomotor rhinitis.

Bromfed-PD *Verum, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Bromhetos *Lafedar, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromhex *McNeil, Swed.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

T Man, Thai.
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Bromhist *Cypress, USA.†*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Bromhist PDX *Cypress, USA.*
Syrup: Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).

Cypress, USA.†
Oral drops: ⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Bromhist-DM *Cypress, USA.†*
Syrup: ⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Cypress, USA.†
Oral drops: ⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs; upper respiratory-tract congestion.

Bromhist-NR *Cypress, USA.†*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).

Bromhistop *Neo Dermos, Arg.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Bromicof *Loeffler, Mex.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromidem *Nycomed, Belg.*
Bromazepam (p. 1041·2).
Insomnia; anxiety.

Bromifen *Neo Quimica, Braz.*
⊗Fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Bromika *Ikapharmindo, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Bromil *EMS, Braz.*
Syrup: Cineole (p. 2479·1); terpineol (p. 2627·2); menthol (p. 2553·2).
Cough.

EMS, Braz.
Pastilles: Menthol (p. 2553·2); terpineol (p. 2627·2); cineole (p. 2479·1); ascorbic acid (p. 2110·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Bromil Grip *EMS, Braz.†*
Paracetamol (p. 115·1); dexchlorpheniramine (p. 620·3); phenylephrine (p. 1672·2); caffeine (p. 1203·3); menthol (p. 2553·2); terpineol (p. 2627·2); cineole (p. 2479·1).

Bromi-Lotion *Gordon, USA.*
Aluminium chlorohydrate (p. 1694·1).
Bromhidrosis; hyperhidrosis.

Brominol-C *Sons, Mex.†*
Dextromethorphan (p. 1660·1); ambroxol (p. 1654·3).
Cough.

Bromiphed *BJ Benjaosoth, Thai.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Bromiramin *Norma (Νορμα), Gr.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory disorders associated with viscous mucus.

Bromitapp *Interhealthcare, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Cold symptoms; allergic rhinitis.

Bromiton *Christo, Hong Kong.†*
Brompheniramine (p. 618·1).

Bromivec *Precimex, Mex.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Bromixen *Maver, Mex.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Bromlamine *Chinta, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Bromma *T Man, Thai.*
Brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

Brommer *Mersifarma, Indon.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Bromo Madelon *St Laurent, Canad.†*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).

Bromo Seltzer
Note: this name may be used for preparations of different composition.
Tower, Canad.†
Sodium citrate (p. 1781·2).
Dyspepsia; gastric hyperacidity.

Warner-Lambert, USA.†
Paracetamol (p. 115·1).
Pain; fever.

Bromo Seltzer Effervescent Granules *Warner-Lambert, USA.†*
Sodium bicarbonate (p. 1781·1); paracetamol (p. 115·1); citric acid (p. 2480·3).
Hyperacidity.

Bromocal
Note: this name may be used for preparations of different composition.
Caldeira & Metelo, Port.†
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromocalcio *Pasteur, Chile.†*
Calcium bromolactobionate (p. 1044·1).
Insomnia; nervous disorders.

Bromocod N *Streuli, Switz.†*
Codeine phosphate (p. 40·2); belladonna (p. 2453·3); drosera (p. 2497·2); ipecacuanha (p. 1667·2); opium (p. 111·3); terpin hydrate (p. 1678·2).
Cough.

Bromocorn *Filofarm, Pol.*
Bromocriptine (p. 895·3).
Prolactinoma; hyperprolactinaemia; menstrual disorders; male and female infertility; lactation inhibition; parkinsonism.

Bromodol *Janssen-Cilag, Arg.; Janssen-Cilag, Gr.*
Bromperidol (p. 1041·3) or bromperidol decanoate (p. 1041·3).
Psychoses; mania; agitation; anxiety.

Bromogen *Uni-Sankyo, India.*
Bromocriptine (p. 895·3).
Parkinsonism; hypogonadism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Bromogex *Gross, Braz.*
Bromopride (p. 1824·2).

Bromohexal *Hexal, Austral.†*
Bromocriptine mesilate (p. 895·3).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism; prolactinomas.

Bromo-Kin *Sanofi-Aventis, Fr.*
Bromocriptine mesilate (p. 895·3).
Lactation inhibition; parkinsonism; hyperprolactinaemia; prolactinomas.

Bromolin *Cipla, India.*
Bromhexine (p. 1656·3) or bromhexine hydrochloride (p. 1656·3); amoxicillin (p. 216·2).
Respiratory-tract infections.

Bromopan *UCI, Braz.*
Bromopride (p. 1824·2).

Bromophar *Qualiphar, Belg.*
Codeine phosphate (p. 40·2).
Cough.

Bromopirin *Sigma, Braz.*
Bromazepam (p. 1041·2); sulpiride (p. 1107·3).
Psychoses.

Bromoson *Unison, Hong Kong; Unison, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased mucus; respiratory-tract disorders associated with increased or viscous mucus.

Bromotec *Teuto, Braz.*
⊗Fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Bromotil *Ariston, Arg.*
Otilonium bromide (p. 2578·2).
Smooth muscle spasm.

Bromotiren *Baldacci, Ital.*
Dibromotyrosine (p. 2336·3).
Hyperthyroidism.

Bromotuss with Codeine *Rugby, USA.†*
Bromazine hydrochloride (p. 617·3); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Bromovent *Bergamo, Braz.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Bromox *Etifar, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromoxil *Vitae, Mex.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Bromoxon *Sanval, Braz.*
Bromazepam (p. 1041·2).
Anxiety.

Bromped *Hua, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; allergic respiratory-tract disorders.

Brom/PE/DM *Brighton, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Bromphen
Note: this name may be used for preparations of different composition.
T Man, Thai.
Brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

Bromphen DX Cough *Muro, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Bromphenex *Ethex, Hong Kong.†*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Brompheniramine Cough *Geneva, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Brompheniramine/Pseudoephedrine DM *Macoven, USA.*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Brom-PP *Jean-Marie, Hong Kong.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).
Respiratory-tract disorders.

Brom-Ramine Compound *Universal, Hong Kong.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).
Respiratory-tract disorders.

Bromsin *Patar, Thai.*
Brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

Bromso *TO-Chemicals, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bromso-Ex *TO-Chemicals, Thai.*
Bromhexine hydrochloride (p. 1656·3); sulfogaiacol (p. 1678·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromsuno *Milano, Thai.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Cold symptoms.

Bromtussia *Asian Pharm, Thai.*
Guaifenesin (p. 1666·2); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; cough.

Bromtussia DC *Asian Pharm, Thai.†*
Guaifenesin (p. 1666·2); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2).
Nasal congestion; cough.

Bromtussin
Note: this name may be used for preparations of different composition.
ANH, Thai.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bromuc *Ariston, Braz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromurex *Pisa, Mex.†*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Bromussyl *Zizhu, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bromxin *Masa, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Bromxine *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.; General Drugs, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromycil *Ace, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess mucus.

Bron 6 *Capo Sole, Ital.*
Chestnut honey (p. 2072·1); propolis (p. 2597·3); althaea (p. 2438·3); erisimo; thyme (p. 2630·2); wild rose; niaouli oil (p. 2569·1).
Food supplement; tonic.

Bronal
Note: this name may be used for preparations of different composition.
Eurodrug, Hong Kong; Eurodrug, Thai.
Levodropropizine (p. 1662·3).
Cough.

Bronalide *Boehringer Ingelheim, Gr.*
⊗Flunisolide (p. 1635·3).
Asthma.

Bronar *Degorts, Mex.*
Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2).
Respiratory-tract disorders.

Bronax *Roemmers, Arg.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Bronax Flex *Roemmers, Arg.*
Meloxicam (p. 86·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Broncafect *Mediherb, Austral.*
Pleurisy root (p. 2593·2); echinacea (p. 2498·1); liquorice (p. 1853·2); marrubium (p. 1668·3); thyme (p. 2630·2); ginger (p. 1844·1).
Cough; cold and influenza symptoms.

Broncaire Expectorant *Biolab, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Obstructive airways disease.

Broncalène *Hepatoum, Fr.*
Pholcodine (p. 1675·1); chlorphenamine maleate (p. 620·3); sodium benzoate (p. 1738·2).
Cough.

Broncalène Nourisson *Tonipharm, Fr.†*
Chlorphenamine maleate (p. 620·3); sodium benzoate (p. 1738·2); tolu balsam (p. 1679·2).
Cough.

Broncard *Labomed, Chile.*
Levodropropizine (p. 1662·3).
Cough.

Broncare *Symbiosis, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1).

Broncatar
Note: this name may be used for preparations of different composition.
Cazi, Braz.
Bromhexine hydrochloride (p. 1656·3); sulfogaiacol (p. 1678·1).
Respiratory-tract congestion.

Broncatox *Saval, Chile.*
Levodropropizine (p. 1662·3).
Cough.

Bronce Sol *Tecnonat, Arg.*
Betacarotene (p. 2051·1).

Broncelix *Pfizer Consumer, NZ.†*
Choline theophyllinate (p. 1207·1); guaifenesin (p. 1666·2).
Cough.

Broncet *TNP, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Bronchalis *Heel, Neth.*
⊗Belladonna (p. 2453·3); sticta pulmonaria (p. 2546·1); antimonium tartaricum (p. 151·2); kreosotum (p. 1659·3); ipecacuanha (p. 1667·2); lobelia inflata (p. 2323·2); hyoscyamus niger (p. 2530·2); bryonia cretica (p. 2461·3).
Homoeopathic preparation.

Bronchalis-Heel *Heel, Austria; Peithner, Hung.; Ebi, Switz.*
⊗Atropa belladonna (p. 2453·3); lobaria pulmonaria (p. 2546·1); kalium stibyltartaricum (p. 151·2); kreosotum (p. 1659·3); cephaelis ipecacuanha; lobelia inflata (p. 2323·2); hyoscyamus niger (p. 2530·2); bryonia cretica.
Homoeopathic preparation.

Heel, Cz.
⊗Belladonna (p. 2453·3); sticta pulmonaria (p. 2546·1); kalii stibii tartras (p. 151·2); creosotum (p. 1659·3); ipecacuanha (p. 1667·2); lobelia inflata (p. 2323·2); hyoscyamus niger (p. 2530·2); bryonia (p. 2461·3).
Homoeopathic preparation.

Bronchathiol *Hepatoum, Fr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Bronchenolo *GSK Consumer, Ital.*
Syrup: Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1); ammonium acetate (p. 1655·3).
Cough.

GSK Consumer, Ital.†
Tablets: Dextromethorphan hydrobromide (adsorbed onto magnesium trisilicate) (p. 1660·1).
Cough.

Bronchenolo Tosse *GSK Consumer, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bronchetab *GSK Consumer, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bronchette *Aspen, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess and viscous mucus.

Bronchial
Note: this name may be used for preparations of different composition.
Herbapol Lublin, Pol.†
Althaea (p. 2438·3); ribwort plantain (p. 2604·2); tilia (p. 2631·3).
Respiratory-tract disorders; cough.

Bronchial Balsam Bells *Euro Lifecare, Ukr.*
Levomenthol (p. 2553·2); anise oil (p. 2444·3); cayenne pepper (p. 2469·3); tolu balsam (p. 1679·2).
Respiratory-tract disorders.

Bronchial Cough
Note: this name may be used for preparations of different composition.
Hylands, Canad.
Kali bichromium (p. 2476·3); rumex crispus (p. 2649·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Pendopharm, Canad.
Ammonium chloride (p. 1656·1); aralia racemosa; poplar buds (p. 2594·2); sanguinaria (p. 2610·1); senega (p. 1677·2); white pine; wild cherry (p. 2647·2).
Cough.

Bronchiase *New Research, Ital.*
Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1).
Cough.

Bronchicum
Note: this name may be used for preparations of different composition.
Cassella-med, Ger.
Thyme (p. 2630·2); cowslip root (p. 2596·2).
Respiratory-tract disorders associated with viscous mucus.

Novum, Neth.
Thyme (p. 2630·2); primula root (p. 2596·2); grindelia (p. 2522·3); burnet saxifrage root (p. 2463·1); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); saponin (p. 2610·2).
Cough.

Sanofi-Aventis, Hung.
Elixir: Pimpinella peregrina; primula (p. 2596·2); quebracho (p. 2601·2); grindelia (p. 2522·3); thyme (p. 2630·2).
Cough.

Aventis, Rus.†
Grindelia (p. 2522·3); saxifraga; primula (p. 2596·2); quebracho (p. 2601·2); thyme (p. 2630·2).
Respiratory-tract disorders.

Sanofi-Aventis, Hung.
Oral drops: Quebracho (p. 2601·2); white soapwort; thyme (p. 2630·2).
Cough.

Sanofi-Aventis, Hung.
Syrup: Pimpinella peregrina; primula (p. 2596·2); rosa; grindelia (p. 2522·3); thyme (p. 2630·2).
Respiratory-tract congestion.

Bronchicum Eliksir *Nattermann, Pol.†*
Grindelia (p. 2522·3); burnet saxifrage (p. 2463·1); primrose root (p. 2596·2); quebracho (p. 2601·2); thyme (p. 2630·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Catarrh.

Bronchicum Elixir *Cassella-med, Ger.*
Thyme (p. 2630·2); cowslip root (p. 2596·2).
Bronchitis; catarrh; cough.

Bronchicum Extra Sterk *Novum, Neth.*
Codeine phosphate (p. 40·2).
Cough.

Bronchicum Husten *Aventis, Rus.†*
Pastilles: Thyme (p. 2630·2).
Cough.

Aventis, Rus.†
Syrup: Thyme (p. 2630·2); rose fruit (p. 2607·1); saxifraga; primula (p. 2596·2); grindelia (p. 2522·3); honey (p. 2072·1).
Cough.

Bronchicum Mono Codein *Cassella-med, Ger.*
Codeine phosphate (p. 40·2).
Cough.

Bronchicum N *Nattermann, Pol.*
Thyme (p. 2630·2).
Catarrh; cough.

Bronchicum S *Sanofi-Aventis, Rus.*
Thyme (p. 2630·2).
Cough.

Bronchicum T *Nattermann, Pol.*
Thyme (p. 2630·2).
Catarrh; cough.

Bronchicum TP *Sanofi-Aventis, Rus.*
Thyme (p. 2630·2); primula root (p. 2596·2).
Cough.

Bronchi-Do *Grasler, Ger.*
Bryonia (p. 2461·3); drosera (p. 2497·2); grindelia robusta (p. 2522·3); hyoscyamus (p. 2530·2).
Homoeopathic preparation.

Bronchil *Siam Bheasach, Thai.*
Guaifenesin (p. 1666·2); theophylline (p. 1229·3).
Obstructive airways disease.

Bronchilet *Piramal, India.*
⊗Salbutamol sulfate (p. 1220·2); etofylline (p. 1208·2).
Obstructive airways disease.

Bronchilite *Holland Pharma, Neth.*
Luffa operculata (p. 2545·3); baryta carbonica (p. 2452·2); lycopodium clavatum (p. 2547·1); drosera rotundifolia (p. 2497·2); rhus toxicodendron (p. 2603·3); sulfur (p. 1721·1); teucrium scorodonia.
Homoeopathic preparation.

Bronchilon *Cesra, Ger.†*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Bronchi-Mereprine *Novum, Belg.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with viscous mucus.

Bronchiole *Bevo, Gr.*
Carbocisteine (p. 1658·1).

Bronchipret *Sanova, Austria; Bionorica, Ger.; Bionorica, Hung.; Bionorica, Indon.†; Darya-Varia, Indon.†; Bionorica, Rus.; Bionorica, Ukr.*
Oral drops; oral liquid: Thyme (p. 2630·2); ivy leaf (p. 2536·2).
Respiratory-tract disorders; bronchitis.

Bionorica, Ger.; Bionorica, Hung.; Bionorica, Indon.†; Darya-Varia, Indon.†; Bionorica, Philipp.†; Pharmalink, Philipp.†
Tablets: Primula root (p. 2596·2); thyme (p. 2630·2).
Bronchitis; respiratory-tract disorders.

Bionorica, Ger.
Pastilles: Thyme (p. 2630·2).
Bronchitis; cold symptoms; cough.

Bronchipret TP *Bionorica, Rus.; Biomed, Switz.; Bionorica, Ukr.*
Primula root (p. 2596·2); thyme (p. 2630·2).
Cough; respiratory-tract disorders.

Bronchipret Tymián a Břečťan *Bionorica, Cz.*
Thyme (p. 2630·2); ivy (p. 2536·2).
Respiratory-tract disorders.

Bronchipret Tymián a Prvosenka *Bionorica, Cz.*
Primula (p. 2596·2); thyme (p. 2630·2).
Respiratory-tract disorders.

Bronchiselect *Dreluso, Ger.*
Drosera (p. 2497·2); bryon. (p. 2461·3); tartar stib. (p. 151·2); spong.; ipecac. (p. 1667·2).
Homoeopathic preparation.

Bronchithym *Astroplant, Austria.†*
Thyme (p. 2630·2); cowslip (p. 2596·2).
Bronchitis.

Bronchitin *Nufarindo, Indon.*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough; asthma.

Bronchitol *Pharmaxis, Denm.; Pharmaxis, Neth.; Pharmaxis, UK.*
⊗Mannitol (p. 1427·3).
Cystic fibrosis.

Bronchitussin
Note: this name may be used for preparations of different composition.
Sopharma, Rus.
⊗Glaucine hydrobromide (p. 1666·1); ephedrine hydrochloride (p. 1663·2); basil oil (p. 2453·1).

Broncho D *Sam-On, Israel.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; respiratory-tract congestion.

Broncho Fertiginhalat *Astellas, Ger.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Broncho Inhalat *Astellas, Ger.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Broncho Munal *Abiogen, Ital.*
Lysates of *Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae; Klebsiella ozaenae; Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Moraxella catarrhalis.*
Respiratory-tract infections.

Sandoz, Rus.
Lyophilised bacterial lysate of: *Streptococcus pneumoniae; Haemophilus influenzae; Klebsiella*

pneumoniae; Klebsiella ozaenae; Staphylococcus aureus; Streptococcus viridans; Streptococcus pyogenes; Moraxella catarrhalis.
Respiratory-tract infections.

Sandoz, Ukr.
Lysates of: *Streptococcus pneumoniae; Streptococcus viridans; Streptococcus pyogenes; Haemophilus influenzae; Klebsiella pneumoniae; Klebsiella ozaenae; Staphylococcus aureus; Moraxella catarrhalis.*
Respiratory-tract infections.

USV, India.
Haemophilus influenzae; Klebsiella pneumoniae; Streptococcus pyogenes; Streptococcus viridans; Streptococcus aureus; Moraxella catarrhalis.

Broncho Saline *Blairex, USA.*
Sodium chloride (p. 1795·1).
Diluent for bronchodilator solutions for inhalation.

Bronchobos *Bosnalek, Rus.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus; otitis media.

Bronchobru *Brupharmexport, Ukr.*
⊗Sodium dibunate (p. 1677·3); ephedrine hydrochloride (p. 1663·2); sodium camsilate (p. 2617·3).
Respiratory-tract disorders.

Bronchocil *Menarini, Belg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Bronchocin *Sopharma, Rus.*
⊗Glaucine hydrobromide (p. 1666·1); ephedrine hydrochloride (p. 1663·2); basil oil (p. 2453·1).
Respiratory-tract disorders.

Bronchocort *Astellas, Ger.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Bronchodam *Filadams, Philipp.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bronchodermine *SERP, Mon.*
Ointment: Cineole (p. 2479·1); guaiacol (p. 1666·1); pine oil (p. 2591·1).
Upper respiratory-tract disorders.

SERP, Mon.
Suppositories: Cineole (p. 2479·1); amylocaine hydrochloride (p. 1979·3); guaiacol (p. 1666·1); pine oil (p. 2591·1).
Upper respiratory-tract disorders.

Bronchodex Pastilles *Prodemdis, Canad.†*
Domiphen bromide (p. 1751·1).

Bronchodex Pastilles Antiseptiques *Prodemdis, Canad.†*
Hexylresorcinol (p. 1755·1).

Bronchodine *Pharmacobel, Belg.*
Codeine phosphate (p. 40·2).
Cough.

Bronchodual *Boehringer Ingelheim, Fr.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Broncho-Entoxin N *Meckel, Ger.*
Arisaema triphyllum; atropa belladonna (p. 2453·3); drosera (p. 2497·2); hyoscyamus niger (p. 2530·2).
Homoeopathic preparation.

Broncho-Euphyllin *Takeda, Ger.*
Theophylline (p. 1229·3); ambroxol hydrochloride (p. 1654·3).
Obstructive airways disease.

Bronchofen *Pharma Nutria, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; rhinitis; sinusitis.

Bronchoforce Chesty Cough Ivy Complex *Bioforce, UK.*
Ivy (p. 2536·2); thyme (p. 2630·2); liquorice (p. 1853·2).
Cough.

Bronchoforton *Winthrop, Ger.†*
Ointment: Eucalyptus oil (p. 2501·2); Norway spruce oil; peppermint oil (p. 1877·1).
Catarrh; cold symptoms.

Winthrop, Ger.†
Capsules: Eucalyptus oil (p. 2501·2); anise oil (p. 2444·3); peppermint oil (p. 1877·1).
Catarrh.

Winthrop, Ger.†
Oral liquid: Ivy (p. 2536·2).
Bronchitis; catarrh.

Bronchoforton Kinderbalsam *Winthrop, Ger.†*
Eucalyptus oil (p. 2501·2); pine needle oil (p. 2591·1).
Cough; respiratory-tract congestion.

Bronchofyl *Remedina, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Bronchogeril *Gerolymatos, Gr.*
Theophylline (p. 1229·3).

Broncho-Injektopas *Pascoe, Ger.*
⊗Drosera (p. 2497·2); antimonium arsenicosum (p. 2445·1); antimonium sulfuratum aurantiacum (p. 2445·1); cuprum (p. 2057·1); eupatorium perfoliatum (p. 2459·1); ipecacuanha (p. 1667·2); lobelia inflata (p. 2323·2); silicea (p. 2208·3); eriodictyon californicum (p. 1665·2).
Homoeopathic preparation.

Broncho-Kid *Sam-On, Israel.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion; cough.

Bronchokod *Sanofi-Aventis, Fr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncholac *Inpac, Thai.*
⊗Guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Broncholate
Note: this name may be used for preparations of different composition.
Sam-On, Israel.
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract disorders; cough.

Sanofi Winthrop, USA.†
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Coughs.

Broncholate Forte *Sam-On, Israel.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Respiratory-tract disorders; cough.

Broncholate Plus *Sam-On, Israel.*
⊗Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders; cough.

Broncholax *Vickmans, Hong Kong.†*
Caffeine (p. 1203·3); pentoxyverine (p. 1672·1); diprophylline (p. 1207·3); guaifenesin (p. 1666·2); thiamine (p. 2102·3).

Broncholin *Thebe, S.Afr.*
Guaifenesin (p. 1666·2).

Broncholine *TO-Chemicals, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Broncholit *Nicholas, Indon.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Broncholitan *Quiris, Ger.*
Ivy (p. 2536·2); thyme (p. 2630·2); liquorice (p. 1853·2).
Respiratory-tract congestion.

Broncholytin *Sopharma, Rus.; Sopharma, Ukr.*
⊗Glaucine hydrobromide (p. 1666·1); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract disorders.

Bronchomed
Note: this name may be used for preparations of different composition.
Euro Lifecare, Ukr.
Lollipops: Liquorice (p. 1853·2); emblica (p. 2532·2); ginger (p. 1844·1); menthol (p. 2553·2).
Cough; upper respiratory-tract disorders.

Euro Lifecare, Ukr.
Syrup: Malabar nut (p. 2549·1); ocimum sanctum; terminalia bellirica (p. 2453·2); cinnamonum iners; sarcostemma brevistigma; myristica malbarica; calotropis gigantea; ginger (p. 1844·1); black pepper (p. 2586·1); cinnamomum cassia (p. 2471·3); myrtus caryophyllus nutmeg (p. 2573·1); rhus succedanea; piper longum.
Cough; upper respiratory-tract disorders.

Spirig, Switz.
Cineole (p. 2479·1); camphor (p. 2466·2); niaouli oil (p. 2569·1).
Respiratory-tract congestion.

Bronchonyl *Pharmasant, Thai.*
Syrup: ⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Pharmasant, Thai.
Tablets: ⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bronchoparat *Astellas, Ger.*
Theophylline sodium glycinate (p. 1229·3).
Obstructive airways disease.

Bronchopas *Pascoe, Ger.*
⊗Antimonium arsenicosum (p. 2445·1); ipecacuanha (p. 1667·2); lobelia inflata (p. 2323·2); eriodictyon californicum (p. 1665·2); grindelia robusta (p. 2522·3).
Homoeopathic preparation.

Bronchopect *Herbapol Poznan, Pol.†*
Ivy (p. 2536·2).
Catarrh.

Broncho-pectoralis Carbocisteine *Medgenix, Belg.*
Carbocisteine (p. 1658·1).

Broncho-pectoralis Codeine *Medgenix, Belg.*
Codeine (p. 40·2).
Cough.

Broncho-pectoralis Pholcodine *Medgenix, Belg.*
Pholcodine (p. 1675·1); sulfogaiacol (p. 1678·1).
Cough and nasal congestion.

Bronchoped *Adcock Ingram, S.Afr.*
⊗Terbutaline sulfate (p. 1228·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough with bronchospasm.

Bronchophan DM *Atlas, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).

Bronchophan Expectorant *Atlas, Canad.*
Guaifenesin (p. 1666·2).
Cough.

Bronchophen
Note: this name may be used for preparations of different composition.
Sunthi Sepuri, Indon.†
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold symptoms.

Bronchophylin *Darya-Varia, Indon.*
Theophylline (p. 1229·3).
Asthma.

Bronchoprex Expectorant *Kenyaku, Thai.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Cough; catarrh.

Bronchoprex Syrup *Kenyaku, Thai.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract disorders.

Bronchopront *Combiphar, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Zuoz, Venez.
Ambroxol (p. 1654·3) or ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bronchorectine au Citral *Mayoly-Spindler, Fr.*
Citral (p. 2480·2); guaiacol (p. 1666·1); terpin hydrate (p. 1678·2); Scots pine oil (p. 2591·2); wild thyme oil (p. 2648·1).
Respiratory disorders.

Bronchoretard *Astellas, Ger.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Bronchorus *Sintez, Rus.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory tract disorders with viscous mucus.

Bronchosal *Ifars, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma.

Bronchosan
Note: this name may be used for preparations of different composition.
Bioforce, Norw.†; Bioforce, Switz.
Ivy (p. 2536·2); thyme (p. 2630·2); liquorice (p. 1853·2).
Cough; respiratory-tract congestion.

Zentiva, Rus.
Bromhexine hydrochloride (p. 1656·3); levomenthol (p. 2553·2); fennel oil (p. 2503·3); anise oil (p. 2444·3); origanum oil (p. 2576·3); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2).
Respiratory-tract congestion and cough.

Zentiva, Cz.†; Zentiva, Ukr.†
Bromhexine hydrochloride (p. 1656·3); menthol (p. 2553·2); fennel oil (p. 2503·3); anise oil (p. 2444·3); origanum oil (p. 2576·3); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bronchosan Pine *Bioforce, UK.*
Norway spruce.
Cough.

Bronchosedal *Johnson & Johnson Consumer, Belg.*
Oral liquid: Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Johnson & Johnson Consumer, Belg.
Syrup: Codeine phosphate (p. 40·2).
Cough.

Broncho-Sern *Truw, Ger.*
Ribwort plantain (p. 2604·2).
Cold symptoms; inflammation of mouth and throat.

Bronchosol
Note: this name may be used for preparations of different composition.
Phytofarm Kleka, Pol.
Thyme (p. 2630·2); primrose root (p. 2596·2); thymol (p. 1772·2).
Cough; respiratory-tract congestion.

Siam Bheasach, Thai.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Bronchosolvin *Ipca, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Cough.

Bronchospasmin *Meda, Ger.; Farmalex, Gr.*
⊗Reproterol hydrochloride (p. 1219·2).
Status asthmaticus.

Bronchospec *Pharmaspec, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease; cough.

Bronchospray
Note: this name may be used for preparations of different composition.
Astellas, Ger.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Bronchostad Hustenlöser *Stada, Ger.*
Ivy (p. 2536·2).
Cold symptoms.

Bronchostop
Note: this name may be used for preparations of different composition.
Kwizda, Austria.
Capsules: Mentholum valerianicum; guaifenesin (p. 1666·2); eucalyptus oil (p. 2501·2); camphor (p. 2466·2).
Cough.

Kwizda, Austria.
Oral drops: Guaifenesin (p. 1666·2); thyme (p. 2630·2); chamomile (p. 2474·1); anise oil (p. 2444·3).
Cough.

Kwizda, Ukr.
Lozenges: Thyme (p. 2630·2).
Cough.

Kwizda, Ukr.
Oral drops: Thyme (p. 2630·2); guaifenesin (p. 1666·2).
Cough.

Kwizda, Ukr.
Syrup: Thyme (p. 2630·2); althaea (p. 2438·3).
Cough.

Metochem, Austria.†
Ointment: Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); pumilio pine oil (p. 2591·1); thyme oil (p. 2630·3).
Catarrh; colds; cough; sore throat.

Bronchosyx comp *Syxyl, Ger.*
Cepaelis ipecacuanha; grindelia robusta (p. 2522·3); kalium iodatum (p. 2336·3).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bronchoton *Vetprom, Rus.*
⊗Ephedrine hydrochloride (p. 1663·2); glaucine hydrobromide (p. 1666·1); basil oil (p. 2453·1).
Respiratory-tract disorders.

Broncho-Truw Erkältungsbalsam *Truw, Ger.†*
Eucalyptus oil (p. 2501·2).
Cold symptoms.

Bronchotussine
Note: this name may be used for preparations of different composition.
Adelco, Gr.
Bromhexine hydrochloride (p. 1656·3).
Respiratory disorders associated with viscous mucus.
Vifor, Switz.†
Butetamate citrate (p. 1658·1); codeine phosphate (p. 40·2).
Cough.

Bronchoval *Sandoz, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broncho-Vaxom *Casasco, Arg.; Nycomed, Austria; Abbott, Belg.; Nycomed, Braz.; UCB, China; Labomed, Chile.; OM, Cz.; Vifor, Ger.; OM, Hung.; Nycomed, Ital.; Grunenthal, Mex.; OM, Philipp.; OM, Pol.; OM, Port.; Grunenthal, Rus.; OM, Switz.; Vifor, Ukr.*
Lysate of: *Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae; Klebsiella ozaenae; Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Moraxella catarrhalis.*
Respiratory-tract infections.

Gap, Gr.; IFET [ΙΦΕΤ], Gr.
Bacterial lysate.
Respiratory-tract infections.

Broncho-vent *Taiwan Biotech, Philipp.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Bronchovit *Gradiens, Hung.*
Thyme oil (p. 2630·3); Scots pine oil (p. 2591·2); eucalyptus oil (p. 2501·2).
Upper respiratory-tract disorders.

Bronchowern *Wernigerode, Rus.*
Ambroxol hydrochloride (p. 1654·3).

Broncimucil *Uriach, Spain.*
Brovanexine hydrochloride (p. 1657·3).
Respiratory-tract disorders associated with increased mucus.

Bronclear
Note: this name may be used for preparations of different composition.
Polipharm, Thai.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncleer
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Broncleer with Codeine *Adcock Ingram, S.Afr.; Propan, S.Afr.*
Codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Bronco Aseptilex Fuerte *Chiesi, Spain.†*
Bromhexine hydrochloride (p. 1656·3); co-trimoxazole (p. 277·3); guaiacol cinnamate (p. 1666·1).
Respiratory-tract infections.

Bronco Asmo *Pond's, Thai.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bronco Asmol *Herbes Universelles, Canad.†*
Ammonium bicarbonate (p. 1655·3); anethole (p. 2443·3); tolu balsam (p. 1679·2); benzoic acid (p. 1738·2); camphor (p. 2466·2); squill (p. 1677·3).

Bronco Etersan *Dallas, Arg.*
Terpineol (p. 2627·2); cineole (p. 2479·1); Scots pine oil (p. 2591·2); turpentine oil (p. 2636·3).
Respiratory-tract disorders.

Bronco Medical *Medical, Spain.*
Sulfogaiacol (p. 1678·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bronco Tonic *Vir, Spain.†*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Broncocalmine *Oriental, Arg.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Broncocent *Blue Sky, Philipp.*
Carbocisteine (p. 1658·1).
Cough.

Broncocilin *Bio Macro, Braz.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).

Broncoclar *UPSA, Fr.*
Syrup: Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.
UPSA, Fr.†
Granules for oral solution: Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncodeina *Pasteur, Chile.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); belladonna liquid extract (p. 2453·3); menthol (p. 2553·2); sodium benzoate (p. 1738·2); terpin hydrate (p. 1678·2).
Cough.

Broncodiazina *Vitoria, Port.†*
⊗Ammonium chloride (p. 1656·1); pentetrazol (p. 2328·3); sodium benzoate (p. 1738·2); sulfadiazine (p. 361·3); drosera (p. 2497·2); tolu balsam (p. 1679·2).
Respiratory-tract disorders.

Broncodil
Note: this name may be used for preparations of different composition.
Symbiosis, India.
Ambroxol hydrochloride (p. 1654·3); cetirizine hydrochloride (p. 619·2); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Broncodin *Universal, Hong Kong.†*
Bromhexine (p. 1656·3); codeine (p. 40·2).
Cough.

Bronco-DM *Universal, Hong Kong.†*
Bromhexine (p. 1656·3); dextromethorphan (p. 1660·1).

Broncodual *Laboratorios Chile, Chile.*
Clobutinol (p. 1658·3).
Cough.

Broncodual Compuesto *Laboratorios Chile, Chile.*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3); ammonium chloride (p. 1656·1).
Cough; obstructive airways disease.

Broncofama *FAMA, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Broncofedrin *Multilab, Braz.*
⊗Salbutamol (p. 1220·2).

Broncofedrina *Janssen-Cilag, Mex.*
⊗Ephedrine (p. 1663·1); dextromethorphan (p. 1660·1).

Broncofenil *Zurita, Braz.*
Guaifenesin (p. 1666·2).
Cough.

Broncoflem *Medica Korea, Philipp.*
Acetylcysteine (p. 1652·2).
Paracetamol overdosage; respiratory-tract congestion.

Broncoflux *Farmasa, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broncoformo Muco Dexa *Gayoso, Spain.†*
⊗Dexamethasone (p. 1630·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sodium benzoate (p. 1738·2).
Respiratory-tract disorders.

Broncofree *Medreich, India.*
Aminophylline (p. 1201·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Broncol
Note: this name may be used for preparations of different composition.
Delta, Braz.†
Eucalyptus (p. 2501·1); ginger (p. 1844·1); siparuna guyanensis; lantana camara; mikania glomerata; belladonna (p. 2453·3); jaborandi.
Cough.

Mirren, S.Afr.†
Dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); panthenol (p. 2582·2).
Cough.

Pharmaland, Thai.†
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncoliber *Tecnimede, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Broncolium *Temis, Arg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Broncomar *Marlop, USA.*
⊗Theophylline (p. 1229·3); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Broncomnes *Bracco, Ital.*
Ambroxol acefyllinate (p. 1201·2).
Bronchospasm; catarrh; respiratory-tract congestion.

Broncomucil *GSK, Ital.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with excess or viscous mucus.

Bronconal *Cifarma, Braz.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour.

Bronconex *Schering-Plough, NZ.*
⊗Mometasone furoate (p. 1644·1).
Asthma.

Broncophilina *Behrens, Venez.*
Aminophylline (p. 1201·2).
Asthma.

Broncophyl Plus *Cosme, India.*
⊗Salbutamol (p. 1220·2); theophylline (p. 1229·3).
Obstructive airways disease.

Bronco-Polimoxil *Legrand, Braz.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Bacterial infections.

Broncoral
Note: this name may be used for preparations of different composition.
Chiesi, Spain.
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Empifarma, Port.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Broncordil *USV, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Broncordil P *USV, India.*
⊗Salbutamol sulfate (p. 1220·2); theophylline (p. 1229·3).
Obstructive airways disease.

Broncorex *Pfizer, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Broncos *Symbiosis, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1).

Broncosed *Noos, Ital.*
Thyme (p. 2630·2); sweet chestnut (p. 2625·1).

Broncosedina *FAMA, Ital.*
Syrup: Cocillana (p. 1659·2); eriodictyon (p. 1665·2); marrubium (p. 1668·3); grindelia (p. 2522·3); juniper (p. 2537·1); compound thyme (p. 2630·2).
Respiratory-tract disorders.
FAMA, Ital.
Pastilles: Cocillana (p. 1659·2); eriodictyon (p. 1665·2); marrubium (p. 1668·3); grindelia (p. 2522·3); juniper (p. 2537·1); compound thyme (p. 2630·2); pumilio pine oil (p. 2591·1); mint oil (p. 2560·1).
Respiratory-tract disorders.

Broncoserum *Ifusa, Mex.*
Sulfogaiacol (p. 1678·1).
Cough.

Broncosulfur *Laborest, Ital.*
Monoterpenol; acetylcysteine (p. 1652·2); dimethyl sulfone (p. 2493·3).
Cough; catarrh.

Broncot *K2 Health & Wellness, Chile.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Broncoteril *Iasis, Gr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Broncoterol *Azevedos, Port.†*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Broncotron-D *Seyer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Broncotusilan *Pasteur, Chile.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Broncovaleas *Valeas, Ital.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Broncovanil *Almus, Ital.*
Guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Bronco-Vaxom *Abdi, Turk.*
Bacterial lysate.

Broncovir *Vir, Spain.*
Co-trimoxazole (p. 277·3); sulfogaiacol (p. 1678·1).
Respiratory-tract infections.

Broncovital
Note: this name may be used for preparations of different composition.
Ifusa, Mex.
Chlorphenamine (p. 620·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Broncozol *Mugi, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broncozone *Ind Biosciences, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Brondecon *Pfizer Consumer, NZ.†*
Choline theophyllinate (p. 1207·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Brondecon Elixir *Pfizer Consumer, Austral.†*
Choline theophyllinate (p. 1207·1).
Obstructive airways disease.

Brondecon Expectorant *Pfizer Consumer, Austral.†*
Choline theophyllinate (p. 1207·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Brondil *Great Eastern, Thai.†; Therapharma, Thai.†*
⊗Etafedrine hydrochloride (p. 1665·2); theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Brondil (Reformulated) *United American, Philipp.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Brondilat
Note: this name may be used for preparations of different composition.
Ache, Braz.
Ambroxol acefyllinate (p. 1201·2).
Obstructive airways disease.
Recalcine, Chile.
Montelukast (p. 1214·3).
Asthma.

Brondilax *Vitarum, Arg.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Brondilex *Biomedis, Indon.†; Medifarma, Indon.†*
Theophylline (p. 1229·3).
Asthma.

Brondisal *GMP, Indon.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Brondix *Pentafarm, Spain.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Brondry *Suphong, Thai.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Brondyneo *Neo Quimica, Braz.*
Ambroxol acefyllinate (p. 1201·2).

Bronex *Euro-Med, Philipp.*
⊗Budesonide (p. 1625·1).
Asthma.

Bronfilil *Mabra, Braz.*
Ambroxol acefyllinate (p. 1201·2).
Obstructive airways disease.

Bron-Hal *Help, Gr.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bronhoxol *Mosfarma, Rus.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bronica *Takeda, Jpn.*
Seratrodast (p. 1225·3).
Asthma.

Bronilis *Leti, Venez.*
Ambroxol acefyllinate (p. 1201·2).
Respiratory-tract congestion.

Bronkaid Dual Action *Sterling, USA.†*
⊗Ephedrine sulfate (p. 1663·2); guaifenesin (p. 1666·2).

Bronkar *Nobel, Turk.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Bronkar-A *Nobel, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Bronkase *Chinta, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bronkeel *Heel, Canad.†*
⊗Antimony potassium tartrate (p. 151·2); beechwood creosote (p. 1659·3); belladonna (p. 2453·3); bryonia (p. 2461·3); hyoscyamus niger (p. 2530·2); ipecac (p. 1667·2); lobelia inflata (p. 2323·2); sticta pulmonaria (p. 2546·1).
Homoeopathic preparation.

Bronkese *Pharmacare, S.Afr.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with viscous mucus.

Bronkese Compound *Aspen Consumer, S.Afr.*
⊗Bromhexine hydrochloride (p. 1656·3); orciprenaline sulfate (p. 1217·3).
Cough associated with bronchospasm and viscous mucus.

Bronkex *Bal, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Bronkids *Great Southern, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Bronkirex *Sanofi-Aventis, Fr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Bronkitose Mielimon *Biofarma, Mex.*
Cineole (p. 2479·1); verbascum (p. 2645·1); sambucus (p. 2609·3).
Respiratory-tract infections.

Bronklast *Farma, Venez.*
⊗Budesonide (p. 1625·1).
Asthma.

Bronko *GSK, India.*
⊗Salbutamol (p. 1220·2).
Bronchospasm.

Bronko Plus *GSK, India.*
⊗Salbutamol (p. 1220·2); theophylline (p. 1229·3).
Obstructive airways disease.

Bronkolin *Nobel, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Bronkonat *Sun, India.*
⊗Salbutamol (p. 1220·2).
Asthma.

Bronkosyrup-EX *GSK, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Obstructive airways disease.

Bronkotuss Expectorant *Hyrex, USA.*
⊗Ephedrine sulfate (p. 1663·2); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Coughs.

Bronkyl *Weifa, Norw.*
Acetylcysteine (p. 1652·2).
Chronic bronchitis; cystic fibrosis.

Bronmix *Indo French, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Bronmucon *Suphong, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bronmycin *Biolab, Singapore; Biolab, Thai.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Bronoday *Okasa, Thai.†; TTN, Thai.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Bronolax *Alkem, India.*
⊗Ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2).
Cough and associated respiratory-tract disorders.

Bronolban *Sons, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bronolban-M *Sons, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Bro-N-Pain *Brovar, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Bronpax
Note: this name may be used for preparations of different composition.
Schering-Plough, Mex.†
Benzonatate (p. 1656·2).
Cough.

Bronpect *Kenyaku, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Bronpect-D *Kenyaku, Hong Kong; Kenyaku, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Bronq *Blue Cross, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Bronq-C *Bernabo, Arg.*
⊗Clenbuterol hydrochloride (p. 1207·2).

Bronquial *OM, Port.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Respiratory-tract congestion.

Bronquicisteina *Iquinosa, Spain.†*
Carbocisteine (p. 1658·1); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Bronquidex *Farmalab, Braz.*
⊗Potassium iodide (p. 2336·3); guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2); sodium benzoate (p. 1738·2); ammonium chloride (p. 1656·1); belladonna (p. 2453·3); lobelia (p. 2323·2).
Respiratory-tract congestion.

Bronquidiazina CR *Faes, Spain.*
Tolu balsam (p. 1679·2); bromhexine (p. 1656·3); sodium benzoate (p. 1738·2); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Bronquimar *Cruz, Spain.†*
Oral suspension: Guaifenesin (p. 1666·2); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Bronquimucil
Note: this name may be used for preparations of different composition.
Arrow, Braz.†
Brovanexine hydrochloride (p. 1657·3).
Respiratory-tract congestion.

Bronquiogen *Prodotti, Braz.†*
Yucca (p. 2649·3); rorippa nasturtium-aquaticum; mikania glomerata; lantana camara; passion flower (p. 2584·1); melissa (p. 2552·3); oleo vermelho; sodium benzoate (p. 1738·2).
Respiratory-tract disorders.

Bronquisedan *Sanofi-Aventis, Arg.*
Butetamate citrate (p. 1658·1); ambroxol hydrochloride (p. 1654·3).
Bronchitis; cough.

Bronquisedan Max *Sanofi-Aventis, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bronquisedan Mucolitico *Gramon, Arg.*
Ambroxol hydrochloride (p. 1654·3); clobutinol hydrochloride (p. 1658·3).
Cough.

Bronquisedan Niños *Sanofi-Aventis, Arg.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bronquisedan Pediatrico *Sanofi-Aventis, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Bronquitós *Legrand, Braz.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); theophylline (p. 1229·3); vitamin B_6 (p. 2105·3).
Obstructive airways disease.

Bronsal *Vedim, Spain.*
⊗Betamethasone sodium phosphate (p. 1623·3); diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Bronsema *F5 Profas, Spain.†*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Bronsim *Siomond, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Bronsolvan *Kalbe, Indon.*
Theophylline (p. 1229·3).
Asthma.

Bronsual *DelBel, Arg.*
Canthaxanthin (p. 2173·2).
Suntanning aid.

Bronsym *Symbiosis, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Brontac-Plus *Symbiosis, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); sodium citrate (p. 1781·2).

Brontal *Sanitas, Chile.*
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1).
Cough; respiratory-tract congestion.

Brontek *Geolab, Braz.*
Ambroxol acefyllinate (p. 1201·2).

Brontermil *Eurodrug, Pak.*
Guaimesal (p. 1667·1).
Cough.

Brontex *Procter & Gamble, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Coughs.

Brontoss *Teuto, Braz.*
⊗Potassium iodide (p. 2336·3); belladonna (p. 2453·3); lobelia (p. 2323·2); diphenhydramine hydrochloride (p. 626·2).
Cough.

Brontus *Chinta, Thai.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Respiratory-tract congestion; cough.

Brontuss DX *Portal, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Bronuck *Senju, Jpn.*
Bromfenac sodium (p. 30·1).
Inflammatory eye disorders; postoperative eye inflammation.

Bronxina *Legrand, Braz.*
Bromhexine (p. 1656·3).

Bronxol *Cifarma, Braz.; Labialfarma, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Bronzearte *Sanofi-Aventis, Arg.*
Canthaxanthin (p. 2173·2).
Suntanning aid.

Brooklax *Group, S.Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

Brooklax Pills *Group, S.Afr.†*
Yellow phenolphthalein (p. 1877·3); aloin (p. 1816·2); capsicum oleoresin (p. 2469·3).
Constipation.

Bropavol *Volta, Chile.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Bropil *Recalcine, Chile.*
⊗Salbutamol (p. 1220·2).

Broptin *IQFA, Mex.*
Bromocriptine (p. 895·3).
Hyperprolactinaemia.

Broquixol *Schering-Plough, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Bros *TRB, Braz.*
Phosphatidyl serine (p. 2589·1).
Cerebrovascular disorders; mental function impairment.

Brosidon *Bros, Gr.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia.

Brosiral *Bros, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Brosol
Note: this name may be used for preparations of different composition.
Lark, India.
⊗Salbutamol (p. 1220·2).
Bronchospasm.

Brosolan *Collins, Mex.†*
Ambroxol (p. 1654·3).
Cough.

Brosolan C *Collins, Mex.†*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Brospec *Prafa, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Brospina *Pisa, Mex.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Brota Rectal Balsamico *Escaned, Spain.†*
⊗Camphor (p. 2466·2); cineole (p. 2479·1); ephedrine hydrochloride (p. 1663·2); niaouli oil (p. 2569·1); quinine sulfate (p. 665·2); sulfogaiacol (p. 1678·1).
Respiratory-tract disorders.

Brotapp *Silarx, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Brotapp DM *Silarx, USA.*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Brotazona *Escaned, Spain.†*
Feprazone (p. 64·3).
Musculoskeletal and joint disorders; gout.

Brotee-D *Technica, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Brotzu *Dey's, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Brovana *Sepracor, USA.*
⊗Arformoterol tartrate (p. 1202·3).
Obstructive airways disease.

Brovex ADT *MCR, USA.†*
Brompheniramine tannate (p. 618·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

BroveX CB *MCR, USA.†*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

BroveX CBX *MCR, USA.†*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Brovex PB *MCR, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

BroveX PB C *MCR, USA.†*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

BroveX PB CX *MCR, USA.†*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

BroveX PB DM *MCR, USA.†*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Brovex PD *MCR, USA.†*
⊗Pseudoephedrine tannate (p. 1676·1); brompheniramine tannate (p. 618·1).
Upper respiratory-tract disorders.

BroveX PEB *Pernix, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Brovex PEB DM *Pernix, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

BroveX PSB *Pernix, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

BroveX PSB DM *Pernix, USA.*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

BroveX PSE *Pernix, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

BroveX PSE DM *Pernix, USA.*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Brovicarpine *Rafarm, Gr.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; arrhythmias.

Brovicton *Bros, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Brovol *Asian Union, Thai.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Brovon *GSK, India.*
⊗Adrenaline (p. 1292·1); atropine methonitrate (p. 1310·2); papaverine hydrochloride (p. 2362·3).
Bronchospasm; emphysema.

Torbet Laboratories, UK.
⊗Adrenaline (p. 1292·1) atropine methonitrate (p. 1310·2); papaverine hydrochloride (p. 2362·3).
Bronchoconstriction.

Browin Junior *Wintech, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Browin-TG *Wintech, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Brown Mixture *British Dispensary, Thai.; GPO, Thai.; Osoth, Thai.*
Liquorice fluid extract (p. 1853·2); antimony potassium tartrate (p. 151·2); camphorated opium tincture.
Cough.

Vickmans, Hong Kong.†
Liquorice (p. 1853·2); camphorated opium (p. 111·3).
Cough; catarrh.

Brox *Aurobindo, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Broxal *Bernofarm, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broxan *Dynamic, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with abnormal mucus.

Broxaquim *Quimica y Farmacia, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broxifil *Filadams, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broxil *GSK, Neth.*
Pheneticillin potassium (p. 338·2).
Bacterial infections.

Broxil-M *Metz, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with abnormal mucus.

Broxitrol *Pharmacare, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Cough with abnormal mucous secretion.

Broxo al Fluoro *SIT, Ital.*
Levomenol (p. 2544·1); sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3).
Gum disorders; halitosis.

Broxodin
Note: this name may be used for preparations of different composition.
SIT, Ital.
Mouthwash; oral gel: Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Vargas, Venez.
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders.

Broxofar *Farcoral, Mex.*
Ambroxol hydrochloride (p. 1654·3).

Broxofar Compuesto *Farcoral, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders with viscous mucus.

Broxoffler *Loeffler, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broxol
Note: this name may be used for preparations of different composition.
Help, Gr.; Boniscontro & Gazzone, Ital.; Carnot, Mex.; Masa, Thai.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Galeno, Venez.
Oxolamine citrate (p. 1671·2) or oxolamine phosphate (p. 1671·2).
Cough.

Huons, Philipp.
Bromhexine hydrochloride (p. 1656·3).
Cough.

Broxol Air *Carnot, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders.

Broxol Plus *Carnot, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders with viscous mucus.

Broxolflem *Galeno, Venez.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Broxolgrip Dia *Galeno, Venez.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Cold symptoms.

Broxolgrip Noche *Galeno, Venez.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine (p. 1676·1).
Cold symptoms.

Broxolim *Tocogino, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Broxolim-C *Tocogino, Mex.*
⊗Ambroxol (p. 1654·3); clenbuterol (p. 1207·2).
Respiratory-tract disorders.

Broxolvan *Novo Pharm, Philipp.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Broxter *Prompt Cure, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Broxytone *IAE, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Bro-Zedex *Wockhardt, India; Wockhardt, Ukr.†*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Brozeet *Alembic, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Brozil *YSP, Malaysia; Yung Shin, Singapore.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Brozol-D *Briskon, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Brozole-D *BL, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Bruace *Jagsonpal, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Brucam *Bruluart, Mex.*
Piroxicam (p. 125·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Brucap *Bruluart, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Brucef *Brussels, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Brucelin *Target, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Brucet *Micro, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Bruciaporri *Giovanardi, Ital.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; verrucas.

Brucilina *Bruluagsa, Mex.*
Ampicillin (p. 218·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Brudol *Elmor, Venez.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3); dihydroergotamine mesilate (p. 672·2).
Vascular headache.

Brufamol *Shalaks, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Brufamol-M *Sarabhai Piramal, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Brufen *Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Cz.; Abbott, Denm.; Abbott, Fr.; Abbott, Gr.; Abbott, Hong Kong; Abbott, India; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Philipp.†; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Knoll, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.†; Abbott, Turk.; Abbott, UK.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Brufen Gel *Abbott, India.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Brufenin *Inpac, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Brufen-MR *Abbott, India.*
Ibuprofen (p. 68·2); tizanidine hydrochloride (p. 2026·2).

Brufix
Note: this name may be used for preparations of different composition.
Brawn, India.
Cefixime (p. 240·3).
Bacterial infections.

Krugher, Ital.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Brugesic *Elmor, Venez.*
Ibuprofen (p. 68·2).
Fever; pain.

Brugesic Plus *Elmor, Venez.*
Ibuprofen (p. 68·2); arginine (p. 2049·1).
Pain; inflammation.

Brugesina *Elmor, Venez.*
Ibuprofen (p. 68·2); hyoscine butylbromide (p. 1845·3).
Pain with spasm.

Brugin *Chinta, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Bruhist Plus *Brawn, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Bruise & Vein Support *Golden Glow, Austral.*
Rutoside (p. 2505·3); citrus bioflavonoids (p. 2505·2).
Soft-tissue injury; varicose veins.

Bruiseze *Bayer Consumer, UK.*
A heparinoid (p. 1401·1).
Soft-tissue injury.

Brulamycin *Teva, Hung.; Teva, Rus.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Biogal, Cz.†; IFET (ΙΦΕΤ), Gr.
Tobramycin (p. 380·1).
Bacterial infections; bacterial eye infections.

Brulex *Bailly, Fr.*
Phenazone (p. 124·1); zinc oxide (p. 1729·1); peru balsam (p. 2587·1); phenol (p. 1763·3); sodium salicylate (p. 132·2).
Burns; sunburn.

Brulidine *Aspen, Austral.†; Sanofi-Aventis, Norw.; Manx, UK.*
Dibrompropamidine isetionate (p. 1750·1).
Skin infections; skin abrasions; burns; napkin rash; otitis externa.

Brulium *Brupharmexport, Ukr.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting.

Brumax *Bruluagsa, Mex.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Brumed *Medreich, Hong Kong.*
Ibuprofen (p. 68·2).
Pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Brumetidina *Bruschettini, Ital.†*
Cimetidine (p. 1827·1).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Brumeton *Bio-Gen, Turk.*
⊗Betamethasone (p. 1623·2); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Brumeton Colloidale S *Bruschettini, Ital.*
⊗Betamethasone (p. 1623·2); sulfacetamide sodium (p. 361·1).
Eye and ear disorders.

Brumixol *Bruschettini, Ital.*
Ciclopirox olamine (p. 575·3).
Fungal skin and vulvovaginal infections.

Brunac *Bruschettini, Ital.; Bio-Gen, Turk.*
Acetylcysteine (p. 1652·2).
Dry eyes; eye disorders.

Brunacod *Brunel, S.Afr.†*
⊗Promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2); codeine phosphate (p. 40·2).
Cough.

Brunacol *Bruluart, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Brunamol *Brunel, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Brunavera *Euroderm, Arg.*
Aloe vera (p. 1693·2); calendula (p. 2465·2); alpha tocopherol (p. 2119·1).
Dry skin.

Brunazine *Brunel, S.Afr.*
Promethazine hydrochloride (p. 638·2).
Motion sickness; nausea; vomiting; hypersensitivity reactions.

Brunex *Pentamedical, Ital.*
Enoxolone (p. 54·2); arbutin (p. 1694·3); kojic acid (p. 1710·2).
Skin hyperpigmentation.

Brunicrom *Bruschettini, Ital.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Bruno *Milano, Thai.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; musculoskeletal and joint disorders.

Bru-O *Brawn, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Bru-OZ *Brawn, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Brupal *Geno, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Brupen *Bruluagsa, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Brupen Compuesto *Bruluagsa, Mex.*
Ampicillin trihydrate (p. 218·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Bruprin *Condrugs, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Brushtox *Dentox, UK.*
⊗Denatured alcohol (p. 1733·1); hydroxybenzoate esters (p. 1756·3); zinc chloride (p. 2126·1).
Disinfection of toothbrushes.

Brusil *Silom, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; fever; pain.

Brusniver *Krasnogorskleksredstva, Rus.*
Myrtillus (p. 2566·2); St John's wort (p. 449·1); bidens tripartita; rose fruit (p. 2607·1).
Urogenital disorders; anorectal disorders.

Brust- und Hustentee
Note: this name may be used for preparations of different composition.
Bad Heilbrunner, Ger.†
Thyme (p. 2630·2); primula root (p. 2596·2).
Respiratory-tract disorders with viscous mucus.

Brust- und Hustentee St Severin *Smetana, Austria.*
Sweet chestnut (p. 2625·1); ribwort plantain (p. 2604·2); verbascum leaf (p. 2645·1); thyme (p. 2630·2); elecampane (p. 1662·3).
Respiratory-tract disorders.

Brustan *Nanxin, China; Ranbaxy, Philipp.†; Ranbaxy, Rus.; Ranbaxy, Thai.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; fever; inflammation.

Brustin *Ranbaxy, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Brutek *Zuventus, India.*
Dexibuprofen (p. 43·1).
Musculoskeletal and joint disorders; dysmenorrhoea.

Brutek-P *Zuventus, India.*
Dexibuprofen (p. 43·1); paracetamol (p. 115·1).

Brux *Cinetic, Arg.*
Omeprazole (p. 1867·2).
Gastric hyperacidity.

Bruxel *Ivax, Arg.*
Proglumetacin maleate (p. 127·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Bruxicam *Bruschettini, Ital.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bryaconeel *Heel, Canad.†*
Aconite (p. 2428·3); bryonia (p. 2461·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Brylcreem Anti-Dandruff *Combe, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Brymont *Blumont, UK.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Bryonia Opodeldoch *Boiron, Fr.*
Bryonia (p. 2461·3); linimentum camphoratum cum ammonia compositum.
Homoeopathic preparation.

Bryophyllum *Weleda, Ger.*
Kalanchoe pinnata.
Inflammation; insomnia.

Bryorheum N *DHU, Ger.*
Bryonia (p. 2461·3); rhus tox. (p. 2603·3); dulcamara (p. 2497·3); phytolacca (p. 2593·2); gnaphalium polycephalum.
Homoeopathic preparation.

Bryper *Brymar, Philipp.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Bryssidine *Bryssica, Fr.*
Ginseng (p. 2513·3); minerals; vitamins.
Tonic.

Brytolin *MPSI, Philipp.*
Syrup: ⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

MPSI, Philipp.
Tablet: ⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

BS *Xepa-Soul Pattinson, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

BS Carino *Carinopharm, Ger.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

BSI Medicated Plaster *Tungfa, Philipp.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); zinc oxide (p. 1729·1); angelica dahurica radix (p. 2443·3); angelicae sinensis radix (p. 2497·1); armeniacae amarum semen; scrophulariae radix; gleditsiae abnormalis fructus; aconiti kusnezoffii radix; allium fistulosum herba; frankincense (p. 2507·3); myrrh (p. 2566·1); yellow beeswax (p. 2170·2); resin.
Muscular pain.

BSI Medicated Spray *Tungfa, Philipp.*
⊗Nux vomica (p. 2573·3); pinellia tuber; drynariae rhizoma; liquorice (p. 1853·2); ginseng (p. 2513·3); huperzia serrata; menthol (p. 2553·2); methyl salicylate (p. 92·1); alcohol (p. 1733·1).
Muscle pain.

B-Six *Sam-On, Israel.*
Vitamin B_6 (p. 2105·3).
Vitamin B_6 supplement.

B-Six-F *Wintech, India.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

BS-ratiopharm *Ratiopharm, Ger.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

BSS *Alcon, Austral.; Alcon, Canad.; Alcon, Fr.†; Alcon, Ger.; AlleMan, Ger.; Serag-Wiessner, Ger.; Alkon (Αλκον), Gr.; Alcon, Israel; Alcon, Malaysia; Alcon, Philipp.; Alcon, S.Afr.†; Alcon, Singapore†; Alcon, Thai.; Alcon, UK; Alcon, USA*
Electrolytes (p. 1775·1).
Eye irrigation; irrigation of ears, nose, and throat.

BSS Compose *Alcon, Fr.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3); oxiglutatione (p. 1555·2).
Eye irrigation.

BSS Plus *Alcon, Austral.†; Alcon, Canad.; Alcon, Ger.; Alcon, Hung.†; Alcon, Israel; Alcon, Malaysia; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.; Alcon, USA.*
Electrolytes (p. 1775·1); glucose (p. 2068·3); oxiglutatione (p. 1555·2).
Eye irrigation.

Alcon, S.Afr.
Electrolytes (p. 1775·1); glucose (p. 2068·3); glutathione (p. 1555·2).
Eye irrigation.

Alkon (Αλκον), Gr.
Electrolytes (p. 1775·1).
Ocular irrigation during ophthalmic surgery.

BT Enema *Yenisehir, Turk.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

B-Tablock *Latinofarma, Braz.*
⊗Levobunolol hydrochloride (p. 2008·3).
Glaucoma.

B-Tasone-G *Beacons, Singapore.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

BTK-Plus *Geritrex, USA.†*
Clorophene (p. 1748·3); orthophenylphenol (p. 1762·3); amylphenol (p. 1736·3).
Disinfectant.

Btn *Zydus, India.*
Biotin (p. 2052·2).

B-Trimin *Bangkok Lab & Cosmetic, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

BTX Ofteno *Volta, Chile.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma.

BTXA *LIBP, Hong Kong.*
Botulinum A toxin (p. 2017·1).
Blepharospasm; hemifacial spasm; strabismus.

BTX-HA Ofteno *Sophia, Mex.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Bu La La *Baima, China.*
A porcine immunoglobulin.

Bu Fu Mai *Qi Du, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Bu Luo Na Tai *Su Lan, China.*
Recombinant human brain natriuretic peptide.

Bu Luo Wei Xin *Duoburuifei, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids.

Bu Mai Ding *C & O, China; C & O, China.*
Tolterodine tartrate (p. 2370·2).

Bu Mai Xin *Xin Si Dun, China.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

BU Pangramin SLIT *Alk-Scherax, Ger.†*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Bu Rui De *TianAn, China.*
⊗Fructose (p. 2068·2); glycerol (p. 2517·2); sodium chloride (p. 1795·1).

Bu Rui Fen *Si Huan Ke Bao, China.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Bu Rui Jin *Si Huan Ke Bao, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids.

Bu Rui Ning *Si Huan Ke Bao, China.*
Puerarin.

Bu Rui Ping *Si Huan Ke Bao, China.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bu Rui Xi *Si Huan Ke Bao, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Buateron *Farmedia, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Bubble Drops *PP Lab, Thai.*
Simeticone (p. 1886·2).
Flatulence; meteorism.

Bubil *Jaka, Rus.†*
Pyrethrins (p. 2161·1); acetic acid (p. 2426·3).

Bucagel *Meda, Port.*
Choline salicylate (p. 39·2).
Mouth disorders.

Bucain *Actavis, Austria; Actavis, Ger.; Actavis, Hung.; Bernofarm, Indon.; DeltaSelect, Ukr.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia; spinal anaesthesia.

Bucal Hyper Sensitive *Grimberg, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2); xylitol (p. 2220·3).
Sensitive teeth; dental caries prophylaxis.

Bucal Tac Whitening Gel *Grimberg, Arg.*
⊗Sodium fluoride (p. 2089·2); xylitol (p. 2220·3); papain (p. 2582·3).

Bucanest *Biodica, Austral.; Biodica, Fr.†*
Articaine hydrochloride (p. 1980·1). Adrenaline acid tartrate (p. 1292·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bucanil *YSP, Malaysia.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bucanyl *Burapha, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Bucaril *Pharmaland, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Buccalin *SIT, Austria.*
Haemophilus influenzae; pneumococci; streptococci; staphylococcus aureus; ox bile extract (p. 2457·2).
Prophylaxis of bacterial infections in patients with colds.

SIT, Ital.
Streptococcus pneumoniae I, II, and III; *Streptococcus haemolyticus; Staphylococcus aureus; Haemophilus influenzae.*
Prophylaxis of bacterial infections in patients with influenza.

Buccaline *Qualiphar, Belg.†; Pharmabroker, NZ.*
Pneumococcus; streptococcus; staphylococcus; *Haemophilus influenzae*; ox bile (p. 2457·2).
Common cold prophylaxis.

Desma, Switz.
Streptococcus haemolyticus; Streptococcus pneumoniae; Staphylococcus aureus; Haemophilus influenzae; ox bile (p. 2457·2).
Common cold prophylaxis.

Buccalsone *Will-Pharma, Neth.†*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Aphthous stomatitis.

Buccapol *Yeni, Turk.*
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Buccasept *Galenica, Gr.†*
Calcium propionate (p. 592·3); cetrimonium bromide (p. 1742·3); tetracaine hydrochloride (p. 1996·3).

Buccastem *Alliance, Irl.; API, NZ; Alliance, UK.*
Prochlorperazine maleate (p. 1098·3).
Vertigo; nausea; vomiting; migraine; vestibular disorders.

Buccobet *DB, Fr.*
⊗Betamethasone valerate (p. 1624·1).
Mouth and throat inflammation.

Buccolam *ViroPharma, Ger.; ViroPharma, Irl.; ViroPharma, UK.*
Midazolam hydrochloride (p. 1085·1).
Epilepsy.

Buccoseptine *Qualiphar, Belg.†*
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Buccosoin *Merck Medication Familiale, Fr.*
Chlorhexidine gluconate (p. 1743·3); chlorobutanol (p. 1747·2).
Oral hygiene.

Bucco-Tantum *Bayer, Switz.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat inflammation.

Bucelon *Celon, India.*
Busulfan (p. 754·3).
Bone marrow transplantation; chronic myeloid leukaemia; polycythaemia vera; essential thrombocythaemia.

Buchex *Bernabo, Arg.*
Hexetidine (p. 1755·1); benzydamine hydrochloride (p. 29·2).
Mouth disorders.

Buckley's Bedtime *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Cough; cold symptoms.

Buckleys Chest Congestion *Novartis, USA.*
Guaifensin (p. 1666·2).
Cough.

Buckley's Complete *Buckley, Canad.*
Paracetamol (p. 115·1); menthol (p. 2553·2).

Buckley's Complete Extra Strength Cough, Cold & Flu Day *Buckley, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cough; cold and influenza symptoms.

Buckley's Complete Extra Strength Cough, Cold & Flu Night *Buckley, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Buckley's Congestion and Cough *Buckley, Canad.*
Guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Buckleys Cough *Novartis, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Buckley's Daytime Cold and Sinus *Buckley, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Buckley's DM *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Dry cough.

Buckley's DM Decongestant *Novartis Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Buckley's Mixture *Novartis Consumer, Canad.*
Ammonium carbonate (p. 1656·1); potassium bicarbonate (p. 1780·3); menthol (p. 2553·2); camphor (p. 2466·2).
Cough.

Buckley's Nighttime Cold and Sinus *Buckley, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Buclen *Meyer Alian, Venez.*
⊗Clenbuterol (p. 1207·2).

Buclimax *Ducto, Braz.†*
Buclizine hydrochloride (p. 618·3); lysine (p. 2079·3); vitamin B substances (p. 2102·3); caffeine (p. 1203·3).
Reduced appetite; tonic.

Buclina *Sanofi-Aventis, Braz.*
Buclizine hydrochloride (p. 618·3).
Reduced appetite.

Buclorhex *Sertex, Arg.*
Chlorhexidine (p. 1743·2); sodium fluoride (p. 2089·2).
Mouth disorders; dental caries prophylaxis.

Buco Bleu *Sandoz, Turk.*
Methylthioninium chloride (p. 1559·1); resorcinol (p. 1718·3).
Mouth and throat disorders.

Buco Regis *Ramon Sala, Spain.*
Ipecacuanha (p. 1667·2); methyl salicylate (p. 92·1); myrrh (p. 2566·1); sulfanilamide (p. 368·1); zinc chloride (p. 2126·1); menthol (p. 2553·2).
Mouth and throat inflammation; pyorrhoea.

Bucoangin N *Northia, Arg.*
Gramicidin (p. 308·3); neomycin (p. 329·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Bucodrin Comp *Fardi, Spain.†*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Bucogel *Gador, Arg.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; dental caries prophylaxis; mouth disinfection.

Bucogerm Tos *Mintlab, Chile.*
Chlorhexidine hydrochloride (p. 1743·3); noscapine (p. 1670·3).
Cough.

Bucometasana *Abbott, Spain.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2); tyrothricin (p. 384·1).
Mouth and throat disorders.

Bucomicina *Pisa, Mex.†*
Streptomycin (p. 359·1).
Bacterial infections.

Buconif *Nycomed, Austria.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Bucort *Orion, Fin.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Bucoseptil *Sanitas, Chile.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders; oral hygiene.

Bucospray *Teofarma, Spain.*
Chlorhexidine gluconate (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Bucotricin *Monserrat, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Budamate *Lupin, India.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).

Budamax *PMC, Austral.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.

Budapp *Dermapharm, Ger.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Budasmal *Laboratorios Chile, Chile.*
⊗Budesonide (p. 1625·1).
Asthma.

Budate *Lupin, India.*
⊗Budesonide (p. 1625·1).
Asthma.

Budaxiu *Maite Xinghua, China.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Budecol *AstraZeneca, Gr.*
⊗Budesonide (p. 1625·1).
Inflammatory bowel disease.

Budecort *AstraZeneca, Braz.; Astellas, Ger.; Cipla, India; Cipla, Malaysia; AstraZeneca, Philipp.; Cipla, Thai.; Oftalmi, Venez.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease; nasal polyps; rhinitis; asthma.

Budeflam *Cipla-Medpro, S.Afr.*
⊗Budesonide (p. 1625·1).
Asthma; allergic rhinitis.

Budelin *Meda, UK.*
⊗Budesonide (p. 1625·1).
Asthma.

Budemar *Biostam (Βιοσταμ), Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Budena *Aldo-Union, Hong Kong; Aldo, Spain.†*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Budenas *Oftalmi, Venez.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Budenase *Cipla, Hong Kong; Cipla, India; Cipla, Malaysia.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Budenid *Teva, Switz.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Budenide *Hoe, Malaysia.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.

Budenite *Aurora, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Budenobronch *Infectopharm, Austria; Infectopharm, Ger.*
⊗Budesonide (p. 1625·1).
Asthma.

Budenocort *AFT, NZ.*
⊗Budesonide (p. 1625·1).
Asthma.

Budenofalk *Falk, Belg.; Biotoscana, Chile; Falk, Cz.; Falk, Denm.; Falk, Fin.; Falk, Ger.; Galenica, Gr.; Falk, Hong Kong; Falk, Hung.; Darya-Varia, Indon.; Falk, Indon.; Falk, Irl.; Falk, Neth.; Falk, Philipp.; Falk, Pol.; Falk, Rus.; Falk, Singapore; Meda, Swed.; Vifor, Switz.; Ali, Turk.; Falk, UK; Falk, Ukr.*
⊗Budesonide (p. 1625·1).
Inflammatory bowel disease; collagenous colitis.

Budeprion *Teva, USA.†*
Bupropion hydrochloride (p. 408·2).
Depression.

Budeprol *Novendia, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Buderen *Balu, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Buderhin *GSK, Pol.*
⊗Budesonide (p. 1625·1).
Rhinitis.

Budes *Hexal, Ger.†*
⊗Budesonide (p. 1625·1).
Obstructive airways disease; rhinitis; nasal polyps.

Budesal *Cipla, India.*
⊗Budesonide (p. 1625·1); salbutamol sulfate (p. 1220·2).
Asthma.

Budesan *Biospray, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Budesitan *Breathe Pharmaceuticals, Irl.*
⊗Budesonide (p. 1625·1).
Asthma.

Budesoderm *Pharmex (Φαρμεξ), Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Budesogen *Generics, Hung.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Budeson *Nycomed, Arg.; Falk, Israel.*
⊗Budesonide (p. 1625·1).
Crohn's disease; asthma; nasal polyps; rhinitis.

Budesonal *Verisfield, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

BudeSpray *Medispray, Thai.*
⊗Budesonide (p. 1625·1).
Asthma.

Budexan *Genetic, Ital.*
⊗Budesonide (p. 1625·1).
Asthma; croup.

Budez *Sun, India.*
⊗Budesonide (p. 1625·1).
Asthma; rhinitis; nasal polyps; inflammatory bowel disease.

Budezonil *Sandoz, Arg.*
⊗Budesonide (p. 1625·1).
Asthma; rhinitis.

Budfor *AstraZeneca, Cz.; AstraZeneca, Irl.; AstraZeneca, Neth.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Asthma; obstructive airways disease.

Budiair *Torrex, Austria; Chiesi, Braz.; Torrex Chiesi, Cz.; Chiesi, Ger.; Chiesi, Gr.; Chiesi, Ital.; Chiesi, Malaysia; Torrex Chiesi, Pol.; Chiesi, Port.; Chiesi, Rus.; Chiesi, Thai.; Chiesi, Turk.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease; asthma.

Budicort *AstraZeneca, Israel.*
⊗Budesonide (p. 1625·1).
Asthma.

Budineb *Caber, Ital.*
⊗Budesonide (p. 1625·1).
Asthma; croup.

Budo-san *Merck, Austria; Falk, Port.*
⊗Budesonide (p. 1625·1).
Crohn's disease.

Budosan *Farmasa, Mex.†*
⊗Budesonide (p. 1625·1).
Crohn's disease.

Budvent *Kopran, India.*
⊗Budesonide (p. 1625·1).
Asthma.

Buenas Noches *ISA, Arg.*
Melatonin (p. 2551·3).
Sleep disorders.

Buer Lecithin Cholesterin Balance *Nycomed, Ger.†*
Soya phospholipids (p. 2092·3).
Hypercholesterolaemia.

Buer Lecithin Plus *Takeda, Ger.*
Soya phospholipids; vitamins.
Tonic.

Buerlecithin *Nycomed, Austria.*
Lecithin (p. 2542·2); with or without vitamins.
Tonic.

Thursday, Austral.†; Penta, Hung.
Soya lecithin (p. 2542·2).
Dietary supplement; tonic.

Buerlecithin Compact *Byk, Austria.†*
Soya lecithin (p. 2542·2).
Tonic.

Bufabron *Bufa, Indon.*
Theophylline (p. 1229·3).
Asthma.

Bufacyl *Medipharm, Chile.*
Octatropine methylbromide (p. 1866·2); phenobarbital (p. 535·2).
Colic; dysmenorrhoea; vomiting in infants.

Bufamoxy *Bufa, Indon.*
Amoxicillin (p. 216·2).
Bacterial infections.

Bufect *Sanbe, Indon.*
Ibuprofen (p. 68·2).
Pain; musculoskeletal and joint disorders.

Bufedil *Abbott, Braz.; Amdipharm, Ger.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Bufenac *Burapha, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Bufencon *YSP, Malaysia; Yung Shin, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Bufenik *Ratiopharm, Pol.*
Ibuprofen (p. 68·2).
Pain; fever.

Bufex Kid *Cosme, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Bufex Plus *Cosme, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Bufexan
Note: this name may be used for preparations of different composition.
Sandoz, Arg.
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Bufex-C *Cosme, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Bufex-CD *Cosme, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Buffered C *Quest, UK.*
Calcium ascorbate (p. 2111·1).

Buffered C 500 *Bio-Health, UK.*
Calcium ascorbate (p. 2111·1).

Buffered Pirin *Gramse, Israel.†*
Aspirin (p. 22·2) and buffering agents.
Fever; musculoskeletal and joint disorders; pain; thrombosis prophylaxis.

Bufferin *BMS, Braz.; Novartis, Braz.; Novartis Consumer, Canad.; Novartis, Gr.; Novartis, USA.*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3), magnesium carbonate (p. 1856·2), and magnesium oxide (p. 1857·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain; thromboembolism prophylaxis; transient ischaemic attacks; myocardial infarction.

BMS, China.
Oral solution: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough; cold symptoms.

BMS, China.
Tablets: Paracetamol (p. 115·1).
Fever; pain.

Bufferin Cold *BMS, China.*
⊗Day tablets, paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; dextromethorphan hydrobromide; pseudoephedrine hydrochloride; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Bufferin Plus *BMS, China.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; cold symptoms.

Buffex *Roberts, USA.*
Aspirin (p. 22·2).
Aluminium glycinate (p. 1817·2) and magnesium carbonate (p. 1856·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever; inflammation; transient ischaemic attacks; myocardial infarction.

Bufidol *Behrens, Venez.*
Nalbuphine (p. 97·3).
Pain.

Bufigen
Note: this name may be used for preparations of different composition.
Pisa, Mex.
Nalbuphine hydrochloride (p. 97·3).
Pain.

Antigen, Irl.†
Ibuprofen (p. 68·2).
Pain; musculoskeletal, joint, and peri-articular disorders; soft-tissue injuries.

Bufilem *Teva, Mex.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Bufimorf *Teva, Hung.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Buflan *Solvay, Ital.†*
Buflomedil hydrochloride (p. 1328·3).
Vascular disorders.

Buflex *Burapha, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Buflocit *CT, Ital.†*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Buflodil *Medichrom, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Buflohexal *Hexal, Austria.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Buflomed *Scott-Cassara, Arg.*
Buflomedil (p. 1328·3).
Cerebral and peripheral vascular disorders.

Genericon, Austria.†
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Buflo-POS *Ursapharm, Ger.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Buflo-Puren *Actavis, Ger.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Buflox *Hexal, Pol.†*
Buflomedil hydrochloride (p. 1328·3).
Intermittent claudication; obstructive arterial disease.

Buformin *Burapha, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Bufyl *Mercury, UK.*
⊗Bupivacaine hydrochloride (p. 1980·3); fentanyl citrate (p. 60·1).
Postoperative pain; labour pain.

Bugazon *Pharmacos Abug, Mex.†*
Captopril (p. 1331·2).
Hypertension.

Bugderm *Neiss, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Bugeron *Burapha, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders; vomiting.

Bugs Bunny *Bayer Consumer, Canad.*
Vitamins with or without minerals.

Miles, USA.
Vitamins.

Buğumentol *Drogsan, Turk.*
Cineole (p. 2479·1); menthol (p. 2553·2); peppermint oil (p. 1877·1); turpentine oil (p. 2636·3).
Respiratory-tract disorders.

Buğusan *Kurtsan, Turk.*
Cineole (p. 2479·1); menthol (p. 2553·2).
Respiratory-tract disorders.

Buğuseptil *Santa, Turk.*
Benzoin tincture (p. 2624·3); menthol (p. 2553·2); niaouli oil (p. 2569·1); cineole (p. 2479·1); turpentine oil (p. 2636·3).
Respiratory-tract disorders.

Bukatel *Panacea, India.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting.

Bukuryoin *Tsumura, Jpn.*
Poria sclerotium; atractylodes lancea rhizome; citrus unshiu peel; ginseng (p. 2513·3); immature orange; ginger (p. 1844·1).
Traditional Kampo medicine.

Bukuryoingohangekobokuto *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; atractylodes lancea rhizome; magnolia bark; citrus unshiu peel; ginseng (p. 2513·3); perilla herb; immature orange; ginger (p. 1844·1).
Traditional Kampo medicine.

Bulasan *Quimica y Farmacia, Mex.*
Cinnarizine (p. 622·1).
Peripheral vascular disease.

Bulboïd *Melisana, Switz.*
⊗Glycerol (p. 2517·2).
Constipation; bowel evacuation.

Bulboshap *Farmagan, Ital.†*
Achillea (p. 2427·3); chamomile (p. 2474·1); cinchona (p. 2478·3); centaurea cyanus; gentian (p. 2512·1); lilly; almond.
Seborrhoeic dermatitis.

Bulgarolax *Laboratorios Chile, Chile.†*
Phenolphthalein (p. 1877·3); cascara (p. 1826·1); aloes (p. 1816·1).
Constipation.

Bulk *Agepha, Austria.†*
Methylcellulose (p. 2197·3).
Constipation.

Bull Frog Marathon Mist *Chattem, USA.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Bull Frog Quick Gel *Chattem, USA.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Bullcef *Evershine, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Bullfrog *Chattem, USA; Chattem, USA.*
Gel SPF 18: SPF 36: Oxybenzone (p. 1715·3); octocrilene (p. 1715·2); octinoxate (p. 1715·1).
Sunscreen.

Chattem, USA.
Stick SPF 18: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Sunscreen.

Bullfrog for Kids *Chattem, USA.*
SPF 18: Octocrilene (p. 1715·2); octinoxate (p. 1715·1) octisalate (p. 1715·2).
Sunscreen.

Bullfrog Sport *Chattem, USA.*
SPF 18: Oxybenzone (p. 1715·3); octocrilene (p. 1715·2); octinoxate (p. 1715·1) octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Bulol *Cosme, India.*
⊗Betaxolol (p. 1322·3).
Glaucoma; ocular hypertension.

Bumaflex N *Nycomed, Arg.*
Naproxen (p. 98·2).
Inflammation.

Bum-Butt-R *Summerberry, Canad.*
Soft paraffin (p. 2211·3); starch (p. 2095·1).

Bumed *Medifive, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; inflammation; pain.

Bumeftyl *Faran, Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Bumelex *Roemmers Rowe, Venez.*
⊗Bumetanide (p. 1329·1).
Oedema; hypertension.

Bumetin *Galeno, Venez.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Bumetone *Greater Pharma, Thai.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Bumex *Validus, USA.†*
⊗Bumetanide (p. 1329·1).
Oedema.

Bumid *Koz, Turk.*
⊗Bumetanide (p. 1329·1).
Oedema.

Buminate *Baxter, Arg.; Baxter, Canad.; Baxter, China; Baxter, Hong Kong; Baxter, Malaysia†; Baxter, Singapore; Baxter, Thai.; Baxter, USA.†*
⊗Albumin (p. 1130·2).
Adult respiratory distress syndrome; hypovolaemia; plasma volume expansion; burns; hypoalbuminaemia; nephrosis; cardiopulmonary bypass surgery; haemolytic disease of the newborn.

Bumps and Bruises
Note: this name may be used for preparations of different composition.
Hylands, Canad.
Arnica montana (p. 2447·2); hypericum perforatum (p. 449·1); bellis perennis (p. 2454·2); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Bumps & Bruises
Note: this name may be used for preparations of different composition.
Weleda, UK.
Arnica (p. 2447·2).
Musculoskeletal and soft-tissue injury.

Bunafon *Intermed, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Bunascan *Fahrenheit, Indon.*
Bupivacaine (p. 1980·3).
Spinal anaesthesia.

Bunase *Okasa, Thai.; TTN, Thai.*
⊗Budesonide (p. 1625·1).
Rhinitis; asthma.

Bunda *Nutricia, Indon.†*
Preparation for enteral nutrition.
Nutritional supplement in pregnant and lactating women.

Bunil *Lundbeck, Port.*
Melperone hydrochloride (p. 1083·2).
Agitation; confusion; alcohol withdrawal syndrome; behaviour disorders; psychoses.

Bunofen *GPO, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Bunogesic *Rusan, India.*
⊗Buprenorphine (p. 30·2).
Pain.

Bunolol *Kleva, Gr.*
⊗Levobunolol hydrochloride (p. 2008·3).

Bunondol *Polfa Warszawa, Pol.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Buntaopoad-Bura *Burapha, Thai.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; pain; fever; inflammation.

Buona *Eurofarma, Braz.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Buovent DP *Kopran, India.*
⊗Budesonide (p. 1625·1).
Asthma.

Bup *Eurofarma, Braz.*
Bupropion hydrochloride (p. 408·2).
Depression; smoking withdrawal.

BUP-4 *Taiho, Jpn.*
Propiverine hydrochloride (p. 2363·1).
Urinary incontinence; urinary frequency.

Bupafen *Biomed, NZ.*
⊗Bupivacaine hydrochloride (p. 1980·3); fentanyl citrate (p. 60·1).
Epidural analgesia.

Bupap *ECR, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1).
Pain.

Bupep *Cipla, India.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Buphenyl *Orphan Pacific, Jpn; Medicis, USA.*
Sodium phenylbutyrate (p. 2518·3).
Urea cycle disorders.

Bupiabbott *Abbott, Braz.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Bupiabbott Plus *Abbott, Braz.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupibil *Hospira, Ital.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Bupicain *Monico, Ital.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupicaina *Scott-Cassara, Arg.*
Bupivacaine (p. 1980·3).
Local anaesthesia.

Bupiforan *Baxter, Fr.†; Baxter, Ital.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupigobbi *Gobbi, Arg.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Bupinex *Richmond, Arg.*
Bupivacaine (p. 1980·3).
Local anaesthesia.

Bupinostrum *Nostrum, Port.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Bupisen *Senese, Ital.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupisolver *AltaSelect, Ital.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupisure *Gentech, India.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Bupivan *Sun, India.*
Bupivacaine (p. 1980·3).
Local anaesthesia.

Bupixamol *Molteni, Ital.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupleurum Complex *Mediherb, Austral.†*
Bupleurum; danshen (p. 2491·3); milk thistle (p. 1561·1).
Liver disorders.

Bupleurum Compound *Phytomedicine, Austral.*
Bupleurum; milk thistle (p. 1561·1); fennel (p. 2503·2); European barberry (p. 2502·1).
Liver disorders.

Buplex *Actavis, Irl.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal, joint,peri-articular, and soft-tissue disorders.

Bupranal *Moscow Endocrine, Rus.*
⊗Buprenorphine (p. 30·2).
Pain.

Bupren *Valeant, Hung.†*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Buprenex *Reckitt & Colman, USA.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Buprenotex *Nycomed, Denm.; Nycomed, Swed.*
⊗Buprenorphine hydrochloride (p. 30·3).
Opioid withdrawal syndrome.

Buprex *Schering-Plough, Port.; Reckitt Benckiser, Spain.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Buprigesic *Neon, India.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Buprine *Siam Bheasach, Thai.†*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Buprinor *AstraZeneca, India.*
⊗Buprenorphine (p. 30·2).
Pain.

Buproban *Teva, USA.*
Bupropion hydrochloride (p. 408·2).
Depression.

Buprodol *Cafar, Venez.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Bupron *Sun, India.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Buprophar *Teva, Belg.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Buprovil *Multilab, Braz.*
Ibuprofen (p. 68·2).

Buproxen *Burapha, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Bupstésic *Uniao Quimica, Braz.*
Bupivacaine (p. 1980·3).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Buquel *Meda, Norw.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Buracard *Burapha, Thai.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Burajel *Burapha, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux.

Burajel AM *Burapha, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Dyspepsia; gastric hyperacidity; peptic ulcer.

Buram *Leo, Irl.†*
⊗Amiloride hydrochloride (p. 1299·1); bumetanide (p. 1329·1).
Oedema.

Burana *Orion, Denm.; Orion, Fin.; Orion, Neth.; Orion, Norw.; Orion, Rus.; Orion, Swed.*
Ibuprofen (p. 68·2) or ibuprofen potassium (p. 68·2).
Pain; inflammation; gout; musculoskeletal, joint, and peri-articular disorders; fever.

Burana-C *Orion, Fin.*
Ibuprofen (p. 68·2); ascorbic acid (p. 2110·3).
Influenza symptoms.

Buraton 10 F *Schulke & Mayr, Ger.†*
Glyoxal (p. 1754·1); formaldehyde (p. 1752·2); glutaral (p. 1753·2); ethylhexanal (p. 1752·1).
Surface disinfection.

Burazin *Kurtsan, Turk.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Burdock Complex *Mediherb, Austral.*
Lappa (p. 2540·1); slippery elm (p. 2617·1); rumex acetosella; rhubarb (p. 1884·2).
Tonic.

Buretic *BJ Benjaosoth, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Diuretic.

Burgerstein CELA *Antistress, Switz.†*
Vitamins; minerals.

Burgerstein Geriatrikum *Antistress, Switz.*
Vitamins; minerals.
Tonic.

Burgerstein TopVital *Antistress, Switz.*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic.

Burinax *Abbott, Braz.*
⊗Bumetanide (p. 1329·1).
Oedema.

Burinex *CSL, Austral.; Leo, Austria; Leo, Belg.; Leo, Canad.; Leo, Denm.; Leo, Fr.; Leo, Ger.†; Leo (Λεο), Gr.; Leo, Hong Kong; Leo, Irl.; Leo, Malaysia; Leo, Neth.; Leo, Norw.; CSL, NZ; Leo, NZ; Leo, Philipp.; Adcock Ingram, S. Afr.; Leo, Singapore; Leo, Swed.; Leo, Switz.†; Leo, UK.†*
⊗Bumetanide (p. 1329·1).
Oedema; forced diuresis; heart failure; sodium retention; hypertension; renal failure; oliguria due to renal failure; liver cirrhosis.

Burinex K *Leo, Gr.; Adcock Ingram, S.Afr.; Leo, Singapore.*
⊗Bumetanide (p. 1329·1); potassium chloride (p. 1793·2).
Oedema.

Burinex med kaliumklorid *Leo, Denm.†*
⊗Bumetanide (p. 1329·1); potassium chloride (p. 1793·2).
Oedema; hypertension.

Burn Aid
Note: this name may be used for preparations of different composition.
JK Biochem, India.
Sulfadiazine silver (p. 362·3).
Burns.

Burn Cream
Note: this name may be used for preparations of different composition.
Watkins, Canad.
Lidocaine hydrochloride (p. 1988·2).

Burn Free *Prevor, Fr.*
A hydrogel dressing.
Burns.

Burn O Sol *Protector, Canad.*
Benzocaine (p. 1980·2); chlorhexidine acetate (p. 1743·2).

Burn Relief *Prime Enterprises, Canad.*
Lidocaine hydrochloride (p. 1988·2).

Burna *Nobel, Turk.*
⊗Sibutramine hydrochloride (p. 2330·2).

Burnaid *Rye, Singapore.*
Melaleuca oil (p. 2551·1); triclosan (p. 1773·2).
Burns; scalds.

Burnazin *Darya-Varia, Indon.*
Sulfadiazine silver (p. 362·3).
Burns.

Burnex *JK Biochem, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Burneze *Seton, Irl.; SSL, UK.*
Benzocaine (p. 1980·2).
Scalds; burns.

Burnheal *Cipla, India.*
Sulfadiazine silver (p. 362·3); chlorhexidine (p. 1743·2) or chlorhexidine hydrochloride (p. 1743·3).
Burns.

Burnil
Note: this name may be used for preparations of different composition.
Intra-Labs, India.
Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).
Kurtsan, Turk.
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion.

Burnkul *Intermed, India.*
Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).

Burnoff *Ethix, India.*
Chlorhexidine (p. 1743·2); sulfadiazine silver (p. 362·3); metronidazole (p. 936·1).

Burnol Plus *Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.*
Aminoacridine hydrochloride (p. 1732·3); cetrimide (p. 1742·1).
Burns; insect bites; skin rashes; wounds.
Reckitt Benckiser, Thai.
Aminoacridine hydrochloride (p. 1732·3); cetrimide (p. 1742·1); thymol (p. 1772·2).
Burns; wounds; insect bites; skin rashes.

Burnosym *Symbiosis, India.*
Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).

Burnowin *Wings, India.*
Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).

Burns Cream *Nelson, UK.*
Echinacea angustifolia (p. 2498·1); calendula officinalis (p. 2465·2); hypericum perforatum (p. 449·1); urtica urens (p. 2639·3).
Homoeopathic preparation.

Burnshield *Burnshield, Israel.*
Melaleuca oil (p. 2551·1).
Burns; scalds.

Burnshield Gel *Travel-Safe, UK.*
Melaleuca oil (p. 2551·1).
Burns; scalds.

Burnsil *Beximco, Philipp.*
Sulfadiazine silver (p. 362·3).
Burns; ulcers.

Buronil *Lundbeck, Austria; Lundbeck, Belg.; Swedish Orphan, Cz.; Medilink, Denm.; Swedish Orphan, Swed.*
Melperone hydrochloride (p. 1083·2).
Sleep disorders; anxiety disorders; dementia; drug and alcohol withdrawal syndromes; psychoses; pain; agitation; schizophrenia; confusion.

Buronon *Abbott, Turk.†*
Melperone hydrochloride (p. 1083·2).
Agitation; anxiety; behaviour disorders.

Buro-Sol *Trans Canaderm, Canad.*
Aluminium acetate (p. 2440·1).
Skin disorders; ear disorders.

Burow's *Rugby, USA.*
Acetic acid (p. 2426·3); aluminium acetate (p. 2440·1).
Ear infections.

Burten *Laboratorios Chile, Chile.*
Ketorolac trometamol (p. 80·2).
Pain.

Bus *Nodysis, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Busansil *Rega, Port.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Buscalm *Wockhardt, India.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Buscalma *Grunenthal, Port.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Buscapina *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Venez.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; aid in gastrointestinal investigation.

Buscapina Compositum *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Venez.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Buscapina Compositum N *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Painful smooth muscle spasm.

Buscapina Fem *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.*
Hyoscine butylbromide (p. 1845·3); ibuprofen (p. 68·2).
Smooth muscle spasm and pain.

Buscapina Plus *Boehringer Ingelheim, Venez.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Pain; smooth muscle spasm.

Buscasan *Boehringer Ingelheim, Arg.*
Omeprazole (p. 1867·2).
Heartburn.

Buscin *LBS, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Visceral spasms.

Buscoduo *Boehringer Ingelheim, Braz.*
Paracetamol (p. 115·1); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm and pain.

Buscofem *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Gr.*
Ibuprofen (p. 68·2).
Dysmenorrhoea; pain.

Buscofen *Boehringer Ingelheim, Ital.*
Ibuprofen (p. 68·2).
Pain.

Buscogast *Boehringer Ingelheim, Ger.*
Omeprazole (p. 1867·2).
Heartburn; acid reflux.

Buscolysin *Sopharma, Pol.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal disorders; smooth muscle spasm; gastrointestinal radiography.

Buscomed *Medlink, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Peptic ulcer; smooth muscle spasm.

Busconet *Sons, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Buscono *Milano, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Buscopalamin *Synco, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Buscopan *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S. Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Eczacibasi, Turk.; Boehringer Ingelheim, UK.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; irritable bowel disease; colic pain; peptic ulcer; aid in radiology or endoscopy.

Buscopan Compositum
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, S.Afr.; Eczacibasi, Turk.†
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm and pain.
Boehringer Ingelheim, Ital.
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Buscopan Compositum N *Unilfarma, Port.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Buscopan Composto *Boehringer Ingelheim, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Buscopan Plus *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Thai.†; Eczacibasi, Turk.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm and pain.

Buscoveran Composto *Bunker, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Buscozol *Boehringer Ingelheim, Neth.*
Omeprazole (p. 1867·2).
Dyspepsia; heartburn.

Bus-D *Nodysis, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal-reflux; dyspepsia.

Busepan *Offenbach, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Buserin *Farm-Synthesis, Ukr.*
⊗Buserelin (p. 2256·2) or buserelin acetate (p. 2256·2).
Endometriosis; uterine fibroids; female infertility; prostatic cancer; breast cancer.

Bushi *Andromaco, Arg.*
Calendula (p. 2465·2); allantoin (p. 1693·1).
Nipple care.

Busilvex *Rovafarm, Arg.; Pierre Fabre, Austria; Pierre Fabre, Belg.; Pierre Fabre, Cz.; Pierre Fabre, Denm.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Irl.; Pierre Fabre, Ital.; Pierre Fabre, Neth.; Pierre Fabre, Norw.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Tema, S.Afr.†; Pierre Fabre, Spain; Pierre Fabre, Swed.; Robapharm, Switz.; Pierre Fabre, Turk.; Pierre Fabre, UK.*
Busulfan (p. 754·3).
Haematopoietic stem-cell transplantation; malignant neoplasms.

Busina *Jofrain, Mex.†*
Hyoscine butylbromide (p. 1845·3).

Buson *Kramer, India.*
Buspirone (p. 1042·1).
Anxiety.

Busonal *Bevo, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Busonid *Biosintetica, Braz.*
⊗Budesonide (p. 1625·1).
Corticosteroid.

Busopin *Jean-Marie, Hong Kong; Jean-Marie, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; dyskinesia; peptic ulcer; post-operative vomiting.

Busosed *Savio, Ital.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Busp *Hexal, Ger.†*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders.

Buspar *Aspen, Austral.; BMS, Austria; BMS, Belg.†; BMS, Braz.; BMS, Canad.†; BMS, Denm.†; BMS, Fin.†; Orion, Fin.†; BMS, Fr.†; BMS, Hong Kong†; BMS, Irl.†; BMS, Ital.†; BMS, Mex.; BMS, Norw.†; BMS, NZ; BMS, Port.†; BMS, S.Afr.; BMS, Spain†; BMS, Swed.†; BMS, Switz.†; BMS, UK†; BMS, USA.†*
Buspirone hydrochloride (p. 1042·1).
Anxiety; mixed anxiety depressive states.

Buspidac *Zydus, India.*
Buspirone (p. 1042·1).
Anxiety.

Buspin *Intas, India.*
Buspirone (p. 1042·1).
Anxiety.

Buspium *Tecnifar, Port.†*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Buspon *Deva, Turk.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Busprina *Farcoral, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm and pain.

Busprina-S *Farcoral, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Bustab *Valeant, Canad.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Buston *Siu Guan, Malaysia; Siu Guan, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; aid in diagnostic procedures.

Bustrix *GSK, Arg.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Busulfex *Orphan, Austral.; Otsuka, Canad.; Kirin, China; Otsuka, Hong Kong; Tzamal, Israel; Kyowa, Jpn; Otsuka, Singapore; Kyowa, Thai.; Biem, Turk.; ESP, USA.*
Busulfan (p. 754·3).
Haematopoietic stem-cell transplantation; malignant neoplasms.

Busulflex *Otsuka, Malaysia.*
Busulfan (p. 754·3).
Haematopoietic stem cell transplantation.

Busuphan *Elder, India.*
Busulfan (p. 754·3).
Bone marrow transplantation; chronic myeloid leukaemia; polycythaemia vera; essential thrombocythaemia.

Busvir *Coniferma, Arg.*
Ritonavir (p. 1013·1).
HIV infection.

Buta Rut B12 *Fabra, Arg.*
Cyanocobalamin (p. 2107·2); piroxicam (p. 125·3).
Inflammation; pain.

Butacinon *TP, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; dysmenorrhoea.

Butacodin *Zarbi (Ζαρμπη), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Butacort *LCH, Hong Kong†; Alphapharm, Malaysia; Mylan, NZ.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Butacort-DP *Zydus, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Butadion *Gedeon Richter, Rus.; Streuli, Switz.†; Gedeon Richter, Ukr.*
Phenylbutazone (p. 125·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; skin trauma and inflammation; haemorrhoids; superficial thrombophlebitis; gout.

Butagan *Anpharm (Ανφαρμ), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Butahale *Reddy, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Butalen *Allen, Mex.*
Phenylbutazone (p. 125·1).
Musculoskeletal and joint disorders.

Butalin
Note: this name may be used for preparations of different composition.
Julphar, UAE.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.
Utopian, Thai.
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Butaline *CCM, Malaysia.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Buta-M *Zydus, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Butamcod *Kocak, Turk.*
Butamirate citrate (p. 1657·3).

Butamidon *Otto, Indon.*
Phenylbutazone (p. 125·1); propyphenazone (p. 127·3); thiamine nitrate (p. 2103·2).
Musculoskeletal and joint disorders.

Butamine *Taro, Israel.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Butamir *Pharmanel, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Butamol *Lafedar, Arg.; Aspen, Austral.; Pharmaland, Thai.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour.

Butaparin *Streuli, Switz.†*
Heparin sodium (p. 1396·3); phenylbutazone (p. 125·1); thymol (p. 1772·2).
Peripheral vascular disorders.

Butapirazol *GSK, Pol.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Buta-Proxyvon *Wockhardt, India.†*
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Butaproxyvon *Wockhardt, India.*
Capsules: Diclofenac sodium (p. 48·3); dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; inflammation; gout.

Butarion *Chew, Thai.†*
Phenylbutazone (p. 125·1); dipyrone (p. 53·3).
Musculoskeletal and joint disorders; gout.

Butartrol *Sanitas, Chile.*
Ibuprofen (p. 68·2); meprobamate (p. 1083·3). Aluminium glycinate (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; musculoskeletal, joint, and peri-articular disorders.

Butarzol *New York Chemical, Thai.*
Phenylbutazone (p. 125·1).
Gout; rheumatic disorders.

Butasona *Fabra, Arg.*
⊗Betamethasone (p. 1623·2), betamethasone sodium phosphate (p. 1623·3), or betamethasone valerate (p. 1624·1).
Corticosteroid.

Butasona RL *Fabra, Arg.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Butavate *GSK, Gr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Butavent *CCM, Malaysia.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Butayonacol *Ifusa, Mex.*
Salicylamide (p. 129·2); phenylbutazone (p. 125·1); colchicine (p. 604·1).
Inflammation; musculoskeletal and joint disorders.

Butazolidin *Fagron, Neth.*
Phenylbutazone (p. 125·1).
Spondyloarthropathies.

Butazolidina *Novartis, Braz.; Padro, Spain.*
Phenylbutazone (p. 125·1).
Lidocaine (p. 1988·1) is included in the injection to alleviate the pain of injection.
Musculoskeletal, joint, and peri-articular disorders; gout.
Sandoz, Mex.
Phenylbutazone sodium (p. 125·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Ankylosing spondylitis; gout; rheumatoid arthritis; arthrosis.

Butazolidine *Novartis, Fr.†*
Phenylbutazone (p. 125·1).
Ankylosing spondylitis; gout; peri-articular disorders.

Butazona *Boehringer Ingelheim, Braz.*
Phenylbutazone calcium (p. 125·1).
Musculoskeletal, joint, and peri-articular disorders; gout.

Butazone *SSP, Thai.*
Phenylbutazone (p. 125·1).
Gout; rheumatic disorders.

Butcher's Per Diem *Virox, Canad.*
Hydrogen peroxide (p. 1755·2).
Disinfection.

Butecam *LKM, Arg.†*
Bromazepam (p. 1041·2).
Anxiety.

Butefina *Vitarum, Arg.†*
Cefalexin (p. 234·1).
Bacterial infections.

Butekont *Med-One, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Butesin
Note: this name may be used for preparations of different composition.
Abbott, Chile.†
Butyl aminobenzoate picrate (p. 1982·3); nitromersol (p. 1761·3).
Burns; insect bites.

Butex *Athlon, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).
Pain.

Butibel *Wallace, USA.*
Belladonna (p. 2453·3); secbutabarbital sodium (p. 1106·2).
Gastrointestinal disorders.

Butidiona *Roux-Ocefa, Arg.*
Tablets: Ibuprofen (p. 68·2).
Inflammation.

Butilamin *Sanval, Braz.†*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Butilamina Compuesta *Plusandex, Venez.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Butilen *Coup, Gr.*
Bromhexine hydrochloride (p. 1656·3).

Butimaxil *Bruluagsa, Mex.*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Butimerin *Ariston, Arg.*
Paste: Benzethonium chloride (p. 1738·1); butimerin; titanium dioxide (p. 1725·1).
Sore nipples; nappy rash.
Ariston, Arg.
Topical powder: ⊗Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); papain (p. 2582·3); butimerin.
Burns; skin infections; ulcers; wounds.

Butimerin Complex *Ariston, Arg.*
⊗Ketoconazole (p. 585·3); hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Butin *Yung Shin, Singapore.†*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; acromegaly; parkinsonism; lactation inhibition.

Butineuron *Lafedar, Arg.*
Gamma-aminobutyric acid (p. 2509·2); pyridoxine hydrochloride (p. 2105·3).
Personality and behaviour disorders; mental function impairment; cerebral injury.

Butiral *Rayere, Mex.*
Hyoscine butylbromide (p. 1845·3).
Muscle spasm.

Butiran *Ecobi, Ital.*
Butamirate citrate (p. 1657·3).
Cough.

Butirol *Drogsan, Turk.*
Butamirate citrate (p. 1657·3).

Butisel *Diba, Mex.*
⊗Dexamethasone (p. 1630·3); phenylbutazone (p. 125·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders.

Butisol *Medpointe, USA.*
Secbutabarbital sodium (p. 1106·2).
Sedative; insomnia.

Butix *Pierre Fabre, Fr.*
Topical gel: Diphenhydramine hydrochloride (p. 626·2).
Pruritus; urticaria; insect stings.

Buto Asma *Aldo-Union, Thai.*
⊗Salbutamol (p. 1220·2).
Bronchospasm.
Aldo, Spain.†
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Buto-Air *Aldo, Spain.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Butoas *Biogalenic, Venez.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Butobloc *Aspen, S.Afr.*
⊗Acebutolol hydrochloride (p. 1289·2).
Angina pectoris; hypertension.

Butocort *Cassara, Arg.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.
D & M, Chile.
⊗Salbutamol sulfate (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Butodol *Neon, India.*
Butorphanol tartrate (p. 33·2).
Pain.

Buton *Mintlab, Chile.*
Papaverine hydrochloride (p. 2362·3); atropine sulfate (p. 1310·2).
Muscle spasm.

Butop *Cipla, India.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Butopan *Biofarma, Turk.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Butosali *Valdecasas, Mex.*
⊗Furosemide (p. 1387·1).
Diuretic.

Butosan *Andromaco, Mex.*
Barrier preparation.
Nappy rash.

Butosol *Northia, Arg.†; Aldo, Spain; Medifarm, Venez.*
⊗Beclometasone dipropionate (p. 1621·2); salbutamol (p. 1220·2).
Obstructive airways disease; asthma.

Butotal *Grunenthal, Chile.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Butotal B *Grunenthal, Chile.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Butovent *Chiesi, Braz.; Chiesi, Thai.†; UCB, Turk.*
⊗Salbutamol (p. 1220·2).
Asthma; obstructive airways disease.

BuTrans *Purdue, Canad.; Mundipharma, Irl.; LTS, Israel; Mundipharma, Neth.; Napp, UK.*
⊗Buprenorphine (p. 30·2).
Pain.

Butrans *Purdue, USA.*
⊗Buprenorphine (p. 30·2).
Pain.

Butrew *Bioquimed, Mex.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal; depression.

Butrin *Stargen, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Butropina *Vincenti, Venez.*
Atropine methonitrate (p. 1310·2); secbutabarbital sodium (p. 1106·2).
Infant colic; habitual neonatal vomiting.

Butrum *Aristo, India.*
Butorphanol tartrate (p. 33·2).
Pain; premedication.

Butt it Out *Paradise, Canad.*
⊗Lobelia (p. 2323·2).
Aid to smoking withdrawal.

Buttercup Infant Cough Syrup *Chefaro, UK.*
Ipecacuanha (p. 1667·2); glucose (p. 2068·3); menthol (p. 2553·2).
Coughs; sore throat.

Buttercup Syrup *Chefaro, UK.*
Squill liquid extract (p. 1677·3); capsicum tincture (p. 2469·3).
Coughs.

Buttercup Syrup (Blackcurrant flavour) *Chefaro, UK.*
Ipecacuanha (p. 1667·2); glucose (p. 2069·1); menthol (p. 2553·2).
Coughs.

Buttercup Syrup (Honey and Lemon flavour) *Chefaro, UK.*
Ipecacuanha (p. 1667·2); glucose (p. 2069·1); menthol (p. 2553·2); honey (p. 2072·1).
Coughs.

Butyl *Masa, Thai.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm.

Butylin *Hovid, Singapore.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Buvacaina *Pisa, Mex.†*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Buvanest *Kalbe, Indon.*
Bupivacaine (p. 1980·3).
Spinal anaesthesia.

Buvasodil *ICN, Pol.†*
Buflomedil hydrochloride (p. 1328·3).
Obstructive peripheral vascular disorders.

Buvastin *Elpen (Ελπεν), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Buventol *Lannacher, Austria†; Orion, Cz.; Orion, Denm.; Orion, Fin.; HRA, Fr.†; Ferrer, Gr.; Orion, Hung.; Orion, Malaysia; Orion, Norw.; Douglas, NZ; Menarini, Pol.; Orion, Singapore; Orion, Swed.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; asthma.

Actavis, Indon.†; Orion, Thai.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Buwin Plus *Intra-Labs, India.*
Ibuprofen (p. 68·2); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Buxon *Saval, Chile.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal; depression.

Buyamin *Biostam (Βιοσταμ), Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Buzetin *Burapha, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Buztin *Tolmann, Philipp.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

BV 17G *Dedousis, Gr.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).

B-Vesil *Daudt, Braz.†*
Oral solution: Dehydrocholic acid (p. 2492·1); glycine (p. 2071·2); choline chloride (p. 2055·2).
Digestive disorders.

Daudt, Braz.†
Tablets: Dehydrocholic acid (p. 2492·1); bovine bile extract (p. 2457·2).
Digestive disorders.

B-Vex PD *Midlothian, USA.*
⊗Brompheniramine tannate (p. 618·1); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

B-Vit *Cazi, Braz.; Soylu, Turk.*
Vitamin B substances (p. 2102·3).

B-Vital *Saga, India.*
Vitamin B substances (p. 2102·3).
Vitamin B supplement.

By-Ache *Cypress, USA.†*
Paracetamol (p. 115·1); salicylamide (p. 129·2); phenyltoloxamine citrate (p. 638·1).
Pain.

Byakkokaninjinto *Tsumura, Jpn.*
Gypsum; anemarrhena rhizome; liquorice (p. 1853·2); ginseng (p. 2513·3); brown rice.
Traditional Kampo medicine.

Byany *Allen, Gr.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).

Byclomine *Major, USA.†*
Dicycloverine hydrochloride (p. 1834·2).
Functional bowel/irritable bowel syndrome.

Bycolen *Landson, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Bydaxin *Nagase, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Bydureon *Lilly, Denm.; Lilly, Ger.; Lilly, Irl.; AstraZeneca, Israel; AstraZeneca, Jpn; Lilly, Neth.; AstraZeneca, Norw.; BMS, Norw.; Lilly, Swed.; AstraZeneca, Switz.; AstraZeneca, UK; BMS, UK; Amylin, USA.*
Exenatide (p. 471·1).
Diabetes mellitus.

Byetta *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; AstraZeneca, Jpn; Lilly, Malaysia; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Amylin, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, Singapore; AstraZeneca, Spain; BMS, Spain; Lilly, Swed.; AstraZeneca, Switz.; Lilly, Thai.; Lilly, Turk.; AstraZeneca, UK; BMS, UK; Amylin, USA.*
Exenatide (p. 471·1).
Diabetes mellitus.

ByFluc *Helsinn Birex, Irl.*
Fluconazole (p. 578·2).
Fungal infections.

ByLans *Teva, Irl.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

By-Madol *Ergha, Irl.; Helsinn Birex, Irl.*
Tramadol hydrochloride (p. 139·2).
Pain.

Bymot *Ergha, Irl.†*
Lamotrigine (p. 527·2).
Epilepsy.

By-Mycin *Helsinn Birex, Irl.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria; amoebiasis.

Byodinoral *MDM, Ital.*
Vitamins; thioctic acid (p. 2629·1).
Neuropathies.

Byol *Sandoz, Cz.†*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Bypro *Fresenius Kabi, Thai.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Bysbalon *Renovati, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Bysclas *Renovati, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

BySec *Ergha, Irl.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

ByStat *Helsinn Birex, Irl.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Bystolic *Forest Laboratories, USA.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension.

Bystrumgel *Akrikhin, Rus.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

ByTrite *Helsinn Birex, Irl.*
Ramipril (p. 1483·3).
Hypertension; nephropathy; heart failure; myocardial infarction.

By-Vertin *Ergha, Irl.*
Betahistine hydrochloride (p. 2455·3).
Vertigo; tinnitus; Ménière's disease.

ByZestra *Ergha, Irl.*
Lisinopril (p. 1420·3).
Heart failure; myocardial infarction; hypertension; diabetic nephropathy.

B-Z Vit *Utopian, Thai.*
Vitamins; zinc (p. 2126·1).
Vitamin supplement.

B-Zyme *Brawn, India.*
⊗Simeticone (p. 1886·2); pancreatin (p. 2579·3); bile.

C-20
Note: this name may be used for preparations of different composition.
Osoth, Thai.
Chlorhexidine gluconate (p. 1743·3).
Mouth infections; oral hygiene.

C-86 *Valuge, Arg.*
Ketoconazole (p. 585·3).
Scalp disorders.

C500 *Rekah, Israel.†*
Vitamin C (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

C 20
Note: this name may be used for preparations of different composition.
Orochemie, Ger.
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

C 1000 *Douglas, Canad.; Nutri-West, Canad.; Pharmetics, Canad.; Tyler, Canad.*
Ascorbic acid (p. 2110·3).

C 3000 *Seroyal, Canad.†*
Ascorbic acid (p. 2110·3).

C Cobistal *Nycomed, Mex.*
Albendazole (p. 149·1); secnidazole (p. 947·3).
Protozoal infections; worm infections.

C Factors "1 000" Plus *Solgar, USA.*
Vitamin C (p. 2110·3); rose hips (p. 2607·1); citrus bioflavonoids complex (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2).
Capillary bleeding.

C Mon *PP Lab, Thai.*
Ascorbic acid (p. 2110·3).
Scurvy.

C Monovit *Esseti, Ital.†*
Sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

C Mox
Note: this name may be used for preparations of different composition.
Meridian, India.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

C Pal *Eagle, Austral.†*
Vitamins; minerals; lysine (p. 2079·3).

C Tri *Zuventus, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

C Vit
Note: this name may be used for preparations of different composition.
Corona, India.
Oral powder: Preparation for enteral nutrition.
Corona, India.
Syrup: Minerals.

CA *Fourrts, India.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1).

Caat *Piramal, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Cabagin *Kowa, Jpn.†*
Methiosulfonium chloride (p. 2558·1); sodium bicarbonate (p. 1781·1); swertia; biodiastase 2000 (p. 2442·1); lipase AP12.
Antacid; flatulence; carminative.

Cabagin S New *Kowa, Jpn.*
Methiosulfonium chloride (p. 2558·1); magnesium hydroxide (p. 1857·2); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); scopolia (p. 2611·3).
Antacid; flatulence.

Cabagin-U *Kowa, Jpn.*
Methiosulfonium chloride (p. 2558·1).
Gastritis; peptic ulcer; liver disease.

Cabal *Dallas, Arg.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cabal-D *Dallas, Arg.*
⊗Pseudoephedrine sulfate (p. 1676·1); cetirizine hydrochloride (p. 619·2).
Allergic rhinitis.

Cabana *LBS, Thai.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2).

Cabaser *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Norw.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK.*
Cabergoline (p. 899·3).
Parkinsonism; lactation inhibition; hyperprolactinaemia.

Cabaseril *Pfizer, Austria; Pfizer, Ger.*
Cabergoline (p. 899·3).
Parkinsonism.

Cabe 2 *Kowa, Jpn.†*
Methiosulfonium chloride (p. 2558·1); sodium bicarbonate (p. 1781·1); magnesium carbonate (p. 1856·2); aluminium hydroxide (p. 1817·2); aluminium magnesium silicate (p. 2168·2); ursodeoxycholic acid (p. 2638·1).
Antacid; flatulence; peptic ulcer.

Cabe 2 New *Kowa, Jpn.*
Aluminium hydroxide (p. 1817·2); hydrotalcite (p. 1845·2); magnesium hydroxide (p. 1857·2); fennel (p. 2503·2); turmeric (p. 2218·1); clove (p. 2481·2).
Antacid; flatulence; peptic ulcer.

Cabera *Teva, Cz.†*
Cabergoline (p. 899·3).
Lactation inhibition; hyperprolactinaemia; adenoma.

Caberex *Arrow, Irl.*
Cabergoline (p. 899·3).
Parkinsonism.

Cabergin *Arrow, Denm.*
Cabergoline (p. 899·3).
Hyperprolactinaemia; lactation inhibition; pituitary adenoma.

Cabergo-TEVA *Teva, Ger.†*
Cabergoline (p. 899·3).
Parkinsonism.

Caberlin *Sun, India.*
Cabergoline (p. 899·3).
Hyperprolactinaemia.

Caberpar *Rontag, Arg.*
Cabergoline (p. 899·3).
Parkinsonism.

Cabertrix *Raffo, Arg.; Tecnofarma, Chile.*
Cabergoline (p. 899·3).
Hyperprolactinaemia; lactation inhibition; prolactin-secreting pituitary adenomas.

Cabgolin *Sun, India.*
Cabergoline (p. 899·3).
Lactation inhibition; hyperprolactinaemia; parkinsonism.

Cabisyl *Rusan, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Cabosoft *Torrent, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Cabotrim *Trima, Israel.*
Cabergoline (p. 899·3).
Hyperprolactinaemia.

Cabral *Solvay, Gr.; Frik, Turk.*
Fenyramidol hydrochloride (p. 64·2).
Skeletal muscle spasm.

Ca-C *Novartis Consumer, Hong Kong; Novartis Consumer, Malaysia; Novartis OTC, Singapore; Sandoz, Switz.; Novartis, Thai.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2).
Calcium deficiency; vitamin C deficiency; adjunct in colds and influenza; calcium supplement; vitamin C supplement.

Novartis Consumer, Port.†
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); calcium gluconate (p. 1783·3).

Cacare *Nang Kuang, Thai.*
Calcitriol (p. 2113·1).
Hypocalcaemia in renal dialysis; renal osteodystrophy.

Cacef *Cachet, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Caceff *Lupin, India.*
Cefalexin (p. 234·1); carbocisteine (p. 1658·1).
Respiratory-tract infections; otitis media.

Cachexan *Polfarmex, Pol.†*
Megestrol acetate (p. 2289·2).
AIDS-associated cachexia; cancer-associated cachexia.

Cachexon *Telluride, USA.*
Glutathione (p. 1555·2).
AIDS-associated cachexia.

Cacio D *Akums, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cacit
Note: this name may be used for preparations of different composition.
Warner Chilcott, Belg.; Warner Chilcott, Fr.; Procter & Gamble, Irl.†; Procter & Gamble, Ital.; Warner Chilcott, Neth.; Procter & Gamble, UK.
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis; dietary supplement.
Procter & Gamble, Port.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cacit D3 *Procter & Gamble, Irl.†; Procter & Gamble, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cacit Vitamina D3 *Procter & Gamble, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cacit Vitamine D3 *Warner Chilcott, Belg.; Warner Chilcott, Fr.; Warner Chilcott, Neth.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cacitate Plus *Finecure, India.*
Syrup: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.
Finecure, India.
Tablets: Calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Cactus compositum *Heel, Austria.*
Cactus (p. 2473·2); spigelia (p. 2621·3); kalium carbonicum (p. 2595·2); glonoinum (p. 1391·2); crataegus (p. 2488·1).
Homoeopathic preparation.

CaD *Will-Pharma, Neth.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cad *Finecure, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cad-11 *Laclin, India.*
Lycopene (p. 2546·2); sodium selenium (p. 2087·1); zinc sulfate (p. 2126·2); vitamins.

Cad Alpha *Finecure, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Cadbe *Cachet, India.*
Vitamins; minerals; trace elements; with or without lysine (p. 2079·3).

Cadcef-S *Daksh, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cade L *Pharmavita, Chile.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Cadec *Admac, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Cadencial Plus *Lafedar, Arg.*
Cinnarizine (p. 622·1); gamma-aminobutyric acid (p. 2509·2); vitamin B_6 (p. 2105·3).
Cerebrovascular disorders.

Cadeno-ZF *Blubell, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Cadens *Zambon, Fr.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia of malignancy; osteoporosis.

Caderyn *General Sanyang, China.*
Sultamicillin (p. 369·1).
Bacterial infections.

Cadesol *Scoshia, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Cadevit *Lafi, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

Cadex *Dexcel, Israel.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Cadexcin-N *TNP, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Bacterial eye and ear infections.

Cadgil *Admac, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Cadgrow-M *Admac, India.*
Vitamins; minerals.

Cadicide *Casil, India.*
Alkaline glutaral (p. 1753·2).

Cadicin *Admac, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Cadicioc *CaDiGroup, Ital.*
Glucomannan (p. 2515·2).
Constipation.

Cadicoff *Cadila, India.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cough.

Cadicoff D *Cadila, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Cadicoff Exp *Cadila, India.*
⊗Guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Cadicon *Pharmasant, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Cadifen *CaDiGroup, Ital.*
Fennel (p. 2503·2); aniseed (p. 2444·2); chamomile (p. 2474·1); liquorice (p. 1853·2); caraway (p. 2470·2); coriander (p. 2486·3).
Digestive disorders; bloating.

Cadifix *Admac, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cadiflam *Admac, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Cadiflam-NP *Admac, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Cadiflur *Cadila, India.*
Flurbiprofen sodium (p. 65·3).
Prevention of intraoperative miosis; postoperative eye inflammation.

Cadigran *Cadila, India.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Cadimasol *Meda, Ital.*
Vitamin D (p. 2112·3); minerals.

Cadimint *CaDiGroup, Ital.*
Peppermint (p. 1877·1); fennel (p. 2503·2); aniseed (p. 2444·2); chamomile (p. 2474·1); liquorice (p. 1853·2); caraway (p. 2470·2); coriander (p. 2486·3).
Gastrointestinal bloating.

Cadine *Casil, India.*
Povidone-iodine (p. 1767·1).

Cadinyl *Medifive, Thai.*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); zinc oxide (p. 1729·1).
Skin irritation.

Cadiphylate *Cadila, India.*
Syrup: ⊗Acefylline piperazine (p. 1200·3); ephedrine hydrochloride (p. 1663·2); phenobarbital (p. 535·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Cadila, India.
Tablets: Acefylline piperazine (p. 1200·3).
Obstructive airways disease.

Cadipip *Admac, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Cadiplat *Oncomed, India.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cadiprim *Cadila, India.*
Polymyxin B sulfate (p. 342·3); trimethoprim (p. 381·2).

Cadiquin *Zydus, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; amoebiasis; rheumatoid arthritis.

Cadisan *Cadillac, Canad.*
Alkyldimethylethylbenzyl ammonium chloride (p. 1736·2); benzalkonium chloride (p. 1737·1).
Disinfection.

Cadisper C *Cadila, India.*
Methyl hesperidin; rutoside (p. 2505·3); vitamin C (p. 2110·3); carbazochrome (p. 1137·1); menadione sodium bisulfite (p. 2122·2); calcium hydrogen phosphate (p. 1783·3).
Haemorrhage.

Cadistin *Zydus, India.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Cadistin Exp *Zydus, India.*
Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); guaifenesin (p. 1666·2); levomenthol (p. 2553·2); sodium citrate (p. 1781·2); terpin hydrate (p. 1678·2); tolu balsam (p. 1679·2).

Caditam *Cadila, India.*
⊗Tamoxifen citrate (p. 860·2).
Anovulatory infertility; breast cancer.

Caditar *Tradiphar, Fr.*
Cade oil (p. 1723·2).
Psoriasis; seborrhoeic dermatitis.

Cadither *Admac, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Caditone *Kopran, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Caditrex *Cadila, India.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Cadiwin *Cadila, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cadizone *Admac, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cadizone-S *Admac, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cadizone-XP *Admac, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cadmag *Anthiea, India.*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Cadmax *Admac, India.*
Diclofenac (p. 48·3).
Pain.

Cadmentin *Admac, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Cadmos *VHB, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Cadmoxin-CS *Admac, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Cadmoxin-LB *Admac, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cado *Simex, Indon.*
Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).
Osteoporosis; calcium supplement.

Cadof *Admac, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Cadol *Admac, India.*
Tramadol (p. 139·2).
Pain.

Cadolac *Cadila, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Cadol-P *Admac, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Cadotin *Standard Chem & Pharm, Thai.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; osteolysis; Paget's disease of bone; osteoporosis; neurodystrophic disorders.

Cadotril *Ordain, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Cadpime *Admac, India.*
Cefepime (p. 239·2).
Bacterial infections.

Cadpo-D *Admac, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Cadpo-N *Admac, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Cadpres *Cadila, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Cadramine *Atlantic, Thai.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2); menthol (p. 2553·2).
Skin irritation.

Cadramine-V *Atlantic, Hong Kong.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2); menthol (p. 2553·2).
Skin disorders.

Cadred *Admac, India.*
Vitamins A, C, and E; lycopene (p. 2546·2); selenium dioxide (p. 2087·1); zinc (p. 2126·1).

Cadria *Cadila, India.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Cadrol *Taj, India.*
⊗Bisoprolol (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Cadsine *Gland, India.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of supraventricular tachycardia; coronary vasodilator during radionuclide myocardial perfusion imaging.

Cadtre *New Research, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Caduet *Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Israel; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).
Hypertension; angina pectoris; hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Caduril *Mediphar, Venez.*
⊗Salicylic acid (p. 1719·1); urea (p. 1727·3).
Seborrhoeic dermatitis of the scalp.

Cadvion *Merck, India.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); vitamin E (p. 2119·1).
Cardiovascular risk reduction.

Cad-Vital *Admac, India.*
Vitamins; minerals; ginseng (p. 2513·3).

Cadyoil *Cady, Ital.*
Emollient.

Cadzid *Admac, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Caedax *MSD, Gr.; Schering-Plough, Port.*
Ceftibuten (p. 252·2).
Bacterial infections.

Caelyx *Schering-Plough, Arg.; Janssen-Cilag, Austral.; Schering-Plough, Austria; Janssen-Cilag, Belg.; Schering-Plough, Braz.; Janssen, Canad.; Schering-Plough, Chile; Ben Venue, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; MSD, Hong Kong; Janssen-Cilag, Hung.; Fulford, India; Schering-Plough, Indon.; Janssen-Cilag, Irl.; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Schering-Plough, Turk.; Janssen-Cilag, UK; Schering-Plough, Ukr.†; Schering-Plough, Venez.*
Liposomal doxorubicin hydrochloride (p. 783·1).
Breast cancer; ovarian cancer; multiple myeloma; AIDS-related Kaposi's sarcoma.

Caext *Dallas, Arg.*
Benzocaine (p. 1980·2); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Mouth and throat disorders.

Cafage *Allenge, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cafage-CL *Allenge, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Cafage-O *Allenge, India.*
Cefpodoxime.
Bacterial infections.

Cafage-S *Allenge, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cafanta *Plus, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cafatine *Major, USA.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Cafatine-PB *Major, USA.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); belladonna (p. 2453·3); pentobarbital sodium (p. 1095·1).
Migraine.

Cafazone-S *Scoshia, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cafcit *IFET (ΙΦΕΤ), Gr.; Bedford, USA.*
Caffeine citrate (p. 1203·3).
Apnoea of prematurity; acute alcohol intoxication; lumbar puncture headache.

Cafe-Kit *Aristo, India.*
1 Capsule, iron carbonyl (p. 2073·1); folic acid (p. 2063·1); colecalciferol (p. 2113·1); 1 tablet, calcium carbonate (p. 1824·3).
Dietary supplement in pregnancy.

Cafenol *Elmor, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Cafepar *Cipla, India.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).

Cafergot *Novartis, Arg.; Novartis, Austral.; Pharma Logistics, Belg.; Novartis, Canad.; Sandoz, Gr.; Amdipharm, Hong Kong; Novartis, Indon.; Novartis, Israel†; Amdipharm, Ital.; Novartis, Malaysia†; Novartis, Mex.; Amdipharm, Neth.; AFT, NZ; Pharmaco, S.Afr.; Amdipharm, Singapore; Novartis, Spain; Novartis, Switz.; Amdipharm, Thai.; Novartis, Turk.; Alliance, UK†; Novartis, USA.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and related vascular headache.

Cafergot N *Novartis, Ger.†*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Headache including migraine.

Cafergot-PB
Note: this name may be used for preparations of different composition.
Novartis, Switz.†
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); total belladonna alkaloids (p. 2453·3); butalbital (p. 1043·3).
Migraine.

Caffedrine *Thompson, USA.*
Caffeine (p. 1203·3).
Fatigue.

Caffetin *Sotex, Rus.; Alkaloid, Ukr.*
Propyphenazone (p. 127·3); paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Caffetin Cold *Alkaloid, Rus.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); ascorbic acid (p. 2110·3).

Caffetin Lady *Alkaloid, Ukr.*
Ibuprofen (p. 68·2).
Dysmenorrhoea.

Caffox *TO-Chemicals, Singapore.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Cafgesic Forte *Cypress, USA.†*
Paracetamol (p. 115·1); magnesium salicylate (p. 85·2); phenyltoloxamine citrate (p. 638·1); caffeine (p. 1203·3).
Pain; fatigue.

Cafiaspirina *Bayer Consumer, Arg.; Bayer, Braz.; Bayer, Chile; Bayer, Port.†; Bayer, Spain.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever; cold and influenza symptoms.

Cafilisador *Farmasa, Braz.*
Dipyrone (p. 53·3); caffeine (p. 1203·3).

Cafinitrina *Kern, Spain.*
Caffeine citrate (p. 1203·3); glyceryl trinitrate (p. 1391·2).
Angina pectoris; biliary-tract spasm; vasospasm.

Caflovan *Biofarma, Mex.*
Soya isoflavones (p. 2620·3); calcium carbonate (p. 1824·3); ergocalciferol (p. 2113·3).
Menopausal disorders; osteoporosis.

Cafnea *Phebra, Austral.*
Caffeine citrate (p. 1203·3).
Apnoea of prematurity.

Cafona *Zota, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cafona-E *Zota, India.*
⊗Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); ephedrine (p. 1663·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cafonate *Miracalus, India; Naprod, Thai.*
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; adjunct to fluorouracil therapy.

Cafox *Cafar, Venez.*
Oxolamine citrate (p. 1671·2).
Cough.

Caftar *Quimica y Farmacia, Mex.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and related vascular headache.

Cafzone *Ind-Swift, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Caginal *Pond's, Thai.*
Clotrimazole (p. 576·2).
Trichomoniasis; vaginal candidiasis.

Cagno *Lepetit, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Caien *Aulo Gelio, Arg.†*
Almond oil (p. 2437·1); sodium laurilsulfate (p. 2210·3); stearyl alcohol (p. 2214·2); cetyl alcohol (p. 2178·2); carbomer (p. 2173·3).
Insecticide.

Cain *Neon, India.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; nausea and vomiting; hiccup.

Caina G *Gray, Arg.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Čaj z Hlohu *Megafyt-R, Cz.*
Crataegus (p. 2488·1).
Cardiac disorders; hypertension.

Čaj z Květu Bezu Černého *Megafyt-R, Cz.*
Sambucus (p. 2609·3).
Cold symptoms; mild diuretic.

Čaj z Listu Senny *Megafyt-R, Cz.*
Senna (p. 1885·1).
Constipation.

Čaj ze Šalvěje *Megafyt-R, Cz.*
Sage (p. 2608·3).
Gastrointestinal disorders; gingivitis; stomatitis; upper respiratory-tract inflammation.

Čajová Směs při Nachlazení *Megafyt-R, Cz.*
Fennel (p. 2503·2); sambucus (p. 2609·3); tilia (p. 2631·3); plantaginis (p. 2604·2); liquorice (p. 1853·2).
Catarrh; cough; fever.

Cal-95 *Lapi, Indon.*
Coral calcium (p. 1783·1); soya isoflavone (p. 2620·3); colecalciferol (p. 2113·1); vitamin K_1 (p. 2122·2); magnesium (p. 1786·3); zinc (p. 2126·1); boron (p. 2052·3).
Osteoporosis; calcium supplement.

Cal-500 *Pro Doc, Canad.*
Calcium carbonate (p. 1824·3).

Cal Alkyline *Eagle, Austral.†*
Calcium carbonate (p. 1824·3); slippery elm (p. 2617·1); glycine (p. 2071·2); equisetum (p. 2500·1); dibasic sodium phosphate (p. 1791·2); spirulina (p. 2622·1); magnesium carbonate (p. 1856·2); ginger (p. 1844·1).
Gastric hyperacidity.

Cal C *Bioglan, Austral.*
Calcium ascorbate (p. 2111·1).
Vitamin C supplement.

Cal Cell *Lapreven, Venez.*
Calcium carbonate (p. 1824·3); ergocalciferol (p. 2113·3).
Osteoporosis.

Cal Ci San *Arvincare, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Cal D *Pro Doc, Canad.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).

Cal D Vita *Bayer, Spain.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cal Mag with D *WN, Canad.*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).

Cal Mag Phos Plus D *Swiss Herbal, Canad.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).

Cal Mag plus Vitamin D *Quest, Canad.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3).

Cal Mag with Vitamin D *Jamieson, Hong Kong.*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Dietary supplement.

Cal Mag with Zinc *Jamieson, Hong Kong.*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement.

Cal Mo Dol *Herbes Universelles, Canad.†*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1); turpentine oil (p. 2636·3); peppermint oil (p. 1877·1).

Cal Plus *Elder, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cal Today *Bionova, India.*
Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Calaband *SSL, Austral.†; Medlock Medical, UK.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Medicated bandage; eczema; leg ulcers.

Calacare *Intas, India.*
Calamine (p. 1697·2); camphor (p. 2466·2); diphenhydramine hydrochloride (p. 626·2).

Calaclear *Humco, USA.*
Pramocaine hydrochloride (p. 1993·3); zinc acetate (p. 2126·1).

Calacort *Galenium, Indon.†*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Caladine *Galenium, Indon.†*
Cream; topical powder: Calamine (p. 1697·2); zinc oxide (p. 1729·1); camphor (p. 2466·2); menthol (p. 2553·2).
Skin irritation.

Galenium, Indon.†
Foam: Skin cleanser.

Galenium, Indon.†
Lotion: Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); zinc oxide (p. 1729·1).
Miliaria; urticaria; sunburn; nappy rash.

Caladiph *Chinta, Thai.*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Pruritus.

Caladryl
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Braz.; Pfizer, India; Pfizer, Indon.†; Chefaro, Port.; Johnson & Johnson, S.Afr.; Johnson & Johnson, Thai.†; Pfizer, Turk.†
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Skin irritation; pruritus; sunburn; heat rash; insect bites; allergic skin reactions.

Elea, Arg.; Omega, Belg.; Johnson & Johnson, Philipp.
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2).
Skin irritation; insect bites; allergic skin reactions.

Johnson & Johnson Consumer, Mex.
Calamine (p. 1697·2); camphor (p. 2466·2).
Skin irritation.

Johnson & Johnson, Canad.†; Pfizer, USA.
Pramocaine hydrochloride (p. 1993·3); calamine (p. 1697·2).
Pruritus; skin irritation.

Omega, Spain.†
Topical solution: Diphenhydramine (p. 626·1); zinc oxide (p. 1729·1).
Pruritus; skin irritation.

Omega, Spain.†
Cream: Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1).
Pruritus; skin irritation.

Caladryl Clear *Johnson & Johnson, Chile.*
Pramocaine hydrochloride (p. 1993·3); camphor (p. 2466·2); zinc acetate (p. 2126·1).
Skin irritation; urticaria.

Johnson & Johnson Consumer, Mex.; Pfizer, USA.
Pramocaine hydrochloride (p. 1993·3); zinc acetate (p. 2126·1).
Skin irritation.

Caladryl D *Elea, Arg.†*
Diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Caladryl Incoloro *Elea, Arg.*
Diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1) or zinc oxide (p. 1729·1).
Skin irritation.

Calaffler *Loeffler, Mex.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Calafol *Alaven, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); calcium (p. 1783·1); colecalciferol (p. 2113·1).

Calagel *Tec, USA.*
Benzethonium chloride (p. 1738·1); diphenhydramine hydrochloride (p. 626·2); zinc acetate (p. 2126·1).
Pruritus.

Calagesic *Humco, USA.*
Calamine (p. 1697·2); pramocaine hydrochloride (p. 1993·3).

Calahyst Frx *United Drug, Thai.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Cal-Aid *Indoco, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2).

Calak
Note: this name may be used for preparations of different composition.
Sarabhai Piramal, India.
Calamine (p. 1697·2).
Pruritic skin disorders.

Shalaks, India.
Calamine (p. 1697·2); zinc oxide (p. 1729·1).

Calakin *Utopian, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2).
Pruritus.

Calalgin *Geritrex, USA.*
Calcium alginate (p. 1136·3).
Wounds.

Calamec *Mecosin, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Skin irritation; urticaria.

Calamed *Cimed, Braz.*
Calamine (p. 1697·2); diphenhydramine (p. 626·1); camphor (p. 2466·2).
Sunburn.

Calamina *Bunker, Braz.†*
Diphenhydramine (p. 626·1) or diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Pruritus; skin irritation.

Calamine Antihistamine *Rougier, Canad.; RW, Canad.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Calamine Lotion
Note: this name may be used for preparations of different composition.
Faulding, Austral.; Gold Cross, Austral.; Floris, Israel; Vitamed, Israel; Osoth, Thai.
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Insect bites; skin irritation; sunburn.

Suphong, Thai.
Calamine (p. 1697·2); camphor (p. 2466·2); menthol (p. 2553·2).
Pruritus.

Calamine and Menthol *Beacons, Singapore.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); menthol (p. 2553·2); phenol (p. 1763·3).

Calamine-D *Umeda, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Allergic skin disorders; pruritus; urticaria; skin irritation.

Calaminol *Vita, Venez.*
Calamine (p. 1697·2); menthol (p. 2553·2); camphor (p. 2466·2).
Skin irritation.

Calamol *ICM, Singapore.*
Calamine (p. 1697·2); with or without menthol (p. 2553·2).
Pruritus.

Calamycin *Pfeiffer, USA.*
Zinc oxide (p. 1729·1); calamine (p. 1697·2); benzocaine (p. 1980·2); chloroxylenol (p. 1748·2); mepyramine maleate (p. 635·1).
Pruritus.

Calamyn *Neo Quimica, Braz.*
Calamine (p. 1697·2); diphenhydramine (p. 626·1); camphor (p. 2466·2).
Pruritus; skin irritation.

Calan
Note: this name may be used for preparations of different composition.
Searle, USA.
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Calanda *Atlantis, Mex.*
Vitamins; minerals.

Calanol *Nakornpatana, Thai.*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2).
Skin irritation.

Calapol *GSK, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Calapro *Medicine Products, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Skin irritation.

Calaptin *Piramal, India.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Calaquin *Gap, Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Calarex *Apex, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Skin irritation; pruritus.

Calarin *TNP, Thai.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Pruritus.

Calasthetic *Adcock Ingram, S.Afr.*
Calamine (p. 1697·2); benzocaine (p. 1980·2); pheniramine maleate (p. 637·2); phenol (p. 1763·3).
Skin irritation; pruritus; sunburn.

Calasyl Original *SM, Venez.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Barrier preparation; skin irritation.

Calasyl Transparente *SM, Venez.*
Zinc acetate (p. 2126·1); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Barrier preparation; skin irritation.

Calato *Ativus, Braz.*
Calcium amino acid chelate (p. 2048·3).
Calcium supplement.

Calax *Odan, Canad.*
Docusate calcium (p. 1836·2).
Constipation.

Calbin *Claris, India.*
Calcium acetate (p. 1783·1).

Calbion
Note: this name may be used for preparations of different composition.
Merck, Spain.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Calbloc
Note: this name may be used for preparations of different composition.
Ashford, Philipp.; Be-Tabs, S.Afr.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Unichem, India.
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Calblock
Note: this name may be used for preparations of different composition.
Daiichi Sankyo, Jpn.
Azelnidipine (p. 1313·2).
Hypertension.

Calbolex *Marching, Hong Kong.†*
Cyproheptadine (p. 624·1); vitamins.

Calbone
Note: this name may be used for preparations of different composition.
Blue Sky, Philipp.; Pharmahof, Thai.†
Calcium carbonate (p. 1824·3).
Calcium supplement.

Lincoln, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calbory *JB Chemicals, India.*
Calcitriol (p. 2113·1); minerals.

Calbrun *Caldeira & Metelo, Port.†*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Cal-C
Note: this name may be used for preparations of different composition.
Key, USA.
Calcium citrate (p. 1783·2).
Calcium supplement.

Laborate, India.
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc sulfate (p. 2126·2).

Calcal *Pfizer, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcalcin *Sato, Thai.†*
Calcium carbonate (p. 1824·3); calcium citrate (p. 1783·2); calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calcan *Atral, Port.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Calcanate *ST, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcanate with D *ST, Thai.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement; calcium deficiency.

Calcap *Osoth, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Cal-Car *SF, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcar *Unison, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Calcarb with Vitamin D *Ivax, USA.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).

Calcarbonate *Millimed, Thai.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Calcarea Compose *Boiron, Fr.*
Calcarea carbonica (p. 1824·3); calcarea fluorica (p. 2053·1); calcarea phosphorica (p. 1784·2).
Homoeopathic preparation.

Calcarea fluor Compuesta *Ximena Polanco, Chile.*
Calcarea fluor. (p. 2053·1); aesculus hipp. (p. 2431·2); carduus mar. (p. 1561·1); hamamelis (p. 2523·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Calcebion *Merck, Venez.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3).
Calcium and vitamin C supplement.

Calcebone *Icon, Philipp.*
Calcium ascorbate (p. 2111·1); calcium hydrogen phosphate (p. 1783·3).
Calcium supplement.

Calcee-D *Medico, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcefol *McNeil & Argus, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2).

Calcefor
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcefor D *Laboratorios Chile, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcemin *Bayer Consumer, Ukr.*
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2); boron (p. 2052·3).
Dietary supplement; osteoporosis.

Sagmel, Rus.
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); manganese sulfate (p. 2081·2); borax (p. 2459·2).
Dietary supplement; osteoporosis.

Calcemin Advance *Bayer Consumer, Ukr.*
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); manganese sulfate (p. 2081·2); borax (p. 2459·2).
Dietary supplement; osteoporosis.

Sagmel, Rus.
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); manganese sulfate (p. 2081·2); boron sulfate.

Calcemin Silver *Bayer Consumer, Ukr.*
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2); boron (p. 2052·3).
Dietary supplement; osteoporosis.

Calceos *koGen, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcet
Note: this name may be used for preparations of different composition.
Mission Pharmacal, USA.
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium supplement.

Teva, Ger.
Calcium acetate (p. 1783·1).
Hyperphosphataemia in chronic renal failure.

Calcet Plus *Mission Pharmacal, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Osteoporosis; pre- and postoperative patients; low-calcium leg cramping; patients with milk allergies; nursing mothers.

Calcetat *Giovanardi, Ital.*
Calcium acetate (p. 1783·1).
Calcium supplement.

Calcetate *Charoon Bhesaj, Thai.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia in renal failure; calcium deficiency; calcium supplement.

Calcevita *Bayer, Swed.*
Ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1); pyridoxine hydrochloride (p. 2105·3); calcium carbonate (p. 1824·3).
Calcium and vitamin deficiency.

Calchan *Ranbaxy, UK.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Calcheck *One Pharma, Philipp.*
Amlodipine besilate (p. 1304·1).
Formerly contained nifedipine.
Hypertension; angina pectoris.

Calchek *Ipca, India.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ipca, Rus.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Calchek L *Ipca, India.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Calchew *Ranbaxy, Thai.†*
Calcium carbonate (p. 1824·3); calcium gluconate (p. 1783·3).
Hypocalcaemia; calcium supplement.

Calci *Hexal, Ger.†*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia of malignancy.

Calci-3 *FDC, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Calci-10 *Pharmathen, Gr.; Pharmathen, Thai.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcia
Note: this name may be used for preparations of different composition.
Assos, Turk.
Calcium (p. 1783·1); vitamins; iron (p. 2073·1).

Medexus, Canad.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Peter Black, UK.
Calcium carbonate (p. 1824·3); vitamins; iron (p. 2073·1).

Calci-Aid *Bayer, Philipp.*
Calcium carbonate (p. 1824·3).
Osteoporosis; calcium deficiency.

Calcial D *Alacan, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcianta *Armoxindo, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; ischaemic heart disease; heart failure.

CalciAPS D3 *APS, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calci-Best
Note: this name may be used for preparations of different composition.
Bestochem, India.
Colecalciferol (p. 2113·1).
Dietary supplement; hypocalcaemia.

Calcibest
Note: this name may be used for preparations of different composition.
Bestochem, India.
Calcitriol (p. 2113·1).
Hyperparathyroidism.

Calcibind *Mission Pharmacal, USA.†*
Sodium cellulose phosphate (p. 1574·2).
Idiopathic hypercalcaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Calcibloc *Westmont, Philipp.*
Nifedipine (p. 1447·2).
Angina pectoris; bradycardia; hypertension.

Calcibon
Note: this name may be used for preparations of different composition.
Biomet, Ger.
Hydroxyapatite (p. 2529·3).
Bone reconstruction.
Novapharma, Venez.
Calcium citrate (p. 1783·2).
Calcium supplement; osteoporosis.

Calcibon D *Novapharma, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteoporosis.

Calcibon D Magnesio *Novapharm, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3).
Dietary supplement.

Calcibon D Soya *Novapharm, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); soya isoflavones (p. 2620·3).
Dietary supplement.

Calcibon Natal *Novapharm, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); folic acid (p. 2063·1).
Dietary supplement for pregnant women.

Calcibone *Stalwart, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calci-BoneD3 *Will-Pharma, Neth.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcibor *Berksam, Turk.*
⊗Carvedilol (p. 1333·1).

Calcibronat *Teofarma, Ital.; Granions, Mon.*
Calcium bromolactobionate (p. 1044·1).
Nervous disorders; insomnia.

Calci-Bruis D3 *Takeda, Neth.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

CalciCaps *Nion, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

CalciCaps with iron *Nion, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3); phosphorus (p. 2589·2); iron (p. 2073·1).
Calcium deficiency; dietary supplement.

CalciCaps M-Z *Nion, USA.*
Calcium (p. 1783·1); vitamin A (p. 2098·3); vitamin D (p. 2112·3); minerals.

Calcicarb *Parma, Hung.*
Calcium carbonate (p. 1824·3).
Hyperphosphataemia in renal dialysis patients.

Calcicard
Note: this name may be used for preparations of different composition.
Ivax, UK.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.
Pharma Dynamics, S.Afr.
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; arrhythmias.

CalciCare-D3 *Orion, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcichell *Ativus, Braz.*
Calcium amino acid chelate (p. 2048·3).
Calcium supplement.

Calci-Chew *Takeda, Belg.; Nycomed, Neth.; R&D, USA.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis; dietary supplement.

Calcichew *Nycomed, China; Leiras, Fin.; Nycomed, Hung.; Shire, Irl.; Adcock Ingram, S.Afr.; Takeda, UK.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; phosphate-binder in renal dialysis; calcium supplement; osteomalacia; hyperphosphataemia.

Calcichew D *Nycomed, China.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis.

Calci-Chew D3 *Nycomed, Neth.; Abdi, Turk.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcichew D_3 *Nycomed, Cz.; Nycomed, Denm.; Leiras, Fin.; Nycomed, Hung.; Shire, Irl.; Nycomed, Israel; Nycomed, Swed.; Takeda, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency; osteomalacia; calcium and vitamin D supplement.

Calcicip *Cipla, India.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; hyperphosphataemia.

Calciclo *Sterop, Belg.*
Calcium chloride (p. 1783·1).
Hypocalcaemia; hyperkalaemia.

Calcicold3 *Fidia, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcicontrol *Vivax, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calci-D *Kocak, Turk.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Calcid *OPC, Philipp.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3).
Vitamin C and calcium deficiency.
Chemo-Drugs, India.
Calcium phosphate (p. 1784·2); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).

Calciday
Note: this name may be used for preparations of different composition.
Medisys, Philipp.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis.

Calcidef *Tecnofarma, Mex.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium supplement.

Calcideron *Mediapharm, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcidia *BayerSante, Fr.*
Calcium carbonate (p. 1824·3).
Hypocalcaemia and hyperphosphoraemia related to kidney disorders; renal osteodystrophy.

Calcidif *Ranbaxy, India.*
Calcium carbonate (p. 1824·3); colecalciferol.
Calcium and vitamin D supplement.

Calcidin *Otto, Indon.*
Syrup: Calcium hydrogen phosphate (p. 1783·3); calcium gluconate (p. 1783·3); vitamins.
Calcium supplement.
Otto, Indon.
Tablets: Calcium hydrogen phosphate (p. 1783·3); calcium lactate (p. 1784·1); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).
Calcium supplement.

Calcidina *Alapis, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calcidine *Biofarma, Turk.*
Calcium magnesium fytate (p. 1553·3); calcium gluconate (p. 1783·3); ergocalciferol (p. 2113·3).
Calcium and vitamin D supplement.

CalciDoc *Biokirch, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Calcidol *Kimia, Indon.*
Vitamins; calcium (p. 1783·1); phosphorus (p. 2589·2); docosahexaenoic acid (p. 1460·1); lysine (p. 2079·3).
Nutritional supplement.

Calcidon *Bayer, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calcidose *Vernin, Fr.*
Calcium carbonate (p. 1824·3).
Osteoporosis; calcium deficiency.

Calcidose Vitamine D *Vernin, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Calcidrine *Abbott, USA.*
Codeine (p. 40·2); calcium iodide (p. 1658·1).
Coughs.

Calcidrops *Medilat, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Calciem *Emcure, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcif *Siomond, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Calcifar *Farcoral, Mex.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Calciferol
Note: this name may be used for preparations of different composition.
Biotika, Cz.; British Dispensary, Thai.; Schwarz, USA.
Ergocalciferol (p. 2113·3).
Vitamin D deficiency; hypocalcaemia; refractory rickets; hypoparathyroidism; familial hypophosphataemia; gastrointestinal, liver, or biliary disease associated with malabsorption of vitamin D.
Pharmascience, Canad.
Colecalciferol (p. 2113·1).

Calciferol Composto *Delta, Braz.*
Ergocalciferol (p. 2113·3); cyanocobalamin (p. 2107·2); calcium gluconate (p. 1783·3); calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2).

Calcifer-Z *Newtramax, India.*
Vitamins; minerals.

Calcifix B12 *Cifarma, Braz.*
Calcium phosphate (p. 1784·2); ergocalciferol (p. 2113·3); sodium fluoride (p. 2089·2); cyanocobalamin (p. 2107·2).
Vitamin and mineral supplement.

Calcifix Irradiado *Cifarma, Braz.*
Calcium phosphate (p. 1784·2); ergocalciferol (p. 2113·3); sodium fluoride (p. 2089·2).
Vitamin D and mineral supplement.

Calciflavone *Meyer, India.*
Isoflavones (p. 2620·3); calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).

Calcifluol *Cimed, Braz.*
Calcium chloride (p. 1783·1); ergocalciferol (p. 2113·3); sodium fluoride (p. 2089·2); sodium phosphate (p. 1791·2); lysine (p. 2079·3).
Nutritional supplement.

Calcifluor *Crinex, Fr.†*
Calcium fluoride (p. 2053·1).
Dental caries prophylaxis.

Calcifolin *Kleva, Gr.; Ibirm, Ital.*
Calcium folinate (p. 2066·3).
Folic acid deficiency; antidote to folic acid antagonists; megaloblastic anaemia.

Calciform *Iasis, Gr.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; hyperphosphataemia.

Calciform D3 *Iasis, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D_3 deficiency; osteoporosis.

Calcifort
Note: this name may be used for preparations of different composition.
Novaduo, India.
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2).

Calciforte *Grimberg, Fr.*
Oral liquid: Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); calcium gluceptate (p. 1783·2); calcium chloride (p. 1783·1); yeast (*Saccharomyces cerevisiae*) (p. 2125·2).
Calcium deficiency; osteoporosis.
Grimberg, Canad.†; Lilly, Gr.
Powder for oral solution: Calcium gluceptate (p. 1783·2); calcium lactate (p. 1784·1); calcium gluconate (p. 1783·3); calcium chloride (p. 1783·1); calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency.
Grimberg, Canad.†
Oral liquid: Calcium gluceptate (p. 1783·2); calcium lactate (p. 1784·1); calcium gluconate (p. 1783·3); calcium chloride (p. 1783·1).
Calcium deficiency.
Grimberg, Fr.†
Powder for oral solution: Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); calcium gluceptate (p. 1783·2); calcium chloride (p. 1783·1); calcium carbonate (p. 1824·3); yeast (*Saccharomyces cerevisiae*) (p. 2125·2).
Calcium deficiency; osteoporosis.

Calciforte Vitamin D_3 *Grimberg, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); yeast (*Saccharomyces cerevisiae*) (p. 2125·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcifox *Diba, Mex.†*
Calcium phosphate (p. 1784·2).
Calcium and phosphorus deficiency.

Calcigard *Torrent, India; Torrent, Malaysia; Steinbach, Philipp.†; Torrent, Rus.; Torrent, Singapore; Torrent, Thai.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; ischaemic heart disease; peripheral vascular disorders; Raynaud's disease; heart failure.

Calcigen *Cadila, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Calcigen D *Madaus, Ger.; Rottapharm, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcigenol
Note: this name may be used for preparations of different composition.
Korangi, Port.
Calcium phosphate (p. 1784·2); ergocalciferol (p. 2113·3).
Calcium and vitamin D supplement; osteoporosis; rickets; tetany.
Sanofi-Aventis, Braz.
Calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2).

Calcigenol B12
Note: this name may be used for preparations of different composition.
Millet-Franklin, Arg.
Calcium phosphate (p. 1784·2); calciferol (p. 2113·3); vitamin B_{12} (p. 2107·2).
Vitamin and calcium supplement; osteoporosis.

Calcigenol Doble *Sanofi-Aventis, Mex.*
Calcium phosphate (p. 1784·2).
Calcium supplement.

Calcigo *Bionet, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).

Calcigran *Labomed, Chile.*
Calcium carbonate (p. 1824·3); calcium hydrogen phosphate (p. 1783·3); ascorbic acid (p. 2110·3); ergocalciferol (p. 2113·3).
Calcium and vitamin D deficiency; osteoporosis.
Nycomed, Norw.
Chewable tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D supplement.

Calcigran D *Labomed, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; rickets; osteomalacia.

Calci-Gry *Teva, Ger.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcihexal
Note: this name may be used for preparations of different composition.
Hexal, Pol.†
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; hypercalcaemia; Paget's disease of bone; bone metastases.

Calciject *Omega, Canad.*
Calcium chloride (p. 1783·1).
Calcium supplement.

Calcijex *Abbott, Austral.; Abbott, Austria; Abbott, Braz.; Abbott, Canad.; Abbott, China; Abbott, Cz.†; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.†; Abbott, Israel†; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.†;*

Abbott, Pol.†; Abbott, Port.; Abbott, Singapore; Abbott, Spain†; Abbott, Turk.; Abbott, UK†; Abbott, USA.
Calcitriol (p. 2113·1).
Hypocalcaemia in dialysis patients; hyperparathyroidism; renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia.

Hanburys, India.
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Calcikind *Mankind, India.*
Capsules: Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Mankind, India.
Oral sachets: Colecalciferol (p. 2113·1).

Calcil *Rowex, Irl.†*
Calcipotriol (p. 1697·2).
Psoriasis of the scalp.

Calcila *Pharma Synth, India.*
Oral suspension: Calcium phosphate (p. 1784·2); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Pharma Synth, India.
Tablets: Calcium carbonate (p. 1824·3); calcium hydrogen phosphate (p. 1783·3); lysine hydrochloride (p. 2079·3); magnesium (p. 1786·3); zinc (p. 2126·1); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).

Calcilac BT *Mibe, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcilac KT *Mibe, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcilar *Lark, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calciless *Sam-On, Israel.*
Dibasic sodium phosphate (p. 1791·2); monobasic potassium phosphate (p. 1790·3).
Calcium oxalate renal calculi.

Calcilo XD *Ross, USA.*
Low calcium, vitamin D-free infant feed.
Hypercalcaemia; osteopetrosis.

Calciluvin *Sanofi-Aventis, India.*
Calcium lactate (p. 1784·1); luvistin.
Hypersensitivity reactions.

Calcimag *Chance, Pol.†*
Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3); calcium gluconate (p. 1783·3); magnesium aspartate (p. 1787·1); potassium citrate (p. 1780·3).
Dietary supplement.

Calcimagon *Takeda, Ger.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; hyperphosphataemia.

Calcimagon-D *Andromaco, Spain.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcimagon-D3 *Takeda, Ger.; Takeda, Switz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcimar *Sanofi-Aventis, Canad.; Rhone-Poulenc Rorer, USA.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; osteoporosis.

Calcimark *Ultramark, India.*
Calcium phosphate (p. 1784·2); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).

Calcimax
Note: this name may be used for preparations of different composition.
Gador, Arg.; Pasteur, Chile.
Calcium citrate (p. 1783·2).
Calcium supplement; hypocalcaemia; osteoporosis.

Meyer, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium; zinc.
Dietary supplement.

Wallace Mfg Chem., UK.
Calcium levulinate (p. 1784·2); calcium chloride (p. 1783·1); vitamins.

Calcimax 500 *Meyer, India.*
Colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3); lysine; boron; magnesium; selenium; zinc.

Calcimax D3 *Basel, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Gador, Arg.; Pasteur, Chile.
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; hypocalcaemia; osteomalacia; osteoporosis.

Calcimax Forte *Meyer, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement.

Calcimax Magnesio *Gador, Arg.*
Colecalciferol (p. 2113·1); pyridoxine hydrochloride (p. 2105·3); minerals.
Dietary supplement; osteoporosis.

Calcimax-OP *Meyer, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Calcimed *Hermes, Ger.; Genesis, Turk.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Medhaus, Philipp.
Calcium ascorbate (p. 2111·1).
Vitamin C deficiency.

Calcimed D3 *Hermes, Ger.; Genesis, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; osteomalacia.

Calcimega *Solas, Indon.*
Calcium hydrogen phosphate (p. 1783·3); docosahexaenoic acid (p. 1460·1); omega-3 fatty acids (p. 1460·1); vitamins.
Calcium supplement.

Calcimex *Frisian Flag, Indon.*
Preparation for enteral nutrition.
Calcium supplement; osteoporosis.

Calcimex Vitagold *Frisian Flag, Indon.*
Nutritional supplement for healthy bones and joints in the elderly.

Calcimex Vitalize *Frisian Flag, Indon.*
Nutritional supplement for healthy bones and joints in adults.

Calcimilk *Cosme, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); phosphorus (p. 2589·2).

Calcimin *Mintlab, Chile.†*
Calcium gluconate (p. 1783·3).
Calcium supplement.

Calcimin-A *Ind Biosciences, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calci-Mix *R&D, USA.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; dietary supplement.

Calcimonio *SM, Venez.*
Oxolamine phosphate (p. 1671·2).
Respiratory-tract disorders.

Calcimore *Taro, Israel.*
Calcium carbonate (p. 1824·3).
Antacid; calcium deficiency.

Calcimusc *Gedeon Richter, Hung.*
Calcium gluconate (p. 1783·3).
Hypocalcaemia; tetany; hyperkalaemia; hypersensitivity reactions; inflammation; oxalic acid, citrate, fluoride, and sodium edetate poisoning.

Calcinase *Cipla, India.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcinate *Tianjin Jinyao, Philipp.*
Calcium gluconate (p. 1783·3).
Hypocalcaemia.

Calcindon *Zydus, India.*
Calcium levulinate (p. 1784·2); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection

Calcinet *Bionet, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcinga *Inga, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calcinol *Raptakos, India; Raptakos, Thai.*
Oral powder: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Raptakos, India.
Syrup: Calcium lactobionate (p. 1784·2); calcium gluconate (p. 1783·3); sodium feredetate (p. 2088·3); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); vitamin A (p. 2098·3).
Formerly contained calcium lactate, calcium gluconate, colecalciferol, vitamin B12, magnesium chloride.

Raptakos, India.
Tablets: Calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2); calcium fluoride (p. 2053·1); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Calcinol Complexo *EMS, Braz.*
Calcium chloride (p. 1783·1); calcium phosphate (p. 1784·2); ergocalciferol (p. 2113·3); sodium fluoride (p. 2089·2); vitamin B_{12} (p. 2107·2).
Vitamin D and mineral supplement.

Calcinol-RB *Raptakos, Thai.*
Calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2); calcium fluoride (p. 2053·1); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Calcinor D *Medifarm, Venez.*
Calcium citrate (p. 1783·2); vitamin D (p. 2112·3); magnesium (p. 1786·3).
Dietary supplement; osteoporosis; muscle cramps; pre-eclampsia.

Calcinorm *Novamen, Arg.†*
Calcium (p. 1783·1); vitamin D (p. 2112·3); magnesium (p. 1786·3).
Dietary supplement.

Calcio *Valma, Chile.†*
Calcium carbonate (p. 1824·3).

Calcio 520 *Knop, Chile.*
Calcium phosphate (p. 1784·2); calcium gluconate (p. 1783·3); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); alfalfa (p. 2433·1); rose fruit (p. 2607·1).
Calcium supplement; osteoporosis.

Calcio Acido *Biotenk, Arg.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcio Cit *TRB, Arg.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis; renal calculi; renal osteodystrophy.

Calcio Cit Simple *TRB, Arg.†*
Calcium citrate (p. 1783·2).
Calcium supplement; hypocalcaemia; osteoporosis; renal calculi; renal osteodystrophy.

Calcio Cm *Labomed, Chile.†*
Calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2); magnesium sulfate (p. 1787·3); vitamin C (p. 2110·3).
Calcium supplement; osteoporosis.

Calcio 20 Complex *Madariaga, Spain.†*
Ascorbic acid (p. 2110·3); calcium phosphate (p. 1784·2); calcium pantothenate (p. 2085·2); cyanocobalamin (p. 2107·2); colecalciferol (p. 2113·1); vitamin A palmitate (p. 2098·3).
Calcium deficiency; osteoporosis.

Calcio D *Arkopharma, Spain; Isdin, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcio Dobetin *Angelini, Ital.*
Cyanocobalamin (p. 2107·2); calcium gluconate (p. 1783·3); calcium gluceptate (p. 1783·2).
Calcium and vitamin B_{12} deficiency.

Calcio 20 Emulsion *Farmasierra, Spain.*
Calcium phosphate (p. 1784·2).
Calcium deficiency; osteomalacia; osteoporosis.

Calcio 20 Fuerte *Madariaga, Spain.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium deficiency; osteoporosis.

Calcio Masticable *AM, Arg.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement.

Calcio Ostelin *Farma, Venez.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calciodex *Hertz, Braz.†*
Vitamins; calcium (p. 1783·1).

Calciodie *SPA, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calciofar *Belfar, Braz.*
Calcium (p. 1783·1); ergocalciferol (p. 2113·3); cyanocobalamin (p. 2107·2); sodium fluoride (p. 2089·2).

Calciofar D *Elmor, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium supplement.

Calciofem *Biofarma, Mex.*
Calcium (p. 1783·1); ergocalciferol (p. 2113·3).
Osteoporosis.

Calciogenol *Etifar, Venez.*
Calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1).

Calciomag D *Tecnonat, Arg.*
Calcium (p. 1783·1); vitamin D (p. 2112·3); magnesium (p. 1786·3).
Dietary supplement.

Calcion *Acdhon, Thai.*
Calcium gluconate (p. 1783·3).
Calcium deficiency; calcium supplement.

Meyer Alian, Venez.
Calcium carbonate (p. 1824·3).

Calcion D Plus *Meyer Alian, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium supplement.

Calcional *Larco, Arg.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis; osteomalacia; rickets.

Calcional Citrato *Larco, Arg.*
Calcium citrate (p. 1783·2).
Osteoporosis; calcium deficiency.

Calcional D3 *Larco, Arg.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Calciopiu *Lafare, Ital.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcior *Delta, Port.*
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency.

Calcioral *Nycomed, Gr.; Sandoz, Port.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; hypoparathyroidism; pseudohypoparathyroidism; osteoporosis; rickets; osteomalacia.

Calcioral D3 *Nycomed, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calcior-D *Delta, Port.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calciosan *Provita, Ital.*
Vitamins; minerals.

Calciovit Puro *Laboratorios Chile, Chile.*
Ergocalciferol (p. 2113·3); calcium hydrogen phosphate (p. 1783·3).
Hypocalcaemia; osteomalacia; rickets.

Calcipac *Inpac, Thai.*
Calcium citrate (p. 1783·2).

Calciparin *Sanofi-Aventis, Ger.†*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Calciparina *Italfarmaco, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Calciparine *Sanofi-Aventis, Arg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Adcock Ingram, S.Afr.†; Sanofi-Aventis, Switz.; Sanofi Synthelabo, Turk.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders; prevention of clotting in extracorporeal circuits.

Calci-Ped *Stiefel, Braz.*
Calcium lactate (p. 1784·1); calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1); cyanocobalamin (p. 2107·2).

Calciperl *Alkem, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calciphar
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Calcitriol (p. 2113·1).
Hypocalcaemia in renal dialysis patients.

Pharmex (Φαρμεξ), Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcipiryna *Polpharma, Pol.†*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal tract.
Fever; pain; thromboembolism prophylaxis.

Calciplex *Khandelwal, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calci-Plus *Forum, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); magnesium stearate (p. 2195·3); zinc oxide (p. 1729·1); manganese sulfate (p. 2081·2).
Food supplement for healthy bones.

Calciplus
Note: this name may be used for preparations of different composition.
Nexus, Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcipot *Meda, Ger.†*
Tablets: Calcium citrate (p. 1783·2); calcium hydrogen phosphate (p. 1783·3).
Calcium deficiency.

Calcipot C *Brady, Austria.*
Vitamin C (p. 2110·3); rutoside (p. 2505·3); calcium citrate (p. 1783·2); calcium glycerophosphate (p. 1783·3).
Calcium and vitamin C deficiency.

Calcipot D_3 *Brady, Austria.*
Colecalciferol (p. 2113·1); calcium citrate (p. 1783·2); calcium glycerophosphate (p. 1783·3).
Calcium and vitamin D deficiency.

Calciprat *Alfa Wassermann, Fr.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calciprat D_3 *Alfa Wassermann, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcipulpe
Note: this name may be used for preparations of different composition.
Septodont, Canad.†
Calcium hydroxide (p. 2465·1).

Calcipure *Ferring, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calci-Rav *Megapharm, Israel.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Calciretard *Kohler-Pharma, Ger.*
Calcium aspartate (p. 1783·1).
Calcium deficiency.

Calcirol *Cadila, India.*
Colecalciferol (p. 2113·1).
Rickets; osteomalacia.

Calcisan *Petrasch, Austria.†*
Calcium hydrogen phosphate (p. 1783·3); calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcisan B + C *Petrasch, Austria.†*
Calcium hydrogen phosphate (p. 1783·3); calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3); thiamine hydrochloride (p. 2103·1).
Calcium, vitamin B_1, and vitamin C deficiency; osteoporosis.

Calcisan C *Petrasch, Austria.†*
Calcium hydrogen phosphate (p. 1783·3); calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3).
Calcium and vitamin C deficiency.

Calcisedron-D *Gedeon Richter, Hung.*
4 Tablets, alendronate sodium (p. 1171·3) (Sedron); 28 tablets, colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3) (CalciviD).
Osteoporosis.

Calcispren *Veltipharm, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcistrong *Lifeon, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); zinc gluconate (p. 2126·2).

Cal-Cit
Note: this name may be used for preparations of different composition.
Vesco, Thai.
Calcium citrate (p. 1783·2).
Calcium supplement; osteoporosis.

Calcit
Note: this name may be used for preparations of different composition.
Allenge, India.
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Soho, Indon.; Zydus Cadila, Thai.
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets; pseudohypoparathyroidism.

Calcit SG *Zydus, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Calcitab *ITF, Port.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis.

Calcitab D *ITF, Port.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; osteoporosis.

Calcitag *Intag, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).

Calcitar *Sanofi-Aventis, Port.†*
Calcitonin (salmon) (p. 1178·1).

Calcite D *Riva, Canad.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement.

Calcitherapy *AG Therapy, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calciton
Note: this name may be used for preparations of different composition.
DAST, Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Inga, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calcitonin *Jelfa, Pol.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; osteoporosis.

Calcitonina *Novartis, Ital.; Onko, Turk.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; hypercalcaemia; Paget's disease of bone.

Calcitoran *Teikoku, Jpn.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcitrat *Recordati, Ger.*
Calcium citrate (p. 1783·2).
Calcium deficiency; osteoporosis.

Cal-Citrate *Bio-Tech, USA.*
Calcium citrate (p. 1783·2).
Calcium supplement.

Calcitrex *Oftalmi, Venez.*
Calcium citrate (p. 1783·2).
Calcium supplement; calcium deficiency; osteoporosis.

Calcitrex D3 *Oftalmi, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcitroject *Faran, Gr.*
Calcitriol (p. 2113·1).

Calcitugg *Nycomed, Swed.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; hyperphosphataemia.

Calcium TO *TO-Chemicals, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcium-600 *Key, USA.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Calcium 500 *Rugby, USA.*
Vitamin D (p. 2112·3); calcium (p. 1783·1).

Calcium Ad *Armoxindo, Indon.*
Calcium gluconate (p. 1783·3); calcium hydrogen phosphate (p. 1783·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Calcium deficiency; calcium, vitamin A, and vitamin D supplement in pregnancy and lactation.

Calcium AL *Aliud, Ger.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcium beta *Betapharm, Ger.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcium Biotika *BB, Cz.*
Calcium gluconate (p. 1783·3); calcium saccharate (p. 2172·3).
Hypocalcaemia; hyperkalaemia; hypermagnesaemia; fluoride poisoning.

Calcium Braun *Braun, Ger.†*
Calcium gluconate (p. 1783·3); calcium saccharate (p. 2172·3).
Calcium deficiency.

Calcium C
Note: this name may be used for preparations of different composition.
Farmaco, Pol.
Calcium lactate gluconate (p. 1784·2); ascorbic acid (p. 2110·3).
Calcium and vitamin C supplement.

Sandoz, Arg.
Sodium calcium edetate (p. 1573·2); ascorbic acid (p. 2110·3).
Heavy metal poisoning.

Calcium C Neo *Zentiva, Cz.†*
Calcium glubionate (p. 1783·2); calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3).
Tonic; osteoporosis.

Calcium Calfit *Herbapol Lublin, Pol.†*
Calcium glubionate (p. 1783·2); calcium lactobionate (p. 1784·2).
Calcium deficiency; osteoporosis.

Calcium Central Poly *Pharmasant, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcium Citrate *Perrigo, Israel.*
Calcium citrate (p. 1783·2); ergocalciferol (p. 2113·3).
Calcium supplement.

Calcium Clear *Nutraceuticals, UK.*
Calcium lactate (p. 1784·1); magnesium carbonate (p. 1856·2).
Calcium supplement.

Calcium D *Pharmasant, Thai.*
Calcium carbonate (p. 1824·3); calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcium + D *Trianon, Canad.†; Maccabi Care, Israel.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; calcium and vitamin D supplement.

Calcium D3 *Novartis, Braz.; Acis, Ger.; Betapharm, Ger.; Ratiopharm, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; calcium and vitamin D deficiency; osteoporosis.

Novartis, Braz.†
Effervescent tablets: Calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcium 500D *Polfa Lodz, Pol.*
Calcium lactogluconate (p. 1783·1); colecalciferol (p. 2113·1); vitamin C (p. 2110·3).
Osteoporosis; osteomalacia; rickets; calcium supplement; immobilisation.

Calcium 500 + D *21st Century, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).

Calcium 600 + D *Nature's Bounty, USA.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).

Rugby, USA.
Calcium (p. 1783·1); vitamin D (p. 2112·3).

Calcium 1000 + D *21st Century, USA.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).

Calcium D Sauter *Labatec, Switz.*
Calcium hydrogen phosphate (p. 1783·3); calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Disorders of calcium and phosphorus metabolism; vitamin C and D deficiencies; calcium supplement.

Calcium D3-Mepha *Mepha, Switz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcium and Ergocalciferol Tablets *Alpharma, UK.*
Calcium lactate 300 mg (p. 1784·1); calcium phosphate 150 mg (p. 1784·2); ergocalciferol 10 µg (p. 2113·3).
Each tablet contains 400 units of vitamin-D activity. They should be crushed or chewed before administration.
Distinguish from Calcium with Vitamin D Tablets (BPC 1973).
Calcium and vitamin D deficiency.

Calcium Factor *Novartis, Chile.†*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteomalacia; osteoporosis; rickets.

Calcium Forte D *Novartis, Chile.†*
Calcium lactogluconate (p. 1783·1); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Hypocalcaemia; osteoporosis.

Calcium Fresenius *Fresenius Kabi, Austria.*
Calcium gluconate (p. 1783·3); calcium saccharate (p. 2172·3).
Hypocalcaemia; osteoporosis.

Calcium Oyster Shell *Novopharm, Canad.†*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Calcium Pharmavit *Walmark, Cz.*
Calcium carbonate (p. 1824·3); riboflavin sodium phosphate (p. 2104·3).
Calcium deficiency; calcium supplement; osteoporosis; osteomalacia; rickets; tetany.

Calcium Picken *Adeka, Turk.*
Calcium gluconate (p. 1783·3); calcium levulinate (p. 1784·2).
Calcium deficiency; calcium supplement.

Calcium Plus Vit-D *Novartis, Turk.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium and vitamin D deficiency.

Calcium Resonium *Sanofi-Aventis, Austral.; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.†; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi Synthelabo, UK.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Calcium Rich Rolaids *Warner-Lambert, USA.*
Magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Hyperacidity.

Calcium Sandoz Forte + D *Novartis, Thai.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcium Stada *Stada, Ger.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcium Syrop *Hasco-Lek, Pol.*
Calcium glubionate (p. 1783·2); calcium lactobionate (p. 1784·2).
Calcium deficiency; rickets; osteomalacia; heavy metal poisoning.

Calcium Unison *Unison, Hong Kong; Unison, Thai.†*
Calcium lactate (p. 1784·1).
Calcium deficiency; calcium supplement.

Calcium Upha *CCM, Malaysia.†*
Calcium lactate (p. 1784·1).
Calcium supplement in pregnancy and lactation.

Calcium Utopian *Utopian, Thai.*
Calcium lactate (p. 1784·1).
Dietary supplement.

Calcium Verla *Verla, Ger.*
Coated tablets; effervescent tablets: Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcium Verla D *Verla, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D_3 deficiency; osteoporosis.

Calcium Wyeth *Pfizer, Port.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).

Calciumade *BioFemme, Philipp.*
High-calcium drink for women.

Calciumcafe *Candioli, Ital.†*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Nutritional supplement.

Calcium-CT *CT, Ger.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calcium-D *Beacons, Singapore.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium and vitamin D supplement.

Euro Lifecare, Ukr.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; osteomalacia.

Calcium-D3 *Nycomed, Rus.; Nycomed, Ukr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-D-Redoxon *Bayer Consumer, Malaysia; Bayer, Singapore; Roche, Turk.*
Calcium (p. 1783·1); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Dietary supplement.

Bayer Consumer, Indon.†
Calcium carbonate (p. 1824·3); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Nutritional supplement.

Calcium-D-Sandoz *Sandoz, Austria; Novartis, Gr.; Sandoz, Hung.; Novartis Consumer, Irl.; Sandoz, Port.; Novartis, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; calcium supplement.

Novartis Consumer, Israel.
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcium-D3-Sandoz *Sandoz, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteoporosis.

Calcium-EAP *Kohler-Pharma, Ger.*
Phosphorylcolamine calcium (p. 2589·3).
Calcium supplement.

Calcium-Folic Acid Plus D *Brookstone, USA.*
Vitamin B substances (p. 2102·3); calcium carbonate (p. 1824·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Dietary supplement.

Calciumfolinat *Pharmalogic, Israel.*
Calcium folinate (p. 2066·3).
Prevention of folic-acid antagonist toxicity; adjunct to fluorouracil therapy.

Sandoz, Hong Kong.
Folinic acid (p. 2066·3).
Reduction of methotrexate toxicity.

Calcium-Sandoz *Novartis, Indon.; Novartis Consumer, Irl.; Novartis, Singapore; Alliance, UK; Novartis Nutrition, Venez.*
Syrup: Calcium glubionate (p. 1783·2); calcium lactobionate (p. 1784·2).
Osteoporosis; calcium deficiency; osteomalacia; neonatal tetany; calcium supplement.

Novartis, Braz.; Sandoz, Ger.†
Calcium gluconate (p. 1783·3); calcium lactobionate (p. 1784·2).
Calcium deficiency.

Sandoz, Arg.; Sandoz, Austria; Novartis Consumer, Canad.; Sandoz, Denm.; Novartis, Fin.†; Sandoz, Fr.; Sandoz, Ger.†; Novartis Consumer, Hong Kong; Sandoz, Hung.; Novartis Consumer, Israel; Sandoz, Ital.; Sandoz, Mex.; Novartis Consumer, Neth.; Sandoz, Norw.; Novartis, NZ†; Sandoz, Port.; Novartis Consumer, S.Afr.; Sandoz, Swed.; Sandoz, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis Nutrition, Venez.
Effervescent tablets; powder for oral solution: Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany; bone demineralisation; allergic disorders.

Novartis Consumer, Austria†; Sandoz, Denm.; Novartis, Fin.; Novartis Consumer, Israel†; Novartis Consumer, Neth.; Sandoz, Swed.; Sandoz, Switz.; Novartis, Turk.
Injection: Calcium glubionate (p. 1783·2).
Calcium deficiency; hypocalcaemia; tetany; rickets; osteomalacia; osteoporosis; hyperkalaemia; poisoning with lead, fluorides, or magnesium; allergic skin disorders.

Novartis, Chile†; Novartis Consumer, Spain.
Calcium lactogluconate (p. 1783·1); calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; rickets; osteomalacia; calcium supplement.

Novartis, India; Novartis, Philipp.†
Chewable tablets: Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Novartis, India.
Injection: Calcium glubionate (p. 1783·2); calcium gluconate (p. 1783·3).

Calcium-Sandoz Bonacal *Novartis, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calcium-Sandoz C *Novartis, Turk.*
Calcium lactate (p. 1784·1); calcium carbonate (p. 1824·3); vitamin C (p. 2110·3).
Calcium deficiency.

Sandoz, Mex.
Calcium lactogluconate (p. 1783·1); ascorbic acid (p. 2110·3).
Calcium and vitamin C supplement.

Calcium-Sandoz D *Sandoz, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-Sandoz + D *Sandoz, Arg.; Novartis, Chile.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; rickets; osteomalacia; tetany; calcium supplement; calcium and vitamin D deficiency.

Calcium-Sandoz D3 *Sandoz, Switz.*
Effervescent tablets: Calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Sandoz, Switz.
Powder for oral solution: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-Sandoz D Osteo *Sandoz, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-Sandoz F *Novartis, Braz.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium deficiency.

Calcium-Sandoz FF *Novartis, Cz.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium supplement; osteomalacia; osteoporosis; renal osteodystrophy; tetany.

Calcium-Sandoz Forte *Novartis, Cz.; Novartis, Indon.; Novartis Consumer, Rus.; Novartis OTC, Singapore.*
Calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2).
Osteoporosis; rickets; osteomalacia; tetany; calcium supplement; renal osteodystrophy.

Sandoz, Pol.
Calcium carbonate (p. 1824·3); calcium lactogluconate (p. 1783·1).
Osteoporosis; rickets; osteomalacia; calcium supplement.

Novartis Consumer, Spain.†
Calcium carbonate (p. 1824·3); calcium glubionate (p. 1783·2).
Calcium deficiency; rickets; osteomalacia; osteoporosis; hypoparathyroidism.

Calcium-Sandoz Forte D *Novartis, Chile.†*
Calcium carbonate (p. 1824·3); calcium lactogluconate (p. 1783·1); colecalciferol (p. 2113·1).
Hypocalcaemia; osteoporosis.

Novartis Consumer, Spain.†
Calcium gluceptate (p. 1783·2); colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Deficiencies of calcium and vitamin D; osteoporosis.

Calcium-Sandoz Junior Growth *Novartis, Indon.*
Calcium (p. 1783·1); iron (p. 2073·1); zinc (p. 2126·1).
Calcium supplement.

Calcium-Sandoz Junior Strength *Novartis, Indon.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Calcium-Sandoz Vit C *Novartis, Indon.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3).
Calcium supplement.

Calcium-Sandoz + Vit C *Novartis Consumer, Israel.†*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); calcium carbonate (p. 1824·3); vitamin C (p. 2110·3).
Calcium and vitamin C supplement.

Calcium-Sandoz + Vitamin C *Sandoz, Hung.; Novartis Consumer, Malaysia†; Sandoz, Philipp.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3).
Calcium and vitamin C deficiency; cold and influenza symptoms; calcium and vitamin C supplement.

Sandoz, Pol.
Calcium carbonate (p. 1824·3); calcium lactogluconate (p. 1783·1); ascorbic acid (p. 2110·3).
Calcium and vitamin C supplement.

Calcium-Sandoz + Vitamina C *Novartis, Braz.*
Calcium carbonate (p. 1824·3); calcium lactobionate (p. 1784·2); ascorbic acid (p. 2110·3).
Calcium and vitamin C supplement.

Calcium-Sorbisterit *Fresenius, Fr.†*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia related to renal insufficiency.

Calciurell *Sanorell, Ger.*
Calcium carbonicum (p. 1824·3).
Homoeopathic preparation.

Calcival *Valdecasas, Mex.*
Calcium citrate (p. 1783·2).
Calcium supplement; calcium deficiency; osteoporosis; osteomalacia, rickets.

Calcivas *Brown & Burk, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Calcivid *Beres, Hung.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calcivit
Note: this name may be used for preparations of different composition.
Elvipe, Gr.
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3).

UB, Switz.
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Calcivit D *Hexal, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D_3 deficiency; osteoporosis.

Calciviton *Tempo Scan Pacific, Indon.*
Vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin K (p. 2122·1); calcium (p. 1783·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1).
Nutritional supplement for healthy bones.

Calcivoran *Vocate, Gr.*
Calcium folinate (p. 2066·3).
Folic acid antidote; megaloblastic anaemia.

Calcivorin *Mintlab, Chile.*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis.

Calcivorin D *Mintlab, Chile.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium and vitamin D supplement; osteoporosis.

Calciyodina *Manuell, Mex.*
Calcium caseinate (p. 2055·2); calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); iodocasein (p. 2336·3).
Rickets; osteomalacia; osteoporosis; calcium supplement; tetany.

Calcizin *Psyco Remedies, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2).

Calco *Jiwa, China; Iasis, Gr.; Lisapharma, Hung.; Medico Uno, Hung.; Lisapharma, Thai.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia; hyperparathyroidism; reflex sympathetic dystrophy.

Calcodol-D3 *Iasis, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

CalCold *McNeil, UK.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Calcom *Panacea, India.*
Calcium carbonate (p. 1824·3); calcitriol (p. 2113·1); zinc sulfate (p. 2126·2).
Osteoporosis.

Calcort *Sanofi-Aventis, Braz.; Galen, Ger.; Shire, Irl.†; Sanofi-Aventis, Mex.; Sanofi-Aventis, Switz.; Shire, UK; Sanofi-Aventis, Venez.*
⊗Deflazacort (p. 1629·3).
Rheumatoid arthritis; corticosteroid.

Calc-Os *Erlimpex, Indon.*
Oyster shell (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement; osteoporosis.

Calcos *Symbiosis, India.*
Syrup: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Symbiosis, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1); copper; magnesium; manganese; zinc.

Calcos Vitamine D_3 *Arkopharma, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

CalCough Children's Soothing Syrup *McNeil, UK.*
⊗Glycerol (p. 2517·2).
Cough.

CalCough Infant Syrup *McNeil, UK.*
⊗Glycerol (p. 2517·2).
Cough.

CalCough Six Plus *McNeil, UK.*
Guaifenesin (p. 1666·2).
Formerly known as CalCough Chesty.
Cough.

CalCough Tickly *Pfizer Consumer, UK.†*
⊗Glycerol (p. 2517·2).
Cough.

Calcrem *Raptakos, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Calc-Up *Medhel, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Calcury *Charak, India.*
⊗Punarnava (p. 2601·1); bergenia pacumbis; tinospora cordifolia; tribulus terrestris (p. 2633·3).
Renal calculi.

Calcusan *Monserrat, Arg.*
Calamine (p. 1697·2); diphenhydramine (p. 626·1).
Allergic skin reactions; skin irritation.

Calcusan Bebe *Monserrat, Arg.*
Vitamin A (p. 2098·3); zinc oxide (p. 1729·1); boric acid (p. 2459·3).

Cal-C-Vita *Bayer Consumer, Arg.; Bayer, Austria; Bayer, Gr.; Bayer, Switz.†*
Calcium carbonate (p. 1824·3); vitamins.
Calcium and vitamin deficiency; bone and teeth disorders; tonic; nutritional supplement; calcium supplement.

Bayer Consumer, S.Afr.
Calcium carbonate (p. 1824·3); vitamin C (p. 2110·3); pyridoxine (p. 2105·3); vitamin D (p. 2112·3).
Calcium and vitamin supplement; tonic.

Bayer, Israel.†
Calcium (p. 1783·1); vitamins.
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cal-C-Vita Fluor *Bayer Consumer, Arg.*
Calcium carbonate (p. 1824·3); sodium fluoride (p. 2089·2); vitamins.
Calcium and fluoride supplement.

Calcy *Alembic, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calcytonil *Medarte, Gr.*
Calcitonin (salmon) (p. 1178·1).

Cal-CZ *Intra-Labs, India.*
Oral suspension: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).

Intra-Labs, India.
Tablets: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Cal-D *Blackmores, Austral.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Greater Pharma, Thai.
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Osteoporosis.

CalD *PSM, NZ.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Cal+D *Verisfield, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Cal-D3 *PC India, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cald 3-Therapy *AG Therapy, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Caldale *Juggat, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Caldar-D *Medipharm, Chile.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium deficiency; osteoporosis.

Cal-De *Meda, Austria.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Caldê *Marjan, Braz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; calcium and vitamin D deficiency.

Caldease *Clonmel, Irl.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Nappy rash; skin irritation; burns; wounds.

Caldece *Sanbe, Indon.; Sanbe, Singapore.*
Vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); calcium carbonate (p. 1824·3).
Calcium and vitamin deficiency.

CaldeCort *Novartis Consumer, USA.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Skin disorders.

Calderol *Organon, USA.*
Calcifediol (p. 2113·1).
Metabolic bone disease; hypocalcaemia associated with renal dialysis.

Caldesene *Clonmel, Irl.*
Calcium undecenoate (p. 596·3).
Nappy rash; skin irritation.

Insight, USA.
Topical powder: Talc (p. 1722·2); zinc oxide (p. 1729·1).
Formerly contained calcium undecenoate.
Nappy rash; minor skin irritation.

Insight, USA.
Ointment: Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin disorders.

Caldesil *Guidotti, Gr.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Caldetri *GMP, Indon.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis.

Caldetrin *Polfa Pabianice, Pol.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; osteomalacia.

Caldeval *Saval, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis; rickets.

Caldic *Nordic, India.*
Oral suspension: Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).

Nordic, India.
Tablets: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Caldikind *Mankind, India.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; hypocalcaemia in hypoparathyroidism.

Caldine
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Fr.
Lacidipine (p. 1417·3).
Hypertension.

Takeda, Philipp.
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Caldium *Egis, Ukr.†*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Caldob *Comed, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Caldolor *Alveda, Canad.; Cumberland, USA.*
Ibuprofen (p. 68·2).
Pain; fever.

Caldoxon *Millimed, Thai.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); vitamin C (p. 2110·3); vitamin B_6 (p. 2105·3).
Calcium and vitamin supplement; osteoporosis.

CalDrink D3 *DiME, UK.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Caldronate *Actavis, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Cal-D-Vita *Bayer, Austria; Bayer Sante, China; Roche, Hong Kong†; Bayer, Swed.; Bayer, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Bayer Consumer, Malaysia.
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Dietary supplement.

Bayer Consumer, Thai.†
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis; osteomalacia.

Calel-D *Rhone-Poulenc Rorer, USA.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Nutritional supplement.

Calendaderm *Knop, Chile.*
Calendula (p. 2465·2).
Homoeopathic preparation.

Calendolon *Weleda, Irl.; Weleda, UK.*
Calendula (p. 2465·2).
Minor wounds and abrasions.

Calendula + *Homeocan, Canad.*
Calendula officinalis (p. 2465·2); cantharis (p. 2469·2); echinacea angustifolia (p. 2498·1); hypericum perforatum (p. 449·1); phytolacca decandra (p. 2593·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Calendula Complexe No 89 *Lehning, Fr.*
Calendula (p. 2465·2); sarsaparilla (p. 2610·3); clematis vitalba; arnica (p. 2447·2); ruta graveolens (p. 2608·2); mercurius nitrosus (p. 2555·3); hamamelis virginiana (p. 2523·3); bellis (p. 2454·2).
Homoeopathic preparation.

Calendula Echinacea Comp *Knop, Chile.*
Calendula (p. 2465·2); echinacea (p. 2498·1); hydrastis (p. 2528·1); helonias (p. 2524·3).
Homoeopathic preparation.

Calendula Nappy Change Cream *Weleda, UK.*
Calendula (p. 2465·2); chamomile (p. 2474·1); almond oil (p. 2437·1).
Nappy rash.

Calendula Ointment *Thompsons, Canad.†*
Calendula (p. 2465·2); comfrey (p. 2484·2); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Calendulan *VSM, Neth.*
Cream; ointment; topical gel; topical spray: Calendula officinalis (p. 2465·2).
Homoeopathic preparation.

VSM, Neth.
Topical emulsion: Calendula officinalis (p. 2465·2); camphora (p. 2466·2).
Homoeopathic preparation.

Calendulène *Thea, Fr.†*
Calendula (p. 2465·2).
Eye hygiene.

Calendulin *Herbapol Wroclaw, Pol.†*
Calendula (p. 2465·2).
Vulvovaginal disorders.

Calendumed *DHU, Austria; DHU, Ger.; Peithner, Hung.*
Calendula urt. (p. 2465·2).
Homoeopathic preparation.

Calex *Rapross, India.*
Microcrystalline hydroxyapatite complex (p. 2529·3).
Osteoporosis.

Calfa-D *Kee, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Calfadol *Faran, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Calfa-Plus *Kee, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).
Osteoporosis; renal osteodystrophy.

Calfate *Angelini, Port.†*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis; duodenitis.

Calferon *Delta, Braz.*
Ergocalciferol (p. 2113·3); vitamin B_{12} (p. 2107·2); calcium gluconate (p. 1783·3); calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2).
Vitamin and mineral supplement.

Calfetos *Medipharm, Chile.*
Clobutinol hydrochloride (p. 1658·3).
Cough.

Calfine *VHB, India.*
Syrup: Calcium lactobionate (p. 1784·2); calcium gluconate (p. 1783·3); magnesium (p. 1786·3); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).

VHB, India.
Tablets: Calcium (p. 1783·1); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Calfine Plus *VHB, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calflavone *Tablets, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); ipriflavone (p. 1185·3).
Osteoporosis.

Calfolex *Sirton, Ital.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity; folic acid deficiency.

Calforte *LCH, Hong Kong.†*
Calcium (p. 1783·1).

Calfovit D3 *Menarini, Denm.†; Menarini, Fin.; Menarini, Swed.; Menarini, UK.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cal-G *Key, USA.*
Calcium gluconate (p. 1783·3).
Calcium supplement.

Calgain *Criticare, India.*
Preparation for enteral nutrition.

Calgayan *Grossman, Mex.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Calgel *McNeil, Cz.; GSK, Pol.; GSK, Rus.; GSK, Turk.; Pfizer Consumer, UK.*
Lidocaine hydrochloride (p. 1988·2); cetylpyridinium chloride (p. 1743·1).
Gingivitis; teething pain.

Calglucon *Marching, Hong Kong.†*
Calcium gluconate (p. 1783·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Calgrow *Aareen, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Calgrow-C *Aareen, India.*
Calcitriol (p. 2113·1); calcium citrate maleate (p. 1783·1).

Calhem Plus *Unijules, India.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); calcium phosphate (p. 1784·2); zinc sulfate (p. 2126·2).

Calhof *Pharmahof, Thai.*
Calcium carbonate (p. 1824·3).

Calibo Calcium *Marching, Hong Kong.†*
Calcium (p. 1783·1); lysine (p. 2079·3); vitamins.

Calibo Chewable *Marching, Hong Kong.†*
Cyproheptadine (p. 624·1); vitamins.

Calibo Multivitamins *Marching, Hong Kong.†*
Vitamins.

Calibon-Z *Intra-Labs, India.*
Chewable tablets: Calcium carbonate (p. 1824·3).
Gastric hyperacidity; hyperphosphataemia.

Intra-Labs, India.
Syrup: Calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1); cyanocobalamin (p. 2107·2); zinc sulfate (p. 2126·2).

Intra-Labs, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Calibral
Note: this name may be used for preparations of different composition.
Pharmacare, Philipp.
Mefenamic acid (p. 85·3).
Fever; pain.

Calibs *Ranbaxy, India.*
Polycarbophil calcium (p. 1879·2).

Calicida Indiano *Gestafarma, Port.*
Topical solution: Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Verrucas; callosities.

Gestafarma, Port.
Ointment: Salicylic acid (p. 1719·1); turpentine oil (p. 2636·3).
Verrucas; callosities.

Calicida Moreno *Moreno, Port.*
Salicylic acid (p. 1719·1).
Warts; calluses.

Calid-C *Health Guard, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2).

Caliderm *Darier, Mex.*
A range of moisturisers and emollients.

Calidiol *Servier, Hung.†; Servier, Pol.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Califig *Merck Consumer, UK.*
Oral liquid: Senna (p. 1885·1); fig (p. 1843·2).
Constipation.

Merck Consumer, UK.
Chewable bar: Senna (p. 1885·1); fig (p. 1843·2); dietary fibre.
Constipation.

Calimal *Sussex, UK.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Calinat *Aesculapius, Ital.†*
Calcium folinate (p. 2066·3).
Folate deficiency; reduction of aminopterin and methotrexate toxicity.

Calinofen *Medimport, Mex.†*
Paracetamol (p. 115·1).
Pain; fever.

Calinol *Adipharm, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Calinta *Intas, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Calio *Osmed, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Caliprene *Lemery, Mex.†*
Pilocarpine hydrochloride (p. 2010·3).
Sjögren's syndrome; xerostomia.

Calista *Ecobrands, UK.*
Fertility test (p. 2596·1).

Calisvit *Menarini, Belg.; Menarini, Ital.; Menarini, Neth.*
Colecalciferol (p. 2113·1); calcium phosphate (p. 1784·2).
Calcium and vitamin D deficiency; osteoporosis.

Calive *Biosync, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calive-Forte *Biosync, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Calix *Meprofarm, Indon.†*
Calcium pidolate (p. 1784·3); curcuminoid; fructo-oligosaccharides (p. 2508·1); vitamins.
Nutritional supplement.

Calixta *Belupo, Cz.†*
Mirtazapine (p. 436·1).
Depression.

Calkariaa *Alkem, India.*
Calcium alginate (p. 1136·3).

Calkem *Alkem, India.*
Aloes (p. 1816·1); liquid paraffin (p. 2191·2).

Cal-Lac *Bio-Tech, USA.*
Calcium lactate (p. 1784·1).
Calcium supplement.

Callergy Clear *Major, USA.*
Pramocaine hydrochloride (p. 1993·3); zinc acetate (p. 2126·1).

Callexe *Casasco, Arg.*
Levetiracetam (p. 531·1).
Epilepsy.

Callicida
Note: this name may be used for preparations of different composition.
Cabuchi, Arg.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); phenol (p. 1763·3); acetic acid (p. 2426·3); benzocaine (p. 1980·2); collodion (p. 1718·2).
Callus removal.
El Monje, Arg.; Gezzi, Arg.
Ointment: Salicylic acid (p. 1719·1).
Callus removal.
El Monje, Arg.
Topical solution: Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); zinc chloride (p. 2126·1).
Callus removal.
Labsa, Arg.
Salicylic acid (p. 1719·1); benzocaine (p. 1980·2).
Lauria, Arg.
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3); lactic acid (p. 2539·1).
Callus removal.

Callicida Cor Pik *Quimifar, Spain.†*
Acetic acid (p. 2426·3); flexible collodion; lactic acid (p. 2539·1); castor oil (p. 2472·1); salicylic acid (p. 1719·1).
Callosities.

Callicida Gras *Quimifar, Spain.†*
Salicylic acid (p. 1719·1).
Callosities.

Callicida Kendu *Urgo, Spain.*
Salicylic acid (p. 1719·1).
Callosities.

Callicida Rojo *Escaned, Spain.†*
Acetic acid (p. 2426·3); flexible collodion; benzocaine (p. 1980·2); salicylic acid (p. 1719·1); iodine tincture (p. 2336·3).
Callosities.

Callicida Salve *Cederroth, Spain.†*
Salicylic acid (p. 1719·1).
Callosities.

Callifugo *Health Plus, Gr.; Mediplants, Gr.*
Salicylic acid (p. 1719·1).
Keratolytic.

Calligraff *Unichem, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc sulfate (p. 2126·2).

Callivoro Marthand *Martinez Llenas, Spain.*
Salicylic acid (p. 1719·1); benzocaine (p. 1980·2).
Callosities.

Callix *Perez Gimenez, Spain.†*
Benzocaine (p. 1980·2); lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Callosities.

Callofin *Alcor, Spain.†*
Salicylic acid (p. 1719·1).
Callosities.

Callous *SSL, Cz.†; SSL, Pol.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Callous Removal Pads *SSL, Irl.*
Salicylic acid (p. 1719·1).
Calluses.

Cally Plus *Shinto, India.*
Thioctic acid (p. 2629·1); vitamins; selenium (p. 2086·3); zinc (p. 2126·1).

Calm *Brauer, Austral.*
Passiiflora incarnata (p. 2584·1); aconitum napellus (p. 2428·3); belladonna (p. 2453·3); chamomilla (p. 2474·1).
Homoeopathic preparation.

Calma
Note: this name may be used for preparations of different composition.
Antula, Swed.
Dimenhydrinate (p. 625·2).
Motion sickness.
Farma 1, Ital.
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Calma D3 *Farma 1, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calmaben *Montavit, Austria.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; sedative.

Calmador *Finadiet, Arg.*
Tramadol hydrochloride (p. 139·2).
Pain.

Calmador Plus *Finadiet, Arg.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Cal-Mag *Quest, Malaysia.*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3).
Dietary supplement.
Seroyal, Canad.†
Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3).

Calmag *Jamieson, Philipp.*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3).
Calcium deficiency; osteoporosis.

Cal-Mag Citrate with Zinc and Vitamin D
Accurex, Canad.; Vita Health, Canad.
Calcium citrate (p. 1783·2); magnesium citrate (p. 1857·1); zinc citrate (p. 2126·2); colecalciferol (p. 2113·1).

Cal-Mag Complete *Purity Life, Canad.*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Calmag D
Note: this name may be used for preparations of different composition.
Gerbex, Canad.
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3).
Nutrilite, Arg.
Ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1); minerals; acerola; alfalfa (p. 2433·1).
Dietary supplement.

Cal-Mag Plus *Quest, UK.*
Minerals.

CalMag Plus *USANA, USA.*
Calcium citrate (p. 1783·2); magnesium amino acid chelate (p. 2048·3); silicon amino acid chelate; boron amino acid chelate; vitamin D (p. 2112·3).
Nutritional supplement.

Cal-Mag plus Vitamin D *Purity Life, Canad.*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3).

Cal-Mag with Vitamin D & Zinc *Pharmetics, Canad.*
Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); zinc gluconate (p. 2126·2); colecalciferol (p. 2113·1).

Cal-Mag & Vitamins C & D *Swiss Herbal, Canad.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Calmagrip *Perez Gimenez, Spain.*
Ascorbic acid (p. 2110·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Calmagrip Forte *Perez Gimenez, Spain.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Calm-Aid *Natures Way, Canad.†*
Cimicifuga (p. 2478·1); lupulus (p. 2546·1); cypripedium pubescens; skullcap (p. 2617·1); valerian (p. 2640·2); wood betony.

Calmal *Gufic, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calman *Ativus, Braz.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); salix (p. 129·2).
Anxiety; insomnia.

Calmane *Bio-Dis, Canad.*
Herbal tea: Chamomile (p. 2474·1); tilia (p. 2631·3); orange; passion flower (p. 2584·1); spearmint (p. 2621·2); vervain (p. 2645·1).
Bio-Dis, Canad.
Tablets: ⊗Crataegus (p. 2488·1); tilia (p. 2631·3); lobelia inflata (p. 2323·2); passion flower (p. 2584·1); valerian (p. 2640·2).

Calmanervin *Sam-On, Israel.*
Elixir: Passion flower (p. 2584·1); valerian (p. 2640·2).
Anxiety; insomnia.
Sam-On, Israel.
Tablets: Passion flower (p. 2584·1); valerian (p. 2640·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Anxiety; insomnia.

Calmante Vitaminado PG *Perez Gimenez, Spain.*
Aspirin (p. 22·2); caffeine (p. 1203·3); thiamine hydrochloride (p. 2103·1).
Pain; fever.

Calmante Vitaminado Rinver *Monik, Spain.†*
Aspirin (p. 22·2); thiamine (p. 2102·3).
Fever; inflammation; pain.

Calmapax *Delta, Braz.*
Chamomile (p. 2474·1); erythrina mulungu (p. 2564·3); melissa (p. 2552·3); passion flower (p. 2584·1).
Sedative.

Calmapic *Diametiss, Canad.†*
Ammonium hydroxide (p. 2441·2); peppermint oil (p. 1877·1).

Calmapica *Perez Gimenez, Spain.*
Ammonia (p. 2441·2).
Insect bites; stings.

Calmapride *Arafarma, Spain.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; aggression in dementia; behaviour disorders in children.

Calmason *Terapeutico, Ital.*
Lupulus (p. 2546·1); giuggiolo; valerian (p. 2640·2); passion flower (p. 2584·1); papaver rhoeas; melissa (p. 2552·3); green tea (p. 2648·2); griffonia (p. 2522·3); vitamin B substances (p. 2102·3); magnesium (p. 1786·3).
Sleep disorders.

Calmasyn *Links, USA.*
Menthol (p. 2553·2); zinc oxide (p. 1729·1).

Calmate *Blue Sky, Philipp.†; Kenyaku, Thai.*
Calcium carbonate (p. 1824·3).
Antacid; calcium supplement.

Calmatel *Almirall, Spain.*
Piketoprofen hydrochloride (p. 125·3).
Peri-articular and soft-tissue disorders.

Calmatol
Note: this name may be used for preparations of different composition.
Farmo Quimica, Chile.
Scholtzia; chamomile (p. 2474·1); tilia (p. 2631·3); mint oil (p. 2560·1); fennel oil (p. 2503·3).
Teething pain.
NewLife, Arg.
Amino acids; vitamins.
Dietary supplement.

Calmatron *Fabop, Arg.*
Lorazepam (p. 1080·3).
Anxiety.

Calmax
Note: this name may be used for preparations of different composition.
Great Eastern, Thai.
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement; osteoporosis; calcium deficiency.
Helsinn Birex, Irl.
Alprazolam (p. 1035·2).
Anxiety.
Media Power, Canad.†
Calcium gluconate (p. 1783·3); magnesium carbonate (p. 1856·2); ascorbic acid (p. 2110·3).

Calmcold *Pharmacia Upjohn, India.*
Syrup: Chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Pharmacia Upjohn, India.
Tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Calmday *Will-Pharma, Belg.*
Nordazepam (p. 1089·3).
Anxiety.

Calme *Elfin, India.*
Suspension: Calcium (p. 1783·1); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).
Elfin, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calme-CT *Elfin, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Cal-med *Medicpharma, Thai.*
Calcium citrate (p. 1783·2).
Dietary supplement.

Calmerphan-L *Doetsch, Grether, Switz.*
Dextromethorphan resin (p. 1660·1).
Cough; bronchitis.

Calmese *Themis, India.*
Lorazepam (p. 1080·3).
Premedication.

Calmésine *Mepha, Switz.*
Dextromethorphan resin (p. 1660·1).
Cough.

Calmettes *Solvay, S.Afr.†*
Valerian (p. 2640·2).
Nervous disorders; anxiety.

Calmex *Johnson & Johnson, Chile.*
Doxylamine succinate (p. 627·3).
Insomnia.
Novopharm, Canad.
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Calmicort *Omega, Fr.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Calmiderm *Tilman, Hong Kong.*
Chamomile (p. 2474·1); calendula (p. 2465·2); urtica (p. 2639·3); menthol (p. 2553·2); lavender oil (p. 2541·1).
Dry skin; skin irritation.

Calmiflorine *Dietetique et Sante, Fr.†*
Crataegus (p. 2488·1); passion flower (p. 2584·1); valerian (p. 2640·2); california poppy (p. 2466·1); sweet orange (p. 2576·2); coriander (p. 2486·3); rosemary (p. 2607·2); liquorice (p. 1853·2); ash (p. 2450·1); sweet chestnut (p. 2625·1); pomme marc.
Nervous disorders; sleep disorders.

Calmin *Gerolymatos, Gr.*
Mefenamic acid (p. 85·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

JK Biochem, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calmina *Pharbio, Pol.*
Lupulus (p. 2546·1); melissa (p. 2552·3); valerian (p. 2640·2).
Insomnia.

Calmin-AF *Combiphar, Indon.*
Vitamins; ferrous fumarate (p. 2060·3); calcium lactate (p. 1784·1); iodine (p. 2336·3).
Anaemias; nutritional supplement in pregnancy.

Calmine *Bouty, Ital.*
Ibuprofen (p. 68·2).
Pain.

Calminex Atleta *Mantecorp, Braz.*
Methyl salicylate (p. 92·1); belladonna (p. 2453·3); camphor (p. 2466·2).
Musculoskeletal and joint disorders.

Calminex H *Mantecorp, Braz.*
Methyl salicylate (p. 92·1); zinc oxide (p. 1729·1); belladonna (p. 2453·3); peru balsam (p. 2587·1); camphor (p. 2466·2).
Musculoskeletal and joint disorders.

Calmiox *Esteve, Spain.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Calmipam *Chalermchai, Thai.*
Diazepam (p. 1063·2).

Calmiplan *Bunker, Braz.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); salix (p. 129·2).
Sedative.

Calmiplant *VSM, Belg.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; sleep disorders.

Calmitch *Christo, Hong Kong.†*
Diphenhydramine (p. 626·1).

Calmix *Overseas, India.*
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1); copper sulfate (p. 2057·2).
Calcium supplement; osteoporosis.

Overseas, India.
Suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).

Calmixène *Juvise, Fr.*
Pimethixene (p. 638·1).
Cough.

Calmlet *Sunthi Sepuri, Indon.†*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder.

Calmo
Note: this name may be used for preparations of different composition.
Eagle, Austral.†
Mistletoe (p. 2560·2); valerian (p. 2640·2); vervain (p. 2645·1); gentian (p. 2512·1); avena (p. 2451·1); passion flower (p. 2584·1); skullcap (p. 2617·1); tansy (p. 2625·3); pulsatilla (p. 2600·2).
Hypnotic; tension; tension headache.

Calmobrul *SVR, Fr.*
Proline (p. 2086·2); water lilly flower; allantoin (p. 1693·1); dexpanthenol (p. 2582·2); vitamin E (p. 2119·1).
Skin irritation; sunburn.

Calmociteno *Medley, Braz.*
Diazepam (p. 1063·2).
Anxiety.

Cal mod *Indian Drugs, India.*
Diazepam (p. 1063·2).

Calmodor *Gerolymatos, Gr.*
Paracetamol (p. 115·1).
Fever; pain.

Calmodren *Sevene, Fr.*
Valeriana officinalis (p. 2640·2); passiflora incarnata (p. 2584·1); crataegus oxyacantha (p. 2488·1).
Homoeopathic preparation.

Calmoflex *Gezzi, Arg.*
Diclofenac sodium (p. 48·3).
Pain.

Calmoflorine *Coup, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Calmogel *Sanofi-Aventis, Ital.*
Isothipendyl hydrochloride (p. 631·2).
Pruritus; insect bites; sunburn.

Calmol
Note: this name may be used for preparations of different composition.
Mentholatum, USA.
Zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1).
Anorectal disorders.

Temis, Arg.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

CalmolinADD *Tribest, S.Afr.†*
Evening primrose oil (p. 2502·2); vitamins; minerals.
Dietary supplement.

Calmonal *Aura, Cz.†*
Salix (p. 129·2); urtica (p. 2639·3); lavender (p. 2541·1); peppermint leaf (p. 1877·1); chamomile (p. 2474·1); lupulus (p. 2546·1).
Bath additive; musculoskeletal and joint disorders.

Calmonex *Delta, Braz.*
Kava (p. 2537·3).
Anxiety.

Calmopirin *Fada, Arg.*
Dextropropoxyphene hydrochloride (p. 43·3) or dextropropoxyphene napsilate (p. 43·3); dipyrone (p. 53·3).
Fever; pain.

Calmoplex *Teofarma, Spain.†*
Codeine phosphate (p. 40·2); hydroxyzine hydrochloride (p. 630·3); propyphenazone (p. 127·3).
Pain.

Calmopyrol *Faran, Gr.*
Piroxicam (p. 125·3).

Calmose *Welt, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium carbonate (p. 1856·2).
Antacid.

Calmosedan *Recalcine, Chile.*
Chlormezanone (p. 1045·1); diazepam (p. 1063·2).
Anxiety; muscle spasm.

Calmoseptine
Note: this name may be used for preparations of different composition.
Calmoseptine, Philipp.
Zinc oxide (p. 1729·1); calamine (p. 1697·2); menthol (p. 2553·2); phenol (p. 1763·3); thymol (p. 1772·2); chlorothymol (p. 1748·2).
Skin irritation; barrier preparation.

Calmoseptine, USA.
Menthol (p. 2553·2); zinc oxide (p. 1729·1).

Calmoseptine, Canad.†
Calamine (p. 1697·2); zinc oxide (p. 1729·1).

Calmotisan *Lehning, Fr.†*
Passion flower (p. 2584·1); melissa (p. 2552·3); valerian (p. 2640·2); asperula; bitter orange (p. 2575·3); red poppy (p. 2207·3).
Nervous disorders; sleep disorders.

Calmount *Arunabh, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); minerals.

Calmox
Note: this name may be used for preparations of different composition.
Biomiicron, India.
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Calmpent *Lloyd, Philipp.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Calmpose *Ranbaxy, India; Ranbaxy, S.Afr.†*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal; muscle spasm; status epilepticus; tetanus; premedication; convulsions; skeletal muscle spasm; alcohol withdrawal syndrome.

Calms Forte *Hylands, Canad.*
Avena sativa (p. 2451·1); calcarea phosphorica (p. 1784·2); chamomilla (p. 2474·1); ferrum phosphorica (p. 2077·1); humulus lupulus (p. 2546·1); kali phosphoricum (p. 1790·3); magnesia phosphoricum (p. 1787·3); natrum phosphoricum (p. 1791·2); passiflora (p. 2584·1).
Homoeopathic preparation.

Calms Forté 4 Kids *Hylands, Canad.*
Aconitum nap. (p. 2428·3); calc. phos. (p. 1784·2); chamomilla (p. 2474·1); cina (p. 2478·3); lycopodium (p. 2546·3); nat. mur. (p. 1795·1); pulsatilla (p. 2600·2); sulphur (p. 1721·1).
Homoeopathic preparation.

Calmtabs *Natural Life, Arg.*
Valerian (p. 2640·2); passion flower (p. 2584·1); celery (p. 2472·3); cataria; lupulus (p. 2546·1); dried orange peel (p. 2575·3).
Sedative.

Calmtec *Technica, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Calmtec-P *Technica, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Calm-U *Wilson, NZ.*
Diphenhydramine hydrochloride (p. 626·2); salicylamide (p. 129·2).
Anxiety; insomnia.

Calmuderm *Leo, Indon.†; Roi Surya, Indon.†*
⊗Urea (p. 1727·3).
Dry skin disorders; hyperkeratosis.

Calmurid
Note: this name may be used for preparations of different composition.
Galderma, Austral.; Galderma, Austria; Galderma, Irl.; Galderma, Israel†; Galderma, Neth.; Jaba, Port.; Galderma, Switz.; Galderma, UK.
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).
Dry skin; hyperkeratosis; ichthyosis.

Ronnet, Arg.
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Royal, Chile.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Calmurid HC *Galderma, Irl.; Galderma, Neth.; Galderma, UK.*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1); hydrocortisone (p. 1640·1).
Hyperkeratosis; skin disorders; dry eczema.

Calmuril *ACO Hud, Fin.; ACO Hud, Swed.*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).
Dry skin; ichthyosis; eczema; keratinisation disorders.

Calmvalera *Hevert, Ger.*
Cimicifuga (p. 2478·1); cocculus (p. 2483·1); cypripedium pubescens; ignatia (p. 2532·1); lilium tigrinum; passiflora incarnata (p. 2584·1); platinum metallicum (p. 2593·1); valeriana (p. 2640·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Calmy *Berksam, Turk.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).

Calmy Plus *Berksam, Turk.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); simeticone (p. 1886·2).

Calmylin *Rougier, Canad.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2).

Calmylin Ace *Rougier, Canad.*
Guaifenesin (p. 1666·2); pheniramine maleate (p. 637·2); codeine phosphate (p. 40·2).
Cough.

Calmylin with Codeine *Rougier, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).

Calmylin Original with Codeine *Rougier, Canad.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2).
Cough.

Calnat *Combiphar, Indon.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Cal-Nate *Ethex, USA.†*
Vitamins; minerals.

Calner *Medipharm, Chile.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; premedication; insomnia; alcohol withdrawal.

Calnet *Wintech, India.*
Suspension: Calcium (p. 1783·1); colecalciferol (p. 2113·1); lysine (p. 2079·3).

Wintech, India.
Tablets: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Calnic *Gracia, Indon.*
Calcium (p. 1783·1).
Calcium supplement.

Calnic Plus *Gracia, Indon.*
Calcium (p. 1783·1); ergocalciferol (p. 2113·3).
Calcium and vitamin D supplement.

Calnier-D *Vannier, Arg.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calnif *Cadila, India.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Calnisan *Gynopharm, Chile.†*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; metastatic bone pain; Paget's disease of bone; reflex sympathetic dystrophy.

Cal nit *Sandoz, Spain.†*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage; mental function impairment.

Calnor *Biological Homeopathic Industries, Canad.†*
Aconite (p. 2428·3); antimony potassium tartrate (p. 151·2); arnica montana (p. 2447·2); baptisia tinctoria (p. 2647·2); belladonna (p. 2453·3); bryonia (p. 2461·3); calcium sulfide crude (p. 1721·3); dulcamara (p. 2497·3); echinacea purpurea (p. 2498·1); ferrum phosphoricum (p. 2077·1); phytolacca decandra (p. 2593·2); poison oak (p. 2603·3); potassium iodide (p. 2336·3); pulsatilla (p. 2600·2); silicon dioxide (p. 2208·3); silver nitrate (p. 2615·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Calnova *Chemo-Drugs, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calnar *Argil, India.*
Preparation for enteral nutrition.

Calobalin *Sandoz, Switz.*
Orlistat (p. 2577·1).
Obesity.

CAL'Ocean *Nestle Proteika, Fr.†*
Calcium (from oyster shells) (p. 1783·1).
Calcium supplement.

Calodin *Syntho, India.*
Calcium chloride (p. 1783·1); potassium iodide (p. 2336·3); sodium chloride (p. 1795·1).

Calodis *Esteve, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calofra *Valeant, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Calogen
Note: this name may be used for preparations of different composition.
Nutricia, Austral.; Nutricia, Cz.
Long-chain triglycerides from vegetable oils.
Dietary supplement.

Support, Braz.; Nutricia, Irl.
Dietary fat supplement.
Food for special diets.

Nutricia, Fin.; Nutricia, Ital.; Nutricia, NZ; Nutricia Clinical, UK.
Arachis oil (p. 2446·1).
Dietary supplement; disorders of amino acid metabolism; carbohydrate malabsorption; ketogenic diet in epilepsy.

ProStrakan, Spain.†
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis.

Caloma Plus *Novell, Indon.*
Cod-liver oil (p. 2056·3); omega-3 fatty acids (p. 1460·1); vitamins; minerals.
Dietary supplement.

CaloMist *Fleming, USA.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Caloplast *Adco, S.Afr.†*
⊗Glycerol (p. 2517·2); boric acid (p. 2459·3).
Boils; carbuncles; skin inflammation.

Caloreen *Nestle, Fr.; IFET (ΙΦΕΤ), Gr.†; Nestle, UK.*
Dextrin (p. 2059·1).
Food for special diets.

Calorex
Note: this name may be used for preparations of different composition.
Kamakshi, India.
Capsules: Grape seed extract (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2).
Kamakshi, India.
Syrup: Vitamins; lycopene (p. 2546·2).
Konimex, Indon.†
Chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).
Cold and influenza symptoms.

Calorich-M *Zee, India.*
Calcium citrate (p. 1783·2); calcitriol (p. 2113·1); mecobalamin (p. 2108·1).

Calorub Forte *Hofmann, Chile.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Calorub Nueva Formula *Hofmann, Chile.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint disorders.

Calorub Sport *Hofmann, Chile.*
Methyl salicylate (p. 92·1); methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2); ethyl salicylate (p. 56·3).
Musculoskeletal and joint disorders.

Caloryne *TO-Chemicals, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Cal-Os *Siam Bheasach, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Calos *Fahrenheit, Indon.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis.

Cal-Os Plus D *Siam Bheasach, Thai.*
Calcium carbonate (p. 1824·3); vitamin D.

Calosbon *Teguhsindo, Indon.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); isoflavone (p. 2620·3).
Menopausal disorders; osteoporosis.

Caloshell *Emcure, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Caloshell-M *Emcure, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); trace elements.

Calosoft *Micro, India.*
Aloe vera (p. 1693·2); calamine (p. 1697·2); liquid paraffin (p. 2191·2).
Emollient.

Calosto *Piramal, India.*
Calcitriol (p. 2113·1).
Hyperparathyroidism; hypoparathyroidism; pseudohypoparathyroidism; rickets; hypocalcaemia.

Caloston *Sanus, Gr.*
Calcitonin (salmon) (p. 1178·1).

Calostrum *Meprofarm, Indon.*
Bovine colostrum (p. 2380·3); docosahexaenoic acid (p. 1460·1); cod-liver oil (p. 2056·3); lysine hydrochloride (p. 2079·3); vitamins; minerals.
Nutritional supplement.

Calotrat *Hertz, Braz.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Hyperkeratosis.

Calox Super *Qualiphar, Belg.*
Denture fixative.

Caloxa *Accord, S.Afr.*
Bicalutamide (p. 749·1).

Calperos *Bouchara-Recordati, Fr.; Teva, Pol.; Bouchara-Recordati, Singapore; Robapharm, Switz.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; rickets; osteomalacia; allergic disorders; calcium supplement.

Calperos D_3 *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Robapharm, Switz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Calpharma *Quimpharma, Mex.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis; rickets; osteomalacia; tetany.

Calphi-M *Merion, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calphos *McNeil & Argus, India.*
Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3).

Calphosan *Glenwood, USA.*
Calcium glycerophosphate (p. 1783·3); calcium lactate (p. 1784·1).
Calcium deficiency.

Calphosfomin *Piramal, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).

Calphron *Nephro-Tech, USA.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Calpic *Elfin, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calpime *Alna, India.*
Cefepime (p. 239·2).
Bacterial infections.

Calplex
Note: this name may be used for preparations of different composition.
Khandelwal, India.
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Mahakam Beta, Indon.
Coral calcium (p. 1783·1); soy germ (p. 2620·3); colecalciferol (p. 2113·1); phytomenadione (p. 2122·2); magnesium (p. 1786·3); zinc (p. 2126·1); boron (p. 2052·3).
Calcium supplement; osteoporosis.

Calplus *Lifestyles, Canad.†*
Vitamins; minerals.

Calplus Kid *Elder, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calplus MZ *Nupharma, Thai.*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement.

CalplusD3 *Guidotti, Ital.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calpol *McNeil, Cz.†; GSK, India; McNeil Healthcare, Irl.; GSK, Philipp.; McNeil, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Thai.; GSK, Turk.; McNeil, UK.*
Paracetamol (p. 115·1).
Fever; pain.

Calpol Night *Pfizer Consumer, UK.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Pain; fever; cold symptoms.

Calpol Plus *GSK, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Calporo *Eagle, Austral.†*
Vitamins; minerals; rose fruit (p. 2607·1); chondrus (p. 2176·3); echinacea (p. 2498·1); equisetum (p. 2500·1); lysine (p. 2079·3); bone powder.
Bone disorders; mineral supplement.

Calporosis D *Mersifarma, Indon.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement; calcium and vitamin D deficiency.

Calpres *Temis, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Calprimum *D&A Pharma, Fr.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Calpro *Neon, India.*
Vitamins; minerals; carbohydrate; protein hydrolysate; sorbitol.

Calpro ZE *Neon, India.*
Vitamins; ferrous fumarate (p. 2060·3); zinc sulfate (p. 2126·2); protein hydrolysate.

Calprofen *McNeil, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Calral *Hiral, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calral-Cal *Hiral, India.*
Calcium (p. 1783·1); calcitriol (p. 2113·1).
Calcium and vitamin D supplement.

Calraze *Agio, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2).

Calrebo *Shince, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).

Calrine *Rhine, India.*
Calcium (p. 1783·1) colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Calris *Symbiosis, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calriz *Ritz, India.*
Suspension: Calcium (p. 1783·1); phosphorus (p. 2589·2).
Ritz, India.
Tablets: Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); zinc sulfate (p. 2126·2).

Calron *East India Pharma, India.*
Calcium gluconate (p. 1783·3); calcium lactobionate (p. 1784·2); ferric ammonium citrate (p. 2060·1); vitain A.

Calrub *Pfizer Consumer, UK.*
Eucalyptus (p. 2501·1); menthol (p. 2553·2).
Respiratory-tract congestion.

Cal-Rutina *Grossman, Mex.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Capillary fragility.

Calsal
Note: this name may be used for preparations of different composition.
Balu, Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.
Salud, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Calsal Plus *Salud, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine (p. 2079·3); magnesium (p. 1786·3); zinc (p. 2126·1).

Calsalettes *Torbet Laboratories, UK.*
Aloin (p. 1816·2).
Constipation.

Calsan *Novartis, Braz.; Novartis Consumer, Canad.; Novartis, Indon.†; Novartis, Mex.; Sandoz, Philipp.*
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency; osteoporosis.

Calsat *Vensat, India.*
Syrup: Calcium (p. 1783·1); colecalciferol (p. 2113·1); lysine (p. 2079·3); vitamin B_{12} (p. 2107·2).
Vensat, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1); minerals.

Calsaton *Votania, Gr.*
Calcitonin (salmon) (p. 1178·1).

Calscot *Scoshia, India.*
Syrup: Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Scoshia, India.
Tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); caffeine (p. 1203·3).

Calscot-AX *Scoshia, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Cals-D3 *Bilim, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Calsed *Sumitomo, Jpn.*
Amrubicin hydrochloride (p. 741·3).
Lung cancer.

Calsein *Manuell, Mex.†*
Calcium caseinate (p. 2055·2).

Calshake *Fresenius Kabi, Irl.; Fresenius Kabi, UK.*
Preparation for enteral nutrition.

Calshine *Eris, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).

Calsical *Teguhsindo, Indon.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Osteoporosis; calcium supplement.

Calsin *Stadmed, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calsivas *Fahrenheit, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Calskin *Ind-Swift, India.*
Calamine (p. 1697·2); camphor (p. 2466·2); diphenhydramine (p. 626·1).

Calslot *Takeda, Jpn.*
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Calsol *Belfar, Braz.*
Calamine (p. 1697·2); diphenhydramine (p. 626·1); camphor (p. 2466·2).

Calsom *Biological Homeopathic Industries, Canad.†*
Aconite (p. 2428·3); coffee (p. 2648·2); gelsemium sempervirens (p. 2511·2); german chamomile (p. 2474·1); hops (p. 2546·1); passion flower (p. 2584·1); silver nitrate (p. 2615·3); sulfur (p. 1721·1); sumbul; valerian (p. 2640·2).
Homoeopathic preparation.

Calsorp *Thaipharmed, Thai.*
Calcium citrate (p. 1783·2).
Calcium deficiency; rickets; osteoporosis.

Calstat *Ind-Swift, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2).

Calstron *Rallis, India.*
Hydroxyapatite (p. 2529·3).
Osteoporosis.

Calsuba *Group, S.Afr.†*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Calsum *Sriprasit, Thai.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Calsun-ZM *Laksun, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Cal-Sup *3M, Austral.; iNova, Malaysia†; iNova, Singapore.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis.

Calsuper Forte *Biological E, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); manganese (p. 2081·2); zinc (p. 2126·1).

Calsure *Winsome, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).

Calsure-M *Winsome, India.*
Colecalciferol (p. 2113·1); boron; calcium; copper; magnesium; zinc (p. 2126·1).

Calsure-OP *Winsome, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Calsus *Indo French, India.*
Vitamins; minerals.

Calswift *Ind-Swift, India.*
Suspension: Calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1); cyanocobalamin (p. 2107·2).
Ind-Swift, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calsym *Symbiosis, India.*
Syrup: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.
Symbiosis, India.
Tablets: Colecalciferol (p. 2113·1); minerals.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Calsyn *Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia of malignancy; osteoporosis; hypercalcaemia.

Calsynar *Sanofi-Aventis, Belg.†; Sanofi-Aventis, Braz.; Sanofi-Aventis, Gr.; Piramal, India; Sanofi-Aventis, Spain; Eczacibasi, Turk.; Sanofi Pasteur, Turk.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; osteoporosis; bone pain in malignancy; hypercalcaemia of malignancy; reflex sympathetic dystrophy.

Caltab
Note: this name may be used for preparations of different composition.
Aglowmed, India.
Suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc gluconate (p. 2126·2).
Aglowmed, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.
Millimed, Thai.
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Caltab Effervescent *Millimed, Thai.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); vitamin C (p. 2110·3); vitamin B_6 (p. 2105·3).
Dietary supplement; osteoporosis.

Caltab Forte *Millimed, Thai.†*
Calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2).
Calcium deficiency; osteoporosis.

Caltab W/Vitamin D *Millimed, Thai.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Caltac *Profic Organic, India.*
Suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).
Profic Organic, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Caltaur *Taurus, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Caltec
Note: this name may be used for preparations of different composition.
Zwitter, Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.
Adley, India.
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2); lidocaine hydrochloride (p. 1988·2).

Calten *Ipca, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Caltera *Verisfield, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Calthicon *Pharmasant, Thai.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Calthrox *Cadila, India.*
Ointment: Erythromycin (p. 291·2); zinc sulfate (p. 2126·2).
Acne.
Cadila, India.
Oral suspension; tablets: Erythromycin stearate (p. 291·3).
Bacterial infections.

Caltin *Neiss, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Caltin-CZ *Neiss, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); zinc (p. 2126·1).

Caltine *Ferring, Canad.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia.

Caltium D *Frankin, Hong Kong.†*
Calcium (p. 1783·1); vitamin D (p. 2112·3).

Calton *Pharminicio, Spain.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Caltop *Lupin, India.*
Syrup: Calcium (p. 1783·1); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).
Lupin, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Caltop-ZM *Vensat, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).

Caltoson Balsamico *Rottapharm, Spain.†*
Cineole (p. 2479·1); benzocaine (p. 1980·2); pholcodine (p. 1675·1); cherry laurel (p. 2475·2); terpineol (p. 2627·2); menthol (p. 2553·2).
Respiratory-tract disorders.

Caltrate
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer Consumer, Canad.; Pfizer Sante, Fr.; Pfizer Consumer, Hong Kong; Lederle, Israel†; Pfizer Consumer, Malaysia; Wyeth Consumer, Mex.; Wyeth Consumer, NZ; Pfizer Consumer, S.Afr.; Pfizer Consumer, Singapore; Pfizer Consumer, Thai.; Lederle, USA.
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis; osteomalacia; hypocalcaemia; phosphate binder; rickets; tetany.
Pfizer, Cz.; Pfizer Consumer, Irl.; Pfizer, Neth.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.
Wyeth Consumer, Ital.; Wyeth, Turk.†
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; calcium supplement.

Caltrate D *Pfizer, China.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

Caltrate + D *Pfizer Consumer, Hong Kong.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis.
Wyeth Consumer, Braz.; Pfizer Consumer, Malaysia; Wyeth Consumer, Mex.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets; tetany.
Wyeth-Whitehall, Arg.; Pfizer Consumer, Thai.; Wyeth, Venez.
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Osteoporosis; calcium supplement; hypocalcaemia.

Caltrate + Iron & Vitamin D *Lederle, USA.*
Calcium carbonate (p. 1824·3); ferrous fumarate (p. 2060·3); vitamin D (p. 2112·3).
Calcium and iron deficiency.

Caltrate + M *Wyeth Consumer, Braz.; Wyeth Consumer, Mex.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); minerals.
Dietary supplement; calcium, vitamin D, and mineral supplement; osteoporosis; rickets; osteomalacia; tetany.

Caltrate Plus *Wyeth Consumer, UK; Lederle, USA.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); boron (p. 2052·3); copper (p. 2057·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1).
Calcium deficiency; bone disorders.
Pfizer Consumer, Austral.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); manganese sulfate (p. 2081·2).
Calcium deficiency; osteoporosis; osteomalacia.
Pfizer Consumer, Canad.
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3); copper oxide (p. 2057·1); magnesium oxide (p. 1857·3); manganese sulfate (p. 2081·2); zinc oxide (p. 1729·1).
Pfizer Consumer, Hong Kong; Wyeth Consumer, Irl.†; Wyeth, Philipp.; Pfizer Consumer, Thai.
Calcium (p. 1783·1); vitamin D (p. 2112·3); copper (p. 2057·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis.
Pfizer Consumer, Malaysia; Pfizer Consumer, Singapore.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); copper (p. 2057·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1).
Dietary supplement; calcium supplement; calcium deficiency.
Pfizer, Cz.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); manganese sulfate (p. 2081·2); borax (p. 2459·2).
Calcium and vitamin D deficiency; osteoporosis.
Whitehall, Pol.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2); copper (p. 2057·1); boron (p. 2052·3).
Calcium, vitamin D, and mineral deficiency; osteoporosis.
Wyeth, NZ.
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3); magnesium (p. 1786·3); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2).
Dietary supplement.

Caltrate + S *Wyeth Consumer, Mex.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); soya bean (p. 2092·3).
Calcium and vitamin D supplement; osteoporosis; rickets; osteomalacia; tetany.

Caltrate Select *Pfizer Consumer, Canad.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement.

Caltrate + Soy *Wyeth Consumer, Hong Kong†; Wyeth Consumer, Singapore.†*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3); soya isoflavones (p. 2620·3).
Calcium deficiency; osteoporosis; osteomalacia; calcium and vitamin D supplement.

Caltrate + Vit D *Pfizer Consumer, Singapore.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement; calcium deficiency.
Lederle, Israel.†
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Caltrate with Vitamin D *Pfizer Consumer, Austral.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; calcium supplement; osteoporosis; osteomalacia.
Pfizer Consumer, Canad.; Wyeth, NZ.
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium and vitamin D supplement; osteoporosis.

Caltrate + Vitamin D *Lederle, USA.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium deficiency.

Caltrate Vitamine D_3 *Pfizer Sante, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Caltrate + Witamina D *Whitehall, Pol.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; osteoporosis.

Caltrax *Pyridam, Indon.*
Calcium (p. 1783·1); vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin B_6 (p. 2105·3).
Dietary supplement.

Caltren *Libbs, Braz.*
Nitrendipine (p. 1456·3).
Hypertension; heart failure; angina pectoris; myocardial infarction.

Caltrex *United Drug, Thai.*
Calcium carbonate (p. 1824·3).
Dietary supplement.

Caltrioject *Faran, Gr.*
Calcitriol (p. 2113·1).
Vitamin D deficiency.

Caltro *Geneva, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Caltrol *Orchid, India.*
Calcitriol (p. 2113·1).
Hyperparathyroidism; hypoparathyroidism; pseudohypoparathyroidism; rickets; hypocalcaemia.

Caltron *Pyridam, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2); boron (p. 2052·3).
Calcium and vitamin D deficiency; calcium supplement.

Caltum *Ethica, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Caltusine *Sanofi-Aventis, Mex.*
Guaifenesin (p. 1666·2); oxolamine citrate (p. 1671·2).
Respiratory-tract disorders.

Calubloc *Actavis, Pol.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Caludec *Samarth, India.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Caluft *Lupin, India.*
Calcitriol (p. 2113·1); minerals.

Calumid *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Thai.; Gedeon Richter, Ukr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Cal-ups *T Man, Thai.*
Calcium carbonate (p. 1824·3).
Antacid; calcium supplement.

Cal-ups Join *T Man, Thai.*
Calcium carbonate (p. 1824·3); cartilage (shark) (p. 2471·3).

Cal-ups-D *T Man, Thai.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Dietary supplement.

Cal-ups-D-Soy *T Man, Thai.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3); soya protein (p. 2092·3).
Dietary supplement.

Caluran *Ranbaxy, India.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Calutex *Aspen, Austral.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Calutide *Cipla, India.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Calutol *Asofarma, Mex.; Nolver, Venez.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Calvakehl *Sanum-Kehlbeck, Ger.*
Calvatia gigantea.
Homoeopathic preparation.

Calvan *Chemiphar, China; Chemiphar, Jpn.*
⊗Bevantolol hydrochloride (p. 1323·2).
The name Calvin has also been used for this preparation.
Hypertension.

Calvasc *Douglas, NZ.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Calvepen *Clonmel, Irl.*
Phenoxymethylpenicillin calcium (p. 338·3).
Bacterial infections.

Calvera *Psyco Remedies, India.*
Aloe vera (p. 1693·2); calamine (p. 1697·2); light liquid paraffin (p. 2191·2).

Calversum *Servier, Turk.*
Perindopril arginine (p. 1466·3); amlodipine (p. 1304·1).

Calvical *Intra-Labs, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calvicef *Help, Gr.*
Ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3); calcium hydroxide (p. 2465·1); calcium hypophosphite (p. 2530·3).

Calvidin *Rottapharm, Gr.; Rottapharm, Irl.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Calvin *Biolab, Thai.*
Calcium (p. 1783·1).
Osteoporosis.

Calvin + D *Biolab, Thai.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Osteoporosis.

Calvin Plus *Biolab, Thai.*
Calcium (p. 1783·1); vitamin D (p. 2112·3); boron (p. 2052·3); copper (p. 2057·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1).
Osteoporosis.

Calvit *Multicare, Philipp.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement; osteoporosis.

Calvit II *Frankin, Hong Kong.†*
Calcium (p. 1783·1); vitamin D (p. 2112·3).

Calvita
Note: this name may be used for preparations of different composition.
Active, India.
Suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Active, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calvita B12 *De Mayo, Braz.†*
Calcium lactate (p. 1784·1); calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).

Calvitalis *Julphar, UAE.*
Vitamins; calcium (p. 1783·1).
Dietary supplement.

Calvite P & D *Cypress, USA.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).

Calvit-L *Technica, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).

Calvitos *Soho, Indon.*
Colecalciferol (p. 2113·1); phytomenadione (p. 2122·2); calcium (p. 1783·1); zinc (p. 2126·1).
Calcium supplement; osteoporosis.

Calvitran *Landson, Indon.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); folic acid (p. 2063·1); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); fructo-oligosaccharides (p. 2508·1).
Nutritional supplement.

Calvive *Novartis, Switz.*
Calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2).
Calcium deficiency; osteoporosis.

Calvon *Zytras, India.*
Vitamin D (p. 2112·3); minerals.

Calvon-A *Zytras, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Calvon-D3 *Zytras, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Calvonin *Kalbe, Indon.*
Isoflavone (p. 2620·3).
Menopausal disorders; osteoporosis.

Calypsol *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.†; Gedeon Richter, Rus.; Gedeon Richter, Thai.; Gedeon Richter, Ukr.†*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia; pain; bronchospasm; hiccups; priapism; analgesic sedative.

Calyptol *Sanofi-Aventis, Ital.; Techni-Pharma, Mon.*
Cineole (p. 2479·1); terpineol (p. 2627·2); pine oil (p. 2591·1); thyme oil (p. 2630·3); rosemary oil (p. 2607·3).
Respiratory-tract congestion.

Calys *MMC, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calyx *Biosciences Pharmakon, India.*
Cyclomethicone (p. 2209·2); isopropyl myristate (p. 2190·3); light liquid paraffin (p. 2191·2); vitamin E (p. 2119·1).

Caly-ZM *Bennet, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).
Dietary supplement.

Cal-Z *Waves, India.*
Suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.
Waves, India.
Tablets: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Calzem
Note: this name may be used for preparations of different composition.
Cazi, Braz.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.
Cipla, India.
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Calzorb *Alembic, India.*
Calcium (p. 1783·1).
Gastric hyperacidity; hyperphosphataemia.

Calzy *Zee, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

CAM
Note: this name may be used for preparations of different composition.
Cambridge Healthcare, UK.
⊗Ephedrine hydrochloride (p. 1663·2).
Bronchospasm; cough.

Cam
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Cam Plus *Mediez, India.*
⊗Alprazolam (p. 1035·2); propranolol (p. 1479·1).

Cam Sun *Prodemdis, Canad.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Cama Arthritis Pain Reliever *Novartis, USA.*
Aspirin (p. 22·2).
Aluminium hydroxide (p. 1817·2) and magnesium oxide (p. 1857·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Arthritis; pain.

Camagel *KRKA, Ukr.*
Aluminium acetotartrate (p. 2440·1); chamomile (p. 2474·1).
Sun burn; nappy rash; insect stings; skin irritation.

Camazol *Xepa-Soul Pattinson, Singapore.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Cambem *UCI, Braz.*
Cambendazole (p. 152·2).
Strongyloidiasis.

Cambia *Mipharm, USA.*
Diclofenac potassium (p. 48·3).
Pain.

Cambic *LBS, Thai.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Camcolit *Norgine, Belg.; Norgine, Irl.; Norgine, Neth.; Norgine, S.Afr.; Norgine, Singapore; Norgine, UK.*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression; mania; aggressive or self-mutilating behaviour; disturbed behaviour.

Camegel-MPS *Radicura, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Camelia *Bernabo, Arg.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Cameloc *Dexa, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Camelox *PannonPharma, Hung.*
Meloxicam (p. 86·3).

Cameo
Note: this name may be used for preparations of different composition.
Medco, USA.
Emollient.
Positif, India.
Ceftriaxone (p. 253·3).
Bacterial infections.

Cameo-S *Positif, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cameton *Moschimfarm, Rus.*
Camphor (p. 2466·2); menthol (p. 2553·2); chlorobutanol (p. 1747·2); eucalyptus oil (p. 2501·2).
Upper respiratory-tract disorders.

Camforte *Svizera, India.*
Cabergoline (p. 899·3).
Hyperprolactinaemia.

Camgesic *Clinifood, Singapore.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Musculoskeletal pain and spasm.

Camidexon *Metiska, Indon.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Camidlin *Gedeon Richter, Hung.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Camigesik *Metiska, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Camilia
Note: this name may be used for preparations of different composition.
Boiron, Canad.
Belladonna (p. 2453·3); chamomilla vulgaris (p. 2474·1); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.
Boiron, Fr.; Boiron, Switz.
Chamomilla vulgaris (p. 2474·1); phytolacca decandra (p. 2593·2); rheum officinale (p. 1884·2).
Homoeopathic preparation.

Camiline *Arkopharma, Fr.*
Green tea (p. 2648·2).
Slimming aid; asthenia.

Camirox *Norma (Νορμα), Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Camisan *Taiwan Biotech, Malaysia.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail infections.

C-Amlo *Corona, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Camlo *Grandix, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

C-Amlo Plus *Corona, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Camlodin *Square, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Camnovate *Clinifood, Singapore.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Camoderm *Goldshield, Hong Kong.†*
Chamomile (p. 2474·1).
Nappy rash; cracked and sore nipples; sore skin conditions.

Camolid *Horus, Fr.*
Chamomile (p. 2474·1).
Eyelid cleanser.

Camolyn *Oftalmi, Venez.*
Chamomile (p. 2474·1); hamamelis (p. 2523·3).
Eye irritation.

Camolyn Plus *Oftalmi, Venez.*
⊗Naphazoline hydrochloride (p. 1669·3); chamomile (p. 2474·1); hamamelis (p. 2523·3).
Eye irritation.

Camomila *Catarinense, Braz.*
Aloes (p. 1816·1); paregoric (p. 111·3); aniseed (p. 2444·2); peppermint leaf (p. 1877·1); melissa (p. 2552·3); chamomile (p. 2474·1); centaury (p. 2473·2); condurango (p. 2485·3); Fuller's earth (p. 1553·2); gentian (p. 2512·1); absinthium (p. 2426·1); quassia (p. 2601·1); rhubarb (p. 1884·2); bixa orellana.
Digestive disorders.

Camomilina C *Theraskin, Braz.*
Chamomile (p. 2474·1); liquorice (p. 1853·2); colecalciferol (p. 2113·1); vitamin C (p. 2110·3); calcium phosphate (p. 1784·2).
Nutritional supplement.

Camoquin *Pfizer, India.†*
Amodiaquine hydrochloride (p. 647·2).
Malaria.

Camox *Utopian, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Campal *Meyer, Venez.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain; inflammation.

Campanex *Cosmopharm, Gr.*
Cimetidine (p. 1827·1).

Campar *Forgo, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Campath *Schering, Arg.; Schering, Braz.†; Bayer Schering, Rus.; Genzyme, USA.*
Alemtuzumab (p. 737·1).
Chronic lymphocytic leukaemia.

Camphoderm N *Li-il, Ger.*
Camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders; catarrh.

Camphodinyl *Distri B3, Fr.†*
Sulfogaiacol (p. 1678·1); codeine (p. 40·2).
Cough.

Campho-Phenique *Sterling, USA; Winthrop Consumer, USA.*
Phenol (p. 1763·3); camphor (p. 2466·2).
Herpes labialis; cuts; burns; insect bites; pain; infections.

Campho-Phenique Cold Sore Treatment & Scab Relief *Bayer, USA.*
Pramocaine hydrochloride (p. 1993·3).

Camphopin *Schoning-Berlin, Ger.†*
Methyl salicylate (p. 92·1); benzyl nicotinate (p. 29·3); camphor (p. 2466·2).
Rheumatic disorders; sciatica; neuralgia; tendinitis; frostbite.

Camphor Linctus Compound *Gold Cross, Austral.*
Camphor (p. 2466·2); tolu balsam (p. 1679·2).
Cough.

Camphrice Du Canada *Homme de Fer, Fr.*
Camphor (p. 2466·2).
Skin disorders.

Campicillin *Cadila, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Campicillin Plus *Cadila, India.*
Ampicillin trihydrate (p. 218·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Campilox *Cadila, India.*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Campilox-LB *Cadila, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Campirex *IQFA, Mex.*
Piroxicam (p. 125·3).
Inflammation.

Campral *Merck, Arg.; Alphapharm, Austral.; Merck, Austria; Merck, Belg.; Mylan, Canad.; Merck, Chile; Merck, Cz.; Merck Sante, Denm.; Merck Serono, Ger.; Merck, Hung.†; Merck Serono, Irl.; Merck, Mex.†; Merck, Neth.; Merck, Norw.; Merck, Pol.; Merck, Port.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Turk.; Merck, UK; Forest Laboratories, USA.*
Acamprosate calcium (p. 1034·2).
Alcoholism.

Camptera *Tuteur, Rus.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Campto *Pfizer, Austria; Pfizer, Belg.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Yakult, Jpn; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.†; Pfizer, Switz.; Pfizer, Thai.; Aventis, Turk.; Pfizer, UK; Pfizer, Ukr.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer; small cell lung cancer; gastric cancer.

Camptolem *Teva, Mex.†*
Irinotecan hydrochloride (p. 812·2).
Malignant neoplasms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Camptosar *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Mex.; Pfizer, NZ; Pfizer, USA; Pfizer, Venez.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer; lung cancer; pancreatic cancer.

Camptotecan *Teva, Rus.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Camrelease-TR *Natco, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; skeletal muscle spasm; seizures; alcohol withdrawal syndrome.

Camrese *Teva, USA.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, ethinylestradiol.
Biphasic oral contraceptive.

Camri *Zydus, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Camrox *Active, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Camryn *Johnson & Johnson, Gr.*
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Camsun *Laksun, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Camzid *Aaron, India.*
Colecalciferol (p. 2113·1); minerals.

Can Vag *Marching, Hong Kong.†*
Clotrimazole (p. 576·2).

Canadiol *Esteve, Spain.*
Itraconazole (p. 583·3).
Fungal infections.

Canadol *Candor, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Canalba *Aspen, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Canamine *Pharmahof, Thai.*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2).
Pruritus.

Canasa *Axcan, USA.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Canasderm *Marching, Hong Kong.†*
Clotrimazole (p. 576·2).

Canasone *TNP, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Canasone CB *TNP, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Fungal skin infections.

Canazol
Note: this name may be used for preparations of different composition.
Sofar, Ital.
Fluconazole (p. 578·2).
Fungal infections.
TO-Chemicals, Thai.
Clotrimazole (p. 576·2).
Fungal skin, oropharyngeal, and vaginal infections; trichomoniasis.

Canazol-BE *TO-Chemicals, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone valerate (p. 1624·1).
Fungal skin infections.

Canazole *Lupin, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Canazole Clotrimazole *Pinewood, Irl.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Canbicef *Candor, India.*
Syrup: Cefixime (p. 240·3).
Bacterial infections.
Candor, India.
Tablets: Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Canbiox *Apatex, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Canbol *Candor, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Canbol Plus *Candor, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Canbol-F *Candor, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Canbra *Candor, India.*
Preparation for enteral nutrition.

Cancap *Ind-Swift, India.*
Fluconazole (p. 578·2).
Fungal infections.

Cancap-Kit *Ind-Swift, India.*
1 Capsule, fluconazole (p. 578·2); 2 tablets, tinidazole (p. 949·2).

Cancap-VT *Ind-Swift, India.*
Clotrimazole (p. 576·2).

Cancid *Sunthi Sepuri, Indon.†*
Fluconazole (p. 578·2).
Fungal infections.

Cancidas *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, India; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Jpn; MSD, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; MSD, Ukr.; Merck, USA; MSD, Venez.*
Caspofungin acetate (p. 574·3).
Candidiasis; aspergillosis.

Cancina *Mayo, Mex.†*
Kanamycin (p. 314·3).
Bacterial infections.

Cancon *Candor, India.*
Vitamin B substances (p. 2102·3); silymarin (p. 1561·2).

Cancyt *Miracalus, India; Naprod, Philipp.*
Cytarabine (p. 774·1).
Leukaemias.

Candacide *Be-Tabs, S.Afr.*
Nystatin (p. 590·3).
Oral candidiasis.

Candacort *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore; Hoe, Thai.*
⊗Clotrimazole (p. 576·2); hydrocortisone (p. 1640·1).
Fungal skin infections.

Candasia *Willow, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Candasia-B *Willow, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2).
Fungal skin infections.

Candaspor *Be-Tabs, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Candazol
Note: this name may be used for preparations of different composition.
Verisfield, Gr.
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration.

Candazole *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Candelong *Brown & Burk, Philipp.*
Candesartan cilexetil (p. 1330·2).
Hypertension.
Micro, India.
Candesartan (p. 1330·2).
Hypertension; heart failure.

Candelong-H *Micro, India.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).

Candemox *Sandoz, Denm.; Sandoz, Fin.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Candemox Comp *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Swed.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candepres HCT *Sandoz, Pol.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candepressin *Liptis, USA.*
Candesartan cilexetil (p. 1330·2).

Candepressin Plus *Liptis, USA.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Canderel *Ali, Turk.*
Aspartame (p. 2169·2).
Sugar substitute.

Canderm *Legrand, Braz.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).

Candermil *LKM, Arg.*
Nystatin (p. 590·3).
Fungal infections.

Candesar *Ranbaxy, India.*
Candesartan (p. 1330·2).
Hypertension.
Ranbaxy, Ukr.
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Candesar H *Ranbaxy, Ukr.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Candesar-H *Ranbaxy, India.*
⊗Candesartan (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candesarstad *Pharmacodane, Swed.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Candesartan Plus *Teva, Israel.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candestad *Stada, Fin.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Candestad Comp *Stada, Fin.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candestan *Medley, India.*
Candesartan (p. 1330·2).
Hypertension; heart failure.

Candex *Burapha, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.
Pasteur, Chile.
Candesartan cilexetil (p. 1330·2).
Hypertension.

Candex Plus *Burapha, Thai.*
⊗Clotrimazole (p. 576·2) betamethasone valerate (p. 1624·1).
Fungal skin infections.

Candex-D *Pasteur, Chile.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candexetil *Ratiopharm, Denm.†; Ratiopharm, Fin.; Teva, Swed.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Candexetil Comp *Ratiopharm, Fin.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candexetil comp *Ratiopharm, Denm.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candexil *Deva, Turk.*
Candesartan cilexetil (p. 1330·2).

Candexil Plus *Deva, Turk.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).

Candez
Note: this name may be used for preparations of different composition.
Imperial, Philipp.
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.
Ind-Swift, India.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Candibec *Glenmark, Philipp.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).
Fungal skin infections.

Candibene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Ratiopharm, Rus.; Ratiopharm, Ukr.*
Clotrimazole (p. 576·2).
Fungal and bacterial skin and vaginal infections; vaginal trichomoniasis.

Candibiotic *Glenmark, India; Glenmark, Rus.; Glenmark, Ukr.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); lidocaine hydrochloride (p. 1988·2).
Ear infections; earache.

Candiclo *Sterling, India.*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Candicon *Daffohils, India.*
Fluconazole (p. 578·2).
Fungal infections.

Candicort *Ache, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Candid *Glenmark, India; Glenmark, Malaysia; Glenmark, Rus.; Glenmark, Singapore; Glenmark, Thai.; Glenmark, Ukr.*
Clotrimazole (p. 576·2).
Fungal ear, mouth, skin, and vaginal infections; trichomoniasis.

Candid B *Glenmark, India; Glenmark, Rus.; Glenmark, Ukr.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2).
Fungal skin and scalp infections.
Glenmark, Malaysia.
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Fungal skin, scalp, nail, and vaginal infections; erythrasma.

Candid Ear Drops *Glenmark, India.*
Clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).
Fungal ear infections.

Candid V6 *Glenmark, Philipp.; Glenmark, Rus.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Candida Yeast Relief *Homeocan, Canad.*
Baptisia tinctoria (p. 2647·2); bryonia alba; candida albicans; echinacea angustifolia (p. 2498·1); thuja occidentalis (p. 2629·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Candid-CL *Glenmark, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).

Candiderm
Note: this name may be used for preparations of different composition.
Ache, Braz.
Ketoconazole (p. 585·3).
Fungal skin infections.
Glenmark, Rus.
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.
Glenmark, Ukr.
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); gentamicin (p. 304·2).
Infected and inflamed skin disorders.

Candiderma *Glenmark, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); gentamicin sulfate (p. 304·2).
Bacterial and fungal skin infections.

Candiderma + *Glenmark, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Bacterial and fungal skin infections.

Candidias *Fabra, Arg.*
Nystatin (p. 590·3).
Fungal infections.

Candidin *Taprak, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Candid-TV *Glenmark, India.*
Clotrimazole (p. 576·2); selenium sulfide (p. 1719·3).
Scalp disorders.

Candifem *Meyer, India.*
Miconazole (p. 588·3); ornidazole (p. 943·1).

Candifen *Greenpharma, Braz.*
Metronidazole (p. 936·1).

Candifix *Arafarma, Spain.*
Fluconazole (p. 578·2).
Fungal infections.

Candigen-BG *Galantica, India.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Candikit-N *Unijules, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Candilax *Cevallos, Arg.†*
Sennosides (p. 1885·2); docusate sodium (p. 1836·2).
Constipation.

Candimax *Zentiva, Cz.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections infections.

Candimicol *Quesada, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Candimon *Andromaco, Mex.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Candimyc *Viofar, Gr.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Candinil *Inga, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Candinox *Deltapharm, Hong Kong†; Charoen, Thai.*
Clotrimazole (p. 576·2).
Fungal mouth, throat, and vaginal infections; trichomoniasis.

Candio *Hermal, Austria.*
Nystatin (p. 590·3).
Fungal infections.

Candio-Hermal *Almirall Hermal, Ger.*
Nystatin (p. 590·3).
Fungal infections.

Candio-Hermal Plus *Almirall Hermal, Ger.*
⊗Nystatin (p. 590·3); fluprednidene acetate (p. 1637·3).
Inflammatory skin disorders with fungal infection.

Candipar *Pharmacore, Indon.*
Fluconazole (p. 578·2).
Fungal infections.

Candiphen *Sons, Mex.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Candiplas *Medochemie, Singapore.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Candipres *Precimex, Mex.*
Amphotericin B (p. 569·2).
Fungal infections.

Candist *Clonmel, Irl.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Candist Plus *Clonmel, Irl.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Candistat *Merck, India.*
Capsules: Itraconazole (p. 583·3).
Fungal infections.

Merck, India.
Cream: Miconazole (p. 588·3).
Fungal skin infections.

Candistatin *Idaman, Singapore.*
Nystatin (p. 590·3).
Vaginal candidiasis.

Candistin *Pharos, Indon.*
Nystatin (p. 590·3).
Candidiasis.

Canditral *Glenmark, India; Glenmark, Malaysia; Glenmark, Rus.; Glenmark, Singapore; Glenmark, Thai.†*
Itraconazole (p. 583·3).
Fungal infections.

Canditrat *Teuto, Braz.*
Nystatin (p. 590·3).
Fungal infections.

Candiva *Glenmark, Philipp.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Candivate *Cosme, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Candix *Prodotti, Braz.†*
Fluconazole (p. 578·2).
Fungal infections.

Candizol *Ache, Braz.; Sandoz, Indon.†; Teva, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Candizole
Note: this name may be used for preparations of different composition.
Micro, Rus.; Aspen Consumer, S.Afr.
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Bal, India.
Miconazole (p. 588·3).
Fungal skin infections.

Mithra, Belg.
Fluconazole (p. 578·2).
Fungal infections.

Candizole-T *Unichem, India.†*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Vaginal candidiasis.

Candor *Argil, India.*
Vitamins; minerals; spirulina (p. 2622·1).

Candoral *Ache, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Candycef *Arunabh, India.*
Cefixime (p. 240·3).
Bacterial infections.

Candyl *Douglas, NZ.*
Piroxicam (p. 125·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Candyvit-C *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamin C (p. 2110·3).
Vitamin C supplement.

Canef *Normal, Port.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Canefo *Medopharm, India.*
Aceclofenac (p. 16·2).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Canefol *Caplin, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; renal colic.

Canefo-Plus *Medopharm, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Canelin *Square, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Canephron N *Bionorica, Ger.; Bionorica, Rus.; Bionorica, Ukr.*
Centaury (p. 2473·2); lovage (p. 2545·3); rosemary (p. 2607·2).
Urinary-tract disorders; renal calculi.

Canergy *Meprofarm, Indon.†*
Levocarnitine fumarate (p. 2053·2); thioctic acid (p. 2629·1); ubidecarenone (p. 2637·1); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Nutritional supplement.

Canerin *TO-Chemicals, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Canesmed *Bayer, Spain.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Canesoral *Bayer Consumer, Austral.; Bayer, Fin.*
Fluconazole (p. 578·2).
Vaginal candidiasis; fungal infections.

Canesoral Combi-Pak *Bayer Consumer, Canad.*
Cream, clotrimazole (p. 576·2); capsule, fluconazole (p. 578·2).
Vulvovaginal candidiasis.

Canesoral Duo *Bayer, Austral.*
1 Capsule, fluconazole (p. 578·2); cream, clotrimazole (Canesten) (p. 576·2).
Vaginal candidiasis.

Canespie Bifonazol *Bayer, Spain.*
Bifonazole (p. 573·3).
Tinea pedis.

Canespie Clotrimazol *Bayer, Spain.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Canespor *Bayer, Cz.; Bayer, Ukr.*
Bifonazole (p. 573·3).
Fungal skin and nail infections; fungal skin infections.

Canespor Set *Bayer, Ukr.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Canespro *Bayer, Hung.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal skin infections.

Canesten *Bayer Consumer, Austral.; Bayer, Austria; Bayer, Braz.; Bayer Consumer, Canad.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, India; Bayer Consumer, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer Consumer, Malaysia; Bayer Consumer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.†; Bayer, Port.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer Consumer, Thai.; Bayer, Turk.; Bayer Consumer, UK; Bayer, Venez.*
Clotrimazole (p. 576·2).
Vaginal trichomoniasis; fungal and bacterial skin and vaginal infections; oropharyngeal candidiasis.

Canesten Bifonazol *Bayer, Austria.*
Bifonazole (p. 573·3).
Fungal foot infections.

Canesten Bifonazol comp *Bayer, Austria.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Canesten Combi *Bayer Consumer, UK.*
Combination pack containing Canesten Cream and Canesten 1 pessary: Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Canesten Duo *Bayer, NZ.*
1 Capsule, fluconazole (p. 578·2); cream, clotrimazole (p. 576·2).
Vaginal candidiasis.

Canesten Extra *Bayer, Ger.; Bayer, Hong Kong.*
Bifonazole (p. 573·3).
Fungal skin infections.

Canesten Extra Nagelset *Bayer, Ger.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Onychomycosis.

Canesten Fluconazole *Bayer, NZ.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Canesten HC *Bayer, Hong Kong; Bayer, Irl.; Bayer, Singapore; Bayer Consumer, UK.*
⊗Clotrimazole (p. 576·2); hydrocortisone (p. 1640·1).
Fungal infections with inflammation.

Canesten Oasis *Bayer Consumer, UK.*
Sodium citrate (p. 1781·2).
Cystitis.

Canesten Once Daily *Bayer Consumer, Austral.*
Bifonazole (p. 573·3).
Fungal skin infections.

Canesten Oral *Bayer Consumer, UK.*
Fluconazole (p. 578·2).
Candidal balanitis; vaginal candidiasis.

Canesten Plus *Bayer, Hung.*
Bifonazole (p. 573·3).
Fungal skin infections.

Canesten Unidie *Bayer, Ital.*
Bifonazole (p. 573·3).
Fungal skin infections.

Canestene *Bayer, Belg.*
Clotrimazole (p. 576·2).
Fungal and bacterial skin infections; vulvovaginal candidiasis; balanitis.

Canestène *Bayer, Switz.*
Clotrimazole (p. 576·2).
Fungal skin and nail infections.

Canestene Derm Bifonazole *Bayer, Belg.*
Bifonazole (p. 573·3).
Fungal skin infections.

Canesten-S *Bayer, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2).
Fungal skin infections.

Caneti *Antibioticos, Mex.†*
⊗Fluticasone (p. 1638·1).

Canex *Akacia, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Canfem VG *Zydus, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Canferon *Takeda, Jpn.†*
Interferon alfa-2a (p. 989·2).
Hepatitis B; hepatitis C; renal cancer; multiple myeloma.

Cangil *Epifarma, Ital.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Canicol *Capriformindo, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Canifug *Zentiva, Cz.; Wolff, Ger.; Wolff, Hung.†*
Clotrimazole (p. 576·2).
Fungal and bacterial skin and vaginal infections; vaginal trichomoniasis.

Canifug Fluco *Wolff, Ger.†*
Fluconazole (p. 578·2).
Fungal infections.

Caniron *Candor, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Caniron-TZ *Candor, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Canison *Agio, India; Agio, Philipp.; Agio, Rus.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Canison Plus *Agio, Rus.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).

Canison-B *Agio, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).
Fungal skin infections.

Canison-BN *Agio, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Canison-C *Agio, India.*
Clotrimazole (p. 576·2); clindamycin (p. 269·3).

Cankexin *HuaXia, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Canmet *Candor, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Canmet-MR *Candor, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Canmet-P *Candor, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Pain.

Canmet-SN *Candor, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Canmik *Candor, India.*
Vitamin B substances (p. 2102·3); thioctic acid (p. 2629·1).

Canmox *Forgo, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Cannact *AstraZeneca, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Canocin *Candor, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Canocin-OZ *Candor, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Canoderm *ACO Hud, Fin.; ACO Hud, Norw.; ACO Hud, Swed.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Canoderma *Candor, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Canol *Jolly-Jatel, Fr.*
Cynara (p. 2490·3); chimaphila; aphloia.
Promotor of digestion and renal function.

Canolen *Biofarma, Turk.; Sahin, Turk.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections; vaginal candidiasis.

Canon *USP, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

CanOral *Bayer, Irl.*
Fluconazole (p. 578·2).
Genital candidiasis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Canozol *Candor, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Canozol-D *Candor, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Canphalac-Sol *Candor, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Canplex *Candor, India.*
Vitamins.

Canrenol *Grunenthal, Belg.*
⊗Potassium canrenoate (p. 1472·2).
Hyperaldosteronism; heart failure; cirrhosis; nephrotic syndrome; hypertension.

Canri *Hospira, Cz.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Canrox *Candor, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Canrox-A *Candor, India.*
Roxithromycin (p. 356·2); ambroxol (p. 1654·3).

Cansartan *Mepha, Switz.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Cansartan Plus *Mepha, Switz.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cansoft *Sun, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Canspar *Candor, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Canstat *Aspen, S.Afr.*
Nystatin (p. 590·3).
Candidiasis.

Cansure *Khandelwal, India.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Cantab *Nobel, Turk.*
Candesartan cilexetil (p. 1330·2).

Cantabilin *Formenti, Ital.; Sandoz, Turk.*
Hymecromone (p. 2530·2).
Biliary-tract disorders; liver disorders; digestive disorders.

Cantabiline *Merck, Belg.; DB, Fr.; Remek, Gr.*
Hymecromone (p. 2530·2).
Digestive disorders; biliary-tract disorders.

Cantalène *Cooperation Pharmaceutique, Fr.*
Muramidase hydrochloride (p. 2565·1); chlorhexidine acetate (p. 1743·2); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Cantar *Reddy, India.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Cantaxel *Pharmacodane, Denm.†; Chandra Bhagat, India; Clonmel, Irl.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Cantel *Pisa, Mex.†*
Ketotifen (p. 631·3).

Canthacur *Paladin, Canad.; Assos, Turk.*
Cantharidin (p. 2469·2).
Warts; molluscum contagiosum.

Canthacur-PS *Assos, Turk.*
Cantharidin (p. 2469·2); podophyllum (p. 1717·1); salicylic acid (p. 1719·1).
Warts; molluscum contagiosum.

Paladin, Canad.
Cantharidin (p. 2469·2); podophyllum resin (p. 1717·1); salicylic acid (p. 1719·1).
Warts; molluscum contagiosum.

Cantharis Med Complex *Dynamit, Austria.*
Belladonna (p. 2453·3); cantharis; chimaphila; sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Cantharone *Dormer, Canad.*
Cantharidin (p. 2469·2).
Warts; molluscum contagiosum.

Cantharone Plus *Dormer, Canad.*
Cantharidin (p. 2469·2); podophyllum resin (p. 1717·1); salicylic acid (p. 1719·1).
Warts.

Canticid *Zydus, India.*
Miconazole (p. 588·3).
Vaginal candidiasis.

Cantil
Note: this name may be used for preparations of different composition.
Hoechst Marion Roussel, USA.
Mepenzolate bromide (p. 1859·1).
Adjunctive therapy in peptic ulcer.

Cantop *Reddy, India.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; small-cell lung cancer; cervical cancer.

Cantret *Natco, India.*
Altretamine (p. 738·3).

Canusal *Wockhardt, UK.†*
Heparin sodium (p. 1396·3).
To maintain patency of in-dwelling intravascular lines.

Canvag *Pharma-Vinci, Denm.*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Canvas *Zydus, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Canzeal *Candor, India.*
Vitamins; ginseng (p. 2513·3).

Canzyme *Candor, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Cao Bo *Shiji Huayang, China.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Caobe *Mayo, Mex.*
Oxolamine (p. 1671·2); ammonium acetate (p. 1655·3); sodium citrate (p. 1781·2).
Cough.

Caopecfar *Alpharma, Mex.†*
Furazolidone (p. 933·3); pectin (p. 2200·3); kaolin (p. 1850·1).
Diarrhoea.

Caosina *Ern, Spain.*
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency; osteoporosis.

Caosina D *Ern, Spain.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cap Loc *Siesta, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Cap Selox *Siesta, India.*
Vitamins; minerals.

Cap Voranin *Ind-Swift, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Capabiotic *Fahrenheit, Indon.†*
Cefaclor (p. 232·3).
Bacterial infections.

Capace *Hexal, Austria†; Cipla, India; Aspen, S.Afr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Capacet *Magna, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3); caffeine (p. 1203·3).
Pain.

Capacit *Liferpal, Mex.*
⊗Salbutamol (p. 1220·2).

Capadex
Note: this name may be used for preparations of different composition.
Aspen, Austral.; Healthcare Logistics, NZ.†
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Scoshia, India.
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Capadol *DHU, Ukr.*
Cimicifuga (p. 2478·1); cyclamen (p. 2490·2); gelsemium (p. 2511·2); sanguinaria (p. 2610·1); iris.
Homoeopathic preparation.

Caparin *Osotspa, Thai.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Capasal *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Scalp disorders.

Capastat *Lilly, Austral.†; IFET [ΙΦΕΤ], Gr.; Pharmaserve, Gr.; Lilly, Rus.; Vianex, Spain; King, UK; Akorn, USA.*
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Capcid *Captab, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Capcid-D *Captab, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

CAPD *Fresenius Medical, Hung.†; Mitra, India; Fresenius Kabi, Israel; Fresenius Medical, Port.*
Electrolytes (p. 1775·1); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Fresenius Medical, Spain.†
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

CAPD/DPCA *Fresenius Medical, Cz.; Fresenius Medical, Hung.; Fresenius Medical, Irl.†; Fresenius Medical, Neth.; Fresenius Medical, Port.; Fresenius Medical, Spain.*
Sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Capebina *LKM, Arg.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer.

Capecit *Richmond, Arg.*
Capecitabine (p. 757·3).
Breast cancer.

Capecitastad *Stada, Neth.*
Capecitabine (p. 757·3).
Breast cancer; colorectal cancer; gastric cancer.

Capecite *Piramal, India.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer; gastric cancer.

Capectan *Microsules, Arg.*
Capecitabine (p. 757·3).

Capefas *Raffo, Arg.*
Capecitabine (p. 757·3).

Capel *Ache, Braz.*
Ketoconazole (p. 585·3); panthenol (p. 2582·2).
Seborrhoeic dermatitis.

Capenon *Daiichi Sankyo, Neth.; Pfizer, Spain.*
Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2).
Hypertension.

Capenon HCT *Daiichi Sankyo, Neth.; Pfizer, Spain.*
⊗Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Capent
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Loperamide (p. 1854·2).
Diarrhoea.

Novartis, Mex.
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin irritation; nappy rash.

Capergyl *Bailleul, Fr.†*
Codergocrine mesilate (p. 389·2).
Mental function disorders.

Capex *Galderma, Canad.; Galderma, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Scalp disorders.

Capex-Bron Exp *Seagull, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Capex-DMR *Seagull, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); terbutaline sulfate (p. 1228·1).

Capexion *Generics, UK.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Capginvit *Atlantic, Hong Kong†; Atlantic, Thai.*
Vitamins.
Dietary supplement.

Caphidol C *Merion, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Caphosol *EUSA, UK; EUSA, USA.*
Calcium phosphate (p. 1784·2).
Dry mouth; oral mucositis associated with cancer chemotherapy or radiotherapy.

Capiclav *Casca, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Capihem *Candor, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Capiibine *Reddy, India.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer; gastric cancer.

Capila Savon *Kurtsan, Turk.*
Sulfur (p. 1721·1).
Acne.

Capilac *Casca, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Capilac XP *Casca, India.*
⊗Amoxicillin trihydrate (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).
Bacterial infections.

Capilarema *Baldacci, Braz.; Baldacci, Port.*
Aminaphthone (p. 1131·3).
Vascular disorders.

Capilet *Pharma Investi, Chile.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octocrilene (p. 1715·2).
Sunscreen.

Capilet Locion Capilar *Pharma Investi, Chile.*
Ginseng (p. 2513·3); lappa (p. 2540·1); soy protein; vitamin B substances (p. 2102·3); zinc gluconate (p. 2126·2).
Hair loss.

Capilfor *Finadiet, Arg.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Capill *Keryos, Ital.*
Centella (p. 1698·3); aesculus (p. 2431·2); red vine (p. 2521·3); myrtillus (p. 2566·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Capillary disorders; oedema.

Capill Venogel *Keryos, Ital.*
Centella (p. 1698·3); biorusol; rutoside (p. 2505·3); aesculus (p. 2431·2); butcher's broom (p. 2463·1); melilot (p. 2552·3).
Peripheral vascular disorders.

Capillarema *Baldacci, Ital.*
Aminaphthone (p. 1131·3).
Capillary disorders.

Capillaron Vertigo *Madaus, Ger.*
Bryonia (p. 2461·3); arnica (p. 2447·2); chenopodium anthelminticum; china (p. 2478·3); petroleum rectificatum (p. 2201·2).
Homoeopathic preparation.

Capilos *Theraskin, Braz.*
Saw palmetto (p. 2363·3); butcher's broom (p. 2463·1); capsicum (p. 2469·3); pilocarpus microphyllus; enoxolone (p. 54·2).
Alopecia.

Capilyte *Sterling, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Capimune *Mylan, UK.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; nephrotic syndrome.

Capin Plus *Kamakshi, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Capin-G *Kamakshi, India.*
Mecobalamin (p. 2108·1); gabapentin (p. 523·3).

Capistan *Pierre Fabre, Cz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Capital *Krugher, Ital.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Capital with Codeine *Carnrick, USA.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Capital Soleil *Vichy, Fr.*
SPF 20; SPF 30; SPF 40; SPF 50+: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Vichy, USA.
SPF 20: Avobenzone (p. 1695·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Capitis *Fecofar, Arg.*
Cream: Permethrin (p. 2159·3).
Pediculosis.

Capitrax *Evacare, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Capitrax Plus *Evacare, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Capitrol *Westwood-Squibb, USA.†*
Chloroxine (p. 260·1).
Seborrhoeic dermatitis.

Capiven *Servier, Denm.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency.

Capivit A + E *GSK, Pol.†*
Vitamin A acetate (p. 2098·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Vitamin A and E deficiency.

Caplenal *Berk, UK.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Caplor *Ind-Swift, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Caplor-AS *Ind-Swift, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Capmerin *Korea United, Philipp.*
Mercaptopurine (p. 820·3).
Leukaemias.

Capmist DM *Capital, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Capobal *Baldacci, Braz.*
Captopril (p. 1331·2).
Hypertension.

Capocid *PC India, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Capocid-DM *PC India, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Capomed *Medlink, Philipp.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Capopharm *Farmakor, Rus.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Caposten *Chinoin, Mex.†*
Hydroxyprogesterone (p. 2285·1).

Capotec *Metrolink, Philipp.*
Captopril (p. 1331·2).
Hypertension; diabetic nephropathy; heart failure; myocardial infarction.

Capoten
Note: this name may be used for preparations of different composition.
Aspen, Austral.; BMS, Belg.; BMS, Braz.; BMS, Canad.; Merck, Chile; BMS, China; BMS, Cz.†; BMS, Denm.†; BMS, Gr.; BMS, Hong Kong†; BMS, Indon.†; BMS, Irl.; BMS, Ital.; BMS, Norw.†; Healthcare Logistics, NZ; BMS, Philipp.†; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Spain; BMS, Thai.†; BMS, UK; Par, USA; BMS, Venez.
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Apotex, India.
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Capotena *BMS, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Capotiasid *Arterium, Ukr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Capotrat *Uniao Quimica, Braz.*
Captopril (p. 1331·2).
Hypertension.

Capotril *Lupin, India.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Capotril-H *Lupin, India.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Capotrineo *Neo Quimica, Braz.*
Captopril (p. 1331·2).

Capox *Geolab, Braz.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Capox H *Geolab, Braz.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Capozid *Paranova, Denm.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Capozide *BMS, Austria; BMS, Ger.†; BMS, Indon.†; BMS, Irl.; BMS, Mex.; BMS, NZ; BMS, Rus.; BMS, S.Afr.†; BMS, Switz.†; BMS, UK; Apothecon, USA; BMS, Venez.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
These ingredients can be described by the British Approved Name Co-zidocapt.
Hypertension; heart failure.

Capral *Frik, Turk.*
Fenyramidol hydrochloride (p. 64·2).
Musculoskeletal and joint pain.

Caprazol *Caprifarmindo, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Caprelsa *AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Denm.; AstraZeneca, Fr.; AstraZeneca, Israel; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK; AstraZeneca, USA.*
Vandetanib (p. 879·1).
Thyroid cancer.

Capremabol *Abolmed, Rus.*
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Caprenem *Caprifarmindo, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Capreo *Concept, India.*
Capreomycin.
Tuberculosis.

Capreostat *Simpex, Rus.*
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Capricyn *Krasfarma, Rus.*
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Caprifim *Caprifarmindo, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Capril
Note: this name may be used for preparations of different composition.
Teuto, Braz.; Boryung, Thai.
Captopril (p. 1331·2).
Hypertension; heart failure.

Captab, India.
Glimepiride (p. 473·2).
Diabetes mellitus.

Caprilate *Eagle, Austral.†*
Sodium octanoate (p. 2574·2); European barberry (p. 2502·1); magnesium chloride (p. 1787·1); zinc gluconate (p. 2126·2); lithium chloride (p. 427·3); sorbic acid (p. 1770·2).
Inhibition of gastrointestinal yeast growth.

Caprill
Note: this name may be used for preparations of different composition.
Pinewood, Irl.†
Captopril (p. 1331·2).
Heart failure; hypertension.

Caprilon
Note: this name may be used for preparations of different composition.
Lavipharm, Gr.
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Leiras, Fin.
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema.

Nutricia, Austral.; Scientific Hospital Supplies, Irl.†; Nutricia, Ital.; SHS, UK.
Preparation for enteral nutrition containing medium-chain triglycerides (p. 2082·2).
Disorders of fat metabolism; malabsorption syndromes; hepatobiliary disorders; pancreatic disorders; steatorrhoea; stagnant-loop syndrome.

Capriltop *Topgen, Belg.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Caprimida *K2 Health & Wellness, Chile.*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis; rickets; tetanus.

Caprimida D *K2 Health & Wellness, Chile; Sinensix, Thai.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis; rickets; osteomalacia; tetanus.

Caprimida D Balance *K2 Health & Wellness, Chile.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2); copper (p. 2057·1); boron (p. 2052·3).
Calcium and vitamin D deficiency; osteoporosis.

Caprin
Note: this name may be used for preparations of different composition.
Pinewood, Irl.; Wockhardt, UK.
Aspirin (p. 22·2).
Thrombosis prophylaxis; pain; fever; inflammation.

Samarth, India.
Heparin (p. 1396·3).
Thromboembolic disorders.

Capritin *Atral, Port.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Capro *Mensana, Hung.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Caproamin *Rottapharm, Spain†; Surgimed, Venez.*
Aminocaproic acid (p. 1131·3).
Haemorrhage.

Caprocat *Catalysis, Arg.*
Aminocaproic acid (p. 1131·3).
Haemorrhage.

Caprocef *Caprifarmindo, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Caprol *Ethica, Indon.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Capros *Medac, Ger.*
⊗Morphine sulfate (p. 92·3).
Pain.

Caprovid *Hovid, Malaysia.*
Fish oil (p. 1460·3).
Dietary supplement.

Capsaïne *Labrha, Fr.*
Capsaicin (p. 35·1); glucosamine (p. 2515·3); chondroitin (p. 2476·1); camphor (p. 2466·2); menthol (p. 2553·2); clove oil (p. 2481·3); frankincense oil (p. 2507·3).
Joint disorders.

Capsain-P *Sun, India.*
Capsaicin (p. 35·1).

Capsalgine *Aroma, Turk.*
Salicylic acid (p. 1719·1); capsicum oleoresin (p. 2469·3); camphor (p. 2466·2); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Capsamol *Worwag, Ger.*
Capsicum (p. 2469·3).
Musculoskeletal and joint pain.

Capsella Complex *Mediherb, Austral.*
Shepherd's purse (p. 2614·2); dong quai (p. 2497·1); paeonia lactiflora; helonias (p. 2524·3).
Dietary supplement; gynaecological disorders.

Capser *Verisfield, Gr.*
Capsaicin (p. 35·1).
Osteoarthritis; postherpetic neuralgia; diabetic peripheral neuropathy.

Capsic *Pierre Fabre Sante, Fr.†*
Balsam: Capsaicin (p. 35·1); methyl nicotinate (p. 91·3).
Muscle warming rub.

Capsicam *Grindex, Rus.; Grindeks, Ukr.*
Dimethyl sulfoxide (p. 2182·2); camphor (p. 2466·2); turpentine oil (p. 2636·3); benzyl nicotinate (p. 29·3); nonivamide (p. 102·3).
Musculoskeletal and joint pain.

Capsicin *Vinas, Spain.*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain; neuropathic pain.

Capsicof *Gelcaps, Mex.*
Benzonatate (p. 1656·2).
Cough.

Capsicolle *Chemopharma, Cz.*
Capsaicin (p. 35·1); belladonna (p. 2453·3); nonivamide (p. 102·3).
Musculoskeletal, joint, and peri-articular pain.

Capsicum + Arthri-Cream *Homeocan, Canad.*
Arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); capsicum annuum (p. 2469·3); hypericum perforatum (p. 449·1); rhus toxicodendron (p. 2603·3); symphytum officinalis (p. 2484·2).
Homoeopathic preparation.

Capsicum comp *MAE, Neth.*
Capsicum (p. 2469·3); glycol salicylate (p. 66·2); histamine hydrochloride (p. 2525·2); methyl nicotinate (p. 91·3).
Musculoskeletal pain; sports injuries.

Capsicum Farmaya *Alacan, Spain.†*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain; neuropathic pain.

Capsicum-Plus *Doctor H, Rus.*
Argentum nitricum (p. 2615·3); bryonia (p. 2461·3); capsicum (p. 2469·3); carbo vegetabilis (p. 1537·3); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Capsidol
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Mex.; Vinas, Spain.
Capsaicin (p. 35·1).
Musculoskeletal and joint disorders; neuropathic pain.

Ranbaxy, India.
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); piroxicam (p. 125·3).

Capsiflu *Gelcaps, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; cough.

Capsi-Gel *Biosel, Turk.*
Capsicum oleoresin (p. 2469·3); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Capsigel N *Herbapol Poznan, Pol.*
Camphor (p. 2466·2); capsaicin (p. 35·1); eucalyptus oil (p. 2501·2); salicylic acid (p. 1719·1); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain; neuralgia.

Capsigyl *Sarabhai Piramal, India.*
Camphor (p. 2466·2); capsicum (p. 2469·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); mephenesin (p. 2025·2); methyl salicylate (p. 92·1); peppermint oil (p. 1877·1).

Capsigyl-D *Shalaks, India.*
Ointment: Capsicum (p. 2469·3); diclofenac sodium (p. 48·3); mephenesin (p. 2025·2); methyl salicylate (p. 92·1).

Shalaks, India.
Topical gel: Camphor (p. 2466·2); capsicum oleoresin (p. 2469·3); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Capsika *Bangkok Lab & Cosmetic, Thai.*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain.

Capsi-med *Gothaplast, Ger.*
Nonivamide (p. 102·3).
Musculoskeletal and joint disorders.

Capsin *Fleming, USA.*
Capsaicin (p. 35·1).
Pain; neuralgia.

Capsina *Bioglan, Norw.; Bioglan, Swed.*
Capsaicin (p. 35·1).
Postherpetic neuralgia.

Capsinat *Caprifarmindo, Indon.; Sanbe, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Capsion *CIS, Cz.; CIS, Fr.; CIS, Neth.; CIS, Port.; CIS, Spain; Schering, UK.*
Iodine-131 (p. 2225·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Capsitop *Stedman, India.*
Capsicum oleoresin (p. 2469·3); diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Capso *Sinclair, Ital.*
Capsicum oleoresin (p. 2469·3); aloe vera (p. 1693·2).
Skin disorders.

Capsoderm *Stada, Denm.†*
Isotretinoin (p. 1706·2).
Acne.

Capsoid *Caps, S.Afr.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Capsola Medi *Ranbaxy, India.*
Capsicum oleoresin (p. 2469·3).

Capsola Plus *Ranbaxy, India.*
Capsicum (p. 2469·3); methyl salicylate (p. 92·1).

Capsolin *SIT, Ital.*
Capsicum oleoresin (p. 2469·3); camphor (p. 2466·2); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2).
Joint and muscle pain; soft-tissue disorders.

Capson *Pharmatrix, Arg.*
Aloe vera (p. 1693·2); calendula (p. 2465·2).
Skin disorders.

Capsorin *Morningside, UK.*
Ciclosporin (p. 1945·2).
Transplant rejection; nephrotic syndrome.

Capsovit *Pharmed, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Capsugen *Vitalink, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Capsuvac *Galen, UK.*
Dantron (p. 1833·3); docusate sodium (p. 1836·2).
These ingredients can be described by the British Approved Name Co-danthrusate.
Constipation.

Capsyl *Genopharm, Fr.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Captabin *Shantha, India.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer; gastric cancer.

Captafer *AIM, Fr.*
Fish cartilage (p. 2471·3); minerals; vitamins.
Dietary supplement for promotion of iron absorption.

Captagon *Meda, Belg.†*
⊗Fenetylline hydrochloride (p. 2322·2).
Narcoleptic syndrome.

Captaton *Biotenk, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Captea *Sanofi-Aventis, Fr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captensin *Kalbe, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Capthydro *Sandoz, Denm.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captimer *MIT, Ger.*
Tiopronin (p. 1578·1).
Liver disorders; cystinuria; heavy metal poisoning; Wilson's disease.

Captin *Krewel, Ger.*
Paracetamol (p. 115·1).
Pain; fever.

Capto *CT, Ger.†; Winthrop, Ger.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Capto Comp *1A, Ger.†; CT, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Capto Plus *Actavis, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captobeta *Betapharm, Ger.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captobeta Comp *Betapharm, Ger.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Capto-Co *Ivax, UK.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
These ingredients can be described by the British Approved Name Co-zidocapt.
Hypertension.

Captodoc *Docpharm, Ger.†*
Captopril (p. 1331·2).
Heart failure; hypertension.

Captodoc Comp *Docpharm, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captoflux *Hennig, Ger.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Captogamma *Worwag, Ger.; Worwag, Hung.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Captogamma HCT *Worwag, Ger.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captogen *Pasteur, Philipp.*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy.

Captohexal *Sandoz, Austral.†; Hexal, Ger.†; Hexal, NZ†; Hexal, S.Afr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captohexal Comp *Hexal, Austria†; Hexal, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captol
Note: this name may be used for preparations of different composition.
Sandoz, Denm.
Captopril (p. 1331·2).
Hypertension; diabetic nephropathy; myocardial infarction; heart failure.

Captolab *Multilab, Braz.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Captolane *Sanofi-Aventis, Fr.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captomed *Cimed, Braz.*
Captopril (p. 1331·2).
Hypertension.

Captomido *Belfar, Braz.*
Captopril (p. 1331·2).

Captomin *Ratiopharm, Fin.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Capton *Royton, Braz.*
Captopril (p. 1331·2).
Hypertension.

Captophar *Julphar, UAE.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captopiril *Bunker, Braz.*
Captopril (p. 1331·2).
Hypertension.

Captopres *Darnitsa, Ukr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captopress
Note: this name may be used for preparations of different composition.
Genepharm, Gr.
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captopril Comp *AbZ, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captopril HCT *Aliud, Ger.†; Sandoz, Ger.†; Stada, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captopril Plus *Verla, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captopril-HCT *Ratiopharm, Austria.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captopron *Cifarma, Braz.*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Captor *Rowex, Irl.; Steinbach, Philipp.*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Captoretic *Hexal, S.Afr.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captor-HCT *Rowex, Irl.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captoser *Serral, Mex.*
Captopril (p. 1331·2).
Hypertension.

Captosina *VP, Spain.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captosol *Sandoz, Switz.*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; left ventricular dysfunction following myocardial infarction.

Captosol comp *Sandoz, Switz.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Captospes+H *Alet, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captostad *Stada, Fin.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captotec *Hexal, Braz.*
Captopril (p. 1331·2).
Hypertension.

Captotec + HCT *Hexal, Braz.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Captovis *Actavis, Denm.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Captral *Silanes, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Captral ASA *Silanes, Mex.*
Captopril (p. 1331·2); aspirin (p. 22·2).
Hypertension; heart failure; diabetic nephropathy; thromboembolic disorders.

Captril *IAE, Philipp.*
Captopril (p. 1331·2).
Hypertension; diabetic nephropathy; heart failure; myocardial infarction.

Captrizin *Prodotti, Braz.†*
Captopril (p. 1331·2).
Hypertension.

Captus *Laboratorios Chile, Chile.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); noscapine (p. 1670·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Capulton *Farmex, Gr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Capval *Infectopharm, Ger.*
Oral drops; oral liquid; tablets: Noscapine resinate or noscapine hydrochloride (p. 1670·3).
Cough and associated respiratory-tract disorders.

Capxcel *Khandelwal, India.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer; gastric cancer.

Capxin *Micro, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Capyla *Sigma, Braz.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Capzacin *Combiphar, Indon.*
Capsaicin (p. 35·1).
Neuropathic pain; osteoarthritis.

Capzasin Quick Relief *Chattem, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2).
Musculoskeletal and joint pain; neuralgias; neuropathy.

Capzasin-HP *Chattem, USA.*
Capsaicin (p. 35·1).
Pain.

Capzasin-P *Chattem, USA.*
Capsaicin (p. 35·1).
Pain.

Carac *Dermik, USA.*
Fluorouracil (p. 795·2).
Actinic keratoses.

Carace *BMS, Irl.†; BMS, UK.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Carace Plus *BMS, Irl.†; BMS, UK.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Caracsol *Dey's, India.*
Calcium dihydrogen phosphate (p. 2464·2); sodium iodide (p. 2337·1).
Cataracts.

Caradine *Millimed, Thai.†*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Carafate *Aspen, Austral.; Healthcare Logistics, NZ; Axcan, USA.*
Sucralfate (p. 1889·1).
Peptic ulcer; duodenal ulcer.

Caralpha *Alpharma, UK.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Caramelle alle Erbe Digestive *Giuliani, Ital.*
Gentian (p. 2512·1); rhubarb (p. 1884·2); boldo (p. 2458·3).
Aid to digestion.

Caramelos Antibioticos
Note: this name may be used for preparations of different composition.
Fecofar, Arg.; Richet, Arg.
Benzocaine (p. 1980·2); tyrothricin (p. 384·1).
Mouth and throat disorders.
HMA, Arg.; Raymos, Arg.
Hexylresorcinol (p. 1755·1); benzocaine (p. 1980·2); tyrothricin (p. 384·1).
Mouth and throat disorders.

Caramelos Antibioticos Lefmar *Biosintex, Arg.*
Tyrothricin (p. 384·1); hexylresorcinol (p. 1755·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Caramelos Oriental *Oriental, Arg.*
Hexylresorcinol (p. 1755·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Caraprol *Chanelle, Fin.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Carasel *Tecnobio, Spain.*
Ramipril (p. 1483·3).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Caraten *Berlin Pharm, Thai.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction following myocardial infarction.

Carato *Saga, India.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Caravel *SPA, Ital.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carb PSE 12 DM *Rivers Edge, USA.*
⊗Dextromethorphan tannate (p. 1660·1); carbinoxamine tannate; pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Carb Pseudo-Tan *Hi-Tech, USA.*
⊗Pentoxyverine tannate (p. 1672·1); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Carba *CT, Ger.†*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; diabetic neuropathy; alcohol withdrawal syndrome; multiple sclerosis; bipolar disorder.

Carbabeta *Betapharm, Ger.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbaccord *Arrow, NZ.*
Carboplatin (p. 759·1).
Ovarian cancer.

Carbacontin *Modi-Mundipharma, India.†*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder.

Carbactive *Cooperation Pharmaceutique, Fr.*
Activated charcoal (p. 1537·3).
Gastrointestinal disorders.

Carbadac *Zydus, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carbaderm
Note: this name may be used for preparations of different composition.
Gebro, Switz.
⊗Urea (p. 1727·3).
Skin disorders.

Carbafen *Liferpal, Mex.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).
Painful skeletal muscle spasm.

Carbaflux *Hennig, Ger.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbagamma *Worwag, Ger.†*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbagen *Generics, UK.*
Carbamazepine (p. 512·2).
Epilepsy.

Carbager-Plus *Streger, Mex.*
Methocarbamol (p. 2025·3); ibuprofen (p. 68·2).
Gout; musculoskeletal, joint and peri-articular disorders; pain; inflammation.

Carbaglu *Orphan, Austria; Orphan, Belg.; Orphan, Cz.; Orphan, Denm.; Orphan, Fr.; Orphan, Ger.; IFET (ΙΦΕΤ), Gr.; Orphan, Irl.; Medison, Israel; Orphan, Ital.; Orphan, Neth.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Orphan Europe, Swed.; Orphan, UK; Accredo, USA.*
Carglumic acid (p. 2471·1).
Hyperammonaemia.

Carbagramon *Gramon, Arg.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia.

Carbalan *Quimica y Farmacia, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; alcohol withdrawal syndrome; neuralgias; diabetic neuropathy.

Carbalax *Chemidex, UK.†*
Monobasic sodium phosphate (p. 1791·1); sodium bicarbonate (p. 1781·1).
Constipation; bowel evacuation.

Carbalepsin *Akrikhin, Rus.*
Carbamazepine (p. 512·2).
Epilepsy.

Carbamann *Mann, Ger.†*
Carbachol (p. 2005·2).
Glaucoma.

Carbamat *Rontag, Arg.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Carbamed *Medihealth, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Carbamid + VAS *Widmer, Ger.*
⊗Tretinoin (p. 1725·2); urea (p. 1727·3).
Skin disorders.

Carbamide Creme Nouvelle Formule *Widmer, Switz.*
⊗Urea (p. 1727·3).
Skin disorders.

Carbamide Emulsion *Widmer, Switz.*
⊗Urea (p. 1727·3).
Skin disorders.

Carbamide + VAS *Widmer, Switz.*
⊗Tretinoin (p. 1725·2); urea (p. 1727·3); dexpanthenol (p. 2582·2).
Skin disorders.

Carbamox *Offenbach, Mex.*
Methocarbamol (p. 2025·3); aspirin (p. 22·2).
Fever; pain; muscle spasm.

Carbamyl *Kopran, India.*
Chlorphenamine maleate (p. 620·3); diethylcarbamazine citrate (p. 153·1).
Worm infections.

Carbapin *Hemofarm, Rus.†; Hemofarm, Ukr.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; neuralgia; alcohol withdrawal syndrome; diabetic neuropathy; diabetes insipidus.

Carbapsy *Sel-J, Philipp.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Carbargal *Roemmers Osmoph, Venez.*
Activated charcoal (p. 1537·3); simeticone (p. 1886·2).
Flatulence; colitis; diarrhoea.

Carbargal con Atropina *Roemmers Osmoph, Venez.*
Activated charcoal (p. 1537·3); simeticone (p. 1886·2); atropine sulfate (p. 1310·2).
Gastrointestinal disorders.

Carbasal *Salus, Mex.*
Carbamazepine (p. 512·2).
Epilepsy.

Carbasma *Grandix, India.*
⊗Carbocisteine (p. 1658·1); salbutamol (p. 1220·2); theophylline (p. 1229·3).

Carbastat *Novartis Ophthalmics, USA.†*
Carbachol (p. 2005·2).
Production of miosis in eye surgery.

Carbasure *Gentech, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carbatab *GM, USA.*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough; respiratory-tract congestion.

Carbatil
Note: this name may be used for preparations of different composition.
Biotech, Venez.
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension.

Carbatol *Torrent, India; Torrent, Singapore.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder; mania; alcohol withdrawal syndrome; glossopharyngeal neuralgia.

Carbatrol *Shire Richwood, USA.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Carbatuss *GM, USA.*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Carbaval *Valdecasas, Mex.†*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia.

Carbazene *Medifive, Thai.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Carbazep *Cryopharma, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; diabetic neuropathy.

Carbazina *Psicofarma, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; diabetic neuropathy; diabetes insipidus; bipolar disorder; alcohol and drug withdrawal syndromes.

Carbellon *Torbet Laboratories, UK.*
Activated charcoal (p. 1537·3); magnesium hydroxide (p. 1857·2); peppermint oil (p. 1877·1).
Dyspepsia; flatulence; gastric hyperacidity.

Carbenem *Verisfield, Gr.*
Meropenem (p. 321·3).
Bacterial infections.

Carbenin *Daiichi Sankyo, China; Daiichi Sankyo, Jpn.*
Panipenem (p. 337·3); betamipron (p. 231·1).
Bacterial infections.

Carbetesil *Ratiopharm, Port.†*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carbex
Note: this name may be used for preparations of different composition.
Nordic, UK.
Oral granules, sodium bicarbonate (p. 1781·1); simeticone (p. 1886·2); solution, anhydrous citric acid (p. 2480·3).
Adjunct to contrast media for gastrointestinal radiography.
Endo, USA.†
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Carbh *Winsome, India.*
Vitamins; minerals.

Carbicalcin *Chiesi, Spain.*
Elcatonin (p. 1178·1).
Paget's disease of bone; hypercalcaemia of malignancy; osteoporosis.

Carbicef *Sun, India.*
Carbocisteine (p. 1658·1); cefalexin (p. 234·1).
Respiratory-tract infections.

Carbidol *Teuto, Braz.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Carbifol *Merion, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Carbilepp *Katwijk, Philipp.†*
Carbamazepine (p. 512·2).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Carbilev *Aspen, S.Afr.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Carbinib *Edol, Port.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; ocular hypertension; pulmonary hypertension.

Carbinom *XL, Philipp.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Carbion *Invision, India.*
Iron (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Carbiran *Allenge, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).
Allenge, India.
Syrup: Iron polymaltose (p. 2077·2).

Carbiset *Nutripharm, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract symptoms.

Carbistad *Stada, Austria.†*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Carbital *Teuto, Braz.*
Phenobarbital (p. 535·2).
Epilepsy.

Carbitone *Medley, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Carbloxal *Sandoz, Indon.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Carbo Betulae Comp *Weleda, S.Afr.†*
Carbo betulae; antimonit; chamomile (p. 2474·1).
Gastrointestinal disorders.

Carbo D3 *Sofar, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Carbo Königsfeld *Muller Goppingen, Ger.*
Carbo coffea (p. 2648·2).
Diarrhoea.

Carbo Plus *Plus, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_2 (p. 2104·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Carbobel *Medgenix, Belg.*
Activated charcoal (p. 1537·3); methenamine (p. 322·3); magnesium citrate (p. 1857·1).
Dyspepsia; diarrhoea; poisoning.

Carbocain *AstraZeneca, Denm.; Dentsply, Norw.; AstraZeneca, Swed.*
Mepivacaine hydrochloride (p. 1992·2).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carbocaina
Note: this name may be used for preparations of different composition.
AstraZeneca, Ital.
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Carbocaine *AstraZeneca, Austral.†; Hospira, Canad.; Adcock Ingram, S.Afr.; Hospira, USA.*
Mepivacaine hydrochloride (p. 1992·2).
Corbadrine (p. 2486·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; regional anaesthesia.

Carbocaïne *AstraZeneca, Fr.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Carbocaine with Neo-Cobefrin *Cook-Waite, USA.*
Mepivacaine hydrochloride (p. 1992·2).
Corbadrine (p. 2486·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carbocal *Farmasierra, Spain; Unison, Thai.*
Calcium carbonate (p. 1824·3).
Hypocalcaemia; osteoporosis; calcium deficiency; calcium supplement; rickets.

Carbocal D *Farmasierra, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Carbocalc *Unison, Thai.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Carbocal-D *Unison, Thai.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Carbo-cell *Cell Pharm, Ger.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carbocin *Cimed, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Carbocit
Note: this name may be used for preparations of different composition.
Imuna, Cz.
Activated charcoal (p. 1537·3); bismuth subgallate (p. 1822·1); citric acid monohydrate (p. 2480·3).
Diarrhoea.

Carbocter *Pharmasant, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Carbocys *T Man, Thai.*
Carbocisteine (p. 1658·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Carbodec *Rugby, USA.*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Carbodec DM *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); carbinoxamine maleate (p. 619·1).
Coughs and cold symptoms.

Carboderm *Darnitsa, Ukr.*
⊗Urea (p. 1727·3).
Keratinisation disorders.

Carbodex *Deva, Turk.*
Carboplatin (p. 759·1).

Carbodex D M *Tri-Med, USA.*
Oral drops: ⊗Dextromethorphan hydrobromide (p. 1660·1); carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Tri-Med, USA.
Syrup: ⊗Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Carbo-Dome *Sandoz, UK.*
Coal tar (p. 1723·2).
Psoriasis.

Carbofan *Bunker, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Carbofen *Scoshia, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Carbofen Forte *Scoshia, India.*
Ascorbic acid (p. 2110·3); iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Carbofer-Z *Bal, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).
Anaemias.

Carboflem *Danlex, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess or viscous mucus.

Carboflex
Note: this name may be used for preparations of different composition.
Convatec, Belg.
Activated charcoal (p. 1537·3).
Wounds.

Convatec, Canad.
Calcium-sodium alginate (p. 1136·3) (p. 2167·3); carmellose sodium (p. 2175·2); activated charcoal (p. 1537·3).
Wounds.

Carbogasol *Montpellier, Arg.*
Oral drops: Simeticone (p. 1886·2).
Meteorism; preparation for radiography.

Montpellier, Arg.
Tablets: Simeticone (p. 1886·2); charcoal (p. 1537·3).
Dyspepsia; meteorism.

Carbogasol Digestivo *Montpellier, Arg.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2); thioctic acid (p. 2629·1); deoxycholic acid (p. 2457·2); dehydrocholic acid (p. 2492·1).
Digestive disorders.

Carbogasol Forte *Montpellier, Arg.*
Simeticone (p. 1886·2).
Dyspepsia; meteorism; preparation for radiography.

Carbogen *Linde, Canad.*
Carbon dioxide (p. 1797·2); oxygen (p. 1799·3).

Carbohidrato 100 *Survival, Arg.*
Maltodextrin (p. 2080·3).
Dietary supplement.

Carbohydrate-Free Mixture *Nutricia, Austral.*
Food for special diets.
Disorders of carbohydrate metabolism.

Carbokebir *Aspen, Arg.*
Carboplatin (p. 759·1).

Carbokem *Alkem, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Carb-O-Lac HP *Geritrex, USA.*
⊗Urea (p. 1727·3); ammonium lactate (p. 1694·3).
Dry skin.

Carbolactanose *Melisana, Belg.*
Lactococcus lactis (p. 2596·3); activated charcoal (p. 1537·3).
Diarrhoea; enterocolitis; re-establishment of gastrointestinal flora; meteorism.

Carbolevure *Pierre Fabre Sante, Fr.*
Saccharomyces cerevisiae (p. 2125·2); activated charcoal (p. 1537·3).
Gastrointestinal disorders.

Robapharm, Switz.
Dried yeast (p. 2125·2); activated charcoal (p. 1537·3).
Gastrointestinal disorders.

Carbolim *Arrow, Braz.*
Lithium carbonate (p. 427·3).
Depression; bipolar disorder; schizophrenia; migraine and vascular headaches; neutropenia.

Carboliq *Lainco, Spain.*
Activated charcoal (p. 1537·3).
Overdosage; acute poisoning.

Carbolit *Raffo, Chile; Psicofarma, Mex.*
Lithium carbonate (p. 427·3).
Bipolar disorder; psychoses; behaviour disorders; migraine; obsessive-compulsive disorder; schizophrenia.

Carbolith *Psyco Remedies, India.*
Lithium.
Mania; bipolar disorder; depression.

Valeant, Canad.
Lithium carbonate (p. 427·3).
Bipolar disorder.

Carbolithium *Cephalon, Ital.*
Lithium carbonate (p. 427·3).
Psychiatric disorders; cluster headache; adjunct in drug-induced leucopenia.

Carbolitium *Eurofarma, Braz.*
Lithium carbonate (p. 427·3).
Depression; bipolar disorder; schizophrenia; migraine and vascular headaches; neutropenia.

Carbomax *Newtramax, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Carbomax Plus *Newtramax, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Carbomed *Tolmann, Philipp.; Medicine Products, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Carbomedac *Medac, Cz.; Medac, Denm.; Medac, Ger.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carbomint *Union Drug, Thai.*
Activated charcoal (p. 1537·3); sodium bicarbonate (p. 1781·1); peppermint oil (p. 1877·1).
Diarrhoea.

Carbomix *Leiras, Fin.; Tonipharm, Fr.; Galenica, Gr.†; IFET (ΙΦΕΤ), Gr.†; Beacon, Irl.; Sirton, Ital.; Norit, Norw.†; Norit, Port.; Abbott, Swed.; Meadow, UK.*
Activated charcoal (p. 1537·3).
Acute poisoning; drug overdosage; flatulence; acute diarrhoea.

Carbomox *Win-Medicare, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); carbocisteine (p. 1658·1).
Respiratory-tract infections; otitis media.

Ca-R-Bon *Greater Pharma, Thai.*
Activated charcoal (p. 1537·3).
Diarrhoea; abdominal distension; poisoning.

Carbon Sulfaguanidina *Valma, Chile.*
Activated charcoal (p. 1537·3); sulfaguanidine (p. 364·3).
Gastrointestinal infections.

Carbon Tabs *Fada, Arg.*
Activated charcoal (p. 1537·3); phthalylsulfathiazole (p. 339·3); homatropine methylbromide (p. 2007·3).
Gastrointestinal disorders.

Carbona *Zota, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); selenium dioxide (p. 2087·1); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Carbone Composto *AFOM, Ital.†; Zeta, Ital.†*
Vegetable charcoal (p. 1537·3); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastrointestinal disorders.

Carbonesia *Geymonat, Ital.*
Activated charcoal (p. 1537·3); magnesium oxide (p. 1857·3); calcium carbonate (p. 1824·3); magnesium peroxide (p. 1759·3).
Diarrhoea.

Carbonet *Smith & Nephew, Austral.; Smith & Nephew, Belg.; Smith & Nephew, Fr.; Smith & Nephew, Irl.; Smith & Nephew, UK.*
Activated charcoal (p. 1537·3).
Malodorous wounds.

Carbonpectate *Chew, Thai.*
Activated charcoal (p. 1537·3); magnesium carbonate (p. 1856·2); pectin (p. 2200·3).
Diarrhoea; flatulence; gastrointestinal disorders.

Carbopa *Intas, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Carbopect *VS, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Carbopekt *Medisorb, Rus.*
Activated charcoal (p. 1537·3).
Dyspepsia; flatulence; gastric hyperacidity; poisoning.

Carbophar *Pharmaffiliates, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Carb-O-Philic *Geritrex, USA.*
Emollient.

Carbophos *Tradiphar, Fr.*
Vegetable charcoal (p. 1537·3); calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2).
Gastrointestinal disorders.

Carboplamin *Vianex (Βιανεξ), Gr.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carboplan *Vianex (Βιανεξ), Gr.; Natco, India.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carboplat *Gobbi, Arg.; Asofarma, Mex.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carboplex *LKM, Arg.†*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Carboplyina *Dentsply, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carboron
Note: this name may be used for preparations of different composition.
Plus, India.
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Plus, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Royal, Chile.
Lithium carbonate (p. 427·3).
Bipolar disorder.

Carbosan *Rowa, Hung.; Rowa, Irl.*
Carbenoxolone sodium (p. 1825·3).
Mouth ulcers; lip sores; aphthous stomatitis.

Carbosen *Senese, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carboseptol *Herbes Universelles, Canad.†*
Menthol (p. 2553·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); zinc oxide (p. 1729·1).

Carbosin *Teva, Belg.; Pharmachemie, Fin.; Chemipharm, Gr.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia†; Pharmachemie, Neth.; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.; Med, Turk.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carbosinol *Biomed, Switz.*
Glycoprotein (PhaseLite).
Obesity.

Carbosint *Boniscontro & Gazzone, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Carbosol
Note: this name may be used for preparations of different composition.
Actavis, Cz.
Carboplatin (p. 759·1).
Ovarian cancer; small cell lung cancer.

Morishita, Philipp.†
Carbocisteine (p. 1658·1).
Cough; respiratory-tract congestion.

Carbosorb *Imuna, Cz.*
Activated charcoal (p. 1537·3).
Diarrhoea.

Carbosorb X *Phebra, Austral.; AFT, NZ.*
Activated charcoal (p. 1537·3).
Drug overdose; poisoning.

Carbosorb XS *Phebra, Austral.; AFT, NZ.*
Activated charcoal (p. 1537·3); sorbitol (p. 2092·1).
Drug overdose; poisoning.

Carbostesin *AstraZeneca, Austria; AstraZeneca, Ger.; AstraZeneca, Switz.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carbosyl *Biomax, India.*
Syrup: Iron carbonyl (p. 2073·1); potassium iodide (p. 2336·3); zinc sulfate (p. 2126·2); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); vitamins.

Biomax, India.
Tablets: Iron carbonyl (p. 2073·1); iodine (p. 2336·3); zinc sulfate (p. 2126·2); vitamins.

Carbosylane *Grimberg, Canad.; Grimberg, Fr.; Lilly, Gr.; Grimberg, Irl.; Grimberg, Israel.*
Activated charcoal (p. 1537·3); dimeticone (p. 1886·2).
Dyspepsia; meteorism; flatulence; gastrointestinal distension.

Carbosymag *Grimberg, Fr.*
Green capsules, activated charcoal (p. 1537·3); simeticone (p. 1886·2); magnesium oxide (p. 1857·3); orange capsules, activated charcoal; simeticone.
Dyspepsia; meteorism.

Carbotec *Columbia, Mex.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carboteen *VHB, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Carbotera *Tuteur, Rus.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carboticon *Interdelta, Switz.*
Activated charcoal (p. 1537·3); simeticone (p. 1886·2).
Flatulence; digestive disorders.

Carbotinal *VHB, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Carbotinol *Korea United, Philipp.; Korea United, Singapore.*
Carboplatin (p. 759·1).
Ovarian cancer; small cell lung cancer.

Carbotos *Esan, Chile.*
Carbocisteine (p. 1658·1).
Cough.

Carbotoss *Greenpharma, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Carbotox *Imuna, Cz.*
Activated charcoal (p. 1537·3); sodium thiosulfate (p. 1576·1).
Diarrhoea; poisoning.

Carbotural *Valeant, Mex.*
Activated charcoal (p. 1537·3).
Flatulence; dyspepsia; diarrhoea; halitosis.

Carbox *Micro, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Carboxine-PSE *Cypress, USA.*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Carboxtie *Bioprofarma, Arg.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Carboyoghurt *SIT, Ital.*
Vegetable charcoal (p. 1537·3); simeticone (p. 1886·2).
Meteorism.

Carbozin *Elfin, India.*
Oral drops: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Elfin, India.
Oral suspension: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); pyridoxine (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Carbozor *Chrispa (Χρισπα), Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

Carca *Intas, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carcef *H & Care, India.*
Cefixime (p. 240·3).
Bacterial infections.

Carcet *Burgeon, India.*
Cetirizine hydrochloride (p. 619·2); diethylcarbamazine citrate (p. 153·1).
Worm infections.

Carcyt *Tema, S.Afr.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Card *Jagsonpal, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Cardace *Sanofi-Aventis, Fin.; Sanofi-Aventis, India; Aventis, Indon.*
Ramipril (p. 1483·3).
Hypertension; heart failure following myocardial infarction; cardiovascular risk reduction; heart failure; myocardial infarction; diabetic nephropathy.

Cardace Comp *Sanofi-Aventis, Fin.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cardace-H *Sanofi-Aventis, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Cardactona *Pasteur, Chile.*
⊗Spironolactone (p. 1499·3).
Heart failure; hyperaldosteronism; hypertension; oedema.

Cardalin *Abbott, Braz.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

Cardasin *Zdorovje, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic ear or eye disorders.

Cardasol *Shree Ganesh, India.*
Amiodarone (p. 1300·1).
Ventricular arrhythmias.

Cardaten *Shree Ganesh, India.*
⊗Atenolol (p. 1308·2).
Arrhythmias; myocardial infarction.

Cardaxen *Spirig, Switz.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Cardaxen plus *Spirig, Switz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Cardbloc *Hexal, Braz.†*
⊗Propranolol (p. 1479·1).

Cardcor *Teuto, Braz.*
Digoxin (p. 1353·3).
Arrhythmias.

Cardec *Macoven, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Cardec DM *Macoven, USA.*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Cardegic *Sanofi-Aventis, Belg.*
Lysine aspirin (p. 84·3).
Thromboembolic disorders.

Cardeloc *TO-Chemicals, Thai.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism.

Cardelol *Med-One, Gr.*
⊗Carteolol hydrochloride (p. 1332·3).

Cardem
Note: this name may be used for preparations of different composition.
Anglo-French Drugs, India.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.
Sanofi-Aventis, Spain.
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.

Carden *Intra-Labs, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Cardenalin *Pfizer, Jpn.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Cardene *Astellas, Neth.; Astellas, UK; EKR, USA.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris.

Cardenol *TO-Chemicals, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; tremor.

Cardensiel *Merck Serono, Fr.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Cardepine *Imperial, Malaysia; Imperial, Philipp.; Great Eastern, Thai.*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension; heart failure; cerebrovascular disorders.

Carder *NTC, Cz.; Gap, Gr.; Farma-Projekt, Pol.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Cardesmo *Shree Ganesh, India.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; perioperative hypertension.

Card-Floe II *Sisu, Canad.†*
Vitamins; minerals.

Cardia *Zydus, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Cardiac D-Dimer *Roche Diagnostics, Mex.†*
Test for D-dimer in blood.
Diagnosis of venous thrombosis and pulmonary embolism.

Cardiac M Myoglobin *Roche Diagnostics, Mex.†*
Test for myoglobin in blood.
Diagnosis of myocardial infarction.

Cardiac T Troponin T *Roche Diagnostics, Mex.†*
Test for troponin T in blood.
Diagnosis of myocardial damage.

Cardiace *Triomed, S.Afr.†*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Cardiactiv *Herbapol Krakow, Pol.*
Crataegus (p. 2488·1); rosemary (p. 2607·2).
Heart failure.

Cardiaforce *Bioforce, Switz.*
Crataegus (p. 2488·1); melissa (p. 2552·3); Malaga wine.
Palpitations; nervous disorders.

Cardiagen HCT *APS, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cardial
Note: this name may be used for preparations of different composition.
Meprofarm, Indon.
Dipyridamole (p. 1362·2).
Angina pectoris; thromboembolism prophylaxis.
T Man, Thai.
Digoxin (p. 1353·3).
Arrhythmias; heart failure.

Cardiamed *CCM, Malaysia.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Cardiamid-Coffein *Polfa Pabianice, Pol.†*
⊗Caffeine (p. 1203·3); nikethamide (p. 2328·2); strychnine (p. 2623·2).
Tonic.

Cardiamidum *Polfa Pabianice, Pol.*
⊗Nikethamide (p. 2328·2).
Hypotension.

CardiASK *Kanonfarma, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardiavit *Ikapharmindo, Indon.*
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Elevated blood homocysteine levels; vitamin deficiency.

Cardiax *Sidus, Arg.*
Aspirin (p. 22·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Thrombosis prophylaxis.

Cardiax-ASS *Drossapharm, Switz.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardiazem *Sanitas, Chile.*
Nitrendipine (p. 1456·3).
Hypertension.

Cardiazol-Paracodina *Abbott, Ital.*
⊗Pentetrazol (p. 2328·3); dihydrocodeine thiocyanate (p. 52·2).
Cough.

Cardibloc
Note: this name may be used for preparations of different composition.
Imperial, Singapore.
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension; cardiovascular disorders.

Cardiblok *Xixia, S.Afr.†*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; hyperthyroidism; phaeochromocytoma; angina pectoris; tachycardia; tremor.

Cardi-Braun *Braun, Spain.*
⊗Trometamol (p. 2635·1); sodium citrate (p. 1781·2); citric acid (p. 2480·3); dibasic sodium phosphate (p. 1791·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); glucose (p. 2068·3).
Induction of cardioplegia.

Cardicap
Note: this name may be used for preparations of different composition.
Caprifarmindo, Indon.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.
Natco, India.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.
Pharmaspec, Philipp.†
Nifedipine (p. 1447·2).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Cardichek *Gland, India.*
Amiodarone (p. 1300·1).
Ventricular arrhythmias.

Cardicon *Labomed, Chile.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; myocardial infarction.

Cardicor *Merck, Denm.; Merck Serono, Irl.; Bayer, Ital.; Merck, S.Afr.; Merck, UK.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure; hypertension; angina pectoris.

Cardicoron *Teuto, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Cardif Beta *Concept, India.†*
⊗Nitrendipine (p. 1456·3); atenolol (p. 1308·2).
Hypertension.

Cardifen *Aspen, S.Afr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Cardiflor *VSM, Neth.*
Cardiospermum halicacabum.
Homoeopathic preparation.

Cardiforce *Torrent, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Cardiject *Sun, India; Danpac, Indon.; Pharmaplan, S. Afr.; Sun, Thai.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Cardikare *Jagsonpal, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Cardikare-H *Jagsonpal, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cardiket *UCB, Cz.; UCB, Ukr.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Cardil *Orion, Denm.; Santa, Gr.; Orion, Malaysia; Orion, Rus.; Orion, Singapore; Orion, Thai.; Orion, Ukr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Cardilan *BB, Cz.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Cardiac disorders; magnesium and potassium depletion.

Cardilane *Lero, Fr.*
Fish oil (p. 1460·1); vitamin E (p. 2119·1).
Dietary supplement; cardiovascular disorders.

Cardilate
Note: this name may be used for preparations of different composition.
Ivax, Irl.†
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Cardilate MR
Note: this name may be used for preparations of different composition.
Ivax, UK.†
Nifedipine (p. 1447·2).
The name Cardilate has also been used for preparations containing eritrityl tetranitrate.
Hypertension; angina pectoris.

Cardilax *Intas, India.*
⊗Alprazolam (p. 1035·2); propranolol hydrochloride (p. 1479·1).

Cardiloc *Unipharm, Israel.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure; hypertension; angina pectoris.

Cardilol
Note: this name may be used for preparations of different composition.
Julphar, UAE.
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; myocardial infarction; migraine; anxiety; tremor; hyperthyroidism; phaeochromocytoma.
Libbs, Braz.
⊗Carvedilol (p. 1333·1).
Angina pectoris; hypertension; heart failure.

Cardilopin *Egis, Cz.; Egis, Hung.; Egis, Pol.; Egis, Rus.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Cardilor *Remedica, Malaysia; Remedica, Thai.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; angina pectoris.

Cardimax
Note: this name may be used for preparations of different composition.
Integrated Pharmaceutical, Philipp.
Levocarnitine (p. 2053·2).
Carnitine deficiency.
USV, India; USV, Ukr.†
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; Ménière's disease; ischaemic heart disease; ischaemic cochlear-vestibular disturbance; ischaemic chorioretinal vascular disorders.

Cardin
Note: this name may be used for preparations of different composition.
Vedim, Pol.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cardinit *Abbott, Mex.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Cardinol *Mylan, NZ.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; anxiety; hypertension; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma; hyperthyroidism; tremor.

Cardinorm
Note: this name may be used for preparations of different composition.
New Research, Ital.
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; myocardial infarction; arrhythmias; hypertension.
Sandoz, Austral.†
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cardinova *Willow, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Cardi-NRG *Bionova, India.*
Ubidecarenone (p. 2637·1); levocarnitine tartrate (p. 2053·2); magnesium (p. 1786·3); vitamin E (p. 2119·1).

Cardio AAS *Sigma, Braz.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardio Aspirin *Bayer Schering, Indon.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardio Cocktail *ForMor, Singapore.*
Vitamins; minerals; carbohydrate; amino acids; grape (p. 2521·3); omega-3 fatty acids (p. 1460·1).
Nutritional supplement.

Cardio Omega Benefits with Vitamin D-3 *Physician Recommended Nutriceuticals, USA.*
Omega-3 fatty acids (p. 1460·1); vitamin D (p. 2112·3).

Cardio Tone
Note: this name may be used for preparations of different composition.
MDR, USA.
Vitamins; minerals; thioctic acid (p. 2629·1); levocarnitine (p. 2053·2); ubidecarenone (p. 2637·1); grape seed (p. 2521·3); green tea (p. 2648·2); crataegus (p. 2488·1); lutein (p. 2079·2); lycopene (p. 2546·2); quercetin (p. 2505·3); zeaxanthin (p. 2125·3).
Dietary supplement.

Cardioace *Vitabiotics, Hong Kong; Vitabiotics, UK.*
Omega-3 fish oil; garlic (p. 2510·3); lecithin (p. 2542·2); vitamins; minerals.

Cardioaspirin *Bayer, Ital.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Cardioaspirina *Bayer, Arg.; Bayer, Chile.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Cardioaspirine *Bayer, Belg.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Cardiobiotral *Bionutre, Arg.*
Ubidecarenone (p. 2637·1); vitamins; amino acids.
Dietary supplement.

Cardioblock *Lafedar, Arg.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Cardiobonisol *Bonimed, Pol.*
Crataegus (p. 2488·1); cynara (p. 2490·3); echinacea purpurea (p. 2498·1); ginkgo biloba (p. 2512·3).
Cardiovascular disorders.

Cardiobron *Fada, Arg.*
Alprostadil (p. 2352·2).

Cardiocalm *Pharmastra, Fr.*
Crataegus (p. 2488·1).
Nervous disorders; insomnia.

CardioCare *MD, Singapore.*
Fish oil (salmon) (p. 1460·3); eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Cardiochek *Pentafarma, Chile.†*
Tests for cholesterol, glucose, or triglycerides.

Cardiocor *Meda, Fr.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Cardiodaron *Zdorovje, Ukr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; Wolff-Parkinson-White syndrome.

Cardiodarone *Valenta, Rus.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Cardiodopa *Royton, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Cardiodoron *Weleda, Austria; Weleda, Ger.; Weleda, Switz.*
Hyoscyamus niger (p. 2530·2); onopordum acanthium; cowslip flower (p. 2596·2).
Cardiac disorders; sleep disorders; circulatory disorders.

Weleda, S.Afr.†
Hyoscyamus (p. 2530·2); onopordon; cowslip (p. 2596·2).
Cardiac disorders; circulatory disorders.

Cardiodyn *Dunner, Switz.*
Crataegus (p. 2488·1).
Cardiac disorders.

Cardio-Essentials *Unicity, Singapore.*
Ubidecarenone (p. 2637·1); levocarnitine (p. 2053·2); L-taurine; crataegus (p. 2488·1).
Dietary supplement.

Cardiofast *Duopharma, Philipp.*
Dopamine hydrochloride (p. 1367·2).
Heart failure; shock.

Cardiofenone *Polifarma, Ital.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Cardiofil *Filofarm, Pol.*
Aspirin (p. 22·2).
Magnesium oxide (p. 1857·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Cardiogoxin *Medipharma, Arg.*
Digoxin (p. 1353·3).

Cardioject *Syxyl, Ger.*
Crataegus (p. 2488·1); convallaria majalis (p. 2486·2); urginea maritima var. rubra (p. 2161·2).
Homoeopathic preparation.

Cardioket *Abbott, Turk.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Cardio-Kreislauf-Longoral *Cassella-med, Ger.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1); crataegus (p. 2488·1).
Cardiovascular disorders.

Cardiol
Note: this name may be used for preparations of different composition.
Bialport, Port.
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Roche, Fin.; YSP, Malaysia.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Cardiol C *Herbapol Wroclaw, Pol.*
Caffeine (p. 1203·3); kola (p. 2648·2); convallaria (p. 2486·2); crataegus (p. 2488·1); valerian (p. 2640·2).
Cardiovascular disorders; tonic.

Cardiolen *Sanitas, Chile.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Cardiolite *Lantheus, Austral.; Lantheus, Cz.†; Lantheus, Fin.; CIS, Fr.; BMS, Ital.; Lantheus, Neth.; Lantheus, Port.†; BMS, Spain; BMS, UK; Du Pont, USA.*
Technetium-99m sestamibi (p. 2228·1).
Diagnosis and location of myocardial infarction; diagnosis of breast cancer; diagnosis and investigation of hyperparathyroidism; assessment of myocardial function.

Lantheus, Israel.†
Tetrakis copper tetrafluoroborate.
Myocardial imaging; breast imaging.

Cardiomagnyl *Nycomed, Rus.; Nycomed, Ukr.*
Aspirin (p. 22·2).
Magnesium hydroxide (p. 1857·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Cardi-Omega 3 *Thompson, USA.*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Cardiomin
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Aminophylline (p. 1201·2).
Obstructive airways disease; status asthmaticus.

Medifarma, Indon.; UAP, Indon.
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Elevated blood homocysteine levels; vitamin deficiency.

Cardionate *Makiz-Pharma, Rus.*
Meldonium (p. 1429·3).
Tonic; cardiac disorders; alcohol withdrawal syndrome; cerebrovascular disorders.

Cardionil
Note: this name may be used for preparations of different composition.
Alacan, Spain.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Ducto, Braz.
Digoxin (p. 1353·3).
Arrhythmias.

Cardionorm
Note: this name may be used for preparations of different composition.
Denver, Arg.
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Cardionox *Alter, Port.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Cardioparin *Chandra Bhagat, India.*
Nadroparin calcium (p. 1443·2).
Thromboembolic disorders.

Cardiophyt A *Lyron, Switz.*
Crataegus (p. 2488·1); valerian (p. 2640·2).
Cardiac disorders.

Cardiopine *Julphar, UAE.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Cardiopirin *Dexcel, Israel.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Cardioplegia *IFET (ΙΦΕΤ), Gr.; Hospira, Hong Kong; Hospira, Indon.; Tempo Scan Pacific, Indon.; Martindale, Irl.; Hospira, Malaysia; Hospira, Singapore; Hospira, Thai.*
Magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); procaine hydrochloride (p. 1994·3).
Induction of cardioplegic arrest in open-heart surgery.

Cardioplegia A *Baxter, Austral.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1).
Induction of cardiac arrest during heart surgery; protection of cardiac muscle during heart surgery.

Cardioplegia Concentrate *Hospira, Austral.*
Magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); procaine hydrochloride (p. 1994·3).
Induction of cardiac arrest during open heart surgery; protection of cardiac muscle during heart surgery.

Cardioplen *Trinity, UK.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Cardioplus
Note: this name may be used for preparations of different composition.
Drugtech, Chile.
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Ipca, India.
Vitamins; minerals.

Cardioplus AM *Drugtech, Chile.*
Olmesartan medoxomil (p. 1459·2); amlodipine (p. 1304·1).
Hypertension.

Cardioplus D *Drugtech, Chile.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cardiopress *MedChem, USA.*
Vitamins; buchu (p. 2461·3); garlic (p. 2510·3); green tea (p. 2648·2); crataegus (p. 2488·1); hibiscus (p. 2525·2); juniper (p. 2537·1); olive leaf (p. 2574·3); bearberry (p. 2453·2).
Dietary supplement.

Cardiopril
Note: this name may be used for preparations of different composition.
Reddy, India.
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Cardio-Pro *British Biologicals, India.*
Ubidecarenone (p. 2637·1); vitamin B substances (p. 2102·3); protein; carbohydrate.

Cardioprotect
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Mex.
Aspirin (p. 22·2); *dl*-alpha tocoferil acetate (p. 2119·2).
Thromboembolism prophylaxis.

Cardiopyrin *Roche, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardioral *IBSA, Neth.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardiorex *Bago, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; heart failure; hypertension.

Cardiosedantol *Lafi, Chile.*
Pentaerithrityl tetranitrate (p. 1465·1); diazepam (p. 1063·2); chlormezanone (p. 1045·1).
Anxiety.

Cardiosel *UAP, Indon.†; Imperial, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension; arrhythmias; myocardial infarction.

Cardioselect N *Dreluso, Ger.*
Crataegus (p. 2488·1); cactus (p. 2473·2); arnica (p. 2447·2); spigelia (p. 2621·3).
Homoeopathic preparation.

Cardiosim *YSS, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Cardiosolupsan *BMS, Fr.†*
Lysine aspirin (p. 84·3).
Thromboembolism prophylaxis.

Cardio-Spect *Medi-Radiopharma, Cz.*
Technetium-99m (p. 2228·1) sestamibi.
Diagnosis of myocardial infarction; diagnosis of myocardial ischaemia and ventricular dysfunction.

Cardiostad
Note: this name may be used for preparations of different composition.
Stada, Denm.; Stada, Fin.
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Stada, Ukr.
⊗Carvedilol (p. 1333·1).
Hypertension; ischaemic heart disease; heart failure.

Cardiostat *Lloyd, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension; arrhythmias; hyperthyroidism; migraine.

Cardiostatin *Makiz-Pharma, Rus.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; coronary atherosclerosis.

Cardiostenol *Molteni, Ital.*
⊗Morphine hydrochloride (p. 92·3); atropine sulfate (p. 1310·2).
Pain; adjuvant in anaesthesia.

Cardiostrep *Kee, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Cardiotab *Interhealthcare, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Cardiotein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Cardiotek Rx *Stewart Jackson, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); arginine hydrochloride (p. 2049·1).

Cardioten
Note: this name may be used for preparations of different composition.
Verheilen, Philipp.
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

OFF, Ital.†
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

Cardiotensin
Note: this name may be used for preparations of different composition.
Schwarz, Pol.†
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Cardiotone *VHB, India.*
Amrinone lactate (p. 1305·1).
Heart failure.

Cardiotonic *Herbapol Krakow, Pol.*
Crataegus (p. 2488·1); valerian (p. 2640·2).
Heart failure.

Cardiovalen *Vifiteh, Rus.*
Adonis vernalis (p. 2431·1); crataegus (p. 2488·1); valerian (p. 2640·2); erysimum

(p. 2524·2); camphor (p. 2466·2); sodium bromide (p. 2461·1).
Heart failure.

Cardiovasc *Rottapharm, Ital.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Cardiovaz *Westward, Philipp.*
Captopril (p. 1331·2).
Hypertension; diabetic nephropathy; heart failure; myocardial infarction.

Cardiover *Landson, Indon.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris.

Cardiovert *Sanofi-Aventis, Philipp.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of supraventricular tachycardia.

Cardioxane *Novartis, Austria; Zodiac, Braz.; Tecnofarma, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.†; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Asofarma, Mex.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Spain; Clinigen, UK; Nolver, Venez.*
Dexrazoxane hydrochloride (p. 1548·1).
Prevention of anthracycline cardiotoxicity.

Cardioxin *Oboi, Philipp.*
Digoxin (p. 1353·3).
Supraventricular arrhythmias; heart failure.

Cardioxipin *Biosintez, Rus.*
Emoxypine hydrochloride.
Ischaemic disorders.

Cardiozen *Equazen, Hong Kong.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); ubidecarenone (p. 2637·1).
Hypertriglyceridaemias; cardiovascular disorders.

Cardip *Francia, Ital.†*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension; heart failure.

Cardiphar *Teva, Belg.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Cardipill *Ordain, India.*
Amlodipine (p. 1304·1); atorvastatin (p. 1309·2).

Cardipin *Intas, India; Spirig, Switz.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome; myocardial infarction.

Cardipin-AT *Ultramark, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Cardipirina *Zuoz, Venez.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Cardiplant *Schwabe, Pol.; Schwabe, Switz.; Schwabe, Ukr.†*
Crataegus (p. 2488·1).
Heart failure; arrhythmias; cardiac disorders.

Cardiplast *Optipharm, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Cardiplegin *Troikaa, India.*
Magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); procaine hydrochloride (p. 1994·3).
Induction of ischaemic cardiac arrest during heart surgery.

Cardipres *ACME, Philipp.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left ventricular dysfunction following myocardial infarction.

Cardipril
Note: this name may be used for preparations of different composition.
Bial, Port.
Imidapril hydrochloride (p. 1409·1).
Hypertension.

Liomont, Mex.
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Cardiprin *Reckitt Benckiser, Austral.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Cardirenal *Lanpharm, Arg.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Cardirene *Sanofi-Aventis, Ital.*
Lysine aspirin (p. 84·3).
Thrombosis prophylaxis.

Cardisan *Sanbe, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Cardisec *Taj, India.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Cardiser *Merck, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Cardismo *Phapros, Indon.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; ischaemic heart disease; heart failure.

Cardisorb *Valeant, Hung.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Cardisoz-AT *Sozin-Flora, India.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Cardispan *Grossman, Mex.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Cardistat *Biological E, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Cardistim *Intra-Labs, India.*
Levocarnitine tartrate (p. 2053·2); lycopene (p. 2546·2); policosanol (p. 1472·1); vitamin E (p. 2119·1).

Carditec *Terramedic, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; heart failure.

Carditrim *Leksredstva, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic vestibular disorders; ischaemic eye disorders.

Cardium *DHA, Singapore.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Cardivas
Note: this name may be used for preparations of different composition.
Sidus, Arg.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Sun, India; Sun, Rus.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Cardivask *Kalbe, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Cardiwell
Note: this name may be used for preparations of different composition.
Torrent, India.
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

CardiWell Omega Q10 *Blackmores, Austral.*
Omega-3 marine triglycerides (p. 1460·3); ubidecarenone (p. 2637·1).
Dietary supplement for cardiovascular health.

Cardiwell Plus *Torrent, India.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).
Stroke prophylaxis.

Cardix *Multilab, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension.

Cardizem *Sanofi-Aventis, Austral.; Boehringer Ingelheim, Braz.; Valeant, Canad.; Ferrosan, Denm.; Pfizer, Fin.; Pfizer, Norw.; Sanofi-Aventis, NZ; Pfizer, Swed.; AbbVie, USA.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Cardogrel *Sandoz, Philipp.; Sandoz, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Card-OK *Vivax, Gr.*
Atorvastatin calcium (p. 1309·2).

Cardol
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Scoshia, India.
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Cardolex *Sanovel, Turk.*
Amlodipine (p. 1304·1); valsartan (p. 1521·2).

Cardomin
Note: this name may be used for preparations of different composition.
Naprod, Philipp.
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Sanovel, Rus.
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Cardomin Plus *Sanovel, Rus.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cardonat *Sperko, Ukr.*
Lysine hydrochloride (p. 2079·3); carnitine chloride (p. 2053·2); pyridoxal phosphate (p. 2105·3); cocarboxylase chloride (p. 2102·3); cobamamide (p. 2107·2).
Asthenia; tonic.

Cardonit *Polfa Warszawo, Pol.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Cardopan *Sanovel, Turk.*
Valsartan (p. 1521·2).

Cardopan Plus *Sanovel, Turk.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).

Cardopar *DHA, Singapore.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Cardopax *Orion, Denm.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Cardoral *Pfizer, Israel.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Cardoreg *Ratiopharm, Denm.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Cardosal *Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Cardosal Plus *Berlin-Chemie, Ukr.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cardosart *Douglas, NZ.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Cardosin *Actavis, Denm.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Cardotard *Tenlec, Denm.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Cardox *Ethypharm, Irl.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Cardoxa *Sriprasit, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Cardoxan *Douglas, NZ.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Cardoxin *Rafa, Israel.*
Dipyridamole (p. 1362·2).
Adjunct to cardiac imaging; nephrotic syndrome; pre-eclampsia; thromboembolism prophylaxis; glomerulonephritis.

Cardoxone *Remedica, Thai.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; migraine.

Cardozin *Actavis, UK.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Cardpin *Ultramark, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Carductal *Tekhnolog, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Ischaemic heart disease; ischaemic cochlear-vestibular disturbance; ischaemic chorioretinal vascular disorders.

Cardugen *Mylan, S.Afr.*
Doxazosin (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Cardular *Pfizer, Ger.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Cardules *Piramal, India.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Cardules Plus *Piramal, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Cardura *Pfizer, Arg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Gr; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Carduran *Pfizer, Braz.; Pfizer, Denm.; Pfizer, Norw.; Pfizer, Spain.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Carduus Plex *Seroyal, Canad.†*
Belladonna (p. 2453·3); black root; celandine (p. 2522·2); cholesterol (p. 2179·1); cinchona officinalis (p. 2478·3); citrullus colocynthis (p. 1833·3); fel tauri (p. 2457·2); lycopodium clavatum (p. 2547·1); milk thistle (p. 1561·1); podophyllum (p. 1717·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Cardyl *Pfizer, Spain.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Cardyn *Tripharma, Turk.*
Atorvastatin calcium (p. 1309·2).

CardZaar *Balu, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Carebin *Pisa, Mex.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Carecof *Intra-Labs, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Carecof Exp *Intra-Labs, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Caredec *Arvincare, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Caredrox *Intra-Labs, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Caredroxyl-LB *Intra-Labs, India.*
Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

Careflu *Farma 1, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic disorders of the respiratory tract.

Carel *Intas, India.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).

Carelet *Servocare, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Careload *Toroy, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension.

Carelol *East West, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carena
Note: this name may be used for preparations of different composition.
Biofarma, Turk.
Aminophylline (p. 1201·2).
Obstructive airways disease.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sanofi-Aventis, Spain.
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin irritation; burns; wounds.

Carencil *Jaba, Port.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; left-ventricular dysfunction; diabetic nephropathy.

Carencyl *Tonipharm, Fr.†*
Vitamins amino acids; minerals.
Tonic.

Careprost *Sun, India.*
Bimatoprost (p. 2004·2).
Glaucoma.

Careprost Plus *Sun, India.*
⊗Bimatoprost (p. 2004·2); timolol (p. 1513·2).
Glaucoma.

Careram *Eisai, Jpn.*
Iguratimod (p. 71·1).
Rheumatoid arthritis.

Caresel *Marfarma, Ital.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1); betacarotene (p. 2051·1); astaxanthin (p. 2170·1).
Nutritional supplement.

Caresens N *Dinno, Fr.*
Test for glucose in blood (p. 2516·3).

Caresol *Laborate, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Caress *MSD, Swed.*
⊗Urea (p. 1727·3).
Dry skin.

Carexan *Pisa, Mex.†*
Itraconazole (p. 583·3).
Fungal infections.

Carexidil *Difa, Ital.; Cantabria, Spain.†*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Careza *Silesia, Chile.*
24 Tablets, ethinylestradiol (p. 2275·3); gestodene (p. 2279·3); 4 tablets, inert.
Combined oral contraceptive.

CareZee *Pharmacare, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ca-Rezz *FNC, USA.*
Triclosan (p. 1773·2).
Skin disinfection.

Carfenil *Chugai, Jpn.*
Lobenzarit sodium (p. 2544·3).
Rheumatoid arthritis.

Carfer *Dr Kumars, India.*
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3).

East West, India.
Capsules: Folic acid (p. 2063·1); iron carbonyl (p. 2073·1); zinc sulfate (p. 2126·2).

Carfol-Z *Armour, India.*
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc gluconate (p. 2126·2); selenium (p. 2086·3); vitamin E (p. 2119·1).

Armour, India.
Tablets: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Carfosid *Titanadria, Ital.*
Iron-rich yeast (p. 2125·2); levocarnitine (p. 2053·2); calcium folinate (p. 2066·3).
Anaemias.

Cargespril *Gelcaps, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Cargosil *Genepharm, Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Cariamyl
Note: this name may be used for preparations of different composition.
Corsa, Indon.; Sanofi Synthelabo, Indon.
Heptaminol acefyllinate (p. 1210·3).
Bronchitis; asthma; dyspnoea.

Prater, Chile.
Cream: Menthol (p. 2553·2); camphor (p. 2466·2); triclosan (p. 1773·2); benzocaine (p. 1980·2).
Skin irritation.

Prater, Chile.
Lotion: Camphor (p. 2466·2); triclosan (p. 1773·2); benzocaine (p. 1980·2).
Skin irritation.

Cariax *Pharma Investi, Chile.*
Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis; oral hygiene.

Cariban *Inibsa, Spain.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting.

Caribbean Breeze Burn Relief *Caribbean Breeze, Canad.*
Lidocaine hydrochloride (p. 1988·2).

Caribbean Breeze Kids Sunscreen *Caribbean Breeze, Canad.*
Lotion SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Caribbean Breeze Sunscreen *Caribbean Breeze, Canad.*
Lotion SPF 15, SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Caribbean Breeze, Canad.
Spray lotion SPF 30, SPF 45: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Caribbean Breeze, Canad.
Spray lotion SPF 12, SPF 15, SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Caricose *Christo, Hong Kong.†*
⊗Amylase (p. 2442·1); papain (p. 2582·3); thiamine hydrochloride (p. 2103·1).
Digestive disorders.

Carident *Chema-Elektromet, Pol.*
⊗Framycetin sulfate (p. 301·2); papain (p. 2582·3).
Mouth disorders.

Caridoxen *Mavi, Mex.*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Carig *Cadila, India.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Carilax *Strallhofer, Austria.*
Fig (p. 1843·2); senna (p. 1885·1).
Constipation.

Carimune *CSL, USA.*
A normal immunoglobulin (p. 2403·3).

Carin
Note: this name may be used for preparations of different composition.
CCM, Hong Kong; CCM, Malaysia; Upha, Singapore.
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; eye irritation; allergic conjunctivitis; urticaria.

Federfarma, Ital.
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; cold and influenza symptoms.

Carina *Cooper (Κοπερ), Gr.*
Glyceryl trinitrate (p. 1391·2).

Carin-Fer *Bryntsalov, Rus.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's disease.

Carinose *Community Pharmacy, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; hay fever.

Carinox *CCM, Malaysia.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Cario *Sienna, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Sienna, India.
Syrup: Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Caripazim *Kutateladze Institute, Ukr.*
Papaya.
Burns; joint disorders; scars; cerebral and spinal arachnoiditis; facial nerve neuritis; inflammatory mouth disorders.

Caripazym *Medflorina, Rus.*
⊗Papain (p. 2582·3).
Burns.

Cariso-Co *PP Lab, Thai.†*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3).
Musculoskeletal disorders.

Carisoma *Wallace, India.*
Carisoprodol (p. 2021·3).
Skeletal muscle spasm.

Carisoma Compound
Note: this name may be used for preparations of different composition.
Wallace, India.
Carisoprodol (p. 2021·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Skeletal muscle pain and spasm.

Carista *Bionova, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Caristop *Maver, Chile.*
Mouthwash: Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Maver, Chile.
Toothpaste: Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2); sodium benzoate (p. 1738·2).
Dental caries prophylaxis.

Caristop Sensitive *Maver, Chile.*
⊗Sodium monofluorophosphate (p. 2091·3); potassium nitrate (p. 1766·2).
Dental caries prophylaxis; hypersensitive teeth.

Caritasone *Chinta, Thai.*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Caritec *Ranbaxy, India.*
Benidipine hydrochloride (p. 1316·1).
Angina pectoris; hypertension.

Carito mono *Maxmedic, Ger.*
Java tea (p. 2536·3).
Urinary-tract disorders.

Cariv *East African, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carived *Cipla, Neth.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carizine *East West, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Cariz-XT *Daksh, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Carl Baders Divinal *Apotheke Heiligen Rupertus, Austria.*
Camphor and camphor spirit (p. 2466·2); methyl salicylate (p. 92·1); salicylic acid (p. 1719·1); salol (p. 129·3); turpentine oil (p. 2636·3); rosemary oil (p. 2607·3); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Carlets 9 11 *Keton, Mex.*
Vitamins.

Carlev *Aamorb, India.*
Diethylcarbamazine; levocetirizine (p. 632·3).
Worm infections.

Carlevod *LKM, Arg.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

CarLich *Winthrop, Ger.†*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carlin *Effik, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Carloc *Cipla, India; Cipla-Medpro, S.Afr.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Carlymox *Mount Mettur, India.*
Amoxicillin (p. 216·2); carbocisteine (p. 1658·1).
Respiratory-tract infections.

Carlytène *Meda, Fr.*
Moxisylyte hydrochloride (p. 1441·3).
Mental function impairment; Raynaud's syndrome.

Carmapine *Pharmasant, Thai.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; glossopharyngeal neuralgia; alcohol withdrawal syndrome; diabetic neuropathy.

Carmaz *Sun, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carmazin *Teuto, Braz.*
Carbamazepine (p. 512·2).
Epilepsy.

Carmed *Surya Dermato, Indon.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders.

Carmeg *Alembic, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carmen
Note: this name may be used for preparations of different composition.
Berlin-Chemie, Ger.
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Nevzat, Turk.
Carboplatin (p. 759·1).

Carmen ACE *Berlin-Chemie, Ger.*
Lercanidipine hydrochloride (p. 1419·3); enalapril maleate (p. 1371·1).
Hypertension.

Carmex *Carma, Canad.*
Ointment SPF 15; stick SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Carmex Lip Balm *Carma, Canad.*
Camphor (p. 2466·2); phenol (p. 1763·3).

Carmex Lip Ointment *Carma, Canad.*
Camphor (p. 2466·2); phenol (p. 1763·3).

Carmian *Teofarma, Ital.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Carmicide *Indoco, India.*
Sodium citrate (p. 1781·2); citric acid (p. 2480·3); ginger oil (p. 1844·1); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3).
Flatulence; colic; griping pain.

Carmicide DPS *Indoco, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Carmin *Elea, Arg.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Carminative Medicine *Srichand, Thai.*
Sodium bicarbonate (p. 1781·1).

Carminative Patar *Patar, Thai.*
Capsicum tincture (p. 2469·3); cardamom tincture (p. 2471·1); strong ginger tincture (p. 1844·1); camphor spirit (p. 2466·2).
Gastrointestinal disorders.

Carminative Sahakarn *United Drug, Thai.*
Capsicum tincture (p. 2469·3); strong ginger tincture (p. 1844·1); camphor spirit (p. 2466·2); compound cardamom tincture (p. 2471·1).
Gastrointestinal disorders.

Carminativo Juventus *Juventus, Spain.*
Anise oil (p. 2444·3); belladonna tincture (p. 2453·3); sodium bicarbonate (p. 1781·1).
Aerophagia; meteorism; vomiting.

Carminativum Babynos *Dentinox, Ukr.*
Fennel (p. 2503·2); coriander (p. 2486·3); chamomile (p. 2474·1).
Meteorism in children; gastrointestinal disorders.

Carminativum Hevert *Hevert, Ger.*
Carbo vegetabilis (p. 1537·3); colocynthis (p. 1833·3); magnesium chloratum (p. 1787·1); nux vomica (p. 2573·3).
Homoeopathic preparation.

Carminativum Hofmann *Hofmann & Sommer, Ger.†*
Peppermint leaf (p. 1877·1); chamomile (p. 2474·1); caraway (p. 2470·2).
Dyspepsia.

Carminativum-Hetterich *Teofarma, Ger.*
Chamomile (p. 2474·1); peppermint leaf (p. 1877·1); caraway (p. 2470·2); fennel (p. 2503·2); dried bitter-orange peel (p. 2575·3).
Gastrointestinal disorders.

Carminex *Adcock Ingram, S.Afr.†*
Magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); sodium citrate (p. 1781·2).
Gastric hyperacidity.

Carmint *Sofar, Ital.*
Peppermint oil (p. 1877·1).
Gastrointestinal disorders.

Carmize *Aspire, UK.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Carmol
Note: this name may be used for preparations of different composition.
Doak, Hong Kong; PharmaDerm, USA.
⊗Urea (p. 1727·3).
Dry skin; hyperkeratosis.

Penta, Hung.
Menthol (p. 2553·2); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); lavender oil (p. 2541·1); melissa (p. 2552·3); nutmeg oil (p. 2573·2); sage oil (p. 2609·1); citronella oil (p. 2481·1); anise oil (p. 2444·3); lemon oil (p. 2543·1); thyme oil (p. 2630·3).
Digestive disorders; nervousness; musculoskeletal and joint pain; insect bites; pruritus; respiratory-tract congestion.

Carmol HC *PharmaDerm, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Corticosteroid.

Carmol Magen-Galle-Darm *Omegin, Ger.†*
Taraxacum (p. 2625·3); peppermint leaf (p. 1877·1); cynara (p. 2490·3).
Biliary-tract disorders.

Carmol Scalp Treatment *Doak, USA.†*
Sulfacetamide sodium (p. 361·1).
Scalp infections.

Carmolis *Santa, Rus.*
Menthol (p. 2553·2); thyme oil (p. 2630·3); anise oil (p. 2444·3); Chinese schisandra oil (p. 2611·2); clove oil (p. 2481·3); lemon oil (p. 2543·1); lavender oil (p. 2541·1); spike lavender oil (p. 2621·3); citronella oil (p. 2481·1); sage oil (p. 2609·1); nutmeg oil (p. 2573·2).
Respiratory-tract inflammation; dyspepsia; nervous disorders; musculoskeletal and joint disorders; neuritis; headache; pruritus.

Schmidgall, Pol.
Anise oil (p. 2444·3); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); lemon oil (p. 2543·1); lavender oil (p. 2541·1); citronella oil (p. 2481·1); sage oil (p. 2609·1); thyme oil (p. 2630·3); menthol (p. 2553·2); melissa (p. 2552·3).
Gastrointestinal disorders; anxiety; insomnia; mood disturbances; headache; respiratory-tract disorders; musculoskeletal and joint disorders; neuralgia; pruritus; insect bites.

Carmolis Fluid *Santa, Rus.*
Menthol (p. 2553·2); pine oil (p. 2591·1); methyl salicylate (p. 92·1); camphor (p. 2466·2); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); rosemary oil (p. 2607·3); thyme oil (p. 2630·3); citronella oil (p. 2481·1); sage oil (p. 2609·1); nutmeg oil (p. 2573·2); anise oil (p. 2444·3); clove oil (p. 2481·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Carmotin *Fada, Arg.†*
Alendronate (p. 1171·3).

Carmox *Indu, India.*
Amoxicillin (p. 216·2); carbocisteine (p. 1658·1).
Respiratory-tract infections.

Carmubris *BMS, Austria; BMS, Ger.†; IFET (ΙΦΕΤ), Gr.*
Carmustine (p. 761·2).
Malignant neoplasms.

Carnabol *Ache, Braz.*
Buclizine hydrochloride (p. 618·3); caffeine (p. 1203·3); carnitine hydrochloride (p. 2053·2); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Tonic; reduced appetite.

Carnation
Note: this name may be used for preparations of different composition.
Cuxson, Gerrard, Canad.; Cuxson, Gerrard, Irl.; Cuxson, Israel; Cuxson, Gerrard, UK.
Salicylic acid (p. 1719·1).
Calluses; corns; verrucas.

Carnation Calcium Plus with Fiber *Nestle, Philipp.†*
Preparation for enteral nutrition.

Carnet *Chia Tai, China.*
Foscarnet sodium (p. 981·1).
Cytomegalovirus retinitis; herpes simplex infections.

Carni Plus *Ikapharmindo, Indon.*
Levocarnitine (p. 2053·2); choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2); nicotinamide (p. 2083·1); zinc amino acid chelate (p. 2048·3); magnesium amino acid chelate (p. 2048·3); manganese amino acid chelate (p. 2048·3); vitamin B_6 (p. 2105·3).
Obesity.

Carniben *Bennett, Gr.*
Levocarnitine (p. 2053·2).

Carnicle *Neiss, India.*
Levocarnitine tartrate (p. 2053·2).

Carnicor *Labomed, Chilet; Sigma-Tau, Philipp.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; heart failure; angina pectoris; arrhythmias; carnitine deficiency.

Sigma-Tau, Spain.
Carnitine (p. 2053·2).
Carnitine deficiency.

Carnidose *Faran, Gr.*
Levocarnitine (p. 2053·2).
Cardiomyopathy; carnitine deficiency.

Carnidyn *Sigma-Tau, Switz.*
Creatine (p. 2488·3); acetylcarnitine taurinate; carnosine; magnesium; zinc; selenium; vitamin E (p. 2119·1).
Tonic.

Carnigen *Sanofi-Aventis, Austria†; Cassella-med, Ger.†*
⊗Oxilofrine hydrochloride (p. 1463·2).
Hypotension; orthostatic hypotension; circulatory disorders.

Carnil *Anfarm, Gr.*
Levocarnitine (p. 2053·2).
Cardiomyopathy; carnitine deficiency.

Carnil AC *Azine, India.*
Aceclofenac (p. 16·2).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Carnil ACP *Azine, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Carnil MR *Azine, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Carnil Plus *Azine, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Carniland *Tverskaya, Rus.*
Glyceryl trinitrate (p. 1391·2); menthyl isovalerate (p. 2554·1); convallaria (p. 2486·2).
Angina pectoris.

Carniprol *Proel, Gr.*
Levocarnitine (p. 2053·2).

Carnisac *Iamatica, Gr.*
Levocarnitine (p. 2053·2).

Carnisin *Leti, Venez.*
Levocarnitine (p. 2053·2).

Carnit *Elder, India.*
Levocarnitine (p. 2053·2); vitamin B substances (p. 2102·3).

Carniten *Riace, Rus.*
Levocarnitine hydrochloride (p. 2053·2).
Carnitine deficiency; cardiac disorders.

Carnitene *Sigma-Tau, China; Sigma-Tau, Hong Kong; Sigma-Tau, Ital.; Santa, Turk.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; myocardial ischaemia; cardiac disorders.

Carnitop *Sanopharm, Gr.*
Levocarnitine tartrate (p. 2053·2).

Carnitor *Sigma-Tau, Canad.; Sigma-Tau, Hong Kong; Elder, India; Sigma-Tau, UK; Sigma-Tau, USA.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; cardiac disorders.

Carnivit *Viofar, Gr.; Polfa Kutno, Pol.†*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Carnol *PDC, India.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor.

Carnon *Ethica, Indon.*
Ubidecarenone (p. 2637·1); levocarnitine fumarate (p. 2053·2).
Dietary supplement.

Carnosin *Samarth, India.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Carnot Colutorio *Esme, Arg.*
Bacitracin (p. 225·3); gramicidin (p. 308·3); benzocaine (p. 1980·2); lidocaine (p. 1988·1).
Mouth disorders.

Carnot Topico *Esme, Arg.*
Aluminium chloride (p. 1693·3); acriflavinium chloride (p. 1732·3); lidocaine hydrochloride (p. 1988·2); eugenol (p. 2501·2).
Mouth disorders.

Carnotprim *Carnot, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; migraine; nausea and vomiting.

Carnovis *Sigma-Tau, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Carnyl *Nycomed, Denm.†*
Aspirin (p. 22·2).
Thromboembolic disorders.

Carnyl-FE *Obsurge, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).
Vitamin C (p. 2110·3) may be included in this preparation to increase the absorption and availability of iron.

Carobel *Cow & Gate, Irl.; Cow & Gate, UK.*
Ceratonia (p. 2178·1).
Nausea and vomiting in pregnancy; dysphagia; feed thickener to control vomiting.

Car-OD *Yash, India.*
Ambroxol hydrochloride (p. 1654·3); cetirizine hydrochloride (p. 619·2).

Carofit *Ajanta, Philipp.*
Carrot extract; betacarotene (p. 2051·1); *d*-alpha tocopherol (p. 2119·1); ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2); selenium dioxide (p. 2087·1).
Dietary supplement.

Ajanta, India.
Cream: Arbutin (p. 1694·3); kojic acid (p. 1710·2); lactic acid (p. 2539·1).

Ajanta, India.
Tablets: Betacarotene (p. 2051·1); carrot; vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Carofit-D *Ajanta, India.*
Carotenoids; chromium (p. 2055·3); selenium (p. 2086·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc sulfate (p. 2126·2).

Carominthe *Lehning, Fr.*
Absinthium (p. 2426·1); artemisia vulgaris; collinsonia canadensis (p. 2622·2); nux vomica (p. 2573·3); lupulinum; mentha piperita (p. 1877·1); acorus calamus (p. 2464·2).
Homoeopathic preparation.

Carone *IQFA, Mex.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Caroneg *Ankom, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2); with or without vitamin B_{12} (p. 2107·2).

Caropram *Khandelwal, India.*
Doxapram (p. 2321·2).
Respiratory failure; respiratory depression.

Carotaben *Hermal, Austria; Hermal, Cz.; Almirall Hermal, Ger.; Almirall, Switz.*
Betacarotene (p. 2051·1).
Erythropoietic protoporphyria; photodermatoses; skin pigmentation disorders.

Carotenos *Natufarma, Arg.*
Ascorbic acid (p. 2110·3); betacarotene (p. 2051·1); alfa tocopherol (p. 2119·1).
Vitamin supplement.

Carotinora *Twardy, Ger.*
Betacarotene (p. 2051·1).
Vitamin A deficiency.

Carovigen *Eras, Turk.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

Carovit *Rottapharm, Ital.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Kocak, Turk.
Betacarotene (p. 2051·1).
Vitamin A deficiency.

Carovit Forte *Rottapharm, Ital.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Carovit Melanin *Rottapharm, Ital.*
Amino acids; vitamins; minerals.
Nutritional supplement.

Carovit Repair *Rottapharm, Ital.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); polysaccharide cartilage extract from marine fish.
Nutritional supplement.

Caroza *Zydus, India.*
Ranolazine (p. 1484·3).
Angina pectoris.

Carpiaton *Fahrenheit, Indon.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; aldosteronism.

Carpigrel *Shrishti, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Carpilo *Chauvin, Fr.†*
⊗Pilocarpine hydrochloride (p. 2010·3); carteolol hydrochloride (p. 1332·3).
Ocular hypertension; glaucoma.

Carpin *Novag, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; diabetic neuropathy; diabetes insipidus; polyuria; polydipsia.

Carpine
Note: this name may be used for preparations of different composition.
Atlantic, Thai.
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Intas, India.
Pilocarpine nitrate (p. 2010·3).
Glaucoma.

Carpinol *Sunways, India.*
Pilocarpine nitrate (p. 2010·3).
Glaucoma.

Carpo-Miotic *Bell, India.†*
Pilocarpine nitrate (p. 2010·3).
Glaucoma.

Carporen *Indoco, India.*
Pilocarpine nitrate (p. 2010·3).
Glaucoma.

Car-Q *Kalbe, Indon.*
Ubidecarenone (p. 2637·1); levocarnitine fumarate (p. 2053·2).
Cardiovascular function; antoxidant.

Carrasyn *Carrington, USA.*
Acemannan (p. 2426·3).
Wounds.

Carreldon *Bama, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Carrier
Note: this name may be used for preparations of different composition.
Casasco, Arg.
Memantine hydrochloride (p. 393·1).
Alzheimer's disease; muscle spasticity.

Carrington's Gripe Water *ICM, Singapore.*
Sodium bicarbonate (p. 1781·1).

Carron *BMW, India.*
Capsules: Iron (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

BMW, India.
Syrup: Iron (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2); cyanocobalamin (p. 2107·2); selenium dioxide (p. 2087·1); vitamin E (p. 2119·1).

Carrox *Sanovel, Turk.*
Zafirlukast (p. 1239·3).
Asthma.

Carsem *Teva, Irl.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Carsemex *TP, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess or viscous mucus; otitis; otorrhoea.

Carsil *Sopharma, Rus.*
Milk thistle (p. 1561·1).
Liver disorders.

Sopharma, Ukr.
Silymarin (p. 1561·2).
Liver disorders.

Carsol *Sandoz, Switz.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; neuralgias; alcohol withdrawal syndrome.

Carsuquin *Degorts, Mex.*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis; trichomoniasis.

Cartab *RPG, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Cartago *Lampugnani, Ital.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine hydrochloride (p. 2515·3); devil's claw root (p. 42·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).
Joint disorders.

Cartan
Note: this name may be used for preparations of different composition.
Demo, China.
Levocarnitine (p. 2053·2).
Quesada, Arg.
Losartan (p. 1422·2).
Hypertension.

Cartan D *Quesada, Arg.*
⊗Losartan (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Carteabak *Thea, Belg.; Farmila, Ital.; Thea, Neth.; Thea, Port.*
⊗Carteolol hydrochloride (p. 1332·3).
Ocular hypertension; glaucoma.

Cartéabak *Thea, Fr.†*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Cartens *Atlas, Arg.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Carteodose *Lamda (Λαμδα), Gr.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma.

Carteol *Meda, Belg.; Mann, Cz.; Chauvin, Israel; SIFI, Ital.; Mann, Pol.; Abdi, Turk.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Cartéol *Chauvin, Fr.*
⊗Carteolol hydrochloride (p. 1332·3).
Ocular hypertension; open-angle glaucoma.

Carteopil *Meda, Belg.†*
⊗Pilocarpine hydrochloride (p. 2010·3); carteolol hydrochloride (p. 1332·3).
Ocular hypertension; glaucoma.

Carters
Note: this name may be used for preparations of different composition.
Therabel, Belg.
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Carters Little Pills *Church & Dwight, Canad.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Cartexan *Bioiberica, Fin.*
Chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis of the hip and knee.

Cartia
Note: this name may be used for preparations of different composition.
GSK, Austral.; Perrigo, Israel; GSK, NZ; Lusofarmaco, Port.
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Watson, USA.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Cartibon *Biofarma, Mex.*
Shark-liver oil (p. 2614·2); vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).
Dietary supplement.

Car-ti-buron *Lafarmen, Arg.*
Cartilage (shark) (p. 2471·3).
Musculoskeletal and joint disorders.

Car-ti-buron Flex *Lafarmen, Arg.*
Glucosamine (p. 2515·3); cartilage (shark) (p. 2471·3); magnesium hydroxide (p. 1857·2).

Carticare *Cadila, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Cartidin *Ranbaxy, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Cartidont *Curaden, Ital.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Cartiel *Obsurge, India.*
Glucosamine sulfate (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Cartiel D *Obsurge, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Cartifact *Medico, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Cartifast-C *XL, Philipp.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Cartifix *Biological E, India.*
Chondroitin (p. 2476·1); glucosamine (p. 2515·3); manganese (p. 2081·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Cartiflex
Note: this name may be used for preparations of different composition.
Galenium, Indon.
Glucosamine (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); dimethyl sulfone (p. 2493·3).
Joint disorders.

ISA, Arg.
Cream: Diethylamine salicylate (p. 51·3); benzocaine (p. 1980·2).

ISA, Arg.
Tablets: Cartilage (shark) (p. 2471·3); minerals; vitamin D (p. 2112·3); carbohydrates; proteins; lipids.

Cartiflex Forte *ISA, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Degenerative joint disorders.

Cartigen *Pharmed, India.*
Capsules; sachets; tablets: Glucosamine sulfate (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

Pharmed, India.
Ointment: Boswellia serrata (p. 2507·3); capsicum (p. 2469·3); cinnamon oil (p. 2479·3); glucosamine sulfate (p. 2515·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Cartigen Plus *Pharmed, India.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate (p. 2515·3); dimethyl sulfone (p. 2493·3); boron; chromium; manganese; selenium; silicon dioxide; vitamin C; colecalciferol; vitamin E; zinc.
Dietary supplement.

Cartijoint *Fidia, Ital.†*
Capsules: Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Fidia, Ital.†
Cream: Chondroitin sulfate (p. 2476·1); hyaluronic acid (p. 2526·2).
Joint disorders.

Cartilag *Eagle, Austral.†*
Cartilage (bovine) (p. 2471·3).
Dietary supplement.

Cartilago T-500 *Knop, Chile.†*
Shark cartilage (p. 2471·3); soya lecithin (p. 2542·2); silicon dioxide (p. 2208·3).
Joint disorders.

Cartilago Vital *AM, Arg.*
Cartilage (shark) (p. 2471·3).
Dietary supplement.

Cartilamine *Troikaa, India.*
Glucosamine sulfate (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Cartilamine DS *Troikaa, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Cartilamine Forte *Troikaa, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Cartilamine Total *Troikaa, India.*
Glucosamine sulfate (p. 2515·3); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).

Cartilamine-SR *Troikaa, India.*
Glucosamine sulfate (p. 2515·3); potassium chloride (p. 1793·2).

Cartiltein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Cartimax *Argenfarma, Arg.*
Cartilage (shark) (p. 2471·3).
Osteoarthritis.

Cartimin *ID, Neth.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Cartimost GM *Aareen, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Cartin *Combiphar, Indon.*
Chondroitin sulfate (p. 2476·1); glucosamine (p. 2515·3); vitamins.
Osteoarthritis.

Cartine *Huons, Philipp.; Tecnifar, Port.†*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Cartipro *Recon, Singapore.*
Glucosamine sulfate (p. 2515·3); ascorbic acid (p. 2110·3).
Joint disorders.

Zydus, India.
Glucosamine hydrochloride (p. 2515·3); ascorbic acid (p. 2110·3).

Cartisafe *Jenburkt, India.*
Glucosamine sulfate (p. 2515·3); calcium (p. 1783·1).
Osteoarthritis.

Cartisark *Pharmed, India.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Cartisorb *Bioiberica, Spain.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Cartispan *Medispan, India.*
Glucosamine sulfate (p. 2515·3); manganese sulfate (p. 2081·2).
Osteoarthritis; rheumatoid arthritis.

Cartivit *Apex, India.*
Chondroitin sulfate (p. 2476·1); red tablets, glucosamine sulfate (p. 2515·3); manganese (p. 2081·2); vitamin C (p. 2110·3); yellow tablets, dimethyl sulfone (p. 2493·3); vitamin E (p. 2119·1).

Cartivix *Jaba, Port.*
Diacerein (p. 45·3).
Osteoarthritis.

Cartiwel *Serum Institute, India.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); dimethyl sulfone (p. 2493·3); manganese (p. 2081·2); vitamin C (p. 2110·3).

Cartiz
Note: this name may be used for preparations of different composition.
Ritz, India.
Diacerein (p. 45·3).
Osteoarthritis.

Wockhardt, India.
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); manganese sulfate (p. 2081·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Cartiz-GM *Ritz, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Cartizole Plus *Pulse, India.*
Cetyl myristoleate (p. 2473·3); glucosamine sulfate potassium chloride (p. 2515·3); dimethyl sulfone (p. 2493·3).

Cartos *Pyridam, Indon.*
Glucosamine sulfate potassium (p. 2515·3).
Osteoarthritis; joint disorders.

Cartrax *Pfizer, Braz.*
Tioconazole (p. 595·3); tinidazole (p. 949·2).
Vulvovaginal infections.

Cartrex *Almirall, Fr.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Cartrilet *Fahrenheit, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Cartril-S *CCM, Hong Kong.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

CCM, Malaysia; Upha, Singapore.†
Glucosamine hydrochloride (p. 2515·3) or glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Cartrimox *Ace, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Cartrodar *Elder, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Cartrol *Abbott, USA.†*
⊗Carteolol hydrochloride (p. 1332·3).
Hypertension.

Cartrosyn *Eurodrug, Philipp.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Cartup *Zydus, India.*
Chondroitin (p. 2476·1); glucosamine (p. 2515·3).

Caruderma *Europharm, Hong Kong.*
⊗Urea (p. 1727·3).
Dry skin.

Carvas
Note: this name may be used for preparations of different composition.
Medley, India.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Meproform, Indon.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Carvasc *Aurobindo, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Carvasc-A *Aurobindo, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Carvasc-L *Aurobindo, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Carvasin *Teofarma, Ital.*
Isosorbide dinitrate (p. 1412·2).
Heart failure; angina pectoris.

Carvastin *Domesco, Philipp.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Carve *TAD, Ger.†*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carvecard *AWD, Ger.†*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carvedexxon *Dexcel, Israel.*
⊗Carvedilol (p. 1333·1).
Heart failure.

Carvedigamma *Worwag, Cz.†; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.; Worwag, Ukr.†*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carvedil *Bago, Arg.; Alkem, India; Behrens, Venez.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carvedil D *Bago, Arg.*
⊗Carvedilol (p. 1333·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Carvedilat *Sigma, Braz.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carvedilen *Specifar, Gr.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Carvel *Taurus, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carvenal *Shin Poong, Rus.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carvepen *Elpen (Ελπεν), Gr.; Elpen, Malaysia; Elpen, Singapore.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carve-Q *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carveratio *Ratiopharm, Fin.; Ratiopharm, Swed.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Carverol *Bio Macro, Braz.*
Activated charcoal (p. 1537·3).

Carvesan *Medopharm, Cz.; Drogsan, Turk.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carvetrend *Pliva, Cz.†; Pliva, Hung.; Piramal, India; Pliva Krakow, Pol.; Pliva, Rus.; Pharma Dynamics, S.Afr.; Pliva, Ukr.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension; angina pectoris; left-ventricular dysfunction; ischaemic heart disease.

Carvexal *Sandoz, Turk.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Carvid *Therapharma, Philipp.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris.

Carvidex *Reddy, Ukr.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; coronary artery disease.

Carvidil *Grindex, Rus.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carvidol *Nanxin, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Carvidon *Micro, India; Brown & Burk, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; Ménière's disease.

Carvil *Zydus, India.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Carvilex *Actavis, Pol.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Carvimed *Comed, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carvipress *Micro, India; Visufarma, Ital.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carvizest *Emcure, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carvol *Teva, Hung.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Carvon *Weleda, Switz.*
Activated charcoal (p. 1537·3); cumin oil.
Flatulence; colic; digestive disorders.

Carvyx *Mylan, Spain.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Carxasin *M & H, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Carylderm *SSL, UK.*
Carbaryl (p. 2150·1).
Pediculosis.

Caryn *General Sanyang, China.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Caryolysine *Genopharm, Fr.†; IFET (ΙΦΕΤ), Gr.*
Chlormethine hydrochloride (p. 765·1).
Malignant neoplasms; malignant effusions; psoriasis; lymphomas; mycosis fungoides.

Caryopin *Chinta, Thai.*
Aluminium hydroxide gel (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); liquorice (p. 1853·2); compound cardamom tincture (p. 2471·1); strong ginger tincture (p. 1844·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); peppermint oil (p. 1877·1).
Peptic ulcer; gastric hyperacidity; abdominal distension; flatulence; heartburn.

Carzec *GSK, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Carzem *Unison, Thai.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Carzep *Taurus, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carzepin *Hovid, Singapore.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carzepine *Condrugs, Thai.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; alcohol withdrawal syndrome; diabetic neuropathy; diabetes insipidus.

Carzilasa *Manuell, Mex.*
Cocarboxylase (p. 2103·1).
Cardiovascular, cerebrovascular, and metabolic disorders.

Carzin *Pharma Dynamics, S.Afr.*
Doxazosin (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Carzine *East West, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Carzin-IPC *Apotex, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Carzoflep *Pisa, Mex.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Casacol *Helsinn Birex, Irl.*
⊗Methoxyphenamine hydrochloride (p. 1669·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough; respiratory-tract congestion.

Casarlic *Liconsa, Neth.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Casbame *Bajamed, Mex.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Casbol *Abbott, Spain.†*
Paroxetine hydrochloride (p. 440·3).
Anxiety disorders; depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Cascade *Lane, UK.*
Bearberry (p. 2453·2); clivers (p. 2481·2); lappa root (p. 2540·1).
Water retention.

Cascahist *Casca, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cascal *Casca, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Cascalax *Will-Pharma, Neth.†*
Casanthranol (p. 1826·1).
Constipation.

Cascara Sagrada Bouzen *Bouzen, Arg.*
Cascara (p. 1826·1); belladonna (p. 2453·3); bile salts (p. 2457·2); phenolphthalein (p. 1877·3).
Constipation.

Cascara Sagrada Oligoplex *Madaus, Arg.*
Sodium picosulfate (p. 1887·2); belladonna (p. 2453·3); cascara (p. 1826·1).
Constipation.

Cascara Sagrada Püler *HMA, Arg.*
Cascara (p. 1826·1); phenolphthalein (p. 1877·3).
Constipation.

Cascazyme *Casca, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders.

Cascef *Casca, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Casclav *Casca, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Cascor *Ranbaxy, Malaysia; Ranbaxy, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Casdom *Casca, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Casdom-P *Casca, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Casdrogen *Cryopharma, Mex.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Caseal *Taiwan Biotech, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; rheumatic disorders.

Casec *Mead Johnson, Israel†; Mead Johnson Nutritionals, USA.†*
Calcium caseinate (p. 2055·2).
Protein supplement.

Caseical *Support, Braz.*
Preparation for enteral nutrition.

Casen Mikroklysma *De Witt, Neth.†*
Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3).
Constipation.

Casenfilus *Casen Fleet, Spain.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of gastrointestinal flora; diarrhoea.

Casenglicol *Casen Fleet, Spain.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Casenlax *Casen Fleet, Spain.*
Macrogol 4000 (p. 2547·3).
Constipation.

Casflox *Casca, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Casflox-OZ *Casca, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Casflox-TZ *Casca, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Casicot *Be-Tabs, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Casiop *Osmed, India.*
Iron choline citrate (p. 2060·2); magnesium chloride (p. 1787·1); manganese chloride (p. 2081·2); protein hydrolysate; carbohydrates.

Casipril *Tunggal Idaman, Indon.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Caslide *Casca, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Caslide-P *Casca, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Caslot *Ranbaxy, India; Ranbaxy, Malaysia.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Cas-Mag *Omega, Canad.*
Cascara (p. 1826·1); magnesium hydroxide (p. 1857·2).

Casodex *AstraZeneca, Arg.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; Zeneca, USA; AstraZeneca, Venez.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Casomide *Clonmel, Irl.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Caspacil *Cazi, Braz.*
Selenium sulfide (p. 1719·3).
Dandruff.

Caspan *Casca, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Caspiselenio *Kin, Spain.†*
Selenium sulfide (p. 1719·3).
Scalp disorders.

Caspod *Casca, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Casprin *YSP, Malaysia.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Caspro *Casca, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Caspro-TZ *Casca, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cassadan *Temmler, Ger.†*
Alprazolam (p. 1035·2).
Anxiety.

Cassilax *Bio-Health, UK.*
Senna (p. 1885·1); aloes (p. 1816·1); cascara (p. 1826·1); taraxacum (p. 2625·3).
Constipation; bloating.

Castaderm *Lannett, USA.*
Resorcinol (p. 1718·3); boric acid (p. 2459·3); phenol (p. 1763·3).
Fungal skin infections.

Castagnus *Herbapol Wroclaw, Pol.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Castase *Nutrialys, Fr.*
Range of preparations for enteral nutrition.

Castel *Syosset, USA.*
Resorcinol (p. 1718·3).
Fungal skin infections.

Castellani mit Miconazol *Hollborn, Ger.*
Miconazole (p. 588·3).
Fungal and bacterial skin infections.

Castellani's Paint *ICM, Singapore.*
Boric acid (p. 2459·3); phenol (p. 1763·3); resorcinol (p. 1718·3).

Castilium *Sanofi-Aventis, Port.*
Clobazam (p. 518·2).
Anxiety disorders.

Castispir *Sandoz, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Castoria
Note: this name may be used for preparations of different composition.
Boie, Philipp.
Senna (p. 1885·1); cucurbita (p. 2489·2); santonica; potassium sodium tartrate (p. 1879·3); sodium bicarbonate (p. 1781·1).
Constipation.

Castufemin *Ardeypharm, Ger.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders; mastalgia.

Casxim *Casca, India.*
Cefixime (p. 240·3).
Bacterial infections.

Casxim-DT *Casca, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cat Complex *Thompsons, Canad.†*
Arsenic trioxide (p. 2448·1); nitric acid (p. 2572·3); potassium dichromate (p. 2476·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Catabex *Pierre Fabre, Belg.*
Dropropizine (p. 1662·2).
Cough.

Catabina *Tecnifar, Port.*
Dropropizine (p. 1662·2).
Cough.

Catabon *Taisho, Jpn.*
Dopamine hydrochloride (p. 1367·2).
Shock.

Cataclot *Ono, Jpn.*
Ozagrel sodium (p. 2579·1).
Cerebrovascular disorders.

Catacol *Alcon, Fr.*
Disodium inosinate (p. 2495·2).
Lens opacities.

Catacrom *Moorfields, UK.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Catafast *Novartis, Mex.*
Diclofenac (p. 48·3).

Novartis, S.Afr.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Novartis, Ukr.
Diclofenac potassium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Cataflam *Novartis, Gr.; Novartis, Hong Kong; Novartis, Irl.; Novartis, Israel; Novartis, Neth; Novartis, Norw.; Novartis Consumer, NZ; Novartis, Pol.; Normal, Port.; Novartis, Thai.; Novartis, Turk.; Novartis, USA.*
Diclofenac potassium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; fever.

Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Hung.; Novartis, Indon.; Novartis, Malaysia; Novartis, Mex.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Venez.
Diclofenac (p. 48·3), diclofenac diethylamine, diclofenac potassium (p. 48·3), diclofenac resinate, or diclofenac sodium.
Pain; inflammation; gout; fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Novartis, Philipp.
Diclofenac colestyramine (p. 48·3) or diclofenac potassium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, and peri-articular disorders.

Cataflex *Cifarma, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Inflammation.

Cataflexym *Cifarma, Braz.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Cataflin *Standard, Philipp.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; colic; gout.

Catalet *Biomed Krakow, Pol.*
Pollen allergen extracts (p. 2593·3) (p. 2434·3).
Hyposensitisation.

Catalin *Senju, China; Vianex (Βιανεξ), Gr.; Allergan, India; Senju, Jpn; Senju, Pol.; Takeda, Thai.*
Pirenoxine (p. 2591·3).
Cataract.

Takeda, Hong Kong; Takeda, Indon.; Takeda, Philipp.; Takeda, Singapore.
Pirenoxine sodium (p. 2591·3).
Cataract; senile cataract.

Catalip *Abbott, Port.*
Fenofibrate (p. 1381·1).
Hypercholesterolaemia.

Catalyd *Duckbill, India.*
⊗Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1); papain (p. 2582·3).

Catalyst *Skymax, India.*
Thioctic acid (p. 2629·1); eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); trace elements; vitamins.

Catanac *Ethica, Indon.; Pharmasant, Thai.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Catapin *Oboi, Philipp.*
Clonidine hydrochloride (p. 1339·1).
Hypertension; pain.

Catapres *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Canad.; IFET (ΙΦΕΤ), Gr.; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Thai.†; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.*
Clonidine hydrochloride (p. 1339·1).
Hypertension; migraine; menopausal flushing.

Boehringer Ingelheim, NZ.
Clonidine (p. 1339·1) or clonidine hydrochloride (p. 1339·1).
Hypertension.

Catapres Diu *Zydus, India.*
⊗Clonidine hydrochloride (p. 1339·1); chlortalidone (p. 1335·2).
Hypertension.

Catapresan *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Unilfarma, Port.; Fher, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Venez.*
Clonidine hydrochloride (p. 1339·1).
Hypertension; menopausal disorders; migraine.

Boehringer Ingelheim, Ital.; Boehringer Ingelheim Promeco, Mex.
Clonidine (p. 1339·1) or clonidine hydrochloride (p. 1339·1).
Hypertension.

Catapressan *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Fr.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Catarest *Centaur, India.*
Potassium iodide (p. 2336·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1).
Cataracts.

Catarrh Cream *Weleda, UK.*
Esculoside (p. 2431·2); berberis fruit (p. 2502·1); prunus spinosa fruit (p. 2458·2); bryonia alba; camphor (p. 2466·2); echinacea purp. (p. 2498·1); mercurius sulph. (p. 2555·3); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Homoeopathic preparation.

Catarrh Mixture *Potter's, UK.*
Boneset (p. 2459·1); lappa root (p. 2540·1); hyssop (p. 2530·3); capsicum (p. 2469·3).
Catarrh.

Catarrh-eeze *Chefaro, UK.*
Marrubium (p. 1668·3); achillea (p. 2427·3); elecampane (p. 1662·3).
Catarrh.

Catarrh-Ex *Thompson, UK.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold symptoms.

Catarrosine *Fecofar, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Catarstat *Bausch & Lomb, Philipp.*
Pyridoxine hydrochloride (p. 2105·3); glycine (p. 2071·2); glutamic acid (p. 2070·2); magnesium-potassium aspartate.
Cataract.

Chauvin, Fr.; Bausch & Lomb, Switz.
Pyridoxine hydrochloride (p. 2105·3); amino acids.
Cataracts; lens opacities.

Catasart *Rowex, Irl.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Catasart Plus *Rowex, Irl.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cataspa *USV, India.*
Diclofenac potassium (p. 48·3); dicycloverine hydrochloride (p. 1834·2).

Catazyme *Stadmed, India.*
Amylase (p. 2442·1); cinnamon oil (p. 2479·3); caraway oil (p. 2470·3); cardamom oil (p. 2471·1).
Dyspepsia; flatulence.

Catazyme-P *Stadmed, India.*
⊗Amylase (p. 2442·1); papain (p. 2582·3).
Dyspepsia; reduced appetite; digestive disorders.

CAT-Barium (E-Z-CAT) *Bracco, Switz.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Categ *Sofar, Ital.*
Green tea (chinese) (p. 2648·2).
Nutritional supplement.

Categor *Sandoz, Arg.*
Capecitabine (p. 757·3).
Breast cancer; colorectal cancer.

Catena *Santhera, Canad.*
Idebenone (p. 392·3).
Friedreich's ataxia.

Catenol *Zydus, India; Cadila, Rus.†; Cadila, Singapore; Zydus Cadila, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine; hyperthyroidism; myocardial infarction.

Catepen *Aspen, Arg.*
Capecitabine (p. 757·3).
Malignant neoplasms.

Caterol *Pharmasant, Thai.*
⊗Procaterol hydrochloride (p. 1219·1).
Bronchospasm.

Catexan *Biogaran, S.Afr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Cathejell
Note: this name may be used for preparations of different composition.
Hospithera, Belg.; Montavit, Neth.; Montavit, Philipp.; Montavit, Port.; Taymed, Turk.
Chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Catheterisation; endoscopy; intubation.

Montavit, Austria; Montavit, Israel.†
Diphenhydramine hydrochloride (p. 626·2); chlorhexidine hydrochloride (p. 1743·3).
Lubrication for catheter insertion; endoscopy; cystoscopy.

Cathejell with Lidocaine *Montavit, Israel; Montavit, Malaysia; Montavit, Rus.; Pharmaplan, S.Afr.; Montavit, Thai.; Mediplus, UK.*
Chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Instrument insertion; catheter insertion.

Cathejell Lidocaine *Montavit, Ukr.*
Chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Catheterisation.

Cathejell mit Lidocain *Montavit, Austria; Pfleger, Ger.†*
Chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Catheterisation; instrument insertion.

Cathejell S *Pfleger, Ger.†*
Chlorhexidine hydrochloride (p. 1743·3).
Catheterisation.

Catheter Preparation *Pfizer, Austral.†*
Chlorhexidine gluconate (p. 1743·3).
Genital disinfection before bladder catheterisation.

Cathflo *Roche, Canad.*
Alteplase (p. 1296·3).
Venous catheter occlusion.

Cathflo Activase *IFET (ΙΦΕΤ), Gr.*
Alteplase (p. 1296·3).

Cathflush *Troikaa, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Cationorm *Excelvision, Malaysia.*
⊗Glycerol (p. 2517·2); poloxamer 188 (p. 2202·1); trometamol (p. 2635·1); cetalkonium chloride (p. 1741·3); tyloxapol (p. 2218·2); trometamol hydrochloride.
Eye irritation.

Catiz Plus *Merck Serono, Arg.*
Saw palmetto (p. 2363·3); pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Catlep *Sumitomo, Jpn; Teikoku Seiyaku, Jpn.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Cato-Bell *Bell, India.†*
Potassium iodide (p. 2336·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1).
Lens opacities; cataract.

Catona *Mavi, Mex.*
Captopril (p. 1331·2).
Hypertension.

Catoplin *Beacons, Singapore.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Catoprol *Medley, Braz.†*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Catoxymag *Raptakos, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).

Catrigel *Vocate, Gr.*
⊗Miconazole nitrate (p. 589·1); fluprednidene acetate (p. 1637·3).
Infected skin disorders.

Catrix
Note: this name may be used for preparations of different composition.
Donell DerMedex, USA.
Emollient and moisturiser.

Triton, India.
Aceclofenac (p. 16·2).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Meda, Ger.†
Collagen (p. 2483·2).
Wounds; burns; ulcers.

Catrix Correction *Donell DerMedex, USA.*
SPF 15: Octinoxate (p. 1715·1); meradimate (p. 1711·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Catrix Lip *Donell DerMedex, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Catrix-P *Triton, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Cats Claw Complex *Mediherb, Austral.†*
Uncaria tomentosum; tabebuia avellanedae; echinacea (p. 2498·1).
Cold symptoms; tonic.

Cats Claw-Echine *Eagle, Austral.*
Uncaria tomentosa; echinacea (p. 2498·1); astragalus; hydrastis (p. 2528·1); lapacho; olive leaf (p. 2574·3).
Respiratory-tract infections.

Cattalorex *Sandoz, Ital.*
Domperidone (p. 1838·1).
Nausea; vomiting; gastro-oesophageal reflux.

Caudaline *Merck, Mex.*
Cilostazol (p. 1337·1).
Occlusive arterial disease; thromboembolism prophylaxis.

Causalon *Phoenix, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Causalon Bronquial *Phoenix, Arg.*
Clofedanol hydrochloride (p. 1659·1); guaifenesin (p. 1666·2); oxatomide (p. 636·3).
Cough.

Causalon Grip *Phoenix, Arg.*
Paracetamol (p. 115·1); oxatomide (p. 636·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract disorders.

Causalon Ibu *Phoenix, Arg.*
Ibuprofen (p. 68·2).
Pain; fever.

Caustinerf Arsenical *Septodont, Fr.*
⊗Ephedrine hydrochloride (p. 1663·2); lidocaine (p. 1988·1); arsenic trioxide (p. 2448·1).

Caustinerf sans Arsenic *Septodont, Fr.*
Lidocaine (p. 1988·1); paraformaldehyde (p. 1763·1).

Cauterex *Ache, Braz.*
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1); gentamicin sulfate (p. 304·2).
Wounds.

Cauteridol *Ederka, Mex.†*
Ranitidine (p. 1882·1).

Cavea *Pharos, Indon.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis; osteomalacia; rickets; hyperphosphataemia.

Cavel *Duopharma, Malaysia.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Cavenor *Indo French, India.*
Arginine (p. 2049·1); proanthocyanidins.

Caveril *Remedica, Thai.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Caverject *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.†; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK; Pharmacia, USA; Pfizer, Venez.*
Alprostadil (p. 2352·2).
Erectile dysfunction; diagnostic aid.

Caverjectdual *Pfizer, Fr.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Caverta *Ranbaxy, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Caviamina *De Mayo, Braz.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); fructose (p. 2068·2).

CaviD *Nycomed, Denm.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cavida *Ethica, Indon.*
Coral calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium supplement.

Cavidin INH *Wockhardt, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Cavigen *Liptis, USA.*
Lyophilised fish roe; ginkgo biloba (p. 2512·3).

Cavilon *3M, Fr.*
Barrier preparation.

3M, UK.
A range of barrier preparations.

Cavinton *Gedeon Richter, China; Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; BioSaude, Port.; Gedeon Richter, Rus.; Gedeon Richter, Singapore; Gedeon Richter, Thai.; Gedeon Richter, Ukr.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; mental function impairment; vascular eye disorders; vestibular disorders.

Cavirip *Shreya, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Cavirox *Roux-Ocefa, Arg.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cavirox Cit *Roux-Ocefa, Arg.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cavit *Cachet, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

CaVit D *Rougier, Canad.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cavit D3 *Merck, Indon.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis.

Cavital *Pharos, Indon.*
Calcium gluconate (p. 1783·3); calcium glycerophosphate (p. 1783·3); Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); lysine hydrochloride (p. 2079·3).
Tonic.

Cavitar RHE *Wockhardt, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Cavit-D3 *Merck, Singapore.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; calcium and vitamin D deficiency; osteoporosis.

Caviter *Wockhardt, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Caviter FD *Wockhardt, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Cavit-PM *Cachet, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); isoflavone (p. 2620·3); magnesium oxide (p. 1857·3).

Cavumox *Siam Bheasach, Malaysia.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Siam Bheasach, Thai.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Cax *Medochemie, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Caxeta *Sun, India.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer; gastric cancer.

Caxidol *Farmaceutica H, Mex.*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Musculoskeletal pain and spasm.

Caxin *Hovid, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Caxlem *Brown & Burk, Philipp.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Caxyl *Admac, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Cayston *Gilead, Austria; Gilead, Canad.; Gilead, Cz.; Gilead, Denm.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Irl.; Gilead, Neth.; Gilead, Pol.; Gilead, Port.; Gilead, Spain; Gilead, UK; Gilead, USA.*
Aztreonam lysine (p. 224·1).
Pseudomonal lung infections in cystic fibrosis.

Cazacombi *KRKA, Cz.; KRKA, Pol.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cazaprol *KRKA, Cz.; KRKA, Pol.*
Cilazapril (p. 1336·2).
Heart failure; hypertension.

Cazetin *Ifars, Indon.*
Nystatin (p. 590·3).
Gastrointestinal candidiasis.

Caziant *Watson, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Caziderm *Cazi, Braz.*
Nitrofurazone (p. 333·1).
Burns; skin infections.

Cazigeran *Cazi, Braz.*
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).

Cazita *Admac, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Cazmar *Fucus, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Cazol *Ind-Swift, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Cazol-B *Ind-Swift, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2).

Cazole *Malpharm, Hong Kong.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Cazole-D *Constant, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Cazosin *Millimed, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

CB-12
Note: this name may be used for preparations of different composition.
Mapro, India.
Folic acid (p. 2063·1); ampoule 1, vitamin C (p. 2110·3); ampoule 2, nicotinamide (p. 2083·1); vitamin B_{12} (p. 2107·2).

CB12
Note: this name may be used for preparations of different composition.
Meda, UK.
Zinc acetate (p. 2126·1); chlorhexidine acetate (p. 1743·2); sodium fluoride (p. 2089·2).
Halitosis.

CB-99 *Charoen, Thai.*
Niclosamide (p. 161·2).
Tapeworm infections.

CB-400 *Charoen, Thai.*
Albendazole (p. 149·1).
Worm infections.

C-Bact *Biosena, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

C-Bactum *VHB, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

C-Band *Corona, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

CBC-PAM *Chandra Bhagat, India.*
Pralidoxime iodide (p. 1571·1).
Organophosphorus poisoning.

C-Bend *Elfin, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Cbic *Cubit, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cbic-TZ *Cubit, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

CBL *Worth, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

CB-Lin *Serum Institute, India.*
Cabergoline (p. 899·3).
Lactation inhibition; hyperprolactinaemia; parkinsonism.

C-1000-C *Novartis, Mex.*
Ascorbic acid (p. 2110·3); calcium lactate gluconate (p. 1784·2).
Calcium and vitamin C supplement.

CC Cap *Intas, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

C-Cal *Corona, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

C-Calcio *EMS, Braz.*
Vitamin C (p. 2110·3); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); vitamin B_6 (p. 2105·3).
Calcium and vitamin supplement.

CCFS *Shreshtha, India.*
Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

CCGO *Intas, India.*
Syrup: Chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1).

Intas, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

C-Cid *Corona, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

CC-Koff *Intas, India.*
Capsules: Bromhexine (p. 1656·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).

Intas, India.
Syrup: Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

CCL *Indi, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

C-Clox *Corona, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); lactobacillus (p. 2596·3).
Bacterial infections.

CCM *GSK, India.*
Calcium citrate malate (p. 1783·1); folinic acid (p. 2066·3); colecalciferol (p. 2113·1).

CC-Nefro *Medice, Ger.*
Calcium carbonate (p. 1824·3).
Hyperphosphataemia.

CCNU *Medac, UK.*
Lomustine (p. 818·1).
Malignant neoplasms.

C-Coated *ANH, Thai.*
Vitamin C (p. 2110·3).
Dietary supplement.

C-Cold *Corona, India.*
Syrup: ⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Corona, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

C-Colotab *Chinta, Thai.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); chlorphenamine maleate (p. 620·3).
Cold symptoms.

C-Cum *Cubit, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

CCZ-Plus *Solitaire, India.*
Calcitriol (p. 2113·1); calcium citrate malate (p. 1783·1); zinc (p. 2126·1).

CD Jevax *Chengdu Institute, Thai.*
A live attenuated Japanese encephalitis virus vaccine (p. 2396·2).
Active immunisation.

CD-Cal *Julphar, UAE.*
Calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1).
Dietary supplement.

CDCV *Hetero, India.*
Cefadroxil (p. 233·2); clavulanic acid (p. 268·3).
Bacterial infections.

C-Dial *Corona, India.*
Metronidazole benzoate (p. 936·1); norfloxacin (p. 333·3).

CD-Oph *Seng, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1); tetryzoline hydrochloride (p. 1678·3).
Inflammatory eye disorders; infected eye disorders.

C-Dox *Shince, India.*
Cefpodoxime.
Bacterial infections.

CDR *Bayer Consumer, Thai.*
Calcium (p. 1783·1); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).
Calcium and vitamin supplement; osteoporosis.

CDR Fortos *Bayer Consumer, Indon.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Osteoporosis; osteomalacia; calcium and vitamin D deficiency.

Bayer Consumer, Thai.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; osteomalacia; calcium and vitamin D supplement.

C-Drox *Corona, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

CDT *CSL, Austral.†; CSL, NZ; CSL, Singapore.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

CE *East West, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Ceabisin *Laquifa, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Ceacont *Ceapharma, Port.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Ceact *Crescent, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Cealb *Graha, Indon.; Sanquin, Neth.; Cankat, Turk.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoalbuminaemia; hyperbilirubinaemia; acute liver failure; ascites; nephrotic syndrome.

Ceanel *Ferndale, UK.*
Cetrimide (p. 1742·1); undecenoic acid (p. 596·3); phenethyl alcohol (p. 1763·2).
Psoriasis; seborrhoeic dermatitis; dandruff.

Cearium *Shince, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

CEA-Scan *Immunomedics, UK; Immunomedics, USA.*
Technetium-99m arcitumomab (p. 2228·1).
Detection of colorectal cancer.

Ceascol *Myrex Ethica, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ceasin *Ceamed, Port.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Ceax *Osmed, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cebac *Sienna, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cebactam *LBS, Thai.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Cebactum *Leben, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cebanex *Orchid, India; Orchid, Rus.; Orchid, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cebarax *Masa, Thai.†*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Cebay *Leben, India.*
Capsules: Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Leben, India.
Dispersible tablets; syrup: Cefixime (p. 240·3).
Bacterial infections.

Cebay TRX *Leben, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cebect
Note: this name may be used for preparations of different composition.
Elfin, India.
Injection: Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Shreya, India.
Tablets: Ciprofloxacin (p. 261·1).
Bacterial infections.

Cebect-TZ *Shreya, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cebedex *Abdi, Turk.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye and ear disorders.

Cébédexacol *Chauvin, Fr.†*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Eye infections.

Cebemyxine *Chauvin, Hong Kong; Chauvin, Hong Kong; Abdi, Turk.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Cébémyxine *Chauvin, Fr.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Cebesin *Bausch & Lomb, Switz.†*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Cébésine *Chauvin, Fr.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Cebex *Otto, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Cebexin *Indian Drugs, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Cebexin-Z *Indian Drugs, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Cebiolon *Merck, Port.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Cebion *Merck, Austria; Merck, Braz.; Merck, Chile; Merck, Ger.†; Galenica, Gr.; Merck, Hung.; Merck, Indon.†; Bracco, Ital.; Merck, Pol.; Merck, Port.; Merck Consumer, Singapore; Merck, Spain; Merck, Venez.*
Ascorbic acid (p. 2110·3) or sodium ascorbate (p. 2111·1).
Vitamin C deficiency; vitamin C supplement.

Cebion Calcico *Merck, Chile.*
Vitamin C (p. 2110·3); calcium carbonate (p. 1824·3); rutoside (p. 2505·3); colecalciferol (p. 2113·1).
Calcium supplement; tonic.

Cebion Calcio *Merck, Braz.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3).
Calcium and vitamin C supplement.

Cebion Febre e Dolore *Bracco, Ital.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Cebion plus Rutin *Merck, Austria.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Nutritional supplement.

Cebion Zinco *Merck, Braz.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc supplement.

Cebionmulti *Merck, Pol.*
Vitamins.

Cebitor *Sanquin, Fin.*
Complement C1 esterase inhibitor (p. 2485·1).
Hereditary angioedema.

Cebopime *Borshchagovskii, Ukr.*
Cefepime (p. 239·2).
Bacterial infections.

Cebragil *Medimar, Gr.*
Piracetam (p. 393·3).

Cebralat *Libbs, Braz.*
Cilostazol (p. 1337·1).
Cerebral and peripheral vascular disorders.

Cebran
Note: this name may be used for preparations of different composition.
Blue Cross, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cebran-TN *Blue Cross, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cebrex *Psyco Remedies, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Cebrex Forte *Psyco Remedies, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2); dicycloverine hydrochloride (p. 1834·2).

Cebrilin *Libbs, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Cebrine *Shince, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Cebrine Plus *Shince, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Cebrin-Fe *PP Lab, Thai.*
Calcium phosphate (p. 1784·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin A (p. 2098·3).
Anaemias.

Cebrium *Community Pharmacy, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebrovascular disorders; vertigo; motion sickness.

Cebrocal
Note: this name may be used for preparations of different composition.
Lafi, Chile.
Gamma-aminobutyric acid (p. 2509·2); gamma-amino beta-hydroxybutyric acid; acetylglutamine (p. 2426·2); vitamin B_6 (p. 2105·3).

Temis, Arg.
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Cebrofort *Baliarda, Arg.*
Nimodipine (p. 1455·2).
Cerebrovascular disorders.

Cebrolux *Densmore, Fr.*
Inulin (p. 2534·3); citicoline (p. 2480·1); vitamins.
Dietary supplement.

Tubilux, Ital.
Vitamins; citicoline (p. 2480·1).
Nutritional supplement.

Cebronfilina *Neo Quimica, Braz.†*
Ambroxol acefyllinate (p. 1201·2).
Respiratory-tract disorders.

Cebrotex Forte *Lusomedicamenta, Port.†*
Benfotiamine (p. 2102·3); calcium magnesium fytate (p. 1553·3); glutamine (p. 2070·3).

Cebroton *Tubilux, Ital.†*
Citicoline sodium (p. 2480·2).
Parkinsonism.

Cebrotone *Fem Care, India.*
Withania somnifera (p. 2450·2).

Cebrotonin *Ritter, Malaysia; Ritter, Singapore.*
Piracetam (p. 393·3).
Mental function impairment in the elderly.

Cebrum *Psyco Remedies, India.*
Chlordiazepoxide (p. 1044·2).
Anxiety; muscle spasm; alcohol withdrawal syndrome; insomnia.

Cebutid *Almirall, Fr.*
Flurbiprofen (p. 65·2).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; thromboembolism prophylaxis.

Cec *Hexal, Austria; Hexal, Ger.†; Sandoz, Mex.; Hexal, S.Afr.†; Basel, Turk.*
Cefaclor (p. 232·3).
Bacterial infections.

Cecal *Cyno, India.*
Calcium carbonate (p. 1824·3); lysine hydrochloride (p. 2079·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Cecal Plus *Cyno, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Cecap *Atlantic, Hong Kong; Atlantic, Malaysia.*
Vitamin C (p. 2110·3).
Tonic; vitamin C deficiency.

Cecarb *Intas, India.*
Carbocisteine (p. 1658·1); cefalexin (p. 234·1).
Respiratory-tract infections.

Cecel *Zee, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Cecenu *Medac, Ger.; Rhone-Poulenc Rorer, Gr.*
Lomustine (p. 818·1).
Malignant neoplasms.

Ceciora T *Elea, Mex.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Ceclobid *EL, Philipp.; YSS, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Ceclor *Aspen, Austral.; Arcana, Austria; Sigma, Braz.; MM, Canad.; Lilly, China; Lilly, Cz.†; Lilly, Gr.; Invida, Hong Kong; Actavis, Hung.; Lilly, Indon.†; Nycomed, Mex.; EuroCept, Neth.; GSK, Philipp.; Teva, Pol.; Medinfar, Port.; Lilly, Rus.; Rottapharm, Spain; Sigma-Tau, Switz.; Abbott, Turk.; Lilly, USA; Farma, Venez.*
Cefaclor (p. 232·3).
Bacterial infections.

Ceclorbeta *Betapharm, Ger.†*
Cefaclor (p. 232·3).
Bacterial infections.

Ceclordox *Nycomed, Mex.*
Cefaclor (p. 232·3); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Cecloretta *Actavis, Hung.*
Cefaclor (p. 232·3).
Bacterial infections.

Cecnoin *Ranbaxy, Braz.*
Isotretinoin (p. 1706·2).
Acne.

Ceco *USP, India.*
Aceclofenac (p. 16·2).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Ceco Plus *USP, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Cecofene *Multilab, Braz.*
Aceclofenac (p. 16·2).

Cecold *Pharmasant, Thai.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Cecon *Pharmacia Upjohn, India; Abbott, Philipp.; Abbott, Port.†; Abbott, USA.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; scurvy.

Cecort *Comed, India.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Ceco-SP *USP, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Cecrisina *Johnson & Johnson, Port.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Cecural *Demo, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Cecure *Cadila, India.*
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Cecurin *Demo, Gr.*
Mebendazole (p. 158·3).

Cedantron *Soho, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Cedate *Profic Organic, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour following intra-uterine fetal death; postcoital oral contraceptive.

Cedate-F *Profic Organic, India.*
Misoprostol (p. 2140·3).
Peptic ulcer; termination of pregnancy.

Cedax *MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; MSD, Neth.; Schering-Plough, Philipp.†; Schering-Plough, Pol.; SIFI, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; Essex, Switz.; MSD, Thai.; Schering-Plough, Turk.; Merck, Ukr.; Schering-Plough, Ukr.; Pernix, USA; Schering-Plough, Venez.*
Ceftibuten (p. 252·2).
Bacterial infections.

Cedbrox *Aurobindo, India.*
Ambroxol (p. 1654·3); cefadroxil (p. 233·2).

Cedel *Zee, India.*
Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and vascular headache.

Cedelate *TNP, Thai.*
Flunarizine (p. 629·3).
Migraine; vestibular disorders.

Cedelin *Patar, Thai.*
Clindamycin phosphate (p. 269·3).
Acne.

Cedia *Invision, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Cedia-AC *Invision, India.*
Aceclofenac (p. 16·2); diacerein (p. 45·3).

Cedigocine *Sandoz, Gr.*
Acetyldigoxin (p. 1290·2).

Cedil *Bactolac, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cedilanid *Novartis, Mex.*
Lanatoside C (p. 1417·3).
Cardiac disorders.

Cedilanide *Novartis, Braz.*
Deslanoside (p. 1351·2).
Heart failure; supraventricular arrhythmias.

Cedine *Rowex, Irl.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux; acid aspiration; adjunct in pancreatic insufficiency.

Cedium *Qualiphar, Belg.*
Benzalkonium chloride (p. 1737·1).
Disinfection of the skin, wounds, and hands.

Cedium Chlorhexidine *Qualiphar, Belg.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection.

Cedixidin *Qualiphar, Belg.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Cednir *Piramal, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Cedocard *Altana, Austria†; Takeda, Belg.; Paladin, Canad.†; Darya-Varia, Indon.; Takeda, Neth.; Pfizer, UK.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Cedoflor *Krasnay Zvezda, Rus.*
Crataegus (p. 2488·1); clover (p. 2482·1); coriander (p. 2486·3); melissa (p. 2552·3);

avena (p. 2451·1); motherwort (p. 2564·2); lupulus (p. 2546·1).
Nervous disorders.

Cedol
Note: this name may be used for preparations of different composition.
Gap, Gr.
Paclitaxel (p. 839·3).
Malignant neoplasms.

Cedon *Blue Cross, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cedon-LB *Blue Cross, India.*
Cefpodoxime proxetil (p. 248·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cedon-P *Blue Cross, India.*
Cefpodoxime proxetil (p. 248·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cedovix *Specifar, Gr.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Topical analgesic.

Cedoxime *Akums, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cedoxime-LB *Akums, India.*
Cefpodoxime proxetil (p. 248·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cedric *Elea, Arg.*
Ivy (p. 2536·2).
Cough.

Cedric Pocket *Elea, Arg.*
Ivy (p. 2536·2); benzocaine (p. 1980·2).
Cough; sore throat.

Cedrin *Mantecorp, Braz.*
⊗Pseudoephedrine sulfate (p. 1676·1); azatadine maleate (p. 616·3).
Nasal congestion.

Cedrina *Sanovel, Turk.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia.

Cedrohexal *Sandoz, Ukr.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Cedrox *East West, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cedroxil *Legrand, Braz.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cedroxim *Leti, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cedroxin *Claris, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cedur *Roche, Belg.; Roche, Braz.; Roche, Ger.†; Actavis, Switz.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

CEE *T Man, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ceedokid *Dexter, India.*
Promethazine (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; motion sickness; insomnia.

Ceedokid Plus *Dexter, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Ceedox *Shalaks, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Ceegeefer *Prosel, Philipp.†*
Vitamins; zinc sulfate (p. 2126·2); lysine (p. 2079·3); taurine (p. 2626·2); chlorella growth factor (p. 2475·3).
Nutritional supplement.

Ceel *Gemi, Pol.*
Ascorbic acid (p. 2110·3); vitamin E (p. 2119·1).
Vitamin C and E deficiency.

Ceelin *Medifarma, Indon.; Pediatrica, Indon.; Pediatrica, Malaysia†; Pediatrica, Philipp.; United Laboratories, Singapore.*
Ascorbic acid (p. 2110·3) or sodium ascorbate (p. 2111·1).
Vitamin C supplement; vitamin C deficiency.

Ceelin Plus *Pediatrica, Philipp.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc deficiency.

Ceemi *Winsome, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Ceenergy *Diamond, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

CeeNU *Merck Serono, Arg.; BMS, Austral.; BMS, Canad.; BMS, Chile†; BMS, Cz.; IFET (ΙΦΕΤ), Gr.; BMS, Mex.; BMS, NZ; BMS, Philipp.†; BMS, S.Afr.†; BMS, Singapore; BMS, Switz.†; BMS Oncology, USA.*
Lomustine (p. 818·1).
Malignant neoplasms.

Ceepro *Lincoln, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cee-protect *Manix, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ceepro-TZ *Lincoln, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ceeptalib *Misha, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ceetrus *Taisho, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

CeeZinc *Sydenham, Philipp.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Dietary supplement.

Cef *Eden, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

CEF-3 *Dankos, Philipp.; Siam Bheasach, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cef-4
Note: this name may be used for preparations of different composition.
Lupin, India.
Cefpirome (p. 247·2).
Bacterial infections.

Siam Bheasach, Malaysia; Siam Bheasach, Thai.
Ceftazidime (p. 250·2).
Bacterial infections.

Cefa Kit *Intag, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefaben *Cazi, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefabene *Cefak, Ger.*
Stipites dulcamarae (p. 2497·3).
Eczema.

Cefabene Cistus Komplex *Cefak, Ger.†*
Cistus canadensis; anacardium (p. 2471·3); arsenicum album (p. 2448·1); berberis aquifolium (p. 2577·1); hydrocotyle asiatica (p. 1698·3); mezereum.
Homoeopathic preparation.

Cefabiot
Note: this name may be used for preparations of different composition.
Sandoz, Mex.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefabiotic *Bernofarm, Indon.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefabol
Note: this name may be used for preparations of different composition.
Abolmed, Rus.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefabrina *Neo Quimica, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Cefabronchin *Cefak, Ger.*
Thyme (p. 2630·2); Iceland moss (p. 2531·2); soapwort (p. 2617·2); burnet saxifrage (p. 2463·1); eucalyptus (p. 2501·1); fennel (p. 2503·2); star anise (p. 2622·1).
Respiratory-tract inflammation.

Cefabroxil *Maver, Mex.*
Cefalexin (p. 234·1); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Cefac *Comed, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefacapxin *Frankin, Hong Kong.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cefacar *Nova Argentia, Arg.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefacef *Caprifarmindo, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Cefacet *Norgine, Fr.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefacidal *BMS, S.Afr.†; BMS, Venez.*
Cefazolin sodium (p. 237·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefacile *BMS, Port.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefacilina *Montpellier, Arg.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefacilina Bronquial *Montpellier, Arg.*
Cefadroxil (p. 233·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Cefacimed *Cimed, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefacin *Bright Future, Hong Kong; Cure Quick, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefaclen *Zentiva, Cz.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cefacloren *Neo Quimica, Braz.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefacloril *Alapis, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefacolin *Northia, Arg.*
Cefotaxime (p. 244·1).
Bacterial infections.

Cefact *Indu, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefactam *Aurobindo, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefacure *Orchid, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefacynar *Cefak, Ger.†*
Cynara (p. 2490·3).
Biliary-tract disorders.

Cefaday *Talent, India; Biofarma, Turk.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefaday-S *Talent, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Cefaday-TZ *Talent, India.*
Ceftriaxone sodium (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefade *Klonal, Arg.*
Cefalotin (p. 235·1).
Bacterial infections.

Cefaden *Eden, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Cefaden-O *Eden, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefadin
Note: this name may be used for preparations of different composition.
Atlantic, Singapore; Atlantic, Thai.
Cefalotin sodium (p. 235·1).
Bacterial infections.

Genepharm, Gr.
Cefamandole (p. 236·2).
Bacterial infections.

Neon, India.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cefadol
Note: this name may be used for preparations of different composition.
Medipharm, Chile.
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Migraine and other vascular headache.

Atlantic, Thai.†
Cefamandole nafate (p. 236·2).
Bacterial infections.

Cefadolor *Cefak, Ger.†*
Guaiacum wood.
Rheumatic disorders.

Cefadolor Arnica Komplex *Cefak, Ger.†*
Arnica montana (p. 2447·2); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Cefadolor H *Cefak, Ger.†*
Guaiacum (p. 2523·1).
Homoeopathic preparation.

Cefadox *OEP, Philipp.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefadril *AGIPS, Ital.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefadrin
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Cefak, Ger.†
⊗Ephedra (p. 1663·1); thyme (p. 2630·2); ammi visnaga (p. 2441·2).
Cough; asthma.

Cefadrox *Cassara, Arg.; Aristo, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefadroxon *Sanval, Braz.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefadur *Cipla, India; Cipla, Malaysia.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefadybasin SE *Cefak, Ger.†*
Secale cornutum (p. 2137·1); espeletia schultzii; espeletia grandiflora; arnica montana (p. 2447·2); plumbum metallicum (p. 2541·3); barium carbonicum (p. 2452·2).
Homoeopathic preparation.

Cefadyn *Cefak, Ger.*
Butcher's broom (p. 2463·1).
Chronic venous insufficiency.

Cefagel *Multilab, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefagen *Maver, Mex.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefager *Gerard, Irl.†*
Cefaclor (p. 232·3).
Bacterial infections.

Cefagil *Cefak, Austria; Cefak, Ger.; Cefak, Hung.; Cefak, Malaysia; Cefak, Ukr.*
Turnera diffusa (p. 2491·3).
Homoeopathic preparation; tonic.

Cefagran *Legrand, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefagrand *Ahimsa, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefagrippin *Cefak, Ger.†*
Aconitum napellus (p. 2428·3); gelsemium sempervirens (p. 2511·2); eupatorium perfoliatum (p. 2459·1).
Homoeopathic preparation.

Cefakind *Mankind, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefakind-P *Mankind, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cefaking *Bennet, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Cefakliman
Note: this name may be used for preparations of different composition.
Cefak, Malaysia.
Cimicifuga (p. 2478·1).
Menopausal disorders.
Cefak, Ger.†
Tablets: Lachesis (p. 2538·3); cimicifuga (p. 2478·1); sepia (p. 2613·1); lilium tigrinum.
Homoeopathic preparation.

Cefakliman H *Cefak, Ger.†*
Lachesis (p. 2538·3).
Homoeopathic preparation.

Cefakliman mono *Cefak, Ger.†; Cefak, Hung.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Cefakliman N *Cefak, Ger.†*
Lachesis mutus (p. 2538·3); sanguinaria canadensis (p. 2610·1); cimicifuga (p. 2478·1); hypericum (p. 449·1).
Homoeopathic preparation.

Cefakliman S *Cefak, Ger.*
Sepia officinalis (p. 2613·1); cimicifuga racemosa (p. 2478·1); crocus sativus (p. 2208·2); juniperus sabina; sanguinaria canadensis (p. 2610·1); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Cefaks *Deva, Turk.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefalan *Merck, Mex.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefaldina *IMA, Braz.†*
⊗Isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Migraine.

Cefalekol *Teva, Hung.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefalektin *Cefak, Ger.†*
Mistletoe (p. 2560·2).
Malignant neoplasms.

Cefalex *PC India, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefalex Plus *Bago, Arg.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Headache.

Cefalex VL *Bago, Arg.*
Dexibuprofen (p. 43·1).
Pain; fever.

Cefalexgobens *Normon, Spain.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cefalexol *Hipolabor, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefalgin *Polfa Pabianice, Pol.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Cefalin
Note: this name may be used for preparations of different composition.
Euphoric, India; BioFemme, Philipp.
Cefalexin (p. 234·1).
Bacterial infections.
EMS, Braz.
Cefalotin sodium (p. 235·1).
Bacterial infections.
Atlantic, Thai.†
Cefazolin sodium (p. 237·3).
Bacterial infections.

Céfaline Hauth *Homme de Fer, Fr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Cefalin-S *Lincoln, India.*
Cefotaxime sodium (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Cefalium *Ache, Braz.*
Paracetamol (p. 115·1); dihydroergotamine mesilate (p. 672·2); metoclopramide hydrochloride (p. 1862·2); caffeine (p. 1203·3).
Migraine.

Cefaliv *Ache, Braz.*
Dihydroergotamine mesilate (p. 672·2); dipyrone (p. 53·3); caffeine (p. 1203·3).
Migraine.

Cefalmin
Note: this name may be used for preparations of different composition.
Labesfal, Port.
Cefradine (p. 249·1).
Bacterial infections.
Sanitas, Chile.
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Migraine and other vascular headache.

Céfaloject *BMS, Fr.†*
Cefapirin sodium (p. 237·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefalom *Help, Gr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefalomicina *Bago, Arg.*
Cefazolin (p. 237·2).
Lidocaine hydrochloride (p. 1988·2) is included in some injections to alleviate the pain of injection.
Bacterial infections.

Cefalong-DS *Reddy, India.*
⊗Cefalexin (p. 234·1); probenecid (p. 607·3).
Bacterial infections.

Cefalor *Vitamed, Israel.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefalotil *Uniao Quimica, Braz.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Cefaluffa *Cefak, Ger.†*
Luffa operculata (p. 2545·3).
Homoeopathic preparation.

Cefalver *Maver, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefalymphat *Cefak, Ger.†*
Calcium fluoratum (p. 2053·1); sulfur (p. 1721·1); aethusa; helianthus ann.; calendula (p. 2465·2).
Homoeopathic preparation.

Cefalymphat H *Cefak, Ger.†*
Aethusa cyn.; helianthus ann.; calendula off. (p. 2465·2).
Homoeopathic preparation.

Cefam
Note: this name may be used for preparations of different composition.
Adley, India.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.
Dollder, Venez.
Cefotaxime sodium (p. 244·1).
Bacterial infections.
Pharma-Marketing, Hung.†; Magis, Ital.
Cefamandole nafate (p. 236·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefamabol *Abolmed, Rus.*
Cefamandole nafate (p. 236·2).
Bacterial infection.

Cefamadar *Cefak, Austria.*
Madar trit.
Homoeopathic preparation.
Cefak, Ger.
Madar.
Homoeopathic preparation.
Cefak, Hung.
Calatropis gigantea.
Homoeopathic preparation.
Cefak, Malaysia; Cefak, Ukr.
Madara.
Tonic; homoeopathic preparation.

Cefamanit *Cefak, Ger.†*
Amanita muscaria.
Homoeopathic preparation.

Cefamar
Note: this name may be used for preparations of different composition.
Mar, Arg.
Cefadroxil (p. 233·2).
Bacterial infections.
Menarini, Thai.†
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefamax
Note: this name may be used for preparations of different composition.
Max, India.
Cefalexin (p. 234·1).
Bacterial infections.
Siam Bheasach, Thai.
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cefamed *Meridian, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefamesin *Cefak, Ger.†*
Symphoricarpos albus.
Homoeopathic preparation.

Cefamezin *Gador, Arg.; Teva, Israel†; Pfizer, Ital.; Astellas, Jpn; Hikma, Port.†; Sotex, Rus.; Astellas, Thai.; Eczacibasi, Turk.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefamox *BMS, Braz.; Merck, Chile; BMS, Mex.; BMS, Swed.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefan *Cefak, Ger.†*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Cefanal *Bunker, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefanalgin *Cefak, Ger.†*
Gelsemium (p. 2511·2); iris (p. 2534·3); cyclamen (p. 2490·2); melilotus off. (p. 2552·3).
Homoeopathic preparation.

Cefanaxil *Teuto, Braz.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefaneuro *Cefak, Ger.*
Avena sativa (p. 2451·1); gelsemium (p. 2511·2); ignatia (p. 2532·1); passiflora incarnata (p. 2584·1).
Homoeopathic preparation.

Cefanex *Apothecon, USA.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefangin *Arterium, Ukr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefangipect *Cefak, Ger.†*
Cactus (p. 2473·2); nitroglycerinum (p. 1391·2); ammi visnaga (p. 2441·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Cefangipect H *Cefak, Ger.†*
Selenicereus grandiflorus (p. 2473·2); crataegus (p. 2488·1); ammi visnaga (p. 2441·2).
Homoeopathic preparation.

Cefanid *Neo Quimica, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefanorm
Note: this name may be used for preparations of different composition.
Cefak, Ger.†; Cefak, Hung.
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome; menstrual disorders; mastalgia.
Simpex, Rus.
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Cefantral *Lupin, India.*
Cefotaxime (p. 244·1).
Bacterial infections.
Lupin, Rus.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefantral-S *Lupin, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Cefanyl *Faran, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Céfaperos *BMS, Fr.†*
Cefatrizine (p. 237·2) or cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Cefaphyllin *Gap, Gr.*
Theophylline (p. 1229·3).

Cefapoten *Del Bel, Arg.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cefar *Cyno, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefarheumin S *Cefak, Ger.†*
Colchicinum (p. 604·1); berberis vulgaris (p. 2502·1); artemisia abrotanum.
Homoeopathic preparation.

Cefarin *Gracia, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefarinol *Gramon, Arg.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cefariston *Ariston, Braz.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Cefarizon *Samjin, Singapore; Pharmakin, Venez.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cefarox *Gracia, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Cefasabal *Cefak, Ger.†; Cefak, Malaysia.*
Saw palmetto (p. 2363·3); solidago (p. 2620·1); aesculus (p. 2431·2).
Micturition disorders; prostatic disorders.
Cefak, Ger.†
Capsules: Saw palmetto (p. 2363·3).
Prostatic disorders.

Cefasel *Cefak, Ger.; Cefak, Ukr.*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Cefasept
Note: this name may be used for preparations of different composition.
Cefak, Ger.
Injection: Lachesis mutus (p. 2538·3); kalium phosph. (p. 1791·1); echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.
Cefak, Ger.†
Tablets: Echinacea (p. 2498·1).
Homoeopathic preparation.
Cefak, Ger.†
Oral drops: Lachesis (p. 2538·3); hydrargyrum cyanat. (p. 2555·3); natrium phosph. (p. 1791·2); kalium phosph. (p. 1791·1); echinacea (p. 2498·1); aqua silicata.
Homoeopathic preparation.

Cefasept N *Cefak, Ger.*
Echinacea (p. 2498·1); kalium phosphoricum (p. 1790·3); lachesis mutus (p. 2538·3); hydrargyrum bicyanatum (p. 2555·3).
Homoeopathic preparation.

Cefasily *Cefak, Malaysia.*
Silymarin (p. 1561·2).
Liver disorders.

Cefasilymarin *Cefak, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Cefasin *Sintesina, Arg.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefasinu *Cefak, Ger.*
Chininum arsenicosum (p. 2601·3); cinnabaris (p. 2555·3); ferrum phosphoricum (p. 2077·1); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Cefaspasmon N *Cefak, Ger.†*
Atropine sulfuricum (p. 1310·2); podophyllum peltatum (p. 1717·1); ammi visnaga (p. 2441·2); chamomilla recutita (p. 2474·1).
Homoeopathic preparation.

Cefasporina *Oriental, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefast *Alkem, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefastad *Stada, Austria.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefastar *Mankind, India.*
Dispersible tablets: Cefadroxil (p. 233·2).
Bacterial infections.

Mankind, India.
Syrup: Cefadroxil (p. 233·2); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Cefasul *Ind-Swift, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Cefasulfon N *Cefak, Ger.†*
Sulfur (p. 1721·1); tartarus stibiatus (p. 151·2); platanus.
Homoeopathic preparation.

Cefasyn *Cipla, India.*
Cefuroxime (p. 255·2) or cefuroxime axetil (p. 255·2).
Bacterial infections.

Cipla-Medpro, S.Afr.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefat
Note: this name may be used for preparations of different composition.
Sanbe, Indon.
Cefadroxil (p. 233·2).
Bacterial infections.

Sintez, Rus.
Cefamandole nafate (p. 236·2).
Bacterial infections.

Cefa-T Kit *Intag, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefataur *Taurus, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefatec *Cefak, Ger.†*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Cefatenk *Biotenk, Arg.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefatin *Roche, Turk.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefatox
Note: this name may be used for preparations of different composition.
Biofarma, Venez.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

P & B, India.
Cefotaxime (p. 244·1).
Bacterial infections.

Cefatrex *BMS, Gr.*
Cefapirin sodium (p. 237·1).
Bacterial infections.

Cefatrin *Gepach, Rus.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefatropin N *Cefak, Ger.†*
Atropinum sulfuricum (p. 1310·2); gelsemium sempervirens (p. 2511·2); artemisia absinthium (p. 2426·1).
Homoeopathic preparation.

Cefatum *CCM, Malaysia.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefaval *Valmor, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefavora *Cefak, Austria; Cefak, Ger.†; Cefak, Ukr.*
Ginkgo biloba (p. 2512·3); viscum album (p. 2560·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Cefavora Cor *Cefak, Ger.*
Selenicereus grandiflorus (p. 2473·2); nitroglycerinum (p. 1391·2); crataegus (p. 2488·1); ammi visnaga (p. 2441·2).
Homoeopathic preparation.

Cefavora G *Cefak, Ger.†*
Ginkgo biloba (p. 2512·3).
Homoeopathic preparation.

Cefax
Note: this name may be used for preparations of different composition.
Inga, India.
Cefalexin (p. 234·1).
Bacterial infections.

1A, Austria.†
Cefaclor (p. 232·3).
Bacterial infections.

Cefaxon
Note: this name may be used for preparations of different composition.
Ariston, Braz.
Cefalexin (p. 234·1).
Bacterial infections.

Kimia, Indon.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefaxona *Pisa, Mex.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefaxone *Lupin, India; Shin Poong, Malaysia; Lupin, Rus.; Shin Poong, Singapore; Lupin, Ukr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefazid *Biochem, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefazil *Italfarmaco, Ital.*
Cefazolin sodium (p. 237·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefazillin *TP, Thai.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cefazime *CJ, Singapore.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefazink *Cefak, Ger.*
Zinc gluconate (p. 2126·2).
Zinc deficiency.

Cefazol *Kalbe, Indon.; General Drugs, Thai.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cefazole *Nutramedica, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cefazovit *Pan-Ject, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cefbact *Cipla, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefbect *Elfin, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefcal *JK Biochem, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Cefcas *Casca, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Cefcem *Om Biotec, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefchamp *Piramal, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Cefcidal *Akums, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefcin *Cinerea, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefcin-SB *Cinerea, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefcin-TJ *Cinerea, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefclor *TP, Thai.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefcon *Concertina, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefcure *Cure Quick, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefdicare *Meyer, India.*
Cefditoren (p. 239·1).
Bacterial infections.

Cefdiel *Ranbaxy, India; Ranbaxy, Malaysia.*
Cefdinir (p. 238·3).
Bacterial infections.

Cef-Dime *Millimed, Thai.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefdime *Promed, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefdina *Zota, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefdinex-SB *Invision, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Cef-Diolan *Medo, Ger.†*
Cefaclor (p. 232·3).
Bacterial infections.

Cefditran *Ranbaxy, India.*
Cefditoren (p. 239·1).
Bacterial infections.

Cefdolife *Lifestyle, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefdox *Sun, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefecon D *Nizpharm, Rus.; Nizhfarm, Ukr.*
Paracetamol (p. 115·1).
Fever; pain.

Cefecon N *Nizpharm, Rus.; Nizhfarm, Ukr.*
Naproxen (p. 98·2); caffeine (p. 1203·3); salicylamide (p. 129·2).
Inflammation; fever; pain.

Cefective *Merck, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefel *Finecure, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefel-B *Finecure, India.*
Bromhexine (p. 1656·3); cefalexin (p. 234·1).

Cefelen *Solara, Mex.†*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Cefelic *Arrow, Braz.*
Sertraline (p. 448·1).

Cefen *Pharmasant, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders; inflammation; pain; fever.

Cefer *Biotenk, Arg.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Cefera *Shreya, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceferro *Teofarma, Ger.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency; iron-deficiency anaemias.

Cefesym *Symbiosis, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefetil *Synmedic, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefexin *Unison, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cefexina *Greenpharma, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefexl *Active, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefexy *Neiss, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefexy-CV *Neiss, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Cefezone *Intas, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceff *Lupin, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Ceff-LA *Lupin, India.*
⊗Cefalexin (p. 234·1); probenecid (p. 607·3).
Bacterial infections.

Cef-G *Globus, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefglobe *Micro, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefglobe-S *Micro, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefgram
Note: this name may be used for preparations of different composition.
Behrens, Venez.
Ceftazidime (p. 250·2).
Bacterial infections.

Bennett, Gr.
Cefprozil (p. 248·2).
Bacterial infections.

Cefi *Khandelwal, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefi XL *Khandelwal, India.*
Cefixime (p. 240·3); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefia *Positif, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefiact *Active, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefic *Profic Organic, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ceficacy *Dallas, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ceficad *Cadila, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Ceficin *Flamingo, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefid
Note: this name may be used for preparations of different composition.
Health Guard, India.
Injection: Ceftazidime (p. 250·2).
Bacterial infections.

Novamed, India.
Tablets: Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cefid-L *Radicura, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Cefies *Medihealth, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefigard *Vanguard, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefigo *Leo, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefigram *United Lifecare, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefika *Ikapharmindo, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Cefikab *Lancer, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefila *Lapi, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cefilan *Medinfar, Port.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefim *Lapi, Indon.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Cefime *Uniroyal, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefimed *Meridian, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefimen-K *Klonal, Arg.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cefimix *Tecnimede, Port.*
Cefixime (p. 240·3).
Bacterial infections.

Cefimo *Pharma-Tech, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefin
Note: this name may be used for preparations of different composition.
Panbiotic, China; Pharmakin, Venez.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.
Remedina, Gr.
Ceftazidime (p. 250·2).
Bacterial infections.

Cefina *Intra-Labs, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Cefinar *Zydus, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefina-SB *Intra-Labs, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefind *Indu, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefine
Note: this name may be used for preparations of different composition.
Finecure, India.
Cefixime (p. 240·3).
Bacterial infections.

Cefio *Osmed, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefiped *Meyer, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefipra *Nexus, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Cefir *Fahrenheit, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Cefirap *Rapross, India.*
Cefixime (p. 240·3); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Cefirax *Saval, Chile.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefirone T *Piramal, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefirone-V *Piramal, India.*
Ceftriaxone (p. 253·3); vancomycin (p. 384·2).
Bacterial infections.

Cefisym *Symbiosis, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefit *Cubit, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefiton *Labesfal, Port.*
Cefixime (p. 240·3).
Bacterial infections.

Cefit-OZ *Cubit, India.*
Cefixime (p. 240·3); ornidazole (p. 943·1).

Cefit-XL *Cubit, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Cefium *Sieger, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Cefiwel *Evershine, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefix
Note: this name may be used for preparations of different composition.
Cipla, India; Cipla, Malaysia; Pharma International, Ukr.
Cefixime (p. 240·3).
Bacterial infections.
Dollder, Venez.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefix LB *Cipla, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefix-CV *Active, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Cefixmycin *Yung Shin, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Cefixoral *Menarini, Ital.*
Cefixime (p. 240·3).
Bacterial infections.

Cefixycin *YSP, Malaysia.*
Cefixime (p. 240·3).
Respiratory-tract infections; urinary-tract infections.

Cefiza *Trumac, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefizel *Zeler, Port.*
Cefixime (p. 240·3).
Bacterial infections.

Cefizox *GSK, India; Kalbe, Indon.; Hikma, Port.; Eczacibasi, Turk.; Fujisawa, USA.†*
Ceftizoxime sodium (p. 253·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefjoy *JB Chemicals, India.*
Dispersible tablets; tablets: Cefpodoxime; *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.
JB Chemicals, India.
Injection: Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefking *Maneesh, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefkor *Douglas, Austral.†*
Cefaclor (p. 232·3).
Bacterial infections.

Cefla *H & Care, India.*
Cefixime (p. 240·3); sulbactam (p. 360·1).
Bacterial infections.

Ceflacid *Collins, Mex.†*
Cefaclor (p. 232·3).
Bacterial infections.

Ceflame *Helax, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Ceflame-K *Helax, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Ceflavit *Aurora, Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Ceflen *Lapreven, Venez.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Ceflet *Ikon, India.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ceflim *Synmedic, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ceflin
Note: this name may be used for preparations of different composition.
Lincoln, India.
Cefotaxime (p. 244·1).
Bacterial infections.

Cefline *Life Line, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ceflorr *Finecure, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Ceflour *YSP, Malaysia.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.
Yung Shin, Hong Kong.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ceflox *Laborate, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ceflox-CF *Laborate, India.*
⊗Ciprofloxacin (p. 261·1); clotrimazole (p. 576·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Ceflox-D *Laborate, India.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).

Ceflox-TZ *Laborate, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cefmac
Note: this name may be used for preparations of different composition.
Ikon, India.
Injection: Ceftriaxone (p. 253·3).
Bacterial infections.
McNeil & Argus, India.
Capsules: Cefadroxil (p. 233·2).
Bacterial infections.

Cefmag *Magnus, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefmandol *General Drugs, Thai.*
Cefamandole (p. 236·2).
Bacterial infections.

Cefmate *Baxter, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefmed *EuroHealthcare, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefmer 1 *Mersifarma, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Cefmetazon *Daiichi Sankyo, China; Daiichi Sankyo, Jpn.*
Cefmetazole sodium (p. 241·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefmix *Cadila, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefmol *Elfin, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefmol-SF *Elfin, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefmol-TZ *Elfin, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).

Cefnaxl *XL, Philipp.*
Cefdinir (p. 238·3).
Bacterial infections.

Cefnet *Gentech, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Cefnij *Sunij, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefnos *Pharos, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Cefo *Medley, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefoact *Active, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefoat *ATOZ, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefob *Trumac, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefobac
Note: this name may be used for preparations of different composition.
Lexus, India.
Injection: Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.
Rusan, India.
Tablets: Ciprofloxacin (p. 261·1).
Bacterial infections.

Cefobac-TD *Rusan, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cefobac-TDH *Rusan, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cefobel-S *Blubell, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefobeta *Tablets, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefobid *Pfizer, Austria; Pfizer, Chile†; Pfizer, China; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Fuji, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Ukr.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefobit *Cubit, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefobocid *Borshchagovskii, Ukr.*
Cefoperazone (p. 243·1).
Bacterial infections.

Cefocef *Centaur, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefocef-DXL *Centaur, India.*
Cefixime (p. 240·3); dicloxacillin (p. 286·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefocef-LB *Centaur, India.*
Cefixime (p. 240·3); lactobacilli (p. 2596·3).
Bacterial infections.

Cefocef-XL *Centaur, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefociclin *Francia, Ital.*
Cefoxitin sodium (p. 246·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefoclav *Medley, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Cefoctam *Darnitsa, Ukr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefoden-SB *BMW, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefodie *Cristalfarma, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injections to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefodime *LBS, Thai.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefodin *MMC, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefodox *Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Scharper, Ital.; Pharma International, Ukr.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefofix *Hikma, Port.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefogard-S *Evershine, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefogen *Cadila, India; Cadila, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefogram
Note: this name may be used for preparations of different composition.
Orchid, India; Orchid, Rus.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.
Orchid, Ukr.
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefoject *Mahakam Beta, Indon.*
Sulbactam (p. 360·1); cefoperazone (p. 243·1).
Bacterial infections.

Cefokil *Global, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Cefo-L *Medley, India.*
Cefixime (p. 240·3); *Lactobacillus* (p. 2596·3).
Bacterial infections.

Cefol *Abbott, Hong Kong†; Abbott, USA.†*
Vitamins.

Cefolac *Macleods, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefolex *Lexus, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefo-LX *Medley, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cefomax *Bago, Arg.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefomic *LBS, Thai.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefomit *Magis, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefom-S *Trumac, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefomycin *Zydus, India.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefonax *Elmor, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefonetic *Arunabh, India.*
Cefpodoxime.
Bacterial infections.

Cefonet-S *Bionet, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefonex *Admac, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefonova *Evolan, Swed.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefoperabol *Abolmed, Rus.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefoperazin *Taisho, Jpn.*
Cefoperazone sodium (p. 243·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefoperazone Plus *Avant, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefoperus *Sintez, Rus.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefophar *Pharos, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefoplus *Aesculapius, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefoprim *DRD, Gr.; Esseti, Ital.†*
Cefuroxime sodium (p. 255·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.
United Biotech, India.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefoprox *Cipla, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefor *Meiji, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ceforal
Note: this name may be used for preparations of different composition.
Astellas, Rus.; Astellas, Ukr.
Cefixime (p. 240·3).
Bacterial infections.
Grunenthal, Port.
Cefadroxil (p. 233·2).
Bacterial infections.
Teva, Israel.
Cefalexin (p. 234·1).
Bacterial infections.

Ceforan *Uniao Quimica, Braz.; General Drugs, Thai.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ceforex *Hauz, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Ceforim
Note: this name may be used for preparations of different composition.
Hetero, India.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.
Sanbe, Indon.
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Ceforiz *Ritz, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Ceforox *Kamakshi, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefortam *Glaxo Wellcome, Port.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceforth *Biochem, India.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Cefos *Osper, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefosal *Finecure, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefosin *Sintez, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefosporen *TRB, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefos-S *Osper, India.*
Cefuroxime (p. 255·2); sulbactam (p. 360·1).
Bacterial infections.

Cefosul *CMG, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefosulbin *Pro-Pharma, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefosun *Sunshine, India.*
Cefpodoxime.
Bacterial infections.

Cefosun S *Sunshine, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefotan *Zeneca, USA.†*
Cefotetan disodium (p. 245·3).
Bacterial infections.

Cefotax *Pharmawealth, Philipp.; Atlantic, Thai.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefotec *Keshav, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefotex *Precimex, Mex.; Gepach, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefotim *Zydus, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Cefotrim *Pharmedic, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefotrix *Eberth, Austria; Eberth, Denm.; Eberth, Ger.; T3A Pharma, Hung.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefovell *Novell, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefovit *Vitamed, Israel.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefox
Note: this name may be used for preparations of different composition.
Health Care, India.
Cefixime (p. 240·3).
Bacterial infections.
Sel-J, Philipp.; Utopian, Thai.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefoxal *Sandoz, Indon.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefoxan *Royton, Braz.†*
Cefoxitin (p. 246·2).
Bacterial infections.

Cefoxid *Alkem, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefoxil *Bal, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefoxim *Biochem, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefoxin *Royton, Braz.†; M & H, Thai.*
Cefoxitin sodium (p. 246·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefoxivit *Vitalis, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Cefozed-S *Zota, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefozin *Bilim, Turk.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefozone *Atlantic, Singapore; Vana, Thai.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefpar
Note: this name may be used for preparations of different composition.
Kapl, Thai.
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.
Karnataka, India.
Cefoperazone (p. 243·1).
Bacterial infections.
Karnataka, Rus.
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefpar SB *Karnataka, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefper *Biolab, Thai.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Cefph *Sanjivani, India.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Cefpil *Psychotropics, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefpime *Global, India.*
Cefepime (p. 239·2).
Bacterial infections.

Cefpo *Finecure, India.*
Cefpodoxime.
Bacterial infections.

Cefpocin *Cinerea, India.*
Cefpodoxime.
Bacterial infections.

Cefpogard *Candor, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefpolar *Lark, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefpro *Verisfield, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Cefraden *Merck, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefradil *Merck, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefradol *Ferron, Indon.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Cefradur *Atral, Port.*
Cefradine (p. 249·1).
Bacterial infections.
Eczacibasi, Turk.
Cefadroxil (p. 233·2).
Bacterial infections.

Cefrag *Magis, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefralon *Aldril, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Cefridem *Dem, Turk.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefriex *Novell, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefril *BMS, S.Afr.†*
Cefradine (p. 249·1).
Bacterial infections.

Cefrin
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Cefpirome (p. 247·2).
Bacterial infections.
Dexa, Philipp.
Cefpirome sulfate (p. 247·2).
Bacterial infections.
Julphar, UAE.
Cefalexin (p. 234·1).
Bacterial infections.

Cefrine *Macleods, India.*
Cefdinir (p. 238·3); lactobacillus (p. 2596·3).
Bacterial infections.

Cefritz *Ritz, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefritz-S *Ritz, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefritz-TZ *Ritz, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefrobactum *Sanjivani, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefrom *Aventis, Austral.†; Sanofi-Aventis, Austria; Sanofi, China; Sanofi-Aventis, Fr.; Hoechst Marion Roussel, Gr.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.†; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Thai.†*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Cefrosan *Sanjivani, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cefrose-S *Rose, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefrub *Chemo-Drugs, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cef-S *Shreshtha, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefs *Shreshtha, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefset *Wintech, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefset-S *Wintech, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefset-TX *Wintech, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefsine *Sunshine, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefsine-S *Sunshine, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefsine-TZ *Sunshine, India.*
Ceftriaxone (p. 253·3); tazobactam sodium (p. 369·3).
Bacterial infections.

Cefsix *Mersifarma, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefson *Dr Alson, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Nevzat, Rus.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefspan *Baiyunshan, China; GSK, India; Kalbe, Indon.; Choseido, Jpn; Astellas, Thai.*
Cefixime (p. 240·3).
Bacterial infections.

Cefs-T *Shreshtha, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Ceftа *Plus, India.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ceftab *Sienna, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Ceftabit *Cubit, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftadime *Lupin, Ukr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftal *Rowex, Irl.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Talent, India.
Cefuroxime (p. 255·2), cefuroxime axetil (p. 255·2), or cefuroxime sodium (p. 255·3).
Bacterial infections.

Ceftamax *Simex, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftaridem *Vocate, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftariz *Ritz, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftas *Intas, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ceftas AL *Intas, India.*
Ambroxol (p. 1654·3); cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).

Ceftas-LB *Intas, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ceftavir *East African, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftax *Hikma, Cz.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ceftaxan *Umeda, Thai.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ceftaz *Cipla, India; Pharmedic, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftazidon *Ariston, Braz.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftazim *Atral, Port.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftazin *Remedina, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Ceftazivit *Pan-Ject, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceften *Teuto, Braz.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftex *Prem, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Ceftibac *Pharmawealth, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftic *Yash, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Ceftichek *Indoco, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Ceftidin *Hetero, India; Lyka, Rus.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftil *Standard, Philipp.; Hanmi, Singapore.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Ceftils *Shreshtha, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Ceftim *Glaxo Allen, Ital.†; Cipan, Port.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftime *Utopian, Thai.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftin *GSK, Canad.; GSK, USA.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Ceftina *Probiomed, Mex.†*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Ceftinex *Bilim, Turk.*
Cefdinir (p. 238·3).
Bacterial infections.

Ceftiol *Laboratorios Chile, Chile.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceftiwin *Parenteral Drugs, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ceftobac *RPG, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ceftocin *Venus, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Ceftomax *Solara, Mex.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cefton *Ariston, Braz.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Ceftop
Note: this name may be used for preparations of different composition.
Ranbaxy, India.
Injection: Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Vensat, India.
Syrup: Cefpodoxime proxetil (p. 248·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ceftop RM *Ind-Swift, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Ceftop-DT *Vensat, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Ceftoral *Vianex (Βιανεξ), Gr.*
Cefixime (p. 240·3).
Bacterial infections.

Ceftorin *Cipla, India.*
Cefditoren pivoxil (p. 239·1).
Bacterial infections.

Ceftra *Health Guard, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Ceftraset *Biosync, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceftraset-S *Biosync, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Ceftrat *Uniao Quimica, Braz.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Ceftrax *Aurobindo, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrex *Biolab, Malaysia; Rhein, Mex.; Biolab, Thai.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ceftriabol *Abolmed, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrialin *Behrens, Venez.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceftrialis *Pan-Ject, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrian *Taurus, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceftriax *Sigma, Braz.*
Ceftriaxone (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ceftriaz *Klonal, Arg.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrifin *Wockhardt, Rus.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceftril *Tablets, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceftrilem *Teva, Mex.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ceftril-S *Tablets, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Ceftrimax *VHB, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Ceftrinal *Farmedia, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Ceftriphin *General Drugs, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftriphine *Daehan, Singapore.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrisone *Akums, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrixon *Pharma Line, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrol *Medihealth, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceftrol-S *Medihealth, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Ceftron *Inga, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftrox *Meiji, Indon.; Pharmawealth, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceftru *Trumac, India.*
Cefpodoxime.
Bacterial infections.

Ceftum
Note: this name may be used for preparations of different composition.
Ferron, Indon.; Arterium, Ukr.
Ceftazidime (p. 250·2).
Bacterial infections.

GSK, India.
Cefuroxime (p. 255·2).
Bacterial infections.

Ceftyl *Aarpik, India.*
Cefpodoxime.
Bacterial infections.

Ceftyl-CV *Aarpik, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Cefu *Prem, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefubir *Birz, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefucil *SRS, Philipp.†*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefucin *Cinerea, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefucos *Symbiosis, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefudix *Neon, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cefu-Hexal *Hexal, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefuhexal *Hexal, Ger.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefulton *River, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Cefum *Health Guard, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefumax *Hikma, Ukr.*
Cefuroxime (p. 255·2).
Bacterial infections.

Manix, Philipp.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefunis *Neiss, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefup *Sanat, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Cefupet *Vista, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefupop *Alna, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefupop-CV *Alna, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Cefupop-XL *Alna, India.*
Cefixime (p. 240·3); dicloxacillin (p. 286·1).
Bacterial infections.

Cefur *Vianex (Βιανεξ), Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefurabol *Abolmed, Rus.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefuracet *Rhein, Mex.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurax *Lindopharm, Israel.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurax-D *Hauz, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cefuretil *AG Therapy, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurex *Ultramed, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurim *Teva, Belg.; General Drugs, Thai.*
Cefuroxime (p. 255·2).
Bacterial infections.

Sandoz, Switz.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurin
Note: this name may be used for preparations of different composition.
Invision, India.
Dispersible tablets; tablets: Cefuroxime axetil (p. 255·2).
Bacterial infections.

Invision, India.
Injection: Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Pharma-Marketing, Hung.†; Magis, Ital.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefurol *Ulagay, Turk.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefuroprol *Novendia, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefuro-Puren *Actavis, Ger.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurox *GSK, Arg.; Basics, Ger.†*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Prafa, Indon.†
Cefuroxime (p. 255·2).
Bacterial infections.

Cefurox-Wolff *Wolff, Ger.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefurus *Sintez, Rus.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefusym *Symbiosis, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefutab-O *Sanjivani, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefute *TP, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Cefutil *Pharma International, Ukr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefuvik *Anglo-French Drugs, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefuzime *Royale, Philipp.; Julphar, UAE.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefvel *Biosync, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cef-Vepan *Indoco, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefvig *Madhav, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefwar *Leben, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cefwin *Ikon, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cefwon *Mediez, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefwon-S *Mediez, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefxi *Medley, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefxin
Note: this name may be used for preparations of different composition.
Standard, Singapore.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cefxi-O *Sinkhai, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cefxitin *Siam Bheasach, Thai.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Cefxon *Lapi, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefyrex *Global, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cefzid *Elfin, India; Ind-Swift, India; Protech, Rus.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefzidime *Chandra Bhagat, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cefzil *BMS, Braz.; BMS, Canad.; BMS, China; BMS, Cz.; BMS, Gr.; BMS, Hung.; BMS, Indon.†; BMS, Pol.†*
Cefprozil (p. 248·2).
Bacterial infections.

Cefzim *Zee, India.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cefzolin *Utopian, Thai.*
Cefazolin (p. 237·2).
Bacterial infections.

Cefzon *Astellas, China; Astellas, Jpn.*
Cefdinir (p. 238·3).
Bacterial infections.

Cefzon SB *Blossoms, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cef-Zone *Millimed, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cefzone-S *Intas, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefzox *Elfin, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cefzox-SF *Elfin, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cefzox-TZ *Elfin, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cefzy *Zee, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceglen *Glenmark, Braz.*
Ascorbic acid (p. 2110·3).

Ceglen Zinco *Glenmark, Braz.*
Ascorbic acid (p. 2110·3); zinc chelate (p. 2048·3).

Ceglution *Ariston, Arg.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Cêgripe *Johnson & Johnson, Port.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Ceham *Alkem, India.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism; head injury.

Cek *Hexal, Pol.†*
Cefaclor (p. 232·3).
Bacterial infections.

Ceklif Plus *Positif, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Cekloteva *Med, Turk.*
Cefaclor (p. 232·3).

Celact *Sun, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celadrin
Note: this name may be used for preparations of different composition.
Reddy, India.
Cetyl myristoleate (p. 2473·3); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Cymbiotics, Malaysia.†
Capsules: Fish oil (p. 1460·3); fatty acids; tocoferil acetate (p. 2119·2).
Dietary supplement.

Cymbiotics, Malaysia.†
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2); fatty acids; vitamin E (p. 2119·1).
Sports injuries; repetitive strain injury; osteoarthritis; rheumatoid arthritis.

Celamina *Glenmark, Braz.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Celamine *Pharmasant, Thai.*
Imipramine hydrochloride (p. 426·2).
Depression; panic attacks; pain; nocturnal enuresis; parkinsonism.

Celanat *Chrispa (Χρισπα), Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Celance *Roemmers, Arg.; Lilly, Braz.†; Lilly, Fr.†; Lilly, Gr.†; Lilly, Irl.; Lilly, Singapore; Lilly, UK.†*
Pergolide mesilate (p. 910·2).
Parkinsonism.

Celanid *Vilar, Rus.*
Lanatoside C (p. 1417·3).
Heart failure; arrhythmias.

Celanid-KMP *Arterium, Ukr.†*
Lanatoside C (p. 1417·3).
Heart failure; arrhythmias.

Celapram *Alphapharm, Austral.; Mylan, NZ.*
Citalopram hydrobromide (p. 411·1).
Depression.

Merck, Braz.
Citalopram (p. 411·1).

Celar *Chemo-Drugs, India.*
Bromhexine hydrochloride (p. 1656·3); phenylpropanolamine hydrochloride (p. 1674·1).

Celascon *Zentiva, Rus.*
Ascorbic acid (p. 2110·3).

Celaskon *Zentiva, Cz.; Zentiva, Ukr.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Celaxin *Pharmavita, Chile.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Celay *Cofasa, Venez.*
Cetirizine hydrochloride (p. 619·2).

Celcib *Khandelwal, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celco *Unison, Thai.†*
Cefaclor (p. 232·3).
Bacterial infections.

Celcox *Lupin, India; Trima, Israel.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celcoxx *Getz, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celdach *Celon, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Celebra *Pfizer, Braz.; Pfizer, Chile; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Israel; Pfizer, Norw.; Pfizer, Swed.*
Celecoxib (p. 36·3).
Familial adenomatous polyposis; osteoarthritis; rheumatoid arthritis; pain; ankylosing spondylitis.

Celebral *Kleva, Gr.*
Piracetam (p. 393·3).

Celebrex *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, China; Pfizer, Cz.; Orifarm, Denm.; Paranova, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, NZ; Pfizer, Philipp.; Pharmacia, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Searle, USA.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; ankylosing spondylitis; dysmenorrhoea; familial adenomatous polyposis; juvenile idiopathic arthritis; colorectal polyps; degenerative joint disorders.

Celecap *Centaur, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celecel *Claris, India.*
Trace elements.

Celectan *Farma, Venez.*
Nitazoxanide (p. 942·2).
Amoebiasis; giardiasis; worm infections.

Célectol *Sanofi-Aventis, Fr.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.

Celectol *Winthrop, UK.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension.

Celedol *Ipca, India.*
Celecoxib (p. 36·3).
Familial adenomatous polyposis; osteoarthritis; rheumatoid arthritis; pain.

Celemax *Cadila, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celemin
Note: this name may be used for preparations of different composition.
Claris, India; Promed, Indon.; Claris, Philipp.
Amino acids; with or without electrolytes (p. 1775·1) or sorbitol (p. 2092·1).
Parenteral nutrition.

Probiomed, Mex.†
Quinfamide (p. 947·1).
Amoebiasis.

Celemix Combi *Claris, India.*
Amino acids; lipid; sorbitol (p. 2092·1).
Parenteral nutrition.

Celemix-G Combi *Claris, India.*
Amino acids; glucose (p. 2068·3); lipid.
Parenteral nutrition.

Celen *Ranbaxy, Braz.†*
Cefalexin (p. 234·1).
Bacterial infections.

Celenid *Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.†*
Cinnarizine (p. 622·1).
Motion sickness; nausea; peripheral vascular disorders; vertigo; vestibular disorders; cerebrovascular disorders; migraine.

Celepid *Claris, India; Promed, Indon.; Claris, Philipp.; Claris, Thai.†*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Celepid MCT-LCT *Claris, India.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2); long-chain triglycerides.
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Celepra *Micro, India.*
Citalopram (p. 411·1).
Depression; bipolar disorder; panic disorder.

Celer C *IAE, Philipp.*
Lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Tonic.

Celerg *Legrand, Braz.*
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Celergin *EMS, Braz.*
⊗Dexchlorpheniramine (p. 620·3); betamethasone (p. 1623·2).

Celermin *Pascual, Philipp.†*
Vitamins; Chlorella growth factor (p. 2475·3); lysine (p. 2079·3); taurine (p. 2626·2).
Dietary supplement.

Celery 3000 *Blackmores, Austral.*
Celery (p. 2472·3); celery seed oil (p. 2472·3).
Arthritis; gout.

Celesdepot *Schering-Plough, Port.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Celesemine *Schering-Plough, Spain.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Celestamin *Aesca, Austria.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity disorders.

Celestamincort *Schering-Plough, Venez.*
⊗Betamethasone (p. 1623·2); loratadine (p. 633·2).

Celestamine *Schering-Plough, Arg.; Mantecorp, Braz.; Schering-Plough, Chile; MSD, Hong Kong; Schering-Plough, Indon.; Essex, Philipp.; Schering-Plough, S.Afr.†; Schering-Plough, Venez.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; inflammatory eye disorders; allergic rhinitis; urticaria; skin disorders.

Célestamine *MSD-Chibret, Fr.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic rhinitis; urticaria.

Celestamine N *MSD, Ger.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Celestamine NS *Schering-Plough, Mex.*
⊗Betamethasone (p. 1623·2); loratadine (p. 633·2).
Hypersensitivity.

Celestamine-L *Schering-Plough, Arg.*
⊗Betamethasone (p. 1623·2); loratadine (p. 633·2).
Hypersensitivity reactions.

Celestan *Aesca, Austria.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3) and betamethasone acetate (p. 1623·2).
Corticosteroid.

Celestan Depot *MSD, Ger.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Celestan solubile *MSD, Ger.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celestan-V *MSD, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Celestene *IFET (ΙΦΕΤ), Gr.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Célestène *MSD-Chibret, Fr.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Célestène Chronodose *MSD-Chibret, Fr.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Celestik *Pyridam, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Celestoderm *Valeo, Canad.; MSD, Fin.; Schering-Plough, Neth.†; Schering-Plough, Ukr.; Schering-Plough, Venez.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Célestoderm *MSD-Chibret, Fr.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Celestoderm cum Garamycin *MSD, Fin.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Celestoderm con Gentalyn *Schering-Plough, Venez.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Celestoderm Gentamicina *MSD, Spain.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Celestoderm-V *MSD, Gr.; Schering-Plough, Indon.; Schering-Plough, Rus.; MSD, Spain; Essex, Switz.†; Schering-Plough, Turk.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Celestoderm-V with Garamycin *MSD, Gr.; Schering-Plough, Indon.; Schering-Plough, Rus.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Celestoderm-V with Neomycin *Schering-Plough, Gr.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).

Celeston *Schering-Plough, Denm.*
Cream: ⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Schering-Plough, Denm.; Schering-Plough, Norw.
Injection: ⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Schering-Plough, Ukr.
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celeston bifas *MSD, Swed.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celeston Chronodose *MSD, Fin.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celeston valerat *MSD, Swed.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Celeston valerat med gentamicin *Schering-Plough, Swed.†*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Celestone *Schering-Plough, Arg.; MSD, Belg.; Mantecorp, Braz.; IFET (ΙΦΕΤ), Gr.; Fulford, India; Schering-Plough, Indon.; Schering-Plough, Ital.; Schering-Plough, Mex.; MSD, Neth.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Essex, Switz.†; Schering, USA; Schering-Plough, Venez.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celestone Chronodose *MSD, Austral.; MSD, Belg.; MSD, Gr.; Schering-Plough, Israel; MSD, Neth.; MSD, NZ; MSD, Switz.; Schering-Plough, Turk.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Celestone Cronodose *Schering-Plough, Arg.; Schering-Plough, Ital.; MSD, Spain.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celestone M *MSD, Austral.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Celestone S *Schering-Plough, Spain.†*
⊗Betamethasone (p. 1623·2); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Celestone Soluspan *Mantecorp, Braz.; Merck, Canad.; Schering-Plough, Mex.; Schering-Plough, S.Afr.; Schering, USA; Schering-Plough, Venez.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celestrat *Uniao Quimica, Braz.*
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Celetil
Note: this name may be used for preparations of different composition.
Geolab, Braz.
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Celetop *Piramal, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Celetta *Juggat, India.*
Vitamins; trace elements.

Celeuk *Takeda, Jpn.*
Celmoleukin (p. 810·1).
Angiosarcoma.

Celevac *Amdipharm, Irl.; Amdipharm, UK.*
Methylcellulose (p. 2197·3).
Constipation; dietary fibre supplement; diarrhoea; diverticular disease; obesity; ostomy management; ulcerative colitis.

Celex
Note: this name may be used for preparations of different composition.
Farmo Quimica, Chile.
Clonixin lysine (p. 40·1).
Pain.

GSK, India.
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Millimed, Thai.
Cefalexin (p. 234·1).
Bacterial infections.

Celexa *Lundbeck, Canad.; Forest Pharmaceuticals, USA.*
Citalopram hydrobromide (p. 411·1).
Depression.

Celexib *InnoGen, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; adenomatous colorectal polyps.

Celexin *Schering-Plough, Braz.†; Bactolac, India; Hovid, Malaysia†; Hovid, Singapore; Atlantic, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Celex-OD *Abbott, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Celfast *Ind-Chemie, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Celfast Plus *Ind-Chemie, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Celfast SR *Ind-Chemie, India.*
Aceclofenac (p. 16·2).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Celfax *Degorts, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Celgem *Alkem, India.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Celib *Unichem, India.†*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis.

Celibron *Elpen (Ελπεν), Gr.*
Ambroxol hydrochloride (p. 1654·3).
Mucolytic.

Celica *Ranbaxy, Austral.*
Citalopram hydrobromide (p. 411·1).
Depression.

Ranbaxy, India.
Citalopram (p. 411·1).
Depression; bipolar disorder; panic disorder.

Ce-Limo *Meda, Austria.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ce-Limo plus 10 Vitamine *Meda, Austria.†*
Vitamins.

Celin *GSK, Hong Kong†; GSK, India.*
Vitamin C (p. 2110·3).
Vitamin C supplement.

Celipres *Ranbaxy, India.*
Celiprolol.
Hypertension.

Ranbaxy, Pol.
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension.

Celipro *Winthrop, Ger.†*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.

Celiprogamma *Worwag, Ger.†*
⊗Celiprolol hydrochloride (p. 1334·2).
Angina pectoris; hypertension.

Celiprol *Leciva, Rus.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.

Celit
Note: this name may be used for preparations of different composition.
Fada, Arg.
Ivy (p. 2536·2).
Respiratory-tract congestion.

Celitol *Elder, India; Zydus, India.*
Cefixime (p. 240·3).
Bacterial infections.

Celium *Utopian, Thai.*
Medazepam (p. 1083·2).
Anxiety.

Celius *Gerolymatos, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Cellactive *Biropharma, Hung.*
Selenium (p. 2086·3); vitamin B substances (p. 2102·3); betacarotene (p. 2051·1); tocoferil acetate (p. 2119·2).
Dietary supplement.

Cellasene *Cinetic, Arg.†*
Bearberry (p. 2453·2); melilot (p. 2552·3); ginkgo biloba (p. 2512·3); bladderwrack (p. 2612·1); centella (p. 1698·3); fish oil (p. 1460·1); borage oil (p. 2459·2); soya lecithin (p. 2542·2); fatty acids.
Cellulite; antoxidant.

Cellasene Gold *Cinetic, Arg.*
Grape (p. 2521·3); ginkgo biloba (p. 2512·3); melilot (p. 2552·3); bladderwrack (p. 2612·1); butcher's broom (p. 2463·1); centella (p. 1698·3); borage oil (p. 2459·2); fish oil (p. 1460·1); fatty acids; soya lecithin (p. 2542·2); lipoic acid (p. 2629·1); black pepper (p. 2586·1); orange oil (p. 2576·2).
Cellulite; circulatory disorders.

Cell-C *Piramal, India.*
Vitamin C (p. 2110·3).

CellCept *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, India; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, USA; Roche, Venez.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Roche, Hung.
Mycophenolate mofetil hydrochloride (p. 1961·2).
Cardiac, renal, or liver transplant rejection.

Cellcristin *Cell Pharm, Ger.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Celldolor *Cell Pharm, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Cellenergy *K2 Health & Wellness, Chile.*
Aloe vera (p. 1693·2); caffeine (p. 1203·3); birch leaf (p. 2457·3); tea (p. 2648·2); capsicum (p. 2469·3); carnitine (p. 2053·2); centella (p. 1698·3); bladderwrack (p. 2612·1); soya bean (p. 2092·3); ivy (p. 2536·2); lupulus (p. 2546·1); pomegranate (p. 164·1); theobroma (p. 2216·1); theobromine (p. 1229·2); theophylline (p. 1229·3).
Cellulite.

Cellex-C *Cellex-C, Canad.*
SPF 30; SPF 32: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Cell-fX *Afexa, Canad.*
Chondroitin (p. 2476·1).

Cellidrin *Hennig, Ger.†*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Cellidrine *Sanofi, Switz.†*
Allopurinol (p. 600·2).
Hyperuricaemia.

Cellmune *Cipla, India.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

cellmustin *Cell Pharm, Ger.*
Estramustine sodium phosphate (p. 790·1).
Prostatic cancer.

Cellobexon *Agepha, Austria.*
Hymetellose (p. 2189·1).
Constipation; obesity.

Celloid Compounds Magcal Plus *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); magnesium phosphate (p. 1787·3); calcium phosphate (p. 1784·2); dibasic potassium phosphate (p. 1791·1); iron phosphate (p. 2077·1).

Celloid Compounds Sodical Plus *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); calcium phosphate (p. 1784·2); iron phosphate (p. 2077·1).

Celloids CF 43 *Blackmores, Austral.†*
Calcium fluoride (p. 2053·1).
Homoeopathic preparation.

Celloids CP 57 *Blackmores, Austral.†*
Calcium phosphate (p. 1784·2).

Celloids CS 36 *Blackmores, Austral.†*
Calcium sulfate (p. 2173·1).

Celloids IP 82 *Blackmores, Austral.†*
Iron phosphate (p. 2077·1).

Celloids MP 65 *Blackmores, Austral.†*
Magnesium phosphate (p. 1787·3).

Celloids PC 73 *Blackmores, Austral.†*
Potassium chloride (p. 1793·2).

Celloids PP 85 *Blackmores, Austral.†*
Potassium phosphate (p. 1790·3).

Celloids PS 29 *Blackmores, Austral.†*
Potassium sulfate (p. 1793·2).

Celloids S 79 *Blackmores, Austral.†*
Silicon dioxide (p. 2208·3).

Celloids SP 96 *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2).

Celloids SS 69 *Blackmores, Austral.†*
Anhydrous sodium sulfate (p. 1888·1).

cellondan *Cell Pharm, Ger.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting associated with cancer chemotherapy and radiotherapy.

Cellosorb *Urgo, Fr.†*
Carmellose (p. 2175·1); white soft paraffin (p. 2211·3).
Wounds; burns.

Cellozina *Biofarma, Venez.*
Cefazolin (p. 237·2).
Bacterial infections.

Cellskinlab C + AHA *Dispolab, Arg.*
Ascorbic acid (p. 2110·3); glycolic acid (p. 1704·3); lactic acid (p. 2539·1).
Light-induced skin damage.

Cellskinlab C + E *Dispolab, Arg.*
Ascorbic acid (p. 2110·3); alpha tocopherol (p. 2119·1).
Light-induced skin damage.

Cellskinlab Hydragel B5 *Dispolab, Arg.*
Hyaluronic acid (p. 2526·2); pantothenic acid (p. 2085·2).
Dry skin disorders.

Cellskinlab Phyto Spot *Dispolab, Arg.*
Arbutin (p. 1694·3); kojic acid (p. 1710·2); thyme (p. 2630·2); cucurbita (p. 2489·2).
Skin pigmentation disorders.

Cellskinlab Serum 15 *Dispolab, Arg.*
Ascorbic acid (p. 2110·3).
Light-induced skin damage.

celltaxel *Cell Pharm, Ger.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Celltech *K2 Health & Wellness, Chile.*
Ginkgo biloba (p. 2512·3); fucus vesiculosus (p. 2612·1); grape (p. 2521·3); melilot (p. 2552·3); borage (p. 2459·1); fish oils (p. 1460·3).
Cellulite.

Celltop *Baxter, Belg.; Baxter Oncology, Fr.; IFET (ΙΦΕΤ), Gr.*
Etoposide (p. 790·2).
Malignant neoplasms.

Cellubril *AstraZeneca, India.*
Docusate calcium (p. 1836·2).
Constipation.

Cellufluid *Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Neth.; Allergan, Port.; Allergan, Swed.; Allergan, Switz.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Allergan, Gr.
Carmellose (p. 2175·1).
Dry eyes.

Cellufresh *Allergan, Austral.; Allergan, Braz.; Allergan, Ger.; Allergan, Ital.; Allergan, Philipp.; Allergan, S.Afr.; Allergan, Spain; Allergan, Thai.; Abdi, Turk.*
Carmellose sodium (p. 2175·2).
Dry eyes; lubricating solution for contact lens; eye irritation.

Cellugel *Alcon, Ger.; Alcon, Malaysia†; Alcon, S.Afr.†*
Hypromellose (p. 2189·2).
Adjunct in ophthalmic surgery.

Cellular Anti-Wrinkle *La Prairie, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Cellular Day Defense *Aloette, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Cellular Moisturizer *La Prairie, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Cellular Time Release Moisture *La Prairie, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Cellulin Retinale *INTES, Ital.*
Retina extract (p. 2444·1).
Eye disorders.

Cellumed *Allergan, Ger.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Celluspan *Fischer, Israel.*
Hyetellose (p. 2188·3).
Aid in gonioscopy.

Cellutex *Bio-Sante, Canad.*
Buchu (p. 2461·3); fennel (p. 2503·2); meadowsweet (p. 2550·2); parsley (p. 2583·3); cherry-laurel (p. 2475·2); taraxacum (p. 2625·3); bearberry (p. 2453·2).

Celluvisc *Allergan, Austral.; Allergan, China; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, India; Allergan, Irl.; Allergan, Israel†; Allergan, Ital.; Allergan, Malaysia; Allergan, Neth.; Allergan, Norw.; Allergan, Philipp.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain†; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Allergan, UK; Allergan, USA.*
Carmellose sodium (p. 2175·2).
Dry eyes; eye irritation.

Cellvital *Pharma Investi, Chile.†*
Selenium yeast (p. 2125·2); zinc gluconate (p. 2126·2); copper gluconate (p. 2057·2); vitamins.
Dietary supplement.

Celmanil *Kyowa, Jpn.*
Timiperone (p. 1111·3).
Schizophrenia.

Celocid *Dexa, Indon.; Ferron, Indon.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Celocort *Legrand, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Celocortin *EMS, Braz.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Celocurin *Meda, Swed.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Celocurine *CSP, Belg.*
Suxamethonium chloride.
Depolarising neuromuscular blocker.

CSP, Fr.
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Celofol *Themis, India.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Celoftal *Alcon, Ger.*
Hypromellose (p. 2189·2).
Aid in eye surgery.

Celol
Note: this name may be used for preparations of different composition.
Emcure, India.
Capsules: Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3).

Emcure, India.
Injection: Calcitriol (p. 2113·1).
Hyperparathyroidism; hypocalcaemic tetany.

Mylan, NZ.
⊗Celiprolol hydrochloride (p. 1334·2).
Angina pectoris; hypertension.

Celomix *Actavis, Denm.; Actavis, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; ankylosing spondylitis; rheumatoid arthritis.

Celonfex *Indeco, Arg.*
Sertraline hydrochloride (p. 448·1).
Panic disorder; depression; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Celonib *Celon, India.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia; myelodysplastic syndromes; dermatofibrosarcoma protuberans; gastrointestinal stromal tumours; systemic mastocytosis; hypereosinophilic syndrome.

Celontin *Erfa, Canad.; Pfizer, USA.*
Mesuximide (p. 533·1).
Absence seizures.

Celovit *Mapra, India.*
Vitamins; trace elements.

Celox
Note: this name may be used for preparations of different composition.
Cure Quick, India.
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

Barrenne, Braz.†
Grape (p. 2521·3).

Celprot *Pisa, Mex.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Celsentri *Pfizer, Arg.; ViiV, Austral.; ViiV, Austria; ViiV, Belg.; GSK, Braz.; ViiV, Canad.; GSK, Chile; Pfizer, China; GSK, Cz.; ViiV, Denm.; ViiV, Fr.; ViiV, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; ViiV, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; ViiV, Neth.; GSK, Norw.; Pfizer, Pol.; ViiV, Port.; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Thai.; ViiV, Thai.; Pfizer, UK.*
Maraviroc (p. 1003·2).
HIV infection.

Celsior *Genzyme, Irl.; Genzyme, Neth.; Genzyme, Spain.*
Solution for preservation of donor organs.

Celtax *Celon, India.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Celtect *Kyowa, Jpn.*
Oxatomide (p. 636·3).
Allergic rhinitis; urticaria; pruritus.

Celtere *Celon, India.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Celtium *Saval, Chile.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Celtura *Novartis, Switz.*
An influenza vaccine (surface antigen H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Celu-Atlas *Atlas, Arg.; Mediderm, Chile.*
Centella (p. 1698·3); ivy (p. 2536·2); bladderwrack (p. 2612·1); butcher's broom (p. 2463·1); caffeine (p. 1203·3).
Cellulite.

Celu-Ikx *Ikx, Arg.*
Siloxanetriol alginate (p. 2088·3); caffeine (p. 1203·3); methylsilanol manuronate (p. 2088·3).
Cellulite.

Cel-U-Jec *Hauck, USA.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Celulase *Rider, Chile.*
Centella (p. 1698·3).
Burns; fibrosis; lipodystrophy; ulcers; venous insufficiency; wounds.

Celulase Con Neomicina *Rider, Chile.*
Centella (p. 1698·3); neomycin sulfate (p. 330·1).
Burns; skin infections; ulcers; wounds.

Celulase Plus *Rider, Chile.*
Centella (p. 1698·3).
Burns; fibrosis; lipodystrophy; ulcers; wounds.

Celulight *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Celulose *Grin, Mex.*
Hypromellose (p. 2189·2).
Aid in ophthalmic procedures; dry eyes.

Celunaf *Grin, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Celupan *BMS, Spain.†*
Naltrexone hydrochloride (p. 1565·1).
Alcoholism; opioid withdrawal.

Celuterol *Nafar, Mex.*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hyperlipidaemias.

Celvapan *Baxter, Cz.; Baxter, Fr.†; Baxter, Irl.; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Pol.; Baxter, Port.; Baxter, UK.†*
An influenza vaccine (H1N1 strain) (p. 2393·3).
Pandemic influenza prophylaxis.

Celvista *Takeda, Thai.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis; breast cancer.

Celyth's *Natiris, Venez.*
Cynodon dactylon; bengal gram; centella (p. 1698·3); taraxacum (p. 2625·3).

Celzar *Celon, India.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Cemado *Francia, Ital.†*
Cefamandole nafate (p. 236·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cemadol *Life Medicare, India.*
Tramadol (p. 139·2).
Pain.

Cémaflavone *Bailleul, Fr.*
Citroflavonoids (p. 2505·2); magnesium ascorbate (p. 1787·1).
Haemorrhoids; venous insufficiency; visual disorders.

Cemalyt *Rottapharm, Spain.*
⊗Triamcinolone (p. 1648·3); centella (p. 1698·3).
Skin disorders.

Cemaquin *Cimex, Switz.†; Teva, Switz.†*
Benzethonium chloride (p. 1738·1); ascorbic acid (p. 2110·3).
Mouth and throat infections.

Cemaxin *Molekule, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cemax-O *Wanbury, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ceme *Ritz, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ceme-CV *Ritz, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Cementin *DHA, Hong Kong; DHA, Singapore.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cemidin *Dexcel, Israel.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cemidon *IFET (ΙΦΕΤ), Gr.; Chiesi, Spain.*
Isoniazid (p. 311·2).
Tuberculosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cemidon B6 *Chiesi, Spain.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Cemol *Inga, India; Pharmasant, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Cemol Codeine *Pharmasant, Thai.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Cemol Cold *Pharmasant, Thai.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; hay fever.

Cempes *Sanovel, Turk.*
Cefdinir (p. 238·3).

Cenafed *Century, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Cenafed Plus *Century, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Cenai *The Forty-Two, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disease; vestibular disorders; migraine; motion sickness.

Cena-K *Century, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Cenalfan *Sigma, Braz.*
Vitamin A acetate (p. 2098·3); vitamin C (p. 2110·3); tocoferil acetate (p. 2119·2).

Cenalfan Plus *Sigma, Braz.*
Vitamins; minerals.

Cenamin *Pharmasant, Thai.*
Vitamins; iron (p. 2073·1); iodine (p. 2336·3).

Cenasic *Pharmasant, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Muscle pain.

Cenat *Rottapharm, Spain.*
Ispaghula (p. 1849·1).
Constipation; functional diarrhoeas.

Cenbufen *Pharmasant, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Cencamat *Pharmasant, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastric hyperacidity.

Cencanyl *Pharmasant, Thai.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Cencenac *Pharmasant, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Cencold *Pharmasant, Thai.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; hay fever.

Cencopan *Pharmasant, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Cendalex *Aldril, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Cendalon *Teva Tuteur, Arg.*
⊗Letrozole (p. 817·1).

Cendexsone *Pharmasant, Thai.†*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Cenebir *Aurora, Gr.*
Epirubicin hydrochloride (p. 787·1).

Cenecon *Pharmasant, Thai.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Ceneo *Esteve, Spain.*
⊗Hydrocortisone buteprate (p. 1640·1).
Skin disorders.

Cenestin *Duramed, USA.*
Synthetic conjugated estrogens, A (p. 2260·2).
Menopausal disorders.

Cenevit *Legrand, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Cenevit Zinco *Legrand, Braz.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).

CenFol *Centurion, USA.*
Folate (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Cenhist *Centurion, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Cenipres *Ferrer, Austria.*
Enalapril maleate (p. 1371·1); nitrendipine (p. 1456·3).
Hypertension.

Cenlidac *Pharmasant, Thai.*
Sulindac (p. 134·2).
Musculoskeletal, joint, and peri-articular disorders.

Cenogen Ultra *US Pharmaceutical, USA.†*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Cenolate *Hospira, USA.†*
Sodium ascorbate (p. 2111·1).
Vitamin C deficiency; scurvy.

Cenopec *Pharmasant, Thai.†*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Cenoza *Aamorb, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Cenoza A *Aamorb, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Cenpadol *Pharmasant, Thai.†*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Musculoskeletal pain and spasm.

Cenpidine *Pharmasant, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Censir *Sanify, India.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Censir Forte *Sanify, India.*
Alprazolam (p. 1035·2); sertraline hydrochloride (p. 448·1).

Centa Skin *Sunward, Singapore.*
Lotion: Salicylic acid (p. 1719·1).
Acne.

Sunward, Singapore.
Ointment: Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Acne.

Centa Vite *Cypress, USA.*
Vitamins; minerals.

Centabel *Andromaco, Chile.*
Centella (p. 1698·3).
Burns; ulcers; venous insufficiency; wounds.

Centabio *Caprifarmindo, Indon.*
Neomycin sulfate (p. 330·1); placenta extract (p. 2444·1).
Burns; ulcers; wounds; skin infections.

Centacid *Centaur, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Centacomb *Europharm, Hong Kong.*
⊗Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Skin infections.

Centagesic *Centaur, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation and photophobia following eye surgery; cystoid macular oedema.

Centagin *Pharmasant, Thai.†*
Dipyrone (p. 53·3).
Pain; fever.

Centany *Medimetriks, USA.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Centapp *Pharmasant, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; nasal congestion.

Centaurin *Kleva, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Centelax *Catarinense, Braz.†*
Centella (p. 1698·3).
Vascular disorders.

Centella Asiatica Compuesta *Lafarmen, Arg.*
Centella (p. 1698·3); nicotinamide (p. 2083·1); selenium (p. 2086·3).

Centella Asiatica Diates *Provefarma, Arg.†*
Centella (p. 1698·3); alpha tocopherol (p. 2119·1).
Dietary supplement.

Centella Asiatica Plus *Biokosma, Arg.*
Centella (p. 1698·3); pyridoxine (p. 2105·3).
Dietary supplement.

Centella Asiatica Spir *New Life, Arg.*
Centella (p. 1698·3); spirulina (p. 2622·1).
Dietary supplement.

Centella Asiatica Vital *AM, Arg.*
Centella (p. 1698·3); vitamin E (p. 2119·1).
Dietary supplement.

Centella Complex *Peter, Ital.*
Tablets: Centella (p. 1698·3); hamamelis (p. 2523·3); aesculus (p. 2431·2); pineapple; vitamin C (p. 2110·3).
Nutritional supplement; circulatory disorders.

Peter, Ital.
Topical gel: Centella (p. 1698·3); aesculus (p. 2431·2); pineapple; hamamelis (p. 2523·3); allantoin (p. 1693·1).

Centella Incaico *Incaico, Arg.*
Centella (p. 1698·3); green tea (p. 2648·2); pyridoxine (p. 2105·3).

Centella Queen Complex *Temis, Arg.*
Cream: Centella (p. 1698·3); marine algae; equisetum (p. 2500·1).
Cellulitis.

Temis, Arg.
Tablets: Bladderwrack (p. 2612·1); vitamin E (p. 2119·1); centella (p. 1698·3); ginkgo biloba (p. 2512·3).
Dietary supplement.

Centella Queen Reductora *Temis, Arg.*
Centella (p. 1698·3); fibre.
Slimming aid; cellulite; venous insufficiency.

Centellacrom *Framingham, Arg.*
Centella (p. 1698·3); chromium tripicolinate (p. 2056·1).
Dietary supplement.

Centellase *Bayer, Ital.; Tai Guk, Singapore.*
Centella (p. 1698·3).
Venous insufficiency; skin ulceration; burns; scars; skin ulcers; wounds; cellulitis.

Centellase de Centella Queen *Temis, Arg.*
Centella (p. 1698·3); bladderwrack (p. 2612·1); ginkgo biloba (p. 2512·3); vitamin E (p. 2119·1).
Cellulite; venous insufficiency.

Centellase Gel *Temis, Arg.*
Centella (p. 1698·3); equisetum (p. 2500·1); caffeine (p. 1203·3); algae (p. 2612·1).
Cellulitis.

Centella-Vit *Fontovit, Braz.†*
Centella (p. 1698·3).

Center-AL *ALK, Canad.*
Range of allergen extracts (p. 2434·3).
Allergen immunotherapy.

Center-Al *Center, USA.*
Range of allergen extracts (p. 2434·3).
Allergen immunotherapy.

Centergy DM *Centurion, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Centeril H *Errekappa, Ital.*
Cream: Zinc oxide (p. 1729·1); centella (p. 1698·3); hamamelis (p. 2523·3); aesculus (p. 2431·2); peppermint (p. 1877·1); menthol (p. 2553·2).
Anorectal disorders.

Errekappa, Ital.
Topical solution: Centella (p. 1698·3); hamamelis (p. 2523·3); aesculus (p. 2431·2).
Anorectal disorders.

Centica *Samjin, Singapore.*
Centella (p. 1698·3).
Burns; scars; skin ulcers; wounds.

Centilux *M4, Spain.*
⊗Methylthioninium chloride (p. 1559·1); naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Centocort *Pharmasant, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Centrac *Pfizer, Gr.*
Prazepam (p. 1098·2).
Anxiety disorders.

Centracetam
Note: this name may be used for preparations of different composition.
UCB, Gr.
Piracetam (p. 393·3).

Centradol *Grunenthal, Irl.†*
⊗Buprenorphine (p. 30·2).
Pain.

Central-B *Rotapharm, Ukr.*
Valerian (p. 2640·2); passion flower (p. 2584·1); crataegus (p. 2488·1).
Nervous disorders; cardiovascular disorders; sedative.

Centramin *Rosch & Handel, Austria.*
Glycine (p. 2071·2); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1); potassium chloride (p. 1793·2).
Pruritus; tetany.

Centrasic *Graha, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Centravim *Terramedic, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Centravit *Pharmasant, Thai.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Centravita Expletus *Unipharm, Mex.*
Vitamins; minerals.

Centrax *Pfizer, Irl.*
Prazepam (p. 1098·2).
Anxiety disorders.

Centrifal *Quimica y Farmacia, Mex.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Centrivon *Macleods, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Pain.

Centrodine *Pharmasant, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).

Centron *Torrent, India.†*
⊗Ormeloxifene (p. 2297·3).
Oral contraceptive.

Centropain *Pharmasant, Thai.*
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal pain.

Pharmasant, Thai.
Gel: Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Centrotabs *Neo Quimica, Braz.*
Vitamins; minerals.

Centrovit *Greenpharma, Braz.†*
Vitamins; minerals.

Centrovite *Rugby, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Centrum *Pfizer Consumer, Canad.; Pfizer, China.*
A range of vitamin and mineral preparations.
Wyeth-Whitehall, Arg.; Pfizer Consumer, Austral.; Pfizer Consumer, Chile; Pfizer Consumer, Hong Kong; Pfizer, Irl.; Wyeth, Israel; Pfizer Consumer, Malaysia; Wyeth Consumer, Mex.; Wyeth, NZ; Wyeth, Philipp.; Wyeth, Rus.; Pfizer Consumer, Singapore; Pfizer Consumer, Thai.; Wyeth, Turk.; Wyeth Consumer, UK; Pfizer Consumer, USA; Wyeth, Venez.
Vitamins; minerals.
Dietary supplement; vitamin and mineral supplement.

Wyeth Consumer, Braz.
Vitamins; minerals; trace elements.

Polifarma, Ital.
Cytidine (p. 2491·1); uridine (p. 2637·3).
Mental function impairment.

Centrum Cardio *Pfizer Consumer, Singapore.*
Phytosterols (p. 1471·2); vitamins; minerals.
Dietary supplement.

Centrum with Lutein *Pfizer, Ukr.*
Vitamins; minerals; lutein (p. 2079·2).

Centwin *Centaur, India.*
Injection: Dicycloverine (p. 1834·2).
Gastrointestinal spasm.

Centaur, India.
Suspension: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Centaur, India.
Tablets: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2); paracetamol (p. 115·1).

Centyl *Leo, Denm.†; Leo, Irl.; Leo, Norw.†*
⊗Bendroflumethiazide (p. 1315·2).
Oedema; hypertension; diabetes insipidus; renal calcium stones.

Centyl K *IFET (ΙΦΕΤ), Gr.; Leo, Irl.; Leo, Swed.; Leo, UK.†*
⊗Bendroflumethiazide (p. 1315·2); potassium chloride (p. 1793·2).
Oedema; hypertension; renal calculi.

Centyl med Kaliumklorid *Leo, Denm.; Leo, Norw.*
⊗Bendroflumethiazide (p. 1315·2); potassium chloride (p. 1793·2).
Oedema; hypertension; diabetes insipidus; renal calcium stones.

Cenvite *Sunward, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).

Cenz *La Pharmaceuticals, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Ceolat *Leyh, Ger.; Solvay, Gr.; Frik, Turk.*
Simeticone (p. 1886·2).
Flatulence; dyspepsia.

Ceolat Compositum *Lannacher, Austria.*
Dimeticone (p. 2209·3); metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Ceo-Two *Beutlich, USA.*
Sodium bicarbonate (p. 1781·1); potassium acid tartrate (p. 1879·2).
Constipation.

Cepa Med Complex *Dynamit, Austria.*
Cepa (p. 2575·2); phosphorus (p. 2589·2); pulsatilla (p. 2600·2); spongia.
Homoeopathic preparation.

Cepacaina *Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Cepacaine
Note: this name may be used for preparations of different composition.
Bayer Consumer, Austral.; Roche, NZ; Adcock Ingram, S. Afr.
Lozenges: Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Cepacilina *Reig Jofre, Spain.†*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections; rheumatic fever.

Cepacilina 633 *Reig Jofre, Spain.†*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2); benzathine benzylpenicillin (p. 227·2).
Bacterial infections; rheumatic fever.

Cepacol *Bayer Consumer, Austral.; Sanofi-Aventis, Braz.; Reckitt Benckiser, Canad.†; Sanofi-Aventis, Hong Kong; Roche, NZ; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Sanofi-Aventis, Venez.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders; oral hygiene.

Adcock Ingram, S.Afr.
Cetylpyridinium chloride (p. 1743·1); benzyl alcohol (p. 1739·3).
Mouth and throat disorders.

Cepacol Anaesthetic *Roche, NZ.†*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Cepacol BE *Sanofi-Aventis, Venez.*
Cetylpyridinium chloride (p. 1743·1); lidocaine (p. 1988·1).
Mouth and throat disorders.

Cepacol Cough
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); sodium citrate (p. 1781·2); cetylpyridinium chloride (p. 1743·1).
Cough; laryngitis.

Bayer Consumer, Austral.
Dextromethorphan hydrobromide (p. 1660·1); cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2); menthol (p. 2553·2).
Cough; sore throat.

Cepacol Cough Discs *AdcockIngram, S.Afr.*
Dextromethorphan hydrobromide (p. 1660·1); cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Cough; sore throat.

Roche, NZ.
Dextromethorphan hydrobromide (p. 1660·1); cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2); menthol (p. 2553·2).
Cough; mouth and throat disorders.

Cepacol Dual Relief Sore Throat + Cough *Combe, USA.*
Benzocaine (p. 1980·2); dextromethorphan hydrobromide (p. 1660·1).
Cough; sore throat.

Cepacol Dual Relief Sore Throat Spray *Combe, USA.*
Benzocaine (p. 1980·2).
Sore throat.

Cepacol Extra Strength *Combe, Canad.†*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Cepacol Fizzlers *Combe, USA.*
Benzocaine (p. 1980·2).
Sore throat.

Cepacol with Fluoride *Combe, Canad.†*
Cetylpyridinium chloride (p. 1743·1); sodium fluoride (p. 2089·2).

Cepacol Maximum Strength Sore Throat *JB Williams, USA.†*
Lozenges: Benzocaine (p. 1980·2); menthol (p. 2553·2); cetylpyridinium chloride (p. 1743·1).
Sore throat.

JB Williams, USA.†
Throat spray: Dyclonine hydrochloride (p. 1987·1); cetylpyridinium chloride (p. 1743·1).
Sore throat.

Cepacol Menta *Sanofi-Aventis, Braz.*
Cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2).
Mouth disorders.

Cepacol Mouthwash *Combe, USA.*
Cetylpyridinium chloride (p. 1743·1).
Minor mouth or throat disorders.

Cepacol Plus *Bayer Consumer, Austral.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Cepacol Regular Strength *Combe, USA.*
Menthol (p. 2553·2).
Sore throat.

Cepacol Sensations *Reckitt Benckiser, Canad.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2).

Cepacol Sensations Cooling *Reckitt Benckiser, Canad.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2).

Cepacol Sensations Sore Throat & Blocked Nose *Reckitt Benckiser, Canad.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2).

Cepacol Sensations Sore Throat & Cough *Reckitt Benckiser, Canad.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2).

Cepacol Sensations Warming *Reckitt Benckiser, Canad.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2).

Cepacol Sore Throat *Roche, NZ.*
Cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2); eucalyptus (p. 2501·1).
Sore throat; mouth infections.

Cepacol Sore Throat + Coating Relief Maximum Numbing *Combe, USA.*
Benzocaine (p. 1980·2); pectin (p. 2200·3).
Sore throat.

Cepacol Sore Throat Maximum Numbing *Combe, USA.*
Benzocaine (p. 1980·2); menthol (p. 2553·2).
Sore throat.

Cepacol Sore Throat Post Nasal Drip *Combe, USA.*
Menthol (p. 2553·2).

Cepacol Spray *Reckitt Benckiser, Canad.†*
Dyclonine hydrochloride (p. 1987·1).
Sore throat.

Cepacol Throat *JB Williams, USA.*
Cetylpyridinium chloride (p. 1743·1).
Sore throat.

Cepacol Ultra Sore Throat Plus Cough *Combe, USA.*
Benzocaine (p. 1980·2); dextromethorphan hydrobromide (p. 1660·1).
Cough; sore throat.

Cepacol Viractin Cold Sore Treatment *JB Williams, USA.†*
Tetracaine (p. 1996·3) or tetracaine hydrochloride (p. 1996·3).
Topical anaesthesia.

Cepadont *Perrigo, Israel.†*
Cetylpyridinium chloride (p. 1743·1); chlorobutanol (p. 1747·2).
Mouth disinfection.

Cepal
Note: this name may be used for preparations of different composition.
Demo, Gr.
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; gastric acid reduction.

Pharmasant, Thai.
Fenbufen (p. 59·1).
Musculoskeletal and joint disorders.

Cepalux *Ratiopharm, Denm.; Ratiopharm, Norw.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Cepan
Note: this name may be used for preparations of different composition.
Unia, Pol.
Allantoin (p. 1693·1); onion (p. 2575·2); chamomile (p. 2474·1); heparin sodium (p. 1396·3).
Scars; keloids.

Ceparidin *Arafarma, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.

Cepasmel *Gemi, Pol.*
Onion (p. 2575·2); garlic (p. 2510·3).
Respiratory-tract disorders.

Cepastat *Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Singapore.*
Phenol (p. 1763·3); menthol (p. 2553·2).
Sore throat; mouth and throat disorders.

SmithKline Beecham Consumer, USA.
Phenol (p. 1763·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Cepastat Cherry *SmithKline Beecham Consumer, USA.*
Phenol (p. 1763·3); menthol (p. 2553·2).
Sore throat.

Cepastil *Gemi, Pol.*
Onion (p. 2575·2); garlic (p. 2510·3).
Respiratory-tract disorders.

Cépazine *Novaxo, Fr.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cep-Bro *Cadila, India.*
Bromhexine hydrochloride (p. 1656·3); cefalexin (p. 234·1).

Cep-DP *Cyno, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Cepezet *Mersifarma, Indon.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; behaviour disorders.

Cepfor *Health Care, India.*
Cefpodoxime.
Bacterial infections.

Cephadex *Cipla, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephadex LB *Cipla, India.*
Cefalexin (p. 234·1); lactobacillus (p. 2596·3).
Bacterial infections.

Cephadol *Shinyaku, Jpn; Shinyaku, Malaysia†; Shinyaku, Philipp.†; Shinyaku, Singapore; Shinyaku, Thai.†*
Difenidol hydrochloride (p. 1835·1).
Vertigo; vestibular disorders; dizziness; postoperative vomiting.

Cephadyn *Atley, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).

Cephaflox *Guardian, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cephagraine *Charak, India.*
Nose drops: Asparagus racemosus (p. 2614·2); ginger (p. 1844·1); liquorice (p. 1853·2).

Charak, India.
Tablets: Ocimum sanctum; piper longum; ginger (p. 1844·1); sodium carbonate (p. 2617·3).

Cephal *Chemo-Drugs, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephalen *Beximco, Singapore.†*
Cefalexin (p. 234·1).
Bacterial infections.

Cephalex *CT, Ger.†; Lexus, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephalexyl *T-Boma, Hong Kong†; Bangkok Lab & Cosmetic, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephalite *Holland Pharma, Neth.*
Phosphoricum acidum (p. 2589·1); arnica montana (p. 2447·2); gelsemium sempervirens (p. 2511·2); hypericum perforatum (p. 449·1); iris versicolor (p. 2534·3); melilotus officinalis (p. 2552·3); sanguinaria canadensis (p. 2610·1); spigelia anthelmia (p. 2621·3).
Homoeopathic preparation.

Cephalkem *Alkem, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephalobene *Ratiopharm, Austria.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephaloplant *Infirmarius, Ger.†*
Cyclamen purp. (p. 2490·2); iris vers. (p. 2534·3); pulsatilla prat. (p. 2600·2); sanguinaria can. (p. 2610·1).
Homoeopathic preparation.

Cephalpet *Vista, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephamax *Pidek, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephanmycin *YSP, Malaysia; Yung Shin, Singapore.*
Cefalexin (p. 234·1).
Bacterial infections.

Cepharil *Reliance, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephation *Meiji, Indon.†*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Cephatrust *Meditech, Austral.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephaxin *Biochem, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephaxon *Toprak, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cephaxtar *Bionet, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephin *T-Boma, Hong Kong†; General Drugs, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Cephix *Toprak, Turk.*
Cefixime (p. 240·3).
Bacterial infections.

Cephoral *Merck Serono, Ger.; Astellas, Switz.*
Cefixime (p. 240·3).
Bacterial infections.

Cephpar *Karnataka, Rus.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Cephulac *Hoechst Marion Roussel, USA.*
Lactulose (p. 1850·3).
Hepatic encephalopathy.

Céphyl *Boiron, Fr.*
Aspirin (p. 22·2); caffeine (p. 1203·3); belladonna; iris versicolor; nux vomica; spigelia; gelsemium.
Pain; fever.

Cephyl
Note: this name may be used for preparations of different composition.
Boiron, Port.†
Aspirin (p. 22·2); ethenzamide (p. 56·2); caffeine (p. 1203·3); belladonna (p. 2453·3); iris versicolor (p. 2534·3); nux vomica (p. 2573·3); spigelia (p. 2621·3); gelsemium (p. 2511·2).
Pain; fever.

Cepiam TR *Natco, India.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Cepim *Polifarma, Ital.; Sintez, Rus.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cepimax *BMS, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cepime *Alembic, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cepime-O *Alembic, India.*
Cefetamet (p. 240·2).
Bacterial infections.

Cepimex *Bruno, Ital.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Cepin *Roemmers Medihe, Venez.*
Sodium ascorbyl phosphate (p. 1720·3); hyaluronic acid (p. 2526·2); dexpanthenol (p. 2582·2).
UV- or weather-induced skin damage.

Cepirom *Orchid, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Cepius *Verisfield, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Ceplac *Manx, UK.*
Erythrosine (p. 2184·3).
Disclosing agent for plaque.

Ceplene *EpiCept, Cz.; Meda, Ger.; EpiCept, Irl.; Meda, Neth.; EpiCept, Norw.; Meda, Pol.; EpiCept, Port.; Meda, Swed.; Meda, UK.*
Histamine hydrochloride (p. 2525·2).
Adjunctive treatment for acute myeloid leukaemia.

Ceplene Plus *Duncan, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Ceplex *Candor, India.*
Cefuroxime (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Ceplox *Sun, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ceplox-TZ *Sun, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cep-MR *Cyno, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1); diclofenac potassium (p. 48·3).

Cepo
Note: this name may be used for preparations of different composition.
Winsome, India.
Syrup: Cefpodoxime.
Bacterial infections.

Winsome, India.
Tablets: Cefpodoxime; *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cepobrom *Maver, Mex.*
Cefalexin (p. 234·1); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Cepocef *Intas, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepocor *Ranbaxy, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepodem *Nanxin, China; Ranbaxy, India; Ranbaxy, S. Afr.; Ranbaxy, Ukr.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepodot *Novaduo, India.*
Cefpodoxime.
Bacterial infections.

Cepodox *Pharma-Tech, India.*
Cefpodoxime.
Bacterial infections.

Cepokem *Taj, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Ceporacin *Bioniche, Canad.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Ceporan *GSK, India.*
Cefaloridine (p. 235·1).
Bacterial infections.

Ceporex *Teofarma, Ital.; GSK, Mex.; GSK, Philipp.; GSK, Singapore; Galen, UK.*
Cefalexin (p. 234·1).
Bacterial infections.

Ceporexin *Investi, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Ceporexin Duo *Investi, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Céporexine *GSK, Fr.†*
Cefalexin (p. 234·1).
Bacterial infections.

Ceporiz *Ritz, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Ceposil *Pisa, Mex.†*
Potassium acetate (p. 1793·1).

Cepotec *Tecnofarma, Mex.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cepotil *Orchid, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepotuf *Vanguard, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepotus *Icarus, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepox *Health Guard, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Cepoxim *Syntro, India.*
Cefpodoxime.
Bacterial infections.

Cepoxit *Auspi, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cepoxit-CX *Auspi, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cepoxit-S *Auspi, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Cepramine *Pharmasant, Thai.†*
Vitamins; minerals.

Ceprandal *Sigma-Tau, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Ceprater *Richmond, Arg.*
Cyproterone (p. 2261·2).

Cepraz *Lapi, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Ceprazo *Global, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Ceprazol *Laboratorios Chile, Chile.†*
Albendazole (p. 149·1).
Worm infections.

Ceprazo-S *Global, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cepriser *Serral, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Ceprof *Epicaris, Arg.†*
Cefprozil (p. 248·2).
Bacterial infections.

Ceprofen *Neo Quimica, Braz.*
Ketoprofen (p. 79·1).

Ceprolen *Indoco, India.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ceprolen-D *Indoco, India.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Ceprotin *Baxter, Austria; Baxter, Belg.; Baxter, Cz.; Baxter, Fin.; Baxter, Ger.; Baxter, Gr.; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.†; Baxter, Pol.; Baxter, Port.; Baxter, Rus.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK; Baxter, USA.*
Protein C (p. 1161·1).
Protein C deficiency; thromboembolic disorders in protein C deficiency.

Ceprozone-S *Intas, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Ceptax *Brown & Burk, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ceptaz *Glaxo Wellcome, USA.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ceptidar *Lupin, India.*
Sulfadiazine silver (p. 362·3).
Infected burns.

Ceptik *Interbat, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Ceptolate *Mylan, NZ.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Cepton *LPC, UK.*
Chlorhexidine gluconate (p. 1743·3).
Acne.

Cepton Medicated *Eastern Pharmaceuticals, Irl.*
Chlorhexidine gluconate (p. 1743·3).
Acne.

Ceptradin *Taj, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ceptrocin *Vysali, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceractiv *Andromaco, Chile.*
⊗Pemoline (p. 2328·2).
Attention-deficit hyperactivity disorder.

Ceradan *Hyphens, Singapore.*
Ceramide (p. 1699·1); cholesterol (p. 2179·1); fatty acids.
Dry skin disorders.

Ceradolan *Takeda, Indon.; Takeda, Philipp.*
Cefotiam hexetil hydrochloride (p. 246·1) or cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Takeda, Singapore†; Takeda, Thai.†
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Ceraklin *Innoderm, Philipp.*
Ceramide (p. 1699·1).
Dry skin; soap substitute.

Ceralide-MD *Unikid, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Ceralide-P *Unikid, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Ceralip *Roche-Posay, Braz.; Roche-Posay, Chile; Roche-Posay, Irl.*
Emollient.
Dry lips; mucous membrane damage.

Céralip *Roche-Posay, Fr.*
Emollient.
Dry lips.

Ceramide Time Complex *Arden, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Ceramil *Pharmanel, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ceranid *Hexal, Philipp.†*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

CeraORS *Cera, USA.*
Sodium (p. 1795·1); potassium (p. 1793·1); citrate.

Cerason *Darnitsa, Ukr.†*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cerasorb *Curasan, Ger.*
Calcium phosphate (p. 1784·2).
Artificial bone and dental enamel.

CeraSport *Cera, USA.*
Sodium (p. 1795·1); potassium (p. 1793·1).

Cérat Inaltérable *Roche-Posay, Fr.†*
Titanium dioxide (p. 1725·1); aluminium silicate (p. 1818·3); white beeswax (p. 2170·2); light liquid paraffin (p. 2191·2).
Barrier ointment.

Ceratim *Pharmawealth, Philipp.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Ceratio *Ratiopharm, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Cerator *Unison, Thai.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; circulatory disorders of the eye and ear.

CeraVe *Valeant, USA.*
Emollient.
Dry skin.

CeraVe SA Renewing *Valeant, USA.*
Salicylic acid (p. 1719·1) in an emollient base.
Dry skin.

Cerax
Note: this name may be used for preparations of different composition.
Millet-Franklin, Arg.
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); turpentine oil (p. 2636·3).
Removal of ear wax.

Pharmasant, Thai.
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; sedative.

Ceraxon *Ferrer, Ukr.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; cerebral trauma.

Nycomed, Rus.
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders.

Cerazet *Orifarm, Denm.; Farma 1000, Ital.; MSD, Spain.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Cerazette *Organon, Arg.; Organon, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Organon, India; Schering-Plough, Indon.; Organon, Irl.; MSD, Israel; Organon, Ital.; Organon, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, UK; Organon, Ukr.; Organon, Venez.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Cerazone-S *Adley, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Cerbon *Confar, Port.*
Pyritinol hydrochloride (p. 394·3).
Mental function disorders; cerebrovascular disorders.

Cerchio *Mediolanum, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cercini *Vitarum, Arg.†*
⊗Salbutamol (p. 1220·2).
Asthma.

Cerclerol *Beta, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Cercul *Phapros, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebral infarction; cerebral trauma; hemiplegia.

Cerdia *Daffohils, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Céréabib *De Bardo, Fr.*
Infant feed.
Cows' milk protein allergy.

Cereales Germees *Boiron, Fr.*
Triticum germinatum; hordeum germinatum; avena sativa (p. 2451·1); gentiana lutea (p. 2512·1); menyanthes trifoliata (p. 2554·2).
Homoeopathic preparation.

Cerebokan *Schwabe, Austria.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Cerebral-Do *Grasler, Ger.*
Cocculus (p. 2483·1); arnica (p. 2447·2); espeletia.
Homoeopathic preparation.

Cerebrino *Mandri, Spain.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Cerebroad *Chinta, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; migraine; vestibular disorders; Raynaud's disease.

Cerebrocurin *NIR, Ukr.*
Brain extract (bovine) (p. 2444·1).
Cerebral and cerebrovascular disorders; mental function impairment; ocular disorders.

Cerebrofil *Ulagay, Turk.*
Piracetam (p. 393·3).

Cerebrofort AA+DHA *Kalbe, Indon.*
Docosahexaenoic acid (p. 1460·1); arachidonic acid (p. 2446·1); eicosapentaenoic acid (p. 1460·2); glutamic acid (p. 2070·2); vitamins.
Nutritional supplement.

Cerebrofort Gold *Kalbe, Indon.*
Arachidonic acid (p. 2446·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); glutamic acid (p. 2070·2); biotin (p. 2052·2); lysine monohydrochloride; vitamins.
Nutritional supplement.

Cerebrolysin *Ever Neuro, Austria; Ever Neuro, China.; Ever Neuro, Cz.; Ebewe, Ger.†; Ebewe, Hong Kong; Ever Neuro, Philipp.; Ebewe, Pol.; Ebewe, Rus.; Ever Neuro, Thai.; Ebewe, Ukr.*
Brain extract (p. 2444·1).
Cerebrovascular disorders; mental function impairment; dementia; depression; Alzheimer's disease; brain injury; ischaemic stroke; nervous system disorders.

Cerebrolysine *Bio Portugal, Port.†*
Porcine brain extract (p. 2444·1).
Dementia; brain injury.

Cerebrovin *Medichrom, Gr.*
Isoxsuprine hydrochloride (p. 2535·2).

Cerebrovit Active *Kalbe, Indon.*
Ginseng (p. 2513·3); caffeine (p. 1203·3); levoglutamic acid; folic acid (p. 2063·1); vitamins; zinc (p. 2126·1); selenium (p. 2086·3).
Tonic.

Cerebrovit X-Cel *Kalbe, Indon.*
Glutamic acid (p. 2070·2); vitamins; selenium (p. 2086·3); zinc (p. 2126·1).
Nutritional supplement.

Cerebrovit Senior *Kalbe, Indon.*
Ginkgo biloba (p. 2512·3); glutamic acid (p. 2070·2); vitamins; minerals; trace elements.
Tonic.

Cerebrum comp *Heel, Neth.*
Ambra grisea (p. 2440·3); conium maculatum (p. 2524·3); cocculus indicus (p. 2483·1); phosphoricum acidum (p. 2589·1); ignatia amara (p. 2532·1); anacardium orientale (p. 2471·3); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Cerebryl *Kwizda, Austria; Kwizda, Hung.*
Piracetam (p. 393·3).
Cerebral disorders; mental function disorders.

Cerebyx *Erfa, Canad.; Parke, Davis, USA.*
Fosphenytoin sodium (p. 523·1).
Epilepsy; seizures during neurosurgery.

Cerecard *Altair, Rus.*
Emoxypine succinate (p. 1371·1).
Cerebrovascular disorders; anxiety; alcohol withdrawal syndrome; myocardial infarction; coronary heart disease; peritonitis.

Cerecetam *Intas, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Ceredase *Genzyme, USA.†*
Alglucerase (p. 2433·1).
Gaucher disease.

Ceredist *Mitsubishi Tanabe, Jpn.*
Taltirelin (p. 2625·2).
Spinocerebellar degeneration.

Cerefolin NAC *Pamlab, USA.*
Calcium levomefolate (p. 2053·1); mecobalamin (p. 2108·1); acetylcysteine (p. 1652·2).
Nutritional supplement.

Ceregen *Diba, Mex.*
Vitamins; minerals.

Ceregin *Interfarma, Ukr.*
Hydrolysed brain of cattle and pigs (p. 2444·1).
Cerebrovascular disorders.

Cerekinon *Tanabe Seiyaku, China; Tanabe, Hong Kong; Mitsubishi Tanabe, Jpn; Mitsubishi Tanabe, Malaysia; Mitsubishi Tanabe, Singapore; Mitsubishi Tanabe, Thai.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; gastritis; gastrointestinal motility disorders.

Cerelac *Nestle, Braz.†*
Preparation for enteral nutrition.

Cerelle *Consilient, UK.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Cereloid *Sun, India.*
Codergocrine mesilate (p. 389·2).
Dementia.

Cereluc *Beta, Arg.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Cerelyte *Raptakos, India.*
Potassium citrate (p. 1780·3); rice flour; sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Ceremax *Kalbe, Indon.*
Nimodipine (p. 1455·2).
Neurological deficit due to cerebral vasospasm following subarachnoid haemorrhage.

Ceremin
Note: this name may be used for preparations of different composition.
Austroplant, Austria.
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.
Polipharm, Thai.
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; migraine; motion sickness.

Cereneu *Pfizer, Thai.*
Fosphenytoin sodium (p. 523·1).
Status epilepticus; seizures associated with neurosurgery.

Cérépar *Mepha, Switz.†*
Cinnarizine (p. 622·1).
Vestibular disorders; vertigo.

Cerepar N *Merckle, Ger.†*
Piracetam (p. 393·3).
Mental function impairment.

Cerepro *Veropharm, Rus.*
Choline alfoscerate (p. 389·2).
Cerebrovascular disorders; mental function disorders.

Cerestab *Amersham, Fr.*
Technetium-99m exametazime (p. 2228·1).
Radionuclide imaging.

Cerestabon *Lusomedicamenta, Port.*
Idebenone (p. 392·3).
Cerebrovascular disorders; mental function disorders.

Cerestar
Note: this name may be used for preparations of different composition.
Ranbaxy, India.
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ceretal *Taiwan Biotech, Thai.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders; circulatory disorders of the eye and ear.

Ceretam *Advance, Malaysia.*
Piracetam (p. 393·3).
Mental function impairment; alcoholism; coma; myoclonus.

Ceretec
Note: this name may be used for preparations of different composition.
GE Healthcare, Austral.; GE Healthcare, Cz.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Irl.; GE Healthcare, Israel; GE Healthcare, Ital.; GE Healthcare, Neth.; GE Healthcare, Port.; GE Healthcare, Spain; GE Healthcare, UK.
Technetium-99m exametazime (p. 2228·1).
Leucocyte labelling; cerebral blood flow scintigraphy.
GE Healthcare, Denm.
Exametazime.
For radiolabelling with technetium-99m to produce technetium-99m exametazime.
Cerebral blood flow scintigraphy.
Tecnoforma, Mex.†
Cinnarizine (p. 622·1).
Vestibular disorders; peripheral vascular disorders.

Cereton
Note: this name may be used for preparations of different composition.
Meprofarm, Indon.
Ginkgo biloba (p. 2512·3); d-methyl amino ethanol; pine bark; nicotinamide (p. 2083·1).
Cerebral and peripheral vascular disorders.
Sotex, Rus.
Choline alfoscerate (p. 389·2).
Cerebrovascular disorders; mental function disorders.

Cerevax *Recalcine, Chile.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cerex *Hexal, Cz.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cerezyme *Genzyme, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Braz.; Genzyme, Canad.; Genzyme, Chile; Genzyme, China; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Irl.; Genzyme, Israel; Genzyme, Ital.; Genzyme, Jpn; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Norw.; Healthcare Logistics, NZ; Genzyme, Pol.; Genzyme, Port.; Genzyme, Rus.; Genzyme, S.Afr.; Genzyme, Spain; Genzyme, Swed.; Sanofi-Aventis, Switz.; Genzyme, Thai.; Sanofi-Aventis, Thai.; Genzyme, Turk.; Genzyme, UK; Genzyme, Ukr.; Genzyme, USA.*
Imiglucerase (p. 2433·2).
Gaucher disease.

Cergem *MSD, Ger.*
Gemeprost (p. 2137·2).
Cervical dilatation.

Cergodun *Duncan, Arg.; Duncan, Hong Kong.*
Nicergoline (p. 2569·1).
Cerebral and peripheral circulatory disorders.

Ceriax *Farmoz, Port.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ceriaxon *Farmedia, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cerin *Molekule, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Cerini *Sanbe, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Ceris *Rottapharm, Fr.; Madaus, Irl.*
Trospium chloride (p. 2371·1).
Bladder instability.

Céris *Orifarm, Denm.*
Trospium chloride (p. 2371·1).
Bladder instability; urinary incontinence.

Cerisa *Stratus, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Ceritec *YSP, Malaysia; Yung Shin, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic conjunctivitis; allergic rhinitis; pruritus.

Ceriton *Ranbaxy, India.*
⊗Erythropoietin (p. 1141·1).
Anaemias; autologous blood transfusion.

Cerivikehl *Sanum-Kehlbeck, Ger.*
Cetraria islandica (p. 2531·2).
Homoeopathic preparation.

Cerizine-FT *Emcure, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cermox *Rontag, Arg.*
Ciclosporin (p. 1945·2).
Transplant rejection.

Cernevit *Baxter Immuno, Arg.; Baxter, Austral.; Baxter, Austria; Clintec, Belg.; Baxter, Chile; Clintec, China; Baxter, Cz.; Baxter, Denm.; Clintec, Fin.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Kalbe, Indon.; Baxter, Irl.; Teva, Israel; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Pol.; Baxter, Port.; Baxter, Rus.; Baxter, Singapore; Clintec, Spain; Baxter, Swed.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK; Baxter, USA.*
Vitamins.
Parenteral nutrition.

Cernévit *Baxter, Fr.; Baxter, Switz.*
Vitamins.
Parenteral nutrition.

Cernilton *Temis, Arg.; Strathmann, Ger.†; Tobishi, Jpn; Graminex, Rus.*
Pollen extract (p. 2593·3).
Prostatitis; benign prostatic hyperplasia; prostatic disorders.

Cernitol *Cernelle, Swed.*
Pollen extract (p. 2593·3).
Benign prostatic hyperplasia.

Cernos *Sun, India.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Cerofene *Medicus, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cerol *Neon, Ukr.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux.

Ceroline *Pileje, Fr.*
Nutritional supplement.
Slimming aid; mood disorders.

Cerom *Piramal, India.*
Cefuroxime (p. 255·2) or cefuroxime axetil (p. 255·2).
Bacterial infections.

Ceron *Cypress, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Rhinitis.

Ceron-DM *Cypress, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; upper respiratory-tract symptoms.

Ceropid *Novell, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cerose DM *Wyeth-Ayerst, USA.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Coughs and cold symptoms.

Cerosel *Biochefa, Pol.†*
Selenium yeast (p. 2125·2).
Selenium deficiency.

Cerosporin *Investi, Arg.*
Phenazone (p. 124·1); neomycin sulfate (p. 330·1); cetrimide (p. 1742·1); sodium carbonate (p. 2617·3).
Ear wax removal.

Cerosteril *Bouty, Ital.*
Benzalkonium chloride (p. 1737·1); quaternium-14; allantoin (p. 1693·1).
Disinfection and cleansing of wounds and burns.

Cerotec *Korea United, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.
Yik Kwan, Hong Kong.†
Cetirizine (p. 619·2).

Cerotor *Torrex Chiesi, Cz.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Cerotto Bertelli *Kelemata, Ital.*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cerovite *Rugby, USA.*
Vitamins; minerals.

Ceroxim *Nanxin, China; Ranbaxy, Hung.; CTS, Israel†; Ranbaxy, Pol.; Ranbaxy, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Ceroxitum *Intas, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Ceroxmed Tex *Bouty, Ital.*
Zinc oxide (p. 1729·1).
Medicated dressing.

Cerozon *Ethica, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Cerplast *Gracia, Indon.*
Gauze impreganted with aluminium silicate (p. 1818·3).
Wounds.

Cerson *Riemser, Ger.*
⊗Flumetasone pivalate (p. 1635·2).
Skin disorders.

Certagen *Ivax, USA.*
Oral liquid: Vitamins; minerals.

Ivax, USA.
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemia.

CertaVite *Major, USA.*
Vitamins; minerals.

Certavite Senior with Antioxidant Nutrients *Major, USA.*
Vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2).
Dietary supplement.

Certican *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Ukr.; Novartis, Venez.*
Everolimus (p. 1957·3).
Transplant rejection.

Certified Decongestant *Prodemdis, Canad.†*
⊗Xylometazoline hydrochloride (p. 1680·1).

Certified Ice *Prodemdis, Canad.†*
Menthol (p. 2553·2).

Certomycin *Aesca, Austria; Essex, Ger.†*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Certorun *Proton, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression.

Certúss *Prodotti, Braz.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Certuss-D *Capellon, USA.*
⊗Clofedanol hydrochloride (p. 1659·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ceru Spray *Ghimas, Ital.*
Chamomile (p. 2474·1).
Aural hygiene.

Cerubidin *Orifarm, Denm.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.*
Daunorubicin hydrochloride (p. 778·3).
Leukaemias.

Cerubidine *Sanofi-Aventis, Belg.; Erfa, Canad.; Sanofi-Aventis, Chile†; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Israel; Sanofi-Aventis, Neth.; Bedford, USA.*
Daunorubicin hydrochloride (p. 778·3).
Malignant neoplasms.

Cérubidine *Sanofi-Aventis, Fr.; Sanofi-Aventis, Switz.†*
Daunorubicin hydrochloride (p. 778·3).
Malignant neoplasms.

Cerucal *AWD, Cz.; Temmler, Ger.; AWD, Hung.; Pliva, Rus.; Teva, Ukr.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal investigation.

Ceruglan *Bryntsalov, Rus.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Ceruklin *Klar Sehen, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).
Ear wax removal.

Cerulan *Rusan, Rus.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Cerulisina *Bouty, Ital.*
Xylene (p. 2220·2).
Ear wax removal.

Cérulyse *Chauvin, Fr.*
Xylene (p. 2220·2).
Ear wax removal.

Cerulyx *Bausch & Lomb, Belg.*
Xylene (p. 2220·2).
Ear wax removal.

Cerumenex *Purdue, Canad.†; Mundipharma, Switz.*
Trolamine polypeptide oleate-condensate (p. 2634·3).
Ear wax removal.

Cerumenex N *Mundipharma, Ger.*
Trolamine polypeptide oleate-condensate (p. 2634·3).
Ear wax removal.

Cerumenol
Note: this name may be used for preparations of different composition.
Desma, Spain.
Potassium hydroxide (p. 2595·3).
Ear wax removal.

Interdelta, Switz.
Paradichlorobenzene (p. 2583·2); chlorobutanol hemihydrate (p. 1747·2); turpentine oil (p. 2636·3); orthodichlorobenzene (p. 2578·1); methoxybutyl acetate.
Ear wax removal.

Céruménol *McNeil, Fr.†*
Polysorbate 80 (p. 2203·3).
Ear wax removal.

Cerumex *Cassara, Arg.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Cerumin *Alcon, Braz.*
Hydroxyquinoline borate (p. 2530·1); trolamine (p. 2634·3).
Ear wax removal.

Cerumol *Thornton & Ross, Irl.; Tamar, Israel; Pharmafrica, S.Afr.; Thornton & Ross, Singapore; Laboratories for Applied Biology, UK.*
Paradichlorobenzene (p. 2583·2); chlorobutanol (p. 1747·2); arachis oil (p. 2446·1).
Ear wax removal.

Paladin, Canad.
Paradichlorobenzene (p. 2583·2); chlorobutanol (p. 1747·2); turpentine oil (p. 2636·3).
Ear wax removal.

Culver, Austral.
Paradichlorobenzene (p. 2583·2); chlorobutanol (p. 1747·2); orthodichlorobenzene (p. 2578·1); arachis oil (p. 2446·1).
Ear wax removal.

Thornton & Ross, Malaysia.
Paradichlorobenzene (p. 2583·2); chlorobutanol (p. 1747·2).
Ear wax removal.

Cerutin *Polfarmex, Pol.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Vitamin C deficiency.

Ceruvin *Ranbaxy, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Ranbaxy, Malaysia; Ranbaxy, Thai.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; myocardial infarction; unstable angina; ischaemic stroke; peripheral arterial disease; acute coronary syndrome.

Ceruvin-A *Ranbaxy, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Ceruxim *Antor, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cervagem *Sanofi-Aventis, Austral.; Sanofi-Aventis, Malaysia; Aventis, NZ†; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.; Sanofi-Aventis, UK.*
Gemeprost (p. 2137·2).
Cervical dilatation; termination of pregnancy.

Cervagème *Sanofi-Aventis, Fr.*
Gemeprost (p. 2137·2).
Cervical dilatation prior to uterine procedures; termination of pregnancy.

Cervarix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.†; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S. Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA.*
A human papillomavirus vaccine (types 16 and 18) (p. 2392·2).
Active immunisation.

Cervas *GMP, Indon.*
Piracetam (p. 393·3).
Mental function disorders; alcoholism.

Cervep *Menarini, Arg.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; thrombophlebitis; scars.

Cervictal *Monte Verde, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Cervicum *Pharmasant, Thai.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Cervidil
Note: this name may be used for preparations of different composition.
CSL, Austral.; Ferring, Canad.; CSL, NZ; Forest Pharmaceuticals, USA.
Dinoprostone (p. 2134·1).
Labour induction.

Merck Serono, Ital.
Gemeprost (p. 2137·2).
Cervical dilatation.

Cervilan *Sanofi-Aventis, Mex.*
Lomifylline (p. 2545·1); dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders.

Cervilane *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile.*
Lomifylline (p. 2545·1); dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders; vestibular disorders.

Cervin *Pasteur, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cervinca *Basi, Port.*
Vincamine (p. 2645·2).
Mental function disorders.

Cerviprime *AstraZeneca, India; AstraZeneca, Philipp.*
Dinoprostone (p. 2134·1).
Cervical dilatation; labour induction.

Cervistin *Ameda, Ukr.*
Dinoprostone (p. 2134·1).
Induction of labour.

Cervoxan *Almirall, Fr.; Decomed, Port.; Tedec Meiji, Spain.*
Vinburnine (p. 2645·2).
Vascular eye disorders; mental function impairment; cerebrovascular disorders.

Cerylana *Intra, Venez.*
Diphenhydramine hydrochloride (p. 626·2); wild lettuce (p. 2647·3); cocillana (p. 1659·2); wild cherry (p. 2647·2).
Cough.

Cerzine *Mepha, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

CES *Valeant, Canad.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis; prostatic cancer.

Cesafe-TZ *Gujarat Terce, India.*
Ceftriaxone sodium (p. 253·3); tazobactam sodium (p. 369·3).
Bacterial infections.

Cesagrip *PGN, Arg.*
Ambay; ascorbic acid (p. 2110·3); camellia sinensis (p. 2648·2).
Influenza.

Cesai *Sanify, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cesal *Flamingo, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cesamet *Investi, Arg.; Valeant, Canad.; Valeant, Mex.; Meda, USA.*
⊗Nabilone (p. 1865·2).
Nausea and vomiting associated with cancer chemotherapy; pain.

Cesavess *Pfizer, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cesbron *Sanofi Synthelabo, Port.†*
⊗Clenbuterol (p. 1207·2).

Cesia *Prasco, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic combined oral contraceptive.

Cesiran *Neon, India.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Ceso *Comed, India.*
Esomeprazole magnesium (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Cesol *Merck, Chile; Merck Serono, Ger.; Merck, Mex.*
Praziquantel (p. 164·1).
Worm infections; cestode infections.

Cesoline *Pharmasant, Thai.*
Hydralazine hydrochloride (p. 1401·2).
Hypertension; heart failure.

Cespire *Neiadas (Νειαδας), Gr.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).

Cesplon *Esteve, Spain.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Cesplon Plus *Esteve, Spain.†*
⊗Hydrochlorothiazide (p. 1403·2); captopril (p. 1331·2).
Hypertension.

Cesracimi *Cesra, Cz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Cesradyston *Cesra, Ger.*
St John's wort (p. 449·1).
Depression.

Cesrafemme *Cesra, Cz.†*
⊗Agnus castus (p. 2432·2).
Mastalgia; premenstrual syndrome.

Cest *Samarth, India.*
Praziquantel (p. 164·1).
Worm infections.

Cester *Ethica, Indon.*
Calcium ascorbate (p. 2111·1); citrus bioflavonoids (p. 2505·2).
Tonic.

Cestox *Merck, Braz.; Merck, Venez.*
Praziquantel (p. 164·1).
Schistosomiasis; cysticercosis; worm infections.

Cesulpin *Darnitsa, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cet-10 *Taiwan Biotech, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Ceta *C & M, USA.*
Skin cleanser.

Ceta Plus *Seatrace, USA.†*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Cetabon *Great Eastern, Thai.†*
⊗Stanozolol (p. 2304·2); vitamin B substances (p. 2102·3).
Anabolic.

Cetabrium *Soho, Indon.†*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; delirium tremens; agitation.

Cetabutol *Soho, Indon.†*
D-Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Cetacaine *Cetylite, Canad.; Cetylite, USA.*
Benzocaine (p. 1980·2); butyl aminobenzoate (p. 1982·3); tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Cetacillin *Soho, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Cetacol *Soho, Indon.†*
Nicotinyl alcohol tartrate (p. 1447·1).
Peripheral vascular disorders.

Cetacort *Healthpoint, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cetacycline-P *Soho, Indon.†*
Tetracycline phosphate complex (p. 373·2).
Bacterial infections.

Cetadex *Geolab, Braz.*
⊗Dexamethasone acetate (p. 1631·1).

Cetadexon *Soho, Indon.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Cetadocure *Stada, Cz.; Pharmacodane, Denm.; EG, Ital.; Centrafarm, Neth.†*
Docetaxel (p. 780·3).
Malignant neoplasms.

Cetadop *Ethica, Indon.*
Dopamine hydrochloride (p. 1367·2).
Cardiogenic shock.

Cetafloxo *Soho, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cetaflu-forte *Atabay, Turk.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Cetagesic *CCM, Malaysia; Duopharma, Singapore.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle pain and spasm.

Cetainty *Innocore, Canad.†*
Alkyldimethylethylbenzyl ammonium chloride (p. 1736·2); benzalkonium chloride (p. 1737·1).
Disinfection.

Cetaklenz *Geritrex, USA.*
⊗Glycerol (p. 2517·2); sodium laurilsulfate (p. 2210·3).
Soap-free skin cleanser.

CetAlergin *ICN, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetalgin *Soho, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Cetalgin-T *Soho, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); caffeine (p. 1203·3).
Pain; tension headache; neuralgia.

Cetallerg *Sandoz, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetalmic *Soho, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Cetam *Taurus, India; Yung Shin, Singapore.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Cetamid *ACME, Philipp.*
⊗Acetazolamide (p. 2001·1).
Epilepsy; glaucoma; heart failure; oedema.

Cetamide *Alcon, Canad.†*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Cetamine
Note: this name may be used for preparations of different composition.
Kela, Belg.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Cetamol *Xepa-Soul Pattinson, Singapore; BJ Benjaosoth, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Cetampril *Labesfal, Port.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Cetan
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.†
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Cetanil *Dabur, India.*
Paracetamol (p. 115·1).
Pain; fever.

Cetanorm *Norma, UK.*
Benzalkonium chloride (p. 1737·1); aldioxa (p. 1692·2); chlorobutanol (p. 1747·2); cetrimide (p. 1742·1).
Nappy rash; wounds.

Cetaphen *SSP, Thai.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Cetaphil *Galderma, Arg.*
A range of skin care preparations.

Galderma, Austral.
A range of soap substitutes and emollients.
Skin cleanser; dry skin; acne.

Galderma, Braz.
A range of skin care products.

Galderma, Chile; Galderma, China; Galderma, Fr.; Galderma, India; Galderma, Malaysia; Galderma, NZ; Galderma, Singapore.
A range of skin cleansers and moisturisers.

Galderma, Hong Kong.
A range of emollients and skin cleansers.

Galderma, Mex.; Galderma, UK.
Soap substitute.

Galderma, Philipp.; Galderma, Thai.
A range of skin cleansers and emollients.

Galderma, USA.
Skin cleanser.

Cetaphil Acne *Galderma, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Cetaphil Antibacterial *Galderma, Mex.*
Soap substitute with triclosan (p. 1773·2).
Skin disorders.

Cetaphil Daily Facial *Galderma, Canad.*
SPF 15: Avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

Galderma, Canad.
SPF 50: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Cetaphil Defense *Galderma, Chile.*
Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1).
Sunscreen.

Cetaphil Locion *Galderma, Chile.*
SPF 15: Avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

Cetaphil UV Defense *Galderma, Arg.*
SPF 50+: Octisalate (p. 1715·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); octocrilene (p. 1715·2); octil triazone (p. 1715·1); drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1).
Sunscreen.

Cetaphil UVA/UVB *Galderma, Singapore.*
SPF 50+: Octisalate (p. 1715·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); octocrilene (p. 1715·2); octil triazone (p. 1715·1); drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1).
Sunscreen.

Cetaphil UVA/UVB Defense *Galderma, Malaysia.*
SPF 50: Ecamsule (p. 1702·1); drometrizole trisiloxane (p. 1702·1); avobenzone (p. 1695·1); octisalate (p. 1715·2); octil triazone (p. 1715·1); octocrilene (p. 1715·2); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Cetapin *Sanofi-Aventis, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Cetapin P *Sanofi-Aventis, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Cetapol *Utopian, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Cetapred *Alcon, Mex.; Alcon, Philipp.†*
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Bacterial eye infections with inflammation.

Cetapril *Dainippon, Jpn.*
Alacepril (p. 1295·3).
Hypertension.

Cetapyrin *Soho, Indon.†*
Phenylbutazone (p. 125·1); propyphenazone (p. 127·3).
Musculoskeletal and joint disorders.

Cetariv *East African, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetasix *Soho, Indon.†*
⊗Furosemide (p. 1387·1).
Oedema; heart failure; nephrotic syndrome; ascites.

Cetathiacol *Soho, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Cetathrocin *Soho, Indon.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Cetatrex *Soho, Indon.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Cetavlex
Note: this name may be used for preparations of different composition.
CS, Port.; Centrapharm, UK.
Cetrimide (p. 1742·1).
Nappy rash; wounds; burns; skin disorders.

Pierre Fabre, Fr.
Chlorhexidine gluconate (p. 1743·3).
Wound disinfection.

Tramedico, Belg.
Cetrimonium bromide (p. 1742·3); chlorhexidine gluconate (p. 1743·3).
Disinfection of wounds, burns. skin, and hands; skin disorders.

Cetavlon *Pierre Fabre, Fr.; Cana, Gr.; ICI, India.*
Cetrimide (p. 1742·1).
Antiseptic; disinfection; bacterial skin infections; wounds.

Cetavol *Pharmasant, Thai.*
Fluphenazine hydrochloride (p. 1075·1); nortriptyline hydrochloride (p. 439·3).
Mixed anxiety depressive states.

Cetax *Aurobindo, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cetaxim *TRB, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Cetaxima *Yung Shin, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cetaz *Uniao Quimica, Braz.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cetazime *T3A Pharma, Hung.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Cetazin *Sigmapharm, Austria.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Cetazine *Hospira, Singapore.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cetazone *Ajanta, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cetazum *Landson, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cetcip *Cipla, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetcip Cold *Cipla, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cetcip-D *Cipla, India.*
Cetirizine (p. 619·2); phenylpropanolamine hydrochloride (p. 1674·1).

Cetebe *GSK Consumer, Austria; GSK Consumer, Ger.; GSK Consumer, Hung.; GSK Consumer, Pol.; GSK Consumer, Rus.; GSK Consumer, Switz.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Cetebe antiGrippal *GSK Consumer, Ger.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Ceteco *Sandoz, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Ceterifug *Padia, Ger.†*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Ceteris *SoSe, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Ceteron *Combiphar, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Cetezol *Ceamed, Port.*
⊗Letrozole (p. 817·1).
Breast cancer.

Cetgel *Universal Medicare, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cethaphil *Galderma, Venez.*
Skin cleanser, soap substitute, or shampoo.

Cethexal *Sandoz, Mex.*
Cetirizine hydrochloride (p. 619·2).
Allergic skin disorders; allergic rhinitis.

Cethixim *Ethica, Indon.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cetialfa *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Ceticad *Zydus, India.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetidac *Eurolab, Arg.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetiderm *Dermapharm, Ger.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetigen *Generics, Hung.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetigran *Pol-Nil, Pol.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetihexal *Hexal, Braz.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetihis *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cetil
Note: this name may be used for preparations of different composition.
Lupin, India.
Cefuroxime (p. 255·2).
Bacterial infections.

Lupin, Ukr.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

CetiLich *Winthrop, Ger.†*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetilsan *Sella, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene; skin and wound disinfection.

Cetimax *Vitabalans, Fin.; Vitabalans, Swed.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Ceti-Med *Medhaus, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Cetimer L *Merck Serono, Arg.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Cetimerck *Merck, Spain.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetimin *Mergers Drugfil, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Cetin *Ind-Swift, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetin Cold *Ind-Swift, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cetin Kid *Ind-Swift, India.*
Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1).

Cetin Plus *Ind-Swift, India.*
⊗Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Cetinac *Inpac, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetinal *Kalbe, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetin-D *Ind-Swift, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cetinject *Lamda (Λαμδα), Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Cetiozone *Pol-Nil, Pol.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Ceti-Puren *Actavis, Ger.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetiram *Alet, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Cetirelief Allergy *Eireceutica, Irl.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; pruritus.

Cetirex *Elter, Venez.*
Cetirizine (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cetirgen *Gabriel, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetirhexal *Hexal, Austria.*
Cetirizine hydrochloride (p. 619·2).
Allergic skin disorders; allergic rhinitis; asthma; urticaria.

Cetirigamma *Worwag, Ger.†*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetirin *Quality, Hong Kong.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetirinax *Actavis, Rus.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Cetiristad *Stada, Austria.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetirivax *Vivax, Venez.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetirivax D *Vivax, Venez.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine sulfate (p. 1676·1).
Hypersensitivity reactions.

Cetiriz *Alkem, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetiriz-D *Alkem, India.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Cetirmar *Synthon, Neth.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Cetirtec *Teuto, Braz.*
Cetirizine hydrochloride (p. 619·2).

Cetisandoz *Sandoz, Belg.*
Cetirizine hydrochloride.
Allergic rhinitis; urticaria.

Cetitev *Teva, Mex.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetiteva *Med, Turk.*
Cetirizine hydrochloride (p. 619·2).

Cetityrol *Sandoz, Turk.*
Cetirizine hydrochloride (p. 619·2).

Cetiva AE *Farmasa, Braz.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Cetivit *Ducto, Braz.*
Ascorbic acid (p. 2110·3).

Cetix *Medinfar, Port.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetixin *Vitabalans, Cz.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetizin *Chinta, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetizine *Lazar, Arg.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetjust *Arunabh, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetjust L *Arunabh, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Cetliv *Daksh, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Cetliv A *Daksh, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Cetlong *RND, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetlong-L *RND, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Cetmac *Ikon, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cet-Mepha Allergie *Mepha, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetmet *Almet, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetmet TCF *Almet, India.*
Ambroxol (p. 1654·3); cetirizine hydrochloride (p. 619·2); dextromethorphan (p. 1660·1).

Cetnaz *Khandelwal, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetobeta *Bunker, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); ketoconazole (p. 585·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Cetocomp *Europharm, Hong Kong.*
Cetylpyridinium chloride (p. 1743·1).
Sore throat.

Cetoconalab *Multilab, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetocort *Teuto, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); ketoconazole (p. 585·3).
Infected skin disorders.

Cetocorten *Cifarma, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone (p. 1623·2).
Fungal skin infections.

Cetoderm
Note: this name may be used for preparations of different composition.
UCI, Braz.
Ketoconazole (p. 585·3).

Cetodol *Brown & Burk, Philipp.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Cetofeb *Worth, India.*
Paracetamol (p. 115·1).
Pain; fever.

Cetofenid *Teuto, Braz.*
Ketoprofen (p. 79·1).

Cetoglutaran *Tradiphar, Fr.†*
Calcium di-oxoglurate (p. 2579·1).
Asthenia.

Cetohexal *Hexal, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetol *Helm, Port.*
Paracetamol (p. 115·1).
Pain; fever.

Cetomed *Cimed, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetomedica *Regiomedica, Neth.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Cetomizol *Greenpharma, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetom-L *Om Biotec, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Cetonax *Janssen-Cilag, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetoneo *Neo Quimica, Braz.*
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Cetonil *Stiefel, Arg.; Stiefel, Braz.*
Ketoconazole (p. 585·3).
Pityriasis; scalp disorders; fungal skin and scalp infections.

Cetonin *Cifarma, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetop Zink *Erlimpex, Indon.*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Cetopic *Medihealth, Mex.*
Sodium ascorbyl phosphate (p. 1720·3); hyaluronic acid (p. 2526·2); tocoferil acetate (p. 2119·2); dexpanthenol (p. 2582·2).
Erythema; melasma.

Cetoquina Y *Solfran, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Cetor *Sanquin, Neth.; Centurion, Turk.*
Complement C1 esterase inhibitor (p. 2485·1).
C1 esterase deficiency.

Cétornan *Chiesi, Fr.*
Ornithine oxoglurate (p. 2085·2).
Nutritional supplement.

Cetoros *Pharos, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; alcoholism.

Cetos *Auspi, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetoteron *Eurofarma, Braz.*
Cyproterone acetate (p. 2261·2).

Cetoxil *Teva, Mex.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Cetoxol *SA Druggists Self Med, S.Afr.†*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Sore throat.

Cetozan *Royton, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetozol *Cazi, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Cetozone *De Mayo, Braz.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Cetra
Note: this name may be used for preparations of different composition.
Active, India.
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).
Xeno, Philipp.
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Cetraben *Hetero, India.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Skin disorders.
Dermacyte, Canad.†
White soft paraffin (p. 2211·3).
Dry skin.

Cetraben Emollient *Genus, UK.*
Bath additive: Light liquid paraffin (p. 2191·2).
Dry skin; eczema.
Genus, UK.
Cream: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry skin; eczema.

Cetract *Active, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetraflux *Salvat, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cetrakam *LKM, Arg.†*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Cetral *Meyer, Venez.*
Cetirizine (p. 619·2).

Cetralon *Julphar, UAE.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Cetraria Complexe No 61 *Lehning, Fr.*
Cetraria (p. 2531·2); eucalyptus (p. 2501·1); sanguisorba (p. 2462·3); ipeca (p. 1667·2); kalium antimonium tartaricum (p. 151·2).
Homoeopathic preparation.

Cetrasol *IAE, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cetraxal *Salvat, Fin.; Salvat, Spain; WraSer, USA.*
Ciprofloxacin (p. 261·1).
Bacterial infections.
Salvat, Neth.
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa.

Cetraxal Comp *Salvat, Fin.*
⊗Ciprofloxacin (p. 261·1); fluocinolone acetonide (p. 1636·1).
Otitis externa.

Cetraxal Plus *Farmasoft, Ukr.*
⊗Ciprofloxacin (p. 261·1); fluocinolone acetonide (p. 1636·1).
Otitis externa.
Salvat, Spain.
⊗Ciprofloxacin hydrochloride (p. 261·2); fluocinolone acetonide (p. 1636·1).
Otitis externa.

Cetrexidin *Vebas, Ital.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Mouth disinfection.

Cetrezol *East West, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetriax *Karnataka, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cetriax-S *Karnataka, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cetricare *Servocare, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetricure *Chanelle, Irl.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; pruritus.

Cetrid *Biomiicron, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetriderm con Triclosan *Gedis, Ital.†*
Triclosan (p. 1773·2).
Skin cleansing.

Cetrifarm *Nuova Farmec, Ital.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection of burns, skin, mucous membranes, and wounds.

Cetrifed-D *Bombay Tablet, India.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Cetriken *Symbiosis, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetril
Note: this name may be used for preparations of different composition.
Health Guard, India.
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.
Medarte, Gr.
Cetirizine hydrochloride (p. 619·2).

Royal, Chile.
Baclofen (p. 2014·3).
Skeletal muscle spasticity in multiple sclerosis.

Cetrilak *Sarabhai Piramal, India; Shalaks, India.*
Cetrimide (p. 1742·1).
Disinfection.

Cetrilan *Theraskin, Braz.*
Cetrimonium bromide (p. 1742·3); calendula oil (p. 2465·2).
Wounds, burns, skin ulcers.

Cetriler *Roux-Ocefa, Arg.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Cetriler D *Roux-Ocefa, Arg.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Cetrilev *Euro Lifecare, Ukr.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Cetrilin *Taj, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetrim *Psychotropics, India.*
Cetrimide (p. 1742·1).
Skin cleanser.

Cetrimed *Medifive, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis; insect bites.

Cetrin
Note: this name may be used for preparations of different composition.
Teva, Hung.
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Vitamed, Israel.
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Disinfectant.

Cetrina-LV *Zota, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Cetrina-MD *Zota, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetrine *Rotam Reddy, China; Reddy, India; Rowex, Irl.; Reddy, Rus.; Reddy, Singapore; Reddy, Thai.†; Reddy, Ukr.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; allergic rhinitis; allergic conjunctivitis; pruritus; urticaria; angioedema; asthma; allergic skin disorders; insect bites; angioneurotic oedema.

Cétrine *Spirig, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetrinets *Westmont, Hong Kong; United Laboratories, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement; vitamin C deficiency.

Cetripharm *Actavis, Hung.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; conjunctivitis; urticaria.

Cetrisan
Note: this name may be used for preparations of different composition.
Sanjivani, India.
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Gedis, Ital.†
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Surface disinfection.

Cetriscabin *Sanofi-Aventis, Pol.†*
Benzyl benzoate (p. 2149·1); cetrimonium bromide (p. 1742·3).
Scabies; pediculosis.

Cetrite *Medopharm, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Cetritop *Alde Medi Impex, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetrivax *Norton, Pol.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetriwal *Wallace, India.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetrixal *Sandoz, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetriz *Actavis, Irl.; ACME, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; pruritus.

Cetrizen *Norton, Pol.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetrizet *Sun, China; Sun, India; Sun, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Cetrizet-D *Sun, India.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Cetrizin
Note: this name may be used for preparations of different composition.
Abbott, Braz.; TO-Chemicals, Singapore; TO-Chemicals, Thai.
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; allergic rhinitis; allergic skin disorders; allergic conjunctivitis; insect bites.

Elpen (Ελπεν), Gr.
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Cetrizine *Cadila, India.*
Cetirizine hydrochloride (p. 619·2).

Cetrol *Universal, Hong Kong.†*
Cetrimide (p. 1742·1).

Cetrolac *Uniao Quimica, Braz.*
Ketorolac trometamol (p. 80·2).
Eye disorders.

Cetron
Note: this name may be used for preparations of different composition.
Cosme, India.
Cefadroxil (p. 233·2).
Bacterial infections.

Raffo, Arg.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Cetrop *Medicus, Gr.*
Piracetam (p. 393·3).

Cetrotide *Merck Serono, Arg.; Merck Serono, Austral.; Serono, Austria; Merck Serono, Belg.; Merck, Braz.; Serono, Canad.; Novartis, Chile†; Merck Serono, China; Serono, Cz.; Merck Serono, Denm.; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.†; Serono, Gr.; Serono, Hong Kong; Merck Serono, Hung.; Serum Institute, India; Merck, Indon.; Merck Serono, Irl.; Merck Serono, Israel; Serono, Ital.; Merck Serono, Malaysia; Merck, Mex.; Merck, Neth.; Serono, Norw.; Healthcare Logistics, NZ; Merck, Philipp.; Serono, Pol.; Serono, Port.; Merck Serono, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
Cetrorelix acetate (p. 2257·2).
Controlled ovarian stimulation.

Cetry Plus *Lifestyle, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Cetryn *Abdi Ibrahim, Indon.†; Abdi, Turk.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetsafe *UniOrange, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Cetta *Suphong, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Cettec *Medicpharma, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cettop *Reliance, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetura *ACE, Neth.*
Estradiol (p. 2271·1).
Delayed puberty; Turner' syndrome.

Cêtussin *Johnson & Johnson, Port.*
Acetylcysteine (p. 1652·2).
Respiratory-tract infections with increased secretions.

Cetussin *Suphong, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Cetven-DT *Vensat, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cetyl
Note: this name may be used for preparations of different composition.
Eras, Turk.
Cetrimide (p. 1742·1).
Skin disinfection.

Lupin, Rus.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cetylcide II *Cetylite, USA.*
Alkyldimethylbenzylammonium chloride (p. 1737·1); alkyldimethylethylbenzylammonium chloride.
Surface disinfection.

Cetylcide-G *Cetylite, USA.*
Glutaral (p. 1753·2).
Instrument disinfection.

Cetylpyridinium B *Pharmaniaga, Malaysia.*
Cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Cetymin *Galenium, Indon.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Cetyrol *Sandoz, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetyryzyna *Egis, Pol.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cetzine *GSK, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cetzine-A *GSK, India.*
Cetirizine hydrochloride (p. 619·2); ambroxol hydrochloride (p. 1654·3).

Cetzone *Grace, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cetzone-S *Grace, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Cetzone-TZ *Grace, India.*
Ceftriaxone sodium (p. 253·3); tazobactam sodium (p. 369·3).
Bacterial infections.

Cetzy *Zee, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Ceumid *Pharma Investi, Chile.*
Levetiracetam (p. 531·1).
Epilepsy.

Ceurox *Medley, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cevaderm *Cevallos, Arg.*
⊗Betamethasone valerate (p. 1624·1); tolnaftate (p. 596·1); gentamicin (p. 304·2).
Skin infections.

Cevadil *GMP, Indon.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Cevalin *Bayer Consumer, Mex.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cevanil *Pharmasant, Thai.*
Pirenzepine hydrochloride (p. 1878·2).
Peptic ulcer.

Cevas *Cadila, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left ventricular dysfunction following myocardial infarction.

Cevax *Vivax, Venez.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cevi-Bid *Geriatric Pharm. Corp., USA.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cevicim *Shince, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cevicort *Cevallos, Arg.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Cevicort NC *Cevallos, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Cevi-drops *Nycomed, Belg.†*
Ascorbic acid (p. 2110·3); calcium ascorbate (p. 2111·1).
Vitamin C supplement; vitamin C deficiency.

Cevigen *Bros, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Cevikap *Medana, Pol.; Medana, Rus.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement; vitamin C deficiency.

Cevilor *Antor, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Cevimin *Flupal, Venez.*
Indometacin (p. 71·2).

Cevinolon *Bros, Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Cevirin *United Biotech, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ce-Vi-Sol *BMS, Mex.†; Mead Johnson, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cevit *Synco, Hong Kong†; Plusandex, Venez.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Cevita *Teuto, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Cevi-Tabs *Ferrosan, Fin.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cevitol *Lannacher, Austria.*
Ascorbic acid (p. 2110·3) or sodium ascorbate (p. 2111·1).
Vitamin C deficiency; methaemoglobinaemia.

Ceviton *Ariston, Braz.†*
Ascorbic acid (p. 2110·3).

Cevizo *Marching, Hong Kong.†*
Ascorbic acid (p. 2110·3).

Cewin *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Cexb *Behrens, Venez.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis.

Cexene *TMN Impex, Thai.*
Dipotassium clorazepate (p. 1056·3).

Cexil *Leben, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cexim
Note: this name may be used for preparations of different composition.
DR Johns, India.
Cefixime (p. 240·3).
Bacterial infections.

Cexime *Medial, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cexime-CL *Medial, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Cexin *Ind-Swift, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cez *Finecure, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cez-A *Finecure, India.*
Ambroxol hydrochloride (p. 1654·3); cetirizine hydrochloride (p. 619·2).

Ceza *Pharmaland, Thai.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; allergic skin disorders.

Cezarius *Hasco-Lek, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Cezcold *Finecure, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cez-D *Finecure, India.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Ceze *Zee, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Cezel-PT *Zee, India.*
Clotrimazole (p. 576·2); povidone-iodine (p. 1767·1); tinidazole (p. 949·2).
Vaginal infections.

Cezera *KRKA, Cz.; KRKA, Pol.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Cezin *UAD, USA.*
Vitamins; minerals.

Ceziren *Pharmanel, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic disorders.

Cezol *Deva, Turk.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cezolin
Note: this name may be used for preparations of different composition.
Daehan, Singapore.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Lupin, India; Lupin, Rus.
Cefazolin (p. 237·2).
Bacterial infections.

Remedina, Gr.
Ketoconazole (p. 585·3).
Fungal infections.

Cezone *Chandra Bhagat, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cezone Plus *Chandra Bhagat, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cezon-S *Dr Alson, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cezoryn *Labormed, Cz.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Cezox *Pharmasant, Thai.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

CFA *Medisys, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

CFC *Medisys, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

C-Fix *Corona, India.*
Cefixime (p. 240·3).
Bacterial infections.

C-Fix-XT *Plus, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

C-Flox
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Corona, India.
Tablets: Ofloxacin (p. 334·3).
Bacterial infections.

Prem, India.
Eye drops; injection: Ciprofloxacin (p. 261·1).
Bacterial infections.

C-Floxacin *SM, Thai.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

C-Flox-M *Corona, India.*
Metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

C-Flox-OZ *Corona, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

C-Fol *Corona, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy; dietary supplement.

C-Fort *Concept, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

C-Furo *Hetero, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

C-FX *Prompt Cure, India.*
Cefixime (p. 240·3).
Bacterial infections.

CG Flox *CMG, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

CG Mez *CMG, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

CGCal *CMG, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

CGCron *CMG, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

CGDole *CMG, India.*
Ornidazole (p. 943·1).
Protozoal infections; anaerobic bacterial infections.

C-Gesic *Corona, India.*
Caffeine (p. 1203·3); ibuprofen (p. 68·2); paracetamol (p. 115·1).

CGM *Arika, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3); zinc (p. 2126·1).
Infected skin disorders.

CG-Mac *CMG, India.*
Tramadol (p. 139·2).
Pain.

CGMag *CMG, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

CGMide *CMG, India.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

CGPan *CMG, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

C-Gra *Corona, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

C-Grel *Triton, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

C-Grel Plus *Triton, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

CGRol *CMG, India.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; hyperthyroidism; myocardial infarction; migraine; heart failure; arrhythmias.

CGRyl *CMG, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

CGT *Libbs, Braz.*
Vitamins; minerals.

CGU WC *Elge, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

CGV-DS *Unikid, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections; otitis media.

CH Syrup *Universal, Hong Kong.†*
Cyproheptadine (p. 624·1).

Cha Xin Na Min *Suilun, China.*
Aminophylline (p. 1201·2); bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3).
Obstructive airways disease.

C-Haem *Corona, India.*
Capsules: Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Corona, India.
Syrup: Folic acid (p. 2063·1); iron choline citrate (p. 2060·2); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2).

Chaibolant *Chinta, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Chalkcap *Charoon Bhesaj, Thai.*
Calcium carbonate (p. 1824·3).
Hyperphosphataemia in chronic renal failure; antacid; calcium supplement; calcium deficiency.

Chalktab
Note: this name may be used for preparations of different composition.
Charoon Bhesaj, Thai.
Calcium carbonate (p. 1824·3).
Hyperphosphataemia in chronic renal failure; antacid; calcium supplement; calcium deficiency.

Kolson's, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Chamberlains Cough Remedy Honey and Liquorice *Pfizer Consumer, S.Afr.†*
Guaifenesin (p. 1666·2).
Cough.

Chamberlains Cough Remedy Peppermint *Pfizer Consumer, S.Afr.†*
Guaifenesin (p. 1666·2).
Cough.

Chamberlains Cough Remedy Regular *Pfizer Consumer, S.Afr. †*
Liquorice (p. 1853·2); ipecacuanha (p. 1667·2).
Cough.

Chamberlains Traditional Colic Remedy *Pfizer Consumer, S.Afr.†*
Chlorobutanol (p. 1747·2); ether (p. 2212·3); blackberry root.
Flatulence; colic.

Chamoca M *Hanosan, Ger.*
Sulfur (p. 1721·1); camphora (p. 2466·2).
Homoeopathic preparation.

Chamomile Blend *Lifeplan, UK.*
Valerian (p. 2640·2); chamomile (p. 2474·1); lupulus (p. 2546·1); passion flower (p. 2584·1).
Herbal supplement.

Chamomilla/Millefolium Comp *Weleda, S.Afr.†*
Chamomilla (p. 2474·1); belladonna (p. 2453·3); millefolium (p. 2427·3); kieserit.
Homoeopathic preparation.

Champione *NB, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Champione-S *NB, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Championyl *Sanofi-Aventis, Ital.*
Sulpiride (p. 1107·3).
Psychoses; dysthymia.

Champix *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.*
Varenicline tartrate (p. 2641·3).
Aid to smoking withdrawal.

Pfizer, Norw.
Varenicline (p. 2641·3).
Aid to smoking withdrawal.

Champs C *Upha, Indon.; Upha, Singapore.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Champs C with Lysine *CCM, Hong Kong; Upha, Indon.; Upha, Singapore.†*
Ascorbic acid (p. 2110·3); lysine hydrochloride (p. 2079·3).
Nutritional supplement; vitamin C supplement.

Champs DHA *Upha, Indon.; CCM, Malaysia; Upha, Singapore.†*
Fish oil (p. 1460·3).
Nutritional supplement.

Champs D-Worms *CCM, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Champs Junior *CCM, Hong Kong.†*
Vitamin C (p. 2110·3).
Vitamin C supplement.

Champs M *Upha, Singapore.†*
Vitamins; with or without lysine (p. 2079·3).

Champs M with Lysine *CCM, Hong Kong.*
Vitamins; lysine (p. 2079·3).
Dietary supplement.

Upha, Indon.
Lysine hydrochloride (p. 2079·3); vitamins.
Nutritional supplement.

Champuacid *Bajer, Arg.*
Zinc undecenoate (p. 596·3); salicylic acid (p. 1719·1); coal tar (Alcoderm) (p. 1723·2).
Scalp disorders.

Chang Le *Guang Da, China.*
Sodium sulfate (p. 1888·1).
Constipation.

Chang Di *Hayao, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Chang Bang *Ya Bang Ai Pu Sen, China.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm.

Chang Er Da *Wuxi No 7, China.*
Flavoxate hydrochloride (p. 2360·1).
Bladder spasm; urinary incontinence; urinary frequency and urgency.

Chang Fu Luo Da *Treeful, China.*
Ligustrazine hydrochloride.

Chang Fu Su *Huazhong, China.*
Ethylenediamine diaceturate.

Chang Fu Wei Na *Huazhong, China.*
Sodium ferulate.

Chang Fu Wei Qin *Huazhong, China.*
Ligustrazine phosphate.

Chang Gui Qing *Tongyong, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Chang Heng Lin *Changzhou, China.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Chang Jian Ning *Qiangji, China.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease; rheumatoid arthritis.

Chang Le Kang *Kexing, China.*
Clostridium butyricum; bifidobacterium.
Diarrhoea.

Chang Ke *Changzhou Siyao, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Chang Li Ning *Eastsea, China.*
Clostridium butyricum.
Restoration of gastrointestinal flora.

Chang Long Lei *Changlong, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Chang Long Qing *Changlong, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Chang Luo Ning *Huabang, China.*
Tegaserod maleate (p. 1893·1).
Constipation; irritable bowel syndrome.

Chang Mei *Lisheng, China.*
Olsalazine sodium (p. 1866·3).
Ulcerative colitis.

Chang Ping *Handu, China.*
Telmisartan (p. 1509·3).

Chang Ran *Jiu Dian, China.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Chang Rui *Chang Fu JieJing, China.*
Aminobutyric acid (p. 2509·2).
Mental function impairment; hypertension; paralysis.

Chang Sheng Fu Kang *Changchun, China.*
Interferon alfa-2b (human, recombinant) (p. 989·2).

Chang Sheng Fu Ming *Changchun, China.*
Interferon alfa-1b (human, recombinant) (p. 989·2).

Chang Sheng De Jia *Changchun, China.*
Interferon alfa-2b (human, recombinant) (p. 989·2).

Chang Sheng Xun Kang *Changchun, China.*
A normal immunoglobulin (p. 2403·3).

Chang Song *Huasen, China.*
Macrogol 4000 (p. 2547·3).

Chang Tai *Jingfukang, China.*
Probucol (p. 1475·2).
Hyperlipidaemias.

Chang Tuo Ning *Lisite, China.*
Penehyclidine hydrochloride.

Chang Wei Rui Da Xin *Duoburuifei, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Chang Wei Xi *Dayinhaiyang, China.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Chang Xiu Lin *Ganli, China.*
⊗Insulin glargine (p. 475·3).
Diabetes mellitus.

Chang Yan Ting *Sunstone, China.*
Montmorillonite.
Diarrhoea.

Chang Ze *ErYe, China.*
⊗Bumetanide (p. 1329·1).
Oedema.

ChangDi *Wo Wu, China.*
Dermatophagoides farinae (p. 2434·3).

Changfu ShengXing *Treeful, China.*
Matrine.

Changfu TianXin *Treeful, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Changfu Yitai *Treeful, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Changfu YouShu *Treeful, China.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Changnuo *Chia Tai, China.*
Seratrodast (p. 1225·3).
Asthma.

ChangTai *Xing'an, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Channel *Micro, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Chantix *Pfizer, USA.*
Varenicline tartrate (p. 2641·3).
Smoking cessation.

Chanyanling *Sunstone, China.*
Gentamicin sulfate (p. 304·2); bismuth carbonate (p. 1821·3).
Gastrointestinal infections.

Chao Qing *Tianmushan, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Chap Stick
Note: this name may be used for preparations of different composition.
Wyeth Consumer, NZ.
Lip Balm Ultra SPF 30+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Conditioner SPF 15: Aloe vera (p. 1693·2) octinoxate (p. 1715·1); oxybenzone (p. 1715·3); vitamin E (p. 2119·1).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Balm SPF 15: Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Balm Strawberry SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Chapped lips; sunscreen.

Chapstick *Wyeth Consumer, Arg.; Pfizer Consumer, Austral.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen for lips; dry or chapped lips; chapped lips; sunscreen.

Robins, USA.
Lip balm SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Robins, USA.
Ointment SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Wyeth, Arg.; Wyeth Consumer, Austral.†
SPF 4: Padimate O (p. 1716·1).
Chapped lips; sunscreen; sunscreen for lips; dry or chapped lips.

Chapstick Lip Moisturizer *Pfizer Consumer, Canad.; Pfizer Consumer, Chile.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen; chapped lips.

Chapstick Medicated *Pfizer Consumer, Chile.*
White soft paraffin (p. 2211·3); camphor (p. 2466·2); menthol (p. 2553·2); phenol (p. 1763·3).
Chapped lips.

Chapstick Medicated Lip Balm *Robins, USA.*
Yellow soft paraffin (p. 2212·1); camphor (p. 2466·2); menthol (p. 2553·2); phenol (p. 1763·3).

Chapstick Mint *Pfizer Consumer, Chile.*
Padimate O (p. 1716·1).
Sunscreen; chapped lips.

Chapstick Regular *Pfizer Consumer, Chile.*
Padimate O (p. 1716·1); titanium dioxide (p. 1725·1).
Sunscreen; chapped lips.

Chapstick Sunblock *Pfizer Consumer, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Chapstick Ultra *Pfizer Consumer, Austral.*
SPF 30+: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen for lips.

Pfizer Consumer, Chile.
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen; chapped lips.

Charac *Omega, Canad.*
Activated charcoal (p. 1537·3).
Poison antidote.

Charac Tol *Omega, Canad.*
Activated charcoal (p. 1537·3); sorbitol (p. 2092·1).
Poison antidote.

Charantia *Herbcare, Philipp.*
Karela.
Supplement for diabetics.

Charbogir *Arkopharma, Belg.*
Activated charcoal (p. 1537·3).
Gastrointestinal disorders with bloating.

Charbon de Belloc *Medgenix, Belg.; Super Diet, Fr.*
Activated charcoal (p. 1537·3).
Meteorism; diarrhoea; gastrointestinal disorders.

Charcoaid *Requa, USA.†*
Activated charcoal (p. 1537·3).
Emergency treatment of poisoning.

Charcoal Plus *Kramer, USA.*
Activated charcoal (p. 1537·3).
Formerly contained simeticone and activated charcoal.
Flatulence.

Charcocaps *Key, Austrol.; Young, USA.*
Activated charcoal (p. 1537·3).
Flatulence.

Charcodote *Pharmascience, Hong Kong; Pharmascience, Israel; Teva, UK.*
Activated charcoal (p. 1537·3) with or without sorbitol (p. 2092·1).
Emergency treatment of poisoning.

Pharmascience, Canad.; Pharmascience, Singapore.
Activated charcoal (p. 1537·3); sorbitol (p. 2092·1).
Emergency treatment of poisoning; poison antidote.

Charcodote Aqueous *Pharmascience, Canad.*
Activated charcoal (p. 1537·3).
Poison antidote.

Charcotabs *Key, Austral.*
Activated charcoal (p. 1537·3).
Flatulence.

Charcotrace *Phebra, Austral.*
Activated charcoal (p. 1537·3).
Detection of breast lesions.

Charflo Aqua *SSK, Turk.*
Activated charcoal (p. 1537·3).
Emergency treatment of poisoning.

Charflo Sorbitol *SSM, Turk.†*
Activated charcoal (p. 1537·3); sorbitol (p. 2092·1).
Emergency treatment of poisoning.

Chariva *Gedeon Richter, Ger.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Charlieu Antipelliculaire *Nigy, Fr.†*
Piroctone olamine (p. 1716·3).
Seborrhoeic dermatitis.

Charlieu Anti-Poux *Mayoly-Spindler, Fr.†*
Permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2).
Pediculosis.

Charlize *Pond's, Philipp.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive; menstrual disorders.

Charlyn *Krugher, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic respiratory-tract disorders.

Charyn *Wermar, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Chase *Shreshtha, India.*
Cefepime (p. 239·2).
Bacterial infections.

Chateal *Afaxys, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Chavita 1 *Rubimed, Neth.*
⊗Carbo vegetabilis (p. 1537·3); ovarium suis (p. 2298·2); silicea (p. 2208·3); testis suis (p. 2304·3); urtica urens (p. 2639·3).
Homoeopathic preparation.

Chavita 2 *Rubimed, Neth.*
⊗Argentum metallicum (p. 2615·1); causticum (p. 2595·3); glandula suprarenalis suis (p. 1648·1); juniperus communis (p. 2537·1); lavandula angustifolia; platinum metallicum (p. 2593·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Chavita 5 *Rubimed, Neth.*
Glandula thyreoidea suis (p. 2345·3); phosphorus (p. 2589·2); thuja occidentalis (p. 2629·3); viola tricolor (p. 2647·3).
Homoeopathic preparation.

Chavita 6 *Rubimed, Neth.*
Cerebrum suis (p. 2444·1); plumbum metallicum (p. 2541·3); staphysagria; viscum album (p. 2560·2).
Homoeopathic preparation.

Check-Mate *BHR, UK.*
Pregnancy test (p. 2596·1).

Checkmox-DX *Novogen, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

CheeTah *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Cheetah *Tyco, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Chefarine *Chefaro, Neth.†*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain; fever.

Chefir *Pfizer, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Chekmet *Piramal, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Chekmet-O *Piramal, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Chek-Stix *Bayer, Austral.†*
Positive and negative controls for tests for glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leucocytes in urine.

ChelaCo *Mediherb, Austral.*
Crataegus (p. 2488·1); milk thistle (p. 1561·1); garlic (p. 2510·3).
Tonic.

Chelated Cal-Mag *GNLD, Austral.†*
Calcium glycinate (p. 1783·1); magnesium glycinate (p. 1786·3).
Calcium and magnesium deficiency.

Chelated Cal-Mag plus Vitamin *Swiss Herbal, Canad.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Chelated Cal-Mag with Vitamin D *GNLD, Austral.*
Calcium amino acid chelate (p. 2048·3); magnesium amino acid chelate (p. 2048·3); colecalciferol (p. 2113·1).
Dietary supplement.

Chelated Mineral *Usana, Hong Kong.†*
Minerals.

Chelated Solamins *Solgar, UK.*
Minerals as amino-acid chelates.

Chelatran *SERB, Fr.†*
Disodium edetate (p. 1550·3).
Digitalis intoxication.

Chelferron *Leben, India.*
Oral liquid: Iron (p. 2073·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).

Leben, India.
Tablets: Iron (p. 2073·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2); ascorbic acid (p. 2110·3).

Chelicur *Hasco-Lek, Pol.*
Greater celandine (p. 2522·2); turmeric (p. 2218·1).
Biliary-tract disorders; liver disorders.

Chelidonium comp
Note: this name may be used for preparations of different composition.
Weleda, Ger.
Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); dryopteris filix-mas (p. 158·3); polypodium vulgare; salix alba; salix purpurea (p. 129·2); salix viminalis; phyllitis scolopendrium; onopordum acanthium; taraxacum (p. 2625·3); urtica dioica (p. 2639·3).
Homoeopathic preparation.

Chelidonium Compose *Boiron, Fr.*
Chelidonium majus (p. 2522·2); taraxacum dens leonis (p. 2625·3); carduus marianus (p. 1561·1); solidago virga aurea (p. 2620·1); cinchona succirubra (p. 2478·3); hydrastis canadensis (p. 2528·1); magnesia muriatica (p. 1787·1).
Homoeopathic preparation.

Chelidonium Plex *Seroyal, Canad.†*
Barberry root (p. 2502·1); celandine (p. 2522·2); dolichos pruriens; goldenrod (p. 2620·1); iris vericolor (p. 2534·3); milk thistle (p. 1561·1); ptelea trifoliata; taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Chelidonium-Homaccord N *Heel, Neth.*
Chelidonium majus (p. 2522·2); belladonna (p. 2453·3).
Homoeopathic preparation.

Cheltin *Pharma Investi, Chile.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency; iron-deficiency anaemia.

Cheltin IV *Pharma Investi, Chile.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Cheltin Folic *Pharma Investi, Chile.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).
Iron and folic acid deficiency; anaemias.

Chemacin *CT, Ital.; CT, Rus.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Chemedox-HT *Chemo-Drugs, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Chemet *Ovation, USA.*
Succimer (p. 1576·3).
Lead poisoning.

Chemicetina *Finderm, Ital.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chemiderm *Iasis, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections.

Chemilaic *Farmanic, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Chemisolv *Farmanic, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Chemists Own Chesty Cough *Chemists Own, Austral.*
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough and cold symptoms.

Chemists Own Chesty Mucus Cough *Chemists Own, Austral.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Chemists Own Childrens Cough & Cold *Chemists Own, Austral.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; cough.

Chemists Own Clozole *Chemists Own, Austral.*
Clotrimazole (p. 576·2).
Fungal skin infections; vaginal candidiasis.

Chemists Own Cold & Allergy *Chemists Own, Austral.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; hypersensitivity reactions.

Chemists Own Cold & Flu Day/Night *Chemists Own, Austral.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); night tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Chemists Own Cold & Flu Relief *Chemists Own, Austral.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Chemists Own Cold Sore *Chemists Own, Austral.*
Aciclovir (p. 964·1).
Herpes labialis.

Chemists Own Coldeze *Chemists Own, Austral.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Chemists Own Cough Suppressant *Chemists Own, Austral.†*
Ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2); menthol (p. 2553·2).
Cough.

Chemists Own Decongestant Nasal Spray *Chemists Own, Austral.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Chemists Own Diarrhoea Relief *Chemists Own, Austral.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Chemists Own Difenacol *Chemists Own, Austral.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough and cold symptoms.

Chemists Own Dolased Day/Night Pain Relief *Chemists Own, Austral.†*
Day tablets, paracetamol (p. 115·1); codeine phosphate (p. 40·2); night tablets, paracetamol; codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain.

Chemists Own Dry Cough *Chemists Own, Austral.*
Pholcodine (p. 1675·1).
Cough.

Chemists Own Dry Raspy Cough *Chemists Own, Austral.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Chemists Own Expectalix *Chemists Own, Austral.*
⊗Ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Chemists Own Hayfever Sinus Relief *Chemists Own, Austral.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Hay fever; nasal and sinus congestion.

Chemists Own Kiddicol *Chemists Own, Austral.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); pholcodine (p. 1675·1).
Cough; cold symptoms.

Chemists Own Natural Laxative with Softener *Chemists Own, Austral.*
Docusate sodium (p. 1836·2); senna leaf (p. 1885·1); sennosides (p. 1885·2).
Constipation.

Chemists Own Pain *Chemists Own, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Chemists Own Pain & Fever *Chemists Own, Austral.*
Paracetamol (p. 115·1).
Fever; pain.

Chemists Own Period Pain *Chemists Own, Austral.*
Naproxen sodium (p. 98·2).
Dysmenorrhoea.

Chemists Own Sinus Relief *Chemists Own, Austral.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Chemists Own Sinus-Pain Relief *Chemists Own, Austral.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinusitis.

Chemists Own De Worm *Chemists Own, Austral.*
Mebendazole (p. 158·3).
Worm infections.

Chemisulide *Farmanic, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Chemitrim *Biomedica, Ital.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Chemix *YSP, Malaysia; Yung Shin, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Chemocetin *Chemo-Drugs, India.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chemocid *Chemo-Drugs, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Chemofer-12 *Chemo-Drugs, India.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Chemo-Drugs, India.
Syrup: Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Chemoprim *Biolab, Hong Kong.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Chemotrex *Medichem, Indon.†*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Chemotrin *PC India, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Chempride *Chemech, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Chemspec *Chemical Specialties, Canad.*
Sodium hypochlorite (p. 1768·3).
Disinfection.

Chemstrip 7 *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, ketones, bilirubin, leukocytes, and pH in urine.

Chemstrip 9 *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes, and pH in urine.

Chemstrip bG *Roche Diagnostics, Canad.†*
Test for glucose in blood (p. 2516·3).

Chemstrip 2 GP *Boehringer Mannheim, USA.*
Test for glucose and protein in urine.

Chemstrip K *Roche Diagnostics, Canad.†; Boehringer Mannheim, USA.*
Test for ketones in urine.

Chemstrip 2 LN *Boehringer Mannheim, USA.*
Test for nitrite and leukocytes in urine.

Chemstrip Micral *Boehringer Mannheim, USA.*
Test for albumin in urine.

Chemstrip 10 with SG *Boehringer Mannheim, USA.*
Test for nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, leucocytes, and specific gravity in urine.

Chemstrip uGK *Boehringer Mannheim, USA.*
Test for glucose and ketones in urine.

Chemstrip uG/K *Roche Diagnostics, Canad.†*
Test for glucose and ketones in urine.

Chemydur *Sovereign, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Chen Gong Zai Xin *Cuccess, China.*
Zinc gluconate (p. 2126·2); ibuprofen (p. 68·2); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Chen Ji Ge *Lukang Chenxin, China.*
Tiopronin (p. 1578·1).

Chen Jing *Lukang Chenxin, China.*
Diclofenac sodium (p. 48·3).
Prevention of intra-operative miosis; eye pain and inflammation; allergic conjunctivitis.

Chen Li *Fudan Fuhua, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Chen Long Luo Xin *Guo Jing, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Chen Rang *Lukang Chenxin, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Chen Sheng Fen *Lukang Chenxin, China.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Chen Wang *Lukang Chenxin, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders.

Chen Ya *Lukang Chenxin, China.*
Oxaliplatin (p. 838·1).
Mannitol (p. 1427·3) is included in this preparation to aid diuresis and reduce renal toxicity.

Chen Yu *Lukang Chenxin, China.*
Azithromycin hydrochloride (p. 221·2).
Bacterial infections.

Chen Ze *Lukang Chenxin, China.*
Apraclonidine hydrochloride (p. 2003·3).

Chen Zheng *Hailing, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Cheng Jing *Dilong, China.*
Gastrodin.

Cheng Li Kang *FuXing, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Cheng Qiang *Conba, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Chengrui *Bausch & Lomb, China.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Chenodal *Manchester Pharma, USA.*
Chenodeoxycholic acid (p. 2475·1).
Gallstones.

Chenofalk *Sigma-Tau, Ger.†; Darya-Varia, Indon.†; Falk, Indon.†; Falk, Israel†; Sigma-Tau, Neth.; Falk, Rus.; Ali, Turk.*
Chenodeoxycholic acid (p. 2475·1).
Cholesterol gallstones.

Chepamed *Promed, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; alcoholism.

Chephapyrin N *MIP, Ger.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Cheracap S *Pharmacia, Braz.*
Chlorphenamine maleate (p. 620·3); aspirin (p. 22·2); caffeine (p. 1203·3).
Cold and influenza symptoms.

Cheracol *Johnson & Johnson, Chile.*
⊗Aspirin (p. 22·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); methoxyphenamine hydrochloride (p. 1669·1).
Cold symptoms.

Pfizer Consumer, Mex.
Aspirin (p. 22·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; allergic rhinitis.

Cheracol Cough *Roberts, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Coughs.

Cheracol D Cough *Roberts, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Cheracol Duo *Pfizer Consumer, Mex.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Cheracol Plus *Lee, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs and cold symptoms.

Cheracol Sore Throat *Roberts, USA.*
Phenol (p. 1763·3).
Sore throat.

Cheratussin DAC *Qualitest, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Cheri *Ind-Chemie, India.*
Capsules: Vitamins minerals.

Ind-Chemie, India.
Chewable tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ind-Chemie, India.
Syrup: Folic acid (p. 2063·1); iron (p. 2073·1).

Cheri 4 Flu *Ranbaxy, Malaysia.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; allergic disorders.

Chericof
Note: this name may be used for preparations of different composition.

Ranbaxy, India.
Capsules; oral sachets; syrup: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Ranbaxy, India.
Lozenges: Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Ranbaxy, Malaysia.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Chericold *Ranbaxy, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Cherifer
Note: this name may be used for preparations of different composition.

GruppoMedica, Philipp.
Chlorella growth factor (p. 2475·3); vitamins; with or without minerals.

Panjon, India.
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Cherry Creme Hand Soap *Zep, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Cherrytone *Life Line, India.*
Dexpanthenol (p. 2582·2); inositol (p. 2533·2); lysine hydrochloride (p. 2079·3); tricholine citrate (p. 2055·2); vitamin B substances (p. 2102·3).

Chescare *Shince, India.*
Bromhexine hydrochloride (p. 1656·3); cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Chest Congestion, Cough & Cold *Pharmetics, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Chest Mixture *Potter's, UK.*
⊗Horehound (p. 1668·3); pleurisy root (p. 2593·2); senega (p. 1677·2); lobelia (p. 2323·2); acetum scillae (p. 1677·3).
Coughs; catarrh.

Chestclear *Dexter, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine (p. 1672·2).

Cheston *Cipla, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Cheston Cold *Cipla, India.*
Tablets: Cetirizine hydrochloride (p. 619·2); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1).
Cold symptoms.

Cipla, India.
Oral suspension: ⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Cheston CS *Cipla, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Cheston DT *Cipla, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Cheston Exp *Cipla, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).

Cheston Meltees *Cipla, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Chesty Cough Relief *Herbal Concepts, UK.*
Senega (p. 1677·2); catechu (p. 2472·3); liquorice (p. 1853·2); tolu (p. 1679·2); coltsfoot (p. 1659·2).
Coughs.

Chetofen *Boniscontro & Gazzone, Ital.*
Ketotifen fumarate (p. 631·3).
Allergic respiratory-tract disorders; allergic skin disorders.

Chetonex *Humana, Ital.*
Vitamins; minerals; alanine (p. 2048·3).
Ketosis; acetonaemia.

Chetotifene *Mylan, Ital.*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis.

Chew-C *Key, USA.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Chewcee *Wyeth, India.*
Vitamin C (p. 2110·3).
Dietary supplement.

Chew-E *Eagle, Austral.†*
d-Alpha tocoferil acid succinate (p. 2119·2).
Vitamin E supplement.

Chewette *Hovid, Malaysia.*
Ascorbic acid (p. 2110·3).
Formerly known as Chewette C.
Vitamin C supplement.

Chewette C *Hovid, Philipp.*
Sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Chewfe-C *Advik, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin C (p. 2110·3).

Chewfol *Sigman, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy; dietary supplement.

Chewoquine *Chew, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; rheumatoid arthritis; amoebiasis.

Chewoquine SC *Chew, Thai.*
Ascorbic acid (p. 2110·3); chloroquine phosphate (p. 650·1); thiamine hydrochloride (p. 2103·1).
Malaria.

Chewtab Multivit *USV, India.*
Vitamins.

Chexid *Aristo, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Chiacaps *Madaus, Arg.*
Sage oil (p. 2609·1).
Hyperlipidaemias.

Chiafibra *Elea, Arg.*
Dietary fibre; magnesium oxide (p. 1857·3); myrtillus (p. 2566·2).
Dietary supplement.

Chiana *Bio-Diat, Norw.*
Peppermint oil (p. 1877·1).
Cold symptoms; gastrointestinal bloating.

Chiaoil *Elea, Arg.*
Chia oil.
Dietary supplement.

Chiaro *Mediolanum, Ital.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Chibro-Cadron *Thea, Fr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Eye disorders.

Chibro-Proscar *MSD-Chibret, Fr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Chibro-Timoptol *Teofarma, Ger.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Chibroxin *Thea, Ger.†; Thea, Pol.; Thea, Spain.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Chibroxine *Thea, Fr.*
Norfloxacin (p. 333·3).
Eye infections.

Chibroxol *Thea, Neth.†; Thea, Port.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Chicle *Labsa, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Chiclida *Andromaco, Mex.*
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Torrents, Spain.
Meclozine (p. 634·3) or meclozine hydrochloride (p. 634·3).
Motion sickness.

Chicovit Pharmaton *Boehringer Ingelheim, Chile.*
Lysine hydrochloride (p. 2079·3); calcium (p. 1783·1); phosphorus (p. 2589·2); vitamins.
Tonic.

Chigg Away *Pierson, USA.*
Benzocaine (p. 1980·2); sulfur (p. 1721·1).

Chiggerex *Scherer, USA.†*
Benzocaine (p. 1980·2); camphor (p. 2466·2); menthol (p. 2553·2).
Skin disorders.

Chigger-Tox *Scherer, USA.†*
Benzocaine (p. 1980·2).
Local anaesthesia.

Chikujountanto *Tsumura, Jpn.*
Pinellia tuber; bupleurum root; ophiopogon tuber; poria sclerotium; platycodon root; immature orange; cyperus rhizome; citrus unshiu peel; coptis rhizome; liquorice (p. 1853·2); ginger (p. 1844·1); ginseng (p. 2513·3); bamboo trunk.
Traditional Kampo medicine.

Chilblains Cream *Nelson, UK.*
Tamus communis.
Homoeopathic preparation.

Chilcee *Blue Sky, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Child Chesty Cough *Numark, UK.*
Diphenhydramine (p. 626·1).
Coughs.

Children's Advil *Wyeth, Singapore.*
Ibuprofen (p. 68·2).
Pain; fever.

Childrens Advil Cold *Pfizer Consumer, Canad.; Whitehall-Robins, USA.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis; upper respiratory-tract disorders.

Children's Allergy Formula *Pharmascience, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Childrens Bufferin *BMS, China.*
Paracetamol (p. 115·1).
Fever; pain.

Childrens Bufferin Cold & Cough Relief *BMS, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Childrens Cepacol *JB Williams, USA.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Childrens Chew Multi & Min *Quest, Canad.†*
Vitamins; minerals.

Childrens Chewable *Adams, Canad.†; GFR, Canad.†; Golden Neo-Life, Canad.†; Hall, Canad.†; Jamieson, Canad.†; Natures Sunshine, Canad.†; Novopharm, Canad.†; Nutricorp, Canad.†; Pharmetics, Canad.†*
Vitamins with or without minerals.

Childrens Chewable Vita-Mins *Seroyal, Canad.†*
Vitamins; minerals.

Children's Clusivol *Wyeth, Philipp.*
Vitamins; minerals.

Childrens Cold and Flu Relief *Brauer, Austral.*
Nux vomica (p. 2573·3); pulsatilla (p. 2600·2); aconitum nap. (p. 2428·3); euphrasia (p. 2502·1); gelsemium (p. 2511·2); rhus tox. (p. 2603·3); arsen. alb. (p. 2448·1); bryonia (p. 2461·3); eupatorium perf. (p. 2459·1); allium cepa (p. 2575·2).
Homoeopathic preparation.

Childrens Coltalin *Fortune, China; Fortune, Hong Kong.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); thiamine hydrochloride (p. 2103·1).
Cold symptoms; upper respiratory-tract allergies.

Children's Coltalin Cold & Flu *Fortune, Hong Kong.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Childrens Cough *VitaHealth, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Childrens Cough, Cold & Allergy *Vita Health, Canad.†*
Diphenhydramine citrate (p. 626·2).

Childrens Cough Relief *Brauer, Austral.*
Aconitum napellus (p. 2428·3); belladonna (p. 2453·3); hepar sulfuris (p. 1721·3); kali bichromicum (p. 2476·3); antimonium tartaricum (p. 151·2); phosphorus (p. 2589·2); bryonia (p. 2461·3); drosera (p. 2497·2); spongia tosta; ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Childrens Diarrhoea Mixture *Unichem, UK.*
Kaolin (p. 1850·1).
Diarrhoea.

Childrens Dimaphen DM Cold & Cough *Major, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Childrens Feverhalt *Pendopharm, Canad.*
Paracetamol (p. 115·1).
Fever; pain.

Children's Formula Cough *Pharmakon, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Childrens Fortolin *Fortune, Hong Kong.†*
Paracetamol (p. 115·1).
Fever; pain.

Childrens Ibuprofen Cold *Major, USA.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Children's Kaopectate *Pharmacia, USA.*
Bismuth salicylate (p. 1821·3).
Formerly contained attapulgite.
Diarrhoea.

Childrens Liquid Allergy *Supplements Aromatik, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Childrens Mapap *Major, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Childrens Motion Sickness Liquid *Tanta, Canad.*
Dimenhydrinate (p. 625·2).

Childrens Motrin *Johnson & Johnson, China.*
Ibuprofen (p. 68·2).
Fever; pain.

Childrens Motrin Cold *McNeil Consumer, USA.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Children's Multivitamins *Cenovis, Austral.*
Vitamins; minerals.

Children's Nostril *Ciba, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Childrens Panadol *GSK Consumer, Austral.; GSK, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Childrens Panadol Cold & Flu *GSK, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Childrens Panadol Cold Relief Elixir *GSK Consumer, Austral.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; fever; pain; nasal congestion.

Childrens PediaCare Nighttime Cough *Pfizer, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Cough.

Childrens Runny Nose Relief *Brauer, Austral.*
Arsenicum album (p. 2448·1); hepar sulfuris (p. 1721·3); kali bichromicum (p. 2476·3); nux vomica (p. 2573·3); euphrasia officinalis (p. 2502·1); natrium muriaticum (p. 1795·1); allium cepa (p. 2575·2); hydrastis canadensis (p. 2528·1); kali iodatum (p. 2336·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Childrens Sleep *Brauer, Austral.*
Arsenicum album (p. 2448·1); belladonna (p. 2453·3); chamomilla (p. 2474·1); aconitum napellus (p. 2428·3); gelsemium (p. 2511·2); nux vomica (p. 2573·3); coffea (p. 2648·2); pulsatilla (p. 2600·2); ignatia (p. 2532·1).
Homoeopathic preparation.

Childrens Sudafed Cold & Cough *Warner-Lambert, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Childrens Sudafed Nasal Decongestant *Warner-Lambert, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Children's SunKist Multivitamins Complete *Ciba, USA.*
Vitamins; minerals.

Children's SunKist Multivitamins + Extra C *Ciba, USA.*
Vitamins.

Childrens Tylenol *Johnson & Johnson, China.*
Paracetamol (p. 115·1).
Fever; pain.

Childrens Tylenol Cold *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; allergy symptoms.

Childrens Tylenol Cold & Cough *Johnson & Johnson, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Childrens Tylenol Cold and Cough *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Childrens Tylenol Cough and Runny Nose *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Childrens Tylenol Decongestant *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Childryl *Mandar, India.*
Pholcodine (p. 1675·1); promethazine hydrochloride (p. 638·2).

Chill Blast *Redken, Canad.†*
Pyrithione zinc (p. 1718·1).

Chill Pill *Cenovis, Austral.*
Rhodiola rosea; lupulus (p. 2546·1).
Anxiety; tonic.

Chilvax *Proel, Gr.*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Chilvit-Cee *QX, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Chimar *Menarini, Port.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).
Adjunct to antibiotics; respiratory-tract congestion; oedema; inflammation.

Chimax *Chiron, UK.*
Flutamide (p. 798·2).
Prostatic cancer.

Chimono *Lusofarmaco, Ital.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

China *Agri-Pharma, Hung.*
Ferric ammonium citrate (p. 2060·1); manganese hypophosphite (p. 2530·3); china; bitter orange (p. 2575·3).
Iron deficiency; iron supplement.

China Med Complex *Dynamit, Austria.*
Acidum phosphoricum (p. 2589·1); calcium phosphoricum (p. 1784·2); china (p. 2478·3); ferrum phosphoricum (p. 2077·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

China Oel *Bio-Diat, Israel; Pronovo, Turk.†*
Peppermint oil (p. 1877·1).
Cold symptoms; gastrointestinal disorders; respiratory-tract disorders.

China-Balsam
Note: this name may be used for preparations of different composition.
Penta, Hung.
Camphor (p. 2466·2); clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); Norway spruce oil; menthol (p. 2553·2).
Cough and cold symptoms; bronchitis; musculoskeletal and joint pain.

Chinacin-T *Chinta, Thai.*
Clindamycin (p. 269·3).
Acne.

China-Eisenwein *Mayrhofer, Austria.†*
Mace flowers (p. 2547·3); gentian (p. 2512·1); bitter-orange peel (p. 2575·3); centaury (p. 2473·2); ceratonia (p. 2178·1); cinchona bark (p. 2478·3); cinnamon (p. 2479·2); ferrous citrate (p. 2073·1); ferrous ascorbate (p. 2060·3).
Tonic.

China-Oil *Penta, Hung.*
Peppermint oil (p. 1877·1).
Gastrointestinal disorders; cold symptoms; musculoskeletal and joint pain.

Chinclona *Chinta, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Chinclonac *Chinta, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Chingasu *Alkem, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Chingazol *Chinta, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections; trichomoniasis; vaginal candidiasis.

Chingazone *Chinta, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone valerate (p. 1624·1).

Chinnol *Chinta, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Chinnolol *Chinta, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; arrhythmias; migraine; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor.

Chinocid *SF, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Chinofen *Chandra Bhagat, India.*
Baclofen (p. 2014·3).
Spasticity.

Chinofucin-LH *Lekhim, Ukr.*
Chlorquinaldol (p. 260·1).
Vulvovaginal infections.

Chinofungin *Sanofi-Aventis, Hung.*
Tolnaftate (p. 596·1).
Fungal skin and nail infections.

Chinopamil *PannonPharma, Hung.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Chinoplus *Angelini, Gr.; Angelini, Ital.; Medagro, Pol.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Chinosol *Dermapharm, Ger.*
Hydroxyquinoline sulfate (p. 2530·1); potassium sulfate (p. 1793·2).
Skin disinfection.

Chinotal *PannonPharma, Hung.*
Pentoxifylline (p. 1465·3).
Peripheral and cerebral vascular disorders; vascular eye disorders.

Chinovate *Chinta, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Chintacold *Chinta, Thai.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Cold symptoms.

Chinta-lax *Chinta, Thai.*
Bisacodyl (p. 1821·1); docusate sodium (p. 1836·2).
Constipation.

Chintamet *Chinta, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Chintaral *Chinta, Thai.*
Ketoconazole (p. 585·3).
Scalp disorders.

Chintasma *Chinta, Thai.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Chintavit *Chinta, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Chinteina *Lafare, Ital.†*
Quinidine sulfate (p. 1481·2).
Arrhythmias.

Chintoral *Chinta, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Chiny *Positif, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Chiny-GP *Positif, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Chiosan *Lafedar, Arg.*
⊗Tetryzoline hydrochloride (p. 1678·3).

Chipil *Fontelabor, Port.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

ChiRhoStim *ChiRhoClin, USA.*
Secretin (synthetic, human) (p. 2612·2).
Assessment of pancreatic function; diagnosis of gastrinoma.

Chiro Des *Kosmidis, Gr.*
Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3).
Disinfection.

Chirocaina *Abbott, Chile; Abbott, Venez.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Chirocaine *Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, China; Abbott, Cz.; AbbVie, Fin.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.†; Abbott, Irl.; Abbott, Ital.; AbbVie, Neth.; Abbott, Port.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Swed.; AbbVie, Switz.; Abbott, Thai.; Abbott, Turk.; AbbVie, UK.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia; pain.

Chirocaïne *Abbott, Fr.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Chirocane *AbbVie, Spain.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Chiroflu *Novartis Vaccines, Port.; Novartis Vaccines, Spain.*
An inactivated influenza vaccine (subunits) (p. 2393·3).
Active immunisation.

Chirofossat *Dreluso, Ger.*
Symphytum (p. 2484·2); arnica (p. 2447·2); gelsemium (p. 2511·2); euphorbium; argentum colloidale (p. 2616·2); calcium carbonic. (p. 1824·3); cobaltum chlorat. (p. 2482·2).
Homoeopathic preparation.

Chirogesic *Hebert, Canad.*
Diethylamine salicylate (p. 51·3).

Chiromas *Novartis Vaccines, Spain.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Chiron Barrier Cream *Portex, UK.*
Aluminium chlorohydrate (p. 1694·1).

Chiron IL-2 *Key Oncologics, S.Afr.*
Aldesleukin (p. 810·1).
Renal cell carcinoma; malignant melanoma.

Chironair Odour Control Liquid *Coloplast, UK.*
A deodorant for use with colostomies and ileostomies.

Chisan *Green Medicine, Swed.*
Schisandra (p. 2611·2); Siberian ginseng (p. 2614·3); rhodiola rosea.
Tonic.

Chisandra *Green Medicine, Swed.*
Schisandra (p. 2611·2); Siberian ginseng (p. 2614·3).
Tonic.

Chitaq *Chitin, Hong Kong.*
N-Acetyl glucosamine (p. 2515·3).
Arthritis.

Chitoderm *Pietrasanta, Ital.*
Poliglusam (p. 2593·2).

Chitodine *IMS, Ital.†*
Iodine (p. 2336·3).
Skin and wound disinfection.

Chito-Lafarmen *Lafarmen, Arg.*
Poliglusam (p. 2593·2).
Obesity.

Chiton *INTES, Ital.*
Vitamin B substances (p. 2102·3); methionine (p. 1558·2); copper (p. 2057·1); zinc (p. 2126·1); omega-3 marine triglycerides (p. 1460·3); omega-6 omega-6marine.
Nutritional supplement.

Chitosano *SIRC, Singapore.*
Poliglusam (p. 2593·2); citrus aurantium (p. 2575·3); garcinia cambogia (p. 2510·2); iodine (p. 2336·3); chromium (p. 2055·3); vitamin C (p. 2110·3); guar gum (p. 475·1); zinc sulfate (p. 2126·2); ferrous gluconate (p. 2061·2); vanadium pentoxide.
Dietary aid in weight reduction.

Chitosyl *Biological E, India.*
Poliglusam (p. 2593·2); ispaghula (p. 1849·1).

Chlamydicin *Heremco, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Chlo Tuss EX *McNeil, USA.*
Clofedanol hydrochloride (p. 1659·1); guaifenesin (p. 1666·2).
Cough.

Chlo-Amine *Hollister-Stier, USA.†*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlobax *Beacons, Singapore.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal disorders.

Chloe *Zentiva, Cz.; Zentiva, Pol.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-induced acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Zentiva, Rus.
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgen-induced acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Chlopazine *Condrugs, Thai.*
Chlorpromazine hydrochloride (p. 1045·2).
Bipolar disorder; schizophrenia; nausea and vomiting; hiccup.

Chlophe *TNP, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlophen *Medicine Products, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlor-3 *Fleming, USA.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Medical condiment; table salt substitute.

Chloracil *Siam Bheasach, Thai.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chloraethyl Dr Henning *Henning Walldorf, Ger.; Henning, Israel.*
Ethyl chloride (p. 1987·1).
Local anaesthesia.

Chlorafast *Arrow, NZ.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chlorafed *Roberts, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Chlorahist *Burapha, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chloraldurat *Pohl, Ger.†; Lubapharm, Switz.†*
Cloral hydrate (p. 1055·2).
Insomnia; sedative; sleep disorders; nervous disorders.

Chloram *PC India, India.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chloramex *Actavis, Indon.; Aspen, Malaysia; Aspen, S. Afr.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chloramin T *Lysoform, Ger.*
Tosylchloramide sodium (p. 1773·1).
Surfæce disinfection; hand disinfection.

Chloramine
Note: this name may be used for preparations of different composition.
Christo, Hong Kong†; Beacons, Singapore.
Chlorphenamine (p. 620·3).
Allergic skin disorders; allergic rhinitis.

CCM, Malaysia.
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Picco, Thai.
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Chloramine-S *Utopian, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chloramno *Milano, Thai.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chloram-P *PP Lab, Thai.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Chloramphecort *Kimia, Indon.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Chloramphecort-H *Kimia, Indon.*
⊗Prednisolone (p. 1645·2); chloramphenicol (p. 257·1).
Infected skin disorders.

Chloramsone *Ranbaxy, India.*
⊗Chloramphenicol (p. 257·1); prednisolone acetate (p. 1645·2).
Infected inflammatory eye and ear disorders.

Chloranic *Norma (Νορμα), Gr.*
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Chlorapred *Demo, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Bacterial eye infections with inflammation.

ChloraPrep *CareFusion, Fin.; CareFusion, Irl.; CareFusion, Neth.; CareFusion, UK.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Chloraprep *Novex, Fr.; CareFusion, Swed.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Chlorascrub *PDI, USA.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Chloraseptic Kids Sore Throat Spray *Prestige, USA.*
Phenol (p. 1763·3).
Formerly known as Childrens Vicks Chloraseptic Spray.
Sore throat.

Chloraseptic Sore Throat *Prestige, USA.*
Lozenges: Benzocaine (p. 1980·2); menthol (p. 2553·2).
Formerly known as Vicks Chloraseptic Sore Throat.
Sore throat.

Prestige, USA.
Throat spray: Phenol (p. 1763·3).
Formerly known as Vicks Chloraseptic.
Minor mouth or throat irritation.

Chloraseptic Total Sore Throat & Cough *Medtech, USA.*
Benzocaine (p. 1980·2); dextromethorphan hydrobromide (p. 1660·1).
Cough; sore throat.

Chloraseptine *Sterop, Belg.*
Tosylchloramide sodium (p. 1773·1).
Disinfection; water purification.

Chlorasol *Seton, Israel.*
Sodium hypochlorite (p. 1768·3).
Cleansing of skin ulcers and pressure sores.

Chloraxin *Cipla, India.*
Chloramphenicol (p. 257·1), chloramphenicol palmitate (p. 257·1), or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Chlorazin *Streuli, Switz.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; pruritus; nausea; vomiting; vertigo; pain.

Chlorazol *Qualiphar, Belg.*
Tosylchloramide sodium (p. 1773·1).
Disinfection.

Chlorbicap *SSP, Thai.*
Thiamine hydrochloride (p. 2103·1).
Thiamine deficiency.

Chlorbiotic *Bernofarm, Indon.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chlorchinaldin *Valeant, Ukr.†*
Chlorquinaldol (p. 260·1).
Stomatitis; glossitis; gingivitis; fungal mouth and throat infections.

Chlorchinaldin H *Chema-Elektromet, Pol.*
⊗Chlorquinaldol (p. 260·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Chlorchol *Adcock Ingram, S.Afr.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chlorcol *Adcock Ingram, S.Afr.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chlordex GP *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Chlordibrax *Utopian, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).

Chlordixide *LSP, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; insomnia.

Chlordon *Acdhon, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlordrine *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Chlorectil Plus *Saga, India.*
Chlorpromazine hydrochloride (p. 1045·2); trihexyphenidyl hydrochloride (p. 917·3).

Chloresium *Rystan, USA.†*
Chlorophyllin copper complex (p. 2178·3).
Wound healing; relief of malodour of wounds and ulcers.

Chloréthyl *Merz, Switz.†*
Ethyl chloride (p. 1987·1).
Local anaesthesia.

Chlorex-A *Cypress, USA.†*
Phenyltoloxamine citrate (p. 638·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Chlorformin *Cadila, India.*
Chlorpropamide (p. 470·1); phenformin hydrochloride (p. 493·1).
Diabetes mellitus.

Chlorgest *Ranbaxy, Thai.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Chlorhex *Milano, Thai.; Polipharm, Thai.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Chlorhexamed *GSK, Austria; GSK Consumer, Ger.; GSK Consumer, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; mouth and throat infections.

Chlorhex-C *Polipharm, Thai.†*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection.

Chlorhexseptic *Pharmascience, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection.

Chlorhist Baby Cough *Sriprasit, Thai.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Chlorhist Cough *Sriprasit, Thai.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).
Cough.

Chlorizok *Dabur, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Chlorleate *Silom, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions; insect bites.

Chlorleate Expectorant *Silom, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; nasal congestion.

Chlor-Mes *Cypress, USA.*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; upper-respiratory-tract allergies.

Chlor-Mes D *Cypress, USA.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Respiratory-tract congestion; rhinitis; sinusitis.

Chlor-Mes Jr *Cypress, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract symptoms associated with allergies; cold symptoms.

Chlormet *Sun, India.*
Chloramphenicol (p. 257·1).
Eye infections.

Chlormet-DM *Sun, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Chlormin *Tai Yu, Philipp.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlormine *DHA, Malaysia; DHA, Singapore.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlorminol *Universal, Hong Kong.†*
Chlorphenamine (p. 620·3).

Chlormixin *Noir, India.†*
Polymyxin B sulfate (p. 342·3); chloramphenicol (p. 257·1).
Bacterial eye infections.

Chlornamol *Beacons, Singapore.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Hypersensitivity reactions; pain; fever.

Chlornicol *Thebe, S.Afr.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chlorocaire *PediaCare, Philipp.*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Chlorochin *Streuli, Switz.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; polyarthritis.

Chlorocin
Note: this name may be used for preparations of different composition.
Jagsonpal, India.
Chloramphenicol (p. 257·1).
Bacterial infections.

Deltapharm, Hong Kong.†
Chloroquine (p. 650·1).

Chlorocollyre *Cooper (Κοπερ), Gr.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chlorocyclinum *Chema-Elektromet, Pol.*
Chlortetracycline hydrochloride (p. 260·2).
Infected skin disorders.

Chlorofarm-S *Biostam (Βιοστάμ), Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Chlorofoz *Am-Europharma, Philipp.*
Chloroquine phosphate (p. 650·1).
Amoebic infections; malaria; lupus erythematosus.

Chlorohex *Colgate-Palmolive, UK.*
Chlorhexidine gluconate (p. 1743·3).
Mouth infections; oral hygiene.

Geistlich, Singapore.
Chlorhexidine (p. 1743·2).
Skin and wound disinfection.

Chlorohistol *Julphar, UAE.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlorolex *Lexica, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; amoebiasis; rheumatoid arthritis.

Chloromag *Merit, USA.*
Magnesium chloride (p. 1787·1).

Chloromagnésion *PPDH, Fr.†*
Magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1).
Magnesium deficiency.

Chloromax *Oboi, Philipp.*
Chloroquine phosphate (p. 650·1).
Malaria.

Chloromycetin *Elea, Arg.; Pfizer, Austral.; Erfa, Canad.; Pfizer, Chile†; Pfizer, Fin.; Pfizer, India; Goldshield, Irl.; Pfizer, Mex.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Swed.; Goldshield, UK; Monarch, USA.†*
Chloramphenicol (p. 257·1), chloramphenicol palmitate (p. 257·1), or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Chloromycetin Ear Drops *Pfizer, India.*
Chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Bacterial ear infections.

Chloromyk *Elvipe, Gr.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Chloronguent *Pharmacobel, Belg.*
Tosylchloramide sodium (p. 1773·1).
Wounds.

Chloropect *Adcock Ingram, S.Afr.*
⊗Kaolin (p. 1850·1); pectin (p. 2200·3); bismuth subcarbonate (p. 1822·1); chloroform and morphine tincture (p. 92·3).
Diarrhoea.

Chloropernazinum *Labor, Pol.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; vestibular disorders; migraine; schizophrenia; mania.

Chloroph *Seng, Hong Kong; Seng, Thai.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chlorophyll *Potter's, UK.*
Kola nut (p. 2648·2); chlorophyllin (p. 2178·3).
Tonic.

Chlorophyllipt *Arterium, Ukr.*
Chlorophylls A and B (p. 2178·3).
Staphylococcal infections.

Vifitekh, Rus.
Eucalyptus (p. 2501·1).
Inflammation; infections.

Chloropotassuril *Melisana, Belg.*
Potassium chloride (p. 1793·2).
Potassium depletion.

Chloroptic *Allergan, Canad.†; Alvia (Αλβια), Gr.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chloro-S *Medic+Aid, Philipp.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Chlorosept *Sani-Marc, Canad.†*
Triclosan (p. 1773·2).

Chlorosin *General Drugs, Thai.†*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Chlorosteran *Coup, Gr.*
Fenofibrate (p. 1381·1).

Chlorotracin *Chew, Thai.†*
Chloramphenicol (p. 257·1); clioquinol (p. 273·1); phthalylsulfathiazole (p. 339·3).
Gastrointestinal infections.

Chloro-V *Vista, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial ear infections.

Chlorphed-LA *Hauck, USA; Roberts, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Chlorphedrine SR *Goldline, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Chlorphemin *Tanabe, Indon.*
⊗Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); alcohol (p. 1733·1).
Cough; respiratory-tract congestion.

Chlorphen *Caps, S.Afr.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Chlorphencap *SSP, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlorphenicol *Rekah, Israel.*
Chloramphenicol (p. 257·1).
Bacterial skin infections.

Chlorpheno *Milano, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlorphenon *Ethica, Indon.†; Soho, Indon.†*
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

Chlor-Pro *Schein, USA.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlorpromasit *Sriprasit, Thai.†*
Chlorpromazine (p. 1045·2).
Behaviour disorders in children; nausea and vomiting; psychoses.

Chlorpromed *Medifive, Thai.*
Chlorpromazine hydrochloride (p. 1045·2).
Sedative; schizophrenia; mania; nausea and vomiting.

Chlor-Pyrad *United Drug, Thai.*
Chloramphenicol (p. 257·1).
Bacterial skin infections.

Chlorpyrimine *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlorquin *Aspen, Austral.†; Healthcare Logistics, NZ.†*
Chloroquine phosphate (p. 650·1).
Malaria; amoebic hepatitis; lupus erythematosus; rheumatoid arthritis and related collagen disease.

Chlorsedyl *Beacons, Singapore.*
⊗Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2).
Hypersensitivity reactions; cough; respiratory-tract congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Chlorsep *Atlantic, Thai.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Chlorsig *Aspen, Austral.; Sigma, Hong Kong; Healthcare Logistics, NZ; Sigma, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Chlorsuccillin *Jelfa, Pol.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

ChlorTan *Cypress, USA.*
Chlorphenamine tannate (p. 620·3).
Hay fever.

ChlorTan D *Cypress, USA.*
Chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Hay fever; sinusitis.

Chlortralim *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlortetracycline hydrochloride (p. 260·2).
Bacterial eye infections.

Chlor-Trimeton *Schering-Plough, Philipp.; Schering-Plough, USA.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Chlor-Trimeton Allergy 4 Hour *Schering-Plough, USA.*
Chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Chlor-Trimeton 4 Hour Relief *Schering-Plough, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Chlor-Trimeton 12 Hour Relief *Schering-Plough, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Chlor-Tripolon *Schering-Plough, Canad.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity disorders; pruritus.

Chlor-Tripolon ND *Schering-Plough, Canad.†*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion.

Chlorumagène *SERP, Mon.*
Magnesium hydroxide (p. 1857·2).
Constipation.

Chlorvescent *Aspen, Austral.*
Potassium chloride (p. 1793·2); potassium bicarbonate (p. 1780·3); potassium carbonate (p. 2595·2).
Potassium deficiency.

Healthcare Logistics, NZ.
Potassium chloride (p. 1793·2).
Potassium deficiency.

Chlorvytol *Tolmann, Philipp.†*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); lysine (p. 2079·3); taurine (p. 2626·2); chlorella (p. 2475·3).
Nutritional supplement.

Chlorzep *Bemed, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).

Chlorzox *Pharmasant, Thai.*
Chlorzoxazone (p. 2022·2).
Skeletal muscle pain and spasm.

Chlosol *Biok, Rus.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium acetate (p. 1781·1).
Hypovolaemia.

Chlotenor *Sandoz, Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Chlotrip *East West, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Choanol N *Hanosan, Ger.*
Veronica virginica; quassia amara (p. 2601·1); strychnos nux-vomica (p. 2573·3); lycopodium clavulatum (p. 2547·1).
Homoeopathic preparation.

Choats Extract of Lettuce Cough Mixture *Pfizer Consumer, S.Afr.†*
Lettuce (p. 2647·3); tolu balsam (p. 1679·2); honey (p. 2072·1).
Cough.

Chocaton *Mirren, S.Afr.*
Vitamins.

Chocovite *Torbet, Irl.†*
Calcium gluconate (p. 1783·3); ergocalciferol (p. 2113·3).
Calcium deficiency.

Chocy *Biomax, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Chofabol *Allen, Mex.*
Magnesium sulfate (p. 1787·3); boldo (p. 2458·3); cynara (p. 2490·3); belladonna (p. 2453·3); peptone (p. 2086·2).
Biliary-tract disorders.

Chofitol *Millet-Franklin, Arg.*
Cynara (p. 2490·3).
Biliary-tract disorders; disorders of fat digestion.

Chofitol Plus *Millet-Franklin, Arg.*
Cynara (p. 2490·3); boldo (p. 2458·3); wild carrot (p. 2647·2); menthol (p. 2553·2).
Biliary-tract disorders; disorders of fat digestion.

Chofrafig *Bio Macro, Braz.*
Choline citrate (p. 2055·2); betaine (p. 2456·1); methionine (p. 1558·2).

Chofranina *De Mayo, Braz.†*
Cascara (p. 1826·1); cynara (p. 2490·3); carmellose (p. 2175·1).
Constipation.

Choice *DKT, India.*
21 Tablets ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Choice DM *Mead Johnson, Philipp.; BMS, USA.*
Preparation for enteral nutrition.
Abnormal glucose tolerance.

BMS, USA.
Test for glycated haemoglobin in blood (p. 2516·3).

Choice DM Daily Moisturizing *BMS, USA.*
Emollient.

Choice DM Gentle Care *BMS, USA.*
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Choijokito *Tsumura, Jpn.*
Rhubarb (p. 1884·2); liquorice (p. 1853·2); mirabilitum.
Traditional Kampo medicine.

Cholagogum *Cassella-med, Ger.*
Cynara (p. 2490·3).
Dyspepsia.

Cholagol *Teva, Cz.*
Frangula bark (p. 1843·3); magnesium salicylate (p. 85·2); turmeric (p. 2218·1); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2).
Biliary and liver disorders.

Teva, Hung.
Frangula (p. 1843·3); magnesium salicylate (p. 85·2); turmeric (p. 2218·1).
Biliary-tract disorders.

Teva, Rus.; Teva, Ukr.
Emodin buckthorn; magnesium salicylate (p. 85·2); turmeric (p. 2218·1); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2).
Biliary-tract disorders.

Chol-Aid *Chefaro, UK.*
Policosanol (p. 1472·1); omega-3 fish oil (p. 1460·3).
Dietary supplement.

Cholal Modificado *Italmex, Mex.*
⊗Liver antitoxin (p. 2444·1); sodium sulfate (p. 1888·1); magnesium sulfate (p. 1787·3); sodium chloride (p. 1795·1); potassium nitrate (p. 1766·2).
Biliary-tract disorders; liver disorders.

Cholamid *Polfa Pabianice, Pol.*
Methylnicotinamide.
Biliary-tract and liver disorders.

Cholan-HMB *Ciba Consumer, USA.*
Dehydrocholic acid (p. 2492·1).
Constipation; biliary stasis.

Chola-Plantin N *Infirmarius, Ger.†*
Berberis vulgaris (p. 2502·1); carduus marianus (p. 1561·1); leptandra; podophyllum peltatum (p. 1717·1).
Homoeopathic preparation.

Cholaplus *Arkopharma, Belg.*
Cynara (p. 2490·3).
Biliary disorders.

Chol-Arbuz NF *Bittermedizin, Ger.*
⊗Pancreatin (p. 2579·3); turmeric (p. 2218·1).
Digestive disorders.

Cholarex *Vachon, Canad.*
Boldo (p. 2458·3).
Digestive disorders.

Cholasyl *Biropharma, Hung.*
Fennel oil (p. 2503·3); peppermint oil (p. 1877·1); cinnamon oil (p. 2479·3); menthol (p. 2553·2).
Gastrointestinal disorders.

Cholavisol *Herbapol Krakow, Pol.*
Taraxacum (p. 2625·3); helichrysum; peppermint leaf (p. 1877·1); achillea (p. 2427·3); frangula bark (p. 1843·3); greater celandine (p. 2522·2).
Digestive disorders.

Cholax *Maver, Chile.*
Senna (p. 1885·1).
Constipation.

Cholbalance *Ikapharmindo, Indon.*
Plant stanol ester (p. 1471·2).
Hyperlipidaemias.

Chol-Do *Grasler, Ger.*
Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); cholesterinum (p. 2179·1); solidago virgaurea (p. 2620·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Cholebine *Mitsubishi, Jpn.*
Colestilan (p. 1345·2).
Hypercholesterolaemia.

Cholecheck *Indoco, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Cholecis *Schering, UK.*
Technetium-99m mebrofenin (p. 2228·1).
Assessment of liver function; hepatobiliary imaging.

Chole-cyl L Ho-Len-Complex *Liebermann, Ger.*
Berberis; carduus marianus (p. 1561·1); cholesterinum (p. 2179·1); colocynthis (p. 1833·3); taraxacum (p. 2625·3).
Homoeopathic preparation.

Cholediam *Mediam, Irl.; Mediam, Neth.†*
Technetium-99m mebrofenin (p. 2228·1).
Radionuclide imaging of the liver and biliary-tract.

Choledius *Talion-A, Ukr.*
Chelidonium majus (p. 2522·2); milk thistle (p. 1561·1); berberis vulgaris (p. 2502·1); podophyllum peltatum (p. 1717·1).
Homoeopathic preparation.

Choledyl *Erfa, Canad.; Galenica, Gr.*
Choline theophyllinate (p. 1207·1).
Obstructive airways disease; asthma.

Choledyl Expectorant *Erfa, Canad.*
Choline theophyllinate (p. 1207·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Cholemax *Marbiopharm, Rus.*
Rose fruit (p. 2607·1).
Cholecystitis.

Cholemed *3DDD, Belg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cholenzim *Biosintez, Rus.*
Bile (p. 2457·2); pancreas (p. 2579·3); intestinal mucous membrane (p. 2444·1).
Gastrointestinal disorders.

Choleodoron *Weleda, Austria; Weleda, Canad.†; Weleda, Ger.†; Weleda, Neth.; Weleda, S.Afr.†; Weleda, Switz.; Weleda, UK.*
Greater celandine (p. 2522·2); Javanese turmeric (p. 2636·2).
Homoeopathic preparation; liver and biliary-tract disorders.

Choléodoron *Weleda, Fr.*
Chelidonium majus (p. 2522·2); curcuma zanthorrhiza (p. 2636·2).
Homoeopathic preparation.

Cholergol *Inga, India.*
Nicergoline (p. 2569·1).
Cerebrovascular insufficiency; peripheral vascular disorders.

Cholescor *Ethica, Indon.*
Monascus purpureus Went.
Hyperlipidaemias.

Cholesol *Herbapol Wroclaw, Pol.*
Chamomile (p. 2474·1); equisetum (p. 2500·1); frangula (p. 1843·3); St John's wort (p. 449·1); rose fruit (p. 2607·1); taraxacum (p. 2625·3); coriander (p. 2486·3); juniper (p. 2537·1); helichrysum; knotgrass (p. 2538·2).
Liver disorders; biliary-tract disorders.

Cholespar *Pharos, Indon.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Cholestad *Littman, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; coronary heart disease.

Cholestagel *Genzyme, Austria; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Irl.; Genzyme, Israel; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Genzyme, Spain; Genzyme, Swed.; Genzyme, UK.*
Colesevelam hydrochloride (p. 1345·1).
Hypercholesterolaemia.

Cholestat
Note: this name may be used for preparations of different composition.
Kalbe, Indon.; Kalbe, Singapore.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; hyperlipidaemias; cardiovascular risk reduction.

Kopran, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Choleste *Ranbaxy, S.Afr.*
Simvastatin (p. 1489·2).

Cholestenorm *Natur Produkt, Rus.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Cholesterol Health *Blackmores, Austral.*
Phytosterols (p. 1471·2); betacarotene (p. 2051·1).
Dietary supplement; hypercholesterolaemia.

Cholesterol Support *Reese, USA.*
Sitosterol (p. 1471·2); zinc citrate (p. 2126·2).

Cholesterolum Complexe No 112 *Lehning, Fr.†*
Atropa belladonna (p. 2453·3); carduus marianus (p. 1561·1); berberis vulgaris (p. 2502·1); leptandra; nux vomica (p. 2573·3); terebenthina; bryonia (p. 2461·3); sulfur (p. 1721·1); cholesterinum (p. 2179·1).
Homoeopathic preparation.

Cholestil *Polfa, Cz.; Polfa Pabianice, Pol.*
Hymecromone (p. 2530·2).
Biliary-tract disorders; liver disorders.

Cholestin *Pharmanex, USA.*
Citrus polymethoxylated flavones; geraniol (p. 2512·2); omega-3 fatty acids (p. 1460·1); tocotrienols.
Formerly contained policosanol.
Nutritional supplement.

Cholesvit *Graha, Indon.*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Hypercholesterolaemia.

Choletec *Bracco, USA.*
Technetium-99m mebrofenin (p. 2228·1).
Hepatobiliary imaging.

Cholevas *Sel-J, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cholevast *Nutramedica, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Cholevist *Domesco, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cholex *Silanes, Mex.*
Menthol (p. 2553·2); pinene (p. 2591·3); menthone (p. 2554·2); borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1).
Biliary-tract disorders.

Cholexamin *Kyorin, Jpn.*
Nicomol (p. 1446·2).
Hyperlipidaemias; peripheral circulatory disorders.

Cholexin *Armoxindo, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cholhepan *Doctum, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Cholhepan N *Schuck, Ger.*
Milk thistle (p. 1561·1); greater celandine (p. 2522·2); aloes (p. 1816·1).
Constipation.

Choliatron *Lusomedicamenta, Port.*
Trepibutone (p. 2633·3).
Biliary-tract disorders.

Cholimed *Metiska, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebral infarction; hemiplegia; pancreatitis.

Cholinaar *Novell, Indon.*
Citicoline (p. 2480·1).
Head injury; stroke; hemiplegia.

Cholinerv *Therapharma, Philipp.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; head injury.

Cholinex *GSK, Pol.*
Choline salicylate (p. 39·2).
Mouth and throat disorders.

Cholinogo *Pasteur, Chile.†*
Peptone (p. 2086·2); magnesium sulfate (p. 1787·3).
Biliary-tract and liver disorders.

Cholinoid *Goldline, USA.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); choline bitartrate (p. 2055·2); inositol (p. 2533·2); lemon bioflavonoids (p. 2505·2).

Cholipin *Vargas, Venez.*
Fenipentol (p. 2503·1); octibenzonium bromide.
Biliary-tract disorders; digestive disorders.

Colipravin *Kleva, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Choliren *Unipharma, Gr.*
Hymecromone (p. 2530·2).
Spasmolytic.

Cholisal *Jelfa, Rus.; Jelfa, Ukr.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Mouth disorders.

Cholisept Intensive *GSK Consumer, Pol.*
Benzalkonium chloride (p. 1737·1); hexylresorcinol (p. 1755·1).
Sore throat.

Cholitilin *Kanonfarma, Rus.*
Choline alfoscerate (p. 389·2).
Cerebrovascular disorders; dementia.

Cholitiline *Firma Ferment, Rus.*
Choline alfoscerate (p. 389·2).
Cerebrovascular disorders; dementia.

Cholitol *Herbapol Krakow, Pol.*
Belladonna (p. 2453·3); greater celandine (p. 2522·2); turmeric (p. 2218·1); peppermint leaf (p. 1877·1); taraxacum (p. 2625·3); valerian (p. 2640·2).
Biliary-tract disorders.

Cholit-Ursan *Stada, Ger.†*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones.

Choliver *Hau Giang, Ukr.†*
Bile extract (p. 2457·2); cynara (p. 2490·3); curcuma longa (p. 2218·1).
Biliary-tract and liver disorders.

Chol-Kugeletten Neu *Dolorgiet, Ger.†*
Greater celandine (p. 2522·2); aloes (p. 1816·1).
Constipation.

Cholo 2-injektopas *Pascoe, Ger.*
Carduus marianus (p. 1561·1); quassia amara (p. 2601·1); taraxacum (p. 2625·3); chelidonium (p. 2522·2); butternut (p. 2463·2); lycopodium (p. 2546·3).
Homoeopathic preparation.

Cholofalk *Falk, Ger.†*
Ursodeoxycholic acid (p. 2638·1).
Primary biliary cirrhosis.

Colografin *Bracco, Canad.; Squibb Diagnostics, USA.*
Meglumine adipiodone (p. 1581·1).
Contrast medium for biliary-tract radiography.

Cholos *Vifiteh, Rus.*
Rose fruit (p. 2607·1).
Vitamin deficiency.

Cholosas *Altayvitamin, Rus.; KVZ, Ukr.*
Rose fruit (p. 2607·1).
Cholecystitis; biliary-tract and liver disorders.

Cholspas *Dolorgiet, Ger.†*
Pipenzolate bromide (p. 1878·1).
Gastrointestinal disorders.

Cholspasmin *Dolorgiet, Ger.*
Hymecromone (p. 2530·2).
Biliary-tract disorders.

Chol-Spasmoletten *Dolorgiet, Ger.*
Hymecromone (p. 2530·2).
Biliary disorders.

Cholstat
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Ivax, Irl.†
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Choludexan *World Medicine, Ukr.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; biliary cirrhosis; gastritis with bile reflux.

Cholvasim *Shin Poong, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Cholvast *Biofarma, Turk.*
Atorvastatin calcium (p. 1309·2).

Cholvastin
Note: this name may be used for preparations of different composition.
Sanbe, Indon.
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Douglas, NZ.
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction; stroke prophylaxis.

Cholyte Plus With Zinc *Pediapharma, Philipp.*
Glucose (p. 2068·3); sucrose (p. 2096·3); electrolytes (p. 1775·1) (p. 1780·1).
Oral rehydration solution; diarrhoea.

Chomelanum *Schur, Ger.†*
Choline stearate.
Burns; insect stings; skin disorders; soft-tissue disorders.

Chondrasil *Farmak, Ukr.†*
Chondroitin sulfate sodium (p. 2476·1); dimethyl sulfoxide (p. 2182·2).
Degenerative joint disorders.

Chondril *Hovid, Malaysia.†*
Chondroitin sulfate (p. 2476·1).
Dietary supplement.

ChondroCelect *TiGenix, Austria; TiGenix, Belg.; TiGenix, Cz.; TiGenix, Irl.; TiGenix, Pol.; TiGenix, Port.; TiGenix, Spain.*
Cartilage (p. 2471·3).
Cartilage defects in the knee.

Chondrogard *Soteks, Rus.*
Chondroitin sulfate (p. 2476·1).
Joint disorders.

Chondroitin Complex *Phytopharm, Ukr.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Degenerative joint disorders.

Chondroitine-Akos *Sintez, Rus.*
Capsules: Chondroitin sulfate (p. 2476·1).
Osteoarthritis; osteochondrosis of the spine.

Sintez, Rus.
Ointment: Chondroitin sulfate (p. 2476·1); dimethyl sulfoxide (p. 2182·2).
Degenerative joint disorders.

Chondrolife *Biok, Rus.*
Chondroitin sulfate (p. 2476·1).
Joint disorders.

Chondrolon *Microgen, Rus.*
Chondroitin sulfate sodium (p. 2476·1).
Degenerative joint disorders.

Chondromel *IBSA, Irl.*
Chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Chondro-PA *Landson, Indon.*
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); minerals; vitamin C (p. 2110·3).
Osteoarthritis.

Chondrostad *Stada, Cz.*
Glucosamine sulfate sodium (p. 2515·3).
Osteoarthritis of the knee.

Chondrosteo *Equilibre Attitude, Fr.*
Glucosamine sulfate (p. 2515·3); maltodextrin (p. 2080·3); chondroitin sulfate (p. 2476·1); devil's claw root (p. 42·3); meadowsweet (p. 2550·2); black currant (p. 2458·1); bamboo; minerals.
Nutritional supplement; musculoskeletal and joint disorders.

Chondrosulf *Genevrier, Fr.*
Chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis of the knee and hip.

Chondroxide *Nizpharm, Rus.; Nizhfarm, Ukr.*
Chondroitin sulfate (p. 2476·1); dimethyl sulfoxide (p. 2182·2).
Degenerative joint disorders; soft-tissue injury; osteoarthritis; osteochondrosis of the spine.

Nizpharm, Rus.
Tablets: Chondroitin sulfate (p. 2476·1).
Osteoarthritis; osteochondrosis of the spine.

Chong Tai *San Lian, China.*
Alanyl glutamine (p. 2070·2).
Parenteral nutrition.

Chooz *Schering-Plough, USA.*
Calcium carbonate (p. 1824·3).
Hyperacidity.

Chophytol *Millet Roux, Braz.; Rosa-Phytopharma, Fr.; Rosa-Phytopharma, Rus.; Uhlmann-Eyraud, Switz.; Rosa-Phytopharma, Ukr.*
Cynara (p. 2490·3).
Gastrointestinal disorders; kidney disorders; liver and biliary-tract disorders.

Chopintac *Nufarindo, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders; gastro-oesophageal reflux.

Choragon *Ferring, Belg.; Ferring, Ger.†; Ferring, Hong Kong; Ferring, Hung.; Ferring, India; Ferring, Malaysia†; Ferring, Mex.; Ferring, Neth.; Ferring, Pol.; Ferring, Rus.; Er-Kim, Turk.; Ferring, UK; Ferring, Ukr.*
⊗Chorionic gonadotrophin (p. 2258·1).
Delayed puberty; male and female infertility; cryptorchidism; male hypogonadism; amenorrhoea.

Choreazine *Alfresa, Jpn.*
Tetrabenazine (p. 2627·3).
Huntington's disease.

Choreito *Tsumura, Jpn.*
⊗Alisma rhizome; polyporus sclerotium; poria sclerotium; gelatin (p. 1154·1); talc (p. 1722·2).
Traditional Kampo medicine.

Choreitogoshimotsuto *Tsumura, Jpn.*
⊗Rehmannia root; peony root; cnidium rhizome; alisma rhizome; polyporus sclerotium; japanese angelica root (p. 2443·3); poria sclerotium; gelatin (p. 1154·1); talc (p. 1722·2).
Traditional Kampo medicine.

Choriolife *Life Medicare, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Cryptorchidism; delayed puberty; male and female infertility.

Choriomon *Meizler, Braz.; Panacea, India; CORNE, Mex.; IBSA, Switz.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility; cryptorchidism; delayed puberty; male hypogonadism.

Choron *Forest Pharmaceuticals, USA.†*
⊗Chorionic gonadotrophin (p. 2258·1).
Prepubertal cryptorchidism; male hypogonadism; male and female infertility.

Chotosan *Tsumura, Jpn.*
Gypsum; citrus unshiu peel; ophiopogon tuber; pinellia tuber; poria sclerotium; ginseng (p. 2513·3); saposhnikovia root; liquorice (p. 1853·2); ginger (p. 1844·1); uncaria hook; chrysanthemum flower.
Traditional Kampo medicine.

Chributan *Chrispa (Χρισπα), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Chricetyl *Chrispa (Χρισπα), Gr.*
Acetylcysteine (p. 1652·2).

Chrispapon *Chrispa (Χρισπα), Gr.*
Niflumic acid (p. 101·2).

Chrisracol *Christo, Hong Kong.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2); terpin hydrate (p. 1678·2); menthol (p. 2553·2).
Cold symptoms; cough; nasal congestion.

Christamol *Christo, Hong Kong.*
Oral suspension; tablets: Paracetamol (p. 115·1).
Pain; fever.

Christo, Hong Kong.†
Capsule: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Christamol Extra *Christo, Hong Kong.†*
Caffeine (p. 1203·3); paracetamol (p. 115·1).

Christatin
Note: this name may be used for preparations of different composition.
Chrispa (Χρισπα), Gr.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Christo, Hong Kong.†
Nystatin (p. 590·3).

Christon *Christo, Hong Kong.†*
Dequalinium (p. 1749·3).

Chrobifen *Elvipe, Gr.*
Ibuprofen (p. 68·2).

Chrocort *Elvipe, Gr.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Chrodin *Elvipe, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

Chrofer *Elvipe, Gr.*
Ferrous fumarate (p. 2060·3).

Chromagen *Ther-Rx, USA.†*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); intrinsic factor (stomach preparation) (p. 2534·2).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Chromagen FA *Ther-Rx, USA.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Chromagen Forte *Ther-Rx, USA.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Chromagen OB *Savage, USA.†*
Vitamins; minerals.

Chromalux *Pharos, Indon.*
Misoprostol (p. 2140·3).
NSAID-associated gastric ulcer.

Chroma-Pak *Smith & Nephew SolaPak, USA.†*
Chromium trichloride (p. 2055·3).
Additive for intravenous total parenteral nutrition solutions.

Chromargon *Richard, Fr.*
Hydroxyquinoline sulfate (p. 2530·1); acriflavinium chloride (p. 1732·3).
Skin infections.

Chromasvelt *Pharma Nord, Fr.†*
Chromium yeast (p. 2125·2).
Appetite suppressant.

Chromazol *Solas, Indon.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhagic disorders.

Chrome *Eagle, Austral.*
Chromium amino acid chelate (p. 2055·3).
Dietary supplement.

Chromelin Complexion Blender *Summers, USA.*
Dihydroxyacetone (p. 1700·1).
Vitiligo; hypopigmentation.

Chromet *Ordain, India.*
Chromium tripicolinate (p. 2056·1); metformin hydrochloride (p. 489·1).

Chrom-O-Red *Germiphene, Canad.*
Erythrosine (p. 2184·3).
Dental disclosing solution.

Chromostat *Emar, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Chromotop *AstraZeneca, India.*
Sodium cromoglicate (p. 1225·3).
Asthma.

Chromoxyl *Elvipe, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Chromo-Z *Lewison, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Chronadalate *Bayer, Fr.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Chron-ASA *Sigma, Braz.*
Mesalazine (p. 1859·2).
Ulcerative colitis; Crohn's disease.

Chronocard *Cesra, Pol.*
Crataegus (p. 2488·1).
Heart failure; arrhythmias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Chronocard N *Cesra, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Chronocorte *Streuli, Switz.†*
⊗Dexamethasone (p. 1630·3); dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Chrono-Indocid *HAC, Fr.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Chronol *Kolson's, India; Charoon Bhesaj, Thai.*
Disulfiram (p. 2495·3).
Alcoholism.

Chronostim *Medifarm Ducray, Venez.*
Saw palmetto (p. 2363·3).
Alopecia.

Chronulac *Hoechst Marion Roussel, USA.†*
Lactulose (p. 1850·3).
Constipation.

Chrozap *Orchid, India.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses in parkinsonism.

Chuan Di *Jianglibao, China.*
⊗Procaterol hydrochloride (p. 1219·1).
Bronchospasm.

Chuan Ning *Kai Bao, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Chuan Qing *San Lian, China.*
Ligustrazine hydrochloride.

Chuan Shan Ning *Yao Wang, China.*
Omacetaxine mepesuccinate (p. 837·3).

Chuan Shu *Tianquan, China.*
Ligustrazine hydrochloride.

Chuan Ting *Sanjiu Yimin, China.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Chuan Xin *Chang Fu Jie Jing, China.*
Ligustrazine hydrochloride.

Chuang Cheng *FangYuan, China.*
Etimicin sulfate (p. 298·2).
Bacterial infections.

Chuang Xing *FangYuan, China.*
Levofloxacin lactate.
Bacterial infections.

Chuanliu *Lianhuan, China.*
Epristeride.
Benign prostatic hyperplasia.

Chuanwei *Chase Sun, China.*
Fasudil hydrochloride (p. 1380·2).
Subarachnoid haemorrhage.

Chufer *Serum Institute, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Chuker *Merisant, Arg.*
Oral liquid: Saccharin sodium (p. 2208·1); calcium cyclamate (p. 2180·2).
Sugar substitute.

Merisant, Arg.
Tablets: Saccharin sodium (p. 2208·1); calcium cyclamate (p. 2180·2); sodium cyclamate (p. 2180·2).
Sugar substitute.

Chulai *Mayinglong, China.*
Imidazole salicylate (p. 71·2).
Musculoskeletal and joint disorders.

Chun Di *Sanye, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Chun Xin *Sanye, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Chuncif *Medizone, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Chuncif-S *Medizone, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Chymase *Indu, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Chymin *Emar, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Chymobel *Blubell, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Chymobel Plus *Blubell, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2); diclofenac potassium (p. 48·3).

Chymodiactin *Link, Austral.†*
⊗Chymopapain (p. 2477·1).
Herniated lumbar intervertebral disc.

Chymol *Anglian, UK.*
Eucalyptus oil (p. 2501·2); terpineol (p. 2627·2); methyl salicylate (p. 92·1); phenol (p. 1763·3).
Chapped skin; chilblains; bruises; sprains.

Chymoral *Cooper (Kopep), Gr.; Elder, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).
Inflammatory disorders.

Chymosoz-D *Sozin-Flora, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2); diclofenac sodium (p. 48·3).

Chymotas *Intas, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Chymotrip *Blubell, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Chymutrip *Bombay Tablet, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Ci Er Tai *Biochem, China.*
Tosufloxacin tosilate (p. 381·2).
Bacterial infections.

Ci He Ying *Double-Crane, China.*
Ozagrel sodium (p. 2579·1).

Ci Ning *C&Y, China.*
Silibinin meglumine.
Liver disorders.

Ci Xing *Gupeng, China.*
Lysine hydrochloride (p. 2079·3).

Ciagen *Craveri, Arg.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Cialis *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, Ukr.; Lilly, USA; Lilly, Venez.*
Tadalafil (p. 2368·1).
Erectile dysfunction; benign prostatic hyperplasia.

Cianofer *Vincenti, Venez.*
Ferric ammonium citrate (p. 2060·1); copper sulfate (p. 2057·2); cyanocobalamin (p. 2107·2).
Anaemias.

Cianomin *Offenbach, Mex.†*
Vitamins; minerals.

Cianon B12 *Ducto, Braz.†*
Cyanocobalamin (p. 2107·2).

Cianotrat *Delta, Braz.*
Vitamin B substances (p. 2102·3).

Cianotrat-Dexa *Delta, Braz.*
⊗Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); dexamethasone (p. 1630·3) or dexamethasone phosphate (p. 1631·1).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuralgia; neuritis.

Ciapar *Fada, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciatyl-Z *Bayer, Ger.*
Zuclopenthixol acetate (p. 1119·1), zuclopenthixol decanoate (p. 1119·2), or zuclopenthixol hydrochloride (p. 1119·2).
Psychoses.

Ciazil
Note: this name may be used for preparations of different composition.
Genepharm, Austral.
Citalopram hydrobromide (p. 411·1).
Depression.

Genepharm, Gr.
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Ciba Vision Cleaner For Sensitive Eyes *Ciba Vision, USA.†*
Cleaning solution for soft contact lenses.

Cibacalcin *Novartis, Gr.*
Calcitonin (human) (p. 1178·1).

Cibacalcine *Novartis, Fr.†*
Calcitonin (human) (p. 1178·1).
Paget's disease of bone; hypercalcaemia of malignancy; osteoporosis.

Cibace *Novartis, S.Afr.*
Benazepril hydrochloride (p. 1314·3).
Hypertension.

Cibacen *Meda, Belg.; Meda, Denm.; Meda, Ger.; Meda, Gr.; Novartis, Indon.†; Meda, Irl.; Novartis, Irl.; Meda, Ital.; Meda, Neth.; Novartis, Philipp.; Meda, Spain; Novartis, Switz.; Novartis, Turk.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure; renal failure; nephropathy.

Cibacène *Meda, Fr.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; glomerulonephropathy.

Cibadrex *Novartis, China; Meda, Fr.; Meda, Ger.; Meda, Gr.; Meda, Ital.; Meda, Neth.; Novartis, S.Afr.; Meda, Spain; Novartis, Switz.; Novartis, Turk.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cibaflam *Novartis, Ger.†*
⊗Fluorometholone (p. 1637·2); gentamicin sulfate (p. 304·2).
Inflammatory eye infections.

Cibalena A *Novartis, Braz.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Cibalgina Dol *Novartis Consumer, Ital.*
Ibuprofen (p. 68·2).
Pain.

Cibalgina Due Fast *Novartis Consumer, Ital.*
Ibuprofen (p. 68·2).
Pain; fever; influenza symptoms.

Cibalginafor *Novartis Consumer, Ital.*
Ibuprofen sodium (p. 68·2).

Cibenol *Astellas, Jpn.*
Cibenzoline succinate (p. 1336·1).
Tachyarrhythmias.

Cibic *Sinopharm, Thai.*
Ascorbic acid (p. 2110·3).
Dietary supplement.

Cibion *Universal, Hong Kong.†*
Ascorbic acid (p. 2110·3).

Cibiotic *Haledew, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cibis
Note: this name may be used for preparations of different composition.
Cadila, India.
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2); dicycloverine hydrochloride (p. 1834·2).

Siam Bheasach, Thai.†
Chlorphenamine maleate (p. 620·3); lidocaine hydrochloride (p. 1988·2); hexachlorophene (p. 1754·1); methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Pruritus; insect bites; eczema; dermatitis; wounds; scalds.

Ciblex *Drugtech, Chile.*
Mirtazapine (p. 436·1).
Depression.

Ciblor *Pierre Fabre Sante, Fr.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Cibor *Berlin Pharm, Rus.*
Bemiparin sodium (p. 1314·2).
Thromboembolic disorders.

Cibral *Ranbaxy, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Cibrato *Mantecorp, Braz.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Cibren *Ethica, Indon.*
Citicoline (p. 2480·1).
Head injury; hemiplegia.

Cibrogan *Roux-Ocefa, Arg.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Cibrom *Sandoz, Mex.*
Citalopram (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Cibronal *Liferpal, Mex.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Cica-Care *Smith & Nephew, Austral.; Smith & Nephew, Fr.; Ro+Ten, Ital.; Smith & Nephew, Philipp.; Smith & Nephew Healthcare, UK.*
Silicone (p. 2209·2).
Hypertrophic and keloid scars.

Cicactive *Uriage, Fr.*
Sodium alginate (p. 2167·3); silanol hydroxyproline (p. 2088·3); dexpanthenol (p. 2582·2); comfrey (p. 2484·2).
Skin damage.

Cicaderma *Boiron, Canad.†; Boiron, Cz.; Boiron, Port.; Boiron, Rus.*
Ledum palustre (p. 2550·1); pulsatilla (p. 2600·2); calendula (p. 2465·2); St John's wort (p. 449·1); achillea (p. 2427·3).
Burns; insect stings; wounds; homoeopathic preparation.

Boiron, Fr.
Calendula officinalis (p. 2465·2); hypericum perforatum (p. 449·1); achillea millefolium (p. 2427·3); ledum palustre (p. 2550·1).
Homoeopathic preparation.

Cicadin *Nordin, Mex.*
Calendula (p. 2465·2).

Cicafem *koGen, UK.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.
Androgen-dependent acne and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Cicafissan *Uhlmann-Eyraud, Switz.*
Casein hydrolysate (p. 2055·2); kaolin (p. 1850·1); bismuth subnitrate (p. 1822·1); zinc oxide (p. 1729·1).
Skin disorders; wounds; burns.

Cicaleïne *Asepta, Mon.*
Ointment: Centella (p. 1698·3); pantothenic acid (p. 2085·2); lipoesters.
Hyperkeratosis of the hands or feet; chapped hands; cracked feet.

Asepta, Mon.†
Dressing: Hydrogel dressing.
Wounds.

Cicalfate *Silesia, Chile; Avene, Fr.; Medifarm Avene, Venez.*
Sucralfate (p. 1889·1); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); zinc oxide (p. 1729·1).
Skin irritation; wounds.

Pierre Fabre Dermo-Cosmetique, Arg.
Sucralfate (p. 1889·1); zinc oxide (p. 1729·1); zinc sulfate (p. 2126·2); copper sulfate (p. 2057·2); thermal spring water.
Skin irritation; skin lesions.

Cicamosa *Reckitt Benckiser, Fr.†*
Mimosa tenuiflora.
Skin damage.

Cicaplast
Note: this name may be used for preparations of different composition.
Roche-Posay, Braz.
Silicone cream (p. 2209·2).
Skin lesions.

Roche-Posay, Chile.
Madecassoside (p. 1698·3); copper gluconate (p. 2057·2); zinc gluconate (p. 2126·2); manganese gluconate (p. 2081·2).
Cicatrisation.

Roche-Posay, Fr.
Zinc gluconate (p. 2126·2); manganese gluconate (p. 2081·2); sodium hyaluronate (p. 2526·2); copper gluconate (p. 2057·2); madecassoside (p. 1698·3).
Skin lesions.

Cicapost *Isdin, Chile.*
⊗Dexpanthenol (p. 2582·2); rose oil (p. 2607·2); glycerol (p. 2517·2); nicotinamide (p. 2083·1); centella triterpenes (p. 1698·3); alpha tocoferil acetate (p. 2119·2); dextran sulfate (p. 2492·2).
Cicatrisation.

Isdin, Port.
⊗Dexpanthenol (p. 2582·2); rose oil (p. 2607·2); glycerol (p. 2517·2); nicotinamide (p. 2083·1); cravagem asiatica triterpenes; alfa

tocoferil acetate (p. 2119·2); dextran sulfate (p. 2492·2).
Cicatrisation.

Cicatendon *Labrha, Fr.*
Spirulina (p. 2622·1); glucosamine sulfate (p. 2515·3); ginseng (p. 2513·3); equisetum (p. 2500·1); minerals.
Joint disorders.

Cicatenol *EMS, Braz.*
Panthenol (p. 2582·2).

Cicatral *Uriach Aquilea OTC, Spain.*
Peru balsam (p. 2587·1); colecalciferol (p. 2113·1); estrone (p. 2275·2); benzocaine (p. 1980·2); vitamin A (p. 2098·3); tyrothricin (p. 384·1).
Burns; ulcers; skin disorders; wounds.

Cicatrene *Farmoquimica, Braz.; Johnson & Johnson, Ital.*
Cream; topical powder: Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3); cysteine (p. 2058·3); glycine (p. 2071·2); threonine (p. 2098·2).
Skin infections.

Johnson & Johnson, Ital.
Topical spray: Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Skin infections.

Cicatrex *Janssen-Cilag, Switz.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); cysteine (p. 2058·3); glycine (p. 2071·2); DL-threonine (p. 2098·2).
Bacterial skin infections; infected wounds and burns.

Cicatrex Baby *Investi, Arg.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Nappy rash; minor abrasions; minor burns.

Cicatrex Biotic *Investi, Arg.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); L-cysteine (p. 2058·3); DL-threonine (p. 2098·2); glycine (p. 2071·2).
Burns; skin infections; wounds.

Cicatridina *Farma Derma, Ital.*
Hyaluronic acid (p. 2526·2).
Skin disorders; wounds; vaginal disorders; anorectal disorders.

Cicatridine *HRA, Fr.*
Pessaries: Sodium hyaluronate (p. 2526·2); centella (p. 1698·3); calendula (p. 2465·2); aloe vera (p. 1693·2); melaleuca oil (p. 2551·1).
Vaginal atrophy; vaginal injury.

HRA, Fr.
Cream: Sodium hyaluronate (p. 2526·2); sorbitol (p. 2092·1); silicone oil (p. 2209·3); chlorhexidine gluconate (p. 1743·3).
Burns; wounds; ulcers.

Cicatrin *GSK Consumer, Port.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); cysteine (p. 2058·3); glycine (p. 2071·2); threonine (p. 2098·2).

GSK, Canad.†
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); cysteine; glycine; threonine.
Infected burns, wounds, and ulcers.

Pfizer Consumer, Austral.†; GSK, Irl.†; Pfizer Consumer, S. Afr.†
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); L-cysteine (p. 2058·3); glycine (p. 2071·2); DL-threonine (p. 2098·2).
Burns; wounds; infected skin disorders; anorectal disorders; skin ulcers.

Cicatrina *Fada, Arg.*
Zinc oxide (p. 1729·1); ichthammol (p. 1705·3).
Skin disorders.

Cicatrizol *Ronnet, Arg.*
Sodium acexamate (p. 2427·3); gentamicin sulfate (p. 304·2).
Burns; wounds.

Cicatrol *Hexa, Arg.*
Zinc undecenoate (p. 596·3); zinc oxide (p. 1729·1); sodium propionate (p. 593·1); salicylic acid (p. 1719·1).
Fungal skin infections; burns; ulcers; wounds.

Cicatryl *Pierre Fabre Sante, Fr.*
Allantoin (p. 1693·1); guaiazulene (p. 2523·1); chlorocresol (p. 1748·1); alpha tocoferil acetate (p. 2119·2).
Superficial burns and wounds.

Cicatul *Raymos, Arg.*
Wheat germ (p. 2647·1); phenoxyethanol (p. 1764·3).
Burns; ulcers; wounds; skin irritation; vulvo-vaginal disorders.

Cicladol *Chiesi, Braz.; Master Pharma, Ital.*
Piroxicam betadex (p. 126·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Ciclamil *LKM, Arg.*
Cyproterone acetate (p. 2261·2).

Silesia, Chile.
Cyclobenzaprine hydrochloride (p. 2023·1).
Musculoskeletal spasm.

Ciclatry *Multilab, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciclem *Pharmacare, Philipp.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cicletan *Pharmanel, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders.

Cicletex *Phoenix, Arg.*
⊗Ciclesonide (p. 1626·3).
Asthma.

Ciclidon *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ciclidoxan *Richmond, Arg.*
Doxycycline (p. 288·1).
Bacterial infections.

Ciclinil *Farmoz, Port.*
Clarithromycin (p. 266·2).
Bacterial infections.

Ciclisan *Sanval, Braz.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Ciclo *Uniao Quimica, Braz.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ciclobrain *Coronet, Indon.*
Piracetam (p. 393·3).
Mental function impairment; alcoholism; cerebral trauma.

Ciclochem *Novag, Spain.*
Ciclopirox olamine (p. 575·3).
Fungal skin, scalp and nail infections; vulvovaginal candidiasis.

Ciclocur *Bayer, Arg.*
White tablets, estradiol valerate (p. 2271·2); light-brown tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Ciclocutan *Dermapharm, Ger.; Dermapharm, Switz.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Ciclodan *Medimetriks, USA.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal nail infections.

Cicloderm *Trima, Israel.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Cicloderm-C *Trima, Israel.*
⊗Ciclopirox olamine (p. 575·3); clobetasone butyrate (p. 1627·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Ciclodin *Unison, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciclofalina *Kern, Spain.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Ciclofemme *Mabra, Braz.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Cicloferon *Liomont, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ciclogyn *Uniao Quimica, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ciclohale *Cipla, India.*
⊗Ciclesonide (p. 1626·3).

Ciclohexal *Hexal, S.Afr.†*
Ciclosporin (p. 1945·2).
Graft-versus-host disease; transplant rejection; psoriasis.

Ciclokapron *Pfizer, Venez.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Ciclokebir *Aspen, Arg.*
Cyclophosphamide (p. 771·1).

Ciclolato *Latinofarma, Braz.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Ciclolux *Allergan, Ital.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Ciclomex *Gynopharm, Chile; Sinensix, Thai.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-Day packs contain 24 active tablets and 4 inert tablets.
Combined oral contraceptive; acne in women.

Ciclomidrin *Latinofarma, Braz.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Ciclopegic *Llorens, Spain.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis.

Ciclopenal *Alcon, Arg.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Cicloplant *Abbott, Mex.†*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Ciclopegicedol *Edol, Port.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis.

Ciclopegico *Allergan, Braz.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Ciclopejico *Alcon Cusi, Spain.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis; uveitis.

Ciclopoli *Taurus, Ger.; Megapharm, Israel; Astellas, Switz.*
Ciclopirox (p. 575·3).
Fungal skin or nail infections.

Polichem, Ital.
Ciclopirox olamine (p. 575·3).
Fungal vaginal infections.

Ciclopren *Veropharm, Rus.*
Ciclosporin (p. 1945·2).
Transplant rejection; rheumatoid arthritis; psoriasis; atopic dermatitis; nephrotic syndrome.

Ciclaprimogyna *Bayer, Braz.*
White tablets, estradiol valerate (p. 2271·2); red tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders.

Cicloral *Sandoz, Austral.; Hexal, Ger.†*
Ciclosporin (p. 1945·2).
Nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; atopic eczema; graft-versus-host disease; uveitis.

Cicloralhexal *Hexal, Austria.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; auto-immune disorders; nephrotic syndrome; rheumatoid arthritis; atopic dermatitis.

Ciclosol *Sandoz, Switz.†*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; uveitis; psoriasis; rheumatoid arthritis; atopic eczema; nephrotic syndrome.

Ciclostar *Medinfar, Port.*
Ciclosporin (p. 1945·2).
Transplantation rejection; graft-versus-host disease; uveitis; nephrotic syndrome; rheumatoid arthritis; psoriasis; atopic eczema.

Ciclotal *Lemery, Mex.†; Lemery, Rus.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only oral contraceptive; endometriosis; malignant neoplasms.

Ciclotetryl *Ingens, Arg.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Ciclotos *Lafi, Chile.*
Codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1).
Cough.

Cicloviral *Medinfar, Port.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Ciclovulon *Sanval, Braz.*
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
Combined oral contraceptive.

Ciclox
Note: this name may be used for preparations of different composition.
Sandoz, Arg.
Clonazepam (p. 519·1).
Epilepsy; panic disorder; obsessive-compulsive disorder.

Oboi, Philipp.†
Cloxacillin sodium (p. 275·1).
Gram-positive bacterial infections.

Cicloxab *Relyo, Gr.*
Inosine pranobex (p. 988·3).

Ciclozinil *Aesculapius, Ital.*
Gentamicin sulfate (p. 304·2).
Infected skin disorders; burns; wounds.

Cicomin *Altfarm, Rus.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Ciconazol *Cimed, Braz.*
Miconazole nitrate (p. 589·1).
Fungal infections.

Cidacid *Tai Yu, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Cidal *Neon, India.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Cidalin
Note: this name may be used for preparations of different composition.
Chemo-Drugs, India.
Tricholine citrate (p. 2055·2).

Perrigo, Israel.†
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Cidalox-TZ *Chemo-Drugs, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cidapex *Biodica, Fr.†*
m-Cresyl acetate (p. 1749·1); parachlorophenol (p. 1763·1).
Root canal infections.

Cidazole *Juggat, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Cidegol C *Hofmann & Sommer, Ger.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Cidermex
Note: this name may be used for preparations of different composition.
Panalab, Arg.
Pantothenic acid (p. 2085·2); cade oil (p. 1723·2).
Scalp disorders.

UCB, Fr.†
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1).
Eye disorders.

Cidetox *Offenbach, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium (p. 1786·3); dimeticone (p. 1886·2).
Gastric hyperacidity.

Cidex *Johnson & Johnson, India; Johnson & Johnson Medical, USA.*
Glutaral (p. 1753·2).
Instrument disinfection.

Cidex OPA *Johnson & Johnson, Ger.; Advanced Sterilization Products, USA.*
o-Phthaldialdehyde (p. 1765·3).
Instrument disinfection.

Cidilin *Errekappa, Ital.*
Citicoline sodium (p. 2480·2).
Parkinsonism.

Cidine
Note: this name may be used for preparations of different composition.
Medifive, Thai.
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Recordati, Spain.
Cinitapride acid tartrate (p. 1831·3).
Gastroparesis; gastro-oesophageal reflux.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cidocal *Neiss, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Cidocan *Obolenskoe, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Cidoclar *Teva, Hung.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Cidogrel *Karnataka, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Cidogrel-A *Karnataka, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Cidokez *Adore, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cidomex *Sanofi-Aventis, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Cidominet *Rafarm, Gr.*
Calcium carbonate (p. 1824·3); calcium lactate (p. 1784·1); vitamin C (p. 2110·3).
Osteoporosis; pregnancy; breast-feeding.

Cidomycin *Sanofi-Aventis, Irl.; Aventis, S.Afr.†; Sanofi, UK.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Cidoresp *Sanofi-Aventis, India.*
Amoxicillin trihydrate (p. 216·2); carbocisteine (p. 1658·1).
Respiratory disorders associated with excessive or viscous mucus.

Cidoston *Med-One, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Cidoten *Schering-Plough, Chile.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cidoten V *Schering-Plough, Chile.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Cidoten Rapilento *Schering-Plough, Chile.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Lidocaine (p. 1988·1) is included in some injections to alleviate the pain of injection.
Corticosteroid.

Cidren *Vocate, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Dry mouth.

Cidrid *Profic Organic, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Cidrin *Abbott, Chile.†*
⊗Metamfetamine hydrochloride (p. 2324·2).
Attention-deficit hyperactivity disorder.

Cidrolex *Metrolink, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cidron *Sandoz, Swed.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cidrops *Zwitter, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cidroxal *Pharmathen, Philipp.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciechocinski *Uzdrowisko Ciechocinek, Pol.†*
Electrolytes (p. 1775·1).
Musculoskeletal and joint disorders; neuralgia; peripheral vascular disorders; skin disorders; respiratory-tract disorders.

Cieldom *Teva Tuteur, Arg.*
Cabergoline (p. 899·3).
Parkinsonism; hyperprolactinaemia; inhibition of lactation.

Ciella *Cooperation Pharmaceutique, Fr.*
Salicylic acid (p. 1719·1).
Eye disorders.

Cif *Uniroyal, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cif Candioli *Candioli, Gr.*
Tetramethrin (p. 2162·2); phenothrin (p. 2160·1).
Head, body, and crab lice.

Cifacure *Medchem, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Cifarcaina *Behrens, Venez.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Cifespasmo *Northia, Arg.*
Hyoscine butylbromide (p. 1845·3).
Muscle spasm.

Cifespasmo Compuesto *Northia, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Muscle spasm; pain.

Cifgen *Genesis, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cifhir *Farmaceutica H, Mex.*
Benzydamine hydrochloride (p. 29·2).
Musculoskeletal, joint, peri-articular, and soft-tissue injury.

Cifilac *PDC, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cifilac-CV *PDC, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Cifin *Pharmacodane, Denm.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifivar *Zota, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cifivar-LB *Zota, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ciflan *Azevedos, Port.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciflex *Suphong, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciflo *Masa, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifloc *Reddy, S.Afr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciflodal *China Chem & Pharma, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciflogex *Cimed, Braz.*
Benzydamine hydrochloride (p. 29·2).
Inflammation; pain.

Ciflolan *Olan-Kemed, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciflon
Note: this name may be used for preparations of different composition.
Lapi, Indon.
Citrus bioflavonoids (p. 2505·2); diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.
Prompt Cure, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciflon-TZ *Prompt Cure, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciflos *Guardian, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciflosin *Deva, Turk.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciflot *Bial, Spain.*
Ciprofloxacin (p. 261·1).
Otitis.

Ciflox
Note: this name may be used for preparations of different composition.
Alcon, Denm.
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Infected ear disorders.
Bayer, Fr.
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.
GL Pharma, Austria; Medley, Braz.†; Roemmers Rowe, Venez.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifloxacin *Verisfield, Gr.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Cifloxager *Gerard, Irl.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifloxatil *Brasterapica, Braz.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cifloxin *Sandoz, Hung.; Lewison, Philipp.; Siam Bheasach, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.
Recalcine, Chile; Quality, Hong Kong.
Ciprofloxacin (p. 261·1).
Bacterial infections.
Siam Bheasach, Malaysia.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Cifloxinal *ProMed, Cz.; Promed, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifloxno *Milano, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifloxtron *Ariston, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifluron *Umut, Turk.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cifolox *LBS, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cifomed *Aglowmed, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cifomed-D *Aglowmed, India.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).

Cifomed-TZ *Aglowmed, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciforion *Orion, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cifox *Rowex, Irl.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cifoxim *Taiwan Biotech, Philipp.*
Cefazolin (p. 237·2).
Bacterial infections.

Cifran *Ranbaxy, Austral.; Ranbaxy, Cz.†; Ranbaxy, Hung.; Ranbaxy, India; CTS, Israel; Merck, Mex.; Douglas, NZ; Ranbaxy, Pol.†; Ranbaxy, Rus.; Ranbaxy, S.Afr.; Ranbaxy, Thai.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.
Nanxin, China; Hind Wing, Hong Kong†; Ranbaxy, Malaysia; Ranbaxy, Ukr.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cifran CT *Ranbaxy, Ukr.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Cifran-CT *Ranbaxy, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cifran-CT-H *Ranbaxy, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cifran-OZ *Ranbaxy, India.*
Ciprofloxacin (p. 261·1); ornidazole (p. 943·1).

Cifzone *Medizone, India.*
Dispersible tablets: Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.
Medizone, India.
Syrup: Cefixime (p. 240·3).
Bacterial infections.

Cigamet *General Drugs, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hyperacidity.

Cigamete *Prodotti, Braz.†*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ciganclor *Richmond, Arg.*
Ganciclovir (p. 982·3).
Viral infections.

Cigmadil *Collins, Mex.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Cigram *Parenteral Drugs, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

Cikavit *Knop, Chile.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Skin irritation; wounds.

Cikedrix *CKD, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

CIL *SMB, Fin.; Winthrop, Ger.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Cilaal *Craveri, Arg.*
Cilostazol (p. 1337·1).
Occlusive arterial disease.

Cilab *Biolab, Thai.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cilacar *JB Chemicals, India.*
Cilnidipine (p. 1337·1).
Hypertension.

Cilacil *Aventis, Turk.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Cilamin *Panacea, India.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; Wilson's disease; cystinuria.

Cilamox *Aspen, Austral.; Sigma, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Cilan *Polfarmex, Pol.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Cilanem *Medreg, Cz.; Ranbaxy, Hung.; Ranbaxy, India.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Cilapenem *Jeil, Thai.*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Cilaril *Trima, Israel.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Cilaril Plus *Trima, Israel.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cilaspen *Sanjivani, Rus.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Cilaspene *Sanjivani, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Cilate *Be-Tabs, S.Afr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Cilatron *Quesada, Arg.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Cilaxoral *Ferring, Swed.*
Sodium picosulfate (p. 1887·2).
Constipation.

Cilazapril Plus *Teva, Israel.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cilclar *Novartis, Braz.; Novartis, Venez.*
Preparation for eye cleansing.
Blepharitis.
Novartis, Chile.
Eyelid and eyelash cleanser.

Cilclox *DWD, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Cilentra *Ranbaxy, India.*
Escitalopram oxalate (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Cilest *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Pol.; Janssen-Cilag, Rus.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Janssen-Cilag, S.Afr.
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Cileste *Janssen-Cilag, Austria.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Cilestoderme *Schering-Plough, Port.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Ciletin *Korea United, Philipp.*
Cilostazol (p. 1337·1).
Occlusive arterial disease; peripheral vascular disorders.

Cilex
Note: this name may be used for preparations of different composition.
Ascent, Austral.
Cefalexin (p. 234·1).
Bacterial infections.

McNeil & Argus, India.
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cilfam *Pharma Nutria, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Cilicaine *Healthcare Logistics, NZ.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Cilicaine V *Aspen, Austral.*
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Cilicaine Syringe *Aspen, Austral.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Cilicaine VK *Aspen, Austral.; Healthcare Logistics, NZ.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Cilift *Aspen, S.Afr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Cilinafosal *Medical, Spain.†*
⊗Ephedrine hydrochloride (p. 1663·2); sulfanilamide sodium mesilate (p. 368·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinafosal Dihidroestreptomicina *Medical, Spain.†*
⊗Dihydrostreptomycin sulfate (p. 286·3); ephedrine hydrochloride (p. 1663·2); sulfanilamide sodium mesilate (p. 368·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinafosal Hidrocortisona *Medical, Spain.†*
⊗Ephedrine hydrochloride (p. 1663·2); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); sulfanilamide sodium mesilate (p. 368·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinafosal Neomicina *Medical, Spain.†*
⊗Ephedrine hydrochloride (p. 1663·2); neomycin sulfate (p. 330·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinon *Ariston, Braz.*
Ampicillin (p. 218·2).
Bacterial infections.

Cilipen
Note: this name may be used for preparations of different composition.
Elofar, Braz.†
Ampicillin (p. 218·2).
Bacterial infections.

Cilisod *Caplin, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Cilixem *Shince, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cilkanol *Zentiva, Cz.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; circulatory disorders; haemorrhoids.

Cillimicina *Normon, Spain.†*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Cilodac *Lupin, India.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Cilodex *Alcon, Braz.; Alcon, Chile; Alcon, Denm.; Alcon, Israel†; Alcon, Mex.; Alcon, NZ; Alcon, S.Afr.; Alcon, Singapore.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders; infected ear disorders; otitis media.

Ciloflox *Be-Tabs, S.Afr.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cilol *Neon, India.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Cilon *Sandoz, Pol.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Cilonast *Sandoz, Pol.*
Citalopram hydrobromide (p. 411·1).
Depression.

Cilopen VK *Ascent, Austral.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Cilopress *Biospray, Gr.*
Citalopram (p. 411·1).
Depression.

Ciloquin *Ioquin, Austral.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear and eye infections.

Ciloram *Novagen, S.Afr.*
Citalopram (p. 411·1).

Cilosol *Unison, Thai.*
Cilostazol (p. 1337·1).
Cerebral and peripheral vascular disorders.

Cilostal *Merck Serono, Arg.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Cilovas *Baliarda, Arg.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Cilox *Alcon, Indon.; Alcon, Norw.*
Ciprofloxacin hydrochloride (p. 261·2).
Eye infections; bacterial keratitis; otitis externa.

Ciloxacin *Alcon, Chile.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Ciloxadex *Alcon, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Ciloxan *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Cz.; Alcon, Denm.; Alcon, Fr.; Alcon, Ger.; Alkon (Αλκον), Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.†; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections; bacterial ear infections.

Ciloxin *Apotex, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cilpen *Antibioticos, Mex.†*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Cilpier *AltaSelect, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cilrag *TO-Chemicals, Thai.*
Garlic (p. 2510·3).
Tonic.

Cilroton *Janssen-Cilag, Gr.; Johnson & Johnson, Gr.*
Domperidone (p. 1838·1).
Delayed gastric emptying; nausea and vomiting; gastro-oesophageal reflux disease; acid aspiration; aid in diagnostic procedures.

Ciltiren *Vocate, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cim *Decomed, Port.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastric hyperacidity; gastrointestinal haemorrhage; Zollinger-Ellison syndrome; gastritis; pancreatic insufficiency.

Cimaas *Cimed, Braz.*
Aspirin (p. 22·2).
Fever; inflammation; pain.

Cimag *TP, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hyperacidity.

Cimagen *Antigen, Irl.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity.

CIMAher *Caif, Arg.*
Nimotuzumab (p. 836·3).
Cerebral glioblastoma; head and neck cancer.

Cimaher *Eurofarma, Braz.*
Nimotuzumab (p. 836·3).

Cimal
Note: this name may be used for preparations of different composition.
Recalcine, Chile.
Citalopram hydrobromide (p. 411·1).
Depression.

Specifar, Gr.
Etofenamate (p. 57·2).
Inflammatory disorders; pain.

Cimascal *Teva, Spain.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Cimascal D *Teva, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Cimcol *Candor, India.*
Oral suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Candor, India.
Tablets: Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Cimdom *Elfin, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Cimebec *Farcoral, Mex.†*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimebeta *Betapharm, Ger.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration.

Cimecard *Cimed, Braz.*
Digoxin (p. 1353·3).

Cimecid *Rotexmedica, Philipp.†*
Cimetidine hydrochloride (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer.

Cimecort *Cimed, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Cimedax *Royton, Braz.*
Cimetidine (p. 1827·1).

Cimedine *Christo, Hong Kong.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Cimedul *Offenbach, Mex.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimefer *Cimed, Braz.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Cimeffer *Reuffer, Mex.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimegast *ICN, Pol.†*
Cimetidine (p. 1827·1).
Gastric hyperacidity; heartburn; dyspepsia.

Cimegripe *Cimed, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Cimegripe Bebe *Cimed, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Cimegripe Dia *Cimed, Braz.*
Yellow tablets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); white tablets, paracetamol.

Cimegripe-77c *Cimed, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Cimehexal *Hexal, Austral.†; Hexal, Ger.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Cimeldine *Clonmel, Irl.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity.

Cimelide *Cimed, Braz.*
Nimesulide (p. 101·3).
Inflammation; pain.

Cimet *Chinta, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Cimeta *Jean-Marie, Hong Kong.*
Cimetidine (p. 1827·1).
Dyspepsia; peptic ulcer.

Cimetag *GSK, Austria†; Teva, Israel†; Julphar, UAE.*
Cimetidine (p. 1827·1).
Acid aspiration; gastrointestinal haemorrhage; dyspepsia; gastro-oesophageal reflux; peptic ulcer; short bowel syndrome; pancreatic insufficiency; Zollinger-Ellison syndrome.

Cimetase *Liomont, Mex.*
Cimetidine (p. 1827·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimetidan *Cimed, Braz.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimetilab *Multilab, Braz.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimetin *PC India, India; T Man, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; pancreatic insufficiency; heartburn.

Cimetinax *Ducto, Braz.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimetine *Sriprasit, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimetival *Sanval, Braz.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimeton *Novartis, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Cimet-P *PP Lab, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Cimex
Note: this name may be used for preparations of different composition.
Multicare, Philipp.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cimexol *Solas, Indon.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastric hypersecretion.

Cimfi *Aamorb, India.*
Aloe vera (p. 1693·2); calamine (p. 1697·2); liquid paraffin (p. 2191·2).

Cimicifuga comp
Note: this name may be used for preparations of different composition.
Weleda, Ger.
Onopordum acanthium; hyoscyamus niger (p. 2530·2); primula veris (p. 2596·2); kalanchoe; cimicifuga (p. 2478·1); motherwort (p. 2564·2).
Menopausal disorders.

Cimicifuga Complexe No 21 *Lehning, Fr.†*
Cimicifuga (p. 2478·1); lilium tigrinum; secale cornutum (p. 2137·1); mercurius corrosivus (p. 2555·2); hydrastis (p. 2528·1); lycopodium clavatum (p. 2547·1); acidum nitricum (p. 2572·3); sabina; aurum muriaticum natronatum (p. 2521·2).
Homoeopathic preparation.

Cimicifuga Compound *Phytomedicine, Austral.*
St John's wort (p. 449·1); cimicifuga (p. 2478·1); wild yam (p. 2648·1); lavender (p. 2541·1).
Menopausal disorders.

Cimicifuga N Oligoplex *Madaus, Ger.*
Cimicifuga (p. 2478·1); crocus (p. 2208·2).
Homoeopathic preparation.

Cimicifuga-Homaccord *Peithner, Hung.*
Cimicifuga racemosa (p. 2478·1); strontium carbonicum.
Homoeopathic preparation.

Cimicin *Stada, Hung.*
Cimicifuga (p. 2478·1).
Menstrual symptoms.

Cimifemine *Zeller, Switz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Cimille *Federfarma, Ital.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Ciminpac *Inpac, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Cimipax *Galien, Fr.†*
Cimicifuga (p. 2478·1).
Nervous disorders; insomnia.

Cimisan *APS, Cz.†; APS, Ger.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Cimispect *Chandra Bhagat, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Cimizt *Morningside, UK.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Combined oral contraceptive.

CimLich *Winthrop, Ger.†*
Cimetidine (p. 1827·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimlok *Be-Tabs, S.Afr.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimogal *Probiomed, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cimulcer *Biolab, Malaysia; Standard, Philipp.†; Biolab, Singapore.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Cimzia *UCB, Austral.; UCB, Austria; UCB, Belg.; UCB, Canad.; UCB, Cz.; UCB, Denm.; UCB, Fr.; UCB, Ger.; UCB, Gr.; UCB, Irl.; UCB, Jpn; UCB, Neth.; UCB, Norw.; UCB, Pol.; UCB, Port.; UCB, Spain; UCB, Swed.; UCB, Switz.; UCB, UK; UCB, USA.*
Certolizumab pegol (p. 39·1).
Rheumatoid arthritis; Crohn's disease; axial spondyloarthritis; psoriatic arthritis; ankylosing spondylitis.

Cina
Note: this name may be used for preparations of different composition.
Zota, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.
Landsteiner, Mex.†
Levofloxacin (p. 315·3).
Bacterial infections.

Cina Complexe No 55 *Lehning, Fr.†*
Asa foetida (p. 2449·3); artemisia cina; cuprum aceticum (p. 2486·2); mercurius corrosivus (p. 2555·2); oleum chenopodium (p. 152·2).
Homoeopathic preparation.

Cina Compose *Boiron, Fr.*
Cinchona succirubra (p. 2478·3); spigelia anthelmia (p. 2621·3); indolum; cuprum metallicum (p. 2057·1); enterokinasum; berberis vulgaris (p. 2502·1); carbo vegetabilis (p. 1537·3); antimonium crudum (p. 2445·1); uranium nitricum.
Homoeopathic preparation.

Cinabel
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); dipyrone (p. 53·3); chlorphenamine maleate (p. 620·3).
Migraine and other vascular headaches.

Cinacris *Ivax, Arg.*
Cinnarizine (p. 622·1); dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders.

Cinact *Active, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinact-D *Active, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Cinactiv *Labomed, Chile.*
Erythromycin-zinc complex (p. 291·2).
Acne.

Cinaderm *Aspen, Braz.*
Neomycin (p. 329·3).
Bacterial skin infections.

Cinadil *Psychotropics, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinadil-D *Psychotropics, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Cinadine *Garec, S.Afr.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; upper gastrointestinal haemorrhage.

Cinaflan *Brasterapica, Braz.*
Diclofenac potassium (p. 48·3).

Cinaleo *Meizler, Braz.*
Bleomycin sulfate (p. 749·3).

Cinalong *UCB, Jpn.†*
Cilnidipine (p. 1337·1).
Hypertension.

Cinam *Sanbe, Indon.*
Sultamicillin (p. 369·1).
Bacterial infections.

Cinamat *Cinerea, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Cinamica *Shreya, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Cinamin *Interhealthcare, Philipp.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinant *Constant, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cinant-TZ *Constant, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cinapen *Elpen (Ελπεν), Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Cinaran *Cazi, Braz.*
Cinnarizine (p. 622·1).

Cinaren *Dollder, Venez.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cinarepa *Cristalfarma, Ital.*
Cynara (p. 2490·3); taraxacum (p. 2625·3); turmeric (p. 2218·1); rosemary oil (p. 2607·3).
Nutritional supplement for liver disorders.

Cinarin *Pharmaspec, Philipp.; Galeno, Venez.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinarite *Belfar, Braz.*
Cinnarizine (p. 622·1).

Cinarix *Royton, Braz.*
Cinnarizine (p. 622·1).

Cinaryl *Themis, India.*
Diphenylpyraline hydrochloride (p. 627·2); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, and paracetamol.

Cinas *Auspi, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Cinatil *Brasterapica, Braz.*
Diclofenac diethylamine (p. 48·3).

Cinatrex *Cifarma, Braz.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Cinatropil *Zdorovje, Ukr.†*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; mental function impairment; depression; vestibular disorders; migraine; motion sickness.

Cina-TZ *Zota, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cinaz
Note: this name may be used for preparations of different composition.
East West, India.
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.
Pentafarma, Port.
Cetirizine hydrochloride (p. 619·2).

Cinazel *IQFA, Mex.*
Carbamazepine (p. 512·2).

Cinazon *Sanval, Braz.*
Cinnarizine (p. 622·1).

Cinazyn *Italchimici, Ital.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cincain *Ophtha, Denm.; Meda, Swed.*
Cinchocaine (p. 1983·2).
Eye disorders.

Cincal-CT *Cinerea, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Cincam-P *Cinerea, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Cincar *Cinerea, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Cincillin *Ind-Swift, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Cinclav *Cinerea, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Cinclox-S *Ind-Swift, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Cincofarm *Angelini, Port.; Angelini, Spain.*
Oxitriptan (p. 440·3).
Migraine; depression; epilepsy.

Cincol *Polfa Warszawa, Pol.*
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2).
Conjunctivitis.

Cincordil *Sigma, Braz.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Cincort *Cinerea, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Cincream *Scaglietti, Ital.*
Zinc oxide (p. 1729·1).
Skin disorders.

Cindala *Medikon, Indon.†*
Clindamycin (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Cindexa *Cinerea, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Cindol *Chiesi, Gr.*
Meglumine indometacin (p. 71·2).
Mosfarma, Rus.
Zinc oxide (p. 1729·1).
Skin disorders.

Cindot *Cinerea, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Cin-Doxy *Medicine Products, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Cinebil *Jaba Recordati, Port.*
Sucralfate (p. 1889·1).

Cinegel *Med-One, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial skin infections.

Cineprac *Liferpal, Mex.*
Trimebutine (p. 2634·1).
Gastrointestinal disorders.

Cinergil *Labomed, Chile.*
Cinnarizine (p. 622·1).
Mental function impairment; peripheral vascular disorders; vertigo.

Cinerine *Pharmasant, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; motion sickness.

Cinet *Medinfar, Port.*
Domperidone (p. 1838·1).
Dyspepsia; nausea; vomiting.

Cinetic
Note: this name may be used for preparations of different composition.
Teofarma, Ital.
Thyroid (p. 2345·3).
Hypothyroidism.

Cinetol *Cristalia, Braz.*
Biperiden hydrochloride (p. 895·1).
Parkinsonism.

Cinfacromin *Cinfa, Spain.†*
Merbromin (p. 1760·1).
Skin disinfection.

Cinfamar *Cinfa, Spain.*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo.

Cinfamar Cafeina *Cinfa, Spain.*
Caffeine (p. 1203·3); dimenhydrinate (p. 625·2).
Motion sickness; vertigo.

Cinfamucol *Cinfa, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Cinfatos *Cinfa, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Cinfatos Complex *Cinfa, Spain.*
⊗Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Cinfatos Descongestivo *Cinfa, Spain.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough; nasal congestion.

Cinfatos Expectorante *Cinfa, Spain.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Cinfavit Complex *Cinfa, Spain.*
Vitamins; ferrous fumarate (p. 2060·3); ginseng (p. 2513·3).
Dietary supplement.

Cinflox *Cinerea, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Cinfloxine *Medicine Products, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cinflox-OZ *Cinerea, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Cinflu *Cinerea, India.*
Fluconazole (p. 578·2).
Fungal infections.

Cingeron *BMW, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cingeron-D *BMW, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Cini *Ind-Swift, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinie *Zentiva, Cz.; Zentiva, Fin.†; Zentiva, Hung.; Zentiva, Pol.*
Sumatriptan succinate (p. 679·2).
Migraine.

Cinigest *Baliarda, Arg.*
Cinitapride (p. 1831·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Cinkef-U *Hospira, Port.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Cinkof *Cinerea, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Cinkona *Ipca, India.*
Quinine dihydrochloride (p. 665·1) or quinine sulfate (p. 665·2).
Malaria.

Cinkos *Med-Care, Turk.*
Zinc oxide (p. 1729·1); white soft paraffin (p. 2211·3); purified talc (p. 1722·2).
Barrier preparation.

Cinmik *Karnataka, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Cinmox-DC *Cinerea, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Cinna *YSP, Malaysia; Yung Shin, Singapore; Millimed, Thai.; T Man, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cinnabene *Ratiopharm, Austria†; Ratiopharm, Cz.†*
Cinnarizine (p. 622·1).
Vestibular disorders; cerebral and peripheral vascular disorders; migraine.

Cinnabloc *Aldril, Philipp.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinnabsin *DHU, Rus.; DHU, Ukr.*
Cinnabaris (p. 2555·3); hydrastis (p. 2528·1); kalium bichromicum (p. 2476·3); echinacea (p. 2498·1).
Homoeopathic preparation.

Cinnageron *Streuli, Switz.*
Cinnarizine (p. 622·1).
Vestibular disorders; cochlear disorders; motion sickness.

Cinnapac *Inpac, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cinnar *Atlantic, Singapore; Atlantic, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Cinnarin *Suphong, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cinnarine *Community Pharmacy, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cinnaron *Remedica, Malaysia; Remedica, Singapore.*
Cinnarizine (p. 622·1).
Motion sickness; vestibular disorders.

Cinnasia *Willow, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinnasia-D *Willow, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Cinnasin *Marching, Hong Kong.†*
Cinnarizine (p. 622·1); vitamin B_6 (p. 2105·3).

Cinnatab *Medicpharma, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cinnaza *Pharmaland, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; migraine.

Cinobac *Bruno, Ital.*
Cinoxacin (p. 261·1).
Urinary-tract infections.

Cinobactin *Lilly, Gr.*
Cinoxacin (p. 261·1).
Bacterial infections.

Cinocap *Farmstandart, Rus.*
Pyrithione zinc (p. 1718·1).
Psoriasis; atopic eczema; seborrhoeic dermatitis.

Cinocil *Farma 1, Ital.*
Cinoxacin (p. 261·1).
Urinary-tract infections.

Cinodin *Candor, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cinodin-TZ *Candor, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cinoflax *Ativus, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cinoflox *Optaderm, Philipp.*
Ofloxacin (p. 334·3).
Bacterial ear or eye infections.

Cinogenta *Ferron, Indon.*
⊗Gentamicin sulfate (p. 304·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Cinol *Cinerea, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Cinol Forte *Cinerea, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Cinol Plus *Cinerea, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Cinolon *Sanbe, Indon.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Cinolon-N *Sanbe, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Cinom *Cinerea, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Cinon *Azevedos, Port.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cinopal *Wyeth-Ayerst, Thai.; Turgut, Turk.†*
Fenbufen (p. 59·1).
Musculoskeletal and joint disorders; pain.

Cinospar *Haledew, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Cinoxen *Ibirn, Ital.†*
Cinoxacin (p. 261·1).
Urinary-tract infections.

Cinpar-CR *Cinerea, India.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Cinpip-TZ *Cinerea, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Cinq sur Cinq *Bayer Sante, Fr.*
Diffuser cartridge; diffuser liquid: Esbiothrine (p. 2149·2).
Insect repellent.

Bayer Sante, Fr.
Lotion: Ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Bayer Sante, Fr.
Mosquito net: Deltamethrin (p. 2152·1).
Insect repellent.

Bayer Sante, Fr.
Spray: Permethrin (p. 2159·3).
Insecticide.

Cinrab *Cinerea, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Cinred *Cinerea, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); lysine (p. 2079·3).

Cinris *Cinerea, India.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Cinris Forte *Cinerea, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Cinrizine *Medifive, Thai.*
Cinnarizine (p. 622·1).
Circulatory disorders; vestibular disorders; migraine; motion sickness.

Cinryze *ViroPharma, Denm.; ViroPharma, Ger.; ViroPharma, Irl.; ViroPharma, Neth.; ViroPharma, Norw.; ViroPharma, Spain; ViroPharma, UK; Lev, USA.*
Complement C1 esterase inhibitor (p. 2485·1).
Hereditary angioedema.

Cintac *JK Biochem, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cintac-D *JK Biochem, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Cintag *Hexal, Braz.*
Cimetidine (p. 1827·1).

Cintar *Patar, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cintidina *Greenpharma, Braz.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cintigo *Wallace, India.*
Cinnarizine (p. 622·1).
Vertigo; tinnitus; Ménière's disease.

Cintilan *Medley, Braz.*
Piracetam (p. 393·3).
Behaviour disorders in children; cerebrovascular disorders; senile dementia.

Cinula *Soho, Indon.*
Cinnamon (p. 2479·2); thioctic acid (p. 2629·1); cyanocobalamin (p. 2107·2).
Diabetes mellitus.

Cinvert *Baroda, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinvit-D *Cinerea, India.*
Colecalciferol (p. 2113·1).

Cinxim *Cinerea, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cinzan *FDC, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Cinzin *Cinerea, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Cinzole *Serum Institute, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Ciocar *Mavi, Mex.†*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Cional *Nycomed, Austria.*
Aluminium formate (p. 1817·1); chamomile (p. 2474·1); sage (p. 2608·3); arnica (p. 2447·2).
Mouth and throat disorders.

Cip *Helios, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cip eco *Sandoz, Switz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipact *Medico, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipad *David, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipadur *Cipla-Medpro, S.Afr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cipalat *Cipla-Medpro, S.Afr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Cipamox *Atral, Port.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Cipancin *Cipan, Port.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Cipanfeno *Cipan, Port.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Cipasid *Siam Bheasach, Thai.*
Cisapride (p. 1831·3).
Gastroparesis; gastro-oesophageal reflux; intestinal pseudo-obstruction; dyspepsia; constipation.

Cipcal *Cipla, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Cipcal M *Cipla, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); minerals.
Calcium and vitamin D deficiency.

Cipcin *Akums, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipcin-TNZ *Akums, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipcorlin *Cipla, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Cipcot *Blubell, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipcot-TZ *Blubell, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciperico *Cimed, Braz.*
St John's wort (p. 449·1).
Depression.

Ciperina *Gache, Venez.*
Piperazine (p. 163·1).
Worm infections.

Ciperus *Ist. Chim. Inter., Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipex *Cipla-Medpro, S.Afr.*
Mebendazole (p. 158·3).
Worm infections.

Cipflocin *Asian Pharm, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipflox *Mylan, NZ.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipflox-TZ *Chemech, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipgen *Cadila, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipgen TZ *Cadila, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Cipgesic *Cipla, India.*
Ibuprofen (p. 68·2).
Fever; pain; inflammation.

Cipgesic Plus *Cipla, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Cipglow *Glories, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipglow-TZ *Glories, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciphin *Zentiva, Cz.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zentiva, Hung.†; Zentiva, Pol.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciphlenat *Natco, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Cipic *Biological E, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipide *APT, Hong Kong.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipiram *Tecnimede, Port.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Cipkind *JK Biochem, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipla-Actin *Cipla-Medpro, S.Afr.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic rhinitis; pruritus.

Ciplacef *Cipla, India; Cipla, Venez.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ciplactin *Cipla, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine.

Cipladine *Cipla, India.*
Povidone-iodine (p. 1767·1).
Disinfection.

Cipladon *Cipla, India.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3).

Cipla-Duovir *Cipla-Medpro, S.Afr.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Ciplanaze *Cipla-Medpro, S.Afr.*
⊗Beclometasone dipropionate (p. 1621·2).

Ciplar *Cipla, India.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension.

Ciplar-H *Cipla, India.*
⊗Propranolol hydrochloride (p. 1479·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ciplasyl *Cipla-Medpro, S.Afr.*
Perindopril (p. 1466·3).

Ciplatec *Cipla-Medpro, S.Afr.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Ciplatrim *Cipla-Medpro, S.Afr.*
⊗Sibutramine (p. 2330·2).
Obesity.

Ciplavasc *Cipla-Medpro, S.Afr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ciplazar *Cipla-Medpro, S.Afr.*
Losartan (p. 1422·2).

Ciplexal *Hexal, Philipp.†; Salutas, Philipp.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Ciplin *Cipla, India.*
Co-trimoxazole (p. 277·3).
Pneumocystis pneumonia; bacterial infections; toxoplasmosis.

Cipliv *Indkus, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Ciploric *Cipla, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Ciplox *Cipla, Cz.; Cipla, Hong Kong†; Ibmed, Hung.; Cipla, Israel; Khandelwal, Philipp.; Atral, Port.; Cipla, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipla, India.
Ciprofloxacin (p. 261·1), ciprofloxacin hydrochloride (p. 261·2), or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciplox D *Cipla, India.*
⊗Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Ciplox TZ *Cipla, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Ciploxx *Cipla-Medpro, S.Afr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipmax *Sam Chun Dang, Hong Kong.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cipmox *Cipla, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Cipnet-OZ *Bionet, India.*
Ciprofloxacin (p. 261·1); ornidazole (p. 943·1).

Cipocal *Pharmex (Φαρμεξ), Gr.*
Calcipotriol (p. 1697·2).
Psoriasis.

Cipofix *Cipla-Medpro, S.Afr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Cipon *Unison, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipona *Zota, India.*
Cefpodoxime.
Bacterial infections.

Ciporic *Euphoric, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipotoz *ATOZ, India.*
Cefpodoxime.
Bacterial infections.

Cipotriol *Bright Future, Hong Kong.*
Calcipotriol (p. 1697·2).
Psoriasis.

Cipozed *Zota, India.*
Cefpodoxime.
Bacterial infections.

Ciprager *Gerard, Irl.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Ciprain *Maver, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipralam *Actavis, Irl.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Cipralan *Continental Pharma, Belg.; BMS, Fr.*
Tablets: Cibenzoline succinate (p. 1336·1).
Arrhythmias.

Cipralex *Lundbeck, Austria; Lundbeck, Canad.; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ger.; Lundbeck, Gr.; Lundbeck, Hung.; Lundbeck, India; Lundbeck, Indon.†; Lundbeck, Israel; Lundbeck, Ital.; Lundbeck, Neth.†; Lundbeck, Norw.; Lundbeck, Port.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Spain; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Turk.; Lundbeck, UK; Lundbeck, Ukr.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder; anxiety.

Cipram *Lundbeck, Cz.†; Anpharm (Ανφαρμ), Gr.; Lundbeck, Hong Kong; Lundbeck, Indon.†; Lundbeck, Malaysia; Lundbeck, Singapore; Lundbeck, Thai.†; Lundbeck, Turk.*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Cipramil *Lundbeck, Austral.; Lundbeck, Belg.; Lundbeck, Braz.; Axon, Chile; Lundbeck, China; Xian-Janssen, China; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ger.; Lundbeck, Irl.; Lundbeck, Israel; Lundbeck, Neth.; Lundbeck, Norw.; Healthcare Logistics, NZ; Lundbeck, Pol.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Swed.; Lundbeck, UK; Lundbeck, Ukr.*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Ciprane *Teuto, Braz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in women.

Cipraned *Anfarm, Gr.*
Citalopram hydrobromide (p. 411·1).

Ciprapine *Pinewood, Irl.; Pinewood, Neth.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Ciprasid *Yeni, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipraz *Razak, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprec *Caprifarmindo, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprenit Otico *Qualigen, Spain.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Ciprex *Bosnalijek, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ethix, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprid *Neon, India.*
Cefazolin (p. 237·2).
Bacterial infections.

Cipridanol *Richmond, Arg.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Cipride
Note: this name may be used for preparations of different composition.
Torrent, India.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipril
Note: this name may be used for preparations of different composition.
Cipla, Hong Kong; Cipla, India.
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Cipril-H *Cipla, India.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ciprind *Indoco, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprinol *KRKA, Cz.; KRKA, Neth.; KRKA, Pol.; KRKA, Rus.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

KRKA, Hung.; KRKA, Ukr.
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprinomyl *Mylan, Denm.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprivax *Vivax, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprix *Geolab, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprixin Dexa *Geolab, Braz.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Cipro *Bayer, Arg.; Bayer, Canad.; Rafa, Israel†; Bayer, Mex.; Sandoz, Ukr.; Bayer, USA.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bayer, Braz.; 1A, Ger.†; Biofarma, Turk.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

LBS, Thai.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Cipro HC *Alcon, Arg.; Alcon, Braz.; Alcon, Hong Kong; Alcon, USA.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa; infected ear disorders.

Cipro Otico *Alcon, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Ciproace *Ranbaxy, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproactin *Servinox, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprobac *Pisa, Mex.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprobach *Steinbach, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprobay *Alkon (Αλκον), Gr.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Bacterial ear infections.

Bayer, China.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Bayer, Ger.
Ciprofloxacin (p. 261·1), ciprofloxacin hydrochloride (p. 261·2), or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Bayer Schering, Cz.; Bayer Schering, Hung.; Bayer Schering, Malaysia; Bayer, Philipp.; Bayer, Pol.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Thai.; Bayer, Ukr.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprobay HC *Alcon, S.Afr.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Alcon, Singapore.
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Otitis externa.

Ciprobay HC Otic *Alcon, Cz.†*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Ciprobel *Nobel, Ukr.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Socobom, Belg.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprobet *Umedica, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprobeta *Betapharm, Ger.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprobid *Cadila, India; Cadila, Rus.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Zydus Cadila, Thai.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprobid-TZ *Zydus, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprobiotic *Cryopharma, Mex.; Emcure, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Emcure, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprobiotic-FC *Emcure, India.*
⊗Ciprofloxacin hydrochloride (p. 261·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Ciprobiotic-TN *Emcure, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprobrin *Bryntsalov, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprocap *Pharma Synth, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipro-Cent *Centaur, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Ciprocep *TO-Chemicals, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprocilin *Legrand, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprocin *Farmsintez, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprocina *Pharmaplan, S.Afr.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprocort *Beta, Arg.*
Cream; topical spray: ⊗Ketoconazole (p. 585·3); hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2).
Infected skin disorders; burns.

Beta, Arg.
Injection: ⊗Dexamethasone sodium phosphate (p. 1631·2); cyproheptadine hydrochloride (p. 624·1).
Inflammation; hypersensitivity reactions.

Beta, Arg.
Pessaries: ⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1); metronidazole (p. 936·1).
Vaginal infections.

Ciprocort D *Beta, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Respiratory-tract disorders.

Ciprocort L *Beta, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Ciproctal *Inkeysa, Spain.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprocton *Viofar, Gr.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprocure *Radicura, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprodac *Cadila, India; Zydus, India.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprodac-TZ *Cadila, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprodel *Citadel, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprodex
Note: this name may be used for preparations of different composition.
Alcon, Canad.; Saval, Chile.
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Bacterial ear infections; bacterial eye infections with inflammation.

Alcon, USA.
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected ear disorders.

Dexcel, Israel.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Parenteral Drugs, India.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprodex-TZ *Parenteral Drugs, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprodine *Sanval, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprodoc *Docpharm, Ger.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprodox *Shreya, Rus.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprofal *Vocate, Gr.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprofar *Elofar, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprofarm *Farmak, Ukr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections; bacterial ear infections.

Ciprofarma *Varifarma, Arg.*
Cyproterone (p. 2261·2).

Ciprofat *Riemser, Ger.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprofen *Biodeal, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Pharma Nutria, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprofex *United Drug, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprofin *Utopian, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproflo *Siu Guan, Malaysia.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproflomed *Ranbaxy, Belg.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproflomyl *Mylan, Denm.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproflox *Elmor, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

CT, Ger.†; Senosiain, Mex.; Sydenham, Philipp.; Spirig, Switz.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprofloxacina D *Pharmadorf, Arg.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).

Ciproflоxil *Greenpharma, Braz.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproflox-Otic *Sertex, Arg.†*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Ciproflox-Puren *Actavis, Ger.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprofrankin *Frankin, Hong Kong.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprofur *Teva, Mex.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprogen *Mylan, S.Afr.; General Drugs, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprogis *Perrigo, Israel.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproglen *Glenmark, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprogyl *Mankind, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipro-Hexal *Hexal, S.Afr.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprohexal *Hexal, Mex.†; Sandoz, Singapore.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Hexal, Ger.†; Sandoz, Ukr.†
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprohof *Pharmahof, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproktan *Kocak, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprol *Aspen, Austral.; Arrow, Hong Kong.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Arrow, S.Afr.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprolabsa *Labsa, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprolacare *La Care, Rus.*
Ciprofloxacin (p. 261·1) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprolar *Lark, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprolar-F *Lark, India.*
⊗Ciprofloxacin (p. 261·1); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Ciprolar-FC *Lark, India.*
⊗Ciprofloxacin hydrochloride (p. 261·2); clotrimazole (p. 576·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Ciprolar-T *Lark, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciproleb *Leben, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprolen *AC Helcor, Hung.; Indoco, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprolet *Reddy, India; Reddy, Singapore.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Reddy, Philipp.; Reddy, Rus.; Reddy, Thai.†
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprolet A *Reddy, Rus.*
Ciprofloxacin hydrochloride (p. 261·2); tinidazole (p. 949·2).
Bacterial infections.

Ciprolet-A *Reddy, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprolet-AH *Reddy, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprolip *UCI, Braz.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Ciprolisina *Carnot, Mex.*
Cyproheptadine hydrochloride (p. 624·1); cyanocobalamin (p. 2107·2).
Tonic.

Ciprolone *Masterlek, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cipromac *Sel-J, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipromark *Ultramark, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cipromark-DX *Ultramark, India.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).

Cipromax *Pidek, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Verheilen, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipromed *Austral, Arg.; S Med, Austria; Actavis, Fin.†; Alde Medi Impex, India; Promed, Rus.; ProMed, Ukr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipromet
Note: this name may be used for preparations of different composition.
Metro, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprom-M *M & H, Thai.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Cipromycetine *Mac, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye and ear infections.

Cipromycin *Medichrom, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipronat *Genom, Rus.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Natco, India.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipronatin *Atabay, Turk.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipronat-TZ *Natco, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipronax *Vivax Optipharm, Venez.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cipronex *Polpharma, Pol.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipronex-E *Nestor, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye and ear infections.

Cipronid *Ducto, Braz.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipronij-TZ *Sunij, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipronom *Uniao Quimica, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Cipronova *Willow, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipropan *Panacea, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipropet *Vista, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipropet-TZ *Vista, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipropharm *Actavis, Hung.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproplex *Teva Tuteur, Arg.*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; male sexual deviation; precocious puberty; androgen dependent acne, alopecia, hirsutism, and seborrhoea in women.

Cipropol *Richter, Pol.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipro-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproquin *Hand-Prod, Pol.; Behrens, Venez.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Kopran, India; Claris, Thai.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipro-saar *MIP, Ger.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproscope *CT, Denm.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproser *Serral, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprosia *Willow, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprosia-D *Willow, India.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).

Ciprosol *Claris, Ital.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprospes *Alet, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprostad *Stada, Austria.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprostat *Apsen, Braz.*
Cyproterone acetate (p. 2261·2).
Male hypersexuality; prostatic cancer.

Ciprosun *Sun, Rus.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprosym *Symbiosis, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprosym-TZ *Symbiosis, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprotal *Marck Biosciences, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprotan *Clonmel, Irl.*
Citalopram hydrobromide (p. 411·1).
Depression.

Ciprotec *Reuffer, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprotek *Indkus, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye and ear infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ciproten *AbZ, Denm.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprotenk *Biotenk, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprotini *Centaur, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprotiz *Medley, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprotor *Torrent, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprotum *Profic Organic, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprotum-TZ *Profic Organic, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipro-TZ *Meridian, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipro-V *Vista, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Otitis media.

Ciprova *Lupin, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lupin, Rus.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciproval *Saval, Chile.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprovar *Zota, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprova-T *Lupin, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprovec *Hy-Gro, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprovec-TZ *Hy-Gro, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprovian *Vianex (Βιανεξ), Gr.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprovid *Millimed, Thai.†*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciprovit *Prohealth, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye and ear infections.

Ciprovit Calcio *Beta, Arg.*
Cyproheptadine hydrochloride (p. 624·1); calcium phosphate (p. 1784·2); cyanocobalamin (p. 2107·2).
Tonic.

Ciprovit Energizante *Beta, Arg.*
Cyproheptadine hydrochloride (p. 624·1); vitamins; ginkgo biloba (p. 2512·3); pyritinol hydrochloride (p. 394·3).
Tonic.

Ciprovit Magnesico *Beta, Arg.*
Cyproheptadine hydrochloride (p. 624·1); vitamins; magnesium chloride (p. 1787·1).
Tonic.

Ciprowin *Alembic, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprowin-TZ *Alembic, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprox *Claris, India; Avex, Malaysia.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproxan *Bayer, Jpn; Pond's, Thai.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproxel *Scheeling, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproxen *Cifarma, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproxin *Bayer, Austral.; Bayer, Denm.†; Bayer Schering, Fin.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer, Norw.; Bayer, Swed.; Bayer, Turk.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Bayer, Austria; Bayer, Neth.; Bayer, NZ; Osoth, Thai.; T Man, Thai.; Bayer, UK.
Ciprofloxacin (p. 261·1), ciprofloxacin hydrochloride (p. 261·2), or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Bayer, Israel.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ciproxin HC *Alcon, Austral.; Alcon, Israel†; Alcon, NZ; Alcon, Switz.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa; infected ear disorders.

Ciproxina
Note: this name may be used for preparations of different composition.
Alcon Cusi, Spain.
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Alcon, Mex.; Bayer, Mex.; Bayer, Port.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Bayer, Venez.
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproxina HC *Alcon, Mex.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Otitis externa.

Ciproxina Simple *Alcon Cusi, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Ciproxine *Bayer, Belg.; Bayer, Switz.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproxin-Hydrocortison *Alcon, Fin.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Ciproxino *Andromaco, Chile.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciproxol *Ain Medicare, Malaysia.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Darnitsa, Ukr.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciproxyl *Bangkok Lab & Cosmetic, Hong Kong.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Farmaline, Thai.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprozee-TZ *Wings, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciprozef *Metro, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciprozen *Klar Sehen, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprozen-D *Klar Sehen, India.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Bacterial eye infections.

Ciprozet *Meridian, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprozol *Mankind, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciprum *Pliva, Cz.†; Pliva, Hung.; Pliva Krakow, Pol.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cips *Shreshtha, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipstryn *Cipla, India.*
Streptomycin sulfate (p. 359·1).
Bacterial infections.

Ciptam *Sun, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciptam-CT *Sun, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciptar *Sanify, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciptec *Cipla, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciptech-CT *Pharma-Tech, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipti *Geno, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciptini *Cipla, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciptrogil *Accure, Rus.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Cip-TZ *Helios, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipure *Finecure, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipure-TZ *Finecure, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipven *Vensat, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipven-TZ *Vensat, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipwin *Purewin, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipwin-TZ *Purewin, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cipzen *Cipla, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation, oedema.

Cipzen D *Cipla, India.*
⊗Serrapeptase (p. 2613·3); diclofenac sodium (p. 48·3).

Cipzen N *Cipla, India.*
⊗Serrapeptase (p. 2613·3); nimesulide (p. 101·3).

Cipzone *Medizone, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cipzone-TN *Medizone, India.*
Ciprofloxacin hydrochloride (p. 261·2); tizanidine (p. 2026·2).

Cipzox *Cipla, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Cipzy *Zee, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cipzy-TZ *Zee, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ciqfadin *IQFA, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciral *Hiral, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciral-TZ *Hiral, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cirantan *AstraZeneca, Neth.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Circadin *Aspen, Austral.; Neurim, Austria; Nycomed, Belg.; Neurim, Cz.; Neurim, Denm.; Lundbeck, Fr.; Desitin, Ger.; Takeda, Gr.; Lundbeck, Hung.; Neurim, Hung.; Neurim, Irl.; Neurim, Israel; Takeda, Neth.; Neurim, Norw.; Healthcare Logistics, NZ; Neurim, Pol.; Neurim, Port.; Novartis Consumer, Rus.; Juste, Spain; Nycomed, Swed.; Neurim, Switz.; Neurim, Thai.; Lundbeck, UK.*
Melatonin (p. 2551·3).
Insomnia; sleep disorders.

Circanetten *Shinyaku, Jpn; Evers, Thai.*
Potassium acid tartrate (p. 1879·2); senna (p. 1885·1); sulfur (p. 1721·1); paraphlebon.
Haemorrhoids; varices.

Circarol *Jin Yang, Malaysia.*
Crataegus (p. 2488·1); melissa (p. 2552·3); ginkgo biloba (p. 2512·3); garlic oil (p. 2510·3).
Circulatory disorders.

Circavite-T *Circle, USA.*
Vitamins; minerals; iron (p. 2073·1).

Circlet *Organon, Cz.; MSD, Israel; Benedetti, Ital.; Organon, Neth.; Organon, Pol.*
Etonogestrel (p. 2277·2); ethinylestradiol (p. 2275·3).
Contraceptive vaginal ring.

Circocric *Biomedica, Gr.*
Cisapride (p. 1831·3).
Gastroparesis; gastro-oesophageal reflux.

Circonyl *TRB, Arg.*
Quinine sulfate (p. 665·2).
Nocturnal leg cramps.

Circula *T Man, Thai.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Circulan
Note: this name may be used for preparations of different composition.
Dong-A, Philipp.; Macropharma, Philipp.
Crataegus (p. 2488·1); ginkgo biloba (p. 2512·3); garlic oil (p. 2510·3); melissa (p. 2552·3).
Circulatory disorders.

Merz, Switz.†
Crataegus (p. 2488·1); passion flower (p. 2584·1).
Cardiac disorders.

Circulat *Polpharma, Pol.†*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Circulatonic *Phytomedica, Fr.†*
Menthol (p. 2553·2); camphor (p. 2466·2); cypress oil (p. 2491·1).
Circulatory disorders.

Circulatorio *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Circulife *New Life, Arg.*
Amino acids; vitamins.
Dietary supplement.

Circuman *T Man, Thai.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Circuvit *Ariston, Arg.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Cirflox Oftal *Klonal, Arg.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Cirflox Otic *Klonal, Arg.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Infected ear disorders.

Cirflox-G *Klonal, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciriax *Rhein, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Roemmers, Arg.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ciriax D *Poen Vision, Mex.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Ciriax Otic *Roemmers, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Ciriax Otic L *Roemmers, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1); lidocaine hydrochloride (p. 1988·2).
Otitis externa.

Cirizine *Biospray, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cirkan à la Prednacinolone *Pierre Fabre, Fr.*
⊗Desonide (p. 1630·1); lidocaine hydrochloride (p. 1988·2); vitamin A palmitate (p. 2098·3); ruscosides; tocoferil acetate (p. 2119·2); heparin sodium (p. 1396·3).
Anorectal disorders.

Cirkuhep *Roha, Spain.*
Cynara (p. 2490·3).
Dyspepsia; digestive disorders.

Cirkulin *Munir, Turk.*
Garlic (p. 2510·3).
Hypertension.

Roha, Rus.
Valerian (p. 2640·2).
Sleep disorders; nervous disorders.

Cirkulin Valerian *Munir, Turk.*
Valerian (p. 2640·2).
Nervous disorders; insomnia.

Cirkulin Valeriana *Naturprodukt, Hung.; Roha, Hung.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Insomnia; anxiety.

Cirkused *Roha, Pol.*
Valerian (p. 2640·2).
Nervous disorders.

Cirloid *Fahrenheit, Indon.*
Codergocrine mesilate (p. 389·2).
Mental function impairment in the elderly.

Cirok *One Pharma, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Yik Kwan, Hong Kong†; Pharmakin, Venez.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cirrus *UCB, Belg.; UCB, Fin.; UCB, Hong Kong†; UCB, Indon.; UCB, Malaysia†; Vedim, Pol.; UCB, Port.†; UCB, Turk.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; allergic rhinitis; cold symptoms.

Ciruela Fibra *Garden House, Arg.†*
Senna (p. 1885·1).

Ciruelax Comp *Andromaco, Mex.*
Senna (p. 1885·1).
Constipation.

Ciruelax Jalea *Andromaco, Mex.*
Senna (p. 1885·1); prune (p. 1881·1).
Constipation.

Ciruelax TE *Ivax, Mex.†*
Senna (p. 1885·1).
Constipation.

Cirulan *Novag, Mex.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders.

Cirulaxia *Nycomed, Arg.*
Chewable tablets: Sodium picosulfate (p. 1887·2).
Constipation.

Nycomed, Arg.
Syrup: Prune (p. 1881·1); senna (p. 1885·1).
Constipation.

Cirus *Ventaglio, Chile.*
Ketoprofen (p. 79·1).
Osteoarthritis; pain; rheumatoid arthritis.

Cisacone *Svizera, India.*
Cisapride (p. 1831·3); simeticone (p. 1886·2).

Cisagast *Promed, Rus.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cisaken *Kendrick, Mex.*
Cinnarizine (p. 622·1).
Motion sickness; cerebrovascular disorders; vestibular disorders.

Cisalone *Svizera, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; delayed gastric emptying.

Cisamod *Dollder, Venez.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Cisanorm *Gufic, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cisapac *Inpac, Thai.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Cisapid *Kopran, India; Inpac, Thai.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Cisapid-MPS *Kopran, India.*
Cisapride (p. 1831·3); simeticone (p. 1886·2).

Cisapro *Zydus, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cisarid *Med-One, Gr.*
Cisapride (p. 1831·3).
Gastroparesis; gastro-oesophageal reflux.

Cisaride *Pharmasant, Thai.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux.

Cisariv *East African, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cisaten DT *Kamron, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cisawal *Wallace, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cisbedal *Actavis, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Ciscutan *Pelpharma, Austria.*
Isotretinoin (p. 1706·2).
Acne.

Cisday *Sandoz, Ger.†*
Nifedipine (p. 1447·2).
Hypertension.

Cisen *Lukang Chenxin, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Cisget *Getwell, India.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cis-Gry *Gry, Ger.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Ciskebir *Aspen, Arg.†*
Cisplatin (p. 766·1).

Cismox *Grandix, India.*
Amoxicillin (p. 216·2); carbocisteine (p. 1658·1); *Lactobacillus sporogenes* (p. 2596·3).
Respiratory-tract infections associated with excessive or viscous mucus.

Cisnaf *CIS, Fr.*
Fluorine-18 labelled sodium fluoride (p. 2224·1).
Radionuclide agent for positron emission tomography.

Ci-Sons *Sons, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cisordinol *Lundbeck, Austria; Lundbeck, Chile; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Hung.; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Port.; Lundbeck, Swed.*
Zuclopenthixol acetate (p. 1119·1), zuclopenthixol decanoate (p. 1119·2), or zuclopenthixol hydrochloride (p. 1119·2).
Psychoses; bipolar disorder; behaviour disorders; mania.

Cispel *Panacea, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cisplagen *Serum Institute, Philipp.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplamin *Vianex (Βιανεξ), Gr.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplamol *Vianex (Βιανεξ), Gr.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplan *Natco, India.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplasan *Sanofi-Aventis, Gr.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplat *Biochem, India.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplatex *Eurofarma, Braz.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cisplatyl *Sanofi-Aventis, Fr.†; Sanofi-Aventis, Gr.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cispride *Klonal, Arg.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Cis-SL *Malar, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cistalgan *Rottapharm, Ital.*
Flavoxate hydrochloride (p. 2360·1); propyphenazone (p. 127·3).
Urinary-tract disorders; spasm of the female genital tract.

Cistalgina *Fortbenton, Arg.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Cistamine *LBS, Thai.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; allergic conjunctivitis; allergic skin disorders.

Cisteen *Miracalus, India; Naprod, Philipp.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cistefi *Terapeutico, Ital.*
⊗Turmeric (p. 2218·1); grindelia (p. 2522·3); cranberry (p. 2488·1); echinacea (p. 2498·1); rose (p. 2607·1); mallow (p. 2549·2); tribulus terrestris (p. 2633·3); couch-grass (p. 2487·2); inulin (p. 2534·3); boldo (p. 2458·3).
Genito-urinary disorders.

Cisteil *Geolab, Braz.*
Acetylcysteine (p. 1652·2).

Cisteine *TNP, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Cisticid *Merck, Braz.; Merck, Chile; Merck, Mex.*
Praziquantel (p. 164·1).
Schistosomiasis; cysticercosis; neurocysticercosis.

Cistidac *Eurolab, Arg.*
Lotion: Carnitine (p. 2053·2); grape (p. 2521·3); urtica (p. 2639·3); butcher's broom (p. 2463·1).
Alopecia; hair fragility.

Eurolab, Arg.
Capsules: L-cystine (p. 2059·1); L-methionine (p. 1558·2); L-lysine (p. 2079·3); zinc (p. 2126·1); biotin (p. 2052·2); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2104·3); thioctic acid (p. 2629·1); inositol (p. 2533·2); ferrous sulfate (p. 2062·2).
Hair and nail disorders.

Cistidil *IDI, Ital.*
L-Cystine (p. 2059·1).
Skin disorders.

Cistiflux *Sofar, Ital.*
Cranberry (p. 2488·1).
Urinary-tract disorders.

Cistimax *Fortbenton, Arg.*
Lotion: Methionine (p. 1558·2); pyridoxine (p. 2105·3); zinc sulfate (p. 2126·2).
Hair loss.

Fortbenton, Arg.
Tablets: ⊗Cystine (p. 2059·1); vitamins; minerals; gelatin (p. 1154·1).

Cistimax Ungueal *Fortbenton, Arg.*
Biotin (p. 2052·2); vitamin E (p. 2119·1); formaldehyde (p. 1752·2).
Nail disorders.

Cistimela *Fabop, Arg.†*
Amiodarone (p. 1300·1).
Arrhythmias.

Cistin *DR Johns, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Cistoit-GF *Homeopathic Pharmacy, Rus.*
Arctostaphylos uva-ursi (p. 2453·2); atropa belladonna (p. 2453·3); lytta vesicatoria (p. 2469·2).
Homoeopathic preparation.

Cistomid *Farma 1, Ital.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Cistriz *Shantha, India.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cistus Canadensis Complexe No 86 *Lehning, Fr.†*
Echinacea (p. 2498·1); viola tricolor (p. 2647·3); natrum phosphoricum (p. 1791·2); cistus canadensis; anemone pulsatilla (p. 2600·2); mercurius corrosivus (p. 2555·2); croton tiglium; cantharis (p. 2469·2); arsenicum album (p. 2448·1); juglans (p. 2463·2).
Homoeopathic preparation.

Cistus canadensis Oligoplex *Madaus, Ger.*
Cistus canadensis; anacardium (p. 2471·3); arsenicum album (p. 2448·1); berberis aquifolium (p. 2577·1); hydrocotyle asiatica (p. 1698·3); mezereum.
Homoeopathic preparation.

Ciszy *Zee, India.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; dyspepsia; gastrointestinal motility disorders.

Cita *Sanofi-Aventis, Cz.*
Citalopram hydrobromide (p. 411·1).
Depression.

Cita Sandoz *Sandoz, Ukr.*
Citalopram hydrobromide (p. 411·1).
Formerly known as Citahexal.
Depression; panic disorder.

Citabax *Ranbaxy, Pol.*
Citalopram (p. 411·1).
Depression; panic disorder.

Citabion *Medicus, Gr.*
Cytarabine (p. 774·1).
Malignant neoplasms.

Citaceph *Citadel, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Citacin *Patar, Thai.*
Neomycin (p. 329·3); bacitracin zinc (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Citacip *Stada, Denm.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citadep *Cipla, India; CPH, Port.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citaforin *Legrand, Braz.*
Citalopram (p. 411·1).

Citagen *Generics, Hung.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citagenin *Ivax, Arg.*
Cytarabine (p. 774·1).
Malignant neoplasms.

Citagran *Germed, Braz.*
Citalopram (p. 411·1).

Citaham *Actavis, Denm.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic attacks.

Cital
Note: this name may be used for preparations of different composition.
Eurodrug, Hong Kong; Eurodrug, Malaysia†; Glenmark, Pol.
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Indoco, India.
Sodium acid citrate (p. 1781·1).
Metabolic acidosis; cystitis; renal calculi.

Citalax *Indeco, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety.

Citalec *Zentiva, Cz.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citalgan *Merck, Mex.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Citalgert *Target, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

CitaLich *Winthrop, Ger.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Citalift *Ranbaxy, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Citalo *Meditech, Austral.*
Citalopram hydrobromide (p. 411·1).
Depression.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Citalodep *Extractum, Hung.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citalogamma *Worwag, Ger.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

CitaloHexal *Sandoz, S.Afr.*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Citalomine *Psyco Remedies, India.*
Citalopram (p. 411·1).
Depression; panic disorder.

Citalon *Sandoz, Cz.; Krewel, Ger.; Sandoz, Hung.†; Hexal, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Citalonte *Stada, Denm.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citalop *East West, India; RPG, India.*
Citalopram (p. 411·1) or citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citaloprol *Novendia, Gr.*
Citalopram hydrochloride (p. 411·1).

Citalop-S *RPG, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Citalo-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Citalor *Pfizer, Braz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Citalorin *Masterfarm, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Citalostad *Stada, Austria.*
Citalopram hydrobromide (p. 411·1).
Depression; anxiety; panic disorder; obsessive-compulsive disorder.

Citalowin *Zentiva, Hung.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Citaloxan *Hospira, Port.*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphoma.

Citalvir *Vir, Spain.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Citamycin *Citadel, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Citanest *AstraZeneca, Austral.; Dentsply, Austral.; AstraZeneca, Belg.; Dentsply, Canad.; AstraZeneca, Neth.; AstraZeneca, NZ; AstraZeneca, Swed.; AstraZeneca, Turk.; AstraZeneca, UK; Dentsply, UK; Dentsply, USA.*
Prilocaine hydrochloride (p. 1994·1). Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

Citanest com Octapressin *AstraZeneca, Braz.*
Prilocaine hydrochloride (p. 1994·1). Felypressin (p. 2502·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest Octapressin *Dentsply, Denm.; Dentsply, Fin.; AstraZeneca, Hong Kong†; Dentsply, Norw.; AstraZeneca, Singapore; Dentsply, Swed.; AstraZeneca, Turk.†*
Prilocaine hydrochloride (p. 1994·1). Felypressin (p. 2502·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest with Octapressin *Dentsply, UK.*
Prilocaine hydrochloride (p. 1994·1). Felypressin (p. 2502·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest Octapressine *Dentsply, Neth.*
Prilocaine hydrochloride (p. 1994·1). Felypressin (p. 2502·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanz *Ranbaxy, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Citapram *Sandoz, Hung.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citaprass *Teuto, Braz.*
Citalopram hydrobromide (p. 411·1).

Citara *Intas, India; Fako, Turk.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Citaratio *Ratiopharm, Cz.†; Ratiopharm, Pol.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citarax *Blausiegel, Braz.*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphoma.

Cita-S *Crescent, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Cita-S Forte *Crescent, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Cita-S Plus *Crescent, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Citax F *Biogam, Arg.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; immune thrombocytopenia; auto-immune disorders.

Citaxin *Pliva Krakow, Pol.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citaz *Kalbe, Indon.*
Cilostazol (p. 1337·1).
Arterial occlusion.

Citazon *Kocak, Turk.*
Thioacetazone (p. 377·2).
Tuberculosis.

Citegin *Egis, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Citel *Mankind, India.*
Escitalopram oxalate (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Citexam *Kocak, Turk.*
Citalopram hydrobromide (p. 411·1).

Citi *DWD, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Citibid *Win-Medicare, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Citicholine *Hexpharm, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebral trauma.

Citidine *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Citidipine *Farmedia, Gr.*
Nifedipine (p. 1447·2).

Citiflux *CT, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; rhinitis.

Citiges *GES, Spain.*
Fluconazole (p. 578·2).
Fungal infections.

Citilat
Note: this name may be used for preparations of different composition.
CT, Ital.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.
Revifar, Gr.
Famotidine (p. 1842·1).

Citilin *Unichem, India; Korea United, Philipp.*
Citicoline (p. 2480·1).
Cerebral trauma; cerebrovascular disorders; parkinsonism; pancreatitis.

Citinoides *Serra Pamies, Spain.†*
Lithium carbonate (p. 427·3); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Dyspepsia; gastrointestinal hyperacidity.

Citinova *Ipca, India.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism; head injury.

Citivir *CT, Rus.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Citizol *Aristo, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Citocaina *Cristalia, Braz.*
Prilocaine hydrochloride (p. 1994·1). Felypressin (p. 2502·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citocartin *Molteni, Ital.; Molteni, Neth.; Molteni, Rus.*
Articaine hydrochloride (p. 1980·1). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citodon *Biophausia, Swed.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Citodox *Pfizer, Arg.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Citofast *Glenmark, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Citofolin *Bracco, Ital.*
Calcium folinate (p. 2066·3).
Folic acid deficiency; antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity.

Citogel *Geymonat, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Citoken T *Kendrick, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; inflammation; pain.

Citol *Abdi, Turk.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Tripharma, Rus.
Citalopram (p. 411·1).
Depression.

Citola *La Pharmaceuticals, India.*
Citalopram (p. 411·1).
Depression; panic disorder.

Citolap *Tum, Turk.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citoles *Abdi, Turk.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Citolixin *Frik, Turk.*
Citalopram hydrobromide (p. 411·1).

Citomid *Laboratorios Chile, Chile†; Teva, Mex.†; Lemery, Rus.; Teva, Thai.†*
Vincristine sulfate (p. 882·3).
Malignant neoplasms; immune thrombocytopenia.

Citon *Neon, India.*
Cyanocobalamin (p. 2107·2).

Citoneurin *Merck, Braz.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; vitamin B supplement.

Citoneuron *Andromaco, Chile.*
Sodium cytidine monophosphate (p. 2491·1); trisodium uridine triphosphate (p. 2638·1); hydroxocobalamin (p. 2107·3).
Myopathy; neuralgia; neuritis.

Citopam *Sun, India.*
Citalopram (p. 411·1).
Depression; panic disorder.

Citophase *Farmila, Ital.*
Cytochrome-c peroxidase (p. 2491·2).
Corneal disorders.

Citoplatina *Meizler, Braz.*
Carboplatin (p. 759·1).

Citoplax *Bergamo, Braz.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Citopram *Santa, Gr.*
Citalopram hydrobromide (p. 411·1).

Citorsal *Ern, Spain.*
Calcium lactate (p. 1784·1); citric acid (p. 2480·3); magnesium sulfate (p. 1787·3); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); tribasic sodium phosphate (p. 1791·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration.

Citos *Nordin, Mex.*
Tolu balsam (p. 1679·2); drosera (p. 2497·2).
Cough.

Citosol *Kyorin, Jpn.*
Thiamylal sodium (p. 1915·1).
General anaesthesia.

Citostal *BMS, Braz.*
Lomustine (p. 818·1).
Malignant neoplasms.

Citovirax *Roche, Ital.*
Ganciclovir (p. 982·3) or ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

Citox *Sun, Mex.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Citra *Plus, India.*
Sodium acid citrate (p. 1781·1).

Citra pH *ValMed, USA.*
Sodium citrate (p. 1781·2).
Hyperacidity.

Citracal *Mission, Austral.; Mission Pharmacal, Hong Kong†; Mission Pharmacal, Singapore†; Mission Pharmacal, USA; Vivax Gynopharm, Venez.*
Calcium citrate (p. 1783·2).
Hypocalcaemia; osteoporosis; calcium supplement; hyperphosphataemia; calcium deficiency.

Citracal D *Vivax Gynopharm, Venez.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Citracal + D *Bayer Consumer, Canad.; Mission Pharmacal, Hong Kong.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Hypocalcaemia; osteoporosis; calcium deficiency; hyperphosphataemia.

Mission Pharmacal, Singapore.†
Calcium citrate (p. 1783·2); vitamin D (p. 2112·3).
Calcium deficiency; osteoporosis.

Citracal + D3 *Bayer, USA.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).

Citracal Plus with Magnesium *Mission Pharmacal, USA.*
Calcium (p. 1783·1); vitamin D (p. 2113·3); pyridoxine (p. 2105·3); minerals.

Citracal Prenatal *Mission Pharmacal, USA.*
Vitamins; minerals.
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement for pregnant and postnatal women.

Citracal Prenatal + DHA *Mission Pharmacal, USA.*
Tablets, Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1) capsules, docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.
Dietary supplement.

Citra-Calcemin *Bayer Consumer, Ukr.*
Minerals; colecalciferol (p. 2113·1).
Dietary supplement.

Citracium *Garden State, Hong Kong.*
Calcium (p. 1783·1).
Calcium deficiency; osteoporosis; hyperphosphataemia.

CitraFleet *Casen Fleet, Denm.; Casen Fleet, Fin.; Aptalis, Fr.; Recordati, Ger.; Casen Fleet, Irl.; CCS, Norw.; Casen Fleet, Port.; Casen Fleet, Spain; CCS, Swed.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).
Bowel evacuation.

De Witt, UK.
Sodium picosulfate (p. 1887·2); magnesium citrate (p. 1857·1).
Bowel evacuation.

Citraglow *Aglowmed, India.*
Sodium acid citrate (p. 1781·1).

Citraglucosolan *Moschimfarm, Rus.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Citrakul *Finecure, India.*
Sodium acid citrate (p. 1781·1).

Citral *Synco, Hong Kong†; Synco, Singapore.*
Potassium citrate (p. 1780·3).

Citralamina *SM, Venez.*
Oxolamine citrate (p. 1671·2).
Respiratory-tract disorders.

Citralite *Aventis, Austral.†*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); tartaric acid (p. 2626·1).
Urinary alkalinisation.

Citralka *Pfizer, India.*
Sodium acid citrate (p. 1781·1).
Acidosis.

Citra-Lock *Dirinco, Neth.*
Sodium citrate (p. 1781·2).
To maintain patency of central venous catheters.

Citramag *Sanochemia, UK.*
Magnesium citrate (p. 1857·1).
Bowel evacuation.

Citramar *Dupomar, Arg.†*
Calcium citrate (p. 1783·2).
Calcium deficiency; osteoporosis.

Citramar D *Dupomar, Arg.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteopenia; osteoporosis.

Citramon Extra *Darnitsa, Ukr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Citramon Forte *Darnitsa, Ukr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); citric acid (p. 2480·3).
Pain; fever.

Citramon Maxi *Darnitsa, Ukr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Citramon P *Biosintez, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Citramon-Borimed *Borisov, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Citramon-F Forte *Phytopharm, Ukr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Citramon-MPF *Mosfarma, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

CitraNatal B-Calm *Mission Pharmacal, USA.*
Oval tablets, vitamins; calcium (p. 1783·1); iron (p. 2073·1); round tablets, vitamin B_6 (p. 2105·3).
Dietary supplement.

CitraNatal Harmony *Mission Pharmacal, USA.*
Folic acid (p. 2063·1); calcium (p. 1783·1); iron (p. 2073·1); vitamin D (p. 2112·3); vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1); docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Citrapak *Ufavita, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3) ascorbic acid (p. 2110·3).
Pain; fever.

Citrarginine *Laphal, Ukr.*
Neutral arginine citrate (p. 2049·1) betaine hydrochloride (p. 2456·1); betaine (p. 2456·1).
Liver disorders.

Zambon, Fr.†
Neutral arginine citrate (p. 2049·1); betaine (p. 2456·1); betaine hydrochloride (p. 2456·1).
Liver disorders.

Citrato Espresso Gabbiani *Montefarmaco, Ital.*
Magnesium oxide (p. 1857·3); magnesium carbonate (p. 1856·2).
Constipation.

Citrato Espresso S. Pellegrino *Sanofi-Aventis, Ital.*
Magnesium hydroxide (p. 1857·2).
Constipation.

Citravescent *Sanofi-Aventis, Austral.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); tartaric acid (p. 2626·1).
Urinary alkalinisation; dyspepsia; heartburn.

Sigma, Singapore.
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Urinary alkalinisation.

Pacific, NZ.†
Sodium citrotartrate (p. 1780·3).
Acidosis; urinary alkalinisation; gastric hyperacidity.

Citravit *Farmstandart, Rus.*
Ascorbic acid (p. 2110·3).

Citravite *Pharmed, India.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Scurvy; adjunct in wounds and infections.

Citraz *Reddy, S.Afr.*
Escitalopram (p. 416·2).
Depression; panic disorder.

Citredici UBT Kit *Cortex, Ital.*
Carbon-13 labelled urea (p. 2470·3).
Diagnosis of gastroduodenal Helicobacter pylori *infection.*

Citrel *Alter, Spain.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Citrex *Deva, Turk.*
Citalopram hydrobromide (p. 411·1).

Citrex Vitamin C *Pharmaniaga, Malaysia.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Citrex Vitamin E *Pharmaniaga, Malaysia.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Citri Slim+Trim *Bioglan, Austral.†*
Garcinia (p. 2510·2); chromium trichloride (p. 2055·3); pectin (p. 2200·3); methylcellulose (p. 2197·3); magnesium amino acid chelate (p. 2048·3).
Dietary supplement; obesity.

Citrihexal *Sandoz, Austral.†*
Calcitriol (p. 2113·1).
Hypocalcaemia; hypoparathyroidism; osteoporosis; rickets.

Citrizan *IDI, Ital.*
Catalase (equine) (p. 2472·2).
Burns; skin ulceration.

Citrizan Antibiotico *IDI, Ital.*
Catalase (equine) (p. 2472·2); gentamicin sulfate (p. 304·2).
Infected burns and skin ulcers.

Citro Jod *Esoform, Ital.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Citro Macalvit *Novartis, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2).

Citro-C
Note: this name may be used for preparations of different composition.
Knop, Chile.
Echinacea (p. 2498·1); ascorbic acid (p. 2110·3).
Respiratory-tract infections.

Citrocarbonate *Hauck, USA; Roberts, USA.*
Sodium bicarbonate (p. 1781·1); anhydrous sodium citrate (p. 1781·2).
Hyperacidity.

Citrocholine *Bailleul, Fr.†*
Oral solution: Choline citrate (p. 2055·2); sodium acid citrate (p. 1781·1); citric acid monohydrate (p. 2480·3); light magnesium carbonate (p. 1856·2).
Dyspepsia.

Bailleul, Fr.†
Oral powder: Sodium citrate (p. 1781·2); magnesium citrate (p. 1857·1); choline citrate (p. 2055·2).
Dyspepsia.

Citrocil *Reig Jofre, Spain.*
Dihydrostreptomycin sulfate (p. 286·3).
Gastrointestinal infections.

Citrocil Alcolico *Manetti Roberts, Ital.†*
Benzalkonium chloride (p. 1737·1); isopropyl alcohol (p. 1758·3).
Instrument disinfection.

Citrocium *Bal, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Citroclorex *Esoform, Ital.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Skin and instrument disinfection.

Citrocola *Argenfarma, Arg.*
Ascorbic acid (p. 2110·3).

Citrodan *Odan, Canad.*
Magnesium citrate (p. 1857·1).
Constipation.

Citroepatina *Bayer, Ital.†*
Betaine monocitrate (p. 2456·1); sorbitol (p. 2092·1); sodium bicarbonate (p. 1781·1); anhydrous citric acid (p. 2480·3).
Digestive disorders.

Citro-Flav *Goldline, USA.*
Citrus bioflavonoids complex (p. 2505·2).
Capillary bleeding.

Citrokalcium *Pharma Patent, Hung.*
Calcium citrate (p. 1783·2).
Calcium supplement; osteomalacia; osteoporosis; rickets.

Citrokehl *Sanum-Kehlbeck, Ger.*
Acidum citricum (p. 2480·3).
Homoeopathic preparation.

Citrol *Rowex, Irl.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citrolithin *Farmanic, Gr.*
Citric acid (p. 2480·3); sodium citrate (p. 1781·2); potassium citrate (p. 1780·3).

Citrolyt *Filofarm, Pol.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Gout; renal calculi.

Citro-Mag *Teva, Canad.*
Magnesium citrate (p. 1857·1).
Constipation; bowel evacuation.

Citromagnesiaca *Farve, Ital.; Nova Argentia, Ital.; Sella, Ital.*
Citric acid (p. 2480·3); magnesium carbonate (p. 1856·2).
Constipation.

Citromax *UniOrange, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3).

Citromax-CT *UniOrange, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2).

Citromed *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Citromed 85 *Esoform, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Skin disinfection.

Citromed Chirurgico *Esoform, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Citromed Chlor *Esoform, Ital.*
Tosylchloramide sodium (p. 1773·1).
Surface disinfection.

Citromed Soap *Esoform, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Skin disinfection.

Citromedics Disinfettante *Esoform, Ital.*
Sodium *o*-phenylphenol (p. 1762·3).
Surface disinfection.

Citromedics Pronto *Sanitas, Ital.†*
Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3).
Instrument disinfection.

Citromel *Knop, Chile.*
Melissa (p. 2552·3).
Anxiety; gastrointestinal disorders.

Citron Chaud DM *Prodemdis, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); dextromethorphan hydrobromide (p. 1660·1); ascorbic acid (p. 2110·3).

Citronil *Orion, Pol.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Citropac *Darnitsa, Ukr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Citropaïn *Iromedica, Switz.*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat pain and inflammation.

Citropepsin *ICN, Pol.*
⊗Citric acid (p. 2480·3); pepsin (p. 2586·1).
Digestive disorders.

Citropiperazina *Bruno, Ital.*
Piperazine citrate (p. 163·1).
Urinary alkalinisation.

Citroplex *Neo Quimica, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Citrosan *Reckitt Benckiser, Neth.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); sodium citrate (p. 1781·2).
Cold and influenza symptoms.

Citrosil
Note: this name may be used for preparations of different composition.
Manetti Roberts, Ital.
Benzalkonium chloride (p. 1737·1).
Disinfection of skin, burns, and wounds.

Citrosil Alcolico Azzuro *Manetti Roberts, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1); sodium nitrite (p. 1574·3).
Instrument disinfection.

Citrosil Alcolico Bruno *Manetti Roberts, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Skin and wound disinfection.

Citrosil Alcolico Incolore *Manetti Roberts, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Skin and wound disinfection.

Citrosil Nubesan *Manetti Roberts, Ital.*
Benzalkonium chloride (p. 1737·1); benzoin resin (p. 2624·3).
Surface disinfection.

Citro-Soda *Adcock Ingram, S.Afr.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); citric acid (p. 2480·3).
Gastric hyperacidity; urinary alkalinisation.

Pharmacia Upjohn, India.
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); sodium citrate (p. 1781·2); tartaric acid (p. 2626·1).
Antacid; urinary alkalinisation; constipation.

Citrosodina *Bayer, Ital.*
Sodium citrate (p. 1781·2).
Gastric hyperacidity.

Citrosol *Otto, Indon.*
Misoprostol (p. 2140·3).
NSAID-associated gastric ulcer.

Citrosteril Ambiente *Sanitas, Ital.*
Benzalkonium chloride (p. 1737·1).
Linen disinfection.

Citrosteril Aspiratori *Sanitas, Ital.*
Orthophenylphenol (p. 1762·3).
Disinfection of aspirators.

Citrosteril Deterferri *Sanitas, Ital.*
Benzalkonium chloride (p. 1737·1).
Instrument disinfection.

Citrosteril Impronte *Sanitas, Ital.*
Glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1).
Disinfection in dentistry.

Citrosteril Pronto *Sanitas, Ital.*
Benzalkonium chloride (p. 1737·1); chlorhexidine (p. 1743·2).
Disinfection in dentistry.

Citrosteril Sterilferri *Sanitas, Ital.*
Glutaral (p. 1753·2).
Instrument disinfection.

Citrosteril Strumenti *Sanitas, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Instrument disinfection.

Citrosystem *Antipiol, Ital.*
Citronella oil (p. 2481·1); basil oil (p. 2453·1); lavender oil (p. 2541·1).
Insect repellent.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Citrotein *Sandoz Nutrition, USA.*
Lactose-, cholesterol-, and gluten-free preparation for enteral nutrition.

Citrovenot *Bros, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Citrovit *Sanofi-Aventis, Braz.; McNeil, Spain.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement; vitamin C deficiency.

Citrovita *Argenfarma, Arg.*
Chewable tablets: Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Dietary supplement.

Argenfarma, Arg.†
Oral solution: Ascorbic acid (p. 2110·3).

Citrucel *GSK, USA.*
Methylcellulose (p. 2197·3).
Constipation; bowel evacuation.

Citrucin *Morishita, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Citrus Calcium + D *Rugby, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).

Citrus-flav C *Fibertone, USA.*
Citrus bioflavonoids complex (p. 2505·2); vitamin C (p. 2110·3); hesperidin (p. 2505·2); acerola; rutoside (p. 2505·3).
Capillary bleeding.

Citta *Eurofarma, Braz.*
Citalopram (p. 411·1).
Depression; anxiety.

Civalex *Hovid, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Civell *Novell, Indon.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Civeran *Qualigen, Spain.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Civertim *Geolab, Braz.*
Cinnarizine (p. 622·1).
Vestibular disorders.

Civic *Dexter, India.*
Cefixime (p. 240·3).
Bacterial infections.

Civigel *Alcon, Fr.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Civir *Biomax, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ciwi *Winsome, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ciwi-TZ *Winsome, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cixin *Geolab, Braz.*
Colchicine (p. 604·1).
Gout.

Cixtor *Solvang, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ciz Cold *Aamorb, India.*
Levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Ciza *Intas, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Cizafast *Claris, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Ciza-MPS *Intas, India.*
Cisapride (p. 1831·3); dimeticone (p. 1886·2).

Cizap *Reliance, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Cizap-MPS *Reliance, India.*
Cisapride (p. 1831·3); simeticone (p. 1886·2).

Cizax *Mantecorp, Braz.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Cizetol *Cipla, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Ciz-L *McNeil & Argus, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Ciz-LE *Aamorb, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Ciz-LE-D *Aamorb, India.*
⊗Levocetirizine (p. 632·3); pseudoephedrine (p. 1676·1).

Cizo *Bosch, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cizon *Cinerea, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Cizon-SB *Cinerea, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cizoren *Stadmed, India.*
Haloperidol (p. 1077·1).
Psychoses; childhood behaviour disorders.

Cizoren Plus *Stadmed, India.*
Haloperidol (p. 1077·1); trihexyphenidyl hydrochloride (p. 917·3).

CK-2 *Degorts, Mex.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Rhinitis; cough.

C-4-Kids *Terramedic, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

CKP *Bell, India.†*
Vitamin C (p. 2110·3); carbazochrome salicylate (p. 1137·1); menadione sodium bisulfite (p. 2122·2); rutoside (p. 2505·3); calcium hydrogen phosphate (p. 1783·3).
Haemorrhagic disorders.

CL tre *Nova Argentia, Ital.*
Trichloroacetic acid (p. 1727·2).
Warts.

CLA 500 *Nutrilite, Arg.*
Conjugated linoleic acid from safflower oil (p. 2509·2).
Dietary supplement.

Clabat *Interbat, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clabax *Ranbaxy, Ukr.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori *eradication; toxoplasmosis.*

Clabel *Nobel, Turk.; Nobel, Ukr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clabet *Umedica, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clabin
Note: this name may be used for preparations of different composition.
Chefaro, Ger.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Corns; calluses; warts.

Interdelta, Switz.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); resorcinol (p. 1718·3).
Corns; warts; calluses; verrucas.

Clacee *Aspen, S.Afr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clacef *Dexa, Indon.; Dexa, Singapore.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clacin
Note: this name may be used for preparations of different composition.
APT, Hong Kong.
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Inga, India.
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Clacina *BioSaude, Port.; GPO, Thai.*
Clarithromycin (p. 266·2).
Bacterial infections; eradication of Helicobacter pylori.

Clacine *Kalbe, Indon.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clacinia *GPO, Thai.*
Clarithromycin (p. 266·2).
Bacterial infections.

C-Lactum *Hanburys, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Clacy *Alembic, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Cladex *Dexa, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Cladia *Medinfar, Port.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Cladostad *Stada, Cz.; Stada, Hung.*
Itraconazole (p. 583·3).
Fungal infections.

Clafel *Elfin, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Claferon-O *Sanofi-Aventis, India.*
Cefixime (p. 240·3).
Bacterial infections.

Clafetam *Ahn-Gook, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clafexim *Coronet, Indon.*
Cefotaxime (p. 244·1).
Bacterial infections.

Clafobrin *Bryntsalov, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clafojen *Sel-J, Philipp.*
Cefotaxime (p. 244·1).
Bacterial infections.

Claforan *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Aventis, NZ†; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Rus.; Aventis, S.Afr.†; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.†; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in some intramuscular injections to alleviate the pain of injection
Bacterial infections.

NCPC, China.
Cefotaxime (p. 244·1).
Bacterial infections.

Clafordil *Ariston, Braz.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Claformin *Orchid, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Clafoxim *Kalbe, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clairette *Stragen, UK.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne or hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Clairo *Weleda, S.Afr.†*
Caraway (p. 2470·2); clove (p. 2481·2); erythraea centaury (p. 2473·2); peppermint leaf (p. 1877·1); achillea (p. 2427·3); hoyae carnosae; aniseed (p. 2444·2); senna (p. 1885·1).
Constipation; digestive disorders.

Clairodermyl *Creme d'Orient, Fr.*
Mequinol (p. 1711·1).
Hyperpigmentation.

Clairyg *LFB, Fr.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency syndromes; hypogammaglobulinaemia; passive immunisation; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone-marrow transplantation.

Clalodine *Pharmasant, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Clambusil *Loeffler, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clamchek *Indoco, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clamed *Darnitsa, Ukr.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clamelle *Cipla-Medpro, S.Afr.; Actavis, UK.*
Azithromycin (p. 221·2).
Chlamydia infection.

Clamentin *Mylan, S.Afr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

YSP, Malaysia.
Amoxicillin trihydrate (p. 216·2) or amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clamet *Essweil, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Clamiben *Teuto, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Clamicin *Medley, Braz.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clamide *Hovid, Hong Kong; Hovid, Singapore.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Clamine-T *Abdi, Turk.*
Clindamycin phosphate (p. 269·3).

Clamist *Wanbury, India.*
Clemastine fumarate (p. 622·3).
Hypersensitivity reactions.

Clamohexal *Hexal, Austral.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clamonex *Yungjin, Singapore.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clamosar *Biochimic, Rus.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clamovid *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Philipp.; Hovid, Singapore.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clamox
Note: this name may be used for preparations of different composition.
Bluefish, Cz.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Inga, India.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clamoxil *Pharmawealth, Philipp.*
Amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clamoxin *Maver, Mex.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clamoxol *Cassara, Arg.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clamoxol Bio *Cassara, Arg.*
Oral suspension (Clamoxol), amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3); capsules, *Lactobacillus rhamnosus*

(p. 2596·3); *Lactobacillus acidophillus* (p. 2596·3).
Bacterial infections.

Clamoxy *Global, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clamoxy A *Global, India.*
Ambroxol (p. 1654·3); amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).

Clamoxyl *Alphapharm, Austral.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

GSK, Austria; Beecham, Port.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

GSK, Belg.; GSK, Fr.; GSK, Spain; GSK, Switz.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Clamoxyl Mucolitico *GSK, Spain.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Clamp *Reddy, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3) or clavulanic acid (p. 268·3).
Bacterial infections.

Clamycin *Lupin, India; Domesco, Philipp.; Sandoz, Switz.†; Julphar, UAE.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Claneksi *Sanbe, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sanbe, Philipp.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clanex *Dr Kumars, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clanic *HiGlance, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clanistil *Neo Quimica, Braz.*
⊗Naphazoline (p. 1669·3); pheniramine (p. 637·2).

Clanoxy *Galpha, India; Galpha, Thai.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clanza *Korea United, Philipp.; One Pharma, Philipp.*
Aceclofenac (p. 16·2).
Inflammation; musculoskeletal and joint disorders; pain.

Clanzoflat *Orfi, Spain.†*
Dimeticone (p. 1886·2); clebopride (p. 1833·1).
Gastrointestinal disorders.

Clapex *Anthiea, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clapharma *Actavis, Indon.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Claquinona *Germed, Braz.*
Hydroquinone (p. 1705·1).

Clar *Hetero, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clara *The Forty-Two, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2).
Pruritus.

Clarac *Ascent, Austral.; Douglas, NZ.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Claradol *Bayer Sante, Fr.*
Paracetamol (p. 115·1).
Pain; fever.

Claradol Caféine *Bayer Sante, Fr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Claradol Codéine *Bayer Sante, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Claral *Intendis, Spain.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Claral Plus *Intendis, Spain.*
⊗Chlorquinaldol (p. 260·1); diflucortolone valerate (p. 1634·1).
Infected skin disorders.

Claramax *Schering-Plough, Austral.†; Schering-Plough, NZ.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Claramid *Pfizer, Fr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Claranta *OEP, Philipp.; Ajanta, Venez.*
Clarithromycin (p. 266·2).
Bacterial infections; leprosy; protozoal infections.

Clarasol *Oftalmi, Venez.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Clarastill *Bruschettini, Malaysia.*
Carmellose (p. 2175·1).
Dry eyes; eye irritation.

Claratyne *MSD, Austral.; Schering-Plough, NZ.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Claravis *Teva, USA.*
Isotretinoin (p. 1706·2).
Acne.

Claraxim *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clarbac *Pentafarma, Port.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarbact *Ipca, India; Ipca, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clareeze Allergy *Eireceutica, Irl.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Clarelux *Pierre Fabre Dermo Kosmetik, Austria; Pierre Fabre, Belg.; Pierre Fabre Dermatologie, Fin.; Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Gr.; Pierre Fabre Dermo-Cosmetique, Irl.; Pierre Fabre, Neth.; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, Spain; Pierre Fabre, Switz.; 3M, UK.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders; scalp disorders.

Clarem *Remedica, Malaysia.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarema *Damor, Ital.*
Suleparoid (p. 1507·2).
Thrombosis prophylaxis; superficial vascular disorders.

Clarens *Alfa Biotech, Ital.*
Sulodexide (p. 1507·3).
Venous ulcers.

Clarex
Note: this name may be used for preparations of different composition.
Elea, Arg.
Erythromycin lactobionate (p. 291·3).
Bacterial conjunctivitis.

Exakta, Mex.
Phenylephrine (p. 1672·2); boric acid (p. 2459·3).
Eye disorders.

Clarex Compuesto *Phoenix, Arg.*
Erythromycin lactobionate (p. 291·3); colistimethate sodium (p. 275·3).
Bacterial eye infections.

Clarexid *Pliva, Cz.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Clargotil *Gedeon Richter, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders; pruritus; allergic conjunctivitis.

Clari *Hanmi, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claribactron *Faran, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claribel *Loyal Advance, Hong Kong.*
Clindamycin phosphate (p. 269·3).
Acne.

Claribid *Pfizer, India.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claribiotic *Baliarda, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claricide *Bilim, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claricin *Livzon, China; Quality, Hong Kong; Waves, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Claricina *Lafedar, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claricip *Cipla, India.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claricof *L'amar Natural Products, Singapore.*
Malabar nut (p. 2549·1); liquorice (p. 1853·2); piper longum; grape (p. 2521·3); ocimum sanctum.
Cough and cold symptoms; sore throat.

Claricort *Schering-Plough, Philipp.; Schering-Plough, Venez.*
⊗Betamethasone (p. 1623·2); loratadine (p. 633·2).
Hypersensitivity reactions.

Clarics *Osper, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarid *Biolab, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Claridase *Ordain, India.*
Syrup: Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ordain, India.
Tablets: ⊗Clarithromycin (p. 266·2); serrapeptase (p. 2613·3).

Clariderm *Stiefel, Thai.†*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Claridex *Schering-Plough, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Claridexultra *Schering-Plough, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).

Claridin *Morepen, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Claridin-D *Morepen, India.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms.

Claridine *Suphong, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Claridon *Schering-Plough, Port.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Claridus *Pharma Line, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarie *Ind-Swift, India; Ind-Swift, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Teva, Irl.
Clarithromycin citrate (p. 266·2).
Bacterial infections.

Clarifex *Difa, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Soap substitute.

Clarifex Scrub *Difa, Ital.*
Chlorhexidine gluconate (p. 1743·3); polyethylene granules (p. 1690·3).
Skin cleanser for oily skin.

Clariflu *MSD, Hong Kong; Schering-Plough, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1).
Allergic rhinitis; cold symptoms; influenza symptoms.

Schering-Plough, Mex.
Loratadine (p. 633·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Allergic rhinitis; cold symptoms.

Clarifriol *Schering-Plough, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1).
Allergic rhinitis; influenza symptoms.

Schering-Plough, Mex.
Loratadine (p. 633·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Allergic rhinitis; cold symptoms.

Clarigen *Biodeal, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clariget *Getz, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarigo *Bionet, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarigrip *Schering-Plough, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1).
Allergic rhinitis; influenza symptoms.

Clarigy *New York Chemical, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

ClariHexal *Hexal, S.Afr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarihexal *Sandoz, Austral.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarihis *Lapi, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Clarihist *LBS, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Claril *Alcon, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Ocular congestion.

Clarilerg *Sandoz, Braz.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Clarimac *Zydus, India.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarimax *Montpellier, Arg.; Andromaco, Chile.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarimex *Pharmex (Φαρμεξ), Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarimid *Epicaris, Arg.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarimil *Apostolou, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarimir *Andromaco, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Clarimir F *Andromaco, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Allergic eye disorders; eye irritation.

Clarimycin *YSP, Malaysia.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarina *Himalaya Herbal, India.*
Aloes (p. 1816·1); rubia cordifolia.
Acne.

Clarinase *Schering-Plough, Austral.†; Aesca, Austria; MSD, Belg.; Schering-Plough, Chile; MSD, China; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.†; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Philipp.; Schering-Plough, Pol.†; MSD, Singapore; MSD, Thai.; Schering-Plough, Turk.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms; pruritus; respiratory-tract congestion.

Clarineo *Neo Quimica, Braz.*
Clarithromycin (p. 266·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Clarinese *Aspen, S.Afr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Clarinet *Vickmans, Hong Kong.†*
Loratadine (p. 633·2).

Clarinex *Schering, USA.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Clarinex-D *Schering-Plough, USA.*
⊗Desloratadine (p. 625·1); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract disorders.

Claripel *GSK, Arg.; Stiefel, Braz.; Stiefel, USA.†*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Claripel Plus *Stiefel, India.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Claripen *Elpen (Ελπεν), Gr.; Elpen, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Claripsine *Actavis, Irl.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Claris *Stratus, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Clarisco *Teofarma, Ital.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Clarisens *Farmstandart, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Clarisoft *Vannier, Arg.*
⊗Phenazone (p. 124·1); ephedrine (p. 1663·1).
Eye disorders.

Claritec *Wanbury, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Claritex *United Drug, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Clariteyes *Schering-Plough, UK.†*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Clarith *Taisho, Jpn; LBS, Thai.*
Clarithromycin (p. 266·2).
Bacterial infections; peptic ulcer.

Clarithro *Aspen, Austral.; Alembic, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarithrobeta *Betapharm, Ger.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori*-associated peptic ulcer.*

Clarithrocid *Cathay, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarithrocin *Libytec, Gr.*
Clarithromycin (p. 266·2).

Clarithrocine *Mepha, Switz.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarithromed *Ranbaxy, Belg.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarithrosin *Sintez, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Claritic *SM, Venez.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claritin *Mantecorp, Braz.; Schering-Plough, Canad.; Schering-Plough, Indon.; MSD, Jpn; Schering-Plough, Philipp.; Schering-Plough, Ukr.; Schering-Plough, USA.*
Loratadine (p. 633·2).
Allergic conjunctivitis; allergic rhinitis; urticaria; pruritus; allergic skin disorders.

Claritin Allergic Congestion Relief *Schering-Plough, Canad.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Claritin Allergy & Sinus *Schering-Plough, Canad.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Claritin Eye *Schering-Plough, USA.*
Ketotifen (p. 631·3).
Allergic conjunctivitis.

Claritin Eye Allergy Relief *Schering-Plough, Canad.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Conjunctivitis.

Claritin Skin Itch Relief *Schering-Plough, Canad.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Claritin-D *Mantecorp, Braz.; Schering, USA.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Nasal congestion; allergic rhinitis.

Claritine *MSD, Belg.; Schering-Plough, Cz.; Schering-Plough, Hung.; MSD, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; MSD, Switz.; Schering-Plough, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; pruritus; allergic skin disorders.

Claritine Active *Schering-Plough, Pol.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Claritino *Milano, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Claritone *Fischer, Israel.*
⊗Glycerol (p. 2517·2); boric acid (p. 2459·3); lacrimol; benzalkonium chloride (p. 1737·1); edetic acid (p. 1550·3).
Dry eyes; eye irritation.

Claritral *Silanes, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claritromax *Prodotti, Braz.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Claritron *Biofarma, Venez.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarituss Plus *Pharmacare, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Cough.

Claritvn *Aesca, Austria; Schering-Plough, Denm.; MSD, Fin.; MSD, Irl.; Schering-Plough, Ital.; Schering-Plough, Norw.; MSD, Swed.; Schering-Plough, UK.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; allergic skin reactions.

Schering-Plough, UK.†
Eye drops: Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Claritvne *Schering-Plough, Arg.; Schering-Plough, Chile; MSD, China; MSD-Chibret, Fr.; Schering-Plough, Gr.; MSD, Hong Kong; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Thai.; Schering-Plough, Venez.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders; allergic conjunctivitis; hypersensitivity reactions; pruritus.

Claritvne Cort *Schering-Plough, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Claritvne D *Schering-Plough, Arg.; Schering-Plough, Gr.; Schering-Plough, S.Afr.†*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms; allergic disorders; upper respiratory-tract congestion.

Schering-Plough, Mex.
Loratadine (p. 633·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Claritvne Plus *MSD, Spain.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Clarium
Note: this name may be used for preparations of different composition.
Desitin, Ger.
Piribedil (p. 911·1).
Parkinsonism.

SMB, Fin.
Clarithromycin (p. 266·2).
Bacterial infections.

Clarivax *Vivax, Venez.*
Clarithromycin (p. 266·2).
Bacterial infections; peptic ulcer.

Clarivir *East African, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clariwin *Micro, India; Brown & Burk, Philipp.; Micro, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarix *Oftalmi, Venez.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; nasal congestion; allergic conjunctivitis; eye congestion.

Clarix Expectorant *Cooperation Pharmaceutique, Fr.*
Carbocisteine (p. 1658·1).
Formerly known as Pectosan Expectorant.
Respiratory-tract congestion.

Clarix Toux Sèche *Cooperation Pharmaceutique, Fr.*
Infant syrup: Pentoxyverine citrate (p. 1672·1).
Formerly known as Pectosan Toux seche.
Cough.

Cooperation Pharmaceutique, Fr.†
Adult syrup: Erysimum (p. 2524·2); pholcodine (p. 1675·1).
Cough.

Clarix Toux Sèche Codéthyline *Cooperation Pharmaceutique, Fr.*
Ethylmorphine hydrochloride (p. 56·3).
Cough.

Claro
Note: this name may be used for preparations of different composition.
ITF, Gr.
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Sandoz, S.Afr.
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.

Clarobiótico *Tecnimede, Port.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claroft *Alcon, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Claroftal *Poen, Arg.*
Sodium cromoglicate (p. 1225·3).
Blepharitis; conjunctivitis.

Clarograf *Justesa Imagen, Arg.; Bayer, Spain.†*
Iopromide (p. 1591·3).
Radiographic contrast medium.

Claromycin *Gap, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claromycine *Spirig, Switz.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claron *Siam Bheasach, Thai.*
Clarithromycin (p. 266·2).
Bacterial infections.

Claropram *Spirig, Switz.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Claropt *Clonmel, Irl.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Clarosip *Grunenthal, Chile†; Grunenthal, Cz.†; Grunenthal, Ger.†; Grunenthal, Irl.†; Grunenthal, Neth.†; Grunenthal, Rus.; Grunenthal, UK.†*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarotadine *Akrikhin, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Clarover *Novartis, Ital.*
Povidone (p. 2204·3).
Dry eyes.

Clarovil *Beta, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clarsin *HPP, Hong Kong.*
Clarithromycin (p. 266·2).
Bacterial infections; leprosy; mycobacterial infections.

Clarus
Note: this name may be used for preparations of different composition.
Mylan, Canad.
Isotretinoin (p. 1706·2).
Acne.

Clarvisan *Allergan, Ital.; Lusomedicamenta, Port.; Alcon Cusi, Spain.†*
Pirenoxine sodium (p. 2591·3).
Cataracts.

Clarvisol *Allergan, Braz.*
Pirenoxine sodium (p. 2591·3).
Cataracts.

Clarvix *Beta, Arg.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Claryl *Pinewood, Irl.; Umedica, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clarzole *Actavis, Cz.; Actavis, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Clasica *Craveri, Arg.*
Pregabalin (p. 545·3).

Clasifel *Stiefel, Chile; Stiefel, Mex.*
Hydroquinone (p. 1705·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1); dioxybenzone (p. 1700·2).
Skin pigmentation disorders.

Clasopan *Ryukakusan, Jpn.†*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Clasprin *Biocon, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Class *Talent, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Class-A *Talent, India.*
Aspirin (p. 22·2); clopidogrel bisulfate (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Classic *Kimia, Indon.*
⊗Furosemide (p. 1387·1).
Oedema; nephrotic syndrome; hypertension.

Classic Prenatal *Rugby, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Formerly known as Prenavite.

Clast
Note: this name may be used for preparations of different composition.
Meiji, Indon.
Clebopride malate (p. 1833·1).
Gastrointestinal disorders.

Nobel, Turk.
Montelukast sodium (p. 1214·3).

Clastec *Avansor, Fin.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Clasteon *Sunovion, Canad.; Beacon, Irl.; Abiogen, Ital.; Beacon, UK.*
Clodronate disodium (p. 1180·3).
Multiple myeloma; hyperparathyroidism; osteoporosis; osteolysis of malignancy; hypercalcaemia of malignancy.

Clastoban *Bayer Sante, Fr.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Clatatin *Molex Ayus, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Clatax *Fahrenheit, Indon.; Sandoz, S.Afr.*
Cefotaxime (p. 244·1).
Bacterial infections.

Clatic *Pasteur, Chile.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clatimox *Candor, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Clatimox Syr *Candor, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clatrocin *Ivax, Mex.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Claudemor *Sankyo, Braz.*
Thromboplastin (p. 1164·1); benzocaine (p. 1980·2); procaine hydrochloride (p. 1994·3); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1); peru balsam (p. 2587·1).
Anorectal disorders.

Clauden *Lohmann, Ger.*
A range of dressings impregnated with thromboplastin (p. 1164·1).
Haemorrhage.

Claudia *Sandoz, Belg.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in females.

Claudic *Biolab Sanus, Braz.*
Cilostazol (p. 1337·1).

Claudicat *Takeda, Ger.; Nycomed, Port.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Clauvmentin *Chandra Bhagat, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavactum *Elder, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavage *Allenge, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavam *Alkem, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ranbaxy, Malaysia; Alkem, Ukr.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavamel *Clonmel, Irl.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavamox *Kalbe, Indon.; Bial, Port.; Grunenthal, Switz.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sandoz, Austria; Taro, Israel.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavant *Columbia, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavasul *Pharmacare, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavbel *Blubell, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavenir *Reig Jofre, Israel.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Claventin
Note: this name may be used for preparations of different composition.
GSK, Fr.
Ticarcillin sodium (p. 378·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Kalbe, Philipp.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Vitamed, Israel.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavepen *Labesfal, Port.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Claver *Zenon, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Claversal *Merck, Austria; Tramedico, Belg.; Recordati, Ger.; Teoforma, Ital.; Nycomed, Port.; Faes, Spain.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Clavid-A *Invision, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clav-ll *Biosync, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavimox *Lark, India; Swiss Parenterals, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavinex *Saval, Chile.*
Potassium clavulanate (p. 268·3); amoxicillin (p. 216·2).
Bacterial infections.

Clavinex Duo *Saval, Chile.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavipen *Worth, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavitrax *Servocare, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavix *Intas, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clavix-AS *Intas, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clavmex *EuroHealth, Philipp.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavmoxy *Great Eastern, Thai.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavnic *Wintech, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavocef *Oboi, Philipp.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clavogard *Biomax, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Clavomax *Harbin, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavomid *Remedica, Malaysia.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Remedica, Thai.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavorex *Indchemie, Philipp.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavotrol *AstraZeneca, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Clavox *United Biotech, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Yuhan, Philipp.
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavoxel *InnoGen, Philipp.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavoxilina Bid *Recalcine, Chile.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavoxin *Pharma Nutria, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clavtax-O *Zuventus, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavter-LB *Dexter, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Clavucid *Astellas, Belg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavucyd *Unipharm, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavulin *GSK, Austral.; GSK, Canad.; Solvay, Ital.; Sanfer, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

GSK, Braz.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Clavulox *GSK, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavulox Duo *GSK, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavu-M *Laborate, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavumed *Alternova, Fin.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Formerly known as Clapharin Comp.
Bacterial infections.

Clavumox *Aspen, S.Afr.; Dollder, Venez.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavunate *Max, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavurion *Orion, Fin.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavuser *Serral, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clavycillin *Apotex, Austral.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Clawkit *Ximena Polanco, Chile.*
Uncaria tomentosa.
Homoeopathic preparation.

Clax *Cadila, India.*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Claxam *Hexal, Braz.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Claxy *Novell, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Claz *Franco-Indian, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Clazide *Pharmahof, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Claz-M *Franco-Indian, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Clazol *OEP, Philipp.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders; intermittent claudication.

CLCD *Sanify, India.*
⊗Beclometasone (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).

Cleactor *Eisai, Jpn.*
Monteplase (p. 1441·1).
Myocardial infarction; pulmonary embolism.

Clean & Clear Continuous Control *Johnson & Johnson, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clean & Clear Foaming Facial Cleanser *Johnson & Johnson, Canad.; Johnson & Johnson, USA.*
Triclosan (p. 1773·2).
Acne; skin cleansing.

Clean & Clear Foaming Facial Wash *Johnson & Johnson, Austral.*
Triclosan (p. 1773·2).
Soap substitute; acne.

Clean & Clear Gel Secativo *Johnson & Johnson, Braz.*
Salicylic acid (p. 1719·1).
Acne.

Clean & Clear Hidratante *Johnson & Johnson, Braz.*
Salicylic acid (p. 1719·1).
Acne.

Clean & Clear Locao Adstringente *Johnson & Johnson, Braz.*
Salicylic acid (p. 1719·1).
Acne.

Clean & Clear Morning Glow *Johnson & Johnson, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Clean & Clear Oil Controlling Toner *Johnson & Johnson, Austral.*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Acne.

Clean & Clear Persa Gel *Johnson & Johnson, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clean & Clear Sabonete Liquido Facial *Johnson & Johnson, Braz.*
Triclosan (p. 1773·2).
Acne.

Clean & Clear Skin Balancing Moisturiser *Johnson & Johnson, Austral.*
Oil-free moisturiser containing salicylic acid (p. 1719·1).
Skin moisturiser.

Clean & Clear Soft *Johnson & Johnson, Canad.†*
Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clean Derm *Rougier, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Clean Hair *Neo Quimica, Braz.*
Permethrin (p. 2159·3).
Pediculosis.

Clean Skin Anti Acne *Mentholatum, Austral.†*
Melaleuca oil (p. 2551·1).
Acne.

Clean Skin Face Wash *Mentholatum, Austral.†*
Melaleuca oil (p. 2551·1); benzalkonium chloride (p. 1737·1).
Acne.

Clean-AC *Avene, Fr.*
Zinc gluconate (p. 2126·2); levomenol (p. 2544·1).
Dry skin following acne treatment.

Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.
Cucurbita (p. 2489·2); zinc gluconate (p. 2126·2).
Acne.

Clean-AF *Floris, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cleanal *Mitsubishi, Jpn.*
Fudosteine (p. 1666·1).
Respiratory-tract congestion.

Cleanance *Pierre Fabre Dermo-Cosmetique, Arg.; Avene, Fr.*
Zinc gluconate (p. 2126·2); salicylic acid (p. 1719·1).
Seborrhoea; acne.

Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Avene, Fr.
Topical gel: Zinc gluconate (p. 2126·2); cucurbita (p. 2489·2).
Seborrhoea.

Pierre Fabre Dermo-Cosmetique, Arg.
Face mask: Kaolin (p. 1850·1); salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); zinc gluconate (p. 2126·2); cucurbita (p. 2489·2); vitamin B_6 (p. 2105·3).
Seborrhoea.

Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.
Topical lotion: Cucurbita (p. 2489·2); zinc gluconate (p. 2126·2); salicylic acid (p. 1719·1).
Seborrhoea; acne.

Silesia, Chile.
Lotion: Zinc gluconate (p. 2126·2).
Seborrhoea; acne.

Cleanance K *Avene, Fr.*
Glycolic acid (p. 1704·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); zinc gluconate (p. 2126·2); cucurbita (p. 2489·2).
Seborrhoea.

Cleancef *Shin Poong, Singapore.*
Cefaclor (p. 232·3).
Bacterial infections.

CleanEars *Naveh, Israel.*
Liquid paraffin (p. 2191·2); squalane (p. 2213·3).
Ear wax removal.

Naveh, Philipp.
Liquid paraffin (p. 2191·2); spearmint oil (p. 2621·2); phytosqualane (p. 2213·3).
Ear wax removal.

Cleanicdent *Polifarma Benessere, Ital.*
Sodium fluoride (p. 2089·2).
Toothpaste; dental caries prevention.

Cleankinol *Legrand, Braz.*
Hydroquinone (p. 1705·1).

Cleanomisin *Yeni, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Cleansing Herbs *Potter's, UK.*
Buckthorn (p. 1824·2); psyllium (p. 1849·1); senna leaves (p. 1885·1); sambucus (p. 2609·3); fennel seed (p. 2503·2); maté (p. 2648·2).
Constipation.

Cleanxate *Sam Chun Dang, Malaysia; Sam Chun Dang, Singapore.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Clear *Alkem, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clear Acne *Dermatological Solutions, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Clear Blue *Novartis, Chile; Volta, Chile.*
Pregnancy test (p. 2596·1).

Leurquin, Hong Kong.
⊗Naphazoline nitrate (p. 1669·3); methylthioninium chloride (p. 1559·1).
Eye irritation.

Clear Capsules *Awareness, Canad.†*
Caraway (p. 2470·2); clove (p. 2481·2); fennel (p. 2503·2); hyssop (p. 2530·3); peppermint (p. 1877·1); thyme (p. 2630·2).

Clear Chest *Laborate, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Clear Cough *Be-Tabs, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Clear Ear *Co-Pharma, UK.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Clear Eyes *Prestige, Canad.; Abbott, NZ; Ross, USA.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Clear Eyes ACR *Abbott, NZ.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.

Clear Eyes Allergy *Prestige, Canad.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).

Clear Eyes CLR *Ross, USA.*
Sodium chloride (p. 1795·1); hypromellose (p. 2189·2).
Moistening drops for contact lenses.

Clear Eyes Contact Lens Relief *Medtech, USA.*
Sorbic acid (p. 1770·2); edetic acid (p. 1550·3).

Clear Eyes for Dry Eyes *Medtech, USA.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Prestige, Canad.
⊗Glycerol (p. 2517·2); carmellose sodium (p. 2175·2).
Dry eyes.

Clear Eyes for Dry Eyes Plus Redness Relief *Prestige, Canad.*
⊗Glycerol (p. 2517·2); hypromellose (p. 2189·2); naphazoline hydrochloride (p. 1669·3).
Dry eyes; eye irritation.

Clear Eyes Plus Redness Relief *Medtech, USA.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Clear Eyes Seasonal Relief *Medtech, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Formerly known as Clear Eyes ACR.
Eye irritation.

Clear Eyes Triple *Prestige, Canad.*
⊗Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3); tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Clear Gel *H & H, India.*
Clindamycin (p. 269·3).
Acne.

Clear Pore On-The-Spot *Johnson & Johnson, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Clear Q *Natural Factors, Canad.†*
Ubidecarenone (p. 2637·1); vitamin E substances (p. 2119·1).

Clear Skin Treatment Repairing *University Medical, Canad.*
Benzoyl peroxide (p. 1696·1).

Clear Sunscreen *Golf America, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clear Tussin 30 *Goldline, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Clear Zinke *Key Sun, Austral.*
SPF 30+ cream: Enzacamene (p. 1703·2); octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Clear Zone *Guthy Renker, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

ClearAc *Hylands, Canad.†*
Berberis vulgaris (p. 2502·1); echinacea augustifolia (p. 2498·1); hepar sulfuricum (p. 1721·3); sulfur iodatum (p. 2624·2).
Homoeopathic preparation.

ClearAc Cleanser *Hylands, Canad.†*
Calendula (p. 2465·2); isopropanol (p. 1758·3); resorcinol (p. 1718·3).
Homoeopathic preparation.

Clearamox *Boehringer Ingelheim, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Clearasil *Reckitt Benckiser, Malaysia.*
Salicylic acid (p. 1719·1).
A range of skin cleansers.

Boots Healthcare, NZ.
Sulfur (p. 1721·1); triclosan (p. 1773·2).
Acne.

Richardson-Vicks Personal Care, USA.
Benzoyl peroxide (p. 1696·1).
Acne.

Clearasil 3 in 1 *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Soap substitute.

Clearasil Acne Control *Reckitt Benckiser, Canad.†*
Resorcinol (p. 1718·3); sulfur (p. 1721·1).

Clearasil Acne Cream *Reckitt Benckiser, Canad.†*
Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne.

Clearasil Active Treatment Cream *Crookes Healthcare, UK.*
Triclosan (p. 1773·2); sulfur (p. 1721·1).
Acne.

Clearasil Antibacterial *Richardson-Vicks Personal Care, USA.*
⊗Triclosan (p. 1773·2); glycerol (p. 2517·2); titanium dioxide (p. 1725·1).
Acne.

Clearasil Benzoyl P *Reckitt Benckiser, S.Afr.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearasil Blackhead Control *Reckitt Benckiser, Austral.*
Salicylic acid (p. 1719·1).
Skin cleanser.

Clearasil Cleanser *Reckitt Benckiser, Canad.†*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Clearstick *Procter & Gamble, USA.*
Salicylic acid (p. 1719·1).

Clearasil Daily Clear Acne B.P. Plus *Reckitt Benckiser, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearasil Daily Face Wash
Note: this name may be used for preparations of different composition.
Procter & Gamble, USA.
Triclosan (p. 1773·2).

Procter & Gamble, Austral.†
Phenoxyisopropanol (p. 1765·1).
Acne.

Clearasil DailyClear *Reckitt Benckiser, Austral.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Deep Cleansing *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil 3 in 1 Deep Cleansing Wash *Reckitt Benckiser, Malaysia.†*
Salicylic acid (p. 1719·1).
Soap substitute.

Clearasil Double Action Pads *Crookes Healthcare, UK.*
Salicylic acid (p. 1719·1).
Formerly known as Clearasil Dual Action Pads.
Acne.

Clearasil Double Clear *Richardson-Vicks, USA.*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1); hamamelis (p. 2523·3).

Clearasil Double Textured Pads *Procter & Gamble, USA.*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).

Clearasil Ice Wash *Reckitt Benckiser, Malaysia†; Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Soap substitute; acne; seborrhoea.

Clearasil Medicated Facial Cleanser *Procter & Gamble, S.Afr.†*
⊗Allantoin (p. 1693·1); alcohol (p. 1733·1); salicylic acid (p. 1719·1).
Acne.

Clearasil Medicated Wipes *Procter & Gamble, Austral.†*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Oil Free Gel Wash *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Pimple Treatment *Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.*
Triclosan (p. 1773·2); sulfur (p. 1721·1); bentonite (p. 2170·3).
Acne.

Clearasil Pimple Treatment Cream *Reckitt Benckiser, Austral.†*
Sulfur (p. 1721·1); triclosan (p. 1773·2).
Acne.

Clearasil Pore Cleansing Lotion *Crookes Healthcare, UK.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Acne.

Clearasil Skin Perfecting Wash *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Stayclear
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Canad.†
Resorcinol (p. 1718·3); sulfur (p. 1721·1).
Acne.

Clearasil Stayclear BP Plus *Reckitt Benckiser, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearasil T *Procter & Gamble, S.Afr.†*
Sulfur (p. 1721·1); triclosan (p. 1773·2); bentonite (p. 2170·3).
Acne.

Clearasil Ultra *Boots Healthcare, NZ.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearasil Ultra Acne Clearing *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Ultra Acne Treatment Cream *Reckitt Benckiser, Austral.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearasil Ultra Deep Pore *Reckitt Benckiser, Malaysia†; Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne; soap substitute.

Clearasil Ultra Overnight *Reckitt Benckiser, Austral.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Ultra Rapid *Reckitt Benckiser, Austral.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Ultra Rapid Action *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Clearasil Ultra Spot Clearing Cream *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1); hydrogen peroxide (p. 1755·2).
Acne.

Clearasil Ultra Spot Clearing Scrub *Reckitt Benckiser, Singapore.*
Salicylic acid (p. 1719·1).
Acne.

Clearblue *Novartis, Braz.; Swiss Precision, Canad.†; Unipath, Israel; Procter & Gamble, Ital.; Pfizer, NZ; Unipath, UK.*
Pregnancy test (p. 2596·1).

Clearblue Easy *Whitehall, Braz.; Whitehall, USA.*
Pregnancy test (p. 2596·1).

Clearblue Easy Ovulation *Unipath, USA.*
Fertility test (p. 2596·1).

Clearblue test d'ovulation *Procter & Gamble, Fr.*
Fertility test (p. 2596·1).

Clearblue test de grossesse *Procter & Gamble, Fr.*
Pregnancy test (p. 2596·1).

Cleardent *Mediline, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Mouth infections; oral hygiene.

Clearex Benzoyl Peroxide *Mediline, Israel.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearex Cover Up *Mediline, Israel.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clearex for Sensitive Skin *Mediline, Israel.*
Salicylic acid (p. 1719·1).
Acne.

Clearine *Novartis, India.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Clearize *Abbott, Venez.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Clearkin *Ind-Swift, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Clearmox *Indoco, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Clearmox-LB *Indoco, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Clearocin *Novartis Consumer, Israel.*
Cetrimonium bromide (p. 1742·3); lidocaine (p. 1988·1); tyrothricin (p. 384·1).
Sore throat; mouth infections.

Clearplan *Unipath, Ital.†; Pfizer, NZ.†*
Fertility test (p. 2596·1).

Clearsing *Duncan, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Clearskin Antibacterial *Avon, Canad.†*
Cream: Benzethonium chloride (p. 1738·1).
Acne.

Clearskin Dual Action *Avon, Canad.†*
Triclosan (p. 1773·2).
Antiseptic; skin cleansing.

Clearskin Professional *Avon, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clearsore *Pinewood, UK.*
Aciclovir (p. 964·1).
Herpes simplex infections of the lips and face.

Cleartop *Cimed, Braz.*
Ketoconazole (p. 585·3).

Cleartuss-D *Cadila, India.*
Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); dextromethorphan (p. 1660·1).

Cleartuss-T *Cadila, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Clear-View
Note: this name may be used for preparations of different composition.
Colgate Oral Care, Austral.†
Demisting solution for dental mirrors and spectacles.

Clearview HCG
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Austral.†; Unipath, UK; Wampole, USA.
Pregnancy test (p. 2596·1).

Clearwax *Cipla, India.*
Paradichlorobenzene (p. 2583·2); benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); turpentine oil (p. 2636·3).
Ear wax removal.

Clearz *Reddy, India.*
Kojic acid (p. 1710·2); vitamin C (p. 2110·3).

Cleating *O2, China.*
Diflunisal (p. 51·3).
Rheumatoid arthritis; osteoarthritis; pain.

Cleblo-CL *Purewin, India.*
Syrup: Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Purewin, India.
Tablets: Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Clebofex *Azevedos, Port.*
Clebopride malate (p. 1833·1).
Gastrointestinal disorders.

Clebolider *Amnol, Ital.†*
Aescin (p. 2431·2); caffeine (p. 1203·3); diosmin (p. 2505·2); turmeric (p. 2218·1); rusco (p. 2463·1); centella (p. 1698·3); arnica (p. 2447·2); ivy (p. 2536·2).
Venous insufficiency.

Cleboril *BB, Ital.; Almirall, Spain.*
Clebopride malate (p. 1833·1).
Nausea and vomiting; gastrointestinal disorders.

Clebudan *Grunenthal, Chile.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps; obstructive airways disease.

Clebutec *Almirall, Port.*
Clebopride malate (p. 1833·1).
Gastrointestinal disorders.

Cleded-AT *Panjon, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Cledex *Panjon, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).

Cledex-AT *Panjon, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Cledex-SF *Panjon, India.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Cledist *Jaldes, Fr.*
Selenium (p. 2086·3); zinc citrate (p. 2126·2); ascorbic acid (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); tagetes; tomato; turmeric (p. 2218·1); grape (p. 2521·3); myrtillus (p. 2566·2); urtica (p. 2639·3).
Dietary supplement.

Cleeravue-M *Stonebridge, USA.*
Minocycline (p. 324·3).
Bacterial infections.

Cleft *Ranbaxy, India.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Clembroxol *Pentafarma, Port.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion and bronchospasm.

Clembumar *Dupomar, Arg.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Clements Iron *Felton, Austral.*
Vitamins; minerals; glucose (p. 2068·3); iron (p. 2073·1).
Iron deficiency; nutritional anaemia.

Clements Tonic *Felton, Austral.*
Vitamins; minerals; ginseng (p. 2513·3); ginkgo biloba (p. 2512·3).
Dietary supplement; tonic.

Clenbunal *RoemmersRowe, Venez.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Clenbuxol *Roemmers Rowe, Venez.*
⊗Clenbuterol (p. 1207·2); ambroxol (p. 1654·3).
Respiratory-tract disorders.

Clendazaf *Zafiro, Mex.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clendix *Rhein, Mex.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clenia *Upsher-Smith, USA.†*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Cleniderm *Soho, Indon.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Clenil *Chiesi, Braz.; Chiesi, Cz.; Chiesi, Gr.; Farmanic, Gr.; Chiesi, Ital.; Chiesi, Malaysia; Chiesi, Port.†; Chiesi, Rus.; Sandoz, S.Afr.; Chiesi, Thai.; UCB, Turk.; Trinity, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease; sinusitis; nasal polyps; allergic rhinitis; asthma.

Clenil Compositum *Chiesi, Braz.; Promedica, Ital.; Chiesi, Thai.†*
⊗Beclometasone dipropionate (p. 1621·2); salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Clenil Forte Jet *Chiesi, Gr.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Clenil Kompoze *UCB, Turk.*
⊗Beclometasone dipropionate (p. 1621·2); salbutamol (p. 1220·2).
Obstructive airways disease.

Clenil Rino *Chiesi, Gr.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Clenilexx *Promedica, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Clenora *DWD, India.*
⊗Cetrimide (p. 1742·1); choline salicylate (p. 39·2); glycerol (p. 2517·2); lidocaine (p. 1988·1); tannic acid (p. 2625·2).

Clenorush *DWD, India.*
⊗Cetrimide (p. 1742·1); choline salicylate (p. 39·2); clotrimazole (p. 576·2); glycerol (p. 2517·2); tannic acid (p. 2625·2).

Clenorush Torche *DWD, India.*
Clotrimazole (p. 576·2).
Oropharyngeal candidiasis.

Clens-100 *Alcon, Braz.*
Cleaning solution for contact lenses.

Alcon, Canad.†
Lubricating and protein-removal solution for contact lenses.

Alcon, Fr.†
Cleansing and wetting solution for contact lenses.

Clentel *Pharma Investi, Chile.*
Clopidogrel bisulfate (p. 1342·3).
Myocardial infarction; unstable angina; cerebrovascular ischaemia.

Clenz *Sun, India.*
Clindamycin (p. 269·3).
Acne.

Clenziderm *Obagi, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Clenzit *Glenmark, Rus.*
Adapalene (p. 1692·1).
Acne.

Clenzit-C *Glenmark, Rus.*
Adapalene (p. 1692·1); clindamycin phosphate (p. 269·3).
Acne.

Clen-Zym *Alcon, UK.*
⊗Pancreatin (p. 2579·3).
Soft contact lens cleanser.

Cleocin *Pfizer, Austral.; Eczacibasi, Turk.; Pharmacia, USA.*
Clindamycin hydrochloride (p. 269·3), clindamycin palmitate (p. 269·3), or clindamycin phosphate (p. 269·3).
Bacterial infections.

Pfizer, Ital.
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

Cleocin T *Eczacibasi, Turk.; Pharmacia, USA.*
Clindamycin phosphate (p. 269·3).
Acne.

Cleofol *Themis, India.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Cleovate *Helviina, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clephin *Medisys, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Clérégil *Merck Medication Familiale, Fr.†*
⊗Deanol aceglumate (p. 2319·1).
Asthenia.

Cléridium *Dexo, Fr.*
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

Cleron *Aegis, Hong Kong†; Aegis, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Cleroptic *Cooper (Κοπερ), Gr.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Clerz *Alcon, USA.*
Range of solutions for contact lenses.

Cletal *Tolmann, Philipp.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Cletus
Note: this name may be used for preparations of different composition.
Sandoz, India.
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

SoSe, Ital.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Clever *Chiesi, Ital.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Cleveron *TRB, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Clevia *Almirall Hermal, Ger.†*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Clevian *Aesculapius, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Cleviprex *Medicines Company, Neth.; Medicines Company, Switz.; Medicines Company, UK; Medicines Company, USA.*
Clevidipine (p. 1338·2).
Hypertension.

Clevosan *Baliarda, Arg.*
Ointment; topical powder: Centella (p. 1698·3); neomycin sulfate (p. 330·1).
Skin disorders.

Baliarda, Arg.
Topical spray: Centella (p. 1698·3); tetracaine (p. 1996·3).
Skin disorders.

Clevyx *Aamorb, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).

C-Lex *McNeil & Argus, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Clexa *Gland, Philipp.†*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of clotting during extracorporeal circulation; unstable angina.

Clexane *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, Venez.*
Enoxaparin sodium (p. 1372·3).
Unstable angina; thromboembolic disorders; myocardial infarction; prevention of clotting during extracorporeal circulation.

Clexane anti Xa-IU *Sanofi-Aventis, Cz.†*
Enoxaparin sodium (p. 1372·3); anti-Xa.
Thromboembolic disorders; unstable angina; prevention of clotting during haemodialysis; myocardial infarction.

Clexiclor *Farma 1, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Cliacil *Aventis, Turk.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Cliad *Interbat, Indon.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome; enterocolitis; peptic ulcer.

Cliane *Bayer, Braz.; Bayer, Chile; Bayer, Mex.; Schering, NZ†; Schering, Venez.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Cliavist *Bayer, Fr.†*
Ferucarbotran (p. 1584·2).
Contrast agent for magnetic resonance imaging.

Clibite *Korea United, Philipp.; Pharma 3, Philipp.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Clibium *Glenmark, Braz.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Clid *Bennet, India.*
Clindamycin (p. 269·3).
Bacterial infections.

Clidacin *Vianex (Βιανεξ), Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clidacor *Pharmacore, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Clidan *Cassara, Arg.*
Clindamycin phosphate (p. 269·3).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Clidan B *Cassara, Arg.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Clidets *Stiefel, Chile.*
Clindamycin phosphate (p. 269·3).
Acne.

Stiefel, Mex.
Clindamycin (p. 269·3).
Acne.

Clidox *Moraceae, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Clifemin *Herbarium, Braz.*
Cimicifuga (p. 2478·1).
Menopausal symptoms.

Clifenal *Biofarma, Mex.†*
Cimicifuga (p. 2478·1).
Menopausal disorders; menstrual disorders.

Climaclod *Mastelli, Ital.*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; multiple myeloma; hyperparathyroidism; osteoporosis.

Climadan *Dankos, Indon.; Dankos, Singapore.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Kalbe, Indon.
Topical gel: Clindamycin phosphate (p. 269·3); zinc acetate (p. 2126·1).
Acne.

Climaderm *Wyeth, Braz.; Wyeth, Chile†; Wyeth, Mex.; Wyeth, Venez.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Climadil *Marjan, Braz.*
Red clover (p. 2482·1).
Menopausal symptoms.

Climafen *Andromaco, Chile.*
⊗Tibolone (p. 2309·2).
Oestrogen deficiency; osteoporosis.

Climage *Biomedica, Gr.*
Fenofibrate (p. 1381·1).

Climagest *Novartis, UK.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; norethisterone (p. 2294·2).
Menopausal disorders.

Climalona *Bago, Arg.†*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Climanor *Resource Medical, UK.*
Medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea; endometriosis.

Climara *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer, China; Bayer Schering, Cz.; Bayer Schering, Denm.†; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Gr.; Bayer, Irl.; Bayer, Ital.; Bayer, Neth.†; Bayer Schering, Norw.†; Bayer, NZ; Bayer, Philipp.; Bayer Schering, Pol.; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Swed.†; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Schering, Turk.; Bayer, USA.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Climara Pro *Bayer, Canad.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

ClimaraPro *Bayer, USA.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

Climasoy *Konsuma, Venez.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Climaston *Abbott, Fr.*
Tablets 1mg/10mg; tablets 2mg/10mg: 14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Abbott, Fr.
Tablets 1mg/5mg: Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Climaston Continu *Euro Registratie, Neth.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Climatik *Marcelle, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Climatix *Investi, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Climatrol Continuo *Gynopharm, Chile.†*
35 Tablets, conjugated oestrogens (p. 2260·1); 35 tablets, medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Climatrol E *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Climatrol HT *Gynopharm, Chile.†*
17 Tablets, conjugated oestrogens (p. 2260·1); 13 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Climatrol HT Ciclico *Vivax Gynopharm, Venez.*
Whte/light blue tablets, conjugated oestrogens (p. 2260·1); light blue tablets, medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Climatrol HT Continuo *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Clima-V *Dewcare, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).
Vaginal infections.

Climaval *Novartis, UK.*
Estradiol valerate (p. 2271·2).
Menopausal disorders.

Climavita *Permamed, Switz.*
Cimicifuga root (p. 2478·1).
Menopausal disorders.

Climaxan *Materia Medica, Rus.*
Cimicifuga (p. 2478·1); lachesis (p. 2538·3); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Climaxol *Lehning, Fr.*
Hamamelis (p. 2523·3); viburnum (p. 2458·1); butcher's broom (p. 2463·1); hydrastis (p. 2528·1); aesculus (p. 2431·2).
Peripheral vascular disorders.

Climdan *Fem Care, India.*
Lotion: Aloes (p. 1816·1); dexpanthenol (p. 2582·2); jojoba oil; piroctone olamine (p. 1716·3); melaleuca oil (p. 2551·1); wheat-germ oil (p. 2647·1).

Fem Care, India.
Shampoo: Aloes (p. 1816·1); dexpanthenol (p. 2582·2).

Climen *Bayer, Austria.*
White tablets, estradiol valerate (p. 2271·2); pink tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
Menopausal disorders; osteoporosis.

Schering, Austral.†; Bayer, Belg.; Bayer, China; Bayer Schering, Cz.; Bayer, Ger.; Bayer, Ital.; Bayer Schering, Pol.; Bayer, Port.; Bayer Schering, Rus.; Bayer, Spain; Bayer, Switz.; Bayer, Turk.; Bayer, Ukr.
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
28-Day packs contain 16 and 12 tablets, respectively.
Menopausal disorders; menstrual disorders; osteoporosis; oestrogen deficiency.

Schering, Hung.†; Bayer Schering, Malaysia; Bayer, Singapore; Bayer, Thai.
16 tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
Menopausal disorders; oestrogen deficiency; osteoporosis; menstrual disorders.

Bayer Schering, S.Afr.
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; cyproterone acetate (p. 2261·2); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Climen 28 *Bayer, Hong Kong†; Bayer Schering, Indon.; Bayer, Philipp.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
Menopausal disorders; osteoporosis; menstrual disorders.

Climene *Bayer, Arg.; Bayer, Braz.*
White tablets, estradiol valerate (p. 2271·2); pink tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
Menopausal disorders; osteoporosis.

Bayer, Chile; Bayer, Mex.; Bayer, Neth.†; Schering, Venez.
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
28-Day packs contain 16 and 12 tablets, respectively.
Menopausal disorders; osteoporosis.

Climène *Bayer, Fr.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
Menopausal disorders; osteoporosis.

Climeril *Shin Poong, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Climesse *Novartis, UK.*
Estradiol valerate (p. 2271·2); norethisterone (p. 2294·2).
Menopausal disorders; osteoporosis.

Climil-80 *Marfarma, Ital.*
⊗Soya isoflavones (p. 2620·3); pueraria lobata; agnus castus (p. 2432·2).
Menopausal disorders.

Climil Complex *Marfarma, Ital.*
⊗Soya (p. 2620·3); pueraria lobata; agnus castus (p. 2432·2); griffonia simplicifolia (p. 2522·3).
Menopausal disorders.

Climil Gel *Marfarma, Ital.*
Soya isoflavones (p. 2620·3); mimosa tenuiflora.
Vaginal dryness.

Climodien *Bayer, Belg.; Bayer Schering, Denm.†; Bayer, Ger.; Schering, Gr.; Bayer, Neth.; Bayer Schering, Norw.†; Bayer, Port.; Bayer Schering, Rus.; Bayer, Spain; Bayer, Swed.†; Bayer, Turk.*
Estradiol valerate (p. 2271·2); dienogest (p. 2267·2).
Menopausal disorders; osteoporosis.

Climodiène *Bayer, Fr.*
Estradiol valerate (p. 2271·2); dienogest (p. 2267·2).
Menopausal disorders.

Climopax *Pfizer, Ger.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Climopax Cydo *Pfizer, Ger.*
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Climopax mono *Pfizer, Ger.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Climox *Embiotic, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Climpen *Macleods, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Climycen *Help, Gr.*
Clindamycin phosphate (p. 269·3).
Vaginal infections.

Climycin *Neon, India.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clin *Schering, Turk.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Clin-3 *Unimarck, India.*
Soap: Allantoin (p. 1693·1) melaleuca oil (p. 2551·1); triclosan (p. 1773·2); vitamin E acetate (p. 2119·2); zinc oxide (p. 1729·1).

Unimarck, India.
Topical gel: Aloes (p. 1816·1); allantoin (p. 1693·1); clindamycin (p. 269·3); nicotinamide (p. 2083·1).

Clinac
Note: this name may be used for preparations of different composition.
Edol, Port.
Erythromycin (p. 291·2).
Acne.

Pacific, Hong Kong.
Clindamycin (p. 269·3).
Acne.

Clinac BPO
Note: this name may be used for preparations of different composition.
Ferndale, USA.
Benzoyl peroxide (p. 1696·1).
Acne.

Clinac OC *Ferndale, Hong Kong.*
Acrylate copolymer; macrogol 400 (p. 2547·3); carbomer 940 (p. 2173·3).
Seborrhoea.

Clinacnyl *Galderma, Chile.*
Clindamycin phosphate (p. 269·3).
Acne.

Clinadil *Stada, Spain.*
Cinnarizine (p. 622·1); dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders.

Clinadol *Gador, Arg.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Clinadryl *Bangkok Lab & Cosmetic, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cold symptoms; hypersensitivity reactions; bronchitis.

Clinagel
Note: this name may be used for preparations of different composition.
Stiefel, Braz.
Clindamycin phosphate (p. 269·3).
Acne.

Stiefel, India.
Allantoin (p. 1693·1); clindamycin phosphate (p. 269·3).
Acne.

Clinal
Note: this name may be used for preparations of different composition.
Andromaco, Arg.
Sulfanilamide (p. 368·1); zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Skin disorders.

Clinamsa *Antibioticos, Mex.†*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clinax *Cinetic, Arg.*
Minocycline (p. 324·3).
Bacterial infections.

Clinaxon *Piramal, India.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism; head injury.

Clinbaxef *Bosch, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Clinbercin *Bernofarm, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clincin *Indi, India.*
Clindamycin (p. 269·3).
Bacterial infections.

Clincina *Labesfal, Port.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clincorp *Valeant, Arg.*
Soap substitute.

Clin-D *Tylid, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clinda *GPO, Thai.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Stragen, Ger.
Clindamycin (p. 269·3).
Bacterial infections.

Clinda VC *Vesco, Thai.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

ClindaBenz *Dermatech, Austral.*
Topical solution, clindamycin hydrochloride (ClindaTech) (p. 269·3); topical gel, benzoyl peroxide (BenzoTech) (p. 1696·1).
Acne.

Clindabeta *Betapharm, Ger.*
Clindamycin (p. 269·3).
Bacterial infections.

Clindabiotic *Uniao Quimica, Braz.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clindac *Sandoz, Austria; Ranbaxy, Malaysia.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Intramed, S.Afr.†
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindac-A *Galderma, India.*
Clindamycin phosphate (p. 269·3).
Acne.

Clindacin *Panalab, Arg.; Akrikhin, Rus.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis; acne.

Lannacher, Pol.†
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clindacin ETZ *Medimetriks, USA.*
Clindamycin phosphate (p. 269·3); isopropyl alcohol (p. 1758·3).
Acne.

Clindacin P *Medimetriks, USA.*
Clindamycin phosphate (p. 269·3); isopropyl alcohol (p. 1758·3).
Acne.

Clindacne *Homeofarm, Pol.; Medicpharma, Thai.*
Clindamycin phosphate (p. 269·3).
Acne.

Theraskin, Braz.
Clindamycin (p. 269·3).
Acne.

Clindacur *Cinetic, Arg.*
Clindamycin phosphate (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

Clindagel *Vocate, Gr.; Galderma, Singapore; Galderma, USA.*
Clindamycin phosphate (p. 269·3).
Acne; vaginal infections.

Clindahexal *Hexal, Ger.†; Hexal, S.Afr.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Sandoz, Ukr.†
Clindamycin (p. 269·3).
Bacterial infections.

Clindal
Note: this name may be used for preparations of different composition.
Merck, Braz.
Azithromycin (p. 221·2).
Bacterial infections.

One Pharma, Philipp.
Clindamycin (p. 269·3).
Bacterial infections.

Clindal AZ *APT, Hong Kong.*
Azithromycin (p. 221·2).
Bacterial infections.

Clindalaf *Lafedar, Arg.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindalin *Union Drug, Thai.*
Clindamycin phosphate (p. 269·3).
Skin infections.

Clindaman *T Man, Thai.*
Clindamycin hydrochloride (p. 269·3).
Acne.

ClindaMax *PharmaDerm, USA.*
Clindamycin phosphate (p. 269·3).
Acne.

Clindamed *Remedina, Gr.*
Clindamycin phosphate (p. 269·3).

Clindamin C *Teuto, Braz.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clindamit *Pan-Ject, Philipp.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindapack *Darier, Mex.*
Clindamycin phosphate (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne; rosacea.

Clindapene *Unichem, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Clindarix *Ariston, Braz.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clinda-saar *MIP, Ger.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindasol
Note: this name may be used for preparations of different composition.
CNP, Ger.
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Stiefel, Canad.
Clindamycin phosphate (p. 269·3); octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Acne.

Clindastad *Stada, Ger.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clinda-T *Valeo, Canad.*
Clindamycin phosphate (p. 269·3).
Acne.

Clindatec *United Biotech, India.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindatech *Dermatech, Austral.; Dermatech, Hong Kong; Arrow, NZ; Dermatech, Philipp.; Dermatech, Singapore.*
Clindamycin hydrochloride (p. 269·3).
Acne.

Clindaval *Valmor, Venez.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindavid *Millimed, Thai.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindaz
Note: this name may be used for preparations of different composition.
Advik, India.
Clindamycin (p. 269·3).
Acne.

Clindazyn *Teva, Mex.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Lemery, Mex.†
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clinderm *Agio, India.*
Clindamycin (p. 269·3).
Acne.

Agio, Philipp.
Clindamycin phosphate (p. 269·3).
Acne.

Clinderm-A *Agio, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Clindesse *Gedeon Richter, Ukr.; Ther-Rx, USA.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

Clindets *Stiefel, Canad.; Stiefel, USA.†*
Clindamycin phosphate (p. 269·3).
Acne.

Clindex *Chelsea, USA.*
Clidinium bromide (p. 1833·2); chlordiazepoxide hydrochloride (p. 1044·2).
Gastrointestinal disorders.

Clindexcin *Mugi, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clindo *Hexal, Pol.†*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindol *Venus, India.*
Clindamycin (p. 269·3).
Bacterial infections.

Clindopax *Lagos, Arg.*
Clindamycin phosphate (p. 269·3).
Acne.

Clindovit *Akrikhin, Rus.*
Clindamycin phosphate (p. 269·3).
Acne.

Clindox *Behrens, Venez.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Clindoxyl *GSK, Arg.; Stiefel, Braz.; Stiefel, Canad.; Stiefel, Denm.; GSK, Fin.; GSK, Singapore; Embil, Turk.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Clinepect *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).

Clinet *Ativus, Braz.*
Red clover (p. 2482·1).

Clinex *Aristopharma, Hong Kong.*
Clindamycin (p. 269·3).
Acne.

Gracia, Indon.
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clinfar *Merck, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Clinfol *Nolver, Venez.*
Clindamycin (p. 269·3).
Bacterial vaginosis.

Clingard *Fulford, India.*
Clindamycin phosphate (p. 269·3).
Acne.

Clingen *Aristo, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).
Vaginal infections.

Clingen Plus *Aristo, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2); metronidazole (p. 936·1).
Vaginal infections.

Clin-Gold *Indkus, India.*
Clindamycin phosphate (p. 269·3).
Acne.

Clingozan *Stada, Cz.; Excalibur, Neth.†; Excalibur, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Clinhair *Emcure, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Clinical Nutrients 50-Plus Men *Integrative, USA.*
Vitamins; minerals; Antioxidant Blend; betaine (p. 2456·1); myrtillus (p. 2566·2); choline (p. 2055·2); cinnamon (p. 2479·2); Digestive Blend; ginseng (p. 2513·3); inositol (p. 2533·2); lutein (p. 2079·2); lycopene (p. 2546·2); saw palmetto (p. 2363·3); Vegetable Blend; zeaxanthin (p. 2125·3).
Dietary supplement.

Clinical Nutrients Prenatal Formula *Integrative, USA.*
Vitamins; minerals; bioflavonoids (p. 2505·2); taraxacum (p. 2625·3).

Clinical Results *Hydron, Singapore.*
A range of moisturising creams for problematic and ageing skin.

Clinicare *Saga, India.*
Clindamycin (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Clinidac *Pharos, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Cliniderm *Wild, Switz.*
Cream: Polyethylene granules (abrasive) (p. 1690·3); salicylic acid (p. 1719·1).
Acne; seborrhoea.

Wild, Switz.
Topical solution: Triclosan (p. 1773·2).
Acne; seborrhoea.

Clinigel *Orion, Austral.; Orion, NZ.*
Lubricating gel.

Clinika *Ikapharmindo, Indon.*
Clindamycin (p. 269·3) or clindamycin phosphate (p. 269·3).
Acne.

Clinikold *Bangkok Lab & Cosmetic, Thai.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; cold symptoms.

Clinimet *Bangkok Lab & Cosmetic, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hyperacidity; Zollinger-Ellison syndrome.

Clinimix *Clintec, Austria; Clintec, Belg.; Baxter, Chile; Baxter, Cz.; Clintec, Fin.; Baxter, Ger.; Baxter, Irl.; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.†; Eczacibasi-Baxter, Turk.; Baxter, UK.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Baxter, China.
Amino acids; glucose (p. 2068·3).
Parenteral nutrition.

Clintec, Denm.; Baxter, Fr.; Baxter, Ital.
Amino acids; carbohydrate; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Baxter, Gr.; Kalbe, Indon.
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Clinimycin *Galen, Irl.†*
Oxytetracycline (p. 337·1).
Bacterial infections.

Clinipred *Bangkok Lab & Cosmetic, Thai.*
⊗Prednisolone (p. 1645·2).
Skin disorders.

Clinique Advanced *Clinique, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Clinique Comfort *Clinique, Canad.†*
Dimeticone (p. 2209·3).

Clinique Skin Supplies *Clinique, Canad.*
Cream SPF 21: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clinique Sun-Care *Clinique, Canad.†*
SPF 15; SPF 30; SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clinique Superbalanced *Clinique, Canad.†*
SPF 20: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Clinique Superdefense Dry *Clinique, Canad.*
SPF 25: Avobenzone (p. 1695·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clinique Superdefense Normal to Dry *Clinique, Canad.†*
SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Clinique Superdefense Normal to Oily *Clinique, Canad.*
SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Clinique Superdefense Oily *Clinique, Canad.*
SPF 25: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Clinishield *Stockhausen, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Clinisorb *CliniMed, UK.*
Activated charcoal (p. 1537·3).
Malodorous wounds.

Clinistix *Bayer Diagnostics, Austral.†; Bayer, Canad.†; Bayer Diagnostics, Irl.†; Bayer, Ital.; Bayer, NZ†; Bayer, Port.†; Bayer Diagnostics, UK.*
Test for glucose in urine (p. 2516·3).

Clinitar *Cambridge Healthcare, UK.†*
Coal tar (Stantar) (p. 1723·2).
Psoriasis; eczema; dandruff; seborrhoeic dermatitis.

Clinitas *Altacor, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Clinitas Gel *Altacor, UK.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Clinitek Microalbumin *Bayer, Austral.†*
Test for albumin and creatinine in urine.

Clinitek Microalbuminuria/Creatinina *Bayer, Arg.*
Test for albumin and creatine in urine.

Clinitest *Bayer, Austral.†; Bayer, Canad.†; Bayer Diagnostics, Irl.†; Bayer, Ital.; Bayer Diabetes Care, Mex.; Bayer, NZ†; Bayer Diagnostics, UK.*
Test for glucose in urine (p. 2516·3).

Clinium
Note: this name may be used for preparations of different composition.
Interbat, Indon.
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sanitas, Chile.
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Ethnor, Indiat; Janssen-Cilag, S.Afr.†
Lidoflazine (p. 1420·2).
Ischaemic heart disease; angina pectoris; myocardial infarction.

Clinivate *Bangkok Lab & Cosmetic, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Clinivate-N *Bangkok Lab & Cosmetic, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Clinjos *Meprofarm, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clinmas *Lapi, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Clinmide *Moraceae, India.*
Clindamycin (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Clinoderm *Bangkok Lab & Cosmetic, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clinofar *GSK, Gr.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Clinogel *Meda, Fr.†*
Isopropyl alcohol (p. 1758·3); triclosan (p. 1773·2).
Hand disinfection.

Clinogel Derma+ *Meda, Fr.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Hand disinfection.

Clinoleic *Baxter, Arg.; Baxter, Austral.; Baxter, Austria; Clintec, Belg.; Baxter, Canad.; Baxter, Cz.; Clintec, Denm.; Clintec, Fin.; Baxter, Ger.; Baxter, Gr.; Baxter, Irl.†; Teva, Israel; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Pol.; Baxter, Port.; Baxter, Singapore; Clintec, Spain; Baxter, Swed.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK.*
Olive oil (p. 2575·1); soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Clintec, China.
Lipids.
Lipid infusion for parenteral nutrition.

Clinoléic *Baxter, Fr.; Baxter, Switz.*
Olive oil (p. 2575·1); soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Clinolipid *Baxter, USA.*
Olive oil (p. 2575·1); soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Clinomat *Gynopharm, Chile.*
Drospirenone (p. 2269·1); estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Clinomel *Baxter Immuno, Arg.; Baxter, Thai.†; Eczacibasi-Baxter, Turk.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipids.
Parenteral nutrition.

Clintec, Gr.; Baxter, Pol.; Adcock Ingram Critical Care, S. Afr.†
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Parenteral nutrition.

Clintec, China.
Amino acids; glucose (p. 2068·3); lipids.
Parenteral nutrition.

Clinopect *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).

Clinopront *Bangkok Lab & Cosmetic, Thai.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Clinorette *Resource Medical, UK.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone (p. 2294·2).
Menopausal disorders; osteoporosis.

Clinoril *MSD, Belg.†; MSD, China; MSD, Hong Kongt; MSD, Irl.†; Neopharmed, Ital.; MSD, Mex.; MSD, NZ; MSD, Swed.†; M & H, Thai.; MSD, UKt; Merck, USA.*
Sulindac (p. 134·2).
Musculoskeletal, joint, and peri-articular disorders; symptoms of upper respiratory-tract infections; gout; pain.

Clinott *LBS, Thai.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Clinovir
Note: this name may be used for preparations of different composition.
T-Boma, Hong Kongt; Pharos, Indon.; Bangkok Lab & Cosmetic, Thai.
Aciclovir (p. 964·1).
Herpesvirus infections.

Clin-Sanorania *Winthrop, Ger.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clinscar *Intra-Labs, India.*
Clindamycin phosphate (p. 269·3).
Acne.

Clinsoft *Invision, India.*
Clindamycin phosphate (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Clintopic *Investi, Arg.*
Clindamycin hydrochloride (p. 269·3).
Acne.

Clinutren *Nestle Clinical, Irl.; Nestle, Ital.; Nestle, UK.*
A range of preparations for enteral nutrition.

Nestle, Fr.
A range of nutritional supplements.

Nestle, Rus.
Preparation for enteral nutrition.

Clinvit *Plants, Ital.*
Royal jelly (p. 2608·1).
Nutritional supplement.

Clinwas *Chiesi, Spain.*
Clindamycin phosphate (p. 269·3).
Acne.

Clio-Betnovate *GSK, Mex.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Cliocort *Universal, Hong Kong.†*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Clioderm-H *Sons, Mex.†*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Clionara *Besins, Ger.; Kade, Ger.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Cliotisona *Belfar, Braz.*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).

Cliovelle *Kade, Denm.; Kade, Fin.; Kade, Ger.; Medlite, Norw.; Kade, Pol.; Campus, Swed.*
Estradiol valerate (p. 2271·2); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Cliovyl *SJA, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Clip *FDC, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Clip Ampoules *Pierre Fabre Sante, Fr.†*
Carmellose (p. 2175·1).
Wounds.

Clip Blessures *Pierre Fabre Sante, Fr.†*
Hydrophilic polyurethane dressing (p. 1718·1).
Wounds.

Clip Brûlures *Pierre Fabre Sante, Fr.†*
Carmellose (p. 2175·1).
Burns.

Clip Derm *Pierre Fabre Sante, Fr.†*
Polyurethane dressing (p. 1718·1).
Wounds.

Clip Hémo *Pierre Fabre Sante, Fr.†*
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Wounds.

Clip Strip *Pierre Fabre Sante, Fr.†*
Polyurethane foam dressing (p. 1718·1).
Wounds.

Clip-MF *FDC, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).
Haemostatic.

Clipostat *Pharmanel, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Clipper *Chiesi, Belg.; Chiesi, Ital.; Chiesi, Spain; Chiesi, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Ulcerative colitis.

Clipto *Quimifar, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Cliptol *Pierre Fabre, Fr.*
Ibuprofen (p. 68·2); menthol (p. 2553·2).
Soft-tissue disorders.

Cliran *Ranbaxy, Mex.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Cliran Zinc *Ranbaxy, Ukr.*
Clindamycin phosphate (p. 269·3); zinc acetate (p. 2126·1).
Acne.

Clirbest *Best, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Clisflex *Sella, Ital.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Clisma Fleet *Casen Fleet, Ital.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Clisma-Lax *Sofar, Ital.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

Clison *Alpharma, Mex.*
Sulindac (p. 134·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Clistanex *Flamingo, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clisteran *Lainco, Spain.*
Sodium lauril sulfoacetate (p. 2210·3); sodium citrate (p. 1781·2).
Bowel evacuation; constipation.

Clistim-DMR *Johnson & Johnson, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); sodium citrate (p. 1781·2).
Cough.

Clistin
Note: this name may be used for preparations of different composition.
Glenmark, Braz.
Loratadine (p. 633·2).
Hypersensitivity reactions.

Johnson & Johnson, India.
Carbinoxamine maleate (p. 619·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Formerly contained dextromethorphan hydrobromide, carbinoxamine maleate, ammonium chloride, and sodium citrate.
Cough.

Clitax *Tecnimede, Port.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Clitaxel *Gobbi, Arg.; Nolver, Venez.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Cliten *Biomedica, Gr.*
Tetracycline hydrochloride (p. 373·2).
Acne.

Clity *Candor, India.*
Vitamin B substances (p. 2102·3).

Clivarin *Abbott, China; Abbott, Cz.†; Abbott, Ger.; Abbott, Gr.; Abbott, Hung.†; Abbott, Pol.†*
Reviparin sodium (p. 1486·3).
Thromboembolic disorders.

Clivarina *Abbott, Ital.*
Reviparin sodium (p. 1486·3).
Thromboembolic disorders.

Clivarine *Abbott, Fr.†; Abbott, Hong Kongt; Abbott, India.*
Reviparin sodium (p. 1486·3).
Thromboembolic disorders.

Cliver *Adley, India.*
Cefpodoxime.
Bacterial infections.

Cliver-A *Adley, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

C-Livo *Corona, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Clivoten *Italfarmaco, Ital.*
Isradipine (p. 1414·2).
Hypertension.

Cliz *ADP, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Clizid *Sandoz, Philipp.*
Gliclazide (p. 472·3).
Diabetes mellitus.

CLM *Croesus, Philipp.*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Clo *Sigma, Braz.*
Clomipramine hydrochloride (p. 412·1).
Depression.

Cloact *Cadila, India.*
Dicycloverine (p. 1834·2); simeticone (p. 1886·2).

Cloat-V *ATOZ, India.*
Clotrimazole (p. 576·2); lactobacillus (p. 2596·3).

Cloba *Intas, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Clobact-GM *Intra-Labs, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1); neomycin (p. 329·3).

ClobaDerm *Auden McKenzie, UK.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobaderm *Intermed, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobaderm-GM *Intermed, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clobasia-GM *Willow, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3); zinc oxide (p. 1729·1).
Infected skin disorders.

Clobasol *Jean-Marie, Hong Kong.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobasone *Pharmaland, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobastar *Gentech, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Clobator *Torrent, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Clobecos-GM *Symbiosis, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clobederm *Jelfa, Pol.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobee-SP *Biocin, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Clobefar *HLB, Arg.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobegalen *Galen, Ger.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobemix *Ascent, Austral.*
Moclobemide (p. 437·2).
Depression.

Cloben *Indoco, India.*
Cream; lotion: ⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2).

Indoco, India.
Topical powder; vaginal tablet: Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Clobendian *Efarmes, Spain.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Cloben-G *Indoco, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); neomycin (p. 329·3).
Formerly contained clotrimazole, beclometasone dipropionate, and gentamicin.
Skin infections; allergic skin disorders.

Clobeplus *Raymos, Arg.*
⊗Clobetasol propionate (p. 1627·1); ammonium lactate (p. 1694·3).
Skin disorders.

Clobequad *Ind-Swift, India.*
⊗Clobetasone butyrate (p. 1627·3); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Cloberis-GM *Symbiosis, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clobert-G *Vickmans, Hong Kong.†*
⊗Clobetasol (p. 1627·1); clotrimazole (p. 576·2); diphenhydramine (p. 626·1); gentamicin (p. 304·2).
Infected skin disorders.

Clobesan *Sanbe, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobesol *Investi, Arg.; Valeant, Braz.; Aristopharma, Hong Kong; GSK, Ital.; Valeant, Mex.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobesol LA *Investi, Arg.*
⊗Clobetasol propionate (p. 1627·1); ammonium lactate (p. 1694·3).
Skin disorders.

Clobesym-GM *Symbiosis, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clobet *Angelini, Ital.*
⊗Clobetasone butyrate (p. 1627·3).
Eye disorders.

Biolab, Malaysia; Biolab, Thai.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobeta-CF *Laborate, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Infected skin disorders.

Clobetaderm *Marching, Hong Kong.†*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Clobeta-G *Loyal Advance, Hong Kong.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); clotrimazole (p. 576·2); clioquinol (p. 273·1).
Infected skin disorders.

Clobetamil *Merck, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobetamil-G *Merck, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Clobetate *Polipharm, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobetavate *Lupin, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobex *AB-Consult, Austria; Galderma, Belg.; Galderma, Canad.; Galderma, Cz.; Galderma, Denm.; Galderma, Fin.; Galderma, Fr.; Galderma, Ger.; Galderma, Gr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Malaysia; Galderma, Neth.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Philipp.; Galderma, Pol.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Spain; Galderma, Swed.; Galderma, Switz.; Galderma, Thai.; Galderma, USA.*
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Clobexpro *Galderma, Mex.*
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Clobimox *BL, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Clobiotic *Indoco, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Clobioxal *Bioresearch, Mex.*
Dicloxacillin (p. 286·1).
Bacterial infections.

Clobir *Actavis, Rus.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; bone metastases; osteolysis of malignancy.

Clobison *Agio, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobium *Ferron, Indon.*
Clobazam (p. 518·2).
Anxiety.

Clobixfoam *Darier, Mex.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clobotil *Andromaco, Chile.*
Clobutinol hydrochloride (p. 1658·3).
Cough.

Clobquad *Ind-Swift, India.*
⊗Clobetasol butyrate (p. 1627·1); gentamicin (p. 304·2); clioquinol (p. 273·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clob-X *Galderma, Arg.; Galderma, Braz.; Galderma, Chile.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cloby *Uniroyal, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clocain *Fourrts, India.*
Clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Clocan *IQFA, Mex.*
Clotrimazole (p. 576·2).
Fungal infections.

Clocef *Teuto, Braz.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Clocephen *Boie, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Clocilin *PC India, India.*
Cloxacillin (p. 274·3).
Bacterial infections.

Clocimide *PP Lab, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Wound cleansing.

Clocip *Cipla, India.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Clocip B *Cipla, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2).
Infected skin disorders.

Clocip NB *Cipla, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); neomycin (p. 329·3).
Infected skin disorders.

Clociver *Maver, Mex.*
Aciclovir (p. 964·1).
Viral infections.

Clocktower *Group, S.Afr.†*
Zinc oxide (p. 1729·1).
Skin disorders; minor cuts and abrasions.

Clocream *Roberts, USA.*
Cod-liver oil (p. 2056·3); colecalciferol (p. 2113·1); vitamin A palmitate (p. 2098·3).
Skin disorders.

Clocreme *Pacific, Hong Kong; Pacific, NZ.†*
Clotrimazole (p. 576·2).
Fungal skin infections; erythrasma; vulvovaginal candidiasis.

Clocsamed *Jumont, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Clodavan *Medipharm, Chile.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clodax *DWD, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Clodax-L *DWD, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Clodaz-V6 *Elfin, India.*
Clotrimazole (p. 576·2); tinidazole (p. 949·2).
Vaginal infections.

Clodel *Delegant, Gr.; Rowex, Irl.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clodelib *Delegant, Gr.*
Clopidogrel (p. 1342·3).

Clodeosten *Boniscontro & Gazzone, Ital.*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; multiple myeloma; hyperparathyroidism; osteoporosis.

Cloder *Nobel, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Cloder Plus *Nobel, Turk.*
Chlorhexidine gluconate (p. 1743·3); benzydamine hydrochloride (p. 29·2).

Cloderm
Note: this name may be used for preparations of different composition.
Hoe, Hong Kong; Cipla, India; Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Dermapharm, Ger.
Clotrimazole (p. 576·2).
Fungal skin infections.

Ikapharmindo, Indon.
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Valeant, USA.
⊗Clocortolone pivalate (p. 1628·1).
Skin disorders.

Cloderm-GM *Cipla, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Skin disorders.

Clodermis *Utopian, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clodian *Sandoz, Arg.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolic disorders.

Clodifen *World Medicine, Ukr.*
Diclofenac sodium (p. 48·3).
Inhibition of peri-operative miosis; inflammation and pain following eye surgery or trauma; cystoid macular oedema.

Clodine *Mount Mettur, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Clodip *Intra-Labs, India.*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Clodip-GM *Intra-Labs, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clodoxin *Plusandex, Venez.*
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting; gastrointestinal motility disorders; gastro-oesophageal reflux.

Clodrel *Unichem, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clodrel Forte *Unichem, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clodrel Plus *Unichem, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clodrobon *Bayer Schering, Fin.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Clodron *1A, Ger.†; Hexal, Ger.†; Sandoz, Ger.†; Fidia, Ital.*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; multiple myeloma; hyperparathyroidism; osteoporosis; hypercalcaemia of malignancy; metastatic bone disease.

Clodron beta *Betapharm, Ger.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; metastatic bone disease.

ClodronSandoz *Sandoz, Ukr.*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy.

Clodus *Zydus, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Clody *Promedica, Ital.*
Clodronate disodium (p. 1180·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Hyperparathyroidism; multiple myeloma; osteoporosis; osteolysis of malignancy.

Cloel *Aesculapius, Ital.*
Cloperastine fendizoate (p. 1659·2).
Cough.

Clofalam *Mahakam Beta, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clofamox *Lamsa, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Clo-Far *Farcoral, Mex.*
Diclofenac potassium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Clofcin *Lark, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Clofcin-M *Lark, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Clofcin-T *Lark, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Clofec *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Atlantic, Thai.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Clofekton *Mitsubishi Tanabe, Jpn.*
Clocapramine hydrochloride (p. 1054·2).
Schizophrenia.

Clofeme *Hexal, Austral.†*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Clofen
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; LCH, Hong Kong†; Alphapharm, Malaysia.†
Baclofen (p. 2014·3).
Skeletal muscle spasm; spasticity; bladder dysfunction.

Dollder, Venez.
Diclofenac potassium (p. 48·3) or diclofenac resinate (p. 48·3).
Inflammation; pain; peri-articular disorders.

Julphar, UAE.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Zeler, Port.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout; inflammation; pain.

Clofenac *Hovid, Hong Kong; Hovid, Malaysia†; Hovid, Singapore; Vivax Optipharm, Venez.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout; pain; inflammation; inflammatory eye disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Clofenak *Medley, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Clofend *Fidia, Ital.*
Levocloperastine fendizoate (p. 1659·1).
Cough.

Clofenid *Cifarma, Braz.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Clofenix *Farmaceutica H, Mex.; Aldril, Philipp.*
Diclofenac sodium (p. 48·3).
Fever; gout; inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Clofen-SP *Sanify, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Clofera *Centrix, USA.*
⊗Clofedanol hydrochloride (p. 1659·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Clofert *Svizera, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Clofexan *Bago, Chile.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Clofil *Filadams, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Cloflam *Mahakam Beta, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cloflow *Aristo, India.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Clofoam *Cipla, India.*
⊗Clobetasol propionate (p. 1627·1).

Clofon *YF Chem, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Clofozine *AstraZeneca, India.*
Clofazimine (p. 273·3).
Leprosy; lepra reactions.

Clofranil *Sun, India.*
Clomipramine (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Sun, Rus.; Sun, Thai.
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; phobic states; narcoleptic syndrome.

Clofre *East West, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clofre AS *East West, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Clofritis *Mersifarma, Indon.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Cloftal *Oftalmi, Venez.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Clofung *Taurus, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2).

Clofung G M *Taurus, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Clofung-G *Taurus, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Clofung-N *Taurus, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).
Infected skin disorders.

Clogar *Self-Care Products, UK.*
Cod-liver oil (p. 2056·3); garlic (p. 2510·3).

Clogem *Sigman, India.*
Cream: ⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Sigman, India.
Lotion: ⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1).

Clogen *Intas, India.*
Clotrimazole (p. 576·2).
Oropharyngeal candidiasis.

Clogin *Interbat, Indon.*
Clopidogrel (p. 1342·3).
Thromboembolic disorders.

Clogombix *1A, Austria.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clogrel *Polpharma, Pol.; Actavis, Switz.†*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clogrelhexal *Hexal, Austria.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clohex *Reddy, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Clohex Plus *Reddy, India.*
Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2); zinc chloride (p. 2126·1).

Clohys *Miklich, Denm.*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Cloisone *Psicofarma, Mex.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Clokeran *Natco, India.*
Chlorambucil (p. 764·1).
Hodgkin's disease; lymphoma; chronic lymphocytic leukaemia.

Clokit *Indoco, India.*
Chloroquine phosphate (p. 650·1).
Malaria; hepatic amoebiasis; rheumatoid arthritis; lupus erythematosus.

Clolar *Genzyme, Canad.; Genzyme, USA.*
Clofarabine (p. 769·3).
Acute lymphoblastic leukaemia.

Clolyse *Akesiss, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clom *Orchid, India.*
Clomipramine (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Clomach *La Pharmaceuticals, India.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Clomacin *Quimica y Farmacia, Mex.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Clomaderm *Gulf Drug, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clomadol *Mount Mettur, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Clomax *Bombay Tablet, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Clomax BN *Bombay Tablet, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Clomax-B *Bombay Tablet, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).
Fungal skin disorders.

Clomax-BG *Bombay Tablet, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Clomaz *LBS, Thai.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Clomazen *Uniao Quimica, Braz.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clomazol *Cifarma, Braz.; Multichem, NZ.*
Clotrimazole (p. 576·2).
Fungal and bacterial skin infections; vulvovaginal candidiasis.

Clomazole *Idaman, Malaysia.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clomenac *Arrow, Braz.*
Memantine (p. 393·1).

Clomene *Organon, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Cloment *Regiomedica, Denm.†; Pharmaplan, S.Afr.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Clomentin *Elder, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Clometide *Caplin, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Premedication; gastric stasis; nausea and vomiting.

Clomet-P *Mount Mettur, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Clomex *Yuyu, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clomhexal *Sandoz, Austral.†; Hexal, Cz.†; Hexal, Ger.†*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Clomic *East West, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clomicin *IQFA, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clomic-M *East West, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Clomic-S *East West, India.*
⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1); lactic acid (p. 2539·1); urea (p. 1727·3); sodium lactate (p. 1781·2).

Clomic-ZM *East West, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1); zinc sulfate (p. 2126·2).

Clomid
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Medley, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Irl.; Bruno, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Duncan, Philipp.; Adcock Ingram, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.†; Sanofi-Aventis, Thai.; Aventis, UK; Sanofi-Aventis, USA.
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; ovulatory failure; male infertility; diagnosis of hypothalamic-pituitary function.

Scoshia, India.
Cefixime (p. 240·3).
Bacterial infections.

Clomidac *Cadila, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Clomid-CL *Scoshia, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Clomidep *Pharmaplan, S.Afr.*
Clomipramine hydrochloride (p. 412·1).
Depression.

Clomid-LB *Scoshia, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Clomifen *Leiras, Fin.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Clomifil *Sunthi Sepuri, Indon.†*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Clomihexal *Sandoz, S.Afr.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Clomin
Note: this name may be used for preparations of different composition.
Medinova (Μεντινοβα), Gr.
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Clominal *Randall, Mex.*
Dicycloverine (p. 1834·2).
Nausea and vomiting.

Clomine *Psychotropics, India.*
Clomipramine (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Clomip *Reliance, India.*
Clomipramine (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Clomipran *Uniao Quimica, Braz.*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; panic disorder; pain; nocturnal enuresis.

Clomirex *Mipharm, Ital.†*
Chlorhexidine (p. 1743·2).
Vaginal infections.

Clomiriv *East African, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Clomistar *Gentech, India.*
Clomipramine hydrochloride (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Clomit *Plus, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Clomitene *LBS, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Clomizil *Gufic, India.*
Clomipramine (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Clompic *Aglowmed, India.*
Ampicillin (p. 218·2) or ampicillin trihydrate (p. 218·2); Cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1).
Bacterial infections.

Clomycin
Note: this name may be used for preparations of different composition.
Neo-Pharma, India.†
Clotrimazole (p. 576·2); gentamicin (p. 304·2).
Skin and nail infections.

Clon *Mediez, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonabay *Bayer, Arg.*
Clonazepam (p. 519·1).
Panic disorder; epilepsy.

Clonac
Note: this name may be used for preparations of different composition.
Arrow, Austral.†; Alapis, Gr.; Faran, Gr.
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders; musculoskeletal and joint disorders; pain; inflammation.

Laborate, India.
Aceclofenac sodium (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Clonac Plus *Laborate, India.*
Aceclofenac sodium (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Clonac-SP *Laborate, India.*
⊗Aceclofenac sodium (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Clonactil *Clonmel, Irl.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; anxiety; depression; behaviour disorders; hiccups.

Clonaderm *Ifars, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clonafit *Mankind, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonagin *Baliarda, Arg.*
Clonazepam (p. 519·1).
Anxiety; epilepsy; panic disorder.

Clonalgin *Chemopharma, Chile.*
Clonixin lysine (p. 40·1).
Pain.

Clonalgin Compuesto *Chemopharma, Chile.*
Clonixin lysine (p. 40·1); ergotamine tartrate (p. 674·1).
Migraine and other vascular headaches.

Clonamox *PannonPharma, Hung.; Clonmel, Irl.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Clonamp *Clonmel, Irl.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Clonapam *Valeant, Canad.; Laboratorios Chile, Chile; ICN, Hung.†*
Clonazepam (p. 519·1).
Anxiety; convulsions; epilepsy; panic attacks; sleep disorders.

Clonapax *Reliance, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonapik *Aarpik, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonaren *Metz, Philipp.†*
Diclofenac sodium (p. 48·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Clonaril *Medifive, Thai.*
Clonazepam (p. 519·1).
Epilepsy; status epilepticus.

Clonasedan *Quesada, Arg.*
Clonazepam (p. 519·1).

Clonate *H & H, India; Hoe, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clonate-F *H & H, India.*
⊗Clobetasol propionate (p. 1627·1); fusidic acid (p. 302·1).

Clonate-G *Gujarat Terce, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2).
Infected skin disorders.

Clonate-GM *Gujarat Terce, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clonatrac *Minova, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonax *Beta, Arg.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonazen 2 *Bouzen, Arg.*
Clonazepam (p. 519·1).
Anxiety; epilepsy.

Clonazine *Clonmel, Irl.†*
Chlorpromazine hydrochloride (p. 1045·2).
Sedative; premedication; hypothermia induction; vomiting; schizophrenia.

Clonazone *Lagepha, Belg.; DB, Fr.†*
Tosylchloramide sodium (p. 1773·1).
Disinfection; disinfection of drinking water.

Clonea *Alphapharm, Austral.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Cloneon *Neon, India.*
Clonidine hydrochloride (p. 1339·1).
Hypertension; pain.

Cloner *Vannier, Arg.*
Clonazepam (p. 519·1).
Anxiety disorders; epilepsy.

Clonetin *CNW, Hong Kong.†*
⊗Clobetasol (p. 1627·1); neomycin (p. 329·3); nystatin (p. 590·3).
Infected skin disorders.

Clonex
Note: this name may be used for preparations of different composition.
Adeka, Turk.
Clozapine (p. 1057·3).
Psychoses.

Corsa, Indon.
Tranexamic acid (p. 1164·2).
Hereditary angioedema; haemorrhage; fibrinolysis.

Saval, Chile; Teva, Israel.
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonfolic *Clonmel, Irl.*
Folic acid (p. 2063·1).
Prevention of neural tube defects.

Clonid-Ophtal *Winzer, Ger.*
Clonidine hydrochloride (p. 1339·1).
Ocular hypertension; glaucoma.

Clonidural *Richmond, Arg.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Clonil *Intas, India.*
Clomipramine hydrochloride (p. 412·1).
Narcoleptic syndrome; obsessive-compulsive disorder; panic disorder; depression.

Clonistada *Stada, Ger.†*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Clonitia *Tunggal Idaman, Indon.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clonix *Lusomedicamenta, Port.*
Clonixin lysine (p. 40·1).
Pain.

Clonixil *Richmond, Arg.*
Clonixin lysine (p. 40·1).
Fever; inflammation; pain.

Clonnirit *Rafa, Israel.*
Clonidine hydrochloride (p. 1339·1).
Menopausal flushing; migraine and other vascular headaches.

Clonocid *Clonmel, Irl.*
Clarithromycin (p. 266·2).
Bacterial infections.

Clonodifen *Tecnofarma, Mex.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Clonopam *Molekule, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonoren *Miklich, Denm.†*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clonotril *Torrent, Braz.; Torrent, India; Torrent, Philipp.; Remedica, Singapore.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clonovate *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clont *Infectopharm, Ger.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; trichomoniasis; amoebiasis; giardiasis.

Clood *Trima, Israel.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clop
Note: this name may be used for preparations of different composition.
Zydus, India.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clopact *Ipca, India.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Clopact A *Ipca, India.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Atherosclerosis.

Clopam
Note: this name may be used for preparations of different composition.
Chandra Bhagat, India.
Injection: Pralidoxime chloride (p. 1571·1).
Organophosphorus poisoning.

East West, India.
Tablets: Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clopamon *Aspen, S.Afr.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; gastrointestinal radiography.

Clopan
Note: this name may be used for preparations of different composition.
Cristalia, Braz.†
Clonazepam (p. 519·1).
Epilepsy.

Clopar *Taurus, India.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain; actinic keratoses; prevention of intra-operative miosis; eye inflammation and pain; allergic conjunctivitis.

Clopar MR *Taurus, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Clopar Plus *Taurus, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Clopar-K *Taurus, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Clopaz *Triton, India.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Clop-E *Zydus, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clopen *Lark, India.*
Cloxacillin (p. 274·3).
Bacterial infections.

Pharmawealth, Philipp.
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Clopes *Metiska, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Clop-G *Zydus, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Clophelin *Moscow Endocrine, Rus.; Darnitsa, Ukr.*
Clonidine (p. 1339·1).
Hypertension; withdrawal syndromes; glaucoma.

Clophen-P *Sanify, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Clopi *Skymax, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopicard *Cipla, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopid *Hetero, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Taro, Israel.
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopida *XL, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopid-AS *Hetero, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clopidep *Extractum, Hung.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidexcel *Dexcel, Israel.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopidim *Specifar, Pol.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidix *Lek-Am, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopido *Platinum, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; unstable angina.

Clopidocard *1A, Ger.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidocor *Sandoz, Ger.†; Sandoz, Neth.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopido-Gran *Legrand, Braz.*
Clopidogrel (p. 1342·3).

Clopidolut *Mibe, Ger.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidonorm *Actavis, Denm.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidostad *Stada, Cz.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidosyn *Farmasyn, Gr.*
Clopidogrel (p. 1342·3).

Clopidrax *Drossapharm, Switz.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopidror *Arrow, Braz.*
Clopidogrel (p. 1342·3).

Clopigamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clopigrel *USV, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopigrel-A *USV, India.*
Aspirin (p. 22·2); clopidogrel bisulfate (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clopikare *Nitro Cadineur, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopilet *Sun, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Sun, Rus.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopimet *Emcure, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopin *Sandoz, Switz.*
Clozapine (p. 1057·3).
Schizophrenia.

Clopine *Hospira, Austral.; Ikapharmindo, Indon.; Douglas, NZ.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses.

Clopinovo *Arti, Pol.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopirad *Indoco, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopirad-A *Indoco, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clopisa *Skymax, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clopisan *Sandoz, Indon.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolic disorders.

Clopistad *Stada, Hong Kong.*
Clopidogrel bisulfate (p. 1342·3).
Cardiovascular risk reduction; myocardial infarction; unstable angina.

Clopitab *Lupin, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopitab-A *Lupin, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clopithan *Plus Pharma, Cz.; Plus Pharma, Hung.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Clopitom *Miklich, Denm.*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopivas *Cipla, Hong Kong; Cipla, India.*
Clopidogrel bisulfate (p. 1342·3).
Cardiovascular risk reduction; thromboembolic disorders.

Cipla-Medpro, S.Afr.
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clopivas AP *Cipla, India.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Thromboembolic disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Clopivaz *Ultramed, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopivid *Hovid, Hong Kong; Hovid, Malaysia.*
Clopidogrel bisulfate (p. 1342·3).
Cardiovascular risk reduction; thromboembolism prophylaxis.

Clopix *Medhaus, Philipp.; Cipla, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clopix Forte *Cipla, Ukr.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Prevention of ischaemic disorders in patients with atherosclerosis; acute coronary syndrome.

Clopixol *2care4, Denm.; Orifarm, Denm.*
Zuclopenthixol hydrochloride (p. 1119·2).
Psychoses.

Lundbeck, China; Euro Registratie, Neth.; Lundbeck, Philipp.†; Lundbeck, Singapore.
Zuclopenthixol decanoate (p. 1119·2) or zuclopenthixol hydrochloride (p. 1119·2).
Psychoses; behaviour disorders; bipolar disorder; dementia.

Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Belg.; Lundbeck, Braz.; Lundbeck, Canad.; Lundbeck, Fr.; Lundbeck, Hong Kong; Lundbeck, India; Lundbeck, Irl.; Lundbeck, Israel; Lundbeck, Ital.; Lundbeck, Malaysia; Lundbeck, Mex.; Lundbeck, NZ; Lundbeck, Pol.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Spain; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.; Lundbeck, UK; Lundbeck, Ukr.
Zuclopenthixol acetate (p. 1119·1), zuclopenthixol decanoate (p. 1119·2), or zuclopenthixol hydrochloride (p. 1119·2).
Psychoses; bipolar disorder; behaviour disorders; dementia; schizophrenia; behavioural disorders; mania; psychomotor hyperexcitability; agitation; senile confusion; mental function impairment; aggression; disturbed behaviour.

Lundbeck, Gr.
Zuclopenthixol (p. 1119·1), zuclopenthixol decanoate (p. 1119·2), or zuclopenthixol hydrochloride (p. 1119·2).
Psychoses.

Clopizide *Essweil, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clopizide-A *Essweil, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Cloplat *Ipca, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

OEP, Philipp.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clop-M *Zydus, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Clop-MG *Zydus, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clopod *Biochem, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolic disorders.

Clopod-A *Biochem, India.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Thromboembolic disorders.

Clopra
Note: this name may be used for preparations of different composition.
Drogsan, Turk.
Clopidogrel bisulfate (p. 1342·3).

Clopram *Douglas, Austral.†*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; narcoleptic syndrome.

Clopramel *Novell, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Clopreg *Kee, India.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Clopress *LCH, Hong Kong†; Mylan, NZ†*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; narcoleptic syndrome; pain; panic.

Cloprez *RPG, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Cloprez-A *RPG, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Clop-S *Zydus, India.*
⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1).

Clopsina *UCI, Braz.*
Chlorpromazine hydrochloride (p. 1045·2).

Clopsine *Psicofarma, Mex.*
Clozapine (p. 1057·3).
Schizophrenia; bipolar disorder; tremor; withdrawal syndromes.

Cloq *TRB, Arg.*
Tramadol hydrochloride (p. 139·2).
Pain.

Cloq Plus *TRB, Arg.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Cloquin *Indoco, India.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; amoebiasis; rheumatoid arthritis.

Clorace *Cofasa, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Cloracef *Ethica, Indon.*
Cefaclor (p. 232·3).
Bacterial infections.

Clorad *ACS Dobfar, Ital.†*
Cefaclor (p. 232·3).
Bacterial infections.

Cloradex *Tubilux, Ital.*
⊗Dexamethasone (p. 1630·3); chloramphenicol (p. 257·1).
Infected inflammatory eye disorders.

Clorafen *Merck, Mex.†*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Clorafenil *Teuto, Braz.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cloraldin *Medinfar, Port.†*
Chlorhexidine gluconate (p. 1743·3).

Cloram Hemidex *Llorens, Spain.†*
⊗Boric acid (p. 2459·3); chloramphenicol (p. 257·1); dexamethasone phosphate (p. 1631·1).
Infected eye disorders.

Cloram Zinc *Llorens, Spain.†*
⊗Chloramphenicol (p. 257·1); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Bacterial eye infections.

Cloramed
Note: this name may be used for preparations of different composition.
Medifive, Thai.†
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Medimport, Mex.†
Chloramphenicol (p. 257·1).
Bacterial infections.

Cloramfeni *Sophia, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cloramfeni Otico *Sophia, Mex.*
Chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Bacterial ear infections.

Cloramidina *Armoxindo, Indon.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clorampast *Pasteur, Chile.*
Chloramphenicol (p. 257·1).
Vulvovaginal infections.

Clorampler *Arlex, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Cloran *Grin, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cloran Otico *Grin, Mex.†*
Chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Bacterial ear infections.

Clorana *Sanofi-Aventis, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Diabetes insipidus; hypertension; oedema; renal calculi.

Cloranmicron *Alcon, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cloranxen *Teva, Pol.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; alcohol withdrawal syndrome; epilepsy.

Clorap *Rapross, India.*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Clorap-S *Rapross, India.*
⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1).

Cloraseptic
Note: this name may be used for preparations of different composition.
Legrand, Braz.
Phenol (p. 1763·3); sodium phenolate; borax (p. 2459·2); thymol (p. 1772·2); menthol (p. 2553·2).
Mouth and throat disorders.

Clorasona *Oftalmi, Venez.*
⊗Chloramphenicol (p. 257·1); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Cloratadd *EMS, Braz.*
Loratadine (p. 633·2).

Cloratadd D *EMS, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).

Cloratenol *Kener, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cloraxene *TO-Chemicals, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Cloraze *Modern Manu, Thai.*
Dipotassium clorazepate (p. 1056·3).

Clorazer *ACS Dobfar, Ital.†*
Cefaclor (p. 232·3).
Bacterial infections.

Clorazin *Tecnofarma, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clorcef *IAE, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Clorcin-Ped *Stiefel, Braz.*
Cefaclor (p. 232·3).
Bacterial infections.

Clordil *Diba, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clordox *Teuto, Braz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Cloretilo Chemirosa *Ern, Spain.*
Ethyl chloride (p. 1987·1).
Local anaesthesia.

Clorexan *IMS, Ital.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Wound disinfection.

Clorexan Ferri *IMS, Ital.†*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Instrument disinfection.

Clorexifarm *Nuova Farmec, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of burns and wounds.

Clorfenil *Rayere, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clorfibrase *Elea, Arg.*
⊗Chloramphenicol (p. 257·1); fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1).
Wounds.

Clorid-B *Intra-Labs, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).

Cloriflox *TS, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Clorifort *Umedica, Philipp.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Cloril *Atlantic, Thai.*
Clozapine (p. 1057·3).
Schizophrenia.

Clorilex *Mersifarma, Indon.*
Clozapine (p. 1057·3).
Schizophrenia.

Clorimet-Z *Zafiro, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Clorina *Lysoform, Ger.*
Tosylchloramide sodium (p. 1773·1).
Surface disinfection; linen disinfection.

Cloriocard *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Gr.; Sandoz, Swed.*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis.

Cloriv *East African, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Clorix *Pharma Dynamics, S.Afr.†*
Moclobemide (p. 437·2).
Depression; social phobia.

Clorizin *Cifarma, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Heart failure; oedema; cirrhosis with ascites; hypertension.

Clorkin *Doctors, Philipp.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus; rheumatoid arthritis.

Clor-K-Zaf *Zafiro, Mex.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium supplement.

Clormetin *WH-Pharma, Cz.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Clornamin *Tianjin Jinyao, Philipp.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Clorocil *Edol, Port.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cloroden *Interpharm, Austria; Medico Uno, Cz.; Alapis, Gr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clorofunon *Parggon, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clorogen *FDC, UK.*
Chloramphenicol (p. 257·1).
Bacterial conjunctivitis.

Clorom *Rowex, Irl.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clorosan *Lachifarma, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin, wounds, and burns.

Clorotan *Reuffer, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Clorotir *Biochemie, NZ†; Novartis, NZ†; Sandoz, Philipp.†; Sandoz, Thai.*
Cefaclor (p. 232·3).
Bacterial infections.

Cloro-Trimetón *Schering-Plough, Mex.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity.

Clorotrimeton *Schering-Plough, Venez.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Clorpactin WCS-90 *Guardian, USA.*
Oxychlorosene sodium (p. 1762·3).
Skin infections; disinfection.

Clorprax *Hexal, Austral.†*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Clorpres *Mylan, USA.*
⊗Clonidine hydrochloride (p. 1339·1); chlortalidone (p. 1335·2).
Hypertension.

Clorprimeton *Schering-Plough, Chile.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Clorpromaz *Uniao Quimica, Braz.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses.

Clortalil *Sigma, Braz.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema; renal calculi.

Clortamina *Biochimico, Braz.*
Ketamine (p. 1905·1).

Clortanol *CT, Ital.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Clortil *Teuto, Braz.*
⊗Chlortalidone (p. 1335·2).
Hypertension.

Clortilen *Sankyo, Venez.*
Clotrimazole (p. 576·2).
Fungal infections.

Clortrin *Vickmans, Hong Kong.†*
Cefaclor (p. 232·3).
Bacterial infections.

Clorxil *Bohm, Spain.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin and wounds.

Cloryvil *Giempi, Venez.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Closanasol *Jelfa, Hung.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Closastene *Valenta, Rus.*
Clozapine (p. 1057·3).
Schizophrenia; bipolar disorder; behaviour disorders.

Closcript *Ranbaxy, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Closderm *Yung Shin, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clos-DX *Forgo, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Closed *Corona, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Closenid *Ducto, Braz.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Clos-GM *Candor, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Closin *Holsten, Ger.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; psychoses; sleep disorders.

Closina *Aspen, Austral.†*
Cycloserine (p. 280·2).
Tuberculosis; urinary-tract infections.

Closol *Fahrenheit, Indon.†*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clospen *Madhav, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Clostagen *Elder, India.*
Clobetasol acetate; neomycin sulfate (p. 330·1).
Infected skin disorders.

Clostedal *Silanes, Mex.*
Carbamazepine (p. 512·2).
Alcohol and benzodiazepine withdrawal syndromes; epilepsy; bipolar disorder; neuralgias; diabetic neuropathy; diabetes insipidus; polyuria; polydipsia.

Clostemin *UCI, Braz.*
⊗Clostebol acetate (p. 2260·1); neomycin sulfate (p. 330·1).

Clostil *Egis, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Clostilbegyt *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Malaysia; Egis, Pol.; Egis, Rus.; Egis, Singapore; Egis, Ukr.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; oligospermia; amenorrhoea; oligomenorrhoea; galactorrhoea; polycystic ovary syndrome.

Clotam *Sandoz, Fin.; Faran, Gr.; Rottapharm, Gr.; koGen, UK.*
Tolfenamic acid (p. 138·3).
Pain; inflammation; musculoskeletal and joint disorders; migraine.

Clotasol *Burapha, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clotassio *Bunker, Braz.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Clotawin *Bestochem, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Clotawin-T *Bestochem, India.*
Injection: Tranexamic acid (p. 1164·2).
Haemorrhage.

Bestochem, India.
Tablets: Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Clotem Plus *Hiral, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Cloten *IQFA, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine (p. 620·3); phenylephrine (p. 1672·2).

Clotest *Trimed, Austral.*
Test for presence of *Helicobacter pylori* in gastric mucosal biopsy samples.

Bripharm, Irl.†
Test for *Helicobacter pylori* from biopsy specimens.

Clothalton *Sarabhai Piramal, India.*
⊗Chlortalidone (p. 1335·2); clonidine hydrochloride (p. 1339·1).
Hypertension.

Clothree *Teva, Israel.*
Clotrimazole (p. 576·2).
Vaginal infections.

Clotide *Biocon, India.*
Eptifibatide (p. 1376·3).
Unstable angina; adjunct in coronary angioplasty.

Clotidone *Apotex, Philipp.†; Pharma 3, Philipp.†*
Ticlopidine hydrochloride (p. 1512·1).
Prevention of platelet loss during extracorporeal stenting; thromboembolic disorders.

Clotigen
Note: this name may be used for preparations of different composition.
Dynamic, Philipp.†
Menadione sodium bisulfite (p. 2122·2).
Haemorrhage.

Vitapan, Braz.†
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotinab *Isu Abxis, Thai.*
Abciximab (p. 1281·1).
Prevention of ischaemic cardiac complications during percutaneous coronary intervention.

Clotix *Ferron, Indon.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clotiz *Zydus Cadila, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clotof-G *Osmed, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2).
Infected skin disorders.

Clotof-GM *Osmed, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Clotof-M *Osmed, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Cloton *TNP, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cough; nasal congestion; rhinitis.

Clotrason *Schering-Plough, Denm.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Infected skin disorders.

Clotrasone *MSD, China; Essex, Philipp.; Desarrollo, Spain.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections.

Clotren *Teuto, Braz.*
Clotrimazole (p. 576·2).
Fungal infections.

Clotrex *Borshchagovskii, Ukr.*
Gentamicin (p. 304·2); clotrimazole (p. 576·2); calendula (p. 2465·2); achillea (p. 2427·3).
Fungal skin infections.

Clotri *Polipharm, Thai.*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Clotri OPT *Optimed, Ger.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotricin *Seng, Thai.*
Clotrimazole (p. 576·2).
Fungal vaginal infections; trichomoniasis.

Clotricina *Diba, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Clotricyd *GSK, Cz.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections; trichomoniasis.

Clotri-Denk *Denk, Hong Kong.*
Clotrimazole (p. 576·2).
Fungal skin infections; fungal and bacterial vaginal infections; trichomoniasis.

Clotriderm *Greenpharma, Braz.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotrigalen *Galen, Ger.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotrigel *Glenmark, Braz.*
Clotrimazole (p. 576·2).

Clotrihexal *Hexal, NZ.†*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Clotrimaderm *Taro, Canad.; Taro, Israel; AFT, NZ.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Clotrim-B *Marching, Hong Kong.†*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Clotrimed *Medicine Products, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotrimin *Medipharm, Chile.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Clotrimin-B *Medipharm, Chile.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Fungal skin infections with inflammation.

Clotrinolon *Jean-Marie, Hong Kong.*
⊗Clotrimazole (p. 576·2); triamcinolone acetonide (p. 1649·1).
Fungal skin infections with inflammation.

Clotrin-V *NuLife, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Clotri-Q *Ariston, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotrisal *Arterium, Ukr.*
Clotrimazole (p. 576·2); salicylic acid (p. 1719·1).
Fungal skin infections.

Clotrisone *Taro, Israel.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections.

Clotrix *Lepetit, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Clotrizan *Prodotti, Braz.†*
Clotrimazole (p. 576·2).
Fungal infections.

Clotrizol
Note: this name may be used for preparations of different composition.
Calox, Venez.
Clotrimazole (p. 576·2).
Fungal infections.

Clotromboz *Sandoz, Gr.*
Clopidogrel (p. 1342·3).

Clotrop *Elfin, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Clotsafe *MSN, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Clottafact *LFB, Fr.*
Fibrinogen (p. 1151·3).
Hypofibrinogenaemia.

Clottagen *LFB, Fr.†*
Fibrinogen (p. 1151·3).

Clouds *Bestochem, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Cloval *Saval, Chile.*
Clobutinol hydrochloride (p. 1658·3).
Cough.

Cloval Compuesto *Saval, Chile.*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3).
Cough.

Clovar-V *Zota, India.*
Clotrimazole (p. 576·2); *Lactobacillus sporogenes* (p. 2596·3).

Clovate *Jelfa, Cz.; Jelfa, Rus.; Cantabria, Spain; Jelfa, Ukr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Clovax *Medbase, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Clovelen *Elpen (Ελπεν), Gr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clovertil *Meprofarm, Indon.†*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Clovex *Arlex, Mex.*
Aciclovir (p. 964·1).
Viral infections.

Clovicol *General Drugs House, Philipp.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Clovillin *General Drugs House, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Clovimax *Vamsler, Philipp.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Clovin *Nakornpatana, Thai.*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Clovir *Cazi, Braz.; XL, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Clovira *M & H, Thai.*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Clovirax *Remek, Gr.; Maneesh, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Cloviron *Helviina, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Clovisone *Ashford, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Clovix
Note: this name may be used for preparations of different composition.
Spirit, Austral.; Medical Pharmaquality, Gr.; ACME, Philipp.
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Clovixime *General Drugs House, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cloviz *General Drugs House, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Clovizeme *Medchem, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Clovizole *Mount Mettur, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; Helicobacter pylori eradication.

Clovizone *Medchem, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Clowin *Arrowin, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

C-Lox *Yacca, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Clox
Note: this name may be used for preparations of different composition.
Caber, Ital.
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Foramen, Philipp.
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

GPO, Thai.†
Cloxacillin (p. 274·3).
Staphylococcal infections.

Cloxa *Christo, Hong Kong†; Community Pharmacy, Thai.; M & H, Thai.; Suphong, Thai.; TO-Chemicals, Thai.; TP, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxacap *Hovid, Singapore.*
Cloxacillin sodium (p. 275·1).
Gram-positive bacterial infections.

Cloxacel *Seven Stars, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxaco *Sel-J, Philipp.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxadil *Teuto, Braz.*
Cloxazolam (p. 1057·2).

Cloxal *Taisheng, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxalin *Siam Bheasach, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxam
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Jaba, Port.
Cloxazolam (p. 1057·2).
Anxiety disorders.

Macrophar, Thai.
Cloxacillin (p. 274·3).
Bacterial infections.

Cloxam Plus *Taurus, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Cloxamed *Medicpharma, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxamp *Christo, Hong Kong.†*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxampi *Vickmans, Hong Kong.†*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxampilin *Christo, Hong Kong.†*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxan
Note: this name may be used for preparations of different composition.
Biomep, Mex.
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Suphong, Thai.
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxanbin *ANB, Thai.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxapene *Mandar, India.*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxasian *Asian Pharm, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxcin
Note: this name may be used for preparations of different composition.
DHA, Hong Kong.
Cloxacillin (p. 274·3).
Staphylococcal infections.

DHA, Singapore.
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Indkus, India.
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Cloxgen *General Drugs, Thai.*
Cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxide *La Pharmaceuticals, India.*
Chlordiazepoxide (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; insomnia.

Cloxide Plus *La Pharmaceuticals, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine (p. 1113·2).

Cloxigen *Dynamic, Philipp.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxil *Foramen, Philipp.; Ranbaxy, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Cloxillin
Note: this name may be used for preparations of different composition.
British Dispensary, Thai.
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Ibirn, Ital.
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Cloxim *Terramedic, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Cloximar Duo *Dupomar, Arg.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Cloxin *Medhaus, Philipp.; Aspen, S.Afr.; Utopian, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxina *Lewison, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Cloxino *Pharmahof, Thai.†*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxinova *Novagen, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Cloxona-O *Sons, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1); phenylephrine hydrochloride (p. 1672·3).
Infected eye disorders.

Cloxpac *Inpac, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxstar *Pharmahof, Thai.†*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Cloxy *Jean-Marie, Philipp.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Cloxydin *Biomedis, Thai.†; Great Eastern, Thai.†*
Dicloxacillin (p. 286·1).
Bacterial infections.

Clozal *Sankyo, Braz.*
Cloxazolam (p. 1057·2).
Anxiety.

Clozalux *Rowex, Irl.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Clozam *Psicofarm, Arg.; Sarabhai Piramal, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Clozamed *Medifive, Thai.*
Clozapine (p. 1057·3).
Schizophrenia.

Clozan *Pfizer, Belg.*
Clotiazepam (p. 1057·2).
Anxiety disorders.

Clozanil *Sanitas, Chile.*
Clonazepam (p. 519·1).
Epilepsy; panic attacks.

Clozarem *Remedica, Malaysia.*
Clozapine (p. 1057·3).
Schizophrenia.

Clozaril *Novartis, Austral.; Novartis, Canad.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Jpn; Novartis, Malaysia; Novartis, NZ; Novartis, Singapore; Novartis, Thai.; Novartis, UK; Novartis, USA.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Clozed *Zota, India.*
Clotrimazole (p. 576·2); lactobacillus (p. 2596·3).

Clozep *Elite, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Clozepate *New Life, Thai.*
Dipotassium clorazepate (p. 1056·3).

Clozepaxel *Pisa, Mex.*
Gabapentin (p. 523·3).
Epilepsy.

Clozer *Sun, Mex.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder; obsessive-compulsive disorder.

Clozil *Jinling, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders.

Clozine *Psychotropics, India.*
Chlorpromazine (p. 1045·2).
Psychoses; intractable hiccup.

Clozine Forte *Psychotropics, India.*
Chlorpromazine hydrochloride (p. 1045·2); trihexyphenidyl hydrochloride (p. 917·3).

Clozine Plus *Psychotropics, India.*
Chlorpromazine hydrochloride (p. 1045·2); trihexyphenidyl hydrochloride (p. 917·3).

Clozol *Cipla, India; Sandoz, Turk.*
Clotrimazole (p. 576·2).
Fungal skin infection; fungal skin infections.

Clozole
Note: this name may be used for preparations of different composition.
Jean-Marie, Hong Kong.
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Psyco Remedies, India.
Fluconazole (p. 578·2).
Fungal infections.

Clusivol *Aspen, S.Afr.*
Syrup: Vitamins; minerals; lysine hydrochloride (p. 2079·3); inositol (p. 2533·2); choline (p. 2055·2).

Wyeth Consumer, Braz.; Wyeth, Philipp.; Wyeth, Venez.
Vitamins; minerals.

Akromed, S.Afr.†
Chewable tablets: Vitamins.

Clusivol Composto *Wyeth Consumer, Braz.*
Vitamins; amino acids; minerals.

Clusivol Pediatric *Wyeth, Philipp.*
Vitamins.

Clusivol Power C *Wyeth, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Cluster *Osmed, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Clustoid *Roxall, Ger.*
Allergen extracts of pollen (p. 2593·3), mites (p. 2434·3), fungus, and animal skin (p. 2434·3).
Allergen immunotherapy.

Cluvax *Gynopharm, Chile.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

Cluvimin *Catalent, Philipp.*
Vitamins; minerals.

Cluyer *Fada, Arg.*
⊗Pethidine (p. 121·3).
Pain.

CLX *Novagen, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Clycin *BMW, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Clydin *Medizone, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Clynox *Micro, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

C-Lysin *Hi-Tec, India.*
Choline dihydrogen citrate (p. 2055·2); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).

C-Lysin Gold *Hi-Tec, India.*
Vitamins; minerals.

Clysmol *Pfizer, Austria.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Clyss-Go *Novag, Mex.; Prospa, Port.*
Docusate sodium (p. 1836·2); sorbitol (p. 2092·1).
Constipation; bowel evacuation.

C-Lyte *Corona, India.*
Electrolytes (p. 1775·1).
Oral rehydration therapy.

Clyvorax *Unipharm, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

CMD Plus *Medial, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

C-Messel *Biomep, Mex.*
Ascorbic acid (p. 2110·3).

C-Met *Corona, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

C-Mic *TNP, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

C-Mide *Corona, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

C-Mide Plus *Corona, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

C-Mine *Corona, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

C-Motil *Ultra, Mex.*
Sennosides A and B (p. 1885·2).
Constipation.

C-Mox
Note: this name may be used for preparations of different composition.
Columbia, S.Afr.†
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

C-Moxy *Life Line, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

C-MR *Corona, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

CMV Immunoglobulin *CSL, Austral.*
A cytomegalovirus immunoglobulin (human) (p. 2381·3).
Passive immunisation.

CMW
Note: this name may be used for preparations of different composition.
Zydus, India.
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

CMW Gentamicin *Johnson & Johnson, NZ.*
Polymethylmethacrylate (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

C-Nac *Corona, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

C-Nate *Plus, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

CNB *Ind-Swift, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).
Infected skin disorders.

C'Nergil *Medinfar, Port.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

C-Nim *Corona, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

C-Nim Plus *Corona, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

CNL Nail Kit *JSJ, USA.*
Topical solution, ciclopirox (p. 575·3); topical capsules, tocopherol (p. 2119·1).
Onychomycosis.

CNN *Ipca, India.*
Minocycline (p. 324·3).
Acne.

C-Nor Plus *Corona, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

CNP *Curex, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Co Amoxin *Coll, Spain.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Co Bucal *Biomed, Spain.*
Alum (p. 2439·1); procaine hydrochloride (p. 1994·3); salicylic acid (p. 1719·1); sodium chlorate (p. 2618·1); thymol (p. 1772·2); cherry laurel water; peppermint oil (p. 1877·1).
Stomatitis; gingivitis; pyorrhoea.

Co Fluocin Fuerte *Smaller, Spain.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Co Trim *Thebe, S.Afr.*
Co-trimoxazole (p. 277·3).

Co-Acepril *Spirig, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Acetan *Kwizda, Austria.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

CoActifed *GSK, Canad.*
Expectorant: ⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

GSK, Canad.
Syrup; tablets: ⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Coag *Intel, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Coagil-VII *Farmstandart, Rus.*
Eptacog alfa (activated) (p. 1147·2).
Haemorrhagic disorders.

Coaguchek *Roche Diagnostics, Ital.*
Test for prothrombin time.

Co-Aleva *OEP, Philipp.*
⊗Ebastine (p. 628·1); betamethasone (p. 1623·2).
Allergic rhinitis; urticaria.

Coalgan *Brothier, Fr.*
Calcium alginate (p. 1136·3).
Haemorrhage.

Coalsyl-S *Psyco Remedies, India.*
Ointment: Coal tar (p. 1723·2); salicylic acid (p. 1719·1); precipitated sulfur (p. 1721·1).

Psyco Remedies, India.
Scalp application: Coal tar (p. 1723·2); salicylic acid (p. 1719·1).

Co-Altria *Ajanta, Philipp.*
Montelukast sodium (p. 1214·3); levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis.

Co-Amclox *Frankin, Hong Kong.†*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Co-Amiloride *Teva, Belg.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

CoAmox
Note: this name may be used for preparations of different composition.
Acino, Switz.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Coamox
Note: this name may be used for preparations of different composition.
Community Pharmacy, Thai.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Co-Amoxi *Mepha, Switz.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ratiopharm, Hung.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ratiopharm, Belg.†
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Co-Amoxicillin *Actavis, Switz.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Co-Amoxicilline *Helvepharm, Switz.; Sandoz, Switz.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Co-Amoxyclav *Sandoz, S.Afr.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Co-Angiosan *Novartis, Austria†; Novartis, Port.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Apap *Rugby, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Coaparin *Polfa Warszawa, Pol.*
Heparin sodium (p. 1396·3).
Thromboembolism prophylaxis.

CoAprovel *Sanofi-Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; BMS, Hung.; Sanofi-Aventis, Hung.; Sanofi Synthelabo, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; BMS, Neth.; Sanofi-Aventis, Neth.; Sanofi BMS, Norw.; Sanofi-Aventis, Philipp.; BMS, Pol.; Sanofi-Aventis, Pol.; BMS, Port.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; BMS, Switz.; Sanofi, Switz.; Sanofi-Aventis, Thai.; BMS, UK; Sanofi-Aventis, UK; Sanofi-Aventis, Venez.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Arbartan *Teva, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Arinate *Dafra, Belg.*
3 Tablets, artesunate (p. 648·2); 3 tablets, sulfametopyrazine (p. 367·3); pyrimethamine (p. 662·3).
Malaria.

Coarol *Andromaco, Chile.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Coartem *Novartis, Indon.; Novartis, Philipp.; Novartis, S.Afr.; Novartis, Thai.; Novartis, USA.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Co-Artesiane *Dafra, Belg.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Coartrin *Medreich, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Coastat *Concept, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Coastat Plus *Concept, India.*
Tranexamic acid (p. 1164·2); etamsylate (p. 1145·2).

Coastat-Gyne *Concept, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Co-Atenolol *Spirig, Switz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

CO-AX *Xeno, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Coax *Kamakshi, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Coax-DX *Kamakshi, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Coaxil *Servier, Cz.; Servier, Hung.; Servier, Pol.; Servier, Rus.; Servier, Ukr.*
Tianeptine sodium (p. 450·2).
Depression; alcohol withdrawal syndrome.

Coba *Triton, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobacta-S *Auspi, India.*
⊗Amoxicillin (p. 216·2); cloxacillin sodium (p. 275·1); serrapeptase (p. 2613·3).

Cobactin *Zambon, Braz.*
Cyproheptadine hydrochloride (p. 624·1); cobamamide (p. 2107·2).
Tonic; reduced appetite.

Cobaday *Gentech, India.*
Injection: Vitamins.

Gentech, India.
Tablets: Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobaday-AV *Gentech, India.*
Thioctic acid (p. 2629·1); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2).

Cobadex
Note: this name may be used for preparations of different composition.
GSK, India.
Vitamin B substances (p. 2102·3).
Dietary supplement.

Maver, Mex.
Ambroxol hydrochloride (p. 1654·3); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract congestion; cough.

Cobadex Forte *GSK, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Cobadex-CZS *GSK, India.*
Vitamin B substances (p. 2102·3); chromium tripicolinate (p. 2056·1); selenious acid (p. 2087·1); zinc sulfate (p. 2126·2).

Cobadex-Z *GSK, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Cobaforte *EG, Ital.*
Cobamamide (p. 2107·2).
Vitamin B_{12} deficiency.

Cobaglobal *Legrand, Braz.*
Cobamamide (p. 2107·2); cyproheptadine hydrochloride (p. 624·1).
Tonic.

Cobal *Mars, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobal Forte *Mars, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Cobal Plus *Arika, India.*
Alpha linoleic acid (p. 2509·2); vitamins; selenium (p. 2086·3); zinc (p. 2126·1).

Cobalamin *Marching, Hong Kong.†*
Cyanocobalamin (p. 2107·2).

Cobalatec *Caps, S.Afr.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Cobaldoze *Kinder, Braz.†*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Cobal-F *Constant, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Cobalfer *Biotech, Venez.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); copper sulfate (p. 2057·2).
Anaemias.

Cobalin-H *Amdipharm, UK.*
Hydroxocobalamin (p. 2107·3).
Anaemia due to B_{12} deficiency; tobacco amblyopia; leber's atrophy.

Cobalip *Triton, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Cobalom *Om Biotec, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Cobal-PG *Arika, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Cobals Plus *Shreshtha, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Cobalvit *Intra-Labs, India.*
Vitamin B substances (p. 2102·3).

Cobalvit Forte *Intra-Labs, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Cobalvit 1ML *Intra-Labs, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Cobalvit Plus *Intra-Labs, India.*
Chromium (p. 2055·3); selenium (p. 2086·3); thioctic acid (p. 2629·1); vitamins.

Cobalvit-D *Intra-Labs, India.*
Oral powder: Minerals; vitamins.

Intra-Labs, India.
Syrup: Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobalvit-GT *Intra-Labs, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Cobalvit-OD *Intra-Labs, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobamet-OD *Sun, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobamin *Santen, Hong Kong; Synco, Hong Kong.*
Cyanocobalamin (p. 2107·2).
Eye disorders; dietary supplement.

Cobamol *Maver, Mex.*
⊗Salbutamol (p. 1220·2).

Cobandaxin *Kobayashi, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Cobanerve *Invision, India.*
Injection: Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Invision, India.
Tablets: Thioctic acid (p. 2629·1); calcium (p. 1783·1); selenium (p. 2086·3); vitamins.

Cobanerve OD *Invision, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Cobanerve Plus *Invision, India.*
Capsules: Thioctic acid (p. 2629·1); vitamins; chromium chloride (p. 2055·3); selenium dioxide (p. 2087·1).
Invision, India.
Injection: Vitamin B substances (p. 2102·3).

Cobanerve-G *Invision, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Cobanerve-HR *Invision, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Cobantril *Interdelta, Switz.*
Pyrantel embonate (p. 165·3).
Nematode infections.

Cobasoft *Torrent, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Cobasol *Pfizer, Austral.*
Cabergoline (p. 899·3).
Parkinsonism.

Cobatin *Alvartis, Mex.*
Clindamycin (p. 269·3).
Bacterial infections.

Cobaver *Evershine, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Cobaver-M *Evershine, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Cobaver-OD *Evershine, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Cobavit *Cifarma, Braz.*
Cyproheptadine hydrochloride (p. 624·1); cobamamide (p. 2107·2).
Reduced appetite.

Cobavital *Abbott, Braz.*
Cobamamide (p. 2107·2); cyproheptadine hydrochloride (p. 624·1).
Tonic; reduced appetite.

Cobaxid *Tecnifar, Port.*
Cobamamide (p. 2107·2).
Anaemias; tonic; neuralgias; neuritis.

Cobay *Millimed, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cobazim *Interbat, Indon.*
Cobamamide (p. 2107·2).
Anorexia; malnutrition; pernicious anaemia.

Co-Becetamol *Gebro, Switz.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Cobederm-H *Sarabhai Piramal, India.†*
⊗Halcinonide (p. 1639·3); econazole nitrate (p. 577·3).
Infected skin disorders.

Cobefen *Sanitas, Chile.*
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Cobenexol Forte *Bayer Consumer, Arg.*
Cocarboxylase (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; radiotherapy-induced vomiting; vomiting of pregnancy; vitamin B deficiency.

Cobenexol Fuerte *Bayer Consumer, Arg.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgias; vitamin B deficiency.

Cobese *Ranbaxy, India.*
Orlistat (p. 2577·1).
Obesity.

Cobesol *Community Pharmacy, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Co-Bespres *Teva, Pol.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Betaloc *Pharmacia, Irl.†*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cobetsol *Bright Future, Hong Kong.†*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Cobex-CL *Orion, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Cobiona *Esteve, Spain.†*
Oxatomide (p. 636·3).
Hypersensitivity reactions.

Co-Biotic *SupHerb, Israel.*
Streptococcus thermophilus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Nutritional supplement.

Co-Biotic Kid *SupHerb, Israel.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Nutritional supplement.

Co-Bisoprolol *Eurogenerics, Belg.; Mylan, Belg.; Ratiopharm, Belg.; Sandoz, Belg.; Teva, Belg.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cobix *Cipla, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain.

Coblona *Zota, India.*
Injection: Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.
Zota, India.
Tablets: Mecobalamin (p. 2108·1); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

Coblona Plus *Zota, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Cobolac *Osmed, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); lactobacillus (p. 2596·3).
Diarrhoea.

Cobotiaxina *Ifusa, Mex.*
Cyanocobalamin (p. 2107·2); pyridoxine (p. 2105·3); thiamine (p. 2102·3).
Anaemias; neuritis.

Cobsa *Arvincare, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Cobsa-G *Arvincare, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Cobury-AX *Hanburys, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Cobury-DX *Hanburys, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cocalate *VHB, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Co-Candésartan *Sandoz, Switz.*
Candesartan cilexetil (p. 1330·2); hydrochlorothiazide.
Hypertension.

Co-Cantab *Nobel, Turk.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Captopril *Genericon, Austria.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Captral *Silanes, Mex.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cocardax *Tiefenbacher, Neth.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Carnetina B12 *Sigma-Tau, Ital.*
Cobamamide (p. 2107·2); levocarnitine (p. 2053·2).
Tonic.

Cocarnit *World Medicine, Ukr.*
Nicotinamide (p. 2083·1); cocarboxylase (p. 2103·1); cyanocobalamin (p. 2107·2); adenosine triphosphate disodium (p. 2430·3).
Neuritis; neuropathy; neuralgia.

Coccila *TNP, Thai.*
Syrup: Furazolidone (p. 933·3); neomycin (p. 329·3); kaolin (p. 1850·1).
Gastrointestinal infections.
TNP, Thai.
Tablets: Diiodohydroxyquinoline (p. 931·1); neomycin sulfate (p. 330·1); phthalylsulfathiazole (p. 339·3); light kaolin (p. 1850·1); furazolidone (p. 933·3).
Gastrointestinal infections.

Cocculine *Boiron, Canad.*
Cocculus indicus (p. 2483·1); colubrine; petroleum (p. 2587·2); tabacum (p. 2632·2).
Homoeopathic preparation.
Boiron, Cz.; Boiron, Fr.; Boiron, Hung.; Boiron, Neth.; Boiron, Port.; Boiron, Rus.; Boiron, Switz.
Cocculus indicus (p. 2483·1); strychnos nux vomica (p. 2573·3); nicotiana tabacum (p. 2632·2); petroleum rectificatum (p. 2587·2).
Homoeopathic preparation.

Cocculus Complexe No 73 *Lehning, Fr.*
Cocculus (p. 2483·1); vinca minor; zincum valerianicum (p. 2641·2); nux vomica (p. 2573·3); pulsatilla (p. 2600·2); plumbum aceticum (p. 2541·3); argentum nitricum (p. 2615·3); glonoinum (p. 1391·2); belladonna (p. 2453·3); artemisia vulgaris.
Homoeopathic preparation.

Cocculus Oligoplex *Madaus, Ger.*
Cocculus (p. 2483·1); belladonna (p. 2453·3); chamomilla (p. 2474·1); cuprum aceticum (p. 2486·2); cytisus laburnum (p. 2538·3); platinum chloratum (p. 2593·1).
Homoeopathic preparation.

Cocef *Symbiosis, India.*
Cefixime (p. 240·3).
Bacterial infections.

Cocefin *Corsa, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cocef-LB *Symbiosis, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Cocet *New Life, Thai.; Poly, USA.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Cochic *Masa, Thai.*
Colchicine (p. 604·1).
Gout.

Cocichimil *Multilab, Braz.*
Colchicine (p. 604·1).

Coci-Fedra *Marching, Hong Kong.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); squill (p. 1677·3); senega (p. 1677·2); cocillana (p. 1659·2).
Cough; nasal congestion; cold symptoms; hay fever.

Coci-Fedra-C *Marching, Hong Kong.†*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3); squill (p. 1677·3); senega (p. 1677·2); cocillana (p. 1659·2).
Cough; nasal congestion; hypersensitivity reactions.

Cocillana *Orion, Fin.*
Ethylmorphine hydrochloride (p. 56·3).
Cough.

Cocillana Christo *Christo, Hong Kong.*
Cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3); menthol (p. 2553·2).
Cough.

Cocillana Co
Note: this name may be used for preparations of different composition.
Vickmans, Hong Kong.†
Cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Cocillana Co w/o Codeine *Universal, Hong Kong.†*
Cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Cocillana Compound
Note: this name may be used for preparations of different composition.
Universal, Hong Kong.
Cocillana (p. 1659·2); euphorbia (p. 2501·3); squill (p. 1677·3); senega (p. 1677·2); codeine phosphate (p. 40·2).
Cough.
Frankin, Hong Kong.†
Cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).
Cough.
Synco, Hong Kong.†
Cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3); menthol (p. 2553·2).
Cough; respiratory-tract congestion.
Vida, Hong Kong.†
Cocillana (p. 1659·2); euphorbia (p. 2501·3); squill (p. 1677·3).
Cold symptoms; cough.

Cocillana Compound with Codeine *Synco, Hong Kong.†*
Cocillana (p. 1659·2); codeine (p. 40·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Cocillana Compound (Non-Narcotic) *Vickmans, Hong Kong.†*
Cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Cocillana-Etyfin *Meda, Swed.*
Ethylmorphine hydrochloride (p. 56·3); senega (p. 1677·2); cocillana (p. 1659·2).
Cough.

Coclox *Community Pharmacy, Thai.†*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Co-Cof *Millimed, Thai.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Cocois *UCB, Irl.; Central Clinical, Pol.; Bioglan, Singapore; Focus, UK.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); precipitated sulfur (p. 1721·1).
Scalp disorders.

Cocois Co *ICM, Singapore.*
Camphor (p. 2466·2); coal tar (p. 1723·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).

Coconium-Gastreu *Reckeweg, Neth.*
Argentum nitricum (p. 2615·3); cocculus indicus (p. 2483·1); conium maculatum (p. 2524·3).
Homoeopathic preparation.

Cocorex *Taj, India.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Coco-Scalp *AFT, NZ.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Scaly scalp disorders.

Cocydal *Xixia, S.Afr.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cocyntal *Boiron, Canad.*
Carbo vegetabilis (p. 1537·3); colocynthis (p. 1833·3); cuprum metallicum (p. 2057·1).
Homoeopathic preparation.

C-OD *GSK, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cod Efferalgan *BMS, Spain.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

COD N 70 *Fresenius Kabi, Ital.†*
Amino acids.
Parenteral nutrition.

Codabrol *Rekah, Israel.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Cough; fever; pain.

Cod-Acamol *Taro, Israel.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Cough; fever; pain.

Codaewon *Daewon, Hong Kong.*
⊗Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2); methylephedrine hydrochloride (p. 1669·2); chlorphenamine maleate (p. 620·3).
Cough.

Co-Dafalgan *BMS, Switz.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Codagesic *Alphapharm, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain; fever.

Codalan
Note: this name may be used for preparations of different composition.
Ceutical, Hong Kong.†
Flutamide (p. 798·2).

Codalax *Mundipharma, Irl.; Napp, UK.*
Dantron (p. 1833·3); poloxamer 188 (p. 2202·1).
These ingredients can be described by the British Approved Name Co-danthramer.
Constipation.

Codal-DH *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Coughs and cold symptoms; allergic rhinitis.

Codal-DM *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Cough; cold symptoms; allergic rhinitis.

Codalgin
Note: this name may be used for preparations of different composition.
Fawns & McAllan, Austral.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Codalgin Plus *Aspen, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Fever; pain.

Codalux *Angelini, Irl.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Co-Dalzad *Novartis, Gr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Codamol
Note: this name may be used for preparations of different composition.
Abiogen, Ital.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.
ANH, Thai.
Paracetamol (p. 115·1).
Fever; pain.

Codant *Antigen, Irl.†*
Codeine phosphate (p. 40·2).
Pain; cough.

Codapane *Alphapharm, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Codaphed *Julphar, UAE.*
⊗Ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Cough.

Codaphed Plus *Julphar, UAE.*
⊗Ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Codarin-A *ANH, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Codasel *Akdeniz, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Codaten *Novartis, Braz.*
Diclofenac (p. 48·3); codeine phosphate (p. 40·2).
Pain; inflammation.

Codaxol *Ratiopharm, Fin.†; Ratiopharm, Norw.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Codeb *Taurus, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Codebromil *Vincenti, Venez.*
Syrup: Codeine (p. 40·2).
Cough.
Vincenti, Venez.
Elixir: Codeine (p. 40·2); thyme (p. 2630·2); drosera (p. 2497·2); Desessartz syrup (p. 1667·2).
Cough.

Codebup *Richmond, Arg.*
Bicalutamide (p. 749·1).

Codecon *Erlimpex, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1); guaifenesin (p. 1666·2).
Nasal congestion; cough.

Codectuss *Cadila, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Codedrill *Pierre Fabre, Fr.*
Codeine phosphate (p. 40·2).
Cough.

Codee-C *Medicpharma, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Codef *Be-Tabs, S.Afr.†*
⊗Codeine phosphate (p. 40·2); mepyramine maleate (p. 635·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Codehist DH *Geneva, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Codeine Contin *Purdue, Canad.*
Codeine (p. 40·2); codeine sulfate (p. 40·3).
Pain.

Codeinllana *Frankin, Hong Kong.†*
Cocillana (p. 1659·2); codeine (p. 40·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Codeipar *Mastercare, Chile.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Codeisan *Teva, Spain.*
Codeine phosphate (p. 40·2).
Cough.

Codelac *Farmstandart, Rus.*
Codeine (p. 40·2); sodium bicarbonate (p. 1781·1); liquorice (p. 1853·2); thermopsia lanceolata.
Cough.

Codelac Broncho *Leksredstva, Rus.*
Ambroxol hydrochloride (p. 1654·3); sodium glycyrrhizate; thermopsia; sodium bicarbonate (p. 1781·1).
Respiratory-tract disorders.

Codelac Broncho with Thymus Serpyllum *Farmstandart, Rus.*
Ambroxol hydrochloride (p. 1654·3); sodium glycyrrhizate; thyme (p. 2630·2).
Respiratory-tract disorders.

Codelac Phyto *Farmstandart, Rus.*
Codeine phosphate (p. 40·2); thyme (p. 2630·2); liquorice (p. 1853·2); thermopsia.
Cough.

Codelasa *Andromaco, Chile.*
Codeine (p. 40·2); ethylmorphine (p. 56·3); homatropine methylbromide (p. 2007·3).
Cough.
Zuoz, Venez.
Codeine (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.
Andromaco, Arg.
Codeine (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Codelmicst *Rusan, Rus.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; cold and influenza symptoms.

Codelsol *Ulagay, Turk.†*
⊗Prednisolone sodium phosphate (p. 1645·3).
Inflammatory eye and ear disorders.

Codelton *Ulagay, Turk.†*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Codelum *Sanova, Austria.†*
Thyme (p. 2630·2); codeine phosphate (p. 40·2).
Cough.

Codenfan *Bouchara-Recordati, Fr.*
Codeine phosphate (p. 40·2).
Pain.

Codepect *Neopharm, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough; cold symptoms; nasal congestion.

Co-Depon *BMS, Gr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Coderan *Novartis, India.*
Codeine (p. 40·2); diclofenac (p. 48·3).

Coderetta N *Valeant, Hung.*
⊗Codeine hydrochloride (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract disorders.

Codergine *Neo Quimica, Braz.*
Codergocrine mesilate (p. 389·2).

Coderit *Chinoin, Mex.*
⊗Codeine hydrochloride (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Coderit N *Valeant, Hung.*
⊗Codeine hydrochloride (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract disorders.

Codermo *Berksam, Turk.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Coderol *Almirall, Spain.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Codesan Comp *Leiras, Fin.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); diphenhydramine hydrochloride (p. 626·2); cocillana (p. 1659·2).
Cough.

Codesia *Asian Pharm, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Codesoft *Ind-Chemie, India.*
Cod-liver oil (p. 2056·3); vitamin E acetate (p. 2119·2).

Codetabs *Leiras, Fin.*
Cocillana (p. 1659·2).
Cough.

Codethyline *Erfa, Belg.*
Ethylmorphine hydrochloride (p. 56·3).
Cough.

Codetol *Laboratorios Chile, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; respiratory-tract congestion.

Codetol PM *Laboratorios Chile, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); avocado leaf (p. 2451·2); eucalyptus leaf (p. 2501·1).
Cough; nasal congestion.

Codex
Note: this name may be used for preparations of different composition.
Uniao Quimica, Braz.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.
Zambon, Ital.
Saccharomyces boulardii (p. 2596·3).
Gastrointestinal disorders.

Codexial *Spirig, Fr.†*
A range of emollients.

Codexial Zinc *Spirig, Fr.†*
White soft paraffin (p. 2211·3); zinc oxide (p. 1729·1).
Skin irritation; dry skin.

Codexine-R *Coup, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Cod-Guaiacol *Vitamed, Israel.*
Sulfogaiacol (p. 1678·1); codeine phosphate (p. 40·2).
Cough.

codi OPT *Optimed, Ger.*
Codeine phosphate (p. 40·2).
Pain.

Codiasp *Codilab, Port.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain; thrombosis prophylaxis.

Codica *Sarabhai Piramal, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Codical *Sam-On, Israel.*
Codeine phosphate (p. 40·2).
Cough.

Codicalm *Welti, Switz.*
Codeine phosphate (p. 40·2).
Cough.

Codicaps mono *UCB, Ger.*
Codeine (p. 40·2).
Cough.

Codicaps Neo *UCB, Ger.*
Codeine (p. 40·2).
Cough.

Codicet *Hua, Thai.; M & H, Thai.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Codiclear DH *Victory, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Codicompren *Desma, Ger.*
Codeine phosphate (p. 40·2).
Cough.

Codicontin *Mundipharma, Belg.†; Mundipharma, Switz.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

Codidol *Mundipharma, Austria.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

Codifos *Cipla, India.*
Codeine phosphate (p. 40·2).

Codigesic *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Co-Dilatrend *Roche, Austria.*
⊗Carvedilol (p. 1333·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Codilergi *Codilab, Port.†*
Diphenhydramine (p. 626·1).
Skin irritation.

Codimal DH *Victory, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); dexchlorpheniramine maleate (p. 621·1).
Cough and cold symptoms.

Codimal DM *Victory, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Coughs.

Codimal PH *Victory, USA.†*
Codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Coughs and cold symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Codimin *Biomedica, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Codimol *Gujarat Terce, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Codin *Zydus, India.*
Codeine sulfate (p. 40·3).
Pain; cough.

Codine *Zydus, India.*
Codeine sulfate (p. 40·3).
Pain; cough.

Codinex *Pinewood, Irl.*
Codeine phosphate (p. 40·2).
Cough.

Co-Diovan *Novartis, Austral.; Novartis, Austria; Novartis, China; Novartis, Cz.†; Orifarm, Denm.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S. Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Diovane *Novartis, Belg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Codipar
Note: this name may be used for preparations of different composition.
Goldshield, Irl.; Mercury, UK.
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
These ingredients can be described by the British Approved Name Co-codamol.
Pain.

Medagro, Pol.
Paracetamol (p. 115·1).
Fever; pain.

Codipar Plus *GSK, Pol.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Codipertussin *Astellas, Austria.*
Codeine polistirex (p. 40·2).
Cough; bronchitis.

Tussin, Ger.
Codeine phosphate (p. 40·2).
Cough.

Codiphen
Note: this name may be used for preparations of different composition.
Community Pharmacy, Thai.
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; parkinsonism; motion sickness; sleep disorders.

Pfizer Consumer, Austral.†
Codeine phosphate (p. 40·2); aspirin (p. 22·2).
Pain; fever.

Codipront *Pfizer, Austria†; CTS, Hong Kong; Ferraz, Lynce, Port; Pfizer, Switz.†; Asmeco, Thai.; Mack, Thai.; Olic, Thai.*
Codeine polistirex (p. 40·2); phenyltoloxamine polistirex (p. 638·1).
Cough.

Kimia, Indon.; Zuoz, Venez.
Codeine (p. 40·2); phenyltoloxamine (p. 638·1).
Cough.

Codipront cum Expectorant *Kimia, Indon.*
Capsule: Codeine (p. 40·2); phenyltoloxamine (p. 638·1); guaifenesin (p. 1666·2).
Cough.

Kimia, Indon.
Syrup: Codeine (p. 40·2); phenyltoloxamine (p. 638·1); guaifenesin (p. 1666·2); thyme (p. 2630·2).
Cough.

Codipront Mono *Pfizer, Austria†; Zuoz, Venez.*
Codeine polistirex (p. 40·2).
Cough.

Codipront N *Galenica, Gr.*
Codeine polistirex (p. 40·2); codeine phosphate (p. 40·2).
Cough.

Kimia, Philipp.
Codeine polistirex (p. 40·2).
Cough.

Co-Diroton *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Codis *Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.†; Reckitt Benckiser, S.Afr.†; Reckitt Benckiser, UK.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; cold and influenza symptoms; fever; inflammation.

Codistar *Mankind, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Codistar Plus *Mankind, India.*
Codeine phosphate (p. 40·2); ibuprofen (p. 68·2).

Coditam *Kimia, Indon.*
Codeine (p. 40·2); paracetamol (p. 115·1).
Pain.

Codivis *CTS, Israel.*
Codeine (p. 40·2); phenyltoloxamine resinate (p. 638·1).
Cough.

Codokuff *Zydus, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Codol
Note: this name may be used for preparations of different composition.
Confar, Port.
Codeine (p. 40·2); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Cough.

Codolax *Vickmans, Hong Kong.†*
Syrup: Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); papaverine hydrochloride (p. 2362·3); guaifenesin (p. 1666·2).
Cough.

Vickmans, Hong Kong.†
Tablets: Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); papaverine hydrochloride (p. 2362·3).
Cough.

Codoliprane *Sanofi-Aventis, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Codomolindon *Zydus, India.*
Codeine sulfate (p. 40·3); paracetamol (p. 115·1).
Pain.

Codoplex *Jean-Marie, Hong Kong.*
Syrup: Codeine phosphate (p. 40·2); papaverine hydrochloride (p. 2362·3); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough.

Jean-Marie, Hong Kong.
Tablets: Codeine phosphate (p. 40·2); papaverine hydrochloride (p. 2362·3); chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2); caffeine (p. 1203·3).
Cough.

Codoplus *Elder, India.*
Codeine sulfate (p. 40·3); paracetamol (p. 115·1).
Pain.

Codopyrin *GSK, India.*
Aspirin (p. 22·2); codeine (p. 40·2); paracetamol (p. 115·1).

Codoric *Euphoric, India.*
⊗Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).

Codorol *Pharmachem, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).

Co-Dorzolamid *Mepha, Switz.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Codotussyl
Note: this name may be used for preparations of different composition.
Genevrier, Singapore.
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with increased or viscous mucus.

Codotussyl Expectorant *Genevrier, Fr.*
Oral solution; lozenges; syrup: Acetylcysteine (p. 1652·2).
Formerly known as Solmucol.
Respiratory-tract congestion.

Codotussyl Maux de Gorge *Genevrier, Fr.*
Lidocaine hydrochloride (p. 1988·2); cetylpyridinium chloride (p. 1743·1); ascorbic acid (p. 2110·3).
Mouth and throat disorders.

Codotussyl Toux Sèche *Genevrier, Fr.*
Pentoxyverine citrate (p. 1672·1).
Cough.

Codox
Note: this name may be used for preparations of different composition.
Comed, India.
Doxycycline (p. 288·1).
Bacterial infections.

Boots Healthcare, Austral.†
Aspirin (p. 22·2); dihydrocodeine tartrate (p. 52·3).
Pain; fever; cough.

Codoxol *Be-Tabs, S.Afr.*
Codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain with tension.

Codral Cold & Flu *Johnson & Johnson, NZ.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Codral Cold & Flu + Cough New Formula *Johnson & Johnson, Austral.*
Day capsules, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); night capsules, paracetamol; dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Codral Cold & Flu New Formula *Johnson & Johnson, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Codral Cough, Cold & Flu Day & Night *Johnson & Johnson, NZ.†*
⊗Day capsules, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night capsules, paracetamol; dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Codral Day & Night New Formula *Johnson & Johnson, Austral.*
Day tablets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2); night tablets, paracetamol; phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Codral Daytime/Nightime *Johnson & Johnson, NZ.†*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); night tablets, paracetamol; pseidoephedrine hydrochloride; triprolidine hydrochloride (p. 642·3).
Cold and influenza symptoms; nasal congestion.

Codral Dry Cough *Pfizer Consumer, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough; nasal congestion.

Codral 4 Flu *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.†*
⊗Paracetamol (p. 115·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Codral Forte *GSK, Austral.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; cough.

Codral Linctus *Johnson & Johnson, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough; nasal congestion.

Codral Nightime *Johnson & Johnson, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Codral Original Chesty Cough *Johnson & Johnson, Austral.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Codral Original Cold & Flu *Johnson & Johnson, Austral.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Codral Original Cold & Flu + Cough Day & Night *Johnson & Johnson, Austral.*
⊗Day capsules, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night capsules, paracetamol; chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Codral Original Cold & Flu Max *Johnson & Johnson, Austral.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Codral Original Day & Night Cold & Flu *Johnson & Johnson, Austral.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); night tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold and influenza symptoms.

Codral Original Dry Cough *Johnson & Johnson, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Codral Pain Relief *Pfizer Consumer, Austral.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Codral Relief Cold & Flu + Decongestant *Johnson & Johnson, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Codral Relief Decongestant *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Codral Relief Mucus Cough & Cold *Johnson & Johnson, Austral.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough; upper respiratory-tract congestion.

Codril *Radicura, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Codril-AT *Radicura, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Codril-DX *Radicura, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Codril-P *Radicura, India.*
Ambroxol (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).

Codrinan *Cimed, Braz.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Codroxil *Comed, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Codryl *Community Pharmacy, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; bronchitis.

Codulax *Tanta, Canad.*
Bisacodyl (p. 1821·1).
Constipation.

Codvit-E *Elnova, India.*
Cod-liver oil (p. 2056·3); vitamin E acetate (p. 2119·2).

Codyl
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough.

Codylex *Anglo-French Drugs, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.

Codylex Plus *Anglo-French Drugs, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Allergic rhinitis.

Codylex-CC *Anglo-French Drugs, India.*
Caffeine (p. 1203·3); cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Codylex-DMR *Anglo-French Drugs, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Codzi *FDC, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Co3E *Davos, Singapore.*
Tocotrienols; *d*-alpha tocopherol (p. 2119·1).

Co3E + CoQ10 *Davos, Singapore.*
Tocotrienols; *d*-alpha tocopherol (p. 2119·1); ubidecarenone (p. 2637·1).

Coease *Advance, USA.*
Sodium hyaluronate (p. 2526·2).
Aid in eye surgery.

Coease-M *David, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Co-Efferalagan *BMS, Ital.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Co-En Q *Corsa, Indon.; Erlimpex, Indon.*
Ubidecarenone (p. 2637·1).
Nutritional supplement.

Co-Enac *Hexal, Austria.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Enalapril *1A, Austria; Eurogenerics, Belg.; Sandoz, Belg.; Hexal, Hung.; Ratiopharm, Hung.; Spirig, Switz.; Teva, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Enalil *Kinder, Braz.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coenaplex *Pharlab, Braz.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).

Co-Enatec *Mepha, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coenrelax *Uriach, Spain.*
Valerian (p. 2640·2).
Insomnia; nervous disorders.

Co-Epherine *Vickmans, Hong Kong.†*
⊗Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); cocillana (p. 1659·2); codeine (p. 40·2); ephedrine (p. 1663·1).

Coepratenz Comp *Solvay, Fin.†*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coepratenz Plus *Solvay, Austria; Abbott, Irl.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Epril *Sandoz, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Exaliv *Maver, Mex.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cough; respiratory-tract congestion; rhinitis.

Cof Q *Cipla, India.*
Lozenge: Dextromethorphan hydrobromide (p. 1660·1); amylmetacresol (p. 1736·3).
Cough.

Cipla, India.
Tablets: Paracetamol (p. 115·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); pheniramine (p. 637·2).
Formerly contained paracetamol, bromhexine, guaifenesin, chlorphenamine, and phenylpropanolamine.
Cough; cold symptoms.

Cof QD *Cipla, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine (p. 620·3); phenylpropanolamine (p. 1674·1).
Cough.

Cof QX *Cipla, India.*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Cofact *Sanquin, Austria; Sanquin, Fin.; Biotest, Ger.; Graha, Indon.; Sanquin, Neth.; Centurion, Turk.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders; coumarin anticoagulant overdose.

Cofaid-DC *Meyer, India.*
Chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1); menthol (p. 2553·2); phenylephrine (p. 1672·2).

Cofaid-EX *Meyer, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).
Bronchitis; bronchial asthma.

Cofal *Alna, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Cofal-D *Alna, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cofamol *Cosme, India.*
Paracetamol (p. 115·1).
Pain; fever.

Cofanol *Nabros, Rus.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); levomenthol (p. 2553·2).
Respiratory-tract disorders.

Cofar-D *Trumac, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Co-Fatrim *T Man, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cofbron *Macrophar, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease; cough.

Cofcodyl *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).

Cofdex *Cipla, India.*
Syrup: Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Cipla, India.
Capsules: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1).

Cofdex CC *Cipla, India.*
⊗Dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2); diphenhydramine (p. 626·1); pseudoephedrine (p. 1676·1); paracetamol (p. 115·1).
Respiratory-tract disorders.

Cofdex Forte *Cipla, India.*
Expectorant: Bromhexine hydrochloride (p. 1656·3); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cough.

Cipla, India.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cough.

Cofdex Plus *Cipla, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Cofdex-P *Cipla, India.*
Bromhexine hydrochloride (p. 1656·3); phenylpropanolamine hydrochloride (p. 1674·1); menthol (p. 2553·2).
Formerly known as Cofdex P and contained dextromethorphan, bromhexine, phenylpropanolamine, and menthol.
Cough.

Cofdyl *Vista, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Cofed *M & H, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms; hay fever.

Cofedron *Azevedos, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Co-Feliberal *Silanes, Mex.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cofen *ICM, Singapore.*
Guaifenesin (p. 1666·2).
Cough.

Cofenac *Cipla, India.*
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Pain; inflammation.

Cipla, India.
Topical gel: Diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Cofendyl *Aspen Consumer, S.Afr.†*
⊗Paracetamol (p. 115·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cofetal *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); pentoxyverine (p. 1672·1); chlorphenamine (p. 620·3); guaifenesin (p. 1666·2).
Cough.

Cofetol *Bright Future, China.*
⊗Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Cough; cold and influenza symptoms; rhinitis.

Cofev *Alna, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Cofeze *Sanat, India.*
Liquorice (p. 1853·2); ocimum sanctum; piper longum; zingiber officinale.

Coffecorn *Filofarm, Pol.*
Caffeine (p. 1203·3); ergotamine tartrate (p. 674·1).
Headache including migraine.

Coffedon *Jaka-80, Rus.†*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Coffekapton *Strallhofer, Austria.*
Caffeine (p. 1203·3).
Fatigue; vascular headache.

Coffepirine *Marcmed, Pol.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Coffetamin *Tatkhimfarm, Rus.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Headache; hypotension.

Coffo Selt *Rosch & Handel, Austria.*
Phenazone (p. 124·1); caffeine (p. 1203·3).
Pain.

Coff-Up *Universal, S.Afr.†*
Pheniramine maleate (p. 637·2); menthol (p. 2553·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Respiratory-tract congestion.

Coficil-Plus *Leksredstva, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Cofigrip *Alcala, Spain.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Cofihist *Cipla, India.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).

Cofi-Tabs *Vitabalans, Fin.†*
Caffeine (p. 1203·3).
Fatigue.

Cofitus *Sanovel, Turk.*
Ambroxol hydrochloride (p. 1654·3).

Co-Flem *Aspen, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Cofles *Euro-Med, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Coflic *Baliarda, Arg.*
Folic acid (p. 2063·1).
Folic acid deficiency; anaemias.

Coflic B6-B12 *Baliarda, Arg.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Folic acid and vitamin B deficiency.

Coflox *Macleods, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Co-Fluenza *Vickmans, Hong Kong.†*
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2); salicylamide (p. 129·2).

Cofnil-N *Idaman, Malaysia.†*
⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); ammonium chloride (p. 1656·1).
Cough; nasal congestion.

Cofol *Cipla, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Cofol-Z *Cipla, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Cofpet-DX *Vista, India.*
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1).

Cofrel
Note: this name may be used for preparations of different composition.
Pfizer, Hong Kong.
Benproperine (p. 1656·2).
Cough.

Scort, Philipp.
Sulfogaiacol (p. 1678·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Cofron *Abbott, Arg.*
Clofedanol hydrochloride (p. 1659·1); bromhexine hydrochloride (p. 1656·3).
Cough.

Cofryl *Cipla, India.*
Diphenhydramine hydrochloride (p. 626·2).

Cofsed *Greater Pharma, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; nasal congestion.

Cofsils *Cipla, India; Cipla, Singapore.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Cofstop-Z *Apex, India.*
Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); zinc (p. 2126·1).

Cofsym *Symbiosis, India.*
Bromhexine hydrochloride (p. 1656·3); cetirizine hydrochloride (p. 619·2); guaifenesin (p. 1666·2); menthol (p. 2553·2); phenylephrine (p. 1672·2).

Coftex-AG *BMW, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); phenylephrine (p. 1672·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Coftex-BT *BMW, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Coftex-DMR *BMW, India.*
Syrup: Chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

BMW, India.
Tablets: Ambroxol (p. 1654·3); cetirizine (p. 619·2); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine (p. 1672·2).

Cofton *Cipla, India.*
Syrup: Chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).
Cough.

Cipla, India.
Tablets: Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Cofton Exp *Cipla, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).

Cofton SF *Cipla, India.*
⊗Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); ephedrine (p. 1663·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Cofura *Panjon, India.*
Ammonium acetate (p. 1655·3); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cofura-DMR *Panjon, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cofvyn *Cipla, India.*
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1).

Co-Gel *Aspen, S.Afr.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Cogenate *General Drugs, Thai.†*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Cogent db+ *Cybele, Philipp.*
⊗Azadirachta (p. 2451·2); fenugreek (p. 2504·1); curcuma (p. 2218·1); Indian gooseberry (p. 2532·2); chebulic myrobalan (p. 2474·3); beleric myrobalan (p. 2453·2); syzygium cumini; tribulus terrestris (p. 2633·3); rotula aquatica.
Herbal dietary supplement for diabetes.

Cogentin *Invida, Austral.; MSD, Austria†; Ovation, Hong Kong; Healthcare Logistics, NZ; MSD, Singapore; MSD, Thai.; IDIS, UK; Akorn, USA.*
Benzatropine mesilate (p. 894·3).
Parkinsonism; drug-induced extrapyramidal disorders; dystonias.

Co-Gesic
Note: this name may be used for preparations of different composition.
Schwarz, USA.
Paracetamol (p. 115·1); hydrocodone tartrate (p. 67·2).
Pain.

Brainware, S.Afr.†
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Cogetine *General Drugs, Thai.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Cogito *Berksam, Turk.*
Memantine hydrochloride (p. 393·1).

Cogiton *Biofarm, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Cogitum *Sanofi-Aventis, Rus.*
Dipotassium acetylaminosuccinate.
Asthenia.

Coglu *Sanify, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Cognex *Genesis, Gr.†; Parke, Davis, USA.†*
Tacrine hydrochloride (p. 396·1).
Alzheimer's disease.

Cognezil *Glenmark, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Cognicer *Bio Portugal, Port.*
Hydrolysed brain extract (porcine) (p. 2444·1).
Mental function impairment.

Cognitiv
Note: this name may be used for preparations of different composition.
Ebewe, Austria; Ebewe, Cz.; Ebewe, Hung.†; Ebewe, Rus.
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism; Alzheimer's disease.

Cognito *Health Perception, UK.*
Phosphatidyl serine (p. 2589·1).
Memory impairment.

Cogof *Biomax, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cogof-A *Biomax, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Cogulax *Pond's, Thai.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Cohemin *Orion, Fin.*
Hydroxocobalamin acetate (p. 2107·3).
Megaloblastic anaemia; vitamin B_{12} deficiency; neuropathies.

Cohero *Ranbaxy, India.*
Vitamins minerals.

Cohexine *Community Pharmacy, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with excess mucus.

Co-Hilos *Nobel, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Co-Hist *Roberts, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Cohistan *Medifarma, Indon.; Biomedis, Thai.†; Great Eastern, Thai.†*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Cohistan Expectorant *Medifarma, Indon.; Great Eastern, Thai.†*
Guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough.

Cohol Sahakarn *United Drug, Thai.*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Cohol UD *United Drug, Thai.*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Cohortan *Reig Jofre, Spain.*
Rectal ointment: ⊗Hydrocortisone (p. 1640·1); tyrothricin (p. 384·1); isopropyl benzatropine mesilate.
Anorectal disorders.

Co-Hypert *Pekana, Neth.*
Aurum muriaticum natronatum (p. 2521·2); baryta carbonica (p. 2452·2); cocculus indicus (p. 2483·1); iberis amara; magnesium muriaticum (p. 1787·1); melilotus officinalis spag (p. 2552·3); sumbulus moschatus; viscum album spag (p. 2560·2).
Homoeopathic preparation.

Coid *Lamsa, Arg.*
⊗Betamethasone (p. 1623·2) or betamethasone valerate (p. 1624·1).
Corticosteroid.

Co-Inhibace *Roche, Belg.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Irbesan *Nobel, Ukr.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Irbewin *Winthrop, S.Afr.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Irda *Nobel, Turk.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).

Cokenzen *Takeda, Fr.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Col
Note: this name may be used for preparations of different composition.
Sykocure, India.
Citicoline sodium (p. 2480·2).
Parkinsonism; head injury; cerebrovascular disorders.

Col 138 *Herbasante, Canad.†*
Cutrullus colocynthis (p. 1833·3); copper (p. 2057·1); delphinium staphisagria; German chamomile (p. 2474·1); magnesium phosphate dibasic (p. 1786·3).
Homoeopathic preparation.

Colaba-B *Dallas, India.*
Injection: Vitamin B substances (p. 2102·3).

Dallas, India.
Tablets: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Colace *Wellspring, Canad.; Purdue, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Colace Infant/Child *Purdue, USA.*
⊗Glycerol (p. 2517·2).
Constipation.

Colachofra *EMS, Braz.*
Sorbitol (p. 2092·1); betaine hydrochloride (p. 2456·1); cynara (p. 2490·3); boldo (p. 2458·3); solanum paniculatum.
Liver disorders.

Colagenan *Herbarium, Braz.†*
⊗Gelatin (p. 1154·1).

Colageno + C *Sigma, Arg.*
Bovine collagen (p. 2483·2); vitamin C (p. 2110·3); magnesium (p. 1786·3).
Arthroses.

Colain *Darya-Varia, Indon.†*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Colamziv *Activo, S.Afr.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).

Colarest *Centaur, India.*
Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2).

Colase *Samarth, India.*
Haemocoagulase (p. 1135·1).
Haemostatic.

Colaskin *Ethica, Indon.*
Marine protein extract; collagen (p. 2483·2); grapeseed extract; betacarotene (p. 2051·1); vitamin E (p. 2119·1); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Colastin-L *Deva, Turk.*
Atorvastatin calcium (p. 1309·2).

Co-Latanoprost *Pfizer, Switz.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Colatus *TNP, Thai.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Colax
Note: this name may be used for preparations of different composition.
Mediherb, Austral.
Tablets: Dill (p. 2493·1); cascara (p. 1826·1); chamomile (p. 2474·1); yellow dock (p. 2649·3); taraxacum (p. 2625·3).
Constipation.

Strassenburg, India.
Sodium picosulfate (p. 1887·2).
Constipation.

OFF, Ital.†
Senna (p. 1885·1); rhubarb (p. 1884·2); cynara (p. 2490·3); boldo (p. 2458·3).
Loss of appetite; digestive disorders; constipation.

Mediherb, Austral.†
Oral liquid: Dill (p. 2493·1); butternut (p. 2463·2); cascara (p. 1826·1); chamomile (p. 2474·1); yellow dock (p. 2649·3); taraxacum (p. 2625·3).
Constipation.

Colazal *Salix, USA.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Colazid *Almirall, Norw.; Meda, Swed.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Colazide *Fresenius Kabi, Austral.; Shire, UK.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

ColBenemid *Merck, USA.*
⊗Probenecid (p. 607·3); colchicine (p. 604·1).
Chronic gouty arthritis.

Colbid *Panjon, India.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).

Colbiocin *SIFI, Ital.; Zambon, Rus.*
Eye drops: Rolitetracycline (p. 356·1); chloramphenicol (p. 257·1); colistimethate sodium (p. 275·3).
Eye infections.

SIFI, Ital.; Zambon, Rus.
Eye ointment: Tetracycline (p. 373·1); chloramphenicol (p. 257·1); colistimethate sodium (p. 275·3).
Eye infections.

Colbutol *Ind-Swift, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Colcap
Note: this name may be used for preparations of different composition.
Asian Union, Thai.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Bright Future, Hong Kong.†
Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Colcaps *Adcock Ingram, S.Afr.*
Syrup: ⊗Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; cough.

Adcock Ingram, S.Afr.†
Effervescent tablets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Adcock Ingram, S.Afr.†
Capsules: Phenylpropanolamine hydrochloride (p. 1674·1); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1); caffeine (p. 1203·3); salicylamide (p. 129·2); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; nasal congestion; rhinitis.

Colchicindon *Zydus, India.*
Colchicine (p. 604·1).
Gout.

Colchico *Medley, India.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Colchicum Complex *Hevert, Ger.*
Berberis (p. 2502·1); colchicum (p. 607·1); ledum (p. 2550·1); phytolacca; spirea (p. 2550·2); sulfur (p. 1721·1); thuja (p. 2629·3).
Homoeopathic preparation.

Colchicum Med Complex *Dynamit, Austria.*
Calcium phosphoricum (p. 1784·2); china (p. 2478·3); colchicum (p. 607·1).
Homoeopathic preparation.

Colchicum-Dispert *Pharmaselect, Hung.; Frik, Turk.*
Colchicine (p. 604·1).
Gout.

Colchily *Pharmasant, Thai.*
Colchicine (p. 604·1).
Gout.

Colchimax
Note: this name may be used for preparations of different composition.
Spedrog, Arg.; Seid, Spain.
Colchicine (p. 604·1); dicycloverine hydrochloride (p. 1834·2).
Gout; hyperuricaemia; scleroderma; venous inflammation.

Vernin, Fr.
Colchicine (p. 604·1); tiemonium metilsulfate (p. 1893·3); opium powder (p. 111·3).
Gout; inflammatory disorders.

Colchin *Greenpharma, Braz.*
Colchicine (p. 604·1).
Gout.

Colchiquim *Quimica y Farmacia, Mex.*
Colchicine (p. 604·1).
Gout; biliary and hepatic cirrhosis.

Colchis *Apsen, Braz.*
Colchicine (p. 604·1).
Gout; scleroderma; psoriasis; sarcoidosis; familial Mediterranean fever.

Colchysat *Ysatfabrik, Ger.*
Colchicum autumnale (p. 607·1).
Gout.

Colcibra *Ranbaxy, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Colcina *Jean-Marie, Hong Kong.*
Colchicine (p. 604·1).
Gout.

Colcine *Pharmahof, Thai.*
Colchicine (p. 604·1).
Gout.

Colcitex *United Drug, Thai.*
Colchicine (p. 604·1).
Gout.

Colcitrat *UCI, Braz.*
Colchicine (p. 604·1).
Gout.

Colcleer *Adcock Ingram, S.Afr.*
Tablets: ⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Adcock Ingram, S.Afr.†
Paediatric syrup: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Colcrys *Takeda, USA.*
Colchicine (p. 604·1).
Acute gout; familial mediterranean fever.

Cold *Sunward, Singapore.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); caffeine (p. 1203·3).

Cold and Allergy Decongestant *Rougier, Canad.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Cold And Allergy Liquid *Tanta, Canad.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold and allergic symptoms.

Cold Calm *Symbiosis, India.*
Caffeine (p. 1203·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Cold Cap *Nufarindo, Indon.*
⊗Salicylamide (p. 129·2); paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2).
Influenza symptoms.

Cold Care
Note: this name may be used for preparations of different composition.
Dossier, Neth.
Echinacea angustifolia (p. 2498·1); allium cepa (p. 2575·2); aconitum napellus (p. 2428·3).
Homoeopathic preparation.

Cold Combat *Blackmores, Austral.*
Andrographis (p. 2443·2).
Cold symptoms.

Cold Control *Reese, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms.

Cold Cream *Vita, Venez.*
Soap substitute.
Dry or sensitive skin.

Cold Cream Avene *Silesia, Chile.*
White beeswax (p. 2170·2); liquid paraffin (p. 2191·2).
Dry skin disorders.

Cold Cream Naturel *Roche-Posay, Fr.*
Cetyl palmitate (p. 2178·3); white beeswax (p. 2170·2); light liquid paraffin (p. 2191·2).
Skin dryness and irritation.

Cold & Flu *Pharmascience, Canad.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Cold & Flu Capsules *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cold & Flu Day/Night *Blackmores, Austral.*
Day capsules, echinacea (p. 2498·1); eucalyptus oil (p. 2501·2); salix (p. 129·2); ocimum sanctum; night capsules, eucalyptus oil; salix; ocimum sanctum; lupulus (p. 2546·1).
Cold and influenza symptoms.

Cold & Flu Daytime *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cold & Flu Nighttime *Pharmetics, Canad.; Vita Health, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cold & Flu Relief
Note: this name may be used for preparations of different composition.
Cenovis, Austral.
Olive leaf (p. 2574·3); calcium ascorbate (p. 2111·1); *Saccharomyces cerevisiae* (p. 2125·2).
Cold and influenza symptoms.

Pharmetics, Canad.
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cold Flu Relief
Note: this name may be used for preparations of different composition.
Perrigo, Canad.
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cold & Flu Tablets Non Drowsy *Or-Dov, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); citrus bioflavonoids (p. 2505·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; hay fever.

Cold and Flu-in-One *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cold & Hot Pain Relief Therapy Patch *Major, USA.*
Menthol (p. 2553·2).

Cold Medication D *Prodemdis, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Cold Medication Extra-Strength Daytime
Confab, Hong Kong.†
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Cold Medication Extra-Strength Nightime
Confab, Hong Kong.†
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Cold Medication N *Prodemdis, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Cold Relief
Note: this name may be used for preparations of different composition.
Unichem, UK.
Capsules: Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Unichem, UK.
Oral powders: Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Cold Relief Daytime
Note: this name may be used for preparations of different composition.
Jamp, Canad.
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Cold Relief Nightime
Note: this name may be used for preparations of different composition.
Jamp, Canad.
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Cold + Sinus *Vita Health, Canad.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Cold Sore *ICN, NZ.†*
Menthol (p. 2553·2); camphor (p. 2466·2); benzoin (p. 2624·3).
Herpes labialis.

Cold Sore Lotion
Note: this name may be used for preparations of different composition.
Rougier, Canad.
Benzoin (p. 2624·3); camphor (p. 2466·2); menthol (p. 2553·2).
Herpes labialis.

Cold Sores & Fever Blisters *Hylands, Canad.*
Antimonium crudum (p. 2445·1); baptisia tinctoria (p. 2647·2); borax (p. 2459·2); natrum muriaticum (p. 1795·1).
Homoeopathic preparation.

Cold Syrup *Supplements Aromatik, Canad.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Cold Tablets with Zinc *Hylands, Canad.†*
Aconitum napellus (p. 2428·3); allium cepa (p. 2575·2); gelsemium sempervirens (p. 2511·2); zinc gluconate (p. 2126·2).
Homoeopathic preparation.

Colda *Sigmapharm, Austria.*
Sage oil (p. 2609·1); cedar leaf oil (p. 2629·3); pumilio pine oil (p. 2591·1); camphor (p. 2466·2); Scots pine oil (p. 2591·2); dexpanthenol (p. 2582·2); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders.

Coldact *Sun, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Coldact Broncho *Ranbaxy, Rus.; Ranbaxy, Ukr.†*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract disorders associated with viscous mucus; influenza and other viral respiratory tract infections.

Coldact Flu Plus *Ranbaxy, Rus.; Ranbaxy, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders; allergic rhinitis.

Coldact Lor Pils *Ranbaxy, Ukr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Infections and inflammation of the mouth and throat.

Coldact Lorpils *Ranbaxy, Rus.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Coldact Plus *Sun, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Coldaid *Rayere, Mex.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Coldan *Sigmapharm, Austria; Kotsopoulos (Κωτσοπουλος), Gr.*
⊗Naphazoline hydrochloride (p. 1669·3).
Ocular irritation; rhinitis; conjunctivitis; sinusitis; sore throat; adjunct in rhinoscopy.

Coldangin *Sigmapharm, Austria.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Coldant *Uniroyal, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); sodium citrate (p. 1781·2).

Coldanyl *Osoth, Thai.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cold symptoms.

Coldap *Osmed, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldarest *Centaur, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Coldargan *Sigmapharm, Austria.*
⊗Silver protein (p. 2616·2); ephedrine levulinate (p. 1663·1); calcium levulinate (p. 1784·2); sodium levulinate.
Rhinitis; sinusitis; mouth and throat disorders.

Sigmapharm, Hung.†
⊗Silver protein (p. 2616·2); ephedrine levulinate (p. 1663·1); calcium levulinate (p. 1784·2).
Mouth and throat disorders; rhinitis; sinusitis.

Coldargic *Nodysis, India.*
Oral drops: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Nodysis, India.
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Nodysis, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Coldargic-P *Nodysis, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine (p. 1672·2).

Coldaside Cold & Flu *Tanta, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Coldaside Cough & Cold *Tanta, Canad.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

Coldastat *Medinova, India.*
Syrup: Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); sodium citrate (p. 1781·2).

Medinova, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldastat-LX *Novaduo, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldastop *Desitin, Hung.*
Vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Cold symptoms.

Desitin, Cz.
Vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2); terpineol (p. 2627·2); lemon oil (p. 2543·1); orange oil (p. 2576·2).
Rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Coldate *Chew, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); paracetamol (p. 115·1).
Cough and cold symptoms.

Coldcap-A *Christo, Hong Kong.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); noscapine (p. 1670·3); caffeine (p. 1203·3); terpin hydrate (p. 1678·2).
Cold and influenza symptoms.

Cold-Care
Note: this name may be used for preparations of different composition.
Trima, Israel.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Coldcure *Bal, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cold-CZ *Biosans, India.*
Chlorphenamine maleate (p. 620·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Coldec *Daksh, India.*
Cetirizine (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldec D *Breckenridge, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract disorders.

Coldec DM *Silarx, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Coldeez *Cipla, India.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Coldeks *Deva, Turk.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); noscapine (p. 1670·3).
Respiratory-tract congestion.

Coldenza *Nelson, UK.*
Gelsemium sempervirens (p. 2511·2).
Homoeopathic preparation.

Coldetab *Chew, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Coldex *Teva, Israel.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms; respiratory-tract congestion.

Coldfin *Elfin, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Cold/Flu Medicine *Perrigo, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cold and influenza symptoms.

Coldfree *Prompt Cure, India.*
⊗Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Coldfri *Medley, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

Cold-FX *Afexa, Canad.*
Ginseng (p. 2513·3).
Cold and influenza symptoms.

Coldgone *Ind-Swift, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldifed *United Drug, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; allergic rhinitis.

Coldilak *Shalaks, India.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Coldin *Sanofi-Aventis, Chile.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with viscous mucus.

Coldistan *Sigmapharm, Austria.*
Eye drops; nasal drops: ⊗Diphenhydramine hydrochloride (p. 626·2); naphazoline hydrochloride (p. 1669·3).
Allergic eye disorders; eye irritation; rhinitis; sinusitis.

Sigmapharm, Austria.
Nasal ointment: Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3); calcium levulinate (p. 1784·2); cetylpyridinium chloride (p. 1743·1); dexpanthenol (p. 2582·2); sage oil (p. 2609·1).
Hay fever; rhinitis; sinusitis.

Coldistop *Sigmapharm, Austria; Proreo, Switz.*
Vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Nasal and sinus disorders; rhinitis.

Coldizo *Soho, Indon.*
Flavonoid compounds (p. 2505·2); troxerutin (p. 2505·3); Sophora japonica; zinc gluconate (p. 2126·2).
Rhinorrhoea; sore throat.

Coldman *Dyota, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Coldmist *Breckenridge, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

Cold-n-Flu-Eze *Thompson & Capper, UK.*
Echinacea purpurea (p. 2498·1).
Cold symptoms.

Coldocap *Asian Pharm, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Coldoff *Stadmed, India.*
Phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Formerly contained phenylephrine hydrochloride, paracetamol, chlorphenamine maleate, and caffeine.
Cold symptoms; allergic rhinitis; sinus congestion.

Coldophthal *Sigmapharm, Austria.*
⊗Naphazoline hydrochloride (p. 1669·3); mercuric oxycyanide (p. 2555·3); boric acid (p. 2459·3).
Conjunctivitis; eye irritation.

Coldosian *Asian Pharm, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Cold-Relief
Note: this name may be used for preparations of different composition.
Rose, India.
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldrest *Moraceae, India.*
Syrup: Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Moraceae, India.
Tablets: Caffeine (p. 1203·3); cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Coldrex
Note: this name may be used for preparations of different composition.
GSK Consumer, Cz.; GSK Consumer, Hung.; GSK, Rus.; GSK Consumer, Ukr.
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); terpin monohydrate (p. 1678·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

GSK Consumer, Fin.
Aspirin (p. 22·2); guaifenesin (p. 1666·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

GSK Consumer, Hung.
Oral powder: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

GSK Consumer, Pol.†
Benzalkonium chloride (p. 1737·1); hexylresorcinol (p. 1755·1).
Sore throat.

Coldrex Broncho *GSK Consumer, Cz.; GSK Consumer, Hung.†; GSK Consumer, Rus.*
Guaifenesin (p. 1666·2).
Cough.

Coldrex Horký *GSK Consumer, Cz.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Coldrex HotRem *GSK Consumer, Pol.; GSK Consumer, Rus.; GSK Consumer, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Coldrex Junior *GSK Consumer, Cz.; GSK Consumer, Hung.; GSK Consumer, Rus.*
Powder for oral solution: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

GSK Consumer, Hung.
Syrup: Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Coldrex MaxGrip *GSK Consumer, Cz.; GSK, Hung.; GSK Consumer, Pol.; GSK Consumer, Rus.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Coldrex MaxGrip C *GSK Consumer, Pol.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3); caffeine (p. 1203·3) terpin hydrate (p. 1678·2).
Cold and influenza symptoms.

Coldrex Maxgrip Lemon *GSK Consumer, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Coldrex MS *SKF, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Coldrex Nite *GSK Consumer, Cz.; GSK Consumer, Rus.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Coldrex Proti Bolesti v Krku *GSK Consumer, Cz.*
Hexylresorcinol (p. 1755·1); benzalkonium chloride (p. 1737·1).
Sore throat.

Coldrex Reformulated *Sanofi Synthelabo, Philipp.†*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; rhinitis; sinusitis.

Coldrif *Sresan, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Coldrin
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Braz.
Cinnarizine (p. 622·1); phenylephrine hydrochloride (p. 1672·3); pentoxyverine citrate (p. 1672·1); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Influenza symptoms.

Teva, Ukr.†
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Coldrine *Hauck, USA; Roberts, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Coldsal *Adeka, Turk.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).

Coldsoft Day *Hovid, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Coldsoft Night *Hovid, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Cold-tab *Burapha, Thai.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold symptoms.

Coldtab-2 *Christo, Hong Kong.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); noscapine (p. 1670·3); caffeine (p. 1203·3); terpin hydrate (p. 1678·2).
Cold and influenza symptoms.

Coldtaur *Taurus, India.*
Eye drops: ⊗Boric acid (p. 2459·3); glycerol (p. 2517·2); borax (p. 2459·2); zinc sulfate (p. 2126·2).

Taurus, India.
Oral suspension: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Taurus, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldvico *Merck, S.Afr.†*
Capsules: Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Merck, S.Afr.†
Syrup: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Coldwafer *Christo, Hong Kong.†*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Cold-War *Invision, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Coldwar *Vensat, India.*
Syrup: ⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Vensat, India.
Tablets: Cetirizine (p. 619·2); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Coldy
Note: this name may be used for preparations of different composition.
Siomond, India.
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Siomond, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

The Forty-Two, Thai.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Coldzep *EuroHealth, Philipp.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; allergic rhinitis.

Coleb *AstraZeneca, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Colebyn *Sanovel, Turk.*
Ezetimibe (p. 1379·2).

Colecalcium *Humana, Ital.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium and vitamin D deficiency.

Coleflux *Finadiet, Arg.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Coleflux Duo *Finadiet, Arg.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hyperlipidaemias.

Colega-3 *Biofarma, Mex.†*
Eicosapentaenoic acid (p. 1460·2).
Dietary supplement.

Colegraf *Estedi, Spain.†*
Iopanoic acid (p. 1591·1).
Contrast medium for biliary-tract radiography.

Colemin *Vifor, Spain.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Colep *Biomax, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Colepren *Randall, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Colergis *Dexa, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Colerin-F *Nostrum, Port.†*
⊗Azintamide (p. 2451·3); pancreatin (p. 2579·3); cellulase (p. 2473·1).
Digestive insufficiency.

Colerragin *Microsules, Arg.*
Rosuvastatin (p. 1488·2).
Hyperlipidaemias.

Colese *Alphapharm, Austral.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Colesken *Kendrick, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; cerebrovascular risk reduction.

Colestase *Sanofi-Aventis, Braz.*
Furazolidone (p. 933·3); diphenoxylate hydrochloride (p. 1835·3).
Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Colesterase *WP, Ital.*
Vitamin E (p. 2119·1); policosanol (p. 1472·1); fermented red rice.
Hypercholesterolaemia.

Colesterminol *Omicron, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Colestid *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Israel; Pfizer, NZ; Pfizer, Port.; Pfizer, Spain; Pfizer, Switz.; Pfizer, UK; Pharmacia Upjohn, USA.*
Colestipol hydrochloride (p. 1345·3).
Hypercholesterolaemia; hyperlipidaemias.

Colestrim *Mega Lifesciences, Thai.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Colestyr *CT, Ger.†*
Colestyramine (p. 1346·1).
Hyperlipidaemias; biliary-tract disorders.

Colesvir *Vir, Spain.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Coleus Complex *Mediherb, Austral.†*
Coleus forskohlii; crataegus (p. 2488·1); valerian (p. 2640·2).
Hypertension.

Colex *Tramedico, Neth.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Colexklysma *Tramedico, Belg.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Colfarit *Bayer, Hung.†*
Aspirin (p. 22·2).
Fever; inflammation; pain; thromboembolism prophylaxis.

Colfed-A *Breckenridge, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Colfene *Elmor, Venez.*
Ibuprofen (p. 68·2); thiocolchicoside (p. 2026·2).
Pain with spasm.

Colfin *Nufarindo, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); phenylpropanolamine hydrochloride (p. 1674·1).
Influenza symptoms; cough.

Colfur *Church, Mex.†*
Oral suspension: Colistin sulfate (p. 275·3); furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Gastrointestinal infections.

Church, Mex.†
Tablets: Colistin sulfate (p. 275·3); furazolidone (p. 933·3).
Gastrointestinal infections.

Colgate Total *Colgate-Palmolive, Irl.; Colgate-Palmolive, Ital.*
Sodium fluoride (p. 2089·2); triclosan (p. 1773·2).
Oral hygiene; dental caries prophylaxis.

Colgen *Gerolymatos, Gr.*
Collagen (p. 2483·2).

Colgen Gargle *Kowa, Jpn.†*
Cetylpyridinium chloride (p. 1743·1); dipotassium glycyrrhizate (p. 2520·3).
Mouth disorders.

Colgen Kowa IB *Kowa, Jpn.*
⊗Ibuprofen (p. 68·2); chlorphenamine maleate (p. 620·3); dihydrocodeine phosphate (p. 52·2); guaifenesin (p. 1666·2); methylephedrine hydrochloride (p. 1669·2); caffeine (p. 1203·3).
Cold symptoms.

Colgen Kowa for Rhinitis *Kowa, Jpn.*
Chlorphenamine maleate (p. 620·3); belladonna alkaloids (p. 2453·3); phenylephrine hydrochloride (p. 1672·3); dipotassium glycyrrhizate (p. 2520·3).

Colgen Maoto *Kowa, Jpn.*
⊗Ephedra (p. 1663·1); cinnamon (p. 2479·2); apricot kernel (p. 2445·3); liquorice (p. 1853·2).
Cold symptoms.

Colgin *Medopharm, India.*
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Medopharm, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Colgit *Alde Medi Impex, India.*
Colistin sulfate (p. 275·3).
Gastrointestinal infections; gastrointestinal decontamination.

Colgout *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ.*
Colchicine (p. 604·1).
Gout; polyarthritis associated with sarcoidosis.

Colhidrol *Teva Tuteur, Arg.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Colibiogen *Laves, Ger.*
Peptide extract from *Escherichia coli.*
Gastrointestinal disorders; hypersensitivity; musculoskeletal and joint disorders; skin disorders.

Colibyl *Herbes Universelles, Canad.†*
Bile salts (p. 2457·2); magnesium sulfate (p. 1787·3); peptone (p. 2086·2).
Digestive disorders.

Colic *Hylands, Canad.*
Chamomilla (p. 2474·1); colocynthis (p. 1833·3); dioscorea (p. 2648·1).
Homoeopathic preparation.

Colic Relief *Brauer, Austral.*
Bryonia (p. 2461·3); chamomilla (p. 2474·1); mag. phos. (p. 1787·3); colocynthis (p. 1833·3).
Homoeopathic preparation.

Colicaid *Meyer, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).
Infant colic; flatulence; dyspepsia; regurgitation.

Colicon *Reese, USA.*
Simeticone (p. 1886·2).

Colicor *Medipharm, Chile.*
Papaverine hydrochloride (p. 2362·3); atropine sulfate (p. 1310·2).
Smooth muscle spasm; dysmenorrhoea.

Colicspam *Leben, India.*
Oral drops; oral suspension: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Leben, India.
Tablets: Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Colide *Constant, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Colidex *Psychotropics, India.*
Dextropropoxyphene (p. 43·2); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Colidimin *Gebro, Austria.*
Rifaximin (p. 355·2).
Gastro-intestinal infections; pre-operative bowel sterilisation.

Colidin *T Man, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis; cold and influenza symptoms.

Colidine *Community Pharmacy, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; sinusitis; rhinitis.

Colidium *Solas, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Colidur *Drogsan, Turk.*
Rifaximin (p. 355·2).

Colief *Clonmel, Irl.†; Forum, UK.*
Tilactase (p. 2631·2).
Infant colic; colic associated with lactose intolerance.

Colifagina *ABC, Ital.*
Lysate of *Escherichia coli; Bacillus pumilus; Morganella morgani; Alcaligenes faecalis; Shigella flexneri; Enterococcus faecalis* (p. 2596·3); *Bacillus subtilis; Proteus vulgaris.*
Gastrointestinal infections; genito-urinary infections.

Coli-Fagina S *ABC, Port.*
Lysates of *Escherichia coli; Bacillus morgani; Bacillus faecalis alcaligenes; E. pseudodysenteriae; Bacillus subtilis; Proteus vulgaris; Enterococcus faecalis* (p. 2596·3); *Bacillus mesentericus.*
Gastrointestinal infections; genito-urinary infections.

Colifilm *Quesada, Arg.*
Loperamide (p. 1854·2).
Diarrhoea; ileostomy management.

ColiFin *Pari, Ger.; Tramedico, Neth.; Vifor, Switz.*
Colistimethate sodium (p. 275·3).
Pseudomonal lung infections in cystic fibrosis.

Colifoam *Aspen, Austral.; Meda, Austria; Meda, Denm.; Meda, Fin.; Meda, Ger.; Meda, Gr.; Meda, Irl.; Meda, Ital.; Schwarz, Norw.†; Healthcare Logistics, NZ; Meda, Port.; Meda, Swed.; Meda, UK.*
⊗Hydrocortisone acetate (p. 1640·1).
Inflammatory bowel disease.

Coligermina *Bruschettini, Ital.*
Simeticone (p. 1886·2); *Lactobacillus sporogenes* (p. 2596·3).

Coligon *Fourrts, India.*
Dicycloverine (p. 1834·2).
Gastrointestinal spasm.

Coligon Plus *Fourrts, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Coligon-O *Fourrts, India.*
Dicycloverine (p. 1834·2); magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Coligyl *Mankind, India.*
Colistin sulfate (p. 275·3).
Gastrointestinal infections; gastrointestinal decontamination.

Colik *Vilco, Gr.*
Homatropine methylbromide (p. 2007·3); hyoscine methobromide (p. 1846·1).

Coliky *Bombay Tablet, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Colimef *Intel, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Colimet *Collins, Mex.†*
Cimetidine (p. 1827·1).
Peptic ulcer.

Colimex *Wallace, India.*
Oral drops: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Colic; irritable bowel syndrome; dysmenorrhoea.

Wallace, India.
Tablets: Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).
Colic; dysmenorrhoea; irritable bowel syndrome.

Colimicina *UCB, Ital.*
Injection: Colistimethate sodium (p. 275·3).
Gram-negative bacterial infections.

UCB, Ital.†; Quimifar, Spain.†
Colistin sulfate (p. 275·3).
Bacterial infections.

Colimil *Milte, Ital.*
Melissa (p. 2552·3); chamomile (p. 2474·1); fennel (p. 2503·2).
Infant colic.

Colimix *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Flatulence; gastrointestinal spasm; infant colic.

Colimune *Sanofi-Aventis, Ger.*
Sodium cromoglicate (p. 1225·3).
Food hypersensitivity.

Colimycine *IFET (ΙΦΕΤ), Gr.*
Colistimethate sodium (p. 275·3).
Bacterial infections.

Sanofi-Aventis, Fr.
Colistin sulfate (p. 275·3) or colistimethate sodium (p. 275·3).
Bacterial infections.

Colina *Ipsen, Ger.*
Smectite (p. 1887·1).
Diarrhoea.

Colina Spezial *Ipsen, Ger.*
Smectite (p. 1887·1); aluminium hydroxide-magnesium carbonate gel (p. 1818·2).
Diarrhoea; gastrointestinal disorders.

Colinctus *DHA, Singapore.*
Codeine phosphate (p. 40·2).

Colinet *Bal, India.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Colinfant *Dyntec, Cz.*
Escherichia coli.
Gastrointestinal infections.

Colinorm *Lancer, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2); dicycloverine hydrochloride (p. 1834·2).

Colinox *DMG, Ital.*
Simeticone (p. 1886·2); *Lactobacillus sporogenes* (p. 2596·3).

Colinsan *Ferring, Ger.†*
Azathioprine (p. 1940·3).
Transplant rejection; rheumatoid arthritis; inflammatory bowel disease; auto-immune disorders; dermatomyositis; polyarteritis nodosa; immune thrombocytopenia.

Colintest-Gastreu *Reckeweg, Ger.*
Nux vomica (p. 2573·3); sulfur (p. 1721·1); lycopodium (p. 2547·1); colocynthis (p. 1833·3).
Homoeopathic preparation.

Colintest-Gastreu R37 *Reckeweg, Neth.*
Alumina (p. 1690·3); lycopodium clavatum (p. 2547·1); nux vomica (p. 2573·3); bryonia cretica.
Homoeopathic preparation.

Colintil *Inibsa, Port.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Coliopan *Eisai, Indon.†; Eisai, Jpn; Eisai, Malaysia.*
Butropium bromide (p. 1824·3).
Painful gastrointestinal spasm.

Colip *Decomed, Port.†*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Coliper *Mintlab, Chile.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Coli-Q *Ariston, Arg.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Coliquifilm *Allergan, Ger.; Allergan, Switz.*
White soft paraffin (p. 2211·3); wool alcohols (p. 2219·2); light liquid paraffin (p. 2191·2).
Eye disorders.

Coliracin *Rafa, Israel.*
Colistimethate sodium (p. 275·3).
Bacterial infections.

Colircusi *Alcon Cusi, Singapore.*
Gentamicin sulfate (p. 304·2).

Colircusi Cicloplejico *Alcon Cusi, Malaysia.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Coliria *Gezzi, Arg.*
⊗Ephedrine (p. 1663·1); phenazone (p. 124·1).
Eye irritation.

Colirid *Zydus, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1); simeticone (p. 1886·2).
Colic; dysmenorrhoea.

Colirio Antibiotico CNH *Lafedar, Arg.*
⊗Hydrocortisone (p. 1640·1); chloramphenicol (p. 257·1); neomycin sulfate (p. 330·1).
Infected eye disorders.

Colirio Iris *Ponce, Venez.*
⊗Ephedrine sulfate (p. 1663·2).
Eye congestion.

Colirio Legrand *Legrand, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Ocular congestion.

Colirio Moura Brasil *Sanofi-Aventis, Braz.*
⊗Zinc sulfate (p. 2126·2); naphazoline hydrochloride (p. 1669·3).
Ocular congestion.

Colirio Oftalmico *Drawer, Arg.*
Chloramphenicol (p. 257·1); neomycin (p. 329·3); phenylephrine (p. 1672·2).

Colirio Teuto *Teuto, Braz.*
⊗Zinc sulfate (p. 2126·2); naphazoline hydrochloride (p. 1669·3).
Ocular congestion.

Coliriocilina Adren Astr *Medical, Spain.†*
⊗Boric acid (p. 2459·3); adrenaline hydrochloride (p. 1292·2); naphazoline hydrochloride (p. 1669·3); procaine hydrochloride (p. 1994·3); zinc sulfate (p. 2126·2).
Eye disorders.

Coliriocilina Prednisona *Medical, Spain.†*
⊗Neomycin sulfate (p. 330·1); prednisone (p. 1647·2).
Eye disorders.

Co-Lisinopril *Eurogenerics, Belg.; Mylan, Belg.; Sandoz, Belg.; Teva, Belg.; Mepha, Switz.; Spirig, Switz.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Lisinostad *Stada, Austria.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Colispas
Note: this name may be used for preparations of different composition.
Bestochem, India.
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Zota, India.
Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Colispas-P *Bestochem, India.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Colistate *Atlantic, Thai.*
Colistimethate sodium (p. 275·3).
Gram-negative bacterial infections.

Colistimicin *Kocak, Turk.*
Colistimethate sodium (p. 275·3).

Colistín Magma *Church, Mex.†*
Colistin sulfate (p. 275·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Gastrointestinal infection.

Colistine *Actavis, Indon.*
Colistin sulfate (p. 275·3).
Gram-negative bacterial infections of the gastrointestinal tract.

Colistineb *Pharma Logistics, Belg.*
Colistimethate sodium (p. 275·3).
Gram-negative bacterial infections.

Colistop
Note: this name may be used for preparations of different composition.
Hexa, Arg.
Phthalylsulfathiazole (p. 339·3); bismuth subcarbonate (p. 1822·1); homatropine methylbromide (p. 2007·3).
Gastro-enteritis.

Indi, India.
Colistin sulfate (p. 275·3).
Gastrointestinal infections; gastrointestinal decontamination.

Colitan *GSK, Pol.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Colite *Simayla, S.Afr.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Colitisane *Lesourd, Fr.†*
Bec de grue; althaea (p. 2438·3); achillea (p. 2427·3); wild pansy (p. 2647·3).
Painful gastrointestinal spasm.

Colitofalk *Falk, Belg.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Coliwell *Lupin, India.*
Asafetida (p. 2449·3); caraway (p. 2470·2); castor oil (p. 2472·1); cinnamon oil (p. 2479·3); fennel oil (p. 2503·3); piper nigrum.

Colixane *Sanitas, Arg.*
Trimebutine maleate (p. 2634·1).

Colixane B *Sanitas, Arg.*
Trimebutine maleate (p. 2634·1); bromazepam (p. 1041·2).

Colixin *Pharmis, Port.*
Colistimethate sodium (p. 275·3).
Gram-negative bacterial infections.

Colixin MPS *Medispan, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1); simeticone (p. 1886·2).

Coliza *DWD, India.*
Injection: Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

DWD, India.
Oral drops: Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).
Infant colic.

Colizole *East India Pharma, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Coljoy *Cadila, India.*
Colchicine (p. 604·1).
Gout.

Colladeen *Lamberts Healthcare, UK.*
Anthocyanidins (p. 2505·2) from flavonoid extracts of bilberry and grapeseed.
Nutritional supplement.

Collafex *Universal Medicare, India.*
Collagen (p. 2483·2).

Collagen T2-Gag *Farmoterapia, Arg.*
Collagen (p. 2483·2); cartilage (p. 2471·3).
Nutritional supplement.

Collapat II *Biomet, Ger.*
Hydroxyapatite (p. 2529·3); collagen (p. 2483·2).
Bone reconstruction.

Collatamp EG *Schering-Plough, UK.*
Collagen (p. 2483·2); gentamicin sulfate (p. 304·2).
Haemorrhage.

Collazin *Selmag, Switz.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Collazole *Biodica, Fr.†*
Metronidazole (p. 936·1).
Periodontitis.

Collerin Expectorant *Coronet, Indon.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Collicort *Collins, Mex.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Collins Elixir *Collins Elixir, UK.*
Ethylmorphine hydrochloride (p. 56·3).
Coughs.

Collins Elixir Decongesant Pasilles *Collins Elixir, UK.*
Menthol (p. 2553·2); eucalyptus (p. 2501·1).
Coughs; nasal congestion.

Collirio Alfa *Bracco, Ital.*
⊗Naphazoline nitrate (p. 1669·3).
Eye irritation.

Collirio Alfa Antistaminico *Bracco, Ital.*
⊗Thonzylamine hydrochloride (p. 642·1); naphazoline nitrate (p. 1669·3).
Conjunctival disorders.

Collis Browne's *Thornton & Ross, UK.*
Tablets: ⊗Light kaolin (p. 1850·1); morphine hydrochloride (p. 92·3); heavy calcium carbonate (p. 1824·3).
Diarrhoea.

Thornton & Ross, UK.
Oral mixture: ⊗Morphine (p. 92·3); peppermint oil (p. 1877·1).
Coughs; diarrhoea.

Collite *Holland Pharma, Neth.*
Chamomilla (p. 2474·1); chelidonium majus (p. 2522·2); collinsonia canadensis (p. 2622·2); hypericum perforatum (p. 449·1); nux vomica (p. 2573·3); plumbum metallicum (p. 2541·3); veratrum album (p. 2644·3).
Homoeopathic preparation.

Collitred *Collins, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Collodene *Universal, S.Afr.†*
Pectin (p. 2200·3); light kaolin (p. 1850·1).
Diarrhoea.

Collomac *Mack, Rus.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); lauromacrogol 400 (p. 2194·1).
Warts; corns; calluses; hyperkeratosis.

Collomack *Recordati, Ger.*
Salicylic acid (p. 1719·1).
Calluses; corns; hard skin; warts.

Mack, Hong Kong†; Zuoz, Venez.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); lauromacrogol 400 (p. 2194·1).
Calluses; corns; hard skin; warts.

Collomak *Asmeco, Thai.; Alex Pharm, Ukr.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); lauromacrogol 400 (p. 2194·1).
Warts; corns; calluses; hard skin.

Collosol
Note: this name may be used for preparations of different composition.
Solvay, India.
Iodine (p. 2336·3).
Hypothyroidism; hyperthyroidism.

Colloss *Biomet, Ger.†*
Collagen (bovine) (p. 2483·2).
Bone reconstruction.

Collubiazol *Millet-Franklin, Arg.*
Pastilles: Tyrothricin (p. 384·1); benzocaine (p. 1980·2); hexylresorcinol (p. 1755·1).
Mouth and throat disorders.

Millet-Franklin, Arg.
Spray: Sulfachrysoidine sodium (p. 361·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Collubiazol N *Medical, Arg.*
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); benzalkonium chloride (p. 1737·1); benzocaine (p. 1980·2).
Mouth and throat inflammation.

Collu-Blache *Tradiphar, Fr.†; Pharmanel, Gr.; Bausch & Lomb, Switz.*
Chlorhexidine gluconate (p. 1743·3); oxybuprocaine hydrochloride (p. 1993·2).
Mouth and throat disorders.

Colludol *Melisana, Belg.; Cooperation Pharmaceutique, Fr.*
Hexamidine isetionate (p. 1754·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Collu-Hextril *Johnson & Johnson, Fr.; Johnson & Johnson, Port.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Collunosol-N *Sanofi, Switz.*
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Collunovar *Dexo, Fr.*
Mouthwash; throat spray: Chlorhexidine gluconate (p. 1743·3).
Mouth and throat infections.

Colluvoxyl *Plantes et Medecines, Fr.†*
Althaea (p. 2438·3).
Mouth and throat disorders.

Collypan *Vifor, Switz.*
⊗Tetryzoline hydrochloride (p. 1678·3); zinc sulfate (p. 2126·2); digitalis (p. 1352·3); hamamelis (p. 2523·3); euphrasia (p. 2502·1).
Eye irritation.

Collyre Bleu *Leurquin, Fr.*
⊗Methylthioninium chloride (p. 1559·1); naphazoline nitrate (p. 1669·3).
Eye irritation.

Collyre Bleu Laiter *Leurquin, Canad.; Uhlmann-Eyraud, Switz.*
⊗Methylthioninium chloride (p. 1559·1); naphazoline nitrate (p. 1669·3).
Eye disorders; eye irritation.

Collyre Vitaphakol *Theodoridis, Gr.*
Adenosine (p. 1291·1); cytochrome C (p. 2491·2); nicotinamide (p. 2083·1); sodium succinate (p. 2620·1); sorbitol (p. 2092·1).

Collyrium for Fresh Eyes *Bausch & Lomb, USA.†*
Borax (p. 2459·2); boric acid (p. 2459·3).
Eye irrigation.

Colmax *Andromaco, Chile.*
Clonixin lysine (p. 40·1).
Pain.

Colme
Note: this name may be used for preparations of different composition.
Croma, Austria†; Farmlux, Rus.; Faes, Spain.
Calcium carbimide (p. 2464·2).
Alcoholism.

Interbat, Indon.
Chloramphenicol (p. 257·1).
Bacterial infections.

Colmesdant *Stendhal, Mex.*
Colistimethate sodium (p. 275·3).
Gram-negative bacterial infections.

Colmibe *Raffo, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Colmifen *Remedica, Singapore.*
Baclofen (p. 2014·3).
Spasticity.

Colmycin *Atlantic, China.*
Colistin sulfate (p. 275·3).
Diarrhoea; dysentery.

Colnar *Sanovel, Turk.*
Rosuvastatin calcium (p. 1488·2).

Colnidin *Reig Jofre, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Colobolina *Fabra, Arg.*
Hyoscine butylbromide (p. 1845·3).
Muscle spasm.

Colobolina D *Fabra, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Muscle spasm; pain.

Colobreathe *Forest Laboratories, Neth.; Forest Laboratories, UK.*
Colistimethate sodium (p. 275·3).
Pseudomonal lung infections in cystic fibrosis.

Colocarb *Expanpharm, Fr.†*
Activated charcoal (p. 1537·3).
Gastrointestinal disorders.

ColoCare *Helena, Canad.†; Helena, USA.*
Test for occult blood in faeces.

Coloclean *Cosme, India.*
Macrogol (p. 2547·3); electrolytes (p. 1775·1).

Colocort *Paddock, USA.*
⊗Hydrocortisone (p. 1640·1).
Anorectal disorders.

Colocynthis-Homaccord *Heel, Neth.*
Colocynthis (p. 1833·3); gnaphalium polycephalum.
Homoeopathic preparation.

Colodium *Hovid, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Colofac *Abbott, Austral.; Solvay, Austria; Abbott, Irl.; Abbott, NZ; Solvay, S.Afr.; Abbott, Thai.; Solvay, UK.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Colofiber *Madaus, Belg.*
Ispaghula (p. 1849·1).
Colopathy; constipation.

Colofoam *Meda, Fr.*
⊗Hydrocortisone acetate (p. 1640·1).
Inflammatory bowel disease.

Colofort *Ipsen, Belg.; Ipsen, Neth.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Coloft *Bright Future, Hong Kong.†*
Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Cologen *TO-Chemicals, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Colognost *Sanochemia, Ger.*
Radio-opaque polyvinyl chloride O-ring.
Diagnosis of colon transit time.

Colokit *Mayoly-Spindler, Fr.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Cololyt *Spirig, Switz.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Colominte *Vitoria, Port.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome.

Colomycin *Forest, Hung.*
Colistin (p. 275·3).
Bacterial infections.

Forest, Irl.; Forest Laboratories, UK.
Colistin sulfate (p. 275·3) or colistimethate sodium (p. 275·3).
Bacterial infections; bowel sterilisation.

Forest Laboratories, Cz.; IFET (ΙΦΕΤ), Gr.; Forest Laboratories, Hong Kong; Forest, Ukr.
Colistimethate sodium (p. 275·3).
Bacterial infections.

Colon Care *Blackmores, Austral.*
Senna (p. 1885·1); buckthorn (p. 1824·2); ispaghula (p. 1849·1); aniseed (p. 2444·2); fennel (p. 2503·2); liquorice (p. 1853·2); bearberry (p. 2453·2); agar (p. 2167·2).
Constipation.

Colon Cleanse *Aminostar, Hung.*
Ispaghula (p. 1849·1).
Constipation; dietary fibre supplement; hypercholesterolaemia.

Colonac *Uniao Quimica, Braz.*
Lactulose (p. 1850·3).
Constipation.

Colonaid *Lafi, Chile.*
Tegaserod (p. 1893·1).
Irritable bowel syndrome in women.

Colonel *Astellas, Jpn.*
Polycarbophil calcium (p. 1879·2).
Irritable bowel syndrome.

Colonil *Quesada, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Colonise *Torrent, India.*
Bacillus mesentericus; Clostridium butyricum; Lactobacillus acidophilus (p. 2596·3); *Enterococcus faecalis* (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Diarrhoea.

Colonlytely *Dendy, Austral.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Colonorm *Mundipharma, Austria.*
Senna (p. 1885·1).
Constipation; anorectal disorders.

Colonprep *Dendy, Austral.*
1 Sachet, macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1) (Colonlytely); 2 sachets, sodium picosulfate (p. 1887·2) (Picolax).
Bowel evacuation.

Colonsoft *Orion, Fin.*
Electrolytes (p. 1775·1); macrogol 4000 (p. 2547·3).
Constipation.

Colonsteril *Orion, Fin.*
Electrolytes (p. 1775·1); macrogol 4000 (p. 2547·3).
Bowel evacuation.

Colopeg *Bayer, Belg.; Bayer Sante, Fr.*
Electrolytes (p. 1775·1); macrogol 3350 (p. 2547·3).
Bowel evacuation.

JB Chemicals, India.
Macrogol (p. 2547·3); electrolytes (p. 1775·1).

Colophos *Spirig, Switz.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Coloplast OAD (Sween) *Coloplast, UK.*
A deodorant for stoma care.

Colo-Pleon *Henning, Ger.; Sanofi-Aventis, Ger.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease.

Colo-Prep *Anmarate, S.Afr.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Colopriv *Expanscience, Fr.†*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal and biliary-tract disorders.

Colorex *Ranbaxy, India.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Colosan mite *Vifor, Switz.*
Sterculia (p. 1888·3).
Constipation; obesity.

Colosan plus *Vifor, Switz.*
Sterculia (p. 1888·3); frangula (p. 1843·3).
Constipation.

Colosan travel *Vifor, Switz.*
Sterculia (p. 1888·3).
Constipation; obesity.

Co-Losartan *Apotex, Belg.; Sandoz, Belg.; Teva, Belg.; Sandoz, Switz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coloscreen *Biolab, NZ; Helena, USA.*
Test for faecal occult blood.

Coloserod *Lazar, Arg.*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome in women.

Colo-Sol *Vifor, Switz.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Colospa *Solvay, India.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Colospan *Hovid, Hong Kong†; Hovid, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Colostrum
Note: this name may be used for preparations of different composition.
Nathura, Ital.
Colostrum (p. 2380·3); melaleuca viridiflora; cypress (p. 2491·1).
Wounds; skin disorders.

Eagle, Austral.†
Milk extract.
Dietary supplement.

Colotal *Perrigo, Israel.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm; irritable bowel syndrome.

Colourless Antiseptic *Rougier, Canad.*
Chloroxylenol (p. 1748·2).
Antiseptic.

Colowash *Zydus, India.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1); sodium benzoate (p. 1738·2).

Coloxet *Egis, Neth.*
Capecitabine (p. 757·3).
Breast cancer; colorectal cancer; gastric cancer.

Coloximina *Quesada, Arg.*
Rifaximin (p. 355·2).
Gastrointestinal infections; hyperammonaemia.

Coloxyl *Aspen, Austral.; Sigma, NZ.*
Oral drops: Poloxamer 188 (p. 2202·1).
Faecal softener; constipation.

Aspen, Austral.; Sigma, NZ.†
Suppositories: Docusate sodium (p. 1836·2); bisacodyl (p. 1821·1).
Constipation; bowel evacuation; faecal softener.

Aspen, Austral.; Sigma, NZ.
Enema; tablets: Docusate sodium (p. 1836·2).
Constipation; bowel evacuation.

Coloxyl with Senna *Aspen, Austral.; Pharmaco, NZ.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.

Colpadak *Belfar, Braz.*
Miconazole (p. 588·3).

Colpagex-N *Marjan, Braz.†*
Neomycin sulfate (p. 330·1); tyrothricin (p. 384·1); nystatin (p. 590·3); sodium propionate (p. 593·1); boric acid (p. 2459·3).
Vulvovaginal infections.

Colpatrin *Teuto, Braz.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vulvovaginal infections.

Colpep *Alkem, India.*
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2); sodium citrate (p. 1781·2).

Alkem, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Colpermin *Germania, Austria; Tillotts, Cz.; Faran, Gr.; Tillotts, Hong Kong; McNeil Healthcare, Irl.; Tillotts, Israel; Tillotts, Singapore; Tillotts, Switz.; Tillotts, Thai.; Adeka, Turk.; McNeil, UK.*
Peppermint oil (p. 1877·1).
Abdominal pain; irritable bowel syndrome; bloating.

Colphen *Adcock Ingram, S.Afr.†*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); sodium salicylate (p. 132·2); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); cetylpyridinium chloride (p. 1743·1).
Cough.

Colphos *Putaowang, China.*
Aluminium phosphate (p. 1818·3).

Colpica *Tropica Mas, Indon.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Colpist *Ativus, Braz.*
Metronidazole benzoate (p. 936·1); nystatin (p. 590·3); benzalkonium chloride (p. 1737·1).
Vulvovaginal infections.

Colpistar *Farmoquimica, Braz.*
Vaginal cream: Metronidazole (p. 936·1); nystatin (p. 590·3); benzalkonium chloride (p. 1737·1); muramidase (p. 2565·1).
Vulvovaginal infections.

Colpistatin *Ache, Braz.*
Metronidazole benzoate (p. 936·1); nystatin (p. 590·3); benzalkonium chloride (p. 1737·1).
Vulvovaginal infections.

Colpixol *Lundbeck, S.Afr.†*
Zuclopenthixol acetate (p. 1119·1).
Psychoses.

Colpocin-T *Demo, Gr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Colpo-Cleaner *Dolhay, Hung.*
Povidone-iodine (p. 1767·1).
Vaginitis.

Colpoestriol *Temis, Arg.*
Estriol (p. 2274·3).
Vulvovaginal disorders; urinary incontinence.

Colpofilin *Lazar, Arg.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Colpofilin Max *Lazar, Arg.*
Miconazole nitrate (p. 589·1); metronidazole (p. 936·1).
Vaginal infections.

Colpogyn *Angelini, Ital.*
Estriol (p. 2274·3).
Menopausal disorders; cervical erosion.

Colpolase *De Mayo, Braz.†*
Topical solution: Neomycin sulfate (p. 330·1); tyrothricin (p. 384·1); hydroxyquinoline sulfate (p. 2530·1); lactic acid (p. 2539·1); menthol (p. 2553·2).
Vulvovaginal infections.

De Mayo, Braz.†
Vaginal capsules; vaginal cream: Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); nystatin (p. 590·3); tinidazole (p. 949·2).
Vulvovaginal infections.

Colposan *Panalab, Arg.*
Clindamycin (p. 269·3); ketoconazole (p. 585·3).
Vaginal infections.

Colposeptine *Merck Serono, China; Theramex, China; Merck Serono, Hong Kong; Theramex, Mon.; Merck, Turk.; Theramex, Ukr.*
Chlorquinaldol (p. 260·1); promestriene (p. 2302·3).
Leucorrhoea; vulvovaginal disorders; vulvovaginal infections.

Colpotrofin *Teva, Spain.*
Promestriene (p. 2302·3).
Vulvovaginal disorders.

Colpotrofine *Merck, Braz.; Nycomed, Braz.*
Promestriene (p. 2302·3).
Menopausal disorders.

Colpotrophine *Merck Serono, Arg.; Merck Serono, China; Theramex, China; Merck Serono, Hong Kong; Theramex, Ital.; AF, Mex.; Theramex, Mon.; Theramex, Port.; Merck Theramex, Singapore†; Vifor, Switz.; Merck, Turk.; Teva, Ukr.*
Promestriene (p. 2302·3).
Vulvovaginal disorders.

Colpradin *Biomep, Mex.*
Pravastatin (p. 1473·1).
Hypercholesterolaemia.

Colprone *Biodim, Fr.*
Medrogestone (p. 2287·3).
Menstrual disorders; menopausal disorders; fibroids; endometriosis.

Colpuril *Nova Argentia, Arg.*
Allopurinol (p. 600·2); colchicine (p. 604·1).
Gout; hyperuricaemia.

Colpuril A *Nova Argentia, Arg.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Colred *British Biologicals, India.*
Preparation for enteral nutrition.

Colrex Plus *Zee, India.*
Chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Colrifax *Benedetti, Ital.*
Rifaximin (p. 355·2).

Colsan *Arvincare, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Colsanac *Pierre Fabre, Port.*
Lactulose (p. 1850·3).
Constipation; hepatic coma; hepatic encephalopathy.

Colsancetine *Sanbe, Indon.*
Chloramphenicol (p. 257·1), chloramphenicol palmitate (p. 257·1), or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Colser *Serral, Mex.*
Bezafibrate (p. 1323·2).
Hypercholesterolaemia.

Colsor
Note: this name may be used for preparations of different composition.
Pickles, UK.
Phenol (p. 1763·3); menthol (p. 2553·2); tannic acid (p. 2625·2).
Herpes labialis.

Seng, Thai.
Aciclovir (p. 964·1).
Herpesvirus infections.

Colsprin *Reckitt Benckiser, India.*
Aspirin (p. 22·2).
Prophylaxis of cerebrovascular disorders or myocardial infarction after by-pass surgery.

Colsprin 325 and 650 *Reckitt Benckiser, India.*
Aspirin (p. 22·2); calcium carbonate (p. 1824·3).

Colstat
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); atropine sulfate (p. 1310·2).
Cold and influenza symptoms.

Coltab *Suphong, Thai.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Coltalin *Fortune, China; Fortune, Hong Kong.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); thiamine hydrochloride (p. 2103·1).
Allergic rhinitis; cold and influenza symptoms; nasal congestion.

Coltalin Cold & Allergy *Fortune, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; allergic disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Coltalin-GP *Fortune, Hong Kong.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cold symptoms; cough.

Coltalin-GP Extra *Fortune, Hong Kong.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); noscapine (p. 1670·3); bromhexine hydrochloride (p. 1656·3).
Cold and influenza symptoms; cough.

Coltalin-ND *Fortune, Hong Kong.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; nasal congestion; sinus congestion.

Coltect *Luxembourg, Israel.†*
Turmeric (p. 2218·1); camelia sinensis (p. 2648·2); L-selenomethionine (p. 2087·1).
Gastrointestinal disorders.

Colther *Farmamust, Gr.*
Tobramycin (p. 380·1).
Eye infections.

Colthiozid *Pharmy, Fr.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Coltramyl *Sanofi-Aventis, Fr.; Korangi, Port.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Coltrax *Sanofi-Aventis, Braz.; Sanofi-Aventis, Venez.*
Thiocolchicoside (p. 2026·2).
Painful muscle spasm.

Columbia Antiseptic Powder *Sturtevant, USA.*
Zinc oxide (p. 1729·1); talc (p. 1722·2); phenol (p. 1763·3); boric acid (p. 2459·3).

Colutóide *Cimed, Braz.*
⊗Prednisolone (p. 1645·2); neomycin sulfate (p. 330·1); bismuth sodium tartrate (p. 1821·3); procaine hydrochloride (p. 1994·3).
Mouth and throat disorders.

Colval *Valmor, Venez.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Colvan *Dynamic, Philipp.*
Capsules: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Colds; cough.

Dynamic, Philipp.
Oral drops; syrup: Phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; nasal congestion; rhinitis; sinusitis.

Colvastina *Pentafarma, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Colver *Farmochimica, Ital.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Coly *Community Pharmacy, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Coly-Mycin M *Pfizer, Austral.†; Erfa, Canad.; JHP, USA.*
Colistimethate sodium (p. 275·3).
Bacterial infections.

Coly-Mycin S Otic *JHP, USA.*
⊗Colistin sulfate (p. 275·3); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); tonzonium bromide (p. 2217·1).
Bacterial ear infections.

Colypan *Farma, Venez.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; dyspepsia.

CoLyte *Pendopharm, Canad.; Meda, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Colza *Bintang Toedjoe, Indon.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cold and influenza symptoms.

Colzuric *Royton, Braz.*
Colchicine (p. 604·1).

Comafusin Hepar *Kalbe, Indon.*
Amino acids; vitamins; electrolytes (p. 1775·1); xylitol (p. 2220·3).
Hepatic insufficiency.

Comagis *Perrigo, Israel.*
⊗Bifonazole (p. 573·3); fluocinonide (p. 1636·3).
Infected skin disorders.

Comaranil *KRKA, Neth.*
⊗Indapamide (p. 1409·2); perindopril erbumine (p. 1467·1).
Hypertension.

Comarol *Sanofi-Aventis, Pol.†*
Diphenhydramine hydrochloride (p. 626·2); lidocaine hydrochloride (p. 1988·2).
Skin irritation.

Comat *Milano, Thai.†*
Clotrimazole (p. 576·2).
Fungal and bacterial vaginal infections; trichomoniasis.

Comax *Tripharma, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).

Comazol *Union Drug, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Comb *New Era, Canad.†*
A range of homoeopathic preparations.
Homoeopathic preparation.

Combac *Natural Balance, Canad.†*
Vitamins; zinc gluconate (p. 2126·2).

Combacid N *Streuli, Switz.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Combactam *Pfizer, Austria; Pfizer, Ger.*
Sulbactam sodium (p. 360·1).
Bacterial infections; adjunct to beta-lactam antibiotics.

Combactan *Bergamo, Braz.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Combact-HIB *Aventis, S.Afr.†*
An adsorbed diphtheria, tetanus, pertussis and haemophilus influenzae conjugate vaccine (p. 2384·2).
Active immunisation.

Combaforte *Zekides, Gr.*
Doxycycline hyclate (p. 288·2).

Combair *Torrex Chiesi, Cz.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Combantrin *Johnson & Johnson, Austral.; Infectopharm, Austria; McNeil Consumer, Canad.; Pfizer, Chile†; Teofarma, Fr.; Pfizer, Gr.; Pfizer, Hong Kong†; Pfizer, Indon.†; Pfizer, Ital.; Pfizer, Mex.; Pfizer, NZ; Johnson & Johnson, Philipp.; Pfizer, Port.; Pfizer Consumer, S.Afr.†; Pfizer, Venez.*
Pyrantel embonate (p. 165·3).
Intestinal nematode infections; worm infections.

Combantrin-1 *Pfizer, NZ.*
Mebendazole (p. 158·3).
Worm infections.

Combantrin-1 with Mebendazole *Johnson & Johnson, Austral.*
Mebendazole (p. 158·3).
Worm infections.

Combantrin-A *Pfizer, India.*
Albendazole (p. 149·1).
Worm infections.

Combar *Pharmacodane, Denm.*
Mirtazapine (p. 436·1).
Depression.

Combaren *Novartis, Ger.†; Novartis, Venez.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Inflammation; pain.

Combec *Mitsubishi Tanabe, Jpn.*
Ufenamate (p. 141·3).
Skin disorders.

Combee *Dewcare, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Combes *Meprofarm, Indon.†*
Poliglusam (p. 2593·2); garcinia cambogia (p. 2510·2); levocarnitine (p. 2053·2); chromium tripicolinate (p. 2056·1); ubidecarenone (p. 2637·1); ascorbic acid (p. 2110·3).
Weight reduction.

Combevit *Synco, Hong Kong.†*
Vitamin B substances (p. 2102·3).

ComBgen *Ethex, USA.†*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).

Combi *Iasis, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Combi Flu *Combiphar, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); phenylpropanolamine (p. 1674·1).
Cold and influenza symptoms.

Combi-ASA *Pharma Start, Ukr.*
Aspirin (p. 22·2).
Magnesium hydroxide (p. 1857·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolic disorders.

Combicef *Combiphar, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Combicetin *Combiphar, Indon.*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Combicid *Bilim, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bilim, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1) or sultamicillin tosilate (p. 369·1).
Bacterial infections.

Combicitrine *Berlico Mulia, Indon.*
Piperazine citrate (p. 163·1).
Ascariasis; enterobiasis.

Combicold *Biomiicron, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Combid *GSK, Thai.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Combiderm
Note: this name may be used for preparations of different composition.
Convatec, Belg.
A polyurethane dressing (p. 1718·1).
Wounds.

Glenmark, Philipp.
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Kalbe, Singapore.
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Combidex *Bilim, Turk.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Combidol
Note: this name may be used for preparations of different composition.
Intas, India.
Haloperidol (p. 1077·1); trihexyphenidyl hydrochloride (p. 917·3).

Combidos *Medopharm, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Combif AR *Medinova, Singapore.*
Bifidobacterium longum (p. 2596·3); milk protein.
Dietary supplement; maintenance of gastrointestinal flora.

Combiflam *Sanofi-Aventis, India.*
Oral suspension; tablets: Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Sanofi-Aventis, India.
Cream: Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Combiflex
Note: this name may be used for preparations of different composition.
Braun, Indon.†
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Breckenridge, USA.†
Paracetamol (p. 115·1); salicylamide (p. 129·2); caffeine (p. 1203·3); phenyltoloxamine citrate (p. 638·1).
Pain.

Combiflex ES *Breckenridge, USA.†*
Paracetamol (p. 115·1); magnesium salicylate (p. 85·2); caffeine (p. 1203·3); phenyltoloxamine citrate (p. 638·1).
Pain.

Combigan *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, India; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Allergan, Malaysia; Allergan, Neth.; Allergan, Norw.; Allergan, NZ; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, S.Afr.; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, Ukr.; Allergan, USA.*
⊗Brimonidine tartrate (p. 2004·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Allergan, Singapore.
⊗Brimonidine tartrate (p. 2004·3); timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Combigan-D *Allergan, Mex.*
⊗Brimonidine tartrate (p. 2004·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Combigesic-DP *Bal, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Combihale-FF *Natco, India.*
⊗Fluticasone propionate (p. 1638·1); formoterol fumarate (p. 1209·2).

Combihext *Sanofi-Aventis, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

CombiKids *Sandoz, Philipp.†*
Syrup, rifampicin (p. 350·3) (Rimactane); oral suspension, pyrazinamide (p. 345·2) (PZA-Ciba); syrup, isoniazid (Nicetal) (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in the Nicetal syrup for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Combilax
Note: this name may be used for preparations of different composition.
KG, Ital.
Lactulose (p. 1850·3); senna (p. 1885·1); cascara (p. 1826·1); vitamin B substances (p. 2102·3).
Gastrointestinal disorders.

Mundipharma, Austral.†
Sennosides (p. 1885·2); docusate sodium (p. 1836·2).
Constipation.

Combilipen *Ufavita, Rus.*
Thiamine hydrochloride (p. 2103·1) or benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuritis; neuralgia; neuropathy.

Combilox *Cachet, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Combilox-LB *Cachet, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Combi-Methoxan *Ad-Drugstel, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Combimist *Zydus, India.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).

Combina 2 *Omega, Irl.*
Test for glucose and ketones in urine.

Combina 3 *Omega, Irl.*
Test for glucose, pH, and protein in urine.

Combina Glucose *Omega, Irl.*
Test for glucose in urine (p. 2516·3).

Combina 9 SG *Omega, Irl.*
Test for glucose, ketones, nitrites, pH, specific gravity, bilirubin, urobilinogen, protein, and blood in urine.

Combinac *Novaduo, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Novaduo, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Novaduo, India.
Topical gel: Diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1); alpha linoleic acid (p. 2509·2); menthol (p. 2553·2).

Combinac-MR *Novaduo, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Combinaison *Robert, Canad.†*
Calcium fluoride (p. 2053·1); calcium phosphate (tribasic) (p. 1784·2); calcium sulfate (p. 2173·1); ferric phosphate (p. 2077·1); magnesium phosphate dibasic (p. 1786·3); potassium chloride (p. 1793·2); potassium phosphate dibasic (p. 1791·1); potassium sulfate (p. 1793·2); sodium chloride (p. 1795·1); sodium phosphate dibasic (p. 1791·2); sodium sulfate (p. 1888·1); silicon dioxide (p. 2208·3).
Homoeopathic preparation.

Combination *New Era, Canad.*
A range of homoeopathic preparations.
Homoeopathic preparation.

Combineb *Breathe Pharmaceuticals, Irl.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Combinplex *Hua, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin supplement.

CombiPack
Note: this name may be used for preparations of different composition.
Sandoz, Philipp.
1 Tablet, rifampicin (p. 350·3); 1 tablet, isoniazid (p. 311·2); 3 tablets, pyrazinamide (p. 345·2).
Tuberculosis.

Combipack
Note: this name may be used for preparations of different composition.
Abdi, Turk.
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).

CombiPatch *Novartis, USA.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders.

Combipen *Medispan, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Combiplasmal *Braun, Ger.†*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Combiplex *Berlico Mulia, Indon.*
Thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); nicotinamide (p. 2083·1); calcium pantothenate (p. 2085·2).
Vitamin B deficiency.

Combipramol *Arrow, Denm.†; Arrow, Neth.†*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Combiprasal *Aldo, Spain.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Combipril *KVZ, Ukr.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Combipul *Cipla, Philipp.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Combiquine-C *Rimsa, Mex.*
Ciprofloxacin (p. 261·1); ascorbic acid (p. 2110·3).
Urinary-tract infections.

Combirice *Baldacci, Ital.*
Rice flour; maltodextrin (p. 2080·3); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration.

Combiron *Ache, Braz.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Combisartan *Menarini, Ital.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Combiseven *Bracco, Ital.*
Patch 1, estradiol (p. 2271·1); patch 2, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Combispas *Medinova, India.*
Oral drops: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Medinova, India.
Tablets: Diclofenac potassium (p. 48·3); fenpiverinium bromide (p. 2504·1); pitofenone hydrochloride (p. 2592·2).

Combistix *Siemens, USA.*
Test for pH, protein, and glucose in urine.

Combit *Cubit, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Combitaz *Lupin, India.*
Ceftazidime (p. 250·2); tazobactam (p. 369·3).

Combither *Aristo, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Combithyrex *Sandoz, Austria.*
Levothyroxine sodium (p. 2339·1); liothyronine sodium (p. 2342·3).
Hypothyroidism.

Combitide *Sun, India.*
⊗Fluticasone propionate (p. 1638·1); salmeterol (p. 1224·1).
Asthma.

Combitropil *Sintez, Rus.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; mental function disorders; vestibular disorders; asthenia; migraine.

Combitub *Simpex, Rus.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol (p. 296·1).
Tuberculosis.

Combitub-Neo *Simpex, Rus.*
Lomefloxacin hydrochloride (p. 319·2); protionamide (p. 345·1); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Combivent *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease; bronchospasm.

Combivir *ViiV, Austral.; ViiV, Austria; ViiV, Belg.; ViiV, Canad.; GSK, Chile; GSK, China; ViiV, Cz.; ViiV, Denm.; GSK, Fin.; ViiV, Fr.; ViiV, Ger.; GSK, Gr.; GSK, Hong Kong; ViiV, Hung.; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; ViiV, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; ViiV, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Combivite *SA Druggists SelfMed, S.Afr.†*
Vitamins.

Combiwin *Wintech, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Combizar *Therapharma, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Combizym *Keller, China; Medinova, Hong Kong; Will-Pharma, Neth.†; Weifa, Norw.; Sankyo, Pol.; Abbott, Swed.; Medinova, Switz.; Medinova, Thai.*
⊗Pancreatin (p. 2579·3); enzymes from *Aspergillus oryzae.*
Pancreatic insufficiency; cystic fibrosis; digestive disorders.

Combizym Compositum *Silesia, Chile†; Solvay, Swed.†; Medinova, Switz.; Medinova, Thai.†*
⊗Pancreatin (p. 2579·3); enzymes from *Aspergillus oryzae*; ox bile (p. 2457·2).
Digestive disorders; pancreatic insufficiency.

Sankyo, Cz.†
⊗Pancreatin (p. 2579·3); enzymes from *Aspergillus*; ox bile extract (p. 2457·2).
Digestive disorders; pancreatic insufficiency.

Combizym Forte *Sankyo, Venez.*
⊗Enzymes from *Aspergillus oryzae*; pancreatin (p. 2579·3); ox bile (p. 2457·2).
Digestive disorders; pancreatic insufficiency; liver and bile disorders.

Combo-AD *Mint, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Combodart *GSK, Belg.; GSK, Denm.; GSK, Irl.; GSK, Neth.; GSK, Port.; GSK, UK.*
Dutasteride (p. 2357·2); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Combodol *Biomedica, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Combozil *Bliss, S.Afr.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).

Combudoron *Weleda, Ger.; Weleda, Irl.†; Weleda, Neth.; Weleda, S.Afr.†; Weleda, Switz.; Weleda, UK.*
Arnica (p. 2447·2); urtica (p. 2639·3).
Burns; insect stings; homoeopathic preparation; insect bites; skin irritation.

Combunex *Lupin, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Combunox *Forest Laboratories, USA.†*
⊗Oxycodone hydrochloride (p. 113·1); ibuprofen (p. 68·2).
Pain.

Combur 3 *Roche Diagnostics, Irl.†*
Test for pH, protein, and glucose in urine.

Combur 7 *Roche Diagnostics, Irl.†*
Test for pH, protein, glucose, ketones, leucocytes, nitrite, and blood in urine.

Combur 9 *Roche Diagnostics, Irl.†*
Test for pH, protein, glucose, ketones, leucocytes, nitrite, blood, urobilinogen, and bilirubin in urine.

Combur 10 *Roche Diagnostics, Irl.†*
Test for specific gravity, nitrite, pH, leucocytes, protein, glucose, ketones, urobilirubin, and blood in urine.

Combur 5 D *Roche Diagnostics, Fr.†; Roche Diagnostics, Irl.†*
Test for pH, protein, glucose, ketones, and blood in urine.

Combur Test *Roche Diagnostics, Austral.†*
Test for pH, protein, and glucose in urine.

Combur 3 Test *Roche Diagnostics, Fr.*
Test for pH, protein, and glucose in urine.

Roche, UK.
Test for glucose, pH, and protein in urine.

Combur 7 Test *Roche Diagnostics, Fr.*
Test for pH, protein, glucose, ketones, leucocytes, nitrites, and blood in urine.

Roche, UK.
Test for blood, glucose, leucocytes, nitrite, pH, and protein in urine.

Roche Diagnostics, Austral.†
Test for pH, protein, glucose, ketones, bilirubin, urobilinogen, and blood in urine.

Combur 8 Test *Roche Diagnostics, Austral.†*
Test for ketones, urobilinogen, bilirubin, blood, nitrite, pH, protein, and glucose in urine.

Combur 9 Test *Roche Diagnostics, Austral.; Roche Diagnostics, Fr.*
Test for leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, and blood in urine.

Combur 10 Test *Roche Diagnostics, Austral.; Roche Diagnostics, Fr.; Roche Diagnostics, Ital.*
Test for specific gravity, leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, and blood in urine.

Combur 2 Test LN *Roche Diagnostics, Fr.*
Test for leucocytes and nitrite in urine.

Combutec-2 *Belkozin, Rus.*
Glutaral (p. 1753·2); hydroxyquinoline sulfate (p. 2530·1); collagen (p. 2483·2); boric acid (p. 2459·3).
Burns; ulcers; wounds.

Combutol *Lupin, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Lupin, Rus.
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Comcort *Comed, India.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Comdasin *Combiphar, Indon.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Acne; gastrointestinal infections.

Comdipin *Combiphar, Indon.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Comedolytic *Fem Care, India.*
Tretinoin (p. 1725·2).
Acne.

Comedrol *Berlico Mulia, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Comelian *Kowa, Jpn.*
Dilazep hydrochloride (p. 1359·1).
Angina pectoris; nephropathy.

Comensal *Medreich, India.*
Saccharomyces boulardii (p. 2596·3).

Comenter *Raffo, Arg.; Asofarma, Mex.; Nolver, Venez.*
Mirtazapine (p. 436·1).
Depression.

Comentin *Ankom, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Co-Mepril *Kwizda, Austria.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Comer *AstraZeneca, Gr.*
⊗Salbutamol sulfate (p. 1220·2).

Cometriq *Exelixis, USA.*
Cabozantinib s-malate (p. 757·1).
Thyroid cancer.

Comfarol Forte *Sanofi-Aventis, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Comfeel *Coloplast, Arg.; Coloplast, Belg.; Coloplast, Fr.; Coloplast, S.Afr.; Coloplast, UK.*
Medicated dressing: Carmellose sodium (p. 2175·2).
Ulcers; pressure sores; wounds; burns.

Coloplast, UK.
Barrier cream.
Peristomal care.

Comfeel Plus *Coloplast, Arg.*
Carmellose sodium (p. 2175·2).
Pressure sores; burns; ulcers; wounds.

Coloplast, Ger.
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Wounds; ulcers.

Coloplast, UK.
Calcium alginate (p. 1136·3); carmellose sodium (p. 2175·2).
Wounds.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Comfeel Plus Transparenter *Coloplast, Ger.*
Carmellose (p. 2175·1).
Wounds; ulcers.

Comfeel Purilon *Coloplast, Arg.*
Calcium alginate (p. 1136·3); carmellose sodium (p. 2175·2).
Ulcers; wounds.

Comfeel SeaSorb *Coloplast, Arg.*
Calcium alginate (p. 1136·3); sodium alginate (p. 2167·3); carmellose sodium (p. 2175·2).
Ulcers; wounds.

Coloplast, UK.
Calcium sodium alginate (p. 1136·3) (p. 2167·3).
Exudating wounds.

Comfora *Nordic Drugs, Fin.; Nordic, Swed.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Comfort Pain Balm *Cadila, India.*
Camphor (p. 2466·2); sweet birch oil (p. 92·1).

Comfort Shield *Sage, Canad.*
Dimeticone (p. 2209·3).

Comfort Tears *Pilkington Barnes-Hind, USA.*
Hyetellose (p. 2188·3).
Dry eyes.

Comfortcaine *Coralite, Canad.†*
Benzocaine (p. 1980·2).
Local anaesthesia.

Comfortcare GP *Pilkington Barnes-Hind, USA.*
Disinfecting, wetting, and soaking solution for gas permeable contact lenses.

Comfortex *Zydus, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Comfortex-CZ *Zydus, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Comfrelieve *Seven Seas, UK.*
Comfrey (p. 2484·2).
Joint pain and inflammation.

Comfrey Plus *Herbal, Israel.*
Comfrey (p. 2484·2); allantoin (p. 1693·1).
Burns; cuts; insect bites; nappy rash; soft-tissue injury.

Comfy *Polipharm, Thai.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); ammonium chloride (p. 1656·1).
Cough; cold symptoms; nasal congestion.

Comhist LA *Procter & Gamble, USA.*
Chlorphenamine maleate (p. 620·3); phenyltoloxamine citrate (p. 638·1); phenylephrine hydrochloride (p. 1672·3).
Rhinorrhoea; nasal congestion.

Co-Micardis *Boehringer Ingelheim, S.Afr.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Comigat *Ankom, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Co-Migroben *Novartis, S.Afr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Comilorid *Mepha, Switz.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; liver cirrhosis with ascites.

Cominar *Casasco, Arg.*
Diacerein (p. 45·3).
Osteoarthritis.

Commit
Note: this name may be used for preparations of different composition.
Elfin, India.
Oral drops: Calcium chloride (p. 1783·1); vitamins; zinc sulfate (p. 2126·2).

Elfin, India.
Syrup: Citrus bioflavonoids (p. 2505·2); vitamins; zinc sulfate (p. 2126·2).

GSK, USA.†
Nicotine polacrilex (p. 2569·3).
Now known as Nicorette.
Aid to smoking withdrawal.

Common Mallow Combination *Seroyal, Canad.†*
Burdock (p. 2540·1); erigeron canadensis; goldenrod (p. 2620·1); mallow (p. 2549·2); sarsaparilla (p. 2610·3); taraxacum officinale (p. 2625·3); urtica dioica (p. 2639·3).
Homoeopathic preparation.

Comoben *ANH, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; skeletal muscle spasm; insomnia.

Comodine Cough *ANH, Thai.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).

Comoprazol *Comomed, Gr.*
Omeprazole (p. 1867·2).

Comosup *Farmasierra, Spain.*
⊗Glycerol (p. 2517·2).
Constipation.

Comox *TO-Chemicals, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Comoxole *Inpac, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Compact Extreme *Avene, Canad.†*
SPF 50: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Compact Protection Intense *Pierre Fabre Dermo-Cosmetique, Canad.†*
SPF 40: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Compact Sorb *Esoform, Ital.*
Sodium polyacrylate.
Spillage of biological fluids.

Compagen *Solfran, Mex.†*
Vitamins; minerals.

Companion Multi for Men *Theralogix, USA.*
Vitamins; trace elements.

50+ Companion Women's Multivitamin *Theralogix, USA.*
Vitamins; trace elements.

Compaser *Aurora, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Compaz *Cristalia, Braz.*
Diazepam (p. 1063·2).
Anxiety.

Compazine *SmithKline Beecham, USA.†*
Prochlorperazine (p. 1098·2), prochlorperazine edisilate (p. 1098·3), or prochlorperazine maleate (p. 1098·3).
Severe nausea and vomiting; psychoses; non-psychotic anxiety.

Comp-Drops 9 *Knop, Canad.†*
Arnica (p. 2447·2); caulophyllum thalictroides (p. 2458·2); cimicifuga racemosa (p. 2478·1); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Comp-Drops 3 Bowel Support *Knop, Canad.†*
Aconitum (p. 2428·3); aluminium oxide (p. 1690·3); bryonia (p. 2461·3).
Homoeopathic preparation.

Comp-Drops 5 Expectorant *Knop, Canad.†*
Belladonna (p. 2453·3); bryonia (p. 2461·3); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); potassium dichromate (p. 2476·3); sabadilla (p. 2611·2).
Homoeopathic preparation.

Comp-Drops 7 Sleepless *Knop, Canad.†*
Coffee (p. 2648·2); oats (p. 2451·1); passion flower (p. 2584·1); potassium phosphate dibasic (p. 1791·1).
Homoeopathic preparation.

Comp-Drops 1 Stress *Knop, Canad.†*
Alfalfa (p. 2433·1); oats (p. 2451·1); passion flower (p. 2584·1); phosphoric acid (p. 2589·1).
Homoeopathic preparation.

Comp-Drops 8 Uri-Tract *Knop, Canad.†*
Barberry root (p. 2502·1); benzoic acid (p. 1738·2); citrullus colocynthis (p. 1833·3); lycopodium (p. 2546·3); pareira brava.
Homoeopathic preparation.

Compeba *Indian Drugs, India.*
Metronidazole (p. 936·1).
Bacterial infections; protozoal infections; Helicobacter pylori eradication.

Compendium *Polifarma, Ital.*
Bromazepam (p. 1041·2).
Anxiety disorders; insomnia.

Compensal *Provit, Mex.†*
Cyanocobalamin (p. 2107·2).

Compensal 11G *Braun, Fr.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1).
Fluid and electrolyte disorders.

Compensal 15G *Braun, Fr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1); calcium gluconate (p. 1783·3).
Fluid and electrolyte disorders.

Compensan *Lannacher, Austria.*
⊗Morphine hydrochloride (p. 92·3).
Opioid withdrawal syndrome.

Compensate *Kamakshi, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3).

Competact *Takeda, Austria; Takeda, Cz.; Takeda, Fr.†; Takeda, Ger.; Takeda, Gr.; Takeda, Hung.; Takeda, Irl.; Takeda, Ital.; Lilly, Mex.; Lilly, Neth.; Takeda, Norw.; Takeda, Pol.; Takeda, Port.; Takeda, Spain; Takeda, Swed.; Takeda, Switz.; Takeda, UK.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Compete *Mission Pharmacal, USA.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemia.

Competor *Leontik, Gr.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Compicare *Yacca, India.*
Capsules: Vitamins; minerals.

Yacca, India.
Oral powder: Dietary protein supplement.

Yacca, India.
Injection: Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Yacca, India.
Oral drops: Vitamins; zinc sulfate (p. 2126·2); lysine hydrochloride (p. 2079·3).

Compicare-XL *Yacca, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Complamin *ACE, Neth.; Doetsch, Grether, Switz.†*
Xantinol nicotinate (p. 1535·3).
Hypercholesterolaemia; cerebral and peripheral vascular disorders.

Riemser, Ger.†
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Complamin spezial *Riemser, Ger.†*
Xantinol nicotinate (p. 1535·3).
Lipid disorders.

Complamina *Zydus, India.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Complan *Meda, Denm.; Heinz-Wattie, NZ; Heinz, UK.*
Preparation for enteral nutrition.

Complatt *Grandix, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Compléal *Macanthy, Mon.†*
A range of dietary supplements.

Compleat *Nestle, Canad.; Nestle, Hong Kong.*
Preparation for enteral nutrition.

Novartis, Braz.; Nestle, USA.
A range of preparations for enteral nutrition.

Complegel Novo *Roemmers, Arg.*
Citicoline (p. 2480·1).
Cerebrovascular disorders.

Complejo B *AM, Arg.; Bioresearch, Mex.; Bruluart, Mex.; Mavi, Mex.; Biogalenic, Venez.; Cofasa, Venez.; Medifarm, Venez.; Spefar, Venez.; Vivax Colmed, Venez.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Complejo B Compositum *Polinac, Venez.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuralgia; neuritis.

Complenatal FF *Pharmaceutical Enterprises, S.Afr.*
Vitamins; minerals.
Prenatal dietary supplement.

Complera *Gilead, USA.*
Emtricitabine (p. 976·3); rilpivirine hydrochloride (p. 1012·1); tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Complete *AMO, UK.*
A range of preparations for contact lens care.

Complete-12 *Ordain, India.*
Cobamamide (p. 2107·2); mecobalamin (p. 2108·1).

Complete Antibiotic Ointment *Taro, Canad.*
Bacitracin zinc (p. 225·3); gramicidin (p. 308·3); lidocaine (p. 1988·1); polymyxin B sulfate (p. 342·3).

Complete Comfort Plus *Advanced Medical Optics, NZ.*
Preparation for contact lens care.

Complete ComfortPlus *AMO, Arg.*
Preparation for contact lens care.

Complete Flu Care 4 Kids *Hylands, Canad.†*
Eupatorium perfoliatum (p. 2459·1); bryonia alba (p. 2461·3); gelsemium sempervirens (p. 2511·2); euphrasia officinalis (p. 2502·1); kali iodatum (p. 2336·3); anas barbariae (p. 2444·1).
Homoeopathic preparation.

Complete Moisture Plus *AMO, Arg.; Visiontec, Arg.*
Solution for contact lens care.

Complete Multi Pre- and Post-Natal *Wampole, Canad.†*
Vitamins; minerals.

Complete Multi-Adult *Wampole, Canad.*
Vitamins; minerals.

Complete Multi-Purpose *AMO, Canad.*
A cleansing, rinsing, disinfecting, storage, and lubricating solution for soft contact lenses.

Complete Prenatal Multivitamin/ Prenatal DHA Combo Pack *VitaMed, USA.*
Tablets, vitamins; minerals; trace elements; capsules, docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Complete Prenatal Multivitamins *VitaMed, USA.*
Vitamins; minerals.
Dietary supplement.

Complete Protein Remover *AMO, Austral.†*
⊗Subtilisin A (p. 2624·1).
Cleaner for soft contact lenses.

Complete Sleep *Natures Own, Austral.*
Ziziphus spinosa; lactium.
Sleep disorders.

Complete Solution *AMO, Austral.*
Cleaning, rinsing, disinfecting, storage, and lubricating solution for soft contact lenses.

Complete-PD *Ordain, India.*
Vitamins; minerals amino acids.

Complete-TD *Ordain, India.*
Vitamins; minerals.

Completia *Nature's Way, Philipp.†*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1); peppermint oil (p. 1877·1); raspberry leaf (p. 2603·1); taraxacum (p. 2625·3); urticaria; peppermint leaf (p. 1877·1); diatomaceous plant; inositol (p. 2533·2); choline bitartrate (p. 2055·2).
Prenatal supplement.

Compleven *Fresenius Kabi, Gr.; Fresenius Kabi, Pol.†*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1); lipids (from soya oil (p. 2092·3)).
Contains egg lecithin.
Parenteral nutrition.

Complevit
Note: this name may be used for preparations of different composition.
GPO, Thai.; KVZ, Ukr.
Vitamins.
Vitamin supplement; vitamin deficiency; tonic.

Pharma Invesli, Chile.†
Vitamins; minerals.

EMS, Braz.†
Buclizine (p. 618·3); gamma-aminobutyric acid (p. 2509·2).
Tonic; reduced appetite.

Complevit Pediatrico *Pharma Invesli, Chile.†*
Vitamins.

Complevitan *Bunker, Braz.*
Vitamin B substances (p. 2102·3).

Complex *Naturpharm, Canad.†; Thompsons, Canad.†*
Ranges of homoeopathic preparations.
Homoeopathic preparation.

Complex 15 *Schering-Plough, Chile; Schering-Plough, USA.*
Emollient and moisturiser.

Complex ADC *Plata, Arg.*
Vitamin A (p. 2098·3); ascorbic acid (p. 2110·3); vitamin D (p. 2112·3).
Nutritional supplement.

Complex B *GSK, India.*
Vitamin B substances (p. 2102·3).

Plata, Arg.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Complex B Calcio Y Magnesio *Plata, Arg.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3).
Nutritional supplement.

Complexe Assistance *Deva, Fr.†*
Clematis; ornithogalum umbellatum; helianthus annuus; impatiens; lotus; prunus (p. 1881·1).
Stress.

Complexe B Compose *Bio-Sante, Canad.†*
Vitamin B substances (p. 2102·3).

Complexo B *EMS, Braz.; Teuto, Braz.*
Vitamin B substances (p. 2102·3).

CompligamV *Soteks, Rus.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuritis; neuralgia; neuropathy.

Complivit *Farmstandart, Rus.*
Vitamins; minerals.

Complivit Oftalmo *Ufavita, Rus.*
Vitamins; copper (p. 2057·1); zinc (p. 2126·1); selenium (p. 2086·3); rutoside (p. 2505·3); zeaxanthin (p. 2125·3); lutein (p. 2079·2).

Complivita *Savoy, India.*
Vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Comploment *SSL, Irl.†*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Comply *Sherwood, USA.*
Lactose-free preparation for enteral nutrition.

Compound Anisodine *Zizhu, China.*
Anisodine hydrobromide; procaine hydrochloride (p. 1994·3).
Ophthalmic ischaemia.

Compound Cocillana *Bright Future, Hong Kong.†*
Cocillana (p. 1659·2); euphorbia (p. 2501·3); squill (p. 1677·3).

Compound Codeine *XingYin, China.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3).
Cough.

Compound Dextromethorphan *Xin Ma, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Compound Diisopropylamine Dichloroacetate *Healthcare Pharma, China.*
Di-isopropylammonium dichloroacetate (p. 1359·1); calcium gluconate (p. 1783·3).

Compound Indometacin *General Pharmaceutical, China.*
⊗Indometacin (p. 71·2); urea (p. 1727·3).
Musculoskeletal, peri-articular, and soft-tissue disorders.

Compound Inhalation of Menthol *McGloin, Austral.†*
Menthol (p. 2553·2); siberian fir oil; creosote (p. 1659·3).
Cold symptoms.

Compound Ketoconazole *Zhaohui, China.*
⊗Ketoconazole (p. 585·3); clobetasol propionate (p. 1627·1).
Fungal skin infections.

Compound Makham Pom *Pharmahof, Thai.*
Indian gooseberry (p. 2532·2).

Compound Mawang Mixture *Thai FD, Thai.*
Solanum indicum; solanum trilobatum; curcuma zedoaria.
Cough.

Compound Neomycin Sulfate *Dongkang, China.*
⊗Neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Compound Norethisterone *Xianju, China.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Compound Norgestrel *Double-Crane, China.*
Norgestrel (p. 2296·1); quinestrol (p. 2303·1).
Combined oral contraceptive.

Compound W *SSL, Irl.†; SA Druggists Self Med, S. Afr.†; SSL, UK; Medtech, USA.*
Salicylic acid (p. 1719·1).
Warts; hyperkeratosis; verrucas.

Compound W Freeze Off *Medtech, USA.*
Dimethyl ether (p. 1798·3); propane (p. 1802·3); isobutane (p. 1799·2).
Warts.

Compoz Night-time Sleep Aid *Medtech, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Compral Headache *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Compralfene *Gifrer Barbezat, Fr.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Compralgyl *Gifrer Barbezat, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Compraz *Combiphar, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Comprilex *Pediatrica, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Comprimes a croquer Estomac *Zeller, Switz.†*
Calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; dyspepsia; meteorism.

Compro *Paddock, USA.*
Prochlorperazine (p. 1098·2).
Nausea and vomiting.

Comptil *Mandar, India.*
Prochlorperazine (p. 1098·2) or prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; psychoses; anxiety; vertigo.

Compulxine *Armstrong, Mex.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Computer Eye Drops *Bausch & Lomb, Hong Kong; Bausch & Lomb, Philipp.*
⊗Glycerol (p. 2517·2).
Dry eyes; eye irritation.

Comrarilin *Specifar (Σπεσιφαρ), Gr.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Comron *Comed, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Comscav *Comed, India.*
Vitamins; minerals.

Comsid *Umedica, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Comsikla *Combiphar, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Comspa *Comed, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Comsporin *Combiphar, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Comstrong *Unison, Thai.†*
Vitamin B substances (p. 2102·3).
Vitamin supplement.

Comtan *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Cz.; Orifarm, Denm.†; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, USA; Novartis, Venez.*
Entacapone (p. 901·2).
Parkinsonism.

Comtaplex *Greater Pharma, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Comtess *Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Ger.; Orion, Irl.; Orion, Neth.; Orion, Norw.; Orion, Pol.; Orion, Port.; Orion, Swed.; Orion, UK.*
Entacapone (p. 901·2).
Parkinsonism.

Comthergin *Rotexmedica, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum atony; postpartum hemorrhage; uterine subinvolution.

Comthycol *Combiphar, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Comtrex *Bristol-Myers Products, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Comtrex Acute Head Cold *BMS, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Comtrex Allergy-Sinus *Bristol-Myers Products, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Comtrex Cold *Novartis, Gr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Comtrex Day & Night Maximum Strength *Bristol-Myers Products, USA.*
⊗Orange caplets, dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); blue tablets, dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Coughs and cold symptoms.

Comtrex Day & Night Multi-Symptom *Bristol-Myers Products, USA.*
⊗Orange caplets, dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); yellow tablets, dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Coughs and cold symptoms.

Comtrex Day/Night Flu Therapy *BMS, USA.*
⊗Day caplets, pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); night caplets, pseudoephedrine hydrochloride; paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Formerly known as Comtrex Flu Therapy & Fever Relief Day & Night Multi-Symptom.
Upper respiratory-tract disorders.

Comtrex Hot Flu Relief *Bristol-Myers Products, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Comtrex Maximum Strength Night-time Cold & Cough *BMS, USA.*
⊗Dextromethorphan (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Comtrex Maximum Strength Sore Throat *BMS, USA.*
Paracetamol (p. 115·1).
Sore throat.

Comtrex Multi-Symptom Deep Chest Cold *BMS, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Comtrex Sinus & Nasal Decongestant *BMS, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Comtrix *Comed, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Comtrix-O *Comed, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Comtro *Combiphar, Indon.*
Clarithromycin (p. 266·2).
Bacterial infections.

Comtus *Comed, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); menthol (p. 2553·2).

Comtusi *Combiphar, Indon.*
Oxomemazine (p. 637·1); guaifenesin (p. 1666·2).
Cough.

Comvax *CSL, Austral.; MSD, Mex.; MSD, NZ; MSD, Singapore; Merck, USA.*
A haemophilus influenzae and hepatitis B vaccine (p. 2388·1).
Active immunisation.

Comvine *Alkem, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Comvit FA *Scheele, Philipp.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); ferrous fumarate (p. 2060·3).
Anaemias.

Comvita C *Interbat, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Nutritional supplement.

Comvita C Plus *Interbat, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Nutritional supplement.

Comvufen *Precimex, Mex.*
Phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias; pre-eclampsia.

Comxicla *Indchemie, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Comxin *Scheele, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Comxytocin *Rotexmedica, Philipp.*
Oxytocin (p. 2143·1).
Postpartum atony; postpartum hemorrhage; labour induction; missed abortion.

Comzid *Comed, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Comzid-M *Comed, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Con Con *Hua, Thai.*
Salicylic acid (p. 1719·1); liquefied phenol (p. 1763·3).
Corns; warts.

Conacid *Purissimus, Arg.*
Folic acid (p. 2063·1).
Anaemias; prevention of neural tube defects in pregnancy; folate deficiency.

Conacort *Geolab, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3).

Conac-P *Constant, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Conac-PT *Constant, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tramadol (p. 139·2).

Conaid *Utopian, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Conal *Cypress, USA.†*
Chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Nasal congestion.

Conamed *Bajamed, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Conamic *Pharmasant, Thai.*
Mefenamic acid (p. 85·3).
Pain; inflammation; musculoskeletal and joint disorders.

Conamid *Flamingo, Philipp.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Conamvag *Micro, Mex.*
Secnidazole (p. 947·3).

Conan *Mitsubishi Tanabe, Jpn.*
Quinapril hydrochloride (p. 1480·2).
Hypertension.

Conart *Advance, Malaysia.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Conatab *Brown & Burk, Philipp.†*
Ketoconazole (p. 585·3).
Fungal infections.

Conaz *Wockhardt, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Conazine *Condrugs, Thai.*
Perphenazine (p. 1095·3).
Anxiety; nausea and vomiting.

Conazol
Note: this name may be used for preparations of different composition.
Alet, Gr.
⊗Miconazole nitrate (p. 589·1); fluprednidene acetate (p. 1637·3).
Infected skin disorders.

Brasterapica, Braz.; Liomont, Mex.
Ketoconazole (p. 585·3).
Fungal infections.

Conazole *DHA, Hong Kong; DHA, Singapore.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Conbo-BC *Marching, Hong Kong.†*
Vitamins; lysine (p. 2079·3).

Conbol *Almet, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Conbriza *Pfizer, Cz.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Neth.; Wyeth, Pol.; Wyeth, Spain; Pfizer, Switz.*
⊗Bazedoxifene acetate (p. 2256·1).
Osteoporosis.

Wyeth Lederle, Port.
⊗Bazedoxifene (p. 2256·1).
Osteoporosis.

Concardio *Sigma, Braz.*
⊗Bisoprolol (p. 1325·3).

Concatag *Lafedar, Arg.*
Neomycin sulfate (p. 330·1).
Bacterial eye infections.

Concavit *Wallace Mfg Chem., UK.*
Vitamins.

Conceive Pregnancy *Quidel, USA.*
Pregnancy test (p. 2596·1).

Conceive Well Gold *Blackmores, Austral.*
Vitamins; minerals; fish oil (p. 1460·3).
Dietary supplement to aid conception.

Concentrado Acido *Reccius, Chile.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); acetic acid (p. 2426·3); glucose (p. 2068·3).
Haemodialysis.

Concentrado Basico *Reccius, Chile.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1).
Haemodialysis.

Concentrated Milk of Magnesia-Cascara *Roxane, USA.†*
Magnesium hydroxide (p. 1857·2); cascara (p. 1826·1).

Conceplan M *Pfizer, Ger.*
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
Combined oral contraceptive.

Concepnor *Neo Quimica, Braz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Concept *Sea-Band, UK.*
Pregnancy test (p. 2596·1).

Conceptio *Granions, Mon.*
Vitamins; minerals; fish oil (p. 1460·1).
Dietary supplement to improve fertility.

Concerta *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Alza, China; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; McNeil Pharmaceutical, USA; Janssen-Cilag, Venez.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Conchae comp. *Weleda, UK.*
Conchae (p. 1824·3); oak bark (p. 2574·1).
Homoeopathic preparation.

Concid *Nitro Organics, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Concid-DM *Nitro Organics, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Concid-DSR *Nitro Organics, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Conciluk *Kendrick, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular dysfunction; nephropathy; heart failure.

Concize *Indoco, India.*
Fluconazole (p. 578·2).
Fungal infections.

Concor *Merck Serono, Arg.; Merck, Austria; Merck, Braz.; Merck, Chile; Merck Serono, China; Merck, Cz.; Merck Serono, Ger.; Merck, Gr.; Merck, Hong Kong; Merck, Hung.; Merck, India; Merck, Indon.; Merck, Israel; Bracco, Ital.; Merck Serono, Malaysia; Merck, Mex.; Merck, Pol.; Merck, Port.; Nycomed, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Switz.; Merck, Thai.; Santa, Turk.; Merck, Ukr.; Takeda, Ukr.; Merck, Venez.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure; arrhythmias; ischaemic heart disease.

Concor Cor *Merck, Cz.; Merck, Hung.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Concor Plus *Merck Serono, Arg.; Merck, Austria; Merck Serono, Ger.; Merck, Hung.; Merck, Port.; Merck, Switz.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Concor-AM *Merck, India.*
⊗Amlodipine besilate (p. 1304·1); bisoprolol fumarate (p. 1325·3).

Concorda *Airflow, NZ.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Concore *Merck, Philipp.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure; hypertension.

Concorz *Sandoz, Austral.†*
Sertraline hydrochloride (p. 448·1).
Depression.

Conda *Beacons, Singapore.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).

Condep *CCM, Malaysia.*
Medroxyprogesterone acetate (p. 2288·1).
Endometrial cancer; renal cancer; endometriosis; breast cancer; progestogen-only injectable contraceptive.

Condiabet *Armoxindo, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Condiuren *Gentili, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Condral
Note: this name may be used for preparations of different composition.
SPA, Ital.
A heparinoid (p. 1401·1).
Osteoarthritis of the knee and hip.

SPA, Cz.†; SPA, Pol.
Chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Condress *Abiogen, Ital.*
Collagen (p. 2483·2).
Cicatrisation of wounds and skin ulcers.

Condroflex *Zodiac, Braz.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis.

Condronac *Sandoz, Port.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Condrorexil *Amnol, Ital.*
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3).
Joint disorders.

Condrosan *Bioiberica, Spain.*
Chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Condrosulf *Sanova, Austria; Labomed, Chile; IBSA, Cz.; IBSA, Hung.; IBSA, Ital.; CORNE, Mex.; IBSA, Port.†; Angelini, Spain; IBSA, Switz.*
Chondroitin sulfate (p. 2476·1).
Osteoarthritis; degenerative joint disorders.

Conducil *Dollder, Venez.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; myocardial infarction.

Conductasa *Teofarma, Spain.*
Pyridoxine oxoglurate (p. 2105·3).
Vitamin B6 deficiency.

Condyline *Nycomed, Austral.; Canderm, Canad.; Galderma, Denm.; Galderma, Fin.; Astellas, Fr.; Nycomed, Hung.; Elder, India; Nycomed, Irl.; Astellas, Ital.; Astellas, Neth.; Galderma, Norw.; CSL, NZ; Astellas, Pol.; Astellas, Port.†; Astellas, Rus.; Galderma, Swed.; Takeda, Switz.; Ardern, UK.*
Podophyllotoxin (p. 1717·1).
Anogenital warts.

Condylox *Nycomed, Austria; Nycomed, China; Wolff, Ger.; Nycomed, Israel; Watson, USA.*
Podophyllotoxin (p. 1717·1).
Anogenital warts.

Conébilox *Negma, Fr.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Conegra *Euro Lifecare, Ukr.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Conervin *Centrum, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Conest *VHB, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Conex Cold & Allergy *Llorens, USA.†*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Conex-B *Constant, India.*
Vitamin B substances (p. 2102·3).

Conexine
Note: this name may be used for preparations of different composition.
Beta, Arg.
Memantine hydrochloride (p. 393·1).
Mental function impairment; spasticity; Alzheimer's disease.

Nolver, Venez.
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Confal *Lupin, India.*
Mefloquine (p. 657·1).
Malaria.

Confer *Merck, Chile.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement.

Conferma 3 Plus *Sanofi-Aventis OTC, Ital.*
Pregnancy test (p. 2596·1).

Confetti Lassativi C M *Giuliani, Ital.*
Senna (p. 1885·1); boldo (p. 2458·3); cascara (p. 1826·1).
Constipation.

Confetto CM
Note: this name may be used for preparations of different composition.
Falqui, Ital.
Bisacodyl (p. 1821·1).
Constipation.

Confez-3 *Shreya, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Confiance *Wassen, UK.*
Vitamins; minerals.

Confiare Prevent *Medley, Braz.*
Chamomile (p. 2474·1); zinc oxide (p. 1729·1).
Dry skin.

Confidelle Progress *Bouty, Ital.*
Pregnancy or fertility test (p. 2596·1).

Confident *GSK, Braz.*
Sodium monofluorophosphate (p. 2091·3).

Confidex *CSL, Belg.; CSL, Fin.; CSL, Norw.; CSL, Swed.*
Factor VIII inhibitor bypassing fraction (p. 1149·2).
Haemorrhagic disorders.

Confido *Himalaya Herbal, India.*
⊗Rauwolfia serpentina (p. 1485·1); tribulus terrestris (p. 2633·3).
Erectile dysfunction.

Himalaya, Ukr.†
⊗Orchis mascula (p. 2576·3); asteracantha longifolia; lactuca serriola; dolichos pruriens; suvarnavanga; rauwolfia serpentina (p. 1485·1); argyreia speciosa; tribulus terrestris (p. 2633·3); leptadenia reticulata; parmelia perlata.
Ejaculation disorders.

Confirm *Durex, Canad.†*
Pregnancy test (p. 2596·1).

Confit
Note: this name may be used for preparations of different composition.
Concept, India.
Vitamins; minerals.

Ranbaxy, Austria.
⊗Verapamil hydrochloride (p. 1522·1); triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Conflu *East India Pharma, India.*
Fluconazole (p. 578·2).
Fungal infections.

Confludin N *Truw, Ger.*
Crataegus (p. 2488·1); convallaria majalis (p. 2486·2); selenicereus grandiflorus (p. 2473·2); urginea maritima (p. 1677·3); spigelia anthelmia (p. 2621·3).
Homoeopathic preparation.

Confobos *Smaller, Spain.†*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Conforgel *Grin, Mex.*
Carbomer (p. 2173·3).
Dry eyes.

Conformal *Ivax, Arg.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; neuralgias.

Conformin *Concertina, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Confort *Sunstone, China.*
Econazole nitrate (p. 577·3).
Vaginal candidiasis; trichomoniasis.

Confortel *Forder, Arg.*
Levomenol (p. 2544·1); pilewort (p. 2590·3).
Skin disorders.

Confortid *Actavis, Denm.; Actavis, Norw.†; Actavis, Swed.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain; gout; renal and biliary colic.

Confortin *Solas, Indon.*
Calamine (p. 1697·2); dexpanthenol (p. 2582·2).
Nappy rash; dry skin; skin irritation; minor wounds.

Confosept Zuurstofwater *Conforma, Belg.*
Hydrogen peroxide (p. 1755·2).
Disinfection.

Congen *Jean-Marie, Philipp.*
Crotamiton (p. 1699·2).
Pruritus; insect bites and stings; scabies.

Congescor *Merck, Ital.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Congest *Trianon, Canad.*
Conjugated oestrogens (p. 2260·1).
Oestrogen therapy.

Congest Aid *Zee, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Congesta D M *Trimarc, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Congestac *Ascher, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Congestaid *Zee, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Congestant *Rugby, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Congestex *Pediapharm, Chile; Recalcine, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); noscapine (p. 1670·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Congestril (Reformulated) *Roddensers, Philipp.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold symptoms.

Congestyl *Meyer, India.*
Syrup: Chlorphenamine (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Meyer, India.
Tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Congex *Buxton, Arg.*
Naproxen (p. 98·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Congox *Wermar, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Conidrin *Uniao Quimica, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); mepyramine maleate (p. 635·1).
Nasal congestion.

Conidrin Baby *Uniao Quimica, Braz.*
Sodium chloride (p. 1795·1).

Conidrin Salina *Uniao Quimica, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Coniel *Kirin, China; Kyowa, Jpn; Kyowa Hakko, Philipp.; Deva, Turk.*
Benidipine hydrochloride (p. 1316·1).
Hypertension; angina pectoris.

Conisan A *Vitorgan, Ger.†*
Fetal bovine extracts: bulbus oculi (p. 2444·1); vasa; placenta (p. 2444·1); lens cristallina; retina; choroidea; corpus vitreum; nervus opticus; cortex cerebri (p. 2444·1); diencephal. (p. 2444·1); aesculinum (p. 2431·2).
Homoeopathic preparation.

Conisan B *Vitorgan, Ger.†*
Fetal bovine extracts: cornea (p. 2444·1); placenta (p. 2444·1); conjunctiva; nasopharyngeal mucosa (p. 2444·1); glandula thymi (p. 2631·1); lien (p. 2444·1); nodus lymphaticus; glandula suprarenalis (p. 2444·1); retina; choroidea; nervus opticus; lens cristallina; corpus vitreum; cortex cerebri (p. 2444·1); diencephal. (p. 2444·1); aesculinum (p. 2431·2).
Homoeopathic preparation.

Conium Complexe No 36 *Lehning, Fr.†*
⊗Conium (p. 2524·3); hydrastis (p. 2528·1); chelidonium (p. 2522·2); kreosotum (p. 1659·3); arsenicum album (p. 2448·1); onopordon; argentum nitricum (p. 2615·3); strychninum (p. 2623·2); cadmium sulfuricum (p. 2463·3); dioscorea (p. 2648·1).
Homoeopathic preparation.

Conjoint *Medley, India.*
Dimethyl sulfone (p. 2493·3); glucosamine (p. 2515·3); chondroitin (p. 2476·1).

Conjonctyl *Sedifa, Mon.*
Sodium methylsilanetriol salicylate.
Skin contour defects.

Conjugase *Elder, India.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; primary ovarian failure; prostatic cancer; osteoporosis.

Conjuncain-EDO *Mann, Ger.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Conjunctilone *Allergan, Port.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Conjunctilone-S *Allergan, Port.*
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Conjunctisan-AN *Vitorgan, Ger.†*
Bulbus oculi fetal (p. 2444·1); lens; vasa fetal; placenta (p. 2444·1); retina; nervus opticus; chorioidea; corpus vitreum; cortex cerebri; diencephalon (p. 2444·1); aesculinum (p. 2431·2).
Homoeopathic preparation.

Conjunctisan-BN *Vitorgan, Ger.†*
Cornea (p. 2444·1); conjunctiva; mucosa nasopharyngeal; thymus fetal (p. 2631·1); lien fetal (p. 2444·1); nodus lymphaticus; glandula suprarenalis; placenta mat. (p. 2444·1); retina; nervus opticus; lens; corpus vitreum; chorioidea; cortex cerebri; diencephalon (p. 2444·1); aesculinum (p. 2431·2).
Homoeopathic preparation.

Conlax *Bliss, India; Continental-Pharm, Thai.*
Bisacodyl (p. 1821·1).
Constipation.

Conludag *Pfizer, Norw.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Conmag *Pharmasant, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); kaolin (p. 1850·1); menthol (p. 2553·2).
Gastric hyperacidity; peptic ulcer.

Conmana *Beta, China.*
Icotinib hydrochloride.
Non-small cell lung cancer.

Conmel *Farmasa, Braz.; Lafi, Chile; Sanofi-Aventis, Mex.; Sanofi-Aventis, Venez.*
Dipyrone (p. 53·3).
Fever; pain; inflammation.

Conmitrip *Condrugs, Thai.*
Amitriptyline (p. 401·1).
Depression; pain.

Conmy *Taiwan Biotech, Malaysia; Taiwan Biotech, Philipp.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Conmycin *Armoxindo, Indon.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Connettivina *Fidia, Hong Kong; Fidia, Ital.*
Sodium hyaluronate (p. 2526·2).
Burns; wounds; ulcers; skin irritation.

Connettivina Plus *Fidia, Ital.*
Sodium hyaluronate (p. 2526·2); sulfadiazine silver (p. 362·3).
Wound; burns; skin ulceration.

Connex *Rayere, Mex.*
Oxeladin citrate (p. 1671·2); ambroxol hydrochloride (p. 1654·3).
Cough; respiratory-tract disorders with increased secretions.

Connivea *Progen, Ital.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); polyphenols; vitamin E (p. 2119·1).
Eye disorders.

Conoran *Ranbaxy, S.Afr.*
Pantoprazole (p. 1875·3).

Co-Normoten *Torrent, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Nortivan *Richter, Pol.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Conotab *Scort, Philipp.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; allergic rhinitis; nasal congestion.

Conotrane *Astellas, UK.*
Benzalkonium chloride (p. 1737·1); dimeticone (p. 2209·3).
Barrier cream.

Co-Novasan *Novartis, Port.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Conovate-N *Community Pharmacy, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Conoxia *Linde Gas, Cz.; AGA, Denm.; AGA, Fin.; Linde Gas, Ger.; Linde Gas, Neth.; AGA, Norw.; Abello, Spain.*
Oxygen (p. 1799·3).
Hypoxia; cluster headache; adjunct in anaesthesia; hyperbaric oxygen therapy.

Conpin *TAD, Cz.†; TAD, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Conpremin *Wyeth, Chile.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Conpremin Pak *Wyeth, Chile.†*
White tablets, conjugated oestrogens (p. 2260·1); blue tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Conpremin Pak Plus *Wyeth, Chile.†*
28 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Conpres
Note: this name may be used for preparations of different composition.
Torrent, India.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

Ranbaxy, Hung.†
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Conpride *Concertina, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Conpride M *Concertina, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Conprim *Condrugs, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Conquer *Bausch & Lomb, China.*
Fluconazole (p. 578·2).
Fungal eye infections.

Conquista *Bayer, Gr.*
Calcium carbonate (p. 1824·3); heavy magnesium carbonate (p. 1856·2).

Conram *Concertina, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Conram H *Concertina, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Conranin *Armoxindo, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastritis; pathological hypersecretory disorders; gastro-oesophageal reflux.

Conrax *Fada, Arg.*
Chlorpromazine (p. 1045·2).
Psychoses; nausea and vomiting; premedication.

Conray *Mallinckrodt, Arg.; Covidien, Austral.; Tyco, Canad.; Covidien, Irl.; Mallinckrodt, UK; Mallinckrodt, USA.*
Meglumine iotalamate (p. 1592·2).
Radiographic contrast medium.

Consac *Ashford, Philipp.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Consec *Jagsonpal, India.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal hyperacidity; dyspepsia.

Consil *Barnes Hind, Arg.†*
Polyvinyl alcohol (p. 2204·2); chlorhexidine gluconate (p. 1743·3).
Disinfecting and wetting solution for gas permeable contact lenses.

Consil Clean *Barnes Hind, Arg.†*
Miranol; norfox.
Cleaning of gas permeable contact lenses.

Consinut *Continental-Pharm, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; nasal congestion.

Consol *Samson-Med, Rus.*
Potassium chloride (p. 1793·2); calcium gluconate (p. 1783·3); magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); lidocaine hydrochloride (p. 1988·2).
Cardioplegia in open-heart surgery.

Constante *Uniao Quimica, Braz.*
Alprazolam (p. 1035·2).
Anxiety.

Constella *Almirall, Neth.; Almirall, UK.*
Linaclotide (p. 1853·1).
Irritable bowel syndrome.

Consticare *Waves, India.*
Ispaghula (p. 1849·1); senna (p. 1885·1).

Constilac *Alra, USA.†*
Lactulose (p. 1850·3).
Constipation.

Constilax *Bros, Gr.*
Norfloxacin (p. 333·3).
Urinary tract infections.

Constipal *Plough, Port.†*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Respiratory-tract congestion.

Constipen *Combiphar, Indon.*
Lactulose (p. 1850·3).
Constipation; encephalopathy.

Constriction *Neo Quimica, Braz.*
Dopamine hydrochloride (p. 1367·2).

Constulose *Barre-National, USA.*
Lactulose (p. 1850·3).
Constipation.

Consu *Sunward, Singapore.*
Salicylamide (p. 129·2); caffeine (p. 1203·3).

Consudine *Condrugs, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Nasal congestion; hypersensitivity reactions; cold symptoms; rhinitis.

Consulf *Advance, Malaysia; Advance, Singapore.†*
Chondroitin sulfate (p. 2476·1).
Dietary supplement; osteoarthritis.

Consumonit *Remedina, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Consupren *Galena, Rus.†; Galena, Thai.†; SPB, Thai.†*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; rheumatoid arthritis; uveitis; nephrotic syndrome; lupus; polymyositis; psoriasis; auto-immune disorders.

Contac
Note: this name may be used for preparations of different composition.
GSK, Chile.†
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Contac AM *GSK, Mex.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Contac C *GSK Consumer, Mex.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Contac Cold Chest Congestion *Meda, Canad.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Contac Cold + Flu *Meda, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Contac Cold + Flu Day & Night *Meda, USA.*
Day tablets, phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); night tablets, phenylephrine hydrochloride; paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Contac Cold & Flu Non-Drowsy Maximum Strength *Meda, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Contac Cold & Sore Throat Non Drowsy *GSK Consumer, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Contac Complete Cough, Cold & Flu *GSK Consumer, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; cough.

Contac Complete Cough Cold and Flu Day & Night *GSK Consumer, Canad.†*
⊗Yellow caplets, pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); blue caplets, diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride; paracetamol.
Cold symptoms.

Contac Complete Cough Cold & Flu Non Drowsy *GSK Consumer, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Contac Cough and Sore Throat *GSK Consumer, Canad.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; sore throat.

Contac Day & Night Allergy Sinus *SmithKline Beecham Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2).

Contac Day and Night Cold & Flu Caplets *SmithKline Beecham Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Coughs and cold symptoms.

Contac Erkältungs-Trunk *GSKConsumer, Ger.†*
Paracetamol (p. 115·1).
Fever; pain.

Contac Erkältungs-Trunk Forte *GSK Consumer, Ger.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Contac 12 Hour Allergy *SmithKline Beecham Consumer, USA.*
Clemastine fumarate (p. 622·3).

Contac Night Cough *GSK Consumer, Canad.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Contac Non Drowsy *GSK, Singapore; GSK Consumer, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Contac NT *GSK, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; allergic rhinitis.

Contac Pain *Inpac, Thai.*
Methyl salicylate (p. 92·1); eugenol (p. 2501·2); menthol (p. 2553·2).

Contac PM *GSK, Mex.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Contac Severe Cold *GSK, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Contac Ultra *GSK, Mex.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Rhinitis.

Contac-CC *GSK, India.*
Phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2).
Nasal congestion; cough; sinusitis; influenza symptoms.

Contact
Note: this name may be used for preparations of different composition.
GSK Consumer, Port.
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.
Magma, Canad.
Chloroxylenol (p. 1748·2).

Contagrin *Grin, Mex.†*
Solution for contact lens care.

Contalax *Omega, Fr.; Fischer, Israel.*
Bisacodyl (p. 1821·1).
Constipation.

Contalgin *Pfizer, Denm.*
⊗Morphine sulfate (p. 92·3).
Pain.

Contan *Novartis, Ukr.†*
Entacapone (p. 901·2).
Parkinsonism.

Contasoft *Grin, Mex.†*
Solution for contact lens care.

Contem *Ahimsa, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Contex *Tripharma, Turk.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); oxolamine citrate (p. 1671·2).
Cold and influenza symptoms; rhinitis; sinusitis.

Contexine *Ranbaxy, Pol.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Conthel *Candor, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Contiflo *Ranbaxy, Braz.; Ranbaxy, India; Ranbaxy, UK.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Contiflo-OD-F *Sun, India.*
Tamsulosin hydrochloride (p. 2369·1); finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Contigen *Baxter, NZ; Bard, UK.*
Bovine dermal collagen (p. 2483·2).
Urinary incontinence.

Conti-Marvelon *Schering-Plough, Chile.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets; ethinylestradiol (p. 2275·3); 2 tablets, inert.
Biphasic oral contraceptive.

Continex *Baliarda, Arg.*
Darifenacin hydrobromide (p. 2354·2).
Bladder hyperactivity.

Continukit *Pascual, Philipp.*
1 Tablet, ethambutol hydrochloride (p. 296·1) (Ethonah); 1 tablet, isoniazid (p. 311·2) (Nyadin); 1 capsule, rifampicin (p. 350·3) (Ricyn).
Tuberculosis.

Continukit Plus *Pascual, Philipp.†*
1 Tablet, ethambutol hydrochloride (p. 296·1); 1 tablet, isoniazid (p. 311·2); 1 capsule, rifampicin (p. 350·3); 1 tablet, vitamins; minerals (Vitalivin-E).
Tuberculosis.

Continupack *Pascual, Philipp.†*
1 Tablet, isoniazid (p. 311·2) (Nyadin); 1 capsule, rifampicin (p. 350·3) (Ricyn).
Tuberculosis.

Continuum Sunscreen *Continuum, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Continuum, Canad.
SPF 25: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Continuum Unifying *Continuum, Canad.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).

Contix *Lek-Am, Pol.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Contour *Bayer, Chile; Bayer Diabetes, UK.*
Test for glucose in blood (p. 2516·3).
Formerly known as Ascensia Microfill.

Contour TS *Bayer Diabetes Care, Arg.*
Test for glucose in blood (p. 2516·3).

Contracep *Sigma, Braz.; TNP, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Contraceptin T *Nizhpharm, Rus.*
Hydroxyquinoline sulfate (p. 2530·1); boric acid (p. 2459·3); tannic acid (p. 2625·2).
Contraceptive.

Contracer *Instituto Tecnologico PET, Port.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide agent for detection of malignant neoplasms by positron emission tomography.

Contracid
Note: this name may be used for preparations of different composition.
Farma-Projekt, Pol.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Umedica, Philipp.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Farma-Projekt, Denm.†
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Contracné *Bailleul, Fr.*
Isotretinoin (p. 1706·2).
Acne.

Contra-Coff *Universal, S.Afr.†*
Pholcodine (p. 1675·1); squill (p. 1677·3).
Cough.

Contractubex *Phoenix, Arg.; Merz, Austria; Biolab Sanus, Braz.; Merz, China; Merz, Cz.; Merz, Ger.; Pharmacare, Gr.; Merz, Hong Kong; Merz, Hung.; Win-Medicare, India; Merz, Mex.; Merz, Philipp.; Merz, Pol.; Merz, Rus.; Merz, Switz.; Assos, Turk.; Merz, Ukr.*
Onion (p. 2575·2); heparin sodium (p. 1396·3); allantoin (p. 1693·1).
Scars; keloids; contracture of joints and tendons.

Contraflux *Actavis, Switz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Contral *Corsa, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Contralg *Remedina, Gr.*
Diclofenac sodium (p. 48·3).

Contralmor *Laboratorios Chile, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); lidocaine (p. 1988·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Contralum Ultra *Almirall, Neth.*
Enzacamene (p. 1703·2); avobenzone (p. 1695·1); sodium 2-phenyl-1*H*-benzimidazole-5-sulfonate (p. 1703·1).
Sunscreen; photosensitive skin disorders.

Contram *Armoxindo, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Contramal *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Fr.; Grunenthal, Hung.; Teva, Hung.; Piramal, India; Formenti, Ital.; Abdi, Turk.*
Tramadol hydrochloride (p. 139·2).
Pain.

Contramutan *Cassella-med, Ger.*
Echinacea angustifolia (p. 2498·1); aconitum (p. 2428·3); belladonna (p. 2453·3); eupatorium perfoliatum (p. 2459·1).
Homoeopathic preparation.

Contraneural Paracetamol/Codeine *Pfleger, Ger.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Contrastin *Dabur, India.*
Sodium amidotrizoate (p. 1581·3); meglumine (p. 2550·3); iodine (p. 2336·3).

Contratemp *Mugi, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Contrathion *IFET, Gr.*
Pralidoxime chloride (p. 1571·1).
Organophosphorus poisoning.

Sanofi-Aventis, Arg.; SERB, Fr.; Sanofi-Aventis, Ital.
Pralidoxime metilsulfate (p. 1571·2).
Organophosphorus poisoning.

Sanofi-Aventis, Braz.; Keymen, Turk.†
Pralidoxime mesilate (p. 1571·1).
Organophosphorus poisoning.

Contravert B_6 *Sanochemia, Austria.†*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3).
Vertigo; vomiting; motion sickness.

Contraxen *Liferpal, Mex.*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).

Contre-Coups de l'Abbé Perdrigeon *Pionneau, Fr.*
Aloes (p. 1816·1).
Soft-tissue injury; skin disorders; superficial wounds.

Contre-Douleurs C *Wild, Switz.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Cold symptoms; fever.

Contre-Douleurs IL *Wild, Switz.*
Ibuprofen lysine (p. 68·3).
Pain; fever.

Contre-Douleurs P *Wild, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Contre-Douleurs plus *Wild, Switz.*
Aspirin (p. 22·2); caffeine (p. 1203·3). Aluminium hydroxide (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Contreet *Coloplast, Belg.†; Coloplast, Ger.†; Coloplast, UK.*
Hydrocolloid hydroactivated silver dressing (p. 2615·1).
Burns; ulcers; wounds.

Contrex *Supra Ferbindo, Indon.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Formerly contained paracetamol, phenylpropanolamine hydrochloride, chlorphenamine maleate, and caffeine.
Cold and influenza symptoms.

Contrexyn *Supra Ferbindo, Indon.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Contril *US Pharmacia, Pol.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Contrin *Geneva, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); intrinsic factor (p. 2534·2); vitamin B_{12} substances (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Contriven *Biopharma, Ukr.*
Aprotinin (p. 1133·2).
Hyperfibrinolysis.

Control
Note: this name may be used for preparations of different composition.
Bayer, Ital.
Lorazepam (p. 1080·3).
Nervous disorders; sedative; convulsions.

Lark, India.
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Bio-Sante, Canad.†
Cascara (p. 1826·1); sennosides A and B (p. 1885·2).
Constipation.

Farmasa, Braz.†
Poliglusam (p. 2593·2); fruit oligosaccharides (p. 2508·1); sodium ascorbate (p. 2111·1); citric acid (p. 2480·3).

Control Acne *Pharmalab, Arg.*
Glycolic acid (p. 1704·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); resorcinol (p. 1718·3); camphor (p. 2466·2); aloe (p. 1693·2); calendula (p. 2465·2).
Acne.

Control K *Merck Serono, Arg.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Controlip *Abbott, Arg.; Abbott, Mex.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Controller *Alta Care, Ital.*
St John's wort (p. 449·1); crataegus (p. 2488·1); kava (p. 2537·3); passion flower (p. 2584·1); lavender oil (p. 2541·1); St John's wort oil (p. 449·1); verbena oil; neroli oil (p. 2568·3).
Nervous disorders.

Controloc *Nycomed, Cz.; Sanofi-Aventis, Gr.; Nycomed, Hung.; Nycomed, Malaysia; Nycomed, Rus.; Nycomed, S.Afr.†*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; pathological hypersecretory disorders.

Nycomed, Israel; Nycomed, Pol.; Takeda, Singapore; Takeda, Thai.; Nycomed, Ukr.
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; pathological hypersecretory disorders; heartburn.

Controloc Control *Nycomed, Irl.; Nycomed, Neth.; Nycomed, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Controlpros *Rontag, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

ControlRx *Omnii, USA.*
Sodium fluoride (p. 2089·2); dimeticone (p. 2209·3); poloxamer 407 (p. 2202·1).
Dental caries prophylaxis.

Controlvas *Amdipharm, Spain.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Controsec *Embiotic, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Controx *Concept, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Contrycal *Teva, Ukr.*
Aprotinin (p. 1133·2).
Pancreatitis; shock; hyperfibrinolytic haemorrhage.

Contrykal *Pliva, Rus.*
Aprotinin (p. 1133·2).
Pancreatitis; haemorrhage.

Contumax
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Macrogol 3350 (p. 2547·3).
Constipation; bowel evacuation.

Casen Fleet, Spain.
Sodium picosulfate (p. 1887·2).
Constipation.

Contus *Stedman, India.*
Paediatric linctus; tablets: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Stedman, India.
Paediatric oral drops: Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Contus-650 *Stedman, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Contus Plus *Stedman, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Contusin
Note: this name may be used for preparations of different composition.
Herbamed, Switz.
Symphytum (p. 2484·2); calendula officinalis (p. 2465·2); arnica montana (p. 2447·2); echinacea purpurea (p. 2498·1).
Homoeopathic preparation.

Lacer, Spain.
Diethylamine salicylate (p. 51·3); aesculus (p. 2431·2).
Musculoskeletal, joint, and soft-tissue disorders.

Contuxin *Continentales, Mex.†*
Oxolamine (p. 1671·2).
Cough.

Contylan *Lejal, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); calcium carbonate (p. 1824·3).
Peptic ulcer; gastritis; gastric hyperacidity; gastro-oesophageal reflux; dyspepsia.

Conucol *Armoxindo, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Convaclon *Baroda, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Conva-cyl Ho-Len-Complex *Liebermann, Ger.*
Cactus (p. 2473·2); camphora (p. 2466·2); china (p. 2478·3); convall. maj. (p. 2486·2); crataegus (p. 2488·1); digital. purp. (p. 1352·3); ferrum met. (p. 2073·1); kal. carbon. (p. 2595·2); strophantus grat..
Homoeopathic preparation.

Convafort *Herbapol Wroclaw, Pol.*
Convallaria (p. 2486·2).
Circulatory disorders.

Convalemin *Cipla, Cz.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Convales *Nouveau, India.*
Glutamine (p. 2070·3).

Convalis *Lekko, Rus.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Convallocor *Hevert, Ger.*
Adonis vernalis (p. 2431·1); convallaria majalis (p. 2486·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Convallysan M *Hanosan, Ger.*
Convallaria majalis (p. 2486·2); apocynum cannabinum; arnica montana (p. 2447·2); adonis vernalis (p. 2431·1); crataegus (p. 2488·1).
Homoeopathic preparation.

Convastabil *Klein, Ger.*
Convallaria (p. 2486·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Conveen Protact *Coloplast, Fr.†*
Barrier cream.

Convenil *Demo, Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Converten *Gentili, Ital.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; asymptomatic left-ventricular dysfunction.

Khandelwal, India.
Enalapril (p. 1371·1).
Hypertension; heart failure.

Convertin *MSD, Israel.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Convifer con Hierro *Degorts, Mex.*
Vitamins; iron (p. 2073·1); lysine (p. 2079·3).
Tonic.

Conviron Forte *Ranbaxy, India.*
Cyanocobalamin (p. 2107·2); ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); zinc (p. 2126·1).

Conviron-TR *Ranbaxy, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Convita *Allenge, India.*
Iron (p. 2073·1); vitamins; zinc (p. 2126·1).

Convits *Continental-Pharm, Thai.*
Vitamin B substances (p. 2102·3); dried yeast (p. 2125·2).
Vitamin B deficiency.

Convolsil *Condrugs, Thai.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder; status epilepticus.

Convoy *Corona, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).

Convulex
Note: this name may be used for preparations of different composition.
Gerot, Austria; Nycomed, Belg.; Gerot, Cz.; Lundbeck, Ger.; Gerot, Hung.; Gerot, Pol.; Lannacher, Rus.; Nycomed, S.Afr.; Gerot, Singapore; Orion, Switz.; Liba, Turk.; Pharmacia, UK.
Valproic acid (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy; febrile convulsions; bipolar disorder; migraine.

Meyer, Venez.
Carbamazepine (p. 512·2).
Epilepsy; neuralgia.

Convuline *Bayer, Fr.*
Ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Convulsan
Note: this name may be used for preparations of different composition.
Actavis, Rus.
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Sanval, Braz.
Carbamazepine (p. 512·2).
Epilepsy.

Convulsofin *AWD, Ger.; Teva, Rus.; Teva, Ukr.*
Calcium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Convulzine *Universal, Hong Kong.†*
Carbamazepine (p. 512·2).

Conysmin *Raam, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Conzace *Biomedis, Philipp.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).
Nutritional supplement.

Conzila *Leontik, Gr.; Medinova (Μεντινοβα), Gr.*
Piroxicam (p. 125·3).
Inflammatory disorders.

ConZip *Vertical, USA.*
Tramadol hydrochloride (p. 139·2).
Pain.

Con-Z-Lin *Sunward, Singapore.*
Salicylamide (p. 129·2); caffeine (p. 1203·3).

Cool Mint Listerine
Note: this name may be used for preparations of different composition.
Pfizer, India.
⊗Benzoic acid (p. 1738·2); alcohol (p. 1733·1); cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Oral hygiene.

Cool Pan *Minova, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cool Rab-It *Minova, India.*
Itopride hydrochloride (p. 1850·1); rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux.

Cool Tears *Raymos, Arg.*
Hypromellose (p. 2189·2).
Eye irritation.

Cool White *Innoderm, Philipp.*
Etiolene plant extracts; vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3).
Natural skin whitening.

Cool Zone D *Minova, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2); simeticone (p. 1886·2).

Coolby Cough *Pharmasant, Thai.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Coolding *Frankin, Hong Kong.†*
Cocillana (p. 1659·2); codeine (p. 40·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3).

Coolips *Mintlab, Chile.*
Cetirizine hydrochloride (p. 619·2).
Nasal congestion; hypersensitivity reactions.

Cool-Joint *Invision, India.*
Oral sachets: Glucosamine (p. 2515·3); calcium (p. 1783·1); mecobalamin (p. 2108·1).

Invision, India.
Tablets: Glucosamine sulfate potassium chloride (p. 2515·3); dimethyl sulfone (p. 2493·3); calcium carbonate (p. 1824·3); manganese (p. 2081·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

CoOlmetec *Daiichi Sankyo, Fr.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coolpep *Invision, India.*
Aluminium hydroxide (p. 1817·2); carmellose (p. 2175·1); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Cooltime *Solitaire, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Coolx *Saviour, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Coop Vitality *Iromedica, Switz.†*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Motion sickness.

Cooperfer *Cooper (Κοπερ), Gr.*
Ferrous sulfate (p. 2062·2).

Copacyl *Arterium, Ukr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Copal
Note: this name may be used for preparations of different composition.
Probiomed, Mex.†
Sulindac (p. 134·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Copal Chest Rub *Guardian, Indon.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Cold and influenza symptoms; nasal congestion; stomach ache; insect bites.

Copalia *Novartis, Cz.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Spain.*
Valsartan (p. 1521·2); amlodipine besilate (p. 1304·1).
Hypertension.

Copalia HCT *Novartis, Cz.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Port.*
⊗Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Copam *Constant, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Copamide *Dey's, India.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Copan *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Copanat *Natco, India.*
Paracetamol (p. 115·1).
Pain; fever.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Copar *Comed, India.*
Metoclopramide hydrochloride (p. 1862·2); paracetamol (p. 115·1).
Migraine.

Copastin *YSP, Malaysia.*
Cloperastine hydrochloride (p. 1659·2).
Cough.

Copator *Tabuk, Hung.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Copaxone *Teva Tuteur, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Biosintetica, Braz.; Teva, Canad.; Teva, Cz.; Teva, Denm.; Teva, Fin.; Teva, Fr.; Teva, Ger.; Teva, Gr.; Teva, Hung.; Teva, Irl.; Teva, Israel; Teva, Ital.; Teva, Mex.†; Teva, Neth.; Teva, Norw.; Sanofi-Aventis, NZ; Teva, Pol.; Sanofi-Aventis, Port.; Teva, Rus.; Teva, S.Afr.; Teva, Spain; Teva, Swed.; Teva, Switz.; Med, Turk.; Teva, UK; Teva, UK; Teva, Ukr.; Teva, USA.*
Glatiramer acetate (p. 2514·3).
Multiple sclerosis.

Cope
Note: this name may be used for preparations of different composition.
Mankind, India.
Cetirizine (p. 619·2).
Hypersensitivity reactions.
Mentholatum, USA.
Aspirin (p. 22·2); caffeine (p. 1203·3). Aluminium hydroxide (p. 1817·2) and magnesium hydroxide (p. 1857·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Cope-D *Mankind, India.*
Ambroxol (p. 1654·3); cetirizine (p. 619·2); phenylephrine (p. 1672·2).

Copegus *Roche, Arg.; Roche, Austria; Roche, Belg.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Genentech, USA.*
Ribavirin (p. 1010·2).
For use with interferon alfa-2a or peginterferon alfa-2a.
Chronic hepatitis C.

Copelia *Bionutre, Arg.*
Amino acids; ipriflavone (p. 1185·3); vitamin B substances (p. 2102·3); zinc (p. 2126·1).
Dietary supplement.

Copercilex *Cooper (Κοπερ), Gr.*
Ampicillin sodium (p. 218·2).
Eye infections.

Coperindo *Ratiopharm, Belg.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Co-Perineva *Pharma-Regist, Hung.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Cophadyl *ICM, Singapore.*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough.

Cophadyl-E *ICM, Singapore.*
⊗Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Cophargel *Community Pharmacy, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Copharmex *Community Pharmacy, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Cophartussin *Community Pharmacy, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough; bronchitis.

Cophekine *Haffkine, India.*
Ammonium chloride (p. 1656·1); menthol (p. 2553·2); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).
Cough.

Cophene No. 2 *Dunhall, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Cophene XP *Dunhall, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Coughs.

Co-Phenylcaine *ENT Technologies, Hong Kong; Faulding, Singapore.*
Lidocaine hydrochloride (p. 1988·2); phenylephrine hydrochloride (p. 1672·3).
Local anaesthesia.

Cophenylcaine *ENT Technologies, Austral.*
Phenylephrine hydrochloride (p. 1672·3); lidocaine hydrochloride (p. 1988·2).
Epistaxis; preparation of nasal mucosa for surgical procedures; aid in upper respiratory-tract investigations.

Cophylac *Valeo, Canad.*
Oral solution: ⊗Normethadone hydrochloride (p. 1670·3); oxilofrine hydrochloride (p. 1463·2).
Cough.

Copidrel *Landson, Indon.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

6-Copin *Ariston, Arg.*
Oral drops; tablets: Hyoscine methobromide (p. 1846·1); chlorpromazine hydrochloride (p. 1045·2); pyridoxine hydrochloride (p. 2105·3); procaine hydrochloride (p. 1994·3).
Vomiting.
Ariston, Arg.†
Injection: Hyoscine methobromide (p. 1846·1); chlorpromazine hydrochloride (p. 1045·2); pyridoxine hydrochloride (p. 2105·3).
Vomiting.

Copinal *Vinas, Spain.*
Zinc acexamate (p. 2427·3).
Peptic ulcer.

Copiron *Microsules, Arg.*
Ibuprofen (p. 68·2).
Fever; pain.

CoPlavix *Sanofi-Aventis, Austral.; Sanofi-Aventis, Israel; Sanofi-Aventis, Thai.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Unstable angina; myocardial infarction; thromboembolism prophylaxis; acute coronary syndrome.
Sanofi-Aventis, Singapore.
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Myocardial infarction; unstable angina.

Coplexina *Sanofi-Aventis, Arg.*
Codergocrine mesilate (p. 389·2).
Cerebrovascular disorders.

Copovan *Hospira, Ital.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Copper-T *Kimia, Indon.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Coppertone *Wainhouse, NZ.*
Lotion SPF 30+: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Balmar, NZ.†
Lotion SPF 15+: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Bug & Sun Adult *Schering-Plough, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); homosalate (p. 1705·1).
Sunscreen.

Coppertone Bug & Sun Kids *Schering-Plough, USA.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octocrilene (p. 1715·2).
Sunscreen.

Coppertone Clear *Schering-Plough, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Continuous *Schering-Plough, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Dry Oil *Schering-Plough, Canad.*
SPF 8: Homosalate (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, Canad.
SPF 10: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Gel *Schering-Plough, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Kids *Schering-Plough, USA.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); homosalate (p. 1705·1); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, USA.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); octocrilene (p. 1715·2).
Sunscreen.
Schering-Plough, Canad.†
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Kids Colorblok *Schering-Plough, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Kids Lotion *Schering-Plough, Canad.*
SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Kids Spray'n Play *Schering-Plough, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Kids Sunblock *Schering-Plough, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Lipkote *Schering-Plough, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Lotion *Schering-Plough, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Moisturizing *Schering-Plough, USA.*
SPF 2: Homosalate (p. 1705·1).
Sunscreen.
Schering-Plough, USA.
SPF 45: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, USA.
SPF 25; SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); homosalate (p. 1705·1); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, USA.
SPF 4; SPF 6; SPF 8; SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Oil-Free *Schering, Canad.†*
SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, Canad.†
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, Canad.†
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Oil-Free Faces *Schering-Plough, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Oil-Free Sunscreen *Schering-Plough, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Spectra 3 *Schering-Plough, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.
Schering-Plough, Canad.†
SPF 50: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Coppertone Sport *Schering-Plough, Canad.*
Lotion SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, Canad.; Schering-Plough, USA.
Lotion SPF 15; SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, USA.
SPF 4; SPF 8; SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Sport Gel *Schering-Plough, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Sport Spray *Schering-Plough, Canad.*
SPF 15: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Spray *Schering-Plough, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Sunblock *Schering-Plough, Canad.†*
SPF 30; SPF 45: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Sunscreen *Schering-Plough, Canad.*
Lotion SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Coppertone Suntan *Schering-Plough, Canad.*
Lotion SPF 4: Octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Coppertone Tan Magnifier *Schering-Plough, USA.*
Gel SPF 4: Ensulizole (p. 1703·1).
Sunscreen.
Schering-Plough, USA.
Lotion SPF 4: Octinoxate (p. 1715·1).
Sunscreen.
Schering-Plough, USA.
SPF 2: Trolamine salicylate (p. 141·2).
Sunscreen.

Coppertone Waterbabies *Schering-Plough, Canad.*
SPF 50; SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.
Schering-Plough, Canad.†; Schering-Plough, USA.
SPF 30; SPF 45: Homosalate (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Co-Prenesa *KRKA, Ukr.*
⊗Perindopril (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Co-Prenessa *KRKA, Hung.; KRKA, Pol.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Coprenessa *KRKA, Denm.; KRKA, Fin.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Copres-M *Obsurge, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Copres-M-20 *Obsurge, India.*
⊗Serrapeptase (p. 2613·3); minerals.

Co-Pressoless *Cifarma, Braz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Pressotec *Teuto, Braz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Prestarium *Servier, Pol.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension; coronary artery disease.

Copriderm *Cadila, India.*
⊗Betamethasone dipropionate (p. 1623·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); sodium lactate (p. 1781·2); urea (p. 1727·3).

Coprim *Community Pharmacy, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Coprin *Smart, S.Afr.*
Aspirin (p. 22·2).

Coprindomid *Arrow, Denm.†*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Coprofen *Community Pharmacy, Thai.*
Ibuprofen (p. 68·2).
Pain; musculoskeletal and joint disorders; fever.

Copsam *Il-Ko, Turk.*
Citalopram hydrobromide (p. 411·1).

Copyrazin *PC India, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Copyrkal *Berlin-Chemie, Ger.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Co-Pyronil *Lilly, Thai.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Coq *Universal Medicare, India.*
Ubidecarenone (p. 2637·1).

Co-Q-10
Note: this name may be used for preparations of different composition.
Merck, Indon.
Cod-liver oil (p. 2056·3); eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); vitamins; ubidecarenone (p. 2637·1).
Tonic; adjunct in cardiac disease.

Coq Forte *Universal Medicare, India.*
Ubidecarenone (p. 2637·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); lycopene (p. 2546·2); selenium (p. 2086·3).

Co.Q.Care *Affy, India.*
Ubidecarenone (p. 2637·1).

Co-Q-Dent *Lupin, India.*
Ubidecarenone (p. 2637·1); betacarotene (p. 2051·1).

Coquelusédal *Elerte, Fr.*
Grindelia (p. 2522·3); gelsemium (p. 2511·2); niaouli oil (p. 2569·1).
Respiratory-tract disorders.

Coquelusédal Nourrissons *Elerte, Fr.*
Grindelia (p. 2522·3); gelsemium (p. 2511·2).

Coquelusédal Paracétamol *Elerte, Fr.*
Paracetamol (p. 115·1); grindelia (p. 2522·3); gelsemium (p. 2511·2).
Respiratory-tract disorders.

Coquelusédal Paracétamol Nourrissons *Elerte, Fr.†*
Paracetamol (p. 115·1); grindelia (p. 2522·3); gelsemium (p. 2511·2).
Pain; fever.

Co-Quinapril *Eurogenerics, Belg.; Sandoz, Belg.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

CoQuinone *Usana, Canad.; Usana, Hong Kong†; Usana, Mex.; Usana, Singapore†; USANA, USA.*
Ubidecarenone (p. 2637·1).
Dietary supplement; coenzyme Q10 supplement.

Coqun *Visufarma, Ital.*
Ubidecarenone (p. 2637·1); tocofersolan (p. 2119·1).
Dry eyes.

Cor
Note: this name may be used for preparations of different composition.
Pascoe, Ger.
Cactus (p. 2473·2); strophanthus (p. 1507·2); aurum metallicum (p. 2521·1).
Homoeopathic preparation.

Prater, Chile.
Esomeprazole (p. 1841·1).
Peptic ulcer.

Cor-4 *Sigman, India.*
Oral drops: Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Sigman, India.
Oral suspension: Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Sigman, India.
Tablets: Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Cor-30 *Pascual, Philipp.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Cor Mio *Hexal, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Cor Plus *Pascoe, Ger.*
Apocynum; cactus (p. 2473·2); convallaria majalis (p. 2486·2); laurocerasus (p. 2475·2); strophanthus (p. 1507·2).
Homoeopathic preparation.

cor tensobon *UCB, Ger.†*
Captopril (p. 1331·2).
Heart failure; hypertension; diabetic nephropathy; myocardial infarction.

Cora
Note: this name may be used for preparations of different composition.
Erbiode, Austria.
Crataegus (p. 2488·1); digitalis purpurea (p. 1352·3); spigelia anthalmia (p. 2621·3); strophantus gratus.
Homoeopathic preparation.

Cora Caine *Coralite, Canad.*
Benzocaine (p. 1980·2); methyl heptyl colamino formylmethyl pyridinium chloride.
Local anaesthesia.

Corabion HC *Merck, Braz.*
Fish oil (p. 1460·1).

Co-Rabolan *Rafarm, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Coracil *Gador, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Coracten *Vianex (Βιανεξ), Gr.; Invida, Hong Kong; Valeant, Thai.†; UCB, UK.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Coradipin *1A, Austria.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Coradona *Farma, Venez.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Corafen *Bernabo, Arg.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Coral
Note: this name may be used for preparations of different composition.
Biosciences Pharmakon, India.
Aloe vera (p. 1693·2); cetrimide (p. 1742·1).
Soap substitute.

SoSe, Ital.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Wermar, Mex.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Coralan *Servier, Austral.; Servier, Israel; Servier, Philipp.; Servier, S.Afr.*
Ivabradine hydrochloride (p. 1415·1).
Angina pectoris.

Servier, Hong Kong; Servier, Indon.; Servier, Malaysia; Servier, Singapore; Servier, Thai.; Servier, Turk.
Ivabradine (p. 1415·1).
Angina pectoris; heart failure.

Coralen *Alter, Spain.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastrointestinal hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Coral-F *Constant, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Coralip *Galex, Cz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Coral-M *Haledew, India.*
Calcium carbonate (p. 1824·3); calcium hydrogen phosphate (p. 1783·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Coralmyn *Bioclon, Mex.*
Snake venom antiserum (p. 2419·1).
Micrurus spp bites.

Coralzul *Farcoral, Mex.*
Furazolidone (p. 933·3); homatropine (p. 2007·3); kaolin (p. 1850·1); pectin (p. 2200·3); diiodohydroxyquinoline (p. 931·1).
Gastrointestinal disorders.

Coramil *Sanofi-Aventis, Swed.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Coramine Glucose *Novartis Sante, Fr.*
⊗Nikethamide (p. 2328·2); glucose monohydrate (p. 2069·1).
Fainting; asthenia.

Co-Ramipril *Sandoz, Belg.; Sandoz, Switz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corangin *Mibe, Ger.†; Novartis, NZ.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Corangin Nitrospray *Mibe, Ger.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction.

Corangine *Novartis, Switz.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Coraphene *Vedim, Port.†*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; premedication.

Corargin *Tekhnolog, Ukr.*
Inosine (p. 2533·1); arginine (p. 2049·1).
Adjunct in ischaemic heart disease, cardiomyopathy, hypertension, disturbed myocardial metabolism.

Coras *Alphapharm, Austral.; LCH, Hong Kong.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Corasan *Dynamit, Austria.*
Cactus (p. 2473·2); crataegus (p. 2488·1); digitalis (p. 1352·3); strophanthus (p. 1507·2).
Homoeopathic preparation.

Corase *Medac, Ger.†*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Co-Rasilez *Novartis, Rus.*
⊗Aliskiren fumarate (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coraspin *Bayer, Turk.*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Coraspir *Armstrong, Mex.*
Lysine aspirin (p. 84·3).
Thromboembolism prophylaxis; pain; fever.

Coraspirina *Bayer, Venez.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Corat *Teva, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Coratol *Scan Lab, Thai.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Corotor *Lek-Am, Pol.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Coraxan *Servier, Rus.; Servier, Ukr.*
Ivabradine hydrochloride (p. 1415·1).
Angina pectoris; heart failure.

Corazem *Farma, Venez.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; myocardial infarction.

Corbar *Adcock Ingram, S.Afr.*
⊗Guaifenesin (p. 1666·2); ephedrine hydrochloride (p. 1663·2); codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); compound cocillana syrup (p. 1659·2).
Cough.

Corbeta *Sarabhai Piramal, India; Idaman, Singapore.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; migraine; myocardial infarction; phaeochromocytoma.

Corbetazine *Sarabhai Piramal, India.*
⊗Propranolol hydrochloride (p. 1479·1); hydralazine hydrochloride (p. 1401·2).
Hypertension.

Corbeton *Alphapharm, Austral.; LCH, Hong Kong.†*
⊗Oxprenolol hydrochloride (p. 1463·2).
Angina pectoris; arrhythmias; hypertension.

Corbin *Pharmadica, Thai.*
Cloxacillin sodium (p. 275·1).
Gram-positive bacterial infections.

Corbinal *Biofarma, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Corbionax *Sanofi-Aventis, Fr.; Winthrop, Port.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Corbis *Roemmers, Arg.; Unichem, India; Reddy, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; heart failure.

Corbis D *Roemmers, Arg.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corbis-H *Unichem, India.*
⊗Bisoprolol (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corbutyl *Sanofi-Aventis, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Corcanfol *Lanpharm, Arg.*
⊗Etilefrine (p. 1379·1).
Hypotension.

Cor-CC *Sigman, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Corcef-SB *Corona, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Corciclen *Allergan, Braz.*
⊗Chlortetracycline hydrochloride (p. 260·2); cortisone acetate (p. 1629·2); bismuth loretinate.
Infected eye disorders.

Cor-4D *Sigman, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine (p. 1672·2).

Cordafen *Polpharma, Pol.†; Polpharma, Rus.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome; cerebrovascular disorders; vascular eye and ear disorders; peripheral vascular disorders; migraine.

Cordaflex *Egis, Hung.; Egis, Rus.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; myocardial infarction; Raynaud's syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cordalat *Kimia, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Cordan *Sandoz, Denm.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Cordanum *AWD, Ger.; Teva, Rus.*
⊗Talinolol (p. 1509·2).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; migraine.

Cordaptive *MSD, Arg.; MSD, Braz.; MSD, Mex.*
Nicotinic acid (p. 2083·1); laropiprant (p. 2540·3).
Hyperlipidaemias.

Corda pur Novo *APS, Ger.†*
Crataegus (p. 2488·1).
Heart failure.

Cordarex
Note: this name may be used for preparations of different composition.
Biosintetica, Braz.
Amlodipine besilate (p. 1304·1).
Hypertension; ischaemic heart disease.
Sanofi-Aventis, Ger.†
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Cordarone *Sanofi-Aventis, Belg.; Pfizer, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi Synthelabo, Turk.; Sanofi-Aventis, Ukr.; Wyeth-Ayerst, USA.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; angina pectoris.

Cordarone X *Sanofi-Aventis, Austral.; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, UK.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Cordazem *Benecor, Philipp.†; Pascual, Philipp.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Cordefla *Dosa, Arg.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Cordes Beta *Ichthyol, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Cordes BPO *Ichthyol, Ger.*
Benzoyl peroxide (p. 1696·1).
Acne.

Cordes Estriol *Ichthyol, Ger.*
Estriol (p. 2274·3).
Vaginal disorders.

Cordes VAS *Ichthyol, Ger.*
Tretinoin (p. 1725·2).
Acne.

Cordesin *Serag-Wiessner, Ger.†*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency; heart failure; myocardial infarction.

Cordesyl *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Cordex *Prosel, Philipp.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Cordi Cor *Egis, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Cordiax
Note: this name may be used for preparations of different composition.
Crinos, Ital.
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.
Drugtech, Chile.
Telmisartan (p. 1509·3).
Hypertension.

Cordiax D *Drugtech, Chile.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cordichin *Abbott, Ger.*
Verapamil hydrochloride (p. 1522·1); quinidine (p. 1481·1).
Arrhythmias.

Cordiet *Armour, India.*
Vitamins.

Cordil
Note: this name may be used for preparations of different composition.
Teuto, Braz.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.
Dexxon, Israel.†
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Cordilat
Note: this name may be used for preparations of different composition.
Tecnofarma, Mex.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.
Cristalia, Braz.
Verapamil hydrochloride (p. 1522·1).

Cordilox *Abbott, Austral.; Ivax, UK.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Cordimedil *Kleva, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Cordimil *Ind-Swift, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Cordinal *Spedrog, Arg.*
Bifemelane hydrochloride (p. 389·2).
Mental function impairment.

Cordinate *Novartis, Ger.*
Valsartan (p. 1521·2).
Heart failure; hypertension; myocardial infarction.

Cordinate plus *Novartis, Ger.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cordinorm *Actavis, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Cordiodoron *Weleda, Ger.†*
Onopordum acanthium; primula veris (p. 2596·2); hyoscyamus niger (p. 2530·2).
Homoeopathic preparation.

Cordipatch *UCB, Fr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Cordipin *KRKA, Cz.; KRKA, Hong Kong; KRKA, Pol.†; KRKA, Rus.; KRKA, Singapore; KRKA, Ukr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; hypertrophic cardiomyopathy; Raynaud's syndrome; peripheral vascular disorders; migraine.

Cordipina
Note: this name may be used for preparations of different composition.
Fanmasa, Braz.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Cordiplast *UCB, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Cordisil *Flupal, Venez.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Cordizem *Kimia, Indon.*
Diltiazem (p. 1359·2).
Angina pectoris.

Cordodopa *Sanofi-Aventis, Port.*
Dopamine hydrochloride (p. 1367·2).
Shock.

Cordran *Aqua, USA; Watson, USA.*
⊗Fludroxycortide (p. 1635·2).
Skin disorders.

Cordron-D *Cypress, USA.†*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Cordron-DM *Cypress, USA.*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs; nasal congestion.

Cordron-HC *Cypress, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Cordymax *Pharmanex, USA.*
Cordyceps sinensis mushroom mycelia.
Fatigue.

Core *Mint, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Corebeta *Ono, Jpn.*
⊗Landiolol hydrochloride (p. 1418·1).
Aid in coronary angiography.

Corectin *Biofarm, Pol.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; ischaemic heart disease.

Coredopril *Sandoz, Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coredryl *GMP, Indon.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Coreg *Roche, Braz.; GSK, USA.*
⊗Carvedilol (p. 1333·1) or carvedilol phosphate (p. 1333·1).
Heart failure; hypertension; angina pectoris.

Corega *Ali, Turk.; GSK Consumer, Venez.*
Adhesive pads: Denture fixative.
GSK Consumer, Venez.
Effervescent tablets: Denture cleaner.
GSK, Braz.
Sterculia (p. 1888·3).

Co-Renistad *Stada, Austria.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Renitec *MSD, Arg.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Mex.; MSD, Neth.; MSD, NZ; MSD, Philipp.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; Abello, Spain; MSD, Venez.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Reniten *MSD, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corenza C *Adcock Ingram, S.Afr.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); moroxydine hydrochloride (p. 1004·1).
Cold and influenza symptoms.

Corenza C Para-C *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); vitamin C (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Coretec *Eisai, Jpn.*
Olprinone hydrochloride (p. 1460·1).
Heart failure.

Corex *Pfizer, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Formerly contained chlorphenamine maleate, codeine phosphate, and menthol.
Cough.

Corex-Dx *Pfizer, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Formerly contained chlorphenamine maleate, dextromethorphan hydrobromide, and menthol.
Cough.

Corexin *Otto, Indon.†*
Salicylamide (p. 129·2); paracetamol (p. 115·1); caffeine (p. 1203·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Corex-T *Pfizer, India.*
Codeine phosphate (p. 40·2); triprolidine hydrochloride (p. 642·3).

Corfen-DM *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cough; respiratory-tract congestion.

Corflo *Wockhardt, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

Corgard
Note: this name may be used for preparations of different composition.
BMS, Arg.; BMS, Belg.†; BMS, Braz.; Merck, Chile; Sanofi-Aventis, Fr.; BMS, Gr.; BMS, Ital.†; BMS, Mex.; BMS, NZ; BMS, S.Afr.†; Sanofi Synthelabo, UK; Pfizer, USA; BMS, Venez.
⊗Nadolol (p. 1442·3).
Angina pectoris; arrhythmias; hypertension; migraine; hyperthyroidism; obstructive cardiomyopathy.
Apotex, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Corgaretic *BMS, Mex.; BMS, S.Afr.†*
⊗Nadolol (p. 1442·3); bendroflumethiazide (p. 1315·2).
Hypertension.

Corge-C *Adley, India.*
⊗Beclometasone dipropionate (p. 1621·2); clioquinol (p. 273·1); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Corgic *Jumont, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Corglycon *Arterium, Ukr.*
Convallaria (p. 2486·2).
Heart failure.

Corgone *Sykocure, India.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Corhinza *Hexpharm, Indon.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

Corhisdin with codeine *Synco, Hong Kong.†*
Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); codeine (p. 40·2); phenylpropanolamine (p. 1674·1).
Cough.

Corhydron *Jelfa, Pol.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cori-3B *ANH, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Cori-C *Medicine Products, Thai.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Coric *BMS, Ger.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Coric Plus *BMS, Ger.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coricide le Diable *Sodia, Fr.*
Salicylic acid (p. 1719·1).
Corns; callosities; verrucae.

Coricidin
Note: this name may be used for preparations of different composition.
Schering-Plough, Indon.
⊗Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); alcohol (p. 1733·1).
Sinusitis; respiratory-tract allergic reactions.
Schering-Plough, USA; Schering-Plough, Venez.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms; cold symptoms.

Coricidin II Chest Congestion and Cough *Schering-Plough, Canad.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Coricidin II Cold and Flu *Schering-Plough, Canad.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Coricidin II Cough and Cold *Schering-Plough, Canad.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Coricidin Expec *Schering-Plough, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Coricidin II Extra Strength Cold and Flu *Schering-Plough, Canad.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Coricidin F *Schering-Plough, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Nasal congestion.

Coricidin HBP Chest Congestion & Cough *Schering-Plough, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Corico *Molekule, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Corico-CS *Molekule, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Corid *Wanbury, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).
Cough.

Corid-B *Wanbury, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).
Cough.

Coridil *Sandoz, Switz.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Coriem *Ranbaxy, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Corifact *CSL, USA.*
A factor XIII preparation (p. 1150·3).
Factor XIII deficiency.

Corifam *Coronet, Indon.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Corifeo *Recordati, Ger.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Corifina *Angelini, Spain.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis; allergic rhinitis.

Coriko-P *Molekule, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Corilax *Community Pharmacy, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain; neuralgia; tension headache.

Corilin *Schering-Plough, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Corilisina *Distriquimica, Spain.†*
Nasal spray: ⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Coriminic *Wanbury, India.*
Syrup: ⊗Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Wanbury, India.
Tablets: ⊗Chlorphenamine (p. 620·3); pseudoephedrine (p. 1676·1).

Coriminic X *Wanbury, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Coriminic Plus *Wanbury, India.*
⊗Chlorphenamine (p. 620·3); pseudoephedrine (p. 1676·1); paracetamol (p. 115·1).

Coriminic-Vaporise *Wanbury, India.*
Camphor (p. 2466·2); chlorothymol (p. 1748·2); cineole (p. 2479·1); menthol (p. 2553·2); terpineol (p. 2627·2).

Corinap *ANH, Thai.*
Sodium bicarbonate (p. 1781·1); cataria; saccharin (p. 2207·3); caraway oil (p. 2470·3); fennel oil (p. 2503·3); cardamom oil (p. 2471·1); anise oil (p. 2444·3).
Gastrointestinal disorders.

Corinfar *AWD, Cz.†; AWD, Ger.; AWD, Hung.; Teva, Rus.; Teva, Ukr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Corinite *Svizera, India.*
Syrup: Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Svizera, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Coriodal *Sanitas, Chile.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine.

Corion *Win-Medicare, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility; recurrent miscarriage; cryptorchidism; male hypogonadism; delayed puberty; pituitary dwarfism.

Corion NP *Win-Medicare, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; menopausal disorders.

Coriovaccine *Columbia, Arg.*
Staphylococcus; Micrococcus; Pneumococcus; Streptococcus; Klebsiella; Moraxella catarrhalis; Haemophilus influenzae; vitamin C (p. 2110·3).

Coripren *Recordati, Spain; Recordati, Ukr.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Coris Grip *Microsules, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); bromhexine (p. 1656·3).
Influenza symptoms.

Corisol *Sandoz, Switz.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections; trichomoniasis.

Coristina D *Mantecorp, Braz.*
Dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); aspirin (p. 22·2).
Cold and influenza symptoms.

Coristina R *Mantecorp, Braz.*
Salicylamide (p. 129·2); dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Influenza symptoms.

Coristina Vitamina C *Mantecorp, Braz.*
Ascorbic acid (p. 2110·3).

Corisul *ANH, Thai.*
Nux vomica (p. 2573·3); cascara (p. 1826·1); asafetida (p. 2449·3); ginger (p. 1844·1); malt amylase (p. 2442·1).
Constipation.

Coritab *Atlantic, Hong Kong.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; nasal congestion; rhinitis.

Coritensil *Roux-Ocefa, Arg.*
⊗Carvedilol (p. 1333·1).

Coritex *Bago, Chile.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Coriton
Note: this name may be used for preparations of different composition.
ANH, Thai.
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Vickmans, Hong Kong.†
Chlorphenamine (p. 620·3).

Coritrope *Sanofi-Aventis, Indon.*
Milrinone lactate (p. 1438·1).
Heart failure.

Coritussal *Mack, Hong Kong.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1); carbinoxamine maleate (p. 619·1).
Cough; rhinitis.

Coriver *Maver, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Corixa *Biotenk, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Corixil *Orifarm, Denm.; Bracco, Ital.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corizin *Greenpharma, Braz.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).

Corizina
Note: this name may be used for preparations of different composition.
Cetus, Arg.
Ascorbic acid (p. 2110·3); paracetamol (p. 115·1); diphenhydramine (p. 626·1).
Influenza symptoms.

Corlan *UCB, Irl.; Auden McKenzie, UK.†*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Aphthous stomatitis.

Corlentor *Servier, Cz.; Servier, Irl.; Stroder, Ital.; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, Spain.*
Ivabradine hydrochloride (p. 1415·1).
Angina pectoris; heart failure.

Corlium *Synco, Hong Kong.†*
Chlordiazepoxide (p. 1044·2).
Anxiety.

Cor-loges *Loges, Ger.*
Crataegus (p. 2488·1); convallaria maj. (p. 2486·2); scilla (p. 1677·3); lachesis (p. 2538·3).
Homoeopathic preparation.

Corlopam *Cephalon, Ital.; Hospira, USA.*
Fenoldopam mesilate (p. 1382·1).
Hypertension.

Corlova *Cadila, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility; cryptorchidism; delayed puberty.

Cormac *Megat, Venez.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Cormadol *Constant, India.*
Tramadol (p. 139·2).
Pain.

Cormagnesin *Meda, Austria; Worwag, Ger.; Worwag, Hung.; Worwag, Rus.; Worwag, Ukr.*
Magnesium sulfate (p. 1787·3).
Magnesium deficiency; premature labour; eclampsia; arrhythmias; myocardial infarction; magnesium supplement; hypertensive crisis.

Cormatic *Megat, Venez.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cormax *ECR, USA.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cormelian *Khandelwal, India.*
Dilazep hydrochloride (p. 1359·1).
Ischaemic heart disease.

Cormisin *Gunsa, Turk.†*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected eye disorders.

Corn *SSL, Pol.*
Salicylic acid (p. 1719·1).
Corns.

Corn and Callous *SSL, Pol.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Corn Huskers *Warner-Lambert, USA.*
Emollient and moisturiser.

Corn Removal Pads *SSL, Irl.*
Salicylic acid (p. 1719·1).
Corns.

Corn Removers *SSL, Irl.*
Salicylic acid (p. 1719·1).
Corns.

Cornalgin *Corsa, Indon.*
Dipyrone (p. 53·3).
Fever; pain.

Cornaron *TAD, Ger.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Corneax *Verisfield, Gr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Corneregel *Riel, Austria†; Mann, Ger.; Kite (Kττε), Gr.; Bausch & Lomb, Hong Kong; Mann, Hung.; Bausch & Lomb, Mex.; Bausch & Lomb, Philipp.; Mann, Pol.; Bausch & Lomb, Rus.; Bausch & Lomb, Ukr.*
Dexpanthenol (p. 2582·2).
Eye disorders; keratitis; corneal injury.

Corni Limp *Sophia, Mex.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Cornina Hansaplast *Beiersdorf, Fin.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Corobion *Coronet, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; muscular weakness; anaemias; hyperemesis gravidarum; paraesthesia.

Corocyd *Coronet, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; Zollinger-Ellison syndrome.

Corodil
Note: this name may be used for preparations of different composition.
Hexal, Denm.
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

TO-Chemicals, Thai.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Corodil Comp *Hexal, Denm.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corodin *Drugtech, Chile.*
Losartan potassium (p. 1422·2).
Hypertension.

Corodin D *Drugtech, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corodrox *Fabop, Arg.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Coroflox *Coronet, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Corogal *Probiomed, Mex.†*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Corolater *Sandoz, Spain.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Corolut-N *Triton, India.*
Norethisterone acetate (p. 2294·3).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer; oral contraceptive.

Coromax *USV, India.*
Eptifibatide (p. 1376·3).
Unstable angina; adjunct in coronary angioplasty.

Coromert *Mertens, Arg.*
Flunarizine (p. 629·3).
Migraine; vertigo.

Coronair *Socobom, Belg.†*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Coronal
Note: this name may be used for preparations of different composition.
Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; ischaemic heart disease.

Coronar *Biolab Sanus, Braz.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Coronaril *Sigma, Braz.*
Verapamil hydrochloride (p. 1522·1).

Coronat *Pentafarma, Port.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris.

Coronax *Fabop, Arg.*
Amiodarone (p. 1300·1).
Arrhythmias.

Coronipin *Dexa, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Coronis *Bilim, Turk.*
⊗Carvedilol (p. 1333·1).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Coro-Nitro *Ayrton, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Coronol *Sarabhai Piramal, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Coronol-AM *Sarabhai Piramal, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Coronovo
Note: this name may be used for preparations of different composition.
Recalcine, Chile.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Sandoz, Arg.
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Coronur *Kern, Spain.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Corophen-A *Evershine, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Corophen-D *Evershine, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Coropres *Roche, Spain.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension; ischaemic heart disease.

Cororell *Sanorell, Ger.*
Crataegus (p. 2488·1).
Homoeopathic preparation.

Corosan
Note: this name may be used for preparations of different composition.
Farmacologico Milanese, Ital.
Dipyridamole (p. 1362·2).
Vascular disorders.

Merck Serono, Arg.
Valsartan (p. 1521·2).
Hypertension.

Corotal *Rosch & Handel, Austria.†*
β-Acetyldigoxin (p. 1290·2).
Heart failure; arrhythmias.

Corotrend
Note: this name may be used for preparations of different composition.
Doctum, Gr.
Diltiazem hydrochloride (p. 1359·2).

Rhein, Mex.†; Teva, Switz.
Nifedipine (p. 1447·2).
Ischaemic heart disease; hypertension; angina pectoris; myocardial infarction.

Corotrop *Sanofi-Aventis, Austria; Sanofi-Aventis, Swed.*
Milrinone lactate (p. 1438·1).
Heart failure.

Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Switz.
Milrinone (p. 1438·1).
Heart failure.

Corotrope *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Spain; Sanofi-Aventis, Venez.*
Milrinone lactate (p. 1438·1).
Heart failure.

Sanofi-Aventis, Belg.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.
Milrinone (p. 1438·1).
Heart failure; circulatory failure.

Coroval *Sandoz, Arg.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Coroval B *Sandoz, Arg.*
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Corovit *Coronet, Indon.*
Syrup: Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Coronet, Indon.
Tablets: Vitamins; minerals.
Dietary supplement.

Coroxin
Note: this name may be used for preparations of different composition.
Community Pharmacy, Thai.
Roxithromycin (p. 356·2).
Bacterial infections.

Corozell *Fresenius Kabi, Austria.*
Potassium chloride (p. 1793·2); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency.

Corpaz *Indeco, Arg.*
⊗Atenolol (p. 1308·2).
Hypertension.

Corpea *Normon, Spain.†*
Molsidomine (p. 1441·1).
Angina pectoris.

Corpotasin CL *Armstrong, Mex.*
Potassium bicarbonate (p. 1780·3); potassium chloride (p. 1793·2); lysine hydrochloride (p. 2079·3).
Potassium and chloride supplement; digitalis intoxication.

Corpotasin GK *Armstrong, Mex.*
Potassium gluconate (p. 1793·2).
Hypokalaemia; digitalis intoxication.

Corpotasin LP *Armstrong, Mex.*
Potassium chloride (p. 1793·2).
Hypokalaemia; digitalis intoxication.

Corpril *Ranbaxy, Hung.†; Ranbaxy, India; Ranbaxy, Thai.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Corpril-AM *Ranbaxy, India.*
Amlodipine (p. 1304·1); ramipril (p. 1483·3).

Corprilor *Rubio, Singapore.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

CorProtect *Ratiopharm, Austria.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; cardiovascular risk reduction.

Cor-Q *Pharos, Indon.*
Ubidecarenone (p. 2637·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Dietary supplement.

Corque *Geneva, USA.*
⊗Hydrocortisone (p. 1640·1); clioquinol (p. 273·1).
Skin disorders.

Correcting Moisturizer *Balley, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Correctol
Note: this name may be used for preparations of different composition.
Alcon, Fr.
Disodium inosinate (p. 2495·2).
Visual disturbances.

Schering-Plough, Canad.; Schering-Plough, USA.
Bisacodyl (p. 1821·1).
Constipation.

Correctol Stool Softener
Note: this name may be used for preparations of different composition.
Schering-Plough, Canad.
Docusate sodium (p. 1836·2).
Constipation.

Corsabalm *Corsa, Indon.*
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); citronella oil (p. 2481·1).
Musculoskeletal and soft-tissue pain; neuralgia.

Corsabutol *Corsa, Indon.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Corsacillin *Corsa, Indon.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Corsacin *Corsa, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Corsaderm *Corsa, Indon.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Corsadol *Corsa, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Corsadryl *Corsa, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Corsafen *Corsa, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Corsagrip *Corsa, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms; cough.

Corsagyl *Corsa, Indon.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis.

Corsal *Ulagay, Turk.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Respiratory-tract congestion.

Corsalit 200 *Corsa, Indon.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration solution; diarrhoea.

Corsamag *Corsa, Indon.*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Epigastric pain; gastric bloating; nausea associated with peptic ulcer; gastric hyperacidity.

Corsamet *Corsa, Indon.*
Cimetidine (p. 1827·1).
Gastritis; duodenitis; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Corsamox *Corsa, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Corsamycin *Corsa, Indon.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Corsamyl *Corsa, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); dexchlorpheniramine maleate (p. 621·1).
Cold and influenza symptoms; cough; bronchitis.

Corsaneuron *Corsa, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; myalgia; diabetic neuropathy; paraesthesia; asthenia.

Corsanural *Corsa, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Corsasep *Corsa, Indon.*
Povidone-iodine (p. 1767·1).
Wounds.

Corsatet *Corsa, Indon.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Corsatrocin *Corsa, Indon.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Corsazinamid *Corsa, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Corsel *Fahrenheit, Indon.*
Ubidecarenone (p. 2637·1); levocarnitine (p. 2053·2).
Nutritional supplement.

Corselect N *Dreluso, Ger.*
⊗Crataegus (p. 2488·1); lobelia inflata (p. 2323·2); valeriana (p. 2640·2); camphora (p. 2466·2); cactus (p. 2473·2); aether sulf. (p. 1900·3); ignatia (p. 2532·1).
Homoeopathic preparation.

Corsenile *Faran, Gr.*
Diltiazem hydrochloride (p. 1359·2).

Corsim *ProMed, Cz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Corsodyl *GSK Consumer, Belg.; GSK Consumer, Cz.; GSK, Fin.; GSK Sante, Fr.; GSK, Hong Kong; GSK Consumer, Irl.; GSK, Israel; GSK, Ital.; GSK Consumer, Neth.; GSK, Norw.; GSK Consumer, Pol.; GSK Consumer, Port.; GSK, S.Afr.; GSK Consumer, Swed.; GSK Consumer, Switz.; GSK Consumer, UK.*
Chlorhexidine gluconate (p. 1743·3).
Mouth infections; oral hygiene; aphthous ulcer; dental caries prophylaxis; gingivitis.

Corsona *Phapros, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Corstanal *Corsa, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Corstat *Medreich, Hong Kong.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hyperlipidaemias.

Cortafrin *Streger, Mex.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Fever; nasal congestion; pain.

Cortafriol C *Sanofi-Aventis, Spain.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); ascorbic acid (p. 2110·3).
Influenza and cold symptoms; pain; fever.

Cortafriol Complex *Sanofi-Aventis, Spain.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Cor-Tagrip
Note: this name may be used for preparations of different composition.
Benitol, Arg.
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); bromhexine (p. 1656·3).
Influenza symptoms.

Cortaid *Pharmacia Upjohn, USA.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Skin disorders.

Cortal
Note: this name may be used for preparations of different composition.
GSK, Philipp.
Aspirin (p. 22·2).
Fever; pain.

Cortal for Adults
Note: this name may be used for preparations of different composition.
GSK, Hong Kong.
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Cortal for Children
Note: this name may be used for preparations of different composition.
GSK, Hong Kong.
Paracetamol (p. 115·1).
Fever; pain.

Cortal Ibuprofen *GSK, Hong Kong.†*
Ibuprofen (p. 68·2).

Cortalen C *Ativus, Braz.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cortamed *Sandoz, Canad.*
⊗Hydrocortisone acetate (p. 1640·1).
Eye disorders.

Cortamine *Interbat, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).

Cortamox *Rivers Edge, USA.†*
⊗Chloroxylenol (p. 1748·2); hydrocortisone (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Skin disorders.

Cortan *Gedeon Richter, Ital.*
Valsartan (p. 1521·2).

Cortancyl *Sanofi-Aventis, Fr.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Cortane-B *Blansett, USA.*
⊗Chloroxylenol (p. 1748·2); pramocaine hydrochloride (p. 1993·3); hydrocortisone (p. 1640·1).

Cortanest Plus *Piam, Ital.*
⊗Fluocinolone acetonide (p. 1636·1); lidocaine hydrochloride (p. 1988·2).
Skin disorders; burns; anogenital disorders.

Cortapaisyl *Merck Medication Familiale, Fr.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Cortare *Teva, Pol.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Cortasthma *Zydus, India.*
⊗Aminophylline (p. 1201·2); ephedrine hydrochloride (p. 1663·2); phenobarbital (p. 535·2).

Cortate
Note: this name may be used for preparations of different composition.
Aspen, Austral.
⊗Cortisone acetate (p. 1629·2).
Corticosteroid.
Schering-Plough, Canad.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortatrigen *Goldline, USA.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B (p. 342·3).
Bacterial ear infections.

Cortax *Ativus, Braz.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Cortaz *Torrent, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cortaz-S *Torrent, India.*
⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1).

Cort-Dome *Miles, USA.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Skin disorders; anorectal disorders.

Cortecyclin *Syntho, India.*
⊗Hydrocortisone (p. 1640·1); tetracycline (p. 373·1).

Cortef *Johnson & Johnson, Canad.; Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Rus.; Pharmacia Upjohn, USA.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Corticosteroid.
Valeant, Austral.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Cortef Feminine Itch *Upjohn, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Pruritus.

Cortel *Corona, India.*
Telmisartan (p. 1509·3).
Hypertension.

Cortel-A *Corona, India.*
Amlodipine (p. 1304·1); telmisartan (p. 1509·3).

Cortel-H *Corona, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan (p. 1509·3).

Cortenema
Note: this name may be used for preparations of different composition.
Aptalis, Canad.
⊗Hydrocortisone (p. 1640·1).
Inflammatory bowel disease.

Corteroid *Montpellier, Arg.*
⊗Betamethasone (p. 1623·2), betamethasone sodium phosphate (p. 1623·3), or betamethasone valerate (p. 1624·1).
Corticosteroid.

Corteroid Gesic *Montpellier, Arg.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3); diclofenac sodium (p. 48·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Gout; musculoskeletal, joint, and peri-articular disorders; neuritis.

Corteroid Retard *Montpellier, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

Cortespasmo *Northia, Arg.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Cortexan Framycetine *Zizine, Fr.*
⊗Hydrocortisone acetate (p. 1640·1); framycetin sulfate (p. 301·2).
Root canal infections.

Cortexin *Geropharm, Rus.; Gerofarm, Ukr.*
Polypeptide brain extract (bovine/porcine) (p. 2444·1).
Head trauma; cerebrovascular disorders; asthenia; mental function impairment; encephalopathy; encephalitis; encephalomyelitis; epilepsy; cerebral palsy; dystonia; cranial-cerebral trauma.

Cort-H *Neon, India.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Corti Biciron N *S & K, Ger.*
⊗Dexamethasone isonicotinate (p. 1631·1); oxytetracycline hydrochloride (p. 337·2).
Infected eye disorders.

Corti Like *Pentamedical, Ital.*
A range of emollients.

Corti-Arscolloid *SIT, Ital.*
⊗Dichlorobenzyl alcohol (p. 1750·2); silver protein (p. 2616·2); dexamethasone sodium phosphate (p. 1631·2).
Stomatitis.

Cortic
Note: this name may be used for preparations of different composition.
Fawns & McAllan, Austral.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Cortic ND
Note: this name may be used for preparations of different composition.
Everett, USA.
⊗Hydrocortisone (p. 1640·1); pramocaine hydrochloride (p. 1993·3); chloroxylenol (p. 1748·2); benzalkonium chloride (p. 1737·1).
Inflammatory ear disorders.

Corticaine *Glaxo, USA.†*
Rectal cream: ⊗Hydrocortisone acetate (p. 1640·1); cinchocaine (p. 1983·2).
Anorectal disorders.
UCB, USA.†
Cream: ⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Cortical *Caber, Ital.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Corticas *Casasco, Arg.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Corticas L *Casasco, Arg.*
⊗Betamethasone (p. 1623·2); loratadine (p. 633·2).

Corticas Retard *Casasco, Arg.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Corticétine *Chauvin, Fr.†*
⊗Framycetin sulfate (p. 301·2); dexamethasone sodium phosphate (p. 1631·2).
Ear disorders.

Corticina *Roemmers-Klinos, Venez.*
⊗Hydrocortisone buteprate (p. 1640·1) or hydrocortisone hydrogen succinate (p. 1640·2).
Corticosteroid.

Corticool *Tec, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Corticorten *Neo Quimica, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Corticosan *Fabra, Arg.*
Losartan potassium (p. 1422·2).
Hypertension.

Cortiderm *Bal, India.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Cortiderma *Mertens, Arg.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Cortiderm-G *Bal, India.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2).
Infected skin disorders.

Cortiderm-GM *Bal, India.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Cortiderm-N *Bal, India.*
⊗Betamethasone (p. 1623·2); neomycin (p. 329·3).
Infected skin disorders.

Cortidex *Sanbe, Indon.; Rayere, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Cortidexason *Dermapharm, Ger.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Cortidexason comp *Dermapharm, Ger.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Cortidro *Sofar, Ital.*
⊗Hydrocortisone acetate (p. 1640·1).
Bites and stings; pruritus; burns; eczema.

Cortiespec *Sesderma, Spain.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Cortifil *Salvat, Neth.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Cortiflam *Mediolanum, Ital.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Cortifluid N *Streuli, Switz.*
⊗Calcium pantothenate (p. 2085·2); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Corti-Fluoral *Bayer, Ital.*
⊗Josamycin propionate (p. 314·2); diflucortolone valerate (p. 1634·1).
Mouth disorders.

Cortifoam *Paladin, Canad.; Megapharm, Israel; Schwarz, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Ulcerative proctitis; colitis; proctitis.

Cortifung-C *Tocogino, Mex.*
Clioquinol (p. 273·1).
Skin infections.

Cortifungin *Sigma, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3).

Cortifung-N *Tocogino, Mex.*
⊗Fluocinolone (p. 1636·1); neomycin (p. 329·3).
Infected skin disorders.

Cortifung-S *Tocogino, Mex.*
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Cortifung-Y *Tocogino, Mex.*
⊗Fluocinolone (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Cortigrin
Note: this name may be used for preparations of different composition.
Collins, Mex.†
Chlorphenamine (p. 620·3); aspirin (p. 22·2).
Cold and influenza symptoms.

Cortigrip *Medipharm, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Cold and influenza symptoms.

Cortigrip Dia/Noche *Medipharm, Chile.*
⊗Day tablets, pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); night tablets, pseudoephedrine hydrochloride; paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Cortigripe *Generis, Port.*
Aspirin (p. 22·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Pain; influenza.

Cortil *Micro, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Cortilate *Micro, India.*
⊗Halcinonide (p. 1639·3).
Skin disorders.

Cortilate-N *Micro, India.*
⊗Halcinonide (p. 1639·3); neomycin (p. 329·3).
Infected skin disorders.

Cortilate-S *Micro, India.*
⊗Halcinonide (p. 1639·3); salicylic acid (p. 1719·1).
Skin disorders.

Cortilona *Offenbach, Mex.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Cortilona Compuesta *Offenbach, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Skin disorders.

Cortimar *Mar, Arg.†*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Cortimax *Zuventus, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Cortimax-S *Zuventus, India.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).

Cortimycin *Medical Ophthalmics, USA.*
Eye drops: ⊗Hydrocortisone (p. 1640·1); neomycin (p. 329·3); polymyxin B (p. 342·3).
Infected eye disorders.
Medical Ophthalmics, USA.
Eye ointment: ⊗Hydrocortisone (p. 1640·1); neomycin (p. 329·3); bacitracin (p. 225·3); polymyxin B (p. 342·3).
Infected eye disorders.

Cortimycine
Note: this name may be used for preparations of different composition.
Abbott, Turk.
⊗Hydrocortisone acetate (p. 1640·1).
Inflammatory eye disorders.

Cortimyk *CCS, Norw.†; CCS, Swed.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Fungal skin infections with inflammation.

Cortimyxin *Sandoz, Canad.*
Eye ointment: ⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Infected eye disorders.
Sandoz, Canad.
Ear drops: ⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Ear disorders.

Cortin *Flamingo, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cortina *Lupin, India.*
Sulfamoxole (p. 368·1); trimethoprim (p. 381·2).
Bacterial infections.

Cort-Inal *Teofarma, Ital.*
⊗Hydrocortisone acetate (p. 1640·1); diprophylline (p. 1207·3).
Bronchial catarrh.

Cortinasal *Spirig, Switz.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Cortineff *Jelfa, Pol.; Polfa Pabianice, Pol.; Pabianice, Rus.; Pabianice, Ukr.*
⊗Fludrocortisone acetate (p. 1634·3).
Adrenocortical insufficiency; adrenogenital syndrome; inflammatory eye disorders; hypotension.

Cortiphenol H *Novartis, Gr.; Novartis, Hong Kong.†*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Bacterial eye infections with inflammation.

Cortiprex *Laboratorios Chile, Chile.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Cortipyren B *Gador, Arg.*
⊗Meprednisone (p. 1642·2).
Corticosteroid.

Cortirel *Curatis, Ger.†; Meduna, Ger.†*
⊗Corticorelin triflutate (p. 1628·2).
Diagnosis of corticotrophic pituitary function.

Cortirell *Sanorell, Ger.†*
⊗Cortisonum (p. 1629·2).
Homoeopathic preparation.

Cortiron *Bayer, Ital.*
Desoxycortone acetate (p. 1630·3) or desoxycortone enantate (p. 1630·2).
Corticosteroid.

Cortisal *Dexo, Fr.*
⊗Dipropylene glycol mono- and disalicylate (p. 66·2); prednisolone (p. 1645·2).
Peri-articular and soft-tissue disorders.

Cortisdin Urea *Isdin, Spain.†*
⊗Fluorometholone (p. 1637·2); urea (p. 1727·3).
Skin disorders.

Cortisedermyl *Cooperation Pharmaceutique, Fr.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortisol
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Psyco Remedies, India.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cortisol-G *Psyco Remedies, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2).
Infected skin disorders.

Cortisolona *Klonal, Arg.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Cortison Chemicet Topica *Teofarma, Spain.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Cortison Chemicetina *Solvay, Ital.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected eye or skin disorders.

Cortison Kemicetin *Sanochemia, Austria.†*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Bacterial eye infections; inflammation.

Cortisonal *Uniao Quimica, Braz.*
⊗Hydrocortisone acetate (p. 1640·1) or hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cortisone *Hovid, Singapore.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortisone-BM *Psyco Remedies, India.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Cortisorell *Sanorell, Ger.*
⊗Cortisonum (p. 1629·2).
Homoeopathic preparation.

Cortispec *Bioceutica, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Infected skin disorders.

Cortisporin *GSK, Canad.; GSK, Mex.; GSK, Philipp.*
Ear drops: ⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); hydrocortisone (p. 1640·1).
Infected ear disorders.

GSK, Canad.
Ointment: ⊗Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); hydrocortisone (p. 1640·1).
Bacterial infections with inflammation.

Monarch, USA.
Cream: ⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Cortisporin-TC *JHP, USA.*
⊗Colistin sulfate (p. 275·3); neomycin sulfate (p. 330·1); hydrocortisone acetate (p. 1640·1); tonzonium bromide (p. 2217·1).
Infected ear disorders.

Cortistamin L *Bago, Arg.*
⊗Betamethasone (p. 1623·2); loratadine (p. 633·2).
Hypersensitivity reactions.

Cortiston *Ariston, Braz.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cortisyl *Aventis, UK.*
⊗Cortisone acetate (p. 1629·2).
Corticosteroid.

Cortitop *Multilab, Braz.*
⊗Dexamethasone acetate (p. 1631·1).
Skin disorders.

Cortival *Aspen, Austral.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Cortixide *Farmedia, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders; allergic rhinitis.

Cortizan *Innoderm, Philipp.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortizol *EMS, Braz.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cortizon *Prodotti, Braz.†*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cortizone *Pfizer, Israel; Chattem, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortizul *Lersan, Arg.†*
Eye drops: ⊗Prednisolone (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Inflammatory eye disorders.

Lersan, Arg.†
Eye ointment: ⊗Prednisolone (p. 1645·2).
Inflammatory eye disorders.

Cortoderm
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Taro, Canad.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortoderm-C *Lennon, S.Afr.†*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Cortola-M *East India Pharma, India.*
⊗Sulfacetamide sodium (p. 361·1); hydrocortisone acetate (p. 1640·1).
Infected eye disorders.

Cortolexan *Anpharm (Ανφαρμ), Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Cortomycetin *Nizhpharm, Rus.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Cortone *Ist. Chim. Inter., Ital.; Merck, USA.†*
⊗Cortisone acetate (p. 1629·2).
Corticosteroid.

Cortop *Hospira, Ital.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Cortopic *Laboratorios Chile, Chile.†*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cortopin *Pinewood, Irl.; Pinewood, UK.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders; insect bites.

Cortoquinol *East India Pharma, India.*
⊗Clioquinol (p. 273·1); hydrocortisone acetate (p. 1640·1).
Fungal skin infections.

Cortos *Raffo, Arg.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Cortosone *Synco, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortran *Rider, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression.

Cortrex *Thorne, Canad.*
Vitamins; zinc (p. 2126·1).

Cortrima *NuLife, India.*
⊗Triamcinolone (p. 1648·3).
Skin disorders.

Cortropin *Pinewood, UK.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cortrosyn *Amphastar, Canad.; Organon (Οργανον), Gr.; Amphastar, USA.*
⊗Tetracosactide (p. 1648·1).
Diagnosis of adrenocortical insufficiency; adrenocorticotrophic hormone; infantile spasm; multiple sclerosis.

Organon, Hong Kong†; MSD, Thai.
⊗Tetracosactide hexa-acetate (p. 1648·1).
Diagnosis of adrenocortical insufficiency.

Cort-S *Neon, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Cortuss *Pharmaland, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Cortygard *Biomax, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Cortyk *Pasteur, Chile.*
⊗Dexamethasone (p. 1630·3).
Nausea and vomiting associated with cancer chemotherapy.

Cortynase *Oftalmi, Venez.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis; sinusitis.

Corubin
Note: this name may be used for preparations of different composition.
Iasis, Gr.
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Lazar, Arg.
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension.

Coruno *Therabel, Belg.*
Molsidomine (p. 1441·1).
Angina pectoris.

Corus
Note: this name may be used for preparations of different composition.
Biomax, India.
Iron sucrose (p. 2078·1).

Biosintetica, Braz.
Losartan potassium (p. 1422·2).
Hypertension.

Corus H *Biosintetica, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corus-FA *Biomax, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Corvadil *Unichem, India; Unichem, S.Afr.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Unichem, Rus.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Corvadil-A *Unichem, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Corvaldinum *Farmak, Ukr.*
Ethyl alpha-bromoisovalerate (p. 1073·1); phenobarbital (p. 535·2); peppermint oil (p. 1877·1); lupulus oil.
Neuroses; angina pectoris; tachycardia; insomnia; vasomotor disorders; hypertension.

Corvalgan *Therabel, Ital.*
Molsidomine (p. 1441·1).
Angina pectoris.

Corvalment *KVZ, Ukr.*
Menthyl isovalerate (p. 2554·1).
Functional cardialgia; angina pectoris; neuroses; motion sickness.

Corvaltab *Pharma Start, Ukr.*
Ethyl alpha-bromoisovalerate (p. 1073·1); phenobarbital (p. 535·2); peppermint oil (p. 1877·1).
Nervous disorders.

Corvamin *Natur Produkt, Rus.*
Molsidomine (p. 1441·1).
Angina pectoris.

Corvasal
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Fr.
Tablets: Molsidomine (p. 1441·1).
Angina pectoris.

Sanofi-Aventis, Fr.†
Injection: Linsidomine hydrochloride (p. 1420·3).
Coronary arterial spasm; cardiac investigations; angina pectoris.

Corvasan *Arterium, Ukr.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; cardiomyopathy; heart failure.

Corvasol *Medipharm, Chile.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Corvaton *Therabel, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Hung.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Switz.*
Molsidomine (p. 1441·1).
Angina pectoris; myocardial infarction; heart failure.

Cor-Vel *Truw, Ger.*
Camphor (p. 2466·2); menthol (p. 2553·2); Norway spruce oil; rosemary oil (p. 2607·3).
Cardiac disorders.

Corvert *Pfizer, Austria; Pfizer, Canad.; Pfizer, Fin.; Pfizer, Fr.†; Alapis, Gr.; Pfizer, Gr.; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pharmacia Upjohn, Rus.; Pfizer, Swed.; Pfizer, Switz.; Pharmacia Upjohn, USA.*
Ibutilide fumarate (p. 1407·2).
Arrhythmias; atrial fibrillation.

Corvex *Platinum, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Corvipas SL *Pascoe, Ger.*
Arnica (p. 2447·2); cactus (p. 2473·2); camphora (p. 2466·2); crataegus (p. 2488·1); scilla (p. 1677·3); strophanthus (p. 1507·2); veratrum (p. 2644·3).
Homoeopathic preparation.

Corvita *Trigen, USA.*
Vitamins; minerals; thioctic acid (p. 2629·1); lutein (p. 2079·2); lycopene (p. 2546·2).
Dietary supplement.

Corvita C *Provefarma, Arg.†*
Ascorbic acid (p. 2110·3); bixa orellana.
Dietary supplement.

Corvita Lax *Provefarma, Arg.†*
Magnesium (p. 1786·3); wheat bran.
Dietary supplement.

Corvite *Vertical, USA.*
Iron (p. 2073·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Corvite FE *Vertical, USA.*
Iron (p. 2073·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); folic acid (p. 2063·1); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Corvite Free *Vertical, USA.*
Vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2); ubidecarenone (p. 2637·1); thioctic acid (p. 2629·1).
Dietary supplement.

Corvitec *Dergam, Fr.*
Fish oil (p. 1460·1); evening primrose oil (p. 2502·2); cartilage (p. 2471·3); vitamins; minerals; grape (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2).
Dietary supplement for eye health.

Corvitin *Borshchagovskii, Ukr.*
Quercetin povidone complex.
Ischaemic heart disease; atherosclerosis.

Corvitol *Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; ischaemic heart disease.

Corvizem *Vitalink, Philipp.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Corvo *TAD, Ger.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Corvo HCT *TAD, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Corvox *Corsa, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Coryfin C *SIT, Ital.*
Menglytate (p. 1669·1); ascorbic acid (p. 2110·3).
Cough; hoarseness.

Coryfin C senza Zucchero *SIT, Ital.*
Echinacea (p. 2498·1); propolis (p. 2597·3).
Dietary supplement.

Coryl *Synco, Hong Kong.†*
⊗Chlorphenamine (p. 620·3); codeine (p. 40·2); ephedrine (p. 1663·1); sodium citrate (p. 1781·2).
Cough.

Corylip *Altfarm, Rus.*
Cocarboxylase hydrochloride (p. 2103·1); riboflavin (p. 2104·3); thioctic acid (p. 2629·1).
Tonic.

Corynil *Medicap, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).

Coryol *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension; ischaemic heart disease.

Coryx *Mirren, S.Afr.†*
Effervescent tablets: ⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride

(p. 1676·1); aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Mirren, S.Afr.†
Syrup: ⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Coryzalia *Boiron, Canad.; Boiron, Cz.; Boiron, Fr.; Boiron, Hung.; Boiron, Neth.; Boiron, Port.; Boiron, Rus.; Boiron, Switz.; Boiran, Ukr.*
Allium cepa (p. 2575·2); belladonna (p. 2453·3); gelsemium sempervirens (p. 2511·2); kalium bichromium (p. 2476·3); pulsatilla (p. 2600·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Corzall *Hawthorn, USA.*
⊗Pentoxyverine citrate (p. 1672·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Corzall Plus *Hawthorn, USA.*
⊗Pentoxyverine citrate (p. 1672·1); pseudoephedrine hydrochloride (p. 1676·1); mepyramine maleate (p. 635·1).
Cough; nasal congestion.

Corzall-PE *Hawthorn, USA.*
Dexchlorpheniramine maleate (p. 621·1); pentoxyverine citrate (p. 1672·1); phenylephrine hydrochloride (p. 1672·3).
Cough; rhinitis; nasal congestion.

Corzi *DWD, India.*
Azithromycin (p. 221·2); zinc acetate (p. 2126·1).

Corzide *BMS, Gr.; King, USA.*
⊗Nadolol (p. 1442·3); bendroflumethiazide (p. 1315·2).
Hypertension.

Corzil *Azevedos, Port.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Cosaar *MSD, Austria; MSD, Switz.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Cosaar Plus *MSD, Austria; Orifarm, Denm.†; Paranova, Denm.†; MSD, Switz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cosacol *Cosme, India.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Cosa-G *Genesis, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Cosalgesic *Alpharma, Hong Kong†; Cox, Hong Kong.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Fever; pain.

Co-Salt *Pfizer, Arg.*
Potassium chloride (p. 1793·2).
Salt substitute.

Cosamide *Alphapharm, Austral.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Cosamin *Nutramax, USA.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); manganese ascorbate.
Nutritional supplement.

Cosamine *Hovid, Malaysia.†*
Glucosamine sulfate potassium (p. 2515·3).
Osteoarthritis.

Cosamine Plus *Hovid, Malaysia.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).
Osteoarthritis; joint disorders.

Cosanol *Orchid, India.*
Policosanol (p. 1472·1).

Cosantin *Kee, India.*
Glucosamine sulfate (p. 2515·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); manganese (p. 2081·2).
Osteoarthritis.

Cosart *Cipla, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Cosartal *Actavis, Irl.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; stroke prophylaxis.

Cosart-H *Cipla, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cosavil *Hub, India.†*
Pheniramine maleate (p. 637·2); paracetamol (p. 115·1).
Cold symptoms.

Cosdox *Symbiosis, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Coscold *Cosme, India.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Coscopin *Biological E, India.*
Paediatric syrup: Noscapine (p. 1670·3); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1).
Cough.

Biological E, India.
Linctus: Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); noscapine (p. 1670·3); sodium citrate (p. 1781·2).
Cough.

Coscopin Plus *Biological E, India.*
Noscapine (p. 1670·3); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3).
Formerly contained noscapine, citric acid, sodium citrate, and ammonium chloride.
Cough.

Coscopin-BR *Biological E, India.*
Ambroxol (p. 1654·3); ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1).
Formerly contained pseudoephedrine, bromhexine hydrochloride, and menthol.
Cough.

Coscoril *Biological E, India.*
Drops: Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Biological E, India.
Syrup: ⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Cos-D *Biosync, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cosdome *Cosme, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Cosdrox *Cosme, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cose-Anal *Will-Pharma, Belg.*
Sodium oleate (p. 2211·2); lauromacrogol 400 (p. 2194·1).
Haemorrhoids.

Co-Sentor *Gedeon Richter, Ukr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cosflox *Cosme, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cosil *Meyer Alian, Venez.*
Enalapril maleate (p. 1371·1).
Hypertension.

Cosilon *Bosnalijek, Rus.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Cositam *Consilient, UK.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Cosivatin *Med-One, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Coskacin *Symbiosis, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Cosklot *Cosme, India.*
Etamsylate (p. 1145·2).
Haemorrhage; menorrhagia.

Cosklot Plus *Cosme, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Coslan *Parke, Davis, Spain.*
Mefenamic acid (p. 85·3).
Fever; inflammation; pain.

Coslax *Symbiosis, India.*
Liquid paraffin (p. 2191·2); phenolphthalein (p. 1877·3).

Coslo *Cosme, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Coslyte *CFL, India.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Cosmegen *Bioprofarma, Arg.; Invida, Austral.; Ovation, Austria; Bago, Braz.; Ovation, Canad.; Lundbeck, Fin.†; IFET (ΙΦΕΤ), Gr.; Ovation, Hong Kong; Wockhardt, India; Lundbeck, Irl.; Lundbeck, Ital.; Armstrong, Mex.; Ovation, Norw.†; Healthcare Logistics, NZ; MSD, Philipp.†; Baxter Oncology, Rus.; Key Oncologics, S.Afr.; MSD, Singapore†; Lundbeck, Swed.†; Pro Concepta, Switz.; MSD, Turk.; IDIS, UK†; Recordati, USA.*
Dactinomycin (p. 776·3).
Malignant neoplasms.

Cosmetin *East West, India.*
Biotin (p. 2052·2).

Cosmiciclina *INTES, Ital.*
Oxytetracycline hydrochloride (p. 337·2); chloramphenicol (p. 257·1); sulfacetamide sodium (p. 361·1).
Bacterial infections of the eye or ear.

CosmoDerm *Inamed, Singapore.*
Collagen (p. 2483·2).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Wrinkles; scars.

CosmoFer *UCB, China.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Cosmofer *Purissimus, Arg.; Brady, Austria; Pharmacosmos, Denm.; Pharmacosmos, Fin.; Teva, Ger.†; Demo, Gr.; Fahrenheit, Indon.; Pharmacosmos, Irl.; Pharmacosmos, Neth.; Pharmacosmos, Norw.; Nebo, Philipp.; Pharmacosmos, Port.; Pharmaplan, S.Afr.; Braun, Spain; Pharmacosmos, Swed.; Pharmacosmos, Thai.; Say, Turk.; Vitaline, UK; Nebo, Venez.*
Iron dextran (p. 2075·3).
Iron deficiency; iron-deficiency anaemia.

CosmoPlast *Inamed, Singapore.*
Collagen (p. 2483·2).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Wrinkles; scars.

Cosmoplast *Medstyle, Chile.†*
Collagen (p. 2483·2).
Wrinkles.

Cosmopril *Cosmopharm, Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Cosmor *Symbiosis, India.*
Meropenem (p. 321·3).
Bacterial infections.

Cosmosol *LKM, Arg.*
A range of sunscreens.

Cosmoxim *Cosmopharm, Gr.*
Piracetam (p. 393·3).

Cosmoxyl *Sarabhai Piramal, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Coso
Note: this name may be used for preparations of different composition.
Zee, India.
Sodium picosulfate (p. 1887·2).

McGloin, Austral.†
Menthol (p. 2553·2); camphor (p. 2466·2); benzyl alcohol (p. 1739·3).
Herpes labialis.

Cosolve *Vargas, Venez.*
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Cosome *Merck, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Formerly contained dextromethorphan hydrobromide, phenylephrine, and chlorphenamine maleate.
Cough; cold symptoms; nasal congestion.

Cosome Exp *Merck, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Cosome-A *Merck, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Cosooth *Sensomed, Philipp.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Cosopt *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; Chibret, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Cos-P *Biosync, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Cospan *Samjin, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Cospanon *Eisai, Jpn.*
Flopropione (p. 2506·1).
Smooth muscle spasm.

Cost *Fada, Arg.*
Ketamine (p. 1905·1).
General anaesthesia.

Costad *Pharmacodane, Swed.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).

Co-Star *Inpac, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Costazole *Crisdy-Na, Philipp.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Costeron-H *Vysali, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Costi *Medochemie, Hong Kong.*
Domperidone (p. 1838·1).
Dyspepsia; digestive disorders; flatulence; gastro-oesophageal reflux; heartburn; nausea and vomiting.

Costil *Pyridam, Indon.*
Domperidone (p. 1838·1).
Dyspepsia; flatulence; nausea and vomiting; epigastric discomfort; hiccups.

Costini *Cosme, India.*
Tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Costrex *Symbiosis, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Costrok *Dewcare, India.*
Citicoline (p. 2480·1).
Head injury; parkinsonism.

Cosudex *AstraZeneca, Austral.; AstraZeneca, NZ.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Co-Sultrin *Valmor, Venez.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cosuric *DDSA Pharmaceuticals, UK.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Cosvate *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cosvate-G *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Cosvate-GM *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cosylan
Note: this name may be used for preparations of different composition.
Recip, Norw.
Ethylmorphine hydrochloride (p. 56·3); cascara (p. 1826·1); menthol (p. 2553·2).
Respiratory-tract irritation; cough.

Co-Symoxyl *Piramal, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Cosyp *Cosme, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); pseudoephedrine (p. 1676·1).

Cosyp-E *Cosme, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Cosyr
Note: this name may be used for preparations of different composition.
Great Eastern, Thai.†; United American, Thai.†
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough.
Medifarma, Indon.†; UAP, Indon.†
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2).
Cough.

Cosyr (Reformulated) *Medichem, Hong Kong.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Coszin *Cosme, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Coszol *Cosme, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Coszol-D *Cosme, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Cotab A *MCR, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Cotab AX *MCR, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Cotabflu *MCR, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Cotalbex *Streuli, Philipp.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Co-Tamgard *Sandoz, Turk.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cotamox *Asian Pharm, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotapp *Utopian, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Cotapp Expectorant *Utopian, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cold symptoms.

Cotar
Note: this name may be used for preparations of different composition.
Brawn, India.
Coal tar (p. 1723·2).
Psoriasis; seborrhoeic dermatitis; dandruff.

Co-Tareg *Normal, Port.; Novartis, S.Afr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cotareg *Europharma, Denm.; Orifarm, Denm.; Novartis, Fr.; Novartis, Ital.; Euro Registratie, Neth.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cotar-K *Brawn, India.*
Coal tar (p. 1723·2); ketoconazole (p. 585·3).

Cotar-S *Brawn, India.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).

Co-Tarsan *Maver, Mex.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; cardiovascular risk reduction.

Cotaryl *FDC, India.*
⊗Urea (p. 1727·3); calcium lactate (p. 1784·1); lactic acid (p. 2539·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1); glycine (p. 2071·2); monobasic sodium phosphate (p. 1791·1); ammonium chloride (p. 1656·1); sodium chloride (p. 1795·1).
Hyperkeratosis; ichthyosis; atopic eczema.

Co-Tasian *Asian Pharm, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotaso *Union Drug, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cotasprin *Natco, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Cotazym *Merck, Canad.; Organon, NZ.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic enzyme deficiency.
Organon, Braz.†; UCB, Ger.
⊗Pancreatin (p. 2579·3).
Pancreatic enzyme deficiency.

Cotazym Forte *Schering-Plough, Indon.*
⊗Pancreatin (p. 2579·3); ox bile extract (p. 2457·2); cellulase (p. 2473·1).
Pancreatic deficiency; digestive disorders.

Cotazym S Forte *Organon, Austral.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic enzyme deficiency.

Cotecxin *Holley-Cotec, China.*
Artenimol (p. 648·2).
Malaria.

Cotemp *Community Pharmacy, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Coten *Aglowmed, India; Interbat, Indon.*
Ubidecarenone (p. 2637·1).
Antoxidant.

Cotenace *Flamingo, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Cotenol *TP, Thai.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Coténolol-Néo *Mepha, Switz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Cotensil *Giempi, Venez.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Cotenzo *Pfizer, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Coteoula *Menarini, Fr.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cotet *Adcock Ingram, S.Afr.†*
Capsules: Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Coteveten *Abbott, Fr.†*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cotham *Constant, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Cotiasar *Bioavenir, Israel; Pentafarma, Port.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension; stroke prophylaxis.

Cotibin Analgesico Antipiretico *Andromaco, Chile.*
Paracetamol (p. 115·1).
Pain; fever.

Cotibin Antigripal *Andromaco, Chile.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Cotibin Compuesto *Andromaco, Chile.*
Tablets: Paracetamol (p. 115·1).
Fever; pain.

Cotibin Dia y Noche *Andromaco, Chile.*
⊗Day tablets, pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); night tablets, pseudoephedrine hydrochloride; paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Cotibin Flu Dia y Noche *Andromaco, Chile.*
Day powders, paracetamol (p. 115·1); noscapine hydrochloride (p. 1670·3); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); night powders, paracetamol; noscapine hydrochloride (p. 1670·3); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Cotibin Plus *Andromaco, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Cotina *Sanitas, Chile.*
Nicotinic acid (p. 2083·1).
Chilblains; hyperlipidaemias; peripheral vascular disorders; venous ulcers.

Cotinazin *Pfizer, Gr.*
Tioconazole (p. 595·3).
Fungal skin and vaginal infections.

Co-Tioctan *Purissimus, Arg.*
Cocarboxylase (p. 2103·1); thioctic acid (p. 2629·1).
Liver disorders; poisoning; metabolic disorders.

Cotone Emostatico *Nova Argentia, Ital.*
Ferric chloride (p. 2504·2).
Styptic.

Cotrane Pholcodine *Sanofi-Aventis, Belg.*
Pholcodine (p. 1675·1).
Cough.

Cotrazid *Terramedic, Philipp.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Cotrazol *Valomed, Spain.†*
Guaifenesin (p. 1666·2); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Cotren *Biopharm, Hong Kong; Biolab, Singapore; Biolab, Thai.*
Clotrimazole (p. 576·2).
Trichomoniasis; fungal skin and vaginal infections.

Co-Tri *Patar, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotriatec *Sanofi-Aventis, Fr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cotribene *Ratiopharm, Austria.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Cotribid Kid *Klar Sehen, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotrim *Ratiopharm, Belg.†; Ratiopharm, Fin.; Ratiopharm, Ger.; Medochemie, Hong Kong; Pyridam, Indon.†; Medochemie, Malaysia; Spirig, Switz.; Picco, Thai.; Lemmon, USA.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Cotrimax *Emcure, India.*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Cotrim-Diolan *Meda, Ger.*
Co-trimoxazole (p. 277·3).
Bacterial infections; fungal mycetoma; paracoccidioidomycosis.

Co-Trimed *Medifive, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Co-Trimexazole *Beacons, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

CotrimHefa *Riemser, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Cotrimhexal *Hexal, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Cotrimol *UAP, Indon.†; Ipca, Rus.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; malaria; toxoplasmosis.

Cotrimox *Inga, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotrimox-Wolff *Wolff, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Cotrimstada *Stada, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; paracoccidioidomycosis.

Cotripharm *Praxipharm, Hung.; Pharmamed, Rus.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; malaria; toxoplasmosis.

Co-Tripirim *Kocak, Turk.*
Co-trimoxazole (p. 277·3).

Cotrisan *Sanitas, Chile.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Cotritev *Teva, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cotriver *Biosel, Turk.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Cotrizole *Medicon, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotrizol-G *Klonal, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Co-tromoxazole *T Man, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Cotron *Pinewood, Irl.*
Dantron (p. 1833·3); poloxamer 188 (p. 2202·1).
Constipation.

Cotuss *Ranbaxy, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Co-Tuss V *Rugby, USA.*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Coughs.

Cotussin *TP, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; nasal congestion.

Co-Tylenol
Note: this name may be used for preparations of different composition.
Johnson & Johnson Consumer, Mex.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Cotyx *Positif, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cotyx-S *Positif, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cou Complex *Thompsons, Canad.†*
Antimony potassium tartrate (p. 151·2); bryonia (p. 2461·3); hahnemanns causticum (p. 2595·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Couffee Mixture *Thai FD, Thai.*
Indian gooseberry (p. 2532·2); solanum indicum; solanum trilobatum.
Cough.

Cough *Arrow, Canad.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Cough & Chest Congestion *Pharmetics, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Cough & Cold *Homeocan, Canad.*
Oral pellets: Belladonna (p. 2453·3); drosera rotundifolia (p. 2497·2); ipeca (p. 1667·2); kali bichromicum (p. 2476·3); pulsatilla (p. 2600·2); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Cough Cold and Flu *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Cough Combat *Blackmores, Austral.*
Ivy (p. 2536·2).
Cough.

Cough Drops
Note: this name may be used for preparations of different composition.
Weleda, UK.
Angelica root (p. 2443·3); cinnamon (p. 2479·2); clove (p. 2481·2); coriander (p. 2486·3); lemon oil (p. 2543·1); melissa leaf (p. 2552·3); nutmeg (p. 2573·1); cherry-laurel water (p. 2475·2).
Homoeopathic preparation.

Cough DS *Suphong, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cold symptoms; cough.

Cough Elixir *Weleda, UK.*
Aniseed (p. 2444·2); horehound (p. 1668·3); althaea root (p. 2438·3); thyme (p. 2630·2); drosera (p. 2497·2); ipecacuanha root (p. 1667·2); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Weleda, S.Afr.†
Thyme (p. 2630·2); aniseed (p. 2444·2); ipecacuanha (p. 1667·2); dulcamara (p. 2497·3); marrubium (p. 1668·3); althaea (p. 2438·3); malt extract (p. 2080·2); drosera (p. 2497·2); pulsatilla (p. 2600·2).
Cough.

Cough EN Expectorant *Metiska, Indon.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Cough EN Plus *Metiska, Indon.*
Dextromethorphan (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine (p. 1674·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; respiratory-tract congestion.

Cough Formula Comtrex *Bristol-Myers Products, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Cough Lozenges *Sutton, Canad.*
Menthol (p. 2553·2).

Cough Nurse *GSK Consumer, UK.*
Diphenhydramine (p. 626·1); pholcodine (p. 1675·1).
Coughs.

Cough Soother Herbal Syrup *Napiers, UK.*
Pleurisy root (p. 2593·2); elecampane (p. 1662·3); marrubium (p. 1668·3); skunk cabbage (p. 2617·1); lobelia inflata.
Cough.

Cough Syrup
Note: this name may be used for preparations of different composition.
Goldline, USA.
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Rougier, Canad.
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1).

Cough Syrup with Codeine *Rougier, Canad.; Supplements Aromatik, Canad.*
⊗Guaifenesin (p. 1666·2); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).

Cough Syrup D M *Supplements Aromatik, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).

Cough Syrup D M Decongestant *Supplements Aromatik, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Cough Syrup D M Decongestant for Children *Supplements Aromatik, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Cough Syrup D M Decongestant Expectorant *Supplements Aromatik, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

Cough Syrup D M Expectorant *Supplements Aromatik, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Cough Syrup Expectorant *Supplements Aromatik, Canad.*
Guaifenesin (p. 1666·2).

Cough Syrup with Guaifenesin & Dextromethorphan *Tanta, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Cough Syrup with Honey *Hylands, Canad.†*
Aconitum napellus (p. 2428·3); antimonium tartaricum (p. 151·2); ipecacuanha (p. 1667·2); spongia tosta.
Homoeopathic preparation.

Cough-C *Universal, Hong Kong.†*
Codeine (p. 40·2).
Cough.

Coughcod *Aspen, S.Afr.†*
⊗Ephedrine hydrochloride (p. 1663·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); codeine phosphate (p. 40·2); mepyramine maleate (p. 635·1).
Cough.

Cough-eeze *Perrigo, UK.*
Ipecacuanha (p. 1667·2); marrubium (p. 1668·3); elecampane (p. 1662·3).
Coughs.

Cough-EN *Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough; rhinitis; respiratory-tract congestion.

Coughlax *Malaysia Chemist, Singapore.*
⊗Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough; respiratory-tract congestion.

Coughlin *Vickmans, Hong Kong.†*
Syrup: Bromhexine (p. 1656·3); noscapine (p. 1670·3); phenylephrine (p. 1672·2); promethazine (p. 638·2).
Vickmans, Hong Kong.†
Tablets: Bromhexine (p. 1656·3); noscapine (p. 1670·3).

Coughnadryl *Condrugs, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; sneezing; nasal congestion.

Cough-X *Ascher, USA.*
Dextromethorphan hydrobromide (p. 1660·1); benzocaine (p. 1980·2).
Coughs.

Couldespir *Alter, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Couldetos *Alter, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Couldina *Alter, Spain.*
Aspirin (p. 22·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Couldina C *Alter, Spain.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Couldina Instant *Alter, Spain.*
Aspirin (p. 22·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Coulergin *Alter, Spain.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Coumadin *BMS, Arg.; Aspen, Austral.; BMS, Braz.; BMS, Canad.; Merck, Chile; BMS, Ger.; Taro, Israel; BMS, Ital.; BMS, Malaysia†; BMS, Mex.; Healthcare Logistics, NZ; Taro, Philipp.; BMS, Singapore†; Eczacibasi, Turk.; BMS, USA; BMS, Venez.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Coumadine *BMS, Fr.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Counterflame *PharmaSwiss, Gr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, an soft-tissue disorders.

Counterpain *BMS, Gr.; PharmaSwiss, Gr.; BMS, Hong Kong†; Taisho, Indon.; BMS, Philipp.†; BMS, S.Afr.; BMS, Singapore; Taisho, Thai.*
Eugenol (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue disorders; respiratory-tract congestion.

BMS, Hong Kong.†
Topical gel: Menthol (p. 2553·2).
Musculoskeletal pain.

Counterpain Cool *Taisho, Indon.; BMS, Singapore; Taisho, Thai.*
Menthol (p. 2553·2).
Musculoskeletal and soft-tissue disorders; muscle and joint pain.

Counterpain Plus *Taisho, Thai.*
Eugenol (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); piroxicam (p. 125·3).
Osteoarthritis.

Counterpain-PXM *Taisho, Indon.*
Eugenol (p. 2501·2); levomenthol (p. 2553·2); methyl salicylate (p. 92·1); piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Coup-Lax Compose *Coup, Gr.*
Tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1).

Courage *Soho, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Coutim *Jagsonpal, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Couvrance *Pierre Fabre, UK.*
SPF 30: A range of covering creams with sunscreens (titanium dioxide (p. 1725·1); octinoxate (p. 1715·1)).
Concealment of skin imperfections.

Covadenyl *Luar, Arg.*
Collagen (p. 2483·2).
Dietary supplement.

Co-Vals *Esteve, Spain.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Co-Valsacor *KRKA, Hung.; KRKA, Pol.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Covamet *Adcock Ingram, S.Afr.*
Cyclizine hydrochloride (p. 623·2).
Nausea; vomiting; vestibular disorders.

Covamlo *Ranbaxy, India.*
Amlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Covan *Pharmascience, Canad.*
⊗Codeine phosphate (p. 40·2); triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms.

Covancaine *Adcock Ingram, S.Afr.*
⊗Phenazone (p. 124·1); urea (p. 1727·3); sulfacetamide sodium (p. 361·1); benzocaine (p. 1980·2).
Otitis media; otitis externa.

Covance *Ranbaxy, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; stroke prophylaxis.

Covance-D *Ranbaxy, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Covancin *BMW, India.*
Vancomycin (p. 384·2).
Bacterial infections.

Covapril *Duopharma, Malaysia.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension.

Covarex *Glenmark, S.Afr.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Covaryx *Centrix, USA.*
⊗Esterified oestrogens (p. 2270·3); methyltestosterone (p. 2291·3).
Menopausal disorders.

Covasc *CCM, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Covastin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Simvastatin (p. 1489·2).
Coronary heart disease; hyperlipidaemias; atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Co-Vatan *Rowex, Irl.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Covatil-CV *Macleods, India.*
Cefuroxime sodium (p. 255·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Covatine *Bailly-Creat, Fr.*
Captodiame hydrochloride (p. 1044·1).
Anxiety.

Covax *Blubell, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Covaxis *Sanofi Pasteur, Ger.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Covax-OZ *Blubell, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Covedaspen *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Covelay *Yung Shin, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Covemarin *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Covemedal *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Coventrol *Gentek, Venez.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Covepet *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Covera *Pfizer, Canad.†; Searle, USA.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension.

Coveram *Servier, Austral.; Servier, Belg.; Servier, Fin.; Servier, Fr.; Servier, Gr.; Servier, Indon.; Servier, Malaysia; Servier, Neth.; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Switz.; Servier, Thai.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension; coronary heart disease; angina pectoris.

Covercard *Egis, Hung.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Coverdosyn *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Coverdyne *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Coverene *Servier, Arg.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension.

Coverex *Egis, Cz.; Egis, Pol.†; Egis, Rus.*
Perindopril erbumine (p. 1467·1).
Hypertension; cardiovascular risk reduction; heart failure.

Egis, Hung.
Perindopril arginine (p. 1466·3) or perindopril erbumine (p. 1467·1).
Heart failure; hypertension; angina pectoris.

Coverex Combi *Egis, Cz.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Coverex Komb *Egis, Hung.*
⊗Perindopril arginine (p. 1466·3) or perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Coverex Prekomb *Egis, Hung.†*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Coverit *Micro, India.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Coverlam *Servier, Ital.*
Perindopril (p. 1466·3); amlodipine besilate (p. 1304·1).

Covermark *Epiderm, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Coversical *Servier, Denm.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension.

Coversidin *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Coversum *Servier, Austria; Servier, Switz.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; cardiovascular risk reduction.

Servier, Ger.
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Coversum Combi *Servier, Switz.*
⊗Perindopril arginine (p. 1466·3) or perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Servier, Ger.†
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Coversyl *Servier, Braz.; Servier, Canad.; Grunenthal, Chile; Servier, Fin.; Serdia, India; Kyowa, Jpn; Sanfer, Mex.; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Spain; Servier, Turk.; Servier, Venez.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Servier, Austral.; Servier, Belg.; Servier, Fr.; Servier, Gr.; Servier, Irl.; Servier, Ital.; Servier, Malaysia; Servier, Neth.; Servier, Port.; Servier, Singapore; Servier, Thai.; Servier, UK.
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; cardiovascular risk reduction; stroke prophylaxis; myocardial infarction.

Coversyl Arginine *SinGad, Denm.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; myocardial infarction.

Coversyl Arginine Plus *SinGad, Denm.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Coversyl Comp *Servier, Fin.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Coversyl Comp Novum *Servier, Denm.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Coversyl Novum *Servier, Denm.; Servier, Swed.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy; cardiovascular risk reduction.

Coversyl Plus *Eutherapie, Belg.; Servier, Braz.; Servier, Canad.; Serdia, India; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Turk.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension; heart failure.

Servier, Austral.; Servier, Irl.; Servier, Malaysia; Servier, Neth.; Servier, Singapore; Servier, Thai.; Servier, UK.
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Coversyl-AM *Serdia, India.*
Amlodipine (p. 1304·1); perindopril (p. 1466·3).

Coversyspes *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Covethanar *Medialyse, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cerebrovascular disorders.

Co-Vibedoze *Delta, Port.†*
Cobamamide (p. 2107·2).
Vitamin B supplement.

Covil *Blubell, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Covil-A *Blubell, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Covinace *Pharmaniaga, Malaysia.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Coviogal *Teva, Hung.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Coviogal Plusz *Teva, Hung.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Covir *Community Pharmacy, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Covita *USV, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Covita Plus *USV, India.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3).

Co-vitala *Bernofarm, Indon.*
Ubidecarenone (p. 2637·1); levocarnitine (p. 2053·2); thioctic acid (p. 2629·1).

Covitasa B12 *Seid, Spain.*
Cyproheptadine hydrochloride (p. 624·1); cobamamide (p. 2107·2).
Tonic.

Covitol *Aspen, Austral.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin disorders; nappy rash.

Covocef-N *Anfarm, Gr.*
Cefixime (p. 240·3).
Bacterial infections.

Covochol *Adcock Ingram, S.Afr.*
Acetylcholine chloride (p. 2003·1).
Production of miosis in eye surgery.

Covocort *Adcock Ingram, S.Afr.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Covomycin *Adcock Ingram, S.Afr.*
⊗Chloramphenicol (p. 257·1); neomycin sulfate (p. 330·1); naphazoline hydrochloride (p. 1669·3).
Eye, ear, and nose infections.

Covomycin-D *Adcock Ingram, S.Afr.*
⊗Chloramphenicol (p. 257·1); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye and ear infections.

Covonac *Community Pharmacy, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint and peri-articular disorders.

Covonia Bronchial Balsam *Thornton & Ross, UK.*
Dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).
Coughs.

Covonia Catarrh Relief *Thornton & Ross, UK.*
Lappa (p. 2540·1); hyssop (p. 2530·3).
Catarrh.

Covonia Cold & Flu *Thornton & Ross, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cold and influenza symptoms.

Covonia Herbal Mucus Cough Syrup *Thornton & Ross, UK.*
Ipecacuanha (p. 1667·2); liquorice (p. 1853·2); Indian squill (p. 1677·3).
Cough.

Covonia Mentholated *Thornton & Ross, UK.*
Menthol (p. 2553·2); squill tincture (p. 1677·3); liquorice (p. 1853·2).
Coughs.

Covonia Night-Time *Thornton & Ross, UK.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Coughs.

Covonia Throat Spray *Thornton & Ross, UK.*
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Sore throat.

Covonia Vapour Drops *Thornton & Ross, UK.*
Menthol (p. 2553·2); peppermint oil (p. 1877·1).
Nasal congestion.

Covorin *Chandra Bhagat, India.*
Calcium folinate (p. 2066·3).
Methotrexate toxicity; megaloblastic anaemia.

Covorit *Laboratorios Chile, Chile.*
Folinic acid (p. 2066·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia; reduction of methotrexate toxicity.

Covosan *Adcock Ingram, S.Afr.†*
⊗Naphazoline hydrochloride (p. 1669·3); antazoline phosphate (p. 615·3); sulfacetamide sodium (p. 361·1).
Conjunctivitis.

Covospor *Adcock Ingram, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Covostet *Adcock Ingram, S.Afr.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Covotop *Adcock Ingram, S.Afr.†*
Chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Ear infections.

Covrix *Sinensix, Thai.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Cow & Gate Formula-S *Nutricia, Hong Kong.†*
Infant feed.
Lactose intolerance; milk protein allergy.

Cow & Gate Pepti-Junior *Nutricia, Hong Kong.*
Infant feed.
Diarrhoea; food hypersensitivity; malabsorption syndromes; malnutrition; short-bowel syndrome.

Coxalgan *Anpharm, Pol.*
Nabumetone (p. 97·1).
Degenerative joint disorders; rheumatoid arthritis.

Coxanturenasi *Teofarma, Ital.*
Pyridoxine hydrochloride (p. 2105·3); pyridoxal phosphate (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Vitamin B_6 and its co-enzyme deficiency.

Coxarthrum *LCA, Fr.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Coxbitor *Domesco, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain.

Coxegesic *Piramal, India.*
Parecoxib (p. 119·3).
Pain.

Coxerin *Macleods, India; Macleods, Rus.*
Cycloserine (p. 280·2).
Tuberculosis.

Coxerin Plus *Macleods, Rus.*
Cycloserine (p. 280·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation in an attempt to limit CNS adverse effects.
Tuberculosis.

Coxet *Anthus, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Coxeton *Polfa Pabianice, Pol.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Coxflam *Cipla-Medpro, S.Afr.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; sciatica.

Coxib *Micro, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Coxid *Aristo, India.*
Rifampicin (p. 350·3).
Bacterial infections.

Coxifact *Medico, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Coxina-3 *Aristo, India.*
1 Capsule rifampicin (p. 350·3); 1 tablet, isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Coxina-4 *Aristo, India.*
1 Capsule rifampicin (p. 350·3); 1 tablet isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1); 2 tablets pyrazinamide (p. 345·2).
Tuberculosis.

Coxinex *Aristo, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Coxium *Eurodrug, Malaysia; Eurodrug, Singapore.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; joint and cartilage disorders.

Millimed, Thai.
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

Coxkit-3 *Cipla, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Coxoral *OEP, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; adenomatous polyposis.

Coxpic *Alpic, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Coxrid *Piramal, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Coxtenk *Biotenk, Arg.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis.

Coxter-2 *Alkem, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Coxter-3 *Alkem, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Coxter-4 *Alkem, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Coxtral *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.*
Nimesulide (p. 101·3).
Pain; musculoskeletal, joint and peri-articular disorders; fever.

Coxulid *Husnu Arsan, Turk.*
Nimesulide (p. 101·3).

Coxumadol *Italfarmaco, Spain.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Coxylan *Sophia, Mex.*
Meloxicam (p. 86·3).
Eye inflammation; cystoid macular oedema.

Coxylate *Symbiosis, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Coxzan *Renata, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; adenomatous polyposis.

Coz *Elfin, India.*
Omeprazole (p. 1867·2) or omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Cozaar *MSD, Austral.; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; cardiovascular risk reduction; myocardial infarction; left-ventricular hypertrophy; stroke prophylaxis.

Cozaar Comp *MSD, Denm.; MSD, Fin.; MSD, Irl.; Euro Registratie, Neth.†; MSD, Norw.; MSD, S.Afr.; MSD, Swed.; MSD, UK.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cozaar Plus *MSD, Belg.; Orifarm, Denm.; MSD, Neth.; MSD, Port.; MSD, Spain.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cozaarex *MSD, Arg.*
Losartan potassium (p. 1422·2).
Left ventricular hypertrophy; hypertension; diabetic nephropathy.

Cozaarex D *MSD, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; left ventricular hypertrophy.

Cozabal *Sun, India.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Cozacin *Cinerea, India.*
Clozapine (p. 1057·3).
Schizophrenia; parkinsonism-associated psychoses.

Cozan *Genesis, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Cozan-O *Genesis, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Cozan-T *Genesis, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Cozapert *Viofar, Gr.*
Losartan potassium (p. 1422·2).

Cozatan *Clonmel, Irl.*
Losartan potassium (p. 1422·2).
Hypertension; stroke prophylaxis; heart failure; diabetic nephropathy.

Cozatan Comp *Clonmel, Irl.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Coz-D *Elfin, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Cozep
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome.
Piramal, India.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Cozetamin *Velka, Gr.*
Dihydroergotamine mesilate (p. 672·2).

Cozine *Candor, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Cozit *Emcure, India.*
Tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Cozole *Metz, Philipp.†; Be-Tabs, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Co-Zomevek *Novartis, S.Afr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Cozy *Ind-Swift, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Cozy Cool *Ind-Swift, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; upper respiratory-tract congestion.

Cozy Kid *Ind-Swift, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Cozy Plus *Ind-Swift, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Cozy-AM *Ind-Swift, India.*
Oral liquid: Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); loratadine (p. 633·2).
Ind-Swift, India.
Tablets: Ambroxol (p. 1654·3); loratadine (p. 633·2).

Cozymin *Unimarck, India.*
Syrup: Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2).
Unimarck, India.
Tablets: Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Unimarck, India.
Oral drops: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Cozymin-AF *Unimarck, India.*
⊗Cetirizine (p. 619·2); pseudoephedrine (p. 1676·1).
Allergic rhinitis.

CP *Bal, India.*
Chromium tripicolinate (p. 2056·1).

CP Bright *Bausch & Lomb, China.*
Zinc sulfate (p. 2126·2); aldioxa (p. 1692·2); sodium hyaluronate (p. 2526·2).
Eye irritation.

CP Cough Syrup *Hovid, Malaysia.*
Carbocisteine (p. 1658·1); promethazine hydrochloride (p. 638·2).
Cough.

CP-Acne Duo *Pharmatrix, Arg.*
Clindamycin phosphate (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

C-Pact *Cure Quick, India.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress incontinence in women.

CP-Atenol *Christo, Hong Kong.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

CPB WC *Elge, USA.*
⊗Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

CP-Betasone *Christo, Hong Kong.†*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

CP-Carba *Christo, Hong Kong.*
Carbamazepine (p. 512·2).
Epilepsy; mania; bipolar disorder; alcohol withdrawal; trigeminal neuralgia; diabetic neuropathy.

CP-Colchi *Christo, Hong Kong.*
Colchicine (p. 604·1).
Gout.

CP-Dexa *Christo, Hong Kong.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

C-Pela *TNP, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; nystagmus; nausea and vomiting; motion sickness.

CP-Enala *Christo, Hong Kong.†*
Enalapril maleate (p. 1371·1).

CP-Enala Co *Christo, Hong Kong.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

CP-Fluoxet *Christo, Hong Kong.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

CPF-TZ *McNeil & Argus, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

CP-Furo *Christo, Hong Kong.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; liver cirrhosis with ascites.

CPG *Kalbe, Indon.*
Clopidogrel (p. 1342·3).
Thromboembolic disorders.

CP-Gliben *Christo, Hong Kong.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

CP-Gliz *Christo, Hong Kong.*
Gliclazide (p. 472·3).
Diabetes mellitus.

CP-Griseo *Christo, Hong Kong.†*
Griseofulvin (p. 582·2).

C-Phenicol *Terramedic, Philipp.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

C-Pime *Osper, India.*
Cefepime (p. 239·2).
Bacterial infections.

C-Pime-T *Osper, India.*
Cefepime (p. 239·2); tazobactam (p. 369·3).
Bacterial infections.

CP-Indap *Christo, Hong Kong.†*
⊗Indapamide (p. 1409·2).

CPink *Wanbury, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

CP-Keto *Christo, Hong Kong.†*
Ketoconazole (p. 585·3).
Fungal skin infections.

C-plan *Polifarma, Turk.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

C-Platin *Blausiegel, Braz.*
Cisplatin (p. 766·1).
Malignant neoplasms.

CP-Loradine *Christo, Hong Kong.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

CP-Lovac *Christo, Hong Kong.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

C-Plus
Note: this name may be used for preparations of different composition.
Hylands, Canad.
Eupatorium perfoliatum (p. 2459·1); euphrasia officinalis (p. 2502·1); gelsemium sempervirens (p. 2511·2); kali iodatum (p. 2336·3).
Homoeopathic preparation.
Plus, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

CP-Lyso *Christo, Hong Kong.*
Muramidase hydrochloride (p. 2565·1).
Chronic sinusitis; respiratory-tract disorders associated with viscous mucus; minor haemorrhage.

CPM *Medicine Products, Thai.*
Syrup: Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Medicine Products, Thai.
Tablets: Chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2).

CPM PSE MSC *Cypress, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); hyoscine methonitrate (p. 1846·1).
Rhinitis.

CP-Metform *Christo, Hong Kong.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

CP-Metolol *Christo, Hong Kong.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; migraine; hyperthyroidism.

CP-Metolol Co *Christo, Hong Kong.†*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

CPM/PE/MSC *Cypress, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Allergic rhinitis.

CPM/PSE/DM *Trigen, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

CPod *NB, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

CPP
Note: this name may be used for preparations of different composition.
P & B, India.
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).
Cold symptoms.
Synco, Hong Kong.†
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; nasal congestion.

CP-Pirox *Christo, Hong Kong.*
Piroxicam (p. 125·3).
Osteoarthritis; musculoskeletal disorders.

CP-Prazo *Christo, Hong Kong.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; benign prostatic hyperplasia; Raynaud's disease.

CP-PTU *Christo, Hong Kong.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

CP-Pyridine *Christo, Hong Kong.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract disorders.

C-Pram *Unichem, India.*
Citalopram (p. 411·1).
Depression; panic disorder.

C-Pram-S *Unichem, India.*
Escitalopram oxalate (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

C-Pram-S Plus *Unichem, India.*
Escitalopram (p. 416·2); clonazepam (p. 519·1).

C-Praz *Corona, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

C-Praz-D *Corona, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

CPressin *Samarth, India.*
⊗Vasopressin (p. 2642·3).
Diabetes insipidus; variceal haemorrhage.

C-Pro *Corona, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

C-Prot *Corona, India.*
Preparation for enteral nutrition.

C-Provit *Corona, India.*
Protein; vitamins.

C-Prox *Plus, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

C-Prox-LB *Plus, India.*
Cefpodoxime proxetil (p. 248·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

CPS Pulver *Brady, Austria; Teva, Ger.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

CP-Test *Astellas, Ital.*
Test for *Helicobacter pylori* infection.

CP-Theo *Christo, Hong Kong.*
Theophylline (p. 1229·3).
Obstructive airways disease.

CP-Tran *Christo, Hong Kong.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders.

C-Quin *Ikon, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; rheumatoid arthritis; amoebiasis.

Crack Free *Vencare, India.*
Honey (p. 2072·1).

Cradol *Alpic, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cradol-P *Alpic, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Craegium *Hexal, Ger.†*
Crataegus (p. 2488·1).
Heart failure.

Crafilm *Francia, Ital.*
Sucralfate (p. 1889·1).
Gastrointestinal disorders associated with hyperacidity.

Cralex *Egis, Hung.*
Activated charcoal (p. 1537·3).
Diarrhoea.

Cralonin *Heel, Austria; Heel, Ger.; Heel, Neth.; Ebi, Switz.*
Crataegus (p. 2488·1); spigelia anthelmia (p. 2621·3); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Cralonin H *Heel, Neth.*
Cactus grandiflorus (p. 2473·2); crataegus oxyacantha (p. 2488·1); kalium carbonicum (p. 2595·2); sarothamnus scoparius (p. 2611·3); spigelia anthelmia (p. 2621·3).
Homoeopathic preparation.

Cramin Forte *Medisys, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Crampex *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Calcium gluconate (p. 1783·3); nicotinic acid (p. 2083·1); colecalciferol (p. 2113·1).
Night cramps.

Crampeze Night Cramps *Brands Worldwide, Austral.*
Rutoside (p. 2505·3); citrus bioflavonoids (p. 2505·2); magnesium (p. 1786·3); pyridoxine hydrochloride (p. 2105·3).
Muscle cramps; night cramps.

Crampeze Pain Relief *Brands Worldwide, Austral.*
Sweet birch oil (p. 92·1); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1).
Muscle cramps; musculoskeletal and joint disorders.

Crampeze PMT Cramps *Brands Worldwide, Austral.†*
Viburnum opulus; calcium hydrogen phosphate (p. 1783·3); magnesium phosphate (p. 1787·3); pyridoxine hydrochloride (p. 2105·3).
Premenstrual syndrome.

Crampeze Stomach Cramps *Brands Worldwide, Austral.*
Chamomile (p. 2474·1); fennel (p. 2503·2); peppermint oil (p. 1877·1); calcium hydrogen phosphate (p. 1783·3); magnesium phosphate (p. 1787·3).
Gastrointestinal cramps; dyspepsia; irritable bowel syndrome; heartburn; flatulence.

Crampiton *Orion, Fin.*
Quinine hydrochloride (p. 665·2); meprobamate (p. 1083·3).
Muscle spasm.

Cramplex *Mediherb, Austral.*
Corydalis tuber; raspberry leaf (p. 2603·1); wild yam (p. 2648·1); viburnum opulus; ginger (p. 1844·1).
Smooth muscle spasm.

Cranagil *Marien, Austria.*
Ammonium carbonicum (p. 1656·1); cephaelis ipecacuanha; gelsemium sempervivens (p. 2511·2); rhododendron.
Homoeopathic preparation.

Cranbe *Elder, India.*
Cranberry extract (p. 2488·1).
Urinary-tract infections.

Cranberry 10,000 *Bullivants, Austral.*
Cranberry (p. 2488·1); ascorbic acid (p. 2110·3).
Cystitis.

Cranberry Complex
Note: this name may be used for preparations of different composition.
Mediherb, Austral.
Bearberry (p. 2453·2); buchu (p. 2461·3); crataeva nurvala; cranberry (p. 2488·1).
Dietary supplement for urinary-tract health.
Cenovis, Austral.†
Cranberry (p. 2488·1); buchu (p. 2461·3); bearberry (p. 2453·2); ascorbic acid (p. 2110·3).
Cystitis; fluid retention.

Cranbiotic Super *Bioglan, Austral.†*
Cranberry (p. 2488·1); taraxacum (p. 2625·3); bearberry (p. 2453·2); buchu (p. 2461·3); solidago (p. 2620·1).
Cystitis.

Cranim-P *Alpic, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Cranio-cyl Ho-Len-Complex *Liebermann, Ger.*
Coffea (p. 2648·2); colocynthis (p. 1833·3); ferrum met. (p. 2073·1); gelsemium (p. 2511·2); ignatia (p. 2532·1); ruta (p. 2608·2); sanguinaria (p. 2610·1); spigelia (p. 2621·3).
Homoeopathic preparation.

Cranoc *Novartis, Ger.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia.

Crantex *Breckenridge, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs.

Cras *Desitin, Ger.*
⊗Buprenorphine hydrochloride (p. 30·3).
Opioid dependence.

Crasia *Alpic, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Crasia-O *Alpic, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Crataefortan *Schwabe, Austria.*
Crataegus (p. 2488·1).
Cardiac disorders.

Crataegan *Austroplant, Austria.*
Crataegus (p. 2488·1).
Cardiac disorders.

Crataegisan *Bioforce, Switz.*
Crataegus (p. 2488·1).
Cardiac disorders.

Crataegitan *Amino, Switz.*
Crataegus (p. 2488·1).
Cardiac disorders.

Crataegus comp
Note: this name may be used for preparations of different composition.
Steigerwald, Ger.
Ether (p. 1900·3); camphora (p. 2466·2); crataegus (p. 2488·1).
Homoeopathic preparation.
Weleda, Ger.
Aurum metallicum (p. 2521·1); cactus grandiflorus (p. 2473·2); onopordum acanthium; hyoscyamus niger (p. 2530·2); primula veris (p. 2596·2); cor bovis (p. 2444·1); crataegus (p. 2488·1).
Homoeopathic preparation.

Crataegus Complexe No 15 *Lehning, Fr.*
Crataegus oxyacantha (p. 2488·1); arnica montana (p. 2447·2); cactus grandiflorus (p. 2473·2); aconitum (p. 2428·3); nux vomica (p. 2573·3); glonoinum (p. 1391·2); apocynum cannabinum; arsenicum album (p. 2448·1).
Homoeopathic preparation.

Crataegus Herzcomplex *Hevert, Ger.*
Cactus (p. 2473·2); crataegus (p. 2488·1); leonurus (p. 2564·2); oleander (p. 2574·3); valerian (p. 2640·2).
Homoeopathic preparation.

Crataegus-Plus *Doctor H, Rus.*
Crataegus laevigata (p. 2488·1); rauwolfia serpentina (p. 1485·1); gelsemium sempervirens (p. 2511·2); gnaphalium obtusifolium; strychnos ignatii (p. 2532·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Crataegutt *Austroplant, Austria; Schwabe, Ger.; Schwabe, Singapore.†*
Crataegus (p. 2488·1).
Cardiac disorders; heart failure.

Cratae-Loges *Loges, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Cratal *Borshchagovskii, Ukr.*
Crataegus (p. 2488·1); motherwort (p. 2564·2); taurine (p. 2626·2).
Ischaemic heart disease; post-radiation syndrome.

Crategil *Naturland, Hung.*
Crataegus (p. 2488·1); black currant (p. 2458·1); melissa (p. 2552·3); magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Cardiovascular disorders.

Cratenox *Knop, Chile.*
Crataegus (p. 2488·1).
Cardiovascular disorders.

Cratex
Note: this name may be used for preparations of different composition.
Cratus, India.
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Cratisone *Cratus, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Cratonic *Herbapol Wrodaw, Pol.*
Crataegus (p. 2488·1).
Heart failure; arrhythmias.

Cratular *Fada, Arg.*
Sertraline (p. 448·1).
Depression.

Cravenorm *Craveri, Arg.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Craveril *Craveri, Arg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Craveril Duo *Craveri, Arg.*
Fenofibrate (p. 1381·1); ezetimibe (p. 1379·2).
Hyperlipidaemias.

Cravisol *Phytofarm Kleka, Pol.*
Crataegus (p. 2488·1); melissa (p. 2552·3); mistletoe (p. 2560·2).
Heart failure; atherosclerosis; hypertension; peripheral vascular disorders.

Cravit *Daiichi Sankyo, China; Daiichi Sankyo, Hong Kong; Santen, Hong Kong; Daiichi, Indon.; Kalbe, Indon.; Daiichi, Jpn; Santen, Jpn; Daiichi, Malaysia; Daiichi Sankyo, Singapore; Santen, Singapore; Daiichi Sankyo, Thai.; Santen, Thai.; Fako, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Cravox *Lapi, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Craztronin *Raam, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

CRB *Croesus, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Cream E45 *Boots Healthcare, NZ.†*
Emollient.
Dry skin.

Creamalin *Inovail, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; heartburn; dyspepsia.

Creamalin HM *Inovail, Philipp.*
Aluminium hydroxide (p. 1817·2); homatropine methylbromide (p. 2007·3).
Peptic ulcer; gastritis; gastric hyperacidity; pyrosis; heartburn.

Creamee *Leo, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).

Creanolona *Bohm, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin (p. 329·3); polymyxin B sulfate (p. 342·3).
Skin infections with inflammation.

Creatile *Fargim, Ital.*
Creatine (p. 2488·3).
Nutritional supplement.

Creatyl *Volchem, Ital.*
Amino acids; with or without carbohydrate.
Nutritional supplement.

Creavit *Pielle, Ital.*
Carnitine (p. 2053·2); creatine (p. 2488·3); minerals; vitamins.
Tonic.

Crebros *Berksam, Turk.*
Levocetirizine hydrochloride (p. 632·3).

Crecil *Vinas, Spain.*
Cystine (p. 2059·1).
Cystine deficiency.

Credanil *Remedica, Singapore.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Credaxol *Quimica y Farmacia, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; mastocytosis; gastro-oesophageal reflux.

Credigyne *Effik, Ital.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Credigynette *Effik, Ital.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Cregar *Rafarm, Gr.*
Captopril (p. 1331·2).

Crelo Blanco *Wellpharma, Ital.*
Emollient.
Dry skin disorders; pharmaceutical base.

Crema Antiinflamatoria *Spineda, Arg.*
Diethylamine salicylate (p. 51·3); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Crema Bier *Bier, Ital.*
Barrier preparation.

Crema De Bismuto *Cevallos, Arg.; Chobet, Arg.; Denver, Arg.; Inmunolab, Arg.; Lafedar, Arg.; Vannier, Arg.*
Bismuth hydroxide (p. 1821·3); pectin (p. 2200·3).
Diarrhoea.

Crema Blanca *Bustillos, Mex.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation disorders.

Crema Compensadora Avene *Silesia, Chile.*
Emollient.
Eczema.

Crema Contraceptiva Lanzas *Faes, Spain.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Crema Dinor's *Nordin, Mex.*
Emollient.

Crema De Ordeñe *Nolt, Arg.*
Vitamin A (p. 2098·3); alpha tocopherol (p. 2119·1); aloe vera (p. 1693·2).
Dry skin disorders.
Spineda, Arg.
Vitamin A (p. 2098·3); benzalkonium chloride (p. 1737·1); zinc (p. 2126·1).
Skin disorders.

Crema Para Paspaduras *Johnson & Johnson, Arg.†*
Allantoin (p. 1693·1); wool fat (p. 2219·3); zinc (p. 2126·1).
Barrier cream.

Crema Para Pieles Intolerantes Avene *Silesia, Chile.*
Emollient.
Dry skin.

Cremadiet *Abbott, India.*
Ispaghula (p. 1849·1).

Cremaffin *Abbott, India.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2).
Constipation.

Cremaffin Plus *Abbott, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2); sodium picosulfate (p. 1887·2).
Constipation.

Cremag *Zuoz, Venez.*
Magaldrate (p. 1856·1).
Gastric hyperacidity.

Cremalax *Abbott, India.*
Sodium picosulfate (p. 1887·2).
Constipation.

Cremalgin *Co-Pharma, UK.†*
Methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2); capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint pain.

Cremalon *Zuoz, Venez.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; meteorism.

Creme Antirougeurs *Avene, Canad.†*
SPF 25: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Aquamucine *Laboratoires Dermo-Cosmetik, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Creme Blanchissante *Daniel, Canad.*
Hydroquinone (p. 1705·1).
Hyperpigmentation disorders.

Creme de Corps *Kiehls, Canad.†*
Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Creme de Dalibour *Cooperation Pharmaceutique, Fr.*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Skin irritation.

Creme Deodorant Multi-Soin Anti-Perspirant *Clarins, Canad.†*
Aluminium chlorohydrate (p. 1694·1).

Creme Ecran Solaire *Therapharma, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Ecran Total *Vichy, Canad.†*
SPF 45: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Crème des 3 Fleurs d'Orient *Creme d'Orient, Fr.†*
Ointment: Mequinol (p. 1711·1).
Hyperpigmentation.

Creme Fondante *Biotherm, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); ecamsule (p. 1702·1).
Sunscreen.

Creme Haute Exigence *Clarins, Canad.*
SPF 20: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Creme de Jour au Retinol *Garraud, Canad.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Laser Hidrante *Dermoteca, Port.†*
⊗Squalane (p. 2213·3); proline (p. 2086·2); urea (p. 1727·3); lactic acid (p. 2539·1); citric acid (p. 2480·3); *dl*-alpha tocopherol (p. 2119·1); butcher's broom (p. 2463·1).
Dry skin; skin irritation.

Crème au Mélilot Composée *Avene, Fr.†*
Dextran sulfate (p. 2492·2); melilot (p. 2552·3); butcher's broom (p. 2463·1).
Skin redness.

Creme Phyllis de Jeunesse *Sopar, Gr.*
Salicylic acid (p. 1719·1); hexachlorophene (p. 1754·1); resorcinol (p. 1718·3); sulfur (p. 1721·1); titanium dioxide (p. 1725·1).

Creme pour Peaux Intolerantes au Soleil *Esthederm, Canad.*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Protectrice Anti-Rides *Somak, Canad.†*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Creme de Soins *Clarins, Canad.†*
SPF 6: Titanium dioxide (p. 1725·1).
Sunscreen.

Creme Solaire *Garraud, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Creme Solaire Anti-Age *Garraud, Canad.†*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Creme Solaire Anti-Rides *Jean d'Estrees, Canad.†*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Solaire Ecran Total *Klorane, Canad.†*
SPF 30: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Creme Solaire Fondante Protection Minimale *Clarins, Canad.*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Creme Solaire Haute Protection *Clarins, Canad.*
SPF 20: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Solaire Haute Protection Special Visage *Clarins, Canad.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Solaire Regions Sensibles *Renaud, Canad.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Creme Solaire Tres Haute Protection Special Enfants *Clarins, Canad.†*
SPF 30: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Creme Solaire Tres Haute Protection Special Intolerances *Clarins, Canad.*
SPF 30: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Solaire Tres Haute Protection Special Peaux Sensibles *Clarins, Canad.*
SPF 30: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Creme de Teinte *Avene, Canad.†*
SPF 30: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Creme Universal *Merck, Braz.*
Emollient.

Creme Visage *Ombrelle, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Crème vulnéraire *Widmer, Switz.*
Kaolin (p. 1850·1); silver (p. 2615·1).
Minor skin lesions and burns.

Cremederme *Bunker, Braz.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Cremefenergan *Sanofi-Aventis, Braz.*
Promethazine (p. 638·2).
Pruritus; insect bites; allergic skin disorders.

Cremgen *Sperko, Ukr.*
⊗Fluocinonide (p. 1636·3); gentamicin sulfate (p. 304·2).
Skin disorders.

Cremicort *Omega, Neth.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cremicort-H *Omega, Belg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Cremin *Mitsubishi Tanabe, Jpn.*
Mosapramine hydrochloride (p. 1088·3).
Schizophrenia.

Creminem *Mintlab, Chile.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Creminem-B *Mintlab, Chile.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Fungal skin infections.

Cremirit *Mintlab, Chile.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Cremisona
Note: this name may be used for preparations of different composition.
Diba, Mex.
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Cremolan *Gebro, Switz.*
Cream: ⊗Urea (p. 1727·3).
Dry skin disorders; hyperkeratosis; eczema.
Gebro, Switz.
Lotion: Triclosan (p. 1773·2).
Skin cleanser.

Cremol-Ritter *Gebro, Switz.*
A range of skin cleansing and emollient preparations.
Skin disorders.

Cremor *Naturland, Hung.*
Aluminium acetotartrate (p. 2440·1).
Skin disorders.

Cremor Capsici Compositus *Pharmachemie, Neth.*
Capsicum (p. 2469·3); glycol salicylate (p. 66·2); histamine hydrochloride (p. 2525·2); methyl nicotinate (p. 91·3).
Musculoskeletal, joint, and soft-tissue disorders.

Cremosan *Quimica y Farmacia, Mex.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Cremsol *Quimifar, Spain.†*
⊗Linseed oil (p. 2544·2); calcium hydroxide (p. 2465·1); benzocaine (p. 1980·2); sulfathiazole (p. 368·3); triamcinolone acetonide (p. 1649·1); zinc oxide (p. 1729·1).
Infected skin disorders.

Cremsor N *LKM, Arg.*
⊗Allantoin (p. 1693·1); coal tar (p. 1723·2); urea (p. 1727·3).
Skin disorders.

Creobic *Katra, Singapore.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Creolina *Pearson, Ital.*
Cresol (p. 1749·1).
Surface disinfection.

Creomulsion *Creomulsion, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Creon *Raffo, Arg.; Abbott, Austral.; Solvay, Belg.; Abbott, Braz.; Abbott, Canad.; Grunenthal, Chile; Abbott, Denm.; Abbott, Fin.; Abbott, Gr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, India; Abbott, Irl.; Abbott, Israel; Solvay, Ital.; Solvay, Malaysia; Italmex, Mex.; Abbott, Neth.; Abbott, Norw.; Boehringer Ingelheim, NZ; Solvay, Philipp.; Solvay, S.Afr.; Abbott, Singapore; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Solvay, UK; AbbVie, USA.*
Pancreatic enzymes (p. 2579·3).
Pancreatic insufficiency; digestive disorders; cystic fibrosis; chronic pancreatitis.

Abbott, China.
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Créon *Abbott, Fr.*
Pancreatic enzymes (p. 2579·3).
Pancreatic insufficiency.

Creo-Rectal *Sandoz, Canad.*
Diphenylpyraline hydrochloride (p. 627·2); guaiacol carbonate (p. 1666·1); camphor (p. 2466·2).
Cough.

Creosedin *Rontag, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Creosoto Composto *Ogna, Ital.*
Creosote (p. 1659·3); phenol (p. 1763·3); lidocaine hydrochloride (p. 1988·2); eugenol (p. 2501·2).
Dental pain.

Creo-Terpin *Lee, USA.*
Dextromethorphan hydrobromide (p. 1660·1).

Cresadex *Drugtech, Chile.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias.

Cresar *Cipla, India.*
Telmisartan (p. 1509·3).
Hypertension.

Crescom *Esoform, Ital.*
Sodium *o*-phenylphenol (p. 1762·3).
Surface disinfection; instrument disinfection.

Cresophene
Note: this name may be used for preparations of different composition.
Septodont, Canad.
⊗Camphor (p. 2466·2); dexamethasone (p. 1630·3); parachlorophenol (p. 1763·1); thymol (p. 1772·2).

Septodont, Fr.; Septodont, Israel.†
⊗Dexamethasone acetate (p. 1631·1); thymol (p. 1772·2).
Dental canal disinfection.

Septodont, Spain.
⊗Dexamethasone (p. 1630·3); hexachlorophene (p. 1754·1); prajmalium bitartrate (p. 1472·2); parachlorophenol (p. 1763·1).
Oral disinfection; dental caries.

Crest Pro-Health *Procter & Gamble, Canad.*
Cetylpyridinium chloride (p. 1743·1).

Crestor *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; AstraZeneca, USA; AstraZeneca, Venez.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias; atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Cresylate *Recsei, USA.*
m-Cresyl acetate (p. 1749·1); isopropyl alcohol (p. 1758·3).
Ear infection.

Creval *Ranbaxy, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Crevet *Prater, Chile.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Crevet Calcio + D3 + C *Prater, Chile.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Calcium supplement.

Crevet L *Prater, Chile.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Crevet-E *Prater, Chile.*
Vitamin E (p. 2119·1).

Crevytin *Tolmann, Philipp.†*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2).

CRH *Ferring, Austria; Ferring, Ger.; Ferring, Neth.*
⊗Corticorelin triflutate (p. 1628·2).
Diagnosis of adrenal disorders; diagnosis of Cushing's syndrome.

Crialix *Filaxis, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Criam *Psicofarma, Mex.*
Magnesium valproate (p. 553·1).
Epilepsy; migraine; bipolar disorder.

Criax *Meprofarm, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

C-Rich *Willow, India.*
Syrup: Vitamins; minerals; lycopene (p. 2546·2).
Willow, India.
Tablets: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

C-Ricin *Patar, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Crifty *Wermar, Mex.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Crilem *Lemery, Mex.†*
Bromocriptine mesilate (p. 895·3).

Crima *Fada, Arg.*
Ceftazidime (p. 250·2).
Bacterial infections.

Crimak *Farmalex, Gr.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Crimanex *Drossapharm, Switz.*
Shampoo; topical solution: Dipyrithione (p. 1701·1); undecenoic acid diethanolamide (p. 596·3).
Scalp disorders.

Crimax *Marien, Austria.*
Acidum hydrofluoricum (p. 2529·1); graphites (p. 2522·1); pel talpae; selenium amorphum (p. 2086·3); thallium metallicum.
Homoeopathic preparation.

Crimson *Pond's, Philipp.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; androgen-associated acne and hirsutism in women.

Crinalsofex *Sofex, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Crino Cordes *Ichthyol, Austria.*
Sodium bituminosulfonate (p. 1706·1); sodium sulfosuccinated undecenoic acid monoethanolamide (p. 596·3).
Scalp disorders.

Crinohermal fem *Almirall Hermal, Ger.*
⊗Fluprednidene acetate (p. 1637·3); estradiol (p. 2271·1).
Female hair loss.

Crinone *Merck Serono, Arg.; Merck Serono, Austral.; Serono, Belg.; Merck, Braz.; Serono, Canad.; Merck, Chile; Merck Serono, China; Serono, Cz.; Merck, Denm.; Merck, Fin.; Merck Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Merck, Hung.; Serum Institute, India; Merck, Indon.; Merck Serono, Irl.; Merck Serono, Israel; Merck Serono, Ital.; Merck Serono, Malaysia; Serono, Mex.†; Merck, Norw.; Healthcare Logistics, NZ; Merck, Philipp.; Merck, Port.; Merck Serono, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Thai.; Serono, Turk.; Serono, UK; Watson, USA; Serono, Venez.*
Progesterone (p. 2300·2).
Female infertility; premenstrual syndrome; dysfunctional uterine bleeding; menstrual disorders; progesterone deficiency; menopausal disorders; secondary amenorrhoea; adjuvant in oestrogen replacement therapy.

Crinoren *Vifor, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Crinoretic *Vifor, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Criotonal *Amnol, Ital.*
Aescin (p. 2431·2); caffeine (p. 1203·3); ruscus; centella (p. 1698·3); arnica (p. 2447·2); hedera; capsicum (p. 2469·3); ginkgo biloba (p. 2512·3); menthol (p. 2553·2).
Skin disorders.

Cripar *Doppel, China; Hormosan, Ger.†; Taurus, Ger.†; Merz, Switz.†*
Dihydroergocryptine mesilate (p. 390·2).
Parkinsonism; migraine; headache; hyperprolactinaemia.

Cripofen *Arlex, Mex.*
Oral drops: Paracetamol (p. 115·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Influenza symptoms.

Cripsa *Caprifarmindo, Indon.; Sanbe, Indon.*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; premenstrual syndrome; acromegaly; parkinsonism.

Criptal *Helios, India.*
Bromocriptine (p. 895·3).
Parkinsonism; hypogonadism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Crisabon *Teva Tuteur, Arg.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Crisacide *LKM, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Crisafeno *LKM, Arg.*
⊗Tamoxifen citrate (p. 860·2).

Crisanta *Cipla, India.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).

Crisapla *LKM, Arg.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Crisarfam *Pharmacare, Philipp.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis, leprosy, and gonorrhoea.

Crisasma *Sintesina, Arg.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Crisazet *LKM, Arg.*
Zidovudine (p. 1024·2).
HIV infection.

Crislaxo *Quimifar, Spain.*
Aloes (p. 1816·1); aniseed (p. 2444·2); cascara (p. 1826·1); senna (p. 1885·1); fennel (p. 2503·2); rhubarb (p. 1884·2); sulfur (p. 1721·1); belladonna (p. 2453·3).
Constipation.

Crismol *Pharma Investi, Chile.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Crismotil *Ultra, Mex.*
Trimebutine (p. 2634·1).
Gastrointestinal disorders.

Crisofimina *Teva Tuteur, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Crisomet *GSK, Spain.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Crisplus *Elea, Arg.*
Orlistat (p. 2577·1).
Obesity.

Cristaclar *Beta, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Cristadoce *Intra, Venez.*
Vitamin B_{12} (p. 2107·2).
Dietary supplement; reduced appetite.

Cristal
Note: this name may be used for preparations of different composition.
Cooperation Pharmaceutique, Fr.
⊗Glycerol (p. 2517·2).
Constipation.

Cristalcrom *Cinfa, Spain.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Cristalin *Uniao Quimica, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).

Cristalmina *Salvat, Spain.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Cristalomicina *Ivax, Arg.*
Ear drops: ⊗Kanamycin sulfate (p. 314·3); hydrocortisone (p. 1640·1); phenazone (p. 124·1); benzocaine (p. 1980·2).
Otitis externa.
Ivax, Arg.
Injection: Kanamycin sulfate (p. 314·3).
Tuberculosis.

Cristalomicina NF *Ivax, Arg.*
⊗Polymyxin B (p. 342·3); neomycin (p. 329·3); hydrocortisone (p. 1640·1); lidocaine (p. 1988·1).
Ear disorders.

Cristalpen *Biolab Sanus, Braz.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Cristan *Shin Poong, Singapore.*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Cristane *Crisdy-Na, Philipp.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Dietary supplement.

Cristerona *Craveri, Arg.*
Estradiol (p. 2271·1); progesterone (p. 2300·2).
Menstrual disorders.

Cristil *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Criten *Tecnofarma, Chile.*
Bromocriptine mesilate (p. 895·3).
Acromegaly; hyperprolactinaemia; parkinsonism.

Critic-Aid Clear *Coloplast, Canad.*
White soft paraffin (p. 2211·3).

Critic-Aid Clear AF *Coloplast, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Criticare HN *Mead Johnson Nutritionals, USA.*
Lactose-free preparation for enteral nutrition.
Mead Johnson, Austral.†
Preparation for enteral nutrition.

Critifol *Piramal, India.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Crivanil *Sandoz, Arg.*
⊗Fluticasone (p. 1638·1).
Asthma.

Crivanil Plus *Sandoz, Arg.*
⊗Fluticasone (p. 1638·1); salmeterol (p. 1224·1).
Asthma.

Crivion *Farmamust, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Crivosin *Pisa, Mex.†*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Crixan *Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Mex.†; Ranbaxy, Singapore; Ranbaxy, Thai.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Crixivan *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.†; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Indinavir sulfate (p. 986·1).
HIV infection.
MSD, Jpn.
Indinavir sulfate ethanolate.
HIV infection.

Crizin *Labesfal, Port.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Crizmat *Farmaceutica H, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Cro 50 *Investigaciones Filosoficas y Cientificas, Mex.*
Ribonuclease (p. 2604·1).
Inflammation.

Croben *Marfarma, Ital.*
Chromium (p. 2055·3).
Nutritional supplement.

Crobextin *Hexal, Philipp.†; Salutas, Philipp.†*
Carboplatin (p. 759·1).
Malignant neoplasms.

Croc Bloc *Croc Bloc, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Crocalcin *Aurora, Gr.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia.

Crocin *GSK, India; Solvay, Philipp.†*
Paracetamol (p. 115·1).
Fever; pain.

Crocin Cold N Flu *GSK, India.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Crocin Pain Relief *GSK, India.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain.

Crof *Alpic, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

CroFab *Altana, USA.*
Crotalidae polyvalent immune fab (p. 2419·1).
Rattlesnake bites.

Crofed *Coronet, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; upper respiratory-tract allergy.

Croferron *Degorts, Mex.*
Ferrous fumarate (p. 2060·3).
Iron deficiency.

Crohnax *Farmina, Pol.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Crohnezine *Vianex (Βιανεξ), Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Croix Blanche *SMB, Belg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Croix Blanche Mono *SMB, Belg.†*
Paracetamol (p. 115·1).
Fever; pain.

Crolidin *Kleva, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Crolim *Ranbaxy, India.*
Tacrolimus (p. 1968·3).
Transplant rejection; Crohn's disease; atopic eczema.

Crolin *Corsa, Indon.*
Citicoline sodium (p. 2480·2).
Head injury; stroke.

Crolisil *Loeffler, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Crolix *Rayere, Mex.*
Roxithromycin (p. 356·2).
Bacterial infections.

Crolom *Bausch & Lomb, USA.*
Sodium cromoglicate (p. 1225·3).
Inflammatory disorders of the eye.

Croloxat *Cell Pharm, Ger.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Crom *SF, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Cromabak *Thea, Belg.; Allergan, Braz.; Thea, Fr.; Pharmex (Φαρμεξ), Gr.; Thea, Hong Kong; Thea, Ital.; Thea, Philipp.; Thea, Port.; Genop, S.Afr.; Pfizer, Singapore; Thea, Switz.; Santa, Turk.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Cromadoses *Thea, Fr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Cromagen AF *Valdecasas, Mex.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; homocystinaemia.

Cromal *Cipla, Hong Kong†; Cipla, India; Cipla, Malaysia.*
Sodium cromoglicate (p. 1225·3).
Asthma; allergic eye disorders; allergic rhinitis.

Crom-Allerg *Rompharm, Rus.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cro-Man-Zin *Freeda, USA.*
Chromium (p. 2055·3); manganese (p. 2081·2); zinc (p. 2126·1).
Mineral supplement.

Cromate *Cosme, India.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromatodol *Croma, Austria.*
Tramadol hydrochloride (p. 139·2).
Pain.

Cromatonbic B12 *Menarini, Spain.*
Cyanocobalamin (p. 2107·2).
Vitamin B12 deficiency.

Cromatonbic Ferro *Menarini, Spain.*
Ferrous lactate (p. 2062·1).
Iron deficiency; iron-deficiency anaemia.

Cromatonbic Folinico *Menarini, Spain.*
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; methotrexate toxicity; adjunct to fluorouracil therapy.

Cromatonferro *Menarini, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in the tablets to increase the absorption and availability of iron.
Iron deficiency; anaemias.

Cromax *Ashford, Singapore.*
Eye drops: Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

C-Rome *Mapra, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Crome *Ferron, Indon.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhagic disorders.

Cromedil *Europhta, Mon.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromese *Pfizer, Austral.†*
Sodium cromoglicate (p. 1225·3).
Asthma.

Cromezin *SoSe, Ital.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Cromidin *Royal, Chile.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Cromisol *Vivax Optipharm, Venez.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromo *Ratiopharm, Ger.; Stulln, Ger.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis; asthma; hypersensitivity reactions.

Cromo Sandoz *Sandoz, Ukr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Cromobene *Ratiopharm, Cz.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Cromocato *Neo Quimica, Braz.*
Sodium cromoglicate (p. 1225·3).

Cromo-COMOD *Ursapharm, Israel.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Cromodal *Zwitter, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Cromodyn *Rappai, Switz.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Cromofer-OD *Dewcare, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2); vitamin B_{12} (p. 2107·2).

Cromofer-XT *Dewcare, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Cromofer-Z *Dewcare, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Cromoftal *Oftalmi, Venez.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Cromogen *Ivax, Irl.†; Norton, Pol.†*
Sodium cromoglicate (p. 1225·3).
Asthma.

Cromoglin *Ratiopharm, Austria; Ratiopharm, Rus.; Ratiopharm, Ukr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders; obstructive airways disease; allergic rhinitis.

Cromohexal *Hexal, Cz.; Hexal, Ger.†; Sandoz, Hung.†; Sandoz, Pol.; Hexal, Rus.; Hexal, S.Afr.; Sandoz, Ukr.†*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis; keratoconjunctivitis; asthma.

Cromolerg *Allergan, Braz.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromolergin UD *Pharmanel, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Cromolux *AFT, Austral.; AFT, NZ.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromolyn *Pendopharm, Canad.; Hind Wing, Hong Kong†; Genmedix, Israel.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromonez-Pos *Ursapharm, Belg.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Cromopharm *Farmak, Ukr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; keratoconjunctivitis; allergic rhinitis.

Crom-Ophtal *Winzer, Ger.; Sanbe, Indon.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; keratoconjunctivitis; allergic rhinitis.

Cromophta-Pos *Ursapharm, Belg.†*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Cromoplex *Aristo, India.*
Vitamins; chromium (p. 2055·3); zinc (p. 2126·1).

Cromo-POS *Farmex, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Cromopp *Dermapharm, Ger.†*
Sodium cromoglicate (p. 1225·3).
Asthma.

Cromoptic *Chauvin, Fr.; Vitamed, Israel.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders; allergic conjunctivitis.

Cromorhinol *Chauvin, Fr.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Cromosandoz *Sandoz, Hung.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis; allergic conjunctivitis.

Cromosoft *Thea, Fr.†*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Cromosol *ICN, Pol.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Cromosol ophta *Sandoz, Switz.*
Sodium cromoglicate (p. 1225·3).
Conjunctivitis.

Cromosol UD *Sandoz, Switz.*
Sodium cromoglicate (p. 1225·3).
Asthma.

Cromotex *Medix, Mex.*
Chromium polynicotinate (p. 2055·3).
Chromium supplement.

Cromoxal *Sandoz, Pol.*
Sodium cromoglicate (p. 1225·3).
Asthma.

Cromozil *Tubilux, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3); sodium cromoglicate (p. 1225·3).
Conjunctivitis.

Cromycin *Croma, Austria.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Cronal *Valdecasas, Mex.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity.

Cronase
Note: this name may be used for preparations of different composition.
GMP, Indon.
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.
Vitamed, Israel.
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Cronassial *Fidia, Singapore.*
Gangliosides (p. 2510·2).

Cronavit *Degorts, Mex.*
Vitamins; iron (p. 2073·1).
Tonic.

Croneparina *Ivax, Arg.; UCB, Gr.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Cronezil *Vianex (Βιανέξ), Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Cronica *Ranbaxy, India.*
Vitamins; minerals; trace elements.

Cronical *Ranbaxy, India.*
Vitamins; minerals; trace elements.

Cronitin *GMP, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Cronizat *Caber, Ital.*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Crono Corticas *Casasco, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cronobe *Biolab Sanus, Braz.*
Cobamamide (p. 2107·2).
Tonic.

Cronobetacort *Cassara, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cronocaps *Medix, Mex.*
Melatonin (p. 2551·3).
Insomnia.

Cronocef *Valeant, Ital.*
Cefprozil (p. 248·2).
Bacterial infections.

Cronocol *EUSA, Port.*
Gentamicin sulfate (p. 304·2).
Bone infections.

Cronocor *Arrow, Braz.*
⊗Carvedilol (p. 1333·1).

Cronocorteroid *Montpellier, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cronodicasone *Baliarda, Arg.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cronodicasone Depot *Baliarda, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Cronodine *Alacan, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Cronogeron *Arrow, Braz.*
Cinnarizine (p. 622·1).
Peripheral vascular disorders; vestibular disorders.

Cronol *Arabis, Spain.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cronolax *Andromaco, Chile.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Cronolevel *Schering-Plough, Arg.; Schering-Plough, Chile; Schering-Plough, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3). Lidocaine (p. 1988·1) is included in some injections to alleviate the pain of injection.
Corticosteroid.

Cronomet *MSD, Braz.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Cronopen *Elea, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Cronopen Balsamico *Elea, Arg.*
Ampicillin sodium (p. 218·2); ampicillin benzathine (p. 218·2); dipyrone (p. 53·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Cronopep *Biotoscana, Chile.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Cronoplex *Delta, Braz.*
Oral solution: Sodium picosulfate (p. 1887·2).
Constipation.
Delta, Braz.†
Suppositories; tablets: Bisacodyl (p. 1821·1).
Constipation.

Cronovera *Pfizer, Mex.; Pfizer, Venez.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Cronus *Tecnofarma, Chile.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

C-Ron-Z *Nestor, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Cropara *Shalaks, India.*
Paracetamol (p. 115·1).
Pain; fever.

Crophen *Shalaks, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Cropinex *Sons, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Cropoz *GSK, Rus.†*
Sodium cromoglicate (p. 1225·3).

Cropoz G *GSK, Pol.†*
Sodium cromoglicate (p. 1225·3).
Food allergy.

Cross *Doctum, Gr.*
Acetylcysteine (p. 1652·2).

Cross Brand Corn Plasters *Wrapsa, S.Afr.†*
Salicylic acid (p. 1719·1).
Corns; calluses; warts.

Crossa *T Man, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Cross-Terrain *Kiehls, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Crotalgin *In Vitro, Hung.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); crotalus atrox toxin (p. 2419·1).
Musculoskeletal and joint pain.

Crotalgin Forte *In Vitro, Hung.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); crotalus atrox toxin (p. 2419·1); cobra venom; menthol (p. 2553·2).
Musculoskeletal and joint pain.

Crotalgina *Esan, Chile.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm and pain.

Crotamitex *Gepepharm, Ger.†*
Crotamiton (p. 1699·2).
Scabies.

Crotamiton H *Pharmaniaga, Malaysia.*
⊗Hydrocortisone (p. 1640·1); crotamiton (p. 1699·2).
Skin disorders.

Crotanol *Roemmers Osmoph, Venez.*
Crotamiton (p. 1699·2).
Pruritus; scabies; pediculosis.

Crotax
Note: this name may be used for preparations of different composition.
Edol, Port.
Valaciclovir hydrochloride (p. 1021·1).
Esan, Chile.
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Crotec-EC *Unimarck, India.*
Vitamins; trace elements; lycopene (p. 2546·2).

Crotorax *Piramal, India; Idaman, Malaysia†; Idaman, Singapore.*
Crotamiton (p. 1699·2).
Scabies; pruritus; pediculosis.

Crotorax-HC *Sarabhai Piramal, India; Idaman, Singapore.*
⊗Crotamiton (p. 1699·2); hydrocortisone (p. 1640·1).
Pruritus; scabies; eczema; neurodermatitis; urticaria.

Crou Complex *Thompsons, Canad.†*
Aconite (p. 2428·3); calcium sulfide crude (p. 1721·3); spongia tosta.
Homoeopathic preparation.

Crovalen *Degorts, Mex.*
Vitamins; iron (p. 2073·1).

Crown Antiseptic Hand Soap *Crown, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Crowne *Master, Chile.†*
⊗Potassium nitrate (p. 1766·2).
Hypersensitive teeth.

C-Rox *Corona, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Croxilex *Ulagay, Turk.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Croydoxin-FM *GSK, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Crozy Plus *Zee, India.*
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Crucef *Aronex, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Cruciale *Aspen, S.Afr.*
Phosphatidyl choline (p. 2588·3).

Cruex *Novartis Consumer, USA.*
Aerosol; cream: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections; nappy rash; minor skin irritation; hyperhidrosis; bromhidrosis.
Novartis Consumer, USA.
Topical powder: Calcium undecenoate (p. 596·3).
Fungal skin infections; nappy rash; minor skin irritation; hyperhidrosis; bromhidrosis.
Novartis, USA.
Topical powder spray: Miconazole nitrate (p. 589·1).
Fungal skin infections.

Cruroheel S *Heel, Canad.†*
Apis mellifica (p. 2445·2); charcoal activated (p. 1537·3); hamamelis virginiana (p. 2523·3);

lycopodium clavatum (p. 2547·1); pulsatilla (p. 2600·2); silicon dioxide (p. 2208·3).
Homoeopathic preparation.

Cruscasohn *Antonetto, Ital.*
Cereal fibre; guar gum (p. 475·1); pectin (p. 2200·3).
Constipation.

Crush *Yacca, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Crusken *GSK Consumer, Ital.*
Dietary fibre.
Delayed gastrointestinal transit.

Cruzafen *Meditrina, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by cancer chemotherapy.

Cruzone *Aronex, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cruzzy *SIT, Ital.*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Cruzzy Shampoo Potenziato alla Sumitrina *SIT, Ital.*
Phenothrin (p. 2160·1).
Pediculosis.

Cryaxon *Bosch, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Cryl *Sophia, Mex.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Cryobutol *Cryopharma, Mex.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Cryocriptina *Cryopharma, Mex.†*
Bromocriptine (p. 895·3).
Lactation inhibition; hyperprolactinaemia.

Cryofaxol *Cryopharma, Mex.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; nephrotic syndrome; lupus erythematosus; rheumatoid arthritis; bone marrow transplantation.

Cryogesic *Acorus, UK.*
Ethyl chloride (p. 1987·1).
Local anaesthesia; testing of regional blockade; testing of tooth vitality.

Cryometasona *Cryopharma, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Cryoperacid *Cryopharma, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Cryopina *Cryopharma, Mex.*
Hyoscine butylbromide (p. 1845·3).

Cryoplex *Cryopharma, Mex.*
Vitamin B substances (p. 2102·3).
Neuritis; anaemias.

Cryopril *Cryopharma, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Cryosid *Cryopharma, Mex.*
Etoposide (p. 790·2).
Malignant neoplasms.

Cryosolona *Cryopharma, Mex.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Cryostatin *Cryopharma, Mex.*
Octreotide (p. 1924·1).
Acromegaly; variceal haemorrhage; hypotension; AIDS-associated diarrhoea; postoperative pancreatic complications; gastropancreatic endocrine tumours.

Cryotol *Cryopharma, Mex.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Cryo-Tropin *Cryopharma, Mex.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome.

Cryoxet *Cryopharma, Mex.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

Cryoxifeno *Pizzard, Mex.*
⊗Tamoxifen (p. 860·2).

Cryptal *Fahrenheit, Indon.*
Fluconazole (p. 578·2).
Fungal infections.

Cryptocur *Sanofi-Aventis, Gr.*
⊗Gonadorelin (p. 2280·2).

Crypton *Novaduo, India.*
Amitriptyline hydrochloride (p. 401·1).
Depression; neuropathic pain; migraine.

Crysanal *Roche, Austral.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Cryselle *Barr, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Crystacal *Cachet, India.*
Capsules: Calcitriol (p. 2113·1); calcium (p. 1783·1); magnesium (p. 1786·3); zinc oxide (p. 1729·1).

Cachet, India.
Syrup: Calcitriol (p. 2113·1); calcium levulinate (p. 1784·2).

Crystacide *Riemser, Ger.; Arriani, Gr.; Mipharm, Ital.; AFT, NZ; CS, Port.; GP, UK.*
Hydrogen peroxide (p. 1755·2).
Skin infections.

Crystacin *Vysali, Philipp.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Crystacit *Be-Tabs, S.Afr.*
Potassium citrate (p. 1780·3); citric acid (p. 2480·3).
Urinary alkalinisation.

Crystal Clear *Douglas, NZ.*
Pregnancy test (p. 2596·1).

Crystal Vits *Danlex, Philipp.*
Vitamins; minerals.
Dietary supplement.

Crystamine *Dunhall, USA.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency; schilling test.

Crystapen *Alveda, Canad.; Bioniche, Canad.; Genus, Irl.; Britannia Pharmaceuticals, UK.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Crystepin *Zentiva, Cz.†; Zentiva, Rus.*
⊗Clopamide (p. 1342·3); dihydroergocristine mesilate (p. 390·1); reserpine (p. 1485·3).
Hypertension.

Crysticillin *Apothecon, USA.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Crystodigin *Lilly, USA.*
Digitoxin (p. 1353·1).
Heart failure; atrial flutter and fibrillation; supraventricular tachycardia.

Crytion *Temis, Arg.*
Sodium aurotiosulfate (p. 132·1).
Rheumatoid arthritis.

Crytioro *Drag, Chile.†*
Sodium aurotiosulfate (p. 132·1).
Rheumatoid arthritis; psoriatic arthritis; juvenile idiopathic arthritis; ankylosing spondylitis; lupus erythematosus; pemphigus.

C-Serra *Corona, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

C-Serra-D *Corona, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

CSI *Unikid, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

CSI-S *Unikid, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

C-Solve *Syosset, USA.*
Vehicle for topical preparations.

CST *Pose, Thai.†*
Clotrimazole (p. 576·2).
Fungal vaginal infections; trichomoniasis.

C-Sylate *Corona, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

C-Sylate Plus *Corona, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

C-System C-Sunguard *Obagi, Canad.*
SPF 30: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

CT1000 *Sigma, Arg.*
Cartilage glycosaminoglycans (shark) (p. 2471·3).
Musculoskeletal and joint disorders; osteoporosis.

CT Ceff *Servocare, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

CT Ceff SM *Servocare, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

CT Ceff-TZ *Servocare, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

CT Spar *Servocare, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

CT Spar SM *Servocare, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

C-Tabs *Ferrosan, Denm.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

C-Tab-SB *Indkus, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

CTabs-Calcico *Labsa, Arg.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Dietary supplement.

CTabs-Correctol *Labsa, Arg.*
Ispaghula (p. 1849·1).

CTabs-Hierrofol *Labsa, Arg.*
Iron (p. 2073·1); folic acid (p. 2063·1).
Dietary supplement.

CTabs-Magnesio *Labsa, Arg.*
Magnesium (p. 1786·3); pyridoxine (p. 2105·3); zinc (p. 2126·1).
Dietary supplement.

CTabs-Noacidx *Labsa, Arg.*
Calcium (p. 1783·1); magnesium (p. 1786·3).
Dietary supplement.

CTabs-Total Vit *Labsa, Arg.*
Ginseng (p. 2513·3); vitamins; minerals.
Dietary supplement.

C-Talo *Alkem, India.*
Citalopram (p. 411·1).
Depression; panic disorder.

C-Tamin *Rekah, Israel.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

C-Tan D *Centurion, USA.†*
Phenylephrine tannate (p. 1672·2); brompheniramine tannate (p. 618·1).
Upper respiratory-tract disorders.

C-Tanna 12D *Prasco, USA.*
Pentoxyverine tannate (p. 1672·1); mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

CTarcal-C *Sanify, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3).

C-Tard *Wyeth Consumer, Ital.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; adjunct in stomatitis and gingivitis.

C-Tax *Zuventus, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

C-Tax P *Emcure, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

C-Tax-O *Zuventus, India.*
Cefixime (p. 240·3).
Bacterial infections.

C-Tax-O XL *Zuventus, India.*
Cefixime (p. 240·3); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

C-Tech *Malar, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

CTL *Hertz, Braz.*
Clotrimazole (p. 576·2).

CTLevo *Sanify, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

CTM
Note: this name may be used for preparations of different composition.
BDH, India.
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

BerlicoMulia, Indon.
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

CTMor-TZ *Aamorb, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

C-Tol
Note: this name may be used for preparations of different composition.
Corona, India.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

CTop *Intas, India.*
Clindamycin phosphate (p. 269·3).
Acne.

CTP *Sepracor, Canad.*
Citalopram hydrobromide (p. 411·1).
Depression.

CTR
Note: this name may be used for preparations of different composition.
Croesus, Philipp.
Co-trimoxazole (p. 277·3).
Bacterial infections.

Liptis, USA.
Atorvastatin (p. 1309·2).

C-Tri *Zuventus, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

C-Tri EM *Emcure, India.*
⊗Cefuroxime (p. 255·2); serrapeptase (p. 2613·3).
Bacterial infections.

C-Tri T *Emcure, Philipp.; Emcure, Thai.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

CTrisana-SB *Sanify, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

C-Tri-T *Zuventus, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

C-Triz *Corona, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

CT-Robes *Kee, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

C-Trol *Elfin, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

C-Tron *Corona, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

C-Trop *Elfin, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

CTrox *Servocare, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

C-Tum *Plus, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

CTX *Shince, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

CT-Xone *Sun, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

CTX-TZ *Shince, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

CTZ *Psychotropics, India.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

CTZ Plus *Psychotropics, India.*
⊗Cetirizine (p. 619·2); pseudoephedrine (p. 1676·1).
Allergic rhinitis.

CTZole *Neon, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Cuadel *Cetus, Arg.*
Diazepam (p. 1063·2).
Anxiety; muscle spasm.

Cuait D *Ariston, Arg.*
Trifluoperazine hydrochloride (p. 1113·2); tranylcypromine sulfate (p. 450·3).
Depression.

Cuait N *Ariston, Arg.†*
Trifluoperazine hydrochloride (p. 1113·2); amobarbital (p. 1037·2).
Insomnia.

Cuait Trifluoperazina *Ariston, Arg.*
Trifluoperazine hydrochloride (p. 1113·2).
Psychoses; anxiety.

Cuantil *Teva Tuteur, Arg.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Cuarcic *Monte Verde, Arg.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Cuartal *Finadiet, Arg.*
Erythromycin (p. 291·2).
Acne.

Cuassicum *Nucleopharm, Arg.*
Quassia (p. 2601·1); thyme oil (p. 2630·3).
Pediculosis.

Cuassicum Prevent *Nucleopharm, Arg.*
Quassia (p. 2601·1).
Pediculosis.

Cuatroderm *Desarrollo, Spain.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1).
Infected skin disorders.

Cuatroepi *Varifarma, Arg.*
Epirubicin (p. 787·1).
Malignant neoplasms.

Cuatromin *Grunenthal, Chile.*
Vitamins.

Cubal *Cure Quick, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Cubicin *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Sunovion, Canad.; AstraZeneca, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; AstraZeneca, Hong Kong; Novartis, Irl.; Cubist, Israel; Novartis, Ital.; MSD, Jpn; AstraZeneca, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; AstraZeneca, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; AstraZeneca, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; AstraZeneca, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Cubist, USA.*
Daptomycin (p. 284·2).
Right-sided infective endocarditis; Gram-positive bacterial skin and soft-tissue infections; Staphylococcus aureus bacteraemia.

Cubison *Nutricia, Austral.†; Nutricia, Cz.; Nutricia, Fin.; Nutricia, Ital.*
Preparation for enteral nutrition.
Dietary management of ulcers and chronic wounds.

Nutricia, Port.
Nutritional supplement.
Bedsores.

Cubitan *Nutricia, Austral.; Support, Braz.; Nutricia, Cz.; Nutricia, Fin.*
Preparation for enteral nutrition.
Dietary management of ulcers and chronic wounds.

Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.
Nutritional supplement.
Bedsores; pressure sores.

Cucal *Cubit, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Cucef
Note: this name may be used for preparations of different composition.
Curex, India.
Injection: Ceftriaxone (p. 253·3).
Bacterial infections.

Elfin, India.
Syrup: Cefalexin (p. 234·1).
Bacterial infections.

Cucef-S
Note: this name may be used for preparations of different composition.
Cubit, India.
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Curex, India.
Ceftriaxone (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Cucet-DT *Cubit, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Cucid *Cubit, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Cucid-DM *Cubit, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Cucid-ES *Cubit, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Cucin *Elfin, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Cucin-O *Elfin, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Cucin-T *Elfin, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Cuclav *Curex, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Cudec *Curex, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Cudom *Cubit, India.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Cudom-P *Cubit, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Cudrox *Elfin, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cue Soluzione Otologica *DMG, Ital.*
⊗Propylene glycol (p. 2205·2); glycerol (p. 2517·2); climbazole (p. 576·2); dipotassium glycyrrhizate (p. 2520·3); acetic acid (p. 2426·3); allantoin (p. 1693·1); essential oils.

Cuenca *Liconsa, Denm.†; Liconsa, Irl.*
Valsartan (p. 1521·2).
Myocardial infarction; heart failure; hypertension.

Cuerpo Amarillo Fuerte *Hormona, Mex.*
Progesterone (p. 2300·2).
Menstrual disorders; threatened miscarriage.

Cufcalm *Uniroyal, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cuf-Dex *Waves, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cufdex-EX *Waves, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Cufdip *Sanify, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Cufer-Z *Curex, India.*
Vitamins; iron carboxyl.

Cufex *Ind-Swift, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); menthol (p. 2553·2).

Cuffmol-P *Lexus, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Cuflox *Cubit, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Cufokin *Misha, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Cufol *Cubit, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy; folic acid supplement.

Cuforte *Cubit, India.*
Vitamin B substances (p. 2102·3).

Cufree *NB, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Cuga *Cadila, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Cuga Plus *Cadila, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Cugat *Cubit, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Cuidaderma *Caldeira & Metelo, Port.*
Zinc oxide (p. 1729·1); almond oil (p. 2437·1); starch (p. 2095·1); talc (p. 1722·2).
Skin irritation.

Cuidado Intimo *Beiersdorf, Chile.†*
Lactic acid (p. 2539·1); levomenol (p. 2544·1).
Feminine hygiene.

Cuidafem *Bernabo, Arg.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Cuine *China Chem & Pharma, Thai.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Cuivramine *Labrha, Fr.*
Glucosamine sulfate (p. 2515·3); ginger (p. 1844·1); copper (p. 2057·1).
Joint disorders.

Cujunsheng *Open, China.*
Bacillus cereus.

Culans *Elfin, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Culex *Curex, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Culexin *Curex, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Culin *Cubit, India.*
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Cullens Headache Powders *Cullen & Davison, UK.*
Aspirin (p. 22·2); caffeine (p. 1203·3).

Culmisa *Taisho, China.*
Aldioxa (p. 1692·2).

Culoc *Cubit, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Cultivo BCG *Teva, Mex.*
BCG vaccine (p. 2378·1).
Bladder cancer.

Culture Care *Lifeplan, UK.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactococcus lactis* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Maintenance of normal gastrointestinal flora.

Culturelle *i-Health, USA.*
Lactobacillus GG (p. 2596·3).

Pharma Dynamics, S.Afr.†
Capsule; chewable tablets: Bifidobacterium longum (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Restoration of intestinal flora.

Pharma Dynamics, S.Afr.†
Oral powder: Bifidobacterium longum (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Restoration of intestinal flora.

Culturelle With Lactobacillus GG *Pediapharma, Philipp.†*
Lactobacillus GG (p. 2596·3); inulin (p. 2534·3).
Restoration of gastrointestinal flora; immunomodulator.

Culturelle VC *Pharma Dynamics, S.Afr.†*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3).
Restoration of vaginal flora.

Culuflex H *Celudrop, Arg.†*
Hyaluronic acid (p. 2526·2); vitamin B_5 (p. 2085·2); vitamin E (p. 2119·1); octinoxate (p. 1715·1).
Skin disorders.

Cumadren *NAM, Ital.*
Melilot (p. 2552·3); manna (p. 1858·2); vitamins; rutoside (p. 2505·3); minerals.
Nutritional supplement.

Cumal *Cubit, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Cumar *Medifarm Ducroy, Venez.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Cumarol *Elea, Arg.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Cumatil-L *Bayer, Arg.†*
Phenytoin (p. 538·2); methylphenobarbital (p. 533·1); phenobarbital (p. 535·2).
Epilepsy.

Cumee *Curex, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Cumee-A *Curex, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Cumef *Cubit, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Cumycin *Curex, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Cunesin *Sigma-Tau, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cunim *Elfin, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Cunim Plus *Elfin, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Cupan *Elfin, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cupan-DSR *Elfin, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Cupanol *Guardian, Indon.; Ern, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Cupax *Kleva, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cuplaton *Orion, Fin.; Orion, Malaysia; Orion, Singapore†; Orion, Ukr.*
Dimeticone (Antifoam M) (p. 1886·2).
Flatulence; abdominal discomfort; meteorism; aerophagia; dyspepsia; aid in gastrointestinal examination; defoamer.

Cuplex
Note: this name may be used for preparations of different composition.
Smith & Nephew, Irl.†; Crawford, UK.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; corns; calluses.

Cubit, India.
Vitamin B substances (p. 2102·3).

Cuplex-L *Cubit, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3).

Cuprenil *Teva, Pol.; Teva, Rus.*
Penicillamine (p. 1567·1).
Heavy metal poisoning; Wilson's disease; cystinuria; rheumatoid arthritis; haemosiderosis; scleroderma.

Cupressin *Takeda, Philipp.; Takeda, Singapore†; Takeda, Thai.*
Delapril hydrochloride (p. 1350·2).
Hypertension.

Cuprimine *Spedrog, Arg.; MSD, Braz.; Valeant, Canad.; Aton, Thai.; Aton, USA.*
Penicillamine (p. 1567·1).
Wilson's disease; cystinuria; rheumatoid arthritis; heavy metal poisoning; scleroderma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cupripen *Omedir, Arg.; IFET (ΙΦΕΤ), Gr.†; Rubio, Spain.*
Penicillamine (p. 1567·1).
Cystinuria; Wilson's disease; heavy-metal poisoning; rheumatoid arthritis.

Cuprocept CCL *Cuprocept, S.Afr.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Cuprofen *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2).
Pain; inflammation; cold and influenza symptoms; fever.

Cuprofen Plus *ReckittBenckiser, UK.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Cuprosodio *Bier, Ital.*
Cetrimide (p. 1742·1); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Personal hygiene.

Cuprosodio Plus *Bier, Ital.*
Chlorhexidine gluconate (p. 1743·3); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Genital hygiene.

Cuprox *Elfin, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

Curab-D *Curex, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Curacao *Age D'or, Singapore.*
Aloe vera (p. 1693·2).
Wound disinfection.

Curacid *Finadiet, Arg.*
Fatty acid glycerides; fatty acid triglycerides; vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Haemorrhoids; skin disorders; vaginal disorders.

Curacil *Kalbe, Indon.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Curacit *Nycomed, Norw.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Curacne *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.; Pierre Fabre, Gr.; Pierre Fabre, Neth.†; Pierre Fabre Dermatologie, Pol.*
Isotretinoin (p. 1706·2).
Acne.

Curacné *Pierre Fabre Dermatologie, Fr.*
Isotretinoin (p. 1706·2).
Acne.

Curadex *Claris, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Curadona *Lainco, Spain.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Curafen *ACME, Philipp.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Curafil *Betamadrileno, Spain.†*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Curakne *Pierre Fabre, Switz.*
Isotretinoin (p. 1706·2).
Acne.

Cural *Curex, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Curalest *Pharmachemie, Neth.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Curam *Biochemie, China; Sandoz, Hong Kong; Hexal, S. Afr.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Novartis, India; Sandoz, Malaysia; Sandoz, Singapore; Sandoz, Thai.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Novartis, NZ.
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sandoz, Austral.; Sandoz, Cz.; Sandoz, Hung.; Sandoz, Pol.†; Sandoz, Venez.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Curanail *Galderma, Fr.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Galderma, UK.
Amorolfine (p. 569·1).
Fungal nail infections.

Curandron *Berlipharm, Neth.†*
Cyproterone acetate (p. 2261·2).
Androgen dependent acne, alopecia, hirsutism, and seborrhoea in women; prostatic cancer; sexual behaviour disorders.

Curanel *Galderma, Switz.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Curantil *Berlin-Chemie, Ukr.*
Dipyridamole (p. 1362·2).
Angina pectoris; heart failure; myocardial infarction; cerebrovascular disorders; thromboembolism prophylaxis; intermittent claudication.

Curantyl *Berlin-Chemie, Rus.*
Dipyridamole (p. 1362·2).
Cerebrovascular disorders; thromboembolism prophylaxis; placental insufficiency; microcirculatory disorders.

Curare comp *Hanosan, Ger.*
Curare; gelsemium sempervirens (p. 2511·2); anamirta cocculus (p. 2483·1); causticum (p. 2595·3); zincum isovalerianicum (p. 2641·2); acidum arsenicosum (p. 2448·1); plumbum aceticum (p. 2541·3); aluminium oxydatum (p. 1690·3).
Homoeopathic preparation.

Curasept *Curaprox, UK.*
Chlorhexidine (p. 1743·2).
Oral hygiene.

Curash *Carter-Wallace, Philipp.*
Zinc oxide (p. 1729·1).
Nappy rash; skin irritation.

Curash Anti-Rash *Church & Dwight, Austral.*
Zinc oxide (p. 1729·1).
Nappy rash; skin irritation; hyperhidrosis.

Curash Baby Wipes *Carter, Austral.*
Vitamin E (p. 2119·1); sorbolene.
Skin cleanser and moisturiser.

Curash Babycare Medicated Nappy Rash Cream *Church & Dwight, Austral.*
dl-Alpha tocoferil acetate (p. 2119·2); zinc oxide (p. 1729·1); almond oil (p. 2437·1).
Nappy rash.

Curaspot *Galderma, Fr.*
Benzoyl peroxide (p. 1696·1).
Acne.

Curasten *Therabel, Fr.†*
Lysine hydrochloride (p. 2079·3); calcium gluceptate (p. 1783·2).
Asthenia.

Curatane *Douglas, Israel.*
Isotretinoin (p. 1706·2).
Acne.

Curatin
Note: this name may be used for preparations of different composition.
Sanova, Austria.
Biotin (p. 2052·2).
Hair and nail disorders.

Carter, Austral.†
Tolnaftate (p. 596·1).
Fungal skin infections.

Curativ
Note: this name may be used for preparations of different composition.
Hypermarcas, Braz.
Povidone-iodine (p. 1767·1).

Curatoderm *Hermal, Austria; Almirall, Belg.; Almirall Hermal, Cz.; Almirall Hermal, Ger.; Almirall, Hung.; Hermal, Israel; Almirall, Pol.; Almirall, Switz.; Crookes Healthcare, UK.*
Tacalcitol (p. 1722·1).
Psoriasis.

Curavisc *Curasan, Ger.*
Hyaluronic acid (p. 2526·2).
Joint disorders.

IDT Impfstoffwerk, Israel.
Sodium hyaluronate (p. 2526·2).
Degenerative joint disorders.

Curazid (Reformulated) *Natrapharm, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Curazink *Stada, Ger.*
Zinc histidinate (p. 2126·1).
Zinc deficiency.

Curban *Rafarm, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Curbexon *Solas, Indon.*
Vitamins; Javanese turmeric (p. 2636·2); docosahexaenoic acid (p. 1460·1); omega-3 fatty acids (p. 1460·1); omega-6 fatty acids (p. 2575·2); glutamic acid (p. 2070·2); bovine colostrum (p. 2380·3); prebiotic.
Dietary supplement; tonic.

Curbisal *Pharbio, Fin.; Pharbio, Norw.; Cederroth, Swed.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Curcix *SoSe, Ital.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Curcuma Plus *Soho, Indon.*
Vitamin B substances (p. 2102·3); betacarotene (p. 2051·1); curcuminoid.
Reduced appetite; hepatitis.

Curcuminoid *Eagle, Austral.*
Curcuma longa; bupleurum root; citrus reticulata peel; ginger (p. 1844·1); corydalis fabacea.
Dietary supplement.

Curcu-Truw *Truw, Ger.*
Javanese turmeric (p. 2636·2).
Dyspepsia.

Cure *Solitaire, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Cure Scab *Laborate, India.*
Sulfiram (p. 2161·3).

C13-Urea *Exalenz, Israel.*
Carbon-13 labelled urea (p. 2470·3).
Test for Helicobacter pylori infection.

Cureact *Cure Quick, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Curebol *Cure Quick, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Curecef *Sel-J, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Curedine *Indkus, India.*
Povidone-iodine (p. 1767·1).

Cureg *Adley, India.*
Camphor (p. 2466·2); iodine (p. 2336·3); menthol (p. 2553·2); potassium iodide (p. 2336·3); tannic acid (p. 2625·2); thymol (p. 1772·2).

Curejoint-AC *Solitaire, India.*
Aceclofenac (p. 16·2); diacerein (p. 45·3).

Curel *Bausch & Lomb, USA.*
Emollient and moisturiser.

Curemax *Solitaire, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Curepin *Solitaire, India.*
Meropenem (p. 321·3).
Bacterial infections.

Curesin *Cure Quick, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

Curethyl *Tradiphar, Fr.*
⊗Alcohol (p. 1733·1).
Alcohol withdrawal syndrome.

Curevital *Solitaire, India.*
Ginseng (p. 2513·3); vitamins; minerals; protein.

Curfos *Interbat, Indon.*
Curcuminoid; fructo-oligosaccharides (p. 2508·1); docosahexaenoic acid (p. 1460·1); arachidonic acid (p. 2446·1); vitamin B substances (p. 2102·3).
Reduced appetite; vitamin supplement.

Curicap *MDS, Belg.; MDS, Cz.; MDS, Neth.†; MDS, Port.; Nordion, Spain.*
Iodine-131 (p. 2225·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Curinflam *Duncan, Arg.*
Diclofenac (p. 48·3) or diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Duncan, Hong Kong.
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Curinflam Plus *Duncan, Arg.*
Diclofenac (p. 48·3); pridinol (p. 2026·1).

Curinflam VL *Duncan, Arg.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Curiosin *Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Gedeon Richter, Philipp.; Gedeon Richter, Rus.; Gedeon Richter, Singapore; Gedeon Richter, Ukr.*
Zinc hyaluronate (p. 2526·2).
Skin disorders; wounds; burns; acne; fistulas; ulcers.

Gedeon Richter, Ukr.
Topical gel: Zinc hyaluronate (p. 2526·2); zinc chloride (p. 2126·1).
Acne.

Curisept *Excelentia, Arg.*
Piroxoline; hydroxyquinoline (p. 2530·1).
Wounds.

Curitaz *Sandoz, S.Afr.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Curity *Kendall, USA.*
Iodine (p. 2336·3).
Disinfection.

Curix *Constant, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Curlem *Lemery, Mex.†*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Curliv *Soho, Indon.*
Schisandra (p. 2611·2); javanese turmeric (p. 2636·2); liquorice (p. 1853·2); choline bitartrate (p. 2055·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Curliv Plus *Soho, Indon.*
Capsules: Silymarin (p. 1561·2); schisandra (p. 2611·2); Javanese turmeric (p. 2636·2); liquorice (p. 1853·2); choline bitartrate (p. 2055·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Soho, Indon.
Syrup: Silymarin (p. 1561·2); schisandra (p. 2611·2); Javanese turmeric (p. 2636·2); liquorice (p. 1853·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Curmunos *Fahrenheit, Indon.*
Echinacea (p. 2498·1); curcumin (p. 2180·1); bovine colostrum (p. 2380·3); lysine hydrochloride (p. 2079·3); docosahexaenoic acid (p. 1460·1); vitamins.
Maintenance of healthy immune system.

Curmyl *Mylan, Spain.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

CuroAx *Simayla, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Curocef *GSK, Austria.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

GSK, Chile.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Curomal *Dermophil Indien, Fr.*
Capsicum oleoresin (p. 2469·3); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Curon-B *Intramed, S.Afr.†*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Curosurf *Ascent, Austral.; Torrex, Austria; Chiesi, Belg.; Chiesi, Braz.; Chiesi, China; Chiesi, Cz.; Nycomed, Denm.; Takeda, Fin.; Chiesi, Fr.; Chiesi, Ger.; Chiesi, Gr.; Chiesi, Hung.; Chiesi, Irl.; SLE, Israel; Chiesi, Ital.; Chiesi, Malaysia; Chiesi, Neth.; Nycomed, Norw.; Douglas, NZ; Chiesi, Pol.; Angelini, Port.; Nycomed, Rus.; Safeline, S. Afr.†; Chiesi, Spain; Nycomed, Swed.; Takeda, Switz.;*

Chiesi, Thai.; Chiesi, Turk.; Trinity, UK; Nycomed, Ukr.; Cornerstone, USA.
Poractant alfa (p. 2599·3).
Neonatal respiratory distress syndrome.

Curox *Cubit, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Curoxim *Elfin, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

GSK, Ital.
Cefuroxime sodium (p. 255·3).
Gram-negative bacterial infections.

Curoxima *GSK, Spain.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Curoxime *Glaxo Wellcome, Port.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Curpol *McNeil, Belg.†*
Paracetamol (p. 115·1).
Pain; fever.

Curran *Community Pharmacy, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Cursil *Transfarma, Indon.*
Phyto cur (p. 2636·2); xanthorrhizae oil (p. 2218·1); silymarin (p. 1561·2).
Liver disorders.

Curson *Soho, Indon.†*
Javanese turmeric (p. 2636·2); lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Hepatitis.

Curtega *Pfizer, Neth.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Curviplex *Graha, Indon.*
Curcumin (p. 2180·1); vitamins; lysine hydrochloride (p. 2079·3).
Reduced appetite.

Curvit *Soho, Indon.*
Vitamin B substances (p. 2102·3); calcium gluconate (p. 1783·3); curcuminoid.
Reduced appetite; vitamin supplement; calcium supplement.

Curvit CL *Soho, Indon.*
Vitamins; calcium hypophosphite (p. 2530·3); arachidonic acid (p. 2446·1); docosahexaenoic acid (p. 1460·1); fructo-oligosaccharides (p. 2508·1); cod-liver oil (p. 2056·3); curcuma.
Nutritional supplement; tonic.

Curyken *Kendrick, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus; urticaria.

Cusate *Pharmasant, Thai.*
Docusate sodium (p. 1836·2).
Constipation.

Cuscutine *Geymonat, Ital.†*
Senna (p. 1885·1); aloin (p. 1816·2).
Constipation.

Cusicrom *Alcon, Cz.†; Alcon Cusi, Malaysia; Alcon, Pol.; Alcon Cusi, Spain; M4, Spain.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders; allergic rhinitis.

Cusimolol *Alcon, Hung.; Alcon, Ital.; Alcon Cusi, Malaysia; Alcon, Pol.; Alcon Cusi, Spain; Alcon, Turk.†*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Cusiviral *Alcon, Hong Kong; Alcon Cusi, Malaysia; Alcon, Pol.†; Alcon Cusi, Singapore.*
Aciclovir (p. 964·1).
Herpes simplex keratitis; herpes eye infections.

Cuspis *Krugher, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Custey *Microsules, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Custodiol
Note: this name may be used for preparations of different composition.
Kohler, Austria; Kohler, Ger.; IFET (ΙΦΕΤ), Gr.; Tramedico, Neth.; Kohler, Rus.
Organ perfusion solution (p. 1775·1).
Cardioplegia.

Pharos, Indon.
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Custoplex *Biogam, Arg.*
Organ perfusion solution (p. 1775·1).

Cut a Cough *Rickard Lanes, UK.*
Squill oxymel.
Cough.

Cuta Crema *Fortbenton, Arg.*
⊗Gentamicin sulfate (p. 304·2); betamethasone (p. 1623·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Cutacelan *Bayer, Arg.; Schering, Venez.*
Azelaic acid (p. 1695·1).
Acne.

Cutaclin *Valeant, Mex.*
Clindamycin phosphate (p. 269·3).
Acne; pyodermas.

Cutacnyl *Galderma, Fr.*
Benzoyl peroxide (p. 1696·1).
Acne.

Cutamir *Cristalfarma, Ital.*
Cardiospermum halicacabum; chamomile (p. 2474·1).
Skin disorders.

Cutanil *ITF, Chile.*
Clotrimazole (p. 576·2); zinc oxide (p. 1729·1).
Fungal skin infections.

Cutanit *Astellas, Spain.*
⊗Fluclorolone acetonide (p. 1634·2).
Skin disorders.

Cutanplast *Mascia Brunelli, Ital.†*
⊗Gelatin (p. 1154·1).
Haemostasis.

Cutanum *Bayer, Ger.†; Jenapharm, Ger.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Cutasept *Bode, Ger.; Pharmachemie, Gr.; Hartmann, Switz.*
Isopropyl alcohol (p. 1758·3); benzalkonium chloride (p. 1737·1).
Skin disinfection.

Cutasept med *Bode, Ger.*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Cutasol-GM *Cubit, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Cutemol *Summers, USA.*
Emollient and moisturiser.

Cutenox *Gland, India.*
Enoxaparin sodium (p. 1372·3).
Unstable angina; thromboembolic disorders.

Cuteplex *Jumont, Philipp.*
Vitamins; with or without ferrous sulfate (p. 2062·2).

Cuteral *Panalab, Arg.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Cuterpès *Chauvin, Fr.*
Ibacitabine (p. 984·3).
Herpes labialis.

Cuticare *DWD, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Cuticlin *Vivax, Venez.*
Isotretinoin (p. 1706·2).
Acne.

Cutiderm *Prodotti, Braz.†*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Skin infections.

Cutidermin Bebe Crema Protectora *Szabo, Arg.†*
Zinc oxide (p. 1729·1).

Cutidermin Bebe Gel Nasal *Szabo, Arg.†*
Sodium chloride (p. 1795·1).

Cutidermin Bebe Polvo *Szabo, Arg.†*
Boric acid (p. 2459·3); resorcinol (p. 1718·3).

Cutidermin Crema Antibacterial *Szabo, Arg.†*
⊗Alcohol (p. 1733·1); glycerol (p. 2517·2); vitamin E (p. 2119·1).

Cutidermin Crema Humect. con Vitamina A *Szabo, Arg.†*
Vitamin A (p. 2098·3).

Cutidermin Crema Regeneradora *Szabo, Arg.†*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); aloe vera (p. 1693·2).

Cutidermin Emulsion Humectante *Szabo, Arg.†*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); allantoin (p. 1693·1).

Cutidermin Spray Humectante *Szabo, Arg.†*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

Cutiflox *Indu, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Cutigard *Aglowmed, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Cutil *Curex, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Cutimix *Kwizda, Austria.*
Zinc oxide (p. 1729·1); talc (p. 1722·2).
Skin disorders.

Cutinova
Note: this name may be used for preparations of different composition.
Argenfarma, Arg.
Acetic acid (p. 2426·3).

Smith & Nephew Healthcare, UK.
Polyurethane foam dressing (p. 1718·1).
Wounds; burns; ulcers.

Cutinova Hydro *Smith & Nephew, Ital.*
Polyurethane dressing (p. 1718·1).
Skin ulcers.

Cutiphile *Braun, Fr.†*
Bismuth subgallate (p. 1822·1); bismuth subnitrate (p. 1822·1); zinc oxide (p. 1729·1).
Skin disorders.

Cutis comp *Heel, Neth.*
Graphites (p. 2522·1); thallium aceticum (p. 2628·3); thuja occidentalis (p. 2629·3); antimonium crudum (p. 2445·1).
Homoeopathic preparation.

Cutisan *Lisapharm, Fr.*
Triclocarban (p. 1773·2).
Skin disorders.

Cutisanol *Millet Roux, Braz.*
Ointment: Magnesium silicate (p. 2195·3); thymol iodide (p. 1772·2); zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1).
Skin disorders.

Millet Roux, Braz.
Topical gel: Zinc oxide (p. 1729·1); bismuth subgallate (p. 1822·1).
Skin disorders.

Cutisitum *Heel, Canad.†*
Aesculus hippocastanum (p. 2431·2); burdock (p. 2540·1); calcium fluoride (p. 2053·1); formic acid (p. 2507·1); goose grass (p. 2481·2); ichthammol (p. 1705·3); ledum palustre (p. 2550·1); nadidum (p. 2567·1); phosphoric acid (p. 2589·1); sanguinarina nitrica homea; selenium (p. 2086·3); sulfur (p. 1721·1); thallium metallicum; thuja occidentalis (p. 2629·3); urtica urens (p. 2639·3).
Homoeopathic preparation.

Cutisoft *Ipca, India.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

cutistad *Stada, Ger.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Cutivat *GSK, Denm.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Cutivate *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK Consumer, Canad.; GSK, China; GSK, Cz.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.†; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; Stiefel, Spain; GSK, Switz.; GSK, Turk.; GSK, UK; GSK, Ukr.; PharmaDerm, USA; GSK, Venez.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Captab, India.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Cutivate-GT *Captab, India.*
⊗Clobetasol (p. 1627·1); gentamicin sulfate (p. 304·2); terbinafine hydrochloride (p. 593·3); zinc sulfate (p. 2126·2).
Infected skin disorders.

Cutivate-MF *Captab, India.*
⊗Clobetasol (p. 1627·1); salicylic acid (p. 1719·1); urea (p. 1727·3).

Cutivate-S *Captab, India.*
⊗Clobetasol (p. 1627·1); salicylic acid (p. 1719·1).

Cutivir *Captab, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Cutizone *Ranbaxy, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Cutizone-T *Ranbaxy, India.*
⊗Mometasone furoate (p. 1644·1); terbinafine (p. 593·3).

Cutret *Captab, India.*
Isotretinoin (p. 1706·2).
Acne.

Cutseal *Rusan, India.*
Enbucrilate (p. 2489·3).

Cutter Advanced *Spectrum Brands, USA.*
Icaridin (p. 2156·3).
Insect repellent.

Cuvarlix *Pharmaniaga, Malaysia.*
Orlistat (p. 2577·1).
Obesity.

Cuvefilm *Perez Gimenez, Spain.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Cuvenax *Perez Gimenez, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Cuvit *Curex, India.*
Vitamins.

Cuvital *Cubit, India.*
Vitamins; minerals; ginseng (p. 2513·3).

Cuvposa *Merz, USA.*
Glycopyrronium bromide (p. 2519·3).
Drooling in children.

Cuwarm *Cubit, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Cuxafenon *TAD, Ger.†*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Cuxim *Cubit, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Cuxone *Cubit, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Cuxone-SL *Cubit, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Cuzen *Cubit, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Cuzen-DP *Cubit, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Cuzen-NM *Cubit, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Cuzid *Curex, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Cu-Zn *Uriage, Fr.*
Copper gluconate (p. 2057·2) or copper pidolate (p. 1720·3); zinc gluconate (p. 2126·2) or zinc pidolate (p. 1720·3).
Skin irritation.

Cuzole *Elfin, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Cuzole-D *Elfin, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Cuzox-MR *Cubit, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

C-Van *Sykocure, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting associated with chemotherapy.

CV-Cef *Bestochem, India.*
Cefpodoxime; potassium clavulanate (p. 268·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

C-Vex *Zentiva, Philipp.*
Pentoxifylline (p. 1465·3).
Circulatory disorders.

C-vimin *Meda, Fin.; Meda, Swed.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

C-Vit
Note: this name may be used for preparations of different composition.
Cipla, India.
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).

Corona, India.
Vitamin B substances (p. 2102·3); minerals.

Novartis Consumer, Austria.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

C-Vitamin *Asofarma, Arg.; BMS, Cz.*
Ascorbic acid (p. 2110·3).
Dietary supplement; vitamin C deficiency.

CVL *Themis Medicare, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction.

CVP *Sterling, India.†*
Citrus bioflavonoids (p. 2505·2); vitamin C (p. 2110·3).
Capillary fragility.

CVP Cellulite *Phoenix, Arg.*
Gel: Arnica (p. 2447·2); aesculus (p. 2431·2); centella (p. 1698·3); caffeine (p. 1203·3).
Cellulite.

Phoenix, Arg.
Tablets: Butcher's broom (p. 2463·1); fucus vesiculosus; centella (p. 1698·3); ginkgo biloba (p. 2512·3); grape (p. 2521·3); vitamin E (p. 2119·1).
Cellulite; circulatory disorders; capillary permeability disorders.

CVP Duo *Phoenix, Arg.*
Bioflavonoids (p. 2505·2); ascorbic acid (p. 2110·3).
Vascular disorders.

CVP Flebo *Phoenix, Arg.*
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Haemorrhoids; varices.

CVP Forte *Phoenix, Arg.*
Ascorbic acid (p. 2110·3); bioflavonoids (p. 2505·2).
Arteriopathy; phlebopathy.

CVS *T Man, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; arrhythmias; migraine; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor.

CV-Sprin *Cadila, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

C-Will *Will-Pharma, Belg.; Will-Pharma, Neth.; Willpharma, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Cx-3 *Zydus, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Cx-4 *Zydus, India.*
1 Tablet, rifampicin (p. 350·3); isoniazid (p. 311·2); 1 tablet ethambutol (p. 296·1). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Cx-5 *Zydus, India.*
1 Capsule, rifampicin (p. 350·3); 2 tablets, pyrazinamide (p. 345·2); 1 tablet, ethambutol (p. 296·1); isoniazid (p. 311·2). Pyridoxine hydrochloride (p. 2105·3) tablets are included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

CX Powder *Adams, UK.*
Chlorhexidine acetate (p. 1743·2).
Skin disinfection.

CX-One *Hanburys, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

CX-Zim *Bionet, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Cyamox *Lero, Fr.*
Gliadin; guar gum (p. 475·1); xanthan gum (p. 2220·1); minerals.
Slimming aid.

Cyanide Antidote Package *Lilly, USA.*
Combination pack: 2 Ampoules, sodium nitrite (p. 1574·3); 2 ampoules, sodium thiosulfate (p. 1576·1); 12 aspirols, amyl nitrite (p. 1540·2).
Cyanide poisoning.

IFET [ΙΦΕΤ], Gr.
Sodium nitrite (p. 1574·3); sodium thiosulfate (p. 1576·1).
Cyanide poisoning.

Cyanokit *Merck, Austria; Merck, Belg.; EMD, Canad.; Merck, Cz.; Swedish Orphan, Denm.; Merck-Lipha, Fr.; Merck Serono, Hong Kong; Merck, Irl.; Merck Serono, Ital.; Merck, Neth.; Swedish Orphan, Norw.; Merck, Pol.; Merck, Port.; Merck Sante, Spain; Swedish Orphan, Swed.; Merck, Switz.; Swedish Orphan, UK; King, USA.*
Hydroxocobalamin (p. 2107·3).
Cyanide poisoning.

Cyaptin *Duckbill, India.*
Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Cyaptin With Calcium *Duckbill, India.*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); cyproheptadine hydrochloride (p. 624·1).

Cyaptin-SF *Duckbill, India.*
Cyproheptadine hydrochloride (p. 624·1); protein hydrolysate; sorbitol (p. 2092·1).

Cyber *Raptakos, India.*
Prazosin (p. 1473·3).
Hypertension; heart failure; Raynaud's syndrome; benign prostatic hyperplasia.

Cybin *VHB, India.*
Cytarabine (p. 774·1).
Leukaemias; lymphomatous meningitis.

Cybufen *Lederle, Indon.†*
Fenbufen (p. 59·1).
Musculoskeletal and joint disorders.

Cybutol *Pharmachemie, Hong Kong; Sandoz, S.Afr.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Cycamil *Drugmaker's Laboratory, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Cycdex *Adley, India.*
⊗Cyclopentolate hydrochloride (p. 2005·3); dexamethasone sodium phosphate (p. 1631·2).

Cycin *Dong, Singapore.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cyclabil *Schering, Fin.†*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Cyclacur *Schering, Gr.; Bayer, Switz.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; norgestrel (p. 2296·1).
Menopausal disorders; menstrual disorders; hormone replacement therapy.

Cycladol *Chiesi, China; Chiesi, Fr.; Ranbaxy, India; Chiesi, Spain†; Chiesi, Turk.*
Piroxicam betadex (p. 126·1).
Pain; musculoskeletal, joint, and peri-articular disorders; gout.

Cyclaid *Medis, Cz.; Medis, Pol.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; psoriasis; nephrotic syndrome; rheumatoid arthritis; atopic eczema.

Cyclasyn *Cipla, India.*
Cyclandelate (p. 1347·1).
Cerebral and peripheral vascular disorders.

Cyclate *Zydus, India.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Cycléane *MSD-Chibret, Fr.†*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Cyclen *Janssen-Ortho, Canad.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Cyclessa *Organon, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Cyclidox *Mylan, S.Afr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria prophylaxis.

Cyclimorph *Amdipharm, Irl.; Aspen, S.Afr.; Amdipharm, UK.*
⊗Morphine tartrate (p. 93·2); cyclizine tartrate (p. 623·2).
Pain.

Cyclimycin *Aspen, S.Afr.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Cycline *Kleva, Gr.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Cyclinex *Ross, USA.*
A range of preparations for enteral nutrition including an infant feed.
Urea cycle disorder; gyrate atrophy.

Cyclivert *Laser, USA.*
Cyclizine hydrochloride (p. 623·2).
Motion sickness.

Cyclivex *Aspen, S.Afr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Cyclo 3
Note: this name may be used for preparations of different composition.
Pierre Fabre, Fr.; Pierre Fabre, Rus.; Pierre Fabre, Singapore.†
Butcher's broom (p. 2463·1); melilot (p. 2552·3).
Circulatory disorders; venous insufficiency; lymphatic insufficiency.

Rovafarm, Arg.; Pierre Fabre, Port.
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Venous insufficiency; haemorrhoids.

Cyclo 3 Fort *Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Pol.; Pierre Fabre, Rus.; Pierre Fabre, Singapore; Pierre Fabre, Thai.; Pierre Fabre, Ukr.*
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Bleeding during oral contraceptive or intra-uterine device use; venous insufficiency; haemorrhoids; circulatory disorders; lymphatic insufficiency; menstrual disorders.

Cyclo 3 Forte *Pierre Fabre, Gr.*
Butcher's broom (p. 2463·1); hesperidin (p. 2505·2); ascorbic acid (p. 2110·3).
Vascular disorders.

Cyclo Plus *Incomed, Rus.*
Cycloserine (p. 280·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation in an attempt to limit adverse CNS effects.
Tuberculosis.

Cycloblastin *Pfizer, Austral.; Pfizer, NZ; Pharmacia, S. Afr.†*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; auto-immune diseases; transplant rejection.

Cyclochek *Indoco, India.*
Domperidone (p. 1838·1); rabeprazole sodium (p. 1881·1).

Cyclocort *Stiefel, Canad.*
⊗Amcinonide (p. 1621·1).
Skin disorders.

Cyclocos *Symbiosis, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Cyclocos-TX *Symbiosis, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Cyclocur *Bayer, Belg.; Bayer, Neth.†*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; norgestrel (p. 2296·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Cyclodex *Platinum, Thai.*
Piroxicam betadex (p. 126·1).
Rheumatoid arthritis; osteoarthritis; pain.

Cyclodol *Leksredstva, Rus.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Cyclodynon *Bionorica, Pol.; Bionorica, Rus.; Biomed, Switz.†; Bionorica, Ukr.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome; menstrual disorders.

Cyclofas *Indoco, India.*
Drotaverine hydrochloride (p. 2497·3).

Cyclofem *Techsphere, Arg.; Concept, Hong Kong; Tunggal Idaman, Indon.†*
Medroxyprogesterone acetate (p. 2288·1); estradiol cipionate (p. 2271·1).
Combined injectable contraceptive.

Cyclofemina *MilletRoux, Braz.; Carnot, Mex.*
Estradiol cipionate (p. 2271·1); medroxyprogesterone acetate (p. 2288·1).
Combined injectable contraceptive.

Cycloferon *Polisan, Rus.; Polisan, Ukr.*
Arachidonic acid (p. 2446·1).
Viral infections; bacterial and fungal infections; connective tissue disorders; degenerative-dystrophic joint disorders; musculoskeletal and joint disorders.

Cyclogest *Actavis, Hong Kong; Cox, Hong Kong; Actavis, Malaysia; Sanofi-Aventis, S.Afr.; Actavis, Singapore; Sanofi-Aventis, Thai.; Assos, Turk.; Actavis, UK.*
Progesterone (p. 2300·2).
Premenstrual syndrome; postnatal depression; female infertility.

Cyclogik *FDC, India.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia; iritis; uveitis.

Cyclogyl *Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Denm.; Alcon, Gr.; Alcon, Hong Kong; Intas, India; Alcon, Malaysia; Alcon, Neth.; Alcon, NZ; Alcon, S.Afr.; Alcon, Singapore†; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, USA; Alcon, Venez.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of cycloplegia and mydriasis; uveitis; iritis.

Cyclogyl-D *Intas, India.*
⊗Cyclopentolate (p. 2005·3); dexamethasone sodium phosphate (p. 1631·2).

Cyclokox *Radicura, India.*
Cycloserine (p. 280·2).
Tuberculosis.

Cyclolest *Chemipharm, Gr.*
Cyclophosphamide (p. 771·1).

Cyclomed
Note: this name may be used for preparations of different composition.
Mediline, Israel.
Aciclovir (p. 964·1).
Herpes simplex infections.

Promed, Rus.; ProMed, Ukr.
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis; inflammatory eye disorders.

Cyclomeff *Indoco, India.*
Mefenamic acid (p. 85·3); dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Cyclomen *Sanofi-Aventis, Canad.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders.

Cyclomine *Vickmans, Hong Kong.†*
Dicycloverine (p. 1834·2).

Cyclominol *Noel, India.†*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm; irritable bowel syndrome.

Cyclomune *Sun, India.*
Ciclosporin (p. 1945·2).
Dry eyes.

Cyclomycine-K *Coup, Gr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Cyclomydril *Alcon, Malaysia; Alcon, S.Afr.; Alcon, Singapore†; Alcon, USA.*
Cyclopentolate hydrochloride (p. 2005·3); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

CycloÖstrogynal *Bayer, Ger.*
11 Tablets, estradiol valerate (p. 2271·2); estriol (p. 2274·3); 10 tablets, estradiol valerate; estriol (p. 2274·3); levonorgestrel (p. 2296·1).
Menopausal disorders.

Cyclo-P *Laborate, India.*
Dextropropoxyphene (p. 43·2); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Cyclopam *Indoco, India.*
Injection: Dicycloverine hydrochloride (p. 1834·2).
Colic; irritable bowel syndrome; dysmenorrhoea.

Indoco, India.
Oral drops; oral suspension: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Colic; irritable bowel syndrome; dysmenorrhoea.

Indoco, India.
Tablets: Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).
Colic; irritable bowel syndrome; dysmenorrhoea.

Cyclopam Plus *Indoco, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Cycloparin *Rovafarm, Arg.*
Heparin (p. 1396·3).

Cyclopent *Sun, India.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia; iritis; uveitis.

Cyclopent Plus *Sun, India.*
Cyclopentolate hydrochloride (p. 2005·3); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

Cyclopent-DM *Sun, India.*
⊗Cyclopentolate hydrochloride (p. 2005·3); dexamethasone sodium phosphate (p. 1631·2).

Cyclophil ME *Biocon, India.*
Ciclosporin (p. 1945·2).
Transplant rejection; psoriasis; atopic eczema; rheumatoid arthritis; nephrotic syndrome.

Cyclophilin *Coup, Gr.*
Cyclandelate (p. 1347·1).

Cycloplatin *Teva, Cz.; Pliva, Hung.; Pliva Lachema, Pol.†; Pliva, Rus.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Cyclopret *Bionorica, UK.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Cyclo-Progynova *Bayer Schering, Indon.; Bayer Schering, Pol.; Bayer Schering, Rus.; Bayer, Thai.; Schering, Turk.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; norgestrel (p. 2296·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Cyclo-Progynova 1 mg *Viatris, UK.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders.

Cyclo-Progynova 2 mg *Viatris, UK.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; norgestrel (p. 2296·1).
Menopausal disorders.

Cyclo-Progynova N *Bayer, Ger.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders.

Cycloptic *Rompharm, Rus.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Cycloral *Sintez, Rus.*
Ciclosporin (p. 1945·2).
Transplant rejection; rheumatoid arthritis; psoriasis; atopic dermatitis; nephrotic syndrome.

Cyclorax *Atlantic, Thai.†*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Cycloreg *Jagsonpal, India.*
Norethisterone (p. 2294·2).
Menstrual disorders; endometriosis; postponement of menstruation.

Cyclorine *Lupin, India.*
Cycloserine (p. 280·2).
Tuberculosis.

Cyclosa *Organon, Ger.†*
7 Tablets, ethinylestradiol (p. 2275·3); 15 tablets, ethinylestradiol; desogestrel (p. 2266·3).
Menstrual disorders.

Cycloserine *King, UK.*
Cycloserine (p. 280·2).
Tuberculosis; urinary-tract infections.

Cycloset *Santarus, USA.*
Bromocriptine (p. 895·3).
Diabetes mellitus.

Cycloson *Pharmachemie, Hong Kong†; World Pioneer, Hong Kong†; Teva, Rus.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Cyclospasmol *Gerolymatos, Gr.; Elder, India.*
Cyclandelate (p. 1347·1).
Cerebral and peripheral vascular disorders.

Cyclostad *Stada, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Cyclosym *Symbiosis, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Cyclosym-TX *Symbiosis, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Cyclotec *United Biotech, India.*
Cycloserine (p. 280·2).
Tuberculosis.

Cyclotelia *Texinfine, Fr.*
Flos salis; padina pavonica (p. 2612·1); vanilla tahitensis (p. 2218·3).
Dietary supplement for mood disorders.

Cycloterol *SMB, Fin.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Cyclotrax *Shin Poong, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage.

Cyclovax *Remedica, Hong Kong.*
Aciclovir (p. 964·1).
Herpesvirus infections of the skin and mucous membranes.

Cyclovent *Pharmachemie, Hong Kong†; World Pioneer, Hong Kong.†*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Cyclovid *Novell, Indon.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Cyclovir *Zydus, India; Cadila, Rus.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Cycloviran *Medichrom, Gr.; Sigma-Tau, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Cyclowin *Ikon, India.*
Oral drops: Dicycloverine hydrochloride (p. 1834·2); dimeticone (p. 1886·2).

Ikon, India.
Tablets: Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Cycloxan *Biochem, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; immunosuppressant.

Cyclozed *Zota, India.*
Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Cyclozed-N *Zota, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Cyclozobid *Piramal, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Cycodine *Utopian, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Cycolsim *Vickmans, Hong Kong.†*
Dicycloverine (p. 1834·2); dimeticone (p. 1886·2).

Cycomin *Rotexmedica, Philipp.*
Phytomenadione (p. 2122·2).
Hypoprothrombinaemic haemorrhage.

Cycortide *Pharmachemie, Hong Kong; Teva, Rus.*
⊗Budesonide (p. 1625·1).
Asthma.

Cycram *Korea United, Hong Kong; Korea United, Singapore.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; bone marrow transplantation.

Cycrame *Miracalus, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Cycrin *Wyeth, Braz.*
Medroxyprogesterone acetate (p. 2288·1).
Abnormal uterine bleeding; secondary amenorrhoea.

Cydifar *Ifars, Indon.†*
Cyproheptadine hydrochloride (p. 624·1).
Allergic disorders.

Cydine *Cosme, India.*
Cyproheptadine (p. 624·1); lysine hydrochloride (p. 2079·3); peptone (p. 2086·2).

Cydonin *Egis, Hung.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cydoxan *Alkem, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

CyEstra *Pharmascience, Canad.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne in women.

Cyfenol *Cifarma, Braz.*
Paracetamol (p. 115·1).
Pain; fever.

Cyfer *Admac, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Cyflox
Note: this name may be used for preparations of different composition.
Cyno, India.
Ofloxacin (p. 334·3).
Bacterial infections.

GreaterPharma, Thai.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cyfloxin *Marching, Hong Kong.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Cyflu *Cyno, India.*
Fluconazole (p. 578·2).
Fungal infections.

Cyfol
Note: this name may be used for preparations of different composition.
Vensat, India.
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).

Cyfolac *Karnataka, India.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); *Lactobacillus sporogenes* (p. 2596·3).
Antibiotic-associated diarrhoea.

Cy-Gesic *Cypress, USA.*
Phenylephrine hydrochloride (p. 1672·3); phenazone (p. 124·1); benzocaine (p. 1980·2).
Earache.

Cygest *Inga, India; Actavis, Indon.*
Progesterone (p. 2300·2).
Female infertility; premenstrual syndrome; dysfunctional uterine bleeding; threatened or recurrent miscarriage; menopausal disorders; amenorrhoea.

Cyheptine *Greater Pharma, Thai.*
Cyproheptadine (p. 624·1).
Reduced appetite; hypersensitivity reactions; pruritus.

Cyka Plus *Positif, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Cyklo-F *Meda, Swed.; Meda, UK.*
Tranexamic acid (p. 1164·2).
Menorrhagia.

Cyklokapron *Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Meda, Denm.; Meda, Fin.; Meda, Ger.; Pfizer, Ger.; Pfizer, Hong Kong†; Pfizer, India; Meda, Irl.; Pfizer, Irl.; Meda, Neth.; Pfizer, Neth.; Meda, Norw.; Pfizer, Norw.; Pfizer Consumer, NZ; Pfizer, Philipp.†; Pfizer, S.Afr.; Pfizer, Singapore; Meda, Swed.; Pfizer, Swed.; Meda, Switz.; Meda, UK; Pfizer, UK; Pfizer, USA.*
Tranexamic acid (p. 1164·2).
Dental extraction in haemophiliacs; hereditary angioedema; fibrinolytic haemorrhage; upper-gastrointestinal haemorrhage; menorrhagia; surgical procedures in those with coagulopathies.

Cyklonova *Alternova, Denm.; Alternova, Swed.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; dental extraction in haemophiliacs; hereditary angioedema; menorrhagia.

Cylat *Lapi, Indon.†*
Cyproheptadine (p. 624·1).
Allergic disorders.

Cylatron *MSD, Switz.*
Peginterferon alfa-2b (p. 989·2).
Melanoma.

Cylert *Abbott, Chile.†*
⊗Pemoline (p. 2328·2).
Attention-deficit hyperactivity disorder.

Cylex *Pharmakon, USA.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Sore throat.

Cyllind *Abbott, Ger.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Cylocide *Shinyaku, Jpn.*
Cytarabine (p. 774·1).
Malignant neoplasms.

Cylocort *Uniao Quimica, Braz.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Cylowam *Konimex, Indon.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cylox *Chemo-Drugs, India.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Cyltabs *Solvay, India.*
Vitamins; minerals; sodium taurocholate (p. 2457·2).
Vitamin and mineral deficiency.

Solvay, Indon.
Vitamins; minerals; trace elements; liver extract (p. 2444·1); ox bile.
Tonic.

Cymalon *Actavis, Irl.; Thornton & Ross, UK.*
Sodium citrate (p. 1781·2); anhydrous citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); sodium carbonate (p. 2617·3).
Cystitis.

Cymalon Cranberry *Thornton & Ross, UK.*
Potassium citrate (p. 1780·3).
Cystitis; urinary-tract infections.

Cymbalta *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Boehringer Ingelheim, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Shionogi, Jpn; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA.*
Duloxetine hydrochloride (p. 415·1).
Depression; anxiety; fibromyalgia; neuropathic pain; musculoskeletal pain.

Cymbi *Juggat, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Cymerin *Mitsubishi Tanabe, Jpn.*
Ranimustine (p. 851·2).
Malignant neoplasms; polycythaemia vera; thrombocythaemia.

Cymerion *Azevedos, Port.*
Zolpidem tartrate (p. 1116·2).
Insomnia; sedative.

Cymévan *Roche, Fr.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

Cymeven *Roche, Ger.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

Cymevene *Roche, Arg.; Roche, Austria; Roche, Chile; Roche, China; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Recordati, Ital.; Roche, Mex.†; Roche, NZ; Roche, Rus.; Roche, Singapore; Roche, Turk.; Roche, Venez.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, India; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Malaysia; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Roche, Ukr.
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cymex
Note: this name may be used for preparations of different composition.
Actavis, Irl.; Actavis, UK.
⊗Urea (p. 1727·3); cetrimide (p. 1742·1); dimeticone (p. 2209·3); chlorocresol (p. 1748·1).
Herpes labialis; cracked lips.

Scoshia, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cymex Ultra *Actavis, UK.*
Aciclovir (p. 964·1).
Herpes labialis.

Cymex-TZ *Scoshia, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cymgen *Lilly, S.Afr.*
Duloxetine.
Depression; neuropathic pain.

Cymi *Lennon, S.Afr.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Cymin *Wockhardt, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Cymine *Pharmasant, Thai.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Gastrointestinal colic and spasm.

Cymoklar *Mylan, Fin.*
Clarithromycin (p. 266·2).
Bacterial infections.

Cynac *Cyno, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Cynacholin *Phytofarm Kleka, Pol.*
Cynara (p. 2490·3).
Gastrointestinal disorders; hyperlipidaemias; atherosclerosis.

Cynac-MR *Cyno, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Cynac-P *Cyno, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).

Cynac-S *Cyno, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Cynac-SP *Cyno, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Cynactil *Tilman, Belg.*
Cynara (p. 2490·3); rosemary (p. 2607·2).
Hepatobiliary disorders.

Cynacur *Hexal, Ger.†*
Cynara (p. 2490·3).
Dyspepsia.

Cynara Complex *World Medico, Canad.†*
Aloe (p. 1816·1); barberry root (p. 2502·1); boldo (p. 2458·3); caraway (p. 2470·2); cascara (p. 1826·1); cynara scolymus (p. 2490·3); lycopodium (p. 2546·3); milk thistle (p. 1561·1); peppermint (p. 1877·1); polygonum; radish; sodium sulfate (p. 1888·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Cynara Compuesta *Ximena Polanco, Chile.*
Cynara scolymus (p. 2490·3); peumus boldo (p. 2458·3); foeniculum vulgare (p. 2503·2); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Cynaramin *Bioforce, Swed.*
Taraxacum (p. 2625·3); boldo (p. 2458·3); cynara (p. 2490·3); peppermint leaf (p. 1877·1).
Digestive disorders.

Cynarex *Roux-Ocefa, Arg.; Herbapol Wrodaw, Pol.*
Cynara (p. 2490·3).
Liver disorders; hypercholesterolaemia; atherosclerosis.

Cynarix *Montavit, Austria; Montavit, Ukr.*
Cynara (p. 2490·3).
Dyspepsia; biliary-tract dyskinesias; cholecystitis; hepatitis; chronic intoxication with hepatotoxins.

Cynarix comp *Montavit, Austria.*
Cynara (p. 2490·3); salverine hydrochloride (p. 2609·2).
Biliary disorders.

Cynaro Bilina *Nutridiver, Spain.†*
Cynara (p. 2490·3); aloes (p. 1816·1).
Biliary-tract disorders; constipation.

Cynarol *Pharmacobel, Belg.*
Cynara (p. 2490·3).
Biliary-tract disorders.

Cynascool *Natiris, Venez.*
Cynara (p. 2490·3); boldo (p. 2458·3); rhubarb (p. 1884·2); solanum melongena.

Cynobac *Strassenburg, India.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); *Lactobacillus sporogenes* (p. 2596·3).
Diarrhoea.

Cynocuatro *Grossman, Mex.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Cynomel *Sanofi-Aventis, Fr.; IFET [ΙΦΕΤ], Gr.; Grossman, Mex.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism; diagnosis of hyperthyroidism.

Cynomycin *Wyeth, India.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Cynoplus *Grossman, Mex.*
Liothyronine sodium (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Cynosal *Lejal, Philipp.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; allergic rhinitis.

Cynosleep *Cyno, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine (p. 1113·2).

Cynovit *Julphar, UAE.*
Cyanocobalamin (p. 2107·2).
Megaloblastic anaemia; vitamin B_{12} deficiency; vitamin B_{12} supplement.

Cynox *Cyno, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Cynozet *Glenmark, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Cynt
Note: this name may be used for preparations of different composition.
Abbott, Braz.; Abbott, Cz.; Lilly, Ger.; Abbott, Gr.; Lilly, Hung.; Lilly, Rus.; Solvay, Rus.; Solvay, S.Afr.; Lilly, Turk.
Moxonidine (p. 1442·1).
Hypertension.

Dollder, Venez.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Cyomin *Forest Pharmaceuticals, USA.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency; schilling test.

Cyotic *Cypress, USA.*
⊗Hydrocortisone (p. 1640·1); pramocaine hydrochloride (p. 1993·3); chloroxylenol (p. 1748·2).
External ear disorders.

Cypa *Nordic, India.*
Clidinium bromide (p. 1833·2); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Cypan *Cyno, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cypan-D *Cyno, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Cypar *Cassella-med, UK.*
Milk thistle (p. 1561·1).
Indigestion.

Cypar Artichoke *Ceuta, UK.*
Cynara (p. 2490·3).
Digestive disorders.

Cypee *Comed, India.*
Cyproheptadine hydrochloride (p. 624·1); lysine hydrochloride (p. 2079·3); peptone (p. 2086·2).

Cypestra *Mepha, Switz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Cypex *Cypress, USA.*
Guaifenesin (p. 1666·2); sulfogaiacol (p. 1678·1).
Coughs.

Cypgo *Osmed, India.*
Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and vascular headache.

Cyphoden *Adley, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and vascular headache.

Cyphos *Intas, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Cypine-TS *Sunshine, India.*
Cyproheptadine (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Cypionax *TP, Thai.*
⊗Testosterone cipionate (p. 2305·1).
Androgenic; erectile dysfunction; delayed puberty in males; breast cancer in females.

Cyp-L *David, India.*
Oral drops: Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and vascular headache.

David, India.
Oral liquid: Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).
Loss of appetite.

Cypolin *Zytras, India.*
Cyprohetadine (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Cypon *Geno, India.*
Cyproheptadine hydrochloride (p. 624·1); dried yeast (p. 2125·2).
Reduced appetite.

Cypon DPS *Geno, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Cypon-I *Geno, India.*
Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Cypral *Meyer Alian, Venez.*
Ciprofloxacin (p. 261·1) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Cyprea-T *Cinerea, India.*
Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Cyprelle *Sandoz, Switz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Cypress *Famy, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive in women with androgenic symptoms.

Cyprest *Polfa Pabianice, Pol.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Cypretyl *Ratiopharm, Fin.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Formerly known as Procetyl.
Androgen-associated acne, hirsutism, and seborrhoea in women; oral contraceptive in women with androgen-associated symptoms.

Cyprin *Intra-Labs, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Cyprin-D *Intra-Labs, India.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).

Cyprin-TD *Intra-Labs, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Cypro *Caldern, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Cyprobit *Cubit, India.*
Cyproheptadine (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Cyprocap *SSP, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Cyproden *BMW, India.*
Cyproheptadine (p. 624·1).
Hypersensitivity; migraine and vascular headaches.

Cyproderm *Dermapharm, Ger.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Cyprodex *Roemmers-Klinos, Venez.*
⊗Cyproheptadine hydrochloride (p. 624·1); dexamethasone acetate (p. 1631·1).
Hypersensitivity disorders.

Cyprodin *Roemmers-Klinos, Venez.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity disorders.

Cyprodine *ANH, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Vickmans, Hong Kong.†
Cyproheptadine (p. 624·1).

Cyprodiol *Eurogenerics, Belg.†; Sun-Farm, Pol.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; androgenisation in females.

CyproGen *Generics, Pol.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne and hirsutism in women.

Cyprogin *Atlantic, Hong Kong; Atlantic, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Migraine; hypersensitivity reactions; reduced appetite; anorexia; pruritus.

Cyprohexal *Sandoz, Austral.*
Cyproterone acetate (p. 2261·2).
Androgenisation in women; prostatic cancer; sexual deviation in men.

Cypro-L *Ikon, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Cypromix *Stragen, Hung.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Combined oral contraceptive in women with androgenic symptoms; androgen-dependent acne and hirsutism in women.

Cypron *Generics, Israel.*
Cyproterone acetate (p. 2261·2).
Androgenisation; male sexual disorders; prostatic cancer.

Cypronam *SSP, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Cyprone *Alphapharm, Austral.*
Cyproterone acetate (p. 2261·2).
Androgenisation in females; prostatic cancer; sexual deviation in men.

Cypronette *Aliud, Ger.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Cyprono *Milano, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Reduced appetite; hypersensitivity reactions; pruritus.

Cypropicco *Picco, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Cyproplex *Teva, Belg.; Teva, Cz.; Pharmachemie, Malaysia†; Pharmachemie, S.Afr.*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; male hypersexuality; precocious puberty; female infertility; androgenisation in women.

Cyprosian *Asian Pharm, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Anorexia; hypersensitivity reactions; pruritus.

Cyprostat *Bayer, Austral.; Bayer, UK.*
Cyproterone acetate (p. 2261·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in females; prostatic cancer; sexual deviation in men.

Cyprostol *Pfizer, Austria.*
Misoprostol (p. 2140·3).
Peptic ulcer.

Cyprotec *Chew, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Anorexia; hypersensitivity reactions; pruritus.

Cyprotin *Beacons, Singapore.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Cyprowal *Wallace, India.*
Cyproheptadine hydrochloride (p. 624·1); lysine hydrochloride (p. 2079·3); peptone (p. 2086·2).

Cyproz *Ritz, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Cyra *Systopic, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Cyra-D *Systopic, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Cyrdanax *Cyathus, Cz.*
Dexrazoxane hydrochloride (p. 1548·1).
Prevention of doxorubicin and epirubicin cardiotoxicity.

Cyress *Astellas, Neth.; Astellas, Port.*
Barnidipine hydrochloride (p. 1314·1).
Hypertension.

Cyriamine *Pharmasant, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Cyrin *Claris, India; Claris, Philipp.*
Ciclosporin (p. 1945·2).
Transplant rejection; psoriasis; atopic eczema; rheumatoid arthritis; nephrotic syndrome; bone-marrow transplantation; graft-versus-host disease.

Cyron *Cyno, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Cyrox *Cyno, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Cyrux *Serral, Mex.*
Misoprostol (p. 2140·3).
Peptic ulcer; gastritis.

CYS *Cyno, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Cys Control *Arkopharma, Fr.*
Cranberry (p. 2488·1).
Urinary-tract disorders.

Cysaxal *Italchimici, Cz.; Italchimici, Hung.; Italchimici, Neth.*
Cyproterone acetate (p. 2261·2).
Prostatic cancer; androgenisation in women.

CYS-D *Cyno, India.*
⊗Serrapeptase (p. 2613·3); diclofenac potassium (p. 48·3).

Cysdexpel *Ad-Drugstel, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Cyserin *VHB, India.*
Cycloserine (p. 280·2).
Tuberculosis.

Cyslev *Raam, Mex.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cysporin *Mayne, Austral.†*
Ciclosporin (p. 1945·2).
Atopic dermatitis; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection.

Cystadane *Orphan, Austral.; Orphan, Austria; Orphan, Belg.; Rare Disease Therapeutics, Canad.; Orphan, Cz.; Swedish Orphan, Denm.; Orphan, Fr.; Orphan, Ger.; Orphan, Irl.; Orphan Medical, Israel; Orphan, Ital.; Orphan, Neth.; Swedish Orphan, Norw.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Swedish Orphan, Swed.; Rare Disease Therapeutics, USA.*
Betaine (p. 2456·1).
Homocystinuria.

Cystagon *Alphapharm, Austral.; Orphan, Austria; Orphan, Belg.†; Orphan, Cz.; Orphan, Denm.; Swedish Orphan, Fin; Orphan, Fr.; Orphan, Ger.; Orphan, Irl.; Orphan, Ital.; Orphan, Neth.; Swedish Orphan, Norw.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Swedish Orphan, Swed.; Orphan, UK; Mylan, USA.*
Mercaptamine bitartrate (p. 2554·3).
Nephropathic cystinosis.

Cystaline *Millimed, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Cystamox *Claris, India.*
Amoxicillin (p. 216·2); carbocisteine (p. 1658·1).
Respiratory-tract infections associated with excessive or viscous mucus.

Cystanin *Mitsubishi Tanabe, Jpn.*
Ethyl cysteine hydrochloride (p. 1665·2).
Respiratory-tract congestion.

Cystaran *Sigma-Tau, USA.*
Mercaptamine hydrochloride (p. 2554·3).
Corneal cystine accumulation in cystinosis.

Cystelis *Armoxindo, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Cystemme *Abbott, UK.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1).
Cystitis.

Cystex
Note: this name may be used for preparations of different composition.
EMS, Braz.
Acriflavinium chloride (p. 1732·3); methenamine (p. 322·3); methylthioninium chloride (p. 1559·1); belladonna (p. 2453·3).
Urinary-tract infections.

Numark, USA.
Methenamine (p. 322·3); sodium salicylate (p. 132·2); benzoic acid (p. 1738·2).
Urinary-tract infections.

Cystichol *Bailleul, Fr.†*
Cystine (p. 2059·1); choline bitartrate (p. 2055·2).
Digestive disorders.

Cysticide *Merck Serono, Ger.; Merck, India; Merck, S. Afr.*
Praziquantel (p. 164·1).
Neurocysticercosis.

Cystilac *Support, Braz.*
Food for special diets.
Cystic fibrosis.

Cystilite *Holland Pharma, Neth.*
Belladonna (p. 2453·3); berberis vulgaris (p. 2502·1); cantharis vesicatoria; dulcamara (p. 2497·3); millefolium (p. 2427·3); nux vomica (p. 2573·3); petroselinum crispum (p. 2583·3); populus tremuloides (p. 2450·3).
Homoeopathic preparation.

Cystine B_6 *Bailleul, Fr.*
Cystine (p. 2059·1); pyridoxine hydrochloride (p. 2105·3).
Nail and hair disorders; eye disorders.

Cystinol Akut *Schaper & Brummer, Ger.; Schaper & Brummer, Ukr.*
Bearberry (p. 2453·2).
Urinary-tract inflammation.

Cystinol Long *Schaper & Brummer, Ger.*
Solidago virgaurea (p. 2620·1).
Renal calculi; urinary-tract disorders.

Cystinol N *Schaper & Brummer, Ger.*
Bearberry leaf (p. 2453·2); solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Cystipret *Bionorica, UK.*
Centaury (p. 2473·2); lovage (p. 2545·3); rosemary (p. 2607·2).
Cystitis.

Cystistat *Eurolab, Arg.; Alveda, Canad.; CytoChemia, Ger.†; Bioniche Teoranta, Singapore†; Teva, UK.*
Sodium hyaluronate (p. 2526·2).
Replacement of bladder glycosaminoglycan in cystitis.

Cystitis Relief *Galpharm, UK; Numark, UK; Thornton & Ross, UK.*
Sodium citrate (p. 1781·2).
Cystitis.

Cystium Solidago *Wernigerode, Ger.†*
Solidago virgaurea (p. 2620·1).
Renal calculi; urinary-tract disorders.

Cysto Hevert *Hevert, Ger.*
Bucco (p. 2461·3); equisetum arvense (p. 2500·1); petroselinum (p. 2583·3); populus tremuloides (p. 2450·3); sabal serrulatum (p. 2363·3); soldidago virgaurea (p. 2620·1); urtica (p. 2639·3).
Homoeopathic preparation.

Cystocalm *Galpharm, UK.*
Sodium citrate (p. 1781·2).
Cystitis.

Cysto-Conray *Mallinckrodt, Arg.; Tyco, Canad.; Mallinckrodt, USA.*
Meglumine iotalamate (p. 1592·2).
Radiographic contrast medium.

Cysto-cyl L Ho-Len-Complex *Liebermann, Ger.*
Cantharis (p. 2469·2); causticum (p. 2595·3); oleum terebinthinae (p. 2636·3); staphisagria; sulfur (p. 1721·1).
Homoeopathic preparation.

Cystoforce *Bioforce, Canad.†*
Bearberry (p. 2453·2); echinacea (p. 2498·1); St John's wort (p. 449·1); rhus aromatica (p. 2603·3); achillea (p. 2427·3); avena (p. 2451·1); belladonna (p. 2453·3); poplar (p. 2450·3).
Urinary-tract disorders.

Cysto-Gastreu R18 *Reckeweg, Neth.*
Berberis vulgaris (p. 2502·1); dulcamara (p. 2497·3); equisetum hyemale; eupatorium purpureum (p. 2522·1).
Homoeopathic preparation.

Cysto-Gastreu S R18 *Reckeweg, Ger.*
Berberis vulgaris (p. 2502·1); dulcamara (p. 2497·3); equisetum hiemale; eupatorium purpureum (p. 2522·1).
Homoeopathic preparation.

Cystografin *Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Cysto-Myacyne N *Schur, Ger.*
Neomycin sulfate (p. 330·1).
Urinary-tract infections.

Cystone *Himalaya Herbal, India.*
Syrup: ⊗Asparagus racemosus (p. 2614·2); punarnava (p. 2601·1); curcuma zedoaria; cyperus rotundus; bergenia pacumbis; tribulus terrestris (p. 2633·3).
Urolithiasis; renal calculi; crystalluria; urinary-tract disorders.

Himalaya Herbal, India.
Tablets: Achyranthes aspera; cyperus scariosus; didymocarpus pedicellata; rubia cordifolia; bergenia pacumbis; vernonia cinerea.
Urolithiasis; renal calculi; crystalluria; urinary-tract disorders.

Himalaya Herbal, Malaysia.
Didymocarpus pedicellata; bergenia pacumbis; rubia cordifolia; cyperus scariosus; achyranthes aspera; onosma bracteatum; vernonia cinerea; lime silicate calx; asphaltum (purified).
Urinary-tract disorders.

Himalaya, Ukr.
Didymocarpus pedicellata; saxifraga ligulata; rubia cordifolia; cyperus scariosus; achyranthes aspera; onosma bracteatum; vernonia cinerea; hajrul yahood bhasma; shilajeet.
Urinary-tract disorders.

Transatlantic, Rus.
Shilapuspha (Didymocarpus pedicellata); Pasanabheda (Saxifraga ligulata); Manjishtha (Rubia cordifolia); Nagarmusta (Cyperus scariosus); Apamarga (Achyranthes aspera); Gojiha (Onosma bracteatum); Sahadevi (Vernonia cinerea); Shilajeet (Purified); Hajrul yahood bhasma.
Ayurvedic remedy; urinary-tract infections; gout; renal calculi.

Himalaya, Singapore.
⊗Didymocarpus pedicellata; saxifraga ligulata; rubia cordifolia; cyperus scariosus; achyranthes aspera; onosma bracteatum; vernonia cinerea; hajrul yahood bhasma; shilajeet (purified); tribulus terrestris (p. 2633·3); mimosa pudica; pavonia odorata; equisetum (p. 2500·1); tectona grandis.
Urinary tract infections; renal calculi.

Cystoplus *Pendopharm, Canad.*
Sodium citrate (p. 1781·2).
Cystitis.

Cystopurin *Bayer, Irl.; Roche Consumer, Irl.; Roche Consumer, UK.*
Potassium citrate (p. 1780·3).
Cystitis.

Cysto-Saar *MIP, Ger.†*
Nitroxoline (p. 333·2).
Urinary-tract infections.

Cystospaz *PolyMedica, USA.†*
Hyoscyamine (p. 1848·1).
Urinary-tract spasm.

Cysto-Urgenin *Madaus, Ger.†*
Cucurbita oil (p. 2489·2).
Bladder irritability.

Cystran *Intas, India.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Cystrin *Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Pol.†; Sanofi Synthelabo, UK.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder disorders; nocturnal enuresis; urinary incontinence; urinary frequency.

Cysview *GE Healthcare, USA.*
Hexaminolevulinate hydrochloride (p. 740·1).
Detection of bladder cancer.

Cytabin *Zydus, India.*
Cytarabine (p. 774·1).
Acute leukaemias; lymphomatous meningitis.

Cytacon *Goldshield, Irl.†; Goldshield, UK.*
Cyanocobalamin (p. 2107·2).
Megaloblastic anaemia; vitamin B_{12} deficiency; tropical sprue.

Cytadren *Novartis, Austral.†*
⊗Aminoglutethimide (p. 739·2).
Breast cancer; Cushing's syndrome.

Cytamen *Mayne, Austral.†; UCB, Irl.; Focus, UK.*
Cyanocobalamin (p. 2107·2).
Anaemia due to B_{12} deficiency; Schilling test; macrocytic anaemias; vitamin B_{12} deficiency.

Cytaraside *Chandra Bhagat, India.*
Cytarabine (p. 774·1).
Acute leukaemias; lymphomatous meningitis.

Cytarine *Dabur, India; Fresenius Kabi, Thai.*
Cytarabine (p. 774·1).
Malignant neoplasms; non-Hodgkin's lymphoma; herpesvirus infection; psoriasis.

Cytax *Intas, India.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Cyteal
Note: this name may be used for preparations of different composition.
Pierre Fabre, Cz.; Pierre Fabre, Philipp.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Singapore; Pierre Fabre, UK; Pierre Fabre, Ukr.
Chlorhexidine gluconate (p. 1743·3); chlorocresol (p. 1748·1); hexamidine isetionate (p. 1754·3).
Disinfection of skin and mucous membranes; vulvovaginal infections; skin infections; hand disinfection.

Cytéal *Pierre Fabre Dermatologie, Fr.*
Chlorhexidine gluconate (p. 1743·3); chlorocresol (p. 1748·1); hexamidine isetionate (p. 1754·3).
Disinfection of skin and mucous membranes.

Cytelium *Silesia, Chile; A-Derma, Fr.; Medifarm A-Derm, Venez.*
Avena (p. 2451·1); zinc oxide (p. 1729·1).
Skin disorders.

Cytigem *Eurolab, S.Afr.*
Gemcitabine hydrochloride (p. 801·2).

Cytine *Douglas, NZ.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastrointestinal haemorrhage; acid aspiration; Zollinger-Ellison syndrome.

Cytistat *Dipa, Indon.*
Sodium hyaluronate (p. 2526·2).
Cystitis.

Cyto B2 *Solace, USA.*
Vitamin B_2 (p. 2104·3).
Dietary supplement.

Cyto-Bifidus *Eagle, Austral.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3); *Lactobacillus brevis* (p. 2596·3); *Lactobacillus lactis* (p. 2596·3) (p. 2596·3).
Gastrointestinal disorders.

Cytobion *Merck Serono, Ger.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Cytobiotect *Biopharma, Ukr.*
A cytomegalovirus immunoglobulin (p. 2381·3).
Passive immunisation.

Cytoblastin *Cipla, India.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cipla-Medpro, S.Afr.
Vinblastine (p. 881·3).

Cytocarb *Cipla, India.*
Carboplatin (p. 759·1).
Ovarian cancer; small-cell lung cancer.

Cytocom *Alkem, India.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Cytocom-E *Alkem, India.*
1 Tablet, efavirenz (p. 975·1); 2 tablets, lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Cytocom-N *Alkem, India.*
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); zidovudine (p. 1024·2).
HIV infection.

Cytocristin *Cipla, India.*
Vincristine sulfate (p. 882·3).
Acute leukaemias.

Cytodec *Ankom, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Cytodec Forte *Ankom, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Cytodrox *Cipla, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms.

Cytoflavin *Polisan, Rus.; Polisan, Ukr.*
Succinic acid (p. 2214·3); inosine (p. 2533·1); nicotinamide (p. 2083·1); riboflavine mononucleotide (p. 2104·3).
Cerebrovascular disorders; asthenia.

Cytofos *Sun, China; Sun, India; Sun, Thai.*
Amifostine (p. 1539·2).
Radiotherapy-associated xerostomia; reduction of toxicity due to alkylating agents and platinum-containing cytotoxics.

CytoGam *CSL, Canad.; Oditas, Turk.; CSL, USA.*
A cytomegalovirus immunoglobulin (p. 2381·3).
Passive immunisation.

Cytogard *Piramal, India.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; Ménière's disease.

Cytogem *Ferron, Indon.*
Gemcitabine (p. 801·2).
Non-small-cell lung cancer; pancreatic cancer.

Reddy, India; Reddy, Rus.; Reddy, Ukr.
Gemcitabine hydrochloride (p. 801·2).
Non-small cell lung cancer; pancreatic cancer; bladder cancer; breast cancer; ovarian cancer.

Cytolog *Zydus, India.*
Misoprostol (p. 2140·3).
Peptic ulcer.

Cytomel *Pfizer, Canad.; ACE, Neth.; Jones, USA.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism; non-toxic goitre; evaluation of thyroid function.

Cytomid *Cipla, India.*
Flutamide (p. 798·2).
Prostatic cancer.

Cytonal *Atafarm, Turk.*
Cytarabine (p. 774·1).
Acute myeloid leukaemia.

Cytop *Wockhardt, India.*
Citalopram (p. 411·1).
Depression; panic disorder.

Cytoplatin *Cipla, India; Cipla, Venez.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cytoposid *Cipla, Rus.*
Etoposide (p. 790·2).
Malignant neoplasms.

Cyto-Protectin *Ethipharm, Pol.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular ischaemia.

Cytorest *Mochida, Jpn.†*
Cytochrome C (p. 2491·2).
Leucopenia; head injury.

CytoRich *Richmond, Arg.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Cytosar *Pfizer, Belg.; Pfizer, Canad.; Pfizer, China; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Israel; Pfizer, Mex.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Ukr.; Pfizer, Venez.*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphoma.

Cytosar-U *Pfizer, Indon.†; Pfizer, Malaysia; Pfizer, Philipp.*
Cytarabine (p. 774·1).
Non-Hodgkin's lymphoma; leukaemias.

Cytosplat *Korea United, Philipp.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Cytotam *Cipla, India.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Cytotec *Pfizer, Austral.; Continental Pharma, Belg.; Pfizer, Braz.†; Pfizer, China; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Searle, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Ali, Turk.; Pfizer, UK; Searle, USA; Pfizer, Venez.*
Misoprostol (p. 2140·3).
Peptic ulcer; gastrointestinal haemorrhage.

Cytotect
Note: this name may be used for preparations of different composition.
Biotest, Austria; Pentafarma, Chile†; Biotest, Cz.; Biotest, Ger.; Biotest, Hong Kong†; Biotest, Hung.; Biotest, Ital.; Biotest, Pol.; Biotest, Switz.; Kansuk, Turk.
A cytomegalovirus immunoglobulin (p. 2381·3).
Passive immunisation.

Paviour, India.
Normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; bone-marrow transplantation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Cytovan *Alkem, India.*
Vancomycin (p. 384·2).
Bacterial infections.

Cytovene *Roche, Canad.; Roche, USA.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infection.

Cytovir *Citomed, Rus.*
Thymogen sodium (p. 2631·1); ascorbic acid (p. 2110·3); bendazol hydrochloride (p. 2454·3).
Viral infections.

Cytovit *Ipca, India.*
Vitamins; minerals.

Cytox *Cipla, Philipp.*
Cytarabine (p. 774·1).
Leukaemias; lymphoma.

Cytoxan *BMS, Canad.†; BMS, Hung.†; BMS, NZ; BMS, Philipp.†*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; nephrotic syndrome.

Cytozen *Charak, India.*
Aloes (p. 1816·1); andrographis (p. 2443·2); punarnava (p. 2601·1).
Liver disorders.

Cytozol *VHB, India.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone; osteoporosis.

Cytra-2 *Cypress, USA.*
Citric acid monohydrate (p. 2480·3); sodium citrate (p. 1781·2).
Metabolic acidosis; urinary alkalinisation.

Cytra-3 *Cypress, USA.*
Citric acid monohydrate (p. 2480·3); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Metabolic acidosis; urinary alkalinisation.

Cytragen *Vonnace, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Cytra-K *Cypress, USA.*
Citric acid monohydrate (p. 2480·3); potassium citrate (p. 1780·3).
Metabolic acidosis; urinary alkalinisation.

Cytra-LC *Cypress, USA.†*
Citric acid monohydrate (p. 2480·3); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Metabolic acidosis; urinary alkalinisation.

Cytrolic *Terramedic, Philipp.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Cytropil *Gracia, Indon.*
Piracetam (p. 393·3).
Mental function disorders; alcoholism; cerebrovascular disorders.

Cytrosar *VHB, India.*
Cytarabine (p. 774·1).
Acute leukaemias; lymphomatous meningitis.

Cytur Test *Roche Diagnostics, Austral.†*
Test for leucocytes in urine.

Cytuss HC *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

Cytuss-HC NR *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); dexbrompheniramine maleate (p. 618·1).
Cold symptoms; cough; allergic rhinitis.

C-Yum *Zydus, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

C-Yum OS *Zydus, India.*
Calcitriol (p. 2113·1); calcium citrate maleate (p. 1783·1).
Calcium and vitamin D supplement.

Cyzine *Pharmasant, Thai.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; allergic skin disorders; allergic conjunctivitis.

CZ-3 *Lupin, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Czam *East West, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Czap *Biosans, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Czar *Aurobindo, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Czar-AM *Aurobindo, India.*
Amlodipine (p. 1304·1); losartan (p. 1422·2).
Hypertension.

Czar-H *Aurobindo, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Czartan *Macleods, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

CZ-Cold *Lupin, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

C-Zid *Emcure, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Czidnate *Sanify, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

CZ-L *Lupin, India.*
⊗Levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

CZN *Daffohils, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Czopress *CMG, India.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; Raynaud's syndrome; benign prostatic hyperplasia.

Czynnik VIII (Metoda M) *Imed, Pol.†*
A factor VIII preparation (p. 1148·1).
Factor VII deficiency.

D3-50 *Bio-Tech, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

4D *Sandoz, Philipp.*
1 Strip, ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

D-204 *Gambro, Israel.*
Electrolytes (p. 1775·1) (p. 1778·2).
Haemodialysis solution.

D-248 *Gambro, Israel.*
Electrolytes (p. 1775·1) (p. 1778·2).
Haemodialysis solution.

D-300 *Gambro, Israel.*
Electrolytes (p. 1775·1) (p. 1778·2).
Haemodialysis solution.

D-326 *Gambro, Israel.*
Electrolytes (p. 1775·1) (p. 1778·2).
Haemodialysis solution.

D1000 *Mason, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

D 400 *Mason, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

D_3 Dots *VitaMed, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

d Epifrin *Allergan, Ger.†*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

D-1000 Extra Strength *21st Century, USA.*
Vitamin D (p. 2112·3); calcium (p. 1783·1).
Dietary supplement.

D 1000 Plus *Mason, USA.*
Calcium (p. 1783·1); vitamin B substances (p. 2102·3); colecalciferol (p. 2113·1).
Dietary supplement.

D-5000 Super Strength *21st Century, USA.*
Colecalciferol (p. 2113·1); calcium (p. 1783·1).

D_3 Vicotrat *Heyl, Ger.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Da Le *Huang Long, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

DA II *Dura, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract symptoms.

Da Bei *TianJing, China.*
Argatroban (p. 1307·2).

Da Chang *Hua Lu, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

DA Chewable *Dura, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Cold symptoms; allergic rhinitis; sinusitis.

Da Er De *Baiyunshan, China.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Da Fei Xin *An Te, China.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Da Fen Gai *Dafo, China.*
Calcitonin (salmon) (p. 1178·1).

Da Fen Ke Chuang *Dafo, China.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Da Fen Ke Quan *Ao Dong, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Da Fen Lin *Dafo, China.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Da Fen Qi Xin *Ao Dong, China.*
Acehytisine hydrochloride.

Da Fen Rong *Dafo, China.*
Clindamycin phosphate (p. 269·3).
Acne.

Da Fen Shu Ji *Dafo, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Da Fen Tai Xing *Ao Dong, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Da Feng *Wantong, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Da Fu Ming *Double-Crane, China.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Da Ji Su *Yangtze River, China.*
Dyclonine hydrochloride (p. 1987·1).

Da Ka *Xianju, China.*
Ropivacaine mesilate.

Da Kai Fu *Guangdong, China.*
Asarone.

Da Li Neng *ZhiJun, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Da Liang *Sha Pu Ai Si, China.*
Puerarin.

Da Lu *ZhenYuan, China.*
Lornoxicam (p. 83·2).
Pain; musculoskeletal and joint disorders.

Da Ma Err *Shouhe Jinhai, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Da Mai *TianJing, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Da Mei Ao Xin *Simcere, China.*
Sodium demethylcantharidate.

Da Nei *Rotam Reddy, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Da Ning *Hengrui, China.*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Da Nuo Xin *Likang, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Da Sheng Rui Li *Xianzhen, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Da Sheng Xin Er *Beifang, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Da Shu Ya *Sichuang, China.*
Telmisartan (p. 1509·3).
Hypertension.

Da Wei Bang *Twinluck, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial skin infections.

Da Wei Ping *Zihua, China.*
Aspirin (p. 22·2); vitamin C (p. 2110·3).

Da Wei Xin *Ke Lun, China.*
Vitamin C (p. 2110·3).

Da Zhi Su *Yaoyou, China.*
Ethylenediamine diaceturate.

Daash *Themis Medicare, India.*
Ocimum sanctum; withania somnifera (p. 2450·2).

Dabao *Xincat, China.*
Tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Dabaz
Note: this name may be used for preparations of different composition.
Accord, Braz.
Vincristine (p. 882·3).
Intas, India.
Dacarbazine (p. 776·1).
Metastatic malignant melanoma; Hodgkin's disease; soft-tissue sarcoma.

Dabby *Ind-Swift, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dabcilin *Dabur, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Dabcilox *Dabur, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Daben *Solfran, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Dabenzol
Note: this name may be used for preparations of different composition.
Filaxis, Arg.
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Dabetil *Liferpal, Mex.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Dabex *Merck, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dabinese *Pfizer, Venez.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Dabonal *Qualigen, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Dabonal Plus *Qualigen, Spain.*
⊗Hydrochlorothiazide (p. 1403·2); enalapril maleate (p. 1371·1).
Hypertension.

Dabrin *Pasteur, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dabroson *Norma (Νορμα), Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Dabsan *Nordin, Mex.*
Cantharis vesicatoria.
Burns; keratosis.

Daburex *Alternavida, Mex.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

Dac *Daehan, Singapore.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Dacam *Laboratorios Chile, Chile.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Dacam RL *Laboratorios Chile, Chile.*
⊗Betamethasone acetate (p. 1623·2); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Dacarb *Eurofarma, Braz.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Dacarba *Chandra Bhagat, India.*
Dacarbazine (p. 776·1).
Metastatic malignant melanoma; Hodgkin's disease; soft-tissue sarcoma.

Dacarbion *Medicus, Gr.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Dacarex *Alkem, India.*
Dacarbazine (p. 776·1).
Metastatic malignant melanoma; Hodgkin's disease; soft-tissue sarcoma.

Dacarin *VHB, India.*
Dacarbazine hydrochloride (p. 776·1).
Malignant neoplasms.

Dacarzine *Khandelwal, India.*
Dacarbazine (p. 776·1).
Metastatic malignant melanoma; Hodgkin's disease; soft-tissue sarcoma.

Dacatic *Orion, Fin.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Dacef *Aspen, S.Afr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Dacepton *Ever Neuro, Neth.*
Apomorphine hydrochloride (p. 892·3).
Parkinsonism.

Dacex-A *Cypress, USA.*
Carbinoxamine maleate (p. 619·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs; nasal congestion.

Dacex-DM *Cypress, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dacex-PE *Cypress, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Coughs; nasal congestion.

Dacin
Note: this name may be used for preparations of different composition.
Pharmalogic, Israel; Lipomed, Switz.
Dacarbazine (p. 776·1).
Malignant neoplasms.
Mersifarma, Indon.
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Dacin-F *Farmaline, Thai.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Daclin
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Clindamycin phosphate (p. 269·3).
Bacterial infections.
Mylan, NZ.
Sulindac (p. 134·2).
Gout; musculoskeletal, joint, and peri-articular disorders.
Tempo Scan Pacific, Indon.
Clindamycin (p. 269·3).
Bacterial infections.

Daclor *DWD, India.*
Chloramphenicol (p. 257·1).
Bacterial infections; psittacosis.

Dacmozen *VHB, India.*
Dactinomycin (p. 776·3).
Malignant neoplasms.

Dacnis *Pharmaffiliates, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Dacnis N *Pharmaffiliates, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Dacogen *Janssen-Cilag, Arg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Pharmachemie, China; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Neth.; Janssen, Philipp.; Janssen-Cilag, Rus.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Johnson & Johnson, Turk.; Janssen-Cilag, UK; Eisai, USA.*
Decitabine (p. 780·1).
Myelodysplastic syndromes; chronic myeloid leukaemia; acute myeloid leukaemia.

Dacortin *Merck, Spain.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Dacotin *Reddy, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Dacpar *Health Care, India.*
Tablets: Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.
Health Care, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dacpar-S *Health Care, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dacplat *Pfizer, Arg.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Dacrio Gel *Alcon, Gr.*
Carbomer (p. 2173·3).
Dry eyes.

Dacriogel *Alcon, Ital.*
Carbomer (p. 2173·3).
Dry eyes.

Dacriose *Novartis Ophthalmics, USA.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Dacriosol *Alcon, Denm.; Alcon, Ital.*
Eye drops: ⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Dacrodil *Teva Tuteur, Arg.†*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms.

Dacrolux *Alcon, Hung.; Alcon Cusi, Malaysia; M4, Spain; Nobel, Turk.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Dacron *Indkus, India.*
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Dacron-Plus *Indkus, India.*
Chlorphenamine maleate (p. 620·3); diclofenac sodium (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Dacryoboraline *McNeil, Fr.†*
Oxedrine tartrate (p. 1463·2); borax (p. 2459·2); boric acid (p. 2459·3).
Eye irritation.

Dacryosérum *Johnson & Johnson, Fr.*
Boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irritation.

Dacrysoline *Leontik, Gr.*
⊗Timolol maleate (p. 1513·2).

Dacryum *Johnson & Johnson, Fr.*
Borax (p. 2459·2); boric acid (p. 2459·3).
Eye irritation.

Dacten *Phoenix, Arg.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Dacten D *Phoenix, Arg.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dactil OB *Sanofi-Aventis, Mex.*
Piperidolate hydrochloride (p. 1878·1).
Dysmenorrhoea; premature labour; threatened miscarriage.
Sanofi-Aventis, Braz.
Piperidolate hydrochloride (p. 1878·1); hesperidin (p. 2505·2); ascorbic acid (p. 2110·3).
Smooth muscle spasm.

Dactino *Chandra Bhagat, India.*
Dactinomycin (p. 776·3).
Malignant neoplasms.

Dactiran *Kyorin, Jpn.*
Piperidolate hydrochloride (p. 1878·1).
Gastrointestinal pain; threatened miscarriage; premature labour.

Dactive *Zydus, India.*
Zolpidem (p. 1116·2).
Insomnia.

Dactron *Darya-Varia, Indon.†*
Dipyrone (p. 53·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Dactylen *Fahrenheit, Indon.*
⊗Alcohol (p. 1733·1); cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Oral hygiene; mouth and throat disorders.

Dacudoses *Thea, Fr.*
Boric acid (p. 2459·3); borax (p. 2459·2).
Eye irritation.

Daczim *Daksh, India.*
Cefixime (p. 240·3).
Bacterial infections.

Daczim-CL *Daksh, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Daczin *Zydus, India.*
Dacarbazine (p. 776·1).
Metastatic malignant melanoma; Hodgkin's disease; soft-tissue sarcoma.

Dadcrome *Dar Al Dawa, Hong Kong.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders; allergic rhinitis.

Dadicil *Best, Mex.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dadosel *Angelini, Spain.†*
Ibuprofen sodium (p. 68·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; fever.

Dadumir *Krugher, Ital.*
Delorazepam (p. 1062·3).
Anxiety; insomnia.

Daedalon *Gedeon Richter, Hung.; Pharmamagist, Hung.*
Dimenhydrinate (p. 625·2).
Motion sickness; vestibular disorders.

Daedalonetta *Pharmamagist, Hung.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting.

Daewo *Costec, Arg.*
Soap: Triclosan (Irgasan DP-300) (p. 1773·2).
Skin and hand disinfection.

Dafalgan *BMS, Belg.; BMS, Fr.; BMS, Port.; Esteve, Spain†; BMS, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Dafalgan Codeina *BMS, Port.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dafalgan Codeine *BMS, Belg.; BMS, Pol.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dafalgan Codéine *BMS, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dafalgan plus C *BMS, Switz.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain; cold symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dafalganhop *BMS, Fr.*
Paracetamol (p. 115·1).
Fever; pain.

Dafenac *Gland, Philipp.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Dafex *Phoenix, Arg.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Daffocid *Daffohils, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Daffocid-O *Daffohils, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Daffolac *Daffohils, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Daffolac-P *Daffohils, India.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2); sodium picosulfate (p. 1887·2).

Daffozyme *Daffohils, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders.

Dafiro *Novartis, Cz.; UCB, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Spain.*
Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2).
Hypertension.

Dafiro HCT *Novartis, Cz.; UCB, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Spain.*
⊗Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Daflon *Servier, Arg.; Servier, Austria; Servier, Belg.; Europharma, Denm.; Servier, Fr.; Servier, Gr.; Servier, Hong Kong; Serdia, India; Sanfer, Mex.; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Thai.; Servier, Turk.; Servier, Venez.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; vascular disorders; haemorrhoids.

Servier, Braz.
Diosmin (p. 2505·2).
Haemorrhoids; venous insufficiency; menorrhagia.

Daflon 500 *Servier, Braz.; Grunenthal, Chile; Servier, Ital.; Servier, Malaysia; Servier, Spain; Servier, Switz.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency; capillary fragility.

Dafloxen *Liomont, Mex.*
Naproxen sodium (p. 98·2).
Pain; fever; inflammation.

Dafloxen-F *Liomont, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Pain; fever; inflammation.

Dafne
Note: this name may be used for preparations of different composition.
Omega, Arg.
Dicycloverine hydrochloride (p. 1834·2); diazepam (p. 1063·2); aluminium glycinate (p. 1817·2); magnesium oxide (p. 1857·3); lidocaine (p. 1988·1); simeticone (p. 1886·2).
Dyspepsia; gastrointestinal motility disorders; peptic ulcer.

Recalcine, Thai.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen dependent acne and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Dafnegil
Note: this name may be used for preparations of different composition.
Angelini, Port.
Nifuratel (p. 941·2); nystatin (p. 590·3).
Vulvovaginal infections.

Medinova, Switz.
Ciclopirox olamine (p. 575·3).
Vulvovaginal candidiasis.

Dafnegil Neo *Merz, Switz.†*
Ciclopirox olamine (p. 575·3).
Vulvovaginal candidiasis.

Dafnegin *Doppel, China; Polichem, Cz.; Pharmex (Φαρμεξ), Gr.; Marvecs, Ital.; Poli, Pol.; Poli, Rus.*
Ciclopirox olamine (p. 575·3).
Candidiasis of the skin and vagina; fungal vulvovaginal infections.

Dafomin *TO-Chemicals, Thai.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Dafor *Gerolymatos, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Daforin *Sigma, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder; bulimia; obesity.

Dafrafin *Dafra, Belg.†*
Sulfametopyrazine (p. 367·3); pyrimethamine (p. 662·3).
Malaria.

Daga
Note: this name may be used for preparations of different composition.
Lampugnani, Ital.
Amino acids.
Nutritional supplement.

Sanofi-Aventis, Thai.†
Paracetamol (p. 115·1).
Pain; fever.

Dagan *Tedec Meiji, Spain.*
Nicardipine hydrochloride (p. 1445·2).
Cerebral ischaemia; hypertension; neurological deficit following subarachnoid haemorrhage.

Dagenol *Mediphar, Venez.*
Menthol (p. 2553·2); camphor (p. 2466·2); avena (p. 2451·1).
Pruritus; insect bites; sunburn.

Dages *Hanlim, China.*
⊗Pepsin (p. 2586·1); papain (p. 2582·3); amylase (p. 2442·1); ursodeoxycholic acid (p. 2638·1); cellulase (p. 2473·1); pancrelipase (p. 2580·1); pancreatin (p. 2579·3).
Digestive disorders.

Dagesil *Basi, Port.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue pain.

Dagol *Cetus, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dagotil *Royal, Chile.*
Risperidone (p. 1103·2).
Schizophrenia.

Dagragel *Meda, Port.*
⊗Gelatin (p. 1154·1); glycerol (p. 2517·2).
Constipation; bowel evacuation.

Dagravit *Meda, Port.*
Vitamins; with or without minerals.

Dagrilan *Medochemie, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Dagynil *Teofarma, Neth.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Dahlia *ITF, Chile.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Dai Ding *TianJing, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Dai Er Ka *NEGPF, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Dai Er Song *Bosen, China.*
Doxapram hydrochloride (p. 2321·2).

Dai Fang *Lukang Chenxin, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Dai Fei Lin *Sine, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Dai Lin *Hayao, China.*
Itopride hydrochloride (p. 1850·1).
Nausea and vomiting; gastrointestinal motility disorders.

Dai Te *Ke Yi, China.*
Diammonium glycyrrhizate (p. 2520·3).

Dai Wei *Tsinghua Yuanxing, China.*
Povidone-iodine (p. 1767·1).

Daibofuto *Tsumura, Jpn.*
Astragalus root (p. 2451·1); rehmannia root; peony root; atractylodes lancea rhizome; angelica acutiloba root (p. 2443·3); eucommia bark; saposhnikovia root; cnidium rhizome; liquorice (p. 1853·2); notopterygium; achyranthes root; jujube; ginseng (p. 2513·3); ginger (p. 1844·1); aconite root (p. 2428·3).
Traditional Kampo medicine.

Daicart *Plus, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Daiet B *Humana, Ital.*
Fatty acids; lipid; vitamins.
Nutritional supplement.

Daijokito *Tsumura, Jpn.*
Magnolia bark; immature orange; rhubarb (p. 1884·2); mirabilitum.
Traditional Kampo medicine.

Daikenchuto *Tsumura, Jpn.*
Ginseng (p. 2513·3); zanthoxylum fruit (p. 2650·1); ginger (p. 1844·1).
Traditional Kampo medicine.

Dailat *Pharmasant, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; swelling.

Daily *Pierre Fabre, Fr.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Triphasic oral contraceptive.

Daily Betic *Optimum, USA.*
Vitamins; minerals; thioctic acid (p. 2629·1); lutein (p. 2079·2).
Dietary supplement.

Daily Complete *Awareness, Canad.*
Vitamins; minerals.

Daily Conditioning *Blistex, USA.*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Daily Defense *Dermalogica, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Vivier, Canad.
SPF 45: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Daily Energy *Enzymatic Therapy, Canad.†*
Vitamins; minerals.

Daily Fatigue Relief *Herbal Concepts, UK.*
Kola (p. 2648·2); damiana (p. 2491·3); saw palmetto (p. 2363·3).
Fatigue.

Daily Gold Pack *Solgar, UK.*
Vitamins; minerals.

Daily Moisturizer Oil Free *Mentholatum, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Daily Moisturizing *Vivier, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Daily Nutrilite *Nutrilite, Arg.*
Alfalfa (p. 2433·1); watercress; parsley (p. 2583·3); acerola; carrott (p. 2647·2); spinach; minerals; vitamins.
Dietary supplement.

Daily One *Pharmetics, Canad.; Nutrifarma, Turk.*
Vitamins; minerals.

Daily Overwork & Mental Fatigue Relief *Herbal Concepts, UK.*
Avena (p. 2451·1); zanthoxylum (p. 2650·1).
Tonic.

Daily Plus *Bioglan, Austral.†*
Vitamins; minerals.

Daily Plus Max *Bioglan, Austral.†*
Ginseng (p. 2513·3); garlic (p. 2510·3); milk thistle (p. 1561·1); bladderwrack (p. 2612·1); lecithin (p. 2542·2); vitamins; minerals.
Tonic.

Daily Produce *Unicity, Singapore.*
Fruit or vegetable juice extracts.
Dietary supplement.

Daily Tension & Strain Relief *Herbal Concepts, UK.*
Asafetida (p. 2449·3); valerian (p. 2640·2); avena (p. 2451·1); passion flower (p. 2584·1).
Tension; strain.

Dailycal *Systopic, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Dailypro *Procure, India.*
Dietary protein supplement.

Dailyton *DKT, Thai.*
Lynestrenol (p. 2287·3).
Progestogen-only oral contraceptive.

Dailyvasc *Xeno, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Dailyvit *Beacons, Singapore.*
Vitamins; with or without minerals.

Daily-Vite *Rugby, USA.*
Vitamins; minerals.

Daiobotampito *Tsumura, Jpn.*
Benincasa seed; peach kernel; moutan bark; rhubarb (p. 1884·2); mirabilitum.
Traditional Kampo medicine.

Daiokanzoto *Tsumura, Jpn.*
Rhubarb (p. 1884·2); liquorice (p. 1853·2).
Traditional Kampo medicine.

Dairy Care *Acertus, Singapore.*
Lactobacillus acidophilus (p. 2596·3); tilactase (p. 2631·2).
Lactose intolerance.

Dairy Ease *Sterling Health, USA.*
Tilactase (p. 2631·2).
Lactase insufficiency.

Dairy Free *SteriMax, Canad.†*
Tilactase (p. 2631·2).
Lactose intolerance.

Dairyaid *Tanta, Canad.*
Tilactase (p. 2631·2).
Lactase insufficiency.

Dairywilf *Keton, Mex.*
Vitamins.

Daisaikoto *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; skullcap root (p. 2617·1); peony root; jujube; immature orange; ginger (p. 1844·1); rhubarb (p. 1884·2).
Traditional Kampo medicine.

Daisamox *Pharmacare, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Daisy
Note: this name may be used for preparations of different composition.
Famy, Thai.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Daisynelle *Stragen, Denm.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Daiticin *Erlimpex, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Daiv *Fada, Arg.*
Diazepam (p. 1063·2).
Anxiety; muscle spasm.

Daiva *Eurofarma, Braz.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive.

Daivobet *Leo, Austral.; Roche, Braz.; Leo, China; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Hong Kong; Leo, Hung.; Win-Medicare, India; Darya-Varia, Indon.; Leo, Indon.; Leo, Israel; Leo, Malaysia; Valeant, Mex.; Leo, Norw.; CSL, NZ; Leo, Philipp.; Leo, Pol.; Leo, Port.; Leo, Rus.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Switz.; Leo, Thai.*
⊗Calcipotriol (p. 1697·2); betamethasone dipropionate (p. 1623·3).
Psoriasis.

Daivonex *Andromaco, Arg.; Leo, Austral.; Leo, Belg.; Roche, Braz.; Andromaco, Chile; Leo, China; Leo, Cz.; Europharma, Denm.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Hong Kong; Leo, Hung.†; Win-Medicare, India; Darya-Varia, Indon.; Leo, Indon.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Valeant, Mex.; Leo, Neth.†; Leo, Norw.†; CSL, NZ; Leo, Philipp.; Leo, Pol.; Leo, Port.; Leo, Rus.; Leo, Singapore; Leo, Spain; Leo, Swed.†; Leo, Switz.; Leo, Thai.*
Calcipotriol (p. 1697·2).
Psoriasis; vitiligo.

Dakar *Sanofi-Aventis, Belg.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Dakgran *Legrand, Braz.†*
Miconazole (p. 588·3).
Fungal skin infections.

Dakin *Cooperation Pharmaceutique, Fr.*
Sodium hypochlorite (p. 1768·3).
Skin, mucous membrane, and wound disinfection.

Dakincooper *Melisana, Belg.*
Sodium hypochlorite (p. 1768·3).
Skin and mucous membrane disinfection.

Dakin's Solution *Century, Canad.*
Sodium hypochlorite (p. 1768·3).

Daklin *Synmedic, India; Synmedic, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Daksol
Note: this name may be used for preparations of different composition.
Galeno, Venez.
Secnidazole (p. 947·3).
Protozoal infections.

Pharmavita, Chile.
Lamotrigine (p. 527·2).
Epilepsy.

Daktacort *Johnson & Johnson Consumer, Belg.; Orion, Fin.; Janssen, Hong Kong; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; McNeil, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Johnson & Johnson, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; McNeil, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Fungal and bacterial skin infections with inflammation.

Johnson & Johnson, India.
⊗Miconazole nitrate (p. 589·1); hydrocortisone acetate (p. 1640·1).
Infected and inflammatory skin disorders.

Daktacort HC *Johnson & Johnson MSD Consumer, UK.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Daktagold *Janssen-Cilag, NZ.*
Ketoconazole (p. 585·3).
Fungal skin infections; seborrhoeic dermatitis.

Daktar *McNeil, Ger.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections.

McNeil, Norw.; McNeil, Swed.
Miconazole nitrate (p. 589·1).
Fungal infections.

Daktarin *Janssen-Cilag, Arg.; Johnson & Johnson, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Chile; Orion, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Gr.; Johnson & Johnson, Gr.; Janssen-Cilag, Indon.; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Johnson & Johnson, Neth.; Johnson & Johnson, NZ; Janssen, Philipp.; Johnson & Johnson, Port.; Pharmasol, Rus.†; Janssen-Cilag, S.Afr.; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Johnson & Johnson MSD Consumer, UK; Janssen-Cilag, Venez.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections; fungal and gram-positive skin infections; candidiasis of the gastrointestinal tract; fungal and Gram-positive bacterial infections; bacterial vaginosis; fungal and Gram-positive bacterial skin infections; oral and gastrointestinal candidiasis; fungal skin, nail, and mouth infections; fungal skin and nail infections; fungal and Gram-positive bacterial skin and mouth infections; candidiasis; tinea pedis.

Janssen-Cilag, Braz.; Xian-Janssen, China; Janssen, Hong Kong; Johnson & Johnson, India; Janssen-Cilag, Malaysia; Janssen-Cilag, Pol.; Janssen-Cilag, Singapore; Janssen-Cilag, Thai.
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections; fungal skin infections; fungal and Gram-positive bacterial skin, mucous membrane, and nail infections; fungal skin and nail infections; fungal infections; fungal and Gram-positive bacterial infections; fungal and gram-positive bacterial infections of the skin and vagina.

Daktarin Diaper *Janssen-Cilag, Indon.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Nappy rash.

Daktarin Gold *Johnson & Johnson MSD Consumer, UK.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Daktarin-T *Johnson & Johnson, India.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).

Daktazol *Neo Quimica, Braz.; Berlico Mulia, Indon.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Daktodor *Johnson & Johnson, Gr.*
⊗Hydrocortisone (p. 1640·1); miconazole nitrate (p. 589·1).
Fungal skin infections with inflammation.

Daktozin *Janssen-Cilag, Arg.; Johnson & Johnson, Austral.; Johnson & Johnson Consumer, Belg.; Janssen-Cilag, Braz.†; Janssen-Cilag, Venez.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Nappy rash with fungal infection; fungal skin infections.

D-Al *Sevapharma, Cz.*
Allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.

Dal *Gynopharm, Chile.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 tablets, inert.
Biphasic oral contraceptive.

Dalace *Ace, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Dalacin *Pfizer, Austria; Pfizer, Belg.; Pfizer, Belg.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Hung.; Max, India; Pfizer, India; Pfizer, Irl.; Pfizer, Pol.; Pfizer, UK; Pfizer, Ukr.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Rus.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Venez.
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Dalacin V *Pfizer, Austral.; Pfizer, Chile†; Pfizer, Mex.; Pfizer, Port.; Pfizer, Switz.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginitis.

Pfizer, Braz.
Clindamycin hydrochloride (p. 269·3).
Bacterial vaginitis.

Dalacin C *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; 2care4, Denm.; Europharma, Denm.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections; toxoplasmosis; malaria; pneumocystis pneumonia.

Max, India; Pfizer, India; Pfizer, Ukr.
Clindamycin (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections; toxoplasmosis; pneumocystis pneumonia; malaria.

Dalacin T *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK.*
Clindamycin phosphate (p. 269·3).
Acne; bacterial infections.

Dalacin T Prewash *Pharmacia, NZ.*
Triclosan (p. 1773·2).
Skin cleansing.

Dalacin Vaginal *Paladin, Canad.; Pfizer, Israel.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

Dalacin VC *Pfizer, S.Afr.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

Dalacine *Pfizer, Fr.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Dalacine T *Pfizer, Fr.*
Clindamycin phosphate (p. 269·3).
Acne.

Dalaclin *LBS, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Dalafar *Nafar, Mex.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Dalagis T *Perrigo, Israel.*
Clindamycin phosphate (p. 269·3).
Acne.

Dalalone *Forest Pharmaceuticals, USA.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dalam *Richmond, Arg.*
Midazolam (p. 1085·1) or midazolam maleate (p. 1085·2).
Sedative; induction of anaesthesia; premedication.

Dalap *Biosintetica, Braz.*
Adapalene (p. 1692·1).
Acne.

Dalatina *Mavi, Mex.*
Clindamycin (p. 269·3).
Acne.

Dalatina V *Mavi, Mex.*
Clindamycin (p. 269·3).
Vaginal infections.

Dalcap *Unichem, India.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Dalcefa *Dallas, India.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Dalcefa-SB *Dallas, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Dalcept *Cuprocept, S.Afr.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Dalcinex *Cipla, India.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Dalcipran *Rovafarm, Arg.; Germania, Austria†; Pierre Fabre, Cz.†; Reprefar, Port.*
Milnacipran hydrochloride (p. 435·3).
Depression.

Dal-E *Dal-Vita, Austral.†*
d-Alpha tocoferil acetate (p. 2119·1).
Minor wounds; skin irritation; burns.

Dalektro *Pekana, Austria.*
Argentum nitricum (p. 2615·3); cobaltum nitricum; cuprum aceticum (p. 2486·2); ferrum metallicum (p. 2073·1); manganum sulfuricum (p. 2081·2); selenium amorphum (p. 2086·3).
Homoeopathic preparation.

Daleron *KRKA, Cz.; KRKA, Rus.*
Paracetamol (p. 115·1).
Pain; fever.

Daleron C *KRKA, Rus.; KRKA, Ukr.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; symptoms of influenza and other respiratory infections; pain.

Daleron Cold 3 *KRKA, Ukr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Symptoms of catarrhal disease and influenza; cough.

Daleron proti chřipce a nachlazení *KRKA, Cz.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Dalex *Vargas, Venez.*
Epirizole (p. 54·3).

Dalfarol *Darya-Varia, Indon.*
d-Alpha tocopherol (p. 2119·1).
Cardiovascular disorders; vitamin E supplement.

Dalfaz *Sanofi-Aventis, Arg.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Dalfusin *Farmak, Ukr.†*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Dalgen *Recordati, Spain.*
Fepradinol hydrochloride (p. 64·2).
Peri-articular disorders; soft-tissue disorders.

Dalgex *Daudt, Braz.†*
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).
Skeletal muscle spasm; pain.

Dalhis *Pharmasant, Thai.†*
Mebhydrolin (p. 634·2).
Hypersensitivity reactions.

Dalia *Farmakopea, Ital.*
Domperidone (p. 1838·1).

Dalibang *Zhi Jun, China.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Daliding *Zhi Jun, China.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Dalidome *Advaita, Mex.*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); camphor (p. 2466·2).
Skin disorders.

Dalifen *Zhi Jun, China.*
Cefixime (p. 240·3).
Bacterial infections.

Dalijing *Zhi Jun, China.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Dalilong *Zhi Jun, China.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Dalipaitan *Zhi Jun, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Daliqing *Zhi Jun, China.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Daliresp *Nycomed, Cz.; Nycomed, Irl.; Rafa, Israel; Takeda, Neth.; Forest Pharmaceuticals, USA.*
Roflumilast (p. 1219·3).
Obstructive airways disease.

Dalishu *Zhi Jun, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Dalisol *Lemery, India; Teva, Mex.†*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer; antidote to folic acid antagonists.

Teva, Thai.
Folinic acid (p. 2066·3).
Megaloblastic anaemia; antidote to folic acid antagonists; adjunct to fluorouracil in colorectal cancer and breast cancer; folate deficiency; reduction of methotrexate toxicity.

Dalium *Piramal, India.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Dalivit *LPC, UK.*
Vitamins.

Dalixin *Zhi Jun, China.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Dallapasmo *Dallas, Arg.*
Homatropine methylbromide (p. 2007·3).
Muscle spasm.

Dallergy *Laser, USA.*
Syrup: Chlorcyclizine hydrochloride (p. 620·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract symptoms.

Laser, USA.
Oral drops: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Laser, USA.
Tablets: Chlorcyclizine hydrochloride (p. 620·2) phenylephrine hydrochloride (p. 1672·3).
Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, and hyoscine methonitrate.
Upper respiratory-tract symptoms.

Dallergy DM *Laser, USA.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Cough; cold symptoms.

Dallergy PE *Palmetto, USA.†*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dallergy-D *Laser, USA.*
Capsules: ⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Laser, USA.
Syrup: Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dallergy-JR *Laser, USA.†*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Allergic rhinitis; nasal congestion.

Dalmacol *Riva, Canad.*
⊗Hydrocodone tartrate (p. 67·2); etafedrine hydrochloride (p. 1665·2); sodium citrate (p. 1781·2); doxylamine succinate (p. 627·3).
Respiratory-tract disorders.

Dalmadorm *Valeant, Braz.; Roche, Gr.; Invida, Hong Kong; Transfarma, Indon.; Valeant, Indon.; Meda, Neth.; Inovail, Singapore†; Meda, Switz.*
Flurazepam hydrochloride (p. 1076·1).
Insomnia.

Meda, Ger.; Valeant, Ital.; Meda, Port.; Pharmaco, S.Afr.†; ICN, Thai.†
Flurazepam monohydrochloride (p. 1076·1).
Insomnia; anxiety.

Dalman *Drogsan, Hong Kong; Drogsan, Turk.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Dalmane *ICN, UK.*
Flurazepam monohydrochloride (p. 1076·1).
Insomnia.

Valeant, Canad.; Meda, Irl.; Valeant, USA.†
Flurazepam hydrochloride (p. 1076·1).
Insomnia.

Dalmapam *Pinewood, Irl.*
Flurazepam monohydrochloride (p. 1076·1).
Insomnia.

Dalmasin *Ferring, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Dalmaxin *Lekhim, Ukr.*
Thiotriazoline (p. 2629·3).
Liver disorders; anorectal or vaginal inflammation and injury.

Dalminette *Norma (Νορμα), Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Dalosar *Benedetti, Ital.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; stroke prevention.

Dalp *Daffohils, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Dalparan *Angelini, Spain.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Dalpas *Biotech, Venez.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Dalpin *United Biotech, India.*
Dalteparin sodium (p. 1348·3).

Dalrich *SM, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Dalsan *Egis, Cz.; Egis, Hung.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Dalsin *Offenbach, Mex.*
Dipyrone (p. 53·3).
Fever; muscle spasm; pain.

Dalsy *Abbott, Braz.; Abbott, Spain.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal, joint, and peri-articular disorders.

Daltazen *Giempi, Venez.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; paroxysmal supraventricular tachycardia; hypertension.

Daltehep *Gland, India.*
Dalteparin sodium (p. 1348·3).
Thromboembolic disorders.

Daltrex *Neon, India.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Daltrix *Dallas, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Daltum *Novagen, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Dalun *Medipharm, Chile.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; anxiety; agitation; premedication.

Dalycrid *Pasteur, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Dalys *Dosa, Arg.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Dalzad *Novartis, Gr.*
Valsartan (p. 1521·2).
Hypertension.

Dalzior *Norton Waterford, Irl.*
Cabergoline (p. 899·3).
Hyperprolactinaemia; lactation inhibition; prolactinoma.

Dalzolston *Ariston, Braz.*
Metronidazole (p. 936·1).

Dam *Terapeutico, Ital.*
Damiana (p. 2491·3); muira-puama; santoreggia; kola (p. 2648·2); cinnamon (p. 2479·2).
Erectile dysfunction.

DAM Antacidum *Corifel, Switz.†*
Calcium carbonate (p. 1824·3); glycine (p. 2071·2); liquorice (p. 1853·2).
Gastric hyperacidity.

Damaben *Caprifarmindo, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastroparesis; nausea and vomiting; gastro-oesophageal reflux.

Daman *Meditrina, Gr.*
Trandolapril (p. 1517·2).

Damason-P *Mason, USA.*
Hydrocodone tartrate (p. 67·2); aspirin (p. 22·2).
Pain.

Damater *Schering-Plough, Braz.*
Vitamins; minerals.

Damax *Offenbach, Mex.*
Estradiol benzoate (p. 2271·1); progesterone (p. 2300·2).

Damelium *Actavis, Rus.*
Domperidone maleate (p. 1838·1).
Nausea; vomiting; hiccups; dyspepsia; gastrointestinal motility disorders.

Damiana and Kola Tablets *Dorwest, UK.*
Kola (p. 2648·2); damiana (p. 2491·3); saw palmetto (p. 2363·3).
Tonic.

Damiana-Plus *Doctor H, Rus.*
⊗Acidum phosphoricum (p. 2589·1); damiana (p. 2491·3); nuphar lutea; panax ginseng (p. 2513·3); vitex agnus castus (p. 2432·2); yohimbinum (p. 2372·3).
Homoeopathic preparation.

Damiclin *Teva, Mex.†*
Clindamycin (p. 269·3).
Bacterial infections.

Damicol *Biol, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Damide *Benedetti, Ital.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Daminate *Sriprasit, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Nasal congestion; cough; cold symptoms.

Daminopen *Antibiotici, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Damixan *Medipharm, Chile.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Damizen *Farmo Quimica, Chile.*
⊗Serrapeptase (p. 2613·3).
Inflammation.

Damizol *Specifar, Gr.*
Midazolam hydrochloride (p. 1085·1).

Damol *Daksh, India.*
Tramadol (p. 139·2).
Pain.

Damoxy *Dabur, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Damoxy-GF *Dabur, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Dampo *Bayer, Neth.*
Ointment for inhalation: Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Cold symptoms.

Dampo bij droge hoest *Bayer, Neth.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dampo Solvopect *Bayer, Neth.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Damsel *Gador, Arg.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Damsella *Gador, Arg.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive; premenstrual dysphoric disorder; acne in females.

Dam-Spas *Helax, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Dam-Spas DPS P *Helax, India.*
Dicycloverine (p. 1834·2); simeticone (p. 1886·2).

Damurgin *Gedeon Richter, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Damuvit *Pyridam, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C deficiency.

Damylin with Codeine *Riva, Canad.*
Ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2).

Damzipil *Merck, Port.†*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dan Ke
Note: this name may be used for preparations of different composition.
Changzhou Siyao, China.
Oral solution; tablets: Risperidone (p. 1103·2).
Schizophrenia.

Liansheng, China.
Injection: Ligustrazine phosphate.

Dan Lun *Liansheng, China.*
Ozagrel (p. 2579·1).

Dan Na Er Bin *Shunxin Xiangyun, China.*
Albumin tannate (p. 1815·1).

Dan Nuo *Liansheng, China.*
Aceglutamide (p. 2426·2).

Dan Quan *Liansheng, China.*
Ethylenediamine diaceturate.

Dan Shen Compound *Phytomedicine, Austral.*
Danshen (p. 2491·3); crataegus (p. 2488·1); valerian (p. 2640·2); coleus forskohlii.
Circulatory disorders.

Dan Sheng *Liansheng, China.*
Matrine.

Dan Tong Jing *Huajin, China.*
Sumatriptan succinate (p. 679·2).
Migraine.

Dan Wei *Yaoda, China.*
Diammonium glycyrrhizate (p. 2520·3).

Dan Ze *Liansheng, China.*
Inosine (p. 2533·1).

Dan Zhong Di Bi Ye *Dandong, China.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Dan Zhu *Southwest, China.*
Ferrous lactate (p. 2062·1).

Danac *Teva, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Danafusin *Orion, Denm.; Orion, Fin.; Orion, Swed.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Danalem *Teva, Mex.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disease; hereditary angioedema.

Danalgin *Kalbe, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Danalone *Trima, Israel.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Danantizol *Gador, Arg.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Danapril *Nafar, Mex.*
Phytomenadione (p. 2122·2).
Hypoprothrombinaemia; vitamin K deficiency bleeding.

Danasin *Kocak, Turk.*
⊗Danazol (p. 2263·2).
Endometriosis; menstrual disorders; benign breast disorders; hereditary angioedema; precocious puberty; lupus erythematosus; immune thrombocytopenia.

Danasone *Hexpharm, Indon.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Danatrol *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.†*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; hereditary angioedema.

Danbutol *Danlex, Philipp.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Dancex *Rowex, Irl.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Dancil *Promed, Rus.*
Ofloxacin (p. 334·3).
Bacterial eye and ear infections.

Dancimin-C *Dankos, Singapore.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Danclear *Zydus, India.*
Aloes (p. 1816·1); ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

Dancor *Merck, Austria; Paranova, Denm.; Merck, Neth.†; Merck, Port.; Merck, Switz.*
Nicorandil (p. 1446·2).
Angina pectoris.

Dancow *Nestle, Indon.*
A range of preparations for enteral nutrition.
Nutritional supplements for children.

Dancure *Psychotropics, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Dandelion Combination *Seroyal, Canad.†*
Balmony; celandine (p. 2522·2); geranium maculatum; milk thistle (p. 1561·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Dandoff *Lupin, India.*
Ketoconazole (p. 585·3).

Dandrazol *Transdermal, UK.*
Ketoconazole (p. 585·3).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Dandrex *Curex, India.*
Ketoconazole (p. 585·3).

Dandrid
Note: this name may be used for preparations of different composition.
Meyer, India.
Menthol (p. 2553·2); miconazole (p. 588·3); tinidazole (p. 949·2); zinc sulfate (p. 2126·2).

Sandoz, UK.
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Dandril *Osoth, Thai.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; dandruff; pityriasis versicolor.

Dandruff *Belvedere, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Dandruff Conditioner *Sutton, Canad.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Dandruff Control Pert 2 in 1 *Procter & Gamble, Austral.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Dandruff Plus *Psychotropics, India.*
Melaleuca oil (p. 2551·1); clotrimazole (p. 576·2); selenium sulfide (p. 1719·3).

Dandruff Shampoo *Norwood, Canad.; Sutton, Canad.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Danelip *Santa, Gr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Danemet *Ivax, Cz.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Daneuron *Hexpharm, Indon.†; Dankos, Singapore.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Peripheral nerve pain; hyperemesis gravidarum; vitamin B deficiency; neuritis.

Danferane *Rivero, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Danfree *Cipla, India.*
Ketoconazole (p. 585·3).
Scalp disorders.

Dang Zhi *Lukang Chenxin, China.*
Liranaftate (p. 588·1).

Dan-Gard *Faulding, Austral.†; Valeo, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Danielle *Gynea, Spain.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Danilax *Danipharm, China; Danipharm, Hong Kong.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Danilon
Note: this name may be used for preparations of different composition.
Biotech, Venez.
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract.
Dexter, Spain.†
Suxibuzone (p. 135·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Danitin *Yung Shin, Philipp.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Danitrin *Deva, Turk.†*
Pentaerithrityl tetranitrate (p. 1465·1).
Angina pectoris.

Danitrin Fort *Deva, Turk.*
Pentaerithrityl tetranitrate (p. 1465·1); meprobamate (p. 1083·3).
Angina pectoris.

Danium *Zentiva, Cz.*
Calcium dobesilate (p. 2464·3).
Diabetic retinopathy; venous insufficiency; haemorrhoids.

Dank *Sandoz, Turk.*
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux.

Danka *Angelini, Ital.*
Levodropropizine (p. 1662·3).
Cough.

DanKe *Liansheng, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Dankit *Rafarm, Gr.*
Erythromycin (p. 291·2).
Acne.

Danlax *Sovereign, UK.*
Dantron (p. 1833·3); poloxamer 188 (p. 2202·1).
Constipation.

Danlixin *Qianjiang, China.*
Isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease; angina pectoris; heart failure.

Danlox *Casasco, Arg.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Danlox Rapido *Casasco, Arg.*
Omeprazole (p. 1867·2); sodium bicarbonate (p. 1781·1).
Peptic ulcer; gastro-oesophageal reflux.

Danoclav *Actavis, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Danocrine *Sanofi Synthelabo, Austral.†; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Indon.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; menorrhagia; hereditary angioedema.

Danoflox *Kalbe, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Danogen *Cipla, India; Cipla-Medpro, S.Afr.; Cipla, Venez.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; menorrhagia; mastalgia; hereditary angioedema.

Danokrin *Sanofi-Aventis, Austria.*
⊗Danazol (p. 2263·2).
Endometriosis; precocious puberty; gynaecomastia; hereditary angioedema.

Danol *Sanofi, Irl.†; Sanofi Synthelabo, Israel; Sanofi-Aventis, Rus.; Sanofi, UK.*
⊗Danazol (p. 2263·2).
Endometriosis; hereditary angioedema; benign breast disorders; menorrhagia; premenstrual syndrome; precocious puberty; gynaecomastia; dysfunctional uterine bleeding.

Danoptin *Pliva-Lachema, Cz.†; Pliva Krakow, Pol.†*
Lamotrigine (p. 527·2).
Epilepsy.

Danovag *Novag, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Danoval *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.*
⊗Danazol (p. 2263·2).
Benign breast disorders; endometriosis; menstrual disorders; precocious puberty; hereditary angioedema; menorrhagia; premenstrual syndrome.

Danovir *Kalbe, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Danoxilin *Actavis, Indon.*
Amoxicillin (p. 216·2).
Bacterial infections.

Danping *Wuhan, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Danpule *Changlian Laifu, China.*
Penciclovir (p. 1008·2).
Herpes simplex infections of the lips or face.

Danruf *Torrent, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; dandruff; pityriasis versicolor.

Dansera *Otto, Indon.*
⊗Serrapeptase (p. 2613·3); thiamine nitrate (p. 2103·2); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); tocoferil acetate (p. 2119·2).
Nutritional supplement.

Danset *Sanify, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.
Specpharm, S.Afr.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Danssan *Duopharma, Hong Kong†; CCM, Malaysia.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Dantalin *Cazi, Braz.*
Phenytoin (p. 538·2).
Epilepsy.

Dantamacrin *Speciality European Pharma, Ger.; Vifor, Switz.*
Dantrolene sodium (p. 2023·3).
Skeletal muscle spasm; spasticity.

Dan-Tar Plus *Valeo, Canad.†*
Polytar (a blend of wood and mineral tars) (p. 1723·2); dipyrithione (p. 1701·1).
Dandruff.

Dantenk *Biotenk, Arg.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Dantoin *Pharmasant, Thai.*
Phenytoin sodium (p. 538·2).

Dantoinal *Biotech, Venez.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Dantrium *Pfizer, Austral.; Speciality European Pharma, Belg.; Methapharm, Canad.; Farmo Quimica, Chile; Sofus, Denm.; Merck Serono, Fr.; IFET (ΙΦΕΤ), Gr.; SpePharm, Irl.; Procter & Gamble, Israel; Formenti, Ital.; Speciality European Pharma, Neth.; Pfizer, NZ; Pharmaco, S.Afr.; Procter & Gamble, UK; JHP, USA.*
Dantrolene sodium (p. 2023·3).
Spasticity; malignant hyperthermia; skeletal muscle spasm.

Dantrolen *Cristalia, Braz.; IFET (ΙΦΕΤ), Gr.†*
Dantrolene sodium (p. 2023·3).
Skeletal muscle spasm; malignant hyperthermia.

Dantron *Hexal, S.Afr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.
Unison, Thai.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Dantroxal *Sandoz, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Dantum *Europharm, Hong Kong.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat inflammation.

Danxipress *Vickmans, Hong Kong.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Anxiety; depression.

Dany *The Forty-Two, Thai.*
Domperidone (p. 1838·1).
Dyspepsia; digestive disorders; nausea and vomiting.

Danzen *Casasco, Arg.; Takeda, Hong Kong; Takeda, Ital.; Takeda, Malaysia; Hormona, Mex.; Takeda, Singapore; Takeda, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; breast engorgement; respiratory-tract congestion; wounds; oedema; sinusitis; cystitis; epididymitis; wisdom tooth pericoronitis; alveolar abscess.

Danzet *Nicholas, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2); selenium (p. 2086·3).
Dietary supplement; tonic.

Danzinin *Inpac, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Danzuo *Lukang Chenxin, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure.

Danzyme *Medicine Products, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; sinusitis; breast engorgement; cystitis; epididymitis; pericoronitis; alveolar abscess; respiratory-tract congestion.

Dao Min Qi *Xincat, China.*
Loratadine hydrochloride.
Hypersensitivity reactions.

Daocon-M *Madhav, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Daohair-S *Farmex, Gr.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis; pityriasis.

Daomet *JB Chemicals, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Daonil *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi-Aventis, UK; Sanofi-Aventis, Venez.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Daonil M *Sanofi-Aventis, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Daono *Milano, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Daopar *Sanofi-Aventis, Gr.*
Glibenclamide (p. 472·1); phenformin hydrochloride (p. 493·1).
Diabetes mellitus.

Daoride *Azine, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Daoride-M *Azine, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Daoride-PM *Azine, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Daoryl *JB Chemicals, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Daoryl-M *JB Chemicals, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Dapa
Note: this name may be used for preparations of different composition.
Alphapharm, Malaysia†; Merck, Malaysia.†
⊗Indapamide (p. 1409·2).
Hypertension.

Dapagut *Angelini, Ital.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; post-traumatic stress disorder; social phobia.

Daparox *Angelini, Ital.; Angelini, Spain.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; anxiety.

Dapa-Tabs *Alphapharm, Austral.; Alphapharm, Hong Kong; Mylan, NZ; Alphapharm, Singapore.*
⊗Indapamide (p. 1409·2).
Hypertension.

Daphne
Note: this name may be used for preparations of different composition.
Mithra, Belg.; Mithra, Hong Kong.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in females; combined oral contraceptive; acne and hirsutism in females.
Pond's, Philipp.
Lynestrenol (p. 2287·3).
Progestogen-only oral contraceptive.

Dapixol *Chemica, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Daplen *Silesia, Chile.†*
Adapalene (p. 1692·1).
Acne.

Dapoder *Duncan, Arg.*
Amino acids; vitamin B_{12} (p. 2107·2).
Tonic.

Dapotum *Sanofi-Aventis, Austria†; BMS, Ger.†; Sanofi Synthelabo, Ger.†; BMS, Switz.†*
Fluphenazine decanoate (p. 1075·1) or fluphenazine hydrochloride (p. 1075·1).
Psychoses; schizophrenia; mania.

Dapril *Medochemie, Cz.; Medochemie, Malaysia; Promed, Rus.; Medochemie, Singapore.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; left-ventricular dysfunction following myocardial infarction.

Dapriton *Marching, Hong Kong.†*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Dapriton-B *Marching, Hong Kong.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).

Daps *Pfizer, Arg.†*
Dapsone (p. 281·2).
Leprosy.

Dapsoderm-X *Remexa, Mex.*
Dapsone (p. 281·2).
Leprosy; dermatitis herpetiformis; bacterial mycetoma.

Daptacel *Aventis Pasteur, USA.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Daptaral *Wyeth, Thai.*
Vitamins; minerals.

Daptril *Pharma-Q, S.Afr.*
⊗Indapamide (p. 1409·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dapule *Changlian Laifu, China.*
⊗Miconazole nitrate (p. 589·1); clobetasol propionate (p. 1627·1).
Skin disorders with fungal infection.

Dapyrin *Hexpharm, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Daralix *Aspen, S.Afr.†*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea; vomiting.

Daram *Bittner, Austria.*
Chamomilla (p. 2474·1); veratrum album (p. 2644·3); colchicum (p. 607·1); arsenicum album (p. 2448·1); podophyllum (p. 1717·1).
Homoeopathic preparation.

Daramal *GSK, S.Afr.*
Chloroquine sulfate (p. 650·2).
Malaria; rheumatoid arthritis; discoid lupus erythematosus.

Daraprim *GSK, Arg.; GSK, Austral.; GSK, Belg.; Farmoquimica, Braz.; GSK, Canad.; GSK, Chile; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong†; GSK, Mex.; GSK, Neth.; GSK, Pol.; Aspen, S.Afr.; GSK, Spain; GSK, Switz.; GSK, UK; Amedra, USA.*
Pyrimethamine (p. 662·3).
Malaria; toxoplasmosis.

Darat *Danlex, Philipp.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Darbie *General Drugs, Thai.*
Sodium bicarbonate (p. 1781·1).
Flatulence; hyperchlorhydria.

Darbin *Darrow, Braz.*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphoma.

Darcef *Alkem, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Darcipireno *Fabra, Arg.†*
Biperiden (p. 895·1).
Parkinsonism.

Dardnil *Hiral, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Dardnil-P *Hiral, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Dardokef *Darya-Varia, Indon.†*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Dardum *Lisapharma, Ital.; Lisapharma, Pol.; Lisapharma, Rus.; Lisapharma, Singapore.*
Cefoperazone sodium (p. 243·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Darederm *Mount Mettur, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1); tolnaftate (p. 596·1).
Infected skin disorders.

Daren
Note: this name may be used for preparations of different composition.
Organon, Jpn.
Emedastine fumarate (p. 628·2).
Allergic rhinitis; allergic skin disorders.

Darflox *Meiji, Thai.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Dargol *Kleva, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Daribur *Darier, Mex.*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); camphor (p. 2466·2).
Skin disorders; hyperhidrosis.

Daric *Phoenix, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Daricon *Pfizer, Hong Kong.*
Oxyphencyclimine hydrochloride (p. 1875·1).
Peptic ulcer.

Darilia *Gedeon Richter, Ukr.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Darilin *Recordati, Ital.*
Valganciclovir hydrochloride (p. 1022·1).
Cytomegalovirus infection.

Darin-KA *Raymos, Arg.*
Dimeticone (p. 2209·3).
Pediculosis.

Dariseb *Darier, Mex.*
Coal tar (p. 1723·2); menthol (p. 2553·2).
Scalp disorders.

Darisec *Elea, Arg.*
Darifenacin hydrobromide (p. 2354·2).
Bladder hyperactivity.

Dariten-OD *Ranbaxy, India.*
Darifenacin (p. 2354·2).

Daritex A *Alternavida, Mex.*
Irinotecan hydrochloride (p. 812·2).
Malignant neoplasms.

Darleton *Alapis, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Darlin *Nycomed, Belg.†*
Senna fruit (p. 1885·1).
Constipation.

Darmas *Laboratorios Chile, Chile.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Darmed *Comed, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).
Diarrhoea; dysentery.

Darmen Salt *Ern, Spain.*
Magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1); dibasic sodium phosphate (p. 1791·2); sodium sulfate (p. 1888·1).
Constipation; dyspepsia; gastric hyperacidity.

Darmol
Note: this name may be used for preparations of different composition.
Schmidgall, Austria; Penta, Hung.; Iromedica, Switz.
Senna (p. 1885·1).
Constipation.

Darmol Pico *Omegin, Ger.*
Sodium picosulfate (p. 1887·2).
Constipation.

Darmspülpulver *Serum-Werk Bernburg, Ger.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Darmspülung *Hexal, Ger.†*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Daro *Remark, Neth.*
Paracetamol (p. 115·1).
Pain; fever.

Daro APC *Heca, Neth.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain.

Daro Hoofdpijnpoeders *Remark, Neth.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Headache.

Daro Retard *Remark, Neth.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Daro Trekzalf *Remark, Neth.*
Ichthammol (p. 1705·3).
Boils.

Daro Zinkzalf *Remark, Neth.*
Zinc oxide (p. 1729·1).
Skin disorders.

Darob *Abbott, Ger.†; Abbott, Pol.; Abbott, Port.; Abbott, Turk.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias; angina pectoris; hypertension; myocardial infarction; hyperthyroidism.

Darolac *Aristo, India.*
Capsules: Bifidobacterium longum (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3).
Diarrhoea.

Aristo, India.
Oral sachets: Bifidobacterium longum (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3).
Diarrhoea.

Darolac Plus *Aristo, India.*
Bifidobacterium longum (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Diarrhoea.

Darolac-IBS *Aristo, India.*
Lactobacillus LP299V NLT (p. 2596·3).
Diarrhoea.

Darolan Hoestprikkeldempende *Heca, Neth.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Darolan Slijmoplossende *Heca, Neth.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with viscous mucus.

Daromefan *Heca, Neth.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Daromide *Aspen, S.Afr.†*
Merbromin (p. 1760·1); sulfanilamide (p. 368·1); acriflavinium chloride (p. 1732·3); cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin infections; wounds.

Daronda *Abbott, Gr.; Stephar, Neth.†*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; uterine fibroids; prostatic cancer; female infertility; breast cancer.

Daronrix *GSK, Cz.; GSK, Irl.; GSK, Neth.; GSK, Pol.; GSK, Port.*
An influenza vaccine (H5N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Darpaz *Rivers Edge, USA.†*
Hyoscyamine sulfate (p. 1848·1); methenamine (p. 322·3); methylthioninium chloride (p. 1559·1); salol (p. 129·3); monobasic sodium phosphate (p. 1791·1).
Urinary-tract disorders.

Darrowped *SA Druggists Self Med, S.Afr.†*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Darsil *Darnitsa, Ukr.*
Silymarin (p. 1561·2).
Liver disorders.

Darstin *Seid, Spain.*
Progesterone (p. 2300·2).
Benign breast disorders.

Dart
Note: this name may be used for preparations of different composition.
Juggat, India.
Paracetamol (p. 115·1); caffeine (p. 1203·3); propyphenazone (p. 127·3).
Pain; fever.

Dartelin *Lek, Pol.†*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye and ear disorders.

Dartobcin *Darya-Varia, Indon.†*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Dartrizon *Degorts, Mex.*
⊗Oxyphenbutazone (p. 114·3); prednisolone (p. 1645·2).
Rheumatism.

Darvalidol *Darnica, Pol.†*
Menthyl isovalerate (p. 2554·1).
Gastrointestinal spasm; migraine; hepatic colic.

Darvocet *Ranbaxy, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Pain.

Xanodyne, USA.†
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Darvocet-N *Xanodyne, USA.†*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain; fever.

Darvolin *Eczacibasi, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Darvon
Note: this name may be used for preparations of different composition.
Pharos, Indon.
Betahistine mesilate (p. 2455·3).
Ménière's disease.

Scoshia, India.
Hydroxyprogesterone (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding.

Xanodyne, USA.†
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Darvon Simple *Lilly, Mex.†*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Darvon-N *Paladin, Canad.†; Xanodyne, USA.†*
Dextropropoxyphene napsilate (p. 43·3).
Pain.

Darxa *Help, Gr.*
Clopidogrel (p. 1342·3).

Daryant-Tulle *Darya-Varia, Indon.*
Framycetin sulfate (p. 301·2).
Burns; wounds; infected skin disorders.

Darzitil *Fabra, Arg.*
Amoxicillin trihydrate (p. 216·2) or amoxicillin sodium (p. 216·2).
Bacterial infections.

Darzitil Plus *Fabra, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Darzitil Plus Duo *Fabra, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Darzitil SB *Fabra, Arg.*
Amoxicillin trihydrate (p. 216·2) or amoxicillin sodium (p. 216·2); pivsulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Darzune *Merck, Mex.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Dasabion *Kimia, Indon.*
Ferrous fumarate (p. 2060·3); vitamins. Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Dasc *EMS, Braz.†*
⊗Pancrelipase (p. 2580·1); bile salts (p. 2457·2); cellulase (p. 2473·1).
Digestive disorders.

Dasen *Takeda, China; Takeda, Jpn.†*
⊗Serrapeptase (p. 2613·3).
Inflammation; breast engorgement; respiratory-tract disorders.

Dashiming *Jingfeng, China.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Dasikon *Neon, India; Neon, Ukr.†*
Gatifloxacin (p. 303·2).
Bacterial infections.

Dasin
Note: this name may be used for preparations of different composition.
Hos & Ins, India.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Daskil *Novartis, Austria†; Novartis, India; LPB, Ital.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Daskyl *Azevedos, Port.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Daslin *RPG, India.*
⊗Diphenhydramine (p. 626·1); ammonium chloride (p. 1656·1); alcohol (p. 1733·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Dasmetrol *Tocogino, Mex.*
Metronidazole (p. 936·1).
Acne; amoebiasis.

Dasogrel-S *SJA, Gr.*
Clopidogrel (p. 1342·3).

Dasomin *Pharmis, Port.*
Dobutamine hydrochloride (p. 1365·3).

Dasselta *KRKA, Denm.; KRKA, Irl.; KRKA, Neth.; KRKA, Spain; KRKA, Swed.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Dastonil *Montpellier, Arg.*
⊗Cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); prasterone sodium sulfate (p. 2299·2); procaine hydrochloride (p. 1994·3).
Tonic.

Dastosin *Astellas, Spain.*
Dimemorfan phosphate (p. 1661·3).
Cough.

Dasuglor *Fada, Arg.*
Cefalotin (p. 235·1).
Bacterial infections.

Datan *Pyridam, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Dateril *Merck, Mex.†*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; neuralgias; diabetic neuropathy.

Datevan *Rontag, Arg.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia.

Datisole *Ajanta, India.*
Tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Datolan *Faes, Spain.*
Zopiclone (p. 1118·1).
Insomnia.

Datril *BMS, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

DaTSCAN *GE Healthcare, Belg.†; GE Healthcare, Cz.; GE Healthcare, Fr.; GE Healthcare, Irl.; GE Healthcare, Israel; GE Healthcare, Ital.; GE Healthcare, Neth.; GE Healthcare, Pol.; GE Healthcare, Port.; GE Healthcare, Spain; GE Healthcare, Switz.; GE Healthcare, UK; GE Healthcare, USA.*
Iodine-123 (p. 2225·1) as ioflupane.
Diagnosis of parkinsonism and dementia.

Daunlip *Montpellier, Arg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Daunobin *Oncomed, India.*
Daunorubicin (p. 778·3).
Acute leukaemias; Kaposi's sarcoma.

Daunoblastin *Pfizer, Austria; Pfizer, Ger.; Pfizer, S.Afr.*
Daunorubicin hydrochloride (p. 778·3).
Leukaemias.

Daunoblastina *Pfizer, Arg.†; Pfizer, Braz.; Pfizer, China; IFET (ΦΦΕΤ), Gr; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Ital.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Venez.*
Daunorubicin hydrochloride (p. 778·3).
Malignant neoplasms.

Daunocin *Meizler, Braz.; Korea United, Singapore.*
Daunorubicin hydrochloride (p. 778·3).
Malignant neoplasms.

Miracalus, India.
Daunorubicin (p. 778·3).
Acute leukaemias; Kaposi's sarcoma.

Daunogobbi *Gobbi, Arg.*
Daunorubicin hydrochloride (p. 778·3).
Malignant neoplasms.

Daunoplus *VHB, India.*
Daunorubicin hydrochloride (p. 778·3).
Acute leukaemias; Kaposi's sarcoma.

Daunorubitec *United Biotech, India.*
Daunorubicin hydrochloride (p. 778·3).
Acute leukaemias; Kaposi's sarcoma.

Daunoside *Chandra Bhagat, India.*
Daunorubicin (p. 778·3).
Acute leukaemias; Kaposi's sarcoma.

Daunotec *Cipla, India.*
Daunorubicin hydrochloride (p. 778·3).
Kaposi's sarcoma.

DaunoXome *Gilead, Austral.†; Gilead, Austria†; Gilead, Braz.†; Gilead, Denm.; Galen, Fin.; Gilead, Fr.; Gilead, Ger.†; Gilead, Gr.; Gilead, Irl.; Diatos, Ital.; Galen, Neth.; Galen, Norw.; Gilead, Port.; Nexstar, Rus.†; Diatos, Swed.†; Galen, UK; Galen, USA.*
Liposomal daunorubicin citrate (p. 778·3).
Kaposi's sarcoma.

Daurocina *Laboratorios Chile, Chile.†*
Daunorubicin (p. 778·3).
Malignant neoplasms.

Dauxona *Northia, Arg.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; heart failure.

Davedax *Marvecs, Ital.*
Reboxetine mesilate (p. 447·1).
Depression.

Davercin *Tarchomin, China; Tarchomin, Hung.; Polfa Tarchomin, Pol.*
Erythromycin cyclocarbonate (p. 291·2).
Bacterial infections; acne.

Daverium *Pharmanel, Gr.; Marvecs, Ital.*
α-Dihydroergocryptine mesilate (p. 390·2).
Parkinsonism; hyperprolactinaemia; lactation inhibition; degenerative cerebral disorders; migraine.

Davicrome *Davi, Port.†*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Davilose *Davi, Port.*
Hypromellose (p. 2189·2).
Dry eyes.

Davinefrina *Davi, Port.*
Phenylephrine hydrochloride (p. 1672·3).
Eye congestion; production of miosis; ocular hypertension; glaucoma; ptosis.

Davitamon *Cinetic, Arg.*
Vitamins.

Davitamon Fem *Chefaro, UK.*
Vitamins; minerals; nutritional supplements.

Davixolol *Davi, Port.†*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Davixon *New Research, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Davliet *Volkspharma, Irl.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Davmorid *YSP, Malaysia.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Davol *BJ Benjaosoth, Thai.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Dawnex *Micro, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Hong Kong Medical, Hong Kong†; Micro, Thai.†
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; narcolepsy; cataplexy.

Dax *DWD, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Daxas *Nycomed, Canad.; Nycomed, Cz.; Nycomed, Denm.; Nycomed, Fr.; Takeda, Ger.; Nycomed, Gr.; Takeda, Neth.; Nycomed, Norw.; Nycomed, Pol.; Nycomed, Port.; Takeda, Spain; Nycomed, Swed.; Takeda, Switz.; Takeda, UK; Nycomed, Ukr.*
Roflumilast (p. 1219·3).
Obstructive airways disease.

Daxet *Fahrenheit, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Daxid *Pfizer, India.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Daxim *Abbott, Chile; Abbott, Venez.*
Levosimendan (p. 1420·1).
Heart failure.

Dax-LA *DWD, India.*
⊗Cefadroxil (p. 233·2); probenecid (p. 607·3).

Daxon *Rhein, Mex.*
Nitazoxanide (p. 942·2).
Amoebiasis; giardiasis; worm infections; trichomoniasis.

Daxotel
Note: this name may be used for preparations of different composition.
Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.; Biogalenic, Venez.
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer.

Laboratorios Chile, Chile.
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Day-5 *Bestochem, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Day Cream *Kamins, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Day Defense Treatment *Dermalogica, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Day Five *PSA, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Day Lotion *Medical Skin Therapy, Canad.†*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Day & Night *Pfizer Consumer, Irl.†*
15 Tablets, paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); 5 tablets, paracetamol; diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Day & Night Cold & Flu *Johnson & Johnson, Austral.†*
⊗Day capsules, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night capsules, paracetamol; dextromethorphan hydrobromide; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Pfizer, NZ.†
⊗Day capsules, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night capsules, paracetamol; chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Day & Night Nurse *GSK Consumer, UK.*
⊗Day capsules, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); pholcodine (p. 1675·1); night capsules, paracetamol; promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Day Nurse *GSK Consumer, Irl.; GSK Consumer, UK.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); pholcodine (p. 1675·1).
Cold and influenza symptoms.

Day Peel *Lierac, Fr.†*
⊗Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); urea (p. 1727·3).
Sun-induced skin damage.

Day Relief Cold and Flu *Banner, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Day Renewal *Aloette, Canad.*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.

14-Day Skin Rescue *Johnson & Johnson, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Dayalets + Iron *Abbott, USA.*
Vitamins; iron (p. 2073·1); folic acid (p. 2063·1).

Dayamin
Note: this name may be used for preparations of different composition.
Abbott, Venez.
Vitamins.

Dayamineral *Abbott, Arg.; Abbott, Spain; Abbott, Venez.*
Vitamins; minerals.
Dietary supplement.

Day-Cal *Sanbe, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3).
Calcium and vitamin D deficiency.

Daycee *Medisys, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Daycef *SarPharm, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Day-C-Vit *Lafayette, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Dayflex C *Apotex, Arg.*
Collagen (p. 2483·2); alpha tocopherol (p. 2119·1).
Hair loss.

Daygrip *Lafedar, Arg.*
Paracetamol (p. 115·1); levophenylephrine hydrochloride (p. 1672·2); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Dayhist
Note: this name may be used for preparations of different composition.
Armoxindo, Indon.
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

The Forty-Two, Thai.
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Dayhist-1 *Major, USA.*
Clemastine fumarate (p. 622·3).
Allergic rhinitis; urticaria.

Daylert *Micro, India.*
Terfenadine (p. 640·3).
Hypersensitivity reactions.

Daylette *Gedeon Richter, Cz.; Gedeon Richter, Spain.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Daylong *Spirig, Fr.*
SPF 30; SPF 50+: Bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3).
Sunscreen.

Daylong actinica *Spirig, Ger.†; Spirig, Switz.*
Bemotrizinol (p. 1695·3); octil triazone (p. 1715·1); amiloxate (p. 1694·1); octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); avobenzone (p. 1695·1).
Sunscreen for patients at risk of photodermatoses; actinic keratoses; photodermatoses.

Daylong Ultra *Spirig, Fr.*
SPF 25: Bemotrizinol (p. 1695·3).
Sunscreen.

Daynol *Millimed, Thai.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Daypro
Note: this name may be used for preparations of different composition.
Pfizer, Canad.; Pfizer, USA.
Oxaprozin (p. 112·3).
Rheumatoid arthritis; osteoarthritis; juvenile idiopathic arthritis.

Scoshia, India.
Dietary protein supplement.

DayQuil Cold & Flu *Procter & Gamble, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

DayQuil D *Procter & Gamble, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Dayrun *CSC, Cz.†*
Oxaprozin (p. 112·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Days *Merck, Mex.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Daysee *Lupin, USA.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, ethinylestradiol.
Combined oral contraceptive.

Daytime Cold & Flu *Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Daytime Cold and Flu Relief *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Daytime Cold Relief *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Daytime Cold/Flu *Perrigo, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Daytime Liqua *Jamp, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Daytime Sinus Relief *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinus disorders.

Daytrana *Noven, USA.*
⊗Methylphenidate (p. 2326·1).
Attention-deficit hyperactivity disorder.

Daytrix *CT, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Dayvit *Ache, Braz.*
Vitamins; minerals.

Dayvital
Note: this name may be used for preparations of different composition.
Invision, India.
Ginseng (p. 2513·3); glutamine (p. 2070·3); grape seed (p. 2521·3); green tea (p. 2648·2); lutein esters (p. 2079·2); vitamins; minerals; trace elements.
Will-Pharma, Neth.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Daywear Plus Multiprotection *Estee Lauder, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Daywear Plus Multiprotection for Oily Skin *Estee Lauder, Canad.†*
SPF 15: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1).
Sunscreen.

Dayzinc *Medisys, Philipp.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc deficiency.

Daze *Novogen, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Daze-D *Novogen, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Daze-DP *Novogen, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Daze-MX *Novogen, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Dazen *Takeda, Fr.†; Chemo-Drugs, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema; respiratory-tract congestion.

Dazil *Universal, Hong Kong.†*
Diltiazem (p. 1359·2).

Dazina-DP *Zota, India.*
⊗Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dazina-Forte *Zota, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Dazine-P *PP Lab, Thai.*
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia; mania; anxiety.

Dazirok *Liconsa, Neth.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dazit *Sun, India; Pharmaplan, S.Afr.*
Desloratadine (p. 625·1).
Seasonal allergic rhinitis; hypersensitivity reactions.

Dazithin *Cryopharma, Mex.*
Thioridazine (p. 1110·2).
Psychoses.

Dazo *Osper, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Dazocan *Apotex, Mex.*
Albendazole (p. 149·1).
Parasitic infections.

Dazole-D *Daksh, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Dazolic *Sun, India; Sun, Rus.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Dazolin
Note: this name may be used for preparations of different composition.
Daksh, India.
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.
Drugtech, Chile.
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.
Offenbach, Mex.
Albendazole (p. 149·1).
Worm infections.
Roux-Ocefa, Arg.
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Dazomet
Note: this name may be used for preparations of different composition.
Fabop, Arg.
Mebendazole (p. 158·3).
Worm infections.
Westmont, Philipp.
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Dazonor *Win-Medicare, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Dazotron *Fabop, Arg.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; trichomoniasis; amoebiasis; giardiasis.

Dazy *Daksh, India.*
Azithromycin (p. 221·2).
Bacterial infections.

D-Bay *Aurobindo, India.*
Metformin (p. 489·1).
Diabetes mellitus.

DBI *USV, India.*
Phenformin hydrochloride (p. 493·1).
Diabetes mellitus.

DBI AP *Montpellier, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

DBI Duo *Montpellier, Arg.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

DBS *Zee, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

DBSix *Cosme, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting of pregnancy.

DC *Piramal, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

DC Softgels *Goldline, USA.*
Docusate calcium (p. 1836·2).
Constipation.

DC Vin *Pentafarma, Port.†*
Vinpocetine (p. 2645·3).
Vascular disorders.

D-Cal *A&Z, China.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

D-Calcium *Farmedia, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

D-Calsor *Orion, Fin.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Vitamin D deficiency; calcium supplement.

DCCK *Amdipharm, Ger.†*
Codergocrine mesilate (p. 389·2).
Hypertension; cerebrovascular insufficiency; mental function impairment.

D-Cef *DWD, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

D-Cin *Daksh, India.*
Amikacin (p. 214·1).
Gram-negative bacterial infections.

D-Clic *Grandix, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

D-Clox *Plus, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

D-Coate *Hua, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

DCol-BR *Cubit, India.*
Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

D-Con *Grandix, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

D-Cort *DWD, India.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

DC-Ped *Sarabhai Piramal, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

D-Cuf *Forgo, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

D-Cure *SMB, Belg.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; dietary supplement; hypoparathyroidism; pseudohypoparathyroidism; osteoporosis.

D-cycloserin *IFET (ΙΦΕΤ), Gr.†*
Cycloserine (p. 280·2).
Tuberculosis.

DDAVP *Ferring, Braz.; Ferring, Canad.; Gynopharm, Chile; IFET (ΙΦΕΤ), Gr.; Ferring, Irl.; Ferring, Port.; Ferring, UK; Aventis, USA.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; haemophilia A; von Willebrand's disease; nocturnal enuresis; test of renal concentrating capacity; polyuria; polydipsia; multiple sclerosis associated nocturia; headache resulting from lumbar puncture; test of fibrinolytic response.
Ferring, S.Afr.
⊗Desmopressin (p. 2355·1).
Diagnosis and treatment of diabetes insipidus; nocturnal enuresis; haemophilia A; von Willebrand's disease.

DDD *DDD, UK.*
Cream: Thymol (p. 1772·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); chlorobutanol (p. 1747·2); titanium dioxide (p. 1725·1).
Cuts; grazes; rashes; spots.
DDD, UK.
Lotion: Thymol (p. 1772·2); menthol (p. 2553·2); salicylic acid (p. 1719·1); chlorobutanol (p. 1747·2); methyl salicylate (p. 92·1).
Rashes; spots.
DDD, Austria.†
Lotion; ointment: Salicylic acid (p. 1719·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); camphor (p. 2466·2).
Skin disorders.

DDLon *Medial, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

DDRetro *Alkem, India.*
Didanosine (p. 972·3).
HIV infection.

Ddrops *Carlson, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

De Ai Xin *Nanhai, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

De Bao Sheng *Tongyong, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

De Bao Xing *Tongyong, China; Xinzhongzheng, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

De Bao Yi *Tongyong, China; Xinzhongzheng, China.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

De Bi Tai *Aoda, China.*
Bismuth aluminate (p. 1821·3).

De Chang *Shuangqi, China.*
Pidotimod (p. 2590·2).
Respiratory- and urinary-tract infections.

De Er *Laolaifu, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine (p. 1676·1).
Cold symptoms.

De Er Fu Xing *De Zhou, China.*
Levofloxacin hydrochloride.
Bacterial infections.

De Er Li Wei *De Zhou, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

De Fu Ka *Guo Jing, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

De Fu Ling *Tianlitai, China.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility.

De Gao Ning *De Zhou, China.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

De Icol *Meda, Belg.; Alcon Cusi, Malaysia.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Infected eye disorders.

De Ji Jin Fei Ke *Huinan Huifa, China.*
Rifamycin sodium (p. 354·3).
Bacterial infections.

De Ji Xin Tong *Wansheng, China.*
Sodium ferulate.

De Kai *Otsuka, China.*
Calcifediol (p. 2113·1).

De Li Er Xin *Tiancheng, China.*
Xylitol (p. 2220·3).

De Li Shu *Haili, China.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).
Stroke prophylaxis.

De Li Tong *Haili, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

De Lu Sheng *Si Huan, China.*
Interleukin-2 (recombinant, human) (p. 810·1).

De Luo Jia *Yang Jiang, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

De Luo Wei *Yang Jiang, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

De Rui Ning *Honglin, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

de STAT *Sherman, USA.†*
Range of solutions for contact lenses.

De Te Kang Bai *Nuo Jin, China.*
Ethylenediamine diaceturate.

De Te Li Er *Biochem, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

De Wei *Baiyunshan, China.*
Clodronate disodium (p. 1180·3).
Bone metastases; hypercalcaemia of malignancy.

De Witt's Analgesic *De Witt, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

De Witt's Antacid *De Witt, UK.*
Oral powder: Magnesium trisilicate (p. 1858·1); light magnesium carbonate (p. 1856·2); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1); light kaolin (p. 1850·1); peppermint oil (p. 1877·1).
Dyspepsia; gastric hyperacidity; heartburn.
De Witt, UK.
Tablets: Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1); peppermint oil (p. 1877·1).
Dyspepsia; gastric hyperacidity; heartburn.

De Witt's K & B Pills *De Witt, UK.*
Bearberry (p. 2453·2); buchu (p. 2461·3).
Fluid retention.

De Witts New Pills *Fleet, Austral.†*
Bearberry (p. 2453·2); buchu (p. 2461·3).
Fluid retention.

De Xing Li *Pude, China.*
Enoxacin (p. 290·2).
Bacterial infections.

De Yi Fen *Hui Yin Bi, China.*
Aceglutamide (p. 2426·2).

De Yi Mei *Hui Yin Bi, China.*
Inosine (p. 2533·1).

De Yi Ning *Hui Yin Bi, China.*
Ethylenediamine diaceturate.

De Yi Rong *Hui Yin Bi, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders.

De Yi Xiang *Hui Yin Bi, China.*
Ligustrazine hydrochloride.

Deacos *Indian Drugs, India.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cold symptoms; cough.

Deacura *Mibe, Cz.; Dermapharm, Ger.*
Biotin (p. 2052·2).
Biotin deficiency.

Deadict *Psychotropics, India.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Deaftol *Wild, Switz.*
Aluminium lactate (p. 2440·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Dealan *Silanes, Mex.*
Coal tar (p. 1723·2); clioquinol (p. 273·1); allantoin (p. 1693·1).
Dandruff.

Dealgic *Marvecs, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.

Deall *Genesis, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Dealyd *Rosch & Handel, Austria.*
Polyphloroglucinol phosphate (p. 1717·3).
Skin disorders; burns; wounds.

Deamcilina *Degorts, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Deamelin *Kyorin, Jpn.*
Glyclopyramide (p. 475·1).
Diabetes mellitus.

Deanxit *Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, China; Lundbeck, Hong Kong; Lundbeck, India; Lundbeck, Singapore; Lundbeck, Spain; Lundbeck, Switz.; Lundbeck, Thai.*
Flupentixol hydrochloride (p. 1074·2); melitracen hydrochloride (p. 434·2).
Psychiatric disorders; depression; anxiety; asthenia; psychosomatic disorders.

Dear-21 *Uni-Sankyo, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).

Deaten *Andromaco, Chile.*
Atomoxetine hydrochloride (p. 2316·3).
Attention-deficit hyperactivity disorder.

Deb *Pfizer, Ital.†*
Tetridamine maleate (p. 137·1).
Vulvovaginitis; cervicitis.

Debacterol *Epien, USA.*
Sulfuric acid (p. 2624·2); sulfonated phenols (p. 1763·3).
Mouth and gum disorders.

Debax *Gebro, Austria.*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Debby *TNP, Thai.*
Nifuroxazide (p. 331·3).
Diarrhoea; dysentery; colitis.

Debdox *Pharmachemie, Neth.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Debecylina *Polfa Tarchomin, Pol.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Debelizyna *Herbapol Pruszkow, Pol.*
Kulthi.
Renal calculi.

Debenal *Med-One, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Debeone *Armstrong, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Debequin *Degorts, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Debequin C *Degorts, Mex.*
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Debgone *Symbiosis, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Debgone-M *Symbiosis, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Debisor *Novag, Mex.*
Isosorbide dinitrate (p. 1412·2).

Deblaston *Madaus, Ger.†; Nycomed, S.Afr.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Debonal *Cryopharma, Mex.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis.

Debretin *Polpharma, Pol.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Debricalm *Pfizer, Fr.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal and biliary-tract disorders.

Debridat *Pfizer, Arg.; Pfizer, Chile; Sigma-Tau, Ital.; Pfizer, Port.; Pfizer, Singapore; Abdi, Turk.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; digestive disorders; gastrointestinal motility disorders.

GSK, Mex.; Parke, Davis, Pol.
Trimebutine (p. 2634·1).
Gastrointestinal motility disorders.

Débridat *Pfizer, Fr.; Uhlmann-Eyraud, Switz.*
Trimebutine (p. 2634·1) or trimebutine maleate (p. 2634·1).
Gastrointestinal and biliary-tract disorders.

Debridat B *Pfizer, Arg.*
Trimebutine maleate (p. 2634·1); bromazepam (p. 1041·2).
Gastrointestinal disorders.

Debril *Monserrat, Arg.*
Naproxen (p. 98·2).
Fever; inflammation; pain.

Debrisan *Pfizer, Gr.; Darier, Mex.; Pharmacia, S.Afr.†; Johnson & Johnson, USA.†*
Dextranomer (p. 1699·3).
Burns; ulcers; wounds; wound cleanser.

Debromu *Menarini, Mex.*
Otilonium bromide (p. 2578·2).
Irritable bowel syndrome; adjunct in endoscopy.

Debrox *Avantgarde, Ital.; GSK, USA.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Debrum *Sigma-Tau, Ital.*
Trimebutine maleate (p. 2634·1); medazepam (p. 1083·2).
Gastrointestinal spasm with a component of anxiety.

Débrumyl *Pierre Fabre Sante, Fr.; Pierre Fabre, Port.*
⊗Deanol pidolate (p. 2319·1); heptaminol hydrochloride (p. 2525·1).
Asthenia.

Debtan *Yung Shin, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

DEC
Note: this name may be used for preparations of different composition.
Synco, Hong Kong.†
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); dexchlorpheniramine maleate (p. 621·1); ammonium chloride (p. 1656·1).
Cough.

Dec
Note: this name may be used for preparations of different composition.
PP Lab, Thai.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Deca
Note: this name may be used for preparations of different composition.
Atlantic, China; Atlantic, Malaysia; Atlantic, Thai.
Fluphenazine decanoate (p. 1075·1).
Schizophrenia.

Deca Nandrobol *Cadila, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Deca-Arodec *Willow, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decadron *Sidus, Arg.; Ache, Braz.; Vianex (Βιανεξ), Gr.; Visufarma, Ital.; MSD, Mex.; Medinfar, Port.; MSD, S. Afr.†; M & H, Thai.†; Merck, USA.†*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Decadron con Ciprofloxina *Sidus, Arg.*
⊗Dexamethasone (p. 1630·3); ciprofloxacin hydrochloride (p. 261·2).
Infected eye disorders.

Decadron Colirio *Ache, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Decadron Nasal *Ache, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Infected nasal disorders.

Decadron con Neomicina *Sidus, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

MSD, Mex.†
Ear/eye drops: ⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected eye disorders; external ear disorders.

Decadron com Neomicina *Medinfar, Port.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Decadron with Neomycin *MSD, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Decadron con Nistatina *MSD, Mex.*
⊗Dexamethasone (p. 1630·3); nystatin (p. 590·3).
Vaginitis.

Decadron Phosphate with Neomycin *Vianex (Βιανεξ), Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Decadron con Tobramicina *Sidus, Arg.*
⊗Dexamethasone (p. 1630·3); tobramycin (p. 380·1).
Infected eye disorders.

Decadronal *Ache, Braz.; MSD, Mex.*
⊗Dexamethasone acetate (p. 1631·1).
Corticosteroid.

Deca-Durabol *Organon, Swed.†*
⊗Nandrolone decanoate (p. 2293·1).
Anaemia; osteoporosis.

Deca-Durabolin *Organon, Arg.; Schering-Plough, Austral.; Organon, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering-Plough, Canad.†; Schering-Plough, Chile; Organon, Cz.; Organon, Fin.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, India; Schering-Plough, Indon.; Organon, Irl.; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.†; MSD, NZ; Schering-Plough, Pol.; Organon, Port.; Adcock Ingram, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Switz.; MSD, Thai.; Organon, UK; Organon, USA; Organon, Venez.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias; male hypogonadism.

Decafar *Lafare, Ital.†*
Ubidecarenone (p. 2637·1).
Coenzyme Q_{10} deficiency.

Decagen *Goldline, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Decain *Dexa, Indon.*
Bupivacaine hydrochloride (p. 1980·3).
Intrathecal anaesthesia.

Deca-Intabolin *Intas, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decal *Menarini, Gr.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Rice Steele, Irl.†
Calcium lactate (p. 1784·1); calcium gluconate (p. 1783·3); calcium phosphate (p. 1784·2); ergocalciferol (p. 2113·3).
Calcium and vitamin D deficiency.

Decalcit *Dekaz, Gr.*
Calcium hydrogen phosphate (p. 1783·3); ergocalciferol (p. 2113·3).

Neves, Port.
Colecalciferol (p. 2113·1); calcium hydrogen phosphate (p. 1783·3).
Rickets; osteoporosis; osteomalacia; calcium and vitamin D deficiency.

Phoenix, Arg.
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis; osteomalacia.

Décalcit *Geistlich, Switz.*
Colecalciferol (p. 2113·1); calcium hydrogen phosphate (p. 1783·3).
Calcium and vitamin D deficiency; rickets; osteomalacia.

Decaldol *Polfa Warszawa, Pol.*
Haloperidol decanoate (p. 1077·2).
Psychoses; chorea; tics.

Deca-Lentermina Complex *Biotech, Venez.*
Hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); vitamin B_6 (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuralgia; neuritis; vitamin B deficiency.

Décalogiflox *Biocodex, Fr.*
Lomefloxacin hydrochloride (p. 319·2).
Urinary-tract infections.

Decalona *Biotech, Venez.*
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Decalvit *Ultramark, India.*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).

Decamax *Novaduo, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decamedin *Tanabe, Indon.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Decameribol *Meridian, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decamevit *KVZ, Ukr.*
Vitamin A acetate (p. 2098·3); alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); thiamine (p. 2102·3); riboflavin (p. 2104·3); pyridoxine (p. 2105·3); folic acid (p. 2063·1); nicotinamide (p. 2083·1); rutoside (p. 2505·3); cyanocobalamin (p. 2107·2); methionine (p. 1558·2).
Vitamin supplement.

Ufavita, Rus.
Vitamins; rutoside (p. 2505·3); methionine (p. 1558·2).

Decan
Note: this name may be used for preparations of different composition.
Baxter, Austria; Clintec, Denm.; Clintec, Fin.; Aguettant, Fr.; Baxter, Irl.; Baxter, Neth.; Baxter, Port.; Clintec, Spain†; Baxter, Swed.; Baxter, UK.
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

YSP, Malaysia; Yung Shin, Singapore.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Yung Shin, Philipp.
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Decan Haloper *Uniao Quimica, Braz.*
Haloperidol decanoate (p. 1077·2).
Psychoses.

Decanazole *Alkem, India.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Decand *Comed, India.*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Decand B *Comed, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).
Fungal skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Decand BG *Comed, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Decaneurabol *Zydus, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis.

Decaneurophen *Ind-Swift, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decanobral *Allen, Mex.*
Vitamins; minerals.

Decapeptyl *Raffo, Arg.; Ferring, Austria; Ipsen, Belg.; Tecnofarma, Chile; Ferring, China; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Ger.; Ferring, Hong Kong; Ferring, Hung.; Ferring, India; Ipsen, Irl.; Ferring, Israel; Ipsen, Ital.; Ferring, Malaysia; Ferring, Neth.; Ferring, Philipp.; Ferring, Pol.; Ipsen, Port.; Ferring, Rus.; Ferring, Singapore; Pharmaplan, S.Afr.†; Ipsen, Spain; Ferring, Swed.†; Ferring, Switz.; Ferring, Thai.; Ferring, Turk.; Ipsen, UK; Ferring, Ukr.; Nolver, Venez.*
⊗Triptorelin (p. 2310·3), triptorelin acetate (p. 2310·3), or triptorelin embonate (p. 2311·1).
Prostatic cancer; breast cancer; ovarian cancer; endometriosis; uterine fibroids; female infertility; precocious puberty; benign prostatic hyperplasia.

Décapeptyl *Ipsen, Fr.*
⊗Triptorelin (p. 2310·3) or triptorelin embonate (p. 2311·1).
Prostatic cancer; female infertility; precocious puberty; fibroids; endometriosis.

Decapinol *Sinclair, Israel; Sinclair, UK.*
Delmopinol hydrochloride (p. 2492·2).
Gingivitis; oral hygiene.

Decapod *Misha, India.*
Cefpodoxime.
Bacterial infections.

Decaquinon *Eisai, Thai.*
Ubidecarenone (p. 2637·1).
Heart failure.

Decara
Note: this name may be used for preparations of different composition.
Decomed, Port.
Losartan potassium (p. 1422·2).
Hypertension; cardiovascular risk reduction; diabetic nephropathy.

Medecor, USA.
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Decaras *Rass, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decarb *Cipla, India.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Decaris *Janssen, Hong Kong; Gedeon Richter, Hung.; Janssen-Cilag, Mex.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Levamisole hydrochloride (p. 157·2).
Worm infections.

Decarise *Global, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decasan *Yuriya-Farm, Ukr.*
Decamethoxine (p. 1749·2).
Infections of skin, mucous membranes, soft tissue, wounds, and mouth; irrigation of body cavities; disinfection of skin and medical equipment.

Deca-Scab *Lafedar, Arg.*
Deltamethrin (p. 2152·1); piperonyl butoxide (p. 2160·2).
Pediculosis; scabies.

Décasept *Streuli, Switz.†*
Dequalinium chloride (p. 1749·3); calcium pantothenate (p. 2085·2); lauromacrogol 400 (p. 2194·1).
Mouth and throat disorders.

Decasone *Aspen, S.Afr.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Decasoz *Sozin-Flora, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decaspray *Merck, USA.†*
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Decasun *Laksun, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decatop *Madhav, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decatrolin *Laborate, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decatylen *Mepha, Hong Kong; Mepha, Malaysia; Mepha, Singapore; Mepha, Ukr.; Mepha, Ukr.*
Dequalinium chloride (p. 1749·3); cinchocaine hydrochloride (p. 1983·2).
Mouth and throat disorders.

Décatylène *Mepha, Switz.†*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Décatylène Neo *Mepha, Switz.*
Dequalinium chloride (p. 1749·3); cinchocaine hydrochloride (p. 1983·2).
Mouth and throat disorders.

Decatyleno *Mepha, Port.*
Cinchocaine hydrochloride (p. 1983·2); dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Decaugh II *Fortune, Hong Kong.†*
Bromhexine (p. 1656·3); noscapine (p. 1670·3).

Decavac *Aventis Pasteur, USA.*
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Decaven
Note: this name may be used for preparations of different composition.
Clintec, Gr.; Baxter, Ital.
Minerals; trace elements.
Parenteral nutrition.

Oftalmi, Venez.
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye or ear disorders.

Vensat, India.
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decavillin *Admac, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Deca-Vi-Sol *BMS, Mex.*
Vitamins.

Decavit *Rowa, Irl.†; Charoen Bhaesaj, Malaysia.*
Vitamins.
Dietary supplement.

Kocak, Turk.
Vitamins; minerals.

Decavitamin *Chinta, Thai.*
Vitamins.

Decdak ST *Wockhardt, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Decdan *Wockhardt, India.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Decdan-N *Merind, India.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Eye disorders.

Decef *East West, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Decentan *Merck, Austria†; Merck Serono, Ger.; Merck, Spain.*
Perphenazine (p. 1095·3).
Psychoses; nausea; vomiting; anxiety; depression; pain.

Decet *RND, India.*
Diethylcarbamazine citrate (p. 153·1).
Loiasis; toxocariasis; filariasis.

Decet-BD *RND, India.*
Cetirizine hydrochloride (p. 619·2); diethylcarbamazine citrate (p. 153·1).

Decet-OD *RND, India.*
Cetirizine hydrochloride (p. 619·2); diethylcarbamazine citrate (p. 153·1).

De-Chlor DM *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cough; respiratory-tract congestion.

De-Chlor HC *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold symptoms; cough.

De-Chlor MR *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Cough; nasal congestion.

De-Chlor NX *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); sulfogaiacol (p. 1678·1).
Cough.

Decho *Milano, Thai.†*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Decholest *Egis, Hung.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Decholin *Miles, USA.*
Dehydrocholic acid (p. 2492·1).
Constipation.

Decidex *Roemmers, Arg.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine sulfate (p. 1676·1).
Respiratory-tract congestion.

Decidex Compuesto *Roemmers, Arg.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1).
Influenza symptoms.

Decidex Plus *Roemmers, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Decil *Johnson & Johnson, India.*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).

Decilone *Westmont, Indon.†; Westmont, Philipp.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Decilop *Santa, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Decitriol *Richmond, Arg.*
Lysine aspirin (p. 84·3).
Inflammation; pain; fever.

Decizox *Biochemix, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Declin *Farmaceutica H, Mex.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Decliten *Ariston, Arg.*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Decloban *Teofarma, Spain.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Declobiotic *Norma (Νορμα), Gr.*
Rifampicin (p. 350·3).

Declofon *Aurora, Gr.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Declomycin *CorePharma, USA.*
Demeclocycline hydrochloride (p. 285·2).
Bacterial infections; intestinal amoebiasis.

Declot *Zydus, India.*
Heparin (p. 1396·3).
Thromboembolic disorders.

Declovir *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Deco *Laborate, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).

Deco Expectorant *Hoe, Malaysia.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders; cough.

Deco Syrup *Hoe, Malaysia.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; cold and influenza symptoms.

Deco-AT *Laborate, India.*
⊗Atropine (p. 1310·2); chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).

Decobel *Ronava, Venez.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Decocon A *Sensomed, Philipp.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Inflammatory eye disorders.

Decocort *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.†*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Fungal and Gram-positive skin infections with inflammation.

Decodeca *Misha, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decoder Micoflu *Almirall, Ital.*
⊗Fluprednidene acetate (p. 1637·3); miconazole (p. 588·3).
Skin disorders with fungal infection.

Decoderm *Hermal, Austria; Reckitt Benckiser, Belg.; Almirall Hermal, Ger.; Merck, Indon.*
⊗Fluprednidene acetate (p. 1637·3).
Skin disorders.

Decoderm 3 *Merck, Indon.*
⊗Fluprednidene (p. 1637·3); neomycin sulfate (p. 330·1); cloxiquine (p. 577·1).
Infected skin disorders.

Decoderm Basiscreme *Almirall Hermal, Ger.*
Emollient.
Skin disorders.

Decoderm bivalent *Almirall, Switz.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Decoderm Comp *Almirall Hermal, Ger.*
⊗Fluprednidene acetate (p. 1637·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Decoderm Compositum *Hermal, Austria; Reckitt Benckiser, Belg.†*
⊗Fluprednidene acetate (p. 1637·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Decoderm tri *Almirall Hermal, Ger.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Decoderm trivalent *Hermal, Austria.†*
⊗Fluprednidene acetate (p. 1637·3); gentamicin sulfate (p. 304·2); cloxiquine (p. 577·1).
Infected skin disorders.

Decoderm Trivalente-N *Galenica, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Decofam Cough *DHA, Hong Kong.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Cough.

DHA, Singapore.
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Decofed
Note: this name may be used for preparations of different composition.
Barre-National, USA†; Major, USA.†
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Vickmans, Hong Kong.†
Linctus: ⊗Codeine (p. 40·2); pseudoephedrine (p. 1676·1); triprolidine (p. 642·3).

Vickmans, Hong Kong.†
Tablets: ⊗Pseudoephedrine (p. 1676·1); triprolidine (p. 642·3).

Decofed-DS *Universal Medikit, India.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Decofed-X *Unijules, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Decofsin *VS, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough; cold symptoms.

Decohistine DH *Morton Grove, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Decol
Note: this name may be used for preparations of different composition.
Alde Medi Impex, India.
Chloramphenicol (p. 257·1).
Bacterial infections.
Utopian, Thai.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough; cold symptoms.
Utopian, Thai.
Tablets: Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.
Idaman, Malaysia.†
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms.
Vickmans, Hong Kong.†
Dequalinium (p. 1749·3).

Decolan *Decomed, Port.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Decolane *Cubit, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decol-C *Intas, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).

De-cold *China Chem & Pharma, Singapore.*
⊗Pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Cold symptoms; allergic rhinitis.

Decold CP *McNeil & Argus, India.*
Chlorphenamine (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Decold Plus *McNeil & Argus, India.*
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Decolfed *Utopian, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Decolgen
Note: this name may be used for preparations of different composition.
Great Eastern, Thai.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; sinusitis; hay fever.
Probus, Indon.
Oral liquid; oral powder: Paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1); chlorphenamine (p. 620·3) or chlorphenamine maleate (p. 620·3).
Cold symptoms; upper respiratory-tract disorders.
Probus, Indon.
Tablets: Paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold symptoms; upper respiratory-tract disorders.
Westmont, Malaysia.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.
United Laboratories, Philipp.†
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Decolgen Cold & Flu *Westmont, Singapore.*
Tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; upper respiratory-tract disorders.

Decolgen Cold & Flu with Vitamin C *Westmont, Singapore.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); vitamin c (p. 2110·3).
Cold and influenza symptoms.

Decolgen Day & Night *Medley, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Decolgen DE *Great Eastern, Thai.†; Westmont, Thai.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; hay fever; sinusitis.

Decolgen Forte *United Laboratories, Philipp.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; rhinitis; sinusitis.

Decolgen No-Drowse *United Laboratories, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms; rhinitis.

Decolgen Non Drowse *Westmont, Singapore.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Decolgen Plus *Great Eastern, Thai.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; hay fever; sinusitis.

Decolgen Prin *Great Eastern, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; hay fever; sinusitis.

Decolgen-P *Sinkhai, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Decolic *KonTest, India.*
Injection: Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.
KonTest, India.
Oral drops; suspension: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Decolic Infant *KonTest, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Decolic-V *KonTest, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Decolite *Intas, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye inflammation.

Decol-N *Intas, India.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1).

Decolone *Merion, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decol-P *Intas, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3); polymyxin B (p. 342·3).

Decolsin *Probus, Indon.*
⊗Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); etafedrine hydrochloride (p. 1665·2); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Decolsin Reformulated *Westmont, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1).
Cough; nasal congestion; headache; fever.

Decomb *Alde Medi Impex, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dec-Ombolin *Om Biotec, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decomed *Elmor, Venez.*
Benzalkonium chloride (p. 1737·1).
Skin cleansing.

Decomic *Klar Sehen, India.*
Boric acid (p. 2459·3); chlorphenamine maleate (p. 620·3); hypromellose (p. 2189·2); phenylephrine hydrochloride (p. 1672·3).

Decomine *East West, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Decomit *Beximco, Singapore.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis; nasal polyps.

Decon
Note: this name may be used for preparations of different composition.
Cadila, India.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.
The Forty-Two, Thai.
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.
Jaapharm, Canad.†
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Decon Lavanda *IP, Ital.*
Levomenol (p. 2544·1); chlorhexidine gluconate (p. 1743·3); lactic acid (p. 2539·1); lysates of lactobacillus (p. 2596·3).
Restoration of vaginal flora.

Decon Nasale *IP, Ital.*
Sodium carboxymethyl beta-glucan (p. 2455·2).
Nasal hygiene.

Decon Ovuli *IP, Ital.*
Wheat (p. 2647·1); phenoxyethanol (p. 1764·3); calendula (p. 2465·2); hamamelis (p. 2523·3).
Vaginal mucosal disorders.

Deconal *Apex, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Deconamine *Kenwood, Hong Kong; Kenwood, USA.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; sinusitis; nasal congestion.

Deconamine CX *Bradley, USA.†*
⊗Guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Deconbol *Almet, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decondine *Sunward, Singapore.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Deconex *Poly, USA.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Deconex DM *Poly, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough; respiratory-tract congestion.

Deconex DMX *Poly, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Decongest *Rougier, Canad.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Decongestant
Note: this name may be used for preparations of different composition.
Boots Healthcare, Irl.
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinus congestion.
Rugby, USA.
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Decongestant Nasal Mist *Confab, Canad.*
⊗Oxymetazoline hydrochloride (p. 1671·3).

Decongestant Nasal Spray
Note: this name may be used for preparations of different composition.
Pharmascience, Canad.; Rougier, Canad.; Supplements Aromatik, Canad.; Confab, Hong Kong.
⊗Xylometazoline hydrochloride (p. 1680·1).

Decongestant Nose Drops *Prodemdis, Canad.*
⊗Xylometazoline hydrochloride (p. 1680·1).

Decongex Plus *Ache, Braz.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Decono *Milano, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Deconomed *Iopharm, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Deconsal I *Cornerstone, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs; nasal congestion.

Deconsal CT *Cornerstone, USA.†*
Phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Décontractyl *Sanofi-Aventis, Fr.*
Ointment: Mephenesin (p. 2025·2); methyl nicotinate (p. 91·3).
Painful muscular disorders.
Sanofi-Aventis, Fr.
Tablets: Mephenesin (p. 2025·2).
Painful muscular disorders.

Decontril *Bioethical, Ital.*
Thiocolchicoside (p. 2026·2).
Spasticity; parkinsonism; neuromuscular pain.

Decordex *Nida, Singapore.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Decorenone *Italfarmaco, Ital.*
Ubidecarenone (p. 2637·1).
Co-enzyme Q_{10} deficiency; metabolic cardiac disorders.

Decorex *Pisa, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Decorfen *Greenpharma, Braz.*
Potassium (p. 1793·1).

Decormin *Ace, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Decortin *Merck Serono, Ger.*
⊗Prednisone (p. 1647·2).
Oral corticosteroid.

Decortin H *Merck Serono, Ger.*
⊗Prednisolone (p. 1645·2).
Oral corticosteroid.

Decort-N *Laborate, India.*
⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3).

Decos *Sriprasit, Thai.†*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough.

Decosan *Ni-The, Gr.*
Dequalinium chloride (p. 1749·3).

Decose *TO-Chemicals, Thai.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Decosil *Collins, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Decostriol *Scherer, China; Mibe, Ger.; Jesalis, Hong Kong; Jesalis, Thai.; Gurel, Turk.*
Calcitriol (p. 2113·1).
Renal osteodystrophy; osteoporosis; hypoparathyroidism; rickets; phosphate excretion disorders; pseudohypoparathyroidism; hyperparathyroidism.

Decosyn *DHA, Singapore.*
Guaifenesin (p. 1666·2).
Cough.

Decotram *Worth, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Decotram-PD *Worth, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).

Decozol *Hoe, Malaysia; Hoe, Singapore.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Decozoom *Syntro, India.*
⊗Nandrolone (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Décramp *IPRAD, Fr.*
Tablets: Magnesium phosphate (p. 1787·3); potassium chloride (p. 1793·2); copper (p. 2057·1); arnica (p. 2447·2).
Skeletal muscle pain.

IPRAD, Fr.
Topical gel: Sweet birch oil (p. 92·1); arnica (p. 2447·2); menthol (p. 2553·2).
Skeletal muscle spasm.

Decrilip *Sanbe, Indon.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Decrina *Intra-Labs, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dectancyl *Sanofi-Aventis, Fr.*
⊗Dexamethasone acetate (p. 1631·1).
Corticosteroid.

Decubal *Actavis, Indon.*
Barrier preparation.
Dry skin; nappy rash; bedsores.

Alpharma, UK.
Emollient.
Dry skin disorders.

Assos, Turk.
Barrier cream.

Deculin *Dexa, Indon.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Decurin *Gray, Arg.†*
Tubocurarine chloride (p. 2040·1).
Competitive neuromuscular blocker.

Decwell *Hanburys, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Decylenes *Rugby, USA.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections; nappy rash; minor skin irritation; hyperhidrosis; bromhidrosis.

Decyline *Corsa, Indon.*
Cream: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Corsa, Indon.
Ointment: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); sodium propionate (p. 593·1); salicylic acid (p. 1719·1).
Fungal skin infections.

Corsa, Indon.
Topical powder: Zinc undecenoate (p. 596·3); calcium propionate (p. 592·3).
Fungal skin infections.

Decyp-P *Alde Medi Impex, India.*
Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Deczone *Daksh, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Deczone-S *Daksh, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Deczone-T *Daksh, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Deczone-TP *Daksh, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Deda *HK Pharm, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety.

Dedile *Ivax, Arg.*
Flutamide (p. 798·2).

Deding *Baiyunshan, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Dediol *Sanofi-Aventis, Ital.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; osteomalacia; rickets; osteoporosis; hypoparathyroidism.

Dedolor *Astellas, Austria.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Dedostryl *Antor, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Dedoxyn *DWD, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Dedralen *Italfarmaco, Ital.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Dedrei *Madaus, Ger.; Rottapharm, Ger.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; osteoporosis.

Dédrogyl *DB, Fr.*
Calcifediol (p. 2113·1).
Hypocalcaemia; rickets; renal osteodystrophy; osteomalacia; vitamin D deficiency.

Dedrogyl *SIT, Belg.; Desma, Ger.; IFET (ΙΦΕΤ), Gr.†; Desma, Port.*
Calcifediol (p. 2113·1).
Renal osteopathy; hypocalcaemia; osteomalacia; hypoparathyroidism; rickets; renal osteodystrophy; vitamin D deficiency.

Dedron *Sanjivani, India.*
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Deeclo *Cadila, India.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Deep Cold *Mentholatum, Canad.*
Menthol (p. 2553·2).

Deep Freeze *Mentholatum, Hung.; Mentholatum, UK.*
Menthol (p. 2553·2); pentane (p. 2201·1).
Musculoskeletal, joint, and soft-tissue disorders.

Deep Freeze Cold Gel *Mentholatum, Irl.; Mentholatum, UK.*
Menthol (p. 2553·2).
Musculoskeletal, joint, and peri-articular disorders.

Deep Heat
Note: this name may be used for preparations of different composition.
Mentholatum, Austral.; Mentholatum, S.Afr.
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Muscular aches and pains.

Mentholatum, Austral.; Mentholatum, Irl.; Mentholatum, Pol.; Mentholatum, Ukr.
Topical spray: Methyl salicylate (p. 92·1); ethyl salicylate (p. 56·3); glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Mentholatum, Irl.; Mentholatum, Rus.
Methyl salicylate (p. 92·1); racementhol (p. 2553·2); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, and soft-tissue pain.

Vianex (Βιανεξ), Gr.; Mentholatum, Ukr.
Eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint and soft-tissue disorders; inflammation.

Deep Heat Maximum Strength *Mentholatum, UK.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue disorders.

Deep Heat Rub *Mentholatum, Hung.; Mentholatum, Israel; Hyde, S.Afr.†; Mentholatum, UK.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders.

Deep Heat Spray *Mentholatum, Hung.; Mentholatum, Israel; Mentholatum, S.Afr.†; Mentholatum, UK.*
Methyl salicylate (p. 92·1); methyl nicotinate (p. 91·3); ethyl salicylate (p. 56·3); glycol salicylate (p. 66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Deep Heating *Mentholatum, Canad.*
Cream; lotion: Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Mentholatum, Canad.
Transdermal patch: Methyl salicylate (p. 92·1).

Deep Relief *Mentholatum, Hung.; Mentholatum, Israel†; Mentholatum, UK.*
Ibuprofen (p. 68·2); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Mentholatum, Rus.; Mentholatum, Ukr.
Ibuprofen (p. 68·2); levomenthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Deepas *Zota, India.*
Diclofenac (p. 48·3); dicycloverine (p. 1834·2).

Deep-Down Rub *SmithKline Beecham, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Deepen-D *Bionet, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Deetipat *Ferrosan, Fin.†*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Defam *Andromaco, Mex.*
Nimesulide (p. 101·3).
Peri-articular and soft-tissue disorders; inflammation; pain.

Defanac *Ranbaxy, UK.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Defantum *Antor, Gr.*
Pravastatin sodium (p. 1473·1).

Défanyl *Eisai, Fr.*
Amoxapine (p. 407·3).
Depression.

Defarol *Adipharm (Αδηφαρμ), Gr.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Defas *Rontag, Arg.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Defatig *Farmasa, Braz.*
Vitamin B substances (p. 2102·3); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Tonic.

Defcin *Cinerea, India.*
Diclofenac sodium (p. 48·3).
Pain.

Defcort *Macleods, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

DeFed *Ferndale, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Defeks *Berk, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract congestion.

Defekton *Mitsubishi Tanabe, Jpn.*
Carpipramine hydrochloride (p. 1044·2) or carpipramine maleate (p. 1044·2).
Schizophrenia; depression.

Defenac *Ranbaxy, UK.*
Diclofenac (p. 48·3).

Defenac-P *Lupin, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Defenorm *KVZ, Ukr.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; irritable bowel syndrome; Crohn's disease; ulcerative colitis; hypercholesterolaemia.

Defense *Future, Canad.*
Echinacea angustifolia (p. 2498·1); allium sativum (p. 2510·3); astragalus membranaceus (p. 2451·1); lentinus edodes; origanum vulgare (p. 2576·3).

Defense UV *Guinot, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Deferon *Dey's, India.*
Capsules: Ferrous fumarate (p. 2060·3); copper sulfate (p. 2057·2); magnesium sulfate (p. 1787·3); zinc (p. 2126·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Dey's, India.
Oral liquid: Ferrous gluconate (p. 2061·2); liver extract (p. 2444·1); vitamin B substances (p. 2102·3); sodium glycerophosphate (p. 2519·2).

Defglu *Neiss, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Deficical B12 *Gross, Braz.*
Calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1); cyanocobalamin (p. 2107·2).
Nutritional supplement.

Defidin *Lupin, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Defidin-A *Lupin, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Défiltran *CSP, Fr.*
⊗Acetazolamide (p. 2001·1).
Soft-tissue injury.

Defin *Liferpal, Mex.*
Dipyrone (p. 53·3).
Pain; fever; inflammation.

Define *React, Arg.*
Pregnancy test (p. 2596·1).

Definity *BMS, Canad.; Lantheus, Chile; Lantheus, Israel; Global, NZ; Lantheus, USA.*
⊗Perflutren (p. 1595·2) in lipid coated microspheres.
Contrast medium for echocardiography and abdominal ultrasound.

Defirin *Ferring, Gr.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; haemophilia; von Willebrand's disease.

Defislez *Sintez, Rus.*
Hypromellose (p. 2189·2).
Eye disorders.

Defixal *Megat, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Defjee *Evershine, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Deflaimmun *Sigma, Braz.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Deflam *Akromed, S.Afr.†*
Oxaprozin (p. 112·3).
Musculoskeletal, joint, and peri-articular disorders.

Deflamat *Astellas, Austria; Actavis, Indon.; Sankyo, Ital.; Tripharma, Turk.*
Diclofenac sodium (p. 48·3).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Andromaco, Chile.
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Fever; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain.

Déflamol *Sofibel, Fr.*
Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Skin irritation; nappy rash.

Deflamon *SPA, Ital.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Deflamox *Sanfer, Mex.*
Naproxen sodium (p. 98·2).
Inflammation; pain.

Deflamox Plus *Hormona, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Deflan *IFET (ΙΦΕΤ), Gr.; Guidotti, Ital.*
⊗Deflazacort (p. 1629·3).
Oral corticosteroid.

Deflanil *Libbs, Braz.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Deflar *Intra-Labs, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Deflaren *Sanval, Braz.*
⊗Dexamethasone (p. 1630·3) or dexamethasone acetate (p. 1631·1).
Corticosteroid.

Deflatop *Astellas, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders.

Deflect *Deb, Canad.†*
SPF 33: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Deflegmin *ICN, Pol.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Deflogen *Uniao Quimica, Braz.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Deflox
Note: this name may be used for preparations of different composition.
Amdipharm, Spain.
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Merck, Mex.
Diclofenac potassium (p. 48·3) or diclofenac resinate (p. 48·3).
Pain; inflammation.

Deflu *Yeni, Turk.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Defluin *Merck Serono, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Defluin Plus *Merck Serono, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Defluina
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Ger.†
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Defluox *ProMed, Cz.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Deflux
Note: this name may be used for preparations of different composition.
Q-Med, USA.
Dextranomer (p. 1699·3); hyaluronic acid (p. 2526·2).
Vesicoureteral reflux.

Defocart *Solitaire, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Defomag *Pharmasant, Thai.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Defomil *Nakornpatana, Thai.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; heartburn; flatulence.

Deforan *Deva, Turk.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Defox *Daksh, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Defradil *Merck, Mex.†*
Cefotaxime (p. 244·1).
Bacterial infections.

Defrozyp *Labormed, Cz.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Defungin *Innoderm, Philipp.†*
Miconazole (p. 588·3).
Fungal skin and nail infections.

Defungo *Siam Bheasach, Thai.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections; trichomoniasis.

Defur *Teva, Pol.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Defza *Dewcare, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Degabina *Rivero, Arg.†*
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

DeGalin *Riemser, Ger.*
Calcium folinate (p. 2066·3).
Folic acid deficiency; prevention of methotrexate toxicity; adjunct to fluorouracil therapy.

Degan *Lek, Cz.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; aid in gastrointestinal examination.

De-Gas *Pfizer, Austral.; Wyeth Consumer, NZ.*
Simeticone (p. 1886·2).
Flatulence.

Degas *RX, Thai.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; gastrointestinal examination.

Degas Extra *Wyeth Consumer, Austral.†*
Simeticone (p. 1886·2); calcium carbonate (p. 1824·3); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Dyspepsia; flatulence.

Degastrol *Deva, Turk.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Degirol *Darya-Varia, Indon.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Deglucos *Suphong, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Degoran *Novartis Consumer, S.Afr.†*
Effervescent tablets: Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); pheniramine maleate (p. 637·2).
Cold and influenza symptoms.

Degoran C *Novartis Consumer, S.Afr.†*
Paracetamol (p. 115·1); vitamin C (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Degoran Cold & Flu *Novartis Consumer, S.Afr.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Degoran Plus *Novartis Consumer, S.Afr.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Degorflan *Degorts, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Degorvit-Plus *Degorts, Mex.†*
Vitamins; minerals.

Degra *Deva, Turk.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Degraler *Bago, Chile.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Degran *Ranbaxy, Thai.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Degranol
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Degrium *Ferron, Indon.*
Flunarizine (p. 629·3).
Migraine; peripheral vascular disorders.

Degurge-D *Tablets, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Dehace *Lannacher, Austria.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

DeHaF *Soho, Indon.*
Psidium guajava; phyllanthus urinaria; carica papaya; curcuma aeruginosa; curcuma domestica.

Dehidrobenzperidol *OTL, Port.†*
Droperidol (p. 1072·1).
Neuroleptanalgesia.

Dehista *Berlico Mulia, Indon.*
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

Dehistine *Cypress, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Dehydral *Valeo, Canad.*
Methenamine (p. 322·3).
Hyperhidrosis.

dehydro sanol tri *Sanol, Ger.*
⊗Bemetizide (p. 1314·2); triamterene (p. 1518·3).
Leg pain associated with venous insufficiency.

Dehydrobenzperidol *ProStrakan, Belg.; ProStrakan, Denm.; ProStrakan, Fin; IFET (ΙΦΕΤ), Gr.; Janssen-Cilag, Gr.; ProStrakan, Neth.*
Droperidol (p. 1072·1).
Sedation; premedication; induction of anaesthesia; nausea and vomiting; agitation; neuroleptanalgesia.

Dehydrosol *San Marino, Philipp.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Diarrhoea; oral rehydration.

Deilém *Nucitec, Mex.†*
Preparation for enteral nutrition.

Deixim *Biomedica, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Dejavu *Eurofarma, Braz.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Dek *Materfarma, Port.*
Benzocaine (p. 1980·2); dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

DEKA
Note: this name may be used for preparations of different composition.
Dayton, USA.
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dexbrompheniramine maleate (p. 618·1).

Dekamin *Monico, Ital.*
Amino acids.
Parenteral nutrition.

Dekar 2 *Pentamedical, Ital.†*
Benzyl benzoate (p. 2149·1); quassia (p. 2601·1).

Dekatin *Ativus, Braz.*
Crataegus (p. 2488·1).
Heart failure.

Dekesi *Wuhan Wujing, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dekinet *Rafa, Israel.*
Biperiden hydrochloride (p. 895·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Dekka
Note: this name may be used for preparations of different composition.
Pond's, Thai.
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection of skin, wounds, and instruments.

Dekkalon *Sinopharm, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection.

Deklarit *Deva, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Dekoferin *Berko, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Dekoferin-Ex *Berko, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

Dekort *Deva, Turk.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dekot *Auspi, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Dekristol *Mibe, Ger.*
Colecalciferol (p. 2113·1).
Rickets; vitamin D deficiency; osteoporosis.

Deksa *Intas, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Deksalon *Sanli, Turk.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Deksamet *Tems, Turk.*
⊗Dexamethasone (p. 1630·3) or dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Deksan *Deva, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Del Aqua *Del-Ray, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Delabarre *Sofibel, Fr.*
Tamarind (p. 1892·2).
Teething pain.

Delacard *Chiesi, Gr.*
Delapril hydrochloride (p. 1350·2).
Hypertension.

Delacet *Herbapol Krakow, Pol.*
Delphinium consolida.
Pediculosis.

Delacor *Charoon Bhesaj, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Deladex *Novagen, S.Afr.*
Didanosine (p. 972·3).

Delage *MMC, India.*
Vitamins; DL-methionine (p. 1558·2); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Delagil
Note: this name may be used for preparations of different composition.
ICN, Cz.; Valeant, Hung.; Alkaloid, Ukr.
Chloroquine phosphate (p. 650·1).
Malaria; rheumatoid arthritis; lupus erythematosus; amoebiasis; photodermatoses.

Dermapharm, Ger.
Phenol-formaldehyde-urea polycondensate sodium sulfate.
Skin disorders.

Meda, Rus.
Chloroquine (p. 650·1).
Malaria; amoebiasis; lupus erythematosus; rheumatoid arthritis; scleroderma; photodermatoses.

Delaien *Southwest Synthetic, China.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension.

Delak *Raffo, Arg.*
Oxybutynin (p. 2361·2).
Urinary-tract disorders.

Delaket *Chiesi, Ital.*
Delapril (p. 1350·2).
Hypertension; heart failure; diabetic nephropathy.

Chiesi, Turk.
Delapril hydrochloride (p. 1350·2).

Delamin *Hindustan Antibiotic, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Delamin LB *Hindustan Antibiotic, India.*
Amoxicillin (p. 216·2); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Delanin *Charoon Bhesaj, Thai.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Delapride *Torrex, Austria†; Chiesi, Turk.*
⊗Delapril hydrochloride (p. 1350·2); indapamide (p. 1409·2).
Hypertension.

Promedica, Ital.
⊗Delapril (p. 1350·2); indapamide (p. 1409·2).
Hypertension.

Delatar *Lek, Cz.†; Lek, Pol.†*
Coal tar (p. 1723·2).
Psoriasis; eczema; lichen planus; keratinisation disorders.

Delatestryl *Theramed, Canad.; Endo, USA.*
⊗Testosterone enantate (p. 2305·1).
Male hypogonadism; delayed puberty (males); breast cancer; androgen therapy.

Delaviral *Demo, Gr.*
Zipeprol hydrochloride (p. 1680·3).

Delaxin *Scoshia, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Delaxin-M *Scoshia, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

menthol (p. 2553·2); methyl salicylate (p. 92·1).

Delazinc *Mericon, USA.*
Zinc oxide (p. 1729·1).
Skin disorders.

Delbitol *Citadel, India.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Delbysen *Renovati, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Delcid *Casca, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1).

Delcon *Citadel, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Delcon Plus *Citadel, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Delcoprep *AlleMan, Ger.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Delcorlon *Synco, Hong Kong†; Synco, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Delecit *MDM, Ital.*
Choline alfoscerate (p. 389·2).
Mental function impairment.

Delegol *Bayer, Ital.†*
Partially chlorinated benzylphenol.
Surface disinfection.

Delepsine *Orion, Denm.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder; migraine.

Deleptin *Stada, Austria.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; diabetes insipidus; diabetic neuropathy; epilepsy; mania; neuralgias.

Delestrogen *JHP, USA.*
Estradiol valerate (p. 2271·2).
Menopausal vasomotor symptoms; vulval and vaginal atrophy; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; prostatic cancer.

Delet *T Man, Thai.†*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Deletus *Piramal, India.*
Dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3); phenylephrine hydrochloride (p. 1672·3).
Formerly contained dextromethorphan hydrobromide, triprolidine hydrochloride, and phenylpropanolamine hydrochloride.
Cough; sinusitis.

Deletus D *Piramal, India.*
Dextromethorphan hydrobromide (p. 1660·1); triprolidine hydrochloride (p. 642·3); phenylephrine hydrochloride (p. 1672·3).
Formerly contained dextromethorphan hydrobromide, triprolidine hydrochloride, phenylpropanolamine hydrochloride, and menthol.
Cough; pharyngitis; laryngitis.

Deletus P *Piramal, India.*
Bromhexine hydrochloride (p. 1656·3); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Formerly contained bromhexine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin.
Cough associated with viscous mucus.

Deletus-BX *Piramal, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Delewal *Aamorb, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Delfen *Johnson & Johnson, Canad.†; Ethnor, India†; Janssen-Cilag, S.Afr.†; Advanced Care, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Delfina Plus *Positif, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Delflex *Fresenius Medical, Canad.*
Glucose (p. 2068·3); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2) (p. 1778·2).
Range of solutions for peritoneal dialysis.

Delfos *AGIPS, Ital.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Delfoza *Delegant, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Delgacin *Medica, Arg.*
Equisetum (p. 2500·1); kola (p. 2648·2); cynodon dactylon; peppermint leaf (p. 1877·1); senna (p. 1885·1); chamomile (p. 2474·1).
Constipation; diuretic.

Delgadol *K2 Health & Wellness, Chile.*
Phaseolus vulgaris (p. 2587·3).
Obesity.

Delgadol Fibra *K2 Health & Wellness, Chile.*
Phaseolus vulgaris (p. 2587·3); soluble fibre (carmellose & glucomannan) (p. 2175·1) (p. 2515·2).
Obesity.

Delgadol Slim *K2 Health & Wellness, Chile.*
Conjugated linoleic acid (p. 2509·2); curcuma longa.
Slimming aid.

Delgadol Vita *K2 Health & Wellness, Chile.*
Phaseolus vulgaris (p. 2587·3); vitamins.
Obesity.

Delical *Lactalis, Fr.*
A range of foods for special diets.
Diarrhoea; lactose intolerance; nutritional supplement.

Delicate Skin Pasta *RCA, Ital.*
Zinc oxide (p. 1729·1).
Skin irritation.

Délidose *CSP, Fr.*
Estradiol (p. 2271·1).
Menopausal disorders.

delimmun *Kora, Ger.*
Inosine pranobex (p. 988·3).
Viral infections.

Delimon *Pharmathen, Gr.*
Diclofenac sodium (p. 48·3).
Prevention of miosis in ophthalmic surgery; musculoskeletal, joint, and peri-articular disorders; gout; pain.

Delin *Atlantic, China; Atlantic, Hong Kong; Atlantic, Malaysia.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders; gingivitis; sore throat; pharyngitis.

Ind-Swift, India.
Injection: Etofylline (p. 1208·2); theophylline (p. 1229·3).

Ind-Swift, India.
Tablets: Theophylline (p. 1229·3).
Bronchospasm.

Delinar *Teva Tuteur, Arg.†*
Mesna (p. 1557·2).

Delipid
Note: this name may be used for preparations of different composition.
Egis, Hung.
Rosuvastatin zinc.
Hypercholesterolaemia.

T Man, Thai.
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Delipoderm *Reig Jofre, Spain.†*
Promestriene (p. 2302·3).
Seborrhoea; acne.

Delipost *Rafarm, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Delipramil *Bruno, Ital.*
Metoclopramide hydrochloride (p. 1862·2).
Gastric hyperacidity; gastrointestinal motility disorders.

Déliproct *Bayer Sante, Fr.*
⊗Prednisolone caproate (p. 1645·3); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Delirek *Shreya, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Delirex *Sanova, Austria.†*
Caroverine hydrochloride (p. 2471·2).
Alcohol and drug withdrawal syndromes.

Delisan *Baliarda, Arg.*
⊗Fluorometholone (p. 1637·2); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Infected skin disorders; burns; ulcers; wounds.

Delisprin *Aristo, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Delitab-HCT *Tiefenbacher, Neth.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Delitan *Lafi, Chile.*
⊗Esterified oestrogens (p. 2270·3); methyltestosterone (p. 2291·3).
Menopausal disorders.

Delitrig *Genericon, Denm.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Delitroxin *Pharmathen, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Delius *Pantafarm, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Deliver *Mead Johnson, Austral.†*
Preparation for enteral nutrition.
Fluid or volume restriction; hypermetabolic states.

Delix
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Ger.; Aventis, Turk.
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; nephropathy; cardiovascular risk reduction.

Delix Plus *Sanofi-Aventis, Ger.; Aventis, Turk.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dellamethasone *Darya-Varia, Indon.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dellasidrex *Darya-Varia, Indon.†*
⊗Reserpine (p. 1485·3); dihydralazine (p. 1358·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dellegra *Sanofi-Aventis, Jpn.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Dellova *Clement, Fr.†*
Bladderwrack (p. 2612·1); java tea (p. 2536·3).
Obesity.

Delmuno *Sanofi-Aventis, Ger.; Aventis, Pol.*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Del-Mycin *Del-Ray, USA.*
Erythromycin (p. 291·2).

Delnil *Sandoz, Denm.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Delnim MD *BMW, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Delnim-P *BMW, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Delnim-SP *BMW, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Delock-MR *Arvincare, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Delok *Piramal, India.*
Duloxetine hydrochloride (p. 415·1).
Depression.

Delonal *MSD, Ger.†*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Delor *Pharma International, Ukr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Delorat *Lazar, Arg.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Delorta *Piramal, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Delos *Dallas, Arg.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rochester, USA.
Benzoyl peroxide (p. 1696·1).
Acne.

Delos Otic *Dallas, Arg.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Ear disorders.

Delotid *DWD, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Delpeg *Vanden Bogaerde, Belg.†*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Delph Sun Lotion *Fenton, UK.*
SPF 25; SPF 30; SPF 50: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1).
Sunscreen.

Fenton, UK.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Delphi *Erfa, Belg.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Delphicol *Wyeth, India.†*
Tricholine citrate (p. 2055·2); acetyl dimethionine; inositol (p. 2533·2); vitamin B_{12} (p. 2107·2).
Liver disorders.

Delphicort *Riemser, Ger.*
⊗Triamcinolone (p. 1648·3), triamcinolone acetonide (p. 1649·1), or triamcinolone diacetate (p. 1649·1).
Corticosteroid.

Delpral *Sanofi-Aventis, Austria.*
Tiapride hydrochloride (p. 1111·2).
Movement disorders; alcohol withdrawal syndrome.

Delrosa *Inovail, Philipp.*
Rose fruit (p. 2607·1); ascorbic acid (p. 2110·3).
Vitamin C supplement.

Invida, Hong Kong.
Vitamin C (p. 2110·3).
Vitamin C supplement.

Delsal *Meyer, Venez.*
Dipyrone (p. 53·3).
Fever; pain.

Delsone *Psychotropics, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Delsoralen *Darya-Varia, Indon.*
Methoxsalen (p. 1711·3).
Vitiligo; psoriasis.

Delsym *Bayer, Irl.†; Roche Consumer, Irl.†; Adams, USA.*
Dextromethorphan polistirex (p. 1660·1).
Cough.

Novartis Consumer, Canad.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Delsym Night Time Cough & Cold *Reckitt Benckiser, USA.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).

Delta 80 *IDI, Ital.*
Benzoyl peroxide (p. 1696·1); cetylpyridinium chloride (p. 1743·1).
Skin disinfection; acne.

Delta Charcoal *Sriprasit, Thai.*
Charcoal (p. 1537·3); magnesium hydroxide (p. 1857·2); belladonna (p. 2453·3); peppermint oil (p. 1877·1).
Flatulence; diarrhoea; gastrointestinal disturbances; poisoning.

Delta Corti *Sophia, Mex.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Inflammatory eye disorders.

Delta 80 Plus *IDI, Ital.*
Benzoyl peroxide (p. 1696·1); cetylpyridinium chloride (p. 1743·1).
Skin disinfection; acne.

Delta T *APT, Hong Kong.†*
Clindamycin phosphate (p. 269·3).
Acne.

Delta Tomanil B12 *Nycomed, Arg.*
⊗Diclofenac sodium (p. 48·3); prednisolone (p. 1645·2); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Musculoskeletal and joint disorders; pain.

Deltacarbon *Sriprasit, Thai.*
Activated charcoal (p. 1537·3).
Flatulence; dyspepsia; diarrhoea; poisoning.

Deltacid *Abbott, Braz.*
Deltamethrin (p. 2152·1).
Scabies; pediculosis.

Deltacid Plus *Solvay, Braz.*
Deltamethrin (p. 2152·1); piperonyl butoxide (p. 2160·2).
Pediculosis; scabies.

Deltacortene *Bruno, Ital.*
⊗Prednisone (p. 1647·2).
Oral corticosteroid.

Deltacortenesol *Bruno, Ital.*
⊗Prednisolone sodium succinate (p. 1646·1).
Corticosteroid.

Deltacortril *Pfizer, Gr.; Pfizer, India; Phoenix, Irl.; Pfizer, Turk.; Alliance, UK.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Delta-D *Freeda, USA.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; dietary supplement.

Deltadex *IFET (ΙΦΕΤ), Gr.*
⊗Dextran 40 (p. 1138·1).

Delta-Diona *Reuffer, Mex.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Deltaflan *Delta, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Deltaflogin *Delta, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Delta-Hadensa *Merz, Austria.*
⊗Prednisolone metasulfobenzoate sodium (p. 1645·3); chlorocarvacrol (p. 1747·3); ichthammol (p. 1705·3); menthol (p. 2553·2); with or without chamomile oil (p. 2474·1).
Anorectal disorders.

Deltajonin *AlleMan, Ger.*
Electrolytes (p. 1775·1); with or without carbohydrates.
Fluid and electrolyte disorders.

Delta-K *Ranbaxy, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Deltalab *Multilab, Braz.*
Deltamethrin (p. 2152·1).
Pediculosis; scabies.

Deltalaf *Lanpharm, Arg.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Deltalax *Delta, Braz.*
Bisacodyl (p. 1821·1).
Constipation.

Deltalipid *AlleMan, Ger.†*
Soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Deltamannit *AlleMan, Ger.*
⊗Mannitol (p. 1427·3).
Renal failure; oedema; forced diuresis.

Deltamid *Volta, Chile; Sophia, Mex.*
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Eye disorders; infected eye disorders.

Deltamidrina *Tubilux, Ital.*
⊗Prednisolone acetate (p. 1645·2); atropine sulfate (p. 1310·2); phenylephrine hydrochloride (p. 1672·3).
Inflammatory eye disorders.

Deltamin *AlleMan, Ger.*
Amino acids; with or without electrolytes (p. 1775·1) and xylitol.
Parenteral nutrition.

Deltapil *Belfar, Braz.*
Deltamethrin (p. 2152·1).

Deltar *Elea, Arg.*
⊗Prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Deltaran *Strathmann, Ger.*
Dexibuprofen (p. 43·1).
Musculoskeletal and joint disorders; pain.

Deltaren *Delta, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Deltarhinol *Aventis, Turk.†*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Deltarhinol-Mono *Melisana, Belg.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Deltarinolo *Sanofi-Aventis, Ital.*
⊗Ephedrine hydrochloride (p. 1663·2); naphazoline nitrate (p. 1669·3).
Nasal congestion.

Deltasolde *Helm, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Deltasolone *Sunward, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Deltasone *Upjohn, USA.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Deltasoralen *Delta, Irl.†*
Methoxsalen (p. 1711·3).
Psoriasis; leucoderma; vitiligo; mycosis fungoides.

Deltasoro *Delta, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Deltastab *Amdipharm, UK.*
⊗Prednisolone acetate (p. 1645·2).
Corticosteroid.

Deltavac *Trimen, USA.*
Sulfanilamide (p. 368·1); aminoacridine hydrochloride (p. 1732·3); allantoin (p. 1693·1).
Vaginal infections.

Deltavagin *Finderm, Ital.*
⊗Betamethasone (p. 1623·2); tyrothricin (p. 384·1); norvaline.
Vaginitis.

Deltavit *Delta, Braz.*
Amino acids; vitamins; minerals.

Deltazen *Sanofi-Aventis, Fr.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension.

Deltazime *CT, Ital.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Deltazine *Septodont, Austral.; Zizine, Fr.*
Articaine hydrochloride (p. 1980·1). Adrenaline acid tartrate (p. 1292·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Deltisan *Valma, Chile.*
Zinc (p. 2126·1); cod-liver oil (p. 2056·3).
Skin disorders.

Deltison *Recip, Swed.*
⊗Prednisone (p. 1647·2).
Magnesium trisilicate (p. 1858·1) and calcium hydrogen phosphate (p. 1783·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Corticosteroid.

Deltisona B *Sanofi-Aventis, Arg.*
⊗Meprednisone (p. 1642·2) or meprednisone hemisuccinate (p. 1642·2).
Corticosteroid.

Delto-cyl Ho-Len-Complex *Liebermann, Ger.*
Bellis per. (p. 2454·2); ferrum met. (p. 2073·1); phosphorus (p. 2589·2); sanguinaria (p. 2610·1).
Homoeopathic preparation.

Deltoram-GP *Continentales, Mex.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Nasal congestion; rhinitis; sinusitis.

Deltron
Note: this name may be used for preparations of different composition.
Exakta, Mex.
⊗Prednisolone (p. 1645·2); chlorphenamine (p. 620·3).
Eye disorders.
Novagen, India.
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Deltrox *Dupomar, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Delufen *Bittner, Austria; Bittner, Rus.; Bittner, Ukr.*
Sinapis nigra (p. 2566·1); euphorbium; pulsatilla (p. 2600·2); luffa (p. 2545·3); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Delursan *Aptalis, Fr.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; liver and biliary disorders.

Delvit *P & B, India.*
Vitamins; lysine hydrochloride (p. 2079·3).

Delyte *T-Boma, Hong Kong.†*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2).

Delzicol *Warner Chilcott, USA.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Dem *Orchid, India.*
Zolpidem (p. 1116·2).
Insomnia.

Dema *T Man, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Demac *Osotspa, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Demacort *Andromaco, Arg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Demadex *Roche, USA.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Demalgon *Extractum, Hung.*
Aminophenazone (p. 21·1); carbromal (p. 1044·1).
Fever; pain.

Demalgonil *Zentiva, Hung.†*
Allobarbital (p. 1035·2); aminophenazone (p. 21·1); urethane.
Fever; pain.

Demalit
Note: this name may be used for preparations of different composition.
Baldacci, Ital.
Soya (p. 2092·3); dioscorea composita.
Menopausal disorders.

Demator *RPG, India.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Dematrac *Dem, Turk.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Demax *Abdi, Turk.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Demazin *Schering-Plough, Austral.*
Delayed-release tablets: ⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion.
Schering-Plough, Austral.†; Schering-Plough, NZ; Schering-Plough, S.Afr.
Syrup: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion.

Demazin Cold & Flu *Schering-Plough, Austral.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Demazin Cold Relief *Schering-Plough, Austral.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory tract congestion.

Demazin Cough & Cold
Note: this name may be used for preparations of different composition.
Schering-Plough, Austral.†
⊗Pseudoephedrine hydrochloride (p. 1676·1); pholcodine (p. 1675·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Demazin Cough, Cold & Flu *Schering-Plough, Austral.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold and influenza symptoms.

Demazin Day & Night *Schering-Plough, Austral.*
⊗Day tablets, paracetamol (p. 115·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Demazin Day/Night Relief *Schering-Plough, Austral.†*
⊗Day tablets, pseudoephedrine sulfate (p. 1676·1); night tablets, dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion.

Demazin NS *Schering-Plough, S.Afr.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic disorders with nasal congestion; rhinitis.

Demazin PE Cold & Flu Relief *Schering-Plough, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Demazin PE Day & Night Cold & Flu Relief *Schering-Plough, Austral.*
Day tablets, paracetamol (p. 115·1); codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3); night tablets, paracetamol; phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Demazin Saline *Schering-Plough, Austral.*
Sea water (p. 2612·1).
Nasal congestion.

Demazole *Adley, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Deme *Duopharma, Philipp.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Demedrox *Uniao Quimica, Braz.*
Medroxyprogesterone (p. 2288·1).

Demelan
Note: this name may be used for preparations of different composition.
Glenmark, Braz.
Glycolic acid (p. 1704·3).
Glenmark, India.
Arbutin (p. 1694·3); kojic acid (p. 1710·2); glycolic acid (p. 1704·3).

Dement *Ali, Turk.*
Donepezil hydrochloride (p. 390·2).

Dementis *Elpen (Ελπεν), Gr.*
Donepezil hydrochloride (p. 390·2).

Demeprazol *Deva, Turk.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Demergin *Demo, Gr.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Demerol *Sanofi-Aventis, Canad.; Hospira, Philipp.; Sanofi Winthrop, USA.*
⊗Pethidine hydrochloride (p. 121·3).
Pain; premedication; adjunct in anaesthesia.

Demerung *Biotecnoquimica, Venez.*
Fucus (p. 2612·1); greater celandine (p. 2522·2); coffea arabica (p. 2648·2); equisetum (p. 2500·1).
Slimming aid.

Demetil *Farmila, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye congestion.

Demetofrin *Biomedica, Gr.*
Ketotifen fumarate (p. 631·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Demetonevrin *Biomedica, Gr.*
Prazepam (p. 1098·2).

Demetovix *Chemica, Gr.*
Zipeprol hydrochloride (p. 1680·3).

Demetrin *Pfizer, Austria; Pfizer, Ger.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Switz.*
Prazepam (p. 1098·2).
Anxiety; skeletal muscle spasm; sleep disorders; nervous disorders.

Demex *Berlin-Chemie, Ger.*
Propyphenazone (p. 127·3).
Pain; fever.

Demi Canderel *Ali, Turk.*
Aspartame (p. 2169·2).
Sugar substitute.

Demiderm *Schering-Plough, Venez.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Demine *Armour, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Demi-Regroton *Rhone-Poulenc Rorer, USA.*
⊗Chlortalidone (p. 1335·2); reserpine (p. 1485·3).
Hypertension.

Demisone *Cadila, India.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Demizolam *Dem, Turk.*
Midazolam (p. 1085·1).
Premedication; sedative.

Demo *Nordic, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Demo D *Osmed, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Demo Elixir pectoral N *Vifor, Switz.†*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2); belladonna (p. 2453·3); drosera (p. 2497·2); ivy (p. 2536·2); ipecacuanha (p. 1667·2).
Cough.

Demobal *Silanes, Mex.*
Moclobemide (p. 437·2).
Depression.

Demo-Cineol *Sandoz, Canad.†*
Cineole (p. 2479·1); guaiacol (p. 1666·1); camphor (p. 2466·2).
Cough.

Democyl *Vifor, Neth.*
Paracetamol (p. 115·1).
Fever; pain.

Demofenac *Demo, Israel.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.

Demogripal C *Vifor, Switz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Demogyl *Demo, Gr.*
⊗Fentanyl (p. 60·1).
Pain.

Demoksil *Deva, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Demol *Nitin, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Demolaxin *Vifor, Switz.†*
Bisacodyl (p. 1821·1).
Constipation.

DemoLibral *Vifor, Switz.†*
Acetylcysteine (p. 1652·2).
Cough.

Demolox *Wyeth, India.*
Amoxapine (p. 407·3).
Depression; mixed anxiety-depressive states.

Demo-MR *Nordic, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Demonatur Capsules contre les refroidissements *Vifor, Switz.*
Brown capsules, thyme oil (p. 2630·3); origanum oil (p. 2576·3); savory oil (p. 2625·1); green capsules, echinacea purpurea (p. 2498·1).
Influenza symptoms.

Demonatur Dragées pour les reins et la vessie *Vifor, Switz.†*
Bearberry (p. 2453·2); solidago virgaurea (p. 2620·1); ononis (p. 2575·3); echinacea (p. 2498·1); Java tea (p. 2536·3).
Urinary-tract disorders.

Demonatur Ginkgo *Vifor, Switz.†*
Ginkgo biloba (p. 2512·3).
Cerebrovascular disease.

Demo-P *Nordic, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

DemoPectol *Vifor, Switz.*
Oral drops: Thyme (p. 2630·2); ivy (p. 2536·2); liquorice (p. 1853·2).
Cough.
Vifor, Switz.
Syrup: Thyme (p. 2630·2); cowslip (p. 2596·2); ivy (p. 2536·2).
Cough.
Vifor, Switz.
Pastilles: Drosera (p. 2497·2); ivy (p. 2536·2); ipecacuanha (p. 1667·2); plantain (p. 2592·3); tolu balsam (p. 1679·2); anise oil (p. 2444·3); orange peel (p. 2575·3); eucalyptus oil (p. 2501·2); mint oil (p. 2560·1); menthol (p. 2553·2).
Cough.

DemoPectol Junior *Vifor, Switz.*
Ivy (p. 2536·2).
Cough.

Demoquine *Demo, Gr.*
Chloroquine sulfate (p. 650·2).

Demoren *Demo, Gr.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Demo-S *Nordic, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Demoson *Mylan, Fin.; Mylan, Swed.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Demo-SP *Nordic, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Demostan
Note: this name may be used for preparations of different composition.
Demo, Gr.
Mefenamic acid (p. 85·3).

Demotest *Pierre Fabre, Spain.†*
⊗Budesonide (p. 1625·1).
Skin disorders.

Demotine *Demo, Gr.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

DemoTussil *Vifor, Switz.*
Noscapine (p. 1670·3); drosera (p. 2497·2); liquorice (p. 1853·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1).
Cough; sinusitis; bronchitis; laryngitis.

DemoTussol *Vifor, Switz.*
Butamirate citrate (p. 1657·3).
Cough.

Demoval *Demo, Gr.*
Flurbiprofen sodium (p. 65·3).

Demovarin *Vifor, Switz.*
Heparin sodium (p. 1396·3).
Superficial vascular disorders.

Demoven N *Vifor, Switz.*
Troxerutin (p. 2505·3); aesculus (p. 2431·2).
Venous insufficiency; soft-tissue disorders.

Demovit *Vifor, Switz.†*
Vitamins; minerals.
Dietary supplement.

Demovit C *Vifor, Switz.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Demoxate *Demo, Gr.*
Flumazenil (p. 1551·3).
Benzodiazepine overdosage.

Demoxin-CB *Alde Medi Impex, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Demozar *Demo, Gr.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Dempol *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Demser *Aton, USA.*
Metirosine (p. 1433·3).
Phaeochromocytoma.

Demsil *Vocate, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Demulen *Pfizer, Canad.*
Etynodiol diacetate (p. 2277·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Demusin *Nupel, Spain.†*
Albumin tannate (p. 1815·1); amylase (p. 2442·1); ethylmorphine hydrochloride (p. 56·3).
Diarrhoea.

Den 141 *Herbasante, Canad.†*
Belladonna (p. 2453·3); coffee (p. 2648·2); ferrum phosphoricum (p. 2077·1); german chamomile (p. 2474·1); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Denacen *Marjan, Braz.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Denaclof *Novartis, Gr.*
Diclofenac sodium (p. 48·3).
Prevention of miosis in ophthalmic surgery.

Denafed *Candor, India.*
Vitamin B substances (p. 2102·3); silymarin (p. 1561·2).

Denamol *TO-Chemicals, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Dena-N *Zota, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Denapranil *CCM, Malaysia.*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; panic disorder; nocturnal enuresis; narcoleptic syndrome.

Denapril *Medinfar, Port.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Denar *Chemo-Drugs, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Denason *Greenpharma, Braz.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Denavir *Novartis Consumer, Canad.; Prestium, USA.*
Penciclovir (p. 1008·2).
Herpes labialis.

Denaxpren *Coll, Spain.†*
Naproxen (p. 98·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Denazox *Remedica, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Dencare *Vensat, India.*
⊗Potassium nitrate (p. 1766·2).

Dencerin *BMW, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Denclor *Ultramark, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).

Dencol *Berko, Turk.*
Choline salicylate (p. 39·2).

Dencold *BMW, India.*
Suspension: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
BMW, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Dencorub *Ponce, Venez.*
Topical gel: Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.
Ponce, Venez.
Topical spray: Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Dencorub Anti-Inflammatory *Church & Dwight, Austral.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, peri-articular and soft-tissue disorders.

Dencorub Arthritis *Church & Dwight, Austral.*
Trolamine salicylate (p. 141·2).
Musculoskeletal and joint pain.

Dencorub Arthritis Ice *Church & Dwight, Austral.*
Menthol (p. 2553·2).
Musculoskeletal pain.

Dencorub Heat Gel *Church & Dwight, Austral.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Dencorub Ice *Ponce, Venez.*
Menthol (p. 2553·2).
Musculoskeletal and joint pain.

Dencorub Pain Relieving Cream *Church & Dwight, Austral.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1).
Musculoskeletal pain.

Dencorub Unción *Ponce, Venez.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Dencure *Elfin, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Dendracin Neurodendtraxcin *Physicians Science & Nature, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Formerly contained benzocaine, menthol, and methyl salicylate.

Denebol *Mili, Ukr.*
Rofecoxib (p. 128·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Denebol Gel *Mili, Ukr.*
Rofecoxib (p. 128·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); phenoxyethanol (p. 1764·3).
Musculoskeletal, joint, and soft-tissue disorders.

Denecort *Cipla, Philipp.*
⊗Budesonide (p. 1625·1).
Asthma.

Denerel *Medochemie, Malaysia; Medochemie, Singapore.*
Ketotifen fumarate (p. 631·3).
Allergic bronchitis; allergic rhinitis; allergic skin disorders; asthma; hypersensitivity reactions.

Denerval *Jaba, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Denex *Medochemie, Malaysia; Medochemie, Singapore.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension.

Denex-P *Excare, India.*
⊗Potassium nitrate (p. 1766·2).

Denex-PF *Excare, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3) or sodium fluoride (p. 2089·2).

Denex-S *Excare, India.*
Strontium chloride (p. 2623·1).

Denfast *BMW, India.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Denfos *Reddy, India.*
Alendronate sodium (p. 1171·3).
Paget's disease of bone; osteoporosis.

Deniban *Sanofi-Aventis, Cz.; Sanofi-Aventis, Ital.*
Amisulpride (p. 1036·3).
Depression.

Denilyte *Denis, India.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).

Denim
Note: this name may be used for preparations of different composition.
Hua, Thai.
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; radiation sickness.

Maneesh, India.
Nimesulide (p. 101·3) or nimesulide betadex (p. 101·3).
Osteoarthritis; pain.

Denim MD *Blossoms, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Denim P *Maneesh, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Denim Plus *Maneesh, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Denkan *CCM, Malaysia.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Dennov *Royal, Chile.*
Soya isoflavones (p. 2620·3); lycopene (Lycomax) (p. 2546·2); ascorbic acid (p. 2110·3).
Skin disorders.

Denof *Bennet, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

De-Nol *Zhong Hao, China; Alapis, Gr.; Gerolymatos, Gr.; Gerolymatos, Hong Kong; Astellas, Ital.; Astellas, Neth.; CSL, NZ; Astellas, Rus.; Astellas, S.Afr.; Brocades, Singapore; Gerolymatos, Thai.; Eczacibasi, Turk.; Astellas, Ukr.*
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer; gastritis; dyspepsia; irritable bowel syndrome.

Denol *Elder, India.*
Tripotassium dicitratobismuthate (p. 1822·2).

De-Noltab *Astellas, UK.*
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer.

Denomix *Combiphar, Indon.*
⊗Desoximetasone (p. 1630·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Denopot *Sanify, India.*
⊗Potassium nitrate (p. 1766·2).

Denorex *Aspen, S.Afr.*
Coal tar (p. 1723·2).
Dandruff; psoriasis; seborrhoeic dermatitis.

Wyeth, Irl.†; Pfizer, Neth.
Coal tar (p. 1723·2); menthol (p. 2553·2).
Psoriasis; seborrhoeic dermatitis; dandruff.

Denorex Dual Force *Ultimark, USA.*
Shampoo, pyrithione zinc (p. 1718·1); shampoo, salicylic acid (p. 1719·1).
Seborrhoeic scalp disorders.

Denorex Everyday *Ultimark, Canad.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis.

Denorex Medicated *Ultimark, Canad.*
Coal tar (p. 1723·2); menthol (p. 2553·2).
Dandruff; pruritus; psoriasis; seborrhoeic dermatitis.

Denoseal *Fourrts, India.*
⊗Potassium nitrate (p. 1766·2).

Denoseal-F *Fourrts, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Denosol
Note: this name may be used for preparations of different composition.
Melisana, Switz.
Camphor (p. 2466·2); cineole (p. 2479·1); thymol (p. 1772·2); menthol (p. 2553·2); pumilio pine oil (p. 2591·1); sage oil (p. 2609·1).
Cold symptoms.

Denovir *Novartis Consumer, Port.†*
Penciclovir (p. 1008·2).

Denpax *Alphapharm, Austral.*
⊗Fentanyl (p. 60·1).
Pain.

Denpot-KF *Sanify, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Denpru *Fada, Arg.*
Protamine (p. 1572·1).
Heparin overdose.

Denquel *Procter & Gamble, USA.*
⊗Potassium nitrate (p. 1766·2).
Sensitive teeth.

Densafe *Elfin, India.*
⊗Potassium nitrate (p. 1766·2).

Densera *BMW, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Densera-D *BMW, India.*
⊗Diclofenac (p. 48·3); magnesium trisilicate (p. 1858·1); serrapeptase (p. 2613·3).

Densera-N *BMW, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Densica Alpha *Cosme, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Densical *Zambon, Fr.; Italfarmaco, Spain.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Densical D *Vitoria, Port.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiencies; osteoporosis.

Densical vitamine D_3 *Zambon, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiencies; osteoporosis.

Densidron *Mepha, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Densiron 68 *Fluoron, Ger.*
⊗Dimeticone (p. 2209·3); perfluorohexyloctane (p. 2586·3).
Ophthalmic tamponade.

Densitium *Farmoquimica, Braz.*
Hyaluronic acid (p. 2526·2).

Density *Future, Canad.*
Vitamins; minerals.

Denson *Siam Bheasach, Thai.†*
⊗Prednisolone (p. 1645·2); nitrofurazone (p. 333·1).
Infected skin disorders.

Densopax *Justesa Imagen, Arg.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Densulin *Denver, Arg.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Denta Plus *Rising Pharmaceuticals, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

DentaGel
Note: this name may be used for preparations of different composition.
Rising Pharmaceuticals, USA.
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentagel
Note: this name may be used for preparations of different composition.
Phytopharm, Ukr.
Metronidazole (p. 936·1); chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Dentagesic *Maver, Chile.*
Clonixin lysine (p. 40·1).
Pain.

Dentaguttal *Mosfarma, Rus.*
Valerian (p. 2640·2); camphor (p. 2466·2); peppermint oil (p. 1877·1).
Toothache.

Dentain *Centaur, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dentakind *Mankind, India.*
Cetrimide (p. 1742·1); tannic acid (p. 2625·2); zinc chloride (p. 2126·1).

Dentaliv *Mintlab, Chile.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Dentamet *Altayvitamin, Rus.*
Metronidazole (p. 936·1); chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Dentan *Meda, Swed.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentap *Pliva, Irl.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dentapaine *Reese, USA.*
Benzocaine (p. 1980·2); clove oil (p. 2481·3).
Toothache.

Dentaplus *Phytopharm, Rus.*
Valerian (p. 2640·2); camphor (p. 2466·2); peppermint oil (p. 1877·1).
Toothache.

Dentarec *K2Health & Wellness, Chile.*
Doxycycline (p. 288·1).
Periodontitis.

Dentasep *Stedman, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).

Dentasep-F *Stedman, India.*
Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2).

Dentaton *Ghimas, Ital.*
Chlorhexidine (p. 1743·2); mallow (p. 2549·2).
Oral hygiene.

Dentex *CSP, Fr.*
Hydrogen peroxide (35%) (p. 1755·2).
Oral hygiene; mouth irritation.

Denti-Care Denti-Freeze *Medicom, Canad.*
Benzocaine (p. 1980·2); tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Denti-Care Topical *Medicom, Canad.*
Benzocaine (p. 1980·2); tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Denticelso *Alcor, Spain.*
Sulfacetamide (p. 361·1); tyrothricin (p. 384·1).
Mouth infections.

Dentiflour *Medifarma, Turk.*
Sodium fluoride (p. 2089·2).

Dentigel *Gouka, Neth.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentikrisos *Quimifar, Spain.†*
Benzocaine (p. 1980·2); tetracaine hydrochloride (p. 1996·3); menthol (p. 2553·2).
Toothache.

Dentilim *Medipharm, Chile.*
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat infections; gingivitis; oral hygiene.

Dentin *Rekah, Israel.*
Eugenol (p. 2501·2); benzocaine (p. 1980·2); chlorobutanol (p. 1747·2).
Toothache.

Dentinale *Montefarmaco, Ital.*
Amylocaine hydrochloride (p. 1979·3); sodium benzoate (p. 1738·2).
Teething pain.

Dentinox
Note: this name may be used for preparations of different composition.
Nycomed, Austria; Dentinox, Rus.; Teva, Switz.; Abdi, Turk.
Lidocaine hydrochloride (p. 1988·2); lauromacrogol 400 (p. 2194·1); chamomile (p. 2474·1).
Teething pain.

DDD, Israel.
Simeticone (p. 1886·2); dill oil (p. 2493·2).
Infant colic.

Penta, Hung.
Chamomile (p. 2474·1); lauromacrogol 400 (p. 2194·1).
Teething pain.

Vemedia, Neth.
Lidocaine hydrochloride (p. 1988·2).
Teething pain.

Nycomed, Austria.†
Oral drops: Chamomile tincture (p. 2474·1); myrrh tincture (p. 2566·1); cetylpyridinium chloride (p. 1743·1); lauromacrogol 400 (p. 2194·1).
Teething pain.

Dentinox Colic *DDD, Irl.*
Simeticone (p. 1886·2).
Infant colic.

Dentinox Colic Drops *DDD, Hong Kong†; DDD, Malaysia; DDD, UK.*
Simeticone (p. 1886·2).
Infant colic.

DDD, Singapore.
Simeticone (p. 1886·2); dill oil (p. 2493·2).
Infant colic.

Dentinox Cradle Cap *DDD, Irl.; DDD, Malaysia; DDD, Singapore; DDD, UK.*
Sodium lauril ether sulfosuccinate (p. 2210·3); sodium lauril ether sulfate (p. 2210·3).
Cradle cap; infant hair and scalp hygiene.

Dentinox N *Dentinox, Ger.; Dentinox, Hung.; Dentinox, Pol.; Dentinox, Ukr.*
Chamomile (p. 2474·1); lidocaine hydrochloride (p. 1988·2); lauromacrogol 400 (p. 2194·1).
Teething pain.

Dentinox Teething Gel *DDD, Hong Kong; DDD, Malaysia; DDD, Singapore; DDD, UK.*
Lidocaine hydrochloride (p. 1988·2); cetylpyridinium chloride (p. 1743·1).
Teething pain; sore gums; denture irritation.

Dentipatch *Noven, USA.†*
Lidocaine (p. 1988·1).
Local anaesthesia.

Dentirol Fluor *Dentirol, Swed.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentisan *Multilab, Braz.†*
Procaine hydrochloride (p. 1994·3); phenol (p. 1763·3); menthol (p. 2553·2); clove oil (p. 2481·3).
Dental pain.

Dentispray *Andromaco, Chile†; Ferraz, Lynce, Port.; Vinas, Spain.*
Benzocaine (p. 1980·2).
Teeth and gum pain; mouth pain; toothache; local anaesthesia.

Dentiva *Nuvora, USA.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); peppermint oil (p. 1877·1); sweet birch oil (p. 92·1); zinc (p. 2126·1).
Oral hygiene.

Dentobaume *Tradiphar, Fr.*
Amylocaine hydrochloride (p. 1979·3); levomenthol (p. 2553·2).
Dental pain.

Dentocaine *Inibsa, Denm.; Inibsa, Fin.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Phoenix, Philipp.
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Dentocar *PannonPharma, Hung.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentogel *Indoco, India.*
Benzalkonium chloride (p. 1737·1); choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).

Dentogen *Anglian, UK.*
Clove oil (p. 2481·3).
Toothache.

Dentohexin *Streuli, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders; oral hygiene.

Dent-O-Kain *Geritrex, USA.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Dentokind *DHU, Ukr.*
Belladonna (p. 2453·3); chamomilla (p. 2474·1); ferrum phosphoricum (p. 2077·1); hepar sulphuris (p. 1721·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Dentolina Plus *Fucus, Arg.†*
Dipyrone (p. 53·3); caffeine (p. 1203·3).
Fever; pain.

Dentomicin *Seid, Spain.†*
Saffron (p. 2208·2); tamarind (p. 1892·2).
Toothache.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dentomycin
Note: this name may be used for preparations of different composition.
Henry Schein, Irl.; Blackwell, UK.
Minocycline hydrochloride (p. 325·1).
Bacterial mouth infections; periodontitis.

Riemser, Ger.†
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Dentopain *Hexal, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever; inflammation.

Dentopain Forte *Hexal, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Dentophar *Qualiphar, Belg.†*
Amylocaine hydrochloride (p. 1979·3); cloral hydrate (p. 1055·2); chloroform (p. 1898·1); menthol (p. 2553·2); thymol (p. 1772·2); eugenol (p. 2501·2).
Dental pain.

Dentosan Azione Intensiva *Johnson & Johnson, Ital.*
Chlorhexidine gluconate (p. 1743·3); peppermint oil (p. 1877·1); geranium oil (p. 2512·2); melissa oil (p. 2553·2); clove oil (p. 2481·3); spearmint oil (p. 2621·2).
Oral hygiene.

Dentosan Extra Fluor *Pfizer Consumer, Ital.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentosan Junior *Pfizer Consumer, Ital.*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Dentosan Mese *Pfizer Consumer, Ital.*
Peppermint oil (p. 1877·1); geranium oil (p. 2512·2); melissa oil (p. 2553·2); clove oil (p. 2481·3); spearmint oil (p. 2621·2); chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Dentosan Ortodontico *Pfizer Consumer, Ital.*
Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2).
Oral hygiene; dental caries prophylaxis.

Dentosan Parodontale *Pfizer Consumer, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Dentosan Sensibile *Pfizer Consumer, Ital.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Gingivitis; hypersensitive teeth.

Dentosedina *Teofarma, Ital.*
Procaine hydrochloride (p. 1994·3); benzocaine (p. 1980·2).
Dental pain.

Dentosept *Phytofarm Kleka, Pol.*
Arnica (p. 2447·2); chamomile (p. 2474·1); peppermint (p. 1877·1); oak bark (p. 2574·1); sage leaf (p. 2608·3); thyme (p. 2630·2); couch-grass (p. 2487·2).
Mouth disorders.

Dentosept A *Phytofarm Kleka, Pol.*
Arnica (p. 2447·2); chamomile (p. 2474·1); peppermint (p. 1877·1); oak bark (p. 2574·1); sage leaf (p. 2608·3); thyme (p. 2630·2); calamus (p. 2464·2); benzocaine (p. 1980·2); borax (p. 2459·2).
Mouth disorders.

Dentoxil *Master, Chile.†*
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

Dentra *Intra-Labs, India.*
Mouthwash: ⊗Chlorhexidine gluconate (p. 1743·3); glycerol (p. 2517·2).

Intra-Labs, India.
Oral gel: Choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).

Intra-Labs, India.
Toothpaste: ⊗Potassium nitrate (p. 1766·2).

Dentromin *Denver, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension.

Dentron *Sanify, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Santa, Gr.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Dentrosym *Symbiosis, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Dent's Extra Strength Toothache Gum *Dent, USA.*
Benzocaine (p. 1980·2).

Dent's Maximum Strength Toothache Drops *Dent, USA.*
Benzocaine (p. 1980·2).

Dentsiblen *GSK, Mex.†*
Mouthwash: ⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3); xylitol (p. 2220·3).
Oral hygiene; dental hypersensitivity.

GSK, Mex.†
Toothpaste: ⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3); aldioxa (p. 1692·2).
Oral hygiene; dental hypersensitivity.

Dentyl *Key, Austral.*
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Dentyl pH *Dendron, UK.*
Triclosan (p. 1773·2); fluoride (p. 2089·2).
Oral hygiene.

Denubil *PierreFabre, Spain.*
⊗Heptaminol hydrochloride (p. 2525·1); deanol pidolate (p. 2319·1).
Mental function disorders.

Denufam *Caprifarmindo, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Denulcer *Stada, Spain.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Denutraxan *Isdin, Spain.*
Pramocaine hydrochloride (p. 1993·3).
Pruritus.

Denvar *Merck, Mex.; Merck, Spain.*
Cefixime (p. 240·3).
Bacterial infections.

Denvercrem *Denver, Arg.*
⊗Gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Denverlax *Denver, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

Denxol *La Pharmaceuticals, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Denyl *Cristalia, Braz.*
Citalopram (p. 411·1).
Depression; obsessive-compulsive disorder; panic attacks.

Denzapine *Clonmel, Irl.; Merz, UK.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Denzo *TO-Chemicals, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; swelling.

Denzolam *Denver, Arg.*
Biperiden hydrochloride (p. 895·1).
Parkinsonism.

Deo *Milano, Thai.†*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

De-Ol *Hoe, Philipp.; Marketlink, Philipp.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Deolin *Unison, Philipp.†; Unison, Thai.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Deolip *Hisun, China.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Deorvit *Picco, Thai.*
Vitamin B substances (p. 2102·3).

Deosan *Biomedica, India.*
Menthol (p. 2553·2); triclosan (p. 1773·2).
Soap substitute.

Deosone *PC India, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Deotrin *Bunker, Braz.*
Deltamethrin (p. 2152·1).

Deoxical *Galeno, Venez.*
Calcium dobesilate (p. 2464·3).
Varices; venous insufficiency.

Deoxidant *Radicura, India.*
Copper (p. 2057·1); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Deoxymykoin *Glenmark, Cz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Depacon *Abbott, Braz.; Abbott, USA.*
Sodium valproate (p. 553·1).
Epilepsy.

Abbott, Philipp.
Valproic acid (p. 553·1).
Epilepsy.

Depain
Note: this name may be used for preparations of different composition.
Saga, India.
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Depakene *Abbott, Arg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Indon.; Kyowa, Jpn.; Abbott, Mex.; Sanofi-Aventis, Philipp.; Abbott, USA.*
Valproic acid (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy; mania; bipolar disorder.

Depakin *Sanofi-Aventis, Ital.; Sanofi Synthelabo, Turk.*
Sodium valproate (p. 553·1) or valproic acid (p. 553·1).
Epilepsy.

Depakin Chrono *Sanofi-Aventis, Ital.; Sanofi Pasteur, Turk.; Sanofi-Aventis, Ukr.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Depakine *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi-Aventis, Ukr.; Abbott, Venez.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder; febrile convulsions.

Sanofi, China.
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Sanofi-Aventis, Neth.
Valproic acid (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy.

Dépakine *Sanofi-Aventis, Fr.*
Sodium valproate (p. 553·1).
Epilepsy; febrile convulsions.

Depakine Chrono *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Switz.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder; mania.

Dépakine Chrono *Sanofi-Aventis, Fr.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Depakine Chronosphere *Sanofi-Aventis, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Depakine Crono *Sanofi-Aventis, Spain.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Depakote *Abbott, Braz.; Sanofi-Aventis, India; Abbott, Indon.; Abbott, Philipp.; Sanofi Synthelabo, UK; AbbVie, USA.*
Valproate semisodium (p. 553·2).
Epilepsy; mania; migraine; bipolar disorder.

Dépakote *Sanofi-Aventis, Fr.*
Valproate semisodium (p. 553·2).
Bipolar disorder.

Depalept *CTS, Israel.*
Sodium valproate (p. 553·1).
Epilepsy.

Depalept Chrono *CTS, Israel.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Depalgos *Molteni, Ital.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Depam *Neiss, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Depamag *Sigma-Tau, Ital.*
Magnesium valproate (p. 553·1).
Epilepsy.

Dépamide *Sanofi-Aventis, Fr.*
Valpromide (p. 553·2).
Bipolar disorder.

Depamide *Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Spain.*
Valpromide (p. 553·2).
Epilepsy; depression; psychomotor agitation; bipolar disorder; aggression.

Depan-F *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Depant *Valeant, Cz.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Depanthol *Stada, Rus.*
Dexpanthenol (p. 2582·2); chlorhexidine gluconate (p. 1743·3).
Burns; wounds; ulcers; infected skin disorders; vaginitis; cervical erosion; cervicitis.

Depantol *Zdorovje, Ukr.*
Dexpanthenol (p. 2582·2).
Skin and mucous membrane lesions; burns; wounds.

Deparex *Viofar, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Deparoc *Aspen, S.Afr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Deparon
Note: this name may be used for preparations of different composition.
Great Eastern, Thai.†; Westmont, Thai.†
Dipyrone (p. 53·3).
Pain.

Westmont, Indon.†
Dipyrone (p. 53·3); meprobamate (p. 1083·3).
Pain.

Depart *Atral, Port.†*
Escitalopram oxalate (p. 416·2).

Depas
Note: this name may be used for preparations of different composition.
Solvay, Ital.; Mitsubishi Tanabe, Jpn.
Etizolam (p. 1073·2).
Anxiety; skeletal muscle spasm; sleep disorders.

Zota, India.
Diclofenac (p. 48·3); dicycloverine (p. 1834·2).

Depasin *Naturkost, Norw.†*
St John's wort (p. 449·1).
Anxiety; depression; insomnia.

Depatox *Progen, Ital.*
Curcumin (p. 2180·1); thioctic acid (p. 2629·1); silymarin (p. 1561·2).
Liver disorders.

Depaxan *Biosintetica, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Depci *Auspi, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Depcid-O *East African, India.*
Magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Depci-TZ *Auspi, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Depefex *Chiesi, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Depel *Zee, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Depen *Wallace, USA.*
Penicillamine (p. 1567·1).
Wilson's disease; cystinuria; rheumatoid arthritis.

Dependal-M *GSK, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Diarrhoea.

Dependex *Amomed, Austria.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol withdrawal syndrome.

Depersolon *Gedeon Richter, Rus.*
⊗Mazipredone hydrochloride (p. 1642·2).
Corticosteroid.

Depgard *Sanat, India.*
St John's Wort (p. 449·1).
Depression.

depGynogen *Forest Pharmaceuticals, USA.*
Estradiol cipionate (p. 2271·1).
Menopausal vasomotor symptoms; female hypogonadism.

Dephandon *Acdhon, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Depicor *Merck, India.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Dépiderm *Uriage, Fr.*
Liquorice (p. 1853·2).
Skin hyperpigmentation.

Depidol *Torrent, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; hiccup; nausea and vomiting.

Depig *Intermed, India.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Depigoid *Leti, Ger.; Novartis, Ger.*
Allergen extracts (p. 2434·3).
Hyposensitisation.

Depig-TM *Intermed, India.*
⊗Hydroquinone (p. 1705·1); mometasone furoate (p. 1644·1); tretinoin (p. 1725·2).

Depik *Aarpik, India.*
Imipramine (p. 426·2).
Depression; nocturnal enuresis.

Depik Forte *Aarpik, India.*
Diazepam (p. 1063·2); imipramine (p. 426·2).

Depik Plus *Aarpik, India.*
Diazepam (p. 1063·2); imipramine (p. 426·2).

Depin *Zydus, India.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Depin-E *Cadila, Rus.; Cadila, Singapore; Zydus Cadila, Thai.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Depiquick *Leti, Ger.; Novartis, Ger.*
Pollen allergen extracts (p. 2593·3) (p. 2434·3).
Hyposensitisation.

Depival *Psyco Remedies, India.*
Nortriptyline.
Depression; nocturnal enuresis.

Depixol *Lundbeck, Irl.; Lundbeck, UK.*
Flupentixol decanoate (p. 1074·2).
Psychoses.

Depizide *Pond's, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Deplam-S *Mankind, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Deplatol *Bushnell, India.*
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

Deplatt *Torrent, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Torrent, Philipp.; Torrent, Singapore.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Deplatt-A *Torrent, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Deplatt-CV *Torrent, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3); atorvastatin (p. 1309·2).

Deplin
Note: this name may be used for preparations of different composition.
Pamlab, USA.
Calcium levomefolate (p. 2053·1).
Folate deficiency.

Sykocure, India.
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

depMedalone *Forest Pharmaceuticals, USA.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Depnil
Note: this name may be used for preparations of different composition.
Cipla, India.
Clomipramine (p. 412·1).
Cataplexy associated with narcolepsy; phobias; obsessive-compulsive disorder; panic disorder; depression.

Cipla-Medpro, S.Afr.
Moclobemide (p. 437·2).
Depression; social phobia.

Depnon *Organon, India.*
Mianserin hydrochloride (p. 434·2).
Depression.

Depo Geston *PT Triyasa Nagamas, China.*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms.

Depo Progestin *DKT, India.*
Medroxyprogesterone (p. 2288·1).
Progestogen-only injectable contraceptive.

Depo-Clinovir *Pfizer, Ger.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Depocon
Note: this name may be used for preparations of different composition.
CCM, Malaysia; Duopharma, Singapore.
Norethisterone enantate (p. 2294·3).
Progestogen-only injectable contraceptive.

Pfizer, Austria.
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Depocort *Nova Argentia, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Depocort Crono *Nova Argentia, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone dipropionate (p. 1623·3).
Corticosteroid.

Depocort Retard *Nova Argentia, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone acetate (p. 1623·2).
Corticosteroid.

DepoCyt *SkyePharma, Canad.; Sigma-Tau, USA.*
Liposomal cytarabine (p. 774·1).
Lymphomatous meningitis; malignant meningitis.

DepoCyte *Mundipharma, Austria; Mundipharma, Belg.; Mundipharma, Cz.; Skyepharma, Denm.; Pacira, Fin.; Mundipharma, Fr.; Mundipharma, Ger.; IFET (ΙΦΕΤ), Gr.; Pacira, Hung.; Mundipharma, Irl.; Mundipharma, Ital.; Mundipharma, Neth.; Mundipharma, Norw.; Pacira, Pol.; Pacira, Port.; Mundipharma, Spain; Mundipharma, Swed.; Mundipharma, Switz.; Napp, UK.*
Liposomal cytarabine (p. 774·1).
Lymphomatous meningitis.

Depo-Dilar *Abdi, Turk.*
⊗Paramethasone acetate (p. 1645·1).
Corticosteroid.

DepoDur *Orphan, Austral.; Flynn, UK; EKR, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Depo-Eligard *Astellas, Belg.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Depofin *Allen, Mex.*
Diiodohydroxyquinoline (p. 931·1); kaolin (p. 1850·1); pectin (p. 2200·3).
Amoebiasis; diarrhoea.

Depogen *Hyrex, USA.*
Estradiol cipionate (p. 2271·1).
Menopausal vasomotor symptoms; female hypogonadism.

Depo-Gestin *ANB, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; dysfunctional uterine bleeding; endometriosis.

Depolan
Note: this name may be used for preparations of different composition.
Gap, Gr.
Risperidone (p. 1103·2).
Psychoses.

GL Pharma, Denm.; Nordic Drugs, Fin.; Nordic, Swed.
⊗Morphine hydrochloride (p. 92·3).
Pain.

Depo-M *Vesco, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; dysfunctional uterine bleeding; endometriosis.

Depomax *Biomax, India.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Depo-Medrol *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Max, India; Pfizer, Indon.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Eczacibasi, Turk.; Pfizer, Ukr.; Pharmacia Upjohn, USA; Pfizer, Venez.*
⊗Methylprednisolone acetate (p. 1642·3).
Lidocaine hydrochloride (p. 1988·2) is included in some injections to alleviate the pain of injection.
Corticosteroid.

Dépo-Médrol *Pfizer, Fr.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Depo-Medrol cum Lidocain *Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol com Lidocaina *Pfizer, Port.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol + Lidocaina *Pfizer, Ital.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol with Lidocaine *Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Israel; Pfizer, NZ; Pfizer, S.Afr.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Depo-Medrol Lidocaine *Pfizer, Switz.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol + Lidocaine *Pfizer, Belg.; Pfizer, Neth.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol z Lidokaina *Pfizer, Pol.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Joint disorders.

Depo-Medrone *IFET (ΙΦΕΤ), Gr.†; Pfizer, Irl.; Pfizer, UK.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Depo-Medrone with Lidocaine *Pfizer, Irl.; Pfizer, UK.*
⊗Methylprednisolone acetate (p. 1642·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders.

Depometikort *Ulagay, Turk.*
⊗Methylprednisolone acetate (p. 1642·3).

Depon *BMS, Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Depon Extra *BMS, Gr.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Depon Maximum *BMS, Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Depon Odis *BMS, Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Depon Plus *BMS, Gr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Depon Vit C *BMS, Gr.*
Paracetamol (p. 115·1); vitamin C (p. 2110·3).
Pain; fever.

Depo-Nisolone *Pfizer, Austral.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Deponit *UCB, Austria; Takeda, Belg.; UCB, China; UCB, Fin.; Schwarz, Ger.†; GSK, Hong Kong; Schwarz, Irl.†; GSK, Israel; Schwarz, Ital.; GSK, Malaysia; Takeda, Neth.; GSK, Philipp.; Schwarz, Rus.; GSK, Singapore†; UCB, Switz.; Adeka, Turk.; UCB, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; coronary heart disease; heart failure; prophylaxis of phlebitis and extravasation.

Depopred *Sun, India.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Depo-Prodasone *Pfizer, Chile.*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms; progestogen-only injectable contraceptive.

Dépo-Prodasone *Pfizer, Fr.*
Medroxyprogesterone acetate (p. 2288·1).
Endometriosis; breast cancer; endometrial cancer.

Depo-Progesno *Milano, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Depo-Progesta *General Drugs, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; endometriosis.

Depo-Progevera *Pfizer, Spain.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; endometrial cancer.

Depo-Provera *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pharmacia, Braz.; Pfizer, Canad.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Max, India; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Eczacibasi, Turk.; Pfizer, UK; Pfizer, Ukr.; Pharmacia Upjohn, USA; Pfizer, Venez.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; malignant neoplasms; endometriosis; menopausal disorders; precocious puberty; anorexia; cachexia.

Dépo-Provera *Pfizer, Fr.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Depo-Ralovera *Pfizer, Austral.*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms; endometriosis; progestogen-only injectable contraceptive.

Deporeva *Elder, Philipp.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; amenorrhoea; endometriosis; progestogen-only oral contraceptive; malignant neoplasms; hormone replacement therapy.

Deposet *VHB, India.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Deposilin *Abbott, Turk.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Deposilin 6.3.3 *Abbott, Turk.*
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Deposit *Roxall, Ger.*
Allergen extracts (p. 2434·3).
Hyposensitisation.

Depostat *Schering, Cz.; Schering, Gr.; Bayer, Rus.*
Gestonorone caproate (p. 2280·1).
Benign prostatic hyperplasia; endometrial cancer; breast cancer.

Deposteron *Sigma, Braz.*
⊗Testosterone cipionate (p. 2305·1).
Breast cancer; androgen deficiency; male hypogonadism; delayed puberty (males).

Depo-subQ Provera *Pharmacia Upjohn, USA.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; endometriosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Depo-Test *Unigen, Thai.*
⊗Testosterone enantate (p. 2305·1).
Testosterone deficiency; male hypogonadism; delayed puberty; breast cancer in women.

Depo-Testadiol *Upjohn, USA.†*
⊗Estradiol cipionate (p. 2271·1); testosterone cipionate (p. 2305·1).
Menopausal vasomotor symptoms; prevention of postpartum breast engorgement.

Depotestogen *Hyrex, USA.†*
⊗Estradiol cipionate (p. 2271·1); testosterone cipionate (p. 2305·1).
Menopausal vasomotor symptoms; prevention of postpartum breast engorgement.

Depot-Hal *Hal, Ger.*
Allergen extracts of pollen (p. 2593·3), fungi, house dust mites (p. 2434·3) and skin (p. 2434·3).
Allergen immunotherapy.

Hal, Neth.
Allergen extracts from house-dust mites (p. 2434·3).
Allergen immunotherapy.

Depotrone *Adcock Ingram, S.Afr.*
⊗Testosterone cipionate (p. 2305·1).
Male hypogonadism; gynaecomastia; menstrual disorders; lactation suppression; mastitis.

Depotrust *Umeda, Philipp.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Depovig *Madhav, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

Deprakine *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Norw.†*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder; migraine; mania.

Deprakine Depot *Sanofi-Aventis, Fin.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Depral *Alkaloida, Hung.*
Sulpiride (p. 1107·3).
Depression; dizziness; nausea and vomiting; schizophrenia; vertigo.

Depralin *Polpharma, Pol.*
Escitalopram (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Depramil *Cipla-Medpro, S.Afr.*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Depramina *Teuto, Braz.*
Imipramine hydrochloride (p. 426·2).
Depression.

Depramine *Adelco, Gr.*
Imipramine hydrochloride (p. 426·2).

Deprancol *Parke, Davis, Spain.†*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Depranil
Note: this name may be used for preparations of different composition.
Duopharma, Singapore.
Clomipramine hydrochloride (p. 412·1).
Depression; narcoleptic syndrome; obsessive-compulsive disorder; panic disorder.

La Pharmaceuticals, India.
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Depranil Plus *La Pharmaceuticals, India.*
Diazepam (p. 1063·2); imipramine hydrochloride (p. 426·2).

Deprax
Note: this name may be used for preparations of different composition.
Saval, Chile.
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Ache, Braz.
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Angelini, Spain.
Trazodone hydrochloride (p. 451·1).
Depression; mixed anxiety depressive disorders.

Deprazolin *Zentiva, Cz.†*
Prazosin hydrochloride (p. 1473·3).
Heart failure; hypertension.

Deprecalm *Lazar, Arg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Deprectal *Psicofarma, Mex.*
Oxcarbazepine (p. 533·2).
Epilepsy; neuropathic pain; migraine; bipolar disorder.

Depredon *Kleva, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Deprefolt *Actavis, Rus.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Depreger *Gerard, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Depreks *Abdi, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Deprelin *Farmo Quimica, Chile.†*
Clomipramine hydrochloride (p. 412·1).
Depression; panic disorder; nocturnal enuresis.

Deprelio *Estedi, Spain.*
Amitriptyline hydrochloride (p. 401·1).
Depression; neuropathic pain.

Deprenil *Terra, Turk.*
Opipramol hydrochloride (p. 440·2).
Depression.

Deprenorm *Kanonfarma, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; vascular eye disorders.

Déprényl *CSP, Fr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Depreram *Kleva, Gr.*
Mirtazapine (p. 436·1).
Depression.

Depresinal *GL Pharma, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Depresix *New Life, Arg.*
Vitamins; trace elements.
Dietary supplement.

Depress *Uniao Quimica, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Depressan *Nycomed, Ger.†; Nycomed, Hung.*
Dihydralazine sulfate (p. 1358·3).
Hypertension.

Depretal *Kleva, Gr.*
Citalopram hydrobromide (p. 411·1).

Deprevex *Klonal, Arg.*
Telmisartan (p. 1509·3).
Hypertension.

Deprevix *Pharmathen, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Deprex
Note: this name may be used for preparations of different composition.
Zentiva, Cz.
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa; mixed anxiety depressive states; premenstrual dysphoric disorder.

Interbat, Indon.
Oxitriptan (p. 440·3); vitamin B_6 (p. 2105·3); ascorbic acid (p. 2110·3).
Depression; headache; myalgia; insomnia.

Deprexan *Unipharm, Israel.*
Desipramine hydrochloride (p. 413·1).
Depression.

Deprexetin *ICN, Pol.*
Fluoxetine (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Deprexin *Gedeon Richter, Hong Kong†; Gedeon Richter, Hung.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Deprexolet *Polfa Pabianice, Pol.*
Mianserin hydrochloride (p. 434·2).
Depression.

Deprexone *JRalph, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Deprezac *Actavis, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Depridol *Extractum, Hung.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal; pain.

Deprigen *Biogened, Pol.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Deprilan *Biosintetica, Braz.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Deprilix *Ratiopharm, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Deprim
Note: this name may be used for preparations of different composition.
Sandoz, Pol.; Sandoz, Rus.; Sandoz, Ukr.
St John's wort (p. 449·1).
Depression; anxiety; nervous disorders; seasonal affective disorder.

AFT, NZ.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Deprive *Atral, Port.†*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Deprivit *KVZ, Ukr.*
St John's wort (p. 449·1).
Depression; nervous disorders; sleep disorders.

Deprivita *Permamed, Switz.*
St John's wort (p. 449·1).
Depression.

Deprivox *Stada, Ukr.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Deprizac *Intas, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Depro *Novaduo, India.*
Medroxyprogesterone (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Deprocid *Sanofi Pasteur, Chile.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Deproctol *Amnol, Ital.*
Thioctic acid (p. 2629·1); diosmin (p. 2505·2); grape (p. 2521·3); melilot (p. 2552·3); zinc (p. 2126·1); vitamins.
Circulatory disorders; haemorrhoids.

Deproist Expectorant with Codeine *Geneva, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Coughs.

Depronal *Pfizer, Belg.†; Pfizer, Neth.†*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Depropin *CCM, Malaysia.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Deprox *Ind-Swift, India.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Deproxin *Siam Bheasach, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Deprozan *Meridian, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Deprozel *Pliva Krakow, Pol.†*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; anxiety; social phobia; post-traumatic stress disorder; panic disorder.

Deprozin *Offenbach, Mex.*
Fluoxetine (p. 417·1).
Depression.

Deprozol *Ache, Braz.*
Secnidazole (p. 947·3).
Bacterial infections; protozoal infections.

Depryl *Cipla, India.*
Trazodone (p. 451·1).
Depression; anxiety.

Depsert *Reliance, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Depset *Eczacibasi, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa; premenstrual dysphoric disorder.

Depsodep *Psychotropics, India.*
Chlordiazepoxide (p. 1044·2); imipramine hydrochloride (p. 426·2).

Depsol *Intas, India.*
Imipramine (p. 426·2).
Depression; nocturnal enuresis.

Depsol Forte *Intas, India.*
Diazepam (p. 1063·2); imipramine (p. 426·2).

Depsol Plus *Intas, India.*
Diazepam (p. 1063·2); imipramine (p. 426·2).

Depsonil *Piramal, India.*
Imipramine hydrochloride (p. 426·2) or imipramine embonate (p. 426·2).
Depression; nocturnal enuresis.

Depsonil-DZ *Piramal, India.*
Imipramine hydrochloride (p. 426·2); diazepam (p. 1063·2).
Mixed anxiety depressive states.

Depsorin *Venus, Hung.*
Lappa (p. 2540·1); calendula (p. 2465·2); chamomile (p. 2474·1); chelidonium (p. 2522·2); St John's wort (p. 449·1).
Psoriasis.

Depten
Note: this name may be used for preparations of different composition.
Psyco Remedies, India.
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Zydus, India.
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension.

Depten-AZ *Psyco Remedies, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Depten-OZ *Psyco Remedies, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Deptral *Bajamed, Mex.*
Sertraline (p. 448·1).
Depression.

Meprofarm, Indon.
Sertraline hydrochloride (p. 448·1).
Depression.

Deptran
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Doxepin hydrochloride (p. 414·2).
Depression.

Deptune *Baroda, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Depulol *Hasco-Lek, Pol.*
Eucalyptus oil (p. 2501·2); Peru balsam (p. 2587·1); rosemary oil (p. 2607·3).
Cold and influenza symptoms; cough.

Depump *Tablets, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Depura *Sanofi-Aventis, Braz.*
Colecalciferol (p. 2113·1).

Depuran *McNeil, Ger.†; Aspen Consumer, S.Afr.*
Senna (p. 1885·1).
Constipation.

Dépuratif Parnel *Poirier, Fr.†*
Lappa (p. 2540·1); wild pansy (p. 2647·3); soapwort (p. 2617·2); fumitory (p. 2508·2).
Gastrointestinal disorders.

Depuratif des Trappistes *Bio-Sante, Canad.*
Barberry root (p. 2502·1); lappa (p. 2540·1); cascara (p. 1826·1); chamomile (p. 2474·1); sage (p. 2608·3); sarsaparilla (p. 2610·3); taraxacum (p. 2625·3).
Constipation.

Depurativo Richelet *Urgo, Spain.†*
Gentian (p. 2512·1); potassium iodide (p. 2336·3); salicylic acid (p. 1719·1); tannic acid (p. 2625·2); iodine (p. 2336·3); cinnamon oil (p. 2479·3); magnesium chloride (p. 1787·1); magnesium bromide (p. 1786·3); nicotinamide (p. 2083·1).
Detoxification.

Dépuratum *Lehning, Fr.*
Birch leaf (p. 2457·3); rosemary leaf (p. 2607·2); juniper (p. 2537·1); rhapontic root (p. 1884·2); fumitory (p. 2508·2); thyme (p. 2630·2); ononis (p. 2575·3).
Digestive disorders.

Depurol *Royal, Chile.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Depwell *Mediez, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Depyret *TO-Chemicals, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Depzac *Cipla, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Depzil *Psyco Remedies, India.*
Donepezil (p. 390·2).
Alzheimer's disease.

Deq *Atlantic, China; Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Dequalinium chloride (p. 1749·3); tyrothricin (p. 384·1).
Mouth and throat disorders.

Dequacaine *Reckitt Benckiser, Irl.; Crookes Healthcare, UK.*
Benzocaine (p. 1980·2); dequalinium chloride (p. 1749·3).
Sore throat; mouth and throat infections.

Dequa-Coff *Aspen, S.Afr.*
⊗Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Dequadin *Wellspring, Canad.; GSK, Hong Kong; GSK, India; Reckitt Benckiser, Irl.; Eurospital, Ital.; GSK Consumer, Malaysia; GSK, Philipp.; GSK, Singapore; GSK, Thai.†; GSK, Turk.; Crookes Healthcare, UK; GSK Consumer, Venez.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Farmoquimica, Braz.
Dequalinium chloride (p. 1749·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Dequadin Mouth Paint *Aspen Consumer, S.Afr.*
Dequalinium chloride (p. 1749·3); lidocaine (p. 1988·1).
Mouth and throat disorders.

Dequa-Flu *Aspen, S.Afr.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); phenyltoloxamine citrate (p. 638·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; sinusitis; rhinitis.

Dequalid *Kela, Belg.*
Dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Dequalinetten *Sigmapharm, Austria.*
Dequalinium chloride (p. 1749·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Dequa-loz *Beacons, Singapore.*
Dequalinium chloride (p. 1749·3).
Sore throat.

Dequasin *GSK, Hong Kong.*
Hexylresorcinol (p. 1755·1); benzalkonium chloride (p. 1737·1).
Mouth and throat disorders.

Dequasine *Miller, USA.*
Vitamin C (p. 2110·3); minerals; amino acids.

Dequaspray *Crookes Healthcare, UK.*
Lidocaine hydrochloride (p. 1988·2).
Formerly known as Strepsils Pain Relief Spray.
Sore throat.

Dequin
Note: this name may be used for preparations of different composition.
Degorts, Mex.
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; respiratory-tract congestion.

De-Quit *Gentech, India.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Dequonal *Nycomed, Austria; Kreussler, Ger.; Pro Concepta, Switz.*
Dequalinium chloride (p. 1749·3); benzalkonium chloride (p. 1737·1).
Mouth and throat infections.

Dequosangola *Eurospital, Ital.*
Dequalinium chloride (p. 1749·3).
Mouth disinfection.

Derain *Leti, Venez.*
Triticum aestivum (p. 2647·1).
Wounds.

Deralbine *Andromaco, Arg.*
Miconazole nitrate (p. 589·1).
Fungal infections.

Deralin *Alphapharm, Austral.; LCH, Hong Kong†; Abic, Israel.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction; tremor; hyperthyroidism; phaeochromocytoma; hypertrophic obstructive cardiomyopathy; fallot's tetralogy.

Deralin-M *Scoshia, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Deramol *LBS, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1).
Cough; cold symptoms.

Derantox *Curatio, India.*
Betacarotene (p. 2051·1); biotin (p. 2052·2); copper (p. 2057·1); manganese (p. 2081·2); selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).

Deratil *Help, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Deratin *Normon, Spain.*
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat infections.

Derbac-M *SSL, Irl.; SSL, NZ; SSL, Singapore; SSL, UK.*
Malathion (p. 2157·2).
Pediculosis; scabies.

Derbec-N *Alkem, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Infected skin disorders.

Derby Cool *Ind-Swift, India.*
Chlorphenesin (p. 575·3); zinc oxide (p. 1729·1); starch (p. 2095·1); talc (p. 1722·2).

Dercason *GMP, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Dercetina *Merck, Mex.*
Cetirizine (p. 619·2).
Hypersensitivity.

Dercin *Egis, Hung.; Egis, Pol.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Dercolina *Casasco, Arg.*
Choline salicylate (p. 39·2).
Mouth disorders.

Dercotex *Sertex, Arg.*
⊗Ketoconazole (p. 585·3); hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Dercualon *Fada, Arg.*
Acenocoumarol (p. 1290·1).

Dercutane *Aldo, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Derebel *Teva Tuteur, Arg.*
Capecitabine (p. 757·3).
Colorectal cancer; breast cancer.

Dereme *Menarini, Spain.†*
⊗Beclometasone salicylate (p. 1621·2).
Skin disorders.

Derfalon *Umeda, Thai.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Derfina *Valeant, Mex.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Dergemate *General Drugs, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dergentil *Vivax, Venez.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Derhotill *Gemi, Pol.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thymol (p. 1772·2); turpentine oil (p. 2636·3).
Cold and influenza symptoms; musculoskeletal pain.

Dericef *Psyco Remedies, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Derichem *Alchemia, Denm.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Dericip *Cipla, India.*
Theophylline (p. 1229·3); etofylline (p. 1208·2).
Bronchospasm.

Dericip Plus *Cipla, India.*
⊗Theophylline (p. 1229·3); ephedrine (p. 1663·1); diazepam (p. 1063·2).

Derifil *Rystan, USA.*
Chlorophyllin copper complex (p. 2178·3).
Ostomy deodorant; reduction of faecal or urinary odour in incontinence.

Deriform *Zydus, India.*
⊗Formoterol (p. 1209·2).
Obstructive airways disease.

Derihaler *Zydus, India.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Deril *Ibirn, Ital.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia; osteoporosis.

Derimod *Cinetic, Arg.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Derin *Vipharm, Cz.; Vipharm, Neth.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; mania.

Derinat *Technomedservis, Rus.*
Sodium deoxyribonucleate (p. 2492·2).
Radiation trauma; peptic ulcer; gastritis; ischaemic heart disease; venous insufficiency; reduction of cancer chemotherapy associated toxicity; infections; stimulating haemopoiesis; rheumatoid arthritis; burns; wounds; ulcers; urogenital disorders; obstructive airways disease; mucous membrane inflammation; haemorrhoids.

Derinide *Zydus, India.*
⊗Budesonide (p. 1625·1).
Asthma.

Derinik *Actavis, Denm.; Actavis, Fin.; Actavis, Swed.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Dérinox *Therabel, Fr.*
⊗Prednisolone (p. 1645·2); naphazoline nitrate (p. 1669·3).
Rhinitis.

Deriphyllin *Zydus, India.*
Etofylline (p. 1208·2); theophylline (p. 1229·3).
Cardiac disorders; respiratory disorders; oedema.

Deripil
Note: this name may be used for preparations of different composition.
Psychotropics, India.
Etofylline (p. 1208·2); theophylline (p. 1229·3).
Reig Jofre, Spain.
Erythromycin (p. 291·2).
Acne.

Deriseptol *Lokman, Turk.*
Cetrimide (p. 1742·1); bismuth subgallate (p. 1822·1); tannic acid (p. 2625·2); aluminium hydroxide (p. 1817·2).
Wounds; burns; skin infections.

Derisone *Zydus, India.*
⊗Beclometasone (p. 1621·2); salbutamol (p. 1220·2).

Deriva *Glenmark, Braz.; Glenmark, India; Glenmark, Malaysia.*
Adapalene (p. 1692·1).
Acne.

Deriva-C *Glenmark, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Deriva-CMS *Glenmark, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Derivatio *Pfluger, Ger.*
Anagallis arvensis; argentum metallicum (p. 2615·1); arnica montana (p. 2447·2); aurum metallicum (p. 2521·1); bryonia cretica; carbo vegetabilis (p. 1537·3); chelidonium majus (p. 2522·2); citrullus colocynthis; cytisus scoparius (p. 2611·3); digitalis purpurea (p. 1352·3); selenicereus grandiflorus (p. 2473·2); silybum marianum (p. 1561·1); smilax (p. 2610·3); stannum metallicum (p. 2632·1); strophanthus gratus; taraxacum officinale (p. 2625·3); veronica virginica; viscum album (p. 2560·2).
Homoeopathic preparation.

Derivatio H *Pfluger, Ger.*
Anagallis arvensis; argentum metallicum (p. 2615·1); arnica montana (p. 2447·2); aurum metallicum (p. 2521·1); bryonia cretica; carbo vegetabilis (p. 1537·3); chelidonium majus (p. 2522·2); citrullus colocynthis; cytisus scoparius (p. 2611·3); digitalis purpurea (p. 1352·3); natrium chloratum (p. 1795·1); selenicereus grandiflorus (p. 2473·2); silybum marianum (p. 1561·1); smilax (p. 2610·3); stannum metallicum (p. 2632·1); strophanthus gratus; taraxacum officinale (p. 2625·3); veronica virginica; viscum album (p. 2560·2).
Homoeopathic preparation.

Derivit *Lokman, Turk.*
Ethacridine lactate (p. 1732·3); bismuth subgallate (p. 1822·1); Kataflon; cod-liver oil (p. 2056·3); calamine (p. 1697·2); zinc oxide (p. 1729·1).
Burns; skin disorders.

Derivon *Wabosan, Austria.*
Cream: Benzyl nicotinate (p. 29·3); diethylamine salicylate (p. 51·3); heparin (p. 1396·3).
Musculoskeletal and joint disorders; soft-tissue disorders; neuralgia.

Derizic *Bevo, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Derm *Lero, Fr.*
Fish oil (p. 1460·1); evening primrose oil (p. 2502·2); grape extract (p. 2521·3); vitamins; selenium (p. 2086·3).
Dietary supplement; skin disorders.

Derm A *Dermpharma, Philipp.*
Tretinoin (p. 1725·2).
Skin disorders; sun-induced skin damage.

Derm Hydralin *Bayer Sante, Fr.*
Glycine (p. 2071·2).
Skin irritation.

Derm Prox *Legrand, Braz.*
Ciclopirox (p. 575·3).

Derma *IFET (ΙΦΕΤ), Gr.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).

Derma Care
Note: this name may be used for preparations of different composition.
Fischer, Israel.
Salicylic acid (p. 1719·1); hamamelis (p. 2523·3); chamomile (p. 2474·1); provitamin B_5.
Seborrhoea; skin cleansing.

Dermabase *Paddock, USA.*
Vehicle for topical preparations.

Dermabel
Note: this name may be used for preparations of different composition.
Farma-Tek, Turk.
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.
Royal, Chile.
Clindamycin phosphate (p. 269·3).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dermabiolene *Farmacologico Milanese, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Dermabiotic *Elmor, Venez.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Bacterial skin infections.

Dermabiotico *Saval, Chile.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Infected skin disorders; burns; wounds.

Dermabiotik *Medikon, Indon.†*
Gentamicin sulfate (p. 304·2).
Skin infections.

Dermablend *L'Oreal, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Dermablend Clarifying *Stalder, Philipp.*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Skin cleanser.

Dermablend Cleansing *Stalder, Philipp.*
Skin cleanser.

Dermablend Colloidal Oatmeal Lotion *Stalder, Philipp.*
Allantoin (p. 1693·1); colloidal oatmeal (p. 2451·1).
Skin irritation; dry skin; pruritus.

Dermablend Skin Moisturizer *Stalder, Philipp.*
Emollient.

Dermablend Sunblock *Stalder, Philipp.*
Cream SPF 24: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Stalder, Philipp.
Lotion SPF 24: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Dermabond *Johnson & Johnson Medical, Arg.†; Ethicon, UK.*
Ocrilate (p. 2490·1).
Tissue adhesive for wound closure and suture support; skin adhesive.

Dermabut *Grunenthal, Port.†*
Colecalciferol (p. 2113·1); vitamin A palmitate (p. 2098·3); zinc oxide (p. 1729·1).
Skin disorders; burns; wounds; varicose veins.

Dermac *Stiefel, Mex.*
Cream: Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne.

Stiefel, Mex.
Soap: Sulfated castor oil (p. 2215·1).
Acne; seborrhoea.

Dermac Crema *Stiefel, Chile.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3); chloroxylenol (p. 1748·2).
Acne.

Dermac Jabon *Stiefel, Chile.*
Soap substitute.
Acne.

Dermacalm
Note: this name may be used for preparations of different composition.
Maccabi Care, Israel.
Dexpanthenol (p. 2582·2).
Skin irritation; dry skin.

Dermacalm-d *Bayer, Switz.*
⊗Hydrocortisone acetate (p. 1640·1); dexpanthenol (p. 2582·2).
Skin disorders.

Derma-Care
Note: this name may be used for preparations of different composition.
Hermal, Israel.†
⊗Lauromacrogol 400 (p. 2194·1); urea (p. 1727·3).
Skin disorders.

Dermacare
Note: this name may be used for preparations of different composition.
Darrow, Braz.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermacerium *Silvestre, Braz.*
Sulfadiazine silver (p. 362·3); cerous nitrate (p. 1699·1).
Bacterial skin infections.

Dermachrome *Sanofi-Aventis, Fr.†*
Chlorhexidine gluconate (p. 1743·3).
Wounds.

Dermacid *Darier, Mex.*
Thymol (p. 1772·2); benzalkonium chloride (p. 1737·1).
Acne; seborrhoea.

Dermacide *Sanofi-Aventis, Gr.*
Hydroxyquinoline (p. 2530·1); salicylic acid (p. 1719·1); sodium laurilsulfate (p. 2210·3); sodium propionate (p. 593·1); tartaric acid (p. 2626·1).

Sinclair, Fr.
Topical solution: Hydroxyquinoline sulfate (p. 2530·1); sodium propionate (p. 593·1); salicylic acid (p. 1719·1); tartaric acid (p. 2626·1).
Cleansing of skin; bacterial skin infections.

Dermaclean
Note: this name may be used for preparations of different composition.
STOM, Ital.
Soap substitute.

Lafedar, Arg.†
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Dermaclob *Cinetic, Arg.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermaclof *Marching, Hong Kong.†*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Dermacne
Note: this name may be used for preparations of different composition.
Bio-Sante, Canad.
Topical lotion: Benzoyl peroxide (p. 1696·1).
Acne.

Bio-Sante, Canad.
Liquid soap; soap: Triclosan (p. 1773·2).

Dermacné *LDA, Arg.*
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3); hamamelis (p. 2523·3).
Acne; folliculitis; seborrhoea.

DermaCo *Mediherb, Austral.*
Sarsaparilla (p. 2610·3); clivers (p. 2481·2); Oregon grape (p. 2577·1); lappa (p. 2540·1); yellow dock (p. 2649·3).
Skin disorders; tonic.

Dermacoat *Century, USA.*
Benzocaine (p. 1980·2); chloroxylenol (p. 1748·2); menthol (p. 2553·2).
Skin disorders.

Dermacol *Vitamed, Israel.*
Emollient.
Dry skin.

Dermacolor *Fox, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Dermacom *Tecnofarma, Chile.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Dermacombin *Taro, Israel.*
⊗Nystatin (p. 590·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Taro, Thai.
⊗Nystatin (p. 590·3); neomycin (p. 329·3); gramicidin (p. 308·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Dermacool *Pern, UK.*
Levomenthol (p. 2553·2) in aqueous cream.
Skin irritation; pruritus.

Dermacort
Note: this name may be used for preparations of different composition.
DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.†
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Marlborough Pharmaceuticals, UK.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Tanabe, Indon.
⊗Hydrocortisone (p. 1640·1); camphor (p. 2466·2).
Skin disorders.

Dermacreme *Potter's, UK.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); liquefied phenol (p. 1763·3).
Antiseptic for minor skin injuries.

Dermacrom *Galderma, Mex.*
Dihydroxyacetone (p. 1700·1).
Tanning agent.

Dermacure *Johnson & Johnson, Neth.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Dermacyd *Sanofi-Aventis, Braz.*
Lactoserum; lactic acid (p. 2539·1).
Female personal hygiene.

Dermades *Pharmacore, Indon.*
⊗Desonide (p. 1630·1).
Skin disorders.

Dermadex
Note: this name may be used for preparations of different composition.
GSK, Arg.
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Teofarma, Ital.
⊗Dexamethasone valerate (p. 1630·3).
Skin disorders.

Tianjin, Philipp.
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Dermadex NN *GSK, Arg.*
⊗Clobetasol propionate (p. 1627·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Dermadine *Cipla-Medpro, S.Afr.*
Povidone-iodine (p. 1767·1).
Skin disinfection; burns; wounds; mouth and throat disorders.

Dermadrate *Valeant, Austral.; Dermatech, Hong Kong; Balmar, NZ†; Dermatech, Singapore.*
⊗Lactic acid (p. 2539·1); urea (p. 1727·3); sodium pidolate (p. 1720·3).
Dry skin.

Dermadrox *Geritrex, USA.*
Ointment: Aluminium hydroxide (p. 1817·2); zinc chloride (p. 2126·1); wool fat (p. 2219·3); calcium carbonate (p. 1824·3); vitamin A (p. 2098·3).
Skin irritation.

Geritrex, USA.
Topical spray: Zinc acetate (p. 2126·1).
Wounds.

Dermafacte *Marching, Hong Kong.†*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Dermafin *YSP, Malaysia.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Dermafine *Shreya, India.*
Terbinafine (p. 593·3).
Fungal skin and nail infections.

Dermafleur *Bloem Beheer, Neth.*
Calcarea carbonica ostrearum (p. 1824·3); lycopodium clavatum (p. 2547·1); sulfur (p. 1721·1); petroleum (p. 2587·2); clematis erecta.
Homoeopathic preparation.

Dermaflex
Note: this name may be used for preparations of different composition.
Neolab, Canad.†
⊗Urea (p. 1727·3).
Emollient; moisturiser.

Dermaflex HC *Triton, Canad.*
⊗Hydrocortisone acetate (p. 1640·1); urea (p. 1727·3).
Skin disorders.

Dermaflogil *NCSN, Ital.*
⊗Diflucortolone valerate (p. 1634·1); kanamycin sulfate (p. 314·3).
Skin disorders.

Dermafree *Delta, Braz.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).

Dermagan *RoLo, Ital.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); vitamin F (p. 2509·2).
Skin disorders.

Dermagen *Corsa, Indon.*
Gentamicin sulfate (p. 304·2).
Skin infections.

Dermagesic *NordMedica, Denm.†*
⊗Fentanyl (p. 60·1).
Pain.

Dermaglos *Andromaco, Arg.*
A range of moisturisers with or without sunscreens.
Dry skin.

Andromaco, Chile.
Vitamin A palmitate (p. 2098·3); allantoin (p. 1693·1); tocoferil acetate (p. 2119·2).
Burns; skin disorders; wounds.

Dermaglos Solar *Pharmasud, Mex.†*
SPF 65: Titanium dioxide (p. 1725·1); octil triazone (p. 1715·1); octinoxate (p. 1715·1); bisoctrizole (p. 1697·1).
Sunscreen.

Pharmasud, Mex.†
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1).
Sunscreen.

Pharmasud, Mex.†
SPF 45: Avobenzone (p. 1695·1); octil triazone (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Sunscreen.

Dermaglow *Canadian Custom Packaging, Canad.†*
SPF 30: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Dermagor *Dermoteca, Port.†*
Emollient.

Dermagor Antitranspirante *Dermoteca, Port.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Dermagor Atopicalm *Coryne de Bruynes, Mon.*
Emollient.

Dermagor Betacade *Coryne de Bruynes, Mon.*
Salicylic acid (p. 1719·1); cade oil (p. 1723·2); cedar oil (p. 2472·3); liquid paraffin (p. 2191·2).
Psoriatic skin disorders.

Dermagor Ecran Solar *Dermoteca, Port.†*
Titanium dioxide (p. 1725·1).
Sunscreen.

Dermagraft *Smith & Nephew, S.Afr.†; Smith & Nephew, UK; Smith & Nephew, USA.*
Human dermal tissue (p. 1720·2).
Diabetic foot ulcers.

Dermagran *Victus, Venez.*
Ointment: Zinc (p. 2126·1); vitamins; minerals.
Barrier preparation; wounds; ulcers; burns.

Victus, Venez.
Topical spray: Zinc (p. 2126·1); vitamin B_6 (p. 2105·3).
Wounds; ulcers; burns.

Dermagran-B *Victus, Venez.*
Hydrophilic wound dressing.

Dermaguard *Choisy, Canad.†*
Benzalkonium chloride (p. 1737·1).

Dermaheal DeAkni *EIG, Malaysia.*
Salicylic acid (p. 1719·1); nicotinamide (p. 2083·1); hamamelis (p. 2523·3); allantoin (p. 1693·1).
Acne.

Dermaheal Post Laser Cream *EIG, Malaysia.*
Royal jelly (p. 2608·1); allantoin (p. 1693·1).
Scars.

Dermaheu *TNP, Thai.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Derm-Aid *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders; anogenital pruritus.

DermAid *Ego, Austral.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Derma-Keri *Darier, Mex.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders.

Dermaknel *GSK, Pol.†*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Skin disorders.

Dermakord *Deva, Turk.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Dermal *Amrutanjan, India.*
Boric acid (p. 2459·3); camphor (p. 2466·2); salicylic acid (p. 1719·1).

Dermal Care *Bayer, Ital.*
⊗Urea (p. 1727·3).
Dry skin and nail disorders.

Dermal G *Pharmaniaga, Hong Kong.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Dermal Therapy *Bayer, USA.*
⊗Urea (p. 1727·3).
Dry skin; hyperkeratotic skin disorders.

Dermalac *Taro, Canad.*
Lactic acid (p. 2539·1).

Dermalact *Albephar, Venez.*
Lactic acid (p. 2539·1).

Dermalar *Teva, Israel.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Dermalex Repair *Interdelta, Switz.*
Emollient.
Eczema.

Dermalibour *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Ducray, Fr.*
Avena (p. 2451·1); zinc oxide (p. 1729·1); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Skin irritation; skin disorders.

Ducray, Fr.
Topical mousse: Avena (p. 2451·1); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); triclosan (p. 1773·2).
Skin cleansing for irritated skin.

Dermalife *Orion, NZ.†*
Vitamin A (p. 2098·3).
Skin disorders.

Dermalife Plus *Orion, Austral.†*
Calamine (p. 1697·2); vitamin A palmitate (p. 2098·3); dimeticone (p. 2209·3).
Burns; cradle cap; minor skin lesions; nappy rash; skin disorders.

Dermalin *United Laboratories, Philipp.†*
Benzoic acid (p. 1738·2); clioquinol (p. 273·1); menthol (p. 2553·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1); cetyl alcohol (p. 2178·2).
Skin infections.

Dermalina *Hypermarcas, Braz.*
Miconazole (p. 588·3).

Dermalisan *Prodotti, Braz.†*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); zinc oxide (p. 1729·1).
Skin disorders.

Dermalite *Holland Pharma, Neth.*
Lycopodium clavatum (p. 2547·1); berberis vulgaris (p. 2502·1); calendula officinalis (p. 2465·2); hypericum perforatum (p. 449·1); selenium metallicum (p. 2086·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Dermaliv *Medipharm, Chile.*
Benzocaine (p. 1980·2); triclosan (p. 1773·2); menthol (p. 2553·2); camphor (p. 2466·2).
Burns; wounds; insect bites; pruritus.

Dermalo
Note: this name may be used for preparations of different composition.
Dermal Laboratories, UK.
Liquid paraffin (p. 2191·2); acetylated wool alcohols (p. 2219·2).
Dry skin.

Dermaloe
Note: this name may be used for preparations of different composition.
Forder, Arg.
Aloe vera (p. 1693·2); allantoin (p. 1693·1).
Barrier preparation.

Dermalog *BMS, Mex.*
⊗Halcinonide (p. 1639·3).
Skin disorders.

Dermalog-C *BMS, Mex.*
⊗Halcinonide (p. 1639·3); nystatin (p. 590·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dermalogica Day Bright *Dermalogica, Canad.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Dermalogica Solar Defense Booster *Dermal Enterprises, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Dermalogica Special Clearing Booster *Dermalogica, Canad.*
Benzoyl peroxide (p. 1696·1).

Dermalogica Ultra Sensitive Face Block *Dermalogica, Canad.†*
SPF 25: Titanium dioxide (p. 1725·1).
Sunscreen.

Dermaman *T Man, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermamina *EMS, Braz.*
⊗Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2); glycerol (p. 2517·2).
Skin disorders.

Dermamist *Alliance, Irl.*
White soft paraffin (p. 2211·3).
Dry skin disorders.

Alliance, UK.
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry skin disorders.

Astellas, Ital.
Emollient.
Dry skin disorders.

Dermamoist *Psychotropics, India.*
⊗Aloe vera (p. 1693·2); glycerol (p. 2517·2); safflower oil (p. 2086·3); skimmed milk powder; vitamin E (p. 2119·1).
Soap substitute.

Dermamycin *Pfeiffer, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Derma-Mykotral *Rosen, Ger.†*
Miconazole nitrate (p. 589·1).
Fungal infections of the skin and mucous membranes.

Derman
Note: this name may be used for preparations of different composition.
CICSA, Mex.
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Dermanci, Turk.
Paracetamol (p. 115·1).
Pain; fever.

Derman Plus *Amuchina, Ital.†*
Triclosan (p. 1773·2).
Hand disinfection.

Derman Talco *CICSA, Mex.*
Benzalkonium chloride (p. 1737·1).

Dermana Crema *Humana, Ital.*
Gamolenic acid (p. 2509·2); omega-3 triglyceride (p. 1460·3); vitamin E (p. 2119·1); vitamin A (p. 2098·3).
Emollient.

Dermana Pasta *Humana, Ital.*
Gamolenic acid (p. 2509·2); omega-3 triglyceride (p. 1460·3); vitamin E (p. 2119·1); vitamin A (p. 2098·3); zinc oxide (p. 1729·1).
Dry skin disorders; skin irritation.

DermaNail *Summers, USA.*
Alpha acetoxy acid.
Nail disorders.

Dermanex *Torrent, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Dermanide *Interbat, Indon.*
⊗Desonide (p. 1630·1).
Skin disorders.

Dermanios Scrub *Anios, Fr.†*
Soap substitute.

Derman-Oil *Humana, Ital.*
Gamolenic acid (p. 2509·2); omega-3 triglycerides (p. 1460·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Bath additive.

Dermanol *Quimica y Farmacia, Mex.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); aluminium subacetate (p. 2440·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Dermanol-C *ICM, Singapore.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected and inflammatory skin disorders.

Dermanova *Wierhom, Arg.*
Vitamin A (p. 2098·3); rosa mosqueta; alpha tocopherol (p. 2119·1).

Dermanox *Takeda, Belg.*
Enoxolone (p. 54·2).
Burns; wounds; skin disorders.

Derma-Pax *Recsei, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Formerly contained mepyramine maleate and chlorphenamine.
Pruritus.

Dermapharm Basis *Dermapharm, Ger.*
Emollient.
Skin disorders.

DermaPhor *DermaRite, USA.*
Soft paraffin (p. 2211·3); wool alcohols (p. 2219·2); liquid paraffin (p. 2191·2); hard paraffin (p. 2188·1).

Dermaplant *Spitzner, Ger.*
Cardiospermum.
Homoeopathic preparation.

Derma-Plantin *Infirmarius, Ger.†*
Acidum silicicum (p. 2208·3); clematis recta; graphites (p. 2522·1); mahonia aquifolium (p. 2577·1); sulfur (p. 1721·1); viola tricolor (p. 2647·3).
Homoeopathic preparation.

DermaPlast Desinfect *IVF, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of wounds.

Dermaral *Corsa, Indon.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Dermarell *Sanorell, Ger.*
Acid silicicum (p. 2208·3).
Homoeopathic preparation.

Dermaren *Areu, Spain.*
⊗Dichlorisone acetate (p. 1633·3).
Skin disorders.

Dermarest *Del, USA.*
Diphenhydramine hydrochloride (p. 626·2); resorcinol (p. 1718·3).
Pruritus.

Insight, Canad.
Salicylic acid (p. 1719·1).
Psoriasis; seborrhoeic dermatitis; dandruff.

Dermarest Dri-Cort *Del, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Dermarest Plus *Del, USA.*
Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Pruritus.

Derma-Rx Lightener *Derma-Rx, Hong Kong.†*
Hydroquinone (p. 1705·1).
Hyperpigmentation.

Dermase *Sanval, Braz.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Skin infections.

Dermaseb *Cassara, Arg.*
Sulfacetamide sodium (p. 361·1).
Acne.

Dermasept Antifungal *Pharmakon, USA.*
Tannic acid (p. 2625·2); zinc chloride (p. 2126·1); benzocaine (p. 1980·2); methylbenzethonium chloride (p. 1760·3); tolnaftate (p. 596·1); undecenoic acid (p. 596·3).
Fungal skin infections.

Dermasept Plus *Germiphene, Canad.†*
Triclosan (p. 1773·2).

Dermasil
Note: this name may be used for preparations of different composition.
Rafa, Israel.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Dermasistem *Bago, Arg.*
Diosmin (p. 2505·2).

Dermaskin *Zekides, Gr.*
Metronidazole (p. 936·1).

Derma-Smoothe/FS *Hill, Canad.; Hill, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Dermasol *Olan-Kemed, Thai.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Dermasolon *Ikapharmindo, Indon.*
⊗Fluocinolone (p. 1636·1) or fluocinolone acetonide (p. 1636·1).
Skin disorders.

Dermasolutions *Novamen, Arg.†*
Caffeine (p. 1203·3); carnitine (p. 2053·2); fucus (p. 2612·1).

Dermasone
Note: this name may be used for preparations of different composition.
ICM, Singapore.
⊗Betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

Dermaspan *Bliss, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Dermaspf Sun Protect *Vital Science, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Vital Science, Canad.†
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Vital Science, Canad.†
SPF 45: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Dermaspraid Antiseptique *Bayer Sante, Fr.†*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1); benzyl alcohol (p. 1739·3).
Wound disinfection.

Dermaspraid Démangeaison *Bayer Sante, Fr.†*
⊗Hydrocortisone acetate (p. 1640·1).
Nettle and insect stings; sunburn.

Dermasten *Offenbach, Mex.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Derma-T *Alchemy, S.Afr.*
Tretinoin (p. 1725·2).

Dermatar
Note: this name may be used for preparations of different composition.
IDI, Ital.
⊗Betamethasone valero-acetate (p. 1623·2); salicylic acid (p. 1719·1); ichthammol (p. 1705·3).
Skin disorders.

Psychotropics, India.
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).

Dermatech Liquid *Dermatech, Austral.†*
⊗Alcohol (p. 1733·1); propylene glycol (p. 2205·2).
Vehicle for topical drugs.

Dermatech Wart Treatment *Dermatech, Austral.; Dermatech, Hong Kong; Dermatech, Singapore.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Dermaten
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Clotrimazole (p. 576·2).
Fungal skin infections.

Sanitas, Chile.
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Dermatin *Pfleger, Ger.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Dermatisan *EMS, Braz.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Dermatix *Valeant, Austral.; Meda, Fr.; Meda, Ger.; Invida, Hong Kong; ICN, Hung.; Transfarma, Indon.; Meda, Irl.; Inovail, Malaysia; Invida, Philipp.; Invida, Singapore; ICN, UK.*
Silicone gel (p. 2209·2).
Hypertrophic and keloid scars; wounds; burns.

Dermatix Fitocream *Valeant, Canad.†*
Wheat germ (p. 2647·1).
Burns; wounds.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dermatix Si *Valeant, Canad.†*
Silicone liquid gel (p. 2209·2).
Scars.

Dermatix Ultra *Invida, Hong Kong; Invida, Philipp.; Invida, Singapore.*
Cyclomethicone (p. 2209·2); vitamin C ester (p. 2110·3).
Keloids and hypertrophic scars.

Valeant, Canad.; Valeant, Mex.
Silicone liquid gel (p. 2209·2).
Scars.

Dermatodoron *Weleda, Austria; Weleda, Ger.; Weleda, S.Afr.†; Weleda, UK.*
Dulcamara (p. 2497·3); lysimachia nummularia.
Eczema; homoeopathic preparation; psoriasis.

Dermatofin *Technobio, Mex.*
⊗Fluocinolone (p. 1636·1); clioquinol (p. 273·1).

Dermatol
Note: this name may be used for preparations of different composition.
Aroma, Turk.
Bismuth subgallate (p. 1822·1).
Skin disorders.

Germed, Braz.
⊗Desonide (p. 1630·1).

Dermatolona *Armstrong, Mex.*
Sodium acexamate (p. 2427·3); cetrimonium bromide (p. 1742·3).
Skin irritation; minor burns and wounds.

Dermatone *Dermatone, Canad.*
Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Dermatone Lips N Face Protector *Dermatone, Canad.*
SPF 23: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Dermatone Moisturising Creme *Dermatone, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Dermatone Skin Protector *Dermatone, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Dermatonics Heel Balm *Dermatonics, UK.*
⊗Urea (p. 1727·3).
Dry skin on soles of the feet.

Dermatop *Sanofi-Aventis, Braz.; Valeant, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Thai.; Aventis, Turk.; Valeant, USA.*
⊗Prednicarbate (p. 1645·1).
Skin disorders; burns.

Dermatovate *GSK, Mex.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermatrans
Note: this name may be used for preparations of different composition.
Rottapharm, Irl.; Bayer, Ital.; Rotta, Port.; Recordati, Spain.
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Rottapharm, Chile.†
Estradiol (p. 2271·1).
Menopausal disorders.

Dermatrex *East West, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Dermaval *Morgan, Ital.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

DermaVeen *Dermatech, Austral.; Dermatech, Hong Kong†; Dermatech, NZ; Dermatech, Singapore.*
A range of skin cleansing and moisturising preparations containing colloidal oatmeal (p. 2451·1).
Dry skin; pruritus; soap-free cleanser; skin irritation.

DermaVite *GSK, USA.*
Vitamins; minerals.

Dermavite *Stiefel, Braz.*
Vitamins; minerals.

Dermavive *UAS, Singapore.*
Colloidal oatmeal (p. 2451·1); sodium pidolate (p. 1720·3).
Dry skin; skin cleansing.

Dermawell *Hovid, Hong Kong.†*
⊗Gramicidin (p. 308·3); neomycin (p. 329·3); nystatin (p. 590·3); triamcinolone (p. 1648·3).
Infected skin disorders.

Dermax
Note: this name may be used for preparations of different composition.
Fischer, Israel.
Triclosan (p. 1773·2).
Acne; eczema; heat rash; impetigo; nappy rash.

Galderma, Braz.
Sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Acne.

Reddy, S.Afr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Dermax Therapeutic Shampoo *Dermal Laboratories, UK.*
Benzalkonium chloride (p. 1737·1).
Dandruff; seborrhoea.

Dermazelaic *Germed, Braz.*
Azelaic acid (p. 1695·1).

Dermazil *Pentafarma, Port.†*
Azelaic acid (p. 1695·1).

Dermazin *Pharmascience, Canad.; Lek, Cz.†; Sandoz, Hong Kong; Lek, Hung.; Lek, Pol.†; Sandoz, Rus.; Sandoz, Thai.; Lek, Ukr.*
Sulfadiazine silver (p. 362·3).
Burns; ulcers; wounds; skin infections.

DermaZinc *Dermalogix, USA.*
Pyrithione zinc (p. 1718·1).

Dermazinc *Sivaderm, Arg.; Dermalogix, Canad.*
Pyrithione zinc (p. 1718·1).
Pityriasis.

Dermazine *Silvestre, Braz.*
Sulfadiazine silver (p. 362·3).
Bacterial skin infections; infected burns; skin ulceration.

Dermazol *Sanval, Braz.; Bailleul, Fr.; Novasorel, Ital.†*
Econazole nitrate (p. 577·3).
Fungal infections.

Dermazole
Note: this name may be used for preparations of different composition.
Hexal, S.Afr.
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Ego, Austral.†
Econazole nitrate (p. 577·3).
Fungal skin infections.

Dermazulen *Zentiva, Cz.*
Guaiazulene (p. 2523·1); chamomile oil (p. 2474·1).
Burns; skin ulcers; wounds.

Dermcasone *Bright Future, Hong Kong.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Dermec *McW, India.*
Cream: Centella (p. 1698·3); liquorice (p. 1853·2).

McW, India.
Soap: Calendula (p. 2465·2); centella (p. 1698·3); chlorhexidine gluconate (p. 1743·3).
Soap substitute.

Der-med *Permamed, Switz.*
Soap substitute.
Skin disorders.

Dermedal *Farmec, Ital.*
Tosylchloramide sodium (p. 1773·1).
Disinfection of burns and wounds; genital hygiene.

Derméol *Cooperation Pharmaceutique, Fr.*
Dodeclonium bromide (p. 1750·3); enoxolone (p. 54·2).
Skin disorders.

Dermesan *Multilab, Braz.*
Benzoyl peroxide (p. 1696·1).
Acne.

Dermestril *Madaus, Austria; Besins, Belg.; Rottapharm, Chinat†; Rottapharm, Cz.; Rottapharm, Fin.†; Rottapharm, Fr.; Madaus, Ger.; Rottapharm, Ger.; Rottapharm, Gr.; Rotta, Hong Kong†; Rottapharm, Hung.; Rottapharm, Irl.; Rottapharm, Ital.; Rottapharm, Neth.†; Delta, Port.; Rottapharm, Spain.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Dermex *Hamilton, Austral.*
Range of barrier creams.

Dermex I *Inopak, Canad.*
Chloroxylenol (p. 1748·2).

Dermexane *Cassara, Arg.*
Cream: ⊗Clobetasol propionate (p. 1627·1); ammonium lactate (p. 1694·3).
Skin disorders.

Cassara, Arg.
Ointment: ⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermexane Capilar *Cassara, Arg.*
⊗Clobetasol propionate (p. 1627·1).
Scalp disorders.

Dermeze *Aspen, Austral.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry skin; eczema.

Dermezil *Cazi, Braz.*
Zinc (p. 2126·1).

Derm-Freeze *Eagle, Austral.†*
Trichlorofluoromethane (p. 1798·2); dichlorodifluoromethane (p. 1798·2).
Pain; local anaesthesia.

Dermic
Note: this name may be used for preparations of different composition.
Roemmers, Arg.
Zinc oxide (p. 1729·1).
Skin disorders.

Kinder, Braz.†
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Acne.

Dermicil *Cipla, India.*
Chlorphenesin (p. 575·3).
Prickly heat.

Dermicin
Note: this name may be used for preparations of different composition.
Volta, Chile.
Clotrimazole (p. 576·2).
Fungal skin infections.

Dermicin B *Volta, Chile.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Fungal skin infections.

Dermicon *Bunker, Braz.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); iodine (p. 2336·3).
Fungal skin infections.

Dermi-cyl *Liebermann, Ger.†*
Calcium hydroxide solution (p. 2465·1).
Skin disorders; burns.

Dermi-cyl L Ho-Len-Complex *Liebermann, Ger.*
Apis (p. 2445·2); crotalus; graphites (p. 2522·1); hepar sulfuris (p. 1721·3); sepia (p. 2613·1); silicea (p. 2208·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Dermidex *Thornton & Ross, UK.*
Lidocaine (p. 1988·1); alcloxa (p. 1692·2); chlorobutanol (p. 1747·2); cetrimide (p. 1742·1).
Skin irritation.

Dermifun *Teva, Mex.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Dermikolin *Aventis, Turk.*
Ointment: Nitrofurazone (p. 333·1).
Skin infections.

Aventis, Turk.
Topical powder: Bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1); boric acid (p. 2459·3); aluminium hydroxide (p. 1817·2).
Skin disorders.

Dermil
Note: this name may be used for preparations of different composition.
Hypermarcas, Braz.
Colecalciferol (p. 2113·1); vitamin A (p. 2098·3); zinc (p. 2126·1).

Dermilia Flebozin *Medifarma, Ital.†*
Zinc oxide (p. 1729·1); myrtillus (p. 2566·2); echinacea (p. 2498·1); hamamelis (p. 2523·3); melilot (p. 2552·3); centella (p. 1698·3).
Tired legs.

Dermilon *Caesaro, Austria.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Skin disorders.

Dermin
Note: this name may be used for preparations of different composition.
Bal, India.
Benzyl benzoate (p. 2149·1).

Fahrvitex, Hung.
Chamomile oil (p. 2474·1); zinc oxide (p. 1729·1).
Burns; inflammatory skin disorders; soft-tissue injury.

Dermine *Instantron, Canad.†*
Benzocaine (p. 1980·2).
Local anaesthesia.

Derminiol *Marvecs, Ital.; Schwabe, Spain.†*
Hamamelis (p. 2523·3).
Superficial skin lesions and burns; inflammation of skin and mucous membranes; skin irritation.

Derminoin *Med-One, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Derminol *Micro, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2); clioquinol (p. 273·1).
Infected skin disorders.

Derm'Intim *A-Derma, Fr.*
⊗Avena (p. 2451·1); glycine (p. 2071·2); glycerol (p. 2517·2).
Personal hygiene.

Dermirit *Morgan, Ital.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Dermisan *Armoxindo, Indon.*
Hexachlorophene (p. 1754·1).
Skin disinfection.

Dermisol *Albephar, Venez.*
⊗Urea (p. 1727·3).

Dermisone Epitelizante *Novartis Consumer, Spain.†*
Amino acids; chloramphenicol (p. 257·1); vitamin A palmitate (p. 2098·3); vitamin F (p. 2509·2).
Wound healing.

Dermisone Tri Antibiotic *Novartis Consumer, Spain.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Skin infections.

Dermithan *Sanofi-Aventis, Arg.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2).
Formerly contained calamine, diphenhydramine, camphorated phenol, and salol.
Pruritus; skin irritation.

Dermithan Incoloro *Sanofi-Aventis, Arg.*
Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1).
Pruritus; skin irritation.

Dermitina *Donini, Ital.*
Hamamelis (p. 2523·3); sodium glutamate (p. 2198·2); fatty acids.
Soap substitute.

Dermitop *Cadila, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); clioquinol (p. 273·1); tolnaftate (p. 596·1).
Infected skin disorders.

Dermitrat *Vitapan, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Dermizan *Bunker, Braz.*
Azelaic acid (p. 1695·1).
Acne.

Dermizin *Gerolymatas, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Dermizol *Roux-Ocefa, Arg.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Dermizol G *Roux-Ocefa, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Dermizol Trio *Roux-Ocefa, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Dermizole *Community Pharmacy, Thai.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections; vaginal trichomoniasis.

Derm-Keta *Galantica, India.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Dermklobal *Nepentes, Pol.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermo *APT, Hong Kong.†*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermo 6 *Pharmadeveloppement, Fr.*
Pyridoxine hydrochloride (p. 2105·3).
Seborrhoea.

Dermo Bell
Note: this name may be used for preparations of different composition.
Remexa, Mex.
Arachis oil (p. 2446·1).
Skin disorders.

Dermo H Infantil *Novartis Consumer, Spain.†*
Dimeticone (p. 2209·3); benzalkonium chloride (p. 1737·1); vitamin A (p. 2098·3); zinc oxide (p. 1729·1).
Burns; skin disorders; wounds.

Dermo Hubber *Teofarma, Spain.*
⊗Bacitracin zinc (p. 225·3); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dermo Quinol *East India Pharma, India.*
Clioquinol (p. 273·1).
Fungal skin infections.

Dermo Silanols *Sedifa, Mon.*
A range of preparations containing silicones (p. 2209·2).
Skin disorders.

Dermo Vagisil Crema *Combe, Arg.*
Benzocaine (p. 1980·2); resorcinol (p. 1718·3).
Vaginal irritation.

Dermobacter *Innotech, Fr.; Innotech, Hong Kong.*
Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3).
Bacterial skin infections; skin and mucous membrane disinfection.

Dermoban *Cazi, Braz.*
Mupirocin (p. 327·2).

Dermobarrina *Reccius, Chile.*
Cream: Resorcinol (p. 1718·3).

Reccius, Chile.
Lotion: Benzalkonium chloride (p. 1737·1); menthol (p. 2553·2).

Dermobene *Legrand, Braz.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Dermobeta
Note: this name may be used for preparations of different composition.
Medichrom, Gr.
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Dermobiosa *IQFA, Mex.*
Lassar's paste.

Dermobras *Remexa, Mex.*
Aluminium oxide (p. 1690·3); triclosan (p. 1773·2).
Skin cleansing.

Dermocare *Darier, Mex.*
Resorcinol (p. 1718·3); calamine (p. 1697·2).
Acne; seborrhoea.

Dermochrom *Medichrom, Gr.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dermocinetic *Geymonat, Ital.*
Levothyroxine sodium (p. 2339·1); aescin (p. 2431·2).
Local build up of adipose tissue; cellulite.

Dermocitran *Imvi, Arg.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Dermocort
Note: this name may be used for preparations of different composition.
Unipharma, Gr.
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Dermocortal *SIT, Ital.*
⊗Hydrocortisone (p. 1640·1).
Insect stings; pruritus; erythema; burns; eczema.

Dermocorte
Note: this name may be used for preparations of different composition.
EMS, Braz.
⊗Ketoconazole (p. 585·3); betamethasone (p. 1623·2).

Dermocrat Plus *Cratus, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3); zinc sulfate (p. 2126·2).
Infected skin disorders.

Dermocrem *Ache, Braz.†*
Wheat germ (p. 2647·1).
Wounds.

Dermocridin *Neo Dermos, Arg.*
Lactic acid (p. 2539·1); menthol (p. 2553·2); panthenol (p. 2582·2); vegetable extracts.
Seborrhoeic dermatitis.

Dermocuivre *Chauvin, Fr.*
Copper sulfate (p. 2057·2); zinc oxide (p. 1729·1).
Skin disorders.

Dermodan *ITF, Chile.*
Tretinoin (p. 1725·2).
Acne; light-induced skin damage.

Dermodan Plus *ITF, Chile.*
Erythromycin (p. 291·2); tretinoin (p. 1725·2).
Acne.

Dermoden *Cifarma, Braz.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Skin disorders.

Dermodex *BMS, Braz.*
Zinc oxide (p. 1729·1); nystatin (p. 590·3).
Infected skin disorders.

Dermodex Prevent *BMS, Braz.*
Zinc oxide (p. 1729·1).

Dermo-Drainol *Boiron, Fr.†*
Carbo ligni officinal (p. 1537·3); dolichos pruriens; arsenicum album (p. 2448·1); apis mellifica (p. 2445·2); rhus vernix; solanum dulcamara (p. 2497·3); causticum (p. 2595·3); petroleum (p. 2587·2); oleander (p. 2574·3); silicea (p. 2208·3).
Homoeopathic preparation.

Dermodrin *Montavit, Austria; Montavit, Ukr.*
Diphenhydramine hydrochloride (p. 626·2).
Skin disorders.

Dermofenac *Pfizer Sante, Fr.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Dermofix *Darya-Varia, Indon.†; Ferrer, Indon.†; Azevedos, Port.; Ferrer, Spain.*
Sertaconazole nitrate (p. 593·2).
Vulvovaginal candidiasis; fungal skin, scalp, and nail infections.

Dermofug *Wolff, Cz.†*
Dodecylbenzenesulfonic acid; ammonium laurilsulfate (p. 2210·3).
Acne; fungal skin infections; seborrhoeic dermatitis.

Dermogard *Indi, India.*
Cream: Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).
Cuts; burns; wounds; bacterial skin infections.

Indi, India.
Topical liquid: Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection; wound cleansing.

Dermogen
Note: this name may be used for preparations of different composition.
Generics, Pol.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Xepa-Soul Pattinson, Singapore.
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Dermoil *Dermofarma, Ital.*
Emollient.
Bath additive; dry skin disorders.

Dermojela *Jean-Marie, Hong Kong.*
Choline salicylate (p. 39·2); benzalkonium chloride (p. 1737·1); menthol (p. 2553·2).
Mouth disorders.

Dermojuventus *Juventus, Spain.†*
Tretinoin (p. 1725·2).
Acne; sunlight-induced skin damage.

Dermokin *Kinder, Braz.†*
Zinc oxide (p. 1729·1); nystatin (p. 590·3).
Skin disorders.

Dermol *Adelco, Gr.*
⊗Prednisolone (p. 1645·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dermal Laboratories, UK.
Benzalkonium chloride (p. 1737·1); chlorhexidine hydrochloride (p. 1743·3); liquid paraffin (p. 2191·2); isopropyl myristate (p. 2190·3).
Dry and pruritic skin disorders.

Mylan, NZ.
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Dermol HC *Dermol, USA.*
⊗Hydrocortisone (p. 1640·1).

Dermolantyl *Chrispa (Χρισπα), Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Dermolate
Note: this name may be used for preparations of different composition.
Adelco, Gr.
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Schering-Plough, USA.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Dermolimp *Belfar, Braz.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).

Dermolin
Note: this name may be used for preparations of different composition.
Lafare, Ital.
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Roberts, USA.
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); mustard oil (p. 2646·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Dermomox *Biosintetico, Braz.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Dermomega *Madaus, Arg.*
Avena (p. 2451·1); sage oil (p. 2609·1).

Dermomycin
Note: this name may be used for preparations of different composition.
Avantgarde, Ital.
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Dermomycin Cort *Avantgarde, Ital.*
⊗Triamcinolone benetonide (p. 1648·3); fusidic acid (p. 302·1).
Inflammatory skin disorders with infection.

Dermomycose Liquido *Reig Jofre, Spain.*
Boric acid (p. 2459·3); phenol (p. 1763·3); rosaniline; resorcinol (p. 1718·3).
Fungal skin infections.

Dermomycose Talco *Reig Jofre, Spain.†*
Neomycin undecenoate (p. 330·1); menthol (p. 2553·2).
Skin infections.

Dermon *Unison, Hong Kong; Unison, Malaysia.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Unison, Thai.†
Miconazole (p. 588·3).
Fungal infections of skin, mucous membranes, and nails.

Dermonit *Nitin, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Dermonorm *GSK, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Dermopan *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Medifarm A-Derm, Venez.*
Avena (p. 2451·1).
Soap substitute; skin cleansing; skin disorders.

Dermopanten *Chema-Elektromet, Pol.*
Dexpanthenol (p. 2582·2).
Skin and mucous membrane disorders; wounds.

Dermoper *Raymos, Arg.*
Permethrin (p. 2159·3).
Scabies.

Dermoper IV *Raymos, Arg.*
Ivermectin (p. 155·1).
Onchocerciasis; strongyloidiasis; scabies.

Dermoperative *Giscard, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2); ketoconazole (p. 585·3).
Infected skin disorders.

Dermopero *Defuen, Arg.*
Ivermectin (p. 155·1).
Onchocerciasis; strongyloidiasis; scabies.

Dermophenazol *Polfa Warszawa, Pol.*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Insect bites and stings.

Dermophil Indien
Note: this name may be used for preparations of different composition.
Dermophil Indien, Fr.; Melisana, Switz.
Peru balsam (p. 2587·1); levomenol (p. 2544·1); salol (p. 129·3).
Emollient.

Dermoplast
Note: this name may be used for preparations of different composition.
Medtech, USA.
Benzocaine (p. 1980·2).
Painful conditions of the skin and perineum.

Remexa, Mex.
⊗Urea (p. 1727·3).
Dry skin disorders.

Medtech, Canad.†
Benzocaine (p. 1980·2); menthol (p. 2553·2).

Dermoplast Antibacterial *Medtech, USA.*
Benzocaine (p. 1980·2); benzethonium chloride (p. 1738·1).
Local anaesthesia.

Dermoplast Poison Ivy Treatment *Medtech, Canad.*
Pramocaine hydrochloride (p. 1993·3).

Dermoplex Antifungal *CCM, Malaysia.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Dermoplex Antiseptic *CCM, Malaysia.*
Cetrimide (p. 1742·1).
Insect bites and stings; minor wounds and burns; nappy rash.

Dermoplex Calamine *CCM, Malaysia.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Insect bites; nappy rash; skin irritation; sunburn.

Dermopur *Pralab, Pol.*
Benzocaine (p. 1980·2); zinc oxide (p. 1729·1); menthol (p. 2553·2).
Skin disorders.

Dermorapid *Remington, Canad.†*
Isopropyl alcohol (p. 1758·3).

Dermorax *Vickmans, Hong Kong.†*
Crotamiton (p. 1699·2).

Dermorelle *IPRAD, Fr.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Dermo-Rest *Eczacibasi, Turk.*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Dermosa Aureomicina *Teofarma, Spain.*
Chlortetracycline hydrochloride (p. 260·2).
Skin infections.

Dermosa Hidrocortisona *Teofarma, Spain.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Dermosalic *Bunker, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Dermosan *Lafedar, Arg.†*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); benzocaine (p. 1980·2); zinc oxide (p. 1729·1).
Skin disorders.

Dermosavit *Coel, Pol.*
Vitamin A (p. 2098·3).
Skin disorders.

Dermoscalp *Remexa, Mex.*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2); resorcinol (p. 1718·3).
Dandruff.

Dermoseptic *Ferrer, Spain.*
Sertaconazole nitrate (p. 593·2).
Fungal skin, scalp, and nail infections.

Dermosol
Note: this name may be used for preparations of different composition.
Psychotropics, India.
Precipitated sulfur (p. 1721·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

YSP, Malaysia; Zyg, Philipp.; Yung Shin, Singapore.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermosolon
Note: this name may be used for preparations of different composition.
Dermapharm, Ger.
⊗Prednisolone (p. 1645·2).
Corticosteroid.
Gedeon Richter, Rus.; Gedeon Richter, Ukr.†
⊗Clioquinol (p. 273·1); prednisolone (p. 1645·2).
Infected skin disorders.

Dermosona
Note: this name may be used for preparations of different composition.
Fecofar, Arg.
⊗Miconazole (p. 588·3); betamethasone valerate (p. 1624·1); gentamicin (p. 304·2).
Infected skin disorders.
Saval, Chile.
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Dermostatin *Legrand, Braz.*
Nystatin (p. 590·3); zinc (p. 2126·1).

Dermo-Sulfuryl *Legras, Fr.*
Precipitated sulfur (p. 1721·1); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Acne.

Dermosupril *Roemmers Medihe, Venez.*
⊗Desonide (p. 1630·1).
Skin disorders.

Dermosupril C *Roemmers Medihe, Venez.*
⊗Desonide (p. 1630·1); clioquinol (p. 273·1).
Infected skin disorders.

Dermotel *Intel, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1); neomycin (p. 329·3).
Infected skin disorders.

DermOtic *Hill, Canad.; Hill, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Otitis externa.

Dermotil *Glenmark, Braz.*
⊗Mometasone furoate (p. 1644·1).

Dermotin A *Remexa, Mex.*
Vitamin A palmitate (p. 2098·3).
Skin disorders.

Dermotivin *Galderma, Braz.; Galderma, Chile; Galderma, Venez.*
Soap substitute.
Seborrhoea.

Dermotrex *East West, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Dermotriad *Fem Care, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Dermo-Trimazen *Multilab, Braz.*
Clotrimazole (p. 576·2).

Dermotrizol *Belfar, Braz.*
Clotrimazole (p. 576·2).

Dermo-Trosyd *Pfizer, Turk.*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Dermotyl *Hetero, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermotyl-M *Hetero, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).
Fungal skin infections.

Dermovagisil *Combe, Spain.*
Lidocaine (p. 1988·1).
Vaginal disorders.

Dermoval
Note: this name may be used for preparations of different composition.
GSK, Fr.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.
Tocogino, Mex.
⊗Betamethasone (p. 1623·2).
Skin disorders.

Dermovan *Healthpoint, USA.*
Vehicle for topical preparations.

Dermovat
Note: this name may be used for preparations of different composition.
GSK, Denm.; GSK, Fin.; GSK, Norw.; GSK, Swed.
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Dermovate
Note: this name may be used for preparations of different composition.
GSK, Austria; GSK, Belg.; Taro, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Neth.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; Sekpharma, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, Venez.
⊗Clobetasol propionate (p. 1627·1).
Skin and scalp disorders.

Dermovate-NN *GSK, Philipp.; Chemidex, UK.†*
⊗Clobetasol propionate (p. 1627·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Skin disorders with bacterial or fungal infection.

Dermovel *Ferron, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Dermovit A *Coel, Pol.*
Vitamin A (p. 2098·3).
Wounds; burns; chilblains.

Dermovit E *Coel, Pol.*
Vitamin E (p. 2119·1).
Varicose ulcer.

Dermovit F *Coel, Pol.*
Vitamin F (p. 2509·2).
Skin disorders.

Dermovitamina *Pasquali, Ital.*
Cod-liver oil (p. 2056·3).
Skin disorders.

Dermowas *Wolff, Ger.*
Dodecylbenzolsulfonic acid trolamine; ammonium laurilsulfate (p. 2210·3).
Skin disorders.

Dermowel *Bright Future, Hong Kong.†*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Dermowin-GM *Wings, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Dermowund *Adler, Austria.†*
Acriflavinium chloride (p. 1732·3); diacetylaminoazotoluene (p. 1749·3); cod-liver oil (p. 2056·3); linseed oil (p. 2544·2); sodium propionate (p. 593·1); zinc oxide (p. 1729·1).
Wounds.

Dermox *Remexa, Mex.*
Methoxsalen (p. 1711·3).
Vitiligo; psoriasis.

Dermoxin
Note: this name may be used for preparations of different composition.
GSK, Ger.; Stiefel, Ger.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.
Bunker, Braz.†
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Skin disorders.

Dermoxinale *GSK, Ger.; Stiefel, Ger.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dermoxyl
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.
Sinclair, Ital.
Urea hydrogen peroxide (p. 1774·2).
Skin disinfection and cleansing.

Dermoys *Percos, India.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).

Derms *Uniao Quimica, Braz.*
Tiabendazole (p. 166·3); neomycin sulfate (p. 330·1).
Skin infections.

Derm's *LDA, Arg.*
Ciclopirox (p. 575·3); salicylic acid (p. 1719·1).
Dandruff; seborrhoeic dermatitis.

Dermtex HC with Aloe *Pfeiffer, USA.*
⊗Hydrocortisone (p. 1640·1); aloe vera (p. 1693·2).
Skin disorders.

Dermtone *BMW, India.*
Trioxysalen (p. 1727·2).

Dermucor-H *Advaita, Mex.*
⊗Mupirocin (p. 327·2); hydrocortisone (p. 1640·1).
Infected skin disorders.

Dermuspray *Warner Chilcott, USA.*
⊗Trypsin (p. 2635·2); peru balsam (p. 2587·1); castor oil (p. 2472·1).
Wounds.

Dermvien *Hautel, Arg.*
Aloe vera (p. 1693·2); panthenol (p. 2582·2).
Dry skin.

Dermyc *Teva, Hung.*
Fluconazole (p. 578·2).
Fungal infections.

Dermylex *Tabbest Busindo, Indon.*
Milk protein (p. 2125·2).
Psoriasis.

Dernilan *Herbapol Wroclaw, Pol.*
Camphor (p. 2466·2); allantoin (p. 1693·1); nicotinamide (p. 2083·1); salicylic acid (p. 1719·1).
Keratinisation disorders.

Derobin *GSK, India.*
Dithranol (p. 1701·2); salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Skin disorders.

Derobin-HC *GSK, India.*
⊗Coal tar (p. 1723·2); dithranol (p. 1701·2); hydrocortisone (p. 1640·1); salicylic acid (p. 1719·1).

Deroctyl *Gap, Gr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Deroidal *Amnol, Ital.*
Diosmin (p. 2505·2); grape (p. 2521·3); melilot (p. 2552·3); zinc (p. 2126·1); vitamins.
Circulatory disorders.

Deroser *Serral, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Derox
Note: this name may be used for preparations of different composition.
DWD, India.
Roxithromycin (p. 356·2).
Bacterial infections.
Hovid, Hong Kong; Hovid, Philipp.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Deroxat *GSK, Fr.; GSK, Switz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic attacks; social phobia; anxiety; post-traumatic stress disorder.

Derozin *Gap, Gr.*
Cinnarizine (p. 622·1).
Vertigo.

Derrumal *Finadiet, Arg.*
Avocado (p. 2451·2); soya (p. 2092·3).
Periodontal disease; osteoarthritis.

Dershine *East West, India.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).

Dersindol *Dermogen, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Dersol *East West, India.*
Salicylic acid (p. 1719·1).
Hyperkeratotic and scaling skin disorders; acne.

Dersupril *Medihealth, Mex.*
⊗Desonide (p. 1630·1).
Skin disorders.

Dersy *Worth, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dersy-AP *Worth, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dertec *Millimed, Thai.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Dertrase *Salvat, Spain.*
⊗Carbamoylglutamic acid; inositol (p. 2533·2); methionine (p. 1558·2); chymotrypsin (p. 2477·3); ribonucleic acid (p. 2604·1); trypsin (p. 2635·2); nitrofurazone (p. 333·1).
Wounds; ulcers; burns; skin disorders.

Dertrin *IQFA, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Derusil *Loeffler, Mex.*
Itraconazole (p. 583·3).
Fungal skin and vaginal infections.

Dervanol *Kurtsan, Turk.*
Bismuth subgallate (p. 1822·1); ethacridine lactate (p. 1732·3); tetracaine hydrochloride (p. 1996·3); aluminium hydroxide (p. 1817·2).
Skin disorders; wounds.

Dervin *Boniscontro & Gazzone, Ital.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Derzid *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Derzid-C *Unison, Hong Kong; Unison, Thai.*
⊗Betamethasone valerate (p. 1624·1); clotrimazole (p. 576·2).
Skin disorders with fungal infection.

Derzid-N *Unison, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Desaflu *Copernico, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic respiratory-tract disorders.

Desagreg *Eurofarma, Braz.*
Ticlopidine hydrochloride (p. 1512·1).

Desal *Biofarma, Turk.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Desaler *Fortbenton, Arg.*
Desloratadine (p. 625·1).

Desaler Cort *Fortbenton, Arg.*
⊗Desloratadine (p. 625·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Desalex *Mantecorp, Braz.; Schering-Plough, Venez.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Desalfa *INTES, Ital.*
Cream: ⊗Dexamethasone isonicotinate (p. 1631·1); lidocaine hydrochloride (p. 1988·2).
Skin disorders; haemorrhoids.
INTES, Ital.
Nasal/ear drops: ⊗Dexamethasone isonicotinate (p. 1631·1); neomycin sulfate (p. 330·1).
Nasal and ear infections.
INTES, Ital.†
Eye ointment: ⊗Dexamethasone isonicotinate (p. 1631·1); phenylephrine hydrochloride (p. 1672·3); neomycin (p. 329·3).
Eye disorders.

Desamix Effe *Savoma, Ital.*
⊗Dexamethasone (p. 1630·3); clotrimazole (p. 576·2).
Infected skin disorders.

Desamix-Neomicina *Savoma, Ital.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Skin disorders.

Desamon *Streuli, Switz.*
Didecyldimethylammonium chloride (p. 1750·3); isopropyl alcohol (p. 1758·3).
Disinfection of instruments, clothing, hands, skin, and mucous membranes.

Desarell *Sanorell, Ger.*
Apis mellifica (p. 2445·2); acidum formicicum (p. 2507·1); galphimia glauca; cardiospermum halicacabum.
Homoeopathic preparation.

Desarrol *Faes, Spain.*
Cyproheptadine hydrochloride (p. 624·1); amino acids.
Tonic.

Desatax *Shreya, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Desaway *Aspen, S.Afr.*
Desloratadine (p. 625·1).
Allergic rhinitis.

Desay *Medirex, Port.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Descodrin *Arrow, Braz.*
Sodium chloride (p. 1795·1).

Descon
Note: this name may be used for preparations of different composition.
Farmasa, Braz.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Descutan *Fresenius Kabi, Swed.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Desdek
Note: this name may be used for preparations of different composition.
Edol, Port.
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Desderman
Note: this name may be used for preparations of different composition.
Schulke & Mayr, Singapore.
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3); orthophenylphenol (p. 1762·3).
Hand disinfection.

Desdol *Medipharm, Chile.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Musculoskeletal spasm.

Desec *TO-Chemicals, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux, Zollinger-Ellison syndrome.

Desefin *Deva, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Deselex *Schering-Plough, S.Afr.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Desenex *Novartis Consumer, Canad.†; Clonmel, Irl.*
Zinc undecenoate (p. 596·3); undecenoic acid (p. 596·3).
Fungal skin infections.

Novartis Consumer, USA.
Cream; foam; ointment; powder; soap; spray powder: Undecenoic acid (p. 596·3) and/or zinc undecenoate (p. 596·3).
Fungal skin infections; minor skin disorders.

Desenex Liquid Spray *Novartis Consumer, USA.†*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Desenex Powder *Novartis, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

DesenexMax *Novartis, USA.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Desenfriol *Schering-Plough, Arg.*
Aspirin (p. 22·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Desenfriol C *MSD, Spain.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Fever; nasal congestion; pain.

Desenfriol D
Note: this name may be used for preparations of different composition.
MSD, Spain.†
Aspirin (p. 22·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Fever; nasal congestion; pain.

Desenfriol Decongestivo *Schering-Plough, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Desenfriolito *Schering-Plough, Arg.*
Aspirin (p. 22·2).
Cold and influenza symptoms.

Desenfriol-Ito Plus *Schering-Plough, Mex.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; cold symptoms.

Desensilium *Biokosma, Fr.†*
Quail's eggs.
Allergic disorders.

Desensyl *Gador, Arg.*
Sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3).
Sensitive teeth.

Desent *Indoco, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Desentol *Meda, Swed.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Desept *Elvipe, Gr.*
Domiphen bromide (p. 1751·1).

Deserein *Medilat, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Deseril *Link, Austral.; Pharma Logistics, Belg.; Amdipharm, Neth.; Alliance, UK.†*
Methysergide maleate (p. 677·1).
Migraine and other vascular headaches; diarrhoea associated with carcinoid disease; cluster headache.

Deserila *Novartis, Braz.*
Methysergide maleate (p. 677·1).
Migraine.

Désernil *CSP, Fr.*
Methysergide maleate (p. 677·1).
Migraine; vascular facial pain.

Desert Pure Calcium *Cal-White, USA.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).

Desfatigan
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
Calcium pangamate (p. 2582·1).

Desferal *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; LPB, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Desferrioxamine mesilate (p. 1544·1).
Aluminium overload; iron overload; iron poisoning.

Desféral *Novartis, Fr.*
Desferrioxamine mesilate (p. 1544·1).
Iron overload; aluminium overload.

Desferin *Europharma, Denm.; Orifarm, Denm.; Padro, Spain.*
Desferrioxamine mesilate (p. 1544·1).
Iron overload; aluminium overload.

Desflam *Merck, Mex.*
Bumadizone calcium (p. 30·2).
Inflammation; peri-articular and soft-tissue disorders.

Desflor *DR Johns, India.*
⊗Potassium nitrate (p. 1766·2).

Desfrin *Uniao Quimica, Braz.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Desgras *Argenfarma, Arg.*
Guar (p. 475·1); fucus (p. 2612·1); phenylalanine (p. 2086·1); ascorbic acid (p. 2110·3); pyridoxine (p. 2105·3).
Slimming aid.

Desgras Burner Fat *Argenfarma, Arg.*
Dietary fibre; inositol (p. 2533·2); amino acids; levocarnitine (p. 2053·2); garcinia (p. 2510·2); ascorbic acid (p. 2110·3); potassium gluconate (p. 1793·2).
Slimming aid.

Desgras Complex *Argenfarma, Arg.*
Guar (p. 475·1); fucus (p. 2612·1); amino acids; guarana (p. 2648·2); ascorbic acid (p. 2110·3); taraxacum (p. 2625·3); potassium gluconate (p. 1793·2).
Slimming aid.

Desgras Piel Naranja *Argenfarma, Arg.*
Centella (p. 1698·3); citrus flavonoids (p. 2505·2); ginkgo biloba (p. 2512·3); inositol (p. 2533·2); ubidecarenone (p. 2637·1).
Cellulite.

Desicol *Pfizer, Chile.†*
Pig bile (p. 2457·2).
Biliary-tract disorders; adjuvant in absorption of fat-soluble vitamins.

Desihex *SM, Venez.*
Soap substitute.

Desiken *Kendrick, Mex.*
Ribavirin (p. 1010·2).
Viral infections.

Desinax *Tecnimede, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; mixed anxiety-depressive states; social phobia.

Desinobon *Alvogen, Neth.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy.

Désintex *Richard, Fr.*
Sodium thiosulfate (p. 1576·1); magnesium thiosulfate (p. 1576·1).
Rhinitis; rhinopharyngitis; dyspepsia.

Désintex Infantile *Richard, Fr.†*
Sodium thiosulfate (p. 1576·1); magnesium thiosulfate (p. 1576·1); calcium gluconate (p. 1783·3); calcium carbonate (p. 1824·3).
Dyspepsia; rhinitis; rhinopharyngitis.

Désintex-Choline *Richard, Fr.†*
Sodium thiosulfate (p. 1576·1); magnesium thiosulfate (p. 1576·1); choline chloride (p. 2055·2).
Dyspepsia.

Desinvag *Casen Fleet, Spain.†*
Benzalkonium chloride (p. 1737·1); furazolidone (p. 933·3).
Vaginal antiseptic; vulvovaginal trichomoniasis.

Desipram *Assos, Turk.*
Desipramine (p. 413·1).

Desirel *Codal Synto, Thai.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety.

Desitin *Sigmapharm, Austria; Johnson & Johnson, Canad.; Johnson & Johnson, Chile; Pfizer, Hong Kong†; Pfizer, Israel; Johnson & Johnson Consumer, Mex.; Johnson & Johnson, USA.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Burns; wounds; nappy rash; skin irritation.

Johnson & Johnson, Philipp.; Pfizer, Rus.; Johnson & Johnson, Singapore; Pfizer, Ukr.
Zinc oxide (p. 1729·1).
Nappy rash; minor burns and cuts.

Desitin Clear *Pfizer, USA.*
Barrier preparation.
Nappy rash.

Desitin Creamy
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Chile.
Zinc oxide (p. 1729·1).
Nappy rash.

Johnson & Johnson, Singapore.
Zinc oxide (p. 1729·1); aloe vera (p. 1693·2); vitamin E (p. 2119·1).
Nappy rash.

Pfizer, USA.
Zinc oxide (p. 1729·1); liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Formerly known as Daily Care.
Nappy rash.

Desitin Nappy Rash Ointment *Johnson & Johnson, Austral.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Nappy rash.

Desitin with Zinc Oxide *Pfizer, USA.*
Corn starch (p. 2095·1); zinc oxide (p. 1729·1).

Desitrend *Desitin, UK.*
Levetiracetam (p. 531·1).
Epilepsy.

Deskan *Baxter, Gr.*
Minerals; trace elements.
Parenteral nutrition.

Desketo *Malesci, Ital.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Recalcine, Chile.
Dexketoprofen (p. 79·1).
Pain.

Deslanol *Uniao Quimica, Braz.*
Deslanoside (p. 1351·2).

Deslo *Ahimsa, Arg.*
Desloratadine (p. 625·1).

Deslocross *Pharmacross, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis.

Deslor *Sun, India.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Deslorana *Legrand, Braz.*
Desloratadine (p. 625·1).

Deslorasam *Samuel, Neth.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Deslorat *Oftalmi, Venez.*
Desloratadine (p. 625·1).
Allergic rhinitis; asthma; allergic skin disorders.

Desloriv *East African, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Desmenat *Kleva, Gr.*
Sulpiride (p. 1107·3).

Desmin *Gedeon Richter, Ger.; Farmaceutica H, Mex.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Combined oral contraceptive.

Desmo-C *Swedpharm, Chile.*
⊗Desmopressin acetate (p. 2355·1).
Nocturnal enuresis; diabetes insipidus.

Desmogalen *Galen, Ger.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; test of renal concentrating capacity; nocturnal enuresis.

Desmoham *Medis, Denm.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

DesmoMelt *2care4, Denm.; Europharma, Denm.; Orifarm, Denm.; Ferring, UK.*
⊗Desmopressin (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

Desmopal *Medis, Denm.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

Desmopress *Ferring, Hung.†*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis.

Desmoprol *Proel, Gr.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; haemorrhagic disorders.

Desmospray *Ferring, Cz.†; Medice, Ger.; Ferring, Irl.; Ferring, Port.; Ferring, UK.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; test of renal concentrating capacity; nocturia associated with multiple sclerosis; nocturnal enuresis; polyuria.

Desmotabs *Ferring, Cz.†; Medice, Ger.; Ferring, Irl.; Ferring, UK.*
⊗Desmopressin acetate (p. 2355·1).
Nocturnal enuresis; diabetes insipidus; polyuria; polydipsia; nocturia.

Desmovital *Er-Kim, Turk.*
⊗Desmopressin acetate (p. 2355·1).

Desnisol *Kener, Mex.*
⊗Prednisolone (p. 1645·2).
Inflammatory eye disorders.

Desnova *Morepen, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Desobel *Effik, Fr.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Desobesi-M *Ache, Braz.*
⊗Fenproporex hydrochloride (p. 2323·1).
Obesity.

Desocort
Note: this name may be used for preparations of different composition.
Galderma, Canad.
⊗Desonide (p. 1630·1).
Skin disorders.

Des-OD *Cadila, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Desodene *Reddy, S.Afr.*
Desloratadine (p. 625·1).
Allergic rhinitis.

Desogen
Note: this name may be used for preparations of different composition.
Organon, USA.
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Desol *Geno, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); turpentine oil (p. 2636·3); paradichlorobenzene (p. 2583·2).
Formerly contained docusate sodium.
Ear wax removal.

Desolett *MSD, Swed.; Organon, Turk.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Desolex *Surya Dermato, Indon.*
⊗Desonide (p. 1630·1).
Skin disorders.

Desolex-N *Surya Dermato, Indon.*
⊗Desonide (p. 1630·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Desolon *Christo, Hong Kong.†*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Desomedine *Bausch & Lomb, Belg.; Bausch & Lomb, Singapore; Chauvin, Singapore.*
Hexamidine isetionate (p. 1754·3).
Eye infections.

Désomédine *Chauvin, Fr.; Bausch & Lomb, Switz.*
Eye drops; nose drops: Hexamidine isetionate (p. 1754·3).
Infections of the eye or nose.

Chauvin, Fr.
Mouthwash: Chlorhexidine gluconate (p. 1743·3); oxybuprocaine hydrochloride (p. 1993·2).
Mouth and throat disorders.

Desomex *Konimex, Indon.†*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Deson *Unison, Hong Kong; Unison, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Desonate *Bayer, USA.*
⊗Desonide (p. 1630·1).
Skin disorders.

Desonax *LPB, Ital.*
⊗Budesonide (p. 1625·1).
Asthma.

Desonil *Gap, Gr.*
Cisapride (p. 1831·3).

Desonix
Note: this name may be used for preparations of different composition.
Sandoz, Swed.
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.

Desonol *Medley, Braz.*
⊗Desonide (p. 1630·1).
Skin disorders.

Desopan *Mochida, Jpn.*
Trilostane (p. 2634·1).
Adrenocortical suppressant.

Desoplus *Lagos, Arg.*
⊗Desonide (p. 1630·1).
Skin disorders.

Desorate *Pond's, Thai.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Desorelle *Medimpex, Belg.†; Sandoz, Denm.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Desoren
Note: this name may be used for preparations of different composition.
Grunenthal, Chile; Grunenthal, Switz.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Vitamed, Israel.
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Ear infections.

Desorus *Cipla, Ukr.†*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Desotap *Novo Pharm, Philipp.†*
Phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; rhinitis; sinusitis.

DesOwen *Galderma, Arg.; Galderma, Austral.; Galderma, Chile; Galderma, China; Galderma, Hong Kong; Galderma, India; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Galderma, USA; Galderma, Venez.*
⊗Desonide (p. 1630·1).
Skin disorders.

Desoxi *Taro, Canad.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Desoxil *Boniscontro & Gazzone, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary disorders.

Desoxyn *Lundbeck, USA.*
⊗Metamfetamine hydrochloride (p. 2324·2).
Attention deficit hyperactivity disorder; obesity.

Despacilina *BMS, Braz.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Despamen *Carnot, Mex.*
⊗Estradiol valerate (p. 2271·2); testosterone enantate (p. 2305·1).
Menopausal disorders; osteoporosis.

Despec NR *International Ethical, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Despec PDC *International Ethical, USA.*
Dihydrocodeine tartrate (p. 52·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Despec-EXP *International Ethical, USA.†*
⊗Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Despec-Tab *International Ethical, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Despeval *Saval, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Despex
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Despigmental *Centrum, Spain.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Despigmentante *Dermoteca, Port.†*
Lactic acid (p. 2539·1); kojic acid (p. 1710·2); enoxolone (p. 54·2); arbutin (p. 1694·3).
Skin hyperpigmentation.

Despol *Geno, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).

Despra *Glenmark, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Desprazole *Medihealth, India.*
Dexrabeprazole sodium (p. 1881·1).

Des-Press *Biodeal, India.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; renal function testing; nocturnal enuresis; von Willebrand's disease; nocturia in multiple sclerosis.

Desquam *Westwood-Squibb, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Desquaman *Hermal, Austria; Olvos, Gr.; Hermal, Israel.*
Pyrithione zinc (p. 1718·1).
Scalp infections; seborrhoeic dermatitis; dandruff.

Desquam-X *Westwood-Squibb, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

DesquamX *Ranbaxy, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Dessolets *SMB, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye congestion.

Destadin *EMS, Braz.*
Desloratadine (p. 625·1).

Destamin *Medifarma, Mex.*
Histamine hydrochloride (p. 2525·2).

Destap *Laboratorios Chile, Chile.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Destar *Sanify, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Destara *Roche, Neth.†; Roche, Port.†*
Ibandronate sodium (p. 1184·2).
Hypercalcaemia of malignancy.

Destilbenol *Apsen, Braz.*
Diethylstilbestrol (p. 2267·3).
Prostatic cancer; breast cancer.

Destolit *Sanofi-Aventis, Port.; Norgine, UK.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; biliary tract disorders.

Destoxican *Pentafarma, Port.*
Naltrexone hydrochloride (p. 1565·1).
Opioid dependence; alcohol dependence.

Destralina *Mavi, Mex.*
Clindamycin (p. 269·3).
Bacterial infections.

Destrepen *Proel, Gr.*
Cefoxitin (p. 246·2).
Bacterial infections.

Destres *Ethix, India.*
Alprazolam (p. 1035·2); melatonin (p. 2551·3).

Destrobac *Teleflex, Ital.; Gebro, Switz.*
Povidone-iodine (p. 1767·1).
Wounds; skin disinfection; burns; infected skin disorders.

Desunin *Meda, UK.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Desuric *ProStrakan, Neth.*
Benzbromarone (p. 603·3).
Hyperuricaemia; gout.

Desval *Ranbaxy, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Desyrel *BMS, Canad.; Cinay, Turk.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety.

DET MS *Amdipharm, Ger.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension.

Detametazon *Dalkhimfarm, Rus.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Detane *Del, USA.†*
Benzocaine (p. 1980·2).
Genital desensitising lubricant.

Detantol *Eisai, Indon.†; Eisai, Jpn; Eisai, Thai.†*
Bunazosin hydrochloride (p. 1329·3).
Hypertension.

Detantol R *Eisai, China.*
Bunazosin hydrochloride (p. 1329·3).
Hypertension.

Detavi *Dosa, Arg.*
Decitabine (p. 780·1).
Malignant neoplasms.

Detaxl *VHB, India.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Detebencil *Roux-Ocefa, Arg.*
Emulsion: Permethrin (p. 2159·3); benzyl benzoate (p. 2149·1); benzocaine (p. 1980·2).
Pediculosis; scabies.

Roux-Ocefa, Arg.
Lotion: Permethrin (p. 2159·3); benzyl benzoate (p. 2149·1).
Pediculosis.

Roux-Ocefa, Arg.
Tablets: Ivermectin (p. 155·1).
Scabies; onchocerciasis; strongyloidiasis.

Detebencil Nit *Roux-Ocefa, Arg.*
Permethrin (p. 2159·3); acetic acid (p. 2426·3).
Pediculosis.

Detect Baby *Blausiegel, Braz.*
Pregnancy test (p. 2596·1).

Detegen *Diba, Mex.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Detemes *Sanova, Austria.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; venous insufficiency; migraine and related vascular headaches.

Deten *Siam Bheasach, Thai.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Detenler *Duncan, Arg.*
Levomepromazine (p. 1079·3).
Psychoses.

Detensiel *Merck Serono, Fr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Détensor *Novartis Consumer, Switz.*
Diphenhydramine hydrochloride (p. 626·2); 8-chlorotheophylline (p. 2475·3).
Sleep disorders.

Detente *Nutri-Source, Canad.†*
Lupulus (p. 2546·1); tilia (p. 2631·3); melissa (p. 2552·3); passion flower (p. 2584·1); valerian (p. 2640·2).

Detergil *Manetti Roberts, Ital.*
Benzalkonium chloride (p. 1737·1).
Wound disinfection; instrument disinfection.

Deteron *Alapis, Gr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Dethamycin *Vitamed, Israel.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye, ear, and nose disorders.

Dethaphrine *Vitamed, Israel.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Infected eye, ear, and nose disorders.

Deticene *Sanofi-Aventis, Chile; Sanofi-Aventis, Gr.; Sanofi-Aventis, Israel†; Sanofi-Aventis, Neth.; Sanofi-Aventis, Port.†; Aventis, Turk.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Déticène *Sanofi-Aventis, Fr.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Detilem *Teva, Mex.†*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Detimedac *Medac, Ger.*
Dacarbazine citrate (p. 776·1).
Malignant neoplasms.

Detolax *Madaus, Thai.; Rottapharm, Thai.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea.

Detox *Reese, USA.*
Red clover (p. 2482·1); liquorice (p. 1853·2); peach bark; orange grape root; stillingla; cascara (p. 1826·1); sarsaparilla (p. 2610·3); lappa root (p. 2540·1); buckthorn (p. 1824·2).
Dietary supplement.

Detox L37 *Homeocan, Canad.*
Aristolochia (p. 2447·1); dulcamara (p. 2497·3); phytolacca; pulsatilla (p. 2600·2); thuja (p. 2629·3); mercurius corrosivus (p. 2555·2); arsenicum iodatum (p. 2448·1); phosphorus (p. 2589·2); acidum nitricum (p. 2572·3); kalium bichromicum (p. 2476·3).
Homoeopathic preparation.

Detox Program *Blackmores, Austral.*
Oral liquid (Digestive Bitters), taraxacum (p. 2625·3); meadowsweet (p. 2550·2); gentian (p. 2512·1); agrimony (p. 2432·3); cinnamon (p. 2479·2); tablets, milk thistle (p. 1561·1); capsules, *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium animalis* (p. 2596·3); sachets (Colon Care), senna (p. 1885·1); buckthorn (p. 1824·2); ispaghula (p. 1849·1); aniseed (p. 2444·2); fennel (p. 2503·2); liquorice (p. 1853·2); bearberry (p. 2453·2); agar (p. 2167·2).
Digestive disorders.

Detoxergon *Baldacci, Port.*
Pirglutargine (p. 2592·2); taurine (p. 2626·2); pyridoxine hydrochloride (p. 2105·3); citric acid (p. 2480·3); sodium citrate (p. 1781·2); calcium citrate (p. 1783·2); potassium citrate (p. 1780·3); magnesium citrate (p. 1857·1).
Liver disorders.

Detoxicon *SIT, Ital.*
Tablets: Glycine (p. 2071·2); acetylmethionine (p. 1558·2).
Alcohol poisoning; adjunct in hepatic steatosis.

Détoxifiance *Lero, Fr.*
Mint (p. 2621·2); chicory (p. 2475·2); radish; birch (p. 2457·3).

Detoxil *Vitabiotics, Ukr.*
Vitamins; minerals; cynara (p. 2490·3); grapefruit; taraxacum (p. 2625·3); methionine (p. 1558·2); phosphatidyl choline (p. 2588·3).
Dietary supplement.

Detoxopirol *Qixing, Ukr.*
Bovine bezoar; aquilaria sinensis; serratula chinensis; phyllostachys nigra; gardenia jasminoides; andrographis (p. 2443·2).
Upper respiratory-tract disorders; herpesvirus infections.

Detraine *Anotaciones, Spain.†*
⊗Hydrocortisone (p. 1640·1); propanocaine hydrochloride (p. 1995·2).
Insect bites and stings; pruritus; skin disorders.

Detralex *Servier, Cz.; Servier, Hung.; Servier, Pol.; Servier, Rus.; Servier, Ukr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Chronic venous insufficiency; haemorrhoids.

Detramol *Filadams, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Detremin *Renapharma, Denm.; Renapharma, Fin.; Renapharma, Norw.; Renapharma, Swed.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; osteoporosis; osteomalacia; hyperparathyroidism; rickets.

Detreomycyna *Chema-Elektromet, Pol.*
Chloramphenicol (p. 257·1).
Bacterial skin infections.

Detrichol *GMP, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Detril *Ni-The, Gr.*
Thioridazine hydrochloride (p. 1110·2).

Detrim *DWD, India.*
Injection: Drotaverine hydrochloride (p. 2497·3).
Gastrointestinal spasm.

DWD, India.
Tablets: Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Detrol *Pfizer, Canad.; Pfizer, USA.*
Tolterodine tartrate (p. 2370·2).
Detrol LA was formerly known as Unidet.
Bladder instability.

Detromb *Antiviral, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Detrovel *Fahrenheit, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Detrunorm *Amdipharm, Irl.; Pharmafrica, S.Afr.; Amdipharm, UK.*
Propiverine hydrochloride (p. 2363·1).
Bladder instability; neurogenic bladder.

Detrusan *Stada, Austria.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Detrusitol *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia Upjohn, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Farmasierra, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, Venez.*
Tolterodine tartrate (p. 2370·2).
Bladder instability; urinary incontinence.

Détrusitol *Pfizer, Fr.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Dětská Čajová Směs *Megafyt-R, Cz.*
Peppermint leaf (p. 1877·1); chamomile (p. 2474·1); fennel (p. 2503·2); althaea (p. 2438·3); liquorice (p. 1853·2).
Digestive system disorders.

Dětský Čaj s Heřmánkem *Leros, Cz.*
Chamomile (p. 2474·1); fennel (p. 2503·2); peppermint leaf (p. 1877·1); althaea (p. 2438·3); raspberry leaf (p. 2603·1); plantaginis (p. 2604·2); lupulus (p. 2546·1); wild thyme (p. 2648·1); sambucus (p. 2609·3); liquorice (p. 1853·2).
Digestive system disorders.

Dettol *Reckitt Benckiser, Austral.; Reckitt Benckiser, Belg.; Reckitt Benckiser, Canad.; Reckitt Benckiser, Gr.; Reckitt Benckiser, Hong Kong†; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Neth.; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.*
Topical liquid: topical solution: medicated soap: Chloroxylenol (p. 1748·2).
Bath additive; bites and stings; burns; minor abrasions; abscesses; boils; disinfection of skin and wounds.

Reckitt Benckiser, Belg.†; Reckitt Benckiser, Cz.; Reckitt Benckiser, NZ†; Reckitt Benckiser, Switz.
Benzalkonium chloride (p. 1737·1).
Wound disinfection; wound cleansing; skin disinfection.

Reckitt Benckiser, India.
⊗Alcohol (p. 1733·1); chloroxylenol (p. 1748·2); terpineol (p. 2627·2).
Wound cleansing; skin disinfection.

Reckitt Benckiser, Hong Kong†; Reckitt Benckiser, Irl.†; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.
Cream: feminine wash; hand soap: Chloroxylenol (p. 1748·2); triclosan (p. 1773·2).
Burns; insect bites and stings; disinfection of skin and wounds; personal hygiene.

Reckitt Benckiser, UK.
Topical spray: Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).
Minor wounds; bites and stings; minor burns.

Reckitt Benckiser, Hong Kong.†
Mouthwash: Cetylpyridinium chloride (p. 1743·1); triclosan (p. 1773·2).
Oral hygiene.

Reckitt Benckiser, Hong Kong.†
Shower foam: Triclosan (p. 1773·2).
Skin disinfection.

Dettol Antiseptic Wash *Reckitt Benckiser, UK.*
Benzalkonium chloride (p. 1737·1).
Wound disinfection.

Dettol Cream *Reckitt Benckiser, Austral.*
Chloroxylenol (p. 1748·2); triclosan (p. 1773·2).
Bites and stings; burns; minor abrasions; skin disorders; skin infections.

Dettol Fresh *Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.†; Reckitt Benckiser, NZ†; Reckitt Benckiser, UK.*
Benzalkonium chloride (p. 1737·1).
Bites and stings; burns; minor abrasions; skin disinfection.

Dettol Liquid Wash *Reckitt Benckiser, Austral.*
Triclosan (p. 1773·2).
Skin cleansing; acne.

Dettol med benzalkoniumchloride *Reckitt Benckiser, Neth.*
Benzalkonium chloride (p. 1737·1).
Wound cleansing.

Dettol Obstetric *Reckitt Benckiser, India.*
Chloroxylenol (p. 1748·2); terpineol (p. 2627·2).
Skin disinfection; vaginal lubricant.

Dettol Sterilon *Reckitt Benckiser, Neth.*
Chlorhexidine gluconate (p. 1743·3).
Wounds; skin disinfection.

Dettolin *Reckitt Benckiser, India.*
⊗Chloroxylenol (p. 1748·2); menthol (p. 2553·2); alcohol (p. 1733·1).
Oral hygiene; periodontitis; gingivitis.

Dettolmed
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Cz.
Chloroxylenol (p. 1748·2).
Disinfection of insect bites and wounds.

Reckitt Benckiser, Spain; Reckitt Benckiser, Swed.
Benzalkonium chloride (p. 1737·1).
Wound disinfection.

Dettolpro *Reckitt Benckiser, Fr.*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Dettolsept *Reckitt Benckiser, Gr.*
Chloroxylenol (p. 1748·2).

Dettonjab *Defuen, Arg.*
Undecenoic acid diethanolamide (p. 596·3); triclosan (p. 1773·2).
Acne.

Detulin *McNeil, Ger.†*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Déturgylone *Sanofi-Aventis, Fr.*
⊗Prednisolone sodium phosphate (p. 1645·3); oxymetazoline hydrochloride (p. 1671·3).
Rhinitis.

Deucoaler *Medipharm, Chile.*
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Deucodol *Medipharm, Chile.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Deucodol Plus *Medipharm, Chile.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinusitis; cold and influenza symptoms.

Deucotos *Medipharm, Chile.*
⊗Codeine (p. 40·2); pseudoephedrine (p. 1676·1); chlorphenamine (p. 620·3).
Bronchitis; cold symptoms; cough.

Deucoval *Medipharm, Chile.*
Naproxen sodium (p. 98·2).
Inflammation; pain.

De-ursil *Sanofi-Aventis, Switz.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Deursil *Sanofi-Aventis, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; biliary dyspepsia.

Devaljin *Deva, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Devalud *Deva, Turk.*
Tizanidine hydrochloride (p. 2026·2).

Devapen *Deva, Turk.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Devaron *Valwater, Neth.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; osteoporosis.

Devasid *Deva, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Deva, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1) or sultamicillin tosilate (p. 369·1).
Bacterial infections.

Devazol *ProStrakan, Spain.*
⊗Letrozole (p. 817·1).
Breast cancer.

Devedryl *Klonal, Arg.*
Loratadine (p. 633·2).

Devikap *Medana, Pol.*
Colecalciferol (p. 2113·1).
Rickets; tetany; osteomalacia; osteoporosis.

Devilan *Biomedica, Cz.*
2-Aminotridecane undecenoate; dipenditum.
Fungal skin infections.

Devils Claw Plus *Eagle, Austral.†*
Devil's claw root (p. 42·3); murraya; celery (p. 2472·3); hesperidin (p. 2505·2).
Arthritis; rheumatism.

Devincal *Kern, Spain.†*
Piracetam (p. 393·3); vincamine (p. 2645·2).
Cerebrovascular disorders.

Deviprost *Reddy, India.*
Carboprost trometamol (p. 2133·1).
Termination of pregnancy; postpartum haemorrhage.

Deviry *Elder, India.*
Medroxyprogesterone (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Devisol *Chema-Elektromet, Pol.*
Calcifediol (p. 2113·1).
Hypocalcaemia; rickets; osteomalacia; renal osteodystrophy; hypoparathyroidism.

Devit-3 *Deva, Turk.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Devita *Novaduo, India.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; hypocalcaemia.

Devitasol Arsenical *Biodica, Fr.†*
⊗Ephedrine hydrochloride (p. 1663·2); lidocaine (p. 1988·1); arsenic trioxide (p. 2448·1).

Devitol *Orion, Fin.*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency.

Devix *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Devixil *Neiadas (Νειαδας), Gr.*
Zipeprol hydrochloride (p. 1680·3).

Devlup *Shince, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Devodil *Remedica, Singapore.*
Sulpiride (p. 1107·3).
Schizophrenia.

Devona *Positif, India.*
Diclofenac (p. 48·3).
Pain.

Devona Plus *Positif, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Devona-S *Positif, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Devotan *Menarini, Gr.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Devrom *Parthenon, Canad.; Parthenon, USA.*
Bismuth subgallate (p. 1822·1).
Ostomy deodorant.

Dew Derm *Shalaks, India.*
Cream: ⊗Lactic acid (p. 2539·1); propylene glycol (p. 2205·2); urea (p. 1727·3); vitamin E (p. 2119·1).

Shalaks, India.
Lotion: ⊗Aloe vera (p. 1693·2); glycerol (p. 2517·2); jojoba oil; vitamin E (p. 2119·1).

Dewax
Note: this name may be used for preparations of different composition.
Ranbaxy, Thai.
Docusate sodium (p. 1836·2).
Ear wax removal.

Vanguard, India.
Chlorobutanol (p. 1747·2); lidocaine (p. 1988·1); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).
Ear wax removal.

Dewcef *Haledew, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Dewcef-S *Haledew, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Dewee *Haledew, India.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).

DeWei *Kangbao, China.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Dewin *Zee, India.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; hypocalcaemia.

Dewmox-CV *Haledew, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Dewormis *GSK, India.*
Levamisole (p. 157·2).
Worm infections.

Dewsoft *Torrent, India.*
Aloe vera (p. 1693·2); vitamin E acetate (p. 2119·2).

Dewzym *Haledew, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1); vitamin B substances (p. 2102·3).

Dex
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.; PP Lab, Thai.
Dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neon, India.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dex Antihist *Pharmaniaga, Hong Kong.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Dex4 Glucose *Can-Am Care, USA.*
Glucose (p. 2068·3).
Hypoglycaemia.

Dexa *Mibe, Ger.; Ratiopharm, Ger.; Ratiopharm, Hung.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Utopian, Thai.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexa ANB *ANB, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexa Biciron *Alcon, Ger.*
⊗Dexamethasone isonicotinate (p. 1631·1); tramazoline hydrochloride (p. 1679·3).
Allergic and inflammatory disorders of the eye.

Dexa Loscon mono *Galderma, Ger.*
⊗Dexamethasone isonicotinate (p. 1631·1).
Scalp disorders.

Dexa N *Hovid, Hong Kong.†*
⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3).
Infected eye disorders.

Dexa Polyspectran *Alcon, Ger.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye and ear disorders.

Dexa Tavegil *Novartis Consumer, Spain.*
⊗Clemastine fumarate (p. 622·3); dexamethasone (p. 1630·3).
Hypersensitivity reactions; inflammatory eye disorders; insect bites and stings; sunburn.

Dexa Teosona *Phoenix, Arg.*
⊗Theophylline (p. 1229·3); dexamethasone (p. 1630·3).
Obstructive airways disease.

Dexa-Aminofilin *Phoenix, Arg.*
⊗Theophylline (p. 1229·3); dexamethasone (p. 1630·3).
Obstructive airways disease.

Dexa-B *Vickmans, Hong Kong.†*
⊗Dexamethasone (p. 1630·3); paracetamol (p. 115·1); vitamin B substances (p. 2102·3).

Dexabene *Ratiopharm, Austria; Recordati, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid; parenteral corticosteroid.

Dexabeta *Betapharm, Ger.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexabion *Merck, Arg.; Merck, Mex.*
Injection: ⊗Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ampoule 2, dexamethasone sodium phosphate (p. 1631·2).
Lidocaine hydrochloride (p. 1988·2) is included in ampoule 2 to alleviate the pain of injection.
Inflammation; neuralgias; neuritis; rheumatoid arthritis; peri-articular disorders.

Dexacap *Dexa, Indon.; Dexa, Singapore.*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

DexaCaps *Herbapol Lublin, Pol.*
Dextromethorphan hydrobromide (p. 1660·1); melissa (p. 2552·3); tilia (p. 2631·3).
Cough.

Dexace *Dexter, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Dexacef *Ferron, Indon.; Dexa, Singapore.*
Cefadroxil (p. 233·2).
Bacterial infections.

Dexace-H *Dexter, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Dexachlor *Cooper (Kopep), Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Infected eye disorders.

Dexacilin *Prodotti, Braz.†*
Eye drops: ⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Prodotti, Braz.†
Injection: ⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexacin *ANB, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye or ear disorders.

Dexacip *Cipla, India.*
⊗Dexamethasone (p. 1630·3); dexamethasone phosphate (p. 1631·1), or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexa-Citoneurin *Merck, Braz.*
⊗Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); dexamethasone (p. 1630·3) or dexamethasone acetate (p. 1631·1).
Neuritis.

dexa-clinit *Hormosan, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Parenteral corticosteroid.

Dexacobal *Uniao Quimica, Braz.*
⊗Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); dexamethasone acetate (p. 1631·1).
Procaine hydrochloride (p. 1994·3) is included in this preparation to alleviate the pain of injection.
Neuritis.

Dexacollyre *Cooper (Kopep), Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexacort
Note: this name may be used for preparations of different composition.
Behrens, Venez.
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Teva, Israel; Darou Pakhsh, Rus.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye and ear disorders; corticosteroid.

Dexacortal *MSD, Swed.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexacortin *Streuli, Switz.†*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexacort-N *Klar Sehen, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).

Dexa-Cronobe *Biolab Sanus, Braz.*
⊗Ampoule A, cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); ampoule B, dexamethasone acetate (p. 1631·1).
Neuritis.

Dexaden *Cifarma, Braz.*
⊗Dexamethasone (p. 1630·3), dexamethasone acetate (p. 1631·1), or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexadent *Chema-Elektromet, Pol.*
⊗Dexamethasone acetate (p. 1631·1); framycetin sulfate (p. 301·2); polymyxin B sulfate (p. 342·3).
Dental infections.

Dexadermil *Legrand, Braz.*
⊗Dexamethasone acetate (p. 1631·1).
Skin disorders.

Dexador *Ativus, Braz.*
⊗Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); dexamethasone phosphate (p. 1631·1).
Procaine hydrochloride (p. 1994·3) is included in the injection to alleviate the pain of injection.
Neuritis.

Dexadoze *Teuto, Braz.*
⊗Ampoule A, dexamethasone acetate (p. 1631·1); ampoule B, thiamine hydrochloride (p. 2103·1); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis.

Dexadutil *Parggon, Mex.*
⊗Dexamethasone (p. 1630·3); phenylbutazone (p. 125·1).
Rheumatism.

DexaEDO *Mann, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexa-Effekton *Teofarma, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Rheumatic disorders.

Dexafar *Faran, Gr.; Faran, Rus.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexafed Cough *Mallard, USA.*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Dexafenicol *Allergan, Braz.*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Dexaflam *Winthrop, Ger.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexaflox *Dexa, Indon.*
Pefloxacin (p. 338·1).
Bacterial infections.

Dexafree *Thea, Fr.; Thea, Pol.; Thea, Port.; Thea, Spain; Thea, Switz.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexafrin *Sophia, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Dexagalen *Galen, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexagel *Mann, Ger.; Bausch & Lomb, S.Afr.; Bausch & Lomb, Thai.†; Bausch & Lomb, Ukr.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexagenta *Croma, Austria.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Dexa-Gentamicin *Ursapharm, Cz.; Ursapharm, Ger.; Ursapharm, Rus.; Ursapharm, Singapore.*
⊗Dexamethasone (p. 1630·3); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Dexagenta-POS *Ursapharm, Belg.; Ursapharm, Neth.; Ursapharm, Switz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Dexagent-Ophtal *Winzer, Ger.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Dexagil *Marjan, Braz.*
⊗Dexamethasone phosphate (p. 1631·1); cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Procaine hydrochloride (p. 1994·3) is included in the vitamin injection to alleviate the pain of injection.
Neuritis.

Dexagin *Farmo Quimica, Chile.*
⊗Dexamethasone tebutate (p. 1630·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1); boric acid (p. 2459·3).
Vaginitis.

Dexaglos *Belfar, Braz.*
⊗Dexamethasone (p. 1630·3).

Dexagrane *Zeiss Meditec, Fr.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Dexagreen *Greenpharma, Braz.*
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Dexagrin *Grin, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexahexal *Hexal, Ger.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexahist *Vickmans, Hong Kong.†*
⊗Chlorphenamine (p. 620·3); dexamethasone (p. 1630·3).

Dexaject *Sterfil, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexak *Berlin-Chemie, Pol.; Menarini, Pol.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Dexal
Note: this name may be used for preparations of different composition.
Marcel, Mex.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Nycomed, Neth.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dexalab *Laborate, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexalaf *Lafedar, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexalergin *Ivax, Arg.*
Cream: ⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); chlorphenamine maleate (p. 620·3).
Skin disorders.

Ivax, Arg.
Injection: ⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Ivax, Arg.
Nasal spray; nose drops: ⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3).
Nasal disorders.

Ivax, Arg.
Syrup; tablets: ⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Dexalgen *Eurofarma, Braz.*
⊗Ampoule I, hydroxocobalamin (p. 2107·3); ampoule II, dipyrone (p. 53·3); dexamethasone sodium phosphate (p. 1631·2).
Neuritis.

Dexalgin *Berlin-Chemie, Rus.*
Dexketoprofen trometamol (p. 79·1).
Pain; musculoskeletal and joint disorders.

Berlin-Chemie, Ukr.
Dexketoprofen (p. 79·1) or dexketoprofen trometamol.
Musculoskeletal and joint disorders; pain.

Dexalin *General Drugs, Thai.*
Piroxicam (p. 125·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; gout.

Dexalin Balm *General Drugs, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); cajuput oil (p. 2464·1); cineole (p. 2479·1).
Lumbago; sciatica; rheumatic conditions.

Dexalocal *Medinova, Switz.*
⊗Dexamethasone (p. 1630·3).
Skin and scalp disorders.

Iasis, Gr.
⊗Budesonide (p. 1625·1).
Skin disorders; allergic rhinitis.

Dexalocal-F *Medinova, Switz.*
⊗Dexamethasone (p. 1630·3); framycetin sulfate (p. 301·2).
Infected skin disorders.

Dexalog-N *Prem, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected inflammatory eye disorders.

DexAlone
Note: this name may be used for preparations of different composition.
DexGen, USA.
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Dexalone
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexaltin *Kayaku, Cz.†; Kayaku, Hong Kong; Kayaku, Malaysia; Kayaku, Singapore; ANB, Thai.*
⊗Dexamethasone (p. 1630·3).
Mouth ulcers; stomatitis; glossitis; mouth disorders.

Dexa-M *Dexa, Indon.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexamac *Mac, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexamag *Shalaks, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexambutol *IFET (ΙΦΕΤ), Gr.*
Ethambutol (p. 296·1).
Tuberculosis.

SERP, Mon.
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Dexambutol-INH *SERP, Mon.†*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Dexamed *Medochemie, Cz.; Anpharm (Ανφαρμ), Gr.†; Medochemie, Rus.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Medochemie, Hong Kong; Medochemie, Singapore.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexameral *LKM, Arg.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexameson *Cristalia, Braz.*
⊗Dexamethasone acetate (p. 1631·1).
Corticosteroid.

Dexamet *Daewon, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexametax *Hertz, Braz.*
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Dexamicin *Grin, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Dexamilan *Parggon, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexamin
Note: this name may be used for preparations of different composition.
Vivax Optipharm, Venez.
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Dexamine *Baroda, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexaminor *Allergan, Braz.*
⊗Dexamethasone (p. 1630·3).
Eye disorders.

Dexamol *Dexcel, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Dexamol Cold Day *Dexcel, Israel.*
⊗Paracetamol (p. 115·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms; nasal congestion.

Dexamol Cold Night *Dexcel, Israel.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms; nasal congestion.

Dexamol Kid *Dexcel, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Dexamol Plus *Dexcel, Israel.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Dexamol PM *Dexcel, Israel.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Pain; fever; insomnia.

Dexamol Sinus Day *Dexcel, Israel.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; nasal congestion.

Dexamol Sinus Night *Dexcel, Israel.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; nasal congestion.

Dexamon *Cipla, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).

Dexamono *Thea, Ital.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexamycin *Teva, Israel.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Inflammatory eye disorders with infection.

Nexus, Gr.
⊗Dexamethasone (p. 1630·3); tobramycin (p. 380·1).
Infected eye disorders.

Dexamytrex *Bausch & Lomb, Arg.; Mann, Ger.; Kite (Κιτε), Gr.; Bausch & Lomb, Neth.; Bausch & Lomb, Philipp.; Angelini, Port.*
⊗Gentamicin sulfate (p. 304·2); dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Mann, Pol.; Mann, Singapore.†
⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Bausch & Lomb, Thai.†
⊗Gentamicin sulfate (p. 304·2); dexamethasone phosphate (p. 1631·1).
Infected eye disorders.

Dexan *Recalcine, Chile.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Dexane *Samarth, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexaneurin *Uniao Quimica, Braz.*
⊗Ampoule A, cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); ampoule B, dexamethasone acetate (p. 1631·1).
Procaine hydrochloride (p. 1994·3) is included in ampoule A of this preparation to alleviate the pain of injection.
Neuritis.

Dexanicol *Pascual, Philipp.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Yik Kwan, Hong Kong.†
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Dexanil *Ducto, Braz.*
Cream: ⊗Dexamethasone acetate (p. 1631·1); neomycin sulfate (p. 330·1).
Ducto, Braz.
Injection: ⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexano *Milano, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexanorm *Dexa, Indon.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Dexanta *Dexa, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence; dyspepsia; heartburn.

Dexa-O *Chinta, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexa-Ophtal *Winzer, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexa-P *PP Lab, Thai.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexaphen-SA *Major, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

DexaPini *Herbapol Lublin, Pol.*
Dextromethorphan hydrobromide (p. 1660·1); fennel (p. 2503·2); Scots pine (p. 2591·1).
Cough.

Dexapolcort *Polfa Tarchomin, Pol.*
⊗Dexamethasone (p. 1630·3).
Allergic skin disorders.

Dexapolcort N *Tarchomin, Hung.†; Polfa Tarchomin, Pol.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dexa-Polyspectran New *Alcon, Belg.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Dexa-POS *Ursapharm, Neth.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexapos *Ursapharm, Ger.; Ursapharm, Rus.*
⊗Dexamethasone sodium metasulfobenzoate (p. 1631·1).
Inflammatory eye disorders.

Dexapostafen *Pfizer, Venez.*
⊗Dexamethasone (p. 1630·3); buclizine hydrochloride (p. 618·3).
Hypersensitivity reactions.

Dexapro *Medicine Products, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexaprof D *Ivax, Arg.*
⊗Loratadine (p. 633·2); dexamethasone (p. 1630·3).
Hypersensitivity reactions.

Dexaquin *Cadila, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); clioquinol (p. 273·1).

Dexar *Rass, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexa-ratiopharm *Ratiopharm, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexa-Rhinaspray *Boehringer Ingelheim, Gr.*
⊗Dexamethasone isonicotinate (p. 1631·1); tramazoline hydrochloride (p. 1679·3); neomycin sulfate (p. 330·1).

Dexa-Rhinaspray Duo *Boehringer Ingelheim, Irl.†*
⊗Tramazoline hydrochloride (p. 1679·3); dexamethasone isonicotinate (p. 1631·1).
Allergic rhinitis.

Dexa-Rhinaspray-N *Boehringer Ingelheim, Gr.*
⊗Dexamethasone isonicotinate (p. 1631·1); tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Dexa-Rhinospray
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Belg.
⊗Tramazoline hydrochloride (p. 1679·3); dexamethasone isonicotinate (p. 1631·1).
Rhinitis.

Dexa-Rhinospray Mono *Mann, Ger.†*
⊗Dexamethasone isonicotinate (p. 1631·1).
Allergic rhinitis.

Dexa-Rhinospray N *Boehringer Ingelheim, Arg.*
⊗Tramazoline hydrochloride (p. 1679·3); dexamethasone isonicotinate (p. 1631·1).
Allergic rhinitis.

Mann, Ger.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Rhinitis.

Dexariv *East African, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexasalyl *Medinova, Switz.*
⊗Dexamethasone (p. 1630·3) or dexamethasone acetate (p. 1631·1); salicylic acid (p. 1719·1).
Skin and scalp disorders.

Dexasia *Willow, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexa-Sine *Alcon, Belg.†; IFET (ΙΦΕΤ), Gr.; Liba, Turk.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Dexa-sine *Alcon, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Dexa-Siozwo *Febena, Ger.*
⊗Dexamethasone acetate (p. 1631·1); peppermint oil (p. 1877·1).
Rhinitis; catarrh; sinusitis.

Dexason *Galenika, Rus.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Teuto, Braz.
⊗Dexamethasone (p. 1630·3), dexamethasone acetate (p. 1631·1), or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexasone *Valeant, Canad.; Atlantic, Hong Kong; Cadila, India; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Hauck, USA.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexasone DPS *Cadila, India.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).

Dexasone N *Christo, Hong Kong.†*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dexasporin *Moore, USA†; Rugby, USA†; URL, USA.†*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye inflammation with bacterial infection.

Dexatamin *CCM, Malaysia; Duopharma, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Dexaton *Vianex (Βιανεξ), Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexatopic *Schering-Plough, Indon.*
⊗Dexamethasone (p. 1630·3); nandrolone decanoate (p. 2293·1); chlorhexidine hydrochloride (p. 1743·3).
Skin disorders.

Organon, Gr.†
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Dexatotal *Paylos, Arg.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dexatrim Max Daytime Appetite Control *Chattem, USA.*
Ginseng (p. 2513·3); caffeine (p. 1203·3); epigallocatechin gallate (p. 1720·2); calcium (p. 1783·1); chromium (p. 2055·3); vitamin B substances (p. 2102·3).

Dexatrim Plus Vitamins *Thompson, USA.*
Caplets: Vitamins; minerals.

Dexatussin *Espefa, Pol.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dexaval *Tecnifar, Port.*
⊗Dexamethasone valerate (p. 1630·3).
Skin disorders.

Dexaval V *Tecnifar, Port.*
⊗Dexamethasone valerate (p. 1630·3); clioquinol (p. 273·1).
Infected skin disorders.

Dexaval A *Tecnifar, Port.*
⊗Dexamethasone valerate (p. 1630·3); chlorphenamine maleate (p. 620·3).
Skin disorders with pruritus.

Dexaval N *Tecnifar, Port.*
⊗Dexamethasone valerate (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Dexaval O *Tecnifar, Port.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Dexaven *Jelfa, Pol.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Jelfa, Rus.
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Dexavison *Teuto, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Dexavita *Wockhardt, India.*
Vitamins; zinc (p. 2126·1).

Dexa-Y *Chinta, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexazol *Dexa, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Dexazona *Bunker, Braz.*
Eye drops; cream: ⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Eye disorders.

Bunker, Braz.
Injection; syrup; tablets: ⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Dexbrolex *Arlex, Mex.*
Ambroxol (p. 1654·3); dextromethorphan (p. 1660·1).

Dexbroxine *Pharmasant, Thai.*
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dexchloramine *CCM, Malaysia; Beacons, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Allergic skin disorders; allergic rhinitis; hypersensitivity reactions.

Dexcin *Syntho, India.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1).

Dexcof *Cipla, India.*
Dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1); diphenhydramine hydrochloride (p. 626·2).
Cough.

Dexcold *Finecure, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Dexcon-DM *Cypress, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dexcon-PE *Cypress, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Dexcophan *Hovid, Hong Kong†; Hovid, Malaysia†; Hovid, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dexcophan Cough *Hovid, Malaysia.†*
⊗Ammonium chloride (p. 1656·1); dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2).
Cough; nasal congestion.

Dexcophan Cough Linctus Plus *Hovid, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Dexcpm *Yash, India.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Dexdor *Orion, Denm.; Orion, Irl.; Orion, Norw.; Orion, Spain; Orion, Swed.; Orion, Switz.; Orion, UK; Orion, Ukr.*
Dexmedetomidine hydrochloride (p. 1063·1).
Sedative.

Dexedrine *Paladin, Canad.; Auden McKenzie, UK†; Amedra, USA.*
⊗Dexamfetamine sulfate (p. 2319·1).
Narcoleptic syndrome; attention-deficit hyperactivity disorder.

Dexef *CSP, Fr.*
Cefradine (p. 249·1).
Bacterial infections.

Dexefrin *Fischer, Israel.*
⊗Dexamethasone sodium phosphate (p. 1631·2); phenylephrine hydrochloride (p. 1672·3); neomycin sulfate (p. 330·1).
Inflammatory eye disorders with infection.

Dexelle *ITF, Chile.*
Dexibuprofen (p. 43·1).
Fever; pain; inflammation.

Dexenac *Raam, Mex.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders; pain; inflammation.

Dexeryl
Note: this name may be used for preparations of different composition.
Pascual, Hong Kong.
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders.

Pierre Fabre Dermo Kosmetik, Ger.
⊗Glycerol (p. 2517·2); white soft paraffin (p. 2211·3).
Dry skin disorders.

Pierre Fabre Sante, Fr.; Pierre Fabre, Switz.
⊗Glycerol (p. 2517·2); white soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry skin disorders; minor burns.

Dexfar-D *Biophar, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Dexfer *Vensat, India.*
Vitamins; iron (p. 2073·1); zinc (p. 2126·1).

DexFerrum *American Regent, USA.*
Iron dextran (p. 2075·3).
Iron deficiency.

DexFol *Rising Pharmaceuticals, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Dexia *RND, India.*
DL-Methionine (p. 1558·2); paracetamol (p. 115·1).

Dexiao *Baiyunshan, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Dexicam *OFF, Ital.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Dexicar *Provit, Mex.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexicool *Invision, India.*
Dexrabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer.

Dexide *Rottapharm, Spain.*
Colextran hydrochloride (p. 1347·1).
Hyperlipidaemias.

Dexidex *Serral, Mex.*
Nitazoxanide (p. 942·2).

Dexidin *Atlas, Canad.*
Chlorhexidine gluconate (p. 1743·3) with or without isopropyl alcohol (p. 1758·3).
Skin disinfection.

Dexigen *Ifars, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Dexigesic-P *Invision, India.*
Dexibuprofen (p. 43·1); paracetamol (p. 115·1).

Dexilal *Silanes, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexilant *Takeda, Canad.; Takeda, USA.*
Dexlansoprazole (p. 1834·2).
Formerly known as Kapidex.
Oesophagitis; gastro-oesophageal reflux.

Deximet *Sons, Mex.*
⊗Indometacin (p. 71·2); dexamethasone (p. 1630·3).
Musculoskeletal and joint disorders; gout; lupus erythematosus; skin disorders.

Deximin *Candor, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

Deximune *Dexcel, Denm.; Dexcel, Ger.; Dexcel, Irl.; Dexcel, Israel; Dexcel, UK.*
Ciclosporin (p. 1945·2).
Transplant rejection; atopic eczema; psoriasis; nephrotic syndrome; rheumatoid arthritis; graft-versus-host disease; uveitis.

Dexion *Umeda, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexipan *Julphar, UAE.*
Dexpanthenol (p. 2582·2).
Skin irritation; wounds.

Dexir *BMS, Belg.; UPSA Conseil, Fr.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

DexIron *Luitpold, Canad.; Mylan, Canad.*
Iron dextran (p. 2075·3).
Iron deficiency.

Dexitis *Fabop, Arg.*
Loratadine (p. 633·2).

Dexium *Sanofi-Aventis, Ger.†*
Calcium dobesilate (p. 2464·3).
Vascular disorders.

Dexiven *Rivero, Arg.*
Calcitriol (p. 2113·1).
Hypocalcaemia in dialysis patients.

Dexkof *Medihealth, India.*
Chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

Dexlerg *Cazi, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Dexlin *Arlex, Mex.*
Nimesulide (p. 101·3).
Inflammation.

Dexly *Hetero, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Dexmetha *Synco, Hong Kong†; Synco, Singapore.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexmethsone *Aspen, Austral.; Aspen, Hong Kong.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexmolex *Molex Ayus, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cough; respiratory-tract allergic disorders.

Dexne *Offenbach, Mex.*
Ear drops: ⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3); lidocaine (p. 1988·1).
Inflammatory ear disorders.

Offenbach, Mex.
Eye drops: ⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3).
Inflammatory eye disorders.

Offenbach, Mex.
Nose drops: ⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3); phenylephrine (p. 1672·2).
Inflammatory nose disorders.

Dexnon *Kern, Spain.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Dexo *Dominguez, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders; cholesterol gallstones.

Dexocort *Kimia, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Dexodil *Psychotropics, India.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Dexodin *IQFA, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Dexof *Glenmark, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dexofan *Nycomed, Denm.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Dexofen *Biophausia, Swed.†*
Dextropropoxyphene napsilate (p. 43·3).
Pain.

Dexoket *Menarini, Cz.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Dexol
Note: this name may be used for preparations of different composition.
Andromaco, Mex.
Ambroxol hydrochloride (p. 1654·3); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract congestion.

SMB, Chile.
Borage (p. 2459·1).
Barrier preparation; dry skin.

Dexolan *Streuli, Switz.†*
⊗Dexamethasone (p. 1630·3); zinc oxide (p. 1729·1).
Skin disorders.

Dexoltryn *Ultra, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Dexolut *Dexa, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with congestion.

Dexomon *Hillcross, UK.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Dexon *General Drugs, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexona *Zydus, India; Jofrain, Mex.†; Cadila, Rus.*
⊗Dexamethasone (p. 1630·3) or dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Cadila, Rus.
Ear/eye drops: ⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected ear and eye disorders.

Zydus, S.Afr.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexona Eye/Ear *Zydus, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Inflammatory ear disorders; bacterial eye infections.

Dexone *The Forty-Two, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Keene, USA.†
⊗Dexamethasone acetate (p. 1631·1).
Corticosteroid.

Dexoph *Seng, Hong Kong.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected ear disorders; infected eye disorders.

Seng, Thai.
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

DexOptifen *Spirig, Switz.†*
Dexibuprofen (p. 43·1).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dexorange *Franco-Indian, India.*
Syrup: Ferric ammonium citrate (p. 2060·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Anaemias.

Franco-Indian, India.
Capsules: Ferric ammonium citrate (p. 2060·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Anaemias.

Dexoren *Indoco, India.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Dexoren-S *Indoco, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).

Dexosyn *Pharos, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Dexosyn Plus *Bell, India.†*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected inflammatory eye disorders.

Dexosyn-C *Bell, India.†*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3).
Corneal lesions; infected inflammatory eye disorders.

Dexosyn-N *Bell, India.†*
⊗Neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Corneal lesions; infected inflammatory eye disorders.

Dex-Otic *Teva, Israel.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected ear disorders.

Dexovon *USV, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Pain.

DexPak *ECR, USA.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexpantol *Kinder, Braz.*
Panthenol (p. 2582·2).

Dex-PC *Elfin, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Dexphen *Lexus, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1).

Dexphen M *Boca, USA.*
Dexchlorpheniramine maleate (p. 621·1); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dexphen w/C *Breckenridge, USA.*
Codeine phosphate (p. 40·2); dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dexpin *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); terpin hydrate (p. 1678·2); chlorphenamine maleate (p. 620·3).
Cough.

Dexprofen *Polfa Kutno, Pol.†*
Dexibuprofen (p. 43·1).
Fever; inflammation; pain.

Dexprofeno *Richmond, Arg.†*
Dextropropoxyphene (p. 43·2); ibuprofen lysine (p. 68·3).
Inflammation; pain.

Dexpure *Emcure, India.*
Dexrabeprazole (p. 1881·1).

Dexrice *Wockhardt, India.*
Preparation for enteral nutrition.

Dexrobel-D *Aamorb, India.*
Dexrabeprazole (p. 1881·1); domperidone (p. 1838·1).

Dexsal *Reckitt Benckiser, Austral.†*
Oral liquid: Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Dyspepsia; flatulence.

Reckitt Benckiser, Austral.†
Oral granules: Sodium citrotartrate (p. 1780·3); tartaric acid (p. 2626·1); glucose (p. 2068·3); sodium bicarbonate (p. 1781·1).
Dyspepsia.

Dexsil Articulations *Dexsil, Fr.*
Monomethylsilanetriol (p. 2088·3); gaultheria procumbens; glucosamine (p. 2515·3); chondroitin (p. 2476·1); ocimum sanctum; eucalyptus citriodora; laurus nobilis; lavandula hydrida; gaultheria fragrantissima; achillea (p. 2427·3).
Joint disorders.

Dexsil Jambes Légères *Dexsil, Fr.*
Monomethylsilanetriol (p. 2088·3); menthol (p. 2553·2).
Heavy legs.

Dexsil Peau *Dexsil, Fr.*
Monomethylsilanetriol (p. 2088·3); simmondsia chinensis; rosa rubiginosa; aniba rosaeodora; sage (p. 2608·3); pelargonium asperum; chamomile (p. 2474·1); helichrysum italicum; jasminum officinalis.
Skin disorders.

Dexsil Silicium *Dexsil, Fr.*
Monomethylsilanetriol (p. 2088·3).
Joint disorders; heavy legs; skin, hair, and nail disorders.

Dexsil Sport *Dexsil, Fr.*
Monomethylsilanetriol (p. 2088·3); gaultheria procumbens; glucosamine (p. 2515·3); chondroitin (p. 2476·1); gaultheria fragrantissima; laurus nobilis; camphor (p. 2466·2); menthol (p. 2553·2).
Muscle and joint pain.

Dexsin *Christo, Hong Kong.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Dexsol *Rosemont, Irl.; Rosemont, Neth.; Rosemont, UK.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexsul *Parggon, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Dextaco *Berlico Mulia, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).

Dextafen *Otto, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Dextamine *Cifarma, Braz.*
⊗Dexchlorpheniramine maleate (p. 621·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Phapros, Indon.
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Dexthasol *Olan-Kemed, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexthasone *Utopian, Thai.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexticort *LBS, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dexton *TP, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dextone *Tocogino, Mex.*
⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3).
Infected eye disorders.

Dextonil *Plusandex, Venez.*
Dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1).
Cough.

Dextracin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Dextral *Molex Ayus, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cough; influenza symptoms.

Dextramet *Hua, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextramine *Clinifood, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Allergic skin disorders; allergic rhinitis; insect bites.

Dextrarine Phenylbutazone *Sanofi-Aventis, Fr.*
Dextran sulfate (p. 2492·2); phenylbutazone (p. 125·1).
Tendinitis.

Dextrasone *Xepa-Soul Pattinson, Singapore.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dextrevit *Valeant, Mex.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); glucose (p. 2068·3).
Neuritis; vitamin deficiencies.

Dextricea *Durban, Spain.†*
Rice; gelatin tannate (p. 2625·2); pectin (p. 2200·3); wheat germ (p. 2647·1).
Diarrhoea.

Dextrifer *Intermed, Gr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Dextrifer-Fol *Intermed, Gr.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Anaemias.

Dextrifer-S *Intermed, Gr.*
Iron sucrose (p. 2078·1).

Dextrim-PC *Adley, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Dextrion *Chaix et du Marais, Fr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium gluconate (p. 1783·3).
Fluid and electrolyte disorders.

Dextro *Osoth, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); terpin hydrate (p. 1678·2); chlorphenamine maleate (p. 620·3).
Cough.

Dextro-5 *Medicine Products, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextro Compound *Medicpharma, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough; cold symptoms.

Dextro Cough
Note: this name may be used for preparations of different composition.
Osoth, Thai.
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough.

Dextro + Dipirona *Richmond, Arg.†*
Dextropropoxyphene hydrochloride (p. 43·3); dipyrone (p. 53·3).
Inflammation; pain.

Dextro GG *Jean-Marie, Hong Kong.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Dextro Plus *Jean-Marie, Hong Kong.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Dextrocidine *Therabel, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextrocilla *Europharm, Hong Kong.*
Dextromethorphan hydrobromide (p. 1660·1); cocillana (p. 1659·2); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Dextrocough *VS, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextrodip *Drawer, Arg.†*
Dextropropoxyphene hydrochloride (p. 43·3); dipyrone (p. 53·3).
Pain.

Dextrodon *Acdhon, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextrodyl *CCM, Malaysia.*
Dextromethorphan hydrobromide (p. 1660·1); promethazine hydrochloride (p. 638·2).
Cough.

Dextrofen *Phapros, Indon.*
Dextromethorphan (p. 1660·1); dexchlorpheniramine maleate (p. 621·1); phenylephrine (p. 1672·2).

Dextrogel *Neoceuticals, UK.*
Glucose monohydrate (p. 2069·1).
Hypoglycaemia.

Dextroject *Omega, Canad.*
Glucose (p. 2068·3).

Dextrolyte *Unipharma, Gr.; Tablets, India.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Dextrolyte-E *Tablets, India.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Dextrolyte-G *Tablets, India.*
Electrolytes (p. 1775·1).
Loss of gastric juice; mild alkalosis; forced diuresis.

Dextrolyte-M *Tablets, India.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders; metabolic acidosis.

Dextrolyte-P *Tablets, India.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders; mild acidosis.

Dextrome *Christo, Hong Kong.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextro-Med *Interdelta, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextromed *Medicine Products, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextromethorphan Compound *Pharmaniaga, Malaysia.*
Dextromethorphan hydrobromide (p. 1660·1); promethazine hydrochloride (p. 638·2).
Cough; upper respiratory-tract disorders.

Dextromine *General Drugs, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Dextropac *Inpac, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextrophen *Vickmans, Hong Kong.†*
Dextromethorphan (p. 1660·1).
Cough.

Dextroral *General Drugs, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextroref *Chemical, Fr.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Dextrose-C *David, India.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1).

Dextrosia *Siam Medicare, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextrosin *Otto, Indon.*
Syrup: Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Otto, Indon.
Tablets: Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Dextrosin Anak *Otto, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2); phenylpropanolamine

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

hydrochloride (p. 1674·1); noscapine (p. 1670·3).
Influenza symptoms.

Dextrosone *Quality, Hong Kong.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; inflammatory eye disorders.

Dextrostat *Shire Richwood, USA.*
⊗Dexamfetamine sulfate (p. 2319·1).
Narcoleptic syndrome; attention deficit hyperactivity disorder.

Dextrostix *Bayer Consumer, Arg.; Bayer Diabetes Care, Mex.*
Test for glucose in blood (p. 2516·3).

Dextrotos *Lafedar, Arg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dextrotuss *Cubit, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1).

Dextur *Biomedica, India.*
Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Dex-Tuss *Cypress, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Dex-Tuss DM *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Dextussin *TO-Chemicals, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2).
Cough; cold symptoms.

Dex-V *Vensat, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Dexvita *Wockhardt, India.*
Vitamins; zinc (p. 2126·1).

Dexxon *Katra, Hong Kong.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Dexyclav *Dexa, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Dexycol *Dexa, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Dexylin *General Drugs, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Dexymox *Dexa, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Dey's Milk of Magnesia *Dey's, India.*
Magnesium hydroxide (p. 1857·2).
Constipation; dyspepsia.

Dezabil *Alpharma, Mex.*
Albendazole (p. 149·1).
Worm infections.

Dezacor *Faes, Spain.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Dezartal *Andromaco, Chile.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Dezcard *Siam Bheasach, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Dezepan *Klonal, Arg.*
Diazepam (p. 1063·2).
Anxiety.

Dezepil *Rafarm, Gr.*
Lamotrigine (p. 527·2).

Dezert *Icarus, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Dezhi *Baiyunshan, China.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Dezor *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore; Hoe, Thai.*
Ketoconazole (p. 585·3).
Fungal skin and scalp infections; seborrhoeic dermatitis; pityriasis capitis.

Dezorol *Profarm, Pol.*
Methenamine (p. 322·3); menthol (p. 2553·2); salicylic acid (p. 1719·1).
Hyperhidrosis of the feet.

Dezrolala *Taj, India.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

DF 118 *GSK, Hong Kong; Galen, Irl.; GSK, Malaysia; Aspen, S.Afr.; Martindale Pharmaceuticals, UK.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

DF Expectorant NP *APT, Hong Kong.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; cough.

DF Multi-Symptom *APT, Hong Kong.†*
Paracetamol (p. 115·1); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); bromhexine hydrochloride (p. 1656·3); salicylamide (p. 129·2); caffeine (p. 1203·3).
Upper respiratory-tract disorders.

DF Night Time *APT, Hong Kong.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Nasal congestion; cough.

D-Feda II *WE, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

D-Fiam *Osoth, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout.

D-Flor *Berko, Turk.†*
Sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1).

D-Fluoretten *Sanofi-Aventis, Ger.*
Colecalciferol (p. 2113·1); sodium fluoride (p. 2089·2).
Rickets; dental caries prophylaxis.

DFM
Note: this name may be used for preparations of different composition.
Ikapharmindo, Indon.
Choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2); vitamin B_6 (p. 2105·3); betaine hydrochloride (p. 2456·1); taraxacum (p. 2625·3); carnitine (p. 2053·2); kelp (p. 2612·1).
Liver disorders.

Psyco Remedies, India.
Disulfiram (p. 2495·3).
Chronic alcoholism.

DFN *Bajer, Arg.*
Diclofenac diethylamine (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

DFO *Ozone, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

DFZ *Ipca, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

DG-6 *Craveri, Arg.*
Lapirium chloride.
Burns; skin, surface, and equipment disinfection; skin infections; nappy rash.

D-Gam *BPL, UK.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

D-Gard *Avinash, India.*
Acetylcysteine (p. 1652·2); chromium polynicotinate (p. 2055·3); folic acid (p. 2063·1); manganese sulfate (p. 2081·2); L-selenomethionine (p. 2087·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

D-Gel *Jamp, Canad.*
Colecalciferol (p. 2113·1).

D-Germ *Biocide, S.Afr.†*
Chlorhexidine gluconate (p. 1743·3).
Hand disinfection.

D-Glip *Grandix, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

DGR *Candor, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

DGR-Plus *Candor, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

DHA *Baldacci, Ital.*
Omega-3 fish oil (p. 1460·3); sunflower oil (p. 2098·1).
Nutritional supplement.

DHA Autobronceante *Ethicus, Arg.*
Dihydroxyacetone (p. 1700·1).
Tanning aid.

DHA Kids *Knop, Chile.*
Fish oil (p. 1460·3).
Nutritional supplement.

DHA Mathern *Knop, Chile.*
Fish oil (p. 1460·3).
Nutritional supplement.

DHA Plus *Hovid, Malaysia.*
Docosahexaenoic acid (p. 1460·1); vitamins.
Dietary supplement.

Dhabesol *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dhacillin *DHA, Singapore.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Dhacocin *DHA, Singapore.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Dhacodine *DHA, Malaysia.*
Pholcodine (p. 1675·1).
Cough.

Dhacopan *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Dhacort *DHA, Hong Kong; DHA, Singapore.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Dhactulose *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Dhagla-Pro *Sanify, India.*
Preparation for enteral nutrition.

Dhalgesic *DHA, Hong Kong†; DHA, Singapore.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders.

Dhalumag *DHA, Malaysia; DHA, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; peptic ulcer.

Dhamol *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Dhamotil *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Dhaperazine *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Prochlorperazine maleate (p. 1098·3).
Ménière's disease; migraine; nausea and vomiting; emotional and mental disturbances.

DHA-Plus *Plus, India.*
Vitamins; minerals.

Dhasedyl *DHA, Hong Kong; DHA, Singapore.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).
Cough.

Dhasedyl DM *DHA, Malaysia; DHA, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).
Cough; nasal congestion.

Dhasolone *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Dhatalin *DHA, Hong Kong; DHA, Singapore.*
⊗Terbutaline sulfate (p. 1228·1).
Asthma; bronchitis; bronchospasm.

Dhatifen *DHA, Hong Kong.*
Ketotifen fumarate (p. 631·3).
Asthma; rhinitis; conjunctivitis.

DHA, Malaysia; DHA, Singapore.
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Dhatracin *DHA, Malaysia; DHA, Singapore.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Dhatrin *DHA, Hong Kong; DHA, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dhavit *Guardian, Indon.*
Vitamins; docosahexaenoic acid (p. 1460·1); curcumin (p. 2180·1); fructo-oligosaccharides (p. 2508·1).
Dietary supplement; appetite stimulant.

Dhaxtra *Jose Lea, Singapore.*
Omega-3 triglycerides (p. 1460·1); arachidonic acid (p. 2446·1); olive oil (p. 2575·1); *d*-alpha tocopherol (p. 2119·1).
Dietary supplement during pregnancy and lactation.

DHC *Mundipharma, Ger.; Extractum, Hung.; Mundipharma, Hung.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

DHC Continus *Mundipharma, Cz.; Napp, Irl.†; Pharmaco, NZ; Norpharma, Pol.; Napp, UK.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

DHC Plus *Purdue Frederick, USA.*
Dihydrocodeine tartrate (p. 52·3); paracetamol (p. 115·1); caffeine (p. 1203·3).

DHE *Inga, India.*
Dihydroergotamine (p. 672·2).
Migraine.

Ratiopharm, Austria; Ratiopharm, Ger.†; Xcel, USA.
Dihydroergotamine mesilate (p. 672·2).
Hypotension; migraine and other vascular headaches; venous insufficiency; cluster headache.

D-Histaplus *Pasteur, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

DHS Sal *Dispolab, Chile.*
Salicylic acid (p. 1719·1).
Dandruff.

DHS Tar *Person & Covey, USA.*
Coal tar (p. 1723·2).
Seborrhoea; scalp disorders.

DHS Tar Gel *Dispolab, Chile.*
Coal tar (p. 1723·2).
Psoriasis.

DHS Zinc *Dispolab, Chile; Person & Covey, USA.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis; scalp disorders.

DHT *Roxane, USA.*
Dihydrotachysterol (p. 2113·2).
Postoperative and idiopathic tetany; hypoparathyroidism.

Di Du *Hualong, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Di La *Yangtze River, China.*
Cefradine (p. 249·1).
Bacterial infections.

Di Anatoxal *Pharmabroker, NZ.†*
An adsorbed diphtheria vaccine (p. 2382·3).
Active immunisation.

Di Bei *BeiLu, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Di Da *Di Ao, China.*
⊗Dexamethasone acetate (p. 1631·1).
Skin disorders.

Di Dolko *Therabel, Fr.†*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Di En An *Weixing Bio Product, China.*
Interferon alfa-2a (human, recombinant) (p. 989·2).
Malignant neoplasms; chronic hepatitis.

Di Er Gan *Dilong, China.*
Oxymatrine.

Di Er Kang Xin *Tiancheng, China.*
⊗Propranolol (p. 1479·1); caffeine (p. 1203·3); phenytoin sodium (p. 538·2).

Di Er Nuo *RenFu, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Di Er Song *Sanofi, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Di Fang *Topfond, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Di Fu Xin *Lv Zhou, China.*
Diclofenac sodium (p. 48·3).
Musculoskeletal pain and inflammation.

Di Gai Na *Sanjing, China.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Di Hong *Hexin, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Di Jia *Ao Dong, China.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Di Ka Ning *Bosen, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Di Ke Luo *Xing Qi, China.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Di Ke Shi *Weiwu Guangming, China.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Di Li *Tongyong, China.*
Inosine (p. 2533·1).

Di Li Jian *Yongguang, China.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Di Li Sheng *Weixing Bio Product, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Di Li Tuo *Yongguang, China.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Conjunctival hyperaemia.

Di Li Xin *Huajin, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Di Ling *Wansheng, China.*
Matrine.

Di Luo An *Livzon, China.*
⊗Prasterone sodium sulfate (p. 2299·2).

Di Mai Xin *Wan Ji, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Di Min *Huabang, China.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Di Na Ke *Dina, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Di Ning *ChangSheng Gene, China.*
Interferon alfa-1b (recombinant, human) (p. 989·2).

Di Nuo Xin *Qi Du, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Di Ou Ping *Guo Yao, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Di Pai *Lukang Chenxin, China.*
Faropenem sodium (p. 298·2).
Bacterial infections.

Di Pu *Xuebao, China.*
Diclofenac potassium (p. 48·3).

Di Retard *Llorens, Spain.*
Diclofenac sodium (p. 48·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders; pain; renal colic.

Di Sai Ping *Disai, China.*
Telmisartan (p. 1509·3).
Hypertension.

Di Sha *SanJiu JiShi, China.*
Propylene glycol alginate sodium.

Di Shan *Xing Qi, China.*
Atropine sulfate (p. 1310·2).
Production of mydriasis.

Di Shi Ning *Jiabo, China.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Di Shuang *Jiqi, China.*
Dipyrone (p. 53·3).
Pain; fever.

Di Shuang An *Dilong, China.*
L-Aspartic acid; potassium; magnesium.

Di Su Ni *Qi Du, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Di Suo *Disha, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Di Te Anatoxal *Berna, Philipp.†; Yeni, Turk.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Di Te Per Anatoxal *Yeni, Turk.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Dl VP *Pharmavita, Chile.*
Valproate semisodium (p. 553·2).
Bipolar disorder; epilepsy; migraine.

Di Wei *Huabang, China.*
Tretinoin (p. 1725·2).
Acne.

Di Wei Xin *Dilong, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids.

Di Xin Ni *Qi Du, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Di Ya Ping *Di Ao, China.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Di Yang *Disai, China.*
Matrine.

Di Yi *Ba Da, China; Luye, China.*
Aceglutamide (p. 2426·2).

Di Yi Ning *Tasly, China.*
Telmisartan (p. 1509·3).
Hypertension.

Di Yi Xin *Tasly, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Di Zhi Ya *Disha, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Dia *Eczacibasi-Baxter, Turk.*
A range of peritoneal dialysis solutions (p. 1778·2).

Dia D *Cimed, Braz.*
Levonorgestrel (p. 2296·1).

Dia-Aktivanad-N *Medice, Ger.*
Bovine liver extract (p. 2444·1); yeast extract (p. 2125·2); caffeine (p. 1203·3).
Tonic.

Diab Dos *Francelab, Arg.*
Metformin (p. 489·1).
Diabetes mellitus.

DiaB Gel *Carrington, USA.*
Acemannan (p. 2426·3).
Diabetic ulcers.

Diaba *Sun, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

DiaBackpain *Diapharm, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

Diabact UBT *Kibion, Denm.; Kibion, Fin.; Kibion, Ger.; Kibion, Irl.; Kibion, Norw.; Kibion, Swed.; Medical Diagnostics, UK.*
Carbon-13 (p. 2470·3) labelled urea.
Test for Helicobacter pylori infection.

Diaba-M *Sun, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea; dysentery.

Diabamet *Rimsa, Mex.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabamyl *Expanpharm, Fr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dia-Ban *Farmanic, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaban *Pascual, Philipp.*
Lagerstroemia speciosa.
Nutritional supplement for diabetics.

Diabanerve *Taj, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Diabasic *Phyto Health, India.*
Curcuma longa; gymnema silvestre; karela; terminalia chebula (p. 2474·3); fenugreek (p. 2504·1).
Diabetes mellitus.

Diabe Pass *Francelab, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diabecon *Himalaya Herbal, India.*
⊗Aloe vera (p. 1693·2); asparagus racemosus (p. 2614·2); indian barberry (p. 2532·1); punarnava (p. 2601·1); curcuma longa; eugenia jambolana; liquorice (p. 1853·2); gymnema silvestre; karela; ocimum sanctum; piper nigrum; pterocarpus marsupium; tinospora cordifolia; tribulus terrestris (p. 2633·3).
Diabetes mellitus.

Diabecontrol *Sanval, Braz.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

DiabeDerm *Bangkok Lab & Cosmetic, Thai.*
⊗Urea (p. 1727·3).
Ichthyosis; hyperkeratotic skin disorders.

Diabeedol *Sriprasit, Thai.†*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Diabefar *Elpen (Ελπεν), Gr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diabefarm *Farmakor, Rus.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabem *Integral Health, Mex.*
Emollient.

Diabemed *Germed, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diabemide *Guidotti, Ital.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Diabemin
Note: this name may be used for preparations of different composition.
Lafedar, Arg.
Glibenclamide (p. 472·1).
Diabetes mellitus.
Osoth, Thai.†
Glipizide (p. 474·1).
Diabetes mellitus.

Diaben
Note: this name may be used for preparations of different composition.
Elea, Arg.
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.
Kinder, Braz.†
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diabend *Bal, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabend-M *Bal, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Diabène *Lehning, Fr.*
⊗Alchemilla vulgaris; kreosotum (p. 1659·3); strychnicum nitricum (p. 2623·2); arsenicum album (p. 2448·1); adrenalinum (p. 1292·1); atropa belladonna (p. 2453·3); syzygium jambolanum; vaccinium myrtillus (p. 2566·2); taraxacum dens leonis (p. 2625·3); natrum phosphoricum (p. 1791·2); helonias dioica (p. 2524·3).
Homoeopathic preparation.

Diabenel *Biofarma, Mex.*
Vitamins.

Diabenol *Greater Pharma, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diaberet *Visufarma, Ital.*
Vitamin E (p. 2119·1); Oligopin; ubidecarenone (p. 2637·1).
Nutritional supplement.

Diaberid *Hizon, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diabesafe *Hong Kong Medical, Hong Kong.†*
Metformin (p. 489·1).
Diabetes mellitus.

Diabeside *Chew, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabesil *Gador, Arg.*
Metformin (p. 489·1).
Diabetes mellitus.

Diabesin *TAD, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabess *Pharmaherb, Hung.*
Taraxacum (p. 2625·3); urtica (p. 2639·3); St John's wort (p. 449·1); myrtillus (p. 2566·2); chicory (p. 2475·2).
Diabetes mellitus.

Diabest *Promed, Rus.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

DiaBeta *Sanofi-Aventis, Canad.; Hoechst Marion Roussel, USA.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diabetab *Bangkok Lab & Cosmetic, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabetamil *Nutrifood, Philipp.*
Calorie-controlled food replacement for diabetics.

Diabetan *Leros, Cz.*
Phaseolus (p. 2587·3); myrtillus (p. 2566·2); sage (p. 2608·3); galega; polygonum avicularis; taraxacum (p. 2625·3); raspberry leaf (p. 2603·1); fennel (p. 2503·2); lappa (p. 2540·1); liquorice (p. 1853·2).
Adjuvant in diabetes mellitus.

Diabetase *Sandoz, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabetasol *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition.
Diabetes mellitus.

Diabetese *T Man, Thai.†*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Diabetex *Germania, Austria.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabetic Tussin *Roberts, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine (p. 1672·2).
Coughs.

Diabetic Tussin Cold & Flu *Health Care Products, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Upper respiratory-tract disorders.

Diabetic Tussin DM *Roberts, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Diabetic Tussin Mucus Relief *Health Care Products, USA.*
Guaifenesin (p. 1666·2).
Cough.

Diabetic Tussin Night Time Cold/Flu Formula *Health Care Products, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); diphenhydramine (p. 626·1).
Upper respiratory-tract disorders.

Diabetická Čajová Směs-Megadiabetin *Megafyt-R, Cz.†*
Galega; phaseolus (p. 2587·3); myrtillus (p. 2566·2); urtica (p. 2639·3); sage (p. 2608·3); taraxacum (p. 2625·3).
Diabetes mellitus.

DiabetiDerm *Health Care Products, USA.*
Emollient.
Health Care Products, USA.
Undecenoic acid (p. 596·3).
Fungal skin infections.

Diabetiks *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; bioflavonoids (p. 2505·2); myrtillus (p. 2566·2); ginkgo biloba (p. 2512·3); green tea (p. 2648·2); pine bark;

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

acetylcysteine (p. 1652·2); taurine (p. 2626·2); ubidecarenone (p. 2637·1); lipoic acid (p. 2629·1).
Tonic.

Diabetisource com Nutrishield *Novartis, Braz.*
Preparation for enteral nutrition.

Diabetmin *Hovid, Hong Kong; Hovid, Malaysia; Gulf Drug, S.Afr.; Hovid, Singapore.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabetnil *Inga, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diabetofort *Leki Natury, Pol.*
Phaseolus (p. 2587·3); birch leaf (p. 2457·3); couch-grass (p. 2487·2); blackberry leaf; rose fruit (p. 2607·1).
Diabetes mellitus.

Diabetol *Polpharma, Pol.†*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Diabeton *Servier, Rus.; Servier, Ukr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabetone
Note: this name may be used for preparations of different composition.
Hizon, Philipp.
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Meyer, India; Vitabiotics, Indon.
Vitamins; minerals; trace elements.
Dietary supplement in diabetes mellitus.

Diabetosol *Herbapol Krakow, Pol.*
Galega officinalis; phaseolus vulgaris (p. 2587·3); taraxacum (p. 2625·3); couch-grass (p. 2487·2); cranberry leaf (p. 2488·1).
Diabetes mellitus.

Diabetrol *Piramal, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1) or metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabetrol-3D *Piramal, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1); rosiglitazone (p. 496·3).
Diabetes mellitus.

Diabe-Tuss DM *Paddock, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Diabetussic *Hasco-Lek, Pol.*
Sulfogaiacol (p. 1678·1).
Catarrh.

Diabetyl *Biotoscana, Chile.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabetyl-G *Biotoscana, Chile.†*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Diabevit *Psychotropics, India.*
Vitamins; minerals.

Diabex *Alphapharm, Austral.; Combiphar, Indon.; Merck, Neth.†; Merck, Port.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabexil *Arrow, Braz.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diabezid *Norma (Νορμα), Gr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabezidum *Jelfa, Pol.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabic *Adley, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabiclor *Mavi, Mex.†*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Diabic-M *Adley, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabiformine *Pfizer, Switz.†*
Chlorpropamide (p. 470·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diabinax *Shreya, Rus.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabinese *Pfizer, Arg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Mex.; Pfizer, Philipp.†; Pfizer, S.Afr.†; Farmasierra, Spain†; Pfizer, Thai.; Pfizer, Turk.*
Chlorpropamide (p. 470·1).
Diabetes mellitus; diabetes insipidus.

Diabion *Merck, Chile; Merck, Mex.*
Vitamins; minerals.

Metiska, Indon.
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); folic acid (p. 2063·1).
Anaemias; nutritional supplement.

Diabitex *Rekah, Israel†; Thebe, S.Afr.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Diabitor *Unison, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

DiaBlack *Diapharm, UK.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Diab-Norm *KRKA, Rus.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Diaborale *Marvecs, Ital.*
Glycyclamide (p. 475·1).
Diabetes mellitus.

Diabose *Micro, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Diabrezide *Molteni, Austria; Molteni, Irl.; Molteni, Ital.; Molteni, Pol.; Molteni, Rus.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diabur-5000 *Roche Diagnostics, NZ.†*
Test for glucose in urine (p. 2516·3).

Diabur-Test 5000 *Roche Diagnostics, Austral.†; Roche Diagnostics, Irl.†; Roche Diagnostics, Ital.; Roche Diagnostics, Mex.†; Roche Diagnostics, UK.*
Test for glucose in urine (p. 2516·3).

Diabuse *Samarth, India.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Diabutil *Elea, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

DiaCalm *Diapharm, UK.*
Valerian (p. 2640·2); St John's wort (p. 449·1).
Anxiety; sleep disorders.

Diacarb *Polpharma, Rus.; Polpharma, Ukr.*
⊗Acetazolamide (p. 2001·1).
Oedema; glaucoma; epilepsy; altitude sickness.

Diacard *Madaus, Ger.*
Valeriana (p. 2640·2); aether sulfuricus (p. 1900·3); camphora (p. 2466·2); cactus (p. 2473·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Diacardyne *Ethypharm, Irl.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diacare
Note: this name may be used for preparations of different composition.
Be-Tabs, S.Afr.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Farmalider, Spain.†
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Combined oral contraceptive in women with androgenic symptoms; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Diace Co *Simayla, S.Afr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Diacer *Phoinix Pharm (Φοινιξ Φαρμ), Gr.; Cadila, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Diaceril *Nexus, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Diachrotin *Taiwan Biotech, Philipp.*
Chromium tripicolinate (p. 2056·1); biotin (p. 2052·2).
Dietary supplement for diabetics.

DiaCimi *Diapharm, UK.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Diacine *Valenta, Rus.*
Mebhydrolin (p. 634·2); zinc sulfate (p. 2126·2).
Hypersensitivity reactions.

Diaclam *East West, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; seizures; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome.

Diaclid *Integrated Pharmaceutical, Philipp.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaclide *Gerard, Irl.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diacneal *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Medifarm Avene, Venez.*
Retinaldehyde (p. 1719·1); glycolic acid (p. 1704·3); thermal water.
Acne.

DiaCo *Mediherb, Austral.*
Achillea (p. 2427·3); echinacea (p. 2498·1); liquorice (p. 1853·2); sambucus (p. 2609·3); tilia (p. 2631·3); ginger (p. 1844·1).
Cold and influenza symptoms.

Diacobal *Orchid, India.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Diacobal Forte *Orchid, India.*
Vitamin B substances (p. 2102·3).

Diacobal Plus *Orchid, India.*
Vitamin B substances (p. 2102·3).

Diacol
Note: this name may be used for preparations of different composition.
Bial, Port.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Fresenius Kabi, Austral.
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

DiaCold *Diapharm, UK.*
Pelargonium sidoides (p. 2585·2).
Upper respiratory-tract infections.

Dia-Colon *Piam, Ital.*
Lactulose (p. 1850·3).
Constipation.

Diacomit *Biocodex, Belg.; Biocodex, Cz.; Biocodex, Denm.; Biocodex, Fr.; Biocodex, Irl.; Meiji, Jpn; Biocodex, Neth.; Desitin, Norw.; Biocodex, Pol.; Biocodex, Port.; Desitin, Swed.; Alan, UK.*
Stiripentol (p. 549·1).
Epilepsy.

Diacon *Bal, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Diacon M *Bal, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Diacor *Pasteur, Chile.*
Mebendazole (p. 158·3).
Worm infections.

Dexo, Fr.†
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diacordin *Zentiva, Cz.; Zentiva, Pol.†; Leciva, Rus.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Diacose *T Man, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

DiaCough *Diapharm, UK.*
Ivy (p. 2536·2).
Cough.

Diacqua *Eurofarma, Braz.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; hypokalaemia; aldosteronism.

Diactal *Neuropharma, Arg.*
Diazepam (p. 1063·2).

Di-Actane *Menarini, Fr.*
Naftidrofuryl oxalate (p. 1443·3).
Mental function impairment in the elderly; cerebral and peripheral vascular disorders.

Diacure
Note: this name may be used for preparations of different composition.
Cure Quick, India.
Diacerein (p. 45·3).
Osteoarthritis.

Vickmans, Hong Kong†; Johnson & Johnson, Neth.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lehning, Fr.
Taraxacum (p. 2625·3); berberis vulgaris (p. 2502·1); juglans regia (p. 2646·1); achillea (p. 2427·3); myrtillus (p. 2566·2); erythrea centaurium (p. 2473·2); natrum phosphoricum (p. 1791·2).
Homoeopathic preparation.

Diacutis *Pierre Fabre Dermatologie, Fr.†*
Sodium fusidate (p. 302·1).
Staphylococcal skin infections.

Diacyclan *Norma (Νορμα), Gr.*
Bencyclane fumarate (p. 1315·1).

DiaDay & Night *Diapharm, UK.*
Melissa (p. 2552·3); valerian (p. 2640·2); passion flower (p. 2584·1).
Anxiety; insomnia; digestive disorders.

Diadef *Sanli, Turk.*
Loperamide (p. 1854·2).
Diarrhoea.

Diadeon *Servier, Cz.; Servier, Port.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diadermina *Plata, Arg.†*
Ammonium stearate.

Diadex *Polinac, Venez.*
Dexpanthenol (p. 2582·2); menthol (p. 2553·2); camphor (p. 2466·2).
Pruritus; skin irritation.

Diadex Phis *Polinac, Venez.*
Soap substitute.

Diadicon *Labomed, Chile.*
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1).
Cough; respiratory-tract congestion.

Diadium *Lapi, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diadon *Acdhon, Thai.*
Diazepam (p. 1063·2).

Diadose *Solitaire, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Di-Adreson-F *ACE, Fin.; Organon, Hung.†; ACE, Neth.*
⊗Prednisolone sodium succinate (p. 1646·1).
Corticosteroid.

Organon, Hong Kong†; MSD, Thai.
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Diaend *Mugi, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Diafac *Phapros, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diafalk *Falk, UK.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Diafat *Sandoz, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diafer *East West, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

DiaFeverfew *Diapharm, UK.*
Feverfew (p. 676·1).
Migraine.

Diafit *Ikapharmindo, Indon.*
Preparation for enteral nutrition.
Diabetes mellitus.

Diafoot *Fourrts, India.*
⊗Allantoin (p. 1693·1); dimeticone (p. 2209·3); glycerol (p. 2517·2); liquid paraffin (p. 2191·2); propylene glycol (p. 2205·2); urea (p. 1727·3).

Diaforin *Brainpharma, Spain.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders in children.

Diaformin *Alphapharm, Austral.; Uniao Quimica, Braz.; Alphapharm, China; Alphapharm, Hong Kong; Camox, S. Afr.; Merck, Singapore; Ali, Turk.; Farmak, Ukr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaformina *Roemmers, Venez.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaformina Plus *Roemmers, Venez.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Diaforte *Cipla, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diafree *Biofarma, Turk.*
Repaglinide (p. 495·2).

Diafuran
Note: this name may be used for preparations of different composition.
Cazi, Braz.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Kramer, Philipp.
Furazolidone (p. 933·3).
Gastrointestinal infections.

Diafuryl *Cooperation Pharmaceutique, Fr.; Mecom, Turk.*
Nifuroxazide (p. 331·3).
Diarrhoea; gastro-enteritis.

Diafusor *MSD, Belg.; Pierre Fabre, Fr.; Pierre Fabre, Port.†; Pierre Fabre, Spain; Pierre Fabre, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Diagen *Generics, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diagesic *Biotech, Venez.*
Diclofenac potassium (p. 48·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Diagit *Interbat, Indon.*
Attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Diagli *Ordain, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaglim *Biochem, India; Sandoz, Mex.; Sandoz, Philipp.; Cipla-Medpro, S.Afr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaglime *Kalbe, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaglimet *Abiogen, Ital.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaglin *Fako, Turk.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaglip
Note: this name may be used for preparations of different composition.
Cipla, India.
Glipizide (p. 474·1).
Diabetes mellitus.

Siam Bheasach, Thai.
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaglip M *Cipla, India.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaglit *Biochem, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Diaglitab *Lafi, Chile.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaglitab Plus *Lafi, Chile.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Diaglitazon *Akrikhin, Rus.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Diaglizide *Farmak, Ukr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaglow *Aglowmed, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).
Diarrhoea.

Diaglucide *Biogaran, S.Afr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaglyc *Teva, Irl.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaglyk *Ashbourne, UK.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaglytason *Farmak, Ukr.†*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Diagnogreen *Hong Kong Medical, Hong Kong.†*
Indocyanine green (p. 2532·3).
Diagnostic agent.

Diagnol *Farmak, Ukr.*
Macrogol (p. 2547·3).
Bowel evacuation.

Diagnosis *Rottapharm, Ital.*
Pregnancy test (p. 2596·1).

Diagran *Teofarma, Ital.*
Vitamins.

Diagran Minerale *Teofarma, Ital.*
Vitamins; minerals.

DiaHarp *Diapharm, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

Diah-Limit *Wockhardt, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diakair *PDC, India.*
Capsules: Vitamins; minerals.

PDC, India.
Oral powder: Preparation for enteral nutrition.

PDC, India.
Oral liquid: Vitamins minerals; lysine hydrochloride (p. 2079·3).

Diakarmon *Help, Gr.*
Gentamicin sulfate (p. 304·2).

Diakit-3 *Zydus, India.*
Slow-release tablets, glimepiride (p. 473·2); metformin (p. 489·1); capsules, ramipril (p. 1483·3).

Diakit-4 *Zydus, India.*
Atorvastatin (p. 1309·2); slow-release tablets, glimepiride (p. 473·2); metformin (p. 489·1); capsules, ramipril (p. 1483·3).

Diakof *Himalaya Herbal, India.*
Malabar nut (p. 2549·1); cinnamomum cassia (p. 2471·3); liquorice (p. 1853·2); nutmeg (p. 2573·1); ocimum sanctum; tinospora cordifolia; grape (p. 2521·3).
Cough in diabetes mellitus.

Dial Complete *Dial, Canad.*
Triclosan (p. 1773·2).
Hand disinfection.

Dialac *Kalbe, Indon.*
Lactobacillus acidophilus (p. 2596·3); ascorbic acid (p. 2110·3); calcium (p. 1783·1); nicotinamide (p. 2083·1); zinc oxide (p. 1729·1); thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3).
Gastrointestinal disorders.

Dialamine *Nutricia, Austral.; Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.*
Food for special diets.
Urea cycle disorders.

Scientific Hospital Supplies, Israel.
Amino acids.
Enteral nutrition.

SHS, UK.
Proteins; carbohydrates; vitamin C (p. 2110·3).
Enteral nutrition.

Dialar *Sandoz, UK.*
Diazepam (p. 1063·2).

Dialeed *Misha, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Dialeli AF *Valdecasas, Mex.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3).
Prevention of neural tube defects; iron-deficiency anaemia.

Dialens *Bausch & Lomb, Port.†*
Chlorhexidine gluconate (p. 1743·3).
Tear deficiency; contact lens care.

Bausch & Lomb, Switz.†
⊗Dextran 70 (p. 1138·3).
Dry eyes; wetting agent for contact lenses.

Dialgin *Collins, Mex.†*
Diiodohydroxyquinoline (p. 931·1); furazolidone (p. 933·3); homatropine (p. 2007·3).
Amoebiasis; diarrhoea.

Dialgine *Intermedica, Switz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Dialgirex *Sanofi-Aventis, Fr.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Dialgyl *Norma (Νορμα), Gr.*
Granisetron hydrochloride (p. 1844·3).

Dialider *Farmalider, Spain.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women; oral contraception in women with androgenic symptoms.

Dialife *Dalmia, India.*
Gymnema silvestre; karela; pterocarpus marsupium; fenugreek (p. 2504·1).
Diabetes mellitus.

Dialinax *Caber, Ital.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dialine *Teva, Israel.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
A range of solutions for peritoneal dialysis.

Dialipon *Farmak, Ukr.*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy; livers disorders.

Dialisis Peritoneal *Baxter, Spain.†*
Electrolytes (p. 1775·1); glucose monohydrate (p. 2069·1) (p. 1778·2).
Peritoneal dialysis.

Dialitika II *Argenfarma, Arg.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Renal calculi.

Diallertest *DBV, Fr.*
Patch test for cow's milk protein allergy (p. 2434·3).

Dial-ND *Neo Dermos, Arg.*
Cystine (p. 2059·1); cysteine (p. 2058·3); methionine (p. 1558·2); vitamin F (p. 2509·2).

Dialon
Note: this name may be used for preparations of different composition.
Eisai, Indon.
Indometacin farnesil (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders.

Julphar, UAE.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dialon-T *Alet, Gr.†; Specifar, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Dialosa *Specifar, Fin.; Specifar, Gr.; Valeant, Hung.; Specifar, Singapore.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Dialox *Aglowmed, India.*
Diloxanide furoate (p. 931·2); dimeticone (p. 1886·2); tinidazole (p. 949·2).
Amoebiasis.

Dialudon *Sigma, Braz.*
Phenytoin (p. 538·2); diazepam (p. 1063·2).
Epilepsy.

Dialume *Rhone-Poulenc Rorer, USA.†*
Aluminium hydroxide (p. 1817·2).
Hyperacidity.

Dialvit *Bichsel, Switz.*
Vitamins.
Dietary supplement in renal failure.

Dialycare *Abbott, Ital.*
Preparation for enteral nutrition.
Renal dialysis.

Dialypro *HAC, Fr.*
Preparation for enteral nutrition.

Dialysol Acide *Soludia, Fr.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); acetic acid (p. 2426·3) (p. 1778·2).
Haemodialysis solution.

Dialysol Bicarbonate *Soludia, Fr.†*
Sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1778·2).
Haemodialysis solution.

Dialyte *Gambro, USA.*
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1778·2).
Peritoneal dialysis solution.

Dialyvite *Hillestad, USA.*
Vitamins; minerals.

Diamaxin *Synergen, Philipp.*
Chromium tripicolinate (p. 2056·1); thioctic acid (p. 2629·1); zinc sulfate (p. 2126·2).
Dietary supplement for diabetics.

Diameb *Precimex, Mex.†*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Diamed *Medicpharma, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia.

Diamel
Note: this name may be used for preparations of different composition.
Benedetti, Ital.
Glimepiride (p. 473·2).
Diabetes mellitus.

SM, Venez.
Fumaric acid (p. 1704·2); wild lettuce (p. 2647·3); ascorbic acid (p. 2110·3); amino acids; zinc sulfate (p. 2126·2); vitamin B substances (p. 2102·3); cranberry (p. 2488·1).
Nutritional supplement in diabetes mellitus.

Diamelitus *Zekides, Gr.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Diamellitis *Mabra, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diamelon *CCM, Malaysia.*
Karela.
Tonic.

DiaMenoCalm *Diapharm, UK.*
St John's wort (p. 449·1); cimicifuga (p. 2478·1).
Menopausal disorders.

Diameprid *Abdi, Turk.; Trifarma, Ukr.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diameride *Intas, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diamet *Bal, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Weifa, Thai.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diamet PG *Bal, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Diamex *Sam Chun Dang, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diamexon *TO-Chemicals, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diamicron *Servier, Arg.; Servier, Austral.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, Canad.; Servier, China; Servier, Denm.; Pharmalab, Fr.; Servier, Ger.; Servier, Gr.; Servier, Hong Kong; Serdia, India; Servier, Indon.; Servier, Irl.; Servier, Ital.; Servier, Malaysia; Servier, Mex.; Servier, Neth.; Servier, NZ; Servier, Philipp.; Servier, Port.; Servier, S.Afr.; Servier, Singapore; Servier, Spain; Servier, Switz.; Servier, Thai.; Servier, Turk.; Servier, UK; Servier, Venez.*
Gliclazide (p. 472·3).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Diamide
Note: this name may be used for preparations of different composition.
Mylan, NZ; Filadams, Philipp.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Hovid, Malaysia.
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diamig *Micro, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

DiaMigraine *Diapharm, UK.*
Feverfew (p. 676·1).
Migraine.

Diamin
Note: this name may be used for preparations of different composition.
Grossman, Mex.
α-Dihydroergocryptine mesilate (p. 390·2).
Hyperprolactinaemia.

Reliance, India.
Imipramine (p. 426·2).
Depression; nocturnal enuresis.

Diamin Plus *Reliance, India.*
Diazepam (p. 1063·2); imipramine (p. 426·2).

Diamine *Euro-Pharm, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Diaminocillina *Salvay, Ital.†*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Diamite *Homeocan, Canad.*
Calcarea fluorica (p. 2053·1); calcaream phosphorica (p. 1784·2); calciarea sulphurica (p. 2173·1); ferrum phosphoricum (p. 2077·1); magnesia phosphorica (p. 1786·3); kali muriaticum (p. 1793·2); kali phosphoricum (p. 1791·1); kali sulphuricum (p. 1793·2); natrum muriaticum (p. 1795·1); natrum phosphoricum (p. 1791·2); natrum sulphuricum (p. 1888·1); silicea (p. 2208·3).
Homoeopathic preparation.

Diamitex *Duopharma, Hong Kong†; CCM, Malaysia.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diamitus *Teva, Hung.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diamixin *Errekappa, Ital.*
Rifaximin (p. 355·2).

Diamol *Chinta, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

DiaMood *Diapharm, UK.*
Valerian (p. 2640·2).
Anxiety; sleep disorders.

Diamotil *Vickmans, Hong Kong.†*
Diphenoxylate (p. 1835·3).
Atropine (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Diamox *Wyeth, Arg.; Aspen, Austral.; Goldshield, Austria; MPI, Belg.; Genom, Braz.; Uniao Quimica, Braz.; Wyeth, Canad.†; Goldshield, Denm.; Goldshield, Fin.†; Sanofi-Aventis, Fr.; Mercury, Ger.; IFET (ΙΦΕΤ), Gr.; Wyeth, Hong Kong†; Wyeth, India; Lederle, Indon.†; Goldshield, Irl.; Teofarma, Ital.; Mercury, Neth.; Goldshield, Norw.; Healthcare Logistics, NZ; Wyeth, Philipp.†; Pharmafrica, S. Afr.; Lederle, Singapore; Abcur, Swed.; Vifor, Switz.; Pfizer, Thai.; Goldshield, UK; Barr, USA.*
⊗Acetazolamide (p. 2001·1) or acetazolamide sodium (p. 2001·1).
Glaucoma; epilepsy; oedema; Ménière's disease; pancreatic disorders; heart failure; premenstrual syndrome; respiratory insufficiency; raised intra-ocular pressure; ocular hypertension; hypercapnia; high-altitude disorders; absence seizures.

Diamprex *Liferpal, Mex.†*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Dian Ke Shu *Hua Lu, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Dian Shu *Qilu, China.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Dian Tai *Hengrui, China.*
Sodium valproate (p. 553·1).
Migraine; bipolar disorder; epilepsy.

Dianben *Merck Sante, Spain.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diane *Bayer, Arg.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer, India; Bayer Schering, Indon.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer Schering, Pol.; Berlifarma, Port.; Bayer Schering, Rus.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Schering, Venez.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Polycystic ovary syndrome; androgen-dependent acne, alopecia, hirsutism, and seborrhoea; oral contraceptive for women with androgenic symptoms.

Bayer, Austral.; Bayer Schering, S.Afr.
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgenisation in women; combined oral contraceptive.

Diane-35 *Bayer, Ukr.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Dianeal *Baxter, Austral.; Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fr.; Baxter, Hung.; Baxter, Indon.†; Baxter, Irl.; Baxter, Israel; Baxter, Neth.; Baxter, Philipp.; Baxter, Port.; Baxter, Rus.; Baxter, Spain; Baxter, Swed.†; Baxter, Switz.†; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, USA.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1) (p. 1778·2).
A range of solutions for peritoneal dialysis.

Baxter, Fin.
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
Peritoneal dialysis.

Baxter, Venez.
Solutions for peritoneal dialysis (p. 1778·2).

Dianeral *Soho, Indon.*
Preparation for enteral nutrition in diabetes mellitus.

Dianerve *Grandix, India.*
Vitamins; minerals; thioctic acid (p. 2629·1).

Dianette *Bayer, Irl.; Schering, UK.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.
Oral contraceptive in women with severe acne; acne and hirsutism in females.

Dianicotyl *IFET (ΙΦΕΤ), Gr.*
Isoniazid (p. 311·2).
Tuberculosis.

Dianid *Biolab, Malaysia; Biolab, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

DiaNight *Diapharm, UK.*
Valerian (p. 2640·2).
Sleep disorders.

DiaNight Plus *Diapharm, UK.*
Valerian (p. 2640·2); passion flower (p. 2584·1).
Sleep disorders.

Diano *Milano, Thai.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; insomnia; psychoneurotic disorders; autonomic disorders.

Dianoct *Silesia, Chile.†*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Dianorm
Note: this name may be used for preparations of different composition.
Eurodrug, Hong Kong†; Micro, India; Merck, Philipp.; Eurodrug, Singapore.
Gliclazide (p. 472·3).
Diabetes mellitus.

Kocak, Turk.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Dianormax *Grunenthal, Chile.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Dianormet *Polfa, Rus.; Teva, Ukr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dianorm-M *Micro, India; Micro Labs, Ukr.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dianosis-MF *Intel, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Dianosis-P3 *Intel, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Dianova *Alternova, Denm.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea; oral contraceptive in women with androgenic symptoms.

Di-Antalvic *Sanofi-Aventis, Fr.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Dianuron *Indo French, India.*
Betacarotene (p. 2051·1); *d*-alpha tocopherol (p. 2119·1); vitamin B substances (p. 2102·3); chromium (p. 2055·3); inositol (p. 2533·2); thioctic acid (p. 2629·1); selenomethionine (p. 2087·1); vanadium; zinc picolinate (p. 2126·1).

Dianutrin *Biological E, India.*
Vitamins; minerals.

Diao Xin Xue Kang *SU, Neth.*
Dioscorea nipponica makino.
Pain.

Diaob *Genesis, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diaob-M *Genesis, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Diapam
Note: this name may be used for preparations of different composition.
Orion, Fin.; Greater Pharma, Thai.; Tems, Turk.
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; insomnia; psychoneurotic disorders; autonomic disorders; pain; status epilepticus; premedication; alcohol withdrawal syndrome; febrile convulsions.

Pasteur, Chile.
Chlormezanone (p. 1045·1); diazepam (p. 1063·2).
Anxiety; musculoskeletal spasm; sleep disorders.

Dia-Par Compuesto *Streger, Mex.*
Nifuroxazide (p. 331·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Diaparene Corn Starch *Personal Care, USA.*
Corn starch (p. 2095·1); aloes (p. 1816·1).
Nappy rash.

Diaparene Diaper Rash *Personal Care, USA.*
Zinc oxide (p. 1729·1).
Nappy rash.

DiaPassion *Diapharm, UK.*
Passion flower (p. 2584·1).
Anxiety.

Diapatol *Teofarma, Ital.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety disorders; depression; insomnia.

Diapectin *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Singapore.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Diapectolin *Medi-Rx, Philipp.*
Furazolidone (p. 933·3).
Gastrointestinal infections.

DiaPelargo *Diapharm, UK.*
Pelargonium sidoides (p. 2585·2).
Upper respiratory-tract infections.

Diaper Guard *Del, USA.*
Dimeticone (p. 2209·3); white soft paraffin (p. 2211·3); vitamin A (p. 2098·3); vitamin D_3 (p. 2112·3); vitamin E (p. 2119·1).
Nappy rash.

Diaper Rash *Goldline, USA; Rugby, USA.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Nappy rash.

Sutton, Canad.
Zinc oxide (p. 1729·1).
Nappy rash.

Diaper-Care *Weleda, Canad.†*
Zinc oxide (p. 1729·1).

Diaperol *Diba, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diaperyl *Medi-Rx, Philipp.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Diapet *Soho, Indon.*
Coix lacryma-jobi semen; psidium guajava; phellodendri radix; turmeric (p. 2218·1); rhizoma coptidis.
Diarrhoea.

Diapex-M *Apotex, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Diaphage *SVUS, Cz.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaphal *Pierre Fabre, Ger.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Oedema; hypertension; ascites.

Diaphin *Diamo, Switz.*
⊗Diamorphine hydrochloride (p. 46·1).
Opioid dependence.

Diaphyllin *Extractum, Hung.; Gedeon Richter, Hung.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Diapill *Ordain, India.*
Thioctic acid (p. 2629·1); inositol (p. 2533·2); taurine (p. 2626·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).

Diapine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; epilepsy.

Diapirid *Farmak, Ukr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diapiride *OM, Port.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diapo *CCM, Malaysia; Beacons, Singapore.*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal syndrome; epilepsy; skeletal muscle spasm; insomnia; premedication; agitation; autonomic disorders; sleep disorders.

Diaprel *Servier, Cz.; Anpharm, Hung.; Anpharm, Pol.; Servier, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diapresan *Bago, Chile.*
Trazodone hydrochloride (p. 451·1).
Depression.

Diapride *Aspen, Austral.; Eurodrug, Hong Kong; Micro, India; Eurodrug, Malaysia; Eurodrug, Mex.; Eurodrug, Philipp.; Eurodrug, Singapore.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diapride Forte *Micro, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Diapride Plus *Micro, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Diaprid-M *Uniroyal, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Diapro *Beximco, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diapulmon *PannonPharma, Hung.*
Thymol (p. 1772·2); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Upper respiratory-tract disorders.

Diaquitte *Peach, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diara *Obolenskoe, Rus.; Burapha, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Diaralia *Boiron, Fr.*
Arsenicum album (p. 2448·1); chinchona rubra (p. 2478·3); podophyllum peltatum (p. 1717·1).
Homoeopathic preparation.

Diaran *Ranbaxy, S.Afr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diarcalm *McGloin, Austral.†*
Oral liquid: Light kaolin (p. 1850·1); pectin (p. 2200·3); catechu (p. 2472·3); aluminium hydroxide (p. 1817·2).
Diarrhoea; stomach pain.

DiaRelax *Diapharm, UK.*
Melissa (p. 2552·3); valerian (p. 2640·2); passion flower (p. 2584·1).
Anxiety; insomnia; digestive disorders.

Diarem *Pharmachemie, Neth.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diaremix *Mili, Ukr.*
Lactobacillus acidophilus (p. 2596·3); loperamide hydrochloride (p. 1854·2); dicycloverine hydrochloride (p. 1834·2).
Diarrhoea.

Diaren *Saval, Chile.*
Nifuroxazide (p. 331·3); activated attapulgite (p. 1820·1).
Diarrhoea.

Diarent *Chew, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarest *Hind Wing, Hong Kong.†*
Diphenoxylate (p. 1835·3).
Atropine (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Diaretyl *Cooperation Pharmaceutique, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarex
Note: this name may be used for preparations of different composition.
Himalaya Herbal, India.
Cyperus rotundus; tinospora cordifolia.
Diarrhoea.

Diareze
Note: this name may be used for preparations of different composition.
Key, Austral.; Boots Healthcare, Irl.†; Boots, UK.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Key, Austral.†
Oral suspension: Attapulgite (p. 1820·1); pectin (p. 2200·3); simeticone (p. 1886·2).
Diarrhoea.

Diarfin
Note: this name may be used for preparations of different composition.
Cinfa, Spain.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarfix *Cristers, Fr.*
Racecadotril (p. 1881·3).
Diarrhoea.

Diargal *bsa, Fr.*
Infant feed.
Diarrhoea.

Diarigoz *Guigoz, Fr.†*
Infant feed.
Diarrhoea.

Diaril
Note: this name may be used for preparations of different composition.
Biofarm, Pol.
Glimepiride (p. 473·2).
Diabetes mellitus.

Diarine *Burapha, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diaris *Poen, Arg.*
Vitamins; minerals.
Dietary supplement.

Diarlop *Jagsonpal, India.*
Capsules: Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Jagsonpal, India.
Oral suspension: Nalidixic acid (p. 328·3).
Diarrhoea.

Diarlop Plus *Jagsonpal, India.*
Capsules: Loperamide (p. 1854·2).
Diarrhoea.

Jagsonpal, India.
Oral suspension: Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Diarlop-CT *Jagsonpal, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Diarman *Berman, Mex.*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Diarmonis *Actavis, Fr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Diarodil *Greater Pharma, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarona
Note: this name may be used for preparations of different composition.
Vincenti, Venez.
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Diarönt mono *CNP, Ger.*
Colistin sulfate (p. 275·3).
Selective gastrointestinal tract decontamination.

Diaropect *Chew, Thai.*
Capsules: Furazolidone (p. 933·3); homatropine methylbromide (p. 2007·3); neomycin sulfate (p. 330·1); phthalylsulfathiazole (p. 339·3).
Diarrhoea.

Chew, Thai.
Syrup: Furazolidone (p. 933·3); light kaolin (p. 1850·1); neomycin sulfate (p. 330·1); pectin (p. 2200·3).
Diarrhoea.

Diarreeremmer *HTP, Neth.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarrest RF
Note: this name may be used for preparations of different composition.
Galen, Irl.†
Loperamide hydrochloride (p. 1854·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2).
Diarrhoea.

Diarrex *Hylands, Canad.*
Arsenicum album (p. 2448·1); chamomilla (p. 2474·1); mercurius viv (p. 2555·3); phosphorus (p. 2589·2); podophyllum peltatum (p. 1717·1).
Homoeopathic preparation.

Diarr-Eze *Pharmascience, Canad.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarrhea *Homeocan, Canad.*
Cinchona officinalis (p. 2478·3); bryonia alba; chamomilla (p. 2474·1); colocynthis (p. 1833·3); ipeca (p. 1667·2); belladonna (p. 2453·3).
Homoeopathic preparation.

Diarrhea Relief *Pharmascience, Canad.; Vita Health, Canad.*
Loperamide hydrochloride (p. 1854·2).

Diarrheel S *Ebi, Switz.*
Argentum nitricum (p. 2615·3); acidum arsenicosum (p. 2448·1); colchicum autumnale; hydrargyrum bichloratum (p. 2555·2); podophyllum (p. 1717·1); veratrum album (p. 2644·3); potentilla erecta (p. 2633·2); citrullus colocynthis (p. 1833·3).
Homoeopathic preparation.

Heel, Neth.
Argentum nitricum (p. 2615·3); arsenicum album (p. 2448·1); colchicum autumnale (p. 607·1); colocynthis (p. 1833·3); mercurius corrosivus (p. 2555·2); podophyllum peltatum (p. 1717·1); veratrum album (p. 2644·3).
Homeopathic preparation.

Diarrhoesan *Jacoby, Austria; Loges, Ger.*
Pectin (p. 2200·3); chamomile extract (p. 2474·1).
Diarrhoea.

Diarrocalmol *Benitol, Arg.*
Phthalylsulfathiazole (p. 339·3); activated charcoal (p. 1537·3).
Diarrhoea.

DiarrStope *Age D'or, Singapore.*
Lactobacillus acidophilus (p. 2596·3).
Gastrointestinal disorders.

Diarstene *Sanofi-Aventis, Ital.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarstop *Giuliani, Ital.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diarzero *Farmakopea, Ital.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diasafe *MSN, India.*
Vitamins; minerals; trace elements; lycopene (p. 2546·2).

Diascan *Home Diagnostics, USA.*
Test for glucose in blood (p. 2516·3).

Diasec *Hexal, Braz.; Armoxindo, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diasectral *Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.*
⊗Acebutolol hydrochloride (p. 1289·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Diasef *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Diaseptyl *Ducray, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of superficial wounds; skin cleansing.

Diaset *Stadmed, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaset-M *Stadmed, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diasgest *Siam Bheasach, Thai.*
Amylase (p. 2442·1); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); aluminium magnesium silicate (p. 2168·2); scopolia (p. 2611·3); vitamin B_1 (p. 2102·3).
Dyspepsia; gastric hyperacidity; gastritis; heartburn; gastrointestinal motility disorders.

Diasim *Symbiotic, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Diasip *Nutricia, Austral.; Support, Braz.; Nutricia, Ital.*
Preparation for enteral nutrition in diabetic patients.

Nutricia-Bago, Arg.; Nutricia, Cz.; Nutricia, Fin.; Nutricia, Irl.; Nutricia, Port.
Preparation for enteral nutrition.
Diabetes mellitus.

Diasistol *Pentafarma, Port.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Diasistol Plus *Pentafarma, Port.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

DiaSleep *Diapharm, UK.*
Valerian (p. 2640·2).
Sleep disorders.

DiaSleep Plus *Diapharm, UK.*
Valerian (p. 2640·2); passion flower (p. 2584·1).
Sleep disorders.

Diaslim *Community Pharmacy, Thai.*
Metformin (p. 489·1).
Diabetes mellitus.

Diasol
Note: this name may be used for preparations of different composition.
Ipca, India.
Diacerein (p. 45·3).
Osteoarthritis.

Diason *Nutricia, China; Nutricia, Ital.*
Preparation for enteral nutrition in diabetic patients.

Nutricia-Bago, Arg.; Nutricia, Cz.; Nutricia, Pol.; Nutricia, Port.
Preparation for enteral nutrition.
Diabetes mellitus; impaired glucose tolerance.

Nutricia, Fin.
Preparations for enteral nutrition.

Diasorane *Darier, Mex.*
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Diasorb
Note: this name may be used for preparations of different composition.
Yeni, Turk.; Columbia, USA.
Activated attapulgite (p. 1820·1).
The name Diasorb has also been used to describe a preparation containing loperamide.
Diarrhoea.

Diastabol *Sanofi-Aventis, Austria; Bayer, China; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Fin.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.†; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.†*
Miglitol (p. 491·3).
Diabetes mellitus.

Diastat
Note: this name may be used for preparations of different composition.
Valeant, Canad.; Valeant, USA.
Diazepam (p. 1063·2).
Epilepsy; convulsions.

Diastix *Bayer Consumer, Arg.; Bayer Diagnostics, Austral.; Bayer, Canad.†; Bayer, India†; Bayer Diagnostics, Irl.; Bayer, Ital.; Bayer Diabetes Care, Mex.; Bayer, NZ†; Bayer Diagnostics, UK.*
Test for glucose in urine (p. 2516·3).

Diaston *Ifars, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diastone *Microsules, Arg.*
Diclofenac sodium (p. 48·3).
Fever; inflammation; pain.

Diastop
Note: this name may be used for preparations of different composition.
Flamingo, Philipp.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Mylan, NZ.
Diphenoxylate hydrochloride (p. 1835·3).
Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Diastrolib *Cephalon, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diasulin *Tobbest Busindo, Indon.*
Amino acids; vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); fumaric acid (p. 1704·2); zinc sulfate (p. 2126·2); lettuce (p. 2647·3); blueberry.
Dietary supplement for diabetes mellitus.

Diaswich *Jagsonpal, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diaswich M *Jagsonpal, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diataal *USV, India.*
Vitamins; minerals; trace elements; dunaliella salina.

Diatabs Reformulated *Biomedis, Hong Kong.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diatabs (Reformulated)
Note: this name may be used for preparations of different composition.
United Laboratories, Philipp.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Diatelan *Reuffer, Mex.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Diathynil *Avantgarde, Ital.*
Biotin (p. 2052·2).
Skin disorders; biotin deficiency; digestive disorders.

Diatica *Unique, Rus.; Unique, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diatin *Ferrer, Spain.†*
Elcatonin (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia of malignancy.

Diatisan *Lehning, Fr.†*
Centaury (p. 2473·2); lupulus (p. 2546·1); juniper (p. 2537·1); bitter-orange peel (p. 2575·3); gentian (p. 2512·1); peppermint leaf (p. 1877·1).
Reduced appetite.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Diatol *Pacific, Hong Kong; Pacific, NZ.†*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Diatrim *Trima, Israel.*
Diacerein (p. 45·3).
Osteoarthritis.

Diatrol
Note: this name may be used for preparations of different composition.
Aurobindo, India.
Gliclazide (p. 472·3).
Diabetes mellitus.

Sunward, Singapore.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Christo, Hong Kong.†
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Diatrol-M *Aurobindo, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Diatussin *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); menthol (p. 2553·2); ammonium chloride (p. 1656·1); theophylline (p. 1229·3).
Formerly known as Adco-Diatussin.
Cough.

Diatx *Pan American, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Diatx Fe *Pan American, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); ferrous fumarate (p. 2060·3).

Diatyl *Procter & Gamble, Braz.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

DiaUrtica *Diapharm, UK.*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Diaval *Valdecasas, Mex.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Diavasc *Biological E, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Diavasc-AT *Biological E, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Diavista *Reddy, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Diavista-M *Reddy, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Diavit *Franco-Indian, India.*
Vitamins; minerals; trace elements; thioctic acid (p. 2629·1).

Mega Lifesciences, Thai.
Vitamins; carotenoids (p. 2176·2); copper (p. 2057·1); chromium (p. 2055·3); zinc (p. 2126·1).
Neuropathy.

Diavitec PD *Yuri, Ukr.*
Sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Diaxone *Europharma, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Diaz *Taro, Israel†; Bangkok Lab & Cosmetic, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm.

Diaze *Ind-Swift, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; seizures; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome.

Diazecalm *Symbiosis, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; seizures; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome.

Diazefast *Sigma, Braz.*
Diazepam (p. 1063·2).
Anxiety.

Diazem
Note: this name may be used for preparations of different composition.
Deva, Turk.
Diazepam (p. 1063·2).
Anxiety; insomnia; alcohol withdrawal syndrome; status epilepticus; febrile convulsions; muscle spasm; premedication.

Medochemie, Rus.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias.

Diazemuls *Pfizer, Canad.; Actavis, Hong Kong; Actavis, Irl.; Teva, Ital.; Actavis, Neth.; CSL, NZ†; Dumex, NZ†; Alpharma, UK.*
Diazepam (p. 1063·2).
Anxiety; premedication; status epilepticus; agitation; delirium tremens; skeletal muscle spasm; convulsions; sedative; alcohol withdrawal syndrome; epilepsy; tetany.

Diazen *Korea United, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diaze-P *Ind-Swift, India.*
⊗Diazepam (p. 1063·2); propranolol (p. 1479·1).

Diazep *AbZ, Ger.†; CT, Ger.†*
Diazepam (p. 1063·2).
Anxiety; premedication; skeletal muscle spasm; status epilepticus.

Diazepion *Chew, Thai.*
Diazepam (p. 1063·2).

Diazero *Minova, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Diazero-M *Minova, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Diazero-PM *Minova, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Diazidan *ICN, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diazide *Inga, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Diazol *EMS, Braz.*
Co-trimoxazole (p. 277·3); calcium carbonate (p. 1824·3); attapulgite (p. 1820·1).
Diarrhoea.

Diazolen *Degorts, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Diazolin *Akrikhin, Rus.*
Mebhydrolin (p. 634·2).
Hypersensitivity reactions.

Diazomid *Sanofi Synthelabo, Turk.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; epilepsy.

Diazon *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Diazox *Grandix, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diazox-MR *Grandix, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Diba *Manetti Roberts, Ital.*
Glutaral (p. 1753·2).
Instrument disinfection; surface disinfection.

Dibacilina *Diba, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Dibact *Svizera, India.*
Cream: Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).
Burns; wounds; skin ulcers.

Svizera, India.
Injection: Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Dibapec Compuesto *Diba, Mex.†*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Dibaprim *Diba, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dibase *Abiogen, Ital.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Dibasona *Diba, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Dibaterr *Diba, Mex.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Dibavytal *Diba, Mex.†*
Vitamins; minerals.

Dibecon *Pharmasant, Thai.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Dibekan *Vargas, Venez.*
Dibekacin sulfate (p. 286·1).
Bacterial infections.

Dibelet *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Dibeline *Universal, Hong Kong.†*
Phenoxybenzamine (p. 1468·1).

Dibemide *Suphong, Thai.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Diben *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Fin.; Fresenius Kabi, Irl.; Fresenius Kabi, Pol.†; Fresenius Kabi, Turk.*
Preparation for enteral nutrition.
Diabetes mellitus; impaired glucose tolerance.

Fresenius Kabi, Ital.
Preparation for enteral nutrition in diabetic patients.

Dibendril *Legrand, Braz.*
Pastilles: Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Legrand, Braz.
Syrup: Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Dibendryl *Macrophar, Thai.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity disorders.

Dibendyl Expectorant *Health Alliance, Hong Kong.†*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1).

Dibenmin *Raam, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Dibent *Hauck, USA.†*
Dicycloverine hydrochloride (p. 1834·2).
Functional bowel/irritable bowel syndrome.

Dibenyline *Link, Austral.†; IFET (ΙΦΕΤ), Gr.; Goldshield, Hong Kong; Rafa, Israel; Link, NZ; SmithKline Beecham, S. Afr.†; Farley, UK.*
Phenoxybenzamine hydrochloride (p. 1468·1).
Phaeochromocytoma; shock; urinary retention due to neurogenic bladder or benign prostatic hyperplasia; Raynaud's syndrome; acrocyanosis.

Dibenzyline *Wellspring, USA.*
Phenoxybenzamine hydrochloride (p. 1468·1).
Phaeochromocytoma.

Dibenzyran *Esparma, Austria; Aristo, Ger.; IFET (ΙΦΕΤ), Gr.*
Phenoxybenzamine hydrochloride (p. 1468·1).
Neurogenic bladder; phaeochromocytoma.

Dibertil *Takeda, Belg.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; adjunct in gastrointestinal examination.

Dibesin *SSP, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Dibeta *Torrent, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dibetasol *Shin Poong, Malaysia†; Shin Poong, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Dibetid *Arlex, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Dibi *Indoco, India.*
⊗Dimeticone (p. 2209·3); allantoin (p. 1693·1); urea (p. 1727·3).

Dibicor *Pik, Rus.*
Taurine (p. 2626·2).
Heart failure; glycoside intoxication; diabetes mellitus.

Dibiglim *1A, Denm.; Novartis, India; Sandoz, Thai.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Dibiglim-P *Novartis, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

Dibimet *Novartis, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Dibimet Plus *Novartis, India.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dibional *Rivero, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Dibizide *Micro, India; Micro, Singapore.*
Glipizide (p. 474·1).
Diabetes mellitus.

Dibizide-M *Micro, India; Micro Labs, Ukr.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diblocin *AstraZeneca, Ger.†*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Dibondrin *Montavit, Austria.*
Diphenhydramine hydrochloride (p. 626·2).
Prophylaxis against anaphylactic shock; hypersensitivity disorders; sedative.

Dibose *Ranbaxy, Malaysia.*
Acarbose (p. 466·2).
Diabetes mellitus.

Dibost *Ethica, Indon.*
Phyllanthus niruri (p. 2590·1); black elderberry (p. 2609·3).
Cold symptoms; tonic.

Dibro-Be Mono *Dibropharm, Ger.*
Potassium bromide (p. 2461·1).
Epilepsy.

Dibromol *Trommsdorff, Ger.†*
Sodium 3,5-dibromo-4-hydroxybenzenesulphonate; bromchlorophen (p. 1740·2); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Dibtrigen *Diba, Mex.†*
Vitamins; minerals.

Dibufen *Diba, Mex.†*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal, joint and peri-articular disorders.

Dibunafon *Royal, Chile.*
Sodium dibunate (p. 1677·3).
Cough.

Dibutasona *Diba, Mex.*
⊗Dexamethasone (p. 1630·3); phenylbutazone (p. 125·1).
Inflammation; rheumatism.

DIC-550 *East West, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicagel *Biodica, Fr.†*
Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Local anaesthesia.

Dicaine *Ultramark, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Dical *Grunenthal, Mex.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; calcium and vitamin D supplement.

Abbott, USA.†
Calcium (p. 1783·1); vitamin D (p. 2112·3); phosphorus (p. 2589·2).
Calcium deficiency; dietary supplement.

Dicalciiplex *Khandelwal, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).
Vitamin deficiency; calcium deficiency.

Dicalcine *Herbes Universelles, Canad.†*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1).
Calcium supplement.

Dical-D *Abbott, Hong Kong.†*
Calcium (p. 1783·1); vitamin D (p. 2112·3); phosphorus (p. 2589·2).
Dietary supplement.

Dicalets-M *Abbott, Gr.*
Vitamins; calcium carbonate (p. 1824·3); ferrous fumarate (p. 2060·3).

Dicalmir *Dicofarm, Ital.*
Fennel (p. 2503·2); chamomile (p. 2474·1); aniseed (p. 2444·2); liquorice (p. 1853·2); cuminum cyminum; coriander (p. 2486·3).
Meteorism; colic.

Dicalys 11 *Fresenius Medical, Swed.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3).
Haemofiltration.

Dicalys 17 *Fresenius Medical, Swed.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2).
Haemofiltration.

Dicam *Biosans, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Dicap *Pacific, NZ.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Dicarb *Inga, India.*
Diethylcarbamazine citrate (p. 153·1).
Loiasis; toxocariasis; filariasis.

Dicarb Inga *Inga, India.*
Chlorphenamine maleate (p. 620·3); diethylcarbamazine citrate (p. 153·1).

Dicarbamin
Note: this name may be used for preparations of different composition.
Valenta, Rus.
Imidazolylethanamide pentandioic acid (Vitaglutam).
Haematoprotection in patients receiving cytotoxic drugs.

Dicard *Intas, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Dicaris *Johnson & Johnson, India.*
Levamisole (p. 157·2).
Worm infections.

Dicaron *Suphong, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Dicarpen *Fada, Arg.*
⊗Carvedilol (p. 1333·1).
Angina pectoris.

Dicartel *Volta, Chile.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Dicarz *Alphapharm, Austral.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Dicasin *Medinova (Μεντινοβα), Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Dicasone *Baliarda, Arg.*
⊗Betamethasone (p. 1623·2); or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Dicasone Complex *Baliarda, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Dicel
Note: this name may be used for preparations of different composition.
Centrix, USA.†
⊗Pseudoephedrine tannate (p. 1676·1); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Dicel CD *Centrix, USA.*
⊗Brompheniramine maleate (p. 618·1); clofedanol hydrochloride (p. 1659·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Dicel DM *Centrix, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1) or dextromethorphan tannate (p. 1660·1); chlorphenamine maleate (p. 620·3) or chlorphenamine tannate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Dicelax *Andromaco, Chile.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Dicentril *Degorts, Mex.†*
Aluminium (p. 2439·2); magnesium (p. 1786·3).
Gastric hyperacidity.

Dicetel *Raffo, Arg.; Abbott, Braz.; Abbott, Canad.; Abbott, China; Solvay, China; Solvay, Cz.†; Abbott, Fr.; Abbott, Gr.; Solvay, Hung.; Solvay, Ital.; Italmex, Mex.; Abbott, Port.; Abbott, Rus.; Abbott, Switz.; Abbott, Thai.; Frik, Turk.; Abbott, Ukr.; Zuoz, Venez.*
Pinaverium bromide (p. 2590·3).
Irritable bowel syndrome; biliary-tract disorders; aid to gastrointestinal examination; smooth muscle spasm; gastrointestinal motility disorders; colitis.

Dicfafena *IQFA, Mex.*
Diclofenac (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dic-FHI *Farmaceutica H, Mex.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dichlotride *M & H, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; premenstrual syndrome.

Dici *Nordic, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Dicigel *Galeno, Venez.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Gastric hyperacidity; smooth muscle spasm.

Dicigon *Parggon, Mex.*
Dicycloverine (p. 1834·2).
Smooth muscle spasm.

Dicil
Note: this name may be used for preparations of different composition.
Royal, Chile.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Dicillin *Sandoz, Denm.; Inpac, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dicimax *Biomax, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Dicimax-G *Biomax, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Dicimox *Indoco, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Dicin *Cinerea, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dicinone *Sanofi-Aventis, Braz.; Esteve, Spain.†*
Etamsylate (p. 1145·2).
Haemorrhage.

Diciosis *Arvincare, India.*
⊗Diclofenac (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dicitrate *Pharmascience, Singapore.*
Sodium citrate (p. 1781·2); citric acid monohydrate (p. 2480·3).
Renal calculi; gout; acidosis; acid aspiration.

Diclabeta *Betapharm, Ger.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Diclac *Hexal, Austral.†; Hexal, Braz.; Sandoz, China; Sandoz, Hung.; Rowex, Irl.; Sandoz, Mex.; Sandoz, Pol.; Sandoz, Rus.; Sandoz, Switz.; Sandoz, Ukr.*
Diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; oedema; fever.

Investi, Arg.
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Volta, Chile.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; fever; gout.

Hexal, Ger.†
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and soft-tissue disorders.

DiclacHexal *Hexal, Austria.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Dicladox *Ivax, Arg.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Diclam *Amrit, India.*
Diclofenac sodium (p. 48·3).
Pain.

Diclamina *Esteve, Spain.†*
Cinnarizine (p. 622·1); heptaminol acefyllinate (p. 1210·3).
Vertigo; vascular headache.

Diclanil *Condrugs, Thai.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diclasia *Willow, India.*
Diclofenac (p. 48·3).
Pain.

Diclax *Douglas, NZ.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Diclectin *Duchesnay, Canad.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Diclegis *Duchesnay, USA.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Diclen *Lamsa, Arg.*
Clonixin lysine (p. 40·1).
Inflammation; pain.

Dicleophen *Sons, Mex.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclex *Meiji, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclin *Merck, Braz.*
Cyproterone (p. 2261·2); ethinylestradiol (p. 2275·3).

Diclo
Note: this name may be used for preparations of different composition.
Betapharm, Ger.; Kade, Ger.
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Pinewood, Irl.; Clinifood, Singapore; Unique, Thai.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout; inflammation.

Diclo P *Uniao Quimica, Braz.*
Diclofenac potassium (p. 48·3).

Dicloabak *Thea, Belg.; Thea, Cz.; Thea, Neth.; Thea, Pol.; Thea, Port.; Thea, Spain; Thea, Switz.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders; inhibition of miosis during cataract surgery; pain and inflammation following eye surgery; cystoid macular oedema.

Dicloact *Cadila, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dicloact Plus *Cadila, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicloat *ATOZ, India.*
Diclofenac sodium (p. 48·3).
Pain.

Dicloat Plus *ATOZ, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicloat-CZ *ATOZ, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dicloat-Gel *ATOZ, India.*
Diclofenac diethylamine (p. 48·3); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Diclobene *Ratiopharm, Austria.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ratiopharm, Rus.; Ratiopharm, Ukr.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Dicloberl *Berlin-Chemie, Pol.; Menarini, Pol.*
Diclofenac (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Berlin-Chemie, Rus.†; Berlin-Chemie, Ukr.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout, pain; inflammation.

Diclobion *Bioton, Pol.†*
Diclofenac (p. 48·3).
Inflammatory eye disorders; prevention of intra-operative miosis; prevention of cystoid macular oedema.

Diclobit *Cubit, India.*
Injection; topical gel: Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Cubit, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclobru *Brupharmexport, Ukr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; renal and biliary colic; inflammation.

Diclocain *Zdorovje, Ukr.*
Diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection
Fever; musculoskeletal, joint, and peri-articular disorders; pain; renal and hepatic colic; inflammation.

Dicloced *Thea, Fr.*
Diclofenac sodium (p. 48·3).
Inhibition of miosis in cataract surgery; eye inflammation and pain following eye surgery.

Diclocil *BMS, Austral.; BMS, Denm.; BMS, Fin.; BMS, Gr.; BMS, Norw.; BMS, NZ†; BMS, Port.; BMS, Swed.†; BMS, Thai.†; BMS, Venez.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclocillin *TO-Chemicals, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclocular *Angelini, Ital.*
Diclofenac sodium (p. 48·3).
Pain and inflammation of the eye.

Diclodan *Pharmacodane, Denm.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation; pain; gout.

Diclo-Denk *Denk, Hong Kong; Denk, Singapore.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Diclodent *Atral, Port.*
Diclofenac (p. 48·3).

Dicloderm Forte *Cruz, Spain.†*
⊗Dichlorisone acetate (p. 1633·3).
Skin disorders.

Diclo-Divido *Actavis, Ger.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Diclodoc *Docpharm, Ger.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Diclodol *Neon, India.*
Diclofenac sodium (p. 48·3).
Pain.

Diclo-DT *Morepen, India.*
Diclofenac (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

DicloDuo *PharmaSwiss, Gr.; PharmaSwiss, Pol.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclodyne *Bliss, India.*
Diclofenac (p. 48·3).
Inflammation; pain.

Diclo-F *Promed, Rus.; ProMed, Ukr.*
Diclofenac sodium (p. 48·3).
Inhibition of miosis in cataract surgery; inflammatory eye disorders; cystoid macular oedema following cataract surgery.

Diclofalm Forte *Reliance, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclofam *Max, India.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Diclofam Plus *Max, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclofan *Boniscontro & Gazzone, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.

Diclofar *Azevedos, Port.*
Diclofenac potassium (p. 48·3).
Pain; inflammation; oedema.

Diclofast *3DDD, Belg.†; Lark, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Specifar, Gr.
Diclofenac potassium (p. 48·3).
Inflammatory disorders.

Diclofast-P *Lark, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclofemed *Ranbaxy, Belg.†*
Diclofenac sodium (p. 48·3).

Diclofen *SVUS, Cz.†; Biochem, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Jean-Marie, Hong Kong.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclofen P *SM, Venez.*
Diclofenac potassium (p. 48·3).
Fever; inflammation; pain.

Diclofenac Flex *Northia, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders with muscle spasm.

Diclofenacol *Rompharm, Rus.*
Diclofenac sodium (p. 48·3); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Diclofenbeta *Betapharm, Ger.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Diclofen-Gel *Borshchagovskii, Ukr.*
Diclofenac sodium (p. 48·3); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diclofetamol *Ducto, Braz.*
Caffeine (p. 1203·3); carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclofilab *Inmunolab, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Dicloflam *Global, India; Molex Ayus, Indon.; Aspen, S. Afr.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Santa, Turk.
Diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dicloflam MR *Global, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dicloflam P *Global, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicloflam Plus *Reliance, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicloflam SP *Global, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dicloflame *Intas, India.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; gout.

Dicloflex *Dexcel, UK.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Dicloflogil *Uniao Quimica, Braz.*
Diclofenac (p. 48·3).

Dicloftal *Lepori, Port.†*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Dicloftil *Bioavenir, Israel; Farmigea, Ital.*
Diclofenac sodium (p. 48·3).
Eye inflammation and pain; inflammatory eye disorders.

Diclogel *Polipharm, Thai.*
Diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Diclogen *Agio, Philipp.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Agio, Rus.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Diclogen Plus *Agio, India.*
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Agio, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Agio, Rus.
Diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Diclogenom *Uniao Quimica, Braz.*
Diclofenac sodium (p. 48·3).
Eye disorders.

Diclogenta *Centaur, India.*
Diclofenac sodium (p. 48·3); gentamicin sulfate (p. 304·2).
Bacterial eye infections with inflammation.

Diclogesic
Note: this name may be used for preparations of different composition.
Dar Al Dawa, Hong Kong†; T Man, Thai.
Diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal and joint disorders; gout.

Torrent, India.
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

TRB, Arg.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Biliary and renal colic; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclogesic Forte *TRB, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Pain; inflammation.

Diclogesic Plus B12 *TRB, Arg.*
⊗Diclofenac potassium (p. 48·3); betamethasone (p. 1623·2); cyanocobalamin (p. 2107·2).
Musculoskeletal and joint disorders; neuropathy.

Diclogesic Relax *TRB, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Diclogesic Spas *Torrent, India.*
Diclofenac sodium (p. 48·3); dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Diclogrand *Ahimsa, Arg.*
Diclofenac (p. 48·3).
Inflammation; pain.

Diclohexal *Hexal, S.Afr.*
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Sandoz, Austral.†; Hexal, NZ.†
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders; dysmenorrhoea; inflammation; pain.

Diclohill-P *Daffohils, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclohof *Pharmahof, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclojet *PharmaSwiss, Gr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Diclo-K *Morepen, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Diclokin *Kinder, Braz.†*
Chloroquine phosphate (p. 650·1).
Malaria.

Diclolab *Laborate, India.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain; prevention of intra-operative miosis; eye inflammation and pain.

Diclolab Plus *Laborate, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclolabsa *Labsa, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Diclolabsa B12 *Labsa, Arg.*
⊗Diclofenac potassium (p. 48·3); betamethasone (p. 1623·2); cyanocobalamin (p. 2107·2).

Diclolabsa Gesic *Labsa, Arg.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Inflammation; pain.

Diclolabsa Relax *Labsa, Arg.*
Diclofenac (p. 48·3); pridinol (p. 2026·1).

Diclolam *Lepetit, Arg.*
Diclofenac (p. 48·3).
Inflammation; pain.

Diclolan *Olan-Kemed, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Dicloma *JK Biochem, India.*
Diclofenac sodium (p. 48·3).
Pain.

Diclomar *Mar, Arg.*
Diclofenac (p. 48·3) or diclofenac potassium (p. 48·3).
Inflammation; pain; musculoskeletal and joint disorders.

Diclomar Flex *Mar, Arg.*
Diclofenac (p. 48·3); pridinol mesilate (p. 2026·1).
Inflammation; muscle spasm; pain.

Diclomax *Torrent, India; Provalis, Irl.†; koGen, UK.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Diclomax Power Gel *Torrent, India.*
Capsaicin (p. 35·1); diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1).

Diclomec *Mecom, Turk.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Abdi Ibrahim, Indon.†
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; pain; inflammation; gout; renal and biliary colic.

Diclomel *PannonPharma, Hung.; Clonmel, Irl.†*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclomelan *Lannacher, Austria.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; gout; renal and biliary colic.

Diclomex *Merckle, Fin.; Ratiopharm, Fin.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation; pain.

Diclomin *Atlantis, Mex.†*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm and hypermotility.

Diclomol
Note: this name may be used for preparations of different composition.
Win-Medicare, India.
Topical gel: Diclofenac diethylamine (p. 48·3).
Soft-tissue disorders.

Win-Medicare, India; Win-Medicare, Thai.†
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain; gout; osteoarthritis; rheumatoid arthritis.

Win-Medicare, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain; gout.

Diclomove *Emcure, India.*
Diclofenac (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Diclomove-MR *Emcure, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Diclomove-P *Emcure, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclomox *Bright Future, China.*
Amoxicillin (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclom-SP *Om Biotec, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Diclon *Sandoz, Denm.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclonac *Lupin, India.*
Diclofenac sodium (p. 48·3) or diclofenac (p. 48·3).
Musculoskeletal and joint disorders; gout; pain.

Diclonac-MR *Lupin, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclonaco *Ducto, Braz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Diclonac-P *Lupin, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclonat *Pliva, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain; fever.

Diclonax *Hertz, Braz.*
Diclofenac (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Diclonet *Bionet, India.*
Diclofenac sodium (p. 48·3).
Pain.

Diclonet-Forte *Bionet, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Diclonex *Nexo, Arg.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Diclonex Flex *Nexo, Arg.*
Diclofenac sodium (p. 48·3); pridinol (p. 2026·1).

Diclonex R *Nexo, Arg.*
Diclofenac sodium (p. 48·3); pridinol (p. 2026·1).
Formerly known as Diclonex Relax.
Musculoskeletal and joint disorders.

Diclonij *Sunij, India.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Diclonij Spas *Sunij, India.*
Diclofenac potassium (p. 48·3); dicycloverine hydrochloride (p. 1834·2).

Diclonij-KMR *Sunij, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Diclonij-KP *Sunij, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclonij-Super *Sunij, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Diclonil *Hertz, Braz.*
Diclofenac (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Diclonip *Sanjivani, India.*
Diclofenac (p. 48·3).
Pain.

Diclono *Pharmahof, Thai.†*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Diclonova *Lupin, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Diclonova MR *Lupin, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclonova P *Lupin, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclonox *Charoen, Thai.*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Diclop *Rafarm, Gr.*
Clopidogrel (p. 1342·3).

Diclopace-Cl *Fem Care, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Diclopax *Actavis, Denm.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Diclopep *Waves, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Diclopep Plus *Waves, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Diclophen *Pro Doc, Canad.†*
Dicycloverine hydrochloride (p. 1834·2); phenobarbital (p. 535·2).
Antispasmodic.

Diclopherol *Olainfarm, Ukr.†*
Diclofenac potassium (p. 48·3).
Soft-tissue disorders; pain and inflammation; migraine; renal and biliary colic.

Diclophlogont *Novartis, Gr.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Diclopisa *Pisa, Mex.*
Diclofenac sodium (p. 48·3).

Dicloplast *Faran, Gr.; IBSA, Israel.*
Diclofenac epolamine (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Diclo-Puren *Actavis, Ger.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dicloral *Lavipharm, Gr.; Athena, Ital.*
Diclofenac (p. 48·3).
Mouth and throat disorders.

Dicloran *Randall, Mex.; Unique, Rus.; Unique, Singapore.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation; pain; soft-tissue disorders.

Unique, India.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Dicloran Plus *Unique, Rus.; Unique, Ukr.*
Diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); linseed oil (p. 2544·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; inflammation.

Dicloran-A *JB Chemicals, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; gout.

Dicloran-MR *JB Chemicals, India.*
Diclofenac potassium (p. 48·3); tizanidine (p. 2026·2).

Dicloran-MS *JB Chemicals, India.*
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); benzyl alcohol (p. 1739·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dicloraster *Esoform, Ital.*
Troclosene (p. 1774·1).
Water purification.

Dicloratio *Ratiopharm, Pol.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to reduce the pain of injection.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

Diclorengel *Trima, Israel.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dicloreum *Alfa Wassermann, Cz.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Wassermann, Ital.; Alfa Wassermann, Pol.
Diclofenac (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Dicloreumol *Cabuchi, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Dicloriz *Ritz, India.*
Tablets: Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Ritz, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Diclo-saar *MIP, Ger.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Diclosal *Biofarma, Venez.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Diclosar-P *Gentech, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Diclosef *Sun, India.*
Diclofenac potassium (p. 48·3); famotidine (p. 1842·1).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Diclosian *Asian Pharm, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Diclosifar *Siphar, Switz.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation; oedema; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; thrombophlebitis.

Diclosim *Symbiotic, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclosodico *Multilab, Braz.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Diclosol *Solfran, Mex.*
Diclofenac (p. 48·3).
Inflammation; pain.

Dicloson *Unison, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Diclospa *Cipla, India.*
Dicycloverine hydrochloride (p. 1834·2); diclofenac sodium (p. 48·3).

Diclospray *Sanofi-Aventis, Port.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Diclostad *Stada, Austria.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; renal and biliary colic.

Diclostar *Cadila, India.*
Diclofenac sodium (p. 48·3).
Pain.

Diclostir *Sigma, Braz.*
Diclofenac colestyramine (p. 48·3).

Diclosyl *Pharmaselect, Austria.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diclosym *Symbiosis, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclotab *Baroda, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclotal *Blue Cross, India.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Diclotal Forte *BlueCross, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclotaren *Farmo Quimica, Chile.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain; inflammation.

Diclotears *Medivis, Ital.*
Diclofenac sodium (p. 48·3).
Eye inflammation.

Diclotec *Lepori, Port.†*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Rheumatoid arthritis; osteoarthritis.

Diclo-Tecno *Tecnofarma, Mex.*
Dicloxacillin (p. 286·1).
Staphylococcal infections.

Dicloton *Royton, Braz.*
Diclofenac potassium (p. 48·3).

Diclotop
Note: this name may be used for preparations of different composition.
DWD, India.
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Topgen, Belg.†
Diclofenac sodium (p. 48·3).

Diclovar *Zota, India.*
Diclofenac sodium (p. 48·3).
Pain.

Diclovar-CZ *Zota, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diclovar-Plus *Zota, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclovit *Lannacher, Austria.*
Diclofenac sodium (p. 48·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Musculoskeletal, joint, and soft-tissue disorders; neuritis; neuralgia; gout.

Nizpharm, Rus.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever; inflammation; renal and hepatic colic.

Diclovith-B *Sons, Mex.*
Ampoule 1, pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2); ampoule 2, diclofenac sodium (p. 48·3).
Neuralgias; neuritis; musculoskeletal and joint disorders; neuropathy.

Diclovol *Arun, UK.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Diclowin *Wings, India.*
Tablets: Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Wings, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); mephenesin (p. 2025·2); methyl nicotinate (p. 91·3); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).

Diclowin Active *Wings, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Diclowin Plus *Wings, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diclox *GPO, Thai.; PP Lab, Thai.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dicloxa *Osoth, Thai.; RX, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dicloxa-MX *Winsome, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Dicloxane *Suphong, Thai.*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Dicloxaquim *Quimica y Farmacia, Mex.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dicloxcin *Suphong, Thai.*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Dicloxgen *General Drugs, Thai.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dicloxia *Asian Pharm, Thai.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dicloxilin *Siam Medicare, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dicloxin *Olan-Kemed, Thai.†*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dicloxman *T Man, Thai.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dicloxno *Milano, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dicloxpac *Inpac, Thai.*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Dicloxsig *Aspen, Austral.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Diclozed *Zota, India.*
Diclofenac sodium (p. 48·3).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Diclozed-Gel *Zota, India.*
Diclofenac diethylamine (p. 48·3); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Diclozed-Plus *ATOZ, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicloziaja *Ziaja, Pol.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diclozip *Ashbourne, UK.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Dicmoxy *BMW, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Dicnac *Almet, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dicnac Gelino *Almet, India.*
Diclofenac (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dicnac MR *Almet, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Dicnac Plus *Almet, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Dicnac-P *Almet, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicnacx *Shince, India.*
Diclofenac potassium (p. 48·3).
Pain.

Dicnacx-P *Shince, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicnacx-S *Shince, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dicnacx-SP *Shince, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dicnap *Osmed, India.*
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Osmed, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dicnap-MR *Osmed, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dico *Finecure, India.*
Diclofenac (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dico P *Finecure, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicodid *Abbott, Ger.†*
Hydrocodone hydrochloride (p. 67·2) or hydrocodone tartrate (p. 67·2).
Cough.

Dicodin *Mundipharma, Fr.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

Dicodral *Dicofarm, Ital.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1) or sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Dicofan *Rivero, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Dicofen
Note: this name may be used for preparations of different composition.
Medreich, Hong Kong.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Dicoflor *Dicofarm, Ital.*
Food containing lactic-acid-producing organisms (p. 2596·3).
Disturbances of the gastrointestinal flora.

Dicogel *Mintlab, Chile.*
Diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Dicogesic *CCM, Malaysia.*
Dihydrocodeine tartrate (p. 52·3).
Pain; cough.

Dicol *Ind-Swift, India; Munir, Turk.*
Diclofenac (p. 48·3).
Inflammation; musculoskeletal and joint disorders; prevention of intra-operative miosis; eye inflammation and pain.

Dicoliv *Ind-Swift, India.*
Injection; tablets: Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Ind-Swift, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dicoliv Plus *Ind-Swift, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicoliv-MR *Ind-Swift, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dicoliv-S *Ind-Swift, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Dicol-MR *Ind-Swift, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dicol-Plus *Ind-Swift, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicol-S *Ind-Swift, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Dic-OM *Lupin, India.*
Diclofenac sodium (p. 48·3); omeprazole (p. 1867·2).

Dicoman *Dicofarm, Ital.*
Dietary fibre.

Dicomex *Drugtech, Chile.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Dicomin
Note: this name may be used for preparations of different composition.
Novamed, India.
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Berlin Pharm, Thai.†
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Di-Con One *Ascent, Austral.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Diconal
Note: this name may be used for preparations of different composition.
Klar Sehen, India.
⊗Xylometazoline hydrochloride (p. 1680·1).
Eye congestion; nasal congestion.

Amdipharm, UK.†
Dipipanone hydrochloride (p. 53·2); cyclizine hydrochloride (p. 623·2).
Pain.

Dicon-I *Brawn, India.*
Dimeticone (p. 1886·2).

Diconpin *TAD, Ger.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Dicopac *Nycomed Amersham, UK.†*
1 capsule, cyanocobalamin (cobalt-57) (p. 2223·3); 1 capsule, cyanocobalamin (cobalt-58) (p. 2223·3); 1 ampoule, cyanocobalamin (p. 2107·2).
Diagnosis of vitamin B_{12} malabsorption.

Dicoplus *Dicofarm, Ital.*
Glucomannan (p. 2515·2).
Constipation; diverticulitis; irritable bowel syndrome.

Dicor *Microkhim, Ukr.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Dicorantil *Sanofi-Aventis, Braz.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Dicorate *Sun, India.*
Valproate semisodium (p. 553·2).
Seizures; bipolar disorder; migraine.

Dicortineff *Jelfa, Pol.; Polfa Warszawa, Pol.*
⊗Fludrocortisone acetate (p. 1634·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Infected eye or ear disorders.

Dicorvin *Meda, Spain.*
Acetylspiramycin (p. 358·3).
Bacterial infections.

Dicorynan *IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Spain.*
Disopyramide (p. 1363·2).
Arrhythmias.

Dicos *Hos & Ins, India.*
Diclofenac sodium (p. 48·3).
Pain.

Dicoterol *Gelcaps, Mex.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Dicotil *Picco, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Dicotuss *Dicofarm, Ital.*
Ivy (p. 2536·2); acetylcysteine (p. 1652·2); zinc (p. 2126·1).
Respiratory-tract congestion.

Dicovit *Dicofarm, Ital.*
Medium-chain triglycerides (p. 2082·2); antoxidants; colecalciferol (p. 2113·1).
Dietary supplement.

Dicovit DK *Dicofarm, Ital.*
Medium-chain triglycerides (p. 2082·2); antoxidants; phytomenadione (p. 2122·2); colecalciferol (p. 2113·1).
Dietary supplement.

Dicron
Note: this name may be used for preparations of different composition.
Kamron, India.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

TP, Thai.
Gliclazide (p. 472·3).
Diabetes mellitus.

Dicron Plus *Kamron, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicron-C *Kamron, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dictyolone *Texinfine, Fr.*
Padina pavonica (p. 2612·1).
Bone and joint disorders.

Diculone *Yash, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicuno *Vitabalans, Denm.; Vitabalans, Fin.; Vitabalans, Swed.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Dicven *Vencare, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dicven Plus *Vencare, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dicyclome-P *Auspi, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Dicyclozed *Zota, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dicymine *Christo, Hong Kong; Pharmasant, Thai.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm; flatulence.

Dicymine Co *Christo, Hong Kong.*
Dicycloverine hydrochloride (p. 1834·2); dimeticone (p. 1886·2).
Gastrointestinal spasm; flatulence.

Dicynene *Reddy, India; OM, Irl.; Sanofi-Aventis, UK.*
Etamsylate (p. 1145·2).
Periventricular haemorrhage in neonates; menorrhagia; haemorrhage.

Dicynone *Sanofi-Aventis, Belg.; Labomed, Chile; OM, Cz.; Vifor, Fr.; Teva, Hung.; Corsa, Indon.; OM, Indon.; Sanofi-Aventis, Ital.; Grunenthal, Mex.; Sandoz, Rus.; OM, Singapore; OM, Switz.; Sandoz, Ukr.; Leti, Venez.*
Etamsylate (p. 1145·2).
Haemorrhage; menorrhagia; metrorrhagia; haemorrhagic disorders; capillary fragility; peripheral vascular disorders.

Diczone Plus *Zee, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Diczone-MR *Adley, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dida *Vitalco, Fr.*
Cinnamon oil (p. 2479·3); fennel oil (p. 2503·3); peppermint oil (p. 1877·1); oregano (p. 2576·3); olive leaf (p. 2574·3); marigold (p. 2465·2); thyme (p. 2630·2); cardamom (p. 2471·1); clove flower (p. 2481·2); garlic (p. 2510·3); nicotinic acid (p. 2083·1).
Restoration of intestinal flora.

Didamega *Larkhall Laboratories, UK.*
Vitamins; minerals.

Didasten *Landsteiner, Mex.†*
Didanosine (p. 972·3).
HIV infection.

Di-Delamine *Commerce, USA; Del, USA.*
Diphenhydramine hydrochloride (p. 626·2); tripelennamine hydrochloride (p. 642·3).
Pruritus.

Dideral *Sanofi Synthelabo, Turk.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; angina pectoris; arrhythmias; tremor; myocardial infarction; migraine.

Didivir *Cipla-Medpro, S.Afr.*
Tenofovir disoproxil fumarate (p. 1018·1); emtricitabine (p. 976·3).
HIV infection.

Didol *Alna, India.*
Tramadol (p. 139·2).
Pain.

Didol-D *Alna, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Didol-P *Alna, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Didralin *Medochemie, Singapore.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure; nephrotic syndrome; hepatic cirrhosis and ascites.

Didrex *Pharmacia, USA.*
⊗Benzfetamine hydrochloride (p. 2318·1).
Obesity.

Didrocal *Pfizer, Austral.; Warner Chilcott, Canad.*
28 White tablets, etidronate disodium (p. 1182·3); 76 blue tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Didrogyl *IFET (ΙΦΕΤ), Gr.; Bruno, Ital.*
Calcifediol (p. 2113·1).
Osteoporosis; osteomalacia; renal osteodystrophy; hypoparathyroidism; rickets; hypocalcaemia; vitamin D deficiency.

Didrokit *Warner Chilcott, Neth.*
Tablets, etidronate disodium (Didronel) (p. 1182·3); tablets, calcium carbonate (Cacit) (p. 1824·3).
Osteoporosis.

Didronat *Kocak, Turk.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; ectopic ossification.

Didronate *Procter & Gamble, Denm.†; Warner Chilcott, Fin.†; Orifarm, Norw.; Procter & Gamble, Swed.†*
Etidronate disodium (p. 1182·3).
Osteoporosis; ectopic ossification; Paget's disease of bone.

Didronate Calcium *Procter & Gamble, Denm.†*
14 Tablets, etidronate disodium (p. 1182·3); 76 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Didronate + Calcium *Warner Chilcott, Fin.†; Warner Chilcott, Swed.*
14 Tablets, etidronate disodium (p. 1182·3) (Didronate); 76 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Didronate + Calsium *Sofus, Norw.†*
14 Didronate tablets, etidronate disodium (p. 1182·3); 76 calcium tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Didronel *Pfizer, Austral.; Sanofi-Aventis, Austria†; Procter & Gamble, Canad.†; Orifarm, Denm.; Paranova, Denm.; Warner Chilcott, Fr.; Procter & Gamble, Ger.†; Procter & Gamble, Irl.†; Procter & Gamble, Israel; Sumitomo, Jpn; Procter & Gamble, Neth.†; Pfizer, NZ; Vifor, Switz.†; Procter & Gamble, UK; MGI, USA; Procter & Gamble, USA.*
Etidronate disodium (p. 1182·3).
Osteoporosis; Paget's disease of bone; ectopic ossification; hypercalcaemia of malignancy.

Didronel Kit *Warner Chilcott, Ger.*
White tablets, etidronate disodium (p. 1182·3); blue tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Didronel PMO *Procter & Gamble, Irl.†; Procter & Gamble, UK.†*
Tablets, etidronate disodium (Didronel) (p. 1182·3); tablets, calcium carbonate (Cacit) (p. 1824·3).
Osteoporosis.

Die Die Ning *Jinshan, China.*
Lappaconitine.

Die Li *Nhwa, China.*
Gabapentin (p. 523·3).
Epilepsy; postherpetic neuralgia.

Diedafont *Sandoz, Ital.*
Domperidone (p. 1838·1).
Nausea and vomiting; abdominal discomfort; gastro-oesophageal reflux.

Dieloft *Medley, Braz.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Diemil *Almirall, Spain.*
Dihydroergocristine mesilate (p. 390·1); piracetam (p. 393·3).
Cerebrovascular disorders; head injury.

Diemon *Pfizer, Arg.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Diencil *Rider, Chile.*
Metesculetol sodium (p. 2557·3); dexpanthenol (p. 2582·2); sodium benzoate (p. 1738·2); allantoin (p. 1693·1).
Gingivitis.

Dienille *LadeePharma, Cz.; LadeePharma, Hung.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive in women with androgen-induced acne; androgen-induced acne in females.

Dienopil *Bago, Arg.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Dienorette *Leon, Cz.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Dienpax *Sanofi-Aventis, Braz.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm; tetanus.

Dientrin *Sanofi-Aventis, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dienzepax *Neo Quimica, Braz.*
Diazepam (p. 1063·2).

Diep Grat *Wassermann, Ital.*
Diclofenac epolamine (p. 48·3).
Gout; musculoskeletal and joint disorders; pain.

Diergo *Pharma Logistics, Belg.*
Dihydroergotamine mesilate (p. 672·2).
Migraine.

Diergospray *CSP, Fr.*
Dihydroergotamine mesilate (p. 672·2); caffeine (p. 1203·3).
Migraine.

Diertina *Pharmanel, Gr.; Daiichi Sankyo, Port.*
Dihydroergocristine mesilate (p. 390·1).
Cerebral and peripheral vascular disorders; dopamine deficiency; hypertension.

Diertine *Tora, Spain.*
Dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders; vascular eye disorders; tinnitus; vertigo.

Di-Ertride *Malaysia Chemist, Singapore.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; diabetes insipidus.

Diesan *CT, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorders; bulimia nervosa.

Diestet *Darier, Mex.*
⊗Mazindol (p. 2324·1).
Obesity.

Diet Complet *Natural Life, Arg.*
Vitamins; minerals; dietary fibre.
Slimming aid.

Diet Sucaryl *Corman, Ital.†*
Sodium cyclamate (p. 2180·2); saccharin (p. 2207·3).
Sugar substitute.

Dietacil *IMA, Braz.†*
Aspartame (p. 2169·2).
Sugar substitute.

Dietasal *Libbs, Braz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Oral rehydration solution.

Diet-Comfort *Materia Medica, Rus.*
Conium (p. 2524·3); cimicifuga (p. 2478·1); sodium chloride (p. 1795·1).
Homoeopathic preparation.

Dietene *Adcock Ingram, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Dietet-In *Selenium Pharma, Hung.*
Chromium (p. 2055·3); manganese (p. 2081·2); zinc (p. 2126·1); nicotinamide (p. 2083·1).
Dietary supplement.

Diethizine *Pond's, Thai.*
Diethylcarbamazine citrate (p. 153·1).
Filariasis; loiasis.

Dietil *Trenker, Thai.†*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Dietmann *Cadila, India.*
Oral sachet: Glucomannan (p. 2515·2).
Diabetes mellitus; obesity; hyperlipidaemias; constipation.

Zydus, India.
Capsules: Glucosamine (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Dietoman
Note: this name may be used for preparations of different composition.
Teofarma, Ital.; Armstrong, Mex.
Glucomannan (p. 2515·2).
Obesity; diabetes mellitus; lipid disorders.

Di-Eudrin *Biotech, Venez.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Diez *Laksun, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Diezime *Recordati, Ital.*
Cefodizime sodium (p. 242·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Difadol *Polfa Warszawa, Pol.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; gout; inflammatory eye disorders.

Difalex *Pharma Nutria, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Difarben *Rayere, Mex.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive disorders.

Difaren *PP Lab, Thai.*
Diclofenac diethylamine (p. 48·3).
Inflammation; pain; osteoarthritis.

Difaterol *Bial, Spain.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Difebril *Cifarma, Braz.*
Dipyrone (p. 53·3).
Pain; fever.

Difedrin *Munir, Turk.*
Diphenhydramine hydrochloride (p. 626·2).
Nasal congestion; pruritus.

Difelene *TNP, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Difemic *Pharmasant, Thai.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).
Gastrointestinal spasm with pain.

Difen
Note: this name may be used for preparations of different composition.
Allergan, Braz.
Pranoprofen (p. 127·1).
Inflammatory eye disorders.

Stulln, Ger.; Gulf Drug, S.Afr.; Nakorn, Thai.†
Diclofenac sodium (p. 48·3).
Prevention of miosis in eye surgery; eye inflammation; pain; musculoskeletal, joint, and peri-articular disorders; gout; inflammation.

Meyer, Venez.
Paracetamol (p. 115·1); caffeine (p. 1203·3); dihydroergotamine mesilate (p. 672·2).
Migraine and other vascular headaches.

Difenac
Note: this name may be used for preparations of different composition.
Lafedar, Arg.; DHA, Hong Kong; Intermed, India; DHA, Singapore; TP, Thai.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dollder, Venez.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Intermed, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Difenac Forte *Lafedar, Arg.*
⊗Diclofenac potassium (p. 48·3); betamethasone (p. 1623·2); cyanocobalamin (p. 2107·2).
Musculoskeletal and joint disorders; neuritis.

Difenac Plus *Intermed, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Difenak *Terra, Turk.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Difenamin *Flamingo, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Difenax
Note: this name may be used for preparations of different composition.
GX, Philipp.
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Difend *Medicus, Gr.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Difene *Temmler, China; Astellas, Irl.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation; renal colic.

Difenet *Nycomed, Denm.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Difengesic *Bangkok Lab & Cosmetic, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Difenic *Intas, India.*
Diclofenac sodium (p. 48·3).
Prevention of intra-operative miosis; eye inflammation and pain.

Difenidrin *Cristalia, Braz.*
Diphenhydramine hydrochloride (p. 626·2).

Difenject *Pharmachem, S.Afr.*
Diclofenac sodium (p. 48·3).

Difeno *Milano, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation.

Difenol *APT, Hong Kong.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Difensic *ANH, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Difensil *Humana, Ital.*
Sicillian red orange.
Tonic.

Difen-Stulln *Medserve, Switz.*
Diclofenac sodium (p. 48·3).
Eye pain and inflammation; prevention of miosis during cataract surgery; cystoid macular oedema.

Diferbest *Best, Mex.*
Naproxen sodium (p. 98·2).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diferin *Grossman, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Difestol *Munir, Turk.*
Lidocaine hydrochloride (p. 1988·2); diphenhydramine hydrochloride (p. 626·2).

Difexon *Bago, Chile.*
Povidone-iodine (p. 1767·1).
Burns; disinfection of mucous membranes and skin; skin infections; ulcers; vaginal infections; wounds.

Differin *Galderma, Arg.; Galderma, Austral.; Galderma, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Canad.; Galderma, Chile; Galderma, China; Galderma, Fin.; Galderma, Ger.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Ital.; Galderma, Malaysia; Galderma, Neth.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Philipp.; Galderma, Pol.; Galderma, Port.; Galderma, Rus.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Swed.; Galderma, Switz.; Galderma, Thai.; Liba, Turk.; Taymed, Turk.; Galderma, UK; Galderma, USA; Galderma, Venez.*
Adapalene (p. 1692·1).
Acne.

Differine *Galderma, Cz.; Galderma, Fr.; Galderma, Spain.*
Adapalene (p. 1692·1).
Acne.

Difflam
Note: this name may be used for preparations of different composition.
iNova, Austral.; iNova, Hong Kong; Meda, Irl.; 3M, NZ; iNova, Philipp.; iNova, Singapore; iNova, Thai.; Meda, UK.
Benzydamine hydrochloride (p. 29·2).
Pain and inflammation of the mouth and throat; musculoskeletal, joint, and soft-tissue pain and inflammation.

Difflam Anti-inflammatory Anti-Bacterial Lozenges *iNova, Singapore.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Difflam Anti-inflammatory Antibacterial Lozenges *iNova, Hong Kong; 3M, NZ.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Difflam Anti-inflammatory Lozenges *iNova, Hong Kong; iNova, Malaysia.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and inflammation.

Difflam Anti-inflammatory Lozenges with Cough Suppressant *iNova, Austral.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1); pholcodine (p. 1675·1).
Sore throat; cough.

Difflam Anti-inflammatory Lozenges (with Antibacterial) *iNova, Malaysia.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Difflam Anti-Inflammatory Lozenges (with cough suppressant) *iNova, Malaysia.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1); pholcodine (p. 1675·1).
Cough; mouth and throat disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Difflam Anti-Inflammatory Throat Spray *iNova, Singapore.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain.

Difflam Anti-inflammatory Throat Spray *iNova, Austral.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain.

Difflam Cough *3M, NZ.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1); pholcodine (p. 1675·1).
Cough; mouth and throat disorders.

Difflam Cough Lozenges *iNova, Singapore.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1); pholcodine (p. 1675·1).
Cough; mouth and throat disorders.

Difflam Forte Anti-Inflammatory Throat Spray *iNova, Malaysia.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain.

Difflam Lozenges *iNova, Austral.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat pain.

Difflam Mouth Gel *iNova, Austral.; iNova, Hong Kong; iNova, Malaysia; 3M, NZ; iNova, Singapore.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth pain and inflammation.

Difflam Orange *iNova, Philipp.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Difflam Solution *iNova, Austral.; iNova, Malaysia.†*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and inflammation.

Difflam-C *iNova, Austral.; iNova, Hong Kong; iNova, Malaysia; 3M, NZ; iNova, Singapore.*
Benzydamine hydrochloride (p. 29·2); chlorhexidine gluconate (p. 1743·3).
Painful and inflammatory mouth and throat disorders; oral hygiene.

Diffu-K *UCB, Fr.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Diffumal *Malesci, Ital.*
Theophylline (p. 1229·3).
Asthma; bronchospasm.

Diffumax *Orion, Hung.†; Menarini, Pol.*
⊗Formoterol fumarate (p. 1209·2).
Asthma; obstructive airways disease.

Diffundox *Winthrop, UK.*
Tamsulosin (p. 2369·1).

Dificid *Optimer, Canad.; Optimer, USA.*
Fidaxomicin (p. 298·3).
Clostridium difficile-associated diarrhoea.

Dificlir *Astellas, Denm.; Astellas, Irl.; Astellas, Norw.; Astellas, Spain; Astellas, Swed.; Astellas, UK.*
Fidaxomicin (p. 298·3).
Clostridium difficile-associated diarrhoea.

Difil-G *Stewart Jackson, USA.*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Asthma.

Difilin *Deva, Turk.*
Diprophylline (p. 1207·3).
Obstructive airways disease.

Difilina
Note: this name may be used for preparations of different composition.
Norma (Νορμα), Gr.
Calcium dobesilate (p. 2464·3).

Difin *Positif, India.*
Diclofenac (p. 48·3).
Pain.

Difin Plus *Positif, India.*
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Positif, India.
Topical gel: Diclofenac (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Difin-S *Positif, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Difiram *Pharmasant, Thai.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Difirin Plus *Genesis, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Difisal *Kramer, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Difisal Plus *Kramer, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Difisal Relax *Kramer, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3).

Difix *Promedica, Ital.*
Calcitriol (p. 2113·1).
Renal osteodystrophy; hypoparathyroidism; pseudohypoparathyroidism; rickets; osteoporosis.

Diflac Plus *Radicura, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Diflam
Note: this name may be used for preparations of different composition.
Interbat, Indon.
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Diflapane *Danlex, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diflazole *Teva, Irl.*
Fluconazole (p. 578·2).
Fungal infections.

Diflazon *KRKA, Cz.†; KRKA, Hong Kong; KRKA, Rus.; KRKA, Ukr.*
Fluconazole (p. 578·2).
Fungal infections.

Diflerix *Medochemie, Hong Kong†; Medochemie, Malaysia.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Diflogin *Chemica, Gr.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Diflorate *Micro, India.*
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Difloxin *Otto, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Di-Flu *Petsiavas, Gr.*
Diflunisal (p. 51·3).

Diflucan *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; IFET (ΙΦΕΤ), Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Vinci, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Diflunazol *Klonal, Arg.*
⊗Econazole (p. 577·2); neomycin (p. 329·3); diflucortolone (p. 1634·1).
Infected skin disorders.

Difluvid *Hovid, Malaysia.*
Fluconazole (p. 578·2).
Fungal infections.

Diflux *Quesada, Arg.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Hypertension.

Difluzol *Stada, Austria; Arterium, Ukr.*
Fluconazole (p. 578·2).
Fungal infections.

Difluzole *Cipla-Medpro, S.Afr.*
Fluconazole (p. 578·2).
Fungal infections.

Difmedol *Faran, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Difmetre *Solvay, Ital.*
Indometacin (p. 71·2); caffeine (p. 1203·3); prochlorperazine maleate (p. 1098·3).
Migraine.

Difnal *Nanxin, China; Ranbaxy, Singapore.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Ranbaxy, Malaysia.
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Difolta *Rafa, Israel.*
Pralatrexate (p. 849·3).
T-cell lymphoma.

Difonate *Pharmanel, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Diform *La Pharmaceuticals, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diformil *Faes, Spain.†*
Metaformaldehyde (Trioxane).
Mouth infections.

Diformiltricina *Faes, Spain.†*
Cetrimonium bromide (p. 1742·3); benzocaine (p. 1980·2); metaformaldehyde (Trioxane); tyrothricin (p. 384·1).
Mouth and throat disorders.

Diformin *Leiras, Fin.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

DiFortan *Emo-Farm, Pol.†*
Naproxen choline (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Difosfen *Omedir, Arg.; Rubio, Singapore; Rubio, Spain†; Rubio, Thai.; TTN, Thai.*
Etidronate disodium (p. 1182·3).
Ectopic ossification; osteoporosis; Paget's disease of bone.

Difosfocin *Magis, Ital.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism.

Difosfonal *SPA, Ital.*
Clodronate disodium (p. 1180·3).
Osteolytic tumours; multiple myeloma; hyperparathyroidism; osteoporosis.

Difosfon-S *SJA, Gr.*
Risedronate sodium (p. 1189·3).

Difoxacil *Quimica y Farmacia, Mex.*
Norfloxacin (p. 333·3).
Bacterial infections.

Difra *Saga, India.*
Adapalene (p. 1692·1).
Acne.

Difrarel *Leurquin, China; Leurquin, Fr.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1).
Diabetic retinopathy; peripheral vascular disorders.

Sigma-Tau, Ger.†; Tecnifar, Port.
Myrtillus (p. 2566·2).
Peripheral vascular disorders; vascular eye disorders; eye disorders.

Difrarel E *Leurquin, Fr.; Leurquin Mediolanum, Hung.†*
Myrtillus (p. 2566·2); vitamin E acetate (p. 2119·2).
Myopias.

Leurquin, Hong Kong.
Vitamin E (p. 2119·1); anthrocyanosides.
Myopias; poor night vision.

Difravision *Leurquin, Fr.*
Myrtillus (p. 2566·2); vitamins; lutein (p. 2079·2); trace elements; zeaxanthin (p. 2125·3); fish oil (p. 1460·1).
Age-related eye disorders.

Difrin *Vitamed, Israel.†*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Diftal *Farmak, Ukr.*
Diclofenac (p. 48·3).
Inflammation following eye surgery or injury; photophobia; inhibition of miosis during cataract surgery; prevention of cystoid macular oedema following cataract surgery.

Diftavax *Sanofi Pasteur, Irl.†; Sanofi Pasteur, Ital.; Sanofi Pasteur, Spain.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Difterivaccine *Statens Serum Institut, Denm.*
An adsorbed diphtheria vaccine (p. 2382·3).
Active immunisation.

Diftet *InterVax, Hong Kong.*
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Dif-Tet-All *Novartis, Braz.†; Novartis Vaccines, Ital.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Diftetkok *InterVax, Hong Kong.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Difu *H & Care, India.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Difur *Cantabria, Spain.*
Polypodium leucotomos.
Skin disorders.

Difuran *The Forty-Two, Thai.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Gastrointestinal infections.

Difusel *Medix, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Difusil *Ivax, Arg.*
Codergocrine mesilate (p. 389·2); cinnarizine (p. 622·1).
Mental function impairment.

Difusin *Zyg, Thai.*
Sodium fusidate (p. 302·1).
Skin infections; infected wounds and burns.

Digacin *Mibe, Ger.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Digal *Probiomed, Mex.*
Dipyridamole (p. 1362·2).

Digaol *Zeiss Meditec, Fr.†*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Digaril *Novartis, Spain.*
Fluvastatin sodium (p. 1385·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Digassim *Vitoria, Port.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Digecap-Zimatico *Sigma, Braz.*
⊗Bromopride (p. 1824·2); dimeticone (p. 1886·2); pancreatin (p. 2579·3); cellulase (p. 2473·1).
Nausea and vomiting; digestive disorders.

Digecool *Biosync, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Digedrat *Farmasa, Braz.; Medley, Braz.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; dyspepsia; postoperative gastrointestinal atony.

Digédryl *Merck Medication Familiale, Fr.*
Anhydrous sodium sulfate (p. 1888·1); monobasic sodium phosphate (p. 1791·1).
Dyspepsia.

Di-Gel *Schering-Plough, Indon.; Schering-Plough, USA.*
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastro-oesophageal reflux; hiatus hernia; gastritis; peptic ulcer; cholecystitis; hyperacidity.

Schering-Plough, Indon.; Plough, Port.†
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastro-oesophageal reflux; hiatus hernia; gastritis; peptic ulcer; cholecystitis; gastric hyperacidity; dyspepsia.

Digems-CT *Medley, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1); simeticone (p. 1886·2).

Digen *Zhi Jun, China.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Digenat *Natufarma, Arg.*
Cynara (p. 2490·3); boldo (p. 2458·3); carqueja (p. 2471·2).
Liver and biliary-tract disorders.

Digene *Abbott, India.*
Chewable tablets: Aluminium hydroxide (p. 1817·2); aluminium magnesium silicate

(p. 2168·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastritis; oesophagitis; hiatus hernia; gastric hyperacidity.

Abbott, India.
Oral gel: Simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); carmellose sodium (p. 2175·2).
Peptic ulcer; gastritis; oesophagitis; hiatus hernia; gastric hyperacidity.

Digene Total *Abbott, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Digenil *Saval, Chile.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive disorders; flatulence.

Digenor *Sanofi-Aventis, Mex.*
Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2).
Oesophagitis; hiatus hernia; gastritis; peptic ulcer; adjunct in gastrointestinal procedures; nausea and vomiting.

Digenor Plus *Sanofi-Aventis, Mex.*
⊗Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2); papain (p. 2582·3).
Gastrointestinal disorders; adjunct in gastrointestinal procedures.

Digenorflat *Baliarda, Arg.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2); dehydrocholic acid (p. 2492·1).
Digestive disorders; preparation for abdominal or pelvic imaging.

Digenta *Interbat, Indon.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Digeodren *Sevene, Fr.*
Taraxacum officinalis (p. 2625·3); berberis vulgaris (p. 2502·1); lappa major (p. 2540·1).
Homoeopathic preparation.

Digeoslor *Sevene, Fr.*
Chelidonium majus (p. 2522·2); raphanus sativus niger; bourdaine (Rhamnus frangula) (p. 1843·3).
Homoeopathic preparation.

Digepepsin *Kenwood, USA.*
⊗Pepsin (p. 2586·1); pancreatin (p. 2579·3); bile salts (p. 2457·2).

Digeplex *Shreya, India.*
Oral drops: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3).
Digestive disorders.

Shreya, India.
Oral liquid: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders.

Shreya, India.
Tablets: ⊗Pancreatin (p. 2579·3).

Digeplex-T *Shreya, India.*
⊗Pancreatin (p. 2579·3); ox bile (p. 2457·2); pepsin (p. 2586·1); amylase (p. 2442·1); dimeticone (p. 1886·2).
Digestive disorders.

Digeplus *Ache, Braz.*
⊗Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2); pepsin (p. 2586·1).
Formerly contained metoclopramide hydrochloride, dimeticone, dehydrocholic acid, cellulase, pepsin, and pancreatin.
Digestive disorders.

Digerab-D *Medihealth, India.*
Domperidone (p. 1838·1); rabeprazole sodium (p. 1881·1).

Digerent *Polifarma, Ital.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal spasm; irritable colon; oesophageal motility disorders.

Digerex *De Mayo, Braz.†*
Bromopride (p. 1824·2).
Nausea and vomiting.

Digervin *Coll, Spain.†*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; gastric hyperacidity peptic ulcer; Zollinger-Ellison syndrome.

Digesan *Sanofi-Aventis, Braz.*
Bromopride (p. 1824·2).
Nausea and vomiting; gastrointestinal motility disorders.

Digesdyn *Nutri-Dyn, Canad.*
⊗Betaine hydrochloride (p. 2456·1); cellulase (p. 2473·1); amylase (p. 2442·1); lipase (p. 2579·3); ox bile extract (p. 2457·2); pancreatin (p. 2579·3); papain (p. 2582·3); pepsin (p. 2586·1); pancreatic proteolytic enzyme (p. 2579·3).
Digestive disorders.

Di-Gesic *Aspen, Austral.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Digespar *Sanofi-Aventis, Chile.*
Metoclopramide hydrochloride (p. 1862·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Digesplen *Craveri, Arg.*
⊗Pancreatin (p. 2579·3); metoclopramide (p. 1862·2); simeticone (p. 1886·2); deoxycholic acid (p. 2457·2).
Gastrointestinal disorders.

Digesprid *Neo Quimica, Braz.*
Bromopride (p. 1824·2).
Nausea and vomiting.

DiGest
Note: this name may be used for preparations of different composition.
Mediherb, Austral.
Ginger (p. 1844·1); gentian (p. 2512·1); chamomile (p. 2474·1); milk thistle (p. 1561·1); taraxacum (p. 2625·3); citrus reticulata.
Digestive disorders.

Digest
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Seroyal, Canad.
⊗Betaine hydrochloride (p. 2456·1); glutamic acid hydrochloride (p. 2070·3); pancreatin (p. 2579·3); papain (p. 2582·3); pepsin (p. 2586·1).
Digestive disorders.

Digest Aid
Note: this name may be used for preparations of different composition.
Golden Glow, Austral.
⊗Cynara (p. 2490·3); fennel (p. 2503·2); ginger (p. 1844·1); gentian (p. 2512·1); bromelains (p. 2460·3).
Digestive disorders.

Swiss Herbal, Canad.†
⊗Papain (p. 2582·3).

Digesta *Seaford, Canad.*
Amylase (p. 2442·1); lipase (p. 2579·3); tilactase (p. 2631·2); sucrase; maltase (p. 2428·1); cellulase (p. 2473·1).
Digestive disorders.

DigestAid *Swiss Caps, UK.*
Cynara (p. 2490·3).
Digestive disorders.

Digestaid
Note: this name may be used for preparations of different composition.
Eagle, Austral.
⊗Betaine hydrochloride (p. 2456·1); pepsin (p. 2586·1); pancreatin (p. 2579·3); ox bile salt (p. 2457·2); bromelain (p. 2460·3); papain (p. 2582·3); potassium chloride (p. 1793·2); gentian (p. 2512·1); fennel (p. 2503·2); peppermint oil (p. 1877·1); chromium chelate (p. 2055·3).
Gastrointestinal disorders.

Digestbem *Eurofarma, Braz.*
Sodium bicarbonate (p. 1781·1); sodium carbonate (p. 2617·3); citric acid (p. 2480·3).
Gastric hyperacidity.

Digestein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Digestelact *Nutricia, Austral.†*
Food for special diets.
Lactose intolerance.

Digestherb *Schwabe, UK.*
Cynara (p. 2490·3).
Digestive disorders.

Digestif Rennie *Bayer Consumer, S.Afr.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Dyspepsia; heartburn.

Bayer, Cz.†; Bayer, Hung.†
⊗Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); papain (p. 2582·3); pancreatin (p. 2579·3).
Dyspepsia; pancreatic insufficiency; gastrointestinal disorders associated with hyperacidity.

Digestil *Teuto, Braz.*
Bromopride (p. 1824·2).
Gastrointestinal disorders.

Digestin
Note: this name may be used for preparations of different composition.
Chew, Thai.
Mamylase; amylase (p. 2442·1); thiamine nitrate (p. 2103·2); scopolia (p. 2611·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); dried aluminium hydroxide gel (p. 1817·2).
Gastrointestinal disorders.

Pharco, Ukr.
⊗Papain (p. 2582·3); pepsin (p. 2586·1); sanzim-2000.
Digestive disorders.

Digestina *Uniao Quimica, Braz.*
Bromopride (p. 1824·2).
Nausea and vomiting.

Digestiol *Herbapol Poznan, Pol.*
Cynara (p. 2490·3).
Disorders of fat digestion; dyspepsia; flatulence; nausea.

Digestion *Homeocan, Canad.*
Boldo (p. 2458·3); carduus marianus (p. 1561·1); chelidonium majus (p. 2522·2); dolichos pruriens; leptandra virginica; lycopodium clavatum (p. 2547·1).
Homoeopathic preparation.

Digestion Calming Drops *Weleda, UK.*
Angelica (p. 2443·3); cinnamon (p. 2479·2); nutmeg (p. 2573·1); melissa (p. 2552·3).
Nausea; digestive disorders.

Digestion Formula *Future, Canad.*
A range of digestive enzyme preparations.

Digestisan *Bioforce, UK.*
Cynara (p. 2490·3); taraxacum (p. 2625·3); boldo (p. 2458·3); milk thistle (p. 1561·1).
Dyspepsia; flatulence.

Digestive
Note: this name may be used for preparations of different composition.
Braun, India.
Preparation for enteral nutrition.

Dorwest, UK.
Ginger (p. 1844·1); hydrastis (p. 2528·1); rhubarb (p. 1884·2); valerian (p. 2640·2).
Dyspepsia; heartburn; gastric hyperacidity; nausea.

Digestive Aid *Blackmores, Austral.*
Althaea (p. 2438·3); fennel (p. 2503·2); ginger (p. 1844·1); gentian (p. 2512·1); peppermint leaf (p. 1877·1); anise oil (p. 2444·3).
Digestive disorders.

Digestive Bio Balance *Blackmores, Austral.*
Lactobacillus reuteri (p. 2596·3).
Digestive disorders.

Digestive Bitters *Blackmores, Austral.*
Taraxacum (p. 2625·3); meadowsweet (p. 2550·2); gentian (p. 2512·1); agrimony (p. 2432·3); cinnamon (p. 2479·2).
Digestive disorders.

Digestive Relief *Principle Healthcare, UK.*
Milk thistle (p. 1561·1).
Dyspepsia.

Digestive Zyme *Bioglan, Austral.†*
⊗Betaine hydrochloride (p. 2456·1); glutamic acid (p. 2070·2); pepsin (p. 2586·1).
Achlorhydria; hypochlorhydria.

Digestivo Antonetto *Antonetto, Ital.*
Anionic resin; glycine (p. 2071·2); calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Digestivo Giuliani *Giuliani, Ital.*
Domperidone (p. 1838·1).
Dyspepsia.

Digestivo S Pellegrino *Sanofi-Aventis, Ital.*
Metoclopramide hydrochloride (p. 1862·2).

Digestodoron *Weleda, Austria.*
Male fern (p. 158·3); polypodium leaf; scolopendrium vulgare; salix leaf (p. 129·2).
Gastrointestinal disorders.

Weleda, UK.
Male fern (p. 158·3); polypodium; scolopendrium; salix alba; salix purpurea (p. 129·2); salix viminalis; salix vitellina.
Homoeopathic preparation.

Weleda, Ger.
Male fern (p. 158·3); polypodium leaf; scolopendrium; salix leaf (p. 129·2).
Gastrointestinal disorders.

Weleda, S.Afr.†
Male fern (p. 158·3); polypodium leaf; pteridium aquilinum leaf; salix alba leaf; salix purpurea leaf (p. 129·2); salix viminalis leaf; salix vitellina leaf; scolopendrium leaf.
Gastrointestinal disorders.

Weleda, Fr.
Aspidium filix-mas (p. 158·3); polypodium vulgare; scolopendrium officinale; salix alba; salix viminalis; salix vitellina.
Homoeopathic preparation.

Digestol
Note: this name may be used for preparations of different composition.
Bio-Sante, Canad.
Anise (p. 2444·2); coriander (p. 2486·3); peppermint (p. 1877·1).
Digestive disorders.

Sante Naturelle, Canad.
⊗Papain (p. 2582·3).

Digestolax *Bio-Sante, Canad.*
⊗Bile extract (p. 2457·2); amylase (p. 2442·1); pancreatin (p. 2579·3); papain (p. 2582·3); pepsin (p. 2586·1); stomach extract (p. 2444·1).
Digestive disorders.

Digestomen *Menarini, Belg.*
⊗Betaine hydrochloride (p. 2456·1); pepsin (p. 2586·1); papain (p. 2582·3); amylase (p. 2442·1); pancreatin (p. 2579·3); pancrelipase (p. 2580·1); cellulase (p. 2473·1).
Digestive disorders due to pancreatic insufficiency.

Digestomen Complex *Menarini, Spain.*
⊗White tablets, pepsin (p. 2586·1); red tablets, papain (p. 2582·3); amylase (p. 2442·1); green tablets, pancreatin (p. 2579·3).
Digestive disorders.

Digestomen-P *Menarini, India.*
Amylase (p. 2442·1); lipase; protease (p. 2598·1).

Diges-Tonic *Herbapol Krakow, Pol.*
Chamomile (p. 2474·1); fennel (p. 2503·2); St John's wort (p. 449·1); peppermint leaf (p. 1877·1); rhubarb (p. 1884·2); rose fruit (p. 2607·1); coriander (p. 2486·3).
Gastrointestinal disorders.

Digestor *Abdi, Turk.*
Cynara (p. 2490·3).
Digestive disorders.

Digex *Pronova, USA.†*
Amylase (p. 2442·1); cellulase (p. 2473·1); hyoscyamine sulfate (p. 1848·1); lipase (p. 2579·3); phenyltoloxamine citrate (p. 638·1); protease (p. 2598·1).
Gastrointestinal disorders.

Digex NF *Pronova, USA.*
Hyoscyamine sulfate (p. 1848·1); phenyltoloxamine citrate (p. 638·1).
Gastrointestinal disorders.

Digezanol *Hormona, Mex.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Digezym
Note: this name may be used for preparations of different composition.
Quality, Hong Kong.
⊗Pancreatin (p. 2579·3); amylase (p. 2442·1); papain (p. 2582·3); lysine (p. 2079·3); vitamin B_1 (p. 2103·1); vitamin B_{12} (p. 2107·2).
Digestive disorders.

Digherbal *Knop, Chile.*
Cynara scolymus (p. 2490·3); taraxacum (p. 2625·3); boldo (p. 2458·3).
Homoeopathic preparation.

Digibar *E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Digibind *GSK, Austral.; GSK, Canad.†; SERB, Fr.†; IFET (ΙΦΕΤ), Gr.; GSK, UK; Glaxo Wellcome, USA.†*
Digoxin-specific antibody fragments (p. 1549·1).
Digoxin or digitoxin toxicity.

Digiclean Antibacterial *Ecolab, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Digiclean E Foam Hand Soap *Ecolab, Canad.*
Chloroxylenol (p. 1748·2).
Skin cleansing.

Digiclean E Hand Soap *Ecolab, Canad.†*
Triclosan (p. 1773·2).
Skin cleansing.

Digiclean Slim-Line *Ecolab, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

DigiFab *Paladin, Canad.; IFET (ΙΦΕΤ), Gr.; Protherics, UK; Protherics, USA.*
Digoxin-specific antibody fragments (p. 1549·1).
Digoxin toxicity.

Digiflux-A *Agio, India.*
Magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Digifungin *Wagner, Hung.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Digimed *corax, Ger.†*
Digitoxin (p. 1353·1).
Heart failure; arrhythmias.

Digimerck *Merck, Austria; Merck Serono, Ger.; Merck, Hung.*
Digitoxin (p. 1353·1).
Heart failure; arrhythmias.

Digirest *Servocare, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Digisan *Ecolab, Canad.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Digisan E *Ecolab, Canad.*
Benzalkonium chloride (p. 1737·1).
Hand disinfection.

Digitage *Plus, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Digitaline *Barrenne, Braz.; Lavipharm, Gr.*
Digitoxin (p. 1353·1).
Arrhythmias; heart failure.

Digitalis Antidote *Roche, Hong Kong.*
Digoxin-specific antibody fragments (p. 1549·1).
Digitalis poisoning.

Digitax *Greenpharma, Braz.†*
Digoxin (p. 1353·3).
Arrhythmias; heart failure.

Digitran *Macleods, India.*
Digoxin (p. 1353·3).
Heart failure; supraventricular arrhythmias.

Diglexol *IQFA, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diglucron *Community Pharmacy, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Digobal *Baldacci, Braz.*
Digoxin (p. 1353·3).

Digocard-G *Klonal, Arg.*
Digoxin (p. 1353·3).

Digosin *Chugai, Jpn.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Digostada *Stada, Ger.†*
β-Acetyldigoxin (p. 1290·2).
Heart failure; arrhythmias.

Digosyp *Cadila, India.*
Digoxin (p. 1353·3).
Heart failure; supraventricular arrhythmias.

Digotab *AWD, Ger.†*
β-Acetyldigoxin (p. 1290·2).
Heart failure; arrhythmias.

Digox *Cadila, India.*
Digoxin (p. 1353·3).
Heart failure; supraventricular arrhythmias.

CT, Ger.†
β-Acetyldigoxin (p. 1290·2).
Heart failure; arrhythmias.

Digoxen *Cifarma, Braz.*
Digoxin (p. 1353·3).
Arrhythmias; heart failure.

Digoxil *Legrand, Braz.*
Digoxin (p. 1353·3).

Digton *Areu, Spain.†*
Sulpiride (p. 1107·3).
Anxiety disorders; psychoses; vertigo.

Digyl *Armour, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

DIH *Hasco-Lek, Pol.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Dihengsai *Haibin, China.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Di-Hydan *Genopharm, Fr.*
Phenytoin (p. 538·2).
Epilepsy; trigeminal neuralgia.

Dihydergot *Novartis, Austral.; Amdipharm, Austria; Pharma Logistics, Belg.; Novartis, Cz.†; Amdipharm, Gr.; IFET (ΙΦΕΤ), Gr.; Novartis, Gr.; Novartis, Indon.†; Novartis, Mex.; Amdipharm, Spain†; Pro Concepta, Switz.; Novartis, Venez.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; orthostatic hypotension; cerebrovascular disorders; migraine; vascular headache; chronic fatigue; vertigo; venous insufficiency; herpes; urinary retention.

Pro Concepta, Switz.
Nasal spray: Dihydroergotamine mesilate (p. 672·2); caffeine (p. 1203·3).
Migraine.

Dihydergot plus *Amdipharm, Ger.; Novartis, Switz.†*
⊗Dihydroergotamine mesilate (p. 672·2); etilefrine hydrochloride (p. 1379·1).
Hypotension.

Dihydral
Note: this name may be used for preparations of different composition.
Dishman, Neth.
Dihydrotachysterol (p. 2113·2).
Hypoparathyroidism; rickets; renal osteodystrophy.

Dihydrocodeine P *Pharmaniaga, Malaysia.*
Dihydrocodeine tartrate (p. 52·3); paracetamol (p. 115·1).
Pain.

DiHydro-CP *Cypress, USA.†*
⊗Dihydrocodeine tartrate (p. 52·3); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

DiHydro-GP *Cypress, USA.†*
⊗Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

DiHydro-PE *Cypress, USA.†*
Dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cough; upper respiratory-tract congestion.

Diidergot *Teofarma, Ital.*
Dihydroergotamine mesilate (p. 672·2).
Migraine and other vascular headache; orthostatic hypotension; cervical spasm; postoperative urinary retention.

Diike *Cadila, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Di-K-Cil *TP, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dikexin *Sanye, China.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; trichomoniasis.

Diklason *Leti, Venez.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Diklofen *Stadmed, India.*
Diclofenac (p. 48·3).
Pain.

Diklonat P *Teva, Pol.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Diklopain *Eczacibasi, Turk.*
Diclofenac sodium (p. 48·3).

Dikloron *Deva, Turk.*
Injection; suppositories; tablets: Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Deva, Turk.
Topical gel: Diclofenac diethylamine (p. 48·3).
Musculoskeletal and joint pain.

Diklo-S *Bilim, Turk.*
Diclofenac sodium (p. 48·3).

Dikloteva *Med, Turk.*
Diclofenac potassium (p. 48·3).

Dikloziaja *Ziaja, Pol.†*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dikof-C *Prem, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Dikonb *NB, India.*
Diclofenac sodium (p. 48·3).
Pain.

Dikpa *Keshav, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Keshav, India.
Tablets: Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dikul *Global, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dikul MR *Global, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dikul P *Global, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dikul SP *Global, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

DIKY *Cyathus, Cz.*
Diclofenac sodium (p. 48·3).
Pain; musculoskeletal and joint disorders.

Diky *CSC, Pol.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue pain.

Dil SE *Osmed, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dilabar *Qualigen, Spain.†*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Dilabar Diu *Qualigen, Spain; Vita, Spain.*
⊗Hydrochlorothiazide (p. 1403·2); captopril (p. 1331·2).
Hypertension.

Dilace *Orchid, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Dilaclan *Q Pharma, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilacor
Note: this name may be used for preparations of different composition.
Teuto, Braz.
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; hypertension; angina pectoris.

Watson, USA.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilacoran *Abbott, Mex.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; heart failure.

Dilacoron *Abbott, Braz.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic cardiomyopathy; migraine and other vascular headaches.

Diladel *Sanofi-Aventis, Ital.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilaflux *Medley, Braz.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Dilahex *Sandoz, Philipp.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Dilahim *Ahimsa, Arg.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Dilaine *Help, Gr.*
Minoxidil (p. 1438·3).

Dilam
Note: this name may be used for preparations of different composition.
BMW, India.
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Lamsa, Arg.†
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Dilamax *Bialfar, Port.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Dilamol *Sanval, Braz.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Dilan *Gunal, Turk.†*
Salicylic acid (p. 1719·1); acetic acid (p. 2426·3); cloral hydrate (p. 1055·2).
Calluses.

Dilanorm *Sanofi-Aventis, Neth.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.

Dilantin *CSP, Fr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia; Pfizer, Venez.*
Phenytoin sodium (p. 538·2).
Arrhythmias; epilepsy; seizures associated with neurosurgery; neuralgia; extrapyramidal syndrome; status epilepticus.

Pfizer, Austral.; Pfizer, Canad.; Pfizer, India; Pfizer, Israel; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Singapore; Pfizer, Thai.; Parke, Davis, USA.
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias; trigeminal neuralgia; seizures associated with neurosurgery; status epilepticus.

Dilantin with Phenobarbital *Pfizer, India.†*
Phenytoin sodium (p. 538·2); phenobarbital (p. 535·2).
Epilepsy.

Dilaprost *Biofarma, Turk.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Dilar
Note: this name may be used for preparations of different composition.
Minerva (Μινερβα), Gr.; Roche, Mex.†
⊗Paramethasone acetate (p. 1645·1).
Corticosteroid.

Dilarmine *Syntex, Mex.†*
⊗Paramethasone acetate (p. 1645·1); chlorphenamine maleate (p. 620·3).
Hypersensitivity; inflammation.

Dilartan *Duncan, Arg.*
Bamethan (p. 1314·1).
Varices.

Dilasidom *Warsaw-Polfa, Rus.; Polfa Warsaw, Ukr.†*
Molsidomine (p. 1441·1).
Heart failure; angina pectoris.

Dilasig *Apotex, Austral.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension.

Dilatair *Ajanta, Philipp.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Dilatam *Abic, Israel; Teva, Philipp.; Pharmacare, S.Afr.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilate *Micro, India.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia; iritis; uveitis.

Dilateron-F *Offenbach, Mex.*
Cinnarizine (p. 622·1).
Vertigo.

Dilatol
Note: this name may be used for preparations of different composition.
Jaba, Port.
Isradipine (p. 1414·2).
Hypertension.

Dilatrane *SERP, Mon.*
Theophylline (p. 1229·3) or theophylline and sodium acetate (p. 1229·3).
Obstructive airways disease.

Dilatrate *Actient, USA.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Dilatrend *Nova Argentia, Arg.; Roche, Austral.; Roche, Austria; Roche, Chile; Roche, China; Roche, Cz.; Roche,*

Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Ital.; Roche, Malaysia; Roche, Mex.†; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, Venez.
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension; cardiomyopathy; ischaemic heart disease; left-ventricular dysfunction; myocardial infarction.

Dilatrend D *Nova Argentia, Arg.*
⊗Carvedilol (p. 1333·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dilaudid *Mundipharma, Austral.; Purdue, Canad.; Purdue, USA.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Dilaudid Cough *Knoll, USA.†*
⊗Hydromorphone hydrochloride (p. 67·3); guaifenesin (p. 1666·2).
Cough.

Dilavax *Sanval, Braz.†*
Nifedipine (p. 1447·2).

Dilavenil *Intermed, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Dilax *Beacons, Singapore.*
Bisacodyl (p. 1821·1).
Constipation.

Dilbloc *Roche, Indon.; Roche, Port.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension; ischaemic heart disease.

Dilcal *Sanofi-Aventis, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Dilcardia *JB Chemicals, India; Danlex, Philipp.; Unique, Rus.†; JB Chemicals, Thai.; Generics, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilcare *Ind-Swift, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Dilceren *Zentiva, Cz.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit due to arterial vasospasm following subarachnoid haemorrhage.

Dilclor *Diba, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Dilcontin *Modi-Mundipharma, India.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilcor
Note: this name may be used for preparations of different composition.
Gross, Braz.; Norpharma, Denm.†
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilem *Ist. Chim. Inter., Ital.; Douglas, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilena *Organon, Hong Kong†; Organon, Mex.; Organon, Port.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Schering-Plough, Braz.
White tablets, estradiol valerate (p. 2271·2); blue tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Dilevocet *Sanify, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Dilevocet-M *Sanify, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Dilevocet-Plus *Sanify, India.*
⊗Levocetirizine (p. 632·3); ambroxol (p. 1654·3); pseudoephedrine (p. 1676·1).

Dilex *Wockhardt, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Dilex-G *Poly, USA.*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Asthma.

Dilfar *Abbott, Port.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilgard *Cipla, India.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilgina *Kopran, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Diligan
Note: this name may be used for preparations of different composition.
UCB, India.
Meclozine hydrochloride (p. 634·3); nicotinic acid (p. 2083·1).
Vertigo; labyrinthitis; Ménière's disease.

Dilinct *Adcock Ingram, S.Afr.*
Etofylline (p. 1208·2); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Dilinct Dry Cough *Adcock Ingram, S.Afr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dilinct Junior *Adcock Ingram, S.Afr.*
Guaifenesin (p. 1666·2).
Cough.

Dilis *Ind-Swift, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Diliter *Boniscontro & Gazzone, Ital.†*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; heart failure; angina pectoris.

Dilium *Seven Stars, Thai.*
Diazepam (p. 1063·2).

Dilizem *Berlin Pharm, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilmen *Menarini, Indon.; Sanbe, Indon.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension.

Dilmin *Ratiopharm, Fin.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilnicon *VHB, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

Dilo-BM *GSK, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Dilocaine *Hauck, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Dilocar *Pensa, Ital.†*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Dilocard *ICN, Pol.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilocea
Note: this name may be used for preparations of different composition.
Ceamed, Port.
Montelukast sodium (p. 1214·3).
Asthma.

Ceamed, Port.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Dilocor *Baroda, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Dilo-DX *GSK, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1).

Dilofen
Note: this name may be used for preparations of different composition.
Metrolink, Philipp.
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

P & B, India.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dilofen-CZ *P & B, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dilofen-MR *P & B, India.*
Chlormezanone (p. 1045·1); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dilofen-P *P & B, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dilomin *Am-Europharma, Philipp.*
Dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Dilona *Mapra, India.*
Diclofenac (p. 48·3).
Pain; prevention of intra-operative miosis; eye inflammation and pain.

Dilona Plus *Mapra, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dilona-SP *Mapra, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).
Oedema; soft-tissue disorders; pain; inflammation.

Dilophen-SP *Uniphar, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dilopin *Munir, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Dilora *Invision, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Dilosyn *GSK, India.*
Methdilazine hydrochloride (p. 635·3).
Hypersensitivity reactions; pruritus; neurodermatitis.

Dilosyn Expectorant *GSK, India.*
Methdilazine hydrochloride (p. 635·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Dilotab
Note: this name may be used for preparations of different composition.
Zee, USA.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Dilotab II *Zee, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Dilotex *Dollder, Venez.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Dilox *Lafi, Chile.*
Ketorolac trometamol (p. 80·2).
Pain.

Diloxin *Pond's, Thai.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Diloxol *Bilim, Turk.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Dilper-INA *Ultra, Mex.*
Cinnarizine (p. 622·1).
Vestibular disorders; motion sickness; mental function impairment.

Dilpeze *Helm, Port.†*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dilpral *Orion, Fin.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; atrial fibrillation.

Dilpril *Ind-Swift, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Dilrène *Sanofi-Aventis, Fr.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Dilrene *Sanofi-Aventis, Hung.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension.

Dilsal *TAD, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dil-Sanorania *Winthrop, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilsave *Emcure, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Dilso *Soho, Indon.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltabeta *Betapharm, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltahexal *Sandoz, Austral.; Hexal, Ger.†; Hexal, NZ.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltam *Rowex, Irl.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltaretard *Betapharm, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilt-CD *Apotex, USA.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltec *Utopian, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; heart failure.

Diltelan *Faran, Gr.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

OEP, Philipp.†
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltem *Lavipharm, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Diltenk *Biotenk, Arg.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; heart failure.

Dilter CD *Natco, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Dilti *CT, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltia *Andrx, USA.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltiacor *Biolab Sanus, Braz.*
Diltiazem hydrochloride (p. 1359·2).
Arrhythmias; hypertension.

Diltiagamma *Worwag, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltiangina *Tecnimede, Port.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Diltiastad *Stada, Austria.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltiaz *Shreya, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Dilticard *Intra-Labs, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Sandoz, Turk.
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltiem *Sanofi-Aventis, Port.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltigesic *Troikaa, India.*
Diltiazem hydrochloride (p. 1359·2).

Diltime *Zydus, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Zydus, Philipp.†
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltin *Cimed, Braz.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Diltipress *Sigma, Braz.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltisyn *Themis, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Diltiwas *Chiesi, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltix *Aristo, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diltizem *Pfizer, Braz.; Nevzat, Turk.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltor *Torrent, Braz.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltotal *Mintlab, Chile.*
Ginseng (p. 2513·3); lecithin (p. 2542·2); procaine hydrochloride (p. 1994·3); vitamins; rutin (p. 2505·3); minerals.

Diltp *Taurus, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Diltrate *Daffohils, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Dilt-XR *Apotex, USA.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Diltzac *Apotex, USA.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilucid *Collins, Mex.†*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Dilucort *Aspen Consumer, S.Afr.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders; anogenital pruritus.

Dilufrin *Sophia, Mex.†*
Phenylephrine (p. 1672·2).
Eye congestion.

Dilum *Tecnifar, Port.*
Isoxsuprine hydrochloride (p. 2535·2).
Premature labour.

Diluplex *Steierl, Austria.*
Colocynthis (p. 1833·3); daphne mezereum; ranunculus bulbosus.
Homoeopathic preparation.

Steierl, Ger.
Colocynthis (p. 1833·3); mezereum; ranunculus bulbosus.
Homoeopathic preparation.

Diluran *Zentiva, Cz.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Dilutex Plus *Kamakshi, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Dilutol
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of clotting in extracorporeal circuits.

Meda, Spain.
⊗Torasemide sodium (p. 1516·3).
Oedema; hypertension.

Diluxina *Diba, Mex.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dilvas *Cipla, India.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Dilvas AM *Cipla, India.*
Enalapril maleate (p. 1371·1); amlodipine besilate (p. 1304·1).
Hypertension.

Dilzanol *Remedina, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilzanton *Juta, Ger.†; Q-Pharm, Ger.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dilzem *Ascent, Austral.; Kwizda, Austria†; Orion, Fin.; Pfizer, Ger.; Pfizer, Hung.; Torrent, India; Cephalon, Irl.; Douglas, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Switz.; Pharmasant, Thai.; Cephalon, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias; coronary spasm; myocardial infarction; adjunct in transluminal coronary angioplasty or bypass surgery.

Dilzene *Sigma-Tau, Ital.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; myocardial ischaemia; arrhythmias.

Dilzen-G *Klonal, Arg.*
Diltiazem (p. 1359·2).
Angina pectoris.

Dilzor *VHB, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Dima *Medochemie, Singapore.†*
Nitrazepam (p. 1089·1).
Insomnia.

Dimacol *Robins, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Wyeth Consumer, Mex.
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Dimagrir *Gador, Arg.*
⊗Mazindol (p. 2324·1).
Obesity.

Dimalan
Note: this name may be used for preparations of different composition.
Filaxis, Arg.
Bicalutamide (p. 749·1).

Dimase *Unison, Thai.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Dimate *APT, Hong Kong.†*
Dimenhydrinate (p. 625·2).
Motion sickness.

Dimaval *Haupt, Cz.; Heyl, Ger.*
Unithiol (p. 1579·1).
Antidote; heavy-metal poisoning.

Lazar, Arg.
Homatropine methylbromide (p. 2007·3); benactyzine hydrochloride (p. 408·2); pentobarbital (p. 1094·3).
Smooth muscle spasm.

Dimavyl *Leti, Venez.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Dimazo *Chinta, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; cold symptoms.

Dimbutol *Polifarma, Turk.*
Ethambutol hydrochloride (p. 296·1).

Dimecaina *Grunenthal, Chile.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Dimed *Tanapat Bhaesaj, Thai.*
Diazepam (p. 1063·2).

Dimedon *Acdhon, Thai.*
⊗Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); mannitol (p. 1427·3); simeticone (p. 1886·2).
Gastric hyperacidity.

Dimefor *Farmoquimica, Braz.; Rhein, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dimefor-G *Rhein, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Diménan *Dexo, Fr.*
Brompheniramine maleate (p. 618·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Dimegan
Note: this name may be used for preparations of different composition.
Senosiain, Mex.
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis.

Dimegan D *Senosiain, Mex.*
Loratadine (p. 633·2); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Dimelin *Shionogi, Jpn.*
Acetohexamide (p. 467·2).
Diabetes mellitus.

Dimenate *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea; vomiting; Ménière's disease.

Dimenine *Pharmahof, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; Ménière's disease.

Dimeno *Milano, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo; nausea and vomiting.

Dimenox *Knop, Chile.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Dimeprost *Columbia, Mex.*
Diethylstilbestrol (p. 2267·3).
Prostatic cancer.

Dimerrin *Unison, Philipp.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; sinusitis; rhinitis.

Dimesian *Asian Pharm, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; menière's disease.

Dimesul *SarPharm, Ital.*
Nimesulide (p. 101·3).
Pain.

Dimet *Infectopharm, Ger.*
Dimeticone (p. 2209·3); lauril alcohol.
Pediculosis.

Dimeta-2 *Christo, Hong Kong.*
Brompheniramine maleate (p. 618·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Dimetabs *Jones, USA.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Diméthane *Leurquin, Fr.*
Pholcodine (p. 1675·1).
Cough.

Dimetane
Note: this name may be used for preparations of different composition.
Wyeth, Gr.; Wyeth Consumer, Thai.†
Brompheniramine maleate (p. 618·1).
Hay fever.

Dimetane DX *Creekwood, USA.†*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dimetane Expectorant C *Pfizer Consumer, Canad.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Dimetane Expectorant DC
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Canad.
Brompheniramine maleate (p. 618·1); hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dimetapp
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer Consumer, Canad.; Pfizer Consumer, Hong Kong; Wyeth Consumer, Mex.; Healthcare Logistics, NZ; Wyeth, Philipp.; Pfizer Consumer, Singapore; Pfizer Consumer, Thai.
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Hay fever; nasal congestion; cold symptoms; allergic rhinitis; allergic conjunctivitis; upper respiratory-tract symptoms; hypersensitivity reactions; respiratory-tract disorders; rhinitis; sinusitis.

Wyeth Consumer, Braz.; Wyeth Consumer, S.Afr.†; Whitehall-Robins, USA; Wyeth, Venez.
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; respiratory-tract disorders; cold and influenza symptoms.

Wyeth, Gr.
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).

Dimetapp Chesty Cough *Pfizer Consumer, Austral.*
Guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Cough.

Dimetapp Chewables for Kids *Pfizer Consumer, Canad.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).

Dimetapp Childrens Cold & Fever *Wyeth Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Upper respiratory-tract disorders.

Dimetapp Childrens Cough & Cold *Pfizer, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Dimetapp Cold *Wyeth Consumer, Canad.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; allergic rhinitis.

Dimetapp Cold, Cough & Flu *Pfizer Consumer, Austral.*
Liquid Capsules: ⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Cough; cold and influenza symptoms.

Dimetapp Cold, Cough & Sinus *Pfizer Consumer, Austral.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; nasal congestion.

Dimetapp Cold & Fever *Whitehall-Robins, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); paracetamol (p. 115·1).
Cold symptoms.

Dimetapp Cold & Flu Day Relief
Note: this name may be used for preparations of different composition.
Wyeth Consumer, Austral.†
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cough; cold and influenza symptoms.

Dimetapp Cold & Flu Night Relief *Wyeth Consumer, Austral.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); doxylamine succinate (p. 627·3).
Cough; cold and influenza symptoms.

Dimetapp Cough, Cold & Flu *Pfizer Consumer, Austral.*
Day & Night Liquid Capsules: ⊗Day capsules, dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); night capsules, dextromethorphan hydrobromide; pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Dimetapp Cough & Congestion *Wyeth Consumer, Canad.†*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Dimetapp Daytime Cold *Wyeth Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; upper respiratory-tract disorders.

Dimetapp Decongestant *Whitehall-Robins, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Dimetapp Decongestant Plus Cough *Whitehall-Robins, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs; nasal congestion.

Dimetapp DM *Pfizer Consumer, Austral.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough.

Whitehall-Robins, USA.
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Dimetapp DM Cold & Cough *Healthcare Logistics, NZ.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough; hay fever; nasal congestion.

Dimetapp DM Cough & Cold *Pfizer Consumer, Canad.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders; cold symptoms.

Dimetapp Expectorante *Whitehall, Braz.†*
Guaifenesin (p. 1666·2).
Cough.

Dimetapp Headcold & Flu *Pfizer Consumer, Austral.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Dimetapp 12 Hour Nasal *Pfizer Consumer, Austral.; Wyeth Consumer, NZ.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Dimetapp Infants Nasal Relief *Pfizer Consumer, Austral.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Dimetapp Long Acting Cough Plus Cold *Wyeth Consumer, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Dimetapp New *Wyeth, Gr.*
Brompheniramine maleate (p. 618·1); phenylpropanolamine hydrochloride (p. 1674·1).

Dimetapp Nighttime Cold *Wyeth Consumer, Canad.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms; upper respiratory-tract disorders.

Dimetapp Nighttime Flu *Whitehall-Robins, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); brompheniramine maleate (p. 618·1).
Coughs and cold symptoms.

Dimetapp Non-Drowsy Flu *Whitehall-Robins, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Coughs and cold symptoms.

Dimetapp Pain & Fever Relief *Pfizer Consumer, Austral.*
Ibuprofen (p. 68·2).
Fever; pain.

Dimetapp PE Nasal Decongestant *Pfizer Consumer, Austral.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Dimetapp PE Sinus Day + Night *Pfizer Consumer, Austral.*
Day capsules, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); night capsules, paracetamol; phenylephrine hydrochloride; chlorphenamine maleate (p. 620·3).
Sinusitis; nasal congestion.

Dimetapp PE Sinus Pain *Pfizer Consumer, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Sinusitis.

Dimetapp PE Sinus Pain + Allergy *Pfizer Consumer, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Sinusitis; allergic rhinitis.

Dimetapp Sinus
Note: this name may be used for preparations of different composition.
Robins, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Nasal congestion.
Wyeth Consumer, Austral.†
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion.

Dimetapp-C *Pfizer Consumer, Canad.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders; cold symptoms.

Dimethicream *Hamilton, Austral.*
Dimeticone (p. 2209·3); cetrimide (p. 1742·1).
Emollient barrier cream.

Dimetil *Mibe, Ger.†*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Dimetiliv *EMS, Braz.*
Dimeticone (p. 1886·2).

Dimetirol *Offenbach, Mex.*
Metamizole magnesium (p. 53·3).
Fever; muscle spasm; pain.

Dimetofan *Vitae, Mex.*
⊗Dextromethorphan (p. 1660·1); pseudoephedrine (p. 1676·1).
Cough.

Dimetriose *Sanofi-Aventis, Austral.; Sanofi-Aventis, Malaysia; Aventis, NZ; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.†; Sanofi-Aventis, UK.†*
⊗Gestrinone (p. 2280·2).
Endometriosis.

Dimetrose *Sanofi-Aventis, Braz.; Marvecs, Ital.*
⊗Gestrinone (p. 2280·2).
Endometriosis.

Dimetus *Charoon Bhesaj, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Dimexol *Glenmark, Cz.*
Mephenoxalone (p. 2025·2).
Skeletal muscle spasm; spasticity.

Dimezin *Teuto, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Dimicaps *Gelcaps, Mex.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; motion sickness.

Dimicin
Note: this name may be used for preparations of different composition.
IQFA, Mex.
Dicloxacillin (p. 286·1).
Bacterial infections.

Dimicina *Codilab, Port.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Diarrhoea.

DiMill *SIT, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye irritation; eye disinfection.

Dimin *TNP, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting.

Diminex Antitusigeno *Vinas, Spain.*
Cineole (p. 2479·1); chlorcyclizine hydrochloride (p. 620·2); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Diminon *Andromaco, Chile.†*
Clonixin lysine (p. 40·1).
Inflammation; pain.

Diminor *Alphrema, Ital.*
Phaseolamin.
Slimming aid.

Diminut *Libbs, Braz.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Dimipra *Pfizer, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Dimipress *Cifarma, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Dimirel *Sanofi-Aventis, Austral.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Dimitone *Roche, Belg.; Roche, Denm.†; Teva, Israel.†*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Dimodan *Sanofi-Aventis, Mex.*
Disopyramide (p. 1363·2).
Arrhythmias.

Dimol *Wallace, India.*
Simeticone (p. 1886·2).
Flatulence; adjunct in gastroscopy and abdominal x-ray; infant colic.

Dimonate *Utopian, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; Ménière's disease.

Dimopen *Bruluagsa, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Dimophen *Nakornpatana, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2).
Cough.

Dimophen DC *Nakornpatana, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Dimor *Nordic, Swed.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Dimorf *Cristalia, Braz.*
⊗Morphine sulfate (p. 92·3).
Pain.

Dimotane Co *Wyeth Consumer, Irl.†; Wyeth Consumer, UK.*
⊗Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Dimotane Expectorant *Wyeth Consumer, UK.*
⊗Brompheniramine maleate (p. 618·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; respiratory-tract congestion.

Dimotic *Candor, India.*
Amoxicillin (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dimotil *Quality, Hong Kong.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea; ostomy management.

Dimsa *Cinetic, Arg.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Dims-GM *Neiss, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Dimzef *CKD, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Din
Note: this name may be used for preparations of different composition.
Hypermarcas, Braz.
Paracetamol (p. 115·1).
Fever; pain.
Mapra, India.
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Dinac
Note: this name may be used for preparations of different composition.
Douglas, Austral.†; Sriprasit, Thai.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.
Zydus, India.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Dinaclon *Vianex (Βιανεξ), Gr.*
Diclofenac sodium (p. 48·3).
Inflammatory disorders.

Dinacode avec codéine *Tradiphar, Fr.*
Syrup: Sodium benzoate (p. 1738·2); wild thyme (p. 2648·1); tolu balsam (p. 1679·2); codeine (p. 40·2).
Cough.
Tradiphar, Fr.†
Suppositories: Codeine (p. 40·2); cineole (p. 2479·1).
Cough.

Dinaflex *Zodiac, Braz.; Tecnofarma, Chile.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders; arthroses.

Dinaflex Duo *Tecnofarma, Chile.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Degenerative joint disorders.

Dinaflox *Quimica y Farmacia, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Dinagen *Hormona, Mex.†*
Piracetam (p. 393·3).
Cerebrovascular disease.

Dinagest *Mochida, Jpn.*
Dienogest (p. 2267·2).
Endometriosis.

Dinal-AP *Sapco, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dinalexin *Pharmathen, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Dinamel *Liferpal, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dinamot *Giempi, Venez.*
Famotidine (p. 1842·1).
Gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Dinapres *Chiesi, Gr.; Master Pharma, Ital.*
⊗Delapril (p. 1350·2); indapamide (p. 1409·2).
Hypertension.

Dinaron *Pfizer, Arg.*
⊗Chorionic gonadotrophin (p. 2258·1).
Female infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Dinate *Jaapharm, Canad.; Seatrace, USA.†*
Dimenhydrinate (p. 625·2).
Motion sickness.

Dinaton *Ache, Braz.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Dinavital C *Merck, Braz.*
Arginine (p. 2049·1); ascorbic acid (p. 2110·3).
Tonic.

Dinaxcinco *Serra Pamies, Spain.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Dinaxil *Tecnifar, Port.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; urticaria; hypersensitivity; asthma.

Dinaxil Capilar *Serra Pamies, Spain.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Dinaxin *Rayere, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dinazide *TO-Chemicals, Thai.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Dincil *Shijiazhuang, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Dincilezan *Regiomedica, Neth.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Dindevan *Aspen, Austral.; Biological E, India.*
Phenindione (p. 1467·3).
Thromboembolic disorders.

Dine *Orchid, India.*
Procyclidine.
Parkinsonism; drug-induced extrapyramidal disorders.

Dinecol *Talent, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dinefec *British Dispensary, Thai.*
Diclofenac diethylamine (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dinemet-M *Rishab, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Dinertone *Azevedos, Port.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Di-Neumobron *Roemmers, Arg.*
Oral solution: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders.
Roemmers, Arg.
Soluble tablets: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); tipepidine hibenzate (p. 1679·1).
Respiratory-tract disorders.
Roemmers, Arg.
Suppositories: Paracetamol (p. 115·1); guaifenesin (p. 1666·2); niaouli oil

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2569·1); cineole (p. 2479·1); camphor (p. 2466·2); terpineol (p. 2627·2).
Respiratory-tract disorders.

Dineurin *Recalcine, Chile.*
Gabapentin (p. 523·3).
Epilepsy.

Dinex *Cipla, India.*
Didanosine (p. 972·3).
HIV infection.

Ding Huan *Yangtze River, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Ding Jun Sheng *Shuangqi, China.*
Lactobacillus (p. 2596·3).

Ding Ke Si *Zhongguan, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Ding Na *Kangnuo, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Ding Rong *Xian Jiaoda, China.*
Tocoferil nicotinate (p. 1516·1).

Ding Shu *Weifang, China.*
Tiopronin (p. 1578·1).

Ding Te *Hisun, China.*
Zidovudine (p. 1024·2).
HIV infection.

Ding Yue *Lukang Chenxin, China.*
Azasetron hydrochloride (p. 1820·2).

Dinghe *Lukang Chenxin, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Dingke *Qilu, China.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin, nail, and vaginal infections.

Dinid *Vargas, Venez.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Diniket *UCB, Ital.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Dinill *Allergan, Braz.*
Benzalkonium chloride (p. 1737·1); boric acid (p. 2459·3).
Eye disorders.

Dinill-D *Allergan, Mex.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

DiNing
Note: this name may be used for preparations of different composition.
Bosen, China.
Sodium demethylcantharidate.

Dining
Note: this name may be used for preparations of different composition.
Hisun, China.
Zolmitriptan (p. 682·2).
Migraine.

Dinisan *ProMed, Cz.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Dinisor *Parke, Davis, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dinisorb *Farmsintez, Rus.*
Isosorbide dinitrate (p. 1412·2).
Myocardial infarction; angina pectoris; pulmonary hypertension; heart failure.

Dinit *Leiras, Fin.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Dinitrile-Vit *Biotech, Venez.*
Succinic dinitrile (p. 2624·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Nervous disorders.

Dinitro-B *Cafar, Venez.*
Succinic dinitrile (p. 2624·1); vitamin B substances (p. 2102·3).
Nervous disorders.

Dinitrobe *Cafar, Venez.*
Vitamin B substances (p. 2102·3).

Dinobroxol *Waas Anita, Spain.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Dinocin
Note: this name may be used for preparations of different composition.
Loeffler, Mex.
Didanosine (p. 972·3).
HIV infection.
NCPC, Philipp.
Ampicillin (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Dino-Cod *Pharma-Q, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).

Dinolan *Farmaceutica H, Mex.*
⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with increased mucus.

Dinopen *Ahn-Gook, Singapore.†*
Diclofenac sodium (p. 48·3); lidocaine hydrochloride (p. 1988·2).
Gout; musculoskeletal and joint disorders; pain.

Dinor *Nucron, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Dino-Retic *Pharma-Q, S.Afr.*
⊗Furosemide (p. 1387·1).

Dinorik *Darnitsa, Ukr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Dinoripe *Reddy, India.*
Dinoprostone (p. 2134·1).
Induction and augmentation of labour; cervical dilatation.

Dinortes *Liconsa, Cz.; Liconsa, Irl.; Liconsa, Neth.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Dinosin *Richmond, Arg.*
Didanosine (p. 972·3).
HIV infection.

Dinospray *Omnimed, S.Afr.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Dinoven *Stada, Spain.†*
A heparinoid (p. 1401·1).
Varices; soft-tissue disorders.

Dinox *Reddy, Rus.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Dinpen *NCPC, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Dintaxin *Keun Wha, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Dintoina *Recordati, Ital.*
Phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia; arrhythmias.

Dintoinale *Recordati, Ital.*
Phenytoin sodium (p. 538·2); methylphenobarbital (p. 533·1).
Epilepsy.

Dintri *Shijiazhuang, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Dio *Sciencex, Fr.*
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility; haemorrhoids.

Dioalgo *Bouchara-Recordati, Fr.†*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Diocaine *Dioptic, Canad.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

Diocalm Dual Action *SSL, UK.*
⊗Morphine hydrochloride (p. 92·3); attapulgite (p. 1820·1).
Diarrhoea.

Diocalm Ultra *SSL, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diocam *Elisium, Arg.*
Clonazepam (p. 519·1).
Anxiety; epilepsy; panic disorder; social phobia.

Diocaps *Berk, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Diocarpine *Dioptic, Canad.*
Pilocarpine hydrochloride (p. 2010·3).
Production of miosis; cholinergic.

Diochloram *Dioptic, Canad.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Diocid *Intra-Labs, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Diocid-D *Intra-Labs, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Diocin *Utopian, Thai.*
Furazolidone (p. 933·3); pectin (p. 2200·3); kaolin (p. 1850·1).
Diarrhoea.

Diocomb SI *Novartis, Braz.*
Tablets, valsartan (p. 1521·2); tablets, simvastatin (p. 1489·2).

Diocor *Pharma Start, Ukr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Diocor Solo *Pharma Start, Ukr.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Dioctyl *UCB, UK.*
Docusate sodium (p. 1836·2).
Constipation.

Dioctyn *Dixon-Shane, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Diodarone *Prodotti, Braz.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Dioderm *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders; eczema; dermatitis.

Diodex *Dioptic, Canad.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Diodolina *Mayo, Mex.*
Diiodohydroxyquinoline (p. 931·1); metronidazole (p. 936·1).
Amoebiasis.

Diodoquin *Glenwood, Canad.; Pfizer, Mex.; Pfizer, Venez.*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Diof *Zuventus, India.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

Diofen *Liptis, USA.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes.

Dioflam *Polychronus, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Dioflan *Arterium, Ukr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Diofluor *Dioptic, Canad.*
Fluorescein sodium (p. 2506·2).
Aid to ophthalmic examination.

Diogent *Dioptic, Canad.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Diohes *Opsonin, Hong Kong.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Diohespan *Aflofarm, Pol.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Diolan *Zentiva, Cz.†*
Ethylmorphine hydrochloride (p. 56·3).
Cough.

Diolasa *Andromaco, Chile.*
Tilactase (p. 2631·2).
Lactose intolerance.

Diolin
Note: this name may be used for preparations of different composition.
Lincoln, India.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diolin-M *Aristo, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Diomega *Dioter, Fr.*
Evening primrose oil (p. 2502·2); fish oil (p. 1460·1).
Menopausal disorders; premenstrual syndrome; dry skin disorders.

Diomicete *Edol, Port.*
Clotrimazole (p. 576·2).
Fungal eye infections.

Diomycin *Dioptic, Canad.*
Erythromycin (p. 291·2).
Bacterial eye infections.

Dion *Monokem, India.*
Tablets: Diclofenac (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.
Monokem, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dion MR *Monokem, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Dionadion *Nafar, Mex.*
Phytomenadione (p. 2122·2).
Hypoprothrombinaemia; vitamin K deficiency bleeding.

Diondel
Note: this name may be used for preparations of different composition.
Roemmers, Arg.
Flecainide (p. 1382·3).
Arrhythmias.

Dionephrine *Dioptic, Canad.*
Phenylephrine hydrochloride (p. 1672·3).

Dionina *Merck Serono, Arg.*
Ethylmorphine hydrochloride (p. 56·3).
Cough.

Dionindon *Zydus, India.*
Ethylmorphine hydrochloride (p. 56·3).
Cough; pain.

Dion-P *Monokem, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Diopentolate *Dioptic, Canad.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Diophenyl-T *Sandoz, Canad.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Diopine *Alvia (Αλβια), Gr.; Allergan, Neth.†; Allergan, Spain.†*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma; raised intra-ocular pressure; ocular hypertension.

Dio-PP *PannonPharma, Hung.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Diopra *Cadila, India.*
Diclofenac sodium (p. 48·3); omeprazole (p. 1867·2).

Diopred *Sandoz, Canad.*
⊗Prednisolone acetate (p. 1645·2).
Eye inflammation.

Dioptears *Dioptic, Canad.*
Polysorbate 80 (p. 2203·3).
Dry eyes.

Dioptec *Dergam, Fr.*
Evening primrose oil (p. 2502·2); salmon oil (p. 1460·1); vitamins; minerals.
Dry eyes.

Diopticon *Dioptic, Canad.*
⊗Naphazoline hydrochloride (p. 1669·3).

Diopticon A *Dioptic, Canad.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).

Dioptimyd *Dioptic, Canad.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Eye disorders.

Dioptrol *Dioptic, Canad.*
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); dexamethasone (p. 1630·3).
Eye disorders.

Dior *TNP, Thai.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-day packs also contain 7 inert tablets.
Combined oral contraceptive.

Dior Bronze Matte Sunshine *Dior, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); oxybenzone (p. 1715·3).
Sunscreen.

Dior Bronze Voile Teinte *Dior, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Dior Plus *Sain, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Dioralyte *Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Korangi, Port.; Sanofi-Aventis, UK.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium acid citrate (p. 1781·1); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Dioralyte Relief *Sanofi, UK.*
Rice powder; sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Diorium *SM, Gr.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Diorouge *Dioptic, Canad.*
Pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).

Diorskin Compact *Dior, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Diorskin Fluide *Dior, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Diorskin Nude *Dior, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Diorskin Pure Light *Dior, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Diorskin Sculpt *Dior, Canad.*
Octinoxate (p. 1715·1).
Sunscreen.

Diosmectal *Malesci, Ital.*
Diosmectite (p. 1887·1).
Gastrointestinal disorders.

Diosmin *Ache, Braz.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Diosmin 500 *Charoen, Thai.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Diosmina Complex *Amnol, Ital.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2); melilot (p. 2552·3); vitamins.
Circulatory disorders.

Diosminex *Lek-Am, Pol.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Diospas *Shalaks, India.*
Dicycloverine (p. 1834·2).
Gastrointestinal spasm.

Diosper *Kleva, Gr.; Kleva, Singapore.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders; venous insufficiency; haemorrhoids.

Diosporin
Note: this name may be used for preparations of different composition.
Dioptic, Canad.
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Dioptic, Canad.†
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Bacterial eye infections.

Diostate *Roberts, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3); phosphorus (p. 2589·2).
Calcium deficiency; dietary supplement.

Diosteo *Indoco, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Diosulf *Dioptic, Canad.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Diosven *CT, Ital.*
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility.

Diotev *Teva, Irl.†*
Valsartan (p. 1521·2).
Myocardial infarction; heart failure.

Diotrope *Dioptic, Canad.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Diotroxin *Aspen, S.Afr.*
Levothyroxine sodium (p. 2339·1); liothyronine sodium (p. 2342·3).
Hypothyroidism.

Diotul *Faes, Spain.†*
Dosmalfate (p. 1839·3).
NSAID-induced peptic ulcer.

Diovan *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Jpn; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy; left ventricular dysfunction.

Diovan A *Novartis, Arg.*
Valsartan (p. 1521·2); amlodipine besilate (p. 1304·1).
Angina pectoris; heart failure; hypertension.

Diovan Amlo *Novartis, Braz.*
Valsartan (p. 1521·2); amlodipine besilate (p. 1304·1).
Hypertension.

Diovan Comp *Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Diovan D *Novartis, Arg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Diovan HCT *Novartis, Braz.; Novartis, Canad.; Novartis, Hung.; Novartis, USA; Novartis, Venez.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Diovan Triple *Novartis, Arg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2); amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Diovan Triplo *Novartis, Braz.*
⊗Tablets, valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2); tablets, amlodipine besilate (p. 1304·1).
Hypertension.

Diovan/Amlibon *Novartis, Venez.*
14 Tablets, valsartan (Diovan) (p. 1521·2); 14 tablets, amlodipine (Amlibon) (p. 1304·1).
Hypertension; angina pectoris.

Diovane *Novartis, Belg.; Paranova, Denm.†*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Diovenor *Innotech, Fr.; Zuoz Innothera, Venez.*
Diosmin (p. 2505·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Diovol
Note: this name may be used for preparations of different composition.
Church & Dwight, Canad.
Caplets; oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Heartburn; dyspepsia.

Church & Dwight, Canad.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2).
Heartburn; dyspepsia.

Wallace, India.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium carbonate (p. 1856·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; hiatus hernia; gastritis.

Carter Horner, Thai.†
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; flatulence.

Church & Dwight, Thai.†
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; flatulence.

Diovol Forte *Wallace, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastritis; heartburn.

Diovol Forte DGL *Wallace, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); liquorice (p. 1853·2).
Peptic ulcer; gastritis; heartburn.

Diovol Plus *Church & Dwight, Canad.; Church & Dwight, Hong Kong.*
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Heartburn; dyspepsia; flatulence; gastritis; gastric hyperacidity; peptic ulcer.

Church & Dwight, Canad.; Church & Dwight, Hong Kong.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Heartburn; dyspepsia; flatulence; gastritis; gastric hyperacidity; peptic ulcer.

Diovol Plus AF *Church & Dwight, Canad.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Heartburn; dyspepsia; flatulence.

Diox *Daehan, Singapore.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Dioxadol *Montpellier, Arg.*
Oral drops: Metamizole magnesium (p. 53·3); paracetamol (p. 115·1).
Fever; pain.

Montpellier, Arg.
Syrup; tablets: Metamizole magnesium (p. 53·3).
Fever; pain.

Dioxaflex *Armstrong, Mex.*
Diclofenac epolamine (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Bago, Arg.
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3), diclofenac epolamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, and soft-tissue disorders.

Bago, Braz.
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Dioxaflex B12 *Bago, Arg.*
⊗Diclofenac sodium (p. 48·3); betamethasone (p. 1623·2); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Joint pain.

Dioxaflex Forte *Bago, Arg.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Pain.

Dioxaflex Gesic *Bago, Arg.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Dysmenorrhoea; soft-tissue disorders.

Dioxaflex Plus *Bago, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint, and peri-articular disorders.

Dioxaflex Protect *Bago, Arg.*
Diclofenac sodium (p. 48·3).
Omeprazole (p. 1867·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Dioxicolagol *Fabra, Arg.*
Cynara (p. 2490·3); boldo (p. 2458·3); belladonna (p. 2453·3); valerian (p. 2640·2); espina colorada.
Liver and biliary-tract disorders.

Dioxis *Hexa, Arg.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Dioxisol *Darnitsa, Ukr.*
Dioxidine; lidocaine (p. 1988·1).
Soft-tissue infections; ulcers; burns; wounds.

Dioxzye *TNP, Thai.*
Simeticone (p. 1886·2).
Flatulence; abdominal discomfort.

Diozinac *Laboratoires d'Anjou, Fr.*
Diosmectite zinc (p. 1887·1); ginkgo flavone (p. 2512·3).
Acne.

Diozinac KS *Laboratoires d'Anjou, Fr.*
Diosmectite zinc (p. 1887·1); salicylic acid (p. 1719·1); ginkgo flavone (p. 2512·3).
Acne.

Dip
Note: this name may be used for preparations of different composition.
Alkem, India.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Merck, Venez.
Sucralfate (p. 1889·1).
Peptic ulcer.

Dip Hot *Mentholatum, Pol.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Dip Rilif *Mentholatum, Pol.*
Ibuprofen (p. 68·2); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dip-A *Alkem, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Dipal *Candor, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Dipal-AT *Candor, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Dipal-F *Biomedica, India.*
Diclofenac potassium (p. 48·3); famotidine (p. 1842·1); paracetamol (p. 115·1).

Dipam *New Life, Thai.*
Diazepam (p. 1063·2).

Dipamona *Roemmers Rowe, Venez.*
Dipyrone (p. 53·3).
Fever; pain.

Dipan *Thorne, Canad.†*
Amylase (p. 2442·1); lipase (p. 2579·3); protease.

Dipana *Promed, Rus.*
Picrorhiza kurroa (p. 2590·2); andrographis paniculata (p. 2443·2); eclipta alba; phyllanthus niruri (p. 2590·1); black nightshade (p. 2458·2); tinospora cordifolia; bacopa (p. 2452·1); punarnava (p. 2601·1); ginger (p. 1844·1); piper longum.
Liver disorders.

Dipankrin *Gedeon Richter, Hung.*
⊗Pancreatin (p. 2579·3); duodenum extract (p. 2444·1).
Gastrointestinal disorders.

Dipatropin *Pasteur, Chile.*
Atropine sulfate (p. 1310·2); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Dipax *Reliance, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; seizures; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome.

Dipazide *Siam Bheasach, Malaysia†; Siam Bheasach, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Dipclo-MR *BMW, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); magnesium (p. 1786·3); paracetamol (p. 115·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dipecfur *Parggon, Mex.*
Diiodohydroxyquinoline (p. 931·1); activated charcoal (p. 1537·3).
Diarrhoea.

Dipemina *Lazar, Arg.; Raffo, Chile.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Dipen *Elpen (Ελπεν), Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Dipenocin *Genepharm, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Dipentum *UCB, Austral.; UCB, Austria; UCB, Canad.; Pfizer, Chile†; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; Pharmacia Upjohn, Gr.; UCB, Hong Kong; UCB, Irl.; UCB, Neth.; UCB, Norw.; Pharmabroker, NZ; UCB, Port.†; AHN, S.Afr.; UCB, Swed.; UCB, Switz.†; Eczacibasi, Turk.†; UCB, UK; UCB, USA.*
Olsalazine sodium (p. 1866·3).
Ulcerative colitis; inflammatory bowel disease.

Dipep *Serum Institute, India.*
Capsules: ⊗Papain (p. 2582·3); amylase (p. 2442·1); pepsin (p. 2586·1); cellulase (p. 2473·1).
Dyspepsia; pancreatic insufficiency; steatorrhoea; diarrhoea; anorexia.

Serum Institute, India.
Oral suspension: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders.

Dipeptamin *Fresenius Kabi, Ger.*
L-Alanyl-L-glutamine (p. 2070·2).
Parenteral nutrition.

Dipeptiven *Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Chile; SSPC, China; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Indon.; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Mex.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK; Fresenius Kabi, Ukr.*
L-Alanyl-L-glutamine (p. 2070·2).
Parenteral nutrition.

Diperflox *Francia, Ital.*
Norfloxacin pivoxil (p. 333·3).
Urinary-tract infections.

Dipergon *Bayer, Gr.*
Lisuride maleate (p. 908·2).
Hyperprolactinaemia; prolactinoma; lactation inhibition; acromegaly.

Diperpen *Francia, Ital.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Dipezona *Omega, Arg.*
Diazepam (p. 1063·2).
Anxiety; epilepsy; muscle spasm; sedation.

Dipform *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3); clioquinol (p. 273·1).
Infected skin disorders.

Dipgenta *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Dipgenta Plus *Fulford, India.*
⊗Clobetasol propionate (p. 1627·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Diphafen *Sons, Mex.*
Difenidol hydrochloride (p. 1835·1).
Nausea and vomiting; vertigo.

Diphamine *Medgenix, Belg.*
Diphenhydramine hydrochloride (p. 626·2).
Pruritus; sunburn; insect stings; urticaria; hypersensitivity reactions.

Diphantoine *Apotex, Neth.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias.

Kela, Belg.
Phenytoin sodium (p. 538·2).
Arrhythmias; epilepsy.

Diphecol *Jagsonpal, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Diphecol-C *Jagsonpal, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Diphedan *PannonPharma, Hung.*
Phenytoin (p. 538·2).
Epilepsy; trigeminal neuralgia.

Diphen *ICM, Singapore.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; bronchial congestion; cold symptoms.

Diphen AF *Morton Grove, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Diphen Tann/ PE Tann/ CT Tann *Brighton, USA.*
Pentoxyverine tannate (p. 1672·1); diphenhydramine tannate (p. 626·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Diphenal *Minerva (Μινερβα), Gr.*
Phenytoin sodium (p. 538·2); phenobarbital (p. 535·2).
Epilepsy.

Diphenamine *Vickmans, Hong Kong.†*
Diphenhydramine (p. 626·1).

Diphenamine Expectorant *Vickmans, Hong Kong.†*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); sodium citrate (p. 1781·2).

Diphendryl Expectorant *TO-Chemicals, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; nasal congestion.

Diphenhist *Rugby, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Diphenhydramine Expectorant *Pharmaniaga, Malaysia.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; bronchial and nasal congestion.

SA Druggists, S.Afr.†
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; respiratory-tract congestion.

Diphenhydramine Expectorant Syrup *Adco, S. Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); chloroform (p. 1898·1).
Cough.

Diphenist *Omega, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

DiphenMax D *Rivers Edge, USA.†*
Phenylephrine tannate (p. 1672·2); diphenhydramine tannate (p. 626·1).
Upper respiratory-tract disorders.

Diphenoxylate A *Pharmaniaga, Malaysia.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Diphereline *Beaufour-Ipsen, China; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Pol.*
⊗Triptorelin (p. 2310·3).
Endometriosis; uterine fibroids; female infertility; prostatic cancer; precocious puberty.

Ipsen, Cz.; Ipsen, Hung.; Medison, Israel; Beaufour-Ipsen, Rus.; Ipsen, Thai.; Ipsen, Ukr.
⊗Triptorelin acetate (p. 2310·3) or triptorelin embonate (p. 2311·1).
Prostatic cancer; precocious puberty; endometriosis; female infertility; uterine fibroids; breast cancer.

Ipsen, Austral.
⊗Triptorelin embonate (p. 2311·1).
Prostatic cancer.

Diphergan *Jelfa, Pol.*
Promethazine hydrochloride (p. 638·2).
Asthma; hypersensitivity reactions; motion sickness; premedication.

Diphos *Procter & Gamble, Ger.†*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; ectopic ossification.

Dipidol *Behrens, Venez.*
Dipyrone (p. 53·3).
Fever; pain.

Dipidolor *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Ger.; Janssen-Cilag, Neth.*
Piritramide (p. 125·3).
Pain.

Dipigina *Belfar, Braz.*
Dipyrone (p. 53·3).

Dipigrand *Ahimsa, Arg.*
Dipyrone (p. 53·3).
Fever; inflammation; pain.

Dipimax *Cimed, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Dipinal *Cifarma, Braz.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Dipinohex *Hexal, Denm.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Dipinosticht *Hexal, Denm.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Dipiperon *Janssen-Cilag, Belg.; Janssen-Cilag, Denm.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen-Cilag, Neth.; Janssen-Cilag, Switz.*
Pipamperone hydrochloride (p. 1098·1).
Behaviour disorders; psychoses; sleep disorders; psychiatric disorders; agitation; restlessness.

Dipipéron *Janssen-Cilag, Fr.*
Pipamperone hydrochloride (p. 1098·1).
Aggressive states; chronic psychoses.

Dipiron *IMA, Braz.†*
Dipyrone (p. 53·3).
Fever; pain.

Dipix *Geolab, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Diplene *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diplene-AF *Fulford, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Diplexil *Tecnifar, Port.*
Sodium valproate (p. 553·1).
Epilepsy.

Diplexil-R *Tecnifar, Port.*
Valproate semisodium (p. 553·2).
Bipolar disorder; epilepsy; migraine and other headaches.

Diplitor *Glenmark, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Diplofen *Novagen, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Novagen, India.
Topical gel: Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); methyl salicylate (p. 92·1).

Diplofen 3D *Novagen, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Diplofen-MR *Novagen, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Diplofen-P *Novagen, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Diplom *Biomax, India.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Diplonim *Pharmatech, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Diplonim-MR *Pharmatech, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Diplovax *Biovac, S.Afr.†*
A measles vaccine (Edmonston-Zagreb strain) (p. 2398·3).
Active immunisation.

Dipni *Omega, Arg.*
Nystatin (p. 590·3).
Candidiasis.

Dipofen *Arlex, Mex.*
Ibuprofen (p. 68·2).
Inflammation.

Dipolip *Win-Medicare, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Dipoquin *Ioquin, Austral.†*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Diporel *Munir, Turk.*
Clopidogrel bisulfate (p. 1342·3).

Dipot *Asian Pharm, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Dipren *Darnitsa, Ukr.†*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain; gout.

Dipres *Precimex, Mex.*
Dipyridamole (p. 1362·2).

Dipress *Symbiosis, India.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Dipress-Plus *Symbiosis, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Dipride *Daksh, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Dipride-M *Daksh, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Diprifol *Dong Kook, Philipp.*
Propofol (p. 1909·3).
General anaesthesia; sedation in ventilated patients; sedation in diagnostic and surgical procedures.

Diprin
Note: this name may be used for preparations of different composition.
Geolab, Braz.
Dipyrone (p. 53·3).
Fever; pain.

Diprivan *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.†; Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.†; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore†; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; Fresenius Kabi, USA; AstraZeneca, Venez.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Di-Pro *Organon, Turk.*
Estradiol benzoate (p. 2271·1); progesterone (p. 2300·2).
Endometriosis; menstrual disorders; menopausal disorders.

Dipro AS *Delta, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Psoriasis.

Diprobase *Essex, Chile†; MSD-Chibret, Fr.; MSD, Hong Kong; MSD, Irl.; Schering-Plough, UK.*
Emollient.
Skin disorders; topical vehicle.

Schering-Plough, Pol.; Schering-Plough, UK.
Ointment: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Skin disorders; emollient.

Diprobath *MSD, Irl.*
Light liquid paraffin (p. 2191·2); isopropyl myristate (p. 2190·3).
Bath additive; dry skin; hyperkeratosis.

MSD, UK.†
Light liquid paraffin (p. 2191·2); isopropyl myristate (p. 2190·3); laureth 4 (p. 2194·1).
Dry skin disorders; hyperkeratoses.

Diprobet *Polipharm, Thai.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprobeta *Bunker, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diprocel *MSD, Hong Kong; Schering-Plough, Malaysia; MSD, Singapore; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprocort *Cifarma, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diproderm *Aesca, Austria; Schering-Plough, Denm.; MSD, Fin.; Schering-Plough, Norw.; MSD, Spain; MSD, Swed.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin and scalp disorders; otitis externa.

Diprodin *Kotra, Malaysia; Kotra, Singapore.*
⊗Diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2).
Cough; cold symptoms; allergic rhinitis.

Diprodol *Sons, Mex.*
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diproex *Unichem, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Diprofast *Schering-Plough, Mex.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diprofol *Taro, Israel; Farmak, Ukr.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Diproform *Schering-Plough, Ital.; Schering-Plough, Philipp.*
⊗Betamethasone dipropionate (p. 1623·3); clioquinol (p. 273·1).
Infected skin disorders.

Diproformo *Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3); clioquinol (p. 273·1).
Infected skin and scalp disorders.

Diproforte *Aesca, Austria.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprofos *2care4, Denm.; Orifarm, Denm.; Schering-Plough, Port.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diprogen
Note: this name may be used for preparations of different composition.
Indkus, India.
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Merck, Canad.
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Diprogenta *Schering-Plough, Arg.; Aesca, Austria; Mantecorp, Braz.; MSD, Ger.; MSD, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Switz.; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Diprolen *Schering-Plough, Denm.; MSD, Fin.; MSD, Swed.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprolene *MSD, Belg.; Merck, Canad.; Essex, Chile†; Schering-Plough, Israel†; Schering-Plough, Neth.; Schering-Plough, NZ†; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Turk.; Schering, USA.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprolène *MSD-Chibret, Fr.; MSD, Switz.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders; scalp disorders.

Diproline *Christo, Hong Kong.†*
Diprophylline (p. 1207·3).

Dipromal
Note: this name may be used for preparations of different composition.
ICN, Pol.
Magnesium valproate (p. 553·1).
Epilepsy.

Dipronova *Unipharm, Mex.†*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diprophos *Aesca, Austria; MSD, Belg.; Schering-Plough, Cz.; Schering-Plough, Hung.; Schering-Plough, Pol.; MSD, Switz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diproquin *Schering-Plough, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); hydroxyquinoline iodochloride (p. 2530·1).
Infected skin disorders.

Diprosalic *Schering-Plough, Arg.; Aesca, Austria; MSD, Belg.; Mantecorp, Braz.; Merck, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; Schering-Plough, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; MSD, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; MSD, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, UK; Schering-Plough, Ukr.; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin and scalp disorders; keratinisation disorders.

Diprosen *Teuto, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diprosis
Note: this name may be used for preparations of different composition.
MSD, Ger.
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Svizera, India.
⊗Betamethasone dipropionate (p. 1623·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); sodium lactate (p. 1781·2); urea (p. 1727·3).
Dry skin disorders; inflamed hyperkeratotic skin disorders.

Diprosone *Schering-Plough, Arg.; MSD, Austral.; MSD, Belg.; Mantecorp, Braz.; Merck, Canad.; Schering-Plough, Cz.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Hong Kong; MSD, Irl.; Schering-Plough, Israel†; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.†; MSD, Neth.; MSD, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.†; Schering-Plough, Port.; Schering-Plough, S. Afr.; MSD, Singapore; MSD, Switz.; MSD, Thai.; Schering-Plough, UK; Schering, USA†; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin and scalp disorders; corticosteroid.

Diprosone Depot *MSD, Ger.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Parenteral corticosteroid.

Diprosone G *Schering-Plough, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Diprosone Y *Schering-Plough, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); clioquinol (p. 273·1).
Infected skin disorders.

Diprosone-OV *Schering-Plough, Indon.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprospan *Mantecorp, Braz.; Schering-Plough, Chile; MSD, China; Schering-Plough, Denm.; MSD, Hong Kong; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Mex.; Essex, Philipp.; Schering-Plough, Rus.; MSD, Singapore; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, Ukr.; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Schering-Plough, Chile.
Cream; ointment: ⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprospan G *Schering-Plough, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Diprosta *Konimex, Indon.†*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Diprostène *MSD-Chibret, Fr.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Diprotop *MSD, Thai.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Diprovate *Fulford, India.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Diprovate Plus *Ranbaxy, India.*
⊗Betamethasone dipropionate (p. 1623·3); zinc sulfate (p. 2126·2).

Diprovate-G *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Diprovate-MF *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); sodium lactate (p. 1781·2); urea (p. 1727·3).
Dry skin disorders; inflamed hyperkeratotic skin disorders.

Diprovate-N *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Diprovate-N Plus *Ranbaxy, India.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1); zinc sulfate (p. 2126·2).

Diprozil *Cimed, Braz.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2).

Dipsalic *Fulford, India.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Seborrhoeic dermatitis; psoriasis.

Dipsalic-F *Fulford, India.*
⊗Clobetasol propionate (p. 1627·1); salicylic acid (p. 1719·1).

Dipt *Rhine, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Diptase *Rhine, India.*
Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); linoleic acid (p. 2509·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dipthen *Dipa, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Dipt-P *Rhine, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).

Dipydol *Valdecasas, Mex.*
Dipyrone (p. 53·3).
Pain.

Dipyrin *Ratiopharm, Fin.†*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Diqfanol *IQFA, Mex.*
Diclofenac (p. 48·3).

Diqing *Tasly, China.*
Temozolomide (p. 865·2).
Malignant glioma.

Diquas *Santen, Jpn.*
Diquafosol tetrasodium (p. 2495·2).
Dry eyes.

Diquertin *Flavir, Rus.*
Dihydroquercetin.
Respiratory-tract disorders; unstable angina; arrhythmias.

Dirab *Hetero, India.*
Dexrabeprazole sodium (p. 1881·1).
Gastrointestinal motility disorders; gastric acidity.

Dirab-D *Hetero, India.*
Dexrabeprazole (p. 1881·1); domperidone (p. 1838·1).
Gastrointestinal motility disorders; gastric acidity.

Diragyl *Piramal, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Dirahist *Teofarma, Ital.*
⊗Triamcinolone (p. 1648·3); chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Diralon *Biotech, Venez.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Diralox *Ifars, Indon.*
Furazolidone (p. 933·3).
Diarrhoea.

Diranite *Caplin, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Dirasec *Piramal, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Dirastan *Zentiva, Cz.†*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Dirax *Medicpharma, Thai.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Direc-2 *Sun, India.*
Diazepam (p. 1063·2).
Anxiety; premedication; seizures; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome.

Direktan *Gerot, Austria.*
Sodium nicotinate (p. 2083·1).
Peripheral vascular disease; decubitus ulcer; sports massage.

Diric *The Forty-Two, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; diabetes insipidus.

Dirine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; diuretic.

Dirinol *Cryopharma, Mex.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Dironorm *Richter, Pol.*
Lisinopril (p. 1420·3); amlodipine besilate (p. 1304·1).
Hypertension.

Diropress *Lek, Rus.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Diroquine *Atlantic, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria; amoebiasis; rheumatoid arthritis.

Diroseal *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Avene, Fr.†*
Retinaldehyde (p. 1719·1); HMC (p. 2505·2); dextran sulfate (p. 2492·2).
Rosacea; skin redness.

Diroton *Gedeon Richter, Cz.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Dirox *Sanofi-Aventis, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Dirox Aler *Sanofi-Aventis, Arg.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal and ocular symptoms of allergy.

Dirret *Best, Mex.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Dirtop *Medipharm, Chile.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Dirui A2 *Dirui, UK.*
Test for glucose and protein in urine.

Dirui A3 *Dirui, UK.*
Test for glucose, pH, and protein in urine.

Dirui A11 *Dirui, UK.*
Test for bilirubin, blood, glucose, ketones, leucocytes, microalbumin, nitrite, pH, protein, specific gravity, and urobilinogen in urine.

Dirulan *Biomedica, Gr.*
Thiocolchicoside (p. 2026·2).

Dirunez *Biomedica, Gr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Disalcid *3M, USA.*
Salsalate (p. 130·1).
Musculoskeletal and joint disorders.

Disalunil *Berlin-Chemie, Ger.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Disanal *Humana, Ital.*
Food for special diets.
Gastrointestinal disorders.

Disaperid *Biogened, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Disbuspan *Prodotti, Braz.†*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Pain; smooth muscle spasm.

Dis-chem *Aspen, S.Afr.*
Carbocisteine (p. 1658·1).

Disci Bamb *Pfluger, Ger.*
Acid. silicicum (p. 2208·3); auri solutio colloidalis (p. 2521·1); bambusa arundinacea/bambusa vulgaris e nodo; calcium phosphoricum (p. 1784·2); discus intervertebralis thoracalis suis; magnesim phosphoricum (p. 1787·3).
Homoeopathic preparation.

Dis-Cinil Complex *Menarini, Ital.*
Dihydroxydibutylether (p. 2493·1); cascara (p. 1826·1); rhubarb (p. 1884·2); boldo (p. 2458·3).
Constipation.

DiscloGel *Colgate Oral Care, Austral.*
Erythrosine (p. 2184·3).
Disclosing agent for dental plaque.

Disclo-Plaque *Colgate Oral Care, Austral.†*
Fluorescein (p. 2506·2).
Disclosing agent for dental plaque.

DiscloTabs *Colgate Oral Care, Austral.*
Erythrosine (p. 2184·3).
Disclosing agent for dental plaque.

Discloxy *Neiss, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Disco *Floxia, Singapore.*
Bearberry (p. 2453·2); octinoxate (p. 1715·1); apricot kernel oil (p. 2587·1); skullcap (p. 2617·1); sophora japonica; kojic acid (p. 1710·2); vitamin A palmitate (p. 2098·3); liquorice (p. 1853·2); heather; achillea (p. 2427·3); grapefruit oil; blueberry.
Skin hyperpigmentation.

Disco-cyl Ho-Len-Complex *Liebermann, Ger.*
Calc. fluorat. (p. 2053·1); calc. phos. (p. 1784·2); magn. phos. (p. 1787·3); magn. sulf. (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Discorid *Bros, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Discotrine *Meda, Denm.; Meda, Fr.; Pfizer, Port.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; prevention of phlebitis and extravasation during intravenous infusion.

Discover *Carter-Wallace, UK.*
Pregnancy test (p. 2596·1).

Discover One Step *Wilson, NZ.*
Pregnancy test (p. 2596·1).

Discover Onestep *Church & Dwight, Austral.*
Pregnancy test (p. 2596·1).

Discover Onestep Pregnancy Planning Kit *Church & Dwight, Austral.*
Fertility test (p. 2596·1).

DisCoVisc *Alcon, Ger.; Alcon, Ital.†; Alcon, Thai.; Alcon, USA.*
Chondroitin sulfate sodium (p. 2476·1); sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Discozal *Bros, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Discral *Tecnofarma, Mex.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Discretal *Beta, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Discretest *Elea, Arg.*
Pregnancy test (p. 2596·1).

Discus comp H *Heel, Neth.*
Kalmia latifolia (p. 2537·2); mercurius praecipitatus ruber (p. 2555·3); asa foetida (p. 2449·3).
Homoeopathic preparation.

Disebrin *Tubilux, Ital.*
Heparin sodium (p. 1396·3).
Eye disorders.

Disel *Andromaco, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Disel Hidrocortisona *Andromaco, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); hydrocortisone (p. 1640·1).
Nasal congestion.

Disento *Nakornpatana, Thai.*
Diiodohydroxyquinoline (p. 931·1); furazolidone (p. 933·3); neomycin sulfate (p. 330·1); phthalylsulfathiazole (p. 339·3); light kaolin (p. 1850·1).
Diarrhoea; gastrointestinal infections.

Disento PF *Nakornpatana, Thai.*
Furazolidone (p. 933·3); pectin (p. 2200·3); light kaolin (p. 1850·1).
Bacterial diarrhoea; enteritis.

Diseon *Teva, Ital.*
Alfacalcidol (p. 2112·3).
Hypoparathyroidism; renal osteodystrophy; rickets; osteomalacia; osteoporosis.

Disepavit *SoSe, Ital.*
Vial 1, cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); nicotinamide (p. 2083·1); vial 2, ascorbic acid (p. 2110·3).
Vitamin B and vitamin C deficiency.

Diseptil *Gedis, Ital.†*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Diseptyl *Rekah, Israel.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Disequens *Novo Nordisk, Arg.*
Red tablets, estradiol (p. 2271·1); white tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Diser *Kee, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).
Inflammation; pain.

Diserim *Apsen, Braz.*
⊗Bendroflumethiazide (p. 1315·2); fluphenazine hydrochloride (p. 1075·1).
Premenstrual syndrome; obesity; oedema.

Diserinal *Boniscontro & Gazzone, Ital.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia; osteoporosis.

Disfabac *Prafa, Indon.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Disflat *OM, Port.*
Simeticone (p. 1886·2).
Flatulence; abdominal distension; meteorism.

Disflatyl *Valeant, Austria†; Meda, Fin.; Solco, Hong Kong†; Pharos, Indon.; Solco, Indon.; Inovail, Malaysia; Invida, Philipp.; Meda, Rus.; Meda, Switz.; Invida, Thai.; Valeant, Ukr.*
Simeticone (p. 1886·2).
Gastrocardiac syndrome; preparation for gastrointestinal investigation; gastrointestinal disorders associated with excess gas.

Invida, Hong Kong; Invida, Singapore.†
Tablets: Dimeticone (p. 1886·2); silicon dioxide (p. 2208·3).
Flatulence; preparation for gastrointestinal investigations.

Disflux *Corsa, Indon.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Disfruta *Maver, Chile.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).
Antacid.

Disfrutab *Maver, Chile.†*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid; flatulence.

Disgradon *Fada, Arg.†*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Disgren
Note: this name may be used for preparations of different composition.
Bago, Arg.; Biosintetica, Braz.; Uriach, Hung.; Sanfer, Mex.; Vifor, Spain; Uriach, Ukr.; Megat, Venez.
Triflusal (p. 1519·3).
Thromboembolic disorders; myocardial infarction; stroke.

Pasteur, Chile.
Aspirin (p. 22·2).
Thromboembolism prophylaxis; pain; fever.

DiShuang *Qianjiang, China.*
Naftopidil (p. 2361·1).

Disifelit *Fada, Arg.*
⊗Droperidol (p. 1072·1); fentanyl (p. 60·1).
Neuroleptanalgesia.

Disigien *AFOM, Ital.*
Benzalkonium chloride (p. 1737·1).
Disinfection of burns and wounds.

Disilden *Interpharma, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Disilox-MPS *Stadmed, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).

Disinal *Silanes, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Disinfecting *Farma-Tek, Turk.†*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Disinfene *AFOM, Ital.†*
Chlorhexidine hydrochloride (p. 1743·3); hydroxyquinoline sulfate (p. 2530·1).
Skin and wound disinfection.

Disinol *Kocak, Turk.*
Chlorobutanol (p. 1747·2); phenol (p. 1763·3); clove oil (p. 2481·3).
Teething pain; mouth and throat pain.

Disintryl *Medinova (Μεντινοβα), Gr.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Disintyl *Zeta, Ital.*
Benzalkonium chloride (p. 1737·1).
Disinfection of wounds, burns, and external genitals.

Disiorange *Indkus, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Disipal *Alapis, Gr.; Astellas, Ital.; CSL, NZ; iNova, S.Afr.; Sovereign, UK.*
Orphenadrine hydrochloride (p. 909·3).
Parkinsonism; drug-induced extrapyramidal disorders; vertigo; skeletal muscle spasm.

Disipan *Bernabo, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Disithrom *Sanopharm, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Diskare *Anglo-French Drugs, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Diskets *Cebert, USA.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal.

Diskolestina *Farmaceutica H, Mex.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Dislaven *Adamed, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Dislep *Bago, Arg.; Silesia, Chile; Ferrer-Novag, Mex.; Leti, Venez.*
Levosulpiride (p. 1108·1).
Delayed gastric emptying; dyspepsia; gastrointestinal motility disorders; nausea and vomiting; vertigo.

Dislipat *Medico Uno, Hung.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Dislipina *Merck, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Dislipor *Andromaco, Chile.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Dismam *Merck, Chile.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Dismaren *Sanofi-Aventis, Arg.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Dismegyn *Gynea, Spain.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Dismen *The Forty-Two, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Dismenol *Merz, Switz.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Pain; fever.

Dismenol N *Simons, Ger.*
Ibuprofen (p. 68·2).
Fever; pain.

Dismenol Neu *Merz, Austria.*
Ibuprofen (p. 68·2).
Pain.

Dismiben *Fabop, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Dismifen *Best, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Dismolan *Lapreven, Venez.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Rivero, Arg.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Dismozon pur *Bode, Ger.*
Magnesium monoperoxyphthalate.
Surface disinfection.

Disnal *Italfarmaco, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; osteoporosis.

Disneumon Mentol *Solvay, Spain.†*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinusitis.

Disneumon Pernasal *Abbott, Spain.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal and sinus congestion.

Disnizyme *Sanify, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Disobrom *Geneva, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Disocain *Concept, India.*
Dried aluminium hydroxide (p. 1817·2); liquorice (p. 1853·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Disocor *Janssen-Cilag, Port.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Disofrin *Schering-Plough, Gr.*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).

Disofrol *MSD, Spain; Schering-Plough, Swed.†; Essex, Switz.†*
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Nasal congestion; upper respiratory-tract disorders; rhinitis.

Disogel *Concept, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); liquorice (p. 1853·2); simeticone (p. 1886·2).
Peptic ulcer; gastro-oesophageal reflux; gastric hyperacidity; gastritis.

Disogram *Ranbaxy, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Disol
Note: this name may be used for preparations of different composition.
Siam Bheasach, Malaysia†; Siam Bheasach, Thai.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Biok, Rus.
Sodium chloride (p. 1795·1); sodium acetate (p. 1781·1).
Fluid disorders; hyperkalaemia.

Disolgas *Arkopharma, Spain.*
Simeticone (p. 1886·2).
Flatulence.

Disolina *Biotech, Venez.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Disomet *Orion, Fin.†*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Disonate
Note: this name may be used for preparations of different composition.
Samarth, India.
Etidronate disodium (p. 1182·3).
Paget's disease of bone; ectopic ossification; osteoporosis.

Disons Dex *Sons, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Disopain *Mitsubishi Tanabe, Jpn.*
Mofezolac (p. 92·2).
Pain; inflammation.

Disophrol *Schering-Plough, Cz.; Schering-Plough, Pol.†; Schering-Plough, Turk.; Schering-Plough, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Allergic rhinitis; otitis media; respiratory-tract congestion; upper respiratory-tract symptoms; nasal congestion; sinusitis.

Disopranil *Prater, Chile.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Disoprivan *AstraZeneca, Ger.; AstraZeneca, Switz.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Disoral *Elder, India.*
Diclofenac (p. 48·3).
Mouth and throat disorders.

Disorate *Mankind, India.*
Valproate semisodium (p. 553·2).
Seizures; bipolar disorder; migraine.

Disothiazide *Dexcel, Israel.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Disotron *Ariston, Braz.*
Heparin sodium (p. 1396·3).

Disoval *La Pharmaceuticals, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Dispaclonidin *OmniVision, Ger.†*
Clonidine hydrochloride (p. 1339·1).
Ocular hypertension; glaucoma.

Dispacromil *OmniVision, Ger.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Dispadex comp *OmniVision, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Bacterial infections and inflammation of the eye.

Dispadol
Note: this name may be used for preparations of different composition.
Actavis, Fr.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal and joint disorders.

Dispalgine *Adelco, Gr.*
Dipyrone (p. 53·3); dicycloverine hydrochloride (p. 1834·2).

Dispatenol *OmniVision, Ger.*
Dexpanthenol (p. 2582·2); polyvinyl alcohol (p. 2204·2).
Dry eyes.

Dispatim *Novartis, Austria; OmniVision, Ger.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Dispedrol *Chrispa (Χρισπα), Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Dispel *Ind-Chemie, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Dispello *Ayrton, UK.*
Salicylic acid (p. 1719·1); zinc chloride (p. 2126·1); hypophosphorous acid (p. 2530·3); pyroxylin (p. 1718·2); colophony resin (p. 2484·2).
Corns; warts.

Dispepci *Pentafarma, Port.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dispeptal *Sanofi-Aventis, India.*
⊗Pancreatin (p. 2579·3); bile salts (p. 2457·2); enzymes from *Aspergillus oryzae*.
Digestive disorders.

Dispeptrin *Cifarma, Braz.†*
Co-trimoxazole (p. 277·3); calcium carbonate (p. 1824·3); attapulgite (p. 1820·1).
Diarrhoea; colitis; dysentery; shigellosis.

Disperbarium *Rovi, Spain.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Dispercarpine *Novartis, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of mydriasis.

Disperin *Orion, Fin.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

DisperMox *Ranbaxy, USA.*
Amoxicillin (p. 216·2).
Bacterial infections.

Dispersadron-C *Novartis, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Bacterial eye infections with inflammation.

Disperzyme *Aksigen, India.*
⊗Bromelains (p. 2460·3); rutoside (p. 2505·3); trypsin (p. 2635·2).

Display *Solea, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye disinfection; eye irritation.

Dispneitrat *IMA, Braz.†*
Aminophylline (p. 1201·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Dispred *JB Chemicals, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Dispred DPS *JB Chemicals, India.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Dispril *Reckitt Benckiser, Belg.†; Ali, Turk.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis; inflammation.

Disprin *Reckitt Benckiser, Austral.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, India; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, UK.*
Aspirin (p. 22·2).
Pain; inflammation; fever; cold and flu symptoms; rheumatism; thromboembolism prophylaxis.

Disprin Direct *Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.; Reckitt Benckiser, UK.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; inflammation; fever.

Disprin Extra *Reckitt Benckiser, UK.*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain; fever.

Disprin Extra Strength *Reckitt Benckiser, Irl.*
Aspirin (p. 22·2).
Pain; fever; inflammation.

Disprin Forte *Reckitt Benckiser, Austral.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; inflammation; fever.

Disprin Paracetamol *Reckitt Benckiser, India.†*
Paracetamol (p. 115·1).
Fever; pain; inflammation.

Disprin Plus *Reckitt Benckiser, S.Afr.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; fever.

Disprina *Sanofi Synthelabo, Mex.†*
Aspirin (p. 22·2).
Fever; pain.

Disprol *Reckitt Benckiser, Irl.†; Reckitt Benckiser, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Disquin *Wockhardt, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Dissen *Andromaco, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Dissenten *SPA, Cz.†; SPA, Ital.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Dissolursil *Farma 1, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; biliary dyspepsia.

Dissolvurol *Dissolvurol, Mon.*
Colloidal silicon dioxide (p. 2209·1).
Musculoskeletal and joint disorders.

Dissowel *Union Drug, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Gastric hyperacidity.

Distaclor *Pharmalink, India; Flynn, Irl.; Inovail, Malaysia; Invida, Singapore†; DKSH, Thai.; Flynn, UK.*
Cefaclor (p. 232·3).
Bacterial infections.

Distalene *Ivax, Arg.*
⊗Anastrozole (p. 742·1).

Distalgesic *Aspen, S.Afr.*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain; fever.

Distamin *Samarth, India.*
Penicillamine (p. 1567·1).
Wilson's disease; cystinuria; cystine calculi; heavy metal poisoning; chronic active hepatitis; rheumatoid arthritis.

Distamine *Alliance, Irl.; Alliance, UK.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; Wilson's disease; cystinuria; heavy metal poisoning; hepatitis; lead poisoning.

Distaneurin *IFET (ΙΦΕΤ), Gr.*
Clomethiazole edisilate (p. 1054·2).

Distaph *Alphapharm, Austral.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Distasil *Milano, Ital.†*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Distaxid *Norgine, Spain.†*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux.

Distec *Permatec, Arg.*
Diclofenac diethylamine (p. 48·3).

Distedon *Adelco, Gr.*
Diazepam (p. 1063·2); clidinium bromide (p. 1833·2).
Peptic and urinary-tract disorders.

Distenil *Sun, India.*
Simeticone (p. 1886·2); activated charcoal (p. 1537·3).
Aerophagia; flatulence; meteorism; irritable bowel syndrome; diverticulosis.

Distensan *Esteve, Spain.*
Clotiazepam (p. 1057·2).
Anxiety; neuroleptanalgesia; premedication.

Distental *Mavi, Mex.*
Pinaverium bromide (p. 2590·3).
Gastrointestinal disorders.

Disteril *Lachifarma, Ital.*
Benzalkonium chloride (p. 1737·1).
Skin, wound, and burn disinfection; genital hygiene.

Distex *Lafi, Chile.*
Flurbiprofen (p. 65·2).
Pain.

Distilbène *Gerda, Fr.*
Diethylstilbestrol (p. 2267·3).
Prostatic cancer.

Distilbene *IFET (ΙΦΕΤ), Gr.*
Diethylstilbestrol (p. 2267·3).

Distimax *Medipharm, Chile.†*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome in women.

Distinon *Samarth, India.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis.

Distocide *Chandra Bhagat, India; Shin Poong, Singapore.*
Praziquantel (p. 164·1).
Schistosomiasis; fluke infections; tapeworm infections; neurocysticercosis.

Distonal *Royal, Chile.*
Desipramine hydrochloride (p. 413·1).
Attention-deficit hyperactivity disorder; bulimia; cocaine withdrawal syndrome; depression; narcoleptic syndrome; pain; panic attacks.

Distone *Ind-Swift, India.*
Capsules: ⊗Punarnava (p. 2601·1); tribulus terrestris (p. 2633·3).
Ind-Swift, India.
Syrup: Ammonium chloride (p. 1656·1); punarnava (p. 2601·1); citric acid (p. 2480·3); elettaria cardamomum; raphanus sativus; borax (p. 2459·2).

Distonin *GSK, Ukr.†*
⊗Belladonna (p. 2453·3); codergocrine mesilate (p. 389·2); propranolol hydrochloride (p. 1479·1); hydroxyzine hydrochloride (p. 630·3).
Neurocirculatory disorders; digestive disturbances; irritable bowel syndrome; premenstrual syndrome; anxiety; phobias.

Distop *Zeler, Port.†*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).

Distraneurin *Cheplapharm, Ger.; AstraZeneca, Switz.*
Clomethiazole (p. 1054·2) or clomethiazole edisilate (p. 1054·2).
Sleep disorders; senile confusion; alcohol withdrawal syndrome; sedative.

Distraneurine *IFET (ΙΦΕΤ), Gr.*
Clomethiazole edisilate (p. 1054·2).
Insomnia and confusion in the elderly; alcohol withdrawal syndrome.

Kern, Spain.
Clomethiazole (p. 1054·2).
Alcohol withdrawal syndrome; insomnia; sedative.

Distreptaza *Biomed Lublin, Pol.; Biomed Warszawa, Pol.; Biomed, Ukr.*
Streptodornase (p. 2623·1); streptokinase (p. 1503·1).
Inflammation; haemorrhoids; abscesses; fistulas; infections; wounds; ulcers.

Disudrin
Note: this name may be used for preparations of different composition.
Mediforma, Indon.; Pediatrica, Indon.
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Pediatrica, Philipp.
Phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Disufen *Angenerico, Ital.*
⊗Sufentanil citrate (p. 132·3).
General anaesthesia; neuroleptanalgesia.

Disulfix *Ariston, Arg.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Disulone *Sanofi-Aventis, Fr.*
Dapsone (p. 281·2); ferrous oxalate (p. 2062·1).
Leprosy; dermatitis herpetiformis; polychondritis; pneumocystis pneumonia.

Disuo *Xuebao, China.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Diswart *Dermatech, Austral.*
Glutaral (p. 1753·2).
Common warts.

Disylate *Osper, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

DIT1-2 *Dunhall, USA.*
Sulfanilamide (p. 368·1); aminoacridine hydrochloride (p. 1732·3); allantoin (p. 1693·1).
Vaginal infections.

Ditalin *Otto, Indon.*
Phenytoin (p. 538·2); phenobarbital sodium (p. 535·3).
Epilepsy; chorea; parkinsonism; trigeminal neuralgia; digitalis-induced arrhythmias.

Ditana *Bajamed, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Ditanrix *GSK, Ital.; Smith Kline & French, Port.; GSK, Spain; GSK, Switz.†*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Ditap *TO-Chemicals, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Ditayod *Solfran, Mex.*
Phthalylsulfathiazole (p. 339·3); clioquinol (p. 273·1).
Amoebiasis.

DiTe Anatoxal *Berna, Austriat; Pharmabroker, NZ.†*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Separate preparations are available for adults and children.
Active immunisation.

DiTe Booster *Statens Serum Institut, Denm.; Statens Serum Institut, Fin.; Statens Serum Institute, Irl.; Statens*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Serum Institut, Norw.; Statens Serum Institut, Port.; Janssen-Cilag, Spain; SSI, Swed.
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Ditec *Boehringer Ingelheim, Rus.†*
⊗Fenoterol hydrobromide (p. 1208·2); sodium cromoglicate (p. 1225·3).

Di-Te-Ki-Booster *Statens Serum Institut, Denm.*
A diphtheria, tetanus and pertussis vaccine (p. 2383·3).
Active immunisation.

Di-Te-Kik *Statens Serum Institut, Fin.†*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Di-Te-Ki-Pol *Statens Serum Institut, Denm.; Statens Serum Institut, Fin.†*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Di-Te-Ki-Pol/Act-Hib *Statens Serum Institut, Denm.*
A diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Ditenside *Miralfarma, Spain.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ditensor *Temis, Spain.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

DiTePer Anatoxal *Pharmabroker, NZ.†*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Dithiaden *Zentiva, Cz.*
Bisulepin hydrochloride (p. 617·3).
Hypersensitivity reactions.

Dithiazide *Phebra, Austral.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Dithrasal *Dermatech, Austral.†; Dermatech, Hong Kong†; Dermatech, Singapore.*
Dithranol (p. 1701·2); salicylic acid (p. 1719·1).
Psoriasis.

Dithrocream *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Dithranol (p. 1701·2).
Psoriasis.

Dithylin *Biolek, Rus.*
Suxamethonium iodide (p. 2037·1).
Depolarising neuromuscular blocker.

Dithyron *Unipharma, Gr.*
Levothyroxine sodium (p. 2339·1); liothyronine sodium (p. 2342·3).
Thyroid disorders.

Diticone *Alapis, Gr.*
Sertraline hydrochloride (p. 448·1).

Ditide *GSK, India.*
⊗Benzthiazide (p. 1316·1); triamterene (p. 1518·3).
Oedema.

Ditizem *Siam Bheasach, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Ditoin *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia; migraine.

Ditomed *Medifive, Thai.†*
Phenytoin sodium (p. 538·2).
Epilepsy.

Ditopax *Schering-Plough, Chile; Schering-Plough, Mex.†*
Tablets: Simeticone (p. 1886·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders; flatulence; gastric hyperacidity.
Schering-Plough, Chile; Schering-Plough, Mex.†
Oral suspension: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders; flatulence; gastric hyperacidity.
Schering-Plough, Arg.†
Chewable tablets: Simeticone (p. 1886·2); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Flatulence; gastric hyperacidity.

Ditopax-F *Schering-Plough, Mex.†*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Flatulence; gastrointestinal hyperacidity.

Ditosil *Schering-Plough, Venez.*
Oral suspension: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Flatulence; gastric hyperacidity.
Schering-Plough, Venez.
Tablets: Simeticone (p. 1886·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2).
Flatulence; gastric hyperacidity.

Ditosil Plus *Schering-Plough, Venez.*
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity.
Schering-Plough, Venez.
Oral suspension: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Flatulence; gastric hyperacidity.

Ditral
Note: this name may be used for preparations of different composition.
Austral, Arg.
Dipyrone (p. 53·3).
Fever; pain.
Berman, Mex.
Tetracycline (p. 373·1).
Bacterial infections.

Ditran
Note: this name may be used for preparations of different composition.
Thaipharmed, Thai.
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; premedication; seizures; alcohol withdrawal syndrome.

Ditranex *Dipa, Indon.†; Prafa, Indon.†*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema.

Ditrei *Italmex, Mex.*
Di-isopropylammonium dichloroacetate (p. 1359·1).
Angina pectoris; myocardial infarction; vascular disorders.

Ditrenil *Siam Bheasach, Thai.*
Nitrendipine (p. 1456·3).
Hypertension.

Ditrevit *Humana, Ital.*
Vitamin D (p. 2112·3); docosahexaenoic acid (p. 1460·1).
Nutritional supplement.

Ditrevit K *Humana, Ital.*
Vitamin D (p. 2112·3); vitamin K (p. 2122·1); docosahexaenoic acid (p. 1460·1).
Nutritional supplement.

Ditrim *Orion, Fin.*
Trimethoprim (p. 381·2); sulfadiazine (p. 361·3).
Bacterial infections; pneumocystis pneumonia.

Ditripentat *Heyl, Cz.*
Calcium trisodium pentetate (p. 1570·3).
Antidote.

Ditripentat-Heyl *Heyl, Ger.*
Calcium trisodium pentetate (p. 1570·3).
Poisoning with heavy or radioactive metals.

Ditropan *Phoenix, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Janssen-Ortho, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi, UK; Janssen, USA.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability; neurogenic bladder; nocturnal enuresis; urinary urgency; urinary incontinence; bladder hyperactivity; cystitis.

Ditropine *Asian Pharm, Thai.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Ditrost *Boniscontro & Gazzone, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Ditterolina *Teva, Mex.*
Dicloxacillin (p. 286·1) or dicloxacillin sodium (p. 286·1).
Bacterial infections.

Ditustat *Teva, Cz.*
Dropropizine (p. 1662·2).
Cough.

Diu Venostasin *Klinge, Ger.*
⊗Tablets, triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2); controlled-release capsules, aesculus (p. 2431·2).
Venous insufficiency.

Diu-Atenolol *Verla, Ger.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Diube *SIT, Ital.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Diublok *Eurofarma, Braz.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Diucomb *Sanol, Ger.; UCB, Ger.*
⊗Bemetizide (p. 1314·2); triamterene (p. 1518·3).
Hypertension; oedema; heart failure.

Diucontin-K *Modi-Mundipharma, India.*
⊗Furosemide (p. 1387·1); potassium chloride (p. 1793·2).
Oedema.

Diufluxx Mono *Ruhrpharm, Ger.*
Java tea (p. 2536·3).
Urinary tract disorders.

Diulo *Desma, Port.*
⊗Metolazone (p. 1434·1).
Hypertension; oedema; ascites associated with liver cirrhosis.

Diumide-K *Pascual, Philipp.*
⊗Furosemide (p. 1387·1); potassium chloride (p. 1793·2).
Oedema.

Diumide-K Continus *Napp, Irl.†*
⊗Furosemide (p. 1387·1); potassium chloride (p. 1793·2).
Oedema.

Diupres
Note: this name may be used for preparations of different composition.
Merck, USA.
⊗Reserpine (p. 1485·3); chlorothiazide (p. 1334·3).
Hypertension.

Diupress
Note: this name may be used for preparations of different composition.
Eurofarma, Braz.
⊗Chlortalidone (p. 1335·2); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Diuprotect *Silesia, Chile.†*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Diur Pot *Northia, Arg.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Diurace *BMS, Neth.†*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Diural
Note: this name may be used for preparations of different composition.
Actavis, Denm.; Actavis, Norw.
⊗Furosemide (p. 1387·1).
Oedema; hypertension; forced diuresis; renal failure.
Austral, Arg.
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.
Silanes, Mex.
⊗Piretanide (p. 1470·3).
Hypertension; oedema; renal failure.

Diuramid *Polpharma, Pol.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; oedema; epilepsy; altitude sickness.

Diuramin *Ratiopharm, Fin.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; ascites.

Diurana *Sanofi-Aventis, Braz.*
⊗Furosemide (p. 1387·1); triamterene (p. 1518·3).
Hypertension; oedema.

Diurapid *Mibe, Ger.†*
⊗Furosemide (p. 1387·1).
Oedema; oliguria; hypertension.

Diurator *Elder, India.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Diured *Biofarm, Pol.*
⊗Torasemide (p. 1516·3).
Oedema.

Diurefo *Pyridam, Indon.†*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Diurek *Boniscontro & Gazzone, Ital.*
⊗Potassium canrenoate (p. 1472·2).
Hyperaldosteronism; hypertension.

Diurem *Cipla, India.*
⊗Metolazone (p. 1434·1).
Hypertension; oedema.

Diuremid
Note: this name may be used for preparations of different composition.
KVZ, Ukr.
⊗Acetazolamide (p. 2001·1).
Oedema; glaucoma; epilepsy; high-altitude disorders.
Menarini, Ital.
⊗Torasemide (p. 1516·3) or torasemide sodium (p. 1516·3).
Oedema; ascites; heart failure; renal failure.

Diuremida *Geolab, Braz.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Diuren *Unipharma, Gr.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; diabetes insipidus; hypercalciuria.

Diurenat *Naturatec, Canad.†*
Buchu (p. 2461·3); juniper berries (p. 2537·1); bearberry (p. 2453·2).

Diurene *Winthrop, Port.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; ascites associated with liver cirrhosis.

Diurepina *Prodotti, Braz.†*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension.

Diuresin *Polfarmex, Pol.*
⊗Indapamide (p. 1409·2).
Hypertension.

Diuresix
Note: this name may be used for preparations of different composition.
Innovata, S.Afr.
⊗Furosemide (p. 1387·1).
Hypertension; oedema.
Menarini, Ital.
⊗Torasemide (p. 1516·3) or torasemide sodium (p. 1516·3).
Oedema; ascites; heart failure; kidney disorders.

Diuretabs *Potter's, UK.*
Buchu leaf (p. 2461·3); juniper berry oil (p. 2537·2); parsley piert (p. 2584·1); bearberry (p. 2453·2).
Fluid retention.

Diuretic *Royton, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).

Diuretic Formula *Natural Factors, Canad.*
Juniper berries (p. 2537·1); parsley (p. 2583·3); taraxacum (p. 2625·3); bearberry (p. 2453·2).

Diuretic Tablets *Pharmetics, Canad.*
Buchu (p. 2461·3); stone root (p. 2622·2); juniper berries (p. 2537·1); bearberry (p. 2453·2).

Diureticae Species No2 *Faros, Rus.*
Bearberry (p. 2453·2); juniper (p. 2537·1); liquorice (p. 1853·2).
Urinary-tract infections.

Diuretikum Verla *Verla, Ger.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Diuretil *Ducto, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Diuret-P *PP Lab, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; diabetes insipidus.

Diurette *Cederroth, Spain.†*
Taraxacum (p. 2625·3); equisetum (p. 2500·1).
Oedema.

Diurevit Mono *Ruhrpharm, Ger.†*
Java tea (p. 2536·3).
Urinary-tract disorders.

Diurex
Note: this name may be used for preparations of different composition.
Alva, Canad.
Pamabrom (p. 1464·1).

Bago, Arg.
⊗Hydrochlorothiazide (p. 1403·2).
Ascites; heart failure; hypertension; nephrotic syndrome; pre-eclampsia.

Lacer, Spain.
⊗Xipamide (p. 1536·1).
Oedema; hypertension.

Orion, Fin.
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; cirrhosis with ascites.

Vickmans, Hong Kong.†
⊗Furosemide (p. 1387·1).

Diurex A *Bago, Arg.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis.

Diurexan *Meda, Port.; Viatris, UK.*
⊗Xipamide (p. 1536·1).
Hypertension; oedema.

Diurezin *Cazi, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Diabetes insipidus; hypertension; oedema; renal calculi.

Diurezin-A *Cazi, Braz.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Diurigen *Goldline, USA.*
⊗Chlorothiazide (p. 1334·3).
Hypertension; oedema.

Diuril
Note: this name may be used for preparations of different composition.
Merck, USA.
⊗Chlorothiazide (p. 1334·3) or chlorothiazide sodium (p. 1335·1).
Oedema; hypertension.

Pharma Nutria, Philipp.†
⊗Furosemide (p. 1387·1).
Hypercalcaemia; hypertension; oedema.

Diurin
Note: this name may be used for preparations of different composition.
Mylan, NZ.
⊗Furosemide (p. 1387·1).
Oedema; hypertension; severe renal impairment.

Diurinat *Soria Natural, Spain.*
Betula alba (p. 2457·3); equisetum (p. 2500·1); corn silk (p. 2487·1); couch-grass (p. 2487·2).
Oedema.

Diurisa *Eurofarma, Braz.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Diurix
Note: this name may be used for preparations of different composition.
Bal, India.
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Teuto, Braz.
⊗Hydrochlorothiazide (p. 1403·2).
Formerly contained furosemide.
Hypertension; oedema.

Diurmessel *Biomep, Mex.*
⊗Furosemide (p. 1387·1).

Diuronis *Hasco-Lek, Pol.*
Chamomile (p. 2474·1); ononis (p. 2575·3); solidago (p. 2620·1); cowberry (p. 2487·3).
Urinary-tract disorders.

Diursan *TAD, Ger.†*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Diu-Safe Cu/375 *Silesia, Chile.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Diuspec *Hizon, Philipp.*
⊗Furosemide (p. 1387·1).
Hypercalcaemia; hypertension; oedema; oliguria.

Diutropan *Nupharma, Thai.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder disorders.

Diuvar *Gracia, Indon.*
⊗Furosemide (p. 1387·1).
Pulmonary oedema.

Diuver *Pliva-Lachema, Cz.†; Pliva Krakow, Pol.; Pliva, Rus.; Pliva, Ukr.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; heart failure.

Diuzid *Hizon, Philipp.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Diuzide *EuroHealth, Philipp.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Diuzine *Teofarma, Spain.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; liver cirrhosis with ascites.

Diva
Note: this name may be used for preparations of different composition.
Elea, Arg.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Reddy, S.Afr.
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea; combined oral contraceptive in women with androgenic symptoms.

Zeroderma, UK.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.
Acne and hirsutism in women.

Diva Total *Elea, Arg.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4, tablets inert.
Combined oral contraceptive.

Divaa *Intas, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Divacon *Jagsonpal, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Divaine *Cipla, India.*
Minocycline (p. 324·3).
Bacterial infections.

Dival *Valmor, Venez.*
Diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, and peri-articular disorders.

Divalex-OD *Crescent, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Divalin *Molekule, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Divalio *Elpen (Ελπεν), Gr.*
Carbocisteine (p. 1658·1).
Mucolytic.

Divalprid-OD *Micro, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Divalpro *Zydus, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Divalrate *Ipca, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Divanon *Tecnofarma, Chile.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginitis; acne.

Divare *Eczacibasi, Turk.*
Donepezil hydrochloride (p. 390·2).

Divaril *Tecnofarma, Chile.*
Mirtazapine (p. 436·1).
Depression.

Divarius *Chiesi, Fr.*
Paroxetine mesilate (p. 440·3).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; anxiety; post-traumatic stress disorder.

Divascan *Berlin-Chemie, Hung.; Menarini, Hung.; Berlin-Chemie, Pol.; Menarini, Pol.*
Iprazochrome (p. 676·3).
Diabetic retinopathy; headache; migraine.

Divascol *VUAB, Cz.*
Tolazoline hydrochloride (p. 1516·2).
Peripheral vascular disorders.

Divask *Kalbe, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Divator *Drogsan, Turk.*
Atorvastatin calcium (p. 1309·2).

Diveine *Outremer, Fr.*
Butcher's broom (p. 2463·1); hamamelis (p. 2523·3); grape (p. 2521·3); citrus bioflavonoids (p. 2505·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Venous insufficiency.

Divelol *Baldacci, Braz.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Divens *Dexa, Indon.*
Phyllanthus niruri (p. 2590·1).
Immunomodulator.

Diver *Serral, Mex.*
Pinaverium bromide (p. 2590·3).

Divert *Meridian, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Divetrin *Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Divexx *Zuventus, India.*
Tablets: Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Zuventus, India.
Topical gel: Capsaicin (p. 35·1); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Divexx-MR *Zuventus, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Divexx-P *Zuventus, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Divicil *BA Farma, Port.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Dividol
Note: this name may be used for preparations of different composition.
Remedica, Singapore.
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; motion sickness.

Zambon, Braz.; Zambon, Ital.
Viminol hydroxybenzoate (p. 142·1).
Pain.

Divifolin *Rottapharm, Ital.*
Calcium folinate (p. 2066·3).
Folate deficiency; folic acid antagonist overdosage.

Divigel *Ferring, Canad.; Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Hung.; Win-Medicare, India; Orion, Irl.; Orion, Malaysia; Orion, Pol.; Orion, Rus.; Orion, Singapore; Orion, Swed.; Orion, Switz.; Orion, Thai.; Orion, Ukr.; Upsher-Smith, USA.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Divina
Note: this name may be used for preparations of different composition.
Orion, Cz.; Paranova, Denm.; Orion, Fin.; CSP, Fr.; Organon (Οργανον), Gr.; Orion, Hung.; Orion, Pol.; Orion, Rus.; Aspen, S.Afr.†; Abdi, Turk.
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; hormone replacement therapy.

Orion, Ukr.†
11 White tablets: estradiol valerate (p. 2271·2); 10 blue tablets: estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Elea, Arg.
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Divina Plus *Orion, Denm.; Orion, Swed.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Diviplus *Orion, Belg.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Divir *GPO, Thai.*
Didanosine (p. 972·3).
HIV infection.

Diviseq *Orion, Cz.; Orion, Pol.; Orion, Rus.; Orion, Switz.†; Orion, Thai.†*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Divisun *Meda, Fin.; Meda, Norw.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; osteoporosis.

Divitren *Orion, Fin.*
70 Tablets, estradiol valerate (p. 2271·2); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Orion, Rus.†
White tablets, estradiol valerate (p. 2271·2); blue tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); yellow tablets, inert.
Menopausal disorders.

Diviva *Orion, Belg.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; oestrogen replacement therapy.

Divoltar *Hexpharm, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.

Divo-M *Zenon, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Divomit *LBS, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; vertigo.

Divon *Micro, India.*
Injection; tablets; topical gel spray: Diclofenac sodium (p. 48·3) or diclofenac (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Micro, India.
Topical gel: Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Divon Plus *Micro, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Divon-S *Micro, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Divopan *ANH, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; premedication; seizures; alcohol withdrawal syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Divorel Plus *Targof, India.*
Chlorzoxazone (p. 2022·2).
Painful skeletal muscle spasm.

Divret *Emcure, India.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Diway *Poly, China.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal motility disorders; irritable bowel syndrome.

Diweijia *Deyer, China.*
Vitamins; zinc sulfate (p. 2126·2); lysine hydrochloride (p. 2079·3); iron glycerophosphate (p. 2519·2).
Vitamin and mineral supplement.

Dix
Note: this name may be used for preparations of different composition.
PC India, India.
Nalidixic acid (p. 328·3).
Lower urinary-tract infections; shigellosis.

Mezina, Denm.†
Senna (p. 1885·1); chamomile (p. 2474·1).
Constipation.

Dixabiox *Rivero, Arg.*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Dixafer *Rivero, Arg.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Dixamid *Norma (Νορμα), Gr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Dixarit *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; 2care4, Denm.; Europharma, Denm.; Orifarm, Denm.; Boehringer Ingelheim, Hong Kong†; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, UK.*
Clonidine hydrochloride (p. 1339·1).
Migraine and other vascular headache; menopausal flushing.

Dixen *Maver, Mex.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Dixer-S *Biophar, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dixfree-SP *Zenacts, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dixi
Note: this name may be used for preparations of different composition.
Arvincare, India.
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Vivax Gynopharm, Venez.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Dixi-35 *Gynopharm, Chile.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Dixian *Huanan, China.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Dixidrol *Rivero, Arg.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Dixiflen *Farcoral, Mex.*
⊗Ox bile (p. 2457·2); pancreatin (p. 2579·3); cellulase (p. 2473·1); dimeticone (p. 1886·2).
Digestive disorders; flatulence.

Dixin *Samarth, India.*
Digoxin (p. 1353·3).
Heart failure; supraventricular arrhythmias.

Dixine *Lavipharm, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Dixip *Adley, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Dixocillin *Siam Bheasach, Thai.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Dixonal *Medix, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Diyaben *Adeka, Turk.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Diyasorb *Yeni, Turk.†*
Attapulgite (p. 1820·1).

Diyenil *Gunsa, Turk.†*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Pruritus.

Diyet Tat *Eczacibasi, Turk.*
Aspartame (p. 2169·2).
Sugar substitute.

Diyet-Lif *Kurtsan, Turk.*
A dietary supplement.

Diyiluo *Tasly, China.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Diyosul *Jofrain, Mex.†*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Diyou *XingQi, China.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Dizan *Pharmaland, Thai.†*
Diazepam (p. 1063·2).
Muscle spasm; psychoneurotic disorders; autonomic disorders.

Dizatec *Genetic, Ital.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Dizec *GSK, India.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2); sodium tauroglycocholate.

Dizem *IQFA, Mex.*
Di-iodohomatropine.
Amoebiasis.

Dizep *Intas, India; Suphong, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; seizures; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome; epilepsy.

Dizepam *Masa, Thai.*
Diazepam (p. 1063·2).
Anxiety.

Dizepax *Unimarck, India.*
⊗Diazepam (p. 1063·2); propranolol (p. 1479·1).

Dizep-P *Prem, India.*
Diazepam (p. 1063·2).
Premedication; spasticity; seizures; skeletal muscle spasm; alcohol withdrawal syndrome; anxiety; insomnia.

Dizer-N *Sienna, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Dizicum *Taj, India.*
Aluminium hydroxide (p. 1817·2).
Antacid; hyperphosphataemia in renal failure.

Dizide *Radicura, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Dizide-M *Radicura, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dizil *Merck, Port.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dizilium *Medikon, Indon.†*
Flunarizine (p. 629·3).
Migraine; vestibular disorders; peripheral vascular disorders.

Dizine *Pharos, Indon.*
Flunarizine (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Dizinil *Julphar, UAE.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vestibular disorders.

Diziron *Glenmark, India.*
Cinnarizine (p. 622·1).
Vestibular disorders; motion sickness.

Dizitab *Amherst, Philipp.*
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Dizmiss *JMI, USA.*
Meclozine hydrochloride (p. 634·3).
Motion sickness; vertigo.

Diznil *Grandix, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; motion sickness.

Dizoflox *Ashford, Philipp.*
Ofloxacin (p. 334·3).
Bacterial ear infections.

Dizolam *Atlantic, Singapore; Atlantic, Thai.†*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Dizole *Alphapharm, Austral.*
Fluconazole (p. 578·2).
Fungal infections.

Dizolo *Copernico, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Dizolvin-Flux *Rayere, Mex.*
Ambroxol hydrochloride (p. 1654·3); levodropropizine (p. 1662·3).
Cough; respiratory-tract disorder congestion.

Dizox *Finecure, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dizzepam *Pond's, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; premedication; seizures; alcohol withdrawal syndrome.

Dizzigo *Intas, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; motion sickness.

Dizzinon *Unison, Philipp.*
Cinnarizine (p. 622·1).
Vestibular disorders; nausea; vomiting; peripheral vascular disorders; motion sickness; migraine.

D3Kal *Sarabhai Piramal, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

DK-Line *Abdi, Turk.†*
⊗Perflunafene (p. 2586·3).
Aid in ophthalmic surgery.

D-Kool *Alembic, India.*
Diclofenac sodium (p. 48·3); rabeprazole (p. 1881·1).

DKTP-Hib *Nederlands Vaccin Instituut, Neth.†*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae B vaccine (p. 2385·3).
Active immunisation.

DLF *Solitaire, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dlianos *Novartis, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).

D-Loratin *Cipla, India.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

D-Lordex *Ind-Swift, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

DLotin MPS *Bombay Tablet, India.*
Diloxanide furoate (p. 931·2); dimeticone (p. 1886·2); tinidazole (p. 949·2).

DLX *Solitaire, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

D-Lyte *T Man, Thai.*
Glucose (p. 2068·3); sucrose (p. 2096·3); sodium (p. 1795·1); chloride; potassium (p. 1793·1); bicarbonate (p. 1780·3).
Fluid and electrolyte disorders.

DM *Mars, India.*
Syrup: Dextromethorphan (p. 1660·1).
Cough.

Mars, India.
Tablets: ⊗Ambroxol (p. 1654·3); desloratadine (p. 625·1); pseudoephedrine (p. 1676·1).

DM Active *Giscard, Arg.*
⊗Deanol (p. 2319·1).
Skin ageing.

DM Children's Cough Syrup *Trillium, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

DM Cough and Cold *Supplements Aromatik, Canad.; Tanta, Canad.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

DM Cough Syrup
Note: this name may be used for preparations of different composition.
Tanta, Canad.; Trillium, Canad.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Prodemdis, Canad.†
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1).
Cough.

DM Creme *Nycomed, Port.*
Glycol salicylate (p. 66·2); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; neuritis.

DM Decongestant *Trillium, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

DM Decongestant-Expectorant *Trillium, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

DM Decongestant-Expectorant-Analgesic *Trillium, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).

DM Expectorant *Trillium, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

DM + Expectorant *Rougier, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

DM Gel *Nycomed, Port.*
Glycol salicylate (p. 66·2); menthol (p. 2553·2); heparin sodium (p. 1396·3).
Soft-tissue injury; muscular pain; neuralgia.

DM Sans Sucre *Trianon, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

4-DMAP *Kohler, Ger.; Tramedico, Neth.†*
4-Dimethylaminophenol hydrochloride (p. 1550·2).
Cyanide, hydrocyanic acid, nitrile, or hydrogen sulfide poisoning.

DMax *Great Southern, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract disorders.

DM-Cordyl *Christo, Hong Kong.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough; cold symptoms.

DM/CPM/PE/GG *Kylemore, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

D-Med
Note: this name may be used for preparations of different composition.
PP Lab, Thai.
Sulfadimethoxine (p. 363·2); trimethoprim (p. 381·2).
Bacterial infections.

DMel *Admac, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

D-Met *Grandix, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

DML *Person & Covey, USA.*
A range of moisturisers.

Dispolab, Chile.†
Emollient.
Dry skin.

DML Facial *Dispolab, Chile.†*
SPF 25: Octinoxate (p. 1715·1); homosalate (p. 1705·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

DML Forte Con Pantenol *Dispolab, Chile.†*
Emollient.
Dry skin.

DMP *Glorious, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

DMP Plus *Glorious, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

DM/PE/CPM *Kylemore, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

DM/PSE/BPM *Kylemore, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Upper respiratory-tract disorders.

DMS Control *INTES, Ital.*
Vitamins; grape (p. 2521·3).
Nutritional supplement.

DMT *Croesus, Philipp.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

DMTX *Douglas, Canad.*
Vitamins; selenium (p. 2086·3).

DN Plus *Sain, India.*
Diacerein (p. 45·3); glucosamine sulfate potassium chloride (p. 2515·3); dimethyl sulfone (p. 2493·3).

DNA-EC *DNA, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Dnaren *Ariston, Braz.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

DNCG *Penta, Ger.*
Sodium cromoglicate (p. 1225·3).
Asthma.

D-Nova *Willow, India.*
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

DNSM *Investigaciones Filosoficas y Cientificas, Mex.*
Dornase alfa (p. 1662·1).
Inflammation.

DNV *Lero, Fr.*
Fish oil (p. 1460·1); melissa (p. 2552·3); vitamins; minerals.
Nervous disorders; sleep disorders.

Doact *Sun, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Doact-TZ *Sun, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Doak-Oil *GSK, Canad.*
Liquid paraffin; isopropyl palmitate; coal tar (p. 1723·2).
Skin disorders.

Doans
Note: this name may be used for preparations of different composition.
Novartis Consumer, USA.
Magnesium salicylate (p. 85·2).
Pain; fever; inflammation.

Doans Backache Pills
Note: this name may be used for preparations of different composition.
LPC, UK.
Paracetamol (p. 115·1); sodium salicylate (p. 132·2).
Pain.
Mentholatum, S.Afr.†
Paracetamol (p. 115·1); sodium salicylate (p. 132·2); buchu (p. 2461·3); aloin (p. 1816·2).
Musculoskeletal pain.

Dobedipil *Stada, Cz.; Pharmacodane, Denm.†; Stada, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dobelor *Grin, Mex.*
Ketorolac trometamol (p. 80·2).
Pain; inflammation.

Dobendan *Reckitt Benckiser, Austria; Reckitt Benckiser, Ger.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Dobendan Cool *Reckitt Benckiser, Ger.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth disorders.

Dobendan Direkt *Reckitt Benckiser, Ger.*
Flurbiprofen (p. 65·2).
Sore throat.

Dobendan Dolo *ReckittBenckiser, Ger.*
Cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Dobendan Junior *Reckitt Benckiser, Ger.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth disorders.

Dobendan Synergie *Reckitt Benckiser, Ger.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth infections.

Dobendan Warm *Reckitt Benckiser, Ger.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth disorders.

Dobesil *Ochoa, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Dobest *Wallace, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Dobet *Oftalmi, Venez.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Dobetin *Angelini, Ital.; Elmor, Venez.*
Cyanocobalamin (p. 2107·2).
Anaemias; neuritis; neuralgia; neuropathy; vitamin B_{12} deficiency.

Dobetin Compuesto *Elmor, Venez.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Peripheral neuropathy; vitamin B deficiency.

Dobetin Totale *Angelini, Ital.*
Hydroxocobalamin (p. 2107·3); thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Neuralgia.

Dobetin Vitamina B1 *Angelini, Ital.*
Thiamine hydrochloride (p. 2103·1).
Neuralgia; neuritis.

Dobexil *Valeant, Cz.*
Calcium dobesilate (p. 2464·3); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Dobica *Nycomed, Cz.; Nycomed, Ger.†*
Calcium dobesilate (p. 2464·3).
Diabetic retinopathy; venous insufficiency; haemorrhoids; capillary fragility.

Dobicard *USV, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobicin *Chandra Bhagat, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Dobid *Chemech, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Dobier *Chandra Bhagat, India.*
Dobutamine (p. 1365·3) or dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dobilet *Aristo, India.*
Calcium dobesilate (p. 2464·3).
Varices; haemorrhoids; diabetic retinopathy.

Dobion *Biosena, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobipro *Salus, Mex.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Dobiron *Legrand, Braz.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3); liver extract (p. 2444·1); gastric mucosa extract (p. 2444·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Dobixin *Zydus, India.*
Doxorubicin (p. 782·3).
Bacterial infections.

Dobkair *PDC, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Dobonis *Neiss, India.*
Dobutamine (p. 1365·3) or dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dobren *Teofarma, Ital.*
Sulpiride (p. 1107·3).
Psychoses; dysthymia.

Dobriciclin *Quimifar, Spain.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Dobroson *Steigerwald, Pol.*
Zopiclone (p. 1118·1).
Insomnia.

Dobtan *Uniao Quimica, Braz.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock.

Dobucard *Scott-Cassara, Arg.; Invision, India.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dobucef *Promed, Indon.*
Dobutamine hydrochloride (p. 1365·3).
Myocardial infarction; open heart surgery; cardiomyopathy; shock.
VHB, India.
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobucin *Troikaa, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobucor *Bayer Schering, Port.; Bayer, Spain.†*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock.

Dobugen *Shree Ganesh, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobuject *Bayer Schering, Cz.; Primex, Fin.; Dexa, Indon.; Leiras, Indon.; Bayer, Israel; Pisa, Mex.; Schering, Philipp.; Bayer Schering, Pol.; Primex, Singapore; Bayer Schering, Thai.; Er-Kim, Turk.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock; circulatory failure; cardiogenic shock.

Dobulex *Delex, Philipp.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock.

Dobunex *Swiss Parenterals, Philipp.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock.
VHB, India.
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobupal *Almiroll, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Dobupum *Kyowa, Jpn.*
Dobutamine hydrochloride (p. 1365·3).
Acute circulatory failure.

Doburan *Dipa, Indon.; Pharmakin, Venez.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.
VHB, India.
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobusol *United Biotech, India.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dobustat *Samarth, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobutabag *Eczacibasi-Baxter, Turk.*
Dobutamine hydrochloride (p. 1365·3).

Dobutabbott *Abbott, Braz.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Dobutam *United Biotech, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Dobutan *Demo, Gr.*
Dobutamine hydrochloride (p. 1365·3).

Dobutasys *Systacare, India.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dobutel *Novell, Indon.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Dobutina *Hospira, Port.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock; cardiac stress testing.

Dobuton *Ariston, Braz.*
Dobutamine hydrochloride (p. 1365·3).

Dobutrex *Aspen, Austral.; Lilly, China; Lilly, Cz.†; Pharmacodane, Denm.; Piramal, India; Sandoz, Mex.; GSK, Philipp.; Sandoz, S.Afr.; Meda, Swed.†; Teva, Switz.; Lilly, Turk.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock; cardiac stress testing.

Dobutrexmylan *Mylan, Belg.*
Dobutamine (p. 1365·3).
Shock.

Dobutrim *Duopharma, Philipp.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock.

Dobutrop *Geo, India.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dobuxin *Behrens, Venez.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Doc *Hermes, Ger.*
Arnica (p. 2447·2).
Musculoskeletal, joint, and soft-tissue disorders.

Docabolin *Organon, Gr.†*
⊗Desoxycortone phenylpropionate (p. 1630·2); nandrolone phenylpropionate (p. 2293·1).

Docacetyl *Docpharma, Belg.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Docaciclo *Docpharma, Belg.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Docaine *M & H, Thai.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Docallopu *Docpharma, Belg.†*
Allopurinol (p. 600·2).
Gout; renal calculi.

Docalprazo *Docpharma, Belg.†*
Alprazolam (p. 1035·2).
Anxiety.

Docamoclaf *Docpharma, Belg.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Docamoxici *Docpharma, Belg.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Docard *Dexxon, Israel†; Dexxon, Philipp.†*
Dopamine hydrochloride (p. 1367·2).
Shock.

Docateno *Docpharma, Belg.†*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; angina pectoris.

Docbetahi *Docpharma, Belg.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Docbisopro *Docpharma, Belg.†*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Docbromaze *Docpharma, Belg.†*
Bromazepam (p. 1041·2).
Anxiety; insomnia.

Docbudeso *Docpharma, Belg.†*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Doccaptopri *Docpharma, Belg.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Doccefaclo *Docpharma, Belg.†*
Cefaclor (p. 232·3).
Bacterial infections.

Doccefuro *Docpharma, Belg.†*
Cefuroxime (p. 255·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Doccimeti *Docpharma, Belg.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux.

Docciproflo *Docpharma, Belg.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Doccyproestra *Docpharma, Belg.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in females.

Docdiclofe *Docpharma, Belg.†*
Diclofenac sodium (p. 48·3).

Docdipyri *Docpharma, Belg.†*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Docdol *Adcock Ingram, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Docdomperi *Docpharma, Belg.†*
Domperidone (p. 1838·1).
Nausea and vomiting; gastroparesis.

Docdonna *Docpharma, Belg.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Docdoxycy *Docpharma, Belg.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doce Alivio *Moreno, Port.*
Phenolphthalein (p. 1877·3); belladonna (p. 2453·3); cascara (p. 1826·1); podophyllum resin (p. 1717·1); hyoscyamus (p. 2530·2).

Docecad *Cadila, India.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docechol *Lafedar, Arg.*
⊗Pepsin (p. 2586·1); amylase (p. 2442·1); papain (p. 2582·3); caffeine (p. 1203·3).
Digestive disorders.

Docefim *Tiefenbacher, Irl.; Tiefenbacher, Neth.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docefrez *Sun, Cz.; Sun, India; Sun, Irl.; Sun, Neth.†; Sun-Farm, Pol.; Sun, Port.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docekebir *Aspen, Arg.*
Docetaxel (p. 780·3).

Docelibbs *Libbs, Braz.*
Docetaxel (p. 780·3).

Doce-Plex *Meyer, Venez.*
Vitamin B substances (p. 2102·3).
Vitamin supplement; tonic.

Docet *Samarth, India.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docetax *Cipla, India.*
Docetaxel (p. 780·3).
Breast cancer; non-small-cell lung cancer.

Docetaxin *Cancernova, Ger.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docetec *United Biotech, India.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docetere *Reddy, Braz.; Reddy, India; Ferron, Indon.; Winthrop, S.Afr.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docfenofi *Docpharma, Belg.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Docflecai *Docpharma, Belg.†*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Docfluoxetine *Docpharma, Belg.†*
Fluoxetine (p. 417·1).
Depression.

Docfurose *Docpharma, Belg.†*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Doci *Naprod, Philipp.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Docin *Pharmasant, Thai.*
Indometacin (p. 71·2).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Docindapa *Docpharma, Belg.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Docirena *Fresenius Kabi, Irl.; Fresenius Kabi, Neth.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Dociretic *Mibe, Ger.*
⊗Propranolol hydrochloride (p. 1479·1); bendroflumethiazide (p. 1315·2).
Hypertension.

Docistin *Biomedis, Philipp.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Docita *Alvartis, Mex.*
Difenidol (p. 1835·1).

Dociteren *Mibe, Ger.*
⊗Propranolol hydrochloride (p. 1479·1); triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dociton *Mibe, Ger.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; myocardial infarction; migraine.

Docitral *Vargas, Venez.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension.

Docivin *Mintlab, Chile.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastrointestinal motility disorders.

Docketoral *Docpharma, Belg.†*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Doclamotri *Docpharma, Belg.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Docline *Atlantic, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doclis *Bial, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Docloraze *Docpharma, Belg.†*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Doclormeta *Docpharma, Belg.†*
Lormetazepam (p. 1082·1).
Insomnia.

Docmebenda *Docpharma, Belg.†*
Mebendazole (p. 158·3).
Worm infections.

Docmeloxi *Docpharma, Belg.†*
Meloxicam (p. 86·3).

Docmetoclo *Docpharma, Belg.†*
Metoclopramide (p. 1862·2).
Nausea and vomiting; gastroparesis.

Docmorfine *Docpharma, Belg.†*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Docofloxacine *Docpharma, Belg.†*
Ofloxacin (p. 334·3).
Bacterial infections.

DocOmega *Vitaflo, UK.*
Docosahexaenoic acid (p. 1460·1); carbohydrates.
Dietary management of inherited metabolic disorders.

Docomepra *Docpharma, Belg.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux.

Docpara *Docpharma, Belg.†*
Paracetamol (p. 115·1).
Pain; fever.

Docparacod *Docpharma, Belg.†*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Docpirace *Docpharma, Belg.†*
Piracetam (p. 393·3).
Cerebrovascular disorders.

Docpiroxi *Docpharma, Belg.†*
Piroxicam (p. 125·3).

DocQlace *Qualitest, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Docraniti *Docpharma, Belg.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Docril *Biomep, Mex.*
Diclofenac (p. 48·3).
Pain.

Docrub *Aspen Consumer, S.Afr.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2).
Soft-tissue disorders; cough; cold symptoms.

Docrutosi *Docpharma, Belg.†*
Troxerutin (p. 2505·3).
Capillary impairment; venous insufficiency.

Docsalbuta *Docpharma, Belg.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Docsed *Aspen, S.Afr.†*
⊗Mepyramine maleate (p. 635·1); codeine phosphate (p. 40·2); pholcodine (p. 1675·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Docsef *Daksh, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Docsi *Biomep, Mex.*
Chlorphenamine (p. 620·3).
Hypersensitivity.

Docsimvasta *Docpharma, Belg.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Docspirochlor *Docpharma, Belg.†*
⊗Hydrochlorothiazide (p. 1403·2); spironolactone (p. 1499·3).

Docspirono *Docpharma, Belg.†*
⊗Spironolactone (p. 1499·3).
Hypertension; heart failure; hyperaldosteronism; cirrhosis with ascites.

Docsulpiri *Docpharma, Belg.†*
Sulpiride (p. 1107·3).
Psychoses.

Doctadryle *Doctum, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Doctamine *Doctum, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Doctamoxifene *Docpharma, Belg.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Docticam *Doctum, Gr.*
Tenoxicam (p. 136·2).
Pain; musculoskeletal, joint, and peri-articular disorders; gout.

Doctinon *Doctum, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Doctistatin *Doctum, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Doctiverine *Doctum, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Doctodermis *Cooberpharm, Spain.*
Biotin (p. 2052·2); triclosan (p. 1773·2).
Skin cleansing.

Doctofril Antiinflamat *Nupel, Spain.†*
Phenylbutazone (p. 125·1); lidocaine (p. 1988·1); methyl nicotinate (p. 91·3); vitamin F (p. 2509·2).
Rheumatic and muscle pain; chilblains.

Doctor 10 Body *Doctor 10, Arg.*
Spirulina (p. 2622·1); centella (p. 1698·3); equisetum (p. 2500·1); thiamine (p. 2102·3).
Cellulite; slimming aid.

Doctor Cough *Lupin, Ukr.*
Liquorice (p. 1853·2); malabar nut (p. 2549·1); ocimum sanctum; ginger (p. 1844·1); piper longum; peppermint (p. 1877·1); albizia; inula racemosa; turmeric (p. 2218·1).
Cough.

Doctor's Choice *Enzymatic Therapy, Canad.*
Vitamins; minerals; trace elements.

Doctor's Choice Calcium *Vita Green, Hong Kong.†*
Calcium carbonate (p. 1824·3).

Doctor's Choice Chewable Vita C-Cal *Vita Green, Hong Kong.*
Calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3).

Doctor's Choice Fortified Bone Support *Vita Green, Hong Kong.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement.

Doctor's Choice Fortified Joint Support *Vita Green, Hong Kong.†*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Nutritional supplement for healthy joints.

Doctor's Choice for Joints *Vita Green, Hong Kong.*
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Doctor's Choice Multivitamins and Minerals for Eyes *Vita Green, Hong Kong.*
Vitamins; minerals; linoleic acid (p. 2509·2); garlic (p. 2510·3); ginkgo biloba (p. 2512·3).
Dietary supplement.

Doctor's Choice Omega 3 *Vita Green, Hong Kong.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).
Dietary supplement.

Doctramado *Docpharma, Belg.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Doctril *Johnson & Johnson, Spain.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Doctrim *Gulf Drug, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Doctrimox *Doctors, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Doculax *Hasco-Lek, Pol.*
Docusate sodium (p. 1836·2).
Constipation; bowel evacuation.

Doculyse *Quies, Fr.*
Docusate sodium (p. 1836·2).
Ear wax removal; ear hygiene.

Docusoft *Reese, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Docusoft Plus *Reese, USA.*
Docusate sodium (p. 1836·2); casanthranol (p. 1826·1).
Constipation.

Docusoft-S *G & W, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Docusol *Typharm, UK; Alliance, USA.*
Docusate sodium (p. 1836·2).
Constipation; bowel evacuation.

Docuspray *Quies, Fr.*
Sea water (p. 2612·1).
Ear hygiene.

Docuxen *Bescansa, Spain.†*
Senna (p. 1885·1); docusate sodium (p. 1836·2).
Constipation.

Doc-Vite *Docmed, S.Afr.†*
Vitamins; minerals.

Docyl *Unison, Thai.*
Doxycycline (p. 288·1).
Bacterial infections.

Dodds *Stella, Canad.†*
Sodium salicylate (p. 132·2).
Musculoskeletal pain.

Dodds Back Ease *Stella, Canad.†*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).

Dodécavit *SERB, Fr.*
Hydroxocobalamin acetate (p. 2107·3).
Vitamin B_{12} deficiency.

Dodemina Tri *Valeant, Mex.*
Hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency; neuritis; neuralgias; metabolic acidosis.

Dodepar *ABC, Port.*
Vitamin B substances (p. 2102·3).
Anaemias; tonic.

Döderlein *Novartis Consumer, Austria.*
Lactobacillus gasseri (p. 2596·3).
Vaginal flora disorders.

Döderlein Med *Novartis Consumer, Ger.†*
Lactobacillus gasseri (p. 2596·3).
Vaginal disorders.

Dodesept *Schulke & Mayr, Austria.*
⊗Orthophenylphenol (p. 1762·3); alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1).
Skin disinfection.

Dodesept Gefarbt *Schulke & Mayr, Austria.*
⊗Orthophenylphenol (p. 1762·3); alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Dodesept N *Schulke & Mayr, Austria.†*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Dodex *Deva, Turk.*
Vitamin B_{12} (p. 2107·2).
Megaloblastic anaemia.

Dodo *Sienna, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Do-Do ChestEze *Novartis Consumer, UK.*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2); caffeine (p. 1203·3).
Bronchial coughs; wheezing; respiratory-tract congestion.

Dodo-MR *Sienna, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Doenza *Sanovel, Turk.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dofacef *Sanbe, Indon.*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Dofaxil *Continentales, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); ambroxol hydrochloride (p. 1654·3).
Cough; respiratory-tract congestion.

Dofec *DWD, India.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dofec Plus *DWD, India.*
Benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dofec-S *DWD, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Dofedrin *Abbott, Mex.†*
⊗Pseudoephedrine (p. 1676·1).
Upper respiratory-tract congestion.

Dofen
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain.
Parggon, Mex.†
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dofene *Caldeira & Metelo, Port.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Doffler *Loeffler, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Dofibra *Melisana, Switz.†*
Fibre.

Dofisan *Berman, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Dofitex *Medipharm, Chile.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Doflatem *Loeffler, Mex.*
Diclofenac (p. 48·3).
Inflammation; pain.

Doflex *Jagsonpal, India.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders; pain.

Doflex Plus *Jagsonpal, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Gout; musculoskeletal and joint disorders; pain.

Dogesic *Yarindo, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Dogmatil *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Hong Kong; Delagrange, Indon.; Soho, Indon.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Philipp.†; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi Synthelabo, Turk.*
Sulpiride (p. 1107·3).
Psychosomatic disorders; psychoses; neuroses; behaviour disorders; post-concussion syndrome; vertigo; migraine; schizophrenia; depression; Ménière's disease; mania; agitation; anxiety disorders; obsessive-compulsive disorder; peptic ulcer.

Dogmatyl *Sanofi-Aventis, Gr.; Astellas, Jpn.*
Sulpiride (p. 1107·3).
Schizophrenia; depression; peptic ulcer; psychoses.

Dogrel *Macleal, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Dohixat *Ifars, Indon.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; amoebiasis.

Doin *Intel, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

DOK *Major, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Dok Plus *Major, USA.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.

Dokard *Daewoo, Philipp.*
Dopamine hydrochloride (p. 1367·2).
Heart failure; shock.

Dokcef *Lupin, Ukr.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Doket *IQFA, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Doketrol *Rivero, Arg.*
Sodium nitroprusside (p. 1497·1).
Hypertension.

Dokselin *Ulkar, Turk.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Doksin *Nevzat, Turk.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doksura *Fako, Turk.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doktacillin *Meda, Swed.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Doktor Mom *Unique, Rus.; Unique, Ukr.*
Ointment: Menthol (p. 2553·2); camphor (p. 2466·2); thymol (p. 1772·2); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2).
Cold symptoms; upper respiratory-tract disorders; cough; myalgia; lumbago; headache.
Unique, Rus.; Unique, Ukr.
Syrup: Ocimum sanctum; liquorice (p. 1853·2); turmeric (p. 2218·1); ginger (p. 1844·1); malabar nut (p. 2549·1); solanum indicum; inula racemosa; cubeb (p. 2489·2); beleric myrobalan (p. 2453·2); aloes (p. 1816·1); menthol (p. 2553·2).
Cough; upper respiratory-tract disorders.
Unique, Rus.
Inhalation: Levomenthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Respiratory-tract congestion.
Unique, Rus.
Topical solution: Eucalyptus oil (p. 2501·2); levomenthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Respiratory-tract congestion; headache.

Doktor Mom Herbal Cough Lozenges *Unique, Rus.; Unique, Ukr.*
Liquorice (p. 1853·2); ginger (p. 1844·1); Indian gooseberry (p. 2532·2); menthol (p. 2553·2).
Upper respiratory-tract disorders; cough.

Dol
Note: this name may be used for preparations of different composition.
Calox, Venez.
Paracetamol (p. 115·1); caffeine (p. 1203·3); dihydroergotamine mesilate (p. 672·2).
Migraine.
3a, India.
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).
PC India, India.
Tramadol (p. 139·2).
Pain.

Dolac *Ethica, Indon.; Rhein, Mex.; Cadila, Rus.*
Ketorolac trometamol (p. 80·2).
Pain.

Dolacen *Labesfal, Port.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Dolacet *Roberts, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Dolact *Intra-Labs, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.
Intra-Labs, India.
Tablets: Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.
Intra-Labs, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Doladamon *Fako, Turk.*
Paracetamol (p. 115·1); ciclonium bromide (p. 1827·1); codeine phosphate (p. 40·2).
Fever; pain.

Dolafen *Ashford, Philipp.*
Ibuprofen (p. 68·2).
Pain; inflammation.

Dolaforte *Chemists Own, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dolak
Note: this name may be used for preparations of different composition.
Bama, Spain.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.
Dollder, Venez.
Ketorolac trometamol (p. 80·2).
Pain.

Dolal
Note: this name may be used for preparations of different composition.
Alapis, Gr.
Paracetamol (p. 115·1).
Pain; fever.
Biocodex, Fr.†
Ethylmethoxy salicylate; phenylpropyl salicylate.
Musculoskeletal and joint pain.

Dolalgial *Sanofi-Aventis, Spain.*
Clonixin lysine (p. 40·1).
Pain.

Dolamide *Ranbaxy, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Dolamin *Farmoquimica, Braz.*
Clonixin lysine (p. 40·1).
Pain.

Dolamin Flex *Farmoquimica, Braz.*
Clonixin lysine (p. 40·1); cyclobenzaprine hydrochloride (p. 2023·1).
Musculoskeletal pain and spasm.

Dolan
Note: this name may be used for preparations of different composition.
Leiras, Fin.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.
Pediatrica, Philipp.
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Dolana *Combiphar, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolanaest *Gebro, Austria; Strathmann, Ger.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia; pain syndromes.

Dolanet
Note: this name may be used for preparations of different composition.
Gramon-Bago, Urug.
Dipyrone (p. 53·3).
Fever; pain.
Sanofi-Aventis, Arg.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Dolantin *Sanofi-Aventis, Ger.†*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Dolantina *Sanofi-Aventis, Braz.; Kern, Spain.*
⊗Pethidine hydrochloride (p. 121·3).
Pain; premedication; smooth muscle spasm.

Dolantine *Sanofi-Aventis, Belg.*
⊗Pethidine hydrochloride (p. 121·3).
Pain; premedication.

Dolapril *Aspen, Austral.*
Trandolapril (p. 1517·2).
Hypertension; myocardial infarction.

Dolar
Note: this name may be used for preparations of different composition.
Lark, India.
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).
Rainbow, Ukr.
Paracetamol (p. 115·1); diclofenac sodium (p. 48·3).
Pain.

Dolaren *Carnot, Mex.*
Cream: Diclofenac diethylamine (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders.
Carnot, Mex.
Tablets: Diclofenac sodium (p. 48·3); carisoprodol (p. 2021·3).
Gout; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.
Nabros, Rus.; Nabros, Ukr.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.
Nabros, Ukr.
Gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1); linseed oil (p. 2544·2).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolargan *Chinoin, Pol.*
⊗Pethidine (p. 121·3).
Pain.
Sanofi-Aventis, Hung.
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Dolarit *Drogsan, Turk.*
Etodolac (p. 57·1).

Dolased Analgesic-Calmative *Chemists Own, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain.

Dolaut *GiEnne, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Dolbutin *Mavi, Mex.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal motility disorders.

Dolce *Oro, Turk.†*
Sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute.

Dolcelox *Medchem, Philipp.*
Celecoxib (p. 36·3).
Rheumatoid arthritis; osteoarthritis.

Dolcet *Janssen, Philipp.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Dolcevin *Minerva (Μινερβα), Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dolcidium *SMB, Belg.*
Indometacin (p. 71·2).
Musculoskeletal, joint and peri-articular disorders; pain; inflammation.

Dolcin
Note: this name may be used for preparations of different composition.
Cinerea, India.
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; hiccup.

Dolcispray *Olvos, Gr.*
Indometacin (p. 71·2).
Inflammatory disorders.

Dolcol *Nichi-Iko, Jpn.*
Pipemidic acid (p. 339·3).
Bacterial infections.

Dolcontin
Note: this name may be used for preparations of different composition.
Lavipharm, Gr.
Dihydrocodeine tartrate (p. 52·3).
Pain.
Mundipharma, Fin.; Pfizer, Norw.; Pfizer, Swed.
⊗Morphine sulfate (p. 92·3).
Pain.

Dolcontral *Mibe, Ger.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.
Polfa Warszawa, Pol.
⊗Pethidine (p. 121·3).
Pain.

Dolcopin *Pasteur, Chile.*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.
Rottapharm, Spain.
Magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1); almasilate (p. 1815·3); alginic acid (p. 2167·2).
Dyspepsia; gastro-oesophageal reflux.

Dolcoplaz *Loeffler, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Dolcy *Alembic, India.*
⊗Pseudoephedrine (p. 1676·1).
Nasal congestion.

Dold *DOT, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1) phenylpropanolamine hydrochloride (p. 1674·1).

Dolean *Lafi, Chile.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dolectran *LKM, Arg.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Doleira *Shince, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolemicin *Gayoso, Spain.*
Metamizole magnesium (p. 53·3).
Pain; fever.

Dolencar *Ceninter, Spain.*
Ibuprofen (p. 68·2).
Pain; fever.

Dolenio *Biocodex, Belg.; Blue Bio, Denm.; Blue Bio, Irl.; Biocodex, Neth.; Blue Bio, Port.; Blue Bio, UK.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.
Biocodex, Fr.; Blue Bio, Gr.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis of the knee.

Dolestan
Note: this name may be used for preparations of different composition.
Krewel, Ger.
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.
Krewel, Ger.†
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Dolestine *Teva, Israel.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Dolevar *AWD, Ger.†*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Dolex
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Clonixin lysine (p. 40·1).
Pain.

Dolexpel *Morishita, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Dolfen
Note: this name may be used for preparations of different composition.
Great Eastern, Thai.
Mefenamic acid (p. 85·3).
Pain.
Neiadas (Νειαδας), Gr.; Pfizer, Gr.
⊗Fentanyl (p. 60·1).
Pain.

Dolfenal *Medifarma, Indon.†; Westmont, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Dolfen-P *Elfin, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Dolfin *Steierl, Ger.*
Cyclamen purpurascens (p. 2490·2); iris versicolor (p. 2534·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Dolflam *Rayere, Mex.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Dolflash *Ethypharm, Irl.*
Paracetamol (p. 115·1).
Pain; fever.

Dolforin *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.*
⊗Fentanyl (p. 60·1).
Pain.

Dolgan *Bioresearch, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Dolgan Flash *Sanofi Synthelabo, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Dolgenal *Tecnofarma, Chile.*
Ketorolac trometamol (p. 80·2).
Pain.

Dolgesic *Novag, Spain.†*
Paracetamol (p. 115·1).
Pain; fever.

Dolgesic Codeina *Novag, Spain.†*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Dolgesik *Mersifarma, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolgic *Athlon, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).
Pain.

Dolgic LQ *Athlon, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3); caffeine (p. 1203·3).
Pain.

Dolgic Plus *Shionogi, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Dolgit *Sanova, Austria; Dolorgiet, Cz.; Merck Serono, Fr.; Dolorgiet, Ger.; Dolorgiet, Hung.; Dolorgiet, Pol.; Promed, Rus.; Amino, Switz.; Abbott, Turk.; Adeka, Turk.; Dolorgiet, Ukr.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolgit-Diclo *Dolorgiet, Ger.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Dolgosin *Boniscontro & Gazzone, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Oromédine *Sanofi-Aventis, Fr.*
Hexamidine isetionate (p. 1754·3); tetracaine hydrochloride (p. 1996·3).
Formerly known as Oromedine.
Mouth and throat disorders.

Doliallergie *Sanofi-Aventis, Fr.*
Loratadine (p. 633·2).
Allergic rhinitis.

Dolibird *Dewcare, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Dolical *Rekah, Israel.†*
Morpholine salicylate (p. 97·1).
Skeletal muscle spasm.

Dolicoccil *Dolisos, Cz.†; Dolisos, Hung.*
Anas barbariae et cordis extractum (p. 2444·1); cuprum gluconicum (p. 2057·2); echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.

Dolide *Embiotic, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Dolide Plus *Embiotic, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Dolider *Pasteur, Chile.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Dolidon *Genopharm, Fr.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Doliib *Panacea, India.*
Rofecoxib (p. 128·3).

Dolikan *Collins, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Dolilite *Holland Pharma, Neth.*
Ceanothus americanus; conium maculatum (p. 2524·3); bryonia alba; lycopodium clavatum (p. 2547·1); carduus marianus (p. 1561·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Dolilux *Farma 1, Ital.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dolinac *Wyeth, Gr.; Teofarma, Ital.*
Felbinac (p. 58·3).
Pain; inflammation.

Doline
Note: this name may be used for preparations of different composition.
Abdi, Turk.; Tripharma, Turk.
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.
Alphapharm, Malaysia.†
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Dolintol *Vir, Spain.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Doliprane *Sanofi-Aventis, Fr.; Piramal, India.*
Paracetamol (p. 115·1).
Fever; pain.

Dolipranelib *Sanofi-Aventis, Fr.*
Paracetamol (p. 115·1).
Fever; pain.

Dolipraneoro *Sanofi-Aventis, Fr.*
Paracetamol (p. 115·1).
Fever; pain.

DolipraneVitamineC *Sanofi-Aventis, Fr.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Dolirelax *Boiron, Fr.†*
Valeriana officinalis (p. 2640·2); ignatia amara (p. 2532·1); hyoscyamus niger (p. 2530·2); crocus sativus (p. 2208·2); silicea (p. 2208·3).
Homoeopathic preparation.

Dolirhume *Sanofi-Aventis, Fr.*
Tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.
Sanofi-Aventis OTC, Fr.
Nasal spray: Thenoate sodium (p. 376·3).
Formerly known as Soufrane.
Nasopharyngeal infections.
Sanofi-Aventis, Fr.
Inhalation: Peru balsam (p. 2587·1); sumatra benzoin (p. 2624·3); eucalyptus (p. 2501·1); lavender oil (p. 2541·1); thyme oil (p. 2630·3); levomenthol (p. 2553·2).
Formerly known as Balsofumine Mentholee.
Respiratory-tract congestion.

DolirhumePro *Sanofi-Aventis OTC, Fr.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; doxylamine succinate (p. 627·3).
Cold symptoms.

Dolisec *Sanofi-Aventis, Gr.*
Sucralfate (p. 1889·1).

Doliségal *Boiron, Fr.†*
Ignatia amara (p. 2532·1); arnica montana (p. 2447·2); nux vomica (p. 2573·3); jalapa (p. 1850·1); kalium carbonicum (p. 2595·2); calcarea phosphorica (p. 1784·2).
Homoeopathic preparation.

Dolistamine *Boiron, Fr.†*
Allium cepa (p. 2575·2); histaminum (p. 2525·2); euphrasia officinalis (p. 2502·1); sabadilla (p. 2611·2); kalium iodatum (p. 2336·3); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Dolitravel *Boiron, Fr.†*
Cocculus indicus (p. 2483·1); tabacum (p. 2632·2); petroleum (p. 2587·2); ignatia amara (p. 2532·1); conium maculatum (p. 2524·3); calcarea carbonica ostrearum (p. 1824·3).
Homoeopathic preparation.

Dolium *Utopian, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dolivaxil *Dolisos, Neth.†*
Influenzinum (p. 2393·3).
Homoeopathic preparation.

Dolizi *Helm, Port.†*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dolizol *Unipharm, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Dolko *Therabel, Fr.; Medicon, India.*
Paracetamol (p. 115·1).
Pain; fever.

Dolmal *Biolink, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolmatil *Europharma, Denm.; Sanofi-Aventis, Irl.; Sanofi-Aventis, UK.*
Sulpiride (p. 1107·3).
Schizophrenia.

Dolmed *Leiras, Fin.*
⊗Methadone hydrochloride (p. 88·3).
Pain; opioid dependence.

Dolmen
Note: this name may be used for preparations of different composition.
Ern, Spain.
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); codeine phosphate (p. 40·2).
Pain; fever; musculoskeletal, joint, and peri-articular disorders.
Sigma-Tau, Ital.
Tenoxicam (p. 136·2).
Musculoskeletal disorders.

Dolmetine *CNN, Philipp.†*
Mefenamic acid (p. 85·3).
Pain.

Dolmina *Zentiva, Cz.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolmisin *Farcoral, Mex.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Dol-Mite *Swiss Herbal, Canad.†*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).

Dolmitin *Nupel, Spain.†*
Cineole (p. 2479·1); diethylamine salicylate (p. 51·3).
Soft-tissue disorders.

Dolnefort *Farcoral, Mex.*
Diclofenac potassium (p. 48·3); vitamin B substances (p. 2102·3).
Pain; neuritis.

Dolnix *Recalcine, Chile.*
Ibuprofen (p. 68·2); dipyrone (p. 53·3); chlormezanone (p. 1045·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolo *Micro, India; Micro, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Dolo Asotrex *Raffo, Arg.*
Meloxicam (p. 86·3); glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis; extra-articular rheumatism.

Dolo Baliartrin *Baliarda, Arg.*
Meloxicam (p. 86·3); glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis; extra-articular rheumatism.

Dolo Bedoyecta *Grossman, Mex.*
Ketoprofen (p. 79·1); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3).
Peripheral neuropathy.

Dolo Demotherm *Vifor, Switz.†*
Dimethyl sulfoxide (p. 2182·2); benzyl nicotinate (p. 29·3); glycol salicylate (p. 66·2).
Musculoskeletal and joint pain.

Dolo Moff *Uniao Quimica, Braz.*
⊗Morphine sulfate (p. 92·3).
Pain.

Dolo Nervobion
Note: this name may be used for preparations of different composition.
Merck Serono, Arg.
Diclofenac sodium (p. 48·3); thiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); mecobalamin (p. 2108·1).
Musculoskeletal and joint pain; neuritis.
Merck, Spain.†
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; renal colic.

Dolo Nervobion 10000 *Merck, Arg.*
Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ampoule 2, diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

Dolo Roll-On *Hevert, Ger.*
Methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Dolo Sanol *Sanol, Ger.†; Schwarz, Ger.†*
Ibuprofen (p. 68·2).
Fever; pain.

Dolo Scanneuron *Tempo Scan Pacific, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Dolo Tomanil *Nycomed, Arg.*
Diclofenac (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolo Winasorb *Recalcine, Chile.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; pain; fever.

Dolo-Arthrosenex *Dermapharm, Switz.*
Glycol salicylate (p. 66·2); heparin sodium (p. 1396·3); camphor (p. 2466·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Arthrosenex M *Riemser, Ger.*
Glycol salicylate (p. 66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Arthrosenex N *Riemser, Ger.*
Glycol salicylate (p. 66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Arthrosetten H *Riemser, Ger.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Dolobak *Micro, India.*
Chlormezanone (p. 1045·1); paracetamol (p. 115·1).

Doloban *Mankind, India.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3).

Dolobene *Ratiopharm, Austria; Mepha, Braz.†; Ratiopharm, China; Ratiopharm, Cz.; Merckle, Ger.†; Mepha, Hong Kong†; Ratiopharm, Hung.; Ratiopharm, Pol.†; Ratiopharm, Rus.; Mepha, Switz.; Ratiopharm, Ukr.*
Dimethyl sulfoxide (p. 2182·2); heparin sodium (p. 1396·3); dexpanthenol (p. 2582·2).
Neuralgias; neuritis; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; superficial thrombophlebitis; skin ulcers; venous insufficiency; inflammation; pain.

Dolobene Cool *Recordati, Ger.*
Isopropyl alcohol (p. 1758·3).
Musculoskeletal, joint, and soft-tissue disorders.

Dolobene Hot *Recordati, Ger.*
Cayenne pepper (p. 2469·3).
Musculoskeletal and joint disorders.

Dolobene Ibu *Recordati, Ger.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders.

Dolobid *M & H, Thai.*
Diflunisal (p. 51·3).
Pain; musculoskeletal and joint disorders.

Dolobid-M *Apotex, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Doloc *Sanitas, Chile.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Dolocalma *Neves, Port.*
Metamizole magnesium (p. 53·3).
Pain; colic; fever.

Dolocam *Rimsa, Mex.*
Meloxicam (p. 86·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolocam Plus *Rimsa, Mex.*
Meloxicam (p. 86·3); methocarbamol (p. 2025·3).
Musculoskeletal, joint, and peri-articular disorders.

Dolocap *Erlimpex, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolocare *Vensat, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Dolocartigen *Rimsa, Mex.*
Meloxicam (p. 86·3); diacerein (p. 45·3).
Degenerative joint disorders.

Dolocatil *Ferrer, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Dolocatil Codeina *Ferrer, Spain.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dolocep *Domesco, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Dolocet *Micro, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Dolochek *Indoco, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Dolochek-P *Indoco, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dolocide K *Kee, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal and joint disorders.

Dolocide KP *Kee, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Inflammation; pain.

Dolocide MR *Kee, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Musculoskeletal, joint, and peri-articular disorders; pain; skeletal muscle spasm.

Dolocide Plus *Kee, India.*
Diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolocin *Quality, Hong Kong.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Fever; pain.

Dolocip *Cipla, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

DoloCitran C *Novartis Consumer, Switz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Dolocod *Astellas, Austria.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Dolocodon *Zentiva, Cz.; Zentiva, UK.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Dolo-Cold *Micro, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Dolocold *Micro, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Dolocrat *Cratus, India.*
⊗Ibuprofen (p. 68·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dolo-cyl
Note: this name may be used for preparations of different composition.
Liebermann, Ger.†
Arnica oil (p. 2447·2); eucalyptus oil (p. 2501·2); St John's wort oil (p. 449·1); juniper oil (p. 2537·2); lavender oil (p. 2541·1); pumilio pine oil (p. 2591·1); rosemary oil (p. 2607·3).
Musculoskeletal pain.

Dolocyl
Note: this name may be used for preparations of different composition.
Novartis Consumer, Port.; Novartis Consumer, Switz.
Ibuprofen (p. 68·2).
Pain; fever.

Dolodart *Juggat, India.*
Paracetamol (p. 115·1).
Pain; fever.

Dolodens *Nupel, Spain.†*
Codeine phosphate (p. 40·2); hydroxyzine hydrochloride (p. 630·3); propyphenazone (p. 127·3).
Pain.

Dolodent
Note: this name may be used for preparations of different composition.
Gilbert, Fr.
Amylocaine hydrochloride (p. 1979·3).
Teething pain.
OBA, Denm.
Benzocaine (p. 1980·2); myrrh (p. 2566·1).
Mouth pain.

Doloderm *Sanofi-Aventis, Ital.*
Methyl butetisalicylate (p. 91·3).
Musculoskeletal and joint pain.

Dolodil *Madhav, India.*
Piroxicam (p. 125·3).

Dolodoc *Docpharm, Ger.†*
Ibuprofen (p. 68·2).
Fever; pain.

Dolodol *Cantabria, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.
Ethix, India.
Tramadol (p. 139·2).
Pain.

Dolo-Esan *Esan, Chile.*
Paracetamol (p. 115·1).
Fever; pain.

Dolo-Esan Periodo Menstrual *Esan, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Dysmenorrhoea.

Dolofar *Medipharm, Chile.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal and joint disorders; pain.

Dolofarma *Maxfarma, Spain.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Dolofast *Bracco, Ital.*
Ibuprofen lysine (p. 68·3).
Musculoskeletal pain; soft-tissue disorders.

Dolofenac
Note: this name may be used for preparations of different composition.
Arlex, Mex.
Diclofenac (p. 48·3).
Inflammation; rheumatism.
Austral, Arg.
Diclofenac sodium (p. 48·3).
Inflammation; pain.
Merck, Indon.
Diclofenac sodium (p. 48·3); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.
Parenteral Drugs, India.
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dolofen-F *Tempo Scan Pacific, Indon.*
Ibuprofen (p. 68·2).
Pain.

Dolofin *Socobom, Belg.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; fever.

Doloflam *Biolab, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; pain.

Doloflam Plus *Vilco, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Doloflam-MR *Vilco, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Dolofort *Astellas, Austria.*
Ibuprofen (p. 68·2).
Pain.

Dolofrix *Penn, Arg.*
Paracetamol (p. 115·1); codeine (p. 40·2).
Pain.

Dolofur *Teva, Mex.†*
Dipyrone (p. 53·3).
Pain; fever.

Dologel
Note: this name may be used for preparations of different composition.
Reddy, India.
Choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).
Reddy, Rus.
Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2); choline salicylate (p. 39·2).
Mouth disorders.

Dologel-CT *Reddy, India.*
Choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2); benzalkonium chloride (p. 1737·1).

Dologen *Kenyaku, Thai.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dologesic
Note: this name may be used for preparations of different composition.
Infinity, Venez.
Ibuprofen (p. 68·2).
Inflammation; pain.

Dologinex *Roemmers Rowe, Venez.*
Clonixin lysine (p. 40·1); pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm.

Dologyne *Arkomedika, Fr.†*
Artemisia vulgaris; chamomile (p. 2474·1).
Pain.

Dolo-Injektopas *Pascoe, Ger.*
Mezereum; verbascum (p. 2645·1); magnesium phosphoricum (p. 1787·3); colocynthis (p. 1833·3); dioscorea villosa (p. 2648·1); chininum arsenicosum (p. 2601·3).
Homoeopathic preparation.

Doloject *Syxyl, Ger.*
Berberis vulgaris (p. 2502·1); colchicum autumnale (p. 607·1); ledum palustre (p. 2550·1).
Homoeopathic preparation.

Dolokam *Cadila, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Doloket *FDC, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; inflammation, pain, and photophobia following ocular surgery; cystoid macular oedema.

Dolo-Ketazon *Recalcine, Chile.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Doloket-O *FDC, India.*
Ketorolac trometamol (p. 80·2); ofloxacin (p. 334·3).

Dolokey *Inkeysa, Spain.†*
Camphor (p. 2466·2); lavender oil (p. 2541·1); methyl salicylate (p. 92·1); expressed mustard oil (p. 2646·1); rosemary oil (p. 2607·3); eucalyptus oil (p. 2501·2); belladonna (p. 2453·3); capsicum (p. 2469·3); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Dolokind *Mankind, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Dolokind Plus *Mankind, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dolokind-AA *Mankind, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dolokind-MR *Mankind, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Dolokoff *Micro, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Dolol *Nycomed, Denm.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolo-Licobion *Berlico Mulia, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.

Dolol-Instant *Takeda, Belg.*
Paracetamol (p. 115·1).
Fever; pain.

Dololup *Lupin, India.*
Piroxicam (p. 125·3).

Dololur *Drossapharm, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Dolomagon *Orion, Ger.*
Dexibuprofen (p. 43·1).
Musculoskeletal and joint disorders; pain.

Dolomate *Jaba Recordati, Port.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Dolomax *Farma, Venez.*
Ketoprofen (p. 79·1).
Pain.

Dolomed
Note: this name may be used for preparations of different composition.
Comed, India.
Suspension; tablets: Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.
Comed, India.
Topical gel: Ibuprofen (p. 68·2); menthol (p. 2553·2); mephenesin (p. 2025·2); methyl salicylate (p. 92·1).

Dolomedil *Kern, Spain.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Dolomed-MR *Comed, India.*
Chlorzoxazone (p. 2022·2); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Dolomed-T *Comed, India.*
Tramadol (p. 139·2).
Pain.

Dolo-Menthoneurin *Nycomed, Austria.*
Diethylamine salicylate (p. 51·3); heparin sodium (p. 1396·3); menthol (p. 2553·2).
Soft-tissue, musculoskeletal, and joint disorders; neuralgia.

Dolomine
Note: this name may be used for preparations of different composition.
Soteks, Rus.
Ketorolac trometamol (p. 80·2).
Pain.

Dolomit *Vis, Pol.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Calcium and magnesium supplement.

Dolomite *Nature's Bounty, USA.*
Dolomite (p. 2497·1).
Dietary supplement.

Dolomo *Astellas, Austria.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Dolomo TN *Astellas, Ger.*
White tablets, aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); blue tablets, aspirin; paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dolomol *Hikma, Rus.†*
Paracetamol (p. 115·1).
Fever; pain.

Dolonase *Medipharm, Chile.*
Ibuprofen (p. 68·2); dipyrone (p. 53·3); chlormezanone (p. 1045·1).
Dysmenorrhoea; musculoskeletal and joint disorders.

Doloneitor *Driburg, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Dolonerv *Gerot, Austria.*
Paracetamol (p. 115·1); vitamin B substances (p. 2102·3).
Pain.

Dolones *Sanbe, Indon.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Dolo-Neurobion
Note: this name may be used for preparations of different composition.
Merck, Indon.
Paracetamol (p. 115·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.
Merck, Mex.
Diclofenac sodium (p. 48·3); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuralgia; neuritis; neuropathy.
Merck, Philipp.
Paracetamol (p. 115·1); vitamin B_1 (p. 2103·2); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; pain.
Merck, Austria.†
Diclofenac sodium (p. 48·3); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3).
Pain; musculoskeletal and joint disorders; neuritis; neuralgia.

Dolo-Neurobionta *Merck, Chile.*
Diclofenac sodium (p. 48·3); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Soft-tissue pain and inflammation.

Doloneuron *Pulse, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).
Neuropathic pain; neuralgia.

Doloneuron-PG *Pulse, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Dolonex *Pfizer, India.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolonil
Note: this name may be used for preparations of different composition.
Lloyd, Philipp.
Paracetamol (p. 115·1).
Pain; fever.
Unique, Thai.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation; pain.

Dolonim *Plus, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Dolo-Niofen *K2Health & Wellness, Chile.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever.

Dolono *RID, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Dolonovag *Gobbi, Arg.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Dolo-Octirona *Laboratorios Chile, Chile.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; musculoskeletal and joint disorders; pain.

Dolo-Pangavit *Church, Mex.*
Diclofenac sodium (p. 48·3); cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Musculoskeletal, joint, and peri-articular disorders; neuritis; neuropathy; pain.

Dolopar *Micro, India.*
Oral drops; suspension; tablets: Paracetamol (p. 115·1).
Pain; fever.
Micro, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dolopas *Norma (Νορμα), Gr.*
Indometacin (p. 71·2).

Dolophine *Roxane, USA.*
⊗Methadone hydrochloride (p. 88·3).
Pain; detoxification and treatment of opioid addiction.

Dolopir *BMW, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Dolopirin C *Amavita, Switz.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

DoloPosterine N *Kade, Ger.*
Cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Doloproct *Bayer, Belg.*
⊗Fluocortolone pivalate (p. 1637·1); lidocaine (p. 1988·1).
Haemorrhoids.
Intendis, Austria; Intendis, Denm.; Jenapharm, Ger.; Intendis, Gr.; Intendis, Hung.; Intendis, Ital.; CSL, NZ; Invida, Philipp.; Intendis, Spain; Bayer, Swed.; Intendis, Turk.; Intendis, Ukr.
⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.
Intendis, Denm.
Rectal cream: ⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2); benzyl alcohol (p. 1739·3).
Anorectal disorders.

Doloprokt *Intendis, Rus.*
⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Dolo-Puren *Actavis, Ger.†*
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Dolopyrin *Aliud, Ger.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Doloquim *Quimica y Farmacia, Mex.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Dolor *Extractum, Hung.†*
Ethylmorphine hydrochloride (p. 56·3); aminophenazone (p. 21·1); phenacetin (p. 124·1).
Pain.

DolorA *Schwarzwalder, Ger.*
Gelsemium (p. 2511·2); spigelia (p. 2621·3); iris (p. 2534·3); cyclamen (p. 2490·2); cimicifuga (p. 2478·1).
Homoeopathic preparation.

Dolorac
Note: this name may be used for preparations of different composition.
Fardi, Spain.
Ibuprofen lysine (p. 68·3).
Inflammation; pain.

Doloral
Note: this name may be used for preparations of different composition.
Atlas, Canad.
⊗Morphine hydrochloride (p. 92·3).
Pain.
Biomiicron, India.
⊗Aceclofenac (p. 16·2); histidine (p. 2072·1); serrapeptase (p. 2613·3).

Doloral P *Biomiicron, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dolorecto *Capsifar, Port.†*
⊗Glycerol (p. 2517·2).
Constipation.

Dolores
Note: this name may be used for preparations of different composition.
Vegemedica, Fr.
Capsules: Salix (p. 129·2); meadowsweet (p. 2550·2); copper (p. 2057·1).
Vegemedica, Fr.
Topical spray: Cedrelopsis grevei oil; arnica (p. 2447·2); aloes (p. 1816·1); eucalyptus citriodora oil.
Muscle and joint pain.
Curtis, Pol.†
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Dolorex
Note: this name may be used for preparations of different composition.
Mecom, Turk.
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Dolorin Cold *Dincsa, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Cold and influenza symptoms.

Dolormin *McNeil, Ger.*
Ibuprofen (p. 68·2), ibuprofen lysine (p. 68·3), or ibuprofen sodium (p. 68·2).
Pain; fever; migraine.

Dolormin mit Ketoprofen *McNeil, Ger.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolormin mit Naproxen *McNeil, Ger.*
Naproxen (p. 98·2).
Pain.

Doloroff-AP *Indoco, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Doloroff-ASP *Indoco, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dolorol *Pharmacare, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Dolorol Forte *Aspen, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Dolorsin *Lafi, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Dolorstad *Stada, Cz.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Dolorsyn *Omega, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Dolorub *Maver, Chile.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Dolorub Capsico *Maver, Chile.*
Capsicum (p. 2469·3).
Pain.

Dolos *Tempo Scan Pacific, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Dolosal *Cristalia, Braz.*
⊗Pethidine hydrochloride (p. 121·3).
Pain; premedication.

Dolosoft *R & D, Mon.*
Devil's claw root (p. 42·3).
Joint pain.

Dolospam *Laboratorios Chile, Chile.*
Atropine sulfate (p. 1310·2); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Dolospan *Emcure, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Dolospasmo *Chemica, Gr.*
Mebeverine hydrochloride (p. 1858·3).

Dolo-Spedifen *Zambon, Switz.*
Ibuprofen arginine (p. 68·2).
Pain; fever.

Dolostat
Note: this name may be used for preparations of different composition.
Blue Cross, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.
Volta, Chile.
Ketoprofen (p. 79·1).
Osteoarthritis; rheumatoid arthritis; pain.

Dolostat-MR *Blue Cross, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Dolostat-PC *Blue Cross, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dolostop
Note: this name may be used for preparations of different composition.
Intermed, Gr.
Nimesulide (p. 101·3).
Inflammatory disorders.
Bayer, Spain.
Paracetamol (p. 115·1).
Pain; fever.

Dolostrip *Ratiopharm, Austria.*
Diclofenac sodium (p. 48·3).
Sports injuries; soft-tissue pain.

Doloswift *Ind-Swift, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Dolotandax *Sandoz, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Pain; fever.

Dolotec *Innotech, Fr.†*
Paracetamol (p. 115·1).
Pain; fever.

Doloteffin *Ardeypharm, Ger.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Doloten *Bago, Chile.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Dolo-Tiaminal *Silanes, Mex.*
Dipyrone (p. 53·3); cyanocobalamin (p. 2107·2); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3).
Neuritis; neuralgia.

Dolotol 12 *Saval, Chile.*
Lysine aspirin (p. 84·3); glycine (p. 2071·2); hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

Dolotral *Stada, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolotram *Pharmaplan, S.Afr.*
Tramadol hydrochloride (p. 139·2).
Pain.
Sun, India.
Tramadol (p. 139·2).
Pain.

Dolotramine *Streuli, Switz.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolotren *Faes, Spain.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolour *Saviour, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Dolour-X *Saviour, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Doloverina *Saval, Chile.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal pain and spasm.

Dolovin *Atral, Port.†*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

DoloVisano M *Kade, Ger.†*
Mephenesin (p. 2025·2).
Skeletal muscle spasm; lumbago; cervical syndrome.

DoloVisano Methocarbamol *Kade, Ger.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Dolo-Voltaren *Novartis, Spain.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Dolowin *Micro, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.
Micro, India.
Topical gel: Aceclofenac (p. 16·2); capsaicin (p. 35·1); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dolowin Forte *Micro, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dolowin Plus *Micro, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dolowin-MR *Micro, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Doloxene *Aspen, Austral.; NordMedica, Denm.†; Aspen, S.Afr.; Meda, Swed.†*
Dextropropoxyphene napsilate (p. 43·3).
Pain.

Doloxene Co *Aspen, S.Afr.*
Dextropropoxyphene napsilate (p. 43·3); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Doloxene-A *Lilly, Braz.*
Dextropropoxyphene napsilate (p. 43·3); aspirin (p. 22·2).
Pain.

Dolozox *Micro, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Dolpar *Esteve, Port.†; Esteve, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolpasse *Fresenius Kabi, Austria.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolpaz *Pasteur, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolphin *Sanovel, Turk.*
Diflunisal (p. 51·3).
Musculoskeletal and joint disorders; pain.

Dolpic Forte *Pasteur, Chile.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome.

Dolpocetmol *Synco, Hong Kong; Synco, Singapore.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Fever; pain.

Dolpoxene *Synco, Singapore.*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.
Synco, Hong Kong.†
Dextropropoxyphene (p. 43·2).
Pain.

Dolprin *Collins, Mex.*
Ibuprofen (p. 68·2).
Fever; pain; juvenile idiopathic arthritis.

Dolprofen *Collins, Mex.†*
Ibuprofen (p. 68·2).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Dolprone *Melisana, Belg.; Sanofi-Aventis, Switz.†*
Paracetamol (p. 115·1).
Pain; fever.

Dolpyc *Teofarma, Ital.*
Capsaicin (p. 35·1).
Musculoskeletal, joint, and soft-tissue pain.

Dolq *Arafarma, Spain.*
⊗Morphine sulfate (p. 92·3).
Pain.

Dolquine *Products & Technology, Spain.*
Hydroxychloroquine sulfate (p. 655·2).
Lupus erythematosus; malaria; rheumatoid arthritis.

Dolriz *Ritz, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dols *Shreshtha, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dols Plus *Shreshtha, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Dolsic *Phapros, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolsin *BB, Cz.*
⊗Pethidine hydrochloride (p. 121·3).
Pain; premedication.

Dolstar *Sanify, India.*
Tramadol (p. 139·2).
Pain.

Dolsten *Medic+Aid, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Doltaque *EG, Fr.†*
Ibuprofen (p. 68·2).
Fever; pain.

Doltarac *Offenbach, Mex.*
Diclofenac (p. 48·3).
Inflammation.

Doltard
Note: this name may be used for preparations of different composition.
Nycomed, Denm.; Nycomed, Pol.
⊗Morphine sulfate (p. 92·3).
Pain.
Ethypharm, Neth.†
Tramadol hydrochloride (p. 139·2).
Pain.

Doltel *Intel, India.*
Tramadol (p. 139·2).
Pain.

Dolten *Pfizer, Arg.*
Ketorolac trometamol (p. 80·2).
Pain.

Doltra *Juste, Spain.*
Ibuprofen (p. 68·2).
Fever; pain.

Doltrahex *Pharmahex, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Doltrix *Maver, Mex.*
Ampoule 1, clonixin lysine (p. 40·1); ampoule 2, hyoscine butylbromide (p. 1845·3).
Smooth muscle pain and spasm.

Dolupérine *Holistica, Fr.*
Curcuma; ginger (p. 1844·1); pepper (p. 2586·1).
Joint disorders.

Dol-u-ron *Neo-Farmaceutica, Port.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Doluvital *Valdecasas, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Dolval *Randall, Mex.*
Ibuprofen (p. 68·2).
Fever; pain.

Dolvan
Note: this name may be used for preparations of different composition.
Gador, Arg.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout; pain; inflammation.
Norma, UK.
⊗Diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms; nasal congestion.

Dolvan Flex *Gador, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint and peri-articular disorders.

Dolven *Eczacibasi, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Dolver *Maver, Mex.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Dolvic *Kaizen, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Dolvifen *Maver, Mex.*
Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ampoule 2, diclofenac sodium (p. 48·3).
Pain; inflammation; neuritis; neuralgia.

Dolviran
Note: this name may be used for preparations of different composition.
Bayer, Port.; Kern, Spain; Bayer, Turk.; Bayer, Venez.
Aspirin (p. 22·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Fever; pain.
Bayer, Mex.
Paracetamol (p. 115·1).
Pain; fever.

Dolviran N *Meda, Ger.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain.

Dolwin *Nortech, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dolwin-T *Nortech, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Dolxen *Maver, Mex.*
Naproxen (p. 98·2).
Inflammation; pain; musculoskeletal and joint disorders.

Dolyzinax *Genepharm, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Dolzam *Zambon, Belg.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dolzy *Hauz, India.*
Diclofenac sodium (p. 48·3).
Pain.

Dolzycam *Sons, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

DOM *Lapi, Indon.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting; hiccups.

Dom *East West, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dom Simecon *Sanitas, Arg.*
Domperidone (p. 1838·1); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastrointestinal motility disorders; nausea and vomiting; gastro-oesophageal reflux.

Doma Grip *Dallas, Arg.*
Guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Domac *Morepen, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domacare *Yacca, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domact *Intra-Labs, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domact-P *Intra-Labs, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domadol *Unichem, India; Unichem, Malaysia; Goldex, S.Afr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Domadol Plus *Unichem, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Domanion *Servier, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Domanion Comp *Servier, Denm.†*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Domar *Eurodrug, Hong Kong; Teofarma, Ital.; Eurodrug, Singapore; Eurodrug, Thai.*
Pinazepam (p. 1097·3).
Anxiety; depression; neuroses; mixed anxiety depressive states; alcoholism; epilepsy; insomnia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dombaz *Zenith, Indon.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting; hiccups.

Dombus *Globus, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domcet *Cipla, India.*
Domperidone (p. 1838·1) or domeperidone maleate (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domci *Dallas, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domcolic *Zydus, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domday *Ordain, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domden *BMW, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domden-P *BMW, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domdon *Bactolac, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dom-DT *Morepen, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domeboro *Advaita, Mex.; Miles, USA.*
Aluminium sulfate (p. 2440·2); calcium acetate (p. 1783·1).
Skin disorders; inflammatory skin conditions.

Domedon *Tempo Scan Pacific, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Domegan *Omega, Rus.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Domel-MT *Intas, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domelong *Inventia, Philipp.*
Pantoprazole sodium (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; nausea and vomiting.

Domenal *Collins, Mex.†*
Dipyrone (p. 53·3).
Fever; pain.

Domenan *Kissei, Jpn.*
Ozagrel hydrochloride (p. 2579·1).
Asthma.

Dome-Paste *Miles, USA.*
⊗Zinc oxide (p. 1729·1); calamine (p. 1697·2); gelatin (p. 1154·1).
Conditions of the extremities requiring protection and support.

Domepraz *Alkem, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domer *Best, Mex.*
Omeprazole (p. 1867·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Domerdon *Asian Pharm, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domerid *Rowex, Irl.*
Domperidone maleate (p. 1838·1).
Nausea; vomiting; upper abdominal discomfort; regurgitation.

Domerit *Ethix, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domeryl *Combiphar, Indon.*
⊗Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); alcohol (p. 1733·1).
Cough; respiratory-tract congestion.

Domes *SoSe, Ital.*
Nimesulide (p. 101·3).
Pain; inflammation.

Domet *Hexpharm, Indon.†; Protech, Rus.*
Domperidone (p. 1838·1).
Nausea; vomiting; hiccups; gastrointestinal motility disorders; dyspepsia.

Dometa
Note: this name may be used for preparations of different composition.
Acdhon, Thai.
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.
Ikapharmindo, Indon.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Domethan *Specifar, Denm.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dometic *Kalbe, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; delayed gastric emptying.

Domevol *Volta, Chile.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia.

Domeway *Armour, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domezol *Moraceae, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domgel *Plus, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Domi
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
Midazolam hydrochloride (p. 1085·1).
Sedative; premedication; induction of anaesthesia.
Duopharma, Singapore.
Midazolam (p. 1085·1).
Sedative; induction of anaesthesia; premedication.
Lincoln, India.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domi-6 *Lincoln, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Domidin *YSP, Malaysia.*
Domiphen bromide (p. 1751·1).
Sore throat.

Domidon *Farmak, Ukr.*
Domperidone (p. 1838·1).
Gastrointestinal motility disorders; nausea and vomiting; gastrointestinal investigations.
Gry, Ger.†
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia.

Domidone *Milano, Thai.†*
Domperidone (p. 1838·1).
Dyspepsia; digestive disorders; gastro-oesophageal reflux; flatulence; hiatus hernia; heartburn; nausea and vomiting.

Domigel *Solfran, Mex.†*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Domiken *Kendrick, Mex.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Domin
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Jpn.
Talipexole hydrochloride (p. 916·2).
Parkinsonism.
Neon, India.
Dopamine hydrochloride (p. 1367·2).
Heart failure.

Domina *Tai Guk, Hong Kong.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Dominadol *Craveri, Arg.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis.

Dominal
Note: this name may be used for preparations of different composition.
Actavis, Indon.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.
Meda, Austria; Meda, Belg.; AWD, Ger.
Prothipendyl hydrochloride (p. 1100·2).
Psychiatric disorders; sleep disorders; pain; pruritus; vomiting; agitation; psychoses.

Dominans *Lundbeck, Ital.*
Nortriptyline hydrochloride (p. 439·3); fluphenazine hydrochloride (p. 1075·1).
Mixed anxiety depressive states.

Domine *Shalaks, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Dominic *Kalbe, Indon.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Dominium
Note: this name may be used for preparations of different composition.
Beta, Arg.
Quetiapine fumarate (p. 1101·1).
Bipolar disorder; schizophrenia.
Tecnofarma, Chile.
Fluoxetine (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder; panic disorder.

Dominox *T Man, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domitil *Bal, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domitrone *Biomedis Oncology, Philipp.*
Mitoxantrone hydrochloride (p. 833·1).
Breast cancer; chronic myeloid leukaemia; non-Hodgkin's lymphoma.

Domi-Up *Lincoln, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Domizol-DS *Macleods, India.*
Domperidone (p. 1838·1); omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domkair *PDC, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domkair-P *PDC, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domlyx *Zytras, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dom-MPS *Morepen, India.*
Domperidone (p. 1838·1); dimeticone (p. 1886·2).

Domne *Raptakos, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domocid *Speciality Meditech, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domocid-PX *Speciality Meditech, India.*
Capsules: Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.
Speciality Meditech, India.
Injection: Pantoprazole (p. 1875·3).

Domol *Miles, USA.*
Bath additive.
Lubrication of the skin; pruritus.

Dom-P *East West, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domp *Community Pharmacy, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; heartburn; dyspepsia; digestive disorders.

Dompan *Medley, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Dompar *Cipla, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domped *Caldem, India; Medispan, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domped-OZ *Medispan, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Dompel *Samnam, Singapore.*
Domperidone (p. 1838·1).
Dyspepsia.

Dompenyl *Korea United, Philipp.*
Domperidone (p. 1838·1).
Nausea and vomiting.

Dompeon *APT, Hong Kong.†*
Domperidone (p. 1838·1).
Dyspepsia; digestive disorders; gastro-oesophageal reflux; flatulence; heartburn; nausea and vomiting.

Domper *Yung Shin, Hong Kong; YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.*
Domperidone (p. 1838·1).
Dyspepsia; gastric distension; nausea; vomiting; gastro-oesophageal reflux; gastrointestinal motility disorders; meteorism.

Domperdone *Polipharm, Thai.*
Domperidone (p. 1838·1).
Dyspepsia; digestive disorders; nausea and vomiting.

Domperi *Ipca, India.*
Domperidone (p. 1838·1).
Digestive disorders; dyspepsia; nausea and vomiting.

Domperid *Hanmi, China.*
Domperidone maleate (p. 1838·1).
Gastrointestinal disorders.

Domperistal *KonTest, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domperitop *Apotex, Belg.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastroparesis.

Domper-M *Bangkok Lab & Cosmetic, Thai.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; delayed gastric emptying.

Domperon *Cadila, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastrointestinal motility disorders.

Domperon Plus *Cadila, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domperone *Dr Zens, Philipp.*
Domperidone maleate (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Domperon-O *Cadila, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Dompesin *Chemopharma, Chile.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastrointestinal motility disorders.

Dompet *Chemo-Drugs, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dompgran *Legrand, Braz.*
Domperidone (p. 1838·1).

Dompliv *EMS, Braz.*
Domperidone (p. 1838·1).

Domp-M *Community Pharmacy, Thai.*
Domperidone maleate (p. 1838·1).
Dyspepsia; digestive disorders; gastro-oesophageal reflux; flatulence; heartburn; peptic ulcer; hiccup; nausea and vomiting; migraine.

Dom-Polienzim *Sanitas, Arg.*
Domperidone (p. 1838·1); lipase (p. 2579·3); amylase (p. 2442·1); protease (p. 2598·1); cellulase (p. 2473·1); simeticone (p. 1886·2).
Gastrointestinal disorders; pancreatic insufficiency.

Dompon *Finecure, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dompon CZ *Finecure, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Dompon F *Finecure, India.*
Domperidone (p. 1838·1); famotidine (p. 1842·1).

Dompon P *Finecure, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Dompra *Magnus, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Dompro *Adley, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dompro-C *Adley, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Domrab *Medley, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Domsedan *Fortbenton, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Domsettler *Lifeon, India.*
Domperidone betadex (p. 1838·1).

Domsi *Sidhbali, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domsin *Helax, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domsin-LA *Helax, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Domsin-O *Helax, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domspas *Psychotropics, India.*
Dicycloverine hydrochloride (p. 1834·2); domperidone (p. 1838·1); paracetamol (p. 115·1).

Domstal *Torrent, India; Torrent, Rus.*
Domperidone (p. 1838·1).
Meteorism; gastroparesis; gastro-oesophageal reflux; nausea; vomiting; hiccups; gastrointestinal motility disorders.

Domstal MPS *Torrent, India.*
Simeticone (p. 1886·2); domperidone (p. 1838·1).

Domstal-CZ *Torrent, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Domstal-O *Torrent, India; Torrent, Rus.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domstal-P *Torrent, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Domstal-RD *Torrent, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domtac *Rapross, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Domtec-P *Technica, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Domtop *Ind-Swift, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Domuderm *Fortbenton, Arg.*
Azulene (p. 2452·1); hamamelis (p. 2523·3).
Skin cleanser.

Domutussina *Proge, Ital.*
Dropropizine (p. 1662·2).
Cough.

Domycine *CCM, Malaysia; Duopharma, Singapore.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Domycotin *Help, Gr.*
⊗Fluprednidene (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections.

Domz *MMC, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Domzole-R *Burgeon, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Don *East African, India.*
Diclofenac (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Don Forte *Crescent, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Don Plus *Crescent, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Dona *Rottapharm, Cz.; Rottapharm, Hung.; Rottapharm, Irl.; Rottapharm, Ital.; Rottapharm, Rus.; Abdi, Turk.; Rottapharm, Ukr.*
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Osteoarthritis; chondromalacia patella; shoulder peri-arthritis.

Madaus, Austria; Madaus, Ger.; Rottapharm, Ger.
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Dona 200-S *Opfermann, Ger.†*
Tablets: Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Donabel *Effik, Spain.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Donaccord *Airflow, NZ.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donaclim *Dergam, Fr.*
Evening primrose oil (p. 2502·2); fish oil (p. 1460·1); vitamins; safranal.
Menopausal disorders.

Donacom *Algol, Norw.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis of the knee.

Madaus, Belg.; Rottapharm, Neth.; Algol, Swed.†
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Donadox *Indeco, Arg.*
Rivastigmine (p. 394·3).
Alzheimer's disease.

Donaflor *Bruno, Ital.*
Lactobacillus acidophilus (p. 2596·3); estriol (p. 2274·3).
Restoration of vaginal flora.

Donagan *TO-Chemicals, Thai.*
Pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Gastrointestinal spasm.

Donalg *Dynacren, Ital.*
Tetracaine hydrochloride (p. 1996·3); sulfogaiacol (p. 1678·1); salicylic acid (p. 1719·1); menthol (p. 2553·2); sage (p. 2608·3); chamomile (p. 2474·1); salix (p. 129·2); ginger (p. 1844·1).
Dental pain.

Donalgin *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Niflumic acid (p. 101·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Donalis *Dergam, Fr.*
Fish oil (p. 1460·1); evening primrose oil (p. 2502·2); vitamins; selenium (p. 2086·3).

Donamet *Abbott, Ital.*
Ademetionine butanedisulfonate (p. 2429·3).
Hepatic cholestasis.

Donamin *Genepharm, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Donaprox *Reuffer, Mex.*
Naproxen (p. 98·2).
Pain.

Donaren *Apsen, Braz.*
Trazodone hydrochloride (p. 451·1).
Depression; neurogenic pain.

Donarot *Rottapharm, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Donarthril *Rafarm, Gr.*
Glucosamine sulfate (p. 2515·3).

Donasure *Gentech, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donataxel *Bioprofarma, Arg.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer; prostatic cancer.

Donatuss DC *Laser, USA.*
Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Donatussin *Laser, USA.*
Syrup: Clofedanol hydrochloride (p. 1659·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, dextromethorphan hydrobromide, and guaifenesin.
Cough.

Laser, USA.
Oral drops: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs.

Donatussin DC *Laser, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs.

Donatussin DM *Laser, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Donaxene *Interbat, Philipp.*
Ketoconazole (p. 585·3).
Fungal infections.

Donaxyl *Abdi, Turk.*
Dequalinium chloride (p. 1749·3).

Donaz *Glenmark, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Done *InnoGen, Philipp.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donecept *Actavis, Hung.; Sun, India; Actavis, Irl.; Actavis, Pol.; Cipla-Medpro, S.Afr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donecleus *Nucleus, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donectil *Valeant, Hung.; ICN, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donegal
Note: this name may be used for preparations of different composition.
Galenus, Gr.
Donepezil hydrochloride (p. 390·2).

Medipharm, Chile.
Domperidone (p. 1838·1).
Gastro-oesophageal reflux; hiccups; nausea; vomiting.

Doneka *Qualigen, Spain.*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Doneka Plus *Qualigen, Spain.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Donelet *Alet, Gr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donelinn *Helsinn Birex, Irl.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donemed *Sun-Farm, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donep *Alkem, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donepes *Richmond, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donepex *Celon, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Doneprion *Orion, Denm.; Orion, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donept *Eisai, Thai.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease; vascular dementia.

Doneratio *Ratiopharm, Denm.†; Ratiopharm, Fin.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donesan *Santa, Gr.*
Donepezil hydrochloride (p. 390·2).

Donespes *Specifar, Denm.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donester *Vocate, Gr.*
Donepezil hydrochloride (p. 390·2).

Donesyn *Vipharm, Hung.; Clonmel, Irl.; Vipharm, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Doneurin *Hexal, Ger.†*
Doxepin hydrochloride (p. 414·2).
Depression; anxiety; withdrawal syndromes.

Donexan *Meprofarm, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; nasal congestion.

Donexan-DX *Meprofarm, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; respiratory-tract congestion.

Donezel *Micro, Philipp.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donezil *Mylan, NZ.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease; vascular dementia.

Dong Gang Tian Le *Xin Donggang, China.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Dong Kang Ming *Dongkang, China.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Dong Quai Complex *Blackmores, Austral.†*
⊗Dong quai (p. 2497·1); avena (p. 2451·1); cimicifuga (p. 2478·1); vitex agnus castus (p. 2432·2); vitamins; minerals.
Menopausal disorders; premenstrual syndrome; uterine cramping.

Dong Yao Qi Rui *Fang Ming, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Dong Yi *Kang Ji Er, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Dongweili *NEGPF, China.*
Levocarnitine (p. 2053·2).
Levocarnitine deficiency.

Donicil *Sigma-Tau, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Doniq *Raymos, Arg.*
Adapalene (p. 1692·1).
Acne.

Donix *Llorens, Spain.*
Lorazepam (p. 1080·3).
Anxiety.

Don-LS *Crescent, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Donmet *Neon, India.*
Metoclopramide hydrochloride (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; gastro-oesophageal reflux.

Don-MR *East African, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Donna
Note: this name may be used for preparations of different composition.
Duopharma, Hong Kong†; CCM, Malaysia.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Donnagel
Note: this name may be used for preparations of different composition.
IQB, Braz.
⊗Metronidazole (p. 936·1); nystatin (p. 590·3); benzalkonium chloride (p. 1737·1); urea (p. 1727·3).
Vulvovaginal infections.

Pfizer Consumer, Austral.
Hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Donnagyl-H *Mission Happiness, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Donnalix *Pfizer Consumer, Austral.*
Hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3).
Gastrointestinal disorders.

Donnamar *Marnel, USA.*
Hyoscyamine sulfate (p. 1848·1).

Donnatab *Pfizer Consumer, Austral.*
Hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3).
Gastrointestinal disorders.

Donnatal *Pharmacare, S.Afr.†; PBM, USA.*
Hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); phenobarbital (p. 535·2).
Irritable bowel syndrome; acute enterocolitis; gastrointestinal disorders; motion sickness; genito-urinary disorders.

Donnox *Microsules, Arg.*
Donepezil (p. 390·2).
Alzheimer's disease.

Donodol *Armstrong, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Donodol Compuesto *Armstrong, Mex.*
Clonixin lysine (p. 40·1); hyoscine butylbromide (p. 1845·3).
Smooth muscle pain and spasm.

Donomix *Laboratorios Chile, Chile.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Fungal skin infections with inflammation.

Donopa *Sol, Neth.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Pain.

Donopez *Alapis, Gr.*
Donepezil hydrochloride (p. 390·2).

Donormyl *UPSA Conseil, Fr.; BMS, Rus.; BMS, Ukr.*
Doxylamine succinate (p. 627·3).
Sleep disorders; insomnia.

Donox *Osoth, Thai.†*
Domperidone (p. 1838·1).
Nausea and vomiting; heartburn; dyspepsia; digestive disorders.

Donpethon *Vipharm, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Donpex *Schafer, Arg.*
Donepezil (p. 390·2).

Donriz *Sanify, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Donset *Daksh, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Donsetron *Emar, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Don't Bug Me *Relax, UK.*
Vitamin B_1 (p. 2102·3); aloe vera (p. 1693·2).
Insect repellent.

Donter *Mintlab, Chile.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Dontisanin *Sanofi-Aventis, Ger.†*
⊗Bromelain (p. 2460·3).
Inflammation.

Dontisolon D *Sanofi-Aventis, Ger.*
⊗Prednisolone (p. 1645·2) or prednisolone acetate (p. 1645·2).
Inflammatory disorders of the mouth.

Dontuxin *Continentales, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Donulide *Rega, Port.*
Nimesulide (p. 101·3).
Pain.

Donum *M & H, Thai.†*
Domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux; heartburn; nausea and vomiting.

Donzeimer *Indeco, Arg.†*
Donepezil (p. 390·2).
Alzheimer's disease.

Dop Due *IP, Ital.*
Potassium (p. 1793·1); magnesium (p. 1786·3).
Potassium and magnesium supplement.

Dopabane *Ariston, Braz.*
Dopamine hydrochloride (p. 1367·2).

Dopaben *Laboratorios Chile, Chile.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dopac *Kalbe, Indon.*
Dopamine hydrochloride (p. 1367·2).
Hypotension; shock; heart failure.

Dopacard
Note: this name may be used for preparations of different composition.
Cephalon, Fr.†; Cephalon, Ger.†; Cephalon, Irl.†; Cephalon, UK.
⊗Dopexamine hydrochloride (p. 1368·3).
Heart failure; adjunct in cardiac surgery.

Piramal, India.
Dopamine (p. 1367·2).
Heart failure.

Dopacef *Chandra Bhagat, India.*
Dopamine (p. 1367·2).
Heart failure.

Dopacis *CIS, Fr.; CIS, Irl.; CIS, Neth.; CIS, Spain.*
Fluorine-18 labelled fluorodopa (p. 2224·1).
Contrast agent for positron emission tomography.

Dopacris *Cristalia, Braz.*
Dopamine hydrochloride (p. 1367·2).

Dopaflex
Note: this name may be used for preparations of different composition.
Baxter, Braz.†
Dopamine (p. 1367·2).
Hypotension; shock; heart failure.

Dopagrand *Ahimsa, Arg.*
Methyldopa (p. 1431·1).
Hypertension.

Dopagyt *Themis, India.*
Methyldopa (p. 1431·1).
Hypertension.

Dopalux *Sandoz, Cz.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Dopam *LBS, Thai.*
Dipotassium clorazepate (p. 1056·3).

Dopamax *Swiss Parenterals, Philipp.*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure; renal failure.

Dopamed
Note: this name may be used for preparations of different composition.
General Drugs, Thai.
Methyldopa (p. 1431·1).
Hypertension.

Dopamet *Medochemie, Hong Kong; Actavis, Indon.; Solvang, Philipp.*
Methyldopa (p. 1431·1).
Hypertension.

Dopametil *Bunker, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Dopamex *Biolab, Thai.*
Dopamine hydrochloride (p. 1367·2).
Shock; hypotension; acute poisoning.

Dopaminex *Abbott, Thai.†*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure.

Dopanis *Neiss, India.*
Dopamine (p. 1367·2).
Heart failure.

Dopaplus *VHB, India.*
Dopamine (p. 1367·2).
Heart failure.

Dopaquel *Accord, S.Afr.*
Quetiapine (p. 1101·1).
Schizophrenia; bipolar disorder.

Dopar
Note: this name may be used for preparations of different composition.
Samarth, India.
Dopamine hydrochloride (p. 1367·2).
Heart failure.

Doparel *Kyorin, Hong Kong.*
Zopiclone (p. 1118·1).
Insomnia.

Doparl *Kyowa, Jpn.†*
Levodopa (p. 902·2).
Parkinsonism.

Dopasian *Asian Pharm, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Dopasol *Shree Ganesh, India.*
Dopamine hydrochloride (p. 1367·2).
Heart failure.

Dopatab *Hovid, Hong Kong.†*
Methyldopa (p. 1431·1).
Hypertension.

Dopatens *Faran, Gr.*
Methyldopa (p. 1431·1).

Dopatral *Austral, Arg.*
Methyldopa (p. 1431·1).
Hypertension.

Dopatropin *Scott-Cassara, Arg.*
Dopamine (p. 1367·2).

Dopegyt *Egis, Cz.; UCB, Ger.; Egis, Hong Kong; Egis, Hung.; Egis, Malaysia; Egis, Pol.; Egis, Rus.; Egis, Thai.†; Egis, Ukr.*
Methyldopa (p. 1431·1).
Hypertension.

Doper *YSP, Thai.†*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Dopergin *Bayer, Austria; Bayer, Ger.; Bayer, Ital.; Bayer, Mex.; Bayer, NZ; Bayer, Spain; Schering, Turk.*
Lisuride maleate (p. 908·2).
Parkinsonism; lactation inhibition; female infertility; acromegaly; amenorrhoea; hyperprolactinaemia; mastitis; premenstrual syndrome; galactorrhoea; prolactinomas; male hypogonadism.

Dopergine *Bayer, Fr.*
Lisuride maleate (p. 908·2).
Menstrual disorders; infertility; galactorrhoea; gynaecomastia in males; parkinsonism; erectile dysfunction.

Dopezil *Ranbaxy, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's dementia.

Dophilin *Taiwan Biotech, Malaysia.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Dopicar *Teva, Israel.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Dopin
Note: this name may be used for preparations of different composition.
Daksh, India.
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ind-Swift, India.
Dosulepin.
Depression.

Union Drug, Thai.
Dopamine hydrochloride (p. 1367·2).
Heart failure.

Dopina *Behrens, Venez.*
Dopamine hydrochloride (p. 1367·2).
Hypotension; shock.

Dopinga *Inga, India.*
Dopamine hydrochloride (p. 1367·2).
Shock.

Dopmin *Orion, Denm.; Orion, Fin.; Orion, Malaysia; Orion, Rus.; Orion, Thai.†; Drogsan, Turk.*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure; adjunct in open heart surgery; hypotension.

Dopnax *Troikaa, Philipp.*
Dopamine hydrochloride (p. 1367·2).
Heart failure.

Dopo Pik *Alckamed, Ital.*
Triclosan (Irgasan 300) (p. 1773·2); trolamine (p. 2634·3); propylene glycol (p. 2205·2).
Skin disinfection.

Dopotril *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Calcipotriol (p. 1697·2).

Dopoxy *Christo, Hong Kong.†*
Dextropropoxyphene (p. 43·2).
Pain.

Doppelherz Aktiv Omega-3 Clean Vessels *Queisser, Ukr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); vitamins.
Cardiovascular disorders.

Doppelherz Cardiovital *Queisser, Rus.*
Crataegus (p. 2488·1).
Heart failure.

Doppelherz Energie Tonikum N *Pharmatika, Hung.*
Vitamin B substances (p. 2102·3); honey (p. 2072·1); invert sugar (p. 2072·3); crataegus (p. 2488·1); valerian (p. 2640·2); lupulus (p. 2546·1).
Tonic.

Doppelherz Energie-Tonikum *Queisser, Cz.†*
Vitamin B substances (p. 2102·3); crataegus (p. 2488·1); valerian (p. 2640·2); lupulus (p. 2546·1).
Tonic.

Doppelherz Energotonik *Queisser, Rus.*
Vitamins; minerals; rutoside (p. 2505·3); choline citrate (p. 2055·2); sea salt (p. 2612·1); honey (p. 2072·1); invert sugar (p. 2072·3); mistletoe (p. 2560·2); St John's wort (p. 449·1); achillea (p. 2427·3); crataegus (p. 2488·1); angelica (p. 2443·3); valerian (p. 2640·2); lupulus (p. 2546·1); bitter orange (p. 2575·3); sage oil (p. 2609·1); rosemary oil (p. 2607·3); melissa oil (p. 2553·2); aromatic infusion; sodium glycerophosphate (p. 2519·2).
Tonic.

Doppelherz Energovital Tonik *Queisser, Pol.†*
Vitamins; minerals; rutoside (p. 2505·3); crataegus (p. 2488·1); St John's wort (p. 449·1); equisetum (p. 2500·1); mistletoe (p. 2560·2); valerian (p. 2640·2); lupulus (p. 2546·1); bitter orange (p. 2575·3); melissa oil (p. 2553·2); sage oil (p. 2609·1); rosemary oil (p. 2607·3).
Tonic.

Doppelherz Energovital Tonik K *Queisser, Pol.*
Crataegus (p. 2488·1); melissa (p. 2552·3); valerian (p. 2640·2); rosemary (p. 2607·2).
Tonic.

Doppelherz Ginseng Aktiv *Queisser, Rus.*
Ginseng (p. 2513·3); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); caffeine (p. 1203·3).
Tonic.

Doppelherz Melissa *Queisser, Rus.*
Melissa (p. 2552·3); angelica (p. 2443·3); cinnamon (p. 2479·2); nutmeg (p. 2573·1); bitter-orange peel (p. 2575·3); citrus fruits peel (p. 2542·3); clove (p. 2481·2).

Doppelherz Nervotonik *Queisser, Rus.*
St John's wort (p. 449·1).
Anxiety; nervous disorders; depression.

Doppelherz Selevit *Queisser, Rus.†*
Selenium yeast (p. 2125·2); vitamins.

Doppelherz Vital Kapseln *Queisser, Pol.†*
Garlic oil (p. 2510·3); ginseng (p. 2513·3); vitamins.
Atherosclerosis; respiratory-tract disorders.

Doppelherz Vitalotonik *Queisser, Rus.*
Crataegus (p. 2488·1); lupulus (p. 2546·1); valerian (p. 2640·2); melissa (p. 2552·3); ginseng (p. 2513·3).
Tonic.

Dopram *Eumedica, Belg.; Meda, Denm.; Meda, Fin.; Genopharm, Fr.; Riemser, Ger.; Wyeth, Gr.; Antigen, Irl.†; Eumedica, Neth.; Meda, Norw.†; Bodene, S.Afr.†; Anpharm, UK; Westward, USA.*
Doxapram hydrochloride (p. 2321·2).
Respiratory depression; respiratory failure.

Doprene *Pharmafabre, Gr.*
⊗Deanol pidolate (p. 2319·1); heptaminol hydrochloride (p. 2525·1).

Dopress
Note: this name may be used for preparations of different composition.
Mylan, NZ.
Dosulepin hydrochloride (p. 414·1).
Depression.

United Biotech, India.
Dopamine hydrochloride (p. 1367·2).
Heart failure.

Doprilamide *Arrow, Austral.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Doproct *Continental Pharma, Thai.*
⊗Hydrocortisone acetate (p. 1640·1); zinc oxide (p. 1729·1); benzocaine (p. 1980·2).
Anorectal disorders.

Dops
Note: this name may be used for preparations of different composition.
Sumitomo, Jpn.
Droxidopa (p. 901·2).
Parkinsonism; orthostatic hypotension.
Hepatoum, Fr.†
Sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2); magnesium hydroxide (p. 1857·2); titanium dioxide (p. 1725·1); magnesium carbonate (p. 1856·2).
Gastrointestinal hyperacidity.

Dopsan *Pond's, Thai.*
Dapsone (p. 281·2).
Dermatitis herpetiformis; leprosy.

Dopyx *RND, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doqua *Sriprasit, Thai.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Dorafem *Fem Care, India.*
Domperidone (p. 1838·1); rabeprazole sodium (p. 1881·1).

Doral *Mitsubishi, Jpn; Questcor, USA.*
Quazepam (p. 1100·3).
Insomnia; premedication.

Doralan *Wermar, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Doralan-Ax *Wermar, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Doralese *Chemidex, UK.*
Indoramin hydrochloride (p. 1410·2).
Benign prostatic hyperplasia.
GSK, Irl.†
Indoramin (p. 1410·2).
Benign prostatic hyperplasia.

Doralgex *Greenpharma, Braz.*
Dipyrone (p. 53·3); orphenadrine (p. 909·2); caffeine (p. 1203·3).

Doralgina *Neo Quimica, Braz.*
⊗Isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Pain; muscle spasm.

Doralin *Menarini, Gr.*
Otilonium bromide (p. 2578·2).
Gastrointestinal smooth muscle spasm; aid in gastrointestinal endoscopy.

Doraliv *Ache, Braz.*
Ibuprofen (p. 68·2).
Fever; pain.

Dora-M *Gentech, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Dorama-neo *Sato, Singapore.*
Calcium chloride (p. 1783·1); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Dry eyes.

Doranbax *Ranbaxy, Mex.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doranic *Helm, Neth.*
Nicorandil (p. 1446·2).
Angina pectoris.

Doran-O *Bestochem, India.*
Injection: Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.
Bestochem, India.
Tablets: Ondansetron hydrochloride (p. 1872·1); ranitidine hydrochloride (p. 1882·1).

Doravit Forte *Laborate, India.*
Thioctic acid (p. 2629·1); carotenoids; lycopene (p. 2546·2); omega-3 fatty acids (p. 1460·1).

Dorbantil *Drugtech, Chile; Recalcine, Chile.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Dorbigot *Nufarindo, Indon.*
Paracetamol (p. 115·1); acetylcysteine (p. 1652·2).
Cough; fever.

Dorcaina *Neo Quimica, Braz.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Dorcal *Candor, India.*
Oral liquid: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.
Candor, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Dorcalor *BA Farma, Port.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Dorcan *Candor, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Dorcan-D *Candor, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Dorciflex *Cifarma, Braz.†*
Dipyrone (p. 53·3); orphenadrine citrate (p. 909·2); caffeine (p. 1203·3).
Pain; muscle spasm.

Dorcol Children's Cold Formula *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Dorcol Children's Cough Syrup *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Dorcol Children's Decongestant *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Dordase-D *Candor, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Dordase-DP *Candor, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dordent *Candor, India.*
⊗Camphor (p. 2466·2); glycerol (p. 2517·2); iodine (p. 2336·3); menthol (p. 2553·2); potassium iodide (p. 2336·3); tannic acid (p. 2625·2); thymol (p. 1772·2).

Dordent-K *Candor, India.*
⊗Potassium nitrate (p. 1766·2).

Doregrippin *Medice, Ger.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Dorehydrin *Sanova, Austria.†*
Codergocrine mesilate (p. 389·2).
Mental function impairment; hypertension; cervical syndrome; migraine and related vascular headache; peripheral vascular disorders.

Do-Re-Me *Intas, India.*
Dosulepin.
Depression.

Dorent *Torrent, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dores *Pyridam, Indon.*
Haloperidol (p. 1077·1).
Psychoses; anxiety.

Doresol *Jelfa, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Doreta *KRKA, Cz.; KRKA, Pol.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Dorfan *Drogsan, Turk.*
Syrup: ⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.
Drogsan, Turk.
Tablets: ⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Respiratory-tract disorders.

Dorfen *Cazi, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Dorfenol *Vitapan, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Dorflan *Cazi, Braz.*
Diclofenac (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Inflammation; pain.

Dorflex *Sanofi-Aventis, Braz.*
Dipyrone (p. 53·3); orphenadrine citrate (p. 909·2); caffeine (p. 1203·3).
Skeletal muscle spasm.

Dorgen
Note: this name may be used for preparations of different composition.
Candor, India.
Vitamin B substances (p. 2102·3); iron (p. 2073·1).
Cazi, Braz.
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dorgex *Greenpharma, Braz.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Dorgil *Hypermarcas, Braz.*
⊗Isometheptene (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).

Doria-F *Zenon, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).

Doriance Solaire *Plantes et Medecines, Fr.†*
Dietary supplement.
Tanning aid.

Doribax *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Ortho, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Thai.; Johnson & Johnson, Turk.; Janssen-Cilag, UK; Shionogi, USA.*
Doripenem (p. 287·2).
Bacterial infections.

Dorical *Legrand, Braz.*
Vitamins; rutoside (p. 2505·3); minerals.
Nutritional supplement.

Doricin *EMS, Braz.*
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine citrate (p. 1203·3).
Skeletal muscle spasm.

Dorico *Sanofi-Aventis, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Doricoflu *Sanitas, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Doricox *Candor, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Doricum
Note: this name may be used for preparations of different composition.
Farmila, Ital.
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Eye, ear, and nose disorders.
Roche, Venez.
Midazolam maleate (p. 1085·2) or midazolam (p. 1085·1).
Sedative.

Doridina *Bunker, Braz.*
⊗Isometheptene hydrochloride (p. 2535·1) or isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Pain.

Doridone *DHA, Hong Kong; DHA, Singapore.*
Domperidone (p. 1838·1).
Nausea and vomiting.

Dorigren *Soma, Braz.*
Ibuprofen (p. 68·2).
Fever; pain.

Dorilax *Ache, Braz.*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3); caffeine (p. 1203·3).
Skeletal muscle spasm.

Dorilen *Legrand, Braz.*
Dipyrone (p. 53·3); adiphenine (p. 2430·3); promethazine (p. 638·2).
Pain.

Doriless *Cifarma, Braz.*
Dipyrone (p. 53·3); promethazine (p. 638·2); adiphenine (p. 2430·3).
Pain; muscle spasm.

Doriman *Vir, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Doriprex *Janssen-Cilag, Rus.*
Doripenem (p. 287·2).
Bacterial infections.

Doris-F *Aronex, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Dorisin *Aspire, UK.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Dorithricin
Note: this name may be used for preparations of different composition.
Medice, Austria; Medice, Ger.; Medice, Hung.; Medice, Singapore.
Tyrothricin (p. 384·1); benzalkonium chloride (p. 1737·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Dorival *Bayer, Spain.†*
Ibuprofen (p. 68·2).
Fever; pain.

Dorixina *Roemmers, Arg.; Rhein, Mex.; Roemmers, Venez.*
Clonixin lysine (p. 40·1).
Pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Dorixina B1 B6 B12 *Roemmers, Arg.*
Clonixin lysine (p. 40·1); thiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Inflammation; pain.

Dorixina Flex *Roemmers, Venez.*
Clonixin lysine (p. 40·1); cyclobenzaprine hydrochloride (p. 2023·1).
Painful smooth muscle spasm.

Dorixina Forte *Roemmers, Arg.*
Injection: Dextropropoxyphene hydrochloride (p. 43·3); dipyrone (p. 53·3).
Pain.
Roemmers, Arg.
Tablets: Clonixin lysine (p. 40·1); dextropropoxyphene napsilate (p. 43·3).
Pain.

Dorixina Relax *Roemmers, Arg.; Rhein, Mex.*
Clonixin lysine (p. 40·1); cyclobenzaprine hydrochloride (p. 2023·1).
Musculoskeletal pain and spasm.

Dorizan *Elpen (Ελτεν), Gr.*
⊗Propranolol hydrochloride (p. 1479·1).

Dorken *UCB, Spain.†*
Dipotassium clorazepate (p. 1056·3); aminohydroxybutyric acid (p. 512·1); pyridoxine hydrochloride (p. 2105·3).
Anxiety disorders; insomnia; epilepsy; behavioural disorders.

Dorlamida *Atlas, Arg.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Dorlamida T *Atlas, Arg.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Dorless *Uniao Quimica, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dorlise *Menarini, Port.*
Frovatriptan succinate (p. 676·2).
Migraine.

Dorlotil *Labatec, Switz.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dorm
Note: this name may be used for preparations of different composition.
Norma (Νορμα), Gr.
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Dormane *Bio-Sante, Canad.*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Formerly contained tilia, passion flower, and valerian.
Nervous disorders.

Dormane Plus *Bio-Sante, Canad.*
Melissa (p. 2552·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Formerly contained tilia, melissa, passion flower, and valerian.
Agitation.

Dormane Tisane *Bio-Sante, Canad.*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Insomnia.

Dormant *Neo Quimica, Braz.*
Midazolam (p. 1085·1).

Dormax *Nobel, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Dormeasan *Bioforce, Swed.; Bioforce, Switz.; Bioforce, UK.*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Insomnia; anxiety; nervous disorders; sleep disorders.

Dormelox *Delta, Braz.*
Meloxicam (p. 86·3).

Dormer 211 *Dormer, Canad.*
Emollient with sunscreens.
Dry skin.

Dormex *Nobel, Canad.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Recalcine, Chile.
Brotizolam (p. 1042·1).
Insomnia.

Dormi *Zenith, Indon.*
Hyoscine butylbromide (p. 1845·3).
Peptic ulcer; smooth muscle spasm.

Dormi Comp *Zenith, Indon.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Dysmenorrhoea; renal colic; biliary colic; gastrointestinal spasm.

Dormicum *Roche, Arg.; Roche, Austria; Roche, Belg.; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Egis, Hung.; Roche, Indon.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.†; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.†; Roche, Turk.*
Midazolam (p. 1085·1), midazolam hydrochloride (p. 1085·1), or midazolam maleate (p. 1085·2).
General anaesthesia; insomnia; premedication; sedative; induction of anaesthesia.

Dormi-cyl L Ho-Len-Complex *Liebermann, Ger.*
Avena sativa (p. 2451·1); coffea (p. 2648·2); lupulus (p. 2546·1); kalium phosphoricum (p. 1790·3); passiflora incarnata (p. 2584·1); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Dormid *Scott-Cassara, Arg.*
Midazolam (p. 1085·1).
Premedication; sedative.

Dormidina *Esteve, Port.; Esteve, Spain.*
Doxylamine succinate (p. 627·3).
Insomnia.

Dormi-Gastreu S R14 *Reckeweg, Ger.*
Avena sativa (p. 2451·1); coffea (p. 2648·2); eschscholzia californica (p. 2466·1); humulus lupulus (p. 2546·1); passiflora incarnata (p. 2584·1); valeriana (p. 2640·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Dormikind *DHU, Ukr.*
Cypripedium pubescens; magnesium carbonicum (p. 1856·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Dormil *Milte, Ital.*
California poppy (p. 2466·1); passion flower (p. 2584·1).
Sleep disorders.

Dormilam *Laboratorios Chile, Chile.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Dormilan *Baliarda, Arg.*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Dormin
Note: this name may be used for preparations of different composition.
Micro, India.
Nitrazepam (p. 1089·1).
Insomnia.

Randob, USA.
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Dorminoctil *Lafi, Chile.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Dormiphen *Lalco, Canad.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Dormiplant
Note: this name may be used for preparations of different composition.
VSM, Belg.†; Marvecs, Ital.; Schwabe, Pol.; Schwabe, Rus.; Schwabe, Spain†; Schwabe, Switz.; Schwabe, Ukr.
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; insomnia; nervous disorders.

Schwabe, Fin.; Schwabe, Neth.; Pharma Hus, Swed.
Valerian (p. 2640·2).
Anxiety; insomnia; sleep disorders; nervous disorders.

Dormiplant Mono *VSM, Belg.*
Valerian (p. 2640·2).
Insomnia.

Dormirax *Burapha, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Dormire *Cristalia, Braz.*
Midazolam hydrochloride (p. 1085·1) or midazolam maleate (p. 1085·2).
Insomnia; premedication.

Dormirel *Cinfa, Spain.*
Doxylamine succinate (p. 627·3).
Insomnia.

Dormium *Uniao Quimica, Braz.*
Midazolam maleate (p. 1085·2).
Sedative.

Dormixal *Demo, Gr.*
Midazolam (p. 1085·1).
General anaesthesia; sedative; premedication.

Dormizol
Note: this name may be used for preparations of different composition.
Duopharma, Philipp.
Midazolam hydrochloride (p. 1085·1).
Premedication; sedative; general anaesthesia.

Sanofi-Aventis, Austral.
Zolpidem tartrate (p. 1116·2).
Insomnia.

Dormodor *Meda, Spain.*
Flurazepam hydrochloride (p. 1076·1).
Insomnia.

Dormodyn *Dunner, Switz.*
Passion flower (p. 2584·1).
Insomnia.

Dormonid *Roche, Braz.*
Midazolam hydrochloride (p. 1085·1) or midazolam maleate (p. 1085·2).
Adjunct in anaesthesia; premedication; sedative; insomnia.

Roche, Chile.
Midazolam (p. 1085·1) or midazolam hydrochloride (p. 1085·1).
General anaesthesia; insomnia; premedication; sedative.

Dormonoct *Sanofi-Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.*
Loprazolam mesilate (p. 1080·2).
Insomnia; premedication.

Dormo-Puren *Actavis, Ger.†*
Nitrazepam (p. 1089·1).
Sleep disorders.

Dormosol *Raffo, Chile.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Dormosyx *Syxyl, Ger.*
Avena sativa (p. 2451·1); passiflora incarnata (p. 2584·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Dormox *Candor, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Dormyl *Gerolymatos, Gr.*
Quazepam (p. 1100·3).

Dornal *Glenmark, Braz.†*
Dipyrone (p. 53·3).
Fever; pain.

Dornalin *Teva, Jpn.*
Beraprost sodium (p. 1316·2).
Occlusive arterial disease; pulmonary hypertension.

Dorner *Astellas, China; Astellas, Indon.; Astellas, Jpn; Astellas, Philipp.; Astellas, Thai.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Dornot *Uniao Quimica, Braz.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Dorofen *Liptis, USA.*
Glucosamine sulfate (p. 2515·3); ginkgo biloba (p. 2512·3).
Intermittent claudication; osteoarthritis.

Dorolad *Verisfield, Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Ocular hypertension; glaucoma.

Dorolid *Domesco, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Dorona *Ducto, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Dorosan *Rottapharm, Cz.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Dorox *M & H, Thai.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Doroxan *Rottapharm, Hong Kong; Rottapharm, Ital.; Rottapharm, Malaysia.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Dorpane *Macrophar, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain; peri-articular disorders; tension headache.

Dorpep *Candor, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).

Dorpiel *Ingens, Arg.*
Tretinoin (p. 1725·2).
Acne.

Dorpinon *Ariston, Braz.†*
Dipyrone (p. 53·3).
Fever; pain.

Dorsal *Silanes, Mex.*
Meloxicam (p. 86·3); carisoprodol (p. 2021·3).
Musculoskeletal and joint disorders.

Dorsamed *World Medicine, Ukr.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Ocular hypertension; glaucoma.

Dorsanol *Multilab, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Dorsedin *EMS, Braz.*
⊗Isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Pain.

Dorsiflex *Lek, Cz.; Will-Pharma, Neth.†; Sandoz, Turk.*
Mephenoxalone (p. 2025·2).
Skeletal muscle spasm; skeletal muscle pain.

Dorsilon *Sandoz, Turk.*
Mephenoxalone (p. 2025·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

Dorsof T *Laboratorios Chile, Chile.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Dorspan Composto *EMS, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Skeletal muscle spasm.

Dortas *Intas, India.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Dortelwestin *Stada, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Dortex *Well, Port.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Dortim *Teva, Irl.; Ursapharm, Neth.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Dor-Timolol *HLB, Arg.*
⊗Dorzolamide (p. 2006·3); timolol (p. 1513·2).
Glaucoma.

Dortsil *Psyco Remedies, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Dortsil-M *Psyco Remedies, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Doryx
Note: this name may be used for preparations of different composition.
Boniscontro & Gazzone, Ital.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Mayne, Austral.; Pfizer, Chile†; Faulding, Singapore†; Warner Chilcott, USA.
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Dorzine *HLB, Chile.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Dorzo Plus T *Stada, Ger.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Dorzol *Oftalmi, Venez.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; intra-ocular hypertension.

Dorzolamid comp *Aliud, Ger.; Ratiopharm, Ger.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Dorzone *Delta, Braz.*
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).
Pain.

Dorzopt *Rompharm, Rus.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Dorzoptic Plus *Cooper (Κοπερ), Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Dorzostill *Bruschettini, Neth.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Bruschettini, Pol.
⊗Dorzolamide (p. 2006·3).
Glaucoma; ocular hypertension.

Dorzotim *Proel, Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).

Dorzo-Vision *OmniVision, Ger.; OmniVision, Switz.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Ocular hypertension; glaucoma.

Dorzox *Cipla, India.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Dorzy *Candor, India.*
⊗Vitamin B substances (p. 2102·3); amylase (p. 2442·1); pepsin (p. 2586·1).

Dorzy DPS *Candor, India.*
Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1).

Dos Dias N *Elea, Arg.*
Injection: Estradiol benzoate (p. 2271·1); hydroxyprogesterone caproate (p. 2285·1).
Amenorrhoea.

Elea, Arg.
Tablets: Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Amenorrhoea.

DOS Softgel *Goldline, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Dosaflex *Richwood, USA.*
Senna (p. 1885·1).
Constipation.

Dosamont *Aledicine, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Dosan *Pacific, NZ.†*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Dosanac *Siam Bheasach, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Dosano *Sandoz, Cz.†*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Dosara *Andromaco, Chile.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Dosara-D *Andromaco, Chile.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dosate *Pharmasant, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux, Zollinger-Ellison syndrome.

Dosatron *Landsteiner, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Dosavastatin *Dosa, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Dosberotec *Boehringer Ingelheim, Ital.*
⊗Fenoterol hydrobromide (p. 1208·2).
Respiratory-tract disorders.

Doscafis *Llorens, Spain.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever; inflammation; musculoskeletal and joint disorders.

Doseptidone *Doctors, Philipp.*
Povidone-iodine (p. 1767·1).
Disinfection.

Doses-O-Son *Realdyme, Fr.*
Bran (p. 1823·3).
Dietary fibre supplement.

Doset Plus *Zee, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Dosier
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Mosapride citrate (p. 1865·2).
Gastro-oesophageal reflux; gastroparesis; dyspepsia; nausea and vomiting.
Casasco, Arg.
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Dosil
Note: this name may be used for preparations of different composition.
Biomedica, India.
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.
Llorens, Spain.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Dosil Enzimatico *Llorens, Spain.*
⊗Doxycycline hyclate (p. 288·2); chymotrypsin (p. 2477·3); trypsin (p. 2635·2).
Bacterial infections.

Dosin *Andromaco, Chile.*
Domperidone (p. 1838·1).
Diabetic gastroparesis; dyspepsia; gastro-oesophageal reflux; nausea; vomiting.

Dosiseptine *Gifrer Barbezat, Fr.; Regen, Switz.†*
Chlorhexidine gluconate (p. 1743·3).
Wound disinfection.

Dosix-F *Orion, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3).
Nausea and vomiting in pregnancy.

Doslax *Raptakos, India.*
Docusate calcium (p. 1836·2).
Constipation.

Dosmin *Remexa, Mex.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Pruritus; urticaria; allergic skin disorders.

Dosodos *Beta, Arg.*
Butamirate citrate (p. 1657·3).
Cough.

Dosoxygénée *Gifrer Barbezat, Fr.*
Hydrogen peroxide (3 per cent) (p. 1755·2).
Wound disinfection.

Dospan Pento *Ivax, Arg.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Dospelin *Medochemie, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dospin *Ajanta, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Dospir *Boehringer Ingelheim, Switz.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Doss
Note: this name may be used for preparations of different composition.
AWD, Ger.
Alfacalcidol (p. 2112·3).
Bone disorders; hypoparathyroidism.
Medichrom, Gr.
Atorvastatin calcium (p. 1309·2).

Dostan
Note: this name may be used for preparations of different composition.
Pfizer, Austral.
Cabergoline (p. 899·3).
Lactation inhibition; hyperprolactinaemia.
Prosel, Philipp.
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Dostein *Carnot, Mex.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Dosteril *Biomep, Mex.*
Lisinopril (p. 1420·3).
Hypertension.

Dostil *Triomed, S.Afr.†*
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Dostineva *Med, Turk.*
Doxazosin mesilate (p. 1369·1).

Dostinex *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Paladin, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, Venez.*
Cabergoline (p. 899·3).
Hyperprolactinaemia; lactation inhibition; pituitary adenoma; prolactinoma; acromegaly.

Dostradixinol *Regiomedica, Neth.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Dosturel *Bros, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dosulfin Bronquial *Investi, Arg.*
⊗Co-trimoxazole (p. 277·3); bromhexine hydrochloride (p. 1656·3); etamivan (p. 2322·2); guaifenesin (p. 1666·2); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Respiratory-tract infections.

Dosulfin Fuerte *Investi, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dotacid *Biomax, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Dotagil *Loeffler, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Dotalsec *Fada, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Dotamin *Neon, India.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Dotarem *Temis, Arg.; Aspen, Austral.; Guerbet, Austria; Guerbet, Belg.; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Hung.; Guerbet, Irl.; Guerbet, Israel; Guerbet, Ital.; Guerbet, Neth.; Guerbet, Norw.; Obex, NZ; Martins & Fernandes, Port.; Guerbet, Rus.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.; Guerbet, Thai.; Guerbet, Turk.; Guerbet, USA; Quifoven, Venez.*
Meglumine gadoterate (p. 1587·1).
Contrast medium for magnetic resonance imaging.

Dotarin *Elder, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Dotarin-MF *Elder, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Dotariv *East African, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Dotbal *Silanes, Mex.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Dotbal-S *Silanes, Mex.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Dotcef *Intel, India.*
Cefixime (p. 240·3).
Bacterial infections.

Doth *Orchid, India.*
Dosulepin.
Depression.

Dothcin *Cinerea, India.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Dothep *Alphapharm, Austral.; Gerard, Irl.; Alphapharm, Malaysia.†*
Dosulepin hydrochloride (p. 414·1).
Depression; mixed anxiety-depressive states.

Dotheris *Symbiosis, India.*
Dosulepin.
Depression.

Dothex *Triton, India.*
Dosulepin.
Depression.

Dothin *Reliance, India.*
Dosulepin.
Depression.

Dothip *Micro, India.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Dothitab *Psyco Remedies, India.*
Dosulepin.
Depression.

Dothrocyn *Yarindo, Indon.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Dotiteva *Teva, Pol.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Dotiz *Verisfield, Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Dotra *Emcure, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Dotra-M *Emcure, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Dotril *Apex, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Dotrim *Yarindo, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dotrin *Sanofi-Aventis, Arg.*
Neomycin sulfate (p. 330·1); hexylresorcinol (p. 1755·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Dotson *Haledew, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Dotur *Sandoz, Austria; Sandoz, Indon.; Sandoz, Pol.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; protozoal infections.
Europharma, Denm.†
Doxycycline (p. 288·1).
Bacterial infections.

Dotvil *Genesis, India.*
Racecadotril (p. 1881·3); *Saccharomyces boulardii* (p. 2596·3).

Double X *Nutrilite, Arg.*
Vitamins; minerals; plant extracts.
Dietary supplement.

Double 'P' Syrup *Universal, Hong Kong.†*
Pholcodine (p. 1675·1); promethazine (p. 638·2).

Double Parrot Brand *Beacons, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Double Strength Children's Tempra *Paladin, Canad.*
Paracetamol (p. 115·1).
Fever; pain.

Double-Action Toothache Kit *Dent, USA.*
Liquid, benzocaine (p. 1980·2); tablets, paracetamol (p. 115·1) (Maranox).

Doublebase *Dermal Laboratories, UK.*
Isopropyl myristate (p. 2190·3); liquid paraffin (p. 2191·2).
Dry skin; pruritus.

Doublecap *Breckenridge, USA.†*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain.

Double-Tussin DM *Reese, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Doulax
Note: this name may be used for preparations of different composition.
Bio-Sante, Canad.
Cascara (p. 1826·1); senna (p. 1885·1).
Constipation.

Douzabox *Denk, Thai.; Sriprasit, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Doval *Innovata, S.Afr.*
Diazepam (p. 1063·2).
Anxiety; depression; premedication; alcohol withdrawal syndrome.

Dovalem *Novag, Mex.*
Ethambutol (p. 296·1).
Tuberculosis.

Dovate *Aspen, S.Afr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Dovavixin *Help, Gr.*
Zipeprol hydrochloride (p. 1680·3).
Cough.

Dove Face *Unilever, Canad.†*
Avobenzone (p. 1695·1); ensulizole (p. 1703·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Dove Fresh Radiance *Unilever, Canad.†*
SPF 8; SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Dove Pro Age *Unilever, Canad.†*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Doven
Note: this name may be used for preparations of different composition.
Eurofarmaco, Ital.
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility.
Vensat, India.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Doveri *Rekah, Israel.†*
Opium (p. 111·3); ipecacuanha (p. 1667·2).
Cough; dyspnoea.

Doverin *Intas, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Dovidin *Anpharm (Ανφαρμ), Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Dovidone *Adley, India.*
Povidone-iodine (p. 1767·1).

Dovizin *Ranbaxy, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dovobet *Leo, Belg.; Leo, Canad.; Leo (Λεο), Gr.; Leo, Irl.; Formenti, Ital.; Leo, Neth.; Adcock Ingram, S.Afr.; Leo, UK.*
⊗Calcipotriol (p. 1697·2); betamethasone dipropionate (p. 1623·3).
Psoriasis.

Dovonex *Leo, Canad.; Paranova, Denm.; Leo (Λεο), Gr.; Leo, Irl.; Teikoku Seiyaku, Jpn; Adcock Ingram, S.Afr.; Leo, UK; Leo, USA.*
Calcipotriol (p. 1697·2).
Psoriasis.

Downtrat *Dosa, Arg.*
⊗Sibutramine (p. 2330·2).
Obesity.

Doxacar *Gerard, Irl.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxacard *Cipla, India.*
Doxazosin (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxacharvi *Disphar, Neth.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxacin *Otto, Indon.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxacor *Hexal, Ger.†; Sandoz, Turk.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxadura *Schein, UK.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxafin *Deva, Turk.*
Desloratadine (p. 625·1).

Doxagal *Teva, Hung.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxagamma *Worwag, Ger.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxagen *Generics, Pol.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxakne *Galen, Ger.*
Doxycycline (p. 288·1).
Acne.

Doxal
Note: this name may be used for preparations of different composition.
CTS, Rus.
Doxycycline hyclate (p. 288·2).
Bacterial infections.
Orion, Fin.
Doxepin hydrochloride (p. 414·2).
Depression; anxiety; insomnia.
Sigma, Braz.
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Vitamin supplement.

Doxaloc *Trima, Israel.†*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxalpha *Alapis, Gr.*
Sodium cromoglicate (p. 1225·3).

Doxamerck *Merck, Turk.*
Doxazosin mesilate (p. 1369·1).

Doxamil *Quimica y Farmacia, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Doxanar *Apogepha, Ger.†*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxane *Rowex, Irl.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxanorm *ICN, Pol.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxapen *Liferpol, Mex.†*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Doxapress *Kwizda, Austria; Micro, India.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxapril *Bago, Arg.*
Lisinopril (p. 1420·3).
Hypertension.

Doxaprost *Uniao Quimica, Braz.*
Doxazosin mesilate (p. 1369·1).

Doxaprostan *Akrikhin, Rus.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxa-Puren *Actavis, Ger.†*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxar
Note: this name may be used for preparations of different composition.
Pharma Nutria, Philipp.
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.
Teva, Pol.
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxaratio *Ratiopharm, Pol.†*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxasin *Fortbenton, Arg.*
Doxazosin (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxasyn *Genthon, Hong Kong.†*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doxat *Universal, Hong Kong.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doxatan *Clonmel, Irl.; Stada, Irl.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxatec *Pentafarma, Port.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Doxatensa *VP, Spain.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxazoflo *Gry, Ger.†*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxcef *Lupin, India.*
Cefpodoxime.
Bacterial infections.

Doxe *TAD, Ger.†*
Doxepin hydrochloride (p. 414·2).
Anxiety disorders; withdrawal syndromes; depression.

Doxedep *La Pharmaceuticals, India.*
Doxepin (p. 414·2).
Depression.

Doxef *Kimia, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Doxel
Note: this name may be used for preparations of different composition.
Clarendon, Irl.
Doxazosin mesilate (p. 1369·1).
Hypertension.
Shantha, India; Nevzat, Turk.
Docetaxel (p. 780·3).
Malignant neoplasms.

Doxemina *Collins, Mex.†*
Hydroxocobalamin (p. 2107·3); thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Neuritis.

Doxetal *Richmond, Arg.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Doxetar *Torrent, India.*
Doxepin hydrochloride (p. 414·2).
Depression.

Doxfil *Shince, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Doxfree *Unichem, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Doxiba *FDC, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Doxibiot *Investi, Arg.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doxibiotic *CTI, Israel.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxican *Azevedos, Port.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Doxicard *Apotex, Hung.*
Doxazosin (p. 1369·1).
Hypertension.

Doxicin *Genexo, Pol.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxicip *Cipla, India.*
Doxycycline (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxiclat *Pierre Fabre, Spain.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxiclav *Aareen, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Doxiclival *Valmor, Venez.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxicon *Vendiz, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxicor *Pharmacore, Indon.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxicrisol *Quimifar, Spain.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxidan *Pharmacia, USA.†*
Delayed-release tablets: Bisacodyl (p. 1821·1).
Constipation.

Doxidol *Savant, Arg.†*
Paracetamol (p. 115·1).
Fever; pain.

Doxifen *Bago, Chile.*
Miconazole nitrate (p. 589·1); tinidazole (p. 949·2).
Balanitis; vaginal infections.

Doxi-Hem *Hemofarm, Rus.*
Calcium dobesilate (p. 2464·3).
Capillary fragility; microangiopathy; venous insufficiency.

Doxil
Note: this name may be used for preparations of different composition.
Alza, Israel; Janssen, USA.
Liposomal doxorubicin hydrochloride (p. 783·1).
AIDS-related Kaposi's sarcoma; breast cancer; ovarian cancer; multiple myeloma.
Merck, Mex.†
Dicloxacillin (p. 286·1).
Bacterial infections.

Doxilan *ATOZ, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxilegrand *Legrand, Braz.†*
Doxycycline (p. 288·1).

Doxilek *Lek, Hung.*
Calcium dobesilate (p. 2464·3).
Chronic venous insufficiency; diabetic retinopathy; haemorrhoids; thrombophlebitis.

Doximal *Cipla-Medpro, S.Afr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doximax Neo *Pfizer, Spain.†*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Doximed *Ratiopharm, Fin.*
Doxycycline (p. 288·1).
Bacterial infections.

Doximon *Zota, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doximycin *Orion, Fin.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxin
Note: this name may be used for preparations of different composition.
Medichem, Indon.†; BioFemme, Philipp.; Asian Pharm, Thai.; The Forty-Two, Thai.
Doxycycline hyclate (p. 288·2).
Bacterial infections.
Intas, India.
Doxepin (p. 414·2).
Depression.

Doxina *Centaur, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxinate
Note: this name may be used for preparations of different composition.
Svizera, India.
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxinate Plus *Svizera, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxine *Mylan, NZ; Pacific, Singapore†; Utopian, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxinin *Inpac, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxinis *Neiss, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Doxinis-CV *Neiss, India.*
Cefpodoxime proxetil (p. 248·1); potassium clavulanate (p. 268·3).
Bacterial infections.

Doxinonflam *Darier, Mex.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxinpac *Inpac, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxi-Om *OM, Port.*
Calcium dobesilate (p. 2464·3).
Vascular disorders.

Doxipil *Psychotropics, India.*
Doxycycline (p. 288·1).
Bacterial infections.
Reig Jofre, Spain.
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxiproct
Note: this name may be used for preparations of different composition.
Abiogen, Ital.
⊗Calcium dobesilate (p. 2464·3); lidocaine hydrochloride (p. 1988·2); dexamethasone acetate (p. 1631·1).
Anorectal disorders.
OM, Cz.; OM, Hung.; OM, Port.; OM, Switz.
Calcium dobesilate (p. 2464·3); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Doxiproct Plus *OM, Cz.; OM, Hung.; Grunenthal, Mex.; OM, Port.; OM, Switz.*
⊗Calcium dobesilate (p. 2464·3); lidocaine hydrochloride (p. 1988·2); dexamethasone acetate (p. 1631·1).
Anorectal disorders.

Doxiprol *Proel, Gr.*
Doxorubicin hydrochloride (p. 783·1).

Doxitab *APT, Hong Kong†; Cipla-Medpro, S.Afr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.
Psyco Remedies, India.
Doxycycline (p. 288·1).
Bacterial infections.

Doxitax *Kocak, Turk.*
Docetaxel (p. 780·3).

Doxiten Bio *Teofarma, Spain.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxiten Enzimatico *Teofarma, Spain.*
⊗Doxycycline hyclate (p. 288·2); chymotrypsin (p. 2477·3); trypsin (p. 2635·2).
Bacterial infections.

Doxithal *Royal, Chile.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxitidin *Vitabalans, Hung.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxitin *Vitabalans, Fin.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxium *Nycomed, Arg.; Ebewe, Austria; Labomed, Chile; Ebewe, Chinat†; OM, Cz.; Sandoz, Hong Kong; Teva, Hung.; Reddy, India; Abiogen, Ital.; OM, Malaysia; Grunenthal, Mex.; Europhta, Mon.; OM, Philipp.; OM,*

Pol.; Johnson & Johnson, S.Afr.†; Esteve, Spain; OM, Switz.; Abdi, Turk.; Leti, Venez.
Calcium dobesilate (p. 2464·3).
Venous insufficiency; diabetic retinopathy; capillary fragility; lymphatic circulatory disorders; retinal circulatory disorders; microangiopathy; haemorrhoids; peripheral vascular disorders; thrombophlebitis; diabetic nephropathy; haemostasis during surgery.

Doxivenil *Biogal-Teva, Hung.†; OM, Switz.†; Leti, Venez.*
Calcium dobesilate (p. 2464·3); dextran sulfate potassium (p. 2492·2).
Venous insufficiency; inflammation.

OM, Port.
Calcium dobesilate (p. 2464·3).
Venous insufficiency; inflammation.

Doxiz *Birz, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Dox-M DT *Moraceae, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Dox-M ST *Moraceae, India.*
⊗Doxycycline (p. 288·1); serrapeptase (p. 2613·3).

Dox-M T Z *Moraceae, India.*
Doxycycline (p. 288·1); tinidazole (p. 949·2); *Lactobacillus sporogenes* (p. 2596·3).

Dox-M-A *Moraceae, India.*
Ambroxol hydrochloride (p. 1654·3); doxycycline (p. 288·1).

Doxma *Hanburys, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Dox-M-OZ *Moraceae, India.*
Doxycycline (p. 288·1); ornidazole (p. 943·1).

Doxobid *Reddy, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Doxobin *Biological E, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Doxobron *Invision, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

DOXO-Cell *Stada, Austria†; Cell Pharm, Ger.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

DOXO-cell *Stada, Port.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxocris *LKM, Arg.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxodin-TR *MMC, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxokebir *Aspen, Arg.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Doxolbran *Phoenix, Arg.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxolem *Zodiac, Braz.; Medicom, Cz.†; Elder, India; Teva, Mex.; Teva, Thai.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxomed *Cipla, India.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxonex *Polpharma, Pol.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Polpharma, Ukr.†
Doxazosin (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Doxonolver *Nolver, Venez.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Doxopeg *Tecnofarma, Chile; Asofarma, Mex.*
Liposomal doxorubicin hydrochloride (pegylated) (p. 783·1).
Ovarian cancer; breast cancer; Kaposi's sarcoma.

Raffo, Arg.; Zodiac, Braz.
Doxorubicin (liposomal) (p. 782·3).
Malignant neoplasms.

Doxorex *Samarth, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Doxorubin *Teva, Belg.†; Chemipharm, Gr.; Khandelwal, India; Pharmachemie, Malaysia; Pharmachemie, Neth.; Asta Medica, NZ; Pharmachemie, Philipp.; Pharmachemie, Thai.; Teva, Thai.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxosafe *HiGlance, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Doxosan *Sanofi-Aventis, Gr.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxotec *Columbia, Mex.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxo-Teva *Med, Turk.*
Doxorubicin hydrochloride (p. 783·1).

Doxotil *Genepharm, Gr.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxovent *Glenmark, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Doxsig *Sigma, Austral.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxsol *Cazi, Braz.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Doxsyn *MDI, S.Afr.†*
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain with tension.

Doxt *Reddy, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxtie *Bioprofarma, Arg.; Armstrong, Mex.†*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxtran *Phoenix, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and soft-tissue disorders; gout.

Doxtran B12 *Phoenix, Arg.*
⊗Diclofenac sodium (p. 48·3); betamethasone (p. 1623·2); vitamin B_{12} (p. 2107·2).
Musculoskeletal, joint, and peri-articular disorders; neuritis; neuropathy.

Doxtran Flex *Phoenix, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Doxtran Gesic *Phoenix, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Peri-articular disorders; dysmenorrhoea.

Doxulip *United Biotech, India.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Doxuran *Sandoz, Braz.*
Doxazosin (p. 1369·1).

Doxure *Unichem, India.*
Doxepin (p. 414·2); menthol (p. 2553·2).

Doxutec *United Biotech, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Doxxo *Pharmahof, Thai.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxy *Ascent, Austral.; Elerte, Fr.; Pharmaniaga, Hong Kong; Vitamed, Israel; Douglas, NZ; Masa, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

S & K, Ger.; USV, India; Pharmachemie, Neth.†
Doxycycline (p. 288·1).
Bacterial infections.

Doxy Comp *CT, Ger.†*
Doxycycline hyclate (p. 288·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Doxy Komb *Meda, Ger.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxy-1 L-DR Forte *USV, India.*
Doxycycline (p. 288·1); *Lactobacillus sporogenes* (p. 2596·3).

Doxy M *Ratiopharm, Ger.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxy Plus *Stada, Ger.†*
Doxycycline hyclate (p. 288·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Doxybene *Ratiopharm, Austria; Ratiopharm, Ukr.*
Doxycycline (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Ratiopharm, Cz.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxycap *McNeil & Argus, India; Hovid, Singapore.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Hovid, Hong Kong.†
Doxycycline (p. 288·1).
Bacterial infections.

Doxycillin *CCM, Malaysia.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxycin *Riva, Canad.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxyclate *TO-Chemicals, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxyclin *Pharmacare, S.Afr.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxycline *General Drugs, Thai.*
Doxycycline (p. 288·1).
Bacterial infections.

Spirig, Switz.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxycom *Community Pharmacy, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxycyclin Al Comp *Aliud, Cz.*
Ambroxol hydrochloride (p. 1654·3); doxycycline hyclate (p. 288·2).
Respiratory-tract infections.

Doxycyl *Aspen, S.Afr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxyderm *Astellas, Austria.*
Doxycycline hyclate (p. 288·2).
Acne.

Doxyderma *Dermapharm, Ger.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxydoc *Docpharm, Ger.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doxydyn *Astellas, Austria.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxyfem-B6 *Fem Care, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxyfene *Adcock Ingram, S.Afr.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain; fever.

Doxyferm *Nordic, Swed.*
Doxycycline (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxyfol *UniOrange, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxyguard *Health Guard, India.*
Doxycycline (p. 288·1); *Lactobacillus sporogenes* (p. 2596·3).

Doxyhexal *Sandoz, Austral.; Hexal, Austria†; Hexal, Cz.; Hexal, Ger.†; Hexal, S.Afr.†*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Doxyhof *Pharmahof, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxy-HP *Riemser, Ger.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doxyla B6 *Maneesh, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxyla B6 Plus *Pure Health, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxylag *Lagap, Switz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxylar *Sandoz, UK.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxylcap *Bangkok Lab & Cosmetic, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxyleb *Leben, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxylets *SMB, Belg.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxylic *Active, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Doxylin *LCH, Hong Kong†; Actavis, Norw.*
Doxycycline (p. 288·1).
Bacterial infections.

Alphapharm, Austral.; Dexcel, Israel; TP, Thai.
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxylin-DT *Moraceae, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxyline *Yung Shin, Singapore.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxylin-TZ *Moraceae, India.*
Doxycycline (p. 288·1); tinidazole (p. 949·2).

Doxylis *Expanscience, Fr.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxylyn *Westfield, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxy-M *Ratiopharm, Ukr.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxyman *T Man, Thai.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxymed *Medicpharma, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxymono *Betapharm, Ger.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doxymycin *Yung Shin, Hong Kong; YSP, Malaysia; Lennon, S.Afr.†; Beacons, Singapore.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Doxyn *Active, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxy-N-Tablinen *Winthrop, Ger.†*
Doxycycline (p. 288·1).
Bacterial infections.

Doxy-P *PP Lab, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxypal-DR *Jagsonpal, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxypalu *Biorga, Fr.*
Doxycycline (p. 288·1).
Malaria.

Doxypharm *Praxipharm, Hung.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxyprotect *PannonPharma, Hung.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxyratio M *Ratiopharm, Pol.*
Doxycycline (p. 288·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Doxyric *Euphoric, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxyril *Reliance, India.*
Doxepin (p. 414·2).
Depression.

Doxysol *Sandoz, Switz.*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Doxystad *Stada, Austria.*
Doxycycline (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxytab *Pro Doc, Canad.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Socobom, Belg.
Doxycycline (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Doxytet *MDI, S.Afr.*
Doxycycline hyclate (p. 288·2).

Doxytex *Centurion, USA.*
Doxylamine succinate (p. 627·3).

Doxytop *Overseas, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Doxytrex
Note: this name may be used for preparations of different composition.
Sanobia, Port.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Unipharma, Gr.
Calcium dobesilate (p. 2464·3).
Capillary disorders.

Doxy-Wolff *Wolff, Ger.†*
Doxycycline (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Doycur *Biomep, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Doyle
Note: this name may be used for preparations of different composition.
Raffo, Arg.
Azithromycin (p. 221·2).
Bacterial infections.

Sawai, Jpn.
Aspoxicillin (p. 220·3).
Bacterial infections.

Dozee *Zee, India.*
Drotaverine (p. 2497·3) or drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Dozee-M *Zee, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Dozefol *Upsifarma, Port.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Dietary supplement.

Dozeneurin *Sigma, Braz.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1).
Vitamin B_1 and B_{12} deficiency.

Dozept *Rowex, Irl.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Dozic
Note: this name may be used for preparations of different composition.
Raffo, Arg.
Risperidone (p. 1103·2).
Psychoses.

Rosemont, UK.
Haloperidol (p. 1077·1).
Psychoses; anxiety; intractable hiccup; nausea and vomiting; motor tics.

Dozilax *Bennett, Gr.*
Donepezil hydrochloride (p. 390·2).

Dozile *Key, Austral.; Wilson, NZ.*
Doxylamine succinate (p. 627·3).
Insomnia.

Dozile Natural *Key, Austral.*
Valerian (p. 2640·2).
Insomnia.

Dozol *Rice Steele, Irl.; Typharm, UK.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Pain; fever; cold and influenza symptoms; sleeplessness.

Dozone *Ozone, Cz.†; Ozone, Hung.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Dozozin *Umeda, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Dozra *Novagen, S.Afr.*
Zidovudine (p. 1024·2).

Dozyl *Abdi, Turk.*
Donepezil hydrochloride (p. 390·2).

DP
Note: this name may be used for preparations of different composition.
Douglas, NZ.
Liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry skin; pruritus.

DP Barrier Cream *Douglas, NZ.†*
Dimeticone (p. 2209·3).

DP Gesic *Cadila, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

DP Gesic MR *Cadila, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

DP Hand Rub *Douglas, NZ.†*
Chlorhexidine (p. 1743·2).
Skin disinfection.

DP Hydrocortisone *Douglas, NZ.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

DP Lotion - HC *Douglas, NZ.*
⊗Hydrocortisone (p. 1640·1); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Skin disorders.

DP Lubricating Gel *Douglas, NZ.*
Lubricating gel.

D-Pam *Douglas, NZ.*
Diazepam (p. 1063·2).
Anxiety; sedative; skeletal muscle spasm.

Dpazox *Saga, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

DPC *Sunij, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

DPCA *Fresenius Medical, Fr.*
Sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3); with or without potassium chloride (p. 1793·2) (p. 1778·2).
Peritoneal dialysis.

Fresenius Medical, Switz.
Glucose (p. 2068·3); electrolytes (p. 1775·1); with or without potassium (p. 1793·1) (p. 1778·2).
Peritoneal dialysis.

DP-Cipro *Douglas, NZ.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

D-Penamine *Alphapharm, Austral.; Mylan, NZ.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; Wilson's disease; heavy metal poisoning; cystinuria.

DPF *Madhav, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

DPF-OD *Corona, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

DPH *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

DPH with Calamine *Frankin, Hong Kong.†*
Calamine (p. 1697·2); cetrimide (p. 1742·1); diphenhydramine (p. 626·1).
Pruritus.

DPM-2 *Biosciences Pharmakon, India.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

DPN *Alclin, S.Afr.†*
Nadide (p. 2567·1).
Drug addiction; alcoholism.

D-Pressin *United Biotech, India.*
⊗Desmopressin (p. 2355·1) or desmopressin acetate (p. 2355·1).
Diabetes insipidus; renal function testing; nocturnal enuresis; von Willebrand's disease; multiple sclerosis associated nocturia.

D-Protin *British Biologicals, India.*
Preparation for enteral nutrition.

DP-Spas *Speciality Meditech, India.*
Diclofenac sodium (p. 48·3) or diclofenac potassium (p. 48·3); dicycloverine hydrochloride (p. 1834·2).

DP-Spas DPS *Speciality Meditech, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

DPT, DT COQ *Sanofi Pasteur, Philipp.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DQM *Pharmaniaga, Malaysia.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Dr Amin *Eurolab, Arg.*
Dimenhydrinate (p. 625·2).
Vertigo; motion sickness.

Dr Dermi-Heal *Quality Formulations, USA.*
Allantoin (p. 1693·1); zinc oxide (p. 1729·1); peru balsam (p. 2587·1); castor oil (p. 2472·1).
Skin disorders.

Dr Edwards Olive *Oakhurst, USA.*
Sennosides (p. 1885·2).
Constipation.

Dr Einst Gold *K2 Health & Wellness, Chile.*
Docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Dr Einstein Mama *K2 Health & Wellness, Chile.*
Docosahexaenoic acid (p. 1460·1).
Dietary supplement in pregnancy and lactation.

Dr Jacobson Cough Syrup *Vickmans, Hong Kong.†*
Guaifenesin (p. 1666·2); noscapine (p. 1670·3); phenylephrine (p. 1672·2).
Cough.

Dr Johnsons Nit & Lice *MPM, UK.*
Melaleuca oil (p. 2551·1); azadirachta (p. 2451·2).
Pediculosis.

Dr Koff *Intas, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).

Dr Mackenzies Veinoids *SA Druggists Self Med, S. Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

Dr Niedermaier Herztonikum *Niedermaier, Ger.†*
Crataegus (p. 2488·1).
Cardiovascular disorders.

Dr Reckeweg *Reckeweg, Cz.†*
A range of homoeopathic preparations.
Homoeopathic preparation.

Dr Rentschler Hustenloser *Rentschler, Cz.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Dr Rentschler Hustenstiller *Rentschler, Cz.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dr. Scheffler Bergischer Kräutertee Blasen- und Nierentee *Scheffler, Ger.†*
Birch leaf (p. 2457·3); java tea (p. 2536·3); solidaga virgaurea (p. 2620·1).
Urinary-tract disorders.

Dr Scheffler Bergischer Kräutertee Husten- und Bronchialtee *Scheffler, Ger.*
Thyme (p. 2630·2); primula root (p. 2596·2).
Respiratory-tract congestion.

Dr. Scheffler Bergischer Kräutertee Nerven- und Beruhigungstee *Scheffler, Ger.†*
Melissa (p. 2552·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Dr Scholl's *Schering-Plough, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Dr Scholl's Athlete's Foot *Schering-Plough, Canad.; Schering-Plough, USA.*
Tolnaftate (p. 596·1).
Tinea pedis.

Dr Scholl's Callus Removers *Schering-Plough, USA.*
Salicylic acid (p. 1719·1).

Dr Scholl's Clear Away *Schering-Plough, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Dr Scholl's Corn Removers *Schering-Plough, USA.*
Salicylic acid (p. 1719·1).

Dr Scholl's Corn/Callus Remover *Schering-Plough, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Dr Scholl's Cracked Heel Relief *Schering-Plough, USA.*
Lidocaine (p. 1988·1).

Schering-Plough, Canad.†
⊗Benzalkonium chloride (p. 1737·1); lidocaine (p. 1988·1); urea (p. 1727·3).

Dr Scholl's Wart Remover *Schering-Plough, USA.*
Salicylic acid (p. 1719·1).

Dr Selby *Sidus, Arg.*
Zinc oxide (p. 1729·1); vitamin D (p. 2112·3); wool fat (p. 2219·3); talc (p. 1722·2).
Burns; wounds; skin disorders.

Dr Smiths *Beta, USA.*
Zinc oxide (p. 1729·1).
Skin disorders.

Dr Smyle *Kopran, India.*
Syrup: ⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Kopran, India.
Tablets: Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Dr Theiss Gripp Drops *Naturwaren, Ukr.†*
Aconite (p. 2428·3); baptisia (p. 2647·2); eupatorium perfoliatum (p. 2459·1); iron phosphate (p. 2077·1); gelsemium evergreen (p. 2511·2).
Homoeopathic preparation.

Dr Theiss Nasal Spray *Naturwaren, Ukr.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis media; nasal congestion.

Dr Theiss Ringelblumen Salbe *Naturwaren, Cz.†*
Calendula (p. 2465·2).
Infected skin ulcers.

Dr Theiss Schweden Krauter *Naturwaren, Cz.†*
Aloes (p. 1816·1); camphor (p. 2466·2); gentian (p. 2512·1); rhubarb (p. 1884·2); myrrh (p. 2566·1); senna (p. 1885·1); angelica (p. 2443·3); zedoary; manna (p. 1858·2); carlinae; saffron (p. 2208·2).
Constipation.

Dr Theiss Schwedenbitter *Naturwaren, Cz.†*
Aloes (p. 1816·1); rhubarb (p. 1884·2); cimicifuga (p. 2478·1); cinnamon (p. 2479·2); cardamom (p. 2471·1); angelica (p. 2443·3); valerian (p. 2640·2); myrrh (p. 2566·1); zedoary; dictamini alba; gentian (p. 2512·1); carlina; camphor (p. 2466·2); tormentil (p. 2633·2); castorei; polyporus officinalis; mace (p. 2547·3); senna (p. 1885·1); nutmeg (p. 2573·1); saffron (p. 2208·2); calamus (p. 2464·2).
Constipation; rheumatism.

Dr Wiemanns Rheumatonikum *Beethoven, Ger.†*
Birch leaf (p. 2457·3); salix (p. 129·2); devil's claw root (p. 42·3); heisteria.
Musculoskeletal and joint disorders.

Dr Williams Pink Pills *Mentholatum, S.Afr.†*
Ferrous sulfate (p. 2062·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2).
Tonic.

Dr Wolff's acne attack *Wolff, Ger.*
Glycolic acid (p. 1704·3).
Acne.

Drab *Reddy, India.*
Diclofenac (p. 48·3); rabeprazole (p. 1881·1).

D-Rabibit *Cubit, India.*
Dexrabeprazole (p. 1881·1).

D-Rabibit-D *Cubit, India.*
Dexrabeprazole (p. 1881·1); domperidone (p. 1838·1).

Dracanyl *Orifarm, Denm.†; AstraZeneca, Gr.*
⊗Terbutaline sulfate (p. 1228·1).
Asthma; obstructive airways disease.

Dracenax *Sandoz, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

DracoAlgin *Draco, Ger.*
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Wounds.

DracoFoam *Draco, Ger.*
Polyurethane foam (p. 1718·1).
Wounds.

DracoHydro *Draco, Ger.*
Carmellose (p. 2175·1).
Wounds.

Dracone *Vitarum, Arg.†*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).

DracoTüll *Draco, Ger.*
Hydrogel dressing.
Wounds.

Drafen *Continentales, Mex.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; atopic eczema.

Drafilyn-Z *Zafiro, Mex.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Drag-D *Gentech, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Dragées aux figues avec du séné *Zeller, Switz.*
Fig (p. 1843·2); senna (p. 1885·1); butterbur (p. 2463·2).
Constipation.

Dragées contre les maux de voyage *Dropa, Switz.†*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Motion sickness.

Dragées Fuca *Hepatoum, Fr.*
Frangula bark (p. 1843·3); cascara (p. 1826·1); bladderwrack (p. 2612·1).
Constipation.

Dragées pour le coeur et les nerfs *Zeller, Switz.*
Crataegus (p. 2488·1); passion flower (p. 2584·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Nervous disorders.

Dragées pour la detente nerveuse *Zeller, Switz.†*
Butterbur (p. 2463·2); valerian (p. 2640·2); passion flower (p. 2584·1); melissa (p. 2552·3).
Nervous disorders.

Dragées pour la détente nerveuse et le sommeil *Phytopharma, Switz.†*
Passion flower (p. 2584·1); valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3).
Nervous disorders; sleep disorders.

Dragées S pour les reins et la vessie *Hanseler, Switz.*
Birch leaf (p. 2457·3); solidago virgaurea (p. 2620·1); bearberry (p. 2453·2).
Urinary-tract disorders.

Dragées sedatives Dr Welti *Welti, Switz.*
Valerian (p. 2640·2); lupulus (p. 2546·1); crataegus (p. 2488·1).
Sleep disorders; nervous disorders.

Dragées Végétales Rex *Lehning, Fr.*
Frangula bark (p. 1843·3); cascara (p. 1826·1).
Constipation.

Dragon Balm *Peter Black, UK.*
Camphor (p. 2466·2); menthol (p. 2553·2); turpentine oil (p. 2636·3); nutmeg oil (p. 2573·2); eucalyptus oil (p. 2501·2); cassia oil (p. 2471·3); pine oil (p. 2591·1); thymol (p. 1772·2); guaiacol (p. 1666·1); peru balsam (p. 2587·1).
Muscular aches.

Dragon Massage Cream *Mediline, Israel.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); capsicum (p. 2469·3).
Musculoskeletal and joint disorders.

Dragon Plaster *Kurtsan, Israel.*
Capsicum (p. 2469·3).
Musculoskeletal and joint disorders.

Dragotab *KB, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; diabetes insipidus.

Dragul *Biomed, Spain.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Drainactil *H2 Pharma, Fr.†*
Boldo (p. 2458·3); birch leaf (p. 2457·3); black currant leaf (p. 2458·1).
Gastrointestinal disorders; kidney disorders.

Draineur *Ecopharma, Chile.*
Green tea (p. 2648·2); Yunnan tea; maté (p. 2648·2); guarana (p. 2648·2); fennel (p. 2503·2); celery (p. 2472·3); barley; grapefruit; radicchio (p. 2475·2); kola (p. 2648·2).
Obesity.

Drainuryl *Erjean, Fr.*
Green tea (p. 2648·2); taraxacum (p. 2625·3); meadowsweet (p. 2550·2); couch-grass (p. 2487·2); cherry.
Water retention.

Dralen *Specifar, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Dralitem *Raffo, Arg.; Tecnofarma, Chile.*
Temozolomide (p. 865·2).
Glioblastoma multiforme; anaplastic astrocytoma.

Dramamine *Johnson & Johnson, Arg.; Pfizer Consumer, Austral.†; Pfizer, Braz.†; RPG, India; Soho, Indon.; Pfizer, Malaysia†; Johnson & Johnson Consumer, Mex.; Pharmacia, NZ†; Pfizer Consumer, Singapore†; Johnson & Johnson, Thai.†; Ali, Turk.; Upjohn, USA.†*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; motion sickness; vertigo; vestibular disorders; Ménière's disease; radiation sickness.

Dramamine Less Drowsy Formula *McNeil Consumer, USA.*
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Dramanate *Pasadena, USA.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Dramasine *Soho, Indon.*
Dimenhydrinate (p. 625·2); vitamin B_6 (p. 2105·3).
Motion sickness; nausea and vomiting; vestibular disorders.

Dramelin *Wescrib, Philipp.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Dramigel *Drug Research, Ital.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Dramin *Nycomed, Braz.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Dramin B6 *Nycomed, Braz.*
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting; vestibular disorders; motion sickness.

Dramin B6 DL *Nycomed, Braz.*
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3); glucose (p. 2068·3); fructose (p. 2068·2).
Nausea and vomiting; vertigo.

Dramina *Jadran, Rus.; Jadran, Ukr.*
Dimenhydrinate (p. 625·2).
Motion sickness; vestibular disorders; Meniere's disease.

Draminal *Confar, Port.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo.

Draminate *RPG, India.*
Dimenhydrinate (p. 625·2).
Formerly known as Dramnate.
Vertigo; Ménière's syndrome; nausea and vomiting.

Dramine
Note: this name may be used for preparations of different composition.
Suphong, Thai.
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; Ménière's disease.

Uriach, Spain.†
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Dramion *Stroder, Ital.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Dramit-GB *Nafar, Mex.*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo.

Dranat *Remedina, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Dranolis *Rafarm, Gr.*
⊗Pindolol (p. 1470·1).

Drapix *Doctum, Gr.*
Povidone-iodine (p. 1767·1).
Disinfection.

Drapolen *GSK, Ukr.*
Benzalkonium chloride (p. 1737·1); cetrimide (p. 1742·1).
Nappy rash; urinary rash; minor burns.

Drapolene *Chefaro, Irl.; GSK, Malaysia; GSK, Philipp.; GSK, Rus.; GSK, Singapore; GSK, Thai.; GSK, Turk.†; Chefaro, UK.*
Benzalkonium chloride (p. 1737·1); cetrimide (p. 1742·1).
Minor wounds and burns; nappy rash; skin irritation caused by urine; prickly heat; cradle cap; skin disorders.

Farmoquimica, Braz.; GSK, China.
Benzalkonium chloride (p. 1737·1); cetrimonium bromide (p. 1742·3).
Skin disorders; barrier preparation; nappy rash; perianal dermatitis; burns; sunburn.

Draspir *Faran, Gr.*
Lysine aspirin (p. 84·3).

Drastirel *Unipharma, Gr.*
Ketoprofen (p. 79·1).
Inflammatory disorders.

Drat-MF *Madhav, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Draverex *IMO, Ital.*
Frangula (p. 1843·3); cascara (p. 1826·1).
Constipation.

Dravom *Specifar, Gr.*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; vertigo.

Dravyr *Drug Research, Ital.; Drug Research, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Draxil *Kener, Mex.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

DraxMibi *Draximage, Neth.*
Technetium-99m sestamibi (p. 2228·1).
Diagnosis and location of myocardial infarction; evaluation of ventricular function; diagnosis of breast cancer; diagnosis of hyperparathyroidism.

Draxmibi *Draximage, Irl.*
Tetrakis(2-methoxyisobutylisonitrile)copper(I) tetrafluoroborate.
For reconstitution with Tc-99m sodium pertechnetate.
Myocardial perfusion scintigraphy; assessment of ventricular function; breast scintigraphy; localisation of hyperfunctioning parathyroid tissue.

Guerbet, Ger.†
Technetium-99m sestamibi (p. 2228·1).
Diagnosis of myocardial ischaemia; assessment of left ventricular function; diagnosis of breast cancer; thyroid imaging.

Drayacol DX *Parggon, Mex.*
Guaifenesin (p. 1666·2); dextromethorphan (p. 1660·1).
Cough.

Drazine *Pharmasant, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; anxiety; motion sickness.

Dreams *IFA, Mex.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Dreamvite *Metro, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3); zinc sulfate (p. 2126·2); taurine (p. 2626·2); docosahexaenoic acid (p. 1460·1); chlorella growth factor (p. 2475·3).
Dietary supplement for children.

Dreemon *Peach, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Dreico *Dosa, Arg.*
Zoledronic acid (p. 1192·3).

Dreierlei *Hofmann & Sommer, Ger.*
Valerian (p. 2640·2); mint oil (p. 2560·1).
Digestive disorders.

Dreisacarb *Brady, Austria; Teva, Ger.*
Calcium carbonate (p. 1824·3).
Calcium supplement; hyperphosphataemia.

Dreisafer *Teva, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

DreisaFol *Teva, Ger.*
Folic acid (p. 2063·1).
Folic acid deficiency; megaloblastic anaemia.

Dreisavit *Brady, Austria.*
Vitamins.

Dreisavit N *Teva, Ger.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin deficiency.

Drelle *Sandoz, Spain.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Drenalin *Ariston, Braz.*
⊗Adrenaline (p. 1292·1).

Drenatan *Germed, Braz.*
Latanoprost (p. 2008·1).

Drenex *United American, Philipp.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Drenidra *Cazi, Braz.*
⊗Chlortalidone (p. 1335·2).
Hypertension.

Dreniformio *Biolab Sanus, Braz.*
⊗Fludroxycortide (p. 1635·2); clioquinol (p. 273·1).
Skin disorders.

Drenison *Biolab Sanus, Braz.*
⊗Fludroxycortide (p. 1635·2).
Skin disorders.

Drenison N *Biolab Sanus, Braz.*
⊗Fludroxycortide (p. 1635·2); neomycin sulfate (p. 330·1).
Skin disorders.

Dren'it *Marfarma, Ital.*
Pineapple; urtica (p. 2639·3); java tea (p. 2536·3); ruscus.
Nutritional supplement.

Drenocol *Lanpharm, Arg.*
Magnesium sulfate (p. 1787·3); boldo (p. 2458·3); peptone (p. 2086·2); liquorice (p. 1853·2).
Biliary-tract disorders.

Drenoflux *Zeler, Port.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2); sodium benzoate (p. 1738·2).
Cough; respiratory-tract congestion.

Drenogrip *Belfar, Braz.*
Dipyrone (p. 53·3); caffeine (p. 1203·3); chlorphenamine (p. 620·3).

Drenol *Pfizer, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Diabetes insipidus; hypertension; oedema; renal calculi.

Drenoxol *Vitoria, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Drenural *Grossman, Mex.*
⊗Bumetanide (p. 1329·1).
Oedema; hypertension; premenstrual syndrome.

Drep *DWD, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2); lidocaine hydrochloride (p. 1988·2).

Drepatil *Fada, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension.

Dresplan *Smaller, Spain.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder.

Dretacen *Sandoz, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Dretine *Teva, Denm.; Teva, Irl.; Teva, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Dretinelle *Teva, Irl.; Teva, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets
Combined oral contraceptive.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Drex *PC India, India.*
⊗Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); pseudoephedrine (p. 1676·1).

Drex Exp *PC India, India.*
⊗Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2); pseudoephedrine (p. 1676·1).

Drexabion *Eadriex, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuritis; neuropathy; alcoholism; neuralgia.

Drexabion OB *Eadriex, Philipp.*
Vitamin B substances (p. 2102·3); ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron-deficiency anaemia.

Drexel *Elmor, Venez.*
Nimesulide (p. 101·3).
Inflammation; pain.

Drez *Stedman, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Drez-S *Stedman, India.*
Chlorhexidine acetate (p. 1743·2); sulfadiazine silver (p. 362·3).

Drez-V *Stedman, India.*
Metronidazole (p. 936·1); miconazole (p. 588·3).

Dr-Fischer Pharma-Gel *Mediline, Israel.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Driclor *Stiefel, Austral.; Stiefel, Fr.; Stiefel, Hong Kong; Stiefel, Irl.†; Stiefel, Malaysia†; Stiefel, Philipp.; GSK, S. Afr.; GSK, Singapore; GSK Consumer, UK.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Dridase *Sanofi-Aventis, Ger.; Nycomed, Neth.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity; neurogenic bladder.

Dridol *ProStrakan, Norw.; ProStrakan, Swed.*
Droperidol (p. 1072·1).
Nausea and vomiting; neuroleptanalgesia.

Dri/Ear *Pfeiffer, USA.*
⊗Isopropyl alcohol (p. 1758·3); glycerol (p. 2517·2).
Formerly contained boric acid and isopropyl alcohol.
Ear disorders.

Drifen *Richmond, Arg.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Driges *Grisi, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

DriHist *Prasco, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Driken *Kendrick, Mex.†*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Drilix *Be-Tabs, S.Afr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Drill
Note: this name may be used for preparations of different composition.
Rovafarm, Arg.; Pierre Fabre, Cz.; Pierre Fabre Sante, Fr.; Pierre Fabre, Hung.†; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, Rus.†
Chlorhexidine gluconate (p. 1743·3); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Pierre Fabre, Hung.
Oral solution: Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Pierre Fabre, Hung.†
Syrup: Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pierre Fabre, Spain.†
Chlorhexidine gluconate (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat infections.

Drill Enrouement *Pierre Fabre, Fr.*
Erysimum (p. 2524·2).
Mouth and throat disorders.

Drill Expectorant *Pierre Fabre Sante, Fr.; Pierre Fabre, Hung.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Drill Mucolitico *Pierre Fabre Dermo-Cosmetique, Port.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Drill Tosse Seca *Pierre Fabre Dermo-Cosmetique, Port.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Drill toux sèche *Pierre Fabre, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Drilozole *Aldril, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Drilyna *Bago, Arg.*
Theophylline (p. 1229·3) or theophylline sodium glycinate (p. 1229·3).
Obstructive airways disease.

Drime *Confar, Port.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Drimen *Coup, Gr.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo; motion sickness.

Driminate *YSP, Malaysia.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea; vomiting; vertigo.

Drimnorth *Northia, Arg.*
Midazolam (p. 1085·1).

Drimon *Teva, Pol.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Drimux A *Gador, Arg.*
⊗Spironolactone (p. 1499·3).
Heart failure; oedema; liver cirrhosis with ascites; nephrotic syndrome; hyperaldosteronism; hypertension.

Drin
Note: this name may be used for preparations of different composition.
Vianex (Βιανεξ), Gr.
Ibuprofen (p. 68·2).

Drina *Silesia, Chile.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Drinalken *Kendrick, Mex.*
Dopamine hydrochloride (p. 1367·2).
Hypotension; shock; extracorporeal circulation.

Drinamil *Sanitas, Chile.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Hypertension; heart failure; oedema.

DriNasal *Mylan, S.Afr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Drinasal S *Merck, S.Afr.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

DrinkaLax *acaSan, Austria.†*
Macrogol 4000 (p. 2547·3).
Constipation.

Drinus
Note: this name may be used for preparations of different composition.
Bros, Gr.
Amoxicillin (p. 216·2), amoxicillin sodium (p. 216·2), or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Kramer, Philipp.
Syrup: Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; sinusitis; rhinitis.

Kramer, Philipp.
Tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; sinusitis; rhinitis.

Dripanina *Ariston, Braz.†*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of clotting during extracorporeal circulation.

Driptane *Abbott, Fr.; Solvay, Philipp.; Fournier, Pol.; Abbott, Rus.; Retsyfarm, Ukr.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability; neurogenic bladder; nocturnal enuresis; bladder hyperactivity.

Drisdol *Sanofi-Aventis, Canad.†; Sanofi Winthrop, USA.*
Ergocalciferol (p. 2113·3).
Rickets; familial hypophosphataemia; hypoparathyroidism.

Drisentin *Sanovel, Turk.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Drisofal *Help, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Drisoftaline *Help, Gr.*
⊗Oxprenolol hydrochloride (p. 1463·2).

Dristan *Wyeth, India; Aspen, S.Afr.†*
Phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); aspirin (p. 22·2).
Upper respiratory-tract congestion; cold and influenza symptoms.

Pfizer Consumer, Canad.; Wyeth, Turk.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; upper respiratory-tract disorders; respiratory-tract congestion.

Pfizer Consumer, Canad.; Pfizer Consumer, S.Afr.
Nasal spray: ⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Pfizer Consumer, Canad.
Nasal spray: Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2).
Nasal congestion.

Pfizer Consumer, Chile.
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Dristan Allergy *Whitehall, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

Dristan Cold
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Hong Kong; Whitehall, USA.
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms; upper respiratory-tract symptoms.

Wyeth, India.†
Phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); paracetamol (p. 115·1).
Cold symptoms.

Dristan Cold Caplets *Whitehall, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Dristan Cold & Flu *Whitehall, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Dristan Cold Maximum Strength *Wyeth Consumer, Hong Kong.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; upper respiratory-tract symptoms.

Dristan Cold Maximum Strength Multi-symptom Formula *Whitehall, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Cold symptoms; hypersensitivity reactions.

Dristan Cold Maximum Strength No Drowsiness Formula *Whitehall, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Dristan Cold Multi-Symptom Formula *Whitehall, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Dristan Cold ND *SA Druggists Self Med, S.Afr.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Dristan Compuesto *Wyeth-Whitehall, Arg.*
Aspirin (p. 22·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Aluminium hydroxide (p. 1817·2) and magnesium carbonate (p. 1856·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Cold symptoms.

Dristan Decongestant Cough Medicine *SA Druggists Self Med, S.Afr.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Dristan Decongestant Nasal Mist *SA Druggists Self Med, S.Afr.†*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2).
Hay fever; sinusitis; cold symptoms.

Dristan Descongestivo *Wyeth-Whitehall, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Dristan Expectorant *Wyeth, India.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); citric acid (p. 2480·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Dristan 12-hr Nasal Decongestant Spray *Whitehall-Robins, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Dristan Juice Mix-in *Whitehall, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Dristan Long Lasting *Whitehall, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Dristan Nasal Drops *Wyeth, India.†*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); menthol (p. 2553·2); cineole (p. 2479·1).
Nasal congestion.

Dristan Nasal Spray *Wyeth, Hong Kong†; Whitehall, USA.*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2).
Nasal congestion.

Dristan ND *Pfizer Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms; upper respiratory-tract disorders; fever; headache; pain.

Dristan Saline Spray *Whitehall, USA.*
Sodium chloride (p. 1795·1).
Inflammation and dryness of nasal membranes.

Dristan Sinus *Whitehall, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Cold and influenza symptoms.

Dritho-Scalp *Dermik, USA.*
Dithranol (p. 1701·2).
Psoriasis.

Drivermide *Nakornpatana, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Drix Bisacodyl *Hermes, Ger.*
Bisacodyl (p. 1821·1).
Constipation.

Drixine *Schering-Plough, Philipp.; Schering-Plough, S. Afr.; Schering-Plough, Venez.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; conjunctivitis.

Drixine Nasal *MSD, Austral.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Drixoral
Note: this name may be used for preparations of different composition.
Schering-Plough, Canad.
Nasal spray: ⊗Oxymetazoline hydrochloride (p. 1671·3).
Upper respiratory-tract congestion.

Schering-Plough, Canad.; Schering-Plough, Hong Kong†; Schering-Plough, Indon.
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion.

Schering-Plough, USA.
⊗Pseudoephedrine sulfate (p. 1676·1); brompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Drixoral Cold & Allergy *Schering-Plough, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Drixoral Cold & Flu *Schering-Plough, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Drixoral Cough & Congestion *Schering-Plough, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Drixoral Cough & Sore Throat *Schering-Plough, USA.*
Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Drixoral Day/Night *Schering-Plough, Canad.†*
⊗Yellow tablets, pseudoephedrine sulfate (p. 1676·1); white tablets, dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate.
Upper respiratory-tract congestion; ear disorders.

Drixoral ND *Schering-Plough, Canad.†*
⊗Pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion; ear disorders.

Drixoral Non-Drowsy Formula *Schering, USA.†*
⊗Pseudoephedrine sulfate (p. 1676·1).
Nasal congestion.

Drixoral Plus *Schering-Plough, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Drixtab *Schering-Plough, Canad.†*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion.

Drizak *Intermed, Gr.*
Carbocisteine (p. 1658·1).

DRN 8103 *BSM, Austria.*
Thallium-201 chloride (p. 2229·2).
Radionuclide imaging.

Droal *Procter & Gamble, Spain.†*
Ketorolac trometamol (p. 80·2).
Pain.

Drobel *Blubell, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Drobel-MF *Blubell, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Drocan *Glories, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Drocanil-A *M & H, Thai.*
Lidocaine (p. 1988·1).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to decrease absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Drocef *Vivax, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Drocon-CS *Cypress, USA.*
⊗Hydrocodone tartrate (p. 67·2); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; upper respiratory-tract congestion.

Drocort *Agio, India.*
⊗Clotrimazole (p. 576·2); hydrocortisone (p. 1640·1).

Drofa *Vensat, India.*
Cefadroxil (p. 233·2); lactic acid bacillus (p. 2596·3).
Bacterial infections.

Drofaron *Vifor, Switz.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence; gastritis.

Drofaz *Specifar (Σπεσιφαρ), Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Drofem *FDC, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Drofic *Servocare, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Drogenil
Note: this name may be used for preparations of different composition.
Essex, Chile†; Fulford, India; MSD, Irl.; Plough, Port.; Schering-Plough, UK.†
Flutamide (p. 798·2).
Prostatic cancer.

Plus, Gr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Droglican *Bioiberica, Spain.*
Chondroitin sulfate (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Drogryl *Drogsan, Turk.*
Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1).
Insect bites; skin irritation.

Drolanin *Merz, Ital.*
Tromantadine hydrochloride (p. 1021·1).
Herpesvirus infections of the skin and mucous membranes.

Droleptan *AFT, NZ.*
Droperidol tartrate (p. 1072·1).
Adjunct to anaesthesia; premedication; psychoses.
Phebra, Austral.; ProStrakan, Fr.; IFET (ΙΦΕΤ), Gr.
Droperidol (p. 1072·1).
General anaesthesia; neuroleptanalgesia; nausea and vomiting; premedication; agitation; aggression; psychoses.

Drolex *Taiwan Biotech, Philipp.*
Cefadroxil (p. 233·2).
Bacterial infections.

Drolid *Candor, India.*
Drotaverine (p. 2497·3); nimesulide (p. 101·3).

Drolid-M *Candor, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Droll *Galenica, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Droma *Osmed, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Dromac *Trumac, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Dromadol *Teva, UK.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Drometak *Precimex, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Dromil Sauco *Vargas, Venez.*
Ammonium acetate (p. 1655·3); sodium benzoate (p. 1738·2); drosera (p. 2497·2); sambucus (p. 2609·3); Desessartz (p. 1667·2); senega (p. 1677·2).
Respiratory-tract congestion.

Dromos *Sigma-Tau, Ital.*
Propionyl-L-carnitine hydrochloride (p. 2053·3).
Cardiac disorders.

Drona *Evershine, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Dronabol *Bangkok Lab & Cosmetic, Thai.*
⊗Methandienone (p. 2291·3).
Osteoporosis; anabolic.

Dronadil *Alpharma, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Dronal *Orchid, India; Sigma-Tau, Ital.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Dronalden *Denver, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Dronalen Plus *MSD, Austral.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Dronalen Plus D-Cal *Ascent, Austral.*
4 Tablets, alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1)(Dronalen Plus); 48 tablets, calcium carbonate (p. 1824·3) (BoneCal).
Osteoporosis.

Dronalent *Chrispa (Χρισπα), Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Dronat *Fortbenton, Arg.*
Alendronate (p. 1171·3).
Osteoporosis.

Dronate-OS *BDH, India.†*
Etidronate disodium (p. 1182·3).
Hypercalcaemia of malignancy; Paget's disease of bone.

Dronatex *Tiefenbacher, Neth.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Dronatifer *Tiefenbacher, Neth.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Dronaval *Saval, Chile.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Dronin *Teva, Pol.*
21 Tablets, ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1); 7 tablets, inert.
Combined oral contraceptive.

Dronis *Sun, India.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

2-Drop *SSL, Gr.*
Salicylic acid (p. 1719·1); camphor (p. 2466·2).
Corns.

Dropain *Ethix, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Dropar *FDC, India.*
Drotaverine (p. 2497·3); paracetamol (p. 115·1).

Dropavix *Arriani, Gr.*
Levodropropizine (p. 1662·3).
Cough.

Dropax *Italfarmaco, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Dropaxin *Italfarmaco, Ital.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Dropcina *Plough, Port.*
Gramicidin (p. 308·3); cetylpyridinium chloride (p. 1743·1); dichlorobenzyl alcohol (p. 1750·2); benzocaine (p. 1980·2).
Mouth and throat disorders.

Droperdal *Cristalia, Braz.*
Droperidol (p. 1072·1).
Psychoses.

Droperol *Troikaa, India.*
Droperidol (p. 1072·1).
Premedication; anaesthesia.

Dropflam *Eupharmed, Ital.*
Diclofenac sodium (p. 48·3).
Anterior eye inflammation.

Dropgel *Eupharmed, Ital.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Dropia *Sanovel, Turk.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Dropia-Met *Sanovel, Turk.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Dropicine *Beta, Arg.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Dropid *Medicine Products, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Dropiltim *Faran, Gr.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Dropilton *Bruschettini, Ital.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Dropodex *Moorfields, UK.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye inflammation.

Dropovit *Wyeth, India.*
Vitamins.

Dropsen *Eyelab, Ital.*
Naproxen sodium (p. 98·2).
Inflammatory eye disorders.

Dropstar *Poen, Arg.; Farmigea, Ital.; Poen Vision, Mex.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Droptimol *Farmigea, Ital.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Dropyal *Bruschettini, Ital.*
⊗Sodium hyaluronate (p. 2526·2); carbomer 941 (p. 2173·3); glycerol (p. 2517·2).
Dry eyes.

Drosemiel *Ximena Polanco, Chile.*
⊗Drosera (p. 2497·2); gelsemium (p. 2511·2); lobelia (p. 2323·2); plantago major (p. 2592·3); flores pectorales; honey (p. 2072·1).
Homoeopathic preparation.

Droser *Drogsan, Turk.*
Sodium chloride (p. 1795·1).

Drosera Complex *Boiron, Canad.*
Arnica montana (p. 2447·2); belladonna (p. 2453·3); cina; cochineal (p. 2179·2); copper (p. 2057·1); corallium rubrum; drosera rotundifolia (p. 2497·2); ferrum phosphoricum (p. 2077·1); goldenrod (p. 2620·1); ipecac (p. 1667·2).
Homoeopathic preparation.

Drosera Complexe No 64 *Lehning, Fr.*
⊗Drosera (p. 2497·2); ipeca (p. 1667·2); thymus vulgaris (p. 2630·2); cuprum aceticum (p. 2486·2); pulsatilla (p. 2600·2); lobelia (p. 2323·2); belladonna (p. 2453·3); viola odorata; coccus cacti (p. 2179·2); veratrum album (p. 2644·3).
Homoeopathic preparation.

Drosera Compose *Boiron, Fr.*
Drosera rotundifolia (p. 2497·2); arnica montana (p. 2447·2); belladonna (p. 2453·3); artemisia cina; coccus cacti (p. 2179·2); corallium rubrum; cuprum metallicum (p. 2057·1); ferrum phosphoricum (p. 2077·1); ipeca (p. 1667·2); solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Drosera Homaccord *Heel, Canad.*
Cuprum aceticum (p. 2486·2); drosera rotundifolia (p. 2497·2).
Homoeopathic preparation.

Drosera Plex *Seroyal, Canad.†*
Arnica montana (p. 2447·2); belladonna (p. 2453·3); cina; cochineal (p. 2179·2); copper (p. 2057·1); corallium rubrum; drosera rotundifolia (p. 2497·2); ferrum phosphoricum (p. 2077·1); goldenrod (p. 2620·1); ipecac (p. 1667·2).
Homoeopathic preparation.

Drosera-Weliplex *Weber & Weber, Ger.†*
Aralia rac.; cephaelis ipec.; cetraria island. (p. 2531·2); drosera (p. 2497·2); grindelia rob. (p. 2522·3); inula helen. (p. 1662·3); sanguinaria canad. (p. 2610·1); solanum dulc. (p. 2497·3).
Homoeopathic preparation.

Drosetil *Leon, Cz.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Drosetux *Boiron, Cz.*
Drosera rotundifolia (p. 2497·2); arnica montana (p. 2447·2); atropa belladonna (p. 2453·3); artemisia cina; coccus cacti (p. 2179·2); corallium rubrum; cupri gluconas (p. 2057·2); ferrosi phosphas (p. 2077·1); ipecacuanha (p. 1667·2); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Boiron, Switz.
Arnica montana (p. 2447·2); cupri gluconas (p. 2057·2); atropa belladonna (p. 2453·3); dactylopius coccus (p. 2179·2); cephaelis ipecacuanha (p. 1667·2); drosera (p. 2497·2); cina; ferrosi phosphas (p. 2077·1); corallium rubrum; solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Dolisos, Hung.
Drosera rotundifolia (p. 2497·2); arnica montana (p. 2447·2); atropa belladonna (p. 2453·3); artemisia cina; coccus cacti (p. 2179·2); cephaelis ipecacuanha; solidago virga aurea (p. 2620·1); coralium rubrum;

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

cuprum gluconicum (p. 2057·2); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Drosétux *Boiron, Fr.*
Drosera rotundifolia (p. 2497·2); arnica montana (p. 2447·2); atropa belladonna (p. 2453·3); artemisia cina; coccus cacti (p. 2179·2); corallium rubrum; cuprum (p. 2057·1); ferrum phosphoricum (p. 2077·1); ipecacuanha; solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Drosiane Diario *Sandoz, Spain.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Drosianelle *Sandoz, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Drosinula
Note: this name may be used for preparations of different composition.
Bioforce, Switz.
Norway spruce buds; drosera (p. 2497·2); ivy (p. 2536·2); pear.
Respiratory-tract disorders.

Biohorma, Neth.
Coccionella (p. 2179·2); drosera rotundifolia (p. 2497·2); hedera helix (p. 2536·2); inula helenium (p. 1662·3); inuline (p. 2534·3); ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Drosithym Efeu Mono *Ysatfabrik, Ger.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Drosithym-N *Ysatfabrik, Ger.†*
Cowslip rhizome (p. 2596·2); thyme (p. 2630·2); drosera (p. 2497·2).
Catarrh; cough.

Drospibel *Effik, Fr.*
Ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Drospil *Effik, Spain.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Drossadin *Drossapharm, Switz.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Drossadinetten *Drossapharm, Switz.*
Aluminium lactate (p. 2440·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Drossadinol *Drossapharm, Switz.*
Aluminium lactate (p. 2440·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Drossafol *Drossapharm, Switz.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folic acid deficiency.

Drossa-Nose *Drossapharm, Switz.*
Sea salt (p. 2612·1).
Nasal dryness.

Drossanose *Drossapharm, Israel.†*
Sea salt (p. 2612·1).
Nasal disorders.

Drosten *Vocate, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Drosure *Effik, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Drosurelle *Effik, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Drosym-MF *Symbiosis, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Drosyn *FDC, India.*
Phenylephrine hydrochloride (p. 1672·3).
Production of cycloplegia and mydriasis; synechiae.

Drosyn-T *FDC, India.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).

Drot *Mapra, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Drotaspa *Shreya, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Drotikind *Mankind, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Drotikind-M *Mankind, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Drotin *Bushnell, India.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Drotin Plus *Bushnell, India.*
Drotaverine hydrochloride (p. 2497·3); paracetamol (p. 115·1).

Drotin-M *Bushnell, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Drotis *Hauz, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Drotizin *Geolab, Braz.*
Hydroxyzine (p. 630·3).

Drotmic *Mediez, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Drotwell *Genesis, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Drotwell-M *Genesis, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Droty *Overseas, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Drovax *Pharos, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Drovera *Svizera, India.*
Drotaverine (p. 2497·3).
Muscle spasm.

Drovet *Taurus, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Drovid *Drogsan, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

Drovit *Prohealth, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Drovitan *Vitae, Mex.*
Alendronate (p. 1171·3).
Osteoporosis.

Droxaine *Daudt, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).
Gastric hyperacidity.

Droxal *Solas, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxbit *Cubit, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxefa *Pharos, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxel *Recalcine, Chile.†*
⊗Propyphenazone (p. 127·3); calcium ascorbate (p. 2111·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); vitamin A (p. 2098·3).
Cold and influenza symptoms.

Droxflora *KonTest, India.*
Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

Droxia *BMS Oncology, USA.*
Hydroxycarbamide (p. 803·1).
Sickle-cell anaemia.

Droxibid *Hindustan Antibiotic, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxiderm *Yung Shin, Philipp.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Droxifan *Meyer, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxil *Klonal, Arg.†; Zee, Philipp.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droximag-P *PP Lab, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); kaolin (p. 1850·1); atropine sulfate (p. 1310·2).
Peptic ulcer; gastrointestinal infection; alkaloid poisoning.

Droxol
Note: this name may be used for preparations of different composition.
Bernabo, Arg.
Alprazolam (p. 1035·2).
Anxiety; panic disorder; mixed anxiety depressive states.

Droxycad *Zydus, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxyceph *Orchid, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Droxyl
Note: this name may be used for preparations of different composition.
Torrent, India.
Cefadroxil (p. 233·2).
Bacterial infections.

Droxyl Clav *Torrent, India.*
Cefadroxil (p. 233·2); clavulanic acid (p. 268·3).
Bacterial infections.

Drozid *Dexa, Philipp.*
Cefadroxil (p. 233·2).
Bacterial infections.

Drozil LB *Zee, India.*
Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

Drüfusan *Syxyl, Ger.*
Acidum silicicum (p. 2208·3); calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); calcium sulfuricum (p. 2173·1); ferrum phosphoricum (p. 2077·1); kalium chloratum (p. 1793·2); kalium phosphoricum (p. 1790·3); kalium sulfuricum (p. 1793·2); magnesium phosphoricum (p. 1787·3); natrium chloratum (p. 1795·1); natrium phosphoricum (p. 1791·2); natrium sulfuricum (p. 1888·1).
Homoeopathic preparation.

Drüfusan N *Syxyl, Ger.†*
Calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); calcium sulfuricum (p. 2173·1); ferrum phosphoricum (p. 2077·1); kalium arsenicosum (p. 2594·3); kalium bromatum (p. 2461·1); kalium chloratum (p. 1793·2); kalium jodatum (p. 2336·3); kalium sulfuricum (p. 1793·2); magnesium phosphoricum (p. 1787·3); manganum sulfuricum (p. 2081·2); natrium chloratum (p. 1795·1); natrium phosphoricum (p. 1791·2); natrium sulfuricum (p. 1888·1); acidum silicicum (p. 2208·3); cuprum metallicum (p. 2057·1).
Homoeopathic preparation.

Drug Screen *Omega, Irl.†*
A range of tests for drugs of abuse.

Druisel *Northia, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Drula Fade *Drula, Canad.*
Hydroquinone (p. 1705·1); oxybenzone (p. 1715·3).

Drum *Pharmatrix, Arg.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Drum B *Pharmatrix, Arg.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Drunen *Andromaco, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Drusen *SIFI, Mex.*
Lutein (p. 2079·2); astaxanthin (p. 2170·1); zeaxanthin (p. 2125·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1).
Dietary supplement.

Drvel *Aarpik, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Dry & Clear *SA Druggists Self Med, S.Afr.†*
Benzoyl peroxide (p. 1696·1).
Acne; rosacea.

Dry & Clear Medicated Skin Cleanser *SA Druggists Self Med, S.Afr.†*
⊗Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); benzethonium chloride (p. 1738·1); alcohol (p. 1733·1).
Acne.

Dry Cough & Cold *Pharmetics, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Dry Cough Syrup *Pharmetics, Canad.; AAH, UK.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Dry Eye Gel *Alcon, Neth.*
Carbomer 934P (p. 2173·3).
Dry eyes.

Dry Eye Omega Benefits with Vitamin D-3 *Physician Recommended Nutriceuticals, USA.*
Omega-3 fatty acids (p. 1460·1); vitamin D (p. 2112·3).

Dry Eyes *Bausch & Lomb, USA.*
Eye drops: Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Bausch & Lomb, USA.
Eye ointment: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Dry Mouth Relief *Colgate Oral, USA.*
Sodium fluoride (p. 2089·2).

DryEars *Naveh, Israel.*
⊗Isopropyl alcohol (p. 1758·3); glycerol (p. 2517·2).
Removal of trapped ear water.

Drygel *Compu, S.Afr.†*
Povidone-iodine (p. 1767·1).
Skin infections; burns; wounds; aphthous ulcers.

Drylin *Merckle, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Dryltac *Legrand, Braz.*
Diclofenac colestyramine (p. 48·3).

DryMax *Jaymac, USA.*
⊗Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

DryMax AF *Jaymac, USA.*
Clofedanol hydrochloride (p. 1659·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Formerly contained clofedanol hydrochloride, chlorphenamine maleate, and pseudoephedrine hydrochloride.
Upper respiratory-tract disorders.

Drynisan *Fecofar, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); mepyramine maleate (p. 635·1).

Drynol *Menarini, Irl.*
Bilastine (p. 617·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Drynoz *Medispan, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Drysol *Dispolab, Arg.; Dispolab, Chile; Darier, Mex.; Person & Covey, USA.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Drytec *GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Irl.; GE Healthcare, Neth.; GE Healthcare, Spain; GE Healthcare, UK.*
Technetium-99m as sodium pertechnetate (p. 2228·1).
Radionuclide imaging; diagnostic agent.

Drytergent *C & M, USA.*
Skin cleanser.

Drytex *C & M, USA.*
Salicylic acid (p. 1719·1); methylbenzethonium chloride (p. 1760·3).
Acne.

Dryvax *Wyeth-Ayerst, USA.†*
A smallpox vaccine (p. 2418·2).
Active immunisation.

DS-15 *Nodysis, India.*
Tablets: ⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).
Nodysis, India.
Topical gel: Diclofenac sodium (p. 48·3).
Pain; inflammation.

DS-24 *Pharmafrica, S.Afr.†*
Vitamins; minerals.

DS Emulsion *Biorga, Hong Kong.†*
Copper pidolate (p. 1720·3); zinc pidolate (p. 1720·3); dimeticone (p. 2209·3); tocoferil acetate (p. 2119·2).
Facial skin irritation.

DS-15 Plus *Nodysis, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

D-Sine *McNeil & Argus, India.*
Didanosine (p. 972·3).
HIV infection.

DSM *Candor, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

DSN *Shreya, India.*
Vitamins; minerals; amino-acids; glutathione (p. 1555·2).

DSO Dressing *Germiphene, Canad.*
Chlorobutanol (p. 1747·2); cinnamaldehyde; cinnamon oil (p. 2479·3); clove oil (p. 2481·3); methyl salicylate (p. 92·1).

Dsorolen *DWD, India.*
Trioxysalen (p. 1727·2).

DSP *Laborate, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

DSQ *Madhav, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

D-S-S *Warner Chilcott, USA.*
Docusate sodium (p. 1836·2).
Constipation.

D-Stress *Synergia, Fr.*
Magnesium glycerophosphate (p. 1787·2); arginine (p. 2049·1); taurine (p. 2626·2); vitamin B substances (p. 2102·3).
Nervous disorders.

DT *Biomed Krakow, Pol.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

DT Coq *Vianex (Βιανεξ), Gr.; Aventis Pasteur, Pol.†*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DT LX-Kid *Apex, India.*
Cefalexin (p. 234·1).
Bacterial infections.

DT Polio *Sanofi Pasteur, Fr.†*
A diphtheria, tetanus, and poliomyelitis vaccine (p. 2386·2).
Active immunisation.

DT Vax *Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Port.; Aventis, S.Afr.†*
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

D-Tabs *Riva, Canad.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

D-Tann *Midlothian, USA.†*
Phenylephrine tannate (p. 1672·2); diphenhydramine tannate (p. 626·1).
Upper respiratory-tract disorders.

D-Tann CD *Midlothian, USA.*
Pentoxyverine tannate (p. 1672·1); diphenhydramine tannate (p. 626·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

DTaP *SSI, Pol.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DTaP-IPV *SSI, Pol.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

D-Tato *Apotex, Mex.*
Benzonatate (p. 1656·2).
Cough.

DTCoq/DTP *Sanofi Pasteur, Thai.†*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DTI *Korea United, Hong Kong.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

DT-Ibuflam *Laborate, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

DTIC *Bayer, Austral.†*
Dacarbazine (p. 776·1).
Malignant neoplasms.

DTIC-Dome *Bayer Schering, S.Afr.; Bayer, USA.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

DTM *Biochem, India.*
Diltiazem (p. 1359·2).
Angina pectoris.

DTN 52 *Finecure, India.*
Tizanidine (p. 2026·2).
Spasticity; skeletal muscle spasm.

DTO *DWD, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

DTP *Biomed Krakow, Pol.; Sanofi Pasteur, Singapore.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DTP Vaccine *Bio Farma, Malaysia; Bio Farma, Thai.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DTPA *Rez, Cz.*
Technetium-99m (p. 2228·1) pentetate.
Radionuclide imaging of the urinary tract and CNS.
Soreq, Israel.
Calcium trisodium pentetate (p. 1570·3) for labelling with technetium-99m.
Radionuclide imaging.

DTP-HB *Bio Farma, Thai.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

DTP-Merieux *Aventis, S.Afr.†*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

DT-reduct *Sanofi Pasteur, Austria.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

D-Triol *Alapis, Gr.*
Calcitriol (p. 2113·1).
Vitamin D deficiency.

DT-Vac *Serum Institute, India.†*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

DTZ *Helsinn Birex, Irl.†*
Diltiazem hydrochloride (p. 1359·2).
Hypertension.

Du Le *Jin Sang Zi, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; ischaemic heart disease.

Du Di *Ke Lun, China.*
Curcuma oil (p. 2218·1).

Du La Bao *Bai Li, China.*
Racecadotril (p. 1881·3).
Diarrhoea.

Du He *Lianhuan, China.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Du Luo Jie *SanJiu, China.*
Flavoxate hydrochloride (p. 2360·1).
Bladder spasm; urinary incontinence; urinary frequency and urgency.

Du Le Ning *Kangerwei, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Du Pei *Nan Guo, China.*
Sodium new houttuyfonate.

Du Ya Xin *Bo Jian, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Dua Activa *Visiontec, Arg.*
Wetting solution for contact lenses.

Dua Elite *Visiontec, Arg.*
Contact lens care solution.

Duab *Nutrivercell, Fr.*
Cranberry (p. 2488·1); propolis (p. 2597·3); zinc sulfate (p. 2126·2).
Urinary-tract disorders.

Duac *GSK, Austral.; GSK, Cz.; GSK, Ger.; Stiefel, Ger.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, Irl.; Stiefel, Israel; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Neth.; USL, NZ; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, Port.; Stiefel, Spain; Leo, Swed.; GSK, Switz.; Stiefel, Thai.; Stiefel, Ukr.; GSK, USA.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Duac Once Daily *Stiefel, UK.*
Benzoyl peroxide (p. 1696·1); clindamycin phosphate (p. 269·3).
Acne.

Duact *GSK, Denm.; GSK, Fin.; GSK, Turk.*
⊗Acrivastine (p. 614·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; respiratory-tract congestion.

Duactin *Pharma International, Ukr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Duafen *Pharmed, Austria.†*
Ibuprofen (p. 68·2).
Pain; fever.

Duagen *2care4, Denm.; Demo, Gr.; Glaxo Allen, Ital.; GSK, Port.; GSK, Spain.†*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Dual Action Complete *Major, USA.*
Calcium carbonate (p. 1824·3); famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2).
Heartburn.

Dual Antigen *Serum Institute, India.*
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Dual Cold *Bactolac, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Dual Gesic *Bactolac, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dual Gesic Plus *Bactolac, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Dualcillin *Bactolac, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Dualflam *Bactolac, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dualgan *ITF, Port.*
Etodolac (p. 57·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Dualgos *Liferpal, Mex.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Fever; pain.

Dualid
Note: this name may be used for preparations of different composition.
Biotech, Venez.
Oxantel embonate (p. 162·2); pyrantel embonate (p. 165·3).
Worm infections.
Duncan, Arg.
Ranitidine (p. 1882·1).
Peptic ulcer.

Dualid S
Note: this name may be used for preparations of different composition.
Ache, Braz.
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Dualizol *Degorts, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis.

Dual-Lax Extra Strong *Lane, UK.*
Senna (p. 1885·1); aloin (p. 1816·2); cascara (p. 1826·1).
Constipation.

Dual-Lax Normal Strength *Lane, UK.*
Senna (p. 1885·1); cape aloes (p. 1816·1); cascara (p. 1826·1).
Constipation.

Duals Nordin *Nordin, Mex.*
Camphor (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2).
Cold and influenza symptoms.

Duals Nordin Adulto *Nordin, Mex.*
Vitamins; aspirin (p. 22·2); caffeine (p. 1203·3).
Influenza symptoms.

Duals Nordin Infantil *Nordin, Mex.*
Vitamins; aspirin (p. 22·2).
Influenza symptoms.

Dualten *Saval, Chile.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension; ischaemic heart disease.

Duamild *Gedeon Richter, Hung.*
Capsules, tamsulosin hydrochloride (p. 2369·1) (Tamsol); tablets, finasteride (p. 2358·3) (Prosterid).
Benign prostatic hyperplasia.

Duan *Klosterfrau, Austria.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Duan Zheng *Di Ao, China.*
Glucosamine sulfate (p. 2515·3).

Duaneo *Klosterfrau, Austria.*
Paracetamol (p. 115·1).
Pain; fever.

Duaneo mit Codein *Klosterfrau, Austria.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); codeine hydrochloride (p. 40·2).
Pain.

Duanibu *Klosterfrau, Austria.*
Ibuprofen (p. 68·2).
Pain; fever.

Duaspir *Montrose, Cz.†*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Duavee *Pfizer, USA.*
⊗Conjugated oestrogens (p. 2260·1); bazedoxifene (p. 2256·1).
Menopausal disorders.

Duavent *United American, Philipp.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Dub *Obsurge, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; premenstrual syndrome; breast cancer; postponement of menstruation.

Dubact *Medico, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; premenstrual syndrome; breast cancer; postponement of menstruation.

Dubagest *Glenmark, India.*
Progesterone (p. 2300·2).
Menstrual disorders; menopausal disorders; female infertility; threatened miscarriage.

Dubam *Norma, UK.*
Topical spray: Methyl salicylate (p. 92·1); ethyl salicylate (p. 56·3); glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3).
Musculoskeletal pain.
Norma, UK.
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2); cineole (p. 2479·1).
Musculoskeletal pain.

Dubatran *Alembic, India.*
Tranexamic acid (p. 1164·2).
Hereditary angioedema; haemorrhage.

Dubatran-MF *Alembic, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Dublace-P *Tablets, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Dublace-SP *Tablets, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Dublact *Tablets, India.*
Paracetamol (p. 115·1); diclofenac (p. 48·3).
Musculoskeletal and joint disorders.

Dubloc *Dewcare, India.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dublock *Alapis, Denm.; Alapis, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Dublon *Fada, Arg.*
⊗Esmolol hydrochloride (p. 1377·3).
Tachycardia; hypertension.

Dubova Kura *Megafyt-R, Cz.†*
Oak bark (p. 2574·1).
Inflammatory disorders of the skin and mucous membranes; haemorrhoids.

Duburina *Duncan, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ducain *Neon, India.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Ducarb *Samarth, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Ducat Plus *Kamakshi, India.*
Linolenic acid (p. 1460·2); vitamin B substances (p. 2102·3).

Ducene *Sauter, Austral.†*
Diazepam (p. 1063·2).
Anxiety disorders; alcohol withdrawal syndrome; skeletal muscle spasm; spasticity.

Duceten *Drugtech, Chile.*
Duloxetine hydrochloride (p. 415·1).
Depression; urinary incontinence; neuropathic pain.

Duchy Herbals Echinacea Relief *Nelson, UK.*
Echinacea purpurea (p. 2498·1).
Cold and influenza symptoms.

Duchy Herbals Hyperi-Lift *Nelson, UK.*
St John's wort (p. 449·1).
Anxiety; low mood.

Duciclon *Degorts, Mex.*
Diclofenac sodium (p. 48·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; neuropathy.

Ducidal-OZ *Obsurge, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ducilamina *Theraskin, Braz.*
Calamine (p. 1697·2).
Skin irritation.

Duclav *Samarth, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ducodin *Hovid, Malaysia.*
Pholcodine (p. 1675·1).
Cough.

Ducort *Zenon, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Ductelmin *Ducto, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Ductocilina *Ducto, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

Ductocina *Ducto, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ductogel *Ducto, Braz.*
Aluminium hydroxide (p. 1817·2).
Antacid.

Ductogeron *Ducto, Braz.*
Cinnarizine (p. 622·1).

Ductomet *Ducto, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Ductonar *Roux-Ocefa, Arg.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Ductopril *Ducto, Braz.*
Captopril (p. 1331·2).
Hypertension.

Ductoveran *Ducto, Braz.*
Papaverine hydrochloride (p. 2362·3); belladonna (p. 2453·3); hyoscyamus (p. 2530·2); boldo (p. 2458·3); star anise (p. 2622·1).

Ductovirax *Ducto, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Dudencer *Tempo Scan Pacific, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Dudot *Alna, India.*
Drotaverine (p. 2497·3) or drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Dudrop *Sun, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).

Duellin *Egis, Hung.†; Egis, Rus.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism; drug-induced extrapyramidal disorders.

Duet *Integrity, USA†; Xanodyne, USA.†*
Vitamins; minerals.

Duet DHA *Eckson, USA.*
Tablets, vitamins; minerals; capsules, omega-3 fatty acids (p. 1460·1).
Dietary supplement.

Duetact *Takeda, USA.*
Pioglitazone hydrochloride (p. 493·1); glimepiride (p. 473·2).
Diabetes mellitus.

Dueva *Menarini, Ital.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Duexis *Horizon, USA.*
Ibuprofen (p. 68·2).
Famotidine (p. 1842·1) is included in this preparation to reduce the risk of peptic ulcer.
Osteoarthritis; rheumatoid arthritis.

Dufaston *Solvay, Ital.*
Dydrogesterone (p. 2270·1).
Endometriosis; female infertility; menopausal disorders; menstrual disorders; threatened or recurrent miscarriage.

Dufex *Cosme, India.*
Diclofenac sodium (p. 48·3); pantoprazole (p. 1875·3).

Dufine *Effik, Port.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Duflegrip *Fecofar, Arg.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); bromhexine hydrochloride (p. 1656·3); pseudoephedrine sulfate (p. 1676·1).

Duflemina *Janssen-Cilag, Arg.*
Calcium dobesilate (p. 2464·3).
Venous insufficiency.

Duflomex *Actavis, Indon.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Primal, Hong Kong.†
Ciprofloxacin (p. 261·1).
Bacterial infections.

Duflox *Daksh, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Duinum *Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; oligospermia.

Duiwelsdrekdruppels *Aspen Consumer, S.Afr.*
Asafetida (p. 2449·3).
Flatulence.

Dukinase *Taj, India.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Dukoral *CSL, Austral.; SBL, Austria; Janssen-Cilag, Belg.; Crucell, Canad.; Sanofi Pasteur, Chile; SBL, Cz.; SBL, Denm.; Crucell, Fin.; Chiron, Fr.; Novartis Vaccines, Ger.; Crucell, Hong Kong; Crucell, Hung.; SBL, Irl.; Berna, Ital.; Sanofi Pasteur, Malaysia; Crucell, Neth.; Crucell, Norw.; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Crucell, Pol.; SBL, Port.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Singapore; Crucell, Spain; SBL, Swed.; Crucell, Switz.; Sanofi Pasteur, Thai.†; Chiron, Turk.†; Masta, UK.*
An oral cholera vaccine (p. 2381·1).
Active immunisation.

Dulac EC *Danone Dumex, Malaysia.*
Infant feed.
Colic; diarrhoea; flatulence; digestive disorders.

Dulac LF *Danone Dumex, Malaysia.*
Infant feed.
Lactose intolerance.

Dulane *Sun, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dulane-M *Sun, India.*
Duloxetine; mecobalamin (p. 2108·1).

Dularell N *Sanorell, Ger.*
Toxicodendron quercifolium (p. 2603·3); solanum dulcamara (p. 2497·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Dulax
Note: this name may be used for preparations of different composition.
Vickmans, Hong Kong.†
Bisacodyl (p. 1821·1).
Constipation.

Dulcacefak *Cefak, Cz.*
Dulcamara (p. 2497·3).
Eczema.

Dulcarhus-Gastreu R11 *Reckeweg, Neth.*
Berberis vulgaris (p. 2502·1); calcarea phosphorica (p. 1784·2); causticum (p. 2595·3); dulcamara (p. 2497·3); rhus toxicodendron (p. 2603·3); rhododendron chrysanthemum.
Homoeopathic preparation.

Dulcaryl *Bilim, Turk.*
Sodium cyclamate (p. 2180·2); saccharin sodium dihydrochloride.
Sugar substitute.

Dulcilarmes *Horus, Fr.*
Povidone (p. 2204·3).
Dry eyes.

Dulciphak *Allergan, Fr.*
Sodium monomethyltrisilanol orthohydroxybenzoate; parahydroxycinnamic acid.
Lens opacities.

Dulcivit *Abigo, Swed.*
Vitamins.

Dulcobalance *Boehringer Ingelheim, UK.*
Macrogol 4000 (p. 2547·3).

Dulcodruppels *Boehringer Ingelheim, Neth.*
Sodium picosulfate (p. 1887·2).
Constipation.

DulcoEase *Boehringer Ingelheim, UK.*
Docusate sodium (p. 1836·2).
Stool softener.

Dulcoenema *Boehringer Ingelheim, Spain.*
⊗Glycerol (p. 2517·2).
Constipation.

Dulcofibre *Boehringer Ingelheim, Singapore.*
Glucomannan (p. 2515·2).
Constipation.

Dulcogotas *Boehringer Ingelheim, Port.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dulcolactol *Boehringer Ingelheim, Indon.*
Lactulose (p. 1850·3).
Constipation.

Dulcolan *Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Dulcolax *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK.*
Capsules; oral liquid: Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Boehringer Ingelheim, USA.
Oral liquid: Magnesium hydroxide (p. 1857·2).
Antacid.

Dulcolax Balance *Boehringer Ingelheim Consumer, USA.*
Macrogol 3350 (p. 2547·3).
Constipation.

Dulcolax Bowel Prep Kit *Boehringer Ingelheim, USA.*
Combination pack: 4 Tablets, bisacodyl (p. 1821·1); docusate sodium (p. 1836·2); 1 suppository, bisacodyl.
Pre-operative bowel preparation.

Dulcolax M Balance *Boehringer Ingelheim, Ger.*
Macrogol 4000 (p. 2547·3).
Constipation.

Dulcolax NP *Boehringer Ingelheim, Ger.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dulcolax Picosulfat *Boehringer Ingelheim, Switz.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dulcolax Picosulphate *Boehringer Ingelheim, Belg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dulcolax SP *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Philipp.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dulcolax Stool Softener *Boehringer Ingelheim Consumer, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Dulcolaxo *Boehringer Ingelheim, Spain; Gervasi, Spain.*
Bisacodyl (p. 1821·1).
Constipation.

Dulcopearls *Boehringer Ingelheim, Neth.*
Sodium picosulfate (p. 1887·2).
Constipation.

Dulcosil *Biotech Naturis, Venez.*
Aspartame (p. 2169·2).
Sugar substitute.

Dulcosol *Piam, Ital.*
A nutritional supplement for infants.

DuLeek-Dp *Seton, USA.*
Levomefolate.

Dulera *Schering, USA.*
⊗Mometasone furoate (p. 1644·1); formoterol fumarate (p. 1209·2).
Asthma.

Dulex *Nitro Organics, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dulife *FDC, India.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dull-C *Freeda, USA.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; scurvy.

Dulocin *Cinerea, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dulojoy *Torrent, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dulot *Lupin, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dulotrac *Minova, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dulovas *Invision, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

Dulox *Verisfield, Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation.

Dulsiluet *PGN, Arg.*
Saccharin sodium (p. 2208·1); cyclamate (p. 2180·2).
Sugar substitute.

Dul-Suc *Prater, Chile.*
Saccharin sodium (p. 2208·1).
Sugar substitute.

Dultavax *Sanofi Pasteur, Hung.; Sanofi Pasteur, Israel; Sanofi Pasteur, Pol.*
A diphtheria, tetanus, and poliomyelitis vaccine (p. 2386·2).
Active immunisation.

DUL-X *Melisana, Switz.*
Bath additive: Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3).
Musculoskeletal and joint pain; cold symptoms.

Melisana, Switz.
Lotion; cream: Menthol (p. 2553·2); star anise oil (p. 2622·2); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); melissa oil (p. 2553·2); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); arnica oil (p. 2447·2).
Musculoskeletal, joint, and soft-tissue disorders.

Dulx *Aarpik, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

DUL-X Cool *Melisana, Switz.*
Comfrey (p. 2484·2); aesculus (p. 2431·2); arnica (p. 2447·2); menthol (p. 2553·2); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3).
Soft-tissue disorders.

DUL-X Sport *Melisana, Switz.*
Menthol (p. 2553·2); red fir oil; rosemary oil (p. 2607·3); eucalyptus oil (p. 2501·2); lemon oil (p. 2543·1).
Musculoskeletal pain.

DUL-X warm *Melisana, Switz.*
Camphor (p. 2466·2); capsaicin (p. 35·1); star anise oil (p. 2622·2); arnica oil (p. 2447·2); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); melissa oil (p. 2553·2); peppermint oil (p. 1877·1); niaouli oil (p. 2569·1); rosemary oil (p. 2607·3); mustard oil (p. 2646·1); thyme oil (p. 2630·3).
Musculoskeletal and joint pain; cold symptoms.

Dumasules *Unimed, India.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Dumasules-Z *Unimed, India.*
Ascorbic acid (p. 2110·3); ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Dumex LF *Dumex, Philipp.†*
Lactose-free infant feed.
Diarrhoea; lactose intolerance.

Dumex Mama *Dumex, Thai.*
Preparation for enteral nutrition.
Dietary supplement for pregnant and lactating women.

Dumex Mama Plus *Dumex, Malaysia†; Dumex, Philipp.†*
Nutritional supplement for pregnant and lactating women.

Dumin *Actavis, Indon.*
Paracetamol (p. 115·1).
Pain.

Dumint *TNP, Thai.*
Sodium bicarbonate (p. 1781·1); peppermint oil (p. 1877·1).
Gastrointestinal disorders.

Dumirox *Europharma, Denm.; Solvay, Ital.; Abbott, Spain.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Dumocalcin
Note: this name may be used for preparations of different composition.
Actavis, Indon.
Calcium hydrogen phosphate (p. 1783·3).
Calcium supplement.

Alpharma, Singapore.†
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Dietary supplement.

Dumocalcin Plus *Actavis, Indon.*
Calcium hydrogen phosphate (p. 1783·3); calcium citrate (p. 1783·2); vitamin D (p. 2112·3).
Calcium and vitamin D supplement.

Dumocycline *Actavis, Indon.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Dumolid *Actavis, Indon.*
Nitrazepam (p. 1089·1).
Insomnia.

Dumore *Lupin, India.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dumotrim *Actavis, Indon.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dumoxin *Actavis, Indon.; Aspen, S.Afr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Dumozol *Actavis, Indon.; Actavis, Port.; Actavis, Switz.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; rosacea.

Dumyrox *Solvay, Gr.; Abbott, Port.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Dun Ling *Xincat, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Duna *Tedec Meiji, Spain.*
Pinazepam (p. 1097·3).
Anxiety.

Dunaden *Duncan, Arg.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Dunason *Alcon, Arg.; Alcon, Braz.; Alcon, Mex.*
Chondroitin sulfate (p. 2476·1).
Dry eyes.

Dunate *Samarth, India.*
Artesunate (p. 648·2).
Malaria.

Duncan *Pharmaland, Thai.†*
Chlorpromazine hydrochloride (p. 1045·2).
Sedative; schizophrenia; mania.

Dunox *Duncan, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Duo Di *Hong Feng, China.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Duo An *Qi Li, China.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Duo Celloids CPIP *Blackmores, Austral.†*
Calcium phosphate (p. 1784·2); iron phosphate (p. 2077·1).

Duo Celloids CPMP *Blackmores, Austral.†*
Calcium phosphate (p. 1784·2); magnesium phosphate (p. 1787·3).

Duo Celloids PCCP *Blackmores, Austral.†*
Potassium chloride (p. 1793·2); calcium phosphate (p. 1784·2).

Duo Celloids PCIP *Blackmores, Austral.†*
Potassium chloride (p. 1793·2); iron phosphate (p. 2077·1).

Duo Celloids PCMP *Blackmores, Austral.†*
Potassium chloride (p. 1793·2); magnesium phosphate (p. 1787·3).

Duo Celloids PPIP *Blackmores, Austral.†*
Potassium phosphate (p. 1790·3); iron phosphate (p. 2077·1).

Duo Celloids PPMP *Blackmores, Austral.†*
Potassium phosphate (p. 1790·3); magnesium phosphate (p. 1787·3).

Duo Celloids PSMP *Blackmores, Austral.†*
Potassium sulfate (p. 1793·2); magnesium phosphate (p. 1787·3).

Duo Celloids PSPC *Blackmores, Austral.†*
Potassium sulfate (p. 1793·2); potassium chloride (p. 1793·2).

Duo Celloids SCF *Blackmores, Austral.†*
Silicon dioxide (p. 2208·3); calcium fluoride (p. 2053·1).

Duo Celloids SPCF *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); calcium fluoride (p. 2053·1).

Duo Celloids SPCP *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); calcium phosphate (p. 1784·2).

Duo Celloids SPIP *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); iron phosphate (p. 2077·1).

Duo Celloids SPMP *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); magnesium phosphate (p. 1787·3).

Duo Celloids SPPC *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); potassium chloride (p. 1793·2).

Duo Celloids SPPP *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); potassium phosphate (p. 1790·3).

Duo Celloids SPPS *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); potassium sulfate (p. 1793·2).

Duo Celloids SPS *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); silicon dioxide (p. 2208·3).

Duo Celloids SPSS *Blackmores, Austral.†*
Dibasic sodium phosphate (p. 1791·2); sodium sulfate (p. 1888·1).

Duo Celloids SSMP *Blackmores, Austral.†*
Sodium sulfate (p. 1888·1); magnesium phosphate (p. 1787·3).

Duo Celloids SSPC *Blackmores, Austral.†*
Sodium sulfate (p. 1888·1); potassium chloride (p. 1793·2).

Duo Celloids SSS *Blackmores, Austral.†*
Sodium sulfate (p. 1888·1); silicon dioxide (p. 2208·3).

Duo Clindacin *Panalab, Arg.*
Gel, benzoyl peroxide (p. 1696·1); topical solution, clindamycin phosphate (p. 269·3).
Acne.

Duo Fo *Ke Lun, China.*
Citalopram hydrobromide (p. 411·1).
Depression; bipolar disorder.

Duo Ling *Chia Tai, China.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Duo Long *Qing Hua Zi Guang Gu Han, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Duo Mi Te Ding *Baiyunshan, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Duo Pa Fei *Qilu, China.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Duo Pai Tong *Rotam Reddy, China.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Duo Qing *Bai Li, China.*
Levofloxacin mesilate.
Bacterial infections.

Duo Réparation *Texinfine, Fr.*
Bottle A: isononyl isonanoate; padina pavonica (p. 2612·1); bottle B: isononyl isonanoate; opuntia ficus-indica.
Scars.

Duo Rui *Bai Ling, China.*
Diethylamine salicylate (p. 51·3).
Musculoskeletal and joint pain.

Duo Shai *Minghua, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Duo Ta Ke Mei *Fengyuan, China.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Duo Xi Lin *Changzhou, China.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Duo Yi *Xinhua, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Duo-Anglucid *Collins, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Duobak *Kocak, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Kocak, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Duobaktam *Eczacibasi, Turk.*
Injection: Ampicillin (p. 218·2); sulbactam (p. 360·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Eczacibasi, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Duobar *Nutricia, Ital.*
Nutritional supplement.
Low protein diets.

Scientific Hospital Supplies, Austral.†; Scientific Hospital Supplies, Irl.
Food for special diets.
Protein restriction.

SHS, UK.
Low protein food for special diets.

Duobetic *Help, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis; allergic conjunctivitis.

Duo-Bil *Lalco, Canad.*
Cynara (p. 2490·3); taraxacum (p. 2625·3).

Duobloc *Sidus, Arg.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Duo-C *Geymonat, Ital.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Duocad *Ranbaxy, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Duo-Caine
Note: this name may be used for preparations of different composition.
Fougera, Israel.
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Duocaine
Note: this name may be used for preparations of different composition.
Amphastar, USA.
Lidocaine hydrochloride (p. 1988·2); bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Duocal *Nutricia, Austral.; Nutricia, Fin.; Nutricia, Fr.; SHS, Irl.; Nutricia, NZ.*
Food for special diets.

SHS, UK.
Protein-free food supplement for special diets.

Duocarnic *Iasimo, Gr.*
Levocarnitine (p. 2053·2).

Duocef *Bergamo, Braz.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Duocet *Mason, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Duochek *Indoco, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Duocid *Pfizer, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Pfizer, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Duoclox *FDC, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Duocom *Vista, Philipp.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections.

Duocort *Orion, Fin.*
⊗Hydrocortisone butyrate (p. 1640·1); chlorhexidine gluconate (p. 1743·3).
Skin disorders.

Duo-Coteczin *Holley-Cotec, China.*
Artenimol (p. 648·2); piperaquine phosphate (p. 659·3).
Malaria.

DuoCover *BMS, Austral.; BMS, Ger.; BMS, Gr.; BMS, Irl.; BMS, Neth.; BMS, Pol.; BMS, Port.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Thromboembolism prophylaxis in acute coronary syndrome.

Duo-CVP *Sanofi-Aventis, Chile.*
Citrobioflavonoids (p. 2505·2); ascorbic acid (p. 2110·3).
Capillary fragility; haemorrhage.

Duodart *GSK, Austral.; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Israel; GSK, Norw.; GSK, Pol.; GSK, Spain; GSK, Switz.*
Dutasteride (p. 2357·2); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Duo-Decadron *Sidus, Arg.; Ache, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); dexamethasone acetate (p. 1631·1).
Corticosteroid.

Duodenel *Nafar, Mex.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Duoderm *Werfen, Arg.; Convatec, Fr.*
A range of hydrocolloid dressings.
Burns; ulcers; wounds.

BMS, Austral.; Convatec, Belg.; Convatec, UK.
Hydrocolloid dressing.
Wounds; burns; skin ulcers.

Abbott, Turk.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts.

Duoderm E *Convatec, Belg.*
A polyurethane dressing (p. 1718·1).
Wounds.

Duoderm Hydrogel *Convatec, Belg.*
A hydrogel dressing.
Wounds.

Duodil *Solvay, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Painful skeletal muscle spasm.

Duodopa *Solvay, Austral.; Solvay, Austria; AbbVie, Belg.; Torrent, Braz.; Abbott, Canad.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; AbbVie, Ger.; Solvay, Gr.; Solvay, Hung.; Abbott, Irl.; Abbott, Israel; Solvay, Ital.; AbbVie, Neth.; Abbott, Norw.; Solvay, Port.; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, UK.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

DuoDote *Survival Technology, USA.*
Atropine (p. 1310·2); pralidoxime chloride (p. 1571·1).
Organophosphorus poisoning.

Duo-Extolen *Specifar, Gr.*
Zipeprol hydrochloride (p. 1680·3).
Cough.

Duofem
Note: this name may be used for preparations of different composition.
Hexal, Ger.†
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Duofemme
Note: this name may be used for preparations of different composition.
Isdin, Spain.
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Duofer *Andreabal, Switz.*
Ferrous fumarate (p. 2060·3); ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Breckenridge, USA.
Haem iron polypeptide (p. 1555·3); polysaccharide-iron complex (p. 2086·2).

Duofer Fol *Andreabal, Switz.*
Ferrous fumarate (p. 2060·3); ferrous gluconate (p. 2061·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; anaemias.

Duofibra *Aesculapius, Ital.*
Ispaghula (p. 1849·1); acacia (p. 2166·1).
Dietary fibre supplement.

Duofilm *GSK, Arg.; Stiefel, Austral.; Stiefel, Belg.; Stiefel, Canad.; Stiefel, Hong Kong; Stiefel, NZ; GSK, Singapore; Schering-Plough, USA.*
Patch: topical gel: Salicylic acid (p. 1719·1).
Warts; benign epithelial tumours; hyperkeratosis; calluses; corns.

GSK, Arg.; Stiefel, Chile.
Topical solution: Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); flexible collodion.
Warts.

GSK, Austral.
Topical solution: Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); collodion.
Warts.

GSK, Austria; Stiefel, Braz.; Stiefel, Canad.; Pharmedex, Cz.; GSK, Fr.; GSK, Ger.; Stiefel, Ger.; GSK, Gr.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, India; GSK, Irl.; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; Stiefel, Thai.; Stiefel, UK; GSK, Ukr.
Topical liquid: Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; keratolytic; calluses; corns; verrucas; hyperkeratosis.

Stiefel, Neth.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); collodion (p. 1718·2).
Warts.

Duoflam
Note: this name may be used for preparations of different composition.
Cristalia, Braz.
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Svizera, India.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Duoflam Gel *Svizera, India.*
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and soft-tissue disorders.

Duoflam Plus *Svizera, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; inflammation; pain.

Duoflam Spy *Svizera, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Duoflex *Rayere, Mex.*
Diclofenac sodium (p. 48·3); carisoprodol (p. 2021·3).
Inflammation; musculoskeletal pain with muscle spasm; pain.

Duoflu *Fortbenton, Arg.*
⊗Fluocinolone acetonide (p. 1636·1).
Seborrhoeic dermatitis.

Duoforte *Stiefel, Arg.; Stiefel, Canad.*
Salicylic acid (p. 1719·1).
Warts.

DuoGalen *Galen, Ger.*
⊗Flumetasone pivalate (p. 1635·2); triclosan (p. 1773·2).
Infected skin disorders.

Duogas
Note: this name may be used for preparations of different composition.
Bracco, Ital.
Sodium bicarbonate (p. 1781·1); anhydrous citric acid (p. 2480·3); dimeticone (p. 1886·2).
Double-contrast radiography of the oesophagus and stomach.

Macrophar, Thai.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Duogastril *Biolab, Philipp.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Duogel *Zytras, India.*
Domperidone (p. 1838·1); magaldrate (p. 1856·1); simeticone (p. 1886·2).

Duogestan *Besins, Belg.*
Tablets, estradiol (p. 2271·1); capsules, progesterone (p. 2300·2).

Duogink *Duopharm, Ger.†*
Ginkgo biloba (p. 2512·3).
Cerebrovascular disorders.

Duoglyze *AstraZeneca, Switz.*
Saxagliptin hydrochloride (p. 499·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Duogynon *CCM, Malaysia.*
Progesterone (p. 2300·2); estradiol benzoate (p. 2271·1).
Amenorrhoea.

Duohist DH *Breckenridge, USA.*
Chlorphenamine maleate (p. 620·3); dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Duokang *Open, China.*
Mannatide.
Malignant neoplasms.

Duokapton *Strallhofer, Austria.†*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain; fever.

Duokliman *Kwizda, Austria.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Oestrogen deficiency; osteoporosis.

Duolaxan *Wassermann, Ital.*
Ispaghula (p. 1849·1); liquid paraffin (p. 2191·2).
Constipation.

Duolaxin *Glenmark, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).

Duolikang *NEGPF, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Duolin *Cipla, India; Cipla, Malaysia; Cipla-Medpro, S. Afr.*
⊗Ipratropium bromide (p. 1211·3); salbutamol (p. 1220·2).
Obstructive airways disease.

Rex, NZ; Cipla, Venez.
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Duolip
Note: this name may be used for preparations of different composition.
Sidus, Arg.
Aciclovir (p. 964·1).
Herpesvirus infections.

Ratiopharm, Cz.†; Merckle, Ger.†; Mepha, Hong Kong.†
Etofylline clofibrate (p. 1379·2).
Hyperlipidaemias.

Duolube *Bausch & Lomb, Canad.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Corneal dryness.

Duoluton-L *Zydus, India.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Menstrual disorders; postponement of menstruation.

Duomax *Multicare, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Duomox *Astellas, Cz.; Astellas, Hung.; Astellas, Pol.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Duonalc *Valeant, Canad.†*
Isopropyl alcohol (p. 1758·3).
Skin cleanser.

Duonalc-E *Valeant, Canad.†*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin cleanser.

Duonalc-E Mild *Valeant, Canad.†*
⊗Alcohol (p. 1733·1).
Skin cleanser.

Duonasa *Normon, Spain.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Duonase *Cipla, India.*
⊗Azelastine hydrochloride (p. 617·1); fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Duonate *URL, USA.*
Phenylephrine tannate (p. 1672·2); mepyramine tannate (p. 635·1).
Upper respiratory-tract disorders.

DuoNeb *Dey, USA.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Duonem *Zydus, India.*
Faropenem (p. 298·2).

Duonor *RPG, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Duopack *Nycomed, Arg.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Duoplant
Note: this name may be used for preparations of different composition.
Stiefel, Mex.; Schering-Plough, USA.
Salicylic acid (p. 1719·1).
Warts; molluscum contagiosum.

Stiefel, Canad.†
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); formaldehyde (p. 1752·2).
Plantar warts.

Duoplant Gel *Stiefel, Chile.*
Salicylic acid (p. 1719·1).
Warts.

DuoPlavin *BMS, Fr.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; BMS, Gr.; Sanofi-Aventis, Gr.; BMS, Irl.; Sanofi, Irl.; BMS, Ital.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; BMS, Pol.; Sanofi-Aventis, Pol.; BMS, Port.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; BMS, Switz.; Sanofi-Aventis, Switz.*
Aspirin (p. 22·2); clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis in acute coronary syndrome.

Duopres *Farma, Venez.*
Amlodipine besilate (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Duopril
Note: this name may be used for preparations of different composition.
BMS, Hung.
⊗Fosinopril (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Neo Quimica, Braz.
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Duorandil *Medreich, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

Duorina *Zizhu, China.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Duorol *Chefaro, Spain.†*
Paracetamol (p. 115·1).
Pain; fever.

Duosar *Nabiqasim, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Duo-Scabil *Perrigo, Israel.*
Crotamiton (p. 1699·2); sulfur (p. 1721·1).
Scabies.

Duosol *Braun, Cz.; Braun, Fin.; Braun, Gr.†; Braun, Ital.; Braun, Neth.; Braun, Pol.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3) (p. 1780·1); with or without potassium chloride (p. 1793·2).
Haemofiltration; haemodialysis.

Duosolin *Pond's, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Duospan *Svizera, India.*
Diclofenac potassium (p. 48·3); dicycloverine hydrochloride (p. 1834·2).

Duotak *PSA, Philipp.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Duotax *Aristo, India.*
Cefotaxime (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Duoton *TP, Thai.*
Progesterone (p. 2300·2); estradiol benzoate (p. 2271·1).
Menstrual disorders.

Duotop *Sun, India.*
Duloxetine; mecobalamin (p. 2108·1).

Duo-Trach Kit *Astra, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Duotrat *Medley, Braz.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).

DuoTrav *Alcon, Arg.; Alcon, Austria; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon,*

Malaysia; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK.
⊗Travoprost (p. 2012·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Duotric *Asian Pharm, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hyperacidity.

Duotrol *USV, India; USV, Ukr.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Duova
Note: this name may be used for preparations of different composition.
Cipla, India.
⊗Tiotropium bromide (p. 1238·1); formoterol fumarate (p. 1209·2).
Obstructive airways disease.

CSP, Fr.
Estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Duoval *Saval, Chile.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Duovel *Sanovel, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Duovent *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; 2care4, Denm.; Orifarm, Denm.; Paranova, Denm.; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, UK†; Oftalmi, Venez.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Duoventrinetten N *Schworer, Ger.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium trisilicate (p. 1858·1); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; heartburn.

Duovir *Cipla, India; Cipla, Venez.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Duovir N *Cipla, India.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2); nevirapine (p. 1005·1).
HIV infection.

Duovir-E *Cipla, India.*
I Tablet, efavirenz (p. 975·1); 2 tablets, lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Duovisc *Alcon, Austral.; Alcon, Singapore.*
1 Syringe, sodium hyaluronate (p. 2526·2); chondroitin sulfate sodium (p. 2476·1) (Viscoat); 1 syringe, sodium hyaluronate (Provisc).
Adjunct in eye surgery.

Alcon, Ger.; Alcon, Malaysia†; Alcon, S.Afr.†; Alcon, Thai.; Alcon, Turk.†
1 Syringe, sodium hyaluronate (p. 2526·2) (Provisc); 1 syringe, sodium hyaluronate; chondroitin sulfate sodium (p. 2476·1) (Viscoat).
Adjunct in eye surgery.

Duovit *KRKA, Cz.*
20 Tablets, vitamins; 20 tablets, minerals; trace elements.
Nutritional supplement.

KRKA, Pol.
Red tablets, vitamins; blue tablets, minerals.
Tonic.

KRKA, Rus.
Vitamins; minerals.

KRKA, Ukr.
Red tablets, vitamins; cyan tablets, minerals.

Duozol *Blausiegel, Braz.*
Tinidazole (p. 949·2); tioconazole (p. 595·3).
Vaginal infections.

Duozone *Novaduo, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Duozyme *Zenacts, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Dupact *Wockhardt, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dupen Ped *Sresan, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Dupent *Uniphar, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Dupent-D *Uniphar, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Duphalac *Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Grunenthal, Chile; Abbott, China; Abbott, Cz.; Abbott, Fin.; Abbott, Fr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, India; Solvay, Indon.; Abbott, Irl.; Solvay, Ital.; Solvay, Malaysia; Italmex, Mex.; Abbott, Neth.; Abbott, Norw.; Healthcare Logistics, NZ; Solvay, Philipp.; Solvay, Pol.; Abbott, Port.; Solvay, Rus.; Solvay, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Solvay, Turk.; Solvay, UK; Abbott, Ukr.; Solvay, USA.†*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation; salmonella enteritis; gastroenteritis.

Dupharon *CNN, Philipp.*
Folic acid (p. 2063·1); vitamin B substances (p. 2102·3); ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; vitamin B deficiency.

Duphaston *Solvay, Austral.†; Abbott, Austria; Solvay, Belg.; Abbott, Braz.; Grunenthal, Chile; Abbott, China; Abbott, Cz.; Abbott, Fr.; Abbott, Ger.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, India; Solvay, Indon.; Abbott, Irl.; Abbott, Israel; Solvay, Malaysia; Italmex, Mex.; Abbott, Neth.; Duphar, NZ†; Solvay, Philipp.; Solvay, Pol.; Abbott, Port.; Solvay, Rus.; Solvay, S.Afr.; Abbott, Singapore; Abbott, Swed.†; Abbott, Switz.; Abbott, Thai.; Solvay, Turk.; Abbott, Ukr.; Zuoz, Venez.*
Dydrogesterone (p. 2270·1).
Premenstrual syndrome; dysmenorrhoea; endometriosis; female infertility; threatened or recurrent miscarriage; dysfunctional uterine bleeding; menopausal disorders; mastopathies; osteoporosis; cancer of breast, uterus, and kidney; infertility; menorrhagia; adjunct to oestrogen replacement; amenorrhoea.

Duplat *Samarth, India.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Duplax *Sanovel, Turk.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Duplicalcio B12 *Medical, Spain.†*
Calcium gluconate (p. 1783·3); calcium levulinate (p. 1784·2) cyanocobalamin (p. 2107·2); isoniazid (p. 311·2).
Tonic; tuberculosis; anaemias.

Duplicam *Hexal, Cz.†*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Duplotrast Weinsaure *Gerot, Austria.*
Tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1); simeticone (p. 1886·2).
Double contrast gastrointestinal radiography.

Dupofol *Dupomar, Arg.*
Folic acid (p. 2063·1).
Anaemias.

Dupox *Bennet, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Duprost *Cipla, India.*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Durab *Uniphar, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Durabac *Poly, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenyltoloxamine citrate (p. 638·1).
Pain.

Durabac Forte *Poly, USA.*
Paracetamol (p. 115·1); magnesium salicylate (p. 85·2); caffeine (p. 1203·3); phenyltoloxamine citrate (p. 638·1).

Durabec *Raptakos, India.*
⊗Beclometasone dipropionate (p. 1621·2); salbutamol (p. 1220·2).

Durabeta *Littman, Philipp.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Durabiotic *Sandoz, Israel.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Durabolin *Organon, India; Organon, Neth.†; Organon, USA.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer.

Duracain *Sintetica, Switz.†*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Duracaina *Behrens, Venez.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Duracaine *AstraZeneca, Arg.*
Bupivacaine hydrochloride (p. 1980·3).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Duracal *Ultramark, India.*
Vitamin D (p. 2112·3).

Duracard *Sun, India.*
Doxazosin (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Sun, Thai.
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Duracare *Blairex, USA.†*
Cleansing solution for soft contact lenses.

Duracef *BMS, Austria; BMS, Belg.; BMS, Cz.; BMS, Fin.†; BMS, Hong Kong†; BMS, Hung.†; BMS, Mex.; BMS, Pol.; BMS, S.Afr.†; Juste, Spain.*
Cefadroxil (p. 233·2).
Bacterial infections.

Duracef Expec *BMS, Mex.*
Cefadroxil (p. 233·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Duraclon *Bioniche, USA.*
Clonidine hydrochloride (p. 1339·1).
Pain.

Duracoll *EUSA, Belg.*
Gentamicin sulfate (p. 304·2); collagen (bovine) (p. 2483·2).
Bone infections.

Duradoce *Atlantis, Mex.*
Hydroxocobalamin (p. 2107·3).
Neuritis; pernicious anaemia.

DuraDox *Julphar, UAE.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Duradox *Intermed, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Duraflex Comfort *Trimarc, USA.*
⊗Aloe (p. 1693·2); capsicum (p. 2469·3); glucosamine (p. 2515·3); menthol (p. 2553·2); methyl salicylate (p. 92·1); urea (p. 1727·3).
Musculoskeletal pain and stiffness.

Duraflu *Poly, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Duragesic *Janssen-Ortho, Canad.; Janssen, USA.*
⊗Fentanyl (p. 60·1).
Pain.

Durahist *Proethic, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Durahist D *Proethic, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dexchlorpheniramine maleate (p. 621·1); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Durajoint *Piramal, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Durajoint-GM *Piramal, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Duralex *American Urologicals, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Duralyn *Raptakos, India; Raptakos, Thai.*
Theophylline (p. 1229·3).
Bronchospasm; asthma.

Duramist Plus *Pfeiffer, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Duramor *Biological E, India.*
⊗Morphine sulfate (p. 92·3).
Pain.

Duramorph *Gray, Arg.; Westward, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Duramycin *Pyridam, Indon.†*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Duran *TNP, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; inflammation; pain; fever.

Duranil *Elea, Arg.; Johnson & Johnson, Chile.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Duranol *OEP, Philipp.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Durapan *Munir, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Durapen *De Mayo, Braz.†*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Duraphat *Colgate-Palmolive, Austria; Colgate-Palmolive, Denm.; Colgate-Palmolive, Fin.; ABC, Fr.; Colgate, Ger.; Colgate-Palmolive, Gr.; Colgate-Palmolive, Irl.; CTS, Israel; Vebas, Ital.; Colgate-Palmolive, Neth.; Colgate-Palmolive, Norw.; Colgate-Palmolive, Port.; Colgate-Palmolive, Swed.; GABA, Switz.; Colgate-Palmolive, UK.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis; sensitive teeth.

Duraprep *3M, Hong Kong.†*
⊗Alcohol (p. 1733·1); iodine (p. 2336·3).
Skin disinfection.

Duraprox *Tramedico, Belg.; Sanofi Pasteur, Chile†; Alapis, Gr.; Biomeks, Turk.*
Oxaprozin (p. 112·3).
Inflammatory disorders; musculoskeletal, joint, and peri-articular disorders; gout.

DuraProxin *Pharmaceutica North America, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Duras *Shreshtha, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Durasal
Note: this name may be used for preparations of different composition.
Prasco, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Raptakos, India; Raptakos, Thai.
⊗Salbutamol (p. 1220·2).
Asthma; bronchospasm; obstructive airways disease.

Durasalyn *Raptakos, India.*
⊗Salbutamol (p. 1220·2); theophylline (p. 1229·3).
Obstructive airways disease.

Durascreen *Pierre Fabre, USA.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Pierre Fabre, USA.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); ensulizole (p. 1703·1); titanium dioxide (p. 1725·1).
Sunscreen.

Durasol *Visiontec, Arg.*
Contact lens care solution.

Durasolets *SMB, Chile.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry eyes.

Duraspas *Ultramark, India.*
Drotaverine (p. 2497·3) or drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

DuraTan Forte *Proethic, USA.†*
⊗Dextromethorphan tannate (p. 1660·1); dexchlorpheniramine tannate (p. 620·3); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Dura-Tap/PD *Dura, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Duratax *Aristo, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Duratears *Alcon, Belg.; Alcon, Chile; Alcon, Gr.; Alcon, Hong Kong; Alcon, Israel; Alcon, Singapore; Alcon, Thai.; Liba, Turk.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3); wool fat (p. 2219·3).
Dry eyes.

Alcon, Austral.
Liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Alcon, Neth.
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Alcon, S.Afr.
Anhydrous liquid lanolin (p. 2219·3).
Dry eyes.

Duratears Free *Alcon, Neth.*
Povidone (p. 2204·3).
Dry eyes.

Duratears Naturale *Alcon, Malaysia; Alcon, USA.*
Liquid paraffin (p. 2191·2); wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Dry eyes.

Duratears Z *Alcon, Neth.*
Liquid paraffin (p. 2191·2); hydrous wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Dry eyes.

Duraten *Bal, India.*
Doxazosin (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Durater *Senosiain, Mex.*
Famotidine (p. 1842·1).
Gastrointestinal hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Durateston *Schering-Plough, Braz.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Anaemia; androgenic; breast cancer; delayed puberty; male hypogonadism.

Duration *Schering-Plough, Hong Kong†; Schering-Plough, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Duratobal *Ferring, Spain.*
Carbetocin (p. 2132·3).
Uterine atony.

Duratocin *Ferring, Arg.; Ferring, Austral.; Ferring, Canad.; Gynopharm, Chile; Ferring, China; Ferring, Cz.; Ferring, Hong Kong; Ferring, Ital.; Ferring, Malaysia; Pharmaco, NZ; Ferring, Philipp.; Ferring, Singapore; Ferring, Thai.*
Carbetocin (p. 2132·3).
Postpartum haemorrhage; uterine atony.

Duratuss *Victory, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Nasal congestion.

Duratuss A *Victory, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Duratuss AC *Victory, USA.†*
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Duratuss CS *Victory, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Duratuss DA *Victory, USA.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Duratuss DM *Victory, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Duratuss GP *Victory, USA.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Coughs.

Duratuss HD *Victory, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Nasal congestion; coughs.

duraultra *OmniVision, Ger.†*
⊗Vitamin A (p. 2098·3); actinoquinol sodium (p. 2429·3); naphazoline nitrate (p. 1669·3).
Eye disorders.

Duraultra N *OmniVision, Ger.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Dura-Vent/DA *Dura, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract symptoms.

Duraxin *Portal, USA.†*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1); salicylamide (p. 129·2).
Upper respiratory-tract disorders.

Durbis *Sanofi-Aventis, Norw.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Sanofi-Aventis, Swed.
Disopyramide (p. 1363·2) or disopyramide phosphate (p. 1363·3).
Ventricular arrhythmias.

Durea *Samarth, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; sickle-cell disease; essential thrombocythaemia.

Dureep *Alkem, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Durela *Medical Futures, Canad.*
Tramadol hydrochloride (p. 139·2).
Pain.

Dur-Elix *3M, Philipp.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Duremid *Chobet, Arg.*
⊗Indapamide (p. 1409·2).
Hypertension.

Durex Sensilube *SSL, UK.*
Vaginal lubricant.
Formerly known as Senselle.

Durezol *Alcon, USA.*
⊗Difluprednate (p. 1634·2).
Inflammation and pain following eye surgery; uveitis.

Durfin *Orifarm, Denm.†*
Ebastine (p. 628·1).
Allergic rhinoconjunctivitis; urticaria.

Durgel *LDA, Arg.*
Centella (p. 1698·3); caffeine (p. 1203·3); levocarnitine (p. 2053·2).
Cellulite.

Duricef *BMS, Canad.†; BMS, Indon.†; BMS, Turk.*
Cefadroxil (p. 233·2).
Bacterial infections.

Duride *Alphapharm, Austral.; LCH, Hong Kong†; Alphapharm, Malaysia†; Mylan, NZ.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Durisal *Yeri, Turk.*
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Durnit *Sanofi-Aventis, Arg.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Durobac *Innovata, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Durobion *Olvos, Gr.*
⊗Diethylaminoethanol malate (p. 2321·1).
Tonic.

Durocin *Antor, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Durodor *Sandoz, Mex.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Duroferon *GSK Consumer, Fin.; GSK Consumer, Norw.; GSK Consumer, Swed.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Durofolin *Biotrends, Gr.*
Calcium folinate (p. 2066·3).
Folic acid antidote; megaloblastic anaemia.

Durogesic *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Johnson & Johnson, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel†; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen, Port.; Janssen, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Johnson & Johnson, Turk.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
⊗Fentanyl (p. 60·1).
Pain.

Durogest *Daksh, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Duro-K *Novartis, Austral.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Durol *Actavis, Indon.*
Vitamin B substances (p. 2102·3); minerals.
Tonic.

Durolane *Smith & Nephew, Canad.; Smith & Nephew, Fr.; Kalbe, Indon.; Smith & Nephew, Ital.*
Hyaluronic acid (p. 2526·2).
Osteoarthritis.

Duromeran *Peseri, Cz.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Duromine *iNova, Austral.; iNova, Hong Kong; iNova, Malaysia; iNova, NZ; iNova, Philipp.; iNova, S.Afr.; iNova, Singapore; 3M, Thai.*
⊗Phentermine (as an ion-exchange resin complex) (p. 2329·2).
Obesity.

Duron *Samarth, India.*
Amiodarone (p. 1300·1).
Ventricular arrhythmias.

Duronitrin *AstraZeneca, Ital.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Durotep *Janssen, Jpn.*
⊗Fentanyl (p. 60·1).
Pain.

Durotram *iNova, Austral.; iNova, NZ.*
Tramadol hydrochloride (p. 139·2).
Pain.

Duro-Tuss
Note: this name may be used for preparations of different composition.
iNova, Hong Kong; iNova, Malaysia; iNova, Singapore.
Pholcodine (p. 1675·1).
Cough.

iNova, S.Afr.†
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol sulfate (p. 1220·2).
Cough associated with bronchospasm.

Duro-Tuss Chesty Cough *iNova, Austral.; 3M, NZ; iNova, Singapore.*
Bromhexine hydrochloride (p. 1656·3).
Formerly known as Duro-Tuss Mucolytic.
Cough; respiratory-tract congestion.

Duro-Tuss Chesty Cough Forte *iNova, Austral.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Duro-Tuss Chesty Cough Plus Nasal Decongestant *iNova, Austral.*
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1).
Sinus and nasal congestion; cough.

Duro-Tuss Cold & Allergy *3M, Austral.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract congestion.

Duro-Tuss Cough *3M, NZ.†*
⊗Pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Duro-Tuss Cough Lozenges *iNova, Singapore.*
Pholcodine (p. 1675·1); cetylpyridinium chloride (p. 1743·1).
Cough; sore throat.

Duro-Tuss Decongestant *3M, Austral.†; iNova, Hong Kong; iNova, Singapore.†*
⊗Pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Duro-Tuss Dry Cough *iNova, Austral.*
Lozenges: Pholcodine (p. 1675·1); cetylpyridinium chloride (p. 1743·1).
Cough; sore throat.

iNova, Austral.; 3M, NZ.
Oral liquid: Pholcodine (p. 1675·1).
Cough.

Duro-Tuss Dry Cough Plus Nasal Decongestant *iNova, Austral.*
⊗Pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; respiratory-tract congestion.

Duro-Tuss Expectorant *iNova, Austral.; iNova, Hong Kong; iNova, Malaysia; 3M, NZ; iNova, Singapore.*
Pholcodine (p. 1675·1); bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Duro-Tuss Lozenges *3M, NZ.*
Pholcodine (p. 1675·1); cetylpyridinium chloride (p. 1743·1).
Cough; sore throat.

Duro-Tuss Mucolytic *iNova, Hong Kong.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Duro-Tuss Mucolytic Cough Liquid *3M, Austral.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Duro-Tuss PE Dry Cough plus Nasal Decongestant *iNova, Austral.*
Pholcodine (p. 1675·1); phenylephrine hydrochloride (p. 1672·3).
Cough; nasal congestion.

Duro-Tuss Sinus *3M, Austral.†; iNova, Malaysia.†*
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion; sinus congestion; nasal congestion.

Duroval *Valmor, Venez.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Durovit *AstraZeneca, India.*
Ascorbic acid (p. 2110·3); ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

Durovit-Fez *AstraZeneca, India.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Durvitan *Anotaciones, Spain.*
Caffeine (p. 1203·3).
Asthenia.

Dusil *Alpharma, Singapore.†*
Aspirin (p. 22·2).
Pain; fever.

Dusodril *Merck, Austria; Merck Serono, Ger.*
Naftidrofuryl oxalate (p. 1443·3).
Peripheral and cerebral vascular disorders; vascular disorders of the brain, ears, and eyes.

Dusopharm *Sopharma, Rus.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders.

Duspatal *Grunenthal, Chile; Abbott, Ger.; Solvay, Ital.; Abbott, Neth.; Abbott, Port.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Duspatalin *Raffo, Arg.; Solvay, Belg.; Abbott, Braz.; Abbott, China; Abbott, Cz.; Abbott, Denm.; Abbott, Fr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Indon.; PSI, Ital.; Solvay, Malaysia; Italmex, Mex.; Delphi, Neth.; Solvay, Philipp.; Solvay, Pol.; Abbott, Rus.; Abbott, Singapore; Abbott, Spain; Abbott, Switz.; Abbott, Ukr.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm; irritable bowel syndrome; enteritis; biliary dyskinesia.

Solvay, Turk.
Mebeverine embonate (p. 1858·3) or mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm.

Duspatin *BerlinPharm, Thai.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm; irritable bowel syndrome.

Duspaverin *Biokem, Turk.; Sandoz, Turk.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm.

Dussedrine *Exakta, Mex.†*
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Dutagen *Ranbaxy, India.*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Dutalfa *Reddy, India.*
Alfuzosin (p. 2351·3); dutasteride (p. 2357·2).

Dutas *Reddy, India.*
Dutasteride (p. 2357·2).
Benign prostatic hyperplasia.

Dutas-T *Reddy, India.*
Dutasteride (p. 2357·2); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Dutaxel *Samarth, India.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Duther *Samarth, India.*
Artemether (p. 648·1).
Malaria.

Duticin *Korea United, Philipp.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Dutin *Ranbaxy, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Dutoprol *AstraZeneca, USA.*
⊗Hydrochlorothiazide (p. 1403·2); metoprolol tartrate (p. 1434·3).
Hypertension.

Dutora-M *Orion, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Dutron *Haledew, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Dutross *TNP, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Dutross-P *TNP, Thai.*
Bromhexine hydrochloride (p. 1656·3); sulfogaiacol (p. 1678·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Duvabel *Blubell, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Duvadilan *Raffo, Arg.; Solvay, Gr.; Solvay, India; Solvay, Indon.; Solvay, Philipp.; Zuoz, Venez.*
Isoxsuprine hydrochloride (p. 2535·2).
Cerebral and peripheral vascular disorders; premature labour.

Duvagin *Infinity, Venez.*
Acetic acid (p. 2426·3).
Vaginal disorders.

Duvanta *Intas, India.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress urinary incontinence in women.

Duvaprine *Ultramed, Philipp.*
Isoxsuprine hydrochloride (p. 2535·2).
Cerebral and peripheral vascular disorders; premature labour.

Duvig *Fada, Arg.*
Dobutamine (p. 1365·3).

Duvodine *Actavis, Indon.†*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane disinfection; wounds; burns.

Duvoid *Paladin, Canad.*
Bethanechol chloride (p. 2456·2).
Urinary retention.

Duxaril *Servier, Hong Kong; Servier, Philipp.; Servier, Singapore; Servier, Thai.†*
Almitrine dimesilate (p. 2315·3); raubasine (p. 1485·1).
Cochleovestibular ischaemia; mental function impairment; stroke; cerebrovascular disorders; chorioretinal ischaemia.

Duxet *Unichem, India.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress urinary incontinence in women.

Duxetin *Gador, Arg.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; anxiety; fibromyalgia.

Duxil
Note: this name may be used for preparations of different composition.
Galenica, Gr.
Carbocisteine lysine (p. 1658·2).
Respiratory-tract congestion.
Servier, China.
Almitrine (p. 2315·3); raubasine (p. 1485·1).
Mental function impairment in the elderly; vascular ear and eye disorders.

Duxim *Daksh, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Duxima *Ecobi, Ital.*
Cefuroxime sodium (p. 255·3).
Gram-negative bacterial infections.

Duxocin *Biochem, India.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Duzac *Sun, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Duzela *Sun, India.*
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress urinary incontinence in women.

Duzela-M *Sun, India.*
Duloxetine hydrochloride (p. 415·1); mecobalamin (p. 2108·1).

Duzen *Prime, Singapore.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

D-Val *Baroda, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Dvella *Gedeon Richter, Ukr.*
Ulipristal acetate (p. 2312·1).
Postcoital oral contraceptive.

D-Vi-Sol *Mead Johnson Nutritionals, Canad.*
Colecalciferol (p. 2113·1).
Vitamin D supplement for breast-fed infants.

D-Vita *Major, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

D-Vital *Will-Pharma, Belg.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

DVN *Overseas, India.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

DVN Plus *Overseas, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

DVN-Forte *Overseas, India.*
Drotaverine hydrochloride (p. 2497·3); paracetamol (p. 115·1).

D-Void *Sun, Braz.*
⊗Desmopressin (p. 2355·1).
Sun, India.
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturia; nocturnal enuresis; test of renal concentrating capacity.

D-Worm
Note: this name may be used for preparations of different composition.
Aspen Consumer, S.Afr.
Mebendazole (p. 158·3).
Worm infections.
Hauz, India.
Albendazole (p. 149·1).
Giardiasis; worm infections.

DX-24 *Vilco, India.*
Doxycycline (p. 288·1).
Bacterial infections.

D-Xanthin *Alna, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Dyalac *Crisdy-Na, Philipp.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Dyamide *Macleods, India.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Dyamide Plus *Macleods, India.*
⊗Spironolactone (p. 1499·3); torasemide (p. 1516·3).

Dyazide *Goldshield, Hong Kong; Goldshield, Irl.; GSK, Mex.†; Decomed, Port.; Pharmafrica, S.Afr.; Goldshield, Thai.; Goldshield, UK; SmithKline Beecham, USA.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
These ingredients can be described by the British Approved Name Co-triamterzide.
Hypertension; oedema.

Dyberzide *Vianex (Βιανεξ), Gr.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).

Dycerin *Glenmark, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Dycerin-A *Glenmark, India.*
Aceclofenac (p. 16·2); diacerein (p. 45·3).

Dycerin-GM *Glenmark, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Dycholium *Novartis Consumer, Canad.*
Dehydrocholic acid (p. 2492·1).
Biliary-tract disorders.

Dycon *Hovid, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dyet *Plus, India.*
Preparation for enteral nutrition.

Dyflex-G *EconoMed, USA.*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Bronchospasm.

Dy-G *Cypress, USA.†*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Asthma.

Dygase *Cypress, USA.*
⊗Pancreatin (p. 2579·3).
Digestive enzyme deficiency.

Dygratyl *Dishman, Fin.; Famar, Gr.; Dishman, Swed.*
Dihydrotachysterol (p. 2113·2).
Hypocalcaemia; hypoparathyroidism; vitamin D deficiency; secondary hyperparathyroidism; rickets; renal osteodystrophy.

DYL *Ajanta, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

DYL-AX *Ajanta, India.*
Ambroxol (p. 1654·3); desloratadine (p. 625·1).

DYL-D *Ajanta, India.*
⊗Desloratadine (p. 625·1); pseudoephedrine hydrochloride (p. 1676·1).

Dylix *Lunsco, USA.*
Diprophylline (p. 1207·3).

Dylock-LB *Embiotic, India.*
Lactic acid bacillus (p. 2596·3); loperamide (p. 1854·2).

Dylofen *Ultra, Mex.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Dyloject *Javelin, UK.*
Diclofenac sodium (p. 48·3).
Pain.

Dymadon *Johnson & Johnson, Austral.*
Paracetamol (p. 115·1).
Pain; fever.

Dymadon Co *Pfizer Consumer, Austral.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dymadon Forte *Johnson & Johnson, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Dymaten *Continentales, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Dymef *Glories, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Dymenate *Keene, USA.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Dymin-P *Glories, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Dymista *Meda, Fin.; Meda, UK; Meda, USA.*
⊗Azelastine hydrochloride (p. 617·1); fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Dymotil *Goldshield, UK.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
These ingredients can be described by the British Approved Name Co-phenotrope.
Diarrhoea.

Dymoxin *Community Pharmacy, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Dyna *Crisdy-Na, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Dyna Jets *Bayer Consumer, S.Afr.*
Vitamins.

Dynabac *Almirall, Fr.†; Lilly, Gr.; Abdi, Turk.*
Dirithromycin (p. 287·1).
Bacterial infections.

Dynabiane *Pileje, Fr.*
Tyrosine (p. 2098·3); ginseng (p. 2513·3); guarana (p. 2648·2); vitamins; rice protein hydrolysate; copper sulfate (p. 2057·2).
Tonic.

Dynacal *Douglas, Canad.*
Vitamins; minerals.

Dynacard *USV, India.*
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

Dynacef *Dexa, Indon.*
Cefradine (p. 249·1).
Bacterial infections.

Dynacil
Note: this name may be used for preparations of different composition.
Hindustan Antibiotic, India.
Ampicillin (p. 218·2).
Bacterial infections.
Sanol, Ger.†; Schwarz, Ger.†
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

Dynacil comp *Sanol, Ger.; UCB, Ger.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dynacin *Par, USA.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Dynacirc *Novartis, Hong Kong; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, S.Afr.; Novartis, Singapore; Novartis, Thai.†; Novartis, Turk.; GSK, USA.*
Isradipine (p. 1414·2).
Hypertension.

Dynaclox *Bal, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Dynacort *Utopian, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Dynadol *Thebe, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Dynafloc *Pharma Dynamics, S.Afr.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Dyna-Hex *Western Medical, USA.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Dynak *Pharma Dynamics, S.Afr.*
Diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dynalix *Biocon, India.*
Enoxaparin (p. 1372·3).
Thromboembolic disorders; prevention of clotting during haemodialysis; unstable angina.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Dynamax *Novaduo, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Dynamet *Cubit, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3).

Dynametron *Thebe, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Dynamic Skin *Dermalogica, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Dynamin
Note: this name may be used for preparations of different composition.
Berk, UK.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.
Ern, Spain.
Vitamin B substances (p. 2102·3); caffeine (p. 1203·3); glutamine (p. 2070·3).
Tonic.

Dynamisan
Note: this name may be used for preparations of different composition.
Novartis Sante, Fr.; Mipharm, Ital.
Arginine glutamate (p. 2049·1).
Asthenia; tonic.
Novartis, Arg.; Novartis, Mex.
Vitamins; minerals; amino acids; ginseng (p. 2513·3).
Nutritional supplement.
Novartis, Chile.
Vitamins; minerals; arginine (p. 2049·1); glutamine (p. 2070·3); ginseng (p. 2513·3).
Tonic.
Novartis Consumer, Switz.
Arginine aspartate (p. 2049·1).
Tonic.

Dynamo *Key, Austral.†*
Caffeine (p. 1203·3); glucose (p. 2068·3); thiamine hydrochloride (p. 2103·1); nicotinic acid (p. 2083·1).
Mental fatigue; drowsiness.

Dynamogen *Faes, Spain.*
Arginine aspartate (p. 2049·1); cyproheptadine ketoglutarate.
Anorexia; weight loss; tonic.

Dynamox *Bal, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Dynamucil *Siphar, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucus.

Dynapar
Note: this name may be used for preparations of different composition.
Troikaa, India.
Enteric-coated tablets; injection; sR tablets: Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain 406 Covers Dynapar, Dynapar SR and Dynapar-AQ.
Troikaa, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.
Troikaa, Philipp.
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Dynapar LD *Troikaa, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Dyna par PPI *Troikaa, India.*
Diclofenac (p. 48·3); rabeprazole (p. 1881·1).

Dynapayne *Salters, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Dynapen-3
Note: this name may be used for preparations of different composition.
Zwitter, Gr.
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Dynaphos C *Sofar, Ital.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; stomatitis; gingivitis.

Dynapres *Reddy, India.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Dynaspor *Thebe, S.Afr.*
Clotrimazole (p. 576·2).
Fungal infections.

Dynasprin *USV, India.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).
Thromboembolic disorders.

Dynastat *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Thai.; Pharmacia, UK; Pfizer, Ukr.*
Parecoxib sodium (p. 119·3).
Pain.

Dynatra *Almirall, Belg.; Zambon, Neth.*
Dopamine hydrochloride (p. 1367·2).
Hypotension; shock.

Dynatussin *Crisdy-Na, Philipp.*
Capsules: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold and influenza symptoms.
Crisdy-Na, Philipp.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); sodium citrate (p. 1781·2).
Cough; cold and influenza symptoms.

Dynavit *Danlex, Philipp.*
Vitamins; chlorella growth factor (p. 2475·3).
Nutritional supplement.

Dynavita *Coup, Gr.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin hydrochloride (p. 2107·2).

Dynax *Farmalex, Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Dynaxon *Winthrop, Turk.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Dynazole *Thebe, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Dynepo *Shire, Cz.†; Shire, Fr.†; Shire, Ger.†; Aventis, Gr.; Shire, Irl.†; Shire, Ital.†; Shire, Neth.†; Shire, Port.†; Shire, Spain†; Shire, UK.†*
⊗Epoetin delta (p. 1141·1).
Anaemia in renal failure.

Dynergum *Biocodex, Port.*
Citrulline malate (p. 2056·3).
Tonic.

Dynex VR *Athlon, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Dynexan *Nycomed, Austria; Adcock Ingram, S.Afr.*
Tetracaine hydrochloride (p. 1996·3); chamomile (p. 2474·1); arnica (p. 2447·2); sage (p. 2608·3); aluminium formate (p. 1817·1).
Aphthous ulcers; denture irritation; cold sores; mouth and throat disorders.
Kreussler, Fr.; Pro Concepta, Switz.
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; painful mouth lesions; mouth and throat disorders.

Dynexan A *Kreussler, Rus.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Dynexan Mundgel *Kreussler, Ger.*
Lidocaine hydrochloride (p. 1988·2); benzalkonium chloride (p. 1737·1).
Painful inflammatory disorders of the mouth.

Dynexan Proaktiv *Kreussler, Ger.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Dynexan Zahnfleischtropfen *Kreussler, Ger.*
Aluminium formate (p. 1817·1).
Mouth and throat inflammation.

Dynexangival *Kreussler, Fr.*
Lidocaine hydrochloride (p. 1988·2).
Painful mouth lesions.

Dynofen *Thebe, S.Afr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Dynolap *Sun, India.*
Olopatadine hydrochloride (p. 636·2).

Dynorm *Roche, Ger.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Dynorm Plus *Roche, Ger.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dynos *Intramed, S.Afr.†*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure.

Dynovase *Gebro, Spain.*
Epoprostenol sodium (p. 1375·1).
Thromboembolism prophylaxis during renal dialysis; pulmonary hypertension.

Dynoxytet *Thebe, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Dynyel *Raam, Mex.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Dyoflux *Dyota, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Dyphylline-GG *Cypress, USA.†*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Asthma; bronchospasm.

Dypracet *Auden McKenzie, UK.*
Dihydrocodeine tartrate (p. 52·3); paracetamol (p. 115·1).
Pain.

Dyprotex *Blistex, USA.*
Dimethicone (p. 2209·3); zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Nappy rash.
Blistex, Israel.
Zinc oxide (p. 1729·1).
Nappy rash.

Dyrade-M *Cipla, India.*
Diloxanide furoate (p. 931·2); metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis.

Dyrenium *SmithKline Beecham, USA.*
⊗Triamterene (p. 1518·3).
Oedema.

Dyrenium compositum *Doetsch, Grether, Switz.†*
⊗Triamterene (p. 1518·3); benzthiazide (p. 1316·1).
Oedema; hypertension.

Dyrset-Eze *Symbiotic, India.*
Sodium picosulfate (p. 1887·2).

Dysalfa *CSP, Fr.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Dysfungal *Roi Surya, Indon.†*
Ketoconazole (p. 585·3).
Fungal skin infections.

Dyskinebyl *Laphal, China.*
Dihydroxydibutylether (p. 2493·1).
Biliary-tract disorders.

Dyskinil *Crescent, India.*
Trihexyphenidyl (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Dyskly *Raam, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Dyslip *East West, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Dyslip-EZ *East West, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Dyslip-TG *East West, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Dysliptin *East West, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Dysliptin-EZ *East West, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Dysliptin-TG *East West, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Dyslor *Biolatina, Chile.†*
Botulinum A toxin (p. 2017·1).
Blepharospasm; hemifacial spasm; spasmodic torticollis; spasticity; facial lines; foot spasticity in cerebral palsy.

Dysmen *Svizera, India.*
Tablets: Mefenamic acid (p. 85·3); dicycloverine hydrochloride (p. 1834·2).
Colic; dysmenorrhoea.
Svizera, India.
Injection: Dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Dysmen 500 *Svizera, India.*
Mefenamic acid (p. 85·3).
Pain.

Dysmen Forte *Svizera, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).
Pain.

Dysmenalgit *Krewel, Ger.*
Naproxen (p. 98·2).
Dysmenorrhoea.

Dysmenic *VS, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal spasm and pain.

Dysmenorm *DHU, Rus.; DHU, Ukr.*
⊗Agnus castus (p. 2432·2); pulsatilla pratensis (p. 2600·2); rosmarinus officinalis (p. 2607·2); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Dysmenorrhoe-Gastreu S R75 *Reckeweg, Ger.*
Caulophyllum (p. 2458·2); cimicifuga (p. 2478·1); magnesium phosphoricum (p. 1787·3); viburnum opulus.
Homoeopathic preparation.

Dysmeryl *Medley, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Dysnilox *Yash, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Dyspagon *Pierre Fabre, Fr.; Pierre Fabre, Port.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Dyspagone *Pharmafabre, Gr.*
Alginic acid (p. 2167·2); magnesium carbonate (p. 1856·2); aluminium hydroxide (p. 1817·2); colloidal silicon dioxide (p. 2209·1).

Dyspamet *Goldshield, Irl.†; Goldshield, UK.*
Cimetidine (p. 1827·1).
Peptic ulcer; reduction of gastric acid secretion; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Dyspas *Embiotic, India.*
Dicycloverine (p. 1834·2); nimesulide (p. 101·3).

Dyspepsin *Herbapol Krakow, Pol.*
Achillea (p. 2427·3); calendula (p. 2465·2); gentian (p. 2512·1); peppermint leaf (p. 1877·1); phaseolus (p. 2587·3); taraxacum (p. 2625·3).
Dyspepsia.

Dysport *Galderma, Arg.; Ipsen, Austral.; Pharma Logistik, Austria; Ipsen, Belg.; Biosintetica, Braz.; Ipsen, Cz.; Ipsen, Denm.; Ipsen, Fin.; Ipsen, Fr.; Ipsen, Ger.; Ipsen, Gr.; Beaufour-Ipsen, Hong Kong; Ipsen, Hung.; Ipsen, Irl.; Ipsen, Israel; Ipsen, Ital.; Beaufour-Ipsen, Malaysia; Biopharmex, Mex.; Ipsen, Neth.; Ipsen, Norw.; Ipsen, NZ; NZ Medical & Scientific, NZ; Ipsen, Philipp.; Ipsen, Pol.; Ipsen, Port.; Ipsen, Rus.; Pharmaplan, S.Afr.; Zuellig, Singapore; Ipsen, Spain; Ipsen, Swed.; Future Health, Switz.; Ipsen, Thai.; Gen, Turk.; Ipsen, UK; Ipsen, Ukr.; Tercica, USA; Nolver, Venez.*
Botulinum A toxin (p. 2017·1).
It is also described as containing abobotulinumtoxinA.
Blepharospasm; hemifacial spasm; spasmodic torticollis; foot spasticity associated with paediatric cerebral palsy; hyperhidrosis; upper limb spasticity following stroke; glabellar lines; anal fissure;

tension headache; oesophageal achalasia; hyperreflexia urinary bladder.

Dystan *Medikon, Indon.†*
Mefenamic acid (p. 85·3).
Pain; fever; menorrhagia.

Dystolise *Motima, Fr.*
Melissa (p. 2552·3); angelica (p. 2443·3); sweet marjoram (p. 2550·1); red-poppy petal (p. 2207·3); lavender oil (p. 2541·1).
Tonic.

dysto-loges N *Loges, Ger.*
Reserpinum (p. 1485·3); gelsemium (p. 2511·2); passiflora incarnata (p. 2584·1); coffea (p. 2648·2); valeriana (p. 2640·2); chamomilla (p. 2474·1).
Homoeopathic preparation.

dysto-loges S *Loges, Ger.*
Gelsemium (p. 2511·2); coffea (p. 2648·2); veratrum; reserpinum (p. 1485·3); passiflora incarnata (p. 2584·1).
Homoeopathic preparation.

Dystonal *Pharmacobel, Belg.*
Dihydroergotamine mesilate (p. 672·2).
Orthostatic hypotension.

Dystonil *Psychotropics, India.*
Trihexyphenidyl hydrochloride (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Dysurgal
Note: this name may be used for preparations of different composition.
Maxmedic, Ger.
Atropine sulfate (p. 1310·2).
Smooth muscle spasm; reduction of gastrointestinal secretions.

Dytac *SMB, Belg.; Mercury, UK.†*
⊗Triamterene (p. 1518·3).
Oedema; ascites; heart failure; hypertension.

Dytan *Hawthorn, USA.†*
Diphenhydramine tannate (p. 626·1).
Hypersensitivity reactions.

Dytan-AT *Cypress, USA.*
Pentoxyverine tannate (p. 1672·1); diphenhydramine tannate (p. 626·1).
Cough.

Dytan-CD *Hawthorn, USA.†*
Pentoxyverine tannate (p. 1672·1); diphenhydramine tannate (p. 626·1); phenylephrine tannate (p. 1672·2).
Cough; coryza; nasal congestion.

Dytan-CS *Hawthorn, USA.*
Pentoxyverine tannate (p. 1672·1); diphenhydramine tannate (p. 626·1); phenylephrine tannate (p. 1672·2).
Coughs.

Dytan-D *Hawthorn, USA.†*
Diphenhydramine tannate (p. 626·1); phenylephrine tannate (p. 1672·2).
Cold symptoms; nasal congestion.

Dytan-DM *Cypress, USA.*
Phenylephrine tannate (p. 1672·2); dextromethorphan tannate (p. 1660·1); diphenhydramine tannate (p. 626·1).
Cough; nasal congestion.

Dytan-HC *Hawthorn, USA.*
Hydrocodone tannate (p. 67·2); phenylephrine tannate (p. 1672·2); diphenhydramine tannate (p. 626·1).
Cough; upper respiratory-tract congestion.

Dyta-Urese *SMB, Belg.; Teva, Neth.*
⊗Triamterene (p. 1518·3); epitizide (p. 1374·2).
Oedema; hypertension.

Dytenzide *Astellas, Belg.; Mercury, Neth.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Dytide *Goldshield, UK.†*
⊗Triamterene (p. 1518·3); benzthiazide (p. 1316·1).
Oedema.

Dytide H *Dermapharm, Austria; Mibe, Ger.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; oedema.

Dytor *Cipla, India.*
⊗Torasemide (p. 1516·3).
Heart failure; hypertension; oedema.

Dytor Plus *Cipla, India.*
⊗Spironolactone (p. 1499·3); torasemide (p. 1516·3).

Dytro-Kem *Taj, India.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Dytuss *Lunsco, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Dyzco *Mediherb, Austral.†*
Blue cohosh (p. 2458·2); cimicifuga (p. 2478·1); wild yam (p. 2648·1); viburnum opulus; ginger (p. 1844·1).
Dysmenorrhoea.

Dyzole *Douglas, NZ.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Dyzolor *ACME, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

DZ *Sunij, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

D-Zol *Mylan, NZ.†*
⊗Danazol (p. 2263·2).
Benign breast disease; endometriosis; hereditary angioedema; menorrhagia.

DZP2 *Pharmasant, Thai.*
Diazepam (p. 1063·2).

E2 *Sun, India.*
Estradiol (p. 2271·1).
Vaginal and vulval atrophy.

E45 *Crookes Healthcare, UK.*
A range of emollient preparations.
Dry skin disorders.

Reckitt Benckiser, Irl.; Reckitt Benckiser, S.Afr.†
Emollient.
Dry skin disorders.

Reckitt Benckiser, Austral.
White soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry skin.

Reckitt Benckiser, Pol.
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2); soft paraffin (p. 2211·3).
Skin disorders.

E-400 *Nutrifarma, Turk.*
Tocoferil acetate (p. 2119·2).

E Cef-OD *Lupin, India.*
Cefalexin (p. 234·1).
Bacterial infections.

E45 Itch Relief *Crookes Healthcare, UK.*
⊗Macrogol lauril ethers (p. 2193·3); urea (p. 1727·3).
Pruritus; scaling skin conditions.

E Keppra *Otsuka, Jpn; UCB, Jpn.*
Levetiracetam (p. 531·1).
Epilepsy.

E Mal *Themis Medicare, India.*
Alpha-beta arteether (p. 648·1).
Formerly contained artemotil.
Malaria.

E Plus *Delta, Braz.†*
dl-Alpha tocoferil acetate (p. 2119·2).

E 200 Plus C *Bio-Sante, Canad.†*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1).

E S *Community Pharmacy, Thai.*
Erythromycin (p. 291·2).
Bacterial infections.

E45 Sun *Crookes Healthcare, UK.†*
SPF 30: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1).
Sunscreen.

Crookes Healthcare, UK.†
SPF 15: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Formerly contained titanium dioxide and zinc oxide.
Sunscreen.

E45 Sun Reflective Sunscreen *Crookes Healthcare, UK.†*
SPF 25; SPF 50: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

E-8 Suprabio *Hovid, Malaysia.*
Vitamin E substances (p. 2119·1).
Vitamin E supplement.

Eaca Balsamico *Nikkho, Braz.*
Aminocaproic acid (p. 1131·3); sodium benzoate (p. 1738·2); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Respiratory-tract congestion.

Eadazine *Chew, Thai.*
Sulfametopyrazine (p. 367·3).
Bacterial infections.

Ealk *Medimar, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

E-Amox *Zota, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

E-Amox CL *Zota, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Eanox *Desitin, Cz.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

EAP-61 *Hanosan, Ger.*
Echinacea (p. 2498·1); hamamelis virginiana (p. 2523·3); boldo (p. 2458·3); carbo vegetabilis (p. 1537·3); argentum nitricum (p. 2615·3).
Homoeopathic preparation.

Eapidil *Eakan, China.*
Naftopidil (p. 2361·1).
Hypertension.

Ear Clear *Key, Austral.; Key, Hong Kong.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Ear Clear For Ear Ache Relief *Key, Austral.*
Phenazone (p. 124·1); benzocaine (p. 1980·2).
Otitis media.

Ear Clear Ear Cleanser *Key, Austral.*
Sodium chloride (p. 1795·1).
Ear cleansing.

Ear Clear for Swimmers Ear *Key, Austral.*
Acetic acid (p. 2426·3); isopropyl alcohol (p. 1758·3).
Otitis externa.

Earache
Note: this name may be used for preparations of different composition.
Homeocan, Canad.
Aurum metallicum (p. 2521·1); capsicum annuum (p. 2469·3); ferrum phosphoricum (p. 2077·1); kalium sulfuricum (p. 1793·2); mercurius vivus (p. 2555·3); thuja occidentalis (p. 2629·3); silicea (p. 2208·3).
Homoeopathic preparation.

Hylands, Canad.
Belladonna (p. 2453·3); calcarea carbonica (p. 1824·3); chamomilla (p. 2474·1); lycopodium (p. 2546·3); pulsatilla (p. 2600·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Earache Relief *Brauer, Austral.†*
Belladonna (p. 2453·3); chamomilla (p. 2474·1); ferrum phos. (p. 2077·1); hepar sulf. (p. 1721·3); kali bich. (p. 2476·3); merc. viv. (p. 2555·3); plantago maj. (p. 2592·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

EarCalm *Forest Laboratories, UK.*
Glacial acetic acid (p. 2426·3).
Superficial ear infections.

Earclear *Wilson, NZ.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Ear-Dry *Scherer, USA.*
Boric acid (p. 2459·3); isopropyl alcohol (p. 1758·3).
Ear disorders.

Earex *Pharmalab, Irl.†; SSL, Singapore; Reckitt Benckiser, UK.*
Arachis oil (p. 2446·1); almond oil (p. 2437·1); rectified camphor oil (p. 2466·2).
Ear wax removal.

Earex Plus *Reckitt Benckiser, UK.†*
⊗Choline salicylate (p. 39·2); glycerol (p. 2517·2).
Earache; ear wax removal.

Ear-Eze *Hyrex, USA.†*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B (p. 342·3).
Bacterial ear infections.

Ear-Gesic *Qualitest, USA.*
Phenazone (p. 124·1); benzocaine (p. 1980·2); phenylephrine hydrochloride (p. 1672·3).

Earinse *Gerolymatos, Hong Kong.*
Sodium chloride (p. 1795·1).
Ear wax removal.

Early Bird
Note: this name may be used for preparations of different composition.
Kent, UK.
Pregnancy test (p. 2596·1).

Mentholatum, Austral.†
Pyrantel embonate (p. 165·3).
Enterobiasis.

EarSol-HC *Parnell, USA.*
⊗Hydrocortisone (p. 1640·1).
Ear inflammation.

EAS Pfrimmer *Kalbe, Indon.*
Amino acids.
Parenteral nutrition in renal failure.

Eascof *Cachet, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Eascof Exp *Cachet, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Eascold *Quality, Hong Kong.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; allergic rhinitis; nasal congestion.

Easepex *MedGen, Philipp.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Ease-PMS *Plus, India.*
Vitamins; minerals; amino acids; trace elements; evening primrose oil (p. 2502·2); soya isoflavones (p. 2620·3).

Easi Breathe *Cipla, India.*
Camphor (p. 2466·2); chlorothymol (p. 1748·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); terpineol (p. 2627·2).
Respiratory-tract disorders.

Easicold *Cipla, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Easifud *Raptakos, India.*
Preparation for enteral nutrition.

Easiphen *Nutricia, Cz.; Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Easofen *Clonmel, Irl.*
Ibuprofen (p. 68·2).
Pain.

EAS-Oral *Fresenius Kabi, Turk.*
Amino acids.
Nutritional supplement.

Easprin *Lotus, USA.*
Aspirin (p. 22·2).
Pain; inflammation; fever.

Easum *Wockhardt, India.*
Preparation for enteral nutrition.

Easy-4 *Panacea, India.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Easy-5 *Panacea, India.*
A diphtheria, tetanus, pertussis, haemophilus influenzae, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Easy Bronz *Bioglan, Austral.†*
Lycopersicon esculatum.
Skin tanning.

Easy Dayz *Cipla, India.*
Naproxen sodium (p. 98·2).

Easy Gel *Teva, Israel.*
Benzydamine hydrochloride (p. 29·2).
Inflammatory disorders.

Easy Lax
Note: this name may be used for preparations of different composition.
Trade Technocrats, Canad.†
Plantago seed (p. 1849·1).
Constipation.

Easylax
Note: this name may be used for preparations of different composition.
Cipla, India.
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).
Constipation.

Sam-On, Israel.
Phenolphthalein (p. 1877·3).
Constipation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Easymagnévie *Sanofi-Aventis, Fr.*
Magnesium oxide (p. 1857·3).
Magnesium supplement; magnesium deficiency.

Easyn *CCM, Malaysia.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Eat Ease *Ranbaxy, India.*
Withania somnifera (p. 2450·2).

Eatcal *Life Line, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Eatcal Forte *Life Line, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Eau Des Carmes *Medgenix, Belg.*
Lemon peel; angelica (p. 2443·3); cinnamon (p. 2479·2); coriander (p. 2486·3); clove (p. 2481·2); melissa (p. 2552·3); nutmeg (p. 2573·1); watercress.
Tonic.

Eau pour les yeux *Zeller, Switz.†*
Zinc sulfate (p. 2126·2); fennel oil (p. 2503·3); saffron (p. 2208·2).
Eye irritation.

Eau Precieuse *Actipharm, Switz.*
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3); tannin (p. 2625·2); cresol soap (p. 1749·1); levomenthol (p. 2553·2); eucalyptus (p. 2501·1).
Skin disorders.

Eau Précieuse *Omega, Fr.†*
A range of preparations containing boric acid (p. 2459·3) and salicylic acid (p. 1719·1).
Seborrhoea.

Eau-de-vie de France Klosterfrau au menthol *Melisana, Switz.*
Camphor (p. 2466·2); menthol (p. 2553·2); thymol (p. 1772·2).
Musculoskeletal, joint, and soft-tissue disorders.

Eavit *Terapeutico, Ital.*
⊗Gelatin (p. 1154·1); wheat-germ oil (p. 2647·1); carrot oil; soya lecithin (p. 2542·2); royal jelly (p. 2608·1); beeswax (p. 2170·2).
Nutritional supplement.

Eavit Plus *Terapeutico, Ital.*
⊗Gelatin (p. 1154·1); wheat-germ oil (p. 2647·1); carrot oil; lecithin (p. 2542·2); royal jelly (p. 2608·1); soya oil (p. 2092·3).
Nutritional supplement.

Eaze *Profic Organic, India.*
⊗Amylase (p. 2442·1); papain (p. 2582·3); simeticone (p. 1886·2).

Ebamin *Jin Yang, Hong Kong.†*
Ginkgo biloba (p. 2512·3).
Cerebral disorders; peripheral vascular disorders.

EBA-P *Blubell, India.*
Ebastine (p. 628·1); phenylephrine (p. 1672·2).

E-Base *Barr, USA.*
Erythromycin (p. 291·2).
Bacterial infections.

Ebast *Micro, India.*
Ebastine (p. 628·1).
Hypersensitivity reactions.

Ebast-DC *Micro, India.*
Ebastine (p. 628·1); phenylephrine hydrochloride (p. 1672·3).

Ebastel *Almirall, Austria; Eurofarma, Braz.; Almirall Hermal, Ger.; Dainippon, Jpn; Almirall, Spain; Elmor, Venez.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders; hypersensitivity reactions.

Ebastel D *Eurofarma, Braz.*
⊗Ebastine (p. 628·1); pseudoephedrine hydrochloride (p. 1676·1).

Ebastion *Lindopharm, Port.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Ebedoce *Ebewe, Austria.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer; prostatic cancer; gastric adenocarcinoma; head and neck cancer.

Ebedoxo *Ebewe, Singapore.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Ebedronat *Medac, Austria.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; multiple myeloma; osteolytic lesions associated with bone metastases in breast cancer.

Ebefen *Ebewe, Austria.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; endometrial cancer.

Ebefolin *Ebewe, Neth.†*
Calcium folinate (p. 2066·3).
Methotrexate toxicity; adjunct to fluorouracil therapy.

Eben *Gufic, India.*
Mebendazole (p. 158·3).
Worm infections.

E-Bend *Zota, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Ebenol *Strathmann, Ger.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Skin disorders.

Ebeoxal *Ebewe, Cz.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Ebeposide *Ebewe, Singapore.*
Etoposide (p. 790·2).
Malignant neoplasms.

Eberelbin *Ebewe, Austria.*
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small cell lung cancer.

Ebermac *Salvat, Spain.*
Eberconazole nitrate (p. 577·2).
Fungal skin infections.

Ebermin *Oktenifarm, Ukr.*
Urogastrone (p. 1894·3); sulfadiazine silver (p. 362·3).
Wounds; ulcers; radiation-induced skin damage; burns.

Ebernet *Reddy, India; Nevzat, Turk.*
Eberconazole (p. 577·2).
Fungal skin infections.

Salvat, Spain.
Eberconazole nitrate (p. 577·2).
Fungal skin infections.

Ebersedin *Bros, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Ebersept *Bros, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Ebertop *Salvat, Spain.*
Eberconazole nitrate (p. 577·2).
Fungal skin infections.

Ebertuss *Bros, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Eberubi *Ebewe, Singapore.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Ebetaxel *Ebewe, Austria; Sandoz, Hong Kong; Ferron, Indon.; Ebewe, Irl.; Ebewe, Israel; Adcock Ingram Critical Care, S.Afr.; Ebewe, Singapore; Liba, Turk.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Ebetrex *Ebewe, Denm.; Ebewe, Fin.; Nordic Drugs, Norw.; Nordic, Swed.; Sandoz, UK.†*
Methotrexate sodium (p. 822·2).
Psoriasis; rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis.

Ebetrexat *Ebewe, Austria; Ebewe, Neth.†; Ebewe, Singapore.*
Methotrexate (p. 822·2) or methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; psoriatic arthritis; rheumatoid arthritis; juvenile idiopathic arthritis.

Ebex *Madhav, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Ebexantron *Ebewe, Austria; Ebewe, Singapore.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms; multiple sclerosis.

Ebexid *Svizera, India.*
Thyroid (p. 2345·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Hypothyroidism.

Ebezolid *Ebewe, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Ebility *Piramal, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Ebios *Asahi, China.*
Dried yeast (p. 2125·2).

Ebirintazide *Liconsa, Neth.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ebitex *Biofarma, Turk.*
Memantine (p. 393·1).

Ebivol *Specifar, Neth.†; Actavis, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Ebix *Lundbeck, Braz.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease; spasticity; parkinsonism.

Ebixa *Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Canad.; Lundbeck, Chile; Lundbeck, China; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Fr.; Lundbeck, Ger.; Lundbeck, Gr.; Lundbeck, Hong Kong; Lundbeck, Hung.; Lundbeck, Irl.; Lundbeck, Israel; Lundbeck, Ital.; Lundbeck, Malaysia; Lundbeck, Mex.; Lundbeck, Neth.; Lundbeck, Norw.; Healthcare Logistics, NZ; Lundbeck, Pol.; Lundbeck, Port.; Lundbeck, S.Afr.; Lundbeck, Singapore; Lundbeck, Spain; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.; Lundbeck, UK.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease; dementia.

Ebiza-L *Reddy, India.*
Vitamins; trace elements; thioctic acid (p. 2629·1).

Ebolin *Beacons, Singapore.*
Bisacodyl (p. 1821·1).
Constipation.

Eborix *Almirall, Mex.*
Clebopride (p. 1833·1).

Ebov *Glenmark, India.*
Etoricoxib (p. 57·3).
Gout; ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; pain.

Ebrantil *Nycomed, Belg.; Nycomed, China; Nycomed, Ital.; Bykomed, Port.; Nycomed, Rus.; Takeda, Switz.; Nycomed, Ukr.*
Urapidil hydrochloride (p. 1520·2).
Hypertension; controlled hypotension; controlled hypotension during surgery; production of controlled hypotension.

Nycomed, Austria; Nycomed, Cz.; Takeda, Ger.; Nycomed, Hung.; Takeda, Neth.; Nycomed, Pol.
Urapidil (p. 1520·2) or urapidil hydrochloride (p. 1520·2).
Hypertension; production of controlled hypotension; controlled hypotension during surgery.

Ebrimycin *PannonPharma, Hung.*
Primycin sulfate; lidocaine (p. 1988·1).
Bacterial skin infections.

Ebrit *Aramis, Hung.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Ebrit HCT *Aramis, Hung.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ebrium *East West, India.*
Chlordiazepoxide (p. 1044·2).
Anxiety; alcohol withdrawal symptoms; insomnia.

Ebromin *Degorts, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Ebromin P *Degorts, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Ebufac *DDSA Pharmaceuticals, UK.*
Ibuprofen (p. 68·2).

Eburdent *Dentsply, Ital.*
Sodium fluoride (p. 2089·2).
Gum disorders.

Eburdent F *Dentsply, Ital.*
Miristalkonium saccharinate (p. 1761·3); sodium fluoride (p. 2089·2).
Oral hygiene; dental caries prophylaxis.

Eburnate *Vannier, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Eburos *Dentsply, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

E-Butol *Beacons, Singapore.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Ebutol
Note: this name may be used for preparations of different composition.
Novartis, India; Novartis, Rus.; Sunward, Singapore.
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Terramedic, Philipp.
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); pyridoxine hydrochloride (p. 2105·3).
Tuberculosis.

EC *Cadila, India.*
Vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); selenium (p. 2086·3); thioctic acid (p. 2629·1).
Antoxidant.

Eca Presan *BMS, Mex.*
Captopril (p. 1331·2).
Hypertension.

Ecadiu *Sandoz, Spain.†*
⊗Hydrochlorothiazide (p. 1403·2); captopril (p. 1331·2).
Hypertension.

Ecafast *Crinos, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

E-Cal *Zota, India.*
Calcium carbonate (p. 1824·3); calcium hydrogen phosphate (p. 1783·3); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Ecalin *Jaka-80, Rus.†*
Econazole nitrate (p. 577·3).
Fungal infections.

Ecalta *Pfizer, Arg.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK.*
Anidulafungin (p. 573·2).
Candidiasis.

Ecamais *Atral, Port.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; oedema.

Ecamannan *CaDiGroup, Ital.*
Glucomannan (p. 2515·2); vitamin E (p. 2119·1); vitamin C (p. 2110·3); betacarotene (p. 2051·1).
Gastrointestinal disorders; obesity; hypercholesterolaemia.

Ecanol *Piramal, India.*
Econazole nitrate (p. 577·3).
Vulvovaginal candidiasis.

E-Cap *Glenmark, India.*
Vitamin E acetate (p. 2119·2).
Vitamin E supplement.

Ecapril
Note: this name may be used for preparations of different composition.
Atral, Port.
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Sandoz, Mex.
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Ecaprilat *Lazar, Arg.*
Enalapril (p. 1371·1).
Heart failure; hypertension.

Ecarotin *Franco-Indian, India.*
Vitamins; minerals.

Ecasil *Biolab Sanus, Braz.*
Aspirin (p. 22·2).
Fever; inflammation; pain; thromboembolism prophylaxis.

Ecasolv *SF, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

E-Cate *Captab, India.*
Kojic acid (p. 1710·2); vitamin C (p. 2110·3).

Ecaten *Teva, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Ecator *Torrent, Braz.; Torrent, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Ecator H *Torrent, Braz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ecator-H *Torrent, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Ecatrol *Ethica, Indon.*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; rickets; hypoparathyroidism.

Ecax *Bago, Chile.*
Meloxicam (p. 86·3).
Inflammation; pain.

Ecazide *BMS, Fr.; BMS, Spain.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Eccarvit Plus *CaDiGroup, Ital.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); ginkgo biloba (p. 2512·3); chromium tripicolinate (p. 2056·1).
Nutritional supplement.

Eccoxolac *Viatris, UK.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis.

ECD3 *Bactolac, India.*
Suspension: Calcium (p. 1783·1); colecalciferol (p. 2113·1); lysine (p. 2079·3).

Bactolac, India.
Tablets: Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ecee *Zydus, India.*
Levonorgestrel (p. 2296·1).
Postcoital contraceptive.

Ecee Plus *Edwards, USA.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); minerals.

E-Cef *Lupin, India; Zota, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ecelecort *Iator, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

E-Cet-MD *Zota, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Echarge *BMW, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Echiherb *Salus, Ger.†*
Echinacea purpurea (p. 2498·1).
Respiratory- and urinary-tract infections.

Echilite *HollandPharma, Neth.*
Aconitum napellus (p. 2428·3); apis mellifica (p. 2445·2); arnica montana (p. 2447·2); belladonna (p. 2453·3); chelidonium majus (p. 2522·2); eupatorium perfoliatum (p. 2459·1); ignatia amara (p. 2532·1); phosphorus (p. 2589·2); bryonia alba; echinacia angustifolia (p. 2498·1); euphorbia resinifera (p. 2501·3).
Homoeopathic preparation.

Echina-B-C *WR Enterprises, Canad.†*
Vitamins; zinc gluconate (p. 2126·2).

Echinaboost *Cederroth, UK.*
Echinacea purpurea (p. 2498·1).
Cold and influenza symptoms.

Echinacea *Potter's, UK.*
Tablets: Echinacea (p. 2498·1).
Skin disorders; immunostimulant.

Potter's, UK.
Elixir: Echinacea (p. 2498·1); wild indigo (p. 2647·2); fumitory (p. 2508·2).
Catarrh; minor skin disorders; immunostimulant.

Echinacea 4000 *Procare, Austral.†*
Echinacea (p. 2498·1); calcium ascorbate (p. 2111·1); zinc amino acid chelate (p. 2048·3).
Upper respiratory-tract symptoms.

Echinacea ACE + Zinc *Blackmores, Austral.*
Echinacea purpurea (p. 2498·1); vitamins; zinc amino acid chelate (p. 2048·3).
Cold and influenza symptoms.

Echinacea Citrus Throat *Blackmores, Austral.*
Echinacea (p. 2498·1); sodium ascorbate (p. 2111·1); eucalyptus oil (p. 2501·2).
Sore throat; cold symptoms.

Echinacea comp
Note: this name may be used for preparations of different composition.
Heel, Neth.
Echinacea angustifolia (p. 2498·1); eupatorium perfoliatum (p. 2459·1); pulsatilla pratensis (p. 2600·2); bryonia cretica (p. 2461·3); phytolacca decandra (p. 2593·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Steigerwald, Ger.
Echinacea pallida (p. 2498·1); lachesis mutus (p. 2538·3); eupatorium perfol. (p. 2459·1); gelsemium sempervir. (p. 2511·2).
Homoeopathic preparation.

Echinacea Complex *Cenovis, Austral.†*
Echinacea (p. 2498·1); vitamins; zinc amino acid chelate (p. 2048·3).
Skin disorders; upper respiratory-tract infections; wounds.

Echinacea Complexe No 40 *Lehning, Fr.*
Echinacea (p. 2498·1); arctium lappa (p. 2540·1); arnica montana (p. 2447·2); phytolacca (p. 2593·2); mercurius corrosivus (p. 2555·2); acidum nitricum (p. 2572·3); scrofularia; sulfur (p. 1721·1).
Homoeopathic preparation.

Echinacea Compositum *Heel, Canad.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); baptisia tinctoria (p. 2647·2); bryonia alba (p. 2461·3); hepar sulphuris calcareum (p. 1721·3); echinacea angustifolia (p. 2498·1); eupatorium perfoliatum (p. 2459·1); euphorbium officinarum; gelsemium sempervirens (p. 2511·2); phosphorus (p. 2589·2); phytolacca decandra (p. 2593·2); rhus toxicodendron (p. 2603·3); pulsatilla (p. 2600·2); sanguinaria canadensis (p. 2610·1); argentum nitricum (p. 2615·3); sulfur (p. 1721·1); thuja occidentalis (p. 2629·3); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Echinacea L40 *Homeocan, Canad.†*
Arctium lappa (p. 2540·1); arnica montana (p. 2447·2); echinacea (p. 2498·1); nitricum acidum (p. 2572·3); phytolacca decandra (p. 2593·2); scrofularia nodosa; sulfur (p. 1721·1).
Homoeopathic preparation.

Echinacea Lozenges *Blackmores, Austral.*
Echinacea purpurea (p. 2498·1); sodium ascorbate (p. 2111·1); eucalyptus oil (p. 2501·2).
Cold and influenza symptoms.

Echinacea Plus Garlix *Blackmores, Austral.*
Echinacea (p. 2498·1); garlic (p. 2510·3).
Respiratory-tract infections.

Echinacea Royale *Eagle, Austral.*
Andrographis (p. 2443·2); echinacea (p. 2498·1); astragalus membranaceous (p. 2451·1); olive leaf (p. 2574·3); schisandra chinensis (p. 2611·2); lapacho; hydrastis (p. 2528·1); phytolacca decandra (p. 2593·2).
Respiratory-tract infections.

Echinacea Urtinktur *Hevert, Ger.†*
Echinacea angustifolia (p. 2498·1); Echinacea pallida (p. 2498·1).
Homoeopathic preparation.

Echinacea-Cosmoplex *Heel, Austria.*
Echinacea angustifolia (p. 2498·1); lachesis mutus (p. 2538·3); natrium carbonicum (p. 2617·3); plantago major (p. 2592·3); hepar sulfuris (p. 1721·3); atropa belladonna (p. 2453·3); phytolacca americana (p. 2593·2); pyrogenium (p. 2601·1); acidum arsenicosum (p. 2448·1); bryonia cretica; toxicodendron quercifolium (p. 2603·3); chamomilla recutita (p. 2474·1); solanum dulcamara (p. 2497·3); hydrargyrum oxydatum rubrum (p. 2555·3); thuja occidentalis (p. 2629·3); pulsatilla pratensis (p. 2600·2); argentum nitricum (p. 2615·3).
Homoeopathic preparation.

Echinacin *Thursday, Austral.†; Madaus, Austria; Madaus, Belg.; Madaus, Cz.; Madaus, Ger.; Rottapharm, Ger.; Rottapharm, Gr.†; Madaus, Hung.; Naturprodukt, Hung.; Rottapharm, Spain; Zeller Madaus, Switz.; Madaus, Thai.†; Rottapharm, Thai.†; HFA Healthcare, UK; Madaus, Ukr.*
Echinacea purpurea (p. 2498·1).
Wounds; respiratory- and urinary-tract infections.

Echinacin akut *Madaus, Ger.; Rottapharm, Ger.*
Aconitum (p. 2428·3); baptisia (p. 2647·2); belladonna (p. 2453·3); bryonia (p. 2461·3); myristica sebifera; echinacea (p. 2498·1).
Homoeopathic preparation.

Echinaction *Herbasante, Canad.†*
Echinacea angustifolia (p. 2498·1); echinacea purpurea (p. 2498·1).
Homoeopathic preparation.

Echinadoron *Weleda, Switz.*
Echinacea (p. 2498·1); calendula (p. 2465·2); chamomile (p. 2474·1); eucalyptus oil (p. 2501·2).
Colds; mouth and throat infections.

Echinaflu *Swiss Caps, UK.*
Echinacea purpurea (p. 2498·1).
Cold and influenza symptoms.

Echinaforce *Aponova, Austria; Bioforce, Canad.; Bioforce, Ger.†; Bioforce, Swed.; Bioforce, Switz.; Bioforce, UK.*
Echinacea (p. 2498·1).
Respiratory- and urinary-tract infections.

Echinaforce Sore Throat Spray *Bioforce, UK.*
Echinacea purpurea (p. 2498·1); sage (p. 2608·3).
Sore throat.

Echinagard *Algol, Swed.*
Echinacea purpurea (p. 2498·1).
Cold symptoms.

Echinaject *Syxyl, Ger.*
Clematis recta; echinacea (p. 2498·1); hedera helix (p. 2536·2).
Homoeopathic preparation.

EchinaMed *Flor de Loto, Spain; Bioforce, Switz.*
Echinacea (p. 2498·1).
Cold symptoms; fever.

Echinamide *Natural Factors, Canad.*
Echinacea purpurea (p. 2498·1).

Echinamide Cold and Cough *Natural Factors, Canad.†*
Echinacea purpurea (p. 2498·1); eucalyptus oil (p. 2501·2); horehound (p. 1668·3); peppermint (p. 1877·1); verbascum (p. 2645·1); wild cherry (p. 2647·2).
Cough; cold symptoms.

Echinapret *Bionorica, UK.*
Echinacea purpurea (p. 2498·1).
Cold and influenza symptoms.

Echinapur *Scheffler, Ger.†; Herbapol Poznan, Pol.; Alpinamed, Switz.*
Echinacea purpurea (p. 2498·1).
Wounds; respiratory- and urinary-tract infections.

Echinarell *Sanorell, Ger.*
Echinacea purpurea (p. 2498·1).
Homoeopathic preparation.

Echinarom *Spagyros, Switz.*
Echinacea (p. 2498·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); juniper oil (p. 2537·2); lavender oil (p. 2541·1); chamomile oil (p. 2474·1); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); savory oil (p. 2625·1); thyme oil (p. 2630·3).
Colds; mouth and throat infections.

Echinasal *Herbapol Wroclaw, Pol.*
Echinacea purpurea (p. 2498·1); ribwort plantain (p. 2604·2); rose fruit (p. 2607·1); thyme (p. 2630·2); grindelia (p. 2522·3).
Catarrh; cough.

Echinatex *Macronova, Swed.†*
Echinacea purpurea (p. 2498·1).
Cold symptoms.

Echinatur *Ritsert, Ger.†*
Echinacea purpurea (p. 2498·1).
Respiratory- and urinary-tract infections.

Echinax *Mega Lifesciences, Thai.*
Echinacea purpurea (p. 2498·1).
Cold symptoms.

Echine *Eagle, Austral.†*
Echinacea angustifolia (p. 2498·1); boneset (p. 2459·1); thuja (p. 2629·3); solidago virgaurea (p. 2620·1); smilax; achillea (p. 2427·3); lappa (p. 2540·1); menyanthes (p. 2554·2); calendula officinalis (p. 2465·2); arnica (p. 2447·2); lachesis (p. 2538·3); rhus tox (p. 2603·3); sulfur (p. 1721·1).
Herbal and homoeopathic antiseptic.

EchinEeze *Natures Aid, UK.*
Echinacea purpurea (p. 2498·1).
Cold and influenza symptoms.

Echinerba *Laboform, Pol.*
Echinacea purpurea (p. 2498·1).
Catarrh.

Echinox *Armoxindo, Indon.*
Echinacea purpurea (p. 2498·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Tonic; infections.

Echiplant *Schwabe, Switz.†*
Echinacea purpurea (p. 2498·1).
Respiratory-tract infections.

Echnatol *Wabosan, Austria.*
Cyclizine hydrochloride (p. 623·2).
Motion sickness; nausea and vomiting.

Echnatol B_6 *Wabosan, Austria.*
Cyclizine hydrochloride (p. 623·2); pyridoxine hydrochloride (p. 2105·3).
Motion sickness; nausea and vomiting; vestibular disorders.

Echovist *Bayer, Austria; Bayer, Ger.; Schering, Hung.†; Perrigo, Israel; Bayer, Swed.†; Bayer, UK.†*
Galactose (p. 1588·1).
Ultrasound contrast medium.

Échovist *Bayer, Fr.†*
Galactose (p. 1588·1).
Ultrasound contrast medium.

Eciclean *Biotoscana, Chile.*
Chamomile flowers (p. 2474·1); sage leaf (p. 2608·3).
Dry mouth; mouth disorders.

E-Cip *Zota, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Eciprax *Labomed, Chile.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder.

E-Cip-TZ *Zota, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Ecitalop *East West, India.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; obsessive compulsive disorder; panic disorder.

Ecitalop-C *East West, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Ecitrix *Ratiopharm, Port.†*
Escitalopram oxalate (p. 416·2).
Depression.

Eclaran *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.; Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, Rus.*
Benzoyl peroxide (p. 1696·1).
Acne.

Eclid *Dexa, Indon.*
Acarbose (p. 466·2).
Diabetes mellitus.

Eclipse Lip and Face *Triangle, USA.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Eclipsol *Darier, Mex.*
Cream SPF 40: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1).
Sunscreen.

Darier, Mex.
Gel SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Darier, Mex.; Darier, Mex.
SPF 50: SPF 30 (Activo); baby SPF 30; kids SPF 30: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Darier, Mex.
Spray SPF 40: Octinoxate (p. 1715·1); homosalate (p. 1705·1).
Sunscreen.

Eclipsol Clarity *Darier, Mex.*
SPF 40: Bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Eclipsol Forte *Darier, Mex.*
SPF 80: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Eclipsol Hydro *Darier, Mex.*
SPF 50: Bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); enzacamene (p. 1703·2).
Sunscreen.

Eclipsol Repelente *Darier, Mex.*
SPF 40: Octinoxate (p. 1715·1); octisalate (p. 1715·2); homosalate (p. 1705·1).
Sunscreen.

Eclipsol Ultra *Darier, Mex.*
SPF 100: Octinoxate (p. 1715·1); bisotrizole (p. 1697·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Eclonac *Jagsonpal, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Eclonac-P *Jagsonpal, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Eclo-P *Shreshtha, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Eclor *Lupin, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Ecloram *Gabriel, Gr.*
Citalopram hydrobromide (p. 411·1).

Eclorion *Norma (Νορμα), Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Eclospan *Wockhardt, India.*
⊗Beclometasone dipropionate (p. 1621·2); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

EC-Morning *Bionova, India.*
Ginger (p. 1844·1); vitamin B_6 (p. 2105·3).

Ecnac-P *Hos & Ins, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Ecnac-SR *Hos & Ins, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ecnagel *Apotex, Arg.*
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3); hamamelis (p. 2523·3).
Skin disorders.

Ecnagel E *Apotex, Arg.*
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3); erythromycin (p. 291·2).
Infected skin disorders.

Ecnagel PB *Apotex, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Eco Lips Lip Balm *Eco Lips, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Eco Tears *Intas, India.*
Carmellose sodium (p. 2175·2).

E-Cob *Zota, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Ecobal *Forgo, India.*
Capsules: Thioctic acid (p. 2629·1); chromium polynicotinate (p. 2055·3); selenium (p. 2086·3); vitamin B substances (p. 2102·3).
Forgo, India.
Injection kit: Folic acid (p. 2063·1); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); vitamin C (p. 2110·3).

Ecobal-OD *Forgo, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Ecobal-Plus *Forgo, India.*
Thioctic acid (p. 2629·1); chromium picolinate (p. 2056·1); vitamin B substances (p. 2102·3).

Ecobec *Teva, Cz.; Teva, Fr.; Teva, Port.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

ecobiosan *Sandoz, Switz.†*
d-Alpha tocopherol (p. 2119·1).
Vitamin E supplement; muscle and connective-tissue disorders associated with dyslipoproteinaemias.

Ecocain *Katsoupas, Gr.; Molteni, Ital.; Julphar, UAE.*
Lidocaine hydrochloride (p. 1988·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ecocare 250 *Ecolab, Canad.*
Triclosan (p. 1773·2).

Ecocare 360 *Ecolab, Canad.*
Benzalkonium chloride (p. 1737·1).

Ecocef
Note: this name may be used for preparations of different composition.
Ind-Chemie, India.
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.
Xeno, Philipp.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ecocillin *Proge, Ital.*
Lactobacillus plantarum (p. 2596·3).
Vaginitis.

Ecoclav *Avva, Rus.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Eco-Clean *Ecolab, Canad.†*
Triclosan (p. 1773·2).

Eco-Clean Elite *Ecolab, Canad.†*
Benzalkonium chloride (p. 1737·1).

Ecocort *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections.

Ecod *Universal Medicare, India.*
Cod-liver oil (p. 2056·3); vitamin E acetate (p. 2119·2).

E-Cod Omega *Universal Medicare, India.*
Cod-liver oil (p. 2056·3); fish oil (p. 1460·1); vitamin A acetate (p. 2098·3); wheat-germ oil (p. 2647·1).

E-Cod Plus *Universal Medicare, India.*
Biotin (p. 2052·2); cod-liver oil (p. 2056·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); tocotrienol; wheat-germ oil (p. 2647·1).

Ecodax *Unique, Rus.; Unique, Ukr.*
Econazole nitrate (p. 577·3).
Fungal skin infections; fungal skin and nail infections; Gram-positive bacterial skin infections.

Ecodax-G *JB Chemicals, India.*
⊗Beclometasone dipropionate (p. 1621·2); econazole nitrate (p. 577·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Ecodergin *Farmigea, Ital.*
Econazole nitrate (p. 577·3).
Vulvovaginal or dermatological fungal and Gram-positive bacterial infections.

Ecoderm
Note: this name may be used for preparations of different composition.
Chew, Thai.
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections.
Johnson & Johnson, S.Afr.†
Econazole nitrate (p. 577·3).
Fungal skin infections.

Ecodipine *Sandoz, Switz.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Ecodolor *Sandoz, Switz.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Ecodurex *Sandoz, Switz.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema; liver cirrhosis with ascites.

Ecofemin *Pharma-Vinci, Rus.*
Lactobacillus acidophilus (p. 2596·3).
Bacterial vaginosis.

Ecofénac *Sandoz, Switz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; gout.

Ecofermenti *Echo, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins.
Disturbances of the gastrointestinal flora.

E-Coff *Ind-Swift, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium (p. 1795·1).

Ecofibra *Echo, Ital.†*
Dietary fibre.
Delayed gastrointestinal transit; obesity.

Ecofilm *Latinofarma, Braz.*
Carmellose sodium (p. 2175·2).
Dry eyes; contact lens lubrication.

Ecoflorina *Ecobi, Ital.*
Lactic-acid-producing organisms (p. 2596·3).
Nutritional supplement.

Ecoflox *Merion, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ecoflox-OZ *Merion, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ecofol *Ecobi, Ital.*
Calcium folinate (p. 2066·3).
Antidote to overdosage with folic acid antagonists; anaemias; folic acid deficiency.

Ecogab *Forgo, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Ecogat A *Torrent, India.*
Ambroxol (p. 1654·3); gatifloxacin (p. 303·2).

Ecogat BCD *Torrent, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

E-Cold *Ind-Swift, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Ecolevid *Avva, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Ecolicin *Mann, Ger.*
Erythromycin lactobionate (p. 291·3); colistimethate sodium (p. 275·3).
Bacterial eye infections.

Ecoline *Biomedica, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Ecoliv *Dewcare, India.*
Cod-liver oil (p. 2056·3); vitamin E (p. 2119·1).

Ecome-LY *Hos & Ins, India.*
Grape (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); betacarotene (p. 2051·1); mecobalamin (p. 2108·1).

Ecomer *Natumin, Pol.*
Greenland shark-liver oil (p. 2614·2).
Infections.

Ecomesol *Aesculapius, Ital.*
Econazole nitrate (p. 577·3).
Fungal and Gram-positive bacterial skin and vulvovaginal infections.

Ecomi *Geymonat, Hong Kong; Geymonat, Ital.*
Econazole nitrate (p. 577·3).
Fungal skin or vulvovaginal infections.

Ecomucyl *Sandoz, Switz.*
Acetylcysteine (p. 1652·2) or acetylcysteine sodium (p. 1652·2).
Respiratory-tract disorders; paracetamol overdosage.

Econ
Note: this name may be used for preparations of different composition.
General Drugs, Thai.
Econazole nitrate (p. 577·3).
Fungal skin infections.

Econac *Goldshield, UK.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Econacort *BMS, UK.†*
⊗Econazole nitrate (p. 577·3); hydrocortisone (p. 1640·1).
Infected skin disorders.

Econal-C *Janpharm, S.Afr.†*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Econase *GSK, India.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Econazine *YSP, Malaysia; Yung Shin, Singapore; YSP, Thai.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Econite *APT, Hong Kong.†*
Econazole nitrate (p. 577·3).
Fungal skin infections.

EconoCee *Gruppo Medica, Philipp.*
Sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Econofix *Lupin, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol (p. 296·1).
Tuberculosis.

Econokit *Pascual, Philipp.*
1 Tablet, isoniazid (p. 311·2) (Nyadin); 1 capsule, rifampicin (p. 350·3) (Ricyn); 3 tablets, pyrazinamide (p. 345·2) (Zapedia); 1 tablet, ethambutol hydrochloride (p. 296·1) (Ethonah).
Tuberculosis.

Econokit-MDR *Pascual, Philipp.*
2 Tablets, pyrazinamide (p. 345·2); 1 capsule, rifampicin (p. 350·3); 1 tablet, isoniazid (p. 311·2); 1 tablet, ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Economy Formula *Natures Peak, Canad.†*
Vitamins; minerals.

Econopack *Pascual, Philipp.*
1 Tablet, isoniazid (p. 311·2) (Nyadin); 1 capsule, rifampicin (p. 350·3) (Ricyn); 3 tablets, pyrazinamide (p. 345·2) (Zapedia).
Tuberculosis.

Econopred *Alcon, Malaysia; Alcon, Singapore.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Econorm *Reddy, India.*
Saccharomyces boulardii (p. 2596·3).

Econormotil *Mepro, Chile.†*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea.

Econova *Glenmark, India.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3).

Econvita *Pasteur, Philipp.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Ecopace *Goldshield, UK.*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction.

Ecophane *Biorga, Fr.†*
Nutritional supplement.
Nail and hair tonic.

Ecopirin *Abdi, Turk.*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Ecoprofen *Sandoz, Switz.†*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; fever.

Ecoprot Plus *Jenburkt, India.*
Preparation for enteral nutrition.

Ecorex *Zambon, Ital.*
Econazole nitrate (p. 577·3).
Fungal or bacterial skin or vulvovaginal infections.

Ecorin *USV, Ukr.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Ecos *Uniao Quimica, Braz.*
Dropropizine (p. 1662·2).
Cough.

Ecosal *Teva, Cz.; Teva, Hung.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; asthma.

Ecosamina *Penn, Arg.*
Chondroitin sulfate (p. 2476·1); glucosamine (p. 2515·3).
Arthroses.

Ecoseptic *Helios, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Ecosette *TS, Ital.*
Piperacillin sodium (p. 340·1). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Ecosmin *USV, India.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction.

Ecosone *Christo, Hong Kong.†*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Ecosporina *Ecobi, Ital.*
Cefradine (p. 249·1).
Bacterial infections.

Ecosprin *USV, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Ecosprin Gold *USV, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2); clopidogrel (p. 1342·3).

Ecosprin-AV *USV, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Ecosta *Brown & Burk, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Ecostat *Skymax, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Ecostatin *BMS, Irl.†; BMS, UK.†*
Econazole nitrate (p. 577·3).
Fungal skin infections; vulvovaginal candidiasis; fungal infections.

Ecosteril *Amsa, Ital.*
Econazole nitrate (p. 577·3).
Fungal and Gram-positive skin and nail infections; vulvovaginitis.

Ecostimulin *Lens, Rus.*
⊗Chorionic gonadotrophin (p. 2258·1).
Female infertility; cryptorchidism; delayed puberty; male hypogonadism.

Eco-Swett *Medica, Arg.*
Stevioside (p. 2214·2).
Sugar substitute.

Ecotam *Sesderma, Spain.*
Econazole nitrate (p. 577·3).
Fungal skin and nail infections.

Ecotrin *Schering-Plough, Arg.; GSK, Chile; Goldshield, Hong Kong†; GSK, Mex.†; Link, NZ†; Pharmafrica, S.Afr.; GSK Consumer, USA.*
Aspirin (p. 22·2).
Fever; pain; inflammation; thromboembolism prophylaxis; musculoskeletal and joint disorders.

Ecotrixon *Bernofarm, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ecovac *Panacea, India.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

EcoVag *Bifodan, Pol.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus gasseri* (p. 2596·3).
Restoration of vaginal flora.

Ecovag *Bifodan, Swed.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus gasseri* (p. 2596·3).
Restoration of vaginal flora.

Ecoval *GSK, Ital.*
⊗Betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

Ecoval con Neomicina *GSK, Ital.†*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Ecovent *Sandoz, Switz.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ecovitamine B12 *Horus, Fr.*
Cyanocobalamin (p. 2107·2).
Corneal injury.

Ecox *Macleods, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Ecoza *Quinnova, USA.*
Econazole nitrate (p. 577·3).
Tinea pedis.

Ecozar *Multicare, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Ecozar Plus *Multicare, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; diabetic nephropathy.

Ecozitrin *Avva, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ecozol *Opsonin, Hong Kong.*
Econazole nitrate (p. 577·3).
Fungal vaginal infections.

Ecozyme *Elder, India.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1).

Ecradin *Med-One, Gr.*
Ketotifen fumarate (p. 631·3).
Hypersensitivity reactions.

Ecreme *Pacific, NZ.†*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Ecridoxan *Help, Gr.*
Etodolac (p. 57·1).
Inflammatory disorders; pain.

Ecriten *Jelfa, Cz.; Jelfa, Pol.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Ecron *Pharos, Indon.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Ecrox *Eczacibasi, Turk.*
Rofecoxib (p. 128·3).
Osteoarthritis; rheumatoid arthritis; pain.

Ectaprim *Liomont, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ectiban *Laboratorios Chile, Chile.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social anxiety disorder.

Ectin *Elfin, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Ectin-A *Elfin, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Worm infections.

Ectiva *Bracco, Ital.†; Nycomed, Mex.; Abbott, S.Afr.; Abbott, Singapore.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Ectodine *Paracelsia, Port.*
Povidone-iodine (p. 1767·1).

Ectofus *Coup, Gr.*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Ectopal *Codal Synto, Thai.*
⊗Danazol (p. 2263·2).
Endometriosis; female infertility; benign breast disorders; hereditary angioedema; gynaecomastia; menorrhagia; precocious puberty.

Ectospasmol *Alapis, Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Ectover *Worth, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Ectren *Menarini, Spain.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Ectrin
Note: this name may be used for preparations of different composition.
EMS, Braz.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.
OEP, Philipp.
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Ectrin Balsamico *EMS, Braz.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Bacterial infections.

Ecuaderm *Roemmers Rowe, Venez.*
Benzoyl peroxide (p. 1696·1).
Acne; rosacea.

Ecuamon *Lazar, Arg.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting.

Ecuor *Biomedica, Gr.*
Codergocrine mesilate (p. 389·2).

Ecur Test *Roche Diagnostics, Austral.†*
Test for glucose, protein, and blood in urine.

Ecur Test and Leucocytes *Roche Diagnostics, Austral.†*
Test for protein, glucose, blood, and leucocytes in urine.

Ecural *MSD, Ger.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders; scalp disorders.

Ecwin *Alembic, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Eczema *Homeocan, Canad.*
Agaricus muscarius; alumina (p. 1690·3); fumaria (p. 2508·2); kalium arsen (p. 2594·3); natrum muriaticum (p. 1795·1); petroleum (p. 2587·2); sepia (p. 2613·1); zea italica.
Homoeopathic preparation.

Eczema Cream *Hamilton, Austral.*
Coal tar (p. 1723·2); dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Eczema; dermatitis.

Eczema L87 *Homeocan, Canad.*
Bellis perennis (p. 2454·2); camphora (p. 2466·2); croton tiglium; dulcamara (p. 2497·3); hydrastis canadensis (p. 2528·1); sambucus nigra (p. 2609·3); sulfur (p. 1721·1); viola tricolor (p. 2647·3); natrum phos (p. 1791·2); scabiosa; arsenicum iodatum (p. 2448·1).
Homoeopathic preparation.

Eczema Ointment
Note: this name may be used for preparations of different composition.
Potter's, UK.
Zinc oxide (p. 1729·1); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); stellaria media.
Eczema.

Eczema Relief *Mediherb, Austral.†*
Calendula (p. 2465·2); myrrh (p. 2566·1).
Eczema.

Eczemol *Plymouth Pharmaceuticals, USA.*
Kali bromatum (p. 2461·1); sulfur (p. 1721·1); niccolum sulphuricum.
Homoeopathic preparation.

Ecziclo *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Ecziclo-G *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2).
Infected skin disorders.

Ecziclo-GM *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Ecziclo-M *Cosme, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 304·2).

Eczmol *Genus, UK.*
Chlorhexidine gluconate (p. 1743·3).
Soap substitute.

Eczop *Faribérica, Port.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Eczo-Wokadine *Wockhardt, India.*
⊗Fluocinolone acetonide (p. 1636·1); povidone-iodine (p. 1767·1).
Infected skin disorders.

Ed A-Hist *Edwards, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; nasal congestion.

Ed A-Hist DM *Edwards, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Ed A-Hist PSE *Edwards, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract disorders.

ED Bron GP *Edwards, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Ed Chlor-PED D *Edwards, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Ed ChlorPed D *Edwards, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

ED Chlorped Jr *Edwards, USA.*
Chlorphenamine maleate (p. 620·3).

ED Tuss HC *Edwards, USA.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

Edalen *Temis, Arg.*
Risperidone (p. 1103·2).
Psychoses.

E-Dalther *Dallas, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Edamox *Remedica, Hong Kong.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Edap *Vitaminerals, Canad.†*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).

Edarbi *Takeda, Irl.; Takeda, Neth.; Takeda, Switz.; Takeda, UK; Arbor, USA.*
Azilsartan kamedoxomil (p. 1313·2).
Hypertension.

Edarbyclor *Takeda, USA.*
⊗Chlortalidone (p. 1335·2); azilsartan kamedoxomil (p. 1313·2).
Hypertension.

Edase-D *Solitaire, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Edase-N *Solitaire, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Edason *Help, Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Ed-Chlor-Tan *Edwards, USA.*
Chlorphenamine tannate (p. 620·3).
Hypersensitivity reactions.

Ed-Chlortan *Edwards, USA.*
Chlorphenamine maleate (p. 620·3).

Edecam *Diba, Mex.†*
Piroxicam (p. 125·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Edecrin *Invida, Austral.; Aton, Canad.; Valeant, USA.*
⊗Etacrynic acid (p. 1378·2) or sodium etacrynate (p. 1378·2).
Oedema; ascites; heart failure; nephrotic syndrome.

Edegra *Sun, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Edelsin *Effik, Spain.*
Ethinylestradiol (p. 2275·3); norgestimate (p. 2295·3).
Combined oral contraceptive.

Edem
Note: this name may be used for preparations of different composition.
Farmak, Ukr.
Desloratadine (p. 625·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.
Wermar, Mex.
Naproxen sodium (p. 98·2).
Inflammation; pain.

Edemalt *DMG, Ital.*
Sodium chloride (p. 1795·1); evening primrose oil (p. 2502·2).

Edemann *Littman, Philipp.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Edemestized *Medis, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hyperlipidaemias; cardiovascular risk reduction.

Edemid *Behrens, Venez.*
⊗Furosemide (p. 1387·1).
Hypertension.

Edemin *Ikapharmindo, Indon.*
⊗Furosemide (p. 1387·1).
Pulmonary oedema.

Edemox *IFET [ΙΦΕΤ], Gr.; Chiesi, Spain.*
⊗Acetazolamide (p. 2001·1).
Oedema; glaucoma; epilepsy; high-altitude disorders.

Eden *Eden, India.*
Cefixime (p. 240·3).
Bacterial infections.

Edenelle *Mylan, Fr.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Edenil *Zambon, Ital.*
Ibuprofen isobutanolammonium (p. 68·2).
Gynaecological disorders.

Edenol *Randall, Mex.*
⊗Furosemide (p. 1387·1).
Oedema; liver cirrhosis with ascites; nephrotic syndrome; hypertension.

E-Derm *Zota, India.*
⊗Fluocinolone (p. 1636·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ederphyt *Doetsch, Grether, Switz.†*
Cream: Phenyl undecenoate (p. 596·3); thymol (p. 1772·2); salicylic acid (p. 1719·1).
Fungal foot infections.

Edestis *Gerolymatos, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Edetil *Biotecnoquimica, Venez.*
Disodium edetate (p. 1550·3).
Digitalis toxicity; hypercalcaemia.

Edeto *Reddy, India.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Edeven *IBI, Ital.*
Topical gel: Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Capillary fragility.
IBI, Ital.†
Injection; tablets: Sodium aescinate (p. 2431·2).
Capillary fragility.

Edevexin *IBI, Ital.*
Aescin (p. 2431·2).
Capillary fragility.

E-Devit *Framingham, Arg.*
Alpha tocopherol (p. 2119·1); collagen (p. 2483·2); elastin (p. 2483·2).
Skin ageing.

E-devit Protectora *Framingham, Arg.†*
Vitamin E (p. 2119·1).

Edex *UCB, Fr.; Lavipharm, Gr.; Actient, USA.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Edexin *Sydenham, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Edge *Elder, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Edge-P *Elder, India.*
Evening primrose oil (p. 2502·2); vitamin E substances (p. 2119·1).

Edge-P Plus *Elder, India.*
Evening primrose oil (p. 2502·2); mecobalamin (p. 2108·1); vitamin E substances (p. 2119·1).

Edhanol *Abbott, Braz.*
Phenobarbital (p. 535·2).
Epilepsy.

Edicin *Lek, Cz.; Sandoz, Pol.; Sandoz, Rus.; Sandoz, Thai.; Sandoz, Turk.; Lek, Ukr.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Edicis *CIS, Fr.*
N, N′-ethylene -(L,L)-dicysteine.
Test of renal function.

E-Diclo-Gel *Zota, India.*
Diclofenac diethylamine (p. 48·3); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Edictum *Phoenix, Arg.*
Clonazepam (p. 519·1).
Panic disorder; epilepsy.

Edidipin *Stichting, Austria.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Edifaringen *Gayoso, Spain.†*
⊗Bacitracin zinc (p. 225·3); benzocaine (p. 1980·2); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); potassium chlorate (p. 2595·2).
Mouth and throat disorders.

Edigastrol *Serra Pamies, Spain.†*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3).
Dyspepsia; gastric hyperacidity.

Edilox-OZ *Solitaire, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Edilox-S *Solitaire, India.*
⊗Ofloxacin (p. 334·3); serrapeptase (p. 2613·3).

E-Dine-M *Zota, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Edinol *Bayer, India.†*
Vitamins; minerals.

Ediol *Synmosa, Thai.*
Estradiol (p. 2271·1).
Oestrogen deficiency; osteoporosis.

Edirol *Chugai, Jpn.*
Eldecalcitol (p. 1182·3).
Osteoporosis.

Ediston *Pierre Fabre, Fr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Editor *Biomiicron, India.*
Lactobacillus sporogenes (p. 2596·3); racecadotril (p. 1881·3).
Diarrhoea.

Edivertin *Quimica y Farmacia, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Edluar *Meda, USA.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Edmudo *Rafarm, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections.

Ednapron *Grin, Mex.†*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Ednyt *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Ednyt HCT *Gedeon Richter, Hung.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ednyt Plus *Gedeon Richter, Hung.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Edodes *Peter, Ital.*
Vitamin B substances (p. 2102·3); arginine (p. 2049·1); sodium carboxymethyl beta-glucan (p. 2455·2).
Tonic.

Edoflo *AstraZeneca, Cz.; AstraZeneca, Irl.; AstraZeneca, Neth.†*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Asthma.

E-Dol *Elfin, India.*
Tramadol (p. 139·2).
Pain.

E-Dol Plus *Elfin, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Edolar *Nevzat, Turk.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis.

Edolfene *Edol, Port.*
Flurbiprofen sodium (p. 65·3).
Prevention of intra- and postoperative miosis; ocular inflammation.

Edolglau *Edol, Port.*
Clonidine hydrochloride (p. 1339·1).
Glaucoma; ocular hypertension.

Edomox *Medopharm, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Edomox-B *Medopharm, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3); *Lactobacillus sporogenes* (p. 2596·3).

Edomox-C *Medopharm, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).

Edorame *Pisa, Mex.*
Magnesium valproate (p. 553·1).
Epilepsy.

Edorin *Candor, India.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Edoti *Ethica, Indon.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; antoxidant.

Edotin *Ferron, Indon.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Edoxil
Note: this name may be used for preparations of different composition.
Eden, India.
Cefadroxil (p. 233·2).
Bacterial infections.

Edoxim *Azine, India.*
Cefpodoxime.
Bacterial infections.

Edoxim-CV *Azine, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Edrigard *Candor, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Edrigyl *Gerolymatos, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Edronax *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pharmacia Upjohn, Rus.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK*
Reboxetine mesilate (p. 447·1).
Depression.

E-Drops *Ranbaxy, Thai.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Edrucef *Alna, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

ED-SPAZ *Edwards, USA.*
Hyoscyamine (p. 1848·1).

ED-TLC *Edwards, USA.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

Edubel *Gynopharm, Chile.*
Polycarbophil (p. 1879·1).
Vaginal atrophy; vaginal dryness.

Educef *XL, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Educiclina *Tecnofarma, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Éductyl *Techni-Pharma, Mon.*
Potassium acid tartrate (p. 1879·2); sodium bicarbonate (p. 1781·1).
Constipation; bowel evacuation.

Edufil
Note: this name may be used for preparations of different composition.
Bennett, Gr.
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.
Peseri, Cz.†
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Edul
Note: this name may be used for preparations of different composition.
Infinity, Venez.
Aspartame (p. 2169·2).
Artificial sweetener.

Edul K-200
Note: this name may be used for preparations of different composition.
Knop, Chile.
Chromium tripicolinate (p. 2056·1).
Chromium deficiency.

Edulsan *Framingham, Arg.*
Stevioside (p. 2214·2).
Sugar substitute.

Edulsan Folic *Framingham, Arg.†*
Folic acid (p. 2063·1).
Dietary supplement.

Eduprim Mucolitico *F5 Profas, Spain.†*
Carbocisteine (p. 1658·1); guaifenesin (p. 1666·2); co-trimoxazole (p. 277·3).
Respiratory-tract infections.

Edurant *Janssen-Cilag, Belg.; Janssen, Canad.; Janssen-Cilag, Denm.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen, Jpn; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Spain; Janssen, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Tibotec, USA.*
Rilpivirine hydrochloride (p. 1012·1).
HIV infection.

Edvo *Unichem, India.*
Edaravone (p. 1370·2).

EEE *Cadila, India.*
Vitamin E (p. 2119·1).

Eelax *Keshav, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Eelovit *Ind-Swift, India.*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

EES *Abbott, Austral.; Methapharm, Canad.; Abbott, Hong Kong†; Pharmacia Upjohn, India; Abbott, Indon.†; Abbott, Malaysia; Abbott, NZ; Abbott, Singapore; Arbor, USA.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections; intestinal amoebiasis.

Eetless *Adcock Ingram, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Eeze *Antula, Denm.; Meda, Fin.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.
Antula, Swed.
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Pain.

Eezeneo *Antula, Swed.*
Diclofenac potassium (p. 48·3).
Pain.

EF *McNeil & Argus, India.*
Efavirenz (p. 975·1).
HIV infection.

Efa *Sifar, Turk.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement.

EFA Compound *Phytomedicine, Austral.*
Fish oil (p. 1460·3); evening primrose oil (p. 2502·2); soya oil (p. 2092·3).
Dietary supplement.

Efabene *Cefak, Swed.*
Dulcamara (p. 2497·3).

Efaclor *CCM, Malaysia.*
Cefaclor (p. 232·3).
Bacterial infections.

Efaderm *Galderma, India.*
Sodium pidolate (p. 1720·3); sodium lactate (p. 1781·2); linoleic acid (p. 2509·2).
Dry skin disorders.

Efadermin *Widmer, Ger.*
Lithium succinate (p. 1710·3); zinc sulfate (p. 2126·2).
Seborrhoeic dermatitis.

Efagel *Mavi, Ital.*
Gamolenic acid (p. 2509·2); vitamin E (p. 2119·1).
Nutritional supplement.

Efalan *Farmalex, Gr.*
Salicylic acid (p. 1719·1); sodium thiosulfate (p. 1576·1).

Efalex *Midsona, Swed.*
Fish oil (p. 1460·1); evening primrose oil (p. 2502·2); thyme oil (p. 2630·3).
Dietary fatty acid supplement.
Nutricia, NZ; Wassen, UK.
Evening primrose oil (p. 2502·2); fish oil (p. 1460·1); thyme oil (p. 2630·3).
Dietary supplement.

Efalife *Uni-Sankyo, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).

Efalith *Widmer, Belg.; Scotia, Irl.†; Widmer, Switz.*
Lithium succinate (p. 1710·3); zinc sulfate (p. 2126·2).
Seborrhoeic dermatitis.

Efamarine *Nutricia, NZ; Efamol, UK.*
Evening primrose oil (p. 2502·2); marine fish oil (p. 1460·3).
Dietary supplement to assist joint mobility.

Efamast *Express Care, NZ†*
Essential fatty acids; gamolenic acid (p. 2509·2).
Mastalgia.

Efamax *Nutricia, NZ.†*
Evening primrose oil (p. 2502·2); fish oil (p. 1460·3); vitamins; minerals; herbs.
Dietary supplement.

Efamed *Medhaus, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Efamed Plus *Medhaus, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Respiratory-tract disorders with bronchospasm and viscous mucus.

Efamol *Nutricia, NZ; Midsona, Swed.; Efamol, UK.*
Evening primrose oil (p. 2502·2).
Dietary supplement.

Efamol PMP *Nutricia Dietary, UK.*
Evening primrose oil (p. 2502·2); vitamins; minerals.
Premenstrual syndrome.

Efanatal *MaxMedica, Swed.†; Nutricia Dietary, UK.*
Evening primrose oil (p. 2502·2); fish oil (p. 1460·1).
Dietary supplement in pregnancy and breast feeding.

Nutricia, NZ.
Polyunsaturated fatty acids; docosahexaenoic acid (p. 1460·1); arachidonic acid (p. 2446·1); gamolenic acid (p. 2509·2).
Dietary supplement during pregnancy and breast feeding.

Efasol *Medica Korea, Malaysia.*
Tretinoin (p. 1725·2); erythromycin (p. 291·2).
Acne.

Efatop-PE *Cosme, India.*
Olive oil (p. 2575·1); sodium lactate (p. 1781·2); sodium pidolate (p. 1720·3); vitamin E acetate (p. 2119·1).

Efavilea *Elea, Arg.†*
Efavirenz (p. 975·1).
HIV infection.

Efavir *Cipla, India; Cipla, Venez.*
Efavirenz (p. 975·1).
HIV infection.

Efaxil *Pinewood, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Efaxin *Specifar, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Efcamon *Nizhpharm, Rus.*
Methyl salicylate (p. 92·1); capsicum (p. 2469·3); camphor (p. 2466·2); clove oil (p. 2481·3); mustard oil (p. 2646·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thymol (p. 1772·2); cloral hydrate (p. 1055·2); cinnamon oil (p. 2479·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Efcoba *Triton, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Efcoba Forte *Triton, India.*
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); selenium (p. 2086·3); thioctic acid (p. 2629·1).

Efcoba Plus *Triton, India.*
Calcium pantothenate (p. 2085·2); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); pyridoxine (p. 2105·3); thiamine (p. 2102·3).

Efcoba-F *Triton, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Efcoben *Triton, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); inositol (p. 2533·2); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Efcorlin *GSK, India.*
Nasal drops: ⊗Hydrocortisone (p. 1640·1); naphazoline nitrate (p. 1669·3).
Nasal congestion.

GSK, India.
Injection: ⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Efcortelan *Chemidex, UK.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Efcortesol *Sovereign, UK.*
⊗Hydrocortisone sodium phosphate (p. 1640·2).
Corticosteroid.

Efcure *Emcure, India.*
Efavirenz (p. 975·1).
HIV infection.

Efdege *Iason, Cz.; Iason, Ital.; Iason, Neth.; Iason, Port.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide agent for positron emission tomography.

Efecient *Panacea, India.*
Sodium ferric gluconate complex (p. 2089·1).
Iron deficiency in haemodialysis renal failure.

Efecoryl Forte *Sidus, Arg.*
⊗Phenylephrine hydrochloride (p. 1672·3); prednisolone acetate (p. 1645·2).
Eye disorders.

Efectal *Neon, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Efectin *Wyeth Lederle, Austria; Pfizer, Cz.; Wyeth, Hung.†; Pfizer, Pol.; Wyeth, Rus.*
Venlafaxine hydrochloride (p. 454·2).
Depression; panic disorder; anxiety; social phobia.

Efectine *Unipharm, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Efectine D *Unipharm, Mex.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; pruritus; urticaria; upper respiratory-tract congestion.

Efective *Farmoz, Port.†*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity.

Efedrosan *Pasteur, Chile.†*
⊗Ephedrine hydrochloride (p. 1663·2).
Asthma; bronchitis.

Efegen *Ranbaxy, S.Afr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Efekton *Stallion, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Efelac *Jenburkt, India.*
Cefixime (p. 240·3); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Efelin *Indoco, India.*
⊗Bromhexine (p. 1656·3); etofylline (p. 1208·2); salbutamol (p. 1220·2).

Efelin-PD *Indoco, India.*
⊗Choline theophyllinate (p. 1207·1); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Efelin-X *Indoco, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline (p. 1228·1).

Efemolin *Novartis, Ger.†*
⊗Fluorometholone (p. 1637·2); tetryzoline hydrochloride (p. 1678·3).
Allergic and inflammatory disorders of the eye.

Efemolina *Novartis, Arg.*
⊗Fluorometholone (p. 1637·2); tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Efemoline
Note: this name may be used for preparations of different composition.
Novartis, Gr.; Novartis, Hong Kong; Novartis, Ital.; Novartis, Philipp.; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.
⊗Fluorometholone (p. 1637·2); tetryzoline hydrochloride (p. 1678·3).
Allergic and inflammatory disorders of the eye.

Efemorf *Nycomed, Cz.*
⊗Morphine sulfate (p. 92·3).
Pain.

E-Fen
Note: this name may be used for preparations of different composition.
Zota, India.
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

E-fen
Note: this name may be used for preparations of different composition.
Teikoku Seiyaku, Jpn.
⊗Fentanyl citrate (p. 60·1).
Pain.

Efen
Note: this name may be used for preparations of different composition.
Micro, India.
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

E-Fen-CZ *Zota, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Efensol *Faes, Spain.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; pruritus associated with biliary obstruction or biliary cirrhosis.

Efepim *Orchid, Rus.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Eferox *Hexal, Pol.†*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer.

E-Fertoc *Vitae, Mex.*
Alpha tocopherol (p. 2119·1).

Efervit *HB, Braz.*
Vitamins.

Efespas *Sarabhai Piramal, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Efestad *Crinos, Ital.*
Desloratadine (p. 625·1).

Efetamol *Italfarmaco, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Efetrin *Alet, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Efeu *Ratiopharm, Ger.*
Ivy (p. 2536·2).
Cough; catarrh.

Efeusaft hysan *Ursapharm, Ger.*
Ivy (p. 2536·2).
Bronchitis; catarrh.

Efevelon *Actavis, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Efevelone *Actavis, Rus.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Efexin *Medikon, Indon.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Efexor *Wyeth, Arg.; Pfizer, Austral.; Pfizer, Belg.; Wyeth, Braz.; Wyeth, Chile; Pfizer, China; Pfizer, Denm.; Pfizer, Fin.; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, Indon.; Pfizer, Irl.; Pfizer, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Wyeth, Philipp.; Pfizer, Port.; Wyeth, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK; Wyeth, Venez.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia; mixed anxiety depressive states.

Efezial *Mylan, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Effaclar *Roche-Posay, Arg.*
Zinc pidolate (p. 1720·3).
Acne; seborrhoea.

Roche-Posay, Braz.; Roche-Posay, Irl.
Zinc pidolate (p. 1720·3); iodopropynyl butyl carbamate (Glycacil) (p. 2156·3).
Acne.

Effaclar Agua Desmaquillante Purificante *Roche-Posay, Chile.*
Zinc PCA (p. 1720·3); iodopropynyl butyl carbamate (Glicacyl) (p. 2156·3).
Skin cleansing.

Effaclar AI *Roche-Posay, Chile.*
Nicotinamide (p. 2083·1); iodopropynyl butyl carbamate (Glicacyl) (p. 2156·3); lipcido C8G; lipo hydroxy acid; chlorhexidine (p. 1743·2).
Acne.

Roche-Posay, Irl.
Nicotinamide (p. 2083·1); piroctone olamine (p. 1716·3); lipo hydroxy acids; iodopropynyl butyl carbamate (Glycacil) (p. 2156·3).
Acne.

Effaclar Duo *Roche-Posay, USA.*
Benzoyl peroxide (p. 1696·1); micro-exfoliating LHA.
Acne.

Effaclar Gel Moussant Purifiant *Roche-Posay, Chile.*
Iodopropynyl butyl carbamate (Glicacyl) (p. 2156·3).
Skin cleansing.

Effaclar H *Roche-Posay, Chile.*
Squalene (p. 2213·3); linoleic acid (p. 2509·2); ceramide 5 (p. 1699·1); levomenol (p. 2544·1); thermal water.
Moisturiser.

Effaclar Hidratante Matificante Activa *Roche-Posay, Chile.*
Zinc PCA (p. 1720·3); lipo hydroxy acid; ascorbyl glucoside; vitamin E (p. 2119·1).
Seborrhoea.

Effaclar K *Roche-Posay, Arg.*
Salicylic acid (p. 1719·1).
Acne.

Roche-Posay, Chile; Roche-Posay, Fr.
Zinc pidolate (p. 1720·3); iodopropynyl butyl carbamate (Glicacyl) (p. 2156·3); salicylic acid (p. 1719·1).
Acne.

Roche-Posay, Irl.
Lipo hydroxy acid; alkyl malate; salicylic acid (p. 1719·1); thermal water; zinc PCA (p. 1720·3); iodopropynyl butyl carbamate (Glycacil) (p. 2156·3).
Acne.

Roche-Posay, Singapore.
Lipo-hydroxy acid; salicylic acid (p. 1719·1); zinc pidolate (p. 1720·3); propylene glycol (p. 2205·2).
Acne.

Effacné *Roche-Posay, Fr.*
Benzoyl peroxide (p. 1696·1).
Acne.

Effadiane *Sinclair, Fr.*
A range of emollients.
Dry skin.

Effadiane relipidantes *Sinclair, Fr.*
Inulin (p. 2534·3); *Bifidobacterium lactis* (p. 2596·3); fish oil (p. 1460·1); borage oil (p. 2459·2).
Skin irritation.

Effasun Dépigmentante *Codexial, Fr.*
Arbutin (p. 1694·3); dioic acid; vitamin C (p. 2110·3).
Skin hyperpigmentation.

Effasun Hydroquin *Codexial, Fr.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Effcal *Lilly, India; Ranbaxy, Malaysia; Ranbaxy, Singapore; Ranbaxy, Thai.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement; calcium supplement; osteoporosis.

Effcil *Boryung, Thai.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Effect Comfort *Ivax, Cz.†*
Paracetamol (p. 115·1).
Pain; fever.

Effective Strength Cough Formula *Barre-National, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Effective Strength Cough Formula Liquid with Decongestant *Barre-National, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Effederm *Sinclair, Fr.*
Tretinoin (p. 1725·2).
Acne; keratinisation disorders; warts.

Effegyn *Effik, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Effekton *Teofarma, Ger.*
Diclofenac sodium (p. 48·3).
Pain; musculoskeletal, joint, and soft-tissue disorders; inflammation; gout.

Effekton mit Ketoprofen *Teofarma, Ger.*
Ketoprofen (p. 79·1).
Soft-tissue injury.

Effentora *Cephalon, Austria; Cephalon, Cz.; Cephalon, Fr.; Teva, Ger.; Cephalon, Irl.; Teva, Neth.; Cephalon, Pol.; Cephalon, Port.; Teva, Spain; Teva, Switz.; Cephalon, UK.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Effer-Activ *Alapis, Gr.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Efferalgan *BMS, Cz.; BMS, Fr.; BMS, Gr.; BMS, Hung.; BMS, Ital.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, Spain; Wyeth, Turk.; BMS, Ukr.*
Paracetamol (p. 115·1).
Fever; pain.

Efferalgan C *BMS, Ital.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Efferalgan Codeine *BMS, Pol.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Efferalgan Codéine *BMS, Fr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Efferalgan Vitamin C *BMS, Cz.; BMS, Pol.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Efferalgan with Vitamin C *BMS, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms; pain.

Efferalgan Vitamina C *BMS, Spain.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Efferalgan Vitamine C *UPSA Conseil, Fr.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Efferalganodis *UPSA Conseil, Fr.*
Paracetamol (p. 115·1).
Fever; pain.

Effercet *Doctum, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Effercitrate *Typharm, UK.*
Potassium citrate (p. 1780·3); citric acid (p. 2480·3).
Cystitis.

Efferflu-C *Pharma Dynamics, S.Afr.†*
Paracetamol (p. 115·1); vitamin C (p. 2110·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Effer-K *Nomax, USA.*
Potassium bicarbonate (p. 1780·3); potassium citrate (p. 1780·3).
Hypokalaemia; potassium depletion.

Effersol *Aspen Consumer, S.Afr.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Urinary alkalinisation.

Efferven *Ranbaxy, India.*
Efavirenz (p. 975·1).
HIV infection.

Effervit Calcium *Altana, Pol.†*
Calcium lactogluconate (p. 1783·1); ascorbic acid (p. 2110·3).
Calcium and vitamin C deficiency.

Effexin *Ildong, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Effexor *Pfizer, Canad.; Abacus, Denm.†; Wyeth-Ayerst, USA.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Pfizer, Fr.
Venlafaxine (p. 454·2) or venlafaxine hydrochloride (p. 454·2).
Anxiety; depression; social phobia; panic disorder.

Effical Plus *Bio-Sante, Canad.†*
Vitamins; minerals.

Efficib *MSD, Cz.; MSD, Irl.; Sigma-Tau, Ital.; MSD, Neth.; MSD, Pol.; MSD, Port.; MSD, Spain.*
Metformin hydrochloride (p. 489·1); sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Efficin *Lupin, India.*
Kanamycin (p. 314·3).
Bacterial infections.

Effico *Forest, Irl.; Pharmax, Irl.*
Nicotinamide (p. 2083·1); thiamine hydrochloride (p. 2103·1); caffeine (p. 1203·3).
Tonic.

Forest Laboratories, UK.
Nicotinamide (p. 2083·1); thiamine hydrochloride (p. 2103·1); caffeine (p. 1203·3); compound gentian infusion (p. 2512·1).
Tonic.

Efficort *Galderma, Chile; Galderma, China; Galderma, Fr.; Galderma, Israel†; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Galderma, Venez.*
⊗Hydrocortisone aceponate (p. 1640·1).
Skin disorders.

Efficover *O2, China.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Effidia *Ethicon, Fr.†*
Sodium hyaluronate (p. 2526·2).
Burns; ulcers; wounds.

Effidiet *Yves Ponroy, Singapore.†*
Nutritional supplement.
Digestive aid.

Effidigest *Nutrisante, Fr.*
Malt barley (p. 2080·2); papaya; *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); lactic acid (p. 2539·1).
Digestive disorders.

Effient *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, Canad.; Lilly, Hong Kong; Lilly, Israel; Lilly, Malaysia; Lilly, NZ; Lilly, Philipp.; Lilly, Singapore; Lilly, USA.*
Prasugrel hydrochloride (p. 1472·3).
Thromboembolism prophylaxis in acute coronary syndrome; thromboembolism prophylaxis in percutaneous coronary intervention.

Effigel *IBSA, Switz.*
Diclofenac epolamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Effimax *Piramal, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Effimax Plus *Piramal, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Effiplen
Note: this name may be used for preparations of different composition.
Effik, Port.
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Effiprev *Effik, Fr.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Effizinc *Expanscience, Fr.*
Zinc gluconate (p. 2126·2).
Acne; acrodermatitis.

Efflumidex *Allergan, Cz.; Allergan, Ger.; Allergan, Hung.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Effontil *Boehringer Ingelheim, Venez.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Efforeen *UCB, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Effort *Elfin, India.*
Vitamins; minerals.

Effortil *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Chile†; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; IFET (ΙΦΕΤ), Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, S.Afr.†; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.†*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension; orthostatic hypotension; vascular headache; cardiovascular collapse; post-operative debility.

Effortil comp *Boehringer Ingelheim, Austria.*
⊗Etilefrine hydrochloride (p. 1379·1); dihydroergotamine mesilate (p. 672·2).
Hypotension.

Effortil plus *Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Switz.†*
⊗Etilefrine hydrochloride (p. 1379·1); dihydroergotamine mesilate (p. 672·2).
Hypotension.

Effox *Vedim, Pol.; Schwarz, Rus.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; pulmonary hypertension; heart failure; ischaemic heart disease.

Effrine *TO-Chemicals, Thai.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Efibact *Molekule, India.*
Cefpodoxime.
Bacterial infections.

Eficiclina *Panalab, Arg.*
Lymecycline (p. 320·1).
Bacterial infections.

Efidac 24 Chlorpheniramine *Hogil, USA.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Efidac 24 Pseudoepehdrine *Hogil, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Efient *Lilly, Austria; Lilly, Belg.; Lilly, Cz.; Lilly, Denm.; Daiichi Sankyo, Fr.; Lilly, Fr.; Daiichi Sankyo, Ger.; Lilly, Ger.; Lilly, Irl.; Daiichi Sankyo, Neth.; Lilly, Norw.; Lilly, Pol.; Lilly, Port.; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, UK.*
Prasugrel hydrochloride (p. 1472·3).
Thromboembolism prophylaxis during percutaneous coronary intervention; acute coronary syndrome.

Lilly, Gr.
Prasugrel (p. 1472·3).
Thromboembolism prophylaxis during percutaneous coronary intervention.

Efigraine *Molekule, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Efikas *Sanovel, Turk.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Efiken *Kendrick, Mex.*
Ketoprofen (p. 79·1).
Osteoarthritis; pain; rheumatoid arthritis.

Efilat *Bioresearch, Mex.*
Potassium (p. 1793·1).
Potassium deficiency.

Efimag *Daiichi Sankyo, Fr.†*
Magnesium pidolate (p. 1787·3).
Magnesium deficiency.

Efimerol *Liferpal, Mex.*
Ketorolac (p. 80·2).
Pain.

Efin-CR *Captab, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Efipime *Orchid, Ukr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Efipres *Neon, India.*
⊗Ephedrine hydrochloride (p. 1663·2).
Hypotension in anaesthesia.

Efiret *Meda, Ital.*
Flupirtine maleate (p. 65·2).
Pain.

Efisol *Actavis, Ukr.*
Dequalinium chloride (p. 1749·3); ascorbic acid (p. 2110·3).
Mouth and throat disorders.

E-Fix *Zota, India.*
Cefixime (p. 240·3).
Bacterial infections.

E-Fix LB *Zota, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Efixano *Dosa, Arg.*
Irinotecan hydrochloride (p. 812·2).
Malignant neoplasms.

Efkalsol *Ni-The, Gr.*
Betaine hydrochloride (p. 2456·1); potassium bicarbonate (p. 1780·3).

Eflagen *Sanbe, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Eflavex *Norton Waterford, Irl.*
Cabergoline (p. 899·3).
Parkinsonism.

Eflevar *Nycomed, Arg.*
Calcium dobesilate (p. 2464·3).
Haemorrhoids; venous insufficiency.

Eflin *Meprofarm, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; sinusitis; rhinitis.

Eflo *Winsome, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Eflobid *Sarabhai Piramal, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Eflone *Ciba Vision, USA.*
⊗Fluorometholone acetate (p. 1637·2).
Eye disorders.

Eflora *Ranbaxy, India.*
Eflornithine hydrochloride (p. 932·1).

Efloran *KRKA, Cz.; KRKA, Rus.; KRKA, Ukr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; amoebiasis; giardiasis; trichomoniasis; Helicobacter pylori eradication.

E-Flox *Zota, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

E-Flu *Zota, India.*
Fluconazole (p. 578·2).
Fungal infections.

Efluvium Anti-caspa *Dermoteca, Port.†*
Salicylic acid (p. 1719·1); ichthammol (p. 1705·3); saw palmetto (p. 2363·3); climbazole (p. 576·2); acetamide monoethanolamide.
Scalp disorders.

Efluvium Anti-seborreico *Dermoteca, Port.†*
Lotion: Salicylic acid (p. 1719·1); panthenol (p. 2582·2); azeoglycine; acetamide monoethanolamide.
Scalp disorders.

Dermoteca, Port.†
Shampoo: Salicylic acid (p. 1719·1); ichthammol (p. 1705·3); saw palmetto (p. 2363·3); acetamide monoethanolamide.
Scalp disorders.

Efluvium Saquetas *Dermoteca, Port.†*
⊗Vitamins; minerals; amino acids; gelatin (p. 1154·1).
Nutritional supplement.

Efmol *Universal, Hong Kong.†*
⊗Ephedrine (p. 1663·1).
Nasal congestion.

Efoceft *Reliance, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Efodil *Lanpharm, Arg.*
⊗Ephedrine hydrochloride (p. 1663·2); silver (p. 2615·1).
Nasal congestion.

Efodine *Fougera, USA.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

E-Folic *Framingham, Arg.*
Folic acid (p. 2063·1); *d*-alpha tocopherol (p. 2119·1); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B_6 and B_{12} deficiency; hyperhomocysteinaemia.

Efomet *Promed, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Eformax *Ivax, Denm.†; Teva, Port.†*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Eforol *Yeni, Turk.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Efortil *Boehringer Ingelheim, Braz.; IFET (ΙΦΕΤ), Gr.; Boehringer Ingelheim, Spain.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Efospar *Reliance, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Efotax *Meprofarm, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Reliance, India.
Cefotaxime (p. 244·1).
Bacterial infections.

Efotin *Beijing Four Rings, Philipp.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Efox Long *UCB, Ukr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Efoxim *Reliance, India.*
Cefixime (p. 240·3).
Bacterial infections.

Efpa *Adeka, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Efpodox *Elfin, India.*
Cefpodoxime.
Bacterial infections.

Efracea *Galderma, Irl.; Galderma, Neth.; Galderma, UK.*
Doxycycline (p. 288·1).
Rosacea.

Efridol *Aesculapius, Ital.*
Nimesulide (p. 101·3).
Pain; inflammation; fever.

Efrin *Fischer, Israel.*
Phenylephrine hydrochloride (p. 1672·3).
Eye congestion; production of mydriasis.

Efrinalin *Ariston, Braz.*
⊗Adrenaline (p. 1292·1).

Efrinol *Prolab, Pol.*
⊗Ephedrine hydrochloride (p. 1663·2).
Nasal congestion.

Efriviral *Aesculapius, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Efrozin *Pharmanel, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Efta *H & Care, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Eftanu *Genesis, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Eftanu-S *Genesis, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Eftian *Pharos, Indon.*
Echinacea purpurea (p. 2498·1); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Infections.

Eftiar Decalin *DORC, Neth.*
⊗Perflunafene (p. 2586·3).
Ophthalmic tamponade.

Eftiar Octane *DORC, Neth.*
⊗Perfluorooctane (p. 2587·1).
Ophthalmic tamponade.

Efton *Ceutical, Hong Kong.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Eftriax *CCM, Malaysia.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Eftrival *Valmor, Venez.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Eftry *Krugher, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Efudex *Valeant, Canad.; Valeant, USA.*
Fluorouracil (p. 795·2).
Skin cancer; actinic keratoses.

Efudix *Investi, Arg.; Valeant, Austral.; Meda, Belg.; Raffo, Chile; Meda, Fr.; Meda, Ger.; Invida, Hong Kong; Meda, Hung.; Valeant, Irl.; Meda, Israel; Valeant, Mex.; Meda, Neth.; Valeant, NZ; Meda, Pol.; Pharmaco, S.Afr.; Inovail, Singapore†; Meda, Switz.; ICN, UK.*
Fluorouracil (p. 795·2).
Premalignant skin lesions; skin cancer; anogenital warts; solar keratosis; senile keratosis.

Efurix *Valeant, Braz.*
Fluorouracil (p. 795·2).
Skin cancer; actinic and senile keratoses.

Efurox *CCM, Malaysia.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Efxine *Pharmasant, Thai.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Efzu *Overseas, India.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Ega *Orchid, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Egaten *Novartis, Fr.; IFET (ΙΦΕΤ), Gr.*
Triclabendazole (p. 167·3).
Fascioliasis.

E-Gati *Zota, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Egaver *Sinnex, Hung.*
Malic acid (p. 2549·2); citric acid (p. 2480·3).
Warts.

Egaver Plusz *Sinnex, Hung.*
Malic acid (p. 2549·2); citric acid (p. 2480·3); zinc sulfate (p. 2126·2).
Warts.

Egazil *Biophausia, Denm.; Biophausia, Norw.; Biophausia, Swed.*
Hyoscyamine sulfate (p. 1848·1).
Gastrointestinal spasm; hypersecretion; irritable bowel syndrome; bladder tenesmus; biliary colic.

Egelif *Leovan, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

E-Gems *Carlson, USA.*
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E supplement.

E-Gen-C *Schering, S.Afr.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Postcoital oral contraceptive.

Egerian *AGIPS, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Égéry *Bailleul, Fr.*
Erythromycin (p. 291·2).
Bacterial infections.

E-Gest *Elfin, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea.

Egestan Folico *Elea, Arg.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Egestan Hierro *Elea, Arg.*
Ferrous gluceptate (p. 2061·2); folic acid (p. 2063·1).
Folic acid and iron supplement; anaemias.

Egg Plus *Megapharm, Israel.*
⊗Albumin (p. 1130·2).
Nutritional protein supplement.

Egibren *Chiesi, Ital.*
⊗Selegiline hydrochloride (p. 914·2).
Psychiatric disorders.

Egicalm *Sanofi-Aventis, Gr.*
Lysine aspirin (p. 84·3).
Pain; fever; inflammation.

Egicalm Cardio *Sanofi-Aventis, Gr.†*
Lysine aspirin (p. 84·3).
Thromboembolism prophylaxis.

Egiferon *PannonPharma, Hung.; Trigon, Hung.*
Interferon alfa (p. 989·2).
Chronic myeloid leukaemia; hairy-cell leukaemia; hepatitis C; herpes simplex infections; warts.

Egifilin *Egis, Hung.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Egilipid *Egis, Cz.; Egis, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Egilitax *Egis, Cz.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Egilok *Egis, Cz.*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Hypertension; myocardial infarction; arrhythmias; hyperthyroidism; migraine; angina pectoris.

Egis, Hung.; Egis, Rus.
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; hyperthyroidism; migraine; heart failure; ischaemic heart disease.

Egis, Ukr.
⊗Metoprolol (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; heart failure; arrhythmias; myocardial infarction; hyperthyroidism; migraine.

Eginor *Moraceae, India.*
Simeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Egira *Sanovel, Turk.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Egistrazol *Egis, Rus.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Egistrozol *Egis, Cz.; Egis, Neth.; Egis, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Egitromb *Egis, Cz.; Egis, Hung.; Egis, Pol.; Egis, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Egityl *Help, Gr.*
Lysine aspirin (p. 84·3); metoclopramide hydrochloride (p. 1862·2).

Eglandin *Sunny Plaza, Hong Kong.†*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Eglek *Masterlek, Rus.*
Sulpiride (p. 1107·3).
Psychoses; nervous disorders; psychosomatic disorders.

Eglidon *Merck, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Eglonil *Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.*
Sulpiride (p. 1107·3).
Schizophrenia; depression; anxiety; behaviour disorders; psychoses; neuroses.

Eglonyl *Sanofi-Aventis, S.Afr.*
Sulpiride (p. 1107·3).
Schizophrenia.

Eglymad *KRKA, Cz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ego Skin Cream *Ego, Austral.*
Emollient.

Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.
⊗Cetyl alcohol (p. 2178·2); glycerol (p. 2517·2); liquid paraffin (p. 2191·2).
Dry skin; barrier cream; emollient.

Egocort *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Egoderm *Ego, Austral.*
Cream: Ichthammol (p. 1705·3).
Skin disorders.

Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.
Ointment: Ichthammol (p. 1705·3); zinc oxide (p. 1729·1).
Skin disorders.

Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.
Cream: Ichthammol (p. 1705·3); allantoin (p. 1693·1).
Skin disorders.

Ego, NZ.
Ointment: Dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Skin disorders.

Egogyn
Note: this name may be used for preparations of different composition.
Bayer, Ital.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

K2 Health & Wellness, Chile; Vivax Gynopharm, Venez.
Vitamin E (p. 2119·1).
Dietary supplement; vitamin E deficiency.

Egolanza *Egis, Cz.*
Olanzapine hydrochloride.
Schizophrenia; bipolar disorder.

Egomax *Klonal, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

EgoPsoryl TA
Note: this name may be used for preparations of different composition.
Ego, Austral.
⊗Sulfur (p. 1721·1); phenol (p. 1763·3); menthol (p. 2553·2); glycerol (p. 2517·2); coal tar (p. 1723·2).
Psoriasis.

Egopsoryl TA
Note: this name may be used for preparations of different composition.
Ego, Hong Kong.
⊗Sulfur (p. 1721·1); phenol (p. 1763·3); coal tar (p. 1723·2); menthol (p. 2553·2); allantoin (p. 1693·1); glycerol (p. 2517·2).
Eczema; psoriasis.

Ego, Malaysia; Ego, NZ; Ego, Singapore.
Sulfur (p. 1721·1); phenol (p. 1763·3); coal tar (p. 1723·2); menthol (p. 2553·2); allantoin (p. 1693·1).
Neurodermatitis; psoriasis.

Egostar *Pentafarma, Port.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Egozinc *Pharmascience, Canad.; Hind Wing, Hong Kong.†*
Zinc sulfate (p. 2126·2).
Haemorrhoids; burns; ulcers; wounds.

Egozinc-HC *Pharmascience, Canad.*
⊗Zinc sulfate (p. 2126·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Egozite Baby *Ego, NZ.*
Zinc oxide (p. 1729·1); dimeticone (p. 2209·3); light liquid paraffin (p. 2191·2).
Barrier cream; nappy rash.

Egozite Baby Cream *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.*
Zinc oxide (p. 1729·1); dimeticone (p. 2209·3); light liquid paraffin (p. 2191·2).
Skin disorders; nappy rash.

Egozite Cradle Cap *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ.*
Salicylic acid (p. 1719·1) in an oil basis.
Cradle cap; seborrhoeic dermatitis.

Egozite Protective Baby Lotion *Ego, Austral.†; Ego, Hong Kong†; Ego, NZ.*
Dimeticone (p. 2209·3).
Nappy rash; barrier preparation.

Ego, Malaysia.†
⊗Dimeticone (p. 2209·3); light liquid paraffin (p. 2191·2); glycerol (p. 2517·2).
Barrier lotion; nappy rash.

Egretta *Ratiopharm, Cz.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Egrifta *EMD Serono, USA.*
⊗Tesamorelin acetate (p. 1931·2).
HIV-associated lipodystrophy.

Egrin
Note: this name may be used for preparations of different composition.
Worth, India.
Domperidone (p. 1838·1); flunarizine hydrochloride (p. 629·3); paracetamol (p. 115·1).

Grin, Mex.†
Alpha tocopherol (p. 2119·1).

Ehrenhöfer-Salbe *Ehrenhofer, Austria.*
Colophony (p. 2484·2); lovage root (p. 2545·3).
Skin disorders; soft-tissue, peri-articular, musculoskeletal, and joint disorders; bronchitis.

Ehrlich *Farmex, Gr.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); camphor (p. 2466·2); benzyl nicotinate (p. 29·3); mink oil; Spanish bog extract; Spanish pepper.

Ehrlich Balsamo *Polinac, Venez.*
Camphor (p. 2466·2); menthol (p. 2553·2); benzyl nicotinate (p. 29·3); capsicum (p. 2469·3).
Musculoskeletal and joint disorders.

Eicebäer *Merck, Austria.*
Thyme (p. 2630·2); senega (p. 1677·2); bitter orange (p. 2575·3).
Respiratory-tract congestion; cough.

Eicosan *Truw, Ger.*
Marine fish oil (p. 1460·3).
Hyperlipidaemias.

Eicosapen *Truw, Ger.; Takeda, Switz.*
Marine fish oil (p. 1460·3).
Hyperlipidaemias.

Eicovis *NBF, Ital.*
Omega-3 triglycerides (p. 1460·3); vitamins; minerals.
Nutritional supplement; eye disorders.

Eidoca *Eicopen, Venez.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Eifcof *Bangkok Lab & Cosmetic, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Eifcof-G *T-Boma, Hong Kong.†*
Dextromethorphan (p. 1660·1).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Eifel *Alapis, Gr.; Bio-Gen, Turk.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

EinsAlpha *Leo, Ger.*
Alfacalcidol (p. 2112·3).
Osteodystrophy; osteomalacia; osteoporosis; rickets; vitamin D deficiency.

Einschlaf-Kapsein extra *Salushaus, Ger.†*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Eiquinon *Eisai, Hong Kong.*
Ubidecarenone (p. 2637·1).
Heart failure.

Eirfem *Niche, Irl.*
⊗Letrozole (p. 817·1).
Breast cancer.

Eironil *Pliva, Irl.†*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Eisen-Sandoz *Sandoz, Ger.†*
Ferrous gluconate (p. 2061·2).
Iron deficiency.

Eisentabletten *Ratiopharm, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Eitan *Vitarum, Arg.†*
Enalapril (p. 1371·1).

Eith *Chemo-Drugs, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ejectil *Profic Organic, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

EK-3 *Wermar, Mex.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

EK Bürger *Ysatfabrik, Ger.†*
Dried bovine parathyroid gland (p. 2444·1).
Homoeopathic preparation.

Ekcef *Willow, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ekcef-S *Willow, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Eki Cabe A *Kowa, Jpn.†*
Ginseng (p. 2513·3); oxoamidine; lupulus (p. 2546·1); swertia.
Antacid; flatulence.

Eki Cabe S *Kowa, Jpn.*
Hydrotalcite (p. 1845·2); oxoamidine; ursodeoxycholic acid (p. 2638·1); ginseng (p. 2513·3).
Antacid; flatulence.

Eki Cabe U *Kowa, Jpn.*
Oxoamidine; hydrotalcite (p. 1845·2); almasilate (p. 1815·3); turmeric (p. 2218·1).
Formerly contained oxoamidine, ginseng, ginger, and turmeric.
Antacid; flatulence.

Ekian *Uriach Aquilea OTC, Spain.†*
Echinacea (p. 2498·1).
Cold symptoms.

Ekilid *Sanofi-Aventis, Mex.*
Sulpiride (p. 1107·3).
Depression; vertigo; schizophrenia.

Ekinaclear *Bio-Health, UK.*
Echinacea purpurea (p. 2498·1).
Skin disorders.

Ekinalife *Bio-Health, UK.*
Echinacea pallida (p. 2498·1); echinacea pupurea.
Cold and influenza symptoms.

Ekinase *Soho, Indon.*
Echinacea purpurea (p. 2498·1); selenium (p. 2086·3).
Immunostimulant.

Ekipental *Tum, Turk.*
Thiopental sodium (p. 1915·1).

Ekipim *Tum, Turk.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Ekistol *Lacer, Spain.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Eklevo *Candor, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Eklipid *Proel, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Eklips *Sanovel, Turk.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Eklips Fort *Sanovel, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Eklips Plus *Sanovel, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Eklira Genuair *Almirall, Denm.; Almirall, Neth.; Almirall, Norw.; Almirall, Spain; Almirall, UK.*
Aclidinium bromide (p. 1201·1).
Obstructive airways disease.

Eklivan *Proel, Gr.*
Somatostatin (p. 1930·3).
Haemorrhage in the upper gastro-intestinal tract.

Eklot *KonTest, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Eklot-MF *KonTest, India.*
Etamsylate (p. 1145·2); mefenamic acid (p. 85·3).

Ekonal *Mitsubishi Tanabe, Jpn.*
Nizofenone fumarate (p. 393·3).
Neurological deficit following subarachnoid haemorrhage.

Ekon-DT *Blue Cross, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Ekon-XL *Blue Cross, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Ekorinol *Sifar, Turk.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Ekosetol *Sifar, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Ekotrofil *Ecobi, Ital.*
Zinc oxide (p. 1729·1); aloe vera (p. 1693·2).
Emollient.

Ekovit *Curtis, Pol.†*
Vitamins; magnesium (p. 1786·3); selenium (p. 2086·3).
Dietary supplement.

EKS *Erfar, Gr.*
Camphor (p. 2466·2); turpentine oil (p. 2636·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar wood oil (p. 2472·3); thymol (p. 1772·2).

Eksedryl Expectorant *Ethica, Indon.*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); alcohol (p. 1733·1).
Cold symptoms; cough; respiratory-tract congestion.

Eksofed *Husnu Arsan, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Eksofed Ekspektoran *Husnu Arsan, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Ekspaz *Abdi, Turk.*
Otilonium bromide (p. 2578·2).

ektebin *Riemser, Ger.†*
Protionamide (p. 345·1).
Tuberculosis.

Ektis *Kapharma, Ukr.*
⊗Ascorbic acid (p. 2110·3); bromelain (p. 2460·3); ginger (p. 1844·1); cynara (p. 2490·3); cranberry (p. 2488·1); actinidia chinensis.
Dyspepsia; heartburn; gastro-oesophageal reflux.

Ektogan *Teofarma, Ital.*
Zinc peroxide (p. 1774·3); zinc oxide (p. 1729·1); magnesium peroxide (p. 1759·3).
Wound disinfection; skin disorders; burns.

Ektosélène *Robapharm, Switz.*
Selenium disulfide (p. 1719·3); sulfur (p. 1721·1).
Scalp disorders.

Ekuba *Teofarma, Ital.*
Vaginal douche: Chlorhexidine gluconate (p. 1743·3).
Personal hygiene.

Ekvacillin *Meda, Norw.; Meda, Swed.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Ekvator *Gedeon Richter, Rus.*
Lisinopril (p. 1420·3); amlodipine besilate (p. 1304·1).
Hypertension.

Gedeon Richter, Ukr.
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Ekxine *Pharmaniaga, Hong Kong.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with viscous mucus.

Ekzegamma *Viofar, Gr.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); zinc undecenoate (p. 596·3).
Infected skin disorders.

Ekze-Mant *Orva, Turk.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Ekzem-Entoxin N *Meckel, Ger.*
Bellis perennis (p. 2454·2); calcium hypophosphorosum (p. 2530·3); graphites (p. 2522·1).
Homoeopathic preparation.

Ekzemsalbe F *Agepha, Austria.*
⊗Hydrocortisone acetate (p. 1640·1).
Eczema.

Ekzevit *Biomedica, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ekzevowen *Weber & Weber, Ger.*
Centella asiat. (p. 1698·3); mahonia aquif. (p. 2577·1); viola tric. (p. 2647·3).
Homoeopathic preparation.

El *Sunij, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Elacur *Riemser, Ger.*
Propyl nicotinate (p. 127·3).
Musculoskeletal and joint disorders; neuralgia.

Elacutan *Riemser, Cz.†; Riemser, Ger.*
⊗Urea (p. 1727·3).
Skin disorders.

Elafax *Gador, Arg.*
Venlafaxine hydrochloride (p. 454·2).
Anxiety; depression; social phobia; panic disorder.

Elagen *Eladon, UK.*
Eleutherococcus senticosis (p. 2614·3).
Tonic.

Elageno OS *Mavi, Ital.*
Folic acid (p. 2063·1); magnesium (p. 1786·3); omega 6 triglycerides; omega 3 triglycerides (p. 1460·3); fatty acids.
Nutritional supplement.

Elamax *Biolab Sanus, Braz.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, cyproterone acetate (p. 2261·2); estradiol valerate (p. 2271·2).
Menopausal disorders.

Elamin *Baroda, India.*
Imipramine (p. 426·2).
Depression.

Elan *UCB, Ital.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Elana *OTW, Ger.†*
Cimicifuga racemosa (p. 2478·1); sanguinaria canadensis (p. 2610·1); juniperis sabina; secale cornutum (p. 2137·1).
Homoeopathic preparation.

Elan-Forte *YSP, Malaysia.*
Chlorhexidine hydrochloride (p. 1743·3); tolnaftate (p. 596·1).
Fungal skin infections.

Elani *Libbs, Braz.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Elanos *Kalbe, Indon.*
Black elderberry (p. 2609·3); echinacea purpurea (p. 2498·1); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1).
Infections.

Elanos Kids *Kalbe, Indon.*
Black elderberry (p. 2609·3); echinacea purpurea (p. 2498·1); zinc picolinate (p. 2126·1).
Infections.

Elantan
Note: this name may be used for preparations of different composition.
Gebro, Austria†; UCB, China; Sanol, Ger.†; Schwarz, Ger.†; GSK, Hong Kong; UCB, Irl.; GSK, Malaysia; Abbott, Mex.; GSK, Philipp.; AHN, S.Afr.; GSK, Singapore†; Schwarz, Thai.†; UCB, UK; Farma, Venez.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure; ischaemic heart disease; pulmonary hypertension.

Elanver *Remedina, Gr.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Elaprase *Shire, Austria; Shire, Belg.; Paladin, Canad.; Shire, Cz.; Shire, Denm.; Shire, Fr.; Shire, Ger.; Shire, Gr.; Genzyme, Hong Kong; Shire, Hung.; Shire, Irl.; Shire, Israel; Genzyme, Jpn; Genzyme, Malaysia; Shire, Neth.; Shire, Norw.; Healthcare Logistics, NZ; Shire, Pol.; Shire, Port.; Shire, Spain; Shire, Swed.; Drac, Switz.; Shire, UK; Shire, USA.*
Idursulfase (p. 2531·3).
Mucopolysaccharidosis II.

Elás *Merck, Port.*
Comfrey (p. 2484·2).
Soft-tissue injury; joint pain.

Elase *Pfizer, Chile; Pfizer, Malaysia.*
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1).
Debridement of wounds.

Élase *Pfizer, Fr.*
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1).
Debridement of ulcers and wounds.

Elaspol *Ono, Jpn.*
Sivelestat sodium (p. 2616·3).
Acute lung injury associated with systemic inflammatory response syndrome.

Elastab *TO-Chemicals, Thai.†*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Elasterin *Phoenix, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Elastoplast *Beiersdorf, Irl.*
Cayenne pepper (p. 2469·3).
Musculoskeletal pain.

Elastyn *Pharos, Indon.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Elate *Crescent, India.*
Dosulepin.
Depression.

Elatec *Servier, Mex.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Elater *Medipharm, Chile.*
Terbinafine (p. 593·3) or terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Elatrol *Teva, Israel.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Elatrolet *Teva, Israel.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Elavil
Note: this name may be used for preparations of different composition.
AA, Canad.; DDSA Pharmaceuticals, UK.
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Am-Europharma, Philipp.
Allopurinol (p. 600·2).
Hyperuricaemia; renal calculi; gout.

Élavil *Gerda, Fr.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Elawox *Riemser, Ger.†*
Urea hydrogen peroxide (p. 1774·2).
Infected wounds.

Elaxic *DWD, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Elaxic-P *DWD, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Elaxine *Aspen, Austral.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Elazor *Sigma-Tau, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Elbaprid *Tiefenbacher, Neth.†*
Tiapride hydrochloride (p. 1111·2).
Neuroleptic-induced extrapyramidal disorders.

Elbat *Genepharm, Gr.*
Flutamide (p. 798·2).
Prostatic cancer.

Elbend *Overseas, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Elbfaxin *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Elbona *Ellara, Rus.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Elbrus *Roemmers, Arg.*
Rasagiline mesilate (p. 912·3).
Parkinsonism.

Elcab *Baroda, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression.

Elcadol *Candor, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Elcal
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.
Elfin, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Elcal-Cit *Elnova, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1).

Elcal-D *Andromaco, Chile.*
Calcium carbonate (p. 1824·3) or calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis; rickets.

Elcal-Z *Elnova, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Elcar *Pik, Rus.*
Levocarnitine (p. 2053·2).
Tonic; gastritis; pancreatitis; carnitine deficiency; hyperthyroidism; skin disorders.

Elcarb *Captab, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc (p. 2126·1).

Elcarbo-Z *Elnova, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

Elcarim *TTK, India.*
Zingiber officinale.

Elce *Ind Biosciences, India.*
Cefixime (p. 240·3).
Bacterial infections.

Elcef *Elfin, India.*
Cefixime (p. 240·3).
Bacterial infections.

Elcef-LB *Elfin, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Elcel *Laboratorios Chile, Chile.†*
⊗Polygeline (p. 1160·3).
Hypovolaemic shock; hypotension.

Elcet *Elfin, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Elcet-P *Elfin, India.*
⊗Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Elcical *Ind Biosciences, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Elcid *Elfin, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Elcin *Elisa, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Elcion *Ranbaxy, India.*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal; muscle spasm.

Elcit *Elite, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Elcitonin *Asahi, China; Asahi, Jpn.*
Elcatonin (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Elclav *Captab, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3) or clavulanic acid (p. 268·3).
Bacterial infections.

Elclox *Elder, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Elclox Plus *Elder, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Elcodil *Faran, Gr.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Elcodrop *Arsmedendi, Gr.*
Omeprazole (p. 1867·2).

Elcofar *Farmedia, Gr.*
Omeprazole (p. 1867·2).

Elcold *Captab, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Elcold-DS *Novogen, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Elcolyt *Elpen (Ελπεν), Gr.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

Elcoman *Sandoz, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Elcontrol *Medhel, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Elcrit *Parke, Davis, Ger.; Pfizer, Ger.*
Clozapine (p. 1057·3).
Schizophrenia.

Elcy *Active, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Elcy-A *Active, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Eldamide *Elder, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; bone marrow transplantation.

Eldazole *Elder, India.*
Simeticone (p. 1886·2); diloxanide furoate (p. 931·2); tinidazole (p. 949·2).

Eldcef *Elder, India.*
Ceftizoxime (p. 253·1).
Bacterial infections.

Eldec
Note: this name may be used for preparations of different composition.
Elfin, India.
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Eldep *Psychotropics, India.*
Imipramine (p. 426·2).
Depression.

Eldep Forte *Psychotropics, India.*
Diazepam (p. 1063·2); imipramine hydrochloride (p. 426·2).

Eldep-M *Psychotropics, India.*
Diazepam (p. 1063·2); imipramine hydrochloride (p. 426·2).

Eldep-Plus *Psychotropics, India.*
Diazepam (p. 1063·2); imipramine hydrochloride (p. 426·2).

Eldepryl *Aspen, Austral.; Orion, Belg.; Orion, China; Orion, Denm.; Orion, Fin.; Themis Medicare, India; Orion, Irl.; Focus Care, Neth.; Orion, Norw.; Douglas, NZ; Reckitt Benckiser, S.Afr.; Orion, Swed.; Orion, UK; Orion, Ukr.; Dey, USA.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Eldequin *Elder, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye infections; otitis externa; otitis media.

Eldercoid *Elder, India.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Elderm *Elder, India.*
⊗Beclometasone dipropionate (p. 1621·2); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).

Eldertonic *Merz, USA.*
Vitamin B substances (p. 2102·3); minerals.

Eldervit *Elder, India.*
Vitamins.

Eldervit-ZC *Elder, India.*
Carotene; chromium (p. 2055·3); copper (p. 2057·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); folic acid (p. 2063·1); grape seed extract (p. 2521·3); manganese (p. 2081·2); mecobalamin (p. 2108·1); selenium dioxide (p. 2087·1); zinc (p. 2126·1).

Eldicet *Recalcine, Chile; Organon, India; Solvay, Philipp.; Abbott, Spain.*
Pinaverium bromide (p. 2590·3).
Gastrointestinal spasm; gastrointestinal radiography; biliary-tract dyskinesia; constipation; irritable bowel syndrome; biliary-tract pain; gastrointestinal pain.

Eldinir *Elpen (Ελπεν), Gr.*
Alendronate sodium (p. 1171·3).

Eldin-MD *Captab, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Eldiron *Elder, India.*
Iron (p. 2073·1); folic acid (p. 2063·1).
Anaemias.

Eldisin *Stada, Austria.*
Vindesine sulfate (p. 884·2).
Malignant neoplasms.

Eldisine *Eurogenerics, Belg.; Pharmacodane, Fin.; EG, Fr.; Cell Pharm, Ger.; IFET (ΙΦΕΤ), Gr.; Lilly, Irl.†; Crinos, Ital.; Stada, Swed.; Teva, Switz.; Genus, UK.*
Vindesine sulfate (p. 884·2).
Malignant neoplasms.

Eldom-P *Captab, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Eldon *Elfin, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Eldopaque *Valeant, Canad.; Pharmex (Φαρμεξ), Gr.; Invida, Hong Kong; Inovail, Malaysia; Valeant, Mex.; Invida, Singapore; Crawford, UK; Valeant, USA.*
Hydroquinone (p. 1705·1) with sunscreens.
Hyperpigmented skin disorders.

Eldoper *Micro, India; Micro, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Eldoper Plus *Micro, India.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).

Eldoquin *Valeant, Canad.; Invida, Hong Kong; Valeant, Malaysia†; Valeant, Mex.; ICN, NZ†; Invida, Singapore; Crawford, UK; Valeant, USA.*
Hydroquinone (p. 1705·1).
Hyperpigmented skin disorders.

Eldrate-S *Ind Biosciences, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Eldrot *Captab, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Eldrot-Plus *Captab, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Eldtam *Elder, India.*
⊗Tamoxifen (p. 860·2).
Breast cancer; anovulatory infertility.

Elebe *Medipharma, Arg.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia.

Eleben *Ind-Swift, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Elebloc *Alcon, Arg.; Alcon Cusi, Spain.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma.

EleCare *Ross, USA.*
Elemental amino-acid based food for special diets.
Food allergies; malabsorption; maldigestion; whole protein intolerance.

Elecasol *Krasnogorskleksredstva, Rus.; Lektravy, Ukr.*
Calendula (p. 2465·2); chamomile (p. 2474·1); liquorice (p. 1853·2); bidens tripartita; sage (p. 2608·3); eucalyptus leaf (p. 2501·1).
Respiratory-tract disorders; mouth disorders; gastrointestinal disorders; skin disorders; gynaecological disorders; urinary-tract disorders.

Elecor *Almirall, Spain.*
⊗Eplerenone (p. 1374·2).
Heart failure.

Elect *Captab, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Elect ORS *Piramal, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Elect-A *Captab, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections; filariasis.

Electa *Positif, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Electa-GP *Positif, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Electrace-ORS *Plus, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) vitamin C (p. 2110·3); zinc (p. 2126·1) (p. 1780·1).
Oral rehydration therapy.

Electral *FDC, India.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Oral rehydration therapy.

Electral RTD *FDC, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Electric Blue Headlice *Apotex, NZ.*
Conditioner: Clove oil (p. 2481·3); lavender oil (p. 2541·1); lemon oil (p. 2543·1); rosemary oil (p. 2607·3); melaleuca oil (p. 2551·1).
Detection of pediculosis.
Apotex, NZ.
Cream: Clove oil (p. 2481·3); lavender oil (p. 2541·1); melaleuca oil (p. 2551·1).
Pediculosis.

Electrobion *Merck, India.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Electrokind *Mankind, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Electrokind-L *Mankind, India.*
Carbohydrate; glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).

Electrolade *Eastern Pharmaceuticals, Irl.†; Actavis, UK.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Electrolit *Pisa, Mex.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Electrolit Pediatrico *Pisa, Mex.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Electrolyte *Fresenius Kabi, Gr.*
Electrolytes (p. 1775·1).

Electropak *Mirren, S.Afr.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Electrorice *Chrispa Alpha, Hong Kong.*
Rice flour; sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Naveh, Israel.
Electrolytes (p. 1775·1); rice flour (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Electro-W *Plus, India.*
Carbohydrate; glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); vitamin C (p. 2110·3); zinc (p. 2126·1) (p. 1780·1).
Oral rehydration therapy.

Eledyl *Mandar, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Eleflox *Ranbaxy, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Elegelin *Sun, India.*
⊗Selegiline (p. 914·2).
Parkinsonism.

Elektra
Note: this name may be used for preparations of different composition.
Craveri, Arg.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Crinos, Ital.
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Elektrolyt *SAD, Denm.*
Electrolyte infusion with glucose (p. 1775·1).
Fluid and electrolyte disorders.

Elelyso *Protalix, Israel; Pfizer, USA.*
Taliglucerase alfa (p. 2433·2).
Gaucher disease.

Elemental 028 *Nutricia, Austral.; SHS, Denm.; Nutricia, Fin.; Scientific Hospital Supplies, Irl.†; Nutricia, Ital.; Nutricia, NZ; SHS, UK.*
Preparation for enteral nutrition.

Elemental Extra *Nutricia, Cz.; Nutricia, Fr.*
Preparation for enteral nutrition.
Crohn's disease.

Elemune *Claris, India.*
L-Alanyl-L-glutamine (p. 2070·2).
Parenteral nutrition.

Elenium *Polfa, Cz.; Tarchomin, Hung.; Polfa Tarchomin, Pol.; Tarchomin, Rus.*
Chlordiazepoxide (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; psychosomatic symptoms; premedication; depression; insomnia; movement disorders; convulsions.

Élénol *Gerda, Fr.†*
Lindane (p. 2157·1); amylocaine hydrochloride (p. 1979·3).
Scabies.

Eleobron *Vamsler, Philipp.*
Guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cough.

Eleomox *Vamsler, Philipp.*
Amoxicillin (p. 216·2).
Bacterial infections.

Eleonor *Sandoz, Belg.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Eleprep *Norgine, Neth.†*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Elepril *Farmasa, Braz.*
⊗Selegiline (p. 914·2).
Parkinsonism.

Elepsin *Andromaco, Arg.†*
Imipramine hydrochloride (p. 426·2).
Depression.

Elequine *Janssen-Cilag, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Eleron *Geno, India.*
Capsules: Ferric hydroxide; folic acid (p. 2063·1).

Geno, India.
Oral drops; syrup: Iron (p. 2073·1).

Elestat *Allergan, Mex.; Allergan, USA.*
Epinastine hydrochloride (p. 628·3).
Allergic conjunctivitis.

Elestrin *Azur, USA.*
Estradiol (p. 2271·1).
Menopausal disorders.

Eleton *Scoshia, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Eletone *Mission Pharmacal, USA.*
Emollient.
Dry skin.

Eleu *Harras-Curarina, Ger.*
Siberian ginseng (p. 2614·3).
Tonic.

Eleu-Kokk *Boehringer Ingelheim, Ger.*
Siberian ginseng root (p. 2614·3).
Tonic.

Eleuphrat *MSD, Austral.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Eleva *Alphapharm, Austral.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; premenstrual dysphoric disorder.

Eleval *Drugtech, Chile.*
Sertraline (p. 448·1).
Depression.

Eleven Seas *Taj, India.*
Cod-liver oil (p. 2056·3).

Elevex *Sensomed, Philipp.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Elevit *Bayer, Austral.; Bayer, Austria; Bayer, Braz.; Bayer, Ital.; Bayer, NZ; Bayer, Spain; Bayer, Turk.*
Vitamins; minerals.
Dietary supplement in pregnancy and breast feeding.

Bayer, Switz.
Vitamins; with or without minerals.

Elevit Pre-Nat *Bayer Consumer, Mex.*
Vitamins; minerals.
Nutritional supplement during pregnancy and lactation.

Elevit Pronatal *Bayer, China; Bayer, Cz.†; Roche, Gr.; Roche, Hong Kong†; Bayer, Hung.; Bayer, Philipp.; Bayer Consumer, Rus.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Bayer, Pol.; Bayer Consumer, Ukr.
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Dietary supplement in pregnancy and lactation; prophylaxis of neural tube defects.

Élévit Vitamine B_9 *Bayer Sante, Fr.*
Vitamins; minerals.

Elfazyme *Elfin, India.*
⊗Alpha-amylase (p. 2442·1); pepsin (p. 2586·1).

Elfenac Plus *Captab, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Elfenac-MR *Captab, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Elfenac-SR *Captab, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Elferri *Svizera, India.*
Vitamin B substances (p. 2102·3); ferrous gluconate (p. 2061·2); yeast (p. 2125·2).
Tonic; anaemias.

Elferri Plus *Svizera, India.*
Vitamins; copper sulfate (p. 2057·2); potassium iodide (p. 2336·3); zinc sulfate (p. 2126·2); lysine (p. 2079·3).

Elferri-TR *Svizera, India.*
Ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

Elferri-Z *Svizera, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); zinc sulfate (p. 2126·2).
Iron, zinc, and folic acid deficiency during pregnancy and lactation.

Elfi *Elder, India.*
Cefixime (p. 240·3).
Bacterial infections.

Elfi-XL *Elder, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Elfol *Captab, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Elgadil *Takeda, Spain.*
Urapidil hydrochloride (p. 1520·2).
Hypertension.

Elgam *Daiichi Sankyo, Spain.†*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Elgnil *Cadila, India.*
Cetirizine hydrochloride (p. 619·2).
Formerly known as ELG Nil.

Elgnil Cold *Cadila, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Elgram *Captab, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Elgrape *Elnova, India.*
Vitamins; grape seed extract (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).

Elgucare *YSP, Malaysia.*
Astragalus membranaceous radix (p. 2451·1); salviae miltiorrhizae radix (p. 2491·3); paederia scandens radix; lycopodium clavatum (p. 2547·1); polygonati officinalis rhizome; ziziphus jujuba fruit; liquorice (p. 1853·2).
Back pain.

Elgydium *Pierre Fabre, Fr.; Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore; Pierre Fabre, Switz.; Ceuta, UK.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders; dental caries prophylaxis; gum disorders.

Rovafarm, Arg.
Chlorhexidine gluconate (p. 1743·3); calcium carbonate (p. 1824·3).
Dental caries prophylaxis.

Elgydium Anti-Placa *K2 Health & Wellness, Chile.*
Calcium carbonate (p. 1824·3); chlorhexidine gluconate (p. 1743·3).
Dental caries prophylaxis; gingivitis.

Elgydium Blancheur *Pierre Fabre Sante, Fr.*
Sodium bicarbonate (p. 1781·1); chondrus crispus (p. 2176·3); chlorhexidine gluconate (p. 1743·3).
Dental hygiene.

Elgydium Blanqueador *Rovafarm, Arg.*
Sodium bicarbonate (p. 1781·1).
Teeth whitener.

Elgydium Dents Sensibiles *Pierre Fabre, Fr.*
Nicomethanol hydrofluoride (p. 2089·2); chlorhexidine gluconate (p. 1743·3).
Dental caries prophylaxis; sensitive gums.

Elgydium Dientes Sensibles *Rovafarm, Arg.; K2 Health & Wellness, Chile.*
Nicomethanol hydrofluoride (p. 2089·2); chlorhexidine gluconate (p. 1743·3).
Dental caries prophylaxis; sensitive teeth.

Elgydium Junior *Rovafarm, Arg.*
Nicomethanol hydrofluoride (p. 2089·2).
Dental caries prophylaxis.

Elgydium Proteccion Caries *Rovafarm, Arg.*
Nicomethanol hydrofluoride (p. 2089·2).
Dental caries prophylaxis.

Elgydium Protection Caries *Pierre Fabre, Fr.*
Nicomethanol hydrofluoride (p. 2089·2).
Dental caries prophylaxis.

Elgydium Protection email *Pierre Fabre Sante, Fr.*
Chlorhexidine gluconate (p. 1743·3); nicomethanol hydrofluoride (p. 2089·2).
Dental caries prophylaxis.

Elgydium Sensitive *Pierre Fabre Sante, Singapore.*
Chlorhexidine gluconate (p. 1743·3); nicomethanol hydrofluoride (p. 2089·2).
Dental caries prophylaxis; hypersensitive teeth.

Elgyfluor *Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore.†*
Nicomethanol hydrofluoride (p. 2089·2); chlorhexidine gluconate (p. 1743·3).
Dental caries prophylaxis.

Elian *Infirmarius, Ger.*
Helianthus tuberosus.
Homoeopathic preparation.

Elibactin *Gerolymatos, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Eliben *Bennett, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Elica *Schering-Plough, Mex.; Schering-Plough, Philipp.; MSD, Spain.*
⊗Mometasone furoate (p. 1644·1).
Skin and scalp disorders.

Elicea *KRKA, Cz.; KRKA, Pol.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Elicocin *Santen, Philipp.*
Erythromycin (p. 291·2); colistimethate sodium (p. 275·3).
Bacterial eye infections.

Elicor *Farmanic, Gr.*
Acetylcysteine (p. 1652·2).
Respiratory disorders associated with viscous mucus.

Elide *Eden, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis; dysmenorrhoea.

Elidel *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Meda, Belg.; Novartis, Braz.; Valeant, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Meda, Fin.; Meda, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Combiphar, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Meda, Neth.; Meda, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore†; Meda, Spain; Meda, Swed.; Meda, Switz.; Meda, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Valeant, USA; Novartis, Venez.*
Pimecrolimus (p. 1716·1).
Atopic eczema.

Elifer *Casasco, Arg.*
Gabapentin (p. 523·3).
Epilepsy.

Elify *Medochemie, Cz.; Pharmacypria, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia.

Eligao *Forgo, India.*
⊗Beclometasone (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2).

Eligard *Raffo, Arg.; Hospira, Austral.; Astellas, Austria; Zodiac, Braz.; Sanofi-Aventis, Canad.; Tecnofarma, Chile; Astellas, Cz.; Astellas, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Ger.; Astellas, Hung.; Ranbaxy, India; Astellas, Irl.; Luxembourg, Israel†; Astellas, Ital.; Astellas, Neth.; Astellas, Norw.; Hospira, NZ; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Astellas, Ukr.; Sanofi Synthelabo, USA.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; uterine myoma; endometriosis.

Elim *Elfin, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Elimcee *Piramal, India.*
Vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2).

Elimer *Nexus, Gr.*
Glucosamine sulfate (p. 2515·3).

Eliminate *Zydus, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Eliminex *Sante Naturelle, Canad.*
Lappa (p. 2540·1); cascara (p. 1826·1); peppermint (p. 1877·1); sarsaparilla (p. 2610·3); senna (p. 1885·1); bearberry (p. 2453·2).

Elimite *Allergan, USA.*
Permethrin (p. 2159·3).
Scabies.

Elimitona *Brauer, Austral.*
Benzoicum acidum (p. 1738·2); berberis aquifolium (p. 2577·1); carbo veg. (p. 1537·3); crataegus monogyna (p. 2488·1); merc. sol. (p. 2555·3); nux vomica (p. 2573·3); silicea (p. 2208·3); sterculia acuminata (p. 2648·2).
Homoeopathic preparation.

Elimitona Slim & Detox *Brauer, Austral.*
Benzoic acidum (p. 1738·2); berberis aq. (p. 2577·1); calc. carb. (p. 1824·3); carbo veg. (p. 1537·3); crataegus (p. 2488·1); graphites (p. 2522·1); merc. sol. (p. 2555·3); nux vom. (p. 2573·3); silicea (p. 2208·3); sterculia (p. 1888·3).
Homoeopathic preparation.

Elina *Reddy, India.*
Mizolastine (p. 636·1).
Allergic rhinitis; urticaria.

Elinap *Kleva, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Elinatecan *Nolver, Venez.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Eliosid *SF, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Elipa *Edol, Port.*
Ketorolac trometamol (p. 80·2).
Ocular inflammation; allergic conjunctivitis.

Eliphorin *Elin, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Eliphos *Hawthorn, USA.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia in renal failure.

Eliptus *PharOS, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Eliquis *BMS, Belg.; BMS, Canad.; Pfizer, Canad.; BMS, Denm.; Pfizer, Denm.; BMS, Fr.; BMS, Ger.; Pfizer, Ger.; BMS, Irl.; Pfizer, Irl.; Pfizer, Israel; BMS, Jpn; BMS, Neth.; BMS, Norw.; Pfizer, Norw.; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, UK; Pfizer, UK; BMS, USA.*
Apixaban (p. 1306·2).
Thromboembolism prophylaxis following hip or knee replacement surgery; stroke and embolism prophylaxis in atrial fibrillation.

Elisamylan *Mylan, Belg.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Elisca *Medreich, Hong Kong.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Elisir Terpina *Teofarma, Ital.*
Terpin hydrate (p. 1678·2); dropropizine (p. 1662·2).
Cough.

Elisone *CBC, Hong Kong.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Elisor *BMS, Fr.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Elissan *Serra Pamies, Spain.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Elitar *Daquimed, Port.*
Nabumetone (p. 97·1).
Musculoskeletal, joint, and peri-articular disorders.

Elite *Bayer, Arg.†*
Test for glucose in blood (p. 2516·3).

Elitek *Sanofi Synthelabo, USA.*
Rasburicase (p. 609·2).
Hyperuricaemia.

Eliten *BMS, Ital.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Elite-P *Elisa, India.*
Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Elithris *Armoxindo, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout.

Elitiran *Mintlab, Chile.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain; fever.

Elitos *Andromaco, Arg.*
Oxeladin citrate (p. 1671·2).
Cough.

Elitos ET *Andromaco, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); tolu (p. 1679·2).
Cough.

Elitox *Ranbaxy, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Elityran *Vianex (Βιανεξ), Gr.*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; uterine fibroids; prostatic cancer; female infertility.

Elival *Elite, India.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder; migraine.

Elivee *Elnova, India.*
Lecithin (p. 2542·2).

E-Livo *Zota, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Eliwel *Sun, India.*
Amitriptyline (p. 401·1).
Depression; neuropathic pain; migraine.

Sun, Rus.†
Amitriptyline hydrochloride (p. 401·1).

Elixifilin *Tora, Spain.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Elixime *Elin, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Elixine *Saval, Chile.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Élixir Bonjean *Dexo, Fr.†*
Melissa (p. 2552·3); bitter-orange peel (p. 2575·3); aniseed (p. 2444·2); cumin seed; catechu (p. 2472·3); peppermint oil (p. 1877·1).
Digestive disorders.

Elixir contre la toux *Weleda, Switz.†*
Aniseed (p. 2444·2); dulcamara (p. 2497·3); ipecacuanha (p. 1667·2); marrubium (p. 1668·3); thyme (p. 2630·2); althaea (p. 2438·3); drosera (p. 2497·2); pulsatilla (p. 2600·2).
Cough.

Elixir Damiana and Saw Palmetto *Potter's, UK.*
Corn silk (p. 2487·1); damiana (p. 2491·3); saw palmetto (p. 2363·3).
Tonic.

Elixir Efelin *Indoco, India.*
⊗Caffeine (p. 1203·3); ephedrine hydrochloride (p. 1663·2); hyoscyamus tincture (p. 2530·2); senega tincture (p. 1677·2); sodium benzoate (p. 1738·2); sodium iodide (p. 2337·1).

Elixir frangulae compositum *Streuli, Switz.*
Frangula bark (p. 1843·3).
Constipation.

Elixir Paregórico *Catarinense, Braz.*
Camphorated opium (p. 111·3).
Diarrhoea; opioid withdrawal syndrome.

Elixir Phenobarb *Suphong, Thai.*
Phenobarbital sodium (p. 535·3).

Élixir Spark *Poirier, Fr.†*
Boldo (p. 2458·3); cynara (p. 2490·3).
Digestive disorders.

Elixofilina *Bayer, Mex.*
Theophylline (p. 1229·3).

Elixophyllin
Note: this name may be used for preparations of different composition.
Caraco, USA.
Theophylline (p. 1229·3).
Obstructive airways disease.

Elixophyllin-GG *Forest Pharmaceuticals, USA.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Elixophyllin-KI *Forest Pharmaceuticals, USA.*
Theophylline (p. 1229·3); potassium iodide (p. 2336·3).
Tenacious mucus in asthma and bronchitis.

ElixSure Childrens Congestion *Taro Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

ElixSure Childrens Cough *Taro Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Elizabeth Arden First Defense Protective *Arden, Canad.†*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Elizabeth Arden Lip Protectant *Arden, Canad.*
SPF 15: Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Elizabeth Arden Perfect Eye *Arden, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Elizabeth Arden Perfect Lip *Arden, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Elizac *Mersifarma, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Eljoint *Elfin, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Elkana *Sanbe, Indon.*
Syrup: Vitamins; minerals; inositol (p. 2533·2); lysine hydrochloride (p. 2079·3).
Vitamin and mineral deficiency.

Sanbe, Indon.
Tablets: Calcium hydrogen phosphate (p. 1783·3); calcium lactate (p. 1784·1); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).
Vitamin and mineral deficiency.

Elkof *Elder, India.*
⊗Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Elkofen *Demo, Gr.*
Nizatidine (p. 1866·1).

ELKO-Mix *Baxter, Ger.†*
Electrolytes (p. 1775·1).
Parenteral nutrition.

Elkopas *Demo, Gr.*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).

Elkostop *Minerva (Μινερβα), Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Elkotheran *Bros, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Elkuf *Elfin, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

ella *CTS, Israel; Hyphens, Singapore; Watson, USA.*
Ulipristal acetate (p. 2312·1).
Postcoital oral contraceptive.

Ellanco *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Lovastatin (p. 1425·2).
Cardiovascular risk reduction; hypercholesterolaemia; atherosclerosis.

ellaOne *HRA, Austria; Besins, Belg.; HRA, Cz.; HRA, Denm.; HRA, Fr.; HRA, Ger.; HRA, Gr.; HRA, Hung.; HRA, Irl.; HRA, Ital.; HRA, Neth.; HRA, Norw.; HRA, Pol.; HRA, Port.; HRA, Spain; Nycomed, Swed.; HRA, UK.*
Ulipristal acetate (p. 2312·1).
Postcoital oral contraceptive.

Ellatun *Infectopharm, Ger.*
⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Ell-Cranell alpha *Galderma, Ger.*
Alfatradiol (p. 2255·2).
Alopecia androgenetica.

Elleacnelle *Stragen, Switz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Elleci *Lampugnani, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Elleffe *Dicofarm, Ital.*
Lactoferrin (p. 2539·3).
Skin disorders.

Ellence *Pharmacia Upjohn, USA.*
Epirubicin hydrochloride (p. 787·1).
Breast cancer.

Elleste Duet Conti *Meda, UK.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Elleste-Duet *Meda, UK.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Elleste-Solo *Meda, UK.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Ellgy *Hoe, Hong Kong.*
Skin cleanser.

Hoe, Philipp.
A range of moisturisers.

Hoe, Singapore.
A range of emollients and skin cleanser.

Ellgy Corns & Warts *Hoe, Malaysia.*
Salicylic acid (p. 1719·1).
Corns; warts; calluses.

Ellgy H2O *Hoe, Malaysia.*
Skin cleanser.

Ellgy H2O ARR *Hoe, Malaysia.*
Saccharide isomerate.
Dry skin.

Ellgy Plus *Hoe, Malaysia.*
Saccharide isomerate; portulaca.
Dry, cracked heels.

Ellgy Plus D Factor *Hoe, Malaysia.*
Saccharide isomerate; portulaca oleracea; colecalciferol (p. 2113·1).
Dry, cracked heels.

Ellimans *Thornton & Ross, UK.*
Turpentine oil (p. 2636·3); acetic acid (p. 2426·3).
Musculoskeletal pain.

Elliots B *Orphan Medical, Israel.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Diluent for intrathecal administration of methotrexate sodium and cytarabine.

Ellisek-S *SJA, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Elmecob *Elder, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Elmecob Plus *Elder, India.*
Vitamin B substances (p. 2102·3); chromium (p. 2055·3); selenium (p. 2086·3); zinc (p. 2126·1); thioctic acid (p. 2629·1).

Elmega-3 *Elnova, India.*
Vitamins; trace elements; docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); grape seed extract (p. 2521·3).

Elmego *Chinta, Thai.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders.

Elmendos *GSK, Austral.†; GSK, Ger.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Elmes *Elder, India.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Elmet *Captab, India.*
Methylergometrine (p. 2137·3).
Postpartum and postabortal haemorrhage.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Elmetacin *Stada, Cz.; Stada, Hung.; Sankyo, Pol.; Ciclum, Port.; Pharmafrica, S.Afr.; Medinova, Switz.; Medinova, Thai.; Sankyo, Venez.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Elmet-G *Elfin, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Elmex *Gebro, Austria; GABA, Belg.; GABA, Cz.; GABA, Fin.; GABA, Ger.; Teva, Hung.; GABA, Israel; Sigma-Tau, Ital.; GABA, Neth.; GABA, Port.; GABA, Switz.*
Topical gel: Olaflur (p. 2085·1); dectaflur (p. 2059·1); sodium fluoride (p. 2089·2).
Dental caries prophylaxis; sensitive teeth.

Gebro, Austria; GABA, Cz.; GABA, Fin.; GABA, Ger.; Teva, Hung.; GABA, Neth.; GABA, Port.; GABA, Switz.
Topical solution: Olaflur (p. 2085·1); dectaflur (p. 2059·1).
Dental caries prophylaxis; sensitive teeth.

Teva, Israel; GABA, Pol.
Mouthwash: Amine fluoride (p. 2085·1); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Elmif *Elder, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; postcoital oral contraceptive; labour induction following fetal death.

Elmik *Elfin, India.*
Amikacin (p. 214·1).
Bacterial infections.

Elmin *Yash, India.*
Mebendazole (p. 158·3).
Worm infections.

Elminex *Cachet, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Elmino *Zentiva, UK.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Elminova *Yash, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Elmiron *Ivax, Arg.; Janssen-Ortho, Canad.; Baker Norton, Hong Kong; Ivax, Hong Kong; Janssen, USA.*
Pentosan polysulfate sodium (p. 1465·1).
Interstitial cystitis.

Elmore Oil *Golden Glow, Austral.*
Melaleuca oil (p. 2551·1); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Elmycin *Elder, India.*
Natamycin (p. 590·2).
Blepharitis; conjunctivitis; keratitis.

Elnacin *Shince, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Elneuro *Elnova, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Elnim-D *Elnova, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Elnim-MD *Captab, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Elnocod *Elnova, India.*
Cod-liver oil (p. 2056·3).

Elnor-TZ *Elisa, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Elnutra *Elnova, India.*
Copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc oxide (p. 1729·1); vitamin A (p. 2098·3); vitamin E acetate (p. 2119·2); arginine (p. 2049·1); lutein (p. 2079·2); lycopene (p. 2546·2).

Elnutra-M *Elnova, India.*
Betacarotene (p. 2051·1); mecobalamin (p. 2108·1); grape seed extract (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2).

Elnutrin *Elder, India.*
Range of preparations for enteral nutrition.

Elo-admix *Fresenius Kabi, Austria.†*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Elobact *GSK, Ger.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Elocom *MSD, Belg.; Mantecorp, Braz.; Merck, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; 2care4, Denm.; Europharma, Denm.; Orifarm, Denm.; Pharmason, Denm.; Schering-Plough, Hung.; Schering-Plough, Israel; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; MSD, Spain; MSD, Switz.; Schering-Plough, Ukr.*
⊗Mometasone furoate (p. 1644·1).
Skin and scalp disorders.

Elocom Plus *MSD, Spain.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Psoriasis.

Elocom-S *Schering-Plough, Rus.; Schering-Plough, Ukr.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Skin disorders; psoriasis.

Elocon *Schering-Plough, Arg.; MSD, Austral.; Aesca, Austria; Schering-Plough, Denm.; Schering-Plough, Fin.; MSD, Gr.; Fulford, India; Schering-Plough, Indon.; MSD, Irl.; Schering-Plough, Ital.; MSD, Neth.; Schering-Plough, Norw.; Schering-Plough, NZ; Essex, Philipp.; Schering-Plough, S.Afr.; MSD, Swed.; Schering-Plough, Turk.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
⊗Mometasone furoate (p. 1644·1).
Skin and scalp disorders; allergic rhinitis; nasal polyps; sinusitis.

Elodius *Boehringer Ingelheim, Braz.*
Tipranavir (p. 1019·3).
HIV infection.

Elof *Positif, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Elofen *Polfarmex, Pol.*
Fenspiride hydrochloride (p. 1209·2).
Cough.

Elofuran *Elofar, Braz.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Elohaes *Fresenius Kabi, Neth.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion.

Eloine *Bayer Schering, Cz.; Bayer, Denm.; Bayer, Spain; Bayer, Swed.; Berlis, Switz.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Eloisin *Alcon Cusi, Spain.*
Eledoisin trifluoroacetate (p. 2499·3).
Dry eyes.

Elolipid *Fresenius Kabi, Ital.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Elome *Ind Biosciences, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

ELO-MEL *Fresenius Kabi, Austria; Fresenius Kabi, Cz.†*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Elomet *MSD, Hong Kong; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, Port.; MSD, Singapore; MSD, Thai.; Schering-Plough, Venez.*
⊗Mometasone furoate (p. 1644·1).
Skin and scalp disorders.

Elon Dual Defense *Dartmouth, USA.*
Undecenoic acid (p. 596·3).
Fungal skin infections.

Elone *Waves, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Elontril *GSK, Austria; GSK, Cz.; GSK, Ger.; GSK, Hung.; Sigma-Tau, Ital.; GSK, Neth.; Bial, Port.; GSK, Spain.*
Bupropion hydrochloride (p. 408·2).
Depression.

Elonva *MSD, Austral.; Organon, Austria; Organon, Belg.; Organon, Cz.; Organon, Denm.; MSD, Ger.; Organon, Gr.; MSD, Israel; MSD, Neth.; Organon, Norw.; Organon, Pol.; Organon, Port.; MSD, Singapore; MSD, Spain; MSD, Swed.; Organon, UK.*
Corifollitropin alfa (p. 2261·1).
Controlled ovarian stimulation.

Elonyl-Z *Ind Biosciences, India.*
Selenium (p. 2086·3); zinc (p. 2126·1).

Elonza *Unison, Thai.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Elopram *Innova, Ital.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression; panic disorder.

Elopro *Pharmacore, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Elorgan *Europharma, Denm.; Sanofi-Aventis, Spain.*
Pentoxifylline (p. 1465·3).
Intermittent claudication; vascular disorders.

Elosalic *MSD, Ger.; MSD, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Pol.; Schering-Plough, S.Afr.†; Schering-Plough, Singapore; MSD, Swed.; Schering-Plough, Turk.; Schering-Plough, Venez.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Psoriasis; skin disorders.

Eloskin *Soho, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Eloson *MSD, China; Pharma International, Ukr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Elosone *Hoe, Hong Kong; Hoe, Malaysia; Blau, Pol.; Hoe, Singapore.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Elotin *Elofar, Braz.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Elotrace *Fresenius Kabi, Austria; Fresenius Kabi, Cz.*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition; trace element deficiency.

Elotrans *Stada, Ger.; Stada, Hung.†; Helvepharm, Switz.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Elovent *Schering-Plough, Gr.; Schering-Plough, Mex.; Schering-Plough, Neth.†; Schering-Plough, Port.*
⊗Mometasone furoate (p. 1644·1).
Asthma; obstructive airways disease.

Elovera *Glenmark, India; Glenmark, Rus.*
Aloe vera (p. 1693·2); vitamin E acetate (p. 2119·2).
Dry skin disorders.

Glenmark, India.
Lotion: Aloe vera (p. 1693·2); avena (p. 2451·1).

Glenmark, Malaysia; Glenmark, Philipp.
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).
Moisturiser; dry skin disorders.

Elovera-SPF *Glenmark, India.*
Aloe vera (p. 1693·2); vitamin E acetate (p. 2119·2); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Formerly contained aloe vera, vitamin E acetate, octinoxate, oxybenzone, and avobenzone.
Sunscreen.

Elox *Guardian, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Eloxatin *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.†; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Thai.; Sanofi Synthelabo, Turk.; Sanofi-Aventis, UK†; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Oxaliplatin (p. 838·1).
Colorectal cancer; oesophagogastric cancer; gastric cancer.

Eloxatine *Sanofi-Aventis, Fr.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Ukr.*
Oxaliplatin (p. 838·1).
Colorectal cancer; ovarian cancer.

Eloxib *Emcure, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Eloxil *Elin, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Elozart *Specpharm, S.Afr.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).

Elozell *Fresenius Kabi, Austria.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Cardiac disorders; potassium and magnesium deficiency; digitalis toxicity.

Elozell spezial *Fresenius Kabi, Austria.*
Potassium chloride (p. 1793·2); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Cardiac disorders; digitalis toxicity; potassium and magnesium deficiency.

Elpegon *Elpen (Ελπεν), Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Elperil *Elpen (Ελπεν), Gr.*
Thioridazine hydrochloride (p. 1110·2).

Elphihormo *Chemica, Gr.*
⊗Nandrolone decanoate (p. 2293·1).

Elpi *Elea, Arg.†*
Clofibrate (p. 1338·3).
Hypercholesterolaemia.

Elpi Lip *Elea, Arg.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Elpicef *Fahrenheit, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Elplat *Yakult, Jpn.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Elpra *Elfin, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Elpra-D *Elfin, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Elpradil *Streuli, Switz.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Elpradil HCT *Streuli, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Elpred *Lancer, India.*
⊗Prednisolone (p. 1645·2) or prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Elpred M *Lancer, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Elprim *Elnova, India.*
Evening primrose oil (p. 2502·2).

Elprox *Captab, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Elquin *Captab, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Elquin-TZ *Captab, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Elrab *Captab, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Elrab-D *Captab, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Elrip *Elite, India.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Elriz *Zuventus, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Elrox *Biopharm, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Elrox-AO *Elnova, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Elsazym *Otto, Indon.*
Oral granules: ⊗Pancreatin (p. 2579·3); vitamin A (p. 2098·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Digestive disorders.

Otto, Indon.
Tablets: ⊗Pancreatin (p. 2579·3); bromelains (p. 2460·3); dimeticone (p. 1886·2).
Dyspepsia; supplement following gastrointestinal surgery.

Elsep *Meda, Fr.*
Mitoxantrone hydrochloride (p. 833·1).
Multiple sclerosis.

Elsoft *Captab, India.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).

Elsol-S *Elfin, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Elsol-T *Elfin, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Elspar *Bago, Braz.; Armstrong, Mex.; Merck, USA.*
Asparaginase (p. 743·3).
Acute lymphocytic leukaemia.

Elstatin *Glenmark, India; Glenmark, Singapore.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction; hypercholesterolaemia.

Elta SilverGel *Swiss-American, USA.*
Silver (p. 2615·1).
Wounds.

Eltacin *Biotiki, Rus.*
Glycine (p. 2071·2); glutamic acid (p. 2070·2); cystine (p. 2059·1).
Heart failure.

Eltair *Scharper, Ital.; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore; Douglas, Thai.†*
⊗Budesonide (p. 1625·1).
Nasal polyps; rhinitis.

Eltéans *Jaldes, Fr.*
Salmon oil (p. 1460·1); borage oil (p. 2459·2); carrot oil; soya oil (p. 2092·3); vitamin E (p. 2119·1).
Nutritional fatty acid supplement.

Elther *Solitaire, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Elthon
Note: this name may be used for preparations of different composition.
Abbott, China.
Itopride hydrochloride (p. 1850·1).
Gastrointestinal motility disorders.

El-Thyro *MJ Biopharm, Thai.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Elthyrone *Abbott, Belg.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Eltocin *Ipca, India.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Eltocin-BR *Ipca, India.*
Bromhexine hydrochloride (p. 1656·3); erythromycin estolate (p. 291·2).

Eltol *Elfin, India.*
Tobramycin (p. 380·1).
Bacterial infections.

Eltor *Sanofi-Aventis, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion.

Eltoven *Roemmers, Chile.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Eltram *Captab, India.*
Tramadol (p. 139·2).
Pain.

Eltroxin *Triton, Canad.; Aspen, Cz.; GSK, Denm.; Sigma, Hong Kong†; GSK, India; Goldshield, Irl.; Perrigo, Israel; Aspen, Neth.; Healthcare Logistics, NZ; GSK, Philipp.; Aspen, Pol.; Aspen, S.Afr.; Aspen, Singapore; Aspen, Thai.; Mercury, UK.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer.

Eltroxine *Sigma-Tau, Switz.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Eltuss *Elder, India.*
⊗Chloroform (p. 1898·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Eltuss-C *Elder, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Eluage *Pierre Fabre Dermo-Cosmetique, Arg.*
Retinaldehyde (p. 1719·1); AHF (p. 1148·1); thermal water of Avene.
Skin ageing.

Elucent Skin Refining Day Cream *Ego, Austral.*
SPF 20: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); avobenzone (p. 1695·1); glycolic acid (p. 1704·3); lactic acid (p. 2539·1).
Dry skin; sunscreen.

Elucin *Ind-Swift, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Elucion *Medifarm Ducray, Venez.*
Surfactant solution.
Protection of scalp against anti-dandruff treatment.

EluDental *Pierre Fabre Sante, Singapore.†*
Chlorhexidine (p. 1743·2).
Gingivitis; dental caries prophylaxis; oral hygiene.

Eludril
Note: this name may be used for preparations of different composition.
Rovafarm, Arg.; Pierre Fabre Sante, Belg.; K2 Health & Wellness, Chile; Pierre Fabre Sante, Fr.; Pierre Fabre, Irl.†; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre Sante, Singapore; Pierre Fabre, Spain†; Pierre Fabre, Switz.; Pierre Fabre, UK.
Chlorhexidine gluconate (p. 1743·3); chlorobutanol (p. 1747·2).
Mouth and throat disorders; mouth disinfection.

Pierre Fabre, Rus.
Chlorhexidine gluconate (p. 1743·3); chlorobutanol (p. 1747·2); chloroform (p. 1898·1).
Mouth disorders.

Pierre Fabre Sante, Fr.; Pierre Fabre, Switz.†; Pierre Fabre, UK.
Mouth spray: Throat spray: Chlorhexidine gluconate (p. 1743·3); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Eludrilpro *Pierre Fabre, Fr.*
Chlorhexidine gluconate (p. 1743·3); chlorobutanol (p. 1747·2).
Mouth disorders.

Elugan *Nordix, Ger.; Nordmark, Ger.*
Simeticone (p. 1886·2).
Gastrointestinal disorders with excess gas.

Elugel *Rovafarm, Arg.; K2 Health & Wellness, Chile; Pierre Fabre, Fr.; Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore.*
Chlorhexidine gluconate (p. 1743·3).
Gum disorders; mouth hygiene; mouth infections.

Elugyn *Pierre Fabre Sante, Belg.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Elukan *Specifar, Cz.; Specifar, Denm.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Elum *Farmasa, Braz.*
Cloxazolam (p. 1057·2).
Anxiety.

Elumatic *CIS, Fr.; CIS, Irl.; CIS, Neth.; CIS, Port.; CIS, Spain.*
Technetium-99m (p. 2228·1).
Radionuclide imaging.

Elumatic III *CIS, Cz.*
Technetium-99m (p. 2228·1).
Radionuclide imaging.

Elure *Aamorb, India.*
Allantoin (p. 1693·1); *d*-alpha tocopherol (p. 2119·1); wool fat (p. 2219·3); liquid paraffin (p. 2191·2); olive oil (p. 2575·1); squalane (p. 2213·3).

Élusanes *Pierre Fabre, Fr.*
A range of herbal preparations.

Élusanes Algues brunes/aloés *Plantes et Medecines, Fr.†*
Fucus (p. 2612·1); aloes (p. 1816·1).
Constipation.

Élusanes Calmodiger *Plantes et Medecines, Fr.†*
Heavy kaolin (p. 1850·1).
Flatulence.

Élusanes Harpagésic *Plantes et Medecines, Fr.†*
Devil's claw root (p. 42·3).
Joint pain.

Élusanes Starphyt *Naturactive, Fr.†*
Ginseng (p. 2513·3); kola (p. 2648·2).
Asthenia.

Elutit-Calcium *Felgentrager, Ger.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Elutit-Natrium *Felgentrager, Ger.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Elvac *Elnova, India.*
Isotretinoin (p. 1706·2).
Acne.

Elvacin *Ethica, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Elvanse *Shire, UK.*
⊗Lisdexamfetamine mesilate (p. 2323·2).
Attention deficit hyperactivity disorder.

Elvas *Captab, India.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Elvecis *Ivax, Arg.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Elvefocal *Ivax, Arg.†*
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; prevention of methotrexate toxicity; antidote to folic acid antagonists.

Elven
Note: this name may be used for preparations of different composition.
Actavis, Hung.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

BMW, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Elvenavir *Ivax, Arg.*
Indinavir sulfate (p. 986·1).
HIV infection.

Elven-P *BMW, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Elvesil *Biomedica, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Elvital-SG *Elnova, India.*
Vitamins; minerals; ginseng (p. 2513·3).

Elvo *Elfin, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Elvorine *Pfizer, Belg.; Pfizer, Fr.*
Calcium levofolinate (p. 2067·1).
Prevention of toxicity induced by methotrexate and other dihydrofolate reductase inhibitors; adjunct to fluorouracil in colorectal cancer; folic acid antagonist toxicity; adjuvant to fluorouracil therapy.

Elvox *Elder, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Elwin-Plus *Elfin, India.*
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1).

Elyfem *Berlis, Switz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Elyn *Ajanta, India.*
Eflornithine hydrochloride (p. 932·1).

Elynor *Brill, Spain.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Elynza *Bilim, Turk.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Elyte *Daksh, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Elyzol *Colgate-Palmolive, Fin.†; Alpharma, Hong Kong†; Alpharma, Mex.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Trichomoniasis; giardiasis; amoebiasis; bacterial mouth infections.

Chemomedica, Austria†; Colgate-Palmolive, Denm.†; Colgate, Ger.†; Colgate-Palmolive, Gr.; CTS, Israel†; Vebas, Ital.; Colgate-Palmolive, Norw.†; Colgate-Palmolive, Port.†; Colgate-Palmolive, Swed.†; Colgate-Palmolive, Switz.†; Colgate-Palmolive, UK.
Metronidazole benzoate (p. 936·1).
Bacterial mouth infections; periodontitis.

Elzar *Pharos, Indon.*
Irbesartan (p. 1411·1).
Diabetic nephropathy; hypertension.

Elzee *Elder, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Elzepam *Ellara, Rus.*
Phenazepam (p. 1096·3).
Anxiety; insomnia; withdrawal syndromes; epilepsy; psychoses; premedication.

Elzox *Elfin, India.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Elzym
Note: this name may be used for preparations of different composition.
Sankyo, Venez.
Enzymes from *Aspergillus oryzae*; simeticone (p. 1886·2).
Digestive disorders; flatulence.

Medinova, Thai.†
Enzyme concentrate from *Aspergillus oryzae*; simeticone (p. 1886·2); ethaverine hydrochloride (p. 2500·2).
Gastrointestinal disorders with excess gas; preparation of gastrointestinal tract for radiological examination.

Emadine
Note: this name may be used for preparations of different composition.
Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, China; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Neth.; Alcon, Norw.; Alcon, Pol.; Alcon, Port.; Alcon, S.Afr.; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.†; Liba, Turk.; Alcon, UK; Alcon, USA.
Emedastine fumarate (p. 628·2).
Allergic conjunctivitis.

Merck, India.
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Émadine *Alcon, Fr.†*
Emedastine fumarate (p. 628·2).
Allergic conjunctivitis.

Emadine AT *Merck, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Emaftol *Ogna, Ital.*
Policresulen (p. 1160·2).
Mouth disinfection.

Emagel *NovaSelect, Ital.*
⊗Polygeline (p. 1160·3).
Plasma volume expansion.

Emagen *Horii, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Emagrim *Chemopharma, Chile.*
Dihydroergotamine mesilate (p. 672·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Vascular headache.

Emama *Eurofarma, Braz.*
dl-Alpha tocoferil acetate (p. 2119·2).

Emandaxin *Choseido, Jpn.†*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Emanera *KRKA, Cz.; KRKA, Denm.; KRKA, Pol.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Emanthal *MM, India.†*
Albendazole (p. 149·1).
Worm infections.

Emanzen *Emcure, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Emanzen-D *Emcure, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Emanzen-DP *Emcure, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Emanzen-N *Emcure, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Emarfen *Minerva (Μινερβα), Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Emasex-A vitex *Kyberg, Ger.*
⊗Vitex agnus castus (p. 2432·2).
Homoeopathic preparation.

Ematrin *Zota, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Emax *Ethica, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Emaxem *Probiomed, Mex.*
Interferon beta (p. 996·1).

Emazole *Rowex, Irl.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger Ellison syndrome.

EMB *Fatol, Hong Kong; Fatol, Rus.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Embatrim *Flamingo, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Embeda *Pfizer, USA.*
⊗Morphine sulfate (p. 92·3).
Naltrexone hydrochloride (p. 1565·1) is included in this preparation to discourage abuse.
Pain.

Embesil *Piramal, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Embeta *Intas, India.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure.

EMB-Fatol *Riemser, Ger.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Embion *Symbiotic, India.*
Injection: Vitamin B substances (p. 2102·3).

Symbiotic, India.
Tablets: Vitamin B substances (p. 2102·3); *Lactobacillus sporogenes* (p. 2596·3).

Embol *Yung Shin, Thai.*
Piracetam (p. 393·3).
Cerebrovascular disorders; mental function impairment; alcohol withdrawal syndrome.

Embrex *Andrx, USA.*
Vitamins; minerals; iron carbonyl (p. 2073·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Embrocacion Gras *Quimifar, Spain.†*
⊗Alcohol (p. 1733·1); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); capsicum (p. 2469·3).
Muscle and joint pain.

Emceph *Emcure, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Emcin *Captab, India.*
Amikacin (p. 214·1).
Bacterial infections.

Emclav *Emar, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Emcolol *Gerard, Irl.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Emcon *Captab, India.*
Ketoconazole (p. 585·3).
Fungal infections.

Emconcor *Merck, Belg.; Merck, Denm.; Merck, Fin.; Merck, Norw.; Merck, Spain; Merck, Swed.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Emconcor Comp *Merck, Fin.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Emcor *Merck Serono, Irl.; Merck, Neth.; Merck, UK.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Emcoretic *Merck, Belg.; Merck, Neth.†; Merck, Spain.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Emcredil *Unichem, India.†*
Ethacridine lactate (p. 1732·3).
Termination of pregnancy.

Emcyt *Pfizer, Canad.; Pfizer, Mex.; Pharmacia Upjohn, USA.*
Estramustine sodium phosphate (p. 790·1).
Prostatic cancer.

Emdalen *Merck, S.Afr.*
Lofepramine hydrochloride (p. 433·2).
Depression.

Emdar *Merck, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Emderm *Emcure, India.*
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Emdes *Synmedic, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Emdon *Macrophar, Thai.*
Nimesulide (p. 101·3).
Musculoskeletal and joint disorders; pain; fever.

Emdopa *Indian Drugs, India.*
Methyldopa (p. 1431·1).
Hypertension.

Emdox *Madhav, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Emdox-TZ *Madhav, India.*
Doxycycline (p. 288·1); tinidazole (p. 949·2).

Emduo *Emcure, India.*
Lamivudine (p. 1000·2); stavudine (p. 1015·3).

Emduo-E *Emcure, India.*
Efavirenz (p. 975·1); lamivudine (p. 1000·2); stavudine (p. 1015·3).

Emduo-N *Emcure, India.*
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); stavudine (p. 1015·3).

Emedal *Norma (Νορμα), Gr.; Target, Gr.*
Metronidazole (p. 936·1).
Acne rosacea; anaerobic bacterial infections; protozoal infections.

Emediba *Diba, Mex.†*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting; vertigo.

Emedrin N *Streuli, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Emedur *Sanofi Synthelabo, Turk.*
Injection; tablets: Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Sanofi Synthelabo, Turk.
Suppositories: Trimethobenzamide hydrochloride (p. 642·2); benzocaine (p. 1980·2).
Nausea and vomiting.

Emedyl *Montavit, Austria.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vestibular disorders.

Emef *Ind-Swift, India.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Emegar *Stada, Cz.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Emegran *Biochem, India.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Emegrav B6 *GMP, Indon.*
Parathiazine teoclate (p. 637·1); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting.

Emeliv *Xepa-Soul Pattinson, Singapore.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; migraine.

Tack Fung, Hong Kong.†
Metoclopramide (p. 1862·2).

Emend *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; Ono, Jpn; MSD, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; MSD, Ukr.; Merck, USA; MSD, Venez.*
Aprepitant (p. 1819·2) or fosaprepitant meglumine (p. 1843·3).
Nausea and vomiting.

Emenil *AstraZeneca, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; gastro-oesophageal reflux; premedication.

Emenorm *Intas, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; gastro-oesophageal reflux; premedication.

Emeproton *Cantabria, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Emeradole *Kyowa, Jpn.*
Eicosapentaenoic acid ethyl ester (p. 1460·2).
Arteriosclerosis obliterans; hyperlipidaemias.

Emeral *Nova Argentia, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Emeran
Note: this name may be used for preparations of different composition.
Biological E, India.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Erlimpex, Indon.
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Emergen *Laboratorios Chile, Chile.*
Sertraline (p. 448·1).
Depression.

Emergency Acne *Mentholatum, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Emergent-Ez *Healthfirst, USA.*
Combination pack: ⊗2 Ampoules, adrenaline (p. 1292·1); 1 ampoule, aminophylline (p. 1201·2); 3 inhalants, ammonia (p. 2441·2); 2 inhalants, amyl nitrite (p. 1540·2); 2 ampoules, atropine (p. 1310·2); 2 ampoules, diphenhydramine hydrochloride (Benadryl) (p. 626·2); tablets, glyceryl trinitrate (p. 1391·2); 1 vial, hydrocortisone sodium succinate (Solu-Cortef) (p. 1640·3); 1 ampoule, pentazocine lactate (Talwin) (p. 120·3); 1 ampoule, trimethobenzamide hydrochloride (Tigan) (p. 642·2); 2 ampoules, diazepam (Valium) (p. 1063·2); 2 ampoules, mephentermine sulfate (Wyamine) (p. 1429·3).
Emergency treatment.

Emergin *Mapra, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Emerxil *Omega, Belg.*
Glycol salicylate (p. 66·2); lidocaine hydrochloride (p. 1988·2); methyl nicotinate (p. 91·3).
Inflammation; pain.

Emes *Doctors, Philipp.*
Dimenhydrinate (p. 625·2).
Motion sickness; Ménière's disease.

Emesafene *ACE, Neth.*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting.

Emeset *Cipla, Cz.; Cipla, India; Cipla, Rus.; Cipla, Thai.; Cipla, Venez.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Emeside *Chemidex, UK.*
Ethosuximide (p. 521·1).
Absence seizures; myoclonic seizures.

Emestal *Saga, India.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Emestal-O *Saga, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emestar Mono *Trommsdorff, Ger.†*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Emestar plus *Trommsdorff, Ger.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Emestat *Obsurge, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Emestop *Ethix, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emetal *Asian Pharm, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Emetic *Elofar, Braz.†*
Metoclopramide (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Emetics *SupHerb, Israel.*
Ginger (p. 1844·1); vitamin B_6 (p. 2105·3).
Nutritional supplement.

Emetil *La Pharmaceuticals, India.*
Chlorpromazine hydrochloride (p. 1045·2).
Intractable hiccup; psychoses.

Emetil DS *La Pharmaceuticals, India.*
Chlorpromazine hydrochloride (p. 1045·2); trihexyphenidyl hydrochloride (p. 917·3).

Emetil Plus *La Pharmaceuticals, India.*
Chlorpromazine hydrochloride (p. 1045·2); trihexyphenidyl hydrochloride (p. 917·3).

Emetostop *Specifar, Gr.*
Meclozine hydrochloride (p. 634·3).
Vertigo.

Emetril *Nevzat, Turk.*
Granisetron hydrochloride (p. 1844·3).

Emetrol *Aspen Consumer, S.Afr.*
Sucrose (p. 2096·3); phosphoric acid (p. 2589·1).
Nausea.

Sanofi Winthrop, USA.
Fructose (p. 2068·2); glucose (p. 2069·1); phosphoric acid (p. 2589·1).
Nausea; vomiting.

Emetron *Gedeon Richter, Hung.; Richter, Pol.; Tecnimede, Port.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Emex
Note: this name may be used for preparations of different composition.
Bennet, India.
Prochlorperazine maleate (p. 1098·3).
Nausea; vomiting; psychoses; anxiety; vertigo.

Mirren, S.Afr.
Invert sugar (p. 2072·3); phosphoric acid (p. 2589·1).
Nausea.

TNP, Thai.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Emezol *Andromaco, Chile.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Emfetal *World Medicine, Ukr.*
Vitamins; minerals.
Dietary supplement.

Emflam *Merck, India.*
Injection; tablets: Diclofenac sodium (p. 48·3).
Formerly contained ibuprofen.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Merck, India.
Topical gel: Diclofenac diethylamine (p. 48·3); diclofenac sodium (p. 48·3).
Pain; inflammation; osteoarthritis.

Emflam Plus *Merck, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; pain.

Emflex *Merck Serono, UK.*
Acemetacin (p. 16·3).
Pain; inflammation; rheumatoid arthritis.

Emflox-TZ *Madhav, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Emfor *Stadmed, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Emforal *Remedica, Singapore; Remedica, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; migraine; obstructive cardiomyopathy; tremor; myocardial infarction.

Emfrastop *Heremco, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Emfurazone *Emcure, India.*
Nitrofurazone (p. 333·1).
Wounds; burns; skin ulcers; skin infections; preparation of surfaces before skin grafting.

Emgard *Medopharm, India.*
Phenobarbital (p. 535·2).
Epilepsy; sedative.

Emgecard *Kwizda, Austria.*
Magnesium aspartate hydrochloride (p. 1786·3).
Magnesium deficiency disorders.

Emgesan *Recip, Fin.; Recip, Swed.*
Magnesium hydroxide (p. 1857·2).
Magnesium deficiency; renal calculi.

Emibion *Guardian, Indon.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); vitamin B_{12} (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Emica *Lincoln, India.*
Amikacin (p. 214·1).
Bacterial infections.

Emicilin *EMS, Braz.*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Probenecid (p. 607·3) is included in some of preparations to reduce renal tubular excretion of the antibiotic.
Bacterial infections.

Emiconazole *Emcure, India.*
Miconazole (p. 588·3).
Fungal skin infections.

Emidon *Karnataka, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Emidon-OM *Karnataka, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Emidoxin
Note: this name may be used for preparations of different composition.
Magis, Ital.
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Emidoxyn
Note: this name may be used for preparations of different composition.
Shreya, India.
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting.

Emidoxyn Forte *Shreya, India.*
Prochlorperazine maleate (p. 1098·3); pyridoxine hydrochloride (p. 2105·3).

Emidrat *EMS, Braz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); sodium phosphate (p. 1791·2); calcium lactate (p. 1784·1); magnesium citrate (p. 1857·1); citric acid (p. 2480·3); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration solution.

Emigo *Zuventus, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emiken *Kener, Mex.*
Domperidone (p. 1838·1).
Nausea and vomiting.

Emikind *Mankind, India.*
Prochlorperazine (p. 1098·2).
Nausea and vomiting; psychoses; anxiety; vertigo.

Emilace *Astellas, China; Astellas, Jpn.*
Nemonapride (p. 1089·1).
Schizophrenia.

Emillan *Valeant, Hung.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Emily *Abic, Israel.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Emin *Cipla, India.*
Promethazine teoclate (p. 638·2).

Eminase *Wellspring, Canad.†; Lavipharm, Gr.*
Anistreplase (p. 1306·1).
Myocardial infarction.

Emineton *Kalbe, Indon.*
Ferrous fumarate (p. 2060·3); copper sulfate (p. 2057·2); cobalt sulfate (p. 2482·2); manganese sulfate (p. 2081·2); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); folic acid (p. 2063·1); calcium hydrogen phosphate (p. 1783·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Eminocs *Wassermann, Neth.*
Diclofenac potassium (p. 48·3).
Pain.

Eminox *Pharmacore, Indon.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Emipril *Captab, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Emisgenta *EMS, Braz.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Emispan *Unimarck, India.*
Promethazine (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; insomnia; motion sickness.

Emispan Plus *Unimarck, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Emispan-H *Unimarck, India.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2).

Emistin *EMS, Braz.*
⊗Clemastine fumarate (p. 622·3); dexamethasone acetate (p. 1631·1).
Hypersensitivity reactions.

Emistop *Claris, Philipp.; Claris, Thai.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Emital *Pliva, Irl.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Emitex *Aspen, S.Afr.*
Cyclizine hydrochloride (p. 623·2).
Nausea; vomiting; motion sickness; vestibular disorders.

Emitin *Cachet, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Emitino *Cachet, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emitus *Icarus, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emival *Farmaceutica H, Mex.†*
Pravastatin (p. 1473·1).

Emixor *Syncom, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Emizof *Gerard, Irl.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting associated with cancer chemotherapy; postoperative nausea and vomiting.

Emizol *Teva, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Emizole *Helviina, Philipp.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Emka *Global, India.*
Amikacin (p. 214·1).
Bacterial infections.

EMLA *Sato, Jpn.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Emla *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; Akorn, USA.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Emlac Forte-BZ *Emar, India.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2).

Emlansa *Emil, Hong Kong.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Emlap *Natura, India.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Emlapatch *AstraZeneca, Fr.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Emletra *Emcure, India.*
Lopinavir (p. 1002·1); ritonavir (p. 1013·1).
HIV infection.

Emlinctus *Emar, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Emlocaine *LBS, Philipp.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Emlodin *Egis, Ukr.*
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Emlosar *Emil, Hong Kong.*
Losartan potassium (p. 1422·2).
Hypertension; cardiovascular risk reduction; diabetic nephropathy; heart failure; myocardial infarction.

Emlucast *Reddy, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Emlyte *MM, India.†*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2).
Oral rehydration therapy.

Emlyte-S *MM, India.†*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3); lactobacillus (p. 1780·1).
Oral rehydration therapy.

Emmenoiasi *Titanadria, Ital.*
Centella (p. 1698·3); couch-grass (p. 2487·2); lupulus (p. 2546·1); melissa (p. 2552·3); zinc (p. 2126·1); copper (p. 2057·1).
Nutritional supplement.

Emnel *Emcure, India.*
Nelfinavir (p. 1004·1).
HIV infection.

Emnil *Vilberry, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Emnorm *Ipca, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Emoclot *Kedrion, Arg.; Biosano, Chile; Trans, India; Kedrion, Ital.; Kedrion, Port.; Kedrion, Rus.; Kedrion, Thai.; Onko, Turk.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; von Willebrand's disease.

Emo-Cort *GSK, Canad.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Emocrat N *Hevert, Ger.†*
Crataegus (p. 2488·1).
Homoeopathic preparation.

Emodan *Korea United, Philipp.*
Ondansetron hydrochloride (p. 1872·1).
Nausea; vomiting.

Emoderm
Note: this name may be used for preparations of different composition.
GSK, India.
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Theraskin, Braz.
⊗Urea (p. 1727·3).
Skin disorders.

Emodol *Jayson, Ukr.†*
Ketorolac trometamol (p. 80·2).
Pain.

Emofix *DMG, Ital.*
Haemostatic barrier ointment with collagen (p. 2483·2).

Emoform
Note: this name may be used for preparations of different composition.
JL Morison, India.
⊗Potassium nitrate (p. 1766·2).
Nycomed, Braz.; Wild, Switz.†
Electrolytes (p. 1775·1).
Hypersensitive teeth; oral hygiene.
McNeil, Fr.†
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis; sensitive gums.

Emoform Actisens *Polifarma Benessere, Ital.*
⊗Sodium fluoride (p. 2089·2); potassium nitrate (p. 1766·2).
Dental caries prophylaxis; sensitive teeth.

Emoform Alifresh *Polifarma Benessere, Ital.*
Zinc chloride (p. 2126·1); chondrus (p. 2176·3); aloes (p. 1816·1); sanguinaria (p. 2610·1); calendula (p. 2465·2); propolis (p. 2597·3); peppermint oil (p. 1877·1).
Halitosis.

Emoform AP *Nycomed, Braz.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Emoform AT *Nycomed, Braz.*
Sodium monofluorophosphate (p. 2091·3); potassium pyrophosphate (p. 2619·3).
Dental caries prophylaxis.

Emoform Clorofila *Nycomed, Braz.*
Electrolytes (p. 1775·1); chlorophyll (p. 2178·3).
Dental caries prophylaxis.

Emoform Dents Sensibles *Johnson & Johnson, Fr.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis; sensitive gums.

Emoform Dientes Sensibles *Gador, Arg.*
Electrolytes (p. 1775·1).
Dental caries prophylaxis; hypersensitive teeth.

Emoform Gencives *Johnson & Johnson, Fr.*
⊗Potassium nitrate (p. 1766·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1).
Gingivitis; sensitive gums.

Emoform Total *Gador, Arg.*
Sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3); triclosan (p. 1773·2); etidronate disodium (p. 1182·3); sodium bicarbonate (p. 1781·1); xylitol (p. 2220·3).
Dental caries prophylaxis.

Emoform-F au fluor *Wild, Switz.†*
Electrolytes (p. 1775·1); sodium monofluorophosphate (p. 2091·3).
Sensitive teeth; oral hygiene; dental caries prophylaxis.

Emoform-Tat *Polifarma Benessere, Ital.*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2); potassium pyrophosphate (p. 2619·3).
Dental tartar.

E-Moist *Zytras, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Emoject *Tum, Turk.*
Metoclopramide hydrochloride (p. 1862·2).

Emoklar *Savio, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Emol *Fischer, Israel.*
Bath additive.
Dry skin.

Emolan *K2 Health & Wellness, Chile.*
Range of soap substitutes and emollients and moisturisers.
Dry skin.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vivax Gynopharm, Venez.
Soap substitute.

Megahealth, Chile.†
SPF 35: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1).
Sunscreen.

Emolan All Sport *Mediderm, Chile.*
SPF 35: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Emolan Barra Protectora Labial *K2 Health & Wellness, Chile.*
SPF 30: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Emolan Bebe Protector Solar *K2 Health & Wellness, Chile.*
SPF 60: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Emolan Bloqueador Solar *K2 Health & Wellness, Chile.*
SPF 60: Enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); ensulizole (p. 1703·1); avobenzone (p. 1695·1).
Sunscreen.

Emolan Fluido Extremo Rostro *K2 Health & Wellness, Chile.*
SPF 50+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); diethylamino hydroxybenzoyl hexyl benzoate.
Sunscreen.

Emolan Fotoprotector Mineral *Megahealth, Chile.*
SPF 60: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Emolan Gel Protector Solar *K2 Health & Wellness, Chile.*
SPF 35: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Emolan H *K2 Health & Wellness, Chile.*
Padimate O (p. 1716·1).
Sunscreen.

Emolan Protector Labial *Mediderm, Chile.*
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Emolan Protector Solar *Megahealth, Chile.†*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Emolan Spray *K2 Health & Wellness, Chile.*
SPF 50: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Emolan Ultra *K2 Health & Wellness, Chile.*
SPF 30: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Emolene *Fulford, India.*
Diazolidinyl urea (p. 1750·1); propylene glycol (p. 2205·2).
Acne.

Emolin Neo *Medihealth, Mex.*
Tocoferil acetate (p. 2119·2); dexpanthenol (p. 2582·2); hyaluronic acid (p. 2526·2).
Dry skin; skin irritation.

Roemmers Medihe, Venez.
Emollient.

Emollia *Gordon, USA.*
Emollient and moisturiser.

Emollin *CD Medical, UK.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Emollient.

Emolytar *Stiefel, Spain.†*
Tar (p. 1723·3); juniper oil (p. 2537·2); coal tar (p. 1723·2); arachis oil (p. 2446·1).
Skin disorders.

Emopaz-D *Alde Medi Impex, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Emopon *Terapeutico, Ital.*
Calcium folinate (p. 2066·3); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); thiamine hydrochloride (p. 2103·1); nicotinamide (p. 2083·1).
Macrocytic anaemia; tonic.

Emorange *Emcure, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Emorect *Emo-Farm, Pol.*
Aesculus (p. 2431·2); arnica (p. 2447·2).
Phlebitis; venous insufficiency; oedema; haematoma.

Emoren *Centroforma, Ital.*
Oxetacaine hydrochloride (p. 1993·1).
Haemorrhoids.

Emorril *SIT, Ital.*
⊗Hydrocortisone acetate (p. 1640·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids; adjunct in anorectal surgery.

Emortrofine *Alphrema, Ital.*
Vitamin E (p. 2119·1); bioflavonoids (p. 2505·2).
Capillary disorders; haemorrhoids.

Emorzim *Pfizer, Gr.*
Carboplatin (p. 759·1).
Ovarian cancer; small-cell lung cancer.

Emosint *Kedrion, Arg.; Kedrion, Ital.; Kedrion, Rus.*
⊗Desmopressin acetate (p. 2355·1).
Haemophilia; von Willebrand's disease.

Emostat *Kafetzis, Gr.†*
Ferric chloride (p. 2504·2).

Emotival
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Lorazepam (p. 1080·3).
Anxiety.

Emotrip *Ipca, India.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states.

Emovat *GSK, Denm.; GSK, Fin.; GSK, Swed.*
⊗Clobetasone butyrate (p. 1627·3).
Skin disorders; eczema.

Emovate *GSK, Austria; GSK, Ger.; GSK, Neth.; Glaxo Wellcome, Port.; Nutricion Medica, Spain; GSK, Switz.*
⊗Clobetasone butyrate (p. 1627·3).
Skin disorders.

Emoxen *Emo-Farm, Cz.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Emoxiron *Caber, Ital.†*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Emoxy-Optic *Sintez, Rus.*
Emoxypine hydrochloride.
Eye disorders.

Emozul *KRKA, Cz.; KRKA, Hung.; Consilient, UK.*
Esomeprazole magnesium (p. 1841·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Empacod *Nycomed, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Empaflun *Egis, Neth.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Empaped *Nycomed, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Empatil *Liferpal, Mex.*
Carisoprodol (p. 2021·3); diclofenac (p. 48·3).

Empecid *Bayer Consumer, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections; vaginal candidiasis.

Empecid Cort *Bayer, Arg.*
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1).
Infected skin disorders.

Empecid Pie *Bayer Consumer, Arg.*
Bifonazole (p. 573·3); crotamiton (p. 1699·2); lidocaine (p. 1988·1); enoxolone (p. 54·2); levomenthol (p. 2553·2).
Tinea pedis.

Empeea *Wyeth, India.*
Medroxyprogesterone (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Empeecetin *Nufarindo, Indon.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Empenox *Demo, Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Emperal *Orion, Denm.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders; aid in gastrointestinal examination.

Emperide *Emcure, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Emperin *Egis, Cz.; Egis, Hung.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Empetus *Emcure, India.*
Ritonavir (p. 1013·1).
HIV infection.

Empirin *Chew, Thai.; Wellcome, USA.*
Aspirin (p. 22·2).
Inflammation; pain; fever; thrombosis prophylaxis; transient ischaemic attacks; myocardial infarction.

Empirin with Codeine *Wellcome, USA.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain.

Empirol *Norma (Νορμα), Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Emplasto Monopolis *Grisi, Mex.*
Copper acetate (p. 2486·2); lead monoxide (p. 2541·3).
Medicated dressing.

Emplusal *Pharmacare, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Emportal *Angelini, Spain.*
Lactitol (p. 1850·3).
Hepatic encephalopathy; constipation.

Emprox *Emar, India.*
Cefpodoxime.
Bacterial infections.

Emprozal *1A, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Empurine *Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.†*
Mercaptopurine (p. 820·3).
Inflammatory bowel disease; leukaemias.

Empynase *Kaken, Jpn.*
⊗Pronase (p. 2597·3).
Inflammation; respiratory-tract congestion.

Emquin *Merck, India.*
Chloroquine phosphate (p. 650·1).
Malaria; hepatic amoebiasis; rheumatoid arthritis; lupus erythematosus.

Emren *Gedeon Richter, Hung.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction; nephropathy.

Emrif *Emcure, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Emrif Kit *Emcure, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Emrox *Madhav, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

EMS Expectorante *EMS, Braz.*
⊗Guaifenesin (p. 1666·2); etafedrine hydrochloride (p. 1665·2); bufylline (p. 1203·3); doxylamine succinate (p. 627·3).
Respiratory-tract disorders.

Emsam *Dey, USA.*
⊗Selegiline (p. 914·2).
Depression.

Emscab *MM, India.†*
Lindane (p. 2157·1); aminoacridine hydrochloride (p. 1732·3).
Scabies; pediculosis.

Emscort *EMS, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Emselex *Novartis, Belg.; Novartis, Cz.; Novartis, Denm.; Bayer, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Zambon, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK.*
Darifenacin hydrobromide (p. 2354·2).
Bladder instability; bladder hyperactivity.

Emser *Siemens, Ger.*
Natural emser salt (see Emser Salz) in isotonic solution.
Nasal congestion.

Emser Inhalationslosung *Siemens, Ger.*
Natural emser salt (see Emser Salz) in isotonic solution.
Respiratory-tract disorders.

Emser Nasensalbe sensitive *Siemens, Ger.*
Natural emser salt (see Emser Salz).
Nasal dryness; cold symptoms.

Emser Pastillen *Siemens, Ger.*
Natural emser salt (see Emser Salz).
Throat disorders.

Emser Salz *Siemens, Ger.*
Natural emser salt (containing lithium, sodium, potassium, magnesium, calcium, manganese, ferrous, ferric, fluoride, chloride, bromide, iodide, nitrite, sulfate, bicarbonate, and carbonate ions).
Upper respiratory-tract disorders.

Emser Sole *Siemens, Ger.*
Cations: sodium, potassium; anions: chloride, sulfate, bicarbonate.
Respiratory-tract disorders.

Emsetron *Sun, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emsexpector *EMS, Braz.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1); guaifenesin (p. 1666·2).

Emsgrip *EMS, Braz.*
Paracetamol (p. 115·1).
Pain; fever.

Ems-Max *EMS, Braz.†*
Azithromycin (p. 221·2).
Bacterial infections.

Emsogen *Nutricia, Ital.; SHS, UK.*
Food for special diets.
Malabsorption syndromes.

Scientific Hospital Supplies, Austral.†; SHS, Denm.; Scientific Hospital Supplies, Irl.†
Preparation for enteral nutrition.

Emsolone *Medopharm, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Emstal *Mars, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emsulate *Purewin, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Emsulide *Emcure, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Emsulide-Fen *Emcure, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Emsulide-MR *Emcure, India.*
Tizanidine (p. 2026·2).
Spasticity; skeletal muscle spasm.

Emsulide-P *Emcure, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Emsunate *Captab, India.*
Artesunate (p. 648·2).
Falciparum malaria.

Emtax *Madhav, India.*
Cefixime (p. 240·3).
Bacterial infections.

Emtax-CL *Madhav, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

EMTB *Emcure, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Emtec *Sanjivani, India.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders; acid aspiration.

Emthexat *Pharmachemie, Fin.†*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis.

Emthexate *Teva, Belg.; Asta Oncologia, Braz.†; Teva, Denm.; Chemipharm, Gr.; Combiphar, Indon.;*

Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Philipp.; Teva, S.Afr.†; Pharmachemie, Singapore; Pharmachemie, Thai.; Teva, Thai.
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis; juvenile idiopathic arthritis; auto-immune skin disorders; graft-versus-host disease; bone marrow transplantation; Wegener's granulomatosis.

Pharmachemie, Neth.; NZ Medical & Scientific, NZ; Teva, Spain†; Er-Kim, Turk.; Med, Turk.
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Emtri
Note: this name may be used for preparations of different composition.
Captab, India.
Ceftriaxone (p. 253·3).
Bacterial infections.

Emcure, India.
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); stavudine (p. 1015·3).

Emtriaxone *Embiotic, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Emtri-S *Captab, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Emtriva *Gador, Arg.; Gilead, Austral.; Gilead, Austria; UCB, Belg.; Gilead, Canad.; Gilead, Cz.; Gilead, Denm.; Gilead, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hung.; Gilead, Irl.; Gilead, Ital.; Stendhal, Mex.; Gilead, Neth.; Gilead, Norw.; Gilead, NZ; Gilead, Pol.; Gilead, Port.; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; Gilead, UK; Gilead, USA.*
Emtricitabine (p. 976·3).
HIV infection.

Emtron *Agio, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Emucin *Emcure, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Emucin-TN *Emcure, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Emucream HC *Ovelle, Irl.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders; insect bites.

Emugent *Emcure, India.*
Gentamicin (p. 304·2).
Eye infections.

Emulave *Johnson & Johnson, Ital.; Johnson & Johnson, Port.†*
Avena (p. 2451·1).
Soap substitute; emollient and cleansing preparations.

Ovelle, Irl.†
Soap substitute.

Emulax
Note: this name may be used for preparations of different composition.
British Dispensary, Thai.
Oral liquid: Liquid paraffin (p. 2191·2); phenolphthalein (p. 1877·3); carmellose sodium (p. 2175·2).
Constipation.

British Dispensary, Thai.
Tablets: Bisacodyl (p. 1821·1).
Constipation.

Emulax MOM *British Dispensary, Thai.*
Magnesium hydroxide (p. 1857·2).
Constipation.

Emulax Senna *British Dispensary, Thai.*
Sennosides (p. 1885·2).
Constipation.

Emuliquen Laxante *Lainco, Spain.*
Sodium picosulfate (p. 1887·2); liquid paraffin (p. 2191·2).
Constipation.

Emuliquen Simple *Lainco, Spain.*
Liquid paraffin (p. 2191·2).
Constipation.

Emulox *Emcure, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Emulsão de Lipidos *Grifols, Port.*
Soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid emulsion for parenteral nutrition.

Emulsão Scott *GSK, Braz.*
Cod-liver oil (p. 2056·3); soya oil (p. 2092·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3); electrolytes (p. 1775·1).
Nutritional supplement.

Emulsão Universal *Merck, Braz.*
Emollient.

Emulsi Factors *Future, Canad.*
Choline citrate (p. 2055·2); folic acid (p. 2063·1); inositol (p. 2533·2); methionine (p. 1558·2); magnesium salts (p. 1786·3); vitamin B_{12} (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).

Emulsiderm *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Isopropyl myristate (p. 2190·3); liquid paraffin (p. 2191·2); benzalkonium chloride (p. 1737·1).
Dry skin disorders.

Emulsion SB *PruGen, USA.*
Emollient.
Dry skin disorders; pruritus.

Emulsion de Scott *GSK, Mex.*
Cod-liver oil (p. 2056·3); calcium phosphate (p. 1784·2).
Vitamin A, vitamin D, and calcium supplement.

Emulsoil *Paddock, USA.*
Castor oil (p. 2472·1).
Constipation.

Emustil *Moorfields, UK.*
Soya oil (p. 2092·3); natural phospholipids (p. 2201·2).
Dry eyes.

Emuxel *Dynamic, Philipp.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Emvasc *Ivax, Irl.†*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Emvate *Captab, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Emverin *Emar, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Emverin-MF *Emar, India.*
Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Emvi *Sanjivani, India.*
Vitamins.

Emvit *Cadila, India.*
Amino acids; vitamins.
Dietary supplement.

Nycomed, S.Afr.
Vitamins; minerals.

Emvita 2 *Rubimed, Neth.*
Calcarea phosphorica (p. 1784·2); ovarium suis (p. 2298·2).
Homoeopathic preparation.

Emvita 3 *Rubimed, Neth.*
⊗Apis mellifica (p. 2445·2); bovista lycoperdon; conium maculatum (p. 2524·3); hepar sulphur (p. 1721·3); ovarium suis (p. 2298·2); testis suis (p. 2304·3).
Homoeopathic preparation.

Emvita 4 *Rubimed, Neth.*
Apis mellifica (p. 2445·2); ovarium suis (p. 2298·2); platinum metallicum (p. 2593·1).
Homoeopathic preparation.

Emvita 6 *Rubimed, Neth.*
⊗Arsenicum album (p. 2448·1); lachesis mutus (p. 2538·3); phosphorus (p. 2589·2); secale cornutum (p. 2137·1); suprarenalis suis (p. 1648·1).
Homoeopathic preparation.

Emvita 7 *Rubimed, Neth.*
⊗Anacardium orientale (p. 2471·3); glandula suprarenalis suis (p. 1648·1); lachesis mutus (p. 2538·3); lycopodium clavatum (p. 2547·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

Emvita 10 *Rubimed, Neth.*
⊗Agnus castus (p. 2432·2); arum triphyllum; hepar sulphur (p. 1721·3); lachesis mutus (p. 2538·3); pancreas suis (p. 2444·1); petroleum (p. 2587·2).
Homoeopathic preparation.

Emvita 11 *Rubimed, Neth.*
Cuprum metallicum (p. 2057·1); ferrum metallicum (p. 2073·1); ignatia amara (p. 2532·1); pancreas suis (p. 2444·1); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Emvita 15 *Rubimed, Neth.*
Apis mellifica (p. 2445·2); glandula thymi suis (p. 2631·1); lachesis mutus (p. 2538·3); phosphorus (p. 2589·2); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Emvita 20 *Rubimed, Neth.*
Apis mellifica (p. 2445·2); phosphorus (p. 2589·2).
Homoeopathic preparation.

Emvita 21 *Rubimed, Neth.*
Arsenicum album (p. 2448·1).
Homoeopathic preparation.

Emvita 26 *Rubimed, Neth.*
Arsenicum album (p. 2448·1); cerebrum suis (p. 2444·1); lycopodium clavatum (p. 2547·1); millefolium (p. 2547·1); plumbum metallicum (p. 2541·3).
Homoeopathic preparation.

Emwepel *Stada, Cz.*
Pramipexole hydrochloride (p. 911·2).

E-Mycin *Alphapharm, Austral.; Mylan, NZ.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

LCH, Hong Kong†; Knoll, USA.
Erythromycin (p. 291·2).
Bacterial infections.

Themis, India.
Erythromycin estolate (p. 291·2).
Bacterial infections.

Emzaclear *Meyer Zall, S.Afr.*
Salicylic acid (p. 1719·1).
Acne.

Emzacort *Emar, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Emzine *Hands, India.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; motion sickness.

Emzok *Ivax, Rus.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; heart failure; migraine.

Teva, Cz.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; heart failure; arrhythmias; migraine.

Emzolam *Miracalus, India.*
Temozolomide (p. 865·2).
Malignant glioma; malignant melanoma.

En *Abbott, Ital.*
Delorazepam (p. 1062·3).
Anxiety disorders; sleep disorders.

En Bi Pu *CSPC, China; Ou Yi, China.*
Butylphthalide.

En Bo Ke *Hong Yi, China; Yawei, China.*
Anti-human interleukin-8 monoclonal antibody.

En Er Xin *ShiJiaZhuang No 4, China.*
Arbidol hydrochloride.

En Fu De *Global, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

En Fu Shuang *Shunfeng, China.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

En Ge Fei *Yaojiang, China.*
Staphylococcal enterotoxin C.

En Jiu Ping *Biochem, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

En Li Ke *Yuan Heng, China.*
Inosine (p. 2533·1).

En Nuo Ni *Hicin, China.*
Cefmenoxime hydrochloride (p. 241·2).
Bacterial infections.

En Nuo Ping *ShiJiaZhuang No 4, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

En Nuo Xin *Nhwa, China.*
Zaleplon (p. 1114·3).
Insomnia.

En Pu Luo *Xiangju, China.*
Ampicillin (p. 218·2).
Probenecid (p. 607·3) is included in this preparation to reduce the renal tubular excretion of ampicillin.
Bacterial infections.

En Tong *Enshi, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

En Zai Shi *Weishi, China.*
A smallpox vaccine (p. 2418·2).
Active immunisation.

Ena *Hennig, Ger.; Menarini, India.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enabeta *Betapharm, Ger.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enabeta comp *Hexal, Denm.; Betapharm, Ger.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enablex *Bago, Arg.; Novartis, Austral.; Novartis, Braz.; Novartis, Canad.; Novartis, Rus.; Bayer Schering, S.Afr.; Novartis, USA.*
Darifenacin hydrobromide (p. 2354·2).
Bladder instability; bladder hyperactivity.

Enabran *Casasco, Arg.†*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; psychomotor agitation; pain; nausea and vomiting.

E-Nac *Greenco, India.*
Diclofenac sodium (p. 48·3).
Prevention of intra-operative miosis; eye inflammation and pain; allergic conjunctivitis.

Enac *Hexal, Austria.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left ventricular dysfunction.

Enac Plus *Hexal, Austria.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

EnAce *Piramal, India.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enace *Hizon, Philipp.; Unique, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enacecor *Pharmacodane, Denm.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

EnAce-D *Piramal, India.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enacodan *Pharmacodane, Denm.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Enacxil *Shince, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Enadigal *Mibe, Ger.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enadigal HCT *Mibe, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enadiol *Laboratorios Chile, Chile.†*
Estradiol valerate (p. 2271·2).
Menopausal disorders; osteoporosis.

Enadiol CC *Laboratorios Chile, Chile.†*
Estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Enadiol MP *Laboratorios Chile, Chile.†*
12 tablets, estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1); 18 tablets, estradiol valerate.
Menopausal disorders.

Enadiol Neta *Laboratorios Chile, Chile.†*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Enador *Gedeon Richter, Irl.*
Ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Enaf *Umeda, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Dysfunctional uterine bleeding; endometriosis; progestogen-only injectable contraceptive.

Enafarm *Farmakor, Rus.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enafilzil *Sigillata, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Enafril *Stirol, Ukr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enahexal *Sandoz, Austral.†; Hexal, Ger.†; Hexal, NZ†; Sandoz, Ukr.†*
Enalapril maleate (p. 1371·1) or enalaprilat (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Enahexal comp *Hexal, Denm.; Hexal, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enahexal Compositum *Sandoz, Ukr.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enahimine *Remedina, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Enahyton *Hexal, Denm.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enal *East West, India.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enalabal *Baldacci, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; angina pectoris; myocardial infarction.

Enalabell *Bellwether, Austral.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enalacomp *Genericon, Austria.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enaladex *Dexcel, Israel.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enaladil *Rhein, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enalafel *Raffo, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enalagamma *Worwag, Ger.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enalagamma HCT *Worwag, Ger.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalamed *Cimed, Braz.*
Enalapril (p. 1371·1).
Hypertension.

Enalap *Mapra, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Saba, Turk.
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enalapoten *Del Bel, Arg.*
Enalapril (p. 1371·1).
Hypertension.

Enalapri *CTS, Israel.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enalapril Comp *Arcana, Austria; Orion, Fin.; Ratiopharm, Fin.; Sandoz, Fin.; Ratiopharm, Ger.; Ratiopharm, Norw.; Ratiopharm, Swed.; Sandoz, Swed.; Stada, Swed.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalapril HCT *Axcount, Ger.†; Sandoz, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalapril Hexal Plus *Hexal, Hung.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalapril plus *1A, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalapril-H *Zdorovje, Ukr.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalapril-HCT *Plus Pharma, Austria; Ratiopharm, Austria; Sandoz, Austria; 1A, Hung.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalapril-saar Plus *MIP, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enala-Q comp *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalatec *Greenpharma, Braz.*
Enalapril (p. 1371·1).
Hypertension.

Enalatidin *Vitabalans, Hung.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enalatin *Vitabalans, Cz.; Vitabalans, Fin.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enaldun *Duncan, Arg.*
Enalapril (p. 1371·1).
Hypertension.

Duncan, Hong Kong.†
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

EnaLich *Winthrop, Ger.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

EnaLich comp *Winthrop, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enalil *Kinder, Braz.†*
Enalapril maleate (p. 1371·1).
Hypertension.

Enalozid *Farmak, Ukr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enalozid Mono *Farmak, Ukr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enalprin *Royton, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Enalten *Saval, Chile.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enalten D *Saval, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enalten DN *Saval, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enam *Reddy, India; Reddy, Rus.; Reddy, Thai.; Reddy, Ukr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Enamate *Glenmark, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Enamaxin *Vitabalans, Denm.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enam-D *Reddy, India.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enam-H *Reddy, Rus.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enamide *Shree Ganesh, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Enan *Labormed, Rus.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enangel *Menarini, Spain.*
Dexketoprofen trometamol (p. 79·1).
Pain; inflammation.

Enanton *Orion, Fin.; Orion, Norw.; Orion, Swed.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; endometriosis; uterine fibroids.

Enantone *Takeda, Austria; Takeda, China; Takeda, Fr.; Takeda, Ger.; Takeda, Hong Kong; Takeda, Ital.; Takeda, Thai.*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; uterine fibroids; breast cancer; prostatic cancer; precocious puberty; menorrhagia; fibromyoma; stimulation of ovulation.

Enantone-Gyn *Takeda, Ger.*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; breast cancer; uterine fibroids.

Enantyum *Menarini, Arg.; Menarini, Austria; Menarini, Belg.; Menarini, Denm.†; Menarini, Fin.†; Menarini, Ital.; Menarini, Neth.; Menarini, Port.; Menarini, Spain; Menarini, Swed.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Enap *KRKA, Cz.; KRKA, Hong Kong; KRKA, Hung.; Rowex, Irl.; KRKA, Pol.†; KRKA, Rus.; Pharma Dynamics, S. Afr.; KRKA, Singapore; KRKA, Ukr.*
Enalapril maleate (p. 1371·1) or enalaprilat (p. 1371·1).
Hypertension; heart failure; hypertensive crisis; left-ventricular dysfunction; diabetic nephropathy.

Enap H *KRKA, Pol.; KRKA, Ukr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enap HL *KRKA, Pol.; KRKA, Ukr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enap-Co *Pharma Dynamics, S.Afr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enap-H *KRKA, Cz.; KRKA, Rus.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enap-HL *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.; KRKA, Singapore.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enapil *Psychotropics, India.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enaplus *Aliud, Ger.†; Stada, Ger.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enapren *MSD, Ital.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enapress *Stada, Port.*
Enalapril maleate (p. 1371·1).

Enapril *Lannacher, Austria; Hexal, Cz.; Hexal, Hung.; Intas, India; Stada, Irl.; YSP, Malaysia; SparMed, Switz.; Intas, Thai.†; Sandoz, Turk.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left ventricular dysfunction.

Enapril-HT *Intas, India.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enapril-LD *Intas, India.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enaprotec *Hexal, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Ena-Puren *Actavis, Ger.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enarenal *Polpharma, Pol.; Polpharma, Rus.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enarese comp *Hexal, Denm.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enaretic *Intas, India.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enaril *Biolab, Singapore; Biolab, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enaros *Medochemie, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Enastros *Aurora, Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Enat *Mega Lifesciences, Malaysia; Mega Lifesciences, Philipp.*
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E deficiency.

Mega We Care, Singapore; Mega Lifesciences, Ukr.
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Enatec *Mepha, Switz.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Enatia *Farmoz, Port.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enatil *Brasterapica, Braz.†*
Enalapril (p. 1371·1).

Enatome *Epitome, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Enatral *Austral, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enatrial *Investi, Arg.†; Volta, Chile.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Enatus *Pielle, Ital.*
Iceland moss (p. 2531·2); plantago; althaea (p. 2438·3); aesculus (p. 2431·2); thyme (p. 2630·2); melissa (p. 2552·3); drosera (p. 2497·2); papaver.
Cough.

Enax *Ativus, Braz.*
Echinacea (p. 2498·1).
Immunostimulant.

Enazil *Pliva Krakow, Pol.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Enbenol *Ind-Swift, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Enblac *Bactolac, India.*
Capsules: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); lactic acid bacillus (p. 2596·3).
Diarrhoea.

Bactolac, India.
Syrup: Vitamin B substances (p. 2102·3); lactobacillus (p. 2596·3).
Diarrhoea.

Enblac-Z *Bactolac, India.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); lactobacillus (p. 2596·3).

Enbrel *Wyeth, Arg.; Pfizer, Austral.; Wyeth, Austria; Pfizer, Belg.; Wyeth, Braz.; Amgen, Canad.; Wyeth, Chile; Pfizer, China; Wyeth, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Wyeth, Hung.; Wyeth, India; Wyeth, Indon.; Pfizer, Irl.; Pfizer, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, Neth.; Pfizer, Norw.; Pfizer, NZ; Wyeth, Philipp.;*

Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Rus.; Pfizer, S. Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK; Amgen, USA; Wyeth, Venez.
Etanercept (p. 55·1).
Rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis; ankylosing spondylitis; psoriasis.

Enbrol *Taj, India.*
Etanercept (p. 55·1).

Enca *Prempharm, Canad.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Encalor *Rafarm, Gr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Encardil *Medley, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Encare *Thompson, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Encebion *Medikon, Indon.†*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; learning difficulties in children.

Encefabol *Merck, Chile.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment.

Encelax *Zydus, India.*
Lactitol (p. 1850·3).

Encentin *East West, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Encentin Plus *East West, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Encentin-AM *East West, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1); thioctic acid (p. 2629·1).

Encentin-M *East West, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Encepan *Interbat, Indon.*
Pyritinol (p. 394·3).
Mental function impairment; cerebral trauma.

Encephabol *Merck, Cz.; Merck Serono, Ger.; Galenica, Gr.; Merck, Hong Kong; Merck, Indon.; Merck, Mex.; Merck, Philipp.; Nycomed, Rus.; Merck, S.Afr.†; Merck, Thai.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment; organic brain disorders; cerebral trauma; dementia; cerebral insufficiency.

Merck, Austria; Merck, India; Merck, Ukr.
Pyritinol (p. 394·3) or pyritinol hydrochloride (p. 394·3).
Organic brain disorders; migraine; dementia; mental function disorders; cerebrovascular disorders.

Encepur *Novartis, Austria; Novartis Vaccines, Cz.; Novartis, Denm.; Novartis Vaccines, Fin.; Novartis Vaccines, Fr.; Novartis Vaccines, Ger.; IFET (ΙΦΕΤ), Gr.; Novartis Vaccines, Hung.; Novartis Vaccines, Pol.; Novartis Vaccines, Rus.; Novartis, Swed.; Novartis, Switz.*
An inactivated tick-borne encephalitis vaccine (p. 2422·1).
Separate preparations are available for infants and children and for older children and adults.
Active immunisation.

Encevac *Astellas, Jpn.*
An inactivated Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Encevir *Microgen, Rus.*
An inactivated tick-borne encephalitis vaccine (p. 2422·1).
Active immunisation.

Encifer *Biotoscana, Chile; Emcure, India; Emcure, Philipp.; Emcure, Thai.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia; iron deficiency.

Encimenal *Alacan, Spain.*
Turmeric (p. 2218·1).
Liver disorders.

Enclor *McNeil & Argus, India; Idaman, Singapore.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Encloxil *Pharmacare, Philipp.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Encodex *CCM, Malaysia.*
Hyoscine methobromide (p. 1846·1).
Gastric hyperacidity; hyperhidrosis; smooth muscle spasm; peptic ulcer.

Encol *Norgine, Denm.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Encold *Elnova, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Encold-P *Allenge, India.*
Oral drops: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Allenge, India.
Tablets: ⊗Chlorphenamine maleate (p. 620·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Encopirin *Perrigo, Pol.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Encorate *Sun, India; Sun, Rus.; Sun, Thai.*
Sodium valproate (p. 553·1).
Migraine; bipolar disorder; epilepsy.

Encorate Chrono *Sun, Rus.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Encortolon *Polfa Pabianice, Pol.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Encorton *Polfa Pabianice, Pol.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Encript *Micro, India.*
Bromocriptine (p. 895·3).
Parkinsonism; hypogonadism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Encrise *Biolab Sanus, Braz.*
⊗Vasopressin (p. 2642·3).

Encypalmed *Trima, Israel.*
⊗Pancreatin (p. 2579·3); ox bile (p. 2457·2).
Formerly contained pancreatin, ox bile, rhubarb, frangula bark, and sodium bicarbonate.
Dyspepsia; gastro-enteritis; meteorism; digestive disorders.

Endace *Samarth, India.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; endometrial hyperplasia; endometriosis.

Endacine *Andromaco, Chile.*
Levosulpiride (p. 1108·1).
Gastrointestinal disorders.

EndaCod-C *Larken, USA.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.

EndaCod-DC *Larken, USA.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

EndaCof-AC *Larken, USA.*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

EndaCof-C *Larken, USA.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

EndaCof-DC *Larken, USA.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

EndaCof-DH *Larken, USA.†*
Brompheniramine maleate (p. 618·1); dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Endacon *Allegis, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Endafed *UAD, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Allergic rhinitis; nasal congestion.

Endagen-HD *Abana, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

Endak *Madaus, Ger.; Rottapharm, Ger.*
⊗Carteolol hydrochloride (p. 1332·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Endal *Pediamed, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs.

Endal CD *Tiber, USA.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Formerly contained codeine phosphate, diphenhydramine hydrochloride, and phenylephrine hydrochloride.
Upper respiratory-tract disorders.

Endal Expectorant *Pediamed, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Endal-HD *Pediamed, USA.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3); hydrocodone tartrate (p. 67·2).
Cough; cold symptoms.

Endal-HD Plus *Pediamed, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

EndaRoid *Larken, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Endcid *Allenge, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Endcoff *EMS, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Endcol Cold & Flu *Pharmacare, S.Afr.†*
Paracetamol (p. 115·1); vitamin C (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Endcol Lozenges *Aspen Consumer, S.Afr.*
Cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Sore throat.

En-De-Kay *Manx, Neth.; Manx, UK.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Endep *Alphapharm, Austral.; LCH, Hong Kong.†*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Enderm *Leben, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Enderm-GM *Leben, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Endhometrol *Boiron, Fr.*
Calendula (p. 2465·2); helonias dioica (p. 2524·3); hydrastis canadensis (p. 2528·1).
Homoeopathic preparation.

Endial *Roemmers, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Endial Met *Roemmers, Arg.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Endiaron
Note: this name may be used for preparations of different composition.
Herbacos, Cz.; Zentiva, Cz.
Chloroxine (p. 260·1).
Infected skin disorders; burns; wounds; gastro-enteritis; disturbance of the intestinal flora; amoebiasis; giardiasis.

Endid *Emcure, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Endida *Strassenburg, India.*
Fluconazole (p. 578·2).
Fungal infections.

Endiex *Zentiva, Cz.; Zentiva, Pol.*
Nifuroxazide (p. 331·3).
Bacterial diarrhoea.

Endioderm *Herbacos Recordati, Cz.*
Chloroxine (p. 260·1).
Skin infections.

Endium *Dexo, Fr.†*
Diosmin (p. 2505·2).
Peripheral vascular disorders; haemorrhoids.

Endix *Dongkwang, Malaysia.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections.

Endlic *BMW, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Endobon *Biomet, Ger.*
Hydroxyapatite (p. 2529·3).
Bone defects.

Endobulin *Baxter Immuno, Arg.; Baxter, Austria†; Baxter, Braz.; Baxter, Cz.†; Baxter, Denm.†; Baxter, Ger.†; Baxter, Ital.; Baxter, Pol.; Baxter, Spain†; Baxter, Switz.†; Eczacibasi-Baxter, Turk.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; autoimmune disorders; hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease.

Endocaina *Lanpharm, Arg.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Endocare *Labomed, Chile.†*
Secretion from *Cryptomphalus aspersa.*
Sun-induced skin damage; drug-induced skin damage.

Endocet *BMS, Canad.; Endo, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain; fever.

Endocin *Adley, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Endoclar *Baliarda, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Endocorion *Elea, Arg.*
⊗Chorionic gonadotrophin (p. 2258·1).
Benign breast disorders; cryptorchidism; delayed puberty; habitual and threatened miscarriage; male and female infertility; menstrual disorders.

Endocris
Note: this name may be used for preparations of different composition.
Cristalia, Braz.
Enoxaparin sodium (p. 1372·3).

Endoepatox *NCSN, Ital.*
Glutathione (p. 1555·2); thioctic acid (p. 2629·1); cysteine (p. 2058·3); milk thistle (p. 1561·1).
Dietary supplement.

Endofalk *Falk, Austria; Falk, Belg.; Biotoscana, Chile; Falk, Denm.; Falk, Fin.; Falk, Ger.; Falk, Gr.; Falk, Neth.; Falk, Norw.; Falk, Port.; Falk, Rus.; Meda, Swed.; Ali, Turk.; Falk, Ukr.*
Macrogol (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; bowel cleansing for endoscopy.

Endofer *Biolab Sanus, Braz.*
Iron polymaltose (p. 2077·2).

Endofolin *Marjan, Braz.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects.

Endogel *Zeiss Meditec, Ger.*
Sodium hyaluronate (p. 2526·2).
Adjunct in cataract surgery.

Endogel Esteril *Rider, Chile.*
Lidocaine hydrochloride (p. 1988·2); chlorhexidine gluconate (p. 1743·3).
Endoscopy; urethral disinfection and anaesthesia.

Endogen *Uni-Sankyo, India.*
Urofollitropin (p. 2312·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Endogest
Note: this name may be used for preparations of different composition.
Cipla, India.
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Endol
Note: this name may be used for preparations of different composition.
Deva, Turk.
Indometacin (p. 71·2).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Endolac *Proge, Ital.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Gastrointestinal disorders.

Endolipide *Braun, Fr.†; Braun, Port.†*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Endolol *Hetero, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Endolor *Keene, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain.

Endomal *Almet, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Endomal-AT *Almet, India.*
Artesunate (p. 648·2).
Malaria.

Endomal-O *Almet, India.*
Artesunate (p. 648·2).
Malaria.

Endomethasone
Note: this name may be used for preparations of different composition.
Septodont, Canad.; Tsaprazis, Gr.†
⊗Dexamethasone (p. 1630·3); hydrocortisone acetate (p. 1640·1); paraformaldehyde (p. 1763·1); thymol iodide (p. 1772·2).

Endometril *Schering-Plough, Indon.*
Lynestrenol (p. 2287·3).
Menstrual disorders; endometriosis; dysfunctional uterine bleeding; mastopathy; endometrial cancer.

Endometrin *Ferring, Canad.; Ferring, Hong Kong; Ferring, Israel; Ferring, Ukr.; Ferring, USA.*
Progesterone (p. 2300·2).
Female infertility.

Endomina *Angelini, Spain.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Endomina Plus *Angelini, Spain.†*
Patch A, estradiol (p. 2271·1); patch B, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Endone *Sigma, Austral.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Endopace *Themis, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Endo-Paractol *Temmler, Ger.*
Simeticone (p. 1886·2).
Adjuvant for endoscopy and double contrast radiography.

Endopeg *Braun, Belg.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Medreich, India.
Macrogol (p. 2547·3); electrolytes (p. 1775·1).

Endophy *Neptunus, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Endoprol *Novartis, Denm.†*
⊗Budesonide (p. 1625·1).
Asthma.

Endoprost *Italfarmaco, Ital.*
Iloprost trometamol (p. 1408·2).
Thromboangiitis obliterans; Raynaud's syndrome; arterial ischaemia.

Endorem *Guerbet, Austria; Codali, Belg.†; Guerbet, Denm.†; Guerbet, Fin.†; Guerbet, Fr.†; Guerbet, Ger.†; Hospital Line, Gr.; Guerbet, Irl.; Guerbet, Ital.; Guerbet, Neth.†; Guerbet, Norw.†; Martins & Fernandes, Port.; Guerbet, Spain†; Gothia, Swed.†; Guerbet, Switz.†; Guerbet, Turk.*
Ferumoxides (p. 1584·2).
Contrast medium for magnetic resonance imaging of the liver.

Endos *Geno, India.*
⊗Amylase (p. 2442·1); docusate sodium (p. 1836·2); pepsin (p. 2586·1); sodium tauroglycocholate.

Endosetin *Nobel, Turk.*
Indometacin (p. 71·2).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Endosgel *Farco, Ger.*
Chlorhexidine gluconate (p. 1743·3).
Gynaecological and urinary-tract procedures; urethral and vaginal endoscopy.

Farco, Austria.†
Chlorhexidine gluconate (p. 1743·3); sodium lactate (p. 1781·2).
Gynaecological and urinary-tract procedures.

Endosin *Nobel, Turk.*
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Endosone *Dongnam, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Endospas *Ultramark, India.*
Paracetamol (p. 115·1); dicycloverine hydrochloride (p. 1834·2).

Endostar *Medgenn, China; Simcere, China.*
Recombinant human endostatin (p. 786·2).
Non-small cell lung cancer.

Endoteel *Heel, Canad.†*
Belladonna (p. 2453·3); berberis aquifolium (p. 2577·1); charcoal activated (p. 1537·3); euphorbium officinarum; euphrasia officinalis (p. 2502·1); graphite (p. 2522·1); phosphorus (p. 2589·2); silicon dioxide (p. 2208·3); silver nitrate (p. 2615·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Endotélon *Sanofi-Aventis, Fr.*
Grape seed (p. 2521·3).
Peripheral vascular disorders; lymphoedema.

Endotelon *Sanofi-Aventis, Chile†; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.†; Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.*
Grape seeds (p. 2521·3).
Venous insufficiency; lymphatic insufficiency; lymphoedema; peripheral vascular disorders.

Endothalyl *TC Pharma-Chem, Thai.*
Clioquinol (p. 273·1); phthalylsulfathiazole (p. 339·3).
Gastrointestinal infections.

Endotine *Septodont, Fr.*
Parachlorophenol (p. 1763·1); *m*-cresyl acetate (p. 1749·1).
Root canal infections.

Endotropina *Fada, Arg.*
Atropine (p. 1310·2).

Endotussin *Prodotti, Braz.†*
Potassium iodide (p. 2336·3); theophylline calcium salicylate (p. 1229·3).
Respiratory-tract congestion.

Endovaz *Unique, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Endoxan *Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Chile; Baxter, China; Baxter Oncology, Cz.; Baxter, Fr.; Baxter Oncology, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Cadila, India; Transfarma, Indon.; Baxter, Israel; Baxter, Ital.; Shionogi, Jpn; Baxter, Neth.; Baxter, NZ; Baxter, Philipp.†; Baxter Oncology, Pol.; Baxter, Port.; Baxter Oncology, Rus.; Sanofi-Aventis, S.Afr.; Baxter Oncology, Singapore; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; transplant rejection; autoimmune disorders; immunosuppressant; scleroderma; rheumatoid arthritis; bone-marrow transplants; lupus erythematosus; haematopoietic stem cell transplantation; multiple sclerosis; nephrotic syndrome.

Endoxana *Baxter, Irl.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Endozol *VHB, India.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; gynaecomastia; hereditary angioedema; endometrial thinning; menorrhagia.

Endrine *Takeda, Belg.*
⊗Ephedrine (p. 1663·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Rhinopharyngeal congestion.

Wyeth, India.
⊗Ephedrine (p. 1663·1); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1).
Nasal congestion.

Endrine Doux *Takeda, Belg.*
⊗Ephedrine (p. 1663·1); eucalyptus oil (p. 2501·2).
Rhinopharyngeal congestion.

Endrine Mild *Wyeth, India.*
⊗Ephedrine (p. 1663·1); camphor (p. 2466·2); cineole (p. 2479·1).
Nasal congestion.

Endrolin *Kalbe, Indon.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; endometriosis.

Endrolyte *Profic Organic, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Endronax *Abbott, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Endrostan *Delta, Braz.*
Alendronate sodium (p. 1171·3).

Endruff *NuLife, India.*
Calcium pantothenate (p. 2085·2); cetrimide (p. 1742·1).

Enducaine *Oriental, Philipp.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; arrhythmias.

Endulza *Valma, Chile.*
Saccharin sodium (p. 2208·1).
Sugar substitute.

Endulzante *Valma, Chile.*
Saccharin sodium (p. 2208·1); sodium cyclamate (p. 2180·2).
Sugar substitute.

Endura
Note: this name may be used for preparations of different composition.
Allergan, Arg.; Allergan, Thai.
⊗Glycerol (p. 2517·2); polysorbate 80 (p. 2203·3).
Dry eye; eye irritation.

Allergan, Braz.
⊗Glycerol (p. 2517·2).

Allergan, Singapore.
⊗Glycerol (p. 2517·2); polysorbate (p. 2203·1).
Dry eyes.

Metagenics, Canad.†
Vitamins; minerals.

Endur-acin *Endurance, USA.*
Nicotinic acid (p. 2083·1).
Hypercholesterolaemia.

Enduracin *Endurance, Rus.*
Nicotinic acid (p. 2083·1).
Hyperlipidaemias.

Endurane *Pharmawealth, Philipp.*
Enflurane (p. 1899·3).
General anaesthesia.

Enduranz *Elder, India.*
Arginine (p. 2049·1); lycopene (p. 2546·2); omega-3 fatty acids (p. 1460·1); policosanol (p. 1472·1).

Endure *Ecolab, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Endure Cida *Ecolab, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Endure Scrub *Ecolab, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Hand disinfection.

Enduron *Abbott, USA.*
⊗Methyclothiazide (p. 1430·3).
Hypertension; oedema.

Enduronyl *Hayao, China.*
⊗Methyclothiazide (p. 1430·3); deserpidine (p. 1350·3).
Hypertension.

Endvir Simplex *Dicofarm, Ital.*
Lactoferrin (p. 2539·3).
Herpesvirus infection.

Eneas *Ferrer, Ger.; Galenica, Gr.; Ferrer, Port.; Ferrer, Spain; Solvay, Turk.; Ferrer, Ukr.*
Enalapril maleate (p. 1371·1); nitrendipine (p. 1456·3).
Hypertension.

Enecal *Elmor, Venez.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; myocardial infarction.

Enecat *Mallinckrodt, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Enediex *Fada, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Enelbin *Zentiva, Cz.; Leciva, Rus.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders; vascular disorders of the eye and ear.

Enelbin-Paste *Cassella-med, Ger.†*
Aluminium silicate (p. 1818·3); zinc oxide (p. 1729·1); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); thyme oil (p. 2630·3); sweet birch oil (p. 92·1).
Musculoskeletal and joint disorders.

Enelbin-Paste N *Cassella-med, Ger.†*
Zinc oxide (p. 1729·1); salicylic acid (p. 1719·1); aluminium silicate (p. 1818·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Enelfa *Dolorgiet, Ger.†*
Paracetamol (p. 115·1).
Pain; fever.

Enem *LBS, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Enema *Sutton, Canad.; Galenowe Olsztyn, Pol.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Enema Casen *Casen Fleet, Spain.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation.

Enema Cooper *Cooper (Κοπερ), Gr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Enemac *Eurospital, Ital.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Enemark *Mallinckrodt, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Enemeez *Alliance, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Enemeez Plus *Alliance, USA.*
Docusate sodium (p. 1836·2); benzocaine (p. 1980·2).
Constipation.

Enemol *Gador, Arg.; Dominion, Canad.; Hind Wing, Hong Kong.†*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Ener A Plus *Orchid, Philipp.*
Vitamins; zinc (p. 2126·1); taurine (p. 2626·2); with or without lysine (p. 2079·3).
Dietary supplement.

Ener B
Note: this name may be used for preparations of different composition.
Medipharm, Chile.
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; vitamin B deficiency.

Ener-B
Note: this name may be used for preparations of different composition.
YSP, Malaysia.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Enerbex *Medikon, Indon.†*
Vitamins; zinc sulfate (p. 2126·2).
Nutritional supplement.

Enerbol *Pliva, Cz.†; Ikapharmindo, Indon.; Pliva, Rus.†*
Pyritinol hydrochloride (p. 394·3).
Cerebral trauma; mental function impairment; cerebrovascular disorders; rheumatoid arthritis; trigeminal neuralgia; migraine.

Enerbolis *Vivo Health, Singapore.*
Phytoandrogens; suHLAs; ubidecarenone (p. 2637·1); chelated zinc (p. 2126·1).
Anabolic.

Ener-C *Orchard, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Enercal *Wyeth Nutrition, Indon.*
A range of preparations for enteral nutrition.

Enercal Plus *Wyeth, Hong Kong†; Wyeth, Malaysia.†*
Lactose-free preparation for enteral nutrition.
Wyeth, Singapore.†
Lactose-free nutritional supplement.

Enercomplex *Provita, Ital.*
Minerals; vitamin C (p. 2110·3); carnitine (p. 2053·2); creatine (p. 2488·3); ginseng (p. 2513·3).
Tonic.

Enercore *Soho, Indon.*
D-Ribose; ubidecarenone (p. 2637·1); levocarnitine fumarate (p. 2053·2); magnesium (p. 1786·3).
Dietary supplement; tonic.

Enerday *K2 Health & Wellness, Chile.*
Ginseng (p. 2513·3); vitamins; erythroxylon catuaba; marapuama.
Tonic.

Ener-Forte *CNN, Philipp.*
Vitamins; with or without iron (p. 2073·1).

Ener-G *General Dietary, UK.*
Gluten-free bread, rice bran, and pasta.
Gluten-sensitive enteropathies.

Energain *Sterling, India.*
Preparation for enteral nutrition.

Energavit *Roemmers, Arg.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Energeia *Sanitalia, Ital.*
Ginseng (p. 2513·3); ginkgo biloba (p. 2512·3); Siberian ginseng (p. 2614·3); minerals.
Nutritional supplement.

Energel *Arcolab, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3); choline bitartrate (p. 2055·2); methionine (p. 1558·2).
Dietary supplement.

Energen *Volchem, Ital.*
Glucose (p. 2068·3) or maltodextrin (p. 2080·3).
Hypoglycaemia; energy loss.

Energex *Zydus, India.*
Preparation for enteral nutrition.

Energiclin *Hebron, Braz.†*
Piracetam (p. 393·3); vitamins.
Tonic.

Energil C *EMS, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Energin
Note: this name may be used for preparations of different composition.
Biosearch, Spain.
Ginseng (p. 2513·3).
Fatigue.
GSK, Ukr.
⊗Vitamins; minerals; royal jelly (p. 2608·1); ginseng (p. 2513·3); wheat-germ oil (p. 2647·1); soya phospholipids; safflower oil (p. 2086·3); arginine (p. 2049·1); lysine (p. 2079·3); orotic acid (p. 2578·1); deanol tartrate (p. 2319·1); plant pollen (p. 2593·3).
Vitamin and mineral supplement; tonic.

Energitum *Zambon, Fr.†*
Arginine glutamate (p. 2049·1).
Asthenia.

Energivit *Scientific Hospital Supplies, Irl.; Nutricia, Ital.*
Protein-free nutritional supplement for infants and children.
Nutricia, Austral.; Nutricia, NZ.
Nutritional supplement for infants and children.
Nutricia, Fr.
Preparation for enteral nutrition.
SHS, UK.
Nutritional supplement for infants.
Ache, Braz.
Piracetam (p. 393·3); fructose (p. 2068·2); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); tocoferil acetate (p. 2119·2).
Alcoholism; behaviour disorders in children; cerebrovascular disorders; senile dementia; vertigo.

Energizante *AM, Arg.*
Vitamins; minerals; arginine (p. 2049·1); choline (p. 2055·2); royal jelly (p. 2608·1); guarana (p. 2648·2); pollen.
Tonic.

Energizante Vital con ginseng *AM, Arg.*
Vitamins; minerals; arginine (p. 2049·1); choline (p. 2055·2); centella (p. 1698·3); ginseng (p. 2513·3); guarana (p. 2648·2); royal jelly (p. 2608·1); pollen.
Tonic.

Energizing Pomegranate Moisturizer *Balley, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Energocarnil *Energon, Gr.*
Levocarnitine (p. 2053·2).

Energoplex *Libbs, Braz.*
Vitamins; fructose (p. 2068·2); arginine (p. 2049·1).
Nutritional supplement.

Energorot *Proel, Gr.*
Glucosamine sulfate (p. 2515·3).

Energotin aktiv *Truw, Ger.*
Taigawurzeln.
Tonic.

Energoton *Darnitsa, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; vascular eye disorders.

Energy Plus
Note: this name may be used for preparations of different composition.
Tecnonat, Arg.
Vitamins; minerals; ginseng (p. 2513·3); guarana (p. 2648·2).
Dietary supplement.
United Lifecare, India.
Glucose (p. 2068·3); sucrose (p. 2096·3); zinc sulfate (p. 2126·2) (p. 1780·1).
Oral rehydration therapy.

Energy-Max *Foramen, Philipp.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Vitamin deficiency.

Energyn-T *DHA, Singapore.*
Vitamins; minerals.

Energyvit
Note: this name may be used for preparations of different composition.
Elmor, Venez.
⊗Ginseng (p. 2513·3); deanol tartrate (p. 2319·1); rutoside (p. 2505·3); vitamins; minerals.
Tonic.

Enerion *Servier, Rus.; Servier, Ukr.*
Sulbutiamine (p. 2103·1).
Asthenia.

Enerject-12 *Anglo-French Drugs, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Enerjets *Chilton, USA.*
Caffeine (p. 1203·3).
Fatigue.

Enerjex *Zydus, India.*
Carbohydrate; ferrous aminoate (p. 2048·3); lysine hydrochloride (p. 2079·3); methionine (p. 1558·2); protein hydrolysate; vitamin B substances (p. 2102·3).

Enerliv *Menarini, Ukr.*
Defatted refined soya bean phospholipids (p. 2092·3).
Liver disorders.

Enerplus *Soho, Indon.*
Adenosine triphosphate (p. 2430·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Muscular weakness; myocardial disorders; fatigue.

Ensersel *Sel-J, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3); taurine (p. 2626·2); chlorella growth factor (p. 2475·3).
Dietary supplement.

Enerseng *Herbarium, Braz.†*
Ginseng (p. 2513·3).
Asthenia.

Enerstress *Diamond, Philipp.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Enerton *Sanbe, Indon.*
Carbohydrates; with or without minerals and trace elements.
Parenteral nutrition.

Enervit *EMS, Braz.*
Succinic dinitrile (p. 2624·1); vitamin B substances (p. 2102·3); fructose (p. 2068·2).
Nutritional supplement.
Enervit, Ital.
Nutritional supplements.

Enervon 33 *Unilab, Philipp.*
Preparation for enteral nutrition.
Nutritional supplement for young children.

Enervon Bright Brand Kid 4 yrs Up *Unilab, Philipp.*
Nutritional milk supplement for children.

Enervon Drops *General Drug, Philipp.*
Vitamins.

Enervon with E & Zinc *United American, Philipp.*
Vitamins; zinc (p. 2126·1).

Enervon with Ginseng & Vitamin E *United American, Malaysia.*
Ginseng (p. 2513·3); vitamin E (p. 2119·1); vitamin B substances (p. 2102·3).
Dietary supplement.
United American, Singapore.
Ginseng (p. 2513·3); vitamin E (p. 2119·1); vitamin B substances (p. 2102·3).
Tonic.

Enervon HP *Unilab, Philipp.*
Preparation for enteral nutrition.

Enervon Prime *Unilab, Philipp.*
Preparation for enteral nutrition.

Enervon with Vitamin C *United American, Singapore.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Enervon-C *United American, Hong Kong; Medifarma, Indon.; United American, Malaysia; United American, Philipp.†; Great Eastern, Thai.*
Tablets: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin deficiencies; vitamin B and C supplement.
United American, Philipp.
Injection: Vitamin B substances (p. 2102·3); coenzyme A (p. 2483·2); nadide (p. 2567·1); vitamin C (p. 2110·3).
Tonic.
United American, Singapore.
Vitamins.

Enervon-C Plus *United American, Hong Kong; Medifarma, Indon.; United American, Malaysia†; United American, Philipp.†*
Vitamins.
Dietary supplement; tonic.

Enervon-E *United American, Philipp.*
d-Alpha tocopherol (p. 2119·1).
Antioxidant.

Enervon-MV *Great Eastern, Thai.†*
Vitamins; zinc (p. 2126·1).

Enerzal *FDC, India.*
Preparation for enteral nutrition.

Enerzip
Note: this name may be used for preparations of different composition.
Catalent, Philipp.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); choline bitartrate (p. 2055·2); inositol (p. 2533·2).
Globus, India.
Glucose (p. 2068·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Enetege *Fada, Arg.*
Glyceryl trinitrate (p. 1391·2).

Enew *Zydus, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).

Enfacare *Biolink, Philipp.*
Aloe vera (p. 1693·2); zinc oxide (p. 1729·1); melaleuca oil (p. 2551·1); coconut oil (p. 2179·3); shea butter (p. 2208·2).
Nappy rash; skin irritation; burns; wounds.

Enfagrow *Mead Johnson, Indon.*
A range of preparations for enteral nutrition in children.
Mead Johnson Nutritionals, Thai.
Preparation for enteral nutrition.
Dietary supplement for infants.

Enfagrow A+ *Mead Johnson, Hong Kong.*
Preparation for enteral nutrition in infants.
Mead Johnson, Philipp.
Nutritional supplement for children.

Enfagrow Lactose Free *Mead Johnson, Philipp.*
Lactose-free infant feed.
Formerly known as Enfagrow Lactofree.
Lactose intolerance.

Enfakid *Mead Johnson Nutritionals, Thai.*
Preparations for enteral nutrition.
Dietary supplement for children.

Enfakid A+ *Mead Johnson, Hong Kong; Mead Johnson, Indon.*
Preparation for enteral nutrition in children.
Mead Johnson, Philipp.
Nutritional milk supplement for children.

Enfalac A+ AR *Mead Johnson Nutritionals, Thai.*
Infant feed.
Gastro-oesophageal reflux.

Enfalac A+ HA *Mead Johnson Nutritionals, Thai.*
Infant feed.
Cows' milk intolerance.

Enfalac A+ Lactofree *Mead Johnson Nutritionals, Thai.*
Lactose-free infant feed.
Lactose intolerance; sucrose intolerance; galactosaemia.

Enfalac A+ Prosobee *Mead Johnson, Malaysia; Mead Johnson Nutritionals, Thai.*
Infant feed.
Cows' milk intolerance; lactose intolerance; galactosaemia.

Enfalac AR *Mead Johnson, Malaysia; Mead Johnson, Singapore.*
Infant feed.
Gastro-oesophageal reflux.

Enfalac HA *Mead Johnson, Malaysia; Mead Johnson, Singapore.*
Infant feed.

Enfalac Lactofree *Mead Johnson, Philipp.*
Lactose-free infant feed.
Lactose intolerance.

Enfalac LF *Mead Johnson, Malaysia; Mead Johnson, Singapore.*
Lactose-free infant feed.
Lactose intolerance.

Enfalyte *Mead Johnson Nutritionals, Canad.*
Rice syrup; sodium chloride (p. 1795·1); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2); citric acid (p. 2480·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

EnfaMama *Mead Johnson, Indon.*
Nutritional supplement for pregnant and breast-feeding women.
Mead Johnson, Malaysia; Mead Johnson, Philipp.
Nutritional supplement for pregnant and lactating women.
Mead Johnson Nutritionals, Thai.
Preparation for enteral nutrition.
Dietary supplement for pregnant and lactating women.

Enfamil AR *BMS, Arg.; Mead Johnson, Braz.; Mead Johnson, Chile; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Irl.; Mead Johnson, Israel; BMS, Mex.; Mead Johnson Nutritionals, UK; BMS, Venez.*
Infant feed.
Gastro-oesophageal reflux.

Enfamil D-Vi-Sol *Mead Johnson Nutritionals, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Enfamil Fer-In-Sol *Mead Johnson Nutritionals, USA.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemias.

Enfamil HA *Mead Johnson, Fr.; Mead Johnson, Indon.; BMS, Mex.*
Infant feed.
Infants with a family history of allergy.

Enfamil HA Digest *Mead Johnson, Ital.*
Infant feed.
Milk intolerance; family history of allergy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Enfamil Natalins Rx *Mead Johnson Nutritionals, USA.*
Vitamins; minerals.
Formerly known as Natalins Rx.

Enfamil Nutramigen *BMS, Arg.*
Infant feed.
Fructosaemia; galactosaemia; protein sensitivity; diarrhoea.

Enfamil O-Lac *Mead Johnson, Hong Kong; Mead Johnson, Irl.; Mead Johnson, Ital.; Mead Johnson Nutritionals, UK.*
Infant feed.
Lactose intolerance.

Enfamil Poly-Vi-Sol *Mead Johnson, Austral.†*
Vitamins.

Enfamil Pregel *Mead Johnson, Ital.*
Infant feed.
Regurgitation.

Enfamil Pregestimil *BMS, Arg.*
Infant feed.
Diarrhoea; galactosaemia; lactose intolerance; pancreatic insufficiency; protein sensitivity; sucrose intolerance.

Enfamil Prosobee *Mead Johnson, Austral.†*
Infant feed.
Cow's milk intolerance; lactose intolerance; galactosaemia; sucrose intolerance.

Enfamil sin Lactosa *BMS, Arg.; Mead Johnson, Chile; BMS, Mex.*
Infant feed.
Lactose intolerance.

Enfamil Soya *BMS, Arg.; Mead Johnson, Israel.*
Soy-based infant feed.
Cows' milk intolerance; diarrhoea; colic; galactosaemia; gastro-oesophageal reflux; eczema; lactose or sucrose intolerance.

Mead Johnson, Chile; BMS, Mex.
Infant feed.
Cow's-milk intolerance; diarrhoea; lactose intolerance.

Enfapro Lactofree *Mead Johnson, Philipp.*
Lactose-free infant feed.
Lactose intolerance.

Enfapro LF *Mead Johnson, Malaysia†; Mead Johnson, Singapore.*
Lactose-free infant feed.
Lactose intolerance.

EnfaSchool A+ *Mead Johnson, Hong Kong.*
Preparation for enteral nutrition.

Enfavit *Coronet, Indon.*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Enfexia *Bilim, Turk.; Bilim, Ukr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Enfinity *Emcure, India.*
Vitamins; minerals.

Enflucide *Yenisehir, Turk.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Enfluthane *AstraZeneca, Braz.*
Enflurane (p. 1899·3).
General anaesthesia.

Enfluvir *Atabay, Turk.*
Oseltamivir phosphate (p. 1006·2).

Enfol *Ativus, Braz.*
Folic acid (p. 2063·1).

Enforan *Richmond, Arg.*
Enflurane (p. 1899·3).
General anaesthesia.

Enfran *Pisa, Mex.†*
Enflurane (p. 1899·3).
General anaesthesia.

Enfriestop *Gayoso, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

En-Ga-Lax *Omega, Arg.*
Casanthranol (p. 1826·1); bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Engatt *Entod, India.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Engatt-DX *Entod, India.*
⊗Dexamethasone (p. 1630·3); gatifloxacin (p. 303·2).

Engerix-B *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; Litha, S. Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk; GSK, UK; GSK, Ukr.; GSK, USA; GSK, Venez.*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Separate preparations are available for children and for adults.
Active immunisation.

Engestol-Hyd *Farmanic, Gr.*
Codergocrine (p. 389·2).
Peripheral vascular disorders.

Engov *DM, Braz.*
Aspirin (p. 22·2); caffeine (p. 1203·3); mepyramine maleate (p. 635·1).
Aluminium hydroxide (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Headache; motion sickness.

Engran *Taisho, Indon.*
Vitamins; minerals.
Dietary supplement.

Engran-HP *BMS, China.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Engystol *Heel, Austria; Heel, Cz.; Ebi, Switz.; Heel, Ukr.*
Vincetoxicum hirundinaria; sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Canad.
Asclepias vincetoxicum folia; sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Ger.
Vincetoxicum; sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Neth.
Sulfur (p. 1721·1); vincetoxicum officinale.
Homoeopathic preparation.

Engystol N *Heel, S.Afr.*
Vincetoxicum; sulfur (p. 1721·1).
Homoeopathic preparation.

Enhamox *Rhiza, Philipp.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Enhance *Chemech, India.*
Ubidecarenone (p. 2637·1); magnesium oxide (p. 1857·3); selenious acid (p. 2087·1); vitamin E acetate (p. 2119·2); zinc sulfate (p. 2126·2).

Enhance Femme *Chemech, India.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); colecalciferol (p. 2113·1).

Enhance for Men *Golden Glow, Austral.*
⊗Tribulus terrestris (p. 2633·3); epimedium sagittatum; Siberian ginseng (p. 2614·3); turnera diffusa (p. 2491·3); vitamins; zinc amino acid chelate (p. 2048·3); histidine (p. 2072·1).
Dietary supplement for men's sexual health.

Enhancer *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Enhancin *Ranbaxy, Cz.†; Labormed, Hung.; Ranbaxy, Mex.; Ranbaxy, Philipp.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ranbaxy, India; Ranbaxy, Malaysia.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Ranbaxy, Singapore.
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Enhansid *Interhealthcare, Philipp.*
Folic acid (p. 2063·1).
Megaloblastic anaemia.

Enhoş *Kansuk, Turk.*
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Bowel evacuation; constipation.

Eni *Grossman, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Enico *Eisai, Indon.*
Tocoferil nicotinate (p. 1516·1).
Atherosclerosis; circulatory disorders; disorders of fat metabolism.

Enidap *Iasis, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Enidazol *East India Pharma, India.*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis.

Enidin *Allergan, Austral.*
Brimonidine tartrate (p. 2004·3).
Ocular hypertension; glaucoma.

Eniflex Duo *Bago, Chile.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis.

E-Nim Plus *Zota, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

E-Nim-MD *Zota, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Enimon *Farmex, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Enison *IFET (ΙΦΕΤ), Gr.; Stada, Spain.*
Vindesine sulfate (p. 884·2).
Malignant neoplasms.

Enit *Gap, Gr.; Ferrer, Port.; Ferrer, Spain; Adeka, Turk.*
Enalapril maleate (p. 1371·1); nitrendipine (p. 1456·3).
Hypertension.

Enivac-HB *Panacea, India.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Enjomin *Codilab, Port.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea; vomiting; vertigo.

Enjoy *HB, Braz.*
Aspirin (p. 22·2); mepyramine (p. 635·1).
Aluminium hydroxide (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Enjuvia *Duramed, USA.*
Synthetic conjugated estrogens, B (p. 2260·2).
Menopausal disorders.

Enkacetyn *Kimia, Indon.*
Chloramphenicol (p. 257·1).
Skin infections.

Enkacort *Kimia, Indon.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Enkapyrin *Kimia, Indon.*
Phenylbutazone (p. 125·1); propyphenazone (p. 127·3).
Arthritis; neuralgia.

Enkasari *Kimia, Indon.*
Abrus (p. 2426·1); liquorice (p. 1853·2); betel; menthol (p. 2553·2).
Scurvy.

Enlacard *Intra-Labs, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Enlace *Wermar, Mex.*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction.

Enlarge *Universal Medicare, India.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); arginine (p. 2049·1).

Enlive *Abbott, Austral.; Abbott, Fr.; Abbott, Irl.†; Abbott, Mex.; Abbott, USA.*
Preparation for enteral nutrition.

Abbott Nutrition, UK.
A range of products for enteral nutrition.

Enlon *Bioniche, USA.*
Edrophonium chloride (p. 686·1).
Reversal of competitive neuromuscular blockade; differential diagnosis of myasthenia gravis.

Enlon-Plus *Bioniche, USA.*
Edrophonium chloride (p. 686·1).
Atropine sulfate (p. 1310·2) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade; curare antagonist.

Enlow *Lincoln, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Ennamax *Actavis, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Urticaria.

Ennds *Oakhurst, USA.*
Chlorophyllin copper complex sodium (p. 2178·3).

Ennos *Lannacher, Austria.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorders; social phobia; anxiety; post-traumatic stress disorder.

Eno
Note: this name may be used for preparations of different composition.
GSK Consumer, Austral.
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); sodium carbonate (p. 2617·3).
Dyspepsia; heartburn.

GSK Consumer, Canad.
Sodium citrate (p. 1781·2).
Dyspepsia.

GSK, Hong Kong†; GSK Consumer, UK; GSK Consumer, Venez.
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); sodium carbonate anhydrous (p. 2617·3).
Dyspepsia; flatulence; nausea; gastric hyperacidity.

SmithKline Beecham, Gr.
Tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1).

GSK Consumer, Port.†
Citric acid (p. 2480·3); sodium carbonate (p. 2617·3).

Enocet-LV *Zenon, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Enodine-S *Emcure, India.*
Povidone-iodine (p. 1767·1).

Enofosforina Vigor *Serra Pamies, Spain.†*
⊗Calcium lactophosphate (p. 1783·1); magnesium glycerophosphate (p. 1787·2); kola (p. 2648·2); pyridoxine (p. 2105·3); sodium glycerophosphate (p. 2519·2); potassium glycerophosphate (p. 2519·2); nicotinamide (p. 2083·1); glycerol (p. 2517·2); manganese glycerophosphate (p. 2519·2).
Tonic.

Enoksetin *Eczacibasi, Turk.*
Enoxacin (p. 290·2).
Bacterial infections.

Enolol *Charoon Bhesaj, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; angina pectoris; myocardial infarction.

Enoparin *Vivax, Venez.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; unstable angina; prevention of clotting during extracorporeal circulation.

Enorden *Finadiet, Arg.*
Amisulpride (p. 1036·3).
Psychoses.

Enore *Pfizer, Neth.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Enorep *Alapis, Gr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

E-Norm *Zytras, India.*
⊗Chlorphenamine (p. 620·3); naphazoline (p. 1669·3); sodium chloride (p. 1795·1); zinc (p. 2126·1).

Enouvim *Pharmacare, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2).

Enouvim OB *Pharmacare, Philipp.*
Vitamins; minerals.

Enoval *Novag, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Enoxalow *Blausiegel, Braz.*
Enoxaparin sodium (p. 1372·3).
Prevention of clotting during haemodialysis.

Enoxarin *Zuventus, India.*
Enoxaparin (p. 1372·3).
Thromboembolic disorders; prevention of coagulation during haemodialysis; unstable angina.

Enoxdowm *Dosa, Arg.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders.

Enoxen *SF, Ital.*
Enoxacin (p. 290·2).
Bacterial infections.

Enoxin
Note: this name may be used for preparations of different composition.
CCM, Hong Kong; CCM, Malaysia.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Upha, Singapore; Charoon Bhesaj, Thai.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Enoxor *Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pharmafabre, Gr.*
Enoxacin (p. 290·2).
Bacterial infections.

Enper *Elea, Arg.†*
Zidovudine (p. 1024·2).
HIV infection.

Enpicortyn *Nicholas, Indon.*
⊗Tetracycline hydrochloride (p. 373·2); hydrocortisone (p. 1640·1).
Infected eye disorders.

Enpir *Synmedic, India.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

En-Por *Polychronus, Gr.*
Alendronate sodium (p. 1171·3).

Enpott *Ranbaxy, Thai.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Enpresse *Barr, USA.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Enpril *Wockhardt, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Enprin *Galpharm, UK.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Enractin *Molekule, India.*
⊗Bromelains (p. 2460·3); rutoside (p. 2505·3); trypsin (p. 2635·2).

Enrich *Abbott, Fr.†; Abbott, Irl.†; Abbott, S.Afr.†; Abbott, Turk.; Abbott Nutrition, UK.*
Preparation for enteral nutrition.

Enriqa *Jenapharm, Ger.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Enromic *Microsules, Arg.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Enron-M *Virgo, Philipp.*
Ammonium chloride (p. 1656·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough.

Ensaid *Charoon Bhesaj, Thai.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Ensamycin *Fulford, India.*
Sisomicin or sisomicin sulfate (p. 357·2).

Ensera *Bombay Tablet, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Enshake *Abbott, UK.*
Preparation for enteral nutrition.

Ensial *Adipharm, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Ensibest *Best, Mex.*
Prazosin hydrochloride (p. 1473·3).
Heart failure; hypertension; frostbite; Raynaud's syndrome; intermittent claudication.

Ensini *Nutricia, Ital.*
Preparation for enteral nutrition.

Ensuite *Deb, Canad.*
Chloroxylenol (p. 1748·2); triclosan (p. 1773·2).

Ensulate *Servocare, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ensules *Macleods, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Ensules Plus *Macleods, India.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Ensure *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Cz.; Abbott, Fr.; Abbott, Hong Kong; Abbott, Indon.; Abbott, Israel; Abbott, Mex.; Abbott, Philipp.; Abbott Nutrition, Singapore; Abbott, Turk.; Abbott, Venez.*
A range of preparations for enteral nutrition.

Abbott, Canad.; Abbott, Chile; Abbott, Irl.; Abbott, NZ.
Preparations for enteral nutrition.

Abbott, China.
A preparation for enteral nutrition.

Abbott, India; Abbott, Malaysia; Abbott, S.Afr.; Abbott, Thai.; Abbott Nutrition, UK.
Preparation for enteral nutrition.

Ross, USA.
A range of lactose-free preparations for enteral nutrition.

Ensure Plus *Abbott, Irl.*
High calorie preparations for enteral nutrition.

Abbott, Ital.; Abbott Nutrition, UK.
High calorie preparation for enteral nutrition.

Abbott Nutrition, Singapore.
High-calorie preparation for enteral nutrition.

Ensure TwoCal *Abbott, Ital.*
Preparation for enteral nutrition.

ENT
Note: this name may be used for preparations of different composition.
Restan, S.Afr.
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline nitrate (p. 1669·3).
Nasal congestion.

Entac *Elin, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer; acid aspiration.

Neon, India.
Ranitidine (p. 1882·1),.
Peptic ulcer; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Entacom *Intas, India.*
Entacapone (p. 901·2).
Parkinsonism.

Entact *Paranova, Denm.; Lundbeck, Gr.; Recordati, Ital.; Lundbeck, Spain.†*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Entagene *Cadila, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); carmellose sodium (p. 2175·2).

Entakon-M *KonTest, India.*
Metronidazole (p. 936·1); tetracycline hydrochloride (p. 373·2).

Entalgic *Thebe, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Entamizole *Abbott, India.†*
Diloxanide furoate (p. 931·2); metronidazole (p. 936·1).
Amoebiasis; giardiasis.

Entamizole Plus *Abbott, India.*
Ornidazole (p. 943·1).
Amoebiasis; giardiasis; trichomoniasis.

Entamizole TN *Abbott, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Entarkin *Sigma, Braz.*
Entacapone (p. 901·2).

Entasid *Cadila, India.*
Chewable tablets: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); almasilate (p. 1815·3).

Cadila, India.
Oral suspension: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Entecet *Nutergia, Fr.*
Hordeum sativum germ; enzymes derived from aspergillus including amylase and protease; lipase derived from rhizopus.
Dyspepsia.

Entera *Fresenius Kabi, Mex.*
Preparation for enteral nutrition.

Enteral
Note: this name may be used for preparations of different composition.
Vargas, Venez.
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Enteraproct *Crinos, Ital.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Enterasin *Crinos, Ital.*
Mesalazine (p. 1859·2).
Ulcerative colitis; Crohn's disease.

Entereg *GSK, USA.*
Alvimopan (p. 1819·2).
Postoperative ileus.

Enterex *Lafi, Chile.*
Preparations for enteral nutrition.

Pisa, Mex.
Preparation for enteral nutrition.

Victus, Venez.
A range of preparations for enteral nutrition.

Enterin *Farmedia, Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Entermid *Nakornpatana, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Entero Micinovo *Bago, Chile.*
Co-trimoxazole (p. 277·3); attapulgite (p. 1820·1).
Diarrhoea.

Entero VU *Temis, Arg.; E-Z-EM, Israel; E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Enterobacilli *Proge, Ital.*
Lactobacillus paracasei (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3); vitamins.
Disturbances of the intestinal flora.

Enterobacticel
Note: this name may be used for preparations of different composition.
Bago, Arg.
Co-trimoxazole (p. 277·3); attapulgite (p. 1820·1).
Diarrhoea.

Enterobene *Ratiopharm, Austria; Ratiopharm, Hung.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Enterocin Compound *Synco, Hong Kong.†*
Furazolidone (p. 933·3); neomycin sulfate (p. 330·1); pectin (p. 2200·3); attapulgite (p. 1820·1); papaverine hydrochloride (p. 2362·3).
Diarrhoea; gastrointestinal infections.

Enterocind *DHU, Ukr.*
Chamomilla (p. 2474·1); cina (p. 2478·3); colocynthis (p. 1833·3); lac defloratum; magnesium chloratum (p. 1787·1).
Homoeopathic preparation.

Enterodes *Moschimfarm, Rus.*
Povidone (p. 2204·3).
Toxaemia.

Entero-Diyod *Serral, Mex.*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis; trichomoniasis; giardiasis; shigellosis.

Enterodyne *Adcock Ingram, S.Afr.†*
⊗Bismuth carbonate (p. 1822·1); calcium carbonate (p. 1824·3); chloroform and morphine tincture (p. 92·3); aromatic ammonia liquid (p. 2441·2); nutmeg oil (p. 2573·2); clove oil (p. 2481·3); cardamom tincture (p. 2471·1); catechu tincture (p. 2472·3); conc. cinnamon water; cinnamon oil (p. 2479·3).
Gastrointestinal disorders.

Enterofactors *Natural Factors, Canad.*
Vitamins; minerals.

Enterofigon *Hertz, Braz.*
Adenosine (p. 1291·1); betaine (p. 2456·1); choline (p. 2055·2); methionine (p. 1558·2).
Liver disorders.

Enteroflox *Dey's, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Enteroflox-T *Dey's, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Enterofuran-M *Dey's, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Enterofuril *Bosnalijek, Ukr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Enterofuryl *Bosnalek, Rus.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Entero-Gastreu R4 *Reckeweg, Neth.*
Chamomilla (p. 2474·1); colocynthis (p. 1833·3); mercurius corrosivus (p. 2555·2); oleander (p. 2574·3); rhus toxicodendron (p. 2603·3); veratrum album (p. 2644·3); phosphoricum acidum (p. 2589·1).
Homoeopathic preparation.

Entero-Gastreu S R4 *Reckeweg, Ger.*
Colocynthis (p. 1833·3); merc. subl. corr. (p. 2555·2); veratrum alb. (p. 2644·3); acidum phosphoricum (p. 2589·1); chamomilla (p. 2474·1).
Homoeopathic preparation.

Enterogermina *Sanofi-Aventis, India; Sanofi-Aventis, Mex.*
Bacillus clausii spores.
Maintenance of gastrointestinal flora.

Sanofi-Aventis OTC, Ital.
Spores of *Bacillus subtilis.*
Gastrointestinal disorders.

Enterogit *Soho, Indon.†*
Activated attapulgite (p. 1820·1).
Diarrhoea.

Enteroguanidine *David, India.*
Diiodohydroxyquinoline (p. 931·1); sulfaguanidine (p. 364·3).

Enterokan *Farmasa, Mex.; Schwabe, Singapore.*
Peppermint oil (p. 1877·1); caraway oil (p. 2470·3).
Gastrointestinal disorders; dyspepsia; irritable bowel syndrome.

Enterokinasum Compose *Boiron, Fr.*
Muqueuse gastrique; muqueuse intestinale (p. 2444·1); enterokinasum; pancreine.
Homoeopathic preparation.

Enterol
Note: this name may be used for preparations of different composition.
Biocodex, Belg.; Biocodex, Cz.; Biocodex, Hung.; Biocodex, Pol.; Biocodex, Rus.; Biocodex, Ukr.
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; antibiotic-associated colitis; restoration of gastrointestinal flora.

Sanitas, Chile.†
Phthalylsulfacetamide (p. 339·2); activated attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Enterol Con Nifuroxacida *Sanitas, Chile.*
Phthalylsulfacetamide (p. 339·2); nifuroxazide (p. 331·3).
Gastrointestinal sterilisation; gastrointestinal infections.

Enterolactis *Sofar, Ital.*
Lactobacillus casei (p. 2596·3); vitamin B substances (p. 2102·3).
Restoration of gastrointestinal flora.

Enterolactis Duo *Sofar, Ital.*
Lactobacillus casei (p. 2596·3); inulin (p. 2534·3).
Restoration of intestinal flora.

Enterolyte *Adcock Ingram, S.Afr.*
Kaolin (p. 1850·1); pectin (p. 2200·3); sodium lactate (p. 1781·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Diarrhoea.

Enteromicin *Silanes, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Enteromicina *Confar, Port.*
Neomycin sulfate (p. 330·1).
Gastro-enteritis.

Enteromycetin *Dey's, India.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Enteromycetin Otic *Dey's, India.*
Chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Otitis externa.

Enteromyk *Elvipe, Gr.*
Phthalylsulfathiazole (p. 339·3); kaolin (p. 1850·1); neomycin sulfate (p. 330·1).

Entéropathyl *Merck Medication Familiale, Fr.†*
Sulfaguanidine (p. 364·3).
Diarrhoea.

Enteroplant *Spitzner, Ger.; Schwabe, Hung.†*
Peppermint oil (p. 1877·1); caraway oil (p. 2470·3).
Dyspepsia; gastrointestinal disorders.

Enteropride *Janssen-Cilag, Mex.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Enteroprin *Metro, Philipp.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Enteroquinol *East India Pharma, India.*
Clioquinol (p. 273·1).
Formerly known as Entero-Quinol.
Amoebic dysentery.

Enteroseven *Federfarma, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins; minerals; inulin (p. 2534·3).
Nutritional supplement; disturbances of the intestinal flora.

Enterosgel *Kreoma-Farm, Ukr.*
Methysilicic acid hydrogel.
Kidney disorders; liver disorders; gastro-intestinal disorders; alcoholic and narcotic intoxication; allergic skin disorders; burns; toxaemia.

Sigma, Rus.
Polycondensation product of 1,1,3,3-tetrahydroxy-1,3-dimethyldisiloxane polyhydrate.
Poisoning; gastrointestinal infections; food and drug hypersensitivity; hyperbilirubinaemia; hyperazotaemia.

Enterosilicona *Estedi, Spain.*
Dimeticone (p. 1886·2).
Flatulence; infant colic; meteorism.

Enterosol *Phytofarm Kleka, Pol.*
Achillea (p. 2427·3); greater celandine (p. 2522·2); oak bark (p. 2574·1); salix purpurea (p. 129·2); sage (p. 2608·3); thyme (p. 2630·2); artemisia abrotanum.
Gastrointestinal disorders.

Enterostop *Teofarma, Ital.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Gastrointestinal infections.

Enterosulfa *Elvipe, Gr.*
Phthalylsulfathiazole (p. 339·3).

Entero-Teknosal *Sophien, Ger.*
Colloidal silicon dioxide (p. 2209·1).
Diarrhoea.

Enter-Out *Medimar, Gr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1); phosphoric acid (p. 2589·1).

Enterovu *Therapex, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Enter-Sal *Nevzat, Turk.*
Sodium salicylate (p. 132·2).
Fever; pain.

Entertainer's Secret *KU, USA.*
⊗Aloe vera (p. 1693·2); carmellose sodium (p. 2175·2); glycerol (p. 2517·2).
Formerly known as Mai-Stir 10.
Throat discomfort.

Enterum *Angelini, Ital.†*
Spores of *Bacillus subtilis.*
Gastrointestinal disorders.

Entex *Purdue, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract congestion.

WraSer, USA.
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Nasal congestion; coughs and cold symptoms.

Entex HC *Athlon, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Entex LA *Andrx, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Entex PAC *WraSer, USA.*
⊗Entex T tablets, pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); Entex S oral liquid, dextromethorphan hydrobromide (p. 1660·1).
Cough.

Entex PSE *Athlon, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs; nasal congestion.

Enthusia *Lupin, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Entia *Teva, Mex.; Teva, Thai.*
Oxaliplatin (p. 838·1).
Malignant neoplasms; colon cancer.

Entianthe *Rafarm, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Entimin *Alde Medi Impex, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Entir *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Entizol *Polpharma, Cz.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Entoban *Herbion, Rus.*
Hollarrhena antidysenterica; myrtle (p. 2566·3); Indian barberry (p. 2532·1); aegle marmelos; oak; butea frondosa.
Diarrhoea.

Herbion, Ukr.
Holarrhena antidysenterica; myrtle (p. 2566·3); Indian barberry (p. 2532·1); aegle marmelos; gall (p. 2508·3); butea frondosa.
Amoebiasis; bacillary dysentery; gastro-intestinal bacterial infections.

Entocir *AstraZeneca, Ital.*
⊗Budesonide (p. 1625·1).
Crohn's disease.

Entocord *Orifarm, Denm.; AstraZeneca, S.Afr.; AstraZeneca, Spain.*
⊗Budesonide (p. 1625·1).
Inflammatory bowel disease.

Entocort *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
⊗Budesonide (p. 1625·1).
Inflammatory bowel disease.

Entodiba *Diba, Mex.†*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Entof DPS *Dey's, India.*
Ofloxacin (p. 334·3).
Bacterial conjunctivitis; corneal ulcer; ear infections.

Entofoam *Cipla, India.*
⊗Hydrocortisone acetate (p. 1640·1).

Entom Nature *Dynacren, Ital.*
Geranium oil (p. 2512·2).
Insect repellent.

Entonox *Linde, Canad.; AGA, Cz.; Linde, Fr.; BOC, Irl.; AGA, Pol.; Afrox, S.Afr.; AGA, Spain; PanGas, Switz.; BOC, UK.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Pain; obstructive airways disease.

Entoplus *Diba, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Entosec *Cipla, India.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis.

Entosorbine-N *Bayer, Neth.*
Albumin tannate (p. 1815·1).
Diarrhoea.

Entox Plus *Forgo, India.*
Vitamins; minerals; *Lactobacillus sporogenes* (p. 2596·3).

Entox-P *Wyeth-Ayerst, Thai.*
Activated attapulgite (p. 1820·1).
Diarrhoea.

Entozyme
Note: this name may be used for preparations of different composition.
Biophar, India.
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

ENTP *Taurus, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

ENTP-A *Taurus, India.*
Amlodipine besilate (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Entrap *Tempo Scan Pacific, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement.

Entrarin *Asian Pharm, Thai.*
Aspirin (p. 22·2).
Pain; fever; inflammation.

Entrasol *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition.

Entre-Cough *Acella, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Entre-Hist PSE *Acella, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).

Entressdruppels HM *SA Druggists, S.Afr.*
Asafetida tincture (p. 2449·3); valerian (p. 2640·2); cassia bark (p. 2471·3); nutmeg (p. 2573·1); lavender oil (p. 2541·1); rosemary oil (p. 2607·3).
Nervous disorders; insomnia; flatulence.

Entrition *Clintec, USA.*
A range of lactose-free preparations for enteral nutrition.

Entrizen *MSD, Neth.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; left-ventricular hypertrophy.

Entrizen/HCT *MSD, Neth.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Entrobar *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Entrocalm *Galpharm, UK.*
Tablets: Kaolin (p. 1850·1).
Diarrhoea.

Galpharm, UK.
Capsules: Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Entrocalm Replace *Galpharm, UK.*
Glucose monohydrate (p. 2069·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); citric acid (p. 2480·3) (p. 1780·1).
Oral rehydration therapy.

Entrocel
Note: this name may be used for preparations of different composition.
Mallinckrodt, USA.†
Hypromellose (p. 2189·2).
Adjunct in gastrointestinal radiography.
Tyco, Canad.†
Methylcellulose (p. 2197·3).

Entrodiar *Medikon, Indon.†*
Psidium guajava; turmeric (p. 2218·1); catechu (p. 2472·3); coptis chinensis.
Diarrhoea.

Entroease *Tyco, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Entrogard *Mugi, Indon.*
Attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Entrolate *Stadmed, India.*
Tinidazole (p. 949·2); diloxanide furoate (p. 931·2).
Amoebiasis.

Entrolax *Galpharm, UK.*
Bisacodyl (p. 1821·1).
Constipation.

Entron *Ethica, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Entrop *Olainfarm, Ukr.*
⊗Fonturacetam (p. 391·3).
Cerebrovascular disorders; mental function impairment.

Entrophen *Pendopharm, Canad.*
Aspirin (p. 22·2).
Musculoskeletal and joint disorders; pain; fever; transient ischaemic attacks; myocardial infarction.

Entrops *J & J DeChane, India.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2).

Entrostat *Dalmia, India.*
Indian barberry (p. 2532·1); cyperus rotundus; zingiber officinale.

Entrox-P *Osmed, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Entrozyme *Stadmed, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Entrozyme Plain *Stadmed, India.*
Clioquinol (p. 273·1).
Amoebic dysentery.

Entrozyme-M *Stadmed, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Entrydil *Orion, Irl.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Entschlackender Abführtee EF-EM-ES *Smetana, Austria.*
Senna (p. 1885·1); equisetum (p. 2500·1); sambucus (p. 2609·3); delphinium consolida.
Constipation.

Entschlackungstee N *Abtswinder, Canad.†*
Betula (p. 2457·3); fennel (p. 2503·2); solidago (p. 2620·1); ononis (p. 2575·3).

ENTsol *Bradley, Singapore.†*
Sodium chloride (p. 1795·1); monobasic potassium phosphate (p. 1790·3); dibasic sodium phosphate (p. 1791·2).
Nasal congestion; throat disorders.

Entsol *PharmaDerm, USA.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal dryness.

Entubate *Piramal, India.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Entumin *Novartis, Israel; Novartis, Ital.*
Clotiapine (p. 1057·1).
Alcohol withdrawal syndrome; anxiety; bipolar disorder; schizophrenia; restlessness; psychoses.

Entumine *Gebro, Switz.*
Clotiapine (p. 1057·1).
Psychoses; anxiety disorders; alcohol withdrawal syndrome; hyperactivity; sleep disorders.

Enturen *Medivis, Ital.*
Sulfinpyrazone (p. 608·3).
Thromboembolic disorders.

Entus *Aflofarm, Pol.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Entuss Expectorant *Hauck, USA; Roberts, USA.*
Oral liquid: Oral liquid: Hydrocodone tartrate (p. 67·2); sulfogaiacol (p. 1678·1).
Coughs.

Hauck, USA; Roberts, USA.
Tablets: Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Coughs.

Entuss-D *Roberts, USA.*
Tablets: ⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Roberts, USA.
Liquid: ⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Entuss-D Jr *Roberts, USA.*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Entwasserungstee *Abtswinder, Canad.†*
Betula alba (p. 2457·3); bearberry (p. 2453·2).

Entzündungstropfen *Heel, Ger.*
Echinacea angustifolia (p. 2498·1); lachesis (p. 2538·3); thuja (p. 2629·3); natrium carbonicum (p. 2617·3); plantago major (p. 2592·3); hepar sulfuris (p. 1721·3); belladonna (p. 2453·3); phytolacca (p. 2593·2); acidum arsenicosum (p. 2448·1); argentum nitricum (p. 2615·3); bryonia (p. 2461·3); rhus toxicodendron (p. 2603·3); chamomilla (p. 2474·1); pulsatilla (p. 2600·2); mercurius praecipitatus ruber (p. 2555·3).
Homoeopathic preparation.

Enuclene *Alcon, Canad.; Alcon, NZ; Alcon, USA.*
Tyloxapol (p. 2218·2).
Lubrication, cleaning, and wetting of artificial eyes.

Enuff *Hetero, India.*
Racecadotril (p. 1881·3).

Enuff Xtra *Hetero, India.*
Racecadotril (p. 1881·3); lactobacillus (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3).

Enulid *Rottapharm, Ital.*
⊗Moexipril hydrochloride (p. 1440·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Enulite *Holland Pharma, Neth.*
Alumina (p. 1690·3); arsenicum album (p. 2448·1); berberis vulgaris (p. 2502·1); causticum (p. 2595·3); equisetum hyemale; hypericum perforatum (p. 449·1); plantago major (p. 2592·3); rhus toxicodendron (p. 2603·3); teribinthinae oleum (p. 2636·3).
Homoeopathic preparation.

Enulose *Barre-National, USA.*
Lactulose (p. 1850·3).
Hepatic encephalopathy.

EnurAid *Hylands, Canad.*
Apis mellifica (p. 2445·2); allium cepa (p. 2575·2); arnica montana (p. 2447·2); belladonna (p. 2453·3); cantharis (p. 2469·2); rhus aromatica (p. 2603·3); equisetum hyem.
Homoeopathic preparation.

Enuran *Biochimico, Braz.*
Enflurane (p. 1899·3).

Enurev *Novartis, Neth.*
Glycopyrronium bromide (p. 2519·3).
Obstructive airways disease.

Enuroplant N *DHU, Ger.*
Plantago major (p. 2592·3); equisetum arv. (p. 2500·1); belladonna (p. 2453·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Enuton *Lyron, Switz.†*
Ginseng (p. 2513·3); kola (p. 2648·2); cinchona (p. 2478·3).
Mental function impairment; tonic.

Env *Haledew, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Envacar *Pfizer, Philipp.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; angina pectoris; cardiovascular risk reduction.

Envas *Cadila, India; Cadila, Rus.; Akacia, S.Afr.; Cadila, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Envas-H *Cadila, India.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Envas-RB *Cadila, India.*
Enalapril maleate (p. 1371·1); losartan potassium (p. 1422·2).

Envelaf *Alkem, India.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Enviage *Novartis, Cz.†; Novartis, Irl.†; Novartis, Neth.†*
Aliskiren fumarate (p. 1295·3).
Hypertension.

Novartis, Gr.†; Novartis, Port.†
Aliskiren (p. 1295·3).
Hypertension.

Envios *Nufarindo, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Enviro-Stress *Vitaline, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals.

Envit Q_{10} *Polfa Pabianice, Pol.†*
Ubidecarenone (p. 2637·1).
Cardiovascular disorders; chronic fatigue syndrome; coenzyme Q10 deficiency.

Enxak
Note: this name may be used for preparations of different composition.
Cazi, Braz.
Dihydroergotamine mesilate (p. 672·2); dipyrone (p. 53·3); caffeine (p. 1203·3).
Migraine.

Enxamed *Cimed, Braz.†*
Feverfew (p. 676·1).

Enyglid *KRKA, Cz.; KRKA, Ger.; TAD, Ger.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Enystin *Kalbe, Indon.*
Nystatin (p. 590·3).
Oral candidiasis.

Enzaprost *Chinoin, Pol.*
Dinoprost trometamol (p. 2133·3).
Termination of pregnancy; uterine evacuation.

Faran, Gr.
Dinoprost (p. 2133·3).
Termination of pregnancy.

Enzaprost F *Chinoin, China; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.*
Dinoprost (p. 2133·3).
Termination of pregnancy; labour induction; uterine evacuation.

Enzar *Elder, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Enzar Forte *Elder, India.*
⊗Pancreatin (p. 2579·3); sodium tauroglycocholate.

Enzar-HS *Elder, India.*
⊗Pancreatin (p. 2579·3).

Enzastar *LKM, Arg.*
Pemetrexed disodium (p. 844·3).
Malignant neoplasms.

Enzian Anaemodoron Drops *Weleda, S.Afr.†*
Honey (p. 2072·1); gentian (p. 2512·1); fragaria vesca; urtica (p. 2639·3).
Anaemias; tonic.

Enzibene *Ratiopharm, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Enzicoba *Farmasa, Braz.*
Cobamamide (p. 2107·2).
Tonic; reduced appetite.

Enzide *Cadila, India.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Enziflur *Bros, Gr.*
⊗Serrapeptase (p. 2613·3).
Inflammatory disorders.

Enzimten *Bernofarm, Indon.*
Ubidecarenone (p. 2637·1).
Dietary supplement.

Enzira *CSL Biotherapies, Irl.; Pfizer, UK.*
An influenza vaccine (split viron) (p. 2393·3).
Active immunisation.

Enzix *Hemofarm, Rus.; Hemofarm, Ukr.*
⊗Tablets, enalapril maleate (p. 1371·1); tablets, indapamide (p. 1409·2).
Hypertension.

Enzodrot *Enzo, India.*
Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Enzofast *Invision, India.*
Capsules: ⊗Vitamin B substances (p. 2102·3); amylase (p. 2442·1); *Lactobacillus sporogenes* (p. 2596·3); papain (p. 2582·3); simeticone (p. 1886·2).

Invision, India.
Syrup: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Enzofer-TR *Intra-Labs, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin C (p. 2110·3).
Iron deficiency in pregnancy.

Enzoflam *Alkem, India.*
Tablets: ⊗Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Alkem, India.
Topical gel: Diclofenac (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Enzolact *Uni-Sankyo, India.*
⊗Activated charcoal (p. 1537·3); *Lactobacillus sporogenes* (p. 2596·3); pancreatin (p. 2579·3).

Enzone *UAD, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine (p. 1993·3).

Enzovexx *Zuventus, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Enzovit *Ethix, India.*
⊗Bile (p. 2457·2); hemicellulase (p. 2473·1); pancreatin (p. 2579·3); simeticone (p. 1886·2).

Enzoxid *Zyg, Thai.*
Benzoyl peroxide (p. 1696·1).
Acne.

Enzybar *Techsphere, Arg.*
⊗High-calorie food with pancreatin (p. 2579·3).
Dietary supplement.

Enzylac Ultra *Assper, Mex.*
Tilactase (p. 2631·2).
Lactose intolerance.

Enzym Comp *Hevert, Ger.*
Dimeticone (p. 1886·2); pancreas extract (p. 2444·1).
Digestive disorders.

Enzymatic Cleaner *Alcon, USA.†*
⊗Pancreatin (p. 2579·3).
Cleansing solution for soft contact lenses.

Enzyme *GNLD, Austral.*
⊗Pancreatin (p. 2579·3); pepsin (p. 2586·1); ox bile (p. 2457·2); papain (p. 2582·3); amylase (p. 2442·1).
Digestive disorders.

Nature's Bounty, USA.
Amylase (p. 2442·1); cellulase (p. 2473·1); lipase (p. 2579·3); protease (p. 2598·1).
Gastrointestinal disorders.

Enzyme Co *Christo, Hong Kong.†*
⊗Amylase (p. 2442·1); pancreatin (p. 2579·3); papain (p. 2582·3); pepsin (p. 2586·1).

Enzyme Digest *Quest, Malaysia; Quest, UK.*
⊗Betaine hydrochloride (p. 2456·1); papain (p. 2582·3); bromelain (p. 2460·3); amylase (p. 2442·1); lipase (p. 2579·3); peppermint oil (p. 1877·1).
Digestive disorders.

Enzyme Plus *Lifeplan, UK.*
⊗Betaine hydrochloride (p. 2456·1); amylase (p. 2442·1); pepsin (p. 2586·1); lipase (p. 2579·3).
Dietary supplement.

Enzymet *Ranbaxy, Thai.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive system disorders; flatulence.

Enzymfort *Kimia, Indon.*
⊗Pancreatin (p. 2579·3); vitamin B substances (p. 2102·3); bile extract (p. 2457·2).
Digestive disorders.

Enzym-Harongan *Schwabe, Ger.*
Haronga; Javanese turmeric (p. 2636·2); pancreas (p. 2444·1).
Digestive system disorders.

Enzymicine *Zizine, Fr.*
Neomycin sulfate (p. 330·1); benzocaine (p. 1980·2).
Dental disorders.

Enzym-Lefax *Bayer, Ger.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive system disorders.

Enzynorm *Pharmaselect, Austria.*
Gastric mucous membrane extract (p. 2444·1).
Gastrointestinal disorders.

Enzynorm f *Nordix, Ger.; Nordmark, Ger.*
Gastric mucous membrane extract (p. 2444·1); amino acids.
Gastrointestinal disorders.

Enzyplex *Westmont, Hong Kong; Medifarma, Indon.; Westmont, Malaysia†; Westmont, Singapore.*
Amylase (p. 2442·1); protease (p. 2598·1); lipase (p. 2579·3); deoxycholic acid (p. 2457·2); dimeticone (p. 1886·2); vitamin B substances (p. 2102·3).
Digestive disorders.

Great Eastern, Thai.†
Rizolipase; amylase (p. 2442·1); protease (p. 2598·1); deoxycholic acid (p. 2457·2); simeticone (p. 1886·2); vitamin B substances (p. 2102·3).
Digestive system disorders with excess gas.

Enzystal *Torrent, Rus.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders.

Enzytel *Intel, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Eofil *Fourrts, India.*
Diethylcarbamazine.
Filariasis; loiasis; toxocariasis.

Eofil Forte *Fourrts, India.*
Chlorphenamine maleate (p. 620·3); diethylcarbamazine.

Eogem *Innopharm, Philipp.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

E-Oil *Nature's Bounty, USA.*
Vitamin E (p. 2119·1).
Vitamin E supplement; skin disorders.

Eolan *Pharmex (Φαρμεξ), Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Eolus *Sigma-Tau, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

E-On *Zota, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Eonic *Gedeon Richter, Cz.; Richter, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Eopon *Pharmex (Φαρμεξ), Gr.*
Etidronate disodium (p. 1182·3).

Eoroxime *Zee, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Eos *Investi, Arg.*
Drospirenone (p. 2269·1); estradiol (p. 2271·1).
Menopausal disorders.

Eostar *Gerot, Austria.†*
Citalopram hydrobromide (p. 411·1).
Depression; anxiety; panic disorder; obsessive-compulsive disorder.

Eovist *Bayer, USA.*
Sodium gadoxetate (p. 1588·1).
Contrast medium for magnetic resonance imaging of the liver.

Eox *Antula, Swed.†*
Naproxen sodium (p. 98·2).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Eoxin *CT, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

EP Mycin *ADP, Philipp.; Boryung, Thai.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

E.P. Mycin *Integra, Philipp.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epabe *Remedina, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Epacaps *Takeda, Switz.*
Marine fish oil (p. 1460·3).
Nutritional supplement; hyperlipidaemias.

Epadel *Mochida, Jpn.*
Eicosapentaenoic acid ethyl ester (p. 1460·2).
Arteriosclerosis obliterans; hyperlipidaemias.

Epaderm *Molnlycke, Austral.; Medlock Medical, UK.*
Yellow soft paraffin (p. 2212·1); emulsifying wax (p. 2184·1); liquid paraffin (p. 2191·2).
Dry skin.

Molnlycke, Austral.
Cream: Yellow soft paraffin (p. 2212·1); white soft paraffin (p. 2211·3); emulsifying wax (p. 2184·1).
Dry skin.

Epadoc *Faran, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Epadoren *Demo, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Epahol *Remedina, Gr.*
Co-trimoxazole (p. 277·3).

Epalat EPS *OFF, Ital.†*
Lactulose (p. 1850·3).
Liver disorders.

Epalfen *Zambon, Ital.; Zambon, Neth.†*
Lactulose (p. 1850·3).
Hepatic encephalopathy; liver cirrhosis; constipation.

Epamin *Elea, Arg.; Pfizer, Mex.; Pfizer, Venez.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; migraine; trigeminal neuralgia; psychoses; arrhythmias; digitalis toxicity; myocardial infarction; seizures associated with neurosurgery.

Pfizer, Chile.
Phenytoin sodium (p. 538·2).
Arrhythmias; epilepsy; seizures associated with neurosurgery.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Epaned *Silvergate, USA.*
Enalapril maleate (p. 1371·1).
Hypertension.

Epanutin *Pfizer, Austria; Pfizer, Belg.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Pol.; Pfizer, S.Afr.; Pfizer, UK.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; non-epileptic convulsions; arrhythmias; trigeminal neuralgia; status epilepticus; seizures associated with neurosurgery or head injury.

Pfizer, C.z.; Pfizer, Hung.; Pfizer, Israel; Pfizer, Neth.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Turk.
Phenytoin sodium (p. 538·2).
Epilepsy; seizures associated with neurosurgery; neuralgias; arrhythmias; status epilepticus; trigeminal neuralgia.

Epaq
Note: this name may be used for preparations of different composition.
Graceway, Mex.
Metronidazole (p. 936·1).
Vaginitis.

Arrow, Austral.†; Ivax, Ger.†
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

E-Par *Zota, India.*
Diclofenac sodium (p. 48·3).
Pain.

Eparema *Nycomed, Braz.; SIT, Ital.*
Cascara (p. 1826·1); boldo (p. 2458·3); rhubarb (p. 1884·2).
Liver disorders; constipation.

Eparema-Levul *SIT, Ital.*
Cascara (p. 1826·1); boldo (p. 2458·3); rhubarb (p. 1884·2); fructose (p. 2068·2).
Constipation.

Epargriseovit *Pfizer, Ital.; Deva, Turk.*
Vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); nicotinamide (p. 2083·1); vitamin C (p. 2110·3).
Anaemias; peripheral neuropathies; tonic.

Eparinlider *Scharper, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Eparinovis *INTES, Ital.*
Heparin sodium (p. 1396·3).
Eye disorders.

Eparmefolin *Bracco, Ital.*
Cyanocobalamin (p. 2107·2); calcium folinate (p. 2066·3).
Folate and vitamin B_{12} deficiency.

Eparven *Pantafarm, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Epasan *Biospray, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Epasan Omega 3 *Maver, Chile.*
Marine fish oils (p. 1460·3).
Dietary supplement; hyperlipidaemias.

Epasel *Sinnex, Hung.*
Fish oil (p. 1460·3); selenium yeast (p. 2125·2).
Cardiovascular risk reduction.

Epasterol *Argenfarma, Arg.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); linoleic acid (p. 2509·2); linolenic acid (p. 1460·2).
Hyperlipidaemias; dietary supplement.

Epatin *Coronet, Indon.*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement.

Epativan *Cimed, Braz.*
Adenosine (p. 1291·1); methionine (p. 1558·2); choline (p. 2055·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Epavir *Sinnex, Hung.*
Fish oil (p. 1460·3); lysine hydrochloride (p. 2079·3).
Herpes simplex infection.

Epaviten *Boniscontro & Gazzone, Ital.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); nicotinamide (p. 2083·1); ascorbic acid (p. 2110·3).
Vitamin B and vitamin C deficiency.

Epax *Vivax, Venez.*
Omega-3 triglycerides (p. 1460·1).
Hyperlipidaemias.

Epaxal *Scott-Cassara, Arg.; Berna, Austria; Janssen-Cilag, Belg.; Berna, Canad.; Biosano, Chile; Berna, China; SBL, Denm.; Crucell, Fin.; Baxter, Gr.; Berna, Hong Kong; Crucell, Irl.; Berna, Israel; Berna, Ital.; Berna, Malaysia; Crucell, Neth.; Crucell, Norw.; Pharmabroker, NZ†; Berna, Philipp.; Berna, Port.; Berna, Singapore; Crucell, Spain; SBL, Swed.; Crucell, Switz.; Crucell, Thai.; Yeni, Turk.; Masta, UK.*
An inactivated hepatitis A vaccine (p. 2388·3).
Active immunisation.

Epazin *Torrent, Philipp.*
Carbamazepine (p. 512·2).
Bipolar disorder; epilepsy; neuropathic pain.

EP&C Essence *Potter's, UK.*
Bayberry bark (p. 2453·1); hemlock spruce; sambucus (p. 2609·3); peppermint oil (p. 1877·1).
Colds; sore throat.

Epcon *La Pharmaceuticals, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Epdantoin *Embil, Turk.*
Phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia.

Epelin *Pfizer, Braz.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia.

E-Pento *Zota, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

E-Pento-D *Zota, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

E-Pep *Zota, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Epexol *Sanbe, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Epez *Torrent, Braz.*
Donepezil hydrochloride (p. 390·2).

EPH *Investigaciones Filosoficas y Cientificas, Mex.*
Alpha tocoferil acetate (p. 2119·2).
Atherosclerosis; erectile dysfunction.

Ephact *Rusan, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Ephact-XR *Rusan, India.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).

Ephecol *Vickmans, Hong Kong.†*
⊗Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); ephedrine (p. 1663·1); squill (p. 1677·3); sulfogaiacol (p. 1678·1).

Ephedrex *Alembic, India.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); phenylpropanolamine hydrochloride (p. 1674·1).

Ephedronguent *Sterop, Belg.†*
⊗Ephedrine (p. 1663·1).
Nasal congestion.

Ephedyl *Synco, Hong Kong†; Synco, Singapore.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).
Cough; cold and influenza symptoms; rhinitis.

Ephedyl DM *Synco, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).

Ephedyl-DM *Synco, Hong Kong.†*
⊗Dextromethorphan (p. 1660·1); ephedrine (p. 1663·1); promethazine (p. 638·2).
Cough.

Ephelia *Ipsen, Ital.†*
Estradiol (p. 2271·1).
Menopausal disorders.

Ephendyln *Universal, Hong Kong.†*
⊗Codeine (p. 40·2); ephedrine (p. 1663·1); promethazine (p. 638·2).

Ephepect Blocker *Bolder, Hong Kong.*
Sodium dibunate (p. 1677·3); dequalinium chloride (p. 1749·3); anise oil (p. 2444·3).
Cough.

Ephepect-Blocker-Pastillen N *Bolder, Ger.*
Sodium dibunate (p. 1677·3); dequalinium chloride (p. 1749·3).
Cough.

Ephepect-Pastillen N *Bolder, Ger.*
Thyme (p. 2630·2); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); fennel oil (p. 2503·3); peppermint oil (p. 1877·1); ammonium chloride (p. 1656·1).
Respiratory-tract disorders.

Epherit *Extractum, Hung.*
⊗Ephedrine hydrochloride (p. 1663·2).
Hypotension; narcoleptic syndrome; respiratory-tract disorders.

Ephron *Medhaus, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Éphydion *Theratech, Fr.†*
Oral drops; tablets: Ethylmorphine hydrochloride (p. 56·3); sodium benzoate (p. 1738·2); grindelia (p. 2522·3).
Cough.

Theratech, Fr.†
Syrup: Ethylmorphine hydrochloride (p. 56·3); sulfogaiacol (p. 1678·1); grindelia (p. 2522·3).
Cough.

Ephydrol *Sinclair, Fr.*
Topical solution (with brush or aerosol spray): Aluminium chloride (p. 1693·3); bisabolol (p. 2544·1); triclosan (p. 1773·2); citronella oil (p. 2481·1).
Formerly contained fioravanti, camphor, menthol, salicyl alcohol, bergamot oil, lemon oil, lavender oil, formaldehyde solution, and plantain.
Hyperhidrosis.

Ephynal *Bayer Consumer, Arg.; Bayer, Belg.†; Bayer, Braz.; Roche, Braz.; Roche, Gr.; Bayer, Ital.; Bayer, S.Afr.†; Bayer, Spain; Bayer, Switz.; Roche Consumer, UK.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency; dietary supplement.

Piramal, India; Bayer, Turk.
Vitamin E (p. 2119·1).
Vitamin E supplement.

Epi EZ *Dey, Canad.†*
⊗Adrenaline (p. 1292·1).
Anaphylactic shock.

Epi Foam
Note: this name may be used for preparations of different composition.
Dispolab, Chile.
Polyurethane foam dressing (p. 1718·1).

Epi Teva *Teva, Ger.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epi Wash *Burnishine, Canad.†*
Chloroxylenol (p. 1748·2).
Skin cleansing.

Epianal *Will-Pharma, Neth.*
Sodium oleate (p. 2211·2); a macrogol lauril ether (p. 2193·3); chlorocarvacrol (p. 1747·3).
Haemorrhoids.

EPIAO *M & H, Thai.*
⊗Epoetin alfa (p. 1141·1).
Anaemias.

Epiao *Sunshine, China.*
⊗Recombinant human erythropoietin (p. 1141·1).
Anaemias; autologous blood transfusion.

Epiate *Unison, Thai.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Epibicin *Ebewe, Gr.*
Epirubicin hydrochloride (p. 787·1).
Breast cancer; gastric cancer; bladder cancer.

Epibra *Santa, Gr.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epi-C *Lafayette, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Epicaine *Duopharma, Philipp.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Epicare
Note: this name may be used for preparations of different composition.
Ecolab, Canad.
Chloroxylenol (p. 1748·2).
Skin cleansing.

Epiccord *Arrow, NZ.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epi-Cell *Stada, Austria†; Cell Pharm, Ger.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epi-cell *Cell Pharm, Denm.; Stada, Port.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epicent *Crescent, India.*
Phenytoin sodium (p. 538·2).
Epilepsy.

EpiCeram *Pediapharm, Canad.; Hyphens, Malaysia; Hyphens, Singapore; PuraCap, USA.*
Emollient.
Dry skin disorders.

Epi-Chrono *Sanofi-Aventis, Irl.†*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Epicina *LKM, Arg.*
Idarubicin (p. 805·2).
Malignant neoplasms.

Epicitrin *Neo Quimica, Braz.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial skin infections.

Epiclodina *Pisa, Mex.*
Clonidine hydrochloride (p. 1339·1).
Pain; withdrawal syndromes.

Epicord *Accord, S.Afr.*
Epirubicin hydrochloride (p. 787·1).

Epicort-GC *Shreya, India.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Epicort-MK *Shreya, India.*
⊗Betamethasone dipropionate (p. 1623·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); sodium lactate (p. 1781·2); urea (p. 1727·3).

Epictal *Ipca, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Epicur *Obolenskoe, Rus.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Epidac *Eurolab, Arg.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting.

Epident *Grands Espaces, Fr.†*
Tooth extract.
Mucous membrane disorders of the nose and throat.

Epi-Derm *Dispolab, Arg.; Dispolab, Chile.*
Silicon (p. 2209·2).
Scars; hypertrophic scars; keloids.

Epiderm *Il-Yang, Singapore.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).

Epidermine *Merck Medication Familiale, Fr.†*
Comfrey (p. 2484·2).
Skin irritation.

Epidosin *TTK, India; Solvay, Indon.; Frik, Turk.*
Valethamate bromide (p. 1895·2).
Smooth muscle spasm; cervical dilatation.

Epidosin Compozitum *Frik, Turk.*
Valethamate bromide (p. 1895·2); paracetamol (p. 115·1).
Smooth muscle spasm.

Epidoxo *LKM, Arg.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epidrat *Mantecorp, Braz.*
Moisturiser.

Epidrin *Excellium, USA.*
⊗Paracetamol (p. 115·1); dichloralphenazone (p. 1071·3); isometheptene mucate (p. 2535·1).
Migraine.

Epidropal *Teofarma, Ger.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Epiduo *Galderma, Arg.; Galderma, Austral.; Galderma, Belg.; Galderma, Braz.; Galderma, Denm.; Galderma, Fin.; Galderma, Fr.; Galderma, Ger.; Galderma, Gr.; Galderma, Hong Kong; Galderma, Ital.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Philipp.; Galderma, Pol.; Galderma, Port.; Galderma, Singapore; Galderma,*

Spain; Galderma, Swed.; Galderma, Switz.; Galderma, Thai.; Galderma, UK; Galderma, USA.
Adapalene (p. 1692·1); benzoyl peroxide (p. 1696·1).
Acne.

Epiestrol *Rottapharm, Chile†; Rottapharm, Irl.†; Pfizer, Ital.; Rotta, Port.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Epifil *Filaxis, Arg.*
Epirubicin (p. 787·1).
Malignant neoplasms.

Epifoam
Note: this name may be used for preparations of different composition.
Meda, Israel; Meda, USA.
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders; skin disorders.

Epifrin *Cristalia, Braz.; Alvia (Αλβια), Gr.*
⊗Adrenaline (p. 1292·1).
Allergan, Canad.†
⊗Adrenaline hydrochloride (p. 1292·2).
Glaucoma.

Epigen *Catalysis, Arg.; Medix, Mex.; Invar, Rus.*
Glycyrrhizic acid (p. 2520·2).
Viral infections of skin and mucous membranes; anogenital discomfort.

Epiglu *Meyer-Haake, Ger.; Synapse, Irl.†; Schuco, UK.*
Ethyl 2-cyanoacrylate (p. 2490·1); polymethylmethacrylate (p. 2558·2).
Wounds; wound closure and suture support.

Epiject
Note: this name may be used for preparations of different composition.
ALK, Spain.†
⊗Adrenaline (p. 1292·1).
Shock; anaphylaxis; heart block.

Epikebir *Aspen, Arg.†*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epiklin *Zyg, Thai.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Epikor *United Douglas, Philipp.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Epilactal *Polpharma, Pol.†*
Lamotrigine (p. 527·2).
Epilepsy.

Epilan
Note: this name may be used for preparations of different composition.
Gerot, Austria.†
Mephenytoin (p. 532·3).
Epilepsy.

Epilan C *Anglo-French Drugs, India.*
Phenytoin sodium (p. 538·2); phenobarbital (p. 535·2).
Epilepsy.

Epilan D *GL Pharma, Cz.*
Phenytoin (p. 538·2).
Epilepsy; seizures associated with neurosurgery; neuralgias.

Epilan-D *Gerot, Austria.*
Phenytoin (p. 538·2).
Epilepsy.

Epilania *Vipharm, Hung.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epilantin
Note: this name may be used for preparations of different composition.
Streuli, Philipp.†
Phenytoin sodium (p. 538·2).
Epilepsy.

Epilem *Teva, Mex.; Lemery, Rus.; Teva, Thai.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epilene C *Captab, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Epilenil *Biolab Sanus, Braz.*
Valproic acid (p. 553·1).
Epilepsy.

Epilepax *Ivax, Arg.*
Lamotrigine (p. 527·2).
Epilepsy.

Epileptal
Note: this name may be used for preparations of different composition.
Farmak, Ukr.
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Tripharma, Turk.
Levetiracetam (p. 531·1).

Epileptil *Teuto, Braz.*
Clonazepam (p. 519·1).
Epilepsy.

Epileptin *Indian Drugs, India.*
Phenytoin (p. 538·2).
Epilepsy.

Epilex *Abbott, India.*
Sodium valproate (p. 553·1).
Epilepsy.

Epilex Chrono *Abbott, India.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).

Epilexter *Novartis, Spain.†*
Oxcarbazepine (p. 533·2).
Epilepsy.

Epilfarmo *Farmoz, Port.*
Oxcarbazepine (p. 533·2).
Epilepsy; trigeminal neuralgia.

Epilim *Sanofi-Aventis, Austral.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, UK.*
Sodium valproate (p. 553·1).
Epilepsy; mania; bipolar disorder; migraine.

Epilim Chrono *Sanofi-Aventis, Irl.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, UK.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; mania.

Epilim Chronosphere *Sanofi-Aventis, Irl.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Epilmax *Cantabria, Spain.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epilobin *Leros, Cz.*
Epilobium; buchu (p. 2461·3); solidago (p. 2620·1); calendula (p. 2465·2).
Urinary-tract disorders.

Epilon *Yung Shin, Hong Kong.*
Hyoscine butylbromide (p. 1845·3); dicycloverine hydrochloride (p. 1834·2); chlordiazepoxide (p. 1044·2); chlorophyllin copper complex sodium (p. 2178·3); aluminium magnesium hydroxide; magnesium oxide (p. 1857·3); aluminium silicate (p. 1818·3).
Dyspepsia; gastric pain; gastritis; gastric hyperacidity; gastrointestinal spasm; peptic ulcer.

Epilyd *Norma (Νορμα), Gr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Epi-Lyt *Valeo, Canad.; GSK, USA.*
⊗Glycerol (p. 2517·2); lactic acid (p. 2539·1).
Dry skin.

Epimate *Psyco Remedies, India; Torrent, Philipp.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epimaxan *Polpharma, Cz.; Polpharma, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epimaz *Ivax, UK.*
Carbamazepine (p. 512·2).

Epimedac *Medac, Cz.; Medac, Ger.; Medac, Gr.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epimil *Ivax, Cz.; Teva, Ukr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Epinal *Alcon, USA.†*
⊗Adrenaline borate complex (p. 1292·1).
Open-angle glaucoma.

Epinat *Nycomed, Norw.*
Phenytoin (p. 538·2).
Epilepsy.

Epi-NC *Neocorp, Ger.†*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epinerve *SIFI, Ital.*
Epigallocatechin gallate (p. 1720·2).
Eye disorders.

Epinil *Inga, India.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Epinitril *Bouchara-Recordati, Fr.; Rottapharm, Gr.; Rottapharm, Irl.; Rottapharm, Ital.; Delta, Port.; Rottapharm, Spain.*
Transdermal patch: Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Epinor *Geo, India.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; shock; gastrointestinal haemorrhage.

Epioftal *Atlas, Arg.*
Epinastine hydrochloride (p. 628·3).
Allergic conjunctivitis.

Epione *Schering-Plough, Port.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

EpiPen *Merck Serono, Arg.; Alphapharm, Austral.; ALK, Austria; Meda, Belg.; Pfizer, Canad.; ALK, Cz.; Meda, Denm.; ALK, Fin.; IFET (ΙΦΕΤ), Gr.; ALK, Hung.; ALK, Irl.†; Meridian, Israel; Merck Serono, Malaysia†; Meda, Neth.; Meda, Norw.; Mylan, NZ; ALK, Pol.; Mylan, Port.†; Merck, S.Afr.; Merck, Singapore; Meda, Swed.; Meda, Switz.; Merck, Thai.; Meda, UK; Dey, USA.*
⊗Adrenaline (p. 1292·1).
Anaphylaxis; anaphylactic shock.

Epi-Pevaryl *McNeil, Ger.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Epi-Pevaryl Pv *McNeil, Ger.*
Econazole (p. 577·2).
Pityriasis versicolor.

Epipevisone *Janssen-Cilag, Ger.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal and Gram-positive bacterial skin infections.

Epiphen *Reliance, India.*
Phenobarbital (p. 535·2); phenytoin sodium (p. 538·2).
Epilepsy.

Epiprocto
Note: this name may be used for preparations of different composition.
Veinfar, Arg.
⊗Lidocaine (p. 1988·1); hydrocortisone (p. 1640·1).

Epicaris, Arg.†
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); aluminium acetate (p. 2440·1); zinc oxide (p. 1729·1).
Anorectal disorders.

EpiQuin *SkinMedica, USA.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Epiral *Zentiva, Cz.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Epiramat *Farmacom, Pol.; Teva, Ukr.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epiramax *Aspen, Austral.; Aspen, Austral.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Ep-Iron Fol *Elnova, India.*
Cobamamide (p. 2107·2); ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Epirub *Nexus, Gr.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epirubitec *United Biotech, India.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epirud *Nexus, Gr.†*
Epirubicin hydrochloride (p. 787·1).

Episcorit *Sanum-Kehlbeck, Ger.*
Echinacea purpura (p. 2498·1).
Respiratory- and urinary-tract infections.

Episec *Odan, Canad.*
Liquid paraffin (p. 2191·2); propylene glycol (p. 2205·2); trolamine stearate.

Episenta *Beacon, UK.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Episil *Cangene, USA.*
⊗Glycerol (p. 2517·2); peppermint oil (p. 1877·1); polysorbate 80 (p. 2203·3); propylene glycol (p. 2205·2); soya lecithin (p. 2542·2).
Oral mucositis.

Sinclair, UK.
Glycerol dioleate; soya lecithin (p. 2542·2); propylene glycol (p. 2205·2); polysorbate 80 (p. 2203·3); peppermint oil (p. 1877·1).
Oral mucositis.

Episindan *Actavis, Hong Kong; Actavis, Hung.; Actavis, Pol.; Actavis, Rus.; Actavis, Singapore.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Episod *Psyco Remedies, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Episoft
Note: this name may be used for preparations of different composition.
Ecolab, Canad.
Triclosan (p. 1773·2).
Skin cleansing.

Glenmark, India.
Emollient.

Episol
Note: this name may be used for preparations of different composition.
Psychotropics, India.
Phenytoin (p. 538·2).
Epilepsy.

Episol Plus *Psychotropics, India.*
Phenobarbital sodium (p. 535·3); phenytoin sodium (p. 538·2).
Epilepsy.

Episol UVA *Mantecorp, Braz.*
SPF 30: Oxybenzone (p. 1715·3); avobenzone (p. 1695·1); octinoxate (p. 1715·1); homosalate (p. 1705·1); octisalate (p. 1715·2).
Sunscreen.

Episol UVA Guard *Schering-Plough, Braz.†*
SPF 15: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Epistatus *IFET (ΙΦΕΤ), Gr.*
Midazolam (p. 1085·1).

Epistaxol *Medical, Spain.*
⊗Adrenaline (p. 1292·1); phenazone (p. 124·1); naphazoline hydrochloride (p. 1669·3); rutoside (p. 2505·3).
Mucous membrane haemorrhage.

Epitab *East West, India.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Epitaloe *Mediwhite, Ital.*
Aloe vera (p. 1693·2).
Corneal trauma.

Epitam *Ali, Turk.*
Levetiracetam (p. 531·1).

Epitan *Reliance, India.*
Phenobarbital (p. 535·2).
Seizures; sedative.

Epitec *Cipla-Medpro, S.Afr.*
Lamotrigine (p. 527·2).
Epilepsy.

Epiteliol-C *Spedrog, Arg.*
Vitamin C (p. 2110·3); hesperidin (p. 2505·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Skin and capillary disorders.

Epitelizante *Novartis, Spain.*
Methionine (p. 1558·2); gentamicin sulfate (p. 304·2); vitamin A palmitate (p. 2098·3).
Corneal damage.

Epitezan *Allergan, Braz.*
Vitamin A (p. 2098·3); chloramphenicol (p. 257·1); amino acids.
Eye infections.

Epithelial AH *Silesia, Chile.*
Avena (p. 2451·1); hyaluronic acid (p. 2526·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Cicatrisation; burns; wounds.

Épithéliale *A-Derma, Fr.*
Avena (p. 2451·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Skin irritation; minor burns.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Epitheliale A-Derma *Pierre Fabre Dermo-Cosmetique, Arg.*
Avena (p. 2451·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Skin disorders.

Epitheliale AH *Pierre Fabre Dermo-Cosmetique, Arg.; Medifarm Ducray, Venez.*
Avena (p. 2451·1); hyaluronic acid (p. 2526·2).
Skin lesions.

Epithra *Glenmark, India.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epitic *Psyco Remedies, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Epitol *Lemmon, USA.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Epitomax *Orifarm, Denm.†; Janssen-Cilag, Fr.; Euro Registratie, Neth.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epitome *Triton, India.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epitop *Micro, India; Micro, Philipp.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epitopic *Gerda, Fr.*
⊗Difluprednate (p. 1634·2).
Skin disorders.

Epitoram *Apotex, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Epitoz *Simayla, S.Afr.*
Topiramate (p. 550·3).
Epilepsy.

Epitrel *Loeffler, Mex.*
Tretinoin (p. 1725·2).
Acne; sun-induced skin damage.

Epitrigine *Plus Pharma, Hung.; Plus Pharma, Pol.*
Lamotrigine (p. 527·2).
Bipolar disorder; epilepsy.

Epitril *Novartis, India.*
Clonazepam (p. 519·1).
Epilepsy.

Epitrogine *Liptis, USA.*
Lamotrigine (p. 527·2).

Epival *Abbott, Canad.; Abbott, Mex.; Abbott, Philipp.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; mania; migraine.

Sun, India.
Sodium valproate (p. 553·1).
Migraine; bipolar disorder; epilepsy.

Epiven *Novell, Indon.*
Gabapentin (p. 523·3).
Epilepsy.

Epivir *ViiV, Austria; ViiV, Belg.; GSK, Braz.; GSK, China; GSK, Cz.; GSK, Denm.; ViiV, Fin.; ViiV, Fr.; GSK, Ger.; ViiV, Gr.; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; ViiV, Neth.; GSK, Norw.; GSK, Pol.; ViiV, Port.; GSK, Rus.; GSK, Singapore; ViiV, Spain; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, USA; GSK, Venez.*
Lamivudine (p. 1000·2).
HIV infection; hepatitis B.

Epix *Baroda, India.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Epixx *Abdi, Turk.*
Levetiracetam (p. 531·1).

Epizam *Cipla, India.*
Clonazepam (p. 519·1).

Ep-Koff *Elnova, India.*
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

EPL *Alfresa, Jpn.*
Polyenephosphatidylcholine.
Liver disorders; hyperlipidaemia.

Eplefa *Synthon, Irl.*
⊗Eplerenone (p. 1374·2).
Heart failure following myocardial infarction.

Epleptin *Pharmaplan, S.Afr.*
Gabapentin (p. 523·3).
Epilepsy.

Epleran *Unichem, India.*
⊗Eplerenone (p. 1374·2).

EPM *Grandix, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

E.P.Mycin *Boryung, Thai.†*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Epobel *Nobel, Turk.*
⊗Epoetin (p. 1141·1).

Epobiokrin *Biopharma, Ukr.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epocaldi *Novell, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); evening primrose oil (p. 2502·2).
Osteoporosis; premenstrual syndrome.

Epocelin *Southwest, China; Shreya, India; Choseido, Jpn.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Epocler
Note: this name may be used for preparations of different composition.
Wyeth Consumer, Braz.
Adenosine (p. 1291·1); methionine (p. 1558·2); choline (p. 2055·2); betaine hydrochloride (p. 2456·1); pyridoxine hydrochloride (p. 2105·3).
Liver disorders.

Wyeth Consumer, Ital.
Kojic acid dipalmitate; azeloglycine.
Hyperpigmentation disorders.

Epocomb *Teva, Rus.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epocrin *Soteks, Rus.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epodox *Nitin, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Epofer *Emcure, India.*
⊗Epoetin alfa (p. 1141·1).
Autologous blood transfusion; anaemias.

Epogam *Strathmann, Ger.; Cosmopharm, Gr.; Zeller, Switz.*
Evening primrose oil (p. 2502·2).
Eczema.

Epogen *Cassara, Arg.; Varifarma, Arg.; Harbin, Philipp.; Amgen, USA.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epogin *Chugai, Jpn.*
⊗Epoetin beta (p. 1141·1).
Anaemias; autologous blood transfusion.

Epoglobin *Ikapharmindo, Indon.*
⊗Epoetin (p. 1141·1).
Anaemias; autologous blood transfusion.

Epokine *CJ, Philipp.; CJ, Thai.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

PMG, Chile.
⊗Epoetin (p. 1141·1).
Anaemias; autologous blood donation.

Epol *Polinac, Venez.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Epolar *Apotex, Hung.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Epolar Trio *Aramis, Hung.*
4 Tablets, alendronate sodium (Epolar) (p. 1171·3); 56 tablets, calcium carbonate (p. 1824·3); colecalciferol (Calcichew D3) (p. 2113·1).
Osteoporosis.

Epomax *Cryopharma, Mex.*
⊗Epoetin (p. 1141·1).
Anaemias.

Eponis 2K *Neiss, India.*
⊗Epoetin (p. 1141·1).
Autologous blood transfusion; anaemias.

EPOO *Shanghai Clonbiotech, Thai.†*
⊗Recombinant human erythropoietin (p. 1141·1).
Anaemias.

Epopen *Esteve, Spain.†*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusions.

Eporatio *Ratiopharm, Austria; Ratiopharm, Cz.; Teva, Fr.; Ratiopharm, Ger.; Ratiopharm, Hung.; Ratiopharm, Irl.; SLE, Israel; Teva, Neth.; Ratiopharm, Pol.; Ratiopharm, Port.; Ratiopharm, Spain; Ratiopharm, Swed.; Ratiopharm, UK.*
⊗Epoetin theta (p. 1141·2).
Anaemias.

Eporon *Dong-A, Thai.†*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Eposal
Note: this name may be used for preparations of different composition.
Galeno, Venez.
Chlordiazepoxide (p. 1044·2).
Anxiety; insomnia.

Sanofi-Aventis, Chile.
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Eposerin *Pfizer, Ital.*
Ceftizoxime sodium (p. 253·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Eposid *Pharmachemie, Denm.*
Etoposide (p. 790·2).
Malignant neoplasms.

Epósido *Blausiegel, Braz.*
Etoposide (p. 790·2).
Malignant neoplasms.

Eposin *Teva, Belg.; Pharmachemie, Fin.; Pharmachemie, Malaysia; Pharmachemie, Neth.; Teva, Norw.; Pharmachemie, Port.; Pharmachemie, S.Afr.; Teva, Swed.; Pharmachemie, Thai.; Teva, Thai.; Mert, Turk.; Medac, UK.*
Etoposide (p. 790·2).
Malignant neoplasms.

Eposino *Shandong Kexing, Philipp.*
⊗Epoetin alfa (p. 1141·1).
Anaemia of chronic renal failure.

Eposis *Daewoong, Thai.*
⊗Epoetin alfa (p. 1141·1).
Anaemias.

Micro, India.
⊗Epoetin (p. 1141·1).
Autologous blood transfusion; anaemias.

Epostim *Farmapark, Rus.*
⊗Epoetin beta (p. 1141·1).
Anaemias; autologous blood transfusion.

EpoTheta *Teva, Switz.*
⊗Epoetin theta (p. 1141·2).
Anaemias.

Epotin *Claris, India; Julphar, UAE.*
⊗Epoetin (p. 1141·1).
Autologous blood transfusion; anaemias.

Julphar, Philipp.
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epotop *VHB, India.*
⊗Epoetin alfa (p. 1141·1).
Autologous blood transfusion; anaemias.

Epotrex-NP *Novell, Indon.*
⊗Epoetin (p. 1141·1).
Anaemias; autologous blood transfusion.

Epovit *Bioextra, Hung.*
Evening primrose oil (p. 2502·2).
Atopic eczema; premenstrual symptoms; vascular disorders; rheumatoid arthritis; multiple sclerosis.

Epovitan *Farmak, Ukr.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epox *Wockhardt, India.*
⊗Epoetin (p. 1141·1).
Autologous blood transfusion; anaemias.

Epoxide *PP Lab, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety.

Eppikajutsuto *Tsumura, Jpn.*
⊗Gypsum (p. 2173·1); ephedra (p. 1663·1); atractylodes lancea rhizome; jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Eppitrexil *Lumar, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Eppy *Smith & Nephew, S.Afr.†*
⊗Adrenaline (p. 1292·1).
Open-angle glaucoma.

Eprasol *Hexal, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Epratenz *Famar, Gr.*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Epratenz Plus *Abbott, Gr.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Eprea *Cinerea, India.*
Valproate semisodium (p. 553·2).
Seizures; bipolar disorder; migraine.

E-Preg *Zota, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Eprex *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Pentafarma, Chile†; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Gr.; Cilag, Hong Kong; Janssen-Cilag, Hung.; Johnson & Johnson, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Gurel, Turk.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Epricin *Shantha, India.*
Epirubicin (p. 787·1).
Malignant neoplasms.

E-Pril *Orchid, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Epril *Hexal, Pol.†; Sandoz, Switz.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Epril Plus *Sandoz, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

E-Prime *Usana, Canad.†; Usana, Singapore.†*
Vitamin E (p. 2119·1).
Vitamin E and antoxidant supplement.

Usana, Hong Kong.†
Vitamin E substances (p. 2119·1).
Vitamin E supplement.

E-Prin *Elder, India.*
Aspirin (p. 22·2).
Pain; fever; musculoskeletal and joint disorders; thromboembolism prophylaxis.

Eprinoc *Sanbe, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Eprodine *Sinopharm, Thai.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Eprofil
Note: this name may be used for preparations of different composition.
Vargas, Venez.
Mebendazole (p. 158·3).
Worm infections.

Columbia, Mex.†
Tiabendazole (p. 166·3).
Pediculosis; scabies.

Eprosartan comp *Ratiopharm, Ger.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Eprotan *Mepha, Switz.*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Eprotan Plus *Mepha, Switz.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Epsicaprom *Bial, Port.*
Aminocaproic acid (p. 1131·3).
Fibrinolysis.

Epsidox *Laboratorios Chile, Chile.*
Etoposide (p. 790·2).
Malignant neoplasms.

Epsilat *Coup, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Epsile *Biofarma, Turk.*
Oxcarbazepine (p. 533·2).

Epsilon *Will-Pharma, Belg.*
Ibuprofen (p. 68·2).
Fever; pain.

Epsin *GSK, Mex.†*
Aciclovir (p. 964·1).
Herpes labialis.

Epsipam *Will-Pharma, Belg.†*
Tetrazepam (p. 1110·1).
Skeletal muscle spasm.

Epsisolde *Helm, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Epsitron *Remedica, Singapore; Remedica, Thai.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Epsoclar *Hospira, Ital.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Epsodilave *Hospira, Ital.*
Heparin sodium (p. 1396·3).
Maintenance of patency of catheters and cannulas.

Epsolin *Zydus, India.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia; ventricular arrhythmias.

Epsom *Rougier, Canad.*
Magnesium sulfate (p. 1787·3).

Epsonal *Pyridam, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Epsoval *La Pharmaceuticals, India.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder; migraine.

ept Stick Test *Warner-Lambert, USA.*
Pregnancy test (p. 2596·1).

Eptadone *Molteni, Ger.; Molteni, Ital.; Molteni, Neth.; Molteni, Spain; Dee, UK.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal; pain.

Eptavis *Sigma-Tau, Ital.*
Lactic-acid-producing organisms (p. 2596·3).
Restoration of intestinal flora.

Eptavit *Leurquin, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Eptico
Note: this name may be used for preparations of different composition.
Elder, India.
Chloramphenicol (p. 257·1).
Bacterial eye infections.
Watsons, Canad.†
Camphor (p. 2466·2); zinc oxide (p. 1729·1).

Eptico-D *Elder, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).

Eptifab *Piramal, India.*
Eptifibatide (p. 1376·3).
Unstable angina; adjunct in coronary angioplasty.

Eptoin *Abbott, India.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia.

Eptonal *Demo, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Eptus *Glenmark, India.*
⊗Eplerenone (p. 1374·2).

Epulor *Vistapharm, USA.*
Preparation for enteral nutrition.

Epzicom *GSK, USA.*
Abacavir (p. 962·3); lamivudine (p. 1000·2).
HIV infection.

Eqinon *Pharmacore, Indon.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation disorders.

Equagesic
Note: this name may be used for preparations of different composition.
Leitner, USA.
Aspirin (p. 22·2); meprobamate (p. 1083·3).
Musculoskeletal pain.
Wyeth, India.
Aspirin (p. 22·2); ethoheptazine citrate (p. 56·2).
Pain; dysmenorrhoea.
Akromed, S.Afr.†
Aspirin (p. 22·2); meprobamate (p. 1083·3); ethoheptazine citrate (p. 56·2).
Tension headache; musculoskeletal spasm.

Equal *Merisant, Canad.; Boots Piramal, India; Nutrasweet, NZ.†*
Aspartame (p. 2169·2).
Sugar substitute.

Equalactin *Numark, Canad.†; Numark, USA.*
Polycarbophil calcium (p. 1879·2).
Diarrhoea; constipation.

Equaleze *Aquamarine, UK.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Equaline *Umedica, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Equaliv *Meyer, Venez.*
Valerian (p. 2640·2); crataegus (p. 2488·1); passion flower (p. 2584·1).
Anxiety.

Equalsweet *Merisant, Arg.*
Aspartame (p. 2169·2).
Sugar substitute.

Equanil *Aspen, S.Afr.*
Meprobamate (p. 1083·3).
Anxiety.

Équanil *Sanofi-Aventis, Fr.†*
Meprobamate (p. 1083·3).
Anxiety; agitation.

Equanox *Linde, UK.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).

Equasym *Shire, Denm.; Shire, Fin.; Shire, Ger.; Shire, Gr.†; Shire, Irl.; Shire, Neth.; Swedish Orphan, Norw.; Shire, Spain; Shire, Swed.; Shire, UK.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder.

Equate All-in-One *AMO, Canad.*
Polihexanide (p. 1766·1).
Disinfectant solution for contact lenses.

Equate Daily Low-Dose *Pharmascience, Canad.*
Aspirin (p. 22·2).

Equate Moisturizing *Belvedere, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Equepin *Valeant, Hung.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia.

Equeta *Valeant, Cz.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Equetro *Shire, USA.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Equibalance *Fresenius Medical, Ital.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3); sodium lactate (p. 1781·2) (p. 1778·2).
Peritoneal dialysis.

Equicalm *Ultramark, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine hydrochloride (p. 1113·2).

Equiceft *Tum, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Equiday *Algol, Fin.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Equiderm *Galderma, Mex.*
Emollient; moisturiser.

Equidral *Biotrading, Ital.*
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1780·1).
Oral rehydration.

Equifan *Bajamed, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Equifem *Elea, Arg.*
Drospirenone (p. 2269·1); estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

EquiHes *Braun, Irl.*
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Hypovolaemia; shock.

Equilibrane *Temis, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Equilibrin *Sanofi-Aventis, Ger.*
Amitriptylinoxide (p. 401·1).
Depression.

Equilibrium
Note: this name may be used for preparations of different composition.
Jagsonpal, India.
Chlordiazepoxide (p. 1044·2).
Anxiety; alcohol withdrawal syndrome.
Luper, Braz.
St John's wort (p. 449·1).
Depression.

Equilibrol Fem *Medica, Arg.*
Soya isoflavones (p. 2620·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Menopausal disorders.

Equilid *Sanofi-Aventis, Braz.; Bruno, Ital.*
Sulpiride (p. 1107·3).
Dysthymia; psychoses; schizophrenia.

Equilon Herbal *Chefaro, UK.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome.

Equimet *Reddy, Ital.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Equin *Aldo-Union, Hong Kong; Aldo-Union, Singapore; Aldo, Spain.†*
Conjugated oestrogens (p. 2260·1).
Dysfunctional uterine bleeding; lactation inhibition; menopausal disorders; osteoporosis; female hypogonadism.

Equinorm *Aspen, S.Afr.*
Clomipramine hydrochloride (p. 412·1).
Depression; cataplexy in patients with narcoleptic syndrome.

Equipax *Parke, Davis, Spain.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Equipro *Cadila, India.*
Bacillus mesentericus; Clostridium butyricum; Lactobacillus acidophilus (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).

Equirab *Bharat, India; Bharat, Philipp.*
A rabies immunoglobulin (equine) (p. 2413·1).
Passive immunisation.

Equirex *Jagsonpal, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Peptic ulcer; irritable bowel syndrome.

Equisedin *Lazar, Arg.*
Bromazepam (p. 1041·2).
Anxiety; depression; panic disorder.

Equisil N *Klein, Ger.†*
Equisetum (p. 2500·1); ribwort plantain (p. 2604·2); sweet chestnut (p. 2625·1); cowslip rhizome (p. 2596·2); verbascum flowers (p. 2645·1); thyme (p. 2630·2); colloidal silicon dioxide (p. 2209·1).
Cough and associated respiratory-tract disorders.

Equitam
Note: this name may be used for preparations of different composition.
Eurofarma, Braz.
Ginkgo biloba (p. 2512·3).
Cerebrovascular disorders.

Equitax *Tum, Turk.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Equiton *Bruschettini, Ital.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Ocular hypertension; glaucoma.

Equitrol *Jagsonpal, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Equivac *Pisa, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression.

Equizolin *Tum, Turk.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Equoral *Laboratorios Chile, Chile; Teva, Cz.; Ivax, Pol.; Ivax, Rus.; Ivax, Thai.; SPB, Thai.; Teva, Ukr.*
Ciclosporin (p. 1945·2).
Transplant rejection; uveitis; nephrotic syndrome; rheumatoid arthritis; psoriasis; atopic eczema; graft-versus-host disease; auto-immune disorders.

Er Fu Mai *Wansheng, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Er Fu Xin *Wansheng, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Er He Yi *Zhenguo, China.*
Paracetamol (p. 115·1).
Fever; pain.

Er Ke Fen *Advance, China.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

Er Qi *Bei Da Gao Ke Hua Tai, China.*
Di-isopropylammonium dichloroacetate (p. 1359·1); sodium gluconate (p. 2618·3).

Er Re An *Twinluck, China.*
Paracetamol (p. 115·1).
Fever; pain.

Er Tong Shu *Changjiang, China.*
Benzbromarone (p. 603·3).
Hyperuricaemia.

Era *AFT, NZ.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erabutol Plus *Pyridam, Indon.*
Ethambutol (p. 296·1); isoniazid (p. 311·2). Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Eracef *Brawn, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Eracid *Svizera, India.*
Pantoprazole sodium (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Eracid-D *Svizera, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Eracillin *Chew, Thai.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Eracin *Cancernova, Ger.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Eraclox *Unison, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Eradacil *Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.†*
Rosoxacin (p. 356·1).
Gonorrhoea; urinary-tract infections.

E-Radicaps *Legrand, Braz.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Eradicil *Vidant, UK.*
Orthophenylphenol (p. 1762·3); chloroxylenol (p. 1748·2).
Disinfection of fabric.

Eradiclox *Morepen, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Eradikit *Euphoric, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Eradix
Note: this name may be used for preparations of different composition.
Pharos, Indon.
Meropenem (p. 321·3).
Bacterial infections.
Sresan, India.
Albendazole (p. 149·1); levamisole hydrochloride (p. 157·2).

Eraldin
Note: this name may be used for preparations of different composition.
Richmond, Arg.
Sevoflurane (p. 1912·3).
General anaesthesia.

Eralfon *Sotex, Rus.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Eralgavvv *Chew, Thai.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Eralpha *Sanify, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Eramet *Arvincare, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); zinc sulfate (p. 2126·2).

Eramycin *Wesley, USA.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Eranz *Wyeth, Arg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Venez.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Eraphage *Guardian, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Erasan *Arvincare, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Erase
Note: this name may be used for preparations of different composition.
Aesthetic Plus, Singapore.
Onion (p. 2575·2); allantoin (p. 1693·1); vitamin E acetate (p. 2119·2); nicotinamide (p. 2083·1); aesculus (p. 2431·2).
Scars.
Ind-Swift, India.
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erase-D *Stalwart, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Erasef *Nevzat, Turk.*
Cefprozil (p. 248·2).
Bacterial infections.

Erasmo *Mepha, Ukr.†*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Erasol *McGloin, Austral.†*
Phenazone (p. 124·1).
Ear ache.

Erasul *Innoderm, Philipp.*
Bio-sulfur (p. 1721·1).
Skin disorders.

Erathrom *Asian Pharm, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Eraxil *Gepepharm, Ger.†*
Crotamiton (p. 1699·2).
Scabies.

Eraxis *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Israel; Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Ukr.; Pfizer, USA.*
Anidulafungin (p. 573·2).
Candidiasis.

Eraxitron *Savio, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Erazaban *Healthcare Brands, Cz.; Tonipharm, Fr.; Healthcare Brands, Irl.; Healthcare Brands, Neth.; Healthcare Brands, Pol.; Healthcare Brands, Port.*
Docosanol (p. 974·3).
Herpes labialis.

Erazon *KRKA, Rus.*
Piroxicam (p. 125·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Erbasit *Biosana, Canad.*
Minerals.

Erbiode Akne *Dynamit, Austria.*
Acidum picrinicum (p. 2634·2); berberis (p. 2502·1); graphites (p. 2522·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Erbiode Allergie *Dynamit, Austria.*
Apis mellifica (p. 2445·2); aralia racemosa; arsenicum album (p. 2448·1).
Homoeopathic preparation.

Erbiode Blasen und Nieren *Dynamit, Austria.*
Acidum nitricum (p. 2572·3); berberis (p. 2502·1); cantharis; sarsaparilla (p. 2610·3).
Homoeopathic preparation.

Erbiode Haarvital *Dynamit, Austria.*
Acidum hydrofluoricum (p. 2529·1); arsenicum album (p. 2448·1); jodum (p. 2336·3); petroleum (p. 2587·2).
Homoeopathic preparation.

Erbiode Heuschnupfen *HWS OTC, Austria.*
Euphorbium; luffa (p. 2545·3); sabadilla (p. 2611·2).
Homoeopathic preparation.

Erbiode Regelbeschwerden *HWS OTC, Austria.*
Belladonna (p. 2453·3); chamomilla (p. 2474·1); viburnum opulus.
Homoeopathic preparation.

Erbiode-Stärkungstropfen *HWS OTC, Austria.*
⊗Acidum phosphoricum (p. 2589·1); agnus castus (p. 2432·2); damiana (p. 2491·3); ginseng (p. 2513·3); sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Erbisol *Erbis, Rus.*
Embryonic-tissue extracts (p. 2444·1).
Hepatitis.

Erbis, Ukr.
Low molecular weight biologically active peptides (glycopeptides, peptides, nucleotides, amino acids).

Erbitrax *Loeffler, Mex.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Erbituks *Merck, Ukr.*
Cetuximab (p. 762·3).
Colorectal cancer; head and neck cancer.

Erbitux *Merck Serono, Arg.; Merck Serono, Austral.; Merck, Austria; Merck, Belg.; Merck, Braz.; BMS, Canad.; Merck, Chile; Boehringer Ingelheim, China; Merck Serono, China; Merck, Cz.; Merck, Denm.; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Merck, Gr.; Merck, Hong Kong; Merck, Hung.; Merck, India; Merck, Indon.; Merck, Irl.; Merck, Israel; Merck, Ital.; Merck Serono, Malaysia; Merck, Mex.; Merck, Neth.; Merck, Norw.; Healthcare Logistics, NZ; Merck, Philipp.; Merck, Pol.; Merck, Port.; Merck, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Thai.; Merck, UK; BMS, USA.*
Cetuximab (p. 762·3).
Colorectal cancer; head and neck cancer.

Erbolin *Biofarma, Turk.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ercaf *Geneva, USA.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and related vascular headache.

Erceevit *Kimia, Indon.*
Vitamins.
Dietary supplement.

Erceflora *Sanofi-Aventis, Philipp.*
Bacillus clausii.
Diarrhoea.

Ercefuryl *Sanofi-Aventis, Cz.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Thai.†; Sanofi Synthelabo, Turk.*
Nifuroxazide (p. 331·3).
Gastrointestinal infections; bacterial diarrhoea.

Ercéfuryl *Sanofi-Aventis, Fr.*
Nifuroxazide (p. 331·3).
Bacterial diarrhoea.

Ercestop *Sanofi-Aventis, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Erco-Fer *Orion, Swed.†*
Ferrous fumarate (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Ercoquin *Medic, Denm.*
Hydroxychloroquine sulfate (p. 655·2).
Malaria; rheumatoid arthritis; photosensitivity; lupus erythematosus.

Ercoril *Medic, Denm.*
Propantheline bromide (p. 1880·1).
Gastrointestinal spasm.

Erdol *Odan, Canad.*
Ergocalciferol (p. 2113·3).
Vitamin D supplement.

Erdomac *Macleods, India.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Erdomed *CSC, Austria; Medicom, Cz.; CSC, Hung.; Medagro, Pol.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion; respiratory-tract disorders.

Erdon *Aristopharma, Hong Kong.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Erdopect *Orion, Fin.*
Erdosteine (p. 1665·1).
Respiratory-tract disorders.

Erdostin *Sandoz, Turk.*
Erdosteine (p. 1665·1).
Respiratory disorders with increased mucus.

Erdotin *Edmond, Denm.; Galen, Irl.; Megapharm, Israel; Rottapharm, Ital.; Edmond, Port.†; Galen, UK.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion; bronchitis.

Erdozet *Glenmark, India.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Erebra *Vilar, Ukr.*
Sea buckthorn (p. 2611·3).
Viral infections.

Erec *Panjon, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Erectalis *Cipla, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

Erectimax *Elnova, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Erectol *Northia, Arg.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Erefil *Medhaus, Philipp.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Erektil *Stirol, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Eremfat *Riemser, Austria; Fatol, Cz.; Riemser, Ger.; Fatol, Rus.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy; brucellosis; meningococcal meningitis prophylaxis; staphylococcal infections; buruli ulcer.

Eremis *Aamorb, India.*
Salicylic acid (p. 1719·1).
Acne; hyperkeratotic and scaling skin disorders.

Erespal *Servier, Ukr.*
Fenspiride hydrochloride (p. 1209·2).
Respiratory-tract disorders; otitis media; allergic rhinitis.

Erevit *Biotika, Cz.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E supplement.

Erfin *Polfarmex, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Erfulyn *Nobel, Turk.*
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Erfuzide *Union Drug, Thai.*
Nifuroxazide (p. 331·3).
Gastrointestinal infections.

Ergafein *Nobel, Turk.*
Paracetamol (p. 115·1); ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Fever; pain.

Ergalea *Taurus, Ger.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Ergam *Gedeon Richter, Hung.*
Ergotamine tartrate (p. 674·1).
Migraine; postpartum atony; postpartum haemorrhage.

Ergamisol *IFET (ΙΦΕΤ), Gr.†; Janssen-Cilag, Israel†; Janssen-Cilag, S.Afr.†*
Levamisole hydrochloride (p. 157·2).
Adjunct to fluorouracil in colon cancer.

Ergenyl *Sanofi-Aventis, Ger.; Sanofi-Aventis, Swed.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Ergenyl Chrono *Sanofi-Aventis, Ger.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Ergenyl Chronosphere *Sanofi-Aventis, Ger.†*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Ergenyl Retard *Sanofi-Aventis, Swed.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

Ergest *Ind-Swift, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ergex *Rimsa, Mex.*
Ranitidine (p. 1882·1); cisapride (p. 1831·3).
Gastro-oesophageal reflux; acid aspiration; gastritis; peptic ulcer; Zollinger-Ellison syndrome; gastrointestinal haemorrhage.

Ergix Douleur et Fievre *Merck Medication Familiale, Fr.*
Ibuprofen (p. 68·2).
Pain; fever.

Ergix Expectorant *Merck Medication Familiale, Fr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Ergix mal de gorge *Merck Medication Familiale, Fr.*
Hexamidine isetionate (p. 1754·3); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Ergix Toux Seche *Merck Medication Familiale, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Ergobel
Note: this name may be used for preparations of different composition.
Coup, Gr.
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Kwizda, Ger.
Nicergoline (p. 2569·1).
Mental function disorders.

Ergobelan *Labomed, Chile.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Vascular headache.

Ergocaf *Probiomed, Mex.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Ergocalm
Note: this name may be used for preparations of different composition.
Teofarma, Ger.
Lormetazepam (p. 1082·1).
Sleep disorders; premedication.

Ergoclavin *Bros, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Ergocrist *Sanopharm, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Ergodavur *Davur, Spain.†*
Dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders; vascular ear, nose, throat and eye disorders; vestibular disorders.

Ergodryl *Erfa, Canad.*
Ergotamine tartrate (p. 674·1); caffeine citrate (p. 1203·3); diphenhydramine hydrochloride (p. 626·2).
Migraine.

Ergofil *Vocate, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Ergogen *Intermed, Gr.*
Levocarnitine tartrate (p. 2053·2).

Ergogin *Cipla, India.*
Methylergometrine (p. 2137·3).

Ergohydrine *Streuli, Switz.†*
Codergocrine mesilate (p. 389·2).
Cerebrovascular disease.

Ergokapton *Strallhofer, Austria.†*
Ergotamine tartrate (p. 674·1).
Migraine and related vascular headaches.

Ergokoffin *OBA, Denm.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Ergo-Kranit Migräne *Krewel, Ger.*
Ergotamine tartrate (p. 674·1).
Migraine.

Ergolaktyna *Polfa Grodzisk, Pol.†*
Bromocriptine (p. 895·3).
Prolactinoma; hyperprolactinaemia; infertility; premenstrual syndrome; benign breast disorders; lactation inhibition; parkinsonism.

Ergolan *Ethypharm, China.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Ergolin
Note: this name may be used for preparations of different composition.
Lincoln, India.
Methylergometrine (p. 2137·3).
Postpartum and postabortal haemorrhage.

Ergomar *Lotus, USA.*
Ergotamine tartrate (p. 674·1).
Migraine and related vascular headache.

Ergomed
Note: this name may be used for preparations of different composition.
Medlink, Philipp.
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Wabosan, Austria.
Codergocrine mesilate (p. 389·2).
Cerebral insufficiency; migraine and related vascular headache; hypertension.

Ergometrin *Uniao Quimica, Braz.*
Methylergometrine maleate (p. 2137·3).

Ergomicon *Offenbach, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Ergon *Biotrading, Ital.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ergonef *ITF, Chile.*
Clonixin lysine (p. 40·1); ergotamine tartrate (p. 674·1).
Headache; migraine.

Ergont *Sigmapharm, Austria.*
Dihydroergotamine mesilate (p. 672·2).
Migraine.

Ergophen *Inga, India.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).

Ergoriv *East African, India.*
Methylergometrine (p. 2137·3).
Postpartum haemorrhage.

Ergosia *Asian Pharm, Thai.*
Ergotamine tartrate (p. 674·1).
Migraine.

Ergospharma *Alpharma, Mex.†*
Itraconazole (p. 583·3).
Fungal infections.

Ergotab *Jagsonpal, India.*
Ergometrine (p. 2136·2).
Formerly contained ergot.
Postpartum or postabortal haemorrhage; management of third-stage labour.

Ergotam *CT, Ger.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; migraine and other vascular headaches; vascular disorders.

Ergotan *Salf, Ital.*
Ergotamine tartrate (p. 674·1).
Migraine and related vascular headache.

Ergotaur *Taurus, India.*
Ergometrine (p. 2136·2).
Postpartum and postabortal haemorrhage; management of third stage of labour; uterine atony.

Ergotika *Ikapharmindo, Indon.*
Codergocrine mesilate (p. 389·2).
Mental function impairment.

Ergotonine *Streuli, Switz.†*
Dihydroergotamine mesilate (p. 672·2).
Fatigue; hypotension; migraine.

Ergotop *Kwizda, Austria; Teva, Cz.; Kwizda, Hung.*
Nicergoline (p. 2569·1).
Peripheral and cerebral vascular disorders; mental function impairment; vestibular disorders.

Ergotrate *Armstrong, Mex.; Bedford, USA.†*
Ergometrine maleate (p. 2136·2).
Postpartum or postabortal haemorrhage.

Ergotyl *Hind Wing, Hong Kong†; Sandoz, Thai.†*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; management of third stage of labour; postpartum uterine atony.

Ergovasan *Montavit, Austria.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; circulatory disorders; migraine and related vascular headaches.

Ergoxina *Klonal, Arg.*
Codergocrine (p. 389·2).

Ergybiol *Nutergia, Fr.*
Trace elements.

Ergyphilus *Nutergia, Fr.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Eri *Andromaco, Arg.*
Erythromycin (p. 291·2).

Eribec *Collins, Mex.†*
Erythromycin (p. 291·2).
Bacterial infections.

Eriber *Berman, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Eribiotic *Teuto, Braz.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Ericaf *Tempo Scan Pacific, Indon.*
Ergotamine (p. 674·1); caffeine (p. 1203·3).
Migraine.

Ericin *Chew, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Eridez *Darnitsa, Ukr.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Eridosis *Orravan, Spain.*
Erythromycin (p. 291·2).
Acne.

Erifostine *Teva Tuteur, Arg.*
Amifostine (p. 1539·2).
Reduction of haematotoxicity and nephrotoxicity associated with chemotherapy.

Erig *Cadila, India.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Erige *Novagen, S.Afr.*
Efavirenz (p. 975·1).

Erigon *Extractum, Hung.*
Codeine hydrochloride (p. 40·2); sulfogaiacol (p. 1678·1).
Cough and cold symptoms.

Erigrand *Ahimsa, Arg.*
Erythromycin (p. 291·2).
Bacterial infections.

Eriken *Kendrick, Mex.*
Cisapride (p. 1831·3).

Eril *Asahi, China; Asahi, Jpn.*
Fasudil hydrochloride (p. 1380·2).
Vasospasm following subarachnoid haemorrhage; cerebral vasospasm following subarachnoid haemorrhage.

Erilon *Biotech, Venez.*
⊗Desonide (p. 1630·1).
Skin disorders.

Erimicin
Note: this name may be used for preparations of different composition.
Cassara, Arg.; D & M, Chile.
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

Sanli, Turk.
Erythromycin (p. 291·2).
Bacterial infections.

Erimin *Sumitomo, Jpn.*
Nimetazepam (p. 1089·1).
Insomnia.

Erimit *TP, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erimycin *Siam Bheasach, Thai.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Erinac *Eris, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Erinac-P *Eris, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Erinmet *Neon, India.*
Ergometrine maleate (p. 2136·2).
Uterine bleeding; management of third stage labour; postpartum haemorrhage.

Erinol *Homeocan, Canad.†*
Calendula off (p. 2465·2); lamium album.
Homoeopathic preparation.

Eriogem *Eriochem, Arg.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Eriolan *Eriochem, Arg.*
Melphalan (p. 819·1).
Malignant neoplasms.

Eriophos *Eriochem, Arg.*
Zoledronic acid (p. 1192·3).

Erios *Mepha, Switz.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Eriox *Eriochem, Arg.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Erioxal *Eriochem, Arg.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Eris Plus *Waves, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections; filariasis.

Erisine *Lafedar, Arg.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Erismycine *Christo, Hong Kong.†*
Erythromycin (p. 291·2).
Bacterial infections.

Erisol
Note: this name may be used for preparations of different composition.
Cassara, Arg.
Erythromycin (p. 291·2).
Acne.

Indoco, India.
Hypromellose (p. 2189·2).
Dry eyes.

Erispan
Note: this name may be used for preparations of different composition.
Dainippon, Jpn.
Fludiazepam (p. 1073·3).
Psychosomatic disorders; autonomic imbalance.

Maver, Mex.
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Eristin *Atlas, Arg.*
Erythromycin lactobionate (p. 291·3); colistimethate sodium (p. 275·3).
Bacterial eye infections.

Eristrol *Progen, Ital.*
⊗Anastrozole (p. 742·1).

Erisuspen *Medifarma, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Erit *Duncan, Arg.*
Erythromycin (p. 291·2).
Bacterial infections.

Eritina
Note: this name may be used for preparations of different composition.
Cristalia, Braz.†
⊗Epoetin alfa (p. 1141·1).
Anaemias.

Eritine *Intas, Thai.*
⊗Epoetin alfa (p. 1141·1).

Eritós *Biolab Sanus, Braz.*
Dropropizine (p. 1662·2).
Cough.

Eritrazon *Cipan, Port.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Eritretin *Assos, Turk.*
Erythromycin (p. 291·2); tretinoin (p. 1725·2).

Eritrex *Ache, Braz.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Eritrex A *Ache, Braz.*
Erythromycin (p. 291·2); azulene (p. 2452·1).
Bacterial skin infections.

Eritril
Note: this name may be used for preparations of different composition.
Northia, Arg.
Enalapril maleate (p. 1371·1).
Hypertension.

Eritril Plus *Northia, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Eritro *Kocak, Turk.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Eritrobron *Casasco, Arg.*
Erythromycin estolate (p. 291·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Eritrocel *Labesfal, Port.*
Erythromycin lactobionate (p. 291·3).
Bacterial infections.

Eritrocina *1x2, Ital.; Amdipharm, Port.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin lactobionate (p. 291·3).
Bacterial infections.

Eritroderm *Valeant, Arg.*
Erythromycin (p. 291·2).
Acne.

Eritrofarm *Raymos, Arg.*
Erythromycin lactobionate (p. 291·3).
Bacterial conjunctivitis.

Eritrogen *Bioprofarma, Arg.*
⊗Epoetin beta (p. 1141·1).
Anaemias; autologous blood transfusion.

Ranbaxy, Thai.
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Eritrogobens *Normon, Spain.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Eritrolat *Liferpal, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Eritromax *Blausiegel, Braz.*
⊗Epoetin (p. 1141·1).
Anaemias.

Eritromed *Bausch & Lomb, Arg.*
Erythromycin estolate (p. 291·2) or erythromycin lactobionate (p. 291·3).
Bacterial eye infections.

Eritropharma *Alpharma, Mex.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Eritropiu *Farma 1, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of the iron.
Iron-deficiency anaemia.

Eritrosif *Sifar, Turk.*
Erythromycin (p. 291·2).
Bacterial infections.

Eritrosol *Solfran, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Eritroveinte *Medinova, Spain.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Eritrovier *Tecnofarma, Mex.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Eritrovis *HLB, Arg.*
Erythromycin (p. 291·2).
Bacterial eye infections.

Eritrowel *Teva, Mex.†*
Erythromycin (p. 291·2).
Bacterial infections.

Erivedge *Roche, Israel; Roche, UK; Genentech, USA.*
Vismodegib (p. 886·3).
Basal cell carcinoma.

Eriwest *Bruluagsa, Mex.*
Erythromycin stearate (p. 291·3); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Eriz *Ritz, India.*
Omega-3 fatty acids (p. 1460·1); omega-6 fatty acids (p. 2575·2); vitamin E (p. 2119·1).

Erjean *Erjean, Fr.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Erka *Aflofarm, Pol.*
Aspirin (p. 22·2); ethenzamide (p. 56·2); caffeine (p. 1203·3).
Pain.

Erkacin *Micro, India.*
Amikacin (p. 214·1).
Bacterial infections.

Erkältungs Bad N *Tetesept, Ger.†*
Eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); thyme oil (p. 2630·3); pine needle oil (p. 2591·1); camphor (p. 2466·2).
Cold symptoms.

Erkältungs-Entoxin *Meckel, Ger.*
Aconitum napellus (p. 2428·3); arum maculatum; drosera (p. 2497·2); echinacea (p. 2498·1).
Homoeopathic preparation.

Erladexone *Malaysia Chemist, Singapore.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Erlan *Landsteiner, Mex.*
⊗Erythropoetin (p. 1141·1).
Anaemias; autologous blood transfusion.

Erlecit *Doctum, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Erlicon *Polychronus, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Erliten *Malaysia Chemist, Singapore.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic bronchitis; hay fever; allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Erlmetin *Malaysia Chemist, Singapore.*
Cimetidine (p. 1827·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; adjunct in pancreatic insufficiency; Zollinger-Ellison syndrome.

Erlvirax *Malaysia Chemist, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ermes *SF, Ital.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ermm-1 *CIS, Cz.*
Erbium-169 citrate (p. 2224·1).
Joint disorders.

Ermofan *Chrispa (Χρισπα), Gr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ermolax *Chrispa (Χρισπα), Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Ermycin *Remedica, Singapore.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Ermysin *Orion, Fin.*
Erythromycin (p. 291·2).
Bacterial infections.

Ermytal *Nordmark, Rus.*
⊗Pancreatin (p. 2579·3).
Digestive disorders; pancreatic insufficiency.

Ernex *Casasco, Arg.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders; vulvovaginal disorders.

Ernex Duo *Casasco, Arg.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Ernodasa *Ern, Spain.*
Streptodornase (p. 2623·1); streptokinase (p. 1503·1).
Inflammation; soft-tissue damage; ulcers.

ERO
Note: this name may be used for preparations of different composition.
Scherer, USA.
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Ero
Note: this name may be used for preparations of different composition.
Lupin, India.
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).

Eroate *Lupin, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Ero-B *Lupin, India.*
Bromhexine hydrochloride (p. 1656·3); erythromycin estolate (p. 291·2).

Erocef *Ethica, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Erocin *Vensat, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Erocot *Nodysis, India.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Erocot-O *Nodysis, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Erocyn *Bactolac, India.*
Erythromycin (p. 291·2) or erythromycin estolate (p. 291·2).
Bacterial infections.

Erodium *Ivax, Arg.*
Bromperidol (p. 1041·3).
Psychoses.

Erod-M *Bestochem, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Erofica *Micro, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Erogran *Hovid, Singapore.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Hovid, Hong Kong.†
Erythromycin (p. 291·2).
Bacterial infections.

Erolcid *Pharmacia Upjohn, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Erolin *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; allergic skin reactions; pruritus.

Eroma *Finecure, India.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Eromed *Comed, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Eromycin *Julphar, UAE.*
Erythromycin (p. 291·2), erythromycin ethyl succinate (p. 291·2), or erythromycin stearate (p. 291·3).
Bacterial infections; intestinal amoebiasis.

Erope *Lincoln, India.*
Meropenem (p. 321·3).
Bacterial infections.

Erosfil *Andromaco, Chile.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Erosil *Pharmanel, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Mucolytic.

Erostatin *Nucleus, Denm.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Erostimin *Micro, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Erostimin 42 *Micro, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Erostin *Micro, India.*
Ebastine (p. 628·1).
Hypersensitivity reactions.

Erostin-DC *Micro, India.*
Ebastine (p. 628·1); phenylephrine (p. 1672·2).

Erotab *Hovid, Hong Kong†; Hovid, Singapore.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erotex *Sperko, Ukr.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Eroton *Phytopharm, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Erouclast *Sandoz, Ital.*
Atorvastatin (p. 1309·2).

Erowgliz *Arrow, Braz.*
Gliclazide (p. 472·3).
Diabetes mellitus.

E-Rox
Note: this name may be used for preparations of different composition.
Zota, India.
Roxithromycin (p. 356·2).
Bacterial infections.

Erox
Note: this name may be used for preparations of different composition.
Micro, India.
Amoxicillin (p. 216·2).
Bacterial infections.

Erox P *Micro, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Eroxade *Osoth, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Eroxet *Brown & Burk, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Erox-L *Micro, India.*
Amoxicillin (p. 216·2); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Eroxmit *Utopian, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Erpaclovir *Alapis, Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Erpecalm
Note: this name may be used for preparations of different composition.
Prisfar, Port.
Thyme oil (p. 2630·3); soapwort (p. 2617·2); lavender (p. 2541·1); lemon (p. 2542·3); chamomile (p. 2474·1); plantain (p. 2592·3); thuja (p. 2629·3); lappa (p. 2540·1); marjoram oil (p. 2550·1).
Herpes labialis.

Diametiss, Canad.†
Melissa (p. 2552·3).

Erpha Livita *Erlimpex, Indon.*
Vitamins; lysine (p. 2079·3); glutamic acid (p. 2070·2); calcium gluconate (p. 1783·3).
Dietary supplement.

Erpha Vit E *Erlimpex, Indon.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Erphacea *Erlimpex, Indon.*
Echinacea purpurea (p. 2498·1); phyllanthus niruri (p. 2590·1); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Immunostimulant.

Erphadrox *Erlimpex, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Erphalanz *Erlimpex, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Erphamol *Erlimpex, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Erphamoxy *Erlimpex, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Erphaseptan *Erlimpex, Indon.*
Povidone-iodine (p. 1767·1).
Mucous membrane, skin, and wound disinfection.

Erphathrocin *Erlimpex, Indon.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erphatrim *Erlimpex, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Erpimycin *Farmedia, Gr.*
Vidarabine (p. 1023·1).
Herpesvirus eye infections.

Erping *Yunmen, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Erpizon *Demo, Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Erradic *Libbs, Braz.*
Capsules, amoxicillin (p. 216·2); tablets, clarithromycin (p. 266·2); capsules, omeprazole (p. 1867·2).
Peptic ulcer.

Erravia *Valeant, Cz.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Erreflog *Adipharm, Gr.; Errekappa, Ital.*
Nimesulide (p. 101·3).
Mouth and throat disorders.

Errkes *Verisfield, Gr.*
Ketorolac trometamol (p. 80·2).
Eye inflammation following cataract surgery.

Errolon *Sandoz, Arg.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Errolon A *Sandoz, Arg.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Oedema; hypertension.

Ersefuryl *Sanofi-Aventis, Rus.*
Nifuroxazide (p. 331·3).
Gastroenteritis.

Erser *Serral, Mex.*
Aciclovir (p. 964·1).
Viral infections.

Ersilan *Teva, Cz.*
Etofylline (p. 1208·2); dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders.

Ersylan *Kimia, Indon.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Ertaczo *Ferrer-Novag, Mex.; Valeant, USA.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections; tinea pedis.

Ertracer *M2i, Irl.*
Fluorine-18 (p. 2224·1) labelled fludeoxyglucose.
Radionuclide agent for positron emission tomography.

Ertycin *Piramal, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Erudan *Unia, Neth.†; Unia, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Ervemin *Ivax, Arg.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Ervevax *GSK, Austral.†; GSK, Mex.†; GSK, NZ; GSK, Rus.†*
A rubella vaccine (attenuated RA 27/3 strain) (p. 2417·1).
Active immunisation.

Ervision *Erlimpex, Indon.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Antoxidant.

Ervopax *Homeocan, Canad.†*
⊗Atropine sulfate (p. 1310·2); corallium rubrum; magnesium phosphate dibasic (p. 1786·3); silicon dioxide (p. 2208·3); vitex agnus castus (p. 2432·2); zinc valerate (p. 2641·2).
Homoeopathic preparation.

Ervossil *Natiris, Venez.*
Ginger (p. 1844·1); chamomile (p. 2474·1); micromeria brownei; star anise (p. 2622·1).
Digestive disorders; dyspepsia.

Ervostal *Inter, Venez.*
Ergotamine tartrate (p. 674·1); crataegus (p. 2488·1); belladonna (p. 2453·3); phenobarbital (p. 535·2).

Erwinase *EUSA, Austria; CGF, Canad.; EUSA, Ger.†; EUSA, Gr.; EUSA, Irl.; EUSA, Neth.; NZ Medical & Scientific, NZ; EUSA, Port.; Beaufour-Ipsen, Singapore; Ipsen, Thai.; OPi, UK.*
Crisantaspase (asparaginase) (p. 743·3).
Acute lymphocytic leukaemia.

Erwinaze *EUSA, USA.*
Asparaginase (p. 743·3).
Acute lymphoblastic leukaemia.

Erxetilan *Leovan, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Éry *Bouchara-Recordati, Fr.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin propionate (p. 291·3).
Bacterial infections.

Ery *Intas, India.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

1A, Ger.†
Erythromycin stearate (p. 291·3).
Bacterial infections.

Eryacne *Galderma, Arg.; Galderma, Austral.; Galderma, Fr.; Galderma, Gr.; Emcure, India; Galderma, Ital.; Galderma, Neth.; Healthcare Logistics, NZ; Galderma, Singapore; Galderma, Thai.; Liba, Turk.; Taymed, Turk.; Galderma, UK; Galderma, Venez.*
Erythromycin (p. 291·2).
Acne.

Eryacnen *Galderma, Braz.; Galderma, Chile; Galderma, Mex.*
Erythromycin (p. 291·2).
Acne.

Eryaknen *Galderma, Austria; Galderma, Ger.; Galderma, Switz.*
Erythromycin (p. 291·2).
Acne.

Eryase *Ducray, Fr.†*
Avena (p. 2451·1); zinc oxide (p. 1729·1); copper sulfate (p. 2057·2).
Nappy rash.

Erybenz *Verisfield, Gr.*
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

Erybeta *Betapharm, Ger.†*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erybid *Methapharm, Canad.*
Erythromycin (p. 291·2).
Bacterial infections.

Erybros *Bros, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Eryc *Mayne, Austral.; Pfizer, Canad.; Biogal-Teva, Hung.†; Hospira, Singapore; Warner Chilcott, USA.*
Erythromycin (p. 291·2).
Bacterial infections.

Erycar *Ace, Philipp.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Erycette *Janssen-Cilag, S.Afr.†; Ortho Dermatological, USA.*
Erythromycin (p. 291·2).
Acne.

Erycin *YSP, Malaysia; Atlantic, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Orion, Denm.
Erythromycin (p. 291·2) or erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Cipla, India.
Erythromycin (p. 291·2) or erythromycin estolate (p. 291·2).
Bacterial infections.

Erycinum *Inresa, Ger.*
Erythromycin lactobionate (p. 291·3).
Bacterial infections.

Erycip *Cipla, India.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erycoat *Nufarindo, Indon.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erycon *TO-Chemicals, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erycream *Faran, Gr.*
Erythromycin (p. 291·2).
Acne.

Erycyn *Micro, Singapore.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erycytol *GL Pharma, Austria.*
Hydroxocobalamin (p. 2107·3).
Vitamin B_{12} deficiency; macrocytic anaemias; neuritis; neuralgia.

Eryderm *Abbott, Indon.; Abbott, Malaysia; Abbott, Mex.; Amdipharm, Neth.; Abbott, S.Afr.; Abbott, Singapore; Pro Concepta, Switz.†; Abbott, USA.*
Erythromycin (p. 291·2).
Acne.

Erydermec *Riemser, Ger.*
Erythromycin (p. 291·2).
Acne.

Ery-Diolan *Meda, Ger.†*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Eryechang *ErYe, China.*
Ozagrel sodium (p. 2579·1).

Eryfer *Cheplapharm, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemias.

Eryfer comp *Cheplapharm, Ger.†*
Ferrous sulfate (p. 2062·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Iron and vitamin deficiency.

Eryfluid *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.; Pierre Fabre Dermatologie, Fr.; Pierre Fabre, Neth.†; Pierre Fabre Dermo-Cosmetique, Port.*
Erythromycin (p. 291·2).
Acne.

Eryfrace *Rafarm, Gr.*
Sulfinpyrazone (p. 608·3).

Erygel *Kleva, Gr.; Merz, USA.*
Erythromycin (p. 291·2).
Acne; skin infections.

Erygine *Germandre, Fr.†*
Enoxolone (p. 54·2); allantoin (p. 1693·1); mallow (p. 2549·2).
Skin irritation in the genital area.

Eryhexal *Hexal, Austral.†; Hexal, Ger.†*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Eryko *MDI, S.Afr.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erylar *Arlex, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Erylide *Brown & Burk, Philipp.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Érylik *Bailleul, Fr.*
Erythromycin (p. 291·2); tretinoin (p. 1725·2).
Acne.

Erylik *D & M, Chile; Bailleul, Hong Kong.*
Erythromycin (p. 291·2); tretinoin (p. 1725·2).
Acne.

Ery-Max *Meda, Norw.; AstraZeneca, Philipp.†; Meda, Swed.*
Erythromycin (p. 291·2) or erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Erymax *Hospira, Irl.; Cephalon, UK.*
Erythromycin (p. 291·2).
Bacterial infections.

Erymed *Surya Dermato, Indon.*
Erythromycin (p. 291·2).
Acne.

Erymed Plus *Surya Dermato, Indon.*
Erythromycin (p. 291·2); tretinoin (p. 1725·2).
Acne.

Erymik *American Biocare, India.*
Amikacin (p. 214·1).
Bacterial infections.

Erymin *Milano, Thai.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Erymycin *Aspen, S.Afr.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Synco, Hong Kong.†
Erythromycin (p. 291·2).
Bacterial infections.

Erymyk *Elvipe, Gr.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erynit *Biosintez, Rus.*
Pentaerithrityl tetranitrate (p. 1465·1).
Ischaemic heart disease; heart failure.

Eryo *Vesco, Thai.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Erypac *Inpac, Thai.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Erypal *Jagsonpal, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Erypark *Pfizer, Chile.†*
Erythromycin (p. 291·2).
Bacterial infections.

Eryped *Abbott, Malaysia†; Abbott, Singapore; Abbott, USA.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections; amoebiasis.

Eryplast *Reckitt Benckiser, Fr.†*
Barrier cream.
Nappy rash.

Erypo *Janssen-Cilag, Austria; Janssen-Cilag, Ger.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Erypro *Biocon, India.*
⊗Epoetin alfa (p. 1141·1).
Autologous blood transfusion; anaemias.

Erysafe *USV, India.†*
Erythromycin (p. 291·2).
Bacterial infections.

Erysanbe *Sanbe, Indon.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erysate *United Drug, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erysia *Willow, India.*
Erythromycin (p. 291·2); zinc sulfate (p. 2126·2).
Acne.

Erysidoron 1 *Weleda, Canad.†; Weleda, Ger.; Weleda, S.Afr.†; Weleda, UK.*
Apis (p. 2445·2); belladonna (p. 2453·3).
Homoeopathic preparation.

Erysidoron 2 *Weleda, Ger.; Weleda, S.Afr.†*
Carbo betulae; sulfur (p. 1721·1).
Homoeopathic preparation.

Weleda, UK.
Birch; sulfur (p. 1721·1).
Homoeopathic preparation.

Weleda, Canad.†
Charcoal activated (p. 1537·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Erysidoron Nr 1 *Weleda, Austria.*
Apis mellifica (p. 2445·2); belladonna planta tota (p. 2453·3).
Homoeopathic preparation.

Erysidoron Nr 2 *Weleda, Austria.*
Carbo betulae; sulfur (p. 1721·1).
Homoeopathic preparation.

Erysil *Silom, Thai.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Erysoft *East West, India.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Erysol *Stiefel, Canad.*
Erythromycin (p. 291·2).
Acne.

Xepa-Soul Pattinson, Singapore.
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Eryson *Beacons, Singapore.*
Erythromycin (p. 291·2) or erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

CCM, Malaysia.
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Eryspans *American Remedies, India.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erystad *Stada, Austria.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erystamine-K *Biostam (Βιοσταμ), Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Erystat *Medpro, S.Afr.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Eryster *Hindustan Antibiotic, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Ery-Tab *Abbott, Thai.†; Arbor, USA.*
Erythromycin (p. 291·2).
Bacterial infections.

Eryteal *Pierre Fabre Dermo-Cosmetique, Arg.*
Cod-liver oil (p. 2056·3); halibut-liver oil (p. 2071·3); zinc oxide (p. 1729·1); cetrimonium bromide (p. 1742·3).
Nappy rash; burns.

Eryth-mycin *Pond's, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erythorate *Inpac, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erythrin *Interbat, Indon.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erythro *AA, Canad.; CT, Ger.; DHA, Hong Kong; DHA, Singapore.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erythrocin *Abbott, UK.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Link, Austral.; Amdipharm, Austria; Methapharm, Canad.; Abbott, Cz.†; Amdipharm, Ger.; Abbott, Gr.; Abbott, Indon.; Amdipharm, Irl.; Biotis, Israel; Abbott, Malaysia†; AFT, NZ; Abbott, Philipp.; Pharmaco, S.Afr.; Abbott, Thai.†; Abbott, USA.
Erythromycin ethyl succinate (p. 291·2), erythromycin lactobionate (p. 291·3), or erythromycin stearate (p. 291·3).
Bacterial infections.

Abbott, Hong Kong†; Pfizer, India; Fako, Turk.
Erythromycin (p. 291·2).
Bacterial infections.

Erythrocine *Pharma Logistics, Belg.; Amdipharm, Neth.; Pro Concepta, Switz.*
Erythromycin ethyl succinate (p. 291·2), erythromycin lactobionate (p. 291·3), or erythromycin stearate (p. 291·3).
Bacterial infections.

Érythrocine *CSP, Fr.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin lactobionate (p. 291·3).
Bacterial infections.

Erythroetin *Arterium, Ukr.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Erythroforte *Pharma Logistics, Belg.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Érythrogel *Bailleul, Fr.*
Erythromycin (p. 291·2).
Acne.

Erythrogel *Biospray, Gr.*
Erythromycin (p. 291·2).
Acne.

Erythrokem *Alkem, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Erythrolar *Lark, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Erythromed *Medicpharma, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erythroped *Amdipharm, Irl.; Abbott, UK.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Erythropen *Elpen (Ελπεν), Gr.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Erythroskin *Zekides, Gr.*
Erythromycin (p. 291·2).

Erythrostim *Microgen, Rus.*
⊗Epoetin beta (p. 1141·1).
Anaemias.

Erythro-Teva *Teva, Israel.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Erythrotrop *Teva, Hung.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Erytomin *Acdhon, Thai.*
Erythromycin (p. 291·2).
Bacterial infections.

Erytop
Note: this name may be used for preparations of different composition.
USV, India.
Cream; topical lotion: Erythromycin (p. 291·2).
Acne.

USV, India.
Topical gel: Clindamycin (p. 269·3).
Acne.

Erytral *Medikon, Indon.†*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Erytrolyve *Ethypharm, Neth.†*
Erythromycin (p. 291·2).
Bacterial infections.

Ery-V *Vista, Philipp.*
Erythromycin (p. 291·2).
Bacterial eye infections.

Erywell *American Biocare, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

ES *Stadmed, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Esafosfina *Biomedica, China; Biomedica, Hong Kong; Biomedica, Ital.; Biomedica, Thai.†*
Fosfructose trisodium (p. 2507·2).
Myocardial infarction; shock; phosphate deficiency; ischaemia of lower limbs; heart failure; obstructive airways disease.

Esafosfina Glutammica *Biomedica, Hong Kong.*
Fosfructose calcium (p. 2507·2); vitamin B substances (p. 2102·3); glutamine (p. 2070·3).
Metabolic disorders.

Esaldox *Recalcine, Chile.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Esalfon
Note: this name may be used for preparations of different composition.
Lafi, Chile.
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Vilco, Gr.
Sulpiride (p. 1107·3).
Psychoses.

Esalfon-D *Lafi, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Esam *Torrent, India.*
Levamlodipine.
Hypertension.

Esam AT *Torrent, India.*
⊗Atenolol (p. 1308·2); levamlodipine.

Esam LT *Torrent, India.*
Levamlodipine; losartan potassium (p. 1422·2).

Esam R *Torrent, India.*
Levamlodipine; ramipril (p. 1483·3).

Esamigran *Esan, Chile.*
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Esamisol *Esan, Chile.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; allergic rhinitis.

Esamisol Compuesto *Esan, Chile.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Esamisol Compuesto Dia y Noche *Esan, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); night tablets, paracetamol; pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Esamlo *Orchid, India.*
Levamlodipine.
Hypertension.

Esamlo AT *Orchid, India.*
⊗Levamlodipine; atenolol (p. 1308·2).
Hypertension; angina pectoris.

Esamlovin *East West, India.*
Levamlodipine besilate (p. 1304·1).
Hypertension.

Esancol *Esan, Chile.*
Nifuroxazide (p. 331·3); phthalylsulfathiazole (p. 339·3).
Diarrhoea.

Esancort *Esan, Chile.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Esanflu *Esan, Chile.*
Ambroxol hydrochloride (p. 1654·3).
Cough.

Esanfrix *Esan, Chile.*
Methyl salicylate (p. 92·1); phenylbutazone (p. 125·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Esanic *Merck, Arg.†*
Idebenone (p. 392·3).
Dementia.

Esanterm *Esan, Chile.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Esantop *Esan, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Esantuss *Esan, Chile.*
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1).
Cough.

Esapent *Pfizer, Ital.*
Omega-3 triglycerides (p. 1460·3).
Hypertriglyceridaemia; cardiovascular risk reduction.

Esarondil *Difa, Ital.*
Methacycline hydrochloride (p. 322·3).
Bacterial infections.

Esavir *Boniscontro & Gazzone, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Esavit *Norton, Ukr.†*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Esbelcaps *Medix, Mex.*
⊗Fenproporex hydrochloride (p. 2323·1); diazepam (p. 1063·2).
Obesity.

Esbeltex *Medix, Mex.*
Glucomannan (p. 2515·2).
Hyperglycaemia; hyperlipidaemias; obesity.

Esbericard novo *Schaper & Brummer, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Esbericum *Schaper & Brummer, Austria; Schaper & Brummer, Ger.*
St John's wort (p. 449·1).
Anxiety; depression; anxiety disorders.

Esberitop *Zeller, Switz.*
Tablets: Thuja (p. 2629·3); echinacea (p. 2498·1); wild indigo (p. 2647·2); vitamin C (p. 2110·3).
Cold symptoms.

Esberitox *MaxMedica, Swed.*
Wild indigo (p. 2647·2); echinacea purpurea; echinacea pallida (p. 2498·1); thuja (p. 2629·3).
Cold symptoms.

Schaper & Brummer, Austria; Schaper & Brummer, Ger.
Thuja (p. 2629·3); wild indigo (p. 2647·2); echinacea (p. 2498·1).
Infections; respiratory-tract and skin infections; tonic.

Schaper & Brummer, Ukr.
Wild indigo (p. 2647·2); echinacea purpurea (p. 2498·1); echinacea pallida; thuja (p. 2629·3).
Cold symptoms.

Schaper & Brummer, China.
Thuja (p. 2629·3); baptisia (p. 2647·2); echinacea (p. 2498·1); ascorbic acid (p. 2110·3).
Infections.

Esberitox mono *Schaper & Brummer, Ger.*
Echinacea purpurea (p. 2498·1).
Respiratory- and urinary-tract infections.

Esberitox N *Schaper & Brummer, Malaysia; Schaper & Brummer, Pol.*
Thuja (p. 2629·3); wild indigo (p. 2647·2); echinacea (p. 2498·1).
Respiratory-tract infections; infections.

Sigma, Austral.
Thuja (p. 2629·3); baptisia tinctoria (p. 2647·2); echinacea purpurea (p. 2498·1); echinacea pallida.
Cold and influenza symptoms.

Esberiven *CSP, Fr.*
Melilot (p. 2552·3); heparin sodium (p. 1396·3).
Peripheral vascular disorders.

Faes, Spain.
Troxerutin (p. 2505·3).
Peripheral vascular disorders.

Craveri, Arg.
Tablets: Coumarin (p. 2487·2); troxerutin (p. 2505·3).
Venous insufficiency; oedema.

Craveri, Arg.
Topical emulsion: Coumarin (p. 2487·2).
Soft-tissue disorders.

Esberiven Fort *CSP, Fr.*
Melilot (p. 2552·3); rutoside (p. 2505·3).
Venous insufficiency; haemorrhoids.

Esboxyl *Filadams, Philipp.*
Carbocisteine (p. 1658·1).
Cough.

Esbriet *Intermune, Denm.; Intermune, Ger.; Intermune, Irl.; Intermune, Neth.; Intermune, Norw.; Intermune, Swed.; Intermune, UK.*
Pirfenidone (p. 2592·1).
Idiopathic pulmonary fibrosis.

Escab Plus *Daffohils, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1); permethrin (p. 2159·3).

Escadra *KRKA, Denm.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Escalar *Hasco-Lek, Pol.*
Aesculus (p. 2431·2); arnica (p. 2447·2); calendula (p. 2465·2).
Venous insufficiency; oedema; soft-tissue injury.

Escandar *San Marino, Philipp.†*
Mefenamic acid (p. 85·3).
Osteoarthritis; pain; rheumatoid arthritis.

Escapelle *Gedeon Richter, China†; Gedeon Richter, Cz.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Richter, Pol.; Gedeon Richter, Rus.; Pharmaplan, S.Afr.; Gedeon Richter, Ukr.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Escapin-N *Streger, Mex.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Escar T *Prater, Chile.*
Centella (p. 1698·3).

Escar T-Neomicina *Prater, Chile.*
Neomycin (p. 329·3); centella (p. 1698·3).

Es-Care *Zee, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Escertal *Zentiva, Pol.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; social phobia; obsessive-compulsive disorder; panic disorder.

Esceven *Herbapol Poznan, Pol.*
Aesculus (p. 2431·2).
Venous insufficiency; oedema.

Escilan *Cantabria, Spain.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Escimylan *Mylan, Spain.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Escin *Cinerea, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Escin Plus *Cinerea, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Esaina Forte *Omega, Arg.*
Aescin (p. 2431·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Escina Omega *Omega, Arg.*
Aescin (p. 2431·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Escinapram *Actavis, Denm.†*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Escinogel *Bouchara-Recordati, Fr.†*
Bamethan sulfate (p. 1314·1); aescin (p. 2431·2).
Peripheral vascular disorders.

Esciprex *Rowex, Irl.*
Escitalopram oxalate (p. 416·2).
Depression.

Esciprox *HLB, Arg.*
Escitalopram oxalate (p. 416·2).
Depression.

Escirdec *Sandoz, Cz.*
Escitalopram oxalate (p. 416·2).
Depression.

Escita *Mediez, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Escita Plus *Mediez, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Escitaburg *Tiefenbacher, Neth.†*
Escitalopram oxalate (p. 416·2).
Depression.

Escitafloc *Tiefenbacher, Neth.†*
Escitalopram oxalate (p. 416·2).
Depression.

Escitaham *Sandoz, Port.†*
Escitalopram oxalate (p. 416·2).
Depression.

Escitalis *Tiefenbacher, Neth.†*
Escitalopram oxalate (p. 416·2).
Depression.

Escitalodeon *Tiefenbacher, Neth.†*
Escitalopram oxalate (p. 416·2).
Depression.

Escitalofi *Winthrop, Neth.†*
Escitalopram oxalate (p. 416·2).
Depression.

Escitan *Medley, Braz.*
Sildenafil (p. 2364·1).

Escitapax *Reliance, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Escitasan *Clonmel, Irl.; Lannacher, Pol.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; anxiety; social phobia; obsessive-compulsive disorder.

Esciterokam *LKM, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Escitil *Egis, Cz.; Egis, Pol.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; anxiety; obsessive-compulsive disorder; social phobia.

Escitomar *Genthon, Irl.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; obsessive-compulsive order; anxiety; social phobia.

Escitotab *Genthon, Irl.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; obsessive-compulsive order; anxiety; social phobia.

Escitrac *Minova, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Escitrac-CZ *Minova, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Escitralix *Ratiopharm, Cz.*
Escitalopram oxalate (p. 416·2).

Escizane *Evalar, Rus.*
Aesculus (p. 2431·2).
Chronic venous insufficiency; soft-tissue inflammation.

Esclebin *Alacan, Spain.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Esclerobion *Merck, Port.*
Vitamin A acetate (p. 2098·3); pyridoxine hydrochloride (p. 2105·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Atherosclerosis; vascular disorders.

Esclerovitan *Merck, Braz.*
Vitamin A (p. 2098·3); vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1).

Merck, Mex.
Vitamins; minerals.

Esclerovitan Antioxidante *Merck Serono, Arg.*
Vitamins; minerals.
Dietary supplement.

Esclerovitan E *Merck Serono, Arg.*
Vitamin A palmitate (p. 2098·3); pyridoxine hydrochloride (p. 2105·3); alpha tocoferil acetate (p. 2119·2).

Esclim *Women First, USA.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Esclima *Solvay, Ital.†*
Estradiol (p. 2271·1).
Menopausal disorders.

Esclox-CL *Prompt Cure, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Escobal *Ester, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Escodaron *Streuli, Switz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Escodyn *Streuli, Switz.†*
Vitamins; minerals.

Escoprim *Streuli, Switz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Escor *Merck, Cz.†; Orion, Fin.; Trommsdorff, Ger.*
Nilvadipine (p. 1455·2).
Hypertension.

EsCordi Cor *Actavis, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Escoretic *Streuli, Switz.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Escotussin *Streuli, Switz.*
Dihydrocodeine thiocyanate (p. 52·2); belladonna (p. 2453·3); drosera (p. 2497·2); guaifenesin (p. 1666·2).
Cough.

Escudo *Lampugnani, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Esculape *Omega, Fr.†*
Eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3); melaleuca oil (p. 2551·1); lavender oil (p. 2541·1); rosewood oil; laurus nobilis oil; clove oil (p. 2481·3); cinnamon oil (p. 2479·3); dementholised mint oil (p. 2560·1).
Cold symptoms.

Esculeol P *HMA, Arg.*
Oral drops: Aesculus (p. 2431·2); rutoside (p. 2505·3).
Haemorrhoids; venous insufficiency.

Medical, Arg.
Ointment: Benzocaine (p. 1980·2); hamamelis (p. 2523·3); camphor (p. 2466·2); rhatany (p. 2603·3).
Haemorrhoids.

Escumycin *Orion, Denm.*
Erythromycin (p. 291·2).
Bacterial infections.

Esdegen *Diba, Mex.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Esdep *Piramal, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Esdil *Medley, India.*
Levamlodipine.
Hypertension.

Esdil AT *Medley, India.*
⊗Levamlodipine; atenolol (p. 1308·2).

ESE *Amdipharm, Port.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Eseflah *Pasteur, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Eselan *Anfarm, Gr.; Dem, Turk.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Anfarm, Thai.; TTN, Thai.
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Eselin *Svizera, India; Sifarma, Ital.*
Etamsylate (p. 1145·2).
Haemorrhage; vascular disorders; menorrhagia.

Esemdent *Schulke & Mayr, Singapore.*
Alexidine (p. 1735·3); phenoxyethanol (p. 1764·3).
Gum disorders; oral hygiene.

Esemtan *Schulke & Mayr, Singapore.*
Soap substitute.
Skin cleansing; wound cleansing; pruritus.

Eser Metaller *Abbott, Turk.*
Copper (p. 2057·1); sodium (p. 1795·1); manganese (p. 2081·2); zinc (p. 2126·1).
Parenteral nutrition.

Esertia *Europharma, Denm.; Orifarm, Denm.; Almirall, Spain.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; social phobia; panic disorder; obsessive-compulsive disorder.

Esete *Teva, Cz.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Esfancy *Aamorb, India.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Esfany *Aamorb, India.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Esfany-CZ *Aamorb, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Esfarase *Sanofi-Aventis, Gr.*
⊗Somatorelin (p. 1930·1).

Esfate-O *Allenge, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Esfix *Rass, India.*
Cefixime (p. 240·3).
Bacterial infections.

Esfolat *Puspa, Indon.*
Folic acid (p. 2063·1); vitamins; minerals.
Dietary supplement.

Esgic *Forest Pharmaceuticals, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Esgic-Plus *Forest Pharmaceuticals, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Esgiderm *Sarabhai Piramal, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); clioquinol (p. 273·1); tolnaftate (p. 596·1).

Esgipyrin *Piramal, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; pain.

Esgipyrin DS *Piramal, India.*
Diclofenac sodium (p. 48·3).
Pain.

Esgipyrin-T *Piramal, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Eshlin *Sunward, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Esia *Alkem, India.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Eside *VHB, India.*
Etoposide (p. 790·2).
Small cell lung cancer; testicular cancer.

Esidrex *Novartis, Fr.; Ciba, Gr.; Novartis, India; Novartis, Ital.; Novartis, Norw.; Sandoz, Spain; Novartis, Swed.; Novartis, Switz.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; diabetes insipidus; lactation inhibition; Ménière's disease; heart failure; hypercalciuria.

Esidrix *Novartis, Ger.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Esiflo *Lupin, India.*
⊗Fluticasone propionate (p. 1638·1); salmeterol (p. 1224·1).
Obstructive airways disease.

Esilgan *Takeda, Indon.; Takeda, Ital.; Takeda, Philipp.*
Estazolam (p. 1072·2).
Insomnia.

Esimil *Ciba, USA.*
⊗Guanethidine monosulfate (p. 1395·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Esine *Minerva (Μινερβα), Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Esinol *Pharmacore, Indon.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Esipral *Avansor, Fin.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Esipram *CNS, Austral.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; social phobia.

Esitalo *Sandoz, Austral.*
Escitalopram oxalate (p. 416·2).
Depression; obsessive-compulsive disorder.

Esitonic *Medihealth, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Esitor *La Pharmaceuticals, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Esitor Forte *La Pharmaceuticals, India.*
Clonazepam (p. 519·1); escitalopram oxalate (p. 416·2).

Esjoy *Gentech, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Esjoy Plus *Gentech, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Eskacef *Julphar, UAE.†*
Cefradine (p. 249·1).
Bacterial infections.

Eskaflam *GSK, Mex.*
Nimesulide (p. 101·3).
Pain; fever; inflammation; peri-articular and soft-tissue disorders.

Eskalit *GSK, Arg.*
Lithium carbonate (p. 427·3).
Mania.

Eskamel *Dermatech, Austral.†; Group, S.Afr.†*
Resorcinol (p. 1718·3); sulfur (p. 1721·1).
Acne.

Eskapar *Armstrong, Mex.†*
Nifuroxazide (p. 331·3).
Diarrhoea.

Eskapar Compuesto *Armstrong, Mex.*
Nifuroxazide (p. 331·3); metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis.

Eskaycillin *GSK, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Eskazine *Goldshield, Spain.†*
Trifluoperazine hydrochloride (p. 1113·2).
Psychoses; anxiety.

Eskazole *GSK, Austral.; GSK, Austria; GSK, Fr.; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; GSK, Israel; Armstrong, Mex.; GSK, Neth.; GSK, Spain.*
Albendazole (p. 149·1).
Intestinal nematode infections; cestode infections; giardiasis; echinococcosis; cysticercosis; capillariasis; trichinosis; strongyloidiasis; neurocysticercosis.

Eskim *Sigma-Tau, Ital.*
Omega-3 triglycerides (p. 1460·3).
Hypertriglyceridaemia; cardiovascular risk reduction.

Eskimo-3 *H & H, Hung.*
Fish oil (p. 1460·3).
Cardiovascular disorders; skin disorders; rheumatoid arthritis.

Cardinova, Swed.†
Omega-3-acid triglycerides.
Cardiovascular health.

Eskinase *Dabur, India.*
Streptokinase (p. 1503·1).
Myocardial infarction; thromboembolic disorders.

Eskold *GSK, India.*
Phenylpropanolamine hydrochloride (p. 1674·1); diphenylpyraline hydrochloride (p. 627·2).
Cold symptoms; rhinitis; nasal congestion; hypersensitivity reactions.

Eskold Expectorant *GSK, India.*
Phenylpropanolamine hydrochloride (p. 1674·1); diphenylpyraline hydrochloride (p. 627·2); guaifenesin (p. 1666·2).
Cold symptoms; cough.

Eskornade
Note: this name may be used for preparations of different composition.
SmithKline Beecham, S.Afr.†
Phenylpropanolamine hydrochloride (p. 1674·1); diphenylpyraline hydrochloride (p. 627·2).
Upper respiratory-tract disorders.

Eskotropil *Eskom, Rus.*
Piracetam (p. 393·3).
Mental function disorders; learning difficulties in children; sickle-cell anaemia; cerebrovascular disorders; alcohol withdrawal syndrome.

Eskuf-AL *Laborate, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Eskuvit *Arterium, Ukr.*
Oral drops: Aesculus (p. 2431·2); thiamine hydrochloride (p. 2103·1).
Venous insufficiency; soft-tissue injury.

Arterium, Ukr.
Tablets: Aesculus (p. 2431·2).
Peripheral vascular disorders.

Eslax *MSD, Jpn.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Eslidine *Nizpharm, Rus.*
Methionine (p. 1558·2).
Liver disorders; psoriasis; atherosclerosis; diabetes mellitus; fatigue.

Eslite *Elder, India.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Eslo *Zuventus, India.*
Levamlodipine.
Hypertension.

Eslo Tan *Zuventus, India.*
Losartan potassium (p. 1422·2); levamlodipine.

Eslo-AT *Zuventus, India.*
⊗Atenolol (p. 1308·2); levamlodipine.

Eslo-D *Zuventus, India.*
⊗Amlodipine (p. 1304·1); hydrochlorothiazide (p. 1403·2).

Eslofen *Essenpharma, Philipp.†*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Eslopram *Eczacibasi, Turk.*
Citalopram hydrobromide (p. 411·1).

Eslorex *Eczacibasi, Turk.*
Escitalopram oxalate (p. 416·2).

Eslo-Ril *Zuventus, India.*
Levamlodipine besilate (p. 1304·1); ramipril (p. 1483·3).

Eslova *Zuventus, India.*
Atorvastatin (p. 1309·2); levamlodipine.

Esmalfort *Delta, Braz.*
Keratin (p. 2538·1); panthenol (p. 2582·2); vitamins.

Esma-PD *Obsurge, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Esmax *Ali, Turk.*
Escitalopram oxalate (p. 416·2).

Esme Topico *Esme, Arg.*
Strontium chloride (p. 2623·1); lidocaine hydrochloride (p. 1988·2).
Hypersensitive teeth.

Esmedent *Esme, Arg.*
Xylitol (p. 2220·3); sodium fluoride (p. 2089·2).
Dental care.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Esmedent Dientes Sens Blanq + Ctrol Sarro *Esme, Arg.*
⊗Potassium nitrate (p. 1766·2); potassium pyrophosphate (p. 2619·3).
Sensitive teeth.

Esmedent Dientes Sensibles *Esme, Arg.*
⊗Potassium nitrate (p. 1766·2); triclosan (p. 1773·2).
Sensitive teeth.

Esmedent con Fluor *Esme, Arg.*
Triclosan (p. 1773·2); sodium fluoride (p. 2089·2); benzocaine (p. 1980·2); allantoin (p. 1693·1).
Dental hygiene; sensitive teeth.

Esmeron *Schering-Plough, Austral.; Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; MSD, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; Schering-Plough, Fr.; Essex, Ger.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Organon, India; Schering-Plough, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Schering-Plough, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Sanofi-Aventis, S.Afr.; MSD, Singapore; Organon, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK; Organon, Ukr.; Organon, Venez.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Esmocard *Orpha-Devel, Cz.; Orpha-Devel, Fin.; Stragen, Ger.; Orpha-Devel, Gr.; Troikaa, India; Orpha-Devel, Irl.; Orpha-Devel, Port.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension.

Esmolan *Cristalia, Braz.*
⊗Esmolol hydrochloride (p. 1377·3).

Esmon *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
⊗Desmopressin (p. 2355·1).
Diabetes insipidus; haemorrhagic disorders.

Esmya *Gedeon Richter, Denm.; Gedeon Richter, Fr.; Gedeon Richter, Neth.; Gedeon Richter, Norw.; PregLem, UK.*
Ulipristal acetate (p. 2312·1).
Uterine fibroids.

Esnadec *Ester, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Esnicol *Essenpharma, Philipp.†*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Esnil *Dewcare, India.*
Aceclofenac (p. 16·2); drotaverine (p. 2497·3).

Esnolol *Emcure, Thai.*
⊗Esatenolol (p. 1377·2).
Hypertension; myocardial infarction; angina pectoris.

Esnopil *Biomedica, India.*
Cetirizine hydrochloride (p. 619·2); diethylcarbamazine citrate (p. 153·1).

Eso 70 *Esoform, Ital.*
Paraformaldehyde (p. 1763·1); hydrogen peroxide 40/45 (p. 1755·2).
Room disinfection.

Eso Deterferri *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1).
Instrument disinfection.

Eso Ferri *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1).
Instrument disinfection.

Eso Ferri Alcolico *Esoform, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Instrument disinfection.

Eso Ferri Plus *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Instrument disinfection.

Eso H1 *Esoform, Ital.*
Glutaral (p. 1753·2).
Instrument disinfection.

Eso S 80 *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3).
Instrument disinfection.

Eso Zim *Esoform, Ital.*
Proteolytic enzymes; sodium laurilsulfate (p. 2210·3); cocamidopropyl betaine.
Instrument disinfection.

Esoalcolico Incolore *Esoform, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Skin, hand, burn, and wound disinfection.

Esobar *Therapex, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Esobax *Ranbaxy, Neth.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esocard *Samarth, India.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension.

Esocetic *Esoform, Ital.*
Peracetic acid (p. 1763·1).
Instrument disinfection.

Esocool *PC India, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esocor P *Acella, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Es-OD *Piramal, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esodar *Cassara, Arg.*
⊗Prednisolone (p. 1645·2); chloramphenicol (p. 257·1).
Infected eye and ear disorders.

Esodax *Munir, Turk.*
Etodolac (p. 57·1).

Esodec *KRKA, Denm.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esodrox *Esoform, Ital.*
Peracetic acid (p. 1763·1).
Instrument disinfection.

Esofag *Micro, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esofag-D *Micro, India.*
Domperidone (p. 1838·1); esomeprazole (p. 1841·1).

Esofenol 60 *Esoform, Ital.*
Sodium *o*-phenylphenol (p. 1762·3).
Surface disinfection.

Esofenol Ferri *Esoform, Ital.*
Orthobenzyl parachlorophenol (p. 1763·1); orthophenylphenol (p. 1762·3).
Instrument disinfection.

Esoflo *Intra-Labs, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esoform 92 *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1); glutaral (p. 1753·2).
Surface disinfection.

Esoform Alcolico *Esoform, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Skin disinfection.

Esoform Jod 75 *Esoform, Ital.*
Povidone-iodine (p. 1767·1).
Hand disinfection.

Esoform Mani-Cute *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin and hand disinfection.

Esoform 7 mc *Esoform, Ital.*
Paraformaldehyde (p. 1763·1).
Surface and room disinfection.

Esoform 70 mc *Esoform, Ital.*
Paraformaldehyde (p. 1763·1).
Room and surface disinfection.

Esoga-RD *Piramal, India.*
Rabeprazole (p. 1881·1); domperidone (p. 1838·1).
Gastric hyperacidity; heartburn.

Eso-Jod *Esoform, Ital.*
Povidone-iodine (p. 1767·1).
Wound disinfection; skin disinfection.

Esolut *Angelini, Ital.*
Progesterone (p. 2300·2).
Luteal insufficiency.

E-Solve *Syosset, USA.*
Vehicle for topical preparations.

Esomac *Cipla, India.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Esomax *Quesada, Arg.*
Esomeprazole (p. 1841·1).

Esomed *Mediline, Israel.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Esomel *KRKA, Denm.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esomep *AstraZeneca, Switz.*
Esomeprazole magnesium (p. 1841·1) or esomeprazole sodium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

InnoGen, Philipp.
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esompro *Sandoz, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esomylan *Generics, Cz.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esonexa *Farmak, Ukr.*
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esonide *Kleva, Gr.; Kleva, Singapore.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders; rhinitis; nasal polyps.

Esonovag *Novag, Mex.*
Conjugated oestrogens (p. 2260·1).
Oestrogen deficiency; osteoporosis; cardiovascular risk reduction in postmenopausal women; atrophic vaginitis; atrophic urethritis.

Esopho-Cat *Therapex, Canad.†*
Barium sulfate (p. 1583·2).
Contrast medium for computerised axial tomography.

Esopral *Orifarm, Denm.; Bracco, Ital.; Euro Registratie, Neth.; Farmagon, Norw.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esopram *Actavis, Ukr.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Esopraz *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Esoprazol *Bago, Arg.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esoprex *Zentiva, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Esorest *Centaur, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esorid *Sun, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Esorid MPS *Sun, India.*
Cisapride (p. 1831·3); dimeticone (p. 1886·2).

Esoriv *East African, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esosan Casa *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1).
Surface disinfection.

Esosan Gel *Esoform, Ital.*
Denatured ethanol (p. 1760·3).
Hand disinfection.

Esosan Gel Mani *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Hand disinfection.

Esosan Pronto *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Skin disinfection.

Esosan Soap *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Esotar *KRKA, Denm.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Esoterica Facial *Medicis, Canad.*
Hydroquinone (p. 1705·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Skin pigmentation disorders.

Esoterica Facial and Sunscreen *Medicis, USA.*
Hydroquinone (p. 1705·1); padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Hyperpigmentation.

Esoterica Fade Cream *Medicis, USA.*
Hydroquinone (p. 1705·1); padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Hyperpigmented skin disorders.

Esoterica Regular *Medicis, Canad.; Medicis, USA.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders; hyperpigmentation.

Esoterica Sunscreen Fade *Medicis, Canad.*
Hydroquinone (p. 1705·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1).

Esoterica Unscented *Medicis, Canad.†*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Esotrax *Cadila, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Esoxium *Cipla, Ukr.*
Esomeprazole (p. 1841·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis; dyspepsia; Zollinger-Ellison syndrome.

Esoxium Combi *Cipla, Ukr.*
14 Tablets, esomeprazole magnesium (p. 1841·1); 14 tablets, clarithromycin (p. 266·2); 14 tablets, amoxicillin (p. 216·2).
Peptic ulcer.

Esoz *Glenmark, India; Galeno, Venez.*
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; heartburn.

Esoz-D *Glenmark, India.*
Esomeprazole (p. 1841·1); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia; nausea and vomiting; flatulence.

Espabion *Degorts, Mex.*
Trimebutine (p. 2634·1).
Gastrointestinal motility disorders.

Espa-Carb *Esparma, Ukr.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Espacil *Valeant, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Espacil Compuesto *Valeant, Mex.*
Hyoscine butylbromide (p. 1845·3); clonixin lysine (p. 40·1).
Smooth muscle pain and spasm.

Espadol *Reckitt Benckiser, Arg.*
Chloroxylenol (p. 1748·2).
Disinfection.

Espafarm *Continentales, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Espa-Lipon *Esparma, Rus.; Esparma, Ukr.*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy; alcoholic polyneuropathy; hepatitis; cirrhosis; atherosclerosis.

Espam *Triton, India.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Espanone *Rhema, Singapore.*
Tocotrienol; ubidecarenone (p. 2637·1).
Hypercholesterolaemia.

E-Spar
Note: this name may be used for preparations of different composition.
Zota, India.
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Espar
Note: this name may be used for preparations of different composition.
Biosans, India.
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Greater Pharma, Thai.
Aspartame (p. 2169·2).
Sugar substitute.

Esparaloz Comp *Actavis, Denm.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Espar-CL *Biosans, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Esparflin *Roemmers Rowe, Venez.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Espasal *Offenbach, Mex.*
Simeticone (p. 1886·2); pipenzolate bromide (p. 1878·1).
Smooth muscle spasm.

Espasevit *Richmond, Arg.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Espasmo Biotenk *Biotenk, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Espasmo Canulase *Novartis Consumer, Port.†*
⊗Cellulase (p. 2473·1); dimeticone (p. 1886·2); glutamic acid hydrochloride (p. 2070·3); metixene hydrochloride (p. 909·2); pancreatin (p. 2579·3); pepsin (p. 2586·1); sodium dehydrocholate (p. 2492·1).

Espasmo Cibalena *Novartis, Arg.*
Propyphenazone (p. 127·3); drofenine hydrochloride (p. 1839·3); codeine phosphate (p. 40·2).

Espasmo Cibalgina *Novartis, Chile; Sandoz, Mex.*
Propyphenazone (p. 127·3); drofenine hydrochloride (p. 1839·3).
Smooth muscle pain and spasm.

Espasmo Cibalgina Compuesta *Novartis, Chile.†*
Propyphenazone (p. 127·3); drofenine hydrochloride (p. 1839·3); codeine phosphate (p. 40·2).
Smooth muscle spasm and pain.

Espasmo Dimetiliv *EMS, Braz.*
Dimeticone (p. 1886·2); homatropine (p. 2007·3).

Espasmo Dioxadol *Bago, Arg.*
Octatropine methylbromide (p. 1866·2); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Espasmo Dolex *Ivax, Arg.*
Clonixin lysine (p. 40·1); pargeverine (p. 1877·1).
Smooth muscle spasm.

Espasmo Flatol *Legrand, Braz.*
Simeticone (p. 1886·2); homatropine methylbromide (p. 2007·3).

Espasmo Ibuprofeno *Elisium, Arg.*
Ibuprofen (p. 68·2); homatropine (p. 2007·3).
Painful smooth muscle spasm.

Espasmo Luftal *EMS, Braz.*
Homatropine methylbromide (p. 2007·3); dimeticone (p. 1886·2).
Smooth muscle spasm.

Espasmo Silidron *GSK, Braz.*
Dimeticone (p. 1886·2); camylofin hydrochloride (p. 2467·1).
Smooth muscle spasm.

Espasmocron *Delta, Braz.†*
Atropine sulfate (p. 1310·2); papaverine hydrochloride (p. 2362·3); thiamine hydrochloride (p. 2103·1); dipyrone (p. 53·3).
Smooth muscle spasm.

Espasmodid Composto *Uniao Quimica, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Espasmofin *Oriental, Arg.*
Homatropine (p. 2007·3); ibuprofen (p. 68·2).
Painful smooth muscle spasm.

Espasmogress *Parggon, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Espasmol *Biotenk, Arg.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Painful smooth muscle spasm.

Espasmotropin *Sintesina, Arg.*
Homatropine methylbromide (p. 2007·3).
Smooth muscle spasm.

Espauz *Glenmark, India.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Espaven
Note: this name may be used for preparations of different composition.
Gezzi, Arg.
Ranitidine (p. 1882·1).
Gastric hyperacidity.

Valeant, Mex.
Dimeticone (p. 1886·2); calcium pantothenate (p. 2085·2).
Gastrointestinal disorders.

Espaven Alcalino *Valeant, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastrointestinal hyperacidity.

Espaven Antigas *Gezzi, Arg.*
Simeticone (p. 1886·2).
Flatulence.

Espaven Enzimatico *Valeant, Mex.*
⊗Pancreatin (p. 2579·3); dimeticone (p. 1886·2); ox bile (p. 2457·2); *Aspergillus niger* cellulase (p. 2473·1).
Gastrointestinal disorders.

Espaven MD *Valeant, Mex.*
Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2).
Gastrointestinal disorders.

Espaven Pediatrico *Valeant, Mex.*
Dimeticone (p. 1886·2).
Dyspepsia; flatulence; meteorism.

Espax *APS, Port.†*
Escitalopram oxalate (p. 416·2).

Especlor *Darya-Varia, Indon.†*
Cefaclor (p. 232·3).
Bacterial infections.

Espectocural *Raymos, Arg.*
Bromhexine (p. 1656·3); benzydamine (p. 29·2).
Cough.

Espeden *Qualigen, Spain.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Espelio *Gerolymatos, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Espenal *Sriprasit, Thai.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Esperal *Sanofi-Aventis, Fr.; Torrent, Indiat; Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Esperan *Taisho, Jpn.*
Oxapium iodide (p. 1874·3).
Gastrointestinal spasm; renal calculi.

Espercil *Grunenthal, Chile.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hyperfibrinolysis.

Esperson *Sanofi-Aventis, Braz.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Thai.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Esperson N *Sanofi-Aventis, Braz.*
⊗Desoximetasone (p. 1630·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Espesan *Nutricia-Bago, Arg.*
Preparation for enteral nutrition.
Dysphagia.

Espesil *Orion, Fin.*
⊗Acebutolol hydrochloride (p. 1289·2).
Angina pectoris; hypertension; arrhythmias; myocardial infarction.

Espestesin *3M Espe, Irl.*
Articaine hydrochloride (p. 1980·1). Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Espeyen *Specifar, Ital.*
Esomeprazole magnesium (p. 1841·1).

Espididol *Zambon, Spain.*
Ibuprofen arginine (p. 68·2).
Pain; fever.

Espidifen *Zambon, Spain.*
Ibuprofen arginine (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; pain; fever.

Espimax *Klonal, Arg.*
⊗Spironolactone (p. 1499·3).
Hypertension.

Espin
Note: this name may be used for preparations of different composition.
Intas, India.
Levamlodipine.
Hypertension.

Taejoon, Singapore.
Dosulepin hydrochloride (p. 414·1).
Depression.

Espinal *Intermed, Gr.*
Citalopram (p. 411·1), citalopram hydrobromide (p. 411·1), or citalopram hydrochloride (p. 411·1).
Depression.

Espin-AT *Intas, India.*
⊗Levamlodipine; atenolol (p. 1308·2).

Espin-LT *Intas, India.*
Levamlodipine; losartan (p. 1422·2).

Espiride *Aspen, S.Afr.*
Sulpiride (p. 1107·3).
Psychoses.

Espirolona *Cazi, Braz.*
⊗Spironolactone (p. 1499·3).
Hypertension.

Espo *Kirin, China; Kirin, Jpn.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; anaemia; autologous blood transfusion.

Espogen *LG, China.*
⊗Recombinant human erythropoietin (p. 1141·1).

LG Life Sciences, India; LG Life Sciences, Thai.
⊗Epoetin alfa (p. 1141·1).
Autologous blood transfusion; anaemias.

Espol *Nizpharm, Rus.*
Coriander oil (p. 2487·1); lavender oil (p. 2541·1); capsicum (p. 2469·3); dimethyl sulfoxide (p. 2182·2); chloroform (p. 1898·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Espontal *Panalab, Arg.*
Tamsulosin hydrochloride (p. 2369·1).

Espra *Zydus, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Espraden *Degorts, Mex.*
Metoclopramide hydrochloride (p. 1862·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastrointestinal disorders.

Espran *Torrent, Braz.*
Escitalopram (p. 416·2).

Esprasone *Seid, Spain.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Esprenit *Hennig, Ger.*
Ibuprofen (p. 68·2) or ibuprofen sodium (p. 68·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Esprit *Bayer, Austral.†*
Test for glucose in blood (p. 2516·3).

Esprit Sensor *Bayer Diagnostics, Irl.†*
Test for glucose in blood.
For use with Esprit Glucometer.

Esprital *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Ukr.*
Mirtazapine (p. 436·1).
Depression.

Espritam *Kleva, Gr.*
Piracetam (p. 393·3).

Espritin *Petrasch, Austria.†*
Lactic acid (p. 2539·1).
Psoriasis.

Esprocy *Nufarindo, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic disorders.

Esprolan *Medana, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Espumisan *Berlin-Chemie, China; Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.; Berlin-Chemie, Pol.; Menarini, Pol.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; flatulence; detergent poisoning; infant colic; meteorism; aerophagia; dyspepsia; preparation for gastrointestinal investigation.

Esputicon *Synteza, Pol.*
Dimeticone (p. 1886·2).
Excess gastrointestinal gas; gastrointestinal investigation.

Esquidon *Merck, Braz.*
Risperidone (p. 1103·2).

Esracain *Rafa, Israel.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias; local anaesthesia; regional anaesthesia.

Esradin *Sigma-Tau, Ital.*
Isradipine (p. 1414·2).
Hypertension.

Esram *Nobel, Turk.*
Escitalopram oxalate (p. 416·2).

Essaim *Ultrapac, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Essamin *Claris, India.*
Amino acids.

Essasin *Prompt Cure, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Essasin-OZ *Prompt Cure, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Essaven *Sanofi-Aventis, Ital.*
Aescin (p. 2431·2); phosphatidyl choline (p. 2588·3).
Venous insufficiency; capillary fragility.

Sanofi-Aventis, Thai.
Aescin (p. 2431·2); rutoside (p. 2505·3); essential phospholipids (p. 2201·2).
Varicose veins; haemorrhoids.

Cassella-med, Ger.†
Capsules: Aesculus (p. 2431·2).
Venous insufficiency; inflammation.

Essaven 60 000 *Cassella-med, Ger.†*
Heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue disorders.

Essaven Neu *Cassella-med, Ger.†*
Aescin (p. 2431·2).
Soft-tissue injuries.

Essavenon *Nattermann, Spain.†*
Topical gel: Aescin (p. 2431·2); phospholipids (p. 2201·2); heparin sodium (p. 1396·3).
Peripheral vascular disorders; soft-tissue disorders.

Ess-Cal *Group, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Essec *KRKA, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Essedin *Legrand, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Esseldon *Anfarm, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Esseliv *Aflofarm, Pol.*
Soya phospholipids.
Liver and biliary-tract disorders.

Essen *Farmasa, Braz.*
⊗Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2); dehydrocholic acid (p. 2492·1); cellulase (p. 2473·1); pepsin

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2586·1); lipase (p. 2579·3); amylase (p. 2442·1); pancreatin (p. 2579·3).
Digestive-system disorders.

Essence Algérienne *Gerda, Fr.*
Cineole (p. 2479·1); menthol (p. 2553·2); guaiacol (p. 1666·1).
Upper respiratory-tract congestion.

Essenfer *Scheele, Philipp.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Anaemias.

Essenmox *Essenpharma, Philipp.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Essens Amara of Groen Amara *Aspen Consumer, S.Afr.*
Cnicus benedictus (p. 2482·2); quassia (p. 2601·1).
Appetite loss.

Essentia *Theralogix, USA.*
Vitamins; minerals; trace elements.

Essential Liquid Mineral *Natures Sunshine, Canad.*
Potassium chloride (p. 1793·2).

Essential Moisture Lip Conditioner *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Essential ProPlus *Nutrisoy, USA.*
Preparation for enteral nutrition.

Essentiale
Note: this name may be used for preparations of different composition.
Gerot, Austria; Cassella-med, Ger.
Essential phospholipids (p. 2201·2).
Liver disorders.

Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.
Essential phospholipids (p. 2201·2); vitamins.
Liver disorders; vitamin supplement.

Nattermann, Pol.
Soya phospholipids.
Liver and biliary-tract disorders.

Sanofi-Aventis, Philipp.
Vitamin B substances (p. 2102·3); vitamin E acetate (p. 2119·2); phosphatidyl choline (p. 2588·3).
Liver disorders.

Essentiale Forte *Sanofi-Aventis, Thai.*
Essential phospholipids (p. 2201·2).
Liver disorders.

Essentiale Forte N *Sanofi-Aventis, Cz.*
Essential phospholipids (p. 2201·2).
Liver disorders.

Essentiale Forte P *Sanofi-Aventis, Philipp.*
Phospholipids (p. 2201·2).
Liver disorders.

Essentiale N *Sanofi, China.*
Phosphatidyl choline (p. 2588·3).
Liver disorders.

Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.
Essential phospholipids (p. 2201·2).
Liver disorders; psoriasis; toxicosis of pregnancy; radiation syndrome.

Essentiale-L *Piramal, India.*
Lecithin (p. 2542·2).
Liver disorders.

Essentials
Note: this name may be used for preparations of different composition.
Usana, Singapore.†
⊗Mega Antioxidant tablets: vitamins; olive extract; bioflavonoids (p. 2505·2); inositol (p. 2533·2); choline bitartrate (p. 2055·2); bromelain (p. 2460·3); thioctic acid (p. 2629·1); ubidecarenone (p. 2637·1); glutathione (p. 1555·2); turmeric (p. 2218·1); lutein (p. 2079·2); Chelated Mineral tablets: minerals.

EssenVida *Darvys, Philipp.*
Ubidecarenone (p. 2637·1).
Dietary supplement.

Esserm *Torrent, India.*
⊗Raloxifene (p. 2303·1).
Osteoporosis.

Essex *Schering-Plough, Denm.; Essex, Ger.; MSD, Switz.*
Emollient.
Skin disorders.

Essigen *Seroyal, Canad.†*
Burdock (p. 2540·1); elm bark (p. 2617·1); goose grass (p. 2481·2); rhubarb (p. 1884·2); rumex acetosa (p. 2620·3); trifolium pratense (p. 2482·1); water cress.
Homoeopathic preparation.

Essigsaure Tonerde-Salbe *Michallik, Ger.*
Aluminium acetotartrate (p. 2440·1).
Soft-tissue disorders.

Ession *Psyco Remedies, India.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Essitol *Athenstaedt, Ger.*
Aluminium acetotartrate (p. 2440·1).
Soft-tissue injury; hyperhidrosis.

Essiver *Nabros, Thai.*
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Essliver *Nabros, Rus.*
Phospholipids (p. 2201·2).
Liver disorders.

Essliver Forte *Nabros, Ukr.*
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Lipid disorders; liver disorders; toxaemia of pregnancy; psoriasis.

Stada, Rus.
Essential phospholipids (p. 2201·2); thiamine mononitrate (p. 2103·2); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); tocoferil acetate (p. 2119·2).
Disorders of lipid metabolism.

Essmol *Sresan, India.*
Paracetamol (p. 115·1).
Pain; fever.

Essmol-3 Plus *Sresan, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Essmol-AF *Sresan, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Essobel *Nobel, Ukr.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Essventia *CORNE, Mex.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

EST *Rosch & Handel, Austria.*
Alum (p. 2439·1); calcium acetate (p. 1783·1); calcium carbonate (p. 1824·3).
Swelling; sprains; bruises; insect bites.

Estab *Indoco, India.*
Esomeprazole magnesium (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Establix
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
Acarbose (p. 466·2).
Diabetes mellitus.

Estacid *Ester, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).

Estacin *Ester, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Estafan *HB, Braz.*
Arginine (p. 2049·1); vitamin C (p. 2110·3).
Nutritional supplement.

Estafilóide *IQB, Braz.†*
A staphylococcal vaccine (toxoid) (p. 2420·2).
Active immunisation.

Estalex *Ifars, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Estalis *Novartis, Arg.†; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.†; Novartis, Fin.; Novartis, Gr.; Novartis, Irl.†; Nycomed, Mex.†; Novartis, Neth.†; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Adcock Ingram, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Estalis Continuous *Novartis, Austral.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estalis Sekvens *Novartis, Fin.†*
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novartis, Norw.†
Patch I, estradiol (p. 2271·1); patch II, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estalis Sequens *Novartis, Austria.†*
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estalis Sequi *Novartis, Austral.; Novartis, Gr.; Novartis, Irl.†; Novartis, Port.; Novartis, Spain; Novartis, Switz.†*
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Novartis, Arg.†; Novartis, Ger.†; Novartis, Ital.
Patch I, estradiol (p. 2271·1); patch II, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Novartis, Cz.†
Patch 1, estradiol (p. 2271·1); patch 2, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novartis, Neth.†
Phase I, estradiol (p. 2271·1); phase II, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novartis, Pol.†
Stage 1, estradiol (p. 2271·1); stage 2, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estalis Sequidot *Novartis, Gr.*
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estalis SQ *Novartis, Braz.*
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estamin *Biolink, Philipp.*
Vitamins; minerals.

Estandron P *Schering-Plough, Braz.*
⊗Estradiol benzoate (p. 2271·1); estradiol phenylpropionate (p. 2271·2); testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2).
Menopausal disorders.

Estandron Prolan *Organon, Turk.*
⊗Estradiol benzoate (p. 2271·1); estradiol phenylpropionate (p. 2271·2); testosterone propionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone phenylpropionate (p. 2305·2).
Menopausal disorders; osteoporosis.

Estandron Prolongado *Organon, Chile.†*
⊗Estradiol benzoate (p. 2271·1); estradiol phenylpropionate (p. 2271·2); testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2).
Menopausal disorders.

Estandron Prolongatum *Organon, Neth.†*
⊗Estradiol benzoate (p. 2271·1); estradiol phenylpropionate (p. 2271·2); testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2).
Menopausal disorders.

Estanolin *Minerva (Μινερβα), Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Estaprol *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Estarylla *Sandoz, USA.*
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Estavam *Precimex, Mex.*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections.

Estazor *Fahrenheit, Indon.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones.

Est-Coff *Ester, India.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); phenylpropanolamine (p. 1674·1).

Estcom *Ester, India.*
Piroxicam (p. 125·3).

Esteban *Teva, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Estecina *Normon, Port.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Normon, Spain.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Esteclin *Syntex, Mex.*
Erdosteine (p. 1665·1).
Respiratory-tract disorders with viscous mucus.

Esteclin Bac *Syntex, Mex.†*
Amoxicillin trihydrate (p. 216·2); erdosteine (p. 1665·1).
Respiratory-tract infections.

Estekor *Actavis, Rus.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Estelle
Note: this name may be used for preparations of different composition.
Ascent, Austral.; Douglas, Singapore.
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive in women with androgenic symptoms; androgen-dependent acne, alopecia, and hirsutism in females; polycystic ovary syndrome.

Taro, Israel; Douglas, Malaysia; Douglas, NZ.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
The 28-day pack also contains 7 inert tablets.
Androgen-dependent acne, alopecia, and hirsutism in women; combined oral contraceptive in women with androgenic symptoms; polycystic ovary syndrome.

Clonmel, Irl.
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Esteprim *Solfran, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ester Aces *Sisu, Canad.*
Betacarotene (p. 2051·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Ester C EVC *Sisu, Canad.†*
Vitamins; zinc (p. 2126·1).

Ester Vit *Bilim, Turk.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Ester-C *Organika, Canad.; Sisu, Canad.; WC Bio-Pharm, Canad.; WN, Canad.*
Vitamin C (p. 2110·3).

Ester-C Plus *Solgar, USA.*
Vitamin C (p. 2110·3); citrus bioflavonoids complex (p. 2505·2); acerola; rose hips (p. 2607·1); rutoside (p. 2505·3); calcium (p. 1783·1).
Capillary bleeding.

Ester-C Plus Multi-Mineral *Solgar, USA.*
Vitamin C (p. 2110·3); citrus bioflavonoids complex (p. 2505·2); acerola; rose hips (p. 2607·1); rutoside (p. 2505·3); calcium (p. 1783·1); magnesium (p. 1786·3); potassium (p. 1793·1); zinc (p. 2126·1).
Capillary bleeding.

Esterflox *Ester, India.*
Ofloxacin (p. 334·3).
Bacterial conjunctivitis; corneal ulcer; ear infections.

Esterflox-OZ *Ester, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Esteria *Newmed, Gr.*
Clindamycin phosphate (p. 269·3).

Esterin *Birochem, Hung.*
Alfalfa (p. 2433·1).
Hyperlipidaemias.

Esterofundina *Braun, Port.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Braun, Spain.
Electrolytes (p. 1775·1) with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Esterofundina de Balance *Braun, Spain.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Esterol *Laborest, Ital.*
Rice oil; vitamin E (p. 2119·1); oleic acid (p. 2200·1); linoleic acid (p. 2509·2); linolenic acid (p. 1460·2); gamma-orizanol.
Nutritional supplement.

Esterol Plus *Laborest, Ital.*
Rice oil; vitamin E (p. 2119·1); policosanol (p. 1472·1); vitamin B substances (p. 2102·3).
Dyslipidaemias.

Estesia *Pharmacore, Indon.*
Prilocaine (p. 1994·1); lidocaine (p. 1988·1).
Local anaesthesia.

Estharil Plus *Om Biotec, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Estibal *Liferpal, Mex.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Esticia *Almirall Hermal, Ger.†*
Chlormadinone acetate (p. 2257·3); mestranol (p. 2291·1).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Estifan *Vifiteh, Rus.*
Echinacea purpurea (p. 2498·1).
Respiratory-tract infections.

Estilax *Cristalfarma, Ital.*
Cascara (p. 1826·1); frangula (p. 1843·3); fruit oligosaccharides (p. 2508·1); kiwi.
Gastrointestinal disorders.

Estilomicin *Beta, Arg.*
Metronidazole (p. 936·1); spiramycin (p. 358·3).
Mouth infections.

Estilsona *Sonphar, Spain.*
⊗Prednisolone steaglate (p. 1646·1).
Corticosteroid.

Estima
Note: this name may be used for preparations of different composition.
Effik, Fr.
Progesterone (p. 2300·2).
Menstrual disorders; menopausal disorders; female infertility; threatened or recurrent miscarriage; benign breast disorders.

Geofman, Philipp.
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; lactation promotion.

Estimoral *Chiesi, Braz.*
Lysate of: *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus mitis*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae.*
Respiratory-tract infections.

Estimul *Nordin, Mex.*
Arnica (p. 2447·2).
Musculoskeletal pain.

Estin *Gracia, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Estinette *Medimpex, Denm.; Effik, Ital.; Effik, Port.; Effik, Switz.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Estinor *Duopharma, Singapore.*
Levonorgestrel (p. 2296·1).

Estinyl *Schering, USA.†*
Ethinylestradiol (p. 2275·3).
Menopausal disorders; female hypogonadism; prostatic cancer; breast cancer.

Estiranox *Greenpharma, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Estival *Specifar, Gr.*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Estivan *Almirall, Belg.; Almirall, Port.†*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Esto
Note: this name may be used for preparations of different composition.
Angelini, Ital.
Alfoscerate olamine.
Mental function impairment in the elderly.

Trima, Israel.
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; anxiety; obsessive-compulsive disorder; social phobia.

esto-gast *Feldhoff, Ger.*
Citronella oil (p. 2481·1); nutmeg oil (p. 2573·2); cinnamon oil (p. 2479·3); clove oil (p. 2481·3).
Digestive disorders.

Estomacurol *Alternavida, Mex.†*
Bismuth citrate (p. 1821·3); sodium bicarbonate (p. 1781·1); aluminium hydroxide (p. 1817·2).
Antacid.

Estomagel *Neo Quimica, Braz.*
Tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastrointestinal hyperacidity; flatulence.

Neo Quimica, Braz.
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Antacid.

Estomazil *DM, Braz.*
Sodium carbonate (p. 2617·3); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Gastric hyperacidity.

Estomepe *Bunker, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Estomil
Note: this name may be used for preparations of different composition.
Merck, Spain.
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Estomina *Fabra, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Estomine *Psyco Remedies, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Estomine Zee *Psyco Remedies, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Estomine-SF *Psyco Remedies, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Estomycin *Columbia, S.Afr.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Estopause *Faran, Gr.*
Estradiol (p. 2271·1); medroxyprogesterone (p. 2288·1).
Hormone replacement therapy.

Estopein *Diba, Mex.*
Ketorolac trometamol (p. 80·2).
Pain; inflammatory eye disorders.

Estovon *Universal Medicare, India.*
Soya isoflavones (p. 2620·3); calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).

Estovon-XT *Universal Medicare, India.*
Soya isoflavones (p. 2620·3); calcium (p. 1783·1); calcitriol (p. 2113·1).

Estovyn-T *Grossman, Mex.*
Tinidazole (p. 949·2).

Estrabeta *Betapharm, Ger.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estrace *Shire, Canad.; BMS, USA.*
Estradiol (p. 2271·1).
Menopausal vasomotor symptoms; vulval and vaginal atrophy; female hypogonadism; female castration; primary ovarian failure; prostatic cancer; breast cancer; osteoporosis; menopausal disorders.

Estracomb *Novartis, Pol.*
4 Patches, estradiol (p. 2271·1) (Estraderm TTS); 4 patches estradiol; norethisterone acetate (p. 2294·3) (Estragest TTS).
Menopausal disorders; osteoporosis.

Novartis, Arg.†; Novartis, Austria†; Novartis, Canad.†; Novartis, Chile†; Novartis, Hong Kong†; Novartis, Hung.†; Novartis, Neth.†; Novartis, Port.†; Novartis, Singapore; Novartis, Switz.†
4 Patches, estradiol (p. 2271·1) (Estraderm); 4 patches, estradiol; norethisterone acetate (p. 2294·3) (Estragest).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Nycomed, Mex.
4 Patches, estradiol (Estraderm TTS); 4 patches, norethisterone acetate (p. 2294·3); estradiol (p. 2271·1) (Estracomb TTS).
Menopausal disorders; osteoporosis.

Novartis, Denm.†
Patch I, estradiol (p. 2271·1); patch II, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders.

Novartis, Ital.†
System A, estradiol (p. 2271·1); system B, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novartis, Spain.†
Patch A, estradiol (p. 2271·1); patch B, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estracomb TTS *Novartis, Gr.*
Estradiol (p. 2271·1); norethisterone (p. 2294·2).
Hormone replacement therapy.

Estracombi *Novartis, Austral.; Novartis, Irl.†; Novartis, S.Afr.†; Novartis, Turk.; Novartis, UK.†*
4 Patches, estradiol (p. 2271·1) (Estraderm); 4 patches, estradiol; norethisterone acetate (p. 2294·3) (Estragest).
Menopausal disorders; osteoporosis.

Novartis, Belg.
Estradiol (p. 2271·1) (Estraderm TTS); estradiol; norethisterone acetate (p. 2294·3) (Estragest TTS).
Menopausal disorders; osteoporosis.

Estracyt *Pfizer, Arg.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; CSP, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, Irl.†; Pfizer, Israel; Pfizer, Ital.; Shinyaku, Jpn; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.†; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, S.Afr.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pharmacia, UK; Pfizer, Ukr.; Pfizer, Venez.*
Estramustine phosphate (p. 790·1) or estramustine sodium phosphate (p. 790·1).
Prostatic cancer.

Estradelle *Sigma, Braz.†*
Estradiol (p. 2271·1).
Menopausal disorders.

Estraderm *Novartis, Arg.†; Novartis, Austral.; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.†; Novartis, Fr.†; Novartis, Ger.†; Novartis, Hong Kong†; Novartis, Hung.†; Novartis, India; Novartis, Irl.†; Novartis, Israel†; Novartis, Ital.; Nycomed, Mex.†; Novartis, Neth.†; Novartis, NZ; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Turk.; Novartis, UK; Novartis, USA.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency; menopausal vasomotor symptoms; vulval and vaginal atrophy; female hypogonadism; female castration; primary ovarian failure.

Estraderm TTS *Novartis, Gr.*
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency.

Estradot *Novartis, Arg.†; Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.†; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Pol.; Novartis, Port.; Adcock Ingram, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, UK; Novartis, Venez.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Estradurin *NordMedica, Austria; NordMedica, Denm.; NordMedica, Fin.; Pfizer, Norw.†; Pharmacia Upjohn, Rus.; NordMedica, Swed.; Pro Concepta, Switz.; Pfizer, Ukr.†*
Polyestradiol phosphate (p. 2299·1).
Mepivacaine hydrochloride (p. 1992·2) is included in this preparation to alleviate the pain of injection.
Prostatic cancer; menopausal disorders; breast cancer; amenorrhoea.

Estradurine *Pfizer, Belg.†*
Polyestradiol phosphate (p. 2299·1).
Mepivacaine hydrochloride (p. 1992·2) is included in this preparation to alleviate the pain of injection.
Prostatic cancer.

Estragest *Novartis, Arg.; Novartis, Braz.; Novartis, Chile; Novartis, Ger.; Novartis, Hung.; Novartis, Switz.; Novartis, Venez.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estragyn *Triton, Canad.*
Vaginal cream: Estrone (p. 2275·2).
Menopausal vaginal symptoms.

Triton, Canad.
Tablets: Esterified oestrogens (p. 2270·3).
Menopausal disorders.

Estrahexal *Hexal, Cz.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estramin *Samarth, India.*
Estramustine phosphate (p. 790·1).

Estramon *Hexal, Austria; Hexal, Ger.†; Sandoz, Gr.; Sandoz, Hung.†; Sandoz, Mex.; Sandoz, Switz.†; Sandoz, Turk.; Sandoz, Ukr.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Estranor *Sandoz, Switz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Estranova CC *Silesia, Chile.†*
Estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Estranova E *Silesia, Chile.†*
Estradiol valerate (p. 2271·2).
Menopausal disorders.

Estranova 30 Simple *Silesia, Chile.†*
13 Tablets, estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1); 17 tablets, estradiol valerate.
Menopausal disorders.

Estranovag *Gobbi, Arg.*
Estramustine (p. 790·1).
Malignant neoplasms.

Estrapatch *Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Hung.†; Pierre Fabre, Pol.†; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, Spain.†*
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estrarona *Silesia, Chile.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis; prostatic cancer.

Estrasorb *Medicis, USA.*
Estradiol (p. 2271·1).
Menopausal vasomotor disorders.

Estratab *Solvay, USA.*
Esterified oestrogens (p. 2270·3).
Menopausal vasomotor symptoms; vulval and vaginal atrophy; oestrogen deficiency; breast cancer; prostatic cancer; osteoporosis.

Estratest *Solvay, USA.†*
⊗Esterified oestrogens (p. 2270·3); methyltestosterone (p. 2291·3).
Menopausal disorders.

Estrava *Merck, Turk.*
Estradiol (p. 2271·1).
Menopausal disorders.

Estrefen *Solfran, Mex.*
Dihydrostreptomycin (p. 286·3); sulfadiazine (p. 361·3).
Diarrhoea.

Estrena *Ratiopharm, Fin.*
Estradiol (p. 2271·1).
Menopausal disorders.

Estreptobroncol *Atral, Port.†*
Ampicillin sodium (p. 218·2); ampicillin benzathine (p. 218·2).
Bacterial infections.

Estreptocarbocaftiazol *Bago, Arg.*
Oral suspension: Phthalylsulfathiazole (p. 339·3); streptomycin sulfate (p. 359·1); charcoal (p. 1537·3); menadione (p. 2122·1).
Diarrhoea; flatulence.

Bago, Arg.
Tablets: Phthalylsulfathiazole (p. 339·3); streptomycin sulfate (p. 359·1); charcoal

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 1537·3); simeticone (p. 1886·2); menadione (p. 2122·1).
Diarrhoea; flatulence.

Estreptopal *Reuffer, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Estreva *Merck, Belg.; Merck, Braz.; Merck, Chile; Lipha, Denm.†; Abbott, Ger.; Merck, Hong Kong; Merck, Indon.†; Bellpharma, Irl.†; Merck, Mex.; Merck, Neth.†; Theramex, Pol.; Theramex, Port.; OM, Switz.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Estréva *Theramex, Mon.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estrex *Lake, USA.*
⊗Cimicifuga racemosa (p. 2478·1); dioscorea villosa (p. 2648·1); sepia (p. 2613·1); adrenalinum (p. 1292·1); oophorinum; orchitinum (p. 2304·3); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Estri-Atlas *Atlas, Arg.; K2 Health & Wellness, Chile; Mediderm, Chile.*
Rose oil (p. 2607·2); hyaluronic acid (p. 2526·2); centella (p. 1698·3); vitamin E (p. 2119·1); elastin (p. 2483·2).
Stretch marks; scars.

Estriel *Mochida, Jpn.*
Estriol (p. 2274·3).
Menopausal disorders; osteoporosis.

Estrifam *Novo Nordisk, Ger.*
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estrifirm *Darier, Mex.*
Emollient.
Stretch marks.

ES-TriGUARD *Vivo Health, Singapore.*
Gymnemic acids; charantin; phytosterols (p. 1471·2); ursolic acid; carnosol; carnosic acid; rosmarinic acid.
Metabolic disorders.

Estrimax *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estrin
Note: this name may be used for preparations of different composition.
Cipla, India.
Conjugated oestrogens (p. 2260·1).
Loeffler, Mex.
⊗Glycerol (p. 2517·2).
Constipation.

Estring *Paladin, Canad.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Norw.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pharmacia, UK; Pharmacia Upjohn, USA.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; postmenopausal atrophy of the vagina or lower urinary tract.

Estrinolon *EMS, Braz.*
Conjugated oestrogens (p. 2260·1).

Estriopax *Neo Quimica, Braz.*
Estriol (p. 2274·3).
Oestrogen deficiency.

Estroact *Kee, India.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Estrocare *Pharmanex, USA.*
Cordyceps sinensis; cimicifuga (p. 2478·1).
Menopausal disorders.

Estrodose *Wyeth Lederle, Ital.*
Estradiol (p. 2271·1).
Menopausal disorders.

Estrofem *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, India; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Thai.; Novo Nordisk, Turk.*
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency; osteoporosis; hypogonadism.

Estrofem N *Novo Nordisk, Switz.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estroffik *Effik, Spain.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estrofort *Rottapharm, Fr.†*
Soya isoflavones (p. 2620·3); *Lactobacillus sporogenes* (p. 2596·3); calcium (p. 1783·1); colecalciferol (p. 2113·1).
Menopausal disorders.

Estrogel *Meda, Austria; Merck, Canad.; Leiras, Denm.; Leiras, Fin.; Faran, Gr.†; Ascend, USA; Biopas, Venez.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estrogenon *Sanval, Braz.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Estrogenus *Teva, Israel.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Estrokad *Kade, Hung.; Kade, Rus.*
Estriol (p. 2274·3).
Menopausal vulvovaginal disorders; urinary-tract disorders.

Estromon *Standard Chem & Pharm, Thai.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis; atrophic vaginitis.

Estronorm *Jenapharm, Ger.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estro-Pause *Adcock Ingram, S.Afr.*
Estradiol valerate (p. 2271·2).
Menopausal disorders.

Estro-Pause N *Adcock Ingram, S.Afr.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; norethisterone (p. 2294·2).
Menopausal disorders.

Estroplast *Adamed, Pol.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Estroplus *Abbott, Braz.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Estroquin *Richmond, Arg.*
Calcium folinate (p. 2066·3).

Estrostep Fe *Warner Chilcott, USA.*
21 Tablets, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
Triphasic oral contraceptive.

Estroven
Note: this name may be used for preparations of different composition.
Estroven, UK.
Soya isoflavones (p. 2620·3); vitamin E (p. 2119·1); vitamin B substances (p. 2102·3); calcium (p. 1783·1); boron (p. 2052·3); selenium (p. 2086·3); iodine (p. 2336·3).
Menopausal disorders.
Amerifit, Canad.†
Vitamins; minerals.

Estroven Nighttime *Estroven, UK.*
Soya isoflavones (p. 2620·3); date seed extract; lupulus (p. 2546·1); vitamin D (p. 2112·3); vitamin B_6 (p. 2105·3); calcium (p. 1783·1); magnesium (p. 1786·3).
Menopausal disorders.

Estulic *Novartis, Belg.; Novartis, Fr.†; Egis, Hung.; Egis, Rus.; Egis, Ukr.*
Guanfacine hydrochloride (p. 1396·1).
Hypertension.

Estxone *Ester, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Estxone-SB *Ester, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Estzyme *Ester, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Esucos *UCB, Austria†; UCB, Fin.†; SIT, Ital.*
Dixyrazine (p. 1071·3).
Anxiety disorders; nervous disorders; depression; premedication; alcohol withdrawal syndrome; postoperative vomiting; sleep disorders.

Esvat *Dexa, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Esvical *More, Philipp.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); simeticone (p. 1886·2).
Calcium supplement; gastric hyperacidity.

Esvicee *More, Philipp.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Esvimin *Medichem, Philipp.†*
Vitamins; minerals.

Esvit C *Laboratorios Chile, Chile.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Esvorin *Opus Materia, Gr.*
Calcium levofolinate (p. 2067·1).
Antidote to folic acid antagonists.

Eszit *Ester, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Eszop *Silesia, Chile.*
Eszopiclone (p. 1072·3).
Insomnia.

Eta Biocortilen *SIFI, Ital.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Eta Biocortilen VC *SIFI, Ital.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); tetryzoline hydrochloride (p. 1678·3).
Infected eye disorders.

E-Tabs *Sigma, Braz.*
dl-Alpha tocoferil acetate (p. 2119·2).

Etabus *Ferring, Mex.*
Disulfiram (p. 2495·3).

Etacin *Ethica, Indon.*
Ciprofloxacin (p. 261·1) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Etaco *Rafarm, Gr.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Etaconil *Tecnofarma, Chile; Nolver, Venez.*
Flutamide (p. 798·2).
Prostatic cancer; benign prostatic hyperplasia; hirsutism.

Etacortilen *SIFI, Ital.; SIFI, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Etadexe-Mez *Moscow Endocrine, Rus.*
Etaden hydrobromide (p. 2500·2).
Corneal lesions.

Etadotbal *Silanes, Mex.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Etagerin *Biofarma, Mex.†*
Milk thistle (p. 1561·1).
Hepatitis.

Etalopro *Clonmel, Irl.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; obsessive-compulsive order; anxiety; social phobia.

Etalpha *Leo, Austria; Pentafarma, Chile; Leo, China; Leo, Denm.; Leo, Fin.; Leo, Neth.; Leo, Norw.; Leo, Port.; Nycomed, Rus.; Leo, Spain; Leo, Swed.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; osteomalacia; hypoparathyroidism; rickets; osteoporosis; vitamin D deficiency; hypocalcaemia; calcium metabolic disorders; hyperparathyroidism in renal failure; pseudohypoparathyroidism; vitamin D supplement.

E-Tam
Note: this name may be used for preparations of different composition.
Sykocure, India.
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Etam
Note: this name may be used for preparations of different composition.
Panjon, India.
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Etan-G *Shalaks, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2).
Infected skin disorders.

Etan-GM *Shalaks, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Etanicozid B6 *Piam, Ital.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Etanorden *Gedeon Richter, Cz.; Gedeon Richter, Denm.; Gedeon Richter, Ital.; Gedeon Richter, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Etaperazin *Tatkhimfarm, Rus.*
Perphenazine (p. 1095·3).
Psychoses; nausea and vomiting; pruritus.

Etaphylline *Corsa, Indon.; Sanofi Synthelabo, Indon.*
Acefylline piperazine (p. 1200·3).
Asthma; dyspnoea; emphysema.

Etapiam
Note: this name may be used for preparations of different composition.
Deltapharma, Gr.
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Piam, Ital.
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Etaretin *Etapharm, Austria.*
Retinal phosphatides; sodium bicarbonate (p. 1781·1).
Eye disorders.

Etasisen *Rafarm, Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Etason *Otto, Indon.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Etaxene *Alfa Wassermann, China; Wassermann, Ital.*
Somatostatin (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery; diabetic ketoacidosis; rheumatoid arthritis.
Alfa Wassermann, Thai.†
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery.

Etazim *Benedetti, Ital.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

ETD *Beacons, Singapore.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); methyl salicylate (p. 92·1).

ETDR *SIFI, Ital.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); rutoside (p. 2505·3); sambucus (p. 2609·3).
Nutritional supplement.

Etec *Raffo, Arg.; Tecnofarma, Chile.*
Vitamin E (p. 2119·1).
Vitamin E supplement; vitamin E deficiency.

Etela *Venus, India.*
Telmisartan (p. 1509·3).
Hypertension.

Etela-H *Venus, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan (p. 1509·3).
Hypertension.

Eterim *Alter, Port.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Etermol Antitusivo *Quimpe, Spain.†*
Benzydamine hydrochloride (p. 29·2); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sodium benzoate (p. 1738·2).
Cough.

Eternex *Dabur, India.†*
Melatonin (p. 2551·3); vitamin B_6 (p. 2105·3).
Sleep disorders; jet lag; circadian rhythm disorders.

Eteron *Cosme, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etex-T *Raproso, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Etfariol *Vilco, Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Etform *Sandoz, Pol.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Etformin *Dey's, India.*
Metformin (p. 489·1).
Diabetes mellitus.

ETH Ciba *Sandoz, Indon.†*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Ethacid *Stadmed, India.*
Etamsylate (p. 1145·2).
Menorrhagia; periventricular haemorrhage.

Ethafy *Sanify, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethaklot *Cosme, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Etham *Pond's, Thai.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Ethamcip *Cipla, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethamizid *Medichem, Philipp.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Pyridoxine (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Ethamolin *Farmoquimica, Braz.; Questcor, USA.*
Monoethanolamine oleate (p. 2562·3).
Oesophageal varices.

Ethams *Chemech, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethamstat *Indi, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethariv *East African, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethasyl *FDC, India.*
Etamsylate (p. 1145·2).
Haemorrhage; menorrhagia.

Ethatol *Biological E, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Ethatyl *Sanofi-Aventis, S.Afr.*
Ethionamide (p. 297·3).
Tuberculosis.

Ethbutol *Pharmasant, Thai.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

EtheDent *Ethex, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Ethi 400 *Dynamic, Philipp.*
Ethambutol (p. 296·1); isoniazid (p. 311·2).
Pyridoxine (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Ethibide *Genus, UK.*
⊗Indapamide (p. 1409·2).
Hypertension.

Ethibloc *Ethicon, Ger.†*
Sodium amidotrizoate (p. 1581·3).
Pre-operative vascular embolisation for renal tumours; packing the residual pancreatic duct after partial resection of the pancreas.

Ethicef
Note: this name may be used for preparations of different composition.
Ethica, Indon.
Cefadroxil (p. 233·2).
Bacterial infections.
Ethix, India.
Cefuroxime (p. 255·2).
Bacterial infections.

Ethicholine *Hospira, Singapore.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Ethiclaf *Ethica, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ethiclox-LB *Ethix, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Ethicol *Ethica, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Ethicoline *Hospira, Malaysia.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Ethidan *Ethica, Indon.*
Clindamycin hydrochloride (p. 269·3).
Gram-positive bacterial infections.

Ethide *Lupin, India; Lupin, Rus.*
Ethionamide (p. 297·3).
Tuberculosis.

Ethidol *Ethica, Indon.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Ethifen *Ethica, Indon.*
Ibuprofen (p. 68·2).
Fever; pain.

Ethiferan *Ethica, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastroparesis; gastro-oesophageal reflux; nausea and vomiting.

Ethifix *Ethica, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Ethiflox *Ethica, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ethigent *Ethica, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Ethigobal *Guardian, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Ethilin *Ethica, Indon.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Ethimax *Overseas, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethimox *Ethica, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ethinex *Ethica, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemorrhage.

Ethinorm-E *Bennet, India.*
Ethinylestradiol (p. 2275·3).
Breast cancer; prostatic cancer.

E-Thio *Concept, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethiobin *Medispan, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethiocid *Themis Medicare, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethiodol *Guerbet, USA.†*
Iodised oil (p. 1589·1).
Contrast medium for hysterosalpingography and lymphography.

Ethiokox *Radicura, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethionam *Chandra Bhagat, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethipramine *Aspen, S.Afr.*
Imipramine hydrochloride (p. 426·2).
Depression; parkinsonism; alcohol withdrawal syndrome; behaviour disorders in children.

Ethiprid *Ethica, Indon.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Ethirfin *Ethypharm, Irl.†; Ethypharm, Port.†*
⊗Morphine sulfate (p. 92·3).
Pain.

Ethirom *Ethica, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Ethirov *Ethica, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Ethisolvan *Ethica, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Ethisone *Chemo-Drugs, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; premenstrual syndrome; breast cancer; postponement of menstruation.

Ethivask *Ethica, Indon.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ethnorub *Johnson & Johnson, India.*
Iodine (p. 2336·3); mephenesin (p. 2025·2); methyl salicylate (p. 92·1).

Etholate *East West, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethomid *Macleods, India; Macleods, Rus.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Ethopil *Ethica, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; behavioural disorders in children; alcoholism.

Ethopul *VHB, India.*
Etoposide (p. 790·2).
Testicular cancer; small cell lung cancer.

ETH-Oxydose *Ethex, USA.†*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Ethrane *Abbott, Austria†; Abbott, China; Abbott, Indon.†; Abbott, Irl.†; Abbott, Ital.; Abbott, Mex.†; Abbott, Philipp.; Abbott, S.Afr.; Abbott, Turk.; Baxter, USA; Abbott, Venez.*
Enflurane (p. 1899·3).
General anaesthesia; anaesthesia and analgesia in obstetrics.

Ethrine *Biomedica, Gr.*
Dipyridamole (p. 1362·2).

Ethver *Sanify, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethyfen *Medicus, Gr.*
Nabumetone (p. 97·1).
Inflammatory disorders; pain.

Ethylate *Life Medicare, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Ethylex *Orpha-Devel, Austria; AOP Orphan, Irl.; Dem, Turk.*
Naltrexone hydrochloride (p. 1565·1).
Alcoholism.

Ethymal *Apotex, Neth.*
Ethosuximide (p. 521·1).
Absence seizures.

Ethyol *Schering-Plough, Austral.; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile†; Schering-Plough, Cz.; Pinnacle, Fin.; Genopharm, Fr.; Essex, Ger.†; Pinnacle, Gr.; Fulford, India; Teva, Israel†; Pinnacle, Ital.; Schering-Plough, Mex.; Pinnacle, Neth.; MSD, NZ; Schering-Plough, Philipp.; USB, Pol.†; Pinnacle, Port.; MedImmune, Rus.; Schering-Plough, S.Afr.; Pinnacle, Spain; Pinnacle, Swed.; Alkopharma, Switz.; MSD, Thai.; Er-Kim, Turk.; Genopharm, UK; Alza, USA; US Bioscience, USA; Schering-Plough, Venez.*
Amifostine (p. 1539·2).
Radiotherapy-associated xerostomia; reduction of renal toxicity due to cyclophosphamide; reduction of neutropenia due to cyclophosphamide, mitomycin, and platinum-containing cytotoxics; reduction of nephrotoxicity due to platinum-containing cytotoxics.

Etiagen *Generics, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Etiasa *Ethypharm, China; Novartis, India.*
Mesalazine (p. 1859·2).
Ulcerative colitis; Crohn's disease.

Etiasel *AstraZeneca, Arg.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia.

Etiaxil *Cooper, Fr.; Interdelta, Switz.*
Aluminium chloride (p. 1693·3) and/or aluminium lactate (p. 2440·2).
Hyperhidrosis.

Etibi *Gerot, Austria; Valeant, Canad.; Pharmed, India.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Etibufen *Ethypharm, China.*
Ibuprofen (p. 68·2).
Pain; fever.

Eticer *Ethypharm, China.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Eticox *East West, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etideme *Montefarmaco, Ital.*
Cimetidine (p. 1827·1).
Gastric hyperacidity.

Etidine *EMS, Braz.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Etidrate *Pacific, NZ.†*
Etidronate disodium (p. 1182·3).
Paget's disease of the bone; ectopic ossification; osteoporosis.

Etidrocal *Sanis, Canad.*
14 Tablets, etidronate disodium (p. 1182·3); 76 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Etidron *Hexal, Ger.†; Pharmanel, Gr.; Abiogen, Ital.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Etifem *Fem Care, India.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; ectopic ossification; osteoporosis.

Etil *CT, Ger.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Etil Adrianol *Klonal, Arg.*
⊗Etilefrine (p. 1379·1).
Hypotension.

Etildopanan *Neo Quimica, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Etilefril *Uniao Quimica, Braz.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Etiltox *AFOM, Ital.*
Disulfiram (p. 2495·3).
Alcoholism.

Etimonis *Ethypharm, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Etindrax *Valdecasas, Mex.*
Allopurinol (p. 600·2).
Hyperuricaemia; calcium oxalate calculi.

Etinoline *Ethypharm, China; Ethypharm, Hong Kong.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Etinox *Ivax, Arg.*
Cream: Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); camphor (p. 2466·2).
Arthroses.
Ivax, Arg.
Granules: Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Arthroses.

Etioven *Sanofi-Aventis, Fr.*
Naftazone (p. 1157·1).
Peripheral vascular disorders.

Etiplus *Biospray, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Etipramid *Ethypharm, China.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Etisec *Novartis, India.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Etisux *Fabop, Arg.*
Erythromycin (p. 291·2).
Bacterial infections.

Etiza *Sarabhai Piramal, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Etizem *Ethypharm, Port.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Etizola *Macleods, India.*
Etizolam (p. 1073·2).

Etmozine *Olainfarm, Rus.*
Moracizine (p. 1441·2).
Arrhythmias.

ETM-T *Acekinetic, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Etna *Gross, Braz.*
Disodium cytidine phosphate (p. 2491·1); uridine triphosphate (p. 2638·1); hydroxocobalamin acetate (p. 2107·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Etnoderm *Koni-Cofarm, Chile.*
Hydroquinone (p. 1705·1).

Eto *Elisa, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Etobion *Medicus, Gr.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etobus *Globus, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Eto-cell *Cell Pharm, Ger.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etoclav *Solitaire, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Etocos *Symbiosis, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etocovit *Richter, Austria.*
d-Alpha-tocopherol (p. 2119·1).
Vitamin E deficiency.

Etocris *UKM, Arg.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etodin *Ulkar, Turk.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; pain.

Etody *Piramal, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etofact *Medico, India.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etofan *Emar, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etofenol *Medichrom, Gr.*
Etofenamate (p. 57·2).
Inflammatory disorders; pain.

Etoflam
Note: this name may be used for preparations of different composition.
Phoenix, Irl.
Etofenamate (p. 57·2).
Musculoskeletal inflammation.
Standard, Philipp.
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etogel *Biospray, Gr.; Zekides, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Eto-Gry *Teva, Ger.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etoina *Klonal, Arg.*
Phenytoin (p. 538·2).
Arrhythmias; epilepsy.

E-tol *Sel-J, Philipp.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Etol *Nobel, Turk.; Nobel, Ukr.*
Etodolac (p. 57·1).
Pain; musculoskeletal and joint disorders; gout.

Etolac *Nanxin, China; Medichrom, Gr.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etolex *Lexus, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etolex-P *Lexus, India.*
Etodolac (p. 57·1); paracetamol (p. 115·1).

Etolon *Celon, India.*
Etoposide (p. 790·2).
Testicular cancer; small cell lung cancer.

Etolor *Intra-Labs, India.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etolor-P *Intra-Labs, India.*
Etodolac (p. 57·1); paracetamol (p. 115·1).

Etom *Intra-Labs, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etomar *Marcmed, Pol.*
Aspirin (p. 22·2); ethenzamide (p. 56·2); caffeine (p. 1203·3).
Pain.

Etomax *Ipca, India.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etomax-P *Ipca, India.*
Etodolac (p. 57·1); paracetamol (p. 115·1).

Etomedac *Medoc, Ger.; Medac, Neth.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etomide *VHB, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Etomin *Sun, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Etomine *Novartis, S.Afr.*
Clotiapine (p. 1057·1).
Schizophrenia.

Etomorase *Biochimico, Braz.*
Etoposide (p. 790·2).

Eton *Pond's, Thai.*
Ethionamide (p. 297·3).
Tuberculosis.

Etonco *Armstrong, Mex.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Etono *ACO Hud, Fin.*
Tripelennamine hydrochloride (p. 642·3).
Insect stings and bites.

Etonolver *Nolver, Venez.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etonox *Deltapharm, Hong Kong†; Choroen, Thai.*
Etodolac (p. 57·1).
Musculoskeletal and joint disorders; pain.

Etopan *Taro, Israel; Eczacibasi, Turk.; Taro, UK.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etopen *Solitaire, India.*
Meropenem (p. 321·3).
Bacterial infections.

Etophylate *Bushnell, India.*
Acefylline piperazine (p. 1200·3).
Obstructive airways disease.

Etopiryna *Polpharma, Pol.*
Aspirin (p. 22·2); ethenzamide (p. 56·2); caffeine (p. 1203·3).
Pain.

Etoplex *USV, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Etopofos *BMS, Austria; BMS, Denm.†; BMS, Fin.†; BMS, Gr.; BMS, Norw.†; BMS, Swed.*
Etoposide phosphate (p. 790·3).
Malignant neoplasms.

Etopophos *BMS, Austral.; BMS, Chino; BMS, Fr.; BMS, Ger.; BMS, Irl.; BMS, NZ; BMS, S.Afr.†; BMS, Switz.; BMS, UK; BMS Oncology, USA.*
Etoposide phosphate (p. 790·3).
Malignant neoplasms.

Etopos *Teva, Mex.†; Teva, Thai.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etopoxan *Baxter, Philipp.†*
Etoposide (p. 790·2).
Small-cell lung cancer; testicular cancer.

Etopres *Psychotropics, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Etopres-AT *Psychotropics, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

EtoPril *Wolff, Ger.*
Dimeticone (p. 2209·3); cyclomethicone (p. 2209·2).
Pediculosis.

Etopro *Valeont, Hung.; ICN, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Etopul *Novell, Indon.; Korea United, Philipp.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etores-TR *Solitaire, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Etori *Symbiosis, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etorica *Micro, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etoril *Psychotropics, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Etosaid *Macleods, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Eto-Salbetol *FDC, India.*
⊗Bromhexine hydrochloride (p. 1656·3); etofylline (p. 1208·2); salbutamol (p. 1220·2).

Etoshine *Sun, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etosid *Cipla, Indio; Kocak, Turk.; Cipla, Venez.*
Etoposide (p. 790·2).
Malignant neoplasms.

Etosin *Asta Oncologia, Braz.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Etosym *Symbiosis, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etosys *Systopic, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Etosys-MF *Systopic, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Etotam *Solitaire, India.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Etotan *Solitaire, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Etoton-AT *Solitaire, India.*
⊗Atenolol (p. 1308·2); losartan potassium (p. 1422·2).

Etotan-H *Solitaire, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Etotan-HR *Solitaire, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2); ramipril (p. 1483·3).

Etotan-R *Solitaire, India.*
Losartan (p. 1422·2); ramipril (p. 1483·3).
Hypertension.

Etoteva *Med, Turk.*
Etodolac (p. 57·1).

Etova *Ipca, India.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Etova-P *Ipca, India.*
Etodolac (p. 57·1); paracetamol (p. 115·1).

Etovas *Solitaire, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Etovas-EZ *Solitaire, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Etoxa *Biofarma, Turk.*
Etodolac (p. 57·1).

Etoxib *Unichem, India.*
Etoricoxib (p. 57·3).
Gout; osteoarthritis; rheumatoid arthritis.

Etoxin *Apsen, Braz.*
Ethosuximide (p. 521·1).

Etoxin-B *Ind-Swift, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline sulfate (p. 1228·1).

Etoxin-B Exp *Ind-Swift, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Etoxisclerol *Ferrer, Spain; Flupal, Venez.*
Lauromacrogol 400 (p. 2194·1).
Varices.

Etoxisklerol *IFET [ΙΦΕΤ], Gr.*
Lauromacrogol 400 (p. 2194·1).
Varices.

Etozox *Cipla, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etrafon *Schering, USA.†*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Mixed anxiety depressive states.

Etrafonil *Dactum, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Etrane *Abbott, Braz.*
Enflurane (p. 1899·3).
General anaesthesia.

Etrat
Note: this name may be used for preparations of different composition.
Astellas, Austria.
Heparin sodium (p. 1396·3); menthol (p. 2553·2); glycol salicylate (p. 66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Etrat Sportgel HES *Klinge, Ger.†*
Glycol salicylate (p. 66·2).
Soft-tissue disorders; sports injuries.

Etrel *Pharmex [Φαρμεξ], Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Etric Plus *Sanify, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Etric-DT *Sanify, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Etrik *Alembic, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etrivex *Golderma, Irl.; Golderma, Port.; Golderma, UK.*
⊗Clobetasol propionate (p. 1627·1).
Scalp psoriasis; psoriasis; skin disorders.

Etro
Note: this name may be used for preparations of different composition.
Allenge, India.
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etrobax *Ranboxy, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etrola *Pharmasant, Thai.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Etrolote *Pharmasant, Thai.†*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

E-Trom *Epitome, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Etronil *Klonal, Arg.*
Metronidazole (p. 936·1).

Etro-P *Allenge, India.*
Etoricoxib (p. 57·3); paracetamol (p. 115·1).

Etrosteron *Elea, Arg.*
Estradiol undecylate (p. 2271·1).
Menopausal disorders.

Etruzil *Egis, Cz.; Egis, Hung.; Egis, Neth.; Egis, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

ETS *Emcure, India.*
Capsules; injection: Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.
Emcure, India.
Transdermal patches: Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Etuamol *Vilco, Gr.*
Vincamine (p. 2645·2).

Etumide *VHB, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Etumina *Novartis, Arg.; Juvise, Spain.*
Clotiapine (p. 1057·1).
Anxiety; insomnia; psychoses; withdrawal syndromes.

Etumine *Novartis, Belg.*
Clotiapine (p. 1057·1).
Psychoses; agitation.

Etyfenac *Ethypharm, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Etyomid *Kocak, Turk.*
Ethionamide (p. 297·3).
Tuberculosis.

Etyzem *Actavis, Ital.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; heart failure; angina pectoris.

EU 2000 *Union Drug, Thai.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Eubetal Antibiotico *SIFI, Ital.*
Eye drops: ⊗Betamethasone sodium phosphate (p. 1623·3); rolitetracycline (p. 356·1); chloramphenicol (p. 257·1); colistimethate sodium (p. 275·3).
Eye disorders.

SIFI, Ital.
Eye ointment: ⊗Betamethasone sodium phosphate (p. 1623·3); tetracycline (p. 373·1); chloramphenicol (p. 257·1); colistimethate sodium (p. 275·3).
Eye disorders.

Eubiol
Note: this name may be used for preparations of different composition.
CNP, Ger.
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea; acne.

Eubiolac *Verla, Ger.*
Calcium lactate (p. 1784·1); tartaric acid (p. 2626·1).
Vaginal infections; restoration of normal vaginal flora.

Eubioz *Lupin, India.*
Bifidobacterium bifidum (p. 2596·3); fructo-oligosaccharide (p. 2508·1); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Diarrhoea.

Eubos *Eubos, Malaysia; Hobein, Malaysia.*
Range of emollients, moisturisers, soap substitutes, and sunscreens.
Skin care.

Hobein, Hong Kong.
Skin cleanser.

Eubos Feminin *Hobein, Hong Kong.*
Chamomile (p. 2474·1); hydrolysed milk and wheat protein; lactic acid (p. 2539·1).
Personal hygiene.

Eucabal *Esparma, Rus.*
Ribwort plantain (p. 2604·2); thyme (p. 2630·2).
Respiratory-tract inflammation; cough.

Eucabal Balsam S *Esparma, Ukr.*
Eucalyptus oil (p. 2501·2); pine oil (p. 2591·1).
Inflammatory disorders respiratory tract.

Eucabal S *Esparma, Rus.*
Eucalyptus oil (p. 2501·2); pine oil (p. 2591·1).
Upper respiratory-tract disorders.

Eucabal Syrup *Esparma, Ukr.*
Plantain acutifoliate (p. 2604·2); thyme (p. 2630·2).
Cough; inflammatory disorders of the respiratory tract.

Eucalcic *Altana, Fr.†*
Calcium carbonate (p. 1824·3).
Renal osteodystrophy.

Eucalimin *Vilar, Rus.*
Eucalyptus leaf (p. 2501·1).
Inflammation; infections.

Eucaliptine *Sanofi-Aventis, Mex.†*
Injection: Guaiacol (p. 1666·1).
Upper respiratory-tract infections.

Sanofi-Aventis, Mex.†
Syrup: Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1).
Cough.

Eucalyptamint *Ciba, USA.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).

Eucalyptine *Hepatoum, Fr.*
Infant suppositories: Cineole (p. 2479·1); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Hepatoum, Fr.
Adult suppositories: Cineole (p. 2479·1); guaifenesin (p. 1666·2); camphor (p. 2466·2).
Respiratory-tract disorders.

Medgenix, Belg.
Capsules: syrup: suppositories for infants: Cineole (p. 2479·1); codeine (p. 40·2).
Cough; respiratory disorders.

Medgenix, Belg.
Suppositories for adults and children: Codeine phosphate (p. 40·2); cineole (p. 2479·1).
Cough.

Eucalyptine Le Brun *Hepatoum, Fr.*
Syrup: Cineole (p. 2479·1); codeine (p. 40·2).
Cough.

Eucalyptine Pholcodine *Medgenix, Belg.*
Cineole (p. 2479·1); camphor (p. 2466·2); phenol (p. 1763·3); guaiacol (p. 1666·1); pholcodine (p. 1675·1).
Respiratory disorders.

Eucalypt-M *Natur Produkt, Rus.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Upper respiratory-tract disorders.

Eucalyptus Cold Balm Dr Theiss *Naturwaren, Ukr.†*
Eucalyptus oil (p. 2501·2); pine fir-needle oil (p. 2591·1); racemic camphor (p. 2466·2).
Cough; inflammatory disorders of the respiratory tract.

Eucalytux *Tilman, Belg.*
Codeine (p. 40·2); sulfogaiacol (p. 1678·1).
Cough.

Eucanol *Pharma Nord, UK.*
Cream: Eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); calendula oil (p. 2465·2).
Insect bites; skin irritation.

Eucapinol *Streuli, Switz.*
Camphor (p. 2466·2); menthol (p. 2553·2); cypress oil (p. 2491·1); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); pumilio pine oil (p. 2591·1); turpentine oil (p. 2636·3); thyme oil (p. 2630·3).
Cold symptoms.

Eucar *Salus, Ital.†*
Levocarnitine hydrochloride (p. 2053·2).
Carnitine deficiency.

Eucarbon
Note: this name may be used for preparations of different composition.
Trenka, Cz.; Peithner, Hung.; Trenka, Israel; Giuliani, Ital.
Senna (p. 1885·1); rhubarb (p. 1884·2); vegetable charcoal (p. 1537·3); sublimed sulfur (p. 1721·1).
Constipation; meteorism; gastrointestinal disorders; flatulence.

Trenka, Austria; Santa, Turk.; Trenka, Ukr.
Vegetable charcoal (p. 1537·3); sulfur (p. 1721·1); senna (p. 1885·1); rhubarb (p. 1884·2); peppermint oil (p. 1877·1); fennel oil (p. 2503·3).
Constipation.

Trenka, Malaysia.
Senna (p. 1885·1); rhubarb (p. 1884·2); charcoal (p. 1537·3); sulfur (p. 1721·1); mint oil (p. 2560·1); fennel oil (p. 2503·3).
Constipation; irritable bowel syndrome.

Camox, S.Afr.†
Senna (p. 1885·1); rhubarb (p. 1884·2); vegetable charcoal (p. 1537·3).
Constipation.

Eucarbon Herbal *Trenka, Malaysia.*
Charcoal (p. 1537·3); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Eucardic *Roche, Irl.; Roche, Neth.; Roche, UK.†*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension; angina pectoris.

Eucarnil *Boniscontro & Gazzone, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Eucaryl *Zizine, Fr.*
⊗Dexamethasone acetate (p. 1631·1); thymol (p. 1772·2).
Root canal infections.

Eucasept *Solagran, Rus.*
Azulene (p. 2452·1); alpha tocoferil acetate (p. 2119·2); peppermint oil (p. 1877·1); fir oil; thymol (p. 1772·2); eucalyptus oil (p. 2501·2).
Rhinitis.

Eucazolin *Farmak, Ukr.*
⊗Xylometazoline (p. 1680·1).
Rhinitis; rhinosinusitis; otitis media.

Eucerin *Beiersdorf, Chile; Beiersdorf, Malaysia.*
Range of emollients.
Dry skin.

Beiersdorf, Irl.; Beiersdorf, UK.
Emollient.
Dry skin.

Beiersdorf, USA.
Emollient; cream base.

Beiersdorf, Thai.†
A range of skin cleansing and emollient preparations.

Beiersdorf, Chile.
Cream; lotion; ointment: ⊗Urea (p. 1727·3).
Dry skin disorders.

Beiersdorf, Chile.
Cream SPF 25: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Beiersdorf, Chile.
Cream-Gel SPF 25: Bemotrizinol (p. 1695·3).
Sunscreen.

Beiersdorf, Chile.
Lotion SPF 40: Iscotrizinol (p. 1706·1); titanium dioxide (p. 1725·1); bemotrizinol (p. 1695·3); avobenzone (p. 1695·1).
Sunscreen.

Beiersdorf, Chile.
Spray SPF 30: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); octil triazone (p. 1715·1).
Sunscreen.

Beiersdorf, Chile.
Topical liquid, SPF 15: Liquorice (p. 1853·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Rosacea.

Beiersdorf, Chile.
Topical liquid SPF 20: Bemotrizinol (p. 1695·3); octil triazone (p. 1715·1); ensulizole (p. 1703·1); octadecenedioic acid.
Hyperpigmentation disorders.

Beiersdorf, Chile.
Cream-gel: Lactic acid (p. 2539·1); sodium lactate (p. 1781·2).
Acne.

Beiersdorf, USA.
SPF 25: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Dry skin; sunscreen.

Eucerin Baby & Mom *Beiersdorf, Chile.†*
A range of skin cleansing and emollient preparations.

Eucerin Correctora Anti-Espinillas *Beiersdorf, Chile.*
Zinc oxide (p. 1729·1); panthenol (p. 2582·2).
Acne.

Eucerin Dry Skin Care Daily Facial *Beiersdorf, USA.*
SPF 20: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); ensulizole (p. 1703·1); octisalate (p. 1715·2).
Sunscreen.

Eucerin Emulsion *Beiersdorf, Chile.†*
Hyaluronic acid (p. 2526·2).
Soap substitute.

Eucerin Higiene Intima *Beiersdorf, Chile.*
Lactic acid (p. 2539·1); levomenol (p. 2544·1).
Feminine hygiene.

Eucerin Hydro-Protect *Beiersdorf, Chile.*
SPF 15: Octocrilene (p. 1715·2); octisalate (p. 1715·2); bemotrizinol (p. 1695·3).
Sunscreen.

Eucerin Itch-Relief *Beiersdorf, USA.*
Menthol (p. 2553·2); evening primrose oil (p. 2502·2).
Pruritus.

Eucerin Micropigmentos *Beiersdorf, Chile.*
SPF 25: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); dexpanthenol (p. 2582·2).
Sunscreen.

Eucerin Moisturizing Face *Beiersdorf, USA.*
SPF 30: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Eucerin Ninos *Beiersdorf, Chile.*
Lotion, SPF 40: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); bemotrizinol (p. 1695·3); iscotrizinol (p. 1706·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Eucerin peau seche *Beiersdorf, Switz.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Eucerin pH5 *Beiersdorf, Arg.*
A range of skin cleansers and emollients.

Beiersdorf, Chile.
A range of skin cleansing and emollient preparations.

Eucerin Piel *Beiersdorf, Arg.*
A range of skin cleansers and moisturisers.

Eucerin Piel Grasa *Beiersdorf, Chile.†*
Cream: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1) panthenol (p. 2582·2); levomenol (p. 2544·1); diazolidinyl urea (p. 1750·1); phenoxyethanol (p. 1764·3).
Acne.

Beiersdorf, Chile.†
Topical gel: Salicylic acid (p. 1719·1).
Acne.

Beiersdorf, Chile.†
Cream-gel: Lactic acid (p. 2539·1); titanium dioxide (p. 1725·1); phenoxyethanol (p. 1764·3).
Acne.

Eucerin Piel Seca *Beiersdorf, Chile.†*
A range of emollient and moisturising preparations.

Eucerin Plus *Beiersdorf, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Dry skin; sunscreen.

Eucerin Q10 Active *Beiersdorf, Chile.*
SPF 15: Ubidecarenone (p. 2637·1); octocrilene (p. 1715·2); octisalate (p. 1715·2); ensulizole (p. 1703·1); titanium dioxide (p. 1725·1).
Sunscreen.

Eucerin Reductor de Sebo/Grasa *Beiersdorf, Chile.*
Gel: Salicylic acid (p. 1719·1).
Skin cleansing; seborrhoea.

Eucerin Shampoo Anticaspa *Beiersdorf, Chile.†*
Climbazole (p. 576·2); piroctone olamine (p. 1716·3); sodium salicylate (p. 132·2).
Dandruff.

Eucerin Shampoo para el Tratamiento de la Caspa *Beiersdorf, Chile.*
Climbazole (p. 576·2); piroctone olamine (p. 1716·3); sodium salicylate (p. 132·2).
Dandruff.

Eucerin Solar *Beiersdorf, Chile.†*
Gel SPF 25: SPF 35: Enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Beiersdorf, Chile.†
SPF 25 pigmented cream: Infant lotion SPF 25: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Beiersdorf, Chile.†
Spray SPF 20: Enzacamene (p. 1703·2); octil triazone (p. 1715·1); avobenzone (p. 1695·1); dicaprylyl ether; diethylhexyl butamido triazone; ensulizole (p. 1703·1).
Sunscreen.

Beiersdorf, Chile.†
Infant topical spray SPF 30: Topical spray SPF 30: Octil triazone (p. 1715·1); enzacamene (p. 1703·2); iscotrizinol (p. 1706·1); ensulizole (p. 1703·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Beiersdorf, Chile.†
SPF 50 Plus: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1); bemotrizinol (p. 1695·3); ensulizole (p. 1703·1).
Sunscreen.

Eucerin Sun Protection 3D *Beiersdorf, Arg.*
SPF 20; SPF 50: A range of sunscreen preparations containing bemotrizinol (p. 1695·3).

Eucerin Sun Sensitive Skin *Beiersdorf, Thai.†*
Face and Body Cream SPF 60: Avobenzone (p. 1695·1); octil triazone (p. 1715·1); ensulizole (p. 1703·1); iscotrizinol (p. 1706·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Beiersdorf, Thai.†
Face Cream SPF 25: Avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octocrilene

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 1715·2); octinoxate (p. 1715·1); isocotrizinol (p. 1706·1); bemotrizinol (p. 1695·3).
Sunscreen.

Beiersdorf, Thai.†
Gel SPF 25: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1).
Sunscreen.

Beiersdorf, Thai.†
Lotion SPF 40: Avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); isocotrizinol (p. 1706·1); bemotrizinol (p. 1695·3).
Sunscreen.

Eucéta *Novartis Consumer, Switz.†*
Aluminium acetotartrate (p. 2440·1).
Skin disorders.

Eucéta avec camomille et arnica *Novartis Consumer, Switz.*
Aluminium acetotartrate (p. 2440·1); chamomile (p. 2474·1); arnica (p. 2447·2).
Skin disorders.

Euchessina CM *Antonetto, Ital.*
Sodium picosulfate (p. 1887·2).
Constipation.

Euchinin *Kimia, Indon.*
Quinine etabonate (p. 665·2).
Malaria.

Eucid *Greater Pharma, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux, Zollinger-Ellison syndrome.

Eucil *Farmasa, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Eucillin *Sigmapharm, Austria.*
Bacitracin (p. 225·3); dequalinium chloride (p. 1749·3); diphenylpyraline hydrochloride (p. 627·2).
Infected skin disorders.

Euciton *Roux-Ocefa, Arg.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Euciton Complex *Roux-Ocefa, Arg.*
Domperidone (p. 1838·1); dipotassium clorazepate (p. 1056·3).
Gastrointestinal disorders.

Euciton Reflux *Roux-Ocefa, Arg.*
Domperidone (p. 1838·1); ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer.

Euciton Stress *Roux-Ocefa, Arg.*
Domperidone (p. 1838·1); alprazolam (p. 1035·2); simeticone (p. 1886·2).
Gastrointestinal motility disorders.

Euclamin *Polpharma, Pol.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euclide *Alkem, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Euclide-M *Alkem, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Euclivir *TAD, Ital.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Euclorina *Bracco, Ital.*
Tosylchloramide sodium (p. 1773·1).
Disinfection of burns, skin, ulcers, wounds, and external genitals.

Eucobal *Cratus, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Eucol
Note: this name may be used for preparations of different composition.
Novapharm, Cz.
Paclitaxel (p. 839·3).
Malignant neoplasms.

Tradiphar, Fr.†
Arginine oxoglurate (p. 2049·1).
Tonic.

Eucoprost *Frosst, Spain.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Eucor *Greater Pharma, Thai.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Eucreas *Novartis, Austria; Novartis, Belg.; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Swed.; Novartis, UK.*
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Eucycline *Demo, Gr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Eudal-SR *UAD, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Eudarona *Troika, Venez.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Eudase *Captab, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Eudase-D *Captab, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Eudase-DP *Captab, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Eudase-MX *Captab, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Eudemine *IFET (ΙΦΕΤ), Gr.; Focus, UK; Goldshield, UK.*
Diazoxide (p. 1351·3).
Hypoglycaemia; hypertensive crises.

Euderm *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia.†*
⊗Urea (p. 1727·3).
Dry skin disorders; pruritus.

Eudermal Pasta *Pentaderm, Ital.*
Barrier cream.

Eudermal Sapone Allo Zolfo pH 5 *Pentaderm, Ital.*
Sulfur (p. 1721·1).
Skin cleansing.

Eudermico *Novogaleno, Ital.*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).
Dry skin disorders.

Eudextran *Medacta, Ital.*
⊗Dextran 40 (p. 1138·1) in sodium chloride or glucose.
Plasma volume expansion; thromboembolic disorders.

Eudiges
Note: this name may be used for preparations of different composition.
Liferpal, Mex.
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders.

Lesvi, Spain.†
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eudigox *Teofarma, Ital.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Eudolene *Savio, Ital.†*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Eudon *Baliarda, Arg.*
Bromazepam (p. 1041·2); clebopride malate (p. 1833·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Eudorlin *Berlin-Chemie, Ger.*
Tablets: Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Eudorlin Extra *Berlin-Chemie, Ger.*
Ibuprofen (p. 68·2).
Fever; pain.

Eudorlin Migrane *Berlin-Chemie, Ger.*
Ibuprofen (p. 68·2).
Migraine and other headaches.

Eudresc *KRKA, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eudrox *Euphoric, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Eudyna *Abbott, Austria; Zydus, India; Nordmark, Indon.; Tunggal Idaman, Indon.*
Tretinoin (p. 1725·2).
Acne.

Eudyne *Delpech, Fr.†*
Avena sativa (p. 2451·1); nux moschata (p. 2573·1); sterculia acuminata (p. 2648·2).
Homoeopathic preparation.

Eufacin *Euphoric, India.*
Rifampicin (p. 350·3).
Bacterial infections.

Eufacin Inh *Euphoric, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Eufacin Plus *Euphoric, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Eufans *Sigma-Tau, Ital.*
Amtolmetin guacil (p. 21·1).
Musculoskeletal and joint disorders; pain.

Eufazid *Euphoric, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Eufen *PP Lab, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Eufenil *Gelcaps, Mex.*
Ibuprofen (p. 68·2).
Fever; pain; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Eufenil M28 *Gelcaps, Mex.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain; fever; inflammation.

Eufertil *IP, Ital.*
Carnitine (p. 2053·2).
Nutritional supplement.

Eufilina *Nycomed, Port.; Takeda, Spain.*
Theophylline (p. 1229·3).
Obstructive airways disease; cor pulmonale.

Nycomed, Spain.†
Suppositories: Aminophylline (p. 1201·2).
Obstructive airways disease; neonatal apnoea.

Eufit *Euphoric, India.*
Spirulina (p. 2622·1).

Euflex *Merck, Canad.*
Flutamide (p. 798·2).
Prostatic cancer.

Euflexxa *Grunenthal, Fr.; Ferring, UK; Ferring, USA.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Eufloxin *Mavi, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Euflux *Sudmedica, Ger.*
Pumilio pine oil (p. 2591·1); camphor (p. 2466·2).
Catarrh.

Eufor *Farmasa, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Euform *Hovid, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Eufox *Lupin, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Eufox-O *Lupin, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Eufox-TZ *Lupin, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Eufusin *Medacta, Ital.*
⊗Succinylated gelatin (p. 1154·1).
Hypovolaemia.

Eugadine Lysine *Universal Drug, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Eugalac *Topfer, Ger.†*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Eugalan Töpfer *Topfer, Ger.†*
Bifidum bacteria; lactulose (p. 1850·3).
Cirrhosis; gastrointestinal disorders.

Eugastrim *Grunenthal, Port.*
Omeprazole (p. 1867·2).
Gastric hyperacidity.

Eugenol-Guaiacolo Composto *Ogna, Ital.*
Eugenol (p. 2501·2); guaiacol (p. 1666·1); lidocaine hydrochloride (p. 1988·2); thymol (p. 1772·2).
Dental extraction pain.

Eugerial *Bago, Arg.; Bago, Braz.; Armstrong, Mex.†*
Nimodipine (p. 1455·2).
Mental function impairment; cerebrovascular disorders; vertigo; tinnitus; ischaemic neurological deficit following subarachnoid haemorrhage; dementia.

Eugerminol *Medix, Mex.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Euglamin *Ratiopharm, Fin.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglim *Zydus, India; Zydus Cadila, Philipp.; Simayla, S. Afr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Euglim-M *Zydus, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Euglim-MP *Zydus, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Euglim-P *Zydus, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

Euglitol *Piramal, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Euglo Plus *Roche, Philipp.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Euglodin *MedChoice, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglotab *ACME, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglucan *Roche, Fr.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglucon *Investi, Arg.; Roche, Austria†; Roche, Belg.; Roche, Braz.†; Pharmascience, Canad.; Roche, Fin.†; Roche, Hong Kong†; Piramal, India; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Philipp.; Roche, Spain; Roche, Swed.†; Roche, Switz.†; Roche, Thai.†; Roche, Venez.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglucon N *Sanofi-Aventis, Ger.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglusid *Roche, Chile.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Euglykon *Roche, Gr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Eugune *Titanadria, Ital.*
Magnesium (p. 1786·3); bioflavonoids (p. 2505·2); proline oxide; lupulus (p. 2546·1); hydroxyapatite (p. 2529·3).
Menopausal disorders.

Eugynin *Gufic, India.*
Asparagus racemosus (p. 2614·2); cinnamon (p. 2479·2); clove (p. 2481·2); piper longum; tinospora cordifolia.

Eugynon *Schering, Hong Kong.†*
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Euhypnos *Pfizer, Gr.; Healthcare Logistics, NZ; Pfizer, Thai.*
Temazepam (p. 1109·1).
Insomnia; sleep disorders.

Euipnos *Teva, Ital.†*
Temazepam (p. 1109·1).
Insomnia.

Euka *Pharmonta, Austria.*
Fennel (p. 2503·2); aniseed (p. 2444·2); rosemary (p. 2607·2); eucalyptus (p. 2501·1); lavender flowers (p. 2541·1); laurel leaves; camphor (p. 2466·2); peppermint oil (p. 1877·1); spearmint oil (p. 2621·2).
Gastrointestinal disorders.

Eukadar *Darier, Mex.*
Calcipotriol (p. 1697·2).
Psoriasis.

Eukaliptiss *Theiss Naturwaren, Pol.*
Eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); camphor (p. 2466·2).
Musculoskeletal pain; neuralgia; respiratory-tract disorders.

Eukalisan N *Steigerwald, Ger.†*
Cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); rutoside sodium sulfate (p. 2505·2).
Procaine hydrochloride (p. 1994·3) is included in this preparation to alleviate the pain of injection.
Liver disorders; peripheral vascular disorders; tonic; neuralgia.

Euketos *CT, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; phlebitis; thrombophlebitis; inflammation; pain.

Eukroma *Yash, India.*
Hydroquinone (p. 1705·1).
Hyperpigmented skin disorders.

Eukroma-SG *Yash, India.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Hyperpigmented skin disorders.

Euky Bear Cough Syrup *Felton, Austral.†*
Chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1); sodium citrate (p. 1781·2).
Cough and cold symptoms.

Euky Bear Eu-Clear Inhalant *Felton, Austral.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Cold symptoms; respiratory-tract congestion.

Euky Bearub *Felton, Austral.*
Eucalyptus oil (p. 2501·2); cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2); rosemary oil (p. 2607·3).
Cold symptoms; nasal congestion; muscular aches and pains.

Eulactol *Eulactol, S.Afr.*
⊗Urea (p. 1727·3).
Dry skin.

Eulanta *Europharm, Hong Kong.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Dyspepsia; flatulence; heartburn.

Eulatin NH *Riemser, Ger.*
Ointment: Bismuth subgallate (p. 1822·1); hamamelis (p. 2523·3); tannic acid (p. 2625·2); yeast (p. 2125·2).
Anorectal disorders.

Riemser, Ger.
Suppositories: Tannic acid (p. 2625·2); bismuth subgallate (p. 1822·1).
Anorectal disorders.

Eulex *KRKA, Port.*
⊗Indapamide (p. 1409·2).
Hypertension.

Eulexin *Schering-Plough, Austral.; MSD, Belg.; Mantecorp, Braz.; Schering-Plough, Denm.†; Schering-Plough, Fin.†; Schering-Plough, Ital.; Schering-Plough, Mex.†; Schering-Plough, Norw.; Schering-Plough, NZ; Schering-Plough, Port.; Schering-Plough, S.Afr.; MSD, Spain; MSD, Swed.; Schering-Plough, Turk.; Schering-Plough, Venez.*
Flutamide (p. 798·2).
Prostatic cancer.

Eulexine *MSD-Chibret, Fr.*
Flutamide (p. 798·2).
Prostatic cancer.

Eulitop *Roche, Belg.; Actavis, Spain.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Eulux *Mediwhite, Ital.*
Chamomile (p. 2474·1); euphrasia (p. 2502·1); centaurea cyanus; hamamelis (p. 2523·3).
Eye irritation.

Eu-Med
Note: this name may be used for preparations of different composition.
Strathmann, Ger.
Phenazone (p. 124·1).
Pain; fever.

Eu-Med Neu *Gebro, Austria.*
Dexibuprofen (p. 43·1).
Pain.

Eumet *Symbiotic, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Eumet-D *Symbiotic, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Eumicel *Cassara, Arg.*
Ketoconazole (p. 585·3).
Scalp disorders.

Eumide *Alpic, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

CCM, Malaysia.
Flutamide (p. 798·2).
Prostatic cancer.

Eumidral *Roemmers Osmoph, Venez.*
Atropine methonitrate (p. 1310·2); secbutabarbital sodium (p. 1106·2).
Infant dyspepsia; infant colic; habitual vomiting; gastrointestinal vagal hypertonia.

Eumik *Euphoric, India.*
Amikacin (p. 214·1).
Bacterial infections.

Euminz *Cassella-med, Ger.*
Peppermint oil (p. 1877·1).
Tension-type headache.

Eumitan *Menarini, Austria.*
Frovatriptan succinate (p. 676·2).
Migraine.

Eumitol *Help, Gr.*
Citalopram hydrochloride (p. 411·1).

Eumol *Arlex, Mex.*
Oxolamine (p. 1671·2).
Cough.

Eumosone *GSK, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Eumosone-G *GSK, India.*
⊗Clobetasone butyrate (p. 1627·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Eumosone-M *GSK, India.*
⊗Clobetasone butyrate (p. 1627·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Eumotil *Baliarda, Arg.*
Trimebutine maleate (p. 2634·1).
Smooth-muscle spasm.

Eumotil-T *Baliarda, Arg.*
Trimebutine maleate (p. 2634·1); bromazepam (p. 1041·2).
Smooth muscle spasm.

Eumovate *Investi, Arg.; GSK, Austral.; GSK, Belg.; Farmoquimica, Braz.; GSK, Hong Kong; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; Sekpharma, S. Afr.†; GSK, Singapore; GSK, Turk.; GSK Consumer, UK; GSK, Venez.*
⊗Clobetasone butyrate (p. 1627·3).
Skin disorders; burns.

EuMunil *Madaus, Ital.*
Echinacea (p. 2498·1).
Immunostimulant; respiratory-tract infections.

Eunades *Pfizer, Braz.*
Etoposide (p. 790·2).
Malignant neoplasms.

Pierre Fabre, Gr.
Vinorelbine tartrate (p. 885·3).

Eundin *Pascual, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Eunerpan *Abbott, Ger.†*
Melperone hydrochloride (p. 1083·2).
Psychiatric disorders; sleep disorders.

Eunice 35-ED *Darier, Mex.*
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgen-dependent acne, alopecia, and hirsutism in women; oral contraception in women with androgenic symptoms.

Eunoctin *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Nitrazepam (p. 1089·1).
Epilepsy; sleep disorders; premedication.

Eupanta D *Alpic, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Eupantol *Nycomed, Fr.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Eupatol *Donini, Ital.*
Cascara (p. 1826·1); boldo (p. 2458·3); rhubarb (p. 1884·2).
Constipation.

Eupatorium N Oligoplex *Madaus, Ger.*
Eupatorium perfoliatum (p. 2459·1); aconitum (p. 2428·3); bryonia (p. 2461·3); echinacea angustifolia (p. 2498·1); tartarus stibiatus (p. 151·2).
Homoeopathic preparation.

Eupen
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Eupept *Cifarma, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Eupeptina *Almirall, Spain.*
Dibasic sodium phosphate (p. 1791·2); magnesium carbonate (p. 1856·2); magnesium phosphate (p. 1787·3); magnesium oxide (p. 1857·3); pepsin carbonate.
Constipation; dyspepsia.

Euphoclox *Euphoric, India.*
Ampicillin (p. 218·2) or ampicillin trihydrate (p. 218·2); cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1).
Bacterial infections.

Euphomin Plus *Juggat, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Euphomox *Euphoric, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Euphon *ACP, Belg.; Mayoly-Spindler, Fr.; Jaba, Port.; Mayoly-Spindler, Singapore.*
Hedge mustard (p. 2524·2).
Cough; mouth and throat disorders; catarrh.

Mayoly-Spindler, Fr.; Jaba, Port.
Syrup: Codeine (p. 40·2); hedge mustard (p. 2524·2).
Cough.

Mayoly-Spindler, Malaysia.
Hedge mustard (p. 2524·2); menthol (p. 2553·2).
Sore throat.

Euphonyl Expectorant *Mayoly-Spindler, Fr.*
Terpin (p. 1678·2); siberian fir oil; niaouli oil (p. 2569·1); eucalyptus oil (p. 2501·2).
Respiratory-tract congestion.

Euphonyl Toux Sèche *Mayoly-Spindler, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Euphorbia Complex *Blackmores, Austral.†*
Passion flower (p. 2584·1); thyme (p. 2630·2); grindelia (p. 2522·3); euphorbia (p. 2501·3); vitamins.
Asthma; bronchitis; catarrh.

Euphorbium comp *Heel, Neth.*
Argentum nitricum (p. 2615·3); euphorbia resinifera; luffa operculata (p. 2545·3); mercurius iodatus ruber (p. 2555·3); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Euphorbium comp SN *Heel, Ger.*
Luffa operculata (p. 2545·3); hepar sulfuris (p. 1721·3); mercurius bijodatus (p. 2555·3); argentum nitricum (p. 2615·3); euphorbium; pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Euphorbium Complexe No 88 *Lehning, Fr.*
Euphorbia; daphne mezererum; petroleum (p. 2587·2); arsenicum iodatum (p. 2448·1); sulfur (p. 1721·1); rhus toxicodendron (p. 2603·3); mahonia (p. 2577·1); acidum nitricum (p. 2572·3); anacardium (p. 2471·3); natrum salicylicum (p. 132·2).
Homoeopathic preparation.

Euphorbium Compositum *Heel, Austria.*
Pulsatilla pratensis (p. 2600·2); luffa operculata (p. 2545·3); hydrargyrum bijodatum (p. 2555·3); mucosa nasalis suis; hepar sulfuris (p. 1721·3); argentum nitricum (p. 2615·3); sinusitis-nosode; euphorbium.
Homoeopathic preparation.

Heel, Canad.
Nasal spray: Hepar sulphuris calcareum (p. 1721·3); euphorbium officinarum; luffa operculata (p. 2545·3); mercurius iodatus ruber (p. 2555·3); mucosa nasalis suis; pulsatilla (p. 2600·2); sinusitis-nosode; argentum nitricum (p. 2615·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Canad.
Oral drops: Asclepias vincetoxicum; echinacea angustifolia (p. 2498·1); hepar sulphuris calcareum (p. 1721·3); euphorbium officinarum; luffa operculata (p. 2545·3); pulsatilla (p. 2600·2); argentum nitricum (p. 2615·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Cz.
Luffa operculata (p. 2545·3); calcii sulfidum (p. 1721·3); euphorbium; pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Euphorbium Compositum S *Heel, S.Afr.†*
Euphorbium; pulsatilla (p. 2600·2); luffa operculata (p. 2545·3); mercurius bijodatus (p. 2555·3); mucosa nasalis suis; hepar sulfuris (p. 1721·3); argentum nitricum (p. 2615·3); sinusitis-nosode.
Homoeopathic preparation.

Euphrasia comp *Weleda, Ger.*
Echinacea (p. 2498·1); euphrasia (p. 2502·1); calendula (p. 2465·2).
Eye disorders.

Euphrasia Complex *Mediherb, Austral.*
Euphrasia (p. 2502·1); solidago (p. 2620·1); echinacea (p. 2498·1); hydrastis (p. 2528·1); capsicum (p. 2469·3).
Respiratory-tract disorders.

Euphrasia Complexe No 115 *Lehning, Fr.*
Euphrasia (p. 2502·1); aconitum (p. 2428·3); solanum dulcamara (p. 2497·3); belladonna (p. 2453·3); apis (p. 2445·2); capsicum (p. 2469·3); rubia; arsenicum album (p. 2448·1).
Homoeopathic preparation.

Euphrasia Compound *Phytomedicine, Austral.*
Euphrasia (p. 2502·1); solidago (p. 2620·1); albizia lebbeck; skullcap (p. 2617·1); capsicum (p. 2469·3).
Sinusitis.

Euphyllin *Nycomed, Austria; Nycomed, Belg.; Nycomed, Cz.; Pharos, Indon.; Nycomed, Pol.; Nycomed, S.Afr.; Takeda, Switz.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Persos, Gr.†
Aminophylline (p. 1201·2) or theophylline hydrate (p. 1229·3).

Euphyllina *Nycomed, Ital.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Euphylline *Nycomed, Fr.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Euphylong *Nycomed, Ger.; Nycomed, Hong Kong; Nycomed, Hung.; Nycomed, Neth.†*
Theophylline (p. 1229·3).
Obstructive airways disease; central respiratory disorders.

Euphypertuis *Bayer Sante, Fr.*
St John's wort (p. 449·1).
Depression.

Euphytose *Bayer Sante, Fr.*
Crataegus (p. 2488·1); passion flower (p. 2584·1); valerian (p. 2640·2); ballota.
Nervous disorders; insomnia.

Euplix *Synthon, Denm.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Eupnase *Bilim, Turk.*
⊗Guaifenesin (p. 1666·2); ephedrine hydrochloride (p. 1663·2); potassium iodide (p. 2336·3).
Respiratory-tract congestion.

Eupnéron *E Pharma, Fr.†*
Eprozinol hydrochloride (p. 1665·1).
Obstructive airways disease.

Eupnol *Rottapharm, Spain.*
Benzethonium chloride (p. 1738·1); cineole (p. 2479·1); cherry laurel (p. 2475·2); procaine hydrochloride (p. 1994·3); terpineol (p. 2627·2); menthol (p. 2553·2).
Mouth and throat disorders.

Eupres *Valeant, Ital.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Eupressin *Biosintetica, Braz.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Eupressin-H *Biosintetica, Braz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Eupressyl *Nycomed, Fr.*
Urapidil (p. 1520·2) or urapidil hydrochloride (p. 1520·2).
Hypertension; controlled hypotension during anaesthesia.

Euproct *Andromaco, Chile.*
Tribenoside (p. 2633·3); lidocaine (p. 1988·1).
Anorectal disorders.

Euprostatin *Sigma, Braz.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Euprotin *Almirall, Spain.†*
Lenograstim (p. 1155·2).
Reduction of neutropenia associated with cancer chemotherapy; mobilisation of autologous peripheral blood progenitor cells.

Eupyric *Euphoric, India.*
Paracetamol (p. 115·1).
Pain; fever.

Euradal *Lacer, Spain.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Euralben *Reuffer, Mex.*
Albendazole (p. 149·1).

Eu-Ran *EuroHealth, Philipp.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eurartesim *Sigma-Tau, Irl.; Sigma-Tau, Neth.; Sigma-Tau, UK.*
Piperaquine phosphate (p. 659·3); artenimol (p. 648·2).
Malaria.

Eurax *Novartis Consumer, Austral.; Novartis Consumer, Austria†; Novartis Consumer, Belg.†; Columbia, Canad.; Novartis, Chile; Novartis Sante, Fr.; Novartis, Gr.; Novartis Consumer, Hong Kong; Novartis Consumer, Irl.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Malaysia; Novartis, Mex.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis Consumer, Port.; Novartis Consumer, S.Afr.; Novartis OTC, Singapore; Novartis Consumer, Switz.; Novartis Consumer, UK; Westwood-Squibb, USA.*
Crotamiton (p. 1699·2).
Pruritus; scabies; pediculosis; urticaria; insect stings.

Eurax Hc *Novartis Consumer, UK.*
⊗Crotamiton (p. 1699·2); hydrocortisone (p. 1640·1).
Eczema; allergic skin disorders; insect bites.

Eurax-Hydrocortisone *Novartis Consumer, Irl.*
⊗Crotamiton (p. 1699·2); hydrocortisone (p. 1640·1).
Pruritic skin disorders.

Euraxsepti *Novartis Sante, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Wound disinfection.

Eurelax *Euphoric, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Eurelix *Sanofi-Aventis, Fr.*
⊗Piretanide (p. 1470·3).
Hypertension.

Eurepa *Torrent, India.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Eurespal *Servier, Pol.; Servier, Rus.*
Fenspiride hydrochloride (p. 1209·2).
Respiratory-tract disorders; otitis media.

Euretico *Casasco, Arg.*
⊗Chlortalidone (p. 1335·2).
Hypertension; heart failure; oedema; diabetes insipidus.

Euretin *Eupharmed, Ital.*
Omega-3 fatty acids (p. 1460·1); astaxanthin (p. 2170·1); myrtillus (p. 2566·2); vitamin E (p. 2119·1).
Dietary supplement.

Euretin Duo *Eupharmed, Ital.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); fatty acids; vitamins; zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement.

Eurifam *Mavi, Mex.*
Rifampicin (p. 350·3).
Tuberculosis.

Eurimax *Flamingo, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Eurivit *Am-Europharma, Philipp.*
Vitamins; with or without minerals.

Eurixor *Richter, Austria; Biosyn, Ger.†; Loges, Ger.†*
Mistletoe (p. 2560·2).
Malignant neoplasms; joint disorders.

Euro A & C *Institute of Immunology, Philipp.*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Euro D *Euro-Pharm, Canad.*
Colecalciferol (p. 2113·1).

Eurobel *Beximco, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Eurobetsol *Europharm, China; Europharm, Hong Kong.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Eurobio BioQ-10 *Medipharm, Malaysia.*
Ubidecarenone (p. 2637·1).
Heart failure.

Eurobio Bio-Vizmax *Medipharm, Malaysia.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); fish oil (p. 1460·1); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1); selenium (p. 2086·3).
Dietary supplement.

Eurobiol *Mayoly-Spindler, Fr.*
Pancreas (porcine) (p. 2444·1).
Pancreatic insufficiency.

Eurocal D3 *1x2, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Euro-Cid *Euro-Med, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer.

Eurocilana *Europharm, Hong Kong.*
Cocillana (p. 1659·2); senega (p. 1677·2); squill (p. 1677·3).
Cough.

Eurocin *EuroHealth, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Euroclear *Euroderm, Arg.*
Sodium laurilsulfate (p. 2210·3).
Skin cleansing preparation.

Euroclovir *Europharm, Hong Kong.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Eurocoal *Bioceutica, Arg.*
Salicylic acid (p. 1719·1); benzalkonium chloride (p. 1737·1); coal tar (p. 1723·2).
Dandruff; seborrhoea.

Eurocof *Am-Europharma, Philipp.*
Guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders.

Euro-Collins *Fresenius Biotech, Thai.†*
Glucose (p. 2068·3); electrolytes (p. 1775·1).
Preservation of donor kidney in transplantation.

Eurocolor *Euroderm, Arg.*
SPF 15; SPF 34; SPF 45: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); vitamin E (p. 2119·1).
Sunscreen.

Eurocolor Bronceador *Euroderm, Arg.*
Oxybenzone (p. 1715·3); vitamin E (p. 2119·1); octinoxate (p. 1715·1).
Sunscreen.

Eurocolor Post Solar *Euroderm, Arg.*
Aloe vera (p. 1693·2); calendula (p. 2465·2).
Emollient.

Eurocolor Sin Sol *Euroderm, Arg.*
Dihydroxyacetone (p. 1700·1).
Tanning agent.

Eurocor *EuroHealth, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Eurocoxin *Am-Europharma, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Eurodal *Gland, Philipp.*
Dalteparin sodium (p. 1348·3).
Thromboembolic disorders; unstable angina; prevention of clotting during extracorporeal circulation.

Euroderm *Mavi, Mex.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Euroderm-A *Euroderm, Arg.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); colecalciferol (p. 2113·1); allantoin (p. 1693·1).
Moisturiser; prevention of stretch marks.

Eurodin *Takeda, Jpn.*
Estazolam (p. 1072·2).
Insomnia; premedication.

Eurodron *Europharm, Hong Kong.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections with inflammation.

Eurofenac *Europharm, Hong Kong.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Eurofer
Note: this name may be used for preparations of different composition.
Euroderm, Arg.
Ferrous sulfate (p. 2062·2).
Iron supplement.
Eurodrug, Hong Kong; Eurodrug, Malaysia; Eurodrug, Philipp.; Eurodrug, Singapore†; Eurodrug, Thai.
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron-deficiency anaemia.

Eurofer-Iron *Eurodrug, Thai.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Euroflam *Renata, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; familial adenomatous polyposis.

Euroflash *Lifescan, Ital.*
Test for glucose in blood (p. 2516·3).

Euroflex *Saval, Chile.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Euroflox *EuroHealth, Philipp.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Euroflu *Euro-Pharma, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic rhinitis; asthma; bronchitis.

Eurogel *Cielle, Ital.*
Royal jelly (p. 2608·1); dried yeast (p. 2125·2); vitamin E (p. 2119·1).
Nutritional supplement.

Eurogesic *Saval, Chile.*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Euroglip *Solitaire, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Euroglip Forte *Solitaire, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

Euroglip-M2 *Solitaire, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Eurogrel *Saval, Chile.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis; cardiovascular risk reduction.

Eurohair *Euroderm, Arg.*
Collagen (p. 2483·2).
Hair loss.

Euro-Ion in D5 *Euro-Med, Indon.; Euro-Med, Philipp.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Euro-Lac *Euro-Pharm, Canad.*
Lactulose (p. 1850·3).

Eurolac *Renata, Philipp.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Eurolam *Solitaire, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Eurolase *Europharm, Hong Kong.*
⊗Papain (p. 2582·3).
Oedema; inflammation.

Eurolat *Mavi, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Eurolev *Renata, Philipp.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Eurolol *Mavi, Mex.*
⊗Metoprolol (p. 1434·3).
Hypertension.

Euromicina *Saval, Chile.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori *eradication.*

Euromucil *Saval, Chile.*
Psyllium (p. 1849·1).
Constipation.

Euronac *Doliage, Fr.*
Acetylcysteine (p. 1652·2).
Corneal ulceration.

Euronal *Mavi, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Europain *Europharm, Hong Kong.*
Paracetamol (p. 115·1).
Fever; pain.

Europave *Euromex, Mex.†*
Verapamil (p. 1522·1).
Arrhythmias; hypertension.

Europep-T *Solitaire, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Europhenicol *Europharm, Hong Kong.*
Chloramphenicol (p. 257·1).
Eye infections.

Europiel *Euroderm, Arg.*
Silicone oil (p. 2209·3).
Barrier preparation.

Europrofen *Euro-Pharm, Canad.*
Ibuprofen (p. 68·2).
Fever; pain.

Eurosef *EuroHealth, Philipp.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Eurosin *Jean-Marie, Hong Kong.*
Crotamiton (p. 1699·2).
Pruritus.

Eurosol *Euro-Med, Indon.; Euro-Med, Philipp.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Eurostan *Am-Europharma, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Eurotapp *Europharm, Hong Kong.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Eurotofi *Mavi, Mex.*
Pentoxifylline (p. 1465·3).

Euroton *Cielle, Ital.*
Ashwagandha (p. 2450·2); maca; muira-puama; ginseng (p. 2513·3); damiana (p. 2491·3); rhodiola.

Eurotretin *Bioceutica, Arg.*
Tretinoin (p. 1725·2).
Acne.

Eurovan *Europharm, Hong Kong.*
Zopiclone (p. 1118·1).
Insomnia.

Eurovir *Saval, Chile.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Eurovit *Teva, Hung.*
Vitamins; with or without minerals.

Eurox *Health Guard, India.*
Cefixime (p. 240·3).
Bacterial infections.

Euroxi *Copernico, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Euroxol *Mavi, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Eurozyme *Europharm, Hong Kong.*
Muramidase hydrochloride (p. 2565·1).
Upper respiratory-tract disorders; haemorrhage; inflammation.

Eurythmic *Troikaa, India.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Eusaprim *GSK, Austria; Genopharm, Belg.; Aspen, Ger.; GSK, Ital.†; GSK, Swed.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections; toxoplasmosis; blastomycosis.

Euserpina Cellulite *Valetudo, Ital.*
Aristolochia (p. 2447·1).
Cellulite.

Eusilen *Cofasa, Venez.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Euskin *Stada, Spain.*
Erythromycin (p. 291·2).
Acne.

Eusovit *Strathmann, Ger.*
d-Alpha tocopherol (p. 2119·1) or *d*-alpha tocoferil acetate (p. 2119·1).
Vitamin E deficiency.

Eustal *Cachet, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Eustidil *Vitoria, Port.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Eutears *Eupharmed, Ital.*
Omega-6 fatty acids (p. 2575·2); omega-3 fatty acids (p. 1460·1); lactoferrin (p. 2539·3); vitamins; zinc (p. 2126·1); astragalus membranaceus (p. 2451·1).
Dietary supplement.

Eutebrol *Tecnofarma, Chile; Asofarma, Mex.*
Memantine hydrochloride (p. 393·1).
Dementia; cerebral trauma; parkinsonism; Alzheimer's disease.

Eutecaina *Andromaco, Chile.*
Lidocaine hydrochloride (p. 1988·2); prilocaine (p. 1994·1).
Local anaesthesia.

Eutens *Grisi, Mex.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris; heart failure; pulmonary hypertension.

Eutensin *GreaterPharma, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Euthirox *Merck, Ukr.*
Levothyroxine sodium (p. 2339·1).
Euthyroid goitre; hypothyroidism; thyroid cancer; Grave's disease; diagnostic suppression of thyroid activity.

Euthyral *Merck Serono, Fr.*
Liothyronine sodium (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Euthyrox *Merck Serono, Arg.; Merck, Austria; Merck, Belg.; Merck, Braz.; EMD, Canad.; Merck Serono, China; Merck, Cz.; Merck, Denm.; Merck Serono, Ger.; Merck, Gr.; Merck, Hung.; Merck, Indon.; Merck Serono, Israel; Merck Serono, Malaysia; Merck, Neth.; Merck, Norw.; Merck, Philipp.; Merck, Pol.; Nycomed, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Swed.; Merck, Switz.; Merck, Thai.; Merck, Turk.; Merck, Venez.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer; euthyroid goitre; adjuvant in obesity; thyroid suppression test.

Euticlavir *Ratiopharm, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Eutimil *GSK, Ital.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Eutirox *Merck, Chile; Bracco, Ital.; Merck, Mex.; Merck, Port.; Merck, Spain.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer.

Eutocol *Craveri, Arg.*
Estradiol hemisuccinate (p. 2271·1).
Labour induction.

Eutonis *Eurofarma, Braz.*
Cloxazolam (p. 1057·2).
Anxiety.

Eutopic *Farmacologico Milanese, Ital.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Eutrim *Mavi, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Eutrodin *GD, Ital.*
Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Barrier cream.

Eutroid *Elea, Arg.*
Levothyroxine sodium (p. 2339·1); liothyronine sodium (p. 2342·3).
Hypothyroidism.

Eutropin *Cristalia, Braz.; Dismedica, Braz.; Novell, Indon.; LG Life Sciences, Thai.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner's syndrome; short children born small for gestational age.

Eutroxsig *Aspen, Austral.; Healthcare Logistics, NZ.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; Hashimoto's thyroiditis; thyroid tumours.

Eutum *Euphoric, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Euvanol *Mediflor, Fr.*
Inhalation: Eucalyptus oil (p. 2501·2); niaouli oil (p. 2569·1); levomenthol (p. 2553·2); Siam benzoin (p. 2614·3).
Respiratory-tract congestion.

Merck Medication Familiale, Fr.
Nasal spray: Geranium oil (p. 2512·2); niaouli oil (p. 2569·1); camphor (p. 2466·2); benzalkonium bromide (p. 1737·1).
Rhinopharyngeal infections.

Euvasten *Primera, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Euvax B *Sanofi Pasteur, Indon.; Sanofi Pasteur, Malaysia; LG Life Sciences, Philipp.; LG, Pol.; LG Chem, Thai.; Berk, Turk.*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Separate preparations are available for adults and for children.
Active immunisation.

Euvaxon *Teva Tuteur, Arg.*
Etoposide (p. 790·2).
Testicular cancer; small-cell lung cancer.

Euvegal *Schwabe, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; insomnia.

Euvegal Balance *Schwabe, Ger.*
Valerian (p. 2640·2).
Insomnia; nervous disorders.

Euvegal Entspannungs- und Einschlaftropfen *Schwabe, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; sleep disorders.

Euvein *General Drugs, Singapore.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Euvekan *Schwabe, Cz.†; Schwabe, Hung.†; Schwabe, Norw.†; Stetifarm, Venez.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; nervous disorders; anxiety; insomnia.

Euvirax *Saval, Chile.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Eu-Visus *Cielle, Ital.*
Myrtillus (p. 2566·2); yeast (p. 2125·2); carrot; wheat-germ oil (p. 2647·1); soya phospholipid.
Dietary supplement.

Euvitol *Bracco, Ital.*
Vitamin A palmitate (p. 2098·3).
Skin disorders.

Euxat *PHT, Ital.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Eva Povi *Unipharma, Gr.*
Povidone-iodine (p. 1767·1).
Disinfection.

Evabit *Zubit, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Evac *Purzer, China.*
Sodium phosphate.
Bowel evacuation.

Evacef *Neon, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Evacef O *Neon, India.*
Cefixime (p. 240·3).
Bacterial infections.

Evacef-S *Neon, India.*
Cefotaxime sodium (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Evac-Q-Mag *Savage, USA.*
Magnesium citrate (p. 1857·1).

Evac-Q-Tabs *Savage, USA.*
Bisacodyl (p. 1821·1).
Formerly contained phenolphthalein.

Evacream *Gambar, Ital.*
Sodium carboxymethyl beta-glucan (p. 2455·2).
Stretch marks.

Evacrine *Motima, Fr.*
Wild cherry (p. 2207·2); ginger (p. 1844·1); wild pansy (p. 2647·3).
Gastrointestinal disorders.

Evacuante Simple *Lainco, Spain.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Evacuate *Dexter, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Evac-U-Gen *Lee, USA.*
Sennosides (p. 1885·2).
Constipation.

Evacuol
Note: this name may be used for preparations of different composition.
Almirall, Spain.
Sodium picosulfate (p. 1887·2).
Constipation.

Franco-Indian, India.
Sterculia (p. 1888·3); sennosides (p. 1885·2).

Evadol *Andromaco, Chile.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm.

Degorts, Mex.
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Evadox *Arika, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).

Evafer *Gambar, Ital.*
Iron (p. 2073·1); folic acid (p. 2063·1).
Anaemia during pregnancy.

Evaflox *Unichem, Malaysia.*
Ofloxacin (p. 334·3).
Bacterial infections.

Evagelin *Help, Gr.*
Bromazepam (p. 1041·2).
Anxiety disorders.

Evagest *Evacare, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Evaglow *Evacare, India.*
Iron carbonyl (p. 2073·1).

Evaglow Plus *Evacare, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Evaglow-M *Evacare, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Evaglow-T *Evacare, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Evagrip *Kite (Κιτε), Gr.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Evalar *Evalar, Rus.*
Immortelle flowers; crataegus (p. 2488·1); St John's wort (p. 449·1); aesculus (p. 2431·2); pine nut; cranberry (p. 2488·1); coriander (p. 2486·3); laminaria (p. 2540·1); rhaponticum carthamoides; honey (p. 2072·1); peppermint leaf (p. 1877·1); pantocrinum; plantain (p. 2592·3); rhodiola rosea; chamomile (p. 2474·1); mountain ash; liquorice (p. 1853·2); achillea (p. 2427·3); rose fruit (p. 2607·1); Siberian ginseng (p. 2614·3).
Asthenia.

Evalen *Ferron, Indon.*
Adapalene (p. 1692·1).
Acne.

Evalin
Note: this name may be used for preparations of different composition.
Ethica, Indon.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Evalon *Organon, India.*
Estradiol (p. 2271·1).
Formerly contained estriol.
Menopausal disorders; vulvovaginal disorders.

Evaluna *Madaus, Ger.; Rottapharm, Ger.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Evamenol *Mosfarma, Rus.*
Eucalyptus oil (p. 2501·2); levomenthol (p. 2553·2).
Rhinitis.

Evamilk *Gambar, Ital.*
Fennel (p. 2503·2); myrtillus (p. 2566·2); wild carrot (p. 2647·2).
Lactation stimulation.

Evamist *Ther-Rx, USA.*
Estradiol (p. 2271·1).
Menopausal disorders.

Evanecia *Biogaran, Fr.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Triphasic oral contraceptive.

Evangio *Rafarm, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Evanol *GSK, Arg.*
Pregnancy test (p. 2596·1).

Evanor *Wyeth, Braz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Evapause *Zambon, Fr.†*
Progesterone (p. 2300·2).
Menstrual disorders; female infertility; menopausal disorders; threatened or recurrent miscarriage.

Evaplan *Elea, Arg.*
Fertility test (p. 2596·1).

Evapril comp *Sigillata, Denm.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Evapro *Wockhardt, India.*
Preparation for enteral nutrition.

Eva-Q *Medley, India.*
Oral powder: Ispaghula husk (p. 1849·1).

Medley, India.
Syrup: Lactitol (p. 1850·3).

Evaren *Indoco, India.*
Aloe vera (p. 1693·2); honey (p. 2072·1); melaleuca oil (p. 2551·1); wheat-germ oil (p. 2647·1).

Evarose *Bailly, Fr.†*
Arnica (p. 2447·2); hamamelis (p. 2523·3); melilot (p. 2552·3); aesculus (p. 2431·2); butcher's broom (p. 2463·1).
Skin redness.

Evarrest *Ethicon, USA.*
Fibrinogen (p. 1151·3); thrombin (p. 1163·2).
Haemorrhage.

Evasen Crema *Gambar, Ital.*
Vitamin E (p. 2119·1).
Cracked nipples.

Evasen Dischetti *Gambar, Ital.*
⊗Potassium sorbate (p. 1770·2); glycerol (p. 2517·2).
Cracked nipples.

Evasen Liquido *Gambar, Ital.*
⊗Potassium sorbate (p. 1770·2); glycerol (p. 2517·2).
Nipple care during lactation.

Evastel *Almirall, Mex.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Evastel-D *Almirall, Mex.*
⊗Ebastine (p. 628·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders; cold symptoms.

Evatest *Elea, Arg.*
Pregnancy test (p. 2596·1).

Evatocin *Neon, India; Neon, Philipp.*
Oxytocin (p. 2143·1).
Termination of pregnancy; postpartum haemorrhage; labour induction; evaluation of fetal distress; incomplete abortion.

Evaton-B12 *Demo, Gr.*
Vitamin B substances (p. 2102·3).

Evaton-D *Demo, Gr.*
Vitamins.

Evaton-T *Demo, Gr.*
Vitamins.

Evavit *Gambar, Ital.*
Vitamins.
Nutritional supplement during pregnancy.

Evazol *Petrasch, Austria; Ravensberg, Ger.†*
Dequalinium chloride (p. 1749·3).
Skin infections; infected wounds.

EVC *Sisu, Canad.†*
Vitamins; minerals.

Ev-Cal *Evershine, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).

Ev-Cal-CT *Evershine, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Evcarom *Medifarm, Rus.*
Chamomile (p. 2474·1); eucalyptus leaf (p. 2501·1).

Eve
Note: this name may be used for preparations of different composition.
Gedeon Richter, Ger.
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
Combined oral contraceptive.

Eve 500
Note: this name may be used for preparations of different composition.
Biofarma, Venez.
Evening primrose oil (p. 2502·2).
Hypercholesterolaemia; eczema; premenstrual syndrome.

Eve Care *Himalaya, Ukr.†*
Saraca indica; dashamoola; symplocos racemosa; tinospora cordifolia; black nightshade (p. 2458·2); punarnava (p. 2601·1); asparagus racemosus (p. 2614·2); aloe vera (p. 1693·2); cyperus rotundus; santalum album (p. 2610·1); malabar nut (p. 2549·1); bombax ceiba; triphala (indian gooseberry (p. 2532·2), beleric myrobalan (p. 2453·2), chebulic myrobalan (p. 2474·3)); trikatu; kasisa godanti bhasma; yashad bhasma.
Menstrual disorders.

Eve Kit *Mapra, India.*
Azithromycin (p. 221·2); fluconazole (p. 578·2); secnidazole (p. 947·3).

Evecare *Himalaya Herbal, India.*
Capsules: Malabar nut (p. 2549·1); aloe vera (p. 1693·2); asparagus racemosus (p. 2614·2); punarnava (p. 2601·1); cyperus rotundus; tinospora cordifolia.
Himalaya Herbal, India.
Syrup: Malabar nut (p. 2549·1); aloe vera (p. 1693·2); punarnava (p. 2601·1); cyperus rotundus; rubia cordifolia; tinospora cordifolia.

Eveglow *Unichem, India.*
⊗Hydroquinone (p. 1705·1); mometasone (p. 1644·1); tretinoin (p. 1725·2).

Evelea *Elea, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Evelle *Pharma Nord, Malaysia.*
Collagen (p. 2483·2); tomato; ascorbic acid (p. 2110·3); zinc (p. 2126·1); selenium yeast (p. 2125·2); vitamin E (p. 2119·1); maritime pine (p. 2590·3); biotin (p. 2052·2).
Dietary supplement for degenerative skin disorders; hyperpigmentation; scars.
Pharma Nord, Singapore.
Collagen (p. 2483·2); tomato; ascorbic acid (p. 2110·3); zinc gluconate (p. 2126·2); selenium yeast (p. 2125·2); *d*-alpha tocoferil acetate (p. 2119·1); maritime pine (p. 2590·3); biotin (p. 2052·2).
Dietary supplement for degenerative skin conditions, pigmentation and scars.

Evening Gold *Larkhall Laboratories, UK.*
Evening primrose oil (p. 2502·2).

Evening Primrose Oil Plus *Banner Pharmacaps, Malaysia.*
Evening primrose oil (p. 2502·2); vitamin E (p. 2119·1).
Dietary supplement.

Eventin
Note: this name may be used for preparations of different composition.
Svizera, India.
⊗Menotrophin (p. 2284·1).
In-vitro fertilisation.

Evépar *Mylan, Fr.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne in women.

Evepearl-MP *Piramal, India.*
Cimicifuga (p. 2478·1); calcium carbonate (p. 1824·3); soya isoflavones (p. 2620·3); colecalciferol (p. 2113·1).

Evepearl-PMS *Piramal, India.*
⊗Agnus castus (p. 2432·2); ginger (p. 1844·1); magnesium (p. 1786·3); manganese (p. 2081·2); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).

Eveprim *Metro, Philipp.*
Evening primrose oil (p. 2502·2).
Premenstrual disorders; menopausal disorders; cervical ripening.

Ever Ce *Konimex, Indon.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Ever E *Konimex, Indon.†*
Vitamin E (p. 2119·1); selenium (p. 2086·3); vitamin B_5 (p. 2105·3).
Premature skin ageing.

Ever Ost *Konimex, Indon.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin D (p. 2112·3); zinc (p. 2126·1).
Nutritional supplement.

Everbate *Evershine, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Evercef *Orchid, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Evercid *Boniscontro & Gazzone, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Everclav *Evershine, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Evercold *Evershine, India.*
Cetirizine (p. 619·2) or cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1) or phenylpropanolamine hydrochloride (p. 1674·1).

Everdox *Evershine, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Everfem *Omega, Arg.*
Pamabrom (p. 1464·1); paracetamol (p. 115·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Everfit *Evershine, India.*
Vitamins; minerals; with or without ginseng (p. 2513·3).

Ever-Fit Cardio *Prisfar, Port.*
Vitamins; minerals.

Ever-Fit Dermo *Prisfar, Port.*
Lutein (p. 2079·2); omega-3 fatty acids (p. 1460·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Antioxidant.

Ever-Fit Plus *Prisfar, Port.*
Vitamins; minerals.

Everflex *Natures Sunshine, Canad.*
Levomenthol (p. 2553·2).
Musculoskeletal and joint pain.

Evergaurd *Evershine, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Evergum *Evershine, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).

Everiden *Zentiva, Cz.†*
Sodium valproate (p. 553·1).
Epilepsy; mania; migraine.

Evermet-G *Evershine, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Evermet-GSR *Evershine, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Everose *Fresenius Medical, Irl.†*
Calcium acetate (p. 1783·1).
Hyperphosphataemia in dialysis patients.

Everpip-TZ *Evershine, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Everpod *Evershine, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Everser *Evershine, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Everser-D *Evershine, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Evertas *Zentiva, Cz.*
Rivastigmine tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Evertine *Farmoz, Port.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Evervent *Rottapharm, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Everyday Face Sunscreen *Hamilton, Austral.*
SPF 30+: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Everyday Stress Formula *Blackmores, Austral.*
Hydrolysed milk protein (Lactium); ginseng (p. 2513·3).
Tonic.

Everyday Sunscreen *Newco, Canad.*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Everything Butt *Altacomp, Canad.*
White soft paraffin (p. 2211·3); zinc oxide (p. 1729·1).

Everzple *Evershine, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Everzyme *Evershine, India.*
Cinnamon oil (p. 2479·3); amylase (p. 2442·1).

Evestrel *Theramex, Ital.*
Phytoestrogens (genistein, daidzein) (p. 2620·3) (p. 2620·3).
Menopausal disorders.
Theramex, Mon.†
Soya bean (p. 2092·3).
Nutritional supplement during the menopause.

Evestrel Jour Nuit *Theramex, Mon.†*
Day tablets, soya (p. 2092·3); selenium yeast (p. 2086·3); night tablets, soya; magnesium oxide (p. 1857·3).
Nutritional supplement during the menopause.

Evestrel Physio Profil *Theramex, Mon.†*
Soya (p. 2092·3); chromium trichloride (p. 2055·3).
Nutritional supplement during the menopause.

Evex *Elvipe, Gr.*
⊗Ephedrine (p. 1663·1); chlorobutanol (p. 1747·2); tyrothricin (p. 384·1).

Eviana *Novo Nordisk, Israel; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Isdin, Spain; Novo Nordisk, Swed.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Eviantrina *Korhispana, Spain.†*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Evica
Note: this name may be used for preparations of different composition.
Geno, India.
Vitamins; selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).
Herbion, Ukr.†
⊗Saraca indica; symplocos racemosa; valeriana wallichii; chamomile (p. 2474·1); agnus castus (p. 2432·2); areca catechu (p. 2446·3).
Vaginal discharge; leucorrhoea; menstrual disorders; postmenopausal haemorrhage.

Evicap *Kocak, Turk.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E supplement.

Evicel *Omrix, Port.; Ethicon, USA.*
Fibrinogen (p. 1151·3); thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.
Omrix, Spain; Janssen-Cilag, Switz.
Vial 1, fibrinogen (p. 1151·3); fibronectin; vial 2, thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.
Omrix, Austria.
Component 1, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); component 2, thrombin (p. 1163·2) on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.
Omrix, Cz.; Omrix, Denm.; Omrix, Fr.; Omrix, Gr.; Omrix, Irl.; Omrix, Norw.; Omrix, Pol.; Omrix, Swed.
Component 1, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); component 2, thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; haemostasis in surgery.
Omrix, Ger.
1 Vial, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); calcium chloride (p. 1783·1); 1 vial, thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.
Omrix, Israel.
Calcium chloride (p. 1783·1); clottable protein; thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

E-Vicotrat *IFET (ΙΦΕΤ), Gr.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Evict *David, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Evicta *Charoon Bhesaj, Thai.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

E-vidon *Abigo, Swed.†*
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E deficiency.

Evifix *Cosmopharm, Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Evigen *Eras, Turk.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E supplement.

Evilin *Merck, Chile.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-associated acne, alopecia, and hirsutism in women.

Eviline *Kotra, Malaysia; Kotra, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; dyspepsia; heartburn; flatulence; gastritis; oesophagitis.

Evimal *Andromaco, Chile.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

E-vimin *Meda, Swed.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Evina
Note: this name may be used for preparations of different composition.
Klonal, Arg.
Ergometrine (p. 2136·2).
Kocak, Turk.
Vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Rodisma, Ger.
d-Alpha tocopherol (p. 2119·1); ascorbic acid (p. 2110·3).
Vitamin E and C deficiency.

Evinolut *Rafarm, Gr.*
Povidone-iodine (p. 1767·1).

Evinopon *Bros, Gr.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders; prevention of miosis in ophthalmic surgery.

Eviol *Gap, Gr.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Eviol-A *Gap, Gr.*
dl-Alpha tocoferil acetate (p. 2119·2); vitamin A acetate (p. 2098·3).
Vitamin A and E deficiency.

Evion *Merck Serono, Arg.; Merck Serono, Ger.†; Galenica, Gr.; Merck, Indon.; Bracco, Ital.; Merck, Philipp.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency; vitamin E supplement.

Merck, India.
Vitamin E (p. 2119·1).
Vitamin E deficiency; abetalipoproteinaemia; fibrocystic breast disease.

Evion Forte *Merck, India.*
Lycopene (p. 2546·2); omega-3 fatty acids (p. 1460·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Evion-LC *Merck, India.*
Levocarnitine (p. 2053·2); vitamin E (p. 2119·1).

Eviper *Torrent, India.*
Perindopril (p. 1466·3).
Hypertension; heart failure; angina pectoris.

Eviper-D *Torrent, India.*
⊗Indapamide (p. 1409·2); perindopril (p. 1466·3).
Hypertension.

Eviplera *Gilead, Denm.; Gilead, Ger.; Janssen-Cilag, Israel; Gilead, Norw.; Gilead, Swed.; Janssen-Cilag, Swed.; Gilead, Switz.; Gilead, UK.*
Emtricitabine (p. 976·3); rilpivirine hydrochloride (p. 1012·1); tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Evipon *Armoxindo, Indon.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Evipress *Senosiain, Mex.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Eviprostat
Note: this name may be used for preparations of different composition.
Evers, Indon.; Pharos, Indon.
Chimaphila umbellata; equisetum (p. 2500·1); manganese chloride (p. 2081·2); populus tremula (p. 2450·3); pulsatilla (p. 2600·2); sodium taurocholate (p. 2457·2); wheat-germ oil (p. 2647·1).
Benign prostatic hyperplasia; epididymitis.

Shinyaku, Jpn.
Wheat-germ oil (p. 2647·1); chimaphila umbellata; populus tremula (p. 2450·3); pulsatilla (p. 2600·2); equisetum (p. 2500·1).
Benign prostatic hyperplasia.

Shinyaku, Singapore.
Wheat-germ oil (p. 2647·1); chimaphila umbellata; populus tremula (p. 2450·3); pulsatilla (p. 2600·2); equisetum (p. 2500·1); choleinic sodium; manganese chloride (p. 2081·2).
Benign prostatic hyperplasia.

Eviprostat N *Evers, Ger.*
Chimaphila umbellata; populus tremula (p. 2450·3); pulsatilla (p. 2600·2); equisetum (p. 2500·1).
Prostatic hyperplasia.

Eviprostat-S *Evers, Ger.*
Saw palmetto (p. 2363·3).
Micturition disorders associated with benign prostatic hyperplasia.

Evir *Cristalia, Braz.*
Efavirenz (p. 975·1).

Evirenz *Alkem, India.*
Efavirenz (p. 975·1).
HIV infection.

Evisco Mistel Urtinktur *Evisco, Ger.*
Viscum album (p. 2560·2).
Homoeopathic preparation.

Evisco Misteltropfen N *Evisco, Ger.*
Viscum album (p. 2560·2); acid picrinicum (p. 2634·2).
Homoeopathic preparation.

Evista
Note: this name may be used for preparations of different composition.
Lilly, Arg.; Lilly, Austral.; Daiichi Sankyo, Austria; Daiichi Sankyo, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Meda, Cz.; Daiichi, Denm.; Daiichi Sankyo, Fin.; Daiichi Sankyo, Fr.; Daiichi Sankyo, Ger.; Daiichi Sankyo, Gr.; Lilly, Hong Kong; Daiichi Sankyo, Hung.; Lilly, Indon.; Daiichi Sankyo, Irl.; Lilly, Israel; Daiichi Sankyo, Ital.; Lilly, Jpn; Lilly, Malaysia; Lilly, Mex.; Daiichi Sankyo, Neth.; Meda, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Daiichi Sankyo, Port.; Lilly, Rus.; Lilly, S.Afr.; Takeda, Singapore; Daiichi Sankyo, Spain; Meda, Swed.; Daiichi Sankyo, Switz.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis; breast cancer.

Evit *Vita Health, Switz.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Elvipe, Gr.
Tocopherol (p. 2119·1).

Pharmacia Upjohn, India.
Vitamin E acetate (p. 2119·2).
Vitamin E supplement.

Evitam *Cipla, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Evitam Natural Plus *Cipla, India.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3).

E-Vitamin *Natur-Drogeriet, Denm.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Evitex
Note: this name may be used for preparations of different composition.
Alcon, Ital.
Vitamin A (p. 2098·3); tocoferil nicotinate (p. 1516·1).
Vitamin A and E deficiency.

Manon, Israel.
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E supplement.

Evitex A E Fuerte *Alcon Cusi, Spain.*
Vitamin A palmitate (p. 2098·3); tocoferil nicotinate (p. 1516·1).
Deficiency of vitamins A and E; skin disorders; eye disorders; recurrent miscarriage; infertility.

Evithrom *Johnson & Johnson, USA.*
Thrombin (p. 1163·2).
Haemorrhage.

Evitol *Lannacher, Austria; Teva, Israel; KRKA, Rus.*
Tocoferil acetate (p. 2119·2).
Vitamin E deficiency; vitamin E supplement.

Evitop *Ind-Swift, India.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Evitop-C *Ind-Swift, India.*
Cod-liver oil (p. 2056·3); vitamin E acetate (p. 2119·2).

Evitrat *Unipharma, Gr.*
Risperidone (p. 1103·2).

E-Vivax *Themis Medicare, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Evocanil *Zodiac, Braz.*
Progesterone (p. 2300·2).
Menstrual disorders; female infertility; benign breast disorders; threatened miscarriage; premature labour; menopausal disorders.

Evociclo *Evolabis, Braz.*
Cyclophosphamide (p. 771·1).

Evoclin *GSK, USA.*
Clindamycin (p. 269·3).
Acne.

Evo-Conti *Janssen-Cilag, Denm.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders.

Evocs-III *Liomont, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Evodazin *Evolabis, Braz.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Evolith DS *Evaux, Fr.†*
Piroctone olamine (p. 1716·3).
Seborrhoea.

Evolox *Evolabis, Braz.*
Ifosfamide (p. 806·1).

Evoltra *Hospira, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Irl.; Sanofi-Aventis, Israel; Genzyme, Ital.; Genzyme, Jpn; Sanofi-Aventis, Neth.; Genzyme, Norw.; Hospira, NZ; Genzyme, Pol.; Genzyme, Port.; Genzyme, Spain; Genzyme, Swed.; Sanofi-Aventis, UK.*
Clofarabine (p. 769·3).
Acute lymphoblastic leukaemia.

Evolve Plus *Intelligent Therapeutics, UK.*
Wool fat (p. 2219·3).
Eczema; psoriasis.

Evomate *Shreya, India.*
⊗Raloxifene (p. 2303·1).
Osteoporosis.

Evomid *Evolabis, Braz.*
Idarubicin (p. 805·2).

Evomixan *Evolabis, Braz.*
Mitoxantrone (p. 833·1).

Evon *Bilim, Turk.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E supplement.

Evopad *Janssen-Cilag, Spain.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Evopic *Alpic, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Evopic-OZ *Alpic, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Evoprim *Bioceuticals, UK.*
Evening primrose oil (p. 2502·2).

Evoquin *Ivax, Arg.*
Hydroxychloroquine sulfate (p. 655·2).
Lupus erythematosus; rheumatoid arthritis.

Evorel *Janssen-Cilag, Arg.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Norw.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, UK.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Evorel Conti *Janssen-Cilag, Arg.; Janssen-Cilag, Fin.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; hormone replacement therapy; osteoporosis.

Evorel Sequi *Janssen-Cilag, Arg.; Janssen-Cilag, Fin.; Janssen-Cilag, Israel; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK.*
4 Patches, estradiol (p. 2271·1) (Evorel); 4 patches, estradiol; norethisterone acetate (p. 2294·3) (Evorel Conti).
Menopausal disorders; hormone replacement therapy; osteoporosis.

Evorubicin *Evolabis, Braz.*
Doxorubicin (p. 782·3).

Evosebor Li-Zn *Evaux, Fr.†*
Zinc gluconate (p. 2126·2); chamomile (p. 2474·1).
Seborrhoea.

Evo-Sequi *Janssen-Cilag, Denm.*
Patch I, estradiol (p. 2271·1); patch II, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders.

Evosten *Eczacibasi, Turk.*
Erdosteine (p. 1665·1).

Evotabina *Evolabis, Braz.*
Vinorelbine (p. 885·3).

Evotaxel *Evolabis, Braz.*
Paclitaxel (p. 839·3).

Evotecan *Evolabis, Braz.*
Topotecan (p. 872·3).

Evothyl *Guardian, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Evotrox *Kappin, UK.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; non-toxic goitre; thyroid cancer.

Evovit *Symbiosis, India.*
Iron carbonyl (p. 2073·1); zinc sulfate (p. 2126·2); vitamins.

Evox *Dewcare, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); omega-3 fatty acids (p. 1460·1); vitamin E (p. 2119·1); wheat-germ oil (p. 2647·1).

Evoxac *Daiichi, USA.*
Cevimeline hydrochloride (p. 2473·3).
Dry mouth associated with Sjögren's syndrome.

Evoxil *Beacon, UK.*
Levofloxacin (p. 315·3).
Bacterial infections.

Evra *Janssen-Cilag, Arg.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Norelgestromin (p. 2294·1); ethinylestradiol (p. 2275·3).
Combined transdermal contraceptive.

Evrisam *Farmak, Ukr.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; mental function impairment; vestibular disorders; migraine.

Evron *Evershine, India.*
Iron sucrose (p. 2078·1).

Ev-Syl *Evershine, India.*
Vitamins; minerals.

Ev-Syl-XT *Evershine, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Ewadyl *Masa, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cold symptoms; hypersensitivity reactions.

Ewofex *Ewopharma, Cz.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Ewoma *Ethica, Indon.*
Rhizoma paridis.
Dietary supplement following childbirth.

Ex3 *Ariston, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Exabet *Fahrenheit, Indon.†*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Exabetin *Fahrenheit, Indon.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Exaccord *Arrow, NZ.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exacin *Asahi, China; Asahi, Jpn.*
Isepamicin sulfate (p. 311·2).
Bacterial infections.

Exacol *Exakta, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Exacor
Note: this name may be used for preparations of different composition.
Anthiea, India.
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Erempharma, Fr.
Cibenzoline succinate (p. 1336·1).
Arrhythmias.

Exact Babies Sunscreen *Norwood, Canad.*
SPF 45: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Clear Sunscreen *Fruit of the Earth, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Cooling and Refreshing *Fruit of the Earth, Canad.*
SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Fruit Flavours *Norwood, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Exact Kids Clear Sunscreen *Fruit of the Earth, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Kids Sunscreen *Norwood, Canad.*
Lotion SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Norwood, Canad.
Spray SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Lip Balm *Norwood, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Exact Lip Balm Regular *Norwood, Canad.*
Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Exact Lip Balm Year-Round Protection *Norwood, Canad.*
Homosalate (p. 1705·1); meradimate (p. 1711·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Sport *Fruit of the Earth, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Exact Sunscreen *Norwood, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

ExacTech *Medisense, UK.*
Test for glucose in blood (p. 2516·3).

Exacyl *Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Polfa Warszawa, Pol.; Sanofi-Aventis, Pol.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders; fibrinolytic haemorrhagic.

Exafenil *Grin, Mex.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Exafil *Degorts, Mex.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; bronchitis; emphysema.

Exaflam *Guardian, Indon.*
Diclofenac potassium (p. 48·3).
Pain; inflammation; peri-articular disorders.

Exagt *Alembic, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Exail *Sigma, Arg.*
Garlic (p. 2510·3); vitamin P (p. 2505·2).
Dietary supplement.

Exalgo *Mallinckrodt, USA.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Exalief *Bial, Cz.†; Bial, Irl.†; Bial, Neth.†; Bial, Pol.†; Bial, Port.†*
Eslicarbazepine acetate (p. 520·3).
Epilepsy.

Exall *Hawthorn, USA.*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Exall-D *Hawthorn, USA.*
⊗Pentoxyverine citrate (p. 1672·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; upper-respiratory tract congestion; otitis media.

Exalver *Maver, Mex.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract congestion.

Exalver G *Maver, Mex.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough.

Exalver Pediatrico *Maver, Mex.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough.

Examel *Alet, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Examic *Blubell, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Examic-MF *Blubell, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Examida *Exakta, Mex.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Examolin *Exakta, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Examsa *Antibioticos, Mex.†*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Exangina *Apotheke Roten Krebs, Austria.†*
Ammonium bromatum (p. 2461·1); belladonna (p. 2453·3); calcium jodatum (p. 1658·1); echinacea (p. 2498·1); mentholum (p. 2553·2); mercurius cyanatus (p. 2555·3).
Homoeopathic preparation.

Exanidon *Regiomedica, Neth.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exarex *MZ, S.Afr.*
Coal tar (p. 1723·2).
Eczema.

Exario *Genesis, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Exart *Zee, India.*
Levocarnitine (p. 2053·2); vitamin E (p. 2119·1).

Exastrin *Exakta, Mex.*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Exavir *UCI, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Exavit *Exakta, Mex.†*
Vitamins; minerals.

Exazen *Vocate, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Exbenzol *Sons, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Exbequil *Liferpal, Mex.*
Dextromethorphan (p. 1660·1); chlorphenamine (p. 620·3); ammonium chloride (p. 1656·1).
Respiratory-tract disorders.

Excan *Arlak, India.*
Ear drops: ⊗Beclometasone (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).

Arlak, India.
Tablets: Fluconazole (p. 578·2).
Fungal infections.

Excedrin
Note: this name may be used for preparations of different composition.

BMS, Braz.; Novartis, Braz.; Novartis Consumer, Canad.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Novartis Consumer, Irl.; Novartis Consumer, Israel; Novartis Consumer, Neth.; Novartis Consumer, S.Afr.†; Novartis, USA.
Paracetamol (p. 115·1); caffeine (p. 1203·3); aspirin (p. 22·2).
Headache; migraine; pain; fever.

Novartis Consumer, S.Afr.†
Oral powder: Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); caffeine citrate (p. 1203·3).
Pain.

Excedrin Back & Body Extra Strength *Novartis Consumer, USA.*
Paracetamol (p. 115·1); buffered aspirin (p. 22·2).
Pain.

Excedrin Migraine *Novartis, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Migraine.

Excedrin PM *Novartis, USA.*
Paracetamol (p. 115·1); diphenhydramine citrate (p. 626·2) or diphenhydramine hydrochloride (p. 626·2).
Pain associated with sleeplessness.

Excedrin Sinus Headache Aspirin Free *Novartis, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Excedrin Tension Headache *Novartis, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Headache.

Excedrinil *Novartis, Cz.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Migraine.

Excef *Ind-Swift, India.*
Cefixime (p. 240·3).
Bacterial infections.

Excegran *Dainippon, Jpn; Eczacibasi, Turk.*
Zonisamide (p. 560·2).
Epilepsy.

Excel *Ranbaxy, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Excel C *Multivitamin Corp, Philipp.*
Sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Excelase-E *Meiji, Indon.*
⊗Amylase (p. 2442·1); sanactase; protease (p. 2598·1); lipase (p. 2579·3); meicelase; pancreatin (p. 2579·3).
Pancreatic enzyme deficiency.

Excelcur MFI *Maeil, Hong Kong.†*
Preparation for enteral nutrition.
Gastro-enteritis.

Excelcur MFI *Maeil, China.*
Preparation for enteral nutrition.
Diarrhoea.

Excelentia Analgesico *Excelentia, Arg.*
Diclofenac diethylamine (p. 48·3).

Excelentia Antialergico *Excelentia, Arg.*
Loratadine (p. 633·2).

Excelentia Antidiarreico *Excelentia, Arg.*
Loperamide (p. 1854·2).
Diarrhoea.

Excelentia Antiespasmodico *Excelentia, Arg.*
Hyoscine butylbromide (p. 1845·3).

Excelentia Antihemorroidal *Excelentia, Arg.*
Lidocaine (p. 1988·1); zinc (p. 2126·1).
Haemorrhoids.

Excelentia Antimicotico *Excelentia, Arg.*
Econazole (p. 577·2).
Fungal skin infections.

Excelentia Solucion Antiseptica *Excelentia, Arg.*
Povidone-iodine (p. 1767·1).

Excelgrow *Maeil, Hong Kong.†*
Preparation for enteral nutrition.

Excelkid *Maeil, Hong Kong.†*
Preparation for enteral nutrition.

Excel-M *Ranbaxy, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Excelox *Sydenham, Philipp.†*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Excelsior *Grisi, Mex.*
Ointment: Salicylic acid (p. 1719·1).
Warts.

Grisi, Mex.
Topical solution: Tolnaftate (p. 596·1).
Fungal skin infections.

Excillin *Sandoz, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Excipial *Spirig, Cz.; Spirig, Singapore; Spirig, Switz.*
Emollient.
Skin disorders.

Abbott, Turk.
⊗Urea (p. 1727·3).
Dry skin disorders.

Excipial U *Spirig, Cz.; Spirig, Singapore; Spirig, Switz.; Spirig, Ukr.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Exclefin *Biomep, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Excopin *Christo, Hong Kong.†*
Noscapine (p. 1670·3).

Excosine-S *Sons, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Exdol *Pendopharm, Canad.*
Paracetamol (p. 115·1); caffeine citrate (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Execalm *Herbasante, Canad.†*
Apis mellifica (p. 2445·2); graphite (p. 2522·1); petroleum (p. 2587·2); sulfur (p. 1721·1); urtica urens (p. 2639·3).
Homoeopathic preparation.

ExeClear-C *Larken, USA.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

ExeClear-DM *Larken, USA.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Exe-Cort *Pinewood, UK.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Executive B *Cenovis, Austral.†; Vitelle, Austral.†*
Vitamins; minerals; valerian (p. 2640·2); passion flower (p. 2584·1).
Vitamin and mineral deficiencies; stress.

Executive B Stress Formula *Blackmores, Austral.*
Vitamins; minerals; passion flower (p. 2584·1); avena (p. 2451·1).
Nutritional supplement; stress.

Executive Sleep Formula *Blackmores, Austral.*
Lupulus (p. 2546·1); passion flower (p. 2584·1); melissa (p. 2552·3).
Insomnia.

Executive Stress *Winsor, Hong Kong.†*
Choline (p. 2055·2); inositol (p. 2533·2); minerals; vitamins.

Exedexe *Julphar, UAE.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

ExeFen DMX *Larken, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

ExeFen-IR *Larken, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

ExeFen-PD *Larken, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Exegen *Genetic, Ital.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exel
Note: this name may be used for preparations of different composition.

Myrex Ethica, Philipp.
Cefalexin (p. 234·1).
Bacterial infections.

Senosiain, Mex.
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Exelderm *Abdi, Turk.; Centrapharm, UK†; Ranbaxy, USA.*
Sulconazole nitrate (p. 593·3).
Fungal skin infections.

Exelmin *UCI, Braz.*
Cambendazole (p. 152·2); mebendazole (p. 158·3).
Worm infections.

Exelon *Novartis, Arg.; Novartis, Austral.; Novartis, Canad.; Novartis, Israel; Novartis, Jpn; Novartis, Norw.; Novartis, NZ; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.*
Rivastigmine (p. 394·3) or rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Exelyte *USV, India.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).

Exemasin *Ratiopharm, Denm.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exembol *Mitsubishi, UK.*
Argatroban (p. 1307·2).
Heparin-induced thrombocytopenia.

Exemed *Cancernova, Ger.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exemedac *Medac, Ger.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exemedica *Regiomedica, Neth.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exemin *Mensana, Hung.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exempla *Fada, Arg.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Exen *Sanovel, Turk.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Exenadil *Med-One, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).

Exepime *Ferron, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Exeption *Cosme, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Exeregio *Cancernova, Neth.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exerge *Piramal, India.*
Thioctic acid (p. 2629·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); lycopene (p. 2546·2); carotenoids; chromium nicotinate (p. 2055·3); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).

Exerge-HC *Piramal, India.*
Betacarotene (p. 2051·1); cupric oxide; manganese (p. 2081·2); sodium selenate (p. 2087·1); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc oxide (p. 1729·1).

Exergin *Guardian, Indon.*
Codergocrine mesilate (p. 389·2).
Mental function impairment.

Exermet *Cipla, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Exermet GM *Cipla, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Exermet Gz *Cipla, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Exermet P *Cipla, India.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Exertial *Baliarda, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Exestan *Pfleger, Ger.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exestea *Valeant, Cz.*
⊗Exemestane (p. 792·2).
Breast cancer.

Exetin-A *Pisa, Mex.*
⊗Epoetin (p. 1141·1).
Anaemias.

ExeTuss-DM *Larken, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Exeu *Hexal, Ger.†*
Eucalyptus oil (p. 2501·2).
Cold symptoms.

Exfac *Floxia, Singapore.*
Emollient.

Exflam *Merck, India.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Mepro, Chile.†
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Exflem *Stada, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Exfoliac *Merck, Malaysia.*
A range of skin care preparations containing alpha hydroxy acids.
Acne; folliculitis; seborrhoea.

Noreva, Fr.
A range of skin-care preparations.
Acne; seborrhoea.

Merck, Indon.†
Cream: Glycolic acid (p. 1704·3).
Acne.

Merck, Indon.†
Foaming gel; tinted cream: Alpha hydroxy acids (p. 1704·3).
Acne.

Merck, Indon.†
Facial scrub: Glycolic acid (p. 1704·3); ammonium lactate (p. 1694·3); lactic acid (p. 2539·1).
Acne.

Exfoliac Sunblock *Merck, Malaysia.*
SPF 25: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); alpha hydroxy acids (p. 1704·3).
Sunscreen for oily skin.

Exfoliderm *Albephar, Venez.*
Polyethylene (p. 1690·3); triclosan (p. 1773·2); imidurea (p. 1758·2).

Exforge *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S. Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.*
Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2).
Hypertension.

Novartis, China.
Valsartan (p. 1521·2); amlodipine (p. 1304·1).
Hypertension.

Exforge D *Novartis, Arg.*
⊗Amlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2); valsartan (p. 1521·2).
Hypertension.

Exforge HCT *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, USA.*
⊗Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ex-GTM *Forgo, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Exhantil *Sons, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastritis; peptic ulcer; dyspepsia.

Exhidrol *Sons, Mex.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence; gastrointestinal motility disorders.

Exhirud *Sanofi-Aventis, Austria.†*
Leech extract (p. 1401·2).
Superficial phlebitis; superficial thrombosis; inflammation; haematoma; frostbite; insect bites; scar pain.

Exhirud Heparin *Winthrop, Ger.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Ex-Histine *WE, USA.*
Phenylephrine (p. 1672·2); chlorphenamine (p. 620·3); hyoscine (p. 1845·3).
Upper respiratory-tract disorders.

Exiadol *Continentales, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Exibral *Bago, Arg.*
Valproic acid (p. 553·1) or magnesium valproate (p. 553·1).
Bipolar disorder; epilepsy; migraine.

Exicross *Pharmacross, Chile.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Exidine *Baxter, USA.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Exido *Prater, Chile.*
Lidocaine hydrochloride (p. 1988·2).
Erectile dysfunction.

Exidol
Note: this name may be used for preparations of different composition.
Perrigo, Israel.
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

SMB, Fr.†
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Exifine *Reddy, India; Reddy, Malaysia; Reddy, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Reddy, Ukr.
Terbinafine (p. 593·3).
Fungal infections of skin, nails, and mucous membranes.

Exifol *Intermed, India.*
Vitamin B substances (p. 2102·3); ferric ammonium citrate (p. 2060·1).

Exigo *Biomedis, Philipp.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Exil
Note: this name may be used for preparations of different composition.
Esoform, Ital.
Cetylpyridinium chloride (p. 1743·1).
Genital hygiene.

Medopharm, India.
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Exil-D *Medopharm, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Exilet *Biosintex, Arg.*
Citronella oil (p. 2481·1).
Insect repellent.

Exime *NK, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Eximia Fortalize *Farmoquimica, Braz.*
Biotin (p. 2052·2); iron (p. 2073·1); zinc (p. 2126·1).

Eximia Temporize *Farmoquimica, Braz.*
Ascorbic acid (p. 2110·3); vitamin E (p. 2119·1).

Eximius *Duncan, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Exinef *Neopharmed, Ital.*
Etoricoxib (p. 57·3).
Gout; osteoarthritis; rheumatoid arthritis.

Exinol *Sankyo, Venez.*
Sucralfate (p. 1889·1).
Gastro-oesophageal reflux; peptic ulcer.

Exion *Ethica, Indon.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Exipan *Perrigo, Israel.*
Piroxicam (p. 125·3).
Inflammation; pain.

Exiplat *Pharmaplan, S.Afr.*
Oxaliplatin (p. 838·1).

Exiplon *Khandelwal, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Exiplon-BR *Khandelwal, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Exiplon-DM *Khandelwal, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Exit
Note: this name may be used for preparations of different composition.
Brawn, India.
Levamisole (p. 157·2); mebendazole (p. 158·3).

Farmasa, Braz.
Cinnarizine (p. 622·1); piracetam (p. 393·3).
Cerebral and peripheral vascular disorders; impaired mental function.

Stadmed, India.
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Exiten Plus *Synokem, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Exituss *Medispan, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); salbutamol (p. 1220·2).

Exjade *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.*
Deferasirox (p. 1541·3).
Iron overload.

Ex-Lax *Novartis Consumer, Canad.; Novartis Consumer, Israel.†*
Sennosides (p. 1885·2).
Constipation.

Novartis Consumer, Irl.†; Novartis Consumer, UK; Novartis Consumer, USA.
Senna (p. 1885·1).
Constipation.

Ex-Lax Gentle Strength *Novartis, USA.†*
Sennosides (p. 1885·2); docusate sodium (p. 1836·2).
Constipation.

Ex-Lax Stool Softener *Novartis Consumer, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Ex-Lax Ultra *Novartis Consumer, USA.*
Bisacodyl (p. 1821·1).
Constipation.

Exlla *Stellar, India.*
Cefpodoxime.
Bacterial infections.

Exlla-CV *Stellar, India.*
Cefpodoxime; clavulanic acid (p. 268·3).

Exlutena *MSD, Swed.*
Lynestrenol (p. 2287·3).
Progestogen-only oral contraceptive.

Exluton *Organon, Arg.; Schering-Plough, Braz.; Schering-Plough, Chile; Schering-Plough, Indon.; Organon, Mex.; Organon, Neth.; Organon, Philipp.; Organon, Rus.; MSD, Thai.; Organon, Ukr.; Organon, Venez.*
Lynestrenol (p. 2287·3).
Progestogen-only oral contraceptive.

Exmer *Excella, India.*
Meropenem (p. 321·3).
Bacterial infections.

Exmo *Actavis, Neth.*
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Exmykehl *Sanum-Kehlbeck, Ger.; Ebi, Switz.*
Candida albicans; candida parapsilosis; penicillium roquefortii.
Homoeopathic preparation.

Exna-K *Micro, India.*
⊗Amiloride hydrochloride (p. 1299·1); furosemide (p. 1387·1).
Hypertension; oedema.

Exocin *Allergan, Denm.; Allergan, Fin.; Allergan, Gr.; Allergan, India; Allergan, Irl.; Allergan, Ital.; Allergan, Port.; Allergan, S.Afr.; Allergan, Spain; Allergan, Thai.; Abdi, Turk.; Allergan, UK.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Exocine *Allergan, Fr.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Exodalina *Sons, Mex.*
Metamizole magnesium (p. 53·3).
Fever; pain.

Exodep *Sun, India.*
Dosulepin.
Depression.

Exoderil *Sandoz, Austria; Sandoz, Cz.; Rentschler, Ger.†; Cooper (Kotep), Gr.; Sandoz, Hong Kong; Sandoz, Hung.; Sandoz, Indon.; Sandoz, Israel; Sandoz, Malaysia; Sandoz, Pol.; Sandoz, Rus.; Eczacibasi, Turk.; Sandoz, Turk.; Sandoz, Ukr.*
Naftifine hydrochloride (p. 590·1).
Fungal and bacterial skin and nail infections.

Exoderm *Marin, USA.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).

Exodolan *Sofex, Port.*
Etodolac (p. 57·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Exodren *Arkochim, Spain.*
Black currant (p. 2458·1); tea (p. 2648·2).
Fluid retention.

Exodus
Note: this name may be used for preparations of different composition.
Ache, Braz.
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; anxiety; social phobia.
Propharm, Gr.
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Exofat
Note: this name may be used for preparations of different composition.
Pharmpartners, Philipp.
Liphosan; oligofructose (p. 2508·1); calcium carbonate (p. 1824·3); magnesium stearate (p. 2195·3); ascorbic acid (p. 2110·3).
Obesity.

Exofil *Loeffler, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1).
Cough.

Exofur *Sons, Mex.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Exogan *Allergan, Philipp.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Exogran *Sandoz, Neth.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Exol *Khandelwal, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Exolit
Note: this name may be used for preparations of different composition.
Medochemie, Hong Kong†; Medochemie, Singapore.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.
Medopharm, India.
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Exolpen *Integrated Pharmaceutical, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Exolyt *Nevada, Swed.†*
Chlorcyclizine hydrochloride (p. 620·2); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Cough.

Exomax *Claris, Philipp.; Pharmaplan, S.Afr.*
Fluconazole (p. 578·2).
Fungal infections.

Exomega *Pierre Fabre Dermo-Cosmetique, Arg.; A-Derma, Fr.; Medifarm A-Derm, Venez.*
Avena (p. 2451·1); omega-6 fatty acids (p. 2575·2).
Skin disorders; atopic eczema.
Silesia, Chile.
Avena (p. 2451·1); omega-6 fatty acids (p. 2575·2); nicotinamide (p. 2083·1).
Atopic eczema.
Piramal, India.
Benzoic acid (p. 1738·2); chlorphenesin (p. 575·3); nicotinamide (p. 2083·1); phenoxyethanol (p. 1764·3).

Exomega Barrera *Silesia, Chile.*
Avena (p. 2451·1); silicones (p. 2209·2).
Barrier preparation.

Exomicol *Maver, Chile.*
Miconazole (p. 588·3); tinidazole (p. 949·2).
Vulvovaginal candidiasis.

Exomuc *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Bouchara, Rus.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Exopred *Allergan, India; Allergan, Philipp.; Allergan, Thai.*
⊗Ofloxacin (p. 334·3); prednisolone acetate (p. 1645·2).
Bacterial eye infections with inflammation.

Exoquin *Sons, Mex.*
Diiodohydroxyquinoline (p. 931·1).
Infectious diarrhoea; amoebiasis.

Exorex *Leda, Canad.; Castalia, Gr.; Ranbaxy, India; Forest, Irl.; Fagron, Neth.; Tosara, Spain; Forest Laboratories, UK.*
Coal tar (p. 1723·2).
Psoriasis.

Exorol *Offenbach, Mex.*
Ketorolac (p. 80·2).
Inflammation; pain.

Exortin *Sons, Mex.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Fever; pain; nasal congestion.

Exorum *Veropharm, Rus.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Exorvit *Sons, Mex.†*
Cyanocobalamin (p. 2107·2).
Anaemias; neuritis.

Exorvit VM *Sons, Mex.†*
Vitamins; minerals.

Exoseptoplix *Medipha, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Superficial wounds.

Exostrept *Biomedica, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Exosurf *GSK, Austral.†; Glaxo Wellcome, Gr.; GSK, Mex.†*
Colfosceril palmitate (p. 2599·2).
Neonatal respiratory distress syndrome.

Exoten-C *MedChem, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Exotoux *Bouchara-Recordati, Fr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Exotran *Beta, Arg.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Exovon *Bernofarm, Indon.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Exowin *Intra-Labs, India.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of coagulation during haemodialysis; unstable angina.

Exox *Triton, India.*
Thioctic acid (p. 2629·1); selenium (p. 2086·3); vitamin E (p. 2119·1).

Expafusin *Kalbe, Indon.*
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion.

Expahes *Eczacibasi-Baxter, Turk.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion.

Expal
Note: this name may be used for preparations of different composition.
Bago, Arg.
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; oedema; hepatic cirrhosis with ascites; nephrotic syndrome; hypertension.
Sons, Mex.†
Pipenzolate bromide (p. 1878·1).
Gastrointestinal disorders.

Expal Compuesto *Sons, Mex.*
Pipenzolate bromide (p. 1878·1); dimeticone (p. 1886·2).
Gastrointestinal disorders.

Expan *Claris, India.*
⊗An etherified starch (p. 1146·1) in sodium chloride.

Expanden *Andromaco, Chile.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); bornyl acetate (p. 2460·2); eucalyptus oil (p. 2501·2).
Nasal congestion.

Expandox *Expanpharm, Fr.†*
Paracetamol (p. 115·1).
Pain; fever.

Expanfen *Expanpharm, Fr.†*
Ibuprofen (p. 68·2).
Fever; pain.

Exparel *Pacira, USA.*
Liposomal bupivacaine (p. 1980·3).
Local anaesthesia.

Expec *Legrand, Braz.*
Oxomemazine hydrochloride (p. 637·1); potassium iodide (p. 2336·3); sodium benzoate (p. 1738·2); guaifenesin (p. 1666·2); ipecacuanha (p. 1667·2).
Respiratory-tract congestion.

Expecdilat *Sigma, Braz.*
Ambroxol acefyllinate (p. 1201·2).

Expecmin *Parggon, Mex.*
Oxolamine (p. 1671·2).
Cough.

Expectalin *Johnson & Johnson, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Expectalin with Codeine *Johnson & Johnson, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2).
Cough.

Expectamin *Legrand, Braz.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Expectamin F *Legrand, Braz.*
Dexchlorpheniramine maleate (p. 621·1).

Expect-D *Daffohils, India.*
Dextromethorphan hydrochloride; guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).

Expectein *Farmedia, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections.

Expectil *Bunker, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2).
Respiratory-tract congestion.

Expectocilin *EMS, Braz.*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Expectomel *Cazi, Braz.*
Rorippa nasturtium-aquaticum; aconite (p. 2428·3); ipecacuanha (p. 1667·2); senega (p. 1677·2); tolu balsam (p. 1679·2); honey (p. 2072·1); guaco.
Respiratory-tract congestion.

Expectorant *Trillium, Canad.*
Guaifenesin (p. 1666·2).
Cough.

Expectorant Cough Formula *Tanta, Canad.*
Guaifenesin (p. 1666·2).

Expectorant Cough Syrup
Note: this name may be used for preparations of different composition.
AAH, UK.
Guaifenesin (p. 1666·2).
Coughs.

Expectorant and Decongestant Cough Syrup *AAH, UK.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Expectorant DM Cough Syrup *Tanta, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Expectorant Syrup *Rougier, Canad.*
Guaifenesin (p. 1666·2).

Expectosan Caramelos *Excelentia, Arg.*
Gramicidin (p. 308·3); neomycin (p. 329·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Expectosan Extra Forte *Excelentia, Arg.*
Bromhexine (p. 1656·3).
Cough.

Expectosan Hierbas y Miel *Excelentia, Arg.*
Adult syrup: Grindelia (p. 2522·3); greater burnet saxifrage (p. 2463·1); cowslip (p. 2596·2); rosa gallica (p. 2207·3); thyme (p. 2630·2).
Cough.
Excelentia, Arg.
Paediatric syrup: Ivy (p. 2536·2); honey (p. 2072·1); vitamin C (p. 2110·3); sodium benzoate (p. 1738·2).
Cough.

Expectosan Novo Te Caliente *Excelentia, Arg.*
Ambroxol (p. 1654·3).

Expectovic *Airela, Braz.*
Guaifenesin (p. 1666·2).

Expectrat *Cazi, Braz.*
Mikania.

Expect-T *Daffohils, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Expectus *Indi, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Expectuss *EMS, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Expectysat N *Ysatfabrik, Ger.*
Primula root (p. 2596·2); thyme (p. 2630·2).
Cold symptoms.

Expectysat T *Ysatfabrik, Ger.*
Thyme (p. 2630·2).
Respiratory-tract disorders.

Expeflen *Diba, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Expel *Medichem, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Expelin *Eurodrug, Mex.*
Carbocisteine lysine (p. 1658·2).
Respiratory-tract disorders.

Expelinct *Adcock Ingram, S.Afr.*
Guaifenesin (p. 1666·2).
Cough.

Expent *Wockhardt, India.*
Pyrantel embonate (p. 165·3).
Worm infections.

Expergesic *Win-Medicare, India.*
⊗Paracetamol (p. 115·1); pentazocine hydrochloride (p. 120·3).
Pain.

Experience *Awareness, Canad.*
Senna (p. 1885·1).
Constipation.

Expetan *Unison, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess or viscous mucus.

Expicin *Sons, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Expigen *ACO Hud, Fin.; Adcock Ingram, S.Afr.*
Polysorbate 20 (p. 2203·2); ammonium chloride (p. 1656·1).
Cough.

Expigment *Abbott, Turk.*
Hydroquinone (p. 1705·1).
Hyperpigmentation disorders.

Expirobacter *Sofar, Ital.*
Carbon-13 labelled urea (p. 2470·3).
Test for gastroduodenal Helicobacter pylori *infection.*

Expit
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Ritsert, Ger.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Explaner *Casasco, Arg.*
Nimodipine (p. 1455·2).
Subarachnoid haemorrhage; cerebrovascular disorders; vestibular disorders.

Expodox *Ind-Swift, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Expodox-CV *Ind-Swift, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Expogin *LBS, Thai.*
Methylergometrine maleate (p. 2137·3).
Management of second and third stage of labour; postpartum haemorrhage; postpartum uterine atony.

Export Salonpas *Vianex (Βιανεξ), Gr.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); glycol salicylate (p. 66·2); thymol (p. 1772·2).

Exportale *Vilar, Rus.*
Lactitol (p. 1850·3).
Constipation; hepatic encephalopathy.

Expose *Wassermann, Ital.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm; spasticity.

Exprep *Mundipharma, Fin.†*
Senna (p. 1885·1).
Bowel evacuation.

Expril *Collins, Mex.†*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Expron *Lilly, Gr.*
Fenoprofen calcium (p. 59·2).
Pain; inflammation; musculoskeletal and joint disorders.

Expros *Astellas, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Exprosol *Stada, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Expulin *Shire, Irl.†*
⊗Pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; respiratory-tract congestion.

Expulin Childrens Cough *Shire, Irl.†*
Pholcodine (p. 1675·1); chlorphenamine maleate (p. 620·3).
Cough.

Expulin Dry Cough *Shire, Irl.†*
Pholcodine (p. 1675·1).
Cough.

Expuryl *Codifra, Fr.*
Cynara (p. 2490·3); taraxacum (p. 2625·3); black currant (p. 2458·1); turmeric (p. 2218·1); green tea (p. 2648·2); chromium (p. 2055·3).
Tonic.

Exputex *Shire, Irl.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excessive or viscous mucus.

Exratuss *Midlothian, USA.*
Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

exrheudon OPT *Optimed, Ger.*
Tablets: Phenylbutazone (p. 125·1).
Acute ankylosing spondylitis; rheumatism; gout.

Exsept *Alcavis, Canad.*
Sodium hypochlorite (p. 1768·3).
Disinfection.

Exsepta *Tentan, Switz.*
Acidum silicicum (p. 2208·3); arnica montana (p. 2447·2); carbo vegetalis (p. 1537·3); echinacea angustifolia (p. 2498·1); graphites (p. 2522·1); myristica sebifera; sulfuris iodidum (p. 2624·2).
Homoeopathic preparation.

Exsolut *Premier Research, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Exsora *NuLife, India.*
⊗Benzoic acid (p. 1738·2); ichthammol (p. 1705·3); salicylic acid (p. 1719·1); triamcinolone acetonide (p. 1649·1).

Extacef *Blue Cross, India.*
Cefixime (p. 240·3).
Bacterial infections.

Extacef-I *Blue Cross, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Extacef-LB *Blue Cross, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Extacef-P *Blue Cross, India.*
Oral drops: Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Blue Cross, India.
Syrup: Cefixime (p. 240·3).
Bacterial infections.

Extacef-Tazo *Blue Cross, India.*
Ceftriaxone sodium (p. 253·3); tazobactam sodium (p. 369·3).
Bacterial infections.

Extacef-XL *Blue Cross, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).

Extal *Talya, Turk.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Extavia *Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Spain; Novartis, Swed.; Novartis, UK; Novartis, USA.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Exten *Zynova, Philipp.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Extencilline *Sanofi-Aventis, Fr.; Sanofi-Aventis, Rus.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Extendryl *Auriga, USA.*
Phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1); chlorphenamine maleate (p. 620·3).
Respiratory congestion; allergic rhinitis; urticaria and angioedema.

Extendryl DM
Note: this name may be used for preparations of different composition.
Auriga, USA.
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Blooming Fields, Philipp.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Extendryl G *Auriga, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Extendryl GCP *Auriga, USA.*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Extendryl PEM *Auriga, USA.*
Hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Extensil *Bernabo, Arg.*
Dapoxetine hydrochloride (p. 2354·2).
Premature ejaculation.

Extenty *IQFA, Mex.*
Mebendazole (p. 158·3).
Worm infections.

External Anti-Pain Oil *Golden Pride, Canad.†; Rawleigh, Canad.†*
Clove oil (p. 2481·3); cajuput oil (p. 2464·1); expressed mustard oil (p. 2646·1); peppermint oil (p. 1877·1).

Exterol *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Extersin *Hexal, Ital.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Extimon *Interbat, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Extin N *Madaus, Ger.; Rottapharm, Ger.*
Ammonium chloride (p. 1656·1).
Urinary-tract infections.

Extina *Prestium, USA.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Extine *Sigma, Austral.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic distress disorder.

Extolen *Specifar (Σπεσιφαρ), Gr.*
Zipeprol hydrochloride (p. 1680·3); chlorphenamine maleate (p. 620·3).

Extosen *Sanitas, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough.

Extovon *Charoen, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Deltapharm, Hong Kong.†
Bromhexine (p. 1656·3).

Extovyl *Juvise, Fr.*
Betahistine mesilate (p. 2455·3).
Vertigo.

Extra *Tulip, Ukr.†*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Extra 11 *Le Naturiste, Canad.*
Vitamins; minerals.

Extra Action Cough *Rugby, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Extra Fast Coltalin Cold & Flu *Fortune, Hong Kong.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; allergic rhinitis.

Extra Once A Day *SunOpta, Canad.*
Vitamins; minerals; trace elements.

Extra Power Pain Reliever *AAH, UK.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Extra Rich Day Defense *Dermalogica, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Extra Stength Sleep Aid *Banner, Canad.; Pendopharm, Canad.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Extra Strength Alka-Seltzer Effervescent Tablets *Bayer, USA.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); aspirin (p. 22·2).
Hyperacidity.

Extra Strength Allergy Sinus *Pendopharm, Canad.; Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Extra Strength Analgesic *Confab, Canad.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Extra Strength Bayer Plus *Sterling Health, USA.*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3), magnesium carbonate (p. 1856·2), and magnesium oxide (p. 1857·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Extra Strength Cold Medication Daytime Relief *Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Extra Strength Cold Syrup *Supplements Aromatik, Canad.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Extra Strength Contac Cold & Sore Throat *Meda, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; sore throat.

Extra Strength Contac Complete Cough, Cold & Flu *Meda, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; coughs.

Extra Strength Daytime Cold Relief *Pendopharm, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold symptoms.

Extra Strength Daytime Cold Relief PE *Vita Health, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Extra Strength Daytime Flu PE *Vita Health, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms; cough.

Extra Strength DM Cough and Cold *Supplements Aromatik, Canad.; Tanta, Canad.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Extra Strength Doans PM *Novartis Consumer, USA.*
Magnesium salicylate (p. 85·2); diphenhydramine hydrochloride (p. 626·2).

Extra Strength Flu Relief Daytime *Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Influenza symptoms.

Extra Strength Flu Relief Nightime *Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Influenza symptoms.

Extra Strength Genaton *Goldline, USA.*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Hyperacidity.

Extra Strength Head Cold and Sinus *Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms.

Extra Strength Mintox Plus *Major, USA.*
Simeticone (p. 1886·2).

Extra Strength Multi-Symptom PMS Relief *Vita Health, Canad.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).

Extra Strength Muscle & Back Pain ASA *Vita Health, Canad.*
Aspirin (p. 22·2); methocarbamol (p. 2025·3).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Extra Strength Muscle & Back Pain Relief *Vita Health, Canad.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).
Pain.

Extra Strength Nighttime Cold Relief *Pendopharm, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Extra Strength Nighttime Cold Relief PE *Vita Health, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Extra Strength Nighttime Flu PE *Vita Health, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms; cough.

Extra Strength Pain Reliever PM *Magno-Humphries, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Insomnia.

Extra Strength Sinus Relief *Pendopharm, Canad.; Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Extra Strength Sinus Relief Nighttime *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Extra Strength Vicks Cough Drops *Procter & Gamble, USA.*
Menthol (p. 2553·2).

Extraa *Alkem, India.*
Range of preparations for enteral nutrition.

Extraboline *Genepharm, Gr.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic.

Extracaine *Ethica, Indon.†*
Lidocaine hydrochloride (p. 1988·2). Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Extrace *Ethica, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Extracta *Bago, Arg.†*
Darifenacin (p. 2354·2).

Extrafer
Note: this name may be used for preparations of different composition.
Saga, India.
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2).
SoSe, Ital.
Sodium ferric gluconate complex (p. 2089·1).
Anaemias.

Extra-Flu *Berlico Mulia, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Extrafoam *Pharmatrix, Arg.*
Skin cleanser.

Extraleci *Gezzi, Arg.*
Povidone-iodine (p. 1767·1).
Skin disinfection; wounds.

Extralife Arthri-Care *Felton, Austral.†*
Turmeric (p. 2218·1); ginger (p. 1844·1); feverfew (p. 676·1); devil's claw root (p. 42·3); lecithin (p. 2542·2).
Musculoskeletal and joint disorders.

Extralife Extra-Brite *Felton, Austral.†*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); lecithin (p. 2542·2).
Alzheimer's disease; mental function disorders.

Extralife Eye-Care *Felton, Austral.†*
Myrtillus (p. 2566·2); ginkgo biloba (p. 2512·3); big marigold; riboflavin (p. 2104·3); zinc gluconate (p. 2126·2).
Eye disorders.

Extralife Flow-Care *Felton, Austral.†*
Saw palmetto (p. 2363·3); urtica (p. 2639·3); pyridoxine hydrochloride (p. 2105·3); zinc gluconate (p. 2126·2).
Benign prostatic hyperplasia; micturition disorders in men.

Extralife Fluid-Care *Felton, Austral.†*
Taraxacum (p. 2625·3); equisetum (p. 2500·1); parsley (p. 2583·3); bearberry (p. 2453·2); solidago (p. 2620·1); pyridoxine hydrochloride (p. 2105·3).
Fluid retention.

Extralife Leg-Care *Felton, Austral.†*
Aesculus (p. 2431·2); butcher's broom (p. 2463·1); centella (p. 1698·3); ginkgo biloba (p. 2512·3); myrtillus (p. 2566·2); hesperidin (p. 2505·2); rutoside (p. 2505·3); ascorbic acid (p. 2110·3).
Varicose veins.

Extralife Liva-Care *Felton, Austral.†*
Milk thistle (p. 1561·1); greater celandine (p. 2522·2); cynara (p. 2490·3); turmeric (p. 2218·1); astragalus; taraxacum (p. 2625·3); lecithin (p. 2542·2).
Acne; gastrointestinal disorders; halitosis; hypersensitivity disorders; hyperlipidaemias; hypoglycaemia; menopausal disorders; migraine; obesity; premenstrual syndrome.

Extralife Meno-Care *Felton, Austral.†*
⊗Soya bean (p. 2092·3); cimicifuga (p. 2478·1); agnus castus (p. 2432·2); dong quai (p. 2497·1); calcium phosphate (p. 1784·2).
Menopausal disorders; osteoporosis.

Extralife Migrai-Care *Felton, Austral.†*
Feverfew (p. 676·1); salix (p. 129·2); magnesium phosphate (p. 1787·3).
Migraine and other headaches.

Extralife PMS-Care *Felton, Austral.†*
⊗Salix (p. 129·2); chaste tree (p. 2432·2); cimicifuga (p. 2478·1); viburnum opulus; bearberry (p. 2453·2); pyridoxine hydrochloride (p. 2105·3); ferrous fumarate (p. 2060·3).
Premenstrual syndrome.

Extralife Sleep-Care *Felton, Austral.†*
Valerian (p. 2640·2); passion flower (p. 2584·1); gentian (p. 2512·1); lupulus (p. 2546·1); magnesium phosphate (p. 1787·3); calcium phosphate (p. 1784·2).
Nervous disorders; sleep disorders.

Extralife Uri-Care *Felton, Austral.†*
Cranberry (p. 2488·1); bearberry (p. 2453·2); buchu (p. 2461·3); pyridoxine hydrochloride (p. 2105·3); ascorbic acid (p. 2110·3); potassium sulfate (p. 1793·2).
Cystitis.

Extrammune *Charak, India.*
Syrup: Cyperus rotundus; liquorice (p. 1853·2); ocimum sanctum; piper longum; tinospora cordifolia.
Charak, India.
Tablets: Curcuma longa.

Extranac *Symbiosis, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Extranase *Rottapharm, Fr.*
⊗Bromelains (p. 2460·3).
Post-traumatic and postoperative oedema.

Extraneal *Baxter, Arg.; Baxter, Austral.; Baxter, Hong Kong; Baxter, Israel; Baxter, Rus.; Adcock Ingram Critical Care, S.Afr.†; Baxter, Singapore; Baxter, USA.*
Icodextrin (p. 2059·2); electrolytes (p. 1775·1) (p. 1778·2).
Peritoneal dialysis.

Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Hung.; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Philipp.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.
Icodextrin (p. 2059·2); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
Peritoneal dialysis.

Extrapan *Qualiphar, Belg.*
Ibuprofen (p. 68·2).
Peri-articular and soft-tissue disorders.

Extrapen *Remek, Gr.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Extraplus *Pierre Fabre, Spain.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint disorders, peri-articular, and soft-tissue disorders.

Extrastatin *SJA, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Extratherm *Phytopharm, Ukr.*
Thermopsis; sodium benzoate (p. 1738·2); sodium bicarbonate (p. 1781·1); ammonium chloride (p. 1656·1).
Cough.

Extrato Hepático Composto *Delta, Braz.*
Methionine (p. 1558·2); choline citrate (p. 2055·2); liver extract (p. 2444·1).
Liver disorders.

Extra-Virt Plus DHA *Virtus, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1). Docusate calcium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Extraza *Veropharm, Rus.*
⊗Letrozole (p. 817·1).
Breast cancer.

Extrazyme *Symbiosis, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Extreme Protection *Floxia, Singapore.*
SPF 70: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Extreme Sun *Darier, Mex.*
SPF 85: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Extropect *Guardian, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Extroplex *Profarma, Ital.*
⊗Anastrozole (p. 742·1).

Extruss *Euro-Med, Philipp.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Extur *Normon, Spain.*
⊗Indapamide (p. 1409·2).
Hypertension.

Extuss *Cypress, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Exubera *Pfizer, Braz.†; Pfizer, Cz.†; Pfizer, Gr.; Pfizer, Neth.†*
⊗Insulin (human) for inhalation (p. 475·3).
Diabetes mellitus.

Exudrol *Lafedar, Arg.*
⊗Dexamethasone (p. 1630·3); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2).
Formerly known as Exudrol con Dexametasona.
Respiratory-tract disorders.

Exudrol-Bude *Lafedar, Arg.*
⊗Budesonide (p. 1625·1).

Exulten *Medichem, Philipp.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Exuracid *Rosch & Handel, Austria.*
Tisopurine (p. 609·1).
Hyperuricaemia; gout; urinary calculi.

Exvile *Tripharma, Turk.*
Naproxen sodium (p. 98·2).

Exxiv *Bial, Port.; Abello, Spain.*
Etoricoxib (p. 57·3).
Gout; osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; pain.

Exxon *Zee, India.*
⊗Chlorphenamine maleate (p. 620·3); methylcellulose (p. 2197·3); naphazoline (p. 1669·3).

Eyclor *Ultramark, India.*
Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3).

Eyclor-Dexa *Ultramark, India.*
⊗Chloramphenicol (p. 257·1); dexamethasone (p. 1630·3); polymyxin B sulfate (p. 342·3).

Eye Dew *Crookes Healthcare, UK.*
⊗Hamamelis (p. 2523·3); naphazoline hydrochloride (p. 1669·3).
Formerly known as Optrex Eye Dew.
Eye irritation.

Eye Drops *Zee, Canad.; Reese, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Eye Glo Moist *CCM, Hong Kong; CCM, Malaysia.*
Hypromellose (p. 2189·2).
Dry eyes.

Eye Glo Plus *CCM, Hong Kong.*
Borax (p. 2459·2); boric acid (p. 2459·3); hamamelis (p. 2523·3).
Eye irritation.

Eye Glo Regular *CCM, Hong Kong.*
Borax (p. 2459·2); boric acid (p. 2459·3).
Eye irritation.

Eye Glo Relief *CCM, Hong Kong.*
Zinc sulfate (p. 2126·2).
Eye irritation.

Eye Health Herbal Plus Formula 4 *Vitelle, Austral.†*
Euphrasia (p. 2502·1); ginkgo biloba (p. 2512·3); betacarotene (p. 2051·1); *d*-alpha tocoferil acid succinate (p. 2119·2); ascorbic acid (p. 2110·3); rutoside (p. 2505·3); hesperidin (p. 2505·2).
Eye strain.

Eye Mo
Note: this name may be used for preparations of different composition.
GSK, Singapore; GSK, Thai.
Boric acid (p. 2459·3); borax (p. 2459·2).
Eye irritation.

Eye Mo Moist *GSK, Hong Kong†; GSK, Singapore.*
Hypromellose (p. 2189·2).
Dry eyes.

Eye Q *Equazen, Hong Kong.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); gamolenic acid (p. 2509·2); vitamin E (p. 2119·1).
Dietary supplement.

Eye Q Equazen *Vifor, Singapore.†*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); gamolenic acid (p. 2509·2); vitamin E (p. 2119·1).
Dietary supplement.

Eye Relief *Vitamed, Israel.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Eye Scrub *Novartis Ophthalmics, USA.†*
Eyelid cleanser.

Eye Vites *Natural Life, Arg.*
Vitamins; minerals; amino acids.

Eye Wash *Niagara, Canad.*
Boric acid (p. 2459·3).
Removal of foreign bodies from the eye.
Bausch & Lomb, Hong Kong.
Boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irrigation.
Zee, Canad.†
Electrolytes (p. 1775·1).
Eye irrigation.

Eyebrex *Allergan, China; Allergan, Gr.; Allergan, India; Allergan, Mex.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Eyebrex-Dexa *Alvia (Αλβια), Gr.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Eye infections.

Eyebright *Simex, Indon.*
Myrtillus (p. 2566·2); vitamin A (p. 2098·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Eyeclean *Genepharm, Gr.*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).

Eyeclof *Genepharm, Gr.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Eyecon *Excelvision, Israel.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Eyecort *Genepharm, Gr.*
⊗Hydrocortisone acetate (p. 1640·1); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Eye-Cure Ph-C *Pharmall, Gr.†*
Kanamycin (p. 314·3).
Eye infections.

Eyedec *Johnson & Johnson, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Eyedex *Siam Bheasach, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Eyedin *Cadila, India.*
Povidone-iodine (p. 1767·1).

Eyedrip *Solitaire, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).

Eyefen *Solitaire, India.*
Flurbiprofen (p. 65·2).
Prevention of miosis during eye surgery; inflammation following eye surgery.

Eyefil *Fourrts, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Eyeflur *Biospray, Gr.*
Flurbiprofen sodium (p. 65·3).

Eye-Gene *LF, Thai.*
Phenylephrine hydrochloride (p. 1672·3); boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irritation.

Eye-Gene Soft *LF, Thai.*
Boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irritation.

Eyegold *Darya-Varia, Indon.†*
Mixed carotenoids (p. 2176·2).
Antoxidant to reduce cataracts and age-related macular degeneration risk.

Eyelube *Sandoz, Canad.*
Hypromellose (p. 2189·2).
Dry eyes.

Eye-Lube-A *Optopics, USA.*
⊗Glycerol (p. 2517·2).
Dry eyes.

EyeMax *Sunpab, Singapore.*
Euphrasia officinalis (p. 2502·1); myrtillus (p. 2566·2); tagetes erecta; calcium ascorbate (p. 2111·1); cupric oxide; *d*-alpha tocoferil acetate (p. 2119·1); zinc oxide (p. 1729·1); fish oil (p. 1460·1).
Eye disorders.

Eyemist *Sun, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Eye-Mo
Note: this name may be used for preparations of different composition.
GSK, Mex.; GSK, Philipp.
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Eyeprost *Douglas, NZ.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Eye-Quin *Cadila, India.*
Moxifloxacin (p. 326·3).
Bacterial conjunctivitis.

Eye-Ruby L *Eng An, Hong Kong.†*
Chlorphenamine (p. 620·3); muramidase (p. 2565·1).

Eye-Ruby Violet *Eng An, Hong Kong.†*
Azulene (p. 2452·1); chlorphenamine (p. 620·3).

Eyesalt *Cooper (Kοπερ), Gr.*
Sodium chloride (p. 1795·1); sodium acetate (p. 1781·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium citrate (p. 1781·2).
Cataract surgery.

Eyestil *SIFI, Mex.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Eye-Stream *Alcon, Austral.; Alcon, Canad.; Alcon, NZ†; Alcon, Singapore†; Alcon, USA.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Eyetobrin *Cooper (Kοπερ), Gr.*
Tobramycin (p. 380·1).
Eye infections.

Eye-Visol *Bilim, Turk.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

EyeVit *HealthAid, UK.*
Vitamins; minerals; amino acids.

Eyevit
Note: this name may be used for preparations of different composition.
Lapi, Indon.
Myrtillus (p. 2566·2); vitamin A (p. 2098·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); selenium (p. 2086·3); zinc (p. 2126·1).
Nutritional supplement for the eyes.

Eyevital *Sunways, India.*
Vitamin A acetate (p. 2098·3); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc (p. 2126·1).

Eyevite *Allergan, Austral.†*
Vitamins; minerals.
Eye disorders.

Eyewash *Sabex, Canad.†*
Electrolyte solution (p. 1775·1).
Eye irrigation.

Eyezep *iNova, Austral.; Douglas, NZ.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Eye-Zine *Ocumed, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Eykosacol *Knop, Chile.*
Fish oil (p. 1460·3).
Hyperlipidaemias; hypertension.

Eylasol *Ratiopharm, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Eylea *Bayer, Fr.; Bayer, Jpn; Bayer, Switz.; Bayer, UK; Regeneron, USA.*
Aflibercept (p. 736·2).
Neovascular (wet) age-related macular degeneration; macular oedema; macular oedema following retinal vein occlusion.

Eyrasil *Diba, Mex.*
⊗Naphazoline (p. 1669·3); pheniramine (p. 637·2).
Eye disorders.

Eysol *Sun, India.*
Hypromellose (p. 2189·2).
Dry eyes.

EZ Char *Paddock, USA.*
Activated charcoal (p. 1537·3).
Poisoning.

EZ Detect *Biomerica, USA.*
Test for occult blood in faeces or urine.

Step, Arg.
Test for occult blood in faeces.

EZ Smart *Exxe, Ital.*
Test for glucose in blood (p. 2516·3).

Eza MPS *Pure Health, India.*
Cisapride (p. 1831·3); simeticone (p. 1886·2).

Ezact
Note: this name may be used for preparations of different composition.
Sun, India.
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Ezaller *Umedica, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Ezaprev *Pharmathen, Port.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

RKG, Ital.
Pramipexole (p. 911·2).

E-Z-Cat *Temis, Arg.; Bracco, Cz.; E-Z-EM, Hung.; E-Z-EM, Israel; Bracco, Neth.; Bracco, Port.; Opakim, Turk.; E-Z-EM, UK.*
Barium sulfate (p. 1583·2).
Contrast medium for computerised axial tomography of the gastrointestinal tract.

Ezcef *EON, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Eze *Gap, Gr.*
⊗Serrapeptase (p. 2613·3).
Inflammatory disorders.

Saga, India.
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Ezede *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders; urticaria.

Ezedoc *Lupin, India.*
Ezetimibe (p. 1379·2).
Sitosterolaemia; hyperlipidaemias.

Ezee *Hovid, Malaysia.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Dyspepsia.

Ezeepara *Piramal, India.*
Paracetamol (p. 115·1).
Pain; fever.

Ezemax-A *Biomax, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Ezentia *Sun, India.*
Ezetimibe (p. 1379·2).
Sitosterolaemia; hyperlipidaemias.

Ezeree ICC *Hoe, Singapore.*
Emollient.
Dry skin.

Ezerem *MSN, India.*
Ezetimibe (p. 1379·2).
Sitosterolaemia; hyperlipidaemias.

Ezerra *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore.*
Emollient.
Eczema; dry skin.

EzeShield *Hoe, Malaysia.*
Emollient.
Dry skin; skin irritation; barrier preparation.

Ezeshield *Hoe, Hong Kong.*
Emollient.
Barrier preparation; dry skin.

Hoe, Singapore.
Emollient; barrier preparation.
Barrier preparation; skin irritation.

Ezetib *Unichem, India.†*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Ezetrol *MSD, Arg.; MSD, Austral.; Aesca, Austria; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; Schering, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; Mediwin, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; Schering-Plough, Indon.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; Schering-Plough, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; Schering-Plough, Philipp.; MSD, Pol.; MSD, Port.; Schering-Plough, Rus.; MSD, S.Afr.; MSD, Singapore; Schering-Plough, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; MSD, Venez.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia; atherosclerosis; hyperlipidaemias.

Ezevas *Micro, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

EZFE *McNeil, USA.*
Iron (p. 2073·1).
Iron supplement.

E-Z-Gas *IFET (ΙΦΕΤ), Gr.; E-Z-EM, Hung.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Production of CO_2 in double contrast radiography of the gastrointestinal tract.

E-Z-Gas II *E-Z-EM, Israel; Bracco, Switz.; E-Z-EM, USA.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); simeticone (p. 1886·2).
Production of CO_2 in double contrast radiography of the gastrointestinal tract.

EZ-Grow *Tolmann, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3); taurine (p. 2626·2); chlorella extract (p. 2475·3).
Vitamin supplement.

Ez-HBT *Metabolic Solutions, USA.*
Carbon-13 (p. 2470·3) labelled urea (Helicosol); test meal (Ensure).
Diagnosis of Helicobacter pylori *infection.*

E-Z-HD *Bracco, Cz.; E-Z-EM, Hung.; E-Z-EM, Israel; Bracco, Neth.; E-Z-EM, Port.; Opakim, Turk.; E-Z-EM, UK; E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Ezibloc *Cadila, India.*
Ezetimibe (p. 1379·2).
Sitosterolaemia; hyperlipidaemias.

Ezida *KRKA, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Eziluk *Elisa, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

E-Zinc *United Laboratories, Philipp.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Ezipol *Kleva, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Ezith *Evershine, India.*
Azithromycin (p. 221·2).
Bacterial infections.

EziTravel *Planet Health, Austral.†*
Ginger (p. 1844·1).
Motion sickness.

Ezixin *Parapharm, Gr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).

Ezlax *Nouveau, India.*
Macrogol 400 (p. 2547·3).

Ezocem *Labormed, Cz.; Labormed, Hung.; Labormed, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Ezol *Moraceae, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

E-Zole *Zota, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

E-Zole-D *Zota, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ezolong *Synmedic, Ukr.*
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Ezoma *Sun, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Ezon-T *Unison, Hong Kong; Unison, Thai.*
Tolnaftate (p. 596·1); triacetin (p. 596·2).
Athlete's foot; ringworm; fungal skin infections.

Unison, Thai.
Ointment: Tolnaftate (p. 596·1).
Fungal skin infections.

Ezopen *Teuto, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ezopta *Biomedica, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Ezor *Lainco, Spain.*
Sodium picosulfate (p. 1887·2).
Constipation.

Ezoran *Ranbaxy, Ital.*
Esomeprazole (p. 1841·1).

Ezorb *Overseas, India.*
Calcium aspartate (p. 1783·1).

Ezorb Forte *Overseas, India.*
Vitamins; minerals.

Ezoret *KRKA, Denm.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ezosina *Solvay, Ital.*
Terazosin hydrochloride (p. 1511·1).
Hypertension.

Ezovir *Alphapharm, Austral.*
Famciclovir (p. 979·1).
Herpesvirus infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

E-Z-Paque *Bracco, Belg.; E-Z-EM, Israel; E-Z-EM, UK; E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

E-Z-Paste *E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Ezta *Zydus, India.*
Ezetimibe (p. 1379·2).
Sitosterolaemia; hyperlipidaemias.

Eztom *Medicamenta, Cz.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Ezulen *Biosintetica, Braz.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Ezumycin *Rafarm, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Ezygard *Promed, Indon.*
Echinacea (p. 2498·1); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1).
Immunostimulant.

E-Zyme *Advance, Malaysia.*
Muramidase hydrochloride (p. 2565·1).
Inflammation; respiratory-tract disorders associated with viscous mucus; minor haemorrhage.

EZZ-C *Medhaus, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Ezzicad *Glenmark, India.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia.

1 + 1-F *Dunhall, USA.*
⊗Hydrocortisone (p. 1640·1); clioquinol (p. 273·1); pramocaine (p. 1993·3).
Skin disorders.

F-5 *P & B, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

F Plus *Triton, India.*
Trifluoperazine (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).

FA *Radicura, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Fa Ai Si *Minhai, China.*
Mitiglinide calcium (p. 492·1).

Fa Duo Lin *Open, China.*
Pazufloxacin mesilate (p. 338·1).

Fa Luo *Topfond, China.*
Spiramycin (p. 358·3).
Protozoal infections.

Fa Si Te *Sunstone, China.*
Benproperine phosphate (p. 1656·2).
Cough.

Faa *Gentech, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Faa Plus *Gentech, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

FAB *Care, Austral.*
Iron amino acid chelate (p. 2048·3); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Tonic.

Fab-12 *RND, India.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).

FAB Co *Medical Research, Austral.†*
Iron (p. 2073·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

FAB Tri-Cal *Medical Research, Austral.†*
Calcium hydrogen phosphate (p. 1783·3); calcium carbonate (p. 1824·3); calcium gluconate (p. 1783·3); zinc oxide (p. 1729·1); magnesium oxide (p. 1857·3); colecalciferol (p. 2113·1).
Nutritional supplement.

Fabahistin *Bayer, S.Afr.†*
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Fabamox *Fabop, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

Fabamox Duo *Fabop, Arg.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Fabelium *Pharmahof, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vertigo; vestibular disorders.

Faberdin *Bernofarm, Indon.†*
Famotidine (p. 1842·1).
Peptic ulcer; pathological hypersecretory disorders.

Fabior *Stiefel, USA.*
Tazarotene (p. 1724·2).
Acne.

Fabitec *Tecnofarma, Mex.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Fabizol *Unichem, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fablex *GPC, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Faboacid *Fabop, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Faboacid Plus *Fabop, Arg.*
Omeprazole (p. 1867·2).

Faboacid R *Fabop, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fabocef *Fabop, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Fabodrox *Fabop, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Faboflem *Fabop, Arg.†*
Diclofenac (p. 48·3).

Fabofurox *Fabop, Arg.*
⊗Furosemide (p. 1387·1).

Fabogesic *Fabop, Arg.*
Ibuprofen (p. 68·2).
Inflammation; pain; fever.

Fabolergic *Fabop, Arg.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Fabomicina *Fabop, Arg.†*
Vancomycin (p. 384·2).
Bacterial infections.

Fabopcilina *Fabop, Arg.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Fabopxicam *Fabop, Arg.†*
Piroxicam (p. 125·3).
Fever; inflammation; pain.

Fabosic *Fabop, Arg.*
Losartan (p. 1422·2).

Fabotenol *Fabop, Arg.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Fabotensil *Fabop, Arg.*
Enalapril (p. 1371·1).
Hypertension.

Fabotensil D *Fabop, Arg.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fabotop *Fabop, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Fabotranil *Fabop, Arg.†*
Diazepam (p. 1063·2).
Anxiety; sedative; skeletal muscle spasm; epilepsy.

Faboxetina *Fabop, Arg.*
Fluoxetine (p. 417·1).
Depression.

Faboxim *Fabop, Arg.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Fabozepam *Fabop, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Fabozolina *Fabop, Arg.*
⊗Naphazoline (p. 1669·3).
Nasal congestion.

Fabracin *Fabra, Arg.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders.

Fabralgina *Fabra, Arg.*
Naproxen (p. 98·2).
Inflammation; pain.

Fabramicina *Fabra, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Fabrapride *Fabra, Arg.†*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Fabrazol *Fabra, Arg.*
Omeprazole (p. 1867·2).

Fabrazyme *Genzyme, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Braz.; Genzyme, Canad.; Genzyme, Chile; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Hung.; Genzyme, Irl.; Genzyme, Israel; Genzyme, Ital.; Genzyme, Jpn; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Norw.; Healthcare Logistics, NZ; Genzyme, Pol.; Genzyme, Port.; Genzyme, Rus.; Genzyme, Spain; Genzyme, Swed.; Sanofi-Aventis, Switz.; Genzyme, Turk.; Genzyme, UK; Genzyme, USA.*
Agalsidase beta (p. 2437·2).
Fabry disease.

Fabroven *Pierre Fabre, Mex.; Pierre Fabre, Spain.*
Ascorbic acid (p. 2110·3); hesperidin methyl chalcone (p. 2505·2); butcher's broom (p. 2463·1).
Peripheral vascular disorders; metrorrhagia; haemorrhoids.

Pierre Fabre, Spain.†
Cream: Melilot (p. 2552·3); butcher's broom (p. 2463·1).
Peripheral vascular disorders.

Fabu Laishi *RAAS, China.*
Fibrinogen (p. 1151·3).
Fibrinogen deficiency.

Fabudol *Volta, Chile.*
Piroxicam (p. 125·3).

Fabulae *VHB, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Fabulaxol *Andromaco, Chile.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

Fabutin *Pharmacos Abug, Mex.†*
Famotidine (p. 1842·1).
Gastric hyperacidity; peptic ulcer.

Fa-c *Pharmahof, Thai.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Face CoTZ *Fallene, USA.*
Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Face Magic *Covermark, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Face Multi-Protection *Biotherm, Canad.*
SPF 50: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Biotherm, Canad.
SPF 15; SPF 30: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Faceclin *Psychotropics, India.*
Clindamycin phosphate (p. 269·3); nicotinamide (p. 2083·1).

Faceclin-A *Piramal, India.*
Adapalene (p. 1692·1); clindamycin phosphate (p. 269·3).
Acne.

Facelit *Collins, Mex.†*
Cefalexin hydrochloride (p. 234·1).
Bacterial infections.

Facer *Emcure, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2); vitamin C (p. 2110·3).

Faces Antiseptic *Ligi, Canad.†*
Isopropyl alcohol (p. 1758·3); thymol (p. 1772·2).
Antiseptic for pierced ears.

Faces Face Colour *Faces, Canad.†*
Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Faces Only *Schering-Plough, USA.*
SPF 6; SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Facetam *Pascual, Philipp.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Facetin-D *Ifusa, Mex.*
Diiodohydroxyquinoline (p. 931·1); phthalylsulfacetamide (p. 339·2); homatropine (p. 2007·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Amoebiasis.

Facetol *Nafar, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Facicam *Senosiain, Mex.*
Piroxicam (p. 125·3).
Dysmenorrhoea; musculoskeletal, joint, peri-articular and soft-tissue disorders; gout.

Facicap *Kamron, India.*
Capsules: Lysine (p. 2079·3); copper sulfate (p. 2057·2); ferrous fumarate (p. 2060·3); magnesium sulfate (p. 1787·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Kamron, India.
Oral liquid: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Facid *Intas, India; Kalbe, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; duodenal ulcer; pathological hypersecretory disorders.

Facidase *Sun, India.*
Hyaluronidase (p. 2527·2).
Hypodermoclysis; enhanced absorption of intramuscular and subcutaneous injections; reduction of extravasation.

Facidex Total *Liomont, Mex.*
Famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Facidin *Yik Kwan, Hong Kong.†*
Famotidine (p. 1842·1).

Facidmol *Liomont, Mex.*
Bismuth salicylate (p. 1821·3).
Gastric hyperacidity; diarrhoea.

Facilgest *Raffo, Arg.*
⊗Metoclopramide hydrochloride (p. 1862·2); pancreatin (p. 2579·3); simeticone (p. 1886·2).
Gastrointestinal motility disorders; digestive disorders; flatulence.

Facimin *Mintlab, Chile.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Facitab *Karnataka, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Facital *Zydus, India.*
Mefloquine (p. 657·1).
Malaria.

Facitor *Mintlab, Chile.*
Aspirin (p. 22·2); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Facocinerin
Note: this name may be used for preparations of different composition.
Zekides, Gr.
⊗Fluorometholone (p. 1637·2).

Facogen *NBF, Ital.*
Lipid; protein; carbohydrate; vitamins; trace elements.
Nutritional supplement.

Facomed *Eupharmed, Ital.*
Cucumis melo; bioflavonoids (p. 2505·2); mirtillo nero; vitamins.
Dietary supplement.

Facort *Biolab, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Facosmina *Amnol, Ital.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2); melilot (p. 2552·3); vitamins.
Circulatory disorders.

Facovit *Teofarma, Ital.*
⊗Testosterone propionate (p. 2305·2); rubidium iodide (p. 2608·2); potassium iodide (p. 2336·3); riboflavin (p. 2104·3).
Cataract; vitreous turbidity.

Fact Plus *Swiss Precision, Canad.†; Advanced Care, USA.*
Pregnancy test (p. 2596·1).

Factane *CAF-DCF, Belg.; LFB, Fr.; LFB, Port.; Er-Kim, Turk.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Faction *Maigal, Arg.*
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Factioneye *Maigal, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Factiv *Veropharm, Rus.*
Gemifloxacin mesilate (p. 304·1).
Bacterial infections of the respiratory tract.

Factive *Ache, Braz.; Oscient, Canad.†; LG, China; Aspen, S.Afr.; Abdi, Turk.; Oscient, USA.*
Gemifloxacin mesilate (p. 304·1).
Bacterial infections.

Factive-5 *Pfizer, Mex.*
Gemifloxacin mesilate (p. 304·1).
Bacterial infections.

Factodin *Faran, Gr.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Factofer *Raymos, Arg.*
Ferrous sulfate (p. 2062·2).
Anaemias.

Factofer B12 *Raymos, Arg.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); ferrous sulfate (p. 2062·2).
Anaemias.

Factopan *Liade, Spain.†*
Ibuprofen (p. 68·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; fever.

Factor AE *Casasco, Arg.*
Vitamin A palmitate (p. 2098·3); vitamin E acetate (p. 2119·2) allantoin (p. 1693·1).
Emollient; barrier preparation.

Factor AF2 *Biosyn, Ger.; Loges, Ger.*
Liver (p. 2444·1) and spleen (p. 2444·1) extract.
Supportive tumour therapy.

Factor AG *Casasco, Arg.*
Simeticone (p. 1886·2).
Gastrointestinal disorders with excess gas; preparation for gastrointestinal procedures.

Factor AG Antiacido *Casasco, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux.

Factor AG Antiespasmodico *Casasco, Arg.*
Simeticone (p. 1886·2); homatropine methylbromide (p. 2007·3).
Gastrointestinal spasm.

Factor Antigripal *Inmunolab, Arg.*
⊗Pseudoephedrine (p. 1676·1); paracetamol (p. 115·1); chlorphenamine (p. 620·3); bromhexine (p. 1656·3).
Influenza symptoms.

Factor Bioenterico *Inmunolab, Arg.†*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Enterococcus faecium* (p. 2596·3); simeticone (p. 1886·2).
Restoration of gastrointestinal flora.

Factor Dermico *Casasco, Arg.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Factor Laxante *Inmunolab, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Factorine *Casasco, Arg.*
Metoclopramide (p. 1862·2); simeticone (p. 1886·2).
Delayed gastric emptying; nausea and vomiting.

Factrel *Wyeth-Ayerst, USA.†*
⊗Gonadorelin hydrochloride (p. 2280·3).
Diagnostic evaluation of anterior pituitary function.

Factus *Roux-Ocefa, Arg.*
Oral drops; oral solution: ⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold and influenza symptoms.
Roux-Ocefa, Arg.
Tablets: ⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); dexbrompheniramine maleate (p. 618·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Facyl *Medley, Braz.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Facyl M *Medley, Braz.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

FAD
Note: this name may be used for preparations of different composition.
Varun, India.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Fad
Note: this name may be used for preparations of different composition.
T Man, Thai.
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

FAD Ophthalmic Soln *Santen, Hong Kong.*
Flavine adenine dinucleotide sodium (p. 2104·3).
Blepharitis; keratitis.

Fada-B *Seven Stars, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Fadacaina *Fada, Arg.*
Procaine (p. 1994·3).
Local anaesthesia.

Fadae *Pharmahof, Thai.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fadafilina *Fada, Arg.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Fadaflumaz *Fada, Arg.*
Flumazenil (p. 1551·3).

Fadagrip *Fada, Arg.*
Paracetamol (p. 115·1); dipyrone (p. 53·3); diphenhydramine hydrochloride (p. 626·2).
Allergic respiratory-tract disorders.

Fadalefrina *Fada, Arg.*
Phenylephrine (p. 1672·2).

Fadalex *Fada, Arg.*
Diphenhydramine (p. 626·1).

Fadalivio *Fada, Arg.*
Naproxen (p. 98·2).
Fever; pain.

Fadametasona *Fada, Arg.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Fadamicina *Fada, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Fadamine *Fada, Arg.*
⊗Metaraminol (p. 1430·1).

Fadanasal *Fada, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); nitrofurazone (p. 333·1); mepyramine maleate (p. 635·1).
Nasal congestion.

Fadastigmina *Fada, Arg.*
Neostigmine (p. 687·1).

Fadatos *Fada, Arg.*
⊗Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); ephedrine hydrochloride (p. 1663·2).
Cold and influenza symptoms; rhinitis.

Fadatos NF *Fada, Arg.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Fadep *Winsome, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fadi *Chia Tai, China.*
Mitiglinide calcium (p. 492·1).

Fadiamone *Sinclair, Fr.*
Soya (p. 2092·3); centella (p. 1698·3).
Skin ageing.

Fadig *Arrow, Braz.†*
Amino acids; vitamin B substances (p. 2102·3).

Fadine *Biolab, Hong Kong†; Aristo, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Fadol *Teva, Mex.†*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Fadril *Pharmahof, Thai.†*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2).
Pruritus.

Fadul *Hexal, Ger.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Fafed *Pharmahof, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Fafen *Pharmahof, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Fafex *Pharmahof, Thai.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Fagastril *Quimifar, Spain†; Kocak, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fageron *Pharmahof, Thai.†*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders; Ménière's disease.

Fagesic *Pharmahof, Thai.†*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Painful skeletal muscle spasm.

Fagizol *Continentales, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; worm infections.

Fagodol *Arafarma, Spain.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Fagofen *Grisi, Mex.†*
Naproxen (p. 98·2).

Fagolip Plus *Cetus, Arg.*
⊗Mazindol (p. 2324·1).
Obesity.

Fagolipo *Libbs, Braz.*
⊗Mazindol (p. 2324·1).
Obesity.

Fagorutin Buchweizen *GSK Consumer, Ger.†*
Tablets: Buckwheat (p. 2462·1); troxerutin (p. 2505·3).
Venous insufficiency.
GSK Consumer, Ger.†
Tea: Buckwheat (p. 2462·1).
Venous insufficiency.

Fagorutin Rosskastanien-Balsam N *GSK Consumer, Ger.†*
Aesculus (p. 2431·2); rutoside sodium sulfate (p. 2505·2); menthol (p. 2553·2).
Venous insufficiency.

Fagorutin Ruscus *GSK Consumer, Ger.†*
Butcher's broom (p. 2463·1).
Chronic venous insufficiency; haemorrhoids.

Fagratyl *Faran, Gr.*
Fenofibrate (p. 1381·1).

Fagus *Allen, Spain.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fagusan *Infectopharm, Ger.*
Guaifenesin (p. 1666·2).
Cough and related respiratory-tract disorders.

Fahifem *Farmaceutica H, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Faifloc *TS, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Fain *Elder, India.*
Sodium hyaluronate (p. 2526·2).
Skin ulcers; wounds.

Fairgenol *FDC, India.*
Dichloroxylenol (p. 1750·2); terpineol (p. 2627·2).
Skin disinfection.

Fairgenol-H *FDC, India.*
Benzalkonium chloride (p. 1737·1); disodium edetate (p. 1550·3).

Fairy ADE *YSP, Malaysia; Yung Shin, Singapore.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Dry skin; emollient.

Fakovit *Zdorovje, Ukr.†*
White tablets, glutamic acid (p. 2070·2); glycine (p. 2071·2); pyridoxine hydrochloride (p. 2105·3); yellow-orange tablets, cysteine (p. 2058·3); ascorbic acid (p. 2110·3).
Cataracts.

Faktu *Nycomed, Cz.; Nycomed, Ger.†; Nycomed, Hong Kong; Ranbaxy, India; Pharos, Indon.; Nycomed, Philipp.; Nycomed, Port.; Takeda, Singapore; Takeda, Switz.*
Policresulen (p. 1160·2); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Faktu akut *Nycomed, Ger.†*
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Faktu mit Hamamelis *Takeda, Ger.*
Hamamelis (p. 2523·3).
Haemorrhoids.

Falacid *Collins, Mex.†*
Quinfamide (p. 947·1).
Amoebiasis.

Falben *GPO, Thai.*
Albendazole (p. 149·1).
Worm infections.

Falciat *ATOZ, India.*
Artesunate (p. 648·2).
Malaria.

Falcicare *United Lifecare, India.*
Artesunate (p. 648·2).
Malaria.

Falcicure *Sterfil, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falcide *Profic Organic, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falcidium *Nodysis, India.*
Artesunate (p. 648·2).
Malaria.

Falcidium-AB *Nodysis, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falcifast *Pharma-Tech, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falcigo *Zydus, India.*
Artesunate (p. 648·2).
Malaria.

Falcigo Plus *Zydus, India.*
Artesunate (p. 648·2); mefloquine (p. 657·1).

Falcimax *Maxo, India.*
Artesunate (p. 648·2).
Malaria.

Falcimax Plus *Maxo, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Falcimax-Q *Maxo, India.*
Quinine sulfate (p. 665·2).
Malaria; nocturnal leg cramps; babesiosis.

Falcinez *Wintech, India.*
Artesunate (p. 648·2).
Malaria.

Falcinil *Zuventus, India.*
Artesunate (p. 648·2).
Malaria.

Falciquin *Saga, India.*
Artesunate (p. 648·2).
Malaria.

Falcirid *Flamingo, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Falcital *Cadila, India.*
Mefloquine (p. 657·1).
Malaria.

Falcither *Intas, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falcitrim *Mepha, Port.*
6 Tablets, mefloquine hydrochloride (p. 657·1); 3 tablets, artesunate (p. 648·2).
Malaria.

Falcized *Zota, India.*
Artesunate (p. 648·2).
Malaria.

Falcol *Farma Lepori, Spain.*
Aceclofenac (p. 16·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Falcon *Vanguard, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Falcon-TZ *Vanguard, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Falcy *Skymax, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falcydol *Skymax, India.*
Artemether (p. 648·1).
Malaria.

Falcyguard *Biosena, India.*
Artesunate (p. 648·2).
Malaria.

Falcynate *Skymax, India.*
Artesunate (p. 648·2).
Malaria.

Falergi *Fahrenheit, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Falerm *Pharmahof, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Falernol *Liferpal, Mex.*
Miconazole (p. 588·3).
Fungal skin infections.

Falete *T Man, Thai.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Falex *Wescrib, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Falfon *Pharmahof, Thai.†*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Skeletal muscle spasm and pain.

Falgos *Sanofi-Aventis, Arg.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Dyspepsia; hangover; pain.

Falic *TRB, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Falicard *AWD, Ger.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; ischaemic heart disease; arrhythmias.

Falimint *Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Acetylaminonitropropoxybenzene.
Cough; mouth and throat disorders.

Falipan *Demo, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Falithrom *Hexal, Ger.†*
Phenprocoumon (p. 1468·3).
Thromboembolism prophylaxis.

Falium *Pharmahof, Thai.†*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Falkamin *Falk, Ger.*
Leucine (p. 2079·1); valine (p. 2098·3); isoleucine (p. 2078·2).
Liver disorders.

Falk, Hong Kong; Darya-Varia, Indon.†; Falk, Indon.†; Falk, Malaysia†; Falk, Philipp.†; Pharmalink, Philipp.†; Falk, Singapore.†
Amino acids; vitamins; trace elements.
Hepatic failure; liver insufficiency; nutritional supplement in liver disorders.

Falmina *NorthStar, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Falmonox *Sanofi-Aventis, Braz.; Sanofi-Aventis, Venez.*
Teclozan (p. 949·1).
Intestinal amoebiasis.

Falno *Winsome, India.*
Artesunate (p. 648·2).
Malaria.

Falot *Pisa, Mex.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Falpar *DWD, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falquigut *Falqui, Ital.*
Sodium picosulfate (p. 1887·2).
Constipation.

Falquilax *Falqui, Ital.*
Senna (p. 1885·1).
Constipation.

Falrap *Raprοss, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Falsigra *Polfarmex, Pol.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Falteria *Flamingo, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Faltidin *Alkem, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Falven *Teva, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Falvin *Recordati, Ital.*
Fenticonazole nitrate (p. 578·1).
Dermatological and gynaecological fungal infections.

Falvit *Jelfa, Pol.*
Vitamins; minerals.

Falz *Ritz, India.*
Artesunate (p. 648·2).
Malaria.

Famacin *Flamingo, Philipp.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Famcilet *Alet, Gr.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Famcin *Indian Drugs, India.*
Rifampicin (p. 350·3).
Bacterial infections.

Famcin H *Indian Drugs, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Famclox *Finecure, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Famec *Tripharma, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famel cum Codein *Brady, Austria.†*
Lactocreosote (p. 1659·3); calcium lactophosphate (p. 1783·1); codeine hydrochloride (p. 40·2).
Cold symptoms; catarrh; asthma; bronchitis.

Famel cum Ephedrin *Brady, Austria.†*
⊗Lactocreosote (p. 1659·3); calcium lactophosphate (p. 1783·1); ephedrine hydrochloride (p. 1663·2).
Cold symptoms; catarrh; asthma; bronchitis.

Famel Original *SSL, UK.*
Creosote (p. 1659·3); codeine phosphate (p. 40·2).
Coughs.

Famethacin *Thebe, S.Afr.*
Indometacin (p. 71·2).

Famicef *Baldacci, Port.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Famidal *Andromaco, Chile.*
Miconazole (p. 588·3); tinidazole (p. 949·2).
Balanitis; vulvovaginal infections.

Famidine *Chew, Thai.*
Sulfadimidine (p. 363·2).
Bacterial infections.

Famidyna *Jelfa, Pol.*
Famotidine (p. 1842·1).
Gastric hyperacidity; heartburn; dyspepsia.

Familin *DHA, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Family Medic First Aid Treatment *Tender, Canad.*
Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).

Family Sunscreen *Jason, Canad.†*
SPF 36: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Familykair *PDC, India.*
Capsules; oral liquid: Vitamins; trace elements.
PDC, India.
Oral drops: Lysine hydrochloride (p. 2079·3); vitamins; zinc sulfate (p. 2126·2).
PDC, India.
Oral powder: Calcium (p. 1783·1); vitamins; ferric ammonium citrate (p. 2060·1); phosphorus (p. 2589·2); soya protein hydrolysate (p. 2092·3); zinc sulfate (p. 2126·2).

Famine *APT, Hong Kong.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Faminex *Lark, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Faminex Forte *Lark, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Famirax *Synmedic, India.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Fam-Lax *Torbet Laboratories, UK.*
Yellow phenolphthalein (p. 1877·3); rhubarb (p. 1884·2).
Constipation.

Fam-Lax Senna *Torbet Laboratories, UK.*
Turkey rhubarb (p. 1884·2); senna leaf (p. 1885·1); carrageenan (p. 2176·3).
Constipation.

Famlov *Arrow, Irl.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Famo *CTS, Israel; Ulkar, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famobeta *Betapharm, Ger.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famoc *Berlin Pharm, Singapore; Berlin Pharm, Thai.†*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famocid *Synco, Hong Kong†; Sun, India; Sanbe, Indon.; Sun, Rus.†; Sun, Thai.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Famodil *Sigma-Tau, Ital.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famodin *Cadila, India; Sandoz, Turk.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Famodine *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; dyspepsia; gastro-oesophageal reflux.

Famodinhexal *Sandoz, Ukr.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastritis.

Famogast *Polpharma, Pol.; Saba, Turk.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastric hyperacidity.

Famogel *Vivax, Venez.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famohexal *Sandoz, Austral.†; Hexal, Austria.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famolta *Jean-Marie, Hong Kong.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Famonerton *Dolorgiet, Ger.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famonext *Cadila, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Famonit *Cadila, Rus.†; Cadila, Singapore.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux.

Famonite *Zydus, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Famonox *Deltapharm, Hong Kong†; Charoen, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famopac *Inpac, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Famopril *Zydus, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Famopsin *Remedica, Hong Kong†; Remedica, Malaysia; Remedica, Singapore; Remedica, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; dyspepsia; gastric hyperacidity; heartburn.

Famorila *Glenmark, Philipp.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; dyspepsia; gastritis; gastro-oesophageal reflux.

Famos *Mensana, Hung.*
⊗Letrozole (p. 817·1).
Breast cancer.

Famosan *ProMed, Cz.; Promed, Rus.*
Famotidine (p. 1842·1).
Peptic ulcer; gastrointestinal haemorrhage; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal hyperacidity; acid aspiration; pancreatitis; dyspepsia.

Famoser *Biofarma, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famoset *Abbott, Braz.*
Famotidine (p. 1842·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famosia *Asian Pharm, Thai.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famosin *GL Pharma, Austria.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Famotab *T-Boma, Hong Kong†; Bangkok Lab & Cosmetic, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Famotec *Julphar, UAE.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Famotep *Yeni, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famotid *Neo Quimica, Braz.*
Famotidine (p. 1842·1).
Peptic ulcer.

Famotin *DHA, Hong Kong; USV, India; DHA, Singapore.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Famotsan *Drogsan, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famowal *Wallace, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Famox *Ache, Braz.; Pacific, Hong Kong; Mylan, NZ; Pacific, Singapore.†*
Famotidine (p. 1842·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famoxal *Silanes, Mex.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Fampisec *San Marino, Philipp.*
Rifampicin (p. 350·3).
Mycobacterial infections.

Fampyra *Biogen, Canad.; Biogen, Denm.; Biogen, Fr.; Biogen, Ger.; Medison, Israel; Biogen, Neth.; Biogen, Norw.; Biogen, Swed.; Biogen, UK.*
Fampridine (p. 686·2).
Multiple sclerosis.

Famri *Pyridam, Indon.*
Rifampicin (p. 350·3).
Tuberculosis.

Famtac *Piramal, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Famtin *Finecure, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Famtine *Shin Poong, Philipp.*
Famotidine (p. 1842·1).
Peptic ulcer; gastrointestinal haemorrhage; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Famto *Antibioticos, Mex.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Famtrex *Cipla, India.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Famucaps *Brunel, S.Afr.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); paracetamol (p. 115·1); atropine sulfate (p. 1310·2).
Upper respiratory-tract disorders.

Famucosolv *BI, Gr.*
Ambroxol hydrochloride (p. 1654·3).

Famulan *Bittner, Austria; Bittner, Rus.*
Allium cepa (p. 2575·2); euphrasia (p. 2502·1); sabadilla (p. 2611·2); kalium jodatum (p. 2336·3); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Famulcer *Inkeysa, Spain†; Plusandex, Venez.*
Famotidine (p. 1842·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity.

Famulco *Stada, Irl.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Famvir *Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.†; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.; Asahi, Jpn; Novartis, Neth.†; Novartis, NZ; Novartis, Port.†; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; SmithKline Beecham, USA.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Novartis, Switz.†
Cream: Penciclovir (p. 1008·2).
Herpes labialis.

Fan Nuo *Kang Dini, China.*
Paracetamol (p. 115·1).

Fan Tan *Bohai, China.*
Telmisartan (p. 1509·3).
Hypertension.

Fanaletas *Lazar, Arg.*
Benzocaine (p. 1980·2); tyrothricin (p. 384·1); chlorophyllin (p. 2178·3); hexylresorcinol (p. 1755·1).
Mouth and throat infections.

Fanalgin *Weifa, Norw.*
Phenazone (p. 124·1); caffeine (p. 1203·3).
Pain.

Fanapt *Megapharm, Israel; Novartis, USA.*
Iloperidone (p. 1079·1).
Schizophrenia.

Fanaxal *Esteve, Spain.†*
⊗Alfentanil hydrochloride (p. 18·2).
General anaesthesia.

Fancal *Pharma-Tech, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Fanciadazol *Novag, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Fanclomax *Blausiegel, Braz.*
Famciclovir (p. 979·1).

Fandall *Maver, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Fandhi *Pharmakin, Venez.*
A factor VIII preparation (p. 1148·1).
Haemophilia A.

Faneng *Simcere, China.†*
Alfacalcidol (p. 2112·3).
Osteoporosis; hypoparathyroidism; rickets; osteomalacia.

Fang Di *Hongxing, China.*
Naftifine hydrochloride (p. 590·1).
Fungal skin infections.

Fang Qing *XinShiDai, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Fang Xi *Huabang, China.*
Acitretin (p. 1690·3).
Acne.

Fangan *Lazar, Arg.*
Ketoconazole (p. 585·3).
Vulvovaginal candidiasis.

Fangan Plus *Lazar, Arg.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); centella (p. 1698·3).
Vulvovaginal infections.

Fango Cream *Bangkok Lab & Cosmetic, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fango-B *Bangkok Lab & Cosmetic, Thai.*
⊗Betamethasone valerate (p. 1624·1); clotrimazole (p. 576·2).
Infected skin disorders.

Fangotherm *Eifelfango, Ger.*
Medicinal mud.
Musculoskeletal and joint disorders; gastrointestinal and urogenital disorders; neuralgia.

Fangtan *LuoXin, China.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Fanhdi *Grifols, Arg.; Grifols, Chile; Grifols, Cz.; Grifols, Ger.; Demo, Gr.; Grifols, Hung.†; Grifols, India; Grifols, Irl.; Grifols, Israel; Grifols, Ital.; Grifols, Malaysia†; Grifols, Port.; Grifols, Rus.; Grifols, Singapore; Grifols, Spain; Grifols, Thai.†; Dem, Turk.; Grifols, UK.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; factor VIII deficiency; von Willebrand's disease.

Fanipos *Teva, Pol.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Fanle *Jialin, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Fanlin *Yangtze River, China.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Fanminbu *Panbiotic, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Fanolyte *Bioprojet, Fr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium citrate (p. 1780·3); citric acid (p. 2480·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Fanomer *Bioprojet, Fr.*
Sea water (p. 2612·1).
Nasal congestion; nasal hygiene.

Fanovir *Frankin, Hong Kong.†*
Aciclovir (p. 964·1).
Viral skin infections.

Fan-P *Alpha Aromatic, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Fansamac *Farmigea, Ital.*
Bufexamac (p. 30·2).
Skin disorders; sunburn; pruritus.

Fansia
Note: this name may be used for preparations of different composition.
Eurodrug, Mex.†
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Fansidar *Roche, Austral.†; Roche, Braz.; Roche, Fr.; IFET (ΙΦΕΤ), Gr.; Roche, Indon.; Roche, Irl.†; Roche, Israel†; Roche, Malaysia; Roche, Philipp.; Roche, Rus.; Roche, S. Afr.; Roche, Switz.†; IDIS, UK; Roche, Ukr.†; Roche, USA.†*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria; toxoplasmosis; pneumocystis pneumonia.

Fansidol
Note: this name may be used for preparations of different composition.
Alapis, Gr.
Itraconazole (p. 583·3).
Fungal infections.

Fansulide *Sofar, Ital.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Fantamax *Sandoz, Singapore.*
⊗Fentanyl (p. 60·1).
Pain.

Fantan *Abbott, Turk.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Fantersol *Proel, Gr.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Fantizole *Taj, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fantomalt *Nutricia, Cz.; Nutricia, Fin.; Nutricia, Ital.; Nutricia, Pol.; Nutricia, Port.; Nutricia, Venez.; Roemmers-Klinos, Venez.*
Maltodextrin (p. 2080·3).
Preparation for enteral nutrition; dietary supplement.

Nutricia, Indon.†
Carbohydrates.
Enteral nutrition.

Fanton *Mandar, India.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Faradil *Sidus, Arg.*
Metoclopramide (p. 1862·2); diazepam (p. 1063·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Faradil Enzimatico *Sidus, Arg.†*
⊗Metoclopramide (p. 1862·2); pancreatin (p. 2579·3); simeticone (p. 1886·2).
Gastrointestinal disorders.

Faradil Novo *Sidus, Arg.*
Bromazepam (p. 1041·2); domperidone (p. 1838·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Faragel-Forte *Faran, Gr.*
⊗Camphor (p. 2466·2); alcohol (p. 1733·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl nicotinate (p. 91·3); turpentine oil (p. 2636·3).
Topical analgesia.

Farakil *Chew, Thai.*
⊗Prednisolone (p. 1645·2); neomycin (p. 329·3).
Infected skin disorders.

Farapon *Fahrenheit, Indon.*
Paracetamol (p. 115·1); ethenzamide (p. 56·2); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Faraxen *Randall, Mex.*
Naproxen (p. 98·2).
Inflammation.

Farbee with Vitamin C *Major, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Farbicil *Pharma Investi, Chile.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Farbion *Fahrenheit, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; facial paresis; peripheral circulatory disorders; ischialgia; herpes zoster; cervical syndrome; chronic rheumatism; hyperemesis gravidarum; diabetic polyneuropathy; anaemias.

Farbovil *Pharmathen, Gr.*
Ketoprofen (p. 79·1).
Pain; inflammation; musculoskeletal and joint disorders.

Farbutin
Note: this name may be used for preparations of different composition.
Farmasintez, Rus.
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis.

IFA, Mex.†
Trimebutine (p. 2634·1).

Farcef *Faran, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Farcolan *Farcoral, Mex.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Dyspepsia; flatulence; gastritis; meteorism; peptic ulcer.

Farcovit B12 *Pharco, Ukr.†*
Vitamins; cynara (p. 2490·3); safflower oil (p. 2086·3); essential phospholipids (p. 2201·2).
Nutritional supplement.

Farcovit Plus *Farcoral, Mex.*
Vitamins; minerals; vegetable extracts.

Farcyclin *Faran, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Fardalan *Faran, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Fardole *Specifar, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Fardolpin *Farcoral, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Farecef *Lafare, Ital.†*
Cefoperazone sodium (p. 243·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Farecillin *SF, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in some injections to alleviate the pain of injection.
Bacterial infections.

Fareclox *SarPharm, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Farelax *Fahrenheit, Indon.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Faremid *Lafare, Ital.*
Pipemidic acid (p. 339·3).
Bacterial infections.

Faremio *Alapis, Gr.*
Iron sucrose (p. 2078·1).

Farengil *Eczacibasi, Turk.*
Benzydamine hydrochloride (p. 29·2).

Fareston *Schering-Plough, Austral.; Orion, Austria; Baxter, Belg.†; Orion, China; Orion, Cz.; Orion, Fin.; CSP, Fr.; Baxter, Ger.†; Orion, Gr.; Orion, Hung.; Orion, Irl.; Schering-Plough, Ital.; Schering-Plough, Mex.†; Baxter, Neth.; Schering-Plough, NZ; Orion, Pol.; Orion, Port.; Orion, Rus.; Schering-Plough, S.Afr.; Schering-Plough,*

Spain†; Orion, Swed.; Orion, Switz.†; MSD, Thai.; Abdi, Turk.; Orion, UK; Orion, Ukr.; ProStrakan, USA.
⊗Toremifene citrate (p. 873·3).
Breast cancer.

Faretrizin *Lafare, Ital.†*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Farfaron *Gemi, Pol.*
Tussilago farfara (p. 1659·2).
Mouth and throat disorders.

Fargan *Johnson & Johnson, Ital.*
Promethazine (p. 638·2).
Skin irritation.

Farganesse *Marvecs, Ital.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; premedication.

Fargem *MJ Biopharm, Thai.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Fargoxin *Fahrenheit, Indon.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Farhex *Berksam, Turk.*
Benzydamine hydrochloride (p. 29·2); chlorhexidine gluconate (p. 1743·3).

Farial *Abbott, Turk.*
⊗Indanazoline hydrochloride (p. 1667·1).
Nasal congestion.

Faribrox *Loeffler, Mex.*
Ambroxol hydrochloride (p. 1654·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; respiratory-tract congestion.

Farin Gola *Montefarmaco, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disinfection.

Faringel *CaDiGroup, Ital.*
Honey (p. 2072·1); chamomile (p. 2474·1); calendula (p. 2465·2); propolis (p. 2597·3); aloe vera (p. 1693·2).
Mouth and throat disorders.

Faringenilo *Diafarm, Spain.*
Benzocaine (p. 1980·2); potassium chlorate (p. 2595·2).
Mouth and throat disorders.

Faringesic *Diafarm, Spain.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Faringin *GSK, Ukr.*
Choline salicylate (p. 39·2).
Mouth and throat disorders.

Faringina *SIT, Ital.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Faringodyl *Ranbaxy, India.*
Chlorphenamine maleate (p. 620·3); codeine (p. 40·2).

Faringopront *Pierre Fabre, Hung.*
Chlorhexidine gluconate (p. 1743·3); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Faringosept *Ranbaxy, Pol.; Ranbaxy, Rus.; Ranbaxy, Ukr.*
Ambazone (p. 1736·2).
Mouth and throat infection and inflammation.

Faringotricina *SIT, Ital.*
Tyrothricin (p. 384·1).
Stomatitis.

Farington *KVZ, Ukr.*
Chlorhexidine hydrochloride (p. 1743·3); ascorbic acid (p. 2110·3).
Mouth and throat disorders.

Farinop *Biokosma, Arg.*
Propolis (p. 2597·3); eucalyptus (p. 2501·1); honey (p. 2072·1).
Dietary supplement.

Farintos *Lamsa, Arg.*
⊗Pseudoephedrine (p. 1676·1); paracetamol (p. 115·1); bromhexine (p. 1656·3).

Farizym *Organon, India.*
Lipase (p. 2579·3); protease (p. 2598·1); amylase (p. 2442·1).
Formerly contained lipase, protease, amylase, cellulase, and bile extract.
Pancreatic deficiency; phytobezoar; fermentative dyspepsia.

Farlac *Farmasa, Braz.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Farlev *Yarindo, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Farlidone *Aurora, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Farlin *Continentales, Mex.*
Dipyrone (p. 53·3).
Pain.

Farlipid *Farmedia, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Farlotac *Farmaline, Thai.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Farludiol *Pfizer, Arg.*
Estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Farludiol Ciclo *Pfizer, Arg.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Farlupost *Pfizer, Chile.†*
Estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1).

Farlutal *Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile†; Pfizer, China; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong†; Pharmacia Upjohn, India; Pfizer, Ital.; Pfizer, Norw.†; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms; functional uterine bleeding; dysmenorrhoea; amenorrhoea; endometriosis; contraception; menometrorrhagia; anorexia and cachexia in chronic disorders; dysfunctional uterine bleeding; menopausal disorders; menorrhagia.

Farlutale *Pfizer, Arg.*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; dysfunctional uterine bleeding; endometrial hyperplasia.

Farlutes *Pfizer, Chile.†*
18 Tablets, estradiol valerate (p. 2271·2); 13 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).

Farmabep *Farmaceutica H, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Farmabes *Fahrenheit, Indon.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; arrhythmias.

Farmabex C *Fahrenheit, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C deficiency; nutritional supplement.

Farmabex Plus *Fahrenheit, Indon.*
Vitamins; zinc (p. 2126·1).
Vitamin and zinc deficiency.

Farmacaina *Farma, Venez.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Farmacarbon *Cinay, Turk.*
Activated charcoal (p. 1537·3).

Farmacef *Farmaline, Thai.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Farmaciclin *Farma 1, Ital.*
Vancomycin hydrochloride (p. 384·2).
Antibiotic-associated colitis.

Farmacne *Wolff, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Farmacorti *Parggon, Mex.*
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Farmacorti YC *Parggon, Mex.*
⊗Fluocinolone (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Farmacrol *Fahrenheit, Indon.*
Oral suspension: Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer; oesophagitis; gastritis; flatulence.

Fahrenheit, Indon.
Tablets: Simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastric hyperacidity; peptic ulcer; oesophagitis; gastritis; flatulence.

Farmadex *Farmak, Ukr.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Farmadipin *Farmak, Ukr.*
Nifedipine (p. 1447·2).
Hypertension.

Farmadol *Fahrenheit, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Farmak, Ukr.†
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Farmadral *Fahrenheit, Indon.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; anxiety; arrhythmias; hypertrophic obstructive cardiomyopathy; essential tremor; hyperthyroidism; phaeochromocytoma; myocardial infarction; migraine.

Farmadura *Pfizer, Irl.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Farmaflebon *Farmasa, Mex.*
Hydroxypolyethoxydodecanol (p. 2193·3).
Oesophageal varices; telangiectasias.

Farmaginax *Rompharm, Rus.*
Benzalkonium chloride (p. 1737·1).

Farmaiod *Nuova Farmec, Ital.*
Povidone-iodine (p. 1767·1).
Disinfection of skin and wounds.

Farmakinase *Farmak, Ukr.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Farmalat *Fahrenheit, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Farmalcohol *Cinfa, Spain.†*
⊗Alcohol (p. 1733·1); cetylpyridinium chloride (p. 1743·1).
Disinfection.

Farmalex *Farmaline, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Farmalor *Farmaceutica H, Mex.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Allergic disorders.

Farmapram *IFA, Mex.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder; alcohol withdrawal syndrome.

Farmaproina *Reig Jofre, Spain.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Farmarest *Farmaceutica H, Mex.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Farmasal *Fahrenheit, Indon.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Farmasept *Nuova Farmec, Ital.*
Didecyldimethylammonium chloride (p. 1750·3).
Disinfection of burns, skin, and wounds.

Farmasul *Rinter Corona, Spain.*
Senna (p. 1885·1); fucus vesiculosus.
Constipation.

Farmasulin H *Farmak, Ukr.*
⊗Insulin (human) (p. 475·3).
Diabetes mellitus; hyperkalaemia; test for investigation of growth hormone secretion.

Farmasulin N 30/70 *Farmak, Ukr.*
⊗Mixture of insulin injection (human recombinant) 30% and isophane insulin injection (human recombinant) 70% (p. 475·3).
Diabetes mellitus.

Farmasulin N NP *Farmak, Ukr.*
⊗Insulin injection (human recombinant) with protamine sulfate and zinc oxide (p. 475·3).
Diabetes mellitus.

Farmavon *Fahrenheit, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Farmaxetina *IFA, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; bulimia nervosa.

Farmazol
Note: this name may be used for preparations of different composition.
Hizon, Philipp.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Farmeban *Farmasa, Mex.*
Diiodohydroxyquinoline (p. 931·1); dimeticone (p. 1886·2).
Amoebiasis.

Farmelox *Farmedia, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Farmemax *Farmedia, Gr.*
Alendronate sodium (p. 1171·3).

Farmiblastina *Pfizer, Spain.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Farmicalcine *Alapis, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Farmicetina *Rontag, Arg.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Farmicina *Pharlab, Braz.*
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Farmidal S *Continentales, Mex.*
Astemizole (p. 616·1).

Farmidil *Relyo, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Farmigras *Bajer, Arg.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Skin cleanser.

Farmin
Note: this name may be used for preparations of different composition.
Fahrenheit, Indon.
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoproteinaemia.

Farmino *Bajer, Arg.*
Skin cleanser.

Farmiver *Continentales, Mex.*
Quinfamide (p. 947·1); albendazole (p. 149·1).
Amoebiasis; giardiasis; worm infections.

Farmocefe *Farmoz, Port.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Farmoftal *HLB, Arg.*
Ketotifen (p. 631·3).

HLB, Chile.
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Farmorol *Farmoz, Port.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Farmorrubicina *Pfizer, Chile.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Farmorubicin *Pfizer, Arg.; Pfizer, Austria; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hung.; Pharmacia Upjohn, India; Pfizer, Israel†; Pfizer, Jpn; Pfizer, Mex.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Actavis, Ukr.; Pfizer, Venez.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Farmorubicina *Pfizer, Braz.; Pfizer, Ital.; Pfizer, Port.; Pfizer, Spain.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Farmorubicine *Pfizer, Belg.; Pfizer, Fr.; Pfizer, Neth.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Farmotal *Marvecs, Ital.*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Farmoten *Fahrenheit, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Farmoxil *Elofar, Braz.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Farmoxyl *Fahrenheit, Indon.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Farm-X *Bajer, Arg.*
Zinc undecenoate (p. 596·3); zinc oxide (p. 1729·1); salicylic acid (p. 1719·1); sodium propionate (p. 593·1); coal tar (Alcoderm) (p. 1723·2).
Burns; fungal skin infections; skin irritation; ulcers; wounds.

Farm-X Duo *Bajer, Arg.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Farm-X Ginecologico *Bajer, Arg.*
Metronidazole (p. 936·1); neomycin sulfate (p. 330·1).
Vaginal infections.

Farna FDG *Molypharma, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for detection of malignant neoplasms by positron-emission tomography.

Farnat *Fahrenheit, Indon.*
Metronidazole (p. 936·1).
Anaerobic infections.

Farnerate *Kuraray, Jpn.†*
⊗Prednisolone farnesil (p. 1645·2).
Skin disorders.

Farnezone *Taiho, Jpn.*
⊗Prednisolone farnesil (p. 1645·2).
Skin disorders.

Farnitin *Lafare, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Farnitran *Fariberica, Port.†*
Nitrendipine (p. 1456·3).
Hypertension.

Farnormin *Fahrenheit, Indon.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Farom *Maruho, Jpn.*
Faropenem sodium (p. 298·2).
Bacterial infections.

Faron *Newcharoen, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Faronem *Ranbaxy, India.*
Faropenem sodium (p. 298·2).

Faronkal *Andromaco, Chile.*
⊗Domperidone (p. 1838·1); pseudoephedrine sulfate (p. 1676·1).
Snoring.

Faroo-XT *Zenacts, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Faros *Cassella-med, Ger.; Vifor, Switz.*
Crataegus (p. 2488·1).
Heart failure; cardiac disorders.

Farozet *Glenmark, India.*
Faropenem (p. 298·2).

Farpain *Fahrenheit, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Farpectol *Farcoral, Mex.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Farpik *Farcoral, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Farris *Aamorb, India.*
Injection: Iron sucrose (p. 2078·1).

Aamorb, India.
Syrup; tablets: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Farsifen *Ifars, Indon.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Farsix *Fahrenheit, Indon.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Farsorbid *Fahrenheit, Indon.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Fartadin *Farcoral, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Fartolin *Fahrenheit, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Fartolin Expectorant *Fahrenheit, Indon.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Fartricon *Farcoral, Mex.*
Metronidazole benzoate (p. 936·1).
Trichomoniasis; giardiasis; amoebiasis.

Fartropin *Continentales, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Fartussin *Farmaline, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Farvicett *Nuova Farmec, Ital.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin, wound, burn, and mucous membrane disinfection.

Farviron *Farmedia, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Farxen *Farcoral, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Inflammation; pain.

Farxiga *BMS, USA.*
Dapagliflozin propanediol (p. 470·2).
Diabetes mellitus.

Farzolam *Medicpharma, Thai.; Pharminar, Thai.*
Alprazolam (p. 1035·2).

Fas-3 Kit *Hetero, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Fasarax *Prater, Chile.*
Hydroxyzine (p. 630·3).

Fascar *Unison, Hong Kong; Unison, Thai.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori infection.

Fasden *Pharmahof, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; pain; gout.

Fasiclor *Maver, Mex.*
Cefaclor (p. 232·3).
Bacterial infections.

Fasicon *East African, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fasidine *Siam Medicare, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Fasigin N *Pfizer, Ital.*
Tinidazole (p. 949·2); nystatin (p. 590·3).
Vulvovaginal trichomoniasis and candidiasis.

Fasigyn *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.†; Pfizer, Israel†; Pfizer, Mex.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Venez.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections; amoebiasis; giardiasis; trichomoniasis; ulcerative gingivitis.

Fasigyn Nistatina *Pfizer, Arg.*
Tinidazole (p. 949·2); nystatin (p. 590·3).
Vaginal trichomoniasis and candidiasis.

Fasigyn VT *Pfizer, Mex.*
Tinidazole (p. 949·2); tioconazole (p. 595·3).
Vaginal fungal and bacterial infections.

Fasigyne *Teofarma, Fr.; Pfizer, Switz.†*
Tinidazole (p. 949·2).
Protozoal infections; anaerobic bacterial infections.

Fasigyn-Nystatin *Pfizer, Indon.†*
Tinidazole (p. 949·2); nystatin (p. 590·3).
Vaginal infections.

Fasinat *Maver, Mex.*
Cefadroxil (p. 233·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Faslodex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ†; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Vetter, Ukr.; AstraZeneca, USA; AstraZeneca, Venez.*
⊗Fulvestrant (p. 800·1).
Breast cancer.

Fasma *Pharmahof, Thai.†*
⊗Terbutaline sulfate (p. 1228·1).
Bronchospasm.

Fasolan *Janssen-Cilag, Mex.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vertigo.

Fasolon *Coronet, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Skin disorders.

Faspic *Zambon, Philipp.; Zambon, Port.*
Ibuprofen arginine (p. 68·2).
Pain; fever; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Zambon, Rus.; Sermmitr, Thai.†; Zambon, Thai.†
Ibuprofen (p. 68·2).
Fever; inflammation; pain; rheumatoid arthritis.

Fasqilon *Filadams, Philipp.†*
Norfloxacin (p. 333·3).
Urinary-tract infections; gonorrhoea.

Fasst *Excare, India.*
Dispersible tablets; syrup: Cefpodoxime.
Bacterial infections.

Excare, India.
Injection: Ceftazidime (p. 250·2).
Bacterial infections.

Fast *Perrigo, Israel.*
Calcium carbonate (p. 1824·3).
Calcium supplement; antacid.

Fast Powder *Medochemie, Singapore.†*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial skin infections; wounds; burns.

Fastaid *Ethix, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Fastan *Pharmahof, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Fastenyl *Meda, Fr.*
Arginine aspartate (p. 2049·1); vitamin C (p. 2110·3).
Tonic.

Fastfen *Cristalia, Braz.*
⊗Sufentanil citrate (p. 132·3).
Pain.

Fastjekt *Allergopharma, Ital.*
⊗Adrenaline (p. 1292·1).
Anaphylactic shock.

Meda, Ger.; Allergopharma, Pol.
⊗Adrenaline hydrochloride (p. 1292·2).
Anaphylaxis.

Fastjel *UFSA, Turk.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint pain.

Fastnac *Lupin, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Fastnac SR *Lupin, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Fastolin *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); brompheniramine (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Fastoric Plus *Plethico, Rus.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold and influenza symptoms.

Fastovorin *Alkem, India.*
Folinic acid (p. 2066·3).

Fastpara *BMW, India.*
Paracetamol (p. 115·1).
Pain; fever.

Fastum *Menarini, Austria; Menarini, Belg.; Raffo, Chile†; Berlin-Chemie, China; Menarini, Cz.; Menarini, Denm.; Menarini, Hong Kong; Berlin-Chemie, Hung.; Menarini, Hung.; Menarini, India; Menarini, Irl.; Genmedix, Israel†; Menarini, Ital.; Menarini, Malaysia; Transfarma, Philipp.; Berlin-Chemie, Pol.; Menarini, Pol.; Menarini, Port.; Menarini, Rus.; Adcock Ingram, S.Afr.; Menarini, Singapore; Menarini, Spain; Menarini, Switz.; Menarini, Thai.; Berlin-Chemie, Ukr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; thrombophlebitis; pain; phlebitis; inflammation; gout.

Fasturtec *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi Pasteur, Turk.; Sanofi Synthelabo, UK; Sanofi-Aventis, Venez.*
Rasburicase (p. 609·2).
Hyperuricaemia.

Fastwax *BMW, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).

Fastway *Reddy, S.Afr.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fasulide *Bunker, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fate Low Protein *Fate, UK.*
A range of low-protein foods for special diets.

Fatec *Pharmahof, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; rhinitis; allergic skin disorders.

Fatel *Pharmahof, Thai.*
Albendazole (p. 149·1).
Worm infections.

Fa-Thalai-Chon *Pharmahof, Thai.*
Andrographis (p. 2443·2).

Father John's Medicine Plus *Oakhurst, USA.*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); guaifenesin (p. 1666·2).
Coughs.

Fatica *Ethica, Indon.*
vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Tonic.

Fatidin *Cipan, Port.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Fatiflox *Servocare, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Fatiflox-OZ *Servocare, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Fatig *Arrow, Braz.*
Vitamins.

Fatigon *Kalbe, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Nutritional supplement.

Fatigue *Homeocan, Canad.*
⊗Alfalfa (p. 2433·1); agnus castus (p. 2432·2); avena sativa (p. 2451·1); phosphoricum acidum (p. 2589·1); phosphorus (p. 2589·2); selenium metallicum (p. 2086·3).
Homoeopathic preparation.

Fatral *Fahrenheit, Indon.*
Sertraline hydrochloride (p. 448·1).
Depression.

Fatyne *Pharmahof, Thai.†*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Faulblastina *Libbs, Braz.*
Vinblastine sulfate (p. 881·3).

Faulcurium *Hospira, Port.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fauldacar *Libbs, Braz.*
Dacarbazine (p. 776·1).

Fauldcarbo *Libbs, Braz.*
Carboplatin (p. 759·1).

Fauldcispla *Libbs, Braz.*
Cisplatin (p. 766·1).

Fauldcita *Libbs, Braz.*
Cytarabine (p. 774·1).

Fauldetic *Hospira, Port.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Fauldexato *Hospira, Port.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis; graft-versus-host disease.

Fauldfluor *Libbs, Braz.*
Fluorouracil (p. 795·2).

Faulding Remedies Epsom Salts *Hind Wing, Hong Kong.†*
Magnesium sulfate (p. 1787·3).

Fauldleuco *Libbs, Braz.*
Calcium folinate (p. 2066·3).

Fauldmetro *Libbs, Braz.*
Methotrexate (p. 822·2).

Fauldoxo *Libbs, Braz.; Mayne, Port.*
Doxorubicin hydrochloride (p. 783·1).

Fauldpami *Libbs, Braz.*
Pamidronate disodium (p. 1186·3).

Fauldvincri *Libbs, Braz.*
Vincristine sulfate (p. 882·3).

Faulplatin *Hospira, Port.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Faultenocan *Hospira, Port.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Faulviral *Hospira, Port.*
Aciclovir sodium (p. 964·1).

Faustan *Temmler, Ger.*
Diazepam (p. 1063·2).
Anxiety disorders; skeletal muscle spasm; premedication; status epilepticus.

Favate *Acekinetic, India.*
Flavoxate (p. 2360·1).
Bladder function disorders.

Fave di Fuca *Bayer, Ital.*
Bladderwrack (p. 2612·1); cascara (p. 1826·1); frangula (p. 1843·3).
Constipation.

Fave de Fuca *Uriach Aquilea OTC, Spain.*
Frangula bark (p. 1843·3); cascara (p. 1826·1); fucus vesiculosus.
Constipation.

Faverin *Aspen, Austral.; Solvay, Hong Kong; Abbott, Irl.; Solvay, Philipp.†; Solvay, S.Afr.; Solvay, Singapore; Abbott, Thai.; Solvay, Turk.; Abbott, UK.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Favic *Aspen, Austral.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Favicin *Cryopharma, Mex.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Favilax *Cinfa, Spain.*
Cascara (p. 1826·1); fucus vesiculosus; frangula bark (p. 1843·3).
Constipation.

Favirab *Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Favistan *Temmler, Ger.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Favlam *USV, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Favolax *Orion, Denm.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Favolife *FDC, India.*
Bifidobacterium breve (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

Favolip *Sarabhai Piramal, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Favorat *Aledicine, Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Favoxil *Perrigo, Israel.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Fa-x *Pharmahof, Thai.*
Simeticone (p. 1886·2).
Flatulence.

Faxe *Blubell, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Faxet *Volta, Chile.*
Lidocaine hydrochloride (p. 1988·2); methylrosanilinium chloride (p. 1761·1).
Antiseptic.

Faxiden *Ifars, Indon.†*
Piroxicam (p. 125·3).
Osteoarthritis; rheumatoid arthritis.

Faxigen *Generics, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Faxim *Cure Quick, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Faximin *Sandoz, Braz.*
Glucosamine (p. 2515·3).

Sandoz, Mex.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Faxine *Wyeth Lederle, Ital.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety.

Faxinorm *Wassermann, Denm.*
Rifaximin (p. 355·2).
Travellers diarrhoea.

Faxiprol *Medico Uno, Cz.; Medico Uno, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; panic disorder; anxiety; social phobia.

Faxiven
Note: this name may be used for preparations of different composition.
Pharmathen, Gr.
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Triton, India.
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Faxolet *Polfa Pabianice, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Faxtin *Ind-Swift, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Faxtin-A *Ind-Swift, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Faxtra *Anthiea, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Fayerex *Lafayette, Philipp.*
Carbocisteine (p. 1658·1).
Cough.

Fayton *Glenmark, Neth.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy.

FazaClo *Azur, Neth.†; Jazz, USA.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Fazactin *Flamingo, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Fazebit *Ultra, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Fazen *Pharmahof, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Fazol
Note: this name may be used for preparations of different composition.
Aurobindo, Philipp.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Dollder, Venez.
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Sinclair, Fr.
Isoconazole nitrate (p. 583·2).
Fungal skin infections.

Fazol G *Sinclair, Fr.*
Isoconazole nitrate (p. 583·2).
Vulvovaginal candidiasis.

Fazolan *Etifar, Venez.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Fazolin
Note: this name may be used for preparations of different composition.
Collins, Mex.
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Siam Bheasach, Thai.
Cefazolin (p. 237·2).
Bacterial infections.

Fazolon *Ariston, Braz.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Fazonil
Note: this name may be used for preparations of different composition.
Pharmawealth, Philipp.
Cefazolin sodium (p. 237·3).
Bacterial infections.

FB *Yacca, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

FB Fer *Pharmasant, Thai.†*
Ferrous fumarate (p. 2060·3); vitamins; calcium (p. 1783·1); phosphorus (p. 2589·2).
Iron-deficiency anaemia; vitamin and mineral supplement.

FBC *Ranbaxy, Thai.*
Ferrous fumarate (p. 2060·3); vitamins; calcium phosphate (p. 1784·2).
Anaemias.

FBC Plus *Ranbaxy, Thai.*
Ferrous fumarate (p. 2060·3); vitamins; calcium phosphate (p. 1784·2); sodium fluoride (p. 2089·2).
Iron-deficiency anaemia; vitamin and mineral supplement.

FBN *Micro, India.*
Flurbiprofen sodium (p. 65·3).
Prevention of miosis during eye surgery; inflammation following eye surgery.

FCE *Bago, Chile.*
Urogastrone (p. 1894·3); sulfadiazine silver (p. 362·3).
Wounds; ulcers; burns.

FC-Kit *Arrowin, India.*
Azithromycin (p. 221·2); fluconazole (p. 578·2); secnidazole (p. 947·3).

F-Clar *Finecure, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

FCN *Intas, India.*
Fluconazole (p. 578·2).
Fungal infections.

F-Con *Lupin, India.*
Fluconazole (p. 578·2).
Fungal infections.

F-Decalin *Fluoron, Ger.*
⊗Perflunafene (p. 2586·3).
Ophthalmic tamponade.

F-Decalin Plus *Fluoron, Ger.*
⊗Perflunafene (p. 2586·3); perfluorohexyloctane (p. 2586·3).
Ophthalmic tamponade.

18F-FDG *BSM, Austria.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Assessment of regional glucose metabolism.

FDG Scan *Mallinckrodt, Cz.†; Tyco, Spain.†*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide diagnostic aid; detection of malignant neoplasms.

FDG Scan F18 *Mallinckrodt, Neth.†*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide diagnostic aid.

FDGCadpet *CAD PET, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for positron emission tomography in oncology, cardiology, and neurology.

FDH *Genesis, India.*
Docosahexaenoic acid (p. 1460·1); folic acid (p. 2063·1).

F-Din *Medimar, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

FDP *Fisiopharma, Ital.*
Fosfructose trisodium (p. 2507·2).
Hypophosphataemia.

Fe *UCB, USA.*
Dried ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

FE Aspartate *Miller, USA.*
Ferrous aspartate (p. 2060·3).
Iron supplement.

Feacef *Bros, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Fealin *Bros, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Feaplex *Bros, Gr.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Fearo *Blubell, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Fearo-FD *Blubell, India.*
Oral drops: Sodium feredetate (p. 2088·3).

Blubell, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Feast *Kamron, India.*
Injection: Folic acid (p. 2063·1); nicotinamide (p. 2083·1).

Kamron, India.
Tablets: Vitamins; minerals; trace elements.

Fe-Back *Nang Kuang, Thai.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia; iron supplement.

Febate *Acekinetic, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Febcid *Micro, India; Micro, Singapore.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Febex *Saga, India.*
Capsules: Calcium hydrogen phosphate (p. 1783·3); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Saga, India.
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Febichol *Noventis, Cz.*
Fenipentol (p. 2503·1).
Liver and biliary-tract disorders.

Febira *Zentiva, Cz.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Febl *Forgo, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Febrate *Umeda, Thai.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Febratic *Roemmers, Arg.; Rhein, Mex.†*
Ibuprofen (p. 68·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Febrax *Rhein, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Pain; fever.

Febrectal
Note: this name may be used for preparations of different composition.
Romofarm, Spain.
Paracetamol (p. 115·1).
Pain; fever.

Febrectol *Sanofi-Aventis, Fr.†*
Suppositories: Paracetamol (p. 115·1); pine needle oil (p. 2591·1).
Pain; fever.

Febrex *Indoco, India.*
Paracetamol (p. 115·1).
Pain; fever.

Febrex Plus *Indoco, India.*
Oral drops; tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Indoco, India.
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2).

Febrex Plus DS *Indoco, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Febricet *Hemofarm, Rus.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Febricod *Douglas, Austral.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Febricol *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Catarrh; cold and influenza symptoms; allergic rhinitis.

Febridol *Ascent, Austral.; Cipla, India; Neves, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Febridol Plus *Ascent, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Febrigrip *Monserrat, Arg.*
⊗Paracetamol (p. 115·1); butetamate citrate (p. 1658·1); pseudoephedrine (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold and influenza symptoms.

Febrilin *Beres, Hung.*
Paracetamol (p. 115·1).
Fever; pain.

Febrilite *Holland Pharma, Neth.*
Aconitum napellus (p. 2428·3); baptisia tinctoria (p. 2647·2); belladonna (p. 2453·3); bryonia alba; eupatorium perfoliatum (p. 2459·1); china officinalis (p. 2478·3); echinacea angustifolia (p. 2498·1); echinacea purpurea (p. 2498·1).
Homoeopathic preparation.

Febrinex *Phapros, Indon.*
Dexchlorpheniramine maleate (p. 621·1); sulfogaiacol (p. 1678·1); paracetamol (p. 115·1).
Influenza symptoms.

Febrinil *Svizera, India; Oboi, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Febrinil-P *Svizera, India.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2).

Febrisan *Nycomed, Cz.; Nycomed, Pol.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Febro-cyl L Ho-Len-Complex *Liebermann, Ger.*
Aconitum (p. 2428·3); apis (p. 2445·2); belladonna (p. 2453·3); china (p. 2478·3); gelsemium (p. 2511·2); kalium jodatum (p. 2336·3); phytolacca (p. 2593·2).
Homoeopathic preparation.

Febrofen *Medana, Pol.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

Febrofid *Akrikhin, Rus.*
Ketoprofen lysine (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; phlebitis; lymphangitis.

Febryn *Sunthi Sepuri, Indon.†*
Ibuprofen (p. 68·2).
Rheumatoid arthritis; osteoarthritis; pain.

Febs *Reckitt Benckiser, Singapore.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Pain; fever; cold and influenza symptoms; sinus congestion.

Febsen *Medley, Braz.*
Ibuprofen (p. 68·2).
Fever; pain.

Febupen *EMS, Braz.*
Oxyphenbutazone (p. 114·3); paracetamol (p. 115·1).
Fever; inflammation; pain.

Feburic *Teijin, Jpn.*
Febuxostat (p. 607·1).
Gout; hyperuricaemia.

Febzin *Actavis, UK.*
Clarithromycin citrate (p. 266·2).
Bacterial infections.

Fecinole *Dosa, Arg.*
⊗Letrozole (p. 817·1).
Breast cancer.

Feco-5 *Enzo, India.*
Vitamins; minerals.

Fecol *Nakornpatana, Thai.*
Capsules; tablets: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; nasal congestion.
Nakornpatana, Thai.
Syrup: Paracetamol (p. 115·1); salicylamide (p. 129·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; nasal congestion.

Fe-Com *Mapra, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Fecontin-F *Modi-Mundipharma, India.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Fecontin-Z *Modi-Mundipharma, India.†*
Ferrous glycine sulfate (p. 2061·3); zinc sulfate (p. 2126·2); folic acid (p. 2063·1).
Iron, zinc, and folic acid deficiency in pregnancy.

Fectim *Trumac, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fectri *Parggon, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Fectrim *DDSA Pharmaceuticals, UK.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Fectrin *Bajamed, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Fedac *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract congestion; allergic rhinitis; cold symptoms; sinusitis.

Fedac Compound *DHA, Hong Kong; DHA, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3); codeine phosphate (p. 40·2).
Upper respiratory-tract congestion; cough; nasal congestion.

Fedac DM *DHA, Singapore.*
⊗Dextromethorphan (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough; cold symptoms.

Fedaloc *Pharma Dynamics, S.Afr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Feday *Biosync, India.*
Syrup: Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3).
Biosync, India.
Tablets: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Feddic *Medicine Products, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Fedil *Standard Chem & Pharm, Thai.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Fedimed *Largen, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Fedin *Sandoz, Mex.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Fedip *Gebro, Austria.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Fedipin *Medikon, Indon.†*
Nifedipine (p. 1447·2).
Angina pectoris; myocardial infarction; hypertension.

Fedivan *Medis, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesteroladmia; cardiovascular risk reduction.

Fedol *Mint, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Fedolen *Viofar, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Fedpros *Raam, Mex.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Fedra *Bayer, Ital.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Fedra-Gel-S *Marching, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Heartburn; dyspepsia; gastric hyperacidity; flatulence.

Fedral *Nycomed, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Fedrer *Hauz, India.*
Sodium feredetate (p. 2088·3).

Fedyclar *Schering-Plough, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Feel Chill *Cadila, India.†*
Zinc oxide (p. 1729·1); alum (p. 2439·1); maize starch (p. 2095·1); boric acid (p. 2459·3); salicylic acid (p. 1719·1); menthol (p. 2553·2).
Prickly heat.

Feel Good *Invision, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Feel Good-HR *Invision, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1).

Feel Naturale *L'Oreal, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Feels *Laboratorios Chile, Chile.*
Carbomer (p. 2173·3).
Vaginal lubricant.

Feen-A-Mint
Note: this name may be used for preparations of different composition.
Elea, Arg.
Sodium picosulfate (p. 1887·2).
Constipation.
Schering-Plough, USA.
Bisacodyl (p. 1821·1).
Constipation.

Feet Athletes Foot and Antifungal *Roma, Canad.†*
Aluminium chlorohydrate (p. 1694·1); undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal foot infections.

Fefa *Saga, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Fefo *NB, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Fef-OD *Waves, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin E acetate (p. 2119·2).

Fefol
Note: this name may be used for preparations of different composition.
Dollder, Venez.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Schering-Plough, Arg.; Pfizer Consumer, Austral.; GSK, India; Intrapharm, Irl.; SmithKline Beecham, S.Afr.†; Intrapharm, UK.
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Fefolato *Bial, Port.*
Folic acid (p. 2063·1); ferrous sulfate (p. 2062·2).
Iron and folic acid deficiency.

Fefol-Vit *SmithKline Beecham, S.Afr.†*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Iron, folic acid, and vitamin deficiency in pregnancy.

Fefol-Z *GSK, India.*
Dried ferrous sulfate (p. 2062·2); zinc sulfate (p. 2126·2); folic acid (p. 2063·1).
Iron, zinc, and folic acid deficiency in pregnancy and lactation.

Fegabiral *Silanes, Mex.*
Sodium phenylbutyrate (p. 2518·3).
Hyperammonaemia; urea cycle disorders; adjunct in proliferative disorders.

FegaCoren *Vitorgan, Ger.*
⊗Protein extracts from: hepar (p. 2444·1); pancreas (p. 2444·1); thymus (p. 2631·1); lien (p. 2444·1); cor; ren (p. 2444·1); aorta; gland. suprarenal. (p. 2444·1); mucosa intest.; amnion (p. 2442·1); testes (p. 2304·3); gland. thyreoidea (p. 2345·3); diencephalon (p. 2444·1).
Cardiovascular and liver disorders.

Fegalgina *Argenfarma, Arg.*
Cynara (p. 2490·3); boldo (p. 2458·3); carrot (p. 2647·2); vitamin C (p. 2110·3); citric acid (p. 2480·3).
Dietary supplement; digestive disorders; liver disorders.

Fegan *Allergan, India.*
Diclofenac (p. 1164·2).
Prevention of intra-operative miosis; eye inflammation and pain; allergic conjunctivitis.

Fegem *Torrent, India.*
Syrup: Iron (p. 2073·1).
Torrent, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Fegenor *Nepalm, Fr.; Leurquin, Hong Kong.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fe-Glow *Prompt Cure, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Fegra *Comed, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fei An *Huabang, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Fei Er *Southwest, China.*
Dimefline hydrochloride (p. 2321·2).

Fei Er Bi *Kang Ji Er, China.*
Hydroxycamptothecin.

Fei Ge Man *Southwest Synthetic, China.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Fei Ge Na *Qilu, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Fei Ke Gan Te *Hualong, China.*
Oxymatrine.

Fei Ke Mai Kang *Hualong, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fei Ke Tan *Yinhu, China.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Fei Ke Wei Kang *Hualong, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Fei Ke Xin Kang *Hualong, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Fei Li Gu *Haochuang, China.*
Vitamin B6 (p. 2105·3).

Fei Li Xing *GuoGuang, China.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Fei Lin *Zhong Bao, China.*
Papaverine hydrochloride (p. 2362·3).

Fei Lu De *Jianfeng, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Fei Ning *Huabang, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Fei Ning Da *C & O, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Fei Si Te *Tongliao, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); caffeine (p. 1203·3).

Fei Su *Kangxin, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Fei Te *Yuhuang, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Fei Te Ai Si *Kang Yuan, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Fei Ting *Kangxin, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Fei De Xing *ShiJiaZhuang No 4, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Fei Xun Qi *Hailing, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Fei Ya Ning *Lianshui, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Fei Yan *Yung Shin, China.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Fei Yue *Yuhuang, China.*
Polypeptides; hypoxanthine.

Feiba *BaxterImmuno, Arg.; Baxter, Austria; Baxter, Belg.; Baxter, Braz.; Baxter, Canad.; Baxter, Chile; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Israel; Baxter, Ital.; Baxter, Malaysia†; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Pol.; Baxter, Port.; Baxter, Rus.; Adcock Ingram Critical Care, S.Afr.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter BioScience, UK; Immuno, USA.*
A factor VIII inhibitor bypassing fraction (p. 1149·2).
Haemorrhagic disorders; haemophilia A.

Feidile *United Lab, China.*
⊗Paracetamol (p. 115·1); triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); caffeine (p. 1203·3); salicylamide (p. 129·2).
Cold and influenza symptoms.

FeiLin *Hengshan, China.*
Fenoprofen calcium (p. 59·2).
Musculoskeletal and joint disorders.

Feimin *Hailing, China; Yangtze River, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Feisaile *Wellso, China.*
Phencynonate hydrochloride.
Motion sickness.

Feisclin *Arlex, Mex.*
Clindamycin (p. 269·3).
Acne.

FeiTe *Tapfond, China.*
Zidovudine (p. 1024·2).
HIV infection.

Feiz *Dewcare, India.*
Adapalene (p. 1692·1); clindamycin (p. 269·3).
Acne.

Fejet *Venus, India.*
Injection: Folic acid (p. 2063·1); hydroxocobalamin (p. 2107·3); iron (p. 2073·1).

Venus, India.
Suspension: Iron carbonyl (p. 2073·1); copper sulfate (p. 2057·2); vitamin B substances (p. 2102·3); manganese sulfate (p. 2081·2); potassium iodide (p. 2336·3); zinc sulfate (p. 2126·2).

Fejet-IV *Venus, India.*
Iron (p. 2073·1).

Fejet-OD *Venus, India.*
Docusate sodium (p. 1836·2); vitamins; copper (p. 2057·1); iodine (p. 2336·3); iron (p. 2073·1); selenium (p. 2086·3); zinc (p. 2126·1).

Fekair *PDC, India.*
Ferrous fumarate (p. 2060·3) or ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Feklon *Klonal, Arg.*
Ferrous sulfate (p. 2062·2).
Iron supplement.

Feksine *Drogsan, Turk.*
Fexofenadine hydrochloride (p. 629·1).

Felanor *LKM, Arg.†*
Clonazepam (p. 519·1).
Anxiety; epilepsy.

Felbamyl *Schering-Plough, Arg.*
Felbamate (p. 522·1).
Epilepsy.

Felbatol *Wallace, USA.*
Felbamate (p. 522·1).
Epilepsy.

Felcam *Sun, India; Mugi, Indon.; Asian Pharm, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Felcar *Medipharm, Chile.*
Fluconazole (p. 578·2).
Fungal infections.

Feldanax *Geolab, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; dysmenorrhoea.

Feldegel *Pfizer, Spain.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Felden *Pfizer, Austria; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Switz.; Pfizer, Turk.*
Piroxicam (p. 125·3).
Pain; inflammation; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Feldene *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; SinGad, Denm.†; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Thai.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Piroxicam (p. 125·3).
Pain; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; fever; inflammation.

Feldène *Pfizer, Fr.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Feldenedi *Pfizer, Venez.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; pain; gout.

Feldex *Sun, India.*
Piroxicam betadex (p. 126·1).
Musculoskeletal and joint disorders; gout; pain.

Feldixid *Galenium, Indon.†*
Benzoyl peroxide (p. 1696·1); sulfur (p. 1721·1).
Acne.

Felexin *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Singapore; Remedica, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Felfar *Faran, Gr.*
Magaldrate (p. 1856·1).
Antacid.

Felgesic *Bangkok Lab & Cosmetic, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Feliberal *Silanes, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; myocardial infarction; angina pectoris.

Felicam *Chinta, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Felicita-OD *Intas, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); chromium polynicotinate (p. 2056·1); inositol (p. 2533·2); mecobalamin (p. 2108·1).

Felicium *Stada, Austria.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Felim *Sandoz, Philipp.†; Sandoz, Thai.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Felina *Naturale, Philipp.*
Vaginal lubricant.
Vaginal dryness and pain.

Felini *Maneesh, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Felipgel-F *Farmaceutica H, Mex.*
Calcitriol (p. 2113·1).
Hypocalcaemia; osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Felipram *Crinos, Ital.*
Citalopram hydrobromide (p. 411·1).
Depression; anxiety disorders.

Felis *Hexal, Braz.†; Hexal, Ger.†; Ilsan, Turk.†*
St John's wort (p. 449·1).
Depression; nervous disorders.

Feliselin *Rafarm, Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Felisio *Sandoz, Cz.†*
St John's wort (p. 449·1).
Depression.

Felison *Bayer, Ital.*
Flurazepam monohydrochloride (p. 1076·1).
Insomnia.

Felix
Note: this name may be used for preparations of different composition.
Elpen (Ελπεν), Gr.
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Positif, India.
Cefpodoxime.
Bacterial infections.

Felixene *Quimifar, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Feliximir *Krugher, Ital.*
Citalopram hydrobromide (p. 411·1).
Depression; anxiety disorders.

Felixina *Indeco, Arg.*
Fluoxetine (p. 417·1).
Depression.

Felixita *Theramex, Mon.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Feliz *Torrent, India.*
Citalopram (p. 411·1).
Depression; bipolar disorder; panic disorder.

Torrent, Philipp.
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder; bulimia.

Feliz-S *Torrent, India.*
Escitalopram (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Feliz-S Plus *Torrent, India.*
Clonazepam (p. 519·1); escitalopram (p. 416·2).

Fellafit *Sahabat, Indon.*
Shark cartilage (p. 2471·3).
Joint disorders.

Felnox *Utopian, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Felo *Mylan, NZ.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Felobeta *Betapharm, Ger.*
Felodipine (p. 1380·3).
Hypertension.

Felobits *Duncan, Arg.*
⊗Atenolol (p. 1308·2).
Hypertension.

Felocor
Note: this name may be used for preparations of different composition.
Hexal, Cz.; Hexal, Ger.†
Felodipine (p. 1380·3).
Hypertension.

Nucitec, Mex.
Fenofibrate (p. 1381·1); folic acid (p. 2063·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus with hyperlipidaemias; cardiovascular risk reduction in patients with diabetes mellitus.

Feloday *AstraZeneca, Ital.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Felodil *Aspen, Austral.; Sandoz, Switz.†*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Felodin *Pharmacodane, Denm.*
Felodipine (p. 1380·3).
Hypertension.

Felodip *Ivax, Rus.; Teva, Ukr.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Felodistad *Stada, Austria.*
Felodipine (p. 1380·3).
Hypertension.

Felodur *AstraZeneca, Austral.*
Felodipine (p. 1380·3).
Hypertension.

Felogamma *Worwag, Ger.*
Felodipine (p. 1380·3).
Hypertension.

Felogard *Cipla, Hong Kong; Cipla, India.*
Felodipine (p. 1380·3).
Hypertension.

Felogel *Sopharma, Pol.*
Diclofenac (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Felohexal *Hexal, Pol.†; Sandoz, Thai.†; Sandoz, Ukr.†*
Felodipine (p. 1380·3).
Hypertension.

Felop *Shou Chan, Philipp.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Felopine *Berlin Pharm, Thai.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Felo-Puren *Actavis, Ger.†*
Felodipine (p. 1380·3).
Hypertension.

Felosma *Bernofarm, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Feloten *Biolab, Thai.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Felotens *Genus, UK.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Felow *Munir, Turk.*
Losartan potassium (p. 1422·2).

Felox *Gracia, Indon.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Felpac *Inpac, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Felpin *Taiwan Biotech, Philipp.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Felrox *Seng, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Felsol *Pasteur, Chile.*
Fluconazole (p. 578·2).
Fungal infections.

Felvosin *Nucleus, Denm.†*
Levofloxacin (p. 315·3).
Bacterial infections.

Felxicam *SSP, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Fem 7 *Merck, Braz.; Merck, Chile; Merck Serono, China; Theramex, China; Abbott, Ger.; Merck, Indon.†; Merck, Mex.; Merck, Neth.†; Richter, Pol.; Merck, Turk.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Fem 7 Combi *Abbott, Ger.*
Phase I, estradiol (p. 2271·1); phase II, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Merck, Chile.
Phase 1, estradiol (p. 2271·1); phase 2, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders; osteoporosis.

Richter, Pol.
Phase I patch, estradiol (p. 2271·1); phase II patch, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Fem 7 Conti *Abbott, Ger.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

Fem Ducha *Arex, Venez.*
Acetic acid (p. 2426·3).
Maintenance of vaginal pH.

Fem pH *Pharmics, USA.*
Glacial acetic acid (p. 2426·3); hydroxyquinoline sulfate (p. 2530·1).
Vaginal disorders.

Fem Plus 50 *Tecnonat, Arg.*
Soya isoflavones (p. 2620·3); selenium (p. 2086·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3).
Dietary supplement.

Fem 7 Sequi *Merck, Neth.†*
Patch I, estradiol (p. 2271·1); patch II, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Fema *Nakornpatana, Thai.*
Diclofenac diethylamine (p. 48·3).

Femadiol *Mepha, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femafit *Kalbe, Indon.; Sanghiang, Indon.*
Nutritional supplement for women with isoflavones.

Femal *Natumin, Malaysia; Natumin, Singapore.*
Pollen extracts (p. 2593·3).
Premenstrual syndrome; menopausal symptoms.

Femal Balans *Antula, Swed.*
Pollen extracts (p. 2593·3).
Premenstrual syndrome; menopausal symptoms.

Female Formula *Watkins, Canad.*
Vitamins; minerals.

Female Y *Douglas, Canad.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1).

Femalon *Silesia, Chile.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Femanest *Sandoz, Denm.; Meda, Swed.*
Estradiol (p. 2271·1).
Oestrogen deficiency; osteoporosis; menopausal disorders.

Femanor *Sandoz, Denm.; Meda, Swed.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Oestrogen deficiency; osteoporosis; menopausal disorders.

Femapak *Solvay, UK.†*
Combination pack: Patches, estradiol (p. 2271·1) (Fematrix); tablets, dydrogesterone (p. 2270·1) (Duphaston).
Menopausal disorders; osteoporosis.

Femapirin *Chefaro, Neth.†*
Ibuprofen (p. 68·2).
Fever; pain.

Femaplex *Genepharm, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Femaprin *Omega, Spain.†*
Ibuprofen (p. 68·2).
Pain; fever.

Femar *Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
⊗Letrozole (p. 817·1).
Breast cancer.

Femara *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Orifarm, Denm.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Orifarm, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
⊗Letrozole (p. 817·1).
Breast cancer.

Fémara *Novartis, Fr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Femarate *Pharmasant, Thai.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Femarelle *Valioravinto, Fin.; Lavipharm, Gr.; Konet, Hong Kong; Svizera, India; Teva, Israel†; Arcon, Norw.; Rx Pharma, Singapore; Seid, Spain; Electi, Swed.; CDL, UK; IFS, USA.*
Linseed (p. 2544·2); DT56a (p. 2620·3).
Dietary supplement; menopausal disorders; osteoporosis.

Femasekvens *Sandoz, Denm.; Meda, Swed.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Oestrogen deficiency; osteoporosis; menopausal disorders.

Femaston *Solvay, Gr.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Hormone replacement therapy.

Fematab *Abbott, Irl.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Fematrix *Solvay, UK.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Fe-Max *Mediherb, Austral.*
Codonopsis pilosulae root; urtica (p. 2639·3); liquorice (p. 1853·2); ashwagandha (p. 2450·2); ginger (p. 1844·1); stevia rebaudiana (p. 2214·2); vitamins; iron amino acid chelate (p. 2048·3).
Tonic.

Femazole Duo *Aspen, Austral.*
Capsule, fluconazole (p. 578·2); cream, clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Femcal-500 *Fem Care, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Femcef *Fem Care, India.*
Cefixime (p. 240·3).
Bacterial infections.

Femcinol-A *Fem Care, India.*
Clindamycin phosphate (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Femcon Fe *Warner Chilcott, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, ferrous fumarate (p. 2060·3).
Formerly known as Ovcon 35 Fe.
Combined oral contraceptive.

Femcort *Fem Care, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Fem-E *Nutri-Advance, Singapore.*
Red clover (p. 2482·1).
Menopausal symptoms.

Femease *Robinson, UK.*
Self-heating adhesive pad.
Dysmenorrhoea.

Femed *Comed, India.*
Syrup: Iron polymaltose (p. 2077·2); vitamin B_{12} (p. 2107·2).

Comed, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Femelle
Note: this name may be used for preparations of different composition.
2care4, Denm.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gynopharm, Chile.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femen *Osotspa, Thai.*
Mefenamic acid (p. 85·3).
Pain.

femena *Hexal, Ger.†*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Femenal *Wyeth, Philipp.†*
Ethinylestradiol (p. 2275·3); norgestrel (p. 2296·1).
Combined oral contraceptive; dysfunctional uterine bleeding; endometriosis.

Femena-Z *Haledew, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Femendol *Biotech Naturis, Venez.*
Chamomile (p. 2474·1); piscidia (p. 2536·3); valerian (p. 2640·2).
Menstrual cramps.

Femerital *Interlogim, Neth.†*
Ambucetamide (p. 2440·3); paracetamol (p. 115·1); caffeine hydrate (p. 1203·3).
Dysmenorrhoea.

Fem-Estroplex *Metagenics, Canad.†*
Vitamins.

Femexin *Elea, Arg.; Elea, Mex.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

FemHRT *Warner Chilcott, Canad.; Warner Chilcott, USA.*
Ethinylestradiol (p. 2275·3); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Femi *Sanol, Ger.; UCB, Ger.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femi Forte *Charak, India.*
⊗Indian barberry (p. 2532·1); cuminum cyminum; tribulus terrestris (p. 2633·3); withania somnifera (p. 2450·2).

Femiane *Bayer, Arg.; Bayer, Braz.; Schering, Venez.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Femibel *Silesia, Chile.†*
Esterified oestrogens (p. 2270·3).
Menopausal disorders; osteoporosis.

Femibion 400 *Merck, Ukr.*
Tablets, vitamins; iodine (p. 2336·3); capsules, docosahexaenoic acid (p. 1460·1); vitamin E (p. 2119·1).
Dietary supplement.

Femibion 800 *Merck, Ukr.*
Vitamins; iodine (p. 2336·3).
Dietary supplement.

Femibion Flore Intime *Merck Medication Familiale, Fr.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3).
Restoration of vaginal flora.

Femibion Grossesse *Merck Medication Familiale, Fr.*
Vitamins; iodine (p. 2336·3).
Dietary supplement for conception and pregnancy.

Femibion Maman Active *Merck Medication Familiale, Fr.*
Vitamins; minerals; *Lactobacillus gasseri* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Dietary supplement.

Femic *Inpac, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Femicaps *Zuoz, Venez.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Femicare *Mint, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Femicept *Famy, Denm.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femicin Tisane pour reins/vessie *Vifor, Switz.†*
Bearberry (p. 2453·2); chamomile (p. 2474·1).
Urinary-tract disorders.

Femicine *Vifor, Switz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femicontin *Speciality Meditech, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Femicur *Schaper & Brummer, Norw.†; MaxMedica, Swed.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Femicur N *Schaper & Brummer, Ger.*
⊗Agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Femi-cyl L Ho-Len-Complex *Liebermann, Ger.*
Cocculus (p. 2483·1); lachesis (p. 2538·3); nux vomica (p. 2573·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Femidause *PNS, Canad.†*
Calcium citrate (p. 1783·2); magnesium citrate (p. 1857·1); vitamin D (p. 2112·3).

Femide *Macrophar, Thai.*
⊗Furosemide (p. 1387·1).
Fluid retention and hypertension in chronic renal failure; oedema.

Femiderm *Novartis, Chile.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Femidin *Taj, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Femidolor *Sandoz, Turk.*
Naproxen sodium (p. 98·2).

Femidot *Novartis, Chile.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Femigel *Medi Challenge, S.Afr.*
Estradiol (p. 2271·1).
Menopausal disorders.

Femigen *2care4, Denm.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femigest *USP, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Femigestrol *Bergamo, Braz.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer.

Femigoa *Pfizer, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femigyne *Ratiopharm, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femihexal *Hexal, Cz.†*
Medroxyprogesterone acetate (p. 2288·1).
Breast cancer; endometrial cancer.

Femijel *Kocak, Turk.*
Estradiol (p. 2271·1).

Femikliman uno *Hexal, Ger.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femilar *Bayer Schering, Fin.*
Cyproterone acetate (p. 2261·2); estradiol valerate (p. 2271·2).
Biphasic oral contraceptive.

Femilla *Steigerwald, Ger.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femi-loges *Loges, Ger.*
Rhapontic rhubarb (p. 1884·2).
Menopausal disorders.

Femilon *Organon, India.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fémilyane *Biorga, Fr.†*
Soap substitute.
Personal hygiene.

Femina
Note: this name may be used for preparations of different composition.
Ache, Braz.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.
General Drug, Philipp.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron-deficiency anaemia; folate deficiency.
Uniphar, India.
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Femina Lactal *CTS, Israel.*
Lactic acid (p. 2539·1); glycogen (p. 2519·2).
Maintenance of vaginal flora.

Feminabiane Conception *Pileje, Fr.*
Tablets, minerals; vitamins; capsules, fish oil (p. 1460·1).
Dietary supplement for conception and pregnancy.

Feminabiane Confort Urinaire *Pileje, Fr.*
Cinnamon (p. 2479·2); cranberry (p. 2488·1).
Urinary discomfort.

Feminabiane Cycle Féminin *Pileje, Fr.*
Borage oil (p. 2459·2); evening primrose oil (p. 2502·2).
Menstrual disorders.

Feminabiane Méno'Confort *Pileje, Fr.*
Borage oil (p. 2459·2); camelina oil; linseed (p. 2544·2); vitamins.
Menopausal disorders.

Féminac *Spirig, Switz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent alopecia, hirsutism, and seborrhoea in women.

Feminalin *Farma Lepori, Spain.†*
Ibuprofen (p. 68·2).
Fever; pain.

Femi-Nan *Eagle, Austral.*
⊗Cimicifuga (p. 2478·1); agnus castus (p. 2432·2); red clover (p. 2482·1); tribulus terrestris (p. 2633·3); dong quai (p. 2497·1); wild yam (p. 2648·1); ashwagandha (p. 2450·2); rehmannia glutinosa; St John's wort (p. 449·1); sage (p. 2608·3); pulsatilla (p. 2600·2); sepia (p. 2613·1); capsella bursa-pastoris (p. 2614·2).
Menopausal disorders.

Feminax
Note: this name may be used for preparations of different composition.
Bayer, Irl.; Roche Consumer, UK.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); hyoscine hydrobromide (p. 1845·3).
Dysmenorrhoea.
Konimex, Indon.†
Paracetamol (p. 115·1); hyoscyamine (p. 1848·1).
Pain.

Feminax Ultra *Bayer, UK.*
Naproxen (p. 98·2).
Dysmenorrhoea.

Femin-Do *Grasler, Ger.*
Aletris farinosa; cyclamen (p. 2490·2); helonias dioica (p. 2524·3); magnesium phosphoricum (p. 1787·3); viburnum opulus.
Homoeopathic preparation.

Feminease *Parnell, USA.*
Vaginal moisturising and lubricating cream with eriodictyon (p. 1665·2).

Feminella *Viofar, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Feminelle *Vifor, Switz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Feminesse *Anglian, UK.*
⊗Sorbic acid (p. 1770·2); glycerol (p. 2517·2); liquid paraffin (p. 2191·2); polycarbophil (p. 1879·1).
Vaginal odour.

Feminet *Dexcel, Israel.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Feminex *Sante Naturelle, Canad.*
Vitamins; minerals.

Feminil *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Norw.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Combined oral contraceptive in women with androgenic symptoms.

Feminine Herbal Complex *GNLD, Austral.*
⊗Wild yam root (p. 2648·1); red sage (p. 2608·3); St John's wort (p. 449·1); vitex agnus castus (p. 2432·2); alchemilla vulgaris; dong quai (p. 2497·1); skullcap (p. 2617·1); ginger (p. 1844·1); taraxacum (p. 2625·3); liquorice (p. 1853·2).
Menstrual disorders.

Feminique *QHP, USA.*
Vinegar (p. 2426·3).
Vaginal disorders.

Feminity *Klonal, Arg.*
Ibuprofen (p. 68·2); hyoscine butylbromide (p. 1845·3).

Feminoflex *Medicus, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Feminol *Laboratorios Chile, Chile.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Feminon A *Cesra, Ger.*
⊗Agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Feminon C *Cesra, Ger.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Feminon N *Cesra, Ger.*
⊗Pulsatilla pratensis (p. 2600·2); vitex agnus castus (p. 2432·2); cimicifuga racemosa (p. 2478·1); phosphorus (p. 2589·2); calcium carbonicum (p. 1824·3).
Homoeopathic preparation.

Feminon PMS *Cesra, Pol.*
⊗Agnus castus (p. 2432·2).
Premenstrual symptoms.

Feminova *Merck, Belg.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Feminova Plus *Merck, Belg.*
Phase I patch, estradiol (p. 2271·1); phase II patch, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Feminova-T *Silesia, Chile.†*
⊗Esterified oestrogens (p. 2270·3); methyltestosterone (p. 2291·3).
Menopausal disorders; osteoporosis.

Feminvit *Ativus, Braz.*
Vitamins; minerals.

Femiplant *PlantaPhile, UK.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femiplante *Farmasierra, Spain.†*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Femiplex *Charak, India.*
⊗Cuminum cyminum; tribulus terrestris (p. 2633·3).

Femiplus
Note: this name may be used for preparations of different composition.
Silesia, Chile.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
The 28-day pack also contains 7 inert tablets.
Combined oral contraceptive.

Femipol *Polfa Pabianice, Pol.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Femipres *UCB, Ital.*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Femipres Plus *UCB, Ital.*
⊗Moexipril hydrochloride (p. 1440·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Femiprim *Armstrong, Mex.*
Ascorbic acid (p. 2110·3).
Bacterial vaginosis; maintenance of vaginal flora and pH.

Femiron *Menley & James, USA.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Femisan
Note: this name may be used for preparations of different composition.
Grossman, Mex.
Ketoconazole (p. 585·3); clindamycin phosphate (p. 269·3).
Vaginitis.
Kern, Switz.
Sweet orange (p. 2576·2); melissa (p. 2552·3); cactus (p. 2473·2); lavender (p. 2541·1); coriander (p. 2486·3); crataegus (p. 2488·1); fennel (p. 2503·2); anserina; passion flower (p. 2584·1); valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Femisana mens *Cheplapharm, Ger.†*
⊗Agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Femisic *Caprifarmindo, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Femistad *Stada, Denm.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Femitab *Prodeal, Canad.†*
Vitamins; minerals.

Femitan *Schwabe, Hung.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femitres *Silesia, Chile.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive; menstrual disorders.

Femity *Theramex, Ital.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

Femixol *Omega, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Femizet *Fresenius Kabi, Thai.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Femizol
Note: this name may be used for preparations of different composition.
Sagmel, Rus.
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.
Douglas, Austral.†
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Femizol-M *Lake, USA.†*
Miconazole nitrate (p. 589·1).
Fungal vaginal infections.

Femm *Muscle Marketing, Canad.†*
Pantothenic acid (p. 2085·2); cyanocobalamin (p. 2107·2).

Femmactive *Le Naturiste, Canad.*
Vitamins; minerals.

Femme
Note: this name may be used for preparations of different composition.
Ache, Braz.
Vitamins; minerals.
Nanjing Baijingyu, Philipp.
21 tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Femme com Flúor *Ache, Braz.*
Vitamins; minerals; sodium fluoride (p. 2089·2).

Femme Fólico *Ache, Braz.*
Folic acid (p. 2063·1).

Femme Free *Ascent, Austral.*
Naproxen (p. 98·2).
Dysmenorrhoea.

Femme Plus *Aus Biomed, Austral.†*
Tuna oil (p. 2098·2); vitamins; minerals.
Dietary supplement in pregnancy and breast feeding.

Femme-F *Aus Biomed, Austral.*
⊗Agnus castus (p. 2432·2); camellia sinensis (p. 2648·2); selenium (p. 2086·3); vitamins; zinc amino acid (p. 2048·3).
Female infertility; premenstrual syndrome.

FemmeVit *Pharmadass, UK.*
Vitamins; minerals; nutritional supplememts.
Premenstrual syndrome.

Femmex Plus *Konsuma, Venez.*
Ibuprofen (p. 68·2).
Dysmenorrhoea.

Femmexultra *Konsuma, Venez.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain; inflammation.

Fem-Mono *Mylan, Denm.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Femodeen *Bayer, Neth.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Femoden *Bayer Schering, Cz.; Bayer Schering, Fin.; Bayer Schering, Hung.; Bayer Schering, Pol.; Bayer Schering, Rus.; Bayer, Ukr.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Femoden ED *Bayer, Austral.†*
21 Tablets, ethinylestradiol (p. 2275·3); gestodene (p. 2279·3); 7 tablets, inert.
Combined oral contraceptive.

Femodene *Bayer, Belg.; Bayer, NZ; Bayer, UK.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Femodene ED *Bayer Schering, S.Afr.*
21 Tablets, ethinylestradiol (p. 2275·3); gestodene (p. 2279·3); 7 tablets, inert.
Combined oral contraceptive.

Femodette *BB, Ital.; Bayer, UK.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Femolin PMS *Tribest, S.Afr.†*
Evening primrose oil (p. 2502·2); vitamins; minerals.
Dietary supplement.

Femom *Agio, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Femorel *Elea, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Femorel Max *Elea, Arg.*
1 Tablet, ibandronate sodium (p. 1184·2); 30 tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Femosa
Note: this name may be used for preparations of different composition.
Mega Lifesciences, Thai.
Cimicifuga (p. 2478·1).
Menopausal disorders; premenstrual syndrome.
Pyridam, Indon.
Cimicifuga (p. 2478·1); red clover (p. 2482·1); isoflavone (p. 2620·3); tyrosine (p. 2098·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); calcium (p. 1783·1); vitamin D (p. 2112·3).
Menopausal disorders; osteoporosis; hypercholesterolaemia.

Femoston *Abbott, Austral.; Solvay, Austria; Solvay, Belg.; Abbott, Braz.; Grunenthal, Chile; Abbott, China; Abbott, Cz.; Abbott, Fin.; Abbott, Ger.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Indon.; Abbott, Irl.; Solvay, Ital.; Solvay, Malaysia; Abbott, Neth.; Abbott, NZ; Solvay, Philipp.†; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Abbott, Singapore; Abbott, Switz.; Solvay, UK; Abbott, Ukr.; Zuoz Solvay, Venez.*
14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.
Solvay, Turk.
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).

Femoston 1/5 *Solvay, Port.; Solvay, Rus.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Femoston 1/10 *Abbott, Thai.*
14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Femoston Conti *Solvay, Austria; Solvay, Belg.; Abbott, Braz.; Grunenthal, Chile; Abbott, Cz.; Abbott, Fin.; Abbott, Ger.; Solvay, Hong Kong†; Abbott, Irl.; Solvay, Ital.; Solvay, Malaysia; Solvay, Pol.; Solvay, S.Afr.; Abbott, Singapore;*

Abbott, Switz.; Abbott, Thai.; Abbott, UK; Zuoz Solvay, Venez.
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Femoston Continu *Abbott, Neth.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Femoston Mini *Solvay, Cz.; Solvay, Pol.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders.

Femoston mono *Abbott, Ger.; Abbott, Switz.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Femovan *Bayer, Ger.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Femozol *Perrigo, Israel.*
⊗Letrozole (p. 817·1).
Breast cancer.

Fem pack *Pfizer, Arg.*
Tablets, estradiol valerate (p. 2271·2); capsules, progesterone (p. 2300·2).
Menopausal disorders; osteoporosis.

Fem Patch *Parke, Davis, USA.*
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency.

Femphascyl *Abbott, Neth.*
14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; dydrogesterone (p. 2270·1).
Oestrogen deficiency; osteoporosis.

Femphascyl Continu *Abbott, Neth.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Fempress *Actavis, Ger.*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Fempress Plus *Actavis, Ger.*
⊗Moexipril hydrochloride (p. 1440·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fempro *Cipla, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Femranette mikro *Aliud, Ger.†*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Femring *Galen, Port.†; Warner Chilcott, USA.*
Estradiol acetate (p. 2271·1).
Menopausal disorders.

Femsedin Kutz *Quimica y Farmacia, Mex.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Femsel *Elmor, Venez.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Femsept *Theramex, Mon.*
Estradiol (p. 2271·1).
Menopausal disorders.

FemseptCombi *Theramex, Mon.*
Patch 1, estradiol (p. 2271·1); patch 2, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Femseptevo *Theramex, Mon.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

Femsete *Theramex, Port.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Femsete Combi *Theramex, Port.*
Phase 1 patch, estradiol (p. 2271·1); phase 2 patch, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Femsete Evo *Theramex, Port.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

FemSeven *Merck, Austria; Ratiopharm, Fin.; Gedeon Richter, Hung.†; Bracco, Ital.; Merck, UK; Merck, Venez.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

FemSeven Combi *Merck, Austria.*
Phase 1 patch, estradiol (p. 2271·1); phase 2 patch, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Merck, Fin.†; Gedeon Richter, Hung.†
Patch 1, estradiol (p. 2271·1); patch 2, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

FemSeven Conti *Merck Serono, Irl.; Merck, UK.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

FemSeven Sequi *Merck Serono, Irl.†; Merck, UK.*
Phase 1, estradiol (p. 2271·1); phase 2, estradiol; levonorgestrel (p. 2296·1).
Menopausal disorders.

Femstrual *Manx, UK.*
Tranexamic acid (p. 1164·2).
Menorrhagia.

Femtozette *Helm, Cz.†*
⊗Letrozole (p. 817·1).
Breast cancer.

Femtrace *Warner Chilcott, USA.*
Estradiol acetate (p. 2271·1).
Menopausal disorders.

Femtran *iNova, Austral.; 3M, NZ.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Femular *Flordis, Austral.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Femulen *Pharmacia, NZ†; Pfizer, UK.†*
Etynodiol diacetate (p. 2277·3).
Progestogen-only oral contraceptive.

Femurest-Conti *Abbott, Irl.*
Estradiol (p. 2271·1); dydrogesterone (p. 2270·1).
Menopausal disorders; osteoporosis.

Femzole *Adcock Ingram, S.Afr.*
⊗Letrozole (p. 817·1).

Fen Le *ZhongXi, China.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus; malaria.

Fen Ke Jing *Kaiyuan, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Fen Li *Anlian, China.*
Dexketoprofen (p. 79·1).

Fen Li Tong *Shi Xin, China.*
Sodium ferulate.

Fen Na Ke *Jiang Kang, China.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Fen Di Ning *De Zhou, China.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Fen Su *Yangtze River, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Fenabbott *Armstrong, Mex.†*
Phenobarbital (p. 535·2).
Epilepsy.

Fenac *Alphapharm, Austral.; Sunward, Hong Kong; Claris, India; LBS, Malaysia; Sunward, Singapore; LBS, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Neves, Port.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fenacaine *LBS, Thai.*
Diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Fever; inflammation; pain; gout.

Fenace *Invision, India.*
Paracetamol (p. 115·1).
Pain; fever.

Fenace Plus *Invision, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Fenacil *Macrophar, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal and joint disorders.

Fenacop *Orifarm, Denm.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation.

Fenacor *Taj, India.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenac-P *PC India, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Fenacta *Actavis, Denm.*
Diclofenac potassium (p. 48·3).
Pain; fever.

Fenactil *Polfa Warszawa, Pol.; Unia, Pol.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; withdrawal syndromes; nausea and vomiting; hiccup; premedication; porphyria; extrapyramidal disorders.

Fenactol *Discovery, UK.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenadec MR *Pure Health, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Fenadec Plus *Maneesh, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Fenadef *Dong Wha, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Fenadin *BMW, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fenadium *Sunward, Hong Kong; Sunward, Singapore.*
Diclofenac sodium (p. 48·3).
Pain; gout; musculoskeletal and joint disorders; inflammation.

Fenadol *Proge, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.

Fenafex *Eadriex, Philipp.; Sriprasit, Thai.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fenaflan *Teuto, Braz.*
Diclofenac diethylamine (p. 48·3) or diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Fenagel *Mavi, Mex.*
Diclofenac (p. 48·3).
Inflammation.

SM, Thai.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Fenagesic *Sunward, Singapore.*
Mefenamic acid (p. 85·3).
Pain.

Fenahex *Sandoz, Philipp.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Fen-Alcon *Alcon, Philipp.†*
Chloramphenicol (p. 257·1).
Eye infections.

Fenalgin
Note: this name may be used for preparations of different composition.
Tocogino, Mex.
Diclofenac (p. 48·3).
Inflammation; pain.

Fenam
Note: this name may be used for preparations of different composition.
Lamda (Λαμδα), Gr.
Etofenamate (p. 57·2).
Inflammation; pain.

Fenamic
Note: this name may be used for preparations of different composition.
Captab, India.
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Siam Bheasach, Thai.
Mefenamic acid (p. 85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenamide *Farmigea, Ital.*
⊗Diclofenamide (p. 2006·3).
Glaucoma.

Fenamin
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Mefenamic acid (p. 85·3).
Musculoskeletal, joint, and soft-tissue disorders; dysmenorrhoea.

Christo, Hong Kong.†
Promethazine (p. 638·2).

Fenamon *Medochemie, Malaysia; Medochemie, Rus.†; Medochemie, Singapore†; Medochemie, Thai.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; heart failure; myocardial infarction; pulmonary hypertension.

Fenantoin *Recip, Swed.*
Phenytoin (p. 538·2).
Epilepsy.

Fenaplus *Modi-Mundipharma, India.†*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; inflammation; pain.

Fenaplus-MR *Modi-Mundipharma, India.†*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Painful muscle spasm; premenstrual syndrome.

Fenaplus-RX *Modi-Mundipharma, India.*
Diclofenac potassium (p. 48·3); metaxalone (p. 2025·2).
Musculoskeletal and joint disorders.

Fenardin *ICN, Pol.*
Fenofibrate (p. 1381·1).
Hypercholesterolaemia.

Fenaren *Uniao Quimica, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac sodium (p. 48·3), or diclofenac resinate (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Bernofarm, Indon.†
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint and peri-articular disorders.

Fenasol *Losan, Denm.*
Ibuprofen potassium (p. 68·2).
Pain, fever.

Fenaspec *Pharmaspec, Philipp.*
Diclofenac sodium (p. 48·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Fenasthma *Biokem, Turk.*
⊗Sodium benzoate (p. 1738·2); ephedrine hydrochloride (p. 1663·2); potassium iodide (p. 2336·3).
Respiratory-tract disorders.

Fenastma *Kaz, Turk.*
Potassium iodide (p. 2336·3); sodium benzoate (p. 1738·2); theophylline (p. 1229·3).

Fenatec *Belfar, Braz.*
⊗Fenoterol (p. 1208·2).

Fenatic *Promed, Indon.*
Ibuprofen (p. 68·2).
Pain; fever.

Fenatil *Neo Quimica, Braz.*
Clomipramine hydrochloride (p. 412·1).

Fenatrop *Gador, Arg.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal spasm.

Fenatrop-A *Gador, Arg.†*
Trimebutine maleate (p. 2634·1); bromazepam (p. 1041·2).
Gastrointestinal disorders.

Fenavel *Novell, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint and peri-articular disorders; gout; pain; inflammation.

Fenax *Andromaco, Chile.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Fenazid *Pharmsintez, Rus.*
Isoniazid ferrous sulfate dihydrate complex.
Tuberculosis.

Fenazil *Sella, Ital.*
Promethazine hydrochloride (p. 638·2).
Allergic skin reactions.

Fenazin *Synco, Hong Kong†; Synco, Singapore.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; sedative; motion sickness.

Fenazol *Abbott, Jpn.*
Ufenamate (p. 141·3).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fenazox *Meiji, Jpn.*
Amfenac sodium (p. 20·3).
Pain; inflammation.

Fenbest *Maneesh, India.*
Diclofenac (p. 48·3).
Inflammation; pain.

Fenbest MR *Maneesh, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Fenbest P *Maneesh, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Fenbest Plus *Maneesh, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Fenbid *GSK, China; Vianex (Βιανεξ), Gr.; Goldshield, UK.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever; musculoskeletal, joint, and soft-tissue disorders.

Fenbid Fenka Pian *GSK, China.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Fenburil *De Mayo, Braz.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Fencel *Celon, India.*
Phenylephrine hydrochloride (p. 1672·3).
Hypotension; paroxysmal supraventricular tachycardia.

Fenceta *Alkem, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Fencol *Ind-Swift, India.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Fendase *Siomond, India.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Fender *Krugher, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation.

Fendi *Mayinglong, China.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fendibina *Northia, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastrointestinal haemorrhage; acid aspiration.

Fendic Plus *Zee, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Fendical *UCI, Braz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fendil
Note: this name may be used for preparations of different composition.
Sinochem, Philipp.
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; renal and biliary colic.

Synco, Hong Kong.†
⊗Codeine (p. 40·2); ephedrine (p. 1663·1); promethazine (p. 638·2).
Cough.

Fendin *Ranbaxy, S.Afr.†*
Terfenadine (p. 640·3).
Hypersensitivity reactions.

Fendiprazol *Northia, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Fendivia *Nycomed, Rus.; Nycomed, Spain.*
⊗Fentanyl (p. 60·1).
Pain.

Fendrix *GSK, Belg.; GSK, Cz.; GSK, Denm.†; GSK, Fr.†; GSK, Ger.; GSK, Gr.; GSK, Irl.; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Port.; GSK, Spain; GSK, Swed.; GSK, UK.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Fendrop *Sun, India.*
⊗Fentanyl (p. 60·1).
Analgesia in anaesthesia; premedication.

Fendyl *Jean-Marie, Hong Kong.*
⊗Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough; cold symptoms.

Fenebra *Pisa, Mex.*
Lamotrigine (p. 527·2).
Epilepsy.

Fenemal *DLF, Denm.; SAD, Denm.; Nycomed, Norw.; Recip, Swed.*
Phenobarbital (p. 535·2).
Epilepsy; withdrawal syndromes; pre-eclampsia; status epilepticus.

Fenergan *Sanofi-Aventis, Arg.; Vitoria, Port.*
Promethazine hydrochloride (p. 638·2).
Allergic rhinitis; allergic conjunctivitis; insomnia; urticaria; pruritus; insect bites.

Sanofi-Aventis, Braz.
Promethazine (p. 638·2).
Hypersensitivity reactions.

Fenergan Expectorante *Sanofi-Aventis, Braz.; Teofarma, Spain.*
Promethazine hydrochloride (p. 638·2); sulfogaiacol (p. 1678·1); ipecacuanha (p. 1667·2).
Upper-respiratory-tract disorders.

Fenergan Topico *Teofarma, Spain.*
Promethazine (p. 638·2).
Cutaneous hypersensitivity reactions.

Fenesin *GPO, Thai.*
Guaifenesin (p. 1666·2).
Cough.

Fenesin DM *Pharma Medica, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Fenezal *Sandoz, Austral.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting; sedative.

Fenfedrin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; cold symptoms.

Feng Le *Asia Pioneer, China.*
Ethylenediamine diaceturate.

Feng Di *Hengrui, China.*
Cefoselis sulfate (p. 244·1).

Feng Du *Si Huan, China; Wellso, China.*
Naloxone hydrochloride (p. 1562·3).
Acute alcohol intoxication.

Feng Da Qi *Asia Pioneer, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Feng Hai Fen *Zhengda Fenghai, China.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Feng Hai Lu *Zhengda Fenghai, China.*
⊗Mannitol (p. 1427·3).

Feng Hai Neng *Zhengda Fenghai, China.*
Fructose (p. 2068·2).

Feng Hai Ping *Zhengda Fenghai, China.*
Fructose (p. 2068·2); sodium chloride (p. 1795·1).

Feng Hai Qing *Zhengda Qingchunbao, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disorders.

Feng Hai Tan *Zhengda Fenghai, China.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Feng Hai Ting *Zhengda Fenghai, China.*
Racecadotril (p. 1881·3).

Feng Ke Nai *Asia Pioneer, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Feng Lai *Hengrui, China.*
⊗Paracetamol (p. 115·1); clemastine fumarate (p. 622·3); pseudoephedrine hydrochloride (p. 1676·1).

Feng Lang *Hengrui, China.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye congestion.

Feng Li Fu *Asia Pioneer, China.*
Rifamycin sodium (p. 354·3).
Bacterial infections including tuberculosis.

Feng Lin *Yao Wang, China.*
Ethylenediamine diaceturate.

Feng Nuo *Fenghuang, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Feng Rui *Yangtze River, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Feng Tong Ding *Poly, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Feng Yu Li *Xinzhongzheng, China.*
Ligustrazine phosphate.

Fengam *Pharmasant, Thai.†*
Tiaprofenic acid (p. 137·1).
Musculoskeletal, joint, and soft-tissue disorders; pain; inflammation; gout.

Fengdaxin *Asia Pioneer, China; Shanghai Pharma, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fengel
Note: this name may be used for preparations of different composition.
Maneesh, India.
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Fengkelin *Asia Pioneer, China; Shanghai Pharma, China.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Fengkesong *Asia Pioneer, China; Shanghai Pharma, China.*
Liposomal amphotericin B (p. 569·2).
Fungal infections.

Fengpaixin *Asia Pioneer, China; Shanghai Pharma, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Fengsaixing *Asia Pioneer, China; Shanghai Pharma, China.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Fengtailing *Asia Pioneer, China; Shanghai Pharma, China.*
Tazobactam sodium (p. 369·3); piperacillin sodium (p. 340·1).
Bacterial infections.

Fengtixin *Asia Pioneer, China; Shanghai Pharma, China.*
Cefotiam (p. 246·1).
Bacterial infections.

Fengzhuxin *Asia Pioneer, China; Shanghai Pharma, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Fengzhuye *Asia Pioneer, China; Shanghai Pharma, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Feniallerg *Novartis Consumer, Switz.*
Dimetindene maleate (p. 626·1).
Hypersensitivity reactions.

Fenibu *Helm, Port.†*
Ibuprofen (p. 68·2).
Pain; fever.

Fenicol *Armoxindo, Indon.; Offenbach, Mex.; Pharmasant, Thai.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Fenicort *Jelfa, Pol.*
⊗Prednisolone sodium tetrahydrophthalate (p. 1645·2).
Corticosteroid.

Fenidantoin S *Italmex, Mex.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Fenidex *Allergan, Braz.*
⊗Dexamethasone (p. 1630·3); chloramphenicol (p. 257·1); tetryzoline hydrochloride (p. 1678·3).
Infected eye disorders.

Fenidin *Merkez, Turk.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Respiratory-tract congestion.

Fenidina *Boniscontro & Gazzone, Ital.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Feniffler *Loeffler, Mex.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy.

Fenigramon *Gramon, Arg.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Fenigyl *Finecure, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Fenil *Tan, India.*
Paracetamol (p. 115·1).
Pain; fever.

Fenilate *Svizera, India.*
⊗Fentanyl (p. 60·1).
Analgesia in anaesthesia; premedication.

Fenilup *Framingham, Arg.*
Phenylalanine (p. 2086·1).
Depression; pain; tonic.

Fenil-V *Vitoria, Port.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis; neuralgia; gout; pain.

Fenim *Bactolac, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Feninox *Gunsa, Turk.†*
Dipyrone (p. 53·3).
Fever; pain.

Fenipic *Novartis Consumer, Switz.*
Aluminium acetotartrate (p. 2440·1); mepyramine maleate (p. 635·1); lidocaine hydrochloride (p. 1988·2).
Insect bites.

Fenipred *Atlas, Arg.*
⊗Prednisolone sodium phosphate (p. 1645·3); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Fenipsorian *Novartis Consumer, Neth.†*
Calcipotriol (p. 1697·2).
Psoriasis.

Fenirax *Multilab, Braz.*
Dexchlorpheniramine maleate (p. 621·1).

Fenisal
Note: this name may be used for preparations of different composition.
Macrophar, Thai.
Baclofen (p. 2014·3).
Skeletal muscle spasticity.

Fenisol *Reuffer, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Fenisole *Novartis Consumer, Switz.†*
Diclofenac sodium (p. 48·3).
Sunburn.

Fenisona *Phoenix, Arg.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis.

Fenistil
Note: this name may be used for preparations of different composition.
Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Cz.; Novartis Consumer, Ger.; Novartis, Gr.; Novartis Consumer, Hung.; Novartis, Indon.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Neth.; Novartis, Philipp.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, Spain; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis Consumer, Ukr.
Dimetindene maleate (p. 626·1).
Hypersensitivity reactions; pruritus; urticaria; insect bites; sunburn; allergic skin disorders; burns; allergic rhinitis; premedication.

Novartis Consumer, UK.
Penciclovir (p. 1008·2).
Herpes labialis.

Fenistil Hydrocort *Novartis Consumer, Ger.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Fenistil Penciclovir *Novartis Consumer, Neth.*
Penciclovir (p. 1008·2).
Herpes labialis.

Fenistil Pencivir *Novartis Consumer, Ger.†; Novartis Consumer, Rus.; Novartis Consumer, Ukr.*
Penciclovir (p. 1008·2).
Herpes labialis.

Fenisun *Novartis Consumer, S.Afr.; Novartis Consumer, Switz.*
Diclofenac sodium (p. 48·3).
Sunburn.

Fenit *Antibioticos, Mex.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fenital *Cristalia, Braz.*
Phenytoin (p. 538·2).
Epilepsy.

Fenitan *Pharmis, Port.*
Phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias associated with digitalis toxicity.

Fenitenk *Biotenk, Arg.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Fenitin *Oboi, Philipp.*
Phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia; arrhythmias; seizures.

Fenitina *Leovan, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Feniton *Teuto, Braz.*
Phenytoin (p. 538·2).
Epilepsy.

Fenitron *Psicofarma, Mex.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Fenivir *Novartis Consumer, Austria; Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Port.; Novartis Consumer, S.Afr.†; Novartis Consumer, Spain; Novartis Consumer, Switz.*
Penciclovir (p. 1008·2).
Herpes labialis.

Fenizolan *Velvian, Ger.*
Fenticonazole nitrate (p. 578·1).
Vulvovaginal candidiasis.

Fenizzard *Pizzard, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Fenlips *Novartis, Israel.*
Penciclovir (p. 1008·2).
Herpes labialis.

Fenn *Sriprasit, Thai.†*
Paracetamol (p. 115·1).
Fever; pain.

Fenna *Haledew, India.*
Syrup: Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Haledew, India.
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Fennic *Picco, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Fennikang *Southwest, China.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Fennings Childrens Cooling Powders *Anglian, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Fennings Little Healers *Anglian, UK.*
Ipecacuanha (p. 1667·2).
Formerly known as Jacksons Little Healers.
Coughs.

Feno *YSP, Malaysia.*
⊗Fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Fenobarb *Samarth, India.*
Phenobarbital (p. 535·2).
Seizures; sedative; hypnotic.

Fenobate *East West, India.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenoben *Celon, India.*
Phenoxybenzamine (p. 1468·1).

Fenobest *Best, Mex.*
⊗Tamoxifen (p. 860·2).
Breast cancer; endometrial cancer.

Fenobeta *Betapharm, Ger.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenobrat *PharmaSwiss, Gr.; PharmaSwiss, Hung.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenobrate *Sanofi-Aventis, Arg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenocin *Actavis, Indon.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Fenoclof *Pharmanel, Gr.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Fenocor *Ordain, India.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenocris *Cristalia, Braz.*
Phenobarbital (p. 535·2) or phenobarbital sodium (p. 535·3).
Epilepsy; sedation; premedication; insomnia; anxiety; hyperbilirubinaemia.

Fenodid *Pisa, Mex.*
⊗Fentanyl citrate (p. 60·1).
General anaesthesia; neuroleptanalgesia.

Fenof *ACME, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenofanton *Juta, Ger.†; Q-Pharm, Ger.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenofex *Ranbaxy, S.Afr.*
Fexofenadine (p. 629·1).

Fenofitop *Topgen, Belg.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenofix *Ingers, Cz.*
Fenofibrate (p. 1381·1).
Hypercholesterolaemia.

Fenoflex *Imperial, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenogal *SMB, Belg.; SMB, Philipp.; Galephar, Turk.; Genus, UK.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenogal Lidose *SMB, Singapore.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenogel *Basi, Port.†*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fenoglide *Santarus, USA.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenokodin *Adeka, Turk.†*
Syrup: ⊗Codeine (p. 40·2); ephedrine hydrochloride (p. 1663·2); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2).
Respiratory-tract congestion.

Adeka, Turk.†
Tablets: Codeine (p. 40·2); ethylmorphine (p. 56·3).
Respiratory-tract congestion.

Fenokomp 39 *Knop, Chile.*
Phenolphthalein (p. 1877·3); citric acid (p. 2480·3); nux vomica (p. 2573·3); belladonna (p. 2453·3).
Constipation.

Fenolaks *Radyum, Turk.*
Sodium bicarbonate (p. 1781·1); phenolphthalein (p. 1877·3).
Constipation.

Fenolax *ICN, Cz.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Fenolip *GL Pharma, Austria; Cipla, India.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Angelini, Port.
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis; allergic conjunctivitis.

Fenomas *Masterfarm, Spain.†*
Ibuprofen lysine (p. 68·3).
Pain; fever; musculoskeletal and joint disorders.

Fenomax *Cipher, Canad.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenomed *Mediorals, Thai.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Feno-Micro *Pro Doc, Canad.; Apotex, Hung.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenopine *Pinewood, Irl.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenopron *Typharm, UK.*
Fenoprofen calcium (p. 59·2).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; pain.

Fenora *Neiss, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Fenora-SF *Neiss, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Fenoratio *Ratiopharm, Pol.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenorin *Lek, Cz.; Lek, Hung.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Fenorit *Scharper, Ital.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Fenosimed *Nucleus, Cz.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fenospin *Pharmadiet, Spain.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Fenostat *Ordain, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenosup *SMB, Belg.; SMB, Fin.; SMB, Malaysia; SMB, Singapore; SMB, Thai.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenoswiss *PharmaSwiss, Hung.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fenotec-Z *Rusan, India.*
Iron carbonyl (p. 2073·1); zinc (p. 2126·1); vitamins.

Fenotral *Munir, Turk.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; motion sickness; vertigo.

Fenovent *Cipla, India.*
⊗Fenoterol (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Fenox
Note: this name may be used for preparations of different composition.
Abbott, Thai.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Knoll, India†; Rolfe, S.Afr.
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline nitrate (p. 1669·3).
Nasal congestion; sinusitis.

Thornton & Ross, UK.
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Fenoxene *Samarth, India.*
Phenoxybenzamine hydrochloride (p. 1468·1).
Phaeochromocytoma; neuropathic bladder.

Fenoxil *Biomep, Mex.*
Nimesulide (p. 101·3).
Pain.

Fenozan *Zambon, Braz.†*
⊗Fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Fenpaed *AFT, NZ; Pinewood, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Fenpic *Zambon, Port.*
Ibuprofen (p. 68·2).
Pain; fever.

Fenris *Interbat, Indon.*
Ibuprofen (p. 68·2).
Fever; pain.

Fensaid
Note: this name may be used for preparations of different composition.
Piramal, India.
Diclofenac (p. 48·3).
Pain; inflammation.

Fensaide *Piramal, India.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Fensaide-P *Piramal, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; pain.

Fensartan *Elea, Arg.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Fensartan D *Elea, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fensedyl *Bernabo, Arg.*
Oxatomide (p. 636·3).
Hypersensitivity reactions.

Fenserr *3a, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Fenshida *Xingsha, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Fensik *Mugi, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Fensipros *Pharos, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Fenspogal *Galena, Pol.*
Fenspiride hydrochloride (p. 1209·2).
Respiratory-tract disorders.

Fenstud *Rusan, India.*
⊗Fentanyl (p. 60·1).
Analgesia in anaesthesia; premedication.

Fent *Neon, India.*
⊗Fentanyl citrate (p. 60·1).
Analgesia in anaesthesia; premedication.

Fenta *Rafa, Israel.*
⊗Fentanyl (p. 60·1).
Pain.

Fenta MX *Sandoz, Pol.*
⊗Fentanyl (p. 60·1).
Pain.

Fentabbott *Abbott, Braz.*
⊗Fentanyl citrate (p. 60·1).
Anaesthesia.

Fentadolon *Mibe, Ger.*
⊗Fentanyl (p. 60·1).
Pain.

Fentadur *Lavipharm, Gr.; Pfizer, Irl.*
⊗Fentanyl (p. 60·1).
Pain.

Fentagesic *Teva, Cz.†; Pliva Krakow, Pol.*
⊗Fentanyl (p. 60·1).
Pain.

Fentahexal *Hexal, Cz.†; Sandoz, Pol.†*
⊗Fentanyl (p. 60·1).
Pain.

Fental
Note: this name may be used for preparations of different composition.
Nexus, Gr.
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Rowex, Irl.
⊗Fentanyl (p. 60·1).
Pain.

Fentalim *Angelini, Ital.*
⊗Alfentanil hydrochloride (p. 18·2).
General anaesthesia; neuroleptanalgesia.

Fentalis *Sandoz, Cz.; Sandoz, UK.*
⊗Fentanyl (p. 60·1).
Pain.

FentaMat *Sandoz, Ger.†*
⊗Fentanyl (p. 60·1).
Pain.

Fentamed *DeltaSelect, Austria.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Fentamorf *Janssen-Cilag, Gr.*
⊗Sufentanil citrate (p. 132·3).

Fentanest *Cristalia, Braz.; Pfizer, Ital.; Janssen-Cilag, Mex.; Janssen, Port.*
⊗Fentanyl citrate (p. 60·1).
Analgesia during anaesthesia; neuroleptanalgesia; general anaesthesia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kern, Spain.
⊗Fentanyl (p. 60·1).
Analgesia during anaesthesia; premedication.

Fentanor *Samarth, India.*
Phentolamine (p. 1468·3).
Phaeochromocytoma; dermal necrosis associated with intravenous infusion of noradrenaline.

Fentaplast *GL Pharma, Austria.*
⊗Fentanyl (p. 60·1).
Pain.

Fentatienil *Angelini, Ital.*
⊗Sufentanil citrate (p. 132·3).
General anaesthesia; neuroleptanalgesia.

Fentatil *Janssen-Cilag, Braz.*
⊗Fentanyl citrate (p. 60·1).
Analgesia during anaesthesia; neuroleptanalgesia.

Fentax *Richmond, Arg.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Fentaxina *Casasco, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Fentazin *Goldshield, Irl.; Goldshield, UK.*
Perphenazine (p. 1095·3).
Anxiety; psychoses; nausea; vomiting; psychomotor agitation; excitement; behaviour disorders.

Fentina *LKM, Arg.*
Memantine hydrochloride (p. 393·1).

Fentizol *Ache, Braz.*
Fenticonazole nitrate (p. 578·1).
Fungal infections.

Fento *Blubell, India.*
Diclofenac sodium (p. 48·3).
Pain.

Fentoin *Sun, India.*
Phenytoin (p. 538·2).
Epilepsy.

Fentoinal *Roemmers Rowe, Venez.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy.

Fentora *Cephalon, USA.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Fentoron *Ratiopharm, Austria.*
⊗Fentanyl (p. 60·1).
Pain.

Fentra *BMW, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Fentrex *USV, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Fentrinol *Fresenius Kabi, Austria.*
⊗Amidefrine mesilate (p. 1655·3).
Rhinitis.

Fentul *Ivax, Arg.†*
Ifosfamide (p. 806·1).
Testicular cancer.

Fénugrène *Legras, Fr.*
Fenugreek (p. 2504·1).
Appetite stimulant.

Fenules *Ranbaxy, Rus.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Ranbaxy, Ukr.†
Ferrous sulfate (p. 2062·2); thiamine nitrate (p. 2103·2); riboflavin (p. 2104·3); nicotinamide (p. 2083·1); calcium pantothenate (p. 2085·2); pyridoxine hydrochloride (p. 2105·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; vitamin B deficiency.

Fenules Baby *Ranbaxy, Ukr.†*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Fenules Complex *Ranbaxy, Rus.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia; iron deficiency.

Fenules Zinc *Ranbaxy, Rus.*
Ferrous sulfate (p. 2062·2); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); zinc sulfate (p. 2126·2).
Dietary supplement.

Fenuril *ACO Hud, Fin.; ACO Hud, Swed.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Fenuril-Hydrokortison *ACO Hud, Swed.*
⊗Urea (p. 1727·3); hydrocortisone (p. 1640·1).
Eczema.

Fenvel *Crinos, Ital.*
⊗Fentanyl (p. 60·1).

Fenyklový Čaj *Megafyt-R, Cz.*
Fennel (p. 2503·2).
Gastrointestinal disorders; catarrh.

Fenylat *Acino, Neth.*
⊗Fentanyl (p. 60·1).
Pain.

Fen-y-Tos *Nordin, Mex.*
Drosera (p. 2497·2); tolu balsam (p. 1679·2).
Cough.

Fenzone Forte *Zee, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Fenzoxe Forte *Zee, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Feocyte *Dunhall, USA.*
Iron (p. 2073·1); liver extracts (p. 2444·1); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); copper (p. 2057·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Feofer *Alna, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Feofol *Vianex (Biazvež), Gr.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

FeoGen *Rising Pharmaceuticals, USA.*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); stomach extract (p. 2444·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

FeoGen FA *Rising Pharmaceuticals, USA.†*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); folic acid (p. 2063·1).
Anaemias.

Feonat *Natco, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

Feonat-Z *Natco, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Feosol *Invida, Philipp.; Meda, USA.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Feospan *Intrapharm, Irl.; Intrapharm, UK.*
Dried ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; iron deficiency.

Feovit *Dynamic, Philipp.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Fep *Madhav, India.*
Paracetamol (p. 115·1).
Pain; fever.

Fepamol *Vensat, India.*
Paracetamol (p. 115·1).
Pain; fever.

Fepanil *Citadel, India.*
Paracetamol (p. 115·1).
Pain; fever.

Feparil *Rottapharm, Spain.*
Topical gel: Diethylamine salicylate (p. 51·3); aescin (p. 2431·2).
Peripheral vascular disorders; soft-tissue injury.

Fephar *Biophar, India.*
Syrup: Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Biophar, India.
Tablets: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Fepiram *Ferron, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; alcoholism.

Fepot *Unimarck, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Fepra *Triton, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis 406 Covers Fepra and Fepra-SR.

Fepra-P *Triton, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Feprax *Ferron, Indon.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Fepril *Idaman, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Feprorex *Medix, Mex.*
⊗Fenproporex hydrochloride (p. 2323·1).
Obesity.

Feprox *Solitaire, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Fer-200 *Hua, Thai.†*
Ferrous fumarate (p. 2060·3); vitamins; calcium phosphate (p. 1784·2).
Anaemias.

Fer Actavis *Actavis, Fr.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Fer AP-HP *AGEPS, Fr.*
Ferrous sulfate (p. 2062·2).

Fer Mylan *Mylan, Fr.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Fer Sandoz *Sandoz, Fr.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Fer UCB *Pierre Fabre Sante, Fr.*
Ferrous chloride (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Fera *Aspen, Austral.*
⊗Letrozole (p. 817·1).
Breast cancer.

Feraheme *Takeda, Canad.; AMAG, USA.*
Ferumoxytol (p. 2063·1).
Iron-deficiency anaemia in chronic kidney disease.

Feraken *Kendrick, Mex.†*
Moclobemide (p. 437·2).
Depression.

Feralice *Alapis, Gr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Feramat *Tripharma, Turk.*
Ferrous fumarate (p. 2060·3).

FeraMAX *BioSyent, Canad.*
Polysaccharide-iron complex (p. 2086·2).
Iron deficiency.

Ferane 35 *Mabra, Braz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Feranid *Intra-Labs, India.*
Syrup: Sodium feredetate (p. 2088·3).

Intra-Labs, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Ferasep *Systopic, India.*
Feracrylum.

Ferasul *APT, Hong Kong.†*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Feratab *Upsher-Smith, USA.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferate Tabs *Major, USA.*
Ferrous gluconate (p. 2061·2).
Iron deficiency.

Ferazin *Shince, India.*
Syrup: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3).

Shince, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Ferbeaplex *Beacons, Singapore.*
Dried ferrous sulfate (p. 2062·2); thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); nicotinamide (p. 2083·1).
Iron-deficiency anaemia; iron deficiency.

Ferbisol *Bial, Spain.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency.

Fercalmin *Utopian, Thai.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium phosphate (p. 1784·2).
Dietary supplement.

Fercayl *Sterop, Belg.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Fercee *Armoxindo, Indon.*
Ferrous fumarate (p. 2060·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron. Docusate sodium (p. 1836·2) is included to reduce the constipating effects of iron.
Iron-deficiency anaemia.

Fercovit *Andromaco, Chile.*
Ferrous fumarate (p. 2060·3); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); vitamins.
Dietary supplement.

Ferdek *Ranbaxy, Thai.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Ferdotax *Feron, India.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Ferdromaco *Andromaco, Arg.*
Ferrous succinate (p. 2062·1).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Fered *Wallace, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Fered-C *Wallace, India.*
Capsules: Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Wallace, India.
Suspension: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Fereg-F *Life Medicare, India.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Fereg-Z *Life Medicare, India.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Ferepat *Coup, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fer-Essence *EuroHealth, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); riboflavin (p. 2104·3); cyanocobalamin (p. 2107·2).
Anaemias; tonic.

Ferfoz Plus *FDC, India.*
Syrup: Sodium feredetate (p. 2088·3).

FDC, India.
Tablets: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); sodium feredetate (p. 2088·3).

Ferganic *Roemmers Osmoph, Venez.*
Iron protein.
Anaemias.

Ferganic Folic *Roemmers Osmoph, Venez.*
Iron protein; folic acid (p. 2063·1).
Anaemia in pregnancy and lactation.

Fer-gen-sol *Goldline, USA.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Fergesol *IAE, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron or folic acid deficiency.

Ferglobin
Note: this name may be used for preparations of different composition.
Pharmacare, Philipp.
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Pure Health, India.
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Ferglow *Biochem, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin C (p. 2110·3).

Fergon
Note: this name may be used for preparations of different composition.
Winthrop Consumer, USA.
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Fergonad-C *Feron, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Fergonad-F *Feron, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Fergonad-M *Feron, India.*
⊗Menotrophin (p. 2284·1).

Ferher *Emar, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Feribest-L *Psychotropics, India.*
Lycopene (p. 2546·2); cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin C (p. 2110·3).

Feric Grow *Kevin, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Ferich
Note: this name may be used for preparations of different composition.
Maneesh, India.
Syrup: Cyanocobalamin (p. 2107·2); iron polymaltose (p. 2077·2).

Maneesh, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Pure Health, India.
Oral drops: Iron polymaltose (p. 2077·2).

Pure Health, India.
Slow-release capsules: Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

Fericip *Cipla, India.*
Capsules; chewable tablets: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Cipla, India.
Oral drops; syrup: Iron polymaltose (p. 2077·2).
Iron deficiency.

Cipla, India.
Capsules: Folic acid (p. 2063·1); iron (p. 2073·1); vitamins.

Fericos-XT *Symbiosis, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Feric-Z *Admac, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamins.

Ferid
Note: this name may be used for preparations of different composition.
Adley, India.
Oral drops; syrup: Iron polymaltose (p. 2077·2).

Adley, India.
Tablets: Folic acid (p. 2063·1); iron (p. 2073·1).

Uniao Quimica, Braz.
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Bacterial skin infections.

Ferid-C *Adley, India.*
Capsules: Iron (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Adley, India.
Syrup: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Feridex *Eiken, Jpn†; Bayer, USA.*
Ferumoxides (p. 1584·2).
Contrast medium for magnetic resonance imaging of the liver.

Feriena *Sienna, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Ferifer
Note: this name may be used for preparations of different composition.
Berko, Turk.
Iron polymaltose (p. 2077·2).

Streger, Mex.
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferigil *Argil, India.*
Iron polymaltose (p. 2077·2).

Ferimax
Note: this name may be used for preparations of different composition.
Bilim, Turk.
Iron polymaltose (p. 2077·2).

Novaduo, India.
Injection: Folic acid (p. 2063·1); hydroxocobalamin (p. 2107·3); iron sorbitol (p. 2077·3).

Novaduo, India.
Oral drops: Sodium feredetate (p. 2088·3).

Novaduo, India.
Syrup: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); sodium feredetate (p. 2088·3).

Novaduo, India.
Tablets: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); sodium feredetate (p. 2088·3); zinc (p. 2126·1).

Ferine *Constant, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ferinject *Vifor, Austral.; Vifor, Austria; Vifor, Cz.; Vifor, Denm.; Vifor, Fin.; Vifor, Fr.; Vifor, Ger.; Vifor, Gr.; Vifor, Irl.; CTS, Israel; Vifor, Neth.; Vifor, Norw.; Vifor, Port.; Vifor, Singapore; Vifor, Spain; Renapharma, Swed.; Vifor, Switz.; Vifor, UK.*
Ferric carboxymaltose (p. 2060·1).
Iron deficiency.

Ferinova *Lupin, India.*
Vitamin B substances (p. 2102·3); iron (p. 2073·1) or ferrous glycine sulfate (p. 2061·3).

Fer-In-Sol *BMS, Arg.; Mead Johnson, Braz.; Mead Johnson Nutritionals, Canad.; Mead Johnson, Chile; BMS, Gr.; BMS, Irl.; Mead Johnson, Ital.; BMS, Mex.; Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.†; BMS, Venez.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia; iron supplement.

Ferion *Orion, Cz.; Orion, Pol.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Feripro *Cachet, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Feripro-Z *Cachet, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Fer-Iron *Rugby, USA.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferisafe *UniOrange, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Ferisan
Note: this name may be used for preparations of different composition.
Invision, India.
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Synco, Hong Kong.†
Ferrous sulfate (p. 2062·2).
Anaemia.

Ferisan-S *Invision, India.*
Iron (p. 2073·1).

Ferisis *Alembic, India.*
Vitamins; iron carbonyl (p. 2073·1); selenium (p. 2086·3); zinc oxide (p. 1729·1).

Feristar
Note: this name may be used for preparations of different composition.
Medinova, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Novaduo, India.
Injection: Iron sucrose (p. 2078·1).

Ferisym-XT *Symbiosis, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Feritas *Intas, India.*
Syrup: Iron polymaltose (p. 2077·2).

Intas, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Feritin *Ind-Swift, India.*
Oral drops; syrup: Iron (p. 2073·1).

Ind-Swift, India.
Tablets: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).

Feritol *Themis Medicare, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).

Feritrin *Dexa, Indon.*
Iron polymaltose (p. 2077·2); vitamin B substances (p. 2102·3); vitamin D (p. 2112·3); calcium lactate (p. 1784·1); copper sulfate (p. 2057·2); potassium iodide (p. 2336·3). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia; nutritional supplement.

Ferium *Emcure, India.*
Capsules; tablets: Iron (p. 2073·1) or iron polymaltose (p. 2077·2); folic acid (p. 2063·1).

Emcure, India.
Chewable tablets; oral drops; syrup: Iron (p. 2073·1) or iron polymaltose (p. 2077·2).

Pasteur, Chile; Emcure, Thai.
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Ferium Tab *Emcure, India.*
Iron (p. 2073·1); folic acid (p. 2063·1).

Ferium-C *Emcure, India.*
Iron (p. 2073·1) or iron polymaltose (p. 2077·2); folic acid (p. 2063·1); vitamin C (p. 2110·3).

Ferium-XT *Emcure, India.*
Iron (p. 2073·1); folic acid (p. 2063·1).

Feriv *GES, Spain.*
Iron sucrose (p. 2078·1).
Iron deficiency.

FeRiva *Avion, USA.*
Iron (p. 2073·1); vitamins.
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Ferive *Dominguez, Arg.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Feriz *Ritz, India.*
Iron (p. 2073·1).

Ferizest *DWD, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Feriz-SF *Ritz, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Ferizyme *Ikon, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Ferlatum *Lifepharma, Ital.; Italfarmaco, Rus.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Ferlatum Fol *Italfarmaco, Rus.*
Iron succinyl-protein complex (p. 2077·3); calcium folinate (p. 2066·3).
Iron and folate deficiency.

Ferlette *QX, Philipp.*
Buclizine hydrochloride (p. 618·3); ferrous fumarate (p. 2060·3); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Appetite stimulant; tonic.

Ferlex *Arlex, Mex.*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Ferli-6 *Continental Pharma, Thai.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Anaemia; vitamin and iron supplement.

Ferlin *Medifarma, Indon.; Pediatrica, Indon.*
Iron (p. 2073·1); vitamin B substances (p. 2102·3).
Nutritional supplement.

Pediatrica, Philipp.
Oral drops: Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia.

Pediatrica, Philipp.
Syrup: Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia.

Ferlixit *Sanofi-Aventis, Ital.*
Sodium ferric gluconate complex (p. 2089·1).
Anaemias; iron deficiency.

Ferlos *Santa, Turk.*
Oral solution: Iron polymaltose (p. 2077·2).

Santa, Turk.
Tablets: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).

Fermalac *Rosell, Canad.†; Rosell, Ukr.*
Lactobacillus rhamnosus (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3).
Restoration of vaginal flora; diarrhoea.

Fermalac Vaginal *Rosell, Canad.; Rosell, Cz.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Adjunct in treatment of vaginal infections; maintenance of normal vaginal flora.

Fermasian *Asian Pharm, Thai.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Fermate *Kenyaku, Thai.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Fermathron *Merck, Braz.; Biomet, Ger.; Biomet Merck, UK.*
Sodium hyaluronate (p. 2526·2).
Degenerative disorders of the knee and other joints; osteoarthritis of the knee.

Fermavisc *OmniVision, Switz.*
Sodium hyaluronate (p. 2526·2).
Contact lens lubricant.

FerMed
Note: this name may be used for preparations of different composition.
Medice, Austria; Medice, Ger.; Medice, Spain.
Iron sucrose (p. 2078·1).
Iron deficiency.

Fermed
Note: this name may be used for preparations of different composition.
Bajamed, Mex.
Cefaclor (p. 232·3).
Bacterial infections.

Mediline, Israel.
Iron sucrose (p. 2078·1).
Iron deficiency.

Fermento *Adeka, Turk.*
⊗Pancreatin (p. 2579·3); dimeticone (p. 1886·2).

Fermento duodenal *Hommel, Ger.†*
⊗Pancreatin (p. 2579·3).
Digestive enzyme deficiency disorders.

Fermentol *Church & Dwight, Canad.*
⊗Pepsin (p. 2586·1).
Dyspepsia without hyperacidity; oral vehicle.

Fermenturto-Lio *Teknofarma, Ital.*
Lactobacillus bulgaricus (p. 2596·3); *Lactobacillus casei* (p. 2596·3).
Maintenance of gastrointestinal flora.

Fermetone Composto *Angelini, Port.*
⊗Bile extract (p. 2457·2); simeticone (p. 1886·2); hemicellulase (p. 2473·1); pancreatin (p. 2579·3).
Digestive disorders.

Fermig *Raam, Mex.*
Sumatriptan succinate (p. 679·2).
Migraine.

Fermil *Arrow, Austral.†*
⊗Clomifene citrate (p. 2259·1).
Female infertility.

Fern *Cadila, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1); *Lactobacillus sporogenes* (p. 2596·3).

Fernadin *Liferpal, Mex.*
Ferrous fumarate (p. 2060·3).
Anaemias.

Fern-C *FERN, Philipp.*
Sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Ferobid-Z *Sterkem, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ferobion *Erlimpex, Indon.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals; lysine hydrochloride (p. 2079·3); sorbitol (p. 2092·1).
Anaemias.

Ferocid *Admac, India.*
Iron polymaltose (p. 2077·2).

Ferocorp *Chandra Bhagat, India.*
Iron sucrose (p. 2078·1).

Ferodan *Odan, Canad.*
Ferrous sulfate (p. 2062·2).
Anaemias.

Ferofast *Alkem, India.*
Syrup: Sodium feredetate (p. 2088·3).

Alkem, India.
Tablets: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); sodium feredetate (p. 2088·3); zinc (p. 2126·1).

Ferofate *Jaapharm, Canad.†*
Ferrous sulfate (p. 2062·2).

Fero-Folic *Teoforma, Gr.; Adcock Ingram, S.Afr.; Teofarma, Switz.; Abbott, USA.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) or Sodium ascorbate (p. 2111·1) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; folic acid deficiency; iron-deficiency anaemia.

Ferofort *Kalbe, Indon.*
Iron carbonyl (p. 2073·1); vitamin B substances (p. 2102·3); zinc (p. 2126·1); lysine hydrochloride (p. 2079·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Feroglobin *Vitabiotics, Hong Kong.*
Iron (p. 2073·1); vitamin B (p. 2102·3); minerals.
Anaemias.

Vitabiotics, Indon.
Capsules: Vitamin B substances (p. 2102·3); iron (p. 2073·1); zinc (p. 2126·1); copper (p. 2057·1).
Iron deficiency; tonic.

Vitabiotics, Indon.
Oral liquid: Vitamin B substances (p. 2102·3); iron (p. 2073·1); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2); lysine hydrochloride (p. 2079·3).
Iron deficiency; tonic.

Vitabiotics, UK.
Capsules: Vitamin B substances (p. 2102·3); folic acid (p. 2063·1); iron (p. 2073·1); copper (p. 2057·1); zinc (p. 2126·1).

Vitabiotics, UK.
Oral liquid: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals; honey (p. 2072·1); malt; lysine (p. 2079·3).

Feroglobin B_{12} *Vitabiotics, Cz.*
Ferrous fumarate (p. 2060·3); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin and mineral supplement.

Feroglobin Kid *Vitabiotics, Indon.*
Vitamins; minerals; iron (p. 2073·1).
Nutritional supplement.

Feroglobin-B12
Note: this name may be used for preparations of different composition.
Vitabiotics, Hung.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Formerly contained ferrous fumarate, folic acid, and vitamin B12.
Anaemias.

Vitabiotics, Rus.
Vitamins; trace elements; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Fero-Grad *Pharma Logistics, Belg.; Adcock Ingram, S. Afr.†; Abbott, USA.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) or sodium ascorbate (p. 2111·1) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Fero-Grad vitamine C *Teoforma, Fr.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Fero-Gradumet *Pharma Logistics, Belg.; Teofarma, Neth.; Teofarma, Spain.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ferokid *Kalbe, Indon.*
Iron (p. 2073·1); vitamins; magnesium (p. 1786·3); copper (p. 2057·1).
Anaemias; nutritional supplement.

Ferol *Ronava, Venez.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Ferolact *Medreich, India.*
Syrup: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); iron succinyl-protein complex (p. 2077·3); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Medreich, India.
Tablets: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Ferom Grow *Om Biotec, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Feromax
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Iron sucrose (p. 2078·1).

Saga, India.
Ascorbic acid (p. 2110·3); iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Ferome *LBS, Thai.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Feromiel *Herbaxt, Fr.†*
Honey (p. 2072·1); iron pidolate.
Nutritional supplement.

Feron
Note: this name may be used for preparations of different composition.
Gland, Philipp.
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Osper, India.
Syrup: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Osper, India.
Tablets: Iron polymaltose (p. 2077·2).

Toray, Jpn.
Interferon beta (p. 996·1).
Malignant neoplasms; hepatitis B; hepatitis C.

Ferona *Sidus, Arg.†*
⊗Fluoxymesterone (p. 2278·1); yohimbine hydrochloride (p. 2372·3); caffeine (p. 1203·3); lysine hydrochloride (p. 2079·3); vitamins; minerals.
Male impotence.

Feronal *Mylan, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Bronchospasm.

Feronerv *Ad-Drugstel, Philipp.*
Vitamin B substances (p. 2102·3); ferrous fumarate (p. 2060·3).
Anaemias; vitamin B deficiencies.

Feronez *Wintech, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Wintech, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Feronia-XT *Zuventus, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Feronyl *Bombay Tablet, India.*
Iron carbonyl (p. 2073·1); vitamins; selenium (p. 2086·3); zinc (p. 2126·1).

Feropenem *Feron, India.*
Meropenem (p. 321·3).
Bacterial infections.

Feropic-XT *Alpic, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Feroplex *Italfarmaco, Pol.*
Iron succinyl-protein complex (p. 2077·3).
Iron-deficiency anaemia.

Ferosal *Ad-Drugstel, Philipp.*
Capsules: Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Iron deficiency; iron-deficiency anaemia.

Ad-Drugstel, Philipp.
Oral drops: Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ad-Drugstel, Philipp.
Syrup: Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron deficiency; iron-deficiency anaemia.

Ferose *Cosme, India.*
Oral drops: Iron polymaltose (p. 2077·2).

Cosme, India.
Syrup: Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Cosme, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Ferose Tab *Cosme, India.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc picolinate (p. 2126·1).

Ferosig *Signova, India.*
Injection: Iron sucrose (p. 2078·1).

Signova, India.
Oral drops; suspension; tablets: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Ferosix *Pharmasant, Thai.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Iron-deficiency anaemia.

Ferotam *Pharos, Indon.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Ferotrinsic *Rugby, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); intrinsic factor (p. 2534·2); vitamin B_{12} substances (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferox *Micro, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).

Micro, India.
Syrup: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Ferozinc *East West, India.*
Ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2).

Ferplex *Bago, Arg.; Italfarmaco, China; Italfarmaco, Cz.; Elder, India; Italfarmaco, Ital.; Italfarmaco, Spain; Abdi, Turk.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Ferplex Fol *Abdi, Turk.*
Iron succinyl-protein complex (p. 2077·3); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Ferplus-B *Chew, Thai.*
Ferrous fumarate (p. 2060·3); vitamins; minerals.
Iron-deficiency anaemia; vitamin deficiency.

Ferracin *Acino, Neth.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Ferradol *Pfizer, India.†*
Ferric ammonium citrate (p. 2060·1); vitamins.
Tonic.

Ferradol Food *Pfizer, India.*
Preparation for enteral nutrition.

Ferralet 90 *Mission Pharmacal, USA.*
Iron (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron. Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Ferranem *Chemopharma, Chile.*
Ferrous sulfate (p. 2062·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability or iron.
Iron-deficiency anaemia.

Ferranim *Sanitas, Chile.*
Ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability or iron.
Iron deficiency; iron-deficiency anaemia.

Ferranin *Nycomed, Arg.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferranin Complex *Nycomed, Arg.*
Iron polymaltose (p. 2077·2); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); folic acid (p. 2063·1).
Anaemias.

Ferranina *Nycomed, Mex.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia; iron deficiency.

Ferranina Complex *Nycomed, Mex.*
Iron polymaltose (p. 2077·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Nutritional supplement; anaemias.

Ferranina Fol *Nycomed, Mex.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron-deficiency anaemias.

Ferrascorbin *Streuli, Switz.†*
Oral drops: Ferrous chloride (p. 2060·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Streuli, Switz.†
Tablets: Ferrous chloride (p. 2060·3); ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Ferrasia *Willow, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Ferrata *Help, Gr.*
Iron polymaltose (p. 2077·2).

Ferretab *GL Pharma, Austria.*
Ferrous fumarate (p. 2060·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency anaemias.

Ferretab Comp *Lannacher, Austria; GL Pharma, Cz.; Lannacher, Rus.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron and folic acid deficiency.

Ferretab Compuesto *Biol, Arg.*
Ferrous fumarate (p. 2060·3); sodium folate (p. 2063·1).
Iron and folic acid deficiency; anaemias.

Ferretts *Pharmics, USA.*
Ferrous fumarate (p. 2060·3).

Ferrevit Pronatal *Abdi, Turk.*
Vitamins; minerals.

Ferrex *Breckenridge, USA.*
Polysaccharide-iron complex (p. 2086·2).
Iron-deficiency anaemia.

Ferrex Forte *Breckenridge, USA.*
Polysaccharide-iron complex (p. 2086·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron-deficiency anaemia.

Ferrex Forte Plus *Breckenridge, USA.†*
Iron (p. 2086·2); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrex PC *Breckenridge, USA.*
Vitamins; minerals; polysaccharide-iron complex (p. 2086·2).
Nutritional supplement.

Ferrex Plus *Breckenridge, USA.*
Iron (p. 2086·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency.

Ferri *Emcure, India.*
Ferric hydroxide or iron dextran (p. 2075·3).

Emcure, Rus.
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia; iron deficiency.

Ferricol
Note: this name may be used for preparations of different composition.
Richmond, Arg.
Ferrous sulfate (p. 2062·2).
Iron supplement.

Columbia, Mex.
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron supplement.

Ferricos *Symbiosis, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2); sorbitol (p. 2092·1).

Ferricrine *Bioprofarma, Arg.†*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Ferricure *Trenker, Belg.*
Polysaccharide-iron complex (p. 2086·2).
Iron-deficiency anaemia.

Ferridal *Parggon, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Ferri-Emina *Lafare, Ital.*
Sodium ferric gluconate complex (p. 2089·1).
Anaemias; iron deficiency.

Ferri-Fol *Emcure, Rus.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron-deficiency anaemia.

Ferrifol *CTS, Israel.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Anaemias.

Ferrigot *Pasteur, Chile.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ferril *Sidhbali, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Ferrimed *Nycomed, S.Afr.*
Chewable tablets; injection; syrup: Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Nycomed, S.Afr.
Capsules: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron deficiency; iron-deficiency anaemia.

Ferrimin *Siomond, India.*
Capsules: Copper sulfate (p. 2057·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); manganese sulfate (p. 2081·2).

Siomond, India.
Syrup: Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3).

Ferrinemia *Help, Gr.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Ferrini *Ativus, Braz.*
Iron amino acid chelate (p. 2048·3).
Iron-deficiency anaemia.

Ferrini Folico *Ativus, Braz.*
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Ferripel *CTS, Israel.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferriprox *Purissimus, Arg.; Orphan, Austral.; Apotex, Austria; Swedish Orphan, Belg.; Chiesi, Braz.; Apotex, China; Apotex, Cz.; Apotex, Denm.; Apotex, Fin.; Swedish Orphan, Fr.; Swedish Orphan, Ger.; Apotex, Gr.; Apotex, Hong Kong; Quamed, Indon.; Apotex, Irl.; Lapidot, Israel; Chiesi, Ital.; Apotex, Malaysia; Swedish Orphan, Neth.; Apotex, Norw.; Healthcare Logistics, NZ; Apotex, Pol.; Apotex, Port.; Apotex, Singapore; Swedish Orphan, Spain; Swedish Orphan, Swed.; PFC, Switz.; Apotex, Thai.; Cankat, Turk.; Swedish Orphan, UK; Apo, USA.*
Deferiprone (p. 1543·1).
Iron overload.

Ferrisat *HAC, Fr.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia; iron deficiency.

Ferriseltz *Gerolimatos (Γερολυματος), Gr.*
Ferric ammonium citrate (p. 2060·1).
Contrast medium for magnetic resonance imaging.

Ferriseptil *Gedis, Ital.†*
Glutaral (p. 1753·2).
Disinfection.

Ferrister *Gedis, Ital.†*
Peracetic acid (p. 1763·1).
Instrument disinfection.

Ferrisun *Sunshine, India.*
Lysine (p. 2079·3); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Ferritamin *Abigo, Swed.†*
Vitamins; iron (p. 2073·1); caffeine (p. 1203·3).

Ferritin Complex *ABC, Ital.*
Sodium ferric gluconate complex (p. 2089·1); calcium folinate (p. 2066·3).
Anaemias.

Ferritin Oti *ABC, Ital.; ABC, Port.*
Sodium ferric gluconate complex (p. 2089·1).
Anaemias; iron deficiency; iron-deficiency anaemia.

Ferritop *Ind-Swift, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Ferritop Iron *Ind-Swift, India.*
Lysine hydrochloride (p. 2079·3); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Ferritop Iron Tonic *Ind-Swift, India.*
Sorbitol (p. 2092·1); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Ferritop Paed *Ind-Swift, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Ferritop-SR *Ind-Swift, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

Ferritop-Z *Ind-Swift, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Ferrivax *Teva, Mex.*
Ferritin (p. 2060·2).
Iron deficiency; iron-deficiency anaemia.

Ferrivax F *Teva, Mex.*
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Anaemias.

FeRRIZ *Nicholas, Indon.*
Sodium feredetate (p. 2088·3).
Iron deficiency.

Ferrlecit
Note: this name may be used for preparations of different composition.
Watson, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Israel; Sanofi-Aventis, USA.
Sodium ferric gluconate complex (p. 2089·1).
Iron deficiency; iron-deficiency anaemia.

Ferrlecit 2 *Sanofi-Aventis, Ger.*
Ferrous succinate (p. 2062·1).
Iron deficiency; iron-deficiency anaemia.

Ferro
Note: this name may be used for preparations of different composition.
Aroma, Turk.
Ferric ammonium citrate (p. 2060·1).
Iron deficiency; iron-deficiency anaemia.

GSK Consumer, Denm.
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Intra-Labs, India.
Syrup: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2); vitamin B_{12} (p. 2107·2).

Intra-Labs, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Sam-On, Israel.
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Ferro Complex *Pharmafar, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in some dosage forms to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferro Drops *Aspen, S.Afr.*
Ferrous sulfate (p. 2062·2).

Ferro Drops L *Aspen, S.Afr.*
Ferrous lactate (p. 2062·1).
Iron-deficiency anaemia.

Ferro Folic *Ingens, Arg.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Ferro Fólico *Armstrong, Mex.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Ferro Grin *Grin, Mex.†*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Anaemias.

Ferro Hepatine *Indo French, India.*
Capsules: Glycine (p. 2071·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Indo French, India.
Syrup: Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferro Sanol *Sanol, Ger.; Specifar, Gr.; GSK, Hong Kong; UCB, Spain; Aroma, Turk.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency; iron-deficiency anaemia.

Ferro sanol *UCB, Switz.*
Ferrous glycine sulfate (p. 2061·3).
Iron-deficiency anaemia; iron deficiency.

Ferro Sanol B *Aroma, Turk.*
Ferrous glycine sulfate (p. 2061·3); vitamin B substances (p. 2102·3).
Iron deficiency; iron-deficiency anaemia.

Ferro sanol comp *Sanol, Ger.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron and vitamin B deficiency; iron-deficiency anaemia.

Ferro sanol duodenal *Sanol, Ger.; UCB, Ger.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency; iron-deficiency anaemia.

Ferro sanol gyn *Sanol, Ger.; UCB, Ger.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Ferro Vitaminico *Laboratorios Chile, Chile.†*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability or iron.
Iron-deficiency anaemia.

Ferro-BC *KB, Thai.*
Ferrous sulfate (p. 2062·2); vitamin B_1 (p. 2102·3).
Dietary supplement.

Ferro-Be-Sian *Asian Pharm, Thai.†*
Ferrous gluconate (p. 2061·2); vitamins.
Iron-deficiency anaemia.

Ferrobest *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferrobet *Montavit, Austria.*
Ferrous fumarate (p. 2060·3).
Iron deficiency anaemias.

Ferro-C with B Complex *Douglas, Canad.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Ferrocal *Rekah, Israel.*
Calcium citrate (p. 1783·2); ferrous citrate (p. 2073·1).
Iron-deficiency anaemia.

Ferroce *Meyer Alian, Venez.*
Ferrous fumarate (p. 2060·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferroce B 12 *Meyer Alian, Venez.*
Ferrous sulfate (p. 2062·2); vitamin B_{12} (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrocebrina *Bajer, Arg.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Bajer, Arg.
Oral solution; syrup: Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ferrocel *Marcel, Mex.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Ferrochelate *David, India.*
Ferric ammonium citrate (p. 2060·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3).
Anaemias.

Ferrochelate-Z *David, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc (p. 2126·1).
Anaemias.

Ferrocin *Famzaschita, Rus.*
Prussian blue (p. 1572·3).
Intoxication with caesium, rubidium, or thallium radioisotopes.

Ferrocin C B12 *P & B, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Ferrocin C B12 Plus *P & B, India.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); protein; vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc gluconate (p. 2126·2).

Ferrocine *Medicine Products, Thai.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium phosphate (p. 1784·2).
Dietary supplement.

Ferrocomp *In Vitro, Hung.*
Iron (p. 2073·1); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2); cobalt (p. 2482·2); folic acid (p. 2063·1); vitamin C (p. 2110·3).

Ferrocomplex *Farmalab, Braz.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3); panthenol (p. 2582·2); liver extract (p. 2444·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferrocur *Effik, Spain.*
Iron succinyl-protein complex (p. 2077·3).
Iron-deficiency anaemia.

Ferrocyte *Eisai, Malaysia; Eisai, Singapore; Eisai, Thai.†*
Ferrous sodium citrate (p. 2073·1).
Iron-deficiency anaemia.

Ferro-Dok *Major, USA.*
Ferrous fumarate (p. 2060·3).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Iron-deficiency anaemias.

Ferrofer *Nanjing Hencer, Philipp.; Nanjing Hencer, Thai.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Ferrofit *Ind-Swift, India.*
Sorbitol (p. 2092·1); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ferro-Folgamma *Worwag, Cz.; Worwag, Hung.; Worwag, Rus.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and vitamin deficiency; anaemias; iron and folic acid supplement.

Worwag, Ger.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and vitamin deficiency.

Ferro-Folic *Abbott, Venez.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrofolin *Bayer, Ital.*
Iron succinyl-protein complex (p. 2077·3); calcium folinate (p. 2066·3).
Folic acid deficiency; iron deficiency; anaemias.

Ferro-Folsan *Desma, Ger.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Ferro-Folsan Plus *Solvay, Philipp.†*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Anaemias; iron deficiency.

Ferrogalfol *Sant Gall, Arg.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Anaemias.

Ferrogamma *Worwag, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Ferrogels Forte *Cypress, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folate deficiency.

Ferrogen *Intas, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron deficiency in pregnancy.

Ferrogen-Z *Intas, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Ferrograd *Teofarma, Ital.; Euro Registratie, Neth.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; iron deficiency.

Teofarma, Irl.; Teofarma, UK.
Dried ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferrograd C *Abbott, Austral.; Teofarma, Irl.; Teofarma, UK.*
Dried ferrous sulfate (p. 2062·2). Sodium ascorbate (p. 2111·1) is included in this preparation to increase the absorption and availability of iron.
Iron supplement; iron-deficiency anaemia.

Teofarma, Ital.; Abbott, NZ.
Ferrous sulfate (p. 2062·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferrograd Fol *Abbott, Austria.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Ferrograd Folic *Teofarma, Irl.; Abbott, Israel; Teofarma, UK.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency; iron-deficiency anaemia.

Teofarma, Hung.; Teofarma, Ital.; Abbott, NZ; Abbott, Pol.†
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; folic acid deficiency; anaemias.

Ferrograd Folico *Teofarma, Port.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Ferro-Gradumet *Abbott, Austral.; Abbott, Austria; Teofarma, Hung.; Abbott, Israel; Abbott, NZ; Abbott, Pol.†; Teofarma, Port.; Abbott, Rus.; Teofarma, Switz.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ferrogyn *SoSe, Ital.*
Ferrous gluconate (p. 2061·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferrohematogen *Farmstandart, Rus.*
⊗Ferrous sulfate (p. 2062·2); albumin (p. 1130·2); ascorbic acid (p. 2110·3); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); copper sulfate (p. 2057·2).
Iron deficiency.

Ferroin *Pisa, Mex.*
Iron dextran (p. 2075·3).
Anaemias.

Ferrolac *Bactolac, India.*
Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Ferrolecum *Zdorovje, Ukr.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Ferroliver *SM, Venez.*
Ferrous fumarate (p. 2060·3); vitamin B_1 (p. 2103·1); vitamin B_{12} (p. 2107·2); copper sulfate (p. 2057·2).
Iron-deficiency anaemia.

FerroLogic *Fresenius Medical, Cz.; Fresenius Medical, Irl.; Fresenius Medical, Neth.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Ferromalt *Knop, Chile.*
Ferrous sulfate (p. 2062·2); malt extract (p. 2080·2).
Iron deficiency; iron-deficiency anaemia.

Ferromas *Mertens, Arg.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ferromax *Weifa, Norw.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Ferrometion *Northia, Arg.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferromia *Eisai, Indon.†; Eisai, Jpn.*
Ferrous sodium citrate (p. 2073·1).
Iron-deficiency anaemia.

Ferromin *Chinta, Thai.*
Ferrous gluconate (p. 2061·2); vitamin B_{12} (p. 2107·2).
Anaemias.

Ferromina *Provita, Ital.*
Ferrous gluconate (p. 2061·2); vitamin C (p. 2110·3); magnesium stearate (p. 2195·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Nutritional supplement.

Ferromixin *Nutrigen, UK.*
Iron (p. 2073·1); vitamin A (p. 2098·3); folic acid (p. 2063·1).
Dietary supplement.

Ferron *Laborate, India.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferronal *CTS, Israel; CTS, Rus.†*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Ferronat *Ivax, Cz.†; Zentiva, Cz.†*
Ferrous fumarate (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Ferro-Nes *Nes, Israel.*
Ferrous gluconate (p. 2061·2).
Iron deficiency.

Ferronil *Teuto, Braz.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferronorm *Medifarm, Venez.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); zinc (p. 2126·1); copper (p. 2057·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron supplement; iron-deficiency anaemia.

Ferronova *Willow, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Ferro-Plan Kit *Intra-Labs, India.*
Ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); red capsules, ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); pyridoxine (p. 2105·3); blue capsules, zinc (p. 2126·1).

Ferroplex
Note: this name may be used for preparations of different composition.
Cimed, Braz.
Ferrous sulfate (p. 2062·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

JRalph, Philipp.
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); cobalt sulfate (p. 2482·2); calcium gluconate (p. 1783·3).
Anaemias; vitamin B deficiency.

Teva, Rus.
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Ferroplex-frangula *ERA, Denm.*
Ferrous tartrate (p. 2062·3); frangula bark (p. 1843·3).
Iron deficiency.

Ferropro *Medicine Products, Thai.*
Ferrous fumarate (p. 2060·3); vitamins; calcium phosphate (p. 1784·2).
Iron-deficiency anaemia.

Ferroprol *Proel, Gr.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Ferroprotina *Faes, Spain.*
Ferritin (p. 2060·2).
Iron deficiency; iron-deficiency anaemia.

Ferroral *Silesia, Chile.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Ferroral Fol *Silesia, Chile.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Iron, folic acid, and vitamin B_{12} deficiency.

Ferroral-Vit *Silesia, Chile.*
Vitamins; minerals.

Ferrosig *Sigma, Austral.; Healthcare Logistics, NZ.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia; iron deficiency.

Ferrosmate *Blue Sky, Philipp.*
Sodium feredetate (p. 2088·3).
Iron supplement.

Ferrosol *Prodotti, Braz.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferrosprint *Marvecs, Ital.*
Sodium ferric gluconate complex (p. 2089·1).
Anaemias.

Ferrostrane *Teofarma, Fr.*
Sodium feredetate (p. 2088·3).
Iron deficiency; iron-deficiency anaemia.

Ferrotabs *Thaipharmed, Thai.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferrotemp *Medix, Mex.*
Ferrous fumarate (p. 2060·3); thiamine hydrochloride (p. 2103·1).
Iron-deficiency anaemia.

Ferro-Terapina *Degorts, Mex.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Ferrototal *Sanval, Braz.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ferrotrat *Medley, Braz.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Iron deficiency; iron-deficiency anaemia.

Ferrotrat B12 Plus *Medley, Braz.*
Ferric ammonium citrate (p. 2060·1); cyanocobalamin (p. 2107·2); carnitine hydrochloride (p. 2053·2); lysine hydrochloride (p. 2079·3); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); sodium glycerophosphate (p. 2519·2).
Iron-deficiency anaemia; reduced appetite.

Ferro-Tre *Mediolanum, Ital.*
Iron acetyltransferrin.
Iron-deficiency anaemias.

Ferrotron
Note: this name may be used for preparations of different composition.
Errelife, Ital.
Amino acids; vitamins; minerals.
Nutritional supplement.

Ferrous Drops *Major, USA.*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Ferrous Sulphate Compound *Pharmacare, S.Afr.†; Pharmagen, S.Afr.†*
Ferrous sulfate (p. 2062·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2).
Iron-deficiency anaemia.

Ferroven *Berksam, Turk.*
Iron sucrose (p. 2078·1).

Ferrovin *Rafarm, Gr.; Lapidot, Israel.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Ferrovir *Technomedservis, Rus.*
Sodium deoxyribonucleate-iron complex.
HIV infection; chronic hepatitis C; herpesvirus infections; tick-borne encephalitis.

Ferrovit
Note: this name may be used for preparations of different composition.
Mega Lifesciences, Malaysia†; Mega Lifesciences, Philipp.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Anaemias.

T Man, Thai.
Ferrous fumarate (p. 2060·3); vitamins; calcium lactate (p. 1784·1); ammonium molybdate (p. 2082·3).
Anaemias; reduced appetite.

Valenta, Rus.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); rutoside (p. 2505·3); vitamins.

Ferro-Vital *Eczacibasi, Turk.†*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferrozinc *Berko, Turk.*
Vitamin C (p. 2110·3); folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); zinc sulfate (p. 2126·2).

Ferrum *Lek, Cz.†*
Iron polymaltose (p. 2077·2) or iron sucrose (p. 2078·1).
Iron deficiency.

Ferrum Complexe No 29 *Lehning, Fr.*
Ferrum metallicum (p. 2073·1); aloe (p. 1816·1); platina muriatica (p. 2593·1); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Ferrum Fol *Khandelwal, India; Vifor, Irl.; Ferraz, Lynce, Port.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Ferrum Fol Hausmann *Nycomed, Gr.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Ferrum H *Aspen, Austral.; Healthcare Logistics, NZ.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferrum Hausman Fort *Abdi, Turk.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Ferrum Hausmann *Nycomed, Gr.; Vifor, Hong Kong; Vifor, Irl.; Ferraz, Lynce, Port.; Vifor, Singapore; Abdi, Turk.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Geymonat, Ital.
Iron sucrose (p. 2078·1).
Iron-deficiency anaemias.

Vifor, Ger.; Vifor International, Switz.
Ferrous fumarate (p. 2060·3) or iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Ferrum Homaccord *Heel, Cz.†*
Ferrum metallicum (p. 2073·1); ferri phosphas (p. 2077·1); ferrosi sulfas (p. 2062·2); ferri chloridum (p. 2504·2); filipendula ulmaria (p. 2550·2).
Homoeopathic preparation.

Ferrum Lek *Sandoz, Pol.; Sandoz, Rus.; Sandoz, Ukr.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia; iron supplement.

Ferrum Phos Comp *Weleda, S.Afr.†*
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); eucalyptus; eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); sabadilla (p. 2611·2).
Homoeopathic preparation.

Ferrum Phosphoricum comp *Weleda, Austria.*
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); sabadilla (p. 2611·2).
Homoeopathic preparation.

Ferrum phosphoricum comp *Weleda, Ger.*
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); eucalyptus; eupatorium perfolatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); sabadilla (p. 2611·2).
Homoeopathic preparation.

Ferrum Verla *Verla, Ger.*
Ferrous gluconate (p. 2061·2).
Iron deficiency.

Ferrum-Quarz *Weleda, Austria.*
Ferrous sulfate (p. 2062·2); quartz.
Migraine and related vascular headaches; tonic.

Fersaday *Goldshield, Irl.†; Goldshield, UK.*
Ferrous fumarate (p. 2060·3).
Iron deficiency.

Fersamal *Goldshield, UK.†*
Ferrous fumarate (p. 2060·3).
Iron deficiency.

Fersinol-Z *World Medicine, Ukr.*
Ferrous sulfate (p. 2062·2); zinc sulfate (p. 2126·2); ascorbic acid (p. 2110·3) vitamin B substances (p. 2102·3).
Dietary supplement.

Fersivag *Novag, Mex.*
Lisinopril (p. 1420·3).

Fersolate-CM *GSK, India.*
Copper sulfate (p. 2057·2); ferrous sulfate (p. 2062·2); manganese sulfate (p. 2081·2).

Ferst *Pharmed, India.*
Capsules: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Pharmed, India.
Oral drops; syrup: Iron polymaltose (p. 2077·2).

Fertavid *Schering-Plough, Cz.; MSD, Irl.; Organon, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.*
Follitropin beta (p. 2278·2).
Male and female infertility.

Fertell *Genosis, UK.*
Fertility test (p. 2596·1).

Fertibex *Fourrts, India.*
Vitamin B substances (p. 2102·3); vitamin E acetate (p. 2119·2).

Ferticlo *Platinum, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Fertifact *Medico, India.*
⊗Clomifene citrate (p. 2259·1).

Fertifol *Effik, Ital.; Effik, Switz.*
Folic acid (p. 2063·1).
Prevention of neural-tube defects; folic acid supplement during pregnancy and lactation.

Fertigyn *Sun, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Cryptorchidism; male hypogonadism; anovulatory infertility.

Fertik *Zee, India.*
⊗Clomifene citrate (p. 2259·1).

Fertilan *Medochemie, China; Codal Synto, Hong Kong.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Fertilin *Ind-Swift, India.*
Clomifene.
Anovulatory infertility.

Unipharm, Turk.
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Fertility Day *Blausiegel, Braz.; Maver, Mex.*
Pregnancy test (p. 2596·1).

Fertilix *Fortbenton, Arg.*
Acetylcarnitine hydrochloride (p. 2053·2); levocarnitine (p. 2053·2).

Fertilphen *Landson, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Fertin
Note: this name may be used for preparations of different composition.
Interbat, Indon.
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Medochemie, Neth.
Glimepiride (p. 473·2).
Diabetes mellitus.

Fertinex *Serono, USA.†*
Urofollitropin (p. 2312·2).
Female infertility.

Fertipeptil *Ferring, Port.*
⊗Triptorelin acetate (p. 2310·3).
Assisted reproduction.

Fertiring *Silesia, Chile.*
Progesterone (p. 2300·2).
Female infertility.

Fertnon *Mabra, Braz.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Fertodur *Schering, Turk.†*
⊗Cyclofenil (p. 2261·2).
Anovulatory infertility.

Fertomcidina-U *Theriaca, Ital.*
Magnesium glycerophosphate (p. 1787·2); salicylic acid (p. 1719·1); sodium iodide (p. 2337·1); ammonium bromide (p. 2461·1).
Wound disinfection.

Fertomid *Cipla, India; Cipla-Medpro, S.Afr.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ferton *Inga, India.*
⊗Clomifene citrate (p. 2259·1).

Fertotab *GSK, India.*
Clomifene.
Anovulatory infertility.

Fertova *Triton, India.*
⊗Clomifene citrate (p. 2259·1).

Fertyl *Renata, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Ferulic *Hiral, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Ferulogic *Chemo-Drugs, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Ferumbo *Borshchagovskii, Ukr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Ferval *Valdecasas, Mex.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia; iron supplement.

Fervex
Note: this name may be used for preparations of different composition.
Andromaco, Mex.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

BMS, Cz.†; UPSA Conseil, Fr.; BMS, Hung.†; BMS, Pol.; Sanofi-Aventis, Rus.
Pheniramine maleate (p. 637·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; upper respiratory-tract disorders.

Hertz, Braz.
Paracetamol (p. 115·1).
Fever; pain.

Fervidus *Amnol, Ital.*
Lactobacillus sporogenes (p. 2596·3); fruit oligosaccharides (p. 2508·1).
Gastrointestinal disorders.

Fervit *Vitoria, Port.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemias.

Ferxal *Silanes, Mex.*
Iron succinyl-protein complex (p. 2077·3).
Iron-deficiency anaemia; iron deficiency.

Ferybar *Pinewood, Irl.†*
Liver extract (p. 2444·1); vitamin B substances (p. 2102·3); minerals.
Vitamin and mineral supplement.

Ferycare *Bestochem, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Ferywel *Bestochem, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Ferz *Geno, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Ferzobat *Interbat, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Ferzun *Medipharm, Chile.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Fesafe *RND, India.*
Iron (p. 2073·1).

Fesema *Etex, Chile.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Feshia *Scoshia, India.*
Iron sucrose (p. 2078·1).

Fesofor *SmithKline Beecham, S.Afr.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Fesofor-Z *GSK, India.*
Dried ferrous sulfate (p. 2062·2); zinc sulfate (p. 2126·2).

Fesoft *Arrowin, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Fesovit *GSK, India.*
Capsules: Folic acid (p. 2063·1); vitamin B substances (p. 2102·3); dried ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; tonic 1406 Dried ferrous sulfate not specified 03.10.

GSK, India.
Elixir: Vitamin B substances (p. 2102·3); dried ferrous sulfate (p. 2062·2).
Nutritional supplement.

Fess *Care, Austral.*
Sodium chloride (p. 1795·1).
Nasal congestion; sinusitis.

Festa *Vensat, India.*
⊗Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Festal *Sanofi-Aventis, India; Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.*
⊗Bile (p. 2457·2); hemicellulase (p. 2473·1); pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders; gastrointestinal tract investigations; enhancement of drug absorption.

Festal N *Sanofi-Aventis, India; Aventis, Turk.*
⊗Pancreatin (p. 2579·3).
Digestive disorders.

Festal Reformulado *Sanofi-Aventis, Venez.*
Lipase (p. 2579·3); amylase (p. 2442·1); protease (p. 2598·1).
Digestive disorders.

Festene *Intra-Labs, India.*
Sodium selenite (p. 2087·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Festive *Laborate, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Festive B *Laborate, India.*
⊗Betamethasone (p. 1623·2); ofloxacin (p. 334·3).

Festive D *Laborate, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Festive-OZ *Laborate, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Festive-TZ *Laborate, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Festone *Novartis, Braz.*
⊗Tamoxifen citrate (p. 860·2).

Festo-TR *DWD, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3).

Fesu *Alna, India.*
Iron sucrose (p. 2078·1).

Fesu-XT *Alna, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Fetamozin *Teva, Hung.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Fetanex *Rowex, Irl.*
⊗Fentanyl (p. 60·1).
Pain.

Fetik *Interbat, Indon.*
Ketoprofen (p. 79·1).
Osteoarthritis; rheumatoid arthritis; gout; ankylosing spondylitis.

Fe-Tinic *Ethex, USA.†*
Polysaccharide-iron complex (p. 2086·2).
Iron-deficiency anaemia.

Fe-Tinic Forte *Ethex, USA.*
Polysaccharide-iron complex (p. 2086·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Iron-deficiency anaemia.

Fetinor *Otto, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Feton *Lincoln, India.*
Chewable tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Lincoln, India.
Syrup: Iron polymaltose (p. 2077·2).

Feton-Z-TR *Lincoln, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc (p. 2126·1).

Fetrace *Wockhardt, India.*
Vitamins; minerals; trace elements.

Fetran-ES *Forgo, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Fetran-MF *Forgo, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Fetrasil *Taj, India.*
⊗Sibutramine (p. 2330·2).
Obesity.

Fetrin *Lunsco, USA.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); intrinsic factor (p. 2534·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Fetrival *Almirall, Port.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Fetrop *Solitaire, India.*
⊗Clomifene citrate (p. 2259·1).

Fetugard *GSK, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Fetugest *Obsurge, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Fetusin *EuroHealth, Philipp.†*
Oxytocin (p. 2143·1).
Labour induction.

Fetylan *Farmamust, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fetzima *Forest Pharmaceuticals, USA.*
Levomilnacipran (p. 427·2).
Depression.

Feudoftal *Bausch & Lomb, Arg.*
Ascorbic acid (p. 2110·3); alpha tocoferil acetate (p. 2119·2); vitamin A palmitate (p. 2098·3).
Vitamin supplement.

Feuille de Saule *Gilbert, Fr.*
Salicylic acid (p. 1719·1).
Corns; callus; verrucas.

Fevacold *Arvincare, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fevamol *Aspen, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Fevapar *Cipla-Medpro, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain with tension.
Xeragen, S.Afr.†
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Fever; pain.

Fevarin *Abbott, Cz.; Abbott, Denm.; Abbott, Fin.†; Abbott, Ger.; Abbott, Hung.; Solvay, Ital.; Abbott, Neth.; Abbott, Norw.; Solvay, Pol.; Solvay, Rus.; Abbott, Swed.; Abbott, Ukr.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Fevastin *Tablets, India.*
Paracetamol (p. 115·1).
Pain; fever.

Fevastin Plus *Tablets, India.*
DL-methionine (p. 1558·2); paracetamol (p. 115·1).
Fever; pain.

Feverall *Alpharma, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Feverfen *Wise, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Feverpain *Teva, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Fevni-P *Stellar, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Fevomax *Candor, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Fevorit *Indoco, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fevorit-LB *Indoco, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Fevovit *H & Care, India.*
Iron carbonyl (p. 2073·1); vitamin B substances (p. 2102·3); zinc (p. 2126·1).

Fevril *Meyer, India.*
Suspension; syrup: Paracetamol (p. 115·1); promethazine (p. 638·2).
Meyer, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Fevrin *Armoxindo, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Fex *Ordain, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Fexadin *Ranbaxy, Rus.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexadyne *Ali, Turk.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexal *Sandoz, Austral.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Fexamed *Medial, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexavil *Sandoz, Turk.*
Fexofenadine hydrochloride (p. 629·1).

Fexaway *Adcock Ingram, S.Afr.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexazol *Molex Ayus, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Fexet *Getz, Philipp.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexgen *Generics, Hung.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Fexid *Overseas, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Overseas, India.
Oral suspension: Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc (p. 2126·1).

Fexidine *Ind-Swift, India; Biofarma, Venez.*
Fexofenadine hydrochloride (p. 629·1).
Hypersensitivity reactions; allergic rhinitis; urticaria.

Fexid-Z *Overseas, India.*
Iron (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Fexigra *Cipla, Cz.; Cipla, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexim
Note: this name may be used for preparations of different composition.
Admac, India.
Cefixime (p. 240·3).
Bacterial infections.
Antula, Swed.†
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia; iron deficiency.

Fexin
Note: this name may be used for preparations of different composition.
Antula, Denm.†; Antula, Norw.†
Ferrous gluconate (p. 2061·2).
Iron deficiency; iron-deficiency anaemia.

F-Exina *Novag, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety-depressive states.

Fexiron *Rivero, Arg.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Fexitage *Plus, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fexizin *Eczacibasi, Turk.*
Fexofenadine hydrochloride (p. 629·1).

Fexmid *Shionogi, USA.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Fexo *Cipla-Medpro, S.Afr.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.
Torrent, India.
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexocare *Melora, Port.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Fexo-D *UCI, Braz.†*
⊗Fexofenadine (p. 629·1); pseudoephedrine (p. 1676·1).

Fexodane *UCI, Braz.*
Fexofenadine hydrochloride (p. 629·1).

Fexodex *Dexter, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexodin *Daksh, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexodine *Europharm, Hong Kong.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexofast *Micro, India; Arrow, NZ; Galena, Pol.; Micro, Rus.; Sandoz, S.Afr.†; Eurodrug, Thai.; Micro Labs, Ukr.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexofed *Kalbe, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Fexofen *Aristo, India; Sanovel, Turk.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexofenaderm *Dermapharm, Ger.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexofep *Extractum, Hung.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexoff-R *Landsteiner, Mex.*
Fexofenadine hydrochloride (p. 629·1).

Fexofin *Eurodrug, Malaysia.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

FexoGen *Generics, Pol.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Fexon *Syndicate, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Fexona *Hetero, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexoplat *Feron, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Fexoquit *Finecure, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexoral *Synergen, Philipp.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexoril *Leti, Venez.*
Fexofenadine hydrochloride (p. 629·1).
Hypersensitivity reactions.

Fexot *Taurus, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexotabs *Sanofi-Aventis, Austral.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexotine *Farmaline, Thai.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Fexotrol *Sun, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Fexova *Ipca, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; allergic skin disorders.

Fe-Z *Mapra, India.*
Ferrous fumarate (p. 2060·3); vitamins; lysine hydrochloride (p. 2079·3); glycine (p. 2071·2); zinc sulfate (p. 2126·2).

Fezec *Unimarck, India.*
Iron carbonyl (p. 2073·1); vitamins; selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Fezee *Euphoric, India.*
Capsules: Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Euphoric, India.
Oral liquid: Calcium lactate (p. 1784·1); ferrous gluconate (p. 2061·2); folic acid (p. 2063·1).
Tonic.

Fezef *Tai Yu, Philipp.†*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Fezlina *Sanat, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Fezocaps *American Remedies, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Fezocar *American Remedies, India.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Fezon *Uniphar, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Fezys-SM *Zytras, India.*
Spirulina (p. 2622·1); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Fezys-XT *Zytras, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Fezys-Z *Zytras, India.*
Iron carbonyl (p. 2073·1); vitamins; zinc sulfate (p. 2126·2).

Fezza *Hauz, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Fezza-S *Hauz, India.*
Iron sucrose (p. 2078·1).

Fezzor *Labormed, Cz.; Labormed, Denm.*
Trandolapril (p. 1517·2).
Hypertension; myocardial infarction; left ventricular dysfunction following myocardial infarction.

FG Ointment *Meiji, Indon.†*
Neomycin sulfate (p. 330·1); gramicidin S hydrochloride (p. 309·1); benzocaine (p. 1980·2); chlorphenamine maleate (p. 620·3); mafenide (p. 320·2).
Skin infections.

FG Troches *Meiji, Indon.*
Neomycin sulfate (p. 330·1); gramicidin S hydrochloride (p. 309·1).
Mouth and throat infections.

F-Gel *Darnitsa, Ukr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

FGF Tabs *Abbott, Austral.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folate deficiency.

FH-12 *Bestochem, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

F6H8 Vitreous Substitute *Fluoron, Ger.*
⊗Perfluorohexyloctane (p. 2586·3).
Ophthalmic tamponade.

Fharder *Farmaceutica H, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

FHB-12 *Bestochem, India.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Fhilterin *Farmaceutica H, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fhisfal *Farmaceutica H, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Fiacin *Biosarto, Spain.†*
⊗Indometacin (p. 71·2); prednisone (p. 1647·2).
Musculoskeletal, joint, and peri-articular disorders.

Fialetta Odontalgica Dr Knapp *Montefarmaco, Ital.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); clove oil (p. 2481·3); colophony (p. 2484·2).
Toothache.

Fiasole *Tetrafarm, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fibalip *Mylan, NZ.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Fibator *Sun, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibator EZ *Sun, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2); fenofibrate (p. 1381·1).

Fiber 5 *Yerba, Canad.*
Ispaghula (p. 1849·1).
Constipation.

Fiber Basics *Hormel, Hong Kong.*
Soluble maltodextrin fibre (p. 2080·3).
Dietary fibre supplement.

Fiber Plus *Yerba, Canad.*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation.

Fiber Therapy Original Texture *Major, USA.*
Ispaghula (p. 1849·1).
Constipation.

Fiberall *Ciba Consumer, USA.*
Oral powder; wafers: Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation; stool softener in haemorrhoids.

Fibercon *Wyeth, Gr.; Lederle, USA.*
Polycarbophil calcium (p. 1879·2).
Constipation; bowel disorders.

Fiberform *Recip, China; Meda, Neth.; Meda, Swed.†*
Wheat bran (p. 1823·3).
Constipation; irritable bowel syndrome; diverticulitis.

Fiberform Mix *Meda, Swed.†*
Wheat bran (p. 1823·3).
Constipation.

Fiberfull *Ponce, Venez.*
Ispaghula (p. 1849·1); avena (p. 2451·1).
Constipation.

Fibergy *Usana, Hong Kong.†*
Preparation for enteral nutrition.
Usana, Singapore.†
Dietary fibre.

Fiberlan *Galagen, USA.*
Lactose-free, gluten-free preparation for enteral nutrition.

Fiber-Lax *Rugby, USA.*
Polycarbophil calcium (p. 1879·2).
Diarrhoea; constipation.

Fiberlax *Herbion, Rus.*
Ispaghula (p. 1849·1).
Constipation.

Fibermate *United Laboratories, Philipp.*
Psyllium (p. 1849·1).
Constipation; dietary fibre supplement; hypercholesterolaemia.
Westmont, Hong Kong.†
Ispaghula (p. 1849·1).
Dietary fibre supplement.

FiberNorm *G & W, USA.†*
Polycarbophil calcium (p. 1879·2).
Constipation.

Fiber-on-Tablet *Jamp, Canad.*
Polycarbophil calcium (p. 1879·2).

Fibersource *Novartis Consumer, Braz.; Novartis Nutrition, Singapore.*
Preparation for enteral nutrition with fibre.

Fibersweet *Pediapharma, Philipp.*
Inulin (p. 2534·3).
Prebiotic dietary fibre supplement.

FibinGluRAAS *RAAS, China.*
Fibrinogen (p. 1151·3); thrombin (p. 1163·2).
Haemorrhage.

Fibingluraas *Shanghai RAAS, Thai.*
1 Vial, fibrinogen (p. 1151·3); 1 vial, thrombin (p. 1163·2).
Haemorrhage.

Fiblaferon *Biosyn, Ger.†*
Interferon beta (human) (p. 996·1).
Viral infections.

Fiblast
Note: this name may be used for preparations of different composition.
Kaken, Jpn.
⊗Trafermin (p. 1725·1).
Skin ulcer.
Rontag, Arg.
Ascorbic acid (p. 2110·3); hesperidin methyl chalcone (p. 2505·2); butcher's broom (p. 2463·1).
Venous insufficiency; haemorrhoids; metrorrhagia.

Fibmet *Sun, India.*
Fenofibrate (p. 1381·1); metformin hydrochloride (p. 489·1).

Fiboran *Nycomed, Gr.; Nycomed, Neth.†*
Aprindine hydrochloride (p. 1306·3).
Arrhythmias.

Fibotab *Torrent, India.*
Polycarbophil calcium (p. 1879·2).

Fibra Line *Investigacion, Mex.†*
A range of dietary fibre supplements.
Gastrointestinal disorders; obesity.

Fibrabene *Legrand, Braz.*
⊗Dornase alfa (p. 1662·1); fibrinolysin (bovine) (p. 1382·3).
Wounds.

Fibracare *Herbarium, Braz.†*
Ispaghula (p. 1849·1).

Fibracol Plus *Johnson & Johnson Medical, Arg.*
Collagen (p. 2483·2); calcium alginate (p. 1136·3).
Wound dressing.

Fibradiet *GSK, India.*
Ispaghula (p. 1849·1).

Fibrafen *Patriot, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibraguar *Fardi, Spain.*
Guar gum (p. 475·1).
Diabetes mellitus.

Fibral
Note: this name may be used for preparations of different composition.
Micro, India.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibralip *Tunggal Idaman, Indon.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Fibramed *Promed, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibran Plus *Obsurge, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Fibranin *Winthrop, Port.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Fibran-M *Obsurge, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Fibranorm *Piam, Ital.*
Fibersol-2; psyllium (p. 1849·1); prune (p. 1881·1); lactic acid (p. 2539·1).
Gastrointestinal disorders.

Fibras Ewe *Sanitas, Arg.*
Ispaghula (p. 1849·1).

Fibrasan *Errekappa, Ital.†*
Cellulose (p. 2177·1).
Gastrointestinal disorders.

Fibrase
Note: this name may be used for preparations of different composition.
Pfizer, Braz.; Pfizer, Mex.
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1); chloramphenicol (p. 257·1).
Infected burns, wounds, and ulcers.
Teofarma, Ital.
Pentosan polysulfate sodium (p. 1465·1).
Thrombosis prophylaxis; peripheral vascular disorders; soft-tissue disorders.

Fibrase SA *Pfizer, Mex.*
⊗Fibrinolysin (bovine) (p. 1382·3); dornase alfa (p. 1662·1).
Burns; ulcers; wounds.

Fibrasol *Maver, Chile.*
Psyllium hydrophillic mucilloid (p. 1849·1).
Constipation.

Fibrate *Kleva, Gr.*
Bezafibrate (p. 1323·2).
Avinash, India.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibrazate *Sandoz, UK.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Fibre Dophilus *Pharmadass, UK.*
Lactobacillus acidophilus (p. 2596·3); Acidophilus bifidus; ispaghula (p. 1849·1).
Fibre supplement; maintenance of gastrointestinal flora.

Fibre Laxative *Perrigo, Canad.*
Polycarbophil calcium (p. 1879·2).
Constipation.

Fibre Plus *Pharmadass, UK.*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation; fibre supplement.

Fibrelief *Manx, UK.†*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; dietary fibre supplement.

Fibreline *Lactalis, Fr.*
Dietary fibre.
Gastrointestinal disorders.

Fibresource *Nestle, Hong Kong.*
Preparation for enteral nutrition.

Fibrex Tabletten
Note: this name may be used for preparations of different composition.
Berlin-Chemie, Ger.
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain.

Fibrezym *Bene, Ger.*
Pentosan polysulfate sodium (p. 1465·1).
Thrombosis prophylaxis.

Fibricor *AR Scientific, USA.*
Fenofibric acid (p. 1381·1).
Hyperlipidaemias.

Fibril
Note: this name may be used for preparations of different composition.
Apotex, Philipp.; Berlin Pharm, Thai.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.
Lupin, India.
Ispaghula (p. 1849·1).

Fibrilan *Farmedia, Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Fibrinase c/Cloranfenicol *Cristalia, Braz.*
⊗Dornase alfa (p. 1662·1); fibrinolysin (p. 1382·3); chloramphenicol (p. 257·1).
Infected wounds.

Fibrinon *Jean-Marie, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage.

Fibrinox *Sandoz, Arg.†*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of clotting in extracorporeal circuits.

Fibro M *Douglas, Canad.*
Magnesium hydroxide (p. 1857·2); ascorbic acid (p. 2110·3).

Fibrocard *Vitoria, Port.†; Galephar, Turk.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Fibrocide *Neo-Farmaceutica, Port.*
Pentosan polysulfate sodium (p. 1465·1).
Thromboembolic disorders.

Fibrogammin *CSL, Austria; CSL, Belg.; CSL, Braz.; CSL, Fr.; CSL, Ger.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; CSL, Israel; CSL, Switz.*
A factor XIII preparation (p. 1150·3).
Factor XIII deficiency; haemorrhagic disorders.

Fibrogammin P *CSL, Arg.; Aventis Behring, Hong Kong†; Aventis Behring, UK.*
A factor XIII preparation (p. 1150·3).
Factor XIII deficiency; wound healing; bone fracture healing; haemorrhagic disorders.

Fibrokinase *Aristo, India.*
Streptokinase (p. 1503·1).

Fibrolan
Note: this name may be used for preparations of different composition.
Pfizer, Austria; Pfizer, Cz.†; Pfizer, Hung.; Parke, Davis, Pol.; Pfizer, Switz.
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1).
Wounds; ulcers; gynaecological surgery; burns; skin infections.
Olan-Kemed, Thai.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibrolax *Giuliani, Ital.*
Ispaghula (p. 1849·1).
Constipation.

Fibrolax Complex *Giuliani, Ital.*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation.

Fibrolip *Anfarm, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Fibromucil *Collins, Mex.*
Ispaghula (p. 1849·1).
Constipation; dietary fibre supplement.

Fibromyalgie *Homeocan, Canad.*
Calcarea phosphorica (p. 1784·2); ignatia amara (p. 2532·1); causticum (p. 2595·3); rhus toxicodendron (p. 2603·3); magnesia phosphorica (p. 1787·3); bryonia alba (p. 2461·3); arnica montana (p. 2447·2); muscles (p. 2444·1); tendons; ligaments.
Homoeopathic preparation.

Fibromyalgine *Labrha, Fr.*
Morning formula, vitamin C (p. 2110·3); acerola; royal jelly (p. 2608·1); ginger (p. 1844·1); meadowsweet (p. 2550·2); Evening formula, meadowsweet; chamomile (p. 2474·1); passion flower (p. 2584·1); couch-grass (p. 2487·2); tyrosine (p. 2098·3).
Mood disorders; sleep disorders.

Fibromyalgine Fort *Labrha, Fr.*
Morning formula, vitamin C (p. 2110·3); acerola; ginseng (p. 2513·3); salix (p. 129·2); sage (p. 2608·3); magnesium (p. 1786·3); tyrosine (p. 2098·3); Evening formula, valerian (p. 2640·2); passion flower (p. 2584·1); salix (p. 129·2); eschscholzia (p. 2466·1); tryptophan (p. 453·2).
Mood disorders; sleep disorders.

Fibronevrina *Ceccarelli, Ital.*
Thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).
Vitamin B_1 and B_{12} deficiency.

Fibronil *Royal, Chile.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibropid *VS, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Fibropil *Psychotropics, India.*
Ispaghula (p. 1849·1); methylcellulose (p. 2197·3).

Fibroplex *Metagenics, Canad.*
Magnesium (p. 1786·3); manganese (p. 2081·2); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2).

Fibroquel *Aspid, Mex.*
Collagen (p. 2483·2).
Burns; haemorrhage; ulcers; wounds.

Fibroraas *Trans, India; Shanghai RAAS, Thai.*
Fibrinogen (p. 1151·3).
Hypofibrinogenaemia.

Fibrorelax *Andromaco, Chile.*
Chlormezanone (p. 1045·1); paracetamol (p. 115·1); glucametacin (p. 66·2).
Musculoskeletal, joint, and soft-tissue disorders.

Fibrosan *Biogalenic, Venez.*
Enalapril (p. 1371·1).
Hypertension.

Fibrosine *Wyeth, Philipp.*
Dietary fibre preparation from corn starch.
Fibre supplement; constipation.

Fibrospes *Specifar, Gr.*
Gemfibrozil (p. 1390·3).

Fibrotin *Bliss, India.*
Guar gum (p. 475·1); lysine (p. 2079·3); DL-methionine (p. 1558·2); carbohydrates; protein.

Fibrotina *Buxton, Arg.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fibrovas *Micro, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fibro-Vein *Craveri, Arg.; Australasian Medical, Austral.; STD, Hung.; STD, Irl.; Mac, Ital.; NZ Medical & Scientific, NZ; STD, Rus.*
Sodium tetradecyl sulfate (p. 2620·1).
Varicose veins; varices; sclerotherapy.

Fibrovein *Omnimed, S.Afr.†; STD, UK.*
Sodium tetradecyl sulfate (p. 2620·1).
Varicose veins.

Fibrovit *Provita, Ital.*
Glucomannan (p. 2515·2); pectin (p. 2200·3); inulin (p. 2534·3); guar (p. 475·1); garcinia cambogia (p. 2510·2).
Dietary fibre supplement.

Fibrox *Saval, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Fibroxol *Aspen, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Fibrozo *Jean-Marie, Hong Kong.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Fibrum *Nutricia-Bago, Arg.*
Preparation for enteral nutrition with fibre.

Fibs *OCFZP, Pol.*
Myrtillus (p. 2566·2).
Eye inflammation; bacterial infections.

Fibsol *Aspen, Austral.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Fica-F *Integris, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Fichtensirup S *Jukunda, Ger.*
Spruce needles.
Catarrh.

Ficlo-Forte *Forgo, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Ficlo-P *Forgo, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Fico *Emcure, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ficonax *Pisa, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fico-P *Emcure, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Ficor *Otto, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; myocardial infarction; hypertension.

Ficortril *Mann, Ger.*
⊗Hydrocortisone acetate (p. 1640·1).
Eye disorders.

Pfizer, Swed.
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Eczema; anogenital pruritus; inflammatory eye disorders.

Fico-SP *Emcure, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Fidagenbeta *Fidia, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Fidato *Fidia, Ital.*
Ceftriaxone sodium (p. 253·3). Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Fiddy *SSP, Thai.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Fidecaina *Fidex, Arg.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Fideine *Bergamo, Braz.*
Bisacodyl (p. 1821·1).
Constipation.

Fidelan *Unipharma, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Fiden-AZ *Candor, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Fidinor *Doctum, Gr.*
Piroxicam (p. 125·3).

Fidium *Rottapharm, Spain.*
Betahistine hydrochloride (p. 2455·3).
Vertigo.

Fidoin-Q *Quimpharma, Mex.*
Ibuprofen (p. 68·2).
Fever; pain.

Fiebrol *Fabop, Arg.*
Dipyrone (p. 53·3).
Fever; pain.

Fiebrolex *Vitarum, Arg.†*
Paracetamol (p. 115·1).
Fever; pain.

Fiebrolito *Fabop, Arg.†*
Paracetamol (p. 115·1).
Fever; pain.

Fiedosin *Nupel, Spain.†*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Fienamina *Recordati, Ital.*
⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Fiery Jack *Pickles, UK.*
Cream: Glycol salicylate (p. 66·2); diethylamine salicylate (p. 51·3); capsicum oleoresin (p. 2469·3); methyl nicotinate (p. 91·3).
Musculoskeletal and joint disorders.

Ransom, UK.
Ointment: Capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint disorders.

Fiesta-Z *United Lifecare, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Fievrinol *Leontik, Gr.*
Flurbiprofen (p. 65·2).

Fifa *Intra-Labs, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Intra-Labs, India.
Oral suspension: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Fifa-AD *Intra-Labs, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Fifolar *Lark, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).

Figalol *Biomedica, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Figatil *Catarinense, Braz.*
Cynara (p. 2490·3); boldo (p. 2458·3); ox bile (p. 2457·2).
Liver disorders.

FI-GCF *Dosa, Arg.*
Filgrastim (p. 1151·3).

Fightox *Piramal, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Figothrom *Chrispa (Χρισπα), Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Figozant *Chrispa (Χρισπα), Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Figrel *Biomedica, Gr.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; eye inflammation.

Figura 1 *Herbapol Lublin, Pol.*
Senna (p. 1885·1).
Constipation.

Figura 2 *Herbapol Lublin, Pol.*
Frangula bark (p. 1843·3).
Constipation.

Figur-Verlan *Verla, Ger.*
Guar gum (p. 475·1).
Obesity.

Fijacid *Bajer, Arg.*
Coal tar (Alcoderm) (p. 1723·2).
Scalp disorders.

Fil Olor *Andromaco, Arg.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); borax (p. 2459·2); benzethonium chloride (p. 1738·1).
Foot care.

Filabac *Filaxis, Arg.*
Abacavir (p. 962·3).
HIV infection.

Filadec *Pond's, Thai.*
Diethylcarbamazine.
Filariasis; loiasis; toxocariasis.

Filair *3M, Chile†; Sodhan, Turk.; 3M, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

Filanc *Continentales, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Filantor *Novag, Spain.†*
⊗Torasemide (p. 1516·3).
Oedema; hypertension.

Filartros *Ivax, Arg.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Filatil *Probiomed, Mex.*
Filgrastim (p. 1151·3).
Neutropenia.

Filaxan *Cinfa, Spain.*
Ispaghula (p. 1849·1).
Constipation.

Filazem *Filadams, Philipp.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Filco-S *Forgo, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Filcrin
Note: this name may be used for preparations of different composition.
Filaxis, Arg.
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer.

Fildlata *Sigillata, Cz.; Sigillata, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Fildrocin *Lloyd, Philipp.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

File *Bouzen, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Filena *Organon, Ital.*
White tablets, estradiol valerate (p. 2271·2); blue tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Filergim *Gedeon Richter, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Filgen *Bioprofarma, Arg.; Chandra Bhagat, India; Ranbaxy, Thai.*
Filgrastim (p. 1151·3).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Filginase *Filaxis, Arg.*
Efavirenz (p. 975·1).
HIV infection.

Filgramega *Pcgen, Arg.*
Filgrastim (p. 1151·3).

Filgrastine *Blausiegel, Braz.*
Filgrastim (p. 1151·3).
Neutropenia associated with cancer chemotherapy.

Filibon *Wyeth, India†; Aspen, S.Afr.†*
Vitamins; minerals.
Supplement for pregnant or lactating women.

Filicine *Adelco, Gr.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; neural tube defects.

Filide *Filaxis, Arg.*
Nevirapine (p. 1005·1).
HIV infection.

Filigel *Codifra, Fr.†*
Avena (p. 2451·1); glucomannan (p. 2515·2); fructose (p. 2068·2); pectin (p. 2200·3); Frutafit; guarana (p. 2648·2).
Obesity.

Filinar *Eurofarma, Braz.*
Ambroxol acefyllinate (p. 1201·2).
Obstructive airways disease.

Filinsel *Biosel, Turk.*
Aminophylline (p. 1201·2).

Fillast *Q-Med, Ital.*
Hyaluronic acid (p. 2526·2).
Wrinkles.

Filmabak *Farmila, Ital.*
Povidone (p. 2204·3); electrolytes (p. 1775·1).
Dry eyes.

Filmcel *Allergan, Braz.*
Hypromellose (p. 2189·2).
Dry eyes.

Filmogen Same *Savoma, Ital.*
Barrier cream.

Filnarine *Teva, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

Filocot *Sanofi-Aventis, Gr.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Filoderma *Ivax, Arg.*
⊗Diflorasone diacetate (p. 1633·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Filoderma Plus *Ivax, Arg.*
⊗Diflorasone diacetate (p. 1633·3); gentamicin sulfate (p. 304·2); econazole nitrate (p. 577·3).
Infected skin disorders.

Filodox *Hos & Ins, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Filomag B_6 *Filofarm, Pol.*
Magnesium aspartate (p. 1787·1); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Filorose *Sanofi-Aventis, Gr.*
Salicylic acid (p. 1719·1); dithranol (p. 1701·2).

Filosfil *Filaxis, Arg.*
Nelfinavir mesilate (p. 1004·1).
HIV infection.

Filotempo *Meda, Port.*
Aminophylline (p. 1201·2).
Asthma; obstructive airways disease.

Filotricin A *Dupomar, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Filpenvag *Novag, Mex.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration; diarrhoea.

Filpril *Alphapharm, Austral.†*
Quinapril hydrochloride (p. 1480·2).
Heart failure; hypertension.

Filstim *Biopharma, Ukr.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Filtaten *Tecnoforma, Mex.*
⊗Fentanyl citrate (p. 60·1).
Analgesia in mechanically ventilated patients; neuroleptanalgesia; anaesthesia.

Filten *Gador, Arg.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Filten D *Gador, Arg.*
⊗Carvedilol (p. 1333·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Filtrosol *Medihealth, Mex.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); ensulizole (p. 1703·1).
Sunscreen.

Roemmers Medihe, Venez.
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); enzacamene (p. 1703·2); ensulizole (p. 1703·1).
Sunscreen.

Filtrum *Avva, Rus.; Sti-Med-Sorb, Ukr.†*
Lignin (p. 2544·1).
Acute poisoning; gastrointestinal disorders; food and drug allergies.

Filtrum HT *Libbs, Braz.*
SPF 20: Sunscreen.

Filup *Union Drug, Thai.*
Methyl salicylate (p. 92·1).
Musculoskeletal pain.

Filxine *Mertens, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Fima HES *Kalbe, Indon.*
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion; shock.

Fimalbumin *Hexpharm, Indon.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoproteinaemia; neonatal hyperbilirubinaemia; shock.

Fimer *LKM, Arg.*
Tegafur (p. 864·2); uracil (p. 2637·3).
Malignant neoplasms.

Fimi *Medico, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fimi-CV *Medico, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).

Fimoplas *Blue Sky, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Fin *Captab, India.*
Terbinafine (p. 593·3).
Fungal skin and nail infections.

Finabald *East West, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Finabald-T *East West, India.*
Finasteride (p. 2358·3); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Finaband *Microsules, Arg.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Finaber *Microsules, Arg.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Finac *C & M, USA.*
Sulfur (p. 1721·1); methylbenzethonium chloride (p. 1760·3).
Acne.

Finacapil *Sandoz, Switz.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Finaccord *Arrow, NZ.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finacea *CSL, Austral.; Bayer, Canad.; Intendis, Denm.; Bayer Sante, Fr.; Unicorp, Hung.; Intendis, Ital.; Intendis, Mex.; Intendis, Neth.; Intendis, Norw.; Intendis, Pol.; Bayer, Port.; Intendis, Spain; Bayer, Swed.; Intendis, Turk.; Bayer, UK; Bayer, USA.*
Azelaic acid (p. 1695·1).
Rosacea; acne.

Finacilen *Microsules, Arg.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Finagalen *MR Pharma, Neth.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

FinaGen *Jenson, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finagrip Forte *Finadiet, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

FinaHAIR *Hexal, Ger.†*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Finahold *MR Pharma, Neth.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finail *Orifarm, Swed.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Finajelf *Jelfa, Cz.; Jelfa, Neth.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finalax *Liferpal, Mex.*
Ispaghula (p. 1849·1).
Constipation.

Finalgel *Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Ukr.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Finalgon *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Ukr.*
Nonivamide (p. 102·3); nicoboxil (p. 101·1).
Peripheral vascular disorders; neuritis; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Finalgon CPD *Boehringer Ingelheim, Ger.*
Cayenne pepper (p. 2469·3).
Formerly known as Finalgon Capsicum.
Musculoskeletal pain.

Finalo *Intas, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Finalop *Libbs, Braz.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Finamed *Mibe, Ger.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finamef *Mepha, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finamicina *Teva, Mex.†*
Rifampicin (p. 350·3).
Tuberculosis.

Finanidda *Gedeon Richter, Neth.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Finanorm *Valeant, Cz.; Valeant, Hung.; ICN, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finap *Raffo, Chile.†*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder.

Finapécia *TKS, Braz.*
Finasteride (p. 2358·3).

Finapil *Dermapharm, Ger.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Finaplac *Epicaris, Arg.†*
Chlorhexidine gluconate (p. 1743·3).
Dental hygiene.

Finaprost *Teva, Denm.; Faran, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finar *Specifar (Σπεσιφαρ), Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finara *Reddy, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finaran *Ranbaxy, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finard *Ardez, Cz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finarid *Teuto, Braz.; Unicure, Philipp.; Nobel, Turk.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finaride *Psyco Remedies, India; Sandoz, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Finartrit *Garden House, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Finas *Intas, Singapore.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Finascar *TAD, Ger.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finaschwarz *MR Pharma, Neth.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finasept *Microsules, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Finast *Reddy, India; Reddy, Philipp.; Reddy, Rus.; Reddy, Singapore; Reddy, Ukr.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finast T *Reddy, India.*
Finasteride (p. 2358·3); tamsulosin (p. 2369·1).
Benign prostatic hyperplasia.

Finasta *Sandoz, Austral.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finastad *Pharmacodane, Denm.; Siegfried, Neth.†*
Finasteride (p. 2358·3).
Alopecia androgenetica; benign prostatic hyperplasia.

Finastat *Active, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finastec *Neo Quimica, Braz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finastep *Extractum, Hung.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finaster *Lek-Am, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finasterax *Drossapharm, Switz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finasterin *Finadiet, Arg.*
Finasteride (p. 2358·3).

Finastid *Neopharmed, Ital.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finastil *Sigma, Braz.*
Finasteride (p. 2358·3).

Finastir *Genepharm, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finate *Franco-Indian, India.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Finaten *Microsules, Arg.*
Bromazepam (p. 1041·2).
Anxiety; alcohol withdrawal syndrome; panic disorder.

Finater *Teva, Mex.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Finateramida *Teva, Mex.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Finatra *Hanmi, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finatux *Jaba, Port.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Finax
Note: this name may be used for preparations of different composition.
Domesco, Philipp.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Reddy, India.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Finaxal *Sandoz, Indon.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finazil *Rafarm, Gr.*
Finasteride (p. 2358·3).

Finazole *Khandelwal, India.*
Ketoconazole (p. 585·3).
Fungal infections.

Fincar *Cipla, Hong Kong; Cipla, India; Cipla-Medpro, S. Afr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fincip *Maver, Chile.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Fincof *USP, India.*
Cetirizine (p. 619·2); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Findaler *Medipharm, Chile.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Findaler-D *Medipharm, Chile.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Findeclin *Finadiet, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Findeclin Combi *Finadiet, Arg.*
4 tablets, alendronate sodium (p. 1171·3); 30 tablets, calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Finderm *Zydus, S.Afr.*
Terbinafine (p. 593·3).

Findol
Note: this name may be used for preparations of different composition.
Temis, Arg.
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Findol Plus *Temis, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Fine *Baroda, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Fineact *Datla, India.*
Diclofenac sodium (p. 48·3).
Pain.

Finecef *Piramal, India.*
Cefpodoxime.
Bacterial infections.

Finecef AM *Piramal, India.*
Ambroxol (p. 1654·3); cefpodoxime.

Finecef-CV *Piramal, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Finecef-T *Piramal, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Finecil *LKM, Arg.*
Abacavir sulfate (p. 963·1).
HIV infection.

Finelium *PP Lab, Thai.*
Flunarizine hydrochloride (p. 629·3).
Vestibular disorders; cerebral and peripheral vascular disorders.

Finemox *Finecure, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Fineorest *Finecure, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Finescar
Note: this name may be used for preparations of different composition.
Biol, Arg.
Silicone oil (p. 2209·2).
Decubitus ulcers; barrier preparation.

SM, Gr.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finetouch *Terumo, Ital.*
Test for glucose in blood (p. 2516·3).

Finetriax *Finecure, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Finetriax-S *Finecure, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Finevin *Berlex, USA.*
Azelaic acid (p. 1695·1).
Acne.

Finex
Note: this name may be used for preparations of different composition.
Hexal, Cz.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Saval, Chile.
Terbinafine (p. 593·3).
Fungal skin and nail infections.

Finezol *Finecure, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Fingras
Note: this name may be used for preparations of different composition.
Phoenix, Arg.
Orlistat (p. 2577·1).
Obesity.

Finibax *Shionogi, Jpn.*
Doripenem (p. 287·2).
Bacterial infections.

Finicort *Gabriel, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections.

Finigas *Apsen, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Finigen *Orifarm, Denm.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Finigraine *3DDD, Belg.†*
Sumatriptan (p. 679·2).

Finimal *Bayer, Neth.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Finimal Zest *Bayer, Neth.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Formerly known as Finimal C.
Pain; fever.

Finish
Note: this name may be used for preparations of different composition.
Biotherm, Canad.†
SPF 10; SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Kowa, Jpn.†
Povidone-iodine (p. 1767·1).

Finitor *Confar, Port.*
Selenium sulfide (p. 1719·3).
Fungal scalp infections.

Finlac *Sons, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Finlepsin *AWD, Ger.; AWD, Pol.; Teva, Rus.; Pliva, Ukr.*
Carbamazepine (p. 512·2).
Epilepsy; alcohol withdrawal syndrome; neuralgias; diabetic neuropathy; multiple sclerosis; bipolar disorder; psychoses.

Finlipol *Microsules, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Finminette *Sandoz, Denm.; Sandoz, Norw.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Finn *Boehringer Ingelheim, Braz.*
Aspartame (p. 2169·2).
Sugar substitute.

Finn Cristal *Boehringer Ingelheim, Braz.*
Saccharin sodium (p. 2208·1); sodium cyclamate (p. 2180·2).
Sugar substitute.

Finnacar *Sigma, Austral.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finocar *Pliva, Irl.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finoptin *Orion, Rus.; Orion, Ukr.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic obstructive cardiomyopathy; pulmonary hypertension.

Finox
Note: this name may be used for preparations of different composition.
Edol, Port.
Finasteride (p. 2358·3).
Alopecia androgenetica.
Solvang, Philipp.
Mefenamic acid (p. 85·3).
Pain.

Finoxi *Finadiet, Arg.†*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Finpecia *Cipla, India; Cipla-Medpro, S.Afr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia androgenetica.

Finpro *Interbat, Indon.; Reddy, S.Afr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finprob *Farcoral, Mex.*
Pipenzolate bromide (p. 1878·1); dimeticone (p. 1886·2).
Gastrointestinal disorders.

Finpros *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finprostat *LKM, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finrexin *Leiras, Fin.*
Aspirin (p. 22·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Fever; pain.

Finster *Emgen, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Fintal *Piramal, India.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; vernal keratoconjunctivitis; asthma; allergic rhinitis.

Fintaxim *Maver, Chile.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Fintaxim G *Maver, Chile.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Finterac *Eurolab, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fintex *Helsinn Birex, Irl.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fintop *Glenmark, India.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Fintral *Douglas, NZ; Polpharma, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fintrid *Rowex, Irl.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fintride *Kopran, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finural *Pfleger, Ger.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Finuret *Bernabo, Arg.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Finxta *Farma-Projekt, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fiona *Reddy, India.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Fiorda *Driburg, Arg.*
Amitriptyline (p. 401·1).

Fioricet *Actavis, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Fioricet with Codeine *Actavis, USA.*
Codeine phosphate (p. 40·2); butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Fiorinal
Note: this name may be used for preparations of different composition.
Novartis, Canad.; Actavis, USA.
Aspirin (p. 22·2); butalbital (p. 1043·3); caffeine (p. 1203·3).
Vascular or tension headaches; pain.
Novartis Consumer, Austral.
Codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Pain.

Fiorinal C *Novartis, Canad.*
Butalbital (p. 1043·3); caffeine (p. 1203·3); aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; tension; anxiety.

Fiorinal Codeina *Novartis, Spain.†*
Capsules: Aspirin (p. 22·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Fiorinal with Codeine *Watson, USA.*
Aspirin (p. 22·2); butalbital (p. 1043·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Tension headache.

Fioritina *Fada, Arg.*
⊗Noradrenaline (p. 1458·2).

Fiosen-A *Medica, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Fiosen-Plus *Frasca, Arg.*
Alpha tocoferol; vitamin A (p. 2098·3); pyridoxine (p. 2105·3).
Vitamin supplement.

Fiotan *Altana, Braz.†*
St John's wort (p. 449·1).
Depression.

Fioton *Phoenix, Arg.*
Ginkgo biloba (p. 2512·3); vitamin E (p. 2119·1).
Mental function impairment; vertigo; vitamin E deficiency.

Fipexiam *Leti, Venez.*
Injection: Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.
Leti, Venez.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

FiProFLAX *Arkopharma, UK.*
Flax oil; fibre; proteins; carbohydrates; lignans.
Dietary supplement.

Firac *Grossman, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Firac Plus *Grossman, Mex.*
Clonixin lysine (p. 40·1); pargeverine hydrochloride (p. 1877·1).
Smooth muscle pain and spasm.

Firazyr *Shire, Austral.; Jerini, Austria; Jerini, Cz.; Shire, Denm.; Shire, Fr.; Shire, Ger.; IFET (ΙΦΕΤ), Gr.; Shire, Gr.; Jerini, Irl.; Medison, Israel; Shire, Neth.; Jerini, Norw.; Jerini, Pol.; Jerini, Port.; Shire, Rus.; Jerini, Spain; Shire, Swed.; Drac, Switz.; Shire, UK; Shire, USA.*
Icatibant acetate (p. 2531·1).
Hereditary angioedema.

Firdapse *BioMarin, Cz.; BioMarin, Denm.; BioMarin, Fr.; BioMarin, Ger.; BioMarin, Irl.; Medison, Israel; BioMarin, Neth.; BioMarin, Pol.; BioMarin, Port.; BioMarin, Swed.; Drac, Switz.; BioMarin, UK.*
Amifampridine phosphate (p. 685·1).
Lambert-Eaton myasthenic syndrome.

Firex *Grin, Mex.†*
Aciclovir (p. 964·1).
Herpes labialis.

Firide *Siam Bheasach, Thai.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Firin *Schwarz, Ger.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Firm Up *Piramal, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Firmagon *Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Ferring, Cz.; Ferring, Denm.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Irl.; Ferring, Israel; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Port.; Ferring, Swed.; Ferring, Switz.; Ferring, UK; Ferring, USA.*
Degarelix acetate (p. 2266·2).
Prostatic cancer.

Firmapol *Leontik, Gr.*
Ketotifen fumarate (p. 631·3).

Firmasta *KRKA, Rus.*
Irbesartan hydrochloride (p. 1411·1).
Hypertension; diabetic nephropathy.

Firmel *Craveri, Arg.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Firsito *Zydus, India.*
Escitalopram oxalate (p. 416·2).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

First Aid Antiseptic Skin Cleanser *Germiphene, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

First Aid Spray *Canadian Custom Packaging, Canad.*
Benzocaine (p. 1980·2).
Local anaesthesia.

First Choice *Polymer Technology, USA.*
Test for glucose in blood (p. 2516·3).

First Defence *Procter & Gamble, Austral.; Procter & Gamble, UK.*
Viscous nasal gel.
Cold prophylaxis.

First Duke's Mouthwash *Cutis, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); hydrocortisone (p. 1640·1); nystatin (p. 590·3).

First Mary's Mouthwash *Cutis, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); hydrocortisone (p. 1640·1); nystatin (p. 590·3); tetracycline hydrochloride (p. 373·2).

First Response *Church & Dwight, Canad.†; Carter-Wallace, UK; Carter-Wallace, USA.*
Pregnancy or fertility test (p. 2596·1).

Firstcin *Takeda, Jpn.*
Cefozopran hydrochloride (p. 247·1).
Bacterial infections.

Fisamox *Aspen, Austral.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Fiscon *Novagen, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fiscon Tab *Novagen, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Fish Factor *Avantgarde, Ital.*
Omega-3 marine triglycerides (p. 1460·3).
Hyperlipidaemias.

Fishaphos *Felton, Austral.†*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Fishogar *Self-Care Products, UK.*
Fish oil (p. 1460·1); garlic (p. 2510·3).

Fisioativ *Glenmark, Braz.*
Panthenol (p. 2582·2); allantoin (p. 1693·1); tocopherol (p. 2119·1).

Fisiobil *Solvat, Spain.*
Dimecrotic acid, magnesium salt (p. 2493·2).
Hepatobiliary disorders.

Fisiocap *Pasteur, Chile.†*
Nutritional supplement.
Hair and nail disorders.

Fisiodar *Abiogen, Ital.*
Diacerein (p. 45·3).
Osteoarthritis.

Fisioderm
Note: this name may be used for preparations of different composition.
Andromaco, Arg.
Sulfadiazine silver (p. 362·3); vitamin A palmitate (p. 2098·3); lidocaine (p. 1988·1).
Infected skin disorders; ulcers; burns.
Dermofarma, Ital.
Soap substitute.

Fisiofer *Labomed, Chile.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Fisiogel *GSK, Arg.*
A range of emollients.
Stiefel, Braz.; Stiefel, Chile; Stiefel, Mex.
Emollient.
Dry skin.

Fisiogen *Zambon, Braz.*
Soya bean (p. 2092·3).
Menopausal symptoms.

Fisiolimp *Pasteur, Chile.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal hygiene.

Fisiolin *Oftalmi, Venez.*
Sodium chloride (p. 1795·1); monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Nasal congestion; nasal cleansing.

Fisiologica *Aplicaciones Farmacodinamicas, Spain.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

Fisiologico *Betamadrileno, Spain†; Neusc, Spain.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

Fisiologico Bieffe Medital *Baxter, Spain.†*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; hypovolaemia.

Fisiologico Braun *Braun, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; hypovolaemia.

Fisiologico Mein *Fresenius Kabi, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; hypovolaemia.

Fisiologico Serra Pamies *Serra Pamies, Spain.†*
Sodium chloride (p. 1795·1).
Diluent for parenterally administered drugs.

Fisiologico Vitulia *Ern, Spain.†*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; hypovolaemia.

Fisiomar *Pasteur, Chile.*
Sea water (p. 2612·1).
Nasal congestion; nasal hygiene.

Fisioren *Ducto, Braz.*
Diclofenac potassium (p. 48·3) or diclofenac resinate (p. 48·3).

Fisioreve CM *Laborest, Ital.*
Tryptophan (p. 453·2); california poppy (p. 2466·1); chamomile (p. 2474·1).
Insomnia; depression.

Fisiorinus *Cazi, Braz.*
Sodium chloride (p. 1795·1).

Fisiotens *Abbott, Gr.; Solvay, Ital.*
Moxonidine (p. 1442·1).
Hypertension.

Fisioton *Ache, Braz.*
Rhodiola rosea.
Tonic.

Fisohex II *Farmasa, Braz.*
Triclosan (p. 1773·2); pyrithione zinc (p. 1718·1).
Skin disinfection.

Fisol *Nature's Way, Philipp.†*
Omega-3 fish oil (p. 1460·3).
Dietary supplement.

Fisomed *SM, Venez.*
Soap substitute.

Fisopred *Sanofi-Aventis, Mex.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Fisox *Forgo, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Fissan
Note: this name may be used for preparations of different composition.
Cana, Gr.
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin disorders.
Group, S.Afr.
Lactic protein hydrolysate (p. 2086·2); zinc oxide (p. 1729·1).
Nappy rash; skin irritation.

Fissan-Pate *Cana, Gr.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1); rapeseed oil (p. 2602·3); kaolin (p. 1850·1); wool fat (p. 2219·3).
Skin disorders.

Fissan-Silberpuder *Trioktivin, Ger.*
Methenamine silver nitrate compound.
Umbilical cord care.

Fista *Laborate, India.*
Boric acid (p. 2459·3); chlorphenamine maleate (p. 620·3); sodium chloride (p. 1795·1); zinc sulfate (p. 2126·2).

Fisterid *Kleva, Gr.*
Finasteride (p. 2358·3).

Fistide *Samarth, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fit *East African, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine (p. 1113·2).

Fitajoint *Combiphar, Indon.*
N-Acetyl glucosamine (p. 2515·3); mint (p. 2621·2); vitamin E (p. 2119·1); lavender oil (p. 2541·1).
Cartilage disorders; musculoskeletal and joint pain.

Fitantis *Zdorovje, Rus.*
Tormentil (p. 2633·2); coltsfoot (p. 1659·2); plantain (p. 2592·3); achillea (p. 2427·3); sage (p. 2608·3).
Gastrointestinal infections; mouth and throat inflammation.

Fitbon *Soho, Indon.*
Glucosamine hydrochloride (p. 2515·3).
Joint disorders.

Fitbon Plus *Soho, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); manganese (p. 2081·2).
Joint disorders.

Fit-C *Soho, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Fitesten *Minskinterkaps, Ukr.*
Pine needle extract (p. 2591·1).
Gastrointestinal disorders.

Fitflam *Finecure, India.*
Ibuprofen (p. 68·2); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Fitgyl *Christo, Hong Kong.†*
Metronidazole (p. 936·1).

Fitin *Medley, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Fitina *Vargas, Venez.*
Pyritinol (p. 394·3).
Mental function impairment; neurological disorders.

Fitin-CF *Medley, India.*
⊗Levocetirizine hydrochloride (p. 632·3); pseudoephedrine (p. 1676·1).

Fitkom *Soho, Indon.*
Chewable tablets: Vitamins.
Dietary supplement; tonic.
Soho, Indon.
Oral syrup: Vitamins; iron (p. 2073·1); inositol (p. 2533·2); lysine hydrochloride (p. 2079·3); taurine (p. 2626·2).
Dietary supplement; tonic.

Fitness *Cipla, India.*
Spirulina (p. 2622·1).

Fitness Iper K *Scaglietti, Ital.*
Emollient.

Fitness Perle di Karite *Scaglietti, Ital.*
Emollient.

Fitness Tabs for Men *MDR, USA.*
AM tablets, vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2); zeaxanthin (p. 2125·3); garlic (p. 2510·3); PM tablets, vitamins; minerals; lutein; lycopene; zeaxanthin; garlic.
Dietary supplement.

Fitness Tabs for Women *MDR, USA.*
AM tablets, vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2); zeaxanthin (p. 2125·3); garlic (p. 2510·3); PM tablets, vitamins; minerals; lutein; lycopene; zeaxanthin; garlic.
Dietary supplement.

Fit-N-Trim *Manix, Philipp.*
Green tea (p. 2648·2); levocarnitine (p. 2053·2).
Dietary supplement.

Fito *Abdi, Turk.*
Wheat germ (p. 2647·1).
Skin disorders.

Fito Stomygen *Stomygen, Ital.†*
Mallow (p. 2549·2); hamamelis (p. 2523·3); chamomile (p. 2474·1); sage (p. 2608·3); calendula (p. 2465·2).
Herbal toothpaste.

Fitoadapt *Ecopharma, Arg.*
Phytosterol (p. 1471·2).
Hypercholesterolaemia.

Fitocassol *Kimia, Indon.*
Centella (p. 1698·3).
Keloid scars.

Fitocreme *Faribérica, Port.*
Wheat germ (p. 2647·1); phenoxyethanol (p. 1764·3).
Burns; ulcers; wounds.

Fitocyd *Unipharm, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Fitodiar *Kimia, Indon.*
Attapulgite (p. 1820·1); psidium guajava; turmeric (p. 2218·1).
Diarrhoea.

Fitoestimulina *Grossman, Mex.*
Wheat germ (p. 2647·1); phenoxyethanol (p. 1764·3).
Burns; ulcers; vaginal lesions; wounds.

Fitoflavona *Dispolab, Chile.*
Soya isoflavones (p. 2620·3).
Menopausal flushes.

Fitogen *Bergamon, Ital.*
Soya oil (p. 2092·3); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Nutritional supplement; menopausal disorders.
Phapros, Indon.
Red clover (p. 2482·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1).
Dietary supplement; menopausal disorders.

Fitogen Plus *Bergamon, Ital.*
Nutritional supplement.

Fitogenase *Bergamon, Ital.*
Soya isoflavones (p. 2620·3); Indian frankincense (p. 2507·3); glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); ananas comosus; omega-3 (p. 1460·1).
Menopausal disorders.

Fitogenos *Framingham, Arg.*
Soya isoflavones (p. 2620·3); vitamin D (p. 2112·3); *d*-alpha tocopherol (p. 2119·1).
Menopausal disorders.

Fitogyn *Casen Fleet, Spain.*
Soya (p. 2092·3); red clover (p. 2482·1).
Menopausal disorders.

Fitokey Ginkgo *Pharminicio, Spain.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral circulatory disorders.

Fitoladius *Merck, Spain.*
Soya (p. 2092·3).
Menopausal disorders.

Fitolax *IMA, Braz.†*
Senna (p. 1885·1); cassia pulp (p. 1826·2); tamarind (p. 1892·2); coriander (p. 2486·3).
Constipation.

Fitonal *Andromaco, Arg.*
Ketoconazole (p. 585·3).
Fungal infections.

Fitoprost *Hasco-Lek, Norw.; Hasco-Lek, Pol.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Fitosonno *Bayer, Ital.*
California poppy (p. 2466·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Insomnia; nervous disorders.

Fitostimoline *Damor, Ital.*
Cream; medicated dressing; pessaries; vaginal wash: Wheat germ (p. 2647·1); phenoxyethanol (p. 1764·3).
Skin disorders; vascular disorders; burns; wounds; vaginal disorders.
Damor, Ital.
Injection: Wheat germ (p. 2647·1).
Skin disorders; vascular disorders; burns; wounds.

Fitosvelt *Arkochim, Spain.†*
Black currant (p. 2458·1); tea (p. 2648·2).
Diuretic.

Fitotos *Koni-Cofarm, Chile.*
Tolu balsam (p. 1679·2); drosera (p. 2497·2); quillaia (p. 2207·1).
Cough.

Fitotranzit *Evalar, Rus.*
Laminaria (p. 2540·1).
Constipation; atherosclerosis; thyroid diseases; iodine deficiency.

Fitoval Antidandruff *KRKA, Ukr.*
Ichthyol light (p. 1705·3).
Seborrhoeic dermatitis of the scalp; psoriasis of the scalp.

Fitoval Capsules *KRKA, Ukr.*
Yeast (p. 2125·2); cystine (p. 2059·1); calcium pantothenate (p. 2085·2); thiamine (p. 2102·3); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); biotin (p. 2052·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1); copper (p. 2057·1).
Hair loss; fragile hair.

Fitoval Lotion *KRKA, Ukr.*
Esculoside (p. 2431·2); ximenynic acid; lauric acid.
Formerly known as Fitoval Plus Lotion.
Alopecia.

Fitoval Shampoo *KRKA, Ukr.*
Sage (p. 2608·3); urtica (p. 2639·3); dexpanthenol (p. 2582·2); lecithin (p. 2542·2); protein.
Hair loss; fragile hair.

Fitoval Shampoo Anti-Hair Loss *KRKA, Ukr.*
Glycogen (p. 2519·2); arnica (p. 2447·2); rosemary (p. 2607·2); hydrolysed wheat protein.
Formerly known as Fitoval Plus Shampoo.
Hair loss; fragile hair; dandruff.

Fitoven *Herbapol Pruszkow, Pol.*
Aesculus (p. 2431·2); crataegus (p. 2488·1); solidago (p. 2620·1); tilia (p. 2631·3); buckwheat (p. 2462·1); scoparium (p. 2611·3); root beet.
Venous thrombosis; phlebitis; oedema.

Fitovit *Unique, Rus.*
⊗Ashwagandha (p. 2450·2); Indian gooseberry (p. 2532·2); asparagus (p. 2450·2); tinospora cordifolia; tribulus terrestris (p. 2633·3); picrorhiza kurroa (p. 2590·2); cyperus scariosus; bacopa (p. 2452·1); chebulic myrobalan (p. 2474·3); piper longum; nutmeg (p. 2573·1).
Tonic.
Unique, Ukr.
⊗Ashwagandha (p. 2450·2); Indian gooseberry (p. 2532·2); shatavari (p. 2614·2); tinospora cordifolia; tribulus terrestris (p. 2633·3); picrorhiza kurroa (p. 2590·2); cyperus scariosus; bacopa monnieri (p. 2452·1); chebulic myrobalan (p. 2474·3); piper longum; nutmeg (p. 2573·1).
Asthenia; mental function impairment; atherosclerosis; reduced appetite.

Fitovital *Catarinense, Braz.†*
St John's wort (p. 449·1).
Depression.

Fitrum *Herbs & Nature, Philipp.*
Green tea extract (p. 2648·2); levocarnitine (p. 2053·2).
Dietary supplement.

Fittig Antimicotico *Andromaco, Chile.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); hexylresorcinol (p. 1755·1); calcium propionate (p. 592·3) or sodium propionate (p. 593·1).
Fungal skin infections.

Fittig Desodorante *Andromaco, Chile.*
Triclosan (p. 1773·2); menthol (p. 2553·2); silicon dioxide (p. 2208·3).
Foot deodoriser.

Fittydent *Reddy, India.*
Dental adhesive: Carmellose (p. 2175·1); polyvinyl acetate (p. 2204·1).
Reddy, India.
Denture cleanser: Sodium perborate monohydrate (p. 1770·1).

Fitzecalm *Julphar, UAE.*
Carbamazepine (p. 512·2).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Fitzine-MD *BMW, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Fivasa *Norgine, Fr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Fivefluro *GSK, India.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fiverdol *Maver, Mex.*
Paracetamol (p. 115·1); naproxen (p. 98·2).
Inflammation; pain.

Fivocil *Alkem, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fivoflu *Dabur, India; Fresenius Kabi, Philipp.; Dabur, Thai.†; Biogalenic, Venez.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fivtum *Alkem, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fix-A *ACME, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Fixacep *Fahrenheit, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Fixam *Solas, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Fixateur phospho-calcique *Bichsel, Switz.*
Calcium carbonate (p. 1824·3).
Hyperphosphataemia.

Fixcanat *Pisa, Mex.†*
Cysteine hydrochloride (p. 2058·3).
Cysteine deficiency.

Fixcef *Laksun, India; Bosch, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Fixcef-CL *Laksun, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).

Fixcom 3 *Natrapharm, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol (p. 296·1).
Tuberculosis.

Fixcom 4 *Natrapharm, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol (p. 296·1).
Tuberculosis.

Fixef *Kalbe, Indon.; Deva, Turk.*
Cefixime (p. 240·3).
Bacterial infections.

Fixeril *Lazar, Arg.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Fixi *Excare, India.*
Dispersible tablets; syrup: Cefixime (p. 240·3).
Bacterial infections.
Excare, India.
Injection: Ceftriaxone (p. 253·3).
Bacterial infections.

Fixical *Expanscience, Fr.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Fixical Vitamine D_3 *Expanscience, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Fixiflox *Servocare, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Fixiflox-D *Servocare, India.*
⊗Ofloxacin (p. 334·3); dexamethasone (p. 1630·3).

Fixiflox-H *Servocare, India.*
Ofloxacin (p. 334·3); hypromellose (p. 2189·2).

Fixiflox-OZ *Servocare, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fixime *Merck, S.Afr.†*
Cefixime (p. 240·3).
Bacterial infections.

Fixiphar *Pharos, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Fixit *Finecure, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fixital *Servocare, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Fixon *Novag, Mex.*
Imipramine (p. 426·2).
Depression.

Fixopan *Farma, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fixoten *Cryopharma, Mex.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Fixsana *Sanify, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fixsana-LB *Sanify, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Fixsav *Saviour, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fixtan *Little Greave, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Fixtrim *Dr Kumars, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fixx *Unichem, India.*
Cefixime (p. 240·3).
Bacterial infections.

Fixx Clav *Unichem, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Fixx LB *Unichem, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Fixxx *XL, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Fizoil *Behrens, Venez.*
Fish oil (p. 1460·3).
Hypercholesterolaemia.

Fizol *Nutramedica, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Nutramedica, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).

Fizyolen *Toprak, Turk.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Fizyolik *SSK, Turk.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Fizyosol *Oro, Turk.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Fizzical *Gulf Drug, S.Afr.*
Calcium carbonate (p. 1824·3).

FKD *Pharma Investi, Chile.*
Sodium bicarbonate (p. 1781·1); sodium fluoride (p. 2089·2); sodium pyrophosphate (p. 2619·3).
Dental whitener; dental caries prophylaxis.

Flaag *Flamingo, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Flabone *Gufic, India.*
Calcium citrate (p. 1783·2); alfacalcidol (p. 2112·3); vitamin C (p. 2110·3).

Flacar *Schwabe, Ger.*
⊗Betaine dihydrogen citrate (p. 2456·1); sorbitol (p. 2092·1); mannitol (p. 1427·3).
Liver disorders.

Flacel *Ace, Philipp.*
Metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis; anaerobic bacterial infections; peptic ulcer; bacterial vaginosis; gingivitis; balantidiasis; blastocystis.

Flacerant *Lloyd, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer.

Flacidon *Gold Coast, Philipp.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Fladalgin *Proel, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Fladex
Note: this name may be used for preparations of different composition.
Dexa, Indon.; Dexa, Singapore.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; amoebiasis; giardiasis; trichomoniasis.

Zdorovje, Rus.; Zdorovje, Ukr.
Fladexsan.
Skin disorders.

Fladexon *Flamingo, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever; inflammation.

Fladolef-B *Proel, Gr.*
Flurbiprofen (p. 65·2).
Inflammatory disorders; pain.

Fladon *Daudt, Braz.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Fladystin *Dexa, Indon.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Flagass *Ache, Braz.*
Simeticone (p. 1886·2).
Flatulence.

Flagass Baby *Ache, Braz.*
Simeticone (p. 1886·2); homatropine methylbromide (p. 2007·3).
Flatulence.

Flagenase *Liomont, Mex.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Flagenase 400 *Liomont, Mex.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1); diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Flagenol *Allen, Mex.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis; anaerobic bacterial infections.

Flagentyl *Sanofi-Aventis, Arg.; Sanofi-Aventis, India; Sanofi-Aventis, Philipp.; Vitoria, Port.; Eczacibasi, Turk.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis; protozoal infections.

Flagepat *Parggon, Mex.*
Metronidazole (p. 936·1).
Amoebiasis.

Flagimax *Belfar, Braz.*
Metronidazole (p. 936·1).

Flago *Biomedica, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Flagocil *Collins, Mex.†*
Diiodohydroxyquinoline (p. 931·1); metronidazole (p. 936·1).
Protozoal infections.

Flagolin *Farmedia, Gr.*
Metronidazole (p. 936·1).

Flagsol *Salas, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Flagyl *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Piramal, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Zambon, Ital.; Sanofi-Aventis, Malaysia†; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Aventis, NZ; Sanofi-Aventis, Philipp.; Vitoria, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Eczacibasi, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Pfizer, USA.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections; bacterial vaginosis; Crohn's disease; amoebiasis; trichomoniasis; giardiasis.

Flagyl Comp *Sanofi-Aventis, Fin.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal trichomoniasis; bacterial vaginosis.

Flagyl Nistatina *Sanofi-Aventis, Braz.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vulvovaginal candidiasis and trichomoniasis.

Flagyl-F *Piramal, India.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1); furazolidone (p. 933·3).
Amoebiasis.

Flagynor *Piramal, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Flagystatin *Sanofi-Aventis, Arg.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Singapore.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vulvovaginal infections; vaginal trichomoniasis and candidiasis.

Flagystatin V *Sanofi-Aventis, Mex.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal trichomoniasis and candidiasis.

Flakefree *Neiss, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Flamace *Biomax, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Flamace-MR *Biomax, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Flamace-P *Biomax, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Flamace-S *Biomax, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

Flamace-SP *Biomax, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Flamacorten *Globo, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Flamador *Sigma, Braz.*
Ketoprofen (p. 79·1).

Flamalit *Vivax, Venez.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Flamanan *Legrand, Braz.*
Paracetamol (p. 115·1); oxyphenbutazone (p. 114·3).
Fever; inflammation; pain.

Flamar
Note: this name may be used for preparations of different composition.
Nabiqasim, Philipp.
Celecoxib (p. 36·3).
Osteoarthritis; pain; rheumatoid arthritis.

Sanbe, Indon.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation following eye surgery.

Indoco, India.†
Methyl nicotinate (p. 91·3); methyl salicylate (p. 92·1); mephenesin (p. 2025·2); menthol (p. 2553·2).
Musculoskeletal, joint and soft-tissue disorders.

Flamar-DP *Indoco, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Flamaret *Xixia, S.Afr.†*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Flamar-MX *Indoco, India.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Formerly contained diclofenac sodium, paracetamol, and chlorzoxazone.
Painful skeletal muscle spasm.

Flamar-P *Indoco, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Flamaryx *Aurobindo, S.Afr.*
Meloxicam (p. 86·3).

Flamasacard *Abbey, UK.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Flamastat *Chiesi, Philipp.*
Piroxicam betadex (p. 126·1).
Musculoskeletal and joint disorders.

Flamatak *Alphanna, UK.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Flamatec *Uniao Quimica, Braz.*
Meloxicam (p. 86·3).

Flamatrat P *Vitapan, Braz.*
Diclofenac (p. 48·3).

Flamax *Replekpharm, Rus.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, peri-articular and soft-tissue disorders; inflammation.

Flamazine *Smith & Nephew, Austral.; Smith & Nephew, Canad.; Smith & Nephew, Denm.; Smith & Nephew, Fin.; Smith & Nephew, Hong Kong†; Smith & Nephew, Irl.; Smith & Nephew, Norw.; Smith & Nephew, NZ; Smith & Nephew, S.Afr.; Smith & Nephew, Thai.; Smith & Nephew Healthcare, UK.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers, and wounds; skin infections.

Flamclov *Flamingo, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Flame *Dexcel, Israel.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Flamebin *Offenbach, Mex.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2).
Respiratory-tract disorders.

Flamecid *Adcock Ingram, S.Afr.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Flamenac *Hexpharm, Indon.†*
Diclofenac potassium (p. 48·3).
Musculoskeletal and joint disorders; gout.

Flamergi *Sanbe, Indon.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye irritation; allergic eye disorders.

Flameril *Novartis, NZ; Normal, Port.; Novartis, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain.

Sandoz, Hung.†
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flamesan *Esan, Chile.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain; peri-articular and soft-tissue disorders.

Flamese *Meridian, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Meridian, India.
Tablets: ⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Flamese-K *Meridian, India.*
Paracetamol (p. 115·1); diclofenac potassium (p. 48·3).
Musculoskeletal and joint disorders.

Flamese-KR *Meridian, India.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3).

Flamesul *Intas, Philipp.†*
Nimesulide (p. 101·3).
Pain; inflammation.

Flamether *Flamingo, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Flametia *Tunggal Idaman, Indon.†*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis.

Flamexin *Chiesi, Cz.; Chiesi, Hung.; Torrex Chiesi, Pol.*
Piroxicam betadex (p. 126·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Flamibazid *Flamingo, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Flamic
Note: this name may be used for preparations of different composition.
Gracia, Indon.
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Siam Bheasach, Thai.
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Flamicef *Flamingo, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Flamicina *Teva, Mex.*
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Flamicort *Dexa, Indon.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Flamide *Rayere, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Flamigel *Aspen, Austral.*
Hydroactive colloid gel.
Burns; wounds.

Flen, Belg.
A hydrogel dressing.
Wounds.

Flamin
Note: this name may be used for preparations of different composition.
Vifiteh, Rus.
Helichrysum.
Biliary-tract disorders.

Flamina *Eurodrug, Thai.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Flaminal *Ark, UK.*
Alginate gel (p. 2167·2); glucose oxidase (p. 2516·3); lactoperoxidase (p. 2539·3).
Wounds.

Aspen, Austral.
Sodium alginate (p. 2167·3); calcium alginate (p. 1136·3); glucose oxidase (p. 2516·3); lactoperoxidase (p. 2539·3).
Wounds.

Flaminase *Formenti, Ital.*
⊗Promelase (p. 2597·3).
Respiratory-tract disorders.

Flaminim *Flamingo, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Flaminis *Nicholas, Indon.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Gastritis; gastric hyperacidity; flatulence; dyspepsia.

Flamir *Bago, Chile.*
Adapalene (p. 1692·1).
Acne.

Flamirex
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Arg.
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flamisul *Premium, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Flamitin *Flamingo, Philipp.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Flammacerium *Qualiphar, Belg.; Solvay, Fr.; Solvay, Gr.; Solvay, Hong Kong; ADOH, Neth.; Solvay, Philipp.; Solvay, Pol.†; Solvay, UK.*
Sulfadiazine silver (p. 362·3); cerous nitrate (p. 1699·1).
Skin infections; infected wounds and burns.

Flammaspray *Sinclair, Fr.*
Oxaceprol (p. 2578·2).
Sunburn.

Flammazine *Sinclair, Austria; Qualiphar, Belg.; 2care4, Denm.; Sinclair, Fr.; Sinclair, Ger.; IFET (ΙΦΕΤ), Gr.; ADOH, Neth.; Solvay, Philipp.; Sinclair, Port.; Sinclair, Spain; Sinclair, Switz.*
Sulfadiazine silver (p. 362·3).
Infected burns; ulcers; infected skin disorders; infected wounds.

Flammazine Cerio *Sinclair, Spain.*
Sulfadiazine silver (p. 362·3); cerous nitrate (p. 1699·1).
Infected burns.

Flamon *Mepha, Switz.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; ischaemic heart disease; hypertension.

Flamorel *Flamingo, Philipp.*
Norfloxacin (p. 333·3).
Bacterial infections.

Flamoset *Flamingo, India.*
Syrup: Cetirizine (p. 619·2).
Hypersensitivity reactions.

Flamingo, India.
Tablets: Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Flamostat *Cimed, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Flamotax *Flamingo, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Flamotryp *Elder, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Flamoxi *Solas, Indon.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Flamozin *Loeffler, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Flamrase *Berk, UK.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Flamtop *Solitaire, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Flamtop-SR *Solitaire, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Flamus *Laboratorios Chile, Chile.*
Lamotrigine (p. 527·2).
Epilepsy.

Flam-X *Axapharm, Switz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Flamydol *Unipharm, Mex.*
Diclofenac potassium (p. 48·3) or diclofenac resinate (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flamygel *Unipharm, Mex.*
Diclofenac diethylamine (p. 48·3).

Flanakin *Kinder, Braz.†*
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Inflammation; pain.

Flanamox *Wolff, Ger.*
Amoxicillin trihydrate (p. 216·2); flucloxacillin sodium (p. 299·2).
Bacterial infections.

Flanaren *Teuto, Braz.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flanax *Bayer, Braz.; Roche, Braz.; Bayer Consumer, Mex.; Roche, Philipp.*
Naproxen sodium (p. 98·2).
Pain; inflammation; fever.

Flancox *Apsen, Braz.*
Etodolac (p. 57·1).
Rheumatoid arthritis; osteoarthritis; inflammation; gout; pain.

Flanders Buttocks *Flanders, USA.*
Zinc oxide (p. 1729·1); peru balsam (p. 2587·1).
Nappy rash.

Flanid *Pierre Fabre, Fr.*
Tiaprofenic acid (p. 137·1).
Musculoskeletal and joint disorders; inflammation; pain.

Flanil *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal pain; insect bites; pruritus.

Flanizol *Delta, Braz.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Vaginal infections.

Flankol *Exakta, Mex.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Flantadin *IFET (ΙΦΕΤ), Gr.; Teofarma, Ital.; Aventis, Turk.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flanzen *Svizera, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation or oedema associated with infection or trauma; sub-conjunctival bleeding; hyphaema; respiratory-tract congestion.

Flanzen-D *Svizera, India.*
⊗Serrapeptase (p. 2613·3); diclofenac sodium (p. 48·3).
Inflammation.

Flanzen-DP *Svizera, India.*
⊗Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Flanzen-MX *Svizera, India.*
⊗Amoxicillin (p. 216·2); serrapeptase (p. 2613·3).

Flanzen-RX *Svizera, India.*
⊗Roxithromycin (p. 356·2); serrapeptase (p. 2613·3).

Flapex *Andromaco, Chile.*
Simeticone (p. 1886·2).
Adjunct in gastrointestinal radiography; gastrointestinal disorders with excess gas.

Flapex E *Andromaco, Chile.*
⊗Simeticone (p. 1886·2); pancreatin (p. 2579·3); pepsin (p. 2586·1); amylase (p. 2442·1); bile (p. 2457·2).
Digestive disorders; flatulence.

Flarex *Alcon, Arg.; Alcon, Austral.; Alcon, Canad.; Alcon, China; Alcon, Cz.; Alcon, Hong Kong; Alcon, Hung.†; Alcon, India; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, Thai.; Nobel, Turk.; Alcon, USA.*
⊗Fluorometholone acetate (p. 1637·2).
Inflammatory eye disorders.

Flary-Forte *Finecure, India.*
Chlorphenamine maleate (p. 620·3); diethylcarbamazine citrate (p. 153·1).

Flaser Forte *Vanguard, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Flaser-D *Vanguard, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Flash *Vent-3, Arg.*
Paracetamol (p. 115·1).
Pain; fever.

Flash Fighters *Holland & Barrett, UK.*
⊗Cimicifuga (p. 2478·1); agnus castus (p. 2432·2).
Menopausal symptoms.

Flashemel *Ratiopharm, Cz.†*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Flasicox *Ifars, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Flason *Ikapharmindo, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Flasorbid *Flamingo, Philipp.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Flataco *Picco, Thai.*
Cascara (p. 1826·1); ginger (p. 1844·1); nux vomica (p. 2573·3); asafetida (p. 2449·3); capsicum (p. 2469·3); amylase (p. 2442·1).
Constipation.

Flatex *Farmasa, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Flaticona *Belfar, Braz.*
Simeticone (p. 1886·2).

Flatin *Prafa, Indon.†*
Tinidazole (p. 949·2).
Amoebiasis; trichomoniasis; giardiasis; anaerobic bacterial infections.

Flatmed *Bajamed, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Flatol *Legrand, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Flaton *Bilim, Turk.*
⊗Pancreatin (p. 2579·3); hemicellulase (p. 2473·1); bile extract (p. 2457·2); simeticone (p. 1886·2).
Digestive disorders; meteorism; pancreatitis.

Flatoril
Note: this name may be used for preparations of different composition.
Almirall, Spain.
Clebopride malate (p. 1833·1); simeticone (p. 1886·2).
Gastro-oesophageal reflux; hiatus hernia; dyspepsia.

Elmor, Venez.
Simeticone (p. 1886·2).
Digestive disorders; flatulence.

Flatron *Little Greave, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Flatsil *Berksam, Turk.*
Simeticone (p. 1886·2).

Flatucid *Soho, Indon.†*
Aluminium magnesium silicate (p. 2168·2); simeticone (p. 1886·2).
Peptic ulcer; gastritis; dyspepsia.

Flatulence *Greater Pharma, Thai.†*
Cascara (p. 1826·1); capsicum (p. 2469·3); amylase (p. 2442·1); ginger (p. 1844·1); nux vomica (p. 2573·3); asafetida (p. 2449·3).
Flatulence; constipation.

Flatulex *Bayer, Switz.*
Chewable tablets: Simeticone (p. 1886·2); caraway oil (p. 2470·3); fennel oil (p. 2503·3); peppermint oil (p. 1877·1).
Excess gastrointestinal gas; preparation for gastrointestinal examination; detergent poisoning.

Bayer, Switz.; Dayton, USA.
Oral drops: Simeticone (p. 1886·2).
Excess gastrointestinal gas; preparation for gastrointestinal examination; detergent poisoning; flatulence.

Dayton, USA.†
Tablets: Simeticone (p. 1886·2); activated charcoal (p. 1537·3).
Flatulence.

Flatunic *Nicholas, Indon.†*
Simeticone (p. 1886·2).
Flatulence; abdominal distension; dyspepsia; defoaming agent in radiography.

Flaval *Cetus, Arg.*
Bamethan (p. 1314·1); diclofenac (p. 48·3); esculoside (p. 2431·2).

Flavamed *Berlin-Chemie, Cz.; Berlin-Chemie, Denm.; Berlin-Chemie, Fin.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Berlin-Chemie, Pol.; Menarini, Pol.
Ambroxol (p. 1654·3) or ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Flavan *Dexo, Fr.*
Leucocianidol (p. 2505·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Flavate *Overseas, India.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Flavedon *Serdia, India.*
Trimetazidine hydrochloride (p. 1520·1).
Ischaemic heart disease.

Flavenos *Biolab Sanus, Braz.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).

Flaveric *Pfizer, Jpn.*
Benproperine phosphate (p. 1656·2).
Cough.

Flavettes *CCM, Hong Kong†; Upha, Indon.; Upha, Singapore.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement; vitamin C deficiency.

Flavettes Cal D3 *CCM, Hong Kong.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement.

Flavettes Neuroforte *CCM, Malaysia.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgias; neuropathy; vitamin B supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Flavia *Pro-Pharma, Ukr.*
Scots pine oil (p. 2591·2); peppermint oil (p. 1877·1); fir oil (p. 2591·1); ammi visnaga (p. 2441·2); motherwort (p. 2564·2); chamomile (p. 2474·1).
Renal calculi.

Flaviastase *Iphym, Fr.†*
Amylase (p. 2442·1); protease (p. 2598·1).
Digestive disorders.

Flavin
Note: this name may be used for preparations of different composition.
Landson, Indon.
⊗Echinacea (p. 2498·1); serrapeptase (p. 2613·3).
Inflammation.

New York Chemical, Thai.
Riboflavin (p. 2104·3).
Riboflavin deficiency; anaemia.

Flavinol *Chew, Thai.*
Acriflavinium monochloride (p. 1732·3); thymol (p. 1772·2).
Wounds; burns.

Flavion *Terapeutico, Ital.*
Tablets: Aesculus (p. 2431·2); centella (p. 1698·3); lemon (p. 2542·3); red vine (p. 2521·3).
Nutritional supplement.

Terapeutico, Ital.
Topical gel: Aesculus (p. 2431·2); catechu (p. 2472·3); solidago virgaurea (p. 2620·1).
Peripheral vascular disorders.

Flavit *Hormona, Mex.*
Bioflavonoids (p. 2505·2); ascorbic acid (p. 2110·3).
Capillary fragility.

Flavit AV *Hormona, Mex.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Pain; hypersensitivity; nasal congestion.

Flavix *Wockhardt, India.*
Venlafaxine hydrochloride (p. 454·2).
Anxiety; depression.

Flavo *Forgo, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Flavobil *Medana, Pol.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Flavobion *Nycomed, Cz.*
Silymarin (p. 1561·2).
Liver disorders.

Flavobion-C *Farmanic, Gr.*
Calcium glycerophosphate (p. 1783·3); vitamin C (p. 2110·3); ergocalciferol (p. 2113·3).
Osteoporosis; pregnancy; breast-feeding.

Flavo-C *Auriga, Hong Kong.†*
Vitamin C (p. 2110·3); ginkgo biloba (p. 2512·3).
Skin hyperpigmentation; skin ageing.

Flavodrei *Chiesi, Spain.*
Soya bean (p. 2092·3).
Menopausal disorders.

Flavogin Plus *Baif, Ital.*
Ginkgo biloba (p. 2512·3); bioflavonoids (p. 2505·2); dog rose; myrtillus (p. 2566·2).
Tonic.

Flavol *Ronava, Venez.*
Troxerutin (p. 2505·3).
Haemorrhoids; varices; phlebitis.

Flavon *General Drugs, Thai.*
Flavonoids (p. 2505·2).
Haemorrhoids; vascular insufficiency.

Norma (Νορμα), Gr.
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Flavonid *Neo Quimica, Braz.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; capillary leakage.

Flavonil *Kinder, Braz.†*
Soya isoflavones (p. 2620·3).
Dietary supplement.

Flavonoid Complex *GNLD, Austral.*
Cranberry (p. 2488·1); kale; green tea (p. 2648·2); red beetroot; mixed berries; grape (p. 2521·3); orange extract; lemon extract; grapefruit.
Flavonoid supplement.

Flavons *Freeda, USA.*
Citrus bioflavonoids complex (p. 2505·2); hesperidin (p. 2505·2).
Capillary bleeding.

Eagle, Austral.†
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); calcium ascorbate (p. 2111·1); hesperidin (p. 2505·2); bioflavonoids (p. 2505·2); rutoside (p. 2505·3); rose fruit (p. 2607·1); boneset (p. 2459·1); echinacea (p. 2498·1); achillea (p. 2427·3).
Tonic; minor wounds.

Flavoquine *Sanofi-Aventis, Fr.†*
Amodiaquine hydrochloride (p. 647·2).
Malaria.

Flavoride *Obsurge, India.*
Flavoxate hydrochloride (p. 2360·1).
Bladder function disorders.

Flavorin *TO-Chemicals, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Flavo-Spa *Utopian, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Flavospas *Elder, India.*
Flavoxate hydrochloride (p. 2360·1).
Bladder function disorders.

Flavosul *Natysal, Spain.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Flavoton *GD, Ital.†*
Bioflavonoids (p. 2505·2); calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Nutritional supplement.

Flavourpac *Vitaflo, Irl.†*
Range of flavours for use with unflavoured protein substitutes.

Flavovenyl *Plan, Switz.*
Capsules; oral drops: Bioflavonoids (p. 2505·2); hesperidin methyl chalcone (p. 2505·2); esculoside (p. 2431·2).
Haemorrhoids; venous insufficiency.

Plan, Switz.
Ointment: Bioflavonoids (p. 2505·2); hesperidin methyl chalcone (p. 2505·2); esculoside (p. 2431·2); menthol (p. 2553·2).
Haemorrhoids; venous insufficiency.

Flavoxen *Alpharma, Mex.*
Naproxen (p. 98·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flavozid *Ecofarm, Ukr.*
Proteflazid (obtained from deschampsia caespitosa and calamagrostis epigeios).
Viral infections.

Flavo-Zinc *Solgar, Canad.†; Solgar, UK.*
Zinc citrate (p. 2126·2); zinc gluconate (p. 2126·2).
Dietary supplement.

Flawless *Body Shop, Canad.†*
SPF 25: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Flaxblutriz *Raam, Mex.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Flaxen *Cantabria, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Flaxendol *Vitae, Mex.*
Naproxen sodium (p. 98·2).
Fever; inflammation; pain.

Flaxenol *Raam, Mex.*
Paracetamol (p. 115·1); naproxen sodium (p. 98·2).
Pain; inflammation; fever.

Flaxin *Merck, Braz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Flaxinac *Solitaire, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Flaxinac-SP *Solitaire, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Flaxinac-SR *Solitaire, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Flaxine *IAE, Philipp.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Flaxtec *Tecnofarma, Mex.*
Metronidazole (p. 936·1).
Amoebiasis.

Flaxvan *Rontag, Arg.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flazal *Neo Quimica, Braz.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flaz-Cort *Cazi, Braz.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flazidem *Flamingo, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Flazlar *Stellar, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flazomel *Flamingo, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Flazymec *Ifars, Indon.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive disorders.

Flebil *Bracco, Ital.*
Troxerutin (p. 2505·3).
Peripheral vascular disorders; haemorrhoids.

Flebil Plus *Bracco, Ital.*
Troxerutin (p. 2505·3); pycnogenol (p. 2590·3).
Venous insufficiency.

Flebitol *Phoenix, Arg.*
⊗Ginkgo biloba (p. 2512·3); heptaminol hydrochloride (p. 2525·1); troxerutin (p. 2505·3).
Phlebitis; premenstrual disorders; venous insufficiency.

Flebo Ikatral *Baliardo, Arg.*
Proanthocyanidin oligomers (p. 2521·3).
Venous insufficiency.

Flebobag Fisio *Grifols, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte depletion; hypovolaemia.

Flebobag Glucosada *Grifols, Spain.†*
Glucose (p. 2068·3).
Parenteral nutrition.

Flebobag Glucosalina *Grifols, Spain.†*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; hypovolaemia.

Flebobag Ringer Lactado *Grifols, Spain.†*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Flebocortid *Lepetit, Ital.; Janssen-Cilag, Mex.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid; parenteral corticosteroid.

Fleboderma *Investi, Arg.*
A heparinoid (p. 1401·1).
Soft-tissue disorders; phlebitis; thrombophlebitis; varicose veins.

Flebodia *Innotech, Ukr.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids; capillary fragility.

Flebodolor *Spedrog, Arg.*
Ruscogenin (p. 2608·3).
Soft-tissue disorders; peripheral vascular disorders.

Fleboflex Glucosada *Grifols, Spain.†*
Glucose (p. 2068·3).
Fluid disorders; parenteral nutrition.

Fleboflex Glucosalina *Grifols, Spain.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Fleboflex Ringer Lactado *Grifols, Spain.†*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Fleboflex Salina Fisiologica *Grifols, Spain.†*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Flebofort *KG, Ital.*
Tablets: Fruit bioflavonoids (p. 2505·2); centella (p. 1698·3); myrtillus (p. 2566·2); melilot (p. 2552·3); ananas gambo.
Circulatory disorders.

KG, Ital.
Topical gel: Menthol (p. 2553·2); myrtillus (p. 2566·2); centella (p. 1698·3); ananas comosus; bioflavonoids (p. 2505·2).
Circulatory disorders.

Flebogamma
Note: this name may be used for preparations of different composition.
Grifols, Arg.; Grifols, Chile; Grifols, Cz.; Grifols, Ger.†; Demo, Gr.; IFET (ΙΦΕΤ), Gr.; Grifols, Hong Kong†; Grifols, India; Grifols, Irl.; Grifols, Israel; Grifols, Ital.; Grifols, Malaysia; Grifols, Neth.; Grifols, NZ; Grifols, Port.; Grifols, Rus.; Grifols, Singapore; Grifols, Spain; Grifols, Swed.; Grifols, Thai.; Dem, Turk.; Grifols, UK; Grifols, USA; Pharmakin, Venez.
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome; immunodeficiency; bone-marrow transplantation; agammaglobulinaemia.

Flebogammadif *Grifols, Cz.; Grifols, Ger.; Grifols, Irl.; Grifols, Port.; Grifols, UK.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; passive immunisation; bone-marrow transplantation.

Flebolider *Amnol, Ital.*
Aescin (p. 2431·2); caffeine (p. 1203·3); diosmin (p. 2505·2); coumarin (p. 2487·2); butcher's broom (p. 2463·1); centella (p. 1698·3); arnica (p. 2447·2); ivy (p. 2536·2); zinc oxide (p. 1729·1).
Inflammation.

Flebon *Ivax, Arg.*
Diosmin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Flebonorm *Amnol, Ital.*
Trivalex (diosmin (p. 2505·2), diosmetin, hesperidin (p. 2505·2)); melilot (p. 2552·3); betula (p. 2457·3).
Circulatory disorders.

Flebopex *Bago, Chile.*
Rutoside (p. 2505·3).
Haemorrhoids; metrorrhagia; retinal haemorrhage; venous insufficiency.

Fleboplast Fisio *Grifols, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; hypovolaemia.

Fleboplast Glucosada *Grifols, Spain.†*
Glucose (p. 2068·3).
Parenteral nutrition.

Fleboplast Glucosalina *Grifols, Spain.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; hypovolaemia.

Flebo-Si *SIFFRA, Ital.†*
Centella (p. 1698·3); aesculus (p. 2431·2); melilot (p. 2552·3); myrtillus (p. 2566·2); rutoside (p. 2505·3).
Circulatory disorders.

Fleboside *Pharmafar, Ital.*
Troxerutin (p. 2505·3); carbazochrome (p. 1137·1).
Capillary fragility; venous insufficiency.

Flébosmil *Socopharm, Fr.†*
Diosmin (p. 2505·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Flebostasin *Daiichi Sankyo, Ital.*
Aesculus (p. 2431·2).
Chronic venous insufficiency; capillary fragility.

Daiichi Sankyo, Spain.
Aescin (p. 2431·2).
Peripheral vascular disorders; oedema.

Flebotein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Flebotrofine *Amnol, Ital.*
Diosmin (p. 2505·2); troxerutin (p. 2505·3); black currant (p. 2458·1); hesperidin (p. 2505·2).
Capillary disorders.

Flebotropin *Bago, Arg.*
Tablets: Flavonoids (p. 2505·2).
Haemorrhoids; venous insufficiency.

Flebovis *Amnol, Ital.*
Centella (p. 1698·3); melilot (p. 2552·3); rutoside (p. 2505·3); vitamin E (p. 2119·1).
Microcirculatory disorders.

Flebovis materna *Amnol, Ital.*
Pineapple; aesculus (p. 2431·2); melilot (p. 2552·3); vitamins.
Microcirculatory disorders.

Flebozin *Medifarma, Ital.*
Melilot (p. 2552·3); aesculus (p. 2431·2); centella (p. 1698·3).
Nutritional supplement.

Flebs *Pierre Fabre, Ital.*
Heparin sodium (p. 1396·3); a heparinoid (p. 1401·1).
Phlebitis; thrombophlebitis; haemorrhoids; soft-tissue injury.

Flebudil *Med-One, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).

Flecagamma *Worwag, Ger.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Flécaïne *Meda, Fr.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Flecajuna *Disphar, Neth.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Flecatab *Alphapharm, Austral.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Flecin *A-Pharma, Denm.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Flecon *Sanify, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flecor-N *Biospray, Gr.; Zekides, Gr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Flectadol
Note: this name may be used for preparations of different composition.
Lafi, Chile.
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Musculoskeletal, joint, and peri-articular disorders; tension headache.

Sanofi-Aventis, Ital.
Lysine aspirin (p. 84·3).
Musculoskeletal and joint disorders; pain.

Flectar *Biomedica, Gr.*
Nizatidine (p. 1866·1).
Peptic ulcer.

Flectoparin *IBSA, Switz.*
Diclofenac epolamine (p. 48·3); heparin sodium (p. 1396·3).
Musculoskeletal, joint and soft-tissue inflammation and pain.

Flector *Sanova, Austria; Therabel, Belg.; Labomed, Chile; IBSA, Cz.; IBSA, Denm.†; IBSA, Fin.†; Genevrier, Fr.; IBSA, Ger.; IBSA, Hong Kong; IBSA, Hung.; Novartis Consumer, Irl.; Bayer, Ital.; Delta, Port.; Genevrier, Singapore; Meda, Swed.†; IBSA, Switz.; Ali, Turk.; Alpharma, USA.*
Diclofenac epolamine (p. 48·3) or diclofenac sodium.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; oedema.

Flector Tissugel Héparine *Genevrier, Fr.*
Diclofenac epolamine (p. 48·3); heparin sodium (p. 1396·3).
Ankle sprains.

Fleefer *Cubit, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Fleelaxat *Cooper (Κοπερ), Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Bowel evacuation.

Fleet *Casen Fleet, Denm.; Casen Fleet, Irl.; Casen Fleet, Ukr.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Fleet Accu-Prep *Fleet, USA.*
Fleet Phospho-Soda; Fleet Relief anorectal wipes.
Bowel evacuation.

Fleet Adulto *Consupharma, Mex.†*
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Fleet Babylax *Rider, Chile; Fleet, Hong Kong†; Fleet, Malaysia†; Fleet, Singapore; Fleet, USA; Zuoz, Venez.*
⊗Glycerol (p. 2517·2).
Constipation; bowel evacuation.

Fleet Bagenema *Fleet, USA.*
Water (p. 2646·2).
Formerly contained liquid castile soap.

Fleet Bisacodyl *Fleet, USA.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Fleet Enema *Kela, Belg.; Fleet, Braz.; McNeil Consumer, Canad.; Rider, Chile; Fleet, China; Pharmakochimiki (Φαρμακοχημικη), Gr.; Fleet, Hong Kong; Combiphar, Indon.; Dexxon, Israel; Fleet, Malaysia; Fleet, Philipp.; Casen Fleet, Port.; Fleet, Singapore; Kozmed, Turk.; Fleet, USA; Zuoz, Venez.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation; constipation.

Fleet Enema Fosf-Sodio *Nycomed, Mex.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Fleet Enema Mineral Oil *McNeil Consumer, Canad.*
Liquid paraffin (p. 2191·2).
Constipation; bowel evacuation.

Fleet Fosfo Soda *Kozmed, Turk.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fleet Fosfosoda *Rider, Chile.*
Monobasic sodium phosphate (p. 1791·1); tribasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Zuoz, Venez.
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fleet Gebruiksklaar Klysma *Fleet, Neth.†*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Fleet Infantil *Consupharma, Mex.†*
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Fleet Laxative *Fleet, NZ†; Fleet, USA.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Fleet Micro-Enema *Fleet, Austral.†*
Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3); sorbitol (p. 2092·1).
Bowel evacuation; constipation.

Fleet Mineral Enema *Fleet, NZ.†*
Liquid paraffin (p. 2191·2).
Constipation; bowel evacuation.

Fleet Pain Relief *Fleet, USA.*
Pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Fleet Pedialax *Consupharma, Mex.†*
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Fleet Phosphate Enema *Baxter, NZ.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Fleet Phospho-Soda *Ferring, Austral.; Casen Fleet, Austria; Kela, Belg.; Fleet, China; Aptalis, Fr.; Eisai, Ger.; Fleet, Hong Kong; Casen Fleet, Hung.; Casen Fleet, Irl.; Fleet, Malaysia; Orifarm, Norw.; Baxter, NZ; De Witt, Pol.; Casen Fleet, Port.; Ferring, Rus.; Fleet, Singapore; De Witt, UK; Fleet, USA.†*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Novis, Gr.
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Laxative.

Fleet Phosposoda *Combiphar, Indon.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fleet Prep Kit No. 1 *Fleet, USA.†*
Combination pack: Fleet Phospho-Soda; Fleet Bisacodyl Tablets (p. 1821·1), 4 tablets; Fleet Bisacodyl Suppositories, 1 suppository.
Bowel evacuation.

Fleet Prep Kit No. 2 *Fleet, USA.†*
Combination pack: Fleet Phospho-Soda; Fleet Bisacodyl Tablets (p. 1821·1), 4 tablets; Fleet Bagenema, 1 enema.
Bowel evacuation.

Fleet Prep Kit No. 3 *Fleet, USA.*
Combination pack: Fleet Phospho-Soda; Fleet Bisacodyl Tablets (p. 1821·1), 4 tablets; Fleet Bisacodyl Enema.
Bowel evacuation.

Fleet PS *Nycomed, Mex.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Fleet Ready-to-Use *Ferring, Austral.; De Witt, Gr.; De Witt, UK.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Flefarmin *Biospray, Gr.; DAST, Gr.; Zekides, Gr.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Flegamin *Pliva, Rus.†*
Bromhexine hydrochloride (p. 1656·3).

Flegamina *Pliva Krakow, Pol.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Flegatussin *Herbapol Lublin, Pol.†*
Bromhexine hydrochloride (p. 1656·3); ribwort plantain (p. 2604·2); verbascum (p. 2645·1).
Cough; respiratory-tract congestion.

Flegyl *Sanofi-Aventis, Venez.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Flelox *Kleva, Gr.*
Meloxicam (p. 86·3).

Flemac *Aramis, Hung.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders.

Flemagon *Coup, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).

Flemex
Note: this name may be used for preparations of different composition.
Johnson & Johnson, S.Afr.; Medinova, Thai.
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased or viscous mucus.

Medhaus, Philipp.
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Precimex, Mex.
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Flemex Jat *Recalcine, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); tolu (p. 1679·2); herbs.
Cough.

Flemex-AC *Medinova, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus; paracetamol poisoning.

Flemeze *Johnson & Johnson, S.Afr.*
⊗Orciprenaline sulfate (p. 1217·3); bromhexine hydrochloride (p. 1656·3).
Cough associated with bronchospasm and viscous mucus.

Flemgo *Thebe, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased or viscous mucus.

Flemibar *Roemmers Rowe, Venez.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Smooth muscle spasm; pain.

Flemibron *Esan, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Flemicaine *Roemmers Rowe, Venez.*
Lidocaine hydrochloride (p. 1988·2); eugenol (p. 2501·2).
Toothache.

Flemiclav *FDC, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Flemiclav-LB *FDC, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Flemiklox-DX *FDC, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Flemiklox-LBX *FDC, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Fleminate *Novagen, Philipp.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Fleming *Medreich, Hong Kong.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Fleminosan *Pharmathen, Gr.*
Clindamycin phosphate (p. 269·3).
Acne.

Flemizyme *Pascual, Hong Kong.*
Muramidase hydrochloride (p. 2565·1).
Haemorrhage; sinusitis; respiratory-tract congestion; adjunct in antibacterial therapy.

Flemkof *Pharmacia Upjohn, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Flemlite *Aspen Consumer, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased or viscous mucus.

Flemmi-Ped *SA Druggists Self Med, S.Afr.†*
Guaifenesin (p. 1666·2).
Cough.

Flemnil *Raptakos, India.*
Bromhexine hydrochloride (p. 1656·3); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).

Flemoclav *Astellas, Rus.; Astellas, Ukr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Flemonex *Doctors, Philipp.*
Guaifenesin (p. 1666·2).
Cough.

Flemonex-DXM *Doctors, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Flemoxin *Astellas, Belg.; Astellas, Denm.; East India Pharma, India; Astellas, Neth.; Astellas, Port.; Astellas, Rus.; Astellas, Ukr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Astellas, Gr.; Gerolymatos, Gr.; CSL, NZ.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Flemoxon *Eurolab, Arg.; Merck, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Flemsol *Diamond, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Flemycin *Elpen (Ελπεν), Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Flenazole *Target, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections.

Flenin *Schuck, Ger.*
Oral drops: Apis (p. 2445·2); arsenicum album (p. 2448·1); chelidonium (p. 2522·2); conium (p. 2524·3); crocus (p. 2208·2); echinacea (p. 2498·1); natrium sulfuricum (p. 1888·1); ruta (p. 2608·2); salvia (p. 2608·3); secale cornutum (p. 2137·1); condurango (p. 2485·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Flenox *Farmak, Ukr.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; unstable angina.

Flentist *Vickmans, Hong Kong.†*
Chlorphenamine (p. 620·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fleridux *Ultra, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Flerovitan *Zekides, Gr.†*
Calcium carbonate (p. 1824·3); calcium lactate (p. 1784·1); ascorbic acid (p. 2110·3).

Flerox *Sanitas, Chile.†*
Flunarizine (p. 629·3).
Mental function impairment; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Flerudin *Janssen-Cilag, Spain.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Fleryl *Zekides, Gr.*
Cinoxacin (p. 261·1).

Flespan *Vargas, Venez.*
Pipethanate ethobromide (p. 1878·2).
Gastrointestinal spasm.

Fleta Bolus *Lupin, India.*
Eptifibatide (p. 1376·3).
Unstable angina; adjunct in coronary angioplasty.

Fletagex *Dermophil Indien, Fr.*
Cod-liver oil (p. 2056·3); vitamin A (p. 2098·3).
Skin disorders.

Fletcher's Arachis Oil *Pharmax, Irl.†*
Arachis oil (p. 2446·1).
Faecal impaction.

Fletchers Castoria *Mentholatum, USA.*
Senna (p. 1885·1).
Constipation.

Fletchers Phosphate Enema *Forest, Irl.†; Pharmax, Irl.†*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Fletchers Sore Mouth Medicine *Advantage, Canad.*
Alum (p. 2439·1); potassium chlorate (p. 2595·2).
Herpes labialis; denture irritation; canker sores.

Fleur *Teva, Cz.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Flevic *Bernabo, Arg.*
Enterococcus faecium (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Flevion *Medicus, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Flevomax *Elea, Arg.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2)
Flavonoids (p. 2505·2).
Venous insufficiency; haemorrhoids.

Flevostol *Bros, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Flevox *Serral, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Flevoxcin *GX, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Flex
Note: this name may be used for preparations of different composition.
Siomond, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Ocean Nutrition, Canad.†
Eicosapentaenoic acid (p. 1460·2).
Dietary supplement.

Flex Metak *Kener, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Flex Omega Benefits with Vitamin D-3
Physician Recommended Nutriceuticals, USA.
Omega-3 fatty acids (p. 1460·1); vitamin D (p. 2112·3).

Flexafen *Diba, Mex.*
Ibuprofen (p. 68·2).
Gout; inflammation; pain; musculoskeletal, joint, and peri-articular disorders.

Flexagen *Lennon, S.Afr.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation; gout.

Flexagil *Blackmores, Austral.; Merck, Hung.*
Comfrey (p. 2484·2).
Joint disorders; soft-tissue pain and inflammation.

Flexagile *Merck, Belg.*
Comfrey (p. 2484·2).
Musculoskeletal and joint pain.

Flexal Vitamin E *Hexal, Ger.†*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Flexalgex *Geolab, Braz.*
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).

Flexalgin *Geolab, Braz.*
Paracetamol (p. 115·1); diclofenac sodium (p. 48·3); carisoprodol (p. 2021·3); caffeine (p. 1203·3).

Flex-All *Martin, Arg.*
Menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue pain.

Flexall *Chattem, USA.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); methyl salicylate (p. 92·1); thyme oil (p. 2630·3).

Flex-all 454 *Chattem, USA.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal pain and stiffness.

Flexamide *Doctors, Philipp.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Flex-A-Min Complex *NBTY, Ukr.†*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis; rheumatoid arthritis.

Flex-A-Min Glucosamin *NBTY, Ukr.†*
Glucosamine sulfate (p. 2515·3).
Musculoskeletal, joint, and peri-articular disorders.

Flexamol *Diba, Mex.†*
Meloxicam (p. 86·3); methocarbamol (p. 2025·3).
Painful skeletal muscle spasm.

Flexan *Tylid, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever.

Flexaphen *Trimen, USA.†*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Musculoskeletal pain.

Flexar *Menarini, India; Menarini, Port.*
Piroxicam (p. 125·3).
Pain; gout; musculoskeletal, joint, and peri-articular disorders.

Flexase *TAD, Ger.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Flexasur *Cymbiotics, Malaysia.*
Capsules: Fish oil (p. 1460·3); esterified fatty acids.
Dietary supplement.

Kalbe, Indon.; Cymbiotics, Malaysia.
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2); cetyl myristoleate (p. 2473·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Kalbe, Indon.
Capsules: Cetyl myristoleate (p. 2473·3); eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Joint disorders; inflammation.

Flexbumin *Baxter, Arg.; Baxter, Belg.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Gr.; Baxter, Irl.; Baxter, Neth.; Baxter, Norw.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Baxter, UK.*
⊗Albumin (p. 1130·2).
Plasma volume expansion; acute respiratory distress syndrome; cardiopulmonary bypass surgery; haemolytic disease of the newborn; hypovolaemia; hypoalbuminaemia; hyperbilirubinaemia; ascites.

Flex-Care *Alcon, Mex.†*
Solution for complete care of soft contact lenses.

Alcon, USA.†
Range of solutions for contact lenses.

Flexdor *Bunker, Braz.*
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).
Skeletal muscle spasm.

Flexea *Expanscience, Fr.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Flexelite *Bros, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Flexen
Note: this name may be used for preparations of different composition.
Italfarmaco, Ital.; Italfarmaco, Rus.
Ketoprofen (p. 79·1) or ketoprofen sodium (p. 79·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Flexeril *McNeil, USA.†*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Flexeze *Goldshield, UK.*
Capsules: Glucosamine sulfate (p. 2515·3); chondroitin (p. 2476·1).
Osteoarthritis.

Goldshield, UK.
Topical gel: Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Flexfree *Omega, Belg.*
Felbinac (p. 58·3).
Soft-tissue, peri-articular, and joint pain and inflammation.

Flexgen *Kramer Novis, USA.*
Vitamin C (p. 2110·3); citrus bioflavonoids (p. 2505·2); crataegus (p. 2488·1); aesculus (p. 2431·2); hesperidin complex (p. 2505·2); rutoside (p. 2505·3); hamamelis (p. 2523·3).

Flexi *Adley, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Flexi Cap *Glenmark, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Flexiban *SIT, Ital.; Meda, Port.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Flexibel *Blubell, India.*
Capsules: Chondroitin (p. 2476·1); glucosamine sulfate (p. 2515·3).

Blubell, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Flexibel-AD *Blubell, India.*
Aceclofenac (p. 16·2); diacerein (p. 45·3).

Flexibel-D *Blubell, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Flexicam *Cratus, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Flexicamin *Sidus, Arg.*
Piroxicam (p. 125·3); carisoprodol (p. 2021·3).
Musculoskeletal, joint, and peri-articular disorders.

Flexicamin A *Sidus, Arg.*
Piroxicam (p. 125·3); carisoprodol (p. 2021·3); dipyrone (p. 53·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flexicamin B12 *Sidus, Arg.*
Tablets: ⊗Piroxicam (p. 125·3); carisoprodol (p. 2021·3); dexamethasone (p. 1630·3); pyridoxine (p. 2105·3); hydroxocobalamin (p. 2107·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis.

Sidus, Arg.
Injection: ⊗Piroxicam (p. 125·3); pyridoxine (p. 2105·3); dexamethasone (p. 1630·3); hydroxocobalamin (p. 2107·3).
Musculoskeletal, joint, peri-articular, and soft tissue disorders; neuritis.

Flexicones *Biodica, Fr.†*
Neomycin sulfate (p. 330·1); benzocaine (p. 1980·2).
Dental disorders.

Flexid
Note: this name may be used for preparations of different composition.
Hoe, Philipp.
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Lek, Rus.
Levofloxacin (p. 315·3).
Bacterial infections.

Flexiderm
Note: this name may be used for preparations of different composition.
Perrigo, Israel.
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Herbapol Poznan, Pol.†
Silymarin phospholipids (p. 1561·2).
Skin disorders.

Flexidol
Note: this name may be used for preparations of different composition.
Cipla, India.
Aceclofenac betadex (p. 16·2).

Raffo, Arg.
Meloxicam (p. 86·3).
Inflammation; pain.

Flexidol Relax *Raffo, Arg.*
Meloxicam (p. 86·3); pridinol (p. 2026·1).
Inflammation; pain; skeletal muscle spasm.

Flexidol-P *Cipla, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Flexidon *Cosmopharm, Gr.*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux disease.

Flexigesic
Note: this name may be used for preparations of different composition.
Invision, India.
Injection; topical gel: Diclofenac sodium (p. 48·3).
Inflammation; pain.

Invision, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Medi-Rx, Philipp.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Flexigesic-K *Invision, India.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Flexigesic-MR *Invision, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Flexigesic-S *Invision, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Flexiglim *Unichem, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Flexiherb *MedicHerb, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

flexi-loges *Loges, Ger.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Flexilor *Glenmark, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Fleximax *Naturactive, Fr.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); devil's claw root (p. 42·3); hyaluronic acid (p. 2526·2).
Dietary supplement; joint degeneration.

Flexi-Melt *Forum, UK.*
Glucosamine hydrochloride (p. 2515·3).
Food supplement for healthy joints.

Fleximin *Merck, Mex.†*
Cefalexin (p. 234·1).
Bacterial infections.

Flexi-muv *Cadila, India.†*
Oil: Guggul (p. 2523·2); vitex negundo; cissus quadrangularis; costus speciosus; melia azadirachta (p. 2451·2); Indian gooseberry (p. 2532·2); chebulic myrobalan (p. 2474·3); beleric myrobalan (p. 2453·2); camphor (p. 2466·2); pinus longifolia; celery (p. 2472·3); cedrus deodara; eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1).

Cadila, India.†
Ointment: Turpentine oil (p. 2636·3); sweet birch oil (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); capsicum (p. 2469·3).
Musculoskeletal pain.

Flexin
Note: this name may be used for preparations of different composition.
Pasteur, Chile.
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Sidus, Arg.
Diclofenac sodium (p. 48·3).
Salt not specified 1.11.

Taro, Israel.
Orphenadrine citrate (p. 909·2).
Skeletal muscle spasm.

Flexin Continus
Note: this name may be used for preparations of different composition.
Napp, Irl.†
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Flexinol *Cipla, India.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Skeletal muscle spasm; musculoskeletal and joint pain.

Flexiplen *Vitarum, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal and joint disorders.

Flexi-T *Prosan, Hong Kong; Family Planning Sales, UK.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Flexital *Sun, India; Sun, Rus.; Sun, Thai.*
Pentoxifylline (p. 1465·3).
Cerebral, ocular, and peripheral vascular disorders.

Flexitol Heel Balm *LaCorium, UK; LaCorium, USA.*
⊗Urea (p. 1727·3) in an emollient base.
Dry, cracked heels; dry skin.

Laderma, Canad.†
⊗Wool fat (p. 2219·3); white soft paraffin (p. 2211·3); urea (p. 1727·3).
Dry skin disorders.

Flexium
Note: this name may be used for preparations of different composition.
Melisana, Belg.
Etofenamate (p. 57·2).
Peri-articular disorders; lumbar spondylosis; soft-tissue injury.

Sidus, Arg.
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders; inflammation; pain.

Flexiver *Maver, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flexivial *Bodene, S.Afr.*
Potassium chloride (p. 1793·2).

Flexivit *Eadriex, Philipp.*
Vitamins; lysine (p. 2079·3); chlorella (p. 2475·3); taurine (p. 2626·2).
Nutritional supplement.

Flexo *Santa, Turk.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Flexocam *Pharma Dynamics, S.Afr.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis; sciatica.

Flexogan *Advance, Singapore.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Flexol *Unipharm, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flexon
Note: this name may be used for preparations of different composition.
Aristo, India.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; pain.

Keene, USA.
Orphenadrine citrate (p. 909·2).
Musculoskeletal pain.

Flexon-MR *Aristo, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flexono *Sanitas, Chile.*
Indometacin (p. 71·2).
Aluminium glycinate (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; pain.

Flexor *Dexa, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Degenerative joint disorders.

Flexove *Grunenthal, Austria; Navamedic, Cz.; Expanscience, Pol.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Flex-OZ *Siomond, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Flexozin *Combiphar, Indon.*
Capsaicin (p. 35·1); methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); vitamin E (p. 2119·1).
Joint disorders.

FlexPen *Novo Nordisk, India.*
⊗Insulin aspart (p. 475·3).
Diabetes mellitus.

Flex-Power Performance Sports *Flex-Power, USA.*
Trolamine salicylate (p. 141·2).
Musculoskeletal and joint disorders.

Flexresan *Centrum, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Flexril-Ord *Apotex, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Flexsa *Mega Lifesciences, Malaysia; Mega Lifesciences, Philipp.; Mega We Care, Singapore; Mega Lifesciences, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; degenerative joint disorders.

Flextinol *Vitae, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Flex-Tonic *Synergia, Fr.*
Vitamin C (p. 2110·3); collagen UC-II (p. 2483·2); silicon (p. 2209·2).
Joint disorders.

Flextoss *Teuto, Braz.*
Dropropizine (p. 1662·2).
Cough.

Flextra
Note: this name may be used for preparations of different composition.
Elder, India.
Glucosamine (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Poly, USA.
Paracetamol (p. 115·1); phenyltoloxamine citrate (p. 638·1).
Pain.

Flextra-D *Elder, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Flexura *Sun, India.*
Metaxalone (p. 2025·2).

Flexura-D *Sun, India.*
Diclofenac potassium (p. 48·3); metaxalone (p. 2025·2).

Flexure *Merck, Chile.*
Glucosamine sulfate sodium chloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis.

Flexxbon *Meyers, Philipp.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Flexy *TP, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal and joint pain and inflammation.

Flicazen *Med-One, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic skin disorders; allergic rhinitis.

Flicum *Distriquimica, Spain.†*
Flubendazole (p. 154·3).
Enterobiasis; ascariasis; trichuriasis; hookworm infections.

Flidaphen *Zwitter, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp disorders.

Flihaler *DAST, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Flimutal *Cryopharma, Mex.*
Flutamide (p. 798·2).
Prostatic cancer.

Flindix *Vitoria, Port.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction; heart failure.

flint *Togal, Ger.*
Poly(butylmethacrylate, methylmethacrylate) (p. 2558·2).
Wounds.

Flintoff *Kinds, India.*
Vitamin C (p. 2110·3); betacarotene (p. 2051·1); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).

Flintstones *Bayer Consumer, Canad.*
Vitamins with or without minerals.

Bayer, USA.
Vitamins; with or without minerals.

Bayer, Philipp.
Vitamins; with or without minerals or iron (p. 2073·1).

Flipal *Royal, Chile.*
Mefenamic acid (p. 85·3).
Pain.

Flisint *Sanofi-Aventis, Fr.*
Fumagillin (p. 933·2).
Microsporidiosis.

Flit Phospho-Soda *Casen Fleet, Ukr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation.

Flitrion *Iator, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Flivas *Asahi, Jpn.*
Naftopidil (p. 2361·1).
Benign prostatic hyperplasia.

Flix *Dinctas, Turk.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Flixid *Novofarm (Νοβοφαρμ), Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Flixocort *Verisfield, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flixoderm *Verisfield, Gr.; GSK, Ital.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flixonase *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, China; GSK, Cz.†; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK Consumer, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Thai.; GSK, Turk.; GSK, Ukr.; GSK, Venez.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Flixonase Allergy & Hayfever 24 Hour *GSK Consumer, Austral.*
⊗Fluticasone propionate (p. 1638·1).
Formerly known as Beconase Allergy & Hayfever 24 Hour.
Allergic rhinitis.

Flixotaide *Glaxo Wellcome, Port.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Flixotide *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Gr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Thai.; GSK, Turk.; Allen & Hanburys, UK; GSK, Venez.*
⊗Fluticasone propionate (p. 1638·1).
Asthma; obstructive airways disease; skin disorders; allergic rhinitis.

GSK, Ukr.
⊗Fluticasone (p. 1638·1) or fluticasone propionate (p. 1638·1).
Asthma.

Flixovate *GSK, Fr.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flixovent *Sanfer, Mex.*
⊗Salmeterol (p. 1224·1); fluticasone (p. 1638·1).
Obstructive airways disease.

Flo Sinus Care *ENT Technologies, Austral.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Nasal irrigation.

Flobacin *Saga, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flobacin-OZ *Saga, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Flobacin-TZ *Saga, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Floban *Geno, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Flocadep *Natiris, Venez.*
Smilax officinalis; taraxacum (p. 2625·3); rosemary (p. 2607·2).

Floccin *Pinewood, Austria.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-convulsive disorder.

Flocet *Collins, Mex.†*
Fluoxetine (p. 417·1).
Depression.

Flochek *Alkem, India.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Flocil *VHB, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Flocin *Adley, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Flocin-TZ *Adley, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Flociprin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Flocipron-T *P & B, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Flo-Coat *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Floctil *Unison, Thai.*
Azithromycin (p. 221·2).
Bacterial infections.

Flocur *Beta, Arg.*
Tolfenamic acid (p. 138·3).
Dysmenorrhoea; headache; migraine.

Flocy *Natco, India; Sun, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Flocy TZ *Sun, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Flodemex *Pasteur, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flodeneu *Remedina, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Flodermol *Juventus, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Flodil
Note: this name may be used for preparations of different composition.
AstraZeneca, Fr.
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Minerva (Μινερβα), Gr.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Flodin Duo *Zodiac, Braz.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Flodisona *Abbott, Gr.*
Flurbiprofen (p. 65·2).

Flodol *Farma 1, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Flodolor *Alta Care, Ital.*
Polygonatum odoratum; meadowsweet (p. 2550·2); aesculus (p. 2431·2); arnica (p. 2447·2); liquorice (p. 1853·2); devil's claw root (p. 42·3); ananas; papaya; peppermint oil (p. 1877·1); juniper oil (p. 2537·2).
Muscle and joint pain.

Flodont *Roemmers Rowe, Venez.*
Benzydamine hydrochloride (p. 29·2).
Mouth inflammation.

Floease *Sun, India.*
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Flogan *Merck, Braz.*
Diclofenac (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flogard *Acekinetic, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flogard-O *Acekinetic, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Flogaren *Ronava, Venez.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Flogel *Cipla, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Flogen *Teva, Mex.*
Naproxen sodium (p. 98·2).
Pain; inflammation.

Flogencyl *Pharmadeveloppement, Fr.*
Aescin (p. 2431·2).
Mouth ulcers.

Flogene
Note: this name may be used for preparations of different composition.
Ache, Braz.
Piroxicam betadex (p. 126·1).
Gout; musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Flogiatrin *Sanofi-Aventis, Arg.*
Carisoprodol (p. 2021·3); piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Flogiatrin B12 *Sanofi-Aventis, Arg.*
Tablets: ⊗Carisoprodol (p. 2021·3); piroxicam (p. 125·3); dexamethasone (p. 1630·3); pyridoxine (p. 2105·3); hydroxocobalamin (p. 2107·3).
Musculoskeletal, joint, and soft-tissue disorders; neuritis.

Sanofi-Aventis, Arg.
Injection: ⊗Piroxicam (p. 125·3); dexamethasone (p. 1630·3); pyridoxine (p. 2105·3); hydroxocobalamin (p. 2107·3).
Musculoskeletal and joint disorders.

Floginax *Teofarma, Ital.*
Naproxen (p. 98·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Flogirax *Aspen, Braz.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flogiren *Sanval, Braz.*
Diclofenac (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flogmed *Farmedia, Gr.*
Nabumetone (p. 97·1).
Inflammatory disorders.

Flogocan *Azevedos, Port.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Flogocort *Bago, Chile.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Flogodisten *Omicron, Arg.*
Niflumic acid (p. 101·2); orphenadrine citrate (p. 909·2); aluminium hydroxide (p. 1817·2).

Flogofenac *Ecobi, Hong Kong†; Ecobi, Ital.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Flogofin *Laboratorios Chile, Chile.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Flogofort *Amnol, Ital.*
⊗Maritime pine (p. 2590·3); aesculus (p. 2431·2); bromelains (p. 2460·3); vitamin B substances (p. 2102·3).
Inflammation; oedema.

Flogofort Cremagel *Amnol, Ital.*
Isodecyl salicylate; 18-beta glycyrrhetic acid (p. 54·2); unsaturated fatty acids; aescin (p. 2431·2); menthol (p. 2553·2); menthyl lactate (p. 2554·1).
Inflammation.

Flogojet *Andromaco, Chile.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flogoken *Kener, Mex.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Flogol *Lazar, Arg.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, and soft-tissue disorders.

Flogolab *Multilab, Braz.*
Benzydamine hydrochloride (p. 29·2).
Inflammation.

Flogolisin *Lazar, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Flogomin *Kinder, Braz.*
Benzydamine (p. 29·2).

Flogoprofen *Chiesi, Hong Kong; Chiesi, Spain.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flogoraft *Angelini, Port.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Flogoral *Ache, Braz.; Angelini, Port.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Flogo-Rosa *Ache, Braz.*
Benzydamine hydrochloride (p. 29·2).
Vaginal irritation.

Flogosine *Ahimsa, Arg.*
Piroxicam (p. 125·3).
Inflammation; pain.

Flogostop
Note: this name may be used for preparations of different composition.
DAST, Gr.
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Ivax, Arg.
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease; rheumatoid arthritis.

Flogoter *Estedi, Spain.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Flogotone *Interpharma, Chile.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Flogovis *Amnol, Ital.*
⊗Aesculus (p. 2431·2); bromelains (p. 2460·3); pineapple; zinc sulfate (p. 2126·2); copper sulfate (p. 2057·2).
Nutritional supplement; inflammation; oedema.

Flogovis IdroGel *Amnol, Ital.*
⊗Aescin (p. 2431·2); bromelains (p. 2460·3).
Inflammation; oedema.

Flogovital *Bago, Arg.*
Niflumic acid (p. 101·2).
Inflammation.

Flogovital NF *Bago, Arg.*
Nimesulide (p. 101·3).
Inflammation.

Flogoxib *Zdorovje, Ukr.*
Celecoxib (p. 36·3).
Rheumatoid arthritis; osteoarthritis.

Flogozyme *Norma (Νορμα), Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Flohale *Cipla, India.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Flohale DP *Cipla-Medpro, S.Afr.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Flokind-F *Mankind, India.*
Finasteride (p. 2358·3); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Floksan *Nevzat, Ukr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floksid *Promed, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Floksin *Sanli, Turk.*
Flucloxacillin (p. 299·1).
Bacterial infections.

Flolac *Solitaire, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); lactobacillus (p. 2596·3).

Flolan *GSK, Austral.; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fr.; IFET (ΙΦΕΤ), Gr.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, UK; Gilead, USA.*
Epoprostenol sodium (p. 1375·1).
Pulmonary hypertension; thrombosis prophylaxis during renal dialysis.

Flolica-OD *RND, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Flolid *CT, Ital.; CT, Rus.*
Nimesulide (p. 101·3).
Pain; fever; inflammation.

Floltec *Greenpharma, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Flomax
Note: this name may be used for preparations of different composition.
CSL, Austral.†; Boehringer Ingelheim, Canad.; CSL, NZ; Astellas, S.Afr.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Chiesi, Ital.
Morniflumate (p. 92·2).
Inflammation; pain; fever.

Flomaxtra *CSL, Austral.; CSL, NZ; Astellas, UK.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Flomed *Boniscontro & Gazzone, Ital.†*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Flomex *Cipla, India.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flomex N *Cipla, India.*
⊗Fluorometholone (p. 1637·2); neomycin (p. 329·3).
Infected eye disorders.

Flomicin *Neo Quimica, Braz.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea.

Flomin *Astellas, Neth.; Astellas, Port.*
Solifenacin succinate (p. 2367·3).
Bladder instability.

Flomist *Cipla, India; Cipla, Malaysia; Cipla-Medpro, S. Afr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Flomon *FDC, India.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flomox *Shionogi, Jpn.*
Cefcapene pivoxil hydrochloride (p. 238·3).
Bacterial infections.

Flonacin *Alpharma, Mex.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flonase *GSK, Canad.; GSK, Jpn†; Aspen, S.Afr.; Glaxo Wellcome, USA.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; rhinitis.

F-Lone *Syntho, India.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Floneks *Terra, Turk.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Flonida *Sarabhai Piramal, India.*
Fluorouracil (p. 795·2).
Actinic keratosis; basal cell carcinoma.

Flonidan *Sandoz, Cz.; Teva, Hung.; Sandoz, Pol.*
Loratadine (p. 633·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Flonital *Anfarm, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Flonorm *Schering-Plough, Mex.*
Rifaximin (p. 355·2).
Bacterial infections of the gastro-intestinal tract; diarrhoea; diverticular disease; hyperammonaemia secondary to hepatic encephalopathy.

Flontalexin *Caber, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Flontin *Natco, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Flopen *Aspen, Austral.*
Flucloxacillin magnesium (p. 299·2) or flucloxacillin sodium (p. 299·2).
Gram-positive coccal infections.

Flo-Pred *Taro, USA.*
⊗Prednisolone acetate (p. 1645·2).
Corticosteroid.

Floprost *Bilim, Turk.*
Tamsulosin hydrochloride (p. 2369·1).

Floquin *Invision, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Flora-BC *Mankind, India.*
Vitamin B substances (p. 2102·3); lactobacillus (p. 2596·3).

florabio Manna-Feigen *Schoenenberger, Ger.†*
Manna (p. 1858·2); fig (p. 1843·2).
Constipation.

florabio naturreiner Heilpflanzensaft *Schoenenberger, Ger.†*
A range of plant extracts.

Florablend *Bionova, India.*
Fructo-oligosaccharides (p. 2508·1); glutamine (p. 2070·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

Florac *Cadila, India.*
Fluorouracil (p. 795·2).

Floracal *Flora, Canad.†*
Minerals; colecalciferol (p. 2113·1).

Floracetam *Sozin-Flora, India.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Floracid *Valenta, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floracor *Mylan, S.Afr.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Floradix *Sal-Bert, Hung.; Salus, UK.*
Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; tonic.

Floradix Eisen *Salus, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency.

Floradix Eisen-Folsäure *Salus, Ger.; Salushaus, Ger.*
Thiamine hydrochloride (p. 2103·1); folic acid (p. 2063·1); riboflavin (p. 2104·3); nicotinamide (p. 2083·1); ferrous gluconate (p. 2061·2).
Tonic.

Floradix Formula *Salus, Canad.*
Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Floradix Kindervital *Salus, Canad.†*
Achillea (p. 2427·3); aniseed (p. 2444·2); carrot; chamomile (p. 2474·1); coriander (p. 2486·3); dried yeast (p. 2125·2); equisetum (p. 2500·1); fennel (p. 2503·2); liquorice (p. 1853·2); malt (p. 2080·2); sweet orange peel (p. 2576·2); peppermint (p. 1877·1); ispaghula (p. 1849·1); rose fruit (p. 2607·1); spinach; urtica (p. 2639·3); watercress; wheat (p. 2647·1).

Floradix Kräuterblut *Duopharm, Ger.†; Salushaus, Ger.†*
Oral liquid: Ferrous gluconate (p. 2061·2); thiamine hydrochloride (p. 2103·1); riboflavin sodium phosphate (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Iron deficiency; tonic.

Duopharm, Ger.†; Salushaus, Ger.†
Tablets: Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); nicotinamide (p. 2083·1).
Tonic.

Floradix mit Eisen *Salus, Ger.; Salushaus, Ger.*
Ferrous gluconate (p. 2061·2).
Iron deficiency.

Floradix Multipretten N *Salushaus, Ger.*
Caraway (p. 2470·2); caraway oil (p. 2470·3); fennel (p. 2503·2); fennel oil (p. 2503·3); aniseed (p. 2444·2) anise oil (p. 2444·3);

coriander (p. 2486·3); coriander oil (p. 2487·1); peppermint leaf (p. 1877·1); peppermint oil (p. 1877·1); absinthium (p. 2426·1); achillea (p. 2427·3).
Gastrointestinal disorders.

Floradix Tab *Salus, Canad.†*
Centaury (p. 2473·2); couch-grass (p. 2487·2); dried yeast (p. 2125·2); folic acid (p. 2063·1); crataegus (p. 2488·1); ferrous gluconate (p. 2061·2); kelp (p. 2612·1); rose fruit (p. 2607·1); spinach; urtica (p. 2639·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Floradot *Sozin-Flora, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Florafem *Salus, Ger.*
Potentilla anserina.
Dysmenorrhoea.

Florafree *Deb, Canad.*
Triclosan (p. 1773·2).
Skin cleansing and disinfection.

Floragermina 6 *Montefarmaco, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins; lactoferrin (p. 2539·3); inulin (p. 2534·3).

Floragink *Duopharm, Ger.*
Ginkgo biloba (p. 2512·3).
Mental function impairment.

Floragyn *Aroma Femi, Israel.*
Lactic-acid-producing organisms (p. 2596·3).
Restoration of vaginal flora.

Florak *Deva, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; anxiety.

Flora-L *McW, India.*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea.

Floral Pas *Gache, Venez.*
Valerian (p. 2640·2); passion flower (p. 2584·1).
Nervous disorders; insomnia.

Floralin *Ceutical, Hong Kong.†*
Domperidone (p. 1838·1).

Floralite *Merck, Chile.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); glucose (p. 2068·3); potassium citrate (p. 1780·3) (p. 1780·1).
Oral rehydration therapy.

Floralyte *Merck, Braz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3).

Floramil *ACME, Philipp.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

Floramin *Bestochem, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Floramycin *Sozin-Flora, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Florane *Pharmawealth, Philipp.*
Isoflurane (p. 1903·2).
General anaesthesia; analgesia in painful procedures.

Floranex *Rising Pharmaceuticals, USA.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3).
Dietary supplement.

Flora-Q *PharmaDerm, USA.*
Lactobacillus acidophilus (p. 2596·3); bifidobacterium; *Lactobacillus paracasei* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Maintenance of gastrointestinal flora.

Floraquin *Ali, Turk.*
Diiodohydroxyquinoline (p. 931·1).
Vaginal infections.

Flora-SB *Mankind, India.*
Bifidobacterium bifidum (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3).

Florasil *Flora, Canad.*
Silicon (p. 2088·3).

Florastor *Medical Futures, Canad.; Biocodex, USA.*
Saccharomyces boulardii (p. 2596·3).
Antibiotic-associated diarrhoea; gastroenteritis.

Florasyl-MF *Sozin-Flora, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Florate *Alcon, Braz.; Alcon, Gr.*
⊗Fluorometholone acetate (p. 1637·2).
Eye disorders.

Floratil *Merck Serono, Arg.; Merck, Braz.; Merck, Mex.; Darvys, Philipp.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; disturbances of intestinal flora; restoration of gastrointestinal flora.

Floravit
Note: this name may be used for preparations of different composition.
Daffohils, India.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); lactobacillus (p. 2596·3).
Salus, Canad.
Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia; dietary supplement.
Flora, Canad.†
Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Floravit Ped *Daffohils, India.*
Vitamin B substances (p. 2102·3); *Lactobacillus acidophilus* (p. 2596·3).

Floraxina *Amhof, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Florazole *Ferring, Canad.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Florcidin *Biotech, Venez.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of gastrointestinal flora.

Florelax *Sanofi-Aventis OTC, Ital.*
Dried yeast (p. 2125·2); lactic-acid-producing organisms (p. 2596·3); chamomile (p. 2474·1); angelica (p. 2443·3); valerian (p. 2640·2); peppermint leaf (p. 1877·1); caraway (p. 2470·2); vitamin B substances (p. 2102·3).
Gastrointestinal disorders.

Floren *Ativus, Braz.*
Lactobacillus acidophilus (p. 2596·3).

Florence *Elea, Arg.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; androgen-induced acne, seborrhoea, hirsutism, and alopecia in females.

Florent *Cifarma, Braz.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Floresse *Roche Consumer, UK.*
Borage oil (p. 2459·2); with or without vitamins.

Florestor *Merck, Venez.*
Saccharomyces boulardii (p. 2596·3).
Restoration of gastrointestinal flora.

Floret *Dexcel, Israel.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Florexal *Silanes, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Florgynal *Galien, Fr.*
Estriol (p. 2274·3); progesterone (p. 2300·2); *Lactobacillus casei* var. *Rhamnosus* (p. 2596·3).
Vulvovaginitis; adjunct in gynaecological surgery during menopause.

Flori *Pharmacon, India.*
Fluconazole (p. 578·2).
Fungal infections.

Florical *Mericon, USA.*
Calcium carbonate (p. 1824·3); sodium fluoride (p. 2089·2).
Dietary supplement.

Floricot *Samarth, India.*
⊗Fludrocortisone acetate (p. 1634·3).
Adrenocortical insufficiency; congenital adrenal hyperplasia.

Florid *Mochida, Jpn.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections.

Florida *Daffohils, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Florida-T *Daffohils, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Floridox *Sozin-Flora, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Floridral *Dicofarm, Ital.*
Glucose (p. 2068·3); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); aspartame (p. 2169·2); lactobacillus (p. 1780·1) (p. 2596·3).
Oral rehydration therapy; diarrhoea; disturbances of the gastrointestinal microbial flora.

Florilax *Floris, Israel.†*
Senna (p. 1885·1).
Constipation.

Florin *Partner, Rus.*
Bifidobacterium bifidum (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3).
Restoration of intestinal flora; digestive disorders.

Florinef *Aspen, Austral.; Paladin, Canad.; Merck, Chile; BMS, Denm.; BMS, Fin; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; BMS, Irl.; BMS, Malaysia; BMS, Mex.; BMS, Neth.; BMS, Norw.; Healthcare Logistics, NZ; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, UK; Monarch, USA.*
⊗Fludrocortisone acetate (p. 1634·3).
Adrenocortical insufficiency; congenital adrenal hyperplasia.

Florinefe *BMS, Braz.*
⊗Fludrocortisone acetate (p. 1634·3).
Adrenocortical insufficiency; congenital adrenal hyperplasia; orthostatic hypotension.

Floriny *Ativus, Braz.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); salix (p. 129·2).
Anxiety disorders.

Florisan *Boehringer Ingelheim, Gr.*
Docusate sodium (p. 1836·2); bisacodyl (p. 1821·1).
Constipation.

Florisan N *Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Gr.*
Bisacodyl (p. 1821·1).
Constipation.

Florised *Zdorovje, Ukr.*
Motherwort (p. 2564·2); lupulus (p. 2546·1); mint (p. 2621·2); valerian (p. 2640·2); liquorice (p. 1853·2).
Neurasthenia; neuroses.

Florisene *Lamberts Healthcare, UK.*
Ferrous glycine sulfate (p. 2061·3); vitamin C (p. 2110·3); vitamin B_{12} (p. 2107·2); lysine (p. 2079·3).
Hair loss in women.

Florlax *Cazi, Braz.*
Senna (p. 1885·1); tamarind (p. 1892·2); coriander (p. 2486·3); cassia pulp (p. 1826·2).
Constipation.

Floroc *Sandoz, Philipp.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Florocid *East India Pharma, India.*
Procaine hydrochloride (p. 1994·3); sodium fluoride (p. 2089·2).

Floron *Elder, Singapore.*
Iron polymaltose (p. 2077·2); vitamin C (p. 2110·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2).
Iron supplement.

Florone *Galderma, Ger.; Pfizer, Gr.; Dermik, USA.*
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Florosan *Sandoz, Switz.†*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea.

Floroxin *Sozin-Flora, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Florsalmin *Zentiva, Cz.*
Sage (p. 2608·3).
Mouth and throat disorders.

Florvis GG *Novartis Consumer, Ital.*
Preparation for enteral nutrition containing *Lactobacillus* GG (p. 2596·3).

Florxine *Elder, Singapore.*
Pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1).
Dietary supplement in pregnancy.

Flosef *Sun, India.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flosep *Mavi, Mex.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flosicron *Pasteur, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Flosin *Menarini, Hung.; Menarini, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Flosine *Quiris, Ger.*
Ispaghula (p. 1849·1).
Constipation; stool softener.

Flossac *Caber, Ital.*
Norfloxacin (p. 333·3).
Bacterial urinary-tract infections.

Flostar *Sanify, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Flosteron *KRKA, Rus.; KRKA, Ukr.*
⊗Betamethasone dipropionate (p. 1623·3); betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Flotac *Novartis, Braz.; Novartis, Chile; Novartis, Mex.; Novartis, Venez.*
Diclofenac colestyramine (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation; gout.

Flotavid *Mersifarma, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flotears *Klar Sehen, India.*
Polyvinyl alcohol (p. 2204·2); povidone-iodine (p. 1767·1).

Flothin *Ranbaxy, India.*
Enoxaparin (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

Flotina *Lampugnani, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Flotiran *Schering-Plough, Port.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Infected skin disorders.

Flotome *Epitome, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Flotral *Ranbaxy, India.*
Alfuzosin (p. 2351·3).
Benign prostatic hyperplasia.

Flotrin *Mibe, Ger.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Flotros *Galen, Irl.; Galen, UK.*
Trospium chloride (p. 2371·1).
Bladder hyperactivity.

Flovacil *Recalcine, Chile.*
Moxifloxacin (p. 326·3).
Bacterial infections.

Flovas *Ipca, India.*
Pitavastatin (p. 1471·1).

Flovent *GSK, Canad.; GSK, USA.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Floves *Pisa, Mex.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Flovid *Hovid, Hong Kong; Hovid, Philipp.; Hovid, Singapore.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flovin *Raam, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Flow *Uniphar, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Flow-OZ *Uniphar, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Flox *Hexal, Braz.; Lark, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Marck Biosciences, Philipp.
Ofloxacin (p. 334·3).
Bacterial infections.

Flox-200 *Caldern, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxacap *Caprifarmindo, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floxacef *Hizon, Philipp.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxacin *Stada, Austria; MSD, Braz.; Medix, Mex.*
Norfloxacin (p. 333·3).
Bacterial infections.

Floxacom *Combiphar, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floxaday *Ranbaxy, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Floxagen *Vonnace, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxager *Streger, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Floxal *Riel, Austria; Mann, Cz.; Mann, Ger.; Mann, Hung.; Mann, Pol.; Bausch & Lomb, Rus.; Bausch & Lomb, Switz.; Bausch & Lomb, Ukr.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Floxamicin *Biotenk, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Floxan
Note: this name may be used for preparations of different composition.
Prodotti, Braz.†
Ciprofloxacin (p. 261·1).
Bacterial infections.

Yik Kwan, Hong Kong†; Sandoz, Indon.†
Ofloxacin (p. 334·3).
Bacterial infections.

Floxanor *Delta, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Floxantina *Degorts, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Floxapen *Actavis, Austria; Actavis, Belg.; GSK, Hong Kong†; GSK, Indon.†; GSK, Mex.†; Actavis, Port.; GSK, S. Afr.†; Actavis, Switz.; GSK, Venez.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

GSK, Austral.†; SmithKline Beecham, Gr.; Actavis, Irl.; Actavis, Neth.; GSK, NZ; GSK, UK.
Flucloxacillin magnesium (p. 299·2) or flucloxacillin sodium (p. 299·2).
Bacterial infections.

Floxaquin-C *Themis Medicare, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxaquin-O *Health Guard, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1); *Lactobacillus sporogenes* (p. 2596·3).

Floxar *Forgo, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxar-OZ *Forgo, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Floxator *Specifar (Σπεσιφαρ), Gr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floxatral *Austral, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Floxbio *Sandoz, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxedol *Edol, Port.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Floxel *United American, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floxelena *Pharmacos Abug, Mex.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxen *Raza, Hong Kong.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Floxet *Egis, Cz.; Egis, Hong Kong; Egis, Hung.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; panic disorder; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Flox-ex *Sandoz, Switz.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Floxicam *Neo Quimica, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Floxicontin *Modi-Mundipharma, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxid *Abbott, Braz.*
Roxithromycin (p. 356·2).
Bacterial infections.

Floxigat *Medley, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Floxigat M *Medley, India.*
Ambroxol (p. 1654·3); gatifloxacin (p. 303·2).

Floxigem *Medley, India.*
Gemifloxacin mesilate (p. 304·1).
Chronic bronchitis; community-acquired pneumonia.

Floxigra *Graha, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxika *Ikapharmindo, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxikair *PDC, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Floxil
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Arg.; Janssen-Cilag, Mex.
Ofloxacin (p. 334·3).
Bacterial infections.

Marck Biosciences, Philipp.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Floxilevo *Deva, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floxil-O *Ind-Swift, India.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Floximed
Note: this name may be used for preparations of different composition.
Burapha, Thai.
Norfloxacin (p. 333·3).
Bacterial infections.

World Medicine, Ukr.
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

Floxin
Note: this name may be used for preparations of different composition.
Be-Tabs, S.Afr.
Norfloxacin (p. 333·3).
Bacterial urinary-tract infections.

Ortho McNeil, USA.
Ofloxacin (p. 334·3).
Bacterial infections.

Sriprasit, Thai.
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; migraine.

Korea United, Philipp.†
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Floxin Otic *Daiichi, USA.*
Ofloxacin (p. 334·3).
Bacterial ear infections.

Floxina *Cazi, Braz.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxine *Cruise, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxine-NT *Cruise, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Floxine-OZ *Cruise, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Floxinol *Millet Roux, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Floxip *Max, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxiren *Indoco, India.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Floxitul *Randall, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Floxium *Arterium, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Floxlevo *Biotenk, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Flox-O *Glenmark, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxocip *Merck, Braz.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Floxol *Duopharma, Philipp.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Floxole *Cosmas, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxole-MZ *Cosmas, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Floxole-NT *Cosmas, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Floxole-OZ *Cosmas, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Floxpar *Invision, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Floxsafe *MSN, India.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Floxsig *Aspen, Austral.*
Flucloxacillin sodium (p. 299·2).
Gram-positive coccal infections.

Floxstat *Janssen-Cilag, Braz.; Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxudem *Dem, Turk.*
Floxuridine (p. 793·3).

Floxur *Wockhardt, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxur-TZ *Wockhardt, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Floxwin XL *Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxy *Millimed, Philipp.; Millimed, Thai.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxyfral *Solvay, Austria; Solvay, Belg.; Abbott, Fr.; Abbott, Switz.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Floxzen *Moraceae, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Floxzen-M *Moraceae, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Floxzen-OZ *Moraceae, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Floxzen-ST *Moraceae, India.*
⊗Ofloxacin (p. 334·3); serrapeptase (p. 2613·3).

Floxzu *Brown & Burk, Philipp.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Flozamin *Minova, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flozastar *Invision, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Flozen Plus *Mankind, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Flozen-AA *Mankind, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Flozen-NS *Mankind, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Flozepan *Lazar, Arg.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Flozol *Glories, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flozul *Farlab, Port.†*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Flu-4 *Haledew, India.*
Oral drops: Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Haledew, India.
Oral suspension: Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Haledew, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Flu-21 *Farma 1, Ital.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Flu, Cold & Cough Medicine *Major, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Flu Oph *Seng, Thai.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flu Stop *GMP, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Fluacort *Meda, Belg.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Fluact *Active, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fluad *Temis, Arg.; Novartis Vaccines, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis, China; Novartis Vaccines, Cz.; Novartis, Denm.; Novartis Vaccines, Ger.; Chiron Vaccines, Hong Kong†; Novartis, Israel; Novartis Vaccines, Ital.; Chiron Vaccines, Philipp.†; Novartis Vaccines, Port.; Novartis Vaccines, Singapore†; Novartis, Switz.; Novartis Vaccines, Thai.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Flual-M *Candor, India.*
⊗Fluocinolone acetonide (p. 1636·1); miconazole nitrate (p. 589·1).
Fungal skin infections.

Fluanxol *Lundbeck, Austral.; Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Canad.; Lundbeck, Chile; Lundbeck, China; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Fr.; Bayer, Ger.; Lundbeck, Gr.; Lundbeck, Hong Kong; Lundbeck, Hung.; Lundbeck, India; Lundbeck, Israel; Lundbeck, Mex.; Lundbeck, Neth.; Lundbeck, Norw.; Healthcare Logistics, NZ; Lundbeck, Philipp.; Lundbeck, Pol.; Lundbeck, Port.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.*
Flupentixol decanoate (p. 1074·2) or flupentixol hydrochloride (p. 1074·2).
Psychoses; depression; anxiety; schizophrenia; mixed anxiety depressive states; alcohol or opioid withdrawal syndromes; nervous disorders.

Lundbeck, Irl.; Lundbeck, UK.
Flupentixol hydrochloride (p. 1074·2).
Depression; mixed anxiety depressive states.

Lundbeck, Malaysia; Lundbeck, Singapore; Lundbeck, Ukr.
Flupentixol (p. 1074·1) or flupentixol decanoate (p. 1074·2).
Anxiety; depression; psychoses; neuroses; psychosomatic disorders.

Fluarix *GSK, Arg.; GSK, Austral.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, USA; GSK, Venez.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Fluaton *Tubilux, Ital.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Fluazur *Novartis, Chile.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Flubason *Sanofi-Aventis, Ital.; Sanofi-Aventis, Spain.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Flubelin *Patar, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders.

Flubery *Hanburys, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flubest *Ali, Turk.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Flubichlor *Entod, India.*
Chloramphenicol (p. 257·1); flurbiprofen sodium (p. 65·3).

Flubiclox *Specialised Therapeutics, Austral.*
Flucloxacillin sodium (p. 299·2).
Gram-positive coccal infections.

Flubifix *Federfarma, Ital.*
Flurbiprofen (p. 65·2).
Mouth and throat disorders.

Flubilar *Madaus, Fr.†*
Sodium methylcamphorate.
Dyspepsia; constipation.

Flubiotic *Pharmazam, Spain.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Flubip *Taurus, India.*
Flurbiprofen sodium (p. 65·3); hypromellose (p. 2189·2).

Flubir *Norma (Νορμα), Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Flubit *Cubit, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flublok *Protein Sciences, USA.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Flu-4-BR *Haledew, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Fluc *Bactolac, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucacid *Euro-Pharma, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Flucadex *Graha, Indon.†*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms; cough.

Flucalin *Ariston, Arg.*
Calcium gluceptate (p. 1783·2); calcium gluconate (p. 1783·3); vitamin C (p. 2110·3).
Nutritional supplement.

Flucalit *Rafarm, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucalup *Lupin, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucalyptol *Zambon, Fr.*
Pholcodine (p. 1675·1).
Cough.

Flucam *Pfizer, Jpn.*
Ampiroxicam (p. 21·1).
Musculoskeletal, joint, and peri-articular disorders.

Flucan *Bombay Tablet, India; Pfizer, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Flucandia *Unison, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Flucandid *Ivax, Irl.†*
Fluconazole (p. 578·2).
Fungal infections.

Flucanid *Alapis, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucanil *Geolab, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Flucanol *Rafa, Israel.*
Fluconazole (p. 578·2).
Fungal infections.

Flucap *Synco, Hong Kong.†*
Caffeine (p. 1203·3); chlorphenamine (p. 620·3); hesperidin (p. 2505·2); paracetamol (p. 115·1); salicylamide (p. 129·2); ascorbic acid (p. 2110·3).

Flucaps *Biotech Naturis, Venez.*
Echinacea angustifolia (p. 2498·1).
Influenza symptoms.

Flucar *Darnitsa, Ukr.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flucare *United Lifecare, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucasia *Willow, India.*
⊗Fluticasone (p. 1638·1).
Skin disorders.

Flucasten *Ipca, NZ.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Flucazol *Cristalia, Braz.; Spirig, Switz.*
Fluconazole (p. 578·2).
Fungal infections.

Flucazole *Mylan, NZ.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Fluccil *Ducto, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Fluccinol N *Arlex, Mex.*
⊗Fluocinolone (p. 1636·1); neomycin (p. 329·3).
Infected skin disorders.

Flucef *SF, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Flucelvax *Novartis Vaccines, USA.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Flucess *Sandoz, Indon.†; Sandoz, Malaysia; Sandoz, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Fluchem *Chemo-Drugs, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fluciderm *Hoe, Malaysia; Hoe, Singapore.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flucil
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Flucloxacillin sodium (p. 299·2).
Gram-positive coccal infections.
Masa, Thai.
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.
Samarth, India.
Fluorouracil (p. 795·2).
Malignant neoplasms.

Flucilium *Utopian, Thai.*
Flunarizine (p. 629·3).
Cerebrovascular disorders.

Flucillin *Pinewood, Irl.*
Flucloxacillin sodium (p. 299·2).
Gram-positive bacterial infections.

Flucin *Agio, India; Agio, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flucinal *SF, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Flucinar *Jelfa, Cz.; Medphano, Ger.; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.; Jelfa, Ukr.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flucinar N *Jelfa, Hung.; Jelfa, Pol.; Jelfa, Ukr.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.
Jelfa, Rus.
⊗Fluocinolone acetonide (p. 1636·1); neomycin (p. 329·3).
Infected skin disorders.

Flucinom *Schering-Plough, Cz.; MSD, Gr.; Schering-Plough, Rus.*
Flutamide (p. 798·2).
Prostatic cancer.

Flucinome *Essex, Switz.†*
Flutamide (p. 798·2).
Prostatic cancer.

Flucirac *Natiris, Venez.*
Hamamelis (p. 2523·3); calendula (p. 2465·2); phyllanthus niruri (p. 2590·1); aloe vera (p. 1693·2).
Phlebitis; haemorrhoids; varices.

Flucis *CIS, Fr.; CIS, Neth.; CIS, Port.; CIS, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for positron emission tomography in cardiology, neurology, and oncology.

Flucistein *Uniao Quimica, Braz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Fluclomix *Ashbourne, UK.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Fluclon *Clonmel, Irl.*
Flucloxacillin sodium (p. 299·2).
Gram-positive bacterial infections.

Fluclox *Stragen, Ger.; Farma 1, Ital.; Manix, Philipp.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Flucloxil *CCM, Malaysia.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.
Duopharma, Hong Kong.†
Flucloxacillin (p. 299·1).
Bacterial infections.

Flucloxin *Douglas, NZ.*
Flucloxacillin sodium (p. 299·2).
Gram-positive bacterial infections.

Fluco *Sandoz, Cz.†*
Fluconazole (p. 578·2).
Fungal infections.

Flucoat *ATOZ, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucobeta *Betapharm, Ger.*
Fluconazole (p. 578·2).
Fungal infections.

Flucocaps *AG Therapy, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoccinum *Knop, Chile.*
Allium sativum (p. 2510·3); arsenicum jodatum (p. 2448·1); gelsemium (p. 2511·2); lachesis (p. 2538·3).
Homoeopathic preparation.

Flucocin
Note: this name may be used for preparations of different composition.
EMS, Braz.
Fluconazole (p. 578·2).
Fungal infections.
Micro, India.
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Flucocin-N *Micro, India.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin (p. 329·3).
Infected skin disorders.

Flucocip *Cadila, India.*
⊗Ciprofloxacin (p. 261·1); clotrimazole (p. 576·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Flucodan *Arrow, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoderm *Dermapharm, Ger.; Dermapharm, Neth.†; Dermapharm, Switz.*
Fluconazole (p. 578·2).
Fungal infections.

Flucodin *Coronet, Indon.*
Paracetamol (p. 115·1); noscapine (p. 1670·3); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Influenza symptoms; cough.

Flucodrug *Med-One, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucofast *Medana, Pol.*
Fluconazole (p. 578·2).
Fungal infections.

Flucofin *Lyofin, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoginkan *Baliarda, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Flucohexal *Hexal, Hung.*
Fluconazole (p. 578·2).
Fungal infections.

Flucol
Note: this name may be used for preparations of different composition.
Belfar, Braz.; Rowex, Irl.
Fluconazole (p. 578·2).
Fungal infections.
Sunward, Singapore.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Acupharm, S.Afr.†; Garec, S.Afr.†
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; sinusitis.
Degorts, Mex.†
⊗Naproxen (p. 98·2); pseudoephedrine hydrochloride (p. 1676·1).
Influenza; rhinitis; sinusitis; upper respiratory-tract congestion.

Flucolab *Laborate, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucolaf *Lafedar, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Flucold
Note: this name may be used for preparations of different composition.
Nabros, Ukr.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3) caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Formerly contained paracetamol, chlorphenamine maleate, caffeine, and phenylpropanolamine hydrochloride.
Cold and influenza symptoms.
Wallace, India.
Oral drops: Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Wallace, India.
Syrup; tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Flucoldex
Note: this name may be used for preparations of different composition.
Nabros, Rus.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; pain; sinusitis; rhinitis.
Nabros, Ukr.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Flucoldex Forte *Nabros, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); terpin hydrate (p. 1678·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Flucoldex-C *Nabros, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Flucoldex-N *Nabros, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; pain; sinusitis; rhinitis.

Flucoldin *Pharmaceutical Factory of St Petersburg, Rus.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; pain.

Flucold-N *Nabros, Ukr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

FlucoLEK *Sandoz, Pol.†*
Fluconazole (p. 578·2).
Fungal infections.

Flucolic *Hertz, Braz.*
Dimeticone (p. 1886·2).

FlucoLich *Winthrop, Ger.*
Fluconazole (p. 578·2).
Fungal infections.

Flucomabol *Abolmed, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Flucomed *Cimed, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Flucomet *Sun, India.*
Fluconazole (p. 578·2).

Flucomix *Bago, Chile.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flucomp *Obolenskoe, Rus.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain; fever.

Flucon
Note: this name may be used for preparations of different composition.
Alcon, Austral.; Alcon, Belg.; Alcon, Cz.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong†; Alcon, Hung.; Alcon, NZ; Alcon, Pol.; Alcon, S.Afr.; Alcon, Thai.
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.
Siu Guan, Malaysia; Taiwan Biotech, Malaysia; Nabros, Philipp.; Roemmers Osmoph, Venez.
Fluconazole (p. 578·2).
Fungal infections.

Fluconal *Libbs, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconapen *Elpen (Ελπεν), Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconastad *Pharmacodane, Denm.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconax *Drossapharm, Switz.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconazin *Hasco-Lek, Pol.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconeo *Neo Quimica, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconer *Mediner, Hung.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconid *Vitapan, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconol *Ain Medicare, Malaysia.*
Fluconazole (p. 578·2).
Fungal infections.

Fluconovag *Gobbi, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Flucontrol Hot *Aflofarm, Pol.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Flucor Day *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Philipp.*
⊗Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Flucor Night *Hovid, Malaysia.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Flucoral *Kalbe, Indon.; Solvang, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoran *Vocate, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoric *Ranbaxy, Hong Kong; Ranbaxy, Hung.†; Euphoric, India; Ranbaxy, Malaysia; Ranbaxy, S.Afr.; Ranbaxy, Ukr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucort *Glenmark, India.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flucorta *Polfamex, Pol.*
Fluconazole (p. 578·2).
Fungal infections.

Flu-Cortanest *Piam, Ital.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Flucort-C *Glenmark, India.*
⊗Fluocinolone acetonide (p. 1636·1); ciclopirox olamine (p. 575·3).
Infected skin disorders.

Flucort-H *Glenmark, India.*
⊗Fluocinolone acetonide (p. 1636·1).
Eczema.

Flucortis *Verisfield, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flucort-MZ *Glenmark, India.*
⊗Miconazole nitrate (p. 589·1); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Flucort-N *Glenmark, India.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Flucos *Cosme, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucosept *Kwizda, Austria.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoside *Syntro, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucostat *Dalkhimfarm, Rus.; Masterlek, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Flucos-TZ *Cosme, India.*
Fluconazole (p. 578·2); tinidazole (p. 949·2).

Flucoti *Fourrts, India.*
Fluconazole (p. 578·2); tinidazole (p. 949·2).

Flucoton *Royton, Braz.*
Fluconazole (p. 578·2).

Flucovar *Zota, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucovein *Hospital Line, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucoxan *Sanitas, Chile; Pisa, Mex.*
Fluconazole (p. 578·2).
Fungal infections; candidiasis.

Flucozal *Aegis, Hong Kong.*
Fluconazole (p. 578·2).
Candidiasis.

Flucozan *Veropharm, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Flucozed *Zota, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flucozen *Cazi, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Flucozol *Drug Research, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flucozole *Siam Bheasach, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Flucozyd *Cadila, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Flucreme-NM *Concept, India.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Fluctin
Note: this name may be used for preparations of different composition.
Gynopharm, Chile.
Fluconazole (p. 578·2).
Fungal infections.

Lilly, Ger.
Fluoxetine hydrochloride (p. 417·1).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluctine *Lilly, Austria; Alpharma, Mex.†; Lilly, Switz.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Flucyl *Bode, Indon.†; Tempo Scan Pacific, Indon.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Fludabine *United Biotech, India.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Fludac *Cadila, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Fludacel *Celon, India.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Fludactil Co *Garec, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Fludakebir *Aspen, Arg.*
Fludarabine (p. 794·1).
Malignant neoplasms.

Fludalibbs *Libbs, Braz.*
Fludarabine phosphate (p. 794·1).

Fludalym *Actavis, Pol.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Fludan *Biolab, Hong Kong; Biolab, Malaysia.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders; peripheral vascular disorders.

Biolab, Thai.
Flunarizine (p. 629·3).
Cerebrovascular disorders; migraine.

Fludan Codeína *Faes, Spain.*
Codeine phosphate (p. 40·2).
Cough.

Fludane
Note: this name may be used for preparations of different composition.
Armoxindo, Indon.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Influenza symptoms.

Vickmans, Hong Kong.†
Brompheniramine (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Fludane Plus *Armoxindo, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Influenza symptoms; cough.

Fludapamide *Spirig, Switz.*
⊗Indapamide (p. 1409·2).
Hypertension.

Fludara *Bayer, Arg.; Genzyme, Austral.; Bayer, Austria; Genzyme, Belg.; Schering, Braz.; Genzyme, Chile; Genzyme, China; Bayer Schering, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Hung.; Zydus, India; Bayer Schering, Indon.; Genzyme, Irl.; Schering, Israel; Bayer, Ital.; Genzyme, Malaysia; Schering, Mex.†; Genzyme, Neth.; Genzyme, Norw.; Healthcare Logistics, NZ; Bayer, Philipp.; Genzyme, Pol.; Genzyme, Port.; Bayer Schering, Rus.; Genzyme, S.Afr.; Sanofi-Aventis, Singapore; Bayer, Swed.; Genzyme, Switz.†; Sanofi-Aventis, Thai.; Bayer, Turk.; Genzyme, UK; Bayer, USA†; Schering, Venez.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma.

Genzyme, Canad.
Fludarabine phosphate sodium (p. 794·1).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma.

Fludarene *Thea, Ital.*
Chromocarb diethylamine (p. 2477·1).
Capillary fragility.

Fludarin *Intas, India.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Fludawn *Micro, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fludecan *Svizera, India.*
Fluphenazine decanoate (p. 1075·1).
Schizophrenia.

Fludecate *Unipharm, Israel; Intramed, S.Afr.†*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Fludent *Actavis, Fin.; Actavis, Swed.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fludep *East West, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fludep Plus *Cipla, India.*
Fluoxetine hydrochloride (p. 417·1); alprazolam (p. 1035·2).

Fludep-AZ *Ultramark, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Fludeten
Note: this name may be used for preparations of different composition.
Alter, Spain.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Fludex *Servier, Austria; Servier, Belg.; Servier, Fr.; Servier, Gr.; Servier, Neth.; Servier, Port.; Servier, Switz.; Servier, Turk.*
⊗Indapamide (p. 1409·2).
Hypertension.

Fludexin *Dexa, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough; allergic rhinitis; sinusitis.

Fludexol-CL *Vitae, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Fludia *Minova, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fludicon *Quality, Hong Kong.*
Fluconazole (p. 578·2).
Fungal infections.

Fludil *Galeno, Venez.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Fludilat *Schering-Plough, Braz.; Organon, Gr.; Schering-Plough, Indon.; Organon, Thai.†; Organon, Venez.*
Bencyclane fumarate (p. 1315·1).
Cerebral and peripheral vascular disorders; vascular disorders.

Fludin
Note: this name may be used for preparations of different composition.
Biological E, India.
Fluorouracil (p. 795·2).
Malignant neoplasms.

Saba, Turk.
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Fludis *Bernofarm, Indon.*
Fluconazole (p. 578·2).
Fungal infections.

Fludisol *Merck, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Fluditec *Innotech, Fr.; Innotech, Rus.; Innotech, Ukr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion; aid in bronchoscopy and bronchography.

Fluditec toux sèche *Innotech, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Fludizol *M & H, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Flu-4-DMR *Haledew, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1).

Fludocel *CPH, Port.*
Fluconazole (p. 578·2).
Fungal infections.

Fludren *Diafarm, Spain.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Fludronef *Iquinosa, Spain.†*
⊗Fludrocortisone acetate (p. 1634·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Eye disorders.

Fludrop
Note: this name may be used for preparations of different composition.
Yash, India.
Flurbiprofen (p. 65·2).
Prevention of miosis during ocular surgery; ocular inflammation following eye surgery.

Fluend
Note: this name may be used for preparations of different composition.
Alliance, S.Afr.†
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Fluental *Sanofi-Aventis, Ital.*
Sobrerol (p. 1677·2); paracetamol (p. 115·1).
Respiratory-tract disorders.

Fluenz *AstraZeneca, Cz.; Medimmune, Denm.; AstraZeneca, Neth.; AstraZeneca, Spain; AstraZeneca, UK.*
A live attenuated influenza vaccine (nasal) (p. 2393·3).
Active immunisation.

Fluexin *Farmaceutica H, Mex.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with thickened mucus.

Flufact *Medico, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flufeme *Sandoz, Austral.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Flufen *Parenteral Drugs, India.*
Flurbiprofen (p. 65·2).
Prevention of miosis during ocular surgery; ocular inflammation following eye surgery.

Flufenal *Roux-Ocefa, Arg.*
Flunarizine (p. 629·3).
Migraine; vertigo.

Flufenan *Cristalia, Braz.*
Fluphenazine enantate (p. 1075·1) or fluphenazine hydrochloride (p. 1075·1).
Psychoses.

FluFly *Julphar, UAE.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Fluforte *Allergan, Chile; Allergan, Mex.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Fluforte N *Allergan, Mex.*
⊗Fluorometholone (p. 1637·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Flufung *East West, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flugal *Square, Malaysia.*
Fluconazole (p. 578·2).
Fungal infections.

Flugalin *Abbott, Hung.; Abbott, Pol.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flugarda *Biocad, Rus.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma.

Flugen
Note: this name may be used for preparations of different composition.
La Pharmaceuticals, India.
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Novartis, Spain.†
⊗Fluorometholone (p. 1637·2); gentamicin sulfate (p. 304·2).
Ocular inflammation following cataract surgery.

Flugeral *Italfarmaco, Ital.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Flugesic *Ikapharmindo, Indon.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

Flugraine *Orchid, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Fluhalt *Ranbaxy, Malaysia.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Fluhexal *Hexal, Mex.†*
Fluconazole (p. 578·2).
Fungal infections.

Flui-Amoxicillin *Zambon, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Fluibron *Chiesi, Braz.; Andromaco, Chile; Chiesi, Ital.; SAnta, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion; respiratory-tract disorders.

Fluibrox *Medichrom, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Fluicare *Ranbaxy, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Fluicis *Glenmark, Braz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Fluicor *Maver, Chile.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Fluidabak *Thea, Fr.*
Povidone (p. 2204·3).
Dry eyes.

Fluidamin *Behrens, Venez.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Fluidamin Plus *Behrens, Venez.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Fluidasa
Note: this name may be used for preparations of different composition.
Teofarma, Spain.
Mepyramine acefyllinate (p. 635·1).
Obstructive airways disease.

Abbott, Mex.
Theophylline (p. 1229·3).
Obstructive airways disease.

Montpellier, Arg.
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Fluide Desalterant Super Hydratant *Clarins, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Fluide Hydratant Quotidien *L'Oreal, Canad.*
SPF 15: Octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Fluide de Jour *Pro-Derma, Canad.*
SPF 20: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Fluide Lift Jour *Clarins, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Fluidelan *Belfar, Braz.*
Potassium iodide (p. 2336·3).

Fluidema *Baldacci, Port.*
⊗Indapamide (p. 1409·2).
Hypertension.

Fluidin
Note: this name may be used for preparations of different composition.
Ativus, Braz.
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Fluidín Mucolítico *Faes, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Flui-DNCG *Pierre Fabre, Ger.†*
Sodium cromoglicate (p. 1225·3).
Asthma.

Fluido Spineda *Spineda, Arg.*
Camphor (p. 2466·2); turpentine oil (p. 2636·3); arnica (p. 2447·2).
Musculoskeletal and joint pain.

Fluidose *Ophtapharm, Switz.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Fluidox
Note: this name may be used for preparations of different composition.
Baldacci, Port.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Recalcine, Chile.
Ivy (p. 2536·2).
Cough.

Fluidrenol *Sofex, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Fluifort *Eurodrug, Hong Kong; Dompe, Ital.; Eurodrug, Malaysia; Riace, Rus.; Eurodrug, Thai.*
Carbocisteine lysine (p. 1658·2).
Respiratory-tract congestion.

Fluijet *Ativus, Braz.*
Ivy (p. 2536·2).

Fluilast *Boniscontro & Gazzone, Ital.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Fluilitic *Geolab, Braz.*
Carbocisteine (p. 1658·1).

Fluimare *Zambon, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Zambon, Switz.
Sea water (p. 2612·1).
Nasal irrigation.

Fluimare Plus *Zambon, Switz.*
Sea water (p. 2612·1); dexpanthenol (p. 2582·2).
Nasal irritation.

Fluimarin *Zambon, Rus.*
Sea water (p. 2612·1).
Nasal hygiene; nasal disorders.

Fluimucil *CSC, Austria; Zambon, Braz.; Labomed, Chile; Zambon, China; Zambon, Cz.; Zambon, Fr.; Pierre Fabre, Ger.; Rafarm, Gr.; Zambon, Hong Kong; Zambon, Hung.; Elder, India; Zambon, Indon.; Zambon, Ital.; Zambon, Malaysia; Zambon, Neth.; Zambon, Philipp.; Zambon, Pol.; Zambon, Port.; Zambon, Rus.; Zambon, Singapore; Zambon, Spain; Zambon, Switz.; Zambon, Thai.; Zambon, Ukr.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; poisoning with paracetamol, acrylonitrile, methacrynitrile, or methyl bromide; urotoxicity caused by ifosfamide and cyclophosphamide.

Fluimucil Antibiotic *Zambon, Belg.; Zambon, Rus.*
Thiamphenicol glycinate acetylcysteinate (p. 376·3).
Bacterial infections of the respiratory tract associated with increased or viscous mucus.

Sermmitr, Thai.†; Zambon, Thai.†
Thiamphenicol (p. 376·3); acetylcysteine (p. 1652·2).
Respiratory-tract infections associated with increased or viscous mucus.

Fluimucil Antibiotico *Zambon, Ital.*
Thiamphenicol glycinate acetylcysteinate (p. 376·3).
Respiratory-tract infections.

Fluimucil Complex *Zambon, Spain.*
Paracetamol (p. 115·1); acetylcysteine (p. 1652·2).
Cold and influenza symptoms.

Fluimucil Grippe Day & Night *Zambon, Switz.*
⊗Day tablets, acetylcysteine (p. 1652·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Fluimucil Solucao Nasal *Zambon, Braz.*
Acetylcysteine (p. 1652·2); benzalkonium chloride (p. 1737·1); sodium chloride (p. 1795·1).
Nasal congestion.

Fluimucil toux grasse *Zambon, Switz.*
Acetylcysteine (p. 1652·2).
Cough.

Fluinol *GSK, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Fluir *Mantecorp, Braz.; Valmor, Venez.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Fluirespir Mare *Zambon, Ital.*
Minerals.
Nasal cleansing; nasal dryness.

Fluisédal *Elerte, Fr.*
Meglumine benzoate; polysorbate 20 (p. 2203·2); promethazine hydrochloride (p. 638·2).
Cough.

Fluisédal sans promethazine *Elerte, Fr.*
Meglumine benzoate; polysorbate 20 (p. 2203·2).
Respiratory-tract congestion.

Fluisolvan *Geolab, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Fluiteína *EMS, Braz.*
Acetylcysteine (p. 1652·2).

Fluitoss *Teuto, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Fluitussin *Zambon, Neth.*
Noscapine hydrochloride (p. 1670·3).
Cough.

Fluixol *Cristalfarma, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Fluka *Cipla, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flukamep *Alna, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flukatril *Proton, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flukezol *Kener, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Flukimex *Theramex, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Flukit *Julphar, UAE.*
Syrup: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Julphar, UAE.
Tablets: Paracetamol (p. 115·1); salicylamide (p. 129·2); promethazine hydrochloride (p. 638·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Flukonorm *Ratiopharm, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Fluktan *Tunggal Idaman, Indon.†*
Famotidine (p. 1842·1).
Peptic ulcer; pathological hypersecretory disorders.

Flukuff *Intas, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

FluLaval *GSK, USA.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Flulem *Laboratorios Chile, Chile†; Teva, Mex.; Teva, Thai.*
Flutamide (p. 798·2).
Prostatic cancer.

Flulium
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Dipotassium clorazepate (p. 1056·3).
Anxiety; depression; dystonias.

Utopian, Thai.†
Flunarizine (p. 629·3).
Cerebrovascular disorders.

Flulon *Santen, Philipp.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flulone *Panalab, Arg.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flulox *Medicine Products, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states.

Flumach *Mayoly-Spindler, Fr.†*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; hypertension; myasthenia gravis; oedema.

Flumadine *Caraco, USA.*
Rimantadine hydrochloride (p. 1012·2).
Influenza A.

Flumage *Gemepe, Arg.*
Flumazenil (p. 1551·3).

Flumanovag *Gobbi, Arg.*
Flumazenil (p. 1551·3).

Flumarc *Raffo, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Flumarin
Note: this name may be used for preparations of different composition.
IBN, Ital.
Morniflumate (p. 92·2).
Pain; fever.

Shionogi, China; Shionogi, Jpn.
Flomoxef sodium (p. 299·1).
Bacterial infections.

Flumark *Dainippon, Jpn.†*
Enoxacin (p. 290·2).
Bacterial infections.

Flumasalen *TO-Chemicals, Thai.†*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Flumates *Mintlab, Chile.†*
⊗Beclometasone dipropionate (p. 1621·2).

Flumax *Gerolymatos, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Flumazen *Scott-Cassara, Arg.; Uniao Quimica, Braz.*
Flumazenil (p. 1551·3).
Benzodiazepine antagonist.

Flumazil *Cristalia, Braz.*
Flumazenil (p. 1551·3).
Reversal of sedative effects of benzodiazepines.

Flumeciclina *Farmila, Ital.†*
⊗Solution A, tetracycline (p. 373·1); solution B, fluorometholone (p. 1637·2).
Infected eye disorders.

Flumed
Note: this name may be used for preparations of different composition.
Medicom, Cz.
Flutamide (p. 798·2).
Prostatic cancer.

Medifive, Thai.
Fluoxetine (p. 417·1).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Zydus, India.
Fluconazole (p. 578·2).
Fungal infections.

Andromaco, Chile.†
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Flumen *Nevzat, Turk.*
Fludarabine phosphate (p. 794·1).

Flumetholon *Santen, China; Santen, Hong Kong; Ferron, Indon.; Santen, Indon.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flumetol
Note: this name may be used for preparations of different composition.
Elmor, Venez.
⊗Fluorometholone acetate (p. 1637·2).
Inflammatory eye disorders.

Faran, Gr.
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Farmila, Ital.
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Interko, Turk.†
⊗Fluorometholone (p. 1637·2); tetryzoline hydrochloride (p. 1678·3).
Inflammatory eye disorders.

Flumetol N *Volta, Chile.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flumetol NF *Sophia, Mex.*
⊗Fluorometholone acetate (p. 1637·2).
Inflammatory eye disorders.

Flumex *Allergan, Braz.*
⊗Fluorometholone (p. 1637·2).
Eye disorders.

Flumex N *Allergan, Braz.*
⊗Neomycin sulfate (p. 330·1); fluorometholone (p. 1637·2).
Infected eye disorders.

Flumexate *Specifar, Gr.*
Flumazenil (p. 1551·3).
Benzodiazepine overdosage.

Flumezin *Mitsubishi Tanabe, Jpn.*
Fluphenazine maleate (p. 1075·1).
Schizophrenia.

Flumezina *Farmila, Ital.*
⊗Fluorometholone (p. 1637·2); tetryzoline hydrochloride (p. 1678·3).
Inflammatory eye disorders.

Flumicin
Note: this name may be used for preparations of different composition.
Collins, Mex.†
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Hovid, Malaysia.†
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Flumicomplex *Alapis, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).

Flumicon *Plus, India; Benedetti, Ital.; Farmstandart, Rus.†*
Fluconazole (p. 578·2).
Fungal infections.

Flumid *Hexal, Ger.†*
Flutamide (p. 798·2).
Prostatic cancer.

Flumidon *Medicus, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Flumig *Unison, Philipp.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo; vestibular disorders; cerebral and peripheral vascular disorders.

Flumil
Note: this name may be used for preparations of different composition.
Zambon, Port.†; Pharmazam, Spain.
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Senosiain, Mex.
⊗Aminophenazone (p. 21·1); buphenine hydrochloride (p. 2462·3); diphenylpyraline hydrochloride (p. 627·2).
Rhinitis; sinusitis.

Flumil Antidoto *IFET (ΙΦΕΤ), Gr.; Pharmazam, Spain.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Fluminex *Ecupharma, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

FluMist *AstraZeneca, Canad.; AstraZeneca, Hong Kong; AstraZeneca, Israel; Medimmune, USA.*
A live attenuated influenza vaccine (p. 2393·3).
Active immunisation.

Flumonac *Zambon, Spain.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucous.

Flumos *AGIPS, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Flumoxal *Janssen-Cilag, Arg.*
Flubendazole (p. 154·3).
Worm infections.

Flump *Torrent, India.*
Penfluridol (p. 1094·3).
Psychoses.

Flumucil *Elder, India.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Flumusa *Symbiotic, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Flumusa-20 *Symbiotic, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flumycon *Teva, Pol.*
Fluconazole (p. 578·2).
Fungal infections.

Flunacross-S *Pharmacross, Chile.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Flunadin *Ifars, Indon.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); noscapine (p. 1670·3).
Influenza symptoms.

Flunadrina *Biofarma, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

Flunagen *Visufarma, Ital.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Flunal
Note: this name may be used for preparations of different composition.
Meyer Alian, Venez.
Fluconazole (p. 578·2).
Fungal infections.

Flunamed *Medicpharma, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders.

Flunaric *Suphong, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders.

Flunarimed *Ranbaxy, Belg.†*
Flunarizine hydrochloride (p. 629·3).
Migraine.

Flunarin *Ache, Braz.*
Flunarizine hydrochloride (p. 629·3).
Hemiplegia; migraine and other vascular headaches; subarachnoid haemorrhage.

FDC, India.
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flunaris *Symbiosis, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flunarium *Greater Pharma, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebrovascular disorders; vertigo; motion sickness.

Flunariz *Beximco, Philipp.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo; vestibular disorders; cerebral and peripheral vascular disorders.

Flunat *Sun, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flunatop *Apotex, Belg.*
Flunarizine hydrochloride (p. 629·3).
Migraine.

Flunatrac *Minova, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flunavert *Hennig, Ger.*
Flunarizine hydrochloride (p. 629·3).
Vertigo; migraine.

Flunax *Graha, Indon.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Flunaz *BMW, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flunazul *Pfleger, Ger.*
Fluconazole (p. 578·2).
Fungal infections.

Flunco *TO-Chemicals, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Flunec *Nortech, India.*
Cream: ⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); miconazole (p. 588·3).

Nortech, India.
Tablets: Fluconazole (p. 578·2).
Fungal infections.

Flunec Combikit *Nortech, India.*
Azithromycin (p. 221·2); fluconazole (p. 578·2); secnidazole (p. 947·3).

Fluner *Geno, India.*
Flunarizine betadex (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Fluneurin *Sandoz, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa; premenstrual dysphoric disorder.

Flunexil *Biochimico, Braz.*
Flumazenil (p. 1551·3).

Flunif *Elfin, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flunil *Intas, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fluninoc *Hexal, Ger.†*
Flunitrazepam (p. 1073·3).
Insomnia.

Flunipam *Actavis, Denm.; Actavis, Norw.†*
Flunitrazepam (p. 1073·3).
Insomnia; premedication.

Fluniprol *Novendia, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin disorders.

Flunisan *Hemofarm, Rus.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Flunita *Jean-Marie, Hong Kong.*
Flunitrazepam (p. 1073·3).
Insomnia.

Flunitop *Pierre Fabre, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma, bronchitis; rhinitis.

Flunizol *Sandoz, Switz.†*
Fluconazole (p. 578·2).
Fungal infections.

Flunobate-N *TNP, Thai.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Flunol *Sopar, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Nobel, Ukr.†
Fluconazole (p. 578·2).
Fungal infections.

Flunolone *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Flunolone-V *Atlantic, Singapore; Atlantic, Thai.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flunova *Zuventus, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flunovon *Novofarm (Νοβοφαρμ), Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin disorders.

Flunox
Note: this name may be used for preparations of different composition.
Roche, Ital.
Flurazepam monohydrochloride (p. 1076·1).
Insomnia.

Flunutrac *Isdin, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Fluo Grin *Grin, Mex.†*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected eye disorders.

Fluocal *Septodont, Canad.†*
Sodium fluoride (p. 2089·2).

Fluocalcic *Meda, Austria.†*
Sodium monofluorophosphate (p. 2091·3); calcium carbonate (p. 1824·3).
Osteoporosis.

Fluocalm *Kleva, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Fluocaril
Note: this name may be used for preparations of different composition.
Procter & Gamble, Belg.
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis; dental hygiene.

Procter & Gamble, Ital.
⊗Potassium fluoride (p. 2089·2); potassium nitrate (p. 1766·2); enoxolone (p. 54·2).
Gum hypersensitivity and pain.

Fluocaril Bi-Fluore *Rider, Chile†; Procter & Gamble, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis OTC, Ital.; Procter & Gamble, Neth.†*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluocaril Bi-Fluoré *Procter & Gamble, Port.*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluocaril blancheur *Procter & Gamble, Fr.†*
Sodium pyrophosphate (p. 2619·3); sodium fluoride (p. 2089·2).
Dental discoloration.

Fluocaril dents sensibles *Procter & Gamble, Fr.†*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2); eugenol (p. 2501·2).
Sensitive teeth.

Fluocaril Junior and Fluocaril Kids *Procter & Gamble, Fr.†*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluocid Forte *Pharminicio, Spain.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluocim *Teva, Switz.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia.

Fluocit *Novasorel, Ital.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluocort-N *Phapros, Indon.; Community Pharmacy, Thai.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Fluocyne *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Fluorescein sodium (p. 2506·2).

Fluoderm *Taro, Canad.; SA Druggists, S.Afr.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluodermo Fuerte *Nupel, Spain.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluodont *Gebro, Austria.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluodontyl *Procter & Gamble, Belg.; Procter & Gamble, Fr.; Procter & Gamble, Spain.†*
Sodium fluoride (p. 2089·2).
Dental hypersensitivity; dental caries prophylaxis; dental hygiene.

Fluodos *ITP, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Contrast agent for detection of malignant neoplasms by positron-emission tomography.

Fluohexal *Sandoz, Austral.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Fluol *Moraceae, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fluomex *Precimex, Mex.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluomint *Daudt, Braz.†*
Sodium monofluorophosphate (p. 2091·3); cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Dental caries prophylaxis; oral hygiene.

Fluomisin *Invar, Rus.*
Dequalinium chloride (p. 1749·3).
Vaginal infections.

Fluomit *Laboratorios Chile, Chile.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Fluomix Same *Savoma, Ital.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluomizin *Pierre Fabre, Ger.; Medinova, Hong Kong; Medinova, Switz.; Medinova, Thai.; Medinova, Ukr.*
Dequalinium chloride (p. 1749·3).
Vaginal infections; vaginal disinfection.

Fluomycin N *Organon, Ger.†*
Dequalinium chloride (p. 1749·3).
Vaginal infections.

Fluon *Dissolvurol, Mon.*
Metesculetol sodium (p. 2557·3); hamamelis (p. 2523·3); aesculus (p. 2431·2); viburnum (p. 2458·1).
Capillary fragility; haemorrhoids; venous insufficiency.

Fluon+ *Dissolvurol, Mon.*
Aesculus (p. 2431·2); hamamelis (p. 2523·3); grape seed (p. 2521·3).
Dietary supplement; peripheral vascular disorders.

Fluonco *VHB, India; Naprod, Philipp.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fluo-Neo *Inpac, Thai.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Fluonid *Allergan, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluonid-N *Biolab, Hong Kong; Biolab, Thai.†*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Fluopiram *Ariston, Arg.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fluor *SMB, Belg.; Crinex, Fr.†; Kin, Spain; Lacer, Spain.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluoracaine *Innovo, Canad.†; Akorn, USA.*
Fluorescein sodium (p. 2506·2); proxymetacaine hydrochloride (p. 1995·3).
Aid to eye examination; local anaesthesia.

Fluoracilo *Pfizer, Chile.†*
Fluorouracil (p. 795·2).

Fluor-A-Day *Pendopharm, Canad.; Dental Health Products, UK.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluor-a-day *Arbor, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluoralfa *INTES, Ital.*
Fluorescein sodium (p. 2506·2).
Diagnosis of eye disorders.

FluorD3 *Dicofarm, Ital.†*
Sodium monofluorophosphate (p. 2091·3); colecalciferol (p. 2113·1).
Fluoride and vitamin D supplement.

Fluordent *Bernabo, Arg.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluordent PX *Bernabo, Arg.*
Mouthwash: Sodium fluoride (p. 2089·2); sodium pyrophosphate (p. 2619·3).
Dental caries prophylaxis; periodontal disease.

Bernabo, Arg.
Toothpaste: Sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis; periodontal disease.

Fluore Stain Strips *Bell, India.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Fluorencil *Rider, Chile.*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2); sodium benzoate (p. 1738·2).
Dental caries prophylaxis.

Fluores
Note: this name may be used for preparations of different composition.
CT, Ital.
Fluconazole (p. 578·2).
Fungal infections.

Fluorescite *Alcon, Arg.; Alcon, Austral.; Alcon, Canad.; Alcon, China; Alcon, Cz.; Alcon, Fin.; Alcon, Hong Kong; Alcon, Israel; Alcon, Malaysia; Alcon, Neth.; Alcon, NZ; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Swed.; Alcon, Thai.; Nobel, Turk.; Alcon, USA.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Fluorets *Smith & Nephew, Austral.†; Akorn, Canad.; Chauvin, Canad.; Dioptic, Canad.; Novartis Ophthalmics, Canad.; Chauvin, Hong Kong; Chauvin, Irl.; Bausch & Lomb, Malaysia; Chauvin, Malaysia; Smith & Nephew, NZ; Bausch & Lomb, S.Afr.; Bausch & Lomb, Singapore; Chauvin, Singapore; Bausch & Lomb, UK; Bausch & Lomb, USA.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Fluorette *Fertin, Norw.; Meda, Swed.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluoretten *Sanofi-Aventis, Ger.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluorex *Crinex, Fr.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluorex Plus *Gerot, Austria.*
⊗Tetracycline hydrochloride (p. 373·2); dequalinium chloride (p. 1749·3); prednisone (p. 1647·2).
Colpitis.

Fluoricare *Otto, Indon.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluoridex Daily Defense Sensitivity Relief *Discus, USA.*
⊗Sodium fluoride (p. 2089·2); potassium nitrate (p. 1766·2).
Dental caries prophylaxis; sensitive teeth.

Fluorigard *Colgate-Palmolive, UK; Colgate-Palmolive, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluorigard Gel-Kam *Colgate-Palmolive, Ital.; Colgate-Palmolive, UK.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Fluorilette *Leiras, Fin.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluor-In *Procter & Gamble, Ital.†; Procter & Gamble, Port.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis; fluoride supplement.

Fluorinse *Procter & Gamble, Ital.; Oral-B, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluor-I-Strip *Bausch & Lomb, USA.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Fluoritab *Fluoritab, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluoritop-MR *ICPA, India.*
Acidulated phosphate sodium fluoride (p. 2089·2).

Fluormex *Chema-Elektromet, Pol.*
Dental gel: Olaflur (p. 2085·1); sodium fluoride (p. 2089·2).
Dental disorders; dental caries prophylaxis.

Chema-Elektromet, Pol.
Dental liquid: Olaflur (p. 2085·1).
Dental disorders; dental caries prophylaxis.

Fluorocaine *Medical Ophthalmics, USA.*
Fluorescein sodium (p. 2506·2); proxymetacaine hydrochloride (p. 1995·3).

Fluorocare *Colgate-Palmolive, Austral.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis; sensitive teeth.

Fluorocort *Lamda (Λαμδα), Gr.*
⊗Fluorometholone (p. 1637·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Fluorogel *Naf, Arg.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluorogel 2001 *Naf, Arg.*
Sodium fluoride (p. 2089·2); xylitol (p. 2220·3).
Dental caries prophylaxis.

Fluorogel 2001 para Dientes Sensibles *Naf, Arg.*
⊗Sodium fluoride (p. 2089·2); xylitol (p. 2220·3); potassium nitrate (p. 1766·2).
Dental caries prophylaxis.

Fluorolex *Fertin, Denm.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluorometil *Alcon, Mex.*
⊗Fluorometholone (p. 1637·2); tetryzoline (p. 1678·3).
Eye disorders.

Fluoro-Ophtal *Winzer, Ger.†*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Fluoroplat *Naf, Arg.*
Diamino silver fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluoroplex *Allergan, Canad.†; Aqua, USA.*
Fluorouracil (p. 795·2).
Actinic keratoses.

Fluoropoen *Poen, Arg.*
⊗Dexamethasone (p. 1630·3); chloramphenicol (p. 257·1); phenylephrine (p. 1672·2).
Conjunctivitis.

Fluoropos *Ursapharm, Cz.; Ursapharm, Ger.; Biem, Turk.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Fluororinil *Farmila, Ital.*
⊗Betamethasone (p. 1623·2); chlorphenamine maleate (p. 620·3).
Rhinitis.

Fluorox *Medical Ophthalmics, USA.*
Fluorescein sodium (p. 2506·2); oxybuprocaine (p. 1993·2).

Fluoro-żel *Farmapol, Pol.*
Sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3).
Dental caries.

Fluorscan *Molypharma, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Contrast agent for detection of malignant neoplasms by positron-emission tomography.

Fluorvas *Llorens, Spain.*
⊗Fluorometholone (p. 1637·2); tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Fluor-Vigantoletten *Merck Serono, Ger.*
Colecalciferol (p. 2113·1); sodium fluoride (p. 2089·2).
Vitamin D deficiency; dental caries prophylaxis; rickets.

Fluoselgine *Teofarma, Fr.*
Domiphen bromide (p. 1751·1); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fluoskin *Biospray, Gr.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Fluossen *ICN, Pol.†*
Sodium fluoride (p. 2089·2).
Osteoporosis.

Fluostérol *Crinex, Fr.*
Sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1).
Dental caries prophylaxis; vitamin D deficiency.

Fluotest *Alcon, Port.; Alcon Cusi, Spain.*
Fluorescein sodium (p. 2506·2); oxybuprocaine hydrochloride (p. 1993·2).
Aid to eye examination.

Fluothane *AstraZeneca, Austral.†; AstraZeneca, Braz.; AstraZeneca, Gr.; Piramal, India; AstraZeneca, Indon.†; AstraZeneca, NZ; AstraZeneca, Turk.*
Halothane (p. 1902·1).
General anaesthesia.

Fluotracer *ITP, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Contrast agent for detection of malignant neoplasms by positron-emission tomography.

Fluotrat *Biolab Sanus, Braz.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluo-Vaso *Allergan, Braz.*
⊗Fluocinolone acetonide (p. 1636·1); naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1); zinc sulfate (p. 2126·2).
Infected eye disorders.

Fluovex *Avex, Malaysia.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa; premenstrual dysphoric disorder.

Fluovitef *Teofarma, Ital.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fluox *Socobom, Belg.†; Theraskin, Braz.; Mylan, NZ.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; premature ejaculation.

Fluoxac *Psicoforma, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa; panic disorder; premenstrual dysphoric disorder.

Fluoxan *Baxter, Philipp.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fluoxebell *Bellwether, Austral.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

FluoxeLich *Winthrop, Ger.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fluoxem *Rider, Chile.*
Flumazenil (p. 1551·3).
Reversal of benzodiazepine-induced sedation; benzodiazepine overdosage.

Fluoxemed *Ranbaxy, Belg.†*
Fluoxetine (p. 417·1).
Depression.

Fluoxe-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fluoxeren *Menarini, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Fluoxgamma *Worwag, Ger.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fluoxibene *Ratiopharm, Austria.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Fluoxifar *Siphar, Switz.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia.

Fluoxin *Hexal, Cz.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; premenstrual dysphoric disorder.

Fluoxine *TO-Chemicals, Thai.*
Fluoxetine (p. 417·1).
Mixed anxiety depressive states.

Fluoxiram *Ariston, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; panic disorder; obsessive-compulsive disorder; bulimia; premenstrual dysphoric disorder.

Fluoxone *SMB, Belg.; Hyphens, Singapore.*
Fluoxetine (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

SMB, Fin.
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fluox-Puren *Actavis, Ger.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Fluoxytil
Note: this name may be used for preparations of different composition.
UCB, Turk.
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

GSK, Mex.†
Dental gel: Sodium monofluorophosphate (p. 2091·3); calcium glycerophosphate (p. 1783·3).
Dental caries prophylaxis.

GSK, Mex.†
Oral drops: Sodium fluoride (p. 2089·2); xylitol (p. 2220·3).
Dental caries prophylaxis.

Fluozoid *Valdecasas, Mex.*
Ethosuximide (p. 521·1).
Epilepsy.

Flupamid *Sanovel, Turk.*
⊗Indapamide (p. 1409·2).
Hypertension.

Flupar *Orion, Fin.†*
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Flupara *BMW, India.*
Paracetamol (p. 115·1).
Pain; fever.

Flupara-N *BMW, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Flupara-SN *BMW, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Flupazine *Psicoforma, Mex.*
Trifluoperazine hydrochloride (p. 1113·2).
Nausea and vomiting; psychoses.

Flupen
Note: this name may be used for preparations of different composition.
East West, India.
Flupentixol (p. 1074·1).
Psychoses; depression.

Zydus, S.Afr.
Flucloxacillin sodium (p. 299·2).
Gram-positive bacterial infections.

Flupen-M *East West, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Flupid *Damor, Ital.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Flupidol *Janssen-Cilag, Gr.*
Penfluridol (p. 1094·3).
Psychoses.

Flupigil *Meda, Ger.*
Flupirtine maleate (p. 65·2).
Pain.

Fluprosin *Pharmacodane, Denm.*
Flutamide (p. 798·2).
Prostatic cancer.

Fluprost *Lisapharma, Hung.; Lisapharma, Ital.*
Flutamide (p. 798·2).
Prostatic cancer.

Flur *Allergan, India.*
Flurbiprofen (p. 65·2).
Prevention of miosis during ocular surgery; ocular inflammation following eye surgery.

Flura *Kirkman, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Flurablastin *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Pfizer, Swed.†
Fluorouracil sodium (p. 795·2).
Malignant neoplasms.

Fluracap *Psychotropics, India.*
Flurazepam hydrochloride (p. 1076·1).
Insomnia.

Fluracedyl *Teva, Belg.; IFET (ΙΦΕΤ), Gr.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Philipp.; Pharmachemie, S.Afr.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Pharmachemie, Neth.
Fluorouracil sodium (p. 795·2).
Malignant neoplasms.

Fluracil *Biochem, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fluradosa *Dosa, Arg.*
Fludarabine phosphate (p. 794·1).
Malignant neoplasms.

Fluralema *Biotech, Venez.*
Flurazepam dihydrochloride (p. 1076·1).
Sleep disorders.

Fluralex
Note: this name may be used for preparations of different composition.
Arlex, Mex.
Fluoxetine (p. 417·1).
Depression.

Lafayette, Philipp.
Carbocisteine (p. 1658·1).
Cough.

Fluran *Ranbaxy, Malaysia.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Flurate *Bausch & Lomb, USA.†*
Fluorescein sodium (p. 2506·2); oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Fluraxid *Eadriex, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Fluraz *Micro, India.*
Flurazepam dihydrochloride (p. 1076·1).
Anxiety; insomnia.

Flurbic *Klonal, Arg.*
Flurbiprofen (p. 65·2).
Inflammation; pain.

Flurbiren *Indoco, India.*
Flurbiprofen sodium (p. 65·3); hypromellose (p. 2189·2).

Flurekain *Croma, Austria.†*
Oxybuprocaine hydrochloride (p. 1993·2); fluorescein sodium (p. 2506·2).
Local anaesthesia.

Fluresin *Samarth, India.*
Fluorescein sodium (p. 2506·2).

Fluress *AMO, Austral.†; Akorn, Canad.; Abigo, Swed.; Akorn, USA.*
Fluorescein sodium (p. 2506·2); oxybuprocaine hydrochloride (p. 1993·2).
Aid to eye examination; local anaesthesia.

Flurets *Oral-B, Austral.†*
Sodium fluoride (p. 2089·2).
Prevention of dental caries.

Flurexil *Novartis, Gr.*
Sodium fluoride (p. 2089·2).

Flurflex *Atabay, Turk.*
Flurbiprofen (p. 65·2).

Fluricin *Seng, Thai.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Flurid *Klar Sehen, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Flu-Ride *United Drug, Thai.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Flurin
Note: this name may be used for preparations of different composition.
Yarindo, Indon.
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

T Man, Thai.
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders.

Flurin Dmp *Yarindo, Indon.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Influenza symptoms.

Flurinol *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Epinastine hydrochloride (p. 628·3).
Allergic rhinitis; asthma; pruritus; allergic skin disorders; hypersensitivity; allergic conjunctivitis.

Flurinol D *Boehringer Ingelheim, Arg.*
⊗Epinastine hydrochloride (p. 628·3); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Boehringer Ingelheim Promeco, Mex.
⊗Epinastine hydrochloride (p. 628·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Flurisone *Micro, India.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flurit *Eczacibasi, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Fluriv *East African, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fluriz *Zytras, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flurizic *Pantafarm, Ital.*
Flurithromycin ethyl succinate (p. 300·2).
Bacterial infections.

Fluro-5 *Deva, Turk.*
Fluorouracil (p. 795·2).

Fluroblastin *Pfizer, Gr.; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Venez.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fluroblastine *Pfizer, Belg.*
Fluorouracil sodium (p. 795·2).
Malignant neoplasms.

Fluro-Ethyl *Gebauer, USA.†*
Ethyl chloride (p. 1987·1); cryofluorane (p. 1798·2).
Topical anaesthesia.

Flurofen *Abbott, Denm.†; Vianex (Βιανεξ), Gr.; Sanofi-Aventis, India.*
Flurbiprofen (p. 65·2).
Musculoskeletal and joint disorders; dysmenorrhoea; pain; inflammation.

Flurolon *Allergan, Denm.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flurop *Davi, Port.*
⊗Fluorometholone (p. 1637·2).
Eye disorders.

Fluroptic *Cooper (Κοπερ), Gr.*
Flurbiprofen sodium (p. 65·3).
Prevention of miosis in ophthalmic surgery.

Flurox
Note: this name may be used for preparations of different composition.
Teva, Mex.; Lemery, Rus.; Lemery, Thai.†
Fluorouracil (p. 795·2).
Malignant neoplasms.

Ocusoft, USA.
Fluorescein sodium (p. 2506·2); oxybuprocaine hydrochloride (p. 1993·2).

Flurozin *Remedica, Thai.†*
Flurbiprofen (p. 65·2).
Musculoskeletal and joint disorders.

Flurpax *Teofarma, Spain.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Flury *East West, India.*
Flunarizine dihydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flusac *Sriprasit, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states.

Flusal *Plus, Gr.*
Omeprazole (p. 1867·2).

Flusan
Note: this name may be used for preparations of different composition.
Eurofarma, Braz.
Fluconazole (p. 578·2).
Fungal infections.
Novag, Mex.
Tolbutamide (p. 504·2).
Diabetes mellitus.

Fluscand *Teva, Swed.†*
Flunitrazepam (p. 1073·3).
Sleep disorders; premedication.

Flusemide *Q Pharma, Spain.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; cerebral vasospasm.

Fluseminal *Anfarm, Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Flusenil *Anfarm, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Flush *RND, India.*
Capsules: ⊗Achyranthes aspera; punarnava (p. 2601·1); hordeum vulgare; tribulus terrestris (p. 2633·3).
RND, India.
Syrup: ⊗Punarnava (p. 2601·1); raphanus sativus; tribulus terrestris (p. 2633·3).

Flusin *Aspen Consumer, S.Afr.†*
Capsules: ⊗Chlorphenamine maleate (p. 620·3) pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.
Aspen Consumer, S.Afr.†
Tablets: ⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Flusin C *Aspen Consumer, S.Afr.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Flusin DM *Aspen Consumer, S.Afr.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); ascorbic acid (p. 2110·3).
Upper respiratory-tract congestion; cough; cold and influenza symptoms.

Flusin S *Aspen Consumer, S.Afr.†*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Flusin Sinus *Aspen Consumer, S.Afr.*
Tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion.
Aspen, S.Afr.
Syrup: ⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).

Flusolgen *Vegal, Spain.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Flusolv *Ecobi, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Flusona *Recalcine, Chile.*
⊗Fluticasone propionate (p. 1638·1).
Asthma; skin disorders; allergic rhinitis.

Flusonal *GSK, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Asthma; obstructive airways disease.

Fluspi *Hexal, Ger.†*
Fluspirilene (p. 1076·3).
Schizophrenia.

Fluspiral *Menarini, Ital.*
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Flusporan *Menarini, Spain.*
Flutrimazole (p. 582·1).
Fungal skin and nail infections.

Fluss *Scharper, Ital.*
⊗Furosemide (p. 1387·1); triamterene (p. 1518·3).
Oedema; ascites; hyperaldosteronism; hypertension.

Flusta *Stalwart, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flustad *Stada, Neth.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Flustaren *Chrispa (Χρισπα), Gr.*
Acetylcysteine (p. 1652·2).
Mucolytic.

Flustat *Be-Tabs, S.Afr.*
Capsules: Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.
Be-Tabs, S.Afr.†
Syrup: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Flustate *Zota, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flustatin *Ratiopharm, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Flusten *Eurofarma, Braz.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Fluster *East West, India.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flusterix *Farmanic, Gr.*
Fusidic acid (p. 302·1).
Bacterial skin infection.

Flustop *Biodeal, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; sinusitis; rhinitis.

Flusyst *Reliance, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fluta *Cell Pharm, Ger.*
Flutamide (p. 798·2).
Prostatic cancer.

Flu-Tab *Guardian, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Flutabene *Ratiopharm, Austria.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutabs *Farmstandart, Rus.*
Paracetamol (p. 115·1).
Fever; pain.

Fluta-Cell *Stada, Malaysia.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutafarm *Farmak, Ukr.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutahexal *Sandoz, S.Afr.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutaide *Alenfarma, Port.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Flutam *Ratiopharm, Hung.; Chandra Bhagat, India.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutamid *Egis, Rus.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutamin *Alphapharm, Austral.; Mylan, NZ·*
Flutamide (p. 798·2).
Prostatic cancer.

Flutamol *Pyridam, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Fever; cough; headache; nasal congestion; allergy.

Flutamol-P *Pyridam, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Fever; cough; headache; nasal congestion; allergy.

Flutan *Medochemie, Singapore; Medochemie, Thai.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutans *Drogsan, Turk.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Flutaplex *Teva Tuteur, Arg.; Teva, Belg.; Teva, Cz.; Chemipharm, Gr.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Neth.†; Teva, Rus.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutarzole *Target, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis; skin disorders.

Flutas *Intas, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Flutasin *Actavis, Hung.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutastad *Stada, Austria.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutaur *Taurus, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flute *Hetero, India.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flutel *Intel, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flutenal *Recordati, Spain.†*
⊗Flupamesone (p. 1648·3).
Skin disorders.

Flutenal Gentamicina *Recordati, Spain.†*
⊗Flupamesone (p. 1648·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Flutenal Sali *Recordati, Spain.†*
⊗Flupamesone (p. 1648·3); salicylic acid (p. 1719·1).
Skin disorders.

Flutepan *Sandoz, Arg.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutex
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Carbocisteine (p. 1658·1).
Pharmacare, S.Afr.†
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.
Syosset, USA.†
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Flutex Co Linctus *Aspen Consumer, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1).
Cough.

Flutex Cold and Flu *Aspen Consumer, S.Afr.†*
Syrup: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.
Aspen Consumer, S.Afr.†
Capsules: Ascorbic acid (p. 2110·3); salicylamide (p. 129·2); paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Flutiamik *Microsules, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Flutibact *GSK, India.*
⊗Fluticasone propionate (p. 1638·1); mupirocin (p. 327·2).

Flutica *Teva, Ger.†*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Flutican *Glenmark, Braz.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Fluticapen *Elpen (Ελπεν), Gr.*
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Fluticaps *Biosintetica, Braz.*
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Fluticare *Hetero, India.*
⊗Fluticasone (p. 1638·1).
Skin disorders.

Fluticare-C *Hetero, India.*
⊗Ciclopirox (p. 575·3); fluticasone propionate (p. 1638·1).

Fluticare-N *Hetero, India.*
⊗Fluticasone propionate (p. 1638·1); neomycin (p. 329·3).

Fluticone *Zydus, India.*
⊗Fluticasone (p. 1638·1).
Allergic rhinitis; nasal polyps.

Fluticort *Cassara, Arg.; D & M, Chile; Biogalenic, Venez.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Fluticrem *Difa, Ital.; Cantabria, Neth.; Cantabria, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flutide
Note: this name may be used for preparations of different composition.
Pharmacodane, Denm.; GSK, Fin.; GSK, Ger.; Euro Registratie, Neth.; Medcor, Neth.; GSK, Norw.; GSK, Swed.
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease; asthma; nasal polyps; allergic rhinitis.
Samarth, India.
Flutamide (p. 798·2).
Prostatic cancer.

Flutiflo *Lupin, India.*
⊗Fluticasone propionate (p. 1638·1).
Asthma; obstructive airways disease.

Flutiform *Mundipharma, Belg.; Mundipharma, Fin.; Mundipharma, Neth.; Mundipharma, Norw.*
⊗Fluticasone propionate (p. 1638·1); formoterol fumarate (p. 1209·2).
Asthma.

flutiform *Napp, UK.*
⊗Fluticasone propionate (p. 1638·1); formoterol fumarate (p. 1209·2).
Asthma.

Fluti-K *Raffo, Arg.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flutikrem *Farmanic, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flutin *Orion, Denm.†; East West, India; Julphar, UAE.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flutinasal *Farmanic, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flutinase *GSK, Switz.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis; nasal polyps.

Flutinax *Teva, Mex.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Flutine *Reliance, India; Teva, Israel; Pharmasant, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states; depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flutini Kit *Intas, India.*
Fluconazole (p. 578·2); tinidazole (p. 949·2).

Flutinol
Note: this name may be used for preparations of different composition.
Latinofarma, Braz.
⊗Fluorometholone acetate (p. 1637·2).
Inflammatory eye disorders.
Pharmaplan, S.Afr.
Fluoxetine hydrochloride (p. 417·1).
Sun, India.
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flutirin *Teva, Hung.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Flutisan *Ratiopharm, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Flutitrim *Trima, Israel; Trima, Singapore.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flutivate *GSK, Braz.; GSK, Chile; GSK, Ger.; Stiefel, Ger.; GSK, India; GSK, Norw.; GSK, Swed.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flutivent *Cassara, Arg.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Flutizal *Vivax, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Flutom *Epitome, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Flutop *Crescent, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flutopic *Systopic, India.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Flutox *Pharmazam, Spain.*
Cloperastine fendizoate (p. 1659·2) or cloperastine hydrochloride (p. 1659·2).
Cough.

Flutrac *Minova, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flutrax *Bioprofarma, Arg.*
Flutamide (p. 798·2).
Prostatic cancer.

Flutric *Chemo-Drugs, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Flutrim *Interbial, Port.†*
Flutrimazole (p. 582·1).
Fungal skin infections.

Flutrop *Tropica Mas, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms; sinusitis; allergic disorders.

Flutrox *Dabur, India.*
Fluconazole (p. 578·2).
Fungal infections.

FluVaccinol *Solvay, Austria; Stada, Ger.†*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Fluvactalin *Actavis, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvacur *Tiefenbacher, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvakarav *Ratiopharm, Cz.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Fluval
Note: this name may be used for preparations of different composition.
KRKA, Rus.
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.
Omninvest, Hung.
An inactivated influenza vaccine (whole virion) (p. 2393·3).
Active immunisation.
Valmor, Venez.
Fluconazole (p. 578·2).
Fungal infections.

Fluvamteva *Med, Turk.*
Fluvoxamine maleate (p. 425·3).

Fluvamyl *Mylan, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following percutaneous coronary intervention.

Fluvanidda *Stada, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvaphar *Ratiopharm, Port.†*
Fluvastatin sodium (p. 1385·1).
Hyperlipidaemias; cardiovascular risk reduction.

Fluvaratio *Ratiopharm, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvastadig *Sandoz, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvastaham *Sandoz, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvastamil *Sandoz, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvastasof *Sandoz, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvastat *UCI, Braz.*
Fluvastatin sodium (p. 1385·1).

Fluvat *Rowex, Irl.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Fluvatamed *Medis, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following percutaneous coronary intervention.

Fluvatifi *Tiefenbacher, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluvator *Torrent, India.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder; social phobia.

Fluvax *CSL, Austral.; CSL, China; Commonwealth Serum, Hong Kong; CSL, Malaysia; Iscotec, Neth.; CSL, NZ; CSL, Singapore.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Fluvaxin *Medintorg, Rus.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Fluvermal *Johnson & Johnson, Fr.; Johnson & Johnson, Port.*
Flubendazole (p. 154·3).
Veterinary names include Flubenol.
Intestinal nematode infections; worm infections.

Fluvermox *Janssen-Cilag, Venez.*
Flubendazole (p. 154·3).
Worm infections.

Fluvert *Medley, Braz.; East West, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Fluvet *Vianex (Βιανεξ), Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Fluviatin *Mylan, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; prevention of coronary events following angioplasty.

Fluviatol *Boehringer Ingelheim Promeco, Mex.*
Oral solution: Amantadine hydrochloride (p. 890·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms; allergic rhinitis.
Boehringer Ingelheim Promeco, Mex.
Tablets: Amantadine hydrochloride (p. 890·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); aspirin (p. 22·2).
Cold and influenza symptoms.

Fluviatol NF *Boehringer Ingelheim Promeco, Mex.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Allergic rhinitis; hay fever.

Fluvic *Pierre Fabre, Fr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Fluvicil *Degorts, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2).
Respiratory-tract congestion; bronchospasm.

Fluvin *Bombay Tablet, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair and nail infections.

Fluvir *Hetero, India.*
Oseltamivir (p. 1006·2).
Influenza.

Fluviral
Note: this name may be used for preparations of different composition.
ID Biomedical, Canad.; ID Biomedical, China.
An inactivated influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Fluvirin *Novartis Vaccines, Fin.†; Novartis, Israel†; Chiron Vaccines, Neth.†; Novartis Vaccines, Port.; Medpro, S.Afr.†; Novartis Vaccines, UK; Novartis Vaccines, USA.*
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Fluvirine *Celltech, Fr.†*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Flu-Vit *Beres, Hung.*
Vitamins; minerals; trace elements; ginseng (p. 2513·3); echinacea (p. 2498·1).

Fluvium *Rekah, Israel.†*
Sodium fluoride (p. 2089·2).
Osteoporosis.

Fluvohexal *Hexal, Ger.†*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Fluvosol *Stada, Fin.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Fluvoxin *Sun, India; Sun, Thai.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Fluwel *Bestochem, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

FluWinox *Zentiva, Hung.†*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Flux
Note: this name may be used for preparations of different composition.
Aarpik, India.
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.
Hexal, Austria.
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder.
Actavis, Norw.
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Fluxacil *Farma 1, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Fluxacina *Laboratorios Chile, Chile.†*
Flucloxacillin (p. 299·1).
Staphylococcal infections.

Fluxadir *Antor, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Fluxal
Note: this name may be used for preparations of different composition.
David, India.
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fluxamol *D & M, Chile.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Asthma.

Fluxarten *GSK, Ital.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Fluxedan *Carnot, Mex.*
Bromhexine hydrochloride (p. 1656·3); oxeladin citrate (p. 1671·2).
Respiratory-tract disorders with viscous mucus.

Fluxen *Arterium, Ukr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Fluxene *Eurofarma, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Fluxes *Sandoz, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Fluxet *Krewel, Ger.; SM, Venez.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder; bulimia nervosa; mixed anxiety-depressive states; premenstrual dysphoric disorder.

Fluxetil *Unison, Malaysia; Unison, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; mixed anxiety depressive states.

Fluxetin *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; anxiety; mixed anxiety depressive states.

Fluxibit *Mavi, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Fluxicap *Arlex, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Fluxidin *Epifarma, Ital.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Fluxifarm *Richmond, Arg.†*
Flumazenil (p. 1551·3).
Reversal of sedative effect of benzodiazepines.

Fluxil
Note: this name may be used for preparations of different composition.
UCB, Austria†; Aegis, Hong Kong; Aegis, Singapore.
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder; bulimia nervosa.
Teuto, Braz.
⊗Furosemide (p. 1387·1).

Fluxilase *Laboris, Braz.*
Fluconazole (p. 578·2).

Fluxim *Duopharma, Philipp.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Fluxin
Note: this name may be used for preparations of different composition.
JK Biochem, India.
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.
Taisheng, Philipp.
Flucloxacillin sodium (p. 299·2).
Bacterial infections.
Unipharma, Gr.
Dipyridamole (p. 1362·2); aspirin (p. 22·2).

Fluxin-AL *JK Biochem, India.*
Alprazolam (p. 1035·2); fluoxetine hydrochloride (p. 417·1).

Fluxinam *Vilco, Gr.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Flu-4-XN *Haledew, India.*
Caffeine (p. 1203·3); cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Fluxol
Note: this name may be used for preparations of different composition.
Farmachrom, Gr.
Atorvastatin calcium (p. 1309·2).
Maver, Mex.
⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Asthma; bronchitis; respiratory-tract congestion.

FluxoMed *S Med, Austria.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluxon *Neo Quimica, Braz.*
Cinnarizine (p. 622·1).
Vertigo.

Fluxpiren *Ariston, Arg.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Fluxstatin *A-Pharma, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Fluxtar *Diffucap, Braz.*
Bromazepam (p. 1041·2).

Fluxum *Alfa Wassermann, China; Alfa Wassermann, Cz.; Alfa Wassermann, Hung.; USV, India; Fahrenheit, Indon.; Wassermann, Ital.; Armstrong, Mex.; Alfa Wassermann, Pol.†; BioSaude, Port.; Gurel, Turk.; Santa, Turk.*
Parnaparin sodium (p. 1464·2).
Thromboembolic disorders; thrombosis prophylaxis; vascular disorders.

Fluxus *Tecnofarma, Chile.*
Flunarizine (p. 629·3).
Mental function impairment; peripheral vascular disorders; vestibular disorders.

Fluz *East West, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Fluzac *Rowex, Irl.; LBS, Thai.; Flupal, Venez.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; bulimia nervosa.

Fluzak *SVUS, Cz.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; premenstrual dysphoric disorder.

Fluzamed *World Medicine, Ukr.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzart *Servocare, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fluze *Zee, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fluzeet *Sanify, India.*
Fluconazole (p. 578·2).
Fungal infections.

Flu-Zep
Note: this name may be used for preparations of different composition.
Marching, Hong Kong.†
Dexchlorpheniramine maleate (p. 621·1); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); salicylamide (p. 129·2); caffeine (p. 1203·3).
Cold and influenza symptoms.

Fluzep
Note: this name may be used for preparations of different composition.
Otto, Indon.
Phenylpropanolamine hydrochloride (p. 1674·1); dexchlorpheniramine maleate (p. 621·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Influenza symptoms.

Fluzet *Ranbaxy, India.*
Caplets: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Ranbaxy, India.
Oral suspension; syrup: Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1) or dextromethorphan hydrochloride; paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Fluzet X *Ranbaxy, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).

Fluzide *Concept, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzine *PP Lab, Thai.*
Fluphenazine hydrochloride (p. 1075·1).
Anxiety; psychoses.

Fluzinum *Arko Diffusion, Switz.*
Anas barbariae hepatis et cordis (p. 2444·1).
Homoeopathic preparation.

FluZiOZ *Zio, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Fluzix *Cazi, Braz.*
Flunarizine hydrochloride (p. 629·3).

Fluzocan *Cipla, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzol *LKM, Arg.; Hexal, S.Afr.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzolam *Aamorb, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Fluzole *Aspen, Austral.; Intra-Labs, India; Biofarma, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzomic *Ferakon, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzon *Cadila, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fluzone *Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Mex.; Sanofi Pasteur, Thai.; Sanofi Pasteur, USA.*
An inactivated influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Fluzon-T *Cadila, India.*
1 Tablet, fluconazole (p. 578·2); 2 tablets, tinidazole (p. 949·2).

Fluzor *Collins, Mex.†*
Fluconazole (p. 578·2).
Fungal infections.

Fluzoral
Note: this name may be used for preparations of different composition.
GPO, Thai.
Fluconazole (p. 578·2).
Fungal infections.
APT, Hong Kong.†
Ketoconazole (p. 585·3).
Fungal scalp infections.

F-Min *Patar, Thai.*
Folic acid (p. 2063·1).
Folate-deficiency anaemias; prophylaxis of neural tube defects.

FML *Allergan, Arg.; Allergan, Austral.; Allergan, Belg.; Allergan, Canad.; Allergan, China; Allergan, Fin.; Allergan, Gr.; Allergan, Hong Kong; Allergan, India; Allergan, India; Allergan, Irl.; Allergan, Israel; Allergan, Malaysia; Allergan, Neth.; Allergan, NZ; Allergan, Philipp.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

FML Neo *Allergan, Arg.; Allergan, Canad.†; Allergan, Gr.; Allergan, India; Allergan, Irl.†; Allergan, Port.; Allergan, S.Afr.; Allergan, Switz.; Allergan, Thai.*
⊗Fluorometholone (p. 1637·2); neomycin sulfate (p. 330·1).
Infected conjunctivitis; inflammatory eye infections.

FML-S *Allergan, USA.†*
⊗Fluorometholone (p. 1637·2); sulfacetamide sodium (p. 361·1).
Inflammatory eye infections.

FML-T *Allergan, India.*
⊗Fluorometholone (p. 1637·2); tobramycin (p. 380·1).

FNI 2B *Armstrong, Mex.†*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; hepatitis C; hepatitis B; anogenital warts.

F-Nil *Laksun, India.*
Paracetamol (p. 115·1).
Pain; fever.

FN-T-Tus *Cadila, India.†*
Beleric myrobalan (p. 2453·2); liquorice (p. 1853·2); malabar nut (p. 2549·1); ocimum sanctum; turmeric (p. 2218·1); galanga; eucalyptus oil (p. 2501·2).
Cough.

Foal-BR *Forgo, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Foamy Sanz *Zep, Canad.*
Benzethonium chloride (p. 1738·1).
Skin disinfection.

Foban *Hoe, Hong Kong; Hoe, Malaysia; AFT, NZ; Hoe, Singapore; Hoe, Thai.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Fobancort *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Foban-Hydro *Hoe, Malaysia.*
⊗Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Foben *Forgo, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Fobet *Mahakam Beta, Indon.*
Cefotaxime (p. 244·1).
Bacterial infections.

Fobidime *Forgo, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fobidime-TZ *Forgo, India.*
Ceftazidime (p. 250·2); tazobactam (p. 369·3).

Fobiven *GL Pharma, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Focal-CZ *Forgo, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Focalin *Novartis, Switz.; Novartis, USA.*
⊗Dexmethylphenidate hydrochloride (p. 2320·3).
Attention-deficit hyperactivity disorder.

Focap *Gratio, India.*
Curcuma longa.

Focetria *Novartis Vaccines, Cz.; Novartis, Fr.; Novartis Vaccines, Irl.; Novartis, Israel; Novartis, Neth.; Novartis Vaccines, Pol.; Novartis Vaccines, Port.; Novartis, Switz.; Novartis, UK.*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Focime-L *Forgo, India.*
Cefixime (p. 240·3).
Bacterial infections.

Foclivia *Novartis Vaccines, Cz.; Novartis Vaccines, Irl.; Novartis, Neth.; Novartis Vaccines, Pol.; Novartis Vaccines, Port.*
An inactivated influenza vaccine (H5N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Focobal Plus *Forgo, India.*
Dexpanthenol (p. 2582·2); vitamin B substances (p. 2102·3).

Focort *Darnitsa, Ukr.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Focri-O *Forgo, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

F-Octane *Fluoron, Ger.*
⊗Perfluorooctane (p. 2587·1).
Ophthalmic tamponade.

F-Octane Light *Fluoron, Ger.*
⊗Perfluorooctane (p. 2587·1); perfluorohexylhexane (p. 2586·3).
Ophthalmic tamponade.

F-Octane Plus *Fluoron, Ger.*
⊗Perfluorooctane (p. 2587·1); perfluorohexyloctane (p. 2586·3).
Ophthalmic tamponade.

Focus
Note: this name may be used for preparations of different composition.
Bayer, Gr.
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Focus 425 *Ocean Nutrition, Canad.†*
Docosahexaenoic acid (p. 1460·1).

Focus Care All-in-One *Ciba Vision, Austral.†*
Cleaning, rinsing, disinfecting, and storage solution for soft contact lenses.

Focus Care One Step *Ciba Vision, Austral.†*
Hydrogen peroxide (p. 1755·2).
Disinfection, neutralisation, and storage of contact lenses.

Fodi *Chang An, China.*
Fosfructose trisodium (p. 2507·2).

Fodiclo *Interbat, Indon.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Fodier *Verisfield, Gr.*
⊗Methylprednisolone aceponate (p. 1642·2).
Skin and scalp disorders.

Fodino *Forgo, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Fodro-M *Forgo, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Foegard *Blubell, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Foetacare *Symbiosis, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemia.

Foetocin *TTK, India.*
Oxytocin (p. 2143·1).
Termination of pregnancy; postpartum haemorrhage; labour induction; evaluation of fetal distress.

Foflu *Forgo, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fofone-S *Forgo, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Fogum *Centaur, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).

Fogyl *Fourrts, Malaysia.*
Metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Foille *Blistex, USA.*
Benzocaine (p. 1980·2); chloroxylenol (p. 1748·2).
Local anaesthesia.
Rider, Chile.
Benzocaine (p. 1980·2).
Skin irritation.

Foille Insetti *Sanofi-Aventis OTC, Ital.*
⊗Hydrocortisone (p. 1640·1).
Insect stings; skin irritation.

Foille Scottature *Sanofi-Aventis OTC, Ital.*
Benzocaine (p. 1980·2); benzyl alcohol (p. 1739·3); chloroxylenol (p. 1748·2).
Burns; skin irritation; wounds.

Foille Sole *Sanofi-Aventis OTC, Ital.*
Benzocaine (p. 1980·2); benzyl alcohol (p. 1739·3); chloroxylenol (p. 1748·2).
Burns; skin irritation; wounds.

Foipan *Ono, Jpn.*
⊗Camostat mesilate (p. 2466·1).
Pancreatitis; gastro-oesophageal reflux.

Fokeston *Rafarm, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Fokin *Forgo, India.*
Amikacin (p. 214·1).
Bacterial infections.

Foko *President Pharmagenesis, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Fokusin *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Fol *Zydus, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Fol Injekt *Winthrop, Ger.†*
Folic acid (p. 2063·1).
Folic acid deficiency.

Fol Lichtenstein *Winthrop, Ger.†*
Folic acid (p. 2063·1).
Folic acid deficiency.

Fol Sang *IQB, Braz.†*
Cyanocobalamin (p. 2107·2); hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); folic acid (p. 2063·1) liver extract (p. 2444·1).
Megaloblastic anaemia.

Folac *Otto, Indon.; Ronava, Venez.*
Folic acid (p. 2063·1).
Folic acid supplement; anaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Folacal *Thorne, Canad.*
Calcium folinate (p. 2066·3).

Folacid *ITF, Chile; Foramen, Philipp.; Synteza, Pol.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy; raised plasma homocysteine; anaemias.

Folacin
Note: this name may be used for preparations of different composition.
Ativus, Braz.
Oral drops; oral solution: Folic acid (p. 2063·1); ascorbic acid (p. 2110·3).
Folic acid deficiency; megaloblastic anaemia.
Ativus, Braz.; Mars, India; Jadran, Rus.; Pfizer, Swed.; Jadran, Ukr.
Folic acid (p. 2063·1).
Folic acid deficiency; megaloblastic anaemia; reduction of folate antagonist toxicity; prevention of neural tube defects in pregnancy.

Folacina *Biocontrol, Arg.*
Folic acid (p. 2063·1).
Folic acid deficiency; megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folacite *Erlimpex, Indon.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Folacom *Combiphar, Indon.*
Folic acid (p. 2063·1).
Prevention of megaloblastic anaemia and neural tube defects in pregnancy.

Folaid *Sterling, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folamil *Dexa, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Folamil Genio *Dexa, Indon.*
Vitamins; minerals; arachidonic acid (p. 2446·1); docosahexaenoic acid (p. 1460·1).
Nutritional supplement in pregnancy and lactation.

Folanemin *Bayer, Ital.*
Calcium levofolinate (p. 2067·1).
Folate deficiency; adjunct to fluorouracil therapy; antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity.

Folanerve *Folares, Philipp.*
Taurine (p. 2626·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Vitamin B deficiency; anaemias.

Folantine *TKS, Braz.*
Folic acid (p. 2063·1).

Folaplus *Meprofarm, Indon.*
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Nutritional supplement in pregnancy and lactation.

Folaport *Richmond, Arg.*
Folic acid (p. 2063·1).
Anaemias; folic acid supplement.

Folarell *Sanorell, Ger.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folate deficiency; antidote to treatment with folic acid antagonists.

Folaren *Ist. Chim. Inter., Ital.*
Calcium folinate (p. 2066·3).
Folate deficiency; antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity.

Folart *Folares, Philipp.*
Folic acid (p. 2063·1).
Folate deficiency; anaemias; prevention of neural tube defects.

Folas *Landson, Indon.*
Folic acid (p. 2063·1).
Prevention of neural tube defects; coronary heart disease; megaloblastic anaemia.

Folastin *Acella, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Dietary supplement.

Folat *ATOZ, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folavit *Kela, Belg.; Sanbe, Indon.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy; anaemias; folic acid deficiency; supplement in pregnancy and lactation.

Folaxin
Note: this name may be used for preparations of different composition.
Berlico Mulia, Indon.
Folic acid (p. 2063·1).
Supplement in pregnancy and lactation.
Zambon, Spain.
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; adjunct to fluorouracil therapy; reduction of methotrexate toxicity.

Fol-B *East West, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folbic RF *Breckenridge, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).
Dietary supplement.

Folbiol *Abdi, Turk.*
Folic acid (p. 2063·1).
Megaloblastic anaemia.

Folbit *Dewcare, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folcare *IFC, Port.*
Minoxidil (p. 1438·3).
Alopecia.

Folcet *Forgo, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Folcet-MT *Forgo, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Folcin-12 Combi *Unimarck, India.*
Folic acid (p. 2063·1); nicotinamide (p. 2083·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Folcodal *Ivax, Arg.*
Cinnarizine (p. 622·1).
Vestibular disorders.

Folcofen *Thebe, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); pholcodine (p. 1675·1); guaifenesin (p. 1666·2).
Cough.

Folcres *Grisi, Mex.*
Minoxidil (p. 1438·3).
Alopecia.
Panalab, Arg.
Finasteride (p. 2358·3).
Alopecia androgenetica.

Folcur *1A, Ger.†*
Folic acid (p. 2063·1).
Folic acid deficiency.

Foldan *Andromaco, Arg.; Uniao Quimica, Braz.*
Tiabendazole (p. 166·3).
Worm infections; nematode infections.

Folderm Pomada *Kinder, Braz.†*
Tiabendazole (p. 166·3); neomycin sulfate (p. 330·1).
Scabies.

Fol-DHA *Forgo, India.*
Docosahexaenoic acid (p. 1460·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Foldivit *Cadila, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Foldox
Note: this name may be used for preparations of different composition.
Roerig, Chile.†
Piroxicam (p. 125·3).
Inflammation; pain.

Folepar B12 *Lisapharma, Ital.*
Folic acid (p. 2063·1); nicotinamide (p. 2083·1); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).
Macrocytic anaemia; deficiency states.

Foleq *Virgo, Philipp.*
Folic acid (p. 2063·1).
Folate deficiency; anaemias; prevention of neural tube defects.

Folera *Svizera, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folergot-DF *Marnel, USA.*
Phenobarbital (p. 535·2); ergotamine tartrate (p. 674·1); belladonna (p. 2453·3).
Gastrointestinal disorders.

Folerin *Novell, Indon.; SMHP, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Folet *Centaur, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folex
Note: this name may be used for preparations of different composition.
Sam-On, Israel.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron and folic acid deficiency.

Fol-G1 *Zydus, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Fol-G2 *Zydus, India.*
Docosahexaenoic acid (p. 1460·1); lycopene (p. 2546·2); folic acid (p. 2063·1); zinc (p. 2126·1).

Folgamma *Worwag, Ger.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Vitamin B_{12} and folic acid deficiency.

Folgamma Mono *Worwag, Ger.†*
Folic acid (p. 2063·1).
Folic acid deficiency; megaloblastic anaemia; antidote to treatment with folic acid antagonists.

Folgard *Upsher-Smith, USA.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Dietary supplement.

FolGravid *SVUS, Cz.*
Docosahexaenoic acid (p. 1460·1).
Dietary supplement in pregnancy.

Folgroom *East West, India.*
Preparation for enteral nutrition.

Foli *CTS, Israel.*
Folic acid (p. 2063·1).
Folic acid deficiency.

Foli Doce *ITF, Chile; Italfarmaco, Spain.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Prevention of neural-tube defects.

Foliage *Terramedic, Philipp.*
Folic acid (p. 2063·1).
Anaemias; folic acid deficiency.

Foliagen *Roux-Ocefa, Arg.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy; megaloblastic anaemia.

Foliamin *Takeda, Thai.*
Folic acid (p. 2063·1).
Anaemias.

Folians *Neopharmed, Ital.*
Finasteride (p. 2358·3).

Folib *Bio-Drug, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Foliben *FIRMA, Ital.*
Calcium folinate (p. 2066·3).
Folate deficiency; antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity.

Foliber *Italfarmaco, Rus.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Folic acid and vitamin B_{12} supplement; prevention of neural tube defects.

Foli-C *Patar, Thai.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; calcium phosphate (p. 1784·2).
Anaemias; dietary supplement.

Folic Acid Plus *Cenovis, Austral.†; Vitelle, Austral.†*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Folic Plus *Assos, Turk.*
Folic acid (p. 2063·1); calcium (p. 1783·1); vitamin D (p. 2112·3).

Folical *Novendia, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; folic acid deficiency.

Folicap *Masterlek, Rus.*
Lidocaine hydrochloride (p. 1988·2); phenazone (p. 124·1).
Otitis media.

Folicard *Gruppo Medica, Philipp.*
Folic acid (p. 2063·1).
Folate deficiency; prevention of neural tube defects; anaemias.

Folicard B-Plus *Gruppo Medica, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Vitamin B supplement; prevention of neural tube defects; megaloblastic anaemia.

Folicare *Medico, India; Scheeling, Philipp.; Rosemont, Thai.†; Rosemont, UK.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy; folate deficiency; folic acid supplement.

FOLI-Cell *Stada, Austria†; Cell Pharm, Ger.; Cell Pharm, Port.*
Calcium folinate (p. 2066·3).
Antidote to treatment with folic acid antagonists; adjunct to fluorouracil therapy.

Folicid *Cell Pharm, Irl.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; adjunct to fluorouracil in colorectal cancer.

Folicil *Bialport, Port.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects.

Folicombin *Mibe, Ger.*
Ammonium iron sulfate (p. 2073·1); folic acid (p. 2063·1).
Iron and folate deficiency.

Folicorin *Uniao Quimica, Braz.*
Calcium folinate (p. 2066·3).

Folicron *Julphar, UAE.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Foliculin *Bharat, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Folicum *Julphar, UAE.*
Folic acid (p. 2063·1).
Folate deficiency.

Folidan *Mylan, Spain.†*
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; methotrexate poisoning; adjunct to fluorouracil therapy.

Folidar *Italfarmaco, Ital.*
Calcium folinate (p. 2066·3).
Folate deficiency; reduction of aminopterin and methotrexate toxicity.

Foliday *Invision, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Foliden *Fourrts, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folidex *ITF, Gr.; Italfarmaco, Ital.; Italfarmaco, Port.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Folifact *Medico, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Folifem *Biofarm, Pol.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Folifemin *Maver, Chile.*
Folic acid (p. 2063·1).

Folifer
Note: this name may be used for preparations of different composition.
Ativus, Braz.
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Anaemias.

Bialport, Port.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Rider, Chile.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron and folic acid deficiency.

Folifer B-12 *Ronava, Venez.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); copper sulfate (p. 2057·2).
Anaemias.

Foliferrin *Maccabi Care, Israel.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Serine (p. 2088·2) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Foliferron *Teofarma, Spain.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3).
Iron and folic acid deficiency.

Folifolin *EMS, Braz.*
Folic acid (p. 2063·1).

Foligan *Desma, Ger.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Foligem *VHB, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Foligest *Bushnell, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Foliglobin *Pharmaceutical Enterprises, S.Afr.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Foligraf *Bharat, India.*
Recombinant follicle-stimulating hormone (p. 2278·2).

Folik *Richter, Pol.*
Folic acid (p. 2063·1).
Prevention of neural tube defects.

Folimac *Ikon, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folimax *Panalab, Arg.*
Folic acid (p. 2063·1).
Folic acid supplement; anaemias.

Folimax B *Panalab, Arg.*
Folic acid (p. 2063·1); biotin (p. 2052·2).
Folic acid and biotin supplement; anaemias.

Folimed *Medicine Products, Thai.*
Folic acid (p. 2063·1).

Foliment *Sanopharm, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Folimet *Medilink, Denm.*
Folic acid (p. 2063·1).
Folate deficiency.

Folimin *Polfa Lodz, Pol.†*
Folic acid (p. 2063·1).
Anaemias; prevention of neural tube defects.

Folimust *Mankind, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folina *Marvecs, Ital.*
Folic acid (p. 2063·1) or sodium folate (p. 2063·1).
Folate deficiency.

American Taiwan, Thai.†
Calcium folinate (p. 2066·3).
Adjunct to fluorouracil therapy; folic acid deficiency; antidote to folic acid antagonists.

Folina-Cell *Eurogenerics, Belg.†*
Folinic acid (p. 2066·3).
Antidote to folic acid antagonists; adjunct in colorectal cancer.

Folinacid *Karamitsos, Gr.*
Calcium folinate (p. 2066·3).

Folinal Plus *Alembic, India.*
Syrup: Iron (p. 2073·1).
Alembic, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Folinato *Faran, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Folinc *Gamot, Philipp.*
Folic acid (p. 2063·1).
Folate deficiency.

Folinemic
Note: this name may be used for preparations of different composition.
Bago, Arg.
Folic acid (p. 2063·1).
Folic acid supplement.

Folinfabra *Fabra, Arg.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists.

Folingrav *Amnol, Ital.*
Folic acid (p. 2063·1).
Folic acid supplement.

Folinoral *Therabel, Fr.*
Calcium folinate (p. 2066·3).
Drug-induced megaloblastic anaemia; methotrexate toxicity.

Folinovo *Hospira, Port.*
Calcium folinate (p. 2066·3).
Reduction of folic acid antagonist toxicity; adjunct to fluorouracil therapy.

Folinoxan *Baxter, Philipp.†*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; antidote to cytostatic folic acid antagonists; megaloblastic anaemia.

Folinz *Apex, India.*
Folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Folio *SteriPharm, Fr.; SteriPharm, Ukr.*
Folic acid (p. 2063·1); potassium iodide (p. 2336·3).
Nutritional supplement in pregnancy; folic acid and iodine supplement.

Folipil *Royal, Chile.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Folirange *Cadila, India.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1).

Folirich-B *Concertina, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Foliron *Medreich, Hong Kong.*
Folic acid (p. 2063·1); iron (p. 2073·1).
Iron and folic acid deficiency during pregnancy.

Folisanin *Sanitas, Chile.*
Folic acid (p. 2063·1).
Folic acid deficiency.

Folistar *Triton, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folistim *Zydus, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Folisure *Wharton, Philipp.*
Folic acid (p. 2063·1).
Folate deficiency; prevention of neural tube defects.

Folital *Sanval, Braz.*
Folic acid (p. 2063·1).
Folic acid supplement.

Folitas *Intas, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folitrax *Ipca, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Folium
Note: this name may be used for preparations of different composition.
Raymos, Arg.
Vaginal lubricant.
Speciality Meditech, India.
Folic acid (p. 2063·1); nicotinamide (p. 2083·1); vitamin B_{12} (p. 2107·2).

Folium OB *Prosel, Philipp.*
Vitamins; zinc sulfate (p. 2126·2).

Foliver *UCB, Fin.*
Folic acid (p. 2063·1).
Folic acid deficiency; megaloblastic anaemia; prevention of neural tube defects; reduction of methotrexate toxicity.

Folivirin *Biotika, Cz.*
⊗Estradiol benzoate (p. 2271·1); testosterone isobutyrate (p. 2305·1).
Menopausal disorders.

Folivit *Siam Bheasach, Thai.*
Folic acid (p. 2063·1).
Anaemias.

Folivit HierroPlus B *Farcoral, Mex.*
Vitamins; folic acid (p. 2063·1); iron (p. 2073·1).
Dietary supplement.

Folivital *Silanes, Mex.*
Folic acid (p. 2063·1).
Folate supplement; prevention of neural tube defects in pregnancy.

Folivoran *Vocate, Gr.*
Calcium levofolinate (p. 2067·1).
Antidote to folic acid antagonists; folic acid deficiency.

Folix
Note: this name may be used for preparations of different composition.
Plus, India.
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folix-Mater *IQB, Braz.†*
Ascorbic acid (p. 2110·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3).

Foliz *Ritz, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Follegon *Organon, Turk.*
Urofollitropin (p. 2312·2).
Male and female infertility.

Follihair *Piramal, India.*
Vitamin B substances (p. 2102·3); minerals; amino acids.

Follilutin *Biosena, India.*
⊗Human menopausal gonadotrophin (p. 2284·1).
Male and female infertility.

Follimon *LG Life Sciences, Thai.*
Urofollitropin (p. 2312·2).
Female infertility.

Follinis *Neiss, India.*
⊗Human menopausal gonadotrophin (p. 2284·1).
Male and female infertility.

Folliova *Uni-Sankyo, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Follistim *Organon, USA.*
Follitropin beta (p. 2278·2).
Male and female infertility.

Follitec *United Biotech, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Follitrin *Ferring, Arg.; Gynopharm, Chile.*
Urofollitropin (p. 2312·2).
Male and female infertility; assisted reproduction in polycystic ovary syndrome.

Follitrop *LG Life Sciences, Rus.*
Follitropin alfa (p. 2278·2).
Female infertility.

Follitrope *LG Life Sciences, Thai.*
Follitropin.
Female infertility.

Follokon *Biosena, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Folmigor *Alapis, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Folnet *Active, India.*
Folic acid (p. 2063·1); nicotinamide (p. 2083·1); riboflavin (p. 2104·3).

Folneu *Cadila, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Folonin *Geolab, Braz.*
Folic acid (p. 2063·1).

Folotyn *Allos, USA.*
Pralatrexate (p. 849·3).
T-cell lymphoma.

Folovit *Polfarmex, Pol.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Folpace *Alaven, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); vitamin E (p. 2119·1); magnesium (p. 1786·3).

Folsafe *Orbit, India.*
Docosahexaenoic acid (p. 1460·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Folsan *Solvay, Austria; Abbott, Ger.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Folsav *Selenium Pharma, Hung.; Valeant, Hung.*
Folic acid (p. 2063·1).
Folic acid deficiency.

Folson *Aglowmed, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Foltanx RF *Breckenridge, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).
Dietary supplement.

Foltene *Silesia, Chile.†*
Tricosaccharides.
Alopecia.

Foltene Research Anticaspa *Silesia, Chile.†*
Tricosaccharides; piroctone olamine (p. 1716·3); pantothenic acid (p. 2085·2); salicylic acid (p. 1719·1).
Dandruff.

Fol-Thrive *Elder, India.*
Docosahexaenoic acid (p. 1460·1); mecobalamin (p. 2108·1); folic acid (p. 2063·1).

Foltran
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Zopiclone (p. 1118·1).
Insomnia.

Roemmers, Chile.
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Foltx *Pan American, USA.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Homocysteinaemia; homocystinuria; nutritional supplement.

Folverlan *Verla, Ger.*
Folic acid (p. 2063·1).
Folic acid deficiency; prophylaxis of neural tube defects.

Folvidon *Abigo, Swed.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folate deficiency; prevention of neural tube defects in pregnancy.

Folvina *Zota, India.*
Folic acid (p. 2063·1); nicotinamide (p. 2083·1); riboflavin (p. 2104·3).

Folvit *Andromaco, Chile.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Folvite *Meda, Fin.; Wyeth, India; Meda, Switz.; Lederle, USA.*
Folic acid (p. 2063·1) or sodium folate (p. 2063·1).
Megaloblastic anaemia; folic acid deficiency; prevention of neural tube defects in pregnancy.

Folwise *Universal Medicare, India.*
Docosahexaenoic acid (p. 1460·1); folic acid (p. 2063·1).

Foly *Chemo-Drugs, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fomacid *Candor, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Fomeda *Orion, Fin.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Fomene
Note: this name may be used for preparations of different composition.
Leti, Venez.
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Angelini, Spain.†
Tetridamine maleate (p. 137·1).
Vaginitis.

Fomentil *SIT, Ital.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thyme oil (p. 2630·3); peru balsam (p. 2587·1); benzoin (p. 2624·3).
Respiratory congestion; rhinitis; sore throat; laryngitis.

Fomepikehl *Sanum-Kehlbeck, Ger.*
Fomitopsis pinicola e muribus mycelii.
Homoeopathic preparation.

Fomicet *Geno, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Fomiral *Silanes, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Fomtide *Sun, India.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).

Fon Wan Ginsenergy *Giuliani, Ital.*
Ginseng (p. 2513·3).
Nutritional supplement.

Fon Wan Memory *Giuliani, Ital.*
Vitamins; Siberian ginseng (p. 2614·3); ginkgo biloba (p. 2512·3).
Nutritional supplement; mental function disorders.

Fonarin B *Mayo, Mex.*
Vitamin B substances (p. 2102·3).

Foncal *BMW, India.*
Calcium gluconate (p. 1783·3); cyanocobalamin (p. 2107·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Foncitril *SERP, Mon.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Urinary alkalinisation; renal calculi.

Fonderyl *Raymos, Arg.*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Fondur *Sandoz, Denm.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Fonergin *Farmasa, Braz.*
⊗Prednisolone (p. 1645·2); framycetin sulfate (p. 301·2); gramicidin (p. 308·3); amylocaine hydrochloride (p. 1979·3); procaine hydrochloride (p. 1994·3).
Mouth disorders.

Fonergine *Benitol, Arg.*
Benzocaine (p. 1980·2); tyrothricin (p. 384·1); bithionol (p. 152·2).
Mouth and throat disorders.

Fonergoral *Ducto, Braz.*
Benzydamine hydrochloride (p. 29·2).

Fongamil *Bailleul, Fr.; Alapis, Gr.; Saninter, Port.*
Omoconazole nitrate (p. 591·3).
Fungal infections.

Fongarex *Besins, Fr.*
Omoconazole nitrate (p. 591·3).
Vaginal candidiasis.

Fongeryl *SERB, Fr.†*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Fongiléine *Gifrer Barbezat, Fr.*
Econazole nitrate (p. 577·3).
Fungal skin and nail infections.

Fongitar *Stiefel, Austral.†; Stiefel, Hong Kong; Stiefel, Philipp.; Stiefel, Port.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.†*
Pyrithione zinc (p. 1718·1); tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2).
Scalp disorders; tinea versicolor.

Fongtit *Sunward, Singapore.*
Salicylamide (p. 129·2); caffeine (p. 1203·3).

Fonicid *Lafare, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Fonim MD *Forgo, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Fonim-P *Forgo, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Fonim-S *Forgo, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Fonlipol *SERP, Mon.*
Tiadenol (p. 1511·3).
Hypercholesterolaemia.

Fontain *Chemo-Drugs, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Fontax *Unison, Thai.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Fontex *Lilly, Belg.; Lilly, Denm.; Lilly, Norw.; Lilly, Swed.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Fonti *TKS, Braz.*
Thiamine (p. 2102·3).

Fontical *TKS, Braz.*
Calcium carbonate (p. 1824·3).

Fontien *Hanmi, China.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Fontol
Note: this name may be used for preparations of different composition.
Duncan, Arg.
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Uniao Quimica, Braz.
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Fontolax *Biolab Sanus, Braz.*
Cassia pulp (p. 1826·2); coriander (p. 2486·3); senna (p. 1885·1); liquorice (p. 1853·2); tamarind (p. 1892·2).
Constipation.

Fonto-Vit B6 *Fontovit, Braz.†*
Pyridoxine hydrochloride (p. 2105·3).

Fonto-Vit C *Fontovit, Braz.†*
Ascorbic acid (p. 2110·3).

Fonto-Vit E *Fontovit, Braz.†*
Vitamin E (p. 2119·1).

Fontula *Bernofarm, Indon.*
Codergocrine mesilate (p. 389·2).
Mental function impairment in the elderly.

Fonvicol *Panpharma, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Fonx *Astellas, Fr.*
Oxiconazole nitrate (p. 591·3).
Fungal skin infections.

Fonzylane *Lafon, China; Cephalon, Fr.†; Lafon, Hong Kong.†*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders; intermittent claudication; Raynaud's syndrome; ischaemia; cochlear-vestibular disorders.

Foot Care *Ind-Swift, India.*
⊗Lactic acid (p. 2539·1); liquid paraffin (p. 2191·2); propylene glycol (p. 2205·2); urea (p. 1727·3).

Foot Zeta *Zeta, Ital.*
Undecenoic acid (p. 596·3); usnic acid (p. 2640·2).
Fungal skin infections; wounds; burns.

Foothy *Otto, Indon.*
⊗Urea (p. 1727·3); fructan; portulaca; vitamin E (p. 2119·1).
Dry skin.

FootSmart *Key, Austral.*
⊗Urea (p. 1727·3); allantoin (p. 1693·1); vitamin E (p. 2119·1); sodium pidolate (p. 1720·3).
Cracked heels.

Fopina *Forgo, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Foprin Plus H *Teva, Cz.†*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fopymin *Akesiss, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Foquin *Forgo, India.*
Quinine sulfate (p. 665·2).
Malaria; nocturnal leg cramps; babesiosis.

For Eyes *Golden Glow, Austral.*
Lutein (p. 2079·2); zinc oxide (p. 1729·1); selenomethionine (p. 2087·1); calcium ascorbate (p. 2111·1); *d*-alpha tocoferil acid succinate (p. 2119·2).
Dietary supplement for eye health.

For Gas *Uniao Quimica, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

For Goodness Face *Avon, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

For Peripheral Circulation Herbal Plus Formula 5 *Vitelle, Austral.†*
Ginkgo biloba (p. 2512·3); crataegus (p. 2488·1); zanthoxylum (p. 2650·1); capsicum (p. 2469·3); rutoside (p. 2505·3); hesperidin (p. 2505·2).
Peripheral vascular disorders.

For Women Active Woman Formula *Blackmores, Austral.†*
Siberian ginseng (p. 2614·3); damiana (p. 2491·3); avena (p. 2451·1); centella (p. 1698·3); minerals; vitamin C (p. 2110·3).
Dietary supplement.

For Women Multi Plus EPO *Blackmores, Austral.†*
Evening primrose oil (p. 2502·2); vitamins; minerals; choline bitartrate (p. 2055·2); bioflavonoids (p. 2505·2); rutoside (p. 2505·3).
Dietary supplement.

Foracet *Solus, India.*
⊗Pentazocine hydrochloride (p. 120·3); paracetamol (p. 115·1).
Pain.

Foracort *Cipla, India; Cipla, Malaysia.*
⊗Formoterol fumarate (p. 1209·2); budesonide (p. 1625·1).
Asthma.

Foradil *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.†; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Schering, USA; Novartis, Venez.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease; bronchospasm; asthma.

Foradil Combi *Novartis, Rus.; Novartis, Turk.*
⊗Powder for inhalation, formoterol fumarate (p. 1209·2); powder for inhalation, budesonide (p. 1625·1).
Obstructive airways disease.

Foradile *Novartis, Austral.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Foragin *Mugi, Indon.*
Dipyrone (p. 53·3).
Fever; pain.

Forair
Note: this name may be used for preparations of different composition.
Chiesi, Cz.†; Chiesi, Ger.; Chiesi, Gr.; Chiesi, Port.
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease; asthma.

Zydus, India.
⊗Salmeterol (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Foralivit *Am-Europharma, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Iron deficiency; iron-deficiency anaemia; vitamin B deficiency.

Foramebex *Foramen, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Foramefer *Foramen, Philipp.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); vitamin B_2 (p. 2104·3).
Anaemias.

Foramol *The Forty-Two, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Forane *Abbott, Arg.; Abbott, Austria; Abbott, Braz.; Baxter, Canad.; Abbott, China; Abbott, Cz.; Abbott, Hong Kong†; Abbott, Hung.; Abbott, India; Abbott, Indon.†; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ†; Abbott, Philipp.; Abbott, Pol.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; AbbVie, Spain; Abbott, Thai.; Abbott, Turk.; AbbVie, UK; Baxter, USA.*
Isoflurane (p. 1903·2).
General anaesthesia.

Foraneural *Mugi, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.

Foransi *Gracia, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Foraseq *Novartis, Braz.; Novartis, Venez.*
⊗Treatment 1, formoterol fumarate (p. 1209·2); treatment 2, budesonide (p. 1625·1).
Asthma.

Forasma
Note: this name may be used for preparations of different composition.
Guardian, Indon.
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

The Forty-Two, Thai.
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Forast *Eczacibasi, Turk.*
⊗Formoterol fumarate (p. 1209·2).

Forastmin *Vedim, Pol.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Forastrol *Foramen, Philipp.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Foratec *Cipla, India; Cipla-Medpro, S.Afr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Foraven *Forum, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Forbest *Valeas, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic respiratory-tract disorders.

Forbetes *Menarini, Indon.; Sanbe, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Forbiotic *Blackmores, Austral.†*
Lactobacillus reuteri (p. 2596·3).
Restoration of normal gastrointestinal flora.

Forbiotin *The Forty-Two, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Forbiphen *Norma (Νορμα), Gr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; dysmenorrhoea.

Forbone *Elisa, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Forbrand *Uragme, Ital.*
⊗Zinc chloride (p. 2126·1); alcohol (p. 1733·1).
Mouth hygiene.

Forbufen *The Forty-Two, Thai.*
Fenbufen (p. 59·1).
Musculoskeletal and joint disorders.

Forcad *Corbridge, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; ischaemic heart disease.

Forcadion *Nutrisante, Fr.*
Fatty acids; lactalbumin; magnesium oxide (p. 1857·3); vitamins.
Tonic.

Forcal *Forgo, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).

Forcal-D *Forgo, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Forcalm *Unichem, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Forcaltonin *Unigene, Neth.†*
Calcitonin (salmon) (p. 1178·1).
Osteoporotic fractures; Paget's disease of bone; hypercalcaemia of malignancy.

Forcan *Cipla, Cz.; Cipla, Hong Kong†; Cipla, India; Cipla, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Forcan TZ *Cipla, India.*
1 Tablet, fluconazole (p. 578·2); 2 tablets, tinidazole (p. 949·2).
Vaginal candidiasis; trichomoniasis; bacterial vaginitis.

Forcanox *Guardian, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Forcap *Kleva, Gr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Forcapil *Arkopharma, Fr.*
Calcium pantothenate (p. 2085·2); biotin (p. 2052·2); pyridoxine (p. 2105·3); folic acid (p. 2063·1); colecalciferol (p. 2113·1); zinc pidolate (p. 1720·3); cystine (p. 2059·1); methionine (p. 1558·2).
Hair and nail tonic.

Cremum, Hung.
Cystine (p. 2059·1); methionine (p. 1558·2); calcium pantothenate (p. 2085·2); pyridoxine hydrochloride (p. 2105·3); zinc pidolate (p. 1720·3); biotin (p. 2052·2).
Supplement for hair and nails.

Forcef *Aristo, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Forcemil *Normon, Spain.*
Vitamins; minerals; ginseng (p. 2513·3).

Forcet *Norma (Νορμα), Gr.*
Sumatriptan succinate (p. 679·2).
Migraine.

Forceval *Unigreg, Irl.†; Alliance, UK.*
Vitamins; minerals.

Forcez *Laksun, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Forcical Vitamine D3 *Automedic, Fr.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); yeast (p. 2125·2).
Calcium and vitamin D deficiency; osteoporosis.

Forcid *Astellas, Cz.†; Astellas, Gr.; Astellas, Hung.; Astellas, Neth.; Astellas, Pol.; Astellas, Port.; Astellas, S.Afr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Forcil *Continentales, Mex.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Forcilen *Specifar, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Forcilin *LKM, Arg.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Forclina *LKM, Arg.*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Forcol-D *Mount Mettur, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Forcremol *Ifusa, Mex.*
Borax (p. 2459·2); phenol (p. 1763·3); alum (p. 2439·1); potassium (p. 1793·1).

Forcrim *Biotech, Venez.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Forcycline *The Forty-Two, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Ford Fibre *Vitelle, Austral.†*
Ispaghula (p. 1849·1).
Constipation; digestive disorders.

Ford Pills *Faulding, Austral.†*
Aloin (p. 1816·2); phenolphthalein (p. 1877·3).
Constipation.

Fordec *Forgo, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Fordep *Atral, Port.†*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Forderm *Ferron, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Fordesia *Kalbe, Indon.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Fordex *Leti, Venez.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Fordiab *Hexpharm, Indon.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Fordib *Mandar, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Fordib MF *Mandar, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Fordilen *Novartis, Arg.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Fordin *Promed, Indon.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Fordiuran *Leo, Spain.*
⊗Bumetanide (p. 1329·1).
Oedema; hypertension.

Fordtran *Streuli, Switz.†*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Forecox *Macleods, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Macleods, Rus.
Rifampicin (p. 350·3); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Forelax *Guardian, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Forene *Abbott, Belg.; Abbott, Chile; Abbott, Denm.†; Abbott, Fin.†; Abbott, Fr.; Abbott, Ger.; Abbott, Neth.†; Abbott, Norw.; Abbott, Port.; Abbott, Swed.; AbbVie, Switz.; Abbott, Venez.*
Isoflurane (p. 1903·2).
General anaesthesia; sedation in mechanically ventilated patients.

Forenium *Abbott, Gr.*
Isoflurane (p. 1903·2).
General anaesthesia.

Foresight *Cantassium Co., UK.*
Vitamins.

Foresight Iron Formula *Cantassium Co., UK.*
Ferrous gluconate (p. 2061·2); copper gluconate (p. 2057·2).

Forex *Keshav, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Forexin *Pharmaland, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Forexine *GX, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Forfig *Eurofarma, Braz.*
Milk thistle (p. 1561·1).

Forfivo *Edgemont, USA.*
Bupropion hydrochloride (p. 408·2).
Depression.

Forgen *Alkem, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Forgesic *Bernofarm, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Forgesic-MR *Forgo, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Forgesic-SP *Forgo, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Forgest *Forgo, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Forgram *Biomedis, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Forhem *Trigenesis, India.*
Iron carbonyl (p. 2073·1); vitamin B substances (p. 2102·3); zinc (p. 2126·2).

Foric *Sam-On, Israel.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Anaemias; folic acid supplement.

Foricef *Promed, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Forich *Zee, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Forielle *Merck, Switz.*
Follitropin alfa (p. 2278·2).
Male and female infertility.

Forifek *Caprifarmindo, Indon.; Sanbe, Indon.*
Cefaclor (p. 232·3).
Bacterial infections.

Forinfec *Lapi, Indon.*
Povidone-iodine (p. 1767·1).
Mouth and throat disorders.

Foristal *Novartis, India.*
Dimetindene maleate (p. 626·1).
Allergic skin disorders; allergic eye disorders; pruritus.

Forit
Note: this name may be used for preparations of different composition.
Health Care, India.
Azithromycin (p. 221·2).
Bacterial infections.

Forjoint *Servocare, India.*
Diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1).

Forkem *Forgo, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Forken *Kendrick, Mex.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Forknow *YSP, Malaysia; Yung Shin, Singapore.*
Flunarizine hydrochloride (p. 629·3).
Migraine; peripheral vascular disease.

Forlax *Ipsen, Austria; Ipsen, Belg.; Beaufour-Ipsen, China; Beaufour-Ipsen, Cz.; Ipsen, Fr.; Beaufour-Ipsen, Hong Kong; Ipsen, Hung.; Beaufour-Ipsen, Malaysia; Ipsen, Neth.; Beaufour-Ipsen, Pol.; Ipsen, Port.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Swed.; Ipsen, Thai.; Ipsen, Ukr.*
Macrogol 4000 (p. 2547·3).
Constipation.

IMA, Braz.†
Sodium picosulfate (p. 1887·2).
Constipation.

Forli *Filaxis, Arg.*
Indinavir (p. 986·1).
HIV infection.

Forlion *Farmedia, Gr.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Forliv *Forgo, India.*
Cyproheptadine (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Forlucyl *Ultra, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Forma 2 *Knop, Chile.*
Phaseolus vulgaris (p. 2587·3).
Aid in weight loss.

Formadon *Gordon, USA.*
Formaldehyde (p. 1752·2).
Hyperhidrosis.

Formador *Forgo, India.*
Tramadol (p. 139·2).
Pain.

Formag *Pileje, Fr.*
Magnesium (p. 1786·3); taurine (p. 2626·2); vitamin B_6 (p. 2105·3).
Magnesium deficiency.

Formagal *SMB, Belg.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formagel *Retinoids, Rus.*
Formaldehyde (p. 1752·2).
Hyperhidrosis.

Formaglyben *KRKA, Cz.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Formalaz *Rivers Edge, USA.*
Formaldehyde (p. 1752·2).
Drying agent in wart removal.

Formalin *Concept, Israel.*
Paraformaldehyde (p. 1763·1).
Instrument disinfection.

Formalyde *Pedinol, USA.*
Formaldehyde (p. 1752·2).
Hyperhidrosis and offensive odour of the feet; drying agent in surgical removal of warts.

Formance *Abbott, Hong Kong; Abbott, Turk.*
Preparation for enteral nutrition.
Pregnancy and lactation.

Formano *Temapharm, Cz.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formare *Libbs, Braz.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formasan *Sanum-Kehlbeck, Ger.*
Acidum formicicum (p. 2507·1).
Homoeopathic preparation.

Format *Northia, Arg.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Formatris *Meda, Ger.; Meda, Spain; Meda, Swed.*
⊗Formoterol fumarate (p. 1209·2).
Asthma; obstructive airways disease.

Formax *Novartis, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Formaxa *SMB, Fin.; Allertec, Gr.; SMB, Port.†*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Forme *Haledew, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formedico *Uragme, Ital.*
⊗Zinc chloride (p. 2126·1); alcohol (p. 1733·1); sodium monofluorophosphate (p. 2091·3).
Mouth disorders.

Formell *Actavis, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formet *Aspen, Austral.; Chemech, India; Steinbach, Philipp.; Strides Arcolab, Singapore.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formetic *Polpharma, Pol.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formetin *Farmstandart, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formic *Elder, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Formica Rufa Compose *Boiron, Fr.*
Formica rufa; belladonna (p. 2453·3); sarsaparilla (p. 2610·3); colocynthis (p. 1833·3); anemone pulsatilla (p. 2600·2); urtica urens (p. 2639·3); solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Formicina *Roemmers Rowe, Venez.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Formic-O *Elder, India.*
Cefixime (p. 240·3).
Bacterial infections.

Formic-XL *Elder, India.*
Cefixime (p. 240·3); dicloxacillin (p. 286·1); lactobacillus (p. 2596·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Formidium *DHU, Ger.*
Acid. formicic. (p. 2507·1).
Homoeopathic preparation.

Formidron *Yaroslavl, Rus.*
Formaldehyde (p. 1752·2).
Hyperhidrosis.

Formigran *GSK Consumer, Ger.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Formin *Alkem, India; Pliva, Rus.; Pharmaland, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Forminal *Alembic, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Gulf Drug, S.Afr.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formisoton *Staufen, Ger.*
Acid. formicicum (p. 2507·1).
Homoeopathic preparation.

Formistin *Lusofarmaco, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Formitex *Pisa, Mex.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; rheumatoid arthritis; autoimmune disorders.

Formitrol *Mipharm, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Formo *Orion, Denm.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formoair *Chiesi, Belg.; Chiesi, Fr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease; asthma; chronic bronchitis.

Formocaps *Biosintetica, Braz.; Stada, Neth.†*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formocarbine *GSK Sante, Fr.*
Activated charcoal (p. 1537·3).
Gastrointestinal disorders.

Formo-Cresol Mitis *Colgate Oral Care, Austral.†*
Formaldehyde (p. 1752·2); cresol (p. 1749·1).
Endodontics.

Formodual *Torrex Chiesi, Austria; Torrex Chiesi, Cz.†; Chiesi, Fr.; Promedica, Ital.; Chiesi, Neth.; Chiesi, Port.; Chiesi, Spain.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Formol *Plata, Arg.†*
Formaldehyde (p. 1752·2).

FormoLich *Winthrop, Ger.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formoline L112 *Biomedica, Ital.; Interdelta, Switz.; SSL, UK.*
Poliglusam (p. 2593·2).
Obesity; hyperlipidaemia; slimming aid.

Formom *Pyridam, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Formonide *Zydus, India.*
⊗Budesonide (p. 1625·1); formoterol (p. 1209·2) or formoterol fumarate (p. 1209·2).

Formopen *Elpen (Ελπεν), Gr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formotec *Cipla, Venez.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formotil *Genepharm, Gr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formotop *Astellas, Ger.*
⊗Formoterol fumarate (p. 1209·2).
Asthma.

Formovent *Italchimici, Cz.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Formoxol *YSP, Malaysia.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

Formula 1
Note: this name may be used for preparations of different composition.
Golden Pride, Canad.†; Rawleigh, Canad.†
Vitamin B_{12} (p. 2107·2).

Formula 2
Note: this name may be used for preparations of different composition.
Golden Pride, Canad.†; Rawleigh, Canad.†
Ascorbic acid (p. 2110·3).

Nutri-Cology, Canad.†
Selenium (p. 2086·3).

Formula III *Nutri-Cology, Canad.†*
Vitamins; minerals.

Formula IV *GNLD, Austral.*
Nutritional supplements; vitamins; minerals.

Formula DE 226 *Herbasante, Canad.†*
Calcium carbonate (p. 1824·3); calcium fluoride (p. 2053·1); manganese (p. 2081·2); phosphorus (p. 2589·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Formula 405 *Doak, USA.*
Skin cleanser.

Formula 3358 *Therapeutic Foods, Canad.†*
Betaine hydrochloride (p. 2456·1); calcium glycerophosphate (p. 1783·3); inositol (p. 2533·2); potassium bicarbonate (p. 1780·3).

Formula 7441 *Douglas, Canad.†*
Chromic chloride (p. 2055·3); nicotinic acid (p. 2083·1).

Formula 7442 *Douglas, Canad.†*
Chromic chloride (p. 2055·3); nicotinic acid (p. 2083·1).

Formula AO *Douglas, Canad.†*
Vitamins; choline bitartrate (p. 2055·2); selenium (p. 2086·3); inositol (p. 2533·2); methionine (p. 1558·2).

Formula B-1 *Normex, Canad.†*
Cascara (p. 1826·1); ox bile (p. 2457·2); senna (p. 1885·1).

Formula B Plus *Major, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemia.

Formula B-Complex *Solgar, Canad.†*
Vitamin B substances (p. 2102·3).

Formula 1 Bio-C *Life Plus, Canad.†*
Vitamin C (p. 2110·3).

Formula 2 Bio-C *Life Plus, Canad.†*
Vitamin C (p. 2110·3).

Formula C 29 *Naturbec, Canad.†*
Magnesium oxide (p. 1857·3); sodium bicarbonate (p. 1781·1).

Formula C 30 *Naturbec, Canad.†*
Calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).

Formula C 36 *Naturbec, Canad.†*
Ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Formula C Doron *Weleda, Canad.†*
Hyoscyamus niger (p. 2530·2); onopordum; primula vulgaris (p. 2596·2).
Homoeopathic preparation.

Formula C Doroon *Weleda, Canad.†*
Hyoscyamus niger (p. 2530·2); magnesium phosphate dibasic (p. 1786·3); onopordum; primula vulgaris (p. 2596·2).
Homoeopathic preparation.

Formula CA 205 *Herbasante, Canad.†*
Helonias (p. 2524·3); sepia officinalis (p. 2613·1); silicon dioxide (p. 2208·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Formula Cal-Phos *Metagenics, Canad.†*
Calcium phosphate (p. 1784·2).

Formula CDC *Seroyal, Canad.*
Vitamin C (p. 2110·3); manganese (p. 2081·2); zinc (p. 2126·1).

Formula CI 207 *Herbasante, Canad.†*
Aesculus hippocastanum (p. 2431·2); arnica (p. 2447·2); barberry root (p. 2502·1); calcium fluoride (p. 2053·1); ginkgo biloba (p. 2512·3); goldenrod (p. 2620·1); grape (p. 2521·3); hamamelis virginiana (p. 2523·3); hydrastis canadensis (p. 2528·1); viburnum opulus.
Homoeopathic preparation.

Formula CT *Metagenics, Canad.†*
Vitamins; minerals.

Formula D Doron *Weleda, Canad.†*
Dulcamara (p. 2497·3); lysimachia nummularia.
Homoeopathic preparation.

Fórmula Dérmica *Darier, Mex.*
Yellow soft paraffin (p. 2212·1).
Skin disorders; ointment basis.

Formula 17605 Diaplex *Therapeutic Foods, Canad.*
⊗Ammonium chloride (p. 1656·1); betaine hydrochloride (p. 2456·1); choline bitartrate (p. 2055·2); inositol (p. 2533·2); pepsin (p. 2586·1); vitamin A (p. 2098·3).

Formula DM 210 *Herbasante, Canad.†*
Belladonna (p. 2453·3); bryonia (p. 2461·3); chamomile (p. 2474·1); cyclamen europaeum (p. 2490·2); delphinium staphisagria; hypericum perforatum (p. 449·1); iris versicolor (p. 2534·3); kalmia latifolia (p. 2537·2); sanguinaria canadensis (p. 2610·1); spigelia (p. 2621·3).
Homoeopathic preparation.

Formula EM *Major, USA.*
Glucose (p. 2068·3); fructose (p. 2068·2); phosphoric acid (p. 2589·1).
Nausea and vomiting.

Formula ES 211 *Herbasante, Canad.*
Artemisia absinthium (p. 2426·1); anacardium orientale (p. 2471·3); a ntimony trisulfide (p. 2445·1); atropa belladonna (p. 2453·3); carbo vegetabilis (p. 1537·3); china pubescens (p. 2478·3); citrullus colocynthus (p. 1833·3); lycopodium (p. 2546·3); robinia coccinea homeo; argentum nitricum (p. 2615·3).
Homoeopathic preparation.

Formula II Especial *Knop, Chile.*
Carduus marianus (p. 1561·1); arsenicum album (p. 2448·1); thuja (p. 2629·3); radium bromatum; lapis albus; kalium jodatum (p. 2336·3).
Homoeopathic preparation.

Formula FA 224 *Herbasante, Canad.†*
Cobalt (p. 2482·2); copper (p. 2057·1); ginseng (p. 2513·3); iron (p. 2073·1); magnesium chloride hexahydrate (p. 1787·1); phosphorus (p. 2589·2); potassium phosphate dibasic (p. 1791·1); selenium (p. 2086·3); silver (p. 2615·1).
Homoeopathic preparation.

Formula FLW *The Results Company, Canad.†*
Vitamins; minerals.

Formula Forte Seniors *Pharmetics, Canad.*
Vitamins; minerals.

Formula Four *Bioglan, Austral.†*
Vitamins; minerals.

Formula FV 213 *Herbasante, Canad.*
Pneumus boldus (p. 2458·3); chelidonium majus (p. 2522·2); cinchona officinalis (p. 2478·3); citrullus colocynthus (p. 1833·3); cynara scolymus (p. 2490·3); solidago virgaurea (p. 2620·1); hydrastis canadensis (p. 2528·1); lycopodium (p. 2546·3); carduus marianum (p. 1561·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Formula G9 *Naturbec, Canad.†*
Menthol (p. 2553·2).

Formula Gly *Seroyal, Canad.†*
Vitamins; minerals.

Formula Gyn *Seroyal, Canad.*
Vitamin B_6 (p. 2105·3); magnesium proteinate (p. 1786·3).

Formula HEPA *Weleda, Canad.†*
Strawberry; vitis vinifera (p. 2521·3).
Homoeopathic preparation.

Formula HH *Inno-Vite, Canad.*
Vitamins; minerals.

Formula Homeo QR 209 *Herbasante, Canad.†*
Aesculus hippocastanum (p. 2431·2); antimony (p. 2445·1); arnica (p. 2447·2); barberry root (p. 2502·1); burdock (p. 2540·1); celandine (p. 2522·2); charcoal activated (p. 1537·3); cholesterol (p. 2179·1); cinchona officinalis (p. 2478·3); cynara scolymus (p. 2490·3); equisetum arvense (p. 2500·1); erigeron canadensis; fucus vesiculosus (p. 2612·1); ginkgo biloba (p. 2512·3); goldenrod (p. 2620·1); grape (p. 2521·3); hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Formula HRT-Minerals *Metagenics, Canad.†*
Minerals.

Formula HSN *General Nutrition, Canad.*
Vitamins; minerals.

Formula IC *The Results Company, Canad.†*
Vitamins; minerals; methionine (p. 1558·2).

Formula INF *Weleda, Canad.*
Aconite (p. 2428·3); bryonia (p. 2461·3); eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Formula for Joints *Golden Glow, Austral.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis.

Formula LF *Numark, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Formula M *Metagenics, Canad.†*
Pantothenic acid (p. 2085·2); vitamin A palmitate (p. 2098·3).

Formula MBC *Weleda, Canad.†*
Calendula (p. 2465·2); dog's mercury; Peruvian balsam (p. 2587·1).
Homoeopathic preparation.

Formula 2 Multivitamin Mineral Complex *Herbalife, Canad.*
Vitamins; minerals.

Formula No 2K *Golden Pride, Canad.†; Rawleigh, Canad.†*
Potassium citrate (p. 1780·3).

Formula OSG
Note: this name may be used for preparations of different composition.
Seroyal, Canad.†
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); minerals.

Formula OST *Metagenics, Canad.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); vitamin C (p. 2110·3).

Formula OSX *Seroyal, Canad.†*
Minerals.

Formula P6 *Naturbec, Canad.†*
Salicylic acid (p. 1719·1).

Formula PC *Metagenics, Canad.†*
Vitamin; selenium (p. 2086·3).

Formula PC 223 *Herbasante, Canad.†*
Calcium fluoride (p. 2053·1); cobalt (p. 2482·2); copper (p. 2057·1); magnesium chloride hexahydrate (p. 1787·1); nickel; phosphorus (p. 2589·2); potassium chloride (p. 1793·2); sulfur (p. 1721·1); zinc (p. 2126·1).
Homoeopathic preparation.

Formula IV Plus *Golden Neo-Life, Canad.*
Vitamins; minerals.

Formula S/E *Douglas, Canad.†*
⊗Ephedra (p. 1663·1).

Formula-4 SX *Abundance, Canad.†*
d-Alpha tocoferil acetate (p. 2119·1); zinc (p. 2126·1).

Formula T4 *Naturbec, Canad.†*
Angelica (p. 2443·3); aniseed (p. 2444·2); calendula (p. 2465·2); caraway (p. 2470·2); centaury (p. 2473·2); coriander (p. 2486·3); fennel (p. 2503·2); melissa (p. 2552·3); peppermint (p. 1877·1).

Formula T1 Tea *Naturbec, Canad.†*
Senna (p. 1885·1).
Constipation.

Formula T5 Tea *Naturbec, Canad.†*
Frangula (p. 1843·3); cascara (p. 1826·1).
Constipation.

Formula T13 Tea *Naturbec, Canad.†*
Calendula (p. 2465·2); corn poppy (p. 2207·3); eucalyptus (p. 2501·1); liquorice (p. 1853·2); tilia (p. 2631·3).

Formula TA 220 *Herbasante, Canad.†*
Tobacco (p. 2632·2).
Homoeopathic preparation.

Formula Thy *Metagenics, Canad.†*
Vitamin B substances (p. 2102·3); minerals.

Formula TLN *Healthy Body Services, Canad.†*
Dibasic calcium phosphate (p. 1784·2); dipotassium phosphate (p. 1791·1); sodium phosphate (p. 1791·2).

Formula TT *Thursday Plantation, Canad.†*
Menthol (p. 2553·2).

Formula TTO *Thursday Plantation, Canad.†*
Menthol (p. 2553·2).

Formula Ultra Pro *Metagenics, Canad.†*
Vitamins; zinc (p. 2126·1).

Formula VIR *Creative Nutrition, Canad.†*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); methionine (p. 1558·2).

Formula VM *Solgar, USA.*
Vitamins.

Formula VM-75 *Solgar, Canad.†; Solgar, UK.*
Vitamins; minerals.

Formulaexpec *Vicks, Spain.*
Guaifenesin (p. 1666·2).
Cough.

Formulat Biosoya *Dicofarm, Ital.*
Infant feed.
Cow's milk intolerance; lactose intolerance.

Formulat Peptidi *Dicofarm, Ital.*
Infant feed.
Cows' milk allergy.

Formulat Pregel *Dicofarm, Ital.*
Infant feed.
Gastro-oesophageal reflux.

Formulat Soya *Dicofarm, Ital.*
Infant feed.
Cow's milk intolerance; lactose intolerance.

Formulation R *G & W, USA.*
⊗Glycerol (p. 2517·2); soft paraffin (p. 2211·3); phenylephrine hydrochloride (p. 1672·3).
Anorectal disorders.

Formulatus *Vicks, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Formule C34 *Naturbec, Canad.*
Piperazine (p. 163·1).
Worm infections.

Formule L2 *Naturbec, Canad.*
Phenazone (p. 124·1); sodium salicylate (p. 132·2).

Formule W *Remark, Neth.*
Salicylic acid (p. 1719·1).
Warts; corns.

Formulex *Valeant, Canad.*
Dicycloverine hydrochloride (p. 1834·2).
Antispasmodic.

Formuly Piel *Assistance, Arg.*
Vitamins; minerals; cystine (p. 2059·1).
Nutritional supplement.

Formuno *Caprifarmindo, Indon.*
Echinacea purpurea (p. 2498·1); phyllanthus niruri (p. 2590·1); black elderberry (p. 2609·3); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Formyco *Sanbe, Indon.; Sanbe, Singapore.*
Ketoconazole (p. 585·3).
Fungal infections; fungal skin and scalp infections.

Formyn *Multilab, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Formyxan *Pisa, Mex.*
Mitoxantrone hydrochloride (p. 833·1).
Breast cancer; non-lymphoblastic leukaemia; non-Hodgkin's lymphoma.

Fornac *Forgo, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Fornac-CZ *Forgo, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Fornac-P *Forgo, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Fornac-SP *Forgo, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Forneuro *Kalbe, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); folic acid (p. 2063·1).
Vitamin B and E deficiency; megaloblastic anaemia.

Fornidd *Sanofi-Aventis, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Forom *NK, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Forone *Forgo, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Forone-SB *Forgo, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Forosa *Sandoz, Gr.; Sandoz, Philipp.; Lek, Rus.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Forotan *Benedetti, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Bronchospasm.

Forpar *Cipla, India.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Forpep *Forgo, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Forres *Kalbe, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Forsace *Fako, Turk.*
Fosinopril sodium (p. 1386·2).

Forsace Plus *Fako, Turk.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).

Forsef *Bilim, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Forses *Forgo, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

ForSlim *Rhema, Singapore.*
Coleus forskohlii.
Slimming aid.

Forsodol *Ozone, Rus.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Forstaf *GSK, India.*
Vancomycin (p. 384·2).
Bacterial infections.

Forsteo *Lilly, Austria; Lilly, Belg.; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hung.; Lilly, Irl.; Lilly, Ital.; Lilly, Neth.; Lilly, Norw.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Elanco, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Turk.; Lilly, UK.*
Teriparatide (p. 1191·2).
Osteoporosis.

Forsuderm *Wooridul, Singapore.*
Sodium fusidate (p. 302·1).
Skin infections.

Fort E *Cazi, Braz.*
dl-Alpha tocoferil acetate (p. 2119·2).

Forta *Nordin, Mex.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Ross, USA.
A range of nutritional supplement preparations.

Forta Shake *Ross, Israel.†*
Preparation for enteral nutrition.

Fortacef *Troikaa, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortacet *Interdelta, Switz.†*
Aluminium acetotartrate (p. 2440·1); chamomile (p. 2474·1); arnica (p. 2447·2).
Skin irritation; insect bites; soft-tissue injuries.

Fortacil *Manuell, Mex.*
Amino acids; minerals.
Tonic; anaemias.

Fortadim *Umeda, Thai.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortafen *Alembic, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Alembic, India.
Topical gel: Aceclofenac (p. 16·2); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Fortafen Plus *Alembic, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Fortaflu *Soho, Indon.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; allergic disorders.

Fortagesic *Sanofi-Aventis, India.*
⊗Paracetamol (p. 115·1); pentazocine (p. 120·3).
Pain.

Fortagyl *Prafa, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Fortakehl *Sanum-Kehlbeck, Ger.; Ebi, Switz.*
Penicillium roquefortii.
Homoeopathic preparation.

Fortal
Note: this name may be used for preparations of different composition.
IFET (ΙΦΕΤ), Gr.
⊗Pentazocine hydrochloride (p. 120·3) or pentazocine lactate (p. 120·3).
Pain.

Sanofi-Aventis, Belg.
⊗Pentazocine (p. 120·3).
Pain.

Fortal Vision *Prisfar, Port.*
Lutein (p. 2079·2); fish oil (p. 1460·1); betacarotene (p. 2051·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Eye disorders.

Fortalis *Interdelta, Switz.*
Methyl salicylate (p. 92·1); salicylic acid (p. 1719·1); formic acid (p. 2507·1); camphor (p. 2466·2); spike lavender oil (p. 2621·3).
Musculoskeletal and joint pain.

Fortam *GSK, Spain; GSK, Switz.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortamet *First Horizon, USA.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Fortamid *Formenti, Ital.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Fortamin *Hexpharm, Indon.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Fortamol *Nordic Drugs, Denm.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Fortanest *Kalbe, Indon.*
Midazolam (p. 1085·1).
Premedication; sedation; general anaesthesia.

Fortapal *GSK, Chile.†*
Ibuprofen (p. 68·2).
Fever; pain.

Fortaplex *Kripps, Canad.*
Vitamin B preparation (p. 2102·3).

Fortasec *Esteve, Spain.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Fortasint *SF, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Bronchospasm.

Fortathrin *Gap, Gr.*
Indometacin (p. 71·2).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Fortavil *Sanitas, Chile.*
⊗Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); deanol tartrate (p. 2319·1).
Tonic.

Fortaz *GSK, Braz.; GSK, Canad.; Glaxo Wellcome, USA.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortazep *Keun Wha, Philipp.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortcinolona *Fortbenton, Arg.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Forte Hirudo *In Vitro, Hung.*
Leech (p. 1418·1); arnica (p. 2447·2).
Soft-tissue injury.

Fortecortin *Merck, Austria; Merck, Cz.; Merck Serono, Ger.; Merck, Spain; Merck, Switz.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Merck, Indon.†
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Fortedol *Teva, Hung.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Fortefog
Note: this name may be used for preparations of different composition.
Agropharm, UK.
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Formerly contained cypermethrin (Fortemethrin), piperonyl butoxide, bioallethrin, and N-octylbicycloheptene dicarboximide.
Insecticide.

Fortege *Alarsin, India.*
Clove (p. 2481·2); piper nigrum; withania somnifera (p. 2450·2); zingiber officinale.

Fortel *Biomerica, USA.*
Fertility test or pregnancy test (p. 2596·1).

Fortelysin *Prafa, Indon.†*
Vitamins; lysine hydrochloride (p. 2079·3); glutamic acid (p. 2070·2); calcium gluconate (p. 1783·3).
Reduced appetite; vitamin supplement.

Forten
Note: this name may be used for preparations of different composition.
Chiesi, Braz.
Amino acids; hydroxocobalamin (p. 2107·3).
Nutritional supplement.

Hexpharm, Indon.†
Captopril (p. 1331·2).
Hypertension; heart failure.

Fortenac *Interdelta, Switz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Forteo *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Hong Kong; Lilly, India; Lilly, Israel; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Philipp.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, USA; Lilly, Venez.*
Teriparatide (p. 1191·2).
Osteoporosis.

Forteprim *Medi-Rx, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Forterra *Help, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Fortesta *Endo, USA.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency.

Fortestomachicae *Herbapol Krakow, Pol.*
St John's wort (p. 449·1); peppermint leaf (p. 1877·1); papaverine hydrochloride (p. 2362·3); valerian (p. 2640·2).
Dyspepsia; reduced appetite; gastrointestinal spasm.

Fortevit *Airela, Braz.*
Iron chelate (p. 2073·1); pyridoxine (p. 2105·3); nicotinamide (p. 2083·1).

Fortevita *Mintlab, Chile.†*
Vitamins.

Fortfen *Aspen, S.Afr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; gout.

Forthane *Abbott, Austral.†; Abbott, NZ.*
Isoflurane (p. 1903·2).
General anaesthesia.

Fortibi *Soho, Indon.*
Morinda citrifolia; zingiber officinale.
Immunostimulant; tonic.

Fortica *ST, Thai.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Hypocalcaemia; osteoporosis; rickets; calcium supplement.

Fortical
Note: this name may be used for preparations of different composition.
Cosme, India.
Suspension: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); lysine (p. 2079·3).

Cosme, India.
Tablets: Minerals; colecalciferol (p. 2113·1).

Serral, Mex.
Diclofenac sodium (p. 48·3); thiamine hydrochloride (p. 2103·1) or thiamine nitrate

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgias; neuropathy.

Tzamal, Israel; Upsher-Smith, USA.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

FortiCare *Nutricia Clinical, UK.*
Preparation for enteral nutrition.

Forticare *Support, Braz.; Nutricia, Cz.; Nutricia, Ital.; Nutricia, Singaporet; SHS, Singapore.†*
Preparation for enteral nutrition.

Forticlav *Sanat, India.*
Amoxicillin trihydrate (p. 216·2) or amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Forticol *Medinfar, Port.*
⊗Deanol acetoglutamate (p. 2319·1); heptaminol hydrochloride (p. 2525·1).
Mental function disorders.

Forticreme *Nutricia, Austral.; Nutricia, Denm.†; Nutricia, Fin.†; Nutricia, Irl.; Nutricia, Ital.†; Nutricia, Port.†; Nutricia Clinical, UK.*
Preparation for enteral nutrition.

Forticrème *Nutricia, Fr.†*
Preparation for enteral nutrition.

Forticrin *Panzera, Ital.*
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); achillea (p. 2427·3); ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Hair loss.

Fortifer *United American, Hong Kong.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); liver (p. 2444·1).
Anaemias.

United American, Philipp.
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Iron deficiency; iron-deficiency anaemia.

Fortifer FA *United American, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia; folate deficiency; prevention of neural tube defects.

Fortified PP *Sarabhai Piramal, India.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).

Fortified Procaine Peni *Alembic, India.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).

Fortifresh *Nutricia, Irl.†; Nutricia Clinical, UK.*
Preparation for enteral nutrition.

Nutricia, Fr.†
High-protein nutritional supplement.

Fortify Complete *Nutricia, Ital.*
Preparation for enteral nutrition.

Fortigel *ProStrakan, Fr.*
⊗Testosterone (p. 2305·1).
Hypogonadism.

Fortijuce *Nutricia, Austral.; Nutricia, Fr.†; Nutricia, Singapore; SHS, Singapore; Nutricia Clinical, UK.*
Preparation for enteral nutrition.

Fortijuice *Nutricia, Irl.; Nutricia, NZ.*
Preparation for enteral nutrition.

Fortil *Constant, India.*
Cyproheptadine (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Fortilan *Ativus, Braz.*
Ginseng (p. 2513·3).
Asthenia.

Fortilut *Gap, Gr.*
Norethisterone (p. 2294·2).
Secondary amenorrhoea; endometriosis; hormone replacement therapy; breast or endometrial cancer.

Fortimax
Note: this name may be used for preparations of different composition.
Medico Uno, Hung.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fortimel *Nutricia, Cz.; Nutricia Clinical, UK.*
Nutritional supplement.

Nutricia, Fr.; Nutricia, Irl.
High-protein nutritional supplement.

Nutricia, Fin.†; Nutricia, Ital.; Nutricia, NZ; Nutricia, NZ.
High-protein preparation for enteral nutrition.

Nutricia, Port.
High protein nutritional supplement.

Fortimicin *Kyowa, Jpn.†*
Astromicin sulfate (p. 220·3).
Bacterial infections.

Fortimin *Vitae, Mex.*
Vitamins; minerals.

Fortine *Bilim, Turk.*
Flurbiprofen (p. 65·2).

Fortini *Nutricia, Denm.†; Nutricia, Fin.†; Nutricia, Fr.†; Nutricia, Irl.; Nutricia, Ital.; Nutricia, NZ; Nutricia, NZ; Nutricia Clinical, UK.*
Preparation for enteral nutrition.

Nutricia, Port.†
Nutritional supplement.

Fortini Multi Fiber *Support, Braz.*
Preparation for enteral nutrition.

Fortini Multi Fibre *Nutricia, Austral.†*
Preparation for enteral nutrition.

Fortinol *Pharmanel, Gr.; Mann, Hung.†; Bausch & Lomb, Ital.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; raised intra-ocular pressure; ocular hypertension.

Fortipine *Goldshield, UK.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Fortisip *Nutricia, Austral.*
Preparations for enteral nutrition.

Nutricia, Fr.†; Nutricia Clinical, UK.
A range of preparations for enteral nutrition.

Nutricia-Bago, Arg.; Nutricia, Irl.; Nutricia, NZ; Nutricia, NZ; Nutricia, Singapore; SHS, Singapore.
Preparation for enteral nutrition.

Fortisone *The Forty-Two, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Fortium *KG, Ital.*
Amino acids; vitamins; creatine (p. 2488·3).
Nutritional supplement.

Fortius *Piramal, India.*
Rosuvastatin (p. 1488·2) or rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias.

Fortix *Inteli, Ukr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Fortofan *Gedeon Richter, Hung.†*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Fortoferin *Bryntsalov, Rus.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortolin *Fortune, Canad.; Fortune, China.*
Paracetamol (p. 115·1).
Pain; fever.

Fortolin Extra *Fortune, Hong Kong.†*
Caffeine (p. 1203·3); paracetamol (p. 115·1).

Fortolin Nite *Fortune, Hong Kong.†*
Paracetamol (p. 115·1); pheniramine (p. 637·2).

Fortonol *Microsules, Arg.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Fortovase *Roche, Arg.*
Saquinavir mesilate (p. 1014·2).
HIV infection.

Roche, Austral.†; Roche, Braz.; Scherer, China; Roche, Gr.; Chugai, Jpn†; Roche, Mex.; Roche, Neth.†; Roche, NZ†; Roche, Rus.; Roche, Singapore; Roche, Thai.†; Roche, Venez.
Saquinavir (p. 1014·2).
HIV infection.

Fortox *Fargo, India.*
Lysine (p. 2079·3); carbohydrate; minerals; nicotinamide (p. 2083·1); protein hydrolysate.

Fortradol *Wassermann, Ital.*
Tramadol hydrochloride (p. 139·2).
Pain.

Fortral *KRKA, Cz.*
⊗Pentazocine (p. 120·3) or pentazocine hydrochloride (p. 120·3).
Pain.

Sanofi-Aventis, Neth.; Sanofi Synthelabo, UK.
⊗Pentazocine hydrochloride (p. 120·3) or pentazocine lactate (p. 120·3).
Pain.

Fortrans *Beaufour-Ipsen, China; Ipsen, Gr.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Ipsen, Cz.; Ipsen, Fr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Malaysia; Beaufour-Ipsen, Pol.; Ipsen, Port.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Ukr.
Macrogol 4000 (p. 2547·3); sodium sulfate (p. 1888·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Bowel evacuation; constipation.

Fortstar *Cadila, India.*
⊗Pentazocine (p. 120·3).
Pain.

Fortum *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fr.; Ratiopharm, Ger.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israelt; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Rus.; Omnimed, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, Venez.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortumset *GSK, Fr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fortusin *Solas, Indon.*
Diphenhydramine hydrochloride (p. 626·2); bromhexine hydrochloride (p. 1656·3); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1); liquorice (p. 1853·2).
Cough.

Fortwin *Ranbaxy, India.*
⊗Pentazocine lactate (p. 120·3).
Pain; premedication.

Fortzaar *MSD, Austria; MSD, Denm.†; MSD-Chibret, Fr.; MSD, Ger.; MSD, Malaysia; MSD, Neth.; MSD, Port.; MSD, S.Afr.; MSD, Spain; MSD, Thai.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; stroke prophylaxis; cardiovascular risk reduction.

Forum C *Strathmann, Ger.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Forumen *Sanbe, Indon.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Forvent *Boehringer Ingelheim, S.Afr.*
Tiotropium bromide (p. 1238·1).
Obstructive airways disease.

Forverm *Elofar, Braz.†*
Mebendazole (p. 158·3); tiabendazole (p. 166·3).
Worm infections.

Forvey *Menarini, Spain.*
Frovatriptan succinate (p. 676·2).
Migraine.

Forvin *Sons, Mex.*
Hydroxocobalamin acetate (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Anaemias; neuritis; neuralgia; neuropathy; vitamin B deficiency.

Forvit *Yarindo, Indon.*
Amino acids; vitamins; calcium gluconate (p. 1783·3).
Nutritional supplement.

Forvite *Lennon, S.Afr.†*
Vitamin B substances (p. 2102·3).
Tonic.

Forxanix *Landsteiner, Mex.*
Ofloxacin (p. 334·3).
Bacterial infections.

Forxiga *AstraZeneca, Denm.; BMS, Denm.; BMS, Neth.; AstraZeneca, UK.*
Dapagliflozin propanediol (p. 470·2).
Diabetes mellitus.

Foryxa *Abdi, Turk.*
⊗Formoterol fumarate (p. 1209·2).

Forza *Ali, Turk.*
Paracetamol (p. 115·1); oxolamine citrate (p. 1671·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Forzaar *SinGad, Denm.†; MSD, Ital.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Forzak *Biosintex, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Forzaten *Menarini, Belg.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Forzaten HCT *Menarini, Belg.*
⊗Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Forzest *Ranbaxy, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

Forzid *United Biotech, India; Kalbe, Philipp.; Atlantic, Thai.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Forzin *Blubell, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Forzole *Fargo, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Forzole Gel *Fargo, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Forzole-D *Fargo, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Fosagen *Aspen, S.Afr.*
Alendronic acid (p. 1171·3).
Osteoporosis.

Fosalan *MSD, Israel.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fosalen *Genepharm, Gr.; Pliva, Irl.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fosamax *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.†; MSD, Irl.; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Abbott, Turk.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone; prevention of fractures.

Fosamax D *MSD, Braz.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Fosamax Plus *MSD, Arg.; MSD, Austral.; MSD, Chile; MSD, China; MSD, Hong Kong; MSD, Indon.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Singapore; MSD, Thai.; Merck, USA.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Fosandron *Iapharm, Gr.*
Alendronate sodium (p. 1171·3).

Fosatur *Cantabria, Spain.†*
Elcatonin (p. 1178·1).
Paget's disease of bone; osteoporosis.

Fosavance *MSD, Austria; MSD, Belg.; Merck Frosst, Canad.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Turk.; MSD, UK.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Fosazom *Vocate, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fosbait *Panacea, India.*
Lanthanum carbonate (p. 1556·2).
Hyperphosphataemia in renal failure.

Fosca-D *Berko, Turk.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1); vitamin C (p. 2110·3).
Osteoporosis.

Foscald3 *FIRMA, Ital.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Foscalvit *Zuoz, Venez.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Foscan *Techsphere, Arg.; Biolitec, Belg.; Biolitec, Cz.; Biolitec, Denm.; Biolitec, Fr.†; Biolitec, Ger.; Biolitec, Gr.; Biolitec, Hung.; Biolitec, Irl.; Biolitec, Israel; Biolitec, Ital.; Biolitec, Neth.; Biolitec, Norw.; Biolitec, Pol.; Biolitec, Port.; Biolitec, UK.*
Temoporfin (p. 865·1).
Photodynamic therapy of head and neck cancer.

Foscavir *AstraZeneca, Austral.; Clinigen, Belg.; AstraZeneca, Braz.; Novex, Fr.; Clinigen, Ger.†; AstraZeneca, Gr.; IFET (ΙΦΕΤ), Gr.; Clinigen, Hung.; Clinigen, Israel; AstraZeneca, Ital.; Nobel, Jpn; Clinigen, Neth.; Clinigen, Norw.†; Clinigen, NZ; Clinigen, Port.; AstraZeneca, Singapore; Clinigen, Spain; Clinigen, Swed.; Proreo, Switz.; Clinigen, UK; Clinigen, USA.*
Foscarnet sodium (p. 981·1).
Cytomegalovirus infections; herpes simplex infections.

Foseal *Emcure, India.*
Sevelamer hydrochloride (p. 1573·1).
Hyperphosphataemia.

Fosemyk *Dekaz, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Fosen *Fahrenheit, Indon.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Fosend *Reddy, India.*
Lanthanum.
Hyperphosphataemia in renal failure.

Fosetic *Spirit, Austral.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosfacid *Collins, Mex.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fosfacol *Sanitas, Arg.*
Sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Fosfafarma *Varifarma, Arg.†*
Dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fosfalax *Lafedar, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Fosfalugel *Astellas, Ital.*
Aluminium phosphate (p. 1818·3).
Gastric hyperacidity.

Fosfamina *Argenfarma, Arg.*
Phospholipids (p. 2201·2); minerals; vitamin B substances (p. 2102·3).
Nutritional supplement.

Fosfarsile Forte *Fitobucaneve, Ital.*
Oral liquid: Royal jelly (p. 2608·1); propolis (p. 2597·3); selenium (p. 2086·3); ginseng (p. 2513·3).
Nutritional supplement.

Fitobucaneve, Ital.†
Tablets: Glucose (p. 2068·3); royal jelly (p. 2608·1); ginseng (p. 2513·3).
Nutritional supplement.

Fosfarsile Junior *Fitobucaneve, Ital.*
Royal jelly (p. 2608·1); vitamins; phosphorus proteinate; cod-liver oil (p. 2056·3).
Nutritional supplement.

Fosfaserin *Amnol, Ital.*
Phosphatidlyserine; glutamine (p. 2070·3); vitamin B substances (p. 2102·3); lecithin (p. 2542·2); caffeine (p. 1203·3); ginseng (p. 2513·3); ginkgo biloba (p. 2512·3).
Nutritional supplement; mental function disorders.

Fosfidex *Pisa, Mex.†*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Fosfitone *Fada, Arg.*
Suxamethonium (p. 2037·1).
Depolarising neuromuscular blocker.

Fosfo Plus *FAMA, Ital.*
Glutamine (p. 2070·3); DL-phosphoserine (p. 2589·1); cyanocobalamin (p. 2107·2).
Tonic.

Fosfoadital *Gobbi, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Fosfobarigraf *Justesa Imagen, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Fosfobion *Sicomed, Rus.*
Adenosine triphosphate sodium (p. 2430·3).
Muscular dystrophy; muscle atony; multiple sclerosis; retinal degeneration; peripheral vascular disorders; supraventricular tachycardia; ischaemic heart disease; labour augmentation.

Fosfocaps *Sigma, Braz.*
Amino acids; vitamins; minerals.

Fosfocil *Senosiain, Mex.*
Fosfomycin calcium (p. 300·3) or fosfomycin sodium (p. 300·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fosfocin *Crinos, Ital.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Fosfocina *Ern, Spain.*
Fosfomycin calcium (p. 300·3) or fosfomycin sodium (p. 300·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fosfocine *Sanofi-Aventis, Fr.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Fosfocrisolo *Zambon, Ital.*
Sodium aurotiosulfate (p. 132·1).
Rheumatoid arthritis.

Fosfo-Dom *Dominguez, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Fosfo-Dom Kit *Dominguez, Arg.*
Oral solution, monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2) (Fosfo-Dom); 4 tablets, bisacodyl (p. 1821·1); 1 suppository, bisacodyl.
Bowel evacuation.

Fosfoevac *Bohm, Spain.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fosfoguaiacol *Ogna, Ital.†*
Guaiacol (p. 1666·1); eucalyptus (p. 2501·1).
Respiratory congestion.

Fosfokalsiyum *Munir, Turk.*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Fosfolax *Coup, Gr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Laxative.

Fosfomik *Finadiet, Arg.*
Terazosin (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Fosfomin *Siam Bheasach, Thai.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Fosfor *Consolidated Chemicals, Irl.†; Ayrton, UK.*
Phosphorylcolamine (p. 2589·3).
Tonic; nutritional supplement.

Fosforal
Note: this name may be used for preparations of different composition.
Etifar, Venez.
Vitamins.
Tonic.

Fosforilasi *Polifarma, Ital.*
Injection: Cocarboxylase (p. 2103·1); riboflavin sodium phosphate (p. 2104·3); pyridoxal phosphate (p. 2105·3); nicotinamide (p. 2083·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Toxicosis; neuritis.

Fosfosoda *Casen Fleet, Spain.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fosfo-Soda Fleet *Casen Fleet, Ital.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

Fosfotonic *Argenfarma, Arg.*
Phospholipids (p. 2201·2); amino acids; vitamin B substances (p. 2102·3); minerals.
Tonic.

Fosfovita *Temis, Arg.*
Lecithin (p. 2542·2); phenylalanine (p. 2086·1); vitamin B substances (p. 2102·3).
Nutritional supplement.

Fosfree *Mission Pharmacal, USA.*
Vitamins; iron (p. 2073·1); calcium (p. 1783·1).
Calcium supplement; nocturnal leg cramping.

Fosgluten Reforzado *Alter, Spain.†*
Calcium magnesium fytate (p. 1553·3); vitamin B substances (p. 2102·3); glutamine (p. 2070·3).
Tonic.

Fosgluten Super Reforcado *Alter, Port.*
Glutamine (p. 2070·3); vitamin B substances (p. 2102·3).
Tonic.

Foshlenn *Raam, Mex.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Fosicard *Actavis, Rus.; Actavis, Ukr.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fosicard H *Actavis, Rus.; Actavis, Ukr.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosicard Plus *Actavis, Hung.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosicol *Gracia, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Fosicomb *BMS, Austria.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosicombi *Menarini, Ital.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosicomp *BMS, Switz.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosinace *Cipla, India.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fosinil *BMS, Belg.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fosinogen *Generics, Cz.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fosinorm *BMS, Ger.†*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fosinorm comp *BMS, Ger.†*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fosipraz *Arrow, Braz.*
Fosinopril (p. 1386·2).

Fosipres *Menarini, Ital.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fosipril *Aspen, Austral.; Julphar, UAE.*
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

Fositen *BMS, Port.; BMS, Switz.†*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fositen Plus *BMS, Port.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fositens *BMS, Austria; Swedish Orphan, Spain.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Fositens Plus *Swedish Orphan, Spain.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Foskina *Glenmark, Philipp.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Foskina-B *Glenmark, Philipp.*
⊗Mupirocin (p. 327·2); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Foslainco *Lainco, Spain.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Fosmicin *Meiji, Indon.; Meiji, Thai.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Meiji, Jpn.
Fosfomycin calcium (p. 300·3).
Bacterial infections.

Fosmicin-S *Meiji, Jpn.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Fosmidex *Dexa, Indon.*
Fosfomycin sodium (p. 300·3).
Prevention of bacterial infections in abdominal surgery.

Fosolin *Zydus, India.*
Fosphenytoin sodium (p. 523·1).
Status epilepticus; seizures.

Fospartan Ginseng *Craveri, Arg.*
Ginseng (p. 2513·3); magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1); adenosine triphosphate (p. 2430·3); vitamin B substances (p. 2102·3).
Tonic.

Fosphen *Intas, India.*
Fosphenytoin sodium (p. 523·1).
Status epilepticus; seizures.

Fosrenol *Shire, Austral.; Shire, Austria; Shire, Belg.; Shire, Canad.; Shire, Cz.; Shire, Denm.; Shire, Fin.; Shire, Fr.; Shire, Ger.; Shire, Gr.; Shire, Hong Kong; Shire, Hung.; Fahrenheit, Indon.; Shire, Israel; Shire, Neth.; Shire, Norw.; Shire, Philipp.; Shire, Port.; Adcock Ingram Critical Care, S. Afr.; Shire, Spain; Shire, Swed.; Opopharma, Switz.; Fresenius Kabi, Thai.; Shire, UK; Shire, USA.*
Lanthanum carbonate (p. 1556·2).
Hyperphosphataemia in chronic renal failure.

Fossical *Medreich, India.*
Risedronate sodium (p. 1189·3).
Paget's disease of bone; osteoporosis.

Fostair *Chiesi, Braz.; 2care4, Denm.; Chiesi, UK.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Fostal *Abbott, Rus.*
Tree pollen allergen extracts (p. 2434·3) (p. 2593·3).
Allergen immunotherapy.

Fosteofos *Arrow, Cz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fostepor *Gerard, Irl.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Foster *Torrex Chiesi, Austria; Chiesi, Ger.; Chiesi, Gr.; Torrex Chiesi, Hung.; Chiesi, Ital.; Chiesi, Neth.; Chiesi, Port.; Chiesi, Rus.; Chiesi, Spain; Chiesi, Turk.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Fosteum *Primus, USA.*
Genistein (p. 2620·3); zinc amino acid chelate (p. 2048·3); colecalciferol (p. 2113·1).
Osteopenia; osteoporosis.

Fostex
Note: this name may be used for preparations of different composition.
Torrex Chiesi, Pol.
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Westwood, USA.
Benzoyl peroxide (p. 1696·1).
Acne.

Fostex Acne Medication Cleansing *Bristol-Myers Products, USA.*
Salicylic acid (p. 1719·1).
Acne; hyperkeratosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fostex Medicated *Westwood-Squibb, USA.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Acne.

Fostimon *Pfizer, Arg.; IBSA, Austria; Mithra, Belg.; Meizler, Braz.; IBSA, Cz.; IBSA, Denm.; IBSA, Fin.; Genevrier, Fr.; IBSA, Hong Kong†; IBSA, Hung.; IBSA, Irl.; IBSA, Israel; IBSA, Ital.; CORNE, Mex.; IBSA, Neth.; IBSA, Norw.; IBSA, Pol.; IBSA, Port.; NordicInfu Care, Swed.; IBSA, Switz.; Ali, Turk.; Pharmasure, UK; IBSA, Ukr.*
Urofollitropin (p. 2312·2).
Female and male infertility.

Fostine *Cadila, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

Fostipur *Angelini, Spain.*
Urofollitropin (p. 2312·2).
Male and female infertility.

Fostoin *Nobel, Jpn.*
Fosphenytoin (p. 523·1).
Status epilepticus; seizures associated with cerebral trauma.

Fostolin *Actavis, Irl.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fosular *Novell, Indon.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Fosval *Saval, Chile.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Fosvital *IMA, Braz.†*
Vitamin B substances (p. 2102·3); amino acids; minerals.
Tonic.

Fotadex *Elea, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Fotamicin *Elea, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Fot-Amsa *Antibioticos, Mex.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fotaram *Sanbe, Indon.; Sanbe, Philipp.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Fotaran *VHB, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Fotax *Neo Quimica, Braz.; M & H, Thai.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Fotex *Elea, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Fotexin *ACME, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Fotexina *Pisa, Mex.*
Cefotaxime sodium (p. 244·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fotia Plus *Bestochem, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Fotia-F *Bestochem, India.*
Benfotiamine (p. 2102·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Fotil *Croma, Austria; Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Ger.; Santen, Gr.; Santen, Hung.; Santen, Neth.†; Santen, Norw.; Santen, Philipp.; Santen, Pol.†; Santen, Rus.; Santen, Swed.*
⊗Pilocarpine hydrochloride (p. 2010·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Fotilan *Ativus, Braz.*
Ginseng (p. 2513·3).
Tonic.

Fotobloc *Panalab, Arg.*
SPF 20; SPF 25: Melanin (p. 1711·1).
Sunscreen.

Fotocollyre *Rafarm, Gr.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Fotocrem *Investi, Arg.*
SPF 15: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Fotocrem 50 *Investi, Arg.*
Cream SPF 50: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); diethylamino hydroxybenzoyl hexyl benzoate; titanium dioxide (p. 1725·1).
Sunscreen.

Investi, Arg.
Foam SPF 50: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); diethylamino hydroxybenzoyl hexyl benzoate; bisoctrizole (p. 1697·1).
Sunscreen.

Fotocrem P *Investi, Arg.*
SPF 34: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

ITF, Chile.
Titanium dioxide (p. 1725·1).
Sunscreen.

Fotocrem Ultra *Valeant, Arg.*
SPF 42; SPF 48: Octinoxate (p. 1715·1); meradimate (p. 1711·2); avobenzone (p. 1695·1); melanin (p. 1711·1); titanium dioxide (p. 1725·1).
Sunscreen.

Fotofil *INTES, Ital.*
⊗Sodium aminobenzoate (p. 2617·2); actinoquinol (p. 2429·3); naphazoline nitrate (p. 1669·3); borax (p. 2459·2).
Conjunctivitis; blepharitis; corneal damage.

Fotoprotector *Isdin, Arg.*
SPF 15: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Isdin, Arg.
SPF 25: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1); octocrilene (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Fotoprotector Extrem *Isdin, Arg.*
Gel SPF 26: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); bisoctrizole (p. 1697·1).
Sunscreen.

Isdin, Arg.
Lotion SPF 36: Lotion SPF 50+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1).
Sunscreen.

Isdin, Arg.
Cream SPF 50+: Bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); bemotrizinol (p. 1695·3); cinnamate; ensulizole (p. 1703·1); enzacamene (p. 1703·2).
Sunscreen.

Isdin, Arg.
Gel cream SPF 40: Gel cream SPF 50+: Bisoctrizole (p. 1697·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); octocrilene (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Isdin, Arg.
Gel SPF 40: Octocrilene (p. 1715·2); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1); avobenzone (p. 1695·1); amiloxate (p. 1694·1).
Sunscreen.

Isdin, Arg.
Moisturizing lotion SPF 50+: Bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); cinnamate; ensulizole (p. 1703·1); octocrilene (p. 1715·2); enzacamene (p. 1703·2).
Sunscreen.

Fotoprotector Extrem Pediatrics *Isdin, Arg.*
SPF 40; SPF 50+: Bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); bemotrizinol (p. 1695·3); cinnamate; ensulizole (p. 1703·1); enzacamene (p. 1703·2).
Sunscreen.

Fotoprotector Extrem UVA *Isdin, Arg.†*
SPF 26: Bisoctrizole (p. 1697·1).
Sunscreen.

Fotoprotector Extrem UVA Plus *Isdin, Arg.†*
Titanium dioxide (p. 1725·1); bisoctrizole (p. 1697·1); octinoxate (p. 1715·1).
Sunscreen.

Fotoprotector Isdin-50 *Isdin, Chile.†*
SPF 50: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); enzacamene (p. 1703·2); zinc oxide (p. 1729·1).
Sunscreen.

Fotoprotector Isdin Dry Oil *Isdin, Chile.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); enzacamene (p. 1703·2); isocotrizinol (p. 1706·1); avobenzone (p. 1695·1).
Sunscreen.

Fotoprotector Isdin Extrem *Isdin, Chile.*
Gel-cream: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); isopropyl palmitate (p. 2191·1); avobenzone (p. 1695·1).
Sunscreen.

Isdin, Chile.
Lotion: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1).
Sunscreen.

Isdin, Chile.†
Gel SPF 25: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); octocrilene (p. 1715·2); enzacamene (p. 1703·2); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Sunscreen.

Fotoprotector Isdin Extrem Pediatrics *Isdin, Chile.*
Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); enzacamene (p. 1703·2); bemotrizinol (p. 1695·3); octil triazone (p. 1715·1).
Sunscreen.

Fotoprotector Isdin Extrem Plus *Isdin, Chile.†*
Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Fotoprotector Isdin F-15 *Isdin, Chile.†*
Topical gel: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Isdin, Chile.†
Stick SPF 15: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Fotoprotector Isdin-25 Pediatrics *Isdin, Chile.†*
Lotion SPF 25: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); ensulizole (p. 1703·1).
Sunscreen.

Isdin, Chile.†
Topical spray SPF 25: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1).
Sunscreen.

Fotoprotector Isdin Ultra 65 *Isdin, Chile.†*
Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); ensulizole (p. 1703·1); bemotrizinol (p. 1695·3).
Sunscreen.

Fotoprotector Isdin Ultra 90 *Isdin, Chile.†*
Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); ensulizole (p. 1703·1); bemotrizinol (p. 1695·3).
Sunscreen.

Fotoprotector Pediatrics *Isdin, Arg.†*
SPF 45; SPF 25: Bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); bemotrizinol (p. 1695·3).
Sunscreen.

Fotoprotector Ultra *Isdin, Arg.*
SPF 65; SPF 90: Bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); octinoxate (p. 1715·1); ensulizole (p. 1703·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1).
Sunscreen.

Fotoprotectores *Isdin, Port.*
SPF 15; SPF 20; SPF 25; SPF 40; SPF 50: A range of sunscreen preparations.

Silesia, Chile.
Cream SPF 50: MPI.
Sunscreen.

Silesia, Chile.
Cream SPF 20: MPI; cinnamate (p. 1699·2).
Sunscreen.

Silesia, Chile.
Milk: Dihydroxyacetone (p. 1700·1).
Tanning aid.

Silesia, Chile.
Stick SPF 20: Titanium dioxide (p. 1725·1); cinnamate (p. 1699·2).
Sunscreen.

Fotoprotetor Isdin *Medley, Braz.†*
SPF 50: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); zinc oxide (p. 1729·1).
Sunscreen.

Fotoprotetor Isdin Extrem *Isdin, Braz.*
Lotion SPF 25: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1).
Sunscreen.

Medley, Braz.
Topical gel/cream SPF 25: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1).
Sunscreen.

Fotoprotetor Isdin Extrem Infantil *Medley, Braz.†*
Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2).
Sunscreen.

Fotoprotetor Isdin Extrem UVA *Medley, Braz.†*
Gel: Bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1).
Sunscreen.

Fotoprotetor Isdin Infantil *Medley, Braz.†*
Titanium dioxide (p. 1725·1); enzacamene (p. 1703·2).
Sunscreen.

Fotoprotetor Spray Isdin *Medley, Braz.†*
SPF 25: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1).
Sunscreen.

Fotoral *Valeant, Mex.*
Vitamins; minerals.

Fotorretin *Poen, Arg.*
Phenylephrine (p. 1672·2); tropicamide (p. 2012·2).
Production of mydriasis.

Roemmers Poen, Venez.
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Fotosol *Cassara, Arg.; D & M, Chile.*
SPF 19: SPF 30: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1).
Sunscreen.

Fotosol Cassara *D & M, Chile.†*
SPF 19: Bisoctrizole (p. 1697·1); octinoxate (p. 1715·1).
Sunscreen.

Fotosol Ultra *D & M, Chile.*
SPF 50: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1).
Sunscreen.

Cassara, Arg.; D & M, Chile.†
SPF 32: SPF 32: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1).
Sunscreen.

Fotosol Ultra 50 *Cassara, Arg.*
Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1).
Sunscreen.

Fotosol Ultra Autobronceante *Cassara, Arg.*
SPF 32: Dihydroxyacetone (p. 1700·1); octinoxate (p. 1715·1); bisoctrizole (p. 1697·1).
Sunscreen; tanning aid.

Fototar *ICN, USA.*
Coal tar (p. 1723·2).
Psoriasis; seborrhoeic dermatitis.

Fotrec DHA *Visufarma, Ital.*
Docosahexaenoic acid (p. 1460·1); omega-3 triglycerides (p. 1460·3).
Nutritional supplement.

Foucacillin *Coup, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Fouch *Rafarm, Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial skin and vaginal infections.

Foudaril *Gap, Gr.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Fourderm *Cipla, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Fourderm AF *Cipla, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin (p. 304·2); clotrimazole (p. 576·2).
Infected skin disorders.

Fourts-B *Fourrts, India.*
Acetylcysteine (p. 1652·2); vitamins; trace elements; amino acids.

Fouz *JB Chemicals, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Fovas *Cadila, India.*
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

Fovital *Bial, Port.*
Folic acid (p. 2063·1).

Fovit-D3 *Forgo, India.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; hypocalcaemia; hypoparathyroidism.

Foxa *Sykocure, India.*
Fluvoxamine (p. 425·3).
Depression; obsessive-compulsive disorder; social phobia.

Foxair *GSK, S.Afr.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Foxantal *Sanofi-Aventis, Neth.†*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Foxeteva *Med, Turk.*
Fluoxetine hydrochloride (p. 417·1).

Foxetin *Gador, Arg.; GPO, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder; mixed anxiety-depressive states.

Foxgoria *Nida, Singapore.*
Norfloxacin (p. 333·3).
Urogenital infections; gonorrhoea.

Foxil
Note: this name may be used for preparations of different composition.
Sarabhai Piramal, India.
Lomefloxacin (p. 319·2).
Bacterial infections.

Foxim *Kalbe, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Foximet *Korea United, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Foxin *Pharmaland, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Foxinon *M & H, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Foxitin *Orchid, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Foxitina *Pentafarma, Port.†*
Levofloxacin (p. 315·3).
Bacterial infections.

Foxolin *Gap, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Foxtin *Ipca, Singapore.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia; premenstrual dysphoric disorder.

Foxydol *Forgo, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Foy *Lepetit, Ital.; Ono, Jpn.*
Gabexate mesilate (p. 2508·2).
Pancreatitis; disseminated intravascular coagulation.

Fozal *Westmont, Philipp.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Fozide *BMS, Gr.*
⊗Fosinopril (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

BMS, Rus.
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Foziretic *Merck Serono, Fr.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fozitec *Merck Serono, Fr.*
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

Foznol *Shire, Irl.; Shire, Ital.*
Lanthanum carbonate (p. 1556·2).
Hyperphosphataemia in renal failure.

Fozole *Forgo, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Fozole-D *Forgo, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Fozyme *Forgo, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

FP Tab *Efupi, Jpn.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

F-Patarmol *Frankin, Hong Kong.†*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

F-Piridon *Frankin, Hong Kong.†*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

F-Podofim *Frankin, Hong Kong.†*
Podophyllum (p. 1717·1); salicylic acid (p. 1719·1).

FPP *Alembic, India.*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2).

F-Psorin *Mediapharm, Gr.*
Calcipotriol (p. 1697·2).
Psoriasis.

FPZ *Triton, India.*
Fluphenazine (p. 1075·1).
Mania; psychoses.

Fracitin *Ashford, Singapore.*
Framycetin sulfate (p. 301·2).
Bacterial ear or eye infections.

Fractal *Pierre Fabre, Fr.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction following coronary angioplasty.

Fractopon *Intermed, Gr.*
Aceclofenac (p. 16·2).

Frade *Gufic, India.*
Framycetin (p. 301·2).
Skin infections.

Frademicina *Janssen-Cilag, Arg.*
Lincomycin (p. 317·1).
Respiratory-tract infections.

Pfizer, Braz.
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Fradilen *Thea, Port.*
Chromocarb diethylamine (p. 2477·1).
Capillary fragility.

Frador *Trinity, UK.*
Menthol (p. 2553·2); chlorobutanol (p. 1747·2); storax (p. 2622·3); benzoin (p. 2624·3).
Mouth ulcers.

Wilson, NZ.†
Menthol (p. 2553·2); chlorobutanol (p. 1747·2); storax (p. 2622·3).
Mouth ulcers.

Fragador *Weleda, UK.*
Cochlearia offic.; conchae (p. 1824·3); fragaria vesca fruit; glycogen (p. 2519·2); lovage (p. 2545·3); mel (p. 2072·1); natrium carb. (p. 2617·3); pimpinella anisum fruit (p. 2444·2); sage leaves (p. 2608·3); wheat germ (p. 2647·1); urtica leaves (p. 2639·3); ferrum phos (p. 2077·1).
Homoeopathic preparation.

Weleda, S.Afr.†
Cochlearia officinalis; conchae; fragaria vesca; glycogenum; levisticum root; sodium carbonate (p. 2617·3); aniseed (p. 2444·2); sage (p. 2608·3); urtica (p. 2639·3); triticum vulgaris; vivianit.
Nervous disorders.

Fragilis *Faran, Gr.*
Glucosamine sulfate (p. 2515·3).

Fragmin *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia Upjohn, India; Pfizer, Israel; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.†; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Eisai, USA; Pfizer, Venez.*
Dalteparin sodium (p. 1348·3).
Thromboembolic disorders; myocardial infarction; unstable angina; prevention of clotting in extracorporeal circuits.

Fragmine *Pfizer, Fr.*
Dalteparin sodium (p. 1348·3).
Thromboembolic disorders; prevention of clotting during haemodialysis; unstable angina; myocardial infarction.

Fragrance-Free Spray Sunscreen *Kinesys, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Frakas *Aspen, Austral.*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Frakidex *Bausch & Lomb, Belg.; Chauvin, Fr.; Chauvin, Hong Kong; Bausch & Lomb, Port.; Bausch & Lomb, Singapore; Chauvin, Singapore; Bausch & Lomb, Switz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); framycetin sulfate (p. 301·2).
Infected eye disorders.

Framacin *Medic+Aid, Philipp.†*
Rifampicin (p. 350·3).
Tuberculosis; nasopharyngeal carriers of Neisseria meningitidis.

Framagon *Bangkok Lab & Cosmetic, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Bronchospasm.

T-Boma, Hong Kong.†
⊗Terbutaline (p. 1228·1).
Obstructive airways disease.

Frame *Triton, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Framebin *Pisa, Mex.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Framex *Gedeon Richter, Rus.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Framykoin *Biomedica, Cz.; Zentiva, Cz.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Infected skin disorders; wounds; ulcers.

Framyxone *Jolly-Jatel, Fr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); framycetin sulfate (p. 301·2); polymyxin B sulfate (p. 342·3).
Ear infections.

Francetin *Mochida, Jpn.*
Neomycin sulfate (p. 330·1).
Ulcers and wounds with bacterial infection.

Frangerton *Medinova (Μεντινοβα), Gr.*
Indometacin (p. 71·2).

Frankacin-T *Vickmans, Hong Kong.†*
Clindamycin (p. 269·3).

Franol
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Braz.
⊗Ephedrine sulfate (p. 1663·2); theophylline (p. 1229·3).
Bronchospasm.

Sanofi-Aventis, Thai.
Theophylline (p. 1229·3).
Obstructive airways disease.

Franxit *Intas, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Franzbranntwein *Klosterfrau, Ger.†*
Camphor (p. 2466·2); pumilio pine oil (p. 2591·1).
Musculoskeletal and joint pain; soft-tissue disorders.

Frateline *Chemica, Gr.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Frauline *Piramal, India.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Fraurs *Francia, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; biliary disorders.

Fravit *Degorts, Mex.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Vitamin deficiency.

Fravitan *Degorts, Mex.*
Vitamins; minerals.

Fraxicilline *Vilco, Gr.*
Ampicillin (p. 218·2).
Bacterial infections.

Fraxiforte *GSK, Switz.*
Nadroparin calcium (p. 1443·2).
Deep-vein thrombosis.

Fraxiparin *GSK, Austria; GSK, Ger.*
Nadroparin calcium (p. 1443·2).
Thromboembolic disorders; prevention of clotting during haemodialysis and haemofiltration.

Fraxiparina *Sanofi-Aventis, Braz.; GSK, Ital.; GSK, Port.; GSK, Spain; GSK, Venez.*
Nadroparin calcium (p. 1443·2).
Prevention of clotting during haemodialysis; thromboembolic disorders; unstable angina.

Fraxiparine *GSK, Arg.; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Turk.; Sanofi Synthelabo, Turk.; GSK, Ukr.*
Nadroparin calcium (p. 1443·2).
Thromboembolic disorders; unstable angina; myocardial infarction; prevention of clotting in extracorporeal circuits.

Fraxiven *Progen, Ital.*
Rutoside (p. 2505·3); centella (p. 1698·3); melilot (p. 2552·3).
Circulatory disorders; haemorrhoids.

Fraxodi *GSK, Belg.; GSK, China; GSK, Fr.; GSK, Ger.; GSK, Hung.; GSK, India; GSK, Ital.; Sanofi Synthelabo, Mex.†; GSK, Neth.; GSK, Pol.; GSK, Port.; GSK, Turk.; Sanofi Synthelabo, Turk.*
Nadroparin calcium (p. 1443·2).
Thromboembolic disorders; prevention of clotting during haemodialysis; unstable angina.

Fray Romano *Ximena Polanco, Chile.*
Honey (p. 2072·1); aloe vera (p. 1693·2).
Tonic.

Frazole *Zim, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Frazoline *Bouchara-Recordati, Hong Kong.†*
⊗Framycetin sulfate (p. 301·2); naphazoline nitrate (p. 1669·3); amylocaine hydrochloride (p. 1979·3).
Nasal infection and congestion.

Frazon *Ferron, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

FreAmine *Eczacibasi-Baxter, Turk.; Victus, Venez.*
Amino acids.
Parenteral nutrition.

FreAmine III *Baxter, Ital.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Braun, Canad.†; Braun, USA.
Amino acids.
Parenteral nutrition.

FreAmine HBC *Braun, Spain; McGaw, USA.*
Amino acids.
Parenteral nutrition.

Freathe *Nycomed, Gr.*
⊗Ciclesonide (p. 1626·3).
Obstructive airways disease.

Frebac *Macrophar, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection of skin, wounds, and instruments.

Frebini *Fresenius Kabi, Chile; Fresenius Kabi, Denm.; Fresenius Kabi, UK.*
A range of preparations for enteral nutrition in children.

Fresenius Kabi, Irl.
Range of preparations for enteral nutrition.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fresenius Kabi, Turk.
A range of preparations for enteral nutrition.

Fre-bre *Self-Care Products, UK.*
Parsley seed (p. 2583·3); peppermint oil (p. 1877·1); spearmint oil (p. 2621·2).

Freccia *Arrowblue, Port.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Frecoseryl *Bausch & Lomb, China.*
Chondroitin sulfate (p. 2476·1); sodium hyaluronate (p. 2526·2).
Eye disorders.

Fredam *Novell, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Fredex *Bausch & Lomb, China.*
⊗Neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2); sodium hyaluronate (p. 2526·2).
Infected eye and ear disorders.

Frednil *Orchid, India.*
Vitamins; selenious acid (p. 2087·1); zinc sulfate (p. 2126·2).

Fredofol *Kleva, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Fredol *Medipharm, Chile.*
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); caffeine (p. 1203·3); chlorphenamine (p. 620·3).
Vascular headache.

Fredyr *Rafarm, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Fredyren *Rafarm, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Free & Clear *Pharmaceutical Specialties, USA.*
Skin cleanser.

Free M *Universal Medicare, India.*
Glucosamine sulfate (p. 2515·3); calcium hydrogen phosphate (p. 1783·3); manganese sulfate (p. 2081·2); vitamin C (p. 2110·3).

Freecad *Wockhardt, India.*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3).
Prevention of cataract and macular degeneration; skin disorders; ischaemic heart disease.

Freedavite *Freeda, USA.*
Vitamins; minerals; iron (p. 2073·1).

Freederm *Dendron, UK.*
Nicotinamide (p. 2083·1).
Acne.

Freederm pH Balance Shampoo *Schering-Plough, Hung.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Freederm Tar *Schering-Plough, Pol.†; Schering-Plough, Rus.*
Coal tar (p. 1723·2).
Seborrhoeic dermatitis; scalp psoriasis.

Freederm Tar Shampoo *Schering-Plough, Hung.*
Coal tar (p. 1723·2).
Scalp disorders.

Freederm Zinc *Schering-Plough, Rus.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Freederm Zinc Shampoo *Schering-Plough, Hung.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Freedom *Magnus, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Freedom Forte *Magnus, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Freedox *Pharmacia Upjohn, Rus.*
Tirilazad mesilate (p. 1515·1).
Subarachnoid haemorrhage in men.

Freeflex *Universal Medicare, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Freeflex Cloruro Sodico *Fresenius Kabi, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Freeflex Glucosa *Fresenius Kabi, Spain.*
Glucose (p. 2068·3).
Fluid disorders; parenteral nutrition.

Freeflex Glucosalina *Fresenius Kabi, Spain.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Freeflex Ringer Lactato *Fresenius Kabi, Spain.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Freenal *Ache, Braz.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Freescab *BMW, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).

Freesept *Rider, Chile.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat hygiene.

Freestom *Sanofi-Aventis, Irl.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Freestyle *Abbott, Irl.†; Abbott Diagnostics, Ital.; Abbott Diabetes Care, UK.*
Test for glucose in blood (p. 2516·3).

Freetop *Janssen-Cilag, Venez.*
Ketoconazole (p. 585·3).
Scalp disorders.

Freezone *SA Druggists Self Med, S.Afr.†; Whitehall, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis; corns; calluses.

Frego *Kalbe, Indon.*
Flunarizine (p. 629·3).
Migraine; cerebral and peripheral vascular disorders.

Freka-cid *Stada, Hong Kong†; Stada, Malaysia†; Stada, Thai.†*
Povidone-iodine (p. 1767·1).
Burns; skin infections; wounds; skin disinfection.

Freka-Clyss *Fresenius Kabi, Ger.†; Fresenius Kabi, Switz.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation; constipation.

Freka-Derm *Fresenius Kabi, Ger.†*
⊗Alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1); orthophenylphenol (p. 1762·3); clorophene (p. 1748·3).
Skin disinfection.

Freka-Drainjet *Fresenius Kabi, Ger.†*
Sodium chloride (p. 1795·1).
Irrigation fluid.

Freka-Drainjet Purisole *Fresenius Kabi, Ger.†*
⊗Sorbitol (p. 2092·1); mannitol (p. 1427·3).
Bladder irrigation.

Freka-Nol *Fresenius Kabi, Ger.†*
⊗Alcohol (p. 1733·1); glyoxal (p. 1754·1); didecyldimethylammonium chloride (p. 1750·3).
Surface and instrument disinfection.

Freka-Sept 80 *Fresenius Kabi, Ger.†*
⊗Alcohol (p. 1733·1); orthophenylphenol (p. 1762·3); clorophene (p. 1748·3); benzalkonium chloride (p. 1737·1).
Hand disinfection.

Freka-Steril *Fresenius Kabi, Ger.†*
Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3).
Hand disinfection; skin disinfection.

FrekaVit *Fresenius Kabi, Ger.; Paesel, Ger.*
Vitamins.
Parenteral nutrition.

Fremet *Recordati, Spain.†*
Cimetidine (p. 1827·1).
Acid aspiration; gastrointestinal haemorrhage; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; short-bowel syndrome; Zollinger-Ellison syndrome.

Fremid *Euro-Med, Philipp.*
⊗Furosemide (p. 1387·1).
Oedema; heart failure; nephrotic syndrome; hypertension; liver cirrhosis.

Fremomet *Frezyderm, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Fremov *East West, India.*
Capsules: Glucosamine sulfate (p. 2515·3); dimethyl sulfone (p. 2493·3).
East West, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Fremov-ME *East West, India.*
Glucosamine sulfate (p. 2515·3); dimethyl sulfone (p. 2493·3); mecobalamin (p. 2108·1); vitamin E acetate (p. 2119·2).

Fremptel *Ranbaxy, Port.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Frenac Plus *Waves, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Frenacil *McNeil, Spain.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucous.

Frenac-MR *Waves, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Frenactil *Janssen-Cilag, Belg.; Euro Registratie, Neth.†*
Benperidol (p. 1041·1).
Delirium; hallucinations; agitation; sexually deviant behaviour; nausea and vomiting; psychoses.

Frenadol *Johnson & Johnson, Spain.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Influenza and cold symptoms; pain; fever; cough.

Frenadol Complex *Johnson & Johnson, Spain.*
Ascorbic acid (p. 2110·3); caffeine citrate (p. 1203·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold and influenza symptoms; cough; pain; fever.

Frenadol Descongestivo *Johnson & Johnson, Spain.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Formerly known as Frenadol PS.
Cold and influenza symptoms; pain; fever; cough.

Frenagar *Johnson & Johnson, Spain.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat infections.

Frenagial *McNeil, Spain.†*
Paracetamol (p. 115·1).
Fever; pain.

Frenal *Sigma-Tau, Spain.†*
Sodium cromoglicate (p. 1225·3).
Asthma; bronchospasm.

Frenal Compositum *Sigma-Tau, Spain.†*
⊗Sodium cromoglicate (p. 1225·3); isoprenaline sulfate (p. 1411·3).
Asthma; allergic bronchitis.

Frenaler *Laboratorios Chile, Chile.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Roemmers, Arg.
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Frenaler Cort *Roemmers, Arg.*
⊗Desloratadine (p. 625·1); betamethasone (p. 1623·2).
Hypersensitivity disorders.

Frenaler-D *Laboratorios Chile, Chile.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine sulfate (p. 1676·1).
Nasal congestion; rhinitis; sinusitis.

Frenalgil *Jaba, Port.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Frenasal *Johnson & Johnson, Spain.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Frenasma *Angelini, Gr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Frenatermin *McNeil, Spain.†*
Ibuprofen sodium (p. 68·2).
Pain; fever; inflammation.

Frenatus *McNeil, Spain.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

French Parad'ox Plus *Arkopharma, Singapore.*
Grape extract (p. 2521·3).
Antoxidant dietary supplement.

Frend *KlarSehen, India.*
Vitamins; trace elements.

Frenidor *Confar, Port.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Frenin *Samarth, India.*
Phenylephrine (p. 1672·2).
Hypotension; paroxysmal supraventricular tachycardia.

Frenolyn *Medochemie, Singapore.*
⊗Budesonide (p. 1625·1).
Asthma.

frenopect *Riemser, Ger.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Frenotos *Columbia, Arg.*
Oxeladin citrate (p. 1671·2).
Cough.

Recalcine, Chile.
Zipeprol hydrochloride (p. 1680·3).
Cough.

Frenotos Muc *Columbia, Arg.*
Oxeladin citrate (p. 1671·2); bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Frenotosse *Cimed, Braz.*
Bromoform (p. 2460·3); tolu balsam (p. 1679·2); sodium benzoate (p. 1738·2).
Cough.

Frenurin *UCI, Braz.*
Oxybutynin hydrochloride (p. 2361·2).
Urinary-tract disorders.

Fres Diab *Simex, Indon.*
Thioctic acid (p. 2629·1); cyanocobalamin (p. 2107·2); chromium picolinate (p. 2056·1).
Diabetic neuropathy.

Frescansol *Volta, Chile.*
Borax (p. 2459·2); sodium bicarbonate (p. 1781·1); boric acid (p. 2459·3).
Hyperhidrosis.

Fresco
Note: this name may be used for preparations of different composition.
Genesis, India.
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Rekah, Israel.
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; peptic ulcer.

Freselamin *Biosel, Turk.†*
Amino acids.
Parenteral nutrition.

Fresenizol *Fresenius Kabi, Mex.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Fresh Clear *Allergan, Braz.*
Phenylephrine hydrochloride (p. 1672·3); polyvinyl alcohol (p. 2204·2).

Fresh Cooling Body Mist *Johnson & Johnson, Canad.*
SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fresh Power Gold *Gemini, Canad.*
Triclosan (p. 1773·2).

Fresh Tears *Allergan, Braz.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Freshex *Forgo, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Freshkote *Focus, USA.*
Povidone (p. 2204·3); polyvinyl alcohol (p. 2204·2).
Dry eyes.

Freshmel *Laboratorios Chile, Chile.*
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat infections.

Freshmel Tos *Laboratorios Chile, Chile.*
Chlorhexidine hydrochloride (p. 1743·3); noscapine (p. 1670·3).
Cough; mouth and throat infections.

Fresh-N-Free *Geritrex, USA.*
Chlorhexidine (p. 1743·2); chlorophyll complex (p. 2178·3).
Oral hygiene.

Freshta Plus *Sienna, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Freshta-DS *Sienna, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Fresky *Aamorb, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Fresofol *Fresenius Kabi, Arg.; Fresenius Kabi, Austral.; Fresenius Kabi, Hong Kong; Fresenius Kabi, India; Fresenius Kabi, Indon.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Mex.; Fresenius Kabi, NZ; Fresenius Kabi, Philipp.; Fresenius Kabi, Singapore; Fresenius Kabi, Thai.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Fresomega *Fresenius Kabi, Mex.*
Omega-3 marine triglycerides (p. 1460·3).
Parenteral nutrition.

Fresubin *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; SSPC, China; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Irl.; Fresenius Kabi, Ital.; Fresenius Kabi, Pol.†; Prisfar, Port.†; Fresenius Kabi, Turk.; Fresenius Kabi, UK.*
A range of preparations for enteral nutrition.

Fresenius Kabi, Cz.; Fresenius Kabi, Indon.; Fresenius Kabi, Mex.; Fresenius Kabi, Philipp.
Preparation for enteral nutrition.

Fresubin Hepa *Fresenius Kabi, India.*
A range of preparations for enteral nutrition.

Fresenius Kabi, Singapore.
Preparation for enteral nutrition in liver disorders.

Fretic *Vendiz, Philipp.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Frevia *AstraZeneca, Arg.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Frexene *Life Concern, Thai.*
Dipotassium clorazepate (p. 1056·3).

Frexocel *Novartis, Gr.*
Lumiracoxib (p. 84·1).
Osteoarthritis.

Freze *Crescent, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Frezep *Mandar, India.*
Selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Frezylin *Frezyderm, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Frialgina
Note: this name may be used for preparations of different composition.
Uriach, Spain.†
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

Friars Balsam *Thornton & Ross, UK.*
Storax (p. 2622·3); sumatra benzoin (p. 2624·3).
Cold symptoms; topical antiseptic.

Friar's Balsam *Rougier, Canad.*
Aloes (p. 1816·1); benzoin; myroxylon balsamum; storax (p. 2622·3).

Fribat *Epifarma, Ital.*
Ceftazidime (p. 250·2).
Bacterial infections.

Friccion Aromatica *Gache, Venez.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Friccion Don Juan *Sophia, Mex.†*
Methyl salicylate (p. 92·1).
Musculoskeletal pain.

Fricold
Note: this name may be used for preparations of different composition.
Farline, Spain.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Leben, India.
Oral suspension: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Leben, India.
Tablets: Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Fricsol *Konsuma, Venez.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Fricsolgel *Konsuma, Venez.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Fridalit *Fada, Arg.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Fridep *Mersifarma, Indon.*
Sertraline hydrochloride (p. 448·1).
Depression.

Friendly Flora *Future, Canad.*
Bifidobacterium bifidum (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3).
Restoration of gastrointestinal flora.

Frifloxacina *Sant Gall, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Frigrip *Otto, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Influenza symptoms; cough.

Friladar *Interbat, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Frilans *CT, Ital.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Frilen *Offenbach, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Friliver Sport *Bracco, Ital.*
A range of nutritional supplements.

Frilix *Pharos, Indon.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders.

Frimaind *SoSe, Ital.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Frimania *Mersifarma, Indon.*
Lithium carbonate (p. 427·3).
Bipolar depression; aggression; self-harm.

Frimig *Orion, Pol.*
Sumatriptan succinate (p. 679·2).
Migraine.

Frimuce *Farline, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Frina *Velka, Gr.*
⊗Propranolol hydrochloride (p. 1479·1).

Frineg *Epifarma, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Frinova *Sanofi-Aventis, Spain.†*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting.

Friobax *Degorts, Mex.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Rhinitis; upper respiratory-tract congestion.

Friomax *Tetrafarm, Arg.*
Menthol (p. 2553·2); camphor (p. 2466·2).

Frionex *Wierhom, Arg.*
Pentane (p. 2201·1); butane (p. 1797·2).
Pain.

Friorub *Hofmann, Chile.*
Menthol (p. 2553·2).
Musculoskeletal and soft-tissue injury.

Fripeintil *Leontik, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Fripi *Monserrat, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Fripos *Nufarindo, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); ascorbic acid (p. 2110·3); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2).
Joint disorders.

Friresp *Farline, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Frisium *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Lundbeck, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sandoz, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Singapore; Aventis, Thai.; Sanofi-Aventis, Thai.; Aventis, UK; Sanofi-Aventis, Venez.*
Clobazam (p. 518·2).
Anxiety; epilepsy; psychosomatic disorders; sleep disorders.

Friso Comfort *Friesland, Singapore.*
Infant feed.
Vomiting; infant colic.

Frisolac Comfort *Dutch Lady, Malaysia.*
Infant feed.
Infant colic; vomiting; constipation.

Frisolac Soy *Friso, Hong Kong.†*
Infant feed.
Cows' milk intolerance; lactose intolerance.

Frisolona *Allergan, Port.*
⊗Prednisolone acetate (p. 1645·2).
Eye disorders.

Frisomum *Friesland, Singapore.*
Nutritional supplement.

Frisocare, Hong Kong.
Preparation for enteral nutrition.
Pregnancy and lactation.

Frisomum Gold *Dutch Lady, Malaysia.*
Nutritional supplement for pregnant and breastfeeding women.

Frisosoy *Friesland, Singapore.*
Soya-based infant feed.

Frisocare, Hong Kong.†
Infant feed.
Cow's milk protein allergy; lactose intolerance.

Frisovom *Friesland, Singapore.*
Infant feed.
Vomiting; colic; constipation.

Fri-Spas *Invision, India.*
Simeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2).

Frispas-P *Invision, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Frispec *Farline, Spain.*
Guaifenesin (p. 1666·2).
Cough.

Fristamin *FIRMA, Ital.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Fritens *Kalbe, Indon.*
Irbesartan (p. 1411·1).
Hypertension.

Fritusil *Farline, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Fritussin *Vickmans, Hong Kong.†*
⊗Ephedrine (p. 1663·1); ethylmorphine hydrochloride (p. 56·3); ipecacuanha (p. 1667·2); squill (p. 1677·3).

Frivent *Schering-Plough, Ital.*
Theophylline (p. 1229·3).
Asthma; bronchospasm.

Frixio *Laboratorios Chile, Chile.†*
Methyl salicylate (p. 92·1); methyl nicotinate (p. 91·3).
Musculoskeletal and joint disorders.

Frixitas *Novell, Indon.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorder.

Frixonil *Vincenti, Venez.*
⊗Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); alcohol (p. 1733·1).
Muscle and joint pain.

Frixopel *EMS, Braz.*
Turpentine oil (p. 2636·3); methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Froben *Abbott, Belg.; Abbott, India; Abbott, Irl.; Abbott, Ital.; Abbott, Neth.†; Abbott, Port.; Knoll, S.Afr.†; Knoll, Singapore; Abbott, Spain; Abbott, Switz.; Abbott, UK.*
Flurbiprofen (p. 65·2).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fro-Cef *Elfin, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Frocimole *Brymar, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Froidir *Orion, Fin.*
Clozapine (p. 1057·3).
Schizophrenia.

Frolicin *ITF, Gr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Frolix *Ali, Turk.*
Flurbiprofen (p. 65·2).

Fromefen *Brymar, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Fromen *Menarini, Cz.*
Frovatriptan succinate (p. 676·2).
Migraine.

Fromentyl *Medinova (Μεντινοβα), Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Fromilid *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Clarithromycin (p. 266·2).
Bacterial infections; eradication of Helicobacter pylori.

Fromirex *Menarini, Neth.*
Frovatriptan succinate (p. 676·2).
Migraine.

Frone
Note: this name may be used for preparations of different composition.
Zee, India.
Cefoperazone (p. 243·1).
Bacterial infections.

Frone-SL *Zee, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Fronil *Xieon, India.*
Minerals; vitamins.

Frontal *Pfizer, Braz.; Solvay, Ital.*
Alprazolam (p. 1035·2).
Anxiety disorders; tremor; insomnia; panic disorders.

Frontin *Egis, Cz.; Egis, Hung.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; premenstrual dysphoric disorder; panic disorder.

Froop *Ashbourne, UK.*
⊗Furosemide (p. 1387·1).
Oedema; oliguria.

Frosinor *GSK, Spain.*
Paroxetine hydrochloride (p. 440·3).
Anxiety disorders; depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Frosstimage Kit (DTPA) *Soreq, Israel.*
Calcium trisodium pentetate (p. 1570·3) for labelling with technetium-99m.
Radionuclide imaging.

Frosstimage Kit (MAA) *Soreq, Israel.*
⊗Albumin macroaggregates (p. 1130·2) for labelling with technetium-99m.
Radionuclide imaging of lung perfusion.

Frosstimage Kit (MDP) *Soreq, Israel.*
Medronic acid (p. 1186·1) for labelling with technetium-99m.
Radionuclide bone imaging.

Frost Cream *Weleda, UK.*
Abrotanum; arnica (p. 2447·2); peru balsam (p. 2587·1); rosemary oil (p. 2607·3); stibium metallicum (p. 2445·1).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Frostsalbe *Weleda, Austria.†*
Abrotanum; arnica (p. 2447·2); ol petrae (p. 2587·2); stibium metallicum (p. 2445·1).
Homoeopathic preparation.

Frotin *Yung Shin, Hong Kong; YSP, Malaysia.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Frova *Elan, USA.*
Frovatriptan (p. 676·2).
Migraine.

Teva, Canad.
Frovatriptan succinate (p. 676·2).
Migraine.

Frovamig *Menarini, Austria.*
Frovatriptan succinate (p. 676·2).
Migraine.

Frovatex *Menarini, Belg.*
Frovatriptan succinate (p. 676·2).
Migraine.

Frovex *Menarini, Irl.*
Frovatriptan succinate (p. 676·2).
Migraine.

Froxal *Probiomed, Mex.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Froximun *Atis, Turk.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

FRS *Lupin, India.*
Copper (p. 2057·1); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Fru *Ind-Swift, India.*
⊗Furosemide (p. 1387·1).
Oedema; pulmonary oedema; oliguria.

Frubiase Calcium forte 500 *Boehringer Ingelheim, Ger.*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); ergocalciferol (p. 2113·3).
Osteoporosis; osteomalacia.

Frubiase Calcium T *Boehringer Ingelheim, Ger.*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1).
Calcium deficiency.

Frubienzym *Boehringer Ingelheim, Ger.†*
Muramidase (p. 2565·1); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Frubiose Calcium *Galenica, Gr.*
Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); phosphoric acid (p. 2589·1); ascorbic acid (p. 2110·3); ergocalciferol (p. 2113·3).

Frubiose Vitamine D *Boehringer Ingelheim, Fr.†*
Ergocalciferol (p. 2113·3); calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1).
Vitamin D and calcium deficiency.

Frubiose-N
Note: this name may be used for preparations of different composition.
Galenica, Gr.
Calcium carbonate (p. 1824·3).

Fru-Co *Ivax, Irl.; Ivax, UK.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
These ingredients can be described by the British Approved Name Co-amilofruse.
Diuresis; oedema; ascites.

Fructan *Sedifa, Ital.*
Fructose (p. 2068·2).
Sugar substitute.

Fructines
Note: this name may be used for preparations of different composition.
Pharmethic, Belg.; DB, Fr.; Ferel, Port.; Uhlmann-Eyraud, Switz.
Sodium picosulfate (p. 1887·2).
Constipation.

Fucus, Arg.
Phenolphthalein (p. 1877·3).
Constipation.

Fructis Anti-Dandruff *Garnier, Canad.*
Pyrithione zinc (p. 1718·1).

Fructodex *Raptakos, India.*
Invert sugar (p. 2072·3).

Fructofin *Enervit, Ital.*
Fructose (p. 2068·2).
Sugar substitute.

Fructosil *Volchem, Ital.*
Fructose (p. 2068·2).
Supplementation of glycogen reserves.

Fructosol *Teva, Hung.*
Fructose (p. 2068·2).
Fluid replacement; parenteral nutrition.

Frugal *Bago, Arg.*
Orlistat (p. 2577·1).
Obesity.

Frugelletten *Bregenzer, Austria.*
Fig (p. 1843·2); senna (p. 1885·1); tamarind (p. 1892·2).
Constipation.

Frugyl *Rusan, Rus.*
Flutamide (p. 798·2).
Prostatic cancer.

Fruit of the Earth *Fruit of the Earth, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up *Fruit of the Earth, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up Baby Sunblock *Fruit of the Earth, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up Dry Sport *Fruit of the Earth, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up Kids *Fruit of the Earth, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up Regular *Fruit of the Earth, Canad.*
SPF 45: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up Sport *Fruit of the Earth, Canad.*
Lotion SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Block-Up Sunblock *Fruit of the Earth, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Continuous Spray *Fruit of the Earth, Canad.*
SPF 30; SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Kids *Fruit of the Earth, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Sport *Fruit of the Earth, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth Sport Continuous Spray *Fruit of the Earth, Canad.*
SPF 15; SPF 30; SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit Flavours Lip Balm *Norwood, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Fruitovit *Cipla, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Fruity Chews *Goldline, USA.*
Vitamins; with or without iron (p. 2073·1).

Frumeron *Remedica, Hong Kong†; Remedica, Singapore; Remedica, Thai.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Frumil *Sanofi-Aventis, Gr.; Geno, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Helios, UK.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
These ingredients can be described by the British Approved Name Co-amilofruse.
Hypertension; oedema; heart failure; ascites.

Frunalia *Pasteur, Chile.†*
Tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1).
Antacid; constipation.

Frusamil *Sanofi-Aventis, Belg.; Sanofi-Aventis, Denm.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Oedema; hypertension.

Frusehexal *Sandoz, Austral.†*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Fruselac *Lupin, India.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Hypertension; ascites; oedema.

Frusema *Imperial, Philipp.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Frusemene *GSK, India.*
⊗Furosemide (p. 1387·1); triamterene (p. 1518·3).

Frusemix *Cipla, India.*
⊗Furosemide (p. 1387·1).

Frusene *Orion, UK.*
⊗Furosemide (p. 1387·1); triamterene (p. 1518·3).
Oedema; ascites; heart failure.

Frusenex *Geno, India.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Frusid *Ascent, Austral.; Douglas, NZ; DDSA Pharmaceuticals, UK.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; ascites; renal failure.

Fruside *Pinewood, Irl.; CCM, Malaysia.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; pulmonary oedema.

Frusil *Suphong, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Frusim *Chandra Bhagat, India.*
⊗Furosemide (p. 1387·1).
Heart failure; pulmonary oedema; oliguria.

Frusix *Cipla, India.*
⊗Furosemide (p. 1387·1).

Frusol *Rosemont, UK.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Frutacid *Calox, Venez.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; calcium supplement.

Frutasal Knop *Knop, Chile.*
Tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1).
Antacid.

Frutcee *Medreich, India.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Frutenor *Rafarm, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

FrutiCal *Jelfa, Pol.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Fruticoline *Columbia, Mex.*
Sennosides (p. 1885·2); avena fibre (p. 2451·1).
Constipation.

Frutin *Prisfar, Port.†*
Natural dolomite (p. 2497·1).
Gastric hyperacidity.

Frutop *Ind-Swift, India.*
Protein preparation.

Frutoplex *Marjan, Braz.*
Fructose (p. 2068·2); ascorbic acid (p. 2110·3); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); nicotinamide (p. 2083·1).
Vitamin supplement.

Frutovena *Chiesi, Braz.*
Fructose (p. 2068·2); riboflavin sodium phosphate (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); ascorbic acid (p. 2110·3); nicotinamide (p. 2083·1).
Vitamin supplement.

Frutovitam *Cristalia, Braz.*
Vitamins.

Fruttasan *Graf Fruttasan, Switz.†*
Senna (p. 1885·1); fig (p. 1843·2).
Constipation.

Fruver *EG, Ital.*
Vitamins.

FS *Biomax, India.*
Tramadol (p. 139·2).
Pain.

FS Plus *Biomax, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

FS-D *Biomax, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

F-Slim *Kalbe, Indon.†*
Phaseolus vulgaris (p. 2587·3); green tea (p. 2648·2); chromium polynicotinate (p. 2055·3).
Obesity.

FSME-Immun *Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Ger.; Baxter, Hung.; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Swed.; Baxter, Switz.*
A tick-borne encephalitis vaccine (p. 2422·1).
Separate preparations are available for infants and children and for adults.
Active immunisation.

FST *Sunward, Singapore.*
Salicylic acid (p. 1719·1).
Keratinisation disorders; acne.

F-Tab *Medicine Products, Thai.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Ftagirol *Biospray, Gr.*
⊗Fenoterol hydrobromide (p. 1208·2).

Ftalined *Help, Gr.*
⊗Labetalol hydrochloride (p. 1416·2).

Ftazidime *Lilly, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ftelile *Rafarm, Gr.*
Nifedipine (p. 1447·2).

Fterosan *Rafarm, Gr.*
Nizatidine (p. 1866·1).

Ftol *Madhav, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Ftol-12 *Madhav, India.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Ftonavil *Vianex (Βιανεξ), Gr.*
Captopril (p. 1331·2).
Hypertension.

Ftorafur *Grindex, Cz.; Neleta, Gr.; Grindex, Hung.; Grindex, Rus.; Grindeks, Ukr.*
Tegafur (p. 864·2).
Malignant neoplasms.

Ftorocort *Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Thai.†; Gedeon Richter, Ukr.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Ftz *McNeil & Argus, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Fu Di *Hengrui, China.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Fu An
Note: this name may be used for preparations of different composition.
Yangtze River, China.
Cream: Liranaftate (p. 588·1).
Fungal skin infections.

Zhonglian, China.
Capsules; tablets: ⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Fu An Er *Longhe, China.*
Rifamycin sodium (p. 354·3).

Fu An Xin *NEGPF, China.*
Fosfomycin trometamol (p. 300·3).
Urinary-tract infections.

Fu Ao *Suzhou No 6, China.*
Aceglutamide (p. 2426·2).

Fu Bang *Haixin, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Fu Bi Ding *Poly, China.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Fu Bo Xin *Lihua, China.*
Huperzine.

Fu Chang *Jinhui, China.*
Troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids.

Fu Da *Maxim, China.*
Fluconazole (p. 578·2).
Fungal infections.

Fu Da Jing *LongRun, China.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Fu Er *Fuzheng, China.*
Omacetaxine mepesuccinate (p. 837·3).

Fu Er Bo *Fuer, China.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Fu Er Da *Sine, China.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Fu Er Jian *Haixin, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Fu Er Li *Nhwa, China.*
Etomidate (p. 1901·1).
General anaesthesia.

Fu Er Ling *Haixin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Fu Er Shuan *TaiYuan, China.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Fu Er Xin *Fubang, China.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid effects.

Fu Fang Xin Nuo Ming Pian *Xingyuan, China.*
Co-trimoxazole (p. 277·3).

Fu Fen *Ke Lun, China.*
Aminomethylbenzoic acid (p. 1132·2).

Fu Ge Qing *Hailing, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Fu Ji Fu *SL Pharm, China.*
Recombinant human basic fibroblast growth factor.

Fu Jie Ting *Hailing, China.*
Rifaximin (p. 355·2).
Gastrointestinal infections.

Fu Kang *Hejigong, China.*
Cream; topical solution; pessaries: Bifonazole (p. 573·3).
Fungal infections.

Qilu, China.
Injection: Fluconazole (p. 578·2).
Fungal infections.

Fu Ke *ShiJiaZhuang No 4, China.*
Fluorouracil (p. 795·2).

Fu Ke Tuo *Fengan, China.*
Spleen aminopeptide (p. 2444·1).

Fu Ke Xing *Hui Pu Sen, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Fu Lai Xi *Jiushi, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Fu Li Ding *Huashidan, China.*
Inosine (p. 2533·1).

Fu Li Sheng *White Swan, China.*
Interferon alfa-2b (recombinant, human) (p. 989·2).

Fu Li Ta Zhi *Hisun, China.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Fu Li Te *Shenyang First, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Fu Li Xin *Huashidan, China.*
Inosine (p. 2533·1).

Fu Lie *Run Bang, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Fu Lu Ke *Ke Lun, China.*
Nefopam hydrochloride (p. 100·2).
Pain.

Fu Lu Na *Ke Lun, China.*
Nefopam hydrochloride (p. 100·2).
Pain.

Fu Lu Ning *Tian Fu, China.*
Tinidazole (p. 949·2).
Protozoal infections; bacterial infections.

Fu Lu Xin *Tian Fu, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Fu Luo Ke *Chang Fu Jie Jing, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Fu Luo Xin *Bai Li, China.*
Ammonium glycyrrhizate (p. 2520·3).

Fu Mei Shu *Wanbei, China.*
Nimesulide (p. 101·3).
Pain.

Fu Mei Song *Xianju, China.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Fu Mei Xin *Wu Zhou Tong, China.*
Sodium new houttuyfonate.

Fu Mi Te *Qi Du, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fu Mi Ting *Lanling, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Fu Neng *Lingnan, China.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Fu Ning *Si Huan, China.*
Bifonazole (p. 573·3).
Fungal vaginal infections.

Fu Nuo Ding *Jialing, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Fu Qi *Si Huan, China; Wellso, China.*
Cream; topical solution: Cream; topical solution: Bifonazole (p. 573·3).
Fungal skin and vaginal infections.

Fu Qi-Hua Yuan *Jinhui, China.*
Injection: Azithromycin (p. 221·2).
Bacterial infections.

Fu Rui *Hengrui, China.*
⊗Letrozole (p. 817·1).
Breast cancer.

Fu Rui Er *Hayao, China.*
Flunarizine hydrochloride (p. 629·3).
Cerebrovascular disorders; motion sickness; vestibular disorders; migraine.

Fu Rui Lin *TianJin, China.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders.

Fu Rui Ming *BeiLu, China.*
Ferric ammonium citrate (p. 2060·1).

Fu Rui Si *Linuo Kefeng, China.*
Amlexanox (p. 1202·2).

Fu Rui Xin *Lai En, China.*
Azithromycin lactobionate.
Bacterial infections.

Fu Ruo Xin *TianAn, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fu Shi Ke *Poly, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Fu Shi Ling *Shyndec, China.*
Foscarnet sodium (p. 981·1).
Herpes simplex infections.

Fu Shi Tan *C & O, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer.

Fu Shu *Shengyuan, China.*
Pentoxifylline (p. 1465·3).

Fu Shu Da *Jingzhu, China.*
Metronidazole (p. 936·1).
Vaginal infections.

Fu Shun *Haixin, China.*
Isosorbide mononitrate (p. 1413·3).

Fu Si Ka *Yaoyou, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Fu Si Ke *Lisheng, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Fu Song *Tapsun, China.*
Benproperine phosphate (p. 1656·2).
Cough.

Fu Su Ke *Hengsheng, China.*
Asarone.

Fu Ta Le *Wan Long, China.*
⊗Dextran 40 (p. 1138·1).

Fu Ta Ning *NCPC, China.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Fu Tai *SanJiu, China.*
Benzoic acid (p. 1738·2).
Acne.

Fu Tai An Tuo *Harbin, China.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).

Fu Tan Le *Actavis, China.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Fu Tan *Huabang, China.*
Penciclovir (p. 1008·2).

Fu Tang Pai Te *Ansheng Kexing, China.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).

Fu Te *Tonglian, China.*
Rifaximin (p. 355·2).

Fu Tong *Haixin, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Fu Wei *Haibin, China; TianJin, China.*
Amoxicillin sodium (p. 216·2); flucloxacillin sodium (p. 299·2).
Bacterial infections.

Fu Xi Kang *Huaxin, China.*
Selenium yeast (p. 2125·2).

Fu Xie Ding *Hengshan, China.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Fu Xin
Note: this name may be used for preparations of different composition.
Hengrui, China.
Dispersible tablets: Roxithromycin (p. 356·2).
Bacterial infections.

Kanglaite, China.
Capsules: Ubidecarenone (p. 2637·1).
Heart failure; angina pectoris; periodontal disease.

Suzhou No 6, China.
Injection: Meglumine adenosine cyclophosphate.

Fu Xin Kang *Jiachen, China.*
Cefixime (p. 240·3).
Bacterial infections.

Fu Xin Tian *ShiKangTe, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Fu Xin Wei *Wei Men, China.*
Sodium new houttuyfonate.

Fu Yan Ning *Yangtze River, China.*
⊗Econazole nitrate (p. 577·3); triamcinolone diacetate (p. 1649·1).
Infected skin disorders.

Fu Yin *Haixin, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Fu Yue *Haixin, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Fu Zhi *Xinzhongzheng, China.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Fu Zhi Ping *Bosen, China.*
Chondroitin sulfate (p. 2476·1).

Fual *Alkem, India.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Fubac *Karnataka, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1).
Infected skin disorders.

Fubaxyn *IAE, Philipp.*†
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Fubecot *Target, Gr.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Fuben *TO-Chemicals, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Fuca
Note: this name may be used for preparations of different composition.
Melisana, Belg.
Senna (p. 1885·1).
Constipation.

Fuca excellent *Melisana, Neth.*
Senna (p. 1885·1).
Constipation.

Fuca N *Melisana, Switz.*†
Senna (p. 1885·1).
Constipation.

Fucandyl *Wermar, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Fucapan *Innova, Spain.*
Frangula bark (p. 1843·3); cascara (p. 1826·1); fucus vesiculosus.
Constipation.

Fucaseptol *Retinoids, Rus.*
Boric acid (p. 2459·3); resorcinol (p. 1718·3); phenol (p. 1763·3).
Skin infections; wounds.

Fucef *Solitaire, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Fucerox *Pisa, Mex.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Fucibet *Europharma, Denm.; Ranbaxy, India; Leo, Irl.; Leo, Spain; Leo, UK.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Fucicort *Roche, Arg.; Leo, Belg.; Andromaco, Chile; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Ger.; Leo (Λεο), Gr.; Leo, Hong Kong; Leo, Hung.; Darya-Varia, Indon.; Leo, Indon.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Valeant, Mex.; CSL, NZ; Leo, NZ; Leo, Philipp.; Leo, Port.; Leo, Rus.; Leo, Singapore; Leo, Switz.; Leo, Thai.; Abdi, Turk.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Fucicream *AG Therapy, Gr.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Fucidin *Roche, Arg.; CSL, Austral.; Leo, Austria; Leo, Belg.; Leo, Canad.; Andromaco, Chile; Leo, China; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo (Λεο), Gr.; Leo, Hong Kong; Leo, Hung.; Darya-Varia, Indon.; Leo, Indon.; Leo, Irl.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Valeant, Mex.; Leo, Neth.; Leo, Norw.; CSL, NZ; Leo, NZ; Leo, Philipp.; Leo, Pol.; Leo, Rus.; Adcock Ingram, S.Afr.; Leo, Singapore; Leo, Swed.; Leo, Switz.; Leo, Thai.; Abdi, Turk.; Leo, UK.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial infections.

Ranbaxy, India.
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Fucidin H *Roche, Arg.; Leo, Canad.; Andromaco, Chile; Leo, Cz.; Leo (Λεο), Gr.; Leo, Hong Kong; Leo, Hung.;*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ranbaxy, India; Leo, Irl.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Leo, Philipp.; Leo, Rus.; Leo, Singapore; Leo, Switz.; Leo, Thai.; Abdi, Turk.; Leo, UK.
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Adcock Ingram, S.Afr.
⊗Sodium fusidate (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Fucidin Hydrocortisone *Leo, Belg.*
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Fucidin + Hydrocortisone *Leo, Neth.†*
⊗Fusidic acid (p. 302·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Fucidin Intertulle *Leo, Malaysia.*
A dressing impregnated with sodium fusidate (p. 302·1).
Wounds; varicose ulcers; abscesses; burns.

Fucidine *Abacus, Denm.*
Sodium fusidate (p. 302·1).
Staphylococcal infections.

Leo, Fr.; Leo, Ger.; Leo, Neth.; Leo, Port.; Leo, Spain.
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial infections.

Fucidine H *Leo, Ger.; Leo, Port.; Leo, Spain.*
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Fucidin-Hydrocortison *Leo, Denm.*
⊗Fusidic acid (p. 302·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Leo, Fin.; Leo, Norw.; Leo, Swed.
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Fucilex *Molex Ayus, Indon.*
Sodium fusidate (p. 302·1).
Skin infections.

Fucin *Pure Health, India.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fucin-B *Ind-Swift, India.*
⊗Beclometasone dipropionate (p. 1621·2); fusidic acid (p. 302·1).

Fucinex *Zuventus, India.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Fucithalmic *Andromaco, Arg.; Leo, Austria; Leo, Belg.; Leo, Canad.; Andromaco, Chile; Leo, China; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Hong Kong; Leo, Hung.†; Win-Medicare, India; Darya-Varia, Indon.; Leo, Indon.; Leo, Irl.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Leo, Neth.; Leo, Norw.; CSL, NZ; Leo, NZ; Leo, Philipp.; Leo, Port.; Leo, Rus.; Adcock Ingram, S.Afr.; Leo, Singapore†; Leo, Spain; Leo, Swed.; Leo, Switz.; Leo, Thai.; Abdi, Turk.; Leo, UK.*
Fusidic acid (p. 302·1).
Bacterial eye infections.

Fucobac *Meprofarm, Indon.*
Fucoidan (p. 2508·1).
Stomach disorders.

Fucoderm *IQFA, Mex.*
Miconazole (p. 588·3).
Fungal skin infections.

Fucon *YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore; YSP, Thai.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Fucorcin *Mosfarma, Rus.*
Boric acid (p. 2459·3); resorcinol (p. 1718·3).
Skin infections; wounds.

Fucosa *Soho, Indon.*
Fucoidan (p. 2508·1).
Gastric ulcer.

Fucotrap *Solas, Indon.*
Fucoidan (p. 2508·1).
Peptic ulcer.

Fucsina Fenica *Marco Viti, Ital.; NewFaDem, Ital.; Nova Argentia, Ital.; Sella, Ital.; Zeta, Ital.*
Boric acid (p. 2459·3); phenol (p. 1763·3); magenta (p. 1759·3); resorcinol (p. 1718·3).
Fungal skin infections.

Fucus Complexe No 111 *Lehning, Fr.*
Fucus vesiculosus (p. 2612·1); antimonium crudum (p. 2445·1); alchemilla vulgaris; thyroidea (p. 2345·3); calcarea acetica (p. 1783·1).
Homoeopathic preparation.

Fucus Especial *Knop, Chile.*
Fucus (p. 2612·1); thiroidinum (p. 2345·3); jodum (p. 2336·3); phytolacca (p. 2593·2); thuja (p. 2629·3).
Homoeopathic preparation.

Fucus L111 *Homeocan, Canad.†*
Calcarea acetica (p. 1783·1); fucus vesiculus (p. 2612·1); antimonium crudum (p. 2445·1); alchemilla vulgaris; thyroidinum (p. 2345·3).
Homoeopathic preparation.

Fucus-Gastreu S R59 *Reckeweg, Ger.*
Fucus vesiculosus (p. 2612·1).
Homoeopathic preparation.

Fudan *Pyridam, Indon.*
Fucoidan (p. 2508·1).
Stomach disorders.

Fudec *Daksh, India.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fudec-B *Daksh, India.*
⊗Beclometasone (p. 1621·2); fusidic acid (p. 302·1).

Fudec-M *Daksh, India.*
⊗Fusidic acid (p. 302·1); mometasone (p. 1644·1).

Fudermex *Prater, Chile.*
Lansoprazole (p. 1851·3).

Fudesix *Help, Gr.*
⊗Furosemide (p. 1387·1).

Fudic *H & H, India.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fudikin *Samjin, Singapore.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Fudirine *PP Lab, Thai.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Fudixing *Changzheng-Xinkai, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Fudone *Wockhardt, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

FUDR *IFET (ΙΦΕΤ), Gr.; Roche, USA.†*
Floxuridine (p. 793·3).
Gastrointestinal adenocarcinoma metastatic to the liver.

Fuera Bicho *Biosintex, Arg.†*
Quassia (p. 2601·1); acetic acid (p. 2426·3).
Pediculosis.

Fuerte *PlantaPhile, UK.*
Wild indigo (p. 2647·2); echinacea purpurea (p. 2498·1); echinacea pallida (p. 2498·1); thuja (p. 2629·3).
Cold symptoms.

Fufang Dan An Pian *Wuhan, China.*
⊗Aminophylline (p. 1201·2); ephedrine hydrochloride (p. 1663·2); sodium cholate (p. 2457·2); promethazine hydrochloride (p. 638·2); chlordiazepoxide (p. 1044·2).
Bronchitis; asthma; emphysema; pulmonary heart disease.

Fufang Lixueping *Minsheng, China.*
⊗Reserpine (p. 1485·3); hydrochlorothiazide (p. 1403·2); dihydralazine sulfate (p. 1358·3); promethazine hydrochloride (p. 638·2); minerals; vitamin B substances (p. 2102·3).
Hypertension.

Fugacar *Janssen-Cilag, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Fugacin *Shin Poong, Singapore.*
Ofloxacin (p. 334·3).
Bacterial infections.

Fugafebril *Northia, Arg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine (p. 1672·2); butetamate citrate (p. 1658·1).

Fuganol *Galenica, Gr.*
Sertaconazole nitrate (p. 593·2).
Fungal infections.

Fugat *Forgo, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Fugaten *Lysoform, Ger.*
⊗Alcohol (p. 1733·1).
Surface disinfection.

Fugentin
Note: this name may be used for preparations of different composition.
Bryntsalov, Rus.
Gentamicin (p. 304·2); fusidic acid (p. 302·1).
Infected disorders of the ear, nose, and sinuses.

Elpen (Ελπεν), Gr.; Elpen, Singapore.†
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Fugerel *Aesca, Austria; MSD, China; MSD, Ger.†; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Philipp.; Schering-Plough, Pol.†; Schering-Plough, Singapore; MSD, Thai.*
Flutamide (p. 798·2).
Prostatic cancer.

Fugin *Cofasa, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Fugolin *Vincenti, Venez.*
Clotrimazole (p. 576·2).
Fungal infections.

Fugras *Biotecnoquimica, Venez.*
Fucus (p. 2612·1); magnesium sulfate (p. 1787·3).
Slimming aid.

Fuhe *HongQi, China.*
Rifampicin (p. 350·3).
Bacterial infections; prophylaxis of meningococcal meningitis.

FuHong *Pude, China.*
Papaverine hydrochloride (p. 2362·3).

FuKang *Hejigong, China.*
Bifonazole (p. 573·3).
Fungal skin and vaginal infections.

Fukangning *Deyer, China.*
Nystatin (p. 590·3).
Vaginal candidiasis.

Fukexin *Shunxin Xiangyun, China.*
Chloramphenicol (p. 257·1); diethylstilbestrol (p. 2267·3).
Vaginitis; cervical erosion; cervicitis.

Fukole *YSP, Malaysia; Yung Shin, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Fukricin *Sanbe, Indon.*
Natamycin (p. 590·2).
Fungal eye infections.

Ful *Haledew, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fulace *Adley, India.*
Minerals; vitamins.

Fuladic *Guardian, Indon.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Skin infections.

Ful-Aid *Mankind, India.*
Vitamins; minerals.

Fulaidi *Hanson, China.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Fulcalrex *Confar, Port.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Fulcin *AstraZeneca, Braz.; AstraZeneca, Indon.; SIT, Ital.; Darier, Mex.; Teofarma, Spain.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Fulcover *Saga, India.*
Itraconazole (p. 583·3).
Fungal infections.

Fulcralex *Confar, Port.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Fulcro *Solvay, Ital.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fulcrosupra *Solvay, Ital.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Fuleqing *NEGPF, China.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Fulexin *Chung-Hwa, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Fulflo *Hauz, India.*
Sodium acid citrate (p. 1781·1).

Fulfyn *Micro, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Fulgest *Micro, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Fulgium *Teofarma, Spain.*
Benzydamine salicylate (p. 29·2).
Peri-articular and soft-tissue disorders.

Ful-Glo *Akorn, USA.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Fulgram
Note: this name may be used for preparations of different composition.
Labomed, Chile.
Norfloxacin (p. 333·3).
Bacterial infections.

Megat, Venez.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

USV, India.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Fulin *Guanghua, China.*
Cefalexin (p. 234·1).
Bacterial infections.

Fulkit *Haledew, India.*
Soap: Ketoconazole (p. 585·3).

Haledew, India.
Tablets: 1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Full-24 *Emcure, India.*
Garlic (p. 2510·3); ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).

Full-365 *Emcure, India.*
Capsules: Vitamins; trace elements.

Emcure, India.
Suspension: Lysine hydrochloride (p. 2079·3); vitamins; trace elements.

Full Calcio D3 *Lafedar, Arg.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement.

Full Marks *SSL, Irl.†; SSL, NZ; SSL, UK.†*
Phenothrin (p. 2160·1).
Pediculosis.

Full Marks Solution *SSL, UK.*
Cyclomethicone (p. 2209·2); isopropyl myristate (p. 2190·3).
Pediculosis.

Full Motion *GNLD, Austral.*
Glucosamine hydrochloride (p. 2515·3); boswellia serrata (p. 2507·3); salix (p. 129·2); zinc gluconate (p. 2126·2).
Joint disorders.

Full Spectrum B *National Vitamin, USA.*
Vitamin B substances (p. 2102·3).

Fullcilina *Elea, Arg.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Fullday *BMW, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Fullgrip
Note: this name may be used for preparations of different composition.
Medipharm, Chile.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Nycomed, Arg.
Levophenylephrine hydrochloride (p. 1672·2); paracetamol (p. 115·1); vitamin C (p. 2110·3).
Influenza symptoms.

Fullgrip Dia y Noche *Medipharm, Chile.*
⊗White tablets (day), paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); blue tablets (night), paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; rhinitis.

Fullzyme *BMW, India.*
Amylase (p. 2442·1); vitamin B substances (p. 2102·3).

Fulnite *Sun, India.*
Eszopiclone (p. 1072·3).

Fulone *Osoth, Thai.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Fulpan *Azine, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Fulpan-D *Azine, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Fulsac *Biofarma, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Fulsed *Ranbaxy, China; Ranbaxy, Cz.†; Ranbaxy, Singapore.*
Midazolam (p. 1085·1).
Premedication; induction of anaesthesia; sedative; general anaesthesia.

Ranbaxy, India; Ranbaxy, Rus.; Ranbaxy, Ukr.
Midazolam hydrochloride (p. 1085·1).
Sedative; premedication; induction of anaesthesia; sleep disorders; general anaesthesia.

Ranbaxy, Malaysia.
Midazolam maleate (p. 1085·2).
Insomnia; premedication.

Fulsivin *Collins, Mex.†*
Griseofulvin (p. 582·2).
Fungal infections.

Fulsovin *Kappin, UK.†*
Griseofulvin (p. 582·2).
Fungal hair, nail, and skin infections.

Fultac *Mavi, Mex.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2).
Respiratory-tract disorders.

Fulterm *Micro, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Fultium-D$_3$ *Internis, UK.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; osteoporosis.

Fuluobi *Minsheng, China.*
⊗Furosemide (p. 1387·1); amiloride (p. 1299·1).
Oedema; ascites.

Fulurit *Eczacibasi, Turk.*
Fluconazole (p. 578·2).

Fulutong *Zambon, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Fuluxian *Changzheng-Xinkai, China.*
Spiramycin (p. 358·3).
Bacterial infections.

Fuluxing *Changzheng-Xinkai, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Fuluyin *Changzheng-Xinkai, China.*
Pidotimod (p. 2590·2).
Infections.

Fulvin *Burapha, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Fulx *Aarpik, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fulyzaq *Salix, USA.*
Crofelemer (p. 1833·3).
HIV-associated diarrhoea.

Fumac *Ankom, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fumaderm *Almirall Hermal, Ger.; Biogen, Ger.*
Dimethyl fumarate (p. 1704·2); calcium monoethyl fumarate (p. 1704·2); magnesium monoethyl fumarate (p. 1704·2); zinc monoethyl fumarate (p. 1704·2).
Psoriasis.

Fumafer *Sanofi-Aventis, Fr.*
Ferrous fumarate (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Fumago *Gradiens, Hung.*
Fumitory (p. 2508·2); borage oil (p. 2459·2).
Skin disorders.

Fumaixin *Hayao, China.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Fumarol *Offenbach, Mex.†*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Fumast *Biofarma, Turk.*
Ketotifen (p. 631·3).
Asthma; allergic rhinitis; allergic conjunctivitis.

Fumatinic *Laser, USA.†*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Fumavit *IQFA, Mex.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Fumecal *Kleva, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Fumeixin *NEGPF, China.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Fumestar *Cadila, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Fumicon *Leovan, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Fumiron + B *Catalent, Philipp.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); citrus bioflavonoids (p. 2505·2).
Iron deficiency; iron-deficiency anaemia; tonic.

Fumycin *Pfizer, India.*
Fluconazole (p. 578·2).
Fungal infections.

Funa *LBS, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Funadel *Delegant, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Funamel *Stada, Cz.*
⊗Exemestane (p. 792·2).
Breast cancer.

Funamix *Advaita, Mex.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Funazole *Khandelwal, India.†*
Ketoconazole (p. 585·3).
Fungal infections.

Funcan *BMW, India.*
Fluconazole (p. 578·2).
Fungal infections.

Funcid *BioFemme, Philipp.†*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Funciobron *Northia, Arg.*
Noscapine (p. 1670·3); chlorphenamine (p. 620·3); phenylephrine (p. 1672·2).

Funciobron B *Northia, Arg.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Funciobron H *Northia, Arg.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Funciogrip *Northia, Arg.†*
Salicylamide (p. 129·2); pyribenzamine; phenylephrine (p. 1672·2).
Cold and influenza symptoms.

Funcort *TNP, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Fundamin *Biomedis, Singapore.*
Vitamin B substances (p. 2102·3).

Fundamin-E *Biomedis, Hong Kong; Biomedis, Singapore; Biomedis, Thai.†; Great Eastern, Thai.†*
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Vitamin supplement.

Medifarma, Indon.; UAP, Indon.; Biomedis, Malaysia.†
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Reduced appetite; neurasthenia; radiation sickness; neuritis; nausea and vomiting; tonic.

Fundan *Meda, Swed.†*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Fundifar *Ifars, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Vitamin deficiency.

Funduscein *Iolab, USA.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Funesta *Misha, India.*
Fluconazole (p. 578·2).
Fungal infections.

Funet *Fahrenheit, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Funga *Vida, Hong Kong†; Chinta, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Fungafine *Norton Waterford, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fungal
Note: this name may be used for preparations of different composition.
Inga, India.
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Fungal-F *Inga, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungan *Ulagay, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Fungard *Finecure, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungares *Guardian, Indon.*
Miconazole nitrate (p. 589·1).
Fungal and bacterial skin and nail infections.

Fungarest *Janssen-Cilag, Chile; Janssen-Cilag, Spain.*
Ketoconazole (p. 585·3).
Fungal hair, nail, and skin infections; seborrhoeic dermatitis.

Fungasil *Clonmel, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fungasol *Guardian, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Fungata *Pfizer, Austria; Pfizer, Ger.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Fungatin *Ferron, Indon.*
Nystatin (p. 590·3).
Candidiasis.

Fungazol
Note: this name may be used for preparations of different composition.
Biolab, Hong Kong†; Biolab, Malaysia; Biolab, Thai.
Ketoconazole (p. 585·3).
Fungal infections.

Osper, India.
Fluconazole (p. 578·2).
Fungal infections.

Fungdor *Candor, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungecyl *Gunsa, Turk.*
Undecenoic acid (p. 596·3); calcium lactate (p. 1784·1); zinc undecenoate (p. 596·3).
Fungal skin and nail infections.

Fungederm *Nucare, UK.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Funger *Med-One, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections.

Fungesten *Hovid, Hong Kong.†*
Clotrimazole (p. 576·2).

Fungi *Patar, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fungi B *Eurofarma, Braz.*
Amphotericin B (p. 569·2).
Fungal infections.

Fungi Cure *Alva, USA.*
Undecenoic acid (p. 596·3).
Fungal skin infections.

Fungi Cure Intensive *Alva, USA.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fungiban *Medopharm, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungi-BC *Yash, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Fungicap *Psychotropics, India.*
Itraconazole (p. 583·3).
Fungal infections.

Fungicare
Note: this name may be used for preparations of different composition.
Vitamed, Israel.
Clotrimazole (p. 576·2).
Fungal skin infections.

Cantabria, Spain.†
Terbinafine hydrochloride (p. 593·3).
Fungal infections of the skin and nails.

Fungicida *Lauria, Arg.*
Zinc undecenoate (p. 596·3); calcium propionate (p. 592·3); sodium propionate (p. 593·1); hexylresorcinol (p. 1755·1); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); thymol (p. 1772·2).
Fungal infections.

Fungicide *Torrent, India.*
Tablets: Ketoconazole (p. 585·3).
Fungal infections.

Torrent, India.
Lotion: Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Fungicidin *Zentiva, Cz.*
Nystatin (p. 590·3).
Candidiasis.

Fungicil *Sandoz, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Fungicip *Cipla, Malaysia.*
Clotrimazole (p. 576·2).
Vaginal infections.

Fungicon
Note: this name may be used for preparations of different composition.
Continental Pharma, Thai.
Cream: Clotrimazole (p. 576·2); melaleuca oil (p. 2551·1).
Fungal skin infections.

Continental Pharma, Thai.
Vaginal tablets: Clotrimazole (p. 576·2).
Trichomoniasis; vaginal candidiasis.

Micro, India.
Fluconazole (p. 578·2).
Fungal infections.

Fungicrem *Andromaco, Mex.†*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Fungicure *Alva, Canad.*
Tolnaftate (p. 596·1).

Fungid *Bestochem, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungiderm
Note: this name may be used for preparations of different composition.
Biospray, Gr.
Bifonazole (p. 573·3).
Fungal skin infections.

Terra-Bio, Ger.†; Konimex, Indon.†; Greater Pharma, Thai.
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections; trichomoniasis.

Rafa, Israel.
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Fungiderm-B *Greater Pharma, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Fungal skin infections.

Fungiderm-K *Greater Pharma, Thai.*
Ketoconazole (p. 585·3).
Fungal infections; pityriasis versicolor; seborrhoeic dermatitis; dandruff.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Fungidermo *Cinfa, Spain.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fungidexan *Almirall Hermal, Ger.*
⊗Clotrimazole (p. 576·2); urea (p. 1727·3).
Fungal and bacterial skin infections.

Fungid-OR *Bestochem, India.*
1 Tablet, fluconazole (p. 578·2); 2 tablets, ornidazole (p. 943·1).

Fungidrops *Yash, India.*
Clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2); propylene glycol (p. 2205·2).

Fungifite *Neiss, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Fungiheal *Kalivis, Gr.*
Salicylic acid (p. 1719·1).

Fungil *Atral, Port.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fungilin *Aspen, Austral.; BMS, Ital.; Healthcare Logistics, NZ; BMS, UK·†*
Amphotericin B (p. 569·2).
Fungal infections.

Fungi-M *Nakornpatana, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin, nail, and hair infections.

Fungimac *Trumac, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fungimax
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vulvovaginal infections.

Ventaglio, Chile.
Fluconazole (p. 578·2).
Fungal infections.

Fungimed *3DDD, Belg.*
Fluconazole (p. 578·2).
Fungal infections.

Fungimon *Trima, Israel.*
Zinc undecenoate (p. 596·3); undecenoic acid (p. 596·3); aluminium chlorohydrate (p. 1694·1).
Fungal skin infections.

Fungina *Micro, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungi-Nail *Kramer, USA.*
Resorcinol (p. 1718·3); salicylic acid (p. 1719·1); chloroxylenol (p. 1748·2); benzocaine (p. 1980·2); isopropyl alcohol (p. 1758·3).
Fungal nail infections; fungal and bacterial skin infections.

Funginail *Perrigo, Israel.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Funginix *Sandoz, Denm.†; Sandoz, Swed.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Funginoc *Torrent, India.*
Ketoconazole (p. 585·3).
Fungal skin infections; seborrhoeic dermatitis.

Funginox *Deltapharm, Hong Kong†; Charoen Bhaesaj, Malaysia; Charoen, Thai.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis; dandruff.

Fungipar *Parggon, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Fungiquim *Quimica y Farmacia, Mex.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin and nail infections.

Fungirox *UCI, Braz.*
Ciclopirox (p. 575·3).
Fungal vaginal infections.

Fungis *Sandoz, Fin.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Fungisan-F *Sresan, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fungisdin *Isdin, Spain.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections.

Fungisept *Lysoform, Ger.*
Didecyldimethylammonium chloride (p. 1750·3).
Surface and fabric disinfection.

Fungisil *Silom, Thai.*
Miconazole nitrate (p. 589·1).
Fungal infections of the skin, nails, and mucous membranes.

Fungisil-T *Silom, Thai.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Fungal infections of the skin, nails, and mucous membranes.

Fungisome *Lifecare, India.*
Amphotericin B (p. 569·2).
Fungal infections.

Fungispor *Caps, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Fungistab *Ajanta, Rus.*
Ketoconazole (p. 585·3).
Fungal infections.

Fungistat
Note: this name may be used for preparations of different composition.
Intermed, Gr.
Econazole nitrate (p. 577·3).

Janssen-Cilag, Mex.; Janssen-Cilag, Venez.
Terconazole (p. 595·2).
Vulvovaginal candidiasis.

Fungistop *Bernofarm, Indon.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Fungitherapy *AG Therapy, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Fungitop *Micro, India.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Fungitop-F *Micro, India.*
⊗Fluocinolone acetonide (p. 1636·1); miconazole nitrate (p. 589·1).

Fungitrazol *Ikapharmindo, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Fungium *Saval, Chile.*
Ketoconazole (p. 585·3).
Fungal infections.

Fungivin *Euphoric, India; The Forty-Two, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Fungizid *Ratiopharm, Ger.*
Clotrimazole (p. 576·2).
Fungal and bacterial vaginal infections; fungal skin infections.

Fungizid Extra *Ratiopharm, Ger.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Fungizin *Utopian, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Fungizol
Note: this name may be used for preparations of different composition.
Euro Generics, Philipp.
Ketoconazole (p. 585·3).
Fungal infections.

Universal, Port.
Itraconazole (p. 583·3).
Fungal infections.

Fungizole *Psyco Remedies, India.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Fungizon *BMS, Braz.; Merck, Chile.*
Amphotericin B (p. 569·2).
Fungal infections.

Fungizona *BMS, Spain.†*
Amphotericin B (p. 569·2).
Fungal infections.

Fungizone *BMS, Austral.†; BMS, Belg.†; BMS, Canad.; Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; BMS, Fin.; BMS, Fr.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; Piramal, India; BMS, Indon.†; BMS, Irl.; BMS, Ital.; BMS, Malaysia; BMS, Neth.; BMS, Norw.†; BMS, NZ†; BMS, Philipp.†; BMS, Port.†; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, Switz.; BMS, Thai.†; Abbott, Turk.; BMS, UK; BMS, Venez.*
Amphotericin B (p. 569·2).
Fungal infections; mucocutaneous leishmaniasis.

Fungnon *Ariston, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Fungo
Note: this name may be used for preparations of different composition.
Verisfield, Gr.; Orion, India.
Fluconazole (p. 578·2).
Fungal infections.

Douglas, NZ.†
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Fungo Farmasierra *Farmasierra, Spain.†*
Ketoconazole (p. 585·3).
Fungal infections.

Fungo Soothing Balm *Ego, Hong Kong.†*
Miconazole nitrate (p. 589·1); bufexamac (p. 30·2).
Infected skin disorders.

Fungo Zeus *Zeus, Spain.*
Ketoconazole (p. 585·3).
Fungal infections.

Fungocina *Lazar, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Fungocop *Fecofar, Arg.*
Boric acid (p. 2459·3); undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal infections.

Fungocop Premium *Fecofar, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fungoid *Pedinol, USA.*
Topical tincture: Miconazole nitrate (p. 589·1).
Fungal nail infections.

Fungoid HC *Pedinol, USA.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Bacterial and fungal skin infections.

Fungolab *Multilab, Braz.†*
Iodine (p. 2336·3); benzoic acid (p. 1738·2).
Fungal skin infections.

Fungolon *Balkanpharma, Rus.†*
Fluconazole (p. 578·2).
Fungal infections.

Fungomax *Behrens, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Fungonax *Teuto, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Fungonazol *Verisfield, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Fungopirox *Royal, Chile.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Fungoral *Janssen-Cilag, Austria; Johnson & Johnson, Gr.; Kimia, Indon.; Janssen-Cilag, Mex.; Janssen-Cilag, Norw.; Janssen-Cilag, Swed.; McNeil, Swed.; Sandoz, Turk.*
Ketoconazole (p. 585·3).
Fungal skin, nail and scalp infections; seborrhoeic dermatitis.

Fungores *ICN, Pol.†*
Ketoconazole (p. 585·3).
Fungal infections.

Fungorin *Orion, Fin.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fungos
Note: this name may be used for preparations of different composition.
Pasteur, Chile.
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Fungosin *Dollder, Venez.*
Itraconazole (p. 583·3).
Fungal infections.

Fungosine *Sanofi Synthelabo, Mex.†*
Ketoconazole (p. 585·3).
Fungal infections.

Fungospor *Verisfield, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Fungostatin *Nobel, Turk.*
Nystatin (p. 590·3).
Candidiasis.

Fungosten *Mulda, Turk.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Fungotek *FDC, India.*
Terbinafine (p. 593·3).
Fungal skin, hair, and nail infections.

Fungoterbine *Nizhfarm, Ukr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Nizpharm, Rus.
Terbinafine (p. 593·3) or terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fungototal *TRB, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Fungotox *Mepha, Switz.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Fungowas *Chiesi, Spain.*
Ciclopirox olamine (p. 575·3).
Cutaneous, mucosal and nail fungal infections.

Fungram *Suan, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Fungster *Pierre Fabre, Belg.*
Terbinafine (p. 593·3).
Fungal nail and skin infections.

Pierre Fabre Dermatologie, Fr.; Pierre Fabre, Gr.; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, Switz.†
Terbinafine hydrochloride (p. 593·3).
Fungal skin, hair and nail infections.

Fungtopic *Vendiz, Philipp.*
Miconazole nitrate (p. 589·1).
Fungal infections of the skin and nails.

Funguard *Astellas, Jpn.*
Micafungin sodium (p. 588·2).
Aspergillosis; candidiasis.

Fungucit *Sandoz, Turk.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Fungueal *Lazar, Arg.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fungur M *Hexal, Ger.†*
Miconazole nitrate (p. 589·1).
Fungal skin and vaginal infections.

Fungus *SF, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Fungusol *Bayer, Spain.*
Boric acid (p. 2459·3); zinc oxide (p. 1729·1).
Fungal skin infections; intertrigo.

Fungustatin *Pfizer, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Fungusteril *DAST, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Funida *Nakornpatana, Thai.*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Funis *Target, Gr.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Funit *Nobel, Turk.; Nobel, Ukr.*
Itraconazole (p. 583·3).
Fungal infections.

Funizol *Megat, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Funolteva *Med, Turk.*
Fluconazole (p. 578·2).

Funscreen *Kinesys, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Funser *Serral, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Funspor *DWD, India.*
Fluconazole (p. 578·2).
Fungal infections.

Funtas *Sanbe, Indon.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Funtex B *Meizler, Braz.*
Amphotericin B (p. 569·2).

Funtoosh *NB, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Funtyl *Cristalia, Braz.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Funzal *Lafi, Chile.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Funzela *Darya-Varia, Indon.; BioFemme, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Funzole *Bosnalijek, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Fupengxing *Changzheng-Xinkai, China.*
Fluconazole (p. 578·2).
Fungal infections.

Fuqi *Qianjiang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Fuqing *Shyndec, China.*
Tretinoin (p. 1725·2); erythromycin (p. 291·2).
Acne.

Fuqixing *Changzheng-Xinkai, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Furab *Forgo, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Furab-D *Forgo, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Furabid *Mercury, Neth.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furab-IT *Forgo, India.*
Itopride; rabeprazole (p. 1881·1).
Gastro-oesophageal reflux.

Furacin *Schering-Plough, Arg.; Mantecorp, Braz.; Boehringer Ingelheim, Chile; GSK, India; Rhein, Mex.; Boehringer Ingelheim, Philipp.; GSK, S.Afr.†; Seid, Spain; Eczacibasi, Turk.; Farma, Venez.*
Nitrofurazone (p. 333·1).
Burns; ulcers; wounds; skin infections; skin disinfection.

Furacine *Limacom, Belg.*
Nitrofurazone (p. 333·1).
Infected wounds and burns; infection prophylaxis for skin grafts.

Furacin-S *GSK, India.†*
⊗Nitrofurazone (p. 333·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Furacin-Sol *Riemser, Ger.*
Nitrofurazone (p. 333·1).
Skin infections; wounds.

Furadantin *Pfizer, Austral.†; Procter & Gamble, Austria; Goldshield, Ger.; GSK, India; Goldshield, Irl.; Meda, Norw.; Pharmacia, NZ†; GSK, S.Afr.†; Meda, Swed.; Goldshield, UK†; Sciele, USA.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furadantina *Schering-Plough, Arg.; Boehringer Ingelheim Promeco, Mex.; Goldshield, Port.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furadantine *Pharma Logistics, Belg.; Merck Serono, Fr.; Vifor, Switz.*
Nitrofurantoin (p. 332·1).
Cystitis; urinary-tract infections.

Furadantine MC *Mercury, Neth.*
Nitrofurantoin (macrocrystalline) (p. 332·1).
Urinary-tract infections.

Furaderm *Toprak, Turk.*
Nitrofurazone (p. 333·1).
Skin infections.

Furadoïne *Merck Serono, Fr.*
Nitrofurantoin (p. 332·1).
Cystitis; urinary-tract infections.

Furadonin *Olainfarm, Rus.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furaginum *Adamed, Pol.; Teva, Pol.*
Furazidin (p. 301·3).
Bacterial infections of the urinary tract.

Furagrand *Ahimsa, Arg.*
⊗Furosemide (p. 1387·1).

Furamag *Olainfarm, Rus.*
Furazidin potassium (p. 301·3).
Bacterial infections.

Olainfarm, Ukr.
Furazidin (p. 301·3).
Bacterial infections.

Furamed *Medicpharma, Thai.*
Furazolidone (p. 933·3); pectin (p. 2200·3); kaolin (p. 1850·1).
Diarrhoea.

Furanthril *Medphano, Ger.; IFET [ΙΦΕΤ], Gr.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; oliguria; forced diuresis.

Furantoina *Ern, Spain.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furasept *Thebe, S.Afr.*
Nitrofurazone (p. 333·1).
Wounds; burns; ulcers; skin infections.

Furasian *Asian Pharm, Thai.*
Syrup: Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea; enteritis.

Asian Pharm, Thai.
Tablets: Furazolidone (p. 933·3).
Diarrhoea; enteritis.

Furasol *Olainfarm, Rus.; Olainfarm, Ukr.*
Furazidin (p. 301·3).
Bacterial infections.

Furasoz *Sozin-Flora, India.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furaxil *Remedina, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Furazol *Abbott, Turk.*
Nitrofurazone (p. 333·1).
Bacterial ear infections.

Furazolidona *Laboratorios Chile, Chile.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Bacterial gastrointestinal infections; giardiasis.

Furdiuren *Chemopharma, Chile; Dollder, Venez.*
⊗Furosemide (p. 1387·1); amiloride (p. 1299·1).
Heart failure; hypertension; hepatic cirrhosis with ascites; oedema.

Furedan *Scharper, Ital.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furesin *Prodotti, Braz.†*
⊗Furosemide (p. 1387·1).
Hypertension.

Furesis *Orion, Fin.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; renal failure.

Furesis comp *Orion, Fin.*
⊗Furosemide (p. 1387·1); triamterene (p. 1518·3).
Oedema.

Furetic *Siam Bheasach, Thai.*
⊗Furosemide (p. 1387·1) or furosemide sodium (p. 1387·1).
Oedema; ascites; eclampsia; barbiturate poisoning; heart failure; renal failure.

Furex *Aspen, S.Afr.*
Nitrofurazone (p. 333·1).
Wounds; burns; ulcers; skin infections.

Furfuril *Roemmers-Klinos, Venez.*
Nitrofurazone (p. 333·1).
Burns; wounds; skin infections; vaginal infections.

Furide *Duopharma, Philipp.; Polipharm, Thai.*
⊗Furosemide (p. 1387·1).
Oedema; liver cirrhosis; nephrotic syndrome; ascites; hypertension.

Furil *OFF, Ital.†*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Berko, Turk.†
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Furin *T Man, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; vestibular disorders.

Furine *Medicine Products, Thai.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furion
Note: this name may be used for preparations of different composition.
Chew, Thai.
Furazolidone (p. 933·3).
Diarrhoea; enteritis.

Orion, India.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Furital *Rivero, Arg.*
⊗Furosemide (p. 1387·1).
Oedema; heart failure; hypercalcaemia.

Furitex *Arlex, Mex.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furix *Investi, Arg.; Nycomed, Denm.; Nycomed, Norw.; Nycomed, Swed.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; forced diuresis; renal failure; nephrotic syndrome.

Furmide *Beacons, Singapore.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furo *AbZ, Ger.†; CT, Ger.†*
⊗Furosemide (p. 1387·1) or furosemide sodium (p. 1387·1).
Oedema; hypertension; ascites; oliguria.

Furo-Aldopur *Kwizda, Ger.†*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Oedema; ascites.

Furobactina *Dexter, Spain.†*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furobeta *Betapharm, Ger.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; oliguria.

Furobid *Alembic, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Furobioxin *Salus, Mex.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Furocef *Taiwan Biotech, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Furocem *Rotexmedica, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Furodermal *Streuli, Switz.†*
Camphor (p. 2466·2); ichthammol (p. 1705·3); bismuth oxyiodogallate (p. 1821·3); thymol (p. 1772·2).
Skin infections.

Furodrix *Streuli, Switz.*
⊗Furosemide (p. 1387·1) or furosemide sodium (p. 1387·1).
Heart failure; oedema; renal failure; oliguria in pregnancy; hypertension; forced diuresis.

Furogamma *Worwag, Ger.*
⊗Furosemide (p. 1387·1).
Ascites; hypertension; oedema; oliguria.

Furohexal *Hexal, Austria.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furoksan *Gunsa, Turk.*
Furazolidone (p. 933·3).
Gastrointestinal infections.

Furolin *Farmanic, Gr.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Furolink *Tai Yu, Philipp.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; oliguria.

Furolnok *Medikon, Indon.†*
Itraconazole (p. 583·3).
Fungal infections.

Furomax *Biomax, India.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Manix, Philipp.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Furome *Epitome, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Furomed *Inpac, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Furomet *Affy, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Furomid *Deva, Turk.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furomida *Belfar, Braz.*
⊗Furosemide (p. 1387·1).

Furomide *Medicpharma, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Furomin *Ratiopharm, Fin.†*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furon *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
⊗Furosemide (p. 1387·1) or furosemide sodium (p. 1387·1).
Oedema; renal failure; forced diuresis; hypertension; heart failure; hypercalcaemic crisis; hypercalcaemia.

Furopectal *SSP, Thai.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Furopectin *PP Lab, Thai.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Bacterial diarrhoea; enteritis.

Furo-Puren *Actavis, Ger.†*
⊗Furosemide (p. 1387·1).
Ascites; hypertension; oedema; oliguria.

Furorese *Hexal, Cz.; Hexal, Ger.†*
⊗Furosemide (p. 1387·1) or furosemide sodium (p. 1387·1).
Oedema; hypertension; ascites; forced diuresis; oliguria.

Furorese Comp *Hexal, Ger.†*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Oedema; ascites.

Furosal *TAD, Ger.†*
⊗Furosemide (p. 1387·1).
Ascites; hypertension; oedema; oliguria.

Furosan *Sanval, Braz.; Teva, Mex.*
⊗Furosemide (p. 1387·1).

Furosantisa *Santisa, Braz.*
⊗Furosemide (p. 1387·1).

Furoscan *Tai Yu, Philipp.*
⊗Furosemide (p. 1387·1).
Heart failure; oedema; renal failure.

Furosem *Medley, Braz.†*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furosemide Composto *Medley, Braz.*
⊗Furosemide (p. 1387·1); potassium chloride (p. 1793·2).
Hypertension; oedema.

Furosemin *Brasterapica, Braz.*
⊗Furosemide (p. 1387·1).

Furosetron *Ariston, Braz.*
⊗Furosemide (p. 1387·1).

Furosix *Delta, Braz.; Landson, Indon.*
⊗Furosemide (p. 1387·1).
Oedema; ascites; hypertension.

Furospir *Mepha, Switz.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Oedema.

Furo-Spirobene *Ratiopharm, Austria.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Aldosteronism; oedema; ascites.

Furostad *Stada, Austria.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furotop *Topgen, Belg.†*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Furotral *Austral, Arg.*
⊗Furosemide (p. 1387·1).
Hypertension.

Furotricina *Finderm, Ital.*
Tyrothricin (p. 384·1); nitrofurazone (p. 333·1).
Gynaecological infections.

Furovenir *Bioavenir, Israel.*
⊗Furosemide (p. 1387·1).
Renal insufficiency; oliguria.

Furox *Mapra, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Furoxil
Note: this name may be used for preparations of different composition.
Torrent, India.
Cefuroxime sodium (p. 255·3).
Bacterial infections.
Vincenti, Venez.
Furazolidone (p. 933·3).
Gastrointestinal infections.

Furoxim *Sel-J, Philipp.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Furoxime *Siam Bheasach, Malaysia.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.
Siam Bheasach, Thai.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Furoxona *Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Furazolidone (p. 933·3).
Gastrointestinal bacterial and protozoal infections; giardiasis; trichomoniasis.

Furoxona CP *Boehringer Ingelheim Promeco, Mex.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Gastrointestinal infections.

Furoxone *GSK, India; Boehringer Ingelheim, Philipp.*
Furazolidone (p. 933·3).
Gastrointestinal infections.

Furoxy *Bosch, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Furozide *ANH, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Furozix *Bunker, Braz.*
⊗Furosemide (p. 1387·1).

Fursemida *Fabra, Arg.; Northia, Arg.; Surar, Arg.; Veinfar, Arg.; Legrand, Braz.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; hypercalcaemia.

Fursol *Sandoz, Switz.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Furtenk *Biotenk, Arg.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Furtipil-L *Uni-Sankyo, India.*
Arginine (p. 2049·1); DL-methionine (p. 1558·2); lycopene (p. 2546·2); folic acid (p. 2063·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc (p. 2126·1).

Furtulon *Roche, China; Chugai, Jpn.*
Doxifluridine (p. 782·3).
Malignant neoplasms.

FuRui *Xieli, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids.

Furuitong *Deyuan, China.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Fusa *Saga, India.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fusacid *Chema-Elektromet, Pol.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fusacort *Saga, India.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).

Fusalar *Teva, Mex.†*
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Fusaloyos *Danval, Spain.*
Fusafungine (p. 302·1).
Upper respiratory-tract infections and inflammation.

Fusepina *Teva, Mex.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Fuseride *Pharmasant, Thai.*
⊗Furosemide (p. 1387·1).
Oedema.

Fusesian *Asian Pharm, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Fusextrine *Sofex, Port.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Fusibact *Cipla, India.*
Fusidic acid (p. 302·1).
Skin infections.

Fusibact-B *East West, India.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).

Fusibet *Farmedia, Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Fusicutan *Dermapharm, Ger.; Dermapharm, Switz.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fusid
Note: this name may be used for preparations of different composition.
Psyco Remedies, India; Chew, Thai.
Fusidic acid (p. 302·1).
Bacterial skin infections.
Gry, Ger.†; Teva, Israel.
⊗Furosemide (p. 1387·1).
Hypertension; oedema; ascites; oliguria.

Fusidate *Aristopharma, Hong Kong.*
Sodium fusidate (p. 302·1).
Gram-positive bacterial skin infections.

Fusiderm *Indi, India.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.
Pharma International, Ukr.
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Fusiderm B *Indi, India.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Pharma International, Ukr.
⊗Fusidic acid (p. 302·1); betamethasone (p. 1623·2).
Infected skin disorders.

Fusidic B *Pharmaniaga, Malaysia.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Fusigen *Geno, India; EON, Philipp.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Fusigen-B *Geno, India.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).

Fusilev *Spectrum, USA.*
Calcium levofolinate (p. 2067·1).
Reduction of methotrexate toxicity; adjunct to fluorouracil in colorectal cancer.

Fusimed *Cassara, Arg.*
Fusidic acid (p. 302·1); hyaluronic acid (p. 2526·2).
Burns; skin infections; ulcers; wounds.

Fusimed B *Cassara, Arg.*
⊗Fusidic acid (p. 302·1); betamethasone (p. 1623·2).
Infected skin, ear, and nose disorders.

Fusimex *SM, Philipp.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; liver cirrhosis.

Fusindac *Viofar, Gr.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Fusindac-H *Viofar, Gr.*
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Fusital *Talent, India.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Fusitop *HLB, Arg.*
Fusidic acid (p. 302·1).
Skin infections; ulcers; wounds.

Fusiwal *Wallace, India.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Fusiwal-B *Wallace, India.*
⊗Beclometasone dipropionate (p. 1621·2); fusidic acid (p. 302·1).

Fusodic *Marching, Hong Kong.†*
⊗Diphenhydramine (p. 626·1); fluocinolone (p. 1636·1); neomycin (p. 329·3).
Infected skin disorders.

Fuson *Agio, India; Pyridam, Indon.; Agio, Philipp.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Fuson-B *Agio, India.*
⊗Beclometasone dipropionate (p. 1621·2); fusidic acid (p. 302·1).

Fuson-H *Agio, India.*
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).

Fusovin *Charoen, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Fusta *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); dextromethorphan (p. 1660·1); diphenhydramine (p. 626·1); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Fustaren *Teva, Mex.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Fustermicina *Teva, Mex.†*
Gentamicin (p. 304·2).
Bacterial infections.

Fustermizol *Teva, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Fustin *Mahakam Beta, Indon.*
Nystatin (p. 590·3).
Candidiasis.

Fusu *Yangtze River, China.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Fusum *Tocogino, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; anxiety; obsessive-compulsive disorder; bulimia nervosa.

Fusycom *Combiphar, Indon.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Skin infections.

Fusys *Zydus, India.*
Fluconazole (p. 578·2).
Fungal infections.

Fusys-TZ *Zydus, India.*
Fluconazole (p. 578·2) tinidazole (p. 949·2).

Futaderm *Interbat, Indon.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Skin infections.

Futalin *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); brompheniramine (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).
Cough; cold symptoms.

Futaline *Merck, Mex.*
⊗Metoprolol (p. 1434·3).

FuTan *Bailu, China.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Futara *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); brompheniramine (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Futasole *Julphar, UAE.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Futasone *Julphar, UAE.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Futeshu *Dihon, China.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Fut-Fit *SSP, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Futiza *Morepen, India.*
Fluconazole (p. 578·2).
Fungal infections.

Futop *Cosme, India.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Futraful *Otsuka, Hong Kong†; Otsuka, Indon.; Taiho, Jpn.*
Tegafur (p. 864·2).
Malignant neoplasms.

Futroken *Kener, Mex.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Futrolit *Sanbe, Indon.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Futura *Marano, Ital.†*
Aspartame (p. 2169·2).
Sugar substitute.

Futura Hostlet *Dansk Droge, Denm.*
Liquorice (p. 1853·2).
Cough.

Futuran
Note: this name may be used for preparations of different composition.
Merck, Spain.
Eprosartan mesilate (p. 1376·2).
Hypertension.

Futuran Plus *Merck, Spain.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Future E *L'Oreal, Canad.*
SPF 15: Ensulizole (p. 1703·1); octocrilene (p. 1715·2).
Sunscreen.

Futuril *Sandoz, Ger.†*
Citalopram (p. 411·1).
Depression; panic disorder.

Fuvatalip *Sandoz, Cz.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Fuviron *Proge, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

FuWei *Haixin, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Fuxal *Cafar, Venez.*
Nitrofurazone (p. 333·1).
Bacterial skin and vaginal infections.

Fuxen *Teva, Mex.†*
Naproxen (p. 98·2).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Fuxilidin *Viofar, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

FuXin
Note: this name may be used for preparations of different composition.
Chia Tai, China.
Capsules; injection: Oxymatrine.
Lunan, China.
Capsules; tablets: ⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Fuxin
Note: this name may be used for preparations of different composition.
Haixin, China.
Azithromycin lactobionate.
Bacterial infections.

Fuxol *Ferring, Mex.*
Furazolidone (p. 933·3).
Gastrointestinal infections.

Fuzeon *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Mex.; Roche, Neth.; Roche, Norw.†; Roche, NZ; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Thai.; Roche, UK; Roche, USA.*
Enfuvirtide (p. 977·2).
HIV infection.

Fuzéon *Roche, Switz.*
Enfuvirtide (p. 977·2).
HIV infection.

Fuzide *Otto, Indon.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Fuzocim *Acino, Switz.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Fuzoltec *Tecnofarma, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Fuzosul *NK, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

F-Vialin *Frankin, Hong Kong.†*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

F-Vita *Medicine Products, Thai.*
Vitamins.
Dietary supplement.

FV-Tone *Daffohils, India.*
Vitamin B substances (p. 2102·3); ferric ammonium citrate (p. 2060·1).

F X Passage *Phoenix, Austria; Worwag, Ger.*
Magnesium sulfate (p. 1787·3).
Constipation; stool softener.

FXT *Sepracor, Canad.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Fybogel *Reckitt Benckiser, Austral.; Reckitt Benckiser, India; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Schering-Plough, Mex.†; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.*
Ispaghula (p. 1849·1).
Dietary fibre supplement; constipation; diverticular disease; spastic colon; irritable bowel syndrome; ostomy management; ulcerative colitis; haemorrhoids; anal fissure; diarrhoea.

Fybogel Mebeverine *Reckitt Benckiser, Irl.; Reckitt Benckiser, UK.*
Ispaghula (p. 1849·1); mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Fycida-M *Genesis, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Fycompa *Eisai, Denm.; Eisai, Norw.; Eisai, Switz.; Eisai, UK; Eisai, USA.*
Perampanel (p. 534·3).
Epilepsy.

Fydocef *Xieon, India.*
Cefixime (p. 240·3); lactic acid bacillus (p. 2596·3).
Bacterial infections.

Fydocep *Xieon, India.*
Cefpodoxime.
Bacterial infections.

Fydof *Xieon, India.*
Ofloxacin (p. 334·3); lactic acid bacillus (p. 2596·3).
Bacterial infections.

Fydogat *Xieon, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Fydogest *Xieon, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Fydoliv *Xieon, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Fydomal *Xieon, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Fydomox *Xieon, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Fydoroxim *Xieon, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Fydozith *Xieon, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Fyflox *Sanify, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Fygek-AS *Aamorb, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Fyline *Armour, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Fyly *Arvincare, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Fymika *Sanify, India.*
Amikacin (p. 214·1).
Bacterial infections.

Fynal *Mankind, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Fynal-OZ *Mankind, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Fysiofer *ITF, Gr.*
Iron succinyl-protein complex (p. 2077·3).
Iron-deficiency anaemia.

Fysiofol *ITF, Gr.*
Iron succinyl-protein complex (p. 2077·3); calcium folinate (p. 2066·3).
Prevention of pregnancy-induced anaemia.

Fyterdin *Unipharm, Mex.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Fytobact *Cadila, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Fytobra *Sanify, India.*
Tobramycin (p. 380·1).
Bacterial infections.

Fytokliman Planta *Leros, Cz.*
St John's wort (p. 449·1); parsley piert (p. 2584·1); origanum (p. 2576·3); melissa (p. 2552·3); lupulus (p. 2546·1); crataegus (p. 2488·1); birch leaf (p. 2457·3).
Menopausal disorders.

Fyton *Izotop, Hung.*
Sodium fytate (p. 1553·3).
For the preparation of technetium-99m sodium fytate for liver scintigraphy.

Fytop *Alkem, India.*
Etoposide (p. 790·2).
Testicular cancer; small cell lung cancer.

Fytosid *Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Rus.; Fresenius Kabi, Thai.; Biogalenic, Venez.*
Etoposide (p. 790·2).
Malignant neoplasms.

Fyzyme *Uniphar, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

F-ZAC *Patar, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Fzin *Biosans, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

F-Zole *Ethix, India.*
Fluconazole (p. 578·2).
Fungal infections.

G20/80 *Kee, India.*
Gentamicin (p. 304·2).
Bacterial infections.

G-204 *Teva, Israel.*
Electrolytes (p. 1775·1) (p. 1778·2).
Haemodialysis.

G-248 *Teva, Israel.*
Electrolytes (p. 1775·1) (p. 1778·2).
Haemodialysis.

G Mycin *BPL, India.*
Gentamicin (p. 304·2).
Eye and ear infections.

G Reg *Orchid, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

GA *Mead Johnson, Fr.; Nutricia, Ital.*
Food for special diets.
Glutaric acidaemia; glutaric aciduria.

GA 1 Anamix *Nutricia, Cz.*
Infant feed.
Glutaric aciduria.

GA1 Anamix *Nutricia, Fr.*
Food for special diets.
Glutaric aciduria type 1.

SHS, Irl.
Infant feed.
Glutaric aciduria.

GA-Amclav *Ascent, Austral.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Gaap Ofteno *Volta, Chile; Sophia, Mex.; Elmor, Venez.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Gaax *Laboratorios Chile, Chile.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Gaax T *Laboratorios Chile, Chile.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Gab *Gufic, India.*
Lindane (p. 2157·1).
Pediculosis; scabies.

Gaba
Note: this name may be used for preparations of different composition.
Hanburys, India.
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabacalma *Arrowblue, Port.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabacap *Zydus, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabacent *Crescent, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabacet *Sanofi-Aventis, Fr.*
Piracetam (p. 393·3).
Mental function disorders; vertigo; dyslexia in children.

Gabacin *Mint, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Gabacross *Pharmacross, Chile.*
Gabapentin (p. 523·3).
Epilepsy.

Gabact *Piramal, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gabadoz *Sandoz, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabafact *Medico, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabafit *Glenmark, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Gabafix M *Aareen, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Gabagamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.; Worwag, Ukr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain; diabetic neuropathy; neuralgia.

Gabahexal *Sandoz, Austral.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabalept *Pliva, Cz.†; Hexal, Denm.; Micro, India; Brown & Burk, Philipp.; Micro Labs, Ukr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

GabaLich *Winthrop, Ger.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabalix *Ratiopharm, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gaballon *Nikkho, Braz.*
Gamma-aminobutyric acid (p. 2509·2); lysine hydrochloride (p. 2079·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); calcium pantothenate (p. 2085·2).
Nutritional supplement.

Gaba-MC *Mediez, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabamed *Generics, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabamerck *Merck, Spain.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabamox *Pentafarma, Port.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabaneurin *Sigma, Braz.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabaneuron *Aristo, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabanext *Piramal, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Gabanez-M *Wintech, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabanicht *Sandoz, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabanox *Sandoz, Cz.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabantin *Iasis, Gr.; Sun, India; Sun, Mex.; M & H, Thai.; Pharma Start, Ukr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabantine *Spirig, Switz.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabapen *Elpen (Ελπεν), Gr.; Pfizer, Jpn.*
Gabapentin (p. 523·3).
Epilepsy.

Gabapentin Forte *Sun, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabapin *Intas, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gaba-PM *Hanburys, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Gabaran *Ranbaxy, Austral.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabaratio *Ratiopharm, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabarone *Ivax, USA.*
Gabapentin (p. 523·3).
Epilepsy; postherpetic neuralgia.

Gabaront *Alet, Gr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabaset *Biofarma, Turk.*
Gabapentin (p. 523·3).

Gabastar M *Lupin, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabata *Alkem, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabatal *Kwizda, Austria.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabatem *Temapharm, Cz.; Temapharm, Pol.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabateva *Med, Turk.*
Gabapentin (p. 523·3).
Epilepsy.

Gabatifin *Generics, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabatin *Neon, India; Aldril, Philipp.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabatine *Aspen, Austral.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabatop *Solitaire, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Gabator *Tarrex Chiesi, Cz.; Torrent, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabator M *Torrent, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabatrex *Intas, Philipp.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain; bipolar disorder.

Gabatur *Cantabria, Spain.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gabax
Note: this name may be used for preparations of different composition.
Temmler, Ger.; Norton, Pol.†
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.
Nikkho, Braz.†
Gamma-aminobutyric acid (p. 2509·2); pyridoxine hydrochloride (p. 2105·3).
Impaired mental function.

Gabaz *Ritz, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabbroral *Pfizer, Belg.; Pfizer, Ital.*
Paromomycin sulfate (p. 943·3).
Bacterial intestinal infections; amoebiasis; giardiasis; bowel sterilisation; hepatic coma.

Gabbryl *Kalbe, Indon.*
Paromomycin sulfate (p. 943·3).
Amoebiasis; hepatic coma.

Gabee *Dr Alson, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gabenil *Remedica, Hong Kong.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabenta *Stichting, Cz.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabental *Pharmanel, Gr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabesato *Bioindustria LIM, Ital.*
Gabexate mesilate (p. 2508·2).
Acute pancreatitis.

Gabex *Andromaco, Chile.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabexal *Sandoz, Indon.*
Gabapentin (p. 523·3).
Epilepsy.

Gabexine *Chiesi, Ital.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabictal *Tecnofarma, Chile.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabil
Note: this name may be used for preparations of different composition.
Biocon, India.
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabimex *Sanofi-Aventis, Arg.*
4-Amino-3-hydroxybutyric acid (p. 512·1).
Behaviour disorders; mental function impairment.

Gabimex Plus *Sanofi-Aventis, Arg.*
4-Amino-3-hydroxybutyric acid (p. 512·1); pyritinol (p. 394·3).
Mental function impairment.

Gabin *Rowex, Irl.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabin-M *Ind-Swift, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabion-M *Zenon, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabir *Birz, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gabirol *Chinoin, Mex.*
Rimantadine hydrochloride (p. 1012·2).
Influenza A.

Gabiten *Ifars, Indon.*
Mebhydrolin (p. 634·2).
Allergic disorders.

Gabiton *Proton, Gr.*
Gabapentin (p. 523·3).

Gabitril *Orphan, Austral.; Cephalon, Austria; Cephalon, Belg.; Torrex Chiesi, Cz.; Cephalon, Denm.†; Cephalon, Fin.†; Cephalon, Fr.; Cephalon, Ger.; Gerolymatos, Gr.; Chiesi, Hung.†; Cephalon, Irl.; Chiesi, Ital.; Cephalon, Pol.; Cephalon, Port.; Cephalon, Spain; Mepha, Switz.; Cephalon, UK; Cephalon, USA.*
Tiagabine hydrochloride (p. 549·3).
Epilepsy; partial seizures.

Gabix *Getz, Philipp.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gablofen *CNS, USA.*
Baclofen (p. 2014·3).
Spasticity.

Gabmylan *Mylan, Spain.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabriglobine *Ivanovo Blood Transfusion, Rus.*
A normal immunoglobulin (p. 2403·3).

Gabrilen *Mibe, Ger.*
Ketoprofen (p. 79·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

Gabrion *Orion, Fin.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabsoft-M *Elnova, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gabtin *Eczacibasi, Turk.*
Gabapentin (p. 523·3).

Gabture *Milpharm, Irl.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gabunat *Strathmann, Ger.*
Biotin (p. 2052·2).
Biotin deficiency.

Gabutin *Siam Bheasach, Thai.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gaby *Siomond, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gacela *Marien, Austria.*
Madar.
Homoeopathic preparation.

Gacida *Sanofi-Aventis, Thai.*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastritis; peptic ulcer; heartburn; gastric hyperacidity.

Gadavist *Bayer, USA.*
Gadobutrol (p. 1585·1).
Contrast medium for magnetic resonance imaging.

Gadinor *Liferpal, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gadital *Italmex, Mex.*
Guaifenesin (p. 1666·2); proxyphylline (p. 1219·2); chlorphenamine maleate (p. 620·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Respiratory-tract disorders.

Gadofem *Gador, Arg.*
Drospirenone (p. 2269·1); estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Gadol *Ronava, Venez.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Gadolax *Gador, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Gadomin *Shanghai Xudong, Philipp.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Gado-MRI *Rafa, Israel.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Gadopril *Gador, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left ventricular dysfunction.

Gadopril D *Gador, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Gadovist *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer, Irl.; Bayer, Ital.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Lusal, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Schering, Turk.; Bayer, UK.*
Gadobutrol (p. 1585·1).
Contrast medium for magnetic resonance imaging.

Gadral *GiEnne, Ital.*
Magaldrate (p. 1856·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis; gastroduodenitis.

G-Advit *GLS, India.*
Vitamins; minerals; ashwagandha (p. 2450·2).

Gadz *Aamorb, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gafudan *Ethica, Indon.*
Fucoidan (p. 2508·1).
Stomach disorders.

Gag-PR *Moraceae, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Gai Er Qing *Ya Bao, China.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Gai Fei *Xincat, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Gai Fu *Langtai, China; SL Pharm, China.*
A recombinant human basic fibroblast growth factor.

Gai Ge En *Southwest, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Gai Heng *Hengrui, China.*
Verapamil hydrochloride (p. 1522·1).

Gai Lei *Yige, China.*
Levocarnitine (p. 2053·2).

Gai Ning *Tiantaishan, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone; bone metastases.

Gai Nuo *Hanson, China; Hengrui, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Gai Nuo Zhen *Zhengda Haier, China.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; hypophosphataemia; hypoparathyroidism; renal osteodystrophy; rickets; osteomalacia.

Gai Qu *Bei Da Gao Ke Hua Tai, China.*
Troxerutin (p. 2505·3).

Gai Rui Ning *Guoda, China.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; Paget's disease of bone; osteoporosis; metastatic bone pain.

Gai San Chun *Zhengda Haier, China.*
Calcitriol (p. 2113·1).
Hyperparathyroidism; rickets.

Gai Shi Te *Hui Yin Bi, China.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Gai Tian Li *Gaitianli, China.*
Calcium (oyster shell) (p. 1783·1).

Gai Di Xin *Dayinhaiyang, China.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Gai Yi *Yige, China.*
Papaverine hydrochloride (p. 2362·3).

Gain Plus *Abbott, Venez.*
Preparation for enteral nutrition.

Gain Total Comfort *Abbott Nutrition, Singapore.*
Hypoallergenic lactose-free infant feed.
Lactose intolerance.

Gainer Masa Musc *Teingro, Arg.*
Amino acids; protein.
Dietary sports supplement.

Gaity *Reddy, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gal *Lennon, S.Afr.†*
Senna (p. 1885·1).
Constipation.

Galacordin *Biomo, Ger.†*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency.

Galactogil *IPRAD, Fr.*
Galega; calcium phosphate (p. 1784·2); malt extract (p. 2080·2).
Lactation insufficiency.

Galactomin *Nutricia, Fr.; Scientific Hospital Supplies, Irl.; SHS, Israel; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Galactosaemia; lactosaemia; lactose, glucose, or galactose intolerance.

Galafem *Jenapharm, Ger.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Galakol *Charak, India.*
⊗Tribulus terrestris (p. 2633·3); ashwagandha (p. 2450·2).

Galaktomin *Terra, Turk.*
Bromocriptine mesilate (p. 895·3).
Female infertility; menstrual disorders; prolactinoma; lactation inhibition; benign breast disorders; hypogonadism; parkinsonism; acromegaly.

Galamed *Labomed, Chile; Ratiopharm, Cz.†*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Galamer *Sun, India.*
Galantamine hydrobromide (p. 391·3).

Galantagen *Mylan, Neth.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Galantase *Mitsubishi Tanabe, Jpn.*
Tilactase (p. 2631·2).
Lactose intolerance.

Galantex *Pharmathen, Neth.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Galantyl *Alphapharm, Austral.; Mylan, NZ.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Galanyl *Viofar, Gr.*
Galantamine hydrobromide (p. 391·3).

Galaren *Fada, Arg.*
Vecuronium (p. 2040·2).
Competitive neuromuscular blocker.

Galavit *Medicor, Rus.*
5-amino-1,2,3,4-tetrahydrophthalazin-1,4-dione sodium salt dihydrate.
Immunodeficiency.
Medikor, Ukr.
5-Amino-1,2,3,4 tetrahydrophthalazin-1,4-dione sodium salt.
Immunomodulator.

Galaxdar *Lacer, Spain.*
Diacerein (p. 45·3).
Osteoarthritis.

Galazolin *Polfa Warsaw, Ukr.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; otitis media.

Galazyme-A *Intra-Labs, India.*
Alpha galactosidase (p. 2437·2).

Galazyme-Pro *Intra-Labs, India.*
Amylase (p. 2442·1); alpha galactosidase (p. 2437·2); tilactase (p. 2631·2); lipase; protease.

Galciclina *Sant Gall, Arg.*
Ampicillin (p. 218·2).
Bacterial infections.

Galcin *Gabriel, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Galcodine *Thornton & Ross, UK.*
Codeine phosphate (p. 40·2).
Dry coughs.

Galdar *GP, Spain.*
⊗Letrozole (p. 817·1).
Breast cancer.

Gale *Purewin, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Galebiron *Plus, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Galebon *Consilient, UK.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Galecin *Probiomed, Mex.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Galedol *Probiomed, Mex.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Galema *KRKA, Ital.*
Galantamine (p. 391·3).
Alzheimer's disease.

Galemin
Note: this name may be used for preparations of different composition.
ACME, Philipp.
Clarithromycin (p. 266·2).
Bacterial infections.

Pharmanel, Gr.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Galenamet *Galen, Irl.†; Galen, UK.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity.

Galenamox *Galen, UK.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Galenic Restaurador Capilar *Neo Dermos, Arg.*
Collagen (p. 2483·2); ginseng (p. 2513·3); aloe vera (p. 1693·2).
Alopecia.

Galenofillipt *Pharmaceutical Factory of St Petersburg, Rus.*
Eucalyptus leaf (p. 2501·1).
Inflammation.

Galenogal *Hertz, Braz.*
Carob; baicuru; sarsaparilla (p. 2610·3); tayuya azougue.

Galenphol *Thornton & Ross, UK.*
Pholcodine (p. 1675·1).
Coughs.

Galepsi *Guardian, Indon.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Galexir *MaxMedica, Swed.*
Cynara (p. 2490·3); gentian (p. 2512·1); curcuma longa.
Indigestion.

Galexos *Janssen, Canad.*
Simeprevir (p. 1015·2).
Chronic hepatitis C.

Galfer *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Ferrous fumarate (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Galfer FA *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia in pregnancy; prevention of megaloblastic anaemia in pregnancy; iron and folic acid deficiency in pregnancy.

Galflux *Guardian, Indon.*
Domperidone (p. 1838·1).
Dyspepsia; epigastric and abdominal fullness; nausea and vomiting.

Galfol *Sant Gall, Arg.*
Folic acid (p. 2063·1).
Folic acid supplement; anaemias.

Galidrin *Probiomed, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Galieve *Reckitt Benckiser, Denm.; Reckitt Benckiser, Fin.; Reckitt Benckiser, Norw.; Reckitt Benckiser, Swed.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux.

Galinerve *Sun, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Galinerve M *Sun, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Galinocort *Vilco, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Galirène *H2 Pharma, Fr.†*
Calcium bromide (p. 2460·3); calcium lactate (p. 1784·1).
Insomnia; nervous disorders.

Galium *Heel, Cz.*
Galium aparine (p. 2481·2); galium mollugo; sedum acre; sempervivum tectorum; caltha palustris; aurum metallicum (p. 2521·1); apis mellifica (p. 2445·2); acidum nitricum (p. 2572·3); pyrogenium (p. 2601·1); urtica urens (p. 2639·3); echinacea angustifolia (p. 2498·1); phosphorus (p. 2589·2); saponaria officinalis (p. 2617·2); clematis recta; thuja occidentalis (p. 2629·3); ononis spinosa (p. 2575·3); juniperus communis; hedera helix (p. 2536·2); betula (p. 2457·3); calcii fluoridum (p. 2053·1); argentum (p. 2615·1).
Homoeopathic preparation.

Galle-Donau *Phafag, Austria; Rotam Reddy, China.*
p,α-Dimethylbenzyl alcohol nicotinate (p. 2493·3); α-naphthylacetic acid (p. 2567·2).
Biliary-tract disorders.

Gallemolan forte *Cesra, Ger.†*
Greater celandine (p. 2522·2); absinthium (p. 2426·1); taraxacum (p. 2625·3).
Dyspepsia; biliary-tract disorders.

Gallen- und Lebertee St Severin *Smetana, Austria.*
Agrimony herb (p. 2432·3); marrubium vulgare (p. 1668·3); peppermint leaf (p. 1877·1); achillea (p. 2427·3); taraxacum (p. 2625·3).
Biliary-tract disorders.

Gallesyn neu *Rosch & Handel, Austria.*
Oral drops: Cynara (p. 2490·3); taraxacum (p. 2625·3); peppermint leaf (p. 1877·1).
Biliary-tract disorders.

Rosch & Handel, Austria.
Tablets: Cynara (p. 2490·3); taraxacum (p. 2625·3); menthol (p. 2553·2).
Biliary-tract disorders.

Gallexier
Note: this name may be used for preparations of different composition.
Sal-Bert, Hung.
Cynara (p. 2490·3); taraxacum (p. 2625·3); gentian (p. 2512·1); curcuma longa; achillea (p. 2427·3); chamomile (p. 2474·1); fennel (p. 2503·2).
Gastrointestinal disorders.

Salushaus, Ger.
Oral liquid: Cynara (p. 2490·3); Javanese turmeric (p. 2636·2); gentian (p. 2512·1); ginger (p. 1844·1); cnicus benedictus (p. 2482·2); menyanthes (p. 2554·2); absinthium (p. 2426·1); fennel (p. 2503·2); cardamom (p. 2471·1); bitter-orange peel (p. 2575·3); chamomile (p. 2474·1); achillea (p. 2427·3); taraxacum (p. 2625·3).
Gastrointestinal disorders.

Salushaus, Ger.
Tablets: Javanese turmeric (p. 2636·2); cynara (p. 2490·3); milk thistle (p. 1561·1); taraxacum (p. 2625·3); chamomile (p. 2474·1); peppermint leaf (p. 1877·1).
Biliary disorders.

Salus, Canad.†
Absinthium (p. 2426·1); calamus (p. 2464·2); chamomile (p. 2474·1); cynara (p. 2490·3); fennel (p. 2503·2); gentian (p. 2512·1); St John's wort (p. 449·1); menyanthes (p. 2554·2); milk thistle (p. 1561·1); taraxacum (p. 2625·3); turmeric (p. 2636·2).

Gallia Anti-Régurgitations *bsa, Fr.*
Infant feed.
Regurgitation.

Gallia Calisma *bsa, Fr.*
Infant feed with *Bifidobacterium breve* (p. 2596·3) and *Streptococcus thermophilus* (p. 2596·3).
Maintenance of gastrointestinal flora.

Gallia Digest *bsa, Fr.*
Infant feed with *Bifidobacterium breve* (p. 2596·3) and *Streptococcus thermophilus* (p. 2596·3).
Digestive disorders.

Gallia HA *bsa, Fr.*
Infant feed.
Milk-protein intolerance.

Gallia Lactofidus *bsa, Fr.*
Infant feed.
Infant colic.

Gallia Soja *bsa, Fr.*
Soy-based infant feed.
Diarrhoea; cows' milk intolerance.

Galliagène *bsa, Fr.*
Infant feed.
Milk-protein intolerance; malabsorption syndromes; diarrhoea.

Gallith *Evers, Ger.*
Ivy (p. 2536·2).
Cholesterol gallstones.

Gallobeta *Betapharm, Ger.†*
Gallopamil hydrochloride (p. 1390·3).
Angina pectoris; arrhythmias; hypertension.

Galloselect *Dreluso, Ger.*
Chamomilla (p. 2474·1); carduus marianus (p. 1561·1); lycopodium (p. 2546·3); chelidonium (p. 2522·2); natrium sulfuricum (p. 1888·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Galloway's Cough Syrup *Chefaro, UK.*
Ipecacuanha liquid extract (p. 1667·2); squill vinegar (p. 1677·3).
Coughs.

Galnora *KRKA, Ger.; TAD, Ger.; KRKA, Spain.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Galocard *Galenus, Pol.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Galol *Elpen (Ελπεν), Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Galopran
Note: this name may be used for preparations of different composition.
Bernabo, Arg.
Mosapride citrate (p. 1865·2).
Dyspepsia; gastro-oesophageal reflux; nausea and vomiting.

Galenus, Gr.
Citalopram hydrobromide (p. 411·1).

Galospa *Galenus, Pol.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Galoxiway *Boots Healthcare, Cz.†*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Galpamol *Galpharm, UK.*
Paracetamol (p. 115·1).
Pain.

Galpent *Galena, Pol.*
Pentaerithrityl tetranitrate (p. 1465·1).
Angina pectoris.

Galperinon *Galena, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Galpharm Flu Relief *Galpharm, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Galprofen *Galpharm, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Galpseud *Thornton & Ross, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Galpseud Plus *Thornton & Ross, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Galstena *Bittner, Austria; Bittner, Rus.; Bittner, Ukr.*
Carduus (p. 1561·1); taraxacum (p. 2625·3); chelidonium (p. 2522·2); natrium sulfuricum (p. 1888·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

Galsya *KRKA, Irl.; Consilient, UK.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Galtamicina *Northia, Arg.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Galten *Galenium, Indon.*
Ubidecarenone (p. 2637·1); levocarnitine (p. 2053·2); vitamin E (p. 2119·1).
Dietary supplement.

Galtes *Boniscontro & Gazzone, Ital.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Galusan *Berenguer Infale, Spain.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Galvenox *Galena, Pol.*
Calcium dobesilate (p. 2464·3).
Vascular disorders; haemorrhoids.

Galvumet *Novartis, Austral.; Novartis, Switz.*
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Galvus *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Dexa, Indon.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.*
Vildagliptin (p. 504·3).
Diabetes mellitus.

Galvus Met *Novartis, Arg.; Novartis, Braz.; Novartis, Chile; Novartis, Malaysia; Novartis, Mex.; Novartis, Rus.; Novartis, Thai.; Novartis, Turk.*
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

GalvusMet *Novartis, Hong Kong.*
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Galvusmet *Novartis, India; Novartis, Indon.; Novartis, Philipp.; Novartis, Singapore; Novartis, Ukr.*
Metformin hydrochloride (p. 489·1); vildagliptin (p. 504·3).
Diabetes mellitus.

Galzin *Teva Tuteur, Arg.; Gate, USA.*
Zinc acetate (p. 2126·1).
Wilson's disease.

Gama *Wan Bang, China.*
Interferon gamma (human, recombinant) (p. 999·1).
Rheumatoid arthritis; malignant neoplasms; viral infections.

Gama Laishi *RAAS, China.*
A normal immunoglobulin (p. 2403·3).
Immunoglobulin deficiency; autoimmune diseases.

Gamacef *Bergamo, Braz.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Gamactrin *Delta, Braz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Gamafine *Haffkine, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia.

Gamaflex *Abdi, Turk.*
Phenprobamate (p. 1096·3).
Skeletal muscle spasm.

Gama-Glob *Zydus, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; bone-marrow transplantation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Gamaglobin *Zydus, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; bone-marrow transplantation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Gamakuil *Embil, Turk.*
Phenprobamate (p. 1096·3).
Skeletal muscle spasm.

Gamalate B6 *Andromaco, Chile; Ferrer, Spain; Ferrer, Ukr.*
Gamma-aminobutyric acid (p. 2509·2); gamma-amino beta hydroxybutyric acid (p. 512·1); magnesium glutamate hydrobromide (p. 2549·1); pyridoxine hydrochloride (p. 2105·3).
Mental function impairment; senility.

Gamaley *Zodley, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).

Gamaline-V *Herbarium, Braz.*
Borage oil (p. 2459·2); wheat-germ oil (p. 2647·1).
Premenstrual syndrome; atopic eczema.

Gamanil *Merck Serono, Irl.*
Lofepramine hydrochloride (p. 433·2).
Depression; mixed anxiety depressive states; panic disorder.

Gamaric *Euphoric, India.*
Lindane (p. 2157·1).
Scabies; pediculosis.

Gamascab *NuLife, India.*
Lindane (p. 2157·1).
Scabies; pediculosis.

Gamastan *Grifols, Canad.; Grifols, USA.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; immunoglobulin deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gamatropin *Alvartis, Mex.†*
⊗Naphazoline (p. 1669·3).

Gamavate *Julphar, UAE.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Gama-Venina *ZLB, Braz.†*
A normal immunoglobulin (p. 2403·3).
Agammaglobulinaemia; chronic demyelinated polyneuropathy; hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; lymphocytic leukaemia; passive immunisation.

Gamavit B6 *Royal, Chile.*
Gamma-aminobutyric acid (p. 2509·2); 4-amino-3-hydroxybutyric acid (p. 512·1); magnesium glutamate hydrobromide (p. 2549·1); pyridoxine hydrochloride (p. 2105·3).
Mental function disorders.

Gamazex *Daksh, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).

Gambaran *Meda, Belg.*
Nabumetone (p. 97·1).
Musculoskeletal, joint, and peri-articular disorders.

Gambex *Aspen Consumer, S.Afr.*
Lindane (p. 2157·1).
Pediculosis.

Gambrosol *Fresenius Medical, Canad.; Gambro, Cz.; Gambro, Denm.; Gambro, Fr.†; Diaverum, Hung.†; Fresenius Medical, Irl.; Fresenius Medical, Neth.; Fresenius Medical, Norw.; Fresenius Medical, Spain†; Fresenius Medical, Swed.; Fresenius Medical, Switz.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Gambro, Port.
Glucose (p. 2068·3); sodium lactate (p. 1781·2); sodium chloride (p. 1795·1); magnesium choride (p. 1787·1) (p. 1778·2).
Peritoneal dialysis.

Game *Dyota, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gameral *Gache, Venez.*
Aloe vera (p. 1693·2); cascara (p. 1826·1).
Constipation.

Gamespir *Cosmopharm, Gr.*
Acemetacin (p. 16·3).
Pain; inflammation; musculoskeletal disorders; spondyloarthritis; gout.

Gamet *Constant, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gametop *Solitaire, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gamibetal *Arrow, Braz.; SIT, Ital.; Italmex, Mex.*
Aminohydroxybutyric acid (p. 512·1).
Impaired mental function; neurosis; premenstrual syndrome; epilepsy.

Gamibetal Complex *SIT, Ital.*
Aminohydroxybutyric acid (p. 512·1); phenobarbital (p. 535·2); phenytoin sodium (p. 538·2).
Epilepsy.

Italmex, Mex.†
4-Amino-3-hydroxybutyric acid (p. 512·1); phenytoin (p. 538·2); phenobarbital (p. 535·2).
Epilepsy.

Gamibetal Plus *SIT, Ital.*
Aminohydroxybutyric acid (p. 512·1); diazepam (p. 1063·2).
Epilepsy; childhood behaviour disorders.

Gamibit *Cubit, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gamikal *Probiomed, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Gamimune *Bayer, Gr.*
A normal immunoglobulin (p. 2403·3).

Gamimune N *Bayer Biological, Hong Kong†; Dipa, Indon.†; Bayer, Philipp.; GenAsia, Philipp.; Talecris, Rus.; Biem, Turk.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; immune thrombocytopenia; bone-marrow transplantation; passive immunisation; hypogammaglobulinaemia; Kawasaki disease; Guillain-Barré syndrome.

Gaminex *Demo, Gr.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; chronic inflammatory demyelinating polyneuropathy; Kawasaki disease; bone marrow transplantation.

Gamlo *CMG, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Gamlo AT *CMG, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Gamma Anti D *Grifols, Spain.†*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Gamma Antihepatitis B *Grifols, Spain.†*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Gamma Antitetanos *Grifols, Spain.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Gamma Anty D *Biomed Lublin, Pol.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of Rhesus sensitisation.

Gamma Anty HBs *Biomed Lublin, Pol.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Gammadin *OFF, Ital.†*
Povidone-iodine (p. 1767·1).
Skin, wound, and mucous membrane disinfection.

Gammadol *Schering-Plough, Mex.*
Ketorolac trometamol (p. 80·2); tramadol hydrochloride (p. 139·2).
Pain.

Gammagard *Baxter, Austria; Baxter, Canad.; Baxter, Cz.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.†; Baxter, Irl.; Baxter, Israel; Baxter, Ital.; Baxter, Neth.; Bioscience, Philipp.; Baxter, Pol.; Baxter, Port.; Baxter, Singapore; Baxter, Spain; Baxter, Swed.; Baxter, Thai.†; Baxter BioScience, UK; Baxter, USA.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; immunodeficiency; bone-marrow transplantation; passive immunisation; autoimmune disorders; nephrotic syndrome; motor neuropathy.

Gammagard SD *Baxter, Belg.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia.

Gammaglob Antihepatitis BP *CSL, Spain.†*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Gamma-Globulin *Green Cross, Malaysia.*
A normal immunoglobulin (p. 2403·3).
Agammaglobulinaemia; hypogammaglobulinaemia; passive immunisation.

Gamma-Globulina *Biomed Lublin, Pol.†*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

Gammaglobulina *Hemoderivados, Arg.; Grifols, Spain.†*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

Gamma-IV *Bharat, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; bone-marrow transplantation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Gammalin *Biopharma, Ukr.*
Herpes simplex immunoglobulin.
Passive immunisation.

Gammalon *Daiichi, Hong Kong; Daiichi, Thai.†*
Gamma-aminobutyric acid (p. 2509·2).
Cerebrovascular disorders; head injury; mental function impairment; amnesia; speech disorders; palsy; hypertension.

Gammanorm *Octapharma, Austria; Octapharma, Belg.; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Fr.; Octapharma, Ger.; Octapharma, Hung.; Octapharma, Irl.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, NZ; Octapharma, Port.; Octapharma, Swed.; Octapharma, Switz.; Octapharma, UK.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immunodeficiency; passive immunisation.

Gamma-OH *SERB, Fr.*
Sodium oxybate (p. 1914·1).
General anaesthesia; sedative.

Gammaplex *Kamada, Israel; BPL, UK; BPL, USA.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; passive immunisation; immune thrombocytopenia; hypogammaglobulinaemia; Guillain-Barré syndrome; Kawasaki disease.

Gammaplus *Fidia, Ital.*
Omega-3 triglycerides (p. 1460·3); omega-6 triglycerides.
Nutritional supplement.

GammaQuin *Sanquin, Neth.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency disorders; passive immunisation.

Gammar
Note: this name may be used for preparations of different composition.
Nikkho, Braz.
Gamma-aminobutyric acid (p. 2509·2).
Impaired mental function; cerebrovascular disorders.

Farma-Tek, Turk.
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Gammaraas *Combiphar, Indon.; Shanghai RAAS, Thai.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; immune thrombocytopenia; Kawasaki disease; hypogammaglobulinaemia; immune deficiency; bone marrow transplant.

Gamma-Scab *Lafedar, Arg.*
Lotion: Lindane (p. 2157·1); lidocaine hydrochloride (p. 1988·2).
Scabies.

Lafedar, Arg.
Shampoo: Lindane (p. 2157·1).
Pediculosis; scabies.

Gammasolde *Helm, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Gammatet *Gador, Arg.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Gamma-Tet P *CSL, Ital.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Gammatetanos *Lab Francais du Fractionnement, Fr.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Gamma-Venin *Gerolymatos, Gr.; ZLB, Gr.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; passive immunisation; Kawasaki disease.

Gamma-Venin P *CSL, Mex.†*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

Gammaxol *Federfarma, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Gamonil *Galenica, Gr.*
Lofepramine hydrochloride (p. 433·2).

Gamophen *Aledicine, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Johnson & Johnson, Austral.; Johnson & Johnson Medical, UK.
Triclosan (p. 1773·2).
Soap substitute; acne; skin cleanser.

Gamunex *Talecris, Austria; Grifols, Canad.; Talecris, Cz.; Grifols, Denm.; Grifols, Fin.; Grifols, Ger.; Dipa, Indon.; Talecris, Israel; Grifols, Neth.; Talecris, Port.; Talecris, Rus.; Grifols, Swed.; Crucell, Switz.; Biem, Turk.; Grifols, UK; Bayer, USA.†*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone-marrow transplantation; graft-versus-host disease; Wiskott-Aldrich syndrome; chronic inflammatory demyelinating polyneuropathy; passive immunisation.

Gan Di *Song He, China.*
Matrine.

Gan Bi Mei *Pacific, China.*
⊗Lactic acid (p. 2539·1); urea (p. 1727·3).

Gan Bi Xin *Zheng An, China.*
Matrine.

Gan Dan *Huashidan, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Gan Fei Lin *Yi Chuang, China.*
Theophylline sodium glycinate.

Gan Fen *Lukang Chenxin, China.*
Aceglutamide (p. 2426·2).

Gan Feng *Lukang Chenxin, China.*
Pentoxifylline (p. 1465·3).

Gan Han *Jiangxi, China.*
⊗Liquorice (p. 1853·2); morphine (p. 92·3).

Gan Ke *Jiangxi, China.*
Inosine (p. 2533·1).

Gan Le Li *Ke Lun, China.*
Fructose (p. 2068·2).

Gan Li Ke Fu *Shengma, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Gan Luo *Tian Yu, China.*
Lysine hydrochloride (p. 2079·3).

Gan Mei *Chia Tai, China.*
Magnesium isoglycyrrhizate.

Gan Mei Duo Lan *Shuang Cheng, China.*
Hyoscine butylbromide (p. 1845·3).

Gan Mu Shu *Deyao, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Gan Ning *Gelalei, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Gan Nuo Xin *JiChuan, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gan Ping *Chia Tai, China.*
Diammonium glycyrrhizinate.

Gan Quan *Guangcai, China.*
Inosine (p. 2533·1).

Gan Ruo Na *Qian Long, China.*
Diammonium glycyrrhizinate.

Gan Sheng Su *Saida, China.*
Transfer factor (bovine) (p. 2633·2).

Gan Su *Yangtze River, China.*
Azasetron hydrochloride (p. 1820·2).

Gan Wei Xin *Huali, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Gan Xin *HaiWang Fuyao, China.*
Oxymatrine.

Gan Du Xin *Hayao, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Gan Yi *Chang Fu Jie Jing, China.*
Matrine.

Gan You Lin *Tongyong, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Gan Yue Xi *C & O, China.*
Irbesartan (p. 1411·1).
Hypertension.

Gan Zhi *Honghui, China.*
Glutathione (p. 1555·2).

Ganaton *Abbott, Cz.; Abbott, India; Abbott, Jpn; Abbott, Malaysia; Abbott, Philipp.; Abbott, Rus.; Abbott, Thai.*
Itopride hydrochloride (p. 1850·1).
Gastrointestinal motility disorders; gastrointestinal symptoms of chronic gastritis; dyspepsia.

Ganaton Total *Abbott, India.*
Itopride hydrochloride (p. 1850·1); pantoprazole (p. 1875·3).

Ganavax *Rontag, Arg.*
Venlafaxine hydrochloride (p. 454·2).
Depression; mixed anxiety-depressive states.

Ganazolo *Ganassini, Ital.*
Econazole (p. 577·2) or econazole nitrate (p. 577·3).
Fungal and Gram-positive bacterial infections.

Ganciclotrat *Uniao Quimica, Braz.*
Ganciclovir sodium (p. 982·3).

Ganda *Chauvin, Irl.†*
⊗Guanethidine monosulfate (p. 1395·2); adrenaline (p. 1292·1).
Glaucoma.

Gandhour *Dermoteca, Port.†*
A range of soap substitutes and moisturisers.

Gandin *Polipharm, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Ganfort *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Braz.; Allergan, Chile; Allergan, Cz.; Allergan, Denm.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, India; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Allergan, Malaysia; Allergan, Neth.; Allergan, Norw.; Allergan, NZ; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, Ukr.*
⊗Bimatoprost (p. 2004·2); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ganforti *Allergan, Mex.*
⊗Bimatoprost (p. 2004·2); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Gangiden *Sandoz, Denm.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Ganglioside *Armstrong, Mex.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Ganguard *Ranbaxy, India.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Ganidin NR *Cypress, USA.†*
Guaifenesin (p. 1666·2).

Ganin *Ferron, Indon.*
Gabapentin (p. 523·3).
Epilepsy.

Ganite *Genta, USA.*
Gallium nitrate (p. 1184·1).
Hypercalcaemia of malignancy.

Gani-Tuss NR *Cypress, USA.†*
Guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Gani-Tuss-DM NR *Cypress, USA.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Ganlixin *Chia Tai, China.*
Diammonium glycyrrhizinate.
Hepatic disorders.

Ganospec *Picco, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

GanPing *Changyuan, China.*
Matrine.

Ganruining *Huajin, China.*
⊗Glycerol (p. 2517·2); fructose (p. 2068·2); sodium chloride (p. 1795·1).
Raised intracranial pressure; cerebral oedema.

GanShuLin N *Dongbao, China.*
⊗Isophane insulin (p. 475·3).
Diabetes mellitus.

GanShuLin R *Dongbao, China.*
⊗Insulin injection (p. 475·3).
Diabetes mellitus.

Gansol *Sanovel, Turk.*
Sulfafurazole diolamine (p. 364·2).
Bacterial eye infections.

Gantai *Qianjiang, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ganticol *Oftalmi, Venez.*
Sulfafurazole (p. 364·1).
Bacterial eye infections.

Gantil *Elpen (Ελτεν), Gr.*
Tolfenamic acid (p. 138·3).
Pain; inflammation; musculoskeletal and joint disorders.

Gantin *Pfizer, Austral.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gantrisin *Roche, USA.†*
Acetyl sulfafurazole (p. 364·1).
Bacterial infections; malaria; nocardiosis; toxoplasmosis.

Ganvirax *Blausiegel, Braz.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

Ganvirel *Ivax, Arg.*
Lamivudine (p. 1000·2).
HIV infection.

Ganvirel Duo *Ivax, Arg.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

GanXin *Qi Du, China.*
Metadoxine (p. 2105·3).
Liver disorders; alcoholism.

Ganxuebao *Wanma, China.*
Chlorophyllin copper complex sodium (p. 2178·3).

Gao Di *Hayao, China.*
⊗Naproxen sodium (p. 98·2); pseudoephedrine hydrochloride (p. 1676·1).

Gao De *Saite, China.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Gao Ju Sheng *Xiehe, China.*
Staphylococcus aureus.

Gao Rui Te *Tai Sheng, China.*
Omacetaxine mepesuccinate (p. 837·3).

Gao Xi *Beijing Union, China.*
Vitamin C (p. 2110·3).

Gao Zi Ke *San Jin, China.*
Nicotinic acid (p. 2083·1).

Gaofen *General Sanyang, China.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Gaoptol *Europhta, Mon.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Gaosédal Codéine *Merck Medication Familiale, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Gaoyi *Jing Xin, China.*
Faropenem sodium (p. 298·2).

Gapentek *Actavis, Rus.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gapenten *Aenorasis, Gr.*
Gabapentin (p. 523·3).

Gapridol *Psicofarma, Mex.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gaproxen *Gap, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Garabet *Oftalmi, Venez.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected eye disorders.

Garabiotic *Bernofarm, Indon.†*
Gentamicin sulfate (p. 304·2).
Skin infections.

Garacin *Delta, Braz.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garacol *EUSA, Neth.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garacoll *Schering-Plough, Mex.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections of bone and soft tissue.

Garakacin *Offenbach, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Garalen *Probiomed, Mex.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garalone *Schering-Plough, Port.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garamat *Schering-Plough, Gr.*
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin sulfate (p. 304·2).
Eye and ear inflammation and infection.

Garamax *Admac, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Garamicina *Mantecorp, Braz.; Schering-Plough, Mex.*
Gentamicin (p. 304·2) or gentamicin sulfate (p. 304·2).
Bacterial infections.

Garamicina-V *Schering-Plough, Mex.†*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Garamin *Prodotti, Braz.†*
Gentamicin (p. 304·2).
Bacterial infections.

Garamycin *Merck, Canad.; EUSA, Cz.; Schering-Plough, Denm.†; Schering-Plough, Gr.; MSD, Hong Kong; Innocoll, Hung.†; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Norw.†; Essex, Philipp.; EUSA, Pol.; Schering-Plough, S.Afr.; MSD, Swed.; MSD, Switz.; MSD, Thai.; Fera, USA.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Fulford, India.
Gentamicin (p. 304·2) or gentamicin sulfate (p. 304·2).
Bacterial infections.

Garapepsin *Medichrom, Gr.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal and gallbladder pain.

Garapon *Armoxindo, Indon.*
Gentamicin sulfate (p. 304·2).
Skin infections.

Garasent *CCM, Malaysia; Duopharma, Singapore.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garasone *Mantecorp, Braz.; Merck, Canad.; Schering-Plough, Cz.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, Philipp.; Schering-Plough, Rus.; MSD, Singapore†; Schering-Plough, Venez.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected ear and eye disorders.

Garazin *Duopharma, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garbilocin *Rafarm, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Garbital *Neo Quimica, Braz.*
Phenobarbital (p. 535·2).

Garbose *YSP, Malaysia.*
Acarbose (p. 466·2).
Diabetes mellitus.

Garceptol *Grunenthal, Chile.*
Dimeticone (p. 1886·2); metoclopramide hydrochloride (p. 1862·2); chlordiazepoxide hydrochloride (p. 1044·2).
Gastrointestinal disorders.

Garcinia Cambogia Compuesta *Lafarmen, Arg.*
Garcinia cambogia (p. 2510·2); chromium tripicolinate (p. 2056·1).
Nutritional supplement.

Garcinia + Fucus *Biokosma, Arg.*
Garcinia cambogia (p. 2510·2); fucus vesiculosus; pantothenic acid (p. 2085·2).
Dietary supplement.

Garcinol Max *Garden House, Arg.*
Tablets: Centella (p. 1698·3); carnitine (p. 2053·2); garcinia cambogia (p. 2510·2).
Cellulite; dietary supplement; slimming aid.

Garcol *Christo, Hong Kong.*
Dimenhydrinate (p. 625·2).
Nausea; vertigo; vestibular disorders; motion sickness.

Gard Plus *Plus, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Gardan *Sanofi-Aventis, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Gardan P
Note: this name may be used for preparations of different composition.
Polfa Pabianice, Pol.†
Dipyrone (p. 53·3); propyphenazone (p. 127·3).
Pain.

Gardasil *MSD, Arg.; MSD, Austral.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Merck Frosst, Canad.; MSD, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Gr.; MSD, Hong Kong; Merck, India; MSD, Indon.; Sanofi Pasteur, Irl.; MSD, Israel; Sanofi Pasteur, Ital.; MSD, Jpn; MSD, Malaysia; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; CSL, NZ; MSD, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; MSD, Thai.; MSD, Turk.; Sanofi Pasteur, UK; MSD, Ukr.; Merck, USA.*
A human papillomavirus vaccine (types 6, 11, 16, and 18) (p. 2392·2).
Active immunisation.

Garden Line *Garden House, Arg.*
Food for special diets.
Slimming aid.

Gardenal *Sanofi-Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Gr.; Piramal, India; Sanofi-Aventis, Spain; Sanofi-Aventis, Venez.*
Phenobarbital (p. 535·2).
Epilepsy; sedative; febrile convulsions; hyperbilirubinaemia; insomnia; nocturnal enuresis.

Sanofi-Aventis, Thai.
Phenobarbital sodium (p. 535·3).
Epilepsy.

Gardénal *Sanofi-Aventis, Fr.*
Phenobarbital (p. 535·2) or phenobarbital sodium (p. 535·3).
Epilepsy.

Gardenale *Sanofi-Aventis, Ital.*
Phenobarbital (p. 535·2).
Insomnia; epilepsy; sedative.

Gardex *Nordic Drugs, Fin.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Gardian *Cipla, India.*
Ascorbic acid (p. 2110·3); choline (p. 2055·2); cyanocobalamin (p. 2107·2); DL-methionine (p. 1558·2); green tea (p. 2648·2); lycopene (p. 2546·2); pyridoxine hydrochloride (p. 2105·3); selenium (p. 2086·3); vitamin E (p. 2119·1).

Gardoton *Raffo, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Raffo, Chile.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Garexin *GMP, Indon.*
Gentamicin sulfate (p. 304·2).
Eye infections.

Garfield *Menley & James, USA.*
Vitamins minerals.

Gargadrin-R *Lafedar, Arg.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); hexylresorcinol (p. 1755·1); benzocaine (p. 1980·2); benzethonium chloride (p. 1738·1).
Mouth and throat disorders.

Gargaletas *Monserrat, Arg.*
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Gargarex *Berko, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat infections.

Gargaril *Puerto Galiano, Spain.*
Chlorhexidine (p. 1743·2); benzocaine (p. 1980·2).
Mouth and throat disorders.

Gargarin *Aflofarm, Pol.; Farmina, Pol.*
Borax (p. 2459·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); sodium benzoate (p. 1738·2); menthol (p. 2553·2).
Mouth and throat disorders.

Gargarisma zum Gurgeln *Krewel, Ger.*
Aluminium chloride (p. 1693·3).
Mouth inflammation.

Gargocetil *Bunker, Braz.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Gargojuice *Belfar, Braz.*
Benzydamine (p. 29·2).

Gargol *Rekah, Israel.*
Thymol (p. 1772·2); chloroxylenol (p. 1748·2); thyme oil (p. 2630·3); boric acid (p. 2459·3); menthol (p. 2553·2); terpineol (p. 2627·2); cineole (p. 2479·1); methyl salicylate (p. 92·1).
Mouth and throat disorders.

Gargomax *Multilab, Braz.*
Cetylpyridinium chloride (p. 1743·1).

Garianes *Nufarindo, Indon.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Garimide *Rochester, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Garion *Generics, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Garlee *Ind-Swift, India.*
Garlic (p. 2510·3).

Garlic Allium Complex *GNLD, Austral.*
Garlic (p. 2510·3); onion (p. 2575·2); chive; leek; rosemary (p. 2607·2).
Dietary supplement.

Garlic and Horseradish + C Complex *Cenovis, Austral.†*
Horseradish (p. 2526·1); garlic (p. 2510·3); sodium ascorbate (p. 2111·1); ascorbic acid (p. 2110·3); fenugreek (p. 2504·1); althaea (p. 2438·3).
Upper respiratory-tract symptoms.

Garlic Pearls *Ranbaxy, India.*
Garlic oil (p. 2510·3).

Garlic-Plus *Ikapharmindo, Indon.*
Garlic (p. 2510·3); vitamin E (p. 2119·1).
Circulation disorders; hyperlipidaemias; hypertension. Style in mimsonline is Garlic Plus.

Garlill *Charak, India.*
Garlic (p. 2510·3); aloes (p. 1816·1); asafetida (p. 2449·3); zingiber officinale.

Garlimega *Cantassium Co., UK.*
Garlic (p. 2510·3).

Garlin *Klar Sehen, India.*
Cetylpyridinium chloride (p. 1743·1); chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2).

Garlix *Blackmores, Austral.†*
Garlic (p. 2510·3).
Cold and influenza symptoms.

Garmastan *Beaco, Hung.; Med, Turk.*
Guaiazulene (p. 2523·1).
Mastitis prophylaxis; skin disorders.

Garnid *Intas, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Garoin *Nicholas Piramal, India.*
Phenytoin sodium (p. 538·2); phenobarbital sodium (p. 535·3).
Epilepsy.

Garol *Kurtsan, Turk.*
Cetylpyridinium chloride (p. 1743·1); thymol (p. 1772·2); menthol (p. 2553·2).
Mouth and throat disorders.

Garonsept *Master, Chile.†*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat infections.

Garra do Diabo *Herbarium, Braz.†*
Devil's claw root (p. 42·3).
Arthroses.

Gartban *Shiono, Jpn.*
Argatroban (p. 1307·2).
Thromboembolic disorders; occlusive arterial disease.

Gartech *Eagle, Austral.†*
Potassium iodide (p. 2336·3); andrographis (p. 2443·2); astragalus; echinacea purpurea (p. 2498·1); garlic (p. 2510·3); European barberry (p. 2502·1); onion (p. 2575·2); origanum oil (p. 2576·3); wild thyme oil (p. 2648·1); garlic oil (p. 2510·3); anise oil (p. 2444·3); savory oil (p. 2625·1); cinnamon oil (p. 2479·3).
Upper respiratory-tract infections.

Gartricin *Toll, Spain.*
Benzocaine (p. 1980·2).
Mouth and throat disorders.

Gartun *Lusomedicamenta, Port.*
Benzydamine hydrochloride (p. 29·2); aluminium lactate (p. 2440·2).
Mouth and throat disorders.

Garydol *Cinfa, Spain.*
Chlorhexidine gluconate (p. 1743·3); benzocaine (p. 1980·2).
Sore throat.

Gas Ban *Roberts, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Flatulence.

Gas Ban DS *Roberts, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence.

Gas Relief *Banner, Canad.; Rugby, USA.*
Simeticone (p. 1886·2).
Flatulence.

Gasbusters *Key, Austral.*
Simeticone (p. 1886·2).
Flatulence.

Gascoal *YSP, Malaysia; Yung Shin, Singapore.*
Simeticone (p. 1886·2).
Flatulence; preparation for gastrointestinal examination.

Gascon *Kissei, China; Kissei, Hong Kong.*
Dimeticone (p. 1886·2).
Flatulence; preparation for gastrointestinal investigations.

Gascop *Valdecasas, Mex.*
Albendazole (p. 149·1).
Worm infections.

Gascopan *Tai Yu, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer.

Gasdol *Bago, Chile.*
Domperidone (p. 1838·1).
Nausea; vomiting; reflux; dyspepsia; pyrosis.

Gasec *Mepha, Braz.†; Mepha, Cz.; Mepha, Malaysia; Mepha, Pol.; Mepha, Port.; Mepha, Singapore; Mepha, Ukr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia; gastritis.

Gasex *Himalaya Herbal, India.*
Syrup: Celery (p. 2472·3); coriander (p. 2486·3); cuminum cyminum; curcuma longa; elettaria cardamomum; fennel (p. 2503·2); mentha arvensis.
Himalaya Herbal, India.
Tablets: Piper nigrum; zingiber officinale.

Gasfamin *Meprofarm, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Gasflat *Fahrenheit, Indon.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive disorders; meteorism; flatulence; preparation for gastrointestinal radiography.

Gasidone *Stallion, Philipp.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; diabetic gastroparesis.

Gasitone *ANB, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity.

Gaskit *Armour, India.*
Oral drops; syrup: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Armour, India.
Tablets: ⊗Amylase (p. 2442·1); pancreatin (p. 2579·3); sodium tauroglycocholate.

Gaslon N *Shinyaku, China; Shinyaku, Jpn.*
Irsogladine maleate (p. 1848·3).
Peptic ulcer; gastritis.

Gas-mad *T Man, Thai.†*
Simeticone (p. 1886·2).
Flatulence.

Gas-Med *T Man, Thai.*
Simeticone (p. 1886·2).
Flatulence.

Gasmilen *Ivax, Arg.*
Ganciclovir (p. 982·3).
Viral infections.

Gas-MM *Milano, Thai.*
Simeticone (p. 1886·2).
Flatulence; preparation for gastrointestinal examination.

Gasmol
Note: this name may be used for preparations of different composition.
Richmond, Arg.
Bromazepam (p. 1041·2).
Anxiety.

Gasmotin *Sumitomo, China; Dainippon, Jpn; Dainippon, Philipp.; Eisai, Thai.*
Mosapride citrate (p. 1865·2).
Gastritis; dyspepsia.

Gas-Nep *Sriprasit, Thai.*
Cataria; sodium bicarbonate (p. 1781·1); caraway oil (p. 2470·3); fennel oil (p. 2503·3); cardamom oil (p. 2471·1); anise oil (p. 2444·3).
Flatulence; gastrointestinal disorders.

Gasnil *Cipla, India.*
Activated charcoal (p. 1537·3); simeticone (p. 1886·2).

Gasoff *Maver, Chile.*
Simeticone (p. 1886·2).
Flatulence; meteorism; infant colic.

Gasopax *Prater, Chile.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Antacid; flatulence.

Gasopep *Solitaire, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gasorab *Solitaire, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Gasorab-D *Solitaire, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Gasorab-T *Solitaire, India.*
Itopride; rabeprazole (p. 1881·1).
Gastro-oesophageal reflux.

Gasorbol *Andromaco, Chile.*
Oral drops: Simeticone (p. 1886·2); pipenzolate bromide (p. 1878·1).
Aerophagia; infant colic.

Gaspalon *Biomedica, Gr.*
Metoclopramide hydrochloride (p. 1862·2).

Gaspaz *Biological E, India.*
Domperidone (p. 1838·1); ranitidine (p. 1882·1).

Gaspen *Yung Shin, Philipp.*
Hydrotalcite (p. 1845·2).
Peptic ulcer; gastritis; hyperacidity.

Gaspiren *Biolab Sanus, Braz.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; gastric hyperacidity; peptic ulcer.

Gasprid *Teva, Pol.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux.

Gassi *Medicine Products, Thai.*
Simeticone (p. 1886·2).
Flatulence.

Gastab
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Sodium bicarbonate (p. 1781·1); cataria.
Flatulence.

APT, Hong Kong.†
Cimetidine (p. 1827·1).
Peptic ulcer; dyspepsia.

Gastabid *Torrent, India.*
Isopropamide (p. 1848·3); trifluoperazine (p. 1113·2).

Gastac *Giempi, Venez.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; heartburn.

Gastacin *Heromycin, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Gastal *Pliva, Rus.*
Hydrotalcite (p. 1845·2); magnesium hydroxide (p. 1857·2).
Formerly contained aluminium hydroxide-magnesium carbonate co-dried gel and magnesium hydroxide.
Gastritis; peptic ulcer; gastro-oesophageal reflux; epigastric pain; heartburn.

Pliva, Cz.†; Teva, Pol.
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; dyspepsia; peptic ulcer; gastro-oesophageal reflux.

Teva, Ukr.
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2).
Peptic ulcer; gastro-oesophageal reflux; gastritis; dyspepsia; gastric irritation; heartburn.

Pliva Krakow, Pol.†
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; dyspepsia; peptic ulcer; gastro-oesophageal reflux.

Gastasil *Heromycin, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Gastec *Bernabo, Arg.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastec Rapido *Bernabo, Arg.*
Omeprazole (p. 1867·2); sodium bicarbonate (p. 1781·1).
Peptic ulcer; gastro-oesophageal reflux.

Gasteel
Note: this name may be used for preparations of different composition.
Fuso, Hong Kong.
Dimeticone (p. 1886·2); aluminium hydroxide (p. 1817·2).
Flatulence.

Gastenorm *Ratiopharm, Rus.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders; aid in abdominal examination.

Gaster
Note: this name may be used for preparations of different composition.
Astellas, China; Astellas, Indon.; Astellas, Jpn.
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis; pathological hypersecretory disorders; gastrointestinal haemorrhage; Zollinger-Ellison syndrome; acid aspiration.

Unison, Thai.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gasterix *Ratiopharm, Fin.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gasterogen *Faran, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Gasterol *Terra, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastica *Mankind, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Gastica Plus *Mankind, India.*
Alpha galactosidase (p. 2437·2); carica papaya; aspergillus niger; aspergillus oryzae; simeticone (p. 1886·2).

Gastidine *Vida, Hong Kong.†*
Cimetidine (p. 1827·1).
Peptic ulcer.

Gastifam *Munir, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastilox *Novum, Neth.*
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastro-oesophageal reflux; peptic ulcer; gastritis; heartburn.

Gastilox Plus Dimeticon *Novum, Neth.*
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Heartburn; peptic ulcer; gastritis.

Gastogyl-M *Biological E, India.*
Metronidazole benzoate (p. 936·1); norfloxacin (p. 333·3).

Gastop *Bajer, Arg.*
Simeticone (p. 1886·2); bismuth carbonate (p. 1822·1).
Gastrointestinal disorders.

Gastosis *Intel, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Gastracid
Note: this name may be used for preparations of different composition.
Meyer, India.
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Natur Produkt, Rus.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Peptic ulcer; gastro-oesophageal reflux; gastritis.
Wagner, Hung.
Aluminium oxide (p. 1690·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.
AWD, Ger.†
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastractiv *Johnson & Johnson, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Gastralgin *Boehringer Ingelheim, Ital.*
Roxatidine acetate hydrochloride (p. 1884·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastran
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Braz.
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; flatulence.
Medifarma, Indon.†
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; peptic ulcer; nausea; gastric pain; heartburn; flatulence; bloating.
Socobom, Belg.†
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux.

Gastranil *Lanpharm, Arg.*
Bismuth hydroxide (p. 1821·3); papaverine hydrochloride (p. 2362·3); aluminium silicate (p. 1818·3); magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1); titanium dioxide (p. 1725·1); calcium carbonate (p. 1824·3); belladonna (p. 2453·3); vitamin B_1 (p. 2102·3).
Gastrointestinal disorders.

Gastranin Zdrovit *Natur Produkt, Pol.*
Ranitidine (p. 1882·1).
Dyspepsia.

Gastrarctin N *Serum-Werk Bernburg, Ger.*
Colloidal silver (p. 2616·2); chamomile flowers (p. 2474·1); peppermint leaf (p. 1877·1).
Gastrointestinal disorders.

Gastrazol
Note: this name may be used for preparations of different composition.
Megat, Venez.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.
Nevzat, Turk.
Pantoprazole (p. 1875·3).

Gastrazole *Meyer, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Gastrazole-D *Meyer, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Gastrec *Tecnofarma, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Gastrex
Note: this name may be used for preparations of different composition.
OM, Port.
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrial *Sanofi-Aventis, Arg.*
Ranitidine (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Gastribien
Note: this name may be used for preparations of different composition.
Decomed, Port.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gastricalm *OJG, Belg.*
Magaldrate (p. 1856·1).
Gastrointestinal disorders associated with hyperacidity.

Gastricholan-L *Sudmedica, Ger.*
Chamomile flowers (p. 2474·1); peppermint leaf (p. 1877·1); fennel (p. 2503·2).
Gastrointestinal disorders.

Gastricumeel *Heel, Austria; Heel, Neth.; Ebi, Switz.*
Acidum arsenicosum (p. 2448·1); stibium sulfuratum nigrum (p. 2445·1); argentum nitricum (p. 2615·3); carbo vegetabilis (p. 1537·3); strychnos nux vomica (p. 2573·3); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Gastricur
Note: this name may be used for preparations of different composition.
Bioquimico, Arg.
Bismuth subnitrate (p. 1822·1); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); frangula (p. 1843·3); methionine (p. 1558·2).
Gastrointestinal disorders.

Gastrid *Pharma Dynamics, S.Afr.*
Lansoprazole (p. 1851·3).

Gastride
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.
Standard, Philipp.
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Gastridin
Note: this name may be used for preparations of different composition.
Bernabo, Arg.
Clebopride malate (p. 1833·1).
Interbat, Indon.; Sandoz, Mex.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; dyspepsia.
MSD, Ital.
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Gastridina *Medibial, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; dyspepsia; acid aspiration.

Gastridin-E *Bernabo, Arg.*
⊗Gastric capsules, clebopride malate (p. 1833·1); pepsin (p. 2586·1); simeticone (p. 1886·2); enteric capsules, pancreatin (p. 2579·3); amylase (p. 2442·1); lipase (p. 2579·3); cellulase (p. 2473·1).
Gastrointestinal disorders.

Gastridol *Medichrom, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Gastrifleur *Bloem Beheer, Neth.*
Baryta carbonica (p. 2452·2); chamomilla (p. 2474·1); colocynthis (p. 1833·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Gastrifom *Tanta, Canad.*
Aluminium hydroxide (p. 1817·2); alginic acid (p. 2167·2).

Gastril *CCM, Malaysia; Duopharma, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; pathological hypersecretory disorders; stress ulcer.

Gastriloc *Verheilen, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

gastri-loges N *Loges, Ger.*
Nux vomica (p. 2573·3); carbo vegetabilis (p. 1537·3); colocynthis (p. 1833·3).
Homoeopathic preparation.

Gastrimut *Normon, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Gastrinal *Meprofarm, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastro-oesophageal reflux; gastritis; hiatus hernia; peptic ulcer.
Lek, Pol.†
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Gastric hyperacidity; peptic ulcer; gastritis.

Gastrin-Do *Grasler, Ger.*
Chamomilla (p. 2474·1); gentiana lutea (p. 2512·1); centaurium erythraea (p. 2473·2).
Homoeopathic preparation.

Gastripan
Note: this name may be used for preparations of different composition.
Recordati, Ger.†
Magaldrate (p. 1856·1).
Peptic ulcer; heartburn; gastric hyperacidity.

Gastriphar *Teva, Belg.*
Sodium alginate (p. 2167·3); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity; gastro-oesophageal reflux.

Gastriselect N *Dreluso, Ger.*
Nux. vom. (p. 2573·3); alumina (p. 1690·3); colocynt. (p. 1833·3).
Homoeopathic preparation.

Gastritec *Parma, Hung.*
Bismuth salicylate (p. 1821·3); raphanus sativus.
Gastrointestinal disorders.

Gastritis Complex *Hevert, Ger.*
Abies nigra; absinthium (p. 2426·1); belladonna (p. 2453·3); bismutum subnitr. (p. 1822·1); carbo veg. (p. 1537·3); hepar sulfuris (p. 1721·3); magnesium carbonicum (p. 1856·2); stibium sulf. nigr. (p. 2445·1).
Homoeopathic preparation.

Gastritol *Klein, Ger.; Dr Klein, Ukr.*
Potentilla anserina; chamomile (p. 2474·1); liquorice (p. 1853·2); angelica (p. 2443·3); cnicus benedictus (p. 2482·2); absinthium (p. 2426·1); St John's wort (p. 449·1).
Dyspepsia; meteorism; gastritis; peptic ulcer; gastrointestinal disorders.

Gastrium
Note: this name may be used for preparations of different composition.
Ache, Braz.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.
Micro, India; Micro, Singapore.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.
Saval, Chile.
Famotidine (p. 1842·1).
Acid aspiration; gastritis; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastriveran *Finadiet, Arg.*
Alizapride (p. 1815·2).
Nausea and vomiting.

Gastri-Vyr *Cazi, Braz.*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Gastriwin *Winthrop, S.Afr.*
Pantoprazole (p. 1875·3).

Gastrix
Note: this name may be used for preparations of different composition.
Chunggei, Philipp.
Rebamipide (p. 1884·1).
Gastritis; gastric ulcer.
Axcan, Cz.†
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Gastro
Note: this name may be used for preparations of different composition.
Cipla, India.
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.
Trima, Israel.
Famotidine (p. 1842·1).
Gastric hyperacidity; heartburn; peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.
Unia, Pol.†
Calamus (p. 2464·2); bismuth subnitrate (p. 1822·1); frangula (p. 1843·3); magnesium carbonate (p. 1856·2); liquorice (p. 1853·2).
Peptic ulcer; gastric hyperacidity; heartburn; hiatus hernia.

Gastro Flora Probiotics *Pediapharma, Philipp.*
Lactobacillus casei (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Gastro Magentabletten *Hevert, Ger.*
Bismutum subnitr. (p. 1822·1); carbo vegetabilis (p. 1537·3); ipecacuanha (p. 1667·2); magnesium phos. (p. 1787·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Gastro MPS *Cipla, India.*
Cisapride (p. 1831·3); simeticone (p. 1886·2).
Gastrointestinal disorders.

Gastro-Ad *Dexa, Indon.†*
Lactobacillus delbrueckii (p. 2596·3); fructose (p. 2068·2).
Maintenance of normal gastrointestinal function.

Gastrobário *Bial, Port.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Gastrobene
Note: this name may be used for preparations of different composition.
Legrand, Braz.
Tablets: Calcium carbonate (p. 1824·3); belladonna (p. 2453·3); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2).
Gastric hyperacidity.
Legrand, Braz.
Oral powder: Calcium carbonate (p. 1824·3); belladonna (p. 2453·3); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2); kaolin (p. 1850·1).
Gastric hyperacidity.
Ratiopharm, Austria.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Gastrobid Continus *Napp, Irl.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; nausea and vomiting.

Gastrobion *Hertz, Braz.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; flatulence.

Gastro-Bismol *Farmaline, Thai.*
Bismuth salicylate (p. 1821·3).
Diarrhoea; dyspepsia; peptic ulcer; gastrointestinal spasm; nausea.

Gastrobonisol *Bonimed, Pol.*
Achillea (p. 2427·3); artemisia abrotanum; St John's wort (p. 449·1); peppermint (p. 1877·1); milk thistle (p. 1561·1); taraxacum (p. 2625·3).
Gastrointestinal disorders.

Gastrobul *Guerbet, Neth.†*
Betaine hydrochloride (p. 2456·1); sodium bicarbonate (p. 1781·1); simeticone (p. 1886·2).
Gas production for double-contrast radiography.

Gastrocaine *Europharm, Hong Kong.*
Oxetacaine (p. 1993·1); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Dyspepsia; peptic ulcer; gastritis; gastro-oesophageal reflux.

Gastrocalm
Note: this name may be used for preparations of different composition.
Bio-Sante, Canad.
Chewable tablets: Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Bio-Sante, Canad.
Oral liquid: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); simeticone (p. 1886·2).
Cassara, Arg.
Metoclopramide (p. 1862·2).

Gastroccult *SmithKline Diagnostics, USA.*
Test for occult blood in gastric contents.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gastrocid *Finecure, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).

Gastrocimet *Brasterapica, Braz.*
Omeprazole (p. 1867·2).

Gastrocote *Actavis, UK.*
Alginic acid (p. 2167·2) or sodium alginate (p. 2167·3); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Dyspepsia; heartburn.

Gastrocrom *Celltech, USA.*
Sodium cromoglicate (p. 1225·3).
Mastocytosis.

Gastrocynésine *Boiron, Cz.; Boiron, Fr.*
Abies nigra; carbo vegetabilis (p. 1537·3); strychnos nux vomica (p. 2573·3); robinia pseudoacacia.
Homoeopathic preparation.

Boiron, Port.
Abies nigra; carbo vegetabilis (p. 1537·3); nux vomica (p. 2573·3); robinia pseudo-acacia.
Homoeopathic preparation.

Gastrocynesine *Boiron, Neth.†*
Abies nigra; carbo vegetabilis (p. 1537·3); nux vomica (p. 2573·3); robinia pseudoacacia.
Homoeopathic preparation.

Gastrodenol *Astellas, Spain.*
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer; gastritis.

Gastrodin
Note: this name may be used for preparations of different composition.
Euro Generics, Philipp.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Gastrodina *Degorts, Mex.*
Cimetidine (p. 1827·1).
Gastric hyperacidity; peptic ulcer.

Gastrodine *Medipharm, Chile.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrodomina *Almirall, Hong Kong†; Almirall, Spain.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastric hyperacidity.

Gastro-Drainol *Boiron, Fr.†*
Argentum nitricum (p. 2615·3); arsenicum album (p. 2448·1); carbo ligni officinal (p. 1537·3); ambra grisea (p. 2440·3); chelidonium majus (p. 2522·2); nux vomica (p. 2573·3); marsdenia condurango (p. 2485·3); asarum europaeum (p. 2449·3); cinchona (p. 2478·3); sodium borate (p. 2459·2).
Homoeopathic preparation.

Gastroenterol *Dermoforma, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins; minerals; plant cts.
Nutritional supplement.

Gastrofam *Atabay, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrofan *Polfa Grodzisk, Pol.†*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Gastrofit *Servocare, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Gastroflat *Bunker, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Gastrofloral *Silesia, Chile.†*
Enterococcus faecium (p. 2596·3).
Diarrhoea.

Gastrofrenal *Marvecs, Ital.*
Sodium cromoglicate (p. 1225·3).
Food hypersensitivity.

Gastrogas *E-Z-EM, Neth.†*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Double-contrast radiography of the gastrointestinal tract.

Gastroge *Klonal, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Gastrogel
Note: this name may be used for preparations of different composition.
Aspen, Austral.; Sigma, Hong Kong; Sigma, Singapore.
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); magnesium hydroxide (p. 1857·2).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Aspen, Austral.; Sigma, Hong Kong.†
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Giuliani, Ital.
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Alpen, Ukr.†
Silicon dioxide (p. 2209·1).
Gastrointestinal disorders.

Zentiva, Cz.†
Magnesium aluminate.
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; pancreatitis; dyspepsia.

Gastrografin *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bracco, Canad.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer, Irl.; Bayer, Ital.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, UK; Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for gastrointestinal radiography.

Gastrografina *Bayer, Port.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for gastrointestinal radiography.

Gastrografine *Bayer, Fr.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for gastrointestinal radiography.

Gastroguttal *Mosfarma, Rus.*
Belladonna (p. 2453·3); valerian (p. 2640·2); peppermint leaf (p. 1877·1); absinthium (p. 2426·1).
Nervous disorders; gastrointestinal disorders; decreased appetite.

Gastrogyl *Biological E, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Gastrogyl Plus *Biological E, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2); dicycloverine hydrochloride (p. 1834·2).

Gastroidam *Tecnifar, Port.†*
Idanpramine sulfate (p. 2531·2).

Gastrokin
Note: this name may be used for preparations of different composition.
Sanitas, Arg.
Mosapride (p. 1865·2).

Gastrokind *DHU, Ukr.*
Arsenicum album (p. 2448·1); croton tiglium; okoubaka; veratrum album (p. 2644·3).
Homoeopathic preparation.

Gastrolan
Note: this name may be used for preparations of different composition.
GL Pharma, Cz.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Gracia, Indon.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Gastrolanzo *Biara, Port.†*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia.

Gastrolav *Vitoria, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gastrolen *Chemopharma, Chile.*
Clidinium bromide (p. 1833·2); chlordiazepoxide (p. 1044·2).
Gastrointestinal pain; genitourinary disorders; irritable colon.

Gastrolene *Faran, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Gastrolets *Fada, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Gastroliber *Pentafarma, Port.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gastrolief *Clonmel, Irl.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Gastrolina Compuesta *Microsules, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Gastrolit *Teva, Pol.; Teva, Ukr.*
Chamomile (p. 2474·1); glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Gastroliv *Cifarma, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Gastroloc
Note: this name may be used for preparations of different composition.
Hexal, Austria.
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Gastrolux *Sanochemia, Ger.; Sanochemia, Switz.*
Sodium amidotrizoate (p. 1581·3); meglumine amidotrizoate (p. 1581·3) or lysine amidotrizoate (p. 1581·2).
Contrast medium for gastrointestinal radiography.

Gastrolyte *First Pharm, S.Afr.*
Glucose (p. 2068·3); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Sanofi-Aventis, Austral.
Effervescent tablet: Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); anhydrous citric acid (p. 2480·3); glucose (p. 2068·3); sodium bicarbonate (p. 1781·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Sanofi-Aventis, Austral.; Sanofi-Aventis, Canad.; Sanofi-Aventis, NZ.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium acid citrate (p. 1781·1); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Gastrolyte-R *Sanofi-Aventis, Austral.*
Rice powder; sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Gastrom *Tanabe Seiyaku, China; Mitsubishi Tanabe, Jpn.*
Ecabet sodium (p. 1840·2).
Peptic ulcer; gastritis.

Gastromal *Polon, Pol.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Peptic ulcer; gastric hyperacidity; gastritis.

Gastromark *Mallinckrodt, USA.*
Ferumoxsil (p. 1584·2).
Contrast medium for magnetic resonance imaging of the gastrointestinal tract.

Gastromax
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Elder, India.
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Gador, Arg.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; gastric hyperacidity.

Mili, Ukr.
Famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastric hyperacidity; meteorism; nausea; gastro-oesophageal reflux; dyspepsia.

Tripharma, Turk.
Omeprazole (p. 1867·2).

Gastromax-O *Elder, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1); simeticone (p. 1886·2); sodium alginate (p. 2167·3).

Gastromed
Note: this name may be used for preparations of different composition.
Euro-Med, Philipp.
Loperamide (p. 1854·2).
Diarrhoea; ostomy management.

Sanitas, Arg.
Sucralfate (p. 1889·1).
Peptic ulcer.

Gastromet *Lafi, Chile.*
Cisapride (p. 1831·3).
Constipation; dyspepsia; gastro-oesophageal reflux; gastroparesis; irritable colon; postoperative ileus.

Gastromine *Vida, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Bloating; gastric hyperacidity; heartburn; peptic ulcer.

Gastromins *Bros, Gr.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Gastromiro *Bracco, Austria; Bracco, Irl.; Bracco, Ital.; Bracco, Neth.; Bracco, Port.; Bracco, UK.*
Iopamidol (p. 1590·3).
Contrast medium for gastrointestinal radiography; contrast medium for computerised tomography.

Gastromol *Cantabria, Spain.†*
Magaldrate (p. 1856·1).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Gastron
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Inga, India.
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Gastronax *Galena, Pol.†*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Gastrone *Crisdy-Na, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Gastronerton *Dolorgiet, Ger.*
Metoclopramide (p. 1862·2) or metoclopramide dihydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Gastronol
Note: this name may be used for preparations of different composition.
Bioforce, Switz.
Aesculus hippocastanum (p. 2431·2); alumina (p. 1690·3); argentum nitricum (p. 2615·3); bryonia cretica; colocynthis (p. 1833·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Elmor, Venez.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastro-Norm
Note: this name may be used for preparations of different composition.
Arterium, Ukr.
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer; dyspepsia.

Gastronorm
Note: this name may be used for preparations of different composition.
Iamatica, Gr.
Omeprazole (p. 1867·2).

Plus Pharma, Cz.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Janssen-Cilag, Ital.†
Domperidone (p. 1838·1).
Dyspepsia; nausea.

Gastropan *Neo Quimica, Braz.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer.

GastroPant *Sandoz, Switz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Gastropaque *Temis, Arg.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Gastropaque Iodo *Temis, Arg.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for gastrointestinal tomography and radiography.

Gastro-Pasc *Pascoe, Ger.*
Argentum nitricum (p. 2615·3); belladonna (p. 2453·3); hydrastis (p. 2528·1); nux vomica (p. 2573·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Gastropax *Lehning, Fr.*
Kaolin (p. 1850·1); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1); magnesium carbonate (p. 1856·2); calcium phosphate (p. 1784·2); sodium bicarbonate (p. 1781·1); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

Gastropect *Aspen, S.Afr.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Gastropen
Note: this name may be used for preparations of different composition.
Morepen, India.
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Gastropen-MPS *Morepen, India.*
Cisapride (p. 1831·3); dimeticone (p. 1886·2).

Gastropensan *Zeler, Port.†*
Basic aluminium carbonate (p. 1817·1); sodium carbonate (p. 2617·3); dimeticone (p. 1886·2).
Dyspepsia.

Gastro-Pepsin *Ceccarelli, Ital.*
⊗Pepsin (p. 2586·1); gastric mucosa (p. 2444·1); hydrochloric acid (p. 2528·3); lactic acid (p. 2539·1); bitter orange (p. 2575·3).
Dyspepsia; hypoacidity.

Gastropharm *Sopharma, Rus.*
Lactobacillus bulgaricus strain 51 (LB-51) (p. 2596·3).
Gastritis; peptic ulcer; protection of the gastrointestinal mucosa from irritants.

Gastropin
Note: this name may be used for preparations of different composition.
Phytopharm, Ukr.
Valerian (p. 2640·2); artemisia; belladonna (p. 2453·3).
Dyspepsia; gastritis.

Gastroplant *DHU, Ger.*
Centaurium erythraea (p. 2473·2); ignatia (p. 2532·1).
Homoeopathic preparation.

Gastro-Plantin N *Infirmarius, Ger.†*
Carduus marianus (p. 1561·1); chamomile recutita (p. 2474·1); potentilla anserina; pulsatilla pratensis (p. 2600·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Gastroplex *Faromed, Austria.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Gastroprazol *Lamsa, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Gastroprozal *Mac, Gr.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gastropulgite *Ipsen, Fr.*
Activated attapulgite (p. 1820·1); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastrointestinal disorders.

Gastrosan
Note: this name may be used for preparations of different composition.
Bioforce, Switz.
Achillea (p. 2427·3); taraxacum (p. 2625·3); melissa (p. 2552·3); gentian (p. 2512·1); cnicus benedictus (p. 2482·2); angelica (p. 2443·3); centaury (p. 2473·2).
Digestive disorders.
Medasta, Swed.
Calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1).
Heartburn; gastro-oesophageal reflux.

Gastrosan fix *Herbapol Lublin, Pol.†*
Althaea (p. 2438·3); chamomile (p. 2474·1); peppermint leaf (p. 1877·1).
Gastrointestinal disorders.

Gastrosed
Note: this name may be used for preparations of different composition.
Roberts, USA.
Hyoscyamine sulfate (p. 1848·1).

Gastrosedol *Nova Argentia, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; systemic mastocytosis.

Gastrosedol Plus *Nova Argentia, Arg.*
Ranitidine hydrochloride (p. 1882·1); domperidone (p. 1838·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia.

Gastrosidin *Sotex, Rus.; Eczacibasi, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastrointestinal haemorrhage.

Gastrosil
Note: this name may be used for preparations of different composition.
ICN, Pol.
Simeticone (p. 1886·2).
Excess gastrointestinal gas; gastrointestinal procedures.
Pfizer, Austria.
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; vomiting.

Gastrosine *Boiron, Canad.†*
Abies nigra; carbo vegetabilis (p. 1537·3); colubrine; robina pseudo-acacia.
Homoeopathic preparation.

Gastrosol *Gradiens, Hung.*
St John's wort (p. 449·1); calendula (p. 2465·2); achillea (p. 2427·3).
Gastrointestinal disorders.

Gastro-Soothe *AFT, NZ.*
Hyoscine butylbromide (p. 1845·3).
Gastro-intestinal spasm.

Gastrosorb *Synco, Hong Kong†; Synco, Singapore.*
Activated attapulgite (p. 1820·1).
Diarrhoea.

Gastrostad
Note: this name may be used for preparations of different composition.
Stada, Fin.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastro-Stop
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Gastrotem *Temis, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastric hyperacidity.

Gastro-Timelets *Temmler, Denm.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Gastrotisane *Lesourd, Fr.†*
Asperula odorata; boldo (p. 2458·3); peppermint leaf (p. 1877·1); fennel (p. 2503·2); taraxacum (p. 2625·3).
Liver and bile disorders.

Gastrotrombina *Biomed Lublin, Pol.*
Thrombin (p. 1163·2).
Gastrointestinal haemorrhage.

Gastrotuss *DMG, Ital.*
Magnesium alginate (p. 2167·2); simeticone (p. 1886·2); dexpanthenol (p. 2582·2); althaea (p. 2438·3); red-poppy (p. 2207·3); zinc oxide (p. 1729·1); sodium carbonate (p. 2617·3).
Gastro-oesophageal reflux.

Gastrovegetalin *Verla, Ger.*
Melissa (p. 2552·3).
Gastrointestinal disorders; sleep disorders.

Gastrovex *Avex, Malaysia.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Gastrovison *Panagakis, Gr.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); colloidal silicon dioxide (p. 2208·3); hypromellose (p. 2189·2); dimeticone (p. 1886·2).
Gas production for double-contrast radiography.

Gastrowell *Dermapharm, Switz.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrox *Greenpharma, Braz.*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.

Gastrozac *Klonal, Arg.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Gastrozepin *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Ukr.*
Pirenzepine hydrochloride (p. 1878·2).
Peptic ulcer; gastritis; duodenitis; gastric hypersecretion.

Gastrozol
Note: this name may be used for preparations of different composition.
Delta, Braz.; Farmstandart, Rus.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.
Dermapharm, Austria; Mibe, Ger.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrozyme *Bio-Drug, India.*
⊗Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1); papain (p. 2582·3); sorbitol (p. 2092·1).
Bio-Drug, India.
Oral drops: Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1).

Gastrucid *Nufarindo, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastritis; peptic ulcer; gastro-oesophageal reflux; pyrosis; flatulence.

Gastrul *Fahrenheit, Indon.*
Misoprostol (p. 2140·3).
NSAID-induced gastric ulcer.

Gastrulcer *Fariberica, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gastrysat *Ysatfabrik, Ger.†*
Chewable tablet: Fennel oil (p. 2503·3); coriander oil (p. 2487·1); caraway oil (p. 2470·3); peppermint oil (p. 1877·1).
Gastrointestinal disorders.
Ysatfabrik, Ger.†
Oral liquid: Fennel oil (p. 2503·3); ginger oil (p. 1844·1); coriander oil (p. 2487·1); caraway oil (p. 2470·3); peppermint oil (p. 1877·1).
Gastrointestinal disorders.

Gastyl *ANB, Malaysia; ANB, Thai.*
Simeticone (p. 1886·2).
Flatulence; abdominal distension; excess gastrointestinal gas.

Gasulsol *Herbes Universelles, Canad.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).

Gas-X *Novartis Consumer, Canad.; General Drugs, Thai.; Novartis Consumer, USA.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; flatulence.

Gas-X with Maalox *Novartis, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Antacid; flatulence.

Gaszym *Ranbaxy, Thai.*
⊗Simeticone (p. 1886·2); pancreatin (p. 2579·3).
Digestive system disorders; flatulence.

Gatalin *Aspire, UK.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Gatdor *Candor, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Gate *Ajanta, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gate-DX *Ajanta, India.*
⊗Dexamethasone (p. 1630·3); gatifloxacin (p. 303·2).

Gateme *Medico, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatex *Osmed, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiba *Acto, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatibact *Micro Labs, Ukr.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatibenz *Admac, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gaticad *Admac, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gaticare *Azine, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gaticas *Casca, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gaticin *Aristo, India; Fahrenheit, Indon.†*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatif *Poen, Arg.; Poen, Chile.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Gatifect *Wockhardt, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiflo *Senju, Jpn.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Gatigo *Intra-Labs, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatigram *Micro, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatigram-OZ *Micro, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Gatijem *Tulip, Ukr.†*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatik *Globus, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatikind *Mankind, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatikind-AM *Mankind, India.*
Ambroxol (p. 1654·3); gatifloxacin (p. 303·2).

Gatikind-OZ *Mankind, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Gatilab *Laborate, India.*
Gatifloxacin (p. 303·2).
Eye infections; ear infections.

Gatilex *Lexus, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatilink *Lincoln, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatilox *Sun, China; Sun, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatilox-DM *Sun, India.*
⊗Gatifloxacin (p. 303·2); dexamethasone (p. 1630·3).

Gatimac *Macleods, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatimax *Pharos, Indon.†*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatimore *Moraceae, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatimore-OZ *Moraceae, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Gatin *East West, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gatina *Zota, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatinar *Melisana, Switz.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Gatinex *Nestor, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatinova *Willow, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gati-OD *PDC, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiom *Om Biotec, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiospi *Auspi, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatipan *Panjon, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiquin *Cipla, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiquin Oz Kit *Cipla, India.*
1 Tablet, gatifloxacin (p. 303·2); 1 tablet, ornidazole (p. 943·1).
Respiratory-tract infections; infected wounds.

Gatisia *Willow, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatispan *Lupin, India; Mosfanna, Rus.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatistac *ATOZ, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatistal *Stallion, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatitoon *Zydus, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gativar *Zota, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatix *Invision, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatiz *Ritz, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatizen *Alkem, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatlak *Laksun, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatme *Medico, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatmor *Aamorb, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatnic *Medihealth, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatofen *Graha, Indon.*
Ketoprofen hydrochloride (p. 79·1).
Musculoskeletal and joint disorders; gout pain.

Gatomed *Aglowmed, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatonin *Teva, Ukr.†*
Gabapentin (p. 523·3).
Epilepsy; postherpetic neuralgia.

Gatonova *Ranbaxy, Ukr.†*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gator *Zuventus, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatovas *CMG, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Gatox *RPG, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatri *Piramal, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatrich *Alembic, India.*
Ambroxol hydrochloride (p. 1654·3); gatifloxacin (p. 303·2).

Gatrid *Symbiosis, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatrid-OZ *Symbiosis, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Gatri-OZ *Piramal, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Gatrital *Symbiosis, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatrix *East West, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Gatt *Cadila, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gattex *NPS, USA.*
Teduglutide (p. 1892·3).
Short bowel syndrome.

Gatus *East West, India.*
Ambroxol hydrochloride (p. 1654·3); gatifloxacin (p. 303·2).

Gatven *Vensat, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatymal *Malar, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gatz *Dewcare, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gaudil *Craveri, Arg.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Gaveril *Bevo, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Gavigard *Reckitt Benckiser, Port.*
Potassium bicarbonate (p. 1780·3); sodium alginate (p. 2167·3).
Gastro-oesophageal reflux.

Gavilast *Reckitt Benckiser, UK.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; heartburn.

GaviLAX *Gavis, USA.*
Macrogol 3350 (p. 2547·3).
Constipation.

GaviLyte *Gavis, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Gavin *Gador, Arg.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain; anxiety; fibromyalgia.

Gavindo *Merck, Mex.*
Gabapentin (p. 523·3); thiamine nitrate (p. 2103·2); cyanocobalamin (p. 2107·2).
Neuropathic pain.

Gavir *United Biotech, India.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Gaviscon
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Austral.; Reckitt Benckiser, Belg.; Reckitt Benckiser, Braz.; Reckitt Benckiser, Chile; Reckitt Benckiser, Cz.; Reckitt Benckiser, Fr.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Hung.; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Novartis Consumer, Ital.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Neth.; Reckitt Benckiser, Philipp.; Reckitt Benckiser, Pol.; Reckitt Benckiser, Port.; Reckitt Benckiser, Rus.; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Spain; Reckitt Benckiser, Thai.; Ali, Turk.; Reckitt Benckiser, Ukr.
Oral liquid: Chewable tablets: Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; gastric hyperacidity; dyspepsia; flatulence; hiatus hernia; heartburn.

Reckitt Benckiser, Austral.; Reckitt Benckiser, Belg.; Reckitt Benckiser, Gr.; Reckitt Benckiser, India; Reckitt Benckiser, Irl.†; Novartis Consumer, Ital.†; Reckitt Benckiser, Malaysia†; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore†; Ali, Turk.
Tablets: Alginic acid (p. 2167·2); sodium bicarbonate (p. 1781·1); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Formerly contained sodium alginate and sodium bicarbonate.
Gastro-oesophageal reflux; heartburn; hiatus hernia; regurgitation; dyspepsia.

GSK Consumer, USA.
Chewable tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Formerly contained aluminium hydroxide, magnesium trisilicate, alginic acid, and sodium bicarbonate.
Heartburn.

Nordic Drugs, Denm.; Nordic Drugs, Fin.; Nordic Drugs, Norw.; Nordic, Swed.
Oral liquid: Sodium alginate (p. 2167·3); aluminium hydroxide (p. 1817·2); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Nordic Drugs, Denm.; Nordic Drugs, Fin.; Nordic Drugs, Norw.; Nordic, Swed.
Tablets: Alginic acid (p. 2167·2); aluminium hydroxide (p. 1817·2); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Reckitt Benckiser, Cz.; Reckitt Benckiser, Thai.
Oral liquid; powder for oral liquid: Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux; heartburn; dyspepsia.

Reckitt Benckiser, Hong Kong.
Tablets: Sodium alginate (p. 2167·3); magnesium trisilicate (p. 1858·1); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).
Formerly contained alginic acid, magnesium trisilicate, aluminium hydroxide, and sodium bicarbonate.
Flatulence; gastro-oesophageal reflux; hiatus hernia; heartburn.

Reckitt Benckiser, NZ.
Infant oral powder: Magnesium alginate (p. 2167·2); sodium alginate (p. 2167·3).
Gastro-oesophageal reflux.

Reckitt Benckiser, NZ.
Oral liquid: Sodium alginate (p. 2167·3); calcium carbonate (p. 1824·3); potassium bicarbonate (p. 1780·3) or sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux.

SmithKline Beecham Consumer, USA.
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); sodium alginate (p. 2167·3).
Dyspepsia.

Essex, Chile.†
Tablets: Alginic acid (p. 2167·2); sodium bicarbonate (p. 1781·1); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux.

Gaviscon Advance
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Belg.; Reckitt Benckiser, Ger.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Irl.; Novartis Consumer, Ital.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Pol.; Reckitt Benckiser, Singapore; Ali, Turk.; Reckitt Benckiser, UK.
Sodium alginate (p. 2167·3); potassium bicarbonate (p. 1780·3).
Gastro-oesophageal reflux; heartburn; dyspepsia; hiatus hernia.

Reckitt Benckiser, S.Afr.†
Sodium alginate (p. 2167·3).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Gaviscon Cool *Reckitt Benckiser, UK.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Heartburn.

Gaviscon Double Action *Reckitt Benckiser, UK.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; gastric hyperacidity.

Gaviscon Double Strength *Reckitt Benckiser, Austral.*
Sodium alginate (p. 2167·3); potassium bicarbonate (p. 1780·3); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux.

Gaviscon Dual Action *Reckitt Benckiser, Thai.*
Oral liquid; powder for oral liquid; tablets: Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Heartburn; dyspepsia; gastro-oesophageal reflux.

Gaviscon Extra Sterk *Reckitt Benckiser, Neth.*
Sodium alginate (p. 2167·3); potassium bicarbonate (p. 1780·3).
Gastro-oesophageal reflux.

Gaviscon Extra Strength
Note: this name may be used for preparations of different composition.
GSK Consumer, USA.
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Dyspepsia.

Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.
Sodium alginate (p. 2167·3); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).
Dyspepsia; gastro-oesophageal reflux; hiatus hernia; heartburn.

Gaviscon Extra Strength Relief Formula
SmithKline Beecham Consumer, USA.
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); simeticone (p. 1886·2).
Hyperacidity.

Gaviscon Forte
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Israel; Reckitt Benckiser, Rus.; Reckitt Benckiser, Ukr.
Sodium alginate (p. 2167·3); potassium bicarbonate (p. 1780·3).
Gastro-oesophageal reflux; heartburn; gastric hyperacidity.

Reckitt Benckiser, Neth.†
Alginic acid (p. 2167·2); algeldrate (p. 1817·2); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1).
Gastro-oesophageal reflux.

Gaviscon Heartburn & Acid Reflux Relief
Prestige, Canad.
Tablets: Alginic acid (p. 2167·2); magnesium carbonate (p. 1856·2).
Heartburn; gastro-oesophageal reflux.

Prestige, Canad.
Oral liquid: Sodium alginate (p. 2167·3); aluminium hydroxide (p. 1817·2).
Heartburn; gastro-oesophageal reflux.

Gaviscon Infant *Reckitt Benckiser, Irl.; Ali, Turk.; Reckitt Benckiser, UK.*
Magnesium alginate (p. 2167·2); sodium alginate (p. 2167·3).
Gastro-oesophageal reflux.

Gaviscon Instants *Reckitt Benckiser, UK.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux.

Gaviscon Kautabletten *Reckitt Benckiser, Ger.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; heartburn.

Gaviscon Maxrelief *Prestige, Canad.*
Alginic acid (p. 2167·2); magnesium carbonate (p. 1856·2).
Heartburn; gastro-oesophageal reflux.

Gavisconell *Reckitt Benckiser, Fr.*
Chewable tablets: Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux.

Reckitt Benckiser, Fr.
Oral suspension: Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux.

Gaviscon-L *Reckitt Benckiser, Gr.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1).

Gavistal *Meprofarm, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Gaviz *Uniao Quimica, Braz.*
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Uniao Quimica, Braz.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Gavonad *Novag, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gavox *Guardian, Indon.†*
Mebendazole (p. 158·3).
Worm infections.

Gaxene *Guardian, Thai.*
Dipotassium clorazepate (p. 1056·3).

Gaxium *Millimed, Thai.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Gayabeksin *Casel, Turk.*
Sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1).
Respiratory-tract congestion.

Gayaben *Bilim, Turk.*
Sulfogaiacol (p. 1678·1); guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2); pentoxyverine citrate (p. 1672·1).
Respiratory-tract congestion.

Gaz Away *Swiss Herbal, Canad.†*
Alpha galactosidase A (p. 2437·2).
Flatulence; bloating.

Gazal-O *Cosme, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Gazim X *CTS, Israel.*
Simeticone (p. 1886·2).
Flatulence.

Gazyme *Cifarma, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Gazyva *Genentech, USA.*
Obinutuzumab (p. 837·1).
Chronic lymphocytic leukaemia.

GB-29 *Corona, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

GB 100 *Sigma, Arg.*
Ginkgo biloba (p. 2512·3); choline bitartrate (p. 2055·2); glycoside flavonoids (p. 2505·2).
Cerebral and peripheral vascular disorders; vestibular disorders.

GB Tablets *Potter's, UK.*
Leptandra virginica; euonymus (p. 1842·1); lappa root (p. 2540·1).
Abdominal discomfort; gall bladder disorders.

GBHC *Shalaks, India.*
Lindane (p. 2157·1).
Scabies; pediculosis.

GB-Lex *Lexus, India.*
Carotenoids (p. 2176·2); ginseng (p. 2513·3); vitamins.

GBN-M *Xieon, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

GBO *Greenco, India.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

GB-Pred AC *Greenco, India.*
⊗Prednisolone sodium acetate (p. 1645·2).
Inflammatory eye disorders.

GBTop *Mint, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).

G C Flex *Panjon, India.*
1 Tablet, chondroitin sulfate sodium (p. 2476·1); 1 tablet, glucosamine sulfate sodium (p. 2515·3); manganese (p. 2081·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

G-Calvit *GLS, India.*
Calcium (p. 1783·1); lysine (p. 2079·3); colecalciferol (p. 2113·1); ashwagandha (p. 2450·2).

G-Care *H & Care, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

GCB *Vensat, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

G-Cebran *Blue Cross, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

G-Cin *Lupin, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

G-Clox *Grandix, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3);
Lactobacillus sporogenes (p. 2596·3).
Bacterial infections.

GCM *Simex, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1); manganese (p. 2081·2); magnesium (p. 1786·3).
Joint disorders; osteoarthritis.

GCobal *CMG, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

GCStab *Micro, India.*
Calcium citrate maleate (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

G-Dil *Gap, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

GDSafe *Ind-Swift, India.*
Colistin sulfate (p. 275·3).
Gastrointestinal infections; bowel sterilisation.

GE *Thai Otsuka, Thai.*
Carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Ge Di *DND, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Ge Chang *Jinghao, China.*
Puerarin.

Ge Da Li *Tiantaishan, China.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Ge La Da Xin *Dongya, China.*
Glutathione (p. 1555·2).

Ge Dan *Chang Fu Jie Jing, China.*
Carbazochrome sodium sulfonate.
Haemorrhage.

Ge Lai Shi *Nuo De, China.*
Bismuth citrate potassium (p. 1822·1); ranitidine (p. 1882·1).

Ge Lan Ting *Bainian Kangxin, China.*
Gatifloxacin mesilate.
Bacterial infections.

Ge Mei Da *Si Huan, China.*
Etimicin sulfate (p. 298·2).

Ge Mei Nai Xin *Run Bang, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Ge Nai Ya *Shuai Ke, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ge Ning *Yingtian, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Ge Ou Shu *SanJiu JiShi, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ge Rui Jia *Yunmen, China.*
Naftopidil (p. 2361·1).

Ge Rui Tong *Qi Du, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ge Rui Xi *Xincat, China.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; dyspepsia; gastro-oesophageal reflux.

Ge Shuang *Sha Pu Ai Si, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Ge Le Si Te *Yige, China.*
Gamma-aminobutyric acid (p. 2509·2).

Ge Tai *Longgui, China.*
Lomefloxacin hydrochloride (p. 319·2).

Ge Wan Si *Renfeng, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Ge Xuan *Jing Wei, China.*
Sulconazole nitrate (p. 593·3).

Gea *Sandoz, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Gealcid *Medagro, Pol.*
Alginic acid (p. 2167·2); aluminium hydroxide (p. 1817·2); sodium bicarbonate (p. 1781·1).
Heartburn; gastro-oesophageal reflux; hiatus hernia; gastritis; peptic ulcer.

Gealgica *Norma (Νορμα), Gr.*
Allopurinol (p. 600·2).

Geavir *Hexal, Denm.; Sandoz, Swed.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Gebauers Spray & Stretch *Gebauer, USA.*
Norflurane (p. 1799·1); pentafluoropropane (p. 1799·2).
Myofascial pain; muscle spasm; sports injury.

Gebenir *Eurodrug, Mex.†*
Fexofenadine (p. 629·1).

Gebina *Aspen, Arg.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Gebrozil *Remek, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gecitam *Caplin, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gecitral *Zimalaya, India.*
Punarnava (p. 2601·1).

Geclave *Glories, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Geclicin *IQFA, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Gecodes *Yuri, Ukr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; haemodilution.

Gecrol *Heaton, Cz.*
Tacrolimus (p. 1968·3).
Heart, kidney, or liver transplant rejection.

Gedarel *Consilient, UK.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gede *Livzon, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Gedizil *Bevo, Gr.*
Gemfibrozil (p. 1390·3).

Gedox *Rishab, India.*
Cefpodoxime.
Bacterial infections.

Gedun *Duncan, Arg.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Geebio *Quamed, Indon.*
Lactobacillus acidophilus (p. 2596·3).
Maintenance of healthy digestion.

Geeox *Cadila, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Geepenil *Orion, Fin.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Geerox *Globus, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Geether *Genesis, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Geeva *Genesis, India.*
Medroxyprogesterone (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; malignant neoplasms; amenorrhoea.

Gefanil *Sumitomo, Jpn.*
Gefarnate (p. 1844·1).
Peptic ulcer; gastritis.

Gefenda *Yangtian, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Gefente *Fenghuang, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Gefer *Grandix, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); pyridoxine (p. 2105·3); zinc sulfate (p. 2126·2).

Geffer *Bayer, Ital.*
Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2); potassium citrate (p. 1780·3); citric acid (p. 2480·3); tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1).
Gastrointestinal disorders associated with hyperacidity.

Gefin *Genericon, Cz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Gefina *Hexal, Fin.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Gefion *Amnol, Ital.*
Gel: Capsicum (p. 2469·3); hamamelis (p. 2523·3); lonicera caprifolium; lonicera japonica.
Capillary disorders.

Amnol, Ital.
Tablets: Pineapple; aesculus (p. 2431·2); melilot (p. 2552·3); vitamins; potassium (p. 1793·1).
Microcirculatory disorders.

Gefitero *Hetero, India.*
Gefitinib (p. 800·2).
Non-small cell lung cancer.

Gefix *Glories, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Gefonib *Miracalus, India.*
Gefitinib (p. 800·2).
Non-small cell lung cancer.

Gefor *Psychotropics, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gefplus *Madhav, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Gefspass *Madhav, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Geftib *Glenmark, India.*
Gefitinib (p. 800·2).
Non-small cell lung cancer.

Geftilon *Celon, India.*
Gefitinib (p. 800·2).
Non-small cell lung cancer.

Geftinat *Natco, India.*
Gefitinib (p. 800·2).
Non-small cell lung cancer.

Gefulvin *Sanofi Synthelabo, Turk.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Gegorvit *Fher, Ital.*
Vitamins; minerals; ginseng (p. 2513·3).
Nutritional supplement.

Gehwol Hühneraugen-Pflaster extra stark *Gerlach, Ger.*
Salicylic acid (p. 1719·1).
Calluses; corns.

Gehwol Hühneraugen-Tinktur *Gerlach, Ger.*
Salicylic acid (p. 1719·1); glacial acetic acid (p. 2426·3).
Corns; callouses.

Gehwol Schälpaste *Gerlach, Ger.*
Salicylic acid (p. 1719·1).
Corns; callouses.

Gei Xin *Jinhui, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Geiluoxian *Baiyunshan, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Gekacin *Glories, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Gekare *GSK, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

GeKaTon *Evalar, Rus.*
Calendula (p. 2465·2); chamomile (p. 2474·1); achillea (p. 2427·3).
Oral inflammation; gastrointestinal inflammation.

Gel 4000 *Bruschettini, Ital.*
Hypromellose (p. 2189·2).
Aid in ophthalmic procedures.

Gel à l'Acétotartrate d'Alumine Defresne *Sanofi-Aventis, Fr.†*
Hesperidin methyl chalcone (p. 2505·2); aluminium acetotartrate (p. 2440·1).
Soft-tissue injury; venous insufficiency.

Gel Antiinflamatorio *Sertex, Arg.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis.

Gel de Calamine *Bailleul, Fr.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Skin irritation.

Gel de consoude *Phytopharma, Switz.†*
Comfrey (p. 2484·2); calendula (p. 2465·2) arnica (p. 2447·2); echinacea (p. 2498·1).
Soft-tissue injury.

Gel Fitotonico *Madaus, Arg.*
Vegetable extracts; menthol (p. 2553·2); creatine (p. 2488·3).
Tired legs.

Gel Glace *Prodemdis, Canad.†*
Menthol (p. 2553·2).

Gel Kam *Scherer, USA.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Gel Rubéfiant *Ducray, Fr.*
Methyl nicotinate (p. 91·3); essential oils.
Hair loss.

Gelacid *Cipla-Medpro, S.Afr.*
Tablets: Alginic acid (p. 2167·2); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); sodium bicarbonate (p. 1781·1).
Dyspepsia; gastro-oesophageal reflux; heartburn.

Cipla-Medpro, S.Afr.
Oral suspension: Sodium bicarbonate (p. 1781·1); sodium alginate (p. 2167·3); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Gelafundin *Braun, Arg.; Braun, Indon.; Buminusantara, Indon.; Pisa, Mex.*
⊗Gelatin polysuccinate (p. 1154·1).
Plasma volume expansion; hypovolaemia; haemodilution; extracorporeal circulation.

Braun, Ger.; Braun, Thai.†
⊗Gelatin polysuccinate (p. 1154·1); electrolytes (p. 1775·1).
Hypovolaemia; pre-operative haemodilution; hypotension; haemodilution; extracorporeal circulation.

Gelafundina *Braun, Port.†; Braun, Spain.*
⊗Gelatin polysuccinate (p. 1154·1); electrolytes (p. 1775·1).
Hypovolaemia; extracorporeal circulation.

Gelafusal *Serum-Werk Bernburg, Ger.; Biomed, NZ.*
⊗Succinylated gelatin (p. 1154·1); electrolytes (p. 1775·1).
Hypovolaemia; shock; haemodilution; pre-operative haemodilution.

Gelagel *Shince, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Gelamxol *Nafar, Mex.*
Ambroxol (p. 1654·3); dextromethorphan (p. 1660·1).
Cough.

Gelan Plus *Chinoin, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Gelar *Arlex, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity.

Gelargin *Zentiva, Cz.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Gelasim *Berman, Mex.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastric hyperacidity.

Gelaspan *Braun, Irl.; Braun, Neth.; Braun, Norw.; Braun, Swed.; Braun, UK.*
⊗Gelatin polysuccinate (p. 1154·1) with electrolytes.
Shock; plasma volume expansion.

Gelaspon *Chauvin ankerpharm, Ger.*
⊗Gelatin (p. 1154·1).
Haemostatic; haemorrhage.

Gelastypt *Sanofi-Aventis, Ger.*
⊗Gelatin (p. 1154·1).
Haemorrhage.

Gelatinol *Samson-Med, Rus.*
⊗Gelatin (p. 1154·1) in sodium chloride.
Hypovolaemia; haemodilution; extracorporeal circulation.

Gelax *Sidus, Arg.*
Psyllium (p. 1849·1); senna (p. 1885·1); bran (p. 1823·3).
Constipation.

Gelbag *Zeiss Meditec, Ger.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Gelbiotic *LKM, Arg.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Gelbiotic Plus *LKM, Arg.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Bacterial skin infections.

Gelbra *KRKA, Spain.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gelcain *Valma, Chile.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Gelcavit *Gelcaps, Mex.*
Vitamins; minerals.

Gelcen *Intramed, Gr.; Centrum, Spain.†*
Capsaicin (p. 35·1).
Rheumatic pain; musculoskeletal and joint pain; neuropathic pain.

Gelcive *Mediderm, Chile.*
Cranberry (p. 2488·1).
Skin disorders; wounds.

Gelclair *Kampar, Chile; Riemser, Ger.; Sinclair, UK; Dara, USA.*
Enoxolone (p. 54·2); povidone (p. 2204·3); sodium hyaluronate (p. 2526·2).
Mouth and throat lesions.

Gelcom *Raam, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Gelconordin *Nordin, Mex.*
Lamium album; aloe vera (p. 1693·2).
Abdominal inflammation.

Geldako *Gelpharma, Mex.*
Ketorolac (p. 80·2).
Pain.

Geldène *Pfizer, Fr.*
Piroxicam (p. 125·3).
Tendinitis; soft-tissue disorders.

Geldex *Gelpharma, Mex.*
Calcitriol (p. 2113·1).

Geldolor *Arkopharma, Fr.*
Capsicum (p. 2469·3); devil's claw root (p. 42·3).
Joint pain.

Geldoren *Vale, Cz.; Richter, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Geldrox Plus *Exakta, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity.

Gelec *Claris, India.*
Glucose (p. 2068·3); electrolytes (p. 1775·1).

Gelenk Albin *Homviora, Ger.*
Colchicum autumnale (p. 607·1); actaea spicata (p. 2478·1); spiraea ulmaria (p. 2550·2); bryonia (p. 2461·3); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Gelerit *Koni-Cofarm, Chile.*
Erythromycin (p. 291·2).
Acne.

Gelestra *Abiogen, Ital.*
Estradiol (p. 2271·1).
Menopausal disorders.

Gelex *Servocare, India.*
Vitamin B substances (p. 2102·3).

Gelfilm *Pharmacia, NZ†; Upjohn, USA.*
⊗Gelatin (p. 1154·1).
Haemostatic; ophthalmic haemostatic.

Gelfix *General Chemicals, Gr.; Alembic, India.*
Collagen (p. 2483·2).
Topical haemostatic.

Gelflex *Bunker, Braz.*
Turpentine oil (p. 2636·3); methyl salicylate (p. 92·1); camphor (p. 2466·2); mustard oil (p. 2646·1); rosemary oil (p. 2607·3); lavender oil (p. 2541·1); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Gelfoam *Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Israel†; Pfizer, Malaysia; Pharmacia, NZ†; Pfizer, Philipp.; Pfizer, Singapore; Upjohn, USA; Pfizer, Venez.*
⊗Gelatin (p. 1154·1).
Minor bleeding during surgery; skin ulcers; wounds; haemorrhage; haemostatic.

Gelhist *Econolab, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Nasal congestion; rhinitis.

Gelicain *DeltaSelect, Ger.†; DeltaSelect, Rus.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Gelicol *Pasteur, Chile.*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Gelictar Fort *Nigy, Fr.†*
Ichthammol (p. 1705·3); salicylic acid (p. 1719·1); resorcinol (p. 1718·3).
Keratinisation disorders; seborrhoeic dermatitis.

Gelidina *Astellas, Spain.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Gelidol *AstraZeneca, Mex.*
Ibuprofen (p. 68·2).
Fever; pain.

Gelidol-X-Press *AstraZeneca, Mex.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain; musculoskeletal and joint disorders.

Gelifend *Velvian, Ger.*
Lactic acid (p. 2539·1); glycogen (p. 2519·2).
Vaginal disorders.

Gelifundol *Biotest, Thai.†*
⊗Oxypolygelatin (p. 1158·1).
Hypovolaemia; resuspension of concentrated erythrocytes.

Gelilact *Lagepha, Belg.†*
Carmellose sodium (p. 2175·2).
Vomiting in infants.

Gelina-M *Aronex, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Géliofil *Effik, Fr.*
Lactic acid (p. 2539·1); glycogen (p. 2519·2).
Vaginal disorders.

Geliofil *Effik, Ital.*
Lactic acid (p. 2539·1); glycogen (p. 2519·2).
Vaginal hygiene.

Geliperm *Geistlich, UK.*
Hydrogel dressing.
Wounds; ulcers; burns.

Gel-Kam *Colgate-Palmolive, Canad.; Colgate-Palmolive, Ital.; Colgate Oral, USA.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis; sensitive gums.

Gel-Kam Dentinbloc *Colgate-Palmolive, Canad.*
Sodium fluoride (p. 2089·2); stannous fluoride (p. 2094·3); hydrogen fluoride (p. 2529·1).
Dental caries prophylaxis.

Gel-Larmes *Thea, Fr.*
Carbomer 974 P (p. 2173·3).
Dry eyes.

Gel-Lido *Apsen, Braz.†*
Lidocaine (p. 1988·1).
Local anaesthesia.

Gel-Malicid *Am-Europharma, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Gelmax *EMS, Braz.*
Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Gelmax Dim *EMS, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).

Gelmicin *Collins, Mex.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Gelminex *Belfar, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2).

Gelminthic *Vonnace, Philipp.*
Pyrantel embonate (p. 165·3).
Worm infections.

Gelnique *Watson, Canad.; Watson, USA.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

GeloBacin *Pohl, Ger.*
⊗1,3-Butanediol (p. 2172·2); glycerol (p. 2517·2); dimethyl sulfoxide (p. 2182·2); dexpanthenol (p. 2582·2).
Ear disorders.

Gelo-Bio *Uniao Quimica, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); turpentine oil (p. 2636·3).

Gelobronchial *Pohl, Ger.*
Thyme (p. 2630·2).
Bronchitis; catarrh.

Gelobufen *Ferrer, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Gelocaps *Biofarma, Turk.*
Capsicum oleoresin (p. 2469·3); camphor (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain.

Gelocast *Smith & Nephew, Austral.; BSN, Ital.*
Zinc oxide (p. 1729·1).
Medicated dressing; ulcers.

Gelocatil *Gelos, Port.; Ferrer, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Gelocatil Codeina *Ferrer, Spain.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Gelocatil Gripe con Felilefrina *Novag, Spain.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Gelocatil Gripe con Pseudoefedrina *Novag, Spain.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Geloderm *SMB, Chile.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; malodorous wounds; rosacea.

Gelodiet *Lactalis, Fr.*
⊗Gelatin (p. 1154·1); sucrose (p. 2096·3).
Dehydration.

Gelodrox *Ferrer, Spain.*
Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Gelodurat *Gebro, Switz.*
Myrtle oil (p. 2566·3); eucalyptus oil (p. 2501·2).
Bronchitis.

Pohl, Ger.
Ointment: Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Bronchitis; cold symptoms.

Pohl, Neth.
Myrtol (p. 2566·3).
Bronchitis.

Gelofeno *Ferrer, Spain.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

Geloforte *Forder, Arg.*
Glycolic acid (p. 1704·3).

Gelofrix *Delta, Braz.*
Turpentine oil (p. 2636·3); methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Gelofusin *Braun, Rus.; Biofarma, Turk.*
⊗Modified gelatin (p. 1154·1).
Plasma volume expansion; haemodilution; extracorporeal circulation.

Braun, Austria.
⊗Gelatin (p. 1154·1); electrolytes (p. 1775·1).
Hypovolaemia; haemodilution.

Gelofusine *Braun, Austral.; Braun, Belg.; Braun, Chile; Braun, China; Braun, Cz.; Braun, Denm.; Braun, Fin.; Braun, Fr.; Bioser (Biosep), Gr.; Braun, Hong Kong; Braun, Hung.; Braun, India; Braun, Irl.; Braun, Ital.; Braun, Neth.; Biomed, NZ†; Braun, Pol.; Braun, Port.; Braun, S.Afr.; Braun, Singapore; Braun, Swed.; Braun, Thai.; Braun, UK; Braun, Ukr.; Behrens, Venez.*
⊗Succinylated gelatin (p. 1154·1) in sodium chloride.
Plasma volume expansion; haemodilution; hypovolaemia; hypotension; shock; extracorporeal circulation; carrier solution for insulin; leucapheresis.

Gelogrip *Gelos, Spain.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

Gelolagar *Fada, Arg.*
Atracurium (p. 2030·1).
Competitive neuromuscular blocker.

Gelomyrtol *Pohl, Austria; Pohl, Ger.; Pohl, Gr.; Pohl, Hong Kong; Pohl-Boskamp, Rus.; Alpinamed, Switz.; Pohl, Thai.†; Pohl-Boskamp, Ukr.*
Myrtol (p. 2566·3).
Bronchitis; sinusitis; respiratory-tract disorders; cough.

Gelona *Zota, India.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Gelonasal *Pohl, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Gelone *Plus, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Gelonic *Dermoteca, Port.†*
Amino acids; minerals.
Hair and nail disorders.

Gelonida
Note: this name may be used for preparations of different composition.
Pfizer, Ger.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Gélopectose *DB, Fr.*
Pectin (p. 2200·3); microcrystalline cellulose (p. 2177·1); hydrated colloidal silicon dioxide (p. 2209·1).
Regurgitation in infants.

Gelopiril *Gelos, Spain.†*
Ibuprofen arginine (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

Geloplasma *Fresenius Kabi, Austria; Fresenius Kabi, Chile; Sanofi-Aventis, Gr.; Fresenius Kabi, Irl.; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, UK.*
⊗Gelatin (p. 1154·1); electrolytes (p. 1775·1).
Plasma volume expansion; shock; hypovolaemia.

Fresenius Kabi, Arg.†; Fresenius Kabi, Cz.; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.
⊗Succinylated gelatin (p. 1154·1).
Hypovolaemia; shock; plasma volume expansion; extracorporeal circulation; haemodilution.

Gelora *Reckitt Benckiser, India.*
Choline salicylate (p. 39·2).
Mouth ulcers; denture irritation; infant teething.

Gelosim *Ferrer, Spain.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

GeloSitin *Pohl, Ger.*
Sesame oil (p. 2614·1); Cetiol CC; orange oil (p. 2576·2); lemon oil (p. 2543·1).
Nasal congestion.

Gelospi *Auspi, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Gelostretch *BSN, Ital.*
Zinc oxide (p. 1729·1).
Medicated dressing.

Gelotradol *Ferrer, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.

Gelotralib *Ferrer, Port.*
Tramadol hydrochloride (p. 139·2).
Pain.

Gelovis *Amnol, Ital.*
Centella (p. 1698·3); capsicum (p. 2469·3); menthol (p. 2553·2).
Venous insufficiency; lymphoedema.

Gelovital *Pohl, Ger.*
Cod-liver oil (p. 2056·3).
Tonic.

Gelox *Ipsen, Fr.*
Montmorillonite; aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

Gelparin *Streuli, Switz.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular inflammation and thrombosis.

Gelpex *Parggon, Mex.*
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Parggon, Mex.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; flatulence.

Gel-Phan *Pierre Fabre Dermatologie, Fr.†*
⊗Gelatin (p. 1154·1).
Fragile hair or nails.

Gelplastan *Tanais, Rus.*
⊗Gelatin (p. 1154·1); kanamycin sulfate (p. 314·3); dried plasma (bovine) (p. 1158·2).
Haemorrhage.

Gelplex *Fresenius Kabi, Ital.*
⊗Polygeline (p. 1160·3).
Plasma volume expansion.

Gelprim *Gelpharma, Mex.*
Nifedipine (p. 1447·2).
Hypertension.

Gelsem *Mediteg, Venez.*
Aloe vera (p. 1693·2); arnica (p. 2447·2); aesculus (p. 2431·2); chamomile (p. 2474·1); calendula (p. 2465·2).

Gelsemium Comp *Hevert, Ger.*
Injection: Aconitum (p. 2428·3); cocculus (p. 2483·1); colocynthis (p. 1833·3); gelsemium (p. 2511·2); lachesis (p. 2538·3); mezereum; nux vomica (p. 2573·3); plumbum aceticum (p. 2541·3); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Hevert, Ger.
Oral drops: Aconitum (p. 2428·3); cocculus (p. 2483·1); colocynthis (p. 1833·3); gelsemium (p. 2511·2); lachesis (p. 2538·3); mezereum; plumbum aceticum (p. 2541·3); rhus toxicodendron (p. 2603·3); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Gelsemium Complexe No 70 *Lehning, Fr.*
Gelsemium (p. 2511·2); colocynthis (p. 1833·3); aconitum (p. 2428·3); chamomilla (p. 2474·1); mezereum; belladonna (p. 2453·3); nux vomica (p. 2573·3); rhus toxicodendron (p. 2603·3); arnica montana (p. 2447·2); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Gelsemium N Oligoplex *Madaus, Ger.*
Gelsemium (p. 2511·2); aconitum (p. 2428·3); gnaphalium polycephalum; mezereum; paris quadrifolia; ranunculus bulbosus.
Homoeopathic preparation.

Gelsemium-Homaccord *Heel, Cz.*
Gelsemium (p. 2511·2); rhus toxicodendron (p. 2603·3); cimicifuga racemosa (p. 2478·1).
Homoeopathic preparation.

Peithner, Hung.
Gelsemium sempervirans (p. 2511·2); toxicodendron quercifolium (p. 2603·3); cimicifuga racemosa (p. 2478·1).
Homoeopathic preparation.

Gelsica *Resinag, Switz.†*
Aluminium chlorohydrate (p. 1694·1).
Burns; ulcers; wounds.

Gelsolets *SMB, Chile.*
⊗Carbomer (p. 2173·3); mannitol (p. 1427·3).
Dry eyes.

Gelstan *Germiphene, Canad.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Gel-Stat *Geritrex, USA.*
⊗Alcohol (p. 1733·1).
Hand cleanser.

Geltazine *Crisdy-Na, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).
Gastritis; heartburn; oesophagitis; peptic ulcer.

GelTears *Chauvin, Irl.; Bausch & Lomb, UK.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Geltim *Thea, Belg.; Thea, Fr.; Thea, Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Gel-Tin *Young, USA.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Gelucom *Christo, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).

Gélucystine *Jolly-Jatel, Fr.*
Cystine (p. 2059·1).
Fragile nails and hair.

Gélufène *Cooperation Pharmaceutique, Fr.*
Ibuprofen (p. 68·2).
Pain; fever.

Gelum *Dreluso, Ger.*
Oral drops; topical gel: Potassium-iron (III)-citrate-phosphate complex.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; liver disorders.

Gelumag *Synco, Hong Kong†; Synco, Singapore.*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; peptic ulcer.

Gelumen *Cipla-Medpro, S.Afr.*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastric hyperacidity.

Gelumina *Menarini, Port.*
Tablets: Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3).
Gastrointestinal disorders.

Gelupin-MPS *Lupin, India.*
Dimeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Géluprane *Sanofi-Aventis, Fr.*
Paracetamol (p. 115·1).
Pain; fever.

Gelusil
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Austral.; Uniao Quimica, Braz.; Parke, Davis, USA.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence; dyspepsia; gastro-oesophageal reflux; hyperacidity.

Cheplapharm, Ger.
Almasilate (p. 1815·3).
Gastric hyperacidity; heartburn; peptic ulcer.

Hemofarm, Rus.
Silodrate.
Gastritis; peptic ulcer; gastro-oesophageal reflux; heartburn; dyspepsia.

Johnson & Johnson, Hong Kong; Pfizer, India; Pfizer, Indon.†; Pfizer, Malaysia; Pharma Dynamics, S.Afr.; Pfizer, Thai.†
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastritis; gastric hyperacidity; heartburn; dyspepsia; peptic ulcer.

Wellspring, Canad.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Gelusil MPS *Pfizer, India; Pfizer, Indon.†; Pfizer, Thai.†*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer; flatulence; bloating; dyspepsia.

Pfizer, India.
Tablets: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); aluminium magnesium silicate (p. 2168·2).

Gelusil N *Janssen-Cilag, Switz.†*
Almasilate (p. 1815·3); milk powder.
Gastrointestinal disorders.

Gelusil Plus *Johnson & Johnson, Hong Kong.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastritis; gastric hyperacidity; heartburn.

Pfizer, India.
Suspension: Aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); sorbitol (p. 2092·1).

Pfizer, India.
Tablets: Aluminium hydroxide (p. 1817·2); aluminium magnesium silicate (p. 2168·2); magnesium hydroxide (p. 1857·2).

Gelusil S *Pharma Dynamics, S.Afr.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence; dyspepsia; gastritis; heartburn; peptic ulcer.

Gelusil-Lac *Cheplapharm, Ger.*
Almasilate (p. 1815·3); fat-free milk powder.
Gastric hyperacidity; heartburn; peptic ulcer.

Gelutrophyl *Jolly-Jatel, Fr.*
Thenoic acid (p. 376·3).
Nasopharyngeal infections.

Gely *Faes, Spain.†*
⊗Glycerol (p. 2517·2).
Barrier preparation; lubricant.

Gem
Note: this name may be used for preparations of different composition.
Madhav, India.
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Nycomed, Norw.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Gem nouvelle formule contre le mal de gorge *Iromedica, Switz.*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

GEM 21S *Osteohealth, USA.*
⊗Becaplermin (p. 1695·2); calcium phosphate (p. 1784·2).
Periodontal disease.

Gem Voyage Dragées contre les maux de voyage *Iromedica, Switz.*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Motion sickness.

Gemabin *Ratiopharm, Denm.†; Rowex, Irl.†*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemadol
Note: this name may be used for preparations of different composition.
Meda, Denm.; Meda, Swed.
Tramadol hydrochloride (p. 139·2).
Pain.

Meda, Ital.
Etofenamate (p. 57·2).
Musculoskeletal, joint, and soft-tissue disorders.

Gemalata *Sigillata, Cz.; Sigillata, Neth.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemasa *Zdravo, Ukr.*
Prourokinase (recombinant).
Hyphema; hemophthalmus; retinal haemorrhage; occlusion of retinal artery; prevention of adhesions in the postoperative period.

Gemase *Technogen, Rus.*
Saruplase (p. 1489·2).
Myocardial infarction; thrombotic eye disorders; prevention of postoperative adhesions.

Gembax *Ranbaxy, India.*
Gemifloxacin or gemifloxacin mesilate (p. 304·1).
Chronic bronchitis; community-acquired pneumonia.

Gembin *Biochem, India.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Gembropac *Inpac, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gemcal *Alkem, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Gemci-Cell *Cell Pharm, Ger.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemcipen *Enorasis, Gr.*
Gemcitabine hydrochloride (p. 801·2).
Bladder cancer; pancreatic cancer; non-small cell lung cancer; ovarian cancer; breast cancer.

Gemcirena *Fresenius Kabi, Cz.; Fresenius Kabi, Fr.†; Fresenius Kabi, Gr.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemcit *Sandoz, Braz.; Fresenius Kabi, Denm.†; Sandoz, Philipp.; Fresenius Kabi, Port.; Dong-A, Thai.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemcitan *Cancernova, Ger.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemcitare *Biocad, Rus.*
Gemcitabine hydrochloride (p. 801·2).
Non-small cell lung cancer; pancreatic cancer.

Gemcite *Lilly, India.*
Gemcitabine hydrochloride (p. 801·2).
Non-small-cell lung cancer; pancreatic cancer; bladder cancer.

Gemcitelb *Tiefenbacher, Denm.†*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemcitera *Tuteur, Rus.*
Gemcitabine hydrochloride (p. 801·2).
Non-small cell lung cancer; pancreatic cancer.

Gemciteva *Teva, Pol.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemcitover *Lens, Rus.*
Gemcitabine hydrochloride (p. 801·2).
Non-small cell lung cancer; pancreatic cancer.

Gemd *Yung Shin, Singapore.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gemdex *Valeant, Hung.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemedac *Medac, Ger.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemer *Sun, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gemer P *Sun, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Gemexin *Zuventus, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemez *Glenmark, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemfi *1A, Ger.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gemfibril *Siam Bheasach, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gemfolid *Genepharm, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gemfos *Alkem, India.*
Risedronate sodium (p. 1189·3).
Paget's disease of bone; osteoporosis.

Gemhal *Sun, Denm.†*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemhexal *Sandoz, Austral.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gemibane *Cipla, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemibid *Invision, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemidac *Daksh, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemide *Arrowin, India.*
Cetrimide (p. 1742·1).
Wound cleansing.

Gemiderm *Lupin, India.*
⊗Beclometasone (p. 1621·2); miconazole (p. 588·3); neomycin (p. 329·3).
Skin infections.

Gemiderma *Gemi, Pol.*
Boric acid (p. 2459·3).
Skin disorders.

Gemif *Hetero, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemifix *Intra-Labs, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Geminate *Genesis, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Geminate Plus *Genesis, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Gemind *Sun, Denm.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemini *Adcock Ingram, S.Afr.*
⊗Antazoline hydrochloride (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Allergic eye disorders; eye irritation.

Gemiol Plus *SIFFRA, Ital.*
Birch leaf (p. 2457·3); abies pectinata; black currant (p. 2458·1); rose fruit (p. 2607·1); oligosaccharides; zinc gluconate (p. 2126·2).
Nutritional supplement.

Gemipar *Gemi, Pol.*
Paracetamol (p. 115·1).
Pain; fever.

Gemistar *Alkem, India.*
Gemifloxacin mesilate (p. 304·1).
Chronic bronchitis; community-acquired pneumonia.

Gemistatin *Geminis, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Gemita *Dabur, India; Fresenius Kabi, Philipp.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Fresenius Kabi, Thai.
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemitab *Micro, India.*
Gemifloxacin mesilate (p. 304·1).
Chronic bronchitis; community-acquired pneumonia.

Gemitin *SMB, Chile.*
Chloramphenicol (p. 257·1).
Bacterial skin infections.

Gemitin con Prednisolona *SMB, Chile.*
⊗Chloramphenicol (p. 257·1); prednisolone acetate (p. 1645·2).
Bacterial skin infections; otitis externa.

Gemitrol *Torrent, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3).

Gemka *Global, India.*
Amikacin (p. 214·1).
Bacterial infections.

Gemko *Kocak, Turk.*
Gemcitabine hydrochloride (p. 801·2).

Gemlipid *Medichrom, Gr.; FIRMA, Ital.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gemnil *Bioavenir, Israel.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Vianex (Bizveş), Gr.
Gemcitabine hydrochloride (p. 801·2).
Bladder cancer; pancreatic cancer; non-small cell lung cancer; ovarian cancer; breast cancer.

Gemodol *Plus, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Gemofas *Raffo, Arg.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Gemot *PSI, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Gemox *RX, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gempar *Cadila, India.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Gempower *Khandelwal, India.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Gempril *MJ Biopharm, Thai.*
Ramipril (p. 1483·3).
Hypertension; heart failure following myocardial infarction.

Gemsharp *Indoco, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemstad *Stada, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemstada *Pharmacodane, Denm.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemtabine *Korea United, Philipp.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemtaz *Pharmaplan, S.Afr.; Sun, Thai.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Sun, India.
Gemcitabine (p. 801·2).
Malignant neoplasms.

Gemtex *Teva, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemtiba *Tiefenbacher, Denm.†*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemtifi *Riemser, Denm.†*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemtro *Lilly, Arg.*
Gemcitabine hydrochloride (p. 801·2).
Bladder cancer; non-small cell lung cancer; pancreatic cancer; breast cancer; ovarian cancer.

Gemven *Vensat, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemvig *Madhav, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gemvit *Medihealth, India.*
Lycopene (p. 2546·2); vitamins.

Gemzar *Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.†; Lilly, Gr.†; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gemzil
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Captopril (p. 1331·2).
Hypertension; heart failure.

APT, Hong Kong.†
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Gen Le Wei *Huazhong, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Génac *Genevrier, Fr.*
Acetylcysteine (p. 1652·2).
Corneal ulceration.

Genac
Note: this name may be used for preparations of different composition.
Goldline, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Rishab, India.
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Genacol *Goldline, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Genac-SP *Rishab, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Genahist *Goldline, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Motion sickness; parkinsonism; insomnia.

Genalen *Gentili, Ital.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Genalfa *INTES, Ital.†*
⊗Gentamicin sulfate (p. 304·2); naphazoline nitrate (p. 1669·3).
Eye infections.

Genalin *BioFemme, Philipp.†*
Vitamins; minerals.

Genalin-F *Great Eastern, Thai.†*
Vitamins; minerals.

Genam *Genericon, Cz.*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Genamic *Genpharma, Arg.†*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Gen-Amilazide *Genpharm, Canad.†*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Genapap *Goldline, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Genaphed *Goldline, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Genaplex *Biotecnoquimica, Venez.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Genaprost *Gentili, Ital.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Genasal *Goldline, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Genasma *Alliance, S.Afr.†*
⊗Aminophylline (p. 1201·2); ephedrine hydrochloride (p. 1663·2).
Asthma.

Genaspor *Goldline, USA.†*
Tolnaftate (p. 596·1).
Fungal skin infections.

Genaton *Goldline, USA.*
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2).
Hyperacidity.

Goldline, USA.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1); alginic acid (p. 2167·2).
Hyperacidity.

Genatuss DM *Goldline, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Genavit *General Drugs, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; beri-beri; nausea and vomiting during pregnancy; anaemia.

Gen-Beclo *Genpharm, Canad.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Genbeclo *Merck, Venez.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Gen-bee with C *Goldline, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Gencalm *Gentech, India.*
Trifluoperazine (p. 1113·2).
Psychoses; nausea and vomiting; anxiety.

Gencalm Plus *Gentech, India.*
Trifluoperazine (p. 1113·2); trihexyphenidyl (p. 917·3).

Gencart *Cosme, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3); manganese sulfate (p. 2081·2); selenium dioxide (p. 2087·1); borax (p. 2459·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Gencef *Genepharm, Gr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Captab, India.
Cefalexin (p. 234·1).
Bacterial infections.

Gencephal *Gentech, India.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Gencetamol *Thebe, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Gencidal *TNP, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Gencin *Actavis, Ger.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gencivol Compuesto *Vincenti, Venez.*
Benzydamine hydrochloride (p. 29·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Gencolax *General Drugs, Thai.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Gen-Combo *Genpharm, Canad.†*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Gencydo *Weleda, Austria; Weleda, Ger.; Weleda, Switz.*
Lemon (p. 2542·3); cydonia.
Hypersensitivity reactions; allergic respiratory-tract disorders.

Weleda, Fr.
Succus citri (p. 2542·3); succus cydoniae.
Homoeopathic preparation.

Weleda, UK.
Lemon juice (p. 2542·3); cydonia seeds.
Homoeopathic preparation.

Gendazel *General Drugs, Thai.*
Albendazole (p. 149·1).
Worm infections.

Gende *Juneng, China.*
Etidronate disodium (p. 1182·3).
Osteoporosis.

Gendecon
Note: this name may be used for preparations of different composition.
Goldline, USA.
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Gendem-MD *Gentech, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Gen-DM *Thai Otsuka, Thai.*
Preparation for enteral nutrition.

Gendol
Note: this name may be used for preparations of different composition.
Gentech, India.
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion; nausea and vomiting.

Dynamic, Philipp.†
Paracetamol (p. 115·1).
Fever; pain.

Gendron *Bentley, Cz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Genebs *Goldline, USA.†*
Paracetamol (p. 115·1).
Pain; fever.

Genecalcin *Genepharm, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Genecar *Genesis, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Genefacort *Genepharm, Gr.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Genefadrone *Genepharm, Gr.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Genefilus F19 *SIFFRA, Ital.*
Lactobacillus paracasei (p. 2596·3); glucosaccharides; vitamin B substances (p. 2102·3).
Nutritional supplement.

Geneleukim *Geneleuk, China.*
A recombinant human granulocyte colony-stimulating factor.
Neutropenia.

Genemicin *Diba, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genepan *GeneriNobel, Austria.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Genephoxal *Genepharm, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Geneprami-D *Genepharm, Gr.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Generaid *Nutricia, Austral.; SHS, Denm.; Scientific Hospital Supplies, Irl.†; Nutricia, Ital.; Nutricia, NZ; SHS, UK.*
Preparation for enteral nutrition.
Nutritional supplement in liver disorders.

Generaid Plus *Scientific Hospital Supplies, Irl.†*
Amino acids; carbohydrates; lipids; vitamins; minerals.
Liver disorders.

Generazole *Nucleus, Denm.†*
Fluconazole (p. 578·2).
Fungal infections.

Genercin *General Drugs, Thai.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Generet *Goldline, USA.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Iron-deficiency anaemias.

Generflon *SoSe, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Genergin *General Drugs, Thai.†*
Dipyrone (p. 53·3).
Fever; pain.

Generiapin *Generis, Denm.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Generit *Genetic, Ital.*
Cetirizine hydrochloride (p. 619·2).

Generix-T *Goldline, USA.*
Vitamins; minerals; iron (p. 2073·1).

Generlac *Morton Grove, USA.*
Lactulose (p. 1850·3).
Constipation.

Generlog *General Drugs, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Généserine *Eisai, Fr.*
Eseridine salicylate (p. 1840·3).
Dyspepsia.

Genesin *Patar, Thai.*
Guaifenesin (p. 1666·2).
Cough.

GeneSoft *Watsin Genetech, China.*
A recombinant human epidermal growth factor derivative.
Corneal damage.

Genetaxyl *Genovate, Thai.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Gen-Eti-Cal *Genpharm, Canad.†*
76 Tablets, calcium carbonate (p. 1824·3); 14 tablets, etidronate disodium (p. 1182·3).
Osteoporosis.

GeneTime *Watsin Genetech, China.*
A recombinant human epidermal growth factor derivative.
Wounds; ulcers; burns.

Genevac-B *Serum Institute, India.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Genexin *Genedec, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia.

Genexol *Pezomed, Hung.; Samyang, Singapore.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer; Kaposi's sarcoma; non-small cell lung cancer.

Geneye AC Allergy *Goldline, USA.†*
⊗Tetryzoline hydrochloride (p. 1678·3); antazoline phosphate (p. 615·3).
Eye irritation.

Genfastat *Genfa, Rus.*
Octreotide (p. 1924·1).
Acromegaly; gastropancreatic tumours; prevention of complications following pancreatic surgery; AIDS-associated diarrhoea.

Genfaxon *Tuteur, Rus.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

Genferon
Note: this name may be used for preparations of different composition.
Biocad, Rus.
Interferon alfa-2 (p. 989·2); taurine (p. 2626·2); benzocaine (p. 1980·2).
Inflammatory genitourinary-tract infections.

Biokad, Ukr.
Interferon alfa-2b (human, recombinant) (p. 989·2).
Urogenital infections.

Genferon Light *Biocad, Rus.*
Taurine (p. 2626·2); interferon alfa-2b (p. 989·2).
Urogenital infections in women and children; viral infections.

Gen-Fibro *LCH, Hong Kong.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

GenFlex *Inovail, Austral.†*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

GenFlex 3 *Inovail, Austral.†*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); krill oil.
Osteoarthritis; rheumatoid arthritis.

GenFlex NKO *Inovail, Austral.†*
Glucosamine hydrochloride (p. 2515·3); krill oil.
Osteoarthritis; rheumatoid arthritis.

GenFlex Plus *Inovail, Austral.†*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Genflox *Cadila, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Genflox TZ *Cadila, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Genfol *Cadila, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Tonic.

Gen-Formula *Thai Otsuka, Thai.†*
Preparation for enteral nutrition.

Genger Exp *Moraceae, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Gengigel *Esme, Arg.; Qualiphar, Belg.; Ricerfarma, Malaysia; Oraldent, UK.*
Hyaluronic acid (p. 2526·2).
Gum disorders; mouth lesions.

Gengisyl *Master, Chile.†*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Gen-Glybe *Genpharm, Canad.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gengraf *Abbott, Braz.; Abbott, Chile†; Abbott, China; Abbott, Hong Kong†; Abbott, Malaysia†; Abbott, NZ†; Abbott, Singapore; Abbott, Thai.†; Abbott, Turk.; Abbott, USA.*
Ciclosporin (p. 1945·2).
Transplant rejection; rheumatoid arthritis; psoriasis; nephrotic syndrome; atopic eczema; endogenous uveitis.

Gengxian *Dongyu, China.*
Lovastatin (p. 1425·2).
Hypercholesterolemia.

GenHeal *Pediatrica, Philipp.; Great Eastern, Thai.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; short children born small for gestational age; Turner' syndrome; Prader-Willi syndrome.

Genheal *United Cell Biotech, China.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency.

GenHevac B *Sanofi Pasteur, Fr.; Sanofi Pasteur, Turk.*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Active immunisation.

Genhydramine *Alliance, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Génia *Vepex, Hung.*
Lactamin (proteose peptone); lactose (p. 2078·3); lactic acid (p. 2539·1); folic acid (p. 2063·1).
Vaginal disorders.

Geniad *TS, Ital.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia; osteoporosis.

Geniceral *Casasco, Arg.*
Idebenone (p. 392·3).
Cerebrovascular disorders; mental function impairment.

Geniclor *Boniscontro & Gazzone, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Geniclox *Sterling, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Genicol *Guardian, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Genin *General Drugs, Thai.*
Quinine sulfate (p. 665·2).
Malaria.

Geninax *Astellas, Jpn; Taisho, Jpn.*
Garenoxacin mesilate (p. 303·2).
Bacterial infections.

Geniol
Note: this name may be used for preparations of different composition.
GSK, Arg.
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Mintlab, Chile.
Paracetamol (p. 115·1).
Fever; pain.

Geniol Compuesto *Mintlab, Chile.*
Day sachets, paracetamol (p. 115·1); noscapine hydrochloride (p. 1670·3); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); night sachets, paracetamol; noscapine hydrochloride; caffeine; ascorbic acid; chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Geniol Flu *Mintlab, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Geniol Flu DN *Mintlab, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); night tablets, paracetamol; pseudoephedrine sulfate; chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Geniol Prevencion *GSK, Arg.*
Aspirin (p. 22·2).
Thromboembolic disorders; pain; fever.

Geniol SC sin Cafeina *GSK, Arg.*
Aspirin (p. 22·2).
Fever; pain.

Geniol-P Compuesto con Clorfenamino *Mintlab, Chile.†*
Paracetamol (p. 115·1); noscapine hydrochloride (p. 1670·3); caffeine

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 1203·3); ascorbic acid (p. 2110·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Genis *Triton, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Genisol *Teofarma, Ital.*
Piroctone olamine (p. 1716·3); disodium sulfosuccinated undecenoic acid monoethanolamide (p. 596·3).
Seborrhoeic dermatitis.

Genite *Goldline, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Coughs and cold symptoms.

Genitoflox *IQB, Braz.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Genivis *Mastelli, Ital.*
Genistein (p. 2620·3).

Gen-K *Goldline, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Genka *Cadila, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Genkind *Elfin, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Genkova *Sons, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gen-Lac *Genpharm, Canad.†*
Lactulose (p. 1850·3).
Constipation.

Genlac *Sigma, Austral.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

GenLei Jintropin *GeneScience, Hong Kong.*
⊗Somatropin (p. 1919·3).
Growth disorders in renal failure; growth hormone deficiency; Turner' syndrome.

Genlide *Cadila, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Genlide Plus *Cadila, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Genlip
Note: this name may be used for preparations of different composition.
Genesis, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.
Teofarma, Ital.
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Genlip-EZ *Genesis, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Genlith *Gentech, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression.

Genlyte *Cadila, India.*
Oral powder; liquid: Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2).
Cadila, India.
Oral sachets: Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2).

Genmac *McNeil & Argus, India.*
Ginseng (p. 2513·3); minerals; vitamins.

Gen-Medroxy *Genpharm, Canad.†*
Medroxyprogesterone acetate (p. 2288·1).

Genmisin *Tum, Turk.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genmole *Cadila, India.*
Paracetamol (p. 115·1).
Pain; fever.

Genmox *Cadila, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Genmycin *Klar Sehen, India.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gen-Nitro *Genpharm, Canad.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Genocin *General Drugs, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria; amoebiasis.

Genoclom *Lapi, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Genocolan *Craveri, Arg.*
Lactulose (p. 1850·3).
Constipation; gastrointestinal infections; hepatic encephalopathy; urinary-tract infections.

Genoflox *XL, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Genofort *Tocogino, Mex.*
Progesterone (p. 2300·2); estradiol (p. 2271·1).

Genogris
Note: this name may be used for preparations of different composition.
Labesfal, Port.†
Nimodipine (p. 1455·2).

Genolaxante *Craveri, Arg.*
Phenolphthalein (p. 1877·3); aloes (p. 1816·1); simeticone (p. 1886·2).
Constipation.

Genolon *Guardian, Indon.*
⊗Gentamicin sulfate (p. 304·2); fluocinolone acetonide (p. 1636·1).
Skin disorders.

Genom *Geofman, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gen-One *Genesis, India.*
Ginseng (p. 2513·3); green tea (p. 2648·2); minerals; vitamin B substances (p. 2102·3).

Genophane *Geno, India.*
Dihydralazine sulfate (p. 1358·3); reserpine (p. 1485·3).

Genoplex Forte *Geno, India.*
Benzyl alcohol (p. 1739·3); choline chloride (p. 2055·2); vitamin B substances (p. 2102·3); lidocaine hydrochloride (p. 1988·2).

Genoptic *Allergan, Austral.; Allergan, Hong Kong†; Allergan, Irl.†; Allergan, NZ; Allergan, Singapore†; Allergan, USA.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Genoral *Pfizer, Austral.*
Estropipate (p. 2275·2).
Oestrogen deficiency; menopausal disorders.

Genosedyl *Geno, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Genotonorm *Pfizer, Belg.; Pfizer, Chile; Pfizer, Fr.; Pfizer, Spain.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner's syndrome; Prader-Willi syndrome; growth disorders in renal failure.

Genotropin *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia Upjohn, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pharmacia, USA; Pfizer, Venez.*
⊗Somatropin (p. 1919·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome; Prader-Willi syndrome; short children born small for gestational age; cachexia and wasting in AIDS; short bowel syndrome; SHOX deficiency; idiopathic short stature.

Genovox *Kleva, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Genox
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Alphapharm, Malaysia†; Mylan, NZ.
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; endometrial cancer.
Genesis, Philipp.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Intas, India.
Oxytocin (p. 2143·1).
Postpartum haemorrhage; labour induction; evaluation of fetal distress.

Genoxacin *Uniao Quimica, Braz.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Genoxal *Baxter, Spain.*
Cyclophosphamide (p. 771·1).
Auto-immune disorders; malignant neoplasms; transplant rejection.

Genozym *Investi, Arg.*
⊗Clomifene citrate (p. 2259·1).
Female infertility.

Genozyme *Geno, India.*
Capsules: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1); dried yeast (p. 2125·2).
Geno, India.
Syrup: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Gen-Payne *Adcock Ingram, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; inflammation; pain.

Genpen *Gentech, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Genpen-D *Gentech, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Genphenil *Generics Pharmacal, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Genprin *Goldline, USA.*
Aspirin (p. 22·2).
Pain; fever; inflammation; transient ischaemic attacks; myocardial infarction.

Genprol *Sandoz, Spain.†*
Citalopram hydrobromide (p. 411·1).
Anxiety; depression; obsessive-compulsive disorder.

Genprot *Cadila, India.*
Protein hydrolysate (p. 2086·2); nicotinamide (p. 2083·1); vitamin B_6 (p. 2105·3); magnesium chloride (p. 1787·1); zinc sulfate (p. 2126·2).
Tonic.

Genquin *Seng, Thai.*
Gentamicin sulfate (p. 304·2); bacitracin (p. 225·3); clioquinol (p. 273·1); glycine (p. 2071·2); threonine (p. 2098·2); cystine (p. 2059·1).
Infected skin disorders.

Genrab *Gentech, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Genrab-D *Gentech, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Genrest *Gentech, India.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Genrest Plus *Gentech, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Genrest-LS *Gentech, India.*
Risperidone (p. 1103·2); trihexyphenidyl (p. 917·3).

Genrex *Rayere, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gensat *Vensat, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Genselax *Doctors, Philipp.*
Ibuprofen (p. 68·2).
Fever; pain; inflammation.

Genser *Serral, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genser Sweet *Genser, Arg.†*
Aspartame (p. 2169·2); acesulfame potassium (p. 2166·2).
Sugar substitute.

Gensi *Genericon, Cz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Gensia *Pharos, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Gensil *General Drugs, Thai.†*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Genspir *Vocate, Gr.*
Paracetamol (p. 115·1).
Fever; pain.

Genster *Sterfil, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genstra *Synthon, Neth.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Gensulin M30, M50 *SciGen, Thai.*
⊗Mixtures of insulin injection (human) 30% or 50% and isophane insulin injection (human) 70% or 50%, respectively (p. 475·3).
Diabetes mellitus.

Gensulin M30, M40, or M50 *Bioton, Pol.*
⊗Mixtures of soluble neutral insulin (human) 30%, 40%, or 50% and isophane insulin (human) 70%, 60%, or 50% (p. 475·3).
Diabetes mellitus.

Gensulin N *Bioton, Pol.; SciGen, Thai.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Gensulin R *Bioton, Pol.; SciGen, Thai.*
⊗Neutral insulin (human) (p. 475·3).
Diabetes mellitus.

Gensumycin *Sanofi-Aventis, Fin.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genta *CT, Ger.†; Grin, Mex.; M & H, Thai.; T Man, Thai.; Ulagay, Turk.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genta Cort B *Laborate, India.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2).

Genta Cort D *Laborate, India.*
⊗Dexamethasone (p. 1630·3); gentamicin (p. 304·2).

Genta Gobens *Normon, Port.; Normon, Spain.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genta Swift *Ind-Swift, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Genta Swift-D *Ind-Swift, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); gentamicin (p. 304·2).

Gentacid *Vonnace, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Gentacidin *Novartis Ophthalmics, USA.†*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentacin *Olan-Kemed, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentacip *Cipla, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentacip D *Cipla, India.*
⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Gentacler *Monserrat, Arg.*
⊗Gentamicin sulfate (p. 304·2); hydrocortisone acetate (p. 1640·1); ketoconazole (p. 585·3).
Infected skin disorders.

Gentacoll *EUSA, Denm.; EUSA, Fin.*
Gentamicin sulfate (p. 304·2).
Bone infections; wound infections; bone infection.

Gentacort
Note: this name may be used for preparations of different composition.
Allergan, Braz.
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected eye disorders.
Novartis, Ital.†
⊗Gentamicin sulfate (p. 304·2); fluorometholone (p. 1637·2).
Infected eye disorders.

Gentacort Plus *Cassara, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin (p. 304·2); clotrimazole (p. 576·2).
Infected skin disorders.

Gentacort-FC *Laborate, India.*
⊗Fluocinolone (p. 1636·1); gentamicin (p. 304·2); miconazole (p. 588·3).

Gentacortin *Merck, Indon.†*
⊗Fluprednidene acetate (p. 1637·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Gentacort-MF *Laborate, India.*
⊗Clotrimazole (p. 576·2); fluocinolone (p. 1636·1); gentamicin (p. 304·2).

Gentacream *Epifarma, Ital.*
Gentamicin sulfate (p. 304·2).
Infected skin disorders.

Gentact *Datla, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentacyl *Darya-Varia, Indon.†*
Gentamicin sulfate (p. 304·2).
Eye infections.

Gentaderm *Cassara, Arg.; TO-Chemicals, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Genta-Dex *CCM, Malaysia.*
⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders with infection.

Gentadex *Farmex, Gr.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); gentamicin sulfate (p. 304·2).
Eye infections.

Gentadexa *Alcon Cusi, Malaysia; Alcon, Port.; Alcon Cusi, Spain.*
⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2); tetryzoline hydrochloride (p. 1678·3).
Infected eye and ear disorders with inflammation.

Gentagen *Genepharm, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentagran *Legrand, Braz.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentagut *Bilim, Turk.*
Gentamicin sulfate (p. 304·2).
Bacterial eye and ear infections.

Gentak *Akorn, Canad.; Akorn, USA.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gental *General Drugs, Thai.; Julphar, UAE.*
Gentamicin sulfate (p. 304·2).
Bacterial infection.

Gentalab *Laborate, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentalene Plus *Ranbaxy, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Gentalene-C *Ranbaxy, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Gental-F *General Drugs, Thai.*
⊗Gentamicin sulfate (p. 304·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Gentalin *Labesfal, Port.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentalline *MSD-Chibret, Fr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentalyn *Schering-Plough, Chile; Schering-Plough, Ital.; Schering-Plough, Venez.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentalyn Beta *Schering-Plough, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Gentam *Amrit, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentamed *Kocak, Turk.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamedin *IFET (ΙΦΕΤ), Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamerck *Merck, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamicil *Greenpharma, Braz.*
Gentamicin (p. 304·2).
Bacterial infections.

Genta-Micron *Alcon, Mex.*
Gentamicin (p. 304·2).
Bacterial eye infections.

Gentamil *Ducto, Braz.; Bruluart, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamilan *Meyer, Venez.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamina *Schering-Plough, Arg.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamisan *Santisa, Braz.*
Gentamicin (p. 304·2).

Gentamisin *Tunggal Idaman, Indon.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentamytrex *Mann, Ger.†; Tramedico, Neth.†; Bausch & Lomb, Philipp.†; Mann, Singapore.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Genta-Oph *Seng, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentapat *Parggon, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentapharma *Fada, Arg.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentaplex *Liptis, USA.*
Lyophilised fish roe; ginkgo biloba (p. 2512·3).
Decreased libido in men.

Gentapro *Ashford, Singapore.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentaren *Andromaco, Arg.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Gentaril *Alkem, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentaron *Ariston, Braz.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentasia *Willow, India.*
Gentamicin sulfate (p. 304·2).
Bacterial ear or eye infections.

Gentasia-D *Willow, India.*
⊗Dexamethasone (p. 1630·3); gentamicin sulfate (p. 304·2).

Gentasol
Note: this name may be used for preparations of different composition.
Ashford, Singapore; Ocusoft, USA.
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Monserrat, Arg.
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Gentasolon *Ikapharmindo, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Gentason *Wagner, Hung.†*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected eye disorders.

Gentasone *Schering-Plough, Chile.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected external ear disorders; bacterial eye infections.

Gentasporin *PC India, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentasporin-HC *PC India, India.*
⊗Gentamicin sulfate (p. 304·2); hydrocortisone acetate (p. 1640·1).

Gentate *Parenteral Drugs, India.*
Gentamicin (p. 304·2).
Bacterial eye infections.

Gentate-B *Parenteral Drugs, India.*
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin sulfate (p. 304·2).

Gentatrim *Trima, Israel.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Gentawin *General Drugs, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentax *Agepha, Austria.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentaxan *Borshchagovskii, Ukr.*
Gentamicin (p. 304·2); tryptophan (p. 453·2); zinc sulfate (p. 2126·2).
Infected burns, ulcers, and wounds; skin infections.

Gentaxin *Gland, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentazaf Z *Zafiro, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentazol *Unipharm, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Genteal *Novartis, Arg.; Novartis, Austral.; Novartis, Braz.; Novartis Ophthalmics, Canad.; Novartis, Chile; Alcon, Ger.; Novartis, Hong Kong; Novartis, India; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Philipp.; Alcon, Singapore; Alcon, Thai.; Novartis, USA; Novartis, Venez.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation; lubricant for contact lens wearers.

Novartis, Austral.; Novartis, Indon.; Novartis, Malaysia; Alcon, Thai.; Novartis, Venez.
Eye gel: Hypromellose (p. 2189·2); carbomer (p. 2173·3).
Dry eyes; eye irritation; lubricant for contact lens wearers.

Genteal Geldrops *Novartis, Canad.*
Hypromellose (p. 2189·2); carmellose sodium (p. 2175·2).
Dry eyes.

Genteal HA *Alcon, Ger.*
Hyaluronic acid (p. 2526·2).
Dry eyes; eye irritation; contact lens comfort.

Gentex *Gentex, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Genthaver *Haver, Turk.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentialoquin *Collins, Mex.†*
Gentamicin (p. 304·2).
Bacterial infections.

Gentiana Complexe No 33 *Lehning, Fr.†*
⊗Gentiana (p. 2512·1); acide sulfuricum (p. 2624·2); kalium carbonicum (p. 2595·2); lobelia inflata (p. 2323·2); nux vomica (p. 2573·3); quassia amara (p. 2601·1); rubia; quercus robur (p. 2574·1).
Homoeopathic preparation.

Gentianella *Pharmatrix, Arg.*
Gentianella achalensis; centella (p. 1698·3); fucus vesiculosus melilot (p. 2552·3); ginkgo biloba (p. 2512·3); caffeine (p. 1203·3).
Cellulite.

Gentiapin *Biogened, Neth.; Biogened, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Genticin *Amdipharm, Irl.; Roche, UK.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genticol *SIFI, Ital.*
Gentamicin sulfate (p. 304·2).
Eye infections.

Genticyn *Piramal, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Genticyn B *Allergan, India.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected eye and ear disorders.

Genticyn Eye/Ear *Allergan, India.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections; ear infections.

Genticyn HC *Allergan, India; Piramal, India.*
⊗Gentamicin sulfate (p. 304·2); hydrocortisone acetate (p. 1640·1).
Allergic and inflammatory eye and ear disorders.

Gentidexa *Leti, Venez.*
Eye ointment: ⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Leti, Venez.
Eye drops: ⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2); tetryzoline hydrochloride (p. 1678·3).
Infected eye disorders.

Gentin *Psyco Remedies, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gentina *Bal, India.*
Gentamicin (p. 304·2).
Bacterial eye infections.

Gentin-MC *Psyco Remedies, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gentipress *Gentili, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Gentiran *Vocate, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Gentisal *Sanitas, Chile.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentisalyl *Maigal, Arg.*
Diclofenac sodium (p. 48·3).

Gentisone HC *Amdipharm, Irl.; Roche, UK.*
⊗Gentamicin sulfate (p. 304·2); hydrocortisone acetate (p. 1640·1).
Otitis externa; bacterial ear infections.

Gentisul *Megat, Venez.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentisyl NF *Benitol, Arg.*
⊗Naphazoline (p. 1669·3).
Nasal congestion.

Gentlax
Note: this name may be used for preparations of different composition.
Purdue Frederick, USA.
Bisacodyl (p. 1821·1).
Constipation.

Gentlax S
Note: this name may be used for preparations of different composition.
Purdue, Canad.†
Bisacodyl (p. 1821·1); docusate sodium (p. 1836·2).
Constipation; bowel evacuation.

Gentle Cream *Geritrex, USA.*
Emollient.
Skin disorders.

Gentle Fresh Defense *State Industrial, Canad.*
Triclosan (p. 1773·2).

Gentle Fresh Sanitizer *State Industrial, Canad.*
Benzethonium chloride (p. 1738·1).

Gentle Iron *Nature's Bounty, USA.*
Ferrous bisglycinate (p. 2061·3).
Iron supplement.

Gentle Rain *Coloplast, Canad.*
Triclosan (p. 1773·2).

Gentle Tears *Euro-Med, Philipp.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Gentlees *Delamac, Austral.*
⊗Hamamelis water (p. 2523·3); glycerol (p. 2517·2); cetylpyridinium chloride (p. 1743·1).
Anogenital wounds; anorectal disorders; nappy rash; nipple care.

Gentocil *Edol, Port.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gentoin *Gentech, India.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Gento-Iron *Solgar, Canad.†*
Iron (p. 2073·1).

Gentoler *Lersan, Arg.†*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentomil *Hospira, Ital.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gent-Ophtal *Winzer, Ger.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Gentopic *Systopic, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin (p. 304·2).
Infected skin disorders.

Gentos
Note: this name may be used for preparations of different composition.
Bittner, Austria; Bittner, Rus.; Bittner, Ukr.
Populus; sabal (p. 2363·3); conium (p. 2524·3); kalium jodatum (p. 2336·3); ferrum picrinicum (p. 2634·2).
Homoeopathic preparation.
Bittner, Hung.
Populus tremuloides (p. 2594·2); serenoa repens (p. 2363·3); conium maculatum (p. 2524·3); ferrum picrinicum (p. 2634·2); kalium jodatum (p. 2336·3).
Homoeopathic preparation.

Gentran *IFET (ΙΦΕΤ), Gr.*
⊗Dextran 40 (p. 1138·1).

Gentran 40 *Baxter, UK; Baxter, USA.*
⊗Dextran 40 (p. 1138·1) in glucose or sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis; extracorporeal circulation.

Gentran 70 *Baxter, UK; Baxter, USA.†*
⊗Dextran 70 (p. 1138·3) in glucose or sodium chloride.
Plasma volume expansion.

Gentravit *Gentech, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Gentreks *Bilim, Turk.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentrex *Seng, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Gentriderm *Seoul Pharma, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected inflammatory skin disorders.

Gentrip *Gentech, India.*
Amitriptyline (p. 401·1).
Depression; neuropathic pain; migraine.

Gentrip Forte *Gentech, India.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).

Gentrip Plus *Gentech, India.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).

Gentrisil *Alliance, S.Afr.†*
Magnesium trisilicate (p. 1858·1); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Gentrisone *Shin Poong, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected inflammatory skin disorders; burns.

Gentrobex *Vysali, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gentussin *General Drugs, Thai.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Genty *Jagsonpal, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gentyl-DM *Indkus, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); gentamicin sulfate (p. 304·2).

Gentyric *Euphoric, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Genu-cyl L Ho-Len-Complex *Liebermann, Ger.*
Apis (p. 2445·2); bryonia (p. 2461·3); causticum (p. 2595·3); dulcamara (p. 2497·3); kalmia (p. 2537·2); petroleum (p. 2587·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Genuhist *Misha, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Genurat *Soria Natural, Spain.*
Bearberry (p. 2453·2); betula alba (p. 2457·3); Scots pine oil (p. 2591·2); calluna vulgaris.
Urinary-tract infections.

Genurin *Recordati, China; Recordati, Ital.; Recordati, Singapore; Elmor, Venez.*
Flavoxate hydrochloride (p. 2360·1).
Genito-urinary tract disorders.

Genurin-S *Sanofi-Aventis, Braz.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract spasm.

Genuten *Pharma Investi, Chile.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Genuxal *Baxter, Braz.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Genvac-B *Serum Institute, Philipp.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Genval-OD *Gentech, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Genvir *Vocate, Gr.*
Gemcitabine hydrochloride (p. 801·2).

Genvol Plus *Cadila, India.*
Camphor (p. 2466·2); chlorothymol (p. 1748·2); cineole (p. 2479·1); menthol (p. 2553·2); terpineol (p. 2627·2).

Genxvast *Hetero, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Genxvast-F *Hetero, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Genzosin *Genovate, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Geocal *Burgeon, India.*
Calcium citrate (p. 1783·2); copper sulfate (p. 2057·2); magnesium hydroxide (p. 1857·2); manganese sulfate (p. 2081·2); borax (p. 2459·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Geocobalamin *Geofman, Philipp.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Geocort *Geo, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Geodon *Pfizer, Braz.; 2care4, Denm.; Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Mex.; Pfizer, S.Afr.; Pfizer, Spain; Pfizer, USA.*
Ziprasidone hydrochloride (p. 1115·2).
Psychoses; bipolar disorder; schizophrenia; mania.
Pfizer, Venez.
Ziprasidone (p. 1115·2) or ziprasidone mesilate (p. 1115·2).
Schizophrenia; bipolar disorder.

Geoflox *Genom, Rus.*
Ofloxacin (p. 334·3).
Bacterial infections.

Geomycine *Schering-Plough, Belg.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Geonyn *Schering-Plough, Gr.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Geophagol *Sanval, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Geopred *Geo, India.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Geopride *Geofman, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ge-Oral *Kansuk, Turk.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Geotril *Ulagay, Turk.†*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Geovin *Shalaks, India.*
Griseofulvin (p. 582·2).
Fungal hair, skin, and nail infections.

Geovita *Rubimed, Neth.*
Cerebrum suis (p. 2444·1); cuprum metallicum (p. 2057·1); ferrum metallicum (p. 2073·1); formicicum acidum (p. 2507·1); silicea (p. 2208·3).
Homoeopathic preparation.

Geoxin *Geo, India.*
Digoxin (p. 1353·3).
Heart failure; supraventricular arrhythmias.

Geozit *Geofman, Philipp.*
Azithromycin (p. 221·2).
Bacterial infections.

Gepacef *Arterium, Ukr.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Gepacef Combi *Arterium, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Gepacod *Sanofi-Aventis, Fin.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Gepan Instill *Pohl, Ger.*
Chondroitin sulfate sodium (p. 2476·1).
Interstitial cystitis.

Gepeprostin *Sandoz, Arg.; Novartis, Braz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Gepex *GP, Spain.*
⊗Exemestane (p. 792·2).
Breast cancer.

Geping *Xiuzheng, China.*
Irbesartan (p. 1411·1).
Hypertension.

Gepride
Note: this name may be used for preparations of different composition.
Intra-Labs, India.
Itopride hydrochloride (p. 1850·1).
Medley, India.
Glimepiride (p. 473·2).
Diabetes mellitus.

Gepride-M *Medley, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Gepromi *Teva, Mex.†*
Progesterone (p. 2300·2).
Menopausal disorders; female infertility; threatened miscarriage.

Geptrong *Novopharma, Rus.*
Honey (p. 2072·1).

Geracin *Reuffer, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Gerafen *Genesis, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Gerakon *Munir, Turk.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Geral *Munir, Turk.*
Benzydamine hydrochloride (p. 29·2); chlorhexidine gluconate (p. 1743·3).

Geralen *Gerot, Austria.*
5-Methoxypsoralen (p. 1714·1).
Psoriasis.
Gerot, Pol.†
Methoxsalen (p. 1711·3).
Skin pigmentation disorders; psoriasis; mycosis fungoides.

Geralgine Plus *Munir, Turk.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Geralgine-Hot *Munir, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine (p. 1676·1).

Geralgine-K *Munir, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Fever; pain.

Geralgine-M *Munir, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Geralgine-P *Munir, Turk.*
Elixir: Paracetamol (p. 115·1).
Fever; pain.
Munir, Turk.
Tablets: Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Geramet *Gerard, Irl.†*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Geramox *Generics, Irl.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Geran *GPC, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Geranil *Neuropharma, Arg.*
Pergolide (p. 910·2).
Parkinsonism.

Geranium Complexe No 108 *Lehning, Fr.†*
Geranium robertianum; veratrum album (p. 2644·3); sulfur (p. 1721·1); cantharis (p. 2469·2); ecballium; aconitum (p. 2428·3); mercurius corrosivus (p. 2555·2); cuprum aceticum (p. 2486·2); sanguisorba (p. 2462·3); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Gerard House Reumalex *Chefaro, UK.*
Guaiacum resin (p. 2523·1); cimicifuga (p. 2478·1); salix (p. 129·2); sarsaparilla (p. 2610·3); poplar bark (p. 2450·3).
Musculoskeletal and joint disorders.

Gerard House Serenity *Chefaro, UK.*
Lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Stress; irritability.

Gerard House Skin *Chefaro, UK.*
Lappa (p. 2540·1); wild pansy (p. 2647·3).
Skin blemishes; eczema.

Gerard House Somnus *Chefaro, UK.*
Valerian (p. 2640·2); lupulus (p. 2546·1); wild lettuce (p. 2647·3).
Insomnia.

Gerard House Water Relief Tablets *Chefaro, UK.*
Bladderwrack (p. 2612·1); clivers (p. 2481·2); ground ivy (p. 2523·1); lappa (p. 2540·1).
Premenstrual water retention.

Geratam *UCB, Belg.; UCB, Cz.*
Piracetam (p. 393·3).
Mental function impairment; myoclonus; cortical myoclonus; vertigo; dyslexia in children.

Geratar *UCB, S.Afr.†*
Inositol nicotinate (p. 1410·3); vitamins; meclozine hydrochloride (p. 634·3); hydroxyzine hydrochloride (p. 630·3).
Cerebrovascular disorders; nocturnal leg cramps; vertigo.

Geravim *Major, USA.*
Vitamin B substances (p. 2102·3); minerals.

Gerax *Gerard, Irl.*
Alprazolam (p. 1035·2).
Anxiety disorders.

Gerber for Moms *Novartis, Philipp.†*
Nutritional supplement for pregnancy and breast feeding.

Gerber Soothe Colic Drops *Nestle, USA.*
Lactobacillus reuteri (p. 2596·3).

Gerbin *Temis, Spain.*
Aceclofenac (p. 16·2).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Gerbloc *Swiss Health, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; migraine; arrhythmias; hyperthyroidism.

Gerdex *Teva, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastritis; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Gerdi *Farmakopea, Ital.*
Domperidone (p. 1838·1).

Gerdilium *Otto, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Gerdom *Waves, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Gerdopan *Waves, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Geref *Serono, Gr.; Serono, Irl.†; Serono, USA.†*
⊗Sermorelin acetate (p. 1930·1).
Test for growth hormone secretion; test of pituitary function.

Serono, Ital.†
⊗Sermorelin (p. 1930·1).
Test for growth hormone secretion.

Gerelax *Gerard, Irl.†; Gerard, Israel.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Gerformin *Gerard, Irl.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Geri SS *Geritrex, USA.*
Emollient.
Dry skin disorders.

Geriacaps *Herbapol Krakow, Pol.*
Garlic (p. 2510·3); ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Geriadyn *Combiphar, Indon.*
Vitamins; minerals.
Dietary supplement.

Geriaforce *Bioforce, Ger.†; Bioforce, Switz.*
Ginkgo biloba (p. 2512·3).
Atherosclerosis; homoeopathic preparation.

Gerial B12 *Allen, Mex.*
Amino acids; vitamin B substances (p. 2102·3); iron (p. 2073·1).

Geriaton *Ache, Braz.*
Vitamins; minerals; ginseng (p. 2513·3).

Geriatric *Herbes Universelles, Canad.†; Boehringer Ingelheim, Gr.†*
Vitamins; minerals.
Cachexia.

Geriatric Pharmaton *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Thai.*
Ginseng (p. 2513·3); vitamins; minerals; lecithin (p. 2542·2).
Tonic.

Geriatrix *Natur Produkt, Pol.*
Caffeine (p. 1203·3); ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Geriavit
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Pol.†; Pharmaton, Rus.†
⊗Deanol tartrate (p. 2319·1); ginseng (p. 2513·3); vitamins; rutoside (p. 2505·3); minerals; lecithin (p. 2542·2).
Tonic.

Geriavita *Phapros, Indon.*
Vitamins; minerals.
Dietary supplement.

Geriavite *Abbott, Braz.*
Vitamins; ginseng (p. 2513·3); inositol (p. 2533·2); rutoside (p. 2505·3).

Geribion *Soma, Braz.*
Vitamins; minerals.

Gericaps *Pharmadass, UK.*
Vitamins; minerals.

Gericarb *Gerard, Irl.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Gericare *Meyer, India.*
Vitamins; trace elements.

Gericin *Seid, Spain.*
Nitrendipine (p. 1456·3).
Hypertension; angina pectoris; Raynaud's syndrome.

Gericomplex *Boehringer Ingelheim, Swed.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Boehringer Ingelheim, S.Afr.†
⊗Vitamins; minerals; deanol tartrate (p. 2319·1); ginseng (p. 2513·3); rutin (p. 2505·3); lecithin (p. 2542·2).
Tonic.

Geri-Dyne *Geritrex, USA.*
Iodine (p. 2336·3).
Disinfectant.

Geriflo *Alembic, India.*
Finasteride (p. 2358·3); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Geriflox *Generics, Irl.*
Flucloxacillin sodium (p. 299·2).
Gram-positive bacterial infections.

Geriforte *Himalaya Herbal, India.*
Syrup: ⊗Achillea (p. 2427·3); malabar nut (p. 2549·1); asparagus racemosus (p. 2614·2); asparagus adscendens (p. 2614·2); Indian barberry (p. 2532·1); punarnava (p. 2601·1); capparis spinosa; centella (p. 1698·3); saffron (p. 2208·2); curcuma longa; elettaria cardamomum; liquorice (p. 1853·2); piper longum; syzygium aromaticum; terminalia chebula (p. 2474·3); tinospora cordifolia; tribulus terrestris (p. 2633·3); grape (p. 2521·3); ashwagandha (p. 2450·2).
Tonic.

Himalaya Herbal, India.
Tablets: Achillea (p. 2427·3); malabar nut (p. 2549·1); asparagus racemosus (p. 2614·2); asparagus adscendens (p. 2614·2); Indian barberry (p. 2532·1); capparis spinosa; centella (p. 1698·3); saffron (p. 2208·2); curcuma longa; elettaria cardamomum; liquorice (p. 1853·2); piper longum; syzygium aromaticum; terminalia chebula (p. 2474·3); ashwagandha (p. 2450·2).
Tonic.

Geri-Hydrolac *Geritrex, USA.*
Ammonium lactate (p. 1694·3).
Skin disorders.

Geri-Lav Free *Geritrex, USA.*
Aloe vera (p. 1693·2); chloroxylenol (p. 1748·2); sodium laurilsulfate (p. 2210·3).
Perineal cleanser.

Gerilide *CPH, Port.*
Nimesulide (p. 101·3).
Pain.

Gerilon *Cifarma, Braz.*
Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3).

Gerimal *Rugby, USA.†*
Codergocrine mesilate (p. 389·2).
Senile dementia.

Gerimax *Pharma Vision, Hung.; Nycomed, Rus.*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic.

Gerimax adultes *Merck Medication Familiale, Fr.†*
Vitamins; minerals; ginseng (p. 2513·3); green tea (p. 2648·2).

Gerimax Ginseng *Nycomed, Rus.; Nycomed, Ukr.*
Ginseng (p. 2513·3).
Tonic.

Gerimax Junior *Dansk, Israel.*
Vitamins; minerals.

Gerimax NF *Dansk, Israel.†*
Vitamins; minerals; ginseng (p. 2513·3).

Gerimax Tonique *Merck Medication Familiale, Fr.†*
Ginseng (p. 2513·3).
Tonic.

Gerimed *Fielding, USA.*
Vitamins; minerals.
Osteoporosis.

Geri-Mucil *Geri-Care, USA.*
Ispaghula (p. 1849·1).

Gerin *Legrand, Braz.*
Amino acids; minerals; vitamins; ginseng (p. 2513·3).
Tonic.

Gerinap *Gerard, Irl.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Geriopen *Misha, India.*
Meropenem (p. 321·3).
Bacterial infections.

Geriot *Goldline, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

Geri-Plus *Herbes Universelles, Canad.†*
Betacarotene (p. 2051·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Geriprost *Ivax, Arg.*
Terazosin hydrochloride (p. 1511·1).
Bladder disorders.

Geri-Protect *Geritrex, USA.*
Perineal barrier ointment.

Geri-Silk *Geritrex, USA.*
Liquid paraffin (p. 2191·2); lanolin oil (p. 2219·3).
Bath additive; dry skin disorders.

Geriso *Sidefarma, Port.*
Linoleic acid (p. 2509·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1); pyridoxine (p. 2105·3); lecithin (p. 2542·2).
Atherosclerosis; hypercholesterolaemia; vascular disorders.

Geri-Soft *Geritrex, USA.*
Emollient.
Skin disorders.

Geritisin *FDC, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia.

Geritol *GSK Consumer, USA.*
Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3); methionine (p. 1558·2).
Iron-deficiency anaemia.

Geritol Complete *Meda, USA.*
Iron (p. 2073·1); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemia.

Geritol Extend *SmithKline Beecham Consumer, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Geritonic *Geriatric Pharm. Corp., USA.*
Ferric ammonium citrate (p. 2060·1); liver fraction (p. 2444·1); vitamin B substances (p. 2102·3); minerals.
Iron-deficiency anaemias.

Geri-Tussin DM *Geri-Care, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Gerivent *Gerard, Irl.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Geri-Vite *Ivax, USA.*
Vitamin B substances (p. 2102·3); minerals.

Gerivix *Neo Quimica, Braz.*
Vitamins; minerals.

Gerlina *Daquimed, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Germanin *Bayer, Ger.*
Suramin sodium (p. 947·3).
Trypanosomiasis; onchocerciasis.

Germentin *Gerard, Irl.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Germex *Lennon, S.Afr.†*
Nitrofurazone (p. 333·1).
Bacterial skin infections; wounds; burns; ulcers.

Germi Stat *Germiphene, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Germi Stat Prep *Germiphene, Canad.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).

Germicid *Egis, Hung.*
Aminophenazone (p. 21·1).
Cold and influenza symptoms.

Germicidal Hand Soap *Ostrem, Canad.*
Chloroxylenol (p. 1748·2).
Hand disinfection.

Germicid-C *Egis, Hung.*
Aminophenazone (p. 21·1); phenobarbital (p. 535·2).
Fever; pain; febrile convulsions.

Germicidin *IMS, Ital.†*
Benzalkonium chloride (p. 1737·1).
Surface and instrument disinfection.

Germikill *Grimberg, Arg.*
⊗Alcohol (p. 1733·1).
Antiseptic.

Germiphene *Germiphene, Canad.*
Benzalkonium chloride (p. 1737·1).
Disinfection.

Germisdin *Isdin, Chile.*
Soap substitute.

Germisdin Antiseptico *Isdin, Port.*
Antiseptic cleanser for skin and hair.

Germisdin Higiene Intima *Isdin, Port.*
Preparation for vaginal hygiene.

Germolene
Note: this name may be used for preparations of different composition.
Bayer Consumer, UK.
Cream; topical spray: Chlorhexidine gluconate (p. 1743·3); phenol (p. 1763·3).
Burns; skin irritation; wounds.

Bayer, Irl.; Bayer Consumer, UK.
Zinc oxide (p. 1729·1); methyl salicylate (p. 92·1); octafonium chloride (p. 1762·2); phenol (p. 1763·3).
Burns; skin irritation; wounds; muscular aches.

Group, S.Afr.†
Ointment: Zinc oxide (p. 1729·1); methyl salicylate (p. 92·1); phenol (p. 1763·3); menthol (p. 2553·2); octafonium chloride (p. 1762·2).
Burns; wounds; skin irritation.

Group, S.Afr.†
Topical liquid: Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Burns; wounds.

Germolene First Aid *Bayer, Irl.*
Chlorhexidine gluconate (p. 1743·3); phenol (p. 1763·3).
Skin irritation.

Germoloids *Bayer Consumer, UK.*
Cream; ointment; suppositories: Lidocaine hydrochloride (p. 1988·2); zinc oxide (p. 1729·1).
Haemorrhoids.

Germoloids HC *Bayer Consumer, UK.*
⊗Hydrocortisone (p. 1640·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Germosept *Medipharm, Chile.*
Benzalkonium chloride (p. 1737·1).
Disinfection of instruments and skin.

Germox *Rishab, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Germozero *Chefaro, Ital.*
Benzalkonium chloride (p. 1737·1); orthophenylphenol (p. 1762·3).
Skin disinfection.

Germozero Dermo *Chefaro, Ital.*
Benzalkonium chloride (p. 1737·1); orthophenylphenol (p. 1762·3); alkyl isoquinoline bromide.
Wound disinfection.

Gernebcin *Infectopharm, Ger.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Gero Forte *IMA, Braz.†*
Vitamins; guarana (p. 2648·2); erythroxylon catuaba.

Gero H3 Aslan *Chefaro, Ger.†*
Procaine hydrochloride (p. 1994·3); benzoic acid (p. 1738·2); potassium disulfite; sodium phosphate (p. 1791·2).
Tonic.

Geroaslan H3 *Sanova, Austria.†*
Procaine hydrochloride (p. 1994·3).
Tonic.

Gerocin *P & B, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gerocin-BM *P & B, India.*
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin (p. 304·2).

Geroderm *WP, Ital.*
Triclosan (p. 1773·2).
Skin cleansing.

Geroderm Zolfo *WP, Ital.*
Sulfur (p. 1721·1); lactic acid (p. 2539·1); triclosan (p. 1773·2).
Skin cleansing in acne.

Gerodorm *Gerot, Austria; GL Pharma, Cz.; Gerot, Hung.*
Cinolazepam (p. 1054·2).
Sleep disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gerodyl *Sandoz, Neth.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; heavy-metal poisoning; cystinuria; Wilson's disease.

Gerofen *Munir, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Gerogelat *Metochem, Austria.†*
Vitamin A palmitate (p. 2098·3); tocoferil acetate (p. 2119·2).
Vitamin A and E deficiency; mucous membrane disorders; hearing loss; tinnitus.

Gerolamic *GL Pharma, Austria; GL Pharma, Hung.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Gerolin *CT, Ital.*
Citicoline sodium (p. 2480·2).
Parkinsonism.

Geromycin *Gerolymatos, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Geronik *Chemica, Gr.*
Cinnarizine (p. 622·1).

Geronpol *Hasco-Lek, Pol.†*
⊗Ginseng (p. 2513·3); troxerutin (p. 2505·3); deanol tartrate (p. 2319·1); vitamins; minerals.
Tonic.

Gerosim *GL Pharma, Austria.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Geroten *Gerard, Irl.†*
Captopril (p. 1331·2).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Gerotralin *Gerot, Hung.†*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia.

Gerotrex H3 *Bunker, Braz.*
Vitamins; amino acids; minerals.

Gerousia *Pharmathen, Cz.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Gerovit *PannonPharma, Hung.*
Vitamins.

Gerovital *EMS, Braz.*
Ginseng (p. 2513·3); rutoside (p. 2505·3); vitamins; minerals.
Nutritional supplement.

Gerovital Dr. Theiss *Naturwaren, Ukr.*
Ferrous lactate (p. 2062·1); vitamins; crataegus (p. 2488·1); motherwort (p. 2564·2).
Tonic.

Gerovital H3 *Sanova, Austria†; Sicomed, Hong Kong.†*
Procaine hydrochloride (p. 1994·3).
Tonic.

Gerovital Zdrovit *Natur Produkt, Pol.*
Crataegus (p. 2488·1); motherwort (p. 2564·2); vitamins; minerals.
Tonic.

Geroxalen *Sanofi-Aventis, Neth.; Liba, Turk.*
Methoxsalen (p. 1711·3).
Vitiligo; psoriasis; eczema.

Gerozac *Gerard, Irl.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Gerpeval *Phytopharm, Ukr.*
Valaciclovir (p. 1021·1).
Herpesvirus infections.

Gerprazol *GL Pharma, Hung.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gerskin *YSP, Malaysia; Yung Shin, Singapore.*
Magnesium oxide (p. 1857·3); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Gertac *Gerard, Irl.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gertalgin *Angelini, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Gertemycin *Angelini, Gr.; Faran, Gr.*
Cefatrizine (p. 237·2) or cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Gertges Pain Powders *Technikon, S.Afr.†*
Aspirin (p. 22·2); caffeine citrate (p. 1203·3).
Fever; pain.

Gertocalm *Angelini, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Gertotus *Angelini, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Gervaken *Kendrick, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Gerxus *Verisfield, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Gery *Geno, India.*
Erythromycin (p. 291·2).
Acne.

Geryl-O *Almet, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

GES *Milupa, Ital.*
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

GES 45 *Milupa, Hong Kong.†*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Milupa, Switz.†
Oral rehydration solution (p. 1780·1).
Diarrhoea; gastro-enteritis.

Gesdyp *Ranbaxy, India.*
⊗Simeticone (p. 1886·2); pancreatin (p. 2579·3).

Gesica *Unison, Thai.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint inflammation; pain.

Gesicain *Piramal, India; Idaman, Singapore.*
Lidocaine (p. 1988·1).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Gesidine *Lilly, Gr.; Stada, Port.†*
Vindesine sulfate (p. 884·2).
Malignant neoplasms.

Gesidol
Note: this name may be used for preparations of different composition.
Manix, Philipp.
Tramadol hydrochloride (p. 139·2).
Pain.

Medipharm, Chile.
Paracetamol (p. 115·1).
Pain; fever; inflammation.

Gesigran *Accord, Mex.*
Sumatriptan succinate (p. 679·2).
Migraine.

Gesika *Reevax, India.*
Enbucrilate (p. 2489·3).

Gesilac *Tecnoforma, Mex.†*
Ketorolac (p. 80·2) or ketorolac trometamol (p. 80·2).
Pain.

Geslutin *Asofarma, Mex.*
Progesterone (p. 2300·2).
Menopausal disorders; female infertility; benign breast disorders; habitual or threatened miscarriage; dysfunctional uterine haemorrhage.

Gesnac-P *Aarpik, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Gesnim *Aarpik, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Gesnim-MR *Aarpik, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Gesnim-P *Aarpik, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Gesnim-S *Aarpik, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Ges-One *Rass, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Gesry *Aamorb, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Gessedil *Egis, Hung.; Egis, Pol.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Gestabil *Combiphar, Indon.*
Sachets: Magaldrate (p. 1856·1).
Antacid; gastritis; peptic ulcer; heartburn.

Combiphar, Indon.
Oral suspension; tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid; flatulence; gastritis; peptic ulcer; heartburn.

Gestabil Forte *Combiphar, Indon.*
Magaldrate (p. 1856·1).
Antacid; gastritis; peptic ulcer; heartburn.

Gestadinona *Schering, Braz.*
Hydroxyprogesterone caproate (p. 2285·1); estradiol valerate (p. 2271·2).
Endometriosis; menopausal disorders; menstrual disorders.

Gestaferron *Arlex, Mex.*
Ferrous fumarate (p. 2060·3).
Anaemias.

Gestageno
Note: this name may be used for preparations of different composition.
Elea, Arg.
Hydroxyprogesterone acetate (p. 2285·1).
Female infertility; hypertrichosis; menstrual disorders; premature labour; threatened or recurrent miscarriage.

Elea, Mex.
Progesterone (p. 2300·2).
Menopausal disorders; female infertility; threatened miscarriage; benign breast disorders.

Gestakadin *Kade, Ger.†*
Norethisterone acetate (p. 2294·3).
Menopausal disorders; menstrual disorders.

Gestamag *Metiska, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastritis; duodenitis; gastro-oesophageal reflux; gastric hyperacidity; dyspepsia; flatulence.

Gestanon *Organon, Gr.*
Allylestrenol (p. 2255·2).

Gestapuran *Leo, Swed.†*
Medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; endometriosis; menstrual disorders.

Gestar *Polfa Pabianice, Pol.†*
Megestrol acetate (p. 2289·2).
Breast cancer; uterine cancer.

Gestarelle *IPRAD-Sante, Fr.*
Vitamins minerals.

Gestarelle S *IPRAD-Sante, Fr.*
Vitamins; minerals; ginseng (p. 2513·3); omega-3 fatty acids (p. 1460·1).
Tonic.

Gestaur *Taurus, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

Gestavit *Lafi, Chile.*
Vitamins; minerals.

Gestefol *Revifar, Gr.*
Fenofibrate (p. 1381·1).

Gester *Merck Serono, Arg.*
Progesterone (p. 2300·2).
Benign breast disorders; female infertility; menopausal disorders; menstrual disorders; threatened or recurrent miscarriage.

Gester-NP *Shinto, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Gestid *Ranbaxy, Rus.*
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Antacid; flatulence.

Gestiferrol *Kela, Belg.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Dietary supplement during pregnancy and lactation; anaemias.

Gestimax *Unimarck, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

Gestin *Bushnell, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gestinol *Libbs, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gestinyl *Stragen, Denm.; Stragen, Fin.; Effik, Spain.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Gestmate *Akesiss, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Gestodelle *Mithra, Belg.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Gestoden Plus *Teva, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gestodilat *Ratiopharm, Denm.; Ratiopharm, Fin.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gestodiol *Finderm, Ital.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Gestofam *Otto, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; pathological hypersecretory disorders; gastro-oesophageal reflux.

Gestofeme *Mithra, Belg.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Gestofit *Ind-Swift, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Gestomikron *Adamed, Pol.*
Medroxyprogesterone acetate (p. 2288·1).
Female infertility; menopausal disorders; metrorrhagia.

Gestomix *Stragen, Hung.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Gestone *IFET [ΙΦΕΤ], Gr.; Ferring, India; Ferring, Israel; NZ Medical & Scientific, NZ; Nordic, UK.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; adjunct in female infertility; threatened or recurrent miscarriage.

Gestonette *Sandoz, Denm.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gestorin *Intra-Labs, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Gestradiol *Neo Quimica, Braz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gestredos *LKM, Arg.*
Gemcitabine hydrochloride (p. 801·2).
Breast cancer; non small-cell lung cancer; pancreatic cancer; ovarian cancer; bladder cancer.

Gestrel *Scoshia, India.*
Aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Gestrelan *Biolab Sanus, Braz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gestrenol *CCM, Malaysia; Duopharma, Singapore.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage.

Gestrocon *Neo Quimica, Braz.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Get In *Cinetic, Arg.*
Lubricating gel.

Get a Tint *Avon, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Get Even *Arbonne, Canad.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Getamisin *Deva, Turk.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Getasin *Gunsa, Turk.†*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Getflox *Finecure, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Getgo *Overseas, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

Gether *Glories, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Getidin *Guardian, Indon.*
Ranitidine (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders.

Getmisi *Teva, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Getoli *Zee, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Getoli D *Zee, India.*
⊗Dexamethasone (p. 1630·3); gatifloxacin (p. 303·2).

Getready *BMW, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Getrid *Evershine, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Getrid-I *Evershine, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Getryl *Getz, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gets-It
Note: this name may be used for preparations of different composition.
Oakhurst, USA.
Salicylic acid (p. 1719·1); zinc chloride (p. 2126·1).
Hyperkeratosis.

Getup *Rafarm, Gr.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Getzar *Getz, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Gévatran *Merck Serono, Fr.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders.

Gevilon *Pfizer, Austria; Pfizer, Ger.; Pfizer, Switz.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Gevital *Indkus, India.*
Ginseng (p. 2513·3); vitamins; minerals.

Gevoflox *Neiss, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Gevrabon *Lederle, USA.*
Vitamin B substances (p. 2102·3); minerals.

Gevral *Lederle, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Whitehall, Braz.†
Vitamins; minerals.

Gevral Protein *Lederle, USA.†*
Dietary protein supplement.

Gevral T *Lederle, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

Gevramycin *MSD, Spain.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Gewacalm *Nycomed, Austria.*
Diazepam (p. 1063·2).
Premedication; eclampsia; status epilepticus; anxiety disorders; sleep disorders; neuroses; panic attacks; phobias; skeletal muscle spasm.

Gewadal *Nycomed, Austria; Nycomed, Rus.†*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Gewapurol *Pharmaselect, Austria.†*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Gex
Note: this name may be used for preparations of different composition.
Rimsa, Mex.
Magaldrate (p. 1856·1); dimeticone (p. 1886·2); famotidine (p. 1842·1).

Talent, India.
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Gexcil *Genesis, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Gexin *Madhav, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Geymocillina *Proel, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Geypirina *Proel, Gr.*
Chloramphenicol (p. 257·1); sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Gezt *Richmond, Arg.*
Gemcitabine hydrochloride (p. 801·2).
Non small-cell lung cancer; pancreatic cancer; bladder cancer.

GF *JB Chemicals, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

GFB *Umeda, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

G-Fen *General Drugs, Thai.*
Ibuprofen (p. 68·2).
Fever; pain; inflammation.

G-Floren *Indoco, India.*
Gemifloxacin mesilate (p. 304·1).
Chronic bronchitis; community-acquired pneumonia.

G-Flox
Note: this name may be used for preparations of different composition.
Intas, India.
Gatifloxacin (p. 303·2).
Bacterial infections.

GFlox
Note: this name may be used for preparations of different composition.
GLS, India.
Ofloxacin (p. 334·3).
Bacterial infections.

GFlox-OZ *GLS, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

GFlu *GLS, India.*
Fluconazole (p. 578·2).
Fungal infections.

GFN Phenylephrine *Cypress, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Coughs; rhinitis; sinusitis.

GFN PSE DM *Cypress, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs; nasal congestion.

GFN/DM *Cypress, USA.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

GFN/DM/PE *Cypress, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Coughs; nasal congestion.

GFN/PSE *Cypress, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; nasal congestion.

G-Formin *East West, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

G.G. Tab *Marching, Hong Kong.†*
Guaifenesin (p. 1666·2).

G-Gel *Arlak, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

GGG-24 *Orchid, India.*
Garlic (p. 2510·3); ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).

Ghoom *Blubell, India.*
Paracetamol (p. 115·1); prochlorperazine (p. 1098·2).

GHRH *Ferring, Belg.; Ferring, Ger.; Ferring, Ital.; Ferring, Neth.; Ferring, Spain; Ferring, Switz.; Ferring, UK.*
⊗Somatorelin acetate (p. 1930·1).
Diagnosis of growth hormone deficiency.

GHRP *Kaken, Jpn.*
⊗Pralmorelin dihydrochloride (p. 1929·1).
Diagnosis of growth hormone deficiency.

G-I
Note: this name may be used for preparations of different composition.
Provit, Mex.†
Gentamicin sulfate (p. 304·2).
Bacterial infections.

GI
Note: this name may be used for preparations of different composition.
T Man, Thai.
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; Zollinger-Ellison syndrome; dyspepsia; gastro-oesophageal reflux.

GI Kit *Biological E, India.*
2 Tablets, amoxicillin (p. 216·2); 2 tablets, clarithromycin (p. 266·2); 2 capsules, omeprazole (p. 1867·2).

Giamebil *Hebron, Braz.*
Spearmint (p. 2621·2).
Smooth muscle spasm.

Gianda
Note: this name may be used for preparations of different composition.
Grunenthal, Chile.
Ethinylestradiol (p. 2275·3); dienogest (p. 2267·2).
Combined oral contraceptive; acne.

Grunenthal, Ger.†
12 Capsules, estradiol valerate (p. 2271·2); 14 capsules, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Gianvi *Teva, USA.*
24 Tablets, ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1); 4 tablets, inert.
Combined oral contraceptive.

Giardil *Phoenix, Arg.*
Furazolidone (p. 933·3).
Diarrhoea; gastroenteritis.

Giarlam *UCI, Braz.*
Furazolidone (p. 933·3).
Cholera; diarrhoea; giardiasis.

Giasemin *Ratiopharm, Fin.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Giasion *Zambon, Ital.*
Cefditoren pivoxil (p. 239·1).
Bacterial infections.

Gibac *Tocogino, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Gibi Forte *Triton, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gibil *Medihealth, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia.

Gibilon *Delta, Braz.*
Ginkgo biloba (p. 2512·3).

Gic *Glories, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Gichtex *Gerot, Austria.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Gichtex plus *Gerot, Austria.*
Allopurinol (p. 600·2); benzbromarone (p. 603·3).
Hyperuricaemia; gout.

Gic-M *Vensat, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Gic-O *Plus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Gic-SR *Glories, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Gidroxyurea *Pliva, Rus.†*
Hydroxycarbamide (p. 803·1).

Gifaril P *Wander, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Gifed *Yarindo, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Giflexcin *Bombay Tablet, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Giflorex *Errekappa, Ital.*
Lactobacillus rhamnosus (p. 2596·3).
Maintenance of gastrointestinal flora.

Gi-Fri *Intermed, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Giftan *Systopic, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Giftan-HC *Systopic, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Giftum *Winsome, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gigacef *Aglowmed, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Gigatrom *Medilusa, Port.†*
Azithromycin (p. 221·2).
Bacterial infections.

Gigemet *Loeffler, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal examination.

Gik *Yuriya-Farm, Ukr.*
Potassium chloride (p. 1793·2) in glucose.
Arrhythmias; hypokalaemia.

Gilax *Mergers Drugfil, Philipp.*
Domperidone (p. 1838·1).
Gastrointestinal motility disorders; nausea; vomiting.

Gilemal *Zentiva, Hung.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gilenya *Novartis, Austral.; Novartis, Canad.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Israel; Novartis, Jpn; Novartis, Neth.; Novartis, Norw.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, USA.*
Fingolimod hydrochloride (p. 2504·3).
Multiple sclerosis.

Gilex *Rekah, Israel.*
Doxepin hydrochloride (p. 414·2).
Anxiety; depression; mixed anxiety depressive states.

Gilfer *Argil, India.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Gilflox *Argil, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Giloba *Mega Lifesciences, Malaysia; Mega We Care, Singapore; Mega Lifesciences, Ukr.*
Ginkgo biloba (p. 2512·3).
Circulatory disorders; cerebral and peripheral vascular disorders; dementia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gilomax *Mega Lifesciences, Thai.*
Ginkgo biloba (p. 2512·3); fish oil (p. 1460·1); lecithin (p. 2542·2).
Mental function impairment; cerebral and peripheral vascular disorders.

Gilotrif *Boehringer Ingelheim, USA.*
Afatinib maleate (p. 736·1).
Non-small cell lung cancer.

Gilphex TR *Gil, USA.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Gilt *Laves, Ger.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Giltuss TR *Gil, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Giludop *Pharmaselect, Austria; Pharmaselect, Gr.; Abcur, Swed.; Frik, Turk.*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure; hypotension.

Gilurytmal *Pharmaselect, Austria; Carinopharm, Ger.; IFET (ΙΦΕΤ), Gr.*
Ajmaline (p. 1295·2).
Arrhythmias.

Gilutensin
Note: this name may be used for preparations of different composition.
Phamar (Φαμαρ), Gr.
Moxonidine (p. 1442·1).

Gimabrol *Collins, Mex.†*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Gimalxina *Collins, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Gimate *Systopic, India.*
Itopride.

Gimip *Medihealth, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gimip-M *Medihealth, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Gimip-PM *Medihealth, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).

Gimonte Sildenafil *Fabra, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Gimonte XXI *Fabra, Arg.*
Carbomers (p. 2173·3).
Lubricant.

Ginac *Ordain, India.*
Diclofenac potassium (p. 48·3); omeprazole magnesium (p. 1867·2).

Ginadox *Pharmacia Upjohn, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Ginaikos *Solvay, Ital.*
Estradiol (p. 2271·1).
Menopausal disorders.

Ginal Cent *Beta, Arg.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); centella (p. 1698·3); polymyxin B sulfate (p. 342·3).
Vulvovaginal infections.

Ginalam *Sigillata, Denm.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Ginal-V *Skymax, India.*
Cream: Clotrimazole (p. 576·2); tinidazole (p. 949·2).
Skymax, India.
Tablets: Clotrimazole (p. 576·2); tinidazole (p. 949·2); lactic acid bacillus (p. 2596·3).

Ginarsan *Ivax, Arg.*
⊗Tamoxifen citrate (p. 860·2).

Ginatex *Baliarda, Arg.*
Estradiol (p. 2271·1).
Menopausal disorders.

Ginaton *Chi Sheng, China.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginazol *Gelcaps, Mex.†*
Miconazole nitrate (p. 589·1).
Fungal or Gram-positive bacterial vulvovaginal infections.

Ginbiloba *Bunker, Braz.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Gincare *YSP, Malaysia; Yung Shin, Singapore.*
Ginkgo biloba (p. 2512·3).
Circulation disorders; peripheral vascular disorders.

Gincer *Cyno, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia.

Gincobem *Cifarma, Braz.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function disorders.

Gincoben *Ipsen, Port.*
Ginkgo biloba (p. 2512·3).
Dementia.

Gincolin *Teuto, Braz.*
Ginkgo biloba (p. 2512·3).

Gincosan *Flordis, Austral.; Boehringer Ingelheim, Chile; Medreg, Cz.; Boehringer Ingelheim, Hung.; DKSH, Malaysia; Ginsana, Switz.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Mental function impairment; tonic.

Gine Canesten *Bayer, Spain.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Gine Micetal *Uriach, Spain.†*
Flutrimazole (p. 582·1).
Vulvovaginal candidiasis.

Gine Zalain *Cantabria, Spain.†*
Sertaconazole nitrate (p. 593·2).
Vulvovaginal candidiasis.

Gineane *Teuto, Braz.*
Norethisterone acetate (p. 2294·3); estradiol (p. 2271·1).
Menopausal disorders.

Ginec *Glenmark, Braz.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); nystatin (p. 590·3); tinidazole (p. 949·2).

Ginecast *Amnol, Ital.*
⊗Griffonia (p. 2522·3); equisetum (p. 2500·1); agnus castus (p. 2432·2); magnesium (p. 1786·3); vitamin B substances (p. 2102·3).
Premenstrual syndrome.

Ginecistin *Amnol, Ital.*
Myrtillus (p. 2566·2); bearberry (p. 2453·2).
Urinary-tract disorders.

Ginecopast *Pasteur, Chile.*
Miconazole nitrate (p. 589·1); tinidazole (p. 949·2).
Vulvovaginal infections.

Ginecopast Dual *Pasteur, Chile.*
Miconazole nitrate (p. 589·1); tinidazole (p. 949·2).
Vulvovaginal candidiasis; balanitis.

Ginecosid *Vargas, Venez.*
Injection: Progesterone (p. 2300·2); estradiol (p. 2271·1).
Amenorrhoea.
Vargas, Venez.
Tablets: ⊗Normethandrone (p. 2297·3); methyloestradiol (p. 2271·1).
Amenorrhoea.

Ginecrin *AbbVie, Spain.*
⊗Leuprorelin acetate (p. 2285·3).
Uterine fibroids; endometriosis; precocious puberty.

Ginedak *Organon, Braz.†*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Ginedazol *Laboratorios Chile, Chile.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Ginedazol Dual *Laboratorios Chile, Chile.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Ginedermofix *Ferrer, Spain.*
Sertaconazole nitrate (p. 593·2).
Vulvovaginal candidiasis.

Ginediol *Elea, Arg.*
Norethisterone enantate (p. 2294·3); estradiol valerate (p. 2271·2).
Combined injectable contraceptive.

Ginedisc *Bayer, Mex.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Gineflor *Medestea, Ital.*
Ibuprofen isobutanolammonium (p. 68·2).
Gynaecological disorders.

Ginefolin *Lafi, Chile.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Ginejuvent *Juventus, Spain.*
Benzalkonium chloride (p. 1737·1); calcium lactate (p. 1784·1); lactic acid (p. 2539·1); chamomile (p. 2474·1).
Vulvovaginal trichomoniasis; vulvovaginal candidiasis.

Ginekit *Synmedic, Ukr.*
Red tablets, azithromycin (p. 221·2); white tablets, secnidazole (p. 947·3); white tablets, fluconazole (p. 578·2).
Urogenital infections.

Gineksin F *Deva, Turk.*
Ginkgo biloba (p. 2512·3).
Mental function impairment; peripheral vascular disorders; vertigo.

Ginelea *Elea, Arg.; Elea, Mex.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ginelea T *Elea, Arg.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Ginemaxim *Knop, Chile.*
Cimicifuga (p. 2478·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Ginenorm *Aesculapius, Ital.*
Ibuprofen isobutanolammonium (p. 68·2).
Gynaecological inflammatory disorders.

Ginepausil *Amnol, Ital.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3); soya isoflavones (p. 2620·3); melissa (p. 2552·3); magnesium (p. 1786·3); red clover (p. 2482·1); tilia (p. 2631·3); dioscorea; vitamin E (p. 2119·1).
Menopausal disorders.

Ginepriston *Mir, Ukr.*
Mifepristone (p. 2138·1).
Postcoital oral contraceptive.

Ginera *Schering, Turk.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ginesal *Farmigea, Ital.*
Benzydamine hydrochloride (p. 29·2).
Gynaecological disorders; vaginal hygiene.

Gineseptina *Lanpharm, Arg.*
Zinc phenolsulfonate (p. 1729·3); tyrothricin (p. 384·1); borax (p. 2459·2); chlorophyll (p. 2178·3).
Mouth and throat disorders.

Ginesse *Farmoquimica, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ginestatin *Organon, Braz.†*
Metronidazole (p. 936·1); nystatin (p. 590·3); benzalkonium chloride (p. 1737·1).
Vulvovaginal infections.

Ginet *Rex, NZ.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive in women with androgenic symptoms; androgen-associated acne, alopecia, hirsutism, and seborrhoea.

Gineton *Med-One, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Ginette *Cipla, India.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne and hirsutism in females.

Cipla-Medpro, S.Afr.
21 Tablets, ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2); 7 tablets, inert.
Androgenisation symptoms; idiopathic hirsutism; acne; combined oral contraceptive.

Ginevit *Gambar, Ital.†*
Vitamins; minerals.
Menopausal disorders; menstrual disorders.

Gingeron *Baliarda, Arg.*
Ginseng (p. 2513·3); magnesium glycerophosphate (p. 1787·2); procaine hydrochloride (p. 1994·3); zinc (p. 2126·1); copper (p. 2057·1); cobalt (p. 2482·2); manganese (p. 2081·2).
Tonic.

Ginger-Vite Forte *Bioglan, Austral.†*
Ginger oil (p. 1844·1); ginger (p. 1844·1); evening primrose oil (p. 2502·2).
Arthritis; rheumatism; sports injuries.

Gingicain D *Sanofi-Aventis, Ger.*
Tetracaine (p. 1996·3); benzalkonium chloride (p. 1737·1).
Local anaesthesia; skin disinfection.

Gingiloba *1A, Ger.†*
Ginkgo biloba (p. 2512·3).
Mental function disorders; peripheral vascular disorders; dizziness; tinnitus.

Gingilone
Note: this name may be used for preparations of different composition.
Farmasa, Braz.
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); troxerutin (p. 2505·3); ascorbic acid (p. 2110·3); benzocaine (p. 1980·2).
Mouth disorders.
Teofarma, Spain.
⊗Ascorbic acid (p. 2110·3); cortisone acetate (p. 1629·2); neomycin sulfate (p. 330·1); rutoside (p. 2505·3).
Stomatitis; mouth ulcers; bleeding gums.

Gingio *Sandoz, Cz.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; tinnitus.

Gingisol *Mediline, Hung.*
Clove oil (p. 2481·3); chamomile oil (p. 2474·1).

Gingium *Hexal, Ger.†; Sandoz, Hung.; Hexal, Rus.*
Ginkgo biloba (p. 2512·3).
Mental function impairment; cerebrovascular disorders; dizziness; headache; intermittent claudication; mental function disorders; tinnitus; peripheral vascular disorders.

Gingkan *Medikon, Indon.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Gingkoforce *Bioforce, UK.*
Ginkgo biloba (p. 2512·3).
Raynaud's syndrome; tinnitus.

Gingobeta *Betapharm, Ger.†*
Ginkgo biloba (p. 2512·3).
Mental function disorders; dizziness; tinnitus; headache; peripheral vascular disorders.

Gingobil *Abdi, Turk.*
Ginkgo biloba (p. 2512·3).
Dementia; peripheral vascular disorders.

Gingol *Kwizda, Austria.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; cervical syndrome.

Gingopret *Bionorica, Ger.*
Ginkgo biloba (p. 2512·3).
Mental function disorders; peripheral vascular disorders; tinnitus; vertigo; headache.

Gingosol *Sandoz, Switz.†*
Ginkgo biloba (p. 2512·3).
Mental function impairment.

Gingviton *Sam Chun Dang, Singapore.*
Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2).

Ginil *Marfarma, Ital.*
Topical liquid: Soya (p. 2092·3); mimosa tenuiflora.
Marfarma, Ital.†
Vaginal tablets: Lactobacillus acidophilus (p. 2596·3); lactic acid (p. 2539·1).

Ginjal *Cowik, Pol.*
Hippocampus coronatus; methylthioninium chloride (p. 1559·1); Java tea (p. 2536·3);

ginseng (p. 2513·3); sonchus arvensis; strobilanthus deyerianus.
Renal calculi.

G1-Injektopas *Pascoe, Ger.*
Bryonia (p. 2461·3); dulcamara (p. 2497·3); ledum (p. 2550·1); colchicum (p. 607·1); berberis (p. 2502·1); phytolacca (p. 2593·2).
Homoeopathic preparation.

Ginkan *Baliarda, Arg.*
Pessaries: Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); centella (p. 1698·3).
Vaginal infections.

Baliarda, Arg.
Tablets: Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Ginkapran *Yungjin, Singapore.*
Ginkgo biloba (p. 2512·3).
Peripheral vascular disorders; cerebral disorders.

Ginkgo biloba comp *Hevert, Ger.*
Aurum colloidale (p. 2521·1); ginkgo biloba (p. 2512·3).
Homoeopathic preparation.

Ginkgo Biloba Forte *Lafarmen, Arg.*
Ginkgo biloba (p. 2512·3); thiamine (p. 2102·3); zinc sulfate (p. 2126·2).
Dietary supplement; mental function disorders.

Ginkgo Biloba Memo Diates *Provefarma, Arg.†*
Ginkgo biloba (p. 2512·3); guarana (p. 2648·2); thiamine (p. 2102·3).
Dietary supplement.

Ginkgo Brahmi *Blackmores, Austral.*
Bacopa (p. 2452·1); ginkgo biloba (p. 2512·3).
Mental function impairment.

Ginkgo Forte *ISA, Arg.*
Ginkgo biloba (p. 2512·3); vitamin B substances (p. 2102·3).
Dietary supplement.

Ginkgobakehl *Sanum-Kehlbeck, Ger.; Ebi, Switz.*
Ginkgo biloba (p. 2512·3).
Homoeopathic preparation.

Ginkgocard *Phytofarm Kleka, Pol.†*
Crataegus (p. 2488·1); ginkgo biloba (p. 2512·3).
Peripheral vascular disorders; fatigue.

Ginkgo-Comp *Heel, Canad.†*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); baryta iodata (p. 2452·2); conium maculatum (p. 2524·3); ginkgo biloba (p. 2512·3); mistletoe (p. 2560·2).
Homoeopathic preparation.

Ginkgofol *Labofarm, Pol.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkgoforce *Ikapharmindo, Indon.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkgoforte *Blackmores, Austral.*
Ginkgo biloba (p. 2512·3).
Mental function impairment.

Ginkgold *Schwabe, Spain.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkgomax *Dansk Droge, Pol.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkgo-PS *Usana, Hong Kong†; Usana, Singapore.†*
Ginkgo biloba (p. 2512·3); lecithin (p. 2542·2).
Mental function disorders; dietary supplement.

Ginkgorell *Sanorell, Ger.*
Ginkgo biloba (p. 2512·3).
Homoeopathic preparation.

Ginkgoum *Evalar, Rus.*
Ginkgo biloba (p. 2512·3).
Mental function disorders; cerebrovascular disorders.

Ginkoba *Nikkho, Braz.; Micro, India; Fher, Ital.*
Ginkgo biloba (p. 2512·3).
Mental function disorders; cerebral and peripheral vascular disorders; dementia.

Ginkobil *Ratiopharm, Ger.*
Ginkgo biloba (p. 2512·3).
Headache; mental function disorders; peripheral vascular disorders; tinnitus; vertigo.

Ginkocer *Ranbaxy, India; Ranbaxy, Philipp.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia; cerebral insufficiency; vertigo.

Ginkodilat *Sandoz, Ger.†*
Ginkgo biloba (p. 2512·3).
Headache; mental function disorders; intermittent claudication; tinnitus; vertigo.

Ginkofar *Biofarm, Pol.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkoftal
Note: this name may be used for preparations of different composition.
Tubilux, Ital.
Bioflavonoids (p. 2505·2); ginkgo biloba (p. 2512·3).
Nutritional supplement; eye disorders.

Ginkogink *Ipsen, Fr.*
Ginkgo biloba (p. 2512·3).
Mental function impairment in the elderly.

Ginkogreen *Greenpharma, Braz.*
Ginkgo biloba (p. 2512·3).

Ginkokán *Schwabe, Spain.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkolab *Multilab, Braz.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Ginkolin *Duopharma, Hong Kong.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral circulatory disorders.

Ginkomax *Garden House, Chile.*
Ginkgo biloba (p. 2512·3).
Cerebrovascular insufficiency.

Ginkomed *Cimed, Braz.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Ginkona *Teguhsindo, Indon.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; tinnitus; vascular eye disorders.

Ginkoplus *Fontovit, Braz.†*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Ginkopur *Spitzner, Ger.*
Ginkgo biloba (p. 2512·3).
Mental function disorders; dizziness; tinnitus; headache; intermittent claudication.

Ginkor *Beaufour, Fr.†*
Ginkgo biloba (p. 2512·3); troxerutin (p. 2505·3).
Peripheral vascular disorders.

Ginkor Fort *Beaufour-Ipsen, China; Ipsen, Cz.; Tonipharm, Fr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.†; Beaufour-Ipsen, Malaysia; Beaufour-Ipsen, Rus.; Ipsen, Thai.; Ipsen, Ukr.*
⊗Ginkgo biloba (p. 2512·3); heptaminol hydrochloride (p. 2525·1); troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids; peripheral vascular disorders.

Ginkor Gel *Beaufour-Ipsen, Rus.; Ipsen, Ukr.*
Ginkgo biloba (p. 2512·3); troxerutin (p. 2505·3).
Venous insufficiency; superficial phlebitis.

Ginkoret *Tubilux, Ital.*
Ginkgo biloba (p. 2512·3); vitamins; lutein (p. 2079·2).
Circulatory disorders.

Ginkoriv *East African, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia.

Ginkoriv Plus *East African, India.*
Betacarotene (p. 2051·1); ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); tocoferil acetate (p. 2119·2); vitamin B_{12} (p. 2107·2); vitamin B_2 (p. 2104·3).

Ginkosen *Tai Guk, Singapore.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Ginkotab *Luper, Braz.*
Ginkgo biloba (p. 2512·3).

Ginkovital *Pharmadass, UK.*
Ginkgo biloba (p. 2512·3).

Ginlac-V *Raproos, India.*
Clotrimazole (p. 576·2); tinidazole (p. 949·2); *Lactobacillus acidophilus* (p. 2596·3).

Gino Cauterex *Ache, Braz.*
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1); gentamicin sulfate (p. 304·2).
Vulvovaginal infections.

Gino Ciriax *Investi, Arg.†*
Ciprofloxacin hydrochloride (p. 261·2).
Genito-urinary tract infections.

Gino Conazol *Kinder, Braz.†*
Tioconazole (p. 595·3).
Fungal vaginal infections.

Gino Dermazine *Silvestre, Braz.†*
Sulfadiazine silver (p. 362·3).
Vaginal bacterial infections; vaginal candidiasis; trichomoniasis.

Gino Fibrase *Pfizer, Braz.*
⊗Fibrinolysin (p. 1382·3); dornase alfa (p. 1662·1); chloramphenicol (p. 257·1).
Vulvovaginal infections.

Gino Kollagenase *Cristalia, Braz.*
⊗Collagenase (p. 2484·1); chloramphenicol (p. 257·1).

Gino Mizonol *Geolab, Braz.*
Miconazole nitrate (p. 589·1).

Gino Tralen *Pfizer, Braz.†*
Tioconazole (p. 595·3).
Vulvovaginal candidiasis.

Gino-Canesten *Bayer, Braz.; Bayer, Port.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Ginocap *Biocontrolfarm, Ital.*
Bearberry (p. 2453·2).

Gino-Clotrimix *Medley, Braz.†*
Clotrimazole (p. 576·2).
Vaginal infections.

Gino-Colon *Geolab, Braz.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).

Gino-Daczol *Cifarma, Braz.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Ginoday *Biocontrolfarm, Ital.*
Birch (p. 2457·3); chlorella (p. 2475·3).

Ginoden *Bayer, Ital.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ginoderm *Gynopharm, Chile.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Gino-Isomax *Prodotti, Braz.†*
Isoconazole nitrate (p. 583·2).
Vaginal infections.

Ginokan *Medikon, Indon.†*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Cerebral and peripheral vascular disorders; tonic.

Ginolax *Biocontrolfarm, Ital.*
Psyllium seed (p. 1849·1); frangula (p. 1843·3).

Gino-Loprox *Sanofi-Aventis, Braz.*
Ciclopirox olamine (p. 575·3).
Vulvovaginal candidiasis.

Gino-Lotremine *Schering-Plough, Port.†*
Clotrimazole (p. 576·2).
Fungal vulvovaginal infections.

Ginolotricomb *Schering-Plough, Venez.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Ginopil *Biocontrolfarm, Ital.*
Pilosella.

Gino-Pletil *Pfizer, Braz.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Ginorectol *Kleva, Gr.; Kleva, Singapore.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ginos *Veropharm, Rus.*
Ginkgo biloba (p. 2512·3).
Vascular disorders; vestibular disorders.

Ginoseptil *Azevedos, Port.†*
Povidone-iodine (p. 1767·1).

Ginosutin *Organon, Braz.†*
Tinidazole (p. 949·2).
Vulvovaginal infections.

Ginosutin-M *Organon, Braz.†*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Ginotarin *Bunker, Braz.*
Miconazole nitrate (p. 589·1).
Fungal skin and vaginal infections.

Gino-Teracin *Neo Quimica, Braz.*
Tetracycline hydrochloride (p. 373·2); amphotericin B (p. 569·2).
Vaginal infections.

Ginotex *Lafi, Chile.*
Estradiol (p. 2271·1); trimegestone (p. 2310·3).
Menopausal disorders.

Gino-Tralen *Pfizer, Venez.*
Tioconazole (p. 595·3).
Vulvovaginal fungal infections; trichomoniasis.

Gino-Travogen *Bayer, Port.*
Isoconazole nitrate (p. 583·2).
Fungal vulvovaginal infections.

Ginotrax *Ativus, Braz.*
Isoconazole nitrate (p. 583·2).
Vaginal infections.

Gino-Trimazen *Multilab, Braz.*
Clotrimazole (p. 576·2).

Gino-Trosyd *Pfizer, Port.*
Tioconazole (p. 595·3).
Fungal vulvovaginal infections.

Ginoven *Biocontrolfarm, Ital.*
Aesculus (p. 2431·2).

Ginoxil *Sinclair, Ital.*
Urea hydrogen peroxide (p. 1774·2).
Vaginal disorders; vaginal hygiene.

Ginoxil Ecoschiuma *Sinclair, Ital.*
Hamamelis (p. 2523·3); aloe vera (p. 1693·2); allantoin (p. 1693·1).
Personal hygiene.

Ginsana *Boehringer Ingelheim, Arg.; Sanova, Austria; Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Cz.†; Tentan, Ger.; Boehringer Ingelheim, Irl.; Fher, Ital.; DKSH, Malaysia†; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Pol.†; Kironfarma, Port.; Boehringer Ingelheim, Rus.; Pharmaton, Singapore†; MaxMedica, Swed.; Ginsana, Switz.; Boehringer Ingelheim, Thai.†*
Ginseng (p. 2513·3).
Tonic; fatigue.

Ginsana Ton *Fher, Ital.*
Ginseng (p. 2513·3); zinc (p. 2126·1).
Tonic.

Ginsavit *Julphar, UAE.*
Vitamins; minerals; ginseng (p. 2513·3).

Ginseng Bioplus Diates *Provefarma, Arg.†*
Ginseng (p. 2513·3); thiamine (p. 2102·3).
Dietary supplement.

Ginsenol *Herbapol Krakow, Pol.*
Ginseng (p. 2513·3).
Tonic.

Ginsex *Delta, Braz.*
Ginseng (p. 2513·3).
Tonic.

Ginsiplex *Servocare, India.*
Ginseng (p. 2513·3); vitamins; minerals.

Ginsomin *Mega Lifesciences, Malaysia; Mega Lifesciences, Philipp.; Mega We Care, Singapore; Mega Lifesciences, Ukr.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Ginsor *UB, Switz.*
Ginseng (p. 2513·3).
Tonic.

Ginsroy *Schumit, Thai.*
Ginseng (p. 2513·3).
Tonic.

Ginsynergy plus Rhodiola *Bioglan, Austral.*
Ginseng (p. 2513·3); Siberian ginseng (p. 2614·3); ashwagandha (p. 2450·2); rhodiola rosea.
Tonic.

Gintox *Allenge, India.*
Ginseng (p. 2513·3); vitamins; minerals.

Ginvapast
Note: this name may be used for preparations of different composition.
Ogna, Ital.
Calcium gluconate (p. 1783·3); procaine hydrochloride (p. 1994·3); cetylpyridinium chloride (p. 1743·1).
Gum disorders; ulcers caused by dental prostheses.
Wild, Switz.
Calcium gluconate (p. 1783·3); procaine hydrochloride (p. 1994·3); vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1).
Gum disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ginvas *Cosme, India.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dementia.

Ginvit *Medihealth, India.*
Ginseng (p. 2513·3); vitamins.

Outremer, Fr.
Siberian ginseng (p. 2614·3); magnesium carbonate (p. 1856·2); vitamin C (p. 2110·3); vitamin B_6 (p. 2105·3).
Tonic.

Gin-Vita *Shin Poong, Singapore.*
Ginseng (p. 2513·3); oryzanol (p. 2578·1); ascorbic acid (p. 2110·3); tocoferil acetate (p. 2119·2); fursultiamine (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); riboflavin tetrabutyrate (p. 2104·3).
Musculoskeletal pain; peripheral vascular disorders; vitamin E supplement.

Giona *Lannacher, Austria; Orion, Cz.; Orion, Denm.; Orion, Malaysia; Orion, Norw.; Orion, Singapore; Orion, Swed.; Orion, Thai.; Abdi, Turk.*
⊗Budesonide (p. 1625·1).
Asthma.

Gioral *Chemica, Gr.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Giovax *Teva, Cz.†*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Giovax plus H *Teva, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Gioxyson *Akrikhin, Rus.; Nizhpharm, Rus.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Giparlix *Loeffler, Mex.*
Triprolidine (p. 642·3); phenylephrine (p. 1672·2).
Allergic rhinitis.

Gipzide *Sriprasit, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Girabloc *Hexpharm, Indon.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Giran *AstraZeneca, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Girasid *Abfar, Turk.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Girheulit HM *Pfluger, Ger.†*
⊗Lithium carbonicum (p. 427·3); colchicum autumnale (p. 607·1); acid. benzoicum (p. 1738·2); urea pura (p. 1727·3); ammonium phosphoricum (p. 2442·1); calcium phosphoricum (p. 1784·2); magnesium phosphoricum (p. 1787·3); natrium phosphoricum (p. 1791·2); acid. silicicum (p. 2208·3); kalium iodatum (p. 2336·3).
Homoeopathic preparation.

Girheulit HOM *Pfluger, Ger.*
⊗Lithium carbonicum (p. 427·3); colchicum autumnale (p. 607·1); acid. benzoicum (p. 1738·2); ammonium phosphoricum (p. 2442·1); acid. silicicum (p. 2208·3); kalium iodatum (p. 2336·3).
Homoeopathic preparation.

Giro *Panacea, India; Panacea, Rus.*
Ornidazole (p. 943·1).
Amoebiasis; giardiasis; protozoal infections; anaerobic bacterial infections.

Giroflox *Braun, Israel; Tecnimede, Spain.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Tecnimede, Port.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Girolac *ABC, Ital.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Giscosamine *E-Pharma, Denm.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Gisfen *More, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Gisistin *Best, Mex.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis; giardiasis.

Gismotal *Biofarma, Turk.*
Trimebutine maleate (p. 2634·1).

Gissicor *Medreich, India; Saimirra, Singapore.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Dietary supplement.

Gissistat *Medreich, India.*
Atorvastatin (p. 1309·2); omega-3 fatty acids (p. 1460·1).

Gistaphen *Olainfarm, Ukr.*
Sequifenadine (p. 640·2).
Allergic disorders.

Gitae *DR Johns, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gitae-M *DR Johns, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gitagamp *Echo, Rus.*
Vitamin B substances (p. 2102·3); sodium N-nicotinyl-gamma-aminobutyrate.
Tonic; chronic alcoholism; extrapyramidal disorders.

GI-Tak *Be-Tabs, S.Afr.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; heartburn.

Gitako *Daehan, Singapore.*
Ginkgo biloba (p. 2512·3).
Peripheral vascular disorders; cerebral function disorders.

Gitar *Comed, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

Gitaramin *Nufarindo, Indon.*
Mefenamic acid (p. 85·3).
Pain; menorrhagia.

Gitas *Interbat, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Gitas Plus *Interbat, Indon.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle pain or spasm.

Gitazone *Millimed, Thai.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Gitrabin *Actavis, Cz.; Actavis, Hong Kong; Actavis, Pol.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gitrak *Ferring, India.*
Itopride.

Gitrasek *Chinoin, Mex.*
Itraconazole (p. 583·3); secnidazole (p. 947·3).

Gitro *Plus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Gittalun *Boehringer Ingelheim, Ger.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Gi-Tune *Intas, India.*
Itopride hydrochloride (p. 1850·1).

Gi-Tune MPS *Intas, India.*
Itopride hydrochloride (p. 1850·1); dimeticone (p. 1886·2).

Gityl *Krewel, Ger.*
Bromazepam (p. 1041·2).
Anxiety; sleep disorders.

Givair *Epifarma, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Givalex *Norgine, Belg.; Norgine, Fr.; Master, Ukr.*
Hexetidine (p. 1755·1); choline salicylate (p. 39·2); chlorobutanol (p. 1747·2).
Mouth and throat disorders.

Givitol *Galen, Irl.†*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); sodium ascorbate (p. 2111·1).
Iron and folic acid deficiency in pregnancy.

Givov *Zee, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gixaderm *Mergers Drugfil, Philipp.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Gixal *Biores, Ital.*
Meloxicam (p. 86·3).
Osteoarthritis; ankylosing spondylitis; rheumatoid arthritis.

G2K *Biological E, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

GLA
Note: this name may be used for preparations of different composition.
Reddy, India.
Gamolenic acid (p. 2509·2).

Glace *GSK, India.*
Betacarotene (p. 2051·1); selenium dioxide (p. 2087·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Glace-X *GSK, India.*
Vitamins; trace elements; docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Glacout *Ingens, Arg.†*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Glactiv *Ono, Jpn.*
Sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Gladase *Glades, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3).
Debridement of necrotic tissue.

Gladase-C *Smith & Nephew, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3); chlorophyllin copper complex sodium (p. 2178·3).
Ulcers; wounds.

Gladem *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Gladio *Abiogen, Ital.*
Aceclofenac (p. 16·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

Gladium *Investi, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Gladius *Pharmanel, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Glador *Lupin, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glafemak *Alvia (Αλβια), Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Glafornil *Merck, Chile; Biotech, Venez.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glakay *Eisai, China; Eisai, Jpn; Eisai, Thai.*
Menatetrenone (p. 2122·2).
Osteoporosis.

Glalfital *Teuto, Braz.*
⊗Dorzolamide (p. 2006·3).

GLA-M *Reddy, India.*
Gamolenic acid (p. 2509·2); mecobalamin (p. 2108·1).

Glamarol *Guardian, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glamaryl *Sanofi-Aventis, S.Afr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glamide *Community Pharmacy, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glamidolo *Faran, Gr.; Angelini, Ital.*
Dapiprazole hydrochloride (p. 2006·2).
Glaucoma; reversal of mydriasis; production of miosis.

Glamigan *Germed, Braz.*
Bimatoprost (p. 2004·2).

Glamin *Fresenius Kabi, Austral.; Fresenius Kabi, China; SSPC, China; Fresenius Kabi, Cz.†; Baxter, Ger.; Fresenius Kabi, India; Fresenius Kabi, Irl.†; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, NZ; Fresenius Kabi, Port.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Switz.†; Fresenius Kabi, UK.*
Amino acids.
Parenteral nutrition.

Glamor
Note: this name may be used for preparations of different composition.
AGIPS, Ital.
Alendronate sodium (p. 1171·3).

Invision, India.
Glimepiride (p. 473·2).
Diabetes mellitus.

Glamor-M *Invision, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glamor-P *Invision, India.*
Glimepiride (p. 473·2); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glamor-PM *Invision, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glamoxin *GSK, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Glamzolid *Vera, Hung.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glandex *Hasco-Lek, Denm.*
⊗Exemestane (p. 792·2).
Breast cancer.

Glandicin *Degorts, Mex.*
Piroxicam (p. 125·3).
Inflammation; pain.

Glandomed *Cell Pharm, Ger.*
Macrogol (p. 2547·3).
Mouth disorders.

Glandosane *Stada, Austria; Cell Pharm, Ger.; Stada, Hong Kong; Fresenius Kabi, Port.†; Helvepharm, Switz.; Cell Pharm, Thai.; Fresenius Kabi, UK.*
Carmellose sodium (p. 2175·2); sorbitol (p. 2092·1); electrolytes (p. 1775·1).
Dry mouth; saliva substitute.

Stada, Malaysia.
Electrolytes (p. 1775·1).
Dry mouth; saliva replacement.

Glandulae-F-Gastreu R20 *Reckeweg, Ger.*
Glandula suprarenalis; glandula thymi (p. 2631·1); hypophysis (p. 2444·1); ovarium (p. 2298·2); pancreas (p. 2444·1); thyreoidinum (p. 2345·3).
Homoeopathic preparation.

Glanique *Asofarma, Mex.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Glanos *GSK, Indon.†*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Glanuta *Valeant, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

GLA-Plus Vitamin E *Shaklee, Canad.*
Essential fatty acids; vitamin E (p. 2119·1).
Nutritional supplement.

Glartin *Biomedica, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Glarzena *Helm, Port.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Glasbor *Rafarm, Gr.*
Baclofen (p. 2014·3).
Spasticity.

Glassia *Kamada, Israel.*
Alpha$_1$-proteinase inhibitor (p. 2438·1).
Alpha$_1$ antitrypsin deficiency.

Glatim *Amhof, Arg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glatix *Invision, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glatix-M *Invision, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glaturin *Ahimsa, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glaub *Uniao Quimica, Braz.*
Brimonidine tartrate (p. 2004·3).

Glaucare *FDC, Philipp.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glaucodose *Faran, Gr.*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Glaucoftal *Teuto, Braz.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).

Glaucogesic *Atlas, Arg.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Glauconide *Llorens, Spain.†*
⊗Diclofenamide (p. 2006·3).
Glaucoma.

Glauco-Oph *Seng, Thai.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Glaucoprost *Poen, Arg.*
Travoprost (p. 2012·1).
Glaucoma; ocular hypertension.

Glaucosan *Hexal, S.Afr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glaucostat
Note: this name may be used for preparations of different composition.
Raymos, Arg.
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.
IFET (ΙΦΕΤ), Gr.†
Aceclidine hydrochloride (p. 2001·1).
Glaucoma.

Glaucostat T *Raymos, Arg.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glauco-Stulln *Stulln, Ger.†*
⊗Pindolol (p. 1470·1).
Glaucoma.

Glaucotens *Valeant, Cz.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Glaucotensil
Note: this name may be used for preparations of different composition.
Poen, Arg.
⊗Pilocarpine hydrochloride (p. 2010·3); timolol maleate (p. 1513·2).
Glaucoma.
Poen, Chile.
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Glaucotensil D *Roemmers Poen, Venez.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Glaucotensil T *Poen, Chile; Roemmers Poen, Venez.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glaucotensil TD *Poen, Arg.*
⊗Dorzolamide (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glaucothil *Alcon, Ger.†*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Glaucotima *ICN, Irl.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glaucotrat *Uniao Quimica, Braz.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Glaucoval *Viofar, Gr.*
Brimonidine tartrate (p. 2004·3).

Glaudin *Mylan, Denm.; Mylan, Fin.†; Mylan, Swed.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Glauko Biciron *S & K, Ger.*
Pilocarpine hydrochloride (p. 2010·3); phenylephrine hydrochloride (p. 1672·3).
Glaucoma.

Glaukostad *Stada, Fin.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Glaumox *AFT, NZ.*
⊗Acetazolamide sodium (p. 2001·1).
Glaucoma; oedema; epilepsy.

Glaunorm *IFET (ΙΦΕΤ), Gr.; Farmigea, Ital.*
Aceclidine hydrochloride (p. 2001·1).
Glaucoma.

Glaunot *Atlas, Arg.*
Travoprost (p. 2012·1).
Glaucoma; ocular hypertension.

Glaupax *OmniVision, Ger.; OmniVision, Switz.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Glauprost *Arrow, Norw.; Rompharm, Rus.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Glauseta *Sanbe, Indon.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Glausolets *SMB, Chile.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glausolets Plus *SMB, Chile.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glautam *Jadran, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glautan *Vitamed, Israel.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Glautelol *Kleva, Gr.*
⊗Carteolol hydrochloride (p. 1332·3).

Glauteolol *Raymos, Arg.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Glautimol
Note: this name may be used for preparations of different composition.
Alcon, Braz.
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.
Farmigea, Ital.
⊗Aceclidine hydrochloride (p. 2001·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Glauvent *Sopharma, Rus.*
Glaucine phosphate (p. 1666·1).
Cough.

Glauxyl *Yuriya-Farm, Ukr.†*
Glucose (p. 2068·3); xylitol (p. 2220·3); sodium acetate (p. 1781·1); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); potassium chloride (p. 1793·2).
Fluid and electrolyte disorders; carbohydrate source.

Glavamin *Fresenius Kabi, Austria†; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Amino acids.
Parenteral nutrition.

Glaveral *Help, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Glavit *Fontovit, Braz.†*
Gamolenic acid (p. 2509·2); linolenic acid (p. 1460·2); oleic acid (p. 2200·1).
Premenstrual syndrome.

Glaxal Base *Wellspring, Canad.*
Emollient.
Dermatological base; dry skin.

Glaxenna *GSK, India.*
Sennoside B (p. 1885·2).
GSK, Rus.
Calcium sennosides (p. 1885·1).
Constipation.

Glazewear *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Glazid *Fako, Turk.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glazide *Galena, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glazidim *GSK, Belg.; GSK, Fin.; GSK, Ital.*
Ceftazidime (p. 250·2).
Bacterial infections.

GLCO *Neon, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gleacer *Altair, Rus.*
Choline alfoscerate (p. 389·2).
Cerebrovascular disorders; dementia.

Gleam *Franco-Indian, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gleether *Neiss, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Gleevec *Novartis, Canad.; Novartis, S.Afr.; Novartis, USA.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia; gastrointestinal stromal tumours; acute lymphoblastic leukaemia; systemic mastocytosis; chronic eosinophilic leukaemia; dermatofibrosarcoma protuberans; hypereosinophilic syndromes; myelodysplastic syndromes; myelodysplastic disease.

Gleitgelen *Wolff, Ger.*
Liquid paraffin (p. 2191·2); medium-chain triglycerides (p. 2082·2).
Vaginal dryness.
Taymed, Turk.
⊗Hyetellose (p. 2188·3); glycerol (p. 2517·2); chlorhexidine hydrochloride (p. 1743·3).
Atrophic vaginitis.

Glemaz *Montpellier, Arg.; Bago, Chile; Montpellier, Rus.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glemicid *Collins, Mex.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glemid *Egis, Cz.; Egis, Pol.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glemisal *Silanes, Mex.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glempid *Egis, Hung.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glen *Rass, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Glenalgesic Blue *Vitaminerals, Canad.†*
Menthol (p. 2553·2).

Glenalgesic Forte *Vitaminerals, Canad.†*
Camphor (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Glencet *Glenmark, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Glencovorin *Glenmark, Braz.*
Calcium folinate (p. 2066·3).

Glendan *Glenmark, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Glenflu *Glenmark, India.*
Fluconazole (p. 578·2).
Fungal infections.

Glenix *Xepa-Soul Pattinson, Malaysia.*
Glimepiride (p. 473·2).
Diabetes mellitus.

G-Lenk *Orifarm, Fin.†*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Glenoxal *Glenmark, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Glen-SB *Rass, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).

Glentek *Glenmark, Neth.*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Glentona Plus *Glenmark, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Glentor *Medipharma, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glen-TZB *Rass, India.*
Ceftriaxone sodium (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Glepark *Glenmark, Cz.; EQL, Fin.; Kleva, Gr.; Glenmark, Irl.; Glenmark, Neth.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Gleperil *Glenmark, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Gletar *Pekana, Neth.*
Aurum muriaticum (p. 2521·1); cynara scolymus (p. 2490·3); dulcamara (p. 2497·3); euphrasia officinalis (p. 2502·1); glonoinum (p. 1391·2); hedera helix (p. 2536·2); ruta graveolens (p. 2608·2); tabacum (p. 2632·2).
Homoeopathic preparation.

Glevate *Glenmark, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Glevo *Glenmark, India; Glenmark, Malaysia; Glenmark, Philipp.; Glenmark, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Glevomicina *Bago, Arg.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Glexar *Epifarma, Ital.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Glez *Aristo, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Gli *Ordain, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliadel *Orphan, Austral.; Link, Fr.; Archimedes, Ger.; MGI, Gr.; MGI, Irl.; Medison, Israel; MGI, Ital.; Nobel, Jpn; MGI, Malaysia; MGI, Neth.; MGI, Port.; Pharmaplan, S. Afr.; Eisai, Singapore; MGI, Spain; BioPro, Thai.†; Archimedes, UK; Arbor, USA.*
Carmustine (p. 761·2).
Glioblastoma multiforme; malignant glioma.

Gliamal *Pliva, Rus.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glianimon *Bayer, Ger.; Menarini, Gr.*
Benperidol (p. 1041·1).
Psychoses.

Glianov *Hikma, Ukr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliansor *Legrand, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliatilin *ITF, Gr.; Italfarmaco, Ital.; Italfarmaco, Pol.; Italfarmaco, Rus.; Italfarmaco, Ukr.*
Choline alfoscerate (p. 389·2).
Mental function impairment; head trauma; mental function disorders; cerebrovascular disorders.

Glibact-M *Active, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Glibamide *CTS, Rus.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibemida *Temis, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gliben *CT, Ger.†; Winthrop, Ger.†; Biolab, Hong Kong†; Abiogen, Ital.; Biolab, Malaysia; Mylan, NZ†; Nobel, Turk.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gliben F *Abiogen, Ital.*
Glibenclamide (p. 472·1); phenformin hydrochloride (p. 493·1).
Diabetes mellitus.

Glibenbeta *Betapharm, Ger.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibenclamon *Sanval, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibendiab *Sigma, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibendoc *Docpharm, Ger.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Glibénèse *Dexo, Fr.; Pfizer, Switz.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Glibenese *Pfizer, Austria; Pfizer, Belg.; Pfizer, Denm.†; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, UK.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Glibenhexal *Hexal, Ger.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibenil
Note: this name may be used for preparations of different composition.
Bangkok Lab & Cosmetic, Thai.
Glipizide (p. 474·1).
Diabetes mellitus.

Cryopharma, Mex.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibenorm *Streuli, Switz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibenval *Valdecasas, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibesifar *Siphar, Switz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibesyn *Medochemie, Malaysia; Medochemie, Singapore.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibet *Cosme, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibetic
Note: this name may be used for preparations of different composition.
La Pharmaceuticals, India.
Glipizide (p. 474·1).
Diabetes mellitus.

Polpharma, Pol.; Polpharma, Ukr.†
Glimepiride (p. 473·2).
Diabetes mellitus.

Teva, Israel; The Forty-Two, Thai.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibetic-MF *La Pharmaceuticals, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Glibex *Biopharm, Rus.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibexil *Royton, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibezid *Jelfa, Hung.; Jelfa, Pol.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glibic *Medicine Products, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glibofor *Farmak, Ukr.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glibomet *Guidotti, Cz.; Menarini, India; Guidotti, Ital.; Berlin-Chemie, Rus.; Ulagay, Turk.; Berlin-Chemie, Ukr.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gliboral *Menarini, Hong Kong; Guidotti, Ital.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glib-ratiopharm *Ratiopharm, Ger.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glic *East West, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glicab *Tempo Scan Pacific, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glicacon *Disphar, Neth.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glicamet *Biochem, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glicamin
Note: this name may be used for preparations of different composition.
Geolab, Braz.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glican *Candor, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glican-M *Candor, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glicaron *Cifarma, Braz.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glicas-M *Casca, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glicavin *Quimica y Farmacia, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glicef *Neiss, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Glicefor *Geolab, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glicef-S *Neiss, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).

Glicef-T *Neiss, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Glicel *Brasterapica, Braz.*
⊗Glycerol (p. 2517·2).
Constipation.

Glicenex *Bago, Chile.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glicenex Duo *Bago, Chile.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glicept *Grandix, India.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gliceramin *Behrens, Venez.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Glicerolax *Dynacren, Ital.*
⊗Glycerol (p. 2517·2); mallow (p. 2549·2); rice starch (p. 2095·1).
Constipation.

Glicerolo microclismi *Mediplants, Gr.*
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Glicerotens *Llorens, Spain.*
⊗Glycerol (p. 2517·2).
Ocular surgery; glaucoma.

Glicero-Valerovit *Teofarma, Ital.*
Sodium glycerophosphate (p. 2519·2); valerian (p. 2640·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Hyperexcitability; tonic.

Glicima *Atlantis, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Glicina-GM *Biochemix, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gliciron *Roemmers, Venez.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glicised *Arterium, Ukr.*
Glycine (p. 2071·2).
Asthenia; tonic.

Glicla *Orchid, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclabit *Polipharm, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclabore *Disphar, Neth.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclada *KRKA, Austria; KRKA, Hong Kong; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclafin *Q Check, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclafin-M *Q Check, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gliclalane *Disphar, Neth.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclamin *Inpac, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gliclan *Fourrts, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclan M *Fourrts, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gliclareze *Disphar, Neth.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclastar M *Zinnia, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gliclatab *Disphar, Neth.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclatan *Tan, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclaz *Khandelwal, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliclaz-M *Khandelwal, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gliclinoz *Alchemia, Denm.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glicmet *East West, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glicobase *Bayer, Ital.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glicoben *Cazi, Braz.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Glicocalcio *Hoch Wertig, Arg.*
Calcium lactate (p. 1784·1); aminoacetic acid (p. 2071·2).
Dietary supplement.

Glicocef *Bergamo, Braz.†*
Ceftriaxone (p. 253·3).
Bacterial infections.

Glicoderm *Remexa, Mex.*
Glycolic acid (p. 1704·3).
Dry skin disorders.

Glicodin *Igefarma, Braz.*
Potassium iodide (p. 2336·3); ammonium chloride (p. 1656·1); hyoscyamus (p. 2530·2).
Respiratory-tract congestion.

Glicodril *Reuffer, Mex.*
Diphenhydramine (p. 626·1).
Hypersensitivity.

Glicofita Plus *Lilly, Braz.†*
Test for glucose in urine (p. 2516·3).

Glicoisdin
Note: this name may be used for preparations of different composition.
Isdin, Arg.
Glycolic acid (p. 1704·3).
Skin disorders.

Isdin, Chile.
Cream: Glycolic acid (p. 1704·3); ammonium glycolate (p. 1704·3); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Skin ageing.

Isdin, Chile.
Gel: Glycolic acid (p. 1704·3); ammonium glycolate (p. 1704·3); aloe vera (p. 1693·2).
Skin ageing.

Glicolic *Medihealth, Mex.*
Glycolic acid (p. 1704·3).
Dry skin disorders; light-induced skin damage.

Glicolic H *Medihealth, Mex.*
Glycolic acid (p. 1704·3); hydroquinone (p. 1705·1).
Hyperpigmentation disorders.

Glicon *Suphong, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glicon-M *Orion, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Gliconorm
Note: this name may be used for preparations of different composition.
Abiogen, Hong Kong; Abiogen, Ital.
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glicorest *Solvay, Ital.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glicorp *Neo Quimica, Braz.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Glicosi-M *Aronex, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glicoxem *Kener, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gliciron *Cipla, India; Siam Medicare, Thai.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glidabet *Hexpharm, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glidan *Roemmers Rowe, Venez.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glidanil
Note: this name may be used for preparations of different composition.
Montpellier, Arg.; Mersifarma, Indon.; Bago, Rus.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Medipharm, Chile.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glidanil-G *Medipharm, Chile.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glide *Franco-Indian, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Gliden *BMW, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliden-MF *BMW, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glidiab
Note: this name may be used for preparations of different composition.
Soho, Indon.
Gliquidone (p. 474·3).
Diabetes mellitus.

Glidiamid *ICN, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glidiet *Win-Medicare, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glidiet-M *Win-Medicare, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glidil *Med-One, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glidipion *Actavis, UK.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glifage *Merck, Braz.*
Metformin (p. 489·1).
Diabetes mellitus.

Glifapen *Ronnet, Arg.*
Amoxicillin (p. 216·2); diclofenac sodium (p. 48·3).
Bacterial infections with inflammation.

Glifarcal *Farcoral, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glifest *Neiss, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Glifil M *Fourrts, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glifix *Bilim, Turk.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glifor *Bilim, Turk.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gliformil *Pharlab, Braz.*
Metformin (p. 489·1).
Diabetes mellitus.

Gliformin
Note: this name may be used for preparations of different composition.
Tempo Scan Pacific, Indon.; Akrikhin, Rus.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Orchid, India.
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glifortex *Andromaco, Chile.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glifortex-G *Andromaco, Chile.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Gligel *LDA, Arg.*
Glycolic acid (p. 1704·3).
Skin photo-ageing; keratinisation disorders.

Glihex *Candor, India.*
Chlorhexidine gluconate (p. 1743·3).

Glihexal *Sandoz, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glikamel *Pharos, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glikare-M *Nitro Cadineur, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glikos *Ifars, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glikron *Deva, Turk.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glim *Grandix, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes Mellitus.

Glimaday *Wockhardt, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimal *Silanes, Mex.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimarex *Taiwan Biotech, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimaryl *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimatin *PharOS, Neth.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia.

Glimauno *Wockhardt, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimax
Note: this name may be used for preparations of different composition.
Ali, Turk.
Glimepiride (p. 473·2).
Diabetes mellitus.

Pharma Nutria, Philipp.; Vesco, Thai.†
Glipizide (p. 474·1).
Diabetes mellitus.

Glimbax *ITF, Gr.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Medagro, Pol.
Diclofenac (p. 48·3).
Mouth and throat inflammation.

Glim-C *Grandix, India.*
Chromium polynicotinate (p. 2055·3); gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimcare *Q Check, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimcare Forte *Q Check, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimcare Plus *Q Check, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimchek *Khandelwal, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimchek M *Khandelwal, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimcip *Cipla, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimcom *Comed, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimec *Primera, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimecure *CureQuick, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimed *Multicare, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimegamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimehexal *Sandoz, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimekomb *Akrikhin, Rus.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimel *Alphapharm, Austral.; Alphapharm, Hong Kong; Merck, Indon.; Alphapharm, Singapore.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glimendin *Specifar, Fin.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimepibal *Baldacci, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimepil *Farmoquimica, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimepiron *AG Therapy, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimeplic *Baliarda, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimeprisan *Hexal, Denm.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimer *Piramal, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimeran *Neo Quimica, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimerax *Drossapharm, Switz.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimerid *Kleva, Gr.; Galeno, Venez.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimeryl *Actavis, Hong Kong.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimépryle *Mepha, Switz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimesan *Sandoz, Pol.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimespes *Specifar, Fin.; Innovact, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimestad *Stada, Austria.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimestar *Mankind, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimestar PM *Mankind, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glimestar-M *Mankind, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimesyn *Sydenham, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimet
Note: this name may be used for preparations of different composition.
Franco-Indian, India.
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mepro, Chile.†
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glimetal *Silanes, Mex.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimetop *RPG, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

GlimeWin *Zentiva, Hung.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimexal *Sandoz, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimexin *Minerva (Μινερβα), Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimfit *Biosync, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimi DM *Shrrishti, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimial *Neves, Port.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimicron *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glimid *Anthus, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimide
Note: this name may be used for preparations of different composition.
CCM, Malaysia; Beacons, Singapore; Pharmahof, Thai.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Beta, Arg.
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Glimid-M *Anthus, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimidot *Triton, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimidot-M *Triton, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimidstada *Stada, Rus.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glimifix *Akesiss, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimifix-M *Akesiss, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimikare *Nitro Cadineur, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimikare-MSR *Nitro Cadineur, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimil *Multilab, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glimin *Taiwan Biotech, Malaysia.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliminfor *Shreya, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimiprex *Aristo, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimiprex MF *Aristo, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimiriv *East African, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimisave *Morepen, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimisave-M *Morepen, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimitab *Centaur, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimitan *Tan, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimizide-M *Essweil, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimizide-PG *Essweil, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glimkap *Karnataka, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimkap M2 *Karnataka, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimosa *Medarte, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimpax *Maxo, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimpax-M *Maxo, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimpid *Ranbaxy, India; Ranbaxy, Malaysia.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimpil *Psychotropics, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimpil-MF *Psychotropics, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimser *Alembic, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimsite *Sanofi-Aventis, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimsite-M *Sanofi-Aventis, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Glimsite-MP *Sanofi-Aventis, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

GlimTek *Ratiopharm, Cz.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

GlimTeva *Teva, Pol.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimtide *Orchid, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimtide Forte *Orchid, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimtide Plus *Orchid, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glimulin *Glenmark, India; Glenmark, Malaysia.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimulin-MF *Glenmark, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimunos *Galenium, Indon.*
Phyllanthus niruri (p. 2590·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Glimy *Reddy, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glimy-M *Reddy, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glimy-MP *Reddy, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glimy-P *Reddy, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

Glimz *Wallace, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glinate *Glenmark, India.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Glinate-MF *Glenmark, India.*
Nateglinide (p. 492·1); metformin (p. 489·1).
Diabetes mellitus.

Glincil *Pharmathen, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glindia *Gedeon Richter, Hung.; Richter, Pol.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glinidd *Evacare, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glinidd-M *Evacare, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glinil *Cipla, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glinil M *Cipla, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glinor *Ratiopharm, Fin.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis; allergic conjunctivitis.

Glinorboral *Silanes, Mex.*
Glibenclamide (p. 472·1); phenformin (p. 493·1).
Diabetes mellitus.

Glinorm *Talent, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glinormax *Teva, Pol.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glinorm-M *Talent, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glinux 70/30 *Probiomed, Mex.*
⊗Human insulin (p. 475·3).
Diabetes mellitus.

Glinux-N *Probiomed, Mex.*
⊗Human insulin (p. 475·3).
Diabetes mellitus.

Gliocarvedil *Bago, Arg.*
⊗Tablets, enalapril maleate (p. 1371·1) (Glioten); tablets, carvedilol (p. 1333·1) (Carvedil).
Hypertension.

Gliolan *Medac, Belg.; Medac, Cz.; Medac, Denm.; Medac, Fr.; Medac, Ger.; Medac, Gr.; Medac, Irl.; Medac, Neth.; Medac, Norw.; Medac, Pol.; Medac, Port.; Medac, Spain; Medac, Swed.; Medac, UK.*
Aminolevulinic acid hydrochloride (p. 740·1).
Malignant glioma.

Glionil *Neo Quimica, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glioral *Galenika, Ukr.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliosartan *Bago, Arg.*
Telmisartan (p. 1509·3).
Hypertension.

Gliosartan Plus *Bago, Arg.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Gliotem *Sun, India.*
Temozolomide (p. 865·2).
Glioblastoma multiforme; malignant glioma; metastatic melanoma.

Glioten *Bago, Arg.; Bago, Braz.; Bago, Chile†; Armstrong, Mex.; Bago, Singapore.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Gliotenzide *Bago, Arg.; Bago, Braz.; Armstrong, Mex.; Bago, Singapore.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Glioz *Reddy, India.*
Temozolomide (p. 865·2).

Glip *East West, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glipal *Iasis, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Glipar *Degorts, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glipep *Hospira, Port.†*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections; pseudomembranous colitis associated with antibiotics.

Gliperid *Merck, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliperide *Medhaus, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliperin *Bennett, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glipid
Note: this name may be used for preparations of different composition.
Genexo, Pol.
Glimepiride (p. 473·2).
Diabetes mellitus.

Glipimed *Medicine Products, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glipimet *Sun, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Glipiran *Ranbaxy, Mex.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glipiren *Korea United, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glipiriv *East African, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glipizon *Suphong, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Gliplex *Farmasa, Braz.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Glipmet *East West, India.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glip-MF *Novagen, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glipomar *Ranbaxy, Ukr.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glipressina *Ferring, Ital.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage.

Gliprex *Medico Uno, Hung.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gliptid *Merck Serono, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gliptide *Crinos, Ital.†*
Sulglicotide (p. 1892·2).
Peptic ulcer; gastrointestinal disorders.

Glipy *Alembic, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glirid *Sandoz, Gr.; Eczacibasi, Turk.; Sandoz, Ukr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glisafe *Indu, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glisafe M *Indu, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glisan *Apotex, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glisend *Konimex, Indon.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Glisodin *Kalbe, Indon.*
Superoxide dismutase (melon) (p. 135·2); gliodin.
Antioxidant.

GliSODine Antioxidant *Isocell, Fr.*
Superoxide dismutase (p. 135·2); gliadin.
Tonic.

GliSODine Défenses *Isocell, Fr.*
Superoxide dismutase (p. 135·2); gliadin; *Lactobacillus rhamnosus* (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3).
Restoration of intestinal flora.

GliSODine Solaire *Isocell, Fr.*
Superoxide dismutase (p. 135·2); gliadin; vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); lycopene (p. 2546·2); borage oil (p. 2459·2).
Tanning aid.

Glisopos *Sanbe, Indon.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Glista *Cadila, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glista-OD *Cadila, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glisu *Biomax, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glita *Stadmed, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glitafor *Invision, India.*
Metformin hydrochloride (p. 489·1); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glital *Talent, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glital-M *Talent, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glita-M *Stadmed, India.*
Metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glitaz *Cathay, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glitisol
Note: this name may be used for preparations of different composition.
Remedica, Hong Kong.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Zambon, Braz.
Thiamphenicol (p. 376·3).
Bacterial infections.

Zambon, Ital.
Thiamphenicol glycinate hydrochloride (p. 377·1).
Bacterial infections.

Glito *Medley, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Glitosslab *Multilab, Braz.†*
Potassium iodide (p. 2336·3).
Cough.

Glitrac-M *Invision, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glitral *Austral, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glitter *Ind-Swift, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Ind-Swift, Philipp.
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glitter-M *Ind-Swift, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glityx *Triton, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glityx-M *Triton, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glitz-MF *Laksun, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glivasol *Stada, Denm.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glivec *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
Imatinib mesilate (p. 807·3).
Acute lymphoblastic leukaemia; chronic myeloid leukaemia; dermatofibrosarcoma protuberans; gastrointestinal stomal tumours; hypereosinophilic syndrome; gastrointestinal stromal tumours; chronic eosinophilic leukaemia; systemic mastocytosis; myelodysplastic disease; myeloproliferative disease.

Novartis, India; Novartis, Ukr.
Imatinib (p. 807·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia; gastrointestinal stromal tumours; myelodysplastic disease; hypereosinophilic syndrome; dermatofibrosarcoma protuberans; systemic mastocytosis.

Glix
Note: this name may be used for preparations of different composition.
Indi, India.
Gliclazide (p. 472·3).
Diabetes mellitus.

Rider, Chile.
Glimepiride (p. 473·2).
Diabetes mellitus.

YSP, Malaysia; Yung Shin, Philipp.
Glipizide (p. 474·1).
Diabetes mellitus.

Gliximina *Denver, Arg.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Glix-M *Indi, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gliza *Stadmed, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glizamed *Alchemia, Denm.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gliza-MF *Stadmed, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glizid *Panacea, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glizide
Note: this name may be used for preparations of different composition.
Daehan, Singapore.
Gliclazide (p. 472·3).
Diabetes mellitus.

Pharmahof, Thai.
Glipizide (p. 474·1).
Diabetes mellitus.

Glizid-M *Panacea, India; Panacea, Thai.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glizigen *SM, Venez.*
Phenoxyethanol (p. 1764·3); hydroxybenzoates (p. 1756·3).
Herpesvirus skin infections.

Tobbest Busindo, Indon.
Glycyrrhizic acid (p. 2520·2).
Herpesvirus infections of mucous membranes.

Glizolan *Rottapharm, Spain.*
Diacerein (p. 45·3).
Osteoarthritis.

Glizon *Douglas, NZ.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glizone *Multicare, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Zydus, India.
Pioglitazone (p. 493·1).
Diabetes mellitus.

Glizone-M *Zydus, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

GLM *Systopic, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Globac *Zydus, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Globac Active *Zydus, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Globac-PM *Zydus, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Globac-Z *Zydus, India.*
Capsules: Ferrous fumarate (p. 2060·3); zinc sulfate (p. 2126·2); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron supplement.

Zydus, India.
Oral liquid: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Globamox *One Pharma, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Globantin *Zhuhai, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Globapen *GX, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Globaxol *GX, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Globazine *Shine, Philipp.*
Chlorpromazine hydrochloride (p. 1045·2).
Schizophrenia; bipolar disorder; behaviour disorders; hiccup; nausea and vomiting; tetanus; premedication.

Globazol *Jinling, Philipp.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Globel *Bennett, Gr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Globex Forte *Zee, India.*
Iron (p. 2073·1); protein; vitamin B substances (p. 2102·3); zinc (p. 2126·1).

Globifer *Medi-Rx, Philipp.*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).
Iron-deficiency anaemia.

Globifex *Mapra, India.*
⊗Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); haemoglobin (p. 1154·3).

Globin *Psyco Remedies, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy; dietary supplement.

Globiron *Aglowmed, India.*
Capsules: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Aglowmed, India.
Oral drops; syrup: Iron polymaltose (p. 2077·2).

Globiron-C *Aglowmed, India.*
Ascorbic acid (p. 2110·3); iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Globiron-Z *Aglowmed, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2).

Globitan *Vivax, Venez.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Globocef *Roche, Gr.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Globoid *Nycomed, Norw.*
Aspirin (p. 22·2).
Fever; pain; rheumatic disorders.

Globuce *Sigma-Tau, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Globuli *Knop, Canad.†*
A range of homoeopathic preparations.
Homoeopathic preparations.

Globuli gegen Fieber und Grippe Nr 1 *Jacoby, Austria.*
Ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Globuli gegen Fieber und Grippe Nr 2 *Jacoby, Austria.*
Atropa belladonna (p. 2453·3).
Homoeopathic preparation.

Globuli gegen Gelenkschmerzen *Jacoby, Austria.*
Acidum benzoicum (p. 1738·2); calcium phosphoricum (p. 1784·2); harpagophytum procumbens (p. 42·3).
Homoeopathic preparation.

Globuli gegen Grippe *Jacoby, Austria.*
Eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); influenzum (p. 2393·3); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Globuli gegen Halsweh Nr 1 *Jacoby, Austria.*
Guajacum officinale (p. 2523·1).
Homoeopathic preparation.

Globuli gegen Halsweh Nr 2 *Jacoby, Austria.*
Apis mellifica (p. 2445·2); atropa belladonna (p. 2453·3); lachesis mutus (p. 2538·3); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Globuli gegen Hautausschlage *Jacoby, Austria.*
Mercurius solubilis (p. 2555·3); natrium chloratum (p. 1795·1); rhus toxicodendron (p. 2603·3); selenium metallicum (p. 2086·3).
Homoeopathic preparation.

Globuli gegen Heiserkeit *Jacoby, Austria.*
Allium cepa (p. 2575·2); apis mellifica (p. 2445·2); verbascum thapsiforme (p. 2645·1).
Homoeopathic preparation.

Globuli gegen Husten Nr 1 *Jacoby, Austria.*
Drosera rotundifolia (p. 2497·2).
Homoeopathic preparation.

Globuli gegen Husten Nr 2 *Jacoby, Austria.*
Antimonium sulfuratum aurantiacum (p. 2445·1); kalium jodatum (p. 2336·3); senega (p. 1677·2).
Homoeopathic preparation.

Globuli gegen Husten Nr 3 *Jacoby, Austria.*
Pertussinum; spongia.
Homoeopathic preparation.

Globuli gegen Kopfschmerzen *Jacoby, Austria.*
Gelsemium sempervirens (p. 2511·2); hepar sulfuris (p. 1721·3); iris versicolor (p. 2534·3); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Globuli gegen Schlafstorungen *Jacoby, Austria.*
Avena sativa (p. 2451·1); hepar sulfuris (p. 1721·3); pulsatilla pratensis (p. 2600·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Globuli gegen Schnupfen Nr 1 *Jacoby, Austria.*
Allium cepa (p. 2575·2).
Homoeopathic preparation.

Globuli gegen Schnupfen Nr 2 *Jacoby, Austria.*
Luffa operculata (p. 2545·3).
Homoeopathic preparation.

Globuli gegen Schnupfen Nr 3 *Jacoby, Austria.*
Hydrargyrum sulfuratum rubrum (p. 2555·3); kalium bichromicum (p. 2476·3); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Globuli gegen Sonnenallergie *Jacoby, Austria.*
Fagopyrum esculentum (p. 2462·1); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Globuman *Faran, Gr.; Berna, Turk.†*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

Globuman Hepatite A *Faran, Gr.*
A hepatitis immunoglobulin (p. 2388·2).
Passive immunisation.

Glocal *Globus, India.*
Syrup: Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Globus, India.
Tablets: Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Glocef
Note: this name may be used for preparations of different composition.
Globus, India.
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Metiska, Indon.
Cefotaxime (p. 244·1).
Bacterial infections.

Glocef-CL *Globus, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Glocerin *Globus, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Glocid *Globus, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Glocip *Globus, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Glocip-TZ *Globus, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Gloclav *Global, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Glocure-Opta *Pascual, Philipp.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension and glaucoma following cataract surgery.

Glocyp *GMP, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic disorders.

Glodox-LB *Glories, India.*
Doxycycline (p. 288·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Gloeye *Sun, India.*
Myrtillus (p. 2566·2).

Glofil *Cypros, USA.*
Iodine-125 (p. 2225·2) as sodium iotalamate.
Evaluation of glomerular filtration rate.

Glofit Plus *Glories, India.*
Ginseng (p. 2513·3); vitamins; minerals.

Glofty *Globus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Glofty-D *Globus, India.*
⊗Ofloxacin (p. 334·3); dexamethasone (p. 1630·3).

Glofty-OZ *Globus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Glohar-C *Taurus, India.*
Folic acid (p. 2063·1); iron carbonyl (p. 2073·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Glohem TR *Medispan, India.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); zinc sulfate (p. 2126·2).

Glomec *Glories, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Glomec Plus *Glories, India.*
Vitamin B substances (p. 2102·3).

Glomeson *Metiska, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Glomethyl *Metiska, Indon.*
Methylergometrine maleate (p. 2137·3).
Uterine haemorrhage.

Glomika *Globus, India.*
Amikacin (p. 214·1).
Bacterial infections.

Glomox-C *Global, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Glonoinum
Note: this name may be used for preparations of different composition.
Boiron, Cz.
Glyceroli trinitras (p. 1391·2).
Homoeopathic preparation.

Glopan *Globus, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Glopan-D *Globus, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Glopenel *IWA, Denm.; Aurora, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis; myocardial infarction; ischaemic stroke; peripheral arterial disease.

Glophyllin *Global, India.*
Etofylline (p. 1208·2); theophylline (p. 1229·3).

Glopir *Gap, Gr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Glopisine *Pharmanel, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Gloriax *Glories, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Gloriax-SB *Glories, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).

Glorixone *Medicus, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Glormin *Siomond, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gloros *New Research, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Glortho Forte *Finecure, India.*
Glucosamine sulfate (p. 2515·3); manganese sulfate (p. 2081·2); selenium dioxide (p. 2087·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Glory *Ethix, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Gloryfen *Help, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Gloryskin *Pharmacon, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Glosilex *Aglowmed, India.*
Chlorhexidine gluconate (p. 1743·3); sulfadiazine silver (p. 362·3).

Glosone *Synmedic, India.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Glossaliv *Sigma, Braz.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); zinc oxide (p. 1729·1); dogfish liver oil.
Skin disorders.

Glossderm *Columbia, Mex.*
Cod-liver oil (p. 2056·3); benzalkonium chloride (p. 1737·1); zinc oxide (p. 1729·1); allantoin (p. 1693·1).
Nappy rash.

Glossithiase *Jolly-Jatel, Fr.*
Thenoate monoethanolamine (p. 376·3); muramidase hydrochloride (p. 2565·1).
Infections of the mouth and throat.

Glossyfin *Doctum, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Glotron *Glories, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Glottyl *Meda, Belg.*
Syrup: Codeine phosphate (p. 40·2).
Cough.

Glovan *Teva, Israel.*
Nonoxinol 9 (p. 2199·1); ricinoleic acid (p. 2604·3).
Contraceptive.

Glovax *BB-NCIPD, Philipp.*
A BCG vaccine (p. 2378·1).
Active immunisation.

Glove Me *Bath & Body Works, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Glovules *Mandar, India.*
Capsules: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Mandar, India.
Syrup: Vitamin B substances (p. 2102·3).

Glovules-LB *Mandar, India.*
Vitamin B substances (p. 2102·3); lactobacillus (p. 2596·3).

Glow *Mega Lifesciences, Malaysia.*
Marine protein; silica; green tea (p. 2648·2); lemon bioflavonoids; hydrolysed collagen; vitamin C (p. 2110·3); lycopene (p. 2546·2); grape (p. 2521·3); vitamin E (p. 2119·1).
Dietary supplement.

Mega Lifesciences, Singapore.
Marine protein; silica (p. 2208·3); green tea (p. 2648·2); lemon bioflavonoids (p. 2505·2); hydrolysed collagen (p. 2483·2); vitamin C (p. 2110·3); lycopene (p. 2546·2); grape (p. 2521·3); dunaliella salina; pine bark (p. 2590·3); vitamin E (p. 2119·1).
Dietary supplement.

Glow Face *Prime Enterprises, Canad.*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Glow and Steady *Bath & Body Works, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Glowcarb *Candor, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Candor, India.
Oral liquid: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Glowcarb-Z *Candor, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Glowone *Aglowmed, India.*
Asparagus racemosus (p. 2614·2); piper longum; ashwagandha (p. 2450·2).

Gloww *Mega Lifesciences, Philipp.*
Marine protein; green tea (p. 2648·2); lemon bioflavonoids (p. 2505·2); hydrolysed collagen (p. 2483·2); vitamin C (p. 2110·3); lycopene (p. 2546·2); grape (p. 2521·3); dunaliella salina; pine bark (p. 2590·3); *d*-alpha tocoferil acetate (p. 2119·1); equisetum (p. 2500·1).
Dietary supplement.

Glozy *Zodley, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Glozyme *Globus, India.*
Oral drops: ⊗Amylase (p. 2442·1); papain (p. 2582·3).

Globus, India.
Syrup: Vitamins; minerals.

GLP *Intra-Labs, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

GLP-M *Intra-Labs, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

GLP-PM *Intra-Labs, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Gluban *Vendiz, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gluben *Dexcel, Israel.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glubes *Kissei, Jpn.*
Mitiglinide calcium (p. 492·1); voglibose (p. 505·3).
Diabetes mellitus.

Glubex-Z *Vensat, India.*
Syrup: Glutamic acid (p. 2070·2); vitamin B substances (p. 2102·3); zinc (p. 2126·1).

Vensat, India.
Tablets: Glutamic acid (p. 2070·2); minerals; vitamin B substances (p. 2102·3); zinc (p. 2126·1).

Glubitor *Imperial, Philipp.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glubose *Aristo, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glubosil *Silom, Thai.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glubrava *Takeda, Cz.; Takeda, Irl.; Takeda, Neth.; Takeda, Pol.; Takeda, Port.; Takeda, Spain.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucadol *Leiras, Fin.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis of the knee.

GlucaGen *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Canad.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Abbott, India; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Novo Nordisk, Neth.; Novo Nordisk, NZ; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Switz.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, Ukr.; Bedford, USA; Novo Nordisk, USA.*
Glucagon hydrochloride (p. 1553·3).
Hypoglycaemia; aid in gastrointestinal examination; assessment of beta-cell secretion; beta-blocker poisoning.

Glucal *Probiomed, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

SA Druggists Self Med, S.Afr.†
Calcium gluconate (p. 1783·3).
Calcium deficiency; calcium supplement.

Glucal B12 *Arrow, Braz.†*
Cyanocobalamin (p. 2107·2); colecalciferol (p. 2113·1); minerals; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Glucalbott Rth *Abbott, Chile.*
Preparation for enteral nutrition in diabetes mellitus.

Glucalcium *Renaudin, Fr.†*
Calcium gluconate (p. 1783·3); calcium gluceptate (p. 1783·2).
Hypocalcaemia.

Glucaminol *Roche, Arg.; Roche, Venez.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucan 5 *Fortune Star, Indon.*
Ganoderma lucidum; Hericium erinaceum; Grifola frondosa; Phellinus linteus; Agaricus blazeii murill.
Immunomodulator; antioxidant; malignant neoplasms.

Glucanet *DMG, Ital.*
Glucan (p. 2455·2).
Nasal cleansing.

Glucanoos *DMG, Ital.*
Glucan (p. 2455·2); vitamins; zinc oxide (p. 1729·1).

Glucantime *Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Spain; Sanofi-Aventis, Venez.*
Meglumine antimonate (p. 926·3).
Leishmaniasis.

Glucar *Glenmark, India; Glenmark, Malaysia; Kocak, Turk.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glucardiamid *GSK, Pol.*
⊗Glucose (p. 2068·3); nikethamide (p. 2328·2).
Hypotension; tonic.

Glucare *IAE, Philipp.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucaron *Chugai, Jpn.*
Aceglatone (p. 735·2).
Bladder cancer.

Glucart *Juggat, India; Shou Chan, Philipp.*
Glucosamine sulfate (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Glucarthroz *Bryssica, Fr.*
Glucosamine sulfate (p. 2515·3); black currant leaf (p. 2458·1).
Dietary supplement; joint disorders.

Glucasulf *Kleva, Gr.*
Glucosamine sulfate (p. 2515·3).

Gluceride *Klonal, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glucerna *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, China; Abbott, Cz.; Abbott, Hong Kong; Abbott, India; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott Nutrition, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott, Venez.*
Preparation for enteral nutrition.
Glucose intolerance.

Abbott, USA.
A range of preparations for enteral nutrition.
Glucose intolerance.

Glucid *Utopian, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucidion *Braun, Fr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Fluid and electrolyte disorders.

Glucidoral *Servier, Fr.†*
Carbutamide (p. 469·3).
Diabetes mellitus.

Glucino *Pharmahof, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucion *Baxter, Belg.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Glucitol *Flupal, Venez.*
Loperamide (p. 1854·2).
Diarrhoea.

Gluco *Masa, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluco Arrumalon *Sidus, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Joint disorders.

Gluco Arrumalon Duo *Sidus, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Gluco Support *Eagle, Austral.*
Gymnema silvestre; cinnamon (p. 2479·2); chromium chloride (p. 2055·3); chromium picolinate (p. 2056·1); thioctic acid (p. 2629·1); magnesium amino acid chelate (p. 2048·3); zinc amino acid chelate (p. 2048·3); biotin (p. 2052·2); colecalciferol (p. 2113·1).
Disorders of glucose metabolism.

Glucoact *Active, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucoact-M *Active, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glucobay *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer, India; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.; Centrofarma, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, Ukr.†; Bayer, Venez.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glucobefol *Biotenk, Arg.†*
Glucosamine sulfate (p. 2515·3); boswellia (p. 2507·3); zinc (p. 2126·1); copper (p. 2057·1); manganese (p. 2081·2).
Joint disorders.

Glucobene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glucobion *Merck, Indon.*
Vitamins; trace elements.
Nutritional supplement in diabetes mellitus.

Glucobloc *Epifarma, Ital.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucobon *Biomo, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucobose *Medley, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glucocal *Beacons, Singapore.*
Glucosamine sulfate (p. 2515·3); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement for healthy bones, cartilage, and teeth.

Gluco-Calcium
Note: this name may be used for preparations of different composition.
Aspen, Thai.
Calcium (p. 1783·1); glucose (p. 2068·3).
Hypocalcaemia.

Glucocard *Menarini, Ital.; Menarini Diagnostics, Port.†*
Test for glucose in blood (p. 2516·3).

Glucocartiflex *ISA, Arg.*
Glucosamine sulfate (p. 2515·3); vitamin B_{12} (p. 2107·2).
Joint disorders.

Glucocemin *Braun, Spain.*
Glucose monohydrate (p. 2069·1).
Hypoglycaemia.

Glucocron *Farmaline, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucodex
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Gliclazide (p. 472·3).
Diabetes mellitus.

Teva, Canad.
Glucose (p. 2068·3).
Oral glucose tolerance test.

Glucodiab *Bangkok Lab & Cosmetic, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glucodisc *Bayer, Port.*
Test for glucose in blood (p. 2516·3).

Glucodown *Hanall, Hong Kong.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucofage *Merck, Venez.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucoferro *Guidotti, Ital.*
Ferrous gluconate (p. 2061·2).
Iron deficiency; iron-deficiency anaemias.

Glucoferro K *Knop, Chile.*
Ferrous gluconate (p. 2061·2).
Iron deficiency; iron deficiency anaemia.

Glucofilm *Bayer, USA.*
Test for glucose in blood (p. 2516·3).

Glucofit *Raptakos, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucofit-M *Raptakos, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucofleks *Disphar, Neth.†*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis of the knee.

Glucoflex-R *National Diagnostic, Austral.; Ambe Medical, UK.*
Test for glucose in blood (p. 2516·3).

Glucofor *Soho, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucoform *Vendiz, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucoformin *Novo Nordisk, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucofree *Farmasyn, Gr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

GlucoGel *BBI, UK.*
Glucose (p. 2068·3).
Hypoglycaemia.

Glucogood *Denver, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucogyl *Mount Mettur, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Glucohexal *Sandoz, Austral.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluco-K *Lafedar, Arg.*
Potassium gluconate (p. 1793·2).
Potassium supplement.

Glucoles *T Man, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucolin *GSK, Arg.*
Glucose monohydrate (p. 2069·1).
Dietary supplement.

Glucolip *Wallace, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glucolon *Generfarma, Spain.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glucolyte
Note: this name may be used for preparations of different composition.
Pascual, Philipp.
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); magnesium gluconate (p. 1787·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration; diarrhoea.

Sintetica-Bioren, Switz.
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Electrolyte and fluid disorders; carbohydrate source.

Yik Kwan, Hong Kong†; Thai Otsuka, Thai.
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

TO-Chemicals, Thai.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucomade *Purewin, India.*
Glucosamine sulfate (p. 2515·3); manganese sulfate (p. 2081·2).

Glucomade-500 *Purewin, India.*
Calcium carbonate (p. 1824·3); glucosamine sulfate (p. 2515·3).

Glucoman *Volchem, Ital.*
Dietary fibre; glucomannan (p. 2515·2); galactomannan (p. 2508·3); minerals.
Disorders of carbohydrate and lipid metabolism; gastrointestinal disorders; obesity.

Glucomed
Note: this name may be used for preparations of different composition.
Expanscience, Denm.†; Expanscience, Neth.; Expanscience, Port.; Merck, Spain†; Vitaflo, Swed.
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Medlink, Philipp.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucomen *Menarini Diagnostics, Fr.†; Menarini, Irl.†; Menarini Diagnostics, UK.*
Test system for measuring glucose in blood (p. 2516·3).

Glucomerck *Merck, Cz.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucomet
Note: this name may be used for preparations of different composition.
Eris, Austral.; Aristopharma, Hong Kong; YSP, Malaysia; Douglas, NZ; Yung Shin, Singapore.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Chemopharma, Chile.
Glimepiride (p. 473·2).
Diabetes mellitus.

Glucometer Elite *Bayer Diagnostics, Irl.†*
Test for glucose in blood (p. 2516·3).

Glucometil 3 *Empresa de Nutricion, Arg.*
Glucosamine (p. 2515·3); chondroitin (p. 2476·1); dimethyl sulfone (p. 2493·3).
Dietary supplement.

Glucometil K *Empresa de Nutricion, Arg.*
Glucosamine (p. 2515·3).
Dietary supplement.

Glucometil K Duo *Empresa de Nutricion, Arg.*
Glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3).
Dietary supplement.

Glucometil Plus *Empresa de Nutricion, Arg.*
Glucosamine (p. 2515·3); calcium (p. 1783·1).
Dietary supplement.

Glucomide *Merck, Ital.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glucomin *Vickmans, Hong Kong†; Dexcel, Israel.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucomin-Plus *Hy-Gro, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Glucomol *Allergan, India.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Glucomore *Hayes, Israel.*
Glucose polymers.
High-calorie supplement.

Glucompet *ACOM, Ital.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide agent for positron emission tomography.

Glucon *Avex, Malaysia.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluconase *Therapharma, Philipp.*
Acarbose (p. 466·2).
Diabetes mellitus.

Gluconeodesum *Biochimic, Rus.*
Povidone (p. 2204·3); glucose (p. 2068·3).
Gastrointestinal infections; liver disorders; sepsis.

Gluconic *Nicholas, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gluconil
Note: this name may be used for preparations of different composition.
Bal, India; Utopian, Thai.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Biolab, Philipp.
Gliclazide (p. 472·3).
Diabetes mellitus.

Gluconil-M *Bal, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucono *Pharmahof, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluconol *Lafi, Chile.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Gluconorm *Ranbaxy, S.Afr.*
Metformin (p. 489·1).
Diabetes mellitus.

Lupin, India.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Farmstandart, Rus.
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Roche, Braz.†; Novo Nordisk, Canad.
Repaglinide (p. 495·2).
Diabetes mellitus.

Gluconorm-G *Lupin, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluconorm-P *Lupin, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Gluconox *Deltapharm, Hong Kong†; Charoen, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucontrol *GX, Philipp.*
Karela; pycnogenol (p. 2590·3); lagerstroemia speciosa; chromium tripicolinate (p. 2056·1).
Dietary supplement for diabetics.

Glucophage *Merck Serono, Arg.; Alphapharm, Austral.; Merck, Austria; Merck, Belg.; Sanofi-Aventis, Canad.; Roche, Chile; BMS, China; Merck, Cz.; Merck Sante, Denm.†; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Petsiavas (Πετσιαβας), Gr.; Merck, Hong Kong; Merck, Indon.; Merck Serono, Irl.; Abic, Israel; Merck Serono, Ital.; Merck Serono, Malaysia; Syntex, Mex.; Merck, Neth.†; Merck, Norw.; Merck, Philipp.; Merck Sante, Pol.; Merck, Port.; Nycomed, Rus.; Merck, S. Afr.; Merck, Singapore; Merck, Swed.; Merck, Switz.; Merck, Thai.; Merck, Turk.; Merck, UK; Nycomed, Ukr.; BMS, USA.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucopirida *Biotenk, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glucoplasmal *Braun, Austria†; Braun, Ger.†*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Glucoplex
Note: this name may be used for preparations of different composition.
Douglas, Canad.
Biotin (p. 2052·2); chromium chelate (p. 2055·3); thiamine hydrochloride (p. 2103·1).

Glucoplus *Farmasyn, Gr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucopolielectrol *Baxter, Spain.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Glucopres *Metrolink, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucoprime *Interhealthcare, Philipp.†; Sunward, Philipp.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucoptic *Klar Sehen, India.*
⊗Betaxolol (p. 1322·3).
Ocular hypertension; glaucoma.

Glucor *Bayer, Fr.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glucored
Note: this name may be used for preparations of different composition.
Coronet, Indon.
Gliclazide (p. 472·3).
Diabetes mellitus.

Sun, India.
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucoreumin *Zambon, Braz.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Glucorich *Intra-Labs, India.*
Ascorbic acid (p. 2110·3); glucose (p. 2068·3); zinc sulfate (p. 2126·2).

Glucorid *CCM, Malaysia.*
Acarbose (p. 466·2).
Diabetes mellitus.

Gluco-Rite *Perrigo, Israel.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glucorix *Alternova, Fin.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

GlucoRos *Rossendorf, Cz.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide agent for positron-emission tomography.

Glucoryl *Alkem, India; Bernofarm, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gluco-S *MD, Singapore; Standard Chem & Pharm, Thai.*
Glucosamine sulfate (p. 2515·3).
Joint and cartilage disorders.

Glucosa *Bangkok Lab & Cosmetic, Thai.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Glucosada *Grifols, Port.*
Glucose (p. 2069·1).
Carbohydrate source; fluid depletion.

Glucosado *Braun, Port.*
Glucose (p. 2069·1).
Carbohydrate source; fluid depletion.

Glucosafe *Sun, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glucosalin *Baxter, Switz.; Bioren, Switz.*
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; carbohydrate source.

Glucosalina *Braun, Spain; Fresenius Kabi, Spain; Grifols, Spain.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Glucosaline *ACS Dobfar, Switz.; Braun, Switz.*
Anhydrous glucose (p. 2069·1) or glucose monohydrate (p. 2069·1); sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; carbohydrate source.

Glucosalino *Braun, Port.*
Sodium chloride (p. 1795·1); glucose (p. 2069·1).
Fluid and electrolyte depletion.

Braun, Spain; Physan, Spain; Tecsolpar, Spain.
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte depletion.

Glucosam *East West, India.*
Glucosamine sulfate (p. 2515·3).
Rheumatoid arthritis; osteoarthritis.

Glucosamate *Kenyaku, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

GlucOsamax *Health Perception, UK.*
Tablet 1, dimethyl sulfone (p. 2493·3); rose fruit (p. 2607·1); omega-3 (p. 1460·1); tablet 2, glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Glucosamil *Verisfield, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Glucosamina Sport *Lafarmen, Arg.*
Glucosamine (p. 2515·3); magnesium lactate (p. 1787·2); vitamin B_{12} (p. 2107·2).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Glucoscan *Lifescan, Ital.*
Test for glucose in blood (p. 2516·3).

Glucose-D *Ind-Swift, India.*
Calcium (p. 1783·1); glucose monohydrate (p. 2069·1); phosphorus (p. 2589·2); vitamin D (p. 2112·3).

GlucoSelene *Wassen, UK.*
Glucosamine sulfate (p. 2515·3); selenium (p. 2086·3); vitamins.

Glucosine *Recip, Fin.; Recip, Port.; Recip, Swed.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Glucosmon *Nycomed, Spain.†*
Glucose (p. 2068·3).
Hypoglycaemia; carbohydrate source.

Glucost *Pascual, Philipp.*
Sodium (p. 1795·1); potassium (p. 1793·1); chloride; citrate; glucose (p. 2068·3) (p. 1780·1).
Oral rehydration.

Glucostabil *Gedeon Richter, Denm.; Gedeon Richter, Rus.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucosteril *Baxter, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.*
Glucose monohydrate (p. 2069·1).
Fluid depletion; carbohydrate source; hypoglycaemia.

Glucostix *Bayer Consumer, Arg.; Bayer, Austral.; Bayer Diagnostics, Irl.†; Bayer, Port.†; Bayer, USA.*
Test for glucose in blood (p. 2516·3).

Glucotec *Maver, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glucotec S *Maver, Mex.*
Metformin (p. 489·1).
Diabetes mellitus.

Glucotem *Temis, Arg.*
Glucose monohydrate (p. 2069·1).
Hypoglycaemia.

Glucotep *Cyclopharma, Fr.*
Fluorine-18 (p. 2224·1) labelled fludeoxyglucose.

Glucotide *Bayer Diagnostics, Irl.†*
Test for glucose in blood (p. 2516·3).

Glucotika *Ikapharmindo, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucotim *Centaur, India.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Glucotrac Plus *Intra-Labs, India.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucotrace *MDS, Belg.; Best Medical, Neth.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Contrast agent for positron-emission tomography.

Glucotrend *Roche Diagnostics, Austral.†*
Test for glucose in blood (p. 2516·3).

Glucotril *Macrophar, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis of the knee.

Glucotrin Flex *Elea, Arg.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Degenerative joint disorders.

Glucotrin Forte *Elea, Arg.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Glucotrin Pro-Flex *Elea, Arg.*
Glucosamine hydrochloride (p. 2515·3).
Degenerative joint disorders.

Glucotrin VL *Elea, Arg.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Glucotrol *Pfizer, China; Pfizer, Hong Kong; Jenburkt, India; Pfizer, Indon.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Turk.; Pfizer, USA.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glucotrol MF *Jenburkt, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Glucovance *Merck Serono, Arg.; Alphapharm, Austral.; Merck, Belg.; Merck, Braz.; Merck, Chile; Merck, Cz.; Merck Serono, Fr.; Merck, Hong Kong; Merck, Indon.; Merck Serono, Malaysia; Merck, Mex.; Merck, Neth.; Merck, Philipp.; Merck, Pol.; Merck, Port.; Nycomed, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Switz.; Merck, Thai.; Merck, Turk.; Merck, Ukr.; BMS, USA; Merck, Venez.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glucoven
Note: this name may be used for preparations of different composition.
Chinoin, Mex.
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glucoven infant
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Ger.†
Carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Glucovit Plus *Zee, India.*
Calcium (p. 1783·1); glucosamine (p. 2515·3); manganese (p. 2081·2); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); vitamin E (p. 2119·1).

Glucozant *Vivax, Gr.*
Glucosamine sulfate (p. 2515·3).

Glucozid *Medley, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucozide *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucozid-M *Medley, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glucozone *Vitalink, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Gluctam *Egis, Hung.; Egis, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glucut *Overseas, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glucut-GMP *Overseas, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glucut-MT *Overseas, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Gludase *Alkem, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

Gludel *Alna, India.*
Zinc gluconate (p. 2126·2).

Gludepatic *Fahrenheit, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gludex *Montpellier, Arg.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Gludex Plus *Montpellier, Arg.*
Rosiglitazone maleate (p. 496·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gludiase *Kyowa, Jpn.†*
Glybuzole (p. 474·3).
Diabetes mellitus.

Gludibit *Lupin, India.*
Lemon (p. 2542·3); gymnema silvestre.

Gludin *MedChoice, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gludon *Merck, Port.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glufan *Rovi, Port.; Rovi, Spain.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Glufast *Eisai, China; Kissei, China; Kissei, Jpn; Eisai, Thai.*
Mitiglinide calcium (p. 492·1).
Diabetes mellitus.

Glufer-C *Nakornpatana, Thai.†*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Glufit *Ind-Swift, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Glufor *Pyridam, Indon.; CTI, Israel.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluformin *Pliva, Cz.†; Pliva Krakow, Pol.; Condrugs, Thai.†; Eras, Turk.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Piramal, India.
Metformin (p. 489·1).
Diabetes mellitus.

Gluformin G *Piramal, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glugenmin *GeneralDrugs, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glugon
Note: this name may be used for preparations of different composition.
KB, Thai.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

United Biotech, India.
Glucagon (p. 1553·3).
Hypoglycaemia; diagnostic aid.

Glukacel *Braun, Norw.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Glukaut *Sanitas, Chile.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glukenil *Lazar, Arg.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Gluketur Test *Sanofi-Aventis, India.*
Test for glucose and ketones in urine.

Glukofen *Sandoz, Turk.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glukolos *Sanbe, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glukonak *Baxter, Swed.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium acetate (p. 1781·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Fluid and electrolyte disorders; carbohydrate source.

Glukos-El *Braun, Swed.*
Carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Glukosel *Braun, Denm.*
Electrolyte infusion with glucose (p. 1775·1).
Fluid and electrolyte disorders; carbohydrate source.

Glukotral *Velka, Gr.*
Glucosamine sulfate (p. 2515·3).

Glulo *Eisai, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glumal *Kyowa, Jpn.*
Aceglutamide aluminium (p. 1814·3).
Peptic ulcer.

Glumedex *Shin Poong, Rus.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glumesa *Pharmasant, Thai.*
Glucosamine (p. 2515·3).

Glumet *Pharmaniaga, Hong Kong; Cipla, India; Pharmaniaga, Malaysia; Imperial, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glumetsan *ProMed, Cz.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glumetza *Valeant, Canad.; Santarus, USA.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glumida *Esteve, Spain.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glumikron *Santa, Turk.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glumin *Ferron, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluminal *Vocate, Gr.*
Glucosamine sulfate (p. 2515·3).

Glunarot *Sanus, Gr.*
Glucosamine sulfate (p. 2515·3).

Glunil *Medopharm, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gluniro *Serra Pamies, Spain.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Glunor *Kalbe, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glunovag *Novag, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glunovag G *Novag, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Glu-Phos *SPA, Ital.*
Disodium glucose-1-phosphate (p. 2070·2).
Glucose deficiency.

Glupozide *APT, Hong Kong.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glupropan *Pisa, Mex.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glurenor *Guidotti, Ital.; Milo, Spain; Menarini, Thai.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Glurenorm *Boehringer Ingelheim, Austria; Menarini, Belg.; Zentiva, Cz.; Astellas, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Rus.; Eczacibasi, Turk.; Boehringer Ingelheim, Ukr.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Glurib *Sarabhai Piramal, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glurib-M *Sarabhai Piramal, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glusa *Sriprasit, Thai.†*
Glucosamine sulfate potassium chloride (p. 2515·3) or glucosamine sulfate sodium chloride (p. 2515·3).
Degenerative joint disorders.

Glusafe *Promed, Indon.*
Touchi extract.
Diabetes mellitus.

Glusafex *Nupharma, Thai.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Degenerative joint disorders.

Glusamin *FMC Pharma, Irl.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Glusamine *Meiji, Thai.†*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Glusamon *Farmedia, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Glusartel *HFA Healthcare, UK.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Gluscan *AAA, Fr.; AAA, Spain.*
Fluorine-18 (p. 2224·1) labelled fludeoxyglucose.
Radionuclide agent for positron emission tomography.

Glusina *Baldacci, Port.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Gluspan *Piramal, India.*
Vitamins; minerals.

Glustar *Galeno, Venez.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Glustin *Takeda, Cz.; Takeda, Irl.; Takeda, Neth.; Takeda, Pol.; Takeda, Port.; Takeda, Spain.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Glustress *Charoon Bhesaj, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gluta *Oriental, Philipp.*
Glutathione (p. 1555·2).
Reduction of cisplatin toxicity.

Glutabasal *Leti, Venez.*
Amino acids; vitamin B substances (p. 2102·3); minerals; glucose (p. 2068·3).
Tonic.

Glutabloc *Umeda, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glutacalcio *Biofarma, Mex.*
Glutamic acid (p. 2070·2); calcium (p. 1783·1); thiamine (p. 2102·3).
Dietary supplement.

Gluta-calcium *Medichrom, Gr.*
Calcium carbonate (p. 1824·3); calcium lactate (p. 1784·1); vitamin C (p. 2110·3).
Osteoporosis; pregnancy; breast-feeding.

Glutacyl Vitaminado *Sanitas, Chile.*
Monosodium glutamate (p. 2198·2); pyridoxine hydrochloride (p. 2105·3); glutamic acid (p. 2070·2).
Mental function impairment.

Glutaferro *Medix, Spain.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency.

Glutafin *Nutricia Dietary, UK.*
Gluten-free food for special diets.

Schar, Ital.
Gluten-free foods for special diets.

Nutricia, Irl.†
A range of gluten-free foods.
Gluten-sensitive enteropathy.

Glutafora *SKL, Braz.*
Glutamine (p. 2070·3).

Glutafos C *Carnot, Mex.†*
Vitamins; minerals.

Glutahyde *GPO, Thai.*
Glutaral (p. 1753·2).

Glutallen *Allen, Mex.*
Vitamins; minerals.

Glutamate BCG *Japan BCG, Malaysia.*
A BCG vaccine (p. 2378·1).
Active immunisation.

Glutamevit *Marbiopharm, Rus.*
Vitamins; minerals; rutoside (p. 2505·3).
Tonic.

Glutamin *Verla, Ger.*
Glutamic acid (p. 2070·2).
Tonic.

Glutamin Fosforo *SIT, Ital.*
Glutamine (p. 2070·3); DL-phosphoserine (p. 2589·1); cyanocobalamin (p. 2107·2).
Tonic.

Glutamine Plus *Fresenius Kabi, Singapore.*
Glutamine (p. 2070·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1); vitamin C (p. 2110·3); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement.

Glutammune *Claris, India.*
Aspartame (p. 2169·2); glutamine (p. 2070·3).

Glutamol *Demo, Gr.*
Alanyl-glutamine (p. 2070·2).
Parenteral nutrition.

Glutapak *Victus, Venez.*
Glutamine (p. 2070·3); maltodextrin (p. 2080·3).
Glutamine supplement.

Glutapak-R *Victus, Venez.*
Glutamine (p. 2070·3); maltodextrin (p. 2080·3); *Lactobacillus reuteri* (p. 2596·3).
Diarrhoea; malabsorption.

Glutaphos *Pascual, Philipp.*
Calcium hydrogen phosphate (p. 1783·3); glutamic acid (p. 2070·2); thiamine hydrochloride (p. 2103·1); vitamin B_{12} (p. 2107·2).
Mental function stimulant.

Glutarex *Ross, USA.*
A range of lysine- and tryptophan-free preparations for enteral nutrition including an infant feed.
Glutaric aciduria type I.

Glutargin *Zdorovje, Rus.; Zdorovje, Ukr.*
Arginine glutamate (p. 2049·1).
Liver disorders.

Glutarol *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Glutaral (p. 1753·2).
Warts.

Glutarsin E *Berlin-Chemie, Hung.*
Glutamic acid (p. 2070·2); arginine hydrochloride (p. 2049·1); electrolytes (p. 1775·1).
Hyperammonaemia.

Glutasey *Alacan, Spain.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Glutasorb *Hormel, Hong Kong.†*
A glutamine-rich preparation for enteral nutrition.

Glutasoz *Sozin-Flora, India.*
Glutathione (p. 1555·2).

Glutathin *Mochida, Jpn.†*
Glutathione (p. 1555·2).
Liver disorders.

Glu-tathion *Kyorin, Hong Kong.*
Glutathione (p. 1555·2).
Drug poisoning; liver disorders; leucopenia; hypertension of pregnancy; hypersensitivity reactions; skin pigmentation disorders; dyspepsia in children.

Glutaven *Teofarma, Ital.*
Glutamine (p. 2070·3).
Mental function impairment.

Glutavigon *Delta, Braz.*
Calcium phosphate (p. 1784·2); calcium glycerophosphate (p. 1783·3); glutamic acid (p. 2070·2); vitamin B substances (p. 2102·3).

Glutazene *Tablets, India.*
Azulene (p. 2452·1); glutamic acid (p. 2070·2).

Gluthion *CT, China.*
Reduced glutathione sodium.
Adjuvant to chemotherapy-induced and radiotherapy-induced toxicity; adjuvant therapy in liver damage.

CT, Ital.
Reduced glutathione sodium (p. 1555·2).
Drug poisoning; adverse effects in radiotherapy.

Gluti-Agil mono
Note: this name may be used for preparations of different composition.
Riemser, Ger.
Glutamic acid (p. 2070·2).
Tonic.

Glutide *Lupin, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glutihyde *Piramal, India.*
Glutaral (p. 1753·2).

Glutilage *Beacons, Singapore.*
Glucosamine sulfate (p. 2515·3).
Joint and cartilage disorders.

Glutilage Plus *Beacons, Singapore.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint and cartilage disorders.

Glutin *Bactolac, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3).

Glutofac *Kenwood, Hong Kong; Kenwood, USA.†*
Vitamins; minerals.

Gluton *Indo French, India.*
Capsules: Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Indo French, India.
Injection: Glutathione (p. 1555·2).

Glutose *Paddock, USA.*
Glucose (p. 2069·1).
Hypoglycaemia.

Glutowin Forte *Micro, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Glutoxim *Vam, Rus.*
Glutathione disodium (p. 1555·2).
Immunodeficiency; ionising radiation trauma; hepatitis B and C; viral infections; tuberculosis; urinary-tract disorders.

Glutril *ICN, Austria†; Meda, Fr.†; Meda, Switz.; Onko, Turk.*
Glibornuride (p. 472·3).
Diabetes mellitus.

Glutrol *Purzer, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glutrop *Tropica Mas, Indon.*
L-glutamine (p. 2070·3).
Dietary supplement for immunocompromised patients.

Gluvas *Dexa, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gluvedus *Pharma Line, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Gluxine *Recip, Norw.†*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis.

Gluxson *Sons, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Gluxyl *Yuri, Ukr.*
Glucose (p. 2068·3); xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition; correction of acid-base balance.

Gluzo *Pharmasant, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gluzolyte *Pharmasant, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gly Care
Note: this name may be used for preparations of different composition.
Kafetzis, Gr.
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Gly Thymol *DHA, Hong Kong.*
⊗Glycerol (p. 2517·2); methyl salicylate (p. 92·1); thymol (p. 1772·2); menthol (p. 2553·2); borax (p. 2459·2); sodium salicylate (p. 132·2); sodium benzoate (p. 1738·2).
Oral hygiene; sore throat; aphthous ulcer.

Glyade *Alphapharm, Austral.; LCH, Hong Kong†; Alphapharm, Malaysia; Merck, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyaha *Shalaks, India.*
Glycolic acid (p. 1704·3).
Acne.

Glyaha-HQ *Shalaks, India.*
Glycolic acid (p. 1704·3); hydroquinone (p. 1705·1).

Glyaha-HQSP *Shalaks, India.*
Glycolic acid (p. 1704·3); hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).

Glyaha-KOJ *Shalaks, India.*
Glycolic acid (p. 1704·3); hydroquinone (p. 1705·1); kojic acid (p. 1710·2).

Glyaha-VIT *Shalaks, India.*
Glycolic acid (p. 1704·3); vitamin A palmitate (p. 2098·3).

Glyamid *Actavis, Indon.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glybera *UniQure, Neth.*
Alipogene tiparvovec (p. 2434·2).
Familial lipoprotein lipase deficiency.

Glybofen *Liptis, USA.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Glyboral *USV, India.*
Covers Glyboral and Glyboral Semi:
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glybotic *Sanbe, Indon.*
Amikacin (p. 214·1).
Bacterial infections.

Glybovin *Aristo, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glyca *Varun, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glycafor *Actavis, Indon.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glycal-A *Globus, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Glycard-M *Cipla, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glycare
Note: this name may be used for preparations of different composition.
Roi Surya, Indon.†
Glycolic acid (p. 1704·3).
Skin ageing.

Glycasia-MF *Willow, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glycate *Nuro, USA.*
Glycopyrronium bromide (p. 2519·3).
Peptic ulcer.

Glycediab *Community Pharmacy, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glycefort *Farmex, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Glycelax *Casen Fleet, Port.; Mosfarma, Rus.*
⊗Glycerol (p. 2517·2).
Constipation.

Glycemin
Note: this name may be used for preparations of different composition.
Professional Health, Canad.†
Vitamins; minerals.

Siam Bheasach, Thai.†
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Glyceol *Chugai, Hong Kong; Chugai, Jpn; Siam Bheasach, Thai.*
⊗Glycerol (p. 2517·2) with fructose and sodium chloride.
Cerebral oedema; raised intracranial pressure; ocular hypertension.

Glycepure *Vegemedica, Fr.*
Cinnamon (p. 2479·2); myrtillus (p. 2566·2); marigold (p. 2465·2); minerals; vitamin B substances (p. 2102·3).
Dietary supplement; blood-sugar control.

Glycerdex *Arjun, UK.*
⊗Glucose (p. 2068·3); glycerol (p. 2517·2).
Nasal dryness.

Glycerin of Borax *Srichand, Thai.*
Borax (p. 2459·2).

Glycerine Thymol Co *Universal, Hong Kong.†*
Eucalyptus (p. 2501·1); menthol (p. 2553·2); sodium salicylate (p. 132·2); thymol (p. 1772·2).

Glycerosteril *Fresenius Kabi, Ger.; Fresenius Kabi, Thai.*
⊗Glycerol (p. 2517·2).
Cerebral oedema.

Glyceryl-T *Rugby, USA.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Bronchospasm.

Glychek *Indoco, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glychek-M *Indoco, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glycicon Mod *Aristo, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glycifer *Nycomed, Denm.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency.

Glycigon *Aristo, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Glycigon-M *Aristo, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glycilax *Engelhard, Ger.*
⊗Glycerol (p. 2517·2).
Constipation.

Glycine-Tur *Thai Otsuka, Thai.*
Glycine (p. 2071·2).
Bladder irrigation in transurethral prostatic resection.

Glycinorm *Ipca, India; Ipca, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glycinorm M *Ipca, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glyciphage *Franco-Indian, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glyciphage PG *Franco-Indian, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glyciphage-G *Franco-Indian, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Glyciphage-P *Franco-Indian, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Glycirid *Indi, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glyciron *Bliss, India.*
Ferrous glycine sulfate (p. 2061·3); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Glyclada *KRKA, Cz.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyclamin *Medreich, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glyco-6 *Micro, India.*
Glycolic acid (p. 1704·3).

Glyco-A *Micro, India.*
Glycolic acid (p. 1704·3).

Glycobate *OEP, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glycodin *Alembic, India.*
Dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); terpin hydrate (p. 1678·2).

Alembic, Rus.; Alembic, Ukr.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); terpin hydrate (p. 1678·2); levomenthol (p. 2553·2).
Respiratory-tract disorders with cough.

Alembic, Ukr.†
Tablets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Symptoms of influenza and other respiratory-tract disorders; fever; headache.

Glycofed *Pal-Pak, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Glycoff *Pharmahof, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Glycolate *Pharmasant, Thai.*
Guaifenesin (p. 1666·2).
Cough.

GlycoLax *Kremers-Urban, USA.*
Macrogol 3350 (p. 2547·3).
Bowel evacuation.

Glycomet *USV, India; USV, Singapore; USV, Ukr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glycomet-GP *USV, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glycomin *Aspen, S.Afr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glycon
Note: this name may be used for preparations of different composition.
Chiesi, Braz.
Potassium iodide (p. 2336·3); ammonium benzoate; tolu balsam (p. 1679·2).
Respiratory-tract congestion.

Siam Bheasach, Thai.
Gliclazide (p. 472·3).
Diabetes mellitus.

Valeant, Canad.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glyconitron *Nikofarm, Gr.*
Glyceryl trinitrate (p. 1391·2).

Glycontrol *Synergia, Fr.*
Thioctic acid (p. 2629·1); carnosine; vitamins; minerals.
Dietary supplement; blood-glucose control.

Glyco-P *Khandelwal, India.*
Glycopyrronium bromide (p. 2519·3).
Protection against muscarinic effects of anticholinesterases used to reverse neuromuscular blockade; peptic ulcer; reduction of secretions.

Glycophos *SSPC, China; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK.*
Sodium glycerophosphate (p. 2519·2).
Phosphate supplement in parenteral nutrition.

Glycophose *Fresenius Kabi, Turk.*
Sodium glycerophosphate (p. 2519·2).

Glycopirida *Sigma, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glycoprep *Fresenius Kabi, Austral.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Glycoprep-C *Fresenius Kabi, Austral.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1); ascorbic acid (p. 2110·3).
Bowel evacuation.

Glycopro *Professional Health, Canad.*
Vitamin B substances (p. 2102·3); inositol (p. 2533·2).

Glycor *USV, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Gly-Coramin *Hanseler, Switz.*
⊗Nikethamide (p. 2328·2); glucose and other reduced sugars (p. 2068·3).
Tonic.

Glycoran *Shinyaku, Jpn.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glycor-C *USV, India.*
Chromium tripicolinate (p. 2056·1); gliclazide (p. 472·3).
Diabetes mellitus.

Glycore *Pharmacore, Indon.*
Glycolic acid (p. 1704·3).
Skin hyperpigmentation.

Glycosept *Teva, Hung.*
Acriflavinium chloride (p. 1732·3); menthol (p. 2553·2); sodium benzoate (p. 1738·2); resorcinol (p. 1718·3).
Mouth and throat disorders.

Glycostigmin *Leiras, Fin.*
Neostigmine metilsulfate (p. 687·2). Glycopyrronium bromide (p. 2519·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Glycotan *Tan, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Glycotana *Harras-Curarina, Ger.*
Syzygium cumini.
Homoeopathic preparation.

Glyco-Thymoline *SERP, Mon.*
Sodium benzoate (p. 1738·2); borax (p. 2459·2); sodium salicylate (p. 132·2); thymol (p. 1772·2); cineole (p. 2479·1); levomenthol (p. 2553·2).
Mouth disorders.

Glycotuss *Pal-Pak, USA.*
Guaifenesin (p. 1666·2).
Coughs.

Glycotuss-dM *Pal-Pak, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Glycovit *Vivipharma, Ital.*
Amino acids; vitamins; minerals.
Nutritional supplement.

Glycovit-D *Glories, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Glycozide *Synmedic, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glycron *Aspen, S.Afr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glycurb *Win-Medicare, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Glycylpressin *Ferring, Austria; Ferring, Ger.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage; haemorrhagic gastritis.

Glycyram *Vifiteh, Rus.*
Ammonium glycyrrhizate (p. 2520·3).
Respiratory-tract congestion; constipation; eczema; asthenia; hypotension; Addison's disease; adrenal insufficiency.

Glycyron *Minophagen, Jpn.*
Ammonium glycyrrhizate (p. 2520·3).
Liver disorders; skin disorders; stomatitis.

Glyderm *Valeant, Hong Kong†; Valeant, Singapore.†*
Esterified glycolic acid (p. 1704·3).
Skin disorders.

Glydiab *Akrikhin, Rus.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glydium *Servier, Denm.; Servier, Fr.; Servier, Irl.; Servier, Neth.; Anpharm, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyfix *Aurobindo, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glyflucan *Legrand, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Glyformin *Remedica, Philipp.; Remedica, Singapore.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glygard *Cipla, India; Cipla-Medpro, S.Afr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glygard M *Cipla, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glygen *General Drugs, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glyhil *Daffahils, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glykacin *Gland, India.*
Amikacin (p. 214·1).
Bacterial infections.

Glykind-M *Mankind, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glykola *Durbin, UK.*
Calcium glycerophosphate (p. 1783·3); caffeine (p. 1203·3); kola liquid extract (p. 2648·2); ferric chloride (p. 2504·2).
Tonic.

Glylak *Shalaks, India.*
Glycolic acid (p. 1704·3).

Glylate *Stada, Hong Kong.*
Guaifenesin (p. 1666·2).
Cough.

Glylin *Lincoln, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glyloc *Cadila, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyloc-M *Cadila, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

GlyMet *Orient, Malaysia.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glymexan *Jelfa, Cz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glymin *Alpha Aromatic, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glymod *Sandoz, Philipp.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Glymol *Biopharm, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Glymox *Globus, India.*
Capsules: Amoxicillin (p. 216·2).
Bacterial infections.

Globus, India.
Syrup: ⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Glymox-Plus *Globus, India.*
Capsules: ⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Globus, India.
Injection: Amoxicillin (p. 216·2); cloxacillin (p. 274·3).

Glynase
Note: this name may be used for preparations of different composition.
Julphar, UAE; Pharmacia Upjohn, USA.
Glibenclamide (p. 472·1).
Diabetes mellitus.

USV, India; USV, Rus.; USV, Singapore; USV, Ukr.
Glipizide (p. 474·1).
Diabetes mellitus.

Glynase MF *USV, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Glyneed *Reliance, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyneed-M *Reliance, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glyni-M *Aronex, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glynit *Geo, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; induction of hypotension during surgery; control of hypertension during surgery.

Glynose *Abdi, Turk.*
Acarbose (p. 466·2).
Diabetes mellitus.

Glyoktyl *Medic, Denm.*
⊗Docusate sodium (p. 1836·2); glycerol (p. 2517·2).
Constipation; bowel evacuation.

Glyori *Orion, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Gly-Oxide *SmithKline Beecham Consumer, USA.*
Urea hydrogen peroxide (p. 1774·2).
Oral inflammation; oral hygiene.

Glyper *Maple, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glyph *Globus, India.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Glyph-C *Globus, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Glyphyllin *Rekah, Israel.†*
Theophylline sodium glycinate (p. 1229·3).
Obstructive airways disease.

Glyph-ZM *Globus, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Glypressin *Ferring, Arg.; Ferring, Belg.; Leciva, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Gr.; Ferring, Hung.; Ferring, Irl.; Ferring, Israel; Ferring, Neth.; Ferring, Norw.; Pharmaco, NZ; Ferring, Philipp.; Ferring, Pol.; Ferring, Spain; Ferring, Swed.; Er-Kim, Turk.; Ferring, UK; Ferring, Ukr.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage; hepatorenal syndrome.

Ferring, China; Ferring, Hong Kong; Ferring, Malaysia; Ferring, Singapore; Ferring, Thai.
⊗Terlipressin (p. 2626·3).
Variceal haemorrhage.

Glypressine *Abacus, Denm.; Orifarm, Denm.; Ferring, Fr.; Ferring, Port.; Ferring, Switz.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage; hepatorenal syndrome.

Glypride *Sun, India; Julphar, UAE.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glyprin *CCM, Hong Kong; CCM, Malaysia; Upha, Singapore.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Glyprolate *Chandra Bhagat, India.*
Glycopyrronium bromide (p. 2519·3).
Protection against muscarinic effects of anticholinesterases used to reverse neuromuscular blockade; peptic ulcer; reduction of secretions.

Glyquin *Valeant, Braz.; Valeant, Singapore.†*
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3).
Hyperpigmented skin disorders.

Valeant, Hong Kong.†
Hydroquinone (p. 1705·1); padimate O (p. 1716·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); glycolic acid (p. 1704·3).
Hyperpigmented skin disorders.

Glyquin XM *Valeant, Canad.; ICN, USA.*
Hydroquinone (p. 1705·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); glycolic acid (p. 1704·3).
Hyperpigmented skin disorders.

Valeant, Singapore.†
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3).
Hyperpigmented skin disorders.

Glyred *Novartis, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyred-M *Novartis, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glyree *Ipca, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Glyree M *Ipca, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glyrep *Emcure, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Glyroz *Aristo, India.*
Gliclazide (p. 472·3); rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Glyryl *Pharmasant, Thai.*
Guaifenesin (p. 1666·2).
Cough.

Glysan *Riemser, Ger.*
Magaldrate (p. 1856·1).
Peptic ulcer; heartburn; gastric hyperacidity.

Glyset *Pfizer, USA.*
Miglitol (p. 491·3).
Diabetes mellitus.

Glysiss *Akesiss, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glysiss-M *Akesiss, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glysomed *Blistex, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Glyteol Balsâmico *Hertz, Braz.†*
Guaifenesin (p. 1666·2); potassium iodide (p. 2336·3); menthol (p. 2553·2).
Cough.

Glytob *Globus, India.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Glytob-D *Globus, India.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected inflammatory eye disorders.

Glytop
Note: this name may be used for preparations of different composition.
Pharmatrix, Arg.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

RPG, India.
Glipizide (p. 474·1).
Diabetes mellitus.

Glytrin *Meda, Denm.; Ayrton Saunders, Irl.; Ayrton, Neth.; AFT, NZ; Sanofi-Aventis, Port.; Pharmasol, Singapore; Meda, Swed.; Hua, Thai.†; Sanofi-Aventis, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Glyvenol *Novartis, Braz.; Novartis, Cz.; Novartis, Gr.; Novartis, Mex.; Novartis, Philipp.; Novartis, Rus.; Novartis, Venez.*
Tribenoside (p. 2633·3).
Venous insufficiency; haemorrhoids; phlebitis; vascular disorders; varices.

Glyverase *Ferring, Mex.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage.

Glyvik-M *Anvik, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Glyvin *Mount Mettur, India.*
⊗Glucose (p. 2068·3); glycerol (p. 2517·2).

Glyvine-S *Mount Mettur, India.*
⊗Glycerol (p. 2517·2); sodium chloride (p. 1795·1).

Glyvion *Globus, India.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Glyzee *Zee, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyzee-M *Zee, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Glyzid *Sunthi Sepuri, Indon.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Glyzide *Julphar, UAE.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Glyzip *Stadmed, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Glyzyl *Medreich, Hong Kong.*
Gliclazide (p. 472·3).
Diabetes mellitus.

GLZ *Alembic, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

GLZ Plus *Alembic, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

GM *Plus, India; Psychotropics, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

GMab Plus *Biocon, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); gamolenic acid (p. 2509·2); mecobalamin (p. 2108·1); zinc (p. 2126·1).

G-Met *East West, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

G-Metrin *Glories, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

GMF *Indkus, India.*
⊗Fluocinolone acetonide (p. 1636·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

GMH *Sun, India.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

GMR *Signova, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

GMR-M *Signova, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

GMT *Indoco, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

G-Mycin *Psychotropics, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Gnaphalium Injektopas SL *Pascoe, Ger.*
Aconitum (p. 2428·3); asa foetida (p. 2449·3); gnaphalium polycephalum; rhododendron; rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

GNC *General Nutrition, Canad.†*
Range of vitamin and mineral preparations.

G-Neuro *Indoco, India.*
Folic acid (p. 2063·1); gabapentin (p. 523·3); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

G-Nil *Orchid, India.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

GNO *Rospaw, Arg.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

GNO CP *Rospaw, Arg.*
Paracetamol (p. 115·1); codeine (p. 40·2).
Fever; pain.

GNorm *Nouveau, India.*
Saccharomyces boulardii (p. 2596·3).

Gnostocardin *Bros, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Gnostoderm *Bros, Gr.*
Miconazole nitrate (p. 589·1).

Gnostol *Bros, Gr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Gnostoval *Bros, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Go Kit *Fresenius Kabi, Austral.*
3 Tablets, bisacodyl (p. 1821·1); 1 sachet, magnesium citrate (p. 1857·1).
Bowel evacuation.

Go Kit Plus *Fresenius Kabi, Austral.*
3 Tablets, bisacodyl (p. 1821·1); 1 suppository, bisacodyl (p. 1821·1); 1 sachet, magnesium citrate (p. 1857·1).
Bowel evacuation.

Goair *Invision, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Goanna Arthritis Cream *Lupin, Austral.*
Trolamine salicylate (p. 141·2).
Musculoskeletal and joint pain.

Goanna Heat Cream *Lupin, Austral.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1); turpentine oil (p. 2636·3); peppermint oil (p. 1877·1); cajuput oil (p. 2464·1); capsicum oleoresin (p. 2469·3).
Musculoskeletal, joint, and soft-tissue pain.

Goanna Oil Liniment *Lupin, Austral.*
Methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); camphor (p. 2466·2); peppermint oil (p. 1877·1); pumilio pine oil (p. 2591·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Goanna Salve *Herron, Austral.†*
Eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1); peppermint oil (p. 1877·1); camphor (p. 2466·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain.

Gobanal *Normon, Spain.†*
Diazepam (p. 1063·2).
Contains pyridoxine hydrochloride.
Anxiety; insomnia; febrile convulsions; skeletal muscle spasm; alcohol withdrawal syndrome.

Gobbibestrol *Gobbi, Arg.*
Diethylstilbestrol (p. 2267·3).
Prostatic cancer.

Gobbicaina *Gobbi, Arg.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Gobbicalm *Gobbi, Arg.*
Dipyrone (p. 53·3); dextropropoxyphene (p. 43·2).
Pain.

Gobbicuronio *Gobbi, Arg.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Gobbidona *Gobbi, Arg.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal syndrome; pain.

Gobbifol *Gobbi, Arg.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Gobbigesic *Gobbi, Arg.†*
Dextropropoxyphene hydrochloride (p. 43·3); ibuprofen lysine (p. 68·3).
Pain.

Gobbinal *Gobbi, Arg.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Gobbizolam *Gobbi, Arg.*
Midazolam (p. 1085·1).
General anaesthesia; sedative.

Gobemicina *Normon, Spain.*
Ampicillin trihydrate (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Gobemicina Retard *Normon, Spain.†*
Ampicillin sodium (p. 218·2); ampicillin benzathine (p. 218·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Goben *CMG, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gobrosan *Apotex, Mex.*
Ibuprofen (p. 68·2).
Rheumatism.

Gocan *Hetero, India.*
Fluconazole (p. 578·2).
Fungal infections.

Gocce Lassative Aicardi *SIT, Ital.*
Sodium picosulfate (p. 1887·2).
Constipation.

Gocce Odontalgiche *Sella, Ital.*
Eugenol (p. 2501·2); chlorobutanol (p. 1747·2).
Toothache.

Goccemed *GSK, Ital.*
Iodine (p. 2336·3).
Oral hygiene.

Gocef *CMG, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Goclav *CMG, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Goclid *Guardian, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Gocold *Cipla, India.*
⊗Guaifenesin (p. 1666·2); bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); paracetamol (p. 115·1).
Cold symptoms.

Gocox-3 *Ipca, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Gocox Compound *Ipca, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2). Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Godamed *Pfleger, Ger.; Pfleger, Israel.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolic disorders; pain; fever; thrombosis prophylaxis.

Godasal *ProMed, Cz.; Pfleger, Ukr.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolic disorders; fever; pain.

Goddards Embrocation *Thornton & Ross, UK.*
Turpentine oil (p. 2636·3); dilute acetic acid (p. 2426·3); dilute ammonia solution (p. 2441·2).
Musculoskeletal and soft-tissue disorders.

Godde *Zee, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Godde-M *Zee, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Godek *Grin, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Godex *Mergers Drugfil, Philipp.*
Capsules: Carnitine orotate (p. 2578·1); liver extract (p. 2444·1); adenine hydrochloride (p. 2430·2); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); cyanocobalamin (p. 2107·2).
Liver disorders.

Mergers Drugfil, Philipp.†
Injection: Carnitine orotate (p. 2578·1); carnitine hydrochloride (p. 2053·2); liver extract (p. 2444·1); adenosine (p. 1291·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Liver disorders.

Godic-S *CMG, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Gofalcy *BMW, India.*
Artesunate (p. 648·2).
Malaria.

Gofel *East African, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gofen *Mega Lifesciences, Thai.*
Ibuprofen (p. 68·2).
Fever; pain.

Goflex *Guardian, Indon.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders.

Goforan *Guardian, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Gofyl *Axon, Chile.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Goipic *Cinfa, Spain.*
Ammonia (p. 2441·2).
Insect stings.

Gokoto *Tsumura, Jpn.*
⊗Gypsum; apricot kernel (p. 2445·3); ephedra (p. 1663·1); mulberry bark; liquorice (p. 1853·2).
Traditional Kampo medicine.

Gola Action *GSK, Ital.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Golacetin *Wellpharma, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Oral disinfection.

Goladin *Sofar, Ital.*
Dequalinium chloride (p. 1749·3).
Oral disinfection.

Golafair *GSK, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disinfection.

Golafen *Kleva, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Golamixin *Teofarma, Ital.*
Tyrothricin (p. 384·1); cetrimonium bromide (p. 1742·3); benzocaine (p. 1980·2).
Rhinitis; sinusitis; nasopharyngitis.

Golapiol *Antipiol, Ital.*
Propolis (p. 2597·3).

Golapiol C *Antipiol, Ital.*
Propolis (p. 2597·3); rose fruit (p. 2607·1).

Golasan *Dynacren, Ital.*
Chlorhexidine gluconate (p. 1743·3) or chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disinfection; oral hygiene.

Rottapharm, Gr.
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Golasept *Zeta, Ital.*
Povidone-iodine (p. 1767·1).
Oral disinfection.

Golaseptine *SMB, Belg.*
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disorders.

Golatux *Antipiol, Ital.*
Ivy (p. 2536·2); echinacea (p. 2498·1).

Golbi *Intas, India.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; primary biliary cirrhosis.

Gold Alka-Seltzer *Bayer Consumer, USA.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); potassium bicarbonate (p. 1780·3).
Hyperacidity.

Gold Bond Anti-Itch *Sanofi Consumer, Canad.*
Dimeticone (p. 2209·3); menthol (p. 2553·2); pramocaine hydrochloride (p. 1993·3).
Pruritus.

Gold Bond Antiseptic First Aid Quick Spray *Chattem, USA.*
Benzethonium chloride (p. 1738·1); menthol (p. 2553·2).
Skin disinfection.

Gold Bond Extra Strength Medicated *Sanofi Consumer, Canad.*
Dimeticone (p. 2209·3); menthol (p. 2553·2).
Emollient.

Gold Bond Foot Pain Relieving *Chattem, USA.*
⊗Menthol (p. 2553·2); capsaicin (p. 35·1); urea (p. 1727·3).

Gold Bond Intensive Healing *Chattem, USA.*
Dimeticone (p. 2209·3); pramocaine hydrochloride (p. 1993·3).

Gold Bond Medicated *Sanofi Consumer, Canad.*
Cream: Menthol (p. 2553·2); pramocaine hydrochloride (p. 1993·3).
Skin disorders.

Sanofi Consumer, Canad.
Lotion: Dimeticone (p. 2209·3); menthol (p. 2553·2).
Emollient.

Gold Bond Medicated Triple Action Relief *Chattem, USA.*
Dimeticone (p. 2209·3); menthol (p. 2553·2); aloe (p. 1693·2).
Emollient.

Gold Bond Pain Relieving Foot Roll-On *Chattem, USA.*
Menthol (p. 2553·2); capsaicin (p. 35·1).

Gold Daktarin *Xian-Janssen, China.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Gold Ray *World Medicine, Ukr.*
Royal jelly (p. 2608·1); betacarotene (p. 2051·1); wheat-germ oil (p. 2647·1); garlic (p. 2510·3).
Dietary supplement.

Gold Theragran *BMS, China.*
Vitamins; minerals; trace elements.
Dietary supplement.

Goldalian *Panagiotis, Gr.*
Amisulpride (p. 1036·3).

Goldamit *Panagiotis, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Goldamycin *Leon, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Goldar
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Zydus, India.
Auranofin (p. 27·3).
Rheumatoid arthritis.

Goldastatin *Leon, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Goldcare
Note: this name may be used for preparations of different composition.
Meyer, India.
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); mecobalamin (p. 2108·1).

Vitabiotics, UK; Vitabiotics, Ukr.
Vitamins; minerals; ginkgo biloba (p. 2512·3); bioflavonoids (p. 2505·2).

Golden Eye
Note: this name may be used for preparations of different composition.
Typharm, Irl.
Dibrompropamidine isetionate (p. 1750·1) or propamidine isetionate (p. 1767·3).
Eye infections.

Typharm, UK.
Chloramphenicol (p. 257·1).
Bacterial conjunctivitis.

Golden Eye Drops
Note: this name may be used for preparations of different composition.
Typharm, UK.
Propamidine isetionate (p. 1767·3).
Eye infections.

Golden Eye Ointment
Note: this name may be used for preparations of different composition.
Typharm, UK.
Dibrompropamidine isetionate (p. 1750·1).
Eye infections.

Goldenrod Combination *Seroyal, Canad.†*
Chimaphila umbellata; damiana (p. 2491·3); eupatorium purpureum (p. 2522·1); goldenrod (p. 2620·1); mallow (p. 2549·2); uva ursi (p. 2453·2).
Homoeopathic preparation.

Goldex Throat Lollies *Goldex, S.Afr.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat infections.

Goldgeist *Gerlach, Ger.*
Pyrethrum (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Goldgesic *Teva, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Goldlily *Schittenhelm, Ger.*
Copper- and gold-wound polyethylene (p. 2057·1) (p. 2521·1).
Intra-uterine contraceptive device.

Goldline *Ranbaxy, Rus.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Goldpride *Gentech, India.*
Amisulpride (p. 1036·3).
Psychoses.

Goldprim *Micro, India.*
Vitamins; minerals; evening primrose oil (p. 2502·2).

Goldtropfen S *DHU, Ger.*
Crataegus (p. 2488·1); aurum chlorat. (p. 2521·1); convallaria majalis (p. 2486·2); ignatia (p. 2532·1); arnica (p. 2447·2).
Homoeopathic preparation.

Golic *Psyco Remedies, India.*
Glycolic acid (p. 1704·3).

Goltor *MSD, Ital.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hyperlipidaemias.

Goltuss *Coup, Gr.*
Oxolamine citrate (p. 1671·2).

Golysine *Maigal, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

GoLytely *Braintree, Canad.; Lilly, Gr.; Kloster, S.Afr.; SSK, Turk.; Braintree, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Gomas Garde B *Grisi, Mex.*
Benzocaine (p. 1980·2).
Mouth and throat disorders.

Gomas Garde G *Grisi, Mex.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Gombarex *Sinnex, Hung.*
English walnut (p. 2646·1); hyssop (p. 2530·3); thyme (p. 2630·2); oak bark (p. 2574·1); ribwort plantain (p. 2604·2); potentilla anserina.
Skin disorders.

Gomcephin *Daewoong, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Gomec *General Drugs, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux, Zollinger-Ellison syndrome.

Gomenol *Gomenol, Fr.*
Niaouli oil (p. 2569·1).
Respiratory-tract congestion.

Gomenoléo *Gomenol, Fr.*
Niaouli oil (p. 2569·1).
Rhinitis; wounds; instrument lubrication.

GON *Sanitas, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Gonablok *Win-Medicare, India.*
⊗Danazol (p. 2263·2).
Endometriosis; fibrocystic breast disease.

Gonacor *Ferring, Arg.; Gynopharm, Chile.*
⊗Chorionic gonadotrophin (p. 2258·1).
Cryptorchidism; delayed puberty; female infertility; male hypogonadism; habitual miscarriage.

Gonadoryl *Mochida, Jpn.†*
⊗Menotrophin (p. 2284·1).

Gonak *Akorn, USA.*
Hypromellose (p. 2189·2).
Gonioscopic examination.

Gonakor *Sanfer, Mex.*
⊗Chorionic gonadotrophin (p. 2258·1); hydroxocobalamin (p. 2107·3).
Hypogonadism; erectile dysfunction; oligospermia.

Gonal-F *Merck Serono, Arg.; Merck Serono, Austral.; Serono, Austria; Serono, Belg.; Merck, Braz.; Serono, Canad.; Merck, Chile; Merck Serono, China; Merck, Cz.; Merck Serono, Denm.; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Merck Serono, Hung.; Serum Institute, India; Merck, Indon.; Serono, Irl.; Merck Serono, Israel; Serono, Ital.; Merck Serono, Malaysia; Serono, Mex.†; Merck, Neth.; Serono, Norw.; Healthcare Logistics, NZ; Merck, Philipp.; Serono, Pol.; Serono, Port.; Merck Serono, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Spain; Serono, Swed.; Merck, Switz.; Merck, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
Follitropin alfa (p. 2278·2).
Male and female infertility.

Gonapeptyl *Ferring, Arg.; Ferring, Belg.; Ferring, Braz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Irl.; Ferring, Ital.; Ferring, Neth.; Ferring, Port.; Ferring, Spain; Ferring, Swed.; Ferring, UK.*
⊗Triptorelin acetate (p. 2310·3).
Prostatic cancer; endometriosis; assisted reproduction; female infertility; uterine fibroids; precocious puberty; pre-operative myoma reduction.

Ferring, Gr.; Ferring, S.Afr.
⊗Triptorelin (p. 2310·3).
Prostatic cancer; endometriosis; infertility; uterine fibroids; precocious puberty.

Gonaphene *Organon, Turk.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Gonasi HP *Amsa, Ital.*
⊗Chorionic gonadotrophin (p. 2258·1).
Amenorrhoea; infertility; threatened or recurrent miscarriage; cryptorchidism; hypogonadism.

Gonavislide *Mochida, Jpn.†*
Pregnancy test (p. 2596·1).

Gonax *Astellas, Jpn.*
Degarelix acetate (p. 2266·2).
Prostatic cancer.

Gonaxine *Motima, Fr.*
Alchemilla; sage (p. 2608·3); achillea (p. 2427·3); alfalfa (p. 2433·1); avena (p. 2451·1).
Tonic for females.

Gondofil *Aurora, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Gondonar *Teva Tuteur, Arg.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Gonem *CMG, India.*
Meropenem (p. 321·3).
Bacterial infections.

Gong Fu Yi Kang *Furen Futong, China.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; hereditary angioedema; pre-surgical endometrial thinning; menorrhagia.

Gong Liang *Mei Do Kang Jia Le, China.*
Matrine.

Gonic *Hauck, USA.†*
⊗Chorionic gonadotrophin (p. 2258·1).
Prepubertal cryptorchidism; male hypogonadism; male and female infertility.

Gonif *Kleva, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Gonilert *Verisfield, Gr.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Gonim *Bionet, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Goniosoft *Ocusoft, USA.*
Hypromellose (p. 2189·2).

Goniosol *Novartis Ophthalmics, USA.*
Hypromellose (p. 2189·2).
Gonioscopic examination.

Alcon, Fr.†
Hyetellose (p. 2188·3).

Gonnaz *XL, Philipp.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gonne Balm *Lane, UK.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Joint and muscular pain.

Gonning *HPP, Hong Kong.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Gonocin *Sel-J, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Gonol *Neo Quimica, Braz.*
Ampicillin (p. 218·2).
Probenecid (p. 607·3) is included in this preparation to reduce renal tubular excretion of the antibiotic.
Bacterial infections.

Gonorcin *General Drugs, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Gonosol *Sun, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Gonotrop F *Win-Medicare, India.*
Urofollitropin (p. 2312·2).
Stimulation of ovulation.

Good Day *BMW, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).

Good Liver *Laborate, India.*
Vitamin B substances (p. 2102·3); silymarin (p. 1561·2).

Good Time *Intra-Labs, India.*
Areca (p. 2446·3); asparagus racemosus (p. 2614·2); mangifera indica; quercus infectoria (p. 2508·3); rubia cordifolia; zingiber officinale.

Gooday *Akesiss, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Goodlac *Biomiicron, India.*
Bifidobacterium longum (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3).

Goodmorn *DWD, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Goodmorn Plus *DWD, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

Goodnight *Bio-Health, UK.*
Vervain (p. 2645·1); lupulus (p. 2546·1); valerian (p. 2640·2); passion flower (p. 2584·1); wild lettuce (p. 2647·3).
Sleep disorders.

Goodnight StopSnore *Swisshealth, UK.*
Sunflower oil (p. 2098·1); peppermint oil (p. 1877·1); sesame oil (p. 2614·1); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Snoring.

Goodypops *Health Imports, UK.*
Echinacea (p. 2498·1); vitamin C (p. 2110·3); pectin (p. 2200·3).
Sore throat.

Goody's Body Pain Powder *Prestige, USA.*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain.

Goody's Cool Orange *Prestige, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Goodys Extra Strength *GSK Consumer, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Goody's Headache Powders *Prestige, USA.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).

Goodys Migraine Relief *Prestige, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).

Goodys PM *Prestige, USA.*
Diphenhydramine citrate (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Gool *CSC, Hung.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Medicom, Cz.
Sodium glucosamine sulfate complex (p. 2515·3).
Osteoarthritis.

Go-On *Rottapharm, Fr.; Madaus, Ger.; Rottapharm, Ger.; Rottapharm, Hong Kong; Rottapharm, Ital.; Rotta, Malaysia; Rotta, Philipp.; Rottapharm, Singapore; Rottapharm, Thai.*
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement; osteoarthritis; joint disorders.

Go-Pain *Glenmark, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain with tension.

MDI, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Go-Pain P *Glenmark, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Gopantam *Altayvitamin, Rus.*
Calcium hopantenate (p. 2465·1).
Cerebrovascular disorders; mental function impairment; micturition disorders.

Gopril *CMG, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Gopten *Abbott, Austral.; Abbott, Braz.; Abbott, Cz.; Abbott, Hung.; Abbott, Indon.; B&S, Irl.; Abbott, Ital.; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, Spain; Abbott, Switz.; Abbott, Turk.; Abbott, UK.*
Trandolapril (p. 1517·2).
Hypertension; left ventricular dysfunction following myocardial infarction.

Goralgin *Guardian, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.

Gordius *Gedeon Richter, Cz.; Gedeon Richter, Hung.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Gordobalm *Gordon, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Gordochom *Gordon, USA.*
Undecenoic acid (p. 596·3); chloroxylenol (p. 1748·2).
Fungal skin infections.

Gordofilm *Gordon, USA.*
Salicylic acid (p. 1719·1).
Verrucas.

Gordogesic *Gordon, USA.*
Methyl salicylate (p. 92·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Gordox *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Aprotinin (p. 1133·2).
Fibrinolytic haemorrhage; pancreatitis; hyperfibrinolytic haemorrhage.

Goreisan *Tsumura, Jpn.*
Alisma rhizome; atractylodes lancea rhizome; polyporus sclerotium; poria sclerotium; cinnamon bark (p. 2479·2).
Traditional Kampo medicine.

Gorgonium *Drossapharm, Switz.*
Heparin (p. 1396·3); allantoin (p. 1693·1); dexpanthenol (p. 2582·2); collagen (p. 2483·2).
Scars.

Gorinsan *Tsumura, Jpn.*
Poria sclerotium; skullcap root (p. 2617·1); liquorice (p. 1853·2); rehmannia root; plantago seed; alisma rhizome; angelica acutiloba root (p. 2443·3); akebia stem; gardenia fruit; peony root; talc (p. 1722·2).
Traditional Kampo medicine.

Gormel *Gordon, USA.*
⊗Urea (p. 1727·3).
Dry skin; hyperkeratosis.

Gorpils *Gepach, Rus.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2).
Mouth and throat disorders.

Gosart *CMG, India.*
Losartan (p. 1422·2) or losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Gosegyne G *Effik, Switz.*
Itraconazole (p. 583·3).
Vulvovaginal candidiasis.

Goselin *Gobbi, Arg.*
⊗Goserelin (p. 2282·3).

Goshajinkigan *Tsumura, Jpn.*
Rehmannia root; achyranthes root; cornus fruit; dioscorea rhizome; plantago seed; alisma rhizome; poria sclerotium; moutan bark; cinnamon bark (p. 2479·2); aconite tuber.
Traditional Kampo medicine.

Goshakusan *Tsumura, Jpn.*
⊗Atracylodes lancea rhizome; citrus unshiu peel; Japanese angelia root; pinellia tuber; poria sclerotium; liquorice (p. 1853·2); platycodon root; immature orange; cinnamon bark (p. 2479·2); magnolia bark; peony root; ginger (p. 1844·1); cnidium rhizome; jujube; angelica dahurica root; ephedra (p. 1663·1).
Traditional Kampo medicine.

Goshuyuto *Tsumura, Jpn.*
Jujube; evodia fruit; ginseng (p. 2513·3); ginger (p. 1844·1).
Traditional Kampo medicine.

Gotabiotic *Poen, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Gotabiotic D *Poen, Arg.*
⊗Tobramycin (p. 380·1); naphazoline hydrochloride (p. 1669·3); dexamethasone phosphate (p. 1631·1).
Bacterial eye infections.

Gotabiotic F *Poen, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

GoTac *Gothaplast, Ger.*
Hydrogel dressing.
Wounds.

GoTa-Derm *Gothaplast, Ger.*
Carmellose (p. 2175·1); pectin (p. 2200·3).
Ulcers; wounds.

Gotalax *Mertens, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Gotal-BE *Galeno, Venez.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Gotalgic *Royal, Chile.*
⊗Polymyxin B (p. 342·3); neomycin (p. 329·3); betamethasone phosphate (p. 1623·2); lidocaine hydrochloride (p. 1988·2).
Otitis externa; otitis media.

Gotaliv *Arrow, Braz.*
⊗Naphazoline (p. 1669·3).

Gotam *CMG, India.*
Tamsulosin (p. 2369·1).
Benign prostatic hyperplasia.

Gotas Binelli *Daudt, Braz.*
Fedrilate (p. 1665·3).
Cough.

Gotas Digestivas *Bunker, Braz.*
Chamomile (p. 2474·1); gentian (p. 2512·1); nux vomica (p. 2573·3); boldo (p. 2458·3).
Digestive disorders.

Gotas Otologicas *Volta, Chile.†*
Lidocaine (p. 1988·1); sulfathiazole sodium (p. 368·3).
Bacterial ear infections.

Gotas Preciosas *Hertz, Braz.*
Cynara (p. 2490·3); belladonna (p. 2453·3); boldo (p. 2458·3); carqueja (p. 2471·2); gentian (p. 2512·1); rhubarb (p. 1884·2).
Liver disorders.

Gotavit *Berman, Mex.*
Vitamins.

Gotaz *CMG, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Goteborg *Driburg, Arg.*
Magnesium (p. 1786·3); riboflavin (p. 2104·3).
Dietary supplement.

Gotely *Tecnofarma, Chile.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Gotera *CMG, India.*
Terazosin (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Gothaplast Capsicum-Wärmepflaster *Gothaplast, Ger.*
Nonivamide (p. 102·3).
Musculoskeletal and joint disorders.

Gothaplast Hornhautpflaster *Gothaplast, Ger.*
Salicylic acid (p. 1719·1).
Calluses; corns.

Gothaplast Hühneraugenpflaster *Gothaplast, Ger.*
Salicylic acid (p. 1719·1).
Calluses; corns.

Gothaplast Rheumamed AC *Gothaplast, Ger.†*
Capsicum (p. 2469·3); arnica (p. 2447·2).
Musculoskeletal and joint disorders.

Gotinal *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion; cold and influenza symptoms; allergic rhinitis; sinusitis.

Gotropil *Guardian, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; alcoholism.

Goutichine *Farmaline, Thai.*
Colchicine (p. 604·1).
Gout.

Goutnil *Inga, India; Inga, Philipp.*
Colchicine (p. 604·1).
Gout; amyloidosis; Behçet's syndrome; familial Mediterranean fever; immune thrombocytopenia; primary biliary cirrhosis; pyoderma gangrenosum.

Gouttes Amara *Weleda, Switz.*
Chicory (p. 2475·2); achillea (p. 2427·3); taraxacum (p. 2625·3); gentian (p. 2512·1); sage (p. 2608·3); absinthium (p. 2426·1); imperatoria; petite centaury (p. 2473·2); juniper (p. 2537·1).
Digestive disorders.

Gouttes aux Essences *Naturactive, Fr.*
Peppermint oil (p. 1877·1); clove oil (p. 2481·3); thyme oil (p. 2630·3); cinnamon oil (p. 2479·3); lavender oil (p. 2541·1).
Respiratory-tract disorders.

Gouttes contre les rhumes des foins *Bucheli, Switz.†*
Allium cepa (p. 2575·2); ambrosia artemisia; ranunculus bulbosus; schoenocaulon officinale (p. 2611·2); solanum lycopersicum.
Homoeopathic preparation.

Gouttes d'Or *UB, Switz.*
Natrii tetrachloroauras (p. 2521·2); camphora (p. 2466·2); convallaria majalis (p. 2486·2); crataegus (p. 2488·1); selenicereus grandiflorus (p. 2473·2); strophanthus hispidus; valerianae (p. 2640·2).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gouttes pour le coeur et les nerfs *Zeller, Switz.*
Crataegus (p. 2488·1); passion flower (p. 2584·1); lupulus (p. 2546·1); olive (p. 2574·3); avens; holly.
Nervous disorders; cardiac disorders.

Goval *Pharma Investi, Chile.*
Risperidone (p. 1103·2).
Psychoses.

Govazol *Guardian, Indon.*
Fluconazole (p. 578·2).
Fungal infections.

Govotil *Guardian, Indon.*
Haloperidol (p. 1077·1).
Psychoses; anxiety; nausea and vomiting; alcoholism.

Gowet *Auspi, India.*
⊗Lactic acid (p. 2539·1); light liquid paraffin (p. 2191·2); propylene glycol (p. 2205·2); urea (p. 1727·3).
Emollient.

Goxil *Pfizer, Spain.†*
Azithromycin (p. 221·2).
Bacterial infections.

Goxyral *Eriochem, Arg.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Gozid *General Drugs, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

GP
Note: this name may be used for preparations of different composition.
Cypress, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.
USV, India.
Glimepiride (p. 473·2).
Diabetes mellitus.

GP-2 Ban *Gland, India.*
Tirofiban (p. 1515·1).
Myocardial infarction; unstable angina.

G-Pill *Taj, India.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

GPM *Psychotropics, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

GPO Cal *GPO, Thai.*
Calcium carbonate (p. 1824·3).

GPO Gesic *GPO, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

GPO-A-Flu *GPO, Thai.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

GPO-L-One *GPO, Thai.*
Deferiprone (p. 1543·1).
Iron overload.

GPO-Trim *GPO, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

GPO-Vir S *GPO, Thai.*
Nevirapine (p. 1005·1); lamivudine (p. 1000·2); stavudine (p. 1015·3).
HIV infection.

GPO-Vir Z *GPO, Thai.*
Zidovudine (p. 1024·2); lamivudine (p. 1000·2); nevirapine (p. 1005·1).
HIV infection.

G-Press *Gap, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

GP-Zide *Millimed, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

GQ *Zydus, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

G-Quin *Helios, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

GR8 *Franco-Indian, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

GR Control Appetite Reducer *GNLD, Austral.*
Amorphophallus rivieri tuber (konjac); hordeum vulgare; avena (p. 2451·1); soya bean (p. 2092·3); acacia (p. 2166·1); citrus sinensis (p. 2576·2).
Slimming aid.

GR Control Thermogenic Enhancer *GNLD, Austral.*
Butternut (p. 2463·2); fucus vesiculosus; taraxacum (p. 2625·3); green tea (p. 2648·2); gymnema silvestre; cayenne pepper (p. 2469·3).
Tonic.

Gra *East West, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Gracef *Gracia, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Graceptor *Astellas, Jpn.*
Tacrolimus (p. 1968·3).
Transplant rejection; graft-versus-host disease.

Gracetam *Graha, Indon.*
Piracetam (p. 393·3).
Cerebral infarction.

Gracevit *Daiichi Sankyo, Jpn; Daiichi Sankyo, Thai.*
Sitafloxacin (p. 357·2).
Bacterial infections.

Gracial *Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Organon, Irl.; Organon, Ital.; Organon, Neth.; Organon, Philipp.; Organon, Port.; MSD, Spain; MSD, Switz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive; acne.

Gracil *Peithner, Austria.*
Apocynum cannabinum; fucus vesiculosus (p. 2612·1); graphites (p. 2522·1); silybum marianum (p. 1561·1); thuja occidentalis (p. 2629·3); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Gradiab *Coronet, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Gradient *Polifarma, Ital.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Grafacef *Graha, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Grafadon *Graha, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Grafco *Graham-Field, USA.*
⊗Silver nitrate (p. 2615·3); potassium nitrate (p. 1766·2).

Grafed *Gracia, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Rhinitis.

Grafeel *Reddy, India.*
Filgrastim (p. 1151·3).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Grafic Forte *Bernabo, Arg.*
Aescin (p. 2431·2); bamethan (p. 1314·1).
Peripheral vascular disorders.

Grafic Retard *Bernabo, Arg.*
Aesculus (p. 2431·2).
Venous insufficiency; haemorrhoids.

Grafin *IQFA, Mex.*
Butylhyoscine (p. 1845·3).

Grafix *Gracia, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Grafola DHA *Metiska, Indon.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement in pregnancy and lactation.

Graftin *Ranbaxy, India.*
Ciclosporin (p. 1945·2).
Transplant rejection; psoriasis; atopic dermatitis; rheumatoid arthritis; nephrotic syndrome.

Grahabion *Graha, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Grail *Trepat, Spain.*
Centella (p. 1698·3).
Venous insufficiency.

Grains de Vals
Note: this name may be used for preparations of different composition.
Nogues, Fr.
Senna (p. 1885·1).
Formerly contained boldo, cascara, and senna.
Constipation.

Grains de Vals Nouvelle formule
Note: this name may be used for preparations of different composition.
Uhlmann-Eyraud, Switz.
Senna (p. 1885·1).
Constipation.

Grains de Vals Senna *Qualiphar, Belg.*
Sennosides B (p. 1885·2).
Constipation.

Gralddep *Continentales, Mex.†*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract disorders; allergic skin disorders.

GR-Alfa *Zydus, India.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; rickets; osteomalacia; hypophosphataemia; renal osteodystrophy; hypoparathyroidism.

Gralise *Depomed, USA.*
Gabapentin (p. 523·3).
Postherpetic neuralgia.

Gramagen *Sandoz, Arg.; Sandoz, Thai.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Gramal *Probiomed, Mex.*
Molgramostim (p. 1156·2).
Reduction of neutropenia associated with cytotoxic therapy or bone marrow transplants.

Gramalil *Astellas, Jpn.*
Tiapride hydrochloride (p. 1111·2).
Behaviour disorders associated with stroke; dyskinesias.

Gramaxin
Note: this name may be used for preparations of different composition.
Antibioticos, Mex.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Gramcal *Novartis Consumer, Canad.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Osteoporosis; calcium supplement.

Gramcep *Vitalink, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Gramcil *Pharmawealth, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Gramcilina *Medley, Braz.†*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Gramclav *Grace, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Gramenox *Medicina, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Gramipen-F *Loeffler, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Gramium *Verisfield, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Grammicin *Siam Bheasach, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Grammidin *Valenta, Rus.; Holding Domestic Medicines, Ukr.*
Gramicidin S (p. 309·1).
Mouth and throat infections.

Grammidin with Anaesthetic Neo *Valenta, Ukr.*
Gramicidin (p. 308·3); oxybuprocaine hydrochloride (p. 1993·2); cetylpyridinium chloride (p. 1743·1).
Infections and inflammation of the mouth and throat.

Grammidin with Anesthetic Neo *Valenta, Rus.*
Gramicidin S hydrochloride (p. 309·1); oxybuprocaine hydrochloride (p. 1993·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Grammidin Neo *Valenta, Rus.*
Gramicidin S hydrochloride (p. 309·1); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Valenta, Ukr.
Gramicidin S (p. 309·1); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Grammixin *Siam Bheasach, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Gramoce A *Vir, Spain.†*
Ascorbic acid (p. 2110·3); vitamin A (p. 2098·3).
Deficiency of vitamins A and C.

Gramocef *Micro, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Gramocef-CV *Micro, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Gramocef-O *Micro, India.*
Cefixime (p. 240·3).
Bacterial infections.

Gramocef-S *Micro, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Gramogyl *Ranbaxy, India.*
Oral suspension: Metronidazole (p. 936·1); nalidixic acid (p. 328·3).
Ranbaxy, India.
Tablets: Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Gramokil *Santa, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Gramol-P *Apotex, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Gramol-SP *Apotex, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Gramoneg *Ranbaxy, India.*
Nalidixic acid (p. 328·3).
Diarrhoea; urinary-tract infections.

Gramoneg-M *Ranbaxy, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Gramoneg-TN *Ranbaxy, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Gramotaz *Micro, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Gramox *Sperko, Rus.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sperko, Ukr.
Amoxicillin (p. 216·2).
Bacterial infections.

Grampenil NF *Nova Argentia, Arg.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Gramplus *Chiesi, Ital.*
Clofoctol (p. 274·3).
Bacterial infections of the respiratory tract.

Gramuno *Graha, Indon.*
Phyllanthi (p. 2590·1); curcuma longa; javanese turmeric (p. 2636·2).
Liver disorders.

Gran *Kirin, China; Kirin, Jpn; Roche, Malaysia; Kyowa, Singapore; Kyowa Hakko Kirin, Thai.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Granaz *Ind-Chemie, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Grandaxin *Egis, Cz.; Egis, Hung.; Mochida, Jpn; Egis, Rus.; Egis, Thai.*
Tofisopam (p. 1112·2).
Anxiety; alcohol withdrawal syndrome; premedication; depression; post-traumatic stress disorder; menopausal disorders; premenstrual syndrome; myasthenia; myopathy; psychiatric disorders; fatigue; autonomic dystonia.

Grandem *Aristo, India.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Grandfer *Grandix, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).

Grand-Pa Headache *Group, S.Afr.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Grandpas Wonder Pine Tar Conditioner *Grandpa Brands, USA.*
Pine tar oil (p. 1723·3).

Grandpherol *Sandoz, Turk.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Granegis *Egis, Cz.; Egis, Hung.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Graneodin
Note: this name may be used for preparations of different composition.
Merck, Chile.
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat infections.

BMS, Arg.
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

BMS, Irl.†
Neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial skin infections.

Graneodin B *BMS, Mex.*
Benzocaine (p. 1980·2).
Mouth and throat disorders.

Graneodin D *BMS, Mex.*
Neomycin (p. 329·3); gramicidin (p. 308·3); benzocaine (p. 1980·2).

Graneodin D Mentol *BMS, Mex.*
Phenylephrine (p. 1672·2); phenylpropanolamine (p. 1674·1); benzocaine (p. 1980·2).
Nasal congestion.

Graneodin N
Note: this name may be used for preparations of different composition.
BMS, Arg.
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); benzocaine (p. 1980·2); noscapine (p. 1670·3).
Cough; mouth and throat disorders.

Graneodin-Tos *Merck, Chile.*
Noscapine (p. 1670·3); chlorhexidine hydrochloride (p. 1743·3).
Cough; mouth and throat infections.

Granexa *Biofarma, Turk.*
Granisetron (p. 1844·3).

Grani di Vals *Geymonat, Ital.†*
Cascara (p. 1826·1); aloes (p. 1816·1); aloin (p. 1816·2).
Constipation.

Granicip *Cipla, India.*
Granisetron (p. 1844·3).
Nausea and vomiting induced by cytotoxics; postoperative nausea and vomiting.

Cipla-Medpro, S.Afr.; Cipla, Venez.
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Graniforce *Mankind, India.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Granigen *Generics, Hung.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Granions *Granions, Mon.*
A range of mineral preparations.

Graniset *Sun, India.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Granisol *Intra-Labs, India; PediatRx, USA.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Granitero *Hetero, India.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Granitril *Pharmaplan, S.Afr.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Granitron *Richmond, Arg.; Orchid, Ukr.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Sandoz, Austria; Verisfield, Gr.
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting; nausea and vomiting induced by chemotherapy.

Granitryl *Alapis, Gr.*
Granisetron hydrochloride (p. 1844·3).

Granix *Teva, USA.*
tbo-Filgrastim (p. 1151·3).
Neutropenia.

Granocol *Schering, NZ.†*
Sterculia (p. 1888·3); frangula bark (p. 1843·3).
Constipation.

Granocyte *Hospira, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Chugai, China; Chugai, Denm.; Sanofi-Aventis, Fin.; Chugai, Fr.; Chugai, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Chugai, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Chugai-Aventis, Norw.†; CSL, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Italfarmaco, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Chugai, Thai.; Eczacibasi, Turk.; Chugai, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, Venez.*
Lenograstim (p. 1155·2).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Granogen *Farmapark, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Granon
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Granisetron (p. 1844·3).
Nausea and vomiting.

Nycomed, Denm.
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Granpam *Towa, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Grans Remedy *Grans Remedy, NZ.*
Zinc oxide (p. 1729·1); zinc undecenoate (p. 596·3); alum (p. 2439·1); talc (p. 1722·2).
Foot odour.

Grant *Elea, Arg.*
Fluorescein (p. 2506·2).
Aid in eye examination.

Granu Fink Blase Kürbiskern *GSK Consumer, Ger.†*
Cucurbita (p. 2489·2); cucurbita oil (p. 2489·2).
Urinary-tract disorders.

Granu Fink Femina *GSK Consumer, Ger.*
Cucurbita oil (p. 2489·2); gewurzsumachrinde (p. 2603·3); lupulus (p. 2546·1).
Bladder disorders.

Granu Fink Kürbiskern *GSK Consumer, Ger.†*
Cucurbita (p. 2489·2).
Urinary-tract disorders.

Granu Fink Prosta *GSK Consumer, Ger.; GSK Consumer, Switz.†*
Cucurbita (p. 2489·2); cucurbita oil (p. 2489·2); saw palmetto (p. 2363·3).
Urinary-tract disorders; benign prostatic hyperplasia.

Granu Fink Prosta forte *GSK Consumer, Ger.*
Cucurbita (p. 2489·2).
Prostatic disorders.

Granudoxy *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Fr.*
Doxycycline (p. 288·1).
Bacterial infections; rosacea; malaria.

Granuflex *Adcock Ingram Critical Care, S.Afr.*
⊗Gelatin (p. 1154·1); pectin (p. 2200·3); carmellose sodium (p. 2175·2).
Wounds; burns; ulcers.

Convatec, Israel; Convatec, UK.
Hydrocolloid dressing.
Burns; skin ulcers; wounds; ulcers.

Granugel *Adcock Ingram Critical Care, S.Afr.*
Pectin (p. 2200·3); carmellose sodium (p. 2175·2).
Wounds.

Convatec, Israel.
Hydrocolloid gel.
Skin ulcers; wounds.

Granugen *Abbott, Austral.†*
Paraffin oil (p. 2191·2); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); paraffin viscous; ethyl vanillin (p. 2185·2); soft paraffin (p. 2211·3).
Minor wounds and ulcers; nappy rash.

Granulax *Lafedar, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Granulderm *Copley, USA.†*
⊗Trypsin (p. 2635·2); peru balsam (p. 2587·1); castor oil (p. 2472·1).
Wounds.

Granulen *Eurofarma, Braz.*
Filgrastim (p. 1151·3).
Neutropenia.

Granulex *Bertek, USA.*
⊗Trypsin (p. 2635·2); peru balsam (p. 2587·1); castor oil (p. 2472·1).
Wound dressing.

Granulokine *Roche, Braz.; Abacus, Denm.†; Genesis, Gr.; Amgen, Ital.; Roche, Philipp.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Granulostim *UCB, China.*
A recombinant granulocyte colony stimulating factor.
Neutropenia.

GranuMed *Rugby, USA.*
⊗Trypsin (p. 2635·2); peru balsam (p. 2587·1); castor oil (p. 2472·1).
Wounds.

Granvit *Plants, Ital.*
Royal jelly (p. 2608·1); wheat-germ oil (p. 2647·1); carrot; soya lecithin (p. 2542·2).
Nutritional supplement.

Graptor *Aamorb, India.*
Gemifloxacin mesilate (p. 304·1).
Chronic bronchitis; community-acquired pneumonia.

Grasalva *Teva, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Grasp *Zep, Canad.*
Chloroxylenol (p. 1748·2).

Grassolind Neutral *Hartmann, Fr.*
White soft paraffin (p. 2211·3); mono- and diglycerides of fatty acids (p. 2186·3).
Burns; ulcers; wounds.

Graster *Little Greave, India.*
Magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Grastim *Reddy, India; Reddy, Ukr.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Gratamin *Gracia, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Graten *Pisa, Mex.*
⊗Morphine sulfate (p. 92·3).
Pain.

Grateva *Teva, Cz.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Gratiella *3DDD, Belg.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in females.

Graton *Triton, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Gravagin *Sperko, Ukr.*
Metronidazole (p. 936·1).
Urogenital trichomoniasis; bacterial vaginosis; infection prophylaxis for intrauterine procedures.

Gravask *Graha, Indon.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Gravastin *Graha, Indon.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Gravergol *Can-Med, Canad.†*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); dimenhydrinate (p. 625·2).
Migraine and other vascular headaches.

Gravida
Note: this name may be used for preparations of different composition.
Beres, Hung.
Vitamins; minerals.

Evacare, India.
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gravidin *Zydus, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gravidinona *Bayer, Mex.*
Hydroxyprogesterone caproate (p. 2285·1); estradiol valerate (p. 2271·2).
Recurrent miscarriage.

Gravifem *VSM, Neth.†*
Cocculus indicus (p. 2483·1); ipecacuanha (p. 1667·2); nux vomica (p. 2573·3); petroleum (p. 2587·2); tabacum (p. 2632·2).
Homoeopathic preparation.

Gravi-Fol *Asconex, Ger.†*
Folic acid (p. 2063·1).
Folic acid deficiency.

Gravigard *SPA, Ital.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Gravigen Plus *Altana, Ital.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Gravimin DHA *Ethica, Indon.*
Vitamins; minerals; trace elements; docosahexaenoic acid (p. 1460·1).
Nutritional supplement in pregnancy and lactation.

Gravinol *Triton, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gravion *Obsurge, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gravis *Sanovel, Turk.*
Zolmitriptan (p. 682·2).

Gravistat *Jenapharm, Cz.; Jenapharm, Ger.; Jenapharm, Pol.†*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Gravitest *Cruciani, Ital.*
Pregnancy test (p. 2596·1).

Gravitor *Sun, India.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis; paralytic ileus; postoperative urinary retention.

Gravol *Church & Dwight, Canad.; Church & Dwight, Hong Kong; Wallace, India; Carter Horner, Philipp.; Church & Dwight, Thai.†*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; vertigo; dizziness; motion sickness; radiation sickness; Ménière's disease.

Gravol Natural Source *Church & Dwight, Canad.*
Ginger (p. 1844·1).
Nausea and vomiting.

Gravolvick *Vickmans, Hong Kong.†*
Dimenhydrinate (p. 625·2).

Gravynon *Kimia, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Gray-F *Gray, Arg.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Grayxona *Gray, Arg.*
Naloxone hydrochloride (p. 1562·3).

Grazax *ALK, Austria; ALK, Cz.; ALK, Denm.; ALK, Fin.; ALK, Fr.; ALK Abello, Ger.; ALK, Gr.; ALK, Irl.; ALK, Ital.; ALK, Neth.; ALK, Norw.; ALK, Pol.; ALK, Port.; ALK, Spain; ALK, Swed.; ALK, Switz.; ALK, UK.*
Grass pollen extracts (*Phleum pratense*) (p. 2593·3) (p. 2434·3).
Allergen immunotherapy; hyposensitisation.

Grazol *Gracia, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Grazolam *Graha, Indon.*
Alprazolam (p. 1035·2).
Anxiety.

GRD *Zydus, India.*
Food for special diets.
Nutritional supplement.

Greater-Gloxa *Greater Pharma, Thai.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Greatofen *Greater Pharma, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Greca *Gedeon Richter, Cz.*
⊗Exemestane (p. 792·2).
Breast cancer.

Grecotens *Genepharm, Gr.*
Piroxicam (p. 125·3).

Gredol *Vensat, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).

Green Antiseptic Mouthwash & Gargle *Lee-Adams, Canad.†*
⊗Alcohol (p. 1733·1); cetylpyridinium chloride (p. 1743·1).

Green Diet *Garden House, Arg.*
Glucomannan (p. 2515·2); guar gum (p. 475·1); seaweed extract.
Dietary supplement; slimming aid.

Green Glo *Hub, USA.*
Green S (p. 2187·3).
Diagnosis of corneal abnormalities.

Green Throat Spray *Clay Park, USA.*
Phenol (p. 1763·3).
Sore throat.

Grefac *Gland, India.*
Enoxaparin (p. 1372·3).
Thromboembolic disorders; prevention of coagulation during haemodialysis; unstable angina.

Grefen *Doetsch, Grether, Switz.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; fever.

G-Reg *Orchid, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Greini *Fada, Arg.*
Amikacin (p. 214·1).
Bacterial infections.

Grelet *Intra-Labs, India.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Grelet-A *Intra-Labs, India.*
Clopidogrel bisulfate (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Greligen *Stargen, Gr.*
Clopidogrel bisulfate (p. 1342·3).

Grelyte *Claris, India.*
Electrolyte infusion with glucose (p. 1775·1).

Grenate *Gentech, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Grendis *Solvay, Indon.; Solvay, Malaysia; Solvay, Philipp.; Abbott, Thai.*
Triflusal (p. 1519·3).
Cardiovascular risk reduction; thromboembolism prophylaxis.

Grenfung *Cevallos, Arg.*
Ketoconazole (p. 585·3).
Fungal infections.

Grenil *Karnataka, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Grenil-F *Karnataka, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Grenis *Genepharm, Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Grenis-Cipro *Genepharm, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Grenis-Oflo *Genepharm, Gr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Grenovix *Genepharm, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Grepid *Pharmathen, Austria; Pharmathen, Cz.; Pharmathen, Denm.; Farmaten, Gr.; Pharmathen, Irl.; Glenmark, Neth.; Pharmathen, Pol.; Pharmathen, Port.; Orifarm, Swed.; Beacon, UK.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Grepiflox *Rivero, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Gres *Piramal, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gretalvite *Vitoria, Port.*
Benzocaine (p. 1980·2); estrone (p. 2275·2); vitamin A (p. 2098·3).
Cracked nipples.

Gretilab *Ahimsa, Arg.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gretivit *Belfar, Braz.*
Vitamins; minerals.

G-Revm *Gap, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Grexin *Pharmasant, Thai.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Greycid *Little Greave, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Gribex Hot *Nobel, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Fever; pain.

Gride *East West, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Gride-M *East West, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Griderm *East West, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair and nail infections.

Grietalgen *Uriach Aquilea OTC, Spain.*
Peru balsam (p. 2587·1); bismuth subnitrate (p. 1822·1); colecalciferol (p. 2113·1); estrone (p. 2275·2); benzocaine (p. 1980·2); vitamin A (p. 2098·3).
Cracked nipples; mastitis.

Grifed *Bayer Consumer, Mex.*
⊗Naproxen sodium (p. 98·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; rhinitis; sinusitis.

Griflux *Labialfarma, Port.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with viscous mucus.

Grifoalpram *Laboratorios Chile, Chile.†*
Alprazolam (p. 1035·2).
Anxiety; panic attacks.

Grifobutol *Laboratorios Chile, Chile.*
⊗Acebutolol (p. 1289·1).
Angina pectoris; arrhythmias; hypertension.

Grifociprox *Laboratorios Chile, Chile.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Grifoclobam *Laboratorios Chile, Chile.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Grifocriptina *Laboratorios Chile, Chile.*
Bromocriptine mesilate (p. 895·3).
Acromegaly; mastodynia; hyperprolactinaemia; lactation suppression; parkinsonism; prolactinoma.

Grifodilzem *Laboratorios Chile, Chile.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Grifoftal-D *Laboratorios Chile, Chile.†*
⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3); polymyxin B (p. 342·3).
Bacterial eye infections with inflammation.

Grifogemzilo *Laboratorios Chile, Chile.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Grifonimod *Laboratorios Chile, Chile.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following cerebral vasospasm.

Grifonitren *Laboratorios Chile, Chile.*
Nitrendipine (p. 1456·3).
Hypertension.

Grifoparkin *Laboratorios Chile, Chile.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Grifopril *Laboratorios Chile, Chile.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Grifopril-D *Laboratorios Chile, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Grifor *Fort, Rus.*
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Grifotaxima *Laboratorios Chile, Chile.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Grifotenol *Laboratorios Chile, Chile.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Grifotriaxona *Laboratorios Chile, Chile.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Grifulin *Teva, Israel.†*
Griseofulvin (p. 582·2).
Fungal skin infections.

Grifulvin *General Drugs, Thai.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Grifulvin V *Ortho Dermatological, USA.*
Griseofulvin (microsize) (p. 582·2).
Fungal skin, hair and nail infections.

Grilinctus *Franco-Indian, India.*
Syrup: Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Cough.

Franco-Indian, India.†
Capsules: Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Grilinctus-BM *Franco-Indian, India.*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3).
Obstructive airways disease with viscous mucus.

Griloc *DR Johns, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Grimal *Grin, Mex.*
⊗Sodium hyaluronate (p. 2526·2); oxymetazoline hydrochloride (p. 1671·3).
Eye congestion; dry eyes.

Grimeral *Biomep, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Grimipenem *Abolmed, Rus.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Grimodin *Egis, Cz.; Egis, Hung.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Grinazole *Septodont, Fr.*
Metronidazole (p. 936·1).
Dental canal disinfection.

Grindelia Complexe No 58 *Lehning, Fr.*
Grindelia (p. 2522·3); cinchona succirubra (p. 2478·3); atropa belladonna (p. 2453·3); chelidonium (p. 2522·2); capsicum (p. 2469·3); ceanothus; nux vomica (p. 2573·3); aloe (p. 1816·1); arsenicum album (p. 2448·1); lycopodium (p. 2546·3).
Homoeopathic preparation.

Grinevel *Filaxis, Arg.*
Ganciclovir sodium (p. 982·3).
Viral infections.

Grinolon *Relyo, Gr.*
Cimetidine (p. 1827·1).

Grinsil *Nova Argentia, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Grinsil Clavulanico *Nova Argentia, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Grinsil Duo *Nova Argentia, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Grinsil Respiratorio *Nova Argentia, Arg.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Grinsil Respiratorio Duo *Nova Argentia, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Grinsil Respiratorio NF *Nova Argentia, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Grinvitals Cereloba Plus *Grindeks, Ukr.*
Ginkgo biloba (p. 2512·3); green tea (p. 2648·2); garlic (p. 2510·3).
Tonic.

Gripaben *Savant, Arg.*
⊗Paracetamol (p. 115·1); bromhexine (p. 1656·3); pseudoephedrine (p. 1676·1).

Gripaben Caramelos *Savant, Arg.*
Gramicidin (p. 308·3); neomycin (p. 329·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Gripaben Descongestivo *Savant, Arg.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Gripace *Lafedar, Arg.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); benzalkonium chloride (p. 1737·1); naphazoline nitrate (p. 1669·3).

Gripagil Husten- und Bronchialtropfen *Steierl, Austria.*
Atropa belladonna (p. 2453·3); cephaelis ipecacuanha; cuprum aceticum (p. 2486·2); drosera (p. 2497·2).
Homoeopathic preparation.

Gripagil-Grippetropfen mit Echinacea *Marien, Austria.*
Ceanothus americanus; cinchona succirubra (p. 2478·3); echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.

Gripakin *Technolabor, Spain.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Gripalcê *Brasterapica, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Gripaljin *Medifarma, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Gripamol *Kocak, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan (p. 1660·1).

Gripanil C *Ahimsa, Arg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Fever; pain.

Gripasan Compuesto *Laboratorios Chile, Chile.*
⊗Paracetamol (p. 115·1); propyphenazone (p. 127·3); pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Gripasan Compuesto DN *Laboratorios Chile, Chile.*
⊗Day tablets, paracetamol (p. 115·1); propyphenazone (p. 127·3); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3); night tablets, paracetamol; propyphenazone; pseudoephedrine hydrochloride; chlorphenamine maleate.
Cold and influenza symptoms.

Gripasan Nueva Formula *Laboratorios Chile, Chile.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Gripavac *Sanofi Pasteur, Spain.†*
An influenza vaccine (p. 2393·3).
Active immunisation.

Gripe Mixture *British Dispensary, Thai.*
Sodium bicarbonate (p. 1781·1); dill oil (p. 2493·2); caraway oil (p. 2470·3); peppermint oil (p. 1877·1).
Flatulence; infant colic.

Gripen *EMS, Braz.*
Dimetindene maleate (p. 626·1); rutoside (p. 2505·3); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Gripen F *EMS, Braz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).

Gripend *US Pharmacia, Rus.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Gripend HotActive *US Pharmacia, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Gripeol *Cifarma, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Gripequin *Wunderpharm, Arg.*
Phenylephrine (p. 1672·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).

Gripetral *Atral, Port.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Gripex
Note: this name may be used for preparations of different composition.
US Pharmacia, Pol.; Synmedic, Ukr.†
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Gripex V *Pharmacia, Pol.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Gripex Control *US Pharmacia, Pol.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Gripex Hot Effect *US Pharmacia, Ukr.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; upper respiratory tract allergy; pain; fever.

Gripex HotActiv *US Pharmacia, Pol.*
Ascorbic acid (p. 2110·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Gripex Hotactive *US Pharmacia, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Influenza symptoms.

Gripex Max *Synmedic, Ukr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Gripex Night *US Pharmacia, Ukr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Gripex Noc *US Pharmacia, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Gripex Start *US Pharmacia, Ukr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Gripexin Limonada Caliente *Labomed, Chile.†*
Paracetamol (p. 115·1); sodium ascorbate (p. 2111·1); caffeine (p. 1203·3); noscapine hydrochloride (p. 1670·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Gripexin Nueva Formula C/Pseudoefedrina *Labomed, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Gripguard *Novartis Vaccines, Fr.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Gripidor *Gestafarma, Port.*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain; fever.

Gripin *Gripin, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Gripin Kase *Gripin, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Gripinew *Medquimica, Braz.*
Salicylamide (p. 129·2); ascorbic acid (p. 2110·3).

Grip-M *Madhav, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Gripofit *Biokosma, Arg.*
Sambucus nigra (p. 2609·3); lapachos; ascorbic acid (p. 2110·3).
Dietary supplement.

Griponal *Merck, Port.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Gripotermon *Prodotti, Braz.†*
Paracetamol (p. 115·1).
Fever; pain.

Gripout *Euro Lifecare, Ukr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Influenza symptoms.

Gripout Baby *Euro Lifecare, Ukr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2).
Influenza symptoms.

Gripout Hotmiks *Euro Lifecare, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Influenza symptoms.

Gripp Heel *Heel, Austria.*
Aconitum napellus (p. 2428·3); lachesis muta (p. 2538·3); bryonia cretica; eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

Heel, Cz.
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); lachesis mutus (p. 2538·3); eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

Grippakit *Ximena Polanco, Chile.*
Arnica (p. 2447·2); belladonna (p. 2453·3); eupatorium; gelsemium (p. 2511·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Grippal *Bayer, Spain.*
Aspirin (p. 22·2); chlorphenamine maleate (p. 620·3); phenylephrine acid tartrate (p. 1672·3).
Influenza and cold symptoms; nasal congestion.

Grippal + C *Ratiopharm, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

grippe *Boiron, Fr.†*
Arnica (p. 2447·2); belladonna (p. 2453·3); eupatorium perfoliatum (p. 2459·1); gelsemium (p. 2511·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Grippe-Gastreu R6 *Reckeweg, Neth.*
Aconitum napellus (p. 2428·3); baptisia tinctoria (p. 2647·2); bryonia cretica; camphora (p. 2466·2); causticum (p. 2595·3); eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); gelsemium sempervirens (p. 2511·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Grippe-Gastreu S R6 *Reckeweg, Ger.*
Aconitum (p. 2428·3); bryonia (p. 2461·3); camphora (p. 2466·2); causticum (p. 2595·3); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); gelsemium (p. 2511·2).
Homoeopathic preparation.

Grippetee St Severin *Smetana, Austria.*
Sambucus flower (p. 2609·3); tilia flower (p. 2631·3); ribwort plantain (p. 2604·2).
Cold symptoms.

Grippex
Note: this name may be used for preparations of different composition.
Hexal, Ger.
Paracetamol (p. 115·1).
Fever; pain.

Unipharm, Rus.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Gripp-Heel *Ebi, Switz.*
Aconitum napellus (p. 2428·3); bryonia cretica; lachesis mutus (p. 2538·3); eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

Heel, Ger.; Peithner, Hung.; Heel, S.Afr.
Aconitum (p. 2428·3); bryonia (p. 2461·3); lachesis (p. 2538·3); eupatorium perfol. (p. 2459·1); phosphor. (p. 2589·2).
Homoeopathic preparation.

Gripp-Heel H *Heel, Neth.*
Aconitum napellus (p. 2428·3); bryonia cretica; eupatorium perfoliatum (p. 2459·1); lachesis mutus (p. 2538·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Grippocitron *Zdorovje, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Grippoflu Extra Cold and Flu *Marbiopharm, Rus.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Grippokaps *Hasco-Lek, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; rhinitis; sinusitis.

Grippol *Microgen, Rus.*
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Grippon *Adcock Ingram, S.Afr.*
Capsules: Paracetamol (p. 115·1); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Adcock Ingram, S.Afr.†
Syrup: ⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); ephedrine (p. 1663·1).
Cold and influenza symptoms.

Grippon Cold & Flu *Adcock Ingram, S.Afr.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Gripponyl
Note: this name may be used for preparations of different composition.
Plantes et Medecines, Fr.†
Cinchona bark (p. 2478·3); salix (p. 129·2); green tea (p. 2648·2).
Fever.

Grippostad *Stada, Austria; Stada, Hung.; Steigerwald, Pol.*
Paracetamol (p. 115·1).
Pain; fever.

Stada, Rus.
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Grippostad C
Note: this name may be used for preparations of different composition.
Stada, Austria; Stada, Cz.†; Stada, Ger.; Stada, Hung.; Steigerwald, Pol.; Stada, Rus.; Stada, Ukr.
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Grippostad Erkältungsbad *Stada, Ger.*
Norway spruce oil; eucalyptus oil (p. 2501·2); levomenthol (p. 2553·2).
Catarrh.

Grippostad Erkältungsbalsam *Stada, Ger.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Respiratory-tract disorders.

Grippostad Erkältungsbalsam mild *Stada, Ger.*
Eucalyptus oil (p. 2501·2); pine needle oil (p. 2591·1).
Respiratory-tract disorders.

Grippostad Heissgetrank *Stada, Ger.*
Paracetamol (p. 115·1).
Pain; fever.

Grippostad Horky Napoj *Stada, Cz.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Grippostad Rhino *Stada, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Grippovac *St Petersburg Institute of Vaccines & Sera, Rus.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Gripps *Pascoe, Ger.*
Sanguinaria (p. 2610·1); aconitum (p. 2428·3); bryonia (p. 2461·3); sabadilla (p. 2611·2); phosphor. (p. 2589·2); arsen. alb. (p. 2448·1); nux vom. (p. 2573·3); gelsemium (p. 2511·2); eupator. perf. (p. 2459·1); kal. bichrom. (p. 2476·3); eucalyptus (p. 2501·1).
Homoeopathic preparation.

Griprid *Blubell, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3).

Gripsay *Delta, Braz.*
Ampoule A, dipyrone (p. 53·3); sodium camsilate (p. 2617·3); guaifenesin (p. 1666·2); cineole (p. 2479·1); niaouli oil (p. 2569·1); ampoule B, mepyramine maleate (p. 635·1); ascorbic acid (p. 2110·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Cold and influenza symptoms.

Gripson *Sons, Mex.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Grisactin *CFL, India.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Griséfuline *Sanofi-Aventis, Fr.*
Griseofulvin (p. 582·2).
Fungal infections.

Grisenova *Dedousis, Gr.*
Griseofulvin (p. 582·2).

Griseo *CT, Ger.*
Griseofulvin (p. 582·2).
Fungal skin infections.

Griseocrem *Ivax, Arg.*
⊗Diflorasone diacetate (p. 1633·3); econazole nitrate (p. 577·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Griseofort *Schering-Plough, Indon.*
Griseofulvin (ultramicronized) (p. 582·2).
Fungal infections of the skin, hair, and nails.

Griseo-Med *Utopian, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Griseoplus *Ivax, Arg.*
⊗Griseofulvin (p. 582·2); econazole nitrate (p. 577·3); hydrocortisone (p. 1640·1); salicylic acid (p. 1719·1); neomycin undecenoate (p. 330·1); boric acid (p. 2459·3).
Infected skin disorders.

Grisetin
Note: this name may be used for preparations of different composition.
Faes, Spain.
Flutamide (p. 798·2).
Prostatic cancer.

Grisflavin *Asian Pharm, Thai.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Grisin *Chinta, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Gris-OD *Reddy, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair and nail infections.

Grisol *Transdermal, Irl.; Forum, UK.*
Griseofulvin (p. 582·2).
Tinea pedis; fungal skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Grisomed *Comed, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Grisonorm *Micro, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Grisoral *Bal, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Grisovex *United Drug, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Grisovin *Investi, Arg.; Aspen, Austral.; GSK, India; GSK, Mex.; GSK, Philipp.; Glaxo Wellcome, Port.†; GSK, Turk.; GSK, Venez.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Grisovina FP *Teofarma, Ital.*
Griseofulvin (p. 582·2).
Fungal skin and nail infections.

Gris-PEG *Pedinol, USA.*
Griseofulvin (ultramicrosize) (p. 582·2).
Fungal skin, hair, and nail infections.

Grisuvin *DHA, Hong Kong; DHA, Malaysia.*
Griseofulvin (p. 582·2).
Fungal infections of skin, hair, and nails.

Grisux Dia y Noche *Prater, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); chlorphenamine (p. 620·3).

Grivin *Phapros, Indon.; Atlantic, Malaysia; Atlantic, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Grizol *Grisi, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

GR8-OD *Franco-Indian, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Grodurex *Grossmann, Switz.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Grofenac *Grossmann, Hong Kong†; Grossmann, Switz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Grofibrat *Richter, Pol.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Gromane *Zydus, India.*
Minoxidil (p. 1438·3).
Alopecia.

Gromazol *Grossmann, Switz.*
Clotrimazole (p. 576·2).
Fungal foot infections.

Gromet-Z *Apex, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3); zinc sulfate (p. 2126·2).

Gromin *Medley, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Grommar *Valeant, Hung.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Groprinosin *Richter, Pol.; Grodzisk, Rus.; Gedeon Richter, Ukr.*
Inosine pranobex (p. 988·3).
Viral infections; herpesvirus infections.

Groseptol *Grodzisk, Rus.; Gedeon Richter, Ukr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Grossenel *Anpharm (Ανφαρμ), Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Grotavit *Armoxindo, Indon.*
Vitamins; minerals.
Dietary supplement in children.

Groven *Filaxis, Arg.†*
Aripiprazole (p. 1038·3).
Schizophrenia.

Grovit *USV, Ukr.†*
Vitamins.
Dietary supplement.

Gro-Vital *Aamorb, India.*
Oral drops: Vitamins.

Aamorb, India.
Oral powder: A range of preparations for enteral nutrition.

Aamorb, India.
Syrup; tablets: Vitamins; minerals.

Grow Advance *Abbott, Hong Kong.*
Preparation for enteral nutrition.

Grow Advance Eye-Q *Abbott, Philipp.*
Preparation for enteral nutrition.
Nutritional supplement for children.

Grow Up *Wockhardt, India.*
Preparation for enteral nutrition.

Growancer *Fontelabor, Port.†*
Finasteride (p. 2358·3).

Growart *Farmex, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Growee *Medifarma, Indon.; Pediatrica, Indon.; Pediatrica, Singapore.†*
Vitamins; lysine hydrochloride (p. 2079·3); taurine (p. 2626·2); choline (p. 2055·2); chlorella (p. 2475·3).
Nutritional supplement in children.

Growee with Chlorella *Pediatrica, Philipp.*
Vitamins; amino acids; chlorella growth factor (p. 2475·3).

Growell *ICM, Singapore.*
Minoxidil (p. 1438·3).
Alopecia.

Growell-PM *Reliance, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Growgen-GM *Bioprofarma, Arg.*
Molgramostim (p. 1156·2).
Neutropenia.

Growise *Aglowmed, India.*
Cyproheptadine hydrochloride (p. 624·1); sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Growject *Sumitomo, Jpn.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome.

Growsure *Dexter, India.*
Preparation for enteral nutrition.

Gruben *Pasteur, Chile.*
Codeine phosphate (p. 40·2); bromoform (p. 2460·3); sodium camsilate (p. 2617·3); belladonna (p. 2453·3); sodium benzoate (p. 1738·2).
Cough.

Grumorph *Grunenthal, Port.*
⊗Morphine sulfate (p. 92·3).
Pain.

Grüncef *Infectopharm, Ger.*
Cefadroxil (p. 233·2).
Bacterial infections.

Grunicef *Grunenthal, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Grunicina *Grunenthal, Mex.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Grupozil *Velka, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

GRX Dyne *Geritrex, USA.*
Povidone-iodine (p. 1767·1).
Antiseptic.

GRX Vitamin E *Geritrex, USA.*
Tocoferil acetate (p. 2119·2).

Grypolek *Kato, Pol.*
⊗Paracetamol (p. 115·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Grypostop *Omega Rex, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Grypostop Mix *Omega Rex, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

GS *GLS, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

GS Forte *GLS, India.*
Ginseng (p. 2513·3); minerals; vitamins.

GS-AP *GLS, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

GSA-Retic *Adcock Ingram, S.Afr.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).

GSCal *GLS, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

GSClav *GLS, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

GSComb *GLS, India.*
Iron carbonyl (p. 2073·1); vitamins; zinc sulfate (p. 2126·2).

GSLB *GLS, India.*
Lactobacillus (p. 2596·3).

GSNim-P *GLS, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

GSO4 *Bal, India.*
Ascorbic acid (p. 2110·3); glucosamine sulfate (p. 2515·3).

GSProx *GLS, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

GS-X *Pharmacon, India.*
Proanthocyanidins; vitamin C (p. 2110·3).

G-Tase *Unichem, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

G-Tase G *Unichem, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

G-Tase M *Unichem, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

G-Ten *Grandix, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

G-Thro *Globus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

GTN Sorbitrate *Piramal, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

GTO Oil *Nutricia, Ital.*
Glyceryl trioleate (p. 2545·2).
Adrenoleucodystrophy.

GTR *Pond's, Thai.*
Glutaral (p. 1753·2).

G-Trol *Orchid, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Gu Ao *Lingnan, China.*
Glutamine (p. 2070·3); azulene sodium.

Gu Er An *Sinobiopharma, China.*
Alanyl glutamine.

Gu Jie *JiangShi, China.*
Polypeptides.

Gu Ping *Jiu Dian, China.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).

Gu Su An *Zhengda Qingchunbao, China.*
Ipriflavone (p. 1185·3).

Gu Su Sheng *Mei Luo, China.*
Matrine.

Gu Tai Ning *Shiqiao, China.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; metastatic bone pain.

Gu Te *Jiu Dian, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Gu Yu *SanJiuJiShi, China.*
Polypeptides.

Gu Yuan *Di Ao, China.*
Calcium carbonate (p. 1824·3).

Gu Zheng *Xinbai, China.*
Compound ossotide.

Gu Zhi *Hualong, China.*
Ethylenediamine diaceturate.

Guaco *Belfar, Braz.*
Mikania.

Guadal *Rafarm, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Guadex *Hoe, Malaysia.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Guafensin *YSP, Malaysia.*
Guaifenesin (p. 1666·2).
Cough.

Guaiacalcium Complex *SIT, Ital.*
Dropropizine (p. 1662·2); sulfogaiacol (p. 1678·1).
Cough.

Guaiacol *Suphong, Thai.*
Guaifenesin (p. 1666·2).
Cough.

Vitamed, Israel.
Sulfogaiacol (p. 1678·1).
Cough.

GUAI/DM *Brighton, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Guaifed *Verum, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Nasal congestion; coughs.

Guaifed-PD *Verum, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Nasal congestion; coughs.

Guaifen *Cassara, Arg.*
Guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Guaifenesin DAC *Cypress, USA.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs and associated respiratory-tract disorders.

Guaifenesin DM *Prasco, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Guaifenesin PSE *Cypress, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; nasal congestion.

Guaifenex DM *Ethex, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Guaifenex PSE *Ethex, Hong Kong†; Ethex, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Guaimax-D *Schwarz, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Guais *Medic+Aid, Philipp.†*
Guaifenesin (p. 1666·2).
Cough.

Guaitab *Muro, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; coughs.

Guaitussin DM *Jamp, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Guaivent *Ethex, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Guai-Vent/PSE *Dura, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Guajacuran *Zentiva, Cz.*
Guaifenesin (p. 1666·2).
Depression; anxiety disorders; pain; skeletal muscle spasm; premedication.

Guajavis *Vis, Pol.*
Guaifenesin (p. 1666·2).
Cough.

Guajazyl *Espefa, Pol.*
Guaifenesin (p. 1666·2).
Cough.

Guamet *Medreich, Hong Kong.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Guamil *Interbat, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Guan Wei *KunMing, China.*
Bulleyaconitine A.

Guan Xin Ke *Jingyou, China.*
Vitamin B_{12} (p. 2107·2); gentamicin sulfate (p. 304·2).

Guan Zhi Ning *Weiao, China.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Guang Di *Jinfeng, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Guang Yi Sha *Taige, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Guangle *Livzon, China.*
Kallidinogenase (pancreatic) (p. 2537·2).
Cerebral and peripheral vascular disorders.

Guanicar *Biotech, Venez.*
Succinylsulfathiazole (p. 360·1); activated charcoal (p. 1537·3).
Gastrointestinal infections.

Guanping *Wansui, China.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Guansha *Double-Crane, China.*
Erythromycin (p. 291·2).
Bacterial infections.

Guaphenyl II *Rivers Edge, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Guar Verlan *Verla, Ger.*
Guar gum (p. 475·1).
Diabetes mellitus; hyperlipidaemias.

Guarafort *Fontovit, Braz.†*
Guarana (p. 2648·2).

Guaramaté *Arkopharma, Fr.†*
Guarana (p. 2648·2); maté (p. 2648·2).
Tonic; weight reduction.

Guarana *Natufarma, Arg.†*
Caffeine (p. 1203·3).
Fatigue.

Guarana Diates *Provefarma, Arg.†*
Guarana (p. 2648·2); calcium pantothenate (p. 2085·2).
Dietary supplement.

Guaranup *Lafarmen, Arg.*
Guarana (p. 2648·2); pyridoxine (p. 2105·3).
Tonic.

Guarcol *Orion, NZ.*
Food thickener (p. 475·1).
Dysphagia.

Guard *Newtramax, India.*
Vitamins; minerals.

Guardian Antacid *Sunward, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).

Guardian Antifungal *Sunward, Singapore.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Guardian Cough *ICM, Singapore.*
Guaifenesin (p. 1666·2).
Cough.

Guardian Expectorant *Sunward, Singapore.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).

Guarem *Orion, Fin.; Orion, Ukr.*
Guar gum (p. 475·1).
Diabetes mellitus; hypercholesterolaemia.

Guarposid *Guardian, Indon.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Guastil *Uriach, Spain; Vifor, Spain.*
Sulpiride (p. 1107·3).
Anxiety; psychoses; vertigo.

Guaxoquim *Quimpharma, Mex.*
Guaifenesin (p. 1666·2); oxolamine citrate (p. 1671·2).
Cough.

Guayalin *Farcoral, Mex.*
Cineole (p. 2479·1); guaiacol (p. 1666·1).
Cough.

Guayaprin *Liferpal, Mex.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Guayaten *Flupal, Venez.*
Minoxidil (p. 1438·3).
Hypertension.

Gubang *CSPC, China.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Gudcef *Mankind, India.*
Cefpodoxime proxetil (p. 248·1); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Gudcerin *Mankind, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Gudef *Berk, Turk.*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Gudi *Xincat, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Gudlac *Balkanpharma, Rus.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Gudlax-Plus *Mankind, India.*
Magnesium hydroxide (p. 1857·2); sodium picosulfate (p. 1887·2).

Gudpres *Mankind, India.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure.

Guéthural *Elerte, Fr.*
Tablets: Guaietolin (p. 1666·2).
Respiratory-tract congestion.

Gufensin *Christo, Hong Kong.*
Guaifenesin (p. 1666·2).
Cough.

Gugaike *Lutan, China.*
Dihydrocodeine tartrate (p. 52·3); paracetamol (p. 115·1).
Pain; fever; cough.

Gug/X *Ximena Polanco, Chile.†*
Plantago major (p. 2592·3); buddleja globosa; chamomilla recutita (p. 2474·1).
Homoeopathic preparation.

Gui Ding Kang *Tianren, China.*
Aluminium phosphate (p. 1818·3).

Gui Long Nuo Ke *Gui Long, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Gui Ping *Jincheng Haisi, China.*
Matrine.

Guiatex PSE *Rugby, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Guiatuss *Goldline, USA.*
Guaifenesin (p. 1666·2).
Coughs; respiratory-tract congestion.

Guiatussin with Codeine Expectorant *Rugby, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Coughs.

Guiatussin DAC *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Coughs.

Guiatussin with Dextromethorphan *Rugby, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Guigoz AC *Guigoz, Fr.*
Infant feed.
Infant colic.

Guigoz AR *Guigoz, Fr.*
Infant feed.
Gastro-oesophageal reflux.

Guigoz HA *Guigoz, Fr.*
Infant feed.
Milk-protein allergy.

Guigoz Transit *Guigoz, Fr.*
Infant feed.
Gastrointestinal disorders.

Gulamyl *Elpen (Ελπεν), Gr.*
Guaifenesin (p. 1666·2); theophylline (p. 1229·3).
Bronchodilator.

Gulaper *Roemmers Osmoph, Venez.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Gulf *Siomond, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Gum HaliControl *Sunstar, Fr.*
Mouthwash: Cetylpyridinium chloride (p. 1743·1); zinc lactate (p. 2126·2); peppermint oil (p. 1877·1); menthol (p. 2553·2).
Halitosis.

Sunstar, Fr.
Toothpaste: Cetylpyridinium chloride (p. 1743·1); zinc lactate (p. 2126·2); peppermint oil (p. 1877·1); menthol (p. 2553·2); sodium fluoride (p. 2089·2).
Halitosis.

Gum PerioBalance *Sunstar, UK.*
Lactobacillus reuteri prodentis (p. 2596·3).
Gum disorders.

Gum SensiPro *Butler, Ger.†*
Methacrylate modified polyacrylic acid; polyethyleneglycoldimethacrylate; potassium fluoride (p. 2089·2).
Hypersensitive teeth.

Gumbaral *AWD, Ger.†*
Ademetionine sulfate tosilate (p. 2430·1).
Degenerative joint disorders.

Gumilk *bsa, Fr.*
Ceratonia (p. 2178·1); maltodextrin (p. 2080·3).
Regurgitation in infants.

Gummi King *Beacons, Singapore.*
Vitamins; minerals.

Gummi King (Calcium + Vit D) *Beacons, Singapore.*
Calcium (p. 1783·1); vitamin D.

Gummi King (Vit C) *Beacons, Singapore.*
Ascorbic acid (p. 2110·3).

Gummies *139673 Canada, Canad.†*
Vitamins.

Gunabion *Sunthi Sepuri, Indon.†*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuropathy; neuralgia; lumbago; migraine; vomiting of pregnancy; tonic.

Gunaceta *Sunthi Sepuri, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Gunacold *Sunthi Sepuri, Indon.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; cough; allergy.

Gunapect *Sunthi Sepuri, Indon.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Gupisone *Julphar, UAE.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Gurfix *Novartis Consumer, Austria.†*
Hexetidine (p. 1755·1); cetylpyridinium chloride (p. 1743·1).
Mouth and throat inflammation.

Gurgellösung-ratiopharm *Ratiopharm, Ger.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Gurik *Zee, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Guronsan
Note: this name may be used for preparations of different composition.
Nycomed, Belg.†; MSD-Chibret, Fr.; Jaba Recordati, Port.
Glucuronamide (p. 2517·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Tonic; asthenia.

Inibsa, Spain.†
Glucuronamide (p. 2517·1); ascorbic acid (p. 2110·3).
Tonic.

Guronsan C *Aspen Consumer, S.Afr.*
Glucurolactone (p. 2517·1); glucuronamide (p. 2517·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Tonic.

Gush *Panacea, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Gusnil *Varun, India.*
Fluconazole (p. 578·2).
Fungal infections.

Gusong *Jida, China.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Guspar *Unicure, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Gustosal *Rafarm, Gr.*
Nicergoline (p. 2569·1).

Guta *Zeppenfeldt, Ger.*
Zinc oxide (p. 1729·1).
Wounds.

Gutalax *Boehringer Ingelheim, Spain.†*
Sodium picosulfate (p. 1887·2).
Constipation.

Gutencef *Merck, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Gutenmox *Merck, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Gutman *Rafarm, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).

Gutpro *JB Chemicals, India.*
Bacillus mesentericus; Clostridium butyricum; Lactobacillus sporogenes (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).

Gutrite *FDC, India.*
Bifidobacterium bifidum (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

Gutron *Dominguez, Arg.; Nycomed, Austria; Silesia, Chile; Nycomed, China; Nycomed, Cz.; Nycomed, Fr.; Nycomed, Ger.; IFET (ΙΦΕΤ), Gr.; Nycomed, Gr.; Nycomed, Hong Kong; Nycomed, Hung.; Nycomed, Israel†; Lusofarmaco, Ital.; Nycomed, Neth.; Douglas, NZ; Nycomed, Pol.; Nostrum, Port.; Nycomed, Rus.; Takeda, Singapore; Nycomed, Spain; Takeda, Switz.*
⊗Midodrine hydrochloride (p. 1437·3).
Orthostatic hypotension; hypotension; urinary incontinence; ejaculation disorders; stress incontinence in women.

Guts *Ind-Swift, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Guttae Stomachicae *Prolab, Pol.*
St John's wort (p. 449·1); peppermint leaf (p. 1877·1); bitter tincture; valerian (p. 2640·2).
Gastric disorders.

Guttalax *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Braz.; Andromaco, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Ukr.*
Sodium picosulfate (p. 1887·2).
Constipation; stool softener; bowel evacuation.

Guttanotte *Sigmapharm, Austria.*
Flunitrazepam (p. 1073·3).
Insomnia.

Gutts *Ind-Swift, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

GV-24 *Genesis, India.*
Myrtillus (p. 2566·2); citrus bioflavonoids (p. 2505·2); lutein (p. 2079·2); lycopene (p. 2546·2); minerals; *meso*-zeaxanthin; zeaxanthin (p. 2125·3).

G-Vit *Plus, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).

GVM *Rishab, India.*
Vitamins; minerals; ginseng (p. 2513·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Gwajatussin *Herbapol Lublin, Pol.*
Sulfogaiacol (p. 1678·1); ribwort plantain (p. 2604·2); verbascum (p. 2645·1).
Cough; respiratory-tract congestion.

GX *Braun, Ger.*
Glucose (p. 2068·3); xylitol (p. 2220·3).
Parenteral nutrition.

Gydrelle *IPRAD, Fr.*
Estriol (p. 2274·3).
Menopausal disorders.

Gydrelle Phyto *IPRAD, Fr.*
Soya isoflavones (p. 2620·3).

Gygel *Marlborough Pharmaceuticals, UK.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Gymiso *Linepharma, Fr.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Gyn-3 *Life Line, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Gynacea *Micro, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2); soya isoflavones (p. 2620·3); colecalciferol (p. 2113·1).

Gynadom *East West, India.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; hereditary angioedema; pre-operative endometrial thinning; menorrhagia.

Gynae-CVP *USV, India.*
Citrus bioflavonoids (p. 2505·2); vitamin C (p. 2110·3); menadione (p. 2122·1); ferrous gluconate (p. 2061·2); calcium lactate (p. 1784·1).
Threatened and recurrent miscarriage; gynaecological haemorrhage.

Gynaelite *Holland Pharma, Neth.*
Alumina (p. 1690·3); ammonium bromatum (p. 2461·1); apis mellifica (p. 2445·2); arnica montana (p. 2447·2); aurum metallicum (p. 2521·1); hypericum perforatum (p. 449·1); kalium carbonicum (p. 2595·2); melilotus officinalis (p. 2552·3); pulsatilla pratensis (p. 2600·2); viburnum opulus.
Homoeopathic preparation.

Gynaemine *Sriprasit, Thai.*
Ergotamine tartrate (p. 674·1); ergometrine maleate (p. 2136·2).
Oxytocic.

Gynae-Pil *Psychotropics, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Gynae-Pil Forte *Psychotropics, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Gynafem *Rimsa, Mex.†*
Butoconazole nitrate (p. 574·2).
Vaginal infections.

GynaHex *Concept, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Antiseptic lubricant for rectal and gynaecological examination.

Gynalgin *ICN, Pol.; Meda, Rus.; Valeant, Ukr.*
Chlorquinaldol (p. 260·1); metronidazole (p. 936·1).
Vaginal infections.

Gynalom *Wockhardt, India.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Gynalpha *CCD, Fr.*
Soya (p. 2092·3).
Menopausal disorders.

Gynalpha Plus *CCD, Fr.†*
Soya (p. 2092·3); chromium (p. 2055·3); selenium (p. 2086·3).
Dietary supplement.

Gynamon *Jenapharm, Ger.†*
Orange tablets, estradiol (p. 2271·1); grey tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Gynapres *Mankind, India.*
Methyldopa (p. 1431·1).
Hypertension.

Gynasafe *Taj, India.*
Clindamycin phosphate (p. 269·3) or clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Gynatam *Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.†; Biogalenic, Venez.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Gynatren *Strathmann, Ger.*
A trichomonal vaccine (p. 2422·2).

Gynax-N *Ativus, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); nystatin (p. 590·3); neomycin sulfate (p. 330·1); tyrothricin (p. 384·1); sodium propionate (p. 593·1); boric acid (p. 2459·3).
Vulvovaginal disorders.

Gynazol
Note: this name may be used for preparations of different composition.
Gedeon Richter, Hung.; Richter, Pol.
Butoconazole nitrate (p. 574·2).
Vulvovaginal candidiasis.

Indian Drugs, India.
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; hereditary angioedema; pre-operative endometrial thinning; menorrhagia.

Gynazole *Aspen, Austral.; Sigma, Braz.; Ferring, Canad.; KV, China; OM, Switz.†; KV, USA.†*
Butoconazole nitrate (p. 574·2).
Vulvovaginal candidiasis.

Gynben *UCI, Braz.*
Tioconazole (p. 595·3); tinidazole (p. 949·2).

Gyncobem *Cifarma, Braz.*
Ginkgo biloba (p. 2512·3).

GynDelta *CCD, Fr.*
Cranberry (p. 2488·1).
Urinary-tract disorders.

GynDelta PRIM *CCD, Fr.*
Cranberry (p. 2488·1); calluna vulgaris; blueberry.
Urinary-tract disorders.

Gynebo *Chew, Thai.*
Clotrimazole (p. 576·2).
Vaginal fungal infections; trichomoniasis.

Gynecon *Continental Pharma, Thai.*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Fungal, trichomonal and bacterial vaginitis.

Gynecon-T *Continental Pharma, Thai.*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1); melaleuca oil (p. 2551·1).
Fungal, trichomonal and bacterial vaginitis.

Gynecort *Combe, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Gynecotex *Veropharm, Rus.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Gynedol *DWD, India.*
Belladonna (p. 2453·3); calcium lactate (p. 1784·1); potassium bromide (p. 2461·1); valerian (p. 2640·2).

Gynéfam *Effik, Fr.*
Vitamins; minerals; omega-3 fatty acids (p. 1460·1).
Nutritional supplement in pregnancy and lactation.

GyneFix
Note: this name may be used for preparations of different composition.
Gynlameda, Ger.
Copper-wound polypropylene thread (p. 2057·1).
Intra-uterine contraceptive device.

Gynefix
Note: this name may be used for preparations of different composition.
Rottapharm, Ital.; Family Planning Sales, UK.
Copper-wound polypropylene thread (p. 2057·1).
Intra-uterine contraceptive device.

Ivax, Arg.
Ascorbic acid (p. 2110·3).
Bacterial vaginosis.

Gynegella P *Rottapharm, Ital.*
Loosestrife (p. 2545·2); oxogluric acid (p. 2579·1).
Vaginal douche.

Gynelle *Eczacibasi, Turk.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Gynelle 375 *CCD, Fr.*
Copper-wound polyethylene (p. 2057·1).
Intra-uterine contraceptive device.

Gyne-Lotremin *MSD, Hong Kong; Schering-Plough, Indon.†; Schering-Plough, Malaysia.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis; vaginitis.

Gyne-Lotrimin *Schering-Plough, USA.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Gynélys *Lero, Fr.*
Cranberry (p. 2488·1); *Lactobacillus fermentum* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Urinary-tract disorders; maintenance of vaginal flora.

Gyneplen *Effik, Spain.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea, in women; combined oral contraceptive in women with androgenic symptoms.

Gynepriston *Stada, Rus.*
Mifepristone (p. 2138·1).
Postcoital oral contraceptive.

GynePro *Innovitelle, Malaysia; United Laboratories, Philipp.*
Chlorhexidine gluconate (p. 1743·3).
Genital disinfection; vaginitis.

Gynera *Schering, Braz.; Bayer, Chile; Schering, Gr.; Bayer, Hong Kong; Bayer Schering, Indon.; Bayer, Israel; Bayer Schering, Malaysia; Bayer, Philipp.; Bayer, Port.; Bayer, Singapore; Bayer, Switz.; Bayer, Thai.; Schering, Venez.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Gynergène Caféiné *CSP, Fr.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Gynerium *Ivax, Arg.*
Ketoconazole (p. 585·3); secnidazole (p. 947·3).
Urogenital candidiasis; trichomoniasis.

Gynerium UD *Ivax, Arg.*
1 Capsule, fluconazole (p. 578·2); 4 tablets, secnidazole (p. 947·3).
Urogenital candidiasis; trichomoniasis.

Gynerol *Invision, India.*
Oral powder: Vitamins; soya protein (p. 2092·3).

Invision, India.
Tablets: Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gynesol *Biolab, Philipp.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Gynest *Marlborough Pharmaceuticals, UK.*
Estriol (p. 2274·3).
Atrophic vaginitis; kraurosis; pruritus vulvae; dyspareunia.

Gynesten-B *Bangkok Lab & Cosmetic, Thai.†*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Infected skin disorders.

Gynestin
Note: this name may be used for preparations of different composition.
Kenyaku, Thai.
⊗Clotrimazole (p. 576·2); urea (p. 1727·3).
Trichomoniasis.

Gynestin 200
Note: this name may be used for preparations of different composition.
Kenyaku, Thai.
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Gynestrel *Recordati, Ital.*
Naproxen sodium (p. 98·2).
Gynaecological disorders.

Gynestril *Mir, Rus.*
Mifepristone (p. 2138·1).
Uterine fibroids.

Gynevac *Vakcina, Hung.*
Lactobacillus acidophilus (p. 2596·3).
Maintenance of vaginal flora.

Gynezol
Note: this name may be used for preparations of different composition.
Gulf Drug, S.Afr.
Clotrimazole (p. 576·2).
Vaginal fungal infections.

Sagmel, Rus.
Miconazole nitrate (p. 589·1).
Fungal vaginal infections.

Gyne-Zole *Marching, Hong Kong.†*
Clotrimazole (p. 576·2).

Gyn-Hydralin *Bayer, Hong Kong.*
Glycine (p. 2071·2).
Genital pruritus; soap substitute.

Gynipral *Nycomed, Austria; Nycomed, Cz.; Nycomed, Rus.; Takeda, Switz.; Nycomed, Ukr.*
⊗Hexoprenaline sulfate (p. 1211·1).
Premature labour.

Gynista *Micro, India.*
⊗Raloxifene (p. 2303·1).
Osteoporosis.

Gyno Canesten *Bayer, China; Bayer, Venez.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Gyno Daknax *Pharlab, Braz.*
Miconazole (p. 588·3).

Gyno Ferro *Adeka, Turk.*
Ferrous glycolsulphate; folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Gyno Iruxol *Abbott, Braz.*
⊗Chloramphenicol (p. 257·1); collagenase (p. 2484·1).
Vulvovaginal infections.

Gyno Zalain *Pfizer, Braz.*
Sertaconazole nitrate (p. 593·2).
Fungal vaginal infections.

Gyno-Canesten *Bayer, Ital.; Bayer, Turk.*
Clotrimazole (p. 576·2).
Fungal vulvovaginal infections; balanitis.

Gynocanesten *Bayer, Chile.*
Clotrimazole (p. 576·2).
Vaginal infections.

Gyno-Canestène *Bayer, Switz.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Gynocastus *Zilly, Ger.*
⊗Vitex agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Gynoclin-V *Janssen-Cilag, Mex.*
⊗Clindamycin phosphate (p. 269·3); terconazole (p. 595·2); fluocinolone acetonide (p. 1636·1).
Vaginal infections.

Gyno-Clotrin *Utopian, Thai.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Gynoco *TO-Chemicals, Thai.†*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Vaginal fungal infections; trichomoniasis.

Gyno-Control *Arkopharma, Fr.*
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement; maintenance of vaginal flora.

Gynocream *Pharma Synth, India.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).

Gyno-Daktar *Janssen-Cilag, Ger.*
Miconazole nitrate (p. 589·1).
Fungal vaginal infections.

Gyno-Daktarin *Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; McNeil, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Gr.; Johnson & Johnson, India; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Johnson & Johnson, Port.; Johnson & Johnson, S.Afr.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Miconazole nitrate (p. 589·1).
Balanitis; vulvovaginal fungal and Gram-positive bacterial infections.

Gynodal *Baxter, Braz.*
Megestrol acetate (p. 2289·2).
Malignant neoplasms.

Gynodan *Uni-Sankyo, India.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; hereditary angioedema; pre-operative endometrial thinning; menorrhagia.

Gynodel *Il-Ko, Turk.*
Bromocriptine mesilate (p. 895·3).
Lactation inhibition; hyperprolactinaemia; female infertility; benign breast disorders; menstrual disorders; acromegaly; prolactinoma; parkinsonism.

Gynoderain *Leti, Venez.*
Triticum aestivum (p. 2647·1).
Vaginal disorders.

Gynodex *Zimalaya, India.*
⊗Pterocarpus santalinus; rubia cordifolia; tribulus terrestris (p. 2633·3).

Gynodian Depot *Bayer, Arg.; Bayer, Austria; Bayer, Chile; Bayer Schering, Cz.; Bayer, Ger.; Theramex, Ital.; Bayer Schering, Pol.†; Schering, Rus.†; Bayer, Switz.; Schering, Venez.*
⊗Estradiol valerate (p. 2271·2); prasterone enantate (p. 2299·2).
Menopausal disorders; osteoporosis.

Gynodiol *Fielding, USA.*
Estradiol (p. 2271·1).
Breast cancer; menopausal disorders; oestrogen deficiency; osteoporosis; prostatic cancer.

Gyno-Femidazol *Richter, Pol.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial vaginal infections.

Gynofen *Bayer, Gr.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Androgen-related acne, alopecia, hirsutism, and seborrhoea in women.

Gynoferon *Kocak, Turk.*
Ferrous sulfate (p. 2062·2); mucoproteose (p. 2564·3); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Gynoflor *Pfizer, Austria; Merck, Belg.; Vivax, Cz.; Pierre Fabre, Ger.; Medinova, Hong Kong; Medico Uno, Hung.; Medinova, Malaysia; Merck, Pol.; Pierre Fabre, Port.; Medinova, Switz.; Medinova, Thai.; Abdi, Turk.; Medinova, Ukr.*
Lactobacillus acidophilus (p. 2596·3); estriol (p. 2274·3).
Vaginal disorders; restoration of vaginal flora; atrophic vaginitis.

Gynoflor E *Invar, Rus.*
Lactobacillus acidophilus (p. 2596·3); estriol (p. 2274·3).
Menopausal atrophic vaginitis; bacterial vaginosis; restoration of vaginal flora.

Gynofol *Rovafarm, Arg.*
Folic acid (p. 2063·1).
Anaemias.

Gynofort *Ethica, Indon.; Hyphens, Malaysia; Gedeon Richter, Rus.; Hyphens, Singapore†; Gedeon Richter, Ukr.*
Butoconazole nitrate (p. 574·2).
Vulvovaginal candidiasis.

Gyno-Fungix *Janssen-Cilag, Braz.*
Terconazole (p. 595·2).
Vulvovaginal candidiasis.

Gynogen
Note: this name may be used for preparations of different composition.
Biolina, Turk.
Genistein (p. 2620·3).
Menopausal disorders.

Uni-Sankyo, India.
⊗Menotrophin (p. 2284·1).

Gynogena *Bangkok Lab & Cosmetic, Thai.*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis; trichomoniasis; anaerobic bacterial infections.

Gynogesic *T-Boma, Hong Kong†; Bangkok Lab & Cosmetic, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Gyno-Icaden *Bayer, Braz.*
Isoconazole nitrate (p. 583·2).
Vulvovaginal candidiasis.

Gynokadin *Besins, Ger.; Kade, Ger.*
Estradiol (p. 2271·1) or estradiol valerate (p. 2271·2).
Menopausal disorders; osteoporosis.

Gynol II *Johnson & Johnson, S.Afr.†; Advanced Care, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Gynolakt *Teva, Ukr.*
Lactobacillus plantarum (p. 2596·3).
Vaginitis; vulvovaginitis.

Gyno-Lomexin *Organon, Turk.*
Fenticonazole nitrate (p. 578·1).
Vulvovaginal candidiasis.

Gynomax *Farmoquimica, Braz.; Embil, Turk.*
Tioconazole (p. 595·3); tinidazole (p. 949·2).
Fungal infections.

Gyno-Mikozal *Julphar, UAE.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Gynomyk *Will-Pharma, Belg.; Jolly-Jatel, Fr.†; Will-Pharma, Neth.*
Butoconazole nitrate (p. 574·2).
Fungal vulvovaginal infections.

Gyno-Mykotral *Rosen, Ger.*
Miconazole nitrate (p. 589·1).
Fungal genital infections.

Gyno-Neuralgin *Pfleger, Ger.*
Ibuprofen (p. 68·2).
Dysmenorrhoea.

Gynonys *Uni-Sankyo, India.*
Injection: Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Uni-Sankyo, India.
Tablets: Allylestrenol (p. 2255·2).
Threatened miscarriage.

Gynopac *Farmoquimica, Braz.*
Cream, tioconazole (p. 595·3); tinidazole (p. 949·2); tablets, secnidazole (p. 947·3).
Vulvovaginal infections.

Gyno-Pevaryl *Janssen-Cilag, Austria; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Pol.; Johnson & Johnson, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Econazole nitrate (p. 577·3).
Fungal balanitis; fungal and Gram-positive vulvovaginal infections.

Gynophilus *Lyocentre, Fr.; Abbott, Ger.*
Lactobacillus casei rhamnosus (p. 2596·3).
Restoration of vaginal flora.

Gynoplix *Bouchara-Recordati, Hong Kong.*
Metronidazole (p. 936·1).
Vaginal infections.

Gyno-Plus
Note: this name may be used for preparations of different composition.
Jin Yang, Malaysia.
Cimicifuga (p. 2478·1); St John's wort (p. 449·1).
Menstrual disorders; menopausal disorders.

Gynopower *Plethico, Ukr.*
Dolichos pruriens; asparagus (p. 2450·2) withania somnifera (p. 2450·2); liquorice (p. 1853·2); saraca indica.
Dietary supplement for women.

Gynorelle *Gynopharm, Chile.*
24 Tablets, chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive; acne.

Gynormal *Andromaco, Arg.*
Cream; pessaries: Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vaginal infections.

Andromaco, Arg.
Tablets: Tinidazole (p. 949·2).
Anaerobic bacterial infections of the vagina; protozoal vaginal infections.

Gynosan *Piramal, India.*
Chlorquinaldol (p. 260·1).

Gynosant *Gerolymatos, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Gynoset *Signova, India.*
⊗Asparagus racemosus (p. 2614·2); punarnava (p. 2601·1); tribulus terrestris (p. 2633·3); ashwagandha (p. 2450·2).

Gynosoya *Arkopharma, Belg.*
Soya (p. 2092·3).
Menopausal disorders.

Gynospor *Garec, S.Afr.†*
Miconazole nitrate (p. 589·1).
Vaginal fungal infections.

Gynostat *Laboratorios Chile, Chile.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Gynostatum *Ranbaxy, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Gynosten *Bangkok Lab & Cosmetic, Thai.*
Clotrimazole (p. 576·2).
Vaginal infections.

Gyno-Tardyferon *Pharmafabre (Фармафамп), Gr.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Pierre Fabre, Rus.; Robapharm, Switz.; Pierre Fabre, Turk.; Pierre Fabre, Ukr.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); mucoproteose (p. 2564·3). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.

Gyno-Terazol *Johnson & Johnson, India.*
Terconazole (p. 595·2).
Vulvovaginal candidiasis.

Gynotocin *Svizera, India.*
Oxytocin (p. 2143·1).
Labour induction; incomplete abortion; postpartum haemorrhage.

Gynotran *Bayer, Arg.; Bayer, Mex.; Embil, Turk.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1).
Vaginal candidiasis; trichomoniasis; bacterial vaginosis; vaginal infections.

Gyno-Travogen *Bayer, Austria; Schering, Pol.†; Bayer Schering, Rus.; Bayer, Singapore; Bayer, Switz.; Schering, Turk.; Bayer, Ukr.*
Isoconazole nitrate (p. 583·2).
Fungal and Gram-positive vaginal infections.

Gynotrim Kit *Svizera, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Gyno-Trimaze *Aspen, S.Afr.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Gyno-Trosyd *Pfizer, Fin.; Teofarma, Fr.; Pfizer, Hong Kong; Pfizer, Malaysia; Pfizer, S.Afr.†; Pfizer, Singapore; Pfizer, Turk.*
Tioconazole (p. 595·3).
Fungal vulvovaginal infections.

Gynova *Milano, Thai.†*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Fungal, trichomonal and bacterial vaginitis.

Gynovel *Genericon, Cz.*
Estradiol valerate (p. 2271·2); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Gynovin *Bayer, Arg.; Bayer, Austria; Bayer, Mex.; Bayer, Spain.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Gynovit *Vargas, Venez.*
Acetic acid (p. 2426·3).
Vulvovaginal disorders.

Gynovite Plus *Optimox, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Gynoxa *Kalbe, Indon.*
Nimorazole (p. 942·1); chloramphenicol (p. 257·1); nystatin (p. 590·3).
Vaginal infections.

Gynoxin *Zambon, Belg.; Recordati, Hung.; Recordati, Irl.; Recordati, Neth.; Recordati, Pol.; Recordati, UK.*
Fenticonazole nitrate (p. 578·1).
Fungal vulvovaginal infections.

GynPolar *Orion, Ger.*
Estradiol (p. 2271·1).
Menopausal disorders.

Gynut-N *Cipla, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; premenstrual syndrome; breast cancer; postponement of menstruation.

Gyonep *Chinta, Thai.*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Vaginal infections.

Gypernik *Veropharm, Rus.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Gyrablock *Medochemie, Cz.; Medochemie, Rus.†; Medochemie, Singapore.*
Norfloxacin (p. 333·3).
Bacterial infections.

Gyracip *Gry, Ger.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Gyracon *Pond's, Thai.*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Fungal, trichomonal and bacterial vaginitis.

Gyrax *Klar Sehen, India.*
Norfloxacin (p. 333·3).

Gyraxen *Korea United, Philipp.*
⊗Tamoxifen (p. 860·2).
Breast cancer.

Gyraze *Aarpik, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Gyrex *Berksam, Turk.*
Quetiapine fumarate (p. 1101·1).

Gyroflox *Gry, Ger.†; Laclin, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Gyros *Sandoz, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Gyselle *Spirig, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Gystat *Comed, India.*
Citrus bioflavonoids (p. 2505·2); ferrous gluconate (p. 2061·2); menadione (p. 2122·1); calcium phosphate (p. 1784·2); vitamin C (p. 2110·3).

Gyterna *Veropharm, Rus.*
⊗Metronidazole (p. 936·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3); prednisolone sodium phosphate (p. 1645·3).
Vaginal infections.

H Bacter *Mabra, Braz.*
Capsules, lansoprazole (p. 1851·3); tablets, clarithromycin (p. 266·2); capsules, amoxicillin trihydrate (p. 216·2).
Helicobacter pylori-associated peptic ulcer.

H2 Bloc *Biomedis, Philipp.*
Famotidine (p. 1842·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; heartburn; gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

H 2 Blocker *Ratiopharm, Ger.*
Cimetidine hydrochloride (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage; hypersensitivity reactions; gastro-oesophageal reflux.

H Tussan *Inibsa, Spain.†*
Anise oil (p. 2444·3); ivy (p. 2536·2); thyme oil (p. 2630·3).
Cough.

Ha Le Te *TianJin, China.*
⊗Halcinonide (p. 1639·3).
Skin disorders.

HAA *Cadila, India.*
Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2); zinc chloride (p. 2126·1).

Haarlemensis *Aspen, S.Afr.*
Precipitated sulfur (p. 1721·1); arachis oil (p. 2446·1); tar (p. 1723·3); turpentine oil (p. 2636·3).
Upper urinary-tract disorders.

Habebion *Medikon, Indon.†*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); vitamin B_{12} (p. 2107·2); intrinsic factor (p. 2534·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; nutritional supplement.

Habekacin *Meiji, Jpn.*
Arbekacin sulfate (p. 220·2).
Methicillin-resistant staphylococcal infections.

Habifac *Pekana, Neth.*
Formicicum acidum (p. 2507·1); nitricum acidum (p. 2572·3); baptisia tinctoria (p. 2647·2); glechoma hederacea spag (p. 2523·1); graphites (p. 2522·1); hepar sulphur (p. 1721·3); thuja occidentalis (p. 2629·3); vincetoxicum officinale.
Homoeopathic preparation.

Habitek *SJA, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic disorders.

Habitrol *Novartis Consumer, Canad.; Novartis Consumer, USA.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Novartis Consumer, NZ.
Nicotine resin (p. 2569·3) or nicotine (p. 2569·3).
Aid to smoking withdrawal.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

HaBiVa *Changchun, China.*
A haemorrhagic fever with renal syndrome vaccine (inactivated, bivalent) (p. 2388·2).
Active immunisation.

Habstal-Cor N *Steierl, Ger.*
Crataegus (p. 2488·1); digitalis purpurea (p. 1352·3); spigelia (p. 2621·3); strophanthus (p. 1507·2).
Homoeopathic preparation.

Habstal-Nerv N *STV, Hung.*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

HAC *Molnlycke, Belg.*
Cetrimonium bromide (p. 1742·3); chlorhexidine gluconate (p. 1743·3).
Wounds; burns; disinfection of skin, instruments, textiles, and surfaces.

Hacdil-S *Molnlycke, Belg.*
Cetrimonium bromide (p. 1742·3); chlorhexidine gluconate (p. 1743·3).
Disinfection of wounds and instruments.

Hacef *Harbin, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Hachemina Fuerte *Medea, Spain.†*
Aminobenzoic acid (p. 1694·2).
Alopecia; leucopenia; eye and skin disorders.

Hachiazule *Toyo Kasei, Jpn.*
Sodium gualenate (p. 1887·1); sodium bicarbonate (p. 1781·1).
Mouth and throat disorders.

Hachimijiogan *Tsumura, Jpn.*
Rehmannia root; cornus fruit; dioscorea rhizome; alisma rhizome; poria sclerotium; moutan bark; cinnamon bark (p. 2479·2); aconite tuber.
Traditional Kampo medicine.

Hacks *Ernest Jackson, UK.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2); vitamin C (p. 2110·3).
Cold symptoms; coughs.

Hacks Blackcurrant *Ernest Jackson, UK.*
Menthol (p. 2553·2); vitamin C (p. 2110·3).
Cold symptoms; coughs.

Hactos *Hubert, UK.*
Capsicum (p. 2469·3); peppermint oil (p. 1877·1); anise oil (p. 2444·3); clove oil (p. 2481·3).
Coughs; cold symptoms; catarrh.

Had3 *Blubell, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 21 13·1).
Calcium and vitamin D supplement.

Hadarax *GreaterPharma, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Pruritus.

Hadensa *Ferrer, Spain.*
Chlorocarvacrol (p. 1747·3); ichthammol (p. 1705·3); menthol (p. 2553·2).
Anorectal disorders.

Hädensa *Kolassa, Austria; Leiras, Fin.*
Suppositories: Monochlorocarvacrol (p. 1747·3); ichthammol (p. 1705·3); chamomile oil (p. 2474·1); menthol (p. 2553·2).
Anorectal disorders.

Merz, Austria; Leiras, Fin.†
Ointment: Monochlorocarvacrol (p. 1747·3); ichthammol (p. 1705·3); menthol (p. 2553·2).
Anorectal disorders.

Hadlinol *Medicus, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Hae 1 Complex *Thompsons, Canad.†*
Hamamelis virginiana (p. 2523·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Hae 2 Complex *Thompsons, Canad.†*
Aesculus hippocastanum (p. 2431·2); aloe vera (p. 1693·2); collinsonia canadensis (p. 2622·2); hydrochloric acid (p. 2528·3).
Homoeopathic preparation.

Haecodes *Yuriya-Farm, Ukr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; haemodialysis.

Haelan *Typharm, UK.*
⊗Fludroxycortide (p. 1635·2).
Skin disorders.

Haem Up *Cadila, India.*
Syrup: ⊗Glycerinated haemoglobin (p. 1154·3); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); zinc sulfate (p. 2126·2); ferric ammonium citrate (p. 2060·1).
Iron-deficiency anaemia.

Haem Up-Z *Cadila, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Haemaccel *CSL, Arg.; AFT, Austral.; DeltaSelect, Austria†; Sanofi-Aventis, Braz.; Piramal, Denm.; DeltaSelect, Ger.†; Piramal, Gr.; Piramal, India; Dexa, Indon.; Piramal, Irl.; Antibioticos, Mex.; Piramal, Neth.; DeltaSelect, Norw.; AFT, NZ; Piramal, Port.; Mednostica, S. Afr.; DeltaSelect, Singapore; Sanofi-Aventis, Thai.; Kora, UK.†*
⊗Polygeline (p. 1160·3).
Extracorporeal circulation; organ perfusion; plasma volume expansion; shock; hypovolaemia; plasma substitute.

Haemanal *Sigmapharm, Austria.*
Hydrastinine hydrochloride (p. 2528·1); chlorocarvacrol (p. 1747·3); zinc oxide (p. 1729·1); tannic acid (p. 2625·2); menthol (p. 2553·2).
Anorectal disorders.

Haemaprot *Troikaa, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Haemarange *Emcure, India.*
Iron polymaltose (p. 2077·2).

Haemate *CSL, Arg.; CSL, Austria; CSL, Belg.; CSL, Braz.; CSL, Cz.; CSL, Denm.; CSL, Fin.; CSL, Ger.; CSL, Gr.; ZLB Behring, Hong Kong†; CSL, Hung.; CSL, Israel; CSL, Ital.; CSL, Neth.; CSL, Norw.; CSL, Port.; CSL, Spain; CSL, Swed.; CSL, Switz.; Farma-Tek, Turk.; Aventis Behring, UK.*
A factor VIII preparation (p. 1148·1).
Haemophilia A; factor VIII deficiency; haemorrhagic disorders; von Willebrand's disease.

Haematinga *Inga, India.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Inga, India.
Oral liquid: Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); sorbitol (p. 2092·1).

Haemato-carb *Haemato, Ger.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Haemato-folin *Haemato, Ger.*
Calcium folinate (p. 2066·3).
Prevention of methotrexate toxicity; adjunct to fluorouracil in colorectal cancer.

Haemato-fu *Haemato, Ger.†*
Fluorouracil (p. 795·2).
Colorectal cancer; breast cancer; pancreatic cancer.

Haematogen *Borshchagovskii, Ukr.*
Defibrinated bovine blood (p. 2444·1).
Anaemias.

Haemato-tron *Haemato, Ger.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Haemaze *VHB, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc (p. 2126·1).

Haemex *HWS OTC, Austria.*
Aesculus (p. 2431·2); aloe (p. 1816·1); ratanhia (p. 2603·3); sepia (p. 2613·1).
Homoeopathic preparation.

Haem-F *Sun, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3).

Haemflow-Z *Akums, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Haemglow *Finecure, India.*
Capsules: Calcium hydrogen phosphate (p. 1783·3); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Finecure, India.
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Haemglow-Z *Finecure, India.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Haemgrow *Fem Care, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Haemiton *AWD, Ger.†; CT, Ger.†; AWD, Rus.†*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Haemocaine *Galenium, Indon.*
⊗Lidocaine hydrochloride (p. 1988·2); aluminium subacetate (p. 2440·1); hydrocortisone acetate (p. 1640·1); zinc oxide (p. 1729·1).
Haemorrhoids.

Haemocare *Servocare, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Haemocomplettan *CSL, Austria; CSL, Braz.; CSL, Cz.; CSL, Fr.†; CSL, Ger.; IFET (ΙΦΕΤ), Gr.; CSL, Hung.; CSL, Israel; CSL, Neth.; CSL, Port.; CSL, Switz.; Farma-Tek, Turk.*
Fibrinogen (p. 1151·3).
Haemorrhage; fibrinogen disorders; hypofibrinogenaemia; haemorrhagic disorders.

Haemocortin *Streuli, Switz.†*
Ointment: ⊗Hydrocortisone acetate (p. 1640·1); bismuth oxychloride (p. 1821·3); lidocaine hydrochloride (p. 1988·2); zinc oxide (p. 1729·1).
Anorectal disorders.

Haemoctin *Biotest, Gr.; Biotest, Ital.; Biotest, Neth.; Biotest, Pol.†; Biotest, Rus.; Biotest, Spain; Biotest, Switz.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A.

Haemoctin SDH *Biogam, Arg.; Biotest, Austria; Biotest, Cz.; Biotest, Ger.; Biotest, Hung.; Paviour, India; Biotest, Israel; Biotest, Port.†; Biotest, Singapore; Biotest, Thai.; Kansuk, Turk.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; factor VIII deficiency.

Haemodez-N *Biochimic, Rus.*
Povidone (p. 2204·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1).
Infections; liver disorders.

Haemodyn *Astellas, Austria.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Haemoetin *Biotest, Turk.†*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Haemo-Exhirud Bufexamac *Winthrop, Ger.†*
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Haemoferon
Note: this name may be used for preparations of different composition.
Shreya, India.
Folic acid (p. 2063·1); iron carbonyl (p. 2073·1); vitamin C (p. 2110·3).

Sperko, Ukr.
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron and folate deficiency anaemia; iron supplement.

Haemogal *Galenium, Indon.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2); vitamin C (p. 2110·3); butcher's broom (p. 2463·1).
Haemorrhoids.

Haemo-Glukotest *Roche Diagnostics, Braz.†; Sanofi-Aventis, India.*
Test for glucose in blood (p. 2516·3).

Haemo-Glukotest 20-800 *Roche Diagnostics, Mex.†*
Test for glucose in blood (p. 2516·3).

Haemokinase *Biosena, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Haemol *Minova, India.*
Vitamin B substances (p. 2102·3); minerals.

Haemolan *Streuli, Switz.†*
Ointment: Lidocaine hydrochloride (p. 1988·2); bismuth oxychloride (p. 1821·3); zinc oxide (p. 1729·1); menthol (p. 2553·2); peru balsam (p. 2587·1).
Anorectal disorders.

Streuli, Switz.†
Suppositories: ⊗Lidocaine hydrochloride (p. 1988·2); bismuth oxychloride (p. 1821·3); zinc oxide (p. 1729·1); menthol (p. 2553·2); peru balsam (p. 2587·1); ethacridine lactate (p. 1732·3); ephedrine hydrochloride (p. 1663·2); hamamelis (p. 2523·3).
Anorectal disorders.

Haemonine *Biotest, Austria; Biotest, Ger.; Biotest, Gr.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Haemopressin *Torrex, Austria; Speciality European Pharma, Fr.; Curatis, Ger.; Meduna, Ger.; IS Pharma, Irl.; IS Pharma, Neth.; Proreo, Switz.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage; gastric haemorrhage.

Haemoproct *Julphar, UAE.*
Tribenoside (p. 2633·3); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Haemoprot *Troikaa, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Haemoprotect *Betapharm, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Haemoprotex *Ind-Swift, India.*
Vitamin B substances (p. 2102·3); iron choline citrate (p. 2060·2); protein hydrolysate (p. 2086·2).

Haemoral *Ritter, Hong Kong.†*
Ointment: Hydroxypolyethoxydodecane (p. 2194·1); bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1); peru balsam (p. 2587·1).
Anorectal disorders.

Ritter, Hong Kong.†
Suppository: Aluminium acetotartrate (p. 2440·1); trichloro-i-butylester of salicylic acid; sodium acetate (p. 1781·1).
Anorectal disorders.

Haemo-Red *Eagle, Austral.*
Iron (p. 2073·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); copper (p. 2057·1); iodine (p. 2336·3); yellow dock (p. 2649·3); urtica (p. 2639·3).
Tonic.

Haemored *Invision, India.*
Vitamins; minerals.

Haemorol *Phebra, Austral.; AFT, NZ.*
Phenol (p. 1763·3).
Haemorrhoids.

Haemorrhoid Cream *Nelson, UK.*
Aesculus hippocastanum (p. 2431·2); calendula officinalis (p. 2465·2); hamamelis virginica (p. 2523·3); paeonia officinalis.
Homoeopathic preparation.

Haemorrhoid-Gastreu N *Reckeweg, Ger.*
Collinsonia canadensis (p. 2622·2); hamamelis (p. 2523·3); nux vomica (p. 2573·3); paeonia officinalis; acidum nitricum (p. 2572·3); aesulus (p. 2431·2); lycopodium (p. 2546·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Haemosol H *Haemotec, Canad.†*
Acetic acid (p. 2426·3); calcium chloride (p. 1783·1); glucose (p. 2068·3); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1) (p. 1778·2).
Haemodialysis.

Haemosolvate *NBI, S.Afr.*
Factor VIII (p. 1148·1).
Haemophilia A; von Willebrand's disease.

Haemosolvex *NBI, S.Afr.*
Factor IX (p. 1149·3).
Coagulation disorders.

Haemostabil *Medpolimer, Rus.*
⊗Dextran 40 (p. 1138·1).
Hypovolaemia; shock.

Haemovital *Pharmadass, UK.*
Vitamins; minerals; nutritional supplements.
Tonic.

Haemo-Z *Laborate, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Haemplus *Wings, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Haemrise *NB, India.*
Ascorbic acid (p. 2110·3); iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Haems *Shreshtha, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc (p. 2126·1).

Haem-Up *Cadila, India.*
Oral liquid: Copper sulfate (p. 2057·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); manganese sulfate (p. 2081·2); vitamin B_{12} (p. 2107·2).

Haem-Up Gems *Cadila, India.*
⊗Copper sulfate (p. 2057·2); ferric ammonium citrate (p. 2060·1); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); glycerinated haemoglobin (p. 1154·3); manganese sulfate (p. 2081·2); vitamin B_{12} (p. 2107·2).

Haemup-C *Cadila, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Haem-XT *Forgo, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Haenal akut *Strathmann, Ger.*
Quinisocaine hydrochloride (p. 1996·1).
Anorectal disorders; insect stings.

Haenal Hamamelis *Strathmann, Ger.*
Hamamelis (p. 2523·3).
Anorectal disorders.

Haepcard *Sandoz, Ital.*
Atorvastatin (p. 1309·2).

HAES-Rheopond *Serag-Wiessner, Ger.†*
⊗Pentastarch (p. 1146·1) in sodium chloride.
Hypovolaemia; shock.

HAES-steril *Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, China; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.†; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Indon.; Fresenius Kabi, Ital.; Fresenius Kabi, Mex.; Fresenius Kabi, Neth.†; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Singaporet; Fresenius Kabi, Swed.†; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.†; Fresenius Kabi, Turk.; Fresenius Kabi, UKt; Fresenius Kabi, Ukr.*
⊗Pentastarch (p. 1146·1) in sodium chloride.
Plasma volume expansion; shock; haemodilution; microcirculatory disorders; hypovolaemic shock.

HAES-sterile *Fresenius Kabi, Israel.*
⊗Pentastarch (p. 1146·1).
Plasma volume expansion; shock; burns.

Hafaxin *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Haff-C-Plex *Haffkine, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Haffkinol *Haffkine, India.*
Cream: Dichloroxylenol (p. 1750·2).

Haffkine, India.
Topical liquid: Terpin hydrate (p. 1678·2).

Hafif *Teva, Israel.*
Carbaryl (p. 2150·1).
Pediculosis.

Hagevir *Cosmopharm, Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Hai Bei Lin *Haida, China.*
Moclobemide (p. 437·2).
Depression; social phobia.

Hai Feng Quan *Qi Li, China.*
Lappaconitine hydrobromide (p. 1418·1).

Hai Fu Wei *Suzhou No 1, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Hai Fu Xin *Lishizhen, China.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Hai Jing Wu *Qi Li, China.*
Lysine hydrochloride (p. 2079·3).

Hai Kang Xin *Guang Do, China.*
Diammonium glycyrrhizinate.

Hai Li Jian *Huatuo Tianya, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Hai Ling Yi *Hailing, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Hai Meng Hui *Tai Sheng, China.*
Nimodipine (p. 1455·2).
Prevention of nerve damage following subarachnoid haemorrhage.

Hai Meng Jing Qing *Tai Sheng, China.*
Asarone.

Hai Mi Ke *Beidefu, China; Zhaohui, China.*
Mebendazole (p. 158·3); levamisole hydrochloride (p. 157·2).

Hai Nuo Xin *Guang Da, China.*
Tiopronin (p. 1578·1).

Hai Pu Mei Xin *Helida, China.*
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Hai Si Bi Da *Jincheng Haisi, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Hai Si Wei *Mei Do Kang Jia Le, China.*
Fructose (p. 2068·2); glucose (p. 2068·3); sodium lactate (p. 1781·2); sodium chloride (p. 1795·1); magnesium chloride (p. 1787·1); monobasic sodium phosphate (p. 1791·1); potassium chloride (p. 1793·2).

Hai Si Xin Da *Jincheng Haisi, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Hai Di Te *Huayuan Century, China.*
Hydrotalcite (p. 1845·2).
Dyspepsia.

Hai Tian Xin *Gupeng, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Hai Wei Ke *Changchun, China.*
A live attenuated hepatitis A vaccine (p. 2388·3).
Active immunisation.

Hai Zhi Lin *Haiji, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Hai Zhi Yuan *Haiji, China.*
⊗Somatropin (human, recombinant) (p. 1919·3).
Growth hormone deficiency; HIV-associated cachexia; short bowel syndrome.

Haibaike *Hiteck Bio, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Haichao *Haini, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Haifuxun *Hailing, China.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Haikela *Hailing, China.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Hailun *Bausch & Lomb, China.*
Levofloxacin hydrochloride.
Bacterial eye infections.

Haimo Laishi *RAAS, China.*
Human coagulation factor VIII (p. 1148·1).
Factor VIII deficiency.

Hainosankyuto *Tsumura, Jpn.*
Platycodon root; liquorice (p. 1853·2); immature orange; peony root; jujube; ginger (p. 1844·1).
Traditional Kampo medicine.

Haiprex *Meda, Denm.*
Methenamine hippurate (p. 323·1).
Urinary-tract infections.

4 Hair *Marlyn, USA.*
Vitamins; minerals; amino acids.

Hair A-Gain *Key, Austral.*
Minoxidil (p. 1438·3).
Hair loss.

Hair Booster *Nature's Bounty, USA.*
Vitamin B substances (p. 2102·3); minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Hair and Nails *Floxia, Singapore.*
Amino acids; urtica (p. 2639·3); zinc oxide (p. 1729·1); hypromellose (p. 2189·2); colloidal silicon (p. 2209·1); vitamin B substances (p. 2102·3).
Dietary supplement for healthy hair and nails.

Hair Nutrition *Cantassium Co., UK.*
Vitamins; minerals.

Hair Regrowth *Vita Health, Canad.*
Minoxidil (p. 1438·3).
Alopecia.

Hair Retreva *Southern Cross, Austral.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Hair Skin & Nails
Note: this name may be used for preparations of different composition.
Bioglan, Austral.
Silica (p. 2208·3); vitamins; minerals.
Dietary supplement.

Cenovis, Austral.
Vitamins; minerals; amino acids; rorippa nasturtium-aquaticum; rose fruit (p. 2607·1); parsley (p. 2583·3); fucus vesiculosus; equisetum (p. 2500·1); rutoside (p. 2505·3); lecithin (p. 2542·2); dried yeast (p. 2125·2); citrus bioflavonoids (p. 2505·2).
Maintenance of healthy hair, skin, and nails.

Hair 4 U *Glenmark, India.*
Minoxidil (p. 1438·3).
Alopecia.

Hairclin *Ariston, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Hairex *Kopran, India.*
Minoxidil (p. 1438·3).
Alopecia.

Hairgain *Perrigo, Israel.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Hairgrow *Dar Al Dawa, Hong Kong.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Hairmonius *Hoe, Malaysia.*
Capillisil; exsymol herbal complex; tocotrienol; dexpanthenol (p. 2582·2).
Hair and scalp tonic.

Hairplus *Euroderm, Arg.*
Lotion: ⊗Salicylic acid (p. 1719·1); calcium pantothenate (p. 2085·2); tricopeptides; collagen (p. 2483·2); urea (p. 1727·3).
Dandruff; seborrhoeic dermatitis.

Euroderm, Arg.
Shampoo: Pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

Hairscience Anti-Dandruff *Ego, Austral.*
Miconazole (p. 588·3).
Scalp disorders.

Hairstim-HGF *Bionova, India.*
Vitamins; minerals; ubidecarenone (p. 2637·1); grape seed extract (p. 2521·3).

Hairtene *Labesfal, Port.†*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Hair-Treat *Rekah, Israel.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

HairVit *Pharmadass, UK.*
Vitamins; minerals; trace elements.

Hairway *Gabriel, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Hairy Lemon *Ascent, Austral.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); guarana (p. 2648·2); ginseng (p. 2513·3).
Tonic.

Haishubi *Haibin, China.*
Sulbactam (p. 360·1); cefoperazone.
Bacterial infections.

Haitaxin *Haibin, China.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Haitishu *Daewon, China.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Haitong *Zhengda Haier, China.*
Mannose ester.
Hyperlipidaemias; ischaemic cerebrovascular disorders; cardiovascular risk reduction.

Haitrax *Alvartis, Mex.*
Omeprazole (p. 1867·2).

Hajime *Main Life, Hong Kong.†*
⊗Atenolol (p. 1308·2).

H-AL *Sevapharma, Cz.*
A range of allergen extracts (p. 2434·3).
Hyposensitisation.

HAL *Hal, Neth.*
A range of allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.

Halac Kit *Acella, USA.*
⊗Ointment, ulobetasol propionate (p. 1650·3); lotion, ammonium lactate (p. 1694·3).
Skin disorders.

Halaven *Eisai, Austria; Eisai, Belg.; Eisai, Cz.; Eisai, Denm.; Eisai, Fin.; Eisai, Fr.; Eisai, Ger.; Eisai, Gr.; Valeant, Hung.; Eisai, Irl.; Neopharm, Israel; Eisai, Ital.; Eisai, Jpn; Eisai, Neth.; Eisai, Norw.; Valeant, Pol.; Eisai, Port.; Eisai, Singapore; Eisai, Spain; Eisai, Swed.; Eisai, Switz.; Eisai, UK; Eisai, USA.*
Eribulin mesilate (p. 788·2).
Breast cancer.

Halazolin *Warsaw-Polfa, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis media.

Halcepin *Vamsler, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Halcicomb
Note: this name may be used for preparations of different composition.
BMS, Venez.
⊗Halcinonide (p. 1639·3); nystatin (p. 590·3).
Infected skin disorders.

Halciderm *Teofarma, Ital.*
Cream: ⊗Halcinonide (p. 1639·3).
Skin disorders.

Teofarma, Ital.
Tincture: ⊗Halcinonide (p. 1639·3); salicylic acid (p. 1719·1).
Skin disorders.

Halciderm Combi *Teofarma, Ital.*
⊗Halcinonide (p. 1639·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Halcion *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pharmacia, Irl.; Pfizer, Israelt; Pfizer, Ital.; Pfizer, Mex.; Pharmacia, NZ; Pfizer, Port.; Pharmacia, Rus.; Pfizer, S. Afr.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pharmacia Upjohn, USA.*
Triazolam (p. 1112·3).
Insomnia.

Halclor *Hindustan Antibiotic, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Haldid *Janssen-Cilag, Denm.*
⊗Fentanyl citrate (p. 60·1).
Analgesia in anaesthesia.

Haldin *Help, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; acid aspiration.

Haldol *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen, Hong Kong; East West, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.†; Janssen-Cilag, UK; Ortho McNeil, USA.; Janssen-Cilag, Venez.*
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion; alcoholism; mania; movement disorders; personality disorders; stuttering; nausea and vomiting; pain; alcohol withdrawal syndrome; agitation; chorea; bipolar disorder; psychosomatic disorders.

Haledol *Haledew, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Haleezy *Charak, India.*
Malabar nut (p. 2549·1); curcuma longa; liquorice (p. 1853·2); ocimum sanctum.

Halenol *Halsey, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Halexin *BMW, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Haley's M-O *Sterling Health, USA.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2).
Constipation.

Half Beta-Prograne *Tillomed, Irl.; Tillomed, UK.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; essential tremor; anxiety; migraine; hyperthyroidism; prophylaxis of gastrointestinal bleeding.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Half Capozide *BMS, Irl.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Half Inderal *AstraZeneca, Irl.; AstraZeneca, UK.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; hypertension; hyperthyroidism; anxiety; migraine; essential tremor; myocardial infarction; prophylaxis of gastrointestinal bleeding; variceal haemorrhage.

Half Securon *Abbott, UK.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; myocardial infarction.

Half Sinemet *MSD, Irl.; BMS, UK.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
These ingredients can be described by the British Approved Name Co-careldopa.
Parkinsonism.

Halfan *GSK, Fr.; Smith Kline & French, Port.; GSK, S.Afr.*
Halofantrine hydrochloride (p. 654·3).
Malaria.

HalfLytely and Bisacodyl Bowel Prep Kit *Braintree, USA.*
Powder for oral solution, macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1); tablets, bisacodyl (p. 1821·1).
Bowel evacuation.

Halfprin *Kramer, USA.*
Aspirin (p. 22·2).
Myocardial infarction.

Haliborange *Eurospital, Ital.; Boots Healthcare, NZ†; Seven Seas, UK.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Haliborange Calcium Plus Vitamin D *Seven Seas, UK.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).

Haliborange Halibonbons *Seven Seas, UK.*
Vitamin C (p. 2110·3).

Haliborange High Strength Vitamin C *Seven Seas, UK.*
Vitamin C (p. 2110·3); with or without vitamin E (p. 2119·1); bioflavonoids (p. 2505·2).

Haliborange Multivitamins *Seven Seas, UK.*
Vitamins; with or without calcium (p. 1783·1) and iron (p. 2073·1).

Haliborange Vitamin C *Seven Seas, Irl.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Halibut
Note: this name may be used for preparations of different composition.
Grunenthal, Port.
Halibut oil (p. 2071·3); zinc oxide (p. 1729·1).
Skin disorders; burns; ulcers; wounds.

Novartis Consumer, Spain.
Benzethonium chloride (p. 1738·1); vitamin A (p. 2098·3); zinc oxide (p. 1729·1).
Burns; cracked nipples; skin irritation; ulcers; wounds.

Halicar *DHU, Austria.*
Cardiospermum urtinktur.
Homoeopathic preparation.

DHU, Cz.; Peithner, Hung.
Cardiospermum halicacabum.
Homoeopathic preparation.

DHU, Ger.
Cardiospermum.
Homoeopathic preparation.

Halidace *Baroda, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Halidol *GSK, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Halidor *Egis, Hung.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Bencyclane fumarate (p. 1315·1).
Cerebral and peripheral vascular disorders; vascular eye disorders; gastrointestinal disorders; urinary-tract spasm; renal calculi; smooth muscle spasm.

Halipepsin *Streuli, Switz.†*
⊗Betaine hydrochloride (p. 2456·1); pepsin (p. 2586·1).
Gastrointestinal disorders.

Halita *Dentaid, Chile.*
Zinc lactate (p. 2126·2); chlorhexidine gluconate (p. 1743·3); cetylpyridinium chloride (p. 1743·1).
Halitosis.

Haliver *Velka, Gr.*
Thiocolchicoside (p. 2026·2).
Muscle relaxant.

Halixim *Haledew, India.*
Cefixime (p. 240·3).
Bacterial infections.

Halixol *Egis, Cz.; Egis, Hung.; Egis, Rus.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Halloo-Wach N *Nycomed, Ger.†*
Caffeine (p. 1203·3); glucose monohydrate (p. 2069·1).
Fatigue.

Halls *Adams, Canad.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Cough; nasal congestion; sore throat.

Halls Defense *Warner-Lambert, USA.*
Vitamin C (p. 2110·3).

Halls Mentholyptus *Adams Confectionery, UK.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Sore throat; cold symptoms; nasal congestion.

Ernest Jackson, Irl.†
Levomenthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Cold symptoms; nasal congestion; sore throat.

Halls Soothers Triple Action *Ernest Jackson, UK.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Halls Sugar Free Mentho-Lyptus *Warner-Lambert, USA.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Sore throats.

Halls Zinc Defense *Warner-Lambert, USA.*
Zinc acetate (p. 2126·1).
Zinc supplement.

Halls-Plus Maximum Strength *Warner-Lambert, USA.*
Menthol (p. 2553·2).

Halmanin *Synthesis, Rus.*
Salicylic acid (p. 1719·1); zinc oxide (p. 1729·1).
Eczema; hyperhidrosis.

Halmezin *Coronet, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); promethazine hydrochloride (p. 638·2); bromhexine hydrochloride (p. 1656·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Halo *Cristalia, Braz.*
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Psychoses.

Halobeta *Laborate, India.*
⊗Ulobetasol propionate (p. 1650·3).
Skin disorders.

Halobid *Crescent, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Halocef *Aristo, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Halodin *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Halofed *Halsey, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Halog *BMS, Braz.; BMS, Canad.†; BMS, Hong Kong†; BMS, Indon.†; Ranbaxy, USA; BMS, Venez.*
⊗Halcinonide (p. 1639·3).
Skin disorders.

BMS, Venez.
Topical solution: ⊗Halcinonide (p. 1639·3); salicylic acid (p. 1719·1).

Halog Capilar *BMS, Braz.*
⊗Halcinonide (p. 1639·3); benzoxonium chloride (p. 1739·2); salicylic acid (p. 1719·1).
Skin disorders.

Halog-E *Piramal, India.*
⊗Econazole (p. 577·2); halcinonide (p. 1639·3).

Halomed *Medifive, Thai.*
Haloperidol (p. 1077·1).
Anxiety; psychomotor agitation; alcohol withdrawal syndrome.

Halomycetin *Wabosan, Austria.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Halonate *Innocutis, USA.*
⊗Ointment, ulobetasol propionate (p. 1650·3); topical mousse, ammonium lactate (p. 1694·3).
Skin disorders.

Halonix *Cadila, India.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Halo-P *PP Lab, Thai.*
Haloperidol (p. 1077·1).
Anxiety; psychomotor agitation.

Halopace *Psychotropics, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Haloper *Teuto, Braz.; CT, Ger.; CTS, Israel; CTS, Rus.†*
Haloperidol (p. 1077·1).
Extrapyramidal disorders; pain; psychoses; vomiting; hiccups; tics; Tourette syndrome; movement disorders; stuttering; nausea and vomiting; behaviour disorders.

Haloperil *Psicofarma, Mex.*
Haloperidol (p. 1077·1).
Psychoses; movement disorders.

Halopidol *Janssen-Cilag, Arg.; Johnson & Johnson, India.*
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Behaviour disorders; psychoses; Tourette's syndrome; tics; anxiety; intractable hiccup; restlessness; confusion.

Halopol *General Drugs, Thai.*
Haloperidol (p. 1077·1).
Anxiety; psychomotor agitation; alcohol withdrawal syndrome; behaviour disorders in children.

Haloran *Hindustan Antibiotic, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Haloran Plus *Hindustan Antibiotic, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Haloseptil *Unipharm, Turk.*
Halazone (p. 1754·1).
Drinking water disinfection.

Halostrol *East West, India.*
⊗Ulobetasol propionate (p. 1650·3).
Skin disorders.

Halostrol-F *East West, India.*
⊗Ulobetasol propionate (p. 1650·3); fusidic acid (p. 302·1).

Halostrol-M *East West, India.*
⊗Ulobetasol propionate (p. 1650·3); miconazole nitrate (p. 589·1).

Halotestin *Pfizer, Gr.*
⊗Fluoxymesterone (p. 2278·1).

Halotex
Note: this name may be used for preparations of different composition.
Triton, India.
Haloperidol (p. 1077·1); trihexyphenidyl (p. 917·3).

Haloton *Triton, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Halovate *Glenmark, India.*
⊗Ulobetasol propionate (p. 1650·3).
Skin disorders.

Halovate-F *Glenmark, India.*
⊗Ulobetasol propionate (p. 1650·3); fusidic acid (p. 302·1).

Halovate-S *Glenmark, India.*
⊗Ulobetasol propionate (p. 1650·3); salicylic acid (p. 1719·1).

Haloxan *Eczacibasi-Baxter, Turk.*
Ifosfamide (p. 806·1).

Haloxen *Remedica, Singapore.*
Haloperidol (p. 1077·1).
Psychoses; tics; anxiety; behaviour disorders; hiccup.

Halozen *Bouzen, Arg.*
Haloperidol (p. 1077·1).

Halset *Novartis Consumer, Austria; Gebro, Cz.; Gebro, Hung.; Biofarm, Pol.; Gebro, Switz.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Halstabletten akute *Ratiopharm, Ger.†*
Cetylpyridinium chloride (p. 1743·1).
Inflammatory disorders of the mouth and throat.

Haltax *Hindustan Antibiotic, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Halycitrol *Tamar, Israel†; Laboratories for Applied Biology, UK.†*
Vitamin A (p. 2098·3); vitamin D substances (p. 2112·3).
Vitamin A and D deficiency; vitamin A and D supplement.

Hamadin N *Schwabe, Ger.*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea; acne.

Hamamelis Comp *Weleda, S.Afr.†*
Hamamelis (p. 2523·3); stibium metallicum (p. 2445·1).
Homoeopathic preparation.

Hamamélis Composé *Boiron, Fr.*
Hamamelis virginiana (p. 2523·3); anemone pulsatilla (p. 2600·2); echinacea angustifolia (p. 2498·1); fluoricum acidum (p. 2529·1); viburnum prunifolium (p. 2458·1); tussilago farfara (p. 1659·2); corylus avellana; aesculus hippocastanum (p. 2431·2).
Homoeopathic preparation.

Hamamelis-Homaccord *Heel, Austria.*
Hamamelis virginiana (p. 2523·3); silybum marianum (p. 1561·1).
Homoeopathic preparation.

Hamarityl *Genepharm, Gr.*
Minoxidil (p. 1438·3).

Hämatopan *Wolff, Ger.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Hämatopan F *Wolff, Ger.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Hamburg Tea *Aspen Consumer, S.Afr.*
Senna (p. 1885·1).
Constipation; bowel evacuation.

Hametan *Abdi, Turk.*
Hamamelis (p. 2523·3).
Haemorrhoids; skin disorders.

Hametum *Schwabe, Austria; Schwabe, Ger.; Spitzner, Ger.; Schwabe, Switz.*
Hamamelis (p. 2523·3).
Skin disorders; haemorrhoids; gingivitis; wounds; sunburn; epistaxis; bleeding gums.

Hametum-N *Schwabe, Switz.*
Hamamelis (p. 2523·3); aesculus (p. 2431·2).
Haemorrhoids.

HÄMFL *Fresenius Medical, Austria.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Haemofiltration.

Hamiltoderm-D *Rafarm, Gr.*
⊗Halcinonide (p. 1639·3).
Skin disorders.

Hamilton Body Wash *Hamilton, Hong Kong.†*
Light liquid paraffin (p. 2191·2); cocoamphodiacetate.
Skin disorders.

Hamilton Dry Skin *Hamilton, Austral.*
Bath oil: Light liquid paraffin (p. 2191·2).
Bath additive; dry skin.

Hamilton, Austral.
Lotion: ⊗Liquid paraffin (p. 2191·2); glycerol (p. 2517·2).
Dry skin.

Hamilton Everyday Face *Hamilton, NZ.*
SPF 30+: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Hamilton Family Sunscreen *Hamilton, Austral.*
Lotion spray SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3).
Sunscreen.

Hamilton, Austral.
SPF 15 cream: Octinoxate (p. 1715·1); octisalate (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Hamilton, Austral.
SPF 30+ cream; SPF 30+ lotion: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hamilton, Austral.
SPF 15 lotion: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Hamilton Lip Balm *Hamilton, Austral.*
SPF 15: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Dry chapped lips; sunscreen.

Hamilton Optimal *Hamilton, Austral.; Hamilton, NZ.*
SPF 30+: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Hamilton Pine Tar with Menthol *Hamilton, Austral.*
Menthol (p. 2553·2); cetrimide (p. 1742·1); dimeticone (p. 2209·3); pine tar (p. 1723·3).
Skin disorders.

Hamilton Quadblock *Hamilton, Austral.; Hamilton, NZ.*
Cream SPF 30+; lotion SPF 30+: Octil triazone (p. 1715·1); titanium dioxide (p. 1725·1); enzacamene (p. 1703·2).
Sunscreen.

Hamilton, Austral.; Hamilton, NZ.
Lipbalm SPF 30+: Enzacamene (p. 1703·2); octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octocrilene (p. 1715·2).
Sunscreen.

Hamilton Sensitive *Hamilton, Austral.; Hamilton, NZ.*
SPF 30+: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hamilton Skin Active Urederm Cleanser *Hamilton, Austral.*
Light liquid paraffin (p. 2191·2); surfactants.
Dry skin; soap substitute.

Hamilton Skin Active Urederm Cream *Hamilton, Austral.*
⊗Urea (p. 1727·3); glycerol (p. 2517·2); liquid paraffin (p. 2191·2).
Dry skin.

Hamilton Skin Repair *Hamilton, Hong Kong.†*
Dimeticone (p. 2209·3); cetrimide (p. 1742·1).
Skin disorders.

Hamilton Skin Therapy *Hamilton, Austral.*
Cream: ⊗Urea (p. 1727·3).
Dry skin.

Hamilton, Austral.
Wash: Soap substitute.

Hamilton Solastick *Hamilton, Austral.*
SPF 30+: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); octocrilene (p. 1715·2).
Sunscreen.

Hamilton, NZ.
Lipbalm SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

Hamilton Sportblock Broad Spectrum Milk *Hamilton, Austral.†*
SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hamilton Sunscreen *Hamilton, NZ.*
Lotion SPF 30+; cream SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hamilton, NZ; Intercare, NZ.
Topical Spray SPF 30+: Lotion SPF 15: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Intercare, NZ.
Cream SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Intercare, NZ.†
Clear Lotion: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

Intercare, NZ.†
Kidscreen; low Allergy Milk: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Intercare, NZ.†
Quadblock Cream SPF 40: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); padimate O (p. 1716·1); titanium dioxide (p. 1725·1).
Sunscreen.

Intercare, NZ.†
Quadblock Milk; water Resistant Milk: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1).
Sunscreen.

Hamilton Toddler *Hamilton, Austral.; Hamilton, NZ.*
SPF 30+: Enzacamene (p. 1703·2); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Hamiltosin *Rafarm, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic disorders.

Hamitan *Safire, Hong Kong.†*
Mefenamic acid (p. 85·3).
Menorrhagia; pain.

Hämoagil plus *Chefaro, Ger.†*
Bufexamac (p. 30·2); lidocaine hydrochloride (p. 1988·2); bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1).
Haemorrhoids.

Hamodam *Haledew, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Hamodam-M *Haledew, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Hamodam-T *Haledew, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Hämo-ratiopharm N *Ratiopharm, Ger.†*
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); lidocaine hydrochloride (p. 1988·2); titanium dioxide (p. 1725·1).
Haemorrhoids; anal fissure.

Hämorrhoidal-Zäpfchen *Weleda, Austria.*
Antimony (p. 2445·1).
Anorectal disorders.

Hamostat *Samarth, India.*
Aminocaproic acid (p. 1131·3).
Haemorrhage.

Hamoxillin *Safire, Hong Kong.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Hamozen-Z *Haledew, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Hamun *Pfizer, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Han Guang *General Sanyang, China.*
Mezlocillin sodium (p. 324·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Han Guang Nuo *Bozhou, China.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Han Guang Tuo *Welman, China.*
Cefixime (p. 240·3).
Bacterial infections.

Han Shi Xin *Haixin, China.*
Ethylenediamine diaceturate.

Han Xin *Hanyu, China.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; metastatic bone pain.

Han Xue *Star, China.*
Aceglutamide (p. 2426·2).

Han Zhu Ting *Xianju, China.*
Mifepristone (p. 2138·1).
Termination of pregnancy; postcoital oral contraceptive.

Hancid *Hands, India.*
Aluminium chlorohydrate (p. 1694·1); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Hand Cream *Kiehls, Canad.†*
SPF 10: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hand Cream Intensive Anti-Ageing *Perlier, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hand Joy *Unison, Thai.*
⊗Alcohol (p. 1733·1); triclosan (p. 1773·2).
Hand disinfection.

Hand Sanitizer
Note: this name may be used for preparations of different composition.
Delon, Canad.
Benzethonium chloride (p. 1738·1).

Norwood, Canad.
⊗Alcohol (p. 1733·1).
Hand disinfection.

Handclens *Woodward, Canad.*
Benzalkonium chloride (p. 1737·1).

Handexin *Teleflex, Ital.*
Chlorhexidine gluconate (p. 1743·3); aminoxide.
Hand disinfection.

Hands On Antiseptic *Kutol, Canad.*
Benzalkonium chloride (p. 1737·1).

Hands On Defense *Kutol, Canad.*
Triclosan (p. 1773·2).

Hands Fresh *Kruger, Canad.*
Benzalkonium chloride (p. 1737·1).

Handscrub *Paracelsia, Port.*
Chlorhexidine gluconate (p. 1743·3).
Hand disinfection; wound disinfection.

Hands2Go *Water Journey, Canad.*
Benzalkonium chloride (p. 1737·1).

Handy Clean *Kalbe, Indon.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Hanex *Madhav, India.*
⊗Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); pseudoephedrine (p. 1676·1).

Hang Da Lai *Minsheng, China.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; arrhythmias; migraine; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; essential tremor.

Hangebyakujutsutemmato *Tsumura, Jpn.*
Citrus unshiu peel; pinellia tuber; atractylodes rhizome; poria sclerotium; gastrodia tuber; astragalus root (p. 2451·1); alisma rhizome; ginseng (p. 2513·3); phellodendron bark; ginger (p. 1844·1); malt (p. 2080·2).
Traditional Kampo medicine.

Hangekobokuto *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; magnolia bark; perilla herb; ginger (p. 1844·1).
Traditional Kampo medicine.

Hangeshashinto *Tsumura, Jpn.*
Pinellia tuber; skullcap root (p. 2617·1); ginger (p. 1844·1); liquorice (p. 1853·2); jujube; ginseng (p. 2513·3); coptis rhizome.
Traditional Kampo medicine.

Hangover Relief *Brauer, Austral.*
Arsen. alb. (p. 2448·1); ferrum metallicum (p. 2073·1); gelsemium sempervirens (p. 2511·2); kali phosphoricum (p. 1790·3); nux vomica (p. 2573·3); selenium metallicum (p. 2086·3); silicea (p. 2208·3); stannum met. (p. 2632·1); phosphoricum acidum (p. 2589·1); picricum acidum (p. 2634·2).
Homoeopathic preparation.

Hania *Verisfield, Gr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Hanizyn *Lumar, Philipp.*
Thiamine nitrate (p. 2103·2); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); ferrous sulfate (p. 2062·2).

Hanlexin *Nhwa, China.*
Triazolam (p. 1112·3).
Insomnia.

HanoCor N *Hanosan, Ger.*
Crataegus (p. 2488·1); selenicereus grandiflorus (p. 2473·2); kalmia latifolia (p. 2537·2); strophanthus gratus; veratrum album (p. 2644·3); convallaria majalis (p. 2486·2); spigelia anthelmia (p. 2621·3); aurum chloratum (p. 2521·1).
Homoeopathic preparation.

HanoFemin *Hanosan, Ger.*
Aletris farinosa; lilium lancifolium; thuja occidentalis (p. 2629·3); gelsemium sempervirens (p. 2511·2); chamaelirium luteum (p. 2524·3); cimicifuga racemosa (p. 2478·1); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

HanoHepan *Hanosan, Ger.*
Chelidonium majus (p. 2522·2); carduus marianus (p. 1561·1); taraxacum officinale (p. 2625·3); citrullus colocynthis (p. 1833·3).
Formerly known as HanoHepar.
Homoeopathic preparation.

HanoNephrin *Hanosan, Ger.*
Arctostaphylos uva-ursi (p. 2453·2); equisetum arvense (p. 2500·1); juniperus communis (p. 2537·1).
Homoeopathic preparation.

HanoOxygen E *Hanosan, Ger.*
Sodium citrate (p. 1781·2); citric acid (p. 2480·3); lactic acid (p. 2539·1); dibasic potassium phosphate (p. 1791·1); ferrous gluconate (p. 2061·2).
Homoeopathic preparation.

HanoToxin M *Hanosan, Ger.*
Injection: Echinacea (p. 2498·1); cinchona pubescens (p. 2478·3); gelsemium sempervirens (p. 2511·2); aconitum napellus (p. 2428·3); apis mellifica (p. 2445·2); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Hanotoxin M *Hanosan, Ger.*
Oral drops; tablets: Echinacea (p. 2498·1); china (p. 2478·3); thuja occidentalis (p. 2629·3); gelsemium sempervirens (p. 2511·2); aconitum napellus (p. 2428·3); apis mellifica (p. 2445·2); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

HanoTussan *Hanosan, Ger.*
⊗Cetraria islandica (p. 2531·2); drosera (p. 2497·2); cephaelis ipecacuanha; lobelia inflata (p. 2323·2); atropa bella-donna (p. 2453·3).
Homoeopathic preparation.

Hanp *Daiichi Sankyo, Jpn.*
⊗Carperitide (p. 1332·3).
Heart failure.

Hansamedic *Beiersdorf, Belg.†*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Hansamedic Warmtepleister *Beiersdorf, Belg.*
Capsaicin (p. 35·1).
Neuropathic pain.

Hansaplast ABC *Beiersdorf, Switz.*
Cayenne pepper (p. 2469·3).
Musculoskeletal and joint pain.

Hansaplast ABC Wärme-Pflaster *Beiersdorf, Austria.*
Cayenne pepper (p. 2469·3).
Musculoskeletal pain.

Hansaplast Antimicotico *Beiersdorf, Chile.†*
Triclosan (p. 1773·2); dichlorobenzyl alcohol (p. 1750·2).

Hansaplast Callous *Beiersdorf, Gr.*
Salicylic acid (p. 1719·1).
Calluses.

Hansaplast Descongestionante *Beiersdorf, Chile.†*
Menthol (p. 2553·2); camphor (p. 2466·2); thymol (p. 1772·2); pine oil (p. 2591·1); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); anfocerina K.
Respiratory-tract congestion.

Hansaplast Emplastro Térmico *Beiersdorf, Port.*
Capsaicin (p. 35·1).
Inflammation.

Hansaplast Footcare *Beiersdorf, Chile.†*
Cream; topical spray: Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis of feet.

Beiersdorf, Chile.†
Topical powder: Triclosan (p. 1773·2); aluminium stearate; camphor (p. 2466·2); menthol (p. 2553·2); purified talc (p. 1722·2).
Hyperhidrosis of feet.

Hansaplast Herbal Heat Plaster *Beiersdorf, UK.*
Capsicum (p. 2469·3); arnica (p. 2447·2).
Musculoskeletal and joint pain.

Hansaplast Leontos *Beiersdorf, Gr.†*
Cayenne pepper (p. 2469·3).

Hansaplast Wärme-Creme *Beiersdorf, Austria.*
Capsaicin (p. 35·1).
Musculoskeletal pain.

Hansaterm *Beiersdorf, Port.; Beiersdorf, Spain.*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain; neuropathic pain.

Hansepran *Piramal, India.*
Clofazimine (p. 273·3).
Leprosy; lepra reactions.

Hansikang *Huang Long, China.*
Vidarabine phosphate (p. 1023·1).
Herpesvirus infections.

Hantina *Apsen, Braz.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Hanzyme *Hands, India.*
Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1).

Hao Chang *Kangya, China.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Hao Kang *Shengfan, China.*
Fluconazole (p. 578·2).
Fungal infections.

Hao Qiang *Tongyong, China.*
Vitamin B_6 (p. 2105·3).

Hao Te *Yong He, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Hao Xin *Weixin, China.*
Isosorbide dinitrate (p. 1412·2).

Haojishi (Cool) *Teikoku Seiyaku, China.*
Compound arnica (p. 2447·2).

Haojishi (Warm) *Teikoku Seiyaku, China.*
Compound capsicum (p. 2469·3).

Haotetong *Hiteck Bio, China.*
Ozagrel sodium.
Acute cerebral infarction.

HaoXin *Haosen, China.*
Asarone.

Hapase *Kowa, Jpn.†*
Tisokinase.
Myocardial infarction.

Hapeast *Candor, India.*
Capsules: Cyproheptadine (p. 624·1); dried yeast (p. 2125·2).
Candor, India.
Syrup: Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Hapgen *Tri-Prime, China.*
Interferon alfa-1b (p. 989·2).
Chronic hepatitis B; chronic hepatitis C; hairy-cell leukaemia; chronic myeloid leukaemia; genital warts; chronic cervicitis; herpes simplex keratitis.

Hapilux *Sandoz, Gr.; Sandoz, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Hapimax *Harbin, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Hapisor *Eisai, Indon.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction.

Hapoctasin *Actavis, UK.*
⊗Buprenorphine (p. 30·2).
Pain.

Happi *Zydus, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Happi-D *Zydus, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Happier *New Hualian, China.*
Estradiol (p. 2271·1).
Oestrogen deficiency.

Happinose *Dendron, UK.*
Menthol (p. 2553·2).
Nasal congestion.

Happisone *Mission Happiness, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Happynap *Apex, India.*
Benzalkonium chloride (p. 1737·1); zinc oxide (p. 1729·1).

Happy'tizer *Cadila, India.†*
Shatavari (p. 2614·2); ginger (p. 1844·1); piper longum; black pepper (p. 2586·1); embelia ribes (p. 154·2); embelica officinalis; fenugreek (p. 2504·1); cuminum cyminum.
Reduced appetite.

Hapsen *Pharos, Indon.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; heart failure; hypertension.

HaPuVa *Changchun, China.*
A haemorrhagic fever with renal syndrome vaccine (bivalent, inactivated) (p. 2388·2).
Active immunisation.

Harbamind *Bajamed, Mex.*
Metformin (p. 489·1).
Diabetes mellitus.

Harbimox *Harbin, Philipp.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Harbipen *Harbin, Philipp.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Hard Nails *Mericon, USA.*
Biotin (p. 2052·2).

Hardic *Teva, Pol.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Harflox *Taurus, India.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Harflox-T *Taurus, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Hargro *Hong Kong Medical, Hong Kong.†*
Minoxidil (p. 1438·3).

Haricon *Condrugs, Thai.*
Haloperidol (p. 1077·1).
Anxiety; psychomotor agitation; alcohol withdrawal syndrome.

Haridol *Atlantic, Thai.*
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Anxiety; psychosomatic disorders; nausea and vomiting; behaviour disorders in children; psychoses.

Haridol-D *Atlantic, China.*
Haloperidol decanoate (p. 1077·2).
Psychoses.

Harifin *TO-Chemicals, Thai.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia androgenetica.

Hariom *Armour, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Harmless *Hi-Tec, India.*
Colistin sulfate (p. 275·3).
Gastrointestinal infections; bowel sterilisation.

Harmogen *Pfizer, UK.†*
Estropipate (p. 2275·2).
Menopausal disorders; osteoporosis.

Harmolax *Schering-Plough, Braz.*
Macrogol 3350 (p. 2547·3).

Harmomed *Kwizda, Austria.*
Dosulepin hydrochloride (p. 414·1); diazepam (p. 1063·2).
Depression.

Harmonet *Wyeth, Arg.; Pfizer, Belg.; Wyeth, Braz.; Wyeth, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmalab, Fr.; Pfizer, Hong Kong; Wyeth, Hung.; Pfizer, Israel; Wyeth Lederle, Ital.; Wyeth, Pol.; Pfizer, Port.; Wyeth, Spain; Pfizer, Switz.; Wyeth, Venez.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.
Wyeth, S.Afr.†
21 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Harmonette *Wyeth Lederle, Austria; Wyeth, Gr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Harmonic-M *Nutrichem Diat, China.*
Preparation for enteral nutrition.

Harmonise *Hamilton, Austral.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Harnal *Astellas, China; Astellas, Hong Kong; Astellas, Indon.; Astellas, Jpn; GSK, Malaysia; Astellas, Philipp.; GSK, Singapore; Astellas, Thai.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Harnsäuretropfen F *Syxyl, Ger.*
Berberis vulgaris (p. 2502·1); colchicum autumnale (p. 607·1).
Homoeopathic preparation.

Harntee 400 N *TAD, Ger.*
Birch leaf (p. 2457·3); java tea (p. 2536·3); solidago (p. 2620·1).
Urinary-tract infections.

Harntee-Steiner *Steiner, Ger.†*
Silver birch (p. 2457·3); java tea (p. 2536·3); solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Harolan
Note: this name may be used for preparations of different composition.
Harbin, Philipp.
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Harongan *Schwabe, Ger.*
Haronga.
Dyspepsia.

Harox *Harbin, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Harpadol *Arkopharma, Fr.; Arkopharma, Neth.; Cedar Health, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

HarpagoCaps *Swiss Caps, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain; bloating; flatulence; reduced appetite.

Harpagofito Orto *Normon, Spain.†*
Devil's claw root (p. 42·3).
Rheumatic and joint pain.

Harpagoforte *Dyckerhoff, Ger.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders; gastrointestinal disorders.

HarpagoMed *Flor de Loto, Spain; Bioforce, Switz.*
Devil's claw (p. 42·3).
Joint pain.

Harpax *Uriach Aquilea OTC, Spain.†*
Devil's claw root (p. 42·3).
Joint pain.

Harpoon *Merck, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Harpoon-DD *Merck, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Harpoon-TZ *Merck, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Hart *Ivax, Arg.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; heart failure; hypertension.

Harten *Sigman, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Hartigard *Torrent, Philipp.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's disease.

Hartil *Egis, Cz.; Egis, Hung.; Egis, Rus.; Egis, Ukr.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; myocardial infarction; cardiovascular risk reduction; diabetic nephropathy.

Hartil HCT *Egis, Hung.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hartil-D *Egis, Rus.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hartil-H *Egis, Cz.; Egis, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hartivit *Alna, India.*
Omega-3 fatty acids (p. 1460·1); vitamin E (p. 2119·1); wheat-germ oil (p. 2647·1).

Hartor *United Biotech, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Hartsorb *Siam Bheasach, Thai.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Hartvasc *Hizon, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Hartylox *Integrated Pharmaceutical, Philipp.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Hartzar *JRalph, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Harvellin *Wescrib, Philipp.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Harvifer *Wescrib, Philipp.*
Ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Iron-deficiency anaemia.

Harzol *Kwizda, Austria; UCB, Ger.*
Sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Hasceral *Hasco-Lek, Pol.*
⊗Salicylic acid (p. 1719·1); urea (p. 1727·3).
Skin disorders.

Hascoderm *Hasco-Lek, Pol.*
Azelaic acid (p. 1695·1).
Acne; hyperpigmented skin disorders.

Hascofungin *Hasco-Lek, Pol.*
Ciclopirox olamine (p. 575·3).
Fungal skin and nail infections.

Hascopiryn *Hasco-Lek, Pol.*
Aspirin (p. 22·2).
Pain; fever.

Hascosept *Hasco-Lek, Pol.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Hascovir *Hasco-Lek, Pol.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Haspas *Savoy, India.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Hassapirin *Mintlab, Chile.*
Aspirin (p. 22·2).
Fever; inflammation; pain.

Hastel *Sambrook, Gr.*
Indometacin (p. 71·2).
Inflammatory disorders.

Hastilan *Continentales, Mex.*
Benzyl benzoate (p. 2149·1).
Scabies; pediculosis.

HA-Tabletten N *Boehringer Ingelheim, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Hate *NEGPF, China.*
Didanosine (p. 972·3).
HIV infection.

Hatmmony *Pisa, Mex.*
Bromazepam (p. 1041·2).
Anxiety disorders.

Hatric *Aristo, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Hatric-2 *Aristo, India.*
⊗Levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Hatric-3 *Aristo, India.*
⊗Levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Hausmann Ferrum *Hong Kong Medical, Hong Kong.†*
Iron preparation (p. 2073·1).

Hautfunktionstabletten N *Heel, Ger.*
Graphites (p. 2522·1); thallium aceticum oxydulatum (p. 2628·3); thuja occidentalis (p. 2629·3); stibium sulfuratum nigrum (p. 2445·1).
Homoeopathic preparation.

Hautfunktionstropfen N *Heel, Ger.*
Graphites (p. 2522·1); thallium aceticum oxydulatum (p. 2628·3); thuja occidentalis (p. 2629·3); stibium sulfuratum nigrum (p. 2445·1).
Homoeopathic preparation.

Haut-Gastreu R60 *Reckeweg, Ger.*
Fumaria officinalis (p. 2508·2); hepar sulfuris (p. 1721·3); juglans (p. 2646·1); sarsaparilla (p. 2610·3).
Homoeopathic preparation.

Havelox *Recordati, Spain.†*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial respiratory-tract infections.

Havina *Synmosa, Thai.†*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders.

Havitall *United Laboratories, Philipp.*
Vitamins; minerals; amino acids; ubidecarenone (p. 2637·1); citrus bioflavonoids (p. 2505·2); ginseng (p. 2513·3); lycopene (p. 2546·2); lutein (p. 2079·2).
Dietary supplement.

Havlane *Sanofi-Aventis, Fr.*
Loprazolam mesilate (p. 1080·2).
Insomnia.

Havpur *Novartis Vaccines, Ger.; Chiron Panacea, India.*
A hepatitis A vaccine (p. 2388·3).
Active immunisation.

Havrix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; Litha, S. Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.†; SmithKline Beecham, USA; GSK, Venez.*
An adsorbed inactivated hepatitis A vaccine (HM 175 strain) (p. 2388·3).
Separate preparations are available for infants and children and for adults.
Active immunisation.

Hawaiian Tropic *Energizer, Canad.*
SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Tanning Research, USA.
Gel SPF 15+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); meradimate (p. 1711·2).
Sunscreen.

Tanning Research, USA.
Lotion SPF 15+; SPF 8+; SPF 10+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); meradimate (p. 1711·2).
Sunscreen.

Tanning Research, USA.
SPF 30+: Octinoxate (p. 1715·1); meradimate (p. 1711·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2); homosalate (p. 1705·1).
Sunscreen.

Tanning Research, USA.
SPF 45+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); meradimate (p. 1711·2).
Sunscreen.

Tanning Research, USA.
SPF 45+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Energizer, Canad.
SPF 4; SPF 8: Octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Solpro, Mex.†
SPF 15+: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Solpro, Mex.†
SPF 10: Octinoxate (p. 1715·1).
Sunscreen.

Hawaiian Tropic After Sun *Energizer, Canad.*
Lidocaine (p. 1988·1).

Hawaiian Tropic Baby Faces *Tanning Research, USA.*
SPF 20: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); meradimate (p. 1711·2).
Sunscreen.

Tanning Research, USA.
SPF 35; SPF 50: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Tanning Research, Canad.†
SPF 50: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Hawaiian Tropic Baby Lotion Sunscreen *Energizer, Canad.*
SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Continuous Flow *Energizer, Canad.*
SPF 10: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Cool Aloe with I.C.E. *Tanning Research, USA.*
Lidocaine (p. 1988·1); menthol (p. 2553·2); aloe vera (p. 1693·2).

Hawaiian Tropic Dark Tanning *Tanning Research, USA.*
Gel SPF 2; gel SPF 4: Ensulizole (p. 1703·1).
Sunscreen.

Tanning Research, USA.
Oil SPF 2; oil SPF 4: Octinoxate (p. 1715·1); padimate O (p. 1716·1).
Sunscreen.

Tanning Research, Canad.†
Lotion SPF 4: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Tanning Research, Canad.†
Oil SPF 4: Octinoxate (p. 1715·1).
Sunscreen.

Hawaiian Tropic Dry Oil *Energizer, Canad.*
SPF 10: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Island Sport *Energizer, Canad.*
Lotion SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Energizer, Canad.
Spray SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Just For Kids *Tanning Research, USA.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); homosalate (p. 1705·1).
Sunscreen.

Tanning Research, USA.
SPF 45: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Hawaiian Tropic Kids *Energizer, Canad.*
SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Oil *Energizer, Canad.*
SPF 4: Octinoxate (p. 1715·1).
Sunscreen.

Hawaiian Tropic Plus *Tanning Research, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Hawaiian Tropic Protective Tanning *Tanning Research, USA.*
SPF 6: Titanium dioxide (p. 1725·1).
Sunscreen.

Tanning Research, Canad.†
Lotion SPF 8: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Tanning Research, Canad.†
Dry oil SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Protective Tanning Dry *Tanning Research, USA.*
Gel SPF 6: Ensulizole (p. 1703·1); sulisobenzone (p. 1722·1).
Sunscreen.

Tanning Research, USA.
Oil SPF 6: Octinoxate (p. 1715·1); homosalate (p. 1705·1); meradimate (p. 1711·2).
Sunscreen.

Hawaiian Tropic Self Tanning Sunblock *Tanning Research, USA.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Sensitive Skin *Energizer, Canad.*
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Sheer Touch *Energizer, Canad.*
SPF 15; SPF 30; SPF 45; SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Splash for Kids *Tanning Research, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Hawaiian Tropic Sport *Tanning Research, USA.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Tanning Research, USA.
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Tanning Research, Canad.†
Lotion SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hawaiian Tropic Sport Sunblock *Tanning Research, Canad.†*
SPF 30: Octinoxate (p. 1715·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone.
Sunscreen.

Hawk *Sterling, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Hawkcopax *LBS, Thai.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; nausea and vomiting; premedication.

Hawkmide *LBS, Thai.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Hawkperan *LBS, Thai.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Haxifal *Erempharma, Fr.*
Cefaclor (p. 232·3).
Bacterial infections.

Haxim *Harbin, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Haxon *Harbin, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Haxotin *Harbin, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Hay Complex *Thompsons, Canad.†*
Arundo mauritanica; euphrasia officinalis (p. 2502·1); onion (p. 2575·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Hay Fever *Brauer, Austral.*
Arsenicum album (p. 2448·1); allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); kali iodatum (p. 2336·3); naphthalinum; sabadilla (p. 2611·2); sinapis nigra (p. 2566·1); ambrosia artemisiaefolia; arsenicum iodatum (p. 2448·1); sticta pulmonaria (p. 2546·1).
Homoeopathic preparation.

Homeocan, Canad.
Allium cepa (p. 2575·2); apis mellifica (p. 2445·2); aralia racemosa; cuprum metallicum (p. 2057·1); sabadilla (p. 2611·2); sticta pulmonaria (p. 2546·1).
Homoeopathic preparation.

Hay Fever & Sinus Relief *Herbal Concepts, UK.*
Echinacea (p. 2498·1); sambucus (p. 2609·3); garlic (p. 2510·3).
Catarrh; hay fever; sinus congestion.

Hay-Crom *Norton Waterford, Irl.; Norton, Rus.; Teva, UK.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders; allergic conjunctivitis.

Hayfebrol *Scot-Tussin, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Hayfever
Note: this name may be used for preparations of different composition.
Hylands, Canad.
Allium cepa (p. 2575·2); ambrosia artemisiafolia; euphrasia officinalis (p. 2502·1); sabadilla (p. 2611·2).
Homoeopathic preparation.

Hayfever & Allergy Relief *Galpharm, UK.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Hayfever Eye Drops *Pliva, UK.†*
Sodium cromoglicate (p. 1225·3).
Ocular symptoms of hay fever.

Hayfever Relief
Note: this name may be used for preparations of different composition.
Peach, UK.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis.

Thornton & Ross, UK.
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Hayfever & Sinus Relief *Herbal Concepts, UK.*
Echinacea (p. 2498·1); sambucus (p. 2609·3); garlic (p. 2510·3).
Catarrh; hay fever; sinus congestion.

Hayleve *Chatfield Laboratories, UK.*
Chlorphenamine (p. 620·3).
Hypersensitivity reactions.

Haymine *Forest Laboratories, UK.*
⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2).
Hypersensitivity reactions.

Hazmolin *Munir, Turk.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Pancreatic insufficiency.

Hazolin *Harbin, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

HB-4 *Ordain, India.*
Cobamamide (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

HB Fast *Biological E, India.*
Chewable tablets: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Biological E, India.
Oral suspension: Iron carbonyl (p. 2073·1).

HB Fast-Z *Biological E, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

HB Plus *Torrent, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

HB Rich *Wockhardt, India.*
⊗Ammonium citrate (p. 2441·3); folic acid (p. 2063·1); haemoglobin (p. 1154·3); vitamin B_{12} (p. 2107·2).

HB Vac *Zydus, India.*
An adsorbed hepatitis B vaccine (surface antigen) (p. 2389·3).
Active immunisation.

HB-Act *Active, India.*
Syrup: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Active, India.
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron deficiency in pregnancy.

HB-Forte *Meridian, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

HB-Norm *Meridian, India.*
Capsules: Ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).

Meridian, India.
Syrup: Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3).

HB-Nova *Willow, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Willow, India.
Syrup: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

HB-Orange *Intas, India.*
Capsules: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Intas, India.
Oral suspension: Copper (p. 2057·1); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); lysine (p. 2079·3); magnesium (p. 1786·3); zinc (p. 2126·1).

HB-Plan Kit *Invision, India.*
Ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); red capsules, ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); blue capsules, zinc sulfate (p. 2126·2).

Hb-Rich *Wockhardt, India.*
Ferrous ammonium citrate (p. 2060·1); folic acid (p. 2063·1); sorbitol (p. 2092·1); vitamin B_{12} (p. 2107·2).

Hb-Rich 300 *Wockhardt, India.*
Calcium carbonate (p. 1824·3); calcium (p. 1783·1); dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

HB-Ron *Sinkhai, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Hbron *Medley, India.*
Syrup: Iron polymaltose (p. 2077·2).

Medley, India.
Tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Hb-Trace *East West, India.*
Vitamins; minerals.

HB-Up *Intas, India.*
Capsules: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Intas, India.
Oral liquid: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

H-B-Vax II *CSL Biotherapies, Austral.; MSD, Hong Kong†; MSD, Indon.; MSD, Mex.; MSD, NZ†; MSD, Rus.; MSD, S.Afr.†; MSD, Thai.†*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Separate preparations are available for children and for adults.
Active immunisation.

HB-Vax-DNA *MSD, Neth.†*
An adsorbed hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Active immunisation.

HBVaxPro *MSD, Arg.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Gr.; MSD, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; MSD, Malaysia; Sanofi Pasteur, Neth.; MSD, NZ; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; MSD, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; MSD, Thai.; MSD, Turk.; Sanofi Pasteur, UK.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

HC *Chinta, Thai.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Hc45 *Reckitt Benckiser, Irl.; Crookes Healthcare, UK.*
⊗Hydrocortisone acetate (p. 1640·1).
Eczema; insect bites; allergic dermatitis.

HC Derma-Pax *Recsei, USA.*
⊗Hydrocortisone acetate (p. 1640·1); mepyramine maleate (p. 635·1); chlorphenamine maleate (p. 620·3).
Skin disorders.

HC Pram *Rivers Edge, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine (p. 1993·3).
Skin disorders.

HC Pramoxine *Veracity, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Hclox *Madhav, India.*
Ampicillin trihydrate (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

H-Cort *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

United Biotech, India.
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

HCQS *Ipca, India; Ipca, Thai.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus; malaria.

HCT *Ratiopharm, Ger.; Kimia, Indon.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure.

HCTad *TAD, Ger.†*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

HCT-Beta *Betapharm, Ger.*
⊗Hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; oedema.

HCT-gamma *Worwag, Ger.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

HCT-ISIS *Actavis, Ger.†*
⊗Hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; oedema.

HCTZ *TO-Chemicals, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

HCU *Nutricia, Ital.*
Food for special diets.
Homocystinuria.

HCU Anamix *Nutricia, Austral.; SHS, Cz.*
Infant feed.
Formerly known as XMET Analog.
Homocystinuria; hypermethioninaemia.

Nutricia, Fr.
Food for special diets.
Homocystinuria.

HCU LV *SHS, Irl.*
Food for special diets.
Homocystinuria; hypermethioninaemia.

HCU-LV *SHS, UK.*
Food for special diets.
Hypermethioninaemia; homocystinuria.

HCY *Mead Johnson, Fr.*
Food for special diets.
Homocystinuria.

HD 85 *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

HD 410 *Orochemie, Ger.*
Isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1); benzylbis(2-hydroxyethyl) cocosalkylammonium chloride.
Hand disinfection.

HD 200 Plus *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

HD-Betasone *Hovid, Singapore.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

HDCV *Sanofi Pasteur, Braz.†; Aventis Pasteur, Turk.†*
A rabies vaccine (Wistar PM/WI 38 strain) (p. 2413·2).
Active immunisation.

HDG *Sigma, Arg.*
Cynara (p. 2490·3); carqueja (p. 2471·2); quercetin (p. 2505·3); cynarine (p. 2491·1).
Liver and biliary-tract disorders; digestive disorders.

HD-Methacin *Hovid, Singapore.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; pain; gout.

He *Ranbaxy, Malaysia.*
Eucommia ulmoides; epimedium sagittatum; cynomorium songarium; psoralea corylifolia.
Dietary supplement.

He An *Wanhe, China.*
Amino acids; vitamins.
Nutritional supplement.

He An Si *Pu Sheng, China.*
Lysine hydrochloride (p. 2079·3).

He Bang Li An *Hebang, China.*
Zaleplon (p. 1114·3).
Insomnia.

He Bao *Tianhedi Sainuo, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

He Chang *Kangya, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

He Er *Double-Crane, China.*
Potassium dehydroandrographolide succinate.

He Er Bei *Lanzhou Bio, China.*
A haemophilus influenzae conjugate vaccine (meningococcal protein conjugate) (p. 2387·2).
Active immunisation.

He Er Kang *Bei Da Gao Ke Hua Tai, China.*
Aminomethylbenzoic acid (p. 1132·2).

He Er Shu *Pacific, China.*
Propiverine hydrochloride (p. 2363·1).
Bladder instability.

He Fu *Southwest, China.*
Ubidecarenone (p. 2637·1).

He Gu *Double-Crane, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

He Ke *Zhonghe, China.*
Levofloxacin mesilate.
Bacterial infections.

He Ke Di Si *GuoRui, China.*
Lafutidine (p. 1851·3).
Peptic ulcer; acid aspiration; gastritis.

He Lai Yi *Jiangxi, China.*
Matrine.

He Li Ke *Heer, China.*
Phentolamine mesilate (p. 1468·3).

He Lin Kou Fu Ye *Helin, China.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

He Mo Sai *Conba, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

He Pu Fu *Qian Long, China.*
Sodium houttuyfonate.

He Pu Ren *HePu, China.*
Zidovudine (p. 1024·2).
HIV infection.

He Pu Xin *Qian Long, China.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

He Ri *Zhonghe, China.*
Thymalfasin (p. 2630·1).
Chronic hepatitis B and C.

He Shu *Lunan, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

He Tai *San Lian, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

He Tan *Kang Le, China.*
Erdosteine (p. 1665·1).

He Tong *Wanma, China.*
Troxerutin (p. 2505·3).

He Wei Yi *Zhonglian, China.*
Metformin hydrochloride (p. 489·1); gliclazide (p. 472·3).
Diabetes mellitus.

He Di Xin *SanJiu JiShi, China.*
Aceglutamide (p. 2426·2).

He Xin *Shengda, China.*
Phentolamine mesilate (p. 1468·3).

He Xing *Yao Wang, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

He Yuan *Kangtai, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

He Yue *Zhonghe, China.*
Propyl gallate (p. 1736·1).

Hea Complex *Thompsons, Canad.†*
Calcium carbonate (p. 1824·3); gelsemium sempervirens (p. 2511·2); iris versicolor (p. 2534·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

4Head *Diomed, UK.*
Levomenthol (p. 2553·2).
Headache.

Head Care *Dossier, Neth.*
Aconitum napellus (p. 2428·3); atropa belladonna (p. 2453·3); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Head & Shoulders *Procter & Gamble, Canad.; Procter & Gamble, USA.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis; dandruff.

Head & Shoulders Intensive Treatment *Procter & Gamble, USA.*
Selenium sulfide (p. 1719·3).
Dandruff; seborrhoeic dermatitis.

Headache *Beacons, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Headache & Migraine *Homeocan, Canad.*
Alumina (p. 1690·3); antimonium crudum (p. 2445·1); argentum nitricum (p. 2615·3); cyclamen europaeum (p. 2490·2); digitalis purpurea (p. 1352·3); glonoinum (p. 1391·2); lycopodium clavatum (p. 2547·1); melilotus officinalis (p. 2552·3).
Homoeopathic preparation.

Headache & Migraine L77 *Homeocan, Canad.*
Argentum nitricum (p. 2615·3); chelidonium (p. 2522·2); cimicifuga (p. 2478·1); cyclamen (p. 2490·2); gelsemium (p. 2511·2); iris versicolor (p. 2534·3); melilotus (p. 2552·3); ruta (p. 2608·2); sanguinaria (p. 2610·1); digitalis (p. 1352·3).
Homoeopathic preparation.

Headache Pads *Sinsin, Israel.*
Eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); menthol (p. 2553·2).
Headache; migraine.

Headgen *Yung Shin, Hong Kong†; YSP, Malaysia; Yung Shin, Singapore.*
Codergocrine mesilate (p. 389·2).
Dementia.

Headmaster *SSL, Irl.†*
Phenothrin (p. 2160·1).
Pediculosis.

Head-O *Otto, Indon.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Headrin Extra Strength *Reese, USA.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).

Headring *Thornton & Ross, Ukr.*
Dimeticone (p. 2209·3).
Pediculosis.

Heads Shampoo *Hamilton, Hong Kong.†*
Econazole nitrate (p. 577·3).
Dandruff; seborrhoeic dermatitis.

Headway *Pacific, Hong Kong; Alphapharm, Malaysia†; Mylan, NZ†*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Headzol *Vaia, Ital.*
Zolmitriptan (p. 682·2).
Migraine.

Heafusine *Braun, Fr.*
⊗Pentastarch (p. 1146·1).
Haemodilution; shock.

Heal *Ordain, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1); sulfadiazine silver (p. 362·3); zinc oxide (p. 1729·1).

Heal Aid Plus *Reese, USA.*
Resorcinol (p. 1718·3); phenol (p. 1763·3).

Healcer *Medispan, India.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Healex *Rallis, India.*
Polyvinyl polymer; benzocaine (p. 1980·2).
Wound dressing.

Healin *Speciality Meditech, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Healing Cream *Nelson, UK.*
Calendula officinalis (p. 2465·2).
Homoeopathic preparation.

Healing Dust *J & J DeChane, India.*
Boric acid (p. 2459·3); turmeric (p. 2218·1).

Healip *Jenson, Gr.; ACO Hud, Swed.†*
Docosanol (p. 974·3).
Herpes labialis.

Healive *Sinovac, China.*
A hepatitis A vaccine (p. 2388·3).
Active immunisation.

Healon *AMO, Austral.; Pfizer, Braz.†; Pfizer, Chile†; Pfizer, Gr.; Pfizer, Hong Kong†; Pharmacia Upjohn, India;*

AMO, Israel; Pharmacia, NZ; Pharmacia Upjohn, Rus.; Genop, S.Afr.; Pfizer, Turk.; AMO, USA.
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Healon Yellow *Kabi Pharmacia, USA.†*
Sodium hyaluronate (p. 2526·2); fluorescein sodium (p. 2506·2).
Adjunct in eye surgery.

Healox *Cipla, Malaysia.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Healpil *Biosync, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Healplus *Sanat, India.*
Cedar wood oil (p. 2472·3); curcuma longa.

Health Care Antiseptic Soap *Inopak, Canad.*
Chloroxylenol (p. 1748·2).

Health Care E-2 Antis Lot Soap *Inopak, Canad.*
Chloroxylenol (p. 1748·2).

HealthAid Boldo-Plus *Pharmadass, UK.*
Boldo (p. 2458·3); taraxacum (p. 2625·3); bladderwrack (p. 2612·1); clivers (p. 2481·2); bearberry (p. 2453·2); juniper oil (p. 2537·2); vitamin B_6 (p. 2105·3).
Formerly known as HealthAid AquaFall.
Water retention.

Healtheries Musseltone *Optima, UK.*
Green-lipped mussel (p. 2522·3).
Musculoskeletal and joint disorders.

Healtheries Musseltone & Glucosamine *Optima, UK.*
Green-lipped mussel (p. 2522·3); glucosamine (p. 2515·3).
Musculoskeletal and joint disorders.

Healthrich *Intas, India.*
Vitamins; minerals; trace elements.

Healthy Defense *Johnson & Johnson, Canad.*
SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Healthy Feet *Pickles, UK.*
Undecenoic acid (p. 596·3); dibrompropamidine isetionate (p. 1750·1).
Fungal skin infections.

Healthy Kidz *Dyna, Philipp.*
Vitamins; taurine (p. 2626·2); lysine hydrochloride (p. 2079·3); chlorella growth factor (p. 2475·3).
Dietary supplement.

Healthy Makeup *Avon, Canad.†*
SPF SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Heartburn Relief
Note: this name may be used for preparations of different composition.
AAH, UK; Numark, UK; Thornton & Ross, UK.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Heart-Free *SM, Gr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Heartil *Life Medicare, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Heat Cream *General Drugs, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Muscle pain; sprains.

Heat Wave *Canadian Custom Packaging, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Heather *Glenmark, USA.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Hebagam *NBI, S.Afr.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Heberbiovac HB *Bago, Chile; Alvartis, Mex.; Biovac, S.Afr.; Heber, Thai.*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Active immunisation.

Heberin *Pasteur, Chile.*
Ivy (p. 2536·2).
Respiratory-tract congestion; cough.

Hebermin
Note: this name may be used for preparations of different composition.
Alvartis, Mex.
Sulfadiazine (p. 361·3).

Heberon Alfa *Alvartis, Mex.*
Interferon (p. 989·2).

Hebert Caramelos *Fecofar, Arg.*
Guaifenesin (p. 1666·2); senega (p. 1677·2).
Respiratory-tract congestion.

Heblopin *Manix, Philipp.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Hebrin *Uniao Quimica, Braz.*
Iodine (p. 2336·3); cade oil (p. 1723·2); salicylic acid (p. 1719·1).
Fungal skin infections.

Hebsbulin *Mitsubishi Tanabe, Jpn.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hebucol *Will-Pharma, Belg.*
Cynara (p. 2490·3).
Biliary-tract disorders.

HEC
Note: this name may be used for preparations of different composition.
Chauvin, Fr.
Tannic acid (p. 2625·2); hamamelis (p. 2523·3); phenazone (p. 124·1).
Burns; nose bleeds.

Bausch & Lomb, Switz.†
Tannin (p. 2625·2); pectin (p. 2200·3); peru balsam (p. 2587·1); hamamelis (p. 2523·3).
Mucous membrane disorders of the nose.

Heclivir *Neo Quimica, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Hecobac *Nufarindo, Indon.*
Clarithromycin (p. 266·2).
Bacterial infections.

Hecocur *Pekana, Canad.†*
Boldo (p. 2458·3); cynara scolymus (p. 2490·3); fringe tree; iberis amara; lycopodium clavatum (p. 2547·1); mandragora officinarum; phosphorus (p. 2589·2); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Hecril *Neiss, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Hectonona *Milo, Spain.*
Dried aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Gastric hyperacidity.

Hectorol *Genzyme, USA.*
Doxercalciferol (p. 2113·3).
Hyperparathyroidism.

Hedazol *Arlex, Mex.*
Mebendazole (p. 158·3).

Hedelicum *Natur Produkt, Pol.*
Liquorice (p. 1853·2); ivy (p. 2536·2); thyme (p. 2630·2).
Cough; respiratory-tract congestion.

Hedelix *Krewel Meuselbach, Cz.; Krewel, Ger.; Phoenix, Hung.; Krewel Meuselbach, Pol.; Krewel, Rus.; Krewel, Ukr.*
Ivy (p. 2536·2).
Respiratory-tract disorders; cough; respiratory-tract congestion.

Hedelix Eucaps *Krewel, Ukr.*
Eucalyptus oil (p. 2501·2).
Respiratory-tract congestion.

Hedensa *Santa, Turk.*
Monochlorocarvacrol (p. 1747·3); chamomile oil (p. 2474·1); menthol (p. 2553·2); ichthammol (p. 1705·3).
Haemorrhoids.

Hedera Complexe No 120 *Lehning, Fr.*
Hedera helix (p. 2536·2); atropa belladonna (p. 2453·3); chamomilla vulgaris (p. 2474·1); kreosotum (p. 1659·3); mercurius corrosivus (p. 2555·2).
Homoeopathic preparation.

Hederasal *Herbapol Wroclaw, Pol.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Hederax *Arese, Braz.*
Ivy (p. 2536·2).

Hederin *Vishpha, Ukr.*
Ivy (p. 2536·2).
Cough; respiratory-tract congestion.

Hederix
Note: this name may be used for preparations of different composition.
Plan, Switz.
Noscapine hydrochloride (p. 1670·3); ivy (p. 2536·2); senega (p. 1677·2); helenium (p. 1662·3); orris; marrubium (p. 1668·3).
Cough.

SIT, Ital.
Codeine hydrobromide (p. 40·2); ivy (p. 2536·2).
Cough.

Hederoin *Herbapol Wroclaw, Pol.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Hedex *GSK Consumer, Irl.; GSK Consumer, Neth.; GSK Consumer, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Hedex Extra *GSK Consumer, Irl.; GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Hedex Ibuprofen *GSK Consumer, UK.*
Ibuprofen (p. 68·2).
Pain; fever; cold and influenza symptoms.

Hedilar *Andromaco, Chile.*
Ivy (p. 2536·2).

Hedix *Sandoz, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Hedonin
Note: this name may be used for preparations of different composition.
Lannacher, Cz.
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Hedrin *Rafa, Israel; Thornton & Ross, UK.*
Dimeticone (p. 2209·3).
Pediculosis.

Hedrin Treat & Go *Thornton & Ross, UK.*
Caprylyl glycol (Activdiol).
Pediculosis.

Heduline *Costec, Arg.*
Salicylic acid (p. 1719·1); triclosan (Irgasan DP-300) (p. 1773·2); dexpanthenol (p. 2582·2).
Seborrhoeic dermatitis.

Heelcare *Wings, India.*
⊗Camphor (p. 2466·2); chlorhexidine gluconate (p. 1743·3); lactic acid (p. 2539·1); methyl nicotinate (p. 91·3); salicylic acid (p. 1719·1); urea (p. 1727·3); zinc oxide (p. 1729·1).

Heemex *Lane, UK.*
Hamamelis (p. 2523·3); compound benzoin tincture; zinc oxide (p. 1729·1).
Haemorrhoids.

Heet
Note: this name may be used for preparations of different composition.
Whitehall, USA.
Methyl salicylate (p. 92·1); camphor (p. 2466·2); capsaicin (p. 35·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Wyeth, Gr.
Methyl salicylate (p. 92·1); levomenthol (p. 2553·2); camphor (p. 2466·2); methyl nicotinate (p. 91·3).

hefasolon *Riemser, Ger.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Hefekapseln *Ratiopharm, Ger.†*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea.

Heferol *Alkaloid, Rus.*
Ferrous fumarate (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Hefovin *DOT, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Hegon *Beta, Arg.*
Zaleplon (p. 1114·3).
Insomnia.

Hégor *Coryne de Bruynes, Mon.*
d-Phenothrin (p. 2160·1).
Pediculosis.

Hegrimarin *Strathmann, Ger.†; Strathmann, Hung.*
Milk thistle (p. 1561·1).
Liver disorders.

Heidi *Siam Bheasach, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Heiisan *Tsumura, Jpn.*
Atractylodes lancea rhizome; magnolia bark; citrus unshiu peel; jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Heilsalbe *Weleda, S.Afr.†*
Calendula (p. 2465·2); mercurialis perennis; stibium met (p. 2445·1); peru balsam (p. 2587·1); resina laricis.
Skin lesions; wounds.

Heimer *Eurofarma, Braz.*
Memantine (p. 393·1).

Heinix *Verman, Fin.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Heipram *Alter, Spain.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder; anxiety.

Heitrin *Amdipharm, Ger.*
Terazosin hydrochloride (p. 1511·1).
Hypertension.

Heiwin *Medhaus, Philipp.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Hekabetol *Fortbenton, Arg.*
Shampoo: Triclosan (p. 1773·2); betanaphthol (p. 152·1).
Seborrhoeic dermatitis.

Fortbenton, Arg.
Soap: Triclosan (p. 1773·2).
Skin cleansing.

HeKeDiSi *Fengyuan, China.*
Bromhexine hydrochloride (p. 1656·3).

Heksa *Polifarma, Turk.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Heksavit *Leiras, Fin.†*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Heksoral *Farmoral, Turk.*
Hexetidine (p. 1755·1).
Oral hygiene.

Hekzoton *Drogsan, Turk.*
Hexetidine (p. 1755·1).
Oral hygiene.

Helaflex *Hela, Swed.*
Devil's claw root (p. 42·3).
Osteoarthritis.

Helal *Roemmers, Venez.*
Albendazole (p. 149·1).
Worm infections.

Helarium *Bionorica, Cz.†; Bionorica, Hung.†; Bionorica, Rus.; Bionorica, Ukr.*
St John's wort (p. 449·1).
Depression; neuroses; agitation; sleep disorders.

Helason *Jelfa, Pol.*
A heparinoid (p. 1401·1); hyaluronidase (p. 2527·2).
Venous thrombosis; soft-tissue injury.

Helatocil *Demo, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Helcon *Polipharm, Thai.*
Codergocrine mesilate (p. 389·2).
Mental function disorders.

Helen *Masa, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Oral contraceptive in women with androgenic symptoms.

Helenil *Roux-Ocefa, Arg.*
Ketoprofen (p. 79·1).
Inflammation; pain.

Helepin-D *Vilar, Rus.*
Desmodium canadian.
Herpesvirus infections.

Helex *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder; depression; mixed anxiety-depressive states; alcohol withdrawal syndrome.

Helibact *RPG, India.*
Amoxicillin (p. 216·2); omeprazole (p. 1867·2); tinidazole (p. 949·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Helical *Medana, Pol.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

HeliCap *Kibion, Cz.†; Kibion, Neth.; Kibion, Port.*
Carbon-14 (p. 2223·2) urea.
Diagnosis of Helicobacter pylori; infection.

Helicid *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; dyspepsia.

Heliclar *Abbott, Belg.; Pharmacia Upjohn, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Helico State *Campro, Neth.*
Carbon-13 (p. 2470·3) labelled urea.
Diagnosis of Helicobacter pylori *infection.*

Helicobacter Test *Utandningstester, Denm.†; INFAI, Ger.; INFAI, Gr.; Fannin, Irl.; Goldfarma, Port.; INFAI, Switz.*
Carbon-13 (p. 2470·3) labelled urea.
Test for Helicobacter pylori infection.

Helicokit *Italchimici, Ital.*
Carbon-13 (p. 2470·3) labelled urea.
Diagnosis of Helicobacter pylori *infection.*

Helicol *Eczacibasi, Rus.; Eczacibasi, Turk.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Helicopac *Sigma, Braz.*
Capsules, lansoprazole (p. 1851·3); tablets, clarithromycin (p. 266·2); tablets, amoxicillin (p. 216·2).
Helicobacter pylori-*associated peptic ulcer.*

Helico-teste *Isomed, Port.*
Carbon-13 (p. 2470·3) labelled urea.
Test for Helicobacter pylori infection.

Helidac *Procter & Gamble, USA.*
Pink tablets, bismuth salicylate (p. 1821·3); white tablets, metronidazole (p. 936·1); orange/white capsules, tetracycline hydrochloride (p. 373·2).
Duodenal ulcer.

Helides *Zentiva, Cz.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Helidonium-Plus *Doctor H, Rus.*
Acidum nitricum (p. 2572·3); berberis vulgaris (p. 2502·1); chelidonium majus (p. 2522·2); lithium carbonicum (p. 427·3); strychnos nux-vomica (p. 2573·3); terebinthina laricina (p. 2636·3).
Homoeopathic preparation.

Heligo *Intas, India.*
Clarithromycin (p. 266·2); lansoprazole (p. 1851·3); tinidazole (p. 949·2).

Heli-Kit *Mayoly-Spindler, Fr.*
Carbon-13 labelled urea (p. 2470·3).
Detection of Helicobacter pylori *infection.*

Helikit *Zydus, India.*
1 Tablet, amoxicillin (p. 216·2); 1 capsule, omeprazole (p. 1867·2); 1 tablet, tinidazole (p. 949·2).

Heliklar *Abbott, Braz.*
Capsules, lansoprazole (p. 1851·3); tablets, clarithromycin (p. 266·2); capsules, amoxicillin (p. 216·2).

Helioban *Galderma, Mex.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hélioblock *Roche-Posay, Braz.*
SPF 40: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Roche-Posay, Braz.†
SPF 30: Drometrizole trisiloxane (p. 1702·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1).
Sunscreen.

Heliocare *Advaita, Mex.*
Octinoxate (p. 1715·1); enzacamene (p. 1703·2); polypodium leucotomos.
Prevention of sun-induced skin damage.

Szama, Arg.; Labomed, Chile.
A range of sunscreens containing polypodium leucotomos.
Topical preps.

Heliopar *Orion, Fin.*
Chloroquine phosphate (p. 650·1).
Malaria; rheumatoid arthritis; amoebiasis; lupus erythematosus; light-sensitive skin disorders.

Heliox *Linde, Canad.*
Helium (p. 1798·3); oxygen (p. 1799·3).

Helipac *Cipla, India.*
2 Tablets, amoxicillin (p. 216·2); 2 tablets, tinidazole (p. 949·2); 2 capsules, omeprazole (p. 1867·2).
Peptic ulcer.

Helipak *Fako, Turk.*
Capsules, lansoprazole (p. 1851·3); tablets, clarithromycin (p. 266·2); tablets, amoxicillin (p. 216·2).
Peptic ulcer.

Helipak A *Orion, Fin.*
Enteric-coated capsules, lansoprazole (Zolt) (p. 1851·3); tablets, amoxicillin (Amorion) (p. 216·2); tablets, metronidazole (Trikozol) (p. 936·1).
Peptic ulcer.

Helipak K *Orion, Fin.*
Enteric-coated capsules, lansoprazole (Zolt) (p. 1851·3); tablets, clarithromycin (Zeclar) (p. 266·2); tablets, amoxicillin (Amorion) (p. 216·2).
Peptic ulcer.

Helipak T *Orion, Fin.*
Enteric-coated capsules, lansoprazole (Zolt) (p. 1851·3); tablets, tetracycline hydrochloride (Oricyclin) (p. 373·2); tablets, metronidazole (Trikozol) (p. 936·1).
Peptic ulcer.

Heliphenicol *Ariston, Arg.*
Butetamate citrate (p. 1658·1).
Cough.

Heliprobe *Kibion, Swed.*
Carbon-14 (p. 2223·2) labelled urea.
Diagnosis of Helicobacter pylori infection.

Helipur *Braun, Ger.; Braun, Ital.*
Chlorocresol (p. 1748·1); clorophene (p. 1748·3); orthophenylphenol (p. 1762·3).
Surface and instrument disinfection; instrument disinfection.

Helipur H plus N *Braun, Ger.*
Glutaral (p. 1753·2); isopropyl alcohol (p. 1758·3); ethylhexanal (p. 1752·1).
Instrument disinfection.

Helirab *Micro, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Helirab-D *Micro, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Helis *Bifarma, Ital.†*
Benzalkonium chloride (p. 1737·1).
Eye disinfection.

Helisal
Note: this name may be used for preparations of different composition.
Cortecs, Irl.†
Test for *Helicobacter pylori* infection.

Heliton
Note: this name may be used for preparations of different composition.
Columbia, Mex.
Nitazoxanide (p. 942·2); tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer.

Helix I *Braun, Ital.*
Sodium *o*-phenylphenol (p. 1762·3).
Instrument disinfection.

Helixate *Bayer, Austria; Bayer, Belg.; CSL, Canad.; Bayer Schering, Cz.; Bayer, Denm.; CSL, Fr.; CSL, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer Schering, Irl.; CSL, Israel; CSL, Ital.; Bayer, Neth.; CSL, Norw.; Bayer, Pol.; Bayer Schering, Port.; CSL, Spain; CSL, Swed.; CSL, Switz.; CSL, UK; Centeon, USA.*
Octocog alfa (p. 1148·2).
Haemophilia A.

Helixderm *Alapis, Gr.*
Alkanna tinctoria oily extract.
Skin healing aid.

Gerolymatos, Singapore.
Alkanna tinctoria.
Skin trauma; burns; ulcers; haemorrhoids.

Helixir *Hexal, Cz.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Helixor *Germania, Austria; Helixor, Ger.; Swissphar, Switz.*
Mistletoe (p. 2560·2) from fir trees, pine trees, or apple trees.
Malignant neoplasms.

Helkoss *Lupin, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Helkoss-D *Lupin, India.*
Domperidone (p. 1838·1); ranitidine (p. 1882·1).

Helleva *Cristalia, Braz.*
Lodenafil carbonate (p. 2360·2).
Erectile dysfunction.

Helmacon *Pasteur, Philipp.*
Mebendazole (p. 158·3).
Worm infections.

Helmazol *Eczacibasi, Turk.*
Levamisole hydrochloride (p. 157·2).
Malignant neoplasms.

Helmex *Infectopharm, Ger.*
Pyrantel embonate (p. 165·3).
Worm infections.

Helmiben *Eurofarma, Braz.*
Mebendazole (p. 158·3); tiabendazole (p. 166·3).
Worm infections.

Helmicide *Atabay, Turk.*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Helmicin *Sanval, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Helmint *Lafedar, Arg.*
Mebendazole (p. 158·3).
Worm infections.

Helmint Compuesto *Lafedar, Arg.*
Mebendazole (p. 158·3); tinidazole (p. 949·2).
Worm infections.

Helmintol *Medley, India.*
Mebendazole (p. 158·3).
Worm infections.

Helmintox *Innotech, Fr.; Innotech, Rus.; Innotech, Ukr.*
Pyrantel embonate (p. 165·3).
Intestinal nematode infections; worm infections.

Helmipar *Saba, Turk.*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Helmisons *Sons, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Helmizol *Teuto, Braz.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).

Helmobleu *Biokem, Turk.*
Methenamine (p. 322·3); methylthioninium chloride (p. 1559·1).
Urinary-tract infections.

Helmo-Blue *Koz, Turk.*
Methenamine (p. 322·3); methylthioninium chloride (p. 1559·1).

Helmontskruie *Lennon, S.Afr.†*
Aloes (p. 1816·1); camphor (p. 2466·2); potassium carbonate (p. 2595·2); rhubarb (p. 1884·2); gentian (p. 2512·1); valerian (p. 2640·2); ginger (p. 1844·1); cardamom fruit (p. 2471·1); myrrh (p. 2566·1); clove oil (p. 2481·3).
Constipation; dyspepsia.

Helo-acid *Rosch & Handel, Austria.*
⊗Citric acid (p. 2480·3); tartaric acid (p. 2626·1); lactic acid (p. 2539·1); pepsin (p. 2586·1).
Digestive disorders.

Heloc *Jenson, Norw.†*
Docosanol (p. 974·3).
Herpes labialis.

Helol
Note: this name may be used for preparations of different composition.
Astellas, Rus.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Helonias Compose *Boiron, Fr.*
Helonias dioica (p. 2524·3); lilium tigrinum; sepia (p. 2613·1); actaea racemosa (p. 2478·1); lonicera caprifolium; belladonna (p. 2453·3); aletris farinosa.
Homoeopathic preparation.

Helopan *Nordix, Ger.; Nordmark, Ger.*
Pancreas powder (porcine) (p. 2579·3).
Pancreatic insufficiency.

Helopanflat *Rosch & Handel, Austria; Abbott, Port.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Gastrointestinal disorders; preparation for gastrointestinal radiography; flatulence; Roemheld syndrome; digestive disorders.

Helopanzym *Rosch & Handel, Austria.*
⊗Pepsin (p. 2586·1); pancreatin (p. 2579·3); porcine bile (p. 2457·2).
Digestive system disorders.

Helopyrin *Rosch & Handel, Austria.*
⊗Ethenzamide (p. 56·2); ascorbic acid (p. 2110·3); flavonoids (p. 2505·2); rutoside (p. 2505·3); ephedrine hydrochloride (p. 1663·2).
Cold symptoms.

Helpa *Adeka, Turk.*
Methenamine anhydromethylenecitrate (p. 322·3).
Urinary-tract infections.

Helpex Anticold *Movi Health, Ukr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Helpex Anticold DX *Movi Health, Ukr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Helpex Anticold Syrup *Movi Health, Ukr.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); bromhexine hydrochloride (p. 1656·3).
Cough; rhinitis.

Helpex Breathe *Movi Health, Ukr.*
Acetylcysteine (p. 1652·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Helpex Effect *Movi Health, Ukr.*
Menthol (p. 2553·2); camphor (p. 2466·2); thymol (p. 1772·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Respiratory-tract disorders; muscle and joint pain.

Helpex Hot Cap *Movi Health, Ukr.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); cetirizine hydrochloride (p. 619·2).
Cold and influenza symptoms; allergic rhinitis.

Helpin *Recalcine, Chile.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Helpoderm *Help, Gr.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Helpogen *Help, Gr.*
⊗Clioquinol (p. 273·1); gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1); tolnaftate (p. 596·1).
Infected skin disorders.

Helpometil *Help, Gr.*
⊗Fluorometholone (p. 1637·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Helporide *Help, Gr.*
Halazone (p. 1754·1).

Helporigin *Help, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Helposol *Help, Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Helposper *Help, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Helposteol *Help, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Helpovion *Medicus, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Helpp *ISA, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Heltine *Wescrib, Philipp.*
Vitamins; ferrous sulfate (p. 2062·2).
Dietary supplement; iron-deficiency anaemia; tonic.

Heltine Plus *Wescrib, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3); lecithin (p. 2542·2).
Dietary supplement; reduced appetite.

Heltiskin *Konimex, Indon.†*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Fungal skin infections.

Heludril *Pharmafabre, Gr.*
Chlorobutanol (p. 1747·2); docusate sodium (p. 1836·2); chlorhexidine gluconate (p. 1743·3).

Helvecin
Note: this name may be used for preparations of different composition.
Helvepharm, Switz.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Helvepedin *Helvepharm, Switz.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Helvetussin *Helvepharm, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Helvevir *Helvepharm, Switz.*
Aciclovir (p. 964·1).
Herpes labialis.

Helzette *Stada, Cz.*
⊗Letrozole (p. 817·1).

Hem *Ind-Swift, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Hem-12 *MMC, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Hem Fe *Wakefield, USA.*
Ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); desiccated gastric substance. Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron. Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Iron deficiency anaemias.

Hema *Vensat, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Hema BP-38 *Chief Medical Supplies, Canad.*
Sodium bicarbonate (p. 1781·1).
Haemodialysis.

Hema Pro *Professional Health, Canad.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Hemabate *Pfizer, Canad.; Pfizer, China; Pfizer, Malaysia; Pfizer, Singapore; Pharmacia, UK; Upjohn, USA.*
Carboprost trometamol (p. 2133·1).
Postpartum haemorrhage; termination of pregnancy.

Hemacaps *Sanbe, Singapore.†*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); ascorbic acid (p. 2110·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); intrinsic factor (p. 2534·2).
Iron-deficiency anaemia.

Hema-Chek *Bayer Diagnostics, UK.*
Test for blood in faeces.

Bayer, USA.
Test for occult blood in faeces.

Hema-Combistix *Bayer Diagnostics, UK; Siemens, USA.*
Test for pH, protein, glucose, and blood in urine.

Bayer Diagnostics, Irl.†
Test for pH, glucose, protein, and blood in urine.

Hemacor *Mint, India.*
Cobamamide (p. 2107·2); ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Hemacord *New York Blood Center, USA.*
Haematopoietic progenitor cells, cord blood (p. 1155·1).
Haematopoietic stem cell transplantation.

Hemadex *Mint, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1); vitamin C (p. 2110·3).

Mint, India.
Oral liquid: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Hemadone *Oboi, Philipp.*
Menadione sodium bisulfite (p. 2122·2).
Vitamin K deficiency.

Hemafer *Unipharma, Gr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Hemafer fol *Unipharma, Gr.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy.

Hemafer-S *Unipharma, Gr.*
Iron sucrose (p. 2078·1).

Hemaflow *Hovid, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Hemafluid *1A, Cz.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Hemafort *Phapros, Indon.*
Ferrous fumarate (p. 2060·3); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); vitamin B_{12} (p. 2107·2); intrinsic factor (p. 2534·2); folic acid (p. 2063·1). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Hémagène Tailleur *Elerte, Fr.*
Ibuprofen (p. 68·2).
Pain; fever.

Hema-K *Taiwan Biotech, Philipp.*
Phytomenadione (p. 2122·2).
Anticoagulant-induced prothrombin deficiency; hypoprothrombinaemia; vitamin K deficiency bleeding.

Hemapaxan *Italfarmaco, Rus.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; unstable angina.

Hemapep *SA Druggists SelfMed, S.Afr.†*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); calcium carbonate (p. 1824·3); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Hemapo *Kalbe, Indon.; Shandon Kexing, Thai.*
⊗Epoetin alfa (p. 1141·1).
Anaemia in renal failure.

Hemarate *BioFemme, Philipp.; Great Eastern, Thai.†*
Ferrous fumarate (p. 2060·3); vitamins.
Iron-deficiency anaemia; vitamin B deficiency.

Hemarate CE *Biomedis, Indon.†; Medifarma, Indon.†*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; vitamin B deficiency.

Hemarexin *Sabex, Canad.†; Sandoz, Canad.†*
Vitamin B substances (p. 2102·3); sodium glycerophosphate (p. 2519·2).

Hemarexin + C *Sandoz, Canad.†*
Vitamins.

Hemasol *Ashford, Singapore.*
Homatropine hydrobromide (p. 2007·3).
Mydriasis and cycloplegia for refraction.

Hemastat *Karnataka, Philipp.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Hemastix *Bayer Diagnostics, Irl.†; Siemens, Ital.; Bayer Diagnostics, UK; Bayer, USA.*
Test for blood in urine.

Hémastix *Siemens, Fr.†*
Test for blood in urine.

Hematest *Bayer, USA.*
Test for blood in faeces.

Hematíase B12 *Gross, Braz.*
Liver extract (p. 2444·1); gastric mucosa extract (p. 2444·1); ferric ammonium citrate (p. 2060·1); cyanocobalamin (p. 2107·2).
Iron-deficiency; anaemias.

Hematinic *Cypress, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Anaemias.

Solgar, UK.
Liver (desiccated) (p. 2444·1); vitamin B_{12} (p. 2107·2); iron (p. 2073·1); calcium ascorbate (p. 2111·1); folic acid (p. 2063·1).
Dietary supplement.

Hematinic Plus *Cypress, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); minerals.
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Hematogen C *Revival & Development, Rus.*
⊗Albumin (p. 1130·2); ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Hematogen C Vita *Geness, Rus.*
⊗Albumin (p. 1130·2); ferrous sulfate (p. 2062·2); betacarotene (p. 2051·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; tonic.

Hematogen Nova *Revival & Development, Rus.*
⊗Albumin (p. 1130·2); ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; tonic.

Hematom *Biolab Sanus, Braz.*
Aescin (p. 2431·2); glycol salicylate (p. 66·2).

Hematrine *Novartis, India.*
Ferrous succinate (p. 2062·1); vitamins.
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias; tonic; dietary supplement.

Hemaviton Action *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); ginseng (p. 2513·3); creatine phosphate (p. 2489·1); caffeine (p. 1203·3); zinc (p. 2126·1).
Dietary supplement.

Hemaviton Brain Nutrient *Bode, Indon.†; Tempo Scan Pacific, Indon.†*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Tonic.

Hemaviton C *Tempo Scan Pacific, Indon.*
Vitamin C (p. 2110·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Immunostimulant; antoxidant.

Hemaviton Energy Drink *Bode, Indon.; Tempo Scan Pacific, Indon.*
Taurine (p. 2626·2); inositol (p. 2533·2); caffeine (p. 1203·3); ginseng (p. 2513·3); royal jelly (p. 2608·1); vitamin B substances (p. 2102·3).
Dietary supplement.

Hemaviton Jreng *Tempo Scan Pacific, Indon.*
Taurine (p. 2626·2); nicotinamide (p. 2083·1); caffeine (p. 1203·3); ginseng (p. 2513·3); royal jelly (p. 2608·1).
Dietary supplement.

Hemaviton Skin Nutrient *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamin C (p. 2110·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement; antioxidant.

Hemaviton Stamina Plus *Tempo Scan Pacific, Indon.*
Vitamins; minerals; ginseng (p. 2513·3); glutamic acid (p. 2070·2); caffeine (p. 1203·3).
Tonic.

Hemax *Bio Sidus, Thai.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Sidus, Arg.; Sidus, China; Hindustan Antibiotic, India.
⊗Epoetin (p. 1141·1).
Anaemias; autologous blood transfusion.

Hemax-Eritron *Biosintetica, Braz.*
⊗Epoetin (p. 1141·1).
Anaemias.

Hembit *Cubit, India.*
Haematin (p. 1555·3); protein; vitamin B substances (p. 2102·3).

Hembran Plus *Brawn, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); vitamin C (p. 2110·3); vitamin B_{12} (p. 2107·2).

Hembran-Fe *Brawn, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1).

Hemcap *Glenmark, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

Hemcort HC *Technilab, Pol.†*
⊗Hydrocortisone acetate (p. 1640·1); zinc sulfate (p. 2126·2).
Anorectal disorders.

Hémédonine *Creme d'Orient, Fr.*
Haematoporphyrin hydrochloride (p. 2523·3).
Tonic.

Hemenatal OB *WH Nutritionals, USA.*
Vitamins; minerals.
Dietary supplement.

Hemenatal OB + DHA *WH Nutritionals, USA.*
Tablets, vitamins; minerals; capsules, omega-3 fatty acids (p. 1460·1).
Dietary supplement.

Hemeran *Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Gr.; Novartis Consumer, Port.; Novartis Consumer, Switz.*
A heparinoid (p. 1401·1).
Phlebitis; haematomas; venous insufficiency; thrombophlebitis.

Hemerven *Interdelta, Switz.*
Diosmin (p. 2505·2).
Haemorrhoids; venous insufficiency.

HemeSelect *SmithKline Diagnostics, USA.*
Test for occult blood in faeces.

Hemestal *Silanes, Mex.*
Metronidazole hydrogen succinate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

HemeTab *WH Nutritionals, USA.*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Dietary supplement.

Hemetiken *Kener, Mex.*
Difenidol (p. 1835·1).
Nausea and vomiting; vertigo.

Hemex *Alde Medi Impex, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Hemfast *Piramal, India.*
⊗Cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); haemoglobin (p. 1154·3); ascorbic acid (p. 2110·3).

Hemfer *Alkem, India.*
Capsules: Cyanocobalamin (p. 2107·2); ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).

Alkem, India.
Oral liquid: ⊗Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); haemoglobin (p. 1154·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Alkem, India.
Syrup: Cyanocobalamin (p. 2107·2); ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Hemfer-A *Alkem, India.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).

Hemforte *Ind-Swift, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Hemglo *Bactolac, India.*
Capsules: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Bactolac, India.
Oral drops: Iron polymaltose (p. 2077·2).

Hemglob-Z *Stallion, India.*
Iron (p. 2073·1); zinc (p. 2126·1).

Hemibe *Rider, Chile.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; gastrointestinal radiography.

Hemicraneal *Desma, Spain.*
Caffeine (p. 1203·3); ergotamine tartrate (p. 674·1); paracetamol (p. 115·1).
Migraine; headache.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hémi-Daonil *Sanofi-Aventis, Fr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Hemidexa Antihistaminico *Llorens, Spain.*
⊗Chlorphenamine maleate (p. 620·3); dexamethasone phosphate (p. 1631·1).
Eye disorders.

Hemifol *Solfran, Mex.*
Vitamin B substances (p. 2102·3).

Hemifolin-Z *Elfin, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); pyridoxine (p. 2105·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).

Hemigoxine Nativelle *Teofarma, Fr.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Hemilift *Ranbaxy, India.*
Iron sucrose (p. 2078·1).

Hemineurin *AstraZeneca, Austral.†*
Clomethiazole (p. 1054·2).
Alcohol withdrawal syndrome; agitation.

Heminevrin *Astra, Gr.; AstraZeneca, Irl.†; AstraZeneca, UK.†*
Clomethiazole (p. 1054·2) or clomethiazole edisilate (p. 1054·2).
Insomnia and confusion in the elderly; alcohol withdrawal syndrome; insomnia; psychoses; anxiety.

AstraZeneca, Cz.; AstraZeneca, Hung.; Sofus, Norw.; AstraZeneca, Pol.; Cheplapharm, Swed.
Clomethiazole edisilate (p. 1054·2).
Alcohol withdrawal syndrome; psychomotor agitation; sedative; insomnia; behaviour disorders and sleep disorders in the elderly; status epilepticus.

Hemiphos *Wyeth, India.*
Vitamin B substances (p. 2102·3); ferrous gluconate (p. 2061·2).

Hémipralon *Ipsen, Fr.†*
⊗Propranolol hydrochloride (p. 1479·1).
Cardiovascular disorders; migraine.

Hemiron *Ace, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron deficiency; anaemias.

Hemiseal *Kalbe, Indon.*
Feracrylum.
Bleeding gums.

Hemklot *Prompt Cure, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Hemkortin-HC *Polmex, Pol.*
⊗Hydrocortisone acetate (p. 1640·1); zinc sulfate (p. 2126·2).
Anorectal disorders.

Hemo
Note: this name may be used for preparations of different composition.
Rekah, Israel.
Ointment: Bismuth subgallate (p. 1822·1); benzocaine (p. 1980·2); zinc oxide (p. 1729·1); chloroxylenol (p. 1748·2); zinc sulfate (p. 2126·2).
Anorectal disorders.

Rekah, Israel.
Suppositories: Bismuth subgallate (p. 1822·1); benzocaine (p. 1980·2); zinc oxide (p. 1729·1); peru balsam (p. 2587·1).
Anorectal disorders.

Hemo 141
Note: this name may be used for preparations of different composition.
Esteve, Spain.
Etamsylate (p. 1145·2).
Haemorrhage.

Hemo Derminiol *Diafarm, Spain.†*
Hamamelis (p. 2523·3).
Haemorrhoids.

Hemo Factor *Bioglan, Austral.†*
Vitamins; iron (p. 2073·1); folic acid (p. 2063·1).
Anaemia.

Hemo Rid
Note: this name may be used for preparations of different composition.
CCM, Hong Kong.
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Hemoal *Reckitt Benckiser, Spain.*
⊗Ephedrine hydrochloride (p. 1663·2); benzocaine (p. 1980·2).
Anorectal disorders.

Hemobief *Baxter, Fr.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Haemofiltration.

Hemobine *Dosa, Arg.*
Cladribine (p. 769·1).

Hemobion
Note: this name may be used for preparations of different composition.
Merck, Indon.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Merck, Mex.
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; iron deficiency.

Merck, Philipp.
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); calcium carbonate (p. 1824·3); vitamin D (p. 2112·3); ascorbic acid (p. 2110·3).
Iron-deficiency anaemia; prevention of neural-tube defects in pregnancy; nutritional supplement.

Hemoblock *Sigma, Braz.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Hemocane
Note: this name may be used for preparations of different composition.
Eastern Pharmaceuticals, Irl.; LPC, UK.
Lidocaine hydrochloride (p. 1988·2); zinc oxide (p. 1729·1); bismuth oxide (p. 1821·3); benzoic acid (p. 1738·2); cinnamic acid (p. 1748·3).
Anorectl disorders; haemorrhoids.

Key, Austral.
Lidocaine (p. 1988·1); allantoin (p. 1693·1); hamamelis (p. 2523·3); zinc oxide (p. 1729·1); chlorhexidine acetate (p. 1743·2).
Haemorrhoids; anal pruritus.

Hemocare *MMC, India.*
Capsules: Copper sulfate (p. 2057·2); ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); magnesium chloride (p. 1787·1); manganese sulfate (p. 2081·2); protein hydrolysate (p. 2086·2); vitamin C (p. 2110·3).

MMC, India.
Syrup: Copper sulfate (p. 2057·2); ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); manganese sulfate (p. 2081·2); protein hydrolysate (p. 2086·2).

Hemoccult *SmithKline Diagnostics, USA.*
A range of tests for occult blood in faeces.

Beckman, Canad.†
Test for occult blood in faeces.

Hemocheck *Preventys, Fr.†*
Test for blood in faeces.

Hemocid *GSK, India.*
Aminocaproic acid (p. 1131·3).
Haemorrhage.

Hemocinol *Elpen (Ελπεν), Gr.*
Dihydroergotamine mesilate (p. 672·2).

Hémoclar *Sanofi-Aventis, Fr.*
Pentosan polysulfate (p. 1465·1).
Soft-tissue disorders.

HemoClin *Paracelsia, Ger.†; Interdelta, Switz.†*
Aloes (p. 1816·1).
Anorectal disorders.

Hemoclot
Note: this name may be used for preparations of different composition.
Ethix, India.
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Solvang, Philipp.
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage.

Hemocol *MBP, Ger.*
Collagen (porcine) (p. 2483·2).
Haemorrhage.

Hemocrat *Cratus, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Hemocromo *Francia, Ital.*
Sodium ferric gluconate complex (p. 2089·1).
Iron-deficiency anaemia.

Hemocyl *Hemocyl, UK.*
Azadirachta (p. 2451·2); berberine (p. 2455·1); mesua ferrea.
Haemorrhoids.

Hemocyte *US Pharmaceutical, USA.*
Tablets: Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Hemocyte Plus *US Pharmaceutical, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); sodium ascorbate (p. 2111·1); vitamin B substances (p. 2102·3); minerals.
Iron-deficiency anaemia; dietary supplement.

Hemocyte-F *US Pharmaceutical, USA.*
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; folate-deficiency anaemias; iron and folic acid supplement.

US Pharmaceutical, USA.
Elixir: Polysaccharide-iron complex (p. 2086·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Anaemias.

Hemo-Cyto-Serum *Hua, Thai.†*
⊗Monosodium glutamate (p. 2198·2); strychnine sulfate (p. 2623·2); iron (p. 2073·1).
Tonic; anaemias.

Hemodase *Vitapan, Braz.*
⊗Hydrocortisone (p. 1640·1); lidocaine (p. 1988·1); bismuth subgallate (p. 1822·1); zinc (p. 2126·1).

Hemodent *Medical Products, Canad.†*
Aluminium chloride (p. 1693·3).

Hemodilax *Elpen (Ελπεν), Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).

Hemodotti *Prodotti, Braz.†*
⊗Rutoside (p. 2505·3); naphazoline hydrochloride (p. 1669·3); hydrocortisone acetate (p. 1640·1); hamamelis (p. 2523·3); amylocaine hydrochloride (p. 1979·3).
Haemorrhoids.

Hemodren *Llorens, Spain.*
⊗Hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Hemo-Fec *Roche Diagnostics, Fr.*
Test for blood in faeces.

Hemofer
Note: this name may be used for preparations of different composition.
GSK, Pol.
Ferrous chloride (p. 2060·3) or ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

GSK, Rus.; Medana, Rus.
Ferric chloride (p. 2504·2) or ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Lafedar, Arg.
Ferrous fumarate (p. 2060·3) or ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Pangaoshou, Philipp.
Angelica (p. 2443·3); sichuan rhizome; astragalus root (p. 2451·1); asiabell root; indian bread; rahmania root; liquorice (p. 1853·2).
Dietary supplement.

Hemofer F *GSK, Pol.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Anaemias.

Hemofer Folic *Lafedar, Arg.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Anaemias.

Hemoferrol *Sintesina, Arg.*
Ferrous fumarate (p. 2060·3) or ferrous sulfate (p. 2062·2).
Anaemias; iron supplement.

Hemofer-Z *Indkus, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Hemofil *Baxter, Braz.; Baxter, Malaysia†; Baxter, Neth.†; Baxter, Pol.; Baxter, Rus.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A.

Hemofil M *Baxter, Arg.; Baxter, Fr.†; Baxter, Gr.; Baxter, Hong Kong; Baxter, India; Baxter, Israel; Bioscience, Philipp.; Baxter, Singapore; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, USA.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; factor VIII deficiency.

Hemofiltracion E2 *Baxter, Spain.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Haemofiltration solution.

Hemofiltracion E4 *Baxter, Spain.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemofiltration solution.

Hemofissural *Baldacci, Port.*
Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); hamamelis (p. 2523·3); tetracaine hydrochloride (p. 1996·3).
Anorectal disorders.

Hemofit *Mission Happiness, India.*
Vitamins; minerals; soy protein (p. 2092·3).

Hemofleb *UCI, Braz.*
Hamamelis (p. 2523·3); davila rugosa; belladonna (p. 2453·3); menthol (p. 2553·2); lidocaine (p. 1988·1).

Hemofol *Cristalia, Braz.*
Heparin sodium (p. 1396·3).

Hemo-G *Prompt Cure, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Hemogenin *Sanofi-Aventis, Braz.*
⊗Oxymetholone (p. 2298·3).
Anaemias; hereditary angioedema; growth retardation.

Hemoglo *Matxin, Singapore.*
Azadirachta indica (p. 2451·2); chebulic myrobalan (p. 2474·3); beleric myrobalan (p. 2453·2); Indian gooseberry (p. 2532·2); andrographis (p. 2443·2); tecomella undulata; picrorhiza kurroa (p. 2590·2); psoralea corylifolia; eclipta alba; crataeva nurvala.
Skin disorders.

Hemohes *Braun, Arg.; Braun, Austria†; Braun, Chile; Braun, China; Braun, Cz.†; Braun, Fin.†; Braun, Ger.; Bioser (Βιοσερ), Gr.; Braun, Indon.†; Braun, Israel; Braun, Neth.†; Biomed, NZ†; Braun, Pol.; Braun, Port.†; Braun, Rus.; Braun, Singapore; Braun, Spain; Braun, Thai.; Braun, Turk.†; Braun, UK.†*
⊗Pentastarch (p. 1146·1) in sodium chloride.
Plasma volume expansion; shock; haemodilution; extracorporeal circulation; hypotension; leucapheresis.

Braun, Switz.†
⊗Pentastarch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion; haemodilution.

Hemo-Ice *Key, Israel.†*
Freezable solution in plastic applicator.
Haemorrhoids.

Hemoinfant *Nucitec, Mex.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); ferrous sulfate (p. 2062·2); zinc sulfate (p. 2126·2).

Hemo-K *Am-Europharma, Philipp.†*
Menadione sodium bisulfite (p. 2122·2).
Vitamin K deficiency; haemorrhagic disease.

Hemolactol *Gambro, Austria; Gambro, Port.; Gambro, Rus.; Gambro, Swed.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium lactate (p. 1781·2) (p. 1778·2).
Haemofiltration; haemodialysis.

Hemolate *Micro, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Hemolax *Hua, Thai.†*
Ferrous fumarate (p. 2060·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); cascara (p. 1826·1).
Iron-deficiency anaemia; beri-beri; vitamin B_{12} deficiency; constipation.

Hemoleven *Lab Francais du Fractionnement, Fr.; IFET (ΙΦΕΤ), Gr.*
A factor XI preparation (p. 1150·3).
Factor XI deficiency.

Hemolex *Lexus, India.*
Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Hemolingual *Pharmakon, Switz.*
Aloe (p. 1816·1); collinsonia canadensis (p. 2622·2); paeonia officinalis.
Homoeopathic preparation.

Hemolok *Themis Medicare, India; Dexa, Indon.*
Feracrylum.
Haemorrhage; skin disinfection; wounds; burns.

Hemolon *Greater Pharma, Thai.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Hemomicin *Hemofarm, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Hemomycin *Hemofarm, Rus.*
Azithromycin (p. 221·2).
Bacterial infections; peptic ulcer.

Hemon *Norma (Νορμα), Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Hemonet *Diafarm, Spain.†*
Tetracaine hydrochloride (p. 1996·3).
Haemorrhoids.

Hemopamid *Hemofarm, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Hemopass *Pentafarma, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Hemopene *Ulagay, Turk.*
Pentoxifylline (p. 1465·3).

Hemo-Pic *ASL, Canad.†*
Menthol (p. 2553·2); resorcinol (p. 1718·3); zinc oxide (p. 1729·1).

Hemoplex
Note: this name may be used for preparations of different composition.
Novell, Singapore.
Ferrous gluconate (p. 2061·2); vitamin C (p. 2110·3); folic acid (p. 2063·1); cobalamin; copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2).
Dietary supplement; iron deficiency.

Hemoprex *Bergamo, Braz.*
⊗Epoetin (p. 1141·1).
Anaemias.

Hemoproct *Belfar, Braz.*
Hamamelis (p. 2523·3).

Hemopure *Biopure, S.Afr.*
⊗Polymerised hemoglobin (bovine) (p. 1155·1).
Anaemia.

Hemoraas *Shanghai RAAS, Thai.*
A factor VIII preparation (p. 1148·1).
Haemophilia A; factor VIII deficiency.

Hemoralgine *Atabay, Turk.*
⊗Chlorhexidine hydrochloride (p. 1743·3); menthol (p. 2553·2); aluminium acetotartrate (p. 2440·1); ephedrine hydrochloride (p. 1663·2); bismuth subgallate (p. 1822·1); tetracaine hydrochloride (p. 1996·3); zinc oxide (p. 1729·1).
Haemorrhoids.

Hemoray *Varifarma, Arg.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Hemorectal *GSK, Pol.*
Bismuth oxide (p. 1821·3); bismuth subgallate (p. 1822·1); bismuth oxyiodogallate (p. 1821·3); boric acid (p. 2459·3); Peru balsam (p. 2587·1); resorcinol (p. 1718·3); zinc oxide (p. 1729·1).
Anorectal disorders.

Hemorhin *Hua, Thai.†*
Docusate sodium (p. 1836·2); spermaceti (p. 2178·2).
Haemorrhoids.

Hemorhinol *Chauvin, Belg.†*
Hamamelis (p. 2523·3); phenazone (p. 124·1); tannic acid (p. 2625·2).
Skin irritation.

Hemorid
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Pharmamagis†, Hung.
Suppositories: ⊗Camphor (p. 2466·2); menthol (p. 2553·2); achillea oil (p. 2427·3); adrenaline hydrochloride (p. 1292·2); procaine hydrochloride (p. 1994·3); ephedrine hydrochloride (p. 1663·2).
Anorectal disorders.

Wagner, Hung.
Rectal ointment: ⊗Camphor (p. 2466·2); menthol (p. 2553·2); achillea oil (p. 2427·3); procaine hydrochloride (p. 1994·3); ephedrine hydrochloride (p. 1663·2).
Anorectal disorders.

Pfizer, Israel.†
Phenylephrine hydrochloride (p. 1672·3); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Hemorid For Women *Thompson, USA.*
Cream: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); pramocaine hydrochloride (p. 1993·3); phenylephrine hydrochloride (p. 1672·3); aloe vera (p. 1693·2).
Anorectal disorders.

Thompson, USA.
Lotion: ⊗Liquid paraffin (p. 2191·2); yellow soft paraffin (p. 2212·1); glycerol (p. 2517·2).
Anorectal disorders.

Thompson, USA.
Suppositories: Zinc oxide (p. 1729·1); phenylephrine hydrochloride (p. 1672·3).
Anorectal disorders.

Hemorigen *Herbapol Wroclaw, Pol.*
Erigeron canadensis.
Haemorrhage.

Hemorogard *Phapros, Indon.*
Graptophyllum pictum citrus bioflavonoids (p. 2505·2).
Haemorrhage; vascular disorders.

Hemorol *Herbapol Wroclaw, Pol.*
Achillea (p. 2427·3); aesculus (p. 2431·2); belladonna (p. 2453·3); benzocaine (p. 1980·2); chamomile (p. 2474·1); tormentil (p. 2633·2); janowca.
Anorectal disorders.

Hemorrane *Faes, Spain.*
⊗Hydrocortisone acetate (p. 1640·1).
Haemorrhoids.

Hemorrhoid Ointment *Jamp, Canad.*
Pramocaine hydrochloride (p. 1993·3); zinc sulfate (p. 2126·2).
Haemorrhoids.

Hemorrhoid Relief *Thai FD, Thai.*
Cissus quadrangularis; senna (p. 1885·1); anacyclus pyrethrum.
Haemorrhoids.

Hemorrhoidal Ointment *Pharmascience, Canad.*
Pramocaine hydrochloride (p. 1993·3); zinc sulfate (p. 2126·2).

Hemorrhoidal Relief *Perrigo, Canad.*
Phenylephrine hydrochloride (p. 1672·3).
Haemorrhoids.

Hemorrhoidal Suppositories *Geritrex, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Haemorrhoids.

Hemorrocort *Demo, Gr.*
⊗Cinchocaine hydrochloride (p. 1983·2); hexachlorophene (p. 1754·1); prednisolone (p. 1645·2); undecenoic acid (p. 596·3).

Hemorroidal *Elvipe, Gr.*
⊗Adrenaline (p. 1292·1); vitamin A (p. 2098·3); benzocaine (p. 1980·2); zinc oxide (p. 1729·1); bismuth oxychloride (p. 1821·3).

Hemorroidal-H *Elvipe, Gr.*
⊗Hydrocortisone acetate (p. 1640·1); hexachlorophene (p. 1754·1); benzocaine (p. 1980·2).

Hemorroisan *Imvi, Arg.*
Lidocaine hydrochloride (p. 1988·2); zinc oxide (p. 1729·1); methyl salicylate (p. 92·1).
Haemorrhoids.

Hemorrolite *Holland Pharma, Neth.*
Belladonna (p. 2453·3); ferrum phosphoricum (p. 2077·1); hamamelis virginiana (p. 2523·3); hepar sulphur (p. 1721·3); lycopodium clavatum (p. 2547·1); natrium muriaticum (p. 1795·1); sulphur (p. 1721·1).
Homoeopathic preparation.

Hemosedan *Takeda, Belg.*
⊗Prednisolone acetate (p. 1645·2); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Hemosin-K *Hormona, Mex.*
Carbazochrome sodium sulfonate (p. 1137·1); vitamin K (p. 2122·1).
Haemorrhage.

Hemosol *Gambro, Austria; Gambro, Cz.; Gambro, Fin.; Teva, Israel; Gambro, Neth.; Gambro, Swed.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); lactic acid (p. 2539·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1778·2).
Haemofiltration; haemodialysis.

Gambro, Norw.; Gambro, Spain.
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemodialysis; haemofiltration.

Gambro, Port.
Lactic acid (p. 2539·1); sodium chloride (p. 1795·1); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1).
Haemofiltration.

Hemosol B0 *Gambro, Denm.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemodialysis; haemofiltration.

Hospal, Fr.; Gambro, Switz.
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); lactic acid (p. 2539·1); sodium bicarbonate (p. 1781·1).
Haemofiltration; haemodialysis.

Hemosol BO *Gambro, Irl.*
Magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1); lactic acid (p. 2539·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1).
Haemodialysis; haemofiltration.

Gambro, Canad.†
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemodialysis solution.

Hemosol LG *Gambro, Canad.*
Calcium chloride (p. 1783·1); glucose (p. 2068·3); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemodialysis solution.

Hemosol LO *Gambro, Canad.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemodialysis solution.

Hemostan *Biomedis, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage.

Hemostat *Meridian, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Hemostop *Foramen, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Hemototal *Grunenthal, Port.*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia; iron deficiency.

Hemotran *Dosa, Arg.*
Acenocoumarol (p. 1290·1).

Hemotrex *Foramen, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Hemoval *Saval, Chile.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Hemovas *Ferrer, Spain.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Hemovasal *Manetti Roberts, Ital.*
Suleparoid (p. 1507·2).
Thrombosis prophylaxis; superficial vascular disorders; soft-tissue disorders.

Hemovin *EuroHealth, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_2 (p. 2104·3); vitamin B_{12} (p. 2107·2).
Anaemias.

Hemovit *Dayton, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Hemovital *Neiadas (Νειαδας), Gr.†*
⊗Ferric ammonium citrate (p. 2060·1); haemoglobin (p. 1154·3).

Hem-Prep *G & W, USA.*
Shark-liver oil (p. 2614·2); phenylmercuric nitrate (p. 1765·2); bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1); benzocaine (p. 1980·2).
Anorectal disorders.

Hemprovit-Fe *Health Care, India.*
Cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); protein hydrolysate (p. 2086·2); pyridoxine hydrochloride (p. 2105·3).

Hemral *Hiral, India.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Hiral, India.
Syrup: Folic acid (p. 2063·1); iron choline citrate (p. 2060·2); lysine (p. 2079·3); vitamin B_{12} (p. 2107·2).

Hemral-CB *Hiral, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Hemril *Upsher-Smith, USA.*
Bismuth subgallate (p. 1822·1); bismuth resorcinol compound (p. 1821·3); benzyl benzoate (p. 2149·1); peru balsam (p. 2587·1); zinc oxide (p. 1729·1).

Hemril-HC *Upsher-Smith, USA.*
⊗Hydrocortisone acetate (p. 1640·1).

Hemsi *Serum Institute, India.*
Capsules; syrup: Ferrous fumarate (p. 2060·3); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3); minerals.
Iron-deficiency anaemia; megaloblastic anaemia.

Serum Institute, India.
Oral drops: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Hemsub *Osmed, India.*
Chewable tablets: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Osmed, India.
Syrup: Iron polymaltose (p. 2077·2).

Hemsyl *Indoco, India.*
Etamsylate (p. 1145·2).
Haemorrhage; menorrhagia.

Hemsyneral-TD *USV, India; USV, Ukr.†*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Iron and folate deficiency anaemia; iron supplement.

Henafurine *Delattre-Hemapurine, Belg.†*
Bisacodyl (p. 1821·1).
Constipation.

Hendevit *Valenta, Rus.*
Vitamins.

Henexal *Pisa, Mex.†*
⊗Furosemide (p. 1387·1).

Heng Ao Pu Kang *Jianfeng, China.*
Penciclovir (p. 1008·2).

Heng Bang *Hanson, China.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Heng Bei *Ya Bang Ai Pu Sen, China.*
Telmisartan (p. 1509·3).
Hypertension.

Heng Bo Lai *Ke Lun, China.*
Ornidazole (p. 943·1).
Protozoal infections; anaerobic bacterial infections.

Heng En *Hanson, China.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Heng Fu *Ang Li Kang, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Heng Jie *Hanson, China.*
Balofloxacin (p. 226·3).

Heng Kang *Zaozhuang, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Heng Di Ke *Ankehengyi, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Heng Li An *Lunan, China; XinShiDai, China.*
Zolmitriptan (p. 682·2).
Migraine.

Heng Luo *Hengrui, China.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Heng Mai *Hengrui, China.*
Oxymatrine.

Heng Mu *Hanson, China.*
Pazufloxacin mesilate (p. 338·1).

Heng Ping *Hengda, China.*
Alginic sodium diester.

Heng Run *Hengsheng, China.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Heng Sen *Hanson, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Heng Shi *Suzhou No 1, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Heng Su *Hengrui, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Heng Te *Hanson, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Heng Xin *Fengyuan, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Heng Xue Su *Lvgu, China.*
Telmisartan (p. 1509·3).
Hypertension.

Heng Yang *Hengrui, China.*
Imrecoxib.

Heng Yi *Hengrui, China.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).

Heng Ze *Hanson, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Heng Zhi *Chang Fu Jie Jing, China.*
Etamsylate (p. 1145·2).

Hengao *Hanson, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Hengyun *Hanson, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Hengzhi *Qilu, China.*
Irsogladine maleate (p. 1848·3).
Peptic ulcer.

Hening *Lyomark, China.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery.

Henovic *Vargas, Venez.*
Ascorbic acid (p. 2110·3); vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).
Dietary supplement.

Henoxil *Mastercare, Chile.*
Enoxaparin sodium (p. 1372·3).

Henplatin *Jiangsu-Hengrui, Philipp.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Hensetron *Jiangsu-Hengrui, Philipp.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Hentaxel *Jiangsu-Hengrui, Philipp.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer.

Hentrozole *Jiangsu-Hengrui, Philipp.*
⊗Letrozole (p. 817·1).
Breast cancer.

Hep *Gland, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Hep B Quin *Centurion, Turk.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepa
Note: this name may be used for preparations of different composition.
Merz, Austria.
Ornithine aspartate (p. 2085·2).
Hyperammonaemia associated with liver disorders.

Venus, India.
Vitamins; minerals; amino acids; choline bitartrate (p. 2055·2); ubidecarenone (p. 2637·1); silymarin (p. 1561·2).

Hepabene *Ratiopharm, Austria†; Ratiopharm, Hung.; Ratiopharm, Rus.; Ratiopharm, Ukr.*
Fumitory (p. 2508·2); milk thistle (p. 1561·1).
Biliary-tract and liver disorders.

HepaBesch *Strathmann, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Hepabig *VHB, India; Green Cross, Malaysia; Green Cross, Philipp.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepabil *Sanitas, Chile.*
⊗Bile extract (p. 2457·2); choline dihydrogen citrate (p. 2055·2); inositol (p. 2533·2); boldo (p. 2458·3); vitamin K (p. 2122·1); pancreatin (p. 2579·3).
Digestive disorders.

Hepabion *Merck, Indon.†*
Essential phospholipids (p. 2201·2); choline (p. 2055·2); soya oil (p. 2092·3); mono and diglycerides; medium-chain triglycerides (p. 2082·2).
Dietary supplement to support liver function.

Hepabionta
Note: this name may be used for preparations of different composition.
Merck, S.Afr.†
Vitamin B substances (p. 2102·3); orotic acid (p. 2578·1); folic acid (p. 2063·1).
Liver disorders.

Hepabiotral *Bionutre, Arg.*
Amino acids; vitamin B substances (p. 2102·3).
Liver disorders.

Hepaboldin *Knop, Chile.*
Herbal extract.
Liver disorders; gastrointestinal disorders.

Hepacaf *CAF-DCF, Belg.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepacalmina *Prisfar, Port.*
Bioflavonoids (p. 2505·2).
Liver disorders.

Hepacap *Neopharm, Thai.*
Essential phospholipids (p. 2201·2); vitamins.
Liver disorders.

Hepacare *Jean-Marie, Hong Kong.*
A heparinoid (p. 1401·1).
Varicose veins; thrombophlebitis; haematomas; hard scars.

Hepaccine-B *Alkem, India; Biovac, S.Afr.†*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Hepacell *Medikon, Indon.†*
Schisandra (p. 2611·2); javanese turmeric (p. 2636·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Hepachofa *Fecofar, Arg.*
Cynara (p. 2490·3); dehydrocholic acid (p. 2492·1).
Biliary-tract disorders.

Hepachol
Note: this name may be used for preparations of different composition.
Bio-Drug, India.
Cascara (p. 1826·1); choline chloride (p. 2055·2); lysine hydrochloride (p. 2079·3); sodium tauroglycocholate; sorbitol (p. 2092·1).

Landson, Indon.
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Hépaclem *Clement Thionville, Fr.†*
Cynara (p. 2490·3); boldo (p. 2458·3); kinkeliba (p. 2538·2); Javanese turmeric (p. 2636·2).
Digestive-system disorders; renal disorders.

Hepaclex *Gland, Philipp.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of clotting during extracorporeal circulation; unstable angina.

Hepacom *Sanofi-Aventis, Pol.†*
Timonacic (p. 2631·3).
Liver disorders.

Hepacor *Intas, India.*
Ornithine aspartate (p. 2085·2).

Hepacur *Medical, Arg.*
Boldo (p. 2458·3); carqueja (p. 2471·2); cynara (p. 2490·3); hyoscyamus (p. 2530·2); belladonna (p. 2453·3).
Biliary-tract disorders.

Hepacyn *Quiris, Ger.*
Cynara (p. 2490·3).
Dyspepsia; biliary-tract disorders.

Hepacynar *Europlant Phytofarm, Pol.*
Cynara (p. 2490·3).
Dyspepsia; hyperlipidaemias.

Hepa-Desicol *Elmor, Venez.*
Pig bile (Desicol) (p. 2457·2).
Digestive disorders.

Hépadial *Biocodex, Fr.*
Dimecrotic acid, magnesium salt (p. 2493·2).
Dyspepsia.

Hepadif *Pro-Pharma, Ukr.*
Capsules: Carnitine orotate (p. 2578·1); liver extract (p. 2444·1); adenine hydrochloride (p. 2430·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2) riboflavin (p. 2104·3).
Liver disorders.

Pro-Pharma, Ukr.
Injection: Carnitine orotate (p. 2578·1); carnitine hydrochloride (p. 2053·2); liver extract (p. 2444·1); adenosine (p. 1291·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Liver disorders.

Reig Jofre, Spain.
Oral solution: Carnitine orotate (p. 2578·1); carnitine (p. 2053·2); vitamin B substances (p. 2102·3); liver extract (p. 2444·1).
Hepatitis; acetonaemia.

Hepadoddi *Merck, Port.*
Dimecrotic acid, magnesium salt (p. 2493·2).
Biliary-tract disorders.

Hepadren *Rovi, Spain.*
Bemiparin sodium (p. 1314·2).
Thrombosis prophylaxis; deep-vein thrombosis; prevention of clotting during haemodialysis.

Hepa-Factor *Max Farma, Ital.*
Folinic acid (p. 2066·3); hydroxocobalamin (p. 2107·3).
Liver disorders; hyperchromic anaemia.

Hepaflex *Baxter, Fin.; Baxter, Norw.*
Heparin sodium (p. 1396·3).
Thrombosis prophylaxis.

Hepaflor *Bio-Sante, Canad.†*
Boldo (p. 2458·3); buchu (p. 2461·3); bearberry (p. 2453·2).

Hepafol *Meyer, Venez.*
Ferric ammonium citrate (p. 2060·1); cyanocobalamin (p. 2107·2).
Anaemias.

Hepafol con B-12 *Meyer, Venez.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); copper sulfate (p. 2057·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Hepafol-F *Farcoral, Mex.*
Vitamins; minerals; garlic (p. 2510·3); royal jelly (p. 2608·1).

Hepafor *Partner, Rus.*
Bifidobacterium bifidum (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3).
Maintenance of normal intestinal flora; intestinal infections.

Hepaforte *Bosnalijek, Ukr.*
Phospholipids (p. 2201·2); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); thiamine nitrate (p. 2103·2); tocoferil acetate (p. 2119·2).
Liver disorders.

Hepagallin N *Pfluger, Ger.†*
Cynara (p. 2490·3).
Dyspepsia; liver disorders.

HepaGam B *Cangene, Canad.; Cangene, Israel; Cangene, USA.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepagard
Note: this name may be used for preparations of different composition.
Phapros, Indon.
Milk thistle (p. 1561·1); cynara (p. 2490·3); curcuma longa.
Liver disorders; dyspepsia.

United Biotech, India.
Ornithine aspartate (p. 2085·2).

Hepa-Gastreu N R7 *Reckeweg, Ger.*
Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); china (p. 2478·3); lycopodium (p. 2546·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Hepa-Gastreu R7 *Reckeweg, Neth.*
Carduus marianus (p. 1561·1); chelidonium majus (p. 2522·2); lycopodium clavatum (p. 2547·1); nux vomica (p. 2573·3); china officinalis (p. 2478·3).
Homoeopathic preparation.

Hepa-Gel *Winthrop, Ger.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Hépagel *Spirig, Switz.*
Heparin sodium (p. 1396·3).
Soft-tissue disorders; peripheral vascular disease.

Hepagen-Plus *VHB, India.*
A hepatitis B vaccine (recombinant) (p. 2389·3).

Hepaglob *Sun, India.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hépagrume *EG, Fr.*
Arginine (p. 2049·1); betaine (p. 2456·1); choline dihydrogen citrate (p. 2055·2); inositol (p. 2533·2); sorbitol (p. 2092·1).
Dyspepsia; constipation.

Hepahealth *Healthyway, Ukr.*
Milk thistle (p. 1561·1); turmeric (p. 2218·1); cynara (p. 2490·3); cnicus benedictus (p. 2482·2); Oregon grape (p. 2577·1); lecithin (p. 2542·2); choline (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2); vitamin B_6 (p. 2105·3); noni.
Liver and biliary tract disorders.

Hepai *Mei Luo, China.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Hepakur *Medical International Systems, Singapore.*
Phosphatidyl choline (p. 2588·3) with other phospholipids.
Liver disorders; hyperlipidaemias.

Hepalac *Berlin Pharm, Thai.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Hepalean *Merck, Canad.†*
Heparin sodium (p. 1396·3).
Thromboembolic disorders; thrombosis prophylaxis.

Hepalean-Lok *Schering-Plough, Canad.†*
Heparin sodium (p. 1396·3).
To maintain patency of intravenous injection devices.

Hepalin *Bergamo, Braz.*
Methionine (p. 1558·2); betaine (p. 2456·1); choline citrate (p. 2055·2); sorbitol (p. 2092·1).
Liver disorders.

Hepalite *Holland Pharma, Neth.*
Carduus marianus (p. 1561·1); chelidonium majus (p. 2522·2); hypericum perforatum (p. 449·1); lycopodium clavatum (p. 2547·1); mercurius solubilis (p. 2555·3); taraxacum officinale (p. 2625·3); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Hepaliv *Intas, India.*
Syrup: Achillea (p. 2427·3); capparis spinosa.

Intas, India.
Tablets: Andrographis (p. 2443·2); berberis (p. 2502·1); punarnava (p. 2601·1); phyllanthus niruri (p. 2590·1).

Hepa-Loges *Loges, Ger.*
Capsules: Milk thistle (p. 1561·1).
Liver disorders.

Hepa-Loges N *Loges, Ger.*
Injection: Taraxacum (p. 2625·3); quassia amara (p. 2601·1); lycopodium (p. 2546·3); myrica cerifera; chelidonium (p. 2522·2).
Homoeopathic preparation.

Hepalon *Micro, India.*
⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Hepamax
Note: this name may be used for preparations of different composition.
Blausiegel, Braz.
Heparin sodium (p. 1396·3).
Prevention of clotting during haemodialysis.

Kalbe, Indon.
PPC; silymarin phytosome (p. 1561·2); schisandra (p. 2611·2); *d*-alpha tocopherol (p. 2119·1).
Liver disorders.

Hepa-Merz
Note: this name may be used for preparations of different composition.
Biolab Sanus, Braz.; Merz, China; Merz, Ger.; Merz, Hong Kong; Merz, Hung.; Win-Medicare, India; Combiphar, Indon.; Merz, Indon.; Merz, Mex.; Merz, Philipp.; Merz, Pol.; Merz, Rus.; Merz, Thai.; Assos, Turk.; Merz, Ukr.
Ornithine aspartate (p. 2085·2).
Liver disorders; hyperammonaemia; hepatic encephalopathy; digestive disorders.

Win-Medicare, India.
Tablets: ⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).
Liver disorders.

Win-Medicare, India.†
Syrup: Ornithine aspartate (p. 2085·2); nicotinamide (p. 2083·1); vitamin B_2 (p. 2104·3).
Liver disorders.

Hepa-Merz KT *Merz, Ger.†*
Ornithine aspartate (p. 2085·2).
Liver disorders.

Hepamin *Trianon, Philipp.*
Silymarin (p. 1561·2); taraxacum flower (p. 2625·3); cynara (p. 2490·3).
Dietary supplement for liver function.

Hépanéphrol *Zambon, Fr.*
Cynara (p. 2490·3).
Fluid retention; digestive disorders.

Hepan-L *Arrowin, India.*
⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Hepanox *Minova, India.*
Enoxaparin (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

Hepa-Pro *British Biologicals, India.*
Preparation for enteral nutrition.

Hepa-Q *Pyridam, Indon.*
Schisandra (p. 2611·2); milk thistle (p. 1561·1); Javanese turmeric (p. 2636·2).
Dietary supplement.

Hepaquifa *Angelini, Port.†*
Dimecrotic acid (p. 2493·2).
Biliary-tract disorders.

Hepar 10% *Baxter, Ger.*
Amino acids.
Parenteral nutrition in liver disorders.

Hepar comp *Heel, Ger.*
Hepar suis (p. 2444·1); cyanocobalaminum (p. 2107·2); duodenum suis (p. 2444·1); thymus suis (p. 2631·1); colon suis; vesica fellea suis (p. 2444·1); pancreas suis (p. 2444·1); china (p. 2478·3); lycopodium (p. 2546·3); chelidonium (p. 2522·2); carduus marianus (p. 1561·1); histamin (p. 2525·2); sulfur (p. 1721·1); avena sativa (p. 2451·1); natrium oxalaceticum (p. 2578·3); 2-oxo-glutaric acid (p. 2579·1); malic acid (p. 2549·2); fumaric acid (p. 1704·2); calcium carbonicum (p. 1824·3); taraxacum (p. 2625·3); cynara scolymus (p. 2490·3); veratrum; thioctic acid (p. 2629·1); orotic acid (p. 2578·1).
Homoeopathic preparation.

Hepar Compositum *Heel, Canad.*
Alpha-liponicum acidum (p. 2629·1); avena sativa (p. 2451·1); calcarea carbonica (p. 1824·3); carduus marianus (p. 1561·1); chelidonium majus (p. 2522·2); cholesterinum (p. 2179·1); cinchona officinalis (p. 2478·3); cynara scolymus (p. 2490·3); histaminum hydrochloricum (p. 2525·2); lycopodium clavatum (p. 2547·1); nadidum (p. 2567·1); sulphur (p. 1721·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Hepar SL *Cassella-med, Ger.*
Cynara (p. 2490·3).
Dyspepsia.

Heparanox H *Pfluger, Ger.*
Berberis vulgaris (p. 2502·1); lycopodium clavatum (p. 2547·1); silybum marianum (p. 1561·1); solidago virgaurea (p. 2620·1); strychnos nux-vomica (p. 2573·3); taraxacum officinale (p. 2625·3); veronica virginica; yucca filamentosa (p. 2649·3).
Homoeopathic preparation.

Heparegen *Jelfa, Pol.*
Timonacic (p. 2631·3).
Liver disorders.

Heparen *Claris, India.*
Heparin (p. 1396·3).
Thromboembolic disorders.

Hépargitol *Elerte, Fr.*
Sachet A, sorbitol (p. 2092·1); citric acid (p. 2480·3); sachet B, arginine hydrochloride (p. 2049·1); sorbitol; anhydrous sodium sulfate (p. 1888·1); sodium phosphate (p. 1791·1).
Dyspepsia; constipation.

Hepar-Hevert *Hevert, Ger.*
Oral drops: Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); taraxacum (p. 2625·3).
Homoeopathic preparation.

Hevert, Ger.
Tablets: Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); leptandra; natrium sulf. (p. 1888·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Hepar-Hevert N *Hevert, Ger.*
Injection: Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); quassia amara (p. 2601·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Heparibene *Ratiopharm, Hung.*
Heparin calcium (p. 1396·3) or heparin sodium (p. 1396·3).
Thromboembolic disorders.

Heparil *Arterium, Ukr.*
Heparin sodium (p. 1396·3).
Peripheral and superficial vascular disorders; soft-tissue injury.

Heparin Comp *Aponova, Austria.*
Heparin sodium (p. 1396·3); arnica (p. 2447·2); aesculus (p. 2431·2).
Soft-tissue injury; superficial vascular disorders.

Heparin Ointment *Akrikhin, Rus.; Nizpharm, Rus.*
Heparin sodium (p. 1396·3); benzocaine (p. 1980·2); benzyl nicotinate (p. 29·3).
Superficial vascular disorders.

Héparinol *Streuli, Switz.†*
Heparin sodium (p. 1396·3); thymol (p. 1772·2).
Haematomas; thrombophlebitis; varices.

Heparizen *Ziaja, Pol.*
Heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue injury; scars; keloids.

Hepar-Magnesium *Weleda, Ger.*
Hepar bovis (p. 2444·1); magnesium hydroxydatum (p. 1857·2).
Homoeopathic preparation.

Heparoid *Zentiva, Cz.; Zentiva, Rus.; Zentiva, Ukr.†*
A heparinoid (p. 1401·1).
Superficial vascular disorders; soft-tissue injury; phlebitis.

Heparon *Nutricia, Ital.*
Preparation for enteral nutrition.
Liver disorders.

Hepar-Pasc *Pascoe, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Hepar-POS *Croma, Austriat; Ursapharm, Ger.*
Cynara (p. 2490·3).
Dyspepsia; biliary-tract disorders; digestive disorders; lipid metabolism disorders.

Heparsil *Stirol, Ukr.†*
Silymarin (p. 1561·2).
Liver disorders.

Heparsitin *Ifars, Indon.*
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); lecithin (p. 2542·2); javanese turmeric (p. 2636·2).
Dietary supplement.

Heparstad *Stada, Ger.*
Cynara (p. 2490·3).
Biliary-tract disorders.

Hepar-Stannum *Weleda, Ger.†*
Hepar bovis (p. 2444·1); stannum hydroxydatum.
Homoeopathic preparation.

Hepartichaut
Note: this name may be used for preparations of different composition.
Bio-Sante, Canad.
Cynara (p. 2490·3); dehydrocholic acid (p. 2492·1).
Biliary tract disorders.

Bio-Sante, Canad.†
Bile extract (p. 2457·2); cynara (p. 2490·3); dehydrocholic acid (p. 2492·1); magnesium oxide (p. 1857·3).
Biliary tract disorders.

Heparviton *Bode, Indon.; Tempo Scan Pacific, Indon.*
Essential phospholipids (p. 2201·2); curcuminoid (p. 2489·3); silymarin (p. 1561·2).
Liver disorders; gallstones.

Heparviton NF *Tempo Scan Pacific, Indon.*
Essential phospholipids (p. 2201·2); curcuminoid (p. 2489·3); oleum xanthorrhizae (p. 2218·1); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Supplement to maintain healthy liver function.

Hepa-S *Vifor, Switz.*
Cynara (p. 2490·3).
Digestive disorders.

Hepa-Salbe *Winthrop, Ger.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Hepasan *MIP, Austria.*
Ornithine aspartate (p. 2085·2).
Liver disorders; hepatic encephalopathy.

Hepaselamin *Biosel, Turk.†*
Amino acids.
Parenteral nutrition.

Hepashield *Pfizer, India.*
A hepatitis B vaccine (surface antigen) (p. 2389·3).
Active immunisation.

Hepasil
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Silymarin (p. 1561·2); oleum xanthorrhizae (p. 2218·1); turmeric (p. 2218·1); echinacea (p. 2498·1).
Liver disorders.

Lapreven, Venez.
Lecithin (p. 2542·2); inositol (p. 2533·2); choline (p. 2055·2); silymarin (p. 1561·2); vitamin B substances (p. 2102·3); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3).
Liver disorders.

Signova, India.
Silymarin (p. 1561·2).
Liver disorders.

Hepasil DTX *Usana, Singapore.†*
Milk thistle (p. 1561·1); green tea (p. 2648·2); turmeric (p. 2218·1); broccoli; cysteine hydrochloride (p. 2058·3); olive oil (p. 2575·1); soya lecithin (p. 2542·2).
Dietary supplement.

Hepasil-B *Daffohils, India.*
Vitamin B substances (p. 2102·3); silymarin (p. 1561·2).

Hepasol
Note: this name may be used for preparations of different composition.
McGloin, Austral.
Vitamins; minerals; liver extract (p. 2444·1).
Tonic.

Hepasol A *Hemofarm, Rus.; Hemofarm, Ukr.*
Amino acids; sorbitol (p. 2092·1); malic acid (p. 2549·2); electrolytes (p. 1775·1); vitamins.
Parenteral nutrition in liver disorders.

Hépasol *Sandoz, Switz.†*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial thrombosis.

Hepasol Neo *Hemofarm, Ukr.*
Amino acids.
Parenteral nutrition in liver disorders.

Hepasol-Neo *Hemofarm, Rus.*
Amino acids.
Parenteral nutrition in liver disorders.

Hepastar *Invision, India; Invision, India.*
Injection; tablets: Ornithine aspartate (p. 2085·2).

Hepasules *Biological E, India.†*
Ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron. Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Hepasules-F *Biological E, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).

Hepasulfol *Franco-Indian, India.*
Anethole trithione (p. 2443·3).
Liver and biliary disorders.

Hepasulfol-AA *Franco-Indian, India.*
Anethole trithione (p. 2443·3); chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Hepasure *Winsome, India.*
Syrup: Ornithine aspartate (p. 2085·2); nicotinamide (p. 2083·1); riboflavin-5-phosphate.

Winsome, India.
Tablets: ⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Hepatalgina *Nycomed, Arg.*
Oral drops: Cynara (p. 2490·3); boldo (p. 2458·3); wild carrot (p. 2647·2); menthol (p. 2553·2).
Dyspepsia; digestive disorders.

Nycomed, Arg.
Tablets: Cynara (p. 2490·3); boldine (p. 2458·3); wild carrot (p. 2647·2); menthol (p. 2553·2); dehydrocholic acid (p. 2492·1); deoxycholic acid (p. 2457·2).
Dyspepsia; digestive disorders.

HepatAmine *Eczacibasi-Baxter, Turk.*
Amino acids.
Parenteral nutrition.

Hepatamine *Braun, Hong Kong; Nutricia, Ital.; McGaw, USA.*
Amino acids.
Parenteral nutrition in hepatic encephalopathy; nutritional supplement in liver disorders.

Nutricia, Austral.
Nutritional supplement.
Hepatic failure.

Hepatate *Mediam, Neth.*
Technetium-99m colloidal tin (p. 2228·1).
Radionuclide imaging of the liver and spleen.

Hepatect *Biotest, Austria; Biotest, Ger.; IFET (ΙΦΕΤ), Gr.; Biotest, Hung.; Biotest, Irl.; Biotest, Israel; Biotest, Neth.; Biotest, Pol.; Biotest, Port.; Biotest, Spain; Biotest, Switz.; Kansuk, Turk.; Biotest, UK.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepatein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Hepathromb *Riemser, Ger.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Hepathrombin
Note: this name may be used for preparations of different composition.
Hemofarm, Ukr.
Heparin sodium (p. 1396·3); allantoin (p. 1693·1); dexpanthenol (p. 2582·2).
Peripheral and superficial vascular disorders; soft-tissue injury.

Teofarma, Ger.
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Hepathrombin H *Hemofarm, Ukr.*
⊗Heparin sodium (p. 1396·3); prednisolone (p. 1645·2); lauromacrogol 400 (p. 2194·1).
Anorectal disorders.

Hepatic-Aid II *Hormel, Singapore.*
Food for special diets.
Liver disorders.

McGaw, USA.†
Preparation for enteral nutrition.
Liver disease.

Hepatical *Nutricia, Ital.*
Preparation for enteral nutrition.
Nutritional supplement in liver disorders.

Hepaticol *Bio-Dis, Canad.*
⊗Boldo (p. 2458·3); cascara (p. 1826·1); choline bitartrate (p. 2055·2); cynara (p. 2490·3); DL-methionine (p. 1558·2); pancreatin (p. 2579·3).

Hepatil *Pliva Krakow, Pol.†*
Ornithine aspartate (p. 2085·2).
Liver disorders.

Hepatilon
Note: this name may be used for preparations of different composition.
Hertz, Braz.
Boldo (p. 2458·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hepatin *Lapi, Indon.*
Curcuminoid (p. 2489·3); silymarin (p. 1561·2); echinacea (p. 2498·1); choline bitartrate (p. 2055·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Hepatitis B Ig-P *Farma-Tek, Turk.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepativax *Sanofi Pasteur, Arg.*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Active immunisation.

Hépatocynesine *Boiron, Fr.†*
Fel suideae; cinchona (p. 2478·3); ipecacuanha (p. 1667·2); kalium carbonicum (p. 2595·2); magnesia muriatica (p. 1787·1); magnesia sulfurica (p. 1787·3); mercurius dulcis (p. 2555·3); natrum benzoicum (p. 1738·2); natrum sulfuricum (p. 1888·1).
Homoeopathic preparation.

Hepatodirectol *Sanitas, Arg.*
Homatropine methylbromide (p. 2007·3); papaverine hydrochloride (p. 2362·3); boldo (p. 2458·3); carqueja (p. 2471·2); cynara (p. 2490·3); crataegus (p. 2488·1); belladonna (p. 2453·3).
Liver and biliary-tract disorders.

Hepatodoron *Weleda, Austria; Weleda, Ger.; Weleda, S.Afr.†; Weleda, Switz.*
Fragaria vesca; grape (p. 2521·3).
Liver disorders; constipation; eczema.

Hépatodrainol *Boiron, Fr.*
Hydrastis canadensis (p. 2528·1); carduus marianus (p. 1561·1); calculi biliarii (p. 2457·2); juglans regia (p. 2646·1); chelidonium majus (p. 2522·2); leptandra virginica; rana bufo (p. 2444·1); mercurius solubilis (p. 2555·3); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Hepatodrainol *Boiron, Neth.†; Boiron, Port.*
Berberis vulgaris (p. 2502·1); hydrastis canadensis (p. 2528·1); silybum marianum (p. 1561·1); chelidonium majus (p. 2522·2); mercurius solubilis (p. 2555·3); juglans regia (p. 2646·1); leptandra virginica; rana bufo (p. 2444·1).
Homoeopathic preparation.

Hepatofalk *Falk, Hong Kong.†*
Tablets: Choline orotate (p. 2578·1); cysteine hydrochloride (p. 2058·3); vitamin B substances (p. 2102·3); folic acid (p. 2063·1); ox bile (p. 2457·2); greater celandine (p. 2522·2); Javanese turmeric (p. 2636·2); cynara (p. 2490·3); taraxacum (p. 2625·3); frangula (p. 1843·3); rhubarb (p. 1884·2).
Liver disorders.

Hepatofalk Planta *Darya-Varia, Indon.†; Falk, Indon.†*
Silymarin (p. 1561·2); chelidonine; javanese turmeric (p. 2636·2).
Liver disorders; colic; dyspepsia.

Falk, Hong Kong.†
Silymarin (p. 1561·2); turmeric (p. 2636·2); greater celandine (p. 2522·2).
Liver disorders.

Falk, Singapore.†
Milk thistle (p. 1561·1); Javanese turmeric (p. 2636·2); greater celandine (p. 2522·2).
Liver disorders; colic; dyspepsia.

Hépatoflorine *Lehning, Fr.†*
Boldo (p. 2458·3); taraxacum (p. 2625·3); peppermint leaf (p. 1877·1); rosemary (p. 2607·2); fennel (p. 2503·2); cynara (p. 2490·3).
Digestive disorders.

Hepatoglobine *Raptakos, India.*
Oral liquid: Liver extract (proteolysed) (p. 2444·1); peptone (p. 2086·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).
Anaemias.

Raptakos, India.†
Capsules: Vitamin B_{12} (p. 2107·2); peptone (p. 2086·2); ferrous fumarate (p. 2060·3); copper sulfate (p. 2057·2); folic acid (p. 2063·1).
Anaemias.

Raptakos, India.†
Oral drops: Vitamin B_{12} (p. 2107·2); peptone (p. 2086·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).
Anaemias.

Hepatoglobine Mikros *Raptakos, India.*
Folic acid (p. 2063·1); peptonised iron (p. 2073·1); vitamin B_{12} (p. 2107·2).

Hepatol *Nutripur, Canad.*
Boldo (p. 2458·3); cynara (p. 2490·3); taraxacum (p. 2625·3).

Hépatopan *Boiron, Fr.†*
Taraxacum dens leonis (p. 2625·3); podophyllum peltatum (p. 1717·1); chelidonium majus (p. 2522·2); hydrastis canadensis (p. 2528·1); rumex alpinus.
Homoeopathic preparation.

Hepator *Bionet, India.*
⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Hepatorell H Leber-Spezifikum *Sanorell, Ger.*
Taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Hepatos
Note: this name may be used for preparations of different composition.
Hevert, Ger.
Milk thistle (p. 1561·1).
Liver disorders.

Teofarma, Ital.
Cascara (p. 1826·1); boldo (p. 2458·3).
Constipation.

Hepatos B12 *Teofarma, Ital.*
Cascara (p. 1826·1); boldo (p. 2458·3); inositol (p. 2533·2); cyanocobalamin (p. 2107·2).
Constipation.

Hepatosol *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition.
Hepatic insufficiency.

Hépato Solutines *Tisane Provencale, Fr.†*
Sodium citrate (p. 1781·2); rosemary (p. 2607·2); lavender (p. 2541·1); thyme (p. 2630·2).
Digestive disorders.

Hepatoum *Hepatoum, Fr.*
Oral liquid: Pulsatilla (p. 2600·2); turmeric (p. 2218·1); peppermint oil (p. 1877·1); alverine citrate (p. 1819·1).
Digestive disorders.

Hepatoum Brûlures d'Estomac *Hepatoum, Fr.†*
Calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2); sodium bicarbonate (p. 1781·1); light magnesium carbonate (p. 1856·2); magnesium hydroxide (p. 1857·2); titanium dioxide (p. 1725·1).
Gastric hyperacidity.

Hepatox *Cifarma, Braz.*
Adenosine (p. 1291·1); DL-methionine (p. 1558·2); betaine (p. 2456·1); choline citrate (p. 2055·2); pyridoxine hydrochloride (p. 2105·3); sorbitol (p. 2092·1).
Liver disorders.

Hepatriet *Craveri, Arg.*
Heparin sodium (p. 1396·3).
Thrombophlebitis.

Hepatrombin *Hemofarm, Rus.*
Allantoin (p. 1693·1); dexpanthenol (p. 2582·2); heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue injury.

Hepatrombin H *Hemofarm, Rus.*
⊗Heparin sodium (p. 1396·3); prednisolone acetate (p. 1645·2); lauromacrogol 400 (p. 2194·1).
Anorectal disorders.

Hepatron C *Schering-Plough, Mex.†*
Capsules, ribavirin (p. 1010·2); injection, interferon alfa-2b (p. 989·2).
Chronic hepatitis C.

Hepatyrix *GSK, Austria; GSK, Ger.; GSK, Irl.; GSK, Israel; GSK, NZ; GSK, UK.*
A hepatitis A and typhoid vaccine (HM175 and Ty2 strains respectively) (p. 2392·1).
Active immunisation.

Hepavax *Berna, Indon.†*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Hepavax-Gene *Biosano, Chile; Berna, China; Crucell, Hong Kong; Berna, Malaysia; Berna, Philipp.; Berna, Pol.; Berna, Thai.; Kocsel, Turk.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Hepa-Vibolex *Rosen, Ger.*
Ornithine aspartate (p. 2085·2).
Hepatic encephalopathy.

Hepaviral *Kalbe, Indon.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Hepavit
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Austria.
Hydroxocobalamin acetate (p. 2107·3).
Anaemias; neurologic disorders; liver disorders.

General Drugs, Thai.
Liver extract (p. 2444·1).
Anaemias.

Littman, Philipp.
Silymarin (p. 1561·2).
Nutritional supplement for liver function.

Hepavite
Note: this name may be used for preparations of different composition.
YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).
Liver disorders; vitamin B supplement.

Adcock Ingram, S.Afr.†
Choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2); vitamin B substances (p. 2102·3); bioflavonoids (p. 2505·2); magnesium sulfate (p. 1787·3); zinc sulfate (p. 2126·2); potassium chloride (p. 1793·2).
Liver disorders; vitamin deficiency.

Hepavud *Khandelwal, India.*
Lamivudine (p. 1000·2).
HIV infection; chronic hepatitis B.

Hepawin *Waves, India.*
Injection: Ornithine aspartate (p. 2085·2).

Waves, India.
Syrup: Ornithine aspartate (p. 2085·2); nicotinamide (p. 2083·1); riboflavin sodium phosphate (p. 2104·3).

Waves, India.
Tablets: ⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Hepawin Plus *Waves, India.*
Ornithine aspartate (p. 2085·2); silymarin (p. 1561·2); tricholine citrate (p. 2055·2); vitamin B substances (p. 2102·3).

Hepaze *Zee, India.*
Ornithine aspartate (p. 2085·2).

Hepazolon *Alifarm, Rus.*
⊗Heparin sodium (p. 1396·3); prednisolone (p. 1645·2); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

HepBQuin *Sanquin, Neth.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hepdine *Pharmasant, Thai.†*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; allergic rhinitis; urticaria.

Hepedren *Parggon, Mex.*
Magnesium sulfate (p. 1787·3); cynara (p. 2490·3); boldo (p. 2458·3).
Biliary-tract disorders.

Hepeel *Heel, Cz.; Peithner, Hung.; Ebi, Switz.*
Lycopodium clavatum (p. 2547·1); chelidonium majus (p. 2522·2); cinchona pubescens (p. 2478·3); myristica fragrans (p. 2573·1); silybum marianum (p. 1561·1); phosphorus (p. 2589·2); veratrum album (p. 2644·3); citrullus colocynthis (p. 1833·3).
Homoeopathic preparation.

Hepeel H *Heel, Neth.*
Carduus marianus (p. 1561·1); cynara scolymus (p. 2490·3); lycopodium clavatum (p. 2547·1); nux vomica (p. 2573·3); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Hepflush *American Pharmaceutical, USA.*
Heparin sodium (p. 1396·3).
To maintain patency of indwelling intravenous catheters.

Hep-Forte *Marlyn, USA.*
Vitamins; amino acids; minerals.

Hepgel *Gland, India.*
Heparin (p. 1396·3).

Hepil *Mertens, Arg.*
Sildenafil (p. 2364·1).

Hepimun *Landson, Indon.*
Phyllanthus niruri (p. 2590·1); javanese turmeric (p. 2636·2).
Immunostimulant; tonic; liver disorders.

Hepimun Plus *Landson, Indon.*
Oral syrup: Phyllanthus niruri (p. 2590·1); javanese turmeric (p. 2636·2); bovine colostrum (p. 2380·3).
Immunostimulant; tonic; liver disorders.

Hepirax *CCM, Malaysia.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Hepitec *GSK, India.*
Lamivudine (p. 1000·2).
HIV infection; chronic hepatitis B.

Hepizol *Helm, Port.†*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Heplant *Spitzner, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Hepliv *Bharat, Philipp.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Hep-Lock *Elkins-Sinn, USA.*
Heparin sodium (p. 1396·3).
To maintain patency of in-dwelling intravenous lines.

Heplock *Gland, India.*
Heparin (p. 1396·3).

Hepofer *Cipla, India.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Hepoline *Little Greave, India.*
Injection: Ornithine aspartate (p. 2085·2).

Little Greave, India.
Syrup: Sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).

Hepon *Immapharma, Rus.*
Synthetic peptide composed of 14 amino-acid residues.
Immunodeficiency; infections.

Hepp Forte *Lupin, India.*
⊗Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); haemoglobin (p. 1154·3); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Hepp-Tone *Lupin, India.*
Calcium lactate (p. 1784·1); ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Heppylor *Farmak, Ukr.*
Hexetidine (p. 1755·1); choline salicylate (p. 39·2); chlorobutanol (p. 1747·2).
Mouth and throat disorders.

Heprin *Gland, Philipp.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Hepro *Casen Fleet, Spain.*
⊗Allantoin (p. 1693·1); aminoacridine hydrochloride (p. 1732·3); hydrocortisone hydrogen succinate (p. 1640·2); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Heprotec *Getz, Philipp.*
Silymarin (p. 1561·2).
Liver disorders.

Hepsal *IFET (ΙΦΕΤ), Gr.; Technopharm, Irl.†; Wockhardt, UK.†*
Heparin sodium (p. 1396·3).
Thromboembolic disorders; anticoagulant; to maintain patency of in-dwelling intravenous lines.

Hepsandinn *Sresan, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Hepsera *GSK, Arg.; Gilead, Austral.; Gilead, Austria; Gilead, Belg.; GSK, Braz.; Gilead, Canad.; GSK, Chile; GSK, China; Gilead, Cz.; Gilead, Denm.; Gilead, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; GSK, Hong Kong; Gilead, Hung.; GSK, Indon.; Gilead, Irl.; GSK, Israel; Gilead, Ital.; GSK, Malaysia; GSK, Mex.; Gilead, Neth.; Gilead, Norw.; Gilead, NZ; GSK, Philipp.; Gilead, Pol.; Gilead, Port.; GSK, Singapore; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; GSK, Thai.; Er-Kim, Turk.; Gilead, UK; Gilead, USA; GSK, Venez.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Hepta *Roemmers, Chile.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; reduction of allogeneic blood transfusion.

Heptadon *Ebewe, Austria.*
⊗Methadone hydrochloride (p. 88·3).
Pain.

Hept-A-Myl *Sanofi-Aventis, Fr.; Corsa, Indon.; Sanofi Synthelabo, Indon.*
⊗Heptaminol hydrochloride (p. 2525·1).
Fatigue; hypotension; resuscitation in neonates.

Heptar *Euroforma, Braz.*
Heparin sodium (p. 1396·3).

Heptasan *Caprifarmindo, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Rhinitis; urticaria; pruritus.

Hep-Tec *Tecnofarma, Mex.*
Heparin (p. 1396·3).
Thromboembolic disorders.

Heptin *Mustafa, Philipp.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Heptodin *GSK, China.*
Lamivudine (p. 1000·2).
Chronic hepatitis B.

Heptodine *GSK, Arg.*
Lamivudine (p. 1000·2).
Chronic hepatitis B.

Heptor *Veropharm, Rus.*
Ademetionine (p. 2429·3).
Liver disorders.

Heptovir *ViiV, Canad.*
Lamivudine (p. 1000·2).
Hepatitis B.

Heptral *Abbott, Rus.*
Ademetionine butanedisulfonate (p. 2429·3).
Hepatic cholestasis; hepatic encephalopathy; cirrhosis; depression; alcohol withdrawal syndrome.

Abbott, Singapore; Abbott, Ukr.
Ademetionine (p. 2429·3).
Liver disorders; hepatitis; hepatic cholestasis; liver cirrhosis; hepatic encephalopathy; depression; alcohol withdrawal syndrome.

Hepudiod *Bausch & Lomb, China.*
Heparin sodium (p. 1396·3).
Phlebitis; soft-tissue injury; frostbite; eczema.

Hepuman *Faran, Gr.; Yeni, Turk.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hep-Zo *Zodak, India.*
Ornithine aspartate (p. 2085·2).

Her Soy Plus *Taiwan Biotech, Philipp.*
Calcium lactate (p. 1784·1); soya bean (p. 2092·3); colecalciferol (p. 2113·1).
Menopausal symptoms; osteoporosis.

Heracillin *Meda, Denm.*
Flucloxacillin sodium (p. 299·2).
Staphylococcal infections.

Meda, Swed.
Flucloxacillin magnesium (p. 299·2) or flucloxacillin sodium (p. 299·2).
Bacterial infections.

Heraclene *Natrapharm, Philipp.*
Cobamamide (p. 2107·2).
Tonic; appetite stimulant.

Heraeus PMMA Kette G *Heraeus, Ger.*
Gentamicin sulfate (p. 304·2); polymethylmethacrylate (p. 2558·2).
Bone and soft-tissue infection.

Heralink *EuroHealth, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); riboflavin (p. 2104·3); cyanocobalamin (p. 2107·2).
Anaemias.

Herax *Novell, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herb and Honey Cough Elixir *Weleda, UK.*
Honey (p. 2072·1); althaea (p. 2438·3); Iceland moss (p. 2531·2); marrubium (p. 1668·3); aniseed (p. 2444·2); sambucus (p. 2609·3); thyme (p. 2630·2).
Cough.

Herba Tone *Herbes Universelles, Canad.†*
Cascara (p. 1826·1); potassium iodide (p. 2336·3); senna (p. 1885·1).
Laxative.

Herbabiloba *Herbapol Poznan, Pol.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Herbaccion Antioxidante *ISA, Arg.*
Vitamin C (p. 2110·3); bearberry (p. 2453·2); betacarotene (p. 2051·1); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).

Herbaccion Bioenergizante *ISA, Arg.*
Ginseng (p. 2513·3).
Tonic.

Herbaccion Celfin *ISA, Arg.*
Centella (p. 1698·3); bladderwrack (p. 2612·1); ginkgo biloba (p. 2512·3); vitamin B_6 (p. 2105·3); carbohydrate.
Dietary supplement.

Herbaccion Diet *ISA, Arg.*
Chromium (p. 2055·3); carnitine (p. 2053·2); bladderwrack (p. 2612·1); carbohydrates.
Obesity.

Herbaccion Ginseng y Magnesio *ISA, Arg.*
Magnesium (p. 1786·3); ginseng (p. 2513·3); carbohydrates.
Tonic.

Herbaccion Lecitina *ISA, Arg.*
Lecithin (p. 2542·2).
Nutritional supplement.

Herbaccion Memory *ISA, Arg.*
Ginkgo biloba (p. 2512·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); soya lecithin (p. 2542·2).

Herbaccion Venotonico *ISA, Arg.*
Aesculus (p. 2431·2).
Vascular disorders.

Herbadent *Aura, Cz.*
Herbarum extract; salicylic acid (p. 1719·1); boric acid (p. 2459·3); citric acid (p. 2480·3); benzocaine (p. 1980·2); peppermint oil (p. 1877·1); clove oil (p. 2481·3); fennel oil (p. 2503·3); agrimony (p. 2432·3); chamomile (p. 2474·1); sage (p. 2608·3); tormentil (p. 2633·2).
Mouth inflammation; oral lesions.

Herbadict *Garuda, Hung.*
Phyllanthus fraternus; tinospora cordifolia; eclipta alba; punarnava (p. 2601·1); asparagus (p. 2450·2); picrorhiza kurroa (p. 2590·2); asphalthum punjabicanum; embelia ribes (p. 154·2); grewiae tenacis; ashwagandha (p. 2450·2); curcuma longa; plumbago zeylanica; calcium carbonate (p. 1824·3); ferric oxide (p. 2186·1); acacia catechu (p. 2457·3); piper longum; black pepper (p. 2586·1); swertia chirata; arjuna (p. 2447·2); Indian gooseberry (p. 2532·2); chebulic myrobalan (p. 2474·3); ginger (p. 1844·1); silver oxide.
Liver disorders.

Herbal *Rider, Chile.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Herbal Booster *Pharmadass, UK.*
Herbs; vitamins.
Tonic.

Herbal Cough Syrup *Health 4 All, Canad.†*
Inula helenium (p. 1662·3); squill (p. 1677·3); coltsfoot (p. 1659·2); wild cherry (p. 2647·2).
Cough.

Herbal Diretic
Note: this name may be used for preparations of different composition.
Pharmetics, Canad.
Buchu (p. 2461·3); celery (p. 2472·3); parsley (p. 2583·3).

Herbal Diuretic
Note: this name may be used for preparations of different composition.
Purity Life, Canad.
Buchu (p. 2461·3); celery seed (p. 2472·3); parsley (p. 2583·3); bearberry (p. 2453·2); juniper (p. 2537·1).

Vita Health, Canad.†
Batilol; bearberry (p. 2453·2); buchu (p. 2461·3); juniper (p. 2537·1); parsley (p. 2583·3).

Herbal Essences No Flakin Way Antidandruff *Procter & Gamble, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Herbal Indigestion Naturtabs *Cantassium Co., UK.*
⊗Skullcap (p. 2617·1); valerian (p. 2640·2); fennel (p. 2503·2); myrrh (p. 2566·1); papain (p. 2582·3); capsicum oleoresin (p. 2469·3).

Herbal Insomnia
Note: this name may be used for preparations of different composition.
Pharmetics, Canad.†
Chamomile (p. 2474·1); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2); wild lettuce (p. 2647·3).
Insomnia.

Purity Life, Canad.†; Vita Health, Canad.†
Chamomile (p. 2474·1); lupulus (p. 2546·1); mistletoe (p. 2560·2); passion flower (p. 2584·1); valerian (p. 2640·2); wild lettuce (p. 2647·3).
Insomnia.

Herbal Laxative
Note: this name may be used for preparations of different composition.
Blackhawk, Canad.†
Aniseed (p. 2444·2); cascara (p. 1826·1); wild yam (p. 2648·1); fennel (p. 2503·2); gentian (p. 2512·1); jalap (p. 1850·1); lappa (p. 2540·1); liquorice (p. 1853·2); senna (p. 1885·1).

Li Chung Yun, Canad.†
Cascara (p. 1826·1); frangula (p. 1843·3); liquorice (p. 1853·2); rhubarb (p. 1884·2); senna (p. 1885·1).

Nutricorp, Canad.†
Cascara (p. 1826·1); senna (p. 1885·1).

Shaklee, Canad.†
Senna (p. 1885·1).
Constipation.

SwissHerbal, Canad.†
Senna leaves (p. 1885·1); cascara (p. 1826·1); rhubarb root (p. 1884·2); gentian root (p. 2512·1).
Constipation.

Herbal Laxative plus Yogurt *Trophic, Canad.†*
Buchu (p. 2461·3); cascara (p. 1826·1); fennel (p. 2503·2); gentian (p. 2512·1); juniper (p. 2537·1); leptandra virginica; liquorice (p. 1853·2); senna (p. 1885·1); yogurt (p. 2649·3).

Herbal Mood Relief *Herbal Research, UK.*
St John's wort (p. 449·1).
Anxiety; low mood.

Herbal Multi-Tar Plus *Valeant, Canad.*
Coal tar (p. 1723·2); cade oil (p. 1723·2); tar (p. 1723·3); pyrithione zinc (p. 1718·1).

Herbal Nerve
Note: this name may be used for preparations of different composition.
Pharmetics, Canad.†; Purity Life, Canad.†
Lupulus (p. 2546·1); skullcap (p. 2617·1); valerian (p. 2640·2).

Swiss Herbal, Canad.†
Valerian root (p. 2640·2); skullcap (p. 2617·1).

Herbal Pain Relief *Cantassium Co., UK.*
Salix bark (p. 129·2); passion flower (p. 2584·1); valerian (p. 2640·2).
Pain.

Herbal Premens *Swisshealth, UK.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Herbal Rest & Relax *GNLD, Austral.*
Damiana (p. 2491·3); melissa (p. 2552·3); skullcap (p. 2617·1); schisandra (p. 2611·2); St John's wort (p. 449·1); passion flower (p. 2584·1); vervain (p. 2645·1); chamomile (p. 2474·1).
Nervous disorders.

Herbal Serenity *Beauticontrol, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Herbal Shampoo and Scalp Treatment *Kiehls, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Herbal Tabs *Lifeforce, Canad.†*
Cascara (p. 1826·1); senna (p. 1885·1).
Constipation.

Herbal Throat Spray *Mediherb, Austral.*
Althaea (p. 2438·3); sage (p. 2608·3); calendula (p. 2465·2); echinacea (p. 2498·1); myrrh (p. 2566·1); clove oil (p. 2481·3).
Mouth and throat disorders.

Herbalacta *Phyto Kemo, Indon.†*
⊗Vitex trifolia; agnus castus (p. 2432·2).
Aid in lactation.

Herbalakt *Herbaria, Hung.*
Aniseed (p. 2444·2); urtica (p. 2639·3); fennel (p. 2503·2); melissa (p. 2552·3); thyme (p. 2630·2); marjoram (p. 2550·1).
Digestive disorders.

HerBalance *Herbamed, Switz.*
Ambra grisea (p. 2440·3); aurum (p. 2521·1); opium (p. 111·3); strychnos ignatii (p. 2573·3).
Homoeopathic preparation.

Herbalax
Note: this name may be used for preparations of different composition.
Bioextra, Hung.
Sennosides A and B (p. 1885·2).
Constipation.

Herbalifeline *Herbalife, Canad.†*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

HerbAllerg *Herbamed, Switz.*
Apis mellifica (p. 2445·2); galphimia glauca; luffa operculata (p. 2545·3); okoubaka aubrevillei.
Homoeopathic preparation.

Herbanat *Naturatec, Canad.†*
Barberry (p. 2502·1); cascara (p. 1826·1); chamomile (p. 2474·1); sage (p. 2608·3); sarsaparilla (p. 2610·3); taraxacum (p. 2625·3); yellow dock (p. 2649·3).

Herbapect *Aflofarm, Pol.*
Primula root (p. 2596·2); sulfogaiacol (p. 1678·1); thyme (p. 2630·2).
Respiratory-tract disorders.

Herbapini *Herbapol Lublin, Pol.*
Codeine phosphate (p. 40·2); fennel (p. 2503·2); Scots pine (p. 2591·1).
Cough.

Herbaprosta-Caps N *Doetsch, Grether, Switz.†*
Cucurbita (p. 2489·2); cucurbita oil (p. 2489·2); java tea (p. 2536·3); ononis (p. 2575·3).
Benign prostatic hyperplasia.

Herbaraphanus *Herbasante, Canad.†*
Boldo (p. 2458·3); cynara (p. 2490·3); radish.

Herbastress *Grindeks, Ukr.*
Passion flower (p. 2584·1); lupulus (p. 2546·1); avena (p. 2451·1); chamomile (p. 2474·1); Siberian ginseng (p. 2614·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Nervous disorders.

Herbaton *Herbapol Poznan, Pol.†*
Birch leaf (p. 2457·3); crataegus (p. 2488·1); fucus vesiculosus (p. 2612·1); urtica (p. 2639·3); condurango bark (p. 2485·3); bitter orange (p. 2575·3).
Digestive disorders; obesity.

Herba-Vision Augenbad *OmniVision, Ger.*
Euphrasia (p. 2502·1); hypromellose (p. 2189·2); sodium hyaluronate (p. 2526·2).
Formerly contained chamomile and euphrasia.
Tired eyes.

Herba-Vision Augentrost *OmniVision, Ger.*
Euphrasia (p. 2502·1); hypromellose (p. 2189·2); sodium hyaluronate (p. 2526·2).
Formerly contained euphrasia and hypromellose.
Eye irritation.

Herba-Vision Blaubeere *OmniVision, Ger.*
Blueberry; hypromellose (p. 2189·2); sodium hyaluronate (p. 2526·2).
Formerly contained blueberry and hypromellose.
Tired eyes.

Herba-Vision Euphrasia *OmniVision, Switz.*
Euphrasia (p. 2502·1); hypromellose (p. 2189·2).
Dry eyes.

Herba-Vision Kamille *OmniVision, Ger.*
Chamomile (p. 2474·1); hypromellose (p. 2189·2).
Tired eyes.

Herba-Vision Myrtillus *OmniVision, Switz.*
Myrtillus (p. 2566·2); hypromellose (p. 2189·2).
Dry eyes.

HerbaVital *Mediherb, Austral.*
Polygonum cuspidatum; milk thistle (p. 1561·1); ginseng (p. 2513·3); pinus massoniana bark; ginkgo biloba (p. 2512·3).
Tonic.

Herbelix *Lane, UK.*
⊗Lobelia (p. 2323·2); tolu solution; sodium bicarbonate (p. 1781·1).
Nasal congestion.

Herbesan
Note: this name may be used for preparations of different composition.
Nycomed, Belg.; Nycomed, Neth.†
Senna (p. 1885·1); fennel (p. 2503·2); peppermint leaf (p. 1877·1); couch-grass (p. 2487·2).
Constipation.

Super Diet, Fr.
Senna (p. 1885·1); aniseed (p. 2444·2); peppermint leaf (p. 1877·1); couch-grass (p. 2487·2).
Constipation.

Herbesser *Tanabe Seiyaku, China; Tanabe, Hong Kong; Tanabe Seiyaku, India; Tanabe, Indon.; Mitsubishi Tanabe, Jpn; Mitsubishi Tanabe, Malaysia; Delta, Port.; Mitsubishi Tanabe, Singapore; Mitsubishi Tanabe, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias; blood pressure control during surgery.

Herbheal Ointment *Potter's, UK.*
Colophony (p. 2484·2); starch (p. 2095·1); sublimed sulfur (p. 1721·1); zinc oxide (p. 1729·1); althaea root (p. 2438·3); stellaria media.
Skin irritation.

Herbie *TO-Chemicals, Thai.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Herbinol *Zydus, India.*
Indian barberry (p. 2532·1); rubia cordifolia.

Herbion Aesculus *KRKA, Rus.; KRKA, Ukr.*
Aesculus (p. 2431·2); melilot (p. 2552·3).
Chronic venous insufficiency; soft-tissue inflammation; peripheral vascular disorders.

Herbion Allium *KRKA, Ukr.*
Oil-based garlic extract (p. 2510·3).
Atherosclerosis; hyperlipidaemias.

Herbion Cowslip Syrup *KRKA, Rus.*
Primula root (p. 2596·2); thyme (p. 2630·2); levomenthol (p. 2553·2).
Respiratory-tract congestion; cough.

KRKA, Ukr.
Cowslip root (p. 2596·2); thyme (p. 2630·2); menthol (p. 2553·2).
Respiratory-tract congestion; cough.

Herbion Drops for the Gallbladder *KRKA, Rus.†; KRKA, Ukr.*
Peppermint leaf (p. 1877·1); cynara (p. 2490·3); agrimony (p. 2432·3); chamomile (p. 2474·1); caraway (p. 2470·2).
Biliary-tract disorders.

Herbion Drops for the Heart *KRKA, Rus.†*
Crataegus (p. 2488·1); mistletoe (p. 2560·2); valerian (p. 2640·2).

Herbion Drops for Heart *KRKA, Ukr.†*
Crataegus (p. 2488·1); mistletoe (p. 2560·2); valerian (p. 2640·2).
Neurocirculatory dystonia; age-related myocardial dystrophy.

Herbion Drops for the Kidneys and Bladder *KRKA, Ukr.†*
Parsley root (p. 2583·3); equisetum (p. 2500·1); bearberry (p. 2453·2); birch leaf (p. 2457·3); ononis (p. 2575·3).
Nephritis; pyelonephritis; cystitis.

Herbion Drops for the Stomach *KRKA, Rus.†; KRKA, Ukr.†*
Gentian (p. 2512·1); centaury (p. 2473·2); chamomile (p. 2474·1); caraway (p. 2470·2).
Anorexia; dyspepsia; meteorism.

Herbion Hypericum *KRKA, Ukr.*
St John's wort (p. 449·1).
Depression.

Herbion Laksana *KRKA, Rus.*
Senna (p. 1885·1).
Constipation.

Herbion Plantaginis Syrup *KRKA, Ukr.*
Ribwort plantain (p. 2604·2); mallow flower (p. 2549·2); ascorbic acid (p. 2110·3).
Cough.

Herbion Plantain Syrup *KRKA, Rus.*
Ribwort plantain (p. 2604·2); mallow flower (p. 2549·2); ascorbic acid (p. 2110·3).

Herbion Sedative Drops *KRKA, Ukr.†*
Valerian (p. 2640·2); lupulus (p. 2546·1); peppermint leaf (p. 1877·1); melissa (p. 2552·3).
Nervous disorders; insomnia.

Herbion Urological Drops *KRKA, Rus.*
Parsley root (p. 2583·3); equisetum (p. 2500·1); bearberry (p. 2453·2); birch leaf (p. 2457·3); ononis (p. 2575·3).
Pyelonephritis; cystitis.

Herbion Urtica *KRKA, Rus.*
Urtica (p. 2639·3); sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Herbion Zen Sen *KRKA, Rus.*
Ginseng (p. 2513·3).
Tonic.

Herbogastrin *Herbapol Pruszkow, Pol.*
Chamomile (p. 2474·1); liquorice (p. 1853·2); St John's wort (p. 449·1); peppermint leaf (p. 1877·1); sage (p. 2608·3).
Digestive disorders.

Herbogesic *Seroyal, Canad.†*
Magnesium salicylate (p. 85·2).

Herbolax
Note: this name may be used for preparations of different composition.
Himalaya Herbal, India.
Liquorice (p. 1853·2); terminalia chebula (p. 2474·3); zingiber officinale.

Seroyal, Canad.†
Cascara (p. 1826·1); rhubarb (p. 1884·2); senna (p. 1885·1); liquorice (p. 1853·2).

Herbolen *Herbapol Poznan, Pol.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); majoram oil (p. 2576·3); pine oil (p. 2591·1); turpentine oil (p. 2636·3).
Respiratory-tract congestion.

Herbolen D *Herbapol Poznan, Pol.†*
Anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); majoram oil (p. 2576·3); pine oil (p. 2591·1).
Respiratory-tract congestion.

Herbopyrine *Herbes Universelles, Canad.†*
Aspirin (p. 22·2); caffeine citrate (p. 1203·3).

Herbulax *Chefaro, UK.*
Frangula bark (p. 1843·3); taraxacum (p. 2625·3).
Constipation.

Hercap *Ativus, Braz.*
Capsicum oleoresin (p. 2469·3).

Herceptin *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, India; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Genentech, USA; Roche, Venez.*
Trastuzumab (p. 875·3).
Breast cancer; gastric cancer; gastro-oesophageal cancer.

Hercivir *Diba, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herclov *Sanbe, Indon.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Hercum *Pharos, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Heria *Mithra, Belg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Heridine *Farmasur, Spain.†*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Herivyl *Libbs, Braz.*
Phentolamine mesilate (p. 1468·3).
Erectile dysfunction.

Herklin *Armstrong, Mex.*
Lotion: Lindane (p. 2157·1); lidocaine (p. 1988·1).
Pediculosis; scabies.

Armstrong, Mex.
Shampoo: Lindane (p. 2157·1).
Pediculosis; scabies.

Herklin NF *Armstrong, Mex.*
Lotion: Phenothrin (p. 2160·1); lidocaine (p. 1988·1).
Pediculosis.

Armstrong, Mex.
Shampoo: Phenothrin (p. 2160·1).
Pediculosis.

Heřmánkový *Megafyt-R, Cz.*
Chamomile (p. 2474·1).
Gastrointestinal disorders; inflammation of the skin and mucous membranes.

Hermes *Qualiphar, Belg.*
Vitamins; minerals.

Hermes Cevitt *Hermes, Ger.; Hermes, Hung.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Hermesetas *Sifar, Turk.; Polinac, Venez.*
Saccharin sodium (p. 2208·1).
Sugar substitute.

Hermesetas Gold *Polinac, Venez.*
Granules: Aspartame (p. 2169·2); acesulfame potassium (p. 2166·2); maltodextrin (p. 2080·3).
Sugar substitute.

Sifar, Turk.†; Polinac, Venez.
Aspartame (p. 2169·2).
Sugar substitute.

Hermess Cevitt *Genesis, Turk.; Vitamed, Turk.*
Ascorbic acid (p. 2110·3).

Hermin *Alembic, India.*
Amino acids; xylitol (p. 2220·3) or sorbitol (p. 2092·1).
Parenteral nutrition.

Hermix-Sofex *Sofex, Port.*
Aciclovir (p. 964·1).
Herpes simplex *infections.*

Hermolepsin *Orion, Swed.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; alcohol withdrawal syndrome.

Hernidisc *Eagle, Austral.*
⊗Vitamins; minerals; bromelains (p. 2460·3); rutoside (p. 2505·3); equisetum (p. 2500·1); bioflavonoids (p. 2505·2); ruta graveolens (p. 2608·2); arnica montana (p. 2447·2); rhus toxicodendron (p. 2603·3); ferrous phosphate (p. 2077·1); hypericum perforatum (p. 449·1).
Dietary supplement for musculoskeletal health; tonic.

Herniol Injekt *Steierl, Ger.*
Acidum arsenicosum (p. 2448·1); lytta vesicatoria.
Homoeopathic preparation.

Hernovir *Nobel, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Heroanson *Heromycin, Thai.*
Niclosamide (p. 161·2); phenolphthalein (p. 1877·3).
Worm infections.

Hero-Benson *Heromycin, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Herocetine-D *Heromycin, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Herogel *Heromycin, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Heroid *Chew, Thai.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; varicose veins; phlebitis; haemorrhoids.

Herolan Aerosol *Laboratorios Chile, Chile.*
⊗Beclometasone (p. 1621·2); salbutamol (p. 1220·2).
Obstructive airways disease.

Heromycin *Heromycin, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Heropedd *Heromycin, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Herpavir *Dolorgiet, Denm.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpclair *Sinclair, Fr.*
Chondrus crispus (p. 2176·3); xanthan gum (p. 2220·1); melissa (p. 2552·3); glycyrrhizic acid (p. 2520·2); dexpanthenol (p. 2582·2); beta-glucan (p. 2455·2).
Herpes labialis.

Herpecin-L *Chattem, USA.*
Dimeticone (p. 2209·3); meradimate (p. 1711·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Formerly contained allantoin and padimate O.
Chapped lips; sunscreen.

Herpeks *Bio-Sen, Turk.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpenon *Polipharm, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herperax *Micro, India; Micro, Rus.; Chinta, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpes Soothing Cream *Homeocan, Canad.*
Gelsemium sempervirens (p. 2511·2); hypericum perforatum (p. 449·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Herpesan *Rowa, Hong Kong; Rowa, Malaysia; Rowa, Singapore.†*
Carbenoxolone sodium (p. 1825·3).
Orofacial lesions; orofacial herpes lesions; mouth ulcers.

Herpes-Gastreu R68 *Reckeweg, Ger.*
Croton tiglium; mezereum; natrium chloratum (p. 1795·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Herpesil
Note: this name may be used for preparations of different composition.
Hexal, Braz.
Aciclovir (p. 964·1).
Herpesvirus infections.

Naturland, Hung.
Chamomile (p. 2474·1); greater celandine (p. 2522·2); melissa (p. 2552·3); solidago (p. 2620·1); pulmonaria; thyme (p. 2630·2); zinc sulfate (p. 2126·2).
Herpesvirus infection.

Herpesin *Pliva Lachema, Pol.*
Aciclovir sodium (p. 964·1).
Herpesvirus infections.

Teva, Cz.; Teva, Hung.; Pliva, Rus.†
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Herpesine *Nikkho, Braz.*
Idoxuridine (p. 985·1).
Herpes simplex infections of the skin and mucous membranes.

Herpesnil *Sofar, Ital.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Herpetad *TAD, Irl.†; Boehringer Ingelheim, UK.*
Aciclovir (p. 964·1).
Herpes labialis.

Herpetrol *Alva, USA.*
Vitamins; zinc (p. 2126·1); lysine (p. 2079·3).

Herpevex *Avex, Malaysia.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpevir *Omega, Fr.; Bryntsalov, Rus.†; Arterium, Ukr.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections; herpes labialis.

Herpex
Note: this name may be used for preparations of different composition.
Torrent, India; InterMed, Philipp.; Hexal, Pol.
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes; herpesvirus infections.

Uniao Quimica, Braz.
Tromantadine hydrochloride (p. 1021·1).
Viral skin infections.

Herpferon *Firn M, Rus.; Zdravo, Ukr.†*
Aciclovir (p. 964·1); interferon alfa (p. 989·2); lidocaine (p. 1988·1).
Herpesvirus infections of the skin and mucous membranes.

Herphonal *Temmler, Ger.*
Trimipramine maleate (p. 453·1) or trimipramine mesilate (p. 453·1).
Depression; pain.

Herpial *Uriach, Spain.*
Aciclovir (p. 964·1).
Herpes labialis.

Herpiclof *Nufarindo, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpid *Astellas, UK.†*
Idoxuridine (p. 985·1) in dimethyl sulfoxide.
Herpesvirus skin infections.

Herpil *Psychotropics, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpilem *Teva, Mex.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpin *Cafar, Venez.*
Aciclovir (p. 964·1).

Herpirax *Pond's, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herpizyg *Zyg, Thai.*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Herplex *Allergan, Canad.†*
Idoxuridine (p. 985·1).
Herpes simplex infections.

Herpolips *Stada, Fin.; Stada, Neth.*
Aciclovir (p. 964·1).
Herpes labialis.

Herpomed *S Med, Austria.*
Aciclovir (p. 964·1).
Herpes labialis.

Herponil *Help, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Herposicc *Pharmaselect, Austria.*
Benzocaine (p. 1980·2); sulfur (p. 1721·1); zinc oxide (p. 1729·1); talc (p. 1722·2); phenol (p. 1763·3).
Herpes labialis.

Herpovax *St Petersburg Institute of Vaccines & Sera, Rus.*
A herpes simplex virus vaccine (p. 2392·2).
Active immunisation.

Herr *RND, India.*
Aloe vera (p. 1693·2); areca (p. 2446·3); asparagus racemosus (p. 2614·2); curcuma longa; ashwagandha (p. 2450·2); zingiber officinale.

Herron Baby Teething Gel *Aspen, Austral.*
Choline salicylate (p. 39·2).
Sore gums; teething pain.

Herronduo *Farma, Venez.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency; iron-deficiency anaemia.

Herrongyn *Farma, Venez.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Herstat *Green Medicine, Swed.†*
Propolis (p. 2597·3).
Mouth ulcers.

Herten *Vir, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Herten Plus *Vir, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hervirax *Pharlab, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herviros *Hermal, Austria.*
Tetracaine hydrochloride (p. 1996·3); aminoquinuride hydrochloride (p. 1736·2).
Infected mouth disorders.

Herz ASS *GL Pharma, Austria.*
Aspirin (p. 22·2).
Ischaemic heart disease; myocardial infarction; thromboembolism prophylaxis.

HerzASS *Ratiopharm, Ger.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Herzkur *Chrispa (Χρισπα), Gr.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Herzovir *Chandra Bhagat, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Herzschutz ASS *Ratiopharm, Austria.*
Aspirin (p. 22·2).
Myocardial infarction; thrombosis prophylaxis; migraine.

Hes Grifols *Grifols, Spain.†*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion.

Hesmin *Interbat, Indon.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Hespan *IFET (ΙΦΕΤ), Gr.; Braun, USA.*
⊗Hetastarch (p. 1146·1) in sodium chloride.
Plasma volume expansion.

Hespander *Fresenius Kabi, Jpn.*
⊗Hetastarch (p. 1146·1).
Plasma volume expansion; haemodilution.

Hespercorbin *Rottapharm, Spain.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Hesra *Baxter, Denm.; Baxter, Fin.; Baxter, Hung.; Baxter, Norw.; Baxter, Swed.*
⊗An etherified starch (p. 1146·1) in electrolytes.
Hypovolaemia; shock; plasma volume expansion.

Hessico *Rivero, Arg.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion.

Hestar *Claris, India; Pisa, Mex.; Claris, Thai.†*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; shock; haemodilution; extracorporeal circulation.

Hestin-B *Psyco Remedies, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Hetaclox *Faran, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Hetacloxacin *Faran, Gr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Hetailin *Livzon, China.*
Aprotinin (p. 1133·2).
Reduction of blood loss in cardiac bypass surgery; haemorrhage; postoperative adhesions.

Hetasorb *Hemofarm, Ukr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; haemodilution.

Heteroid *Chew, Thai.*
Diosmin (p. 2505·2).
Venous insufficiency; varicose veins; phlebitis; haemorrhoids.

Hetrazan *Wyeth, India.*
Diethylcarbamazine citrate (p. 153·1).
Filariasis; eosinophilia.

Heumann Beruhigungstee Tenerval *Winthrop, Ger.*
Valerian root (p. 2640·2); melissa (p. 2552·3); valerian oil (p. 2640·2).
Nervous disorders.

Heumann Blasen- und Nierentee Solubitrat uro *Winthrop, Ger.*
Birch leaf (p. 2457·3); solidaga virgaurea (p. 2620·1).
Urinary-tract disorders.

Heumann Bronchialtee Solubifix T *Winthrop, Ger.*
Althaea (p. 2438·3); liquorice (p. 1853·2); primula root (p. 2596·2); anise oil (p. 2444·3); thyme oil (p. 2630·3).
Respiratory-tract disorders.

Heumann Magentee Solu-Vetan *Winthrop, Ger.*
Liquorice root (p. 1853·2); peppermint leaf (p. 1877·1); peppermint oil (p. 1877·1).
Gastrointestinal disorders.

Heumann Verdauungstee Solu-Lipar *Winthrop, Ger.*
Boldo (p. 2458·3); milk thistle (p. 1561·1); peppermint oil (p. 1877·1).
Digestive disorders.

Heumann's Blasen- und Nierentee *Sanova, Austria.*
Birch leaf (p. 2457·3); solidago (p. 2620·1).
Bladder and urinary-tract disorders.

Heumann's Bronchialtee *Sanova, Austria.*
Althaea (p. 2438·3); liquorice (p. 1853·2); cowslip root (p. 2596·2); anise oil (p. 2444·3); thyme oil (p. 2630·3).
Catarrh; bronchitis; cough.

Heuschnupfenmittel
Note: this name may be used for preparations of different composition.
DHU, Ger.
Luffa operculata (p. 2545·3); galphimia glauca; cardiospermum.
Homoeopathic preparation.

Dreluso, Ger.
Luffa operculata (p. 2545·3).
Homoeopathic preparation.

Heuschnupfenmittel DHU *DHU, Austria.†*
Luffa operculata (p. 2545·3); galphimia glauca; cardiospermum.
Homoeopathic preparation.

Hevaz *Bliss, S.Afr.*
Efavirenz (p. 975·1).

Hevert Stoffwechsel-Tee N *Hevert, Ger.†*
Javanese turmeric (p. 2636·2); taraxacum (p. 2625·3); peppermint leaf (p. 1877·1); achillea (p. 2427·3).
Gallbladder disorders.

Hevert-Activon Kreislauftropen *Hevert, Ger.†*
Camphora (p. 2466·2); cola (p. 2648·2); crataegus (p. 2488·1); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Hevert-Blasen-Nieren-Tee N *Hevert, Ger.†*
Java tea (p. 2536·3); birch leaf (p. 2457·3); equisetum (p. 2500·1); ononis (p. 2575·3); couch-grass (p. 2487·2); gartebohnenhulsen.
Urinary-tract disorders.

Hevert-Dorm *Hevert, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Hevertnier Complex N *Hevert, Ger.†*
Acid benz. (p. 1738·2); berberis (p. 2502·1); lycopodium (p. 2546·3); solidago virg. (p. 2620·1).
Homoeopathic preparation.

Hevertotox *Hevert, Ger.*
Oral drops: Baptisia (p. 2647·2); bryonia (p. 2461·3); kalium chlorat. (p. 1793·2); echinacea (p. 2498·1); lachesis (p. 2538·3); silicea (p. 2208·3); thuja (p. 2629·3).
Homoeopathic preparation.

Hevert, Ger.
Tablets: Apis (p. 2445·2); atropinum sulf. (p. 1310·2); cinnabaris (p. 2555·3); echinacea (p. 2498·1); hepar. sulf. (p. 1721·3); kalium bichrom. (p. 2476·3); kalium chloratum (p. 1793·2); lachesis (p. 2538·3); silicea (p. 2208·3); spongia.
Homoeopathic preparation.

Heviran *Polpharma, Pol.; Polpharma, Ukr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Hevit *Sanjivani, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Hevizos *Teva, Hung.*
Epervudine.
Herpesvirus infections.

Hevox *Kleva, Gr.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Hevronaz *Rafarm, Gr.*
Mupirocin (p. 327·2).
Skin infections.

Hevtin *Pharos, Indon.†; Scherer, Indon.†*
Ornithine aspartate (p. 2085·2).
Liver disorders; dietary supplement.

Hewallergia Complex *Hevert, Ger.*
Apis (p. 2445·2); galphimia glauca; kalium bichromicum (p. 2476·3); marum verum; verbascum (p. 2645·1).
Homoeopathic preparation.

Heweberberol *Hevert, Ger.*
Berberis spag. (p. 2502·1); carduus benedictus (p. 2482·2); ceanothus; equisetum (p. 2500·1); fumaria (p. 2508·2); ononis (p. 2575·3); solidago (p. 2620·1).
Homoeopathic preparation.

Hewechol Artischockendragees *Hevert, Ger.†*
Cynara (p. 2490·3).
Dyspepsia.

Hewecyst Blasen-Nieren *Hevert, Ger.†*
Cantharis (p. 2469·2); causticum (p. 2595·3); dulcamara (p. 2497·3); petroselinum (p. 2583·3); populus tremuloides (p. 2450·3); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Hewedolor neuro *Hevert, Ger.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nerve pain.

Hewedolor plus Coffein *Hevert, Ger.†*
Procaine hydrochloride (p. 1994·3); caffeine (p. 1203·3).
Nerve pain.

Hewedolor Procain *Hevert, Ger.*
Procaine hydrochloride (p. 1994·3).
Pain.

Heweformica *Hevert, Ger.*
Acidum formicicum (p. 2507·1).
Homoeopathic preparation.

Hewekzem novo N *Hevert, Ger.*
Chamomile oil (p. 2474·1); dexpanthenol (p. 2582·2); vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Skin disorders.

Hewelymphon N *Hevert, Ger.†*
Ammonium bituminosulfonicum (p. 1705·3); berberis aquifolium (p. 2577·1); bufo (p. 2444·1); calcium carbonicum (p. 1824·3); kreosotum (p. 1659·3); natrium chloratum (p. 1795·1); pulsatilla (p. 2600·2); silicea (p. 2208·3); thuja (p. 2629·3).
Homoeopathic preparation.

Heweneural *Hevert, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Neuromuscular disorders.

Hewepsychon Mono *Hevert, Ger.†*
Hypericum (p. 449·1).
Homoeopathic preparation.

Hewepsychon uno *Hevert, Ger.†*
St John's wort (p. 449·1).
Depression.

Hewerheum N *Hevert, Ger.†*
Acidum benzoicum (p. 1738·2); bryonia (p. 2461·3); colchicum (p. 607·1); kalmia (p. 2537·2); ledum (p. 2550·1); rhus toxicodendron (p. 2603·3); spiraea ulmaria (p. 2550·2); sulfur (p. 1721·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Hewesabal mono *Hevert, Ger.†*
Sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Heweselen *Hevert, Ger.†*
Selenium (p. 2086·3).
Homoeopathic preparation.

Hewesoor N *Hevert, Ger.†*
Arsenicum album (p. 2448·1); borax (p. 2459·2); condurango (p. 2485·3); mercurius subl. corrosivus (p. 2555·2); thuja (p. 2629·3).
Homoeopathic preparation.

Hewethyreon N *Hevert, Ger.*
Lycopus virg. (p. 2462·2); hederea hel. (p. 2536·2); jodum (p. 2336·3); leonurus card (p. 2564·2); spongia; thyreoidinum suis (p. 2345·3).
Homoeopathic preparation.

Heweurat N *Hevert, Ger.*
Belladonna (p. 2453·3); berberis (p. 2502·1); lithium carbonicum (p. 427·3); urtica (p. 2639·3).
Homoeopathic preparation.

Heweven Complex *Hevert, Ger.*
Aesculus hippocast. (p. 2431·2); hamamelis (p. 2523·3); millefolium (p. 2427·3).
Homoeopathic preparation.

Heweven Phyto *Hevert, Ger.†*
Aesculus (p. 2431·2).
Haemorrhoids; venous insufficiency.

Hewletts *Kestrel, UK.†*
Zinc oxide (p. 1729·1); hydrous wool fat (p. 2219·3); arachis oil (p. 2446·1); white soft paraffin (p. 2211·3).
Dry skin; nappy rash.

Hewon *Sidhbali, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Hexa Clean *Suphong, Thai.*
Hexachlorophene (p. 1754·1).
Skin disinfection.

Hexabencil *Sandoz, Arg.*
Permethrin (p. 2159·3); benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Hexabir *Birz, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Hexa-Blok *Hexal, S.Afr.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Hexabotin *Sandoz, Denm.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Hexabrix *Temis, Arg.; Aspen, Austral.; Guerbet, Austria; Codali, Belg.; Tyco, Canad.; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.†; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; R+N, Gr.; Guerbet, Hung.; Guerbet, Irl.; Guerbet, Israel; Guerbet, Ital.; Guerbet, Neth.; Guerbet, Norw.; Obex, NZ; Martins & Fernandes, Port.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.; Guerbet, Thai.; Guerbet, Turk.; May & Baker, UK; Guerbet, USA; Quifoven, Venez.*
Meglumine ioxaglate (p. 1593·2); sodium ioxaglate (p. 1593·2).
Radiographic contrast medium.

Hexacorton *Orva, Turk.*
⊗Prednisolone acetate (p. 1645·2).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hexacortone *Spirig, Switz.*
⊗Prednisolone acetate (p. 1645·2).
Skin disorders.

Hexacyl *Sanum-Kehlbeck, Ger.*
Sulfur (p. 1721·1); lycopodium (p. 2546·3); berberis (p. 2502·1).
Homoeopathic preparation.

Hexa-Defital *Sandoz, Arg.†*
Lotion: Lindane (p. 2157·1); benzocaine (p. 1980·2).
Pediculosis; scabies.

Sandoz, Arg.†
Shampoo: Lindane (p. 2157·1).
Pediculosis.

Hexa-Defital Crema Enjuague *Sandoz, Arg.*
Acetic acid (p. 2426·3).
Pediculosis.

Hexa-Defital NF *Investi, Arg.*
Deltamethrin (p. 2152·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Hexa-Defital Plus *Investi, Arg.*
Acetic acid (p. 2426·3); permethrin (p. 2159·3).
Pediculosis.

Hexadilat *Sandoz, Denm.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Hexadol *Otto, Indon.; Otto, Malaysia.*
Hexetidine (p. 1755·1).
Mouth and throat disorders; oral hygiene.

Hexadrol *Organon, USA.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Hexaglucon *Sandoz, Denm.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Hexagon *Omega, Irl.†*
Test for detection of antibodies to *Helicobacter pylori* in blood, serum, or plasma.

Hexakapron *Teva, Israel.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema; fibrinolysis.

Hexal Konazol Shampoo *Hexal, Austral.†*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; dandruff.

Hexalacton *Sandoz, Denm.*
⊗Spironolactone (p. 1499·3).
Ascites; hyperaldosteronism; oedema; heart failure.

Hexalectol *Rider, Chile.*
Glutamic acid (p. 2070·2); pyridoxine (p. 2105·3).
Mental function impairment.

Hexalen
Note: this name may be used for preparations of different composition.
Mayne, Austral.†; Eisai, Canad.; IDIS, Neth.†; Teva, Rus.; American Taiwan, Thai.†; Eisai, USA.
Altretamine (p. 738·3).
Ovarian cancer.

Johnson & Johnson, Gr.
Hexetidine (p. 1755·1).
Mouth infections.

Hexalense *Zeiss Meditec, Fr.†*
Aminocaproic acid (p. 1131·3).
Eye irritation.

Hexaler *Investi, Arg.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Hexaler Bronquial *Investi, Arg.*
⊗Mometasone (p. 1644·1).
Asthma.

Hexaler Cort *Investi, Arg.*
⊗Desloratadine (p. 625·1); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Hexaler Nasal *Investi, Arg.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis.

Hexaler Plus *Investi, Arg.*
⊗Desloratadine (p. 625·1); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Hexalgin *Hexpharm, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuralgia; neuritis.

Hexalid *Sandoz, Denm.*
Diazepam (p. 1063·2).
Anxiety; spasticity; alcohol withdrawal syndrome.

Hexal-Lisinopril Co *Hexal, S.Afr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hexal-MPA *Hexal, S.Afr.*
Medroxyprogesterone acetate (p. 2288·1).
Dysfunctional uterine bleeding; endometriosis; menopausal disorders; amenorrhoea.

Hexalyse
Note: this name may be used for preparations of different composition.
Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Bouchara, Rus.
Biclotymol (p. 1740·1); muramidase hydrochloride (p. 2565·1); enoxolone (p. 54·2).
Mouth and throat disorders.

Bouchara-Recordati, Ukr.
Biclotymol (p. 1740·1); muramidase (p. 2565·1); enoxolone (p. 54·2).
Mouth and throat disorders.

Gerolymatos, Gr.
Hexetidine (p. 1755·1).
Mouth infections; oral hygiene.

Hexamedal *Welti, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders; oral hygiene.

Hexamet *Hexal, S.Afr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Hexamidin *Akrikhin, Rus.*
Primidone (p. 547·1).
Epilepsy.

Hexamon Bufexamac *Schoning-Berlin, Ger.†*
Bufexamac (p. 30·2); lidocaine hydrochloride (p. 1988·2); bismuth subgallate (p. 1822·1).
Haemorrhoids.

Hexamycin *Sandoz, Denm.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Hexanios G+R *Anios, Fr.†*
Polihexanide (p. 1766·1); didecyldimethylammonium chloride (p. 1750·3).
Instrument disinfection.

Hexaniton *Ni-The, Gr.*
Inositol nicotinate (p. 1410·3).

Hexanurat *Sandoz, Denm.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Hexapindol *Sandoz, Denm.*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Hexapneumine *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong.*
Adult syrup; paediatric syrup: Biclotymol (p. 1740·1); chlorphenamine maleate (p. 620·3); pholcodine (p. 1675·1).
Cough.

Bouchara-Recordati, Fr.†
Adult suppositories: Biclotymol (p. 1740·1); cineole (p. 2479·1); pholcodine (p. 1675·1).
Cough.

Bouchara-Recordati, Fr.†
Infant syrup: Biclotymol (p. 1740·1); chlorphenamine maleate (p. 620·3); tolu balsam (p. 1679·2).
Cough.

Bouchara-Recordati, Hong Kong.†
Infant syrup: Biclotymol (p. 1740·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); tolu balsam (p. 1679·2).
Cough; fever.

Bouchara-Recordati, Hong Kong.†
Tablets: Biclotymol (p. 1740·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Hexapneumine for Children *Bouchara-Recordati, Ukr.†*
Pholcodine (p. 1675·1); chlorphenamine maleate (p. 620·3); biclotymol (p. 1740·1).
Cough.

Hexaporine *Texinfine, Fr.*
Pomegranate (p. 164·1).
Fluid and electrolyte imbalance.

Hexaquart plus *Braun, Ger.*
Didecyldimethylammonium chloride (p. 1750·3); laurylamine dipropylenediamine (p. 1759·2); cocospropylendiamin-1,5-bisguanidinium acetate.
Surface and instrument disinfection.

Hexaquart S *Braun, Ger.*
Didecyldimethylammonium chloride (p. 1750·3); benzalkonium chloride (p. 1737·1).
Fungal skin infection prophylaxis; surface disinfection.

Hexaquine *Gomenol, Fr.*
Quinine benzoate (p. 665·1); thiamine hydrochloride (p. 2103·1); niaouli oil (p. 2569·1).
Nocturnal muscle cramps.

Hexaretic *Hexal, S.Afr.†*
⊗Amiloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Hexarhume *Bouchara-Recordati, Fr.*
Biclotymol (p. 1740·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Hexarone *Hexal, S.Afr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Hexaseptine *Gifrer Barbezat, Fr.*
Hexamidine isetionate (p. 1754·3).
Bacterial skin infections; skin and mucous membrane disinfection.

Hexasoptin *Sandoz, Denm.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Hexaspray *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Decaforma, Port.; Bouchara, Rus.; Bouchara-Recordati, Ukr.*
Biclotymol (p. 1740·1).
Mouth and throat disorders.

Hexastat *ProStrakan, Fr.*
Altretamine (p. 738·3).
Malignant neoplasms.

Hexatate *Concept, Israel.†*
Chlorhexidine acetate (p. 1743·2).
Disinfection of catheters and medical devices.

Hexatrin *Servocare, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Hexatrione *Dexo, Fr.*
⊗Triamcinolone hexacetonide (p. 1649·2).
Musculoskeletal and joint disorders.

Hexavac *Sanofi Pasteur, Chile†; Sanofi Pasteur, Gr.; Sanofi Pasteur, Hung.†*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p. 2385·1).
Active immunisation.

Hexavit *Indian Drugs, India; Altayvitamin, Rus.; Dalkhimfarm, Rus.; Farmstandart, Rus.; Marbiopharm, Rus.; Uralbiopharm, Rus.; Valenta, Rus.; Veropharm, Rus.; KVZ, Ukr.*
Vitamins.

Hexavitamin *Utopian, Thai.; Upsher-Smith, USA.*
Vitamins.

Hexavitamins *Novopharm, Canad.†*
Vitamins.

Hexazide *Hexal, S.Afr.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Hexbio *YSP, Malaysia; Yung Shin, Singapore.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus lactis* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3).
Dietary supplement.

Hexene
Note: this name may be used for preparations of different composition.
Osoth, Thai.
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Sunward, Singapore.
Griseofulvin (p. 582·2).
Fungal hair, nail, and skin infections.

Hexer *Hexpharm, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; duodenal ulcer.

Hexiben *Sidus, Arg.*
Calcium peroxide (p. 1741·3); sodium monofluorophosphate (p. 2091·3).
Dental whitener.

Hexicon *Nizpharm, Rus.; Nizhfarm, Ukr.*
Chlorhexidine gluconate (p. 1743·3).
Vaginal infections; skin and mucous membrane infections.

Hexide *Dey's, India.*
Chlorhexidine (p. 1743·2).
Oral hygiene; gingivitis.

Milano, Thai.
Chlorhexidine gluconate (p. 1743·3).
Antiseptic lubricant for vaginal examination.

Hexident *Meda, Swed.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disinfection; oral hygiene.

Hexidin
Note: this name may be used for preparations of different composition.
Barnes Hind, Arg.†; Zedchem, S.Afr.†
Chlorhexidine gluconate (p. 1743·3).
Disinfecting solution for soft contact lenses; lubricant for gynaecological examinations.

Hexidine *ICPA, India; BJ Benjaosoth, Thai.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection; oral hygiene; gingivitis.

Christo, Hong Kong.†
Chlorhexidine (p. 1743·2).

Hexidol *Torrent, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Hexidol Forte *Torrent, India.*
Trihexyphenidyl (p. 917·3); haloperidol (p. 1077·1).

Hexidol Kit *Torrent, India.*
6 Tablets, haloperidol (p. 1077·1); 6 tablets, trihexyphenidyl hydrochloride (p. 917·3).

Hexidol Plus *Torrent, India.*
Trihexyphenidyl (p. 917·3); haloperidol (p. 1077·1).

Hexigel
Note: this name may be used for preparations of different composition.
ICPA, India.
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Hexil *Inmunolab, Arg.†*
Chlorhexidine gluconate (p. 1743·3).
Disinfection.

Hexil Antiseptico *Inmunolab, Arg.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Skin disinfection.

Hexilak *Shalaks, India.*
Allantoin (p. 1693·1); onion (p. 2575·2); heparin sodium (p. 1396·3).

Hexilium *Pharmasant, Thai.*
Flunarizine (p. 629·3).
Vestibular disorders; cerebral and peripheral vascular disorders.

Hexilon *Kalbe, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Hexil-P *Inmunolab, Arg.*
Chlorhexidine (p. 1743·2).
Skin disinfection.

Heximar *Shalaks, India.*
Calcipotriol (p. 1697·2).

Heximar-B *Shalaks, India.*
⊗Betamethasone (p. 1623·2); calcipotriol (p. 1697·2).

Heximet *Svizera, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole benzoate (p. 936·1).

Heximox *Bombay Tablet, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

HeXin *Zhonghe, China.*
Thymopentin (p. 2631·1).

Hexiprep *ICPA, India.*
Chlorhexidine (p. 1743·2).

Hexiprep-T *ICPA, India.*
⊗Chlorhexidine (p. 1743·2); alcohol (p. 1733·1).

Hexisol *Christo, Hong Kong.†*
Chlorhexidine (p. 1743·2).

Hexit *Odan, Canad.*
Lindane (p. 2157·1).
Scabies; pediculosis.

Hexodane Handrub *ICM, Singapore.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Hand and skin disinfection.

Hexokain *Nycomed, Denm.*
Benzocaine (p. 1980·2); chlorhexidine hydrochloride (p. 1743·3).
Mouth disorders; oral hygiene.

Hexomedine
Note: this name may be used for preparations of different composition.
Melisana, Belg.; Sanofi-Aventis, Venez.
Hexamidine isetionate (p. 1754·3).
Skin infections; mouth and throat disorders.
Melisana, Belg.†; Sanofi-Aventis, Braz.
Throat spray: Hexamidine isetionate (p. 1754·3); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Hexomédine *Sanofi-Aventis, Fr.*
Topical gel; topical solution: Hexamidine isetionate (p. 1754·3).
Bacterial skin infections.

Hexon *GMP, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with viscous mucus.

Hexopal *Clonmel, Irl.; Genus, UK.*
Inositol nicotinate (p. 1410·3).
Peripheral vascular disorders; intermittent claudication; Raynaud's syndrome.

Hexoral
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Austria; McNeil, Ger.; Johnson & Johnson, Rus.; McNeil, Ukr.
Hexetidine (p. 1755·1).
Mouth and throat disorders.
McNeil, Cz.; Johnson & Johnson, Rus.
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Hexoraletten N *McNeil, Cz.†; McNeil, Ger.†*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Hexos *Abdi, Turk.*
Olopatadine hydrochloride (p. 636·2).

Hexoscrub *ICM, Singapore.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Hextan *Pasteur, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Hextend *Biotime, Canad.*
⊗Hetastarch (p. 1146·1).
Plasma volume expansion.

Hextrate *Hexal, Philipp.†; Salutas, Philipp.†*
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis.

Hextril *McNeil, Belg.; Johnson & Johnson, Fr.; Johnson & Johnson, Neth.; Johnson & Johnson, Port.; Janssen-Cilag, Switz.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Hextriletten *Janssen-Cilag, Switz.†*
Cetylpyridinium chloride (p. 1743·1); dichlorobenzyl alcohol (p. 1750·2); lidocaine hydrochloride (p. 1988·2).
Sore throat; mouth inflammation.

Hextrimint *Janssen-Cilag, Switz.†*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2).
Mouth and throat disorders.

Hexvix *GE Healthcare, Austria; Ipsen, Belg.; GE Healthcare, Cz.; Photocure, Denm.; Photocure, Fin.; Ipsen, Fr.; Ipsen, Ger.; Ipsen, Gr.; Ipsen, Irl.; GE Healthcare, Ital.; Ipsen, Neth.; Photocure, Norw.; Satis, Port.; Ipsen, Spain; Photocure, Swed.; Future Health, Switz.; Ipsen, UK.*
Hexaminolevulinate hydrochloride (p. 740·1).
Detection of bladder cancer.

Hexymer *Mersifarma, Indon.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

HF *Fresenius Medical, Hung.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); potasssium chloride; calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1).
Haemofiltration solution.
Fresenius Medical, Switz.†
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Haemofiltration.

HFS *Gojo, Canad.*
Triclosan (p. 1773·2).

HG Cal *Health Guard, India.*
Calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

HG Zyme *Health Guard, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

HHSone *H & H, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

HHT *Sidus, Arg.; Pentafarma, Chile; Landsteiner, Mex.†*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner's syndrome; growth disorders in renal failure; AIDS-related cachexia.

Hi Potency B Compound *Swiss Herbal, Canad.†*
Vitamin B substances (p. 2102·3).

Hi Potency Cal *Swiss Herbal, Canad.†*
Calcium carbonate (p. 1824·3).

Hi Potency Multi *Natural Factors, Canad.†*
Vitamins; minerals.

Hi Potency Stress B with C *Lee-Adams, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Hiact-P *Dyota, India.*
⊗Dimeticone (p. 1886·2); fructo-oligosaccharides (p. 2508·1); pancreatin (p. 2579·3).

Hialid *Santen, China; Santen, Hong Kong; Ferron, Indon.; Santen, Indon.; Santen, Philipp.; Santen, Singapore; Santen, Thai.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; keratoconjunctival injury.

Hialudorf *Pharmadorf, Arg.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hibadren *Stada, Austria.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Hiberix *GSK, Austral.; GSK, China; GSK, Cz.; GSK, Fin.; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.†; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; Litha, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK†; GSK, USA; GSK, Venez.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (p. 2387·2).
Active immunisation.

Hibernal *Egis, Hung.*
Chlorpromazine hydrochloride (p. 1045·2).
Schizophrenia; nausea and vomiting; hiccups.

Hibesor *Blue Cross, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

HIBest *Aventis Pasteur, India.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (p. 2387·2).
Active immunisation.

Hi-Beston *Tanabe, Indon.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Hibi *Molnlycke, UK.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Hand and skin disinfection.

Hibicet *Cana, Gr.; Regent Medical, Irl.; Molnlycke, Thai.†*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Antiseptic; disinfection.

Hibicet concentraat *Regent Medical, Neth.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection.

Hibicet verdunning *Regent Medical, Neth.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Disinfection.

Hibiclens *Regent, USA.†*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Hibida *Rez, Cz.*
Technetium-99m (p. 2228·1) mebrofenin.
Radionuclide imaging of the liver and biliary tract.

Hibidil *Molnlycke, Belg.; Regent, Canad.†; Molnlycke, Fr.; CPS Cito, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Skin, mucous membrane, wound, and instrument disinfection; skin infections.

Hibiguard *Molnlycke, Belg.†*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of hands and skin.

Hibimax *Molnlycke, Spain.†*
Chlorhexidine gluconate (p. 1743·3).
Burns; instrument disinfection; skin disinfection; skin disorders; wounds.

Hibiron *Otto, Indon.†*
Iron dextran (p. 2075·3).
Iron deficiency.

Hibiscott *Scott-Cassara, Arg.*
Chlorhexidine (p. 1743·2).
Skin disinfection.

Hibiscrub *Scott-Cassara, Arg.; Molnlycke, Belg.; Molnlycke, Fr.; Regent Medical, Irl.; Regent Medical, Neth.; Regent Medical, Norw.; AstraZeneca, S.Afr.†; Molnlycke, Spain; Regent Medical, Swed.; CPS Cito, Switz.; Molnlycke, Thai.†; Regent Medical, UK.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Hibisol *Regent Medical, Irl.†; Regent Medical, Neth.; SSL, Singapore; Regent Medical, UK.†*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Hibisprint *CSP, Fr.†*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Hibistat
Note: this name may be used for preparations of different composition.
Zeneca, USA.
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.
Regent, Canad.†
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Hand disinfection.

Hibital *Globopharm, Switz.†*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin and hand disinfection.

Hibitane *Tramedico, Belg.; Tramedico, Belg.; AstraZeneca, Braz.; Pfizer, Canad.; Bioglan, Denm.; Molnlycke, Fr.; Molnlycke, Fr.; Cana, Gr.; Regent Medical, Irl.; Bioglan, Norw.; AstraZeneca, NZ†; CS, Port.; Glenmark, S.Afr.; Bioglan, Swed.; Globopharm, Switz.†; Molnlycke, Thai.†; Centrapharm, UK.*
Chlorhexidine gluconate (p. 1743·3).
Antiseptic; mouth infections; skin, burn, and wound disinfection; gynaecological and obstetric lubricant and disinfectant; vaginal infections; instrument disinfection.
Omega, Spain.
Pastilles: Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.
GSK Consumer, Belg.†
Pastilles: Chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.
GSK Consumer, Neth.†
Chlorhexidine hydrochloride (p. 1743·3).
Mouth infections.

Hibitane Teinture *Globopharm, Switz.†*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Hibitanol *Kocak, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Hibizene *Regent, Ital.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Disinfection of burns, wounds, and external genitalia.

Hiblok *Nufarindo, Indon.*
⊗Atenolol (p. 1308·2).
Hypertension.

Hibon *Mitsubishi Tanabe, Hong Kong.*
Riboflavin tetrabutyrate (p. 2104·3).
Vitamin B_2 deficiency.

Hi-Bone *Otto, Indon.*
Genistein (p. 2620·3); calcium phosphate (p. 1784·2); phytomenadione (p. 2122·2); colecalciferol (p. 2113·1).
Osteoporosis.

Hibor *Elder, India; Rovi, Spain; Dem, Turk.*
Bemiparin sodium (p. 1314·2).
Thromboembolism prophylaxis.

Hibrid *Shreya, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

HibTITER *Wyeth, Gr.; Wyeth, India; Wyeth, Pol.; Wyeth, Singapore.*
A Haemophilus influenzae conjugate vaccine (p. 2387·2).
Active immunisation.

Hibumine *IFET(ΙΦΕΤ), Gr.*
⊗Albumin (p. 1130·2).

Hical *Meprofarm, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); zinc sulfate (p. 2126·2); sodium fluoride (p. 2089·2).
Calcium and vitamin D_3 deficiency.

Hicalol *Chin Teng, China.*
Calcitriol (p. 2113·1).

Hicaryl *Eadriex, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Hicee *Takeda, Jpn; Takeda, Thai.*
Vitamin C (p. 2110·3).
Vitamin C deficiency; vitain C supplement.

Hicef *Samarth, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Hicef-T *Samarth, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Hicet *Micro, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Hicet-AX *Micro, India.*
Ambroxol hydrochloride (p. 1654·3); cetirizine hydrochloride (p. 619·2).

Hicet-DC *Micro, India.*
Cetirizine (p. 619·2); phenylephrine (p. 1672·2).

Hicet-L *Micro, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Hicip *Intra-Labs, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Hicip-TZ *Intra-Labs, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Hicloran *Labesfal, Port.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hico *Ifars, Indon.*
Heparin sodium (p. 1396·3).
Haematoma; superficial thrombophlebitis.

Hicobal *Health Guard, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Hicon *Draximage, USA.*
Iodine-131 (p. 2225·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Hiconcil *BMS, Braz.; BMS, Fr.†; BMS, Hong Kong†; KRKA, Pol.; KRKA, Rus.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.
KRKA, Ukr.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hiconcil-NS *BMS, S.Afr.†*
Amoxicillin trihydrate (p. 216·2); nystatin (p. 590·3).
Bacterial infections; candidiasis.

Hi-Cor *C & M, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hicort *Zee, India.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hicortal *Alter, Port.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Hicortin *Itaca, Braz.†*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hicoseen *Iromedica, Switz.†*
Butamirate citrate (p. 1657·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Hicoseen N *Iromedica, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Hicox *Systopic, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Hidalone *Schering-Plough, Port.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hidantal *Sanofi-Aventis, Braz.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Arrhythmias; epilepsy; neuralgia; skeletal muscle spasm.

Hidantin *Yeni, Turk.*
Phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia.

Hidantina *Vitoria, Port.*
Phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias.

Hidantoina *Sanofi-Aventis, Mex.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy.

Hidex *BMS, Mex.*
Iron dextran (p. 2075·3).
Anaemias.

Hidiclo *Hiral, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Hidiclo Plus *Hiral, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Hidiclodase *Hiral, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Hidil *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Hidol *Haledew, India.*
Paracetamol (p. 115·1).
Pain; fever.

Hidonac *Zambon, Hong Kong; Zambon, Indon.; Zambon, Ital.; Zambon, Malaysia; Zambon, Philipp.; Zambon, Singapore; Zambon, Thai.*
Acetylcysteine (p. 1652·2).
Paracetamol, carbon tetrachloride, arsenic, metallic mercury, and yellow phosphorus poisoning; cyclophosphamide-induced haemorrhagic cystitis.

Hidrabene *Legrand, Braz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Oral rehydration therapy.

Hidracid C20 *Farmoquimica, Braz.*
Ascorbic acid (p. 2110·3).

Hidrafil *GSK, Arg.; Stiefel, Braz.; Stiefel, Chile; Stiefel, Mex.*
Lotion: SPF 14: Cream SPF 14: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Sunscreen.

Stiefel, Chile†; Stiefel, Mex.
Gel SPF 20: SPF 20: Sulisobenzone (p. 1722·1); ensulizole (p. 1703·1).
Sunscreen.

Hidrafix *Nycomed, Braz.*
Sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Hidrafix 90 *Nycomed, Braz.*
Potassium citrate (p. 1780·3); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Hidral *Biocontrol, Arg.*
Hydralazine (p. 1401·2).
Hypertension.

Hidramox *Church, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hidramox-M *Church, Mex.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Hidrapel *Stiefel, Braz.*
Moisturiser.

Hidrapel Plus *Stiefel, Braz.*
⊗Urea (p. 1727·3).
Skin disorders.

Hidraplus *Farma, Venez.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration.

Hidrasec *Silesia, Chile; Abbott, China; Ferrer, Gr.; GSK, Indon.†; Ferrer-Novag, Mex.; Bioprojet, Neth.; Solvay, Philipp.; Abbott, Thai.; Abbott, UK; Leti, Venez.*
Racecadotril (p. 1881·3).
Diarrhoea.

Hidrasit *Sandoz, Turk.*
Hydrotalcite (p. 1845·2).

Hidrasix *Serral, Mex.*
Isoniazid (p. 311·2).
Tuberculosis.

Hidratacion Total (Linear Blistex) *Rider, Chile.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hidratagel *Barnes Hind, Arg.†*
Hyetellose (p. 2188·3); non-ionic surfactants.
Cleansing and wetting solution for soft contact lenses.

Hidratant *Biotech, Arg.*
Benzalkonium chloride (p. 1737·1).
Cleansing solution for soft contact lenses.

Hidratante Enriquecida *Silesia, Chile.*
Emollient.
Dry skin.

Hidratante Ligera *Silesia, Chile.*
Emollient.
Dry skin.

Hidratante VG *Isdin, Port.*
⊗Polyglycerylmethacrylate; glycerol (p. 2517·2); carbomer (p. 2173·3).
Vaginal lubricant.

Hidratante VV *Isdin, Port.*
Polyglycerylmethacrylate; lauromacrogol (p. 2194·1); borage oil (p. 2459·2); levomenol (p. 2544·1).
Vulval lubricant.

Hidratarvin *Arex, Venez.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration.

Hidrate *Unichem, India.*
Cream; lotion: Aloe vera (p. 1693·2); light liquid paraffin (p. 2191·2); squalene (p. 2213·3); vitamin E (p. 2119·1).
Emollient.

Unichem, India.
Soap: ⊗Glycerol (p. 2517·2).

Hidrathea *Thea, Spain.*
Sodium chloride (p. 1795·1).
Eye irritation.

Hidratil *Ducto, Braz.*
Sodium chloride (p. 1795·1); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Hidrazida *Merck, Port.*
Isoniazid (p. 311·2).
Tuberculosis.

Hidrazim *Multilab, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).

Hidrenox A *Ivax, Arg.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Hidribet *Roemmers Medihe, Venez.*
⊗Urea (p. 1727·3); dimeticone (p. 2209·3).
Dry skin; barrier preparation.

Hidribet 5/5 *Roemmers Medihe, Venez.*
⊗Urea (p. 1727·3); octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Dry skin; sunscreen.

Hidrion *Gross, Braz.*
⊗Furosemide (p. 1387·1); potassium chloride (p. 1793·2).
Hypertension; oedema.

Hidrium *Saval, Chile.*
⊗Furosemide (p. 1387·1); amiloride (p. 1299·1).
Heart failure; hepatic cirrhosis; hypertension.

Hidroaltesona *Alter, Spain.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hidrocilina *Grossman, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Hidrocin *Ache, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Hidrocisdin *Isdin, Spain.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hidroclorozil *IMA, Braz.†*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Hidrocort *Behrens, Venez.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Hidrocorte *Legrand, Braz.*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Skin disorders.

Hidrocortex *Bergamo, Braz.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Hidro-Doce *Meyer, Venez.*
Hydroxocobalamin (p. 2107·3).
Neuralgia; neuritis.

Hidro-Energy *Hoch Wertig, Arg.*
Maltodextrin (p. 2080·3); electrolytes (p. 1775·1).
Dietary supplement.

Hidrofenil *Grin, Mex.†*
⊗Hydrocortisone (p. 1640·1); phenylephrine (p. 1672·2).
Eye disorders.

Hidroferol *Faes, Spain.*
Calcifediol (p. 2113·1).
Rickets; osteomalacia; hypoparathyroidism; osteodystrophy; hypophosphataemia.

Hidrofosmin *Sanfer, Mex.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; auto-immune disorders.

Hidrofrut *Lagos, Arg.*
Alpha hydroxy acids (p. 1704·3).

Hidrofugal *Beiersdorf, Chile.†*
Cream; roll-on: Aluminium chlorohydrate (p. 1694·1); aluminium chloride (p. 1693·3).
Hyperhidrosis.

Beiersdorf, Chile.†
Stick; topical spray: Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Hidrofugal Forte *Beiersdorf, Chile.†*
Aluminium chlorohydrate (p. 1694·1); aluminium chloride (p. 1693·3).
Hyperhidrosis.

Hidrofundin *Braun, Spain.*
⊗Mannitol (p. 1427·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Forced diuresis; maintenance of urinary volume.

Hidrogel
Note: this name may be used for preparations of different composition.
Omega, Arg.
Vaginal lubricant.
Vaginal dryness.

Raffo, Chile.
Polycarbophil (p. 1879·1).
Vaginal dryness.

Roi Surya, Indon.†
Hydroquinone (p. 1705·1); kojic acid (p. 1710·2); gluconolactone (p. 2515·2).
Melasma; hyperpigmented skin.

Hidrolac *Lagos, Arg.*
⊗Lactic acid (p. 2539·1); urea (p. 1727·3).
Skin disorders.

Hidrolan *Geolab, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Hidrolid *Ariston, Arg.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms.

Hidromed *Cimed, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).

Hidrona *Teva, Mex.†*
⊗Chlortalidone (p. 1335·2).
Oedema; hypertension.

Hidronovag Complex *Gobbi, Arg.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Hidropeek *EMS, Braz.*
Hydroquinone (p. 1705·1).

Hidropharm *Alpharma, Mex.*
⊗Chlortalidone (p. 1335·2).
Oedema; hypertension.

Hidropid *Recalcine, Chile.†*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Heart failure; hypertension; oedema.

Hidroplus *Lagos, Arg.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Hidroplus CL *Lagos, Arg.*
Collagen (p. 2483·2).
Skin disorders.

Hidropolicin *Grin, Mex.†*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); hydrocortisone acetate (p. 1640·1).
Infected eye disorders.

Hidropolivit *Menarini, Spain.*
Vitamins.

Hidropolivit Mineral *Menarini, Spain.*
Vitamins; minerals.
Tonic.

Hidropril *Neo Quimica, Braz.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hidroquilaude *Dermofarm, Spain.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Hidroquin *Remexa, Mex.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Hidroronol *Labomed, Chile.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; premenstrual tension.

Hidroronol T *Labomed, Chile.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Heart failure; hepatic cirrhosis; hypertension; nephrotic syndrome; oedema.

Hidrosaluretil *Chiesi, Spain.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; diabetes insipidus; renal calculi.

Hidrosam *Szama, Arg.*
Collagen (p. 2483·2); elastin (p. 2483·2); reticulin.
Skin disorders.

Hidrosam T *Szama, Arg.*
Tretinoin (p. 1725·2); collagen (p. 2483·2); elastin (p. 2483·2); reticulin.
Acne; photoageing; skin pigmentation disorders.

Hidrosan
Note: this name may be used for preparations of different composition.
Coup, Gr.
Codergocrine mesilate (p. 389·2).

Uniao Quimica, Braz.
⊗Hydrochlorothiazide (p. 1403·2).

Hidroskin *Lagos, Arg.*
A range of moisturisers and skin cleansers containing glycolic acid (p. 1704·3).

Hidrosol *Pacific, NZ.†*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Hidroten *Belfar, Braz.*
Sodium (p. 1795·1); potassium (p. 1793·1); glucose (p. 2068·3).

Hidrotisona *Sanofi-Aventis, Arg.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hidroxil B12 B6 B1 *Almirall, Spain.*
Hydroxocobalamin (p. 2107·3); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Vitamin B deficiency.

Hidroxine *TKS, Braz.*
Hydroxyzine hydrochloride (p. 630·3).

Hidroxogel *Delta, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastrointestinal hyperacidity; flatulence.

Hidrozona *SM, Venez.*
⊗Hydrocortisone hydrogen succinate (p. 1640·2).
Corticosteroid.

Hidyn H *Ativus, Braz.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Hiedrix *Laboratorios Chile, Chile.*
Ivy (p. 2536·2).
Respiratory-tract disorders; cough.

Hielorub *Maver, Chile.†*
Menthol (p. 2553·2).
Sports injuries.

Hierbal *Kener, Mex.*
Chlorphenamine (p. 620·3).
Hypersensitivity.

Hierro Dupofol *Dupomar, Arg.†*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Anaemias.

Hierro Folico *Columbia, Arg.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and vitamin supplement.

Hierro Plus *Plata, Arg.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; dietary supplement.

Hierrocal Z-Plus *Farcoral, Mex.*
Calcium (p. 1783·1); iron (p. 2073·1); zinc (p. 2126·1).

Hierroquick *Purissimus, Arg.*
Iron (p. 2073·1); folic acid (p. 2063·1).
Anaemias.

Hif *Hiral, India.*
Fluconazole (p. 578·2).
Fungal infections.

Hifamonil *Raymos, Arg.*
Sodium perborate (p. 1770·1).

Hifamonil Crema *Raymos, Arg.*
⊗Miconazole (p. 588·3); betamethasone valerate (p. 1624·1); gentamicin (p. 304·2).
Infected skin disorders.

Hif-AS *Hiral, India.*
1 Tablets, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Hifen *Hetero, India.*
Cefixime (p. 240·3).
Bacterial infections.

Hifenac *Intas, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Hifenac-D *Intas, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Hifenac-MR *Intas, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Hifenac-P *Intas, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Hifen-CV *Hetero, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Hifen-DS *Hetero, India.*
Cefixime (p. 240·3).
Bacterial infections.

Hifen-LXX *Hetero, India.*
Cefixime (p. 240·3); dicloxacillin (p. 286·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

HiFi-L *Hy-Gro, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Hiflux *Farmasa, Braz.*
Ambroxol acefyllinate (p. 1201·2).
Respiratory-tract disorders.

Higan *Unison, Thai.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Higesan *Esoform, Ital.*
Sodium *o*-phenylphenol (p. 1762·3).
Surface disinfection.

High Energy *Lafarmen, Arg.*
Glucose (p. 2068·3); fructose (p. 2068·2).

High Potency Cal-Mag Plus *Quest, Canad.†*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); vitamin D (p. 2112·3).

High Potency D *Nature's Bounty, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

High Potency N-Vites *Nion, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

High Protection *Jacsim, Canad.†*
SPF 30: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

High Protection Cream *Roche-Posay, Canad.*
SPF 45: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

High Protection Sunscreen *Norwood, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

High Resolution *Lancome, Canad.†*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

High-C *Beacons, Singapore.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Highmix *Krasfarma, Rus.*
Amino acids; sorbitol (p. 2092·1).
Parenteral nutrition.

Higicler *Latinofarma, Braz.*
Benzalkonium chloride (p. 1737·1); boric acid (p. 2459·3); hamamelis (p. 2523·3); chamomile (p. 2474·1); borax (p. 2459·2).
Eye irritation.

Higiemax *Eczane, Arg.*
Mouthwash: Cetylpyridinium chloride (p. 1743·1).
Oral hygiene.
Eczane, Arg.
Topical gel: ⊗Alcohol (p. 1733·1).
Hand cleanser.

Higienizador Manos *Sanitas, Arg.*
⊗Alcohol (p. 1733·1); alpha tocopherol (p. 2119·1).
Hand cleansing.

Higlucem *Lazar, Arg.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Higo *APS, Port.†*
⊗Hydrochlorothiazide (p. 1403·2); valsartan (p. 1521·2).
Hypertension.

Higromil *Multilab, Braz.*
⊗Chlortalidone (p. 1335·2).

Higrotensin *Visfarm, Spain.†*
⊗Chlortalidone (p. 1335·2); metoprolol tartrate (p. 1434·3).
Hypertension.

Higroton *Novartis, Braz.; Sandoz, Mex.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema; renal calculi; heart failure; ascites.

Higroton Blok *Sandoz, Mex.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Higroton Reserpina *Novartis, Braz.*
⊗Chlortalidone (p. 1335·2); reserpine (p. 1485·3).
Hypertension.

Higrotona *Amdipharm, Spain.*
⊗Chlortalidone (p. 1335·2).
Oedema; hypertension; diabetes insipidus.

Higroton-Res *Sandoz, Mex.*
⊗Chlortalidone (p. 1335·2); reserpine (p. 1485·3).
Hypertension.

Hijuven *Eisai, Hong Kong†; Eisai, Malaysia; Eisai, Philipp.†*
dl-Alpha tocoferil nicotinate (p. 1516·1).
Atherosclerosis; hyperlipidaemias; peripheral vascular disorders; arteriosclerosis obliterans.

Hilcid *Daffohils, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Hileflox *HiGlance, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Hilin *Reddy, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Hill's Balsam Chesty Cough *LPC, UK.*
Guaifenesin (p. 1666·2).
Coughs.

Hill's Balsam Chesty Cough for Children *LPC, UK.*
Citric acid (p. 2480·3); ipecacuanha (p. 1667·2).
Coughs.

Hill's Balsam Chesty Cough Pastilles *LPC, UK.*
Compound benzoin tincture; peppermint oil (p. 1877·1); ipecacuanha (p. 1667·2); menthol (p. 2553·2).
Cough and cold symptoms.

Hill's Balsam Dry Cough *LPC, UK.*
Pholcodine (p. 1675·1).
Coughs.

Hill's Balsam Extra Strong *LPC, UK.*
Compound benzoin tincture; peppermint oil (p. 1877·1); ipecacuanha (p. 1667·2); menthol (p. 2553·2).
Coughs and cold symptoms.

Hill's Balsam Nasal Congestion Pastilles *LPC, UK.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Nasal congestion.

Hill-V *Daffohils, India.*
Clotrimazole (p. 576·2); lactobacillus (p. 2596·3); tinidazole (p. 949·2).

Hill.Vite *Hillestad, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Hilos *Nobel, Turk.*
Losartan potassium (p. 1422·2).

Hilyte *Sigman, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Hilyte-P *Sigman, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Hima-Pasta *Mundipharma, Switz.*
Zinc sulfate (p. 2126·2); zinc oxide (p. 1729·1).
Herpes labialis.

Himcolin
Note: this name may be used for preparations of different composition.
Himalaya Herbal, India.
Cinnamomum cassia (p. 2471·3); syzygium aromaticum.
Himalaya, Rus.
Celastrus paniculatus; hibiscus abelmoschus; prunus dulcis; vitex negundo; cotton root bark; pistacia vera; nutmeg (p. 2573·1); mace (p. 2547·3); syzygium aromaticum; cinnamon (p. 2479·2).
Erectile dysfunction.

Himcospaz *Himalaya Herbal, India.*
Celery (p. 2472·3); zedoary; zingiber officinale.

Himetin *Dong, Singapore.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer.

Himolan *Karnataka, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Hi-Mom *Hetero, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Himost *Svizera, India.*
Light liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Emollient.

Himox *Westmont, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Himox Plus *Solitaire, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); probenecid (p. 607·3).
Bacterial infections.

Himox-B *Solitaire, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

Himox-LS *Solitaire, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3); serrapeptase (p. 2613·3).

Himplasia *Himalaya Herbal, India.*
⊗Areca (p. 2446·3); asparagus racemosus (p. 2614·2); tribulus terrestris (p. 2633·3).

Hinac *Intas, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Hincomox *Teuto, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hindrox *Chemo-Drugs, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Hinemox *HiGlance, India.*
Moxifloxacin (p. 326·3).
Bacterial infections.

Hineoflox *HiGlance, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Hinepox *HiGlance, India.*
Pefloxacin (p. 338·1).
Bacterial infections.

Hingfong-Essenz Hofmanns *Hofmann & Sommer, Ger.*
Valerian (p. 2640·2); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); camphor (p. 2466·2).
Nervous disorders; circulatory disorders.

Hinuron-E *Icon, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Neuritis; neuralgia; neuropathy; vitamin B deficiency; chronic hepatitis.

Hioariston *Ariston, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Pain; smooth muscle spasm.

Hiocin *Biofarma, Venez.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hioscina Compuesta *Drawer, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Gastrointestinal spasm.

Hiospan *Teuto, Braz.*
Hyoscine butylbromide (p. 1845·3).
Skeletal muscle spasm.

Hiospan Composto *Teuto, Braz.*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Skeletal muscle spasm; pain.

Hiosultrina *Ultra, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hiosultrina-F *Ultra, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Hioxyl *Quinoderm, Irl.†*
Hydrogen peroxide (p. 1755·2).
Skin ulcers; wounds; skin infections.

Hipalen *Braun, Chile.*
Preparation for enteral nutrition.

Hipara *Decomed, Port.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Hipato-P *Alpha Aromatic, India.*
Andrographis paniculata (p. 2443·2); punarnava (p. 2601·1); tinospora cordifolia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hipax *Baliarda, Arg.*
St John's wort (p. 449·1).
Depression.

Hipcedan *Abamed, Spain.*
St John's wort (p. 449·1).
Asthenia.

Hipebe *Landsteiner, Mex.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Hipecor *Merck, Chile.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Hipeksal *Leiras, Fin.*
Methenamine hippurate (p. 323·1).
Urinary-tract infections.

Hipen *Zydus, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hipenox *Zydus, India.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Hipenox LB *Zydus, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

HiPep *Mediherb, Austral.*
Liquorice (p. 1853·2); chamomile (p. 2474·1); meadowsweet (p. 2550·2); chamomile oil (p. 2474·1).
Gastrointestinal disorders.

Hiperbiotico *Atral, Port.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Hiperbiotico Retard *Atral, Port.*
Ampicillin sodium (p. 218·2); ampicillin benzathine (p. 218·2).
Bacterial infections.

Hipercol *Angelini, Port.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; cranial trauma.

Hiperdipina *Tecnimede, Port.*
Nitrendipine (p. 1456·3).
Angina pectoris; hypertension.

Hiperex *Eurofarma, Braz.*
St John's wort (p. 449·1).
Depression.

Hiperflex *Recalcine, Chile.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Hipericin *Herbarium, Braz.†*
St John's wort (p. 449·1).
Depression.

Hiperico *Herbarium, Braz.†; Natysal, Spain†; Uriach Aquilea OTC, Spain.†*
St John's wort (p. 449·1).
Depression; sleep disorders; tonic.

Hiperikan *Farmasa, Mex.*
St John's wort (p. 449·1).
Depression.

Hiperinat *Natufarma, Arg.*
St John's wort (p. 449·1).
Depression.

Hiperlex *BMS, Spain.†*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Hiperlex Plus *BMS, Spain.†*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hiperlipen *Sanofi-Aventis, Venez.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Hipermessel *Biomep, Mex.*
Methyldopa (p. 1431·1).
Hypertension.

Hipernolol *Neo Quimica, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension.

Hiperogyn *Madaus, Ital.*
Magnesium (p. 1786·3); cimicifuga (p. 2478·1); St John's wort (p. 449·1).
Insomnia; menstrual disorders; menopausal disorders.

Hiperozida *Farmoz, Port.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hiperpril *Cafar, Venez.*
Enalapril maleate (p. 1371·1).
Hypertension.

Hipersac *Bunker, Braz.*
St John's wort (p. 449·1).
Depression.

Hipersar *Ulagay, Turk.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Hipersar Plus *Ufsa, Turk.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).

Hipersel *LKM, Arg.*
Vitamin E (p. 2119·1); betacarotene (p. 2051·1); vitamin C (p. 2110·3); selenium oxide (p. 2087·1).
Dietary supplement.

Hiperson *Medipharm, Chile.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Hiperson-D *Medipharm, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hipertal *Samjin, Philipp.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Hipertan *Gramon, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension.

Hipertene *Bial, Spain.*
Imidapril hydrochloride (p. 1409·1).
Hypertension.

Hipertensal *Finadiet, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Hipertensal Combi *Finadiet, Arg.*
Tablets, amlodipine besilate (p. 1304·1); tablets, atorvastatin calcium (p. 1309·2).
Hypertension; angina pectoris; hypercholesterolaemia.

Hiperterona *Greenpharma, Braz.*
Amiodarone (p. 1300·1).

Hipertex *Rayere, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic neuropathy.

Hipertil
Note: this name may be used for preparations of different composition.
Chiesi, Braz.
Delapril hydrochloride (p. 1350·2); manidipine hydrochloride (p. 1427·2).
Hypertension.
Normal, Port.†
Captopril (p. 1331·2).
Hypertension; myocardial infarction; heart failure; diabetic nephropathy; diabetic retinopathy.

Hiperton *Grin, Mex.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Hipexal *Volta, Chile.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Hipnazolam *Sigma, Braz.*
Midazolam hydrochloride (p. 1085·1) or midazolam maleate (p. 1085·2).
Insomnia; premedication.

Hipnodem *Ivax, Arg.*
Zaleplon (p. 1114·3).
Insomnia.

Hipnopento *Gray, Arg.*
Thiopental sodium (p. 1915·1).
General anaesthesia; hypnotic.

Hipnosedon *Roche, Gr.*
Flunitrazepam (p. 1073·3).
Insomnia.

Hipnoz *Pharos, Indon.*
Midazolam (p. 1085·1).
Sedative; premedication; general anaesthesia.

Hipo Femme *Andromaco, Mex.*
Miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Hipo Sport *Andromaco, Mex.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Hipoartel *Andromaco, Chile; Faes, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Hipoartel Plus *Faes, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hipobar *Cipan, Port.†*
Enalapril maleate (p. 1371·1).

Hipocol *Valdecasas, Mex.*
Nicotinic acid (p. 2083·1).
Hypercholesterolaemia; pellagra.

Hipoden *Andromaco, Mex.*
Lidocaine hydrochloride (p. 1988·2).
Teething pain.

Hipoderme *Teuto, Braz.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Barrier preparation.

Hipodermon *Neo Quimica, Braz.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); boric acid (p. 2459·3); zinc oxide (p. 1729·1).
Barrier preparation; emollient.

Hipodex *Bunker, Braz.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); neomycin sulfate (p. 330·1); benzethonium chloride (p. 1738·1).
Infected skin disorders; barrier preparation.

Hipodox *Rishab, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Hipofagin S *Sigma, Braz.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Hipofisina *Biol, Arg.*
Oxytocin (p. 2143·1).
Postpartum haemorrhage; postpartum uterine atony; labour induction.

Hipofitein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Hipofol *Hipolabor, Braz.*
Folic acid (p. 2063·1).

Hipoge *SMB, Chile.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Hipoglis *Nevzat, Turk.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Hipoglos *Andromaco, Chile.*
Halibut-liver oil (p. 2071·3); boric acid (p. 2459·3); zinc oxide (p. 1729·1).
Skin disorders; burns; ulcers; wounds.
Andromaco, Mex.
Vitamin A (p. 2098·3); zinc oxide (p. 1729·1); allantoin (p. 1693·1); boric acid (p. 2459·3); talc (p. 1722·2).
Skin disorders.
Andromaco, Arg.
Vitamin A (p. 2098·3); zinc oxide (p. 1729·1).
Nappy rash; nipple care; skin disorders; burns; ulcers.
Procter & Gamble, Braz.
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Skin disorders.

Hipoglos Cicatrizante *Andromaco, Arg.*
Zinc undecenoate (p. 596·3); sodium propionate (p. 593·1); diiodohydroxyquinoline (p. 931·1); boric acid (p. 2459·3); zinc oxide (p. 1729·1).
Wounds; skin irritation; ulcers; hyperhidrosis.

Hipoglos Cremoso *Andromaco, Mex.*
Zinc oxide (p. 1729·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1); allantoin (p. 1693·1); aloe vera (p. 1693·2).
Nappy rash.

Hipoglos con Hidrocortisona *Andromaco, Arg.*
⊗Hydrocortisone (p. 1640·1); vitamin A (p. 2098·3); cod-liver oil (p. 2056·3); boric acid (p. 2459·3).
Skin disorders.

Hipoglucin *Laboratorios Chile, Chile.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Hipoglucin DA *Laboratorios Chile, Chile.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Hipoglut *Gador, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Hipoglut Met *Gador, Arg.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Hipokinon *Psicofarma, Mex.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; extrapyramidal disorders.

Hipokort *Orva, Turk.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Hipokort Arti *Orva, Turk.*
⊗Pramocaine hydrochloride (p. 1993·3); hydrocortisone acetate (p. 1640·1).

Hipolixan *Bago, Arg.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.
Pasteur, Chile.
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Hipolter *Ranbaxy, Mex.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Hipomeril *Teuto, Braz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Hiporhamin *Vilar, Rus.*
Sea buckthorn (p. 2611·3).
Viral infections.

Hiposan *Sanval, Braz.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Skin disorders; barrier preparation.

Hiposem *Labofarm, Pol.*
Aesculus (p. 2431·2).
Venous insufficiency; oedema.

Hiposterol *Laboratorios Chile, Chile.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Hipoten
Note: this name may be used for preparations of different composition.
Klonal, Arg.
⊗Carvedilol (p. 1333·1).
Angina pectoris; hypertension.
Sanval, Braz.
Captopril (p. 1331·2).
Hypertension.

Hipotensil *Medinfar, Port.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy; diabetic retinopathy.

Hipotermal *Sanval, Braz.†*
Aspirin (p. 22·2).
Fever; pain.

Hipotest *Marlop, USA.*
Vitamins; minerals; iron (p. 2073·1).

Hipotosse *Labesfal, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Hipovastin *Gador, Arg.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Hipover *Drugtech, Chile.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Hipovit *Casca, India.*
Preparation for enteral nutrition.

Hi-Po-Vites *Hudson, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Hippro *Deltapharm, Hong Kong†; Charoen, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Hippuran
Note: this name may be used for preparations of different composition.
Mallinckrodt, Cz.; Mallinckrodt, Neth.
Iodine-123 (p. 2225·1) as sodium iodohippurate.
Radionuclide investigation of renal function.

Hippurin *Yeni, Turk.*
Methenamine hippurate (p. 323·1).
Urinary-tract infections.

Hipranol *CCM, Malaysia.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; anxiety; migraine; tremor; arrhythmias; hyperthyroidism.

Hiprazole *Hiral, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Hipres
Note: this name may be used for preparations of different composition.
Cipla, India.
⊗Atenolol (p. 1308·2).
Hypertension.

KRKA, Cz.
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Hipres-D *Cipla, India.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Hiprex *iNova, Austral.; Meda, Fin.; 3M, Israel; iNova, Malaysia; Meda, Norw.; 3M, NZ; 3M, Philipp.†; Meda, Swed.; 3M, UK; Sanofi-Aventis, USA.*
Methenamine hippurate (p. 323·1).
Urinary-tract infections.

Hipril *Micro, India; Micro, Singapore.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Hipril-A *Micro, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Hiprogin *CCM, Malaysia.*
Hydroxyprogesterone caproate (p. 2285·1).
Amenorrhoea; recurrent miscarriage.

Hiprogress *Finecure, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Hi-Q *Biomiicron, India.*
Capsules: Idebenone (p. 392·3); arginine (p. 2049·1); selenium (p. 2086·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Biomiicron, India.
Tablets: Ubidecarenone (p. 2637·1); folic acid (p. 2063·1); arginine (p. 2049·1); lycopene (p. 2546·2); sodium selenite (p. 2087·1); vitamin E acetate (p. 2119·2); zinc oxide (p. 1729·1).

Hi-Q Plus *Biomiicron, India.*
Capsules: Idebenone (p. 392·3); levocarnitine (p. 2053·2); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Biomiicron, India.
Tablets: Ubidecarenone (p. 2637·1); levocarnitine tartrate (p. 2053·2); sodium selenite (p. 2087·1); zinc sulfate (p. 2126·2).

Hirabezole *HiGlance, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Hirapine *CCM, Malaysia.*
Nevirapine (p. 1005·1).
HIV infection.

Hiremon *Demo, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Hireto *Aamorb, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Hi-ringl *Sato, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Hirobriz *Novartis, Cz.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Spain.*
⊗Indacaterol maleate (p. 1211·2).
Obstructive airways disease.

Hirox
Note: this name may be used for preparations of different composition.
Medizone, India.
Roxithromycin (p. 356·2).
Bacterial infections.

Vargas, Venez.
Heparin sodium (p. 1396·3).
Bruises.

Hirtonin *Takeda, Jpn.*
Protirelin tartrate (p. 2344·2).
Prolonged disturbance of consciousness; spinocerebellar degeneration.

Hirucrème *Bayer Sante, Fr.*
Hirudin (p. 1401·2).
Peripheral vascular disorders; anorectal disorders.

Hirudoid *Ivax, Arg.; Key, Austral.; Stada, Austria; Neocare, Belg.; Sankyo, Braz.; Silesia, Chile†; Medinova, China; Stada, Cz.; Stada, Denm.; Stada, Fin.; Stada, Ger.; Farmalex, Gr.; Medinova, Hong Kong; Stada, Hung.; CFL, India; Medinova, Indon.†; Crinos, Ital.; Neocare, Neth.; Stada, Norw.; Wilson, NZ; Medinova, Philipp.; Sankyo, Pol.; Ciclum, Port.; Medinova, Singapore; Stada, Spain; Stada, Swed.; Medinova, Switz.; Medinova, Thai.; Santa, Turk.; Genus, UK; Sankyo, Venez.*
A heparinoid (p. 1401·1).
Haematoma; superficial thrombophlebitis; varices; scars; superficial phlebitis; inflammation; bruising; venous insufficiency; oedema; wounds; haemorrhoids; sunburn; ichthyosis; prevention of extravasation during parenteral administration; cicatrisation; superficial vascular disorders; burns; variceal ulcers.

Hiruflog *Crinos, Ital.*
Ketoprofen (p. 79·1).

Hiruscar *Medinova, Philipp.*
Onion (p. 2575·2); allantoin (p. 1693·1); aloe vera (p. 1693·2); heparinoids (p. 1401·1); nicotinamide (p. 2083·1); tocoferil acetate (p. 2119·2).
Scars; keloids.

Medinova, Singapore.
Onion (p. 2575·2); a heparinoid (p. 1401·1); allantoin (p. 1693·1); aloe vera (p. 1693·2); nicotinamide (p. 2083·1); vitamin E (p. 2119·1).
Scars; keloids.

His *Elfin, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Hiscifed *Greater Pharma, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Nasal congestion; hypersensitivity reactions; cold symptoms; rhinitis; otitis media.

Hiscolgen *Greater Pharma, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Hisdaron *Chew, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Hisdec *QX, Philipp.*
Brompheniramine maleate (p. 618·1); phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Hiskast *Stellar, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Hislorex *Konimex, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Hi-Smart *San Marino, Philipp.*
Vitamins; zinc sulfate (p. 2126·2); taurine (p. 2626·2); lysine (p. 2079·3).
Dietary supplement.

Hi-Smart Teens *San Marino, Philipp.*
Vitamins; ferrous fumarate (p. 2060·3); calcium lactate (p. 1784·1); zinc sulfate (p. 2126·2); taurine (p. 2626·2); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Hismazine *CCM, Malaysia.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Hisnofil *Ranbaxy, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Hisone *Samarth, India.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

His-P *Elfin, India.*
⊗Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Hispadol *Farmaceutica H, Mex.*
Haloperidol (p. 1077·1).
Psychoses; movement disorders.

Hispatrel *Farmaceutica H, Mex.†*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Hispazzon *Farmaceutica H, Mex.†*
Ketoconazole (p. 585·3).
Fungal skin infections.

Hispen *Genesis, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Hisplex *Biotenk, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions; urticaria.

Hispokyn *Misha, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Hisracon *Condrugs, Thai.*
Loratadine (p. 633·2).
Allergic skin disorders; hay fever; asthma.

Hista *Pharmasant, Thai.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Skin irritation.

Hista-Bloc
Note: this name may be used for preparations of different composition.
Intas, Philipp.; Standard, Philipp.
Famotidine (p. 1842·1).
Dyspepsia; gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Histac *Nanxin, China; Ranbaxy, Cz.†; Labormed, Hung.; Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Mex.†; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; gastric hyperacidity; dyspepsia; short bowel syndrome; gastrointestinal haemorrhage; pancreatitis.

Histacet *Medreich, Hong Kong.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Histachek *Indoco, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Histaclar *Gerard, Irl.*
Loratadine (p. 633·2).
Allergic rhinitis; idiopathic chronic urticaria.

Histacol DM *Breckenridge, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Histacold *Minova, India.*
Paracetamol (p. 115·1).
Pain; fever.

Histacon *Aspen, S.Afr.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms; allergic rhinitis; sinusitis.

Histacort *BioFemme, Philipp.*
Cream: ⊗Prednisolone (p. 1645·2).
Skin disorders.

BioFemme, Philipp.
Tablets: ⊗Chlorphenamine maleate (p. 620·3); prednisolone (p. 1645·2).
Skin disorders.

Histacyl Cutan N *Streuli, Switz.*
Diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2); levomenthol (p. 2553·2).
Skin disorders.

Histadex *Vitamed, Israel.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine hydrochloride (p. 1676·1).
Hypersensitivity reactions; respiratory-tract congestion.

Histadin *Uniao Quimica, Braz.; SMB, Fin.; Azevedos, Port.; Nobel, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Histadin D *Uniao Quimica, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).

Histadine *Burapha, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Histadryl
Note: this name may be used for preparations of different composition.
BJ Benjaosoth, Thai.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); potassium citrate (p. 1780·3).

Parggon, Mex.
Syrup: Diphenhydramine (p. 626·1).
Hypersensitivity.

Parggon, Mex.
Tablets: Chlorphenamine (p. 620·3).
Hypersensitivity.

Histafast *Cipla Chanelle, Denm.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Histafed *Trima, Israel.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Hypersensitivity reactions; respiratory-tract congestion.

Histafed Comp *Trima, Israel.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough; upper respiratory-tract infections.

Histafed Expectorant *Trima, Israel.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; hypersensitivity reactions; respiratory-tract congestion.

Histafen
Note: this name may be used for preparations of different composition.
Xepa-Soul Pattinson, Hong Kong†; Dey's, India.
Terfenadine (p. 640·3).
Hypersensitivity reactions; allergic rhinitis; allergic skin reactions.

Douglas, NZ.
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Olainfarm, Rus.
Sequifenadine (p. 640·2).
Allergic rhinitis; conjunctivitis; urticaria; angioedema; pruritus.

Histafilin *Estedi, Spain.†*
Theophylline (p. 1229·3).
Obstructive airways disease; paroxysmal dyspnoea; heart failure.

Histafren *Unipharma, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Histagesic Modified *Jones, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Histaglobin *Sidus, Arg.; Germania, Austria†; Mirren, S. Afr.†*
A normal immunoglobulin (p. 2403·3); histamine hydrochloride (p. 2525·2).
Hypersensitivity reactions.

Histaglobulin *Serum Institute, India.*
A normal immunoglobulin (p. 2403·3); histamine hydrochloride (p. 2525·2); sodium thiosulfate (p. 1576·1).
Allergic skin disorders; asthma; migraine.

Histaglobulina *Biomed Lublin, Pol.*
Normal immunoglobulin (p. 2403·3); histamine hydrochloride (p. 2525·2).
Hypersensitivity reactions.

Histagra *Khandelwal, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Histagrip para adultos *Calox, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine (p. 620·3).
Influenza symptoms.

Histagrip pediatrico *Calox, Venez.*
Paracetamol (p. 115·1); chlorphenamine (p. 620·3).
Influenza symptoms.

Histak *Ranbaxy, S.Afr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux; acid aspiration; heartburn.

Histakof *Kopran, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Histalen *Andromaco, Chile.*
Cetirizine (p. 619·2) or cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Histalen D *Andromaco, Chile.†*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Histaler *Duncan, Arg.*
Diphenhydramine (p. 626·1).
Hypersensitivity reactions; sedative; vomiting.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Histalet *Numark, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Histalet X *Numark, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Histalgane *Spirig, Switz.*
Nonivamide (p. 102·3); benzyl nicotinate (p. 29·3); glycol salicylate (p. 66·2); dimethyl sulfoxide (p. 2182·2).
Musculoskeletal, joint, and peri-articular pain.

Histalgane mite *Spirig, Switz.*
Glycol salicylate (p. 66·2); dimethyl sulfoxide (p. 2182·2).
Musculoskeletal, joint, and peri-articular pain.

Histalino *Arlex, Mex.*
Astemizole (p. 616·1).
Hypersensitivity.

Histalix
Note: this name may be used for preparations of different composition.
Wallace Mfg Chem., UK.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Coughs.

Histaloc
Note: this name may be used for preparations of different composition.
Cipla, India.
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Julphar, UAE.
Promethazine hydrochloride (p. 638·2).
Hypersensitivity; motion sickness; insomnia; premedication; nausea and vomiting.

Histalor *Reddy, Singapore.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Histamed
Note: this name may be used for preparations of different composition.
Cimed, Braz.
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).

Metz, Philipp.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Premier, S.Afr.†
Lotion: Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2); benzocaine (p. 1980·2).
Skin irritation.

Histamed Compound *Adcock Ingram, S.Afr.*
Chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3); salicylamide (p. 129·2); paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; sinusitis; allergic rhinitis.

Histamin *Neo Quimica, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Histamine-Care *Trima, Israel.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Hypersensitivity reactions; rhinitis.

Histamino Corteroid L *Montpellier, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Histamix D *Hebron, Braz.*
⊗Pseudoephedrine (p. 1676·1); loratadine (p. 633·2).

Histan *Siam Bheasach, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; anxiety.

Histanova *Alternova, Fin.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Histantil *Pharmascience, Canad.*
Promethazine hydrochloride (p. 638·2).
Antihistamine.

Histaoph *Seng, Thai.*
⊗Antazoline hydrochloride (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Allergic eye disorders; conjunctivitis.

Histapaisyl *Merck Medication Familiale, Fr.*
Isothipendyl hydrochloride (p. 631·2).
Allergic rhinitis; urticaria.

Histapan *Sanbe, Indon.*
Mebhydrolin napadisilate (p. 634·2).
Allergic disorders.

Histapharm *Apotex, Denm.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Histaril *Aldril, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Histaritin *Medikon, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Histaser *Serral, Mex.*
Astemizole (p. 616·1).
Hypersensitivity.

Histasin *Actavis, Hong Kong.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Histastop *Pyridam, Indon.†*
Terfenadine (p. 640·3).
Allergic disorders.

Histatab *Pharmasant, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Histatab D *Breckenridge, USA.*
⊗Dexchlorpheniramine maleate (p. 621·1); hyoscine methonitrate (p. 1846·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Histatab Plus *Century, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Histatapp *Pharmasant, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Histatec *Streuli, Switz.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Histatrol *ALK, Canad.; ALK, USA.*
Histamine phosphate (p. 2525·2).
Diagnosis of hypersensitivity.

Hista-Tussin *Pharmasant, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; nasal congestion.

Histaverin *Estedi, Spain.*
Codeine phosphate (p. 40·2).
Cough.

Histavert *Pulse, India.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Hista-X *Axapharm, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Histax *Recalcine, Chile.*
Cetirizine (p. 619·2) or cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Histaxin *Medo, Austria.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic skin disorders.

Histazine
Note: this name may be used for preparations of different composition.
East West, India.
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; motion sickness; insomnia.

Trima, Hong Kong†; Trima, Israel.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Histec *Orion, Fin.; VS, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; hypersensitivity reactions.

Histek *Helsinn Birex, Irl.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; idiopathic chronic urticaria.

Histenol II *Zee, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Histenol-Forte *Zee, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Histergan *Wing Wai, Hong Kong†; Norma, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Histex *Teamm, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Histex CT *Teamm, USA.*
Carbinoxamine maleate (p. 619·1).
Hypersensitivity reactions.

Histex I/E *Teamm, USA.*
Carbinoxamine maleate (p. 619·1).
Allergic rhinitis.

Histex HC *Teamm, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); hydrocodone tartrate (p. 67·2); carbinoxamine hydrochloride (p. 619·1) or carbinoxamine maleate (p. 619·1).
Coughs; respiratory-tract congestion; rhinitis.

Histex PD *Teamm, USA.*
Carbinoxamine (p. 619·1).
Allergic rhinitis.

Histex SR *Teamm, USA.†*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Allergic rhinitis; cold symptoms; sinusitis.

Histiacil Flu *Sanofi-Aventis, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Histiacil G *Sanofi-Aventis, Mex.*
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Histiacil NF *Sanofi-Aventis, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Histiacil T *Sanofi-Aventis, Mex.*
⊗Chlorphenamine (p. 620·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Histiacil Tex *Sanofi-Aventis, Mex.†*
⊗Chlorphenamine (p. 620·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Histica *M & H, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Histidon *Nutricia, Ital.*
Food for special diets.
Histidinaemia.

Histigen *Generics, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Histigo *Ifars, Indon.*
Betahistine mesilate (p. 2455·3).
Vestibular disorders.

Molekule, India.
Betahistine (p. 2455·3).
Ménière's disease.

Histimed *3DDD, Belg.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Histimerck *Generics, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Histimet *Janssen-Cilag, Arg.*
Levocabastine (p. 632·2).
Allergic conjunctivitis; allergic rhinitis.

Histin *Kenyaku, Thai.*
Carbinoxamine maleate (p. 619·1).
Allergic rhinitis; allergic skin disorders.

Histina *Solara, Mex.†*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Histinex D *Ethex, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Histinex HC *Ethex, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Coughs.

Histinex PV *Ethex, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Histisynt *Actavis, Hung.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Histoacryl *IFET (ΙΦΕΤ), Gr.; Braun, UK.*
Enbucrilate (p. 2489·3).
Wound closure and suture support.

Histodil *Gedeon Richter, Rus.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Histodor *Aspen, S.Afr.*
Cream: Mepyramine maleate (p. 635·1); diphenhydramine hydrochloride (p. 626·2).
Skin disorders; insect bites.

Aspen, S.Afr.†
Tablets: Mepyramine maleate (p. 635·1); promethazine hydrochloride (p. 638·2); caffeine (p. 1203·3).
Hypersensitivity reactions.

Histodor Expectorant *Aspen, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Histodryl *Biolab, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; cold symptoms.

Histofen *Xeno, Philipp.†*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Histo-Fluine P *Richard, Fr.*
Aesculus (p. 2431·2); hamamelis (p. 2523·3); shepherd's purse (p. 2614·2); pulsatilla (p. 2600·2); esculoside (p. 2431·2).
Peripheral vascular disorders.

Histofreezer *koGen, UK.*
Dimethyl ether (p. 1798·3); propane (p. 1802·3); isobutane (p. 1799·2).
Warts.

Histogenol *Biofarma, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Histoglob *Bharat, India.*
A normal immunoglobulin (p. 2403·3).

Histol *Julphar, UAE.*
Pheniramine maleate (p. 637·2).
Hypersensitivity.

Histol Exp *Julphar, UAE.†*
Pheniramine maleate (p. 637·2); ammonium chloride (p. 1656·1).
Cough.

Histolyn-CYL *ALK, USA.†*
Histoplasmin (p. 2526·1).
Diagnostic test.

Histop *Salvat, Spain.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Histopen *Bernabo, Arg.†*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Historan *Ilacsan, Turk.*
Diphenhydramine (p. 626·1); ammonium chloride (p. 1656·1); citric acid (p. 2480·3).

Histor-D *Roberts, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Histor-D Timecelles *Roberts, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract symptoms.

Historil *Acuition, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Histox *Mavi, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Hist-PSE *Cypress, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms; allergic rhinitis.

Histrine *Ferron, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Histussin HC *Victory, USA.*
Dexbrompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); hydrocodone tartrate (p. 67·2).
Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, and hydrocodone tartrate.
Coughs and cold symptoms.

Hiszine *Suphong, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Hi-Tar *ICM, Singapore.*
Coal tar (p. 1723·2).
Psoriasis; seborrhoeic dermatitis.

Hitem-MD *Sigman, India.*
Paracetamol (p. 115·1).
Pain; fever.

Hitocobamin M *Hishiyama, Thai.†*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Hito-EN *Taj, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Hitrax *Alvartis, Mex.†*
Omeprazole (p. 1867·2).

Hitrazole *Choongwae, Singapore.*
Itraconazole (p. 583·3).
Fungal infections.

Hi-Trex *VHB, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Hitrizin *Deva, Turk.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Hitz *Dexter, India.*
Paracetamol (p. 115·1).
Pain; fever.

Hitz-NP *Dexter, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Hivas *HiGlance, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Hi-Vegi-Lip *Freeda, USA.*
⊗Pancreatin (p. 2579·3); pancrelipase (p. 2580·1).
Deficiency of digestive enzymes.

Hivent *Euro-Med, Indon.; Euro-Med, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Hives *Hylands, Canad.*
Apis mellifica (p. 2445·2); natrum muriaticum (p. 1795·1); urtica urens (p. 2639·3); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Hivid *Roche, Austral.†; Roche, Gr.; Chugai, Jpn†; Roche, Mex.; Roche, Rus.; Roche, Singapore; Roche, Thai.†; Roche, Turk.; Roche, Venez.*
Zalcitabine (p. 1023·2).
HIV infection.

Hivit *Behrens, Venez.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Hivotex *Kleva, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Hixilerg *EMS, Braz.*
Hydroxyzine hydrochloride (p. 630·3).

Hixizine *Theraskin, Braz.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; nausea and vomiting; vertigo; Ménière's disease; anxiety.

Hi-Z *Otsuka, Jpn.*
Oryzanol (p. 2578·1).
Hyperlipidaemia; menopausal disorders; irritable bowel syndrome.

Hizaar *MSD, Ital.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hizentra *CSL, Belg.; CSL, Canad.; CSL, Denm.; CSL, Fr.; CSL, Ger.; CSL, Irl.; CSL, Neth.; CSL, Norw.; CSL, Spain; CSL, Swed.; CSL, Switz.; CSL, UK; CSL, USA.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; passive immunisation.

Hizialos *Wynn, Port.†*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Hizin *Unichem, Singapore; Ranbaxy, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions; pruritus; nausea and vomiting.

Hizone *Shin Poong, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Hizy *Hos & Ins, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Hjerdyl *Sandoz, Denm.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Hjertealbyl *Actavis, Denm.*
Aspirin (p. 22·2).
Ischaemic heart disease; thrombosis prophylaxis.

Hjertemagnyl *Nycomed, Denm.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Hjertemin *Medic, Denm.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Hloh *Kneipp, Cz.†*
Crataegus (p. 2488·1).
Cardiac disorders; hypertension.

HL-ysta *Ultra, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

HMG *Angelini, Spain.*
⊗Menotrophin (p. 2284·1).
Male infertility; female infertility.

HMG Ferring *Ferring, Arg.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

H-Mide *LBS, Thai.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

HM-PAO Kit *Rez, Cz.†*
Technetium-99m (p. 2228·1) exametazime.
Radionuclide imaging of the brain.

HMT *Hos & Ins, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

HN 25 *Milupa, Port.*
Preparation for enteral nutrition.

HND *H & Care, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Hobatadine *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Loratadine (p. 633·2).

Hobaticam *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Hobatmycine *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Hobatolex *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Hobatstress *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Hobs *Aamorb, India.*
⊗Ulobetasol propionate (p. 1650·3).
Skin disorders.

Hobs-S *Aamorb, India.*
⊗Ulobetasol propionate (p. 1650·3); salicylic acid (p. 1719·1).

Hobutide *Health Biotech, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Hocef *Hos & Ins, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Hocef-S *Hos & Ins, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Hocef-T *Hos & Ins, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Hochuekkito *Kracie, Jpn; Tsumura, Jpn.*
Astragalus root (p. 2451·1); atractylodes rhizome; ginseng (p. 2513·3); angelica acutiloba root (p. 2443·3); bupleurum root; jujube; citrus unshiu peel; liquorice (p. 1853·2); cimicifuga rhizome; ginger (p. 1844·1).
Traditional Kampo medicine.

Hocid *Savoy, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Hodernal *Rottapharm, Spain.*
Liquid paraffin (p. 2191·2).
Constipation.

Hoebedic *Hoe, Philipp.*
⊗Fusidic acid (p. 302·1); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Hoebenate *Hoe, Philipp.*
⊗Betamethasone dipropionate (p. 1623·3); sodium fusidate (p. 302·1).
Infected skin disorders.

Hoemal *Hoe, Malaysia; Hoe, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Hoevenol *Hoernecke, Ger.*
Capsules: Aesculus (p. 2431·2).
Venous insufficiency; soft-tissue injury.
Hoernecke, Ger.
Topical emulsion: Methyl salicylate (p. 92·1); aesculus (p. 2431·2).
Peripheral vascular disorders; venous insufficiency; haemorrhoids.

Hofcomant *Merz, Austria; Sevens, Gr.*
Amantadine sulfate (p. 890·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Hofergot *Pharmahof, Thai.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Hoffmannstropfen *Hofmann & Sommer, Ger.*
⊗Ether (p. 2212·3); alcohol (p. 1733·1).
Tonic.

Hoffmans Druppels *Aspen Consumer, S.Afr.*
Anaesthetic ether (p. 1900·3).
Colic; flatulence.

Hofim *Hos & Ins, India.*
Cefixime (p. 240·3).
Bacterial infections.

Hofim-C *Hos & Ins, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Hoflo *Hos & Ins, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Hoflo-O *Hos & Ins, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Hoflox-O *H & Care, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Hofodilan *Landsteiner, Mex.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Hofra *Pharmahof, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Hofra B *Pharmahof, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Infected skin disorders.

Hoftrex *Hovid, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Hoggar Balance *Stada, Ger.*
Passion flower (p. 2584·1).
Nervous disorders.

Hoggar N *Stada, Thai.*
Doxylamine succinate (p. 627·3).
Hypersensitivity reactions; pruritus.

Hoggar Night *Stada, Ger.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Hokunalin *Abbott, Jpn.*
⊗Tulobuterol (p. 1239·2).
Obstructive airways disease.

Holadren *Laboratorios Chile, Chile.*
Alendronate sodium (p. 1171·3).
Osteoporosis bone.

Hold
Note: this name may be used for preparations of different composition.
Juggat, India.
Sodium chloride (p. 1795·1).
Nasal congestion.
Salud, India.
Vitamins; minerals; trace elements.

Hold DM *Ascher, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Holdestin *Pasteur, Philipp.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Holergie *Steigerwald, Neth.*
Ammi visnaga (p. 2441·2); arundo donax; cardiospermum halicacabum; galphimia glauca; luffa operculata (p. 2545·3).
Homoeopathic preparation.

Holetar *KRKA, Cz.†; KRKA, Rus.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; atherosclerosis; hypercholesterolaemia.

Holgyeme *Effik, Fr.; Effik, Switz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Holisten *Demo, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Holofusine *Braun, Switz.†*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Holomagnesio *Phoenix, Arg.*
Magnesium citrate (p. 1857·1).
Magnesium deficiency.

Holomagnesio Antioxidante *Phoenix, Arg.*
Magnesium lactate (p. 1787·2); vitamin E (p. 2119·1).

Holomagnesio B6 *Phoenix, Arg.*
Magnesium citrate (p. 1857·1); pyridoxine hydrochloride (p. 2105·3).
Tonic.

Holomagnesio Vital *Phoenix, Arg.*
Ginseng (p. 2513·3); arginine N-acetylasparaginate (p. 2049·1); magnesium carbonate (p. 1856·2); magnesium stearate (p. 2195·3).
Tonic.

Holomine *Vickmans, Hong Kong.†*
Hyoscine (p. 1845·3).

Holoxan *Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Chile; Baxter, China; Baxter Oncology, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter Oncology, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Zydus, India; Transfarma, Indon.; Baxter, Ital.; Baxter, Neth.; Baxter Oncology, Norw.; Baxter, NZ; Baxter, Philipp.; Baxter Oncology, Pol.; Baxter, Port.; Baxter Oncology, Rus.; Sanofi-Aventis, S.Afr.; Baxter Oncology, Singapore; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Holoxan Uromitexan *Zydus, India.*
Ifosfamide (p. 806·1); mesna (p. 1557·2).
Malignant neoplasms.

Holoxane *Baxter, Braz.*
Ifosfamide (p. 806·1).
Testicular cancer.

Holtresis *Pasteur, Philipp.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

HOM *Nutricia-Bago, Arg.; Nutricia, Fr.; Nutricia, Ital.*
Food for special diets.
Homocystinuria.

Homarin *Klar Sehen, India.*
Homatropine hydrobromide (p. 2007·3).

Homatrop *Llorens, Spain.†*
Homatropine hydrobromide (p. 2007·3).
Production of mydriasis and cycloplegia; uveitis.

Homéoaftyl *Boiron, Fr.*
Borax (p. 2459·2); kalium bichromicum (p. 2476·3); sulfuricum acidum (p. 2624·2).
Homoeopathic preparation.

Homeocare Allerlo *Timm, Neth.*
Luffa operculata (p. 2545·3); histaminum muriaticum (p. 2525·2); arsenicum iodatum

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2448·1); sanguinaria canadensis (p. 2610·1); causticum (p. 2595·3); galphimia glauca.
Formerly known as Homeocare allergo.
Homoeopathic preparation.

Homeocare Cyclo *Timm, Neth.*
⊗Agnus castus (p. 2432·2); cimicifuga racemosa (p. 2478·1); kalium carbonicum (p. 2595·2); pulsatilla pratensis (p. 2600·2); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

Homeocare Digesto *Timm, Neth.*
Chamomilla (p. 2474·1); colocynthis (p. 1833·3); cuprum metallicum (p. 2057·1); nux vomica (p. 2573·3); veratrum album (p. 2644·3).
Formerly known as Homeocare digestie.
Homoeopathic preparation.

Homeocare Exercito *Timm, Neth.*
Colchicum autumnale; rhus toxicodendron (p. 2603·3); ledum palustre (p. 2550·1); dulcamara (p. 2497·3); symphytum officinale (p. 2484·2); bryonia alba.
Formerly known as Homeocare beweging.
Homoeopathic preparation.

Homeocare keelspray *Timm, Neth.*
Baryta carbonica (p. 2452·2); apis mellifica (p. 2445·2); belladonna (p. 2453·3); chamomilla (p. 2474·1); phytolacca decandra (p. 2593·2); plantago major (p. 2592·3).
Homoeopathic preparation.

Homeocare Nervo *Timm, Neth.*
Cuprum aceticum (p. 2486·2); cyclamen europaeum (p. 2490·2); gelsemium sempervirens (p. 2511·2); hypericum perforatum (p. 449·1); passiflora incarnata (p. 2584·1); sepia officinalis (p. 2613·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Homeocare neusspray *Timm, Neth.*
Ambra grisea (p. 2440·3); euphorbia resinifera; luffa operculata (p. 2545·3); pulsatilla pratensis (p. 2600·2); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Homeocare Revito *Timm, Neth.*
Aconitum napellus (p. 2428·3); echinacea purpurea (p. 2498·1); eupatorium perfoliatum (p. 2459·1); lachesis mutus (p. 2538·3); phytolacca decandra (p. 2593·2); sulfur (p. 1721·1).
Formerly known as Homeocare weerstand.
Homoeopathic preparation.

Homeocare siroop *Timm, Neth.*
Aralia racemosa; bryonia alba; drosera rotundifolia (p. 2497·2); ipecacuanha (p. 1667·2); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Homeocare Uro *Timm, Neth.*
Berberis vulgaris (p. 2502·1); cantharis vesicatoria; petroselinum crispum (p. 2583·3); phytolacca decandra (p. 2593·2); populus tremuloides (p. 2450·3); solidago virgaurea (p. 2620·1).
Formerly known as Homeocare urinewegen.
Homoeopathic preparation.

Homeocare Vasco *Timm, Neth.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); hamamelis virginiana (p. 2523·3); secale cornutum (p. 2137·1); nux vomica (p. 2573·3).
Formerly known as Homeocare doorbloeding.
Homoeopathic preparation.

Homeocoksinum *Homeocan, Canad.*
Anas barbariae hepatis et cordis (p. 2444·1).
Homoeopathic preparation.

Homeodel 15 *Homeodel, Canad.†*
Alnus glutinosa; betula alba (p. 2457·3); euphrasia officinalis (p. 2502·1); histamine (p. 2525·2); onion (p. 2575·2); populus tremula, flos (p. 2450·3); quercus robur (p. 2574·1); sabadilla (p. 2611·2); salix alba (p. 129·2); sambucus nigra (p. 2609·3); ulmus procera flos.
Homoeopathic preparation.

Homeodel 21 *Homeodel, Canad.†*
Hydrastis canadensis (p. 2528·1); onion (p. 2575·2); potassium dichromate (p. 2476·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Homéodent *Boiron, Port.†*
Calendula officinalis (p. 2465·2); plantago major (p. 2592·3); cochlearia armoracia (p. 2526·1); hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Homéodose 8 *Boiron, Fr.†*
Kreosotum (p. 1659·3); asa foetida (p. 2449·3); sticta pulmonaria (p. 2546·1); aurum muriaticum (p. 2521·1); kalii dichromas (p. 2476·3).
Homoeopathic preparation.

Homéodose 20 *Boiron, Fr.†*
Hamamelis virginiana (p. 2523·3); pulsatilla (p. 2600·2); aesculus hippocastanum (p. 2431·2); carduus marianus (p. 1561·1); calcarea fluorica (p. 2053·1).
Homoeopathic preparation.

Homéodose 24 *Boiron, Fr.†*
Ulmus campestris; arctium lappa (p. 2540·1); viola tricolor (p. 2647·3); mercurius solubilis (p. 2555·3); lycopodium (p. 2546·3).
Homoeopathic preparation.

Homeo-Form I *Homeocan, Canad.†*
Cupric acetate (p. 2486·2); hyoscyamus niger (p. 2530·2); oats (p. 2451·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Homoeopathic preparation.

Homeo-Form AL *Homeocan, Canad.†*
Aralia racemosa; copper (p. 2057·1); onion (p. 2575·2); sabadilla (p. 2611·2); sticta pulmonaria (p. 2546·1).
Homoeopathic preparation.

Homeo-Form AR *Homeocan, Canad.†*
Apis mellifica (p. 2445·2); arnica montana (p. 2447·2); benzoic acid (p. 1738·2); colchicum (p. 607·1); causticum (p. 2595·3); sodium carbonate anhydrous (p. 2617·3).
Homoeopathic preparation.

Homeo-Form C *Homeocan, Canad.†*
Baptisia tinctoria (p. 2647·2); bryonia (p. 2461·3); echinacea angustifolia (p. 2498·1); mistletoe (p. 2560·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Homeo-Form CA *Homeocan, Canad.†*
Coffea tosta (p. 2648·2); delphinium staphisagria; gelsemium sempervirens (p. 2511·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Homeo-Form CO *Homeocan, Canad.†*
Aluminium oxide (p. 1690·3); croton oil (p. 42·3); magnesium carbonate (p. 1856·2); silver nitrate (p. 2615·3).
Homoeopathic preparation.

Homeo-Form F *Homeocan, Canad.†*
⊗Alfalfa (p. 2433·1); oats (p. 2451·1); phosphoric acid (p. 2589·1); phosphorus (p. 2589·2); selenium (p. 2086·3); vitex agnus castus (p. 2432·2).
Homoeopathic preparation.

Homeo-Form G *Homeocan, Canad.†*
Bryonia (p. 2461·3); ipecac (p. 1667·2); pulsatilla (p. 2600·2); robinia pseudoacacia; sulfur (p. 1721·1).
Homoeopathic preparation.

Homeo-Form M *Homeocan, Canad.†*
Gelsemium sempervirens (p. 2511·2); phosphoric acid (p. 2589·1); picric acid (p. 2634·2); valerian (p. 2640·2).
Homoeopathic preparation.

Homeo-Form ME *Homeocan, Canad.†*
Bryonia (p. 2461·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Homeo-Form MI *Homeocan, Canad.†*
Aluminum oxide (p. 1690·3); antimony trisulfide (p. 2445·1); cyclamen europaeum (p. 2490·2); lycopodium clavatum (p. 2547·1); melilot (p. 2552·3); nitroglycerin (p. 1391·2); silver nitrate (p. 2615·3).
Homoeopathic preparation.

Homeo-Form P *Homeocan, Canad.†*
Alfalfa (p. 2433·1); lactic acid (p. 2539·1); oyster shells (p. 1824·3); rubia tinctorum; silicon dioxide (p. 2208·3); sodium sulfate (p. 1888·1).
Homoeopathic preparation.

Homeo-Form PMT *Homeocan, Canad.†*
Cimicifuga racemosa (p. 2478·1); hydrastis canadensis (p. 2528·1); hyoscyamus niger (p. 2530·2); lycopodium clavatum (p. 2547·1); nitric acid (p. 2572·3); sabina.
Homoeopathic preparation.

Homeo-Form R *Homeocan, Canad.†*
Belladonna (p. 2453·3); drosera rotundifolia (p. 2497·2); ipecac (p. 1667·2); potassium dichromate (p. 2476·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Homeo-Form S *Homeocan, Canad.†*
Alder buckthorn (p. 1843·3); fucus vesiculosus (p. 2612·1); potassium iodide (p. 2336·3).
Homoeopathic preparation.

Homeo-Form Sl *Homeocan, Canad.†*
Calcium sulfide crude (p. 1721·3); euphrasia officinalis (p. 2502·1); hydrastis canadensis (p. 2528·1); onion (p. 2575·2); sticta pulmonaria (p. 2546·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Homeo-Form ST *Homeocan, Canad.†*
Asafetida (p. 2449·3); oats (p. 2451·1); silver nitrate (p. 2615·3); valerian (p. 2640·2).
Homoeopathic preparation.

Homeo-Form T *Homeocan, Canad.†*
⊗Delphinium staphisagria; lobelia inflata (p. 2323·2); magnesium phosphate dibasic (p. 1786·3); thuja occidentalis (p. 2629·3); tobacco (p. 2632·2).
Homoeopathic preparation.

Homéofortil *Boiron, Fr.†*
Sarcolacticum acidum (p. 2539·1); arnica montana (p. 2447·2); solidago virga aurea (p. 2620·1); ruta graveolens (p. 2608·2); cuprum metallicum (p. 2057·1).
Homoeopathic preparation.

Homéogéne 9 *Boiron, Cz.*
Hydrargyri aminochloridum (p. 1711·2); pulsatilla pratensis (p. 2600·2); euspongia officinalis; bryonia (p. 2461·3); bromum (p. 2461·2); belladonna (p. 2453·3); phytolacca decandra (p. 2593·2); arum triphyllum; arnica montana (p. 2447·2).
Homoeopathic preparation.

Homéogène 9 *Boiron, Fr.; Boiron, Port.*
Mercurius solubilis (p. 2555·3); anemone pulsatilla (p. 2600·2); spongia tosta; bryonia (p. 2461·3); bromum (p. 2461·2); atropa belladonna (p. 2453·3); phytolacca (p. 2593·2); arum triphyllum; arnica (p. 2447·2).
Homoeopathic preparation.

Boiron, Switz.
Arnica montana (p. 2447·2); atropa belladonna (p. 2453·3); arum triphyllum; bromum (p. 2461·2); bryonia cretica; euspongia officinalis; mercurius solubilis hahnemanni (p. 2555·3); phytolacca americana (p. 2593·2); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Homeogene 9 *Boiron, Hung.*
Arum triphyllum; arnica montana (p. 2447·2); bromum (p. 2461·2); spongia tosta; atropa belladonna (p. 2453·3); mercuris solubilis (p. 2555·3); pulsatilla vulgaris (p. 2600·2); phytolacca decandra (p. 2593·2); bryonia dioica (p. 2461·3).
Homoeopathic preparation.

Boiron, Neth.†
Mercurius solubilis (p. 2555·3); pulsatilla vulgaris (p. 2600·2); spongia tosta; bryonia alba; bromium (p. 2461·2); belladonna (p. 2453·3); phytolacca decandra (p. 2593·2); arum triphyllum; arnica montana (p. 2447·2).
Homoeopathic preparation.

Homéogène 14 *Boiron, Fr.†*
Antimonium tartaricum (p. 151·2); bryonia (p. 2461·3); crataegus oxyacantha (p. 2488·1); drosera (p. 2497·2); ipeca (p. 1667·2).
Homoeopathic preparation.

Homéogène 21 *Boiron, Fr.†*
Cocculus (p. 2483·1); tabacum (p. 2632·2); nux vomica (p. 2573·3).
Homoeopathic preparation.

Homéogène 22 *Boiron, Fr.†*
Aloe (p. 1816·1); cinchona (p. 2478·3); cynara scolymus (p. 2490·3); hydrastis (p. 2528·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Homéogène 41 *Boiron, Fr.†*
Arnica montana (p. 2447·2); anemone pulsatilla (p. 2600·2); solanum dulcamara (p. 2497·3); rhus toxicodendron (p. 2603·3); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Homéogène 46 *Boiron, Canad.; Boiron, Fr.*
Ballota foetida; hyoscyamus niger (p. 2530·2); nux moschata (p. 2573·1); passiflora (p. 2584·1); stramonium (p. 2622·3).
Homoeopathic preparation.

Homéogrippe *Boiron, Fr.†*
Aconitum napellus (p. 2428·3); antimonium tartaricum (p. 151·2); atropa belladonna (p. 2453·3); ipecacuanha (p. 1667·2); solanum dulcamara (p. 2497·3); bryonia dioica (p. 2461·3).
Homoeopathic preparation.

Homeoknop Bioactiv O Weight Loss Aid *Knop, Canad.†*
Antimony trisulfide (p. 2445·1); coffee (p. 2648·2); sodium chloride (p. 1795·1).
Homoeopathic preparation.

Homeoknop Ikoplex 13 *Knop, Canad.†*
Goldenrod (p. 2620·1); potassium chloride (p. 1793·2); potassium phosphate, dibasic (p. 1791·1); sodium chloride (p. 1795·1); sodium sulfate (p. 1888·1).
Homoeopathic preparation.

Homéomunil *Boiron, Fr.*
Influenzinum (p. 2393·3).
Homoeopathic preparation.

Homéoplasmine *Boiron, Canad.; Boiron, Fr.*
Acidum boricum (p. 2459·3); bryonia alba (p. 2461·3); calendula officinalis (p. 2465·2); phytolacca decandra (p. 2593·2); benzoinum (p. 2614·3).
Homoeopathic preparation; skin irritation.

Boiron, Switz.
Benzoe (p. 2614·3); bryonia cretica; calendula officinalis (p. 2465·2); phytolacca americana (p. 2593·2).
Homoeopathic preparation.

Boiron, Port.†
Calendula officinalis (p. 2465·2); phytolacca decandra (p. 2593·2); bryonia dioica (p. 2461·3); benzoe (p. 2614·3).
Homoeopathic preparation.

Homéoptic *Boiron, Fr.*
Euphrasia officinalis (p. 2502·1); calendula officinalis (p. 2465·2); magnesia carbonica (p. 1856·2).
Homoeopathic preparation.

Homeoptic *Boiron, Neth.†*
Calendula officinalis (p. 2465·2); euphrasia officinalis (p. 2502·1); magnesium carbonicum (p. 1856·2).
Homoeopathic preparation.

Homeo-S-Asp *Delano, Canad.*
Arnica montana (p. 2447·2); dulcamara (p. 2497·3); euphrasia officinalis (p. 2502·1); silicon dioxide (p. 2208·3); zinc oxide (p. 1729·1).
Homoeopathic preparation.

Homeostres *Boiron, Rus.*
Aconitum napellus (p. 2428·3); belladonna (p. 2453·3); calendulae officinalis (p. 2465·2); chelidonium majus (p. 2522·2); jequirity (p. 2426·1); viburnum opulus.
Homoeopathic preparation.

Homéovox *Boiron, Canad.; Boiron, Fr.*
Aconitum napellus (p. 2428·3); arum triphyllum; belladonna (p. 2453·3); bryonia (p. 2461·3); calendula officinalis (p. 2465·2); ferrum phosphoricum (p. 2077·1); hepar sulphur (p. 1721·3); kalium bichromicum (p. 2476·3); mercurius solubilis (p. 2555·3); populus candicans; spongia tosta.
Homoeopathic preparation.

Homeovox *Boiron, Cz.*
Aconitum napellus (p. 2428·3); arum triphyllum; ferrum phosphoricum (p. 2077·1); calendula officinalis (p. 2465·2); euspongia officinalis; belladonna (p. 2453·3); hydrargyri aminochloridum (p. 1711·2); calcii sulfidum (p. 1721·3); kalii dichromas (p. 2476·3); populus candicans; bryonia (p. 2461·3).
Homoeopathic preparation.

Boiron, Hung.; Boiron, Port.; Boiron, Rus.; Boiron, Ukr.
Aconitum napellus (p. 2428·3); arum triphyllum; calendula officinalis (p. 2465·2); spongia tosta; ferrum phosphoricum (p. 2077·1); atropa belladonna (p. 2453·3); mercuris solubilis (p. 2555·3); hepar sulphuris calcareum (p. 1721·3); kalium bichromicum (p. 2476·3); populus candicans; bryonia dioica (p. 2461·3).
Homoeopathic preparation.

Boiron, Neth.
Aconitum napellus (p. 2428·3); arum triphyllum; ferrum phosphoricum (p. 2077·1); calendula officinalis (p. 2465·2); spongia tosta;

mercurius solubilis (p. 2555·3); hepar sulphur (p. 1721·3); kalium bichromicum (p. 2476·3); populus candicans; belladonna (p. 2453·3); bryonia alba.
Homoeopathic preparation.

Boiron, Switz.
Aconitum napellus (p. 2428·3); arum triphyllum; atropa belladonna (p. 2453·3); bryonia cretica; euspongia officinalis; ferri phosphas (p. 2077·1); hepar sulfuris (p. 1721·3); kalii dichromas (p. 2476·3).
Homoeopathic preparation.

Homer *SoSe, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Homex *Adley, India.*
Hyprolose (p. 2189·1).
Dry eyes.

Homide *Indoco, India.*
Homatropine hydrobromide (p. 2007·3).

Hominex *Ross, USA.*
A range of methionine-free preparations for enteral nutrition including an infant feed.
Vitamin B_6-nonresponsive homocystinuria or hypermethioninaemia.

Homme-F *Aus Biomed, Austral.*
Levocarnitine tartrate (p. 2053·2); acetyllevocarnitine hydrochloride; ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); *d*-alpha tocoferil acid succinate (p. 2119·2); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); sodium selenate (p. 2087·1); zinc amino acid chelate (p. 2048·3); lycopene (p. 2546·2); ubidecarenone (p. 2637·1); camellia sinensis; grape (p. 2521·3); bovine whey (p. 2125·2).
Dietary supplement for men.

Homocalmefyba *Northia, Arg.*
Piroxicam (p. 125·3).
Inflammation.

Homocisteon Compuesto *Purissimus, Arg.*
⊗Amylase (p. 2442·1); papain (p. 2582·3); pancrelipase (p. 2580·1); cysteine (p. 2058·3); vitamin B substances (p. 2102·3).
Digestive disorders; pancreatic insufficiency.

Homoclomin *Eisai, Hong Kong; Eisai, Indon.; Eisai, Jpn; Eisai, Thai.†*
Homochlorcyclizine hydrochloride (p. 630·2).
Allergic rhinitis; pruritus; urticaria.

Homocyst *Ordain, India.*
Choline bitartrate (p. 2055·2); vitamin B substances (p. 2102·3); betaine (p. 2456·1).

Homoderma *Brauer, Austral.*
Arsen. alb. (p. 2448·1); calendula (p. 2465·2); clematis recta; graphites (p. 2522·1); lycopodium (p. 2546·3); mezereum; sepia (p. 2613·1); rhus tox. (p. 2603·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Homogrin *Grin, Mex.*
Homatropine hydrobromide (p. 2007·3).
Production of mydriasis and cycloplegia; uveitis.

Homoxid *Anglo-French Drugs, India.*
Vitamins; selenium (p. 2086·3).

Homtamin-G Plus *Korea United, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3); aloe; lecithin (p. 2542·2).
Tonic.

Homvioartrin *Homviora, Ger.*
Ledum palustre (p. 2550·1); bryonia cretica; phytolacca americana (p. 2593·2); guaiacum (p. 2523·1).
Homoeopathic preparation.

Homviocorin *Homviora, Austria.*
Adonis vernalis (p. 2431·1); convallaria majalis (p. 2486·2); crataegus (p. 2488·1); scilla (p. 1677·3).
Homoeopathic preparation.

Homviocorin spezial *Homviora, Ger.*
Glonoinum (p. 1391·2); convallaria majalis (p. 2486·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Homviocorin-N *Homviora, Ukr.*
Adonidis vernalis (p. 2431·1); scilla (p. 1677·3); solidago virgaurea (p. 2620·1); convallaria majallis (p. 2486·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Homvio-Em *Homviora, Ger.*
Apomorphinum hydrochloricum (p. 892·3); cocculus (p. 2483·1).
Homoeopathic preparation.

Homviohepan *Homviora, Ger.*
Chelidonium majus (p. 2522·2); dioscorea villosa (p. 2648·1); magnesium sulfuricum (p. 1787·3); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Homvio-Nervin *Homviora, Ukr.*
Sepia (p. 2613·1); ambra (p. 2440·3); hyoscyamus (p. 2530·2); ignatia (p. 2532·1).
Homoeopathic preparation.

Homvio-Prostan *Homviora, Ukr.*
Pareira brava; populus tremuloides (p. 2450·3); sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Homvio-Reuman *Homviora, Ukr.*
Colchicum (p. 607·1); actaea (p. 2478·1); spiraea ulmaria (p. 2550·2); bryonia (p. 2461·3); ruta (p. 2608·2).
Homoeopathic preparation.

Homvio-Rin *Homviora, Ger.*
Oral solution: Chondrodendron tomentosum; populus tremuloides (p. 2450·3); sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Homviora, Ger.
Tablets: Populus tremuloides (p. 2450·3).
Homoeopathic preparation.

Homviotensin *Homviora, Austria; Homviora, Ukr.*
Reserpinum (p. 1485·3); rauwolfia serpentina (p. 1485·1); viscum album (p. 2560·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Homviora, Ger.
Cactus (p. 2473·2); viscum album (p. 2560·2); rauwolfia (p. 1485·1); crataegus (p. 2488·1).
Homoeopathic preparation.

Hondra-Syla *Farmak, Ukr.*
Capsules: Chondroitin sulfate (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Degenerative joint disorders.

Farmak, Ukr.
Ointment: Chondroitin sulfate sodium (p. 2476·1).
Degenerative joint disorders.

Hondrea *Alkem, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; sickle-cell disease; essential thrombocythaemia.

Hondrofen *Biosintez, Rus.*
Diclofenac sodium (p. 48·3); chondroitin sulfate sodium (p. 2476·1); dimethyl sulfoxide (p. 2182·2).
Musculoskeletal, joint, and soft-tissue disorders.

H-One *Terramedic, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Honey Blend Herbal Cough Syrup *Health 4 All, Canad.*
Honey (p. 2072·1); horehound (p. 1668·3); inula helenium (p. 1662·3); verbascum thapsus (p. 2645·1); wild cherry (p. 2647·2).
Cough.

Honey Herb Cough Drops *Ricola, Canad.†*
Achillea (p. 2427·3); althaea (p. 2438·3); cowslip (p. 2596·2); horehound (p. 1668·3); mallow (p. 2549·2); peppermint (p. 1877·1); burnet saxifrage (p. 2463·1); ribwort plantain (p. 2604·2); sage (p. 2608·3); sambucus (p. 2609·3); thyme (p. 2630·2); veronica officinalis.
Cough.

Honey & Molasses *Lane, UK·*
⊗Ipecacuanha liquid extract (p. 1667·2); marrubium (p. 1668·3); squill vinegar (p. 1677·3); capsicum (p. 2469·3); peppermint oil (p. 1877·1); tolu solution; honey (p. 2072·1); molasses (p. 2096·3); glycerol (p. 2517·2); liquorice (p. 1853·2); anise oil (p. 2444·3).
Coughs.

Honeysip *McW, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Hong Bang *Haobang, China.*
Ozagrel sodium (p. 2579·1).

Hong Fei Kang *Feihong, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Hong Kang Wei *Yi Kang, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Hong Kang Wei Si *Duoburuifei, China.*
Nefopam hydrochloride (p. 100·2).
Pain.

Hong Qiang *Yangtze River, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Hong Tai *Ertong, China.*
Calcium gluconate (p. 1783·3).
Calcium supplement.

Hong Ting *Deyao, China.*
Ethylenediamine diaceturate.

Hong Wei Li Di *Duoburuifei, China.*
Piracetam (p. 393·3).
Mental function impairment.

Hong Xu Guang *Hong Yi, China.*
Fluconazole (p. 578·2).
Fungal infections.

Hong Xu Lai *Hong Yi, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Hong Xu Ming *Hong Yi, China.*
Ligustrazine phosphate.

Hong Xu Yang *Hong Yi, China.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Hong Yi An *Wantong, China.*
Ethylenediamine diaceturate.

Hong Yu Shu *Duoburuifei, China.*
Aminomethylbenzoic acid (p. 1132·2).

Hong Yuan *Shengtai, China.*
Deproteinized calf blood (p. 2444·1).

Hong Yuan Da *Guo Feng, China.*
Polysaccharide-iron complex (p. 2086·2).

Hongal *Ahimsa, Arg.*
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1).
Fungal skin infections.

Hongjidi *Xincat, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Hongosan *Nupel, Spain.†*
⊗Acedoben (p. 2426·2); aluminium chlorohydrate (p. 1694·1); cetrimonium bromide (p. 1742·3); dexamethasone (p. 1630·3); salicylic acid (p. 1719·1).
Fungal skin infections.

Hongoseril *Isdin, Spain.*
Itraconazole (p. 583·3).
Fungal infections.

Honguil *Raymos, Arg.*
Tioconazole (p. 595·3).
Fungal vaginal infections.

Honguil Plus *Raymos, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Honitus *Dabur, India.*
Malabar nut (p. 2549·1); zedoary; shudh honey (p. 2072·1); mentha arvensis; ocimum sanctum; piper nigrum; zingiber officinale.

Honsa *M & H, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus.

Honvan *Baxter, Gr.; Zydus, India.*
Fosfestrol sodium (p. 2279·1).
Prostatic cancer.

Honvol *Baxter, Canad.†*
Fosfestrol sodium (p. 2279·1).
Prostatic cancer.

Honygra *Bennet, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Honzil *Arlex, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Hooky *Neiss, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Hopace *Micro, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Hopace-AM *Micro, India.*
Amlodipine (p. 1304·1); ramipril (p. 1483·3).

Hopace-H *Micro, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Hopaq *Hoe, Philipp.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Skin infections.

Hopecard *Aristo, India.*
Ramipril (p. 1483·3).
Heart failure; hypertension.

Hopecard AM *Aristo, India.*
Amlodipine besilate (p. 1304·1); ramipril (p. 1483·3).

Hopecard H *Aristo, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Hoperam *Zinnia, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Hopram
Note: this name may be used for preparations of different composition.
Arlex, Mex.
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Hops *Millimed, Thai.†*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Horac *Micro, India.*
Betacarotene (p. 2051·1); chromium (p. 2055·3); acetylcysteine (p. 1652·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc oxide (p. 1729·1).

Horacort *Ifarm, Pol.†*
⊗Budesonide (p. 1625·1).
Asthma.

Horamine *Hovid, Singapore.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Hovid, Hong Kong.†
Chlorphenamine (p. 620·3).

8 Horas *Elea, Arg.*
Eszopiclone (p. 1072·3).
Insomnia.

Horehound and Aniseed Cough Mixture *Potter's, UK.*
⊗Pleurisy root (p. 2593·2); elecampane (p. 1662·3); horehound (p. 1668·3); skunk cabbage (p. 2617·1); lobelia (p. 2323·2).
Coughs.

Horehound Plus Cough Syrup *Brooke Green, UK; English Herbal Medicines, UK.*
Pleurisy root (p. 2593·2); elecampane (p. 1662·3); marrubium (p. 1668·3); skunk cabbage (p. 2617·1); lobelia inflata.
Cough.

Horestyl *Kleva, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Horex *Exakta, Mex.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Horf *YSP, Malaysia; Yung Shin, Singapore.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Horizant *GSK, USA.*
Gabapentin enacarbil (p. 524·1).
Restless legs syndrome; postherpetic neuralgia.

Hormeel H *Heel, Neth.*
Cyclamen europaeum (p. 2490·2); pulsatilla pratensis (p. 2600·2); sepia officinalis (p. 2613·1); viburnum opulus.
Homoeopathic preparation.

Hormeel S *Heel, Cz.*
Acidum nitricum (p. 2572·3); moschus (p. 2198·2); sepia officinalis (p. 2613·1); cyclamen europaeum (p. 2490·2); strychnos ignatii (p. 2532·1); capsella bursa-pastoris (p. 2614·2); senecio nemorensis ssp. fuchsii (p. 2612·3); erigeron canadensis; viburnum opulus; pulsatilla pratensis (p. 2600·2); cypripedium pubescens; myristica fragrans (p. 2573·1); calcii carbonas (p. 1824·3); aquilegia vulgaris; origanum majorana (p. 2550·1).
Homoeopathic preparation.

Peithner, Hung.
Acidum nitricum (p. 2572·3); moschus moschiferus (p. 2198·2); cyclamen europaeum (p. 2490·2); strychnos ignatii (p. 2532·1); capsella bursa-pastoris (p. 2614·2); cypripedium calceolus var. pubescens; myristica fragrans (p. 2573·1); senecio

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

nemorensis ssp. fuchsii (p. 2612·3); conyza canadensis; viburnum opulus; pulsatilla pratensis (p. 2600·2); aquilegia vulgaris; origanum marjorana (p. 2550·1); calcium carbonicum (p. 1824·3); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

Hormeel SN *Heel, Rus.*
Acidum nitricum (p. 2572·3); aquilegia vulgaris; calcium carbonicum (p. 1824·3); conyza canadensis; cyclamen purpurascens (p. 2490·2); myristica fragrans (p. 2573·1); origanum majorana (p. 2550·1); pulsatilla pratensis (p. 2600·2); sepia officinalis (p. 2613·1); strychnos ignatii (p. 2532·1); viburnum opulus.
Homoeopathic preparation.

Hormocervix
Note: this name may be used for preparations of different composition.
MilletRoux, Braz.
Estriol (p. 2274·3).
Vulvovaginal disorders.

Hormodausse *Sandoz, Canad.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Hormodiol *Omega, Arg.*
Estradiol (p. 2271·1).
Menopausal disorders.

Hormodose *Farmasa, Braz.*
Estradiol (p. 2271·1).
Menopausal disorders.

Hormogel *Silesia, Chile.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Hormolax *Hormona, Mex.†*
Ispaghula (p. 1849·1).
Constipation.

Hormonin *Shire, Hong Kong†; Amdipharm, UK.*
Estriol (p. 2274·3); estradiol (p. 2271·1); estrone (p. 2275·2).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Hormoniol *Teuto, Braz.*
Estriol (p. 2274·3).
Menopausal disorders.

Hormoral *Silesia, Chile.*
Progesterone (p. 2300·2).
Menstrual disorders; menopausal disorders; benign breast disorders.

Hormoskin *Germed, Braz.*
⊗Fluocinolone acetonide (p. 1636·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).

Hormotrop *Bergamo, Braz.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome.

Horn *Dey's, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Hornel *Taisho, Jpn.*
Falecalcitriol (p. 2113·3).
Hyperparathyroidism; osteomalacia; rickets.

Horosten *Yuriya-Farm, Ukr.*
Decamethoxine (p. 1749·2).
Disinfection of skin, bedsores, and wounds; skin infections.

Horpeg *Cubit, India.*
Progesterone (p. 2300·2).
Dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Horphagen uno *Strathmann, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Horsechestnut Complex *Mediherb, Austral.*
Butcher's broom (p. 2463·1); aesculus (p. 2431·2); ginkgo biloba (p. 2512·3).
Vascular disorders.

Horsulin *Terramedic, Philipp.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Hosboral *Quimifar, Spain.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hosedyl DM *Hovid, Malaysia.*
Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

Hosiclav *Hos & Ins, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Hosicort *Hos & Ins, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Hosik *Hos & Ins, India.*
Amikacin (p. 214·1).
Bacterial infections.

Hosit *Emcure, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Hosit Plus *Windlas, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Hosither *Hos & Ins, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Hosit-L *Emcure, India.*
Levocarnitine (p. 2053·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Hosizone *Hos & Ins, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Hoslin *Hos & Ins, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Hosliv *Hos & Ins, India.*
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).

Hosolvan DM *Hovid, Malaysia.*
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Hosolvon *Hovid, Singapore.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Hovid, Hong Kong.†
Bromhexine (p. 1656·3).

Hospasol *Gambro, Fr.; Gambro, Neth.; Gambro, Port.; Gambro, Spain.*
Sodium bicarbonate (p. 1781·1).
Haemodialysis; haemofiltration.

Hospidermin *Lysoform, Ger.*
⊗Alcohol (p. 1733·1); potassium thiocyanate; 5-chloro-2-hydroxybenzoic acid.
Skin disinfection.

Hospisept *Lysoform, Ger.*
⊗Propyl alcohol (p. 1768·1); alcohol (p. 1733·1).
Hand disinfection; skin disinfection.

Hospital Skin Care Lotion *Smith & Nephew, Austral.*
Dimeticone (p. 2209·3).
Barrier preparation; dry skin.

Hostacortin H *Sanofi-Aventis, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Hostacyclin *Sanofi-Aventis, Gr.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Hostacycline *Sanofi-Aventis, India.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Hostan *Hovid, Hong Kong†; Hovid, Singapore.*
Mefenamic acid (p. 85·3).
Pain; inflammation; musculoskeletal and joint disorders.

Hosterona *Craveri, Arg.*
Progesterone (p. 2300·2); estradiol hemisuccinate (p. 2271·1).
Menstrual disorders.

Hot Coldrex *GSK Consumer, Neth.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Hot Flush & Menopause Relief *Brauer, Austral.; Brauer, Austral.*
Belladonna (p. 2453·3); lachesis (p. 2538·3); sepia (p. 2613·1); pulsatilla (p. 2600·2); amyl nitrosum (p. 1540·2); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Hot Ize *ANB, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); cineole (p. 2479·1); cajuput oil (p. 2464·1); peppermint oil (p. 1877·1).
Musculoskeletal, joint, and soft-tissue disorders.

Hot Lemon *Prodemdis, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).

Hot Lemon Cough and Colds Relief DM *Jamp, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).

Hot Lemon Relief *Apotex, Canad.; Jamp, Canad.*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).

Hot Lemon Relief for Symptoms of Cold and Flu *Pharmetics, Canad.*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Hot Lemon Relief for Symptoms of Cough and Cold *Pharmetics, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).

Hot Lemon Relief for Symptoms of Cough, Cold & Flu *Pharmetics, Canad.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Hot Stuff *Mueller, Canad.†*
Capsicum oleoresin (p. 2469·3); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).

Hotemin *Egis, Cz.; Egis, Hung.; Egis, Pol.†*
Piroxicam (p. 125·3).
Peri-articular and soft-tissue disorders; gout; inflammation; musculoskeletal and joint disorders; pain.

Hou Ding Nuo *Xianju, China.*
Mifepristone (p. 2138·1).
Termination of pregnancy; postcoital oral contraceptive.

Hou Pu *Wei Kang, China.*
Lomerizine hydrochloride (p. 676·3).

12 Hour Antihistamine Nasal Decongestant *URL, USA.*
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

12 Hour Cold
Note: this name may be used for preparations of different composition.
Goldline, USA.
⊗Pseudoephedrine sulfate (p. 1676·1); dexbrompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Hova *Novartis Consumer, Austria; Gebro, Cz.; Gebro, Hung.; Biofarm, Pol.; Gebro, Switz.*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders; anxiety disorders.

Hova Expectorant *Hovid, Singapore.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).

Hovalin *AstraZeneca, Gr.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia.

Hovasc *Hovid, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Hovicor *Hovid, Philipp.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hovid Q10 Plus *Hovid, Malaysia.†*
Vitamins; ubidecarenone (p. 2637·1).

Hovid Q-10 SupraBio + L-Carnitine *Hovid, Malaysia.*
Ubidecarenone (p. 2637·1); levocarnitine fumarate (p. 2053·2).
Dietary supplement.

Hovite *Raptakos, India.*
Vitamins; with or without minerals.

Hovizol *Hovid, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hovnizym HM *Pfluger, Ger.*
Crotalus horridus e veneno sicc.; lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Hox Alpha *Strathmann, Ger.*
Urtica (p. 2639·3).
Rheumatic disorders.

Hozen *Biochemix, India.*
Hydroxyzine (p. 630·3).
Pruritus; premedication.

Hoziac *Pierre Fabre Dermatologie, Cz.†*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

H3P *Hydron, Singapore.*
A range of moisturisers with or without sunscreen.
Skin ageing.

HP Kit *Sun, India.*
2 Tablets, amoxicillin (p. 216·2); 2 capsules, omeprazole (p. 1867·2); 2 tablets, tinidazole (p. 949·2).

HPB *Panalab, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

HPB Complex *Thompsons, Canad.†*
Barium chloride (p. 2452·3); gold (p. 2521·1); mistletoe (p. 2560·2); nitroglycerin (p. 1391·2).
Homoeopathic preparation.

HPC Depot *BPL, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

H-Peran *LBS, Thai.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Hp-Pac *Takeda, Canad.*
Capsules, lansoprazole (Prevacid) (p. 1851·3); tablets, clarithromycin (Biaxin) (p. 266·2); capsules, amoxicillin trihydrate (p. 216·2).
Helicobacter pylori-associated peptic ulcer.

HPR Plus *PruGen, USA.*
Emollient.

Hpvir *Geolab, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

HQTor *Torrent, India.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; systemic lupus erythematosus; malaria.

H-R Lubricating Jelly *Wallace, USA.*
Vaginal lubricant.

HR Pedia Kit *Pediatrica, Philipp.*
Oral suspension, rifampicin (p. 350·3) (Rimaped); syrup, isoniazid (p. 311·2), pyridoxine hydrochloride (p. 2105·3) (Comprilex).
Tuberculosis.

H_2RA *Arrow, NZ.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; heartburn; dyspepsia.

H-Rax *Captab, India.*
Hydroxyzine (p. 630·3).
Anxiety; pruritus; premedication.

HRF
Note: this name may be used for preparations of different composition.
GNLD, Austral.
Elecampane (p. 1662·3); urtica (p. 2639·3); thyme (p. 2630·2); sambucus (p. 2609·3); aniseed (p. 2444·2); liquorice (p. 1853·2); bayberry bark (p. 2453·1); chamomile (p. 2474·1).
Dietary supplement; respiratory-system disorders.

Tramedico, Belg.; Intrapharm, Irl.; Tramedico, Neth.†; Intrapharm, UK.
⊗Gonadorelin hydrochloride (p. 2280·3).
Test of pituitary function; anovulatory infertility; test of hypothalamic function; sterility or delayed puberty due to hypogonadotrophic hypogonadism.

Akromed, S.Afr.†
⊗Gonadorelin (p. 2280·2).
Diagnostic aid; anovulatory infertility.

HRI Calm Life *Jessup, UK.*
Jamaica dogwood (p. 2536·3); lupulus (p. 2546·1); skullcap (p. 2617·1); chamomile (p. 2474·1); valerian (p. 2640·2).
Restlessness; irritability.

HRI Clear Complexion *Jessup, UK.*
Sarsaparilla (p. 2610·3); iris versicolor (p. 2534·3); lappa (p. 2540·1).
Skin disorders.

HRI Golden Seal Digestive *Jessup, UK.*
Ginger (p. 1844·1); myrrh (p. 2566·1); hydrastis (p. 2528·1); rhubarb (p. 1884·2); valerian (p. 2640·2).
Dyspepsia; flatulence.

HRI Good Mood *Herbal Research, UK.*
St John's wort (p. 449·1).
Anxiety; low mood.

HRI Night *Jessup, UK.*
Valerian (p. 2640·2); passion flower (p. 2584·1); wild lettuce (p. 2647·3); vervain (p. 2645·1); lupulus (p. 2546·1).
Insomnia.

HRI Water Balance *Jessup, UK.*
Taraxacum (p. 2625·3); buchu (p. 2461·3); parsley piert (p. 2584·1); bearberry (p. 2453·2).
Water retention.

HRIG *Cadila, India.*
A rabies immunoglobulin (human) (p. 2413·1).
Passive immunisation.

HRx *Julphar, UAE.*
Lubricant.

HRZ Pedia Kit *Pediatrica, Philipp.*
Oral suspension, rifampicin (p. 350·3) (Rimaped); syrup, isoniazid (p. 311·2), pyridoxine hydrochloride (p. 2105·3) (Comprilex); oral suspension, pyrazinamide (p. 345·2) (Zinaplex).
Tuberculosis.

HS *Blubell, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

HSN *Nutrilite, Arg.*
Collagen (p. 2483·2); ascorbic acid (p. 2110·3); acerola; grape seed (p. 2521·3); cystine (p. 2059·1); biotin (p. 2052·2).
Dietary supplement.

HSN Formula *Jamieson, Canad.†*
Vitamins; minerals.

H-Stat *Psyco Remedies, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

HT *Genesis, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

H-Tab *Pharmaland, Thai.*
Haloperidol (p. 1077·1).
Psychoses; mania; hypomania.

Hu Chuan *Double-Crane, China.*
Fructose (p. 2068·2).

Hu Er Xing *Zhongxing Hanfang, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Hu Fei Te *Xinganjiang, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Hu Gu *Double-Crane, China.*
Lincomycin hydrochloride (p. 317·1).
Anaerobic bacterial infections.

Hu Kang *Yangtze River, China.*
Fleroxacin (p. 298·3).

Hu Qi *Xinzhongzheng, China.*
Fluconazole (p. 578·2).
Fungal infections.

Hu Tai *Hejigong, China.*
⊗Naphazoline (p. 1669·3).

Hu Tian Bao *Tongyong, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Hu Yue *Yao Wang, China.*
Inosine (p. 2533·1).

Hua Di *Youhua, China.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Hua An Mai *Hua Lu, China.*
Sodium ferulate.

Hua Chang *YiHua, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Hua Er Fu *Huajin, China.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections.

Hua Er Ling *Chung-Hwa, China.*
⊗Paracetamol (p. 115·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Hua Jie Wei *Hua Lu, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Hua Jin *Lukang Chenxin, China.*
Biapenem (p. 231·1).

Hua Kang Da *Hua Lu, China.*
Fluorouracil (p. 795·2).

Hua Ke *Huaxin, China.*
Propiverine hydrochloride (p. 2363·1).
Neurogenic bladder; idiopathic detrusor instability.

Hua Ke Bi *Chung-Hwa, China.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).

Hua Mai Tong *Hua Lu, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Hua Na Fu *Huana, China.*
Colloidal bismuth pectin.

Hua Pu Le *Hua Lu, China.*
Omacetaxine mepesuccinate (p. 837·3).

Hua Qu *Qi Du, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Hua Le Sha *Huanan, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Hua Shi *Yi Hua, China.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Hua Shi Ai Er *Hua Lu, China.*
Arginine hydrochloride (p. 2049·1).

Hua Shi Xin *Hua Lu, China.*
Fluconazole (p. 578·2).
Fungal infections.

Hua Shuang Jie *Gaitianli, China.*
Nimesulide (p. 101·3).
Pain.

Hua Xian Mei *Huazhong, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Hua Xin *Tiantian, China.*
Flunarizine hydrochloride (p. 629·3).

Hua Yi *Huazhong, China.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).

Hua Yi Mai *Hua Lu, China.*
Ozagrel sodium (p. 2579·1).

Huafen *Cuccess, China; Cuccess, China.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Huan Er Bo *Si Huan, China.*
⊗Erythropoietin (recombinant, human) (p. 1141·1).
Anaemias; autologous blood transfusion.

Huan Tong *Lunan, China.*
Ligustrazine hydrochloride.

Huang Xing Yun Shu *Yun Feng, China.*
Nimesulide (p. 101·3).
Pain.

Huanli *Twinluck, China.*
Ciclopirox (p. 575·3).
Superficial fungal infections.

Huanshifen *United Lab, China.*
Ibuprofen (p. 68·2).
Pain; fever.

Huaren XinShu *Huaren, China.*
Isosorbide mononitrate (p. 1413·3).

Huashu *Huajin, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Huato Pills *Dao-Pharm, Ukr.*
Ginseng (p. 2513·3); lycium chinense; ophiopogon japonicus; gentiana macrophylla; dong quai (p. 2497·1); angelica dahurica (p. 2443·3); ligusticum sinense; chinese cinnamon (p. 2471·3); evodia; sophora japonica; honey (p. 2072·1); activated charcoal (p. 1537·3).
Cerebral ischaemia.

Huayu *Huajin, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Huber *Helm, Port.†*
Paracetamol (p. 115·1).
Pain; fever.

Huberplex *Teofarma, Spain.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; insomnia; alcohol withdrawal syndrome; skeletal muscle spasm.

Huchogon *Biosena, India.*
⊗Chorionic gonadotrophin (p. 2258·1).

Hucog *Bharat, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Huddy-Pe *T Man, Thai.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Hui Le *Jin Lan, China.*
Aceglutamide (p. 2426·2).

Hui Bai Shi *Zhonghui, China.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Hui Bang *Jin Lan, China.*
⊗Terbutaline sulfate (p. 1228·1).
Premature labour; bronchospasm.

Hui Er Ding *HeBei, China.*
Emtricitabine (p. 976·3).
HIV infection.

Hui Fei Shun *Pfizer, China.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Hui Fu De *Kangbao, China.*
Bifonazole (p. 573·3).

Hui He *Meitong, China.*
Metronidazole benzoate (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Hui Ji *Zhonghui, China.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Hui Jie *Qilu, China.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Hui Ke *Wecome, China.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain.

Hui Luo Ping *YuHui, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Hui Min *Tianpu, China.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Hui Ning *Pacific, China.*
Zaleplon (p. 1114·3).
Insomnia.

Hui Quan Lin *Kang Yuan, China.*
Potassium sodium dehydroandroandrographolide succinate.

Hui Rui Ke *Hui Ren, China.*
Levofloxacin lactate.
Bacterial infections.

Hui Te Ning *Hanson, China.*
Zaleplon (p. 1114·3).
Insomnia.

Hui Teng *Suzhong, China.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

Hui Ting *Zhonghui, China.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Hui Xin Sha *Hui Ren, China.*
Cefixime (p. 240·3).
Bacterial infections.

Hui Yi Kang *Chengdu Institute, China.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Hui You *Jin Lan, China.*
Gamma-aminobutyric acid (p. 2509·2).

Huile de Bain Therapeutique *Atlas, Canad.*
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2).
Skin disorders.

Huile Gomenolée *Gomenol, Fr.*
Niaouli oil (p. 2569·1).
Nasal disorders.

Huile de millepertuis A. Vogel (huile de St. Jean) *Bioforce, Switz.*
St John's wort (p. 449·1); sunflower oil (p. 2098·1).
Superficial burns and wounds.

Huile Po-Ho A. Vogel *Bioforce, Switz.*
Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); caraway oil (p. 2470·3); fennel oil (p. 2503·3).
Muscular tension; headache; cold symptoms.

Huiliwei *Chengdu Institute, China.*
A varicella-zoster vaccine (p. 2423·3).
Active immunisation.

Huining *Yuanlijian, China.*
Rebamipide (p. 1884·1).
Gastritis; peptic ulcer.

Huiyuan *Zhuoyikangna, China.*
⊗Bumetanide (p. 1329·1).
Oedema; hypertension; renal failure.

Humacain *Teva, Hung.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Humacarpin *Teva, Hung.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Humacart 3/7 *Lilly, Jpn.†*
⊗A mixture of insulin injection (human, prb) and isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Huma-Doxylin *Teva, Hung.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Humafactor-8 *Teva, Hung.*
A factor VIII preparation (p. 1148·1).
Factor VIII deficiency; haemophilia A.

Humafactor-9 *Teva, Hung.*
A factor IX preparation (p. 1149·3).
Factor IX deficiency; haemophilia B.

Huma-Folacid *Teva, Hung.*
Folic acid (p. 2063·1).
Folic acid deficiency.

Humaglobin *Human BioPlazma, Hung.; Teva, Rus.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; passive immunisation; auto-immune disorders; immunodeficiency; immune thrombocytopenia; juvenile rheumatoid arthritis; hypoproteinaemia; Kawasaki disease; Guillain-Barré syndrome.

Humal *Rosch & Handel, Austria.*
Humic acid (p. 2618·3); salicylic acid (p. 1719·1).
Rheumatism.

Humalac A and C *Teva, Hung.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Humalac B *Teva, Hung.*
Hypromellose (p. 2189·2).
Dry eyes.

Humalog *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, India; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
⊗Insulin lispro (p. 475·3).
Diabetes mellitus.

Humalog Basal *Lilly, Cz.; Lilly, Gr.; Lilly, Port.*
⊗Isophane insulin lispro (p. 475·3).
Diabetes mellitus.

Humalog Mix 25 *Lilly, Braz.; Lilly, Chile; Lilly, Indon.; Lilly, Malaysia; Lilly, Mex.; Lilly, Norw.; Lilly, Rus.; Lilly, Singapore; Lilly, Thai.; Lilly, Venez.*
⊗Mixture of insulin lispro 25% and isophane insulin lispro 75% (p. 475·3).
Diabetes mellitus.

Humalog Mix 25 and 50 *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Canad.; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, India; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Neth.; Lilly, NZ; Lilly, Pol.; Lilly, Port.; Lilly, S.Afr.; Lilly, Spain; Lilly, Swed.; Lilly, Turk.; Lilly, UK.*
⊗Mixtures of insulin lispro 25 and 50% and protamine insulin lispro 75 and 50% respectively (p. 475·3).
Diabetes mellitus.

Humalog Mix 75/25 and 50/50 *Lilly, USA.*
⊗Mixtures of isophane insulin lispro 75% and 50% and insulin lispro 25% and 50% respectively (p. 475·3).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Humalog Mix25 and Mix50 *Lilly, Hung.*
⊗Mixtures of insulin lispro 25% and 50% and isophane insulin lispro 75% and 50% respectively (p. 475·3).
Diabetes mellitus.

Humalog NPL *Lilly, Cz.†; Lilly, Gr.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Neth.; Lilly, Pol.; Lilly, Spain.†*
⊗Isophane insulin lispro (p. 475·3).
Diabetes mellitus.

Humamet *Invida, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Human Fastact *USV, India.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Human Insunorm *Glenmark, India.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Human Longact *USV, India.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Human Monotard *Novo Nordisk, India.*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Human Prodica *Sarabhai Piramal, India.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Human Rapidica *Sarabhai Piramal, India.*
⊗Neutral insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Human Rapimix *Sarabhai Piramal, India.*
⊗Biphasic insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Human Zinulin *Sarabhai Piramal, India.*
⊗Insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Humana AR *Humana, Ital.*
Infant feed.
Gastro-oesophageal reflux; regurgitation.

Humana HA *Humana, Ital.*
Infant feed.
Food intolerance.

Humana Sinelac *Humana, Ital.*
Infant feed.
Milk intolerance.

Humana SL *Humana, Pol.*
Infant feed.
Cows' milk allergy; lactose and sucrose intolerance.

Humana z MCT *Humana, Pol.*
Preparation for enteral nutrition.

Humanalbin *CSL, Ger.*
⊗Albumin (p. 1130·2).
Hypovolaemia.

Humanext N *Cadila, India.*
⊗Insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

Humanilusin *Cryopharma, Mex.*
⊗Human insulin (p. 475·3).
Diabetes mellitus.

Human-Mixact *USV, India.*
⊗Mixture of insulin injection (human) 30% and isophane insulin (human) 70% (p. 475·3).
Diabetes mellitus.

Humapen *Lilly, India.*
⊗Insulin injection (p. 475·3).
Diabetes mellitus.

Humapent *Teva, Hung.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of cycloplegia and mydriasis.

Huma-Pronol *Teva, Hung.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; essential tremor; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma; tachycardia.

Humaqua *Teva, Hung.*
Water for injections (p. 2646·3).

Humaspect *Organon Teknika, Gr.†*
Technetium-99m (p. 2228·1) votumumab.

Huma-Spiroton *Teva, Hung.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; hypertension; liver cirrhosis; nephrotic syndrome; oedema.

Humate-P *CSL, Canad.; Aventis, USA.*
A factor VIII preparation (p. 1148·1).
Haemophilia A; von Willebrand's disease.

Humatin *Pfizer, Austria; Erfa, Canad.; Pfizer, Ger.; IFET (ΙΦΕΤ), Gr.; Pfizer, Ital.; Parke, Davis, Spain; Pfizer, Switz.; Parke, Davis, USA.*
Paromomycin sulfate (p. 943·3).
Gastrointestinal bacterial infections; taeniasis; hepatic coma; hepatic encephalopathy; ameobiasis; pre-operative bowel decontamination.

Humatrope *Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong†; Lilly, Hung.; Lilly, India; Lilly, Ital.; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.†; Lilly, Port.; Lilly, Rus.; Lilly, S. Afr.; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner's syndrome; growth disorders in renal failure; Prader-Willi syndrome; SHOX deficiency; short children born small for gestational age; cachexia and wasting in AIDS; short bowel syndrome; idiopathic short stature.

Humavent *WE, USA.*
Guaifenesin (p. 1666·2).

Humax-Alpha-R *Sresan, India.*
Thioctic acid (p. 2629·1); vitamins; trace elements.

Huma-Zolamide *Teva, Hung.*
⊗Acetazolamide (p. 2001·1).
Altitude sickness; epilepsy; glaucoma; oedema.

Humectante *Alcon Cusi, Spain.*
Hypromellose (p. 2189·2); sodium chloride (p. 1795·1).
Dry eyes in contact lens wearers.

Humectante Bucal *Pharmatrix, Arg.*
Carmellose sodium (p. 2175·2); sorbitol (p. 2092·1); electrolytes (p. 1775·1).
Artificial saliva.

Humegon *Organon, Austral.†; Organon, Gr.; Organon, India; Organon, Irl.†; Organon, Turk.; Organon, USA.†*
⊗Menotrophin (p. 2284·1).
Male and female infertility; hypogonadism.

Humenza *Sanofi Pasteur, Fr.†; Sanofi Pasteur, Pol.*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Humer *Urgo, Ukr.*
Sea water (p. 2612·1).
Nasal congestion; nasal hygiene.

Humet-R *Humet, Hung.*
Humic acid (p. 2618·3); potassium (p. 1793·1); magnesium (p. 1786·3); iron (p. 2073·1); zinc (p. 2126·1); manganese (p. 2081·2); copper (p. 2057·1); vanadium; cobalt (p. 2482·2); molybdenum (p. 2082·3); selenium (p. 2086·3).
Dietary supplement; tonic.

Humex
Note: this name may be used for preparations of different composition.
Urgo, Fr.
Eye drops: Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.
Urgo, Belg.†
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Humex Allergie Cetirizine *Urgo, Fr.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Humex Allergie Loratadine *Urgo, Fr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Humex Cold *Urgo, Cz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Humex état Grippal *Urgo, Fr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Humex Expectorant *Urgo, Fr.*
Lozenges: Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.
Urgo, Fr.
Syrup: Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Humex Fournier *Urgo, Fr.*
Benzalkonium chloride (p. 1737·1).
Nasal infections.

Humex Gorge Irritée *Urgo, Fr.†*
Enoxolone (p. 54·2); lidocaine hydrochloride (p. 1988·2); hedge mustard (p. 2524·2); menthol (p. 2553·2).
Sore throat.

Humex Inhaler *Urgo, Fr.*
Inhaler stick: Levomenthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Respiratory-tract congestion.

Humex Mal de Gorge *Urgo, Fr.*
Mouthwash: Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.
Urgo, Fr.
Pastilles: Biclotymol (p. 1740·1).
Mouth and throat disorders.

Humex Nosní *Urgo, Cz.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Humex Pro Děti *Urgo, Cz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Humex Rhinite Allergique *Urgo, Fr.*
⊗Day tablets, pseudoephedrine hydrochloride (p. 1676·1); night tablets, cetirizine hydrochloride (p. 619·2).
Allergic rhinitis.

Humex Rhume *Urgo, Fr.*
⊗Tablets (daytime), paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); capsules (evening), paracetamol; chlorphenamine maleate (p. 620·3).
Cold symptoms.

Humex Rhume des Foins *Urgo, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Humex Toux Sèche Dextromethorphane *Urgo, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Humex Toux Seche Pholcodine *Urgo, Fr.†*
Pholcodine (p. 1675·1).
Cough.

Humibid *Carolina, USA.*
Guaifenesin (p. 1666·2); sulfogaiacol (p. 1678·1).
Formerly contained guaifenesin.
Coughs.

Humibid DM *Carolina, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sulfogaiacol (p. 1678·1).
Formerly contained dextromethorphan hydrobromide and guaifenesin.
Coughs.

Humibid Maximum Strength *Adams, USA.*
Guaifenesin (p. 1666·2).
Cough.

Humiderm
Note: this name may be used for preparations of different composition.
Szama, Arg.
Emollient.

Humiderma *Darier, Mex.*
Emollient (Higroplex).
Dry skin disorders.

Humidus *Curatio, India.*
Aloe vera (p. 1693·2); squalane (p. 2213·3); wheat-germ oil (p. 2647·1).

Humin *Claris, India.*
⊗Albumin (p. 1130·2).
Hypovolaemic shock; hypoproteinaemia; neonatal hyperbilirubinaemia.

Huminsulin 30/70 and 50/50 *Lilly, India.*
⊗Mixtures of soluble insulin injection (human) and isophane insulin injection respectively in the proportions indicated (p. 475·3).
Diabetes mellitus.

Huminsulin Basal *Lilly, Austria; Lilly, Ger.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Huminsulin Basal (NPH) *Lilly, Switz.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Huminsulin L *Lilly, India.*
⊗Insulin zinc suspension (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Huminsulin N *Lilly, India.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Huminsulin Normal *Lilly, Austria; Lilly, Ger.; Lilly, Switz.†*
⊗Neutral insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Huminsulin Profil III *Lilly, Austria; Lilly, Ger.; Lilly, Switz.†*
⊗A mixture of neutral insulin injection (human, prb) 30% and isophane insulin injection (human, prb) 70% (p. 475·3).
Diabetes mellitus.

Huminsulin R *Lilly, India.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Humira *Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, China; Abbott, Cz.; Abbott, Denm.; AbbVie, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Jpn; Abbott, Malaysia; Abbott, Mex.; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, Turk.; Abbott, UK; Abbott, Ukr.; AbbVie, USA; Abbott, Venez.*
Adalimumab (p. 17·2).
Rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; Crohn's disease; psoriasis; juvenile idiopathic arthritis; spondyloarthropathies; ulcerative colitis; axial spondyloarthritis.

HuMist Nasal Mist *Scherer, USA.*
Sodium chloride (p. 1795·1).
Nasal irritation.

Humodar B *Indar, Rus.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Humodar B100 *Indar, Ukr.*
⊗Insulin protamine (human) (p. 475·3).
Diabetes mellitus.

Humodar C25 100 *Indar, Ukr.*
⊗A mixture of soluble insulin (human) 25% and insulin protamine (human) 75% (p. 475·3).
Diabetes mellitus.

Humodar K25-100 *Indar, Rus.*
⊗A mixture of soluble insulin (human) 25% and isophane insulin (human) 75% (p. 475·3).
Diabetes mellitus.

Humodar R100 *Indar, Ukr.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

HuMoG *Bharat, Rus.*
⊗Follicle-stimulating hormone (p. 2278·2); luteinising hormone (p. 2287·1).

Humog *Bharat, India.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Female and male infertility; assisted conception.

Humorap *Bago, Arg.; Bago, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Humoval *Steierl, Ger.*
Cistus canadensis; acidum silicicum (p. 2208·3); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Humoxal
Note: this name may be used for preparations of different composition.
Urgo, Fr.
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinusitis.

Humstard *Cadila, India.*
⊗Mixture of soluble insulin injection (human) 30% and isophane insulin injection (human) 70% (p. 475·3).
Diabetes mellitus.

Humulin I *Lilly, Irl.; Lilly, Ital.; Lilly, UK.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Humulin 30/70 *Lilly, Austral.; Lilly, Canad.; Lilly, Indon.; Lilly, Ital.; Lilly, Malaysia; Lilly, S.Afr.; Lilly, Singapore.*
⊗A mixture of insulin injection (human, prb) 30% and isophane insulin (human, prb) 70% (p. 475·3).
Diabetes mellitus.

Humulin 70/30 *Lilly, Arg.; Lilly, Braz.; Lilly, Chile; Lilly, China; Lilly, Hong Kong; Lilly, Israel; Lilly, Mex.; Lilly, NZ; Lilly, Philipp.; Lilly, Thai.; Lilly, USA; Lilly, Venez.*
⊗A mixture of isophane insulin injection (human) 70% and insulin injection (human) 30% (p. 475·3).
Diabetes mellitus.

Humulin L *Lilly, Canad.†; Lilly, Chile; Lilly, Gr.; Lilly, Hong Kong†; Lilly, Mex.†*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Humulin Lenta *Lilly, Braz.*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Humulin M3 *Lilly, Cz.; Lilly, Hung.; Lilly, Irl.; Lilly, Port.; Lilly, Rus.; Lilly, UK.*
⊗Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70%, respectively (p. 475·3).
Diabetes mellitus.

Humulin M3 (30/70) *Lilly, Pol.*
⊗A mixture of soluble insulin (human) 30% and isophane insulin 70% (p. 475·3).
Diabetes mellitus.

Humulin M 70/30 and 80/20 *Lilly, Turk.*
⊗Mixtures of isophane insulin injection (human) and insulin injection (human) in the proportions indicated (p. 475·3).
Diabetes mellitus.

Humulin M1, M2, M3, M4, M5 *Lilly, Gr.*
⊗Mixtures of insulin injection (human) 10%, 20%, 30% 40%, or 50% and isophane insulin injection (human) 90%, 80%, 70% 60%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Humulin Mix 30/70 *Lilly, Swed.†*
⊗A mixture of insulin injection (human, prb) 30% and isophane insulin injection (human, prb) 70% (p. 475·3).
Diabetes mellitus.

Humulin N *Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Israel; Lilly, Malaysia; Lilly, Mex.; Lilly, Pol.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, Turk.; Lilly, USA; Lilly, Venez.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Humulin N (NPH) *Lilly, Philipp.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Humulin NPH *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, China; Lilly, Denm.; Lilly, Fin.; Lilly, Gr; Lilly, Norw.; Lilly, NZ; Lilly, Port.; Lilly, Rus.; Lilly, Swed.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Humulin R *Lilly, Arg.; Lilly, Austral.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Pol.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, Turk.; Lilly, USA; Lilly, Venez.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Humulin R (Regular) *Lilly, Philipp.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Humulin Regular *Lilly, Braz.; Lilly, Denm.; Lilly, Fin.; Lilly, Gr.; Lilly, Port.; Lilly, Rus.; Lilly, Swed.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Humulin S *Lilly, Irl.; Lilly, UK.*
⊗Insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Humulin UL *Lilly, Gr.*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Humulina 30:70 *Lilly, Spain.*
⊗Mixture of insulin injection (human, prb) and isophane insulin injection (human, prb) (p. 475·3) respectively in the proportions indicated.
Diabetes mellitus.

Humulina NPH *Lilly, Spain.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Humulina Regular *Lilly, Spain.*
⊗Insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Humuline 30/70 *Lilly, Belg.; Lilly, Neth.*
⊗A mixture of neutral insulin injection (human, biosynthetic) 30% and isophane insulin injection (human, biosynthetic) 70% (p. 475·3).
Diabetes mellitus.

Humuline NPH *Lilly, Belg.; Lilly, Neth.*
⊗Isophane insulin injection (human, biosynthetic) (p. 475·3).
Diabetes mellitus.

Humuline Regular *Lilly, Belg.; Lilly, Neth.*
⊗Neutral insulin injection (human, biosynthetic) (p. 475·3).
Diabetes mellitus.

Humulus Compound *Integria, Austral.*
Lupulus (p. 2546·1); valerian (p. 2640·2); passion flower (p. 2584·1); ashwagandha (p. 2450·2).
Insomnia.

Humunis *Neiss, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Humyl *FDC, India.*
Preparation for enteral nutrition.

Humylub Ofteno *Sophia, Mex.*
Chondroitin sulfate sodium (p. 2476·1); sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Hungree *Laborate, India.*
Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and vascular headache.

Hunperdal *Gedeon Richter, Hung.*
Risperidone (p. 1103·2).

Huntred *Akesiss, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Huntred-Z *Akesiss, India.*
ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Huo Mu *Treeful, China.*
⊗An etherified starch in sodium chloride (p. 1146·1).

Huo Nuo Lin *Yimin, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Huo Ping *Qi Du, China.*
Telmisartan (p. 1509·3).
Hypertension.

Huoligai *Sine, China.*
Calcium (p. 1783·1).

Huperloid *Rafarm, Gr.*
Codergocrine (p. 389·2).
Peripheral vascular disorders.

Hurplex *Alpharma, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Hurricaine *Levy, Israel; Clarben, Spain; Beutlich, USA.*
Benzocaine (p. 1980·2).
Local anaesthesia; mouth pain.

Hurtiz-DSR *Aurel, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Husk *Intersound, Hung.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea.

Husky *Karnataka, India.*
Ispaghula (p. 1849·1).

Hustab *Phapros, Indon.*
Bromhexine hydrochloride (p. 1656·3); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Cough; respiratory-tract congestion.

Hustab P *Phapros, Indon.*
Bromhexine (p. 1656·3).
Cough; respiratory-tract congestion.

Hustadin *Guardian, Indon.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Hustagil Anticold Cream *Penta, Hung.*
Thyme oil (p. 2630·3); pine oil (p. 2591·1); eucalyptus oil (p. 2501·2); clove oil (p. 2481·3).
Cough; cold and influenza symptoms.

Hustagil Cough *Dentinox, Hung.; Penta, Hung.*
Thyme (p. 2630·2).
Cough.

Hustagil Thymian-Hustensaft *Dentinox, Ger.*
Thyme (p. 2630·2).
Cough and associated respiratory-tract disorders.

Hustagil Thymiantropfen *Dentinox, Ger.*
Thyme (p. 2630·2).
Cough and associated respiratory-tract disorders.

Hustazol *Mitsubishi Tanabe, Jpn.*
Cloperastine fendizoate (p. 1659·2) or cloperastine hydrochloride (p. 1659·2).
Cough.

Hustazol-C *Tokeda, Thai.*
⊗Cloperastine hydrochloride (p. 1659·2); sulfogaiacol (p. 1678·1); *dl*-methylephedrine hydrochloride (p. 1669·2).
Cough.

Husteel *Heel, Cz.; Peithner, Hung.; Heel, Neth.*
Arsenii triiodidum (p. 2448·1); belladonna (p. 2453·3); cupri acetas (p. 2486·2); causticum (p. 2595·3); urginea maritime (p. 1677·3).
Homoeopathic preparation.

Heel, Canad.†
Belladonna (p. 2453·3); cupric acetate (p. 2486·2); causticum (p. 2595·3); squill (p. 1677·3).
Homoeopathic preparation.

Husten ACC *Hexal, Austria.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous secretions.

Hustenlöser *1A, Austria.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Hustensaft Weleda *Weleda, Austria.*
Althaea (p. 2438·3); solanum dulcamara (p. 2497·3); marrubium vulgare (p. 1668·3); anisi (p. 2444·2); serpylli (p. 2648·1); thymi vulgaris (p. 2630·2); drosera (p. 2497·2); cephaelis ipecacuanha; pulsatilla (p. 2600·2); stipites.
Respiratory-tract disorders.

Hustenstiller
Note: this name may be used for preparations of different composition.
Ratiopharm, Ger.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Hutrope *Lilly, Arg.; Lilly, Chile.*
⊗Somatropin (p. 1919·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome; idiopathic short stature; SHOX deficiency; short children born small for gestational age.

Huxley's Wintogeno *Actavis, Malaysia.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

H-Vit *Systopic, India.*
Biotin (p. 2052·2).

Hvit *Pharma Investi, Chile.*
Biotin (p. 2052·2).
Dietary supplement.

HVP Chelated Multi Mineral *Valeant, Canad.*
Minerals.

HY *Biopol, Hung.*
Hymatomelanic acid.
Wounds; burns; acne; insect bites; frostbite.

Hyabak *Biotech, Arg.; Thea, Fr.; Thea, Ger.; Farmila, Ital.; Thea, Spain†; Spectrum, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation; contact lens lubricant.

Hyaferone *Vitafarma, Rus.*
Sodium hyaluronate (p. 2526·2); interferon alfa-2b (p. 989·2).
Herpesvirus infections; chlamydia; gardnerella vaginalis; mycoplasmosis; ureaplasmosis.

Hya-ject *DJO, Ger.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Hya-ject Plus *DJO, Ger.*
⊗Sodium hyaluronate (p. 2526·2); mannitol (p. 1427·3).
Synovial fluid replacement.

Hyal *LG, China; LG Life Sciences, Malaysia; Shin Poong, Malaysia.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye procedures; osteoarthritis of the knee; shoulder periarthritis.

Hyalart *Bago, Arg.; Meda, Ger.; Angelini, Gr.; SPA, Ital.; Grunenthal, Port.; Chiesi, Spain.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis; joint disorders.

Hyalase *Sanofi-Aventis, Austral.; IFET (ΙΦΕΤ), Gr.; LCH, Hong Kong†; Wockhardt, Irl.; CP, Israel; Artex, NZ; Xixia, S.Afr.†; CP Pharmaceuticals, Singapore; Wockhardt, UK.*
Hyaluronidase (p. 2527·2).
Extravasation; promotion of tissue fluid and blood resorption; hypodermoclysis; enhancement of absorption of other drugs; enhanced absorption of intramuscular and subcutaneous injections; oedema; haematomas; increase effectiveness of local anaesthesia; postpartum haemorrhage.

Hyalcrom *Bausch & Lomb, Arg.*
⊗Sodium cromoglicate (p. 1225·3); naphazoline hydrochloride (p. 1669·3); hyaluronic acid (p. 2526·2).
Eye disorders.

Hyalcrom NF *Bausch & Lomb, Arg.; Bausch & Lomb, Mex.*
Ketotifen fumarate (p. 631·3); sodium hyaluronate (p. 2526·2).
Allergic conjunctivitis.

Hyalein *Santen, Jpn.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Hyalgan *Chemedica, Austria; Kela, Belg.; Medexus, Canad.; Silesia, Chile; Fidia, Cz.; Nycomed, Denm.; Leiras, Fin.; Expanscience, Fr.; Fidia, Hong Kong; CSC, Hung.; Combiphar, Indon.; Fidia, Indon.; Fidia, Irl.; Fidia, Ital.; Fidia, Malaysia; Douglas, NZ; Fidia, Pol.; CSC, Rus.; TRB, Singapore; Bioiberica, Spain; Nycomed, Swed.; Fidia, Thai.; Bilim, Turk.; Shire, UK; Fidia, USA; Leti, Venez.*
Sodium hyaluronate (p. 2526·2).
Degenerative joint disorders; orthopaedic surgery; osteoarthritis.

Hyalgesic HP *Standard Homeopathic, Canad.†*
Belladonna (p. 2453·3); epiphegus virginiana; gelsemium sempervirens (p. 2511·2); ipecac (p. 1667·2); iris versicolor (p. 2534·3).
Homoeopathic preparation.

Hyalgesic LBP *Standard Homeopathic, Canad.†*
Benzoic acid (p. 1738·2); colchicum (p. 607·1); poison oak (p. 2603·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Hyaline *LCA, Fr.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Hyalistil *SIFI, Ital.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hyalix *Medihealth, Mex.; Roemmers Medihe, Venez.*
Moisturiser.
Dry skin.

Hyalofemme *Fidia, Israel.*
Hyaluronic acid benzyl ester (Hydeal-D).
Vaginal dryness; vaginal irritation.

Hyalofill *Convatec, UK.*
Hyaff (p. 2526·2).
Ulcers; wounds.

Hyalofill-F *Fidia, Ital.*
Hyaff (p. 2526·2).
Wounds; ulcers.

Hyaltec, Arg.
Hyaluronic acid (p. 2526·2).
Ulcers; wounds.

Hyalogran *Fidia, Ital.*
Hyaff (p. 2526·2); sodium alginate (p. 2167·3).
Ulcers.

Hyaltec, Arg.
Hyaluronic acid (p. 2526·2); sodium alginate (p. 2167·3).
Ulcers; wounds.

Hyalomatrix-PA *Hyaltec, Arg.*
Hyaluronic acid (p. 2526·2); silicone (p. 2209·2).
Artificial skin.

Hyalomb *Bausch & Lomb, Arg.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hyaloph *Sanbe, Indon.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hyalosilver *Fidia, Ital.*
Sodium hyaluronate (p. 2526·2); colloidal silver (p. 2616·2).
Wounds; burns.

Hyalox *Sophia, Mex.*
⊗Oxymetazoline hydrochloride (p. 1671·3); sodium hyaluronate (p. 2526·2).
Eye irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hyalozima *Apsen, Braz.*
Hyaluronidase (p. 2527·2).
Reduction of extravasation; enhancement of absorption of intramuscular and subcutaneous injections.

Hyalpur Moustique *Celso, Arg.*
Ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Hyalubrix *Meda, Ger.; Fidia, Ital.*
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement.

Hyaludermin *TRB, Braz.*
Sodium hyaluronate (p. 2526·2).
Wounds; ulcers.

Hyalugel *Expanscience, Fr.*
Hyaluronic acid (p. 2526·2).
Gum inflammation or injury.

Hyalur *Drossapharm, Switz.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Hyaluron
Note: this name may be used for preparations of different composition.
Beiersdorf, Chile.
SPF 10; SPF 15: Octinoxate (p. 1715·1); bemotrizinol (p. 1695·3); octil triazone (p. 1715·1); sodium hyaluronate (p. 2526·2); soya (p. 2092·3).
Wrinkles; skin ageing; sunscreen.

Maigal, Arg.
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders.

Hexal, Ger.†
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement.

Hyaluzinc *Pierre Fabre, Fr.*
Zinc hyaluronate (p. 2526·2).
Burns; ulcers; wounds.

Hyan *Famy, Thai.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Hyanit N *Strathmann, Ger.†*
⊗Urea (p. 1727·3).
Dry skin disorders.

Hya-Ophtal *Winzer, Ger.*
Sodium hyaluronate (p. 2526·2).
Aid in eye surgery.

Hyaral *Farmak, Ukr.*
Sodium hyaluronate (p. 2526·2).
Adjunct in ocular surgery.

Hyasol *Bausch & Lomb, Arg.; Bausch & Lomb, Mex.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Hyason *Riemser, Neth.*
Hyaluronidase (p. 2527·2).
Adjunct to local anaesthesia of the eye.

Hyate:C *Ipsen, Gr.†; Ipsen, UK.†*
A porcine factor VIII:C preparation (p. 1148·1).
Haemophilia in patients with antibodies to human factor VIII.

Hybet *Arvincare, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Hybloc *Mylan, NZ.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Hybolin *Hyrex, USA.*
⊗Nandrolone phenylpropionate (p. 2293·1) or nandrolone decanoate (p. 2293·1).
Breast cancer; anaemia in renal disease.

Hybreed-H *East West, India.*
⊗Hydrochlorothiazide (p. 1403·2); olmesartan medoxomil (p. 1459·2).

Hybutin *Jean-Marie, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency; neuralgia; neuritis; neuropathy.

Hybutyl *Pharmaland, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hycal
Note: this name may be used for preparations of different composition.
Sysmed, India.
Calcium (p. 1783·1); phosphorus (p. 2589·2); zinc sulfate (p. 2126·2).

Hycalvit *Ultramark, India.*
Calcium glubionate (p. 1783·2); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).

Hycamtin *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; SmithKline Beecham, Irl.; GSK, Israel; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; small-cell lung cancer; cervical cancer.

Hycef *Grandix, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Hycemia *Guardian, Indon.†*
Allopurinol (p. 600·2).
Gout.

Hyceral *Condrugs, Thai.*
Codergocrine mesilate (p. 389·2).
Mental function impairment; peripheral vascular disorders.

Hycet *Eclat, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Hychlozide *Pharmasant, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Hycibex *Pharmed, India.*
Syrup: Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Pharmed, India.
Capsules: Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); *Lactobacillus sporogenes* (p. 2596·3).

Hycibex-Z *Pharmed, India.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); vitamin E acetate (p. 2119·2); lactobacillus (p. 2596·3); zinc sulfate (p. 2126·2).

Hycid *XL, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hycimox *Pharmed, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Hycin *Saga, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Hyclean *Ranbaxy, India.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).

Hycocin *Rekah, Israel.†*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected eye, ear, and nose disorders.

HycoClear Tuss *Ethex, USA.*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Coughs.

Hycodan
Note: this name may be used for preparations of different composition.
BMS, Canad.
Hydrocodone tartrate (p. 67·2).
Cough.

Endo, USA.†
Hydrocodone tartrate (p. 67·2); homatropine methylbromide (p. 2007·3).
Cough.

Hycolloid Ultra Thin *Geritrex, USA.*
Hydrocolloid dressing.
Wounds.

Hycomine
Note: this name may be used for preparations of different composition.
BMS, Canad.†
Hydrocodone tartrate (p. 67·2); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1).
Cough; upper respiratory-tract congestion.

Hycomine Compound *Endo, USA.*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Coughs and cold symptoms.

Hycomycin *Teva, Israel.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Hycor *Sigma, Austral.*
⊗Hydrocortisone acetate (p. 1640·1).
Inflammatory eye disorders.

Hycort *CCM, Malaysia; Umedica, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Ind-Swift, India.
⊗Hydrocortisone acetate (p. 1640·1) or hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Valeant, Canad.
⊗Hydrocortisone (p. 1640·1).
Inflammatory diseases of the gastrointestinal tract.

Hycortil *Rotexmedica, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Hycosan *Scope, UK.*
Hyaluronic acid (p. 2526·2).
Dry eyes.

HycoSan5 *Pharma Medica, Switz.*
Sodium hyaluronate (p. 2526·2).
Contact lens lubrication.

Hycoson *AstraZeneca, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hycotuss *Endo, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Hydab *Dabur, India; Fresenius Kabi, Philipp.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; psoriasis; radiosensitiser; sickle cell disease; beta-thalassaemia.

Hydac *Sanofi-Aventis, Fin.*
Felodipine (p. 1380·3).
Hypertension.

Hydal *Mundipharma, Austria.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Hydantin *Orion, Fin.*
Phenytoin (p. 538·2).
Epilepsy.

Hydase *Akorn, USA.†*
Hyaluronidase (p. 2527·2).
To increase the absorption and dispersion of injected drugs; hypodermoclysis; adjunct in urography.

Hydase-D *Hy-Gro, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Hyde *Shalaks, India.*
Hydroquinone (p. 1705·1).
Hyperpigmented skin disorders.

Hydent *Piramal, India.*
Sodium monofluorophosphate (p. 2091·3); zinc sulfate (p. 2126·2).

Hydent K *Piramal, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Hyderax *HLB, Arg.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; premedication; pruritus.

Hydergin *Novartis, Austria; Defiante, Fin.; Sigma-Tau, Ger.; Novartis, Indon.; Swedish Orphan, Swed.*
Codergocrine mesilate (p. 389·2).
Shock; cerebral and peripheral vascular disorders; hypertension; cervical syndrome; mental function impairment; migraine and other vascular headache.

Hydergina *Novartis, Arg.; Defiante, Ital.; Novartis, Mex.; Defiante, Spain.*
Codergocrine mesilate (p. 389·2).
Mental function impairment; cerebral and peripheral vascular disorders; hypertension; migraine and other vascular headache.

Hydergine *Defiante, Belg.; Novartis, Braz.; SteriMax, Canad.; Novartis, China; Sigma-Tau, Fr.; Defiante, Gr.; Novartis, Hong Kong; Novartis, India; Novartis, Israel; Novartis, Malaysia; Novartis, Philipp.; Defiante, Port.; Novartis, Singapore; Novartis, Switz.; Novartis, Thai.; Novartis, USA.*
Codergocrine mesilate (p. 389·2).
Mental function impairment; migraine and other vascular headaches; hypertension; dementia; cerebral and peripheral vascular disorders; vascular eye disorders.

Hyderm
Note: this name may be used for preparations of different composition.
ACO Hud, Denm.; ACO Hud, Fin.; ACO Hud, Swed.
⊗Hydrocortisone (p. 1640·1).
Skin disorders; anogenital pruritus.

Labomed, Chile.
⊗Urea (p. 1727·3).
Skin disorders.

Taro, Canad.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Hydex PD *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3).
Coughs; nasal congestion; allergic rhinitis.

Hydil *Psychotropics, India.*
Hydroxyzine (p. 630·3).
Anxiety; pruritus; premedication.

Hydiphen *AWD, Pol.†*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; panic disorder; narcoleptic syndrome.

Hydoftal *Agepha, Austria.*
⊗Hydrocortisone (p. 1640·1); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Inflammatory eye disorders.

Hydoftal sine neomycino *Agepha, Austria.†*
⊗Hydrocortisone (p. 1640·1); hydrocortisone acetate (p. 1640·1).
Inflammatory eye disorders.

Hydopa *Alphapharm, Austral.; LCH, Hong Kong.†*
Methyldopa (p. 1431·1).
Hypertension.

Hydra *Otsuka, Jpn.*
Isoniazid (p. 311·2).
Tuberculosis.

Hydra Bain/Bath *Texel, Canad.†*
Benzalkonium chloride (p. 1737·1).

Hydra Moisturizing Lotion *Orchard, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Hydrabak *Farmila, Ital.*
Sodium chloride (p. 1795·1).
Comfort drops for contact lenses.

Hydrabis *Bioderma, Venez.*
Barrier preparation.

Hydra-C *Marcelle, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hydracid *Farmoquimica, Braz.*
Ascorbic acid (p. 2110·3).

Hydracort *Galderma, Fr.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hydracuivre *SVR, Fr.*
Zinc pidolate (p. 1720·3); copper pidolate (p. 1720·3); sodium pidolate (p. 1720·3); allantoin (p. 1693·1).
Dry skin; skin irritation.

Hydracur *Lero, Fr.*
Black currant (p. 2458·1); taraxacum (p. 2625·3); rose fruit (p. 2607·1); hibiscus (p. 2525·2); cherry (p. 2207·2); meadowsweet (p. 2550·2).
Diuretic.

Hydraderm *Sigma, Austral.*
Moisturiser.

Sigma, Hong Kong.
A range of skin moisturisers.

Hydrafresh *L'Oreal, Canad.*
Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Hydragel *Bayer Sante, Fr.†*
Vaginal lubricant.

Hydragel B5 CKL *Dispolab, Chile.*
Hyaluronic acid (p. 2526·2); pantothenic acid (p. 2085·2).
Skin disorders.

Hydral *Alembic, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Hydralin *Bayer, Hong Kong; Roche Nicholas, Hong Kong.*
Sodium perborate (p. 1770·1); borax (p. 2459·2); sodium bicarbonate (p. 1781·1); sodium carbonate anhydrous (p. 2617·3).
Genital pruritus.

Hydralin Apaisa *Bayer, Fr.*
Skin cleanser.
Urogenital cleansing.

Hydralin Classic *Bayer, Fr.*
Soap: Borax (p. 2459·2).
Skin cleansing in gynaecological care.

Bayer, Fr.
Powder for topical solution: Sodium perborate (p. 1770·1); borax (p. 2459·2); sodium bicarbonate (p. 1781·1); sodium carbonate anhydrous (p. 2617·3).
Skin cleansing in gynaecological care.

Hydralin Gyn *Bayer Sante, Fr.*
Glycine (p. 2071·2).
Vulvovaginal hygiene.

Hydralin Lubrifiant *Bayer, Fr.*
Vaginal lubricant.

Hydralin Soyeux *Bayer, Fr.*
Camellia japonica.
Vulvovaginal hygiene.

Hydralyte *River Foods, Austral.; Hydration, Canad.*
Oral rehydration preparations (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Hydration, Singapore.
Glucose (p. 2068·3); sodium (p. 1795·1); potassium (p. 1793·1); chloride; citrate (p. 1780·1).
Diarrhoea; oral rehydration therapy; vomiting.

Hydramax + *Chanel, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hydramox *Caber, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Hydran
Note: this name may be used for preparations of different composition.
Chandra Bhagat, India.
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; sickle-cell disease; essential thrombocythaemia.

Teva, Israel.†
Sodium chloride (p. 1795·1); anhydrous trisodium citrate; potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Hydranorme *Roche-Posay, Braz.†; Roche-Posay, Irl.*
Emollient.
Dry skin; psoriasis.

Hydraphase *Roche-Posay, Braz.*
Emollient.

Roche-Posay, Chile.
Moisturiser.
Dry skin disorders.

Hydraphase Ojos *Roche-Posay, Chile.*
Sodium hyaluronate (p. 2526·2); caffeine (p. 1203·3).
Dry skin.

Hydraphase UV *Roche-Posay, Canad.*
Octinoxate (p. 1715·1); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hydraphase UV Eyes *Roche-Posay, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Hydraphase XL *Roche-Posay, Chile.*
SPF 15: Drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2).
Sunscreen.

Hydrapres *Omedir, Arg.; Rubio, Spain.*
Hydralazine hydrochloride (p. 1401·2).
Heart failure; hypertension.

Hydrares *Pharmasant, Thai.*
⊗Reserpine (p. 1485·3); hydralazine hydrochloride (p. 1401·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hydra-Seal *Immanence Integral, Canad.*
SPF 25: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Hydrasense *Schering-Plough, Canad.*
Isotonic desalinated sea water (p. 2612·1).
Nasal congestion; nasal dryness.

Hydrastart *Lero, Fr.*
Elderberry (p. 2609·3); ash (p. 2450·1); couch-grass (p. 2487·2); black tea (p. 2648·2); chromium (p. 2055·3).
Slimming aid.

Hydrastis Compose *Boiron, Fr.*
Hydrastis canadensis (p. 2528·1); cinchona succirubra (p. 2478·3); scrofularia; crataegus oxyacantha (p. 2488·1); chelidonium majus (p. 2522·2); condurango (p. 2485·3); ceanothus.
Homoeopathic preparation.

Hydrating B5 Gel *Dispolab, Chile.†*
Sodium hyaluronate (p. 2526·2); pantothenic acid (p. 2085·2).
Skin disorders.

Hydratone *Forder, Arg.*
Hyaluronic acid (p. 2526·2); panthenol (p. 2582·2).
Dry skin.

Hydra-zide
Note: this name may be used for preparations of different composition.
Par, USA.
⊗Hydralazine hydrochloride (p. 1401·2); hydrochlorothiazide (p. 1403·2).

Hydrazide
Note: this name may be used for preparations of different composition.
Cipla, India.
⊗Hydrochlorothiazide (p. 1403·2).
Oedema.

Otsuka, Jpn.†
Isoniazid (p. 311·2).
Tuberculosis.

Hydrea *BMS, Austral.; BMS, Belg.; BMS, Braz.; BMS, Canad.; Merck, Chile; Paranova, Denm.; BMS, Fin.; BMS, Gr.; BMS, Hong Kong†; Sarabhai Piramal, India; Taisho, Indon.; BMS, Irl.; BMS, Mex.; Euro Registratie, Neth.; Orifarm, Norw.; BMS, NZ; BMS, Port.†; BMS, Rus.; BMS, S.Afr.; BMS, Spain; BMS, Swed.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; polycythaemia vera; sickle-cell disease; essential thrombocythaemia.

Hydréa *BMS, Fr.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; essential thrombocythaemia.

Hydreasyn *Farmasyn, Gr.*
Hydroxycarbamide (p. 803·1).

Hydrene *Alphapharm, Austral.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Hydreringsvæske *SAD, Denm.*
Sodium chloride (p. 1795·1); sodium lactate (p. 1781·2).
Fluid and electrolyte disorders.

Hydresc *KRKA, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hydrex
Note: this name may be used for preparations of different composition.
Adams, Hong Kong; Ecolab, Irl.; Ecolab, Neth.†; Ecolab, Thai.; Adams, UK.
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection; hand disinfection.

Orion, Fin.
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; diabetes insipidus; hypertension.

Hydride *Micro, India.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; diabetes insipidus.

Hydrigoz *Guigoz, Fr.†*
Maltodextrin (p. 2080·3); sucrose (p. 2096·3); sodium chloride (p. 1795·1); citric acid (p. 2480·3); potassium citrate (p. 1780·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Hydrinate *CCM, Malaysia.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Hydrine
Note: this name may be used for preparations of different composition.
Korea United, Singapore.
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; sickle-cell disease; essential thrombocythaemia.

TO-Chemicals, Thai.
Codergocrine mesilate (p. 389·2).
Cerebrovascular disorders; mental function impairment.

Hydrisalic *Pedinol, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratotic skin.

Hydrisea *Pedinol, USA.*
Emollient and moisturiser.

Hydrisinol *Pedinol, USA.*
Emollient and moisturiser.

Hydrite *Westmont, Philipp.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration.

Hydro *Quinnova, USA.*
⊗Urea (p. 1727·3).
Dry skin.

Hydro Cobex *Kripps, Canad.*
Hydroxocobalamin (p. 2107·3).

Hydro Cordes *Ichthyol, Ger.*
Allantoin (p. 1693·1); dexpanthenol (p. 2582·2); ethyl linoleate (p. 2509·2).
Skin disorders.

Hydro DP *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Coughs; upper respiratory-tract congestion.

Hydro Santa *Biomed, Switz.†*
A range of preparations containing eriodictyon (p. 1665·2).
Vaginal dryness; dry mouth; nasal dryness.

Hydroagisten *Perrigo, Israel.*
⊗Hydrocortisone acetate (p. 1640·1); clotrimazole (p. 576·2).
Skin disorders with fungal infection.

Hydrocad *Cadila, India.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; systemic lupus erythematosus; malaria.

Hydrocare *Allergan, USA.*
Range of solutions for soft contact lenses.

AMO, Arg.
Prolase.
Protein remover for soft contact lenses.

Hydro-Cebral *Ratiopharm, Ger.*
Codergocrine mesilate (p. 389·2).
Mental function disorders.

Hydrocerin *Geritrex, USA.*
Cream: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool alcohols (p. 2219·2).
Product basis.

Geritrex, USA.
Lotion: Liquid paraffin (p. 2191·2); wool alcohols (p. 2219·2).
Product basis.

Hydrocerin Plus *Geritrex, USA.*
⊗Alpha hydroxy; urea (p. 1727·3).
Dry skin.

Hydrocet *Carnrick, USA.†*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Hydrochlorzide *Xepa-Soul Pattinson, Singapore.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Hydrocil Instant *Numark, USA.*
Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation.

Hydrocin-N *Vickmans, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1); neomycin (p. 329·3).

Hydroclean *Hartmann, Fr.*
Sodium polyacrylate; cellulose (p. 2177·1).
Wounds; ulcers; burns.

Hydroclonazone *DB, Fr.*
Tosylchloramide sodium (p. 1773·1).
Water purification.

Hydrocobamine *Takeda, Neth.*
Hydroxocobalamin hydrochloride (p. 2107·2).
Megaloblastic anaemia; vitamin B_{12} deficiency.

Hydrocodeinon *Streuli, Switz.†*
Hydrocodone hydrochloride (p. 67·2).
Cough.

Hydrocodin *Alkaloida, Hung.*
Dihydrocodeine tartrate (p. 52·3).
Cough; pain.

Hydrocodone CP *Morton Grove, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Hydrocodone GF *Morton Grove, USA.*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Upper respiratory-tract symptoms.

Hydrocodone HD *Morton Grove, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Hydrocoll *Hartmann, Belg.*
A hydrocolloid dressing.
Wounds.

Hartmann, Fr.
Carmellose sodium (p. 2175·2).
Burns; ulcers; wounds.

Hydrocort *YSP, Malaysia; Chema-Elektromet, Pol.; Yung Shin, Singapore.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Hydrocort & Neomycin Biorex *LCH, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1); neomycin (p. 329·3).

Hydrocortancyl *Sanofi-Aventis, Fr.*
⊗Prednisolone (p. 1645·2) or prednisolone acetate (p. 1645·2).
Corticosteroid.

Hydrocortison med Terramycin *Pfizer, Denm.*
⊗Hydrocortisone (p. 1640·1); oxytetracycline hydrochloride (p. 337·2).
Infected skin disorders.

Hydrocortison med Terramycin og Polymyxin-B *Pfizer, Denm.*
⊗Hydrocortisone acetate (p. 1640·1); oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Infected ear or eye disorders.

Hydrocortisone compositum *Streuli, Switz.†*
⊗Hydrocortisone acetate (p. 1640·1); zinc stearate (p. 2221·2).
Skin disorders.

Hydrocortistab *Sovereign, UK.*
⊗Hydrocortisone acetate (p. 1640·1).
Corticosteroid.

Hydrocortisyl *Sanofi-Aventis, Irl.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hydrocortone *MSD, Austria; MSD, Irl.; Pro Concepta, Switz.; Auden McKenzie, UK†; MSD, USA.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

MSD, Port.
⊗Hydrocortisone acetate (p. 1640·1).
Corticosteroid.

Hydrocream *Paddock, USA.*
Vehicle for topical preparations.

Hydrocutan *Dermapharm, Ger.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid; skin disorders.

Hydrocutan mild *Dermapharm, Ger.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hydroderm
Note: this name may be used for preparations of different composition.
Aesca, Austria.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

ICM, Singapore.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Pacific, NZ.
Dewaxed oil-soluble lanolin fraction (p. 2219·3); liquid paraffin (p. 2191·2).
Pruritus; dry skin disorders.

Hydroderm-C *ICM, Singapore.*
⊗Hydrocortisone acetate (p. 1640·1); clioquinol (p. 273·1).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hydrodexan *Almirall Hermal, Ger.*
⊗Hydrocortisone (p. 1640·1); urea (p. 1727·3).
Skin and scalp disorders.

HydroDiuril *Merck, USA.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Hydrofer-3 *Mediapharm, Gr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Hydrofluoric Acid Antidote *Malaysia Chemist, Singapore.*
Calcium gluconate (p. 1783·3).
Hydrofluoric acid burns.

Hydroflux *Intermed, Gr.*
⊗Furosemide (p. 1387·1).
Oedema; oliguria due to renal failure; heart failure; hypertension.

Hydroform *GSK, Austral.*
⊗Hydrocortisone (p. 1640·1); clioquinol (p. 273·1).
Skin disorders.

Hydroftal *HLB, Arg.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; high-altitude disorders.

Hydro-Funga *Vida, Hong Kong.†*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Fungal skin infections with inflammation.

Hydrofusin *Alapis, Gr.*
⊗Fusidic acid (p. 302·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Hydrogalen *Galen, Ger.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hydrogesic *Edwards, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Hydro-GP *Cypress, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Allergic rhinitis; cold symptoms; coughs.

Hydro-Iodoquinol *Seton, USA.*
⊗Hydrocortisone acetate (p. 1640·1); diiodohydroxyquinoline (p. 931·1).

Hydrol *Specpharm, S.Afr.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Hydrolac *Milk Industries, Israel.*
Protein hydrolysate (p. 2086·2).
Nutritional protein supplement.

Hydrolate *Asian Pharm, Thai.*
Mebhydrolin (p. 634·2).
Hypersensitivity reactions.

Hydro-Less *Aspen, S.Afr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Hydromal
Note: this name may be used for preparations of different composition.
Sanbe, Indon.
Electrolytes (p. 1775·1); maltose (p. 2081·1).
Carbohydrate source; fluid and electrolyte disorders.

Hydromax *Forder, Arg.*
Moisturiser.

Hydromed *Medilink, Denm.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Hydromega *Carrare, Fr.*
Sea buckthorn oil (p. 2612·1).
Dry skin; skin irritation.

Hydromet
Note: this name may be used for preparations of different composition.
MSD, Braz.; Vianex (Βιανεξ), Gr.
⊗Hydrochlorothiazide (p. 1403·2); methyldopa (p. 1431·1).
Hypertension.

Alpharma, USA.
Hydrocodone tartrate (p. 67·2); homatropine methylbromide (p. 2007·3).
Cough.

Hydromol *Alliance, Irl.; Alliance, UK.*
Cream: Sodium pidolate (p. 1720·3); isopropyl myristate (p. 2190·3); liquid paraffin (p. 2191·2); sodium lactate (p. 1781·2).
Dry skin.

Quinoderm, Irl.; Alliance, UK.
Emollient: Light liquid paraffin (p. 2191·2); isopropyl myristate (p. 2190·3).
Dry skin conditions.

Alliance, UK.
Ointment: Yellow soft paraffin (p. 2212·1); cetomacrogol emulsifying wax (p. 2184·1).
Dry skin; soap substitute.

Cooper (Κοπερ), Gr.
Liquid paraffin (p. 2191·2); isopropyl myristate (p. 2190·3).

Hydromol HC Intensive *Alliance, UK.*
⊗Hydrocortisone (p. 1640·1); urea (p. 1727·3).
Dry skin disorders.

Hydromol Intensive *Alliance, UK.*
⊗Urea (p. 1727·3).
Dry skin.

Hydromoor *Moorfields, UK.*
Hypromellose (p. 2189·2).
Dry eyes.

Hydromorph *Purdue, Canad.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Hydromycin *PP Lab, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Hydron CP *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; coughs; cold symptoms.

Hydron EX *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); sulfogaiacol (p. 1678·1).
Cough.

Hydron KGS *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); sulfogaiacol (p. 1678·1).
Cough.

Hydron PSC *Cypress, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Coughs; hay fever; respiratory-tract congestion.

Hy-Drop *Bausch & Lomb, Ital.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hydropane *Halsey, USA.*
Hydrocodone tartrate (p. 67·2); homatropine methylbromide (p. 2007·3).
Coughs.

Hydropel *C & M, USA.*
Topical barrier preparation.

Hydrophed *Rugby, USA.*
⊗Theophylline (p. 1229·3); ephedrine sulfate (p. 1663·2); hydroxyzine hydrochloride (p. 630·3).
Bronchospasm.

Hydrophil *Omega, Canad.*
⊗Urea (p. 1727·3); white soft paraffin (p. 2211·3).
Dry skin.

Hydrophilic *Rugby, USA.*
Vehicle for topical preparations.

Hydropres *Merck, USA.*
⊗Hydrochlorothiazide (p. 1403·2); reserpine (p. 1485·3).
Hypertension.

Hydroquin *Sun, India; Sun, Thai.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; malaria; lupus erythematosus; juvenile arthritis.

Hydrosal *Valeo, Canad.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Hydrosan *Wabosan, Austria.*
⊗Chlortalidone (p. 1335·2).
Hypertension; heart failure; oedema.

Hydrosil *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; heartburn; meteorism; peptic ulcer; dyspepsia; gastro-oesophageal reflux; flatulence.

HydroSkin *Rugby, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hydrosol Polyvitaminé *Pharmadeveloppement, Fr.*
Vitamins.

Hydroson *Dermapharm, Ger.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hydrosone *Christo, Hong Kong.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Teva, Canad.
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

HydroSorb *Hartmann, Fr.*
A hydrogel dressing.
Wounds.

Hydrospor *Vendiz, Philipp.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Ear infections.

Hydrotab *Actavis, UK.*
Malic acid (p. 2549·2); sodium fluoride (p. 2089·2).
Dry mouth.

Hydrotopic *Vendiz, Philipp.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Hydrotricine *Sanofi-Aventis, Ital.; Vitoria, Port.; Unipharm, Turk.*
Tyrothricin (p. 384·1).
Bacterial stomatitis; mouth and throat infections.

Hydrotride *Beacons, Singapore.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Hydrotrim *Mega Lifesciences, Philipp.†*
Hydroxycitric acid.
Dietary supplement for weight loss.

Hydro-Tussin HG *Ethex, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

HydroVal *Taro, Canad.*
⊗Hydrocortisone valerate (p. 1640·3).
Skin disorders.

Hydrovit *Stada, Rus.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Hydrox
Note: this name may be used for preparations of different composition.
Cipla, Philipp.
Hydroxycarbamide (p. 803·1).
Chronic myeloid leukaemia; myeloproliferative disorders.

T Man, Thai.
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Hydrox-12 *Neon, India.*
Hydroxocobalamin chloride (p. 2107·3).

Hydroxo-B12 *Aspen, Austral.*
Hydroxocobalamin chloride (p. 2107·3).
Vitamin B_{12} deficiency anaemias; optic neuropathies.

Hydroze *Unichem, India.*
Hydroxyzine (p. 630·3).
Anxiety; pruritus; premedication.

Hydrozide
Note: this name may be used for preparations of different composition.
Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.; Medicine Products, Thai.
⊗Hydrochlorothiazide (p. 1403·2).
Diuretic; hypertension; oedema.

Hydrozide Plus *Medicine Products, Thai.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Oedema; hepatic cirrhosis with ascites; hypertension.

Hydrozole *GSK, Austral.; Stiefel, India.*
⊗Hydrocortisone (p. 1640·1); clotrimazole (p. 576·2).
Infected skin disorders.

Hydryllin *Ali, Turk.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Respiratory-tract congestion.

Hyflex *Laboratorios Chile, Chile.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Breckenridge, USA.†
Paracetamol (p. 115·1); phenyltoloxamine citrate (p. 638·1).
Pain.

Hyflon *Elmor, Venez.*
Hidrosmin (p. 2505·2).
Venous insufficiency.

Hyflox *Masa, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Hyforil *Ranbaxy, Austral.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hy-GAG *Curasan, Ger.*
Sodium hyaluronate (p. 2526·2).
Degenerative joint disorders.

Hygaine *Dabur, India.*
Minoxidil (p. 1438·3).
Alopecia.

Hygeen *Ethix, India.*
Chlorhexidine (p. 1743·2).
Oral hygiene; gingivitis.

HyGel *Aletheia, USA.*
Sodium hyaluronate (p. 2526·2).

Hygeol *Pendopharm, Canad.†*
Sodium hypochlorite (p. 1768·3).
Disinfection; wound cleansing.

Hygienist *Bayer, Ital.*
Chlorocresol (preventol CMK) (p. 1748·1); clorophene (preventol BP) (p. 1748·3); orthophenylphenol (preventol extra) (p. 1762·3).
Surface disinfection.

Hygienist Pavimenti e Piastrelle *Bayer, Ital.*
Benzalkonium chloride (p. 1737·1).
Surface disinfection.

Hygine *Soma, Braz.*
Triclosan (p. 1773·2).
Soap substitute.

Hygroton *Novartis, Arg.; Novartis, Austral.; Pharma Logistics, Belg.; Mibe, Ger.; Amdipharm, Gr.; Sandoz, Hung.; Novartis, Indon.; AFT, NZ; Novartis, Pol.; Amdipharm, Port.; Novartis, S.Afr.; Novartis, Switz.; Novartis, Turk.†; Alliance, UK; Rhone-Poulenc Rorer, USA.†*
⊗Chlortalidone (p. 1335·2).
Heart failure; hypertension; oedema; renal calculi; diabetes insipidus; liver cirrhosis with ascites.

Hygroton-Reserpine *Amdipharm, Gr.; Novartis, Switz.†*
⊗Chlortalidone (p. 1335·2); reserpine (p. 1485·3).
Hypertension.

Hyiodine *Contipro, Malaysia.*
Sodium hyaluronate (p. 2526·2); potassium iodide (p. 2336·3); iodine (p. 2336·3).
Wound disinfection; infected wounds.

Hykophos *Leben, India.*
Vitamin B substances (p. 2102·3).

Hykor *Pharma 3, Philipp.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Hy-KXP *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); sulfogaiacol (p. 1678·1).
Cough.

Hylaform *Collagen Aesthetics, NZ; Inamed, Singapore†; Inamed, USA.†*
Hylan B (p. 2526·2).
Skin contour defects; facial wrinkles.

Medstyle, Chile.†
Hyaluronic acid (p. 2526·2).
Facial wrinkles.

Hylagene *Hylands, Canad.*
Cinchona officinalis (p. 2478·3); hydrastis canadensis (p. 2528·1); phosphoricum acidum (p. 2589·1); kali bichromicum (p. 2476·3).
Homoeopathic preparation.

Hylagesic APF *Hylands, Canad.*
Arnica montana (p. 2447·2); bryonia alba (p. 2461·3); cimicifuga racemosa (p. 2478·1); guiacum officinale (p. 1666·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Hylak *Ratiopharm, Austria.*
Metabolic products of lactic-acid producing organisms (p. 2596·3); lactic acid (p. 2539·1); amino acids.
Gastrointestinal disorders; liver disorders; skin disorders.

Ratiopharm, Ukr.
Lactobacillus helveticus (p. 2596·3).
Restoration of gastrointestinal flora; gastrointestinal disorders.

Hylak Forte *Ratiopharm, Cz.*
Metabolic products of: *Escherichia coli*; *Enterococcus faecalis* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3).
Gastrointestinal disorders.

Ratiopharm, Rus.; Ratiopharm, Ukr.
Escherichia coli; *Enterococcus faecalis* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3).
Restoration of gastrointestinal flora; gastrointestinal disorders; skin disorders.

Hylak forte *Ratiopharm, Austria.*
Metabolic products of lactic-acid producing organisms (p. 2596·3); metabolic products of Gram-positive and Gram-negative intestinal flora; lactic acid (p. 2539·1); amino acids.
Gastrointestinal disorders; liver disorders; skin disorders.

Hylak N *Recordati, Ger.†*
Metabolic products of *Lactobacillus helveticus* (p. 2596·3).
Gastrointestinal disorders.

Hylak Plus *Recordati, Ger.†*
Metabolic products of *Lactobacillus helveticus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3).
Gastrointestinal disorders.

Hylamine HF *Hylands, Canad.*
Euphrasia officinalis (p. 2502·1); ambrosia artemisiifolia; allium cepa (p. 2575·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Hylan *Stulln, Ger.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylands Bioplasma *Hylands, Canad.*
Calcarea fluorica (p. 2053·1); calcarea phosphorica (p. 1784·2); calcarea sulphuricum (p. 2173·1); ferrum phosphoricum (p. 2077·1); magnesia phosphorica (p. 1786·3); kali phosphoricum (p. 1791·1); kali sulphuricum (p. 1793·2); silicea (p. 2208·3); natrum muriaticum (p. 1795·1); natrum phosphoricum (p. 1791·2); natrum sulphuricum (p. 1888·1).
Homoeopathic preparation.

Hylands Cough *Hylands, Canad.*
Antimonium tartaricum (p. 151·2); bryonia (p. 2461·3); causticum (p. 2595·3); hepar sulfuricum (p. 1721·3).
Homoeopathic preparation.

Hylands Flu *Hylands, Canad.*
Eupatorium perfoliatum (p. 2459·1); bryonia (p. 2461·3); gelsemium sempervirens (p. 2511·2); euphrasia officinalis (p. 2502·1); kali iodatum (p. 2336·3); anas barbaria hepatis et cordis (p. 2444·1).
Homoeopathic preparation.

Hylands Formula C *Hylands, Canad.*
Chamomilla (p. 2474·1); humulus lupulus (p. 2546·1); avena sativa (p. 2451·1); passiflora incarnata (p. 2584·1).
Homoeopathic preparation.

Hylands Formula CA *Hylands, Canad.*
Berberis vulgaris (p. 2502·1); hepar sulfuris calcareum (p. 1721·3); echinacea angustifolia (p. 2498·1); sulphur iodatum (p. 2624·2).
Homoeopathic preparation.

Hylands Formula CF *Hylands, Canad.*
Calcarea phosphorica (p. 1784·2); ferrum phosphoricum (p. 2077·1); chamomilla (p. 2474·1); humulus lupulus (p. 2546·1); magnesia phosphorica (p. 1786·3); avena sativa (p. 2451·1); passiflora incarnata (p. 2584·1); kali phosphoricum (p. 1791·1); natrum phosphoricum (p. 1791·2).
Homoeopathic preparation.

Hylands Formula CS *Hylands, Canad.*
Aconitum napellus (p. 2428·3); antimonium tartaricum (p. 151·2); ipecac (p. 1667·2); spongia tosta.
Homoeopathic preparation.

Hylands Formula CZ *Hylands, Canad.*
Aconitum napellus (p. 2428·3); gelsemium sempervirens (p. 2511·2); allium cepa (p. 2575·2).
Homoeopathic preparation.

Hylands Formula E *Hylands, Canad.*
Apis mellifica (p. 2445·2); arnica montana (p. 2447·2); belladonna (p. 2453·3); cantharis (p. 2469·2); allium cepa (p. 2575·2); rhus aromatica (p. 2603·3); equisetum hyemale (p. 2500·1).
Homoeopathic preparation.

Hylands Formula F *Hylands, Canad.*
Anas barbariae hepatis et cordis (p. 2444·1); bryonia alba (p. 2461·3); eupatorium perfoliatum (p. 2459·1); euphrasia officinalis (p. 2502·1); gelsemium sempervirens (p. 2511·2); kali iodatum (p. 2336·3).
Homoeopathic preparation.

Hylands Formula MC *Hylands, Canad.*
Cimicifuga racemosa (p. 2478·1); citrullus colocynthis (p. 1833·3); magnesia phosphorica (p. 1786·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Hylands Formula NT *Hylands, Canad.*
Calcarea phosphorica (p. 1784·2); ferrum phosphoricum (p. 2077·1); magnesia phosphorica (p. 1787·3); kali phosphoricum (p. 1791·1); natrum phosphoricum (p. 1791·2).
Homoeopathic preparation.

Hylands Formula PI *Hylands, Canad.*
Croton tiglium; rhus toxicodendron; xerophyllum asphodeloides.
Homoeopathic preparation.

Hylands Formula S *Hylands, Canad.*
Hydrastis canadensis (p. 2528·1); calcarea carbonica (p. 1824·3); kali bichromicum (p. 2476·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Hylands Gas *Hylands, Canad.*
Asafoetidia (p. 2449·3); ignatia amara (p. 2532·1); lycopodium clavatum (p. 2547·1); nux moschata (p. 2573·1).
Homoeopathic preparation.

Hylands Headache *Hylands, Canad.*
Belladonna (p. 2453·3); ipecacuanha (p. 1667·2); iris versicolor (p. 2534·3); gelsemium sempervirens (p. 2511·2).
Homoeopathic preparation.

Hylands Hemorrhoids *Hylands, Canad.*
Aesculus hippocastanum (p. 2431·2); calcarea fluorica (p. 2053·1); nux vomica (p. 2573·3); ratanhia (p. 2603·3).
Homoeopathic preparation.

Hylands Insomnia *Hylands, Canad.*
Hyoscyamus niger (p. 2530·2); ignatia amara (p. 2532·1); kali phosphoricum (p. 1790·3).
Homoeopathic preparation.

Hylands Kinder-BW *Hylands, Canad.*
Belladonna (p. 2453·3); rhus aromatica (p. 2603·3); equisetum hyemale (p. 2500·1).
Homoeopathic preparation.

Hylands Kinder-CL *Standard Homeopathic, Canad.†*
Chamomile (p. 2474·1); citrullus colocynthis (p. 1833·3); dioscorea villosa (p. 2648·1).
Homoeopathic preparation.

Hylands Kinder-T *Standard Homeopathic, Canad.†*
Belladonna (p. 2453·3); calcium phosphate tribasic (p. 1784·2); chamomile (p. 2474·1); coffee (p. 2648·2).
Homoeopathic preparation.

Hylands LCQ *Hylands, Canad.*
Aconitum napellus (p. 2428·3); cinchona officinalis (p. 2478·3); gnaphalium polycephalum; ledum palustre (p. 2550·1); magnesia phosphorica (p. 1786·3); viscum album (p. 2560·2); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Hylands Leg Cramps *Hylands, Canad.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); ledum palustre (p. 2550·1); magnesia phosphorica (p. 1787·3); rhus toxicodendron (p. 2603·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Hylands Menstrual Cramps *Hylands, Canad.†*
Cimicifuga racemosa (p. 2478·1); colocynthis (p. 1833·3); magnesia phosphorica (p. 1787·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Hylands Motion Sickness *Hylands, Canad.*
Cocculus indicus (p. 2483·1); nux vomica (p. 2573·3); petroleum (p. 2587·2); tabacum (p. 2632·2).
Homoeopathic preparation.

Hylands PMS *Hylands, Canad.*
Caulophyllum thalictroides (p. 2458·2); cocculus indicus (p. 2483·1); gelsemium sempervirens (p. 2511·2); viburnum opulus.
Homoeopathic preparation.

Hylands Sinus *Hylands, Canad.†*
Calcarea carbonica (p. 1824·3); hydrastis canadensis (p. 2528·1); kali bichromicum (p. 2476·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Hylands Sore Throat *Hylands, Canad.*
Baryta carbonica (p. 2452·2); belladonna (p. 2453·3); mercurius iodatus ruber (p. 2555·3); phytolacca decandra (p. 2593·2).
Homoeopathic preparation.

Hylands Upset Stomach *Hylands, Canad.*
Carbo vegetabilis (p. 1537·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Hylands Vaginitis *Hylands, Canad.†*
Candida albicans; carbolicum acidum (p. 1763·3); kreosotum (p. 1659·3); natrum muriaticum (p. 1795·1).
Homoeopathic preparation.

Hylaprin *Hylands, Canad.*
Caulophyllum thalictroides (p. 2458·2); cocculus indicus (p. 2483·1); gelsemium sempervirens (p. 2511·2); viburnum opulus.
Homoeopathic preparation.

Hylaquell BC *Hylands, Canad.*
Kali bichromicum (p. 2476·3); sanguinaria canadensis (p. 2610·1); rumex crispus (p. 2649·3).
Homoeopathic preparation.

Hylase
Note: this name may be used for preparations of different composition.
ECR, USA.
Sodium hyaluronate (p. 2526·2).
Wounds.

Riemser, Austria; Riemser, Cz.; Riemser, Ger.
Hyaluronidase (p. 2527·2).
Adjunct in ocular surgery; adjuvant to increase absorption and dispersion of drugs; urological procedures; orthopaedic surgery; myocardial infarction; inflammation; haematoma; oedema.

Riemser, Ger.
Sodium chloride (p. 1795·1).

Hylatopic *Onset, USA.*
Emollient.

Hylavir FB *Standard Homeopathic, Canad.†*
Antimony trisulfide (p. 2445·1); baptisia tinctoria (p. 2647·2); sodium borate (p. 2459·2); sodium chloride (p. 1795·1).
Homoeopathic preparation.

Hylenex *Baxter, USA.*
Hyaluronidase (p. 2527·2).
To increase the absorption and dispersion of injected drugs; hypodermoclysis.

Hyles *Berlin Pharm, Thai.*
⊗Spironolactone (p. 1499·3).
Aldosteronism; ascites; hypertension; oedema.

Hylex *Lexus, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Hylira *Hawthorn, USA.*
Sodium hyaluronate (p. 2526·2).
Xerosis.

Hylo-Care *Ursapharm, Ger.; Visufarma, Ital.; Pharma Medica, Switz.; Scope, UK.*
Sodium hyaluronate (p. 2526·2); dexpanthenol (p. 2582·2).
Dry eyes; nasal dryness.

Hylo-COMOD *Croma, Fr.; Ursapharm, Ger.; Ursapharm, Israel; Visufarma, Ital.; Ursapharm, Malaysia; Ursapharm, Rus.; Pharma Medica, Switz.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; lubrication of contact lenses; eye irritation.

Hylo-Forte *Scope, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylo-Gel *Ursapharm, Ger.; Pharma Medica, Switz.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylo-Lasop *Ursapharm, Ger.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylomax-COMOD *Ursapharm, Rus.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery; dry eyes.

Hylone *Hos & Ins, India.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Hylo-Parin *Ursapharm, Ger.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Hylorase *Biosena, India.*
Hyaluronidase (p. 2527·2).
Hypodermoclysis; enhance absorption of intramuscular and subcutaneous injections; reduction of extravasation.

Hylos *Synmedic, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Hylo-Tear *Scope, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylovis *TRB, Fr.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylo-Vision *OmniVision, Ger.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hylo-Vision HD Plus *OmniVision, Ger.*
Sodium hyaluronate (p. 2526·2); allantoin (p. 1693·1).
Dry eyes.

Hylozar-COMOD *Ursapharm, Rus.*
Sodium hyaluronate (p. 2526·2); dexpanthenol (p. 2582·2).
Dry eyes.

Hyltrin *Farmalider, Spain.*
Ibuprofen arginine (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Hyluprotect *Thea, Ital.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Hymecel *Novartis, Gr.*
Hypromellose (p. 2189·2).

Hymed *Medifive, Thai.*
Codergocrine mesilate (p. 389·2).
Cerebrovascular disorders; mental function impairment.

Hymelose *Klar Sehen, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Hymidin *Nipro Genepha, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Hymin *Intra-Labs, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Hymin Plus *Intra-Labs, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Hymnox *Roxall, Ger.†*
Allergen extract of *Apis mellifera* (p. 2434·3) or *Vespula* spp. (p. 2434·3).
Allergen immunotherapy; diagnosis of hypersensitivity.

Hymoist *FDC, India.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Hynasal *DWD, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Hynasal-XL *DWD, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Hyne *Psyco Remedies, India.*
Hydroquinone (p. 1705·1).
Hyperpigmented skin disorders.

Hyneurin *Vendrell, Spain.*
St John's wort (p. 449·1).
Asthenia.

Hynidase *Shreya, India.*
Hyaluronidase (p. 2527·2).
Enhancement of absorption of intramuscular and subcutaneous injections; reduction of extravasation.

Hynot *H & Care, India.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

HyoMax *Aristos, USA.*
Hyoscyamine sulfate (p. 1848·1).

Hyomide *Beacons, Hong Kong; CCM, Malaysia; Beacons, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hyophen *BioComp, USA.*
Methenamine (p. 322·3); benzoic acid (p. 1738·2); salol (p. 129·3);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).

Hyopt *Virchow, India.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Hyosman *T Man, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hyosman Plus *T Man, Thai.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Gastrointestinal disorders.

Hyosmed *Medifive, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; gastrointestinal motility disorders.

Hyosophen *Rugby, USA.*
Atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); hyoscyamine hydrobromide (p. 1848·1) or hyoscyamine sulfate (p. 1848·1); phenobarbital (p. 535·2).
Gastrointestinal disorders.

Hyospan *Cipla, India; Polipharm, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer; gastroduodenitis; postoperative nausea and vomiting.

Hyospas *Neon, India.*
Hyoscine butylbromide (p. 1845·3).
Nausea and vomiting; premedication; smooth muscle spasm.

Hyospasmol *Aspen, S.Afr.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm.

Hyostan *Pharmaland, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; nausea and vomiting.

Hyosun *Sunward, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hyoswift *Ind-Swift, India.*
Hyoscine butylbromide (p. 1845·3).
Nausea and vomiting; premedication; smooth muscle spasm; motion sickness.

Hyozin *Union Drug, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; nausea and vomiting; peptic ulcer.

Hypa *Biosans, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Hypace *Pascual, Philipp.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Hypa-D *Biosans, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Hypadil *Kowa, Jpn.*
⊗Nipradilol (p. 2009·3).
Glaucoma; ocular hypertension.

Hypam *Mylan, NZ.*
Triazolam (p. 1112·3).
Insomnia.

Hypan *Takeda, Belg.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Hypaque *Sanofi-Aventis, Braz.; GE Healthcare, Canad.†; Intrapharm, UK.*
Sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

GE Healthcare, USA.†
Meglumine amidotrizoate (p. 1581·3) or sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Hypaque-M *Sanofi-Aventis, Braz.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

GE Healthcare, Canad.†
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Hypaque-M, Hypaque-76 *GE Healthcare, USA.†*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Hypart *Neiss, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Hypart-H *Neiss, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hypen *Shinyaku, Jpn.*
Etodolac (p. 57·1).
Musculoskeletal and joint disorders; pain; inflammation.

Hyper Hep B *Talecris, Hong Kong; Biem, Turk.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hyperamine *Braun, Fr.; Braun, UK.*
Amino acids.
Parenteral nutrition.

Hypercal
Note: this name may be used for preparations of different composition.
Nelson, UK.
Calendula officinalis (p. 2465·2); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Hypercaps *Herbapol Krakow, Pol.*
St John's wort (p. 449·1).
Depression.

Hyperchol *Ikapharmindo, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Hypercor *Sriprasit, Thai.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Hypercrit *Delta, Arg.; Landsteiner, Mex.†; Biogalenic, Venez.*
⊗Epoetin (p. 1141·1).
Anaemias.

Pentafarma, Chile.
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Hyperdix *Servier, Philipp.†; Servier, Thai.†*
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Hyperesa *Dolorgiet, Ger.†*
Valerian (p. 2640·2); St John's wort (p. 449·1).
Nervous disorders; insomnia.

Hypereze *Pharmcom, Denm.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Hyperforat *Klein, Ger.*
St John's wort (p. 449·1).
Depression; nervous disorders.

Hyperforat Nervo *Klein, Ger.*
Hypericum perforatum (p. 449·1); valeriana officinalis (p. 2640·2); strychnos ignatii (p. 2532·1).
Homoeopathic preparation.

Hyperforat Vita *Klein, Ger.*
Hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Hypergel *Molnlycke, Austral.; Molnlycke, Canad.; Molnlycke, Fr.*
Hypertonic saline debriding agent (p. 1795·1).
Wounds; ulcers.

Molnlycke, Belg.
A hydrogel dressing.
Wounds.

Hypergo *Renata, Philipp.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

HyperHAES *Fresenius Kabi, Austria; Fresenius Kabi, China; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Hung.; Fresenius Kabi, Irl.; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.; Fresenius Kabi, UK†; Fresenius Kabi, Ukr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; shock; hypovolaemia.

HyperHep B *Grifols, Canad.; Dipa, Indon.; Perrigo, Israel; Bayer, NZ; Grifols, USA.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Hyperherba *Labofarm, Pol.*
St John's wort (p. 449·1).
Depression.

Hyperhes *Fresenius Kabi, Fr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; shock.

HyperiCalm *MedicHerb, UK.*
St John's wort (p. 449·1).
Depression; anxiety.

Hypericon *Swiss Caps, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Hypericum Complexe No 26 *Lehning, Fr.*
Melilotus (p. 2552·3); viburnum opulus; arnica (p. 2447·2); atropa belladonna (p. 2453·3); secale cornutum (p. 2137·1); arsenicum iodatum (p. 2448·1); phosphorus (p. 2589·2); rhus toxicodendron (p. 2603·3); hypericum (p. 449·1).
Homoeopathic preparation.

Hyperidrine *Bio-Health, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Hyperiforce *Aponova, Austria; Bioforce, Canad.†; Vogel, Fin.; Bioforce, Switz.; Bioforce, UK.*
St John's wort (p. 449·1).
Anxiety; nervous disorders; depression; sleep disorders; low mood.

Hyperiforce comp *Bioforce, Switz.*
St John's wort (p. 449·1); melissa (p. 2552·3); lupulus (p. 2546·1).
Depression; nervous disorders; sleep disorders.

Hyperiforte *Blackmores, Thai.*
St John's wort (p. 449·1).
Anxiety.

Hyperigreen *Greenpharma, Braz.†*
St John's wort (p. 449·1).

Hyperikan *Schwabe, Cz.†; Stetifarm, Venez.*
St John's wort (p. 449·1).
Depression.

Hyperil *Ferron, Indan.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction.

Hyperilite *Holland Pharma, Neth.*
Avena sativa (p. 2451·1); cyclamen europaeum (p. 2490·2); hypericum perforatum (p. 449·1); gelsemium sempervirens (p. 2511·2); passiflora incarnata (p. 2584·1); valeriana officinalis (p. 2640·2); ignatia amara (p. 2532·1).
Homoeopathic preparation.

HyperiMed *Bioforce, Switz.*
St John's wort (p. 449·1).
Depression; nervous disorders; sleep disorders.

Hyperiplant *VSM, Belg.; VSM, Neth.; Schwabe, Switz.*
St John's wort (p. 449·1).
Depression; nervous disorders; insomnia.

Hyperium *Servier, Arg.; Servier, Braz.; Servier, Fr.; Servier, Gr.; Servier, Port.; Servier, Turk.; Servier, Venez.*
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Hyperlex *Servier, Hung.*
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Hyperlipen *Sanofi-Aventis, Belg.; Sanofi-Aventis, Switz.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Hyperlite *Braun, Spain.*
Electrolytes (p. 1775·1).
Fluid and electrolyte depletion.

Hyperliz *Remedina, Gr.*
Lisinopril (p. 1420·3).
Hypertension.

HyperLYS Anamix *Nutricia, Fr.*
Food for special diets.
Hyperlysinaemia.

Hyperlyte *Braun, Canad.; Eczacibasi-Baxter, Turk.; McGaw, USA.*
A range of electrolyte infusions (p. 1775·1).
Fluid and electrolyte disorders.

Hypermin *Bioforce, Swed.*
St John's wort (p. 449·1).
Depression; anxiety.

Hypermol *Pacific, NZ.†*
⊗Timolol maleate (p. 1513·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; migraine.

Hypermycin *Prafa, Indon.†*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis.

Hypernol *DHA, Hong Kong; DHA, Singapore.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Hypernorm *Auspi, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Hyperol *Meditop, Hung.*
Urea hydrogen peroxide (p. 1774·2).
Skin and mucous membrane infections.

Hyperosedat *Gal, Pol.†*
St John's wort (p. 449·1).
Depression.

Hyperphen *Aspen, S.Afr.*
Hydralazine hydrochloride (p. 1401·2).
Hypertension.

Hyperpoll *Neocare, Belg.*
Cetirizine hydrochloride (p. 619·2).

Hyperprost
Note: this name may be used for preparations of different composition.
Nizpharm, Rus.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Robugen, Ger.
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

HyperRab *Grifols, Canad.; Talecris, Hong Kong; Perrigo, Israel; Talecris, USA.*
A rabies immunoglobulin (p. 2413·1).
Formerly known as BayRab.
Passive immunisation.

Hyperretic *Pharmasant, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hepatic cirrhosis with ascites; hypertension.

HyperRho S/D *Bayer, Canad.†; Talecris, Canad.†; Dipa, Indon.; Talecris, Rus.; Talecris, USA.*
An anti-D immunoglobulin (p. 2377·1).
Formerly known as BayRho-D.
Prevention of rhesus sensitisation.

HyperRho-D *Talecris, Hong Kong; Biem, Turk.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Hypersalt *Vista, Philipp.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Hypersol *Cassara, Arg.; Jawa, India.*
Sodium chloride (p. 1795·1).
Nasal dryness; nasal hygiene.

Hypersol B *Cassara, Arg.*
⊗Budesonide (p. 1625·1).

Hyperstat *Schering, USA.†*
Diazoxide (p. 1351·3).
Hypertension.

Hypertel *Polychronus, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Hyperten *Gelnova, Philipp.†*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Hyper-Tet *Talecris, Hong Kong.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

HyperTET *Perrigo, Israel.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Hypertet *Grifols, Canad.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Hyperthree *JRalph, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Hyperton-Opta *Optaderm, Philipp.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Hyperval *Sidroga, Switz.*
St John's wort (p. 449·1).
Depression; nervous disorders; insomnia.

Hypetin *Intra-Labs, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Hypetor *Medhaus, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; migraine.

Hyphed *Cypress, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough.

Hy-Phen *Ascher, USA.†*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).

Hypher *Hailing, China.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Hyphoral *Ipca, India.*
Lotion: Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dandruff.

Ipca, India.
Tablets: Ketoconazole (p. 585·3).
Fungal infections.

Hyplafin *Plus Pharma, Cz.; Plus Pharma, Hung.; Plus Pharma, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Hypneine *Zizine, Fr.†*
Concentrated ammoniac solution (p. 2441·2); ammonium carbonate (p. 1656·1).
Solution for dental use.

Hypnodorm *Alphapharm, Austral.; Teva, Israel.*
Flunitrazepam (p. 1073·3).
Insomnia.

Hypnoforin *Intermed, Gr.*
Zolpidem tartrate (p. 1116·2).

Hypnogen *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Zentiva, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Hypnoket *Chandra Bhagat, India.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Hypnomidate *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Pol.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Spain; Janssen-Cilag, Turk.; Janssen-Cilag, UK.*
Etomidate (p. 1901·1).
General anaesthesia.

Hypnomidato *Janssen, Port.*
Etomidate (p. 1901·1).
General anaesthesia.

Hypnonorm *Intermed, Gr.*
Zolpidem tartrate (p. 1116·2).

Hypnor *Pharmascript, S.Afr.*
Flunitrazepam (p. 1073·3).
Insomnia.

Hypnorex *Sanofi-Aventis, Ger.*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression; mania.

Hypnoril *Reliance, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Hypnotex *PC India, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Hypnothane *Neon, India.*
Halothane (p. 1902·1).
General anaesthesia.

Hypnovel *Roche, Austral.; Roche, Fr.; Roche, Irl.; Roche, NZ; Roche, UK.*
Midazolam hydrochloride (p. 1085·1).
Sedative; premedication; induction of anaesthesia; general anaesthesia; insomnia.

Hypobhac *Phapros, Indon.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Hypoca *Astellas, China; Astellas, Jpn; Astellas, Philipp.†; Astellas, Thai.†*
Barnidipine hydrochloride (p. 1314·1).
Hypertension.

Hypochylin *Recip, Fin.; Recip, Swed.*
Glutamic acid hydrochloride (p. 2070·3).
Hypochylia.

HypoCol *Asiapharm, Singapore.*
Red yeast rice (p. 2603·1).
Hyperlipidaemias.

Hypocol *Asiapharm, Malaysia.*
Red yeast rice (p. 2603·1).
Hyperlipidaemias.

Hypodine *Pharmasant, Thai.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Hypodol *Ivax, Arg.*
Lornoxicam (p. 83·2).
Pain; musculoskeletal and joint disorders.

Hypodyn *Novartis, Austria.†*
⊗Dihydroergotamine mesilate (p. 672·2); etilefrine hydrochloride (p. 1379·1).
Hypotension.

Hypofil *Sanbe, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Hypoguard Supreme Plus *Hypoguard, UK.*
Test for glucose in blood (p. 2516·3).

Hypol *Felton, Austral.*
Oral emulsion: Cod-liver oil (p. 2056·3); soya oil (p. 2092·3).
Dietary supplement.

Hypol Cherry *Felton, Austral.*
Cod-liver oil (p. 2056·3); omega-3 marine triglycerides (p. 1460·3); minerals; astragalus.
Tonic.

Hypolac *Noos, Ital.*
Infant feed.
Food intolerance.

Hypolar Retard *Sandoz, UK.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Hypolip
Note: this name may be used for preparations of different composition.
Vera, Hung.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Hypoloc *Menarini, Austria; Menarini, Belg.; Menarini, Denm.; Menarini, Fin.; Menarini, Gr.; Menarini, Neth.; Menarini, Port.; Menarini, Swed.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Hypoloc Comp *Menarini, Fin.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hypoloc Plus *Menarini, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hypomide *Aspen, S.Afr.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Hypophos *Samarth, India.*
Calcium acetate (p. 1783·1).

Hypophysis Complexe No 31 *Lehning, Fr.†*
Viscum album (p. 2560·2); leonurus cardiaca (p. 2564·2); calcarea acetica (p. 1783·1); lycopus virginicus (p. 2462·2); spongia; chamomilla (p. 2474·1); arsenicum iodatum (p. 2448·1); sulfur (p. 1721·1); hypophysine (p. 2444·1); cinchona succirubra (p. 2478·3).
Homoeopathic preparation.

Hyporetic *Menarini, Belg.; Menarini, Neth.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hyporolam *Biofarmkombinat, Rus.*
Laminaria (p. 2540·1); sea buckthorn (p. 2611·3).

Hyposia *Asian Pharm, Thai.*
⊗Etilefrine (p. 1379·1).
Hypotension.

Hyposin *VS, Thai.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; benign prostatic hyperplasia; Raynaud's syndrome.

Hypostamine *Chiesi, Fr.†*
Tritoqualine (p. 643·3).
Hypersensitivity reactions.

Hypotears
Note: this name may be used for preparations of different composition.
Novartis, Canad.; Novartis Ophthalmics, USA.
Eye ointment: White soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2).
Dry eyes.

Novartis, Canad.; Novartis Ophthalmics, Singapore.
Eye drops: Polyvinyl alcohol (p. 2204·2).
Dry eyes; eye irritation.

Novartis, Cz.
Vitamin A palmitate (p. 2098·3); carbomer 940 (p. 2173·3).
Dry eyes.

Novartis, Hong Kong; Novartis, Ital.; Novartis, Switz.; Novartis Ophthalmics, USA.
Eye drops: Polyvinyl alcohol (p. 2204·2); macrogol 400 (p. 2547·3).
Dry eyes; eye irritation.

Novartis, Malaysia.
Polyvinyl alcohol (p. 2204·2); macrogol (p. 2547·3).
Dry eyes.

Novartis, Philipp.
Vitamin A palmitate (p. 2098·3).
Dry eyes.

Adcock Ingram, S.Afr.†
Povidone (p. 2204·3).
Dry eyes; contact lens lubricant.

Hypotears E *Novartis, Israel.*
Povidone (p. 2204·3).
Dry eyes.

Hypotears Plus *Novartis, Arg.; Novartis, Braz.; Novartis, Cz.; Novartis, Hong Kong; Novartis, India; Novartis, Mex.; Alcon, Thai.†; Novartis, Venez.*
Povidone (p. 2204·3).
Dry eyes; lubricant for contact lenses.

Hypoten
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Sodium nitroprusside (p. 1497·1).
Hypertension; controlled hypotension during surgery; heart failure; left ventricular dysfunction.

Orion, Pol.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Hikma, Rus.†
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Hypotensor *Angelini, Gr.; Faran, Gr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Hypothiazid *Sanofi-Aventis, Hung.; Sanofi-Aventis, Rus.; Chinoin, Ukr.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; diabetes insipidus; hypercalciuria; renal calculi.

Hypotonax *Baxter, Belg.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Electrolyte and fluid disorders.

Hy-Po-Tone *Aspen, S.Afr.*
Methyldopa (p. 1431·1).
Hypertension.

Hypotonicka *Megafyt-R, Cz.†*
Crataegus (p. 2488·1); mistletoe (p. 2560·2); polygonum aviculare; raspberry leaf (p. 2603·1); melissa (p. 2552·3).
Hypertension.

Hypotonie-Gastreu R44 *Reckeweg, Ger.*
Crataegus (p. 2488·1); laurocerasus (p. 2475·2); oleander (p. 2574·3); spartium scoparium (p. 2611·3).
Homoeopathic preparation.

Hypotrit *Ebewe, Austria.*
Urapidil hydrochloride (p. 1520·2).
Hypertension.

Hypotylin *Zentiva, Cz.*
⊗Metipamide (p. 1433·3).
Hypertension.

Hypovase *Pfizer, Irl.†; Pfizer, UK.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; Raynaud's syndrome; benign prostatic hyperplasia.

Hypozar *Sieger, Gr.*
Losartan potassium (p. 1422·2).
Hypertension.

Hypren *AstraZeneca, Austria.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; nephropathy; cardiovascular risk reduction.

Hypren plus *AstraZeneca, Austria.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hypress *KRKA, Hong Kong.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Hypril *Intas, Philipp.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Hypril-A *Micro Labs, Ukr.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Hypro *Celon, India.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Hyprocel *IAE, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Hyprofil *Filadams, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; migraine; hyperthyroidism.

Hyprogres *Global, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Hypromax *Ashford, Philipp.*
Hypromellose (p. 2189·2).
Dry eyes.

Hyprosafe *BMW, India.*
Hydroxyprogesterone (p. 2285·1).
Recurrent miscarriage; amenorrhoea; abnormal uterine bleeding; endometrial cancer.

Hyprosia *Asian Pharm, Thai.†*
⊗Etilefrine (p. 1379·1).
Hypotension.

Hyprosin *LCH, Hong Kong†; Pacific, NZ.†*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; Raynaud's disease; benign prostatic hyperplasia.

Hyprosol *Dzwon, India.†*
Hypromellose (p. 2189·2).
Dry eyes.

Hypurin 30/70 *Wockhardt, UK.*
⊗Mixture of neutral insulin injection (porcine, highly purified) 30% and isophane insulin injection (porcine, highly purified) 70% (p. 475·3).
Diabetes mellitus.

Hypurin Isophane *Aspen, Austral.; LCH, Hong Kong†; CP Pharma, Switz.; Wockhardt, UK.*
⊗Isophane insulin injection (bovine, highly purified) (p. 475·3).
Diabetes mellitus.

Hypurin Lente *LCH, Hong Kong†; Wockhardt, UK.*
⊗Insulin zinc suspension (30% amorphous, 70% crystalline) (bovine, highly purified) (p. 475·3).
Diabetes mellitus.

Hypurin 30/70 Mix *CP Pharma, Switz.*
⊗A mixture of insulin injection (porcine) and isophane insulin injection (porcine) respectively in the proportion indicated (p. 475·3).
Diabetes mellitus.

Hypurin Neutral *Aspen, Austral.; LCH, Hong Kong†; CP Pharma, Switz.; Wockhardt, UK.*
⊗Neutral insulin injection (bovine, highly purified) (p. 475·3).
Diabetes mellitus.

Hypurin NPH *Wockhardt, Canad.*
⊗Isophane insulin (porcine) (p. 475·3).
Diabetes mellitus.

Hypurin Protamine Zinc *LCH, Hong Kong†; Wockhardt, UK.*
⊗Protamine zinc insulin injection (bovine, highly purified) (p. 475·3).
Diabetes mellitus.

Hypurin Regular *Wockhardt, Canad.*
⊗Soluble insulin (porcine) (p. 475·3).
Diabetes mellitus.

Hyrase *Bionova, India.*
Ubidecarenone (p. 2637·1); arginine (p. 2049·1); lycopene (p. 2546·2); selenium (p. 2086·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Hyric *Interbat, Indon.*
Syzygium polyanthum; physalis angulata (p. 2590·1); sonchus arvensis; plantain (p. 2592·3).
Hyperuricaemia.

Hyruan *LG Pharm, Hong Kong; LG Life Sciences, Malaysia; LG Life Sciences, Thai.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee; periarthritis of the shoulder; degenerative joint disorders; adjunct in orthopaedic surgery.

Hysadrac *Iasis, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Hysan *Ursapharm, Ger.; Kivema, Israel; Pharma Medica, Switz.†*
Sodium hyaluronate (p. 2526·2).
Nasal dryness.

Hysan Schnupfenspray *Ursapharm, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Hysartas *Intas, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Hyscopan *Armoxindo, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hyséké *Bailleul, Fr.*
Sodium pidolate (p. 1720·3); zinc pidolate (p. 1720·3); enoxolone (p. 54·2).
Dry skin.

Hyséké Solaire *Bailleul, Fr.*
SPF 25; SPF 50: Bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); enoxolone (p. 54·2).
Sunscreen.

Hysept *Patrin, USA.*
Sodium hypochlorite (p. 1768·3).
Disinfection.

Hysite *Pfizer, NZ.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Hyskon *Dermatech, Austral.†; Pharmacia, USA.*
⊗Dextran 70 (p. 1138·3) in glucose.
Aid to hysteroscopy.

Hy-Sone *PC India, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hysone
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Roberts, USA.
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Inflammatory skin disorders.

Hysopan *Denk, Hong Kong.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Hy-Spa *Medicine Products, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer; gastroduodenitis.

Hysron *Kyowa, Jpn.*
Medroxyprogesterone acetate (p. 2288·1).
Menstrual disorders; female infertility; threatened and recurrent miscarriage.

Hyss *Alna, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Hysticlar *Mintlab, Chile.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Hystin *Geolab, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Hystolan *Dexa, Indon.*
Isoxsuprine hydrochloride (p. 2535·2).
Uterine relaxant; peripheral vascular disorders.

Hytacand *Europharma, Denm.; Orifarm, Denm.; AstraZeneca, Fr.; AstraZeneca, Port.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

HyTan *Prasco, USA.†*
Hydrocodone tannate (p. 67·2); chlorphenamine tannate (p. 620·3).
Cough.

Hytas *Accord, Braz.*
Methotrexate (p. 822·2).

Hytaz *Therapharma, Philipp.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Hytel *East West, India.*
Telmisartan (p. 1509·3).
Hypertension.

Hytel-H *East West, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan (p. 1509·3).
Hypertension.

Hyten *Sain, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Hytenza *Watson, S.Afr.*
Losartan (p. 1422·2).

Hyteron-M *Hos & Ins, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Hythalton *Sarabhai Piramal, India.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema; premenstrual syndrome.

Hytide *Embiotic, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Hytisone *Atlantic, Hong Kong.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Atlantic, Thai.
⊗Hydrocortisone acetate (p. 1640·1).
Inflammatory skin disorders.

Hyton *Scoshia, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1); zinc sulfate (p. 2126·2).

Hytone *Dermik, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Hytos Plus *Uniao Quimica, Braz.*
Clobutinol hydrochloride (p. 1658·3); doxylamine succinate (p. 627·3).
Cough.

Hytosol *Klar Sehen, India.*
Sodium chloride (p. 1795·1).

Hytrin *Abbott, Austral.; Pharma Logistics, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, China; Amdipharm, Cz.; Abbott, Gr.; Abbott, Hong Kong; Amdipharm, Hung.; Abbott, India; Abbott, Indon.; Amdipharm, Irl.; Biotis, Israel; Abbott, Malaysia; Abbott, Mex.; Amdipharm, Neth.; Abbott, NZ; Abbott, Philipp.; Amdipharm, Pol.; Amdipharm, Port.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Amdipharm, UK; Abbott, USA; Abbott, Venez.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia; heart failure; Raynaud's syndrome.

Hytrin BPH *Pro Concepta, Switz.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Hytrine *CSP, Fr.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Hytrinex *Amdipharm, Swed.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Hytrol *Sun, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Hytrol-AM *Sun, India.*
Amlodipine besilate (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Hyver *Evershine, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Hyvisc *Sun, India.*
Sodium hyaluronate (p. 2526·2).

Hyvon-Spas *Hy-Gro, India.*
Dextropropoxyphene (p. 43·2); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Hyzaar *MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; Orifarm, Denm.†; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, NZ; MSD, Philipp.; MSD, Pol.; Frosst, Port.; MSD, Rus.; MSD, Singapore; MSD, Thai.; MSD, Turk.; Merck, USA.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; stroke prophylaxis; left-ventricular hypertrophy; cardiovascular risk reduction.

MSD, Venez.
Losartan potassium (p. 1422·2).
Hypertension.

Hyzaar Plus *MSD, Hong Kong; MSD, Venez.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; left ventricular hypertrophy.

Hyzan *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Hyzart *Domesco, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Hyzide *East West, India.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; diabetes insipidus.

Hyzin *Hawon, Philipp.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Hyzine *Utopian, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Hyzole-DP *Obsurge, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Hyzole-P *Obsurge, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

I-10 *Invision, India.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1).

I Fen F *Patar, Thai.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Ial *Bausch & Lomb, Ital.; Chemedica, Switz.; Fidia, Thai.; Interko, Turk.†*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Ialex *Aspen, Austral.*
Cefalexin (p. 234·1).
Bacterial infections.

Ialoclean *Farma Derma, Ital.*
Hyaluronic acid (p. 2526·2).
Mouth and throat disorders.

Ialugen *IBSA, Switz.*
Sodium hyaluronate (p. 2526·2).
Wounds; burns; ulcers.

Ialugen Plus *IBSA, Cz.; IBSA, Hung.; IBSA, Switz.*
Sodium hyaluronate (p. 2526·2); sulfadiazine silver (p. 362·3).
Burns; ulcers; wounds.

Ialum *Bausch & Lomb, Ital.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Ialunara *IBSA, Ger.*
Sodium hyaluronate (p. 2526·2); centella (p. 1698·3); chamomile (p. 2474·1); *dl*-alpha tocoferil acetate (p. 2119·2).
Vaginal disorders.

Ialurex *Bausch & Lomb, Ital.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Ialuset *Genevrier, Fr.*
Hyaluronic acid (p. 2526·2).
Leg ulcers; wounds.

Ialuset Plus *Genevrier, Fr.*
Sodium hyaluronate (p. 2526·2); sulfadiazine silver (p. 362·3).
Burns; infected skin disorders; wounds.

Ialutim *Bausch & Lomb, Ital.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Iamacalcin *Iamatica, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Iamastatin *Iamatica, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Iamaxicam *Iamatica, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Iamin *Merck, Mex.†*
Prezatide copper acetate (p. 1718·1).
Burns; ulcers; wounds.

Iamin Hydrating Gel *Procyte, USA.*
Prezatide copper acetate (p. 1718·1).
Burns; ulcers; wounds.

Iasan *Unipharma, Gr.*
Aceclofenac (p. 16·2).

Iasibon *Pharmathen, Cz.; Pharmathen, Denm.; Aspire, Irl.; Glenmark, Neth.*
Ibandronate sodium (p. 1184·2).
Hypercalcaemia of malignancy; bone metastases; osteolysis of malignancy.

Pharmathen, Pol.
Ibandronic acid (p. 1184·2).
Metastatic bone disease; hypercalcaemia of malignancy.

Iasvest *Iapharm, Gr.; Loevar, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Iaten *Iapharm, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

I-Bact *Intra-Labs, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Ibadrox *Labomed, Chile.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Ibagenit *Mylan, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Ibalgin *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; fever; pain.

Ibalgin Sport *Zentiva, Pol.*
Ibuprofen (p. 68·2); a heparinoid (p. 1401·1).
Musculoskeletal, joint, and soft-tissue disorders; superficial vascular disorders.

Ibames *Andromaco, Chile.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Ibamyl *Mylan, Fin.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

IbandroMylan *Mylan, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Ibanleg *Bernabo, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Ibaril *Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Bipharma, Neth.; Sanofi-Aventis, Norw.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Ibarin *Laboratorios Chile, Chile.*
Fluconazole (p. 578·2).
Fungal infections.

Ibax *Sandoz, Mex.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

IBC *Pacific, Philipp.*
Vitamin B substances (p. 2102·3); ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron and vitamin supplement for pregnancy.

Ibedox *Polinac, Venez.*
Hydroxocobalamin (p. 2107·3).
Neurological disorders.

Ibelac *Intra-Labs, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3).

Ibelac-TR *Intra-Labs, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2); *Lactobacillus sporogenes* (p. 2596·3).

Ibeln *Cratus, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Ibemiral *Almirall, Mex.*
Omeprazole (p. 1867·2).

Iben Forte *Apex, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Iben Plus *Apex, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibercal *Merck, Spain.*
Calcium pidolate (p. 1784·3).
Osteoporosis; hypocalcaemia.

Ibercal D *Merck, Spain.*
Calcium pidolate (p. 1784·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Iberet *Abbott, Hong Kong†; Abbott, Indon.; Armstrong, Mex.†; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) or sodium ascorbate (p. 2111·1) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron and vitamin B deficiency.

Iberet-Folic *Abbott, Hong Kong†; Abbott, Indon.; Abbott, Malaysia; Abbott, Philipp.; Abbott, Singapore.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron
Vitamin B and C deficiency; folic acid deficiency; iron-deficiency anaemia; iron deficiency.

Ibergal *Anpharm (Ανφαρμ), Gr.*
Codergocrine mesilate (p. 389·2).

Iberin Folico *Abbott, Braz.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Iberogast *Steigerwald, Austria; Steigerwald, Ger.; Phytotec, Hung.; Steigerwald, Neth.; Steigerwald, Pol.; Heel, Spain; Green Medicine, Swed.; Bionorica, Ukr.*
Iberis amara; angelica (p. 2443·3); chamomile (p. 2474·1); caraway (p. 2470·2); milk thistle (p. 1561·1); melissa (p. 2552·3); peppermint leaf (p. 1877·1); greater celandine (p. 2522·2); liquorice (p. 1853·2).
Gastrointestinal disorders; dyspepsia.

Steigerwald, Cz.
Iberis; angelica (p. 2443·3); chamomile (p. 2474·1); caraway (p. 2470·2); milk thistle (p. 1561·1); melissa (p. 2552·3); peppermint leaf (p. 1877·1); greater celandine (p. 2522·2); liquorice (p. 1853·2).
Gastrointestinal disorders.

Permamed, Switz.
Iberis amara; angelica (p. 2443·3); milk thistle (p. 1561·1); cuminum cyminum; chamomile (p. 2474·1); greater celandine (p. 2522·2); liquorice (p. 1853·2); melissa (p. 2552·3); peppermint leaf (p. 1877·1).
Digestive disorders.

Iberol *Ingens, Arg.; Abbott, Braz.; Abbott, Chile†; Armstrong, Mex.†*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia; vitamin B deficiency.

Ingens, Arg.; Abbott, Braz.
Oral drops: Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Pharmacia Upjohn, India.†
Oral liquid: Ferrous sulfate (p. 2062·2); vitamins.
Anaemias.

Pharmacia Upjohn, India.
Tablets: Ferrous sulfate (p. 2062·2); desiccated liver (p. 2444·1); vitamins.
Anaemias.

Iberol C *Abbott, Venez.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Iberol Folico *Abbott, Chile.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folate deficiency; iron-deficiency anaemia.

Iberomint *Steigerwald, Ger.†*
Chamomile (p. 2474·1); caraway (p. 2470·2); peppermint leaf (p. 1877·1).
Gastrointestinal disorders.

Ibeth-N *Intra-Labs, India.*
⊗Betamethasone (p. 1623·2); neomycin (p. 329·3).

Ibexone *Takeda, Belg.*
Codergocrine mesilate (p. 389·2).
Mental function impairment.

Ibiamox *Genepharm, Austral.; Douglas, NZ.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Siam Bheasach, Thai.
Amoxicillin (p. 216·2).
Bacterial infections.

Ibifen *IBI, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Ibilex *Alphapharm, Austral.; Siam Bheasach, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Ibimezolo *IBI, Ital.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ibimicyn
Note: this name may be used for preparations of different composition.
Genepharm, Austral.
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ibis
Note: this name may be used for preparations of different composition.
Menarini, Spain.
Bilastine (p. 617·3).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Pharmaland, Thai.
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Ibios, Fr.†
Camphor (p. 2466·2); lidocaine (p. 1988·1).
Musculoskeletal, joint, and peri-articular pain.

Ibitazina *Ibigen, Ital.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Ibition
Note: this name may be used for preparations of different composition.
Farmanic, Gr.
Phenylephrine hydrochloride (p. 1672·3).

Peseri, Cz.†
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Ibixacin *IBI, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ibodezil *Coup, Gr.*
Ibuprofen (p. 68·2).

Iboflam *Glenmark, S.Afr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Iboo *Teva, Israel.*
Ibuprofen (p. 68·2).
Pain; fever.

I-Boric *Entod, India.*
⊗Camphor (p. 2466·2); menthol (p. 2553·2); naphazoline nitrate (p. 1669·3); phenylephrine hydrochloride (p. 1672·3).

Ibosure *Sandoz, Neth.†*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders.

Ibotec *Fariberica, Port.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris.

Ibrex *Cadila, India.*
Tobramycin (p. 380·1).
Eye infections.

Ibrofen *TO-Chemicals, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Ibrufhalal *Halal, UK.*
Ibuprofen (p. 68·2).
Pain; inflammation.

Ibrumac *Macleods, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Ibruvon Forte *Macleods, India.*
Dextropropoxyphene hydrochloride (p. 43·3); ibuprofen (p. 68·2).

IBS *Daffohils, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

IBS Eze *Brauer, Austral.*
Antim. crud. (p. 2445·1); argent. nit. (p. 2615·3); arsen. alb. (p. 2448·1); carbo veg. (p. 1537·3); chelidonium (p. 2522·2); colocynthis (p. 1833·3); lycopodium (p. 2546·3); nat. sulf. (p. 1888·1); nux vom. (p. 2573·3); podophyllum (p. 1717·1).
Homoeopathic preparation.

IBS Relief *Mylan, UK.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Ibsinorm *Sun, India.*
Tegaserod (p. 1893·1).
Chronic idiopathic constipation; irritable bowel syndrome.

IB-Stat *Inkine, USA.†*
Hyoscyamine sulfate (p. 1848·1).

IBU *Austell, S.Afr.*
Ibuprofen (p. 68·2).

Ibu *ISA, Arg.; Andromaco, Chile; Kade, Ger.; Osper, India; Actavis, Switz.; Sandoz, Switz.; Pose, Thai.†; Boots, USA.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation; gout; musculoskeletal, joint, and soft-tissue disorders.

Ibu-600 *Yeni, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibu-4, -6, -8 *Truxton, USA.*
Ibuprofen (p. 68·2).

Ibu Evanol *GSK, Arg.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibu Evanol Extra *GSK, Arg.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Inflammation; pain.

Ibu Evanol Plus *GSK, Arg.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain; fever.

Ibu Kitadol *Laboratorios Chile, Chile.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever; inflammation.

ibu-Attritin *Tussin, Ger.†*
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibubenitol *Benitol, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibuberl *Berlin-Chemie, Cz.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibubeta *Betapharm, Ger.*
Ibuprofen (p. 68·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibubid *Natco, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Ibubid Plus *Sun, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibu-Buscapina *Boehringer Ingelheim, Arg.*
Ibuprofen (p. 68·2); hyoscine butylbromide (p. 1845·3).
Pain with muscle spasm.

Ibucalmin *Tetrafarm, Arg.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Ibucaps *Zuoz, Venez.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Ibucare *PSM, NZ.†*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibucet *East West, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibucler *Monserrat, Arg.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Ibuclin *Reddy, India; Reddy, Rus.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; fever; pain.

Ibucod *Aspen, S.Afr.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Inflammation; pain.

Farmalider, Spain.
Ibuprofen arginine (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Ibucode Plus *Arrow, NZ.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain; inflammation.

Ibucoden *Farma, Venez.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Ibucon *Volta, Chile; Concept, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation; musculoskeletal and joint disorders.

Ibucon Plus *Concept, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibudol
Note: this name may be used for preparations of different composition.
Stedman, India.
Ibuprofen (p. 68·2); tramadol hydrochloride (p. 139·2).

Ibudol-A Kid *Stedman, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibudolofrix *Penn, Arg.*
Ibuprofen (p. 68·2); codeine (p. 40·2).
Pain.

Ibudolor *Actavis, Cz.; Stada, Ger.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibudone *Proethic, USA.*
Hydrocodone tartrate (p. 67·2); ibuprofen (p. 68·2).
Pain.

Ibudristan *Wyeth Consumer, Arg.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Ibuf *Finecure, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Ibufabra *Fabra, Arg.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Fever; inflammation; pain.

Ibufac *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders; pain; fever.

Ibufarmalid *Farmalider, Spain.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

Ibufem
Note: this name may be used for preparations of different composition.
Biotenk, Arg.
Ibuprofen (p. 68·2); homatropine methylbromide (p. 2007·3).
Dysmenorrhoea; smooth muscle spasm.

Galpharm, UK.
Ibuprofen (p. 68·2).
Dysmenorrhoea.

Ibufen *Dexcel, Israel; Medana, Pol.; Akrikhin, Rus.; Beacons, Singapore; Cinfa, Spain; Abbott, Turk.; Polpharma, Ukr.; Vargas, Venez.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain; gout; musculoskeletal, joint, and peri-articular disorders; soft-tissue injury.

Ibufen-L *Amino, Switz.*
Suppositories: Ibuprofen lysine (p. 68·3); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Amino, Switz.
Tablets: Ibuprofen lysine (p. 68·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Ibufex *United Drug, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibufix *Investi, Arg.*
Ibuprofen (p. 68·2).
Fever; gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibuflam *Winthrop, Ger.†; Graceway, Mex.*
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain; fever; soft-tissue disorders.

Ibuflamar-P *Indoco, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; pain.

Ibuflex *Legrand, Braz.; Rayere, Mex.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Ibufran *Neo Quimica, Braz.*
Ibuprofen (p. 68·2).

Ibufull *Lafedar, Arg.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Fever; pain; inflammation.

Ibugan *Sanofi-Aventis, Thai.*
Ibuprofen (p. 68·2).
Pain; musculoskeletal, joint, and soft-tissue disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ibugel *GSK, Gr.†; Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Ibuprofen (p. 68·2).
Neuralgia; musculoskeletal, joint, and soft-tissue disorders.

Ibugesic *Cipla, India; Cipla-Medpro, S.Afr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever; inflammation.

Ibugesic Plus *Cipla, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; pain.

Ibugesic Plus-NF *Cipla, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibugesic-M *Cipla, India.*
Methocarbamol (p. 2025·3); ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Ibugin *GSK, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Ibu-Hepa *Zentiva, Cz.*
Ibuprofen (p. 68·2); a heparinoid (p. 1401·1).
Inflammation; soft-tissue disorders; venous insufficiency.

Ibuhexal *Hexal, Ger.†*
Ibuprofen (p. 68·2) or ibuprofen sodium (p. 68·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibukey *Pharminicio, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue pain and inflammation.

Ibukids *LBS, Thai.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibulam *Lamsa, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibulan *Olan-Kemed, Thai.*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal and joint disorders.

Ibuleve *Diomed, Irl.†; Dermal, Israel; Pfizer, S.Afr.; GSK, Singapore; Dendron, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ibulgia *Biosintex, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibulium *Medicine Products, Thai.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Ibu-Lysin *Ratiopharm, Ger.*
Ibuprofen lysine (p. 68·3).
Pain; fever.

Ibum *Hasco-Lek, Pol.*
Topical gel: Ibuprofen (p. 68·2); levomenthol (p. 2553·2).
Musculoskeletal and joint pain; neuralgia.

Hasco-Lek, Pol.
Capsules; oral suspension: Ibuprofen (p. 68·2).
Fever; pain.

Ibum Grip *Hasco-Lek, Pol.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Ibumac *Belmac, Spain.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal, joint, and peri-articular disorders; gout; pain.

Ibumac Plus *Profic Organic, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibuman *T Man, Thai.*
Ibuprofen (p. 68·.
Fever; inflammation; pain.

Ibumar *Mar, Arg.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Ibumax
Note: this name may be used for preparations of different composition.
Vitabalans, Cz.; Vitabalans, Denm.; Vitabalans, Fin.; Vitabalans, Hung.; Cipla-Medpro, S.Afr.; Vitabalans, Swed.; Utopian, Thai.
Ibuprofen (p. 68·2).
Fever; gout; inflammation; pain; musculoskeletal, joint, and soft-tissue disorders.

Mission Happiness, India.
Oral drops: Paracetamol (p. 115·1).
Pain; fever.

Mission Happiness, India.
Tablets: Paracetamol (p. 115·1); diclofenac potassium (p. 48·3); magnesium trisilicate (p. 1858·1).

Ibumed *Pharmacobel, Belg.; GSK, S.Afr.*
Ibuprofen (p. 68·2).
Pain; fever.

Ibumet P *Mount Mettur, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibumetin *Nycomed, Austria; Nycomed, Denm.; United Nordic, Denm.; Leiras, Fin.; Nycomed, Norw.; Nycomed, Swed.*
Ibuprofen (p. 68·2).
Gout; pain; inflammation; fever; musculoskeletal, joint, and soft-tissue disorders.

Ibumil *Losan, Denm.*
Ibuprofen potassium (p. 68·2).
Pain; fever.

Ibumol *Brown, India; Aspen Consumer, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Inflammation; pain; musculoskeletal and joint disorders.

Ibumousse *Dermal Laboratories, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Ibumultin *Lazar, Arg.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Ibun *Lincoln, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibunastizol *Bago, Arg.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Cold and influenza symptoms.

Ibunate *Gulf Drug, S.Afr.*
Ibuprofen (p. 68·2).

Ibunij *Sunij, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibu-Novalgina *Sanofi-Aventis, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibup *Bouzen, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibupac *Inpac, Thai.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibupain *Sandoz, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Ibupain Forte *Sandoz, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; inflammation; pain.

Ibupal *Jagsonpal, India.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain.

Ibupar *Polfa Pabianice, Pol.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibupar-M *Chemo-Drugs, India.*
Ibuprofen (p. 68·2); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Ibupas *Sigma-Tau, Ital.*
Ibuprofen (p. 68·2).

Ibuped *Healthprime, Philipp.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; fever.

Ibupen *APT, Hong Kong.†*
Ibuprofen (p. 68·2).
Pain; fever.

Ibupirac *Pfizer, Arg.; Chemopharma, Chile.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ibupirac Compuesto *Chemopharma, Chile.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Ibupirac Fem *Pfizer, Arg.*
Ibuprofen (p. 68·2); homatropine methylbromide (p. 2007·3).
Dysmenorrhoea; smooth muscle spasm.

Ibupirac Flex *Pfizer, Arg.*
Ibuprofen (p. 68·2); chlorzoxazone (p. 2022·2).
Musculoskeletal and joint disorders; pain.

Ibupirac Flu *Chemopharma, Chile.*
⊗Ibuprofen (p. 68·2); pseudoephedrine (p. 1676·1).
Cold and influenza symptoms; nasal congestion.

Ibupirac Migra *Pfizer, Arg.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3); ergotamine tartrate (p. 674·1).
Migraine.

Ibupiretas *Pfizer, Arg.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Ibupril *Teuto, Braz.*
Ibuprofen (p. 68·2).

Ibuprin *Vivax Gynopharm, Venez.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibuproct *Galenica, Gr.; Olvos, Gr.*
Trimebutine (p. 2634·1); ruscogenin (p. 2608·3).
Rectal disorders.

Ibuprofan *Bunker, Braz.*
Ibuprofen (p. 68·2).

Ibuprofenix *Phoenix, Arg.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibuprofex *Sertex, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibuprom *US Pharmacia, Pol.; US Pharmacia, Rus.; US Pharmacia, Ukr.*
Ibuprofen (p. 68·2).
Fever; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ibuprom Sinus *US Pharmacia, Ukr.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Ibuprom Zatoki *US Pharmacia, Pol.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Ibuprox *Ratiopharm, Norw.; Ferrer, Spain.†*
Ibuprofen (p. 68·2).
Fever; pain; musculoskeletal, joint, and peri-articular disorders; gout.

Ibu-Proxyvon *Wockhardt, India.*
Ibuprofen (p. 68·2); dextropropoxyphene hydrochloride (p. 43·3).
Musculoskeletal and joint disorders; pain.

Ibura *Shreya, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Iburamin Cold *Berko, Turk.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Ibu-ratiopharm *Ratiopharm, Ger.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Iburic Plus *Euphoric, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Iburion *Orion, Cz.; Orion, Pol.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

Ib-u-ron *Bene, Ger.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibusal *Orion, Fin.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal and joint disorders; gout.

Ibuscent *Alpex, Switz.†*
Ibuprofen (p. 68·2).
Pain; fever.

Ibusi *Mertens, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibusifar *Siphar, Switz.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Ibusol *Cassara, Arg.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Ibuspan *Emcure, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Ibuspan-P *Emcure, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibuspel *Specifar (Σπεσιφαρ), Gr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Ibuspray *Dermal Laboratories, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Ibustar *Berlin-Chemie, Denm.*
Ibuprofen (p. 68·2).
Pain; fever.

Ibustick *Farmasierra, Spain.*
Ibuprofen (p. 68·2).
Pain; inflammation.

Ibustrin *Pfizer, Cz.; Pfizer, Ital.; Pfizer, Mex.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia Upjohn, Rus.; Pfizer, Venez.*
Indobufen (p. 1410·1).
Thromboembolic disorders; thrombosis prophylaxis.

Ibusumal *Purissimus, Arg.†*
Ibuprofen (p. 68·2).
Pain.

Ibusynth *AstraZeneca, India.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Ibu-Tab *Alra, USA.*
Ibuprofen (p. 68·2).
Rheumatoid arthritis; osteoarthritis; pain; fever.

Ibutab *Zee, USA.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibutabs *Orion, Fin.*
Ibuprofen (p. 68·2).
Fever; pain.

Ibutad *TAD, Ger.†*
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibutan *Meyer Alian, Venez.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibutard *Borshchagovskii, Ukr.*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ibutenk *Biotenk, Arg.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibu-Tetralgin *Craveri, Arg.*
Ibuprofen (p. 68·2); ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Ibutin *Galenica, Gr.*
Trimebutine (p. 2634·1).
Gastrointestinal and gallbladder pain.

Ibutop
Note: this name may be used for preparations of different composition.
Sanova, Austria; Omega, Belg.; Dolorgiet, Denm.; Omega, Fr.; Chefaro, Ger.†; Dolorgiet, Hung.
Ibuprofen (p. 68·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Overseas, India.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibutop Cuprofen *SSL, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ibutop Ralgex *SSL, UK.†*
Ibuprofen (p. 68·2).
Musculoskeletal pain; inflammation.

Ibuvix *Geolab, Braz.*
Ibuprofen (p. 68·2).

Ibuwin *Wings, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Ibux *Weifa, Norw.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibuxfar *Wunderpharm, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibuxim *Savant, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ibuxim Fem *Savant, Arg.*
Ibuprofen (p. 68·2); hyoscine butylbromide (p. 1845·3).

Ibuxin *Ratiopharm, Fin.*
Ibuprofen (p. 68·2).
Fever; pain; musculoskeletal and joint disorders; gout.

Ibuzidine *Fada, Arg.*
Ibuprofen (p. 68·2).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Ibuzin *Apofri, Swed.*
Ibuprofen lysine (p. 68·3).
Pain; fever; rheumatoid arthritis; osteoarthritis.

IC Green *Akorn, Israel†; Akorn, USA.*
Indocyanine green (p. 2532·3).
Ophthalmic angiography; determination of cardiac output and liver blood flow.

Icaden *Intendis, Braz.; Bayer, Mex.; Intendis, Mex.; Schering, Venez.*
Isoconazole (p. 583·2) or isoconazole nitrate (p. 583·2).
Fungal skin infections; fungal and Gram-positive vulvovaginal infections.

Icandra *Novartis, Cz.; Schwarz, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Port.; Novartis, Spain.*
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

ICaps *Alcon, Canad.*
Vitamins; minerals.

Icaps *Alcon, Chile; Alcon, USA.*
Vitamins; minerals.
Dietary supplement.

Alcon, Hong Kong; Alcon, Thai.†
Vitamins; minerals; lutein (p. 2079·2).
Macular degeneration.

Alcon, Mex.; Alcon, Singapore; Alcon, UK.
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement.

Icaps Areds *Alcon, Thai.*
Vitamins; minerals.
Dietary supplement for healthy vision.

ICaps Lutein and Zeaxanthin *Alcon, Canad.*
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3).

Icaps Plus *Alcon, Arg.*
Vitamins; minerals; cysteine (p. 2058·3).
Dietary supplement.

Icar *Hawthorn, USA.*
Carbonyl iron (p. 2073·1).
Iron deficiency; iron supplement.

Icar Prenatal *Hawthorn, USA.†*
Tablets, vitamins; minerals; chewable tablets, calcium carbonate; soft gel capsules, omega-3 marine triglycerides.
Nutritional supplement during pregnancy and lactation.

Icar-C Plus *Hawthorn, USA.*
Carbonyl iron (p. 2073·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Folate deficiency; iron-deficiency anaemia.

Icaz *Daiichi Sankyo, Fr.; Wander, Philipp.*
Isradipine (p. 1414·2).
Hypertension.

Ice Cool *Hovid, Malaysia.†*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal pain.

Ice Cool Stress & Tension Relief *Amirose, UK.*
Menthol (p. 2553·2).
Headache; tension.

Ice Gel *Mentholatum, Austral.*
Menthol (p. 2553·2).
Muscular aches and pains.

Ice Gel Therapy *Sutton, Canad.*
Menthol (p. 2553·2).
Musculoskeletal and joint pain.

Icee *Sarthak, India.*
⊗Camphor (p. 2466·2); glycerol (p. 2517·2); iodine (p. 2336·3); menthol (p. 2553·2); potassium (p. 1793·1); tannic acid (p. 2625·2); thymol (p. 1772·2).

Icee Mth W sh *Sarthak, India.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).

Icegel *Universal Medicare, India.*
Menthol (p. 2553·2).

Icel *Zydus, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; dysmenorrhoea; familial adenomatous polyposis.

Icelac *Stalwart, India.*
Vitamin B substances (p. 2102·3); *Lactobacillus sporogenes* (p. 2596·3).

Icenac *Daffohils, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Icenac-P *Daffohils, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Icer *Evershine, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Icer-D *Evershine, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Icerin *Intra-Labs, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Icerin-GM *Intra-Labs, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Icer-MS *Evershine, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Iceron *Alna, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Icetazol *IQFA, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Icey *Laborate, India.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).

ICG-Pulsion *Pulsion, Ger.; IFET (ΙΦΕΤ), Gr.; Pulsion, Irl.; Pulsion, Israel; Pulsion, Neth.; Pulsion, Singapore.*
Indocyanine green (p. 2532·3).
Diagnostic agent.

Ichthalgan forte *Ichthyol, Austria.*
Heparin sodium (p. 1396·3); ictasol (p. 1706·1).
Musculoskeletal, joint, and peri-articular disorders.

Ichtho-Bad *Ichthyol, Austria; Ichthyol, Ger.; Medinova, Switz.*
Ichthammol (p. 1705·3).
Bath additive; hyperhidrosis; musculoskeletal and joint disorders; neuralgia; pelvic disorders; skin disorders; superficial circulatory disorders; wounds; genito-urinary disorders.

Ichthocortex *Erfar, Gr.*
⊗Hydrocortisone acetate (p. 1640·1); ichthammol (p. 1705·3).

Ichthocortin *Ichthyol, Ger.*
⊗Hydrocortisone acetate (p. 1640·1); ictasol (p. 1706·1).
Skin disorders.

Ichthoderm *Ichthyol, Ger.*
Ictasol (p. 1706·1).
Scalp disorders.

Ichtholan *Ichthyol, Austria; Ichthyol, Ger.; Medinova, Switz.*
Ichthammol (p. 1705·3).
Pyoderma; musculoskeletal, joint, and peri-articular disorders; thrombophlebitis; sports injuries; skin disorders.

Ichtholan spezial *Ichthyol, Ger.*
Ichthammol (p. 1705·3).
Musculoskeletal and joint disorders.

Ichtholan T *Ichthyol, Ger.*
Ictasol (p. 1706·1).
Skin disorders.

Ichthopaste *Smith & Nephew, Austral.; Smith & Nephew, Ital.; Smith & Nephew, UK.*
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1).
Medicated bandage; skin ulcers; skin disorders.

Ichthoseptal *Ichthyol, Ger.†*
Chloramphenicol (p. 257·1); ictasol (p. 1706·1).
Infected skin disorders.

Ichthosin *Ichthyol, Ger.*
Ictasol (p. 1706·1).
Skin disorders.

Ichthraletten *Ichthyol, Ger.*
Sodium bituminosulfonate (p. 1706·1).
Skin disorders.

Ichthyol *Ichthyol, Ger.*
Ichthammol (p. 1705·3).
Skin disorders.

Ichtiyol-Zalf *Nufarindo, Indon.*
Ichthammol (p. 1705·3).
Abscess.

Ichtopaste *Smith & Nephew, Canad.*
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1).
Leg ulcers.

Ichtoxyl *Herbacos Recordati, Cz.*
Ichthammol (p. 1705·3).
Skin disorders.

Icidil *Piramal, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Icidob *Piramal, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Icikinase *Piramal, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Icin *Ind Biosciences, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Icip *Elder, India.*
Ciprofloxacin (p. 261·1).
Bacterial eye infections; bacterial ear infections.

Iclodex *Medilife, Philipp.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections with inflammation.

I-Clom *Yung Shin, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Iclopid *Polfa Pabianice, Pol.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Iclusig *Ariad, UK; Ariad, USA.*
Ponatinib hydrochloride (p. 848·2).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia.

Icobit *Cubit, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Icobit-MR *Cubit, India.*
Aceclofenac (p. 16·2); tizanidine (p. 2026·2).

Icobit-P *Cubit, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Icobit-Plus *Cubit, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Icobit-S *Cubit, India.*
⊗Aceclofenac (p. 16·2); serrapeptase (p. 2613·3).

I-Cof *Vesco, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Icol *Alcon Cusi, Spain.*
⊗Chloramphenicol (p. 257·1) or chloramphenicol succinate (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Icolid *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Icolid CPM *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough.

Icolid DX *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); terpin hydrate (p. 1678·2); chlorphenamine maleate (p. 620·3).
Cough.

Icolid Expectorant *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Icolid Plus *Greater Pharma, Thai.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; cough.

Icolyte-P *Ives, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).

Icona *Farmaline, Thai.†*
Itraconazole (p. 583·3).
Fungal infections.

Iconal *Anpharm (Ανφαρμ), Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Iconcee *Hizon, Philipp.*
Sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Icop *Biosans, India.*
Teicoplanin (p. 369·3).
Bacterial infections.

Icoplax *Richmond, Arg.*
Vancomycin (p. 384·2).
Bacterial infections.

Icor *Novaduo, India.*
Iron sucrose (p. 2078·1).

Icoran *Biomedica, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Icorsan *Tocogino, Mex.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Icparil *ICPA, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Icrate *Cratus, India.*
Syrup: Sodium feredetate (p. 2088·3).

Cratus, India.
Tablets: Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2).

Icthaband *Medlock Medical, UK.*
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1).
Medicated bandage.

Ictinal *UCB, Gr.*
Hydroxyzine hydrochloride (p. 630·3).

Ictiomen *Casen Fleet, Spain.*
Ichthammol (p. 1705·3); talc (p. 1722·2); menthol (p. 2553·2).
Skin disorders.

Ictotest *Bayer, Austral.†; Bayer Diagnostics, UK; Bayer, USA.*
Test for bilirubin in urine.

Ictus *Biolab Sanus, Braz.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Ictyane *Silesia, Chile; Ducray, Fr.*
⊗Glycerol (p. 2517·2); white soft paraffin (p. 2211·3).
Dry skin disorders.

Pierre Fabre Dermo-Cosmetique, Arg.
A range of moisturisers and soap substitutes.

Ictyane HD *Ducray, Fr.*
⊗Hydroxydecine; white soft paraffin (p. 2211·3); glycerol (p. 2517·2); shea butter (p. 2208·2).
Dry skin disorders.

Icy Hot *Pharmacia, S.Afr.†; Chattem, Singapore; Chattem, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Icy Hot Back Pain Relief *Chattem, USA.*
Menthol (p. 2553·2).

Icy Hot Pain Relieving *Chattem, USA.*
Menthol (p. 2553·2).
Musculoskeletal and joint pain.

Icy Hot PM *Chattem, USA.*
Lotion: Menthol (p. 2553·2).

Chattem, USA.
Topical patch: Capsaicin (p. 35·1); menthol (p. 2553·2).
Musculoskeletal and joint pain; neuralgias.

Icy Hot Pop & Peel *Chattem, USA.*
Menthol (p. 2553·2).

Icy Hot Pro-Therapy *Chattem, USA.*
Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Icy Hot Roll *Chattem, USA.*
Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Icy Rub *Kato, Pol.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); thymol (p. 1772·2).
Musculoskeletal, joint, and soft-tissue pain.

Ida *The Forty-Two, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ida-D *The Forty-Two, Thai.*
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Idalev *Invision, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Idalez *Invision, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Idalez Plus *Invision, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Idalprem *Novartis Consumer, Spain.†*
Lorazepam (p. 1080·3).
Anxiety; insomnia; alcohol withdrawal syndrome; nausea and vomiting.

Idamen *Nevzat, Turk.*
Idarubicin hydrochloride (p. 805·2).

Idamycin *Pfizer, Canad.; Pfizer, Mex.; Pharmacia Upjohn, USA.*
Idarubicin hydrochloride (p. 805·2).
Leukaemias; breast cancer.

Idapride *Invision, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Idapride-M *Invision, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Idapride-PM *Invision, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Idaptan *Danval, Spain.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Idarac *Sanofi-Aventis, Fr.; Sanofi-Aventis, Thai.*
Floctafenine (p. 64·3).
Pain.

Idaralem *Teva, Mex.†; Lemery, Thai.†*
Idarubicin hydrochloride (p. 805·2).
Acute leukaemias; breast cancer.

Idasal *Omega, Spain.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis.

Idazole *Chew, Thai.*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis; necrotising ulcerative gingivitis; Helicobacter pylori *eradication.*

IDC *Pharmaland, Thai.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Idealite *Rafarm, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Idec *Invision, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Idecortex *Pentafarma, Port.*
Idebenone (p. 392·3).
Mental function disorders.

Ideg *Unikid, India.*
Amikacin (p. 214·1).
Bacterial infections.

Idelol *Medicine Products, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension.

Idena *Raffo, Arg.*
Ibandronate (p. 1184·2).
Osteoporosis.

Tecnofarma, Chile.
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Idenimo *Fortbenton, Arg.*
Idebenone (p. 392·3); nimodipine (p. 1455·2).
Cerebrovascular disorders.

Ideobron *Mertens, Arg.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Allergic disorders of the respiratory tract.

Ideogrip *GP, Arg.*
Loratadine (p. 633·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Idéolaxyl *GSK Sante, Fr.*
Aloes (p. 1816·1); senna (p. 1885·1).
Constipation.

Ideos *Innotech, Cz.†; Meda, Denm.; Innotech, Fin.; Innotech, Ger.; Vianex (Biuvež), Gr.; Innotech, Hung.; Innotech, Irl.; Rottapharm, Ital.; Innotech, Neth.†; Innothera, Pol.†; Innotech, Port.; Innotech, Rus.; Warner Chilcott, Spain; Meda, Swed.; Innotech, Ukr.†; Zuoz, Venez.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency; calcium supplement; hyperparathyroidism.

Idéos *Innotech, Fr.; Innotech, Norw.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Idesal *Help, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Idesar Plus *Nufarindo, Indon.*
Phyllanthi; vitamin B substances (p. 2102·3); bovine colostrum (p. 2380·3); black elderberry (p. 2609·3); echinacea (p. 2498·1); ganoderma lucidum; thymomodulin (p. 2631·1).
Dietary supplement; tonic.

Idesole *Phoenix, Arg.*
Idebenone (p. 392·3).
Mental function impairment.

Idesole Plus *Phoenix, Arg.*
Idebenone (p. 392·3); nimodipine (p. 1455·2).
Cerebrovascular disorders.

IDflu *Sanofi Pasteur, Cz.; Sanofi Pasteur, Hung.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Idibend *Indian Drugs, India.*
Mebendazole (p. 158·3).
Worm infections.

Idicin *Indian Drugs, India.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; dysmenorrhoea.

Idifulvin *Indian Drugs, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Idiglobin *Indian Drugs, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_2 (p. 2104·3); vitamin C (p. 2110·3).

Idilan *Ikon, India.*
Isoxsuprine (p. 2535·2) or isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

Idilin *Indian Drugs, India.*
Tetracycline (p. 373·1).
Bacterial infections.

Idimox *Indian Drugs, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Idinir *Invision, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Idiquin *Indian Drugs, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Idizone *Indian Drugs, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Idle *Klonal, Arg.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Ido-C *Abigo, Swed.*
Ascorbic acid (p. 2110·3).
Some tablets also contain sodium ascorbate.
Vitamin C deficiency.

Ido-E *ACO Hud, Fin.†; McNeil, Norw.†; ACO, Swed.†*
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E deficiency.

Idol *Ind Biosciences, India.*
Tramadol (p. 139·2).
Pain.

Idom *Biokanol, Ger.†*
Dosulepin hydrochloride (p. 414·1).
Depression.

Idomethine *Kowa, Jpn.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Idometrin-D *Aaron, India.*
Diloxanide furoate (p. 931·2); tinidazole (p. 949·2).

Idon *Saval, Chile.*
Domperidone (p. 1838·1).
Gastrointestinal disorders; gastrointestinal investigations; parkinsonism.

Idotrim *Orion, Swed.*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Idotyl *Ferrosan, Denm.†*
Aspirin (p. 22·2).
Inflammation; musculoskeletal and joint disorders; pain.

Idovit *Vitamed, Israel.†*
Povidone-iodine (p. 1767·1).
Wounds; burns; bacterial and fungal skin infections; skin disinfection.

Idoxen *Dollder, Venez.*
Venlafaxine (p. 454·2).
Anxiety; depression.

Idoxy *Ikon, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Idracal *Bruno, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; rickets.

Idracemi *Farmigea, Ital.*
Eye drops: ⊗Hydrocortisone sodium phosphate (p. 1640·2).
Eye disorders.

Farmigea, Ital.
Eye ointment: ⊗Hydrocortisone hydrogen succinate (p. 1640·2); neomycin sulfate (p. 330·1); chloramphenicol (p. 257·1).
Eye disorders.

Idracemi Eparina *Farmigea, Ital.*
⊗Hydrocortisone sodium phosphate (p. 1640·2); heparin sodium (p. 1396·3).
Eye disorders.

Idranox *Gap, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Idravita *Humana, Ital.*
Oral rehydration preparation (p. 1780·1).

Idren *Baif, Ital.*
Camelia sinensis (green tea) (p. 2648·2); bitter orange (p. 2575·3); rhodiola rosea; ananas sativus; taraxacum (p. 2625·3); centella (p. 1698·3).
Cellulite.

Idrinol *Soteks, Rus.*
Meldonium (p. 1429·3).

Idrofos *Sun, India.*
Ibandronic acid (p. 1184·2) or ibandronate (p. 1184·2).

Idrolax *Ipsen, Irl.*
Macrogol 4000 (p. 2547·3).
Constipation.

Idroplurivit *Menarini, Ital.*
Vitamins.

Idroquark *Polifarma, Ital.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Idroskin *Mavi, Ital.*
Collagen (p. 2483·2).
Dry skin.

Idroskin C *Mavi, Ital.*
Hyaluronic acid (p. 2526·2); vitamin C (p. 2110·3).
Dry skin.

Idrostamin *Gap, Gr.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Idrovel *Savoma, Ital.*
Emollient.

Iducher *Farmigea, Ital.*
Idoxuridine (p. 985·1).
Herpesvirus infections of the eye.

Idulea *Elea, Arg.*
Idoxuridine (p. 985·1).
Herpesvirus infections of the eye, face, lips, and genitals.

Idune *Genevrier, Fr.*
Sodium hyaluronate (p. 2526·2).
Skin contour defects.

Idurin *Klar Sehen, India.*
Idoxuridine (p. 985·1).
Herpes simplex keratitis.

Idustatin *Sanofi-Aventis OTC, Ital.*
Cream: Idoxuridine (p. 985·1).
Herpes simplex infections of the skin and mucous membranes.

Idyl *Multicare, Philipp.*
Ibuprofen (p. 68·2).
Inflammation; musculoskeletal and joint disorders; pain.

Iecatec *Tedec Meiji, Spain; Meiji, Thai.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Iecilline *Ulagay, Turk.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Iesef *Ulagay, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Iesetum *Ulagay, Turk.*
Ceftazidime (p. 250·2).
Bacterial infections.

Iespor *Ulagay, Turk.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ifa Acxion *Investigacion, Mex.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Ifa Lose *Investigacion, Mex.†*
⊗Mazindol (p. 2324·1).
Obesity.

Ifa Norex *Investigacion, Mex.†*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Ifa Reduccing *Investigacion, Mex.†*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Ifacap *Mayne, Mex.†*
Carboplatin (p. 759·1).
Ovarian cancer.

Ifa-Certez *Investigacion, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Ifa-Certez Duo *Investigacion, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2); metformin hydrochloride (p. 489·1).
Obesity associated with diabetes mellitus.

Ifact *Medico, India.*
Ivermectin (p. 155·1).
Worm infections.

Ifadac *Mayne, Mex.†*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Ifadex *Cryopharma, Mex.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifa-Diety *Investigacion, Mex.*
⊗Fenproporex hydrochloride (p. 2323·1).
Obesity.

Ifadox *Mayne, Mex.†*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Ifa-Fonal *Investigacion, Mex.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; spasticity.

Ifamet *Mayne, Mex.†*
Methotrexate (p. 822·2).
Malignant neoplasms.

Ifamul *Guardian, Indon.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; endocrine adenoma.

Ifapidin *Egis, Pol.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Ifarab *Mayne, Mex.†*
Cytarabine (p. 774·1).
Malignant neoplasms.

Ifavac *Mayne, Mex.†*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Ifavor *Mayne, Mex.†*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia; reduction of methotrexate toxicity; adjunct to fluorouracil therapy in colorectal cancer.

Ifaxol *Mayne, Mex.†*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

IFB *Globus, India.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Ifcit *Siomond, India.*
Syrup: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Siomond, India.
Tablets: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2); magnesium hydroxide (p. 1857·2).

Ifemed *Medifive, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Ifenec *Italfarmaco, Ital.*
Econazole (p. 577·2) or econazole nitrate (p. 577·3).
Fungal infections; Gram-positive bacterial infections.

Italfarmaco, Rus.
Econazole nitrate (p. 577·3).
Fungal skin and vaginal infections.

Ifentil *Biomep, Mex.*
Ibuprofen (p. 68·2).
Pain.

iFerex *Nnodum, USA.*
Iron (p. 2073·1).
Iron supplement.

iFerex Forte *Nnodum, USA.*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Dietary supplement.

Ifex *Baxter, Canad.; Baxter, USA.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifex-M *Biochem, India.*
Ifosfamide (p. 806·1); mesna (p. 1557·2).
Malignant neoplasms.

Iffeza *Mundipharma, Neth.*
⊗Fluticasone propionate (p. 1638·1); formoterol fumarate (p. 1209·2).
Asthma.

Ificef *Unique, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ificipro *Unique, Rus.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Unique, Thai.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Unique, Ukr.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ifimol *JB Chemicals, India.*
Paracetamol (p. 115·1).
Pain; fever.

Ifiral *JB Chemicals, India; Unique, Philipp.; Unique, Rus.*
Sodium cromoglicate (p. 1225·3).
Food allergy; mastocytosis; allergic rhinitis; allergic conjunctivitis.

Ifirmacombi *KRKA, Irl.; KRKA, Neth.; KRKA, Spain.*
⊗Irbesartan hydrochloride (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ifirmasta *KRKA, Cz.; KRKA, Denm.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.; KRKA, Spain.*
Irbesartan hydrochloride (p. 1411·1).
Hypertension; diabetic nephropathy.

Ifistatin *Unique, Singapore.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hyperlipidaemias.

Ifizol *Unique, Rus.†*
Cefazolin (p. 237·2).
Bacterial infections.

Iflacef *Candor, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Iflacort *Pharos, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Iflerit *Velka, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

I-Flex *Phapros, Indon.*
Rose fruit (p. 2607·1).
Joint disorders.

Iflox *Medilife, Philipp.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Ifloxin *Ashford, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Corneal ulcers; bacterial conjunctivitis.

IFO-Cell *Stada, Malaysia.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

IFO-cell *Cell Pharm, Ger.; Cell Pharm, Thai.†*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifocip *Cipla, India.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifocris *LKM, Arg.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

I-Fol *Laksun, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Ifolem *Laboratorios Chile, Chile; Teva, Mex.; Teva, Thai.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

I-Folic *Blackmores, Austral.*
Potassium iodide (p. 2336·3); folic acid (p. 2063·1).
Dietary supplement; prevention of neural tube defects.

Ifomida *Asofarma, Mex.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifomid-M *United Biotech, India.*
1 Vial, ifosfamide (p. 806·1); 3 ampoules, mesna (p. 1557·2).

Ifor *Medix, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ifos
Note: this name may be used for preparations of different composition.
Cipla, India.
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifosmixan *Richmond, Arg.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifoxan *Baxter Oncology, Israel.†*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifoxan with Mesna *Alkem, India.*
Ifosfamide (p. 806·1); mesna (p. 1557·2).

Ifuchol *Ifusa, Mex.*
Cynara (p. 2490·3); boldo (p. 2458·3); turmeric (p. 2218·1).
Digestive disorders.

Ifupasil *Ifusa, Mex.*
Passion flower (p. 2584·1); salix (p. 129·2); crataegus (p. 2488·1).
Nervous disorders.

Ifupeptol Magnesiado *Ifusa, Mex.*
Magnesium sulfate (p. 1787·3).
Hypersensitivity.

Ifurax *ADP, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

IFX *Gobbi, Arg.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ifyasco-Z *Sanify, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Ifycal *Sanify, India.*
Minerals; trace elements; colecalciferol (p. 2113·1).

Ifycal-AD *Sanify, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Ifycal-C *Sanify, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Ifycal-D3 *Sanify, India.*
Calcium (p. 1783·1); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).

Ifycarb *Sanify, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Ifycarb-Z *Sanify, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1); vitamin C (p. 2110·3).

Ifycet *Sanify, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1) or phenylpropanolamine hydrochloride (p. 1674·1).

Ifycet-DT *Sanify, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Ifyclo-G *Sanify, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Ifydrox *Sanify, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Ifytrox *Sanify, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ifytrox-SB *Sanify, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Ifytrox-TB *Sanify, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Ifyzyme *Sanify, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

IG Tetano *Kedrion, Philipp.†*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Ig Vena *Kedrion, Austria; Kedrion, Ger.; Kedrion, Gr.; Kedrion, Ital.; Kedrion, Port.; Kedrion, Switz.; Kedrion, Thai.; Onko, Turk.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immunodeficiency; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone-marrow transplantation; passive immunisation.

Ig Vena N *Biosano, Chile.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immunodeficiency disorders; immune thrombocytopenia; myasthenia gravis; Guillain-Barré syndrome; Kawasaki disease.

IgA (Alpha Chain) *Sanofi-Aventis, India.*
Alpha-chain specific antisera to human IgA (goat).

Igamad *Grifols, Chile; Grifols, Cz.; Grifols, Ital.; Grifols, Spain; Grifols, Thai.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Igamplia *Grifols, Cz.; Grifols, Spain.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; hypogammaglobulinaemia.

Igantet *Grifols, Arg.; Grifols, Chile; Demo, Gr.; Grifols, India; Grifols, Ital.; Grifols, Malaysia; Grifols, Singapore.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Igantibe *Grifols, Arg.; Grifols, Chile; IFET (ΙΦΕΤ), Gr.; Grifols, Ital.; Grifols, Spain; Grifols, Thai.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Igantid *Grifols, Arg.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Igardex *Ind-Swift, India.*
⊗Camphor (p. 2466·2); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); naphazoline hydrochloride (p. 1669·3); phenylephrine (p. 1672·2).

Igastrum *Pharos, Indon.*
Bovine colostrum (p. 2380·3); vitamins.
Dietary supplement.

Igastrum Plus *Pharos, Indon.*
Vitamins; bovine colostrum (p. 2380·3); calcium (p. 1783·1); docosahexaenoic acid (p. 1460·1); lysine (p. 2079·3).
Dietary supplement; tonic.

IgéE *Grands Espaces, Fr.†*
Black currant (p. 2458·1); raspberry (p. 2207·2).
Cold symptoms.

I-Gesic *Centaur, India.*
Diclofenac sodium (p. 48·3).
Inhibition of miosis in cataract surgery; eye inflammation and pain; allergic conjunctivitis.

IgG (Alpha Chain) *Sanofi-Aventis, India.*
Alpha-chain specific antisera to human IgA (goat).

Igiol *Lamda (Λαμδα), Gr.*
Povidone-iodine (p. 1767·1).

Igir *Velka, Gr.*
Loratadine (p. 633·2).

I-Glo *Aspen, S.Afr.*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Iglodep *Metiska, Indon.*
Sertraline hydrochloride (p. 448·1).
Depression.

Iglodine *Fecofar, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Iglodine Flex *Fecofar, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Inflammation; pain; musculoskeletal disorders.

Iglü *Diomed, UK.*
Mouth gel: Aminoacridine hydrochloride (p. 1732·3); lidocaine hydrochloride (p. 1988·2).
Mouth ulcers, sore gums.

Diomed, UK.
Pastilles: Benzalkonium chloride (p. 1737·1); Compound Benzoin Tincture BP.
Mouth ulcers; sore gums.

IgM (Mu Chain) *Sanofi-Aventis, India.*
Mu-chain specific antisera to human immunoglobulin.

Ignatia-Homaccord *Heel, Austria; Ebi, Switz.*
Strychnos ignatii (p. 2532·1); moschus moschiferus (p. 2198·2).
Homoeopathic preparation.

Ignava *Health Biotech, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Ignis
Note: this name may be used for preparations of different composition.
Alembic, India.
Domperidone (p. 1838·1); esomeprazole magnesium (p. 1841·1).

Sanovel, Turk.
Aripiprazole (p. 1038·3).

Igol *Raptakos, India; Raptakos, Thai.*
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome.

Igrexa *Atlantis, Mex.*
Nimesulide (p. 101·3).
Pain; fever; musculoskeletal and joint disorders.

Igroseles *UCB, Ital.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Igroton *Amdipharm, Ital.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema.

Igroton-Lopresor *Daiichi Sankyo, Ital.*
⊗Chlortalidone (p. 1335·2); metoprolol tartrate (p. 1434·3).
Hypertension.

Igroton-Reserpina *Amdipharm, Ital.*
⊗Chlortalidone (p. 1335·2); reserpine (p. 1485·3).
Hypertension.

Iguassina *Zambon, Braz.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

IHD *Stadmed, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ihope *Taiwan Biotech, Philipp.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses in parkinsonism.

Ihtiyol *Cagdas, Turk.; Gunsa, Turk.; Lokman, Turk.; Oro, Turk.; Sifa, Turk.*
Ichthammol (p. 1705·3).
Eczema.

iiCare *Mega Lifesciences, Philipp.*
Myrtillus (p. 2566·2); lutein (p. 2079·2); betacarotene (p. 2051·1).
Age-related macular degeneration.

IJM-Gel *Candor, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Ika *Emcure, India.*
⊗Cetirizine (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Ika Sariawan *Ikapharmindo, Indon.*
Abrus precatorius (p. 2426·1); betel; liquorice (p. 1853·2); peppermint oil (p. 1877·1).
Mouth ulcers; mouth hygiene.

Ikacetamol *Ikapharmindo, Indon.*
Paracetamol (p. 115·1).
Pain; fever.

Ikacin *Cinerea, India.*
Amikacin (p. 214·1).
Bacterial infections.

Ikaclomin *Teva, Israel.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; oligospermia.

Ikacor *Teva, Israel.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Ikacycline *Ikapharmindo, Indon.*
Tetracycline hydrochloride (p. 373·2).
Skin infections.

Ikaderm *Ikapharmindo, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Ikadryl *Ikapharmindo, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Ikadryl DMP *Ikapharmindo, Indon.*
Syrup: Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Ikapharmindo, Indon.
Tablets: Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Ikaflux *Cifarma, Braz.*
Potassium iodide (p. 2336·3); guaifenesin (p. 1666·2).
Cough.

Ikagen *Ikapharmindo, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Ikametin *Plus Pharma, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis; bone metastases.

Ikamicetin *Ikapharmindo, Indon.*
Chloramphenicol (p. 257·1).
Skin infections; eye infections.

Ikamoxyl *Ikapharmindo, Indon.*
Amoxicillin (p. 216·2).
Bacterial infections.

Ikamoxyl Plus *Ikapharmindo, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Ikaneuron *Ikapharmindo, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; neuropathy; migraine; paraesthesia; vomiting of pregnancy; vitamin B deficiency.

Ikaneuron Plus *Ikapharmindo, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis.

Ikaphen *Ikapharmindo, Indon.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Ikapress *Teva, Israel.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension.

Ikapril *Polfa Pabianice, Pol.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Ikaprim *Ikapharmindo, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections; toxoplasmosis.

Ikaran *Pierre Fabre, Fr.*
Dihydroergotamine mesilate (p. 672·2).
Migraine; hypotension; venous insufficiency.

Ikatin *Pisa, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Ikatral *Baliarda, Arg.*
Proanthocyanidin oligomers (p. 2521·3).
Venous insufficiency; circulatory disorders of the eye.

Ikatral Periferico *Baliarda, Arg.*
Proanthocyanidin oligomers (p. 2521·3); pentoxifylline (p. 1465·3).
Vascular disorders.

Ikelan *Medochemie, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Ikériane *Ducray, Fr.*
Cream: Guanidine glycolate (p. 1704·3).
Dry skin disorders.

Ducray, Fr.
Face scrub: Salicylic acid (p. 1719·1).
Skin cleanser.

Ikeriane *Pierre Fabre Dermo-Cosmetique, Arg.*
Guanidine glycolate (p. 1704·3).
Dry skin disorders.

Ikestatina *United Biotech, India; Crinos, Ital.; Neopharma, Venez.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery; diabetic ketoacidosis; gastrointestinal radiography.

Ikka *Hauz, India.*
Amikacin (p. 214·1).
Bacterial infections.

Ikleen *Parenteral Drugs, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Ikobel *Rafarm, Gr.*
Tobramycin (p. 380·1).
Eye infections.

Ikolan *Investi, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Ikoplex 5 *Knop, Canad.†*
Calcium phosphate tribasic (p. 1784·2); magnesium phosphate dibasic (p. 1786·3); phosphoric acid (p. 2589·1); potassium phosphate dibasic (p. 1791·1); silicon dioxide (p. 2208·3).
Homoeopathic preparation.

Ikoplex 12 *Knop, Canad.†*
Arnica (p. 2447·2); belladonna (p. 2453·3); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens (p. 2511·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Ikoplex 14 *Knop, Canad.†*
Magnesium chloride hexahydrate (p. 1787·1); magnesium phosphate dibasic (p. 1786·3); sodium chloride (p. 1795·1); sodium sulfate (p. 1888·1).
Homoeopathic preparation.

Ikoplex 21 *Knop, Canad.†*
Ferrum phosphoricum (p. 2077·1); potassium sulfate (p. 1793·2); silicon dioxide (p. 2208·3); dibasic sodium phosphate (p. 1791·2).
Homoeopathic preparation.

Ikoplex 11 Digestion Aid *Knop, Canad.†*
Charcoal activated (p. 1537·3); ferrum phosphoricum (p. 2077·1); graphite (p. 2522·1); potassium phosphate dibasic (p. 1791·1); sodium chloride (p. 1795·1).
Homoeopathic preparation.

Ikoplex No 1 *Knop, Chile.*
Calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); kalium phosphoricum (p. 1790·3); magnesium phosphoricum (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 2 *Knop, Chile.*
Calcium phosphoricum (p. 1784·2); ferrum metallicum (p. 2073·1); kalium phosphoricum (p. 1790·3); natrium phosphoricum (p. 1791·1); natrium sulfuricum (p. 1888·1).
Homoeopathic preparation.

Ikoplex No 3 *Knop, Chile.*
⊗Ephedrin hidrochlor (p. 1663·2); kalium chloratum (p. 1793·2); magnesium phosphoricum (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 4 *Knop, Chile.*
Calcium phosphoricum (p. 1784·2); calcium fluoratum (p. 2053·1); magnesium phosphoricum (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 5 *Knop, Chile.*
⊗Kalium phosphoricum (p. 1790·3); ammonium phosphoricum (p. 2442·1); kalium chloratum (p. 1793·2); magnesium phosphoricum (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 6 *Knop, Chile.*
Cactus (p. 2473·2); calcium floratum (p. 2053·1); calcium phosphoricum (p. 1784·2); magnesium phosphoricum (p. 1787·3); natrium chloratum (p. 1795·1).
Homoeopathic preparation.

Ikoplex No 7 *Knop, Chile.*
Graphites (p. 2522·1); ferrum phosphoricum (p. 2077·1); natrium chloratum (p. 1795·1); natrium sulfuricum (p. 1888·1); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 8 *Knop, Chile.*
Natrium chloratum (p. 1795·1); natrium sulfuricum (p. 1888·1); ferrum phosphoricum (p. 2077·1); kalium chloratum (p. 1793·2); kalium phosphoricum (p. 1790·3); kalium sulfuricum (p. 1793·2); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 9 *Knop, Chile.*
Zincum metallicum (p. 2126·1); calcium phosphoricum (p. 1784·2); kalium chloratum (p. 1793·2); kalium phosphoricum (p. 1790·3); magnesium phosphoricum (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 10 *Knop, Chile.*
Magnesium peroxyd (p. 1759·3); magnesium phosphoricum (p. 1787·3); calcium fluoratum (p. 2053·1); natrium phosphoricum (p. 1791·1); natrium sulfuricum (p. 1888·1).
Homoeopathic preparation.

Ikoplex No 11 *Knop, Chile.*
Carbo sanguine; ferrum phosphoricum (p. 2077·1); kalium phosphoricum (p. 1790·3); magnesium peroxyd (p. 1759·3); natrium chloratum (p. 1795·1).
Homoeopathic preparation.

Ikoplex No 12 *Knop, Chile.*
Eupatorium perfoliatum (p. 2459·1); arnica (p. 2447·2); belladonna (p. 2453·3); gelsemium (p. 2511·2); sulfuro (p. 1721·1).
Homoeopathic preparation.

Ikoplex No 13 *Knop, Chile.*
Solidago (p. 2620·1); kalium chloratum (p. 1793·2); kalium phosphoricum (p. 1790·3); natrium chloratum (p. 1795·1); natrium sulfuricum (p. 1888·1).
Homoeopathic preparation.

Ikoplex No 14 *Knop, Chile.*
Natrium sulfuricum (p. 1888·1); natrium chloratum (p. 1795·1); magnesium chloratum (p. 1787·1); magnesium phosphoricum (p. 1787·3).
Homoeopathic preparation.

Ikoplex No 15 *Knop, Chile.*
Silicea (p. 2208·3); calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); kalium chloratum (p. 1793·2); natrium phosphoricum (p. 1791·2).
Homoeopathic preparation.

Ikoplex No 17 *Knop, Chile.*
Kalium chloratum (p. 1793·2); kalium sulfuricum (p. 1793·2); natrium chloratum (p. 1795·1); natrium sulfuricum (p. 1888·1); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 18 *Knop, Chile.*
Pulsatilla (p. 2600·2); ferrum phosphoricum (p. 2077·1); kalium chloratum (p. 1793·2); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Ikoplex No 19 *Knop, Chile.*
Alumina (p. 1817·2); ferrum phosphoricum (p. 2077·1); kalium phosphoricum (p. 1790·3); kalium sulfuricum (p. 1793·2); natrium chloratum (p. 1795·1); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 20 *Knop, Chile.*
Magnesium phosphoricum (p. 1787·3); calcium phosphoricum (p. 1784·2); kalium chloratum (p. 1793·2); kalium sulfuricum (p. 1793·2); natrium phosphoricum (p. 1791·2); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 21 *Knop, Chile.*
Natrium phosphoricum (p. 1791·2); ferrum phosphoricum (p. 2077·1); kalium sulfuricum (p. 1793·2); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 22 *Knop, Chile.*
Kalium sulfuricum (p. 1793·2); kalium chloratum (p. 1793·2); calcium phosphoricum (p. 1784·2); ferrum phosphoricum (p. 2077·1); natrium phosphoricum (p. 1791·2).
Homoeopathic preparation.

Ikoplex No 23 *Knop, Chile.*
Phosphorus (p. 2589·2); ferrum phosphoricum (p. 2077·1); kalium chloratum (p. 1793·2); magnesium phosphoricum (p. 1787·3); silicea (p. 2208·3).
Homoeopathic preparation.

Ikoplex No 24 *Knop, Chile.*
Arsenicum album (p. 2448·1); calcium fluoratum (p. 2053·1); kalium phosphoricum (p. 1790·3); natrium phosphoricum (p. 1791·2); silicea (p. 2208·3).
Homoeopathic preparation.

Ikorel *Sanofi-Aventis, Austral.; 2care4, Denm.; Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Bilim, Turk.; Sanofi, UK.*
Nicorandil (p. 1446·2).
Angina pectoris.

Ikotril *Sanofi-Aventis, Gr.*
Nicorandil (p. 1446·2).
Angina pectoris.

Iktorivil *Roche, Swed.*
Clonazepam (p. 519·1).
Epilepsy; status epilepticus.

Ikx Autobronceante *Ikx, Arg.†*
Dihydroxyacetone (p. 1700·1).
Tanning aid.

Ikx Gel Reductor *Ikx, Arg.†*
Phosphatidyl choline (p. 2588·3); caffeine (p. 1203·3); guarana (p. 2648·2).

IL-33 *Istanbul, Turk.*
Trichloroacetic acid (p. 1727·2); monochloroacetic acid (p. 1714·3); dichloroacetic acid.
Warts.

IL HWA *Allcura, Ger.; Solmer, Switz.*
Ginseng (p. 2513·3).
Tonic.

Ilaris *Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, USA.*
Canakinumab (p. 34·2).
Cryopyrin-associated periodic syndromes; gout; juvenile idiopathic arthritis.

Ilast Care *Horus, Fr.; Chemedica, Ger.*
Sodium hyaluronate (p. 2526·2); allantoin (p. 1693·1); vitamin A palmitate (p. 2098·3).
Eyelid care; dry eyes; eye irritation.

Ilast Hydra *Horus, Fr.*
Sodium hyaluronate (p. 2526·2); allantoin (p. 1693·1).
Eyelid cleanser.

Ilast O'Clean *Horus, Fr.*
Sodium hyaluronate (p. 2526·2); allantoin (p. 1693·1).
Eyelid cleanser; face cleanser.

Ilast Post-Op *Horus, Fr.*
Sodium hyaluronate (p. 2526·2); allantoin (p. 1693·1); vitamin A palmitate (p. 2098·3).
Postoperative eyelid care.

Ilaten *Lamsa, Arg.*
⊗Atenolol (p. 1308·2).
Hypertension.

I-Lax *Plus, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Ilaxten *Menarini, UK.*
Bilastine (p. 617·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

I-Laxx *Lumar, Philipp.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Pain; inflammation; fever.

Ilcass *Varifarma, Arg.*
Interleukin-2 (p. 810·1).

Ilcid *Utopian, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Ildamen *Zydus, India; Transfarma, Philipp.; Sidefarma, Port.*
Oxyfedrine hydrochloride (p. 1464·1).
Heart failure; angina pectoris; myocardial infarction; arrhythmias.

Ildecep *Ildong, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; acid aspiration.

Ilduc *Baliarda, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ilduc Duo *Baliarda, Arg.*
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Ilefrin *GMP, Indon.*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Ilens *Ashford, Philipp.*
Potassium iodide (p. 2336·3); sodium iodide (p. 2337·1).
Dry eye disorders.

Ilet *MSN, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ilet-B *MSN, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Iletin N *Lilly, India.*
⊗Isophane insulin injection (bovine and porcine, highly purified) (p. 475·3).
Diabetes mellitus.

Iletin II Pork Lente *Lilly, Canad.†*
⊗Insulin zinc suspension (porcine) (p. 475·3).
Diabetes mellitus.

Iletin II Pork NPH *Lilly, Canad.†*
⊗Isophane insulin injection (porcine) (p. 475·3).
Diabetes mellitus.

Iletin II Pork Regular *Lilly, Canad.†*
⊗Neutral insulin injection (porcine) (p. 475·3).
Diabetes mellitus.

Iletin R *Lilly, India.*
⊗Insulin injection (bovine and porcine, highly purified) (p. 475·3).
Diabetes mellitus.

Ilevro *Alcon, USA.*
Nepafenac (p. 101·1).
Eye pain and inflammation following cataract surgery.

Ilezol *Medimport, Mex.*
⊗Mazindol (p. 2324·1).
Obesity.

Ilgaper *Actavis, Pol.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Ilgem *Rafarm, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Ilgen *Bioprofarma, Arg.*
Interleukin-2 (p. 810·1).
Metastatic melanoma; renal cancer.

Iliaclor *VEG, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Iliadin *Merck, Chile; Merck, Denm.†; Galenica, Gr.; Merck, Hong Kong; Merck, Indon.; Seven Seas, Irl.†; Merck, Malaysia; Merck, Mex.; Merck, Norw.†; Merck, S. Afr.; Merck Consumer, Singapore; CCS, Swed.; Merck, Thai.; Santa, Turk.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; catarrh; conjunctivitis; otitis media; rhinitis; ear disorders; sinusitis; cold symptoms; pharyngitis; laryngitis; syringitis; nasopharyngitis.

Ilidar *Pasteur, Chile.*
Flutamide (p. 798·2).
Prostatic cancer; benign prostatic hyperplasia; hirsutism.

Ilides *Bioresearch, Mex.*
Albendazole (p. 149·1).
Worm infections.

Ilimit *Pharma Investi, Chile.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Ilinol *PharmaInvesti, Chile.*
Hydroxychloroquine sulfate (p. 655·2).
Malaria; lupus erythematosus; rheumatoid arthritis; asthma; diabetes mellitus; porphyria cutanea tarda; pulmonary embolism; Sjögren's syndrome.

Iliocin *Offenbach, Mex.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Ilio-Funkton *Robugen, Ger.*
Dimeticone (p. 1886·2).
Reduction of gastrointestinal gas.

Ilja Rogoff *Bayer, Ger.*
Garlic (p. 2510·3); mistletoe (p. 2560·2); crataegus (p. 2488·1); sophora japonica; lupulus (p. 2546·1).
Vascular disorders.

Ilkoten *Umut, Turk.*
Tenoxicam (p. 136·2).

Illa *Pietrasanta, Ital.*
Pregnancy test (p. 2596·1).

illina *Sandoz, Ger.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Illovex *Pharma Dynamics, S.Afr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; mixed anxiety depressive states.

Illument *Pliva, Hung.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Illumina *TMCi, Philipp.*
Glutathione (p. 1555·2); thioctic acid (p. 2629·1).
Nutritional supplement; uV-induced skin damage; premature skin ageing.

Ilman *Demo, Gr.*
Flunitrazepam (p. 1073·3).
Insomnia.

Iloban
Note: this name may be used for preparations of different composition.
Merck, Braz.
Cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; anaemias.

Iloc *Sophia, Mex.*
Acetylcholine (p. 2003·1).
Production of miosis.

Ilocet *Ashford, Philipp.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Ilomedin *Bayer, Austria; Bayer Schering, Cz.†; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Berlimed, Israel; Bayer Schering, Malaysia; Bayer Schering, Norw.; Bayer, NZ; Bayer Schering, Pol.; Berlimed, Port.; Bayer Schering, Rus.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Schering, Turk.*
Iloprost trometamol (p. 1408·2).
Peripheral vascular disorders; thromboangiitis obliterans; pulmonary hypertension; Raynaud's syndrome.

Ilomédine *Bayer, Fr.*
Iloprost trometamol (p. 1408·2).
Thromboangiitis obliterans; Raynaud's syndrome.

Ilomedine *Bayer, Neth.*
Iloprost trometamol (p. 1408·2).
Thromboangiitis obliterans; peripheral ischaemia.

Ilon *Cesra, Ukr.*
Refined turpentine oil (p. 2636·3); venice turpentine.
Skin and soft-tissue inflammation.

Faran, Gr.
Turpentine; colophony (p. 2484·2); turpentine oil (p. 2636·3); rosemary oil (p. 2607·3); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3).

Ilon Abszess *Caesaro, Austria.*
Venice turpentine; turpentine oil (p. 2636·3).
Furunculosis; abscess; paranitium.

Cesra, Cz.; Cesra, Ger.
Turpentine; turpentine oil (p. 2636·3).
Skin disorders.

Ilopan *Savage, USA.*
Dexpanthenol (p. 2582·2).
Paralytic ileus; intestinal atony.

Ilopar *Pharmanel, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Ilos *Pharos, Indon.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders; stroke prophylaxis.

Ilosin *Collins, Mex.†*
Erythromycin (p. 291·2).
Bacterial infections.

Ilosone *More, Mex.; GSK, Philipp.; Aspen, S.Afr.; DKSH, Thai.†; Farma, Venez.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Lilly, Braz.; Valeant, Braz.
Erythromycin (p. 291·2) or erythromycin estolate (p. 291·2).
Bacterial infections.

Ilostal *Merck, Chile.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Iloticina *Investi, Arg.*
Erythromycin (p. 291·2).
Acne.

Ilotycin *Fera, USA.*
Erythromycin (p. 291·2).
Bacterial eye infections.

Ilotycin TS *Aspen, S.Afr.*
Erythromycin (p. 291·2).
Acne.

Ilotycin-A *Aspen, S.Afr.*
Tretinoin (p. 1725·2).
Acne.

Ilozef *Shenzhen, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Ilsatec *Boehringer Ingelheim Promeco, Mex.*
Lansoprazole (p. 1851·3).
Gastrointestinal hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

I-Lube
Note: this name may be used for preparations of different composition.
FDC, India.
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Ilube
Note: this name may be used for preparations of different composition.
Ashford, Philipp.
Hypromellose (p. 2189·2).
Dry eyes.

Moorfields, Irl.†; Moorfields, UK.
Acetylcysteine (p. 1652·2); hypromellose (p. 2189·2).
Dry eye syndromes; dry eyes.

Ilufren *Cantabria, Spain.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia.

Iluminoderm *Hautel, Arg.*
Padimate O (p. 1716·1).
Sunscreen.

Iluminoderm Lips *Hautel, Arg.*
Homosalate (p. 1705·1); titanium dioxide (p. 1725·1).
Sunscreen.

Iluminoderm Plus *Hautel, Arg.*
Homosalate (p. 1705·1); titanium dioxide (p. 1725·1).
Sunscreen.

I-Lute *Bionova, India.*
Myrtillus (p. 2566·2); copper (p. 2057·1); lutein (p. 2079·2); manganese (p. 2081·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zeaxanthin (p. 2125·3); zinc (p. 2126·1).

Iluvien *Alimera, UK.*
⊗Fluocinolone acetonide (p. 1636·1).
Diabetic macular oedema.

ILV-AM *Nutricia, Cz.*
Food for special diets.
Metabolic disorders.

Ilvico
Note: this name may be used for preparations of different composition.
Merck, S.Afr.
Capsules: Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Seven Seas, Irl.; Merck, Spain; Merck, Venez.
Brompheniramine maleate (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; nasal congestion; pain; cold and influenza symptoms.

Merck, Venez.
Syrup: ⊗Brompheniramine maleate (p. 618·1); methylephedrine hydrochloride (p. 1669·2); codeine phosphate (p. 40·2).
Cough.

Merck, S.Afr.†
Syrup: ⊗Brompheniramine maleate (p. 618·1); sodium ascorbate (p. 2111·1); methylephedrine hydrochloride (p. 1669·2); phenazone (p. 124·1); sodium salicylate (p. 132·2); codeine phosphate (p. 40·2).
Cold and influenza symptoms; allergic rhinitis; sinusitis.

Merck, S.Afr.†
Tablets: Brompheniramine maleate (p. 618·1); calcium ascorbate (p. 2111·1); propyphenazone (p. 127·3); salicylamide (p. 129·2); quinine hydrochloride (p. 665·2); caffeine (p. 1203·3).
Cold and influenza symptoms; allergic rhinitis; sinusitis.

Ilvico N *Merck, Port.*
Brompheniramine maleate (p. 618·1); calcium ascorbate (p. 2111·1); caffeine (p. 1203·3); paracetamol (p. 115·1).
Cold symptoms; fever; pain.

Ilvitrim *Pharmachem, S.Afr.*
Co-trimoxazole (p. 277·3).

I-L-X *Kenwood, USA.*
A range of preparations containing iron (p. 2073·1), liver extracts (p. 2444·1), and vitamin B substances.
Vitamin C (p. 2110·3) is included in some preparations to increase the absorption and availability of iron.
Iron-deficiency anaemias.

I-L-X B_{12} *Kenwood, USA.*
Iron preparation with vitamins.

Ilyx *Triton, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

IM 75 *Montpellier, Arg.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; patent ductus arteriosus.

Imacillin *Meda, Denm.; Meda, Norw.*
Amoxicillin (p. 216·2).
Bacterial infections.

Meda, Swed.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Imacort *Spirig, Cz.; Spirig, Switz.; Delta Medical, Ukr.*
⊗Clotrimazole (p. 576·2); hexamidine isetionate (p. 1754·3); prednisolone acetate (p. 1645·2).
Infected skin disorders.

Imadrax *Sandoz, Denm.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Imagenil *Gerube, Jpn.*
Ioxilan (p. 1593·3).
Radiographic contrast agent.

Imagent *Alliance, USA.*
⊗Perflexane lipid microspheres (p. 1595·1).
Contrast medium for echocardiography.

Imagent GI *Alliance, USA.*
⊗Perflubron (p. 2586·2).
Adjunct to magnetic resonance imaging of the gastrointestinal tract.

Imagopaque *Amersham, Austria†; Amersham, Gr.*
Iopentol (p. 1591·2).
Radiographic contrast medium.

Imakrebin *Alvogen, Neth.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia; myelodysplastic/myeloproliferative disease; hypereosinophilic syndrome;

gastrointestinal stromal tumours; dermatofibrosarcoma protuberans.

Imalek *Sun, India.*
Imatinib (p. 807·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia; myelodysplastic diseases; dermatofibrosarcoma protuberans; gastrointestinal stromal tumours; systemic mastocytosis; hypereosinophilic syndrome.

Imalet *Best, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Imanol *Biosintex, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Imap *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Ger.; Janssen-Cilag, Neth.*
Fluspirilene (p. 1076·3).
Anxiety; insomnia; psychoses; schizophrenia.

Imasemamed *Medis, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction following coronary angioplasty.

Imatet *Amson, Philipp.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Imatib *Aspen, Arg.*
Imatinib (p. 807·3).

Cipla, India.
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia.

Imation *Pisa, Mex.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Imavermil *IMA, Braz.†*
Albendazole (p. 149·1).
Worm infections.

I-Max
Note: this name may be used for preparations of different composition.
Patriot, Philipp.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Imax
Note: this name may be used for preparations of different composition.
Aristo, India.
Iron carbonyl (p. 2073·1); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc (p. 2126·1).

Imazol
Note: this name may be used for preparations of different composition.
Spirig, Austria; Spirig, Cz.; Spirig, Neth.; Spirig, Pol.; Spirig, Switz.; Spirig, Ukr.; Meyer, Venez.
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Spirig, Switz.; Orva, Turk.
Cream: Clotrimazole (p. 576·2); hexamidine isetionate (p. 1754·3).
Fungal skin infections.

Spirig, Ger.
Clotrimazole (p. 576·2); phenethyl alcohol (p. 1763·2).
Fungal skin infections.

Teva, Mex.†
Itraconazole (p. 583·3).
Fungal infections.

Imazol comp *Spirig, Ger.*
⊗Clotrimazole (p. 576·2); hexamidine isetionate (p. 1754·3); prednisolone acetate (p. 1645·2).
Fungal skin infections.

Imazol Duo *Spirig, Austria; Spirig, Neth.*
Clotrimazole (p. 576·2); hexamidine isetionate (p. 1754·3).
Bacterial and fungal skin infections.

Imazol Plus *Spirig, Cz.; Spirig, Ger.; Spirig, Pol.*
Clotrimazole (p. 576·2); hexamidine isetionate (p. 1754·3).
Fungal and bacterial skin infections.

Imbibe *Ipca, India.†*
Ezetimibe (p. 1379·2).
Hyperlipidaemias.

Imbistad *Bajamed, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Imboost *Soho, Indon.*
Echinacea (p. 2498·1); zinc picolinate (p. 2126·1).
Immunostimulant.

Imboost C *Soho, Indon.*
Echinacea (p. 2498·1); vitamin C (p. 2110·3).
Immunostimulant.

Imboost Force *Soho, Indon.*
Echinacea purpurea (p. 2498·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Imbran *Elder, India.*
Rice bran (p. 1823·3).

Imbruvica *Pharmacyclics, USA.*
Ibrutinib (p. 805·1).
Mantle cell lymphoma.

Imbun *Recordati, Ger.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Imdex *CCM, Hong Kong; CCM, Malaysia; Upha, Singapore; CCM, Thai.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Imdur *AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, China; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Thai.; AstraZeneca, UK; Key, USA.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; ischaemic heart disease; myocardial infarction; heart failure.

Ime-Cila *Piramal, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Imecitin *Actavis, Cz.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Imecol *Andromaco, Chile.*
Phthalylsulfathiazole (p. 339·3); nifuroxazide (p. 331·3).
Diarrhoea.

Imectin *Pulse, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Imectin Forte *Pulse, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Imedeen *Gobbi, Arg.*
Marine proteins; ascorbic acid (p. 2110·3); zinc gluconate (p. 2126·2).
Dietary supplement.

Imedeen Prime Renewal *Ferrosan, Fr.†*
Soya isoflavones (p. 2620·3); marine proteins; white tea (p. 2648·2); vitamin C (p. 2110·3); lycopene (p. 2546·2); grape seed (p. 2521·3); vitamin E (p. 2119·1); zinc (p. 2126·1); chamomile (p. 2474·1).
Dietary supplement for postmenopausal skin ageing.

Imedeen Tan Optimizer *Ferrosan, Fr.†*
Lycopene (p. 2546·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Dietary supplement for promotion of safe tanning.

Imedeen Time Perfection *Ferrosan, Fr.†*
Marine proteins; acerola; tomato; grape seed (p. 2521·3).
Dietary supplement for protection against skin ageing.

Imefer *Jumont, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron, vitamin B, and folic acid deficiency.

Imegul *Arkomedika, Fr.†*
Cascara (p. 1826·1); ispaghula (p. 1849·1).
Constipation.

Imelastin *Genesis, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Imelde *Medica, Arg.*
Barrier preparation.

Imerid *Hizon, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Imeron *Bracco, Ger.*
Iomeprol (p. 1590·3).
Radiographic contrast medium.

Imeson *Taurus, Ger.*
Nitrazepam (p. 1089·1).
Sleep disorders.

Imet
Note: this name may be used for preparations of different composition.
Berlin-Chemie, Ukr.
Ibuprofen (p. 68·2).
Pain; fever.

Imeth *Nordic, Fr.*
Methotrexate (p. 822·2).
Psoriasis; rheumatoid arthritis.

Imex
Note: this name may be used for preparations of different composition.
Merz, Ger.; Farmasyn, Gr.; Assos, Turk.
Tetracycline hydrochloride (p. 373·2).
Acne; bacterial skin infections.

DR Johns, India.
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Imferon *Shreya, India.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Imferon F-12 *Shreya, India.*
Folic acid (p. 2063·1); iron dextran (p. 2075·3); vitamin B_{12} (p. 2107·2).

Imferon Forte *Shreya, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Imflac *Ascent, Austral.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; peri-articular and soft-tissue disorders.

Imflamol *Panjon, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Imflamol-C *Panjon, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Imflamol-ZX *Panjon, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Imforce *Mahakam Beta, Indon.*
Echinacea angustifolia (p. 2498·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Imforce Plus *Mahakam Beta, Indon.*
Echinacea purpurea (p. 2498·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1); vitamin C (p. 2110·3).
Immunostimulant.

Imgalt *Jaldes, Fr.*
Bifidobacterium bifidum (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3).
Maintenance of intestinal flora.

Imicil *Lyofin, Gr.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Imi-Cila *Piramal, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Imidazyl *Recordati, Ital.*
⊗Naphazoline nitrate (p. 1669·3).
Conjunctivitis.

Imidazyl Antistaminico *Recordati, Ital.*
⊗Naphazoline nitrate (p. 1669·3); thonzylamine hydrochloride (p. 642·1).
Conjunctivitis.

Imidex *Medix, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Imidil *Hetero, India; Lyka, Rus.*
Clotrimazole (p. 576·2).
Balanitis; fungal infections of the skin and mucous membranes.

Imidil B *Hetero, India.*
⊗Beclometasone (p. 1621·2); benzyl alcohol (p. 1739·3); clotrimazole (p. 576·2).

Imidil Plus *Hetero, India.*
⊗Beclometasone dipropionate (p. 1621·2); benzyl alcohol (p. 1739·3); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Imidil-CV *Hetero, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).

Imigen *Mylan, S.Afr.*
Sumatriptan (p. 679·2).
Migraine.

Imigran *GSK, Arg.; GSK, Braz.; GSK, Chile; GSK, Hong Kong; GSK, Malaysia; GSK, NZ; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Thai.; GSK, Venez.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

GSK, Austral.; GSK, Austria; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK.
Sumatriptan (p. 679·2) or sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

GSK, Mex.
Sumatriptan hemisulfate (p. 679·2) or sumatriptan succinate (p. 679·2).
Migraine.

Imigrane *2care4, Denm.; GSK, Fr.*
Sumatriptan (p. 679·2).
Migraine; vascular facial pain.

Imigranradis *Glaxo Wellcome, Port.*
Sumatriptan succinate (p. 679·2).
Migraine.

Imiject *GSK, Fr.*
Sumatriptan succinate (p. 679·2).
Vascular facial pain.

Imimor *Royal, Chile.*
Imiquimod (p. 985·2).
Anogenital warts.

Imimore *Panalab, Arg.*
Imiquimod (p. 985·2).
Anogenital warts.

Imin *Yung Shin, Singapore.*
Inosine pranobex (p. 988·3).
Herpes zoster; measles.

Iminem *United Biotech, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Iminen *Teva, Mex.†*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Imipam *La Pharmaceuticals, India.*
Diazepam (p. 1063·2); imipramine hydrochloride (p. 426·2).

Imipecil *Northia, Arg.*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Imipem *Neopharmed, Ital.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Imipra *Cristalia, Braz.*
Imipramine hydrochloride (p. 426·2).
Depression.

Imiprom *Chrispa (Χρισπα), Gr.†*
⊗Fluocortolone caproate (p. 1637·1).
Skin disorders.

Imiquad *Glenmark, India.*
Imiquimod (p. 985·2).

Imistatin *Richmond, Arg.*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Imitag *Pliva, Irl.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Imitop *Sanat, India.*
Cilastatin sodium (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Imitrex *GSK, Belg.; GSK, Israel; GSK, USA.*
Sumatriptan (p. 679·2) or sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

GSK, Canad.
Sumatriptan hemisulfate (p. 679·2) or sumatriptan succinate (p. 679·2).
Migraine.

GSK, Indon.†
Sumatriptan succinate (p. 679·2).
Migraine.

Imix *Laboratorios Chile, Chile.*
Moxifloxacin (p. 326·3).
Bacterial infections.

Imizine *Zizine, Fr.*
Metronidazole (p. 936·1).
Root canal infections.

IMM-4 *Biomax, India.*
Bifidobacterium longum (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3).

Immard *Ipca, Rus.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus; light-induced skin disorders; malaria.

Ipca, Ukr.
Hydroxychloroquine (p. 655·2).
Rheumatoid arthritis; juvenile arthritis; systemic lupus erythematosus; photodermatitis; malaria.

Immodin *Sevapharma, Cz.*
Leucocytes (p. 1155·3).
Immune-system disorders.

Immubron *Bruschettini, Ital.*
Lysates of: *Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Klebsiella pneumoniae; Klebsiella ozaenae; Haemophilus influenzae; Moraxella catarrhalis;* strains of *Streptococcus pneumoniae.*
Respiratory-tract infections.

Immu-cea *Interbat, Indon.*
Caplets: Echinacea purpurea (p. 2498·1); zinc picolinate (p. 2126·1); vitamin C (p. 2110·3).
Immunostimulant.

Interbat, Indon.
Syrup: Echinacea (p. 2498·1); zinc picolinate (p. 2126·1).
Immunostimulant.

Immucothel *Biosyn, Austria.*
Immunocyanin.
Bladder cancer.

Biosyn, Neth.
Immunocyanine.
Bladder cancer.

ImmuCyst *Sanofi Pasteur, Arg.; Sanofi-Aventis, Austral.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi-Aventis, Braz.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile†; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Holsten, Ger.†; Gerolymatos, Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Alliance, Irl.; Sanofi Pasteur, Israel; Wassermann, Ital.; Sanofi Pasteur, Malaysia; Aventis, NZ; Inibsa, Port.; Sanofi Pasteur, Singapore; Inibsa, Spain†; CytoChemia, Switz.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.; Cambridge, UK.*
A BCG vaccine (p. 2378·1).
Bladder cancer.

Immucytal *Pierre Fabre, Ital.*
Ribosomal fractions of *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* membrane fraction of *Klebsiella pneumoniae.*
Otorhinolaryngeal infections; bronchial infections.

Immudynal *Ardeypharm, Ger.*
Echinacea purpurea (p. 2498·1).
Homoeopathic preparation.

Immugrip *Pierre Fabre, Fr.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Immukin *Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, UK.*
Interferon gamma-1b (recombinant) (p. 999·1).
Iinfections in chronic granulomatous disease and malignant osteopetrosis.

Immukine *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Neth.*
Interferon gamma-1b (recombinant) (p. 999·1).
Infections in chronic granulomatous disease; infections in malignant osteopetrosis.

Immulem *Teva, Mex.†*
Ciclosporin (p. 1945·2).
Transplant rejection.

Immulina *Vital Life, UK.*
Extract of *Spirulina platensis*(*Arthrospira platensis*) (p. 2622·1).
Dietary supplement.

Immumil Plus *Milte, Ital.†*
Propolis (p. 2597·3); echinacea (p. 2498·1); thyme (p. 2630·2); acerola.
Cold symptoms.

Immunace
Note: this name may be used for preparations of different composition.
Meyer, India.
Vitamins; minerals; carnitine (p. 2053·2).
Vitabiotics, Indon.
Vitamins; minerals; levocarnitine tartrate (p. 2053·2); cystine hydrochloride; bioflavonoids (p. 2505·2).
Dietary supplement.
Vitabiotics, UK.
Vitamins; minerals; bioflavonoids (p. 2505·2).

Immunace Forte *Meyer, India.*
Vitamins; minerals; trace elements; amino acids; lycopene (p. 2546·2).

Immunace Plus *Meyer, India.*
Vitamins; minerals; trace elements; amino acids; citrus bioflavonoids (p. 2505·2).

Immun-Aid *McGaw, USA.*
Preparation for enteral nutrition.
Immunosuppression.

Immunal *Lek, Cz.; Lek, Pol.; Lek, Rus.; Sandoz, Ukr.*
Echinacea (p. 2498·1).
Respiratory-tract infections; influenza; infections.

Immunate *Baxter, Arg.; Baxter, Austria; Baxter, Braz.; Baxter, Cz.; Baxter, Fin.; Baxter BioScience, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Israel; Baxter, Ital.; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Rus.; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; factor VIII deficiency; von Willebrand's disease.

Immune Boost *Johnson & Johnson, Austral.†*
Lactoferrin (bovine) (p. 2539·3).
Immune system tonic.

Immune Boost with Andrographis *Golden Glow, Austral.*
Andrographis (p. 2443·2); sambucus (p. 2609·3) calcium ascorbate (p. 2111·1).
Immune system support.

Immune Formula *Nutravite, Canad.†*
Astragalus; black seed; echinacea (p. 2498·1); grape seed (p. 2521·3).

Immune Support *K-PAX, USA.*
Vitamins; minerals; nutritional supplements.

Immune Support Protein Blend *K-PAX, USA.*
Preparation for enteral nutrition.

Immunex
Note: this name may be used for preparations of different composition.
Leksredstva, Rus.
Echinacea pupurea (p. 2498·1).
Respiratory-tract disorders; herpesvirus infections.
Ordain, India.
Calcium ascorbate (p. 2111·1).

Immunex CRP *Wampole, USA.*
Test for C-reactive protein in serum.

Immunicare *MedChem, USA.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3); selenium (p. 2086·3); ARA-6; beta glucan (p. 2543·2); uncaria tomentosa; curcumin (p. 2180·1); garlic (p. 2510·3); grape seed (p. 2521·3); graviola; green tea (p. 2648·2); Herbal Complex; ginseng (p. 2513·3); lycopene (p. 2546·2); Mushroom Complex; olive leaf (p. 2574·3); pine bark; pomegranate (p. 164·1); quercetin (p. 2505·3); raspberry (p. 2207·2).
Dietary supplement.

Immunine *Baxter Immuno, Arg.; Baxter, Austria; Baxter, Braz.; Baxter, Canad.; Baxter, Cz.; Baxter BioScience, Ger.; Baxter, Gr.; Baxter, Hung.†; Baxter, India; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, Pol.; Baxter, Port.; Baxter, Rus.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
A factor IX preparation (p. 1149·3).
Factor IX deficiency; haemophilia B; haemorrhagic disorders.

Immunix *Unique, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Immuno GoodWay *GoodWay, Indon.*
Nutritional supplement.

Immuno HBS *IFET (ΙΦΕΤ), Gr.*
A hepatitis B immunoglobulin (p. 2389·1).

Immuno Theiss *Naturwaren, Ukr.*
Oral drops: Echinacea purpurea (p. 2498·1).
Respiratory-tract infections.
Naturwaren, Ukr.
Tablets: Echinacea (p. 2498·1); racementhol (p. 2553·2).
Respiratory-tract infections and inflammation.

Immunobion *Rodisma, Ger.*
Echinacea purpura (p. 2498·1).
Infections.

Immunocal *Immunotec, Canad.*
Whey protein isolate (bovine).
Glutathione deficiency.

Vinova, Malaysia; Immunotec, USA.
Preparation for enteral nutrition.
Glutathione deficiency.

ImmunoDefence *Blackmores, Austral.*
Lactoferrin (p. 2539·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Cold and influenza symptoms; tonic.

Immunoflazid *Ecofarm, Ukr.*
Proteflazid (from deschampsia caespitosa and calamagrostis epigeios).
Influenza and SARS; bacterial and fungal infections.

Immunofort *Leki Natury, Pol.*
Lappa (p. 2540·1); aronia melanocarpa; chamomile (p. 2474·1); echinacea purpurea (p. 2498·1); urtica (p. 2639·3).
Upper respiratory-tract infections; wounds.

ImmunoGam *Cangene, Neth.†*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

ImmunoHBs *Kedrion, Ital.; Kedrion, Thai.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Immunokind *DHU, Ukr.*
Calcium carbonicum (p. 1824·3); calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); sulfur jodatum (p. 2624·2).
Homoeopathic preparation.

Immunokine *Oxo, Thai.*
Tetrachlorodecaoxide (p. 2628·2).
Post-radiation-therapy syndromes; cystitis; proctitis; mucositis.

Immunomaxe *Immapharma, Rus.*
Acid peptidoglycans.
Bacterial and viral infections.

Immunomega *Larkhall Laboratories, UK.*
Vitamins; minerals.

Immunoplus *KVZ, Ukr.*
Echinacea (p. 2498·1).
Adjunct in respiratory and urinary tract infections.

Immunoprin *Ebewe, Austria; Ebewe, Cz.; Ebewe, Denm.; Ebewe, Ital.; Ebewe, Neth.; Sandoz, Swed.*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection.

Immunorel *Reliance, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; bone-marrow transplantation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Immunorell *Sanorell, Ger.*
Eupatorium perfoliatum (p. 2459·1); echinacea (p. 2498·1); ferrum phosphoricum (p. 2077·1); hepar sulfuris (p. 1721·3).
Homoeopathic preparation.

Immunorho *Kedrion, Arg.; Biosano, Chile; Kedrion, Ital.; Onko, Turk.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Immunorm
Note: this name may be used for preparations of different composition.
Ordain, India.
Bifidobacterium bifidum (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); bovine colostrum (p. 2380·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boullardii* (p. 2596·3).
Ratiopharm, Rus.
Echinacea (p. 2498·1).
Infections of the respiratory and urinary-tract.

Immunoro *Kedrion, Rus.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Immunosin *Westmont, Philipp.*
Inosine pranobex (p. 988·3).
Viral infections.

Immunosporin *Novartis, Ger.*
Ciclosporin (p. 1945·2).
Atopic dermatitis; rheumatoid arthritis; psoriasis; uveitis.

Immunostim
Note: this name may be used for preparations of different composition.
Urgo, Fr.
Lactobacillus helveticus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3) *Bifidobacterium infantis* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); ascorbic acid (p. 2110·3).
Immunostimulant.

Herbapol Lublin, Pol.†
Siberian ginseng (p. 2614·3).
Tonic; atherosclerosis.

Immunostim Levure *Urgo, Fr.*
Sacharomyces boulardii (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3)*Bifidobacterium longum* (p. 2596·3).
Diarrhoea.

Immunostim Stress *Urgo, Fr.*
Lactobacillus helveticus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Restoration of intestinal flora.

Immuno-Ton *Arterium, Ukr.*
Siberian ginseng (p. 2614·3); St John's wort (p. 449·1); echinacea (p. 2498·1).
Asthenia; physical and mental stress.

Immunotrofina *DMG, Ital.*
Vitamins; minerals.

Immunovenin *Microgen, Rus.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; passive immunisation.

Immunozig *Interko, Turk.†*
A varicella-zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Immunped Zinc Plus *Pediatech, Singapore.*
Zinc (p. 2126·1); ascorbic acid (p. 2110·3).
Adjunct to oral rehydration therapy for colds and diarrhoea; tonic.

Immun-up *Dicofarm, Ital.*
Echinacea (p. 2498·1); beta-glucan (p. 2455·2).
Immunostimulant.

Immun-up Junior *Dicofarm, Ital.*
Echinacea (p. 2498·1); beta-glucan (p. 2455·2); zinc (p. 2126·1).
Immunostimulant.

Immupress *Symbiotic, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Immuseven *Baxter, Ger.*
A factor VII preparation (p. 1147·1).
Factor VII deficiency.

Immusol *Dabur, India.*
Ciclosporin (p. 1945·2).
Transplant rejection; psoriasis; atopic dermatitis; rheumatoid arthritis; nephrotic syndrome.

Immutone *Pharmadass, UK.*
Shark-liver oil (p. 2614·2).

Immuvac *Cadila, India.*
A leprosy vaccine (p. 2397·2).
Active immunisation.

Immuvit *Rueckert, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3); Siberian ginseng (p. 2614·3); ubidecarenone (p. 2637·1).
Tonic.

Immuvital *Rueckert, Singapore.*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic.

Immuwash *DMG, Ital.*
Carboxymethyl beta-glucan (p. 2455·2).
Nasal cleansing.

Immuzinc
Note: this name may be used for preparations of different composition.
Berko, Turk.
Elderberry (p. 2609·3); echinacea (p. 2498·1); propolis (p. 2597·3); vitamin C (p. 2110·3); zinc (p. 2126·1).
Tonic.

Medlink, Philipp.
Zinc sulfate (p. 2126·2).
Nutritional supplement.

Imnit *Reddy, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Imnovid *Celgene, UK.*
Pomalidomide (p. 847·3).
Multiple myeloma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Imoclone *Orion, Denm.*
Zopiclone (p. 1118·1).
Insomnia.

Imocur
Note: this name may be used for preparations of different composition.
Mylan, Fin.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Imodan *Hexpharm, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imodium *Johnson & Johnson, Austral.; Janssen-Cilag, Austria; Johnson & Johnson Consumer, Belg.; McNeil Consumer, Canad.; Xian-Janssen, China; McNeil, Cz.; McNeil, Denm.; McNeil, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; McNeil, Ger.; Johnson & Johnson, Gr.; Johnson & Johnson, Hong Kong; Johnson & Johnson, Hung.; Johnson & Johnson, India; Janssen-Cilag, Indon.; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Johnson & Johnson, Ital.; Johnson & Johnson, Malaysia; Janssen-Cilag, Mex.; Johnson & Johnson, Neth.; McNeil, Norw.; Johnson & Johnson, NZ; Johnson & Johnson, Philipp.; Janssen-Cilag, Pol.; Johnson & Johnson, Port.; Johnson & Johnson, Rus.; Johnson & Johnson, S.Afr.; Johnson & Johnson, Singapore; Johnson & Johnson, Spain; McNeil, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; McNeil, UK; McNeil, Ukr.; Janssen, USA; McNeil Consumer, USA; Janssen-Cilag, Venez.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management; control of intestinal transit time.

Imodium Advanced *Johnson & Johnson, Austral.; McNeil Consumer, Canad.; Johnson & Johnson, NZ; McNeil Consumer, USA.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; abdominal discomfort; flatulence; excess gastrointestinal gas.

Imodium akut N duo *McNeil, Ger.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; flatulence.

Imodium Combi *McNeil, Neth.†*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; flatulence.

Imodium Comp *McNeil, Norw.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; flatulence.

Imodium complex *McNeil, Ger.†*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; flatulence.

Imodium Duo *Johnson & Johnson Consumer, Belg.; Johnson & Johnson, Neth.; Johnson & Johnson, Spain; Janssen-Cilag, Switz.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Formerly known as Imodium complex.
Formerly known as Imodium Plus.
Diarrhoea; flatulence.

Imodium Duo Action *McNeil, Cz.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea with flatulence or abdominal discomfort.

Imodium Multi-Symptom Relief *McNeil Consumer, USA.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).

Imodium Plus *Janssen-Cilag, Austria; McNeil, Cz.; McNeil, Denm.; McNeil, Fin.; McNeil, Ger.†; Johnson & Johnson, Gr.; Johnson & Johnson, Hong Kong; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Pol.; Johnson & Johnson, Port.; Johnson & Johnson, Rus.; Johnson & Johnson, S.Afr.; McNeil, Swed.; Janssen-Cilag, Thai.†; Johnson & Johnson MSD Consumer, UK.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; abdominal discomfort; flatulence; ostomy management; excess gastrointestinal gas.

Imodium Pro *McNeil, Fin.†*
Loperamide oxide (p. 1854·2).
Diarrhoea; ileostomy management.

Imodiumcaps *Johnson & Johnson, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imodiumduo *Johnson & Johnson, Fr.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; flatulence.

Imodiumlingual *Johnson & Johnson, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imodonl *Christo, Hong Kong.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Imodul *Tempo Scan Pacific, Indon.*
Capsules: Echinacea (p. 2498·1); vitamin C (p. 2110·3); zinc (p. 2126·1).
Immunostimulant.

Tempo Scan Pacific, Indon.
Oral syrup: Echinacea (p. 2498·1); zinc (p. 2126·1).
Immunostimulant.

Imoflox *Sel-J, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Imogam *Sanofi Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Indon.; Aventis Pasteur, Turk.†*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Imogam Rabia *Sanofi Pasteur, Arg.; Sanofi Pasteur, Spain.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Imogam Rabies *Ranbaxy, India; Sanofi Pasteur, Israel; Sanofi Pasteur, Thai.†; Sanofi Pasteur, USA.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Imogam Rage *Sanofi Pasteur, Fr.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Imogas *McNeil, Denm.; McNeil, Ger.; McNeil Healthcare, Irl.; Pfizer Consumer, Ital.; McNeil, Norw.; Johnson & Johnson, Port.*
Simeticone (p. 1886·2).
Flatulence; reduction of gastrointestinal gas; preparation for gastrointestinal investigations.

Imogaze *McNeil, Swed.*
Simeticone (p. 1886·2).
Flatulence.

Imol *Zydus, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Imol Plus *Zydus, India.*
Caffeine (p. 1203·3); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Imolans *Landsteiner, Mex.†*
Nimodipine (p. 1455·2).

Imolone *Vickmans, Hong Kong.†*
Zopiclone (p. 1118·1).

Imolope *Orifarm, Denm.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imomed *Medikon, Indon.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imonogas *Johnson & Johnson Consumer, Belg.; Johnson & Johnson, Fr.; Johnson & Johnson, Spain.*
Simeticone (p. 1886·2).
Flatulence.

Imonox *Medicine Products, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imorab *Aventis Pasteur, India.*
A rabies immunoglobulin (equine) (p. 2413·1).
Passive immunisation.

Imore *Soho, Indon.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imosa *Corsa, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imosan *Arvincare, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Imosec *Janssen-Cilag, Braz.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Imoseptyl *Johnson & Johnson, Fr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Imot *Sophia, Mex.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Imotec *Rafarm, Gr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Imotest Tuberculin *Vianex (Βιανεξ), Gr.*
Tuberculin PPD (p. 2635·3).
Tuberculosis diagnosis.

Imotoran *Rayere, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; diabetic nephropathy.

Imovane *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Meda, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Meda, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Meda, Swed.; Sanofi-Aventis, Switz.; Eczacibasi, Turk.; Sanofi-Aventis, Ukr.*
Zopiclone (p. 1118·1).
Insomnia; sleep disorders.

Imovax DT *Sanofi Pasteur, Arg.; Sanofi Pasteur, Chile; Honest Ability, Hong Kong†; Sanofi Pasteur, Israel.*
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Imovax Meningo A & C *Aventis, S.Afr.†*
A meningococcal vaccine (p. 2401·3).
Active immunisation.

Imovax Meningo A+C *Aventis Pasteur, Turk.†*
A meningococcal vaccine (p. 2401·3).
Active immunisation.

Imovax Pneumo 23 *Sanofi Pasteur, S.Afr.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Imovax Polio *Sanofi Pasteur, Arg.; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, China; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Aventis Pasteur, India; Sanofi Pasteur, Indon.; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Jpn; Sanofi Pasteur, Norw.; Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Rus.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Swed.*
An inactivated poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Imovax Rabbia *Sanofi Pasteur, Ital.†*
A rabies vaccine (p. 2413·2).
Active immunisation.

Imovax Rabies *Sanofi Pasteur, Canad.; Aventis Pasteur, India; Sanofi Pasteur, USA.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Imovax Tetano *Sanofi Pasteur, Ital.*
A tetanus vaccine (p. 2421·1).
Active immunisation.

Imovexil *Aledicine, Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Imoviral *Cristalfarma, Ital.*
Catechu (p. 2472·3); shiitake; beta-glucan (p. 2455·2); black currant (p. 2458·1).
Nutritional supplement.

Imoviral Junior *Cristalfarma, Ital.*
Echinacea (p. 2498·1); acerola; arabinogalactan; beta-glucan (p. 2455·2); zinc (p. 2126·1).
Immunostimulant.

Imox
Note: this name may be used for preparations of different composition.
Gracia, Indon.
Echinacea purpurea (p. 2498·1); elderberry (p. 2609·3); vitamin C (p. 2110·3); garlic (p. 2510·3); zinc oxide (p. 1729·1).
Immunostimulant; antoxidant.

Ipca, India.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Imox-Clo *Ipca, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Imox-Clo LB *Ipca, India.†*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); lactobacillus (p. 2596·3).
Bacterial infections.

Imoxy *Medley, Braz.*
Imiquimod (p. 985·2).
Anogenital warts; actinic keratoses; superficial basal cell carcinoma.

Imozop *Sandoz, Denm.*
Zopiclone (p. 1118·1).
Insomnia.

Impact *Nestle, Fin.; Nestle, Ital.; Nestle, Turk.; Nestle, USA.*
Preparations for enteral nutrition.

Novartis, China; Novartis, Cz.; Nestle, Fr.; Zeon, India; Nestle, UK.
Preparation for enteral nutrition.

Novartis, Braz.
A range of preparations for enteral nutrition.

Impalamycin *Bros, Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Impavido *Paladin, Ger.*
Miltefosine (p. 829·3).
Leishmaniasis.

Impaza *Materia Medica, Rus.*
Endothelial nitric oxide synthase antibodies.
Homoeopathic preparation.

Impedil *Phoenix, Arg.*
Etamsylate (p. 1145·2).
Haemorrhage.

Impelium *TO-Chemicals, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Impetex *Teofarma, Ital.; Roche, Turk.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Impidol *Andromaco, Chile.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Implanon *Schering-Plough, Austral.; Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; MSD, China; Organon, China; Organon, Cz.; Organon, Denm.; Organon, Fin.†; Schering-Plough, Fr.†; MSD, Ger.; Organon (Οργανον), Gr.; Organon, Hung.; Schering-Plough, Indon.; Organon, Irl.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.†; MSD, NZ; Organon, Port.; MSD, Singapore; MSD, Spain; MSD, Swed.†; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK†; Organon, USA; Organon, Venez.*
Etonogestrel (p. 2277·2).
Progestogen-releasing implantable contraceptive.

Implanta *Hanmi, China.*
Ciclosporin (p. 1945·2).
Transplant rejection; psoriasis; atopic eczema; rheumatoid arthritis; nephrotic syndrome.

Implementor *Pentafarma, Port.*
Pirlindole hydrochloride (p. 446·3).
Depression.

Implicane *Tecnofarma, Chile.*
Sertraline (p. 448·1).
Depression.

Importal *Novartis Consumer, Austria; ACRAF, Belg.; Novartis Sante, Fr.; Novartis Consumer, Ger.†; Novartis, Gr.; ACRAF, Neth.; Novartis, NZ; Novartis Consumer, Port.; Novartis, Swed.; Zambon, Switz.; Novartis, Thai.†; Novartis, Turk.*
Lactitol (p. 1850·3).
Constipation; hepatic encephalopathy.

Importal Ex-Lax *Novartis, Fin.†*
Lactitol (p. 1850·3).
Constipation; hepatic encephalopathy.

Imposergon *Rafarm, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Impovituss *Rafarm, Gr.*
Etodolac (p. 57·1).

Impramine *Sun, India.*
Imipramine (p. 426·2).
Depression; nocturnal enuresis.

Impregon *Fleming, USA.*
Tetrachlorosalicylanilide.
Napkin disinfection.

Impresial *Zambon, Indon.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Imprex *Ratiopharm, Port.*
⊗Indapamide (p. 1409·2); perindopril erbumine (p. 1467·1).
Hypertension.

Imprida *Novartis, Cz.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Lacer, Spain.*
Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2).
Hypertension.

Imprida HCT *Novartis, Cz.; Novartis, Irl.; Novartis, Neth.†; Novartis, Pol.; Novartis, Port.*
⊗Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Impril *Valeant, Canad.*
Imipramine hydrochloride (p. 426·2).
Depression.

Imprine *Stadmed, India.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Improdex *Claris, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).

Improlyte *Claris, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).

Impromen *Janssen-Cilag, Belg.; Formenti, Ital.; Janssen-Cilag, Neth.*
Bromperidol (p. 1041·3).
Psychoses; schizophrenia.

Janssen-Cilag, Ger.
Bromperidol lactate (p. 1041·3).
Schizophrenia.

Impromox *Almet, India.*
Amoxicillin (p. 216·2); lactobacillus (p. 2596·3).
Bacterial infections.

Improntal *Rottapharm, Spain.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Improve *Forgo, India.*
Protein powder.

Improved Once A Day *Quest, UK.*
Vitamins; minerals.

Improved Versal *Clay Park, Hong Kong.†*
Zinc oxide (p. 1729·1); calamine (p. 1697·2).
Anorectal disorders.

Improvil *Pfizer, Austral.*
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Improvox *Tempo Scan Pacific, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Impruv *GSK, USA; Stiefel, USA.*
Emollient.
Dry skin.

Impugan *Actavis, Indon.; Actavis, Swed.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; renal insufficiency; nephrotic syndrome.

Impuls *Iromedica, Switz.†*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat pain and inflammation.

Impuls à la consoude *Alpinamed, Switz.*
Comfrey (p. 2484·2); St John's wort (p. 449·1); calendula (p. 2465·2); peppermint (p. 1877·1); echinacea purpurea (p. 2498·1).
Soft-tissue injury.

Impuls dragées pour la vessie et les reins *Iromedica, Switz.*
Bearberry (p. 2453·2); birch leaf (p. 2457·3); solidago (p. 2620·1).
Urinary-tract disorders.

Impuls pastilles pour les bronches *Iromedica, Switz.*
Anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); solidago (p. 2620·1); menthol (p. 2553·2); liquorice (p. 1853·2).
Cough; sore throat.

Impuls pour les veines *Alpinamed, Switz.*
Butcher's broom (p. 2463·1).
Soft-tissue injury; venous insufficiency; scars.

Imrest *Alphapharm, Austral.*
Zopiclone (p. 1118·1).
Insomnia.

I-M-Safe *Esma, India.*
Cefixime (p. 240·3).
Bacterial infections.

Imsimol *Shince, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

I-M-Sure *Esma, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Imtrate *Ascent, Austral.; Douglas, NZ.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

IMTV-AM *Nutricia, Cz.*
Food for special diets.
Methylmalonic acidaemia; propionic acidaemia.

Imucell WGP *Biopolymer, Philipp.†*
WGP beta 1,3/1,6 glucan.
Dietary supplement.

Imudator *Pyridam, Indon.*
Echinacea (p. 2498·1); zinc picolinate (p. 2126·1); phyllanthus niruri (p. 2590·1); ganoderma lucidum.
Immunostimulant; renal calculi; wound healing; liver disorders.

Imuderm *Goldshield, UK.†*
Oil: Light liquid paraffin (p. 2191·2); almond oil (p. 2437·1).
Dry skin disorders.

Goldshield, UK.†
Cream: ⊗White soft paraffin (p. 2211·3); fractionated coconut oil (p. 2082·2); glycerol (p. 2517·2).
Skin disorders.

Imudon *Abbott, Ukr.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Lactobacillus lactis* (p. 2596·3); *Lactobacillus fermentum* (p. 2596·3); *Streptococcus pyogenes* group A; *Enterococcus faecium* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3); *Streptococcus sanguis; Staphylococcus aureus; Klebsiella pneumoniae; Corynebacterium pseudodiphtheriticum; Fusobacterium nucleatum; Candida albicans.*
Mouth and throat disorders.

Solvay, Rus.
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus fermentum* (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Lactobacillus debrulcki* subsp. lactis (p. 2596·3); *Streptococcus pyogenes; Enterococcus faecalis* (p. 2596·3); *Enterococcus faecium* (p. 2596·3); *Streptococcus sangius; Staphylococcus aureus; Klebsiella pneumoniae; Corynebacterium pseudodiphtheriticum; Fusobacterium nucleatum; Candida albicans.*
Mouth and throat disorders.

Solvay, Cz.†
Lysates of *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Lactobacillus lactis* (p. 2596·3); *Lactobacillus fermentum* (p. 2596·3); *Streptococcus pyogenes; Enterococcus faecium* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3); *Streptococcus sanguis; Staphylococcus aureus; Klebsiella pneumoniae; Corynebacterium pseudodiphtheriae; Fusobacterium nucleatum; Candida albicans.*
Mouth disorders.

Imufor
Note: this name may be used for preparations of different composition.
Gracia, Indon.
Echinacea (p. 2498·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1); vitamin C (p. 2110·3).
Immunostimulant.

Imuger *Gerard, Irl.*
Azathioprine (p. 1940·3).
Immunosuppressant.

Imugins *Schumit, Thai.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Imukin *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Ital.; Fisher, Neth.†; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.*
Interferon gamma-1b (rbe) (p. 999·1).
Infections in chronic granulomatous disease; infections in malignant osteopetrosis.

Imulan *Soho, Indon.*
Phyllanthus niruri (p. 2590·1); curcuma longa; selenium (p. 2086·3).
Immunostimulant.

Imulate *Aspen, Austral.*
Mycophenolate mofetil (p. 1961·1).
Organ transplant rejection.

Imumax *Teguhsindo, Indon.*
Bee propolis (p. 2597·3); echinacea (p. 2498·1); selenium (p. 2086·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Imunace *Shionogi, Jpn.*
Teceleukin (p. 810·1).
Angiosarcoma; kidney cancer.

Imunal Plus *Novell, Indon.*
Echinacea (p. 2498·1); phyllanthus niruri (p. 2590·1); zinc picolinate (p. 2126·1).
Immunostimulant.

Imunax *Ativus, Braz.*
Echinacea (p. 2498·1).

Imuneks *Nevzat, Turk.*
Beta-glucan (p. 2455·2) from *Saccharomyces cerevisiae.*
Tonic.

Imunen *Cristalia, Braz.*
Azathioprine (p. 1940·3).
Immunosuppressant.

Imuneprim *IQB, Braz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Imunex *Galenium, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Imunin *Norton, Ukr.†*
⊗Indian gooseberry (p. 2532·2); premna integrifolia; sida; bambusa arundinacea; malabar nut (p. 2549·1); aegle marmelos; phyllanthus niruri (p. 2590·1); pueraria tuberosa; solanum indicum; cinnamon (p. 2479·2); grape (p. 2521·3); amomum subulatum; elettaria cardamomum; gmelina arborea; seasame seed; tribulus terrestris (p. 2633·3); tinospora cordifolia; terminalia chebula (p. 2474·3); leptadenia reticulata; zedoary; martynia diandra; pistacia integerrima; gymnema balsamicum; solanum xanthocarpum; saffron (p. 2208·2); gymnema lactiferum; clove (p. 2481·2); teramnus labialis; phaseolus trilobus; cyperus scariosus; mesua ferrea; nelumbio speciosum; stereospermum suaveolens; piper longum; iris germania; uraria picta; punarnava (p. 2601·1); sandalwood (p. 2610·1); asparagus racemosus (p. 2614·2); desmodium gangetiamum; oroxylum indicum; cinnamomum tamala.
Immunostimulant.

Imunnal *Herbarium, Braz.†*
Echinacea (p. 2498·1).
Cold symptoms.

Imuno Max *Herbarium, Braz.†*
Uncaria tomentosa.
Herpes simplex infections of the skin.

Imunocin *Gufic, India.*
Punarnava (p. 2601·1); ocimum sanctum; piper longum; tinospora cordifolia; ashwagandha (p. 2450·2).

Imunoest *Sanofi-Aventis, Braz.*
A BCG vaccine (p. 2378·1).
Active immunisation.

Imunofan *Bionox, Rus.*
Hexapeptide.
Immunodeficiency disorders; inflammatory disorders.

Imunofar *Faran, Gr.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; psoriasis; atopic eczema; nephrotic syndrome; rheumatoid arthritis.

Imunoferon *Fariberica, Port.*
Glicofosfopeptical (p. 2515·1).
Immunodeficiency.

β-Imunoferon 1a *Arterium, Ukr.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

β-Imunoferon 1b *Arterium, Ukr.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Imunogard *Puspa, Indon.*
Echinacea (p. 2498·1); black elderberry (p. 2609·3); phyllanthus niruri (p. 2590·1); zinc picolinate (p. 2126·1); vitamin C (p. 2110·3); selenium (p. 2086·3).
Immunostimulant.

Imunogreen *Greenpharma, Braz.†*
Echinacea purpurea (p. 2498·1).

Imunolife *Psychotropics, India.*
Vitamins; trace elements; amino acids; ubidecarenone (p. 2637·1); glutathione (p. 1555·2); lutein (p. 2079·2).

Imunomet *Matxin, Singapore.*
Asparagus racemosus (p. 2614·2); commiphora wightii; liquorice (p. 1853·2); beleric myrobalan (p. 2453·2); chebulic myrobalan (p. 2474·3); Indian gooseberry (p. 2532·2); piper longum.
Respiratory-tract disorders.

Imunor *Imunomedica, Cz.*
Transfer factor (p. 2633·2).
Immune-system disorders.

Imunorix *Abbott, Rus.; Polichem, Ukr.*
Pidotimod (p. 2590·2).
Infections of the respiratory and urinary tracts.

Imunos *Lapi, Indon.*
Caplets: Echinacea (p. 2498·1); zinc picolinate (p. 2126·1); selenium (p. 2086·3); ascorbic acid (p. 2110·3).
Immunostimulant.

Lapi, Indon.
Oral syrup: Echinacea (p. 2498·1); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Immunostimulant.

Imunovir *Helix, Canad.; Kora, Irl.†; NZ Medical & Scientific, NZ; Kora, UK.*
Inosine pranobex (p. 988·3).
Subacute sclerosing panencephalitis; viral infections.

Imunoxa *Gador, Arg.†*
Lamivudine (p. 1000·2).
HIV infection.

Imunoxa Complex *Gador, Arg.†*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Imunvit *Simex, Indon.*
Echinacea (p. 2498·1); calcium ascorbate (p. 2111·1).
Immunostimulant.

Imunvit Plus *Simex, Indon.*
Echinacea (p. 2498·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Immunostimulant.

Imuprel *Adcock Ingram, S.Afr.†*
⊗Isoprenaline hydrochloride (p. 1411·3).
Shock; heart block; bronchospasm.

Imupret *Bionorica, Ger.; Bionorica, Ukr.*
Althaea (p. 2438·3); chamomile (p. 2474·1); equisetum (p. 2500·1); English walnut (p. 2646·1); achillea (p. 2427·3); oak bark (p. 2574·1); taraxacum (p. 2625·3).
Throat infections; upper respiratory-tract inflammation and infection.

Imuprin *Remedica, Hong Kong; Remedica, Thai.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Imuprine *Mylan, NZ.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Imuran *Biotoscana, Arg.; Aspen, Austral.; GSK, Belg.; GSK, Braz.; Triton, Canad.; GSK, Chile; GSK, China; Aspen, Cz.; GSK, Gr.; Aspen, Hong Kong; Aspen, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; Perrigo, Israel; Aspen, Malaysia; GSK, Mex.; Aspen, Neth.; Healthcare Logistics, NZ; GSK, Philipp.; GSK, Pol.; Aspen, Port.; GSK, Rus.; GSK, S.Afr.; Aspen, Singapore; Aspen, Thai.; GSK, Turk.; Co-Pharma, UK; Prometheus, USA.*
Azathioprine (p. 1940·3) or azathioprine sodium (p. 1940·3).
Transplant rejection; rheumatoid arthritis; Crohn's disease; haemolytic anaemia; lupus erythematosus; dermatomyositis; periarteritis nodosa; pemphigus; immune thrombocytopenia; pyoderma gangrenosum; chronic hepatitis; autoimmune disorders.

Imurek *Aspen, Austria; Aspen, Ger.; Pro Concepta, Switz.*
Azathioprine (p. 1940·3) or azathioprine sodium (p. 1940·3).
Transplant rejection; auto-immune disorders; rheumatoid arthritis; systemic lupus erythematosus; skin disorders; hepatitis; auto-immune haemolytic anaemia; immune thrombocytopenia.

Imurel *GSK, Denm.; Aspen, Fin.; HAC, Fr.; Orion, Norw.; UCB, Spain; Orion, Swed.*
Azathioprine (p. 1940·3).
Auto-immune disorders; transplant rejection; immunosuppressant; lupus erythematosus; rheumatoid arthritis.

Imuron-Vac *Medgamal, Rus.*
A BCG vaccine (p. 2378·1).
Bladder cancer.

Imusera *Mitsubishi Tanabe, Jpn.*
Fingolimod hydrochloride (p. 2504·3).
Multiple sclerosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Imusporin *Cipla, India; Cipla, Rus.; Cipla, Venez.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; psoriasis; rheumatoid arthritis; nephrotic syndrome; atopic eczema.

Imustat *Darnitsa, Ukr.*
6-Bromo-5-hydroxy-1-methyl-4-dimethylaminomethyl-2-phenylthiomethylindole-3-carboxylic acid hydrochloride ethyl ester.
Viral infections.

Imustrum *Erlimpex, Indon.*
Prebiotic; bovine colostrum (p. 2380·3); curcuminoid; docosahexaenoic acid (p. 1460·1); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3); zinc sulfate (p. 2126·2).
Nutritional supplement.

Imutrex *Cipla, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; rheumatoid arthritis; psoriasis; Crohn's disease.

Imuvac *Abbott, UK.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Imuvit
Note: this name may be used for preparations of different composition.
Rueckert, Malaysia; Asetris, Switz.†; Rueckert, Thai.
Ginseng (p. 2513·3); vitamins; minerals.
Tonic; vitamin and mineral deficiency.

Sterkem, India.
Vitamins; minerals; trace elements; lycopene (p. 2546·2).

Imuvital *Vita Health, Switz.†*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic.

Imuxgen *Bioprofarma, Arg.*
Mycophenolate mofetil (p. 1961·1).
Prevention of renal, cardiac, and hepatic transplant rejection.

Imuzat *Elder, India.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

In *Systopic, India.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

In A Wink Moisturising *Novartis, Austral.*
Hypromellose (p. 2189·2).
Dry eyes.

In Cil-Vk *Thebe, S.Afr.*
Phenoxymethylpenicillin potassium (p. 338·3).

Inabutol Forte *Themis Chemicals, India.†*
Isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Inac *Wintac, Singapore; Zydus Cadila, Singapore.*
Diclofenac sodium (p. 48·3).
Rheumatism; gout.

Zydus, India.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Inace *Win-Medicare, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Inacid *Iroko, Spain.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Inac-P *Zydus, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Inadine *Systagenix, Irl.; Systagenix, Ital.; Systagenix, UK.*
Povidone-iodine (p. 1767·1).
Wounds; skin ulcers; burns; wound dressing.

Inadril *Inpac, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Inadryl *Interbat, Indon.*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2); alcohol (p. 1733·1).
Cough; nasal congestion.

Inadryl Plus *Interbat, Indon.*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2); alcohol (p. 1733·1); sodium citrate (p. 1781·2).
Cough; nasal congestion; sneezing.

Inalacor *GSK, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Inaladuo *GSK, Spain.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Inalan *Nizhpharm, Rus.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastritis; peptic ulcer; gastro-oesophageal reflux; dyspepsia.

Inalar *Federfarma, Ital.*
⊗Xylometazoline hydrochloride (p. 1680·1); domiphen bromide (p. 1751·1).
Nasal congestion.

Inalcort *Caber, Ital.†*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Inalgex *Grunenthal, Port.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Inalone *GSK, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Inalpin *Qualiphar, Belg.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Inamid *Nufarindo, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Inane *Kamakshi, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Inane-P *Kamakshi, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Inapas *USV, India.*
Sodium aminosalicylate (p. 215·2); isoniazid (p. 311·2).
Tuberculosis.

Inaprol *Bilim, Turk.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal and joint disorders; pain; inflammation.

Inapsin *Janssen-Cilag, S.Afr.*
Droperidol (p. 1072·1).
Postoperative nausea and vomiting.

Inapsine *Akorn, USA.†*
Droperidol (p. 1072·1).
Nausea and vomiting in surgical and diagnostic procedures; premedication; neuroleptanalgesia.

Inaspir *Almirall, Spain.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Inat *Siomond, India.*
⊗Atenolol (p. 1308·2); indapamide (p. 1409·2).

Inavir
Note: this name may be used for preparations of different composition.
Daiichi Sankyo, Jpn.
Laninamivir octanoate (p. 1002·1).
Influenza.

GPO, Thai.
Indinavir (p. 986·1).
HIV infection.

Inbac Kit *Intag, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Inbec *Emcure, India.*
Indinavir (p. 986·1).
HIV infection.

Inbion *Interbat, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); intrinsic factor (p. 2534·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Inbutol *Yuriya-Farm, Ukr.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Incad *Bushnell, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement; calcium deficiency.

Incaico *Incaico, Arg.*
Boldo (p. 2458·3); chamomile (p. 2474·1).

Incaico Serenidad *Incaico, Arg.*
Valerian (p. 2640·2); tilia (p. 2631·3); peppermint (p. 1877·1); chamomile (p. 2474·1).

Incal *Indo Pacific, India.*
Oral Suspension: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Indo Pacific, India.
Tablets: Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Incardel *Pisa, Mex.*
Acarbose (p. 466·2).
Diabetes mellitus.

Inca's Gold *Larkhall Laboratories, UK.*
Jojoba oil.

Incebral *Soria Natural, Spain.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Incee-Vit *Interhealthcare, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Incef *Intra-Labs, India.*
Dispersible tablets; syrup: Cefixime (p. 240·3).
Bacterial infections.

Intra-Labs, India.
Injection: Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Incef-CL *Intra-Labs, India.*
Cefixime (p. 240·3); dicloxacillin (p. 286·1); lactobacillus (p. 2596·3).
Bacterial infections.

Incef-CV *Intra-Labs, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Incef-LB *Intra-Labs, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

Incef-SB *Intra-Labs, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Incef-TZ *Intra-Labs, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Incel *Darrow, Braz.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Incelin *Interbat, Indon.*
Citicoline (p. 2480·1).
Head injury; stroke; hemiplegia; mental function impairment in the elderly.

Incena *Bittner, Ukr.*
Capsicum (p. 2469·3); belladonna (p. 2453·3); pulsatilla (p. 2600·2); apis (p. 2445·2); lachesis (p. 2538·3).
Homoeopathic preparation.

Incet *Vensat, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Incet-L *Indo Pacific, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Incez *Intra-Labs, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Inchingoreisan *Tsumura, Jpn.*
Alisma rhizome; atractylodes lancea rhizome; polyporus sclerotium; poria sclerotium; artemisia capillaris flower; cinnamon bark (p. 2479·2).
Traditional Kampo medicine.

Inchinkoto *Tsumura, Jpn.*
Artemisia capillaris flower; gardenia fruit; rhubarb (p. 1884·2).
Traditional Kampo medicine.

Incid *Verheilen, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Incidal-OD *Bayer Schering, Indon.; Bayer, Thai.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic rhinitis; allergic skin disorders.

Incidin *Ecolab, Ger.*
Foam: ⊗Propyl alcohol (p. 1768·1); alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1); glucoprotamine (p. 1753·2).
Equipment disinfection.

Ecolab, Ger.
Liquid: Isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1).
Equipment disinfection.

Incidin extra N *Ecolab, Ger.*
Glucoprotamine (p. 1753·2); benzalkonium chloride (p. 1737·1).
Surface disinfection.

Incidin perfekt *Ecolab, Ger.*
Formaldehyde (p. 1752·2); glyoxal (p. 1754·1); glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1); oligo(di(iminoimidocarbonyl)iminohexamethylene).
Surface disinfection.

Incidin Plus *Ecolab, Ger.*
Glucoprotamine (p. 1753·2).
Surface disinfection.

Incidin Spezial
Note: this name may be used for preparations of different composition.
Ecolab, Ital.†
⊗Alcohol (p. 1733·1); glyoxal (p. 1754·1); glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1).
Surface disinfection.

Incid-L *Bayer, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Incidur *Ecolab, Ger.*
Glutaral (p. 1753·2); glyoxal (p. 1754·1).
Surface disinfection.

Incidur Spray *Ecolab, Ital.†*
⊗Alcohol (p. 1733·1); benzalkonium chloride (p. 1737·1); 5-bromo-5-nitro-1,3-dioxacyclohexane.
Disinfection of surfaces and instruments.

Incil *Alliance, S.Afr.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Incitin *Bernofarm, Indon.†*
Mebhydrolin napadisilate (p. 634·2).
Allergic disorders.

Incivek *Vertex, Canad.; Vertex, USA.*
Telaprevir (p. 1016·3).
Chronic hepatitis C.

Incivo *Janssen-Cilag, Belg.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK.*
Telaprevir (p. 1016·3).
Chronic hepatitis C.

Inclarin *Interbat, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Inclens *Cofasa, Venez.*
⊗Furosemide (p. 1387·1).
Diuretic.

Inclovir *Interbat, Indon.*
Valaciclovir (p. 1021·1).
Herpesvirus infections.

Incloz *Intel, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Inco *Siu Guan, Philipp.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Incobal Plus *Indo Pacific, India.*
Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Incobal-OD *Indo Pacific, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Incognito *Incognito, UK.*
Cymbopogon winterianus; eucalyptus citriodora; camphor (p. 2466·2); pelargonium graveolens.
Insect repellent.

Incold *Indo Pacific, India.*
Syrup: Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Indo Pacific, India.
Tablets: Caffeine (p. 1203·3); cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Incoliquid *Inco, Gr.*
Hexachlorophene (p. 1754·1).

Inconex *Sandoz, UK.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Incontinol *Millet Roux, Braz.*
Oxybutynin hydrochloride (p. 2361·2).
Urinary-tract disorders.

In-Control *Golden Glow, Austral.*
Cucurbita (p. 2489·2); soya isoflavones (p. 2620·3).
Bladder weakness.

Inconturina mono *OTW, Ger.*
Populus tremuloides (p. 2450·3).
Homoeopathic preparation.

Incoril *Bago, Arg.; Bago, Braz.; Bago, Chile.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; heart failure; hypertension; arrhythmias.

Incosit *Utopian, Thai.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.

Incough-DX *Indo Pacific, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Increlex *Ipsen, Austria; Ipsen, Belg.; Ipsen, Cz.; Ipsen, Denm.†; Ipsen, Fr.; Ipsen, Ger.; Ipsen, Gr.; Ipsen, Irl.; Tercica, Israel; Ipsen, Ital.; Ipsen, Neth.; Ipsen, Norw.; Tercica, Pol.; Ipsen, Port.; Ipsen, Spain; Ipsen, Swed.; Ipsen, UK; Tercica, USA.*
⊗Mecasermin (p. 1929·2).
Growth failure in children and adolescents; growth hormone deficiency.

Incremin
Note: this name may be used for preparations of different composition.
Wyeth, India.
Ferric pyrophosphate (p. 2060·2); lysine hydrochloride (p. 2079·3).

Wyeth, Philipp.
Iron (p. 2073·1); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia; nutritional supplement.

Incremin Con Hierro *Wyeth, Mex.*
Ferric pyrophosphate (p. 2060·2); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Iron-deficiency anaemia; iron and vitamin B deficiency.

Incremin Iron *Pfizer Consumer, Austral.*
Ferric pyrophosphate (p. 2060·2); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Incremin with Iron *Lederle, Indon.†; Wyeth Consumer, NZ.*
Iron (p. 2073·1); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Dietary supplement; iron deficiency; iron-deficiency anaemia.

Increph *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; acid aspiration.

Incresil *Permatec, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Incuria *Sanovel, Turk.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Ind
Note: this name may be used for preparations of different composition.
Concertina, India.
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

McNeil & Argus, India.
Indinavir (p. 986·1).
HIV infection.

Ind Clav *Indchemie, Thai.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Ind Complex *Thompsons, Canad.†*
Antimony trisulfide (p. 2445·1); charcoal activated (p. 1537·3); potassium carbonate (p. 2595·2).
Homoeopathic preparation.

Indac *Indo Pacific, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Indacar *Pharmacodane, Denm.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indacard *Intra-Labs, India.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Indaco *Pharmaidea, Ital.*
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.

Indaflex
Note: this name may be used for preparations of different composition.
Andromaco, Mex.
Indometacin (p. 71·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Lampugnani, Ital.
⊗Indapamide (p. 1409·2).
Hypertension.

Indahexal *Sandoz, Austral.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indalgin *Orion, Fin.*
Indometacin (p. 71·2); ethylmorphine hydrochloride (p. 56·3).
Pain.

Indalix *Quality, Hong Kong; CCM, Malaysia; Triomed, S. Afr.†*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Indamid
Note: this name may be used for preparations of different composition.
Sandoz, Turk.
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Pisa, Mex.†
Clindamycin (p. 269·3).
Bacterial infections.

Indamix DM *Centurion, USA.†*
⊗Dexchlorpheniramine tannate (p. 620·3); dextromethorphan tannate (p. 1660·1); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Indamol *Teofarma, Ital.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indanorm *Julphar, UAE.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indanox *Guardian, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Indap *ProMed, Cz.; Orchid, India; Pro.Med, Rus.; ProMed, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Indap-AT *Orchid, India.*
⊗Atenolol (p. 1308·2); indapamide (p. 1409·2).

Indapen *Torrent, Braz.; Polpharma, Pol.; Biofarma, Turk.; Polpharma, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Indapres *Richter, Pol.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indapress *Labomed, Chile.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indapsan *Sanofi-Aventis, Pol.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Inda-Puren *Actavis, Ger.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Indarzona *Streger, Mex.*
⊗Indometacin (p. 71·2); dexamethasone (p. 1630·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Indarzona-N *Streger, Mex.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Indastad *Stada, Hung.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indaxin-B6 *Ind-Swift, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Indcef *Ind Biosciences, India.*
Cefixime (p. 240·3).
Bacterial infections.

Indcel *Ind-Swift, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Indclav *Ind-Chemie, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Indcobal *Ind Biosciences, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Indcon *Ind Biosciences, India.*
Fluconazole (p. 578·2).
Fungal infections.

Indease *Alkem, India.*
Indinavir sulfate (p. 986·1).
HIV infection.

Indent *Intel, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Indeparin *Gland, India.*
Ardeparin sodium (p. 1307·1).

Inderal *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; Pfizer, Canad.; Cana, Gr.; AstraZeneca, Hong Kong; Piramal, India; AstraZeneca, Indon.†; AstraZeneca, Irl.; AstraZeneca, Israel†; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S. Afr.; AstraZeneca, Singapore†; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, UK; Akrimax, USA; Baxter, USA; AstraZeneca, Venez.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias; angina pectoris; myocardial infarction; migraine; essential tremor; hypertrophic subaortic stenosis; phaeochromocytoma; anxiety; hyperthyroidism; hypertrophic obstructive cardiomyopathy; variceal haemorrhage; fallot's tetralogy; thyrotoxic crisis; glaucoma.

Inderalici *AstraZeneca, Mex.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; migraine; essential tremor; anxiety; variceal haemorrhage; hyperthyroidism; obstructive cardiomyopathy; phaeochromocytoma; glaucoma.

Inderm *Neocare, Belg.; Dermapharm, Ger.; Centrafarm, Neth.; Sankyo, Venez.*
Erythromycin (p. 291·2).
Acne.

Indermil *Tyco, UK.*
Enbucrilate (p. 2489·3).
Wound closure.

Inderyth *Indoco, India.*
Erythromycin (p. 291·2).
Bacterial infections.

Indexon *Interbat, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Indian Brandee
Note: this name may be used for preparations of different composition.
OTC Concepts, UK.
Capsicum (p. 2469·3); compound cardamom tincture (p. 2471·1).
Dyspepsia; flatulence.

Potter's, UK.
Capsicum (p. 2469·3); ginger (p. 1844·1); compound rhubarb tincture (p. 1884·2).
Colic; dyspepsia.

Indian Health - Centella *Labsa, Arg.*
Centella (p. 1698·3); alpha tocopherol (p. 2119·1).
Dietary supplement.

Indian Health - Garcinia *Labsa, Arg.*
Garcinia cambogia (p. 2510·2); alpha tocopherol (p. 2119·1); centella (p. 1698·3).
Dietary supplement.

Indian Health - Levadura *Labsa, Arg.*
Yeast (p. 2125·2); vitamin B substances (p. 2102·3).
Dietary supplement.

Indian Health - Urucum *Labsa, Arg.*
Bixa orellana; betacarotene (p. 2051·1); alpha tocopherol (p. 2119·1).
Dietary supplement.

Indiaral *Gifrer Barbezat, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Indical *Indi, India.*
Calcium carbonate (p. 1824·3); magnesium hydrochloride; zinc sulfate (p. 2126·2); vitamin D (p. 2112·3).

Indican *Sidus, Arg.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Indicarb *Zydus, India.*
Procarbazine.

Indicontin *Modi-Mundipharma, India.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Indigestion
Note: this name may be used for preparations of different composition.
Hylands, Canad.
Cinchona officinalis (p. 2478·3); hydrastis canadensis (p. 2528·1); kali bichromicum (p. 2476·3); phosphoricum acidum (p. 2589·1).
Homoeopathic preparation.

Homeocan, Canad.†
Basilicum (p. 2453·1); podophyllum (p. 1717·1); chamomilla (p. 2474·1); sulfur (p. 1721·1); lycopodium (p. 2546·3); colchicum (p. 607·1); belladonna (p. 2453·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Indigestion and Flatulence *Cantassium Co., UK.*
⊗Capsicum oleoresin (p. 2469·3); valerian (p. 2640·2); fennel (p. 2503·2); myrrh (p. 2566·1); papain (p. 2582·3).

Indigestion Mixture *Potter's, UK.*
Meadowsweet (p. 2550·2); gentian (p. 2512·1); euonymus (p. 1842·1).
Dyspepsia; heartburn; flatulence.

Indigestion Relief
Note: this name may be used for preparations of different composition.
Herbal Concepts, UK.
Leptandra virginica; capsicum (p. 2469·3); fringetree bark; ginger (p. 1844·1).
Dyspepsia; nausea; colic.

Indigon *IQFA, Mex.*
Dipyrone (p. 53·3).
Fever; inflammation; muscle spasm; pain.

Indikof-A *Alkem, India.*
Cetirizine (p. 619·2); dextromethorphan hydrochloride; menthol (p. 2553·2).

Indikof-B *Alkem, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Indikof-C *Alkem, India.*
Chlorphenamine maleate (p. 620·3); codeine sulfate (p. 40·3).

Indilac *Ind-Swift, India.*
Bacillus mesentericus; Clostridium butyricum; Lactobacillus sporogenes (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).

Indilan *Landsteiner, Mex.*
Indinavir sulfate (p. 986·1).
HIV infection.

Indilea *Elea, Arg.†*
Indinavir sulfate (p. 986·1).
HIV infection.

Indinax *Eurofarma, Braz.*
Indinavir (p. 986·1).
HIV infection.

Indipam *Balkanpharma, Rus.; Actavis, UK.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Indir *Helm, Port.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indirab *Bharat, Philipp.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Inditest *Reder, Mex.†*
Pregnancy test (p. 2596·1).

Inditor *Ipca, India.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indiur *Gedeon Richter, Rus.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indiure *Gedeon Richter, Ukr.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Indiva *Pharos, Indon.*
Citrus bioflavonoids (p. 2505·2); diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Indivan *Cipla, India; Cipla, Venez.*
Indinavir sulfate (p. 986·1).
HIV infection.

Indivina *Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Ger.; Orion, Hung.; Orion, Irl.; Orion, Norw.; Orion, Pol.; Orion, Rus.; Orion, Swed.; Orion, Switz.; Orion, Thai.†; Orion, UK; Orion, Ukr.†*
Estradiol valerate (p. 2271·2); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Indix *Pliva Krakow, Pol.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indlide *Ind Biosciences, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Indlith *Ind-Swift, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression.

Indo *CT, Ger.; CCM, Malaysia; Beacons, Singapore; Acdhon, Thai.; Asian Union, Thai.*
Indometacin (p. 71·2).
Gout; pain; musculoskeletal, joint, and soft-tissue disorders; inflammation; oedema.

Indo EDO *Mann, Ger.*
Indometacin (p. 71·2).
Prevention of intra-operative miosis; postoperative eye pain and inflammation.

Indo Top *Ratiopharm, Ger.*
Indometacin (p. 71·2).
Peri-articular and soft-tissue disorders.

Indobact *Ind Biosciences, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Indobene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Indometacin (p. 71·2).
Aluminium glycinate (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain.

Indobiotic *Chauvin, Fr.; Bausch & Lomb, Port.; Abdi, Turk.*
Indometacin (p. 71·2); gentamicin sulfate (p. 304·2).
Inflammation and bacterial infections after eye surgery.

Indoblok *Gulf Drug, S.Afr.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; hypertension; arrhythmias; phaeochromocytoma; anxiety.

Indobol *Adley, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Indo-bros *Bros, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Indocalm *Koni-Cofarm, Chile.*
Lidocaine (p. 1988·1); sulfathiazole (p. 368·3).
Ear infections.

Indocap *Tack Fung, Hong Kong†; Jagsonpal, India; Xepa-Soul Pattinson, Singapore.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.

Indocarsil *Solfran, Mex.†*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Indocef *Indo Pacific, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Indocef-SB *Indo Pacific, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Indocid *Aspen, Austral.; Iroko, Austria; Lundbeck, Belg.; MSD, Braz.; MSD, Fin.†; HAC, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; Aspen, Hong Kong; Cipla, India; Johnson & Johnson, Ital.; MSD, Mex.; MSD, Neth.†; MSD, Norw.†; Iroko, Port.; MSD, S.Afr.; MSD, Singapore; Future Health, Switz.; M & H, Thai.†; MSD, Turk.; Aspen Medical, UK; MSD, Venez.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain; fever; prevention of oedema and miosis during cataract extraction; oedema; trismus; closure of patent ductus arteriosus in premature neonates.

Indocid PDA *Invida, Austral.; Ovation, Canad.†; Lundbeck, Irl.†; Lundbeck, Neth.†; Healthcare Logistics, NZ; IDIS, UK.*
Indometacin sodium (p. 71·2).
Closure of patent ductus arteriosus.

Indocin
Note: this name may be used for preparations of different composition.
Helax, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Pharmasant, Thai.; Iroko, USA; Sandoz, USA.
Indometacin (p. 71·2).
Bursitis; tendinitis; musculoskeletal and joint disorders; gout.

Merck, Israel; MSD, Singapore; Lundbeck, USA.
Indometacin sodium (p. 71·2).
Closure of patent ductus arteriosus.

Indocin PDA *Ovation, Hong Kong.*
Indometacin sodium (p. 71·2).
Closure of patent ductus arteriosus.

Indocin-D *Helax, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Indocin-OZ *Helax, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Indocolir *Chauvin ankerpharm, Ger.; Abdi, Turk.*
Indometacin (p. 71·2).
Inflammation following eye surgery; prevention of miosis during eye surgery.

Indocollirio *Bausch & Lomb, Ital.*
Indometacin (p. 71·2).
Prevention of miosis and inflammation during cataract surgery.

Indocollyre *Chauvin, Austria; Bausch & Lomb, Belg.; Chauvin, Cz.; Chauvin, Fr.; Chauvin, Hong Kong; Chauvin, Hung.; Chauvin, Israel; Bausch & Lomb, Neth.; Chauvin, Pol.; Bausch & Lomb, Port.; Bausch & Lomb, Rus.; Bausch & Lomb, Singapore; Chauvin, Singapore; Chauvin, Thai.†; Bausch & Lomb, Ukr.*
Indometacin (p. 71·2).
Prevention of intra-operative miosis; cystoid macular oedema; eye inflammation and pain following eye surgery; prevention of ocular oedema following eye surgery.

Indocontin *BMPC, China; Remek, Gr.*
Indometacin (p. 71·2).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis; gout.

Indo-Cort *Biospray, Gr.*
⊗Fluorometholone (p. 1637·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Indocycline *Nufarindo, Indon.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Indocyp *Indo Pacific, India.*
Cyproheptadine (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Indodec *Adley, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Indof *Ind Biosciences, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Indof OZ *Ind Biosciences, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Indofen *Adley, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain; prevention of intra-operative miosis; eye inflammation and pain.

Indofenac-P *Indo Pacific, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Indoflam *Zydus, India.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain; prevention of miosis during cataract surgery.

Indofrin *Darya-Varia, Indon.†*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Indofrin-A *Darya-Varia, Indon.†*
⊗Antazoline phosphate (p. 615·3); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Allergic eye disorders; conjunctivitis.

Indogenta *Adley, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Indogesic *TRB, Arg.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Indolam *Indo Pacific, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Indolar SR *Sandoz, UK.*
Indometacin (p. 71·2).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Indolgina *Uriach, Spain.†*
Indometacin (p. 71·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Indolone *Ind Biosciences, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Indolpara *Rishab, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Indom *INTES, Ital.*
Indometacin (p. 71·2).
Prevention of miosis and inflammation during cataract surgery.

Indoman *Berman, Mex.; T Man, Thai.*
Indometacin (p. 71·2).
Inflammation; musculoskeletal and joint disorders; gout; pain.

Indo-Mathacin *T Man, Thai.†*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.

Indomed *MSD, Israel; Greater Pharma, Thai.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; rheumatic fever; inflammation; dysmenorrhoea.

Indomee *MSD, Swed.†*
Indometacin (p. 71·2).
Gout; musculoskeletal, joint and peri-articular disorders.

Indomelan *Lannacher, Austria.*
Indometacin (p. 71·2).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout; oedema.

Indomen *YSP, Malaysia; Yung Shin, Singapore.*
Indometacin (p. 71·2).
Inflammation; musculoskeletal and joint disorders.

Indometh *SSP, Thai.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.

Indomethol *Specifar, Gr.*
Indometacin (p. 71·2).
Inflammatory disorders.

Indometin *Orion, Fin.; ANH, Thai.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain; inflammation; fever.

Indomet-ratiopharm *Ratiopharm, Ger.*
Indometacin (p. 71·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Indomin *Hikma, Rus.†*
Indometacin (p. 71·2).

Indonilo *Sigma-Tau, Spain.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; gout.

Indono *Milano, Thai.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; rheumatic fever.

Indop *Fahrenheit, Indon.*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure.

Indo-paed *1A, Ger.†*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Indophtal *Bausch & Lomb, Switz.*
Indometacin (p. 71·2).
Inflammatory eye disorders; prevention of intra-operative miosis; prevention of cystoid macular oedema after cataract surgery.

Indopres *Borshchagovskii, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Indoprex *Demo, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Indopril *Apotex, Austral.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease.

Ind-Orange *Ind-Swift, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Indoriv *East African, India.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Indoson *Nufarindo, Indon.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Indotard *CTI, Israel.†*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Indotex *Rontag, Arg.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; pain.

Indotrin *Liferpal, Mex.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Indo-Trustman *T Man, Thai.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.

Indovasin *Sopharma, Rus.*
Indometacin (p. 71·2); troxerutin (p. 2505·3).
Musculoskeletal, joint, and peri-articular disorders; venous insufficiency; haematoma.

Indovenol *Borshchagovskii, Ukr.*
Troxerutin (p. 2505·3); indometacin (p. 71·2).
Venous insufficiency; haemorrhoids; peri-articular and soft-tissue disorders.

Indovis *CTS, Israel; CTS, Rus.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; musculoskeletal, joint, and soft-tissue disorders; gout; pain; inflammation.

Indox *Ind-Swift, India.*
Oxytocin (p. 2143·1).
Postpartum haemorrhage; labour induction; evaluation of fetal distress.

Indoxen *Quality, Hong Kong; Sigma-Tau, Ital.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Indoxone *Ind Biosciences, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Indoxone-S *Ind Biosciences, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Indoxyl *GSK, Austria; Stiefel, Chile; GSK, Gr.; Stiefel, Mex.*
Clindamycin phosphate (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

Indozid *Adley, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Indozul *Degorts, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa; premenstrual dysphoric disorder.

Indozyme *Indo Pacific, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Indpad *Ind Biosciences, India.*
Cefpodoxime.
Bacterial infections.

Inducmina *Gray, Arg.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Inductal
Note: this name may be used for preparations of different composition.
Roemmers, Arg.
Eszopiclone (p. 1072·3).
Insomnia.

InductOs *Wyeth, Austria; Medtronic, Belg.; Wyeth, Cz.; Wyeth, Denm.; Medtronic, Fin.; Medtronic, Fr.; Wyeth, Gr.; Pfizer, Irl.; Medtronic, Neth.; Medtronic, Norw.; Wyeth,*

Pol.; Wyeth Lederle, Port.; Medtronic, Spain; Medtronic, Swed.; Pfizer, Switz.; Wyeth, UK.
Dibotermin alfa (p. 1177·2).
Tibia fracture; degenerative disc disease; anterior lumbar spine fusion.

Indufol *Teva, Mex.*
Propofol (p. 1909·3).
General anaesthesia.

Induken *Kendrick, Mex.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Indulfan *Ecolab, Ital.†*
Glyoxal (p. 1754·1); benzalkonium chloride (p. 1737·1).
Surface disinfection.

Indulgeze *Thompson & Capper, UK.*
Milk thistle (p. 1561·1).
Dyspepsia.

Indumir *Gelcaps, Mex.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Indurgan *Amdipharm, Spain.†*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Indurin *Terra, Turk.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Indusil *Recordati, Ital.*
Cobamamide (p. 2107·2).
Vitamin B_{12} deficiency.

Indux *Sigma, Braz.*
⊗Clomifene citrate (p. 2259·1).
Female infertility.

Induxin *Kalbe, Indon.*
Oxytocin (p. 2143·1).
Labour induction; incomplete abortion; postpartum uterine bleeding.

Induzepam *Finadiet, Arg.*
Clonazepam (p. 519·1).
Panic disorder.

Ind-Vit *Ind Biosciences, India.*
Vitamins.

Inedit *Maver, Mex.*
Cefadroxil (p. 233·2).
Bacterial infections.

Inegy *MSD, Austria; MSD, Belg.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hung.; Schering-Plough, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Neth.; Schering-Plough, Neth.; MSD, Norw.; MSD, Port.; MSD, Rus.; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Turk.; MSD, UK.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Inelin *Kleva, Gr.*
Nicergoline (p. 2569·1).

Ineltano *Richmond, Arg.*
Halothane (p. 1902·1).
General anaesthesia.

I-Nem *Glenmark, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Inem *Laboratorios Chile, Chile.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Inerson *Interbat, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Inerve *Trigenesis, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3); selenium (p. 2086·3).

Inespecin *Biol, Arg.*
Salmonella typhi glycolipids.
Infection prophylaxis.

Inesprin *Prisfar, Port.†*
Lysine aspirin (p. 84·3).
Fever; pain.

Inestom *Help, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Ineurope *Pharmacie Centrale des Armees, Fr.*
Atropine sulfate (p. 1310·2); avizafone hydrochloride; pralidoxime metilsulfate (p. 1571·2).
Nerve agent exposure.

Inexium *2care4, Denm.; Europharma, Denm.; AstraZeneca, Fr.; Farmagon, Norw.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

INF *Bioprofarma, Arg.; Ranbaxy, Thai.†*
Interferon alfa-2b (p. 989·2).
Anogenital warts; hepatitis B and C; malignant neoplasms.

Inf IC *Metagenics, Canad.†*
Vitamin C (p. 2110·3).

Infabact *Invision, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Infacalm *Tianda, Hong Kong.*
Ibuprofen (p. 68·2).
Fever; pain.

Infacet *Protea, S.Afr.†*
Promethazine hydrochloride (p. 638·2); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever; nasal congestion.

Infacol *Nice Pak, Austral.; Forest, Canad.; IFET (ΙΦΕΤ), Gr.; Forest Laboratories, Hong Kong; Forest, Hung.; Forest, Irl.; Pfizer, NZ; Forest Laboratories, Pol.; Pfizer Consumer, Singapore†; Forest Laboratories, UK; Forest, Ukr.*
Simeticone (p. 1886·2).
Colic; flatulence; meteorism.

Infacol Probiotic *Forest Laboratories, UK.*
Lactobacillus reuteri (p. 2596·3).
Maintenance of healthy gastrointestinal flora.

Infacolic *Medihelm, Gr.*
Dimeticone (p. 1886·2).
Infant colic.

Infactum *Venus, India.*
Cefpodoxime proxetil (p. 248·1); clavulanic acid (p. 268·3).
Bacterial infections.

Infaderm *Goldshield, UK.*
Light liquid paraffin (p. 2191·2); almond oil (p. 2437·1).
Dry skin disorders.

Infadil *Shince, India.*
Paracetamol (p. 115·1).
Pain; fever.

Infadin *Zentiva, Cz.†*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency; osteoporosis; osteomalacia; tetany; hypocalcaemia; hypophosphataemia; hypoparathyroidism.

Infadolan *Herbacos Recordati, Cz.*
Vitamin A acetate (p. 2098·3); ergocalciferol (p. 2113·3).
Burns; wounds; ulcers; skin disorders.

Infadrops *Goldshield, UK.*
Paracetamol (p. 115·1).
Fever; pain.

Infaflor *Pediapharma, Philipp.*
Fluoride (p. 2089·2).
Dental caries prophylaxis.

Infafren Compuesto *Pisa, Mex.†*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).

Infafren Simple *Pisa, Mex.†*
Homatropine (p. 2007·3).

Infagel *Vector, Rus.*
Interferon alfa-2b (p. 989·2).
Hepatitis B; hepatitis C; malignant neoplasms.

Infaglobin *Invision, India.*
Oral drops: Ferrous gluconate (p. 2061·2); zinc gluconate (p. 2126·2); vitamins.
Invision, India.
Syrup: Vitamin B substances (p. 2102·3); minerals.

Infaglobin Plus *Invision, India.*
Vitamins.

Infalgina *Pisa, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Infalyte *Mead Johnson Nutritionals, USA.*
Electrolytes (p. 1775·1); rice syrup solids (p. 1780·1).
Formerly known as Ricelyte.
Oral rehydration therapy.

Infanate Balance *Acella, USA.*
Calcium (p. 1783·1); iron (p. 2073·1); vitamins; docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Infanrix *GSK, Austral.; GSK, China; GSK, Cz.; GSK, Fin.†; GSK, Ger.; GSK, Gr.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong†; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.†; GSK, NZ; GSK, Philipp.; Smith Kline & French, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, Ukr.; SmithKline Beecham, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Infanrix DTPa *GSK, Pol.; GSK, S.Afr.; GSK, Turk.†*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Infanrix DTPa-IPV *GSK, Switz.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Infanrix DTPa-IPV+Hib *GSK, Switz.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Infanrix HepB *GSK, Austral.†; GSK, Gr.; GSK, NZ.*
A diphtheria, tetanus, acellular pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Infanrix Hexa *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, Ukr.; GSK, Venez.*
A diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p. 2385·1).
Active immunisation.

Infanrix Hib *GSK, Austral.; GSK, Cz.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, NZ; GSK, Port.; GSK, Singapore; GSK, Spain.†*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Infanrix + Hib *GSK, China.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Infanrix IPV *GSK, Austral.; GSK, Belg.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Thai.; GSK, UK; GSK, Ukr.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Infanrix IPV + Hib *GSK, Cz.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Thai.; GSK, UK; GSK, Venez.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Infanrix IPV-HIB *GSK, Turk.†*
An adsorbed diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Infanrix Penta *GSK, Austral.; GSK, Cz.; GSK, Gr.; GSK, Irl.; GSK, Ital.†; GSK, Neth.; GSK, NZ; GSK, Pol.; GSK, Port.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and hepatitis B vaccine (p. 2386·1).
Active immunisation.

Infanrix Polio *GSK, Cz.; GSK, Fin.; GSK, Swed.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Infanrix Polio + Hib *GSK, Fin.; GSK, Norw.; GSK, Swed.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Infanrix Polio IPV - Hib *GSK, Israel.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Infanrix Tetra *GSK, Denm.; GSK, Gr.; GSK, Port.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Infanrixhexa *GSK, Fr.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p. 2385·1).
Active immunisation.

Infanrixquinta *GSK, Fr.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Infanrixtetra *GSK, Fr.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Infant Bufferin Cold Relief *BMS, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; upper respiratory-tract disorders.

Infant Gaviscon *Reckitt Benckiser, Austral.*
Magnesium alginate (p. 2167·2); sodium alginate (p. 2167·3).
Gastro-oesophageal reflux.

Reckitt Benckiser, S.Afr.
Alginic acid (p. 2167·2); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux.

Infant Tempra *BMS, Canad.*
Paracetamol (p. 115·1).
Fever, pain.

Infantaire *Altaire, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Infantol *Church & Dwight, Canad.*
Vitamins.
Dietary supplement.

Infants Motrin *McNeil Consumer, Canad.*
Ibuprofen (p. 68·2).
Fever; pain.

Infants Tylenol *McNeil Consumer, Canad.*
Paracetamol (p. 115·1).
Pain; fever.

Infant's Tylenol *Johnson & Johnson, China.*
Paracetamol (p. 115·1).
Fever; pain.

Infant-Sed *Marching, Hong Kong.†*
Dill oil (p. 2493·2); dimeticone (p. 1886·2); pipenzolate bromide (p. 1878·1).

Infapain *Alliance, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Infapain Forte *Thebe, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Infasoy *Cow & Gate, Irl.; Nucitec, Mex.; Wyeth, NZ†; Aspen Consumer, S.Afr.; Cow & Gate, UK.*
Infant feed.
Lactose intolerance; galactosaemia; cows' milk intolerance; lactase deficiency; gluten intolerance.

Infasurf *Ony, Israel; Ony, Ukr.; ONY, USA.*
Calfactant (p. 2599·2).
Neonatal respiratory distress syndrome.

Infatem *IQFA, Mex.*
Dipyrone (p. 53·3).

Infatrim *Molex Ayus, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections; toxoplasmosis.

Infatrini *Nutricia, Austral.*
Infant feed.
Disease-related malnutrition.

Support, Braz.; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia Clinical, UK.
Preparation for enteral nutrition in infants.

Infatrini LCP *Nutricia, Denm.*
Preparation for enteral nutrition in infants.

Infavit *Farcoral, Mex.*
Vitamins; lysine (p. 2079·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Infazyme *Invision, India.*
⊗Amylase (p. 2442·1); vitamin B substances (p. 2102·3); pepsin (p. 2586·1).

Infectina *Hospital Line, Gr.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

InfectoBicillin *Infectopharm, Ger.*
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

InfectoCef *Infectopharm, Ger.*
Cefaclor (p. 232·3).
Bacterial infections.

InfectoCillin *Infectopharm, Ger.*
Oral solution; tablets: Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Infectocillin *Infectopharm, Ger.*
Injection: Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

InfectoCipro *Infectopharm, Ger.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Infectoclont *Infectopharm, Ger.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Infectocortikrupp *Infectopharm, Ger.*
⊗Prednisolone acetate (p. 1645·2).
Corticosteroid.

InfectoCortiSept *Infectopharm, Ger.*
⊗Halometasone (p. 1639·3); triclosan (p. 1773·2).
Skin disorders.

InfectoDell *Infectopharm, Ger.*
Potassium hydroxide (p. 2595·3).
Molluscum contagiosum.

InfectoDexaKrupp *Infectopharm, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

InfectoDiarrstop LGG *Infectopharm, Ger.*
Lactobacillus rhamnosus (p. 2596·3); electrolytes (p. 1775·1); glucose (p. 2068·3).
Diarrhoea.

InfectoDiarrstop LGG Mono *Infectopharm, Ger.*
Lactobacillus rhamnosus (p. 2596·3).
Diarrhoea.

InfectoFlam
Note: this name may be used for preparations of different composition.
Infectopharm, Ger.
Sulfadiazine silver (p. 362·3).
Burns.

Infectoflam *Novartis, Belg.†; Novartis, China; Novartis, Philipp.; Novartis Ophthalmics, Singapore; Novartis, Switz.†; Novartis, Thai.†*
⊗Fluorometholone (p. 1637·2); gentamicin sulfate (p. 304·2).
Infected and inflammatory eye disorders.

InfectoFos *Infectopharm, Ger.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

InfectoGenta *Infectopharm, Ger.*
Gentamicin sulfate (p. 304·2).
Bacterial skin and eye infections.

InfectoGingi *Infectopharm, Ger.*
Sage (p. 2608·3); chamomile (p. 2474·1); lidocaine (p. 1988·1).
Mouth disorders.

InfectoGripp *Infectopharm, Ger.*
⊗Zinc histidine; dexpanthenol (p. 2582·2); xylitol (p. 2220·3); glycerol (p. 2517·2); peppermint (p. 1877·1).
Cold and influenza symptoms.

InfectoHoney *Infectopharm, Ger.*
Manuka honey (p. 2072·1).
Wounds; burns; skin grafts.

InfectoHoney Alginat *Infectopharm, Ger.†*
Manuka honey (p. 2072·1); calcium alginate (p. 1136·3).
Wounds; burns; skin grafts.

InfectoKrupp *Infectopharm, Ger.*
⊗Adrenaline acid tartrate (p. 1292·2).
Obstructive airways disease.

InfectoMox *Infectopharm, Ger.*
Amoxicillin (p. 216·2).
Bacterial infections.

InfectoMycin *Infectopharm, Ger.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Infectomyk *Infectopharm, Ger.*
Natamycin (p. 590·2).
Bacterial eye infections.

InfectoOpticef *Infectopharm, Ger.*
Cefixime (p. 240·3).
Bacterial infections.

InfectoPedicul *Infectopharm, Ger.*
Lotion: Permethrin (p. 2159·3).
Pediculosis.

InfectoPyoderm *Infectopharm, Ger.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Infectoroxit *Infectopharm, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Infectoscab *Infectopharm, Austria; Infectopharm, Cz.; Infectopharm, Ger.; Infectopharm, Hung.; Infectopharm, Pol.*
Permethrin (p. 2159·3).
Scabies.

InfectoSoor *Infectopharm, Ger.*
Ointment: Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Napkin rash.

Infectopharm, Ger.
Oral gel: Miconazole (p. 588·3).
Mouth and throat candidiasis.

InfectoStaph *Infectopharm, Ger.†*
Oxacillin sodium (p. 336·2).
Staphylococcal infections.

InfectoSupramox *Infectopharm, Ger.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

InfectoTrimet *Infectopharm, Ger.*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Infectotrimet *Infectopharm, Austria.*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Infectovac Flu *Infectopharm, Ger.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

InfectoZidim *Infectopharm, Ger.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Infectrin
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Braz.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

IN FeD *Schein, USA.*
Iron dextran (p. 2075·3).
Iron deficiency.

Infeflox *Verisfield, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Infekor *One Pharma, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Infekt *Teva, Denm.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Infekt 1-Injektopas N *Pascoe, Ger.*
Echinacea (p. 2498·1); aconitum (p. 2428·3); bryonia (p. 2461·3); lachesis (p. 2538·3); aurum metallicum (p. 2521·1).
Homoeopathic preparation.

Infekt-Komplex L Ho-Fu-Complex *Liebermann, Ger.*
Aconitum (p. 2428·3); apis (p. 2445·2); belladonna (p. 2453·3); echinacea (p. 2498·1); gelsemium (p. 2511·2); guajacum (p. 2523·1); kalium jodatum (p. 2336·3).
Homoeopathic preparation.

Infektoten *Herbapol Lublin, Pol.†*
Salix (p. 129·2); sambucus (p. 2609·3); meadowsweet (p. 2550·2).
Fever.

Infeld *Interbat, Indon.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Infelon *Caprifarmindo, Indon.*
⊗Mesterolone (p. 2291·1).
Male hypogonadism; male infertility.

Infen *Emcure, India.*
Dexketoprofen trometamol (p. 79·1).

Infenac *Inpac, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Inferax *IFET (ΙΦΕΤ), Gr.*
Interferon alfacon-1 (p. 989·2).

Infergen *Three Rivers, Canad.†; Astellas, China; IFET (ΙΦΕΤ), Gr.; Yamanouchi, Gr.; Three Rivers, USA.*
Interferon alfacon-1 (p. 989·2).
Hepatitis C.

Inferon *Microgen, Rus.*
Interferon alfa (p. 989·2).

Inferose *Frik, Turk.*
Iron sucrose (p. 2078·1).

Inferoxin *Farmoz, Port.*
Roxithromycin (p. 356·2).
Bacterial infections.

Infer-Z *Indo Pacific, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).

Indo Pacific, India.
Syrup: Folic acid (p. 2063·1); iron polymaltose (p. 2077·2); vitamin B_{12} (p. 2107·2).

Infesol *Berlin-Chemie, Ger.*
Amino acids.
Parenteral nutrition.

Infesol 40 *Berlin-Chemie, Ukr.*
Amino acids; xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Infesol 100 *Berlin-Chemie, Ukr.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Infesol E *Berlin-Chemie, Ger.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Infesol XE *Berlin-Chemie, Ger.*
Amino acids; electrolytes (p. 1775·1); xylitol (p. 2220·3).
Parenteral nutrition.

Infester *Gerolymatos, Gr.*
Tioconazole (p. 595·3).
Fungal nail infections.

Infex
Note: this name may be used for preparations of different composition.
Recalcine, Chile.
Clarithromycin (p. 266·2).
Bacterial infections.

Elofar, Braz.†
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Infexin *Solvang, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Infexo *Esma, India.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Infez-4 *Shreya, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); 2 caplets, pyrazinamide (p. 345·2); 1 caplet, rifampicin (p. 350·3).
Tuberculosis.

Infezol *Berlin-Chemie, Rus.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Infibran *Tradiphar, Fr.†; CS, Port.†*
Wheat bran (p. 1823·3).
Constipation.

Infi-Camphora *Infirmarius, Ger.*
Camphora (p. 2466·2); carbo vegetabilis (p. 1537·3); convallaria majalis (p. 2486·2); crataegus (p. 2488·1); ephedra distachya; natrium pangametinum (p. 2582·1); natrium tetrachloroauratum (p. 2521·2); selenicereus grandiflorus (p. 2473·2); strophanthus gratus; veratrum album (p. 2644·3).
Homoeopathic preparation.

Infi-China *Infirmarius, Ger.*
China (p. 2478·3); acidum phosphoricum (p. 2589·1); anamirta cocculus (p. 2483·1); aurum metallicum (p. 2521·1); chamaelirium luteum (p. 2524·3); hypericum (p. 449·1); kalium phosphoricum (p. 1790·3); selenium (p. 2086·3); sepia officinalis (p. 2613·1); nux vomica (p. 2573·3); aurum chloratum (p. 2521·1); cerium chloratum; cobaltum chloratum (p. 2482·2); cuprum sulfuricum (p. 2057·2); cyanocobalamin (p. 2107·2); ferrum sesquichloratum (p. 2504·2); magnesium chloratum (p. 1787·1); magnesium sulfuricum (p. 1787·3); nikotinamidum (p. 2083·1); rutinum solubile (p. 2505·3); zincum sulfuricum (p. 2126·2).
Homoeopathic preparation.

Infi-Echinacea *Infirmarius, Ger.*
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); echinacea ang. (p. 2498·1); echinacea purpurea (p. 2498·1); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens (p. 2511·2); lachesis mutus (p. 2538·3); phosphorus (p. 2589·2); veratrum album (p. 2644·3).
Homoeopathic preparation.

Infifer N *Infirmarius, Ger.*
Ferrum phosphoricum (p. 2077·1); agaricus; aluminium oxydatum (p. 1690·3); arnica montana (p. 2447·2); artemisia cina; calcium carbonicum (p. 1824·3); camphora (p. 2466·2); cuprum metallicum (p. 2057·1); iris versicolor (p. 2534·3); kalium carbonicum (p. 2595·2); pulsatilla pratensis (p. 2600·2); sepia off. (p. 2613·1); stibium sulfuratum nigrum (p. 2445·1); nux vomica (p. 2573·3).
Homoeopathic preparation.

Infigripp *Infirmarius, Ger.*
Aconitum napellus (p. 2428·3); arnica montana ex planta tota (p. 2447·2); atropa belladonna (p. 2453·3); bryonia (p. 2461·3); cinchona pubescens (p. 2478·3); drosera (p. 2497·2); eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens (p. 2511·2); polygala senega (p. 1677·2).
Homoeopathic preparation.

Infihepan *Infirmarius, Ger.*
Atropa belladonna (p. 2453·3); calcium carbonicum (p. 1824·3); chelidonium majus (p. 2522·2); china (p. 2478·3); cynara scolymus (p. 2490·3); natrium sulfuricum (p. 1888·1); phosphorus (p. 2589·2); carduus marianus (p. 1561·1); achillea millefolium (p. 2427·3); aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); bellis perennis (p. 2454·2); calendula officinalis (p. 2465·2); carbo vegetabilis (p. 1537·3); chamomilla recutita (p. 2474·1); cyanocobalaminum (p. 2107·2); echinacea ang. (p. 2498·1); echinacea purpurea (p. 2498·1); hepar suis (p. 2444·1); hamamelis (p. 2523·3); hepar sulfuris (p. 1721·3); lophophytum leandri; mercurius solubilis (p. 2555·3); nicotinamidum (p. 2083·1); rutinum solubile (p. 2505·3); symphytum officinale (p. 2484·2); veratrum album (p. 2644·3).
Homoeopathic preparation.

Infilex *Pekana, Canad.†*
Asclepias vincetoxicum; cinchona officinalis (p. 2478·3); echinacea angustifolia (p. 2498·1); horehound (p. 1668·3); pulsatilla (p. 2600·2); silver nitrate (p. 2615·3); tree of heaven; water cress.
Homoeopathic preparation.

Infinerval *Infirmarius, Ger.*
Acidum phosphoricum (p. 2589·1); ambra grisea (p. 2440·3); avena sativa (p. 2451·1); coffea arabica (p. 2648·2); passiflora incarnata (p. 2584·1); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Infiossan *Infirmarius, Ger.*
Symphytum officinale (p. 2484·2); calcium fluoratum (p. 2053·1); ruta graveolens (p. 2608·2); strontium carbonicum.
Homoeopathic preparation.

Infi-Symphytum *Infirmarius, Ger.*
Symphytum officinale (p. 2484·2); acidum silicicum (p. 2208·3); acorus calamus (p. 2464·2); alchemilla vulgaris; calcium carbonicum (p. 1824·3); calcium phosphoricum (p. 1784·2); cimicifuga racemosa (p. 2478·1); cyanocobalaminum (p. 2107·2); equisetum arvense (p. 2500·1); fabiana imbricata; nicotinamidum (p. 2083·1); gnaphalium polycephalum; pyridoxinum hydrochloricum (p. 2105·3); thiaminum nitricum (p. 2103·2); tocopherolum aceticum (p. 2119·2); china (p. 2478·3); gelsemium sempervirens (p. 2511·2); sepia officinalis (p. 2613·1); toxicodendron quercifolium (p. 2603·3).
Homoeopathic preparation.

Infi-tract V *Infirmarius, Ger.*
Oral drops: ⊗Angelica (p. 2443·3); gentian (p. 2512·1); Javanese turmeric (p. 2636·2); santonica root eberwurz; myrrh (p. 2566·1); saffron (p. 2208·2); vitamin C (p. 2110·3); mannitol (p. 1427·3).
Digestive disorders.

Infla-Ban *Triomed, S.Afr.†*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; gout.

Inflabion *Help, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Inflaced *Dexo, Fr.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Inflacort *Bilim, Turk.*
⊗Budesonide (p. 1625·1).
Asthma.

Infladase *Centaur, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Infladase Forte *Centaur, India.*
⊗Serrapeptase (p. 2613·3); cobalt (p. 2482·2); manganese (p. 2081·2); zinc (p. 2126·1).
Formerly known as Infladase.
Inflammation; pain; breast engorgement; pericoronitis; alveolar abscess.

Infladex *Legrand, Braz.*
Diclofenac sodium (p. 48·3).

Inflaflur *Alapis, Gr.*
Flurbiprofen sodium (p. 65·3).
Inhibition of intraoperative miosis.

Inflaforte *Verisfield, Gr.*
Diclofenac sodium (p. 48·3).
Osteoarthritis.

Inflagel *EMS, Braz.*
Tenoxicam (p. 136·2).

Inflahit *Aurel, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Inflahit-P *Aurel, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Inflahit-SP *Aurel, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Inflakod *Plus, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Inflalid *Legrand, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Inflam
Note: this name may be used for preparations of different composition.
Corsa, Indon.
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Inflamac *Spirig, Switz.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation; fever.

Inflamafertin *NIR, Ukr.*
Complex placental regulatory peptides (p. 2444·1).
Female infertility; inflammatory diseases of genitourinary tract; postoperative pelvic adhesions; scleroderma; rheumatoid arthritis.

Inflamase
Note: this name may be used for preparations of different composition.
Amnol, Ital.
⊗Aesculus (p. 2431·2); bromelain (p. 2460·3); zinc sulfate (p. 2126·2); copper sulfate (p. 2057·2).
Inflammation; oedema.

Inflamase IdroGel *Amnol, Ital.*
⊗Aescin (p. 2431·2); bromelains (p. 2460·3).
Inflammation; oedema.

Inflamase-N *Zekides, Gr.*
Piroxicam (p. 125·3).

Inflamate *TO-Chemicals, Thai.†*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; rheumatic fever.

Inflamax *Elofar, Braz.*
Diclofenac sodium (p. 48·3).

Inflamene *Chiesi, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Inflameri *Merion, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Inflamex *Biofarma, Turk.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Inflamma *Suphong, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Inflammide *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Malaysia†; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore.†*
⊗Budesonide (p. 1625·1).
Asthma; rhinitis.

Inflanac *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Inflanan *Marjan, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Inflanaze *Boehringer Ingelheim, S.Afr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Inflanefran *Allergan, Ger.*
⊗Prednisolone acetate (p. 1645·2).
Eye disorders.

Inflanegent *Allergan, Ger.*
⊗Prednisolone acetate (p. 1645·2); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Inflanox
Note: this name may be used for preparations of different composition.
Mavi, Mex.
Naproxen (p. 98·2).
Fever; inflammation; pain.

Inflapen *GSK, India.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Inflarax *Zdorovje, Ukr.*
Amikacin (p. 214·1); nimesulide (p. 101·3); benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).
Wounds; inflammatory skin disorders.

Inflaryl-AD *Geno, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Inflased *Bilim, Turk.*
Diclofenac sodium (p. 48·3).
Prevention of miosis during cataract surgery; postoperative eye inflammation; allergic conjunctivitis.

Inflasic *Blue Sky, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Inflason *Berlico Mulia, Indon.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Inflastat *Sensomed, Philipp.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Inflax *Ativus, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Inflazen *Esma, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Inflazone
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Phenylbutazone (p. 125·1).
Ankylosing spondylitis.
Centaur, India.
Diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); mephenesin (p. 2025·2); capsicum oleoresin (p. 2469·3).
Musculoskeletal, joint, and soft-tissue disorders; inflammation; pain.

Inflexal *Scott-Cassara, Arg.; Berna, Austria; Crucell, Belg.†; Biosano, Chile; Berna, China; Berna, Cz.†; Crucell, Denm.; Crucell, Fin.; Baxter BioScience, Ger.†; Faran, Gr.; IFET (ΙΦΕΤ), Gr.; Crucell, Hong Kong; Berna, Ital.; Berna, Malaysia; Crucell, Neth.; Berna, Philipp.; Crucell, Pol.; Berna, Port.; Berna, Rus.; Crucell, Swed.; Crucell, Switz.; Crucell, Thai.; Yeni, Turk.; Berna, Ukr.†*
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Formerly known as Viroflu.
Active immunisation.

Infliplus *HLB, Arg.†*
⊗Budesonide (p. 1625·1).

Inflobact *Invision, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Inflobact-D *Invision, India.*
⊗Ofloxacin (p. 334·3); dexamethasone phosphate (p. 1631·1).

Inflobact-OZ *Invision, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Inflobid *Intra-Labs, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Inflobid TZ *Intra-Labs, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Inflobid-D *Intra-Labs, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Inflobid-NXT *Intra-Labs, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Inflobid-OZ *Intra-Labs, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Infloc *SFD, Port.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Infloran *SIT, Austria; Berna, Hong Kong†; SIT, Ital.; Europharma, Philipp.; SIT, Spain; Desma, Switz.; SIT, Thai.*
Bifidobacterium infantis (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3).
Diarrhoea; dyspepsia; gastrointestinal disorders; enterocolitis; constipation; digestive disorders in infants on artificial diets; restoration of intestinal flora.

Infloran Bio *SIT, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins.
Dietary supplement.

Inflox *Evershine, India; Indo Pacific, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Infloxa *Alpharma, Mex.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Inflox-OZ *Indo Pacific, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Influaforce *Bioforce, Switz.†*
Eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); aconitum napellus (p. 2428·3); baptisia tinctoria (p. 2647·2); bryonia cretica; echinacea purpurea (p. 2498·1); gelsemium (p. 2511·2); lachesis (p. 2538·3).
Homoeopathic preparation.

InfluASS *Ratiopharm, Austria.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Influenza symptoms.

Influbene
Note: this name may be used for preparations of different composition.
Ratiopharm, Austria.†
⊗Paracetamol (p. 115·1); etilefrine hydrochloride (p. 1379·1); butetamate citrate (p. 1658·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Influbene C *Mepha, Switz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Influbene N *Mepha, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Influblock *Polpharma, Rus.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Influenza symptoms.

Influcid *DHU, Rus.; DHU, Ukr.*
Aconitum (p. 2428·3); gelsemium (p. 2511·2); ipecacuanha (p. 1667·2); phosphorus (p. 2589·2); bryonia (p. 2461·3); eupatorium perfoliatum (p. 2459·1).
Homoeopathic preparation.

Infludo *Weleda, Austria; Weleda, Ger.; Weleda, Switz.*
Aconitum napellus (p. 2428·3); bryonia radix (p. 2461·3); eucalyptus folium (p. 2501·1); eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2); sabadilla semen (p. 2611·2).
Homoeopathic preparation.

Weleda, Fr.
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); sabadilla officinarum (p. 2611·2).
Homoeopathic preparation.

Weleda, Neth.
Aconitum napellus (p. 2428·3); bryonia cretica; eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Weleda, UK.
Aconitum napellus (p. 2428·3); eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); phosphorus (p. 2589·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Weleda, S.Afr.†
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3); eupatorium perfoliatum (p. 2459·1); sabadilla (p. 2611·2); eucalyptus; phosphorus (p. 2589·2).
Homoeopathic preparation.

Influenza A (H1N1) Monovalent Vaccine *GSK, Canad.†; CSL, USA; Medimmune, USA; Novartis, USA; Sanofi Pasteur, USA.*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Influex *Steigerwald, Ger.*
Oral tincture; tablets: Aconitum napellus (p. 2428·3); apis mell. (p. 2445·2); echinacea (p. 2498·1); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Influject *Baxter, Neth.†*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Influk *Knap, Chile.*
Eupatorium perfoliatum (p. 2459·1); bryonia (p. 2461·3); belladonna (p. 2453·3); ferrum phos. (p. 2077·1); arsenicum jodat (p. 2448·1).
Homoeopathic preparation.

Influmed *Iodosan, Ital.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); isopropamide iodide (p. 1848·3).
Cold and influenza symptoms.

Influmed C *Iodosan, Ital.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); isopropamide iodide (p. 1848·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Influnorm *Leksredstva, Rus.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Fever; pain; sinusitis; rhinitis.

Influostim *Serolab, Switz.*
Anas barbariae, hepatis et cordis extractum (p. 2444·1).
Homoeopathic preparation.

Influpiol C *Antipiol, Ital.*
Vitamin C (p. 2110·3); propolis (p. 2597·3); salix (p. 129·2); dog rose.

Influpozzi *Novartis, Ital.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Influrin *Slavic, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Influsplit SSW *GSK, Ger.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Influtux *Antipiol, Ital.*
Hedera; propolis (p. 2597·3); dog rose; echinacea (p. 2498·1).

Influvac *Raffo, Arg.; Abbott, Austral.; Solvay, Austria; Abbott, Canad.; Grunenthal, Chile; Abbott, China; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Solvay, Hong Kong; Solvay, Hung.; Abbott, Irl.; Abbott, Israel; Solvay, Malaysia; Abbott, Neth.; Abbott, Norw.; Healthcare Logistics, NZ; Solvay, Philipp.; Abbott, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Abbott,*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Solvay, Turk.; Abbott, UK; Abbott, Ukr.
An inactivated influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Influvac S *Abbott, Belg.; Solvay, Ital.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Influvirus *Hardis, Ital.†*
An influenza vaccine (p. 2393·3).
Active immunisation.

Influvit
Note: this name may be used for preparations of different composition.
DHU, Ger.
Aconitum (p. 2428·3); nux vomica (p. 2573·3); eupatorium perfol. (p. 2459·1); gelsemium (p. 2511·2); kal. phosphoric. (p. 1790·3).
Homoeopathic preparation.
Recordati, Ital.
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); propyphenazone (p. 127·3).
Pain; fever.

Influ-Zinc *Marfarma, Ital.*
Zinc gluconate (p. 2126·2); vitamin C (p. 2110·3); selenium (p. 2086·3); echinacea (p. 2498·1); salix (p. 129·2).
Dietary supplement.

Influ-Zinc Gola *Marfarma, Ital.*
Zinc acetate (p. 2126·1); zinc citrate (p. 2126·2); liquorice (p. 1853·2).
Mouth disorders.

Infocer *Little Greave, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Infomel *Bevo, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Inf-Oph *Seng, Thai.*
⊗Prednisolone acetate (p. 1645·2).
Conjunctivitis.

Infor *Prater, Chile.*
Procaine hydrochloride (p. 1994·3); ginseng (p. 2513·3); vitamins; rutoside (p. 2505·3); linolenic acid (p. 1460·2); linoleic acid (p. 2509·2); minerals.

Infor E *Prater, Chile.*
Vitamins; minerals.

Infor Q10 *Prater, Chile.*
Vitamins; ubidecarenone (p. 2637·1).

Inforcer *Little Greave, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Informin *Gap, Gr.*
Phenformin hydrochloride (p. 493·1).
Diabetes mellitus.

Infortin *Prater, Chile.*
Vitamins.

Inforton *Prater, Chile.*
Vitamins.

Infostat *Bioproforma, Arg.*
Interferon alfa-2a (p. 989·2).
Hepatitis C; malignant neoplasms.

Infoxin *Life Line, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Infoxin-OZ *Life Line, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Infoxon *Acekinetic, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Infoxon-S *Acekinetic, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Infoxon-T *Acekinetic, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Infracyanine *SERB, Fr.*
Indocyanine green (p. 2532·3).
Diagnostic aid.

Infragil *Pekana, Neth.*
Ailanthus glandulosa; argentum nitricum (p. 2615·3); china officinalis (p. 2478·3); echinacea angustifolia (p. 2498·1); lachesis mutus (p. 2538·3); marrubium vulgare (p. 1668·3); nasturtium officinale; vincetoxicum officinale.
Homoeopathic preparation.

Infralax *EMS, Braz.*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); caffeine (p. 1203·3).

Inframin *Fresenius Kabi, Ital.*
Amino acids.
Parenteral nutrition in renal failure.

Infrarub
Note: this name may be used for preparations of different composition.
SA Druggists Self Med, S.Afr.†
Methyl nicotinate (p. 91·3); histamine hydrochloride (p. 2525·2); glycol salicylate (p. 66·2); capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint disorders.

Infree *Eisai, Jpn; Eisai, Philipp.*
Indometacin farnesil (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders.

Infufer *Sandoz, Canad.*
Iron dextran (p. 2075·3).
Iron deficiency.

Infukoll *Gobbi, Arg.*
⊗Succinylated gelatin (p. 1154·1); electrolytes (p. 1775·1).
Plasma volume expansion.
Beacon, UK.†
⊗Pentastarch (p. 1146·1) in sodium chloride.
Plasma volume expansion.

Infukoll HES *Gobbi, Arg.; Serum-Werk Bernburg, Ger.; UCB, Ger.; Serum-Werk Bernburg, Rus.; Serum-Werk Bernburg, Thai.†*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; hypovolaemia; shock; microcirculatory disorders; haemodilution.

Infulgan *Yuri, Ukr.*
Paracetamol (p. 115·1).
Pain; fever.

Infulid *Neiss, India.*
Linezolid (p. 317·3).
Bacterial infections.

Infumal
Note: this name may be used for preparations of different composition.
Sanbe, Indon.
Maltose (p. 2081·1).
Diabetes mellitus; carbohydrate source.

Infumorph *Westward, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Infuplas *Fresenius Kabi, Ital.*
⊗Succinylated gelatin (p. 1154·1).
Shock; hypovolaemia.

Infurox *Servocare, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Infusamin *Teva, Hung.*
Amino acids; with or without carbohydrates and electrolytes (p. 1775·1).
Parenteral nutrition.

Infusan D *Sanbe, Indon.*
Glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Infusan M *Sanbe, Indon.*
⊗Mannitol (p. 1427·3).
Raised intracranial pressure; renal failure.

Infusan R+D *Sanbe, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Infusan Ring-AS *Sanbe, Indon.*
Electrolytes (p. 1775·1).
Acidosis; shock.

Infusan-NS *Sanbe, Indon.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Infusan-RL *Sanbe, Indon.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Infuse Bone Graft *Medtronic, USA.*
Dibotermin alfa (p. 1177·2).
Maxillofacial and dental bone grafting.

Infuvite *Baxter, USA.*
Vitamins.
Parenteral nutrition.

Ingacillin *Inga, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Ingacycline *Inga, India.*
Tetracycline (p. 373·1).
Bacterial infections.

Ingafol *Inga, India.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy; folic acid deficiency.

Ingagen-M *Inga, India.*
Methylergometrine maleate (p. 2137·3).
Uterine haemorrhage; uterine atony.

Ingahist *Inga, India.*
Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Ingahist Plus *Inga, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylephrine hydrochloride (p. 1672·3).

Ingahist-X *Inga, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Ingametil *Inga, India.*
Prochlorperazine maleate (p. 1098·3).
Nausea; vomiting; psychoses; anxiety; vertigo.

Ingaquine *Inga, India.*
Chloroquine (p. 650·1).
Malaria; systemic lupus erythematosus; amoebiasis; rheumatoid arthritis.

Ingaron *Pharmaclon, Rus.*
Interferon gamma (p. 999·1).
Psoriasis; leishmaniasis; mycobacterial infections; leprosy; rheumatoid arthritis; eczema.

Ingastri *Faes, Spain.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastric hyperacidity.

Ingatol *Nufarindo, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vinca minor.
Circulation disorders; vitamin B supplement.

Ingavirin *Valenta, Rus.*
Imidazolylethanamide pentandioic acid (vitaglutam).
Influenza.
Valenta, Ukr.
Imidazolyl ethenamide pentandioxy acid.
Respiratory viral infections.

Ingavit B6 *Inga, India.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 supplement.

Ingavit B12 *Inga, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Ingebrax *Ingens, Arg.†*
Tobramycin (p. 380·1); diclofenac sodium (p. 48·3); sodium hyaluronate (p. 2526·2).
Eye disorders.

Ingebut *Ingens, Arg.†*
Butenafine (p. 574·2).
Fungal skin infections.

Ingeclof *Ingens, Arg.†*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Ingedex *Ingens, Arg.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Ingeflox *Ingens, Arg.†*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Ingelets *Ingens, Arg.†*
Erythromycin (p. 291·2).
Bacterial eye infections.

Ingemet *Ingens, Arg.†*
⊗Betamethasone valerate (p. 1624·1); salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Skin disorders.

Ingen *Invision, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Ingepsor *Ingens, Arg.†*
Fumaric acid esters (p. 1704·2).
Psoriasis.

Ingeshamp *Ingens, Arg.†*
Coal tar (p. 1723·2).
Seborrhoeic dermatitis.

Ingesic Forte *Indo Pacific, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Ingesic-MR *Indo Pacific, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Ingesic-P *Indo Pacific, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Ingestants Extracts *Trupharm, Israel.*
Food allergen extracts (p. 2434·3).
Skin testing; immunotherapy.

Ingetim *Ingens, Arg.†*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Ingitril *Microgen, Rus.*
Aprotinin (p. 1133·2).
Pancreatic disorders; parotitis; haemorrhage; angioedema; shock.

INH *Kocak, Turk.*
Isoniazid (p. 311·2).
Tuberculosis.

INHA *Mersifarma, Indon.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Inhalador Medex *Sidus, Arg.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); sassafras oil (p. 2610·3); thymol (p. 1772·2).
Respiratory-tract congestion.

Inhalan *Casasco, Arg.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Inhalante Yatropan *Sanofi-Aventis, Braz.*
⊗Ephedrine (p. 1663·1); menthol (p. 2553·2); cineole (p. 2479·1); tolu (p. 1679·2); lavender oil (p. 2541·1); benzoin (p. 2624·3); sodium guaiacol sulfanilamide.
Respiratory-tract congestion.

Inhalants And Epidermal Extracs *Trupharm, Israel.*
Inhalants epidermal allergen extracts (p. 2434·3).
Skin testing; immunotherapy.

Inhalex
Note: this name may be used for preparations of different composition.
Cipla, India.
Ambroxol (p. 1654·3).
Respiratory-tract disorders.
Silom, Thai.
⊗Ipratropium bromide (p. 1211·3); fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Inhalipt *Altayvitamin, Rus.; Binnofarm, Rus.; Farmstandart, Rus.; Leksredstva, Rus.; Moschimfarm, Rus.*
Sulfanilamide (p. 368·1); sulfathiazole sodium (p. 368·3); thymol (p. 1772·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1).
Throat disorders.

Inhalo Rhinathiol *Sanofi-Aventis, Belg.*
Menthol (p. 2553·2); cineole (p. 2479·1).
Upper respiratory-tract disorders.

Inhalol *Profarm, Pol.*
Pine oil (p. 2591·1); thyme oil (p. 2630·3); peppermint oil (p. 1877·1); turpentine oil (p. 2636·3).
Upper respiratory-tract congestion.

Inhalvicks *Vicks, Spain.*
Camphor (p. 2466·2); menthol (p. 2553·2).

Inhaphytol No 1 *Krasnogorskleksredstva, Rus.*
Chamomile (p. 2474·1); sage (p. 2608·3).
Throat disorders.

Inhaphytol No 2 *Krasnogorskleksredstva, Rus.*
Chamomile (p. 2474·1); eucalyptus leaf (p. 2501·1).

INH-Ciba *Sandoz, Indon.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in the 400mg tablets and the oral syrup for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Inhep *Sun, India.*
Heparin (p. 1396·3).
Thromboembolic disorders.

Inhex *Intag, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Inhibac *Pharmaland, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin disinfection.

Inhibace
Note: this name may be used for preparations of different composition.
Merck, Austria; Roche, Austria; Roche, Belg.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Hong Kong†; Roche, Hung.; Chugai, Jpn; Roche, NZ; Roche, Pol.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.†; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, Venez.
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Inhibace comp *Roche, Swed.†*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Inhibace Plus *Merck, Austria; Roche, Austria; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Hung.; Roche, NZ; Roche, Pol.; Roche, S.Afr.; Roche, Spain; Roche, Switz.; Roche, Turk.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Inhibestril *Teva, Pol.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Inhibin *Meda, Neth.*
Hydroquinine hydrobromide (p. 2529·2).
Nocturnal muscle cramps.

Inhibisam *Richmond, Arg.†*
Indinavir (p. 986·1).
HIV infection.

Inhibit *Deb, Canad.*
Chloroxylenol (p. 1748·2); triclosan (p. 1773·2).

Inhibitron *Liomont, Mex.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Inhibril *Yurtoglu, Turk.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Inhiplex *Adipharm, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Inhipraz *Bernofarm, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Inhipump *Pharos, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Inhitril *Bernofarm, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Inibace *Roche, Ital.; Roche, Port.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Inibace Plus *Roche, Ital.; Roche, Port.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Inibex S *Medley, Braz.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Inibina *Apsen, Braz.*
Isoxsuprine hydrochloride (p. 2535·2).
Premature labour; threatened miscarriage; cerebral and peripheral vascular disorders.

Inibsacain *Inibsa, Spain.*
Bupivacaine hydrochloride (p. 1980·3).
Adrenaline (p. 1292·1) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Inicox *Farmoquimica, Braz.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders; dysmenorrhoea.

Inigrin *Grin, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Inim *Sandoz, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Inimur *Taurus, Ger.†; Polichem, Ital.*
Nifuratel (p. 941·2).
Fungal infections; trichomoniasis; bacterial infections.

Inimur Complex *Polichem, Ital.*
Nifuratel (p. 941·2); nystatin (p. 590·3).

Inimur Myko *Taurus, Ger.†*
Ciclopirox olamine (p. 575·3).
Fungal vaginal infections.

Inipepsia *Mayoly-Spindler, Fr.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Inipomp *Nycomed, Fr.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Inissiate *Indoco, India.*
Sodium monofluorophosphate (p. 2091·3).

Inistolin Antitusivo Pediatrico *Johnson & Johnson, Spain.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Inistolin Expectorante Pediatrico *Johnson & Johnson, Spain.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Iniston Antitusivo *Johnson & Johnson, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Iniston Antitusivo y Descongestivo *Johnson & Johnson, Spain.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough; nasal congestion.

Iniston Descongestivo *Johnson & Johnson, Spain.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms; nasal congestion.

Iniston Expectorante y Descongestivo *Johnson & Johnson, Spain.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cough; nasal congestion.

Iniston Mucolitico *Johnson & Johnson, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Iniston Mucus *Johnson & Johnson, Spain.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Initiss *Crinos, Ital.*
Cilazapril (p. 1336·2).
Hypertension.

Initiss Plus *Crinos, Ital.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Inivical *Nafar, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Injectafer *Vifor, Belg.; American Regent, USA.*
Ferric carboxymaltose (p. 2060·1).
Iron-deficiency anaemia; iron deficiency.

Injectrax *Blausiegel, Braz.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Injeflex *Zodiac, Braz.*
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Joint disorders.

Injek *Neon, India.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding; anticoagulant antidote.

Inkacin *Intra-Labs, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Inkontan *Montavit, Austria.*
Trospium chloride (p. 2371·1).
Bladder instability.

Inkurin *Interbat, Indon.*
Cucurbita (p. 2489·2).
Urinary incontinence.

Inlacta DHA *Interbat, Indon.*
Omega-3 marine triglycerides (p. 1460·3); vitamin E (p. 2119·1).
Dietary supplement in pregnancy and lactation.

Inleusin *Sunshine, China.*
Interleukin-2 (recombinant, human) (p. 810·1).
Malignant neoplasms.

Inlex *Mergers Drugfil, Philipp.*
Carnitine orotate (p. 2578·1); amino acids; adenine hydrochloride (p. 2430·2); vitamin B substances (p. 2102·3).
Liver disorders.

Inlife *Medispan, India.*
Meropenem (p. 321·3).
Bacterial infections.

Inloxy *Intra-Labs, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Inloxy-LB Kid *Intra-Labs, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Inloxy-SLB *Intra-Labs, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Inlyta *Pfizer, Denm.; Pfizer, Jpn; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Switz.; Pfizer, UK; Pfizer, USA.*
Axitinib (p. 745·1).
Renal cell carcinoma.

Inmatrol *Interbat, Indon.*
⊗Dexamethasone (p. 1630·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Eye disorders with infection.

Inmecin *Sterkem, India.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Inmecin-P *Sterkem, India.*
Indometacin (p. 71·2); paracetamol (p. 115·1).

Inmox *Intra-Labs, India.*
Capsules; dispersible tablets; syrup: Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Intra-Labs, India.
Eye drops: Moxifloxacin (p. 326·3).
Bacterial eye infections.

Inmox Clav *Intra-Labs, India.*
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Inmucel *Pasteur, Chile.*
Vitamin C (p. 2110·3); *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus casei* (p. 2596·3).
Nutritional supplement.

Inmunef *Teva, Mex.†*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Inmunex Plus *Victus, Venez.*
Preparation for enteral nutrition.

Inmunoartro *Beta, Arg.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Inmunoferon *Cantabria, Spain.*
Glicofosfopeptical (p. 2515·1).
Immunotherapy.

Inmunofit *Biokosma, Arg.*
Ginseng (p. 2513·3); lapachos; ascorbic acid (p. 2110·3).
Dietary supplement.

Inmunogrip *Gezzi, Arg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).

Inmunogrip C *Gezzi, Arg.*
Phenylephrine (p. 1672·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain; upper respiratory-tract congestion.

Inmunogrip T Caliente *Gezzi, Arg.*
Paracetamol (p. 115·1).
Influenza symptoms.

Inmunol *Andromaco, Mex.*
Glicofosfopeptical (p. 2515·1).
Immunostimulant.

Inmunologico *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Inmunoprin *Tecnofarma, Chile; Asofarma, Mex.*
Thalidomide (p. 867·3).
Erythema nodosum leprosum; Behçet's syndrome; malignant neoplasms; adjunct in HIV infection; multiple myeloma.

Inner Shade *Planet Biotechnologies, Canad.†*
Folic acid (p. 2063·1); nicotinamide (p. 2083·1); cyanocobalamin (p. 2107·2).

Inno Rheuma *Naturland, Hung.*
Cream: Camphor (p. 2466·2); menthol (p. 2553·2); rosemary oil (p. 2607·3).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Naturland, Hung.
Oil: Lavender oil (p. 2541·1); rosemary oil (p. 2607·3); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Inno Rheuma Forte *Naturland, Hung.*
Rosemary oil (p. 2607·3); camphor (p. 2466·2); menthol (p. 2553·2); capsaicin (p. 35·1).
Musculoskeletal, joint, and soft-tissue pain.

Innobion *Farmaceutica H, Mex.*
⊗Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); dexamethasone sodium phosphate (p. 1631·2); lidocaine hydrochloride (p. 1988·2).
Neuralgia; neuritis; musculoskeletal, joint, and peri-articular disorders.

Innobloc *Innoderm, Philipp.*
SPF 24: Titanium dioxide (p. 1725·1).
Sunscreen.

Innodesone *Innoderm, Philipp.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Innogem *PannonPharma, Hung.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Innohep *Leo, Belg.; Leo, Canad.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Gr.; Leo, Hong Kong; Leo, Irl.; Leo, Malaysia; Leo, Neth.; Leo, Norw.; CSL, NZ; Leo, NZ; Leo, Philipp.; Leo, Port.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Thai.; Abdi, Turk.; Leo, UK; Leo, USA.†*
Tinzaparin sodium (p. 1514·2).
Thromboembolic disorders; prevention of clotting during haemodialysis or extracorporeal circulation; unstable angina.

InnoLet N *Novo Nordisk, Jpn.*
⊗Isophane insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

InnoLet R *Novo Nordisk, Jpn.*
⊗Insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

InnoLet 10R, 20R, 30R, 40R, and 50R *Novo Nordisk, Jpn.*
⊗Mixtures of insulin injection (human, recombinant) 10%, 20%, 30%, 40% and 50% and isophane insulin (human, recombinant) 90%, 80%, 70%, 60%, and 50% respectively (p. 475·3).
Diabetes mellitus.

InnoPran *Akrimax, USA.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension.

Innosensitive *Faran, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Innosfen *Bergamo, Braz.*
Alfacalcidol (p. 2112·3).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; hyperparathyroidism; rickets; osteomalacia.

Innospore *Austell, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Innova Cd *Laboratorios Chile, Chile.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Innovace *MSD, Irl.; MSD, UK.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Innovair *Chiesi, Denm.; UCB, Fin.; Chiesi, Fr.; Chiesi, Swed.; UCB, Turk.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Innoxiderm *Innoderm, Philipp.*
Sulfadiazine silver (p. 362·3).
Burns.

Innozide *MSD, Irl.; MSD, UK.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Inobes *Prafa, Indon.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Inocar *Abbott, Spain.*
Cilazapril (p. 1336·2).
Heart failure; hypertension.

Inocar Plus *Abbott, Spain.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Inocard *Imperial, Philipp.†*
Dobutamine hydrochloride (p. 1365·3).
Heart failure.

Inocin *Bombay Tablet, India.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Inoclim *Innotech, Fr.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Inocor *Sanofi Winthrop, Israel†; Sanofi Winthrop, USA.*
Amrinone lactate (p. 1305·1).
Heart failure.

Sanofi Synthelabo, Mex.†
Amrinone (p. 1305·1).
Heart failure.

Inod'ail *Arkopharma, Fr.*
Garlic (p. 2510·3).
Venous insufficiency.

Inoderm *Meprofarm, Indon.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Inofer *Lisapharm, Fr.*
Ferrous succinate (p. 2062·1).
Succinic acid (p. 2214·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Inoflex *Mustafa, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Inoflox *Biomedis, Malaysia†; Biomedis, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Inofungin *Bergamo, Braz.*
Nystatin (p. 590·3).
Vaginal candidiasis.

Inogat-O *Biomax, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Inoject *Gland, India.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Inokain *Promed, Rus.; ProMed, Ukr.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Inokat *Atlas, Arg.*
Disodium inosinate (p. 2495·2).
Cataract; opacity and haemorrhage of the vitreous humour.

Inolaxine *Globopharm, Switz.†*
Sterculia (p. 1888·3).
Constipation.

Inolaxol *Abbott, Swed.*
Sterculia (p. 1888·3).
Constipation; adjunct in treatment of diarrhoea.

Inolin *Primal, Hong Kong†; Tanabe, Indon.; Mitsubishi Tanabe, Jpn.*
⊗Tretoquinol hydrochloride (p. 1239·1).
Obstructive airways disease.

INOmax *INO Therapeutics, Canad.; INO Therapeutics, Cz.; AGA, Denm.; Linde, Fr.; Linde Gas, Ger.; AGA, Gr.; INO Therapeutics, Irl.; INO Therapeutics, Ital.; Linde Gas, Neth.; INO Therapeutics, Pol.; INO Therapeutics, Port.; INO Therapeutics, Spain; AGA, Swed.; PanGas, Switz.; INO Therapeutics, USA.*
Nitric oxide (p. 1457·1).
Neonatal respiratory distress syndrome; pulmonary hypertension.

Inomet *Ulkar, Turk.*
Indometacin (p. 71·2).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Inon *Sato, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).

Inongan *Sofibel, Fr.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Muscle pain.

Inopamil *Zambon, Neth.†*
⊗Ibopamine hydrochloride (p. 1407·1).
Heart failure.

Inopectol *Nycomed, Belg.†*
Camphor (p. 2466·2); cineole (p. 2479·1); guaiacol (p. 1666·1); menthol (p. 2553·2); pine oil (p. 2591·1).
Rhinitis; sinusitis.

Inophylin *Medichrom, Gr.*
⊗Metoprolol tartrate (p. 1434·3).

Inopin *Siam Bheasach, Thai.*
Dopamine hydrochloride (p. 1367·2).
Shock.

Inorial *Pierre Fabre, Fr.*
Bilastine (p. 617·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Inorine *Ind-Swift, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Inorine-M *Ind-Swift, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Inosert *Ipca, India.*
Sertraline hydrochloride (p. 448·1).
Depression.

Inositech *Bio-Tech, USA.*
Inositol (p. 2533·2).

Inotop *Torrex, Austria.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock; cardiac stress testing.

Inotrex *Lilly, Gr.; Ferraz, Lynce, Port.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock; cardiomyopathy; myocardial infarction; cardiac surgery.

Inotrin *Medicus, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Inotrop
Note: this name may be used for preparations of different composition.
Fahrenheit, Indon.
Dobutamine hydrochloride (p. 1365·3).
Heart failure; arrhythmias.
Samarth, Philipp.
⊗Noradrenaline acid tartrate (p. 1458·2).
Cardiac arrest; hypotension.

Inotropin *Bago, Arg.*
Dopamine hydrochloride (p. 1367·2).
Heart failure; shock.

Inotropisa *Pisa, Mex.†*
Dopamine hydrochloride (p. 1367·2).
Shock; cardiac surgery; hypovolaemia.

Inotyol
Note: this name may be used for preparations of different composition.
Urgo, Belg.; Fournier, Denm.; Fournier, Norw.; Abbott, Swed.
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Skin disorders; psoriasis; eczema; superficial wounds and burns.
Brady, Austria.
Ointment: Ichthammol (p. 1705·3); hamamelis (p. 2523·3); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Skin disorders; wounds; burns.
Brady, Austria.
Topical powder: Ichthammol (p. 1705·3); hamamelis (p. 2523·3); zinc oxide (p. 1729·1); calcium carbonate (p. 1824·3).
Skin disorders.
Urgo, Fr.; Urgo, Israel.
Ichthammol (p. 1705·3); hamamelis (p. 2523·3); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); siam benzoin (p. 2614·3).
Skin disorders; burns; wounds.

Inova
Note: this name may be used for preparations of different composition.
Ikon, India.
Capsules: Vitamins; cupric oxide; zinc oxide (p. 1729·1).
Ikon, India.
Oral powder: Preparation for enteral nutrition.
JSJ, USA.
Topical pad, benzoyl peroxide (p. 1696·1); topical capsules, tocopherol (p. 2119·1).
Acne.

Inova Acne Control *JSJ, USA.*
Topical pad, benzoyl peroxide (p. 1696·1); salicylic acid (p. 1719·1); topical capsules, tocopherol (p. 2119·1).
Acne.

Inovad *Fahrenheit, Indon.*
Milrinone (p. 1438·1).
Heart failure.

Inovan *Kyowa, Jpn.*
Dopamine hydrochloride (p. 1367·2).
Shock; anuria; oliguria.

Inovas-F *Invision, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Inovelon *Eisai, Austria; Eisai, Belg.; Eisai, Cz.; Eisai, Denm.; Eisai, Fr.; Eisai, Ger.; Eisai, Gr.; Eisai, Hung.; Eisai, Irl.; Megapharm, Israel; Eisai, Ital.; Eisai, Jpn; Eisai, Neth.; Eisai, Norw.; Eisai, Pol.; Eisai, Port.; Eisai, Spain; Eisai, Swed.; Eisai, Switz.; Eisai, UK.*
Rufinamide (p. 548·3).
Lennox-Gastaut syndrome.

Inovic *Ferraz, Lynce, Port.*
⊗Eplerenone (p. 1374·2).
Heart failure following myocardial infarction.

Inox
Note: this name may be used for preparations of different composition.
Hovid, Hong Kong; Hovid, Malaysia; Hovid, Philipp.
Itraconazole (p. 583·3).
Fungal infections.
Indo Pacific, India.
Capsules: Vitamins; trace elements.
Indo Pacific, India.
Syrup: Vitamins; zinc (p. 2126·1).

Inoxel *Boryung, Thai.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Inoxi *Psyco Remedies, India.*
Minoxidil (p. 1438·3).
Alopecia.

Inoxin *Dexa, Indon.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Inoxzel *Indoco, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

In-OZ *Osper, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Inpained *Bajamed, Mex.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Inpamide *Pharmasant, Thai.*
⊗Indapamide (p. 1409·2).
Hypertension.

Inpan *Evershine, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Inpan-D *Evershine, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Inpanol *DHA, Hong Kong; DHA, Singapore.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Inpenam *Intra-Labs, India.*
Meropenem (p. 321·3).
Bacterial infections.

Inpepsa *Fahrenheit, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Inpime *Profic Organic, India.*
Cefepime (p. 239·2).
Bacterial infections.

Inpramine *Inpac, Thai.*
Imipramine hydrochloride (p. 426·2).
Depression.

Inprax *Degorts, Mex.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Inpro *Kaizen, India.*
Carbohydrate; ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); methionine (p. 1558·2); protein hydrolysate (p. 2086·2); zinc sulfate (p. 2126·2).
Tonic.

Inpront *Laboratorios Chile, Chile.†*
Moclobemide (p. 437·2).
Depression.

Inprosyn-HP *Wescrib, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Inprovit *Intra-Labs, India.*
Calcium (p. 1783·1); iron (p. 2073·1); protein; vitamins; zinc (p. 2126·1).

In-quadeicren *CBC, Hong Kong.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); nystatin (p. 590·3).
Skin disorders.

Inquetia *Ariston, Arg.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Inquixol *Inquifave, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Inreq *Q Pharma, Spain.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Inrox *Intra-Labs, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Inrozol *Gabriel, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Insaar *Interbat, Indon.*
Losartan potassium (p. 1422·2).
Hypertension.

Insadol *Expanpharm, Fr.†; Expanpharm, Rus.; Uhlmann-Eyraud, Switz.†*
Maize (p. 2487·1).
Mouth disorders; dental disorders.

Insanovin *Azerfarm, Rus.*
⊗Prednisolone (p. 1645·2); theophylline (p. 1229·3); chloroquine phosphate (p. 650·1); ephedrine hydrochloride (p. 1663·2).

Insect Écran *Cooper, Fr.*
Paediatric spray; special tropical spray: Icaridin (p. 2156·3).
Insect repellent.
Cooper, Fr.
Solution; spray: Permethrin (p. 2159·3).
Insect repellent for clothing and bedding.
Cooper, Fr.
Topical gel spray: Diethyltoluamide (p. 2153·1).
Insect repellent.

Insects Extracts *Trupharm, Israel.*
Insect allergen extracts (p. 2434·3).
Skin testing; immunotherapy.

Insensye *MSD, Austral.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Inseptin-MF *Indian Drugs, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Insertec *Baliarda, Arg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Inside *Meda, Fin.; Antula, Swed.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Inside Brus *Antula, Norw.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Insider *Skymax, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Insidon *Novartis, Austria; Novartis, Ger.†; Novartis, Gr.; Gebro, Switz.; Novartis, Turk.*
Opipramol hydrochloride (p. 440·2).
Anxiety disorders; psychosomatic symptoms; sleep disorders; depression.

Insifu *Hos & Ins, India.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Insig *Aspen, Austral.*
⊗Indapamide (p. 1409·2).
Hypertension.

Insipim *Hos & Ins, India.*
Cefepime (p. 239·2).
Bacterial infections.

Insiron-AD *Hos & Ins, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Inslide *Ind Biosciences, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Insocaps *Infinity, Venez.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders.

Insogen *Nycomed, Mex.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Insogen Plus *Italmex, Mex.*
Metformin hydrochloride (p. 489·1); chlorpropamide (p. 470·1).
Diabetes mellitus.

Insol *Pharmaspec, Philipp.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Insom
Note: this name may be used for preparations of different composition.
Vulm, Cz.
Zolpidem tartrate (p. 1116·2).
Insomnia.
Lennon, S.Afr.†
Flunitrazepam (p. 1073·3).
Insomnia.

Insoma *Pacific, NZ.†*
Nitrazepam (p. 1089·1).
Insomnia.

Insomed *Pharmahex, Philipp.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Insomer *Hos & Ins, India.*
Meropenem (p. 321·3).
Bacterial infections.

Insomin
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Opipramol hydrochloride (p. 440·2).
Depression.
Orion, Fin.; Psyco Remedies, India.
Nitrazepam (p. 1089·1).
Insomnia; epilepsy; premedication.

Insomnal
Note: this name may be used for preparations of different composition.
Rougier, Canad.
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Insomnia *Homeocan, Canad.*
Avena sativa (p. 2451·1); cuprum aceticum (p. 2486·2); hyoscyamus niger (p. 2530·2); passiflora incarnata (p. 2584·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Insomnia Passiflora *Homeocan, Canad.†*
Avena sativa (p. 2451·1); belladonna (p. 2453·3); passiflora inc (p. 2584·1); secale cornutum (p. 2137·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Insomniger *Generics, Irl.*
Temazepam (p. 1109·1).
Insomnia; premedication.

Insomnium *Gador, Arg.*
Zopiclone (p. 1118·1).
Insomnia.

Insopin *CCM, Malaysia.*
Zopiclone (p. 1118·1).
Insomnia.

Inspar *Waves, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Inspiral *Ipca, India.*
⊗Methylphenidate (p. 2326·1).
Narcolepsy; hyperactivity disorders.

Inspirol *Sandoz, Arg.*
Montelukast (p. 1214·3).
Asthma; bronchospasm.

Inspirol Heilpflanzenöl *Riemser, Ger.†*
Peppermint oil (p. 1877·1).
Cold symptoms; gastrointestinal disorders.

Inspirol P *Riemser, Ger.†*
Myrrh (p. 2566·1).
Mouth and throat inflammation.

Inspiron *Arterium, Ukr.*
Fenspiride hydrochloride (p. 1209·2).
Respiratory-tract disorders.

Inspra *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile†; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA.*
⊗Eplerenone (p. 1374·2).
Heart failure following myocardial infarction; cardiovascular risk reduction; heart failure; hypertension.

Insprin-ER *Avinash, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Instacare *Ciba Vision, Austral.†*
Cleaning and disinfectant solutions for soft contact lenses.

Instacodin *Aglowmed, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Instacyl *Streuli, Switz.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold symptoms.

Instalax *Knop, Chile.*
Senna (p. 1885·1); linseed (p. 2544·2); fennel (p. 2503·2); liquorice (p. 1853·2).
Constipation.

Instana *Daiichi Sankyo, Spain.†*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Instant Hand Sanitizer
Note: this name may be used for preparations of different composition.
Dissan, Canad.
Benzethonium chloride (p. 1738·1).
Hand disinfection.

Instant Rub *Pendopharm, Canad.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Instantin *Orion, Denm.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Instanyl *Nycomed, Austria; Takeda, Belg.; Nycomed, Cz.; Nycomed, Denm.; Takeda, Fr.; Nycomed, Ger.; Nycomed, Gr.; Nycomed, Irl.; Takeda, Neth.; Nycomed, Norw.; Nycomed, Pol.; Nycomed, Port.; Nycomed, Spain; Nycomed, Swed.; Nycomed, UK.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Instaret *Unipharma, Gr.*
Acetic acid (p. 2426·3).
Mild bacterial or fungal infections of the outer ear.

Instaryl *Aglowmed, India.*
⊗Bromhexine (p. 1656·3); phenylephrine (p. 1672·2); salbutamol (p. 1220·2).

Instaryl-Cold *Aglowmed, India.*
Syrup: Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2).
Aglowmed, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Instaryl-D *Aglowmed, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Instaryl-P *Aglowmed, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Instenon *Nycomed, Hong Kong; Nycomed, Rus.; Nycomed, Ukr.*
⊗Hexobendine hydrochloride (p. 1401·1); etamivan (p. 2322·2); etofylline (p. 1208·2).
Cerebrovascular disorders.

Insti *Herbion, Rus.*
Ivy (p. 2536·2); malabar nut (p. 2549·1); viola odorata; liquorice (p. 1853·2); chinese tea (p. 2648·2); fennel (p. 2503·2); eucalyptus (p. 2501·1); valerian (p. 2640·2).
Symptomatic treatment of respiratory-tract infections.
Herbion, Ukr.
Salix alba (p. 129·2) malabar nut (p. 2549·1); viola odorata; liquorice (p. 1853·2); thea sinensis (p. 2648·2); fennel (p. 2503·2); eucalyptus globulus (p. 2501·1); valerian (p. 2640·2).
Symptomatic treatment of respiratory-tract infections.

Instillagel *Raffo, Arg.†; Germania, Austria; Melisana, Belg.; Pharmascience, Canad.; Farco, Cz.; Farco, Denm.; Hepatoum, Fr.; Farco, Ger.; Allertec, Gr.; Farco, Hong Kong; Farco, Hung.; Farco, Irl.; Farco, Neth.; Farco, Port.; Abbott, Swed.; CliniMed, UK.*
Lidocaine hydrochloride (p. 1988·2); chlorhexidine gluconate (p. 1743·3).
Catheterisation; cystoscopy; endoscopy; urethroscopy.
Farco, Rus.
Lidocaine hydrochloride (p. 1988·2); chlorhexidine hydrochloride (p. 1743·3).
Catheterisation; endoscopy.

Instink *Sunthi Sepuri, Indon.†*
⊗Tribulus terrestris (p. 2633·3); saw palmetto (p. 2363·3); damiana (p. 2491·3); ginseng (p. 2513·3); muira-puama; sarsaparilla (p. 2610·3).
Dietary supplement for men.

Insto *Sterling, Indon.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Instrunet *Inibsa, Port.*
A range of solutions for skin and instrument disinfection.

Insucar *Apotex, Mex.*
Isosorbide dinitrate (p. 1412·2).

Insucare-N *Ranbaxy, India.*
⊗Isophane insulin injection (p. 475·3).
Diabetes mellitus.

Insugen-30/70 *Biocon, Thai.*
⊗A mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p. 475·3).
Diabetes mellitus.

Insugen 30/70 and 50/50 *Biocon, India.*
⊗Mixtures of soluble insulin injection (human) 30% or 50% and isophane insulin injection (human)70% or 50% respectively (p. 475·3).
Diabetes mellitus.

Insugen-N *Biocon, India; Biocon, Thai.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insugen-R *Biocon, India; Biocon, Thai.*
⊗Soluble insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insuget 70/30 *Getz, Philipp.*
⊗A mixture of isophane insulin injection (human, recombinant) 70% and insulin injection (human, recombinant) 30% (p. 475·3).
Diabetes mellitus.

Insuget-N *Getz, Philipp.*
⊗Insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

Insuget-R *Getz, Philipp.*
⊗Isophane insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

Insulact *Farma Iberica, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Insulatard *Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Malaysia; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insulatard HM *Novo Nordisk, Arg.; Novo Nordisk, Chile; Novo Nordisk, India; Novo Nordisk, Indon.; Novo Nordisk, Philipp.; Novo Nordisk, Switz.*
⊗Isophane insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Insulatard MC *Novo Nordisk, NZ.*
⊗Isophane insulin injection (porcine, monocomponent) (p. 475·3).
Diabetes mellitus.

Insulex 70/30 *Pisa, Mex.*
⊗A mixture of isophane insulin injection (human) 70% and soluble insulin injection (human) 30% (p. 475·3).
Diabetes mellitus.

Insulex N *Pisa, Mex.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Insulex R *Pisa, Mex.*
⊗Insulin (human) (p. 475·3).
Diabetes mellitus.

Insulidd L *Marvel, Rus.†*
⊗Insulin zinc suspension (crytalline 70%, amorphous 30%) (human) (p. 475·3).
Diabetes mellitus.

Insulin Basal *Braun, Ger.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insulin Comb 30/70 *Braun, Ger.*
⊗Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p. 475·3).
Diabetes mellitus.

Insulin Lt *Tarchomin, Rus.†*
⊗Insulin zinc suspension (crystalline 70%, amorphous 30%) (porcine) (p. 475·3).
Diabetes mellitus.

Insulin Maxirapid *Tarchomin, Rus.†*
⊗Neutral insulin (porcine) (p. 475·3).
Diabetes mellitus.

Insulin Rapid *Braun, Ger.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insulin Reaction *Sherwood, USA.*
Glucose (p. 2069·1).
Hypoglycaemia.

Insulinum Lente *Polfa Tarchomin, Pol.*
⊗Insulin zinc suspension (porcine) (p. 475·3).
Diabetes mellitus.

Insulinum Maxirapid *Polfa Tarchomin, Pol.*
⊗Insulin injection (porcine) (p. 475·3).
Diabetes mellitus.

Insulinum Semilente *Polfa Tarchomin, Pol.†*
⊗Insulin zinc suspension (porcine) (p. 475·3).
Diabetes mellitus.

Insulinum Ultralente *Polfa Tarchomin, Pol.†*
⊗Insulin zinc suspension (porcine) (p. 475·3).
Diabetes mellitus.

Insuman 25/75 and 50/50 *Sanofi-Aventis, India.*
⊗Mixtures of neutral insulin injection (human) and isophane insulin injection (human) in the proportions indicated (p. 475·3).
Diabetes mellitus.

Insuman Basal *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Spain†; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, UK.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Insuman Comb *Sanofi-Aventis, S.Afr.*
⊗A mixture of soluble insulin injection (human, biosynthetic) 30% and isophane insulin injection (human, biosynthetic) 70% (p. 475·3).
Diabetes mellitus.

Insuman Comb 15, 25, 30, 50 *Sanofi-Aventis, Cz.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain.†*
⊗Mixtures of soluble insulin injection (human) 15%, 25%, 30%, or 50% and isophane insulin injection (human) 85%, 75%, 70%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Insuman Comb 15, 25, 30, and 50 *Sanofi-Aventis, Neth.*
⊗Mixtures of insulin injection (human, recombinant) 15%, 25%, 30%, or 50% and isophane insulin (human, recombinant) 85%, 75%, 70%, or 50% respectively (p. 475·3).
Diabetes mellitus.

Insuman Comb 15, 25, and 50 *Sanofi-Aventis, Austria; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, UK.*
⊗Mixtures of soluble insulin injection (human) 15%, 25%, and 50% and isophane

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

insulin injection (human) 85%, 75%, and 50% respectively (p. 475·3).
Diabetes mellitus.

Insuman Comb 15, 25, 50 *Sanofi-Aventis, Pol.*
⊗Mixtures of insulin injection (human) 15, 25, or 50% and isophane insulin 85, 75, or 50% (human), respectively (p. 475·3).
Diabetes mellitus.

Insuman Comb 25 *Sanofi-Aventis, Fin.; Sanofi-Aventis, Norw.†; Sanofi-Aventis, Rus.; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.*
⊗Mixture of soluble insulin (human) 25% and isophane insulin (human) 75% (p. 475·3).
Diabetes mellitus.

Insuman Comb 85N/15R and 75N/25R *Sanofi-Aventis, Braz.*
⊗Mixtures of isophane insulin injection (human) 85% and 75% and soluble insulin injection (human) 15% and 25% respectively (p. 475·3).
Diabetes mellitus.

Insuman Infusat *Sanofi-Aventis, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.†; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain†; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.*
⊗Soluble insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insuman N *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Venez.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Insuman 15R/85N, 25R/75N, 50R/50N *Sanofi-Aventis, Mex.*
⊗Mixtures of soluble insulin injection (human) 15%, 25%, or 50% and isophane insulin injection (human) 85%, 75%, or 50% respectively (p. 475·3).
Diabetes mellitus.

Insuman 100N *Sanofi-Aventis, Mex.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insuman R *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Mex.; Sanofi-Aventis, Venez.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insuman Rapid *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Spain†; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, UK.*
⊗Soluble insulin injection (human) (p. 475·3).
Diabetes mellitus.

Insumet *Cadila, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Insuneo N *Neo Quimica, Braz.*
⊗Isophane insulin (p. 475·3).
Diabetes mellitus.

Insunex *Medopharm, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Insup *Alacan, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Insuplant *ProStrakan, Fr.†*
⊗Insulin (human) (p. 475·3).
Diabetes mellitus.

Insuran NPH *IBCH, Rus.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Insuran R *IBCH, Rus.*
⊗Soluble insulin (human) (p. 475·3).
Diabetes mellitus.

Insusym *Ultra, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Insusym-Forte *Ultra, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Insuven *Grunenthal, Chile.*
Diosmin (p. 2505·2).
Capillary fragility; venous insufficiency.

Intabion *Intas, India.*
Injection: Vitamin B substances (p. 2102·3).

Intas, India.
Syrup: Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Intac *Coral, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; acid aspiration; Zollinger-Ellison syndrome.

DWD, India.
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration; dyspepsia.

Intacal-D *Intas, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Intacid-MPS *Intas, India.*
Chewable tablets: Aluminium hydroxide (p. 1817·2); almasilate (p. 1815·3); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Intas, India.
Syrup: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Intaclox-D *Intas, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Intacob *Intag, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Intacof-S *Intag, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Intacorlin *Intas, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Intacoxia *Intas, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Intadine *Intas, India.*
Povidone-iodine (p. 1767·1).
Disinfection.

Intafer *Zuoz, Venez.*
Oral drops; tablets: Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Zuoz, Venez.
Syrup: Iron polymaltose (p. 2077·2); cyanocobalamin (p. 2107·2).
Iron-deficiency anaemia.

Intaferfol *Zuoz, Venez.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Anaemias.

Intagenta *Intas, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Intagesic *Intas, India.*
Tablets: Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Intas, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Intagesic-MR *Intas, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Intagra *Intas, India; Interchem, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Intagyl *Intas, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Intal *Phoenix, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis, Ger.; Teva, Hung.†; Sanofi-Aventis, Irl.; Sanofi-Aventis, Jpn; Sanofi-Aventis, Mex.; Douglas, NZ; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Eczacibasi, Turk.; Sanofi-Aventis, UK; King, USA.†*
Sodium cromoglicate (p. 1225·3).
Asthma; allergic rhinitis; bronchitis; allergic conjunctivitis; food allergy.

Intalfa *Intas, India.*
Interferon alfa-2b (p. 989·2).

Intalith *Intas, India.*
Lithium.
Bipolar disorder; mania; depression.

Intalka *Intas, India.*
Sodium acid citrate (p. 1781·1).

Intalon *Intas, India.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).

Intamox-D *Intas, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Intanza *Sanofi Pasteur, Austral.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fr.†; Sanofi Pasteur, Ger.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Irl.; Sanofi Pasteur, Neth.; Sanofi-Aventis, NZ; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.; Sanofi Pasteur, UK.*
An intradermal inactivated influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Intapan
Note: this name may be used for preparations of different composition.
Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.
Nalbuphine hydrochloride (p. 97·3).
Adjunct in general anaesthesia; pain.

Intag, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Intapan-D *Intag, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Intard *Julphar, UAE.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Intase *Indu, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Intase DF *Indu, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Intavisc *Intas, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Intavital *Intas, India.*
Colecalciferol (p. 2113·1); ginseng (p. 2513·3); minerals.

Intax *Intra-Labs, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Intaxel
Note: this name may be used for preparations of different composition.
Dabur, Hong Kong†; Fresenius Kabi, Hung.†; Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Rus.; Fresenius Kabi, Thai.; Biogalenic, Venez.
Paclitaxel (p. 839·3).
Breast cancer; non-small cell lung cancer; ovarian cancer; AIDS-related Kaposi's sarcoma.

Laboratorios Chile, Chile.
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Intazide *Intas, India.*
Balsalazide (p. 1820·2).
Ulcerative colitis.

Intazin *Intas, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Intazyme *Intas, India.*
Capsules: ⊗Activated charcoal (p. 1537·3); amylase (p. 2442·1); pepsin (p. 2586·1).

Intas, India.
Syrup: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Inteban *Dainippon, Jpn.*
Indometacin (p. 71·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain; fever; gout.

Intecar *David, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3); manganese (p. 2081·2); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2).

Intefen *Sunshine, China.*
Interferon alfa-2a (recombinant, human) (p. 989·2).
Chronic hepatitis B; chronic hepatitis C; malignant neoplasms; anogenital warts; herpes zoster.

Inteflora *Adcock Ingram, S.Afr.*
Saccharomyces boulardii (p. 2596·3).
Restoration of gastrointestinal flora.

Integra
Note: this name may be used for preparations of different composition.
Intra-Labs, India.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Quimica y Farmacia, Mex.†
Vitamins; minerals.

Integra F *US Pharmaceutical, USA.*
Iron (p. 2073·1); vitamin B_3 (p. 2083·1); vitamin C (p. 2110·3); folic acid (p. 2063·1).
Dietary supplement.

Integra Plus *US Pharmaceutical, USA.*
Iron (p. 2073·1); vitamins.
Dietary supplement.

Integra-E *Yuhan, Philipp.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Integrilin *Schering-Plough, Austral.; GSK, Austria; GSK, Belg.; Merck, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; MSD, Hong Kong; GSK, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; GSK, Ital.; Schering-Plough, Malaysia; GSK, Neth.; GSK, Norw.; MSD, NZ; Schering-Plough, Philipp.†; GSK, Pol.; GSK, Port.; GSK, Rus.; Schering-Plough, S.Afr.; MSD, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; MSD, Thai.; GSK, UK; GSK, Ukr.; Schering, USA.*
Eptifibatide (p. 1376·3).
Myocardial infarction; unstable angina; prevention of ischaemic cardiac complications in coronary angioplasty or atherectomy.

Integrobe *Northia, Arg.*
Dipyrone (p. 53·3).
Inflammation; pain.

Integrobe Plus *Northia, Arg.*
Dipyrone (p. 53·3); ergotamine (p. 674·1); caffeine (p. 1203·3).
Migraine.

Integrovin *Liferpal, Mex.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3).

Integrum *Atlas, Arg.*
Heparin sodium (p. 1396·3); onion (p. 2575·2); allantoin (p. 1693·1).
Hypertrophic and keloid scars.

Intelec *Buxton, Arg.*
Galantamine (p. 391·3).
Alzheimer's disease.

Intelecta *Unipharma, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Intelektan *Biofarm, Pol.†*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Mental function impairment; fatigue.

Intelence *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Centocor, USA; Tibotec, USA.*
Etravirine (p. 978·2).
HIV infection.

Intellan *Herbion, Ukr.*
Ginkgo biloba (p. 2512·3); centella (p. 1698·3); bacopa (p. 2452·1); coriander (p. 2486·3); amomum subulatum; Indian gooseberry (p. 2532·2).
Mental function impairment; mental and physical stress; anxiety; depression.

Intemipril *Sandoz, Mex.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction.

Intenoal *Intel, India.*
Bromhexine hydrochloride (p. 1656·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Intense Clear *L'Oreal, Canad.*
Pyrithione zinc (p. 1718·1).

Intensit *AstraZeneca, Arg.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; obstructive sleep apnoea; shift-work sleep disorder.

Inter 2-B *Delta, Arg.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; chronic hepatitis B and C; anogenital warts.

Interal *Gosnii, Rus.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; infections.

Interbi *Interbat, Hong Kong; Interbat, Indon.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Interbion *Biospray, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Interco *Interbat, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Intercon *Interbat, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Intercostal-Gastreu *Reckeweg, Ger.*
Arsenicum album (p. 2448·1); colocynthis (p. 1833·3); ranunculus bulbosus; rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Intercron *Flexpharma, Fr.*
Sodium cromoglicate (p. 1225·3).
Food hypersensitivity.

Intercyton *UCB, Fr.*
Flavodate sodium (p. 2505·2).
Circulatory eye disorders; haemorrhoids; menometrorrhagia associated with intra-uterine devices; venous insufficiency; capillary fragility.

Interderm *Interpharma, Spain.*
⊗Gentamicin sulfate (p. 304·2); nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Interdoxin *Interbat, Indon.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Interfam *Interbat, Hong Kong; Interbat, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; duodenal ulcer; pathological hypersecretory disorders.

Interferon Alfanative *BioNative, Indon.†; Fahrenheit, Indon.†*
Interferon alfa (natural human) (p. 989·2).

Interflox *Interbat, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Interhistin *Interbat, Indon.*
Mebhydrolin napadisilate (p. 634·2).
Allergic disorders.

Interlong *Neptunus, China.*
Interferon alfa-2b (p. 989·2).
Hepatitis; anogenital warts; herpes zoster; malignant neoplasms.

Intermax-Alpha *Raffo, Chile.†*
Interferon alfa (p. 989·2).
Hepatitis B; hepatitis C; malignant neoplasms.

Intermezzo *Purdue, USA.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Intermic *Interbat, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemorrhage.

Intermoxil *Interbat, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Internase *Quality, Hong Kong.*
⊗Bromelains (p. 2460·3).
Soft-tissue inflammation and oedema.

Internolol *Interbat, Indon.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Interome *Interbat, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Interpec *Interbat, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Interpim *Interbat, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Interpril *Interbat, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Interquin *Interbat, Indon.*
Hydroquinone (p. 1705·1); sunscreen.
Skin hyperpigmentation.

Interquin Plus *Interbat, Indon.*
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3).
Skin hyperpigmentation.

Intersun *Interbat, Indon.*
Cream SPF 35: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1).
Sunscreen.

Interbat, Indon.
Lotion SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Intervask *Interbat, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Intervein *Gerolymatos, Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Intervit *San Marino, Philipp.*
Calcium lactate (p. 1784·1); vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin D (p. 2112·3).
Nutritional supplement.

Interzinc *Interbat, Indon.*
Zinc sulfate (p. 2126·2).
Zinc supplement.

Interzol *Interbat, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

IntestAid *Pro Bio, UK.*
Food for special diets.
Irritable bowel syndrome.

Intestamin *Fresenius Kabi, Cz.*
Preparation for eneral nutrition.

Fresenius Kabi, Turk.
Preparation for enteral nutrition.

Intestifalk *2care4, Denm.; Europharma, Denm.; Falk, Spain.*
⊗Budesonide (p. 1625·1).
Inflammatory bowel disease.

Intestinal Bulking Agent II *Inno-Vite, Canad.†*
Clove (p. 2481·2); plantago (p. 1849·1); taraxacum (p. 2625·3).

Intestinex *Marin, USA.*
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement.

Intestinol *Kocak, Turk.*
⊗Pancreatin (p. 2579·3); ox bile (p. 2457·2); medicinal charcoal (p. 1537·3).
Dyspepsia; flatulence; digestive disorders.

Rosch & Handel, Austria.†
⊗Pancreatin (p. 2579·3); sodium cholate (p. 2457·2); duodenum extract (p. 2444·1); charcoal (p. 1537·3).
Gastrointestinal disorders.

IntestoBalance *Eagle, Austral.*
Bifidobacterium animalis (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3).
Digestive disorders.

Intesul *Beta, Arg.*
Mosapride citrate (p. 1865·2).
Gastritis; gastro-oesophageal reflux; gastroparesis.

Intétrix *Ipsen, Fr.*
Tiliquinol (p. 949·2); tiliquinol lauril sulfate (p. 949·2); tilbroquinol (p. 949·2).
Intestinal amoebiasis.

Intetrix *Ipsen, Rus.; Ipsen, Ukr.*
Tiliquinol (p. 949·2); tiliquinol lauril sulfate (p. 949·2); tilbroquinol (p. 949·2).
Amoebiasis.

Inthacine *The Forty-Two, Thai.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Inthesa-5 *Fahrenheit, Indon.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Inticol *Neiss, India.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism; head injuries.

Intidrol *Interbat, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Intifen *Interbat, Indon.*
Ketotifen fumarate (p. 631·3).
Asthma.

Intim *ICIM, Ital.*
Hamamelis (p. 2523·3); levomenol (p. 2544·1).
Personal hygiene.

Intima *Pascual, Philipp.†*
Lactic acid (p. 2539·1); chamomile (p. 2474·1); aloe vera (p. 1693·2); sodium lactate (p. 1781·2).
Feminine hygiene.

Intob *Intra-Labs, India.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Intobutaz *Demo, Gr.*
Indometacin (p. 71·2).

Intocel *Sidus, Arg.*
Cladribine (p. 769·1).
Hairy-cell leukaemia.

Intodine *Intel, India.*
Povidone-iodine (p. 1767·1).

Intomin *Vilco, Gr.*
Indometacin (p. 71·2).

Intra *Eurofarma, Braz.*
Lubricating gel.

Intrabet *Intra-Labs, India.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Intracal *Intra-Labs, India.*
Calamine (p. 1697·2).
Pruritus.

Intracef
Note: this name may be used for preparations of different composition.
Intra-Labs, India.
Cefuroxime (p. 255·2) or cefuroxime axetil (p. 255·2).
Bacterial infections.

Bergamo, Braz.†
Ceftazidime (p. 250·2).
Bacterial infections.

Pharmacare, S.Afr.†
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Intracef-CV *Intra-Labs, India.*
Cefuroxime (p. 255·2); clavulanic acid (p. 268·3).
Bacterial infections.

Intradec *Intra-Labs, India.*
⊗Nandrolone (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemia.

Intradermi *Eberth, Ger.†*
Troxerutin (p. 2505·3); aesculus (p. 2431·2).
Venous insufficiency.

Intradex *Intra-Labs, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Intradine *Intra, Venez.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Intradol *Intra-Labs, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Intradyn *Intra, Venez.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Intrafat *Nihon, Jpn.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intrafer
Note: this name may be used for preparations of different composition.
AstraZeneca, Arg.
Iron dextran (p. 2075·3).
Iron deficiency.

Geymonat, Ital.
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Vianex (Βιανεξ), Gr.; Intra-Labs, India.
Iron sucrose (p. 2078·1).

Unipharm, Mex.
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Anaemias.

Intrafer F-800 *Unipharm, Mex.*
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron deficiency; folate deficiency; iron-deficiency anaemia.

Intrafer TF *Unipharm, Mex.*
Iron amino acid chelate (p. 2048·3); folic acid (p. 2063·1).
Anaemias.

Intrafusin *Baxter, Ger.; Fresenius Kabi, Irl.*
Amino acids.
Parenteral nutrition.

Fresenius Kabi, UK.
Amino acids; with or without electrolytes (p. 1775·1).

Intrafusin E *Baxter, Ger.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Intrafusin SX-E *Kalbe, Indon.*
Amino acids; sorbitol (p. 2092·1); xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Intragam *CSL, Austral.; CSL, NZ; NBI, S.Afr.; CSL, Singapore.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; auto-immune disorders; bone marrow transplantation; immune thrombocytopenia; immunodeficiency; Kawasaki disease; hypogammaglobulinaemia.

Intragam P *CSL Biotherapies, Hong Kong.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; immune thrombocytopenia; bone marrow transplantation; Kawasaki disease; Guillain-Barré syndrome.

Intragat *Intra-Labs, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Intragat-AM *Intra-Labs, India.*
Ambroxol (p. 1654·3); gatifloxacin (p. 303·2).

Intragat-O *Intra-Labs, India.*
Gatifloxacin (p. 303·2); ornidazole (p. 943·1).

Intragen *Intra-Labs, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Intragen-D *Intra-Labs, India.*
⊗Dexamethasone (p. 1630·3); gentamicin (p. 304·2).

Intragesic *Intra-Labs, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Intra-Labs, India.
Tablets: Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Intra-Labs, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Intragesic-MR *Intra-Labs, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Intraglobin *Biotest, Austria†; Intra Pharma, Irl.†; Biotest, Ital.†; Biotest, Rus.; Biotest, Thai.†; Kansuk, Turk.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; passive immunisation; immune thrombocytopenia; Kawasaki disease; hypogammaglobulinaemia; Guillain-Barré syndrome; immunodeficiency disorders; Wiskott-Aldrich syndrome.

Intraglobin F *Biotest, Gr.; Biotest, Hong Kong; Biotest, Israel; Biotest, Pol.; Mednostica, S.Afr.†; Biotest, Singapore.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; passive immunisation; Kawasaki disease; immunodeficiency; bone marrow transplantation.

Intragly *Intra-Labs, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Intragly-M *Intra-Labs, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Intrait de Marron d'Inde P *H2 Pharma, Fr.*
Aesculus (p. 2431·2); metesculetol sodium (p. 2557·3).
Haemorrhoids.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Intralgis *Urgo, Fr.*
Ibuprofen (p. 68·2).
Fever; pain; peri-articular and soft-tissue disorders.

Intralipid *Fresenius Kabi, Austral.; Fresenius Kabi, Austria; Fresenius Kabi, Canad.; SSPC, China; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Indon.; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.†; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK; Fresenius Kabi, Ukr.; Baxter, USA.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intralipide *Fresenius Kabi, Fr.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intralipos *Mitsubishi, China; Mitsubishi, Indon.; Mitsubishi Guangzhou, Singapore.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intraliv *Intra-Labs, India.*
Injection; tablets: Ornithine aspartate (p. 2085·2).

Intra-Labs, India.
Syrup: Cyperus rotundus; piper longum; piper nigrum; terminalia chebula (p. 2474·3); tinospora cordifolia; zingiber officinale.

Intraliv-UD *Intra-Labs, India.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; primary biliary cirrhosis.

Intralon *Darier, Mex.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Intralor *Intra-Labs, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Intramed Trichazole *Fresenius Kabi, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Intramet *Intra-Labs, India.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Intramin *Baxter, Ger.†*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Intramol-V6 *Intra-Labs, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Intrasept *Farmo Quimica, Chile.*
Thiomersal (p. 1771·3).
Skin and wound disinfection.

Intrasite *Smith & Nephew, Irl.*
Hydrogel wound dressing.
Wounds.

Smith & Nephew, Belg.
A hydrogel dressing.
Wounds.

Smith & Nephew, Ital.
Hydrogel dressing.
Wounds; ulcers.

Smith & Nephew, Austral.
Crilanomer (p. 1699·2).
Wounds.

Smith & Nephew, Fr.
Carmellose sodium (p. 2175·2); propylene glycol (p. 2205·2).
Wounds.

Smith & Nephew Healthcare, UK.
Carmellose (p. 2175·1).
Wound dressing.

Smith & Nephew, S.Afr.
Carmellose sodium (p. 2175·2).
Wound dressing.

Intraspir *Tecnifar, Port.†*
Lysine aspirin (p. 84·3).
Fever; pain.

Intrastigmina *Lusofarmaco, Ital.; Lusofarmaco, Port.*
Neostigmine metilsulfate (p. 687·2).
Abdominal distension; urinary retention; myasthenia gravis; intestinal atony; menstrual disorders.

Intrataxime *Torlan, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Intratect *Biotest, Austria; Biotest, Ger.; Biotest, Gr.; Biotest, Hung.; Biotest, Irl.; Kamada, Israel; Biotest, Ital.; Biotest, Neth.; Biotest, Pol.; Biotest, Rus.; Biotest, Spain; Biotest, Switz.; Biotest, UK·*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; passive immunisation; bone-marrow transplantation; immunodeficiency.

Intraval *Aventis, NZ.†*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Intraval Sodium *Piramal, India.*
Thiopental sodium (p. 1915·1).
General anaesthesia; status epilepticus; raised intracranial pressure.

Intra-Vite *Roche, Austral.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin deficiencies; vitamin supplement.

Intrazolina *Torlan, Spain.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Intrazoline *Torlan, Rus.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Intrazyme *Intra-Labs, India.*
Capsules: ⊗Vitamin B substances (p. 2102·3); *Lactobacillus sporogenes* (p. 2596·3); papain (p. 2582·3); simeticone (p. 1886·2).

Intra-Labs, India.
Oral drops: ⊗Vitamin B substances (p. 2102·3); pepsin (p. 2586·1); amylase (p. 2442·1).

Intrazyme Tonic *Intra-Labs, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Intrenon *VUAB, Cz.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid depression; opioid overdosage.

Intricef *Caprifarmindo, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Intricon *Great Eastern, Thai.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); liver (p. 2444·1).
Anaemias.

Intril *Torrent, Thai.*
⊗Indapamide (p. 1409·2).
Hypertension.

Intrinsa *Warner Chilcott, Cz.†; Warner Chilcott, Fr.†; Warner Chilcott, Ger.†; Warner Chilcott, Irl.†; Procter & Gamble, Ital.†; Procter & Gamble, Neth.†; Procter & Gamble, Pol.†; Procter & Gamble, Port.†; Procter & Gamble, Spain†; Warner Chilcott, Swed.†; Procter & Gamble, UK.†*
⊗Testosterone (p. 2305·1).
Sexual hypoactivity in women following oophorectomy and hysterectomy.

Intrix *Pharos, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Intrizin *Interbat, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Introlan *Galagen, USA.*
Lactose-free, gluten-free preparation for enteral nutrition.

Introlite *Abbott Nutrition, UK.*
Preparation for enteral nutrition.

Ross, USA.
Lactose-free preparation for enteral nutrition.

Intron *Schering-Plough, Venez.*
Interferon alfa-2b (p. 989·2).
Chronic hepatitis; malignant neoplasms.

Intron A *MSD, Austral.; Mantecorp, Braz.; Merck, Canad.; MSD, China; MSD, Hong Kong; Schering-Plough, Hung.; Fulford, India; Fulford, India; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Mex.; MSD, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, Ukr.; Schering, USA; Schering-Plough, Venez.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; anogenital warts; chronic hepatitis B; chronic hepatitis C; laryngeal papillomatosis.

Intron A Peg *Schering-Plough, Arg.*
Peginterferon alfa-2b (rbe) (p. 989·2).
Chronic hepatitis C.

IntronA *Schering-Plough, Austria; MSD, Belg.; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Schering-Plough, Gr.; Schering-Plough, Indon.; MSD, Irl.; Schering-Plough, Ital.; MSD, Neth.; MSD, Norw.; MSD, Swed.; Schering-Plough, UK.*
Interferon alfa-2b (rbe) (p. 989·2).
Formerly known as Intron A.
Malignant neoplasms; chronic hepatitis B; chronic hepatitis C; anogenital warts.

Intropaste *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Intropin *Sanofi Synthelabo, S.Afr.†*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure.

Intrum Plus *Interbat, Indon.*
Bovine colostrum (p. 2380·3); vitamins; docosahexaenoic acid (p. 1460·1).
Nutritional supplement.

Intuban *Farmak, Ukr.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Intunal *Meprofarm, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dexchlorpheniramine maleate (p. 621·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Influenza symptoms.

Intuniv *Shire, USA.*
Guanfacine hydrochloride (p. 1396·1).
Attention deficit hyperactivity disorder.

Inulac *Corypharma, Ital.*
Lactic-acid-producing organisms (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Inulax *Cadila, India.*
Ispaghula (p. 1849·1).

Inuvair *Chiesi, Belg.; Janssen-Cilag, Ger.; UCB, Gr.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Inuver *Chiesi, Ital.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Inuvic *Leti, Venez.*
Montelukast (p. 1214·3).
Asthma.

Inuxair *Chiesi, Norw.*
⊗Beclometasone dipropionate (p. 1621·2); formoterol fumarate (p. 1209·2).
Asthma.

Invac-B *Intas, India.*
A hepatitis B vaccine (surface antigen) (p. 2389·3).
Active immunisation.

Invanz *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Infectopharm, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; Merck, India; MSD, Indon.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Merck, Turk.; MSD, UK; MSD, Ukr.; Merck, USA; MSD, Venez.*
Ertapenem sodium (p. 290·3).
Bacterial infections.

Invast *Aspen, Austral.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Inveda *Janssen-Cilag, Mex.*
Paliperidone (p. 1093·1).

Invega *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Xian-Janssen, China; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.†; Janssen-Cilag, Ger.†; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen, Jpn; Janssen-Cilag, Malaysia; Janssen-Cilag, Neth.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Janssen, USA.*
Paliperidone (p. 1093·1).
Schizophrenia; bipolar disorder.

Inversine *Layton, USA.†*
Mecamylamine hydrochloride (p. 1429·1).
Hypertension.

Invert *Anthus, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Invex *Abbott, Braz.*
⊗Prednicarbate (p. 1645·1).
Corticosteroid.

Inviclot *Fahrenheit, Indon.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Invicorp *Evolan, Denm.; Douglas, NZ.*
Aviptadil (p. 2642·3); phentolamine mesilate (p. 1468·3).
Erectile dysfunction.

Invidon *Invision, India.*
Trimetazidine hydrochloride (p. 1520·1).
Ménière's disease; angina pectoris.

Invigan
Note: this name may be used for preparations of different composition.
Bago, Chile.†
Ornidazole (p. 943·1).
Anaerobic bacterial infections; dracunculiasis; protozoal infections.

Invirase *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ†; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Roche, USA.*
Saquinavir mesilate (p. 1014·2).
HIV infection.

Invisifiber *Nutrilite, Arg.*
Maltodextrin (p. 2080·3); inulin (p. 2534·3).
Dietary fibre supplement.

Invites RX *Breckenridge, USA.*
Vitamin C (p. 2110·3); vitamin B substances (p. 2102·3); zinc (p. 2126·1).
Dietary supplement.

Invivac *Abbott, Irl.†; Solvay, Neth.†; Abbott, Norw.†; Solvay, Port.; Solvay, UK.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Invoigin *Chew, Thai.†*
Dipyrone (p. 53·3).
Fever; pain.

Invokana *Janssen-Cilag, UK; Janssen, USA.*
Canagliflozin (p. 469·2).
Diabetes mellitus.

Invomit *Interbat, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Invoril *Ranbaxy, China; Ranbaxy, Cz.†; Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; ischaemic heart disease.

Invozide *Ranbaxy, India.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Inway *Evershine, India.*
Preparation for enteral nutrition.

Inyesprin *Aristo, Spain.*
Lysine aspirin (p. 84·3).
Pain; fever; musculoskeletal, joint, and peri-articular disorders; thromboembolism prophylaxis.

Inza
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Alphapharm, Hong Kong; Alphapharm, Singapore.
Naproxen (p. 98·2).
Musculoskeletal, joint, and soft-tissue disorders; pain; inflammation.

Aspen, S.Afr.
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; gout.

Konimex, Indon.†
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Inzana *Konimex, Indon.†*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Inzelloval *Kohler-Pharma, Ger.†*
Minerals.

Inzeton *Sandoz, Turk.*
Opipramol hydrochloride (p. 440·2).
Depression.

Inzitan *Kern, Spain.*
⊗Cyanocobalamin (p. 2107·2); dexamethasone (p. 1630·3); thiamine hydrochloride (p. 2103·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Myalgia; neuralgia; neuritis.

Inzofresh *Mankind, India.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Inzolam
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
Triazolam (p. 1112·3).
Insomnia.

Inpac, Thai.
Alprazolam (p. 1035·2).
Anxiety.

Inzolen *Kohler, Ger.*
Electrolytes (p. 1775·1); trace elements.
Electrolyte disorders; metabolic disorders.

Inzu *Dexter, India.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Inzury *Velka, Gr.*
⊗Furosemide (p. 1387·1).

IOA *MSD, Irl.*
24 Tablets, nomegestrol acetate (p. 2294·1); estradiol (p. 2271·1); 4 tablets, inert.
Combined oral contraceptive.

Ioa *MSD, Neth.*
24 Tablets, nomegestrol acetate (p. 2294·1); estradiol (p. 2271·1); 4 tablets, inert.
Combined oral contraceptive.

Iobet *FDC, India.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Iobid DM *Iomed, USA.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Iobrim *FDC, India.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Iobrix *Taejoon, Thai.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Iocandin *Candor, India.*
Povidone-iodine (p. 1767·1).
Wound infection.

Iocandin Sol *Candor, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Iocandin-M *Candor, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Iocare *Ioltech, Ital.*
Electrolytes (p. 1775·1).
Eye irrigation.

Iocare Balanced Salt Solution *Iocom, UK; Novartis Ophthalmics, USA.*
Electrolytes (p. 1775·1).
Eye irrigation.

Iocare BSS *Zeiss Meditec, Ger.*
Electrolytes (p. 1775·1).
Eye irrigation.

Iodal *Iomed, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Iodantipyrin *Tomskhimfarm, Rus.*
Phenyldimethyliodopyrazolone.
Tick-borne encephalitis.

Iodax *Rekah, Israel.†*
Iodine (p. 2336·3); potassium iodide (p. 2336·3).
Disinfection of minor cuts and bruises.

Iode *Pepin, Canad.†*
Iodine (p. 2336·3); potassium iodide (p. 2336·3).

Iodep *Novara, Arg.*
Povidone-iodine (p. 1767·1).
Skin, mucous membrane, and instrument disinfection; wounds; burns; skin infections.

Iodesin *EMS, Braz.*
Oxomemazine hydrochloride (p. 637·1); potassium iodide (p. 2336·3); sodium benzoate (p. 1738·2); guaifenesin (p. 1666·2); ipecacuanha (p. 1667·2).
Respiratory-tract congestion.

Iodetal *Sanval, Braz.*
Sulfogaiacol (p. 1678·1); potassium iodide (p. 2336·3); tolu balsam (p. 1679·2).
Respiratory-tract congestion.

Iodeton *Cazi, Braz.*
Potassium iodide (p. 2336·3).
Cough.

Iodetoss *Ducto, Braz.*
Potassium iodide (p. 2336·3).
Cough.

Iodex
Note: this name may be used for preparations of different composition.
EMS, Braz.
Iodine (p. 2336·3).
Skin infections.

Qualiphar, Belg.; Lee, USA.
Povidone-iodine (p. 1767·1).
Disinfection of skin, burns, wounds, and instruments; infected skin, mouth, and throat disorders.

Iodex Clasico *GSK, Mex.*
Iodine (p. 2336·3); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Iodex Cristal *GSK, Mex.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); cineole (p. 2479·1).
Musculoskeletal pain; cold symptoms.

Iodex with Methyl Salicylate *Lee, USA.*
Iodine (p. 2336·3); methyl salicylate (p. 92·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Iodex com Salicilato de Metila *EMS, Braz.*
Iodine (p. 2336·3); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Iodex con Salicilato de Metilo *Polinac, Venez.*
Iodine (p. 2336·3); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain; soft-tissue disorders.

Iodicare *Vitamed, Israel.*
Povidone-iodine (p. 1767·1).
Skin and wound disinfection; burns; skin infections.

Iodiflor *Floris, Israel.*
Povidone-iodine (p. 1767·1).
Skin and wound disinfection; burns; skin infections.

Iodina *Orravan, Spain.*
Povidone-iodine (p. 1767·1).
Skin, wound, and burn disinfection.

Iodine Tincture *Floris, Israel.*
Iodine (p. 2336·3); potassium iodide (p. 2336·3).
Antiseptic.

Iodispray *Floris, Israel.*
Povidone-iodine (p. 1767·1).
Burn and wound disinfection.

Iodocollyre *Cooper (Κοπερ), Gr.*
Sodium iodide (p. 2337·1); calcium chloride (p. 1783·1).
Glaucoma.

Iodocomb *Berlin-Chemie, Rus.*
Levothyroxine sodium (p. 2339·1); potassium iodide (p. 2336·3).
Goitre.

Iodoflex *Smith & Nephew, Irl.; Smith & Nephew Healthcare, UK.*
Cadexomer-iodine (p. 1741·2).
Leg ulcers; wounds; exudating wounds.

Smith & Nephew, USA.
Iodine (p. 2336·3).
Wounds.

Iodolab *Labesfal, Port.*
Povidone-iodine (p. 1767·1).
Disinfection.

Iodolan *East India Pharma, India.*
Povidone-iodine (p. 1767·1).

Iodomarin *Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Potassium iodide (p. 2336·3).
Iodine-deficiency disorders; goitre.

Iodomax *Lafedar, Arg.*
Povidone-iodine (p. 1767·1).
Skin disinfection; skin infections.

Iodopen *American Pharmaceutical, USA.*
Sodium iodide (p. 2337·1).
Additive for intravenous total parenteral nutrition solutions.

Iodopengha *Biodica, Fr.†*
Lidocaine (p. 1988·1); eugenol (p. 2501·2).
Dental disorders.

Iodosan Clorexidina *GSK Consumer, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Dental hygiene.

Iodosorb *Smith & Nephew, Austral.; Smith & Nephew, Canad.; Smith & Nephew, Ger.; Smith & Nephew, Gr.; Smith & Nephew, Ital.; Smith & Nephew, Malaysia; Smith & Nephew, Neth.†; Smith & Nephew, S.Afr.†; Smith & Nephew Healthcare, UK; Smith & Nephew, USA.*
Cadexomer-iodine (p. 1741·2).
Skin ulcers; wounds; infected wounds; antiseptic.

Iodosteril *IMS, Ital.†*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Iodoten *Sanitas, Ital.*
Povidone-iodine (p. 1767·1).
Wound disinfection.

Iodotope *Squibb Diagnostics, USA.†*
Iodine-131 (p. 2225·3) as sodium iodide.
Thyroid cancer; hyperthyroidism.

Iodovidon *Altayvitamin, Rus.*
Povidone-iodine (p. 1767·1).
Vaginitis; trichomoniasis.

Iodovine *Intermed, Gr.*
Povidone-iodine (p. 1767·1).

Iodo-Vit
Note: this name may be used for preparations of different composition.
Vitamed, Israel.
Povidone-iodine (p. 1767·1).
Skin and wound disinfection; burns; skin infections; vaginal infections.

Iodoxide *Nizhfarm, Ukr.*
Povidone-iodine (p. 1767·1).
Vaginal infections.

Iodoxyd *Nizpharm, Rus.*
Povidone-iodine (p. 1767·1).
Vaginal infections.

Iodum Complexe No 118 *Lehning, Fr.*
Iodum (p. 2336·3); aconitum (p. 2428·3); anemone pulsatilla (p. 2600·2); kalium bichromicum (p. 2476·3); mercurius corrosivus (p. 2555·2).
Homoeopathic preparation.

Iofed *Iomed, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms.

Ioglime *Sanify, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Iohexagita *Agfa, Ger.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Ioiro *Regional Health, NZ.†*
Ioidol.
Radiographic contrast medium.

Iolebate *Sanify, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc (p. 2126·1).

Iomeron *Regional Health, Austral.; Bracco, Austria; Bracco, Belg.; Bracco, China; Bracco, Cz.; Bracco, Denm.; Bracco, Fin.; Bracco, Gr.; IDS, Hong Kong†; Bracco, Hung.; Bracco, Irl.; Bracco, Israel; Bracco, Ital.; Eisai, Jpn; Bracco, Neth.; Bracco, Norw.; Regional Health, NZ; Bracco, Port.; Bracco, Spain; Bracco, Swed.; Bracco, Switz.; Santa, Turk.; Bracco, UK.*
Iomeprol (p. 1590·3).
Radiographic contrast medium.

Iomléron *Bracco, Fr.*
Iomeprol (p. 1590·3).
Radiographic contrast medium.

Ional *Nichi-Iko, Jpn.*
Secobarbital sodium (p. 1106·3).
Sedative; premedication; induction of anaesthesia.

Ionamin *Celltech, USA.†*
⊗Phentermine (as an ion-exchange resin complex) (p. 2329·2).
Obesity.

Ionax Astringent *Healthpoint, USA.*
Salicylic acid (p. 1719·1); allantoin (p. 1693·1).
Acne.

Ionax Foam *Healthpoint, USA.*
Skin cleanser.

Ionax P *Galderma, Fr.†*
Piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1).
Dandruff.

Ionax Scrub *Galderma, Arg.; Galderma, Braz.; Galderma, Chile; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Healthpoint, USA; Galderma, Venez.*
Polyethylene granules (abrasive) (p. 1690·3).
Acne; seborrhoea; oily skin.

Ionax T *Galderma, India.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders.

Ionet *Cetus, Arg.*
Loperamide (p. 1854·2).
Diarrhoea.

Ionic-Z *Esma, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Ionik *Obolenskoe, Rus.*
⊗Indapamide (p. 1409·2) or indapamide hydrochloride (p. 1409·2).
Hypertension.

Ionil
Note: this name may be used for preparations of different composition.
Galderma, Austral.; Biosintetica, Braz.; Galderma, Philipp.†; Healthpoint, USA.
Salicylic acid (p. 1719·1).
Seborrhoeic dermatitis; scalp disorders; dandruff.

Galderma, Gr.
Coal tar (p. 1723·2).
Psoriasis; chronic eczema; seborrhoeic dermatitis.

Ionil Champu *Galderma, Spain.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders.

Ionil Plus *Galderma, Mex.†; Healthpoint, USA.†*
Salicylic acid (p. 1719·1).
Dandruff; seborrhoeic dermatitis; scalp psoriasis.

Ionil Rinse *Galderma, Austral.†*
Hydrolised collagen proteins (p. 2483·2).
Dry brittle hair.

Ionil-T
Note: this name may be used for preparations of different composition.
Galderma, Arg.; Galderma, Austral.; Biosintetica, Braz.; Galderma, Chile; Galderma, Hong Kong; Galderma, Mex.†; Galderma, NZ; Galderma, Philipp.†; Galderma, Singapore; Valeant, USA.
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders; dandruff; scalp psoriasis; seborrhoeic dermatitis.

Ionil-T Plus *Galderma, Mex.†; Healthpoint, USA.†*
Coal tar (p. 1723·2).
Scalp psoriasis; seborrhoeic dermatitis; scalp disorders.

Ionitan *Aguettant, Fr.*
Electrolytes (p. 1775·1).
Parenteral nutrition.

Ionolyte *Fresenius Kabi, Neth.*
Sodium acetate (p. 1781·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Fluid and electrolyte disorders.

Ionosol-T *Hospira, USA.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Ionosteril *Fresenius Kabi, Port.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Plasma substitute.

Fresenius Kabi, Rus.; Fresenius Kabi, Ukr.
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Ion-O-Trate *Abbott, Philipp.†*
Potassium chloride (p. 1793·2).
Potassium supplement.

Ionoven *Fresenius Kabi, Fr.*
Electrolyte infusion (p. 1775·1).

Ionozem *Pfizer, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Ionsys *Ortho McNeil, USA.†*
⊗Fentanyl hydrochloride (p. 60·1).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Iopac *Dey's, India.*
Iopanoic acid (p. 1591·1).

Iopamigita *Insight, Cz.; Agfa, Ger.; Agfa, Neth.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Iopamiro *Bracco, China; Bracco, Gr.; IDS, Hong Kong†; Bracco, Hung.; Bracco, Israel; Bracco, Ital.; Bracco, Neth.; Regional Health, NZ†; Bracco, Port.; Bracco, Rus.; Bracco, Singapore; Bracco, Spain; Bracco, Switz.; Santa, Turk.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Iopamiron *Bayer, Arg.; Schering, Braz.; Bracco, Fr.; Schering, Venez.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Iopanchol *Genepharm, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Iopar *FDC, India.*
⊗Acetazolamide (p. 2001·1).
Diuresis; glaucoma; epilepsy; high-altitude disorders.

Iopasen *Senese, Ital.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Iopathek *Medithek, Ger.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Iophen *Rugby, USA.*
Iodinated glycerol (p. 1667·2).
Coughs.

Iophen C-NR *Qualitest, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Iophen DM-NR *Qualitest, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Iophen NR *Qualitest, USA.*
Guaifenesin (p. 1666·2).
Cough.

Iopidine *Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Canad.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Jpn; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Port.; Alcon, S. Afr.; Alcon, Singapore†; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA.*
Apraclonidine hydrochloride (p. 2003·3).
Glaucoma; ocular hypertension; control of intra-ocular pressure following eye surgery.

Iopimax *Alcon Cusi, Spain.*
Apraclonidine hydrochloride (p. 2003·3).
Glaucoma; prevention of ocular hypertension in laser surgery.

Iopox *Denver, Arg.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Ioprep *Johnson & Johnson, India.*
Iodine (p. 2336·3); sodium iodide (p. 2337·1).
Skin disinfection; burns; ulcers; wounds.

Ioprost *FDC, India.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Ioptame *Cadila, India.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Ior Epocim *Meizler, Braz.*
⊗Epoetin (p. 1141·1).

Ior LC *Alvartis, Mex.*
Filgrastim (p. 1151·3).
Neutropenia.

Ior T3 *Kexing, China.*
Muromonab-CD3 (p. 1960·1).
Transplant rejection.

Ioril *Zee, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Ior-T3 *Pisa, Mex.†*
Muromonab-CD3 (p. 1960·1).
Renal transplant rejection.

Iort3 *USV, India.*
A factor VIII preparation (human monoclonal) (p. 1148·1).

Iosal II *Iomed, USA.†*
⊗Pseudoephedrine (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Iosalide *Astellas, Ital.*
Josamycin (p. 314·2) or josamycin propionate (p. 314·2).
Bacterial infections.

Iosat *Anbex, Israel; Anbex, USA.*
Potassium iodide (p. 2336·3).
Blockade of thyroid uptake of radioiodine.

Iosopan *Goldline, USA.†*
Magaldrate (p. 1856·1).
Hyperacidity.

Iosopan Plus *Goldline, USA.†*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Hyperacidity.

Iostop *Petsiavas, Gr.†*
Inosine pranobex (p. 988·3).

Iotim *FDC, India.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Iotim-Plus *FDC, India.*
⊗Pilocarpine (p. 2010·2); timolol maleate (p. 1513·2).

Iotussin HC *Iomed, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Iovic *Petsiavas, Gr.*
Flurbiprofen (p. 65·2).

IP6 *Sigma, Arg.*
Nicotinamide (p. 2083·1); chromium tripicolinate (p. 2056·1); vitamin C (p. 2110·3).
Dietary supplement.

Ipacare *H & Care, India.*
Cefepime (p. 239·2).
Bacterial infections.

Ipalat
Note: this name may be used for preparations of different composition.
Cofasa, Venez.
Clotrimazole (p. 576·2).
Fungal skin infections.

Ipamid *KVZ, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Ipamide *Dabur, India.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Ipamide with Mesna *Dabur, India.†*
Ifosfamide (p. 806·1); mesna (p. 1557·2).
Malignant neoplasms.

Ipamix *Visufarma, Ital.*
⊗Indapamide (p. 1409·2).
Hypertension.

Ipant *Ind Biosciences, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Ipasin *Vifor, Switz.*
Crataegus (p. 2488·1); aesculus (p. 2431·2).
Cardiac disorders.

Ipaton *Egis, Cz.; Egis, Hung.; Egis, Ukr.†*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis; maintenance of extracorporeal circulation; stroke prophylaxis.

Ipavit Minerale *NCSN, Ital.*
Vitamins; minerals.

Ipcacin *Ipca, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Ipcacin Kid *Ipca, India.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2); vitamin B_6 (p. 2105·3).
Tuberculosis.

Ipcamox *Austell, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ipcazide *Ipca, India.*
Isoniazid (p. 311·2); vitamin B_6 (p. 2105·3).
Tuberculosis.

IPD
Note: this name may be used for preparations of different composition.
Ind Biosciences, India.
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.
Taiho, Jpn.
Suplatast tosilate (p. 1227·3).
Asthma; allergic rhinitis; atopic eczema.

Ipeca Complexe No 65 *Lehning, Fr.*
Hedera helix (p. 2536·2); polygala senega (p. 1677·2); hyoscyamus (p. 2530·2); atropa belladonna (p. 2453·3); ipeca (p. 1667·2).
Homoeopathic preparation.

Ipeca Composé *Boiron, Fr.*
Ipeca (p. 1667·2); antimonium tartaricum (p. 151·2); drosera rotundifolia (p. 2497·2); anemone pulsatilla (p. 2600·2); phellandrium aquaticum; ferrum phosphoricum (p. 2077·1); antimonium sulfuratum aureum (p. 2445·1); bryonia (p. 2461·3).
Homoeopathic preparation.

Ipecavom *Elpen (Ελπεν), Gr.*
Ipecacuanha (p. 1667·2).
Induction of vomiting in poisoning.

Ipecee *Cadila, India.*
Caffeine (p. 1203·3); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Ipecor *Ashford, Philipp.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Ipegen *Jenson, Neth.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ipene *Ind Biosciences, India.*
Lycopene (p. 2546·2); vitamins.

Ipental *Ipca, Rus.†*
⊗Pancreatin (p. 2579·3); ox bile (p. 2457·2); hemicellulase (p. 2473·1).

Ipenxin *Farmaceutica H, Mex.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

IperClean *UCB, Ital.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); monobasic sodium phosphate (p. 1791·1).
Nasal hygiene.

Iperdix *Servier, China; Servier, Hong Kong.†*
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Iperisan *Marjan, Braz.*
St John's wort (p. 449·1).
Depression.

Iperol *LBS, Thai.*
⊗Ipratropium bromide (p. 1211·3); fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Iperplasin *CSC, Austria†; Medinfar, Port.*
Mepartricin (p. 588·1).
Benign prostatic hyperplasia.

Iperten *Chiesi, Fr.; Torrex Chiesi, Hung.; Chiesi, Ital.*
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Iperton *Kleva, Gr.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ipertrofan *SPA, Cz.; SPA, Ital.; SPA, Philipp.†; SPA, Pol.; Prospa, Port.; SPA, Rus.*
Mepartricin (p. 588·1).
Benign prostatic hyperplasia; pelvic pain syndrome.

Ipesandrine *Novartis Consumer, Port.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Iphox *Korea United, Philipp.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Iphsaflex *Interpharma, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Ipibiofen *IPI, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

I-Pill *Cipla, India.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Ipirasa *Esteve, Spain.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ipirovet *Proel, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; acid aspiration.

IPM *Cadila, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Magnesium trisilicate (p. 1858·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Ipneb *Lupin, India.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipnolor *Krugher, Ital.*
Lormetazepam (p. 1082·1).
Insomnia.

Ipnopen *Lafi, Chile.*
Flunitrazepam (p. 1073·3).
Insomnia.

Ipnovel *Roche, Ital.*
Midazolam hydrochloride (p. 1085·1).
Premedication; sedative; general anaesthesia.

Ipoazotal Complex *SIT, Ital.*
Arginine hydrochloride (p. 2049·1); ornithine hydrochloride (p. 2085·2); citrulline (p. 2056·3); acetylaspartic acid; aceglumic acid; calcium oxoglurate (p. 2579·1).
Hyperammonaemia.

Ipocol
Note: this name may be used for preparations of different composition.
Lagap, Switz.
Colestyramine (p. 1346·1).
Hypercholesterolaemia; biliary-tract disorders.

Sandoz, UK.
Mesalazine (p. 1859·2).
Ulcerative colitis.

Ipod *Invision, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Ipodex
Note: this name may be used for preparations of different composition.
Intra-Labs, India.
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Medilife, Philipp.
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections.

Ipodex-CV *Intra-Labs, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Ipodine *GPO, Thai.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Ipogras *Laboratorios Chile, Chile.*
⊗Sibutramine (p. 2330·2).
Obesity.

Ipol *Sanofi Pasteur, Austral.; Sanofi-Aventis, NZ; Sanofi Pasteur, USA.*
An inactivated poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Ipolab *SF, Ital.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Ipolipid *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Ipomex *Ivax, Arg.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Iporam *Ashford, Philipp.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial eye infections.

Iporel *Jelfa, Pol.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

IPP *Sandoz, Pol.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ippi Verde *Ecolab, Ital.†*
Triclosan (Irgasan DP 300) (p. 1773·2).
Skin and hand disinfection.

Ipraalox *Sanofi-Aventis, Fr.; Sanofi-Aventis, Neth.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Iprabon *Zambon, Braz.†*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Iprabron *Prieto, Arg.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipradol *Nycomed, Hong Kong; Intramed, S.Afr.†*
⊗Hexoprenaline sulfate (p. 1211·1).
Obstructive airways disease; premature labour.

Ipradual *Prieto, Arg.*
⊗Ipratropium bromide (p. 1211·3); fenoterol (p. 1208·2).
Obstructive airways disease.

Ipralin *Biogalenic, Venez.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ipramid *Farmedia, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Ipramist *Zydus, India.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipramol *Teva, Denm.; Teva, Fin.; Teva, Gr.; Teva, Hong Kong; Ivax, Irl.; Ivax, Malaysia; Teva, Neth.; Teva, Port.; Ivax, Rus.; Teva, Swed.; Teva, Switz.; Ivax, UK.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ipran *Drugtech, Chile.*
Escitalopram (p. 416·2).
Depression.

Ipranase *Cipla, India.*
Ipratropium bromide (p. 1211·3).
Nasal congestion.

Ipraneo *Neo Quimica, Braz.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Iprasalb *Prieto, Arg.*
⊗Ipratropium bromide (p. 1211·3); salbutamol (p. 1220·2).
Obstructive airways disease.

Iprateral *Innova, Thai.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipratop *AstraZeneca, India.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipratrin *Alphapharm, Austral.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipratrogen *Unither, Fr.*
Ipratropium bromide (p. 1211·3).
Asthma.

Ipravent *Pfizer, Austral.; Cipla, India; Breathe Pharmaceuticals, Irl.; Cipla, Rus.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipraxa *Teva, Fin.; Teva, Neth.; Teva, Norw.; Teva, Port.; Teva, Swed.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Ipredniz *Medilife, Philipp.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Ipreg *Intra-Labs, India.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); thiamine nitrate (p. 2103·2); tyrosine sodium (p. 2098·3); vitamin E acetate (p. 2119·2).

Ipren *Nycomed, Denm.; McNeil, Swed.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint and soft-tissue disorders; pain; fever; inflammation.

Ipres *Vedim, Pol.; Schwarz, Rus.*
⊗Indapamide (p. 1409·2).
Hypertension.

Ipreziv *Takeda, Neth.*
Azilsartan kamedoxomil (p. 1313·2).
Hypertension.

Ipri V *Vannier, Arg.*
Vitamin E acetate (p. 2119·2); vitamin C (p. 2110·3); betacarotene (p. 2051·1).
Antoxidant preparation.

Ipri V Plus *Vannier, Arg.*
Vitamin E acetate (p. 2119·2); vitamin C (p. 2110·3); betacarotene (p. 2051·1); zinc (p. 2126·1); selenium (p. 2086·3).

Ipri V Total *Vannier, Arg.*
Vitamin E acetate (p. 2119·2); vitamin C (p. 2110·3); betacarotene (p. 2051·1); zinc (p. 2126·1); selenium (p. 2086·3); copper (p. 2057·1); manganese (p. 2081·2).

Ipridol *Oxytech, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3); ipriflavone (p. 1185·3).

Iprivask *Aventis, USA.*
Desirudin (p. 1351·1).
Deep-vein thrombosis prophylaxis following hip replacement.

Iprobac *ACME, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Iproben *Mepha, Switz.*
Ibuprofen (p. 68·2).
Pain; fever.

I-Profen *Osoth, Thai.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Iprolan *Sandoz, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ipromax *ADP, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Iprox *Novell, Indon.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Iproxin *Plusandex, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ipsatol
Note: this name may be used for preparations of different composition.
Orion, Fin.
Biperiden hydrochloride (p. 895·1).
Parkinsonism; drug-induced extrapyramidal disorders.

Ipsilon *Nova Argentia, Arg.; Nikkho, Braz.*
Aminocaproic acid (p. 1131·3).
Haemorrhage; fibrinolytic haemorrhage.

Ipsita *Bal, India.*
Candesartan (p. 1330·2).
Hypertension; heart failure.

Ipso Urea *Difa, Ital.*
⊗Urea (p. 1727·3); ammonium lactate (p. 1694·3); lactic acid (p. 2539·1).
Dry skin conditions.

Ipsodol *Angelini, Spain.*
Capsicum oleoresin (p. 2469·3).
Diabetic neuropathy.

Ipsoflog *Epifarma, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Ipson *Saval, Chile.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ipson-D *Saval, Chile.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; nasal congestion.

Ipstyl *Ipsen, Denm.; Ipsen, Ital.; Ipsen, Norw.*
Lanreotide acetate (p. 1923·2).
Acromegaly; neuroendocrine tumours; carcinoid tumours.

Ipsumor *Aurobindo, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Ip-Taz *Rass, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

IPV
Note: this name may be used for preparations of different composition.
Sanofi Pasteur, Braz.†
An inactivated poliomyelitis vaccine (p. 2411·1).
Active immunisation.

IPV Merieux *Sanofi Pasteur, Ger.*
An inactivated poliomyelitis vaccine (type 1, 2, and 3) (p. 2411·1).
Active immunisation.

Ipvent *Cipla-Medpro, S.Afr.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

IPV-Virelon *Novartis Vaccines, Cz.†; Novartis Vaccines, Ger.†*
An inactivated poliomyelitis vaccine (trivalent) (p. 2411·1).
Active immunisation.

Iqcona *IQFA, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Iqfacilina *IQFA, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Iqfadina *IQFA, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Iqfamicina *IQFA, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Iqfasol *IQFA, Mex.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Iqmem *Lupin, India.*
Centella (p. 1698·3).

Iquinol *ADP, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Iquinol Otic *Medilife, Philipp.*
Ofloxacin (p. 334·3).
Bacterial ear infections.

Iquix *Vistakon, USA.*
Levofloxacin (p. 315·3).
Bacterial eye infections.

Ira *Cassara, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections; peptic ulcer.

Irabel *Pharma-Regist, Hung.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Iracliton *Help, Gr.†*
⊗Betamethasone sodium phosphate (p. 1623·3).

Irahex *Sandoz, Philipp.*
Piracetam (p. 393·3).
Cerebrovascular disorders; dyslexia; myoclonus; vertigo.

Iralgesic *Darou Pakhsh, Rus.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Iraplax *Accord, Mex.*
Irinotecan hydrochloride (p. 812·2).
Malignant neoplasms.

Irays *Pharmacon, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Irazem *Roemmers, Arg.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder; depression.

Irazol *Ashford, Philipp.*
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Allergic eye disorders; ocular congestion.

Irbec *Liconsa, Cz.; Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbenahyp *Genepharm, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbenidda *Pharmacodane, Denm.†; Centrafarm, Neth.†*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbenox *Sandoz, Thai.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irberan *Ranbaxy, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbesan *Rowex, Irl.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbesartan HCT *Sanofi-Aventis, Cz.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Irbest *Biochem, India.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbewin *Winthrop, S.Afr.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irbez *Emcure, India.*
Tegaserod (p. 1893·1).
Chronic idiopathic constipation; constipation-predominant irritable bowel syndrome.

Irbezyd Combi *Polpharma, Cz.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Irbosyd *Fahrenheit, Indon.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Ircal *Allergan, Austral.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry eyes.

Ircon *Kenwood, USA.*
Iron carbonyl (p. 2073·1).
Formerly contained ferrous fumarate.
Iron-deficiency anaemias.

Ircor *Hos & Ins, India.*
Iron sucrose (p. 2078·1).

Ircor-FA *Hos & Ins, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Ircos *Ashford, Philipp.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); hydrocortisone acetate (p. 1640·1).
Bacterial ear infections.

Irda *Nobel, Turk.*
Irbesartan (p. 1411·1).

Irebetan *KVZ, Ukr.*
Irbesartan (p. 1411·1).
Hypertension.

Ireito *Tsumura, Jpn.*
Magnolia bark; atractylodes lancea rhizome; alisma rhizome; polyporus sclerotium; citrus unshiu peel; atractylodes rhizome; poria sclerotium; cinnamon bark (p. 2479·2); ginger (p. 1844·1); jujube; liquorice (p. 1853·2).
Traditional Kampo medicine.

Iremax *Guardian, Indon.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Iremod *Simcere, China.*
Iguratimod (p. 71·1).
Rheumatoid arthritis.

Iremofar *Unipharma, Gr.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions.

Irenat *Sigmapharm, Austria; Bayer, Cz.; Bayer, Ger.; Bayer, Pol.†*
Sodium perchlorate (p. 2343·2).
Hyperthyroidism; adjunct in radionuclide brain scanning; thyroid block during radio-imaging of other organs.

Irenax *Sandoz, Arg.; Sandoz, Braz.; Sandoz, Thai.†*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irenor *Juste, Spain.*
Reboxetine mesilate (p. 447·1).
Depression.

Iresolamin *Leontik, Gr.*
Codergocrine mesilate (p. 389·2).

Iressa *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fr.; AstraZeneca, Ger.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, UK; AstraZeneca, USA†; AstraZeneca, Venez.*
Gefitinib (p. 800·2).
Non-small cell lung cancer.

Iret *Cosme, India.*
Isotretinoin (p. 1706·2).
Acne.

Iretensa *Fahrenheit, Indon.*
Irbesartan (p. 1411·1).
Hypertension.

Ireven *Pharmathen, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Irex *Micro, India.*
Syrup: Sodium feredetate (p. 2088·3).
Micro, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Irex-12 *Micro, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Irex-12 Tonic *Micro, India.*
Folic acid (p. 2063·1); iron choline citrate (p. 2060·2); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2).

Irex-TR *Micro, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Irfen *Mepha, Switz.; Mepha, Ukr.*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal, joint, and soft-tissue disorders; fever.

Irgaman *Teleflex, Ital.*
Triclosan (Irgasan DP 300) (p. 1773·2).
Skin disinfection.

Irgapan *Dexa, Indon.*
Phenylbutazone (p. 125·1).
Musculoskeletal and joint disorders.

Iricalcin *Vocate, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Iricam *US Pharmacia, Neth.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irican *Fresenius Kabi, Philipp.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Iricar *DHU, Rus.; DHU, Ukr.*
Cardiospermum halicacabum.
Homoeopathic preparation.

Iricil *Cantabria, Spain.†*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Iricil Plus *Cantabria, Spain.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Iridil *Montefarmaco, Ital.*
Hamamelis (p. 2523·3); chamomile (p. 2474·1); euphrasia (p. 2502·1); mallow (p. 2549·2).
Eye irritation.

Iridina *Ultra, Hung.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Iridina Due *Montefarmaco, Ital.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Iridina Light *Montefarmaco, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye irritation; eye disinfection.

Iridus *Sanofi-Aventis, Mex.*
Naftidrofuryl oxalate (p. 1443·3).
Peripheral vascular disorders.

Sanofi-Aventis, Venez.
Naftidrofuryl (p. 1443·3).
Cerebral and peripheral vascular disorders.

Iridux *Sanofi-Aventis, Braz.*
Naftidrofuryl oxalate (p. 1443·3).
Vascular disorders.

Iriflexin *Pharmathen, Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Irifone *Pharmathen, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Irifrin *Promed, Rus.*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation; iridocyclitis; diagnosis of eye disorders.

Irigal *Gobbi, Arg.*
⊗Neomycin sulfate (p. 330·1); hydrocortisone (p. 1640·1); lidocaine (p. 1988·1); boric acid (p. 2459·3); zinc oxide (p. 1729·1).
Wounds.

Irigan *Klar Sehen, India.*
Electrolytes (p. 1775·1).
Eye irrigation.

Irilens *Montefarmaco, Ital.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Irimist *Indoco, India.*
Borax (p. 2459·2); boric acid (p. 2459·3); hypromellose (p. 2189·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).

Irin *Biomedica, Gr.*
Hexetidine (p. 1755·1).
Oral hygiene.

Iriniozol *Rafarm, Gr.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Irino *American Taiwan, Thai.†*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinocam *Kocak, Turk.*
Irinotecan hydrochloride (p. 812·2).

Irinocan *Demo, Gr.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinoccord *Arrow, NZ.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinogen *Bioprofarma, Arg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinolibbs *Libbs, Braz.*
Irinotecan hydrochloride (p. 812·2).

Irinoll *Venus, Thai.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinomed *Medison, Israel.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer; small cell lung cancer; gastric cancer.

Irinomedac *Medac, Ger.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinosin *Teva, Belg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinosor *Ratiopharm, Denm.†*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinotas *Eurolab, S.Afr.*
Irinotecan hydrochloride (p. 812·2).

Irinotel *Dabur, India; Fresenius Kabi, Thai.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irinotesin *Actavis, Hong Kong; Actavis, Pol.; Actavis, Singapore; Sindan, Thai.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Cancernova, Ger.
Irinotecan (p. 812·2).
Colorectal cancer.

Irinoxin *Valeant, Cz.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Iris Med Complex *Dynamit, Austria.*
Apis mellifica (p. 2445·2); coffea (p. 2648·2); iris (p. 2534·3); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Iri-Sol *Ocumed, USA.*
Eye irrigation.

Irisol Plus *Indoco, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Iris-Plus *Doctor H, Rus.*
Iris versicolor (p. 2534·3); lycopodium clavatum (p. 2547·1); phosphorus; carbo vegetabilis (p. 2219·1).
Homoeopathic preparation.

Iristamina *Montefarmaco, Ital.*
⊗Thonzylamine hydrochloride (p. 642·1); naphazoline nitrate (p. 1669·3).
Conjunctivitis; eye irritation.

Iristan-V *Biostam (Βιοστατμ), Gr.*
Cinoxacin (p. 261·1).

Iristop *Biomedica, Gr.*
Miconazole nitrate (p. 589·1).
Fungal vaginal infections.

Iritec *Vianex (Βιανεξ), Gr.; Vianex, Neth.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Iriten *Veropharm, Rus.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irivisc *Indoco, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Irix *Sanofi-Aventis, Arg.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Irix Biotic *Sanofi-Aventis, Arg.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Eye infections with congestion.

Irix Clasico *Sanofi-Aventis, Arg.*
⊗Ephedrine (p. 1663·1); phenazone (p. 124·1).
Eye irritation; allergic conjunctivitis.

Irix Lagrimas *Sanofi-Aventis, Arg.*
⊗Macrogol 400 (p. 2547·3); hypromellose (p. 2189·2); glycerol (p. 2517·2).
Dry eyes; eye irritation.

Irix Solution Multiproposito *Sanofi-Aventis, Arg.*
Protein removal, wetting, and disinfecting solution for contact lenses.

Irizz *Probiomed, Mex.*
Alprazolam (p. 1035·2).
Anxiety.

Irkan *Almirall, Port.*
Irinotecan hydrochloride (p. 812·2).
No indics.

Irnocam *Reddy, Braz.; Reddy, India; Ferron, Indon.; Reddy, Malaysia; Reddy, Rus.; Reddy, Ukr.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Irobex *Radicura, India.*
Vitamin B substances (p. 2102·3); iron choline citrate (p. 2060·2); protein hydrolysate.

Irobon *Roddensers, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia; vitamin B supplement.

Irocafe *Finecure, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).

Irocid-Z *Admac, India.*
Iron carbonyl (p. 2073·1); vitamins; zinc sulfate (p. 2126·2).

Irocopar c C *Schmidgall, Austria.†*
Carbasalate calcium (p. 36·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Irocophan *Schmidgall, Austria.*
Carbasalate calcium (p. 36·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Irodate-FA *Invision, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

Irofact-SF *Medico, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Irofer *Forgo, India.*
Iron sucrose (p. 2078·1).

Irofol-AZ *Anglo-French Drugs, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Irofur *Cosmas, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Irolar *Stellar, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).

Iro-Life *Life Line, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1); vitamin C (p. 2110·3).

Life Line, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).

Iromax *Cruise, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Iromin *Schmidgall, Austria.*
Carbasalate calcium (p. 36·2).
Cold symptoms; pain; fever.

Iromin Vitamin C *Schmidgall, Austria.*
Carbasalate calcium (p. 36·2); calcium ascorbate (p. 2111·1).
Cold and influenza symptoms.

Iromin-Chinin-C *Schmidgall, Austria.†*
Carbasalate calcium (p. 36·2); quinine hydrochloride (p. 665·2); calcium ascorbate (p. 2111·1).
Cold symptoms; pain; fever.

Iromin-G *Mission Pharmacal, USA.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); calcium (p. 1783·1); vitamins.
Iron-deficiency anaemia.

Iromost *Arunabh, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1); vitamin C (p. 2110·3).

I-RON *Patar, Thai.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Iron-200 *Christo, Hong Kong.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Iron Beacons *Beacons, Singapore.*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Iron Complex *Integrative, USA.*
Ferrous succinate (p. 2062·1); vitamin B_{12} (p. 2107·2); chlorophyll (p. 2178·3); liver extract (p. 2444·1); vitamin C (p. 2110·3); folic acid (p. 2063·1).

Iron Max *Golden Glow, Austral.*
Ferrous fumarate (p. 2060·3); iron amino acid chelate (p. 2048·3); vitamin B substances (p. 2102·3).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron supplement for women.

Iron Melts *Douglas, Singapore.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Vitamin and iron supplement.

Iron Plus *Cenovis, Austral.*
Ferrous fumarate (p. 2060·3); vitamins.
Vitamin and iron supplement; tonic.

Iron 100 Plus *Cypress, USA.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement.

Irona *Zota, India.*
Folic acid (p. 2063·1); iron choline citrate (p. 2060·2); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2).

Ironac *Forgo, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).

Ironac-S *Forgo, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).

Irona-P3 *Zota, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Irona-Plus *Zota, India.*
Calcium (p. 1783·1); iron (p. 2073·1); colecalciferol (p. 2113·1).

Ironate *Help, Gr.*
Iron dextran (p. 2075·3).
Iron deficiency.

Chemo-Drugs, India.
Capsules: Copper sulfate (p. 2057·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); manganese sulfate (p. 2081·2); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Chemo-Drugs, India.
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Ironcrose *Target, Gr.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Irondex *Tocogino, Mex.*
Iron dextran (p. 2075·3).

Ironeed *Micro, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Ironfer *Uniao Quimica, Braz.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Ironfol *Alpharma, Mex.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Anaemias.

Iron-Gold *Indkus, India.*
Copper sulfate (p. 2057·2); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); manganese sulfate (p. 2081·2).

Ironifol *Radicura, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Radicura, India.
Oral liquid: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Ironifol-Z *Radicura, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Ironorm *Wallace Mfg Chem., UK.*
Capsules: Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Iron deficiency.

Wallace Mfg Chem., UK.
Oral drops: Ferrous sulfate (p. 2062·2).
Iron deficiency.

Wallace Mfg Chem., UK.
Syrup: Ferric ammonium citrate (p. 2060·1); vitamin B substances (p. 2102·3); minerals.
Iron deficiency.

Ironotel *Biochimico, Braz.*
Irinotecan (p. 812·2).

Irontona *Brauer, Austral.†*
Angelica (p. 2443·3); ascorbic acid (p. 2110·3); kola (p. 2648·2); ferrous sulfate (p. 2062·2); alfalfa (p. 2433·1); ginseng (p. 2513·3); urtica (p. 2639·3); aurum muriaticum (p. 2521·1); calcarea phosphorica; ferrum metallicum (p. 2073·1); ferrum phosphoricum (p. 2077·1); hypericum perforatum (p. 449·1); kali phosphoricum (p. 1790·3); magnesia phosphorica; phosphoricum acidum (p. 2589·1).
Tonic.

Ironup *Grandix, India.*
Iron carbonyl (p. 2073·1); cobamamide (p. 2107·2); folic acid (p. 2063·1); pyridoxine (p. 2105·3); zinc methionine sulfate.

Ironyl *Guardian, Indon.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Iropect pastilles pour les bronches *Iromedica, Switz.*
Codeine phosphate (p. 40·2).
Cough.

Iroplex
Note: this name may be used for preparations of different composition.
Wellhealth, Philipp.
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia.

Irorange *Daniel Pasteur, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Irored *Dexter, India.*
Sodium feredetate (p. 2088·3).

Irosoft *Varun, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

Irosol *Stadmed, India.*
Oral drops: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Stadmed, India.
Oral suspension: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3).

Irospan *Fielding, USA.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Irossgold *Yash, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin E acetate (p. 2119·2); zinc (p. 2126·1); sodium selenite (p. 2087·1).

Yash, India.
Suspension: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Irosym *Symbiosis, India.*
Vitamins; minerals.

Irotel *Intel, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Irotussin *Iromedica, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Irovel *Sun, India.*
Irbesartan (p. 1411·1).
Hypertension.

Irovel-H *Sun, India.*
⊗Hydrochlorothiazide (p. 1403·2); irbesartan (p. 1411·1).

Irovista *Alna, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Iroviton Multivitamin *Schmidgall, Austria.*
Vitamins; hesperidin (p. 2505·2).

Iroviton Vitamin C *Schmidgall, Austria.*
Sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Irozys *Zytras, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Irpax *Anpharm, Pol.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension.

Irprestan *Actavis, Hung.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irprestan HCT *Actavis, Hung.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Irradial *Ivax, Arg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Irribow *Astellas, Thai.*
Ramosetron hydrochloride (p. 1881·3).
Diarrhoea-predominant irritable bowel syndrome in men.

Irriclens *Convatec, UK·*
Sodium chloride (p. 1795·1).
Wound cleansing and irrigation.

Irricutan *Biosintex, Arg.*
Calamine (p. 1697·2); diphenhydramine (p. 626·1).
Skin irritation.

Irrigasol *Claris, India.*
Electrolytes (p. 1775·1).

Irrigor *Andromaco, Chile.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Irripod *Pharmachem, UK.*
Sodium chloride (p. 1795·1).
Irrigation and cleansing of wounds and burns; eye irrigation.

Irrisol *Baxter, Neth.*
Chlorhexidine gluconate (p. 1743·3).
Catheter disinfection.

Irritos *Faes, Spain.†*
Phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Irrodan *Nikolakopoulos (Νικολακοπουλος), Gr.†; Biomedica, Hong Kong; Biomedica, Ital.†; Biomedica, Thai.†*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

IRS 19 *Abbott, Ukr.*
Lysates of *Streptococcus pneumoniae* type I, II, III, V, VIII, XII; *Haemophilus influenzae* type B; *Klebsiella pneumoniae* ssp. pneumoniae; *Staphylococcus aureus*; *Acinetobacter calcoaceticus* type baumanii; *Moraxella catarrhalis*; *Neisseria subflava types* flava; *Neisseria subflava types* perflava; *Streptococcus pyogenes group A; Streptococcus dysgalactiae group C; Enterococcus faecium (p. 2596·3); Enterococcus faecalis (p. 2596·3); Streptococcus group A.*
Respiratory-tract infections.

Solvay, Rus.
Lysates of *Streptococcus pneumoniae*; *Haemophilus influenzae* type B; *Klebsiella pneumoniae*; *Staphylococcus aureus*; *Acinetobacter calcoaceticus*; *Moraxella catarrhalis*; *Neisseria subflava*; Streptococcus groups A, C, G; *Enterococcus faecium* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).
Respiratory-tract infections.

Solvay, Pol.†
Lysate of *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Streptococcus dysgalactiae*; *Enterococcus faecium* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3); *Streptococcus* Group G; *Staphylococcus aureus*; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Neisseria flava*; *Neisseria perflava*; *Klebsiella pneumoniae*; *Acinetobacter calcoaceticus baumanni*.
Respiratory-tract infections.

Irsalico *Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Irtan
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Ger.; Allergan, Mex.
Nedocromil sodium (p. 1216·2).
Allergic conjunctivitis; allergic rhinitis.

Ikapharmindo, Indon.
Irbesartan (p. 1411·1).
Hypertension.

Irtan Plus *Ikapharmindo, Indon.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Irtopan *Biotech, Venez.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders; aid in gastrointestinal investigations.

Irtra *Shionogi, Jpn.*
⊗Irbesartan (p. 1411·1); trichlormethiazide (p. 1519·3).
Hypertension.

Irum *Daffohils, India.*
Capsules: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); ascorbic acid (p. 2110·3).

Daffohils, India.
Syrup: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

Irumed *Belupo, Rus.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Irunine *Veropharm, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Irus *Arvincare, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Iruxol *Abbott, Arg.; Abbott, Braz.; Smith & Nephew, Fin.†; Smith & Nephew, Ital.; Pliva, Rus.†*
⊗Collagenase (p. 2484·1); chloramphenicol (p. 257·1).
Burns; ulcers; wounds; skin infections.

Abbott, Venez.
⊗Collagenase (p. 2484·1).
Ulcers; wounds.

Iruxol Mono *Smith & Nephew, Belg.; Abbott, Braz.; Smith & Nephew, Gr.; Smith & Nephew, Hong Kong†; Smith & Nephew, Switz.*
⊗Collagenase (p. 2484·1).
Ulcers; wounds; burns; skin healing.

Smith & Nephew, Cz.; Smith & Nephew, Fin.; Smith & Nephew, Hung.†; Smith & Nephew, Irl.; Smith & Nephew, Malaysia; Smith & Nephew, S.Afr.; Smith & Nephew, Spain.
⊗Collagenase (p. 2484·1); protease (p. 2598·1).
Burns; wounds; ulcers; debridement in skin disorders.

Iruxol N *Smith & Nephew, Ger.†*
Enzymes from *Clostridium histolyticum* (proteases).
Skin ulcers and wounds.

Iruxol Neo *Smith & Nephew, Spain.*
⊗Collagenase (p. 2484·1); neomycin sulfate (p. 330·1).
Burns; wounds; ulcers.

Iruxolum mono *Nordmark, Austria.*
Enzymes from *Clostridium histolyticum.*
Necrotic ulcers; wounds.

Iruzid *Belupo, Rus.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Irvask *Kalbe, Indon.*
Irbesartan (p. 1411·1).
Hypertension.

Irvell *Novell, Indon.*
Irbesartan (p. 1411·1).
Hypertension.

Irven *Help, Gr.*
Irbesartan (p. 1411·1).

Irvira *TNP, Thai.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Irwax *Ashford, Philipp.*
Docusate sodium (p. 1836·2).
Ear wax removal.

IS 5 Mono *Ratiopharm, Ger.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Isa Flex *ISA, Arg.*
Vitamin D (p. 2112·3); magnesium (p. 1786·3); calcium (p. 1783·1).
Dietary supplement; tonic.

Isac *Systopic, India.*
Isotretinoin (p. 1706·2).
Acne.

Isaflavon *ISA, Arg.*
Calcium (p. 1783·1); soya isoflavones (p. 2620·3).
Menopausal disorders.

Isagesic *Doctors, Philipp.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Isairon *Marvecs, Ital.*
Chondroitin sulfate–iron complex (p. 2055·3).
Iron-deficiency anaemias; iron deficiency.

Isalax Fibras *ISA, Arg.*
Vitamin C (p. 2110·3); ispaghula (p. 1849·1).
Constipation.

Isalok *Farmaprojects, Denm.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; heart failure.

Isame *Medochemie, Cz.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Isangina *UCB, Fin.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isaprandil *Farmakopea, Ital.*
Metoclopramide hydrochloride (p. 1862·2).
Gastric hyperacidity; nausea.

Isarin *Zenon, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Isaspin *SSK, Turk.*
Aspirin (p. 22·2).

Isatol *Bausch & Lomb, USA.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Isavir *Pisa, Mex.*
Aciclovir sodium (p. 964·1).
Herpesvirus infections; cytomegalovirus infections.

Isbis *Zydus, India.*
Ispaghula (p. 1849·1).

Iscador *Weleda, Austria; Weleda, Ger.; Weleda, Switz.*
Mistletoe (p. 2560·2) from apple trees, pine trees, or oak trees.
Neoplasms.

Iscador c Arg *Weleda, Ger.*
Mistletoe (p. 2560·2) from apple trees or oak trees; silver carbonate (p. 2615·1).
Neoplasms.

Iscador c Cu *Weleda, Ger.*
Mistletoe (p. 2560·2) from apple trees or oak trees; malachite.
Neoplasms.

Iscador c Hg *Weleda, Ger.*
Mistletoe (p. 2560·2) from apple trees, elm trees, oak trees, or pine trees; mercury (p. 2555·3).
Neoplasms.

Iscept *Grandix, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1) or metformin hydrochloride (p. 489·1).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Iscept-P *Grandix, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Ischemol A *Famila, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3); chlorphenamine maleate (p. 620·3).
Eye disorders.

Iscom *Comed, India.*
Isoxsuprine (p. 2535·2).
Premature labour.

Iscover *BMS, Arg.; BMS, Austral.; BMS, Braz.; BMS, Cz.; BMS, Denm.†; BMS, Ger.; BMS, Gr.; BMS, Irl.; BMS, Mex.; BMS, Neth.; BMS, Pol.; BMS, Spain.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis; acute coronary syndrome; thromboembolism prophylaxis; unstable angina; myocardial infarction.

Iscucin *Wala, Ger.*
Mistletoe (p. 2560·2) from apple trees, fir trees, linden trees, pine trees or poplar trees.
Neoplasms; inflammatory disorders.

Isdiben *Isdin, Chile; Isdin, Port.; Isdin, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Isdil *East West, India.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Isdinium *Isdin, Spain.*
⊗Hydrocortisone buteprate (p. 1640·1).
Haemorrhoids.

Iselpin *Wyeth, Philipp.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Isenia *Ophtalkener, Mex.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Isenia-Dex *Ophtalkener, Mex.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

I-Sense *Akorn, USA.*
Vitamins.

Isentress *MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, UK; MSD, Ukr.; Merck, USA.*
Raltegravir potassium (p. 1009·3).
HIV infection.

Isepacin *Schering-Plough, Hong Kong.†*
Isepamicin sulfate (p. 311·2).
Bacterial infections.

Isepacine *Schering-Plough, Turk.*
Isepamicin sulfate (p. 311·2).
Bacterial infections.

Isephca S *Iso, Ger.†*
Thyme (p. 2630·2).
Cough.

Isest *Ester, India.*
Iron sucrose (p. 2078·1).

Iset *Casasco, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Isib *Ashbourne, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Isicom *Desitin, Cz.; Desitin, Ger.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Isiflu *Medifarm, Venez.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Isiflu V *Berna, Ital.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Isiflu Zonale *Scott-Cassara, Arg.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Isifluor *Rottapharm, Ital.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Isigrip Zonale *Kedrion, Ital.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Isiko-Plus *Sienna, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Isilax *Cifarma, Braz.*
Bisacodyl (p. 1821·1).
Constipation.

Isilung *Nycomed, Belg.†*
Eprazinone hydrochloride (p. 1664·3).
Respiratory-tract disorders.

Isimig *Zambon, Fr.*
Frovatriptan succinate (p. 676·2).
Migraine.

ISINO *Sifauman, Port.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Isipredon *Heremco, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Isis
Note: this name may be used for preparations of different composition.
Centrum, Spain.
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Investi, Arg.
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Isis Fe *Investi, Arg.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, iron polymaltose (p. 2077·2).
Combined oral contraceptive.

I-Site *Sun, India.*
Vitamins; minerals; glutathione (p. 1555·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3).

Isiven *Scott-Cassara, Arg.; Interko, Turk.†*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; passive immunisation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Iskédyl *Pierre Fabre, Fr.*
Dihydroergocristine mesilate (p. 390·1); raubasine (p. 1485·1).
Mental function disorders of the elderly; vascular eye disorders.

Iskemil *Ache, Braz.*
Dihydroergocristine mesilate (p. 390·1).
Impaired mental function.

Isketam *Ache, Braz.*
Piracetam (p. 393·3); dihydroergocristine mesilate (p. 390·1).
Impaired mental function.

Iski *Stadmed, India.*
Diltiazem (p. 1359·2).
Angina pectoris.

Iskidrop *MDM, Ital.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Iskimil *Royal, Chile.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Isla-Mint *Engelhard, Ukr.*
Iceland moss (p. 2531·2).
Upper respiratory-tract disorders.

Isla-Moos *Engelhard, Ukr.*
Iceland moss (p. 2531·2).
Upper respiratory-tract disorders.

Islet *Cruise, India.*
Vitamins; minerals.

Isloglib *Craveri, Arg.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Islopir *Craveri, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Islotin *Craveri, Arg.*
Metformin (p. 489·1) or metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ismacrol *IPI, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Ismanton *Juta, Ger.†; Q-Pharm, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Ismelin *Novartis, Austral.†; IFET (ΙΦΕΤ), Gr.; Amdipharm, UK.†*
Guanethidine monosulfate (p. 1395·2).
Hypertensive crisis; hypertension; regional nerve blocks.

Ismexin *Ratiopharm, Fin.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ismigen *Lallemand, Ukr.*
Lysates of *Streptococcus pneumoniae; Haemophilus influenzae* type B; *Klebsiella pneumoniae; Staphylococcus aureus; Moraxella catarrhalis; Streptococcus pyogenes* group A; *Streptococcus viridans; Klebsiella ozaenae.*
Respiratory-tract infections.

Merck Serono, Arg.; Zambon, Ital.
Lysates of: *Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Klebsiella pneumoniae; Klebsiella ozaenae; Haemophilus influenzae; Moraxella catarrhalis; Streptococcus pneumoniae.*
Respiratory-tract infections.

Teva, Mex.
Lysates of *Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Klebsiella pneumoniae; Klebsiella ozaenae; Haemophilus influenzae; Moraxella catarrhalis; Streptococcus pneumoniae.*
Respiratory-tract infections.

Ismin *Aliud, Cz.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Ismo *HLB, Chile; Riemser, Ger.; Piramal, India; Adienne, Ital.; Roche, Malaysia; Riemser, Norw.; Healthcare Logistics, NZ; Pharmakern, Port.; Pharmaco, S.Afr.; Roche, Singapore; Riemser, Swed.; Riemser, Thai.; Roche, UK; Reddy, USA; Roche, Venez.*
Isosorbide mononitrate (p. 1413·3).
Heart failure; angina pectoris; myocardial infarction; ischaemic heart disease; pulmonary hypertension.

Ismorin *Piramal, India.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction.

Ismotic *Alcon, USA.†*
⊗Isosorbide (p. 1412·2).
Raised intra-ocular pressure.

Ismox *Riemser, Fin.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Iso *Lacer, Spain.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Iso Mack *Pfizer, Austria†; Mack, China; Mack, Cz.†; Pfizer, Switz.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; pulmonary hypertension; myocardial infarction; pulmonary oedema.

Isoacne *Pierre Fabre, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Isoact *Active, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Iso-Aret *Shalaks, India.*
Isotretinoin (p. 1706·2).
Acne.

ISO-Augentropfen C *Iso, Ger.*
Conium (p. 2524·3); euphrasia (p. 2502·1); hamamelis (p. 2523·3); populus; thuja (p. 2629·3).
Homoeopathic preparation.

Iso-B *Tyson, USA.*
Vitamins.

Isobar
Note: this name may be used for preparations of different composition.
Chiesi, Fr.
⊗Methyclothiazide (p. 1430·3); triamterene (p. 1518·3).
Hypertension.

Jean-Marie, Philipp.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Isobenil *Westward, Philipp.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Isobest *Glenmark, India.*
Isotretinoin (p. 1706·2).
Acne.

Iso-Betadine *Meda, Belg.*
Povidone-iodine (p. 1767·1).
Disinfection of the skin and mucous membranes; wounds; burns; ulcers; skin infections; vulvovaginal infections; mouth and throat infections.

Isobide *Kowa, Jpn; Patar, Thai.*
Isosorbide dinitrate (p. 1412·2).
Glaucoma; renal calculi; Ménière's disease; raised intracranial pressure; angina pectoris; heart failure.

Isobinate *General Drugs, Thai.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Isobloc *Casasco, Arg.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Isobloc D *Casasco, Arg.*
⊗Carvedilol (p. 1333·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Isobranch *Bieffe, Ital.*
L-Isoleucine (p. 2078·2); L-leucine (p. 2079·1); L-valine (p. 2098·3).
Hepatic encephalopathy; post-trauma disorders.

Isocaine *Novocol, Canad.; Novocol, Israel; Novocol, USA.*
Mepivacaine hydrochloride (p. 1992·2).
Corbadrine (p. 2486·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

IsoCal
Note: this name may be used for preparations of different composition.
Ethica, Indon.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); glycine (p. 2071·2).
Nutritional supplement for healthy bones.

Isocal *Mead Johnson, Israel; Mead Johnson, Philipp.; Novartis Nutrition, Singapore.*
Preparation for enteral nutrition.

Nestle, Thai.; Mead Johnson Nutritionals, USA.
A range of lactose-free preparations for enteral nutrition.

Nestle, Hong Kong.
A range of preparations for enteral nutrition.

Isocar *Offenbach, Mex.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Isocard
Note: this name may be used for preparations of different composition.
Gerda, Fr.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Isocaren *Pharmanel, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Isocef *Recordati, Ital.*
Ceftibuten (p. 252·2).
Bacterial infections.

IsoCell *Antonetto, Ital.*
Vitamins; minerals; plant extracts.

Isochinol *Vifor, Switz.*
Quinisocaine hydrochloride (p. 1996·1).
Skin disorders; wounds; burns; haemorrhoids.

Isochol *Zentiva, Cz.*
Hymecromone (p. 2530·2).
Biliary-tract disorders.

Isochron *Forest Pharmaceuticals, USA.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Isocillin *Sanofi-Aventis, Ger.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Isoclar *Boniscontro & Gazzone, Ital.†*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Isocolan *Giuliani, Ital.; Sanofi-Aventis, Switz.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation; colonic lavage.

Isocomb *Akrikhin, Rus.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isocor *Merck, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isocort *Perrigo, Israel.*
⊗Isoconazole nitrate (p. 583·2); diflucortolone valerate (p. 1634·1).
Fungal skin infections.

IsoCrom *Pari, Ger.†*
Sodium cromoglicate (p. 1225·3).
Asthma.

Isocross *Pharmacross, Chile.*
Isotretinoin (p. 1706·2).
Acne.

Isocural *Pierre Fabre, Belg.*
Isotretinoin (p. 1706·2).
Acne.

Isodeksol *Ulagay, Turk.†*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Isodem *Solitaire, India.*
Zolpidem (p. 1116·2).
Insomnia.

Isoderm
Note: this name may be used for preparations of different composition.
Alkapharm, Singapore.
Skin and scalp cleanser.
Dermapharm, Ger.
Isotretinoin (p. 1706·2).
Acne.
Orva, Turk.
Bufexamac (p. 30·2).
Skin disorders.

Isodermal *Kleva, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Isodex
Note: this name may be used for preparations of different composition.
Teva, Hung.
Glucose monohydrate (p. 2069·1).

Isodexam *Sensomed, Philipp.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Isodexid *Medi-Rx, Philipp.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isodilan *Klonal, Arg.*
Isoxsuprine (p. 2535·2).

Isodine *Mahakam Beta, Indon.; Mundipharma, Indon.; Meiji, Jpn; Boehringer Ingelheim Promeco, Mex.; Meda, Port.†; Meiji, Thai.*
Povidone-iodine (p. 1767·1).
Mouth and throat infections; skin, mucous membrane, and instrument disinfection; vaginitis; burns; wounds; skin infections; ulcers; oral hygiene; vulvovaginal disinfection.

Isodinitrat *Farmak, Ukr.†*
Isosorbide dinitrate (p. 1412·2).
Myocardial infarction; left ventricular failure; angina pectoris.

Isodiur *Italfarmaco, Spain.*
⊗Torasemide sodium (p. 1516·3).
Oedema; hypertension.

Isodo Tbal *Silanes, Mex.*
Isoniazid (p. 311·2).
Tuberculosis.

Isodol *Magis, Ital.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Isodonna *Rottapharm, Spain.†*
Soya bean (p. 2092·3).
Menopausal disorders.

Isodril *Merck Medication Familiale, Fr.*
Chlorhexidine gluconate (p. 1743·3); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Isodrink *Volchem, Ital.*
Isotonic rehydration solution.

Isodur *Sandoz, Denm.; AstraZeneca, Swed.†; Galen, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Iso-Eremfat *Riemser, Ger.; Fatol, Rus.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Isoface *Valeant, Braz.†; Valeant, Mex.; Vivax Gynopharm, Venez.*
Isotretinoin (p. 1706·2).
Acne; seborrhoea; rosacea.

Isofact *Medico, India.*
Isotretinoin (p. 1706·2).
Acne.

Isofebril Vitamine C *Ratiopharm, Fr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Isofed *Macleods, India.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis; cold and influenza symptoms.

Isofem *Meprofarm, Indon.†*
Isoflavone (p. 2620·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1); calcium (p. 1783·1); zinc (p. 2126·1).
Menopausal disorders; osteoporosis.

Isofenal *SoSe, Ital.*
Ketoprofen (p. 79·1).
Pain; inflammation.

Isofer *Zenacts, India.*
Cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Isoflav *Raptakos, India; Raptakos, Malaysia; Raptakos, Singapore.*
Soya isoflavones (p. 2620·3).
Dietary supplement.

Isoflavin *Biolina, Turk.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Isoflavine *Herbarium, Braz.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Isoflon *Proel, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Isoflu (Combipack) *Marketlink, Philipp.*
3 Tablets, paracetamol (p. 115·1); 6 tablets, inosine pranobex (p. 988·3).
Pain; fever; viral infections.

Isofludem *Dem, Turk.*
Isoflurane (p. 1903·2).

Isofor *Safeline, S.Afr.*
Isoflurane (p. 1903·2).
General anaesthesia.

Isoforine *Cristalia, Braz.*
Isoflurane (p. 1903·2).
General anaesthesia.

Isofra *Bouchara, Rus.; Bouchara-Recordati, Ukr.*
Framycetin sulfate (p. 301·2).
Bacterial infections of the upper respiratory tract.

Isofredil *Vocate, Gr.*
Amisulpride (p. 1036·3).

I-Soft *Noreva, Fr.*
Cream: Ictasol (p. 1706·1); ammonium lactate (p. 1694·3).
Hyperkeratotic skin disorders.

Isoftalmol *IQFA, Mex.†*
Sulfacetamide (p. 361·1).

Isofundin *Braun, Port.; Braun, Spain.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Isofundine *Braun, Fr.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1); sodium acetate (p. 1781·1); malic acid (p. 2549·2).

Isogaíne *Clarben, Port.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Isogaine *Clarben, Spain.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

IsoGalen *Galen, Ger.*
Isotretinoin (p. 1706·2).
Acne.

Isogel
Note: this name may be used for preparations of different composition.
GSK, India; GSK, NZ†; Potter's, UK.
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome; diarrhoea; colostomy management.
Lalema, Canad.†
Isopropyl alcohol (p. 1758·3).

Isogen
Note: this name may be used for preparations of different composition.
Perrigo, Israel.
Isoconazole nitrate (p. 583·2).
Fungal skin infections.

Isogeril *Gerolimatos (Γερολυματος), Gr.*
Isotretinoin (p. 1706·2).
Acne.

Isoglaucon *Agepha, Austria; Alcon, Ger.; Alcon, Ital.; Alcon Cusi, Spain.†*
Clonidine hydrochloride (p. 1339·1).
Glaucoma.

Isogrow *Bieffe, Ital.*
Amino acids.
Parenteral nutrition in neonates.

Isogutt *Winzer, Ger.†*
Eye drops: Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Ocular burns.

Isogutt akut *Winzer, Ger.*
Sodium chloride (p. 1795·1).
Eye injuries and burns.

Isogyn
Note: this name may be used for preparations of different composition.
Finderm, Ital.
Isoconazole nitrate (p. 583·2).
Fungal vulvovaginal infections.

Isohes *Braun, Spain.*
⊗Pentastarch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion.
Eczacibasi-Baxter, Turk.
⊗Pentastarch (p. 1146·1) in sodium chloride.
Plasma volume expansion.

Isohexal *Hexal, Austral.†*
Isotretinoin (p. 1706·2).
Acne.

Isoket *Sidus, Arg.; UCB, Austria; UCB, China; UCB, Cz.; Sanol, Ger.; UCB, Ger.; GSK, Hong Kong; Pharos, Indon.†; Schwarz, Irl.; GSK, Israel; GSK, Malaysia; Abbott, Mex.; GSK, Philipp.; Schwarz, Pol.†; Neo-Farmaceutica, Port.; Schwarz, Rus.; UCB, Rus.; AHN, S.Afr.; GSK, Singapore†; UCB, Switz.; Schwarz, Thai.; UCB, UK; UCB, Ukr.; Farma, Venez.*
Isosorbide dinitrate (p. 1412·2).
Myocardial infarction; heart failure; angina pectoris; coronary spasm during angiography; prolongation of ischaemia tolerance during angioplasty; coronary circulatory disorders; pulmonary hypertension; cor pulmonale.

Isokin *Warner, India.*
Isoniazid (p. 311·2).
Tuberculosis.

Isokin-300 *Pfizer, India.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isokin-T Forte *Pfizer, India.*
Isoniazid (p. 311·2); thioacetazone (p. 377·2).
Tuberculosis.

Isokoxi *Shreya, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Isola Capsicum N *IVF, Switz.*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain; neuralgia.

Isola Capsicum N Plus *IVF, Switz.*
Capsaicin (p. 35·1); sweet birch oil (p. 92·1).
Musculoskeletal and joint pain; neuralgia.

Isolan
Note: this name may be used for preparations of different composition.
Galagen, USA.
Lactose-free, gluten-free preparation for enteral nutrition.

Isolife *Garden House, Arg.*
Soya isoflavones (p. 2620·3).

Isolin *Samarth, India.*
⊗Isoprenaline sulfate (p. 1411·3).
Cardiac arrest; bradycardia; asystole.

Isolone *Medilife, Philipp.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Isolong *CTI, Israel†; CTS, Rus.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Isolyte
Note: this name may be used for preparations of different composition.
Braun, Hong Kong†; Baxter, Ital.; Eczacibasi-Baxter, Turk.; McGaw, USA.
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.
Braun, Canad.
A range of electrolyte infusions with or without glucose (p. 1775·1).
Fluid and electrolyte disorders.
Fresenius Kabi, Cz.
Sodium acetate (p. 1781·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Fluid and electrolyte disorders; metabolic acidosis.

Isomack *Zuoz, Venez.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction; heart failure; pulmonary oedema.

Isomax *Prodotti, Braz.†*
Isoconazole nitrate (p. 583·2).
Fungal skin infections.

Isomel *Dexcel, Irl.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Isomenopace *Vitabiotics, Indon.*
Vitamins; minerals; soya isoflavones (p. 2620·3).
Menopausal disorders.

Isomeran *Servier, Gr.*
⊗Dexfenfluramine hydrochloride (p. 2320·3).

Isomerine N *Schering-Plough, Arg.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1); guaifenesin (p. 1666·2).
Cough; rhinitis.

Isomet *M & H, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Isomicot *Prieto, Arg.*
Isoconazole (p. 583·2).
Fungal skin and vaginal infections.

Isomide
Note: this name may be used for preparations of different composition.
Zee, India.
Pyrazinamide (p. 345·2).
Tuberculosis.

Isomil *Abbott, Arg.; Abbott, Chile; Abbott, Cz.; Abbott, Malaysia; Abbott, Thai.; Ross, USA; Abbott, Venez.*
Lactose-free soy protein infant feed.
Lactose intolerance; diarrhoea; galactosaemia; cows' milk intolerance.
Abbott, Austral.
Milk substitute.
Milk intolerance; galactosaemia; lactose intolerance.
Abbott, Braz.
Soya based milk substitute.
Enteral nutrition.
Abbott, Canad.; Abbott, India; Abbott, Indon.; Abbott, Ital.; Abbott, Philipp.; Abbott, Pol.; Abbott, S.Afr.†; Abbott, Singapore.
Infant feed.
Lactose intolerance; cows' milk intolerance; gluten intolerance; diarrhoea; galactosaemia.
Abbott, China.
Lactose-free infant feed.
Cows' milk intolerance; lactose intolerance; diarrhoea.
Abbott, Mex.; Abbott Nutrition, UK·†
Lactose-free preparation for special diets.
Lactase deficiency; milk and lactose intolerance.

Isomil DF *Ross, USA.*
Lactose-free soy protein infant feed with fibre.
Diarrhoea.

Isomin *Cipla, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isomina *Megat, Venez.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; gastritis; peptic ulcer; heartburn; Zollinger-Ellison syndrome.

Isomol *Marpha, Ger.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Isomon *Riemser, Gr.; Roche, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Isomonat *Cheplapharm, Austria.*
Isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease; pulmonary hypertension; heart failure.

Isomonit *Sandoz, Austral.; Sandoz, China; Hexal, Ger.†; Sandoz, Indon.; Rowex, Irl.; Sandoz, Philipp.; Hexal, Pol.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; ischaemic heart disease; myocardial infarction; heart failure.

Isomytal *Shinyaku, Jpn.*
Amobarbital (p. 1037·2).
Anxiety; insomnia.

IsonaRif *Versapharm, USA.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Isonate *Shou Chan, Philipp.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isonefrine *Tubilux, Ital.*
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

Isonep *Sensomed, Philipp.*
Neomycin (p. 329·3); polymyxin B sulfate (p. 342·3).
Eye infections.

Isonep H *Sensomed, Philipp.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye disorders; eye infections.

Isonex *Pfizer, India.*
Isoniazid (p. 311·2).
Tuberculosis.

Isoniac *Klonal, Arg.*
Isoniazid (p. 311·2).
Tuberculosis.

Isoniaton *Sanval, Braz.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Isonicid *PannonPharma, Hung.*
Isoniazid (p. 311·2).
Tuberculosis.

Isonid
Note: this name may be used for preparations of different composition.
Concept, Philipp.
Isoniazid (p. 311·2).
Tuberculosis.

Isonorm *Lupin, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isontyn *Abbott, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Isopan *BMW, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger Ellison syndrome.

Isopask *Farmasintez, Rus.*
Isoniazid (p. 311·2); sodium aminosalicylate (p. 215·2).

Isopelet *Zentiva, Cz.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Isopen *Siam Bheasach, Thai.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Isoplasmal G *Braun, Spain.*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Isoplex *IS Pharma, UK.*
⊗Succinylated gelatin (p. 1154·1); electrolytes (p. 1775·1).
Hypovolaemic shock.

Isoporum *Diba, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Isopreg *Global, India.*
Isoxsuprine (p. 2535·2).
Premature labour.

Isoprim *Tolmann, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isoprinosine *Sanofi-Aventis, Belg.; Andromaco, Chile; Ewopharma, Cz.; Sanofi-Aventis, Fr.; Riemser, Ger.†; Unipharma, Gr.; Ewopharma, Hung.; Medifarma, Indon.; Pediatrica, Indon.; Newport, Irl.; Armstrong, Mex.; Newport, Philipp.; Teva, Rus.; Teva, Ukr.*
Inosine pranobex (p. 988·3).
Viral infections; immunodeficiency; subacute sclerosing leucoencephalitis.

Isoprodian *Fatol, Austria.†*
Isoniazid (p. 311·2); protionamide (p. 345·1); dapsone (p. 281·2).
Mycobacterial infections including leprosy.

Isoprotil *Azevedos, Port.*
Isotretinoin (p. 1706·2).
Acne.

Isoproxal *Lazar, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Isoptin *Abbott, Austral.; Abbott, Austria; Abbott, Canad.; Abbott, China; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Vianex (Βιανέξ), Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, USA.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; arrhythmias; angina pectoris; myocardial infarction; heart failure; coronary spasm; hypertrophic cardiomyopathy.

Isoptin plus *Abbott, Ger.*
⊗Verapamil hydrochloride (p. 1522·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Isoptina *Abbott, Chile.*
Verapamil (p. 1522·1).
Angina pectoris; hypertension.

Isoptine *Abbott, Belg.; Abbott, Fr.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Isoptino *Abbott, Arg.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Isopto Alkaline *Alcon, Fin.; Alcon, Irl.†; Alcon, UK.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Isopto B 12 *M4 Pharma, Spain.*
Cyanocobalamin (p. 2107·2).
Corneal damage.

Isopto Carpina *Alcon, Arg.; Alcon Cusi, Spain.*
Pilocarpine hydrochloride (p. 2010·3).
Ocular hypertension; glaucoma; reversal of mydriasis.

Isopto Carpine *Alcon, Austral.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Fin; Alcon, Gr.; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Norw.†; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore†; Alcon, Thai.; Alcon, USA.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension; production of miosis; cholinergic; production of mydriasis; raised intra-ocular pressure; reversal of mydriasis.

Isopto Cetamide *Alcon, USA.†*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Isopto Cetapred *Alcon, Braz.; Alcon, Gr.; Alcon, Mex.; Alcon, Philipp.†*
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Infected eye disorders; inflammatory eye disorders.

Isopto Dex *Alcon, Ger.*
⊗Dexamethasone (p. 1630·3).
Eye disorders.

Isopto Fenicol *Alcon, Arg.; Alcon, Hong Kong†; Alcon, Singapore.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Isopto Flucon *Alcon Cusi, Spain.*
⊗Fluorometholone (p. 1637·2).
Eye disorders.

Isopto Karbakolin *Alcon, Swed.†*
Carbachol (p. 2005·2).
Glaucoma.

Isopto Max *Alcon, Ger.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Isopto Maxidex *Alcon, Arg.; Alcon, Norw.; Alcon, Swed.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Isopto Maxitrol *Alcon, Gr.*
⊗Dexamethasone (p. 1630·3); polymyxin B (p. 342·3); neomycin sulfate (p. 330·1).
Inflammation and allergy of the eye.

Isopto Plain *Alcon, Fin.; Alcon, Irl.†; Alcon, Swed.; Alcon, UK; Alcon, USA.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Isopto Tears *Alcon, Belg.; Alcon, Canad.; Alcon, Hong Kong; Alcon, Switz.; Alcon, Thai.†; Alcon, USA.*
Hypromellose (p. 2189·2).
Dry eyes; keratitis; keratoconjunctivitis sicca.

Isoptomax *Alcon, Arg.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Isopuramin *Bieffe, Ital.*
A range of amino-acid infusions.
Parenteral nutrition.

Iso-Puren *Actavis, Ger.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Isoradin *YSP, Malaysia.*
⊗Isoconazole nitrate (p. 583·2); diflucortolone valerate (p. 1634·1).
Fungal skin infections with inflammation.

Isoram *Bieffe, Ital.*
L-Arginine (p. 2049·1); L-isoleucine (p. 2078·2); L-leucine (p. 2079·1); L-valine (p. 2098·3).
Hepatic encephalopathy; post-trauma disorders.

Isoran *Biochimico, Braz.*
Isoflurane (p. 1903·2).

Isorane *Piramal, India.*
Isoflurane (p. 1903·2).

Isorat *Munir, Turk.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isorbid *Pharos, Indon.; Armstrong, Mex.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction; cor pulmonale.

Isordil *Wyeth, Arg.; Aspen, Austral.; Sigma, Braz.; Wyeth, India; Sunthi Sepuri, Indon.†; Wyeth, Indon.†; Teofarma, Neth.; Wyeth, Philipp.; Aspen, S.Afr.; Wyeth-Ayerst, Thai.†; Fako, Turk.; Valeant, USA.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; ischaemic heart disease.

Isore *Ashford, Philipp.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Isorel *Novipharm, Austria.*
Mistletoe (p. 2560·2) from fir trees, apple trees or pine trees.
Malignant neoplasms.

Isorem *Remedica, Hong Kong; Remedica, Thai.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Isoren *Bieffe, Ital.*
Amino acids.
Parenteral nutrition in renal failure.

Isoret *BMW, India.*
Isotretinoin (p. 1706·2).
Acne.

Isorgan *Infinity, Venez.*
Soap substitute.

Isoriac *Pierre Fabre, Ital.*
Isotretinoin (p. 1706·2).
Acne.

Isoric *Interbat, Indon.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Iso-Rifa *PC India, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Isorifam *Biochem, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Iso-Ripharmed *Pharmed, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Isoriv *East African, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

Isorythm *SERP, Mon.*
Disopyramide (p. 1363·2) or disopyramide phosphate (p. 1363·3).
Arrhythmias; prevention of cardiac shock in patients with implantable defibrillators.

Isos *Neon, India.*
Streptomycin sulfate (p. 359·1).
Bacterial infections.

Isoselect *Bieffe, Ital.*
Amino acids.
Parenteral nutrition; hepatic encephalopathy.

Isoskin *Biospray, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Isosol
Note: this name may be used for preparations of different composition.
Merkez, Turk.
Povidone-iodine (p. 1767·1).
Oral hygiene; skin disorders; vaginal infections; skin disinfection.

Shree Ganesh, India.
⊗Isoprenaline hydrochloride (p. 1411·3).
Bronchospasm during anaesthesia; arrhythmias; heart block; shock; diagnostic agent.

Ulagay, Turk.
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Isosor *Vitabalans, Fin.†; Vitabalans, Pol.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isosource *Novartis, Braz.; Nestle, Canad.; Novartis Nutrition, Cz.; Nestle, Denm.; Novartis, Fin.; Novartis Nutrition, Fr.†; Nestle, Hong Kong; Nestle, Ital.; Nestle, UK; Nestle, USA.*
A range of preparations for enteral nutrition.

Nestle, Turk.
Preparations for enteral nutrition.

Novartis Nutrition, Singapore.
Preparation for enteral nutrition.

Isospan *PannonPharma, Hung.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Isospray *Biotech, Venez.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Isosteril *Fresenius Kabi, Switz.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Isosupra Lidose *SMB, Belg.*
Isotretinoin (p. 1706·2).
Acne.

Isotamine *Valeant, Canad.*
Isoniazid (p. 311·2).
Tuberculosis.

Isotamine B *Valeant, Canad.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isotane *Micro, India; Pacific, NZ†; Shanghai Yanan, Thai.*
Isotretinoin (p. 1706·2).
Acne.

Isotard
Note: this name may be used for preparations of different composition.
ProStrakan, UK.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Isotein HN *Sandoz Nutrition, USA.*
Lactose-free, gluten-free preparation for enteral nutrition.

Isoten *Meda, Belg.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; cardiac hyperkinetic syndrome; heart failure.

Isotenk *Biotenk, Arg.*
Isoxsuprine hydrochloride (p. 2535·2).
Dysmenorrhoea; peripheral vascular disorders; premature labour; threatened miscarriage.

Isotic Adretor *Fahrenheit, Indon.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Isotic Azora *Fahrenheit, Indon.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Allergic or inflammatory eye disorders.

Isotic Betaracin *Fahrenheit, Indon.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected eye disorders.

Isotic Cetride *Fahrenheit, Indon.†*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Isotic Clearin *Fahrenheit, Indon.†*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Isotic Cycloma *Fahrenheit, Indon.*
Atropine sulfate (p. 1310·2).
Production of mydriasis; prevention of synechiae; uveitis; glaucoma.

Isotic Enpigi *Fahrenheit, Indon.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Eye infections.

Isotic Frizin *Fahrenheit, Indon.*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Isotic Ixodine *Fahrenheit, Indon.†*
Idoxuridine (p. 985·1).
Viral keratitis.

Isotic Neolyson *Fahrenheit, Indon.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Isotic Nepafrin *Fahrenheit, Indon.†*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); phenylephrine hydrochloride (p. 1672·3).
Eye infections.

Isotic Renator *Fahrenheit, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Eye infections.

Isotic Salmicol *Fahrenheit, Indon.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Isotic Tearin *Fahrenheit, Indon.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3); glycerol (p. 2517·2).
Eye irritation; dry eyes.

Isotic Timact *Fahrenheit, Indon.*
Gentamicin sulfate (p. 304·2).
Eye infections.

Isotic Tobrizon *Fahrenheit, Indon.*
⊗Dexamethasone (p. 1630·3); tobramycin (p. 380·1).
Infected eye disorders.

Isotic Tobryne *Fahrenheit, Indon.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Isotin *Affy, India.*
Isotretinoin (p. 1706·2).
Acne.

Isotol
Note: this name may be used for preparations of different composition.
Diaco, Ital.
⊗Mannitol (p. 1427·3).
Raised intracranial pressure; ocular hypertension.

Zee, India.
Ethambutol (p. 296·1).
Tuberculosis.

Isotonax *Baxter, Belg.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Isotone Kochsalz *Baxter, Ger.; Braun, Ger.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Isotonische Kochsalzlösung *Baxter, Ger.; Eifelfango, Ger.; Fresenius Kabi, Ger.; Serum-Werk Bernburg, Ger.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; respiratory-tract disorders.

Isotop *Esma, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Isotrate
Note: this name may be used for preparations of different composition.
Unipharma, Gr.; Berlin Pharm, Thai.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Isotret *Hexal, Ger.†*
Isotretinoin (p. 1706·2).
Acne.

Isotretin *Sandoz, Cz.†*
Isotretinoin (p. 1706·2).
Acne.

Isotrex *Stiefel, Arg.; GSK, Austral.; GSK, Austria; Stiefel, Braz.; Stiefel, Chile; Stiefel, China; Stiefel, Denm.; Stiefel, Ger.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, Indon.; Stiefel, Irl.; Stiefel, Israel†; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, Port.; GSK, S.Afr.; GSK, Singapore; Stiefel, Spain; Stiefel, Thai.; Stiefel, UK.*
Isotretinoin (p. 1706·2).
Acne.

Isotrex Eritromicina *Stiefel, Spain.*
Isotretinoin (p. 1706·2); erythromycin (p. 291·2).
Acne.

Isotrexin *GSK, Austria; Stiefel, Braz.; GSK, Cz.; Stiefel, Ger.; Stiefel, Hung.; Stiefel, Irl.; Stiefel, Ital.; Stiefel, Pol.; Stiefel, Port.; Stiefel, Rus.; GSK, Singapore; Stiefel, Thai.; Embil, Turk.; Stiefel, UK; Stiefel, Ukr.*
Isotretinoin (p. 1706·2); erythromycin (p. 291·2).
Acne.

Isotrexol *Stiefel, Braz.*
Isotretinoin (p. 1706·2); ensulizole (p. 1703·1); avobenzone (p. 1695·1); octinoxate (p. 1715·1).

Isotriz *Ritz, India.*
Isotretinoin (p. 1706·2).
Acne.

Isotroin *Iasis, Gr.; Cipla, India.*
Isotretinoin (p. 1706·2).
Acne.

Iso-Urea *Roche-Posay, Chile.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Isovist *Bayer, China; Bayer, Ger.; Panagakis, Gr.; Bayer Schering, Hung.†; Bayer, Neth.†; Schering, NZ†; Schering, S.Afr.†; Bayer, Switz.†; Bayer, UK.†*
Iotrolan (p. 1592·3).
Radiographic contrast medium.

Isovit
Note: this name may be used for preparations of different composition.
Deva, Turk.
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isovon
Note: this name may be used for preparations of different composition.
Alembic, India.
Soya isoflavones (p. 2620·3); vitamins; minerals.

Alembic, Singapore.
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Isovorin *Wyeth, Denm.; Pfizer, Fin.; Wyeth, Gr.; Pfizer, Norw.†; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Spain; Pfizer, Swed.; Wyeth, UK.*
Calcium levofolinate (p. 2067·1).
Adjunct to fluorouracil in colorectal cancer; antidote to folic acid antagonists; megaloblastic anaemia; reduction of high dose methotrexate toxicity; methanol poisoning.

Isovue *Regional Health, Austral.†; Bracco, Canad.; Regional Health, NZ; Squibb Diagnostics, USA.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Isowin *Arrowin, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

Isox
Note: this name may be used for preparations of different composition.
Plus, India.
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Saval, Chile.
Meloxicam (p. 86·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Senosiain, Mex.
Itraconazole (p. 583·3).
Fungal infections.

Isoxan
Note: this name may be used for preparations of different composition.
Miracalus, India.
Ifosfamide (p. 806·1); mesna (p. 1557·2).

NHS, Fr.
Vitamins; minerals.

Isoxilan *BioFemme, Philipp.*
Isoxsuprine hydrochloride (p. 2535·2).
Threatened abortion; premature labour; dysmenorrhoea; peripheral vascular disorders.

Isoxin *Pascual, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for prophylaxis of peripheral neuropathy.
Tuberculosis.

Isoxsan *Sanify, India.*
Isoxsuprine hydrochloride (p. 2535·2).
Peripheral vascular disorders.

I-Soyalac *Nutricia-Loma Lindar, USA.*
Corn- and lactose-free soy protein infant feed.

Isozid *Riemser, Ger.; Fatol, Rus.*
Isoniazid (p. 311·2).
Tuberculosis.

Isozid Comp *Fatol, Rus.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isozid comp N *Riemser, Ger.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isozid-H *Gebro, Austria.*
Hexetidine (p. 1755·1); isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1).
Skin disinfection.

Isozol *Nichi-Iko, Jpn.*
Thiamylal sodium (p. 1915·1).
General anaesthesia; convulsions.

Isozyloram *Ranbaxy, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Ispa gel *Pharma Dynamics, S.Afr.; LPC, UK.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; irritable bowel syndrome; diverticular disease.

Ispenoral *Rosen, Ger.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Isprinol *Novell, Indon.*
Inosine pranobex (p. 988·3).
Viral infections.

Isquelium *Rider, Chile.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Isryl *Systopic, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Isryl-M *Systopic, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Issium *Lifepharma, Ital.*
Flunarizine hydrochloride (p. 629·3).
Vertigo.

Issobevit *Proel, Gr.*
Vitamins; minerals; lysine (p. 2079·3).

Issopres *Elpen (Ελπεν), Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Istalar *Pharmafabre, Gr.*
Mequitazine (p. 635·2).

Istalol *Ista, USA.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Istamex *Adelco, Gr.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Istam-Far *Faran, Gr.*
Cyproheptadine hydrochloride (p. 624·1).

Istaminol *Elvipe, Gr.*
Chlorphenamine maleate (p. 620·3).

Istan *Elin, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Istantal *Farmakopea, Ital.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Istasol *Grin, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye disorders.

Istefral *Mintlab, Chile.*
Sulpiride (p. 1107·3).
Depression.

Isticilline *Norma (Νορμα), Gr.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Istin *Pfizer, Irl.; Pfizer, UK.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Istivac *Sanofi Pasteur, Arg.; Sanofi Pasteur, Port.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Istodax *Celgene, USA.*
Romidepsin (p. 855·2).
Cutaneous T-cell lymphoma; peripheral T-cell lymphoma.

Istolde *Actavis, Irl.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Istopril *Codal Synto, Thai.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Istotosal *DAST, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Istrum *Wockhardt, India.*
Bovine colostrum (p. 2380·3).

Isudrine *BoehringerIngelheim, Fr.†*
Aluminium phosphate (p. 1818·3); magnesium oxide (p. 1857·3).
Gastrointestinal disorders.

Isuprel *Hospira, Austral.; Hospira, Belg.; Abbott, Cz.†; Hospira, Fr.; Hospira, Gr.; Abbott, Indon.†; Abbott, Israel†; Hospira, NZ; Hospira, Thai.; Hospira, USA.*
⊗Isoprenaline hydrochloride (p. 1411·3).
Heart block; Stokes-Adams attacks; cardiac arrest; bronchospasm during anaesthesia; heart failure; shock; arrhythmias; pulmonary hypertension; overdose of beta blockers or calcium channel blockers; hypoperfusion syndrome; carotid sinus hypersensitivity.

I-Supres *Medilife, Philipp.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Isvedon *Life Medicare, India.*
Trimetazidine (p. 1520·1).
Angina pectoris; Ménière's disease.

Iszu *Aamorb, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

IT SD-T *Purissimus, Arg.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

I-Tab *Pascual, Philipp.*
Vitamins; minerals.

Itaclox *Rafarm, Gr.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Itagil *Actavis, Port.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Itaka *Roemmers, Venez.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Itakem *Actavis, Cz.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Italdermol *Italmex, Mex.*
Wheat germ (p. 2647·1); phenoxyethanol (p. 1764·3).
Burns; wounds; ulcers.

Italker *Italmex, Mex.†*
Ketorolac trometamol (p. 80·2).
Pain.

Italnik *Italmex, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Italon *Offenbach, Mex.*
Indometacin (p. 71·2).
Inflammation.

Italprid *Teofarma, Ital.*
Tiapride hydrochloride (p. 1111·2).
Movement disorders; alcohol withdrawal syndrome; behaviour disorders; gastrointestinal motility disorders; headache.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ital-Ultra *Italmex, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Italviron *Italmex, Mex.*
Asparagine; acetylglutamine (p. 2426·2); pyridoxine (p. 2105·3); phosphorylserine.
Memory disorders.

Itami *Fidia, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Marvecs, Neth.†
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Itamol *Berlico Mulia, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Mavi, Mex.
Bismuth salicylate (p. 1821·3).
Peptic ulcer; diarrhoea.

Itan *Saval, Chile.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Itane *Pharmasant, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Itapredin *Rafarm, Gr.*
Indometacin (p. 71·2).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Itaspor *Intas, India.*
Itraconazole (p. 583·3).
Fungal infections.

Itastab *Rafarm, Gr.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).

Itax
Note: this name may be used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Rus.
Phenothrin (p. 2160·1).
Pediculosis.

Pierre Fabre Dermo Kosmetik, Ger.†
Cyclomethicone (p. 2209·2); castor oil (p. 2472·1).
Pediculosis.

Itax Antipoux *Ducray, Fr.*
Shampoo: Phenothrin (p. 2160·1).
Pediculosis.

Itcan *Hetero, India.*
Itopride hydrochloride (p. 1850·1).

Itch Care *Kiwi, Neth.*
Urtica dioica (p. 2639·3).
Homoeopathic preparation.

Itch Eze *Thornton & Ross, UK.*
OsmoCare.
Pruritus; skin irritation.

Itch Relief *Reckitt Benckiser, Irl.*
⊗Macrogol lauril ethers (p. 2193·3); urea (p. 1727·3).
Pruritic skin disorders.

Itchasia *Willow, India.*
Boric acid (p. 2459·3); clotrimazole (p. 576·2); ichthammol (p. 1705·3); menthol (p. 2553·2); zinc oxide (p. 1729·1).

Itchicos *Symbiosis, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Itchicure *Symbiosis, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Itchipol *Symbiosis, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Itch-Soothe *AFT, NZ.*
Crotamiton (p. 1699·2).
Pruritus; scabies.

Itch-X *Ascher, USA.*
⊗Hydrocortisone (p. 1640·1).
Formerly contained pramocaine hydrochloride and benzyl alcohol.
Local anaesthesia.

Itchy Eye Drops *Major, USA.†*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Itcozol *Douglas, NZ.*
Itraconazole (p. 583·3).
Fungal infections.

Itearz *Medilife, Philipp.*
Hypromellose (p. 2189·2).
Tear deficiency.

ITE-B12 Forte *Purissimus, Arg.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); ferric ammonium citrate (p. 2060·1); liver extract (p. 2444·1).
Anaemias.

Itedal *Dicofar, Arg.*
Paracetamol (p. 115·1).
Pain; fever.

Itedal Plus *Dicofar, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Pain; fever; nasal congestion; cold and influenza symptoms.

Item Antipoux *Dermophil Indien, Fr.*
Lotion; shampoo: Phenothrin (p. 2160·1).
Pediculosis.

Iteol-3 *AstraZeneca, India.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin disinfection.

Iteol-H *AstraZeneca, India.*
Benzalkonium chloride (p. 1737·1).

Iterax *UCB, Indon.; GSK, Philipp.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; premedication; pruritus.

Iterium *Servier, Austria.*
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Itex *Pascual, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Itha *Alna, India.*
Azithromycin (p. 221·2).
Bacterial infections.

I-Thro *Zubit, India.*
Azithromycin (p. 221·2).
Bacterial infections.

I-Throcin *TC Pharma-Chem, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Itiflox *Ashford, Philipp.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Itinerol B_6 *Vifor, Switz.*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3); caffeine (p. 1203·3).
Nausea and vomiting; motion sickness.

Itires *Pekana, Canad.*
Baryta carbonica (p. 2452·2); cistus canadensis; conium maculatum (p. 2524·3); echinacea angustifolia (p. 2498·1); scrophularia nodosa; galium aparine (p. 2481·2); juglans regia (p. 2646·1); kali iodatum (p. 2336·3).
Homoeopathic preparation.

Itisona *Galeno, Venez.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

ITN *Alna, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Itnogen *ProStrakan, Belg.; ProStrakan, Spain.*
⊗Testosterone (p. 2305·1).
Male hypogonadism.

Itodal *Laboratorios Chile, Chile.*
Itraconazole (p. 583·3).
Fungal infections.

Itokine *Zydus, India.*
Itopride hydrochloride (p. 1850·1).

Itomed
Note: this name may be used for preparations of different composition.
ProMed, Ukr.
Itopride hydrochloride (p. 1850·1).
Gastrointestinal disorders.

Chemo, Neth.†
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

I-Tone *Sanjivani, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Itonorm *Gufic, India.*
Itopride hydrochloride (p. 1850·1).

I-Top *Ind-Swift, India.*
⊗Boric acid (p. 2459·3); chlorobutanol (p. 1747·2); chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3); sodium chloride (p. 1795·1); zinc sulfate (p. 2126·2).

Itoplus *Medley, India.*
Itopride; rabeprazole (p. 1881·1).
Gastro-oesophageal reflux.

Itopraz *Cosme, India.*
Itopride; rabeprazole (p. 1881·1).
Gastro-oesophageal reflux.

Itoprid *Cipla, India.*
Itopride hydrochloride (p. 1850·1).
Nausea and vomiting; gastrointestinal motility disorders.

Itorab *Cipla, India.*
Itopride hydrochloride (p. 1850·1); rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux.

Itorbe *Aarpik, India.*
Itopride hydrochloride (p. 1850·1); rabeprazole (p. 1881·1).
Gastro-oesophageal reflux.

Itorex *Tecnopharma, Ital.*
Cefuroxime sodium (p. 255·3).
Gram-negative bacterial infections.

Itotor-OD *Torrent, India.*
Itopride hydrochloride (p. 1850·1).

Itoxaril *LKM, Arg.*
Irinotecan (p. 812·2).
Colorectal cancer.

Wermar, Mex.
Irinotecan hydrochloride (p. 812·2).
Malignant neoplasms.

Itoz *Wallace, India.*
Itopride hydrochloride (p. 1850·1).

Itra *East West, India; Macrophar, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Itrabene *Ratiopharm, Austria.*
Itraconazole (p. 583·3).
Fungal infections.

Itrabest *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Itrac *Cassara, Arg.*
Itraconazole (p. 583·3).
Fungal infections.

Itracan *Cipla, India.*
Itraconazole (p. 583·3).
Fungal infections.

Itracic *Ciclum, Port.*
Itraconazole (p. 583·3).
Fungal infections.

Itracol *Hexal, Ger.†*
Itraconazole (p. 583·3).
Fungal infections.

Itracon *Med-One, Gr.; Unison, Hong Kong; Unison, Malaysia; Unison, Thai.; Farmak, Ukr.*
Itraconazole (p. 583·3).
Fungal infections.

Itraconal *Polychronus, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Itraconbeta *Betapharm, Ger.*
Itraconazole (p. 583·3).
Fungal infections.

Itraconep *Extractum, Hung.*
Itraconazole (p. 583·3).
Fungal infections.

Itraconol *EMS, Braz.†*
Itraconazole (p. 583·3).
Fungal infections.

Itracosid *Carbel, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Itracotan *Royton, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Itraderm *Dermapharm, Ger.; Dermapharm, Switz.*
Itraconazole (p. 583·3).
Fungal infections.

ItraGen *Generics, Pol.*
Itraconazole (p. 583·3).
Fungal infections.

Itragen *Generics, Hung.*
Itraconazole (p. 583·3).
Fungal infections.

Itrahexal *Hexal, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Itral *Ameda, Ukr.*
Itraconazole (p. 583·3).
Fungal infections.

Itralex *EMS, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Itralfa *Chrispa (Χρισπα), Gr.*
Itraconazole (p. 583·3).
Fungal infections.

ItraMerck *Generics, Pol.*
Itraconazole (p. 583·3).
Fungal infections.

Itramicol *Moschimfarm, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Itranax *Janssen-Cilag, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Itranol *Rafa, Israel.*
Itraconazole (p. 583·3).
Fungal infections.

Itranstad *Stada, Hong Kong.*
Itraconazole (p. 583·3).
Fungal infections.

Itraproton *Proton, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Itrasix *Sinensix, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Itraspor *Sigma, Braz.; Suan, Gr.; Eczacibasi, Turk.*
Itraconazole (p. 583·3).
Fungal infections.

Itrastad *Stada, Denm.*
Itraconazole (p. 583·3).
Fungal infections.

Itravil *Investigacion, Mex.†*
⊗Clobenzorex hydrochloride (p. 2318·3).
Obesity.

Itraviron *Farmedia, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Itraxel *Normal, Port.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; autism.

Itrazen *Kaizen, India.*
Itraconazole (p. 583·3).
Fungal infections.

Itrazol *Biolab Sanus, Braz.; Verisfield, Gr.; Vertex, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Itrazole *Mylan, NZ; Millimed, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Itrin *Sigmar, Ital.*
Terazosin hydrochloride (p. 1511·1).
Hypertension.

Itrizole *Janssen, Jpn.*
Itraconazole (p. 583·3).
Fungal infections.

Itrole *Chemo-Drugs, India.*
Itraconazole (p. 583·3).
Fungal infections.

Itrop *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.*
Ipratropium bromide (p. 1211·3).
Bradycardia; arrhythmias.

Itrop Plus *Cipla, India.*
Tropicamide (p. 2012·2); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

Ittiolo *AFOM, Ital.; Almus, Ital.; Marco Viti, Ital.; NewFaDem, Ital.; Polifarma Benessere, Ital.; Sella, Ital.; Zeta, Ital.*
Ichthammol (p. 1705·3).
Skin disorders.

Itworks *Intas, India.*
Ispaghula (p. 1849·1).

Ityolate CE *RCA, Ital.*
Ichthammol (p. 1705·3); zinc oxide (p. 1729·1).
Skin disorders.

Itzgon *Kee, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).
Painful skeletal muscle spasm.

Itzol *Lapi, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Iugr *Candor, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Iuronico Biotic *Paylos, Arg.*
Sodium hyaluronate (p. 2526·2); sulfadiazine silver (p. 362·3).

Iuronicoderm *Paylos, Arg.*
Hyaluronic acid (p. 2526·2).
Skin disorders.

IV Augclav *VHB, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

IVA Anamix *Nutricia, Fr.; Nutricia, Ital.*
Food for special diets.
Isovaleric acidaemia.

SHS, Cz.
Infant feed.
Isovaleric acidaemia; disorders of leucine metabolism.

Iva Anamix *Nutricia, Fr.*
Infant feed.
Isovaleric acidaemia.

Ivabid *Piramal, India.*
Ivabradine hydrochloride (p. 1415·1).
Angina pectoris.

Ivabrad *Ind-Swift, India.*
Ivabradine (p. 1415·1).
Angina pectoris.

Ivadal *Sanofi-Aventis, Austria; Sanofi-Aventis, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Ivagalmin *Genepharm, Cz.; Genepharm, Neth.; Galex, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Ivagan *Arex, Venez.*
Dihydroergotamine mesilate (p. 672·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Headache.

I-Valex *Ross, USA.*
A range of leucine-free preparations for enteral nutrition including an infant feed.
Leucine catabolism disorders.

Ivaliten *Lavipharm, Gr.*
Phenothrin (p. 2160·1).
Head, body, and crab lice.

Ivamycin *Elpen (Ελπεν), Gr.*
Doxycycline (p. 288·1).
Bacterial infections.

Ivan *Arlak, India.*
Aloe vera (p. 1693·2); chlorhexidine (p. 1743·2); vitamin E (p. 2119·1).
Soap substitute.

Ivanes *Ikapharmindo, Indon.*
Ketamine hydrochloride (p. 1905·1).
Anaesthesia; analgesia in obstetrics.

Ivarest *Rider, Chile; Blistex, USA.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Minor skin irritation; allergic skin reactions; pruritus.

Ivast *ADP, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Ivatrim *Sydenham, Philipp.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ivazine *Unichem, India.*
Ivabradine (p. 1415·1).

Ivcef *Aurobindo, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Ivecop *Shalaks, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Ivecop-AB *Shalaks, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Ivedal *Sanofi-Aventis, S.Afr.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Ivegam-CMV *CAF-DCF, Belg.*
A cytomegalovirus immunoglobulin (p. 2381·3).
Passive immunisation.

Ivel *Abbott, Mex.†*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Anxiety; insomnia.

Ivel mono *Sandoz, Ger.†*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Ivelip *Baxter Immuno, Arg.; Baxter, Austral.; Clintec, China; Kalbe, Indon.; Teva, Israel; Baxter, NZ; Baxter, Pol.†; Baxter, Singapore; Baxter, Thai.†; Eczacibasi-Baxter, Turk.; Baxter, UK; Baxter, Venez.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Ivélip *Baxter, Fr.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Ivemend *MSD, Austria; MSD, Cz.; MSD, Denm.†; MSD-Chibret, Fr.†; MSD, Ger.; MSD, Gr.; MSD, Irl.; MSD, Neth.; MSD, Norw.; MSD, Pol.; MSD, Port.; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, UK·*
Fosaprepitant meglumine (p. 1843·3).
Nausea and vomiting associated with cancer chemotherapy.

Ivepaque *GE Healthcare, Fr.†*
Iopentol (p. 1591·2).
Radiographic contrast medium.

Ivepred *Sun, India.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Ivercid *East West, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Ivercid-A *East West, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Ivermec *UCI, Braz.*
Ivermectin (p. 155·1).
Onchocerciasis.

Ivernax *Phyto-Sante, Canad.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); belladonna (p. 2453·3); bryonia alba (p. 2461·3); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens (p. 2511·2); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Iversan *Sanify, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Iver-Sol *Psyco Remedies, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Iverstar *BMW, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Ivertal *Panalab, Arg.*
Ivermectin (p. 155·1).
Onchocerciasis; strongyloidiasis; scabies.

Iverzole *JK Biochem, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Ivetra *Torrent, Philipp.*
Levetiracetam (p. 531·1).
Epilepsy.

Ivexterm *Valeant, Mex.*
Ivermectin (p. 155·1).
Worm infections.

IVF-C *LG Life Sciences, Thai.*
⊗Chorionic gonadotrophin (p. 2258·1).
Cryptorchidism; hypogonadotrophic hypogonadism; menstrual disorders; threatened or recurrent miscarriage; male and female infertility.

IVF-M *Biochem, India; LG Life Sciences, Thai.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

IV-Globulin *Zydus, India; Green Cross, Malaysia.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; Kawasaki disease; immune thrombocytopenia; Guillain-Barré syndrome; agammaglobulinaemia; immunodeficiency; bone-marrow transplantation.

IV-Globulin S *Green Cross, Philipp.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

IVheBex *Lab Francais du Fractionnement, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; LFB, Neth.; LFB, Port.; Er-Kim, Turk.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Ividol *Rafarm, Gr.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure.

Iviglob *VHB, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; bone-marrow transplantation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Ivimax *VHB, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Ivimicin *FDC, India.*
Amikacin (p. 214·1).
Bacterial infections.

Ivipime *VHB, India.*
Cefepime (p. 239·2).
Bacterial infections.

Ivirome *VHB, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Iviroxime *VHB, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

I-Vit *Elder, India.*
Trace elements; minerals.

Ivit *Elder, India.*
Trace elements; minerals.

I-Vit Plus *Elder, India.*
Trace elements; minerals; ubidecarenone (p. 2637·1).

Ivitax *VHB, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

I-Vite *Yu Sheng, Singapore.*
Vitamins; minerals; lutein (p. 2079·2).
Nutritional supplement.

I-Vite Protect *Rugby, USA.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); copper (p. 2057·1); sodium (p. 1795·1); zinc (p. 2126·1).
Dietary supplement.

i-Vitein *Indrugco, Singapore.*
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement.

Ivix *Cinetic, Arg.*
Capsules: Amino acids; vitamins; minerals; ginkgo biloba (p. 2512·3); soya protein.
Dietary supplement.

Cinetic, Arg.
Topical solution: Minoxidil (p. 1438·3).
Alopecia.

Ivix Fin *Cinetic, Arg.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Ivixone *VHB, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ivíz *Bausch & Lomb, China.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Ivmetro *Torrent, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Ivor
Note: this name may be used for preparations of different composition.
Rovi, Austria; Vianex (Βιανεξ), Gr.; Sigma-Tau, Ital.; Rovi, Port.
Bemiparin sodium (p. 1314·2).
Thromboembolic disorders; thromboembolism prophylaxis.

Plus, India.
Ivermectin (p. 155·1).
Worm infections; scabies.

Ivoral *Aurochem, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Ivorat *Gineladius, Austria.*
Bemiparin sodium (p. 1314·2).
Deep vein thrombosis.

Ivori *Invision, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Ivorin *Greater Pharma, Thai.*
Levodropropizine (p. 1662·3).
Cough.

Ivormax *Vianex (Βιανεξ), Gr.*
Bemiparin sodium (p. 1314·2).
Thromboembolic disorders.

IV-Pro *Claris, Philipp.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Ivracain *Sintetica, Switz.*
Chloroprocaine hydrochloride (p. 1983·1).
Local anaesthesia.

Ivumir *Dicofarm, Ital.*
Cranberry (p. 2488·1).
Urinary-tract disorders.

Ivy Block *Enviroderm, USA.*
Bentoquatam (p. 1696·1).
Prophylaxis against poison ivy-, oak-, or sumac-induced contact dermatitis.

Ivy Dry *Ivy Corp, USA.*
Zinc acetate (p. 2126·1).
Minor skin irritation.

Ivy Wash *Humco, USA.*
Pramocaine hydrochloride (p. 1993·3).

Ivydol *Sidhbali, India.*
Tramadol (p. 139·2).
Pain.

Ivynall *Brymar, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Ivy-Rid
Note: this name may be used for preparations of different composition.
Medique, USA.
Benzocaine (p. 1980·2).

Iwadil *Millimed, Thai.†*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).
Cough; nasal congestion.

Iwamet *Masa, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; systemic mastocytosis.

Iwata *Cadila, India.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease; rheumatoid arthritis.

Iwazin *Masa, Thai.*
Tyrothricin (p. 384·1); benzethonium chloride (p. 1738·1); benzocaine (p. 1980·2).
Mouth and throat infections.

Ixacor *Roemmers, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Ixana *Medical, Arg.*
Lozenges: Hexylresorcinol (p. 1755·1) sodium benzoate (p. 1738·2); senega (p. 1677·2); ambay.
Mouth and throat disorders.

Medical, Arg.
Syrup: Guaifenesin (p. 1666·2); sodium benzoate (p. 1738·2); senega (p. 1677·2); squill (p. 1677·3); ambay.
Cough.

Ixel *Rovafarm, Arg.; Pierre Fabre, Austria; Roche, Braz.; Silesia, Chile; Pierre Fabre, Cz.; Pierre Fabre, Fin.; Pierre Fabre, Fr.; Pierre Fabre, Hong Kong; Pierre Fabre, Israel; Pierre Fabre, Pol.†; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Thai.; Pierre Fabre, Turk.*
Milnacipran hydrochloride (p. 435·3).
Depression.

Ixempra *BMS, Arg.; BMS, Chile; BMS, Fr.†; BMS, Israel; BMS, NZ; BMS, Singapore; BMS, Switz.; BMS, Thai.; BMS, USA.*
Ixabepilone (p. 814·3).
Breast cancer.

Ixense *Takeda, Jpn†; Takeda, Thai.*
Apomorphine hydrochloride (p. 892·3).
Erectile dysfunction.

Ixia *Menarini, Spain.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Ixia Plus *Menarini, Spain.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ixiaro *Intercell, Austria; Novartis, Belg.; Novartis, Canad.; Novartis Vaccines, Cz.; Crucell, Denm.; Novartis, Fr.; Novartis Vaccines, Ger.; Novartis Vaccines, Irl.; Neopharm, Israel; Novartis Vaccines, Neth.; Intercell, Norw.; Novartis Vaccines, Pol.; Novartis Vaccines, Port.; Novartis Vaccines, Spain; Crucell, Swed.; Novartis, Switz.; Novartis Vaccines, UK; Novartis, USA.*
An inactivated Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Ixicrol *Novag, Mex.*
Paroxetine (p. 440·3).

Ixidol *Biomax, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ixime *Lupin, Malaysia; Lupin, Rus.; Lupin, Ukr.*
Cefixime (p. 240·3).
Bacterial infections.

Ixium *Farmoquimica, Braz.*
Imiquimod (p. 985·2).

Ixopolet *Best, Mex.*
dl-Alpha tocoferil acetate (p. 2119·2).
Antioxidant.

Ixor
Note: this name may be used for preparations of different composition.
Soho, Indon.
Roxithromycin (p. 356·2).
Bacterial infections.

Phoinix Pharm (Φοινιξ Φαρμ), Gr.†
⊗Budesonide (p. 1625·1).
Also known as Ιχωρ (Ichor).
Allergic rhinitis; skin disorders.

Ixoten *Baxter, Ger.; Baxter, Gr.*
Trofosfamide (p. 878·1).
Malignant neoplasms.

Ixprim *Grunenthal, Fr.; Sanofi-Aventis, Fr.; Grunenthal, Irl.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Iyafin *TNP, Thai.*
Junior syrup: ⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough.

TNP, Thai.
Syrup: ⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough.

TNP, Thai.
Tablets: Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough.

Iyara Ma-Weang *T Man, Thai.*
Solanum trilobatum; Indian gooseberry (p. 2532·2); liquorice (p. 1853·2).
Respiratory-tract disorders associated with viscous mucus.

Izabel *Zytras, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Izac *TNP, Thai.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth infections.

Izacef *Intramed, S.Afr.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Izadima *Pisa, Mex.*
Ceftazidime (p. 250·2).
Bacterial infections.

Izart *Integra, Philipp.*
Irbesartan (p. 1411·1).
Hypertension.

Izeal *FDC, India.*
Vitamin B substances (p. 2102·3); trace elements; lutein (p. 2079·2).
Dietary supplement.

I-Zen *Klar Sehen, India.*
Vitamins; trace elements; eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); lutein (p. 2079·2).

Izepox *Labormed, Cz.*
⊗Indapamide (p. 1409·2).
Hypertension.

Izerin *Rafarm, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Izetafin *Rafarm, Gr.*
Macrogol 3350 (p. 2547·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1).
Bowel evacuation.

Izid *Intra-Labs, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Izilox *Bayer, Fr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Izinor *Rafarm, Gr.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Izodeks *Eczacibasi-Baxter, Turk.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Izofran *GSK, Chile.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Izoleks *Biosel, Turk.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Izolen *Polifarma, Turk.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Izoltil *Help, Gr.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Izomix *Biosel, Turk.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Izonit *Lek, Pol.†*
Isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease.

Izotek *Blau, Pol.*
Isotretinoin (p. 1706·2).
Acne.

Izotziaja *Ziaja, Pol.*
Isotretinoin (p. 1706·2).
Acne.

Izra *Unichem, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Izra-D *Unichem, India.*
Domperidone (p. 1838·1); esomeprazole (p. 1841·1).

Jaa Pyral *Jaapharm, Canad.*
Pyrantel embonate (p. 165·3).

Jaa Tetra *Jaapharm, Canad.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Jaaps Health Salt *Askit, UK.*
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); potassium sodium tartrate (p. 1879·3).
Dyspepsia; heartburn; constipation.

Jaba B_{12} *Jaba Recordati, Port.*
Cobamamide (p. 2107·2).
Vitamin B_{12} deficiency; neuralgia; neuritis.

Jabastatina *Jaba Recordati, Port.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Jabasulide *Jaba Recordati, Port.*
Nimesulide (p. 101·3).
Pain.

Jabón del Tío Nacho *Bustillos, Mex.*
Tar (p. 1723·3); resorcinol (p. 1718·3); sulfur (p. 1721·1).
Skin disorders; scalp disorders.

Jabonacid *Bajer, Arg.*
Chloroxylenol (p. 1748·2); cetrimide (p. 1742·1); bornyl acetate (p. 2460·2).
Skin and scalp cleanser.

Jabonoil *Panalab, Arg.*
Trichlorosalicylanilide.
Emollient.

Jacanzole *Sanify, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Jack & Jill *Novartis Consumer, Canad.*
Guaifenesin (p. 1666·2); mepyramine maleate (p. 635·1).
Cough; cold symptoms.

Jack & Jill Bedtime *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Jack & Jill Children's Formula Cough Liquid *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Jack & Jill Cough & Cold *Novartis Consumer, Canad.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Jack & Jill Cough Cold & Flu *Buckley, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cough; cold and influenza symptoms.

Jack & Jill Thin Strips Cough *Buckley, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Jack & Jill Thin Strips Cough & Cold *Buckley, Canad.†*
Diphenhydramine hydrochloride (p. 626·2).

Jackson's All Fours *Anglian, UK.*
Guaifenesin (p. 1666·2).
Coughs.

Jackson's Bronchial Balsam *Anglian, UK.*
Guaifenesin (p. 1666·2).
Coughs.

Jacksons Herbal Laxative *Anglian, UK.*
Cascara (p. 1826·1); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Jackson's Lemon Linctus *Anglian, UK.*
⊗Glycerol (p. 2517·2); honey (p. 2072·1).
Coughs; sore throat.

Jacksons Mentholated Balm *Anglian, UK.*
Eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); terpineol (p. 2627·2); menthol (p. 2553·2).
Musculoskeletal pain; respiratory-tract congestion.

Jackson's Pain & Fever *Anglian, UK.*
Sodium salicylate (p. 132·2).
Formerly known as Jacksons Febrifuge.
Cold and influenza symptoms; musculoskeletal, joint, and soft-tissue disorders.

Jackson's Troublesome Coughs *Anglian, UK.*
⊗Ipecacuanha (p. 1667·2); glycerol (p. 2517·2); honey (p. 2072·1).
Coughs.

Jacomox *Actavis, Neth.†*
Moxonidine (p. 1442·1).
Hypertension.

Jacpar *Keshav, India.*
Aceclofenac sodium (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Jactuss *Coup, Gr.*
Zipeprol hydrochloride (p. 1680·3).
Cough.

Jacutin
Note: this name may be used for preparations of different composition.
Almirall Hermal, Ger.
Topical solution: Dimeticone (p. 2209·3).
Pediculosis.

Almirall Hermal, Ger.
Topical spray: Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Hermal, Austria†; Hermal, Hung.†; Hermal, Malaysia†; Herrmann, Pol.†; Hermal, Singapore; Almirall, Switz.†; Boots, Thai.†; Hermal, Thai.†
Lindane (p. 2157·1).
Pediculosis; scabies.

Hermal, Singapore.
Topical emulsion: Lindane (p. 2157·1); benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Jade *Craveri, Arg.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Jade MD 24 contains 24 active tablets and 4 inert tablets.
Combined oral contraceptive.

Jadelle *Bayer Schering, Fin.; Bayer Schering, Neth.†; Bayer Schering, Norw.†; Bayer, NZ; Bayer Schering, Port.; Bayer, Spain†; Bayer, Swed.†; Bayer, Thai.; Schering, Venez.*
Levonorgestrel (p. 2296·1).
Progestogen-only contraceptive implant.

Jadix *Farmazak, Gr.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Jaga *Aldril, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Neuritis; neuralgia; neuropathy; joint pain; vitamin B deficiency.

Jagaplex *Aldril, Philipp.*
Oral drops: Vitamins.

Aldril, Philipp.
Syrup; tablets: Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Jagcin *Jagsonpal, India.†*
Paracetamol (p. 115·1).
Fever; pain.

Jaglax *Jagsonpal, India.*
Phenolphthalein (p. 1877·3).

Jagquin *Jagsonpal, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; amoebiasis; rheumatoid arthritis.

Jagril-Spas *Jagsonpal, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Jaizzy *Aamorb, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Jaizzy-GM *Aamorb, India.*
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3).

Jakafi *Incyte, USA.*
Ruxolitinib phosphate (p. 855·3).
Myelofibrosis.

Jakavi *Novartis, Denm.; Novartis, Norw.; Novartis, Switz.; Novartis, UK.*
Ruxolitinib phosphate (p. 855·3).
Myelofibrosis.

Jalcium *Jagsonpal, India.*
Minerals; colecalciferol (p. 2113·1).

Jalcium-T *Jagsonpal, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Jaloplast *Kela, Belg.*
A hydrogel dressing.
Wounds.

Jaloskin *Fidia, Ital.*
Hyaff (p. 2526·2).
Wounds.

Jalra *Novartis, Cz.; UCB, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Esteve, Spain.*
Vildagliptin (p. 504·3).
Diabetes mellitus.

Jalyn *GSK, Canad.; GSK, USA.*
Dutasteride (p. 2357·2); tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Jamaican Sarsaparilla *Potter's, UK.*
Sarsaparilla root (p. 2610·3); capsicum (p. 2469·3); liquorice (p. 1853·2); peppermint oil (p. 1877·1).
Skin disorders.

Jamax-S *SJA, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Jamieson Total Energy *Jamieson, Philipp.*
Siberian ginseng (p. 2614·3); bee pollen (p. 2593·3); royal jelly (p. 2608·1); kola nut (p. 2648·2); wheat grass.
Nutritional supplement.

Jamyle *Velvian, Neth.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Jamylène *AJC, Fr.*
Docusate sodium (p. 1836·2).
Constipation.

Janacin *Biolab, Hong Kong†; Biolab, Malaysia; Biolab, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Janartan *KRKA, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Janbol *Keshav, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Jancef *Hiral, India.*
Cefixime (p. 240·3).
Bacterial infections.

Jandox *Hiral, India.*
Cefpodoxime.
Bacterial infections.

Jangee *LadeePharma, Cz.; LadeePharma, Hung.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Janogrel *Miklich, Denm.*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Jantoven *Upsher-Smith, USA.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Januet *MSD, Israel.*
Metformin hydrochloride (p. 489·1); sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Janumet *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, India; MSD, Irl.; MSD, Ital.; MSD, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, UK; MSD, Ukr.; Merck, USA.*
Sitagliptin phosphate (p. 500·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Januvia *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, India; MSD, Indon.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Jpn; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA.*
Sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Japan Freeze-Dried Tuberculin *Vaccina, S.Afr.†*
Tuberculin purified protein derivative (p. 2635·3).
Tuberculosis test.

Japanöl *Liebermann, Ger.*
Mint oil (p. 2560·1).
Cold symptoms; dyspepsia; myalgia.

Japlor *Sanify, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Japol *Salus, Fin.; MaxMedica, Swed.*
Partially dementholised mint oil (p. 2560·1) mentha arvensis piparescens.
Indigestion; cold symptoms; cough; musculoskeletal pain; pruritus.

Jaquedryl *Pfizer, Chile.*
Ergotamine tartrate (p. 674·1); caffeine citrate (p. 1203·3); diphenhydramine hydrochloride (p. 626·2).
Migraine and other vascular headache.

Jarabe de Capulin *Nordin, Mex.†*
⊗Ammonium chloride (p. 1656·1); ephedrine (p. 1663·1).
Cough.

Jarabe Garde *Grisi, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Jarabe Manceau *Alcor, Spain.*
Senna (p. 1885·1); coriander (p. 2486·3); pyrus malus.
Constipation.

Jarabe de Manzanas *Ifusa, Mex.*
⊗Mannitol (p. 1427·3); senna (p. 1885·1).
Constipation.

Jarabe Palto Compuesto con Miel Adulto *Maver, Chile.*
Avocado leaf (p. 2451·2); eucalyptus oil (p. 2501·2); tolu balsam (p. 1679·2); honey (p. 2072·1).
Cough.

Jarabe Palto Compuesto con Miel Infantil *Maver, Chile.†*
Avocado (p. 2451·2); honey (p. 2072·1).
Cough.

Jarabe de Rabano Yodado *Grisi, Mex.*
Raphanus sativus; iodine (p. 2336·3).

Jarsin *Klosterfrau, Austria; Cassella-med, Cz.; Cassella-med, Ger.; Vifor, Switz.*
St John's wort (p. 449·1).
Depression; anxiety; insomnia.

Jarvis *Gedeon Richter, Hung.; Gedeon Richter, Neth.; Richter, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Jasimenth CN *Bolder, Ger.*
Dequalinium chloride (p. 1749·3); ascorbic acid (p. 2110·3).
Mouth and throat disorders.

Jasmine *Bayer, Fr.*
Ethinylestradiol betadex clathrate (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Jasminelle *Bayer, Fr.*
Drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3).
Combined oral contraceptive.

Jasminellecontinu *Bayer, Fr.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Jatamansin NF *Nova Argentia, Arg.*
Diosmin (p. 2505·2).
Jatamansin formerly contained troxerutin.
Haemorrhoids; venous insufficiency.

Jatrosom *Aristo, Ger.*
Tranylcypromine sulfate (p. 450·3).
Depression.

Jaundif *Akums, India.*
Karela; terminalia chebula (p. 2474·3).

Javipren *Elpen (Ελπεν), Gr.*
Diclofenac sodium (p. 48·3).

Javlor *Pierre Fabre, Austria; Pierre Fabre, Cz.; Pierre Fabre, Denm.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Irl.; Pierre Fabre, Israel; Pierre Fabre, Ital.; Pierre Fabre, Neth.; Pierre Fabre, Norw.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Spain; Pierre Fabre, Swed.; Pierre Fabre, UK.*
Vinflunine tartrate (p. 885·1).
Urothelial-tract cancer.

Jawkepta *Charoon Bhesaj, Thai.*
Tyrothricin (p. 384·1); benzethonium chloride (p. 1738·1).
Mouth and throat infections.

Jaxe *Hiral, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Jayacin *Danpac, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Jaydisyn *Sel-J, Philipp.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Jay-Phyl *Jaymac, USA.*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Jayzyme *Om Biotec, India.*
⊗Activated charcoal (p. 1537·3); amylase (p. 2442·1); papain (p. 2582·3).

Jcanzole *Sanify, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

J-COF DHC *Jaymac, USA.*
⊗Brompheniramine maleate (p. 618·1); dihydrocodeine tartrate (p. 52·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Jean Siagra *Laborate, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Jeanine *Jenapharm, Cz.; Bayer Schering, Pol.; Bayer Schering, Rus.; Jenapharm, Ukr.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Jebik V *Osaka University, Jpn.*
An inactivated Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Jecktofer *Cosme, India.*
Iron sorbitol (p. 2077·3).
Iron-deficiency anaemia.

Jecktofer Plus *Cosme, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2).

Jécopeptol *Tradiphar, Fr.†*
Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); sodium bicarbonate (p. 1781·1); boldo (p. 2458·3); kinkeliba (p. 2538·2); euonymus (p. 1842·1).
Digestive disorders.

Jectocef *Lakeside, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Jectocos *CFL, India.*
Capsules: Folic acid (p. 2063·1); iron (p. 2073·1); vitamin C (p. 2110·3); zinc (p. 2126·1).
Formerly contained iron sorbitol.

Cosme, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Jectocos Plus *CFL, India.*
Iron sorbitol (p. 2077·3); folic acid (p. 2063·1); hydroxocobalamin acetate (p. 2107·3).
Anaemias.

Jectofer *Eczacibasi, Turk.†*
Iron sorbitol (p. 2077·3).
Iron-deficiency anaemia.

Jekovit *Orion, Fin.*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency.

Jelgrad *KRKA, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Jellicor *Pfizer, India.*
Chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1).

Jellin *Teofarma, Ger.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Jellin Basis *Grunenthal, Ger.†*
Emollient.
Skin disorders.

Jellin-Neomycin *Teofarma, Ger.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Jelliproct *Teofarma, Ger.*
⊗Fluocinonide (p. 1636·3); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Jellywash *Prevor, Fr.*
Sodium chloride (p. 1795·1).
Jellyfish stings.

Jelonet *Smith & Nephew, Austral.; Smith & Nephew, Fr.; Smith & Nephew, Ital.; Smith & Nephew, S.Afr.; Smith & Nephew Healthcare, UK.*
Soft paraffin (p. 2212·1).
Wound dressing; burns.

Jemizym *Jean-Marie, Hong Kong.*
Muramidase hydrochloride (p. 2565·1).
Haemorrhage; respiratory-tract disorders.

Jemta *Ebewe, Ital.; Ebewe, Neth.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Jenacard *Mibe Jena, Ger.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Jenamazol *Quintesence, Cz.*
Clotrimazole (p. 576·2).
Vulvovaginal infections.

Jenaril *Stada, Denm.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Jenaspiron *Mibe Jena, Ger.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; oedema; ascites.

Jencevac *Shantha, India.*
A Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Jencycla *Lupin, USA.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Jengimiel *Jengimiel, Venez.*
Adult syrup: Ginger (p. 1844·1); honey (p. 2072·1).
Sore throat; cough.

Jengimiel, Venez.
Paediatric syrup: Ginger (p. 1844·1); honey (p. 2072·1); aloe vera (p. 1693·2).
Cough.

Jengimiel Sabila *Jengimiel, Venez.*
Ginger (p. 1844·1); aloe vera (p. 1693·2); honey (p. 2072·1).
Cough and cold symptoms.

Jenloga *UPM, USA.*
Clonidine hydrochloride (p. 1339·1).

Jenoquine *Julphar, UAE.†*
Levofloxacin (p. 315·3).
Bacterial infections.

Jénovérine *Boiron, Fr.†*
Oleum jecoris aselli (p. 2056·3); calcarea carbonica (p. 1824·3); calcarea fluorica (p. 2053·1); calcarea hypophosphorica (p. 2530·3); manganum nucleinicum; ferrum phosphoricum (p. 2077·1); silicea (p. 2208·3); flavum (p. 1721·1).
Homoeopathic preparation.

Jenoverine *Boiron, Neth.†*
Calcarea carbonica ostrearum (p. 1824·3); calcarea fluorica (p. 2053·1); calcarea hypophosphorosa (p. 2530·3); silicea (p. 2208·3); ferrum phosphoricum (p. 2077·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Jensar *Unique, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Jentadueto *Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.*
Linagliptin (p. 488·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jeny-FMP *TNP, Thai.*
21 Tablets, norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Jepale *Simcere, China.*
Pemetrexed disodium (p. 844·3).
Malignant pleural mesothelioma.

Jepaso *Simcere, China.*
Nedaplatin (p. 834·3).
Malignant neoplasms.

Jeprab *Sanify, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Jeprab-D *Sanify, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Jeprolol *Mibe Jena, Ger.*
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias; hypertension; migraine; myocardial infarction.

Jeracin *Nufarindo, Indon.*
Erythromycin (p. 291·2).
Acne.

Jeraklin *Darya-Varia, Indon.†*
Tretinoin (p. 1725·2).
Acne.

Jern C *Medic, Denm.*
Ferrous fumarate (p. 2060·3); ascorbic acid (p. 2110·3).
Iron deficiency.

Jersin *Andromaco, Mex.†*
Aciclovir (p. 964·1).
Herpes labialis.

Jertz *Diba, Mex.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Jespect *CSL Biotherapies, Austral.; CSL, NZ.*
An inactivated Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Jesscool *Konimex, Indon.†*
Thyme (p. 2630·2); bitter-orange peel (p. 2575·3); chicory root (p. 2475·2).
Sore throat; scurvy; cracked lips; constipation.

Jet Lag *Homeocan, Canad.*
Arnica montana (p. 2447·2); bellis perennis (p. 2454·2); chamomilla (p. 2474·1); ipecacuanha (p. 1667·2); lycopodium clavatum (p. 2547·1).
Homoeopathic preparation.

Jetepar *Rotta, Hong Kong†; Rotta, Malaysia; Rottapharm, Singapore.†*
Betaine glucuronate (p. 2456·1); diolamine glucuronate (p. 2517·1); nicotinamide ascorbate (p. 2083·1).
Liver disorders; biliary-tract disorders.

Rotta, Philipp.
Betaine glucuronate (p. 2456·1); diolamine glucuronate (p. 2517·1); nicotinamide (p. 2083·1) or nicotinamide ascorbate (p. 2083·1).
Liver disorders.

Jetmonal *Adeka, Turk.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Jetmox *Elder, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Jetokain *Adeka, Turk.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Jetomisol-P *Johnson & Johnson, India.*
Tetramisole (p. 166·3); phenolphthalein (p. 1877·3).
Worm infections.

Jetosel *Biosel, Turk.*
Lidocaine hydrochloride (p. 1988·2). Adrenaline (p. 1292·1) is included as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Jetositol *Johnson & Johnson, India.*
Inositol (p. 2533·2); hydroxymethylnicotinamide (p. 2530·1); vitamin B_{12} (p. 2107·2).

Jetrea *Alcon, UK; ThromboGenics, USA.*
Ocriplasmin (p. 2574·1).
Vitreomacular adhesion.

Jets *Freeda, USA.*
Vitamins; lysine (p. 2079·3).

Jevacain *Esma, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

JE-Vaccine *Kaketsuken, Thai.†*
An inactivated Japanese encephalitis vaccine, Beijing strain (p. 2396·2).
Active immunisation.

JE-Vax *Aventis Pasteur, Austral.†; Biken, Canad.†; Sanofi Pasteur, USA.†*
An inactivated Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Jevity *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, China; Abbott, Cz.; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Thai.; Abbott, Turk.; Abbott, Venez.*
Preparation for enteral nutrition.

Abbott Nutrition, Singapore.
Lactose-free preparation for enteral nutrition with fibre.

Abbott, UK.
A range of preparations for enteral nutrition.

Ross, USA.
Preparation for enteral nutrition with fibre.

Jevtana *Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, UK; Sanofi-Aventis, USA.*
Cabazitaxel (p. 756·2).
Prostatic cancer.

Jexime-LB *Keshav, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Jext *ALK, Denm.; ALK, Fin.; ALK, Irl.; ALK, Neth.; ALK, Norw.; ALK, Spain; ALK, Swed.; ALK, Switz.*
⊗Adrenaline acid tartrate (p. 1292·2).
Anaphylaxis.

Jezil *Pfizer, Austral.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

JF Sulfur *Galenium, Indon.†; Galenium, Malaysia.*
Sulfur (p. 1721·1).
Fungal skin infections; acne; seborrhoea; skin disorders.

Jflo *Om Biotec, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Jflo-OZ *Om Biotec, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

JHP Rödler *McNeil, Ger.*
Mint oil (p. 2560·1).
Cold symptoms; gastrointestinal disorders; headache.

Ji De *Guangji, China.*
Tinidazole (p. 949·2).

Ji Di *LuoXin, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Ji Ai Mu *Jiangzhong, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Ji Bai Fu *Hengrui, China.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).

Ji Feng *Lunan, China.*
Matrine.

Ji Fu De *Global, China.*
Ligustrazine hydrochloride.

Ji Jia *Hengrui, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Ji Kang Ning *Ji BeiEr, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Ji Ke *Sunstone, China.*
Piroxicam (p. 125·3).

Ji Li *Shuang Jing, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ji Li Da *Lunan, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ji Li Qing *Kaiyuan, China.*
Rifaximin (p. 355·2).

Ji Luo *Kaicheng, China.*
Cefixime (p. 240·3).
Bacterial infections.

Ji Luo Yin *Zhongke Yuan, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Ji Mei *KunMing, China.*
Kitasamycin acetate.

Ji Ni Le Er *Jiang Kang, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Ji Ping *Baijingyu, China.*
Lomefloxacin hydrochloride (p. 319·2).

Ji Shi Da *Double-Crane, China.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Ji Shu *Lunan, China.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Ji Song *Lunan, China.*
Diclofenac potassium (p. 48·3).

Ji Tai *Shuang Cheng, China.*
Thymalfasin (p. 2630·1).
Chronic hepatitis B and C.

Ji Wei *Watson, China.*
Risedronate sodium (p. 1189·3).
Paget's disease of bone; osteoporosis.

Ji Xi Tong *Wan Bang, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus inections.

Ji Xiang Hong *Jixiang, China.*
Aminomethylbenzoic acid (p. 1132·2).

Ji You *Rui Er, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Jia Bo *C & O, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Jia Dai Bao *Qilu, China.*
A Pseudomonas aeruginosa vaccine (p. 2412·3).

Jia Dan *Bei Da Gao Ke Hua Tai, China.*
Naproxen sodium (p. 98·2).

Jia Er *Jiabin, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Jia Fei *Yung Shin, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Jia Feng *Shuai Ke, China.*
Ligustrazine phosphate.

Jia Di Fu *Sine, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia He Luo *Xinhua, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Jia He Mei *Huaren, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Jia Heng Xing *Hengda, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia Ji Ning *Hayao, China.*
Clarithromycin (p. 266·2).
Bacterial infections.

Jia Jia Gai *Tefeng, China.*
Calcium gluconate (p. 1783·3).

Jia Jian *Chang Fu Jie Jing, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Jia Ke *Bei Da Gao Ke Hua Tai, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Jia Kui Long *Double-Crane, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia Li *Younite, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia Li Bao *Zhonglian, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Jia Li Bo *Ke Lun, China.*
Pentoxifylline (p. 1465·3).

Jia Li Ke *ShiJiaZhuang No 4, China.*
Gatifloxacin lactate.
Bacterial infections.

Jia Li Ning *Kangtai, China; Zhongsheng Haitian, China.*
Gatifloxacin mesilate.
Bacterial infections.

Jia Lin Hao *Ahua Bio, China.*
⊗Epoetin (p. 1141·1).
Anaemia in renal failure.

Jia Luo Ling *Treeful, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia Luo Tan *Weiqida, China.*
Mezlocillin sodium (p. 324·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Jia Mai Xin *Yatai, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia Ming *Xing Qi, China.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Jia Nai *Qi Du, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Jia Le Ning *Taihe, China.*
Metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Jia Nuo Mei *Hengsheng, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Jia Nuo Qi *Hengsheng, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Jia Nuo Shun *Hengsheng, China.*
Ibandronate sodium (p. 1184·2).
Hypercalcaemia of malignancy; osteoporosis; bone metastases.

Jia Nuo Tai *Hengsheng, China.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Jia Nuo Xin *Jianfeng, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Jia Pu Le *Pingyuan, China.*
Lorazepam (p. 1080·3).
Anxiety; vomiting associated with chemotherapy; premedication.

Jia Pu Xi *Zhongrui Kangzhi, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Jia Qi *Haini, China.*
Donepezil hydrochloride (p. 390·2).
Dementia; Alzheimer's disease.

Jia Qi Ya *Qilu, China.*
Thiamazole (p. 2345·2).

Jia Rui *Bausch & Lomb, China.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Jia Se Yi *Sine, China.*
Telmisartan (p. 1509·3).
Hypertension.

Jia Shen *Shuai Ke, China.*
Ethylenediamine diaceturate.

Jia Su Lun *Nhwa, China.*
Doxapram hydrochloride (p. 2321·2).
Respiratory depression.

Jia Tai *Jinjian, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia Le Tong Tai *Mei Da Kang Jia Le, China.*
Oxaliplatin (p. 838·1).

Jia Le Tong Xin *Mei Da Kang Jia Le, China.*
Pazufloxacin mesilate (p. 338·1).

Jia Xin *Ke Lun, China.*
Vitamin C (p. 2110·3).

Jia Yi *Topfond, China.*
Liranaftate (p. 588·1).

Jia Yi Ke *Qilu, China.*
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).

Jia Yi Ni *Yabang, China.*
Pazufloxacin mesilate (p. 338·1).

Jia Yi Xin *Foshan Shuanghe, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Jia You *Ya Bao, China.*
Adenosine triphosphate disodium (p. 2430·3); magnesium chloride (p. 1787·1).

Jia Ze *Dayinhaiyang, China.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Jiadi *Pharmachemie, China.*
Megestrol acetate (p. 2289·2).
Malignant neoplasms.

Jiakang *Dawnrays, China.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Jialixin *Xinchang, China.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Jialuoning *Yangtze River, China.*
Dezocine (p. 45·2).
Pain.

Jian Ao *C & O, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Jian Bai *Beiyi Union, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Jian Er Xin *Shengtai, China.*
Diltiazem hydrochloride (p. 1359·2).
Arrhythmias.

Jian Fang Neng *Southwest, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Jian Lang Chen *Jianlang, China.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Jian Lang Xing *Yueyang No 3, China.*
Oxiracetam (p. 393·3).
Dementia; organic brain syndrome.

Jian Tian Neng *Yaoyou, China.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdose; reversal of opioid effects.

Jian Yi *Fengan, China.*
Aceglutamide (p. 2426·2).

Jian Zhi Ting *Xing'an, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Jiang Ke *Jin Si Li, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Jiang Li Shu *Haili, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jiang Shuang *Neptunus, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Jiang Xi *Haisen, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Jiangke *Union Chem & Pharm, China.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Jiannipai *CP Guojian, China.*
Recombinant humanised anti-CD25 monoclonal antibodies.
Transplant rejection.

Jianqi *Qianjiang, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Jiao Tai *Shu Tai Bao, China.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan (p. 1660·1).

Jiaxin *Jing Xin, China.*
Prulifloxacin (p. 345·1).

Jida BenTe *Jida, China.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Jidabokuippo *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); cnidium rhizome; nuphar rhizome; oak bark (p. 2574·1); liquorice (p. 1853·2); rhubarb (p. 1884·2); clove (p. 2481·2).
Traditional Kampo medicine.

Jidox *DR Johns, India.*
Cefixime (p. 240·3).
Bacterial infections.

Jidox-C *DR Johns, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Jie Le *Man Xiu Lei Dun, China.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Jie Ao *Wei Kang, China.*
Vitamin B_6 (p. 2105·3).

Jie Bei *TianJing, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Jie Bin *Shiji Huayang, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Jie Dan *Chang Fu Jie Jing, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Jie Fu *HuaLiDa, China.*
Interferion alfa-2b (recombinant, human) (p. 989·2).

Jie Jie *Hui Feng, China.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; pain.

Jie Ke *Pingyuan, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Jie Ke Da *Hui Yin Bi, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Jie Ke Pai *Changyi, China.*
Benproperine phosphate.

Jie Li *Lixin, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Jie Li Ping *Zhiying, China.*
Ligustrazine phosphate.

Jie Li Qing *Zhiying, China.*
Matrine.

Jie Li Shu *Zhiying, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Jie Li Tai *Zhiying, China.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Jie Luo Lin *Yimin, China.*
Tinidazole (p. 949·2).

Jie Luo Wei *Ke Lun, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Jie Nai *Chang Fu Jie Jing, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Jie Ning *Xinhua, China.*
Aspirin (p. 22·2).

Jie Ping *Tiancheng, China.*
Urapidil (p. 1520·2).
Hypertension.

Jie Qing *LuoXin, China.*
Lappaconitine hydrobromide (p. 1418·1).

Jie Rong *Lukang Chenxin, China.*
Levofloxacin lactate.
Bacterial infections.

Jie Rui Na *Nuo Jin, China.*
Enoxacin gluconate.
Bacterial infections.

Jie Sai *TianJing, China.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Jie Shi *TianJing, China.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Jie Tai *Rongchang, China.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Jie Tong *Sha Pu Ai Si, China.*
Urapidil (p. 1520·2).
Hypertension.

Jie Wei Su *Ke Lun, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Jie Zhi *Sanchao, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Jie Zong *Double-Crane, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

JieAn *Tai Ping, China.*
Aspirin (p. 22·2); magnesium carbonate (p. 1856·2); aldioxa (p. 1692·2).

JieFu *Binhu Shuanghe, China.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Jieheqing *Baiyunshan, China.*
Isoniazid aminosalicylate (p. 311·2).
Tuberculosis.

JieLi *LuoXin, China.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; vaginal trichomoniasis; giardiasis; amoebiasis.

Jielite *Wei Kang, China.*
Ampicillin sodium (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

JieNing *Tiancheng, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Jiening *Bei Te, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Jieqi *Ruizhu, China.*
Levofloxacin hydrochloride.
Bacterial eye infections.

Jiexin *Zhongkai, China.*
A recombinant human granulocyte colony-stimulating factor.
Neutropenia.

Jieyiwei *Chengdu Institute, China.*
A live Japanese encephalitis vaccine (p. 2396·2).
Active immunisation.

Jiffy *Amrutanjan, India.*
⊗Caffeine (p. 1203·3); ephedrine hydrochloride (p. 1663·2); paracetamol (p. 115·1); propyphenazone (p. 127·3).

Jiffy Medi+ Plus *Brovar, S.Afr.†*
Salicylic acid (p. 1719·1).
Calluses.

Jihao *Hengrui, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Jiinkokato *Tsumura, Jpn.*
Atractylodes lancea rhizome; rehmannia root; peony root; citrus unshiu peel; asparagus tuber (p. 2450·2); angelica acutiloba root (p. 2443·3); ophiopogon tuber; phellodendron bark; liquorice (p. 1853·2); anemarrhena rhizome.
Traditional Kampo medicine.

Jiinshihoto *Tsumura, Jpn.*
Cyperus rhizome; bupleurum root; lycium bark; peony root; anemarrhena rhizome; citrus unshiu peel; angelica acutiloba root (p. 2443·3); ophiopogon tuber; atractylodes rhizome; poria sclerotium; fritillaria bulb; liquorice (p. 1853·2); mentha herb.
Traditional Kampo medicine.

Jijufen *Jiuyuan, China.*
Oprelvekin (p. 1157·2).
Chemotherapy-induced thrombocytopenia.

JiLi *JiChuan, China.*
Nimodipine (p. 1455·2).

Jilifen *Huadong, China; Jiuyuan, China; Jiuyuan, Thai.†*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Jimaixin *NCPC, China.*
⊗Epoetin (p. 1141·1).
Anaemia in renal insufficiency.

Jimax *KB, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Jimin FuXin *Jimin, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Jimin Weixin *Jimin, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Jimuxin *NCPC, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.
Neutropenia.

Jin De *Nuo De, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Jin Ao Kang *Conba, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Jin Bo Rui *Neptunus, China; Qilu, China.*
Idebenone (p. 392·3).

Jin Chang *Jifeng, China.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Jin Chen *C-Dragon, China.*
Cefixime (p. 240·3).
Bacterial infections.

Jin Da *Changlian Laifu, China.*
Ornidazole (p. 943·1).
Amoebiasis; anaerobic bacterial infections.

Jin Da Xin *Ba Da, China.*
Lappaconitine hydrobromide (p. 1418·1).

Jin Er Li *Shiqiao, China.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Jin Er Lun *Yiqiao, China.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced depression; acute alcohol poisoning.

Jin De Fei *Neptunus, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Cold symptoms; seasonal allergic rhinitis.

Jin Fu Ning *Jinsai, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Jin Ge Duo Na *Baiyi, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Jin Jie Shu *Sanjing Aifuxi, China.*
Aceglutamide (p. 2426·2).

Jin Kai Ke *Changzhou Siyao, China.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Jin Kang Ling Li *Jinhua, China.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease; dementia.

Jin Kui An *Jinma, China.*
Gatifloxacin mesilate.
Bacterial infections.

Jin Lang *Puhua, China.*
Capsaicin (p. 35·1).

Jin Lei Sai Qiang *Jinsai, China.*
A recombinant human granulocyte colony-stimulating factor.

Jin Lei Sai Yuan *Jinsai, China.*
A recombinant human granulocyte-macrophage colony-stimulating factor.

Jin Li Chen *C-Dragon, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Jin Li Shu *Baiyunshan, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Jin Di Lin *Jinsai, China.*
Octreotide acetate (p. 1924·1).
Variceal haemorrhage; acromegaly; endocrine neoplasms; prevention of complications following pancreatic surgery.

Jin Lu Kang *Jintai, China.*
Interleukin-2 (recombinant, human) (p. 810·1).

Jin Luo *Qilu, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left ventricular dysfunction following myocardial infarction.

Jin Lv Xin *Hengji, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Jin Mao *Mao Xiang, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Jin Meng *Henghe, China.*
Zopiclone (p. 1118·1).
Insomnia.

Jin Di Na *NEGPF, China.*
Rimantadine hydrochloride (p. 1012·2).
Influenza A.

Jin Niu Er *Shengbaoluo, China.*
⊗Clobetasol (p. 1627·1); tretinoin (p. 1725·2).

Jin Nuo
Note: this name may be used for preparations of different composition.
Dawnrays, China.
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; dyspepsia.

Fenghuang, China.
Azithromycin lactobionate.
Bacterial infections.

Jin Nuo Er Man *Baiqiuen, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Jin Nuo Xing *Jinyu, China.*
Omacetaxine mepesuccinate (p. 837·3).

Jin Pai Qi *Lijun, China.*
Azithromycin sulfate.
Bacterial infections.

Jin Ping Tang *Dayang, China.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jin Shan Qin *Jinshi, China.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Jin Shuang Qi *Shuangqi, China.*
Bifidobacterium; lactobacillus; *Streptococcus thermophilus* (p. 2596·3).

Jin Shun *Hanfang, China.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Jin Si Ping *Luye Sike, China.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Jin Su Rui *Hengji, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Jin Wei *Duoburuifei, China.*
Matrine.

Jin Xi Su *Hanfang, China.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; small-cell lung cancer; cervical cancer.

Jin Xin Tai *Double-Crane, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Jin Ya Jie *Hengji, China.*
Norfloxacin (p. 333·3).
Bacterial infections.

Jin Yang Bo Tai *Zhongxing Hanfang, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Jin Yi Xin *Jingyou, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Jin Yu Star *Jinyu, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Jin Zhou *Tian Fu, China.*
Fluconazole (p. 578·2).
Fungal infections.

Jinbo *TianJin, China.*
Azithromycin maleate.
Bacterial infections.

Jinclox *Om Biotec, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Jinda *Kwizda, Austriat; Riemser, Ger.*
Cimicifuga (p. 2478·1).
Menopausal disorders; premenstrual syndrome.

Jindele *Livzon, China.*
Ranitidine bismuth citrate (p. 1883·3).
Peptic ulcer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

JinDeSi *HuaXia, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual syndrome.

Jindian *Neptunus, China.*
Potassium iodate (p. 2336·3).
Iodine deficiency.

Jing Dan *Huashidan, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Jing Kang *Nhwa, China.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Jing Lu *Sha Pu Ai Si, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; acid aspiration; pathological gastric acid secretion.

Jing Ning *Sanjiu Yimin, China.*
Arginine hydrochloride (p. 2049·1).

Jing Ping *Team, China.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Jing Tan Song *Minsheng, China.*
Raceanisodamine hydrochloride.

Jing Wei *Boke, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Jing Xin *Double-Crane, China.*
Sodium ferulate.

Jing Yu *Baijingyu, China.*
Ketoconazole (p. 585·3).
Fungal skin infections.

JinGanTai *Baili Tianhua, China.*
Transfer factor (against hepatitis B) (p. 2633·2).

Jingkang *Hua Lu, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

JinHe *Zhonglian, China.*
Tinidazole (p. 949·2).

Jini *Cadila, India.*
Ginkgo biloba (p. 2512·3).

Jinkangpuli *Conba, China.*
Naproxen (p. 98·2).
Pain.

Jinquan *Ao Tuo Kang, China.*
Gentamicin sulfate (p. 304·2); procaine hydrochloride (p. 1994·3); vitamin B_{12} (p. 2107·2).
Gastritis.

Jinsoin *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; pueraria root; platycodon root; citrus unshiu peel; jujube; ginseng (p. 2513·3); liquorice (p. 1853·2); immature orange; perilla; ginger (p. 1844·1); peucedanum root.
Traditional Kampo medicine.

Jinteli *Teva, USA.*
Ethinylestradiol (p. 2275·3); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

JinTong *Jinchang, China.*
Rimantadine hydrochloride (p. 1012·2).

Jintropin *Jinsai, China.*
⊗Growth hormone (human, recombinant) (p. 1919·3).
Growth hormone deficiency; cachexia; short bowel syndrome.

Jintropine *Europharm, Rus.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure.

JinWei *Sanghai, China.*
Vitamins.

JinWeiHe *BSPC, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Jinxieke *Changzhou Siyao, China.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Jinxili *Xincat, China.*
Rifaximin (p. 355·2).
Gastrointestinal infections.

Jinxin *LuoXin, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

JinZhenXing *Jinghua Huixing, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jiouting *Jiuyuan, China.*
Palonosetron hydrochloride (p. 1875·1).
Nausea and vomiting.

Jipailin *Huadong, China; Jiuyuan, China.*
Heparin sodium (p. 1396·3).
Thrombosis prophylaxis.

Jisaixin *NCPC, China.*
A recombinant human granulocyte colony-stimulating factor.
Neutropenia.

JiShu *Jiu Dian, China.*
Levodropropizine (p. 1662·3).
Cough.

Jitrocelvý *Megafyt-R, Cz.*
Plantaginis (p. 2604·2).
Respiratory-tract disorders; skin disorders; wounds.

Jiu An Suxin *Jiu An, China.*
Citicoline sodium (p. 2480·2).
Parkinsonism; cerebrovascular disease; brain injury.

Jiu Ao *Tian Yu, China.*
Ranitidine hydrochloride (p. 1882·1).
Pathological gastric acid production; peptic ulcer; acid aspiration.

Jiu Bang *Yabang, China.*
Cefixime (p. 240·3).
Bacterial infections.

Jiu Bao Ka Di *Honglin, China.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Jiu Bao Ke *Honglin, China.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Jiu Li *Qingjiang, China.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

Jiu Ning *Shengying, China.*
Diclofenac potassium (p. 48·3).

Jiu Nuo *Xinhua, China.*
Enoxacin (p. 290·2).
Bacterial infections.

Jiu Ren *Topfond, China.*
Troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids.

Jiu Tai *Jiu Tai, China.*
Chlorhexidine (p. 1743·2).

Jiubaofen *Honglin, China.*
Ibuprofen (p. 68·2).
Pain; fever.

Jiubaopine *Honglin, China.*
Nifedipine (p. 1447·2).
Hypertension; ischaemic heart disease; angina pectoris.

JiuLi *XinShiDai, China.*
Zidovudine (p. 1024·2).
HIV infection.

Jiuyue *Jiu Dian, China.*
Cilnidipine (p. 1337·1).
Hypertension.

Jivak *Alna, India.*
Ubidecarenone (p. 2637·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); arginine (p. 2049·1); selenium (p. 2086·3).

JiWei *Ouhua, China.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Jizusoippo *Tsumura, Jpn.*
Cnidium rhizome; atractylodes lancea rhizome; forsythia fruit; lonicera leaf and stem; saposhnikovia root; liquorice (p. 1853·2); schizonepeta tenuifolia; carthamus tinctorius; rhubarb (p. 1884·2).
Traditional Kampo medicine.

J-Max *Jaymac, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

J-Max DHC *Jaymac, USA.*
Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2).
Cough.

J.Navit *Pharmasant, Thai.†*
Vitamins.

Jobenguaan *CIS, Neth.†*
Iodine-131 (p. 2225·3) iobenguane.
Radioimaging of malignant neoplasms.

Jocet *Unique, Rus.*
⊗Salbutamol sulfate (p. 1220·2); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); levomenthol (p. 2553·2).
Respiratory-tract disorders.

Jocin *DR Johns, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Jod beta *Betapharm, Ger.*
Potassium iodide (p. 2336·3).
Goitre; iodine deficiency.

Jod plus *Selenium Pharma, Hung.†*
Potassium iodide (p. 2336·3).
Iodine deficiency; iodine supplement.

Jodbalance *Nycomed, Rus.*
Potassium iodide (p. 2336·3).
Goitre.

Jodetten *Henning, Ger.†; Sanofi-Aventis, Ger.†*
Potassium iodide (p. 2336·3).
Iodine-deficiency disorders.

Jodgamma *Worwag, Ger.*
Potassium iodide (p. 2336·3).
Iodine-deficiency disorders.

Jodi *Gemi, Pol.*
Povidone-iodine (p. 1767·1).
Disinfection of skin and wounds.

Jodid *Merck, Austria; Merck Serono, Ger.; Ratiopharm, Ger.; Merck, Hung.; Merck, Philipp.; Merck, Pol.; Merck, Rus.*
Potassium iodide (p. 2336·3).
Iodine-deficiency disorders; goitre.

Jodieci *Esoform, Ital.*
⊗Povidone-iodine (p. 1767·1); alcohol (p. 1733·1).
Infected skin disorders; disinfection of skin and superficial wounds.

Jodisol *Spofa, Cz.*
Povidone-iodine (p. 1767·1).
Disinfection of skin, wounds, and mucous membranes.

Jodix *Orion, Fin.*
Potassium iodide (p. 2336·3).
Protection of the thyroid from radio-iodine.

Jodlauge, Tölzer *Jodquellen, Ger.*
Anions: chloride, bromide, iodide, bicarbonate; cations: sodium, magnesium, potassium, calcium.
Circulatory disorders.

Jodo Calcio Vitaminico *Bruschettini, Ital.*
Sodium iodide (p. 2337·1); potassium iodide (p. 2336·3); rubidium iodide (p. 2608·2); calcium gluconate (p. 1783·3); ascorbic acid (p. 2110·3).
Cataracts.

Jodocourir *Diapit, Gr.*
Povidone-iodine (p. 1767·1).

Jodocur *Farmacologico Milanese, Ital.*
Povidone-iodine (p. 1767·1).
Mouth and throat infections.

Jodogard *Gedis, Ital.†*
Povidone-iodine (p. 1767·1).
Skin, hand, and surface disinfection.

Jodol *Alapis, Gr.*
Ondansetron hydrochloride (p. 1872·1).

Jodomax *Selenium Pharma, Hung.†*
Potassium iodate (p. 2336·3).
Hyperthyroidism; protection of the thyroid from radio-iodine.

Jodoplex *Streuli, Switz.*
Povidone-iodine (p. 1767·1).
Skin, hand, and mucous-membrane disinfection; wounds; ulcers; burns; infected skin disorders.

Jodoplex Teinture *Streuli, Switz.†*
⊗Povidone-iodine (p. 1767·1); isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1).
Skin disinfection; wounds.

Jodosan *Faran, Gr.; Brenntag, Norw.†*
Iodine (p. 2336·3).
Disinfection of skin and wounds.

Jodosept *Biosintez, Rus.*
Povidone-iodine (p. 1767·1).
Skin disinfection; instrument disinfection; skin and vaginal infections; wounds.

Jodthyrox *Merck, Austria; Merck, Cz.; Merck Serono, Ger.; Merck, Pol.; Nycomed, Rus.*
Levothyroxine sodium (p. 2339·1); potassium iodide (p. 2336·3).
Goitre; iodine-deficiency disorders; hypothyroidism.

Jofen *Lamda (Λαμδα), Gr.*
Baclofen (p. 2014·3).
Spasticity.

Jogen *General Drugs House, Philipp.*
Cloxacillin sodium (p. 275·1).
Gram-positive bacterial infections.

Joglit *DR Johns, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Johanicum *Apomedica, Austria.*
St John's wort (p. 449·1).
Depression.

John Plunketts Protective Day Moisturiser *Plunkett, Austral.*
SPF 15: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Emollient; sunscreen.

John Plunketts Sunspot Cream *Plunkett, Austral.*
Salicylic acid (p. 1719·1).
Actinic keratosis.

Johnson's Antiseptic Powder *Pharmedica, S.Afr.†*
Benzethonium chloride (p. 1738·1).
Skin disorders.

Johnson's Baby Clear *Johnson & Johnson, Thai.*
Ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Johnson's Baby Creme Contra Assaduras *Johnson & Johnson, Braz.*
Barrier cream.
Nappy rash.

Johnson's Baby Double Protection Powder *Johnson & Johnson, Philipp.*
Talc (p. 1722·2); magnesium stearate (p. 2195·3); zinc oxide (p. 1729·1).
Nappy rash.

Johnson's Baby Loção Anti-Mosquito *Johnson & Johnson, Braz.*
Ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Johnson's Baby Nappy Cream *Pharmedica, S.Afr.*
Zinc oxide (p. 1729·1).
Napkin rash; skin irritation.

Johnson's Baby Sorbolene *Johnson & Johnson, Philipp.*
Soap substitute.

Johnson's Baby Sunblock *Johnson & Johnson, USA.*
SPF 15: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Johnson & Johnson, USA.
SPF 30: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1) octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Johnson's Diaper Rash *Johnson & Johnson, Canad.†*
Zinc oxide (p. 1729·1).
Nappy rash.

Johnson's Sabonete Liquido Anti-Septico *Johnson & Johnson, Braz.*
Triclosan (p. 1773·2).
Soap substitute.

Joincerin *Torrent, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Joint *Rontag, Arg.*
Oxaceprol (p. 2578·2).
Musculoskeletal and joint disorders.

Joint Action *Lifeplan, UK.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2).
Musculoskeletal and joint disorders.

Joint Care
Note: this name may be used for preparations of different composition.
Mega We Care, Singapore.
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Tempo Scan Pacific, Indon.
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); manganese (p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1); selenium (p. 2086·3).
Joint disorders.

Joint Care Plus *Tempo Scan Pacific, Indon.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); manganese

(p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1); selenium (p. 2086·3).
Joint disorders.

Joint Ease *Eagle, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); boswellia serrata (p. 2507·3); milk thistle (p. 1561·1); grape seed (p. 2521·3); curcuma longa; murraya exotica; lecithin (p. 2542·2); vitamins; minerals.
Joint disorders.

Joint Formula Advanced *Blackmores, Austral.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate sodium chloride (p. 2515·3); manganese gluconate (p. 2081·2); borax (p. 2459·2).
Osteoarthritis.

Joint Formula Advanced with MSM Booster *Blackmores, Austral.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate sodium chloride (p. 2515·3); dimethyl sulfone (p. 2493·3).
Joint pain.

Joint Guard *Psychotropics, India.*
Chondroitin sulfate (p. 2476·1); glucosamine hydrochloride (p. 2515·3); dimethyl sulfone (p. 2493·3).

Joint Mobility *Bioglan, Austral.*†
Glucosamine sulfate (p. 2515·3); turmeric (p. 2218·1); Indian frankincense (p. 2507·3); capsicum (p. 2469·3); zinc gluconate (p. 2126·2); manganese amino acid chelate (p. 2048·3).
Musculoskeletal and joint disorders.

Joint & Muscle Cream *Brauer, Austral.*
Arnica (p. 2447·2); bellis perennis (p. 2454·2); bryonia alba; St John's wort (p. 449·1); kalmia latifolia (p. 2537·2); marsh tea (p. 2550·1); rue (p. 2608·2); ranunculus bulbosus; rhus toxicodendron (p. 2603·3); apis mel. (p. 2445·2); belladonna (p. 2453·3); camphora (p. 2466·2); strontium carb.; symphytum (p. 2484·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Joint & Muscle Oral Spray *Brauer, Austral.*†
Apis mellifera (p. 2445·2); bryonia (p. 2461·3); rhus toxicodendron (p. 2603·3); causticum (p. 2595·3); colchicum autumnale; ledum palustre (p. 2550·1); merc. sol. (p. 2555·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Joint Support *Eurosup, Ital.*
Glucosamine sulfate (p. 2515·3); acetyl glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1).
Cartilage disorders.

Jointace
Note: this name may be used for preparations of different composition.
Meyer, India.
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.
Nobel, Turk.
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Musculoskeletal and joint disorders.
Vitabiotics, UK.
Topical gel: Glucosamine (p. 2515·3); chondroitin (p. 2476·1).
Musculoskeletal and joint disorders.
Vitabiotics, Indon.
Glucosamine sulfate (p. 2515·3); dimethyl sulfone (p. 2493·3); colecalciferol (p. 2113·1); manganese (p. 2081·2); zinc (p. 2126·1); copper (p. 2057·1); boron (p. 2052·3); vitamin C (p. 2110·3).
Joint disorders; osteoarthritis.
Vitabiotics, UK.
Tablets: Collagen (p. 2483·2); glucosamine (p. 2515·3); chondroitin (p. 2476·1); vitamins; ginger (p. 1844·1); minerals.
Dietary supplement.
Vitabiotics, UK.
Capsules: Glucosamine (p. 2515·3); omega-3 fish oil; cod-liver oil (p. 2056·3); vitamins; trace elements.
Nutritional supplement.
Vitabiotics, UK.
Effervescent tablets: Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); magnesium (p. 1786·3).
Nutritional supplement.

Jointace Forte *Meyer, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate potassium chloride (p. 2515·3).

Jointace-DN *Meyer, India.*
Glucosamine sulfate potassium chloride (p. 2515·3); dimethyl sulfone (p. 2493·3).

JointCare Max *Seven Seas, UK.*
Glucosamine sulfate (p. 2515·3); cod-liver oil (p. 2056·3); marine collagen (p. 2483·2).
Joint disorders.

JointEeze *Natures Aid, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

Joint-e-Licious *Naturopathica, UK.*
Glucosamine hydrochloride (p. 2515·3).
Joint pain.

Jointfit *Combiphar, Indon.*
Cream: Glucosamine hydrochloride (p. 2515·3); glucosamine sulfate (p. 2515·3).
Joint disorders.
Combiphar, Indon.
Powder for oral solution: Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); colecalciferol (p. 2113·1); collagen (p. 2483·2); vitamin C (p. 2110·3); calcium lactate gluconate (p. 1784·2).
Bone and joint disorders.
Combiphar, Indon.
Topical gel: N-Acetyl glucosamine (p. 2515·3); aloe vera (p. 1693·2); vitamin E (p. 2119·1).
Joint disorders.

JointFlex
Note: this name may be used for preparations of different composition.
SmartScience, Singapore.
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); camphor (p. 2466·2); peppermint oil (p. 1877·1); tocoferil acetate (p. 2119·2).
Joint and peri-articular disorders.

Jointflex
Note: this name may be used for preparations of different composition.
Alterna, Canad.†
Camphor (p. 2466·2).

Jointil *Sanat, India.*
Boswellia serrata (p. 2507·3); curcuma longa; cyperus rotundus; zingiber officinale.
Osteoarthritis; rheumatoid arthritis.

Jointil Orthopedic oil *Sanat, India.*
Boswellia serrata (p. 2507·3); curcuma longa; zingiber officinale.

Jointmax *YSP, Malaysia.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Jointop *Intra-Labs, India.*
Capsules: Glucosamine sulfate (p. 2515·3); dimethyl sulfone (p. 2493·3); colecalciferol (p. 2113·1).
Intra-Labs, India.
Topical oil: Camphor trigonella (p. 2466·2); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1).

Joints in Motion *Golden Glow, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Jolessa *Barr, USA.*
84 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Jolethin *Daiichi Sankyo, China.*
Iodized lecithin.

Jolice *Cure Quick, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Jolistar *Mankind, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Jolivel *Torrent, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Jolivette *Watson, USA.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Jolyon-MD *Lupin, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Jomax *Taurus, Ger.*†
Bufexamac (p. 30·2).
Skin disorders.

Jonac *Zydus, India.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Jonac Plus *Zydus, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Jonctum Cica *Sinclair, Fr.*
Oxaceprol (p. 2578·2).
Skin irritation.

Jonexa *Genzyme, Hong Kong.*
Sodium hyaluronate (p. 2526·2).
Joint disorders; osteoarthritis of the knee.

Jonosteril *Fresenius Kabi, Ger.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Jonosteril Basic z Glukoza *Fresenius Kabi, Pol.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Jonty *Alkem, India.*
Vitamins; minerals; trace elements; glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); carbohydrate.

Jopamiro *Bracco, Austria.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Jope *DR Johns, India.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Jopram *DR Johns, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Josacine *Astellas, Fr.*
Josamycin (p. 314·2) or josamycin propionate (p. 314·2).
Bacterial infections.

Josalid *Sandoz, Austria.*
Josamycin (p. 314·2).
Bacterial infections; toxoplasmosis.

Josamina *Ferrer, Spain.*
Josamycin propionate (p. 314·2).
Bacterial infections.

Josamy *Astellas, China; Astellas, Jpn.*
Josamycin propionate (p. 314·2).
Bacterial infections.

Josenta *Deutsche, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Joset *Unique, Ukr.*
⊗Salbutamol sulfate (p. 1220·2); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Respiratory-tract disorders.

Josh-IN *Auspi, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Josilvite + Calcium *Pharmacare, Philipp.*
Calcium lactate (p. 1784·1); vitamins.
Nutritional supplement.

Josir *Boehringer Ingelheim, Fr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Jotac *Keshav, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Jotac-D *Keshav, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Jotexin *Chew, Thai.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Jouvence
Note: this name may be used for preparations of different composition.
Aroli-Aromes, Fr.
Calophyllum oil; beeswax (p. 2170·2); lanolin (p. 2219·3).
Dry skin disorders.

Jouvence de l'Abbé Soury *Omega, Fr.*
Topical gel: Hamamelis (p. 2523·3); viburnum (p. 2458·1).
Capillary fragility; venous insufficiency.
Omega, Fr.
Oral solution; tablets: Hamamelis (p. 2523·3); calamus (p. 2464·2); piscidia (p. 2536·3); viburnum (p. 2458·1).
Peripheral vascular disorders.

Jovadolin *Gedeon Richter, Neth.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Jovia *Medichem, Philipp.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Jovin *Ind-Swift, India.*
St John's wort (p. 449·1).

Jowidarmin *Hanosan, Ger.*
Echinacea (p. 2498·1); kalium chloricum (p. 1793·2); thuja occidentalis (p. 2629·3); strychnos nux-vomica (p. 2573·3); gelsemium sempervirens (p. 2511·2); aconitum nepellus (p. 2428·3); arnica montana (p. 2447·2); eupatorium perfoliatum (p. 2459·1); cinchona pubescens (p. 2478·3); acidum arsenicosum (p. 2448·1); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Jox
Note: this name may be used for preparations of different composition.
DR Johns, India.
Ofloxacin (p. 334·3).
Bacterial infections.
Teva, Cz.; Ivax, Rus.; Teva, Ukr.
Povidone-iodine (p. 1767·1); allantoin (p. 1693·1).
Mouth and throat disorders.

Joxar *Chemica, Gr.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Joxcy *DR Johns, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Jox-TZ *DR Johns, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Joyce *Aamorb, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc sulfate (p. 2126·2).

Joy-Rides *GSK Consumer, UK.*
Hyoscine hydrobromide (p. 1845·3).
Motion sickness.

Joysun *YSP, Malaysia.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Infected eye and ear disorders.

Joyzol *Wockhardt, India.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Jozide *DR Johns, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Jozide-M *DR Johns, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

JP Tone *Jagsonpal, India.*
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).
Anaemias; tonic.
Jagsonpal, India.
Injection: Vitamin B substances (p. 2102·3).

JP Tone-TR *Jagsonpal, India.*†
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Anaemias; tonic.

JP-Cilin *Jagsonpal, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Jsoskleran *Iso, Ger.*
Arnica (p. 2447·2); aconitum (p. 2428·3); avena (p. 2451·1); echinacea (p. 2498·1); solidago (p. 2620·1); vincetoxicum; populus.
Homoeopathic preparation.

Jsostoma S *Iso, Ger.*
Cochlearia; hydrastis (p. 2528·1); matr. chamomilla (p. 2474·1); nasturtium (p. 2454·3); sarsaparilla (p. 2610·3); scrophularia nod.; strychnos nux vomica (p. 2573·3); veronica; tussilago farfara (p. 1659·2).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Jstat *Indo French, India.*
Atorvastatin (p. 1309·2); ubidecarenone (p. 2637·1); selenium (p. 2086·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

J-Tan *Jaymac, USA.*
Brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

J-Tan D *Jaymac, USA.†*
Brompheniramine tannate (p. 618·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

J-Tan D HC *Jaymac, USA.†*
⊗Brompheniramine maleate (p. 618·1); hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ju He Li *Qilu, China.*
A human recombinant interleukin-2 (p. 810·1).

Ju Ke *Meitong, China.*
Lactobacillus complex (p. 2596·3).

Ju Tai *Jutai, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ju Ye Mei Qing *Yaoda, China.*
Matrine.

Juan *Cadila, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Jucapt *Juta, Ger.†; Q-Pharm, Ger.†*
Captopril (p. 1331·2).
Heart failure; hypertension.

Jucitron *Unijules, India.*
Sodium acid citrate (p. 1781·1).

Jucolon *Anpharm, Pol.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Jucurba *Strathmann, Ger.*
Capsules; tablets: Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders.

Judom *DR Johns, India.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia; migraine.

Juformin *Juta, Ger.†; Q-Pharm, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jufurix *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Jugam *Natco, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Juglanex *Europe Biofarm, Rus.*
English walnut (p. 2646·1).
Chronic venous insufficiency.

Jula *Fem Care, India.*
Aloe vera (p. 1693·2).

Julab *Biolab, Hong Kong†; Biolab, Thai.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

JuLax *Shreya, India.*
Bisacodyl (p. 1821·1).
Constipation.

Juliane *Zentiva, Neth.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Juliet *Bayer, Austral.*
21 Tablets, ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2) 7 tablets, inert.
Combined oral contraceptive; androgenisation in women.

JulMag *Julphar, UAE.*
Magnesium carbonate (p. 1856·2); ascorbic acid (p. 2110·3).
Dietary supplement.

Julmentin *Julphar, UAE.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Royale, Philipp.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Julphacef *Julphar, UAE.*
Cefradine (p. 249·1).
Bacterial infections.

Julphamox *Julphar, UAE.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Julphapen *Julphar, UAE.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Julphasole *Julphar, Malaysia.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Julvitalis *Julphar, UAE.*
Vitamins.
Dietary supplement.

Jumax *Torrent, India.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Jumex *Ivax, Arg.; Sanofi-Aventis, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Chiesi, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Philipp.; Chinoin, Pol.; Novartis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Sanofi-Aventis, Venez.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism; dementia; Alzheimer's disease.

Jumexal *Sanofi-Aventis, Switz.†*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Jumexil *Chiesi, Braz.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Jumihaidokuto *Tsumura, Jpn.*
Platycodon root; bupleurum root; cnidium rhizome; poria sclerotium; saposhnikovia root; liquorice (p. 1853·2); schizonepeta tenuifolia; ginger (p. 1844·1); oak bark (p. 2574·1); aralia rhizome.
Traditional Kampo medicine.

Jumo *Psychotropics, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Jumocip *Psychotropics, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Jumslim *Probiomed, Mex.*
Tamsulosin (p. 2369·1).
Benign prostatic hyperplasia.

Jumtab *Probiomed, Mex.*
Interferon beta (p. 996·1).

Jun Di *Lunan, China.*
Faropenem sodium (p. 298·2).

Jun Ao *Ke Lun, China.*
Lysine hydrochloride (p. 2079·3).

Jun Da Ke *Boda, China.*
Aceglutamide (p. 2426·2).

Jun Da Kui *New Asiatic, China.*
Ligustrazine phosphate.

Jun Da Tan *New Asiatic, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Jun Da Yuan *New Asiatic, China.*
Oxymatrine.

Jun Er Qing *Lunan, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Jun Fen *Lukang Chenxin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Jun Fu Le *Ya Bao, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Jun Jia *Jiangxi, China.*
Micronomicin sulfate (p. 324·2).

Jun Jian *Lierfan, China.*
Sodium new houttuyfonate.

Jun Jie *Lunan, China.*
Azithromycin (p. 221·2) or azithromycin lactobionate.
Bacterial infections.

Jun Jing *Jinyang, China.*
Ligustrazine phosphate.

Jun Kai *Si Huan Ke Bao, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Jun Ke Duo *Tailong, China.*
Pazufloxacin mesilate (p. 338·1).

Jun Li Da *Shengyong, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jun Lie Xin *Neptunus, China.*
Naftopidil (p. 2361·1).

Jun Neng *Hanmi, China.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Jun Ning *Yangtze River, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Jun Pu *SanJiu JiShi, China.*
Pazufloxacin mesilate (p. 338·1).

Jun Qiang *Tongyong, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Jun Qing *Runkang, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Jun Ran *Jiangxi, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Jun Shi Da Xin *Tiancheng, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Jun Te *Hisun, China.*
Cefixime (p. 240·3).
Bacterial infections.

Jun Wei *Jiangxi, China.*
Micronomicin sulfate (p. 324·2).

Jun Wei Qing *Tianlong, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Jun Xin
Note: this name may be used for preparations of different composition.
En Ze Jia Shi, China.
Levofloxacin lactate.
Bacterial infections.

Jun Yi
Note: this name may be used for preparations of different composition.
Yangzhou No 3, China.
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Junamac *Cantassium Co., UK.*
Vitamins; minerals.

Junchoto *Tsumura, Jpn.*
Rehmannia root; angelica acutiloba root (p. 2443·3); skullcap root (p. 2617·1); immature orange; apricot kernel (p. 2445·3); magnolia bark; rhubarb (p. 1884·2); peach kernel; hemp fruit; liquorice (p. 1853·2).
Traditional Kampo medicine.

Junel Fe *Barr, USA.*
21 Tablets, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Junelic *Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Jungamals *Nu Skin, Canad.*
Vitamins; minerals.

Jungborn *Taro, Israel.*
Oral granules: Senna (p. 1885·1).
Constipation.

Taro, Israel.†
Teabags: Senna (p. 1885·1); tilia (p. 2631·3); caraway (p. 2470·2); aniseed (p. 2444·2); fennel (p. 2503·2); bearberry (p. 2453·2); chamomile (p. 2474·1); peppermint leaf (p. 1877·1).
Constipation.

Jungle *Sagmel, Rus.*
Vitamins; with or without minerals.

Jungle Formula Insect Repellent *Chefaro, UK.*
Diethyltoluamide (p. 2153·1).

Junidom *Elder, India.*
Domperidone (p. 1838·1).
Nausea and vomiting.

Junifen *Reckitt Benckiser, Spain.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Junifree *Elder, India.*
Bisacodyl (p. 1821·1).
Constipation.

Junik *Astellas, Ger.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Junimol
Note: this name may be used for preparations of different composition.
Elder, India.
Paracetamol (p. 115·1).
Pain; fever.

Heromycin, Thai.
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Junior Algon *Elvipe, Gr.*
Aspirin (p. 22·2); paracetamol (p. 115·1). Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever.

Junior Citrex *Pharmaniaga, Malaysia.*
Vitamins; omega-3 marine triglycerides (p. 1460·3) or lysine (p. 2079·3).
Nutritional supplement.

Junior Citrex Cal-Mag-D3 *Pharmaniaga, Malaysia.*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Dietary supplement.

Junior Ideal Quota *Cantassium Co., UK.*
Vitamins; minerals.

Junior Kao-C *Torbet Laboratories, UK.*
Calcium carbonate (p. 1824·3); light kaolin (p. 1850·1).
Diarrhoea.

Junior Strength Cold DM *Vita Health, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Juniorlanzol *Cipla, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Juniorvit *Pharmadass, UK.*
Vitamins; minerals.

Juniperus Complexe No 6 *Lehning, Fr.*
Juniperus (p. 2537·1); mercurius corrosivus (p. 2555·2); terebinthina; acidum nitricum (p. 2572·3); sabal serulata (p. 2363·3); thuya occidentalis (p. 2629·3); cantharis (p. 2469·2); atropa belladonna (p. 2453·3); chelidonium (p. 2522·2); dulcamara (p. 2497·3).
Homoeopathic preparation.

Juniz *Elder, India.*
Diazepam (p. 1063·2).
Anxiety.

Junizac *Juta, Ger.†; Q-Pharm, Ger.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

JunQing *Qi Li, China.*
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias.

JunXin
Note: this name may be used for preparations of different composition.
Chia Tai, China.
Netilmicin sulfate (p. 331·1).
Bacterial infections.

JunYi
Note: this name may be used for preparations of different composition.
Pengyao, China.
Ethylenediamine diaceturate.

Jurnista *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Alza, Israel†; Janssen-Cilag, Ital.; Janssen, Philipp.; Janssen-Cilag, Port.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Switz.; Johnson & Johnson, Turk.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Jusgo *Indi, India.*
Linseed oil (p. 2544·2); diclofenac diethylamine (p. 48·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); benzyl alcohol (p. 1739·3).
Musculoskeletal, joint, and soft-tissue disorders.

Jusgo-MR *Indi, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Jusline 30/70 *Julphar, UAE.*
⊗A mixture of insulin injection (human) 30% and isophane insulin (human) 70% (p. 475·3).
Diabetes mellitus.

Jusline N *Julphar, UAE.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Jusline R *Julphar, UAE.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Jusprin *Julphar, UAE.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Just for Kids
Note: this name may be used for preparations of different composition.
3M Espe, USA.
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Justegas *Juste, Spain.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Justelax *Juste, Spain.†*
Sennosides A and B (p. 1885·2).
Bowel evacuation.

Justin
Note: this name may be used for preparations of different composition.
Ifars, Indon.
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Neon, India.
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Justor *Chiesi, Fr.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Justum *Sandoz, Arg.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; delirium tremens; alcohol withdrawal; panic disorder.

Jutabis *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Jutabloc *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias; hypertension; myocardial infarction; migraine.

Jutaclin *Juta, Ger.†; Q-Pharm, Ger.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Jutacor comp *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Jutadilat *Juta, Ger.†; Q-Pharm, Ger.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Jutadol *Juta, Ger.†; Q-Pharm, Ger.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Jutafenac *Juta, Ger.†; Q-Pharm, Ger.†*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Jutagilin *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Jutalar *Juta, Ger.†; Q-Pharm, Ger.†*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Jutalex *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Jutamox *Juta, Ger.†; Q-Pharm, Ger.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Jutapress *Juta, Ger.†; Q-Pharm, Ger.†*
Nitrendipine (p. 1456·3).
Hypertension.

Jutaxan *Juta, Ger.†; Q-Pharm, Ger.†*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Jutussin *Reckeweg, Ger.*
Belladonna (p. 2453·3); bryonia (p. 2461·3); cuprum aceticum (p. 2486·2); drosera (p. 2497·2); sticta (p. 2546·1).
Homoeopathic preparation.

Jutussin R9 *Reckeweg, Neth.*
Belladonna (p. 2453·3); cuprum aceticum (p. 2486·2); sticta pulmonaria (p. 2546·1); bryonia cretica; drosera rotundifolia (p. 2497·2).
Homoeopathic preparation.

Juv 110 *Phonix, Ger.*
Acer negundo; condurango (p. 2485·3); fraxinus americana; gallae (p. 2508·3); haematoxylon campechianum; lycopodium (p. 2546·3); prunus padus e cortice; raphanus; scrophularia nodosa; thuja (p. 2629·3); ulmus campestris; viscum album (p. 2560·2).
Homoeopathic preparation.

Juvederm *Allergan, NZ; Allergan, Singapore; Allergan, USA.*
Hyaluronic acid (p. 2526·2).
Lidocaine hydrochloride (p. 1988·2) is included in some injections to reduce the pain of injection.
Facial wrinkles and folds.

Juvederm Ultra XC *Allergan, Thai.*
Hyaluronic acid (p. 2526·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Facial wrinkles and folds.

Juvela
Note: this name may be used for preparations of different composition.
Eisai, Jpn.
Tocoferil acetate (p. 2119·2) or tocoferil nicotinate (p. 1516·1).
Hypertension; hyperlipidaemias; peripheral circulatory disorders.

Scientific Hospital Supplies, UK.
A range of low-protein foods for special diets.

Scientific Hospital Supplies, Irl.†
Food for special diets.
Gluten-sensitive enteropathies.

Juvelon *Eisai, Indon.*
Vitamins.
Dietary supplement.

Juvelon B *Eisai, Indon.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Juvelon E+ *Eisai, Philipp.*
Vitamins.

Juvelon-C *Eisai, Indon.*
Ascorbic acid (p. 2110·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Nutritional supplement.

Juvenia *Floxia, Singapore.*
Emollient.
Skin ageing; wrinkles.

Juvenlife *New Life, Arg.*
Trace elements; vitamins.
Dietary supplement.

Juvent *Chemo-Drugs, India.*
Vitamins; trace elements.

Juvental *Hennig, Ger.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Juverital *Labormed, Cz.; Labormed, Denm.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Juvigor *Roux-Ocefa, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Juvinate *Biophar, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Juvisync *Merck, USA.*
Sitagliptin phosphate (p. 500·1); simvastatin (p. 1489·2).
Cardiovascular risk reduction; hyperlipidaemias; diabetes mellitus.

Juvit *Hasco-Lek, Pol.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Juvit D_3 *Hasco-Lek, Pol.*
Colecalciferol (p. 2113·1).
Rickets; osteomalacia; vitamin D_3 deficiency.

Juvit Multi *Hasco-Lek, Pol.*
Vitamins.

Juxtapid *Aegerion, USA.*
Lomitapide mesilate (p. 1421·3).
Hypercholesterolaemia.

Juzentaihoto *Tsumura, Jpn.*
Astragalus root (p. 2451·1); cinnamon bark (p. 2479·2); rehmannia root; peony root; cnidium rhizome; atractylodes lancea rhizome; angelica acutiloba root (p. 2443·3); ginseng (p. 2513·3); poria sclerotium; liquorice (p. 1853·2).
Traditional Kampo medicine.

Jvastor *Sanify, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Jvastor-EZ *Sanify, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

J-Wort *Lupin, India.*
St John's wort (p. 449·1).

Jyomik *Biocin, India.*
Amikacin (p. 214·1).
Bacterial infections.

K1 *Sivaderm, Arg.*
Phytomenadione (p. 2122·2).

K-10 *GSK, Canad.*
Potassium chloride (p. 1793·2).
Potassium depletion.

K-50 *Valeant, Mex.*
Menadione sodium bisulfite (p. 2122·2).
Haemorrhagic disorders.

K + 10 *Edwards, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

K 1000 *Hanosan, Ger.*
Artemisia absinthium (p. 2426·1); betula pendula (p. 2457·3); gentiana lutea (p. 2512·1); arnica montana (p. 2447·2); panax ginseng (p. 2513·3).
Homoeopathic preparation.

K to Z *Affy, India.*
Ketoconazole (p. 585·3).

Ka Le *Southwest, China.*
Etamsylate (p. 1145·2).
Haemorrhage.

Ka Bei *Southwest, China.*
Bromhexine hydrochloride (p. 1656·3).

Ka Bo *BSPC, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Ka Kai *Kang Yuan, China.*
Pentoxifylline (p. 1465·3).

Ka Di Ke *Daxin, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Ka Lun *Chang Fu Jie Jing, China.*
Troxerutin (p. 2505·3).

Ka Luo Xin *Tianxin, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Ka Ma Duo *Yinhu, China.*
Potassium sodium dehydroandrographolide succinate.

Ka Mai *Huadong, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ka Na Lin *Lai Mei, China.*
Carbon nanoparticles.

Ka Nai Xin *CLS, China.*
Foscarnet sodium (p. 981·1).

Ka Ni Ya *KeRui, China.*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension.

K-A Plus *Diamond, Philipp.*
⊗Vitamins; minerals; ginseng (p. 2513·3); deanol (p. 2319·1); inositol (p. 2533·2); choline chloride (p. 2055·2); linoleic acid (p. 2509·2); lysine hydrochloride (p. 2079·3).
Tonic.

Ka Qu *Wan Te, China.*
Zolmitriptan (p. 682·2).
Migraine.

Ka Rui Lin *AnJieLun, China.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Ka Rui Si *Guanghua, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ka Shu Tai *Jiu Tai, China.*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension.

Ka Tai Ka *Livzon, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ka Wei An *Zhebei, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Ka Xi Nuo *RenFu, China.*
Enoxacin gluconate.
Bacterial infections.

Käärmepakkaus *Lyocentre, Fin.†*
⊗Dexamethasone (p. 1630·3).
Snake bites; bee and wasp stings.

Kaban *Chiesi, Ger.†*
⊗Clocortolone pivalate (p. 1628·1); clocortolone caproate (p. 1628·1).
Skin disorders.

Kabanimat *Chiesi, Ger.†*
⊗Clocortolone pivalate (p. 1628·1); clocortolone caproate (p. 1628·1).
Skin disorders.

Kabian *Temis, Arg.*
Pregabalin (p. 545·3).
Epilepsy.

Kabikinase *Pharmacia Upjohn, Gr.; Pharmacia Upjohn, India; Pfizer, Turk.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

KabiMix *Fresenius Kabi, Port.*
Amino acids; glucose (p. 2068·3); lipids; electrolytes (p. 1775·1).
Parenteral nutrition.

Fresenius Kabi, Irl.†
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).

Kabimmune *Fresenius Kabi, India.*
Carbohydrates; glutamine (p. 2070·3).

Kabipro *Fresenius Kabi, India.*
Preparation for enteral nutrition.

Kabitrol *Kamakshi, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Kabiven *Fresenius Kabi, Arg.; Fresenius Kabi, Austral.; Fresenius Kabi, Austriat; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Indon.; Fresenius Kabi, Irl.; Fresenius Kabi, Malaysiat; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, NZ; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Spain; Fresenius Kabi, UK; Fresenius Kabi, Ukr.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, China; SSPC, China.
Glucose (p. 2068·3); amino acids; lipids.
Parenteral nutrition.

Fresenius Kabi, Denm.; Fresenius Kabi, Fr.; Fresenius Kabi, Ital.
Amino acids; carbohydrate; lipid (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, Fin.; Fresenius Kabi, Mex.; Fresenius Kabi, Swed.
Amino acids; carbohydrates; electrolytes (p. 1775·1); lipids (from soya oil (p. 2092·3)).
Contains egg phospholipids.
Parenteral nutrition.

Fresenius Kabi, Israel; Fresenius Kabi, Singapore; Fresenius Kabi, Thai.
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)).
Parenteral nutrition.

Fresenius Kabi, Port.
Amino acids; carbohydrates; lipids; electrolytes (p. 1775·1).
Parenteral nutrition.

Fresenius Kabi, Turk.
Amino acids; glucose (p. 2068·3); lipids; electrolytes (p. 1775·1).
Parenteral nutrition.

Kabizol *Fresenius Kabi, Chile.*
Metronidazole (p. 936·1).
Bacterial infections; protozoal infections.

Kaboping *Huadong, China.*
Acarbose (p. 466·2).
Diabetes mellitus.

Kacerutin *Purissimus, Arg.*
Vitamin K (p. 2122·1); rutoside (p. 2505·3); vitamin C (p. 2110·3).
Capillary haemorrhage.

KA-Cilone *SM, Thai.†*
⊗Triamcinolone acetonide (p. 1649·1); kanamycin sulfate (p. 314·3).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kacina *Zota, India.*
Amikacin (p. 214·1).
Bacterial infections.

Kacinth-A *Intramed, S.Afr.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kadaleks *Eczacibasi-Baxter, Turk.*
Potassium chloride (p. 1793·2) in glucose.
Hypokalaemia.

Kadalex *Diaco, Ital.*
Potassium chloride (p. 1793·2).
Hypokalaemia; arrhythmias.

Kadcyla *Genentech, USA.*
Ado-trastuzumab emtansine (p. 875·3).
Breast cancer.

KadeFungin *Kade, Ger.*
Clotrimazole (p. 576·2).
Fungal and bacterial infections of the vagina.

KadeFungin Milchsäurekur *Kade, Ger.*
Lactic acid (p. 2539·1).
Restoration of vaginal flora.

Kadeks *Eczacibasi-Baxter, Turk.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1) in glucose.
Fluid and electrolyte disorders; carbohydrate source.

Kadian *Abbott, Canad.; Actavis, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Kadiflam *Metiska, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Kaditic *Ifars, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Kadiur *GiEnne, Ital.*
⊗Potassium canrenoate (p. 1472·2); butizide (p. 1329·3).
Hyperaldosteronism.

Kadol *Teofarma, Ital.*
Phenylbutazone (p. 125·1).
Musculoskeletal and soft-tissue disorders.

Kadolax *Hua, Thai.*
Bisacodyl (p. 1821·1).
Constipation.

Kadolin *Abbott, Turk.*
Cade oil (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders.

Kadryl *T Man, Thai.*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Pruritus.

KA-EN *Otsuka, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Kaergona Hidrosoluble *Ern, Spain.†*
Menadione (p. 2122·1).
Hypoprothrombinaemia.

Kafa *Vifor, Switz.†*
Paracetamol (p. 115·1).
Pain; fever.

Kafa plus cafeine *Vifor, Switz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Kafalgin *Sanli, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Kafban *Bionet, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Kafenac *Almirall, Ital.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders; pain.

Kafi *Vensat, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Kafi-S *Vensat, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Kafi-TBZ *Vensat, India.*
Ceftriaxone sodium (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Kaflam *Kalbe, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Kaflan *Novartis, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Kafran *Solfran, Mex.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kafsir *Sandoz, Indon.*
⊗Ammonium chloride (p. 1656·1); paracetamol (p. 115·1); ephedrine hydrochloride (p. 1663·2); liquorice (p. 1853·2); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough; nasal congestion; fever; headache.

Kaftax *Umedica, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Kaftensar *Kimia, Indon.*
Losartan potassium (p. 1422·2).
Hypertension.

Kaftrim *Kimia, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Kagocel *Alex Pharm, Ukr.*
Cagocel.
Influenza and other respiratory viral infections; herpesvirus infections; urogenital chlamydial infections.

Kai Le Di *Duoburuifei, China.*
Dipyridamole (p. 1362·2).

Kai Bao Min *Wuxi No 7, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Kai Bao Wei Yuan *Xinyi, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Kai Er *Ethypharm, China.*
Nicergoline (p. 2569·1).
Occlusive arterial disease; mental function impairment.

Kai Er Ding *Zhengtai Jinhu, China.*
Lofexidine hydrochloride (p. 1556·3).

Kai Fen *Tide, China.*
Flurbiprofen axetil (p. 65·2).
Pain.

Kai Fu Fei *Suzhou No 1, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Kai Fu Lin *Changzhou, China.*
Captopril (p. 1331·2).

Kai Fu Te *Changzhou, China.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Kai Fu Xin *Livzon, China.*
Tinidazole (p. 949·2).
Trichomoniasis; bacterial infections.

Kai Ge La Fei *Huaren, China.*
Papaverine hydrochloride (p. 2362·3).

Kai Ji Wei *Tuopeng, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Kai Ke *Changzhou Siyao, China.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bipolar disorder.

Kai Ke Zhi *Kaicheng, China.*
Cefprozil (p. 248·2).
Bacterial infections.

Kai Lai Li Ke *Carelife, China.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Kai Lai Zhi *Carelife, China.*
Epinastine hydrochloride (p. 628·3).

Kai Li Da *General Sanyang, China.*
Amoxicillin (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Kai Li Jin Si *Huaren, China.*
Troxerutin (p. 2505·3).

Kai Li Kang *Tianpu, China.*
Kallidinogenase (p. 2537·2).
Cerebrovascular disorders.

Kai De Long *San Ai, China.*
Matrine.

Kai Luo *Kaifu, China.*
Gamma-aminobutyric acid (p. 2509·2).

Kai Mai *Qian Long, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Kai Mai Si *Hui Ren, China.*
Actarit (p. 17·1).

Kai Di Mi Ding *Zhenao, China.*
Cardiomyopeptide.

Kai Na *Xinyi, China.*
Tiopronin (p. 1578·1).

Kai Nai Jin *Wuxi No 7, China.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency.

Kai Nai Yin *Wuxi No 7, China.*
Aminocaproic acid (p. 1131·3).
Haemorrhage.

Kai Ning *Kaifu, China.*
Chloroprocaine hydrochloride (p. 1983·1).
Local anaesthesia.

Kai Le Ning *Yaoyou, China.*
Tegaserod maleate (p. 1893·1).
Constipation; irritable bowel syndrome.

Kai Nuo *Sine, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Kai Qi *Qianjiang, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Kai Quan *Tong Yong Tong Meng, China.*
Enoxacin (p. 290·2).
Bacterial infections.

Kai Rui *Bausch & Lomb, China.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Kai Shi *Jianmin, China.*
Carmellose sodium (p. 2175·2).

Kai Shu *Jiachen, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Kai Shun *Xin Ma, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Kai Si *General Sanyang, China.*
Cefoperazone sodium (p. 243·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Kai Su Te *Kangde, China.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Kai Te Li *Hengrui, China.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Kai Ti *Jiu Fu, China.*
Calcium citrate (p. 1783·2).

Kai Ting *Tangshi, China.*
Itopride hydrochloride (p. 1850·1).
Nausea and vomiting; gastrointestinal motility disorders.

Kai Tong *Yuhua, China.*
Alprostadil (p. 2352·2).

Kai Wei Ke *General Sanyang, China.*
Mezlocillin sodium (p. 324·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Kai Wei Xin *Tuopeng, China.*
Isosorbide dinitrate (p. 1412·2).
Heart failure; angina pectoris.

Kai Xi Lai *Si Huan Ke Bao, China.*
Diammonium glycyrrhizate.

Kai Xin *Youcare, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Kai Xing *Tuopeng, China.*
Fluconazole (p. 578·2).
Fungal infections.

Kai Yao *Kaifu, China.*
Bulleyaconitine A.

Kai Yin *General Sanyang, China.*
⊗Carbocisteine (p. 1658·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract disorders.

Kai Yu *Kaifu, China.*
Vitamin B_1 (p. 2102·3); vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3); nicotinamide (p. 2083·1); sodium pantothenate (p. 2085·2).

Kai Ze *Suzhong, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Kaicid *Kaizen, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Kaicid-O *Kaizen, India.*
Magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Kaicip *Kaizen, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Kaidilong *Gosun, China.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Kaidixin *Gosun, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Kaidor *Krugher, Ital.*
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Kaifa *General Sanyang, China.*
Ampicillin sodium (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Kaifang *Qilu, China.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Kaiflox *Kaizen, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Kaifu *Kawin, China.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; chronic hepatitis C; chronic hepatitis B; genital warts.

Kaike *Changzhou Siyao, China.*
Bepridil hydrochloride (p. 1316·2).
Angina pectoris.

Kaikeli *Hwang, China.*
Cetylpyridinium chloride (p. 1743·1).

KaiLaiTong *Keruide, China.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm.

Kailanxin *Hayao, China.*
Sultamicillin (p. 369·1).
Bacterial infections.

Kailasa *Duncan, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

KaiLin *Rui Yang, China.*
Mezlocillin sodium (p. 324·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Kailuo *Southwest Synthetic, China.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Kaimil *Lisapharma, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Kainever *Lusomedicamenta, Port.*
Estazolam (p. 1072·2).
Insomnia; premedication.

Kainike *Xinbao, China.*
Kallidinogenase (pancreatic) (p. 2537·2).
Vascular disorders.

Kaion Retard *Andromaco, Chile.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kairase *PDC, India.*
⊗Amylase (p. 2442·1); vitamin B substances (p. 2102·3); pepsin (p. 2586·1); peptone (p. 2086·2).

Kairasec *Liconsa, Neth.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Kaircef *PDC, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Kaircef-S *PDC, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Kairfee *PDC, India.*
Capsules: Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

PDC, India.
Oral drops: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

PDC, India.
Syrup: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

Kairflu *PDC, India.*
Fluconazole (p. 578·2).
Fungal infections.

Kairlact *PDC, India.*
Bovine colostrum (p. 2380·3).

Kairnac *PDC, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Kairnac-P *PDC, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Kaisheng *Southwest Synthetic, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Kaishi *Tide, China.*
Alprostadil (p. 2352·2).
Peripheral vascular disorders.

Kaituss *Kaizen, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Kaiweifu *Xudong Haipu, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure.

KaiXiLai *Xinyi, China.*
Tiopronin (p. 1578·1).

Kaizem *Wockhardt, India.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Kajodan *GL Pharma, Neth.*
Potassium iodide (p. 2336·3).
Nuclear accidents involving release of radioactive isotopes of iodine.

Kajos *Meda, Norw.; Meda, Swed.*
Potassium citrate (p. 1780·3).
Hypokalaemia; potassium supplement.

Kakkonto *Tsumura, Jpn.*
⊗Pueraria root; jujube; ephedra herb (p. 1663·1); liquorice (p. 1853·2); cinnamon bark (p. 2479·2); peony root; ginger (p. 1844·1).
Traditional Kampo medicine.

Kakkontokasenkyushin'i *Tsumura, Jpn.*
⊗Pueraria root; jujube; ephedra (p. 1663·1); liquorice (p. 1853·2); cinnamon (p. 2479·2); peony root; magnolia flower; cnidium rhizome; ginger (p. 1844·1).
Traditional Kampo medicine.

Kal Zarevet *Perrigo, Israel.†*
Calcium carbonate (p. 1824·3).
Antacid; calcium supplement.

Kala
Note: this name may be used for preparations of different composition.
Bernabo, Arg.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.
Freeda, USA.
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement.

Kalac *Universal, Hong Kong.†*
Calcium lactate (p. 1784·1).

Kalamin *Sandoz, Turk.*
Oxolamine citrate (p. 1671·2).
Cough.

Kalanchin *Vifiteh, Rus.*
Kalanchoe.
Gastritis; enterocolitis.

Kalaz D3 *Savio, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Kalbamin *Kalbe, Indon.*
Amino acids.
Parenteral nutrition.

Kalbeten *Sam-On, Israel.*
Bismuth salicylate (p. 1821·3).
Abdominal cramps; diarrhoea; dyspepsia; flatulence; nausea.

Kalbion *Hexpharm, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Kalbitor *Neopharm, Israel; Dyax, USA.*
Ecallantide (p. 1139·3).
Hereditary angioedema.

Kal-Cee *Hua, Thai.*
Vitamins; calcium carbonate (p. 1824·3).
Dietary supplement.

Kalcef *Kalbe, Indon.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Kalcidon *Abigo, Fin.†; Abigo, Swed.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; hyperphosphataemia; osteoporosis; calcium supplement.

Kalcifend *Misha, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Kalciferol *SAD, Denm.†*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency.

Kalcinol-N *Kalbe, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Kalcinova *KRKA, Rus.*
Vitamins; minerals.
KRKA, Ukr.
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3); pyridoxine hydrochloride (p. 2105·3); calcium (p. 1783·1); phosphorus (p. 2589·2).
Vitamin and mineral supplement.

Kalcipos *Recip, Fin.; Recip, Swed.*
Calcium carbonate (p. 1824·3).
Osteoporosis; calcium deficiency; hyperphosphataemia.

Kalcipos-D *Recip, Fin.; Meda, Irl.; Meda, Neth.; Meda, Norw.; Recip, Swed.; Meda, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Kalcipos-D3 *Meda, Switz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Kalcitena *ACO, Swed.†*
Calcium carbonate (p. 1824·3).
Osteoporosis; calcium deficiency; hyperphosphataemia.

Kalcor *Ranbaxy, Port.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Kaldil Diet *Higate, Arg.*
Sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute.

Kaldyum *Egis, Cz.; Egis, Hung.; Egis, Pol.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium deficiency.

Kalenite *Yerba, Canad.†*
Frangula (p. 1843·3); clove (p. 2481·2); yellow dock (p. 2649·3).

Kaleorid *Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Norw.; Leo, Swed.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium supplement.

Kaletra *Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; AbbVie, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK; Abbott, USA; Abbott, Venez.*
Lopinavir (p. 1002·1); ritonavir (p. 1013·1).
HIV infection.

Kalferon *Kalbe, Indon.*
Interferon alfa-2b (p. 989·2).
Chronic hepatitis.

Kal-Forte *Hua, Thai.*
Calcium carbonate (p. 1824·3); calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1).
Calcium deficiency.

Kalfoxim *Kalbe, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Kalgaron *Rafa, Israel.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Kalgriff *KSK, Irl.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Kalgut *Mitsubishi Tanabe, Jpn.*
Denopamine (p. 1350·3).
Heart failure.

Kalhar *Kalpataru, India.*
Glucosamine sulfate (p. 2515·3); vitamins.

Kaliale *Effik, Fr.†*
Cyproterone acetate (p. 2261·2).
Hirsutism in females; prostatic cancer.

Kaliber *Kalpataru, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Kalibex *Konimex, Indon.†*
Dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3).
Cough; nasal congestion; allergic disorders.

Kalicid *Belfar, Braz.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).

Kalicor *Lek, Cz.†*
Piracetam (p. 393·3).
Cerebral disorders; vertigo; dementia; memory function impairment.

Kalidin *T Man, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Kalidren *Fako, Turk.*
Diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Kaliglutol *Streuli, Switz.†*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kaliject *Pharmadica, Thai.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kalijev *Lek, Cz.†*
Potassium iodide (p. 2336·3).
Prevention of contamination with radioactive iodine.

Kalilactasol *Gambro, Austria; Gambro, Irl.; Gambro, Port.; Gambro, Switz.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Haemofiltration; haemodialysis.

Kalima *Theraskin, Braz.*
Soap.
Dry skin disorders.

Kalimat *Lek, Pol.†*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Kalimate *Kowa, Jpn; Kowa, Malaysia; Kowa, Philipp.; Kowa, Thai.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Kalinor *Desma, Ger.; Abbott, Turk.*
Potassium citrate (p. 1780·3); potassium bicarbonate (p. 1780·3).
Hyperchloraemic acidosis; urinary-tract infections; urinary alkalinisation; potassium deficiency, particularly in association with metabolic acidosis.

Kalinorm *Leiras, Fin.†*
Potassium chloride (p. 1793·2).
Potassium supplement; hypokalaemia.

Kalinor-retard P *Desma, Ger.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Kalinox *Air Liquide, Belg.; Air Liquide, Denm.; Air Liquide, Fr.; Air Liquide, Spain; Carbagas, Switz.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Analgesia in anaesthesia and painful procedures; pain.

Kaliolite *Merck, Mex.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kalioral *Fresenius Kabi, Austria.*
Anhydrous potassium citrate (p. 1780·3); potassium bicarbonate (p. 1780·3); citric acid (p. 2480·3).
Potassium deficiency; oedema.

Kalipar *Tempo Scan Pacific, Indon.*
Potassium aspartate (p. 1793·1).
Potassium supplement.

Kaliphos *Sterop, Belg.*
Monobasic potassium phosphate (p. 1790·3); dibasic potassium phosphate (p. 1791·1).
Hypophosphataemia.

Kalipoz *GSK, Pol.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Kalisol *Orion, Fin.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kali-Sterop *Sterop, Belg.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kalitake *Dipa, Indon.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia in renal failure.

Kalitrans *Stada, Ger.*
Potassium bicarbonate (p. 1780·3).
Potassium deficiency.

Kalium *AstraZeneca, Philipp.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium supplement.
Verla, Ger.
Potassium citrate (p. 1780·3).
Hypokalaemia.

Kalium Durules *Teva, Hung.†*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Kalium Iodatum Complexe No 84 *Lehning, Fr.†*
Viscum album (p. 2560·2); crataegus oxyacantha (p. 2488·1); solidago (p. 2620·1); arnica montana (p. 2447·2); kalium iodatum (p. 2336·3); atropa belladonna (p. 2453·3); secale cornutum (p. 2137·1); aurum colloidum (p. 2521·1).
Homoeopathic preparation; in vidal 2.10 as Complexe Lehning Kalium Iodatum No 84.

Kalium Muriaticum Complexe No 41 *Lehning, Fr.†*
Kalium muriaticum (p. 1793·2); vinca minor; petasites officinal (p. 2463·2); atropa belladonna (p. 2453·3); bryonia (p. 2461·3); staphysagria; mercurius corrosivus (p. 2555·2).
Homoeopathic preparation.

Kalium Phos Comp *Weleda, S.Afr.†*
Aurum met (p. 2521·1); kalium phosphoricum (p. 1790·3); kephalodoron.
Homoeopathic preparation.

Kalium Phosphoricum Complexe No 100 *Lehning, Fr.*
Kalium phosphoricum (p. 1790·3); ferrum phosphoricum (p. 2077·1); ambra grisea (p. 2440·3); yohimbinum muriaticum (p. 2372·3); muira puama.
Homoeopathic preparation.

Kalium Retard *Nycomed, Swed.†*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium supplement.

Kalium-Normin *Valeant, Ukr.*
Potassium chloride (p. 1793·2).
Hypokalaemia; cardiac glycoside overdosage.

Kalium-R *Valeant, Hung.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Kalixocin *Alphapharm, Austral.*
Clarithromycin (p. 266·2).
Bacterial infections.

Kalkurenal
Note: this name may be used for preparations of different composition.
Darya-Varia, Indon.; Muller Goppingen, Indon.
Berberis (p. 2502·1); rubia tinctorum; saxifraga granulata; lithium hydrochloride; magnesium borocitrate; sodium phosphate (p. 1791·2).
Renal calculi.

Kallistat *Biosena, India.*
Aprotinin (p. 1133·2).
Haemorrhage; adjunct in open heart surgery.

Kalloplast *DM, Braz.*
Topical solution: Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Keratinisation disorders.
DM, Braz.
Plasters: Salicylic acid (p. 1719·1).
Keratinisation disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kalma
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; LCH, Hong Kong.†
Alprazolam (p. 1035·2).
Anxiety; panic disorder.
Stada, Austria; Stada, Ger.†
Tryptophan (p. 453·2).
Depression; sleep disorders; agitation in parkinsonism.

Kalmafta *Andromaco, Chile.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Kalmalin *Bago, Arg.*
Lorazepam (p. 1080·3).
Anxiety.

Kalmaline-AC *Coup, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Kalm-B *Cantassium Co., UK.*
Vitamins; minerals.

Kalmeco *Kalbe, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Kalmethasone *Hexpharm, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Kalmia Complexe No 18 *Lehning, Fr.*
Kalmia latifolia (p. 2537·2); helleborus; conium maculatum (p. 2524·3); argentum colloidum (p. 2616·2); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Kalmicetine *Kalbe, Indon.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Kalmiren *Aegis, Hong Kong.†*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Kalmodine *Coup, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Kalmol Extra *Specifar, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Kalmopyrin *Gedeon Richter, Hung.*
Aspirin (p. 22·2).
Calcium gluconate (p. 1783·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Kalmosan *Kurtsan, Turk.*
⊗Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1); camphor (p. 2466·2); glycerol (p. 2517·2).
Pruritus.

Kalmox *Keshav, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).

Kalmoxillin *Kalbe, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Kalms *Amis, Hung.; Lane, Pol.; Lane, UK.*
Lupulus (p. 2546·1); valerian (p. 2640·2); gentian (p. 2512·1).
Restlessness; irritability; menopausal disorders; sleep disorders; nervous disorders; stresses and strains.

Kalms Day *Lane, UK.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Anxiety.

Kalms Night *Lane, UK.*
Valerian (p. 2640·2).
Sleep disorders.

Kalms Sleep *Lane, UK.*
Passion flower (p. 2584·1); lupulus (p. 2546·1); valerian (p. 2640·2); vervain (p. 2645·1); wild lettuce (p. 2647·3).
Insomnia.

Kalnex *Kalbe, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemorrhage.

Kalnormin *ICN, Cz.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kaloba *Schwabe, Austria; Nycomed, Braz.; Pharma Investi, Chile; Schwabe, Cz.; Schwabe, Hung.; Phapros, Indon.; Schwabe, Indon.; Schwabe, Malaysia; Schwabe, Neth.; Schwabe, Philipp.; Schwabe, Singapore; Schwabe, Spain; MaxMedica, Swed.; Schwabe, Switz.; Schwabe, UK; Roemmers, Venez.*
Pelargonium sidoides (p. 2585·2).
Cold symptoms; bronchitis; symptomatic treatment of upper respiratory-tract infections; cough.

Kaloban *Schwabe, Belg.*
Pelargonium sidoides (p. 2585·2).
Cold symptoms.

Kalopsis *Roux-Ocefa, Arg.*
⊗Ephedrine (p. 1663·1); phenazone (p. 124·1).
Eye disorders.

Kalopsis Lagrimas *Roux-Ocefa, Arg.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Kalory *Sienna, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).

Kalpanax *Kalbe, Indon.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); povidone-iodine (p. 1767·1).
Fungal skin infections.

Kalpastic *BDH, India.†*
Rutoside (p. 2505·3); vitamin C (p. 2110·3); acetomenaphthone (p. 2122·1); calcium gluconate (p. 1783·3).
Capillary fragility.

Kalpha *Servocare, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Kalpicilin *Hexpharm, Indon.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Kalpiren *Medochemie, Rus.†*
Enalapril maleate (p. 1371·1).

Kalpress *Novartis, Spain.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Kalpress Plus *Novartis, Spain.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kalsifluor *Sandoz, Turk.*
Sodium fluoride (p. 2089·2); calcium phosphate (p. 1784·2); calcium gluconate (p. 1783·3); ergocalciferol (p. 2113·3).
Dental caries prophylaxis; osteoporosis; dietary supplement.

Kalsinus *Sam-On, Israel.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; Eustachian-tube congestion.

Kalsis *SM, Venez.*
Calcium carbonate (p. 1824·3); magnesium chloride (p. 1787·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); sodium selenite (p. 2087·1).
Osteoporosis.

Kalsiv *Maccabi Care, Israel.*
Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation.

Kalspare *DHP, UK.*
⊗Chlortalidone (p. 1335·2); triamterene (p. 1518·3).
Hypertension; oedema; ascites.

Kaltazone *TC Pharma-Chem, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Kalten *Teofarma, Spain; Globopharm, Switz.†; BPC, UK.*
⊗Atenolol (p. 1308·2); amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kalter *Phoenix, Arg.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function impairment.

Kaltiazem *Fabra, Arg.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris.

Kalticol *Kalbe, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Kaltin MF *Abbott, India.*
Metronidazole (p. 936·1); furazolidone (p. 933·3).
Gastrointestinal infections.

Kaltocarb *Convatec, Israel.*
Calcium alginate (p. 1136·3); sodium alginate (p. 2167·3); activated charcoal (p. 1537·3).
Malodorous wounds.

Kaltostat *Convatec, Irl.†; Convatec, Israel; Convatec, Ital.; Adcock Ingram Critical Care, S.Afr.*
Calcium alginate (p. 1136·3); sodium alginate (p. 2167·3).
Wound dressing; wounds; leg ulcers.
Werfen, Arg.; Convatec, Belg.; Convatec, Canad.; Convatec, UK.
Calcium alginate (p. 1136·3).
Wounds; haemostatic wound dressing.
Convatec, Port.
Calcium sodium alginate (p. 2167·3) (p. 1136·3).
Haemostatic wound dressing.

Kaltrim *Offenbach, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Kaltrofen *Kalbe, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue disorders; gout.

Kaluo *Sine, China.*
Betacarotene (p. 2051·1).

Kaluril
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
⊗Amiloride hydrochloride (p. 1299·1).
Oedema; hypertension; ascites.
Teva, Israel.
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Kal-Vit-D *Hua, Thai.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Osteoporosis; osteomalacia; calcium and vitamin D supplement.

Kalxetin *Kalbe, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia; premenstrual dysphoric disorder.

Kalyamon B12 *Janssen-Cilag, Braz.*
Minerals; vitamin B_{12} (p. 2107·2); vitamin D_3.

Kalydeco *Vertex, Denm.; Vertex, Neth.; Vertex, Norw.; Vertex, UK; Vertex, USA.*
Ivacaftor (p. 2536·1).
Cystic fibrosis.

Kalymin *Temmler, Ger.; Pliva, Rus.*
Pyridostigmine bromide (p. 689·2).
Gastrointestinal atony; bladder atony; myasthenia gravis.

Kalzana *Zydus, India.*
Syrup: Calcium (p. 1783·1); calcium gluconate (p. 1783·3); calcium hypophosphite (p. 2530·3); calcium lactobionate (p. 1784·2); colecalciferol (p. 2113·1); nicotinamide (p. 2083·1); vitamin A palmitate (p. 2098·3); vitamin C (p. 2110·3).
Formerly contained calcium phosphate and colecalciferol.
Dietary supplement; calcium deficiency.
Zydus, India.
Tablets: Calcium (p. 1783·1); calcium hydrogen phosphate (p. 1783·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).

Kalzin *Unimarck, India.*
Injection: Colecalciferol (p. 2113·1).
Unimarck, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Kalzin-C *Unimarck, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Kam *Pharmacon, India.*
Amikacin (p. 214·1).
Bacterial infections.

Kam Rho-D *Teva Tuteur, Arg.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Kamacaine *Kamada, Israel.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Kamadol *Karnataka, India.*
Tramadol (p. 139·2).
Pain.
Kimia, Indon.
Tramadol hydrochloride (p. 139·2).
Pain.

Kamadol-P *Karnataka, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Kamaflam *Kimia, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Kamagel *KRKA, Pol.; KRKA, Rus.*
Aluminium acetotartrate (p. 2440·1); chamomile (p. 2474·1).
Skin irritation; soft-tissue injury; bruising; sprains.

Kamagra *Ajanta, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Kaman *Savio, Ital.*
Paromomycin sulfate (p. 943·3).
Gastro-enteritis; gastrointestinal sterilisation; intestinal amoebiasis; hepatic coma.

Kamapharm *Kamada, Hong Kong.†*
⊗Albumin (p. 1130·2).
Shock; hypoproteinaemia; hepatic cirrhosis; nephrosis; burns; hyperbilirubinaemia; erythroblastosis fetalis.

Kambakutaisoto *Tsumura, Jpn.*
Jujube; liquorice (p. 1853·2); common wheat seed.
Traditional Kampo medicine.

Kame *Kotra, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Kamelyn *Krugher, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Kamfart *Bosnalijek, Ukr.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); benzyl nicotinate (p. 29·3); menthol (p. 2553·2).
Musculoskeletal and joint pain; neuralgia.

Kamfolin *Munir, Turk.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Kamicin *Christo, Hong Kong.*
Clotrimazole (p. 576·2).
Vaginitis.

Kamident *Zdorovje, Ukr.*
Lidocaine hydrochloride (p. 1988·2); chamomile (p. 2474·1); thymol (p. 1772·2).
Inflammatory disorders of the mouth.

Kamikihito *Tsumura, Jpn.*
Astragalus root (p. 2451·1); bupleurum root; jujube seed; atractylodes lancea rhizome; ginseng (p. 2513·3); poria sclerotium; polygala root; gardenia fruit; jujube; angelica acutiloba root (p. 2443·3); liquorice (p. 1853·2); ginger (p. 1844·1); saussurea root; longan fruit.
Traditional Kampo medicine.

Kamil Blue *Fischer, Israel.*
Liquid soap: Azulene (p. 2452·1); chamomile (p. 2474·1).
Skin cleansing; skin disorders.
Fischer, Israel.
Lotion: ⊗Azulene (p. 2452·1); glycerol (p. 2517·2); silicone (p. 2209·2); panthenol (p. 2582·2).
Barrier preparation; skin disorders.
Fischer, Israel.
Ointment: Chamomile (p. 2474·1); panthenol (p. 2582·2); wool fat (p. 2219·3); white soft paraffin (p. 2211·3); silicone (p. 2209·2); zinc oxide (p. 1729·1).
Barrier preparation; skin disorders.
Fischer, Israel.
Topical oil: Azulene (p. 2452·1).
Barrier preparation; skin cleansing.

Kamillen *Biotecnoquimica, Venez.*
Chamomile (p. 2474·1).
Skin disorders.

Kamillenbad Intradermi *Eberth, Ger.†*
Chamomile oil (p. 2474·1).
Anogenital disorders; bath additive; skin and mucous membrane disorders.

Kamillen-Bad Ritsert *Ritsert, Ger.†*
Chamomile oil (p. 2474·1).
Bath additive; inflammation of skin and mucous membranes; anorectal disorders.

Kamillex *Streuli, Switz.*
Chamomile (p. 2474·1).
Skin disorders; wounds; burns; mouth and throat inflammation.

Kamillin *Robugen, Ger.*
Chamomile (p. 2474·1).
Gastrointestinal disorders; skin and mucous membrane disorders.

Kamillin Medipharm *Iromedica, Switz.*
Chamomile (p. 2474·1).
Inflammation of skin and mucous membranes.

Kamillofluid *Amino, Switz.*
Chamomile (p. 2474·1).
Skin disorders; mouth and throat disorders.

Kamillosan
Note: this name may be used for preparations of different composition.
Meda, Belg.; Ache, Braz.; Meda, Cz.†; Meda, Cz.†; Meda, Ger.†; Zydus, India; Transfarma, Indon.; Chefaro, Irl.; Sanfer, Mex.; Pharmafrica, S.Afr.†; Meda, Switz.; Goldshield, UK; Zuoz, Venez.
Chamomile (p. 2474·1).
Chapped skin; nappy rash; sore nipples; skin irritation; digestive disorders; mouth and throat disorders; gastrointestinal spasm; irritable bowel disorders; vulvovaginal irritation; respiratory-tract disorders; burns; ulcers; inflammation of mucous membranes; wounds.

Meda, Austria; Zydus, India.
Chamomile oil (p. 2474·1).
Mouth and throat disorders; skin disorders; gastrointestinal disorders; respiratory-tract disorders; anal disorders; vulvovaginal disorders; cold symptoms.

Meda, Austria.
Mouth spray: Chamomile oil (p. 2474·1); peppermint oil (p. 1877·1); anise oil (p. 2444·3).
Mouth and throat disorders.

Meda, Switz.
Buccal spray: Chamomile (p. 2474·1); peppermint oil (p. 1877·1); anise oil (p. 2444·3).
Mouth and throat disorders.

Kamillosan M
Note: this name may be used for preparations of different composition.
Meda, Thai.
Chamomile (p. 2474·1); chamazulene (p. 2474·1); essential oil.
Mouth and throat disorders.

Transfarma, Philipp.
Anise oil (p. 2444·3); bergamot oil (p. 2455·1); chamomile (p. 2474·1); cineole (p. 2479·1); methyl salicylate (p. 92·1); peppermint oil (p. 1877·1); pine-needle oil (p. 2591·1); sage oil (p. 2609·1).
Mouth and throat disorders.

Kamillosan Mundspray *Meda, Ger.†*
Chamomile (p. 2474·1); peppermint oil (p. 1877·1); anise oil (p. 2444·3).
Mouth and throat disorders.

Kamillosan Ocean *Meda, Ital.*
Sea water (p. 2612·1); chamomile (p. 2474·1).
Nasal irrigation and hygiene.

Kamillosan-N *Zydus, India.*
Chamomile (p. 2474·1); peppermint oil (p. 1877·1); anise oil (p. 2444·3).
Mouth and throat disorders.

Kamiloderm *Remexa, Mex.*
Chamomile (p. 2474·1); vitamin A (p. 2098·3).
Skin disorders.

Kamilon *Offenbach, Mex.*
Nalidixic acid (p. 328·3).
Urinary-tract disorders.

Kamilosan *Meda, Port.*
Chamomile (p. 2474·1).
Burns; skin disorders; wounds; oropharyngeal hygiene; haemorrhoids; gastrointestinal disorders; nasal congestion; vaginal hygiene; varicose veins.

Kamilotract *Urgo, Israel.*
Chamomile (p. 2474·1); sage (p. 2608·3).
Mucous membrane inflammation in the mouth; blepharitis.

Kamin *Bosch, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kamina *Hikma, Port.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kamiren *KRKA, Cz.; Niche, Irl.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Kamishoyosan *Tsumura, Jpn.*
Bupleurum root; peony root; atractylodes lancea rhizome; angelica acutiloba root (p. 2443·3); poria sclerotium; gardenia fruit; moutan bark; liquorice (p. 1853·2); ginger (p. 1844·1); mentha herb.
Traditional Kampo medicine.

Kamistad *Stada, China; Stada, Hong Kong; Stada, Singapore†; Stada, Thai.†*
Lidocaine hydrochloride (p. 1988·2); thymol (p. 1772·2); chamomile (p. 2474·1).
Inflammatory disorders of the mouth.

Stada, Cz.; Stada, Ger.; Stada, Rus.; Stada, Ukr.
Lidocaine hydrochloride (p. 1988·2); chamomile (p. 2474·1).
Inflammatory disorders of the mouth.

Kamistad Gel N *Stada, Hong Kong; Stada, Thai.*
Lidocaine hydrochloride (p. 1988·2); chamomile (p. 2474·1).
Inflammatory disorders of the mouth.

Kamitrin *Saga, India.*
Amitriptyline (p. 401·1).
Depression; neuropathic pain; migraine.

Kamolas *Solas, Indon.*
Paracetamol (p. 115·1).
Pain; fever.

Kamox *LKM, Arg.†*
Diclofenac diethylamine (p. 48·3).

Kamoxin *Chew, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Kamozyme *Kamron, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders; reduced appetite.

Kamozyme-EP *Kamron, India.*
⊗Simeticone (p. 1886·2); bile (p. 2457·2); pancreatin (p. 2579·3).

Kampex *Hufort, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Kampi *Biomax, India.*
Cefepime (p. 239·2).
Bacterial infections.

KamRAB *Kamada, Thai.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

KamRab *Kamada, Israel.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Kamrab *Landsteiner, Mex.†*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

KamRHO *Kamada, Rus.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

KamRho-D *Kamada, Israel.*
An anti-D immunoglobulin (p. 2377·1).
Immune thrombocytopenic purpura; prevention of rhesus sensitisation.

Kamsa *Arvincare, India.*
Amikacin (p. 214·1).
Bacterial infections.

Kamtac *Kamron, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration; dyspepsia.

Kamulvit *Ikapharmindo, Indon.*
Vitamins; calcium (p. 1783·1).
Dietary supplement.

Kan Jang *Green Medicine, Swed.*
Malabar nut (p. 2549·1); Siberian ginseng (p. 2614·3); echinacea purpurea (p. 2498·1).
Cold symptoms.

Kana
Note: this name may be used for preparations of different composition.
Maver, Mex.
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kanabiotic *Bernofarm, Indon.†*
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kanacitrin *Rider, Chile.*
Potassium citrate (p. 1780·3); citric acid monohydrate (p. 2480·3).
Metabolic acidosis; urinary alkalinisation; renal calculi; uric acid nephropathy.

Kanafosal *Medical, Spain.†*
⊗Ephedrine hydrochloride (p. 1663·2); kanamycin sulfate (p. 314·3); naphazoline hydrochloride (p. 1669·3); procaine hydrochloride (p. 1994·3); sulfanilamide sodium mesilate (p. 368·1).
Nasal congestion and infection.

Kanafosal Predni *Medical, Spain.†*
⊗Ephedrine hydrochloride (p. 1663·2); kanamycin sulfate (p. 314·3); naphazoline hydrochloride (p. 1669·3); prednisone (p. 1647·2); procaine hydrochloride (p. 1994·3); sulfanilamide sodium mesilate (p. 368·1).
Nasal congestion and infection.

Kanakion *Roche, Braz.; Roche, Port.*
Phytomenadione (p. 2122·2).
Haemorrhagic disorders; vitamin K deficiency.

Kanam *Flamingo, India.*
Meropenem (p. 321·3).
Bacterial infections.

Kanamac *Macleods, India.*
Kanamycin (p. 314·3).
Bacterial infections.

Kanamytrex *Alcon, Ger.*
Kanamycin sulfate (p. 314·3).
Bacterial eye infections.

Kana-P *PP Lab, Thai.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; Helicobacter pylori *eradication.*

Kanapat *Parggon, Mex.*
Kanamycin (p. 314·3).
Bacterial infections.

Kanapomada *Medical, Spain.†*
⊗Kanamycin sulfate (p. 314·3); prednisolone (p. 1645·2); trypsin (p. 2635·2); urea (p. 1727·3); lidocaine (p. 1988·1).
Infected skin disorders.

Kanarco *Armoxindo, Indon.*
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kana-Stulln *Stulln, Ger.*
Kanamycin sulfate (p. 314·3).
Bacterial eye infections.

Kanavig *Alcon, Belg.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Kanavit *BB, Cz.; Zentiva, Cz.; Medphano, Ger.†*
Phytomenadione (p. 2122·2).
Haemorrhagic disorders; vitamin K deficiency.

Kanazima *Kinder, Braz.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Kancin *Alembic, India.*
Kanamycin (p. 314·3).
Bacterial infections.

Atlantic, Malaysia; Atlantic, Thai.†
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kancin-Gap *Gap, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kancin-L *Atlantic, Singapore.*
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kandex
Note: this name may be used for preparations of different composition.
Burapha, Thai.
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Teva, Fin.†
Bicalutamide (p. 749·1).
Prostatic cancer.

Kandicin *Bernabo, Arg.*
Cefadroxil (p. 233·2).
Bacterial infections.

Kandistat *Kinder, Braz.†*
Nystatin (p. 590·3).
Vulvovaginal candidiasis.

Kandistatin *Metiska, Indon.*
Nystatin (p. 590·3).
Candidiasis.

Kandizol *Nobel, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Kandor CZ *Kalpataru, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Kandril *Kinder, Braz.†*
Sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2).

Kandrodec *Kalpataru, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Kandrozid *Mylan, Fin.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Kandy *Biosans, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Kanegan *Pharmasant, Thai.†*
Pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Irritable bowel syndrome.

Kaneuron *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Phenobarbital (p. 535·2).
Epilepsy.

Kanezin *Swiss Pharm, Thai.†*
Clotrimazole (p. 576·2).
Vaginal candidiasis; trichomoniasis.

Kan-Fresh *Kalpataru, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Kang Bi De *Hengli, China.*
Paracetamol (p. 115·1); zinc gluconate (p. 2126·2).

Kang Chu *Rui Nian Qian Jin, China.*
Telmisartan (p. 1509·3).
Hypertension.

Kang Da Li Cun *Tian Fu, China.*
Aceglutamide (p. 2426·2).

Kang Da Li Ping *Tian Fu, China.*
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; adjunct to fluorouracil for colorectal cancer.

Kang Da Li Te *Tian Fu, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Kang Da Wei *Dong Fang, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Kang Da Xin *Huachuang, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left ventricular dysfunction following myocardial infarction.

Kang En *Laitai, China.*
Ozagrel sodium (p. 2579·1).

Kang Er Ning *Kangnuo, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Kang Er Shu Ning *Kangkeer, China.*
⊗Salbutamol (p. 1220·2).
Bronchospasm.

Kang Er Ting *Livzon, China.*
Perospirone hydrochloride (p. 1095·3).
Schizophrenia.

Kang Fei *Baiyunshan, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Kang He Su *Haohai, China.*
An epidermal growth factor (human, recombinant).

Kang Ji Xing *Lingkang, China.*
Potassium sodium dehydroandroandrographolide succinate.

Kang Ka *Gaoxin, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Kang Lai Er *Xia Du, China.*
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; adjunct to fluorouracil for colorectal cancer.

Kang De Li *Hailisheng, China.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Kang Li Jian *San Lian, China.*
Azithromycin lactobionate.
Bacterial infections.

Kang Li Ning *Hualan, China.*
Thrombin (human) (p. 1163·2).

Kang Li Shu *Xinzhongzheng, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Kang Li Tuo *Ke Lun, China.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kang Li Xing *Tongyong, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Kang Li Yin *Duoburuifei, China.*
Fluconazole (p. 578·2).
Fungal infections.

Kang Lie Su *Yellow River, China.*
Finasteride (p. 2358·3).

Kang Ling *Tianlong, China.*
Piracetam (p. 393·3).
Mental function impairment.

Kang Mai Xin *Pu Luo Kang Yu, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Kang Ming *Shengbao, China.*
Hyoscyamus (p. 2530·2); chondroitin sulfate (p. 2476·1).

Kang Neng *Gejiu, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Kang Ni *Haikou, China.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Kang Ning *Shunfeng, China.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Kang Pa Si *Yang Jiang, China.*
Aceglutamide (p. 2426·2).

Kang Pai *Lukang Medicine, China.*
Cefixime (p. 240·3).
Bacterial infections.

Kang Pu Li *Aodong Baoyi, China.*
Carbocisteine (p. 1658·1).

Kang Pu Xin *Hualan, China.*
Fibrin glue (p. 1151·2).

Kang Qi *Shunfeng, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Kang Rong *Chen Pai, China.*
Piracetam (p. 393·3).
Mental function impairment.

Kang Sai Ning *Wuhan Institute, China.*
A streptococcus group A vaccine.

Kang Si Ai *Bao Long, China.*
Thymosin.
Immunomodulator.

Kang Si Ke Wei *Ke Lun, China.*
Arginine hydrochloride (p. 2049·1).

Kang Si Ping *Hualan, China.*
A factor VIII preparation (p. 1148·1).
Haemophilia A.

Kang Tai *Shunfeng, China.*
Diclofenac sodium (p. 48·3).

Kang Tai Ke Qing *SKF, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Kang Tong Su *Lingkang, China.*
Tiopronin (p. 1578·1).

Kang Di Xin *Jinshi, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Kang Xin
Note: this name may be used for preparations of different composition.
Chia Tai, China.
Lactitol (p. 1850·3).

Kang Yu Deng Tong *Pu Luo Kang Yu, China.*
⊗Paracetamol (p. 115·1); methylephedrine hydrochloride (p. 1669·2); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); sulfogaiacol (p. 1678·1); caffeine (p. 1203·3).

Kang Zan *Haite Sihuan, China.*
Rufloxacin hydrochloride (p. 357·1).
Bacterial infections.

Kangen *General Drugs, Thai.*
Kanamycin acid sulfate (p. 314·3).
Bacterial infections.

Kanglaite *Kanglaite, Rus.*
Koiksa seed oil.
Non-small cell lung cancer.

Kangliding *Xinzhongzheng, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Kanglineng *Likang, China.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Kanglinuo *NEGPF, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine.
Influenza symptoms.

KangTing *San Lian, China.*
Potassium dehydroandrographolide.

KangXin
Note: this name may be used for preparations of different composition.
Tianquan, China.
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Kanin *LBS, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer; gastroduodenitis; nausea and vomiting.

Kaniz *Plus, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Kank-A *Blistex, Canad.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Canker sores; mouth irritation.

Blistex, Israel.
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1); benzoin tincture (p. 2624·3).
Mouth irritation.

Blistex, USA.
Benzocaine (p. 1980·2); compound benzoin tincture.
Mouth disorders.

Kank-A Soothing Beads *Blistex, USA.*
Benzocaine (p. 1980·2).
Mouth and throat disorders.

Kank-Eze *Rider, Chile.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth disorders.

Kanny *Kalpataru, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Kanokad *LFB, Fr.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Kanolone *LBS, Malaysia; LBS, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid; musculoskeletal and joint disorders; skin and mouth disorders.

Kan-Ophtal *Winzer, Ger.†*
Kanamycin sulfate (p. 314·3).
Bacterial eye infections.

Kanormal *German Remedies, India.†*
Sterculia (p. 1888·3); frangula bark (p. 1843·3).
Constipation.

Kanosole *LBS, Philipp.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Kanova *Lainco, Spain.*
⊗Glycerol (p. 2517·2).
Constipation.

Kanox *CCM, Malaysia.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Kanoxin *Actavis, Indon.†*
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kanrenol *Teofarma, Ital.*
⊗Potassium canrenoate (p. 1472·2).
Hyperaldosteronism; hypertension.

Kanset *Kalpataru, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Kansilak *Kansuk, Turk.*
⊗Sorbitol (p. 2092·1); Tween 80 (p. 2203·3); sodium citrate (p. 1781·2); glycerol (p. 2517·2).

Kantec *Daiichi Sankyo, Jpn.*
Malotilate (p. 2549·3).
Liver cirrhosis.

Kantrenol *Medinova (Μεντινοβα), Gr.*
Acetylcysteine (p. 1652·2).
Mucolytic.

Kantrex *BMS, Mex.*
Kanamycin (p. 314·3).
Bacterial infections.

Apothecon, USA†; BMS, Venez.
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kantrexil *Adcock Ingram, S.Afr.*
Kanamycin sulfate (p. 314·3); dimevamide (p. 2494·1); pectin (p. 2200·3); bismuth subcarbonate (p. 1822·1); activated attapulgite (p. 1820·1).
Gastro-enteritis.

Kanzuk *Kansuk, Turk.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Mouth and throat disorders.

Kao Fu Ke *Aolida, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Kao Fu Ting *Hayao, China.*
Levodropropizine (p. 1662·3).
Cough.

Kaobrol *Venipharm, Fr.*
Magnesium carbonate (p. 1856·2); calcium carbonate (p. 1824·3); heavy kaolin (p. 1850·1).
Gastrointestinal disorders.

Kaodene Non-Narcotic *Pfeiffer, USA.*
Kaolin (p. 1850·1); pectin (p. 2200·3); bismuth salicylate (p. 1821·3).
Diarrhoea.

Kaodin *Nordin, Mex.*
Furazolidone (p. 933·3).
Diarrhoea.

Kaofuryl *Bros, Gr.*
Nifuroxazide (p. 331·3).

Kaolin Mixture *Chew, Thai.*
Kaolin (p. 1850·1); pectin (p. 2200·3).

Kaolin Mixture w / Pectin *Osoth, Thai.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kaologeais *Erempharma, Fr.†*
Magnesium oxide (p. 1857·3); meprobamate (p. 1083·3); magnesium sulfate (p. 1787·3); kaolin (p. 1850·1); sterculia (p. 1888·3).
Gastrointestinal disorders.

Kaomagma *Sigma, Braz.*
Kaolin (p. 1850·1); aluminium hydroxide (p. 1817·2); pectin (p. 2200·3).
Diarrhoea.

Kaomix *ICM, Singapore.*
Light kaolin (p. 1850·1); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Diarrhoea.

Kaomuth *Bailly-Creat, Fr.*
Kaolin (p. 1850·1); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

Kaomycin *Armstrong, Mex.†*
Neomycin sulfate (p. 330·1); kaolin (p. 1850·1); pectin (p. 2200·3).
Gastro-enteritis.

Kaon *Montpellier, Arg.; Savage, USA.*
Potassium gluconate (p. 1793·2).
Hypokalaemia; potassium depletion.

Kaon-Cl *Savage, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Kaonol *Mediderm, Chile.*
Ivermectin (p. 155·1).
Worm infections.

Kao-Paverin *Reese, USA.*
Capsules: Loperamide hydrochloride (p. 1854·2).

Reese, USA.
Oral liquid: Kaolin (p. 1850·1); pectin (p. 2200·3); bismuth salicylate (p. 1821·3).

Kaopectal *Silom, Thai.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea; food poisoning; dysentery.

Kaopectate
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Gr.; Pharmacia Upjohn, Gr.; Pfizer, Indon.†; Johnson & Johnson Consumer, Mex.†
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Paladin, Canad.
Attapulgite (p. 1820·1).
Diarrhoea; cramps.

Pfizer Consumer, USA.
Bismuth salicylate (p. 1821·3).
Gastrointestinal disorders.

Kaopectate Maximum Strength *Upjohn, USA.*
Attapulgite (p. 1820·1).
Diarrhoea.

Kaopectin *Christo, Hong Kong; Vitamed, Israel.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kao-Spen *Century, USA.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kaostatex *Aspen Consumer, S.Afr.*
Kaolin (p. 1850·1); pectin (p. 2200·3); sodium lactate (p. 1781·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Diarrhoea.

Kaosyl *Anfarm, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Kaotate *Pfizer, Indon.†*
Activated attapulgite (p. 1820·1).
Diarrhoea.

Kao-Tin *Major, USA.*
Bismuth salicylate (p. 1821·3).
Gastrointestinal disorders.

Kapake *Galen, Irl.; Galen, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain.

Kapanol *GSK, Austral.; GSK, Austria; GSK, Belg.†; GSK, Fr.†; GSK, Ger.†; GSK, Neth.; GSK, NZ†; GSK, Switz.; GSK, Thai.*
⊗Morphine sulfate (p. 92·3).
Pain; opioid withdrawal syndrome.

Kaparlon-S *Anfarm, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Kapavit *Elvipe, Gr.*
Menadione sodium bisulfite (p. 2122·2).

Kapdox *Novagen, India.*
Cefpodoxime.
Bacterial infections.

Kapdox CL *Novagen, India.*
Cefixime (p. 240·3).
Bacterial infections.

Kapecfuran *Novag, Mex.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kapectolin *United Research, USA.†*
Bismuth salicylate (p. 1821·3).
Diarrhoea.

Kapedoxin *Erlimpex, Indon.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Kapidex *Takeda, Jpn.†*
Dexlansoprazole (p. 1834·2).

Kapidin *Zentiva, Cz.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Kapilin *GSK, India.*
Menadione sodium bisulfite (p. 2122·2).

Kaplon *Teva, UK.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Kaplus *K2 Health & Wellness, Chile.*
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis; osteomalacia; rickets; hypocalcaemia; renal osteodystrophy.

Kaplus-D *K2 Health & Wellness, Chile.*
Calcium citrate (p. 1783·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis; osteomalacia; rickets; hypocalcaemia; renal osteodystrophy; hypoparathyroidism.

Kapnax *Sandoz, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Kapocin *Macleods, India.*
Capreomycin.
Tuberculosis.

Macleods, Rus.
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Kaposalt *Tecnofarma, Mex.*
Potassium bicarbonate (p. 1780·3); potassium tartrate (p. 1793·3); citric acid (p. 2480·3).
Hypokalaemia.

Kapril
Note: this name may be used for preparations of different composition.
DHA, Singapore; Nevzat, Turk.
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Karnataka, India.
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Kapril-H *Karnataka, India.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kaprofen *Siam Bheasach, Thai.†*
Ketoprofen (p. 79·1).
Gout; musculoskeletal and joint disorders; inflammation; pain.

Kaprogest *Jelfa, Pol.†*
Hydroxyprogesterone caproate (p. 2285·1).
Threatened or recurrent miscarriage; endometriosis; menstrual disorders; female infertility.

Kaprolam *Karnataka, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Kapset *Nufarindo, Indon.*
Myrtillus (p. 2566·2); grape seed (p. 2521·3); lutein (p. 2079·2); zeaxanthin (p. 2125·3); lycopene (p. 2546·2); thioctic acid (p. 2629·1); vitamins.
Dietary supplement for healthy eye function.

Kapsiplast *3M, Pol.*
Belladonna (p. 2453·3); capsicum (p. 2469·3).
Neuromuscular pain.

Kapstat *Claris, India.*
Calcium polystyrene sulfonate (p. 1541·2).

Kaptate *PP Lab, Thai.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kaptin *Julphar, UAE.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kaptin II *Julphar, UAE.*
Activated attapulgite (p. 1820·1).
Diarrhoea.

Kaptoril *Deva, Turk.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Kapvay *Shionogi, USA.*
Clonidine hydrochloride (p. 1339·1).
Attention deficit hyperactivity disorder.

Kapyl *Positif, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Kapyl-D *Positif, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Kara *Polipharm, Thai.*
Ketoconazole (p. 585·3).
Scalp disorders.

Karat *Kalpataru, India.*
Artesunate (p. 648·2).
Malaria.

Karayal *Erempharma, Fr.*
Magnesium oxide (p. 1857·3); magnesium sulfate (p. 1787·3); kaolin (p. 1850·1); sterculia (p. 1888·3).
Gastrointestinal disorders.

Karazepin *Terra, Turk.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Karbagen *Generics, Pol.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Karbalex *Liba, Turk.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Karbasal *CCS, Swed.*
⊗Urea (p. 1727·3).
Dry skin.

Karbasif *Yeni, Turk.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Karberol *Munir, Turk.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Karbicombi *KRKA, Spain.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Karbinal *Tris, USA.*
Carbinoxamine maleate (p. 619·1).
Rhinitis; allergic reactions.

Karbis *KRKA, Neth.; KRKA, Pol.; KRKA, Spain.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Karbolytt *Fresenius Kabi, Norw.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Karbonetas *Argenfarma, Arg.†*
Yeast (p. 2125·2); activated charcoal (p. 1537·3).
Dietary supplement.

Karboseptin *Munir, Turk.*
Vegetable charcoal (p. 1537·3); sulfur (p. 1721·1); senna (p. 1885·1); rhubarb (p. 1884·2); phenolphthalein (p. 1877·3).
Dyspepsia; constipation.

Kardalept *Pro Vita, Hung.*
Crataegus (p. 2488·1); valerian (p. 2640·2).
Heart failure.

Kardegic *Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Port.†*
Lysine aspirin (p. 84·3).
Thrombosis prophylaxis; unstable angina; myocardial infarction.

Kardégic *Sanofi-Aventis, Fr.; Sanofi-Aventis, Switz.*
Lysine aspirin (p. 84·3).
Thrombosis prophylaxis; myocardial infarction; unstable angina.

Kardia *Panacea, India.*
Dobutamine (p. 1365·3).
Heart failure; cardiac stress testing.

Kardiket *Schwarz, Rus.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction.

Kardil *Atabay, Turk.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Kardilat *Fako, Turk.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Kardin *Zee, India.*
Trimetazidine (p. 1520·1).
Angina pectoris; Ménière's disease.

Kardionin *Zeller, Switz.*
Crataegus (p. 2488·1).
Heart disorders.

Kardioplex *SAD, Denm.†*
Electrolytes (p. 1775·1); procaine hydrochloride (p. 1994·3).
Cardioplegia in open heart surgery.

Kardisentin *Sandoz, Turk.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Kardogrel *Pharma-Regist, Hung.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Kardopal *Orion, Fin.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Kardozin *Deva, Turk.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hypertension.

Karelyne *Tria, Gr.*
Almond oil peroxide (p. 2437·1).

Kareof-OZ *Kalpataru, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Karet *Armstrong, Mex.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Karibe *Cadila, India.*
Capsules: Vitamins; minerals; trace elements.
Cadila, India.
Syrup: Vitamins; minerals; trace elements; lysine hydrochloride (p. 2079·3).

Karicare AR *Nutricia, NZ.*
Infant feed.
Gastro-oesophageal reflux.

Karicare Food Thickener *Nutricia, NZ.*
Pregelatinised maize starch (p. 2095·1).
Gastro-oesophageal reflux in infants; dysphagia.

Karicare Goat *Nutricia, Austral.*
Infant feed.
Cow's milk intolerance; lactose intolerance.

Karicare Goat Milk *Nutricia, NZ.*
Infant feed.
Cow's milk intolerance.

Karicare HA *Nutricia, Austral.*
Infant feed.
Family history of allergy.

Karicare De Lact Infant *Nutricia, NZ.*
Infant feed.
Lactose intolerance.

Karicare Soy *Nutricia, Austral.*
Infant feed.
Cow's milk or lactose intolerance.

Karicare Soya *Nutricia, NZ.*
Infant feed.
Cow's milk intolerance; galactosaemia; lactose intolerance.

Karidine *Karen, China.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain and irritation.

Karidium
Note: this name may be used for preparations of different composition.
Lorvic, USA.
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Sanofi-Aventis, Arg.
Clobazam (p. 518·2).
Anxiety; epilepsy.

Karigel *Lorvic, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Karigel-N *Lorvic, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Karil *Novartis, Ger.†*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Karile *Phoenix, Arg.*
Nortriptyline hydrochloride (p. 439·3); perphenazine (p. 1095·3).
Depression; mixed anxiety depressive states.

Karilex *Arlex, Mex.*
Cinnarizine (p. 622·1).

Karin
Note: this name may be used for preparations of different composition.
Trima, Israel.
Clarithromycin (p. 266·2).
Bacterial infections.

Karison *Dermapharm, Ger.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Kariva *Barr, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 tablets, inert.
Sequential-type oral contraceptive.

Karlit *Biotenk, Arg.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Karlor *Aspen, Austral.*
Cefaclor (p. 232·3).
Bacterial infections.

Karma *Schwabe, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Karma mood *Schwabe, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Karmelitus *Cadila, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Karmikin *Bruluart, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Karmosan *Darier, Mex.*
⊗Urea (p. 1727·3).
Skin disorders; wounds.

Karnatakaiv *Kaizen, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Karnim *Unijules, India.*
Guggul (p. 2523·2); karela; ocimum sanctum.

Karnodyl *Genopharm, Fr.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias.

Karoksen *Munir, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Karon *Zentiva, Cz.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Karpin *Unipharma, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Karplat *Cadila, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

Kartal *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Karum *Sanovel, Turk.*
Clopidogrel bisulfate (p. 1342·3).

Karvea *Sanofi-Aventis, Austral.; BMS, Cz.; BMS, Ger.; BMS, Gr.; BMS, Irl.; BMS, Ital.; BMS, Neth.; Sanofi-Aventis, NZ†; BMS, Pol.; BMS, Port.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Turk.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Karvezide *Sanofi-Aventis, Austral.; BMS, Cz.; BMS, Ger.; BMS, Gr.; BMS, Irl.; BMS, Ital.; BMS, Neth.; Sanofi-Aventis, NZ†; BMS, Pol.; BMS, Port.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Turk.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Karvil *Torrent, Braz.; Torrent, Philipp.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Karvol *Reckitt Benckiser, Irl.; Crookes Healthcare, UK.*
Chlorobutanol (p. 1747·2); menthol (p. 2553·2); Scots pine oil (p. 2591·2); pumilio pine oil (p. 2591·1); terpineol (p. 2627·2); thymol (p. 1772·2).
Respiratory-tract congestion; cold symptoms.

Boots Healthcare, NZ.
Menthol (p. 2553·2); pine oil (p. 2591·1); cinnamon oil (p. 2479·3).
Nasal congestion.

Reckitt Benckiser, Israel.
Menthol (p. 2553·2); cinnamon oil (p. 2479·3); terpineol (p. 2627·2); chlorobutanol (p. 1747·2); scots pine oil (p. 2591·2); thymol (p. 1772·2); pumilio pine oil (p. 2591·1).
Cold symptoms.

Permark, S.Afr.†; Reckitt Benckiser, Singapore.
Chlorobutanol (p. 1747·2); menthol (p. 2553·2); cinnamon oil (p. 2479·3); pine oil (p. 2591·1); terpineol (p. 2627·2); thymol (p. 1772·2).
Upper respiratory-tract congestion.

Karvol Plus *Indoco, India.*
Menthol (p. 2553·2); terpineol (p. 2627·2); chlorothymol (p. 1748·2); camphor (p. 2466·2); cineole (p. 2479·1).
Upper respiratory-tract congestion; cold symptoms.

Kary Uni *Santen, China; Santen, Hong Kong; Ferron, Indon.; Santen, Indon.; Santen, Philipp.; Santen, Singapore; Santen, Thai.*
Pirenoxine (p. 2591·3).
Cataract.

Kas *Nutricia-Bago, Arg.*
Preparation for enteral nutrition.
Cows' milk protein allergy; diarrhoea; pancreatic insufficiency; soya allergy.

Kasark *Arterium, Ukr.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Kasark H *Arterium, Ukr.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kasark HD *Arterium, Ukr.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kas-Bah *Potter's, UK.*
Buchu (p. 2461·3); clivers (p. 2481·2); couch-grass (p. 2487·2); equisetum (p. 2500·1); bearberry (p. 2453·2); senna (p. 1885·1).
Urinary and bladder discomfort.

Kasimaixin *Huadong, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Kasino *Minova, India.*
Amikacin (p. 214·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kasiping *Huadong, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Kasitrin *Ratiopharm, Port.†*
Atorvastatin calcium (p. 1309·2).

Kaskadil *Lab Francais du Fractionnement, Fr.†; Er-Kim, Turk.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Kasmal *Silanes, Mex.*
Ketotifen fumarate (p. 631·3).
Asthma; bronchitis; allergic rhinitis; allergic conjunctivitis; urticaria; atopic eczema.

Kasmucol *Teva, Mex.*
Ambroxol acefyllinate (p. 1201·2).
Respiratory-tract disorders.

Kasnol *Sedate, Rus.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2); menthol (p. 2553·2).
Respiratory-tract disorders.

Kasporin *Meditab, Thai.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; rheumatoid arthritis; psoriasis; nephrotic syndrome.

Kassemox *Square, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Kast *RND, India.*
Montelukast (p. 1214·3).
Asthma; allergic rhinitis.

Kastair *United American, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Kastipron *YSP, Malaysia.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased mucus.

Kastlutemon *Synthon, Neth.*
Montelukast sodium (p. 1214·3).
Asthma.

Kastorion *OEP, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Kastovin *Eurodrug, Mex.*
Levodropropizine (p. 1662·3).
Cough.

Kata *Errekappa, Ital.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; myocardial infarction; arrhythmias; hypertension.

Katabexin *Medichrom, Gr.*
Betahistine hydrochloride (p. 2455·3).
Vertigo.

Katabios *SIT, Ital.*
Vitamins.

Katadolon *Ache, Braz.; AWD, China; Teva, Israel; AWD, Pol.; AWD, Rus.; Teva, Ukr.*
Flupirtine maleate (p. 65·2).
Pain.

AWD, Ger.; Teva, Ger.
Flupirtine gluconate (p. 65·2) or flupirtine maleate (p. 65·2).
Pain.

Katagrip *Lepori, Port.†*
Paracetamol (p. 115·1).
Fever; pain.

Katalem *Teva, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; gastritis; Zollinger-Ellison syndrome.

Kataljin *Sanli, Turk.*
Camphor (p. 2466·2); thymol (p. 1772·2); benzocaine (p. 1980·2); menthol (p. 2553·2); coconut oil (p. 2179·3); cedar leaf oil (p. 2629·3); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Kataljin-P *Sanli, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Katamisine *Technobio, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Katapekt *Vitabalans, Fin.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); thyme (p. 2630·2).
Cough.

Kataprin *Sanli, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Katarin *Biofarma, Turk.*
Paracetamol (p. 115·1); oxolamine citrate (p. 1671·2); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Katarin Forte *Biofarma, Turk.*
⊗Paracetamol (p. 115·1); oxolamine citrate (p. 1671·2); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Katasma *Bruschettini, Ital.*
Diprophylline (p. 1207·3).
Obstructive airways disease.

Kataval *Farmigea, Ital.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1).
Skin disorders.

Katen *Zentiva, Cz.†*
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias.

Katena *Belupo, Rus.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Katerex *Peithner, Austria.*
Strychnos nux vomica (p. 2573·3); nicotiana tabacum (p. 2632·2); carbo vegetabilis (p. 1537·3).
Homoeopathic preparation.

Kathargon *Farmedia, Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Bowel evacuation.

Kathrex *Myrex Ethica, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Kathricol *Mediapharm, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Katifen *General Drugs, Thai.*
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Katin *Sanitas, Chile.*
Menadione (p. 2122·1); bile salts (p. 2457·2).
Biliary-tract and liver disorders; coumarin anticoagulant overdosage; hypoprothrombinaemia.

Katinol *Chrispa (Χρισπα), Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Kationen *Fresenius Kabi, Austria.*
Trace elements.
Parenteral nutrition.

Kativil *Cofasa, Venez.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; subendocardial fibroelastosis.

Katoderm *Deverge, Ital.*
Emollient.
Skin irritation.

Katogel *Deverge, Ital.*
Emollient.
Skin irritation; dry skin.

Katomed *Deverge, Ital.*
Silver (p. 2615·1).
Burns; skin ulcers; wounds.

Kato-Nasal *Kato, Pol.*
Mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; sinusitis.

Katosilver *Deverge, Ital.*
Silver sucralfate.
Prevention of decubitus ulcers; skin irritation.

Katoxyn *Deverge, Ital.*
Silver (p. 2615·1); benzoyl peroxide (p. 1696·1); kaolin (p. 1850·1); calcium gluconate (p. 1783·3).
Disinfection of wounds and burns; skin irritation.

Katrasic *Kalbe, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Katrax *Hua, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus.

Katrum *Arafarma, Spain.*
Capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint pain; neuropathic pain.

Katsin *M & H, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Kattwicor *Kattwiga, Ger.*
Arnica montana (p. 2447·2); crataegus (p. 2488·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Katya *Stragen, Cz.; Stragen, UK.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Kavaderm *Relyo, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Kavagren *Greenpharma, Braz.†*
Kava (p. 2537·3).

Kavahexal *Hexal, Braz.†*
Kava (p. 2537·3).

Kavakan *Ativus, Braz.*
Kava (p. 2537·3).
Anxiety; tension; insomnia.

Kavamed *Cimed, Braz.*
Kava (p. 2537·3).
Anxiety.

Kavasedon *Sigma, Braz.*
Kava (p. 2537·3).
Anxiety.

Kavelor *Megat, Venez.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Kåvepenin *Meda, Swed.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Kaveri *Cassella-med, Ger.*
Ginkgo biloba leaf (p. 2512·3).
Mental function impairment; intermittent claudication; vestibular disorders; headache.

Kavipen *Maver, Mex.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Ka-vit *Infectopharm, Ger.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency; vitamin K deficiency bleeding.

Kavit *Cristalia, Braz.*
Phytomenadione (p. 2122·2).

Kavocil *Swiss Parenterals, Philipp.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Kawacin *Synthiko, India.*
Amikacin (p. 214·1).
Bacterial infections.

Kawin Di Ning *Kawin, China.*
Ozagrel sodium (p. 2579·1).
Cerebrovascular disorders.

Kawin Nuotong *Kawin, China.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced depression; opioid overdosage; alcohol poisoning; diagnosis of opioid overdosage.

Kaxitel *Admac, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Kay Ciel *Stadmed, India.*
Potassium chloride (p. 1793·2).

Kaybend *Kaizen, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Kay-Cee-L *Geistlich, Irl.; Geistlich, UK.*
Potassium chloride (p. 1793·2).
Potassium deficiency; hypokalaemia.

Kaycin *Cadila, India.*
Kanamycin (p. 314·3).
Bacterial infections.

Kayexalate *Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Thai.; Sanofi Winthrop, USA; Sanofi-Aventis, Venez.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Sanofi-Aventis, Belg.
Calcium polystyrene sulfonate (p. 1541·2) or sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Kayivis *Vincenti, Venez.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); acetic acid (p. 2426·3); collodion (p. 1718·2).
Calluses; warts; keratinisation disorders.

Kayken *Korea United, Philipp.*
Polysaccharide-K (p. 2594·1).
Colorectal cancer; small-cell lung cancer.

Kaylid-P *Kaizen, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Kayliv *Solitaire, India.*
⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Kaylyte *Thaipharmed, Thai.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium supplement.

Kaypen *Hindustan Antibiotic, India.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Kaytrix-C *Solitaire, India.*
Trifluoperazine (p. 1113·2); trihexyphenidyl (p. 917·3).

Kaytwo *Eisai, Jpn.*
Menatetrenone (p. 2122·2).
Vitamin K deficiency; haemorrhagic disorders.

Kayun *NEGPF, China.*
Carboprost methyl (p. 2133·1).
Postpartum haemorrhage; termination of pregnancy.

Kayval *Solitaire, India.*
Valproate semisodium (p. 553·2).
Epilepsy; bipolar disorder; migraine.

Kayvir *Solitaire, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Kaywan *Eisai, Jpn.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency.

Kayzid *Solitaire, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Kaz
Note: this name may be used for preparations of different composition.
Kaz, Canad.†
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); peppermint oil (p. 1877·1).

Kazano *Takeda, USA.*
Alogliptin benzoate (p. 467·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Kazepin *Gunsa, Turk.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Kazibrox *Kaizen, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).

Kazibrox-BT *Kaizen, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Kazicold *Kaizen, India.*
⊗Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Kazifer-Z *Kaizen, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Kazinal *Asian Pharm, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

KB Alu *KB, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

KB Bendazole *KB, Thai.*
Mebendazole (p. 158·3).
Worm infections.

KB Biscod *KB, Thai.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

KB Calo *KB, Thai.*
Zinc oxide (p. 1729·1); calamine (p. 1697·2); camphor (p. 2466·2); diphenhydramine (p. 626·1).
Pruritus.

KB Cymedin *KB, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

KB Dextro *KB, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

KB Dramine *KB, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; Ménière's disease.

KB Duode *KB, Thai.*
Oxyphencyclimine (p. 1875·1).
Peptic ulcer; irritable bowel syndrome; neurogenic bowel disturbances.

KB Famate *KB, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

KB Fedamol *KB, Thai.*
Paracetamol (p. 115·1); chlorphenamine (p. 620·3); phenylephrine (p. 1672·2); dextromethorphan (p. 1660·1).
Cough; cold symptoms.

KB Gin *KB, Thai.*
Oral drops: Paracetamol (p. 115·1).
Fever; pain.

KB, Thai.
Syrup: Paracetamol (p. 115·1); diphenhydramine (p. 626·1).
Fever; pain.

KB Gyding *KB, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders; Ménière's disease.

KB Meta *KB, Thai.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; gastro-oesophageal reflux.

KB Peramide *KB, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

KB Pophedin *KB, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

KB Ramine *KB, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

KB Syrup *KB, Thai.*
Ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

KB Syrup with Antihistamine *KB, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

KB Tazone *KB, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

KB Tribemin *KB, Thai.*
Vitamin B substances (p. 2102·3).

KB Vinecin *KB, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

KBDC *KB, Thai.*
Chlorphenamine (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

K-Bicarb *Bio-Tech, USA.*
Potassium bicarbonate (p. 1780·3).

K-Bind *Zydus, India.*
Calcium polystyrene sulfonate (p. 1541·2).

K-C *Century, USA.*
Kaolin (p. 1850·1); pectin (p. 2200·3); bismuth subcarbonate (p. 1822·1).
Diarrhoea.

K-Carb *Blue Cross, India.*
Acarbose (p. 466·2).
Diabetes mellitus.

K-Card *Wockhardt, India.*
Potassium chloride (p. 1793·2).

Kcentra *CSL, USA.*
Prothrombin complex concentrate (p. 1149·3).
Reversal of vitamin K antagonist-induced bleeding.

K-Cil *TP, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

K-Cip *Admac, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

K-Cip-TZ *Admac, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

K-Cit *Reddy, India.*
Citric acid monohydrate (p. 2480·3); potassium citrate (p. 1780·3).

San Marino, Philipp.
Potassium citrate (p. 1780·3).
Metabolic acidosis; urinary alkalinisation.

K-Citra *Seaford, Canad.*
Potassium citrate (p. 1780·3).
Potassium supplement.

KC-Lite *Biomedica, India.*
Cyclomethicone (p. 2209·2); kojic acid (p. 1710·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

KCl-retard *Novartis Consumer, Austria; Novartis, Ger.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

K.C.M.C *Knop, Chile.*
Carmellose (p. 2175·1); marine algae; cholic acid (p. 2457·2).
Obesity.

K-Cor *Macleods, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

K-Dent *Centaur, India.*
⊗Potassium nitrate (p. 1766·2).

K-Dent-F *Centaur, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Kdesin *Tedequim, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Dental care.

Kdiron *Julphar, UAE.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Kdol-P *Kalpataru, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

K-Drops *Alapis, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

KD-Unase *VHB, India.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

K-Dur *Merck, Canad.; Schering-Plough, Mex.; Key, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

KDZyme *Kaizen, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Ke Di *Kedi, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Ke Ai Lin *TianJin, China.*
Clioquinol (p. 273·1).
Fungal skin infections.

Ke Ai Ning *Gejiu, China.*
Disodium norcantharidin.

Ke Ai Si *Lifeike, China.*
Zidovudine (p. 1024·2).
HIV infection.

Ke Ao Sha *Ri Zhongtian, China.*
Cefixime (p. 240·3).
Bacterial infections.

Ke Ao Si *Kangnaike, China.*
Ranitidine hydrochloride (p. 1882·1).
Pathological gastric acid secretion; peptic ulcer; acid aspiration.

Ke Bin *Zhaohui, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Ke Chang *Haoao, China.*
Levodropropizine (p. 1662·3).
Cough.

Ke Da Kang *Bo Jian, China.*
Fluconazole (p. 578·2).
Fungal infections.

Ke Ding *Sancai, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Ke Le Er *Ou Yi, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Ke Er Le *Yong He, China.*
Isosorbide mononitrate (p. 1413·3).

Ke Er Sheng *Southwest Synthetic, China.*
Clindamycin palmitate hydrochloride (p. 269·3).
Bacterial infections.

Ke Fei *Laitai, China.*
Levocarnitine (p. 2053·2).

Ke Fen Qi *Southwest Synthetic, China.*
Troxipide (p. 1894·3).
Gastric ulcer; gastritis.

Ke Fu *Zhaohui, China.*
Doxifluridine (p. 782·3).
Malignant neoplasms.

Ke Jie Xing *Ankexinxing, China.*
Ligustrazine hydrochloride.

Ke Ke *Changzhou Siyao, China.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Ke Lao Er Kang *HongQi, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Ke Li *Sanofi, China.*
Digoxin (p. 1353·3).
Arrhythmias; heart failure.

Ke Li An *United Lab, China.*
⊗Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2); pseudoephedrine hydrochloride (p. 1676·1); sulfogaiacol (p. 1678·1).
Cough; cold symptoms.

Ke Li Ke *Renhe, China.*
Paracetamol (p. 115·1); amantadine hydrochloride (p. 890·3).

Ke Li Qing *South Ocean, China.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Ke Li Su *Double-Crane, China.*
Calfactant (p. 2599·2).

Ke Li Tai *South Ocean, China.*
Tinidazole (p. 949·2).
Protozoal infections; bacterial infections.

Ke Li Ting *United Lab, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Ke Li Xian *Tsinghua Yuanxing, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ke Li Yu *Mayinglong, China.*
Levodropropizine (p. 1662·3).
Cough.

Ke Lin Ao *Si Huan, China.*
Cinepazide maleate (p. 1338·1).

Ke Lin Da *Liaoyuan Yadong, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ke Lin Dun *Jinri, China.*
Cefixime (p. 240·3).
Bacterial infections.

Ke Ma Nuo *Wanma, China.*
Irsogladine maleate (p. 1848·3).

Ke Mai Ning *Shengma, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Ke Man Xin *KeRui, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ke Mei Xin *AnJieLun, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ke Mi *SSPC, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Ke Mi Ya *Ke Lun, China.*
Inosine (p. 2533·1).

Ke Ni *Fang Sheng, China.*
Secnidazole (p. 947·3).
Protozoal infections.

Ke Ni Bang *Ankang, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ke Ni You *Yibang, China.*
Levocarnitine (p. 2053·2).

Ke Pai *Wanjie High Tech, China.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Ke Pai Ning *Xinglin Baima, China.*
Benproperine phosphate (p. 1656·2).

Ke De Ping *Southwest Synthetic, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ke Ping *Zhaohui, China.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Ke Pu Nuo *Jincheng Haisi, China.*
Chloroprocaine hydrochloride (p. 1983·1).
Local anaesthesia.

Ke Pu Tuo *Jincheng Haisi, China.*
Levocarnitine (p. 2053·2).

Ke Ran Fu *San Jin, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Ke Rui Qi *Wenchun, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ke Rui Te *Yaoyou, China.*
Di-isopropylammonium dichloroacetate (p. 1359·1); sodium gluconate (p. 2618·3).

Ke Di Sheng *Wanjie High Tech, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ke Shuai *Star, China.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Ke Su *Sinobiopharma, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Ke Suo *Haixin, China.*
Matrine.

Ke Tai Fu *Huali Nanhu, China.*
Artenimol (p. 648·2); piperaquine phosphate (p. 659·3).
Malaria.

Ke Tai Shu *Xiuzheng, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Ke Te *Sanshun, China.*
Benproperine phosphate (p. 1656·2).

Ke Te Jia *Ke Lun, China.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Ke Tong *Xidian, China.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Ke Tuo *Southwest Synthetic, China.*
Doxifluridine (p. 782·3).
Malignant neoplasms.

Ke Wei *ChangJiang, China.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Ke Wei De *Nanxin, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left ventricular dysfunction following myocardial infarction.

Ke Xin Lin *C & O, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Ke Yan Li *Liuan Huayuan, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ke Yi *Zhaohui, China.*
⊗Exemestane (p. 792·2).
Breast cancer.

Ke Yu *Xia Du, China.*
Sodium ferulate.

Ke Ze Pu *JinYao, China.*
Lidocaine hydrochloride (p. 1988·2).

Ke Zhi *Changxing, China.*
⊗Aminophylline (p. 1201·2); methoxyphenamine hydrochloride (p. 1669·1); noscapine (p. 1670·3); chlorphenamine maleate (p. 620·3).

Kéal *EG, Fr.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Kebili *Baiyunshan, China.*
Cefradine (p. 249·1).
Bacterial infections.

Kebir *Aspen, Arg.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Kebirtecan *Aspen, Arg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Kebirterona *Aspen, Arg.*
Cyproterone (p. 2261·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kebirzol *Aspen, Arg.*
⊗Letrozole (p. 817·1).

Kecal *Keshav, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Kecheng *Zhaohui, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Keciflox *Pfleger, Ger.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Kecnitril *Proula, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Ked *Yash, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation, and photophobia following eye surgery; cystoid macular oedema.

Kedacillin *Takeda, Indon.; Hormona, Mex.†; Takeda, Philipp.*
Sulbenicillin sodium (p. 360·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Kedbumin *Kedrion, USA.*
⊗Albumin (p. 1130·2).

KeDi *Kedi, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Kediar *Kener, Mex.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kedrialb *Marketlink, Philipp.*
⊗Albumin (p. 1130·2).
Albumin deficiency.

Kedrop *Grin, Mex.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Kedu *NEGPF, China.*
Zidovudine (p. 1024·2).
HIV infection.

Keduo *LKM, Arg.*
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Keduxing *Livzon, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Keeneuron *Kee, India.*
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Kee, India.
Tablets: Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

KeenMind *Flordis, Austral.*
Bacopa (p. 2452·1).
Mental function impairment.

Keep Alert *Reese, USA.*
Caffeine (p. 1203·3).

Keeper *Kalpataru, India.*
Zinc (p. 2126·1).

Keeper Plus *Kalpataru, India.*
Lycopene (p. 2546·2); vitamins.

Keep-Fit *Kalpataru, India.*
Ginseng (p. 2513·3); minerals; vitamins.

Keep-Top *Kalpataru, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Keether *Kalpataru, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Kefabiotic *IFET (ΙΦΕΤ), Gr.*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Kefadim *EuroCept, Belg.; Lilly, Braz.; Antibioticos, China; Lilly, China; Lilly, UK.*
Ceftazidime (p. 250·2).
Bacterial infections.

Kefage *Ind-Chemie, India.*
Cefepime (p. 239·2).
Bacterial infections.

Kefalex *Ratiopharm, Fin.*
Cefalexin (p. 234·1).
Bacterial infections.

Kefalgin *Extractum, Hung.*
Ergotamine tartrate (p. 674·1); belladonna (p. 2453·3); caffeine (p. 1203·3); aminophenazone (p. 21·1).
Migraine.

Kefalomax *Biochimico, Braz.*
Cefalotin (p. 235·1).
Bacterial infections.

Kefalospes *Specifar (Σπεσιφαρ), Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Kefamin *Biomed, Spain.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Kefarin *Elvipe, Gr.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Kefaxim *ABL, Braz.†*
Cefotaxime (p. 244·1).
Bacterial infections.

Kefaxin *Elvipe, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Kefazim *Astro, Austria.*
Ceftazidime (p. 250·2).
Bacterial infections.

Kefazin *Vitamed, Israel.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Kefazol *Lilly, Braz.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Kefbactam *Elder, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Kefchek *Indoco, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Kefdil-AX *Ajanta, India.*
Ambroxol (p. 1654·3); cefadroxil (p. 233·2).

Kefdure *Sanat, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Kefei *Shenyang First, China.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Cough.

KefenTech *Jeil, Malaysia; JE IL, Singapore.*
Ketoprofen (p. 79·1).
Pain; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders.

Kefenting *Southwest Synthetic, China.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders; pain; fever.

Kefexin *Orion, Fin.*
Cefalexin (p. 234·1).
Bacterial infections.

Kefezy *Brown & Burk, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Kefive Plus *Crescent, India.*
Thioctic acid (p. 2629·1); carotenoids (p. 2176·2); chromium (p. 2055·3); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); manganese (p. 2081·2); mecobalamin (p. 2108·1); selenium (p. 2086·3).

Kefix *Ethix, India.*
Cefixime (p. 240·3).
Bacterial infections.

Keflaxina *Hexal, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Keflex *Aspen, Austral.; Arcana, Austria; Lilly, Braz.; Pendopharm, Canad.; Pharmacodane, Denm.; Lilly, Gr.; Ranbaxy, India; Flynn, Irl.; Lilly, Mex.; EuroCept, Norw.; Duncan, Philipp.†; Actavis, Pol.; Aspen, S.Afr.; Meda, Swed.; DKSH, Thai.; Flynn, UK; Shionogi, USA.*
Cefalexin (p. 234·1).
Bacterial infections.

Keflin *Ivax, Arg.; ABL, Braz.; Lilly, Braz.; Sandoz, Mex.; EuroCept, Neth.; EuroCept, Norw.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Keflin Neutral *Aspen, Austral.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Keflogen *Genepharm, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Keflor *Alphapharm, Austral.; Nanxin, China; Ranbaxy, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Kefloridina *Stada, Spain.*
Cefalexin (p. 234·1).
Bacterial infections.

Kefloxin *Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Mex.*
Cefadroxil (p. 233·2).
Bacterial infections.

Kefnir *Glenmark, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Kefodime *Medley, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Kefolit *Salus, Mex.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Kefolor *Actavis, Fin.*
Cefaclor (p. 232·3).
Bacterial infections.

Keforal *Ivax, Arg.; EuroCept, Belg.; ABL, Braz.†; Sciencex, Fr.; Crinos, Ital.; EuroCept, Neth.; Farma, Venez.*
Cefalexin (p. 234·1).
Bacterial infections.

Kefort *Liconsa, Irl.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Kefotam *Vitamed, Israel.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Kefotax *Aspen, S.Afr.; Sandoz, S.Afr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Kefox
Note: this name may be used for preparations of different composition.
ABL, Braz.
Cefoxitin sodium (p. 246·2).
Bacterial infections.

CT, Philipp.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Kefozil *Biochimico, Braz.*
Cefotaxime (p. 244·1).
Bacterial infections.

Kefpod *Glenmark, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Kefrenex *Axxon, Neth.†; Axxon, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Kefsid *Fako, Turk.*
Cefaclor (p. 232·3).
Bacterial infections.

Kefstar *Wockhardt, India; Wockhardt, Rus.*
Cefuroxime (p. 255·2).
Bacterial infections.

Wockhardt, Philipp.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Kefsurge *Indoco, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Kefsyn *GX, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Keftaz *Sandoz, S.Afr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Keftid *Galen, Irl.; Galen, UK.*
Cefaclor (p. 232·3).
Bacterial infections.

Keftil *Zynova, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Keftra *Ipca, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Keftragard *Ipca, India.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Keftriaxone *Vitamed, Israel.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Keftron *ABL, Braz.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Kefuel *Dallas, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Kefurim *Vitamed, Israel.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Kefurox *EuroCept, Belg.; Orchid, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Kefzen *Ind-Chemie, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Kefzol *Aspen, Austral.; Astro, Austria; EuroCept, Belg.; Lilly, Gr.; EuroCept, Neth.; Lilly, Rus.; Sandoz, S.Afr.; Teva, Switz.*
Cefazolin sodium (p. 237·3).
Lidocaine hydrochloride (p. 1988·2) is included in the solvent for intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Keigairengyoto *Tsumura, Jpn.*
Skullcap root (p. 2617·1); phellodendron bark; coptis rhizome; platycodon root; immature orange; schizonepeta tenuifolia; bupleurum root; gardenia fruit; rehmannia root; peony root; cnidium rhizome; angelica acutiloba root (p. 2443·3); mentha herb; angelica dahurica root; saposhnikovia root; forsythia fruit; liquorice (p. 1853·2).
Traditional Kampo medicine.

Keihito *Tsumura, Jpn.*
Atractylodes lancea rhizome; poria sclerotium; dioscorea rhizome; ginseng (p. 2513·3); nelumbo seed; crataegus fruit (p. 2488·1); alisma rhizome; citrus unshiu peel; liquorice (p. 1853·2).
Traditional Kampo medicine.

Keimax *MSD, Ger.*
Ceftibuten (p. 252·2).
Bacterial infections.

Keimicina *Zambon, Ital.*
Kanamycin sulfate (p. 314·3).
Vulvovaginal bacterial infections.

Keiran *Pharmakin, Venez.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Keishibukuryogan *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); peony root; peach kernel; poria sclerotium; moutan bark.
Traditional Kampo medicine.

Keishibukuryogankayokuinin *Tsumura, Jpn.*
Coix seed; cinnamon bark (p. 2479·2); peony root; peach kernel; poria sclerotium; moutan bark.
Traditional Kampo medicine.

Keishikajutsubuto *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); peony root; atractylodes lancea rhizome; jujube; liquorice (p. 1853·2); ginger (p. 1844·1); aconite root (p. 2428·3).
Traditional Kampo medicine.

Keishikaryukotsuboreito *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); peony root; jujube; oyster shell; longgu; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Keishikashakuyakudaioto *Tsumura, Jpn.*
Peony root; cinnamon bark (p. 2479·2); jujube; liquorice (p. 1853·2); rhubarb (p. 1884·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Keishikashakuyakuto *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); peony root; jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Keishininjinto *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); liquorice (p. 1853·2); atractylodes lancea rhizome; ginseng (p. 2513·3); ginger (p. 1844·1).
Traditional Kampo medicine.

Keishito *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); peony root; jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Kekona *Esma, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Kekrinal *Help, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Kela *TO-Chemicals, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Kelac *Richmond, Arg.; Giempi, Venez.*
Ketorolac trometamol (p. 80·2).
Pain; inflammation.

Intas, India.
Ketorolac (p. 80·2) or ketorolac trometamol (p. 80·2).
Pain.

Kelamild *TO-Chemicals, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Kelaplus *TO-Chemicals, Thai.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Fungal skin infections with inflammation.

Kelargine *Kela, Belg.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Kelate *Sanify, India.*
Etamsylate (p. 1145·2).
Haemorrhage.

Kelatine *Medirex, Port.*
Penicillamine (p. 1567·1).
Heavy-metal poisoning; rheumatoid arthritis; Wilson's disease; cystinuria.

Kelcer *Armour, India.*
Syrup: Calcium (p. 1783·1); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).

Armour, India.
Tablets: Boron (p. 2052·3); calcium (p. 1783·1); lysine hydrochloride (p. 2079·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Kelcer Plus *Armour, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).

Keldor *GP, Arg.*
Naproxen (p. 98·2).
Pain; fever.

Kelefusin *Pisa, Mex.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Kelfen *Roemmers Osmoph, Venez.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal and joint disorders; pain.

Kelfer *Vianex (Βιανεξ), Gr.; Cipla, India; Cipla, Malaysia; Cipla, Singapore; Cipla, Thai.*
Deferiprone (p. 1543·1).
Iron overload.

Kelfex *Combiphar, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Kelfizine W *Pfizer, Irl.*
Sulfametopyrazine (p. 367·3).
Bacterial infections.

Kelicardina *Herbapol Wroclaw, Pol.*
Ammi visnaga (p. 2441·2); convallaria (p. 2486·2); crataegus (p. 2488·1); rutoside (p. 2505·3).
Circulatory disorders.

Keli-med *Permamed, Switz.*
Garlic (p. 2510·3); hyoscyamus (p. 2530·2); allantoin (p. 1693·1); heparin sodium (p. 1396·3); avobenzone (p. 1695·1); enzacamene (p. 1703·2).
Scars.

Kelin *Helm, Port.†*
Paracetamol (p. 115·1).
Pain; fever.

Keliping *South Ocean, China.*
Felodipine (p. 1380·3).
Hypertension; ischaemic heart disease; angina pectoris; heart failure.

Kelisaike *South Ocean, China.*
Secnidazole (p. 947·3).
Trichomoniasis.

KeLiTing *Kowloon, China.*
Benproperine phosphate (p. 1656·2).

Kelly *Sigma, Braz.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Kelnac *Daiichi Sankyo, Jpn; Sankyo, Thai.†*
Purified plau-noi extract (plaunotol) (p. 1879·1).
Gastric ulcer; gastritis; peptic ulcer.

Kelnor *Barr, USA.*
Ethinylestradiol (p. 2275·3); etynodiol diacetate (p. 2277·3).
Combined oral contraceptive.

Keloc *Approved Prescription Services, UK.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Kelo-Cote *LKM, Arg.; Sinclair, Fr.; Sinclair, Ger.; Axelia, Indon.; Advanced Biotechnologies, Israel.*
Polysiloxane (p. 2209·3); silicon dioxide (p. 2208·3).
Aid in skin healing; hypertrophic and keloid scars.

Kelo-cote *Medigroup, Austral.*
Silicone (p. 2209·2).
Hypertrophic and keloid scars.

Interdelta, Switz.†
Polysiloxane (p. 2209·3); silicon dioxide (p. 2208·3).
Scars.

Kelocyanor *IFET (ΙΦΕΤ), Gr.*
Dicobalt edetate (p. 1548·3).
Cyanide poisoning.

Kélocyanor *SERB, Fr.*
Dicobalt edetate (p. 1548·3).
Cyanide poisoning.

Kelosoft *Chemomedica, Austria; Geistlich, Switz.*
Hyoscyamus oil (p. 2530·2).
Nasal disorders; scars.

Kelp Plus 3 *Larkhall Laboratories, UK.*
Kelp (p. 2612·1); vitamin B_6 (p. 2105·3); soya lecithin (p. 2542·2); cider vinegar.

Kelsef *Tradiphar, Fr.†*
Cefradine (p. 249·1).
Bacterial infections.

Keltican *Ferrer, Ukr.*
Trisodium uridine triphosphate (p. 2638·1); disodium uridine diphosphate (p. 2495·2); disodium uridine monophosphate (p. 2495·2); disodium cytidine phosphate (p. 2491·1).
Neuropathy.

Keltican N *Trommsdorff, Ger.†*
Disodium uridine phosphate (p. 2495·2); disodium cytidine phosphate (p. 2491·1). Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuritis; neuralgia; neuropathy.

Keltrina *Multilab, Braz.*
Permethrin (p. 2159·3).
Pediculosis.

Kélual *Ducray, Fr.*
Keluamid (p. 1710·2).
Seborrhoeic dermatitis.

Kelual *Pierre Fabre Dermo-Cosmetique, Arg.*
Keluamid (p. 1710·2).
Seborrhoeic dermatitis.

Kélual DS *Ducray, Fr.*
Cream: Glycolic acid (p. 1704·3); guanidine carbonate; crotamiton (p. 1699·2); enoxolone (p. 54·2); saw palmetto (p. 2363·3); keluamid (p. 1710·2); piroctone olamine (p. 1716·3).
Irritant and oily skin conditions.

Ducray, Fr.
Mousse; shampoo: Ciclopirox olamine (p. 575·3); pyrithione zinc (p. 1718·1); enoxolone (p. 54·2); keluamid (p. 1710·2).
Scalp disorders.

Kelual Zinc *Pierre Fabre Dermo-Cosmetique, Arg.*
Keluamid (p. 1710·2); zinc sulfate (p. 2126·2).
Skin disorders.

Kélual Zinc *Ducray, Fr.†*
Keluamid (p. 1710·2); zinc sulfate (p. 2126·2).
Seborrhoeic dermatitis.

Keluoqu *Livzon, China.*
Tramadol hydrochloride (p. 139·2); ibuprofen (p. 68·2); ketongnin.
Pain.

Kelvin *Leben, India.*
Paracetamol (p. 115·1).
Pain; fever.

Kelvin Plus *Leben, India.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2).

Kelvin-P *Leben, India.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2).

Kem *Forgo, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Kemadren *Aspen, Spain.*
Procyclidine hydrochloride (p. 912·2).
Parkinsonism; drug-induced extrapyramidal disorders.

Kemadrin *GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Denm.; GSK, Hung.; GSK, India; Aspen, Irl.; GSK, Israel; GSK, NZ; Pro Concepta, Switz.; Auden McKenzie, UK; GSK, UK.*
Procyclidine hydrochloride (p. 912·2).
Parkinsonism; drug-induced extrapyramidal disorders.

Kemanat *Microsules, Arg.*
Ketorolac (p. 80·2) or ketorolac trometamol (p. 80·2).
Pain.

Kemeol *Interdelta, Switz.†*
⊗Ephedrine (p. 1663·1); neroli oil (p. 2568·3); eucalyptus oil (p. 2501·2).
Rhinitis.

Kemerhinose *Interdelta, Switz.†*
Sodium chloride (p. 1795·1); benzododecinium bromide (p. 1739·2).
Nasal congestion.

Kemial *Janssen-Cilag, Arg.*
Vaginal and rectal lubricant.

Kemian *United Lab, China.*
Triprolidine hydrochloride (p. 642·3).
Allergic disorders.

Kemicetin *Sanochemia, Austria.†*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Kemicetine *Pharmacia Upjohn, Gr.; Pfizer, Hong Kong; Mac, India; Kalbe, Indon.; Pfizer, Philipp.†; Deva, Turk.*
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Pfizer, Singapore†; Pfizer, UK.
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Kemicetine Antiozena *Mac, India.*
Chloramphenicol (p. 257·1); estradiol dipropionate (p. 2271·2); colecalciferol (p. 2113·1).

Kemiderm *Berlico Mulia, Indon.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Kemipen *Elpen (Ελπεν), Gr.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Kemlosar *Alchemia, Ital.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Kemlosar comp *Actavis, Denm.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kemocarb *Biochimico, Braz.; Dabur, India; Alternavida, Mex.; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Kemonex *Chemo-Drugs, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Kemoplat *Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Rus.; Fresenius Kabi, Thai.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Kemopride *Chemo-Drugs, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Kemopride MPS *Chemo-Drugs, India.*
Cisapride (p. 1831·3); dimeticone (p. 1886·2).

Kemoprim *Ulagay, Turk.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Kemora *Olan-Kemed, Thai.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; nausea and vomiting; premedication.

Kemorifa *Chemo-Drugs, India.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Kemoter *Elea, Arg.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Kemox *Rishab, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Kemox Plus *Rishab, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Kemphor *Salusif, Port.*
Zinc chloride (p. 2126·1); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Mouth disorders.

Kempi *Pfizer, Spain.†*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea.

Kemsol
Note: this name may be used for preparations of different composition.
Excalibur, Canad.
Alkyldimethylethylbenzyl ammonium chloride (p. 1736·2); benzalkonium chloride (p. 1737·1).
Disinfectant.

Axxess, Canad.†
Dimethyl sulfoxide (p. 2182·2).
Scleroderma.

Kemstro *Schwarz, USA.†*
Baclofen (p. 2014·3).
Skeletal muscle spasm and spasticity.

Kemtelo *Sigillata, Denm.; Sigillata, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Kemudin *Basi, Port.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Kemzid *Unison, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Ken Te Ling *Hailisheng, China.*
A smectite (p. 1887·1).

Kenacef *Medikon, Indon.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Kenacomb
Note: this name may be used for preparations of different composition.
BMS, Arg.; Aspen, Austral.; BMS, China; BMS, Hong Kong†; Sarabhai Piramal, India; BMS, Irl.†; BMS, Malaysia; BMS, Mex.; Healthcare Logistics, NZ; BMS, Philipp.†; BMS, S.Afr.†; BMS, Thai.†
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); nystatin (p. 590·3).
Infected skin disorders; otitis externa; infected ear disorders.

BMS, Venez.
⊗Triamcinolone acetonide (p. 1649·1); gramicidin (p. 308·3); nystatin (p. 590·3).
Infected skin disorders.

Protasis, Gr.
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Kenacombin Novum *BMS, Swed.†*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Fungal skin infections.

Kenacort *BMS, Arg.; Piramal, India; Taisho, Indon.; BMS, Mex.; Dermapharm, Switz.; BMS, Venez.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

BMS, Fr.; IFET (ΙΦΕΤ), Gr.; BMS, Ital.; BMS, Philipp.†
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid; skin disorders.

Kenacort-A *BMS, Arg.; Aspen, Austral.; BMS, Belg.; BMS, Chile†; BMS, China; BMS, Gr.; BMS, Hong Kong†; Taisho, Indon.; BMS, Neth.; Healthcare Logistics, NZ; BMS, Philipp.†; Dermapharm, Switz.; BMS, Thai.†; BMS, Turk.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid; skin disorders; musculoskeletal, joint, and peri-articular disorders; inflammatory lesions.

Dermapharm, Switz.
Tincture: ⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Skin disorders.

Kenacort-A Solubile *Dermapharm, Switz.*
⊗Triamcinolone acetonide dipotassium phosphate (p. 1648·3).
Corticosteroid.

Kenacort-T *BMS, Fin.†; BMS, Norw.; BMS, Swed.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid; mouth disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kenacort-T comp *BMS, Swed.†*
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Skin disorders; otitis externa.

Kenadion *Samarth, India.*
Phytomenadione (p. 2122·2).
Antidote to coumarin anticoagulants in hypoprothrombinaemia.

Kenalcol *BMS, Fr.†*
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1); benzalkonium chloride (p. 1737·1).
Skin disorders.

Kenalfin *Gufic, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Kenalin *Kendrick, Mex.*
Sulindac (p. 134·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Kena-Lite *Nupharma, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Kenalog *BMS, Canad.; BMS, China; BMS, Denm.; KRKA, Hung.; BMS, Irl.†; BMS, UK; BMS, USA; Ranbaxy, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth lesions; corticosteroid.

BMS, Rus.; KRKA, Rus.; KRKA, Ukr.
⊗Triamcinolone (p. 1648·3) or triamcinolone acetonide (p. 1649·1).
Corticosteroid.

BMS, Venez.
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Psoriasis.

Kenalog Comp med Mycostatin *BMS, Denm.†*
⊗Triamcinolone acetonide (p. 1649·1); gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Kenalog Dental *BMS, Mex.*
⊗Triamcinolone (p. 1648·3).
Mouth disorders.

Kenalog in Orabase *Aspen, Austral.; BMS, Hong Kong†; Taisho, Indon.; BMS, Malaysia; BMS, NZ; BMS, S. Afr.; BMS, Singapore; BMS, Thai.†; Apothecon, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions; mouth disorders.

Kenalog-S *Piramal, India.*
⊗Triamcinolone acetonide (p. 1649·1); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Infected inflammatory eye disorders.

Kenalyn *Silom, Thai.†*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Kenantist *BMS, Indon.†*
⊗Triamcinolone (p. 1648·3); carbinoxamine maleate (p. 619·1).
Allergic disorders.

Kenaprol *Kener, Mex.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension.

Kenaxef *Keun Wha, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Kenazol
Note: this name may be used for preparations of different composition.
PC India, India; Pharmasant, Thai.; Roemmers Osmoph, Venez.
Ketoconazole (p. 585·3).
Fungal infections.

Kendrick, Mex.†
Etoposide (p. 790·2).
Malignant neoplasms.

Kenazole *Pharma International, Ukr.*
Ketoconazole (p. 585·3).
Infections of skin and hair associated with Pityrosporum.

Kenbrid *Kendrick, Mex.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure.

Kenciclen *Kener, Mex.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria; amoebiasis.

Kendaron *Darya-Varia, Indon.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Kendix *EG, Fr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Kendo *ABC, Ital.*
Ibuprofen (p. 68·2).

Kendol *Ophtalkener, Mex.*
Ketorolac trometamol (p. 80·2).
Eye disorders.

Kendolit *Kendrick, Mex.*
Ketorolac (p. 80·2) or ketorolac trometamol (p. 80·2).
Pain.

Kendural *Teofarma, Switz.*
Ferrous sulfate (p. 2062·2).
Sodium ascorbate (p. 2111·1) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Kendural C *Teofarma, Ger.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemias.

Kendural-Fol-500 *Teofanna, Ger.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemias.

Kene *Neo-Derm, Philipp.*
Cetylpyridinium chloride (p. 1743·1); lactic acid (p. 2539·1).
Vaginal hygiene.

Kenedril *Biospray, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Kenefen *Pharmasant, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; bronchitis; hypersensitivity reactions.

Kenergon *Magistra, Switz.*
Lidocaine (p. 1988·1).
Premature ejaculation.

Kenesil *Cantabria, Spain.*
Nimodipine (p. 1455·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Kenet *Patar, Thai.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Kenetrol *Darya-Varia, Indon.†*
Eye drops: Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); phenylephrine hydrochloride (p. 1672·3).
Bacterial eye infections.

Darya-Varia, Indon.†
Eye ointment: Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Kenfix *Sanovel, Turk.*
Thiocolchicoside (p. 2026·2).

Keng Qiang *Cuccess, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Kenhancer *Green Cross, Malaysia; Sang-A Pharm, Singapore.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Kenicef *Taiho, Jpn.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Kenicet *Kendrick, Mex.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic skin disorders; allergic rhinitis; allergic conjunctivitis.

Kening *Sine, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Keno *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Kenofen *Ildong, Malaysia.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint and soft-tissue disorders.

Kenoket *Kendrick, Mex.*
Clonazepam (p. 519·1).
Epilepsy.

Kenolan *Kendrick, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Kenonel *Marnel, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Kenong *Yangtze River, China.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Kenoral *General Drugs, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Kenrovir *Darya-Varia, Indon.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Kensedal *Precimex, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Kensodic *Kendrick, Mex.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Kenspa *Kenyaku, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Smooth muscle spasm; gastrointestinal disorders.

Kenstatin *Kendrick, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Kenta *Kinds, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kentacef *BMS, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Kenta-D *Kinds, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Kentadin *Kendrick, Mex.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Kentera *Nicobrand, Austria; EuroCept, Belg.; Nicobrand, Cz.; Nicobrand, Denm.; Nicobrand, Fin.; Recordati, Ger.; Nicobrand, Gr.; Nicobrand, Irl.; Nicobrand, Neth.; Nicobrand, Norw.; Nicobrand, Pol.; Jaba Recordati, Port.; Orion, Swed.; Orion, Switz.; Recordati, UK.*
Oxybutynin (p. 2361·2).
Bladder instability; urinary incontinence.

Kentimol *Darya-Varia, Indon.†*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Kenvastin *Kener, Mex.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Kenwood Therapeutic Liquid *Kenwood, USA.*
Vitamins; minerals.

Kenyamine *Kenyaku, Hong Kong.†*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Kenyna *Kendrick, Mex.†*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; steatorrhoea.

Kenzar *ACME, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Kenzar Plus *ACME, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kenzen *Takeda, Fr.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Kenzoflex *Collins, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Kenzolol *Kendrick, Mex.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage; mental function disorders; vestibular disorders.

Keol-C *Air Liquide, Neth.*
Oxygen (p. 1799·3).
Hypoxia.

Keolium *Stallergenes, Neth.*
Grass pollen allergen extracts (p. 2434·3).
Allergen immunotherapy.

Keol-S *Air Liquide, Spain.*
Oxygen (p. 1799·3).
Mechanical ventilation; nebulisation.

Keon *Darvys, Philipp.*
Ketoprofen (p. 79·1).
Pain; fever.

Keparin *Neon, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Kepcet *Ascent, Austral.*
Levetiracetam (p. 531·1).
Epilepsy.

Kephalodoron *Weleda, Austria.*
Ferrous sulfate (p. 2062·2); silicon dioxide (p. 2208·3).
Vasomotor headache; migraine; nervous disorders.

Weleda, S.Afr.†
Ferrum sulphate (p. 2062·2); quartz.
Homoeopathic preparation.

Kephazon *United Biotech, India.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Kephazon-S *United Biotech, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Kepinol *Pfleger, Ger.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Kepivance *Invida, Austral.; Biovitrum, Austria; Swedish Orphan, Belg.; Swedish Orphan, Canad.; Biovitrum, Cz.; Biovitrum, Denm.; Biovitrum, Fin.; Biovitrum, Fr.; Swedish Orphan, Ger.; Biovitrum, Gr.; Amgen, Hung.; Amgen, Irl.; Megapharm, Israel; Biovitrum, Ital.; Amgen, Neth.; Swedish Orphan, Norw.; Amgen, Pol.; Biovitrum, Port.; Biovitrum, Spain; Biovitrum, Swed.; Cosan, Switz.; Biovitrum, UK; Biovitrum, USA.*
⊗Palifermin (p. 2579·1).
Oral mucositis associated with myelotoxic therapy or radiotherapy.

Keplat *Hisamitsu, Cz.; Hisamitsu, Hung.; Sigma-Tau, Ital.; Hisamitsu, Port.*
Ketoprofen (p. 79·1).
Pain; musculoskeletal, joint, and soft-tissue disorders.

Keppra *HLB, Arg.; UCB, Austral.; UCB, Austria; UCB, Belg.; UCB, Canad.; GSK, Chile; UCB, China; UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; UCB, Gr.; GSK, Hong Kong; UCB, Hung.; UCB, India; UCB, Indon.; UCB, Irl.; UCB, Israel; UCB, Ital.; GSK, Malaysia; UCB, Mex.; UCB, Neth.; UCB, Norw.; UCB, NZ; GSK, Philipp.; UCB, Pol.; UCB, Port.; UCB, Rus.; AHN, S.Afr.; GSK, Singapore; UCB, Spain; UCB, Swed.; UCB, Switz.; GSK, Thai.; UCB, Turk.; UCB, UK; UCB, Ukr.; UCB, USA.*
Levetiracetam (p. 531·1).
Epilepsy.

Keppur *Drossapharm, Switz.*
Cream: Heparin sodium (p. 1396·3); comfrey (p. 2484·2); St John's wort oil (p. 449·1); calendula oil (p. 2465·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; venous insufficiency.

Drossapharm, Switz.
Topical gel: Heparin sodium (p. 1396·3); comfrey (p. 2484·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; venous insufficiency.

Keprilan *Benedetti, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).

Kepsidol *Kener, Mex.*
Haloperidol (p. 1077·1).

Keptan *Pfleger, Austria.*
Primula root (p. 2596·2).
Respiratory-tract disorders.

Keptrix *Biolab, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Keqi *Qianjiang, China.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Kera *Keshav, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Keracnyl *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.*
Topical gel: ⊗Saw palmetto (p. 2363·3); zinc salicylate (p. 1719·1); glycerol (p. 2517·2); glycolic acid (p. 1704·3).
Skin cleansing; acne.

Ducray, Fr.
Cream: Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); lactic acid (p. 2539·1); saw

palmetto (p. 2363·3); zinc salicylate (p. 1719·1); levomenol (p. 2544·1).
Acne; seborrhoea.

Pierre Fabre Dermo-Cosmetique, Arg.
Cream: Saw palmetto (p. 2363·3); zinc salicylate (p. 1719·1); glycolic acid (p. 1704·3); salicylic acid (p. 1719·1); lactic acid (p. 2539·1); levomenol (p. 2544·1); stearyl glycyrrhetinate.
Acne.

Ducray, Fr.
Face mask: Glycolic acid (p. 1704·3); zinc salicylate (p. 1719·1); kaolin (p. 1850·1).
Seborrhoea.

Ducray, Fr.
Topical mousse: Poly hydroxy acids; glycolic acid (p. 1704·3); saw palmetto (p. 2363·3); zinc salicylate (p. 1719·1).
Acne; seborrhoea.

Piramal, India.
Zinc salicylate (p. 1719·1).
Acne.

Keracnyl eau nettoyante *Ducray, Fr.†*
Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); levomenol (p. 2544·1); hamamelis (p. 2523·3).
Skin cleanser for oily skin.

Keracnyl Stop Bouton *Silesia, Chile.*
Ammonium glycyrrhizate (p. 2520·3); lactamide; glycolic acid (p. 1704·3); salicylic acid (p. 1719·1); hamamelis (p. 2523·3).
Acne.

Keracnyl stop bouton *Ducray, Fr.*
Ammonium glycyrrhizate (p. 2520·3); lactamide; glycolic acid (p. 1704·3); salicylic acid (p. 1719·1); hamamelis (p. 2523·3).
Acne.

Keradan *Medimetriks, USA.*
Emollient.

Keraderm *Dermapharm, Neth.*
Acitretin (p. 1690·3).
Psoriasis; ichthyosis; lichen planus; keratinisation disorders.

Keraffler *Loeffler, Mex.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; allergic conjunctivitis; urticaria; atopic eczema.

Kerafilm *Ducray, Fr.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Corns; calluses; verrucae.

Kerafilmver *Pierre Fabre, Ital.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Verrucas; hyperkeratosis.

Keraflex *Sifarma, Ital.*
⊗Carbocisteine (p. 1658·1); malic acid (p. 2549·2); mucopolysaccharides; urea (p. 1727·3); allantoin (p. 1693·1).
Cicatrisation.

Keraflox *Crinos, Ital.; ACRAF, Port.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Kerafoam *Onset, USA.*
⊗Urea (p. 1727·3).
Dry skin.

Keral *Menarini, Irl.; Menarini, Mex.; Menarini, UK.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Keralac *PharmaDerm, USA.†*
⊗Urea (p. 1727·3).
Skin and nail disorders.

Keralin *East India Pharma, India.*
⊗Hydrocortisone acetate (p. 1640·1); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Corns; fungal infections.

Keralyt *Summers, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Keranin *Quimifar, Spain.†*
Acetic acid (p. 2426·3); flexible collodion; lactic acid (p. 2539·1); castor oil (p. 2472·1); salicylic acid (p. 1719·1).
Warts.

Keranon *Pentamedical, Ital.*
Salicylic acid (p. 1719·1).
Keratinisation disorders.

Kérapil *Noreva, Fr.*
Ammonium lactate (p. 1694·3).
Keratinisation disorders.

Kerarer *LKM, Arg.*
Ketorolac trometamol (p. 80·2).
Pain.

Kerasal *Alterna, Canad.; Spirig, Cz.; Orva, Turk.; Delta Medical, Ukr.*
⊗Salicylic acid (p. 1719·1); urea (p. 1727·3).
Skin disorders.

Kérasal *Spirig, Switz.*
⊗Salicylic acid (p. 1719·1); urea (p. 1727·3).
Skin and scalp disorders.

Kerasal AL *Taro Consumer, USA.*
Ammonium lactate (p. 1694·3).
Emollient.

Kerasal Ultra *Alterna, USA.*
⊗Ammonium lactate (p. 1694·3); urea (p. 1727·3).
Dry skin.

Kerasex *Revifar, Gr.*
Codergocrine mesilate (p. 389·2).

Kerastil *Loeffler, Mex.*
Aciclovir (p. 964·1).
Herpes simplex infections of the lips and face.

Keratex *Fem Care, India.*
Sesame oil (p. 2614·1).

Keratinamin *Kowa, Jpn.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Keratine *Biofarma, Mex.*
Vitamins.

Keratisdin *Isdin, Spain.†*
Lactic acid (p. 2539·1).
Skin disorders.

Kerato Biciron *S & K, Ger.*
Calcium pantothenate (p. 2085·2).
Corneal injury.

Keratol HC *Breckenridge, USA.*
⊗Hydrocortisone acetate (p. 1640·1); urea (p. 1727·3).
Skin disorders.

Keratolip *Qualifarma, Ital.*
Betacarotene (p. 2051·1); propolis (p. 2597·3).
Emollient for lips.

Keratolit *ICN, Pol.†*
⊗Salicylic acid (p. 1719·1); urea (p. 1727·3).
Skin disorders.

Keratolysin *RiC, Pol.†*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Corns.

Keratopic *Cassara, Arg.*
⊗Urea (p. 1727·3).
Dry skin disorders; hyperkeratosis.

Keratoplastica *Ogna, Ital.*
Betacarotene (p. 2051·1).
Skin disorders.

Kératosane *Uriage, Fr.*
⊗Urea (p. 1727·3).
Dry skin disorders; hyperkeratotic skin disorders.

Keratosis *Widmer, Austria.*
⊗Urea (p. 1727·3); dexpanthenol (p. 2582·2).
Hyperkeratotic skin disorders.

Keratosis forte *Widmer, Austria.*
⊗Urea (p. 1727·3); dexpanthenol (p. 2582·2); tretinoin (p. 1725·2).
Skin disorders.

Keratospor *Perrigo, Israel.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Kératyl *Chauvin, Fr.†*
⊗Nandrolone sodium sulfate (p. 2293·2).
Eye disorders.

Keratyl *Chauvin, Thai.†*
⊗Nandrolone sodium sulfate (p. 2293·2).
Eye disorders.

Kerberan *Medico Uno, Hung.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Keri *Novartis Consumer, USA.*
A range of emollients and moisturisers.

BMS, Hong Kong†; Novartis, UK.
Liquid paraffin (p. 2191·2).
Dry skin.

Keri Daily UVB/A *Novartis Consumer, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Keri Silky Smooth *Mentholatum, Austral.†*
Emollient.
Dry skin disorders.

Keri Vit E *BMS, Hong Kong.†*
Vitamin E (p. 2119·1).
Facial wrinkles; scars.

Keritmon *Best, Mex.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Keritrina *Crinos, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Kerium Anticaspa -Caspa Grasa *Roche-Posay, Chile.*
Salicylic acid (p. 1719·1); zinc pidolate (p. 1720·3); lipo hydroxy acid; piroctone olamine (p. 1716·3); capryloyl glycine (p. 2173·3).
Seborrhoeic dermatitis.

Kerium Anticaspa -Caspa Seca *Roche-Posay, Chile.*
Capryloyl glycine (p. 2173·3); lipohydroxy acid; piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1); arginine (p. 2049·1).
Dry scalp disorders.

Kerium Anticaspa Intensivo *Roche-Posay, Chile.*
Salicylic acid (p. 1719·1); piroctone olamine (p. 1716·3); capryloyl glycine (p. 2173·3); lipohydroxy acid; nicotinamide (p. 2083·1).
Scalp disorders.

Kerium Intensive *Roche-Posay, Fr.†*
Salicylic acid (p. 1719·1); piroctone olamine (p. 1716·3).
Dandruff.

Kerlofin *Aledicine, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Kerlon *Sanofi-Aventis, Fin.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.*
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; angina pectoris.

Kerlone *Sanofi-Aventis, Belg.; Sanofi, China; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Lavipharm, Gr.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Singapore; Sanofi, USA.†*
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; angina pectoris.

Kerlong *Sanofi-Aventis, Jpn.*
⊗Betaxolol hydrochloride (p. 1322·3).
Angina pectoris; hypertension.

Kernosan 24 *Kern, Switz.*
Chamomile (p. 2474·1); boldo (p. 2458·3); cynara (p. 2490·3); fennel (p. 2503·2); agrimony (p. 2432·3); cnicus benedictus (p. 2482·2); centaury (p. 2473·2); chicory (p. 2475·2); achillea (p. 2427·3); taraxacum (p. 2625·3); liquorice (p. 1853·2); turmeric (p. 2218·1).
Digestive disorders.

Kernosan 26 *Kern, Switz.*
Condurango (p. 2485·3); chamomile (p. 2474·1); melissa (p. 2552·3); clover; cumin; fennel (p. 2503·2); cnicus benedictus (p. 2482·2); centaury (p. 2473·2); achillea (p. 2427·3); taraxacum (p. 2625·3); thyme (p. 2630·2); urtica (p. 2639·3); gentian (p. 2512·1); liquorice (p. 1853·2); calamus (p. 2464·2); white clay.
Digestive disorders.

Kernosan Eau Dentifrice *Kern, Switz.†*
Oak bark (p. 2574·1); clove (p. 2481·2); chamomile (p. 2474·1); spearmint (p. 2621·2); sage (p. 2608·3); sandalwood (p. 2610·1); myrrh (p. 2566·1); echinacea (p. 2498·1); galanga; rhatany root (p. 2603·3); sanguinaria (p. 2610·1); fennel (p. 2503·2); liquorice (p. 1853·2); star anise (p. 2622·1); mint oil (p. 2560·1).
Oral hygiene.

Kernosan Elixir *Kern, Switz.*
Aniseed (p. 2444·2); horseradish (p. 2526·1); calamus (p. 2464·2); fennel (p. 2503·2); ivy (p. 2536·2); imperatoria root; Iceland moss (p. 2531·2); burnet saxifrage root (p. 2463·1); plantain seed (p. 2592·3); oak bark (p. 2574·1); primula root (p. 2596·2); liquorice (p. 1853·2).
Cough; catarrh; bronchitis.

Kernosan Heidelberger Poudre *Kern, Switz.*
Absinthium (p. 2426·1); aniseed (p. 2444·2); caraway (p. 2470·2); fennel (p. 2503·2); juniper (p. 2537·1); achillea (p. 2427·3); burnet saxifrage root (p. 2463·1).
Digestive system disorders.

Kernosan Huile de Massage *Kern, Switz.*
Eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); sweet birch oil (p. 92·1); camphor (p. 2466·2).
Musculoskeletal, joint, and peri-articular pain.

Kerodex *Miba, Ital.*
Barrier cream.

Whitehall, USA.
Topical barrier preparation.

Kerol *Doak, USA†; PharmaDerm, USA.†*
⊗Urea (p. 1727·3).
Dry skin disorders.

Keromask *Network Health & Beauty, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Keromicil *Miba, Ital.*
Cream: Kaolin (p. 1850·1); zinc oxide (p. 1729·1); melaleuca oil (p. 2551·1); azadirachta oil (p. 2451·2).
Barrier cream.

Miba, Ital.
Topical liquid: Melaleuca oil (p. 2551·1); azadirachta oil (p. 2451·2).
Skin disinfection.

Keron *Keshav, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Keroxime *ABL, Braz.*
Cefuroxime (p. 255·2).
Bacterial infections.

Kerr Insta-Char *Vistapharm, USA.*
Activated charcoal (p. 1537·3).
Poisoning.

Kerstipon *Pharmathen, Cz.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Kertyol *Pierre Fabre Dermo-Cosmetique, Arg.*
Kertyol; salicylic acid (p. 1719·1).
Dandruff.

Medifarm Ducray, Venez.
Salicylic acid (p. 1719·1); benzyl benzoate (p. 2149·1); cetrimonium chloride (p. 1742·3); crotamiton (p. 1699·2); piroctone olamine (p. 1716·3).
Dandruff.

Silesia, Chile.
Kertyol; ichthammol (p. 1705·3); crotamiton (p. 1699·2); salicylic acid (p. 1719·1).
Scalp disorders.

Kertyol PSO *Ducray, Fr.*
Cream: ⊗Sulfur (p. 1721·1); Kertyol; glycolic acid (p. 1704·3); glycerol (p. 2517·2).
Seborrhoeic dermatitis.

Ducray, Fr.
Shampoo: Sulfur (p. 1721·1); salicylic acid (p. 1719·1); ictasol (p. 1706·1).
Dandruff.

Kertyol S
Note: this name may be used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.
Kertyol; salicylic acid (p. 1719·1); zinc salicylate (p. 1719·1).
Dandruff.

Kertyol Shampooing *Ducray, Fr.†*
Kertyol; salicylic acid (p. 1719·1); saw palmetto (p. 2363·3); piroctone olamine (p. 1716·3).
Dandruff.

Kertyol-S
Note: this name may be used for preparations of different composition.
Piramal, India.
Crotamiton (p. 1699·2); salicylic acid (p. 1719·1).

Ducray, Fr.†
Shampoo: Kertyol; salicylic acid (p. 1719·1); glycolic acid (p. 1704·3).
Scalp disorders.

Ducray, Fr.†
Cream: ⊗Kertyol; glycolic acid (p. 1704·3); glycerol (p. 2517·2); keluamid (p. 1710·2).
Seborrhoeic dermatitis.

KeRuiTe *Meichuang, China.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Kerun *Sanye, China.*
Bufexamac (p. 30·2).
Inflammatory skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kesol *DMG, Ital.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Kespar *Keshav, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Kess *Filaxis, Arg.*
Lamivudine (p. 1000·2).
HIV infection.

Kess Complex *Filaxis, Arg.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Kessar *Pharmacia, Braz.†; Pfizer, Chile; Pfizer, Gr.; Orion, Ital.; Pfizer, Philipp.†; Pfizer, S.Afr.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Kest *Torbet Laboratories, UK.*
Magnesium sulfate (p. 1787·3).
Constipation.

Kestilumar *Sigillata, Denm.*
Montelukast sodium (p. 1214·3).
Asthma.

Kestin *Almirall, Fr.*
Ebastine (p. 628·1).
Allergic rhinitis; urticaria.

Kestine *Almirall, China; Almirall, Denm.; Almirall, Fin.; Novis, Gr.; Eisai, Hong Kong†; Almirall, Irl.†; Almirall, Ital.; Almirall, Neth.; Almirall, Norw.; Almirall, Port.; Nycomed, Rus.; Aspen, S.Afr.; Almirall, Singapore; Nycomed, Swed.; Eczacibasi, Turk.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria; hypersensitivity reactions; pruritus.

Kestinlyo *Almirall, Fr.*
Ebastine (p. 628·1).
Allergic rhinitis; urticaria.

Kestomatine *Sanofi-Aventis, Belg.*
Algeldrate (p. 1817·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence; drug-induced gastric irritation.

Kestox *Verman, Fin.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Kestrone *Hyrex, USA.*
Estrone (p. 2275·2).
Female hypogonadism; female castration; primary ovarian failure; menopausal vulval and vaginal atrophy; abnormal uterine bleeding; prostatic cancer; breast cancer.

KeSu *Yangtze River, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Keta *Samarth, India.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketacor *Duopharma, Philipp.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketafast *Taj, India.*
Ketamine (p. 1905·1).
General anaesthesia.

Ketafung *East West, India.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Ketaject *Astrapin, Philipp.†*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketajet *Sterfil, India.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Ketajex *Claris, India.*
Ketamine (p. 1905·1).
General anaesthesia.

Ketalar *Elea, Arg.†; Hospira, Austral.; Pfizer, Belg.; Pfizer, Braz.; Erfa, Canad.; Pfizer, Fin.; Warner-Lambert, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Norw.; Hospira, NZ; Pfizer, Port.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; JHP, USA.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketalgin
Note: this name may be used for preparations of different composition.
Farmstandart, Rus.
Ketorolac trometamol (p. 80·2).
Pain.

Kétalgine *Amino, Switz.*
⊗Methadone hydrochloride (p. 88·3).
Pain; opioid withdrawal syndrome.

Ketalin *Probiomed, Mex.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketam *Sun, India.*
Ketamine (p. 1905·1).
General anaesthesia.

Ketamax *Rotexmedica, Philipp.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Troikaa, India.
Ketamine (p. 1905·1).
General anaesthesia.

Ketanest *Pfizer, Fin.; Parke, Davis, Ger.; Pfizer, Ger.; EuroCept, Neth.*
Esketamine hydrochloride (p. 1905·1).
General anaesthesia; regional anaesthesia; status asthmaticus.

Scott-Cassara, Arg.; Pfizer, Austria; IFET (ΙΦΕΤ), Gr.; Parke, Davis, Pol.
Ketamine hydrochloride (p. 1905·1).
General anaesthesia; analgesia in anaesthesia; status asthmaticus.

Ketanov *Ranbaxy, India; Sel-J, Philipp.; Ranbaxy, Rus.; Ranbaxy, Ukr.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketapi *Pentafarma, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Ketartrium *Benedetti, Ital.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Ketas *Kyorin, Jpn.*
Ibudilast (p. 1211·2).
Asthma; cerebrovascular disorders.

Ketasma *Sun, India.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Ketava *Atlantic, Malaysia.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketazide *Mead Johnson, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).

Ketazol
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.; Vargas, Venez.
Ketoconazole (p. 585·3).
Fungal infections.

Korea United, Philipp.
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketazon
Note: this name may be used for preparations of different composition.
Siam Bheasach, Thai.
Ketoconazole (p. 585·3).
Fungal infections.

Ketek *Aventis, Austria†; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.†; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Jpn†; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Aventis, Pol.; Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Aventis, Thai.†; Aventis, Turk.; Aventis, UK; Aventis, USA; Sanofi-Aventis, Venez.*
Telithromycin (p. 371·3).
Bacterial infections.

Keten
Note: this name may be used for preparations of different composition.
Berko, Turk.
Green tea (p. 2648·2); flax seed; cinnamon (p. 2479·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); chromium (p. 2055·3).
Dietary supplement.

Siam Bheasach, Thai.
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Ketensin *Janssen-Cilag, Neth.; ProStrakan, Neth.*
Ketanserin tartrate (p. 1415·3).
Hypertension.

Ketero *Akums, Philipp.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Ketesgel *Tecefarma, Spain.*
Dexketoprofen trometamol (p. 79·1).
Musculoskeletal and joint disorders.

Ketesse *Menarini, Austria; Menarini, Belg.; Menarini, Cz.; Menarini, Denm.; Menarini, Fin.; Menarini, Fr.; Ferron, Indon.; Lusofarmaco, Ital.; Menarini, Port.; Menarini, Singapore; Menarini, Spain; Menarini, Swed.; Menarini, Switz.; Ulagay, Turk.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Ketfren *Indeco, Arg.*
Ketoprofen (p. 79·1).
Inflammation; pain.

Ketidin *Montpellier, Arg.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Ketifen *Biolab, Hong Kong†; Biolab, Malaysia; Biolab, Thai.†*
Ketotifen fumarate (p. 631·3).
Asthma; bronchitis; hypersensitivity reactions; allergic rhinitis; allergic conjunctivitis.

Ketilept *Egis, Cz.; Egis, Hung.; Egis, Philipp.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; psychoses.

Ketin *Adley, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation and photophobia following eye surgery; cystoid macular oedema.

Ketipinor *Orion, Fin.; Orion, Malaysia; Orion, Pol.; Orion, Singapore.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Ketiron *Atral, Port.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Ketlac *Neon, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketlur *Sun, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis.

Ketlur Plus *Sun, India.*
Ketorolac trometamol (p. 80·2); ofloxacin (p. 334·3).

Ketmin *Themis Medicare, India.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Keto
Note: this name may be used for preparations of different composition.
Vitabalans, Fin.; Biokem, Turk.; Valmor, Venez.
Ketoprofen (p. 79·1).
Pain; inflammation; musculoskeletal and joint disorders; fever; gout.

Cipla, India; Koz, Turk.
Ketoconazole (p. 585·3).
Fungal infections.

Masa, Thai.
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Yung Shin, Hong Kong; YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.
Ketorolac trometamol (p. 80·2).
Pain.

Keto Plus *Glenmark, Rus.; Glenmark, Ukr.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Pityriasis; seborrhoeic dermatitis; dandruff.

Keto Z *Alta Care, Ital.*
Ketoconazole (p. 585·3); dexpanthenol (p. 2582·2); pyrithione zinc (p. 1718·1); vitamin E (p. 2119·1).
Dandruff.

KetoCal *Nutricia, Austral.; Nutricia, Fr.*
Preparation for ketogenic diet.
Epilepsy.

Ketocal *Nutricia, China.*
Preparation for special diets.

Nutricia, Cz.; Scientific Hospital Supplies, Irl.
Food for ketogenic diet.
Epilepsy.

Nutricia, Denm.; Nutricia, Hong Kong.
Preparation for ketogenic diet.
Epilepsy.

Nutricia, Ital.
Preparation for ketogenic diet in epilepsy.

SHS, UK.
Food for ketogenic diets.
Epilepsy.

Ketocare *Servocare, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketocef *Pliva, Rus.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ketocev *Cevallos, Arg.*
Ketotifen (p. 631·3).

Ketocid
Note: this name may be used for preparations of different composition.
Pyridam, Indon.
Amino acids.
Nutritional supplement.

Trinity, UK.
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Ketocine *Medicine Products, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketoco *Ind-Swift, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketocon *Opsonin, Hong Kong.*
Ketoconazole (p. 585·3).
Fungal infections.

Keto-Cure *Tarbis, Spain.*
Ketoconazole (p. 585·3).
Fungal skin and nail infections.

Ketocure *Laborate, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketodan *Medimetriks, USA.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Kétoderm *Janssen-Cilag, Fr.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Ketoderm *Taro, Canad.; Terra, Turk.*
Ketoconazole (p. 585·3).
Fungal skin infections; vaginal candidiasis.

Ketodex *Berlin-Chemie, Hung.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Keto-Diabur *Roche Diagnostics, Braz.†*
Test for glucose and ketones in urine.

Keto-Diabur 5000 *Roche Diagnostics, Austral.*
Test for glucose and ketones in urine.

Keto-Diabur Test *Roche Diagnostics, Irl.†*
Test for glucose and ketones in urine.

Keto-Diabur Test 5000 *Roche, Arg.; Roche Diagnostics, Fr.; Roche Diagnostics, Mex.; Roche Diagnostics, NZ†; Roche Diagnostics, UK.*
Test for glucose and ketones in urine.

Ketodiaburtest 5000 *Roche, Chile; Roche Diagnostics, Ital.*
Test for glucose and ketones in urine.

Keto-Diastix *Bayer Consumer, Arg.; Bayer, Austral.; Bayer, Canad.†; Bayer, Chile; Bayer Diagnostics, Irl.†; Bayer, Ital.; Bayer, NZ†; Bayer Diagnostics, UK.*
Test for glucose and ketones in urine.

Kéto-Diastix *Bayer, Fr.*
Test for glucose and ketones in urine.

Ketodiastix *Bayer, Port.*
Test for glucose and ketones in urine.

Ketodin *Sperko, Ukr.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketodol
Note: this name may be used for preparations of different composition.
Taiwan Biotech, Philipp.
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Wassermann, Ital.
Ketoprofen (p. 79·1).
Sucralfate (p. 1889·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Ketodrops *Cipla, India.*
Ketorolac trometamol (p. 80·2).

Ketodur
Note: this name may be used for preparations of different composition.
Biospray, Gr.
Ketoprofen (p. 79·1).
Inflammatory disorders.

Ketof *Hexal, Cz.; Hexal, Ger.†*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis; allergic skin disorders; asthma; hypersensitivity reactions.

Ketofan *Emar, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketofar *Farcoral, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketofarm *Teikoku, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketofen
Note: this name may be used for preparations of different composition.
Asian Pharm, Thai.
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.
PC India, India; Hovid, Malaysia; Korea United, Philipp.†; Nobel, Turk.†
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain; inflammation; gout.

Ketoflam *Adcock Ingram, S.Afr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Ketoflex *Merck, Mex.; ACO Hud, Swed.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Ketoflox *Allergan, India.*
Ketorolac trometamol (p. 80·2); ofloxacin (p. 334·3).

Ketofreel *Torrent, Rus.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketoftil *Farmigea, Ital.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Ketogan *Pfizer, Denm.; Pfizer, Norw.*
Ketobemidone hydrochloride (p. 78·3); 3-dimethylamino-1,1-diphenylbuten-(1)-hydrochloride.
Pain.
Pfizer, Swed.
Ketobemidone hydrochloride (p. 78·3); N,N-dimethyl-4,4-diphenyl-3-buten-2-amine hydrochloride.
Pain.

Ketogan Novum *Pfizer, Swed.*
Ketobemidone hydrochloride (p. 78·3).
Pain; adjunct in regional anaesthesia.

Ketogeno *Neo Dermos, Arg.*
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Ketohexal *Hexal, S.Afr.†*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis; allergic skin disorders; asthma.

Ketoisdin *Isdin, Spain.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketolac *Altayvitamin, Rus.; American Taiwan, Thai.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketolan *Olan-Kemed, Thai.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Ketolar *Parke, Davis, Spain.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketolas *Dallas, India.*
Ketorolac trometamol (p. 80·2).
Pain; allergic conjunctivitis; pain, inflammation and photophobia following eye surgery; cystoid macular oedema.

Ketolef *Biosintex, Arg.*
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Kétolium *McNeil, Fr.†*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketolog *Claris, Philipp.*
Amino acids.
Nutritional supplement in renal failure.

Ketolong *Darnitsa, Ukr.*
Ketorolac (p. 80·2).
Pain.

Keto-med *Permamed, Switz.*
Ketoconazole (p. 585·3).
Fungal scalp disorders.

Ketomed
Note: this name may be used for preparations of different composition.
Medhaus, Philipp.
Ketorolac trometamol (p. 80·2).
Pain.
Surya Dermato, Indon.; Medihealth, Mex.; Medifive, Thai.; Roemmers Medihe, Venez.
Ketoconazole (p. 585·3).
Fungal infections; scalp disorders.

Ketomex *Ratiopharm, Fin.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; inflammation; pain; fever; gout.

Ketomizol *Reuffer, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketomousse *Mipharm, Ital.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1).
Dandruff.

Ketonal *Lek, Cz.; Sandoz, Pol.; Lek, Rus.; Sandoz, Ukr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

Ketonal-D *PC India, India.*
Analgin (p. 53·3); ketoprofen (p. 79·1).

Ketonazol *Lafedar, Arg.; Bunker, Braz.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Ketonazole *Polipharm, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketonex
Note: this name may be used for preparations of different composition.
Ross, USA.
A range of isoleucine-, leucine-, and valine-free preparations for enteral nutrition including an infant feed.
Maple syrup urine disease; beta-ketothiolase deficiency.
Zytras, India.
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketonic *Piramal, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketopac *Inpac, Thai.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; fungal skin infections.

Ketopain *Soho, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Ketopatch *Emcure, India.*
Ketoprofen (p. 79·1).

Keto-PC *Laborate, India.*
Chlorphenamine maleate (p. 620·3); ketorolac trometamol (p. 80·2); phenylephrine hydrochloride (p. 1672·3).

Ketopharm *Raymos, Arg.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; postoperative eye inflammation.

Ketopil *Psychotropics, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketopine *Pinewood, Irl.; AFT, NZ.*
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Ketoplus
Note: this name may be used for preparations of different composition.
Glenmark, Malaysia.
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.
SF, Ital.
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; phlebitis.

Ketoprof *SM, Venez.*
Ketoprofen (p. 79·1).
Inflammation; musculoskeletal and joint disorders; pain.

Ketoprom *GSK, Pol.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular pain.

Ketopronil *Unia, Pol.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketoptic *Oftalmi, Venez.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Ketoral
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Ketorolac trometamol (p. 80·2).
Pain.
Community Pharmacy, Thai.; Bilim, Turk.
Ketoconazole (p. 585·3).
Fungal infections.

Ketorax *Pfizer, Norw.*
Ketobemidone hydrochloride (p. 78·3).
Pain.

Ketores *ICN, Pol.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders.

Ketorid *Sun, India.*
Ketotifen (p. 631·3).
Allergic conjunctivitis.

Ketoril *Vitae, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketorin *Orion, Fin.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain; inflammation; fever; gout.

Ketorol *Reddy, India; Reddy, Rus.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketoselect *Menarini, Ital.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, and peri-articular disorders; thrombophlebitis.

Ketosil *Silom, Thai.†*
Ketoconazole (p. 585·3).
Fungal infections.

Ketosis *Scoshia, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Ketoson *CCS, Swed.†*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketospor *AC Helcor, Hung.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketospray *Cyathus, Austria; Cyathus, Denm.; Goodwill, Hung.; Megapharm, Israel; Medagro, Pol.*
Ketoprofen (p. 79·1).
Soft-tissue pain and inflammation; musculoskeletal, joint, and peri-articular disorders.

Ketosteril *Fresenius Kabi, China; Fresenius Kabi, Cz.; Fresenius Kabi, Ger.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Indon.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.†; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, Ukr.*
Amino acids.
Nutritional supplement in renal failure

Ketostix *Bayer, Austral.; Bayer, Canad.; Bayer, Ital.; Bayer, NZ.*
Test for ketones in urine.
Bayer Diagnostics, Irl.; Bayer Diagnostics, UK.
Test for ketones in urine, plasma, and serum.
Bayer, S.Afr.†
Test for ketones in urine, serum, plasma, and milk.

Ketotar *Psychotropics, India.*
Coal tar (p. 1723·2); ketoconazole (p. 585·3).

Ketotif *Kopran, India.*
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Ketotisan *Wabosan, Austria.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Ketotisin *Chemopharma, Chile.*
Ketotifen (p. 631·3).
Hypersensitivity reactions.
Dollder, Venez.
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; hypersensitivity reactions.

Ketotop *Pacific, China; Pacific, Philipp.*
Ketoprofen (p. 79·1).
Inflammation; pain.

Ketovail *Approved Prescription Services, UK.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain; inflammation.

Ketovate *Bal, India.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Ketovid *Hovid, Hong Kong; Hovid, Philipp.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketovite *IFET (ΙΦΕΤ), Gr.; Paines & Byrne, Irl.; Paines & Byrne, NZ†; Paines & Byrne, UK.*
Vitamins.
Dietary supplement.
Paines & Byrne, Irl.
Oral liquid: Vitamin A (p. 2098·3); choline chloride (p. 2055·2); ergocalciferol (p. 2113·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Ketoz *Blubell, India.*
Ketoconazole (p. 585·3).
Fungal infections.

Ke-Toza *Blubell, India.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Ketozal *Pond's, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketozoe *Adley, India.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketozol *Christo, Hong Kong; Rowex, Irl.; Perrigo, Israel; Mepha, Switz.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Ketozole *DHA, Hong Kong; Ranbaxy, India; DHA, Singapore.†*
Ketoconazole (p. 585·3).
Fungal infections.

Ketozoral *Darnitsa, Ukr.*
Ketoconazole (p. 585·3).
Fungal infections.

Ketozotan *CCM, Malaysia.*
Ketoconazole (p. 585·3).
Fungal infections.

Kétrel *Bailleul, Fr.*
Tretinoin (p. 1725·2).
Acne.

Ketrel
Note: this name may be used for preparations of different composition.
Celon, Pol.
Quetiapine fumarate (p. 1101·1).
Schizophrenia.
Saninter, Port.
Tretinoin (p. 1725·2).
Acne; psoriasis.

Ketricin *Ferron, Indon.*
⊗Triamcinolone (p. 1648·3) or triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Ketrizin *Esseti, Ital.†*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Ketrobat *Interbat, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Ketroc *Intra-Labs, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Ketrol *Reddy, India.*
Ketorolac (p. 80·2).
Pain.

Ketros *Pharos, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; gout.

Ketsia *Celon, India.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Ketum *Farma 1000, Ital.; Norton, Ukr.†*
Ketoprofen (p. 79·1).
Musculoskeletal pain; musculoskeletal and joint pain.

Kétum *Menarini, Fr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketur-Test *Roche Diagnostics, Irl.†; Roche Diagnostics, Ital.; Roche Diagnostics, NZ†; Roche Diagnostics, UK.*
Test for ketones in urine.

Ketya *Abdi, Turk.*
Quetiapine (p. 1101·1).

Ketz *Peerage, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ketzy *Zee, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation and photophobia following eye surgery; cystoid macular oedema; pain.

Keunmixin *Keun Wha, Philipp.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Keunzef *Keun Wha, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Keval *Pharmacos Abug, Mex.†*
Lansoprazole (p. 1851·3).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kevatril *Roche, Ger.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Kevindol *SoSe, Ital.*
Ketorolac trometamol (p. 80·2).
Musculoskeletal and joint disorders.

Kevis *Chefaro, Ital.*
Pyrithione magnesium (p. 1718·1); iceland moss (p. 2531·2).
Seborrhoeic dermatitis.

Kevixkeni *Kendrick, Mex.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Kevrox *Kaizen, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Kevrox-S *Kaizen, India.*
⊗Roxithromycin (p. 356·2); serrapeptase (p. 2613·3).

Kevrox-SA *Kaizen, India.*
⊗Ambroxol hydrochloride (p. 1654·3); roxithromycin (p. 356·2); serrapeptase (p. 2613·3).

Kevtam *Alphapharm, Austral.*
Levetiracetam (p. 531·1).
Epilepsy.

Kevtram *Kaizen, India.*
Tramadol (p. 139·2).
Pain.

Kevtram-DP *Kaizen, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Kevtram-P *Kaizen, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Keweijia *Luye, China.*
Potassium citrate (p. 1780·3).
Hypokalaemia; renal calculi.

Kexelate *Adcock Ingram Critical Care, S.Afr.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Kexidil *Kener, Mex.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Kexin *Zhaohui, China.*
Ketoconazole (p. 585·3).
Fungal skin infections.

K-Exit *Omega, Canad.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Kexone *Medispan, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Kexone Plus *Medispan, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Key *Ind-Swift, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation and photophobia following eye surgery; cystoid macular oedema.

Keydol *Roemmers-Klinos, Venez.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Keyi *Zhaohui, China.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis.

Keylyte *Wallace, India.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Keyou *Zhaohui, China.*
Penciclovir (p. 1008·2).
Orofacial herpes infections; genital herpes infections.

Key-Pred-SP *Hyrex, USA.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Keysal *Novagen, S.Afr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Keyuan *Zhaohui, China.*
Calcium dobesilate (p. 2464·3).
Microcirculatory disorders; venous insufficiency.

Keyven *Kedrion, Ital.*
A normal immunoglobulin (p. 2403·3).

Kez *Pharma Dynamics, S.Afr.*
Ketoconazole (p. 585·3).
Pityriasis versicolor; pityriasis capitis; seborrhoeic dermatitis.

Kezar *Aamorb, India.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3).

Kezol *Stada, Swed.†*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Kezole *BMW, India; Pharmahof, Thai.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Kezon *Osoth, Thai.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Kezoral *CCM, Malaysia; Upha, Singapore.†*
Ketoconazole (p. 585·3).
Fungal infections.

K-Fenac *Cipla, India.*
Diclofenac potassium (p. 48·3).

K-Fenak *Cipla-Medpro, S.Afr.*
Diclofenac potassium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

K-Flebo *Kedrion, Ital.*
Potassium aspartate (p. 1793·1).
Hypokalaemia; hyperammonaemia.

Kfol-Z *Keshav, India.*
Iron carbonyl (p. 2073·1); vitamin C (p. 2110·3); zinc (p. 2126·1).

K-G Elixir *Geneva, USA.*
Potassium gluconate (p. 1793·2).
Hypokalaemia; potassium depletion.

K-Gat *Kaizen, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

K-Gel
Note: this name may be used for preparations of different composition.
Medstyle, Chile.
Phytomenadione (p. 2122·2); arnica (p. 2447·2).
Bruising.

K-Gem *Blue Cross, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

K-Glim *Blue Cross, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

K-Glim M *Blue Cross, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

KGS-PE *Cypress, USA.*
Phenylephrine hydrochloride (p. 1672·3); sulfogaiacol (p. 1678·1).
Coughs; upper respiratory-tract congestion.

KGT *Keshav, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

KH3 *Diapharm, Gr.; Bamford, NZ.*
Procaine hydrochloride (p. 1994·3); haematoporphyrin (p. 2523·3); magnesium carbonate (p. 1856·2); magnesium phosphate (p. 1787·3); potassium chloride (p. 1793·2); sodium phosphate (p. 1791·2).
Tonic.

Riemser, Austria.
Procaine hydrochloride (p. 1994·3); haematoporphyrin (p. 2523·3).
Tonic.

Riemser, Hong Kong.
Procaine hydrochloride (p. 1994·3); haematoporphyrin (p. 2523·3); electrolytes (p. 1775·1).
Tonic.

Raffo, Arg.†
Procaine (p. 1994·3); ginseng (p. 2513·3); alfa tocoferol.
Tonic.

Schwarzhaupt, Thai.†
Procaine hydrochloride (p. 1994·3); haematoporphyrin (p. 2523·3); magnesium carbonate (p. 1856·2); sodium hydrogen phosphate; potassium chloride (p. 1793·2); dibasic magnesium phosphate (p. 1786·3).
Reduced physical and mental capacity in the elderly.

Khalli *Hauz, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Khamin Chan *Pharmahof, Thai.*
Curcuma longa.

Khasigo *Cadila, India.*
Ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3); sodium citrate (p. 1781·2).

Khedezla *Par, USA.*
Desvenlafaxine.
Depression.

Kiadon *Merck, Chile; Merck, Venez.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; ear disorders; eye disorders; vestibular disorders; tonic.

Kiatrium *Gross, Braz.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Kibilis *Gerolymatos, Gr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's dementia.

Kibocal *Uni-Sankyo, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Kibocal-M *Uni-Sankyo, India.*
Boron (p. 2052·3); calcium carbonate (p. 1824·3); copper (p. 2057·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Kickkof *Kalpataru, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

KickStart Detox *Blackmores, Austral.*
Cynara (p. 2490·3); lappa (p. 2540·1); bitter orange peel (p. 2575·3); choline bitartrate (p. 2055·2).
Tonic.

Kid Kare Childrens Cough/Cold *Rugby, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Kid Kare Pediatric Nasal Decongestant *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Kidazom *Aspen, Braz.*
Granisetron (p. 1844·3).

Kidbar *Piam, Ital.*
Food for special diets.
Phenylketonuria.

Kidcal *Farma, Venez.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Calcium supplement; calcium deficiency.

Kidcet *Invision, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Kidcet-Cold *Invision, India.*
Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Kiddi *Boehringer Ingelheim, Arg.; Pharmaton, Israel.*
Lysine hydrochloride (p. 2079·3); vitamins; minerals.
Nutritional supplement.

Boehringer Ingelheim, China.
Vitamins; minerals; lysine (p. 2079·3).
Dietary supplement.

Kiddi Choo *Boehringer Ingelheim, S.Afr.*
Vitamins; minerals.

Kiddi Pharmaton *Boehringer Ingelheim, Indon.; Pharmaton, Indon.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Ukr.*
Lysine hydrochloride (p. 2079·3); minerals; vitamins.
Nutritional supplement; tonic.

Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Hong Kong†; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.
Vitamins; minerals; lysine (p. 2079·3).
Tonic; dietary supplement.

Kiddie Estamin *Biolink, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2); chlorella (p. 2475·3).

Kiddie Prime *Primera, Philipp.*
Vitamins; minerals; amino acids; chlorella growth factor (p. 2475·3).

Kiddigum *Adco, S.Afr.†*
Benzocaine (p. 1980·2).
Teething; aphthous ulcers.

Kiddilets *United Laboratories, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Kiddirel *Metz, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2); chlorella growth factor (p. 2475·3).

Kiddis *Intra-Labs, India.*
Whey protein (p. 2125·2); vitamins.

Kiddyfen *Abdi, Turk.*
Ibuprofen (p. 68·2).

Kiddyflu *Caps, S.Afr.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Kid-Eeze *Austell, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Fever; pain.

Kidi *Alpha Aromatic, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Kidicare *Meyer, India.*
Vitamins; minerals; lysine (p. 2079·3).

Kidikol *Nufarindo, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Influenza symptoms.

Kidimun *Pyridam, Indon.*
Phyllanthus niruri (p. 2590·1); Echinacea angustifolia (Polinacea) (p. 2498·1); zinc picolinate (p. 2126·1).
Immunostimulant.

Kidiron *Thaipharmed, Thai.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Kidkof *Thaipharmed, Thai.*
Guaifenesin (p. 1666·2).
Cough.

Kidmin *Otsuka, Indon.; Otsuka, Jpn; Thai Otsuka, Thai.*
Amino acids.
Parenteral nutrition.

Kidodent *Indoco, India.*
Mouthwash: Sodium fluoride (p. 2089·2); triclosan (p. 1773·2); xylitol (p. 2220·3).

Indoco, India.
Toothpaste: Sodium monofluorophosphate (p. 2091·3).

Kidofen *Aflofarm, Pol.*
Ibuprofen (p. 68·2).
Fever; pain.

Kidonax *Unipharm, Mex.*
Nitazoxanide (p. 942·2).
Protozoal infections; worm infections.

Kidpred *Piramal, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Kidral *Claris, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Kidrolase *Bioprofarma, Arg.; EUSA, Canad.; EUSA, Cz.; EUSA, Fr.; EUSA, Israel.*
Asparaginase (p. 743·3).
Malignant neoplasms.

Kidrolyte *Claris, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Kidrox *Cadila, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Kids
Note: this name may be used for preparations of different composition.
IQFA, Mex.
Vitamins.
Norwood, Canad.†
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kid's
Note: this name may be used for preparations of different composition.
Levlad, Canad.
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Kids Alcohol-free Sunscreen *Kinesys, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Kids Allergies *Homeocan, Canad.*
Pulsatilla (p. 2600·2); allium cepa (p. 2575·2); arsenicum album (p. 2448·1); nux vomica (p. 2573·3); euphrasia (p. 2502·1); sabadilla (p. 2611·2); sticta pulmonaria (p. 2546·1); aralia racemosa; cuprum metallicum (p. 2057·1).
Homoeopathic preparation.

Kids Calm *Homeocan, Canad.*
Asa foetida (p. 2449·3); ignatia amara (p. 2532·1); valerian officinalis (p. 2640·2); avena sativa (p. 2451·1); argentums nitricum (p. 2615·3); tarentula hispanica; hyoscyamus niger (p. 2530·2); paeonia; stramonium (p. 2622·3); cocculus indicus (p. 2483·1).
Homoeopathic preparation.

Kid's Colic *Homeocan, Canad.*
Chamomilla (p. 2474·1); colocynthis (p. 1833·3); dioscorea vilosa (p. 2648·1); magnesia phosphorica (p. 1787·3).
Homoeopathic preparation.

Kids Cough & Cold Phytux *Homeocan, Canad.*
Drosera rotundifolia (p. 2497·2); arnica (p. 2447·2); bryonia (p. 2461·3); cetraria islandica (p. 2531·2); belladonna (p. 2453·3); coccus cacti (p. 2179·2); corallium rubrum; stannum metallicum (p. 2632·1).
Homoeopathic preparation.

Kids Cream Sunscreen *Kinesys, Canad.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Kids' Earache *Homeocan, Canad.*
Belladonna (p. 2453·3); capsicum annuum (p. 2469·3); ferrum phosphoricum (p. 2077·1); arsenicum album (p. 2448·1); pyrogenium (p. 2601·1).
Homoeopathic preparation.

Kids Fruity Fishies *Blackmores, Austral.*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement for children.

Kid's Hand Gel *Amakris, Canad.*
Benzalkonium chloride (p. 1737·1).

Kids Immunities *Blackmores, Austral.*
Vitamins; zinc oxide (p. 1729·1).
Dietary supplement for children.

Kids Mineral Minds *Blackmores, Austral.*
Vitamins; minerals.
Dietary supplement for children.

Kids Multi *Blackmores, Austral.*
Vitamins; minerals.
Dietary supplement.

Kids Pour Enfants *Energizer, Canad.*
SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kids Powder Dri Sunscreen *Energizer, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kids Splash *Energizer, Canad.†*
SPF 50: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kids Spray-on Sunscreen *Kinesys, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Kids Sunblock *Tanning Research, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kids Sunscreen *Energizer, Canad.*
Stick SPF 50: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kinesys, Canad.
Cream SPF 30+: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Kinesys, Canad.
Spray SPF 30+: Avobenzone (p. 1695·1); meradimate (p. 1711·2); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Kinesys, Canad.
Cream SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Kinesys, Canad.
Spray SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Prime Enterprises, Canad.
SPF 50: Avobenzone (p. 1695·1); ensulizole (p. 1703·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Norwood, Canad.†
SPF 45: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kid's Sunscreen *Jason, Canad.†*
SPF 46: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Kids Tear Free *Energizer, Canad.*
Lotion SPF 50; lotion SPF 60: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Energizer, Canad.
Spray SPF 50; spray SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Kids' Teething *Homeocan, Canad.*
Arnica montana (p. 2447·2); borax (p. 2459·2); chamomilla (p. 2474·1); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Kids-Pro *British Biologicals, India.*
Preparation for enteral nutrition.

Kidstart *Foodscience, Canad.†*
Vitamins; minerals.

Kidz Kit 2 *Natrapharm, Philipp.*
Oral suspension, rifampicin (p. 350·3) (Natricin Forte); syrup, isoniazid (p. 311·2) (Curazid Forte).
Pyridoxine hydrochloride (p. 2105·3) is included in the Curazid Forte syrup for prophylaxis of peripheral neuropathy.
Tuberculosis.

Kidz Kit 3 *Natrapharm, Philipp.*
Oral suspension, pyrazinamide (p. 345·2) (Zcure); oral suspension, rifampicin (p. 350·3) (Natricin Forte); syrup, isoniazid (p. 311·2) (Curazid Forte).
Pyridoxine hydrochloride (p. 2105·3) is included in the Curazid Forte syrup for prophylaxis of peripheral neuropathy.
Tuberculosis.

KIE *Laser, USA.*
⊗Ephedrine hydrochloride (p. 1663·2); potassium iodide (p. 2336·3).
Coughs.

KI-Expectorante *Cimed, Braz.*
Oxomemazine hydrochloride (p. 637·1); potassium iodide (p. 2336·3); guaifenesin (p. 1666·2); sodium benzoate (p. 1738·2); ipecacuanha (p. 1667·2).
Respiratory-tract congestion.

Kifadene *Kimia, Indon.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Kifarol *Pharmanik (Φαρμανικ), Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kifarox *Kimia, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Kifen *Farbio, Port.*
Ibuprofen (p. 68·2).
Pain; fever.

Kifenip *Sons, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Kifluzol *Kimia, Indon.*
Fluconazole (p. 578·2).
Fungal infections.

Kifugan *Siu Guan, Malaysia.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Kihito *Tsumura, Jpn.*
Astragalus root (p. 2451·1); jujube seed; ginseng (p. 2513·3); atractylodes rhizome; poria sclerotium; longan aril; polygala root; jujube; angelica acutiloba root (p. 2443·3); liquorice (p. 1853·2); ginger (p. 1844·1); saussurea root.
Traditional Kampo medicine.

Kiklin *Astellas, Jpn.*
Bixalomer (p. 1541·2).
Hyperphosphataemia in renal dialysis patients.

Kikyoto *Tsumura, Jpn.*
Liquorice (p. 1853·2); platycodon root.
Traditional Kampo medicine.

Kilios *Pfizer, Chile.*
18 Tablets, estradiol (p. 2271·1); 13 tablets, estradiol; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Kilkof *Bell, UK.*
Cetylpyridinium chloride (p. 1743·1); benzoin tincture (p. 2624·3); ipecacuanha tincture (p. 1667·2); capsicum tincture (p. 2469·3).
Coughs; cold symptoms; sore throat.

Killa *T Man, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Wound disinfection.

Killavon *Lysoform, Ger.*
Benzalkonium chloride (p. 1737·1).
Surface disinfection; fungal skin infections.

Kilnits *Andromaco, Chile.*
Permethrin (p. 2159·3).
Pediculosis.

Kilo-Nit *Herbaria, Hung.*
Fucus vesiculosus; betula (p. 2457·3); urtica (p. 2639·3); rose fruit (p. 2607·1); condurango (p. 2485·3).
Aid to weight loss.

Kilonum *Frik, Turk.*
Lithium carbonate (p. 427·3).
Mania; bipolar disorder; depression; behaviour disorders.

Kilor *Menarini, Spain.*
Ferritin (p. 2060·2).
Iron deficiency; iron-deficiency anaemia.

Kilovit *Italmex, Mex.*
Vitamins; minerals.

Kilpane *GSK, India.*
Eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal disorders.

Kilsol *Biomedica, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic disorders.

Kimacef *Arterium, Ukr.*
Cefuroxime (p. 255·2).
Bacterial infections.

Kimafan *Duopharma, Hong Kong†; CCM, Malaysia.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Kimcare Antibacterial *Kimberly-Clark, Canad.†*
Topical lotion: Chloroxylenol (p. 1748·2).
Kimberly-Clark, Canad.†
Topical solution: Triclosan (p. 1773·2).

Kimcare Instant Hand Sanitizer *Kimberly-Clark, Canad.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Kimet *Zuventus, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; heart failure.

Kimite *Myung Moon, China.*
Hyoscine (p. 1845·3).
Motion sickness.

Kimotab *Mochida, Jpn.†*
⊗Bromelains (p. 2460·3); trypsin (p. 2635·2).
Inflammation.

Kimoxil *Kimia, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Kin *Andromaco, Chile.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Kin Soff *Kanion, Israel.†*
Pyrethrum (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Kinalgin *Ivax, Arg.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Kinaplase *Ivax, Arg.*
Zonisamide (p. 560·2).
Epilepsy.

Kinaplat *Cadila, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Kinasten *Kinder, Braz.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Kinateva *Med, Turk.*
Quinapril hydrochloride (p. 1480·2).

Kincef *Plus, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Kind *Solitaire, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Kind 0-6 Caltrivat *VSM, Neth.*
Calcarea fluorica (p. 2053·1); calcarea phosphorica (p. 1784·2); sulphur iodatum (p. 2624·2); calcarea carbonica ostrearum (p. 1824·3).
Homoeopathic preparation.

Kind 0-3 Chamodent *VSM, Neth.*
Belladonna (p. 2453·3); chamomilla (p. 2474·1); ferrum phosphoricum (p. 2077·1); hepar sulphur (p. 1721·3); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Kind 0-3 Cinababy *VSM, Neth.*
Chamomilla (p. 2474·1); cina maritima; colocynthis (p. 1833·3); magnesium muriaticum (p. 1787·1); lac vaccinum defloratum.
Homoeopathic preparation.

Kind 0-6 Kindigest *VSM, Neth.*
Arsenicum album (p. 2448·1); croton tiglium; okoubaka aubrevillei; veratrum album (p. 2644·3).
Homoeopathic preparation.

Kind 0-6 Kinditherm *VSM, Neth.*
Aconitum napellus (p. 2428·3); belladonna (p. 2453·3); chamomilla (p. 2474·1); ferrum phosphoricum (p. 2077·1); gelsemium sempervirens (p. 2511·2).
Homoeopathic preparation.

Kind 0-6 Kindival *VSM, Neth.*
Cypripedium pubescens; magnesium carbonicum (p. 1856·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Kind 0-6 Nisykind *VSM, Neth.*
Aconitum napellus (p. 2428·3); bryonia cretica; eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens (p. 2511·2); ipecacuanha (p. 1667·2); phosphorus (p. 2589·2).
Homoeopathic preparation.

Kind Plus *Solitaire, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kind 0-6 Rinikind *VSM, Neth.*
Allium cepa (p. 2575·2); kalium iodatum (p. 2336·3); luffa operculata (p. 2545·3); pulsatilla pratensis (p. 2600·2); silicea (p. 2208·3).
Homoeopathic preparation.

Kind 0-6 Tussikind *VSM, Neth.*
Syrup: Antimonium sulfuratum auratum (p. 2445·1); bryonia alba; drosera rotundifolia (p. 2497·2); eucalyptus globulus (p. 2501·1); ipecacuanha (p. 1667·2); spongia tosta.
Homoeopathic preparation.

VSM, Neth.
Tablets: Antimonium sulfuratum auratum (p. 2445·1); bryonia alba; drosera rotundifolia (p. 2497·2); ipecacuanha (p. 1667·2); spongia tosta.
Homoeopathic preparation.

Kindaren *Kinder, Braz.†*
Diclofenac sodium (p. 48·3).

Kindcalcio *Kinder, Braz.†*
Calcium phosphate (p. 1784·2); cyanocobalamin (p. 2107·2); ergocalciferol (p. 2113·3); sodium fluoride (p. 2089·2).

Kindcef *Solitaire, India.*
Cefpodoxime.
Bacterial infections.

Kindcetin *Kinder, Braz.†*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).

Kindclav *Solitaire, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Kindelmin *Kinder, Braz.†*
Mebendazole (p. 158·3).
Worm infections.

Kinder Biovital *Bayer Consumer, Rus.*
Vitamins; minerals; lecithin (p. 2542·2).

Bayer, Ukr.
Vitamins; with or without lecithin (p. 2542·2).
Dietary supplement.

Bayer, Pol.†
Ferric sodium citrate (p. 2073·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Iron deficiency; tonic.

Kinder Luuf *Apomedica, Austria.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); thymol (p. 1772·2).
Cough and cold symptoms; catarrh.

Kinder Luuf Balsam *Volmix, Hung.*
Camphor (p. 2466·2); turpentine oil (p. 2636·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar oil (p. 2472·3); thymol (p. 1772·2).
Respiratory-tract disorders.

Kindercal *Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition.

Kindergen *Nutricia, Austral.; Nutricia, Ital.*
Preparation for enteral nutrition in infants and children.
Nutritional support in dialysis patients; renal failure.

Nutricia, NZ; Scientific Hospital Supplies, NZ.
Preparation for enteral nutrition in children.
Renal failure.

Scientific Hospital Supplies, Irl.†; SHS, UK.
Preparation for enteral nutrition.
Renal failure.

Kinderval *Omicron, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Kinderval Max *Omicron, Arg.*
Permethrin (p. 2159·3); benzocaine (p. 1980·2); benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Kinderval RI *Omicron, Arg.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Kindinorm *DHU, Ukr.*
Calcium hypophosphorosum (p. 2530·3); chamomilla (p. 2474·1); cuprum metallicum (p. 2057·1); kalium phosphoricum (p. 1790·3); staphisagria; valeriana (p. 2640·2).
Homoeopathic preparation.

Kind-MD *Solitaire, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Kindomet *Kinder, Braz.†*
Methyldopa (p. 1431·1).
Hypertension.

Kindpasm *Kinder, Braz.†*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Skeletal muscle spasm; pain.

Kindvom *Solitaire, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Kinectine *Anglo-French Drugs, India.*
Aceclofenac betadex (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Kinectine P *Anglo-French Drugs, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Fever; pain.

Kinectine-MR *Anglo-French Drugs, India.†*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine (p. 2026·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Kinedak *Ono, Jpn.*
Epalrestat (p. 470·3).
Diabetic neuropathy.

Kinedril *Vilar, Rus.*
Caffeine (p. 1203·3); moxastine (p. 636·2).
Motion sickness; vertigo.

Kinedryl *Noventis, Cz.*
Moxastine teoclate (p. 636·2); caffeine (p. 1203·3).
Motion sickness; vestibular disorders; Ménière's disease.

Kinerase *Valeant, Braz.; Invida, Hong Kong; Valeant, Mex.; Inovail, Philipp.; Invida, Singapore; Valeant, USA.*
A range of preparations containing kinetin (p. 1710·2).
Photodamaged skin; skin hyperpigmentation; emollient.

Kineret *Invida, Austral.; Biovitrum, Austria; Amgen, Canad.; Biovitrum, Cz.; Biovitrum, Denm.; Amgen, Fin.; Biovitrum, Fr.; Swedish Orphan, Ger.; Biovitrum, Gr.; Amgen, Irl.; Biovitrum, Irl.; Megapharm, Israel; Biovitrum, Ital.; Swedish Orphan, Neth.; Swedish Orphan, Norw.; Amgen, Pol.; Biovitrum, Port.; Biovitrum, Spain; Biovitrum, Swed.; Biovitrum, UK; Swedish Orphan, USA.*
Anakinra (p. 21·2).
Rheumatoid arthritis; neonatal-onset multisystem inflammatory disease.

Kinerton *Vivax, Venez.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Kinésamine *Monin, Fr.*
Glucosamine sulfate (p. 2515·3); zinc gluconate (p. 2126·2); silica (p. 2208·3); manganese gluconate (p. 2081·2).
Dietary supplement; joint disorders.

Kinespir *Teva, Belg.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Kinestase *Liomont, Mex.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; gastroparesis; dyspepsia; impaired gastric motility.

Kinestrel *Psicofarma, Mex.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism.

Kinesys Sun Stick *Kinesys, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Kinetal *Cipla, India.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Kinetix *Lupin, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Kineto *Systopic, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; breast engorgement; pericoronitis; alveolar abscess; pain.

Kineto DP *Systopic, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Kineto-D *Systopic, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Kinetone Advance *Abbott, India.*
Vitamins; minerals.

Kinetra *Sanovel, Turk.*
⊗Carvedilol (p. 1333·1).

Kinevac *Bracco, Canad.; Bracco, USA.*
Sincalide (p. 2616·3).
Diagnosis of biliary-tract and pancreatic disorders.

Kinex
Note: this name may be used for preparations of different composition.
Psicofarma, Mex.
Biperiden hydrochloride (p. 895·1).
Extrapyramidal disorders; parkinsonism.

Strassenburg, India.
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Kinfil *Nova Argentia, Arg.*
Enalapril (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Kinfil D *Nova Argentia, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kingcef *Shreya, India.*
Cefepime (p. 239·2).
Bacterial infections.

Kingcox *Cadila, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Kingzyme *Arunabh, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Kinidin *Astra, Gr.; IFET (ΙΦΕΤ), Gr.*
Quinidine (p. 1481·1) or quinidine bisulfate (p. 1481·2).

AstraZeneca, Rus.
Quinidine sulfate (p. 1481·2).
Arrhythmias.

AstraZeneca, Austral.†; AstraZeneca, Irl.†; AstraZeneca, Philipp.†
Quinidine bisulfate (p. 1481·2).
Arrhythmias.

Kinidine *IFET (ΙΦΕΤ), Gr.*
Quinidine bisulfate (p. 1481·2).
Arrhythmias.

Kiniduron *Orion, Fin.*
Quinidine bisulfate (p. 1481·2).
Arrhythmias.

Kinin *Nycomed, Denm.; SAD, Denm.; IFET (ΙΦΕΤ), Gr.; Recip, Swed.*
Quinine hydrochloride (p. 665·2).
Malaria; night cramps; myotonia.

Kinito *Zentiva, Cz.*
Itopride hydrochloride (p. 1850·1).
Dyspepsia; nausea and vomiting.

Kinitron *Gerolymatos, Gr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Kinnoferon 2A *Bergamo, Braz.*
Interferon alfa-2a (p. 989·2).
Malignant neoplasms; chronic hepatitis B; chronic hepatitis C.

Kinocin *Kamakshi, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Kinogen
Note: this name may be used for preparations of different composition.
Geymonat, Ital.
⊗Tyrothricin (p. 384·1); hydrocortisone sodium succinate (p. 1640·3).
Vulvovaginal infections.

Taiwan Biotech, Philipp.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Kinolymphat *PGM, Ger.†*
Acid. hydrochloricum (p. 2528·3); hydrargyrum chloratum (p. 2555·2); acid. arsenicosum (p. 2448·1); petroleum rectificatum (p. 2201·2).
Homoeopathic preparation.

Kinopox *Kamakshi, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Kinopox-CV *Kamakshi, India.*
Cefpodoxime proxetil (p. 248·1); potassium clavulanate (p. 268·3).
Bacterial infections.

Kinor *Medihealth, Mex.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Calluses; warts; hyperkeratosis.

Kinoves *Samjin, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Kinox
Note: this name may be used for preparations of different composition.
Air Liquide, Fr.
Nitrous oxide (p. 1908·1).

Benedetti, Ital.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Kinrix *GSK, USA.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Kinser-DP *Kinds, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Kinski *Athena, Ital.*
Piroxicam (p. 125·3).

Kinson *Alphapharm, Austral.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

KintaVital *Uhlmann-Eyraud, Switz.*
Ginseng (p. 2513·3).
Tonic.

Kinuréa H *Neitum, Fr.*
Quinine and urea hydrochloride (p. 2601·3).
Anorectal disorders.

Kinussen *Kleva, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Kinzal *Bayer, Switz.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Kinzalkomb *Bayer, Belg.; Bayer Schering, Cz.; Bayer, Fin.; Bayer, Ger.; Bayer Schering, Irl.; Bayer, Neth.; Bayer, Pol.; Bayer Schering, Port.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kinzalmono *Bayer, Belg.; Bayer Schering, Cz.; Bayer, Fin.; Bayer, Ger.; Bayer Schering, Irl.; Bayer, Neth.; Bayer, Pol.; Bayer Schering, Port.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction; diabetic nephropathy.

Kinzalplus *Bayer, Switz.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kinzy *Abdi, Turk.*
Solifenacin succinate (p. 2367·3).

Kionex *Paddock, USA.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Kiovig *Baxter, Arg.; Baxter, Austria; Baxter, Belg.; Baxter, Cz.; Baxter, Denm.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Irl.; Baxter, Israel; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone marrow transplantation; passive immunisation; immunodeficiency; toxic shock syndrome; multifocal motor neuropathy; graft-versus-host disease.

Kiper *Monserrat, Arg.*
Paracetamol (p. 115·1); butetamate citrate (p. 1658·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Also known as Kipergrip.
Cold and influenza symptoms.

Kipferon *Alfarm, Rus.*
Normal immunoglobulins (p. 2403·3); interferon alfa (p. 989·2).
Urogenital chlamydial infections.

Kipling *Effik, Ital.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Kipres *Kyorin, Jpn.*
Montelukast sodium (p. 1214·3).
Asthma.

Kir *Raffo, Arg.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Kira *Klosterfrau, Austria; Lichtwer, Canad.†; Riemser, Ger.; Cassella-med, UK.*
St John's wort (p. 449·1).
Depression; anxiety; nervous disorders.

Kira Prem *Ceuta, UK.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Kira Restful Sleep *Cassella-med, UK.*
Valerian (p. 2640·2).
Insomnia.

Kirana *Synthon, Neth.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Kiraza *Medizone, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Kirga *Gedeon Richter, Cz.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Kiri *Lampugnani, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamin B substances (p. 2102·3).
Disturbances of the gastrointestinal flora.

Kirik *Chemica, Gr.*
Flurbiprofen (p. 65·2).

kirim *Hormosan, Ger.*
Bromocriptine mesilate (p. 895·3).
Parkinsonism.

kirim gyn *Taurus, Ger.†*
Bromocriptine mesilate (p. 895·3).
Lactation inhibition; hyperprolactinaemia.

Kirin *Medochemie, Hong Kong; Medochemie, Rus.*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea.

Kirnom *Wockhardt, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Kiro Rub *Confab, Canad.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Kirom *Eurofarma, Braz.*
Teicoplanin (p. 369·3).
Bacterial infections.

Kiron-UP *Kinds, India.*
Syrup: Sodium feredetate (p. 2088·3).
Kinds, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Kirsan *Ativus, Braz.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Kirum *Raffo, Arg.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Kirumelle *Raffo, Arg.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Kisan *CCM, Malaysia.*
Phytomenadione (p. 2122·2).
Haemorrhage.

Kiss Therapy Lip Balm *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Kissimin *Argenfarma, Arg.*
Glucose (p. 2068·3).
Dietary supplement.

Kistan *Candor, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Kit
Note: this name may be used for preparations of different composition.
Continental Pharma, Thai.
Paracetamol (p. 115·1).
Fever; pain.
Sigman, India.
Fluconazole (p. 578·2).
Candidal balanitis; vaginal candidiasis.

Kit Kat *Mapra, India.*
Mebendazole (p. 158·3).
Worm infections.

Kit Rosaclean *Ache, Braz.*
Lactic acid (p. 2539·1).

Kit For Tc-99 Labeled DIPA *Soreq, Israel.*
Di-isopropylammonium dichloroacetate (p. 1359·1) for labelling with technetium-99m.
Radionuclide imaging.

Kitacne *Fortbenton, Arg.*
Erythromycin (p. 291·2).
Acne.

Kitadol *Laboratorios Chile, Chile.*
Paracetamol (p. 115·1).
Fever; pain.

Kitadol Max *Laboratorios Chile, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Kitadol Noche *Laboratorios Chile, Chile.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Kitadol Periodo Menstrual *Laboratorios Chile, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine (p. 635·1).
Menstrual disorders.

Kitapen
Note: this name may be used for preparations of different composition.
Arrow, Braz.
Quetiapine (p. 1101·1).

Kit-3D *Sigman, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Kitnos *Pfizer, Braz.; Pfizer, Mex.; Pfizer, Philipp.*
Etofamide (p. 933·2).
Protozoal infections; amoebiasis.

Kitoles *Soho, Indon.†*
Poliglusam (p. 2593·2); nicotinamide (p. 2083·1); chromium tripicolinate (p. 2056·1).
Hyperlipidaemias; to increase weight loss.

Kiton
Note: this name may be used for preparations of different composition.
Sigman, India.
Ketoconazole (p. 585·3).

Kitonail *Polichem, Austria; Castalia, Gr.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Kivexa *GSK, Arg.; ViiV, Austral.; ViiV, Austria; GSK, Braz.; ViiV, Canad.; GSK, Cz.; GSK, Denm.; ViiV, Fin.; ViiV, Fr.; ViiV, Ger.; GSK, Hong Kong; ViiV, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Mex.; ViiV, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; ViiV, Port.; GSK, Rus.; GSK, S. Afr.; GSK, Singapore; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Thai.*
Abacavir sulfate (p. 963·1); lamivudine (p. 1000·2).
HIV infection.
ViiV, Belg.; GSK, Chile; ViiV, Gr.; GSK, UK.
Abacavir (p. 962·3); lamivudine (p. 1000·2).
HIV infection.

Klabax *Nanxin, China; Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Pol.; Izvarino, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klabet *Wermar, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klabion *Polpharma, Pol.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klacid *Abbott, Austral.; Abbott, Austria; Abbott, China; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Abbott, Hong Kong; Abbott, Hung.; Abbott, India; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, Ukr.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klacid HP 7 *Abbott, Austral.*
Capsules, omeprazole (Probitor) (p. 1867·2); capsules, amoxicillin trihydrate (p. 216·2); tablets, clarithromycin (Klacid) (p. 266·2).
Helicobacter pylori*-associated peptic ulcer.*
Abbott, Malaysia.
Tablets, pantoprazole sodium (Controloc) (p. 1875·3); tablets, amoxicillin (Ospamox) (p. 216·2); tablets, clarithromycin (Klacid) (p. 266·2).
Helicobacter pylori*-associated peptic ulcer.*

Klacin *Cipla, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klaciped *Abbott, Switz.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klafenac *Galeno, Venez.*
Diclofenac (p. 48·3) or diclofenac potassium (p. 48·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; inflammation; pain.
Interpharma, Chile.
Diclofenac potassium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; inflammation; fever.

Klafotaxim *Be-Tabs, S.Afr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Klaider *Krugher, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Klaira *Bayer, Ital.*
Estradiol valerate (p. 2271·2); dienogest (p. 2267·2).
Combined oral contraceptive.

Klallergine *Obolenskoe, Rus.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Klamacin *Hua, Thai.*
Clotrimazole (p. 576·2).
Trichomoniasis.

Klamaxin *Ulagay, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klamer *Atabay, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klamoks *Bilim, Thai.†; Bilim, Turk.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Klamoric *Candor, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Klamox *Bilim, Ukr.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Klamycin *Mylan, NZ.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klandryn *Gentian, Denm.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Klaram *Actavis, Irl.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klaret *Hizon, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klaretop *Santa, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarexid *Pliva, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klarexyl *Viofar, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarfast *Cadila, Rus.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Klargen *Dynamic, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klaribros *Bros, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaricid *Abbott, Arg.; Abbott, Braz.; Abbott, Chile; Orifarm, Denm.; Abbott, Gr.; Abbott, Mex.; EU, Neth.†; Abbott, Philipp.; Abbott, UK; Abbott, Venez.*
Clarithromycin (p. 266·2) or clarithromycin lactobionate (p. 266·2).
Bacterial infections; adjunct in Helicobacter pylori eradication.

Klaricin *Micro, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klaricit *Pharma Start, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klarid *LBS, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klaridex *Dexcel, Israel.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaridol *Shreya, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders; urticaria; pruritus.

Klarifar *Farmedia, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarifect *Minerva (Μινερβα), Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarifer *Bryntsalov, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Klarigen
Note: this name may be used for preparations of different composition.
Copyfarm, Denm.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis.
Generics, Hung.; Merck, Pol.
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klariger *Gerard, Irl.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klarim *Morepen, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klarimac *Alet, Gr.; Ashford, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klarithran *Ranbaxy, S.Afr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarithrin *Iapharm, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarix *Maver, Mex.; QX, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klarizon *Biotech, S.Afr.*
Clarithromycin (p. 266·2).

Klarmin *ICN, Pol.*
Clarithromycin (p. 266·2).
Bacterial infections; peptic ulcer.

Klarmyn *Sandoz, Mex.; Sandoz, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarolid *Sandoz, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaromin *Eczacibasi, Rus.; Eczacibasi, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaron *Dermik, Israel†; Dermik, USA.*
Sulfacetamide sodium (p. 361·1).
Acne.

Klaroxil *Biochimico, Braz.*
Clarithromycin (p. 266·2).

Klaroxin *Iasis, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klarpharma *Alpharma, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaryne *Hua, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Klaryz *Terramedic, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klas *Elmor, Venez.*
Ambroxol theophyllinate (p. 1201·2).
Respiratory-tract congestion.

Klasine *Nobel, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klasinomycin *Khandelwal, India.*
Aclarubicin (p. 735·2).

Klasol *Drogsan, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaspar *Klar Sehen, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Klassak *Shreya, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

β-Klatinol *Synmedic, Ukr.*
Tablets, pantoprazole (p. 1875·3); tablets, clarithromycin (p. 266·2); tablets, amoxicillin (p. 216·2).
Peptic ulcer associated with Helicobacter pylori.

Klavic *Karnataka, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Klavoclav *Misha, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Klavunat *Atabay, Turk.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Klavupen *Toprak, Turk.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Klavux *Crinos, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Klax *Toprak, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klaxon *Pasteur, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Klaz *United Laboratories, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klazidem *Demo, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

KLB6 *Nature's Bounty, USA.*
Pyridoxine hydrochloride (p. 2105·3); soya lecithin (p. 2542·2); kelp (p. 2612·1); cider vinegar.

KLB6 Fruit Diet *Natural Life, Arg.*
Kelp (p. 2612·1); lecithin (p. 2542·2); vitamin B_6 (p. 2105·3); glucomannan (p. 2515·2); grapefruit; bearberry (p. 2453·2); cider vinegar; phenylalanine (p. 2086·1).
Obesity.

Klean-Prep *Norgine, Austria; Norgine, Belg.; Helix, Canad.; Norgine, Fin.†; Norgine, Fr.; Norgine, Ger.; Kite (Κιτε), Gr.; Helsinn Birex, Hong Kong; Helsinn Birex, Irl.; Norgine, Ital.; Norgine, Neth.; Healthcare Logistics, NZ; Helsinn, Port.; Norgine, S.Afr.; Norgine, Singapore; UCB, Spain; Norgine, Switz.; Norgine, UK.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Klebicil *Greenpharma, Braz.*
Amikacin (p. 214·1).
Bacterial infections.

Kleen-San *Dustbane, Canad.*
Benzethonium chloride (p. 1738·1).

Klenac *Klonal, Arg.*
Ketorolac (p. 80·2).
Eye disorders.

Klenyl *Mediphar, Venez.*
Soap: Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Acne; seborrhoea.

Mediphar, Venez.
Topical gel: Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne; seborrhoea.

Klenz *Kalpataru, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Klenz-D *Kalpataru, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Klenzit *Glenmark, Philipp.*
Adapalene (p. 1692·1).
Acne.

Kleore *Nizhpharm, Rus.*
⊗Betamethasone valerate (p. 1624·1); urea (p. 1727·3).
Skin disorders.

Kleotrat *Kleva, Gr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Klepisal *Actavis, Denm.; Actavis, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Klerant *Eczacibasi, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klerimed *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klerist-D *Nutripharm, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Kleron *Maxpharma, Ukr.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Klesidren *Chrispa (Χρισπα), Gr.*
Thiocolchicoside (p. 2026·2).
Muscle relaxant.

Klevasin *Kleva, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Klever *Kalpataru, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Kleverol *Jadran, Ukr.*
Red clover (p. 2482·1).
Menopausal symptoms.

Klevistamin *Kleva, Gr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Klexane *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Port.†; Sanofi-Aventis, Swed.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; prevention of clotting in extracorporeal circulation.

Kliacef *SoSe, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Kliane *Bayer Schering, Cz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Klick *Kalpataru, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Klidibrax *Sandoz, Indon.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal hypermotility.

Klimadynon *Bionorica, Austria; Bionorica, Ger.; Bionorica, Hong Kong; Bionorica, Indon.†; Darya-Varia, Indon.†; Bionorica, Rus.; Bionorica, Singapore; Bionorica, Spain; Biomed, Switz.; Biomeks, Turk.; Bionorica, Ukr.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Klimakt-Heel *Peithner, Hung.*
Sanguinaria canadensis (p. 2610·1); sepia officinalis (p. 2613·1); sulfur (p. 1721·1); strychnos ignatii (p. 2532·1); simarouba cedron; stannum metallicum (p. 2632·1); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Klimaktolan *VSM, Neth.*
Cimicifuga racemosa (p. 2478·1); ignatia amara (p. 2532·1); lachesis mutus (p. 2538·3); sanguinaria canadensis (p. 2610·1); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

Klimaktoplan *DHU, Rus.*
Cimicifuga (p. 2478·1); sepia (p. 2613·1); lachesis (p. 2538·3); ignatia (p. 2532·1); sanguinaria (p. 2610·1).
Homoeopathic preparation.

Klimaktoplan N *DHU, Ukr.*
Cimicifuga (p. 2478·1); sepia (p. 2613·1); ignatia (p. 2532·1); sanguinaria (p. 2610·1).
Homoeopathic preparation.

Klimaktoplant *DHU, Austria.*
Cimicifuga (p. 2478·1); sepia (p. 2613·1); ignatia (p. 2532·1); sanguinaria (p. 2610·1).
Homoeopathic preparation.

Klimaktoplant N *DHU, Ger.*
Cimicifuga (p. 2478·1); sepia (p. 2613·1); ignatia (p. 2532·1); sanguinaria (p. 2610·1).
Homoeopathic preparation.

Klimaktosin *Meckel, Ger.*
⊗Agnus castus (p. 2432·2).
Homoeopathic preparation.

Klimalanin *Bouchara, Rus.*
Beta-alanine (p. 2048·3).
Menopausal flushing.

Klimapur
Note: this name may be used for preparations of different composition.
Kwizda, Austria.
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Medico Uno, Hung.†
Cimicifuga (p. 2478·1).
Menopausal disorders.

Klimased *Vishpha, Ukr.*
Passion flower (p. 2584·1); tilia (p. 2631·3); oregano (p. 2576·3); sage (p. 2608·3); melissa (p. 2552·3).
Menopausal disorders; hypertension; nervous disorders.

Klimasol *Phytofarm Kleka, Pol.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Klimastress *Medichrom, Gr.*
Maprotiline hydrochloride (p. 433·3).

Klimater *Mabra, Braz.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Klimax *Herbapol Krakow, Pol.*
Shepherd's purse (p. 2614·2); cimicifuga (p. 2478·1); lupulus (p. 2546·1); motherwort (p. 2564·2); melissa (p. 2552·3).
Menopausal disorders.

Klimax-Gastreu R10 *Reckeweg, Neth.*
Cimicifuga racemosa (p. 2478·1); lachesis mutus (p. 2538·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Klimax-Gastreu S R10 *Reckeweg, Ger.*
Cimicifuga (p. 2478·1); lachesis (p. 2538·3); sanguinaria (p. 2610·1).
Homoeopathic preparation.

Klime *Madhav, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Klimicin *Lek, Cz.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Lek, Hung.; Sandoz, Pol.; Sandoz, Thai.†
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Lek, Rus.†
Clindamycin (p. 269·3).

Klimin *Pharmax, Hung.*
Borage oil (p. 2459·2); cod-liver oil (p. 2056·3); sodium fluoride (p. 2089·2); manganese chloride (p. 2081·2); chromium chloride (p. 2055·3); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3).
Dietary supplement.

Klimodien *Bayer Schering, Cz.; Bayer, Ukr.†*
Estradiol valerate (p. 2271·2); dienogest (p. 2267·2).
Menopausal disorders.

Klimonorm *Jenapharm, Cz.; Jenapharm, Ger.; Jenapharm, Hung.; Jenapharm, Pol.; Bayer, Rus.; Jenapharm, Thai.†; Jenapharm, Ukr.*
9 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Klimovit *Gradiens, Hung.*
Magnesium aspartate (p. 1787·1); royal jelly (p. 2608·1); tocoferil acetate (p. 2119·2).
Menopausal symptoms.

Klimyn *IQFA, Mex.*
⊗Furosemide (p. 1387·1).

Klina *Royal, Chile.*
Clindamycin (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

Klincosal *Roemmers, Venez.*
Bismuth subcarbonate (p. 1822·1); calcium carbonate (p. 1824·3); kaolin (p. 1850·1); pectin (p. 2200·3); carmellose (p. 2175·1).
Gastrointestinal disorders.

Klincyn *Henan, Philipp.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Klinda *RX, Thai.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Klindacin T *Polfa Tarchomin, Pol.*
Clindamycin phosphate (p. 269·3).
Acne; bacterial skin infections.

Klindagol *Orion, Fin.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Klindan *Bilim, Turk.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Idol, Thai.†
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Klindaver *Biosel, Turk.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Klindex *Amherst, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Kliner *Sanitas, Chile.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes; eye irritation.

Klinit *Haledew, India.*
Mouth paint: Cetrimide (p. 1742·1); tannic acid (p. 2625·2); zinc chloride (p. 2126·1).

Haledew, India.
Toothpaste: ⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3); triclosan (p. 1773·2).

Klinna *Greater Pharma, Thai.*
Clindamycin phosphate (p. 269·3).
Acne.

Klinoksin *Deva, Turk.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Klinomycin *Valeant, Ger.†*
Minocycline hydrochloride (p. 325·1).
Acne.

Klinotab *Teofarma, Belg.*
Minocycline hydrochloride (p. 325·1).
Acne.

Klinotal *Roemmers-Klinos, Venez.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Klinoxid *Valeant, Ger.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Klinset *Bernofarm, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Klinzal *Affy, India.*
Emollient.

Kliofem *Novo Nordisk, UK.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Oestrogen deficiency; osteoporosis.

Kliogest *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Silesia, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, Norw.†; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore†; Novo Nordisk, Swed.†; Novo Nordisk, Turk.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency; hormone replacement therapy.

Kliogest N *Novo Nordisk, Ger.; Novo Nordisk, Switz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Klion *Gedeon Richter, Hung.; Pharmamagist, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; rosacea; peptic ulcer; trichomoniasis; giardiasis; amoebiasis.

Klion-D *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Kliophyt *Meligen, Rus.*
Anise (p. 2444·2); crataegus (p. 2488·1); calendula (p. 2465·2); epilobium angustifolium; coriander (p. 2486·3); honey (p. 2072·1); peppermint leaf (p. 1877·1); plantain (p. 2592·3); motherwort (p. 2564·2); chamomile (p. 2474·1); liquorice (p. 1853·2); Siberian pine cedar seeds; caraway (p. 2470·2); achillea (p. 2427·3); lupulus (p. 2546·1); birch fungus; bidens tripartita; rose fruit (p. 2607·1); Siberian ginseng (p. 2614·3).
Menopausal disorders.

Kliotex *Solvay, Rus.*
White soft paraffin (p. 2211·3).
Burns; ulcers; wounds.

Kliovance *Novo Nordisk, Austral.; Novo Nordisk, NZ; Novo Nordisk, UK.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Klipaks *Ulagay, Turk.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Anxiety; alcohol withdrawal syndrome.

Klipal Codéine *Pierre Fabre, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Kliran *Bernofarm, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Klismacort *Bene, Ger.*
⊗Prednisolone (p. 1645·2).
Rectal corticosteroid.

Klispel *Ativus, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Klistier *Fresenius Kabi, Ger.†*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Klitopsin *Toprak, Turk.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Klizin *Cimed, Braz.*
Buclizine (p. 618·3); vitamin B substances (p. 2102·3).
Tonic; reduced appetite.

KLN *Roche Consumer, UK.*
Kaolin (p. 1850·1); pectin (p. 2200·3); sodium citrate (p. 1781·2); peppermint oil (p. 1877·1).
Diarrhoea.

Klobecort *2M, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Klodamin *Adeka, Turk.*
Chlorhexidine gluconate (p. 1743·3); benzydamine hydrochloride (p. 29·2).

Kloderma *Surya Dermato, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Klodigan *Actavis, Denm.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Klodin
Note: this name may be used for preparations of different composition.
Savio, Ital.
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.
Umut, Turk.
Loratadine (p. 633·2).

Klodip *Kopran, India.*
Amlodipine (p. 1304·1).
Angina pectoris.
Pharmascript, S.Afr.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Klodip Ace *Kopran, India.*
Amlodipine besilate (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Klodipin *APS, Port.†*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Klog *Global, India.*
Carbazochrome (p. 1137·1).

Klomazole *Klonal, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Klomen *Kocak, Turk.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Klomeprax *Klonal, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Klomicina *Klonal, Arg.*
Roxithromycin (p. 356·2).
Bacterial infections.

Klomox *Lincoln, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Klonacid *Klonal, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Klonac-P *Kalpataru, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Klonac-XS *Kalpataru, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Klonadryl Antialergico *Klonal, Arg.*
Diphenhydramine (p. 626·1).

Klonafenac *Klonal, Arg.*
Diclofenac (p. 48·3).
Inflammation; pain.

Klonalcrom *Klonal, Arg.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Klonalfenicol *Klonal, Arg.*
Chloramphenicol (p. 257·1), chloramphenicol palmitate (p. 257·1), or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Klonalflox *Klonal, Arg.*
Ofloxacin (p. 334·3).
Bacterial infections.

Klonalmox *Klonal, Arg.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Klonalol *Klonal, Arg.*
⊗Timolol (p. 1513·2).
Ocular hypertension.

Klonam *Klonal, Arg.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Klonametacina *Klonal, Arg.*
Indometacin (p. 71·2).
Inflammation; pain.

Klonamicin *Klonal, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Klonamicin Compuesto *Klonal, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Klonaprost *Klonal, Arg.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Klonarizol *Klonal, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Klonastin *Klonal, Arg.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Klonat *Sandoz, Indon.†*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Klonatropina *Klonal, Arg.*
Atropine (p. 1310·2).
Production of mydriasis.

Klonaza *Atlantis, Mex.*
Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2); clonixin lysine (p. 40·1).
Smooth muscle spasm.

Klonazol *Klonal, Arg.†*
Fluconazole (p. 578·2).
Fungal infections.

Klondroxil *Klonal, Arg.*
Cefadroxil (p. 233·2).
Bacterial infections.

Klonocarpina *Klonal, Arg.*
Pilocarpine (p. 2010·2).
Glaucoma.

Klonopin *Genentech, USA.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Klonovan *Klonal, Arg.*
Chloramphenicol (p. 257·1); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Bacterial eye infections.

Klontar *Ashford, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial ear and eye infections.

Klopide *Aldril, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Klopik *Biotenk, Arg.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; atherosclerosis.

Klopis *Fako, Turk.*
Clopidogrel bisulfate (p. 1342·3).

Klopoxid *Nycomed, Denm.*
Chlordiazepoxide (p. 1044·2).
Anxiety; alcohol withdrawal syndrome.

Kloptimar *Alchemia, Cz.; Actavis, Denm.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

K-Lor *Abbott, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Kloral *SAD, Denm.*
Cloral hydrate (p. 1055·2).
Convulsions.

Kloramin *Hua, Thai.*
Chlorphenamine maleate (p. 620·3).
Allergic skin disorders; hypersensitivity reactions; insect bites.

Kloramixin *Armoxindo, Indon.*
Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Kloramixin D *Armoxindo, Indon.*
⊗Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections.

Klorane Bebe Eryteal *Pierre Fabre Dermo-Cosmetique, Arg.*
Cod-liver oil (p. 2056·3); halibut-liver oil (p. 2071·3); zinc oxide (p. 1729·1); cetrimonium bromide (p. 1742·3).

Klorasüksinat *Ulagay, Turk.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Klor-Con *Upsher-Smith, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Klor-Con/EF *Upsher-Smith, USA.*
Potassium bicarbonate (p. 1780·3); potassium citrate (p. 1780·3).
Hypokalaemia.

Klor-De *Medentech, Israel.*
Troclosene sodium (p. 1774·1).
Surface and instrument disinfection.

Kloref *Adelco, Gr.*
Betaine hydrochloride (p. 2456·1); potassium bicarbonate (p. 1780·3).
Hypokalaemia; potassium depletion.
Abbott, S.Afr.†; Alpharma, UK.†
Betaine hydrochloride (p. 2456·1); potassium bicarbonate (p. 1780·3); potassium chloride (p. 1793·2); potassium benzoate (p. 1793·1).
Hypokalaemia; potassium depletion.

Kloreniss *PharOS, Neth.*
Clarithromycin citrate (p. 266·2).
Bacterial infections.

Klorfen *Karnataka, Philipp.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Klorfeson *Molex Ayus, Indon.*
⊗Chloramphenicol (p. 257·1); prednisolone (p. 1645·2).
Infected skin disorders.

Klorheksol *Merkez, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Klorhex *Drogsan, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; skin disinfection.

Klorhexol *Leiras, Fin.*
Chlorhexidine gluconate (p. 1743·3).
Hand and skin disinfection.

Klornik *Swiss Parenterals, Philipp.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Kloroben *Drogsan, Hong Kong; Drogsan, Turk.*
Benzydamine hydrochloride (p. 29·2); chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders; oral hygiene.

Klorpo *Beacons, Singapore.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome.

Klorproman *Orion, Fin.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; alcohol withdrawal syndrome; sedative; nausea and vomiting; pain.

Klorvess *Novartis, USA.*
Oral effervescent granules: Potassium chloride (p. 1793·2); potassium bicarbonate (p. 1780·3); potassium citrate (p. 1780·3); lysine hydrochloride (p. 2079·3).
Potassium depletion; hypokalaemic-hypochloraemic alkalosis.
Novartis, USA.
Effervescent tablets: Potassium chloride (p. 1793·2); potassium bicarbonate (p. 1780·3); lysine hydrochloride (p. 2079·3).
Potassium depletion; hypokalaemic-hypochloraemic alkalosis.
Novartis, USA.
Oral liquid: Potassium chloride (p. 1793·2).
Potassium depletion; hypokalaemic-hypochloraemic alkalosis.

Kloryl *Unimarck, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Kloryl-G *Unimarck, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).

Kloryl-M *Unimarck, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).

Klorzide *Zydus, India.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; diabetes insipidus.

Klosartan *Klonal, Arg.*
Losartan (p. 1422·2).
Hypertension.

Klosartan-D *Klonal, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kloser-D *Nortech, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Klosidol *Bago, Arg.*
Dextropropoxyphene hydrochloride (p. 43·3) or dextropropoxyphene napsilate (p. 43·3); dipyrone (p. 53·3).
Pain.

Klosidol B1 B6 B12 *Bago, Arg.*
Dextropropoxyphene hydrochloride (p. 43·3) or dextropropoxyphene napsilate (p. 43·3); dipyrone (p. 53·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Joint pain; neuralgia.

Klostenal *Bracco, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Ulcerative colitis.

Klosterfrau Aktiv *Klosterfrau, Pol.*
Garlic oil (p. 2510·3); wheat-germ oil (p. 2647·1); St John's wort (p. 449·1); vitamin A (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Tonic.
Klosterfrau, Ger.†
Garlic (p. 2510·3); vitamin A (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Tonic.

Klosterfrau Allergin *Klosterfrau, Ger.*
Adhatoda vasica (p. 2549·1).
Homoeopathic preparation.

Klosterfrau Franzbranntwein *Klosterfrau, Ger.†*
⊗Menthol (p. 2553·2); camphor (p. 2466·2); alcohol (p. 1733·1).
Musculoskeletal, joint, and soft-tissue disorders.

Klosterfrau Franzbranntwein Latschenkiefer *Klosterfrau, Ger.†*
Topical lotion: ⊗Camphor (p. 2466·2); pumilio pine oil (p. 2591·1); alcohol (p. 1733·1).
Musculoskeletal, joint, and soft-tissue disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Klosterfrau Franzbranntwein Menthol *Klosterfrau, Ger.†*
Topical solution: ⊗Menthol (p. 2553·2); alcohol (p. 1733·1).
Musculoskeletal, joint, and soft-tissue disorders.

Klosterfrau, Ger.†
Topical gel: Menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders.

Klosterfrau Melisana *Klosterfrau, Cz.; Phytotec, Hung.*
Melissa (p. 2552·3); elecampane (p. 1662·3); angelica (p. 2443·3); ginger (p. 1844·1); clove (p. 2481·2); galanga; black pepper (p. 2586·1); gentian (p. 2512·1); nutmeg (p. 2573·1); dried bitter-orange peel (p. 2575·3); cinnamon (p. 2479·2); cassiae floris (p. 2471·3); cardamom (p. 2471·1).
Respiratory-tract disorders; gastrointestinal disorders; pain; nervous disorders; sleep disorders; digestive disorders; cold and influenza symptoms; neuralgia; muscle pain.

Klosterfrau Melissengeist *Klosterfrau, Austria.*
Melissa (p. 2552·3); elecampane (p. 1662·3); gentian (p. 2512·1); dried bitter-orange peel (p. 2575·3); angelica (p. 2443·3); ginger (p. 1844·1); clove (p. 2481·2); galganga; cinnamon (p. 2479·2); nutmeg (p. 2573·1); black pepper (p. 2586·1); cardamom (p. 2471·1).
Tonic.

Klosterfrau, Ger.
⊗Melissa (p. 2552·3); elecampane (p. 1662·3); angelica (p. 2443·3); ginger (p. 1844·1); clove (p. 2481·2); gentian (p. 2512·1); piper nigris; galanga; nutmeg (p. 2573·1); dried bitter-orange peel (p. 2575·3); cinnamon bark (p. 2479·2); cardamom (p. 2471·1); alcohol (p. 1733·1).
Tonic.

Klosterfrau Nervenruh Dragées *Melisana, Switz.*
Lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Klotaren *Kimia, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Klotinex *Blubell, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Klotriptyl *Orion, Fin.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Depression; insomnia.

Klotrix *Apothecon, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Kloty *Blubell, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Klout *Pediamed, USA.*
Acetic acid (p. 2426·3); isopropyl alcohol (p. 1758·3); sodium laurilsulfate (p. 2210·3).
Pediculosis.

Klov *Zee, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Klovireks-L *Nevzat, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Klox *Hetero, India.*
Cloxacillin (p. 274·3).
Bacterial infections.

Kloxamp *Karnataka, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Klox-D *Hetero, India.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Kloxitas *Umedica, Philipp.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Klozapol *Egis, Pol.*
Clozapine (p. 1057·3).
Psychoses.

Klozivex *Torrent, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Klyndaken *Kendrick, Mex.†*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Klysmol *Demo, Gr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

K-Lyte *Apothecon, USA.*
Potassium bicarbonate (p. 1780·3).
Potassium deficiency.

Wellspring, Canad.
Potassium citrate (p. 1780·3).
Potassium depletion.

K-Lyte DS *Apothecon, USA.*
Potassium bicarbonate (p. 1780·3); potassium citrate (p. 1780·3).
Potassium deficiency.

K-Lyte/Cl *Wellspring, Canad.†; Apothecon, USA.*
Potassium chloride (p. 1793·2).
Potassium deficiency; potassium depletion.

Apothecon, USA.†
Effervescent tablets: Potassium chloride (p. 1793·2); potassium bicarbonate (p. 1780·3).
Potassium deficiency.

Klyx *Ferring, Denm.; Ferring, Fin.; Pharmachemie, Neth.; Ferring, Norw.; Ferring, Swed.*
Docusate sodium (p. 1836·2); sorbitol (p. 2092·1).
Constipation; bowel evacuation.

Klyx Magnum *Ferring, Switz.†*
⊗Docusate sodium (p. 1836·2); dried magnesium sulfate (p. 1786·3); urea (p. 1727·3).
Bowel evacuation; constipation.

Klyzen *Pharmahof, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

KM Gel *LKM, Arg.*
Adapalene (p. 1692·1).
Acne.

K-Met *Blue Cross, India.*
Metformin (p. 489·1).
Diabetes mellitus.

KMG Plus *Seroyal, Canad.†*
Vitamin B_6 (p. 2105·3); magnesium (p. 1786·3); potassium (p. 1793·1).

KMH *M & H, Thai.*
Kanamycin sulfate (p. 314·3).
Bacterial infections.

Kmin *Prem, India.*
Ketamine (p. 1905·1).
General anaesthesia.

K-Mix *Xepa-Soul Pattinson, Singapore.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3).
Urinary-tract disorders.

K-Mizol *Arlex, Mex.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections.

KMR *Medihealth, India.*
Tablets: Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Medihealth, India.
Topical gel: ⊗Alcohol (p. 1733·1); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

KMS *Kao, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

KN Solution *Otsuka, Jpn.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Knac *AstraZeneca, India.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

K-Nat *KonTest, India.*
Menadione sodium bisulfite (p. 2122·2).

Kneipp Arnika Salbe S *Kneipp, Ger.*
Arnica oil (p. 2447·2); sunflower oil (p. 2098·1).
Musculoskeletal, joint, and soft-tissue disorders.

Kneipp Cholesterin Control *Kneipp, Ger.†*
Ispaghula (p. 1849·1).
Hypercholesterolaemia.

Kneipp Erkältungsbad Spezial *Kneipp, Ger.*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2).
Bath additive; catarrh.

Kneipp Gute Nacht *Kneipp, Ger.†*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Sleep disorders.

Kneipp Husten- und Bronchial-Tee *Kneipp, Ger.†*
Fennel (p. 2503·2); cowslip flowers and calyx (p. 2596·2); thyme (p. 2630·2); ribwort plantain (p. 2604·2).
Respiratory-tract congestion.

Kneipp Rheumabad Spezial *Kneipp, Ger.†*
Juniper oil (p. 2537·2); turpentine oil (p. 2636·3) sweet birch oil (p. 92·1).
Bath additive; musculoskeletal and joint disorders.

Knit *Haledew, India.*
⊗Potassium nitrate (p. 1766·2).

Knobel Comprimés N *Streuli, Switz.†*
Senna (p. 1885·1).
Constipation.

Knobel Huile N *Streuli, Switz.†*
Ethyl nicotinate (p. 56·3); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); volatile mustard oil (p. 2646·1).
Musculoskeletal and joint disorders.

Knoful *YSP, Thai.†*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Kno-OL *Kalpataru, India.*
Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Kno-Paine *Continental Pharma, Thai.†*
Dipyrone (p. 53·3).
Pain.

Knowful *YSP, Malaysia.*
Piracetam (p. 393·3).
Mental function disorders.

Koact *Aurobindo, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Koal *Ethicus, Arg.*
Salicylic acid (p. 1719·1).
Scalp disorders.

Koate *Cristalia, Braz.; Dipa, Indon.; Talecris, Israel; Talecris, Rus.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A.

Koate-DVI *Teva Tuteur, Arg.; Bayer, Chile†; Talecris, Hong Kong; Bayer, Philipp.; Biem, Turk.; Kedrion, USA.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; von Willebrands disease.

Koate-HP *Bayer, Gr.*
A factor VIII preparation (p. 1148·1).

Kobit *Candor, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Kobit-AS *Candor, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Kobit-M *Candor, India.*
Atorvastatin (p. 1309·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Kobixam *KB, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Kobralgin *In Vitro, Hung.*
Arnica (p. 2447·2); cobra venom.
Musculoskeletal and joint pain; neuralgia.

Ko-Cap *Sriprasit, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Kocef *MDI, S.Afr.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Kocefan *Mediolanum, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Kochsalz *Braun, Austria.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Kochsalz mit Glucose *Braun, Ger.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Kocip *Ester, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Kodamid *Nycomed, Denm.*
Codeine phosphate (p. 40·2); caffeine (p. 1203·3); propyphenazone (p. 127·3); salicylamide (p. 129·2).
Magnesium hydroxide (p. 1857·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Kodan *Schulke & Mayr, Austria.*
Isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1); orthophenylphenol (p. 1762·3); hydrogen peroxide solution 30% (p. 1755·3).
Skin disinfection.

Kodan forte *Schulke & Mayr, Switz.*
Isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1); orthophenylphenol (p. 1762·3).
Skin disinfection.

Kodan Tinktur Forte *Schulke & Mayr, Ger.*
Isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1); orthophenylphenol (p. 1762·3).
Skin disinfection.

Kodapon *Gulf Drug, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Kodel *Columbia, Mex.*
Bromhexine hydrochloride (p. 1656·3); codeine phosphate (p. 40·2).
Cough; respiratory-tract congestion.

Kodimagnyl *Nycomed, Denm.; SAD, Denm.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Magnesium hydroxide (p. 1857·2) is included in some dosage forms in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Kodipar *Nycomed, Denm.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Kofan *Bosnalek, Rus.; Bosnalijek, Ukr.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain; fever.

Kofanol *Nabros, Ukr.†*
Pastilles: Liquorice (p. 1853·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); anise oil (p. 2444·3); peppermint oil (p. 1877·1); pine oil (p. 2591·1).
Cold and influenza symptoms; bronchitis; allergic rhinitis; cough.

Nabros, Ukr.†
Syrup: Diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Symptoms of respiratory-tract inflammation and infection; cough; allergic rhinitis.

Kofarest *Centaur, India.*
Syrup: ⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough associated with viscous mucus.

Centaur, India.
Lozenges: Cetylpyridinium chloride (p. 1743·1); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).
Cough; sore throat.

Centaur, India.
Oral drops: Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Kofarest Expectorant *Centaur, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).
Cough.

Kofarest-C *Centaur, India.*
Chlorphenamine maleate (p. 620·3); codeine (p. 40·2); menthol (p. 2553·2).

Kofarest-DX *Centaur, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Kofarest-H *Centaur, India.*
Malabar nut (p. 2549·1); cinnamomum cassia (p. 2471·3); curcuma longa; liquorice (p. 1853·2); honey (p. 2072·1); ocimum sanctum; piper longum.
Cough.

Kofaxin *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Kofban *Auspi, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); menthol (p. 2553·2); phenylephrine (p. 1672·2).

Kofban-EX *Auspi, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Kofemin *Robugen, Ger.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Kofend-D *Bal, India.*
Dextromethorphan (p. 1660·1).
Cough.

Kofend-X *Nordic, India.*
Ammonium chloride (p. 1656·1); bromhexine (p. 1656·3); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Kofepar *Pliva Krakow, Pol.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Kofevit *Polfa Lodz, Pol.†*
Caffeine (p. 1203·3); levocarnitine (p. 2053·2); vitamins; calcium lactogluconate (p. 1783·1); magnesium hydroaspartate.
Tonic.

Kofex
Note: this name may be used for preparations of different composition.
Bal, India.
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
GSK, Pol.†
Caffeine and sodium benzoate (p. 1203·3).
Fatigue.

Kof-Eze *Roberts, USA.*
Menthol (p. 2553·2).
Coughs; sore throats.

Koffazon *Recip, Swed.*
Caffeine (p. 1203·3); phenazone (p. 124·1).
Pain.

Koffex
Note: this name may be used for preparations of different composition.
Actavis, Indon.
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2); alcohol (p. 1733·1).
Cough.

Koffex for Children *Actavis, Indon.*
⊗Ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2); ammonium chloride (p. 1656·1); citric acid (p. 2480·3); tolu syrup.
Cough.

Koffex DM *Teva, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Koffisal *Nycomed, Denm.*
Caffeine (p. 1203·3); phenazone salicylate (p. 124·2); salicylamide (p. 129·2).
Pain.

Kofgard *Mapra, India.*
Dextromethorphan (p. 1660·1).
Cough.

Kofkul *Finecure, India.*
⊗Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine (p. 1676·1).

Koflet *Himalaya Herbal, India.*
Lozenges: Black catechu (p. 2457·3); cinnamon (p. 2479·2); elettaria cardamomum; syzygium aromaticum; terminalia chebula (p. 2474·3).
Cough.
Himalaya Herbal, India.
Syrup: Malabar nut (p. 2549·1); cinnamomum cassia (p. 2471·3); liquorice (p. 1853·2); nutmeg (p. 2573·1); ocimum sanctum; tinospora cordifolia; grape (p. 2521·3).
Cough.

Kofli *CTS, Israel.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Kofmed *Utopian, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; cold symptoms.

Kofol *Charak, India.*
Ocimum sanctum.

Koforil *Finecure, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Kof-Rid *Dalmia, India.*
⊗Malabar nut (p. 2549·1); piper longum; piper nigrum; tribulus terrestris (p. 2633·3); zingiber officinale.
Cough.

Kofrid *Meridian, India.*
Syrup: Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough.
Meridian, India.
Tablets: Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Kofrid Plus *Meridian, India.*
Ambroxol (p. 1654·3); cetirizine hydrochloride (p. 619·2); menthol (p. 2553·2).

Kofrid-D *Meridian, India.*
Cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylpropanolamine hydrochloride (p. 1674·1).

Kofron *Guidotti, Spain.*
Clarithromycin (p. 266·2).
Bacterial infections.

Kofryl-P *Bactolac, India.*
Ammonium chloride (p. 1656·1); bromhexine (p. 1656·3); dextromethorphan (p. 1660·1); menthol (p. 2553·2); phenylpropanolamine (p. 1674·1).

Koftame *ICPA, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Koftone *Wings, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).
Cough.

Kogenate *Bayer, Arg.; Bayer, Belg.; Bayer, Braz.; Bayer, Chile; Bayer, China; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer Schering, Malaysia; Bayer, NZ; Bayer, Singapore; Bayer, Thai.; Bayer, Turk.; Bayer, USA.*
A factor VIII preparation (p. 1148·1).
Haemophilia A ; haemorrhagic disorders.

Bayer, Austral.; Bayer, Austria; Bayer, Canad.; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, Pol.; Bayer Schering, Port.; Bayer, Rus.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, UK.
Octocog alfa (p. 1148·2).
Haemorrhagic disorders; factor VIII deficiency; haemophilia A.

Kogra *Landsteiner, Mex.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Kogrel *Sandoz, Malaysia.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Kohle-Compretten *Merck, Ger.; Merck, Norw.*
Activated charcoal (p. 1537·3).
Diarrhoea; acute poisoning.

Kohle-Hevert *Hevert, Ger.*
Activated charcoal (p. 1537·3).
Diarrhoea; acute poisoning.

Kohlensäurebad Bastian *Bastian, Ger.*
Sodium bicarbonate (p. 1781·1).
Bath additive; cardiac and circulatory disorders.

Kohle-Pulvis *Kohler, Ger.*
Activated charcoal (p. 1537·3).
Diarrhoea; acute poisoning.

Kohle-Tabletten *Cheplapharm, Ger.*
Activated charcoal (p. 1537·3).
Diarrhoea; acute poisoning.

Kohrsolin *Bode, Ger.†*
Glutaral (p. 1753·2); 1,6-dihydroxy-2,5-dioxahexane (p. 1750·3); polymethylolurea derivative.
Surface and instrument disinfection.

Kohrsolin extra *Bode, Ger.*
Glutaral (p. 1753·2); 1,6-Dihydroxy-2,5-dioxahexane (p. 1750·3); didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Kohrsolin FF *Bode, Ger.*
Glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1); didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Kóide *Eurofarma, Braz.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Kóide D *Eurofarma, Braz.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).

Koiz *Dewcare, India.*
Shampoo: Aloes (p. 1816·1); ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dewcare, India.
Soap: Ketoconazole (p. 585·3).

Koji *Patar, Thai.*
Colchicine (p. 604·1).
Gout.

Kojivit *Micro, India.*
Arbutin (p. 1694·3); kojic acid dipalmitate; octinoxate (p. 1715·1).
Skin hyperpigmentation.

Ko-Kure *Sriprasit, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Kolampept *Teuto, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastrointestinal hyperacidity; flatulence.

Kolanticon *Peckforton, UK.*
Aluminium hydroxide (p. 1817·2); dicycloverine hydrochloride (p. 1834·2); light magnesium oxide (p. 1857·3); simeticone (p. 1886·2).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux; gastritis.

Kolantyl *Medley, Braz.*
Chewable tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); methylcellulose (p. 2197·3); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.
Medley, Braz.
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); methylcellulose (p. 2197·3).
Gastric hyperacidity.
Adcock Ingram, S.Afr.†
Oral gel: Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3); methylcellulose (p. 2197·3).
Gastrointestinal disorders.
Adcock Ingram, S.Afr.†
Wafers: Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); methylcellulose (p. 2197·3); magnesium trisilicate (p. 1858·1).
Gastrointestinal disorders.

Kolantyl DMP *Medley, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); methylcellulose (p. 2197·3); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Kolbet *Toyama, Jpn.*
Iguratimod (p. 71·1).
Rheumatoid arthritis.

Kold Time *Laborate, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Kol-DC *Forgo, India.*
Caffeine (p. 1203·3); cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Kolderon *Hauz, India.*
Chlorphenamine (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Koldy *Sienna, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Kolephrin *Pfeiffer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Kolephrin GG/DM *Pfeiffer, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Kolephrin/DM *Pfeiffer, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Koleskol *Metiska, Indon.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Kolestop *Omni, UK.*
Sitosterol (p. 1471·2); beta sitostanol (p. 1471·2).
Nutritional supplement to reduce serum cholesterol.

Kolestor *Eczacibasi, Turk.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Kolestran *Sandoz, Turk.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; pruritus; diarrhoea.

Kolevas *EMS, Braz.*
Atorvastatin (p. 1309·2).

Kolexan *Biomep, Mex.*
Albendazole (p. 149·1).

Kolez *Biofarma, Turk.*
Ezetimibe (p. 1379·2).

Kolibel *Sanitas, Chile.*
⊗Clofedanol hydrochloride (p. 1659·1); pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Kolibri *Wassermann, Ital.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Kolincin *CBC, Hong Kong.*
Clindamycin phosphate (p. 269·3).
Acne.

Kolispas *Psychotropics, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Kolivit *Soho, Indon.*
Bovine colostrum (p. 2380·3); lysine hydrochloride (p. 2079·3); docosahexaenoic acid (p. 1460·1); vitamins.
Dietary supplement.

Kolkatriol *Phapros, Indon.*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Kolkin *Duncan, Arg.*
⊗Furosemide (p. 1387·1).
Hypertension.

Kollagenase *Cristalia, Braz.*
⊗Collagenase (p. 2484·1).
Wounds; skin ulcers.

Kollagenase com cloranfenicol *Cristalia, Braz.*
⊗Collagenase (p. 2484·1); chloramphenicol (p. 257·1).
Wounds; skin ulcers.

Kollalysin *St Petersburg Institute of Vaccines & Sera, Rus.*
⊗Collagenase (p. 2484·1).
Wounds; ulcers.

Kollateral *Ursapharm, Ger.†*
Moxaverine hydrochloride (p. 2564·2).
Cerebral, coronary, and peripheral vascular disorders.

Kollosteril *Lafedar, Arg.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Kolme *Faes, Ukr.*
Carbimide.
Alcoholism.

Kolossorb *Alfa Wassermann, Fr.*
Montmorillonite beidellitique.
Digestive disorders.

Kolpitrat *Medley, Braz.*
Metronidazole benzoate (p. 936·1); nystatin (p. 590·3); benzalkonium chloride (p. 1737·1).
Vaginal infections.

Kolplex *Collins, Mex.†*
Vitamins.

Kolq *Blue Cross, India.*
Lozenges: Cetylpyridinium chloride (p. 1743·1).
Blue Cross, India.
Oral drops: Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Blue Cross, India.
Syrup; tablets: Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); zinc gluconate (p. 2126·2).

Kolq Inhalant *Blue Cross, India.*
Camphor (p. 2466·2); chlorothymol (p. 1748·2); cineole (p. 2479·1); menthol (p. 2553·2); terpineol (p. 2627·2).

Kolsin *Ulagay, Turk.*
Colchicine (p. 604·1).
Gout.

Kolsuspension *Abigo, Swed.*
Activated charcoal (p. 1537·3).
Poisoning.

Komasin *Medinova (Μεντινοβα), Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Kombat *Kalpataru, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Kombetin *Pharmafar, Ital.*
Strophanthin-K (p. 1507·2).
Cardiac disorders.

Kombevit-C *Deva, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Kombiglyze *AstraZeneca, Belg.; AstraZeneca, Switz.*
Saxagliptin hydrochloride (p. 499·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

BMS, USA.
Saxagliptin (p. 499·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Kombi-Kalz *Meda, Cz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Kombina *Dey's, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Kombinil-Duo *Promed, Rus.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye and ear disorders.

Kombivit *Streuli, Switz.†*
Vitamins.

Komboglyze *BMS, Neth.; BMS, Spain; AstraZeneca, UK.*
Saxagliptin hydrochloride (p. 499·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Komezol *Konpharma, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Komfer *Kocak, Turk.*
Iron succinyl-protein complex (p. 2077·3).

Komfer Fol *Kocak, Turk.*
Iron succinyl-protein complex (p. 2077·3); calcium folinate (p. 2066·3).

Komil *Goldshield, UK.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
These ingredients can be described by the British Approved Name Co-amilofruse.
Oedema; liver cirrhosis with ascites.

K-Omistron *Mayo, Mex.*
Neomycin (p. 329·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Kompazin *Medis, Denm.†*
Mirtazapine (p. 436·1).
Depression.

Kompensan *McNeil, Ger.; Johnson & Johnson, Port.; Janssen-Cilag, Switz.†; Pfizer, Turk.*
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Gastric hyperacidity; gastrointestinal disorders; peptic ulcer; gastro-oesophageal reflux.

Kompensan-S *Johnson & Johnson, Port.*
Dihydroxyaluminum sodium carbonate (p. 1835·2); dimeticone (p. 1886·2).
Gastrointestinal disorders.

Kompro *Plus, India.*
Preparation for enteral nutrition.

Kon *Captab, India.*
Fluconazole (p. 578·2).
Fungal infections.

Kona *M & H, Thai.*
⊗Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms; nasal congestion.

Konact *Actavis, Fin.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; pityriasis capitis.

Konaderm *Valeant, Mex.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Kona-K *Duopharma, Philipp.*
Phytomenadione (p. 2122·2).
Hypoprothrombinaemia; vitamin K deficiency bleeding.

Konakion *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Chile; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.†; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding; hypoprothrombinaemia; vitamin K deficiency; haemorrhagic disorders; coumarin overdose; phenylbutazone overdose; salicylate overdose.

Konakion MM *Roche, Turk.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding; vitamin K deficiency.

Konaturil *IQFA, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Konaz *Chemo-Drugs, India; Utopian, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Konazal *Actavis, Norw.†*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis.

Konazol *PP Lab, Thai.; Kurtsan, Turk.*
Ketoconazole (p. 585·3).
Fungal infections.

Konazole *Daewon, Philipp.*
Ketoconazole (p. 585·3).
Fungal infections.

Kondon's Nasal *Kondon, USA.*
⊗Ephedrine (p. 1663·1).
Nasal congestion.

Kondremul *Insight, USA.*
Liquid paraffin (p. 2191·2).
Constipation.

Kondro *Panacea, India.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis.

KONDROnova *Panacea, Rus.*
Chondroitin sulfate (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Kondro-OD *Panacea, India.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

Konex *Serra Pamies, Spain.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Kongest *Eczacibasi, Turk.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Koni *Medial, India.*
Fluconazole (p. 578·2).
Fungal infections.

Konibalm *Konimex, Indon.†*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Konicortil *Koni-Cofarm, Chile.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Koniderm *Koni-Cofarm, Chile.*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Konidin *Konimex, Indon.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Konifungil *Koni-Cofarm, Chile.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Konigen *Konimex, Indon.†*
Gentamicin sulfate (p. 304·2).
Skin infections.

Konirub *Mepro, Chile.†*
Methyl nicotinate (p. 91·3); methyl salicylate (p. 92·1); benzocaine (p. 1980·2).
Musculoskeletal and joint disorders.

Konjunktival *Alcon, Hong Kong.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Conjunctivitis.

Konor *Italzama, Ital.*
Tar (p. 1723·3).
Seborrhoeic dermatitis.

Konor Fluid *Italzama, Ital.*
Barrier cream.

Konorderm *Italzama, Ital.*
Inositol (p. 2533·2); nicotinamide (p. 2083·1); vitamin E (p. 2119·1); betacarotene (p. 2051·1); selenium (p. 2086·3); L-cystine (p. 2059·1).
Antoxidant nutritional supplement.

Konovid *TO-Chemicals, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Konstitutin *Holsten, Ger.*
Siberian ginseng (p. 2614·3).
Tonic.

Konsyl *GSK, Arg.; Konsyl, China; Konsyl, Israel; Konsyl, USA.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; irritable bowel syndrome.

Konsyl-D *Konsyl, USA.*
Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation.

Kontagripp
Note: this name may be used for preparations of different composition.
Sandoz, Ger.†
Ibuprofen (p. 68·2).
Pain; fever.

Kontal *Etnovia, Fin.*
Niclosamide (p. 161·2).
Worm infections.

Kontic *Coup, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Kontil *Bilim, Turk.*
Pyrantel embonate (p. 165·3).
Ascariasis; oxyuriasis.

Kontrabat *Bernofarm, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1).
Cold symptoms; cough.

Kontrac *Fourrts, India.*
Misoprostol (p. 2140·3).
Peptic ulcer; termination of pregnancy.

Kontracept *Polfa Pabianice, Pol.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Kontratex *Mosfarma, Rus.*
Benzalkonium chloride (p. 1737·1).

Kontroger *Streger, Mex.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Kontryhelová Nať *Megafyt-R, Cz.*
Parsley piert (p. 2584·1).
Diarrhoea; menstrual disorders; menopausal disorders; inflammation of skin and mucous membranes; wounds.

Konverge *Menarini, Irl.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Konverge Plus *Menarini, Irl.*
⊗Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Konveril *Nobel, Turk.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Konveril Plus *Nobel, Turk.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Konvermex *Konimex, Indon.†*
Pyrantel embonate (p. 165·3).
Worm infections.

Konyne *Biem, Turk.†*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Konzol *Kalpataru, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Konzol-D *Kalpataru, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Koolnox *Charoen, Thai.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Deltapharm, Hong Kong.†
⊗Chlorphenamine (p. 620·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Koolzon *Hufort, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Kooz *Kinds, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Kopamex *Konimex, Indon.†*
Povidone-iodine (p. 1767·1); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Fungal skin infections.

Kopaq *Kocsel, Turk.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Kopen *Athlone, Irl.*
Phenoxymethylpenicillin potassium (p. 338·3).
Gram-positive bacterial infections.

Kopiryna *Medicofarma, Pol.†*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Kopodex *Drugtech, Chile.*
Levetiracetam (p. 531·1).
Epilepsy.

Koprak *Tocogino, Mex.*
Ketorolac (p. 80·2).
Pain.

Kopřivový Čaj *Megafyt-R, Cz.*
Urtica (p. 2639·3).
Urinary-tract disorders; rheumatic disorders.

Koptilan *Coup, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Koptin *Chinoin, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Korandil
Note: this name may be used for preparations of different composition.
Remedica, Singapore; Remedica, Thai.
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Sun, India.
Nicorandil (p. 1446·2).
Angina pectoris.

Kordexa *Kocak, Turk.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Kordobis *Pliva, Cz.†*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Korec *Sanofi-Aventis, Fr.†*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Kored *Dey's, India.*
Phenylmercuric nitrate (p. 1765·2); sodium chloride (p. 1795·1).

Kořen Puškvorce *Leros, Cz.†*
Calamus (p. 2464·2).
Dyspepsia; anorexia; gastrointestinal spasm; diarrhoea; inflammation of the mouth and throat.

Koretic *Sanofi-Aventis, Fr.†*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Korgivit-E *Diamond, Philipp.†*
Vitamin E (p. 2119·1); bee pollen (p. 2593·3); ginseng (p. 2513·3); lecithin (p. 2542·2); calcium pantothenate (p. 2085·2).
Tonic.

Korifen *Collins, Mex.†*
Dipyrone (p. 53·3); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Cold and influenza symptoms.

Korint *Sanovel, Turk.*
Memantine hydrochloride (p. 393·1).

Korisma *Cratus, India.*
Aloe vera (p. 1693·2); jojoba oil; wheat-germ oil (p. 2647·1).

Korlym *Corcept, USA.*
Mifepristone (p. 2138·1).
Cushing's syndrome.

Kormakin *One Pharma, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Kornam *Lek, Cz.; Sandoz, Pol.; Sandoz, Rus.; Lek, Ukr.†*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Korodin *Robugen, Austria; Robugen, Ger.*
Camphor (p. 2466·2); crataegus (p. 2488·1).
Cardiovascular disorders.

Korolinda *Robugen, Ger.*
Crataegus (p. 2488·1); camphora (p. 2466·2).
Homoeopathic preparation.

Koronatera *Dao-Pharm, Ukr.*
Ligusticum chuanxiong; borneol (p. 2460·2).
Angina pectoris; nitrate intolerance; vegetative dystonia; anxiety; premenstrual syndrome; menopausal disorders.

Koro-Nyhadin *Robugen, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Korovit Kreislauf *Robugen, Ger.*
Camphor (p. 2466·2).
Hypotension.

Korseng *Self-Care Products, UK.*
Ginseng (p. 2513·3).

Korsolex AF *Bode, Ger.*
N-Dodecylpropan-1,3-diamine (p. 1759·2); laurylamine dipropylenediamine (p. 1759·2).
Instrument disinfection.

Korsolex basic *Bode, Ger.*
Glutaral (p. 1753·2); dihydroxydioxahexane (p. 1750·3).
Instrument disinfection.

Korsolex Extra *Bode, Ger.*
Dihydroxydioxahexane (p. 1750·3); glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1); didecyldimethylammonium chloride (p. 1750·3).
Instrument disinfection.

Korsolex FF *Bode, Ger.*
Glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1); didecyldimethylammonium chloride (p. 1750·3).
Instrument disinfection.

Korsolex Plus *Bode, Ger.*
Laurylamine dipropylenediamine (p. 1759·2); didecyldimethylammonium chloride (p. 1750·3).
Instrument infection.

Korsolex-Endo-Disinfectant *Bode, Ger.*
Glutaral (p. 1753·2).
Disinfection of endoscopes.

Kortezor *Biomedis, Philipp.*
Ketorolac trometamol (p. 80·2).
Pain.

Kortikoid-ratiopharm *Ratiopharm, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Kortisetin *Bilim, Turk.*
⊗Prednisolone (p. 1645·2); clioquinol (p. 273·1).
Inflammatory eye disorders.

Kortos *Embil, Turk.*
Cream: ⊗Hydrocortisone acetate (p. 1640·1); benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1); bismuth subgallate (p. 1822·1).
Haemorrhoids.

Embil, Turk.
Suppositories: ⊗Hydrocortisone acetate (p. 1640·1); lauromacrogol 400 (p. 2194·1).
Haemorrhoids.

Korylan *Zentiva, Cz.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Kosamine *Siam Bheasach, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Kososan *Tsumura, Jpn.*
Cyperus rhizome; perilla herb; citrus unshiu peel; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Kostal *Royal, Chile.†*
Cilostazol (p. 1337·1).
Intermittent claudication.

Kostalerg *Rafarm, Gr.*
⊗Propranolol hydrochloride (p. 1479·1).

Kosteo *Aspen, Austral.*
Calcitriol (p. 2113·1).
Hypocalcaemia; osteoporosis.

Kotamin *CCM, Malaysia.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Kotor Articulations *Kotor, Fr.*
Javanese turmeric (p. 2636·2); vitamin E (p. 2119·1); vitamin C (p. 2110·3); linseed oil (p. 2544·2); fish oil (p. 1460·1); pepper; rosemary (p. 2607·2).
Dietary supplement; joint disorders.

Kotor Meno *Kotor, Fr.*
Soya (p. 2092·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); perslane oil.
Dietary supplement; menopausal disorders.

Kou Tai *Nanyue, China.*
Chlorhexidine (p. 1743·2).

Koujin *Tsumura, Jpn.*
Red ginseng (p. 2513·3).
Traditional Kampo medicine.

Kovan *Laboratorios Chile, Chile.*
Vancomycin (p. 384·2).
Gram-positive bacterial infections.

Kovia *Stratus, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3).

Kovilen *Mediolanum, Ital.*
Nedocromil sodium (p. 1216·2).
Ocular hypersensitivity reactions.

Kovinal *Mediolanum, Ital.*
Nedocromil sodium (p. 1216·2).
Allergic rhinitis.

Koviran *Kolson's, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Kovitox *In Vitro, Hung.*
Cobra venom; crotalus viridis toxin (p. 2419·1); vipera russellini toxin; arnica (p. 2447·2).
Musculoskeletal and joint stiffness.

Kovotherm *Anpharm (Ανφαρμ), Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Koxcure *Akums, India.*
Ambroxol hydrochloride (p. 1654·3); acetylcysteine (p. 1652·2).

Koxi *Shreya, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Kozec *Han Seo, Philipp.*
Ketoconazole (p. 585·3).
Fungal skin, hair, and nail infections.

Kozifed *Servocare, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Kozlik *Kneipp, Cz.*
Valerian (p. 2640·2).
Nervous disorders.

Kozoksin *Biokem, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

Kozole *Brawn, India.*
Fluconazole (p. 578·2).
Fungal infections.

Kozylex *IWA, Irl.; Apothecon, Neth.†*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

KP *PP Lab, Thai.*
Phytomenadione (p. 2122·2).
Haemorrhagic disorders.

KP-12 *Kalpataru, India.*
Vitamin B substances (p. 2102·3).

K-Pain *Darya-Varia, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Kpeitton *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Mefenamic acid (p. 85·3).

K-Pek II *Rugby, USA.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

K-Phos MF *Beach, USA.*
Monobasic potassium phosphate (p. 1790·3); monobasic sodium phosphate (p. 1791·1).
Urinary acidification.

K-Phos Neutral *Beach, USA.*
Dibasic sodium phosphate (p. 1791·2); monobasic potassium phosphate (p. 1790·3); monobasic sodium phosphate (p. 1791·1).
Phosphorus supplement.

K-Phos No.2 *Beach, USA.*
Monobasic potassium phosphate (p. 1790·3); monobasic sodium phosphate (p. 1791·1).
Urinary acidification.

K-Phos Original *Beach, USA.*
Monobasic potassium phosphate (p. 1790·3).
Urinary acidification.

K-Pio *Blue Cross, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

K-Pio-G *Blue Cross, India.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1).
Diabetes mellitus.

K-Pio-M *Blue Cross, India.*
Metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

KPM *Kalpataru, India.*
Cefepime (p. 239·2).
Bacterial infections.

KPN *Freeda, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

KP-Plegia *VHB, India.*
Magnesium (p. 1786·3); potassium (p. 1793·1); procaine (p. 1994·3).
Induction of cardioplegia in open-heart surgery.

K-Profen *Medix, Mex.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders.

KPT *Keshav, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Krabinex *Korea United, Philipp.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms.

Krallendorn *Immodal, Austria.*
Uncaria tomentosa.
Rheumatoid arthritis.

Krama
Note: this name may be used for preparations of different composition.
Duncan, Arg.
Alprazolam (p. 1035·2).
Anxiety.
Miba, Ital.†
Barrier cream.

Kramerin *Demo, Gr.*
Chloramphenicol palmitate (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Kramollex *Kramer, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Kramon *Kramer, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Krampdruppels *Aspen Consumer, S.Afr.*
Valerian (p. 2640·2); lavender (p. 2541·1); solvent ether (p. 2212·3).
Nervous disorders; colic; flatulence.

Kranos *Nufarindo, Indon.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Krashaemodes *Krasfarma, Rus.*
Povidone (p. 2204·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); sodium bicarbonate (p. 1781·1); magnesium chloride (p. 1787·1).
Shock; toxaemia; pre-eclampsia.

Krasule *Kalpataru, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Kratalgin *Kwizda, Austria.*
Ibuprofen (p. 68·2).
Pain.

Kratium *Medochemie, Hong Kong.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; premedication; skeletal muscle spasm; sleep disorders; febrile convulsions; spasticity; status epilepticus.

Kratol *Molekule, India.*
⊗Mannitol (p. 1427·3); glycerol (p. 2517·2).

Kräuterlax *Dolorgiet, Ger.*
Aloes (p. 1816·1).
Constipation.

Krautin *Pharmanel, Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Kreasim *Tekhnolog, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Krebs *Sigma, Arg.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Nutritional supplement.

Krebs E *Sigma, Arg.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3).

Krebs Plus *Sigma, Arg.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); selenium (p. 2086·3); manganese (p. 2081·2); copper (p. 2057·1).
Macular degeneration; tonic.

Kredex *Roche, Austral.†; Roche, Belg.; Roche, Fr.; Roche, Swed.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Kredit *Royal, Chile.*
Levetiracetam (p. 531·1).
Epilepsy.

Kremezin *Mitsubishi Tanabe, Jpn.*
AST-120 (p. 1541·1).
Renal failure.

Kremil *Great Eastern, Thai.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity.

Kremil-S
Note: this name may be used for preparations of different composition.
Great Eastern, Thai.
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); simeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal disorders.
United Laboratories, Philipp.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Krenosin *Sanofi-Aventis, Fr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Krénosine *Sanofi-Aventis, Switz.*
Adenosine (p. 1291·1).
Supraventricular tachycardia.

Kreon *Abbott, Austria; Abbott, Cz.; Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; Abbott, Ger.; Solvay, Hung.; Orifarm, Norw.; Abbott, Pol.; Abbott, Port.; Solvay, Rus.; Abbott, Spain; Frik, Turk.; Abbott, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders.

Kreosotum Complexe No 62 *Lehning, Fr.*
Kreosotum (p. 1659·3); chelidonium (p. 2522·2); terebinthina; stannum (p. 2632·1); silicea (p. 2208·3).
Homoeopathic preparation.

Krestin *Daiichi Sankyo, Jpn.*
Polysaccharide-K (p. 2594·1).
Malignant neoplasms.

Kretos *Glenmark, India.*
Etoricoxib (p. 57·3).
Gout; osteoarthritis; rheumatoid arthritis; pain.

Kreval *Frik, Turk.*
Butamirate citrate (p. 1657·3).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kriadex *Psicofarma, Mex.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder; obsessive-compulsive disorder; anxiety; mania; alcohol withdrawal syndrome.

Krimbeson *Nufarindo, Indon.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Krimson *Sun, India.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Krinolis *Actavis, Denm.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Krinuven *Fresenius Kabi, Ital.*
Amino acids; glucose (p. 2068·3); lipid; with or without electrolytes (p. 1775·1).
Contains egg phospholipids.
Parenteral nutrition.

Kriolen *Rafarm, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Kriomelt *Alfatreid, Rus.*
Honey (p. 2072·1).

Kripti *Lincoln, India.*
Bromocriptine (p. 895·3).
Parkinsonism; hypogonadism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Kriptiser *Serral, Mex.†*
Bromocriptine (p. 895·3).

Kripton *Alphapharm, Austral.*
Bromocriptine mesilate (p. 895·3).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism.

Kriptonal *Chemopharma, Chile.*
Bromocriptine (p. 895·3).
Acromegaly; benign breast disorders; female infertility; hyperprolactinaemia; lactation inhibition; menstrual disorders; parkinsonism; prolactinomas.

Krisovin *CCM, Malaysia; Beacons, Singapore.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Kristalose *Bertek, USA.*
Lactulose (p. 1850·3).
Constipation.

Kristapen *Deva, Turk.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Kristasil *Bilim, Turk.*
Benzylpenicillin (p. 228·1).
Bacterial infections.

Krisxon *Sons, Mex.*
Trimebutine (p. 2634·1).
Gastrointestinal motility disorders.

Kritel *Monserrat, Arg.*
Sodium picosulfate (p. 1887·2).
Bowel evacuation; constipation.

Kritel Enema *Monserrat, Arg.*
Sodium phosphate (p. 1791·1).
Bowel evacuation.

Krobicin *Mavi, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Kroko *Allied Drug, S.Afr.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Corns; calluses; warts.

Kronoderm *Rafarm, Gr.*
Sulfabenzamide (p. 360·3); sulfathiazole (p. 368·3); sulfacetamide (p. 361·1).
Vaginal infections.

Kronofed-A *Ferndale, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Kronys *Formenti, Ital.*
Macrogol 4000 (p. 2547·3).
Constipation.

Kropanol *Sintez, Rus.†*
Pantogematogen (deer antler velvet).
Tonic; asthenia.

Krople Żołądkowe *Aflofarm, Pol.; Farmina, Pol.; Hasco-Lek, Pol.; Herbapol Krakow, Pol.*
St John's wort (p. 449·1); peppermint leaf (p. 1877·1); tinctura amara; valerian (p. 2640·2).
Digestive disorders.

Herbapol Lublin, Pol.
St John's wort (p. 449·1); peppermint leaf (p. 1877·1); tinctura amara (absinthium (p. 2426·1), menyanthes (p. 2554·2), bitter orange (p. 2575·3), calamus (p. 2464·2)); valerian (p. 2640·2); propyphenazone (p. 127·3).
Gastrointestinal disorders.

Farmina, Pol.†
St John's wort (p. 449·1); peppermint leaf (p. 1877·1); tinctura amara (absinthium (p. 2426·1), menyanthes (p. 2554·2), bitter orange (p. 2575·3), calamus (p. 2464·2)); valerian (p. 2640·2); propyphenazone (p. 127·3); allobarbital (p. 1035·2).
Digestive disorders.

Krovaneg *Italchimici, Ital.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

KRRT *Knop, Chile.*
Nopal.
Alcoholism.

Krucef *Krugher, Ital.†*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Krudipin *Krugher, Ital.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Kruidvat *Marel, Neth.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain; fever.

Kruidvat Antischimmelcreme *Marel, Neth.*
Miconazole nitrate (p. 589·1).
Candidiasis of the skin and nails.

Kruidvat Antischimmelpoeder *Marel, Neth.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Kruidvat Anti-worm *Marel, Neth.*
Mebendazole (p. 158·3).
Worm infections.

Kruidvat APC *Marel, Neth.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Kruidvat Diarreeremmer *Marel, Neth.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Kruidvat Hoestdrank Broomhexine *Marel, Neth.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Kruidvat Hoestdrank Noscapine *Marel, Neth.*
Noscapine hydrochloride (p. 1670·3).
Cough.

Kruidvat Hoestelixer *Pharmethica, Neth.†*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Kruidvat Hoesttabletten Acetylcysteine *Marel, Neth.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Kruidvat Hoesttabletten Broomhexine *Marel, Neth.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Kruidvat Homeopathie Bzzz *Schwabe, Neth.†*
Echinacea pallida (p. 2498·1); ledum palustre (p. 2550·1).
Homoeopathic preparation.

Kruidvat Homeopathie Influ-complex *Schwabe, Neth.†*
Aconitum napellus (p. 2428·3); bryonia cretica; eucalyptus globulus (p. 2501·1); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirans (p. 2511·2).
Homoeopathic preparation.

Kruidvat Homeopathie Meno *Schwabe, Neth.†*
Cimicifuga racemosa (p. 2478·1).
Homoeopathic preparation.

Kruidvat Homeopathie Nachtrust *Schwabe, Neth.†*
Coffea cruda (p. 2648·2).
Homoeopathic preparation.

Kruidvat Homeopathie Neusspray *Schwabe, Neth.†*
Allium cepa (p. 2575·2); kalium iodatum (p. 2336·3); luffa operculata (p. 2545·3); pulsatilla pratensis (p. 2600·2); silicea (p. 2208·3).
Homoeopathic preparation.

Kruidvat Homeopathie Spier- en gewrichtsgel *Schwabe, Neth.†*
Ledum palustre (p. 2550·1); symphytum officinale (p. 2484·2).
Homoeopathic preparation.

Kruidvat Hooikoortstabletten *Marel, Neth.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Kruidvat Hydrogel *Marel, Neth.*
Benzoyl peroxide (p. 1696·1).
Acne.

Kruidvat Koortslipcreme *Pharmethica, Neth.*
Aciclovir (p. 964·1).
Herpes labialis.

Kruidvat Laxeerdrank *Marel, Neth.*
Lactulose (p. 1850·3).
Constipation.

Kruidvat Laxeertabletten *Marel, Neth.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Kruidvat maagzuuremmer Omeprazole *Marel, Neth.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Kruidvat maagzuurremmer ranitidine *Marel, Neth.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity.

Kruidvat Neusdruppels *Healthypharm, Neth.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Kruidvat PPC *MAE, Neth.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain.

Kruidvat Reistabletten *Pharmethica, Neth.†*
Cyclizine hydrochloride (p. 623·2).
Motion sickness; nausea and vomiting.

Kruidvat Spierbalsem *MAE, Neth.*
Capsicum (p. 2469·3); glycol salicylate (p. 66·2); histamine hydrochloride (p. 2525·2); methyl nicotinate (p. 91·3).
Musculoskeletal and joint pain.

Krusade *Kalpataru, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Kruses Fluid Magnesia *Felton, Austral.*
Magnesium bicarbonate.
Gastric hyperacidity; magnesium deficiency.

Krust *Biosciences Pharmakon, India.*
Hydroxyzine (p. 630·3).
Anxiety; pruritus; premedication.

Krustat *Krugher, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Kruxade *Krugher, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Kruxagon *Krugher, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Kruzin *Krugher, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Kryptocur *Sanofi-Aventis, Austria; Sanofi-Aventis, Ger.; Sanofi-Aventis, Ital.*
⊗Gonadorelin (p. 2280·2).
Cryptorchidism.

Sanofi-Aventis, Switz.†
⊗Gonadorelin acetate (p. 2280·3).
Cryptorchidism.

KryptoScan *Mallinckrodt, Cz.; Mallinckrodt, Irl.; Mallinckrodt, Neth.*
Krypton-81m (p. 2226·3).
Diagnosis of pulmonary embolism; radionuclide lung studies.

Krystexxa *Savient, USA.*
Pegloticase (p. 609·1).
Gout.

Krytantek *Sophia, Mex.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2); brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

K-Sein *Nucitec, Mex.*
Calcium caseinate (p. 2055·2).
Dietary supplement.

Ksenakvin *Promed, Rus.; ProMed, Ukr.†*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

K-sept *Concept, Israel.*
Troclosene sodium (p. 1774·1).
Formerly known as Klorsept.
Disinfection of equipment, surfaces, and water.

Ksilidin *Biosel, Turk.*
Lidocaine (p. 1988·1).
Local anaesthesia.

K-sorb *Concept, Israel.*
Troclosene sodium (p. 1774·1).
Adsorption of biohazard.

KSR *Alphapharm, Hong Kong; Merck, Indon.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

K-Tab *Abbott, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

KTC *Yash, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

K-Thrombin *Sigma, NZ.†*
Menadione sodium bisulfite (p. 2122·2).
Prothrombin deficiency; vitamin K deficiency.

KTM *Guardian, Indon.*
Ketamine (p. 1905·1).
General anaesthesia; pain.

K-Trip *FDC, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

K-Trip Plus *FDC, India.*
⊗Chymotrypsin (p. 2477·3); diclofenac potassium (p. 48·3); trypsin (p. 2635·2).

K-Tron *Karnataka, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ku Sen *Kang Yuan, China.*
Oxymatrine.

Ku Shu *KeRui, China.*
Oxymatrine.

Ku Xin *Xincat, China.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Kuai Di *Hayao, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Kuai Li *Lunan, China.*
Mosapride citrate (p. 1865·2).

Kuai Wu You *Open, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Kuai Yu *LuoXin, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Kucil *Khandelwal, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Kudamin *Shince, India.*
Oral drops: Vitamins; zinc sulfate (p. 2126·2).

Shince, India.
Syrup: Vitamins; copper sulfate (p. 2057·2); lysine hydrochloride (p. 2079·3).

Shince, India.
Tablets: Vitamins; minerals.

Kudamin Gold *Shince, India.*
Vitamins; minerals; amino acids.

Kudox *Rishab, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Kudzu *Vilberry, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Kuff-D *Intas, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylpropanolamine (p. 1674·1).

Kuffdac *Daksh, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Kuffdac-C *Daksh, India.*
Cetirizine (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylpropanolamine hydrochloride (p. 1674·1).

Kuffdryl *Intas, India.*
Capsules: Diphenhydramine (p. 626·1).
Hypersensitivity reactions; motion sickness.

Intas, India.
Syrup: Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1).

Kuffex DM *Perrigo, Israel.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Kuff-Q *Intas, India.*
Syrup: ⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Intas, India.
Tablets: Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Kuff-X *Intas, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Kufgen-D *Genesis, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1).

Kufgen-X *Genesis, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Kufkair *PDC, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Kufkair-P *PDC, India.*
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

PDC, India.
Tablets: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Kufma *Wings, India.*
⊗Ammonium chloride (p. 1656·1); citric acid (p. 2480·3); diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2); sodium citrate (p. 1781·2).

Kufnil-A *Zodak, India.*
Ambroxol (p. 1654·3); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Kufnil-D *Zodak, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).

Kufol-Z *Genesis, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Kufro *Andromaco, Mex.†*
Nitrofurazone (p. 333·1).
Cervicitis; vaginitis.

Kühlprednon *Gerot, Austria.*
⊗Prednisolone (p. 1645·2).
Skin disorders.

Kui An *Sanhome, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Kui Er Tai *Wan Long, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Kui Jian *Otsuka, China.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Kui Ke *Huaxin, China.*
Cefixime (p. 240·3).
Bacterial infections.

Kui La Lan *Anlian, China.*
Dexketoprofen trometamol (p. 79·1).

Kui Tai *Wan Long, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Kui Yan *Jingfang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Kui Yin *Sanhome, China.*
Loratadine (p. 633·2).

Kuiflex *Abdi, Turk.*
Phenprobamate (p. 1096·3); paracetamol (p. 115·1).
Skeletal muscle spasm.

Kuilil *Embil, Turk.*
Phenprobamate (p. 1096·3); paracetamol (p. 115·1).
Skeletal muscle spasm.

Kuinuoxian *Baiyunshan, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

KuiTai *Zhongjia, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Kulent-O *Hos & Ins, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Kulfi *Obsurge, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Kulinet *Rafarm, Gr.*
Cyproheptadine hydrochloride (p. 624·1).

Kull *Abigo, Norw.*
Activated charcoal (p. 1537·3).
Acute poisoning; diarrhoea.

Kuminta *Nufarindo, Indon.*
Curcuminoid; vitamin B substances (p. 2102·3); betacarotene (p. 2051·1); lysine hydrochloride (p. 2079·3); bovine colostrum (p. 2380·3); docosahexaenoic acid (p. 1460·1); glutamic acid (p. 2070·2).
Tonic.

Kun Bai *Tai Sheng, China.*
Amoxicillin sodium (p. 216·2); flucloxacillin sodium (p. 299·2).
Bacterial infections.

Kun Bang *Wansheng, China.*
Disodium cytidine triphosphate (p. 2491·1).

Kun Da *Linhai, China.*
Naftopidil (p. 2361·1).

Kun Li Yu *Taiyang, China.*
Omeprazole (p. 1867·2).

Kun Ning *Guodi, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Kun Te *Hisun, China.*
Flucloxacillin sodium (p. 299·2).
Staphylococcal infections.

Kundo-V *Admac, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Kunstig Tårevæske *Ophtha, Norw.†*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Kuo Shu *Bei Da Gao Ke Hua Tai, China.*
Papaverine hydrochloride (p. 2362·3).

Kupa *M & H, Thai.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Kurab *Rishab, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Kurab-D *Rishab, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Kuracid *Sandoz, Denm.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux.

Kuramed *Cimed, Braz.*
Lidocaine (p. 1988·1); benzalkonium chloride (p. 1737·1).

Kurapel *Ivax, Arg.*
Silicone oil (p. 2209·3).
Barrier preparation.

Kürbin *Melisana, Switz.†*
Cucurbita oil (p. 2489·2).
Nutritional supplement.

Kurdase Plus *Rishab, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Kurdase-D *Rishab, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Kurecal-CZ *Rishab, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Kurecet *Rishab, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Kurecet-M *Rishab, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Kurecip *Rishab, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Kurecip-TZ *Rishab, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Kureflox *Rishab, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Kureflox-OZ *Rishab, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Kurelam-F *Rishab, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

Kurepane *Rishab, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kurepane-D *Rishab, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Kurgan *Normon, Port.†; Normon, Spain.*
Cefazolin sodium (p. 237·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Kuril *Copyfarm, Denm.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Kuriosin *Gedeon Richter, Ukr.*
Topical gel: Zinc hyaluronate (p. 2526·2); zinc chloride (p. 2126·1).
Acne.

Gedeon Richter, Ukr.
Topical solution: Zinc hyaluronate (p. 2526·2).
Wounds; ulcers; fistulas.

Kuroment *Ratiopharm, Cz.†*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Kurovent *Italchimici, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Kursept *Orva, Turk.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Kurvelo *Lupin, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Kuterid *Lek, Cz.; Sandoz, Pol.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Kutesan *Plurisystem, Ital.*
Emollient.

Kutoin *Mersifarma, Indon.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Kutrase *Schwarz, USA.†*
Lipase (p. 2579·3); amylase (p. 2442·1); protease (p. 2598·1).
Functional dyspepsia devoid of organic pathology (nervous dyspepsia).

Kuvan *Merck Serono, Austral.; Merck, Austria; Merck, Belg.; BioMarin, Canad.; Merck Serono, China; Merck, Cz.; Merck, Denm.; Merck Serono, Fr.; Merck Serono, Ger.; Merck, Gr.; Merck, Hung.; Merck Serono, Irl.; Merck Serono, Israel; Merck, Neth.; Merck, Norw.; Healthcare Logistics, NZ; Merck, Pol.; Merck, Port.; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck Serono, UK; BioMarin, USA.*
Sapropterin hydrochloride (p. 2610·2).
Hyperphenylalaninaemia.

Ku-Zyme *Schwarz, USA.†*
Lipase (p. 2579·3); amylase (p. 2442·1); protease (p. 2598·1).
Functional dyspepsia due to enzyme deficiency or imbalance.

Ku-Zyme HP *Schwarz, USA.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Kventiax *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; psychoses.

KVI *Dewcare, India.*
Vitamin K (p. 2122·1).

Kvilla *ACO Hud, Fin.*
Quillaia (p. 2207·1); ammonium chloride (p. 1656·1).
Cough.

KW *Lagos, Arg.*
Aloe vera (p. 1693·2); camphor (p. 2466·2); mallow (p. 2549·2); chamomile (p. 2474·1); vitamin F (p. 2509·2).
Pruritus.

Kwai *Klosterfrau, Austria; Cassella-med, Ger.; Solvay, Ital.; Lichtwer, UK.*
Garlic (p. 2510·3).
Atherosclerosis; dietary supplement.

Kwelcof *Ascher, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Kwell
Note: this name may be used for preparations of different composition.
GSK, Arg.; GSK, Braz.
Permethrin (p. 2159·3).
Pediculosis.

Kwell Reformulated *GSK, Philipp.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Kwellada
Note: this name may be used for preparations of different composition.
Ali, Turk.
Permethrin (p. 2159·3).
Scabies; pediculosis.

Kwellada-P *Prestige, Canad.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Kwell-P *Ali, Turk.*
Pyrethrin (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Kwells
Note: this name may be used for preparations of different composition.
Bayer Consumer, Austral.; Bayer, Irl.; Bayer, UK.
Hyoscine hydrobromide (p. 1845·3).
Motion sickness.

Kwetaplex *Adamed, Neth.; Adamed, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Kwetinor *Lek, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Kwinil *Intas, India.*
Quinine dihydrochloride (p. 665·1) or quinine sulfate (p. 665·2).
Malaria; nocturnal leg cramps.

KxG *Concept, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Catheter disinfection.

Kxime *Kalpataru, India.*
Cefixime (p. 240·3).
Bacterial infections.

Kxone-SL *Kalpataru, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

K-Y *Johnson & Johnson, Arg.; Johnson & Johnson, Chile; Polive, Fr.†; Johnson & Johnson, Israel; Johnson & Johnson, Ital.; Johnson & Johnson, NZ.*
Lubricating gel.
Vaginal lubricant; lubrication of mucous membranes and instruments; catheterisation; endoscopy.

Johnson & Johnson, India.
Lubricating jelly.
Rectal and vaginal lubrication.

Johnson & Johnson, UK.
Lubricating gel for vaginal and rectal use.

Johnson & Johnson, USA.
Vaginal lubricant.

K-Y-6 *Bruluart, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Kybernin *CSL, Ger.; CSL, Switz.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Kybernin P *CSL, Arg.; CSL, Austria; CSL, Braz.; CSL, Cz.; CSL, Gr.; CSL, Hung.; CSL, Indon.; Dexa, Indon.; CSL, Ital.; CSL, Port.; CSL, Spain; Farma-Tek, Turk.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency; disseminated intravascular coagulation.

Kydrot *Kaizen, India.*
Drotaverine (p. 2497·3).
Antispasmodic.

Kyflam *Actavis, Irl.*
Diclofenac potassium (p. 48·3).
Pain; inflammation; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Kylevo *Kaizen, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Kylevo-OZ *Kaizen, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Kylipram *Balu, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Kylotan *Gedeon Richter, Cz.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction.

Kylotan Plus H *Gedeon Richter, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Kymazol *Rafarm, Gr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Kymovil Plus *Vilberry, India.*
⊗Chymotrypsin (p. 2477·3); diclofenac potassium (p. 48·3); trypsin (p. 2635·2).

Kynamro *Genzyme, USA.*
Mipomersen sodium (p. 1440·1).
Familial hypercholesterolaemia.

Kynapine *Medochemie, Denm.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Kyolic *Quest, Malaysia; Birger Ledin, Swed.; Quest, UK.*
Garlic (p. 2510·3).
Cold symptoms; dietary supplement.

Kyolic 101 *Quest, Canad.†*
Garlic (p. 2510·3); brewers yeast (p. 2125·2); kelp (p. 2612·1).

Kyolic 102 *Quest, Canad.†*
Garlic (p. 2510·3); enzyme complex; rice protein complex.

Kyolic Formula 103 *Purity Health, Canad.†*
Calcium ascorbate (p. 2111·1).
Dietary supplement.

Kyolic Formula 106 *Purity Health, Canad.†*
d-Alpha tocoferil acid succinate (p. 2119·2).

Kyprolis *Onyx, USA.*
Carfilzomib (p. 760·3).
Multiple myeloma.

Kyrin *Silom, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Kytinon ABC *Asmopul, Arg.*
Lidocaine (p. 1988·1); porcine skin (p. 1720·2); polysaccharides.
Mouth disorders.

Kytinon ATM *Asmopul, Arg.*
Porcine skin (p. 1720·2); mucopolysaccharides; chloroxylenol (p. 1748·2).
Wounds.

Kytinon Hemostatico *Asmopul, Arg.*
Porcine skin (p. 1720·2).
Burns; skin grafts.

Kytinon Kit *Asmopul, Arg.*
Porcine skin (p. 1720·2).
Wounds.

Kytinon Lamina *Asmopul, Arg.*
Porcine skin (p. 1720·2).
Burns.

Kytinon Q4 *Asmopul, Arg.*
Porcine skin (p. 1720·2).
Wounds.

Kytril *Hospira, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.†; Roche, Fin.; Roche, Fr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; GSK, NZ†; Roche, Philipp.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA†; Roche, Venez.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Kytta *Bracco, Ital.*
Comfrey root (p. 2484·2).
Musculoskeletal, joint, and soft-tissue disorders.

Kytta Baume *Iromedica, Switz.†*
Comfrey (p. 2484·2); methyl nicotinate (p. 91·3).
Musculoskeletal pain.

Kytta Pommade *Iromedica, Switz.*
Comfrey (p. 2484·2).
Musculoskeletal pain; wounds; soft-tissue injury.

Kytta-Balsam f *Merck, Ger.*
Comfrey (p. 2484·2); methyl nicotinate (p. 91·3).
Musculoskeletal, joint, and soft-tissue disorders; local circulatory disorders.

Kytta-Plasma f *Merck, Ger.*
Comfrey (p. 2484·2).
Soft-tissue disorders.

Kytta-Salbe f *Merck, Ger.*
Comfrey (p. 2484·2).
Soft-tissue disorders.

Kytta-Sedativum *Merck, Ger.*
Tablets: Valerian (p. 2640·2); lupulus (p. 2546·1); passion flower (p. 2584·1).
Agitation; sleep disorders.

Merck, Ger.†
Oral drops: Valerian (p. 2640·2).
Agitation; sleep disorders.

Kytta-Sedativum für den Tag *Merck Selbstmedikation, Ger.*
Passion flower (p. 2584·1).
Nervous disorders.

Kyucal *Nichi-Iko, Jpn.*
AST-120 (p. 1541·1).
Renal failure.

Kyukikyogaito *Tsumura, Jpn.*
⊗Rehmannia root; peony root; angelica acutiloba root (p. 2443·3); liquorice (p. 1853·2); cnidium rhizome; gelatin (p. 1154·1); artemisia leaf.
Traditional Kampo medicine.

Kyypakkaus *Orion, Fin.*
⊗Hydrocortisone (p. 1640·1).
Snake bites; bee and wasp stings.

KZ *H & H, India.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Kzidime *Kalpataru, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

KZL *Solitaire, India.*
Ketoconazole (p. 585·3).
Fungal infections.

L-5 *Solitaire, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

L-30 *Brawn, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

L 8 *Lehning, Fr.*
Acide benzoicum (p. 1738·2); ononis spinosa (p. 2575·3); coccus cacti (p. 2179·2); hexaminum (p. 322·3); herniaria glabra (p. 2525·1); atropa belladonna (p. 2453·3); colchicum (p. 607·1); apocynum cannabinum; solidago (p. 2620·1); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

L 25 *Lehning, Fr.*
⊗Viscum album (p. 2560·2); hydrastis canadensis (p. 2528·1); gossypium; secale cornutum (p. 2137·1); adrenalinum (p. 1292·1); senecio (p. 2612·3); aloe (p. 1816·1); chamomilla (p. 2474·1); china rubra (p. 2478·3); cuprum sulfuricum (p. 2057·2); cimicifuga (p. 2478·1); magnesia muriatica (p. 1787·1); calcarea hypophosphorica (p. 2530·3).
Homoeopathic preparation.

L 28 *Lehning, Fr.*
⊗Hamamelis virginiana (p. 2523·3); china rubra (p. 2478·3); adrenalinum (p. 1292·1); secale cornutum (p. 2137·1); vinca minor; clematis; hydrastis canadensis (p. 2528·1); carduus marianus (p. 1561·1); trillium pendulum; calcarea muriatica (p. 1783·1).
Homoeopathic preparation.

L 52 *Lehning, Fr.*
Eupatorium perfoliatum (p. 2459·1); aconitum napellus (p. 2428·3); bryonia alba; arnica montana (p. 2447·2); gelsemium sempervirens (p. 2511·2); cinchona (p. 2478·3); atropa belladonna (p. 2453·3); drosera (p. 2497·2); polygala senega (p. 1677·2); eucalyptus globulus (p. 2501·1).
Homoeopathic preparation.

L 72 *Lehning, Fr.*
Sumbulus; oleum gaultheriae (p. 92·1); cicuta virosa; asa foetida (p. 2449·3); corydalis formosa; ignatia (p. 2532·1); valeriana officinalis (p. 2640·2); staphysagria; avena sativa (p. 2451·1); hyoscyamus (p. 2530·2).
Homoeopathic preparation.

L 107 *Lehning, Fr.*
Cinchona succirubra (p. 2478·3); arsenicum album (p. 2448·1); bryonia (p. 2461·3); nux vomica (p. 2573·3); mercurius corrosivus (p. 2555·2); chamomilla (p. 2474·1); colocynthis (p. 1833·3); ipeca (p. 1667·2); belladonna (p. 2453·3); potentilla anserina.
Homoeopathic preparation.

L 114 *Lehning, Fr.*
Dolichos; nux vomica (p. 2573·3); lycopodium (p. 2546·3); amylium hydratum; leptandra; podophyllum peltatum (p. 1717·1); carduus marianus (p. 1561·1); chelidonium (p. 2522·2); peumus boldo (p. 2458·3).
Homoeopathic preparation.

L52 Cough & Cold *Homeocan, Canad.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); belladonna (p. 2453·3); china rubra (p. 2478·3); drosera (p. 2497·2); eucalyptus glob (p. 2501·1); eupatorium perfoliatum (p. 2459·1); gelsemium sempervirens (p. 2511·2); polygala senega (p. 1677·2).
Homoeopathic preparation.

La Edad De Oro *Cinetic, Arg.*
Evening primrose oil (p. 2502·2); borage oil (p. 2459·2); soya isoflavones (p. 2620·3); vitamin E (p. 2119·1).
Dietary supplement.

La Ke Fei *Jinma, China.*
Ferrous lactate (p. 2062·1).

LA Morph *Douglas, NZ.†*
⊗Morphine sulfate (p. 92·3).
Pain.

La Mu *Southwest, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

La pommade du Dr Brand *Baren-Apotheke, Switz.*
Zinc oxide (p. 1729·1); bismuth subnitrate (p. 1822·1).
Burns; wounds; skin irritation.

La Tez *Piramal, India.*
Tazarotene (p. 1724·2).
Psoriasis.

LAA *Bombay Tablet, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Laaglyda *Consilient, UK.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Labace *Hiral, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Labace-P *Hiral, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Labcaína *Pharlab, Braz.*
Lidocaine (p. 1988·1).

Labchlor *Laborate, India.*
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Labdec *Admac, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Labdiazina *Neves, Port.*
Sulfadiazine (p. 361·3).
Bacterial infections.

Labdic Relief *Laborate, India.*
Tablets: Chlorphenamine maleate (p. 620·3); diclofenac (p. 48·3); magnesium (p. 1786·3); paracetamol (p. 115·1).
Laborate, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Label *Ache, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Labelphen *Chrispa (Χρισπα), Gr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Labenda *Medicine Products, Thai.*
Albendazole (p. 149·1).
Worm infections.

Labentrol *Chrispa (Χρισπα), Gr.; SJA, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Labesol *Shree Ganesh, India.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension; controlled hypotension in anaesthesia.

Labestran *Chrispa (Χρισπα), Gr.*
Indometacin (p. 71·2).

Labeta *Geo, India.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension; controlled hypotension in anaesthesia.

Labetasol *Armedica, Gr.*
⊗Budesonide (p. 1625·1).

Labicef-S *Admac, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Labigeron *Teuto, Braz.*
Cinnarizine (p. 622·1).

Labil *Celon, India.*
⊗Labetalol or labetalol hydrochloride (p. 1416·2).
Hypertension; controlled hypotension in anaesthesia.

Labileno *GSK, Spain.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Labilex *Pharmathen, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Labimiq *Labomed, Chile.*
Imiquimod (p. 985·2).
Anogenital warts; actinic keratoses; basal cell carcinoma.

Labioline Plus *Qualiphar, Belg.†*
SPF 15: Eusolex; titanium dioxide (p. 1725·1).
Chapped lips; sunscreen.

Labirin *Apsen, Braz.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Labistatin *Sandoz, Arg.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Labistatin Duo *Sandoz, Arg.*
Simvastatin (p. 1489·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Labmet *Laborate, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; premedication.

Labmox *Laborate, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Labocaina *Combe, Ital.*
Benzocaine (p. 1980·2); resorcinol (p. 1718·3); chlorothymol (p. 1748·2).
Pruritus.

Labocane *Combe, Ger.†*
Benzocaine (p. 1980·2).
Pruritus; eczema.

Labocef *Laborate, India.*
Cefixime (p. 240·3).
Bacterial infections.

Labocef-CV *Laborate, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Labocet *Laborate, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Laboceta *Laborate, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Labocip-TZ *Laborate, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Labocne *Labomed, Chile.†*
Erythromycin (p. 291·2).
Acne.

Labocof *Laborate, India.*
Syrup: Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).
Laborate, India.
Tablets: Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Labocort *Laborate, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Labocton *Viofar, Gr.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Labodrex *Meda, Spain.†*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Laboether *Laborate, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Laboflur *Laborate, India.*
Flurbiprofen sodium (p. 65·3).
Prevention of intra-operative miosis; postoperative eye inflammation.

Labolac *Laborate, India.*
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation, and photophobia following eye surgery; cystoid macular oedema.

Labomycin *Laborate, India.*
Clindamycin phosphate (p. 269·3).
Acne.

Labonac *Laborate, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Labopal *GSK, Spain.†*
Benazepril hydrochloride (p. 1314·3).
Heart failure; hypertension; renal failure.

Labopene-C *Laborate, India.*
Adapalene (p. 1692·1); clindamycin phosphate (p. 269·3).
Acne.

Laboplex *Laborate, India.*
Vitamin B substances (p. 2102·3); minerals.

Laboriodine *Biosintetica, Braz.†*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Labortina *Kleva, Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Labosalic *Labomed, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Labosept *Laboratories for Applied Biology, UK.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Labosol *Labomed, Chile.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Labosol-GM *Laborate, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole nitrate (p. 589·1).

Labosona *Labomed, Chile.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Labosona G *Labomed, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Labotensil *Labomed, Chile.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Labovita *Bionova, India.*
Vitamins.

Laboxantryl *Chrispa (Χρισπα), Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Labsa Otic *Labsa, Arg.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Ear infections.

Labsa Otic L *Labsa, Arg.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1); lidocaine (p. 1988·1).
Ear disorders.

Labsacalm *Labsa, Arg.*
Diphenhydramine (p. 626·1); calamine (p. 1697·2).
Skin irritation; pruritus.

Labsalerg-B *Labsa, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).

Labsamax *Labsa, Arg.*
Sildenafil (p. 2364·1).

Labscab *Laborate, India.*
Lindane (p. 2157·1).
Scabies; pediculosis.

Labsidex *Labsa, Arg.*
Ranitidine (p. 1882·1).

Labstix *Siemens, Canad.†; Bayer Diagnostics, Irl.†; Siemens, Ital.; Bayer Diagnostics, UK; Siemens, USA.*
Test for pH, protein, glucose, ketones, and blood in urine.

Labstix SG *Bayer Diagnostics, Irl.†; Bayer Diagnostics, UK.*
Test for pH, protein, glucose, ketones, blood, and specific gravity in urine.

Labsyna Caf *Labsa, Arg.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Fever; inflammation; pain.

Labsyna Fem *Labsa, Arg.*
Ibuprofen (p. 68·2); hyoscine butylbromide (p. 1845·3).

Labtocin *Laborate, India.*
Oxytocin (p. 2143·1).
Termination of pregnancy; postpartum haemorrhage; labour induction; evaluation of fetal distress.

Laburide *Kela, Belg.*
Pheneturide (p. 535·2).
Epilepsy.

Labxone *Hiral, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Labxone-SB *Hiral, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Labzone *Admac, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Lac Stop *Rontag, Arg.*
Cabergoline (p. 899·3).
Hyperprolactinaemias; inhibition of lactation.

Lacalm *La Pharmaceuticals, India.*
Chlorpromazine hydrochloride (p. 1045·2); trifluoperazine hydrochloride (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).

Lacalm Plus *La Pharmaceuticals, India.*
Trifluoperazine hydrochloride (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).

Lacalut *Naturwaren, Ital.*
Aluminium lactate (p. 2440·2); aluminium fluoride (p. 2089·2); aluminium hydroxide (p. 1817·2); silicon dioxide (p. 2208·3).
Oral hygiene; gum disorders; sensitive teeth.

Lac-B *Hiral, India.*
⊗Amylase (p. 2442·1); *Lactobacillus sporogenes* (p. 2596·3); papain (p. 2582·3); vitamin B substances (p. 2102·3).

Lacbon *Kimia, Indon.*
Lactobacillus sporogenes (p. 2596·3).
Gastrointestinal disorders; skin disorders.

Laccoderme à l'huile de cade *Pierre Fabre, Fr.†*
Rectified cade oil (p. 1723·2); hyoscyamus oil (p. 2530·2); salicylic acid (p. 1719·1).
Psoriasis; seborrhoeic dermatitis.

Lacdigest *Italchimici, Ital.; Pro Farma, Switz.; Nevzat, Turk.*
Tilactase (p. 2631·2).
Lactase deficiency.

Lac-Dol
Note: this name may be used for preparations of different composition.
Genepharm, Austral.
Lactulose (p. 1850·3).
Constipation.

Lacdol
Note: this name may be used for preparations of different composition.
Wermar, Mex.
Ketorolac trometamol (p. 80·2).
Pain.

Lac-Dose *Rugby, USA.*
Tilactase (p. 2631·2).
Lactose intolerance.

Lace *Acekinetic, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lacedim *Lapi, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Lacerdermol *Lacer, Spain.†*
Biotin (p. 2052·2); calcium pantothenate (p. 2085·2); vitamin A (p. 2098·3).
Skin disorders; fragile nails; blepharitis; glossitis.

Lacerdermol Complex *Lacer, Spain.†*
Vitamin B substances (p. 2102·3); vitamin A (p. 2098·3).
Skin disorders; seborrhoeic blepharitis.

Lacerol *Lacer, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Lacetilina *Pentafarma, Port.†*
Acetylcarnitine hydrochloride (p. 2053·2).
Mental function disorders.

Lacfen-P *Laclin, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Lacgel *Hetero, India.*
Lactic acid (p. 2539·1).
Formerly contained lactic acid and glycogen.
Vaginal disorders.

Lachemistol *Wiedemann, Ger.*
Lachesis mutus (p. 2538·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Lachesis Complexe No 122 *Lehning, Fr.*
Lachesis (p. 2538·3); kalium carbonicum (p. 2595·2); bryonia (p. 2461·3); cactus grandiflorus (p. 2473·2); glonoinum (p. 1391·2).
Homoeopathic preparation.

Lachess *Knop, Chile.*
Cactus (p. 2473·2); lachesis (p. 2538·3); sepia (p. 2613·1).
Homoeopathic preparation.

Lac-Hydrin *BMS, Braz.†; BMS, Mex.; BMS, NZ†; Ranbaxy, USA.*
Ammonium lactate (p. 1694·3).
Dry skin disorders; pruritus; xerosis; ichthyosis vulgaris.

Laciclav *Icarus, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Lacidofil *Rosell, Canad.; Rosell, Cz.; Dexa, Indon.; Lallemand, Pol.; Pharm Union, Ukr.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Maintenance of normal gastrointestinal function; diarrhoea; antibiotic-associated diarrhoea; gastroenteritis; dyspepsia; necrotising enterocolitis; atopic eczema; lactose intolerance; chronic fatigue syndrome.

Laciken *Kendrick, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Lacimen *GSK, Spain.*
Lacidipine (p. 1417·3).
Hypertension.

Lacin *Atlantic, Thai.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Lacipil *GSK, Braz.; GSK, China; GSK, Cz.; Europharma, Denm.; Orifarm, Denm.; GSK, Gr.; GSK, Hong Kong†; GSK, Hung.; GSK, Indon.†; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Turk.; GSK, Venez.*
Lacidipine (p. 1417·3).
Hypertension.

Lacipron *Acto, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Lacirex *Guidotti, Ital.*
Lacidipine (p. 1417·3).
Hypertension.

Lacitens *GSK, Gr.*
Lacidipine (p. 1417·3).
Hypertension.

Lacium *Pro-Pharma, Ukr.*
Bifidobacterium bifidum (p. 2596·3); *Bifobacteriuum lactis* (p. 2596·3); *Enterococcus faecium* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Lacivas *Sun, India.*
Lacidipine (p. 1417·3).
Hypertension.

Laclomox *Meridian, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Laclorhex *Sertex, Arg.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

LAC-Lotion *Paddock, USA.*
Ammonium lactate (p. 1694·3).
Emollient.

Laclouse *Osper, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lac-M *Madhav, India.*
Lactobacillus (p. 2596·3).

Lacoldin *Lapi, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; allergic rhinitis.

Lacom *Comed, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Lacom-CV *Comed, India.*
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Lacom-CV 625 *Comed, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Lacomin *Best, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Laconest *Medifarma, Turk.*
Lidocaine hydrochloride (p. 1988·2).

Lacons *Mahakam Beta, Indon.*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Lac-Oph *Seng, Hong Kong; Seng, Thai.*
Hypromellose (p. 2189·2).
Wetting solution for contact lenses; dry eyes.

Lacophen *Lapi, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Lacophtal *Winzer, Ger.*
Povidone (p. 2204·3).
Dry eye disorders.

Lacorene *Spedrog, Arg.*
Arginine aspartate (p. 2049·1).
Tonic.

Lacovin *Galderma, Spain.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Lacrate *Acekinetic, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastrointestinal haemorrhage.

Lacrate-O *Acekinetic, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Lacrest *Chandra Bhagat, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lacribase *Tubilux, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye disinfection.

Lacribell *Latinofarma, Braz.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Lacridos *Oftalmi, Venez.*
⊗Dextran 70 (p. 1138·3).
Dry eyes.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lacrifilm *Uniao Quimica, Braz.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Lacrifluid *Europhta, Mon.; Ophtapharm, Switz.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Lacri-Gel
Note: this name may be used for preparations of different composition.
Medical Ophthalmics, USA.
Soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Lacrigel
Note: this name may be used for preparations of different composition.
Farmigea, Ital.; Europhta, Mon.
Carbomer 980 (p. 2173·3).
Dry eyes; eye disinfection.

Sunways, India.
Hypromellose (p. 2189·2).
Dry eyes.

Lacrigel A *Novartis, Braz.*
Vitamin A palmitate (p. 2098·3).
Dry eyes.

Lacrigel C *Winzer, Ger.†*
Carbomer (p. 2173·3).
Dry eyes.

Lacrigest *Biosintex, Arg.*
Hypromellose (p. 2189·2).
Dry eyes.

Lacril
Note: this name may be used for preparations of different composition.
Allergan, Braz.; Allergan, Denm.; Allergan, Venez.
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Allergan, Canad.†; Allergan, USA.
Hypromellose (p. 2189·2).
Dry eyes.

Lacrilens *Tubilux, Ital.*
Carmellose (p. 2175·1).
Contact lens care.

Lacri-Lube *Allergan, Austral.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry eyes.

Allergan, Chile; Allergan, USA.
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); non-ionic lanolin derivatives (p. 2219·3).
Dry eyes.

Allergan, Fin.; Allergan, Irl.; Allergan, UK.
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool alcohols (p. 2219·2).
Dry eyes.

Lacrilube *Allergan, Ital.; Allergan, NZ.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool alcohols (p. 2219·2).
Dry eyes.

Allergan, Spain.
White soft paraffin (p. 2211·3).
Dry eyes.

Allergan, Malaysia; Allergan, Singapore.†
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); non-ionic lanolin derivatives (p. 2219·3).
Dry eyes.

Lacrilux *Tubilux, Ital.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Lacrima
Note: this name may be used for preparations of different composition.
Lagad, UK.
Omega-3 fatty acids (p. 1460·1); gamolenic acid (p. 2509·2); zinc (p. 2126·1); thioctic acid (p. 2629·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Dry eyes.

Lacrima Plus *Alcon, Braz.; Alcon, Mex.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Lacrimal *Polfa Warszawa, Pol.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Lacrimal OK *Allergan, Ger.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Lacrimalfa *INTES, Ital.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); monobasic sodium phosphate (p. 1791·1); magnesium sulfate (p. 1787·3).
Dry eyes.

Lacrimart
Note: this name may be used for preparations of different composition.
Baif, Ital.
Methylcellulose (p. 2197·3).
Dry eyes; eye disinfection.

Oftalmi, Venez.
Eye drops: ⊗Dextran 70 (p. 1138·3).
Dry eyes.

Lacrimax *Ingens, Arg.†*
Chondroitin sulfate (p. 2476·1); aprotinin (p. 1133·2); sodium hyaluronate (p. 2526·2).
Eye disorders; dry eyes.

Lacrimol *Fischer, Israel.*
Eye drops: Povidone (p. 2204·3); hyetellose (p. 2188·3).
Dry eyes.

Fischer, Israel.†
Eye ointment: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Lacrimos *Lupin, India.*
Carmellose (p. 2175·1).
Dry eyes.

Lacrinmune *Bausch & Lomb, Arg.*
Ciclosporin (p. 1945·2).
Keratoconjunctivitis sicca.

Lacrinorm *Bausch & Lomb, Belg.; Chauvin, Fr.; Farmigea, Ital.; Bausch & Lomb, Neth.; Bausch & Lomb, Switz.*
Carbomer (p. 2173·3).
Dry eyes.

Lacrisan *Cadila, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Lacrisert *Aton, Canad.; IDIS, Fin.†; IDIS, Fr.; IDIS, Neth.†; MSD, Swed.†; Aton, USA.*
Hyprolose (p. 2189·1).
Dry eyes; exposure keratitis; decreased corneal sensitivity.

Lacrisic *Alcon, Ger.*
⊗Hypromellose (p. 2189·2); povidone (p. 2204·3); glycerol (p. 2517·2).
Dry eyes.

Lacrisifi *SIFI, Ital.; Zambon, Rus.; Teka, Turk.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Lacrisol
Note: this name may be used for preparations of different composition.
Bruschettini, Ital.
Hypromellose (p. 2189·2).
Eye disinfection; dry eyes.

Micro, India.
Polyvinyl alcohol (p. 2204·2); povidone-iodine (p. 1767·1).

Lacri-Stulln *Stulln, Ger.; Medserve, Switz.*
Povidone (p. 2204·3).
Dry eyes.

Lacrisyn *Galena, Rus.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Lacri-Tears *Medical Ophthalmics, USA.*
⊗Hypromellose (p. 2189·2); dextran (p. 1138·3).
Dry eyes.

Lacri-Vision *OmniVision, Ger.*
Hypromellose (p. 2189·2).
Dry eyes.

Lacrofarm *Orifarm, Denm.; Orifarm, Fin.; Orifarm, Swed.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Lacromycin *Fischer, Israel.*
Gentamicin sulfate (p. 304·2).
Eye infections.

Lacry+ *Europhta, Mon.†*
Vitamins; minerals; plant extracts.
Dietary supplement for dry eye disorders.

Lacrycon *Thea, Switz.*
⊗Sodium hyaluronate (p. 2526·2); carbomer 981 (p. 2173·3); glycerol (p. 2517·2).
Dry eyes.

Lacrypos *Alcon, Belg.†; Alcon, Fr.†*
Chondroitin sulfate sodium (p. 2476·1).
Dry eyes; eye disorders.

Lacrystat *Meda, Belg.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Lacrytube *Meda, Belg.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3); wool fat (p. 2219·3).
Keratoconjunctivitis sicca; corneal protection in comatose or anaesthetised patients.

Lacryvisc *Alcon, Chile; Alcon, Fr.; Alcon, Hong Kong; Alcon, Mex.; Alcon, Philipp.; Alcon, Port.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, Venez.*
Carbomer (p. 2173·3).
Dry eyes; eye irritation.

Lacsil *Almet, India.*
Vitamin B substances (p. 2102·3); zinc (p. 2126·1) lactobacillus (p. 2596·3).

Lacson *Aspen Consumer, S.Afr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; portal hypertension.

Lacspan *Kissei, Hong Kong.*
Lysates of *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).
Restoration of gastrointestinal flora.

Lactacin *Solas, Indon.*
Sauropus androgynus; thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Nutritional supplement in lactation.

Lactacrat *Cratus, India.*
Asparagus racemosus (p. 2614·2); fennel (p. 2503·2); liquorice (p. 1853·2); nigella sativa; ocimum sanctum; piper longum.

Lactacyd *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile; Sanofi, China; PHC, Indon.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.†*
Lactic acid (p. 2539·1); milk serum (p. 2125·2).
Skin cleanser; genital hygiene; skin disorders; vulvovaginal hygiene; vulvovaginal disorders.

Sanofi-Aventis, Hong Kong; Sanofi Synthelabo, India.
Lactic acid (p. 2539·1).
Skin and genital hygiene.

Lactacyd Antibatterico *GSK Consumer, Ital.†*
Triclosan (p. 1773·2).
Skin disinfection.

Lactacyd Derma *GSK Consumer, Ital.*
Milk serum (p. 2125·2); lactic acid (p. 2539·1).
Acne; soap substitute.

Lactacyd FH *Sanofi, China.*
Lactic acid (p. 2539·1).

Lactacyd Intimo *GSK Consumer, Ital.*
Milk serum (p. 2125·2); lactic acid (p. 2539·1).
Genital hygiene.

Lactacyd Lentivo *GSK Consumer, Ital.*
Lactic acid (p. 2539·1); arnica (p. 2447·2); rice protein.
Soap substitute; skin irritation.

Lactacyd VG *Sanofi-Aventis, Philipp.*
Lactic acid (p. 2539·1).
Genital hygiene in females.

Lactaderm *Sanofi Synthelabo, Philipp.†*
⊗Calendula (p. 2465·2); glycerol (p. 2517·2); amino acids.
Infant skin cleanser.

Lactafar *Fahrenheit, Indon.*
Nutritional supplement in pregnancy and lactation.

Lactafem *Andromaco, Chile.*
Desogestrel (p. 2266·3).
Progesterone-only oral contraceptive.

Lactagard *Ipca, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Lactagogue *Thai FD, Thai.*
Zingiber zerumbet; euphorbia hirta (p. 2501·3); xantolis cambodiana.

LactaGreek *Novell, Singapore.*
Sauropus androgynus; fenugreek (p. 2504·1); vitamin B_{12} (p. 2107·2); calcium hydrogen phosphate (p. 1783·3).
Dietary supplement in lactation.

Lacta-Gynecogel *Medgenix, Belg.*
Lactic acid (p. 2539·1).
Anogenital infections.

Lactaid *McNeil Consumer, Canad.; McNeil Consumer, USA.*
Tilactase (p. 2631·2) from *Aspergillus oryzae* or *Kluyveromyces lactis.*
Lactose intolerance; lactase insufficiency.

Lactal *Hetero, India.*
Lactic acid (p. 2539·1).
Bacterial vaginosis.

Lactamam *Novell, Indon.*
Sauropus androgynus; fenugreek (p. 2504·1).
Dietary supplement in lactation.

Lactamax *Beta, Arg.*
Cabergoline (p. 899·3).
Hyperprolactinaemia; lactation inhibition; prolactinomas.

Lactamil *Sari Husada, Indon.*
Nutritional supplement in pregnancy and lactation.

Lactamox *Novell, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Lactare *TTK, India.*
Capsules: Garlic (p. 2510·3); asparagus racemosus (p. 2614·2); liquorice (p. 1853·2); fenugreek (p. 2504·1); withania somnifera (p. 2450·2).

TTK, India.
Oral granules: ⊗Asparagus racemosus (p. 2614·2); cuminum cyminum; cyperus rotundus; liquorice (p. 1853·2); tribulus terrestris (p. 2633·3).

Lac-Tas *Dominguez, Arg.*
Tilactase (p. 2631·2).
Lactose intolerance.

Lactasol *Gambro, Austria; Gambro, Denm.†; Gambro, Fin.†; Gambro, Port.; Gambro, Swed.†; Gambro, Switz.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2) (p. 1778·2).
Haemofiltration; haemodialysis.

Krasfarma, Rus.
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Lactec *Otsuka, Jpn.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Lactec D *Otsuka, Jpn.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Lactec G *Otsuka, Jpn.*
Electrolytes (p. 1775·1); sorbitol (p. 2092·1).
Fluid and electrolyte disorders; carbohydrate source.

Lactecon *Solvay, Cz.†; Solvay, Fin.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lacteeze *Gelda, Canad.; GenAsia, Philipp.*
Tilactase (p. 2631·2).
Lactase intolerance; dietary supplement.

Lacteol *Aptalis, Ger.; Pohl, Ger.; Bruschettini, Ital.*
Lactobacillus fermentum (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3).
Diarrhoea.

Menarini, Belg.; Axcan, Hong Kong; BioSaude, Port.; Axcan, Singapore; Ramon Sala, Spain; Biopas, Venez.
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Lactéol *Axcan, Fr.; Gebro, Switz.*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea.

Lacteol Cron *Carnot, Mex.*
Lactobacillus fermentum (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Lacteol Fort *Axcan, China; Beijing Union, China.*
Lactobacillus (p. 2596·3).
Diarrhoea.

Carnot, Mex.
Lactobacillus acidophilus (Boucardii) (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Lactes *Anglo-French Drugs, India.*
Tilactase (p. 2631·2).

LacTEST *Venter, Spain.*
Gaxilose.
Diagnosis of lactose intolerance.

Lactiale *Farmak, Ukr.*
Lactobacillus casei (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Bifidobacterium breve*

(p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Bifobacteriuum longum* (p. 2596·3) or *Bifidobacterium infantis* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Lactibiane Candisis *Pileje, Fr.*
Lactobacillus helveticus (p. 2596·3).
Dietary supplement; digestive disorders; vaginal disorders.

Lactibiane Défenses *Pileje, Fr.*
Bifidobacterium longum (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); andrographis (p. 2443·2); zinc citrate (p. 2126·2); vitamin C (p. 2110·3).
Dietary supplement; immunostimulant.

Lactibiane Enfant *Pileje, Fr.*
Bifidobacterium longum (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Lactococcus lactis* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); vitamin D (p. 2112·3).
Dietary supplement; digestive disorders in children; immunostimulant.

Lactibiane Iki *Pileje, Fr.*
Bifidobacterium lactis (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3).
Dietary supplement; digestive disorders.

Lactibiane Protect *Pileje, Fr.*
Lactobacillus rhamnosus (p. 2596·3).
Dietary supplement; digestive disorders.

Lactibiane Référence *Pileje, Fr.*
Bifidobacterium longum (p. 2596·3); *Lactobacillus helveticus* (p. 2596·3); *Lactococcus lactis* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Dietary supplement; gastrointestinal disorders.

Lactibiane Voyage *Pileje, Fr.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus casei* (p. 2596·3).
Dietary supplement; motion sickness.

Lactibon *Raymos, Arg.; Medihealth, Mex.; Roemmers Medihe, Venez.*
Lactic acid (p. 2539·1).
Skin cleansing; soap substitute.

Lacticare
Note: this name may be used for preparations of different composition.
GSK, USA.
Lactic acid (p. 2539·1); liquid paraffin (p. 2191·2).
Emollient and moisturiser.

Stiefel, Arg.; Stiefel, Braz.; Stiefel, Fr.†; Stiefel, Indon.†; Stiefel, Irl.†; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, S.Afr.†; Stiefel, Singapore; Stiefel, Thai.
Lactic acid (p. 2539·1); sodium pidolate (p. 1720·3).
Dry skin disorders; hyperkeratosis.

Lacticare-HC *Stiefel, India; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, Thai.; Stiefel, USA.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Lactid HC *Cassara, Arg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Lactiderm *Cassara, Arg.*
⊗Ammonium lactate (p. 1694·3); urea (p. 1727·3).
Dry skin.

Lactifiber *Akums, India.*
Ispaghula (p. 1849·1); lactitol (p. 1850·3).

Lactiflora *Reddy, India.*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea.

Lactigriet *Isdin, Port.*
Dexpanthenol (p. 2582·2); chlorhexidine (p. 1743·2).
Sore nipples.

Lactihep *Sun, India.*
Lactitol (p. 1850·3).

Lactil *Laboratorios Chile, Chile.*
Lactobacillus rhamnosus (p. 2596·3).
Diarrhoea.

Lactinette *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Lactinex *Becton Dickinson, USA.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3).
Dietary supplement.

Omega, Arg.
Lactobacillus acidophilus (p. 2596·3).
Restoration of vaginal flora.

Lactinol *Pedinol, USA.*
Lactic acid (p. 2539·1).
Dry skin.

Lactinol-E *Pedinol, USA.†*
Lactic acid (p. 2539·1); vitamin E (p. 2119·1).
Dry skin.

Lactipan
Note: this name may be used for preparations of different composition.
Sigma, Braz.; Italmex, Mex.
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea; restoration of intestinal flora.

IBI, Ital.†
Lactococcus lactis (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3).
Gastrointestinal disorders.

Lactisona *Stiefel, Port.; Stiefel, Spain.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Lactisporin *Pielle, Ital.*
Lactic-acid-producing organisms (p. 2596·3); dried yeast (p. 2125·2); vitamin B substances (p. 2102·3).
Restoration of normal gastrointestinal flora.

Lactisyn *Franco-Indian, India.*
Lactobacillus lactis (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Lactococcus lactis* (p. 2596·3).
Diarrhoea; hepatic encephalopathy.

Lactivis *Fitobucaneve, Ital.*
Capsules: Vitamins; *Lactobacillus acidophilus* (p. 2596·3); dried yeast (p. 2125·2); dried yogurt (p. 2649·3).
Nutritional supplement.

Fitobucaneve, Ital.
Powder for oral liquid: Vitamins; lactic-acid-producing organisms (p. 2596·3).
Nutritional supplement.

Lacto Calamine
Note: this name may be used for preparations of different composition.
Schering-Plough, UK.
Cream: Calamine (p. 1697·2); zinc oxide (p. 1729·1); hamamelis (p. 2523·3).
Dry skin; sunburn.

Schering-Plough, UK.
Lotion: Calamine (p. 1697·2); zinc oxide (p. 1729·1); hamamelis (p. 2523·3); phenol (p. 1763·3).
Sunburn; skin irritation.

Lacto Calcium *Innopharm, Singapore.*
Calcium (p. 1783·1); phosphorus (p. 2589·2).
Calcium supplement; osteoporosis.

Lacto Care *Acertus, Malaysia.*
Tilactase (p. 2631·2); *Lactobacillus acidophilus* (p. 2596·3).
Lactose intolerance.

Lacto Vagin *UCI, Braz.*
Tyrothricin (p. 384·1); hydroxyquinoline (p. 2530·1); tannic acid (p. 2625·2); lactic acid (p. 2539·1); acetic acid (p. 2426·3); camphor (p. 2466·2).
Vulvovaginal disorders.

Lacto-B *Novell, Indon.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Streptococcus thermophillus* (p. 2596·3); vitamins.
Diarrhoea; lactose intolerance.

Lactobacil *Infar, India.*
Lactobacillus acidophilus (p. 2596·3).

Lactobacilos *Biotech Naturis, Venez.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of gastrointestinal flora.

Lactobacterin *Microgen, Rus.*
Lactobacillus acidophilus (p. 2596·3).
Maintenance of vaginal flora.

Lactofiltrum *Sti-Med-Sorb, Rus.*
Lignin (p. 2544·1); lactulose (p. 1850·3).
Maintenance of intestinal flora.

Lactobion *Pharma Synth, India.*
Vitamin B substances (p. 2102·3); *Lactobacillus sporogenes* (p. 2596·3).

Lactobus-V *Globus, India.*
Capsules: Vitamin B substances (p. 2102·3); lactobacillus (p. 2596·3).

Globus, India.
Syrup: Vitamin B substances (p. 2102·3); lactobacillus (p. 2596·3); vitamin C (p. 2110·3).

Lactocal *Alkem, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).

Lactocal-F *Laser, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Supplement for pregnant or lactating women.

Lactocef *Cadila, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Lacto-Cev *Cevallos, Arg.*
Ammonium lactate (p. 1694·3).
Skin disorders.

Lacto-Cev Zn *Cevallos, Arg.*
Ammonium lactate (p. 1694·3); zinc gluconate (p. 2126·2).
Skin disorders.

Lactocil *Gelcaps, Mex.†*
Lactobacillus acidophilus (p. 2596·3).
Restoration of intestinal flora.

Lactoclav *Cachet, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Lactocom Forte *Cadila, India.*
Lactic-acid-producing organisms (p. 2596·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Lactocrem *Giscard, Arg.*
⊗Urea (p. 1727·3); alpha hydroxy acids (p. 1704·3).
Dry skin.

Lactocrem Bebe *Giscard, Arg.*
Allantoin (p. 1693·1); zinc oxide (p. 1729·1); vegetable extracts.
Barrier preparation.

Lactocur *Sandoz, Austral.*
Lactulose (p. 1850·3).
Constipation.

Lactodrox-DT *Sienna, India.*
Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

Lactoferment *Gebro, Switz.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of gastrointestinal flora; diarrhoea.

Lactoferrina *Chiesi, Spain.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Lactofilm *LDA, Arg.*
Sodium laurilsulfate (p. 2210·3).
Skin cleanser.

Lactofiltrum-ECO *Abba, Ukr.*
Lignin (p. 2544·1); lactulose (p. 1850·3).
Gastrointestinal disorders.

Lactofilus *Llorente, Spain.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of the gastrointestinal flora.

Lactofree *Mead Johnson Nutritionals, USA.*
Lactose-free infant feed.

Lactogenes *Medispan, India.*
Lactobacillus (p. 2596·3).

Lactogermine *Humana, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins.
Nutritional supplement.

LactoGG *PaediHealth, Hong Kong.*
Lactobacillus rhamnosus (p. 2596·3); inulin (p. 2534·3).
Dietary supplement.

Lacto-Key *Key, USA.*
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement.

Lactolas *Monelli, Ital.*
Lactulose (p. 1850·3); inulin (p. 2534·3); rhubarb (p. 1884·2); frangula (p. 1843·3); senna (p. 1885·1); vitamin B substances (p. 2102·3).
Nutritional supplement.

Lactolife *Fitolife, Ital.*
Dried yeast (p. 2125·2); lactic-acid-producing organisms (p. 2596·3).
Gastrointestinal disorders; nutritional supplement.

Lactolus *Intas, India.*
Lactobacillus (p. 2596·3).

Lactomaior *Geymonat, Ital.*
Lactic-acid-producing organisms (p. 2596·3); fruit oligosaccharides (p. 2508·1); vitamin B substances (p. 2102·3).
Restoration of gastrointestinal flora.

Lactomannan *CaDiGroup, Ital.*
Glucomannan (p. 2515·2); lactulose (p. 1850·3).
Constipation; obesity.

LactoMax *SteriMax, Canad.*
Tilactase (p. 2631·2) from *Aspergillus oryzae.*
Lactose intolerance.

Lactomol-D *Swedpharm, Chile.*
Tilactase (p. 2631·2); colecalciferol (p. 2113·1).
Lactose intolerance.

Lactomorrhuol *Delpech, Fr.*
Cod-liver oil (p. 2056·3).
Dietary supplement.

Lactomox *Biological E, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Lactomun *Pro-Pharma, Ukr.*
Bifobacteriuum bifidum (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); *Lactococcus lactis* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Lactonic
Note: this name may be used for preparations of different composition.
Dabur, India.
Asparagus racemosus (p. 2614·2); cuminum cyminum; liquorice (p. 1853·2); spinacia oleracea.
Stimulation of lactation.

Garuda, Hung.
Asparagus (p. 2450·2); dill (p. 2493·1); ipomoea digitata; liquorice (p. 1853·2); spinacia oleracea; cuminum cyminum; panchtrimool (cynodon dactylon, sugar cane, desmostachya bipinnata, saccharum arundinaceum, saccharum spontaneum).
Aid in lactation.

Lactonorm *Geymonat, Ital.*
Lactobacillus acidophilus (p. 2596·3).
Disturbances in vaginal flora.

Lactopan *Forder, Arg.*
Cetyl alcohol (p. 2178·2).
Skin cleanser.

Lactopectin *Sanofi Synthelabo, Mex.†*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Lactophilus *Orion, Fin.*
Lactobacillus rhamnosus (p. 2596·3).
Restoration of gastrointestinal flora.

Lactoplus *LDA, Arg.*
⊗Lactic acid (p. 2539·1); urea (p. 1727·3); vitamin E (p. 2119·1); avena (p. 2451·1); sunscreen agents.
Dry skin disorders; eczema.

Lactoprotein-C *Biopharma, Ukr.*
⊗Albumin (p. 1130·2); sorbitol (p. 2092·1); electrolytes (p. 1775·1).
Hypovolaemia; hypoproteinaemia.

Lactopurum *Pfluger, Ger.†*
Acid. lacticum (p. 2539·1).
Homoeopathic preparation.

Lactor *Phapros, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Lactorin *Orion, Cz.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactosanol *Vedim, Pol.†*
Tilactase (p. 2631·2).
Lactose intolerance.

Lactoscrub *LDA, Arg.*
Mallow (p. 2549·2); calendula (p. 2465·2).
Skin cleanser.

Lactosec *Aspen, S.Afr.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin deficiency; nausea and vomiting in pregnancy; neuropathy.

Lactospore *Bactolac, India.*
Lactobacillus (p. 2596·3).

Lactovaginal *Biomed Krakow, Pol.*
Lactobacillus rhamnosus (p. 2596·3).
Restoration of vaginal flora.

Lactovis *Ebi, Switz.*
Acidum lacticum (p. 2539·1).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lactovit
Note: this name may be used for preparations of different composition.
Fitoben, Ital.
Dried yeast (p. 2125·2); rosa canina; spirulina (p. 2622·1); eleutherococcus (p. 2614·3); myrtillus (p. 2566·2); *Lactobacillus acidophilus* (p. 2596·3).
Dietary supplement.
Medispan, India.
Vitamin B substances (p. 2102·3); *Lactobacillus sporogenes* (p. 2596·3).

Lactovita *Sanofi Synthelabo, Mex.†*
Lactobacillus acidophilus (p. 2596·3).
Restoration of intestinal flora.

Lactra *Intra-Labs, India.*
Lactobacillus (p. 2596·3).

Lactrase *Schwarz, Canad.†; UCB, China; Schwarz, USA.*
Tilactase (p. 2631·2).
Lactose intolerance; lactase insufficiency.

Lactrex
Note: this name may be used for preparations of different composition.
Galderma, Arg.
Ammonium lactate (p. 1694·3).
Dry skin disorders.
Galderma, Braz.; Galderma, Mex.; Galderma, Venez.
Allantoin (p. 1693·1); ammonium lactate (p. 1694·3).
Cicatrisation; dry skin.
SDR, USA.†
Lactic acid (p. 2539·1).
Emollient.

Lactrime *Forder, Arg.*
Glycolic acid (p. 1704·3).
Moisturiser.

Lactrol *Raptakos, India.*
Lactobacillus acidophilus (p. 2596·3).

Lactucol *Distrifarma, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Lactucos *Symbiosis, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactuflor *Rosen, Ger.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactugal *Intrapharm, Irl.†; Intrapharm, UK.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

LactuGel *CNP, Ger.*
Lactulose (p. 1850·3).
Constipation.

Lactul *YSP, Malaysia; Yung Shin, Philipp.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactulac *Kocak, Turk.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactulade *CNP, Ger.*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Lactulax *Samarth, India; Ikapharmindo, Indon.; Senosiain, Mex.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactulin *Meyer, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactuliv *Legrand, Braz.*
Lactulose (p. 1850·3).

Lactulol *Hasco-Lek, Pol.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactulon *Lazar, Arg.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactulona *Sankyo, Braz.; Sankyo, Venez.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactus *ICM, Singapore.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactusan *Sanify, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactuverlan *Verla, Ger.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lactuvit *Yuriya-Farm, Ukr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; hepatic coma; cirrhosis.

Lacvel *Pliva, Rus.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Lacven *Vensat, India.*
Lactobacillus (p. 2596·3).

Lac-xim *Sel-J, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ladar *Millimed, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ladasten *Lekko, Rus.*
⊗Bromantan (p. 2318·2).
Asthenia.

Ladazol *Adcock Ingram, S.Afr.*
⊗Danazol (p. 2263·2).
Endometriosis; mastalgia; hereditary angioedema.

Laderm *Galderma, Braz.*
Almond oil (p. 2437·1).
Dry skin disorders; soap substitute.

Ladevina *LKM, Arg.*
Lenalidomide (p. 816·1).
Myelodysplastic syndromes.

Ladex *Allenge, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Ladex-P *Allenge, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Ladiades *Ultra, Mex.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Ladinin *Pharmathen, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Ladip *Glaxo Allen, Ital.*
Lacidipine (p. 1417·3).
Hypertension.

Ladiwin *Zydus, India.*
Lamivudine (p. 1000·2).
HIV infection.

Ladocort *LBS, Thai.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Ladogal *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, India; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Sanofi-Aventis, Venez.*
⊗Danazol (p. 2263·2).
Benign breast disorders; endometriosis; hereditary angioedema; mastalgia; gynaecomastia; menorrhagia; precocious puberty; pre-operative endometrial thinning.

Ladonna *Sandoz, Switz.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lador *Empifarma, Port.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Ladose *Lilly, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Ladropen *Berk, UK.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Lady
Note: this name may be used for preparations of different composition.
Pond's, Philipp.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Lady-35
Note: this name may be used for preparations of different composition.
Masa, Thai.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Oral contraceptive in women with androgenic symptoms.

Lady Guard *Kowa, Jpn.†*
Flavoxate hydrochloride (p. 2360·1).

Ladybon *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Ladylen *Mertens, Arg.*
Miconazole nitrate (p. 589·1); tinidazole (p. 949·2).
Vaginal infections.

Ladylen Duo *Mertens, Arg.*
Tinidazole (p. 949·2).
Bacterial infections; trichomoniasis.

Ladymega *Cantassium Co., UK.*
Vitamins; minerals.

Lady-Ten 35 *Laboratorios Chile, Chile.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, hirsutism, and menstrual disorders.

Ladytone *Vitabiotics, UK.*
Vitamins; minerals.

Ladyvital *Pharmadass, UK.*
Vitamins; minerals; nutritional supplements.

Laennec *Rana, Rus.*
Placenta hydrolysate (p. 2444·1).
Hepatitis.

Laevolac *Fresenius Kabi, Austria; Fresenius Kabi, China; Keller, China; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Roche, Ital.; Fresenius Kabi, Neth.; Douglas, NZ†; Ferraz, Lynce, Port.; Greater Pharma, Thai.; Ulagay, Turk.*
Lactulose (p. 1850·3).
Constipation; disturbances of gastrointestinal flora; hyperammonaemia; hepatic encephalopathy; gum disorders; salmonellosis; hepatic cirrhosis.

Laevomycetin *Arterium, Ukr.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Laevovit D_3 *Fresenius Kabi, Austria.†*
Colecalciferol (p. 2113·1).
Vitamin D supplementation; rickets; osteomalacia.

Lafactin *Apotex, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Lafalos *Sanbe, Indon.*
Menthol (p. 2553·2); eugenol (p. 2501·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Lafalos Plus *Sanbe, Indon.*
Menthol (p. 2553·2); eugenol (p. 2501·2); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3); vitamin E (p. 2119·1).
Musculoskeletal and joint pain.
Sanbe, Singapore.
Menthol (p. 2553·2); eugenol (p. 2501·2); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3); vitamin E acetate (p. 2119·2).
Musculoskeletal and joint pain.

Lafamme *Jenapharm, Ger.; Bayer, Neth.; Lusal, Port.*
Estradiol valerate (p. 2271·2); dienogest (p. 2267·2).
Menopausal disorders.

LAfamo *Cipla, Hong Kong.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lafarcaina *Elmor, Venez.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2); thymol (p. 1772·2).
Sore throat.

Lafarclor *Lafare, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Lafarin *Lafare, Ital.†*
Cefalexin (p. 234·1).
Bacterial infections.

Lafaxin *Interpharma, Chile.†*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Lafaxon *Ingers, Cz.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety disorders; panic disorder.

Lafaxven *Sandoz, Mex.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Lafeaspirina *Lafedar, Arg.*
Aspirin (p. 22·2).
Fever; inflammation; pain.

Lafecaina *Lafedar, Arg.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lafedoxin *Lafedar, Arg.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Lafelax *Lafedar, Arg.*
Lactulose (p. 1850·3).
Constipation.

Lafen *Datla, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Lafene *Pfizer, Denm.*
⊗Fentanyl (p. 60·1).
Pain.

Lafeprazol *Lafedar, Arg.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).

Laferobion *Biopharma, Ukr.*
Interferon alfa-2b (p. 989·2).

Laferon *Interpharmbiotek, Ukr.*
Interferon alfa-2b (p. 989·2).
Viral infections; multiple sclerosis; malignant neoplasms.

Lafevir *Lafedar, Arg.*
Aciclovir (p. 964·1).

Lafexina *Lafedar, Arg.*
Cefalexin (p. 234·1) or cefalexin lysine (p. 234·1).
Bacterial infections.

Laff *Pharmed, India.*
Fructo-oligosaccharides (p. 2508·1); *Lactobacillus sporogenes* (p. 2596·3).

Laffed *Lafayette, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Laffter *Alde Medi Impex, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lafigesic *Recalcine, Chile.*
Clonixin lysine (p. 40·1).
Inflammation; pain.

Lafigin *Drugtech, Chile.*
Lamotrigine (p. 527·2).
Epilepsy.

Lafin *Loeffler, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lafix *Concept, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Laflanac *Lapi, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Laflox *Datla, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Laflox-O *Datla, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Lafol *Meda, Ger.†*
Folic acid (p. 2063·1).
Folic acid supplement.

Lafor *Actavis, Spain.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Laforte *Jenburkt, India.*
⊗Curcuma longa; tribulus terrestris (p. 2633·3); withania somnifera (p. 2450·2).

La-Fu *Pliva, Cz.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Lafunomyl *Mylan, Fin.; Mylan, Swed.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Lafurex *Lafare, Ital.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Lagarmicin *Medicalia, Spain.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Lagas *Promed, Indon.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Lagatrim *Thebe, S.Afr.; Lagap, Switz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Lagenbach *Remexa, Mex.*
Senna (p. 1885·1).
Constipation.

Lagesic
Note: this name may be used for preparations of different composition.
Datla, India.
Tramadol Hydrochloride (p. 139·2).
Pain.

Laser, USA.
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1).
Pain.

Lagesil *Lapi, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; excess gastrointestinal gas.

Lagosa *Worwag, Cz.; Worwag, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Worwag, Pol.
Silymarin (p. 1561·2).
Liver disorders.

Lagotran *Beta, Arg.*
Lamotrigine (p. 527·2).
Epilepsy.

Lagricel *Sophia, Mex.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Lagricel Ofteno *Volta, Chile; Elmor, Venez.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Lagrifilm Plus *Allergan, Mex.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Lagrima Artificial *Poen, Arg.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Lagrima Dorf *Pharmadorf, Arg.*
Hypromellose (p. 2189·2).
Dry eyes.

Lagrimas Artificiales
Note: this name may be used for preparations of different composition.
Alcon, Venez.; Oftalmi, Venez.
⊗Dextran 70 (p. 1138·3).
Dry eyes.

Andromaco, Chile.
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Laboratorios Chile, Chile.
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Lagundex *QX, Philipp.*
Vitex negundo.
Cough; bronchospasm.

Lagylan *Arlex, Mex.*
Metronidazole (p. 936·1).
Amoebiasis.

Lahep *GPO, Thai.*
Lamivudine (p. 1000·2).
HIV infection; hepatitis B.

Lahexy *La Pharmaceuticals, India.*
Trihexyphenidyl hydrochloride (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Lai Di *Hengrui, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Lai An *Pude, China.*
Lysine hydrochloride (p. 2079·3).

Lai Bi Lin *Fengyuan Tushan, China.*
Lysine aspirin (p. 84·3).

Lai Bi Xin *Fengyuan Tushan, China.*
Diclofenac sodium (p. 48·3).

Lai Ding Jia *SanJiu JiShi, China.*
Potassium chloride (p. 1793·2).

Lai Duo Fei *Wanma, China.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Lai Fu Long *Beisheng Hansheng, China.*
Interferon alfa-2b (human, recombinant) (p. 989·2).

Lai Fu Le Xin *Jinyu, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Lai Kang *Ao Tuo Kang, China.*
Fluconazole (p. 578·2).
Candidiasis.

Lai Li Qing *Lai Mei, China.*
Rifaximin (p. 355·2).

Lai Luo Er *Fengyuan Tushan, China.*
Naftopidil (p. 2361·1).

Lai Mei Jing *Lai Mei, China.*
Pazufloxacin mesilate (p. 338·1).

Lai Mei Kang *Lai Mei, China.*
Inosine (p. 2533·1).

Lai Mei Qing *Lai Mei, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Lai Mei Xing *Lai Mei, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Lai Qi *Dikang Changjiang, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Lai Qie Li *Dongfeng, China.*
Amoxicillin sodium (p. 216·2); sulbactam (p. 360·1).
Bacterial infections.

Lai Sai *Ao Tuo Kang, China.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Lai Si *Sine, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Lai Si Duo Wei *Duoburuifei, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Lai Ting *Xinchang, China.*
Progesterone (p. 2300·2).

Lai Xi Li *Xin Gang Union, China.*
Levofloxacin lactate.
Bacterial infections.

Lai Yi *Ao Tuo Kang, China.*
Flumazenil (p. 1551·3).
Reversal of benzodiazepine-induced sedation.

Lai Yi Fen *Zhong Yi, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Laibixin *Taiyang, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Laif *Steigerwald, Austria; Steigerwald, Cz.; Steigerwald, Ger.; Steigerwald, Hung.; Samuelow, Israel; Steigerwald, Neth.; Steigerwald, Ukr.*
St John's wort (p. 449·1).
Depression; nervous disorders.

Laijia *Xinchang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Laikan *Farmasa, Mex.*
Kava extract (p. 2537·3).
Anxiety.

Laikexin *Xinchang, China.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Laila-35 ED *Aspen, Austral.*
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgen-dependent acne and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Lailixin *Xinchang, China.*
Levofloxacin lactate.
Bacterial infections.

Laimolin *Flupol, Venez.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Laimoqualin *Vargas, Venez.*
Dequalinium chloride (p. 1749·3); lidocaine (p. 1988·1).
Mouth and throat disorders.

Lainema *Lainco, Spain.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Laiping *Xinchang, China.*
Miglitol (p. 491·3).
Diabetes mellitus.

Laira *Nobel, Turk.*
Citalopram hydrobromide (p. 411·1).

Lairesp *Lainco, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Lais *FGK, Hung.*
A range of allergen preparations (p. 2434·3).
Hyposensitisation.

Lait Auto-Bronzant *Clarins, Canad.*
SPF 6: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Lait Ecran Enfants *Vichy, Canad.†*
SPF 35: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Lait Protecteur *Ombrelle, Canad.*
Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Laitan *Nycomed, Braz.*
Kava (p. 2537·3).
Tension; anxiety.

Laitos *Lainco, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Laitun *Pasteur, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Laiwoxing *Changzheng-Xinkai, China.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lakafin *Verisfield, Gr.*
Tioconazole (p. 595·3).
Fungal nail infections.

Lakalsik *Nufarindo, Indon.*
Calcium lactate (p. 1784·1).
Calcium supplement.

Lakamed *T Man, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux disease; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Lak-Am-Lact *Shalaks, India.*
Ammonium lactate (p. 1694·3).

Lakan *CCM, Malaysia; Duopharma, Singapore.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lakcid *Biomed Lublin, Pol.*
Lactobacillus rhamnosus (p. 2596·3).
Maintenance of gastrointestinal flora.

Lakcip *Laksun, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lakdine *Shalaks, India.*
Povidone-iodine (p. 1767·1).

Lakea *Lek, Cz.; Sandoz, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; cardiovascular risk reduction.

Lakea HCT *Sandoz, Pol.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lakmox *Laksun, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lakmox-CL *Laksun, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Lakpam *Shalaks, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; skeletal muscle spasm; seizures; alcohol withdrawal syndrome.

Lakpride *Shalaks, India.*
Cisapride (p. 1831·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Lakrima *Bittner, Austria.*
Piper methysticum (p. 2537·3); argentum nitricum (p. 2615·3); kalium phosphoricum (p. 1790·3); pulsatilla (p. 2600·2); strophanthus (p. 1507·2).
Homoeopathic preparation.

Lakrimont *Blumont, Fin.*
Carbomer 980 (p. 2173·3); cetrimide (p. 1742·1).
Dry eyes.

Laksafenol *Liba, Turk.*
Phenolphthalein (p. 1877·3).
Constipation.

Laksotek *Unipharm, Turk.*
Bisacodyl (p. 1821·1).
Constipation.

LaktaFit *Dexa, Indon.*
Placenta extract (p. 2444·1); vitamin B_{12} (p. 2107·2); calcium hydrogen phosphate (p. 1783·3).
Lactation insufficiency.

Lakten *Shalaks, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Laktipex *Abbott, Swed.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laktobion *Sanghiang, Indon.*
Lactoferrin (p. 2539·3); lactulose (p. 1850·3); bifidobacteria (p. 2596·3).
Immunomodulator; restoration of gastrointestinal flora.

Laktol *Sanofi Synthelabo, Turk.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laktomag *Chance, Pol.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Laktomag B_6 *Chance, Pol.*
Magnesium aspartate (p. 1787·1). Pyridoxine (p. 2105·3) is included in this preparation to increase the absorption of magnesium.
Magnesium deficiency.

Laktovit Forte *Mili, Ukr.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); *Lactobacillus sporogenes* (p. 2596·3).
Colitis; restoration of gastrointestinal flora; disorders of the vaginal flora; skin disorders.

Lala *Osoth, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Lalax *Orion, Fin.†*
Lactitol (p. 1850·3).
Constipation; hepatic encephalopathy.

Lalide *Medochemie, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Lalithium *La Pharmaceuticals, India.*
Lithium.
Bipolar disorder.

Lama
Note: this name may be used for preparations of different composition.
Stadmed, India.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Pharmaland, Thai.†
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Lamafer *Bros, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Lamagramm *Medichrom, Gr.*
⊗Fluocinonide (p. 1636·3).

Lamaline *Abbott, Fr.*
Paracetamol (p. 115·1); opium (p. 111·3); caffeine (p. 1203·3).
Pain.

Lamater *Wockhardt, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lamazone *Newcharoen, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lambda
Note: this name may be used for preparations of different composition.
Isdin, Port.
Cream: Triclosan (p. 1773·2); aluminium hydroxide (p. 1817·2).
Hyperhidrosis.

Isdin, Port.
Roll-on: Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Lambda, Port.
⊗Letrozole (p. 817·1).
Breast cancer.

Lambdalina *Isdin, Port.; Isdin, Spain.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Lambdaxel *Isdin, Spain.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lamberin *Anpharm (Ανφαρμ), Gr.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Lambeta *Farmedia, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Lambipol *GSK, Belg.; GSK, Neth.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lambliquin *Novag, Mex.*
Metronidazole (p. 936·1); diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Lamblit *Novag, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis.

Lambroxol *Bright Future, Hong Kong.†*
Ambroxol (p. 1654·3).

Lambucid *Hexpharm, Indon.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Epigastric pain; gastric pain; bloating.

Lambutol *Atlantic, Thai.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Lamcin *Cinerea, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Lamcoin *Pond's, Thai.*
Clofazimine (p. 273·3).
Leprosy.

Lamda *Cadila, India.*
Lamivudine (p. 1000·2).
HIV infection.

Lamda-Z *Cadila, India.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Lamdra *Bioquimed, Mex.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lameco Plus *La Pharmaceuticals, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Lameco-OD *La Pharmaceuticals, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Lamepil *Ipca, India.*
Lamotrigine (p. 527·2).
Epilepsy.

Lamepon *Biomedica, Gr.*
Thiocolchicoside (p. 2026·2).

Lamepril *Ipca, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lameptil *Sandoz, Pol.; Sandoz, Rus.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lameson *Lapi, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Lametec *Cipla, India.*
Lamotrigine (p. 527·2).
Epilepsy.

Lametic *Landson, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Lameton *Sandoz, Cz.†; Sandoz, Ukr.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lametta *Vipharm, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lameutral *Teva, Irl.*
Lamotrigine (p. 527·2).
Epilepsy.

Lamexim *ICN, Pol.*
Lamotrigine (p. 527·2).
Epilepsy.

Lami *Cristalia, Braz.; McNeil & Argus, India.*
Lamivudine (p. 1000·2).
HIV infection; chronic hepatitis B.

Lami Plus *McNeil & Argus, India.*
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); zidovudine (p. 1024·2).

Lamia *Genexo, Pol.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamibergen *Paylos, Arg.*
Lamivudine (p. 1000·2).
HIV infection.

Lamican *Kanonfarma, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lamicon *Farmak, Ukr.*
Terbinafine (p. 593·3).
Fungal infections of the skin, hair, scalp, and nails.

Lamicosil *Novartis Consumer, Spain.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lamicstart *GSK, Fr.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamictal *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA; GSK, Venez.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamictin *GSK, S.Afr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamidac *Zydus, India.*
Lamivudine (p. 1000·2).
Chronic hepatitis B.

Lamiderm
Note: this name may be used for preparations of different composition.
Qualiphar, Belg.; Gifrer Barbezat, Fr.
Trolamine (p. 2634·3).
Burns.

Vianex (Βιανεξ), Gr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Lamidum *Ranbaxy, Ukr.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamidus *Ranbaxy, Austral.; Zydus, India; Zydus, S.Afr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamifen *Wander, Philipp.; Phytopharm, Ukr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lamigard *Labormed, Hung.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin, scalp, and nail infections.

Lamigen *Alvia (Αλβια), Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Lamiger *Gerot, Cz.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamilea *Elea, Arg.*
Lamivudine (p. 1000·2).
HIV infection.

Lamilept *Teva, Pol.*
Lamotrigine (p. 527·2).
Epilepsy.

Laminox *Abdi, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lamioflur *Heel, Cz.†*
Lamium album; creosotum (p. 1659·3); geum urbanum; aluminii oxidum (p. 1817·2); rumex obtusifolius; platinum metallicum (p. 2593·1); alchemilla vulgaris; natrii carbonas monohydricus (p. 2618·1); asterias rubens; kalii sulfidum crudum (p. 1721·3); acidum nitricum (p. 2572·3); hydrastis canadensis (p. 2528·1); daphne mezereum; viola tricolor (p. 2647·3).
Homoeopathic preparation.

Lamirax *Elea, Arg.*
Lamotrigine (p. 527·2).
Epilepsy.

Lamisil *Novartis Consumer, Arg.; Novartis, Austral.; Novartis Consumer, Austral.; Novartis, Belg.; Novartis, Canad.; Novartis, China; Novartis, Cz.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.; Novartis, Mex.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Spain; Novartis, Thai.; Novartis, Turk.; Novartis, UK.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections of the skin, hair, scalp, and nails.

Novartis, Austria; Novartis, Braz.; Novartis, Chile; Novartis, Denm.; Novartis, Hung.; Novartis Consumer, Hung.; Novartis, Israel; Novartis, Malaysia; Novartis Consumer, Neth.; Novartis, Norw.; Novartis, Rus.; Novartis OTC, Singapore; Novartis, Swed.; Novartis, Switz.; Novartis Consumer, Ukr.; Novartis, USA; Novartis, Venez.
Terbinafine (p. 593·3) or terbinafine hydrochloride (p. 593·3).
Fungal infections of the skin, hair, scalp, and nails.

Lamisil AF Defense *Novartis Consumer, USA.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Lamisil Odor Eze *Novartis, NZ.†*
Aloe vera (p. 1693·2); aluminium starch octenylsuccinate; corn starch (p. 2095·1); silicon dioxide (p. 2208·3); talc (p. 1722·2).
Foot odour.

Lamisilate *Novartis, Braz.*
Terbinafine (p. 593·3).

Novartis Sante, Fr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Lamisilatt *Novartis Consumer, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

LamisilDermgel *Novartis Sante, Fr.*
Terbinafine (p. 593·3).
Fungal skin infections.

Lamispor *Cipla-Medpro, S.Afr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lamitel *Rompharm, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Lamitor *Torrent, Braz.; Torrent, India; Torrent, Philipp.; Torrent, Rus.; Reddy, S.Afr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamitrin *Hexal, Austral.†; GSK, Hung.; GSK, Pol.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamivir *Cipla, India; GPO, Thai.; Cipla, Venez.*
Lamivudine (p. 1000·2).
HIV infection.

Lamivir S *Cipla, India.*
Lamivudine (p. 1000·2); stavudine (p. 1015·3).
HIV infection.

Lamivox *Aurobindo, India.*
Lamivudine (p. 1000·2).
HIV infection; chronic hepatitis B.

Lamiwin *Alembic, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lamix *Merck, Port.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamizol-O *Leben, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Lamna-C *Alna, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Lamo *TAD, Ger.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamocas *Casasco, Arg.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamoctril *Teuto, Braz.*
Lamotrigine (p. 527·2).

Lamodex
Note: this name may be used for preparations of different composition.
Dexcel, Israel.
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Guardian, Indon.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Lamogin *FDC, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamogine *Alphapharm, Austral.; Montrose, Cz.†; Trima, Israel.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamolep *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

LamoMerck *Generics, Pol.*
Lamotrigine (p. 527·2).
Epilepsy.

Lamomylan *Mylan, Spain.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamonte-BG *Geno, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Lamopan *Medis, Neth.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamo-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamorig *Unichem, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamoro *Pinewood, Irl.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamostad *Alkem, India.*
Lamivudine (p. 1000·2); stavudine (p. 1015·3).

Lamostad-N *Alkem, India.*
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); stavudine (p. 1015·3).

Lamosyn *Sun, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamot *Alet, Gr.*
Lamotrigine (p. 527·2).

Lamotax *Ranbaxy, Cz.*
Lamotrigine (p. 527·2).
Epilepsy.

Lamotri *Hexal, Cz.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamotrig *Actavis, Ger.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamotrigal *Cipla, Neth.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamotrihexal *Hexal, Pol.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamotril *Omedir, Arg.†*
Lamotrigine (p. 527·2).
Epilepsy.

Lamotrin *Actavis, Hong Kong; Pharma Start, Ukr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamotrine *Mepha, Switz.*
Lamotrigine (p. 527·2).
Epilepsy.

Lamotrix *Uniao Quimica, Braz.; Medochemie, Cz.; Medochemie, Gr.; Medochemie, Malaysia; Glenmark, Pol.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamox *Richter, Pol.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lamoxy *Hetero, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lamoxy-BX *Hetero, India.*
Amoxicillin trihydrate (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

Lamozor *Orion, Pol.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lampicin
Note: this name may be used for preparations of different composition.
Bright Future, Hong Kong.†
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Grunenthal, Mex.†
Ampicillin (p. 218·2), ampicillin sodium (p. 218·2), or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Lampit *Bayer, Chile.*
Nifurtimox (p. 941·3).
Trypanosomiasis.

Lampo *Chemo-Drugs, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lampoflex *Lampugnani, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Lampopram *Lampugnani, Ital.†*
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Lampral *Biotech, Venez.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Lampren *Novartis, Jpn; Novartis, Neth.; Padro, Spain.†*
Clofazimine (p. 273·3).
Leprosy.

Lamprene *Novartis, Austral.; Scanpharm, Cz.; IFET (ΙΦΕΤ), Gr.; Novartis, NZ; Novartis, USA.*
Clofazimine (p. 273·3).
Leprosy.

Lamprène *Novartis, Fr.*
Clofazimine (p. 273·3).
Leprosy.

Lamsyn-Z *Synmedic, India.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Lamuna *Hexal, Ger.†*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lamuran *SIT, Ital.*
Raubasine (p. 1485·1).
Peripheral circulatory disorders.

Lamuvid *Sarabhai Piramal, India.*
Lamivudine (p. 1000·2).
HIV infection; chronic hepatitis B.

Lamuzid *Zydus, India.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Lamzid *Aspen, S.Afr.*
Zidovudine (p. 1024·2); lamivudine (p. 1000·2).
HIV infection.

Lan Di *Haini, China.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Lan *Intas, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lan Le *Topfond, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Lan Gui *Qi Du, China.*
Citicoline sodium (p. 2480·2).

Lan Pu *Lukang Chenxin, China.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lan Qi *Jincheng Haisi, China.*
Rifamycin sodium (p. 354·3).

Lan Sha *Winsunny, China.*
Olmesartan medoxomil (p. 1459·2).

Lan Xi Duo *Tuo Bin, China.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; dyspepsia; hypersecretory disorders.

Lan Xin *Qi Du, China.*
Matrine.

Lan Xu *Qi Du, China.*
Inosine (p. 2533·1).

Lan Yu *Nuokang, China.*
Sodium new houttuyfonate.

Lanabal *Landson, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Lanacane
Note: this name may be used for preparations of different composition.
Combe, Irl.; Combe, Israel†; Combe, Spain; Combe, UK; Combe, USA.
Benzocaine (p. 1980·2).
Skin irritation; skin disorders; local anaesthesia.
Formula, NZ.
Benzocaine (p. 1980·2); resorcinol (p. 1718·3).
Skin irritation.

Lanacane Anti-Bacterial First Aid *Reckitt Benckiser, Canad.*
Benzethonium chloride (p. 1738·1); benzocaine (p. 1980·2).

Lanacane Medicated Cream *Reckitt Benckiser, Canad.*
Benzocaine (p. 1980·2); resorcinol (p. 1718·3).
Skin disorders.

Lanacane Medicated Powder *Combe, UK.*
Menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation.

Lanacetine *Landson, Indon.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Lanacine *Lannacher, Austria.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Lanacol *Landson, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Lanacordin *Kern, Spain.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Lanacort *Combe, Israel; Combe, Ital.; Combe, UK; Combe, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Lanadexon *Landson, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Lanafine *Niche, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lanaflex *Nutricia, Ital.*
Food for special diets.
Phenylketonuria.

Lanagerin *Zentiva, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Lanaginkola *Landson, Indon.; Pertiwi Agung, Malaysia.*
Ginkgo biloba (p. 2512·3).
Dementia; tonic; circulatory disorders.

Lanagogum *Landson, Indon.*
Greater celandine (p. 2522·2); turmeric (p. 2218·1); spinaceae; lecithin (p. 2542·2); peppermint oil (p. 1877·1); turmeric oil (p. 2218·1).
Digestive disorders.

Lanakeloid *Landson, Indon.; Pertiwi Agung, Malaysia; Pertiwi Agung, Singapore.*
Centella (p. 1698·3).
Burns; wounds; circulatory disorders.

Lanakeloid-E *Landson, Indon.*
Centella (p. 1698·3); vitamin E (p. 2119·1).
Burns; wounds.

Pertiwi Agung, Malaysia; Pertiwi Agung, Singapore.
⊗Centella (p. 1698·3); vitamin E (p. 2119·1); glycerol (p. 2517·2).
Skin disorders.

Lanamol *Landson, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Lanamont *Chrispa (Χρισπα), Gr.; SJA, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Lanaphilic *Medco, USA.*
⊗Urea (p. 1727·3).
Dry skin; hyperkeratosis.

Medco, USA.
Vehicle for topical preparations.

Lanaprost *Landson, Indon.†; Pertiwi Agung, Malaysia; Pertiwi Agung, Singapore.*
Saw palmetto (p. 2363·3).
Male tonic; benign prostatic hyperplasia.

Lanareuma *Landson, Indon.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Lanarif *Landson, Indon.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Lanate *Douglas, Malaysia; Douglas, NZ†; Douglas, Singapore.*
Ammonium lactate (p. 1694·3).
Dry skin disorders.

Lanatilin *Wabosan, Austria.*
β-Acetyldigoxin (p. 1290·2).
Heart failure.

Lanaven *Landson, Indon.*
Soya bean (p. 2092·3); aesculus (p. 2431·2); citrus complex.
Venous disorders.

Lanaven Plus *Landson, Indon.†*
Aesculus (p. 2431·2); citrus complex; lecithin (p. 2542·2); grape seed (p. 2521·3).
Venous disorders.

Lanavision *Landson, Indon.*
Capsules: Myrtillus (p. 2566·2).
Circulatory eye disorders.

Landson, Indon.
Syrup: Myrtillus (p. 2566·2); betacarotene (p. 2051·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin B substances (p. 2102·3).
Circulatory eye disorders.

Lanavision Plus *Landson, Indon.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1); vitamin A (p. 2098·3); pyridoxine hydrochloride (p. 2105·3); tocopherol acetate (p. 2119·2); chromium (p. 2055·3); zinc (p. 2126·1); selenium (p. 2086·3); taurine (p. 2626·2); glutamine (p. 2070·3); cysteine hydrochloride (p. 2058·3); lecithin (p. 2542·2).
Circulatory eye disorders.

Lanbaixing *Minsheng, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Lanbax *Ranbaxy, Pol.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanbica *Sandoz, Cz.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Lanbicamid *GL Pharma, Hung.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Lancap *Pharma Dynamics, S.Afr.*
Lansoprazole (p. 1851·3).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Lance *Candor, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lance-D *Candor, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lancef *Landson, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Lancer *East West, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lancerol *Arterium, Ukr.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lancetan *Prolab, Pol.*
Ribwort plantain (p. 2604·2).
Respiratory-tract congestion.

Lanceticum *Theiss Naturwaren, Pol.*
Ribwort plantain (p. 2604·2).
Cough; catarrh.

Lanchek *Euphoric, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lancibay *Bayer, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lancid *Micro, India; Kalbe, Indon.; Micro, Rus.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; dyspepsia; Zollinger-Ellison syndrome.

Lancidom *Micro, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lanciprol *Med-One, Gr.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Lancitone-CS *Avalanche, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); zinc (p. 2126·1).

Lancitone-CZ *Avalanche, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc (p. 2126·1).

Lancizin *Avalanche, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Lancolin *Landson, Indon.*
Citicoline sodium (p. 2480·2).
Head injury; hemiplegia; mental function impairment.

Lancus *Cadila, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Landaco *Landsteiner, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Landel *Zeria, Jpn.*
Efonidipine hydrochloride ethanolate.
Hypertension; angina pectoris.

Landex *Egis, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

LanDi *ZhongTian, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Landia *Actavis, Hung.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Landip *Micro, India.*
Lercanidipine (p. 1419·3).
Hypertension.

Lando *Pyridam, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Landolaxin *Faran, Gr.*
Lisinopril (p. 1420·3).
Hypertension.

Landrolen *Landsteiner, Mex.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Lands *Hands, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Landstav *Landsteiner, Mex.†*
Stavudine (p. 1015·3).
HIV infection.

Landvir *Landsteiner, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Laneli *Medley, Braz.*
Vitamins; minerals.

Lanetik *Special Product's Line, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).

Lanex
Note: this name may be used for preparations of different composition.
Lavipharm, Gr.
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*
SoSe, Ital.
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Lanexat *Roche, Braz.; Roche, Chile; Roche, Fin.†; Roche, Mex.; Roche, Swed.; Roche, Venez.*
Flumazenil (p. 1551·3).
Benzodiazepine overdosage; reversal of benzodiazepine-induced sedation.

Lanfast *Julphar, UAE.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lanfetil *Landsteiner, Mex.*
Mycophenolate mofetil (p. 1961·1).
Renal, cardiac, or hepatic transplant rejection.

Lanfix *Landson, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Lanfluzol *Landsteiner, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Lang De *Hailing, China.*
Lysine hydrochloride (p. 2079·3).
Cerebral ischaemia; cerebral trauma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lang Du *Wu Zhou Tong, China.*
Liver peptide hydrolysate (p. 2444·1).

Lang Fan *Kang Ji Er, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Lang Ji De *Yi Ao, China.*
Enoxacin gluconate.
Bacterial infections.

Lang Ming *Kangnuo, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Lang Ning *Haixin, China.*
Troxerutin (p. 2505·3).

Lang Qing *GuoGuang, China.*
⊗Bumetanide (p. 1329·1).
Oedema; hypertension.

Lang Rui *Ke Lun, China.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; bronchitis.

Lang Su *Dayinhaiyang, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Lang Yi *Langyi, China.*
Nystatin (p. 590·3); nifuratel (p. 941·2).

Lang Yue *Lifeshine, China.*
Levofloxacin hydrochloride.
Bacterial eye infections.

Langastrol *Medipharm, Chile.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Langerin *Zentiva, Cz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Langes *Sperko, Ukr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Langiprav *Boniscontro & Gazzone, Ital.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Langjing *Simcere, China.*
Clemastine fumarate (p. 622·3).
Hypersensitivity reactions.

Langoran *Sanofi-Aventis, Fr.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Langtian *Sine, China.*
Moclobemide (p. 437·2).
Depression.

Laniazid *Lannett, USA.*
Isoniazid (p. 311·2).
Tuberculosis.

Lanicor *HLB, Arg.; Teofarma, Ger.; Vargas, Venez.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Lanip *Winsome, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanip-D *Winsome, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lanirapid *Chugai, Jpn; Kern, Spain.*
Metildigoxin (p. 1433·1).
Heart failure; arrhythmias.

Lanitop *Cheplapharm, Austria; EuroCept, Belg.; Riemser, Ger.; Farmalex, Gr.; Riemser, Gr.; Roche, Hong Kong†; Adienne, Ital.; Pharmakern, Port.; Vargas, Venez.*
Metildigoxin (p. 1433·1).
Heart failure; arrhythmias.

Lanmer *Landson, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Lannapril *GL Pharma, Austria.*
Ramipril (p. 1483·3).
Hypertension.

Lannapril plus *GL Pharma, Austria.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lannatam *Lannacher, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Lano *Biosans, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Lanoc *GL Pharma, Austria.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine.

Lanocardique *Faran, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Lanodil *Landson, Indon.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Lanodizol *Diba, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Lanogard *Quest, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanogastro *Teuto, Braz.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Lanol
Note: this name may be used for preparations of different composition.
Hetero, India.
Paracetamol (p. 115·1).
Pain; fever.
Nakornpatana, Thai.
Calamine (p. 1697·2); zinc oxide (p. 1729·1); phenol (p. 1763·3); camphor (p. 2466·2); menthol (p. 2553·2).
Skin disorders.

Lanolept *Lannacher, Austria.*
Clozapine (p. 1057·3).
Schizophrenia.

Lanolone *Sriprasit, Malaysia.*
Allopurinol (p. 600·2); benzbromarone (p. 603·3).
Hyperuricaemia.

Lanolor *Squibb, USA.*
Emollient and moisturiser.

Lanol-Zinc *Valmor, Venez.*
Zinc oxide (p. 1729·1).
Skin disorders.

Lanomycin *Pharmathen, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Lanopin *Molekule, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Lan-O-Smooth *Geritrex, USA.*
wool fat (p. 2219·3).
Emollient.

Lanotan *Mann, Hung.; Farmak, Ukr.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Lanotan T *Farmak, Ukr.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Lanotrix *Medochemie, Singapore.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lanovit *Otto, Indon.*
Vitamins; minerals.
Tonic.

Lanox *Gland, Philipp.*
Digoxin (p. 1353·3).
Supraventricular arrhythmias; heart failure.

Lanoxin *Roemmers, Arg.; Aspen, Austral.; GSK, Belg.; Pharmascience, Canad.; Glaxo Wellcome, Gr.; Sigma, Hong Kong†; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; Aspen, Malaysia; Aspen, Malaysia; GSK, Mex.; Aspen, Neth.; Orion, Norw.; Healthcare Logistics, NZ; GSK, Philipp.; Aspen, Port.; GSK, S.Afr.; Aspen, Singapore; Orion, Swed.; Aspen, Thai.; Co-Pharma, UK; Covis, USA.*
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Lanoz *Osper, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanpirome *Landson, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Lanpracid *Pharos, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Lanpro *Unichem, India; Unichem, Malaysia.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lanrec *KRKA, Fin.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansacid *Actavis, Hung.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansazol *Sandoz, Turk.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lans-DX *Zydus, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lansec *Cipla, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lansek A *Investi, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lansenol *Landsteiner, Mex.*
Difenidol hydrochloride (p. 1835·1).
Nausea and vomiting; vertigo.

Lanset *Purewin, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lansi Kit *Zydus, India.*
1 Tablet, amoxicillin (p. 216·2); 1 capsule, lansoprazole (p. 1851·3); 1 tablet, tinidazole (p. 949·2).

Lansiclav *Landson, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Lansinoh *Key, Austral.; Lansinoh, USA.*
Wool fat (p. 2219·3).
Nipple care; emollient.

Lansinoh Diaper Rash *Lansinoh, USA.*
Wool fat (p. 2219·3); zinc oxide (p. 1729·1); dimeticone (p. 2209·3).
Nappy rash.

Lanso *Iasis, Gr.; Keshav, India; Taro, Israel; Noripharma, Malaysia.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; hypersecretory disorders; dyspepsia.

Lanso Tad *TAD, Ger.†*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansobene *Ratiopharm, Austria.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Lans-OD *Zydus, India; Wintac, Malaysia.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; hypersecretory disorders; dyspepsia.

Lansodin *ACME, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lansodom *Medley, Braz.†*
Lansoprazole (p. 1851·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Lansofast *Zydus, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lansofed *Moschimfarm, Rus.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lansogamma *Worwag, Ger.†*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansogen *Generics, Hung.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansohexal *Hexal, Austria.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansol *Moraceae, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

LansoLek *Sandoz, Pol.†*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lansoloc *Cipla, S.Afr.*
Lansoprazole (p. 1851·3).
Gastric hyperacidity; heartburn; dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Lansomac *McNeil & Argus, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lansone *Gedeon Richter, Hung.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansoprax *Drossapharm, Switz.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lansoprid *Medley, Braz.†*
Lansoprazole (p. 1851·3); bromopride (p. 1824·2).
Gastro-oesophageal reflux; dyspepsia.

Lansoprol *Genericon, Cz.; Nobel, Turk.; Nobel, Ukr.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastritis; gastric hyperacidity; dyspepsia.

Lansoptol *KRKA, Hung.; KRKA, Rus.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanso-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansor *Sanovel, Turk.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Lansoram *Labormed, Cz.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansoriv *East African, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lansovax *Vivax, Venez.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansox *Takeda, Ital.; Pharmout, Port.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansoyl *Ivax, Arg.; McNeil, Belg.; Johnson & Johnson, Fr.; Actipharm, Switz.*
Liquid paraffin (p. 2191·2).
Constipation.

Lansoÿl *Aurium, Canad.*
Liquid paraffin (p. 2191·2).
Constipation.

Lansoz *Finecure, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanspep *Khandelwal, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanspro *Ind-Chemie, India; XL, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lanspro-D *Ind-Chemie, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lansu *Changzhou Siyao, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Lansyn *Synthon, Neth.*
Olanzapine benzoate (p. 1089·3).
Schizophrenia; mania.

Lantac *Laborate, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration; dyspepsia.

Lantacid *Christo, Hong Kong.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Flatulence; gastric hyperacidity; heartburn; dyspepsia.

Lantanon *Organon, Ital.; Adcock Ingram, S.Afr.; MSD, Spain.*
Mianserin hydrochloride (p. 434·2).
Depression.

Lantarel *Pfizer, Ger.*
Methotrexate sodium (p. 822·2).
Rheumatoid arthritis; psoriatic arthritis; psoriasis; juvenile idiopathic arthritis.

Lanterbine *Ethypharm, Hong Kong.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Lanthonate *Micro, India.*
Lanthanum carbonate (p. 1556·2).
Hyperphosphataemia in renal failure.

Lantiapin *Gerot, Hung.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Lantidin *Hanlim, Philipp.*
Phenytoin sodium (p. 538·2).
Epilepsy; status epilepticus; seizures associated with neurosurgery or head injury; trigeminal neuralgia.

Lantiflam *Landson, Indon.*
Ketoprofen (p. 79·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Lantigen B *Bruschettini, Ital.*
Antigen extracts of: *Streptococcus pneumoniae; Streptococcus pyogenes; Moraxella catarrhalis; Staphylococcus aureus; Klebsiella pneumoniae; Haemophilus influenzae* type b.
Upper respiratory-tract infections.

Lusomedicamenta, Port.
Antigenic extracts from *Streptococcus pneumoniae; Streptococcus pyogenes; Moraxella catarrhalis; Staphylococcus aureus; Klebsiella pneumoniae; Haemophilus influenzae.*
Respiratory-tract disorders.

Lantil *KRKA, Fin.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lantipain *Landson, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Lantiseptic *Summit, USA.*
Wool fat (p. 2219·3); beeswax; wool alcohols; liquid paraffin; soft paraffin.
Dry skin.

Lantiseptic Multi-Purpose *Summit, USA.*
Menthol (p. 2553·2); zinc oxide (p. 1729·1); in an emollient base.

Lanton *Rafa, Israel.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders; dyspepsia.

Lantox *Nike-Med, Rus.*
Botulinum A toxin (p. 2017·1).
Blepharospasm; hemifacial spasm; strabismus; spasmodic torticollis; spasticity.

Lantrea *Pliva Krakow, Pol.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lantrom *Landsteiner, Mex.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Lantulos *Landson, Indon.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lanturol *Landson, Indon.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Lantus *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi Pasteur, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Aventis, USA; Sanofi-Aventis, Venez.*
⊗Insulin glargine (p. 475·3).
Diabetes mellitus.

Lanvis *GSK, Arg.; Aspen, Austral.; GSK, Belg.; GSK, Braz.; Triton, Canad.; GSK, Chile; GSK, Cz.; Genopharm, Fr.; GSK, Gr.; Aspen, Hong Kong; GSK, Irl.; Perrigo, Israel; GSK, Malaysia; Aspen, Neth.; Healthcare Logistics, NZ; GSK, Pol.; Aspen, S.Afr.; GSK, Swed.; Pro Concepta, Switz.; Aspen, Thai.; GSK, Turk.; GSK, UK.†*
Tioguanine (p. 871·3).
Leukaemias.

Lanvone *KRKA, Fin.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanx *Elea, Arg.*
⊗Spironolactone (p. 1499·3).
Oedema; heart failure; cirrhosis; nephrotic syndrome; hyperaldosteronism; hypertension.

Lanxes *Aamorb, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lanxes-A *Aamorb, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Lanxes-H *Aamorb, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lanz *Sigma, Braz.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Lanzaar *Berlin Pharm, Thai.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; stroke prophylaxis.

Lanzabel *Nobel, Rus.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lanzacor *Neo Quimica, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Lanzamed *Germed, Braz.*
Olanzapine (p. 1089·3).

Lanzap *Reddy, India; Reddy, Rus.; Reddy, Ukr.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome; systemic mast cell disease; pancreatitis.

Lanzapin *Biogened, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

Lanzatol *Focus Farma, Neth.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzedin *Biofarma, Turk.*
Lansoprazole (p. 1851·3).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzee *Zee, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanzee-DM *Zee, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lanzek *Lilly, Austral.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder; schizophrenia.

Lanzep *Terramedic, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastric hyperacidity.

Lanziop *Norton Waterford, Irl.†*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzip *Cubit, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanzo *Zydus, India; Pfizer, Norw.; Pfizer, Swed.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; hypersecretory disorders; dyspepsia.

Lanzoacid *Lafedar, Arg.*
Lansoprazole (p. 1851·3).

Lanzogastro *BioSaude, Port.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzogen *Kromme Rijn Apotheek, Pol.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzohex *Hexal, Philipp.†*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Lanzol *Ache, Braz.; Verisfield, Gr.; Cipla, Hong Kong; Cipla, India; Rowex, Irl.; Mylan, NZ; Teva, Spain; Dollder, Venez.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; heartburn; dyspepsia; gastritis.

Lanzole *Chunggei, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Lanzopen *Morepen, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lanzopept *Geolab, Braz.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzopral *Roemmers, Arg.; Pharma Investi, Chile; Roemmers, Venez.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Lanzopral Heli-Pack *Pharma Investi, Chile.*
Capsules, lansoprazole (p. 1851·3); tablets, amoxicillin trihydrate (p. 216·2); tablets, clarithromycin (p. 266·2).
Helicobacter pylori *eradication.*

Lanzopran *Ranbaxy, Austral.; Royton, Braz.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Lanzor *Sanofi-Aventis, Fr.; Aventis, Ger.†; Sanofi-Aventis, S.Afr.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; heartburn; dyspepsia; gastric hyperacidity.

Lanzostad *Steigerwald, Pol.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lanzox *Kalbe, Indon.*
Botulinum A toxin (p. 2017·1).
Strabismus; blepharospasm; hemifacial spasm.

Lanzul *KRKA, Cz.; KRKA, Pol.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lao Mai Na *Xinbeijiang, China.*
Urapidil (p. 1520·2).
Hypertension; hypertensive emergencies.

Lap *Plus, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lap Plus *Plus, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lapainol *Orpha-Devel, Irl.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Lapase *Cypress, USA.*
⊗Pancreatin (p. 2579·3).
Digestive enzyme deficiency.

Lapenax *Novartis, Arg.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses in parkinsonism.

Lapenza *Smart Intermed, Gr.*
Olanzapine (p. 1089·3).

Lapibal *Lapi, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; tinnitus; vertigo; vitamin B_{12} deficiency.

Lapibion *Lapi, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Neuritis; neuralgia; neuropathy; asthenia; morning sickness.

Lapibroz *Lapi, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lapicef *Lapi, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Lapices Epiderm Metadier *Prats, Spain.†*
Dithranol (p. 1701·2); salicylic acid (p. 1719·1).
Skin disorders.

Lapidar 4 *Kunzle, Switz.*
Rutoside (p. 2505·3); aescin (p. 2431·2).
Venous insufficiency.

Lapidar 10 *Kunzle, Switz.*
Tablets: Frangula bark (p. 1843·3); senna (p. 1885·1); liquorice (p. 1853·2).
Constipation.

Lapiden *Actavis, Hung.*
⊗Indapamide (p. 1409·2).

Lapifed *Lapi, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; sinusitis; allergic disorders.

Lapifed DM *Lapi, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; rhinitis; nasal congestion.

Lapifed Expectorant *Lapi, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Lapiflox *Lapi, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lapikot *Lapi, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Lapimox *Lapi, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Lapimuc *Lapi, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Lapirom *Lapi, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Lapisiv *Lapi, Indon.*
Syrup: Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); ammonium chloride (p. 1656·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; cold symptoms.

Lapi, Indon.
Tablets: Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Cough; cold symptoms.

Lapistan *Lapi, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Lapixime *Lapi, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Lapol *Confar, Port.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lapozan *Medochemie, Cz.; Medochemie, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Lapra-D *Kaizen, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lapraz *Sanbe, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Laprazol *Vianex (Βιανεξ), Gr.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lapril *Jean-Marie, Hong Kong; Pharmasant, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Laprilen *Baldacci, Port.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Laprost *Oftalmi, Venez.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Laprost Plus *Micro, India.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Laproton *Tempo Scan Pacific, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lapsus *Klonal, Arg.*
Fluoxetine (p. 417·1).
Depression.

Laquifun *Panalab, Arg.*
Amorolfine (p. 569·1).
Fungal nail infections.

La-Quin *Stadmed, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Lara
Note: this name may be used for preparations of different composition.
Alkem, India.
Losartan potassium (p. 1422·2).
Hypertension.

Larabel *Grunenthal, Cz.†*
24 Tablets, chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Laracit *Laboratorios Chile, Chile; Teva, Mex.; Teva, S.Afr.*
Cytarabine (p. 774·1).
Leukaemias; lymphomas.

Laractyl *Patriot, Philipp.*
Chlorpromazine hydrochloride (p. 1045·2).
Anxiety; hiccup; nausea and vomiting; psychoses.

Laradex *Eurolab, S.Afr.*
⊗Letrozole (p. 817·1).

Larafen *Sandoz, UK.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

Laragon *Roemmers, Arg.*
Silymarin (p. 1561·2).
Liver disorders.

Lara-H *Alkem, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Laraned *Euraned, Gr.*
Glucosamine sulfate (p. 2515·3).

Larap *La Pharmaceuticals, India.*
Pimozide (p. 1096·3).
Schizophrenia; monosymptomatic hypochondria; paranoid states; Tourette syndrome.

Larapam
Note: this name may be used for preparations of different composition.
Sandoz, UK.
Tramadol (p. 139·2).
Pain.

Larbex *Teva, Neth.*
⊗Budesonide (p. 1625·1).
Asthma.

Larch Resin comp. *Weleda, UK.*
Ananassa fruit; lavender oil (p. 2541·1); larch resin.
Sore eyes.

Larcooral *Columbia, Arg.*
Staphylococcus; Micrococcus; Pneumococcus; Streptococcus; Klebsiella; *Moraxella catarrhalis; Haemophilus influenzae*; ascorbic acid (p. 2110·3).
Respiratory-tract infections.

Laremid *Polfa Warszawa, Pol.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Laremide *Lafedar, Arg.*
Acetylcarnitine hydrochloride (p. 2053·2).

Larenase *La Pharmaceuticals, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; hiccup.

Largactil *Sanofi-Aventis, Austral.; Sanofi-Aventis, Chile; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Teofarma, Ital.; Sanofi-Aventis, NZ; Vitoria, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Spain; Eczacibasi, Turk.; Sanofi-Aventis, UK.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; anxiety; agitation; behaviour disorders; induction of hypothermia; nausea and vomiting; depression; pain; premedication; schizophrenia; bipolar disorder; sleep disorders; autism; intractable hiccup; neuroses.

Sanofi-Aventis, Mex.
Chlorpromazine (p. 1045·2).
Psychoses; behaviour disorders; nausea and vomiting.

Largal Ultra *Septodont, Canad.*
Cetrimonium bromide (p. 1742·3); disodium edetate (p. 1550·3).

Largatrex
Note: this name may be used for preparations of different composition.
Vitoria, Port.†
Chlorpromazine hydrochloride (p. 1045·2).

Large Ecran *Guinot, Canad.*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Largo *Beacons, Singapore.*
Chlorpromazine hydrochloride (p. 1045·2).
Sedative; psychoses; nausea and vomiting; premedication.

Largopen *Bilim, Turk.*
Amoxicillin (p. 216·2), amoxicillin sodium (p. 216·2), or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Largy *Biophar, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Largy-M *Biophar, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Lariago *Ipca, India.*
Chloroquine phosphate (p. 650·1).
Malaria; hepatic amoebiasis; rheumatoid arthritis; lupus erythematosus.

Lariam *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Swed.; Roche, Switz.; Roche, UK; Roche, Ukr.; Roche, USA.†*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Laricid *Biofarma, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Laridox *Ipca, India.*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria.

Larifikehl *Sanum-Kehlbeck, Ger.*
Laricifomes officinalis e mycelio.
Homoeopathic preparation.

Larig *Rowex, Irl.*
Lamotrigine (p. 527·2).
Bipolar disorder; epilepsy.

Larigox *Globus, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Larimef *Ipca, India.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Larinate *Ipca, India.*
Artesunate (p. 648·2).
Malaria.

Larinate Kit *Ipca, India.*
3 Tablets, artesunate (p. 648·2); 1 tablet, pyrimethamine (p. 662·3); 1, 2, or 3 tablets, sulfadoxine (p. 363·3).
Malaria.

Larinate-MF *Ipca, India.*
3 tablets, artesunate (p. 648·2); 6 tablets, mefloquine (p. 657·1).
Malaria.

Laringex *Cazi, Braz.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Larit *Chemo-Drugs, India.*
Clarithromycin (p. 266·2).
Bacterial infections.

Larither *Ipca, India.*
Artemether (p. 648·1).
Malaria.

Larithro *Verisfield, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Laritol *Maver, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Laritol D *Maver, Mex.*
Loratadine (p. 633·2); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis.

Laritol Ex *Maver, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Laritol G *Maver, Mex.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); loratadine (p. 633·2).
Allergic rhinitis; cold symptoms.

Larixin *Taisho, Jpn.*
Cefalexin (p. 234·1).
Bacterial infections.

Larizin *Hizon, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections.

Larjancaina *Veinfar, Arg.*
Lidocaine hydrochloride (p. 1988·2). Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Larjanfilina *Veinfar, Arg.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Larmabak *Sidus, Arg.; Pfizer, Chile†; Thea, Fr.; Pharmex (Φαρμεξ), Gr.; Thea, Hong Kong; Thea, Philipp.†; Pfizer, Singapore; Santa, Turk.; Pfizer, Venez.*
Sodium chloride (p. 1795·1).
Dry eyes; eye wash.

Larmadex *Bayer, Arg.*
⊗Goserelin acetate (p. 2282·3).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids; female infertility.

Larmax D *Andromaco, Chile.†*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Larmécran *Thea, Fr.†*
Povidone (p. 2204·3).
Dry eyes; contact lens lubricant.

Larmes Artificielles *Teofarma, Fr.*
Sodium chloride (p. 1795·1).
Dry eyes.

Larmycetin *Lark, India.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Laromin *Kleva, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Laroscorbine *Bayer Sante, Fr.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; asthenia.

Larotabe *Bayer, Chile.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1); selenium (p. 2086·3); manganese (p. 2081·2).
Antoxidant preparation.

Bayer Consumer, Arg.
Betacarotene (p. 2051·1); calcium ascorbate (p. 2111·1); vitamin E (p. 2119·1); minerals.
Antoxidant preparation.

Larover *Aglowmed, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Laroxyl *Teofarma, Fr.; Roche, Ital.; Deva, Turk.; Roche, Turk.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis; migraine; headache; neuropathic pain.

Larpose *Cipla, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication.

Larprim *Lark, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Larry *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Ketoconazole (p. 585·3).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis; scalp disorders.

Lars *Duncan, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Larsen *Fada, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Larsimal *Poen, Arg.*
⊗Fluorometholone (p. 1637·2); tetryzoline (p. 1678·3).
Inflammatory eye disorders.

Lartan *Avinash, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lartan-AM *Avinash, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Lartan-H *Avinash, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lartavan *Liconsa, Neth.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Lartil *CCM, Malaysia.*
Prochlorperazine mesilate (p. 1098·3).
Nausea; vomiting; psychoses; anxiety.

Lartokaz *Liconsa, Cz.; Liconsa, Neth.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Larus *Gedeon Richter, Cz.; Richter, Pol.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Larutan *Salvay, Port.†*
Eprosartan mesilate (p. 1376·2).
Hypertension.

LarvE *SMTL, UK.*
Sterile larvae of *Lucilia sericata* (p. 1711·1).
Infected or necrotic wounds.

Larvin *Farmex, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Larvitan *Cimed, Braz.*
Vitamins.

Larydol *Dolisos, Canad.†*
Apis mellifica (p. 2445·2); arum triphyllum; belladonna (p. 2453·3); echinacea angustifolia (p. 2498·1); calcium sulfide crude (p. 1721·3); phytolacca decandra (p. 2593·2).
Homoeopathic preparation.

Larylin Husten-Löser Pastillen *Cheplapharm, Ger.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscid or excessive mucus.

Larylin Husten-Stiller *Robugen, Ger.*
Dropropizine (p. 1662·2).
Cough.

Laryngarsol *Sanofi-Aventis, Belg.†*
Lozenges: Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Laryng-O-Jet *Celltech, UK.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Loryngomedin N *Artegodan, Ger.†*
Hexamidine isetionate (p. 1754·3).
Mouth and throat disorders.

Laryngsan *Opfermann, Ger.†*
Camphor (p. 2466·2); peppermint oil (p. 1877·1).
Cold and influenza symptoms; laryngitis; pharyngitis.

Larynsol *Herbes Universelles, Canad.†*
Benzoic acid (p. 1738·2); chlorobutanol (p. 1747·2); cineole (p. 2479·1).

Lary-Phory *Dr P, Ger.*
Carmellose (p. 2175·1); sodium chloride (p. 1795·1); magnesium chloride (p. 1787·1).
Dry mouth; mouth and throat lubricant.

Larzid *Malar, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Lasa *Grunenthal, Port.*
Famotidine (p. 1842·1).
Gastric hyperacidity.

Lasa con Codeina *Foes, Spain.*
⊗Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Lasain *Inibsa, Spain.†*
Metamizole magnesium (p. 53·3).
Pain; fever.

Lasal *Lapi, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Lasal Expectorant *Lapi, Indon.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Lasalar-Y *Alpharma, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Lasalar-Y Simple *Alpharma, Mex.*
Clioquinol (p. 273·1).
Skin infections.

Lasanol *Sanopharm, Gr.*
Glucosamine hydrochloride (p. 2515·3).

Lasapride *ITF, Gr.*
Cisapride (p. 1831·3).
Gastric motility disorders.

Lasazin *Leovan, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Lasea *Spitzner, Ger.*
Lavender oil (p. 2541·1).
Anxiety.

Laser *Princeps, Ital.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; neuralgia; gout.

Laservis *Chemedica, Ger.; Chemedica, Switz.*
Sodium hyaluronate (p. 2526·2).
Aid in laser treatment of the eye; adjunct in ocular procedures.

Lasgan *Lapi, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

L-Asicet *Willow, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

L-Asiflox *Willow, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lasikal *Borg, UK.*
⊗Furosemide (p. 1387·1); potassium chloride (p. 1793·2).
Oedema.

Lasilacton *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austria; Sanofi-Aventis, Mex.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Ascites; oedema; heart failure; nephrotic syndrome; hyperaldosteronism.

Lasilactona *Sanofi-Aventis, Braz.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Hypertension; oedema.

Lasilactone *Sanofi-Aventis, India; Sanofi-Aventis, Switz.; Borg, UK.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Oedema; hypertension; ascites.

Lasiletten *Sanofi-Aventis, Neth.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Lasilix *Sanofi-Aventis, Fr.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Lasiride *Sanofi-Aventis, Arg.; Sanofi-Aventis, India.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Hypertension; oedema.

Lasitace *Sanofi-Aventis, Austria.*
⊗Furosemide (p. 1387·1); ramipril (p. 1483·3).
Heart failure.

Lasitone *Sanofi-Aventis, Ital.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Oedema.

Lasiven *Umeda, Thai.*
⊗Furosemide (p. 1387·1).
Oedema; heart failure; forced diuresis.

Lasix *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Ger.†; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Aventis, USA; Sanofi-Aventis, Venez.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; nephrotic syndrome; forced diuresis; heart failure; cirrhosis with ascites; oliguria; barbiturate poisoning; toxaemia of pregnancy.

Laslonvita *Valenta, Rus.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3); ethambutol hydrochloride (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Lasmalin *Lapi, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Lasoartro *Bayer, Ital.*
Ketoprofen lysine (p. 79·1).
Musculoskeletal and joint disorders; inflammation.

Lasoberon *Boehringer Ingelheim, Venez.*
Sodium picosulfate (p. 1887·2).
Constipation.

Lasole *Cure Quick, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lasole-D *Cure Quick, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lasolvan *Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion; neonatal respiratory distress syndrome.

Lasonil *Bayer, Gr.*
A heparinoid (p. 1401·1); hyaluronidase (p. 2527·2).

Bayer Consumer, Austral.†; Bayer, NZ; Bayer, Port.†; Bayer, Turk.
A heparinoid (p. 1401·1).
Bruising; haematomas; thrombophlebitis; varicose ulcers; soft-tissue injury.

Lasonil Gel *Bayer, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Lasonil N *Bayer, Gr.*
A heparinoid (p. 1401·1).

Lasoprol *Aegis, Hong Kong; Aegis, Singapore.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Laspal *Sanofi-Aventis, Pol.†*
Lysine aspirin (p. 84·3).
Fever; pain.

Laspar *Aspen, S.Afr.*
Asparaginase (p. 743·3).
Lymphoblastic leukaemias.

L-Aspase *Miracalus, India.*
Asparaginase (p. 743·3).
Lymphoblastic leukaemia.

Laspiro *Room, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; pain.

LAsprin *Cipla, Hong Kong.†*
Aspirin (p. 22·2).
Thromboembolic disorders.

Lassadermil *Edol, Port.*
Zinc oxide (p. 1729·1).
Skin disorders; minor burns and wounds.

Lassativi Vetegali *AFOM, Ital.†; Ogna, Ital.†*
Aloes (p. 1816·1); rhubarb (p. 1884·2).
Constipation.

Lassen *Iasis, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Lastacaft *Vistakon, USA.*
Alcaftadine (p. 615·1).
Allergic conjunctivitis.

Lastace *Ranbaxy, Mex.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction.

La-Stavir *GPO, Thai.*
Lamivudine (p. 1000·2); stavudine (p. 1015·3).
HIV infection.

Lastet *Kayaku, China; Kayaku, Cz.†; Cancernova, Ger.; Kayaku, Hung.†; Khandelwal, India; Pfizer, Ital.†; Kayaku, Jpn; Kayaku, Malaysia; Kayaku, Philipp.; Euro Nippon Kayaku, Pol.†; Kayaku, Rus.; Kayaku, Singapore; Kayaku, Thai.; Onko, Turk.*
Etoposide (p. 790·2).
Malignant neoplasms.

Lasticom *Tubilux, Ital.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Lastin *Meda, Fin.; Meda, Norw.; Meda, Swed.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis; allergic eye disorders; allergic conjunctivitis.

Lastinem *Venus, India.*
Cilastatin (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Norton, Ukr.†
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Lastrim *Chew, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Lastuss *FDC, India.*
Dextromethorphan (p. 1660·1) or dextromethorphan hydrobromide (p. 1660·1).
Cough.

Lastuss-D *FDC, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Lasuzef *Sel-J, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

LAtac *Cipla, Hong Kong.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Latacris *PH&T, Irl.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latalux *Jelfa, Cz.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latandrops *Vianex (Βιανεξ), Gr.*
Latanoprost (p. 2008·1).

Lataneau *Exelixis, Gr.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Lataneau Plus *Alapis, Irl.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Latanoflax *Sidus, Arg.†*
Latanoprost (p. 2008·1).
Glaucoma.

Latanomed *Dermapharm, Switz.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Latanopress *Roemmers Poen, Venez.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latanostad Comp *Stada, Denm.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Latano-Vision *OmniVision, Switz.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Latanox *Jadran, Ukr.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latapres *Valeant, Hung.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latar *Servocare, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Latariz *Sigillata, Neth.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Lataz *Rafarm, Gr.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Late *Vensat, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Latesil *CS, Port.*
Flufenamic acid (p. 65·1); myrtecaine (p. 1993·1); diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Latesyl *Roth, Austria.*
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Laticort *Almirall Hermal, Ger.; Medphano, Ger.; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.; Jelfa, Ukr.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Laticort-CH *Jelfa, Pol.†*
⊗Hydrocortisone butyrate (p. 1640·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Latilin *La Pharmaceuticals, India.*
Amitriptyline (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Latim *Cipla, India.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Latimodorf *Pharmadorf, Arg.*
⊗Latanoprost (p. 2008·1); timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Latim-POS *Ursapharm, Neth.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Latimvista *Sandoz, Spain.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Latiotim *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Norw.; Sandoz, Swed.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Latisona B *Biotenk, Arg.†*
⊗Meprednisone (p. 1642·2) or meprednisone hemisuccinate (p. 1642·2).
Corticosteroid.

Lotisse *Allergan, Canad.; Allergan, Israel; Allergan, Singapore; Allergan, USA.*
Bimatoprost (p. 2004·2).
Hypotrichosis of the eyelashes.

LAtiwen *Cipla, Hong Kong.†*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication.

Latlas *Atlas, Arg.*
Carbomer 974P (p. 2173·3); polyvinyl alcohol (p. 2204·2); lysine (p. 2079·3).
Dry eyes.

Latlas Fresh *Atlas, Arg.*
Carbomer 974P (p. 2173·3); polyvinyl alcohol (p. 2204·2); lysine hydrochloride (p. 2079·3); camphor (p. 2466·2); menthol (p. 2553·2).
Dry eyes.

Latlas Tears *Atlas, Arg.*
Hypromellose (p. 2189·2).
Dry eyes.

Latochek *Indoco, India.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Latochek-T *Indoco, India.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Latocom *Sun, India.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Latodrops *Intas, India.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Latof *Saval, Chile.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latof-T *Saval, Chile.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Latonid *Anasco, Fin.†*
Meloxicam (p. 86·3).
Osteoarthritis.

Latonina *Faran, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Latop *Rowex, Irl.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latop-D *La Pharmaceuticals, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Latoprost *Sun, China; Sun, India.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latoren *Anfarm, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Latotryd *Atlantis, Mex.*
Erythromycin (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Latran *Farmzaschita, Rus.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Latrea *PharOS, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Latren *Yuriya-Farm, Ukr.*
Pentoxifylline (p. 1465·3).
Cerebral, ocular, and peripheral vascular disorders.

Latrigil *Stada, Cz.†; Stada, Ukr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Latrigin *Baliarda, Arg.; Ultra, Mex.; KVZ, Ukr.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Latrimet *Lamda (Λαμδα), Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Latrix XM *Stratus, USA.*
⊗Urea (p. 1727·3).

Latropil *Lapi, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; behaviour disorders in children; alcoholism; asthenia.

Latrovin *Aurora, Gr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Latsol *Antibioticos, Mex.*
Latanoprost (p. 2008·1).
Glaucoma.

Lattulac *Sofar, Ital.*
Lactulose (p. 1850·3).
Hepatic encephalopathy; cirrhosis; constipation.

Latuda *Sunovion, Canad.; Takeda, Switz.; Sunovion, USA.*
Lurasidone hydrochloride (p. 1083·1).
Schizophrenia; bipolar disorder.

Latusin *Sano, Turk.†*
⊗Ephedrine hydrochloride (p. 1663·2); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2); codeine (p. 40·2).
Respiratory-tract congestion.

Latusol *Siegfried, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Latycin *Boucher & Muir, Austral.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial eye infections.

Latys *Leovan, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Laudamonium *Ecolab, Ger.*
Benzalkonium chloride (p. 1737·1).
Skin and surface disinfection.

Launol *Laboratorios Chile, Chile.*
Deltamethrin (p. 2152·1); piperonyl butoxide (p. 2160·2).
Pediculosis; scabies.

Laura *Ranbaxy, S.Afr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lauracalm *Socobom, Belg.†*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Laurak
Note: this name may be used for preparations of different composition.
Qualigen, Spain.
Levetiracetam (p. 531·1).
Epilepsy.

Laurette *Bayer Schering, Fin.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lauricin *Sons, Mex.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Laurimic *Effik, Spain.*
Fenticonazole nitrate (p. 578·1).
Fungal skin and nail infections; vulvovaginal candidiasis.

Laurimicina *Mavi, Mex.†*
Erythromycin (p. 291·2).
Bacterial infections.

Laurina *Organon, Cz.; Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hung.; Schering-Plough, Hung.; Organon, Neth.; Organon, Port.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
28-day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Laurinol Plus *Szama, Arg.*
Undecenoic acid diethanolamide (p. 596·3); cade oil (p. 1723·2); vitamin B_6 (p. 2105·3).
Psoriasis; scalp disorders.

Lauritran *Chinoin, Mex.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Lauroderme *Baldacci, Port.*
Salicylic acid (p. 1719·1); zinc oxide (p. 1729·1).
Skin inflammation and irritation.

Lauroderme Po *Baldacci, Port.*
Salicylic acid (p. 1719·1); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Skin disorders.

Lauromicina *New Research, Ital.*
Ointment: ⊗Fluocinolone acetonide (p. 1636·1); erythromycin stearate (p. 291·3).
Infected skin disorders.

New Research, Ital.
Tablets: Erythromycin stearate (p. 291·3).
Bacterial infections.

Lauter *E-Pharma, Ital.*
Domperidone (p. 1838·1).

Lav Ofteno *Sophia, Mex.*
Boric acid (p. 2459·3); borax (p. 2459·2).
Eye disorders.

Lavacole *Mosfarma, Rus.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Lavagin *Mayrhofer, Austria.†*
Lactic acid (p. 2539·1); sodium lactate (p. 1781·2).
Vaginal disorders.

Lavanda Sofar *Sofar, Ital.*
Anhydrous citric acid (p. 2480·3); sodium citrate (p. 1781·2); alum (p. 2439·1); phenol (p. 1763·3).
Vaginal disinfection.

Lavandula Compound *Phytomedicine, Austral.*
Lavender (p. 2541·1); ashwagandha (p. 2450·2); valerian (p. 2640·2); St John's wort (p. 449·1).
Anxiety.

Lavandula Oligoplex *Madaus, Arg.*
Lavender (p. 2541·1); calendula (p. 2465·2); hamamelis (p. 2523·3); arnica (p. 2447·2); comfrey (p. 2484·2).

Lavanid *Serag-Wiessner, Ger.*
Electrolytes (p. 1775·1); polihexanide hydrochloride (p. 1766·1).
Wound cleansing.

Lavarix *Ifars, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1).
Joint disorders.

Lavasept
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Rus.; Braun, Switz.
Polihexanide (p. 1766·1).
Bone and soft-tissue infections; wounds; skin and instrument disinfection; skin infections; burns.

Farmo Quimica, Chile.
Triclosan (p. 1773·2).
Hand disinfection; skin infections.

Lavaz *Ratiopharm, Cz.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Lavaza *Orion, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lavazyme *Sun, India.*
Capsules: Simeticone (p. 1886·2); amylase (p. 2442·1); *Lactobacillus acidophilus* (p. 2596·3).

Sun, India.
Oral drops; syrup: Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase from *Aspergillus oryzae* (p. 2442·1).

Lavement au Phosphate *Norgine, Belg.†*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Lavenax *Sigillata, Denm.†*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Lavenil *Bilim, Turk.*
Levodropropizine (p. 1662·3).

Lavenum *Synthesis, Rus.*
Heparin sodium (p. 1396·3).
Joint and soft-tissue disorders; thrombophlebitis.

Laver *Neopharm, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Laveran
Note: this name may be used for preparations of different composition.
Unicure, India.
Proguanil hydrochloride (p. 661·3).
Malaria.

Laverio *Elpen (Ελπεν), Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Lavesta *HCS, Neth.†*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lavesten *Stada, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Lavestra *KRKA, Hung.; KRKA, Spain.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; cerebrovascular risk reduction.

Lavestra H *KRKA, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Laveta *Alembic, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Laveta-A *Alembic, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3).

Laveta-D *Alembic, India.*
⊗Levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Lavichthol *Ichthyol, Austria.†*
Ictasol (p. 1706·1).
Skin disorders.

Laviest *Franco-Indian, India.†*
Saccharomyces cerevisiae (p. 2125·2).
Moniliasis after antibiotic therapy; vitamin B deficiency.

Lavinol *Qualigen, Spain.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lavi-Press *Lavipharm, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Lavir *Emcure, India.*
Lamivudine (p. 1000·2).
HIV infection; chronic hepatitis B.

Laviril *Jenburkt, India.*
Nutmeg (p. 2573·1); withania somnifera (p. 2450·2).

Lavisa *Gynea, Spain.*
Fluconazole (p. 578·2).
Fungal infections.

Lavistina *Tabuk, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Lavoclen *Prasco, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Lavoflox *Datla, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lavolen *Lacer, Spain.†*
Trisodium polysaccharide sulfate; a nonoxinol (p. 2199·1).
Contraceptive.

Lavomax *Nizpharm, Rus.; Nizhfarm, Ukr.*
Tilorone (p. 1019·2).
Viral infections.

Lavoptik *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ketotifen (p. 631·3).
Allergic eye disorders.

Lavoriz *Datla, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lavoxen *Daehan, Singapore.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Lavoxin *Ethical, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; lactation promotion.

Lawarin *ProMed, Cz.*
Warfarin sodium clathrate (p. 1527·1).
Thromboembolic disorders.

Lawenol *Prolab, Pol.*
Lavender oil (p. 2541·1).
Musculoskeletal and joint pain; neuralgia; skin disinfection.

Lax Ewe Jalea *Sanitas, Arg.†*
Liquid paraffin (p. 2191·2).
Bowel evacuation.

Lax Pills *G & W, USA.*
Sennosides (p. 1885·2).
Constipation.

Laxabene *Alter, Spain.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea.

Laxabixal *Roha, Spain.*
Bisacodyl (p. 1821·1).
Constipation.

Laxabon *Biophausia, Norw.; Biophausia, Swed.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Laxacaps *Gelcaps, Mex.*
Senna (p. 1885·1); prune (p. 1881·1).
Bowel evacuation; constipation.

Laxacin *Alexso, USA.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.

Laxacod *Galenium, Indon.†*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Lax-a-Day *Pendopharm, Canad.*
Macrogol 3350 (p. 2547·3).
Constipation.

Laxadilac *Galenium, Indon.†*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxadin *Teva, Israel.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxadinas *Nutridriver, Spain.†*
Cynara (p. 2490·3); aloes (p. 1816·1).
Constipation.

Laxadine *Galenium, Indon.*
⊗Phenolphthalein (p. 1877·3); liquid paraffin (p. 2191·2); glycerol (p. 2517·2).
Constipation; bowel evacuation.

Laxador *SA Druggists Self Med, S.Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

Laxador Senna *Aspen, S.Afr.*
Sennosides (p. 1885·2).

Laxadoron *Weleda, UK.*
Caraway (p. 2470·2); clove (p. 2481·2); centaury (p. 2473·2); peppermint leaf (p. 1877·1); achillea (p. 2427·3); senna leaf (p. 1885·1); aniseed (p. 2444·2); nectar hoyae carnosae.
Homoeopathic preparation.

Laxadryl *ANH, Thai.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxafytol *Tilman, Belg.*
Cascara (p. 1826·1).
Constipation.

Laxagetten *CT, Ger.*
Bisacodyl (p. 1821·1).
Constipation.

Laxal *Julphar, UAE.*
Calcium sennosides (p. 1885·1).
Constipation.

Laxalpin *Kwizda, Austria.†*
Senna (p. 1885·1); frangula bark (p. 1843·3); fennel (p. 2503·2); chamomile (p. 2474·1); guaiacum wood; liquorice (p. 1853·2); sambucus (p. 2609·3); adiantum capillus veneris; potassium sodium tartrate (p. 1879·3).
Constipation.

Laxamalt *Actipharm, Switz.*
Liquid paraffin (p. 2191·2).
Constipation.

Laxamex *Konimex, Indon.†*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxamin *Temis, Arg.*
Oral drops: Sodium picosulfate (p. 1887·2).
Constipation.

Temis, Arg.
Tablets: Bisacodyl (p. 1821·1).
Constipation.

Laxamix *Agropharm, Pol.†*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation.

Laxamucil *Orion, Fin.*
Ispaghula (p. 1849·1).
Constipation.

Laxan
Note: this name may be used for preparations of different composition.
Chew, Thai.
Methocarbamol (p. 2025·3).
Musculoskeletal pain.

JB Chemicals, India.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxana *Ifars, Indon.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxanat *Naturatec, Canad.*
Cascara (p. 1826·1); liquorice (p. 1853·2); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Laxans
Note: this name may be used for preparations of different composition.
Aliud, Ger.
Bisacodyl (p. 1821·1).
Constipation.

Laxans-ratiopharm *Ratiopharm, Ger.*
Bisacodyl (p. 1821·1).
Constipation.

Laxans-ratiopharm Pico *Ratiopharm, Ger.*
Sodium picosulfate (p. 1887·2).
Constipation.

Laxante Arceli *Gezzi, Arg.*
Liquid paraffin (p. 2191·2).
Constipation.

Laxante Bescansa Aloico *Bescansa, Spain.†*
Aloin (p. 1816·2); belladonna (p. 2453·3); phenolphthalein (p. 1877·3); rhubarb (p. 1884·2).
Constipation.

Laxante Bescansa Normal *Bescansa, Spain.†*
Senna (p. 1885·1).
Constipation.

Laxante Olan *Puerto Galiano, Spain.*
Senna (p. 1885·1).
Constipation.

Laxante Salud *Puerto Galiano, Spain.*
Senna (p. 1885·1).
Constipation.

Laxante Sanatorium *Santiveri, Spain.†*
Aloes (p. 1816·1); aniseed (p. 2444·2); sulfur (p. 1721·1); senna (p. 1885·1); chamomile (p. 2474·1).
Constipation.

Laxantil *Chemopharma, Chile.*
Sodium picosulfate (p. 1887·2).
Bowel evacuation; constipation.

Laxantis Species No 1 *Zdorovje, Rus.*
Buckthorn (p. 1824·2); urtica (p. 2639·3); achillea (p. 2427·3).
Constipation.

Laxantol *Herbapol Krakow, Pol.†*
Couch-grass (p. 2487·2); caraway (p. 2470·2); frangula (p. 1843·3); linseed (p. 2544·2); rhubarb (p. 1884·2).
Constipation; meteorism.

Laxarec *Galenium, Indon.*
Sodium laurilsulfate (p. 2210·3); macrogol 400 (p. 2547·3); sodium citrate (p. 1781·2); sorbitol (p. 2092·1).
Constipation; bowel evacuation.

Laxarin *Orion, Ukr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; hepatic coma.

Laxarol
Note: this name may be used for preparations of different composition.
ICM, Singapore.
Liquid paraffin (p. 2191·2).
Constipation.

Laxaron *Merck Medication Familiale, Fr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxasan
Note: this name may be used for preparations of different composition.
Gebro, Austria.
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Gebro, Switz.
Sodium picosulfate (p. 1887·2); fennel oil (p. 2503·3); peppermint oil (p. 1877·1).
Constipation.

Laxasium *Fahrenheit, Indon.*
Magnesium hydroxide (p. 1857·2).
Constipation; indigestion.

Laxat *Medinfar, Port.†*
Ispaghula (p. 1849·1).
Constipation; hypercholesterolaemia; ostomy regulation; irritable bowel syndrome.

Laxatab *Micro, India.*
Sodium picosulfate (p. 1887·2).

Laxatan M *Cassella-med, Ger.*
Macrogol (p. 2547·3); inulin (p. 2534·3); electrolytes (p. 1775·1).
Constipation.

Laxataur *Taurus, India.*
Ispaghula (p. 1849·1).

Laxatil *Nutripur, Canad.*
Frangula (p. 1843·3); aloe (p. 1816·1); rhubarb (p. 1884·2).
Constipation.

Laxatin *Nitro Organics, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxative Compound *Teva, Israel.*
Aloin (p. 1816·2); phenolphthalein (p. 1877·3); aloes (p. 1816·1); ipecacuanha (p. 1667·2); belladonna (p. 2453·3).
Constipation.

Laxative Pills *Tanta, Canad.*
Sennosides (p. 1885·2).

Laxative & Stool Softener *Rugby, USA.*
Docusate sodium (p. 1836·2); casanthranol (p. 1826·1).
Constipation.

Laxative Tablets *Herbal Concepts, UK.*
Aloes (p. 1816·1); cascara (p. 1826·1); senna (p. 1885·1); valerian (p. 2640·2).
Constipation.

Laxatol *Omega, Gr.; Roche, Gr.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Laxavit *Kela, Belg.*
⊗Docusate sodium (p. 1836·2); glycerol (p. 2517·2).
Constipation.

Laxbene
Note: this name may be used for preparations of different composition.
Ratiopharm, Austria.
Suppositories: Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Ratiopharm, Austria; Ratiopharm, Hung.
Bisacodyl (p. 1821·1); dimeticone (p. 1886·2).
Constipation; bowel evacuation.

Laxclav *Helax, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Laxclav-LB *Helax, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).

Laxcodyl *Pharmasant, Thai.*
Bisacodyl (p. 1821·1).
Constipation.

Laxeerdragees *Healthypharm, Neth.†*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxeerdrank *Apotex, Neth.; Healthypharm, Neth.; Katwijk, Neth.; Leidapharm, Neth.*
Lactulose (p. 1850·3).
Constipation.

Laxeersiroop *Pharmachemie, Neth.*
Lactulose (p. 1850·3).
Constipation.

Laxeertabletten *DA, Neth.; Healthypharm, Neth.; SDG, Neth.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxeerzetpillen *Healthypharm, Neth.†*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxen
Note: this name may be used for preparations of different composition.
St Carlos, Philipp.
Senna (p. 1885·1).
Constipation; bowel evacuation.

Laxene *Pharmador, S.Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

Laxette *Medpro, S.Afr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxettes *Mentholatum, Austral.*
Sennosides (p. 1885·2).
Constipation.

Laxicare *Azine, India.*
Suspension: Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2); sodium picosulfate (p. 1887·2).

Azine, India.
Tablets: Sodium picosulfate (p. 1887·2).

Laxicare Soft *Azine, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxicon *Stadmed, India.*
Docusate calcium (p. 1836·2).
Constipation.

Laxicona *Baliarda, Arg.*
Bisacodyl (p. 1821·1); simeticone (p. 1886·2).
Constipation; bowel evacuation.

Laxido *Tramedico, Belg.; Galen, Fin.; Galen, Irl.; Nordic, Swed.; Galen, UK.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; faecal impaction.

Laxifin *Lupin, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).

Laxigal *Teva, Rus.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Laxikal Forte *Teva, Israel.*
Senna (p. 1885·1).
Constipation; bowel evacuation.

Laxil
Note: this name may be used for preparations of different composition.
Mapra, India.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxilo *Amido, Fr.†*
Aloes (p. 1816·1); senna (p. 1885·1); sterculia (p. 1888·3).
Constipation.

Laximo *Lexus, India.*
Cefixime (p. 240·3).
Bacterial infections.

Laximo-XL *Lexus, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Laxinat *Alkem, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Laxiplant Soft *Schwabe, Switz.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea.

Laxiriva *Sandoz, Fin.; Sandoz, Swed.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Laxiruela *Garden House, Arg.*
Jelly: Senna (p. 1885·1); tamarind (p. 1892·2); prune (p. 1881·1); grape (p. 2521·3); honey (p. 2072·1).
Constipation.

Garden House, Arg.
Tablets: Senna (p. 1885·1).
Constipation.

Laxiruela Ciruela Fibra *Garden House, Arg.*
Senna (p. 1885·1).
Constipation.

Laxit *Duckbill, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); carmellose sodium (p. 2175·2).
Constipation.

Laxit Plus *Duckbill, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2); sodium picosulfate (p. 1887·2).
Constipation.

Laxitab
Note: this name may be used for preparations of different composition.
Biofarm, Pol.
Rhubarb (p. 1884·2).
Constipation.

Ranbaxy, Thai.†
Bisacodyl (p. 1821·1).
Constipation.

Laxitose *Duckbill, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxive *Gufic, India.*
Fennel (p. 2503·2); ispaghula (p. 1849·1).
Constipation.

Laxkair *PDC, India.*
Sodium picosulfate (p. 1887·2).

Laxlb *Helax, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Laxoberal *Boehringer Ingelheim, Chile†; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.†; Boehringer Ingelheim, Swed.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Laxoberon *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Indon.; Teijin, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Switz.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Laxobus *Globus, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxocodyl *Julphar, UAE.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxodal *Baldacci, Port.*
Sodium picosulfate (p. 1887·2).
Constipation.

Laxodiex *Innova, Spain.*
Frangula bark (p. 1843·3); cascara (p. 1826·1); fucus vesiculosus.
Constipation.

Laxodyl *Shalaks, India; Sunward, Singapore.*
Bisacodyl (p. 1821·1).
Constipation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Laxofalk *Falk, Ger.*
Macrogol 4000 (p. 2547·3).
Constipation.

Laxogeno *Grunenthal, Chile.*
Oral solution, magnesium citrate (p. 1857·1); oral powder, sodium bicarbonate (p. 1781·1); tablets, bisacodyl (p. 1821·1); suppositories, bisacodyl.
Bowel evacuation.

Laxol
Note: this name may be used for preparations of different composition.
Daudt, Braz.
Castor oil (p. 2472·1).
Constipation.

Herbapol Wroclaw, Pol.
Docusate sodium (p. 1836·2).
Constipation.

Laxolax *Laboratoires Swisse, Canad.*
Aloes (p. 1816·1); senna (p. 1885·1); frangula (p. 1843·3); ispaghula (p. 1849·1).
Formerly contained aloes and senna.
Constipation.

Laxolax Phyto *Laboratoires Swisse, Canad.†*
Casanthranol (p. 1826·1); ginger (p. 1844·1); rhubarb (p. 1884·2).

Laxolin *Bombay Tablet, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxolyne *Julphar, UAE.*
⊗Glycerol (p. 2517·2).
Constipation.

Laxonarol *Farmo Quimica, Chile.*
Liquid paraffin (p. 2191·2).
Constipation.

Laxopeg *Fourrts, India.*
Macrogol (p. 2547·3).

Laxopic *Zytras, India.*
Sodium picosulfate (p. 1887·2).

Laxopol
Note: this name may be used for preparations of different composition.
Pohl, Ger.†; Pohl, Israel.
Castor oil (p. 2472·1).
Constipation.

Unia, Pol.†
Docusate sodium (p. 1836·2).
Constipation.

Laxorin *Orion, Fin.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxose *Indi, India; Pinewood, Irl.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Laxovar *Infinity, Venez.*
Sennosides A and B (p. 1885·2).
Constipation.

Laxsol *Sigma, NZ.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.

Laxsotrin *Catarinense, Braz.†*
Cascara (p. 1826·1).
Constipation.

Laxsure *Duckbill, India.*
Sodium picosulfate (p. 1887·2).
Constipation.

Lax-Tab *AFT, Austral.; AFT, NZ.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Laxtam *Merck, Braz.*
Senna (p. 1885·1); cassia pulp (p. 1826·2); tamarind (p. 1892·2); coriander (p. 2486·3); liquorice (p. 1853·2).
Constipation.

Laxtra *Tramedico, Neth.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; faecal impaction.

Laxuave Enteral *Elea, Arg.*
Liquid paraffin (p. 2191·2).
Constipation.

Laxuave Jalea *Elea, Arg.*
Liquid paraffin (p. 2191·2).
Constipation.

Laxuave Sen *Elea, Arg.*
Senna (p. 1885·1).
Constipation.

Laxucil *Novopharm, Canad.†*
Ispaghula (p. 1849·1).
Constipation.

Laxvital *Maxfarma, Spain.†*
Carmellose (p. 2175·1); docusate sodium (p. 1836·2); casanthranol (p. 1826·1).
Constipation.

Laxygal *Teva, Cz.; Teva, Hung.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Laxyl *Solfran, Mex.†*
Diazepam (p. 1063·2).

Laxysat Bürger *Ysatfabrik, Ger.†*
Bisacodyl (p. 1821·1).
Constipation.

Laxzyme *Helax, India.*
Syrup: ⊗Amylase (p. 2442·1); papain (p. 2582·3).

Helax, India.
Tablets: ⊗Activated charcoal (p. 1537·3); pancreatin (p. 2579·3); simeticone (p. 1886·2).

Laycef *Biophar, India.*
Cefixime (p. 240·3).
Bacterial infections.

Layo *Comed, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamins; zinc sulfate (p. 2126·2).

Laz
Note: this name may be used for preparations of different composition.
Active, India; Dexa, Indon.
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Hetero, India.
Azithromycin (p. 221·2).
Bacterial infections.

Laza *Vilberry, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Lazafin *Novell, Indon.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; rheumatoid arthritis; Crohn's disease.

Lazalgena *Lazar, Arg.*
Clonixin lysine (p. 40·1).
Fever; inflammation; pain.

Lazanda *Archimedes, USA.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Lazap *Lyofin, Gr.*
Olanzapine (p. 1089·3).

Lazapix *IWA, Denm.; Apothecon, Neth.†*
Olanzapine (p. 1089·3).
Schizophrenia; mania; bipolar disorder.

Lazar-Cort *Lazar, Arg.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Lazar-Cort Complex *Lazar, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Laz-AX *Hetero, India.*
Ambroxol hydrochloride (p. 1654·3); azithromycin (p. 221·2).
Bacterial infections.

Lazercreme *Pedinol, USA.*
Vitamin E (p. 2119·1); vitamin A (p. 2098·3).
Minor skin irritation.

Lazerformaldehyde *Pedinol, USA.*
Formaldehyde (p. 1752·2).
Warts; hyperhidrosis; bromhidrosis (feet).

Lazeril *Stada, Denm.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

LazerSporin-C *Pedinol, USA.*
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); hydrocortisone (p. 1640·1).
Bacterial ear infections.

Lazid
Note: this name may be used for preparations of different composition.
Allenge, India.
Ceftazidime (p. 250·2).
Bacterial infections.

Emcure, India.
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Lazid-E *Emcure, India.*
Efavirenz (p. 975·1); lamivudine (p. 1000·2); zidovudine (p. 1024·2).

Lazid-N *Emcure, India.*
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); zidovudine (p. 1024·2).

Lazine *Hetero, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lazine Plus *Hetero, India.*
Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3).

Lazine-D *Hetero, India.*
Levocetirizine hydrochloride (p. 632·3); phenylephrine hydrochloride (p. 1672·3).

Lazine-M *Hetero, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Lazinevir *Richmond, Arg.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2); nevirapine (p. 1005·1).
HIV infection.

Lazith *Admac, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Lazitrom *Azevedos, Port.†*
Azithromycin (p. 221·2).
Bacterial infections.

Lazoc *Biosans, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Lazocin *Allenge, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Lazocin Forte *Allenge, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Lazol *Ifars, Indon.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Lazopip *Admac, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Laztie *Bioprofarma, Arg.†*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

LB Ether *Laborate, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

L'Batzeket *Concept, Israel.*
Sodium chloride (p. 1795·1).
Dry eyes.

LBC *Greenco, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

LBCef *Wallace, India.*
Dispersible tablets; tablets: Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Wallace, India.
Suspension: Cefixime (p. 240·3).
Bacterial infections.

LBDix *Medispan, India.*
Lactobacillus (p. 2596·3).

LB-Drox *Laborate, India.*
Oral drops; tablets: Cefadroxil (p. 233·2); lactobacillus (p. 2596·3).
Bacterial infections.

LB-Drox DPS *Laborate, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

L-Beplex *Anglo-French Drugs, India.*
Vitamins; lactobacillus (p. 2596·3); zinc sulfate (p. 2126·2).

L-Bex *Lincoln, India.*
Capsules: Betacarotene (p. 2051·1); grape seed etract (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); magnesium sulfate (p. 1787·3); selenium (p. 2086·3); zinc (p. 2126·1).

Lincoln, India.
Injection: Folic acid (p. 2063·1); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); vitamin C (p. 2110·3).

L-Bio *Lapi, Indon.*
Rice starch (p. 2095·1); maltodextrin (p. 2080·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Lactobacillus lactis* (p. 2596·3).
Restoration of gastrointestinal flora and gastrointestinal function.

LBX *Novagen, Philipp.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

LC-4 *Trimarc, USA.*
Lidocaine (p. 1988·1).
Local anaesthesia.

LC-5 *Trimarc, USA.*
Lidocaine (p. 1988·1).
Anorectal disorders.

L-Carn *Sigma-Tau, Ger.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

L-Cartin FF *Otsuka, Jpn.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

L-CBit *Cubit, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

LCBit-P *Cubit, India.*
⊗Levocetirizine hydrochloride (p. 632·3); pseudoephedrine (p. 1676·1).

LCD *Intas, India.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

L-Cef
Note: this name may be used for preparations of different composition.
Admac, India.
Injection: Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Novogen, India.
Syrup: Cefixime (p. 240·3).
Bacterial infections.

Novogen, India.
Tablets: Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

L-Cet *Allenge, India; Nodysis, India.*
Levocetirizine (p. 632·3) or levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

L-Cetridoc *Glenmark, India.*
Levocetirizine (p. 632·3).
Rhinitis; bronchitis; urticaria.

L-Cetrizet *Sun, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

L-Cetron *Cosme, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

LCF *Lupin, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

L-Cimexyl *Cimex, Singapore.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

L-Cin *Lupin, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

L-Cin-A *Lupin, India.*
Ambroxol hydrochloride (p. 1654·3); levofloxacin (p. 315·3).

L-Cin-OZ *Lupin, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

L-Cit *Laborate, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

L-Cit Plus *Laborate, India.*
Levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

LC-Mox *Almet, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

LCN *Glories, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

LCN-Plus *Glories, India.*
⊗Levocetirizine (p. 632·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

L-Cot *Lupin, India.*
1 Tablet, clarithromycin (p. 266·2); 1 capsule, omeprazole (p. 1867·2); tinidazole (p. 949·2).

LCP *Nutricia, Ital.*
Fish oil (p. 1460·1); borage oil (p. 2459·2); vegetable oil; vitamin E (p. 2119·1).
Phenylketonuria; amino-acid disorders.

LCR *Corona, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

LCRal *Hiral, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

LCRal Plus *Hiral, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

LCZ *Rapross, India.*
Levocetirizine (p. 632·3) or levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

L-CZN *Daffohils, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

LCZ-Plus *Rapross, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

LCZ-XP *Rapross, India.*
Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); levocetirizine (p. 632·3); menthol (p. 2553·2).

LDA *AstraZeneca, India.*
Aspirin (p. 22·2).

L-Dacin *Utopian, Thai.*
Suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Utopian, Thai.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); peppermint oil (p. 1877·1).
Gastric hyperacidity.

LD-Caine *Millimed, Thai.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

L-Divon *Micro, India.*
Benzyl alcohol (p. 1739·3); diclofenac (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

LDNil *MSN, India.*
Rosuvastatin (p. 1488·2).
Hyperlipidaemias.

L-Dom *Symbiosis, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

LDTor *Torrent, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

LDTor-Z *Torrent, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

LDZin *Medizone, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Le Le *Guofeng Weiao, China.*
Ocimum oil.

Le La An *Hubei Pharmaceutical, China.*
Lorazepam (p. 1080·3).
Anxiety; premedication; chemotherapy-induced vomiting.

Le Baume Ehrlich *Clinique Lafontaine, Canad.†*
Capsicum oleoresin (p. 2469·3); methyl nicotinate (p. 91·3).

Le Bei Xin *Yuanlijian, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Le Dun Kang *Man Xiu Lei Dun, China.*
Sulfamethoxazole sodium.

Le Dun Qing *Man Xiu Lei Dun, China.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); hyetellose (p. 2188·3).

Le Er Tai *Tianji, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Le Fan *Double-Crane, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Le Fei *ZhenYuan, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; allergic rhinitis; sinusitis.

Le Fu Ting *Wan Te, China.*
Bupropion hydrochloride (p. 408·2).
Depression.

Le Gai *Kang Yuan, China.*
Ligustrazine phosphate.

Le Huo *Tiancifu, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Le Jia *Hengrui, China.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1); sodium acetate (p. 1781·1); sodium citrate (p. 1781·2); calcium gluconate (p. 1783·3).

Le Jing Yi *President Pharmagenesis, China.*
Tinidazole (p. 949·2).

Le Ka Ning *Pude, China.*
Carbazochrome sodium sulfonate.

Le Kang *Saite, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Le Lai *Jing Xin, China.*
Gatifloxacin mesilate.
Bacterial infections.

Le Lang *Hengrui, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Le Pai *Hengrui, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Le Pu Mei Xin *Huawei, China.*
Kitasamycin acetate (p. 315·2).

Le Shang *Nanda, China.*
Low-molecular-weight heparin sodium (p. 1426·1).

Le Shi Pu Kang *Yaokay, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Le Tan *Qian Jin Xiang Jiang, China.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Le Tan Sunscreen Lotion *Creative Brands, Austral.†*
SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Le Wei
Note: this name may be used for preparations of different composition.
Bai Yang, China.
Miconazole nitrate (p. 589·1).

Huabang, China.
Tazarotene (p. 1724·2).
Psoriasis; skin photoageing; acne.

Le Wei Jing *Shule, China.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Le Xi Qing *Zhang Shu, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Le Yi Fu *Xin Si Dun, China.*
Metronidazole benzoate (p. 936·1).

Le You *Huahai, China.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Le Zai *Haibin, China.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Le Zhi Na *Tai An, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Le Zyncet *Unichem, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Le Zyncet-A *Unichem, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Le Zyncet-D *Unichem, India.*
Levocetirizine (p. 632·3); phenylephrine (p. 1672·2).

Leanimol *Leantik, Gr.*
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Leanor *Aspen Consumer, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Leap *Comed, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Learnol Plus *Dalmia, India.*
Centella (p. 1698·3).
Mental function impairment.

Lebact *Abbott, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lebact-AM *Abbott, India.*
Ambroxol (p. 1654·3); levofloxacin (p. 315·3).

Lebact-O *Abbott, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Lebaode *Livzon, China.*
⊗Menotrophin (p. 2284·1).
Female infertility.

Lebec-D *Admac, India.*
⊗Diclofenac (p. 48·3); serrapeptase (p. 2613·3).

Lebec-MR *Admac, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Lebec-NP *Admac, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Lebel *Nobel, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leben-Celtics *Investigacion, Mex.*
Orlistat (p. 2577·1).
Obesity.

Lebensart *Bioquimed, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety-depressive disorders; obsessive-compulsive disorder; bulimia nervosa; premenstrual dysphoric disorder; panic disorder.

Leber Albin *Homviora, Ger.*
Lycopodium (p. 2546·3); nux vomica (p. 2573·3); yucca filamentosa (p. 2649·3); quassia amara (p. 2601·1).
Homoeopathic preparation.

Leberetic *Ern, Spain.†*
Potassium sulfate (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1).
Liver disorders.

Leber-Galletropfen *Heel, Ger.*
Chelidonium majus (p. 2522·2); strychnos nux vomica (p. 2573·3); berberis vulgaris (p. 2502·1); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Lebergin *Laborate, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Leberinfusion *Fresenius Kabi, Austria.*
Arginine (p. 2049·1); malic acid (p. 2549·2); sodium hydroxide (p. 2619·1); potassium hydroxide (p. 2595·3).
Liver disorders.

Lebersal *Ern, Spain.*
Magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1); dibasic sodium phosphate (p. 1791·2); sodium sulfate (p. 1888·1).
Gastrointestinal disorders; hepatic insufficiency.

Lebertran plus *Twardy, Ger.*
Cod-liver oil (p. 2056·3); fish-liver oil; ergocalciferol (p. 2113·3).
Nutritional supplement.

Lebic *Actavis, Ger.†*
Baclofen (p. 2014·3).
Skeletal muscle spasm or spasticity.

Lebilon *Pharmathen, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Lebocar *Pfizer, Arg.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Lebopride *Spyfarma, Spain.†*
Sulpiride (p. 1107·3).
Anxiety disorders; psychoses; vertigo.

Lebrocetin *Liferpal, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Lebzone *Admac, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Lecadol Plus C *Sandoz, Ukr.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Lecal *Lexus, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Lecalpin *Actavis, Irl.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lecardop *Teva, Cz.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Lecarge *Klonal, Arg.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Lecarna *Bennett, Gr.; Verisfield, Gr.*
Levocarnitine tartrate (p. 2053·2).
Carnitine deficiency.

Lecef *Micro, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Lecerein *Lexus, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Lecerein-GM *Lexus, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Lecerein-P *Lexus, India.*
Diacerein (p. 45·3); paracetamol (p. 115·1).

Lecetzy *Zee, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Leche Autobronceante *Silesia, Chile.*
Dihydroxyacetone (p. 1700·1).
Artificial suntan.

Leche de Magnesia Normex *Quimica y Farmacia, Mex.*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; constipation.

Leche de Magnesia Phillips *GSK, Arg.; GSK, Chile.*
Magnesium hydroxide (p. 1857·2).
Dyspepsia; heartburn; constipation; antacid.

Lecibral *Desma, Spain.*
Nicardipine hydrochloride (p. 1445·2).
Cerebrovascular disorders; hypertension; angina pectoris.

Lecicarbon *Athenstaedt, Ger.; Athenstaedt, Switz.*
Sodium bicarbonate (p. 1781·1); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Brady, Austria.
Sodium bicarbonate (p. 1781·1); potassium acid tartrate (p. 1879·2).
Constipation.

Lecicarbon A *Aspire, UK.*
Sodium bicarbonate (p. 1781·1); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Leciderm *Darier, Mex.†*
Lecithin (p. 2542·2).
Dry skin disorders.

Lecikur *Agepha, Austria.†*
Lecithin (p. 2542·2); caffeine (p. 1203·3).
Tonic.

Lecimar *Spyfarma, Spain.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive disorder; bulimia; obsessive-compulsive disorder.

Leciplus *Nutrition & Sante, Ital.*
Phospholipids (p. 2201·2); vitamins.
Nutritional supplement.

Lecitan *Pliva Krakow, Pol.†*
Soya lecithin (p. 2542·2).
Hypercholesterolaemia; tonic.

Lecitina E *Nutrilite, Arg.*
Soya lecithin (p. 2542·2); soya protein (p. 2092·3); *d*-alpha tocoferil succinate (p. 2119·2).
Dietary supplement.

Lecitone *Nutrisante, Fr.*
Dietary supplements containing phospholipids (p. 2201·2).
Tonic.

Yves Ponroy, Singapore.
Dietary supplement.

Lecitrol *Interbat, Indon.*
Polygonum cuspidatum; resveratrol (p. 2603·2); lecithin (p. 2542·2).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lecivar *Infinity, Venez.*
Soya lecithin (p. 2542·2).
Hyperlipidaemias.

Lecivar Plus *Infinity, Venez.*
Soya lecithin (p. 2542·2); vitamin B_6 (p. 2105·3); kelp (p. 2612·1); malic acid (p. 2549·2).
Slimming aid.

Lecivit *Life Line, India.*
Lecithin (p. 2542·2).

Lecivit-S *Life Line, India.*
Lecithin (p. 2542·2); silymarin (p. 1561·2).

Lecivriens *Ratiopharm, Cz.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Leclav *Lexus, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Leclor A *Provit, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Leclub *Pharmacon, India.*
Betacarotene (p. 2051·1); black grapefruit seed extract; lutein (p. 2079·2); lycopene (p. 2546·2); mecobalamin (p. 2108·1).

Leclyte *David, India.*
Calcium lactate (p. 1784·1); potassium chloride (p. 1793·2); magnesium sulfate (p. 1787·3); sodium chloride (p. 1795·1); sodium acid phosphate (p. 1791·1); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

David, India.
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Leclyte-W *David, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1780·1).
Oral rehydration therapy.

Lecope *Mankind, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lecope-AD *Mankind, India.*
⊗Ambroxol (p. 1654·3); levocetirizine (p. 632·3); pseudoephedrine (p. 1676·1).
Cold symptoms; allergic rhinitis; sinusitis.

Lecope-DX *Mankind, India.*
⊗Dextromethorphan hydrobromide (p. 1660·1); levocetirizine hydrochloride (p. 632·3); pseudoephedrine hydrochloride (p. 1676·1).

Lecor *Sperko, Ukr.*
Nifuroxazide (p. 331·3).
Diarrhoea; bowel sterilisation.

Lecourse *Cyno, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lecrav *Pyridam, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lecrolyn *Santen, Cz.†; Santen, Denm.; Santen, Fin.; Santen, Hung.; Santen, Norw.; Santen, Philipp.†; Santen, Pol.†; Santen, Rus.; Santen, Swed.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Lecron *Mylan, Cz.; Pharos, Ital.*
Tacrolimus (p. 1968·3).
Heart, kidney, or liver transplant rejection.

Lectan *Diba, Mex.*
⊗Meprednisone (p. 1642·2).
Corticosteroid.

Lectil *Bouchara-Recordati, Fr.*
Betahistine hydrochloride (p. 2455·3).
Vertigo.

Lectopam *Roche, Canad.*
Bromazepam (p. 1041·2).
Anxiety; sedative.

Lectrum *Sandoz, Arg.; Novartis, Braz.; Sandoz, Indon.; Teva, Mex.*
⊗Leuprorelin acetate (p. 2285·3).
Uterine fibroids; prostatic cancer; endometriosis; precocious puberty; breast cancer.

Lecur *Dexa, Indon.*
Essential phospholipids (p. 2201·2); turmeric (p. 2218·1); vitamin E (p. 2119·1).
Liver function aid.

Lecy *Bennet, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lecyp *East African, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Lecytyna E *KRKA, Pol.*
Lecithin (p. 2542·2); vitamin E (p. 2119·1).
Tonic.

Leczine-A *BMW, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Leczine-MD *BMW, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Leda-Rix *Proula, Venez.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Leday *Burgeon, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Leday-CC *Burgeon, India.*
Levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Ledclair *IFET (ΙΦΕΤ), Gr.; Sinclair, Irl.†; Durbin, UK.*
Sodium calcium edetate (p. 1573·2).
Heavy metal poisoning; hypercalcaemia.

Ledcure *Samarth, India.*
Sodium calcium edetate (p. 1573·2).

Ledent *Lexus, India.*
⊗Potassium nitrate (p. 1766·2).

Ledercort *Wyeth, Arg.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Wyeth, India.
⊗Triamcinolone (p. 1648·3) or triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Ledercort-N *Wyeth, India.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Lederfen *Wyeth, Irl.†; Goldshield, UK.†*
Fenbufen (p. 59·1).
Musculoskeletal and joint disorders.

Lederflam Plus *Wyeth, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Lederfolat *Teofarma, Ger.*
Calcium folinate (p. 2066·3).
Folate deficiency.

Lederfolin *Wyeth, Irl.†; Wyeth Lederle, Ital.; Pfizer, Spain.*
Calcium folinate (p. 2066·3).
Reduction of folic acid antagonist toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer; methotrexate toxicity; folic acid deficiency; antidote to folic acid antagonists.

Lederfoline *Pfizer, Fr.; Teofarma, Port.*
Calcium folinate (p. 2066·3).
Folic acid deficiency; prevention of methotrexate toxicity; reduction of folic acid antagonist toxicity; megaloblastic anaemia.

Lederlind *Riemser, Ger.*
Nystatin (p. 590·3).
Fungal infections of the skin and mucous membranes.

Lederlon *Riemser, Ger.*
⊗Triamcinolone hexacetonide (p. 1649·2).
Parenteral corticosteroid.

Ledermix *Henry Schein, Irl.; CPS Cito, Switz.; Blackwell, UK.*
⊗Paste, triamcinolone acetonide (p. 1649·1); demeclocycline calcium (p. 285·2); cement, triamcinolone acetonide; demeclocycline hydrochloride (p. 285·2); solution, eugenol (p. 2501·2).
Bacterial infection and inflammatory disorders in dentistry.

Hind Wing, Hong Kong.
⊗Triamcinolone acetonide (p. 1649·1); demeclocycline hydrochloride (p. 285·2).
Bacterial infections and inflammatory disorders in dentistry.

Neopharm, Israel.
⊗Triamcinolone acetonide (p. 1649·1); demeclocycline calcium (p. 285·2).
Bacterial infection and inflammatory disorders in dentistry.

Riemser, Ger.
⊗Paste, triamcinolone acetonide (p. 1649·1); demeclocycline calcium (p. 285·2); cement, triamcinolone acetonide; demeclocycline hydrochloride (p. 285·2).
Bacterial infection and inflammatory disorders in dentistry.

Ledermix Fluorid *Riemser, Ger.*
Olaflur (p. 2085·1); dectaflur (p. 2059·1); sodium fluoride (p. 2089·2).
Dental caries prophylaxis; hypersensitive teeth.

Ledermycin *Wyeth, Gr.; Wyeth, India; EuroCept, Neth.; Goldshield, UK.†*
Demeclocycline hydrochloride (p. 285·2).
Hyponatraemia; bacterial infections.

Lederpax *Wyeth, Gr.*
Erythromycin (p. 291·2).
Acne.

Lederplex *Wyeth, India.*
Choline dihydrogen citrate (p. 2055·2); vitamin B substances (p. 2102·3); liver extract (p. 2444·1).

Lederspan *Meda, Denm.; Meda, Fin.; Meda, Norw.; Meda, Swed.*
⊗Triamcinolone hexacetonide (p. 1649·2).
Corticosteroid; musculoskeletal, joint, and peri-articular disorders.

Ledertepa *EuroCept, Neth.*
Thiotepa (p. 871·1).
Bladder cancer.

Ledertrexate *Wyeth, Austral.†; Biodim, Fr.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Pfizer, Belg.; Wyeth, Mex.
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis; juvenile idiopathic arthritis.

Ledertrexato *Pfizer, Port.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Ledi *Kawin, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration; gastrointestinal haemorrhage.

Ledion *Help, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Ledocar *Unison, Philipp.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Ledopsan *Teva, Port.; Teva, Spain.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Ledor *Candor, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Ledoren *Boniscontro & Gazzone, Ital.*
Nimesulide (p. 101·3).
Pain.

Ledox *Weifa, Norw.†*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Ledoxan *Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.†*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; bone marrow transplantation; auto-immune disorders.

Ledoxina *Laboratorios Chile, Chile; Teva, Mex.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Ledric *Candor, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Ledron *Aspen, Arg.*
Zoledronic acid (p. 1192·3).

Ledronin *Farmanic, Gr.; Iasis, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ledum Complexe No 81 *Lehning, Fr.*
Ledum palustre (p. 2550·1); colchicum (p. 607·1); cinchona succirubra (p. 2478·3); ulmus campestris; acidum benzoicum (p. 1738·2).
Homoeopathic preparation.

Ledum Med Complex *Dynamit, Austria.*
Arnica (p. 2447·2); ledum (p. 2550·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Lee *Shreya, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leebec-NP *Admac, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Leecon *Admac, India.*
Fluconazole (p. 578·2).
Fungal infections.

Leedol *Admac, India.*
Tramadol (p. 139·2).
Pain.

Leedol-P *Admac, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Leedom *Bestochem, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Leefbid *Cruise, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leeflox *Centaur, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leegra *Uniroyal, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Leeloo *Theramex, Mon.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Leemax *Admac, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Leemoxin-CS *Admac, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3); serrapeptase (p. 2613·3).

Leemoxin-LB *Admac, India.*
Amoxicillin (p. 216·2); lactobacillus (p. 2596·3).
Bacterial infections.

Leena *Watson, USA.*
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Leepime *Admac, India.*
Cefepime (p. 239·2).
Bacterial infections.

Leetop *Admac, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Leetop-D *Admac, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux.

Leeviz *Admac, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Leez *Plus, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lefa Enteril L *Fecofar, Arg.*
Loperamide (p. 1854·2).
Diarrhoea.

Lefax
Note: this name may be used for preparations of different composition.
Adley, India.
Diacerein (p. 45·3).
Osteoarthritis.

Bayer, Cz.; Bayer, Ger.
Simeticone (p. 1886·2).
Meteorism; flatulence; aid in gastrointestinal examination; anti-foaming agent in radiography of the gastrointestinal tract.

Lefax Activolax *Bayer, Ger.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Lefax-G *Adley, India.*
Diacerein (p. 45·3); glucosamine sulfate potassium chloride (p. 2515·3).

Lefaxin *Bayer, Austria.*
Simeticone (p. 1886·2).
Flatulence.

Lefcar *GSK, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; cardiac disorders.

Lefen *Wuhan Wujing, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

Leferdivin *Asconex, Ger.†*
Vitamin B substances (p. 2102·3); phosphatidyl choline (p. 2588·3); ferrous citrate (p. 2073·1); glutamic acid (p. 2070·2).
Tonic.

Leffrin *Suphong, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine (p. 1672·2).
Cold symptoms.

Lefkacid *Knop, Chile.*
Calcium carbonate (p. 1824·3); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Lefkaflam *Knop, Chile.*
Arnica (p. 2447·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3).
Musculoskeletal, joint, and peri-articular disorders; oedema.

Lefkur *Knop, Chile.*
Cucurbita oil (p. 2489·2).
Benign prostatic hyperplasia.

Leflobact *Sintez, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefloc *Darnitsa, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leflocin *Yuriya-Farm, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leflokin *Vera, Hung.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leflox *Nanxin, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Lefloxin *Sandoz, Mex.; Synergen, Philipp.; Siam Bheasach, Thai.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefluar *Rontag, Arg.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Lefluartil *Arafarma, Spain.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Leflucross *Pharmacross, Chile.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Leflumax *Elea, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefno *Ipca, India.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Lefos *Guardian, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefosan *Pharminicio, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Lefosin *Munir, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefosym *Symbiosis, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefosym-OZ *Symbiosis, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Lefoxin *Shreya, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lefra *Torrent, India.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Lefrine *Cadila, India; Grin, Mex.†*
Phenylephrine hydrochloride (p. 1672·3).
Mydriasis; conjunctival congestion; nasal congestion.

Leftose *Shinyaku, Hong Kong†; Shinyaku, Jpn; Shinyaku, Singapore; Shinyaku, Thai.†*
Muramidase hydrochloride (p. 2565·1).
Inflammation; haemorrhage; sinusitis; allergic rhinitis; infections; adjunct in antibiotic therapy.

Lefukang *Chengdu Institute, China.*
Bacillus cereus.
Gastrointestinal disorders.

Lefumide *Cipla, India.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Lefunzol *Epifarma, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Lefuxin *Livzon, China.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Leg Cramps with Quinine *Hylands, Canad.*
Aconitum napellus (p. 2428·3); cinchona officinalis (p. 2478·3); gnaphalium polycephalum; magnesia phosphorica (p. 1787·3); rhus toxicodendron (p. 2603·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Leg Magic *Covermark, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Legadyn *Dunner, Switz.*
Cynara (p. 2490·3).
Digestive disorders.

Legain *Health Care, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Legalon *Bayer, Chile; Madaus, China; Madaus, Hong Kong; Nycomed, Mex.; Madaus, Philipp.; Madaus, Pol.; Nycomed, S.Afr.; Madaus, Singapore; Rottapharm, Spain; Madaus, Thai.; Madaus, Ukr.; Zuoz, Venez.*
Silymarin (p. 1561·2).
Liver disorders; disorders of lipid metabolism; alcohol-induced hepatic disorders.

Flordis, Austral.; Madaus, Austria; Madaus, Belg.; Nycomed, Braz.; Madaus, Cz.; Madaus, Ger.; Rottapharm, Ger.; Madaus, Hung.; Rottapharm, Ital.; Madaus, Malaysia; Neo-Farmaceutica, Port.; Madaus, Rus.
Milk thistle (p. 1561·1).
Liver disorders; poisoning with alcohol and drugs.

IFET (ΙΦΕΤ), Gr.
Silibinin (p. 1561·2).
Mushroom poisoning.

Légalon *Rottapharm, Fr.; Zeller Madaus, Switz.*
Milk thistle (p. 1561·1).
Liver disorders.

Legalon Plus *Madaus, Ital.*
Oral granules; tablets: Silymarin (p. 1561·2); superoxide dismutase (p. 135·2).
Dietary supplement in liver disorders.

Madaus, Ital.
Syrup: Silymarin (p. 1561·2); epigallocatechin gallate (p. 1720·2).
Dietary supplement in liver disorders.

Legalon SIL *Madaus, Belg.; Madaus, Ger.; Rottapharm, Ger.; Madaus, Hung.; Neo-Farmaceutica, Port.; Rottapharm, Spain; Madaus, Ukr.*
Disodium silibinin dihemisuccinate (p. 1561·1).
Mushroom poisoning.

Légalon SIL *Zeller Madaus, Switz.*
Disodium silibinin-C-2',3-dihydrogen succinate (p. 1561·1).
Mushroom poisoning.

Le-Gami *Lexus, India.*
Gemifloxacin.
Chronic bronchitis; community-acquired pneumonia.

Leganto *Bayer, Ger.; Schwarz, Irl.*
Rotigotine (p. 914·1).
Restless legs syndrome; parkinsonism.

Legapas *Pascoe, Ger.*
Cascara (p. 1826·1).
Constipation.

Legatrin PM *Columbia, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Legatrin Rub *Columbia, USA.*
Menthol (p. 2553·2); benzocaine (p. 1980·2).

Legederm *Schering-Plough, Ital.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Legendal *Zambon, Neth.; Zambon, Switz.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Legifol CS *Pfizer, Braz.*
Calcium folinate (p. 2066·3).

Legil
Note: this name may be used for preparations of different composition.
Galenus, Gr.
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Leginsol OB *Crisdy-Na, Philipp.*
Vitamins; minerals.

Leginsol Vita *Crisdy-Na, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3).

Leginsol-E *Crisdy-Na, Philipp.*
Vitamins; minerals; Siberian ginseng (p. 2614·3); lecithin (p. 2542·2); choline bitartrate (p. 2055·2).
Tonic.

Legius *Benefoot, UK.*
Activated charcoal (p. 1537·3).
Wounds.

Legofer *ITF, Chile; Elpen (Ελπεν), Gr.; Italfarmaco, Port.*
Iron succinyl-protein complex (p. 2077·3).
Iron-deficiency anaemia; iron deficiency.

Legofolin *Elpen (Ελπεν), Gr.*
Iron succinyl-protein complex (p. 2077·3); calcium folinate (p. 2066·3).

Legram *Novagen, S.Afr.*
Lamivudine (p. 1000·2).

Legres *Soho, Indon.*
Leucoselect phytosome (oligomeric polyphenols prepared from *Vitis vinifera* (p. 2521·3)); lycopene (p. 2546·2).
Antoxidant.

Legreskin *Soho, Indon.*
Marine protein extract; collagen (p. 2483·2); vitamin E (p. 2119·1); leucoselect phytosome (oligomeric polyphenols prepared from *Vitis vinifera* (p. 2521·3)); lycopene (p. 2546·2).
Antoxidant; nutritional supplement for healthy skin.

Lehist *MMC, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lehnigrip *Lehning, Cz.†*
Eupatorium perfoliatum (p. 2459·1); aconitum napellus (p. 2428·3); bryonia (p. 2461·3); arnica montana (p. 2447·2); gelsemium (p. 2511·2); cinchona succirubra (p. 2478·3); belladonna (p. 2453·3); drosera (p. 2497·2); polygala senega (p. 1677·2); eucaluptus globulus (p. 2501·1).
Homoeopathic preparation.

Lehydan *Nevada, Swed.*
Phenytoin (p. 538·2).
Epilepsy.

Lei ka *Lanling, China.*
Levocarnitine (p. 2053·2).

Lei Mai Xin *Yatai, China.*
Ramosetron hydrochloride (p. 1881·3).

Lei Ning *SL Pharm, China.*
Loratadine (p. 633·2).

Lei Sai Long *Jinghua, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Lei Te Mai Xing *Aolin, China.*
Cefmenoxime hydrochloride (p. 241·2).
Bacterial infections.

Leiba *Uniao Quimica, Braz.*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea; restoration of intestinal flora.

Leicester *Polifarma, Ital.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Leicita *BAG, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Leicladin *Belmed, Rus.*
Cladribine (p. 769·1).
Hairy-cell leukaemia.

Leiguar *Tentan, Switz.*
Guar gum (p. 475·1).
Diabetes mellitus; hyperlipidaemias.

Leioderm *Riemser, Ger.†*
Hydroxyquinoline sulfate (p. 2530·1).
Impetigo.

Leioderm P *Riemser, Ger.*
⊗Hydroxyquinoline sulfate (p. 2530·1); prednisolone (p. 1645·2).
Infected skin disorders.

Leios *Wyeth, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Leiracid *Abalon, Spain.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Leite de Magnesia de Phillips *GSK, Braz.*
Magnesium hydroxide (p. 1857·2).
Constipation.

Leite Magnesia Phillips *GSK Consumer, Port.*
Magnesium hydroxide (p. 1857·2).
Constipation; gastro-oesophageal reflux; gastric hyperacidity.

Lejia *Shunxin Xiangyun, China.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Lek *Blue Cross, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leka *Worwag, Ger.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Leklin *Unique, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Lekoklar *Lek, Cz.; Lek, Hung.; Sandoz, Pol.; Lek, Rus.; Lek, Ukr.†*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Lekoprost *Gedeon Richter, Cz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Lekoptin *Lek, Cz.; Lek, Pol.†; Lek, Rus.†; Sandoz, Ukr.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; hypertension; angina pectoris; peripheral vascular disorders; migraine.

Lekosen *Lek, Pol.†*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Lek-OZ *Blue Cross, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Lekran *Pro-Pharma, Ukr.*
Bifidobacterium bifidum (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); cranberry (p. 2488·1); vitamin C (p. 2110·3).
Maintenance of normal gastrointestinal flora; urinary-tract disorders.

Lektinol *Madaus, Austria; Madaus, Ger.; Rottapharm, Ger.*
Mistletoe (from populus) (p. 2560·2).
Malignant neoplasms.

Lekuicin *Dexa, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lelco *Raymos, Arg.*
SPF 20: Amiloxate (p. 1694·1); bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Lelco Labial *Defuen, Arg.*
Amiloxate (p. 1694·1); titanium dioxide (p. 1725·1).
Sunscreen for lips.

Lelco P Ultra *Defuen, Arg.*
SPF 34+: Amiloxate (p. 1694·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octocrilene (p. 1715·2); ensulizole (p. 1703·1).
Sunscreen.

Lelco sin Sol *Raymos, Arg.*
Dihydroxyacetone (p. 1700·1).
Artificial tanning.

Lelco Spray *Raymos, Arg.*
SPF 15: Amiloxate (p. 1694·1); avobenzone (p. 1695·1).
Sunscreen.

Lelco Ultrablock *Defuen, Arg.†*
SPF 65: Amiloxate (p. 1694·1); ensulizole (p. 1703·1); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); bisoctrizole (p. 1697·1); octil triazone (p. 1715·1).
Sunscreen.

Lelco Ultrablock Extreme *Raymos, Arg.*
SPF 75: Bisoctrizole (p. 1697·1); amiloxate (p. 1694·1); titanium dioxide (p. 1725·1); octil

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

triazone (p. 1715·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); ensulizole (p. 1703·1).
Sunscreen.

Lelemi *CPU, China.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Lelong Pommade *Zambon, Fr.*
Peru balsam (p. 2587·1); vitamin A (p. 2098·3).
Skin disorders.

Lem *Obolenskoe, Rus.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Lema C *Ern, Spain.*
Ascorbic acid (p. 2110·3); sodium perborate (p. 1770·1).
Mouth and throat inflammation; pyorrhoea; halitosis.

Lemal *Lexus, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Lemaxil *Ist. Chim. Inter., Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lemazol
Note: this name may be used for preparations of different composition.
Vargas, Venez.
Diethylamine salicylate (p. 51·3); myrtecaine (p. 1993·1).
Musculoskeletal and joint disorders.

Lemblastine *Laboratorios Chile, Chile; Teva, Mex.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Lembrol *Sanofi-Aventis, Arg.*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal syndrome; skeletal muscle spasm; spasticity; epilepsy.

Lemdopa *Teva, Mex.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Lemed *Aglowmed, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lemeiting *Si Bao, China.*
Lafutidine (p. 1851·3).
Peptic ulcer; gastritis; acid aspiration.

Lemeng *Tiantaishan, China.*
Nalmefene hydrochloride (p. 1562·1).

L-Emental *Hormel, Israel; Hormel, Singapore.*
Preparation for enteral nutrition.

Lemeron *Teva, Mex.†*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; hepatitis B; hepatitis C.

Lemesil *Anfarm, Gr.†*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Lemibet *Teva, Mex.†*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Lemicin *Admac, India.*
Amikacin (p. 214·1).
Bacterial infections.

Lemidal *Casasco, Arg.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Lemiflox *Teva, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Lemil *Fecofar, Arg.*
Bismuth salicylate (p. 1821·3); bismuth subgallate (p. 1822·1); boric acid (p. 2459·3).

Lemlax *Co-Pharma, UK.*
Lactulose (p. 1850·3).
Constipation.

Lemna-C Kid *Alna, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Lemnis Fatty Cream *CSL, NZ.†*
Emollient.
Barrier cream; emollient.

Lemnis Fatty Cream HC *CSL, NZ.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Lemo *Yash, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemo Linctus *Yash, India.*
Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemocin *Novartis Consumer, Austria; Novartis Consumer, Belg.*
Tyrothricin (p. 384·1); cetrimide (p. 1742·1); lidocaine (p. 1988·1).
Mouth and throat disorders.

Novartis Consumer, Ger.†; Novartis, Indon.; Novartis Consumer, Israel; Novartis Consumer, Switz.
Tyrothricin (p. 384·1); cetrimonium bromide (p. 1742·3); lidocaine (p. 1988·1).
Mouth and throat disorders.

Lemocin CX *Novartis Consumer, Ger.†*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Lemod *Hemofarm, Rus.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Lemogen *Gentech, India.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Lemohist *Hiral, India.*
Suspension: Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Hiral, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Lemohist-BG *Hiral, India.*
Bromhexine (p. 1656·3); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).

Lemohist-C *Hiral, India.*
Cetirizine (p. 619·2); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Lemon Balm *Seroyal, Canad.†*
Catnep; dill (p. 2493·1); german chamomile (p. 2474·1); melissa officinalis (p. 2552·3); oil of chamomile roman (p. 2474·1); peppermint (p. 1877·1).
Homoeopathic preparation.

Lemont-LC *Emar, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast (p. 1214·3).

Lemo-P *Yash, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemophar *Alpharma, Mex.*
Hyoscine butylbromide (p. 1845·3).

Lemorcan *Leovan, Gr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Lemotussin-DM *Seneca, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sulfogaiacol (p. 1678·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Lemoxol *Demo, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Lemsip
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Austral.; Reckitt Benckiser, Belg.
Paracetamol (p. 115·1).
Cold and influenza symptoms; pain; fever.

Reckitt Benckiser, Rus.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Chesty Cough *Reckitt Benckiser, Irl.*
Guaifenesin (p. 1666·2).
Cough.

Lemsip Children's Cold Relief *Reckitt Benckiser, Irl.†*
Paracetamol (p. 115·1).
Cold and influenza symptoms.

Lemsip Childrens Six+ Cold & Flu Relief *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Cold & Flu *Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Singapore.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Reckitt Benckiser, Singapore.
Caplets: Ascorbic acid (p. 2110·3); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Reckitt Benckiser, Irl.
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Breathe Easy *Reckitt Benckiser, Singapore.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Reckitt Benckiser, UK.
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Lemsip Cold & Flu With Caffeine *Reckitt Benckiser, Irl.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Head Cold *Reckitt Benckiser, Singapore.*
Paracetamol (p. 115·1).

Lemsip Cold & Flu Headcold *Reckitt Benckiser, NZ.*
Paracetamol (p. 115·1); menthol (p. 2553·2).
Cold and influenza symptoms.

Lemsip Cold & Flu Max Strength *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Max Strength Capsules *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Original *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Original, Cold & Flu Max *Reckitt Benckiser, NZ.*
Paracetamol (p. 115·1).
Cold and influenza symptoms.

Lemsip Cough & Cold with Caffeine *Reckitt Benckiser, Irl.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); anhydrous caffeine (p. 1203·3).
Cold and influenza symptoms; cough.

Lemsip Cough & Cold Chesty Cough *Reckitt Benckiser, UK.*
Guaifenesin (p. 1666·2).
Cough.

Lemsip Cough & Cold Dry Cough *Reckitt Benckiser, UK.*
⊗Honey (p. 2072·1); terpeneless lemon oil (p. 2543·1); glycerol (p. 2517·2); citric acid (p. 2480·3).
Coughs; sore throat.

Lemsip Cough Max for Mucus Cough & Cold *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cold and influenza symptoms; cough.

Lemsip with Decongestant *Reckitt Benckiser, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Decongestant & Flu *Reckitt Benckiser, Irl.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Dry Cough *Reckitt Benckiser, Irl.*
⊗Glycerol (p. 2517·2); honey (p. 2072·1); citric acid (p. 2480·3).
Cough; sore throat.

Lemsip First Signs Cold & Flu *Reckitt Benckiser, Austral.*
Echinacea (p. 2498·1); zinc sulfate (p. 2126·2); ascorbic acid (p. 2110·3); garlic oil (p. 2510·3).
Cold and influenza symptoms.

Lemsip First Signs Cold & Flu Day + Night *Reckitt Benckiser, Austral.*
Day capsule, echinacea (p. 2498·1); zinc sulfate (p. 2126·2); ascorbic acid (p. 2110·3); garlic oil (p. 2510·3); night capsule, echinacea; zinc sulfate (p. 2126·2); ascorbic acid (p. 2110·3); valerian (p. 2640·2).
Cold and influenza symptoms.

Lemsip Flu 12Hr *Reckitt Benckiser, UK.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Lemsip Flu Strength
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, NZ.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Lemsip Lozenges *Reckitt Benckiser, Austral.†*
Cetylpyridinium chloride (p. 1743·1).
Sore throat.

Lemsip Max *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Max All Day Cold & Flu *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Max All Day Flu Relief *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Max All Night Cold & Flu *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Max All Night Flu Relief *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Max Cold & Flu *Reckitt Benckiser, Singapore.*
Capsules: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Reckitt Benckiser, Singapore.
Granules for oral solution: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Lemsip Max Cough & Cold *Reckitt Benckiser, Irl.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms; cough.

Lemsip Max Flu *Reckitt Benckiser, UK.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Lemsip Max Multi-Relief *Reckitt Benckiser, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Formerly known as Lemsip Pharmacy Max Cold & Flu + Chesty Cough.
Cold and influenza symptoms; cough.

Lemsip Max Relief Capsules *Reckitt Benckiser, Irl.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Lemsip Max Sinus & Flu *Reckitt Benckiser, Irl.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Lemsip Max Strength Sinus Relief *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold symptoms; sinusitis.

Lemsip Multi-Relief *Reckitt Benckiser, Irl.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cold and influenza symptoms; cough.

Lemsip Pharmacy Flu Strength *Reckitt Benckiser, Singapore.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Reckitt Benckiser, Irl.†
⊗Ascorbic acid (p. 2110·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Lemsip Pharmacy Flu Strength Daytime *Reckitt Benckiser, Austral.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Lemsip Pharmacy Flu Strength Nightime *Reckitt Benckiser, Austral.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; cold and influenza symptoms.

Lemsip Pharmacy Powercaps *Reckitt Benckiser, UK.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Lemsip Sinus *Reckitt Benckiser, Irl.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Sinusitis.

Lemsip Sore Throat *Reckitt Benckiser, UK.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Lemsip Throat Lozenges *Reckitt Benckiser, NZ.*
Cetylpyridinium chloride (p. 1743·1).
Sore throat.

Lemsip Vapo-Patches *Reckitt Benckiser, UK.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Respiratory-tract congestion.

Lemtosid *Teva, Mex.†*
Benzonatate (p. 1656·2).
Cough.

Lemyflox *Teva, Mex.†*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Lemytriol *Teva, Mex.†*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; pseudohypoparathyroidism; rickets.

Len B Co *SA Druggists Self Med, S.Afr.†*
Vitamin B substances (p. 2102·3).

Len VK *Aspen, S.Afr.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Lena cut *Taiho, Jpn.*
Lentinan (p. 2543·2).
Gastric cancer.

Lenadol *Aspen Consumer, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); caffeine (p. 1203·3).
Pain and associated tension; fever.

Lenadrin *Raam, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Lenafen *Aspen, S.Afr.*
Ibuprofen (p. 68·2).
Fever; pain.

Lenagesic *Wockhardt, India.*
Paracetamol (p. 115·1); mefenamic acid (p. 85·3).

Lenaken *Serral, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Lenamet *Aspen, S.Afr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; heartburn.

Lenangio *Reddy, India.*
Lenalidomide (p. 816·1).

Lenapain *Aspen, S.Afr.*
Doxylamine succinate (p. 627·3); codeine phosphate (p. 40·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain and associated tension.

Lenar *Biomedica, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Lenarvit *Utopian, Thai.*
Vitamins.

Lenasone *Aspen, S.Afr.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Lenazine *Aspen, S.Afr.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions.

Lenazine Forte *Aspen, S.Afr.*
⊗Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Lencar *Elder, India.*
Levocarnitine (p. 2053·2).

Lendacin *Lek, Cz.; Teva, Hung.; Sandoz, Pol.; Sandoz, Rus.; Lek, Ukr.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Lenditro *Aspen, S.Afr.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder; nocturnal enuresis.

Lendorm *Boehringer Ingelheim, Austria.*
Brotizolam (p. 1042·1).
Sleep disorders.

Lendormin *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Ger.; Crocus, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Neth.; Unilfarma, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Venez.*
Brotizolam (p. 1042·1).
Insomnia; sleep disorders; premedication; anxiety.

Lendral *Melora, Port.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Lendronal *Lafedar, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Lenea *Gynial, Austria.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Leneda *Advaita, Mex.*
Adapalene (p. 1692·1).
Acne; hyperpigmentation disorders.

Lenerve *East West, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Lenex
Note: this name may be used for preparations of different composition.
Lexus, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Zee, India.
Tablets: Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Lengout *Aspen, Austral.*
Colchicine (p. 604·1).
Gout.

Lenicalm *Boiron, Fr.†; Boiron, Ital.*
Asperula odorata; crataegus (p. 2488·1); tilia (p. 2631·3).
Sleep disorders; nervous disorders; insomnia.

Lenicet *Athenstaedt, Ger.*
Aluminium diacetate hydroxide; aluminium hydroxide (p. 1817·2).
Skin disorders.

Lenicort *2M, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Lenid *United Biotech, India.*
Lenalidomide (p. 816·1).

Lenident *Zeta, Ital.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Lenide-T *Pharmacare, S.Afr.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Lenidolor *Menarini, Ital.*
Meclofenamic acid (p. 85·2) or meclofenamate sodium (p. 85·2).
Pain; musculoskeletal and joint disorders.

Lenifren *Biodelta, Ital.*
Magnesium (p. 1786·3); melissa (p. 2552·3); St John's wort (p. 449·1); rhodiola rosea; vitamins.
Nutritional supplement.

Lenil *Zeta, Ital.*
Chlorhexidine hydrochloride (p. 1743·3).
Disinfection of wounds and burns.

Lenin-D *Vensat, India.*
Diclofenac (p. 48·3); linseed oil (p. 2544·2).

Lenipasta *Novogaleno, Ital.*
Zinc oxide (p. 1729·1); rice starch (p. 2095·1); enoxolone (p. 54·2).
Wounds; skin irritation.

Lenirit *EG, Ital.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Lenirose *Novogaleno, Ital.*
Sulfur (p. 1721·1); titanium dioxide (p. 1725·1); panthenol (p. 2582·2); rusco; calendula (p. 2465·2); oryzanol (p. 2578·1); enoxolone (p. 54·2).
Skin irritation; rosacea; seborrhoeic dermatitis.

Lenisolone *Aspen, S.Afr.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Lenistar *Boniscontro & Gazzone, Ital.†*
Butamirate citrate (p. 1657·3).
Cough.

Lenitin *Teva, Israel.†*
Bromazepam (p. 1041·2).
Anxiety; tension; premedication; sedative.

Lennacol *Intramed, S.Afr.†*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Lennamine *Lennon, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Leno *Bestochem, India.*
Alpha galactosidase A (p. 2437·2).

Lenobio *Delta, Arg.*
Lenograstim (p. 1155·2).
Neutropenia.

Lenocef *Pharmacare, S.Afr.†*
Cefalexin (p. 234·1).
Bacterial infections.

Lenocin *General Drugs, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Leno-EZ *Bestochem, India.*
Alpha galactosidase A (p. 2437·2); amylase (p. 2442·1); tilactase (p. 2631·2); protease (p. 2598·1); lipase (p. 2579·3).

Lenolax *Aspen Consumer, S.Afr.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Lenomol *Ankom, India.*
Dextromethorphan (p. 1660·1); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Lenor *Lexus, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lenor-P *Lexus, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lenotac *Procter & Gamble, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Lenova-MF *Intra-Labs, India.*
Folic acid (p. 2063·1); levocarnitine (p. 2053·2); mecobalamin (p. 2108·1).

Lenovate *Aspen, S.Afr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

LENOXe *Air Liquide, Denm.; Air Liquide, Fr.; Air Liquide, Neth.; Air Liquide, Port.; Air Liquide, Spain.*
Xenon (p. 1917·3).
General anaesthesia; adjunct in general anaesthesia.

Lenoxin *Aspen, Ger.*
Digoxin (p. 1353·3).
Heart failure; tachycardia.

Lenpryl *Probiomed, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Lens Lubricant *Bausch & Lomb, USA.†*
Wetting solution for hard contact lenses.

Lens Plus *Advanced Medical Optics, NZ.*
Rinsing solutions for contact lenses.

Allergan, USA.
Range of solutions for soft contact lenses.

AMO, Austral.
Sodium chloride (p. 1795·1).
Rinsing, cleaning, and storage of soft and gas permeable contact lenses.

Lentamine *Elvipe, Gr.*
Riboflavin (p. 2104·3); minerals.

Lentard *Novo Nordisk, India.*
⊗Insulin zinc suspension (porcine, highly purified) (amorphous 30%, crystalline 70%) (p. 475·3).
Diabetes mellitus.

Lentaron *Novartis, Gr.†; Novartis, Turk.†*
⊗Formestane (p. 799·2).
Breast cancer.

Lente *Novo Nordisk, USA.*
⊗Insulin zinc suspension (bovine or porcine) (p. 475·3).
Diabetes mellitus.

Lente Iletin II *Lilly, USA.†*
⊗Insulin zinc suspension (porcine) (p. 475·3).
Diabetes mellitus.

Lenteclin *Aristo, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Lentermina Complex *Biotech, Venez.*
Hydroxocobalamin (p. 2107·3); pyridoxine hydrochloride (p. 2105·3); thiamine phosphate chloride.
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Neurological disorders.

Lentisol *Barnes Hind, Arg.†*
Polyvinyl alcohol (p. 2204·2).
Wetting solution for hard contact lenses.

Lentisulin-CPI *Cadila, India.*
⊗Insulin zinc suspension (porcine, highly purified) (p. 475·3).
Diabetes mellitus.

Lentisulin-HPI *Cadila, India.*
⊗Insulin zinc suspension (crystalline 70%, amorphous 30%) (p. 475·3).
Diabetes mellitus.

Lentisulin-HPI-400 *Cadila, India.*
⊗Insulin injection (porcine, highly purified) (p. 475·3).
Diabetes mellitus.

Lento Nit K *Optima, Ger.*
Potassium iodide (p. 2336·3); calcium chloride (p. 1783·1); sodium thiosulfate (p. 1576·1).
Eye care.

Lentocilin *Atral, Port.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Lentocilin S *Atral, Port.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Lentocit *Ankom, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lentogesic *Adcock Ingram, S.Afr.*
Capsules: Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1); glutamine (p. 2070·3).
Pain.

Adcock Ingram, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain.

Lentogest *Amsa, Ital.*
Hydroxyprogesterone caproate (p. 2285·1).
Threatened or recurrent miscarriage; menstrual and menopausal disorders; infertility.

Lento-Kalium *Teofarma, Ital.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Lentolith *Adcock Ingram, S.Afr.†*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lentomyk *Elvipe, Gr.*
Doxycycline (p. 288·1).

Lentopenil *Grossman, Mex.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Lentoquine *Sanofi-Aventis, Spain.*
Hydroquinidine hydrochloride (p. 1407·1).
Arrhythmias.

Lentostamin *Italmex, Mex.†*
Carbinoxamine (p. 619·1); phenylpropanolamine (p. 1674·1); mepyramine (p. 635·1).

Lentrin *Metiska, Indon.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Lentusin *Chobet, Arg.*
Dihydrocodeine resinate (p. 52·2); phenyltoloxamine resinate.
Cough.

Lenurex-K *Lennon, S.Afr.†*
⊗Cyclopenthiazide (p. 1347·2); potassium chloride (p. 1793·2).
Hypertension; oedema; diabetes insipidus.

Lenuxin *Gedeon Richter, Cz.; Richter, Pol.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder; anxiety.

Lenyl *Lexus, India.*
Vitamins; minerals.

Lenyl-C *Lexus, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin E acetate (p. 2119·2).

LenzaGel *Pharmaceutica North America, USA.*
Lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2).

LenzaPatch *Pharmaceutica North America, USA.*
Lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2).

Leo-99 *Deltapharm, Hong Kong†; Charoen, Thai.†*
Niclosamide (p. 161·2).
Taeniasis; worm infections.

Leo-400 *Charoen, Thai.†*
Albendazole (p. 149·1).
Worm infections.

Leoben *BMW, India.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).

Leobet-GM *BMW, India.*
⊗Beclometasone (p. 1621·2); gentamicin (p. 304·2); miconazole (p. 588·3).

Leobet-GZ *BMW, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); zinc sulfate (p. 2126·2).

Leobet-NC *BMW, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Leocip *Vilberry, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leo-Doce *Salfran, Mex.†*
Hydroxocobalamin (p. 2107·3).
Neuritis; anaemias.

Leodrin *Gynopharm, Chile; Recalcine, Chile; Serral, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Leodrin Duo Biterapia *Recalcine, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Leodrin Plus *Recalcine, Chile.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Leof *Biochemix, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leofenac-MR *Emar, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine hydrochloride (p. 2026·2).

Leofenac-SP *Emar, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Leoflox *Alpha Aromatic, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Leogab-M *Solitaire, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Leogumil *Leovan, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Leolide *Vanguard, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Leomoxyl *Guardian, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Leon
Note: this name may be used for preparations of different composition.
Reddy, India.
Levofloxacin (p. 315·3).
Bacterial infections.

TP, Thai.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Leona *Hexal, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Leoncon *Pharmanel, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Leonite *Solitaire, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Leonitren *Medinova (Μεντινοβα), Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Leonore *Hexal, Austria; Rowex, Irl.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Leophen *Charoen, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

Leopin *Purity Life, Canad.†*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Leoplexamin *Chrispa (Χρισπα), Gr.*
Nefopam hydrochloride (p. 100·2).

Leoprime *Leo, India.*
Primaquine.
Malaria.

Leoriv *East African, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Leoron *CNN, Philipp.†*
Vitamin B_1 (p. 2103·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency.

Leother *Leo, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Leovinezal *Alapis, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Leozole *BMW, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Leozole-B *BMW, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).

Leparox *Solitaire, India.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Leparson *Dexa, Indon.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Lepex *SMB, Chile.*
Povidone (p. 2204·3).
Dry eyes.

Lepez *Symbiotic, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lepheton *Meda, Swed.*
⊗Ethylmorphine hydrochloride (p. 56·3); ephedrine hydrochloride (p. 1663·2).
Cough.

Lephos *Candor, India.*
Oral drops: Vitamins; zinc sulfate (p. 2126·2).

Candor, India.
Oral liquid: Vitamin B substances (p. 2102·3); zinc (p. 2126·1); lysine hydrochloride (p. 2079·3).

Lepicol *Lepicol, Hong Kong.*
Ispaghula (p. 1849·1); inulin (p. 2534·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3).
Constipation.

Lepicortinolo *Decomed, Port.*
⊗Prednisolone (p. 1645·2) or prednisolone sodium succinate (p. 1646·1).
Corticosteroid.

Lepit *Epitome, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lepit-A *Epitome, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Lepit-AM *Epitome, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Lepit-MK *Epitome, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Lepitrin *Adcock Ingram, S.Afr.*
Losartan potassium (p. 1422·2).
Hypertension.

Leplex *Lexus, India.*
Capsules: Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Lexus, India.
Syrup: Vitamin B substances (p. 2102·3).

Leponex *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S. Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Turk.; Novartis, Ukr.; Novartis, Venez.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses in parkinsonism.

Léponex *Novartis, Switz.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Lepravir *Virgo, Philipp.*
Dapsone (p. 281·2).
Leprosy.

Leprid *LKM, Arg.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Leprocure *Zimalaya, India.*
Oryza sativa.

Leprofen *Lanpharm, Arg.*
⊗Anastrozole (p. 742·1).

Lepromix MB *Pond's, Thai.*
Rifampicin (p. 350·3); dapsone (p. 281·2); clofazimine (p. 273·3).
Leprosy.

Lepromix PB *Pond's, Thai.*
Rifampicin (p. 350·3); dapsone (p. 281·2).
Leprosy.

Lepsitin *Pliva, Rus.*
Gabapentin (p. 523·3).
Neuropathic pain; epilepsy.

Lepsitol *Metiska, Indon.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Leptanal *Janssen-Cilag, Norw.; Janssen-Cilag, Swed.*
⊗Fentanyl citrate (p. 60·1).
Pain; adjunct in neuroleptanalgesia.

Leptard *Cristalia, Braz.*
Oxcarbazepine (p. 533·2).

Leptazine *Roemmers Rowe, Venez.*
Trifluoperazine hydrochloride (p. 1113·2).
Anxiety; nausea and vomiting.

Leptic *Chobet, Arg.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Lepticur *Sanofi-Aventis, Fr.*
Tropatepine hydrochloride (p. 918·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Leptilan *Dolorgiet, Ger.; Novartis, Mex.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Leptinorm *Torrent, Rus.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders in dementia; bipolar disorder.

Leptokin *Pharmathen, Gr.*
Gemfibrozil (p. 1390·3).

Leptol *Ulagay, Turk.*
Haloperidol (p. 1077·1).

Leptopsique *Psicofarma, Mex.*
Perphenazine (p. 1095·3).
Anxiety disorders; psychoses; pain; nausea and vomiting.

Leptos *Abbott, India.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Lepur *Elpen (Ελπεν), Gr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lerana *Heaton, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lercadip *Gador, Arg.; Abbott, Austral.; Recordati, Gr.; Innova, Ital.; Recordati, Spain; Fako, Turk.; Zuoz, Venez.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercamen *Berlin-Chemie, Rus.*
Lercanidipine (p. 1419·3).
Hypertension.

Berlin-Chemie, Ukr.
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercan *Abbott, Austral.; Pierre Fabre, Fr.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercaprel *Recordati, Austria; Herbacos, Cz.; Recordati, Gr.; Recordati, Neth.†*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercapress
Note: this name may be used for preparations of different composition.
Pierre Fabre, Fr.; Recordati, Spain.
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Trima, Israel.
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercaril *Recordati, Irl.*
Lercanidipine hydrochloride (p. 1419·3); enalapril maleate (p. 1371·1).
Hypertension.

Lercastad *Pharmacodane, Denm.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercatio *Hexal, Denm.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercaton *Berlin-Chemie, Hung.; Menarini, Hung.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lercinigen *Generics, Denm.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lerdip *Zambon, Neth.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lerez *Glenmark, India.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lerfimin *Mintlab, Chile.*
Benzocaine (p. 1980·2); benzethonium chloride (p. 1738·1); benzyl alcohol (p. 1739·3).
Burns; insect bites.

Lergan *Viofar, Gr.*
⊗Serrapeptase (p. 2613·3).
Inflammatory disorders.

Lergia *Mecosin, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Lergicyl *Eurowest, Philipp.†*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Lergigan *Recip, Swed.*
Promethazine hydrochloride (p. 638·2).
Anxiety; tension; sleep disorders; sedative; premedication; hypersensitivity reactions; nausea; vertigo; alcoholism; pruritus; motion sickness.

Lergigan comp *Recip, Swed.*
⊗Promethazine hydrochloride (p. 638·2); caffeine (p. 1203·3); ephedrine sulfate (p. 1663·2).
Anxiety; tension; sleep disorders; sedative; premedication; hypersensitivity reactions; nausea; vertigo; alcoholism; pruritus; motion sickness.

Lergilite *Holland Pharma, Neth.*
⊗Apis mellifica (p. 2445·2); calcarea carbonica ostrearum (p. 1824·3); galphimia glauca; hepar sulphur (p. 1721·3); lobelia inflata (p. 2323·2); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Lergitec *Atral, Port.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder; autism.

Lergosin *Degorts, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Lergosin A *Degorts, Mex.*
⊗Dexamethasone (p. 1630·3); chlorphenamine (p. 620·3).

Lerid *Mint, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Leride *Hufort, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Lerin
Note: this name may be used for preparations of different composition.
Allergan, Braz.
⊗Naphazoline hydrochloride (p. 1669·3); zinc phenolsulfonate (p. 1729·3).
Ocular congestion.
Troikaa, India; Troikaa, Philipp.
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Leritone *Yves Ponroy, Canad.†*
Vitamins.

Lerivon *Organon, Arg.; Organon, Belg.; Organon, Cz.; Organon, Pol.; Organon, Rus.; Organon, Ukr.*
Mianserin hydrochloride (p. 434·2).
Depression.

Lerka *Abbott, India.*
Lercanidipine (p. 1419·3).
Hypertension.

Lermex *Sriprasit, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Lernup *Helm, Port.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Léro *Lero, Fr.*
Vitamins; minerals fish oil (p. 1460·1).
A range of dietary supplements.

Lero Pervulane *Lero, Fr.*
Docosahexaenoic acid (p. 1460·1); zinc (p. 2126·1); vitamin A (p. 2098·3); vitamin B_2 (p. 2104·3); lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement.

Lerogin *Recalcine, Chile.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal disorders; urinary-tract disorders.

Leroy *Pharmacon, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lerpin *Herbacos Recordati, Cz.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lersan Lagrimas *Lersan, Arg.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Lerskin *Nufarindo, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Lertamine *Schering-Plough, Chile.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.
Schering-Plough, Mex.
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Lertamine D *Schering-Plough, Mex.*
Loratadine (p. 633·2); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Lertamine Extra *Schering-Plough, Chile.†*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Lertazin *KRKA, Hung.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Lertec *Recordati, Neth.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lertus
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Diclofenac colestyramine (p. 48·3).
Pain; musculoskeletal, joint, and peri-articular disorders; inflammation.
Tecnofarma, Chile.
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Lertus CD *Asofarma, Mex.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Pain; musculoskeletal, joint, and peri-articular disorders; gout.

Leruze *Rafarm, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Lervasc *Lupin, India.*
Lercanidipine (p. 1419·3).
Hypertension.

Lervitan *Royal, Chile.*
Duloxetine hydrochloride (p. 415·1).
Depression; obsessive-compulsive disorder; urinary incontinence in women.

Lerzam *Rottapharm, Spain.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lerzin
Note: this name may be used for preparations of different composition.
Galpha, India.
Levocetirizine (p. 632·3).
Hypersensitivity reactions.
Ifars, Indon.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Lesacid *Cipla-Medpro, S.Afr.*
Cimetidine (p. 1827·1).

Lesaclor *Mavi, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Lesaten *Mavi, Mex.*
⊗Atenolol (p. 1308·2).

Lesbest *Best, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Lescol *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.*
Fluvastatin sodium (p. 1385·1).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction; coronary heart disease; hyperlipidaemias; prevention of cardiac complications in patients undergoing angioplasty; ischaemic heart disease.

Leset *Ipca, India.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; allergic skin disorders.

L'Esfal *Farmak, Ukr.*
Phosphatidyl choline (p. 2588·3) from soybean.
Liver and biliary-tract disorders.

Lesfat *Tolmann, Philipp.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Lesflam *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Diclofenac potassium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Leshcutan *Teva, Israel.*
Paromomycin sulfate (p. 943·3); methylbenzethonium chloride (p. 1760·3).
Cutaneous leishmaniasis.

Lesichol *Landson, Indon.*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Supplement for supporting liver function.
Pertiwi Agung, Malaysia.
Phosphatidyl choline (p. 2588·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement.
Pertiwi Agung, Singapore.
Phosphatidyl choline (p. 2588·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement.

Lesidas *Kalbe, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Lesiden *Mavi, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Lesie *Worth, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lesifit *Sandoz, Indon.*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Vitamins A, B, and E deficiency; nutritional supplement for liver function.

Lesiorepar *Amnol, Ital.*
Hyaluronic acid (p. 2526·2); echinacea (p. 2498·1).
Wound dressing.

Lesipar *Lapi, Indon.*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement.

Lesofat *Dr Zens, Philipp.*
Orlistat (p. 2577·1).
Obesity.

Lesopen *Lejal, Philipp.*
Homatropine methylbromide (p. 2007·3).
Gastrointestinal spasm; peptic ulcer.

Lesopril *Themis Medicare, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lesozap-D *AldeMedi Impex, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lespeflan *Dalkhimfarm, Rus.*
Lespedeza bicolor.
Renal insufficiency.

Lespenephryl *UCB, Rus.*
Lespedeza capitata.

Lespid *Charoon Bhesaj, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Lessfat *Ximena Polanco, Chile.*
Lessonia nigrescens; antimonium crudum (p. 2445·1); calotropis gigantea; graphites (p. 2522·1); phytolacca decandra (p. 2593·2).
Homoeopathic preparation.

Lessin *HPP, Hong Kong.*
Ofloxacin (p. 334·3).
Bacterial infections.

Lessina *Barr, USA.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Lessmusec *Brunel, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased or viscous mucus.

Lesstrol *Troikaa, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lesstrol-AM *Troikaa, India.*
Amlodipine (p. 1304·1); atorvastatin (p. 1309·2).

Lesstrol-EZ *Troikaa, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lesstrol-N *Troikaa, India.*
Atorvastatin (p. 1309·2); nicotinic acid (p. 2083·1).

Lest *Ester, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lestace *Actavis, Irl.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lestal *RPG, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lestamil *Teuto, Braz.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).

Lestara *Ardez, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lesten
Note: this name may be used for preparations of different composition.
Vir, Port.
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lestid *Pfizer, Denm.; Pfizer, Fin.†; Pfizer, Gr.; Pfizer, Norw.; Pfizer, Swed.*
Colestipol hydrochloride (p. 1345·3).
Hypercholesterolaemia; hyperlipidaemias.

Lestremor *Flamingo, Philipp.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Lestric *Ranbaxy, India; Ranbaxy, Malaysia.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction; hypercholesterolaemia.

Lestrin *Cedar Health, UK.*
Sitosterol (p. 1471·2); beta sitostanol (p. 1471·2).
Food supplement.

Lestron *Bernofarm, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Lesuride *Sun, India.*
Levosulpiride (p. 1108·1).
Dyspepsia; gastro-oesophageal reflux; irritable bowel syndrome.

Lesvatin *Gracia, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Let *Siomond, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Leta-GM *Lexus, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin (p. 304·2); miconazole (p. 588·3).

Letairis *Gilead, USA.*
Ambrisentan (p. 1298·2).
Pulmonary hypertension.

Letansil *IQB, Braz.†*
Diazepam (p. 1063·2).
Anxiety.

Letara *Douglas, NZ.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letaris *Synthon, Neth.†*
⊗Letrozole (p. 817·1).
Breast cancer.

Letequatro *Upsifarma, Port.†*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Leterzin *Panagiotis, Gr.*
Risperidone (p. 1103·2).

Letgo *Orion, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Lether *Admac, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Lethro *Forgo, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Lethyl *Aspen, S.Afr.*
Phenobarbital (p. 535·2).
Insomnia; anxiety; migraine.

Leticia *Gedeon Richter, Irl.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Combined oral contraceptive.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Letinnov *Farmaceutica H, Mex.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Letin-Tran *Sanofi-Aventis, Pol.†*
Cod-liver oil (p. 2056·3).
Dietary supplement.

Letisan *Leti, Venez.*
Ascorbic acid (p. 2110·3); citrus bioflavonoids (p. 2505·2).

Letix *Adley, India.*
Cefixime (p. 240·3).
Bacterial infections.

Letix-C *Adley, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Letizen *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; pruritus; angioedema.

Letmylan *Generics, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Let-Nasal *Sertex, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Letocor *Chandra Bhagat, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letomode *Kleva, Gr.*
Fenofibrate (p. 1381·1).

Letonal *Otto, Indon.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; hepatic cirrhosis; aldosteronism; hypokalaemia; nephrotic syndrome.

Letondal *Finadiet, Arg.*
Ambroxol hydrochloride (p. 1654·3); paracetamol (p. 115·1); oxatomide (p. 636·3).
Cold and influenza symptoms; allergic rhinitis.

Letop *Sandoz, Gr.; Sandoz, Turk.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Letoripe *Miracalus, India; Naprod, Philipp.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letraccord *Arrow, NZ.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrafem *Ariti, Gr.*
⊗Letrozole (p. 817·1).

Letralan *ICN, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrazan *Italchimici, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letregio *Regiomedica, Denm.; Regiomedica, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letride *Cipla, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroarom *Cancernova, Ger.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroblock *Pfleger, Ger.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letro-cell *Cell Pharm, Ger.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrodotril *Teva, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrofarm *GP, Arg.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrofem *Hikma, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroger *Lannacher, Cz.†*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroks *Biem, Turk.*
⊗Letrozole (p. 817·1).

Letrolan *Avansor, Fin.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroman *Synthon, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letromara *Farmak, Ukr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letromataz *Teva, Hung.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letromedac *Medac, Cz.; Medac, Ger.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letromedica *Regiomedica, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letronofi *Winthrop, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letronorm *Plus Pharma, Hung.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letropar *Tropica Mas, Indon.*
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); lecithin (p. 2542·2).
Dietary supplement.

Letropen *Enorasis, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroregiozol *Regiomedica, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrose *Anstar, Rus.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrosil *Tropica Mas, Indon.*
Curcumin (p. 2180·1); silymarin (p. 1561·2); vitamin E (p. 2119·1); soy lecithin (p. 2542·2).
To maintain healthy liver function.

Letrotera *Tuteur, Rus.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrovena *Oncogenerika, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letroveres *Synthon, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrox *Berlin-Chemie, China; Berlin-Chemie, Cz.; Berlin-Chemie, Hung.; Menarini, Hung.; Berlin-Chemie, Pol.; Menarini, Pol.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; goitre; thyroid cancer.

Letroz *Sun, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letrozette *Ratiopharm, Cz.*
⊗Letrozole (p. 817·1).

Letrozin *Meditrina, Gr.; Synthon, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lets *Samarth, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letter *Sanofi-Aventis, Port.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Letus *Unison, Hong Kong; Unison, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Letydol *Leti, Venez.*
Paracetamol (p. 115·1); dihydroergotamine mesilate (p. 672·2); caffeine (p. 1203·3).

Letynol *Norma (Νορμα), Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Letz *Chemech, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letzo *Rowex, Irl.*
⊗Letrozole (p. 817·1).
Breast cancer.

Letzol *VHB, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

leu *Nutricia, Ital.*
Food for special diets.
Isovaleric acidaemia.

Leu-AM *Nutricia, Cz.*
Food for special diets.
Disorders of leucine metabolism.

Leucin *Bergamo, Braz.*
Filgrastim (p. 1151·3).
Neutropenia induced by cytotoxic agents.

Leucinferon *Intekor, Rus.*
Interferon alfa (p. 989·2).
Hepatitis B; hepatitis C.

Leuco *Chinta, Thai.*
Tinidazole (p. 949·2).
Bacterial vaginosis; acute necrotising ulcerative gingivitis; giardiasis; trichomoniasis; Helicobacter pylori *eradication; amoebiasis.*

Leuco-4 *Expanscience, Fr.†*
Adenine (p. 2430·2).
Asthenia.

Leuco Hubber *Teofarma, Spain.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Vulvovaginal inflammatory disorders.

Leucocalcin *LKM, Arg.*
Calcium levofolinate (p. 2067·1).

Leucocitim *Blausiegel, Braz.*
Molgramostim (p. 1156·2).
Neutropenia.

Leucodin *Darrow, Braz.*
Mequinol (p. 1711·1).
Skin hyperpigmentation.

Leucodinine B *DB, Fr.*
Mequinol (p. 1711·1).
Hyperpigmentation.

Leucodinine-M *Unipharma, Gr.*
Mequinol (p. 1711·1).
Hyperpigmentation.

Leucogen
Note: this name may be used for preparations of different composition.
Ache, Braz.
Thymomodulin (p. 2631·1).
Immunodeficiencies; leucopenia.
Kalbe, Indon.
Filgrastim (p. 1151·3).
Neutropenia.

Leucoginase *VHB, India.*
Asparaginase (p. 743·3).
Lymphoblastic leukaemia.

Leucomax *Sandoz, Gr.; Schering-Plough, Gr.; Novartis, Indiat; Schering-Plough, Irl.†; Schering-Plough, NZ; Schering-Plough, Thai.; Novartis, Turk.*
Molgramostim (p. 1156·2).
Myelodysplastic syndromes; aplastic anaemia; reduction of neutropenia induced by cytotoxic therapy, bone-marrow transplantation, and ganciclovir therapy.

Leuconolver *Nolver, Venez.*
Folinic acid (p. 2066·3).
Megaloblastic anaemia.

Leucorin *Samarth, India.*
Folinic acid (p. 2066·3).

Leuco-Scint *Medi-Radiopharma, Cz.*
Technetium-99m (p. 2228·1) exametazime.
Localisation of infection and inflammation.

Leucostim *Biocad, Rus.; Dem, Turk.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Leucotrofina *Bago, Arg.*
Thymomodulin (p. 2631·1).
Leucopenia.

Leucyt *Fresenius Kabi, Philipp.*
Cytarabine (p. 774·1).
Leukaemias.

Leukase *Merck, Austria.†*
⊗Framycetin sulfate (p. 301·2); trypsin (p. 2635·2).
Infected skin disorders; infected burns and wounds.

Leukase N *Dermapharm, Ger.*
Ointment; topical powder: Framycetin sulfate (p. 301·2).
Infected skin disorders; infected wounds.
Dermapharm, Ger.
Topical gel: Framycetin sulfate (p. 301·2); lidocaine hydrochloride (p. 1988·2).
Infected skin disorders; infected wounds.

Leukast *GX, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma.

Leukeran *GSK, Arg.; Aspen, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Triton, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; Aspen, Fin; Aspen, Ger.; GSK, Gr.; IFET (ΙΦΕΤ), Gr.; Aspen, Hong Kong; GSK, India; GSK, Irl.; Perrigo, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; Aspen, Neth.; GSK, Norw.; Healthcare Logistics, NZ; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; Aspen, Spain; GSK, Swed.; Pro Concepta, Switz.; Aspen, Thai.; GSK, Turk.; GSK, UK.*
Chlorambucil (p. 764·1).
Malignant neoplasms; macroglobulinaemia; nephrotic syndrome; polycythaemia vera; immunosuppressive therapy.

Leukichtan *Ichthyol, Austria.*
Ictasol (p. 1706·1); cod-liver oil (p. 2056·3).
Skin disorders; wounds; burns.
Ichthyol, Ger.
Ictasol (p. 1706·1).
Wounds; ulcers.

Leukine *Genzyme, USA.*
Sargramostim (p. 1162·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Leukocel *Celon, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; sickle-cell disease; essential thrombocythaemia.

Leukocim *Meizler, Braz.*
Filgrastim (p. 1151·3).

Leuko-G *Zimalaya, India.*
Malabar nut (p. 2549·1); cuminum cyminum; syzygium aromaticum.

Leukokine *Novell, Indon.*
Filgrastim (p. 1151·3).
Neutropenia.

LeukoNorm *CytoChemia, Ger.†*
Leucocytes (p. 1155·3).
Immunological disorders.

Leukoprol *Kyowa, Jpn.*
Mirimostim (p. 1156·2).
Neutropenia.

LeukoScan *Immunomedics, Cz.; Immunomedics, Irl.; Immunomedics, Ital.; Immunomedics, Neth.; Immunomedics, Pol.; Immunomedics, Port.; Immunomedics, Spain.*
Technetium-99m (p. 2228·1) sulesomab.
Bone scanning agent.

Leunase *Sanofi-Aventis, Austral.; Kirin, China; Kyowa, Hong Kong; Biochem, India; Kyowa, Indon.; Kyowa, Jpn; First Pharmaceutical, Malaysia; Sanfer, Mex.; Aventis, NZ; Kyowa Hakko, Philipp.; Kyowa, Singapore; Kyowa Hakko Kirin, Thai.; Onko, Turk.*
Colaspase (p. 743·3).
Lymphomas; acute leukaemias.

Leuplin *Takeda, Jpn.*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; prostatic cancer; precocious puberty; breast cancer; uterine fibroids.

Leuprofact *Zydus, India.*
⊗Leuprorelin (p. 2285·3).
Prostatic cancer; endometriosis; uterine fibroids; precocious puberty.

Leuprol *Farmazak, Gr.*
⊗Leuprorelin (p. 2285·3).
Endometriosis; uterine fibroids; prostatic cancer.

Leuprone *Hexal, Ger.†*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Leupro-Sandoz *Sandoz, Ger.†*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Leustat *Janssen-Cilag, Arg.; Janssen-Cilag, UK.*
Cladribine (p. 769·1).
Hairy-cell leukaemia; chronic lymphocytic leukaemia.

Leustatin *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Cz.†; Janssen-Cilag, Fin.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Cilag, Hong Kong; Janssen-Cilag, Israel†; Janssen-Cilag, Ital.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.†; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singaporet†; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen, USA; Janssen-Cilag, Venez.*
Cladribine (p. 769·1).
Hairy-cell leukaemia; chronic lymphocytic leukaemia; acute myeloid leukaemia; lymphocytic lymphoma; Waldenstroms macroglobulinaemia; non-Hodgkins lymphoma.

Leustatine *Janssen-Cilag, Fr.*
Cladribine (p. 769·1).
Hairy-cell leukaemia.

Leutiral *Silanes, Mex.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Leutrol *Abbott, Braz.; BoehringerIngelheim, Ital.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Leuzan *Richmond, Arg.*
Tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Leuzotev *Lemery, Thai.; Teva, Thai.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; osteolysis of malignancy.

Levace *Acekinetic, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levacet *Pharmakon, USA.*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1); salicylamide (p. 129·2); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Levact
Note: this name may be used for preparations of different composition.
Mundipharma, Belg.; Norpharma, Denm.; Astellas, Fin.; Mundipharma, Fr.; Mundipharma, Ger.; Mundipharma, Gr.; Astellas, Irl.; Astellas, Ital.; Astellas, Neth.; Mundipharma, Norw.; Mundipharma, Spain; Napp, UK.
Bendamustine hydrochloride (p. 746·2).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma; multiple myeloma; non-Hodgkins lymphoma.
Zytras, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Levact-OZ *Zytras, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Levalastine *Biomedica, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Levall *Auriga, USA.*
Phenylephrine hydrochloride (p. 1672·3); pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Formerly contained phenylephrine hydrochloride, hydrocodone tartrate, and guaifenesin.
Coughs.

Levall 5.0 *Auriga, USA.*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Levall 12 *Auriga, USA.*
Pentoxyverine tannate (p. 1672·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Levalon *Micro, India.*
Capsules: Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).
Micro, India.
Tablets: Silymarin (p. 1561·2).
Liver disorders.

Levam *Lafedar, Arg.*
Levamisole hydrochloride (p. 157·2).

Levamin
Note: this name may be used for preparations of different composition.
Genepharm, Gr.
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.
Pisa, Mex.
Amino acids.
Parenteral nutrition.

Levan *Multicare, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levana *Interchem, Ukr.*
Levan.
Sleep disorders.

Levant *Focus, Hung.†; Ranbaxy, India; Ranbaxy, Malaysia.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Levantes *Mediolanum, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Levantol Procaina *Mertens, Arg.*
Calcium phosphate (p. 1784·2); methionine (p. 1558·2); pyritinol hydrochloride (p. 394·3); procaine hydrochloride (p. 1994·3); vitamin B substances (p. 2102·3).
Asthenia; mental function impairment.

Levaquin *Janssen-Cilag, Arg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen, USA; Janssen-Cilag, Venez.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levars *Arsmedendi, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Levasil *Micro Labs, Ukr.*
Silymarin (p. 1561·2); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2) calcium pantothenate (p. 2085·2); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1).
Liver disorders.

Levate *Valeant, Canad.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Levatol *Actient, USA.*
⊗Penbutolol sulfate (p. 1464·3).
Hypertension.

Levator *Maxo, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levaxin *Nycomed, Norw.; Nycomed, Swed.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer.

Levazide *Pyridam, Indon.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Levazyr *Actavis, Denm.; Actavis, Fin.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Levbid *Meda, USA.*
Hyoscyamine sulfate (p. 1848·1).
Gastrointestinal disorders; urinary-tract disorders; biliary and renal colic; rhinitis; parkinsonism.

Levcin *Sandoz, Braz.*
Levofloxacin (p. 315·3).

Levecetam *Psyco Remedies, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Levedad *Raymos, Arg.*
Diclofenac sodium (p. 48·3).
Postoperative eye inflammation.

Levedo *Fontovit, Braz.†*
Brewer's yeast (p. 2125·2).

Levedol *Dermogen, Spain.*
Ibuprofen (p. 68·2).
Fever; pain.

Leveglutan *Bunker, Braz.*
Dried yeast (p. 2125·2); vitamin B substances (p. 2102·3).
Dietary supplement.

Level *Biolab Sanus, Braz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Level Up *Garden House, Arg.*
Ginseng (p. 2513·3); minerals; vitamins.
Dietary supplement.

Levelina *Ern, Spain.*
Bifonazole (p. 573·3).
Fungal skin and nail infections.

Levemir *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Canad.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, India; Novo Nordisk, Indon.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, Ukr.; Novo Nordisk, USA.*
⊗Insulin detemir (p. 475·3).
Diabetes mellitus.

Lev-End *Berksam, Turk.*
Levetiracetam (p. 531·1).

Levend *Blubell, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levenor *Apotex, Hung.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Lever *Johnson Diversey, Canad.*
Triclosan (p. 1773·2).
Hand disinfection.

Lever San *Diversey Lever, Canad.†*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Levera *Intas, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Leverctin *EMS, Braz.*
Ivermectin (p. 155·1).

Leverest *Medico, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Leverest Plus *Medico, India.*
Levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Leverest-AM *Medico, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine (p. 632·3).

Leverest-MK *Medico, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Leveron *Vesco, Thai.*
Silymarin (p. 1561·2).
Liver disorders.

Levesam *Abbott, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Levest
Note: this name may be used for preparations of different composition.
Morningside, UK.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.
Teva, Spain.
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Levetrim *Trima, Israel.*
Levetiracetam (p. 531·1).
Epilepsy.

Levex *EuroHealth, Philipp.; Lagap, Switz.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levexx *Zydus, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Levical *Elnova, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).

Levicarb *Elnova, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc sulfate (p. 2126·2).

Levicin
Note: this name may be used for preparations of different composition.
Tanic, Gr.
Levocarnitine (p. 2053·2).
Deltapharm, Hong Kong.†
Levofloxacin (p. 315·3).
Bacterial infections.

Levicit *Elnova, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1).

Levicitam *Pharma Start, Ukr.*
Levetiracetam (p. 531·1).
Epilepsy.

Leviden *Toho, Hong Kong.†*
Liver hydrolysate (p. 2444·1).
Liver disorders.

Levifer *Elnova, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Levifusa *Ifusa, Mex.*
Yeast (p. 2125·2).
Dietary supplement.

Levinan *Link, UK.*
Levomepromazine maleate (p. 1079·3).
Nausea and vomiting.

Levineuro *Elnova, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Levinox *Santa, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Leviogel *SIT, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular pain and inflammation.

Levipil *Sun, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Levistan *Giempi, Venez.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Levisticum S *Hanosan, Ger.*
Levisitcum officinale (p. 2545·3); rosmarinus officinalis (p. 2607·2); acidum benzoicum (p. 1738·2); urtica urens (p. 2639·3); cantharis (p. 2469·2); juniperus communis (p. 2537·1); equisetum arvense (p. 2500·1); hypericum perforatum (p. 449·1); uva ursi (p. 2453·2); betula alba (p. 2457·3).
Homoeopathic preparation.

Levital Plus *SIFFRA, Ital.*
Rutoside (p. 2505·3); ascorbic acid (p. 2110·3); centella (p. 1698·3); melilot (p. 2552·3); aesculus (p. 2431·2); ananas comosus; myrtillus (p. 2566·2).
Circulatory disorders.

Levitam *Aspen, Austral.*
Levetiracetam (p. 531·1).
Epilepsy.

Levitra *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; GSK, Hong Kong; Bayer, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.; Bayer Schering, Port.; Bayer, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, Ukr.; GSK, USA; Schering-Plough, USA; Bayer, Venez.*
Vardenafil hydrochloride (p. 2372·1).
Erectile dysfunction.

Levium *Hexal, Ger.†*
Levomepromazine maleate (p. 1079·3).
Pain; psychoses.

Levlen ED *Bayer, Austral.; Bayer, NZ.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Levloc *Cadila, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levo *Trima, Israel.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoace *Biosync, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levoact *Active, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levobact *Micro, India; Brown & Burk, Philipp.; Micro Labs, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levobel *Effik, Spain.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Levobenz *Admac, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levobet *PSA, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levobeta C *Betapharm, Ger.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levobos *Arunabh, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Levobren *GiEnne, Ital.*
Levosulpiride (p. 1108·1).
Gastrointestinal disorders; migraine; headache; vertigo; nausea and vomiting.

Levobus *Globus, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levo-C *Aliud, Ger.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levoc *Biosans, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levocad *Admac, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levocar *Stada, Austria; Sandoz, Fin.; Sandoz, Swed.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levocarb *Biolab Sanus, Braz.; 1A, Ger.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levocarbhexal *Sandoz, Ukr.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levocarnil *DAST, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Lévocarnil *Sigma-Tau, Fr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Levocarvit *Aesculapius, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Levocas *Casca, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levocep *Extractum, Hung.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Levocet *Hetero, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levocet Plus *Hetero, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3).

Levocet-D *Hetero, India.*
Levocetirizine hydrochloride (p. 632·3); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis.

Levocetile *Korea United, Philipp.*
Acetylcarnitine (p. 2053·2).
Cerebrovascular disorders.

Levocetira *Tiefenbacher, Neth.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Levocet-M *Hetero, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast sodium (p. 1214·3).
Asthma.

Levocetriwal *Wallace, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levocets *Shreshtha, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levocide *Cadila, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levocide-OZ *Cadila, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Levocin *Sanbe, Indon.; Getz, Philipp.; LBS, Thai.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levocina *Cryopharma, Mex.*
Levomepromazine maleate (p. 1079·3).
Psychoses.

Levoclic-M *Quest, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Levocof *Valeant, Mex.*
Levodropropizine (p. 1662·3).
Cough.

Levocomp *Hexal, Ger.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levocos *Symbiosis, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levocos-OZ *Symbiosis, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Levocuor *Nexus, Gr.*
Levocarnitine tartrate (p. 2053·2).
Carnitine deficiency.

Levodak *Zodak, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoday *Zydus, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoden *BMW, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levodexan *Grin, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Infected eye disorders.

Levodil *Psychotropics, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levodop *Neuraxpharm, Ger.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levodopa Comp *Ratiopharm, Ger.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levodopa comp B *Stada, Ger.†*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Levodopa comp C *Stada, Ger.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levo-F *Arrowin, India.*
Folic acid (p. 2063·1); levocarnitine (p. 2053·2).

Levofamil *Andromaco, Chile.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levofenil *Grin, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1); phenylephrine hydrochloride (p. 1672·3).
Inflammatory eye infections.

Levoff *Biochem, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levofin *Duopharma, Philipp.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Levoflow *Biophar, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoflox *Cipla, India; LBS, Philipp.; GPO, Thai.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoflox Oz *Cipla, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).
Bacterial infections.

Levofolene *Bayer, Ital.*
Calcium levofolinate (p. 2067·1).
Folate deficiency anaemia; antidote to folic acid antagonists.

Levofolic *Lamepro, Belg.; Medac, Cz.; Medac, Fin.; Medac, Gr.; Medac, Pol.; Medac, Port.*
Sodium levofolinate (p. 2066·3).
Reduction of folate antagonist toxicity; adjunct to fluorouracil therapy; reduction of methotrexate toxicity.

Levo-Forte *Arrowin, India.*
Folic acid (p. 2063·1); levocarnitine (p. 2053·2); vitamin E (p. 2119·1).

Levofox *Dr Alson, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levo-FQ *Venus, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levofree *Chauvin, Fr.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis.

Levogastrol *Salvat, Spain.*
Levosulpiride (p. 1108·1).
Dyspepsia.

Levogenix *Genetic, Ital.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Levoglutil Vitaminado *Spedrog, Arg.*
Glutamine (p. 2070·3); vitamin B_6 (p. 2105·3); cyanocobalamin (p. 2107·2); calcium lactate (p. 1784·1); magnesium gluconate (p. 1787·2).
Tonic.

Levogo *Invision, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levogo Plus *Invision, India.*
Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Levogram *Akesiss, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levogrm *UnitedLifecare, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levogyl *Maneesh, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Levogynon *Bayer, Ger.†*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Levohexal *Sandoz, Austral.†*
Levodopa (p. 902·2); Carbidopa (p. 900·3).
Parkinsonism.

Levohext *Sanofi-Aventis, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levohill *Daffohils, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoid *Ache, Braz.*
Levothyroxine sodium (p. 2339·1).

Levokab *Lancer, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levokair *PDC, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levokem *Alkem, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levokom *Pharma Start, Ukr.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levokuin *Sandoz, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levola *Intra-Labs, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levolab *Laborate, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levolac *Leiras, Fin.; Fresenius Kabi, Norw.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Levolacin *Medicus, Gr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levolak *Laksun, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levolam *Lamsa, Arg.*
Levomepromazine maleate (p. 1079·3).
Psychoses.

Levolet *Reddy, Rus.; Reddy, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levolife *Life Line, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levolin *Cipla, India.*
⊗Levosalbutamol sulfate (p. 1213·3).
Asthma; bronchospasm.

Levolon *PDC, India; Bilim, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levom *Medico, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levomag *Magnus, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoman *Maneesh, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levomax *ACME, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levomecol *Akrikhin, Rus.; Nizhpharm, Rus.*
Chloramphenicol (p. 257·1); methyluracil.
Bacterial skin infections.

Levomed
Note: this name may be used for preparations of different composition.
Mediez, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Thai.
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levomet
Note: this name may be used for preparations of different composition.
Unison, Hong Kong; Unison, Singapore; Unison, Thai.
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levometil *Zelenaya Dubrava, Rus.*
Chloramphenicol (p. 257·1); methyluracil.
Wounds.

Levomin *Dermapharm, Switz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Levomine *Andromaco, Arg.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; allergic skin disorders; pruritus.

Levomir *Shchelkovskii, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Levomol *Cipla, India.*
Levamisole (p. 157·2).
Worm infections.

Levomycetin *Lekko, Rus.; Chew, Thai.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Levon *Azine, India; Enzo, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levonat *Atabay, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levonelle *Bayer, Austral.; Medimpex, Irl.; Bayer, Ital.; Bayer, NZ; Medimpex, Port.†; Bayer, UK.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Levonez *Wintech, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levonic *Nicholas, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levonidin *Yeni, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levonis *TS, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Levonitrin *Svizera, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levonor *Polfa Warszawa, Pol.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Circulatory failure; shock; vasoconstrictor in local anaesthesia.

Levonova *Bayer, Swed.†*
Levonorgestrel (p. 2296·1).
Progestogen-releasing intra-uterine contraceptive device; menorrhagia.

Levonox *PSA, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levopa-C *Wallace, India.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Levopar *Meprofarm, Indon.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Hexal, Ger.†
Levodopa (p. 902·2); benserazide (p. 894·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Levopar Plus *Teva, Israel.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Levopet *Vista, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levophar *Uniphar, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levophed *Hospira, Austral.; Hospira, Belg.; Abbott, Braz.; Hospira, Canad.; IFET (ΙΦΕΤ), Gr.†; Hospira, Hong Kong; Hospira, Indon.; Transfarma, Indon.; Hospira, Irl.†; Hospira, Israel; Hospira, Malaysia; Hospira, NZ; Hospira, Philipp.; Hospira, Singapore; Hospira, Thai.; Hospira, USA.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Cardiac arrest; hypotension; shock.

Lévophta *Chauvin, Fr.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis.

Levopil *Psychotropics, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoplus *Montefarmaco, Ital.*
⊗Dietary fibre; lactulose (p. 1850·3); lactitol (p. 1850·3); mannitol (p. 1427·3).

Levopraid *Therabel, Belg.; Abbott, Ital.*
Levosulpiride (p. 1108·1).
Gastrointestinal disorders; headache; vertigo; depression; psychoses; psychosomatic syndromes.

Levoprime *Farma Iberica, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoprolin *Proel, Gr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levopront *Dompe, Cz.; Dompe, Hung.; Combiphar, Indon.; Dompe, Philipp.; Dompe, Pol.; Mack, Rus.; Noventure, Thai.; Abdi, Turk.; Zuoz, Venez.*
Levodropropizine (p. 1662·3).
Cough.

Levoptin *Archifar, Thai.*
⊗Chloramphenicol (p. 257·1); prednisolone sodium phosphate (p. 1645·3); naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Levoquin *Cipla, India; OEP, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levora *Watson, USA.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Levorax *Ankom, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levordiol *Sigma, Braz.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); pyridoxine hydrochloride (p. 2105·3); 7 tablets, pyridoxine hydrochloride.
Triphasic oral contraceptive.

Levoreact *Johnson & Johnson, Ital.*
Levocabastine hydrochloride (p. 632·2).
Allergic rhinitis.

Levores *Novell, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levorid *Cipla, India.*
Levocetirizine (p. 632·3).
Allergic rhinitis; urticaria.

Levorid D *Cipla, India.*
⊗Levocetirizine (p. 632·3); pseudoephedrine (p. 1676·1).
Allergic rhinitis.

Levoride *Psyco Remedies, India.*
Levosulpiride (p. 1108·1).
Dyspepsia; gastro-oesophageal reflux; irritable bowel syndrome.

Levorigotax *Prater, Chile.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levoril *Acto, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levorin *Blausiegel, Braz.*
Calcium levofolinate (p. 2067·1).
Anaemias; antidote to folic acid antagonists.

Levoriz *Ritz, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levoriz Plus *Ritz, India.*
Levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Levoriz-AM *Ritz, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine (p. 632·3).

Levoriz-MK *Ritz, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Levosan *Sanus, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Levosh *Keshav, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levosidh *Sidhbali, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levosin *Nizhpharm, Rus.*
Chloramphenicol (p. 257·1); sulfadimethoxine (p. 363·2); methyluracil; trimecaine (p. 1997·3).
Wounds.

Levosip *Sipra, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levosiz *Systopic, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levosoz *Sozin-Flora, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levospan *Pharmatech, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levospan-OZ *Pharmatech, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Levospi *Auspi, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levostab *Formenti, Ital.*
Levocabastine hydrochloride (p. 632·2).
Allergic rhinitis; allergic conjunctivitis.

Levostar *Intra-Labs, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levostar Plus *Intra-Labs, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

Levostar Plus Exp *Intra-Labs, India.*
Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); levocetirizine (p. 632·3).

Levostar-AM *Intra-Labs, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Levostar-D *Intra-Labs, India.*
Levocetirizine (p. 632·3); phenylpropanolamine hydrochloride (p. 1674·1).

Levostar-R *Intra-Labs, India.*
Rupatadine (p. 640·1).
Allergic rhinitis; urticaria.

Levostran *Cipla, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levosym *Symbiosis, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levosym-OZ *Symbiosis, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Levotab *Medihealth, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levotac *Cristalia, Braz.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levotan *Tan, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Levotas *Intas, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levotec
Note: this name may be used for preparations of different composition.
Servocare, India; United Biotech, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Levotech *Pharma-Tech, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoteva *Med, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levothroid *IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Spain; Forest Laboratories, USA.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; TSH suppression.

Lévothyrox *Merck Serono, Fr.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Levotin *Molekule, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Levotin Plus *Molekule, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast (p. 1214·3).

Levotiron *Abdi, Turk.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Lévotonine *Panpharma, Fr.*
Oxitriptan (p. 440·3).
Myoclonus.

Levotoz *ATOZ, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levotra *Azine, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levotra-A *Azine, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Levotra-M *Azine, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Levotran *Evershine, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levotrin
Note: this name may be used for preparations of different composition.
GSK, Arg.
Liothyronine sodium (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism.
Medihealth, India.
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levotrin-M *Medihealth, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Levotrin-P *Medihealth, India.*
Levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Levotum *Profic Organic, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levotuss *Therabel, Belg.; Arriani, Gr.; Dompe, Ital.; Dompe, Neth.; Dompe, Port.; Rottapharm, Spain.*
Levodropropizine (p. 1662·3).
Cough.

Levovanox *Genetic, Ital.*
Vancomycin hydrochloride (p. 384·2).
Antibiotic-associated colitis.

Levovent *Genetic, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Levovid *Bernofarm, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levovist *Bayer, Austral.; Bayer, Fr.†; Bayer, Ger.†; IFET (ΙΦΕΤ), Gr.; Bayer, Ital.; Schering, NZ†; Bayer, Spain†; Bayer, Switz.†*
Galactose (p. 1588·1).
Ultrasound contrast medium; contrast medium for echocardiography.

Levowal *Radicura, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levowok *Wockhardt, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levox *Claris, India; Westmont, Philipp.; Claris, Thai.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxa *Actavis, Hung.; Actavis, Pol.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxacin *GSK, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxal *Sandoz, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxigram *Mitim, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxin *Apsen, Braz.; Incepta, Hong Kong; Osmed, India; Marck Biosciences, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxl *XL, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levoxyl *Jones, USA.*
Levothyroxine sodium (p. 2339·1).
Formerly known as Levoxine.
Hypothyroidism; TSH suppression.

Levoz *Ethix, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levozef *Metro, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levozin
Note: this name may be used for preparations of different composition.
Moraceae, India.
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.
Orion, Fin.
Levomepromazine maleate (p. 1079·3).
Psychoses; agitation; pain; insomnia.

Levozine
Note: this name may be used for preparations of different composition.
Cristalia, Braz.
Levomepromazine maleate (p. 1079·3).
Psychoses; pain in obstetrics; premedication; adjunct in general anaesthesia.
Sandoz, Cz.
Levocetirizine hydrochloride (p. 632·3).

Levoz-M *Plus, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Levrea *Cinerea, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Levrison *Rovi, Spain.†*
An inactivated influenza virus vaccine (p. 2393·3).
Active immunisation.

Levrix *Tecnifar, Port.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Levron *Rontag, Arg.*
Levetiracetam (p. 531·1).
Epilepsy.

Levrox *Rider, Chile.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Levroxa *Ranbaxy, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Levsin *UCB, Hong Kong; Alaven, USA.*
Hyoscyamine sulfate (p. 1848·1).
Gastrointestinal disorders; partial heart block associated with vagal activity; adjunct to hypotonic duodenography; premedication; improvement of radiological visibility of the kidneys; biliary and renal colic; rhinitis; parkinsonism; gastrointestinal and renal disorders associated with smooth muscle spasm.

Levsinex *Alaven, USA.†*
Hyoscyamine sulfate (p. 1848·1).
Gastrointestinal disorders; biliary and renal colic; rhinitis; parkinsonism; urinary-tract disorders.

Levtam *Unichem, India.*
Levetiracetam (p. 531·1).
Epilepsy.

Levucal *Pasteur, Chile.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteomalacia; osteoporosis; rickets; tetany.

Levucal D *Pasteur, Chile.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; osteoporosis.

Levulan Kerastick *Coherent, Canad.; Stiefel, Chile; Dusa, Thai.; DUSA, USA.*
Aminolevulinic acid hydrochloride (p. 740·1).
Actinic keratoses.

Levulin L *Marvel, Rus.†*
⊗Insulin zinc suspension (crystalline 70%, amorphous 30%) (porcine) (p. 475·3).
Diabetes mellitus.

Levunolol *Luar, Arg.*
⊗Levobunolol (p. 2008·3).
Ocular hypertension.

Levure Or *Grimberg, Fr.†*
Potassium bromoaurate; dried yeast (p. 2125·2).
Rheumatic disorders.

Levurinetten *Novartis Consumer, Austria.†*
Dried yeast (p. 2125·2); vitamin B substances (p. 2102·3).
Skin disorders.

Levusid *Quesada, Arg.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Levzed *Zubit, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Levzed-A *Zubit, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Levzed-MK *Zubit, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

LeWei *Wanle, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Lewel *Sigman, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lewensessens *Aspen Consumer, S.Afr.*
Aloes (p. 1816·1); ginger (p. 1844·1); rhubarb (p. 1884·2); gentian (p. 2512·1); myrrh (p. 2566·1); galanga; turmeric (p. 2218·1).
Constipation; gastric disorders.

Lewimycin *Lewison, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Lewinex *Lewison, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Lewixin *Lewison, Philipp.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lexa
Note: this name may be used for preparations of different composition.
Arvincare, India.
Cefalexin (p. 234·1).
Bacterial infections.

Landson, Indon.
Levofloxacin (p. 315·3).
Bacterial infections.

Lexacin *Verisfield, Gr.; Shince, India; Umut, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lexacorton *Molex Ayus, Indon.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Lexacrol *Molex Ayus, Indon.*
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence; bloating.

Molex Ayus, Indon.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence; bloating.

Lexadium *Molex Ayus, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lexagin *Molex Ayus, Indon.*
Dipyrone (p. 53·3).
Pain.

Lexahist *Molex Ayus, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic disorders; pruritus.

Lexalgin *Danlex, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Lexam *Aspen, Austral.*
Escitalopram oxalate (p. 416·2).
Depression.

Lexamil *Cipla-Medpro, S.Afr.*
Escitalopram (p. 416·2).
Depression; panic disorder.

Lexapram *Molex Ayus, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Lexapro *Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Braz.; Lundbeck, Chile; Lundbeck, China; Xian-Janssen, China; Lundbeck, Hong Kong; Lundbeck, Irl.; Mochida, Jpn; Lundbeck, Malaysia; Lundbeck, Mex.; Lundbeck, Neth.; Healthcare Logistics, NZ; Lundbeck, Philipp.; Lundbeck, Pol.; Lundbeck, Singapore; Lundbeck, Thai.; Forest Pharmaceuticals, USA; Abbott, Venez.*
Escitalopram oxalate (p. 416·2).
Anxiety; depression; panic disorder; obsessive-compulsive disorder; social phobia.

Lexaprofen *Molex Ayus, Indon.*
Ibuprofen (p. 68·2).
Fever; pain; rheumatoid arthritis.

Lexatin *Roche, Spain.*
Bromazepam (p. 1041·2).
Anxiety.

Lexaurin *KRKA, Cz.*
Bromazepam (p. 1041·2).
Anxiety disorders; insomnia; depression.

Lexavit *Molex Ayus, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Lexavite *Bajer, Arg.*
Liquid paraffin (p. 2191·2).
Bowel evacuation.

Lexavon *Molex Ayus, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Lex-B *Forgo, India.*
Vitamin B substances (p. 2102·3).

Lexcid *Lexus, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Lexcid-DM *Lexus, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux.

Lexcin *Lexus, India.*
Amikacin (p. 214·1).
Bacterial infections.

Lexcof *Cipla, India.*
Lozenges: Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Cipla, India.
Oral liquid: Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cough.

Lexcomet *Molex Ayus, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Lexemin *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lexeroll *Valeant, Hung.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lexet *Teva, Mex.*
Pravastatin sodium (p. 1473·1).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Lexfast *Sigma, Braz.*
Bromazepam (p. 1041·2).

Lexfer-Z *Cubit, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Lexflox *Lexus, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lexflox-TZ *Lexus, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Lexfor *TNP, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Lexi *Clinbaxy, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lexib *Foramen, Philipp.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; adenomatous colorectal polyps.

Lexicom *Alpha Aromatic, India.*
Lactobacillus sporogenes (p. 2596·3).

Lexid *Solas, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Lexiflox
Note: this name may be used for preparations of different composition.
Eris, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Duopharma, Hong Kong†; LBS, Philipp.
Norfloxacin (p. 333·3).
Urinary-tract infections; bacterial infections.

Lexigor *Vivax, Gr.*
Omeprazole (p. 1867·2).

Lexil *Roche, Ital.*
Bromazepam (p. 1041·2); propantheline bromide (p. 1880·1).
Gastrointestinal disorders.

Lexilin *Rotam Reddy, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Lexilium *Remedica, Hong Kong.†*
Bromazepam (p. 1041·2).
Anxiety.

Lexillin *Symbiosis, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Lexime *Cosmas, India.*
Cefixime (p. 240·3).
Bacterial infections.

Lexime-CV *Cosmas, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Lexin *Biotenk, Arg.; Teuto, Braz.; Hikma, Ukr.*
Cefalexin (p. 234·1).
Bacterial infections.

Lexincef *Serra Pamies, Spain.†*
Cefalexin (p. 234·1).
Bacterial infections.

Lexinor *AstraZeneca, Philipp.†; AstraZeneca, Swed.†; AstraZeneca, Thai.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Lexipad *Korea United, Philipp.*
Cefadroxil (p. 233·2).
Bacterial infections.

Lexipil *Psychotropics, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Lexiscan *Astellas, USA.*
Regadenoson (p. 1485·2).
Coronary vasodilator during radionuclide myocardial perfusion imaging.

Lexiva *GSK, Israel; GSK, USA.*
Fosamprenavir calcium (p. 980·1).
HIV infection.

Lexivit *Lewison, Philipp.*
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3).

Lexivit-E *Korea United, Philipp.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Lexmodine *Molex Ayus, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; pathological hypersecretory disorders.

Lexmox *Lexus, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lexmox-DC *Lexus, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Lexo *Flupal, Venez.*
Oxolamine citrate (p. 1671·2) or oxolamine phosphate (p. 1671·2).
Cough.

Lexobron *Roemmers, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lexoderil *Advaita, Mex.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Lexof *Lexus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Lexof-OZ *Lexus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Lexof-TZ *Lexus, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Lexomil *Roche, Fr.*
Bromazepam (p. 1041·2).
Anxiety; alcohol withdrawal syndrome.

Lexoquin *Health Guard, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lexosedin *Mylan, Ital.*
Butamirate citrate (p. 1657·3).
Cough.

Lexostad *Stada, Ger.†*
Bromazepam (p. 1041·2).
Anxiety disorders; insomnia.

Lexotan *Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Denm.; Roche, Hong Kong; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S. Afr.; Roche, Singapore; Roche, Thai.*
Bromazepam (p. 1041·2).
Anxiety; insomnia; psychosomatic disorders; phobias; obsessive-compulsive disorders; agitation.

Lexotanil *Roche, Arg.; Roche, Austria; Roche, Chile; Roche, Ger.; Roche, Gr.; Roche, Switz.; Roche, Venez.*
Bromazepam (p. 1041·2).
Anxiety; psychosomatic disorders; insomnia.

Lexpec *Rosemont, UK.*
Folic acid (p. 2063·1).
Anaemias.

Lexpram *Arlex, Mex.*
Meloxicam (p. 86·3).
Inflammation.

Lextarol *Biomedica, Gr.; Pharmacypria, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Lextor *Casasco, Arg.*
Escitalopram oxalate (p. 416·2).
Depression.

Lextrasa *GB, Ital.*
Mesalazine (p. 1859·2).
Crohn's disease; ulcerative colitis.

Lextril *Glenmark, Pol.*
Perindopril erbumine (p. 1467·1).
Hypertension; cardiovascular risk reduction.

Lexum *Westmont, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Lexuss *Centurion, USA.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.

Lexxema *Italfarmaco, Spain.*
⊗Methylprednisolone aceponate (p. 1642·2).
Skin disorders.

Lexyl *Metz, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lexzepam *Mersifarma, Indon.*
Bromazepam (p. 1041·2).
Anxiety.

Lexzin *Lexus, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

PSA, Philipp.
Levofloxacin (p. 315·3).
Bacterial infections.

Lexzin-P *Lexus, India.*
⊗Levocetirizine (p. 632·3); pseudoephedrine (p. 1676·1).

Leyuan *Huahai, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Lezasin *Pascual, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lezdes-P *Aamorb, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lezepan *Neo Quimica, Braz.*
Bromazepam (p. 1041·2).

Lezer *Zytras, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lezine *Lexus, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Lezine-P *Lexus, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Lezo
Note: this name may be used for preparations of different composition.
Cadila, India.
Capsules: Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Cadila, India.
Tablets: Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Lezo-AM *Cadila, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3).

Lezol *Intas, Philipp.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lezone *Admac, India.*
Injection: Ceftriaxone (p. 253·3).
Bacterial infections.

Admac, India.
Syrup: Cefpodoxime.
Bacterial infections.

Lezone-LB *Admac, India.*
Cefpodoxime; lactobacillus (p. 2596·3).
Bacterial infections.

Lezone-S *Admac, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Lezone-XP *Admac, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Lezpain *YSP, Malaysia.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Le-Zyncet-M *Unichem, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

LF *Finecure, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

LF 100 *Dicofarm, Ital.*
Sweet chestnut (p. 2625·1).
Cellulite; lymphatic stasis.

LFast *Cadila, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

LFast-AM *Cadila, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine (p. 632·3).

LFC Med *Medizone, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

L-Flo *Nordic, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

L-Flox *Lupin, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

L-Floxin *Laborate, India.*
Moxifloxacin (p. 326·3).
Bacterial conjunctivitis.

LG *Kalpataru, India; United Lifecare, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

LG Espogen *LG Life Sciences, India.*
⊗Erythropoietin (p. 1141·1).
Anaemias; autologous blood transfusion.

LG Eutropin *LG Life Sciences, India.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure; Prader-Willi syndrome; short children born small for gestational age; cachexia and wasting in AIDS; short bowel syndrome; SHOX deficiency.

LG Euvax B *LG Life Sciences, India.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

LG Follimon *LG Life Sciences, India.*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary syndrome.

LG Hyal *LG Life Sciences, India.*
Sodium hyaluronate (p. 2526·2).
Adjunct in cataract surgery.

LG Hyruan *LG Life Sciences, India.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

LG Intermax Alpha *LG Life Sciences, India.*
Interferon alfa (p. 989·2).

LG IVF-C *LG Life Sciences, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

LG Plus *Kalpataru, India.*
Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1).

LGNil *Cadila, India.*
Cetirizine (p. 619·2).

LGP *Little Greave, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

LGP-H *Little Greave, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

LG-Plus *United Lifecare, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).

LG-Thral *Anvik, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Li La *Haite Sihuan, China.*
Ipriflavone (p. 1185·3).

Li De *Jinshi, China.*
Pidotimod (p. 2590·2).

Li Di *Mingxing, China.*
Imiquimod (p. 985·2).

Li Le
Note: this name may be used for preparations of different composition.
Kangmei, China.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Nanda, China.
Povidone-iodine (p. 1767·1).

Li An *Pu Luo Kang Yu, China.*
Rimantadine hydrochloride (p. 1012·2).

Li Ao Jia *Livzon, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer.

Li Bai Lu *Taikang, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Li Bang *Haobang, China.*
Ozagrel sodium.

Li Bang Te *Libang, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Li Bei Er *Dawnrays, China.*
Sparfloxacin lactate.
Bacterial infections.

Li Bei Jia *Shuang Cheng, China.*
Potassium chloride (p. 1793·2).

Li Bei Si *C & O, China.*
Calcium dobesilate (p. 2464·3).
Microvascular disorders; venous insufficiency; haemorrhoids.

Li Bi De *Yangtian, China.*
Bismuth aluminate (p. 1821·3).

Li Bi Fu *Haisike, China.*
Dolasetron mesilate (p. 1837·2).

Li Chuan *Double-Crane, China.*
Ligustrazine hydrochloride.

Li Da An *San Lian, China.*
Lysine hydrochloride (p. 2079·3).

Li Da Fei *Rui Yang, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Li Da Mei *Aibujia, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Li Dao *Jiuhe, China.*
Nabumetone (p. 97·1).

Li Le Er *Dong Fang, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Li Er Fan *Yixin, China.*
Mannatide.

Li Er Ning *Lierfan, China.*
Octreotide acetate (p. 1924·1).

Li Er Quan *Mingxing, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Li Er Shu *Ke Yi, China.*
Matrine.

Li Fan You *Ya Bang Ai Pu Sen, China.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).

Li Fen Neng *Hayao, China.*
Interferon alfa-2b (human, recombinant) (p. 989·2).

Li Fu
Note: this name may be used for preparations of different composition.
Binhu Shuanghe, China.
Inosine (p. 2533·1).

Chung-Hwa, China.
Roxithromycin (p. 356·2).
Bacterial infections.

Li Fu Jun An *Shenghuaxi, China.*
Ziprasidone hydrochloride (p. 1115·2) or ziprasidone mesilate (p. 1115·2).
Schizophrenia; bipolar disorder.

Li Fu Xin *Livzon, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Li Gan *Chang Fu Jie Jing, China.*
Matrine.

Li Ge Shi *Sha Pu Ai Si, China.*
Ligustrazine phosphate.

Li Hong *Huayu, China.*
Clindamycin hydrochloride.

Li Huan *Baijingyu, China.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Li De Jia *Ke Yi, China.*
Enoxacin (p. 290·2).
Bacterial infections.

Li Jia *Wanhui Shuanghe, China.*
Demethylcantharidin.

Li Jian *C & O, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infections.

Li Jian Ke *Lijian, China.*
Cefixime (p. 240·3).
Bacterial infections.

Li Jian Xin *Lijian, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Li Jiang *Yijian, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Li Du Ka Ning *Wushi, China.*
Ethylenediamine diaceturate.

Li Ka Ting *Hua Shen, China.*
Iodine-131 metuximab (p. 2225·3).

Li Kang Ping *Baiyi, China.*
Lappaconitine hydrobromide (p. 1418·1).

Li Ke Le *Ke Yi, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Li Ke Bang *Qiyun, China.*
Amlexanox (p. 1202·2).

Li Ke Chang *Ke Yi, China.*
Levofloxacin mesilate.
Bacterial infections.

Li Ke Duo *Sichuan Pharmaceutical, China.*
Piperacillin sodium (p. 340·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Li Ke Fei *Haixin, China.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Li Ke Fen *Ke Yi, China.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Li Ke Ji *Ke Yi, China.*
Apomorphine hydrochloride (p. 892·3).
Erectile dysfunction.

Li Ke Jie *Ke Yi, China.*
Imiquimod (p. 985·2).

Li Ke Ming *Ke Yi, China.*
Ganciclovir (p. 982·3).

Li Ke Ning *Ke Yi, China.*
Doxepin hydrochloride (p. 414·2).

Li Ke De Nuo *Ke Yi, China.*
Bismuth subcitrate.

Li Ke Ping *Ke Yi, China.*
Aciclovir (p. 964·1).

Li Ke Qing *Limin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Li Ke Shuang *Ke Yi, China.*
Penciclovir (p. 1008·2).

Li Ke Si *Lai Mei, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Li Ke Wei *Ke Yi, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Li Ke Xin *Ke Yi, China.*
Aciclovir (p. 964·1).

Li Lai Ke *Dongzhitang, China.*
Telmisartan (p. 1509·3).
Hypertension.

Li Lei Te *Dadeli, China.*
Calcium folinate (p. 2066·3).

Li Li De *Haili, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Li Li Le *Haili, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Li Li Kai
Note: this name may be used for preparations of different composition.
Haili, China.
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).

Haishen Liansheng, China.
Azithromycin (p. 221·2).
Bacterial infections.

Li Li Ning *Nuo De, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Li Li Nuo *Haili, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Li Li Xing *Haishen Liansheng, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Li Lin *Yaoyou, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine (p. 620·3).
Influenza symptoms; cough.

Li Ling *Yangtze River, China.*
Tretinoin (p. 1725·2).

Li Ling Qi *Haishen Tongzhou, China.*
Sertaconazole nitrate (p. 593·2).

Li Luo Lan *Jianfeng, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Li Luo Xin *Li Jie Xun, China.*
Ligustrazine phosphate.

Li Mai Qin *United Lab, China.*
Ligustrazine hydrochloride.

Li Mai Qing *Zhaoke, China.*
A low-molecular-weight heparin calcium (p. 1426·1).

Li Mai Xin *Yatai, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Li Mei Song *Si Bao, China.*
Nimesulide.

Li Meng Le *Libang, China.*
Ropivacaine mesilate.
Local anaesthesia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Li Meng Xin *Libang, China.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Li Mian *Bangmin, China.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Li Min *Southwest Synthetic, China.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; pruritus; urticaria.

Li Ning Ge *Winsunny, China.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Li Di Nuo *Banzhou, China.*
Benzocaine (p. 1980·2); zinc oxide (p. 1729·1).

Li Nuo Ke *Shengquan, China.*
Nimesulide (p. 101·3).
Pain.

Li Nuo Sheng *Wu Zhou Tong, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Li Ou *Jianfeng, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Li Pu Su *Luye Sike, China.*
Liposomal paclitaxel (p. 839·3).
Malignant neoplasms.

Li Qi *Yangtze River, China.*
Azithromycin lactobionate.

Li Qing *Huayang, China.*
Matrine.

Li Quan *Chengyi, China.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Li Rui Min *LuoXin, China.*
Gastrodin.
Neurasthenia; vertigo; trigeminal neuralgia; occipital neuralgia; vascular headache; migraine.

Li Shen *Xinhua, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Li Sheng Bei Fen *Huazhong, China.*
Gamma-aminobutyric acid (p. 2509·2).

Li Sheng Mai *Shuanglu Lisheng, China.*
Sodium ferulate.

Li Sheng Si Tai *Wu Zhou Tong, China.*
Polypeptides; inosine (p. 2533·1).

Li Sheng Su *SL Pharm, China.*
A recombinant human granulocyte macrophage colony-stimulating factor.

Li Sheng Yuan *SL Pharm, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Li Shu
Note: this name may be used for preparations of different composition.
Lixin, China.
Citicoline sodium (p. 2480·2).
Tsinghua Yuanxing, China.
Diclofenac sodium (p. 48·3).
Xinjiang, China.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Li Shu Da *Si Bao, China.*
Simvastatin (p. 1489·2).

Li Shu Ka *Sine, China.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Li Shu Kang *Li Jie Xun, China.*
Aceglutamide (p. 2426·2).

Li Shu Tong *Chengshi, China.*
Nimesulide (p. 101·3).

Li Si De *Jianfeng, China.*
Amlodipine L-aspartate.
Angina pectoris; hypertension.

Li Si Ping *Lijian, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Li Si Qing *Tongyong, China; Xinzhongzheng, China.*
Sodium new houttuyfonate.

Li Sui *Double-Crane, China.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Li Te Er Xin *Lisite, China.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Li Te Xin *Lisite, China.*
Octreotide acetate (p. 1924·1).

Li Tian Lin *Nanmei, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Li Tong *Yazhou, China.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).

Li Tuo *Lukang Chenxin, China.*
Ropivacaine mesilate.
Local anaesthesia.

Li Tuo Gan *WusuliJiang, China.*
Citicoline sodium (p. 2480·2).

Li Wei *Jinling, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Li Wei Er *Taibao, China.*
Nevirapine (p. 1005·1).
HIV infection.

Li Wei Kang *Weigao, China.*
Liranaftate (p. 588·1).

Li Wei Ting *Chung-Hwa, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; acid aspiration.

Li Wen *Sailike, China.*
Telmisartan (p. 1509·3).
Hypertension.

Li Xie *Baijingyu, China.*
A smectite (p. 1887·1).

Li Xin *Tianhedi Sainuo, China.*
Clarithromycin lactobionate (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Li Xin Da *Wandashan, China.*
Ligustrazine hydrochloride.

Li Xin Kang *Libang, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Li Xin Mei *Huaneng, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Li Xin Qi *Huaneng, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Li Xin Tong *Pu Luo Kang Yu, China.*
Isosorbide mononitrate (p. 1413·3).

Li Xing *Topfond, China.*
Fluconazole (p. 578·2).

Li Ya Er *Hayao, China.*
A granulocyte-macrophage colony-stimulating factor.

Li Ya Jin *Hayao, China.*
A granulocyte colony-stimulating factor.

Li Ya Mei *Hayao, China.*
Interferon alfa-2b (human, recombinant) (p. 989·2).

Li Yan Jia *Huabang, China.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Li Yan Zhuo *Huabang, China.*
⊗Desonide (p. 1630·1).
Skin disorders.

Li Yang *Rui Yang, China.*
Mezlocillin sodium (p. 324·1).
Bacterial infections.

Li Yi Ping *Kangkeer, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Li Yue Xi *Nhwa, China.*
Midazolam (p. 1085·1) or midazolam maleate (p. 1085·2).
Insomnia.

Li Ze *Nanda, China.*
Povidone-iodine (p. 1767·1).

Li Zhen *Topfond, China.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Li Zhi *Chengyi, China.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Li Zhu Jun Le *Livzon, China.*
Penciclovir (p. 1008·2).

Li Zhuo *Xinhua, China.*
Tribendimidine.
Hookworm infections; ascariasis.

Liaderyl *Kleva, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Lialda *Shire, USA.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Liamycin *Coup, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Lian He Tang Ding *Sanjing, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Lian Huan *Lianhuan, China.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Nasal congestion; cough.

Lian Jia *Xinhua, China.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain.

Lian Jiang *Aoer, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Lian Li Ke *Zhi Jun, China.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).

Lian Shuang *Lianhuan, China.*
Cetirizine hydrochloride (p. 619·2).

Lian Tong *Rui Yang, China.*
Ligustrazine phosphate.

Liana *Ratiopharm, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Liang Bang *Hanyin, China.*
Huperzine.

Liang Bo *Yatai, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Liang Ke *Changzhou Siyao, China.*
Piroxicam (p. 125·3).

Liang Qi *Zhongdan, China.*
Liranaftate (p. 588·1).

Liang Shu *Man Xiu Lei Dun, China.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).

Liangqi *Ruizhu, China.*
Cetylpyridinium chloride (p. 1743·1).
Bacterial conjunctivitis.

Lianhuan Erding *Lianhuan, China.*
Felodipine (p. 1380·3).
Hypertension.

Lianke *Hayao, China.*
Sulbactam sodium (p. 360·1).
Bacterial infections.

Liao Sha *LuoXin, China.*
Enoxacin gluconate.
Bacterial infections.

Liasten *Enzim, Ukr.†*
Glucosaminylmuramyl pentapeptide in dextran 40.
Immunodeficiency; neutropenia; passive immunisation.

Liatamolo *Sigillata, Ital.*
Paracetamol (p. 115·1).
Fever; pain.

Liatriz *Solfran, Mex.*
Meclozine (p. 634·3); pyridoxine (p. 2105·3).
Nausea and vomiting.

Libakcil *Abolmed, Rus.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Libalaks *Liba, Turk.*
⊗Sorbitol (p. 2092·1); Tween 80 (p. 2203·3); sodium citrate (p. 1781·2); glycerol (p. 2517·2).
Constipation.

Libamic *Zafiro, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Libang Zhikelu *Zhi Jun, China.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); ammonium chloride (p. 1656·1); chlorphenamine (p. 620·3).
Cough.

Libavit B_6 *Liba, Turk.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency; isoniazid neuropathy; idiopathic sideroblastic anaemia; premenstrual syndrome.

Libavit K *Liba, Turk.*
Menadione sodium bisulfite (p. 2122·2).
Vitamin K deficiency.

Lib-CT *East West, India.*
Chlordiazepoxide (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; insomnia.

Libeeda for Men *Nutravite, Canad.*
⊗Bee pollen (p. 2445·2); damiana (p. 2491·3); ginseng (p. 2513·3); tribulus terrestris (p. 2633·3).

Libeeda for Women *Nutravite, Canad.*
⊗Damiana (p. 2491·3); ginkgo biloba (p. 2512·3); red clover (p. 2482·1); tribulus terrestris (p. 2633·3); wild yam (p. 2648·1).

Libefor *Quim-Far, Venez.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Libeli *Grunenthal, Port.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Libenar *GSK Consumer, Ital.*
Sodium chloride (p. 1795·1).
Nasal hygiene; nasal dryness.

Libenta *Liba, Turk.*
Sodium calcium edetate (p. 1573·2).
Heavy metal poisoning.

Libeprosta *Pharmafabre (Φαρμαφαεμπρ), Gr.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Liberal *Asian Pharm, Thai.*
Flunarizine hydrochloride (p. 629·3).
Vestibular disorders; cerebrovascular disorders.

Liberan
Note: this name may be used for preparations of different composition.
Apsen, Braz.
Bethanechol chloride (p. 2456·2).
Urinary.
Carnot, Mex.
Simeticone (p. 1886·2).
Flatulence.

Liberanit *Trommsdorff, Ger.†*
Acetic acid (p. 2426·3).
Pediculosis.

Liberat *Laboratorios Chile, Chile.*
Orlistat (p. 2577·1).
Obesity.

Liberate *Biem, Turk.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Liberator *Schering-Plough, Canad.†*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Liberaxim *Pisa, Mex.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Liberel *Kwizda, Austria.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Liberol Baby N *Doetsch, Grether, Switz.*
Eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1); star anise oil (p. 2622·2); juniper oil (p. 2537·2).
Cold symptoms.

Liberol Dragées contre la toux *Doetsch, Grether, Switz.†*
Thyme (p. 2630·2); ivy (p. 2536·2).
Cough.

Liberol N *Doetsch, Grether, Switz.*
Camphor (p. 2466·2); pumilio pine oil (p. 2591·1); thyme oil (p. 2630·3); eucalyptus oil (p. 2501·2).
Cold symptoms.

Liberol Pastilles contre la toux *Doetsch, Grether, Switz.†*
Thyme (p. 2630·2); senega root (p. 1677·2).
Cough.

Liberol Sirop contre la toux *Doetsch, Grether, Switz.†*
Thyme (p. 2630·2); ivy (p. 2536·2); senega root (p. 1677·2); liquorice (p. 1853·2).
Cough.

Liberprost *Lanpharm, Arg.; LKM, Arg.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Libertek *Nycomed, Cz.; Nycomed, Irl.; Takeda, Neth.; Takeda, Spain.*
Roflumilast (p. 1219·3).
Obstructive airways disease.

Libertrim *Carnot, Mex.*
Trimebutine (p. 2634·1) or trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; gastrointestinal motility disorders.

Libertrim SDP *Carnot, Mex.*
Trimebutine (p. 2634·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Libertrim SII *Carnot, Mex.*
Trimebutine (p. 2634·1); simeticone (p. 1886·2).
Gastrointestinal motility disorders; irritable bowel syndrome.

Libexin *Sanofi-Aventis, Hung.; Khandelwal, India; Sanofi-Aventis, Rus.; Chinoin, Ukr.*
Prenoxdiazine hydrochloride (p. 1675·3).
Cough.

Libexin Muco *Sanofi-Aventis, Rus.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with viscous mucus.

Libexin Mucolitico *Teofarma, Ital.*
Prenoxdiazine hibenzate (p. 1675·3); carbocisteine (p. 1658·1).
Cough.

Libiam *Libbs, Braz.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Libidomega *Cantassium Co., UK.*
Amino acids; vitamins; minerals.

Libidon *Medichrom, Gr.*
Povidone-iodine (p. 1767·1).

Libiocid *Rayere, Mex.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Libiplus *Delta, Braz.*
Vitamins; yohimbine hydrochloride (p. 2372·3); glutamic acid (p. 2070·2); calcium magnesium fytate (p. 1553·3).
Tonic.

Libiqi *Kawin, China.*
Tiopronin (p. 1578·1).
Liver disorders.

Libitus *Leben, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylpropanolamine hydrochloride (p. 1674·1).

Libitus Plus *Leben, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Libkol *Saba, Turk.*
Chlordiazepoxide hydrochloride (p. 1044·2); pipenzolate bromide (p. 1878·1).
Gastrointestinal disorders; smooth muscle pain.

Liblan *YSP, Malaysia.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Enterocolitis; irritable bowel syndrome; peptic ulcer.

Libmet *Daffohils, India.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; heart failure.

Libna *Plus, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Libolar *Quim-Far, Venez.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Libotasin *Coup, Gr.*
Cinnarizine (p. 622·1).

Libotryp *Wockhardt, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety-depression.

Libracor *Merck, Port.†*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Libradin *Sigma-Tau, Ital.; Astellas, Neth.; Astellas, Port.†; Grunenthal, Spain†; Santa, Turk.*
Barnidipine hydrochloride (p. 1314·1).
Hypertension.

Librax *Meda, Fin.; Meda, Fr.; IFET (ΙΦΕΤ), Gr.; Meda, Gr.; Invida, Hong Kong; Piramal, India; Transfarma, Indon.; Valeant, Ital.; Meda, Port.; Pharmaco, S.Afr.†; Inovail, Singapore†; Meda, Switz.; Invida, Thai.; Onko, Turk.; Farma, Venez.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Anxiety; autonomic symptoms of anxiety and tension; peptic ulcer; dyspepsia; biliary dyskinesia; ureteric spasm; dysmenorrhoea; smooth muscle spasm; irritable bowel syndrome; nocturnal enuresis.

Valeant, Canad.; Valeant, USA.
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Peptic ulcer (adjunct); irritable bowel syndrome; gastrointestinal disorders associated with anxiety.

Libraxin *Investi, Arg.; Raffo, Chile.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal and genitourinary disorders associated with anxiety; colitis; irritable colon; nocturnal enuresis; peptic ulcer; smooth muscle spasm.

Librentin *Westmont, Indon.†; Westmont, Philipp.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Librium *Meda, Ger.; Invida, Hong Kong; Teva, Hung.; Piramal, India; Transfarma, Indon.; Valeant, Indon.; Pharmaco, S.Afr.†*
Chlordiazepoxide (p. 1044·2).
Anxiety; skeletal muscle spasm; sleep disorders; alcohol withdrawal syndrome.

Meda, Irl.; Valeant, Ital.; Meda, UK; Valeant, USA.
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; insomnia; skeletal muscle spasm; premedication.

Librocef *Hexpharm, Indon.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Librocol *Lagap, Switz.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Smooth muscle spasm; nocturnal enuresis; dysmenorrhoea.

Librodan *Hexpharm, Indon.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Librodep *Ultramark, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Librofed *Kalbe, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Librofem *LPC, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Libroman *Dekaz, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp disorders.

Libronil
Note: this name may be used for preparations of different composition.
Hexpharm, Indon.†
Glibenclamide (p. 472·1).
Diabetes mellitus.

Libronil-R
Note: this name may be used for preparations of different composition.
Coup, Gr.
Bromazepam (p. 1041·2).
Anxiety disorders.

Librospas *Ultramark, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Librosym *Symbiosis, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine (p. 1113·2).

Librotop *Ultramark, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine hydrochloride (p. 1113·2).

Librozym *Hexpharm, Indon.†*
⊗Amylase (p. 2442·1); pancreatin (p. 2579·3); pepsin (p. 2586·1); Javanese turmeric (p. 2636·2).
Digestive disorders.

Librozym Plus *Hexpharm, Indon.†*
⊗Amylase (p. 2442·1); pancreatin (p. 2579·3); pepsin (p. 2586·1); simeticone (p. 1886·2).
Digestive disorders.

Libure *Aamorb, India.*
Mebeverine (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Licab *Torrent, India.*
Lithium carbonate (p. 427·3).
Mania; hypomania; bipolar disorder.

Licain *Actavis, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Licaine *Bryntsalov, Rus.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias; local anaesthesia.

Licarb *RX, Hong Kong; RX, Thai.*
Lithium carbonate (p. 427·3).
Bipolar disorder; behaviour disorders; depression; mania.

Licarbetida *Liconsa, Neth.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Licarbium *Rekah, Israel.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Licco *Baldacci, Braz.*
Lycopene (p. 2546·2).

Lice Blaster *Douglas, NZ.*
Malabar nut (p. 2549·1); echinacea (p. 2498·1); melaleuca oil (p. 2551·1); stemona sessifolia root.
Pediculosis.

Lice Care *ICM, Singapore.*
Malathion (p. 2157·2).
Pediculosis; scabies.

Lice Killing *Perrigo, Canad.*
Piperonyl butoxide (p. 2160·2); pyrethrins (p. 2161·1).
Pediculosis.

Licealiz *Lamoiyan, Philipp.*
Pyrethrin (p. 2161·1).
Pediculosis.

Lice-Enz *Cosmed, Gr.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Lichensa *Tetrafarm, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Lichol *Vianex (Βιανεξ), Gr.*
Fenofibrate (p. 1381·1).

Licide *Reese, USA.*
Pyrethrum (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Licilon *Sanval, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Licla *Daewon, Hong Kong.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Liclav *Abolmed, Rus.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Licobevit *Berlico Mulia, Indon.*
Thiamine nitrate (p. 2103·2).
Vitamin B_1 deficiency.

Licobion *Berlico Mulia, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; peripheral nervous system disorders.

Licobondrat *Liconsa, Ital.*
Ibandronic acid (p. 1184·2).

Liconsa, Neth.
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Licodexon *Berlico Mulia, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Licodium *Berlico Mulia, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Licodril *Berlico Mulia, Indon.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1).
Cough.

Licodril DMP *Berlico Mulia, Indon.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Licofel *Berlico Mulia, Indon.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Licoforte *Cantabria, Spain.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Licoften *Remedica, Malaysia; Remedica, Singapore.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic disorders.

Licogenta *Berlico Mulia, Indon.*
Gentamicin sulfate (p. 304·2).
Skin infections.

Licogin *Berlico Mulia, Indon.*
Dipyrone (p. 53·3).
Pain.

Licokalk *Berlico Mulia, Indon.*
Calcium lactate (p. 1784·1).
Calcium deficiency.

Licokalk Plus *Berlico Mulia, Indon.*
Calcium lactate (p. 1784·1); vitamin D (p. 2112·3).
Calcium deficiency; calcium supplement.

Licoklin *Berlico Mulia, Indon.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Licoklor *Berlico Mulia, Indon.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Licolin *Liconsa, Irl.; Liconsa, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Licolos *Liconsa, Denm.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Licomet *Berlico Mulia, Indon.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Licon *Life Concern, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).

Liconam *Berlico Mulia, Indon.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency; isoniazid-induced peripheral neuritis.

Liconar *Biolab, Singapore.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections; fungal hair and nail infections.

Licopec *Berlico Mulia, Indon.*
Activated attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Licopene *Herbarium, Braz.†*
Lycopene (p. 2546·2); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Dietary supplement.

Licopenox *Sigma, Arg.*
Lycopene (p. 2546·2).
Antoxidant.

Licopid *Peptek, Rus.*
GMDP (p. 2520·3).
Secondary immunodeficiency.

Licoplex *Berlico Mulia, Indon.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Licoprima *Berlico Mulia, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections; toxoplasmosis.

Licoprox *Berlico Mulia, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Licoric *Berlico Mulia, Indon.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Licosolon *Berlico Mulia, Indon.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Licostan *Berlico Mulia, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Licostrata *Cantabria, Spain.*
Hydroquinone (p. 1705·1).
Hyperpigmentation.

Licovir *Berlico Mulia, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections of the skin and mucous membranes.

Licovit *Ativus, Braz.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); lycopene (p. 2546·2).
Skin disorders.

Licoxid *Myralis, Braz.*
Lycopene (p. 2546·2); vitamin E (p. 2119·1); vitamin A (p. 2098·3).

Lictora *Talmann, Philipp.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Lictyn *Sandoz, Austria†; Sandoz, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Licuagen *Elea, Arg.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Licuamon *Merck, Arg.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).
Atherosclerosis; thromboembolic disorders.

Lidaltrin *Lacer, Spain.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Lidaltrin Diu *Lacer, Spain.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

LidaMantle *Doak, USA.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

LidaMantle HC *Doak, USA.†*
⊗Lidocaine hydrochloride (p. 1988·2); hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Skin disorders.

Lidanest *Surar, Arg.*
Lidocaine (p. 1988·1).
Adrenaline (p. 1292·1) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidanil *Novartis, Turk.*
Mesoridazine (p. 1084·2).
Anxiety; agitation; behaviour disorders.

Lidaprim
Note: this name may be used for preparations of different composition.
Nycomed, Austria; Nycomed, Gr.; Nycomed, Hong Kong; Nycomed, Rus.†
Sulfametrole (p. 368·1); trimethoprim (p. 381·2).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Lidatrim *Nycomed, Neth.†*
Sulfametrole sodium (p. 368·1); trimethoprim (p. 381·2).
Bacterial infections.

Lidazoc *Egis, Cz.*
⊗Metoprolol (p. 1434·3).

Lidazon *Vifor, Switz.*
Cetylpyridinium chloride (p. 1743·1); dichlorobenzyl alcohol (p. 1750·2); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Lidazon Actilong *Vifor, Switz.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Lid-Care *Novartis, Austral.; Novartis, Canad.†; Novartis, NZ; Novartis, Turk.; Alcon, UK.†*
Eyelid cleanser.

LiDCO *Interdelta, Switz.*
Lithium chloride (p. 427·3).
Measurement of cardiac output.

LiDe *Pidi, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Lidemol *Valeo, Canad.; Stiefel, Philipp.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Lidène *Cooperation Pharmaceutique, Fr.*
Doxylamine succinate (p. 627·3).
Insomnia.

Lident Adrenalina *Cosmo, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Lident Adrenor *Cosmo, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) and noradrenaline acid tartrate (p. 1458·2) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Liderclox *Progen, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Liderfeme *Farmalider, Spain.*
Ibuprofen (p. 68·2).
Pain; fever.

Liderfen *Farmalider, Port.*
Ibuprofen (p. 68·2).
Musculoskeletal and soft-tissue pain.

Liderma *Teva, Switz.†*
Isotretinoin (p. 1706·2).
Acne.

Liderman *Jacoby, Austria.†*
Oxiconazole nitrate (p. 591·3).
Fungal and Gram-positive bacterial skin infections.

Lideropram *Actavis, Denm.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Lidesthesin *Ritsert, Ger.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidestol *Munir, Turk.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidevin *Lab Pharmaceutique, Ukr.*
Disulfiram (p. 2495·3); adenine (p. 2430·2); nicotinamide (p. 2083·1).
Alcoholism.

Lidevine *Tradiphar, Rus.*
Disulfiram (p. 2495·3); adenine (p. 2430·2); nicotinamide (p. 2083·1).
Chronic alcoholism.

Lidex *Valeo, Canad.; Minerva (Μινερβα), Gr.; Stiefel, Philipp.; Medicis, USA.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Lidex NGN *Stiefel, Philipp.*
⊗Fluocinonide (p. 1636·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Lidial *Bunker, Braz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidil *Roemmers, Arg.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; conjunctivitis.

Lidil Cort *Roemmers, Arg.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis; nasal polyps.

Lidiprine *CBC, Hong Kong.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Lido *DR Johns, India.*
Fluconazole (p. 578·2).
Fungal infections.

Lido Tea *Trima, Israel.†*
Senna (p. 1885·1); caraway (p. 2470·2); liquorice (p. 1853·2); chamomile (p. 2474·1); peppermint leaf (p. 1877·1).
Constipation.

Lidobag *Eczacibasi-Baxter, Turk.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias.

Lidocabbott *Abbott, Braz.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; arrhythmias.

Lidocadren *Abic, Israel.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidocaina Spray *Ogna, Ital.*
Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Local anaesthesia and disinfection in dentistry.

Lidocard *Orion, Fin.; Braun, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Ventricular tachycardia; arrhythmias.

Lidocation *Weimer, Thai.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidocaton *Hong Kong Medical, Hong Kong.†*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidochlor *Unique, Rus.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidocor *Medichrom, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Lidocorit *Gebro, Austria.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias.

LidoCort *Aristos, USA.*
⊗Hydrocortisone acetate (p. 1640·1); lidocaine (p. 1988·1).
Anorectal disorders.

Lidocort Proct *Northia, Arg.*
⊗Hydrocortisone (p. 1640·1); lidocaine (p. 1988·1).

Lidocosil *Negrin, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Noradrenaline hydrochloride (p. 1458·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidodan *Odan, Canad.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidodent *Marmir, Pol.*
Lidocaine hydrochloride (p. 1988·2); cetylpyridinium chloride (p. 1743·1).
Gingivitis; teething pain.

Lidoderm *IFET (ΙΦΕΤ), Gr.; Endo, USA.*
Lidocaine (p. 1988·1).
Postherpetic neuralgia; local anaesthesia.

Lidodex *Bernofarm, Indon.*
Lidocaine hydrochloride (p. 1988·2).
Subarachnoid anaesthesia.

Lidofast *Angelini, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidoflex *Baxter, Braz.†*
Lidocaine (p. 1988·1).

Lidogel *Neo Quimica, Braz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lido-Hyal *Ogna, Ital.; Wild, Switz.†*
Hyaluronidase (p. 2527·2); lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; prophylaxis of soft-tissue disorders.

Lidoject *Hexal, Ger.†; Labesfal, Port.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; haemorrhoids.

Lidojet *Uniao Quimica, Braz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidomax *Vivier, Canad.*
Lidocaine (p. 1988·1).

Lidomex *Kowa, Jpn.*
⊗Prednisolone valeroacetate (p. 1645·2).
Skin disorders.

Lidomyxin *Sandoz, Canad.*
Polymyxin B sulfate (p. 342·3); lidocaine hydrochloride (p. 1988·2).
Ear infections, pain, and pruritus.

Lidonest *AstraZeneca, Indon.†*
Lidocaine (p. 1988·1).
Local anaesthesia.

Lidonet *Adipharm, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidong *Hanmi, China.*
Lactulose (p. 1850·3).
Constipation; hepatic coma; hepatic encephalopathy.

Lidonostrum *Nostrum, Port.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; catheterisation; endoscopy; tracheal intubation.

Lidopass *Neckerman, Braz.*
Lidocaine (p. 1988·1).

LidoPen *Survival Technology, USA.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias.

Lidoposterin *Kade, Pol.*
Lidocaine (p. 1988·1).
Anorectal disorders.

LidoPosterine *Kade, Ger.†*
Lidocaine (p. 1988·1).
Anorectal disorders.

LidoPro *Terrain, USA.*
Capsaicin (p. 35·1); lidocaine (p. 1988·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Lidosel *Biosel, Turk.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias.

Lidosen *Senese, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidosite *Braun, USA.†*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidosporin *Farmoquimica, Braz.*
Polymyxin B sulfate (p. 342·3); lidocaine (p. 1988·1).
Ear infections.

Pfizer Consumer, Canad.†
Ear drops: Polymyxin B sulfate (p. 342·3); lidocaine hydrochloride (p. 1988·2).
Ear infections.

Lidospray *Apsen, Braz.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Lidoston *Ariston, Braz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lidoxin *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Lidrian *Baxter, Fr.†; Baxter, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Lie He Suo *Yangshengtang, China.*
Bifonazole (p. 573·3).

Lie Luo *Wanhui Shuanghe, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Lie Qin *Ya Bang Ai Pu Sen, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Lieqi *General Sanyang, China.*
Ticarcillin sodium (p. 378·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Lievitosohn *Antonetto, Ital.*
Saccharomyces cerevisiae (p. 2125·2); vitamin B substances (p. 2102·3).
Restoration of normal gastrointestinal flora.

Lievitovit *Perfetti, Ital.*
Dried yeast (p. 2125·2); vitamin B substances (p. 2102·3).
Restoration of normal gastrointestinal flora.

Lifaxon *Lyka, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Life 2 *Raffles, Singapore.*
Zhenjiang hengshun vinegar; pure safflower oil (p. 2086·3); pearl powder; vegetable oil.

Life 10 *Puspa, Indon.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1); lecithin (p. 2542·2).
Tonic.

Life Acne *Prime Enterprises, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Life Brand Daily Low Dose ASA *Pharmascience, Canad.†*
Aspirin (p. 22·2).

Life Brand Kids Sunscreen *Fruit of the Earth, Canad.*
Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Life Brand Sport Sunscreen *Fruit of the Earth, Canad.*
Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Life Brand Sunscreen *Fruit of the Earth, Canad.*
SPF 15: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Life Brand Sunthera 3 *Fruit of the Earth, Canad.*
Aerosol SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 15: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Fruit of the Earth, Canad.
SPF 30; lotion SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Life Brand Sunthera 3 Baby *Fruit of the Earth, Canad.*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Life Brand Sunthera 3 Face *Fruit of the Earth, Canad.*
Lotion SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Life Brand Sunthera 3 Kids *Fruit of the Earth, Canad.*
Aerosol SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
Lotion: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Life Brand Sunthera 3 Sport *Fruit of the Earth, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Life Dandruff *Ultrapac, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Life Drops *Potter's, UK.*
Capsicum (p. 2469·3); sambucus (p. 2609·3); peppermint oil (p. 1877·1).
Cold symptoms; sore throat.

Life Essentials *Nu Skin, Canad.†*
Vitamins; minerals.

Life + Quality *Esme, Arg.*
Quassia amara (p. 2601·1).
Pediculosis.

Lifebutol-H *Life Line, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Lifecare *Solitaire, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Lifecare-A *Solitaire, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Lifecare-C *Solitaire, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Lifecare-SB *Solitaire, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Lifecare-T *Solitaire, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Lifecell *Pfizer, Arg.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Female and male infertility.

Lifegram *Liferpal, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Lifemin *Pro-Pharma, Ukr.*
Lupulus (p. 2546·1); wild yam root (p. 2648·1); pearl powder; pueraria root; Chinese angelica (p. 2497·1); cimicifuga (p. 2478·1).
Menopausal disorders.

Lifen *Soho, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lifenac *Liferpal, Mex.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Lifepak *Nu Skin, Canad.†*
Vitamins; minerals.

Liferamin *Liferpal, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Lifercal *Leovan, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Lifermycin *Leovan, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Liferol *Master Pharma, Ital.*
⊗Formoterol fumarate (p. 1209·2).
Bronchospasm; obstructive airways disease.

Liferost *Biostam (Βιοσταμ), Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Liferxina *Liferpal, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Liferzit *Medinova (Μεντινοβα), Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Liferzol *Liferpal, Mex.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Lifes-Biotic *Ratiopharm, UK.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Bacillus coagulans*; *Bifidobacterium bifidum* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); vitamin B substances (p. 2102·3).
Dietary supplement.

Lifestyles *Ansell, Canad.†; Ansell, NZ.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Lifezar *Prafa, Indon.; Therapharma, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Lifferon *Vector, Rus.*
Interferon alfa-2b (p. 989·2).
Hepatitis B, C, and D; viral infections; malignant neoplasms; multiple sclerosis.

Lifibron *Metiska, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lifin *Teva, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Liflo *Zenon, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lifogem *Samarth, India.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Lifored *Life Line, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lifo-Scrub *Bioser, Gr.; Braun, Neth.; Braun, Port.†; Braun, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Lift *Aaron, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lift Lumiere *Chanel, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Lifta *Abdi, Turk.*
Tadalafil (p. 2368·1).

Liftactiv CXP *Vichy, Canad.*
SPF 20: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Lifter *Saval, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

LiFu *Shengbaoluo, China.*
Metronidazole (p. 936·1).

Lifuding *Hayao, China; Jiabin, China.*
Famotidine (p. 1842·1).
Peptic ulcer.

Lifurox
Note: this name may be used for preparations of different composition.
Lilly, China.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Proula, Venez.
⊗Furosemide (p. 1387·1).
Oedema; heart failure; hypertension; forced diuresis.

Lifuxing *Double-Crane, China.*
Levofloxacin mesilate.
Bacterial infections.

Lifuzhi *Tianshi Libeite, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Light Iron *Maccabi Care, Israel.*
Ferrous bisglycinate (p. 2048·3).
Iron deficiency.

Lightening *Mac, Ital.*
Glycolic acid (p. 1704·3); fytic acid (p. 1553·3).
Hyperpigmentation disorders.

Lightgen *Teijin, Jpn.*
⊗Dihydrocodeine phosphate (p. 52·2); methylephedrine hydrochloride (p. 1669·2); chlorphenamine maleate (p. 620·3).
Cough.

Lightning Cough Remedy *Potter's, UK.*
Liquorice (p. 1853·2); anise oil (p. 2444·3).
Coughs.

Lignaform *Therascience, Mon.†*
Preparation for enteral nutrition.

Lignamid *Amnol, Ital.*
Linseed (p. 2544·2); urtica (p. 2639·3); red orange complex.
Prostatic disorders.

Lignocad *Cadila, India.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in the injection as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic
Local anaesthesia.

Lignocip *Cipla, India.*
Lidocaine (p. 1988·1).
Arrhythmias; local anaesthesia.

Lignodent *Chandra Bhagat, India.*
Lidocaine (p. 1988·1).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic
Local anaesthesia.

Lignoloc *Chandra Bhagat, India.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic
Local anaesthesia.

Lignopad *Mundipharma, Singapore.*
Lidocaine (p. 1988·1).
Post herpetic neuralgia.

Lignosafe *Stedman, India.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic
Local anaesthesia.

Lignospan *Tsaprazis, Gr.; Septodont, Irl.; Septodont, Israel; Septodont, Neth.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lignox *Indoco, India.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic
Local anaesthesia.

Ligofragmin *Pfizer, Arg.*
Dalteparin sodium (p. 1348·3).
Thromboembolic disorders; prevention of clotting in extracorporeal circuits.

Ligosan *Heraeus, Ger.*
Doxycycline hyclate (p. 288·2).
Paradontitis.

LiHuan *Deyao, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Lijunpaishu *Lijun, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Lijunpaitong *Lijun, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Lijunsha *Lijun, China.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Lik *Siomond, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Likacin *Kleva, Gr.; Lisapharma, Hung.; Lisapharma, Ital.; Medifarm, Venez.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Likang Kesong *Likang, China.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Likangle *Livzon, China.*
A nerve growth factor (mouse).

Lik-B *Siomond, India.*
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3).

LiKe *Jimin, China.*
Lincomycin hydrochloride (p. 317·1).
Anaerobic bacterial infections.

Likelin *Hospira, China.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia; folate deficiency.

Likenil *Antibioticos, Spain.*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Likexin *Deyer, China.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Lik-Gel *Amnol, Ital.†*
Menthol (p. 2553·2); peppermint (p. 1877·1); aesculus (p. 2431·2); pineapple; centella (p. 1698·3); equisetum (p. 2500·1); ginkgo biloba (p. 2512·3); devil's claw root (p. 42·3); achillea (p. 2427·3); ginger (p. 1844·1); meadowsweet (p. 2550·2); myrtillus (p. 2566·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Likopid *Peptek, Ukr.*
GMDP (p. 2520·3).
Immunostimulant.

Likuden M *Aventis, Ger.†*
Griseofulvin (microfine) (p. 582·2).
Fungal infections.

Likurmin *Kalbe, Indon.*
Curcuminoid; lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Nutritional supplement in children.

Lilac *Getz, Philipp.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

LiLing *Nuokang, China.*
Asarone.

Li-Liquid *Rosemont, UK.*
Lithium citrate (p. 427·3).
Mania; psychoses; depression.

Liluokang *Daxin, China.*
Riboflavin tetrabutyrate (p. 2104·3).
Thrombosis; atherosclerosis; vitamin B_2 deficiency.

Lima *Zimalaya, India.*
Asparagus racemosus (p. 2614·2); turpentine oil (p. 2636·3).

Lima C *Cazi, Braz.*
Siparuna guyanensis; cetylpyridinium chloride (p. 1743·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Limai *Livzon, China.*
Sodium ferulate; aspirin (p. 22·2); cinnarizine (p. 622·1); vitamin B_1 (p. 2102·3).
Cerebrovascular ischaemia.

Limaixian *Lijun, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Limanovit E *Hippokrat, Rus.*
Laminaria (p. 2540·1); alpha tocopherol (p. 2119·1).
Tonic.

Limarcan *Sanofi-Aventis, Port.*
Miglitol (p. 491·3).
Diabetes mellitus.

Limarin *Serum Institute, India.*
Silymarin (p. 1561·2).
Liver disorders.

Limas *Taisho, Jpn.*
Lithium carbonate (p. 427·3).
Mania.

Limasip *BerlicoMulia, Indon.†*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Pain.

Limatic *Arlex, Mex.*
Lamotrigine (p. 527·2).
Epilepsy.

Limbatrilin *Raffo, Chile.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Depression; anxiety.

Limbial *Chiesi, Ital.*
Oxazepam (p. 1092·2).
Nervous disorders; anxiety; insomnia.

Limbik *Psicofarma, Mex.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Limbitrol *Meda, Austria; Valeant, Braz.; Meda, Fin.; Crescent, India; Pharmaco, S.Afr.†; Meda, Switz.; Valeant, USA.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states; depression; insomnia.

Transfarma, Indon.; Valeant, Indon.
Chlordiazepoxide (p. 1044·2); amitriptyline (p. 401·1).
Mixed anxiety depressive states.

Limbitryl *Valeant, Ital.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states.

Limbival *Micro, India.*
Amitriptyline (p. 401·1) or amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Limbrel *Primus, USA.*
Flavocoxid (p. 2505·2).
Osteoarthritis.

Limcee *Piramal, India.*
Vitamin C (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency; vitamin C supplement.

Limclair *Sinclair, Irl.†*
Trisodium edetate (p. 1550·3).
Hypercalcaemia; calcareous corneal opacities.

Limectant *Biotech, Arg.*
Sodium laurilsulfate (p. 2210·3).
Cleansing solution for soft contact lenses.

Limed *Medifive, Thai.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Limepisil *AAA, Denm.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Limeral *PlusPharma, Hung.; Actavis, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Limerick *CT, Ital.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Limerix *Ivax, Arg.*
Haloperidol (p. 1077·1).
Psychoses.

Limet *Cure Quick, India.*
Linezolid (p. 317·3).
Bacterial infections.

Limethason *Mitsubishi, China; Green Cross, Hong Kong†; Mitsubishi Tanabe, Jpn.*
⊗Dexamethasone palmitate (p. 1630·3).
Rheumatoid arthritis.

Limexx *Kwizda, Austria.†*
Tyrothricin (p. 384·1); benzalkonium chloride (p. 1737·1).
Mouth and throat disorders.

Limezapine *Ranbaxy, Denm.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Limfocept *Gedeon Richter, Cz.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Limican *Pharmafar, Ital.*
Alizapride hydrochloride (p. 1815·2).
Nausea and vomiting.

Limidrax *Serral, Mex.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Limifen *Janssen-Cilag, Spain.*
⊗Alfentanil hydrochloride (p. 18·2).
General anaesthesia.

Limiprol *Sons, Mex.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Limnos *CT, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Limonada Roge *Zasu, Arg.*
Magnesium citrate (p. 1857·1).
Constipation.

Limonade Asepta *Teva, Canad.*
Sodium tartrate (p. 1888·2).
Constipation.

Limonata Citromagnes *Mediplants, Gr.*
Magnesium carbonate (p. 1856·2).
Dyspepsia.

Limone *CliniMed, UK.*
A deodorant spray for stoma care.

Limontar *Biotiki, Rus.*
Citric acid monohydrate (p. 2480·3); succinic acid (p. 2214·3).
Asthenia.

Limovan *Sanofi-Aventis, Spain.*
Zopiclone (p. 1118·1).
Insomnia.

Limox *Biomedica, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Limoxin
Note: this name may be used for preparations of different composition.
Liferpal, Mex.
Amoxicillin (p. 216·2).
Bacterial infections.

Pharos, Indon.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Limozidim *Farmedia, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Limpacid *Bajer, Arg.*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Limpele Ginecologico *Dovalle, Braz.*
Miconazole (p. 588·3); benzalkonium chloride (p. 1737·1); zinc (p. 2126·1).

Limpiador Concentrado RGP *Bausch & Lomb, Arg.*
Cleaning solution for hard contact lenses.

Limpidex *Sigma-Tau, Ital.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Limptar N *Cassella-med, Ger.*
Quinine sulfate (p. 665·2).
Night cramp.

Limustin *Landsteiner, Mex.*
Tacrolimus (p. 1968·3).
Kidney or liver transplant rejection.

Limzer *Inventia, Ukr.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Peptic ulcer; delayed gastric emptying; gastroparesis; reflux oesophagitis; dyspepsia.

Lin *Admac, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lin Bi *Double-Crane, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Lin Guan *LuoXin, China.*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Lin Ke Hong *Hicin, China.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infection.

Lin Ke Jia *Hicin, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Lin Ke Shu *Hicin, China.*
Zolmitriptan (p. 682·2).
Migraine.

Lin Mai Xin *Yatai, China.*
Dimefline hydrochloride (p. 2321·2).

Lin Qing *Bei Shi, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Lin So Peppermint Cough *Sunward, Singapore.*
Ammonium chloride (p. 1656·1).

Lin Xi *Double-Crane, China.*
Matrine.

Lin Yuan Fang Xin *Aodong Liyuan, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Lin Yuan Ji Tai *Aodong Liyuan, China.*
Matrine.

Lin Yuan Li Shu *Aodong Liyuan, China.*
Lappaconitine hydrobromide (p. 1418·1).

Lin Yuan Luo Ke *Aodong Liyuan, China.*
Troxerutin (p. 2505·3).

Lina *Zota, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Linac *Ethica, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Linacal *Pentafarma, Port.*
Acarbose (p. 466·2).
Diabetes mellitus.

Linaiqin *NCPC, China.*
Sodium bicarbonate (p. 1781·1); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; dyspepsia.

Linam *Farmaceutica H, Mex.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Linaox-Clav *Sanify, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Linasen BTX *Chemopharma, Chile.*
Acetyl hexapeptide-3.
Wrinkles.

Linatecan *Tecnofarma, Chile.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Linatera *BayerSchering, Fin.; Bayer, Pol.*
24 Tablets, ethinylestradiol betadex clathrate (p. 2275·3); drospirenone (p. 2269·1); 4 tablets, inert.
Combined oral contraceptive.

Linatil *Hexal, Fin.; Sandoz, Swed.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Linatil Comp *Hexal, Fin.; Sandoz, Swed.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Linatis *Eurofarma, Braz.*
Norethisterone (p. 2294·2).

Linatron *Ariston, Braz.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Linazine *Asian Pharm, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; migraine; motion sickness.

Linbac *Sandoz, Mex.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Linbi *Sandoz, Ukr.*
Bifidobacterium animalis lactis (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Lincaina *Braun, Port.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline hydrochloride (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lincee *Abbott, India.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).

Lincil *Kern, Spain.*
Nicardipine hydrochloride (p. 1445·2).
Cerebrovascular disorders; hypertension; angina pectoris.

Lincitrax *Novaduo, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Linco *Medikon, Indon.†; ANB, Thai.; General Drugs, Thai.*
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Atlantic, Malaysia.
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Lincocilin *Vesco, Thai.*
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Lincocin *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; IFET (ΙΦΕΤ), Gr.; Pharmacia Upjohn, Gr.; Pfizer, Hong Kong; Max, India; Pfizer, Indon.; Pfizer, Ital.; Pfizer, Mex.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Thai.; Eczacibasi, Turk.; Pfizer, Ukr.†; Pharmacia Upjohn, USA; Pfizer, Venez.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincocina *Pfizer, Port.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincocine *Pfizer, Fr.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincoflan *Bunker, Braz.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincolan *Olan-Kemed, Thai.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Lincomax *Millimed, Thai.†*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Lincomiral *Ducto, Braz.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincono *Milano, Thai.*
Lincomycin (p. 317·1).
Bacterial infections.

Linco-P *PP Lab, Thai.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincopat *Parggon, Mex.*
Lincomycin (p. 317·1).
Bacterial infections.

Lincophar *Pharos, Indon.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincosa *LBS, Malaysia.*
Lincomycin hydrochloride (p. 317·1).

Zota, India; LBS, Thai.
Lincomycin (p. 317·1).
Anaerobic infections.

Lincotuss *Macleods, India.*
Codeine phosphate (p. 40·2).
Pain; cough.

Lincotuss-P *Macleods, India.*
Phenylpropanolamine hydrochloride (p. 1674·1); pholcodine (p. 1675·1); promethazine hydrochloride (p. 638·2).
Cough; nasal congestion.

Lincovax *Delta, Braz.*
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Lincover *Maver, Mex.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lincox
Note: this name may be used for preparations of different composition.
Renata, Philipp.
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; pain; adenomatous polyposis.

T Man, Thai.
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Lincozin *Taj, India.*
Lincomycin hydrochloride (p. 317·1).
Anaerobic infections.

Linctifed *GSK, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Linctodyl *Pharmaceutical Enterprises, S.Afr.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); ammonium chloride (p. 1656·1).
Cough.

Linctosan *Garec, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Linctus Codein *AstraZeneca, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

Linctus Tussi Infans *Adcock Ingram, S.Afr.†*
Ipecacuanha (p. 1667·2); squill (p. 1677·3); tolu (p. 1679·2).
Cough.

Linctus-DX *AstraZeneca, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).

Lincy *Plus, India.*
Lincomycin (p. 317·1).
Anaerobic infections.

Lincyn
Note: this name may be used for preparations of different composition.
Promed, Indon.
Lincomycin (p. 317·1).
Bacterial infections.

Samjin, Philipp.
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Lindacil *Sandoz, Mex.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Lindacyn *Coronet, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Lindan *Corsa, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Lindasol *Kleva, Gr.*
Clindamycin phosphate (p. 269·3).
Acne.

Lindaxa *Zentiva, Cz.†; Zentiva, Hung.†; Zentiva, Pol.†; Zentiva, Rus.; Zentiva, Ukr.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Lindell *Neo-Denn, Philipp.*
Permethrin (p. 2159·3).
Scabies; pediculosis.

Lindemicina *Greenpharma, Braz.*
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Lindemil *Abbott, Spain.*
Alum (p. 2439·1); benzalkonium chloride (p. 1737·1).
Vaginal antiseptic; vulvovaginal trichomoniasis (adjuvant).

Lindep *Orchid, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; premenstrual dysphoric disorder.

Lindex *Bago, Chile.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Lindeza *Piso, Mex.*
Orlistat (p. 2577·1).
Obesity.

Lindilan *Sanofi-Aventis, Venez.*
Ketoprofen (p. 79·1).
Pain.

Lindilane *Grunenthal, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Lindine *Pharmaland, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Lindisc *Bayer, Arg.; Schering, Braz.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Lindisc Duo *Berlimed, Braz.*
Patch 1, estradiol (p. 2271·1); patch 2, estradiol; levonorgestrel (p. 2296·1).

Lindormin *Boehringer Ingelheim Promeco, Mex.*
Brotizolam (p. 1042·1).
Insomnia.

Lindoxyl *Meda, Ger.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Lindron *KRKA, Cz.†; KRKA, Pol.†; KRKA, Rus.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Lindynette *Gedeon Richter, Cz.; Sandoz, Denm.; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Gedeon Richter, Rus.; Gedeon Richter, Thai.; Gedeon Richter, Ukr.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Line *Arvincare, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; premenstrual dysphoric disorder.

Line Flush *CMG, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Linea *Diapit, Gr.*
⊗Diethylpropion hydrochloride (p. 2321·1).

Linea F *Angelini, Ital.*
Benzalkonium chloride (p. 1737·1); benzydamine hydrochloride (p. 29·2).
Disinfection of wounds and burns.

Linella *Medica Nord, Swed.*
Senna (p. 1885·1).
Constipation.

Lines *Glorious, India.*
Lincomycin hydrochloride (p. 317·1).
Anaerobic infections.

Linessa *Merck, Canad.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Lineuron *Admac, India.*
Vitamin B substances (p. 2102·3).

Linex *Lek, Rus.; Sandoz, Ukr.*
Lysates of *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium infantis* v.liberorum (p. 2596·3); *Enterococcus faecium* (p. 2596·3).
Restoration of gastrointestinal flora.

Linex forte *Sandoz, Ukr.*
Bifidobacterium animalis lactis (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Linex Immuno *Sandoz, Ukr.*
Lactobacillus rhamnosus (p. 2596·3); selenomethionine (p. 2087·1); zinc oxide (p. 1729·1).
Dietary supplement; immunomodulator.

Linfarden *Continentales, Mex.*
Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2).
Respiratory-tract disorders.

Linfoderm *Vargas, Venez.*
Hemlock (p. 2524·3); colchicum (p. 607·1); digitalis (p. 1352·3); podophyllum (p. 1717·1); hyoscyamus (p. 2530·2); calendula (p. 2465·2).
Inflammation.

Linfodermina *Amnol, Ital.*
Melilot (p. 2552·3).
Veno-lymphatic disorders.

Linfoflu *Noos, Ital.*
Resveratrol (p. 2603·2); glucan (p. 2455·2); zinc (p. 2126·1); arginine (p. 2049·1); calcium folinate (p. 2066·3).

Linfoglobulina *Genzyme, Arg.†; Sanofi Pasteur, Chile.†*
Antilymphocyte immunoglobulin (horse) (p. 1939·2).
Aplastic anaemia; transplant rejection; graft-versus-host disease.

Linfoguard *Amnol, Ital.†*
Melilot (p. 2552·3); java tea (p. 2536·3); taraxacum (p. 2625·3); milk thistle (p. 1561·1).
Fluid retention.

Linfoiodine *Noos, Ital.†*
Arginine (p. 2049·1); vitamin B substances (p. 2102·3); potassium iodide (p. 2336·3).

Linfol *Omega, Arg.*
Pessaries: ⊗Metronidazole (p. 936·1); nystatin (p. 590·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3); lidocaine (p. 1988·1).
Vulvovaginal infections.

Omega, Arg.
Tablets: Metronidazole (p. 936·1); nystatin (p. 590·3).
Anaerobic bacterial infections; protozoal infections.

Linfol Cicatrizante *Omega, Arg.*
Metronidazole (p. 936·1); centella (p. 1698·3); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Vulvovaginal infections.

Linfol Dermico *Omega, Arg.*
⊗Ketoconazole (p. 585·3); hydrocortisone (p. 1640·1); gentamicin (p. 304·2).
Bacterial and fungal skin infections.

Linfolipase *Amnol, Ital.*
Acetylcarnitine (p. 2053·2); coleus forskohlii; guarana (p. 2648·2); caffeine (p. 1203·3); ubidecarenone (p. 2637·1); green tea (p. 2648·2); salix (p. 129·2).

Linfonorm *Amnol, Ital.*
Maltezyme; betula (p. 2457·3); rhodiola rosea; copper (p. 2057·1); zinc (p. 2126·1).
Lymphatic disorders; fluid retention.

Linfonorm Cremagel *Amnol, Ital.*
Maltezyme; Linfozyme (liposomal combination of aescin (p. 2431·2) and melilot (p. 2552·3)); phosphatidyl choline (p. 2588·3); caffeine (p. 1203·3); ivy (p. 2536·2); menthol (p. 2553·2).
Oedema.

Linfovenodren *Amnol, Ital.†*
Coumarin (p. 2487·2).
Circulatory disorders.

Ling Di *Hailing, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Ling Bo Kang *Huaxin, China.*
Pyritinol hydrochloride (p. 394·3).

Ling Ding *Yao Wang, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ling Jia Qin *Huaxin, China.*
Sodium ferulate.

Ling Jin Hong *Lingkang, China.*
Gastrodin.

Ling Nuo *Wan Lian, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Ling Shuang *Ya Bao, China.*
Diltiazem hydrochloride (p. 1359·2).

Ling Xin *Lunan, China.*
Isosorbide dinitrate (p. 1412·2).

Ling Zhi PsP *Sahabat, Indon.†*
Polysaccharide peptide from *Ganoderma lucidum.*
Immunomodulator.

Linglanxin *Hayao, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Lingo *Siam Bheasach, Thai.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Lingopen *Viofar, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Lingxu *Hailing, China.*
Ampicillin (p. 218·2).
Bacterial infections.

Linicin *Meda, UK.*
Dimeticone (p. 2209·3).
Pediculosis.

Linid *Zydus, India.*
Linezolid (p. 317·3).
Bacterial infections.

Liniderm *Remexa, Mex.*
Almond oil (p. 2437·1); calcium hydroxide (p. 2465·1).
Burns; skin disorders.

Linif *Menarini, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Linimento Naion *Puerto Galiano, Spain.*
⊗Camphor (p. 2466·2); alcohol (p. 1733·1); salicylic acid (p. 1719·1); turpentine; menthol (p. 2553·2); soft soap (p. 2212·3); capsicum (p. 2469·3); methyl salicylate (p. 92·1); rosemary (p. 2607·2); lavender (p. 2541·1).
Rheumatic and muscle pain.

Linin *Mosfarma, Rus.*
Zinc oxide (p. 1729·1); boric acid (p. 2459·3).
Dermatitis; lichen planus.

Liniplant *Spitzner, Ger.*
Eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1).
Upper respiratory-tract disorders.

Linipon *Adelco, Gr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Linipril *Plus Pharma, Hung.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Linisol *Braun, Belg.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; arrhythmias.

Linitul *Bama, Spain.*
Peru balsam (p. 2587·1); castor oil (p. 2472·1).
Burns; wounds.

Linji *Lifeshine, China.*
Vitamins.
Parenteral nutrition.

Link
Note: this name may be used for preparations of different composition.
Actavis, Denm.; Actavis, Fin.; Actavis, Norw.; Actavis, Swed.†
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastro-oesophageal reflux; gastric hyperacidity; heartburn; peptic ulcer; gastritis; dyspepsia.

Ind-Swift, India.
Lincomycin hydrochloride (p. 317·1).
Anaerobic infections.

Linka *Global, India.*
Lincomycin (p. 317·1).
Anaerobic infections.

Linkam *Kamron, India.*
Lincomycin (p. 317·1).
Anaerobic infections.

Linkoles *Aroma, Turk.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Linkomed *Kocak, Turk.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Linkosol *Biosel, Turk.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Linkus *Herbion, Rus.*
Malabar nut (p. 2549·1); liquorice (p. 1853·2); piper longum; viola odorata; hyssop (p. 2530·3); tormentil (p. 2633·2); cordia latifolia; ziziphus jujuba; althaea (p. 2438·3); onosma bracteatum.
Respiratory-tract disorders.

Herbion, Ukr.
Malabar nut (p. 2549·1); liquorice (p. 1853·2); piper longum; viola odorata; hyssop (p. 2530·3); tormentil (p. 2633·2); cordia latifolia; althaea (p. 2438·3); common ziziphus; onosma bracteatum.
Respiratory-tract congestion.

Linkus Lor *Herbion, Rus.*
Malabar nut (p. 2549·1); liquorice (p. 1853·2); piper longum; viola odorata; hyssop (p. 2530·3); galanga.
Respiratory-tract disorders.

Linmox *Ajanta, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Linmycin *Atlantic, Thai.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Linna-Oil *Knop, Chile.*
Linseed oil (p. 2544·2).
Essential fatty acid supplement.

Linobol *Medichrom, Gr.*
Diclofenac sodium (p. 48·3).

Linocid *Orchid, India.*
Gamolenic acid (p. 2509·2).

Linodiab *Pyridam, Indon.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Linoeparol *Agropharm, Pol.†*
Evening primrose oil (p. 2502·2).
Skin disorders.

Linoforce *Bioforce, Canad.; Bioforce, Switz.; Bioforce, UK.*
Linseed (p. 2544·2); senna (p. 1885·1); frangula (p. 1843·3).
Constipation.

Linol *Vianex (Βιανεξ), Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Linola *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.; Wolff, Pol.; Alcina, Switz.*
Linoleic acid (p. 2509·2); 9,11-octadecadienoic acid (p. 2509·2).
Skin disorders.

Linola Akut *Wolff, Ger.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Linola Gamma *Linderma, UK.†*
Evening primrose oil (p. 2502·2).
Formerly known as Gammaderm.
Dry skin disorders.

Linola gamma *Wolff, Ger.*
Evening primrose oil (p. 2502·2).
Skin disorders.

Linola gras *Alcina, Switz.*
Linoleic acid (p. 2509·2); 9,11-octadecadienoic acid (p. 2509·2).
Skin disorders.

Linola mi-gras *Teva, Switz.†*
Linoleic acid (p. 2509·2); 9,11-octadecadienoic acid (p. 2509·2).
Skin disorders.

Linola Urea *Wolff, Cz.†; Wolff, Ger.; Wolff, Hung.*
⊗Urea (p. 1727·3).
Dry skin.

Linola Urée *Alcina, Switz.*
⊗Urea (p. 1727·3).
Skin disorders.

Linola Wundgel *Wolff, Ger.*
Poloxamer 407 (p. 2202·1); phenoxyethanol (p. 1764·3); octenidine hydrochloride (p. 1762·2).
Infected wounds.

Linolacort Beta *Wolff, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Linolacort Hydro *Wolff, Ger.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Linolacort Triam *Wolff, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Linoladiol *Montavit, Austria.*
Estradiol (p. 2271·1).
Vaginal disorders.

Linoladiol N *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.*
Estradiol (p. 2271·1).
Skin disorders; vaginal disorders; oestrogen deficiency.

Linoladiol-H N *Wolff, Ger.*
⊗Estradiol (p. 2271·1); prednisolone (p. 1645·2).
Vaginal disorders.

Linola-Fett *Wolff, Cz.; Wolff, Ger.*
Linoleic acid (p. 2509·2); 9,11-octadecadienoic acid (p. 2509·2).
Skin disorders.

Montavit, Austria.†
Fatty acids; betacarotene (p. 2051·1); vitamin E (p. 2119·1).
Skin disorders.

Linola-Fett Furdoolaj *Wolff, Hung.*
Bath additive; emollient.

Linola-Fett Olbad *Wolff, Cz.*
Emollient.
Bath additive; dry skin disorders.

Linola-Fett-N Ölbad *Wolff, Ger.*
Bath additive; emollient.

Linola-H N *Wolff, Ger.; Wolff, Hung.†*
⊗Prednisolone (p. 1645·2).
Skin disorders.

Linola-H-Fett N *Wolff, Cz.†; Wolff, Ger.; Wolff, Hung.†*
⊗Prednisolone (p. 1645·2).
Skin disorders.

Linola-sept *Wolff, Ger.*
Clioquinol (p. 273·1).
Infected skin disorders.

Linomag *Ziololek, Pol.*
Vitamin F (p. 2509·2).
Skin disorders.

LinoMed *Flor de Loto, Spain; Bioforce, Switz.*
Linseed (p. 2544·2); senna (p. 1885·1); frangula bark (p. 1843·3).
Constipation.

Linoplus *Abbott, India.*
Linezolid (p. 317·3).
Bacterial infections.

Linopril *East West, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Linoril *Stadmed, India.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; diabetic nephropathy.

Linosept *Micro, India.*
Linezolid (p. 317·3).
Bacterial infections.

Linosin *Deva, Turk.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Linospan *Cipla, India.*
Linezolid (p. 317·3).
Bacterial infections.

Linospril *Kendrick, Mex.†*
Lisinopril (p. 1420·3).
Hypertension.

Linosun *Silesia, Chile.*
Lynestrenol (p. 2287·3).
Progestogen-only oral contraceptive.

Linotar *EpiPharm, Austral.†; MZ, S.Afr.†*
Coal tar (p. 1723·2).
Skin and scalp disorders.

Linoten *Mayne, Spain.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolytic lesions in multiple myeloma and bone metastases associated with breast cancer; Paget's disease of bone.

Linotor *Pharma International, Ukr.*
Lisinopril (p. 1420·3).
Hypertension; myocardial infarction.

Linox *Unichem, India.*
Linezolid (p. 317·3).
Bacterial infections.

Linoxa *Nevzat, Turk.*
Oxaliplatin (p. 838·1).

Linoxal *Sandoz, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Linoxid *Kocak, Turk.*
Linezolid (p. 317·3).

Linprel *Baliarda, Arg.*
Pregabalin (p. 545·3).
Anxiety; epilepsy; neuropathic pain; fibromyalgia.

Lintaz *Aurobindo, India.*
Piperacillin sodium (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Lintop *Vensat, India.*
Lincomycin (p. 317·1).
Anaerobic infections.

Lintos *Wassermann, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Lintran *Shreya, India.*
Linezolid (p. 317·3).
Bacterial infections.

Lintrip *Reddy, S.Afr.*
Levofloxacin (p. 315·3).

Lintropsin *Tropica Mas, Indon.*
Lincomycin (p. 317·1).
Bacterial infections.

Linvas *Zydus, India.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; diabetic nephropathy.

Linzess *Forest Pharmaceuticals, USA.*
Linaclotide (p. 1853·1).
Irritable bowel syndrome; chronic constipation.

Linzi *Neon, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Linzid *United Biotech, India.*
Linezolid (p. 317·3).
Bacterial infections.

Liobac *Sriprasit, Thai.*
Baclofen (p. 2014·3).
Muscle spasticity.

Liocort *Ronava, Venez.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Liod *Bennet, India.*
Lincomycin (p. 317·1).
Anaerobic infections.

Liofen *Sun, India.*
Baclofen (p. 2014·3).
Spasticity.

Liofora *Bayer, Gr.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Bayer Schering, Fin.; Bayer, Irl.; Bayer, Spain; Bayer, Swed.
Drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Bayer, Neth.
Drospirenone (p. 2269·1); ethinylestradiol betadex.
Combined oral contraceptive.

Liolactil *Teva, Mex.; Elmor, Venez.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of gastrointestinal flora; diarrhoea.

Lioliv *Biolek, Ukr.†*
Lecithin (p. 2542·2); mefenamate aluminium.
Hepatitis; gilbert's syndrome; cirrhosis.

Liomagen *Chrispa (Χρισπα), Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Liometacen *Promedica, Ital.; Chiesi, Thai.†*
Meglumine indometacin (p. 71·2).
Musculoskeletal and joint pain.

Lion *Filaxis, Arg.*
Stavudine (p. 1015·3).
Viral infections.

Lion Cleansing Herbs *Potter's, UK.*
Buckthorn (p. 1824·2); psyllium seed (p. 1849·1); senna (p. 1885·1); sambucus (p. 2609·3); fennel (p. 2503·2); maté (p. 2648·2).
Constipation.

Lional *Landson, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Lioram *Mantecorp, Braz.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Lioresal *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; IFET (ΙΦΕΤ), Gr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Geigy, USA; Novartis, Venez.*
Baclofen (p. 2014·3).
Trigeminal neuralgia; skeletal muscle spasm; spasticity.

Liorésal *Novartis, Fr.; Novartis, Switz.*
Baclofen (p. 2014·3).
Skeletal muscle spasm or spasticity.

Lioresyl *Novartis, Chile.*
Baclofen (p. 2014·3).
Skeletal muscle spasm or spasticity.

Liosanne *Sandoz, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Liosmin *Faran, Gr.*
Diosmin (p. 2505·2).

Liotir *Amsa, Ital.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism.

Liotixil *Boniscontro & Gazzone, Ital.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Lioton *Menarini, Austria; Menarini, Cz.; Menarini, Hong Kong; Berlin-Chemie, Hung.; Menarini, Hung.; Transfarma, Philipp.; Berlin-Chemie, Pol.; Menarini, Pol.; Menarini, Rus.; Menarini, Switz.; Berlin-Chemie, Ukr.*
Heparin sodium (p. 1396·3).
Venous insufficiency; soft-tissue disorders; superficial vascular disorders; oedema; scars; keloids; varices; soft-tissue injury; haematoma.

Liotondol *Sanofi-Aventis, Ital.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Liotontrauma *Sanofi-Aventis, Ital.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Soft-tissue injury.

Liotrex
Note: this name may be used for preparations of different composition.
Investigacion, Mex.†
Liothyronine sodium (p. 2342·3).
Hypothyroidism.

Liovel *Takeda, Jpn.*
Alogliptin benzoate (p. 467·2); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Lioxam *Grunenthal, Pol.†*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Liozim *Farmanova, Ital.*
Fructose (p. 2068·2); acacia honey (p. 2072·1); lactic-acid-producing organisms (p. 2596·3).
Nutritional supplement.

Lip Balm *Kiehls, Canad.*
SPF 4: Octinoxate (p. 1715·1).
Sunscreen.

Kiehls, Canad.; Norwood, Canad.
SPF 20: SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Croc Bloc, Canad.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kamins, Canad.
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Norwood, Canad.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Norwood, Canad.
SPF 15: Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Lip Block Sunscreen *Norwood, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Lip Care Balm *Deserving Thyme, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Lip Care with Vitamin E *BodyShop, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lip Conditioner *MAC, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Lip Conditioner Lip Balm *Blistex, Canad.*
Camphor (p. 2466·2); phenol (p. 1763·3); menthol (p. 2553·2); meradimate (p. 1711·2); padimate O (p. 1716·1).
Sunscreen.

Lip Formula *Bath & Body Works, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Lip FX *Cover FX, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lip Ice *Aloe Care, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lip Infusion *Blistex, Canad.; Rider, Chile.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Formerly contained octinoxate and oxybenzone.
Sunscreen.

Lip Massage *Blistex, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Lip Medex *Blistex, USA.*
Camphor (p. 2466·2); phenol (p. 1763·3).
Oral lesions.

Blistex, Canad.†
Camphor (p. 2466·2); phenol (p. 1763·3); menthol (p. 2553·2).
Herpes labialis; dry, cracked lips.

Lip Plumping *Johnson & Johnson, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lip Protection *Vichy, Canad.*
Drometrizole trisiloxane (p. 1702·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Lip Saver *Arbonne, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Lip Tone *Blistex, USA.*
SPF 15: Octinoxate (p. 1715·1); meradimate (p. 1711·2).
Sunscreen.

Lip Treatment *Shaklee, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lipabol *Zydus, India.*
Riboflavin tetrabutyrate (p. 2104·3).

Lipaco *CCM, Malaysia.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

LipaCreon *Abbott, Jpn.*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Lipactin *Widmer, Austria; Widmer, Belg.; Canderm, Canad.; Widmer, Fin.; Widmer, Ger.; Widmer, Philipp.; Widmer, Switz.*
Heparin sodium (p. 1396·3); zinc sulfate (p. 2126·2).
Herpes simplex infections of the lips and orofacial area.

Lipagent *Fahrenheit, Indon.*
Methionine (p. 1558·2); choline bitartrate (p. 2055·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders; vitamin and amino acid deficiency.

Lipai *Xinhua, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Lipancrea *Polfa Warszawa, Pol.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Lipanon *Farmasa, Braz.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipanor *Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; CTS, Israel; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Lipanthyl *Solvay, Austria; Abbott, Belg.; Abbott, China; Fournier, Cz.; Fournier, Fin.; Abbott, Fr.; Solvay, Gr.; Fournier, Hong Kong; Gedeon Richter, Hung.; Solvay, Indon.; Fournier, Malaysia; Solvay, Philipp.; Fournier, Pol.; Solvay, Port.†; Solvay, Rus.; Solvay, S.Afr.; Abbott, Singapore; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Fournier, Turk.; Solvay, Turk.; Fournier, Ukr.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias; atherosclerosis.

Lipanthylnano *Solvay, Belg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipantil *Abbott, Irl.; Solvay, UK.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipaprav *Gerard, Irl.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction.

Liparex *Finadiet, Arg.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Liparex Duo *Finadiet, Arg.*
Tablets, atorvastatin calcium (p. 1309·2); tablets, ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Liparex Plus *Finadiet, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Liparin *Guardian, Indon.*
Silymarin (p. 1561·2).
Nutritional supplement for liver function.

Liparin-S *Bilim, Turk.*
Heparin sodium (p. 1396·3).

Liparison *Novartis, Spain.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipascor
Note: this name may be used for preparations of different composition.
Asiapharm, Malaysia; Asiapharm, Singapore.
Red yeast (p. 2603·1).
Hyperlipidaemias; hypercholesterolaemia.

Servier, Venez.
⊗Benfluorex hydrochloride (p. 1315·3).
Hyperlipidaemias; hyperglycaemia.

Lipathrec *Verisfield, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Lipaven *Progen, Ital.*
Lespedeza; java tea (p. 2536·3); birch (p. 2457·3); myrtillus (p. 2566·2); melilot (p. 2552·3); ascorbic acid (p. 2110·3).
Nutritional supplement.

Lipaxan *Italfarmaco, Ital.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia.

Lipaz *Daquimed, Port.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lipazil *Ascent, Austral.; Douglas, NZ.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Lipazym *Bittermedizin, Ger.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Lipcor
Note: this name may be used for preparations of different composition.
Abbott, Austria.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipcut *Sandoz, Fin.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Lipcy *Comed, India.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Lipcy-A *Comed, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Lipcy-MR *Comed, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Lipdaune *Sofex, Port.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Lip-Down *Veltipharm, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Lipemia *Verisfield, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Lipemol *BMS, Spain.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipenil *Proge, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipep *Savoy, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Liperial *Solvay, Gr.; Solvay, Ital.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Liperol
Note: this name may be used for preparations of different composition.
Rayere, Mex.†
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Lipex
Note: this name may be used for preparations of different composition.
Elea, Arg.
Policosanol (p. 1472·1).
Hypercholesterolaemia.

MSD, Austral.; MSD, NZ.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; hyperlipidaemias; coronary atherosclerosis.

Lipexal *Farmaten, Gr.*
Simvastatin (p. 1489·2).

Lip-Eze *GSK Consumer, Austral.*
SPF 30+: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); octocrilene (p. 1715·2).
Dry, cracked, and chapped lips; sunscreen.

Lipezet *Abbott, India.*
Ezetimibe (p. 1379·2).
Hyperlipidaemias; sitosterolaemia.

Lipi *Dey's, India.*
Glipizide (p. 474·1).
Diabetes mellitus.

Lipibec *Ivax, Arg.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipibec Duo *Ivax, Arg.*
Tablets, atorvastatin calcium (p. 1309·2); tablets, ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipibec Plus *Ivax, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipiblock *Germed, Braz.*
Orlistat (p. 2577·1).

Lipicard *USV, India; USV, Ukr.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipicard AV *USV, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipichek *Indi, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipicon *Concertina, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipicor *Intas, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipicure *Intas, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipicure-AS *Intas, India.*
Aspirin (p. 22·2); atorvastatin (p. 1309·2).

Lipid *Stadmed, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipidavit *Rodisma, Ger.†*
Garlic (p. 2510·3); alpha tocoferil acetate (p. 2119·2); lecithin (p. 2542·2).
Hyperlipidaemias.

Lipidavit SL *Rodisma, Ger.*
Soya bean phospholipids (p. 2092·3).
Hypercholesterolaemia.

Lipidem *Braun, Austria; Braun, Denm.; Braun, Ger.; Braun, Irl.; Braun, Norw.; Braun, Thai.; Braun, UK.*
Omega-3 triglycerides (p. 1460·1); medium-chain triglycerides (p. 2082·2); soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Braun, Fr.; Braun, Ital.
Medium-chain triglycerides (p. 2082·2); soya oil (p. 2092·3); omega-3 triglycerides (p. 1460·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipidex *Sandoz, S.Afr.*
Simvastatin (p. 1489·2).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Lipidil *Abbott, Austral.; Chiesi, Braz.; Fournier, Canad.; Royal, Chile†; Abbott, Ger.; Abbott, Gr.; Fournier-Gerolymatos, Gr.; Fournier, Hung.; Italmex, Mex.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias; hypercholesterolaemia.

Lipidless *Angelini, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lipidra *Nobel, Turk.*
Atorvastatin calcium (p. 1309·2).

Lipidrop *Sresan, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipidrop-V *Sresan, India.*
Atorvastatin (p. 1309·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Lipiduce *Unison, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipidys *Medifive, Thai.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipi-EZ *Intas, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipifen *Raffo, Arg.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipifol Plus *Meyer, India.*
Atorvastatin (p. 1309·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Lipiforce *Forder, Arg.*
Phospholipids (p. 2201·2); ceramide (p. 1699·1).

Lipigan *Nexus, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipigard *Julphar, UAE.*
Atorvastatin (p. 1309·2).

Lipigem *Alphapharm, Austral.; Littman, Philipp.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction; coronary heart disease.

Lipigran *Legrand, Braz.*
Atorvastatin (p. 1309·2).

Lipikar *Roche-Posay, Arg.; Roche-Posay, Braz.; Roche-Posay, Irl.*
Emollient.
Dry skin disorders.

Roche-Posay, Chile.
Range of emollients and moisturisers.
Dry skin disorders.

Roche-Posay, Fr.
Emollient preparations.
Dry skin disorders.

Lipikar Xerand *Roche-Posay, Braz.*
Emollient.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lipikind *Mankind, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipikind-AM *Mankind, India.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).
Hypertension; angina pectoris; hyperlipidaemias; atherosclerosis.

Lipikind-EZ *Mankind, India.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipiles *Ind-Chemie, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipilfen *Ethypharm, China; Schwartz, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipilim *Atlantic, Hong Kong.†*
Clofibrate (p. 1338·3).
Hyperlipidaemias.

Lipilo *Ethypharm, China.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipi-M *Dey's, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Lipimibe *Penn, Arg.†*
Simvastatin (p. 1489·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipimix *Kalbe, Indon.*
Phospholipids (p. 2201·2); medium-chain triglycerides (p. 2082·2).
Dry eyes; corneal damage.

Tubilux, Ital.
⊗Phospholipid; medium-chain triglycerides (p. 2082·2); soya oil (p. 2092·3); glycerol (p. 2517·2).
Dry eyes.

Lipin *Biolek, Ukr.*
Lyophilised egg phosphatidyl choline (p. 2588·3).
Respiratory insufficiency; myocardial infarction; angina pectoris; hepatitis; cholecystitis; cirrhosis; ulcerative colitis; toxaemia of pregnancy; fetal hypoxia; pyelonephritis; diabetic nephropathy; glomerulonephritis; polycystic kidney; renal impairment.

Lipinorm *Kalbe, Indon.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; coronary heart disease.

Lipinox *Umut, Turk.*
Amlodipine (p. 1304·1).

Lipiocis *CIS, Fr.†*
Iodine-131 (p. 2225·3) in iodised oil.
Liver cancer with portal vein thrombosis.

Lipiodol *Temis, Arg.; Aspen, Austral.; Guerbet, Austria; Codali, Belg.; Therapex, Canad.; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Hung.; Guerbet, Irl.; Guerbet, Israel; Guerbet, Ital.; Guerbet, Neth.; Obex, NZ; Martins & Fernandes, Port.; Guerbet, Switz.; Guerbet, Turk.; May & Baker, UK; Quifoven, Venez.*
Iodised oil (p. 1589·1).
Radiographic contrast medium; iodine deficiency.

Lipiodol Ultra-Fluide *Guerbet, Thai.*
Iodised oil (p. 1589·1).
Radiographic contrast medium; iodine deficiency.

Lipira
Note: this name may be used for preparations of different composition.
Combiphar, Indon.
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Emcure, India.
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipirex *Sanofi-Aventis, Cz.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipiric *Euphoric, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipirol
Note: this name may be used for preparations of different composition.
Novell, Indon.
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); alpha tocoferil acetate (p. 2119·2).
Liver disorders; hyperlipidaemias.

Taj, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipiscor *Sanum-Kehlbeck, Ger.*
Marine fish oil (p. 1460·3).
Hyperlipidaemias.

Lipison *Unison, Hong Kong; Unison, Philipp.†; Unison, Singapore; Unison, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; ischaemic heart disease.

Lipisorb *Mead Johnson Nutritionals, USA.*
Lactose-free food for special diets.

Lipistat
Note: this name may be used for preparations of different composition.
Knop, Chile.
Yeast extract from Monascus purpureus.
Hypercholesterolaemia.

RPG, India.
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Sigma, Braz.
Atorvastatin (p. 1309·2).

Lipistatina *Germed, Braz.*
Simvastatin (p. 1489·2).

Lipistorol *Hovid, Hong Kong; Hovid, Singapore.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipitab *Meyer, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipitaksin *Fako, Turk.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Lipitin-S *Flamingo, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipitor *Elea, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; ChemVet, Denm.; Orifarm, Denm.; Paranova, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Bioindustria, Ital.; Astellas, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias; atherosclerosis.

Lipitrol *Julphar, UAE.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Lipitrop *Tropica Mas, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipium-Raldex *Farmachrom, Gr.*
Atorvastatin calcium (p. 1309·2).

Lipivas
Note: this name may be used for preparations of different composition.
Elder, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Nabiqasim, Philipp.
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Lipivas EZ *Elder, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipix *Platinum, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipizem *Gerolymatos, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipizile *Integrated Pharmaceutical, Philipp.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; ischaemic heart disease.

Lipizyl *Abbott, India.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Liplat *Esteve, Spain.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Liple *Mitsubishi Tanabe, Jpn.*
Alprostadil (p. 2352·2).
Peripheral vascular disorders; maintenance of patent ductus arteriosus; skin ulcers; mesenteric arterial portography.

Lipless *Biolab Sanus, Braz.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Liplofin *Lifestyle, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Liplow *Gap, Gr.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipmagik *Reese, USA.*
⊗Benzocaine (p. 1980·2); phenol (p. 1763·3); alcohol (p. 1733·1).

Lipneo *Hypermarcas, Braz.*
Ciprofibrate (p. 1338·1).

Lipo Cordes *Ichthyol, Ger.*
Allantoin (p. 1693·1); dexpanthenol (p. 2582·2); ethyl linoleate (p. 2509·2).
Skin disorders.

Lipo Sol *Widmer, Philipp.†; Widmer, Switz.*
Triclosan (p. 1773·2).
Acne; seborrhoea.

Lipoacid *Dermoteca, Port.*
Thioctic acid (p. 2629·1); ascorbic acid (p. 2110·3) octadecenedioic acid; sunscreens.
Skin ageing.

Lipoacid Combi *Dermoteca, Port.*
Thioctic acid (p. 2629·1); cysteine (p. 2058·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); eicosapentaenoic acid (p. 1460·2).
Skin ageing; dietary supplement.

Q-Med, Ital.
Thioctic acid (p. 2629·1); cysteine (p. 2058·3); vitamin E (p. 2119·1); eicosapentaenoic acid (p. 1460·2).
Nutritional supplement.

Lipoarteriosan *Bernabo, Arg.*
Atorvastatin calcium (p. 1309·2); amlodipine besilate (p. 1304·1).
Angina pectoris; hyperlipidaemias; hypertension.

Lipobalsamo *Teofarma, Ital.*
Cineole (p. 2479·1); guaiacol (p. 1666·1).
Respiratory-tract disorders.

Lipobase *Astellas, Cz.; Astellas, Hung.; Yamanouchi, NZ; Astellas, UK.*
Emollient.
Skin disorders; diluent for Locoid Lipocream; dry skin; pruritus.

LIPObind *Goldshield, UK.*
Fibre complex from cactus leaves.
Aid to weight control.

Mercury, Austral.
Opuntia ficus-indica.
Slimming aid.

Lipoblock *Fabop, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Lipocambi *Bernabo, Arg.*
Atorvastatin calcium (p. 1309·2).
Cardiovascular risk reduction.

Lipocambi Plus *Bernabo, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Cardiovascular risk reduction; hyperlipidaemias.

Lipochol *Takeda, Hong Kong; Takeda, Thai.*
Orotic acid (p. 2578·1); thioctic acid amide (p. 2629·1); methionine (p. 1558·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); inositol (p. 2533·2).
Liver disorders.

Lipocid *Orchid, India.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Lipociden *Liconsa, Spain.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipocin *Kener, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Lipocinetic *Investigacion, Mex.†*
Citric acid (p. 2480·3).
Hypercholesterolaemia.

Lipoclin
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Sumitomo, Jpn.
Clinofibrate (p. 1338·3).
Hyperlipidaemias.

Lipocol *Merz, Ger.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; diarrhoea; pruritus associated with biliary obstruction.

Lipocort *CSL, NZ.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Lipocut *Biocon, India.*
Orlistat (p. 2577·1).
Obesity.

Lipoderm *Spirig, Singapore.*
SPF 16; SPF 20; SPF 25: Bemotrizinol (p. 1695·3); octisalate (p. 1715·2); octinoxate (p. 1715·1).
Sunscreen.

Lipoderm C *Remexa, Mex.*
Emollient.

Lipoderm Cool Liposomal Hydration *Spirig, Singapore.*
Emollient.
Dry skin.

Lipodial *Adipharm, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipo-Dox *American Taiwan, Thai.*
Liposomal doxorubicin hydrochloride (p. 783·1).
Kaposi's sarcoma; ovarian cancer; breast cancer; multiple myeloma.

Lipodox *Biolek, Ukr.; Sun, USA.*
Liposomal doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Lipoenergy *Activa Sport, Ital.*
Choline (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2); carnitine (p. 2053·2); vitamin B_6 (p. 2105·3).
Nutritional supplement.

Lipofacton *Organon, Braz.†*
Clofibrate (p. 1338·3); nicotinyl alcohol tartrate (p. 1447·1).
Hyperlipidaemias.

Lipofactors & Niacin *Naka, Canad.†*
Choline bitartrate (p. 2055·2); inositol (p. 2533·2); nicotinic acid (p. 2083·1).

Lipoféine *Arkopharma, Fr.*
Caffeine (p. 1203·3).
Localised fat reduction.

Lipofen *Vitoria, Port.; Nobel, Turk.; Nobel, Ukr.; Kowa, USA.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipofene *Teofarma, Ital.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipoferon *Jadran, Ukr.*
Interferon alfa-2b (p. 989·2).
Hepatitis B and C; allergic rhinoconjunctivitis; chlamydia infection; tick-borne encephalitis; asthma; influenza; SARS.

Lipofin *Fabop, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Lipofix *Bal, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipofix-EX *Bal, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipoflavon *Biolek, Ukr.†*
Lecithin (p. 2542·2); quercetin (p. 2505·3).
Corneal wounds; postoperative keratitis; inflammatory eye diseases; myocardial infarction; angina pectoris; myocarditis; prevention of cardiodystrophy due to antineoplastic chemotherapy.

Lipoflavonoid *Numark, USA.*
Vitamins; lemon bioflavonoids (p. 2505·2).

Lipofor *Remedica, Hong Kong; Remedica, Malaysia†; Remedica, Singapore.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Lipoford *Oxford Laboratories, Rus.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipofundin *Braun, Chile; Braun, UK.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipofundin MCT *Braun, Ger.; Braun, Hung.†; Braun, Ital.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipofundin MCT/LCT *Braun, Arg.; Braun, Chile; Braun, China; Braun, Cz.†; Bioser (Βιοσερ), Gr.; Braun, Hong Kong; Braun, India; Braun, Indon.†; Braun, Irl.†; Braun, Israel; Pisa, Mex.; Braun, Neth.†; Braun, Pol.; Braun, Rus.; Braun, S.Afr.†; Braun, Singapore; Braun, Switz.; Braun, Thai.; Braun, Turk.; Braun, UK; Braun, Ukr.; Behrens, Venez.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipofundin MCT/LCT-E *Braun, Arg.†*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2); alpha-tocopherol (p. 2119·1).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipofundin mit MCT *Braun, Austria.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg phospholipid.
Lipid infusion for parenteral nutrition.

Lipofundin N *Braun, Arg.; Braun, Ger.; Braun, Hong Kong†; Pisa, Mex.; Braun, Pol.; Braun, Singapore; Braun, Thai.†*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipofundin S *Braun, Ital.; Braun, Thai.†*
Soya oil (p. 2092·3).
Lipid infusion for parenteral nutrition.

Lipofundina MCT/LCT *Braun, Port.; Braun, Spain.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipogen
Note: this name may be used for preparations of different composition.
Goldline, USA.
Vitamin B substances (p. 2102·3).
It may also contain vitamin C.

Ranbaxy, S.Afr.
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipoglutaren
Note: this name may be used for preparations of different composition.
Craveri, Arg.
Rosuvastatin (p. 1488·2).
Hypercholesterolaemia.

Lipograsil *Uriach Aquilea OTC, Spain.†*
Cynara (p. 2490·3); cascara (p. 1826·1); bladderwrack (p. 2612·1).
Obesity.

Lipohep *Medagro, Pol.*
Heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue injury.

Lipohexal *Hexal, Cz.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipoicin *Takeda, Thai.*
Thioctic acid (p. 2629·1).
Liver disorders.

Lipoite *Angelfarma, Port.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipokemia *Fecofar, Arg.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Lipolac *Bausch & Lomb, Mex.; Angelini, Spain.*
Carbomer (p. 2173·3).
Dry eyes; eye irritation.

Lipolest *Deco, Hung.*
Ispaghula (p. 1849·1); guar gum (p. 475·1).
Hypercholesterolaemia.

Lipolin *Bausch & Lomb, Philipp.*
Carbomer (p. 2173·3).
Dry eyes.

Lipolip *TO-Chemicals, Thai.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Lipolo *Macrophar, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Lipolotion
Note: this name may be used for preparations of different composition.
Elder, India.
Vitamin A palmitate (p. 2098·3).

Lipomal *Aflofarm, Pol.*
Tilia (p. 2631·3).
Fever.

Lipomax
Note: this name may be used for preparations of different composition.
Bago, Arg.
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Forder, Arg.
Glycolic acid (p. 1704·3).

Lipomed MCT/LCT *Sanbe, Indon.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Lipid infusion for parenteral nutrition.

Lipomega *Nutri-Well, Hong Kong.*
Omega-3 marine triglycerides (p. 1460·3).
Hypercholesterolaemia.

Lipo-Merz *Merz, Ger.†; Merz, Hong Kong; Medinfar, Port.*
Etofibrate (p. 1379·2).
Hyperlipidaemias.

Lipomin *Nexus, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Kapharma, Ukr.
Green tea (p. 2648·2); hydroxycitrate complex; chromium tripicolinate (p. 2056·1); kidney bean extract (p. 2587·3); myrtillus (p. 2566·2); dry grape; miracle fruit (p. 2560·2); bitter orange (p. 2575·3); fennel (p. 2503·2); galega officinalis; ginger (p. 1844·1).
Obesity.

Lipomix *Grifols, Spain.*
Medium-chain triglycerides (p. 2082·2); soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipomul *Roberts, USA.†*
High calorie preparation containing maize oil for enteral nutrition (p. 2080·2).

Lipona *Sedico, Rus.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Liponit *Teka, Turk.*
Lecithin (p. 2542·2); sodium chloride (p. 1795·1).
Eye irritation.

Liponol *Rugby, USA.*
Vitamin B substances (p. 2102·3); methionine (p. 1558·2).

Liponorm
Note: this name may be used for preparations of different composition.
Blue Cross, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lazar, Arg.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Gentili, Ital.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Kapharma, Ukr.
Garcinia quaesita (p. 2510·2); grapefruit; fennel (p. 2503·2); bitter orange (p. 2575·3); Siberian ginseng (p. 2614·3); fucus vesiculosus; ginger (p. 1844·1); myrtillus (p. 2566·2); miracle fruit (p. 2560·2); tea (p. 2648·2); aniseed (p. 2444·2); capsicum (p. 2469·3); vitamins; minerals; amino acids; poliglusam (p. 2593·2).
Obesity.

Liponorm Duo *Lazar, Arg.*
Tablets, atorvastatin calcium (p. 1309·2); tablets, ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Liponorm-EZ *Blue Cross, India.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Lipontal *Meyer Alian, Venez.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipophage *Franco-Indian, India.*
Orlistat (p. 2577·1).
Obesity.

Lipopharm *Medphano, Ger.*
Soya phospholipid (p. 2092·3).
Hypercholesterolaemia.

Lipophoral *Servier, Gr.*
⊗Benfluorex (p. 1315·3).
Hyperlipidaemias.

Lipoplus *Bioser (Βιοσερ), Gr.*
Medium-chain triglycerides (p. 2082·2); soya oil (p. 2092·3); fish oil (p. 1460·3).
Lipid infusion for parenteral nutrition.

Braun, Belg.; Braun, Cz.; Braun, Fin.; Braun, Neth.; Braun, Port.; Braun, Rus.; Braun, Spain; Braun, Swed.; Braun, Switz.
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2); omega-3 triglycerides (p. 1460·1).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipoprav *Global, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Lipopress *Comomed, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Liporégul *Lero, Fr.*
Fish oil (p. 1460·1); vitamins; minerals.
Dietary supplement.

Liporest *Centaur, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Liporex *Genepharm, Gr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Liporon *General Drugs, Thai.*
Choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2); vitamin B substances (p. 2102·3).
Liver disorders.

Liposcler *UCB, Spain.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Liposerin *Landson, Indon.†*
Phosphatidyl serine (p. 2589·1); phosphatidyl choline (p. 2588·3).
Memory function adjuvant.

Liposic *Bausch & Lomb, Arg.; Bausch & Lomb, Belg.; Bausch & Lomb, Braz.; Mann, China; Chauvin, Fr.; Mann, Ger.; Kite (Κιτε), Gr.; Bausch & Lomb, Hong Kong; Pharma-Global, Irl.; Teva, Israel; Bausch & Lomb, Neth.; Bausch & Lomb, Port.; Bausch & Lomb, Switz.; Bausch & Lomb, Thai.; Bausch & Lomb, UK.†*
Carbomer (p. 2173·3).
Dry eyes.

Liposin *Pharos, Indon.*
Bacitracin (p. 225·3); lidocaine hydrochloride (p. 1988·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Skin infections.

Liposinol *Biomed, Switz.*
Vegetable fibre.
Obesity.

InQpharm, Malaysia.
Opuntia ficus-indica leaf.
Weight reduction.

Liposit
Note: this name may be used for preparations of different composition.
Novartis, Spain.
Fluvastatin sodium (p. 1385·1).
Hyperlipidaemias; cardiovascular risk reduction.

Liposol *Biotenk, Arg.*
Orlistat (p. 2577·1).
Obesity.

Liposom *Fidia, Ital.*
Hypothalamic phospholipids (p. 2444·1).
Parkinsonism.

Liposomas *GSK, Arg.*
Cholesterol (p. 2179·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); soya oil (p. 2092·3); vitamin E (p. 2119·1).
Sun-induced skin disorders; sunscreen.

Liposorb *Metro, Philipp.*
Liphosan; ascorbic acid (p. 2110·3); chromium tripicolinate (p. 2056·1).
Obesity.

Lipostabil
Note: this name may be used for preparations of different composition.
Cassella-med, Ger.
Soya phospholipids (p. 2092·3).
Hypercholesterolaemia; fat emboli.

Lipostat *Aspen, Austral.; BMS, Irl.; BMS, NZ†; BMS, Philipp.†; BMS, UK.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis; myocardial infarction; stroke prophylaxis.

Lipostatin *Alapis, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipostop
Note: this name may be used for preparations of different composition.
Denver, Arg.
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Liposyn *Hospira, Canad.; Hospira, Ital.; Abbott, Mex.†; Abbott, Turk.†*
Safflower oil (p. 2086·3); soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Liposyn II *Hospira, USA.*
Safflower oil (p. 2086·3); soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Liposyn III *Hospira, USA.*
Soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipotalon *Recordati, Ger.*
⊗Dexamethasone palmitate (p. 1630·3).
Rheumatic disorders.

Lipotears *Abdi, Turk.*
Carbomer (p. 2173·3).

Lipotex *Medley, Braz.†*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Lipothin *TO-Chemicals, Thai.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipothioxon *Sotex, Rus.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Lipothymal *Septodont, Fr.†*
Concentrated ammoniac solution (p. 2441·2); ammonium carbonate (p. 1656·1).

Lipotop *Spirig, Fr.†*
A range of emollient and barrier preparations.

Lipotriad *Numark, USA.*
Vitamins; minerals.

Lipotril *Sanitas, Chile.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipotropic *Recalcine, Chile.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Lipotropic Factors *Solgar, UK.*
Choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2).
Dietary supplement.

Lipout *InQPharm, Philipp.*
Vegetable fibre.
Dietary supplement.

Lipovas
Note: this name may be used for preparations of different composition.
Ranbaxy, Irl.
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Sandoz, Turk.
Simvastatin (p. 1489·2).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Tempo Scan Pacific, Indon.
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lipovast *Anpharm (Ανφαρμ), Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lipovastatin *Klonal, Arg.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipovenoes *Fresenius Kabi, Cz.†; Bioser (Βιοσερ), Gr.; Fresenius Kabi, Indon.; Fresenius Kabi, Mex.; Fresenius Kabi, Port.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

SSPC, China.
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovenos *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.†*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovenös *Fresenius Kabi, Ger.; Fresenius Kabi, Switz.†; Fresenius Kabi, Turk.*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovenös MCT *Fresenius Kabi, Ger.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg phospholipid.
Lipid infusion for parenteral nutrition.

Lipovenos MCT/LCT *Fresenius Kabi, Arg.*
Soya oil (p. 2092·3); lipids; triglycerides (p. 2082·2).
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Chile.
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovenos PLR *Fresenius Kabi, Arg.*
Soya oil (p. 2092·3); lipids.
Lipid infusion for parenteral nutrition.

Lipovisc *Bausch & Lomb, Ital.*
Carbomer (p. 2173·3).
Dry eyes.

Lipovitasi D *Atlantis, Mex.*
Carnitine (p. 2053·2).

Lipovitasi-Or *Atlantis, Mex.*
Carnitine orotate (p. 2578·1); thiamine nitrate (p. 2103·2); DL-methionine (p. 1558·2).
Liver disorders; chronic fatigue syndrome; hyperammonaemia.

Lipový *Megafyt-R, Cz.*
Tilia (p. 2631·3).
Catarrh; cold symptoms; cough.

Lipox *Laboratorios Chile, Chile.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

TAD, Ger.†
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Lipozid
Note: this name may be used for preparations of different composition.
Innovact, Gr.
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Pharma Nutria, Philipp.†
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; ischaemic heart disease.

Lipozil *M & H, Thai.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lipozyme *Nutri-Dyn, Canad.†*
⊗Ox bile (p. 2457·2); pancreatin (p. 2579·3); pepsin (p. 2586·1).

Lipra *Pentafarma, Port.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Liprace *Ascent, Austral.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Liprachol *Sandoz, Austral.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipraken *Kener, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Lipram *Global, USA.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Lipratif *Tiefenbacher, Neth.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Liprazid *Borshchagovskii, Ukr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lipreren *Labomed, Chile.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Lipribela *Belupo, Cz.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lipribela plus H *Belupo, Cz.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Liprikaine *T Man, Thai.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Lipril *Lupin, India; Merck, Port.; Borshchagovskii, Ukr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lipril-AM *Lupin, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Lipril-H *Lupin, India.*
⊗Hydrochlorothiazide (p. 1403·2); lisinopril (p. 1420·3).
Hypertension.

Liprimar *Pfizer, Hung.†; Pfizer, Rus.; Pfizer, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipro *Siu Guan, Malaysia.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Liprocil *Nestle, Fr.*
Medium-chain triglycerides (p. 2082·2); vitamins.
Nutritional supplement.

Liproct *YSP, Malaysia.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Liprolog *Lilly, Cz.; Berlin-Chemie, Ger.; Lilly, Irl.; Lilly, Neth.; Lilly, Pol.; Lilly, Port.*
⊗Insulin lispro (p. 475·3).
Diabetes mellitus.

Liprolog Basal *Lilly, Cz.; Lilly, Port.*
⊗Isophane insulin lispro (p. 475·3).
Diabetes mellitus.

Liprolog Mix 25 and 50 *Lilly, Cz.; Berlin-Chemie, Ger.; Lilly, Irl.; Lilly, Neth.; Lilly, Port.*
⊗Mixtures of insulin lispro 25% and 50% and isophane insulin lispro 75% and 50% respectively (p. 475·3).
Diabetes mellitus.

Liproqy *Caprifarmindo, Indon.*
Ubidecarenone (p. 2637·1); lycopene (p. 2546·2); vitamin E (p. 2119·1); grape seed (p. 2521·3); epigallocatechin gallate (p. 1720·2).
Tonic.

Liprox *Biofarm, Pol.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Liproxal *Biofarm, Pol.*
Cynara (p. 2490·3).
Digestive disorders; hypercholesterolaemia.

Lip-Sed *Pfizer, NZ.†*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lipsin *Abbott, Austria; Caber, Ital.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipsorex *Sanofi, Canad.*
Benzethonium chloride (p. 1738·1); menthol (p. 2553·2); thymol (p. 1772·2).

Lipsorex Plus *Sanofi, Canad.*
Lidocaine (p. 1988·1); benzethonium chloride (p. 1738·1); menthol (p. 2553·2); thymol (p. 1772·2).

Liptonorm *Biopharm, Rus.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Liptrat *Uniao Quimica, Braz.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Liptruzet *MSD, USA.*
Ezetimibe (p. 1379·2); atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lipuqi *Neptunus, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Lipur *Pfizer, Fr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Lipuro *Braun, Philipp.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Lipus *BA Farma, Port.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lipuxin *Neptunus, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Lipvas *Cipla, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Lipvastin *Clonmel, Irl.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lipway *Cathay, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lipz Lipbalm *Hamilton, Austral.*
SPF 30+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Lipz Ointment *Hamilton, Austral.*
SPF 30+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); avobenzone (p. 1695·1); menthol (p. 2553·2); aloe vera (p. 1693·2).
Sunscreen.

Liqing *Yaoyou, China.*
Alfacalcidol (p. 2112·3).
Osteoporosis.

Liquadd *Auriga, USA.†*
⊗Dexamfetamine sulfate (p. 2319·1).
Attention deficit hyperactivity disorder.

Liqualon *Synco, Hong Kong.†*
Benzocaine (p. 1980·2); dequalinium (p. 1749·3).

Liquémine *Drossapharm, Switz.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders; hyperlipidaemias.

Liquemine *Roche, Braz.; Roche, Turk.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Liqufruta Garlic Cough Medicine *Chefaro, UK.*
Garlic oil (p. 2510·3); guaifenesin (p. 1666·2).
Coughs.

Liqui C *Vitality, Canad.†*
Vitamin C (p. 2110·3).

LiquiBand *Medlogic, UK.*
Enbucrilate (p. 2489·3).
Tissue adhesive for wound closure and suture support.

Liquibid *Capellon, USA.*
Guaifenesin (p. 1666·2).

Liquibid-D *Capellon, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract symptoms.

Liquibid-PD *Capellon, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Liquicet *Mallinckrodt, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Liqui-Char *Oxford Pharmaceuticals, Irl.; Jones, USA.*
Activated charcoal (p. 1537·3).
Emergency treatment of poisoning.

Liqui-Coat HD *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Liquicough DM *Breckenridge, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Liquid Cal-Mag plus Vitamin D and Phosphorus *Valeant, Canad.*
Colecalciferol (p. 2113·1); calcium (p. 1783·1); magnesium (p. 1786·3); phosphorus (p. 2589·2).

Liquid Pred *Muro, USA.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Liquid Soap Pre-Op *Orion, NZ.*
Triclosan (p. 1773·2).
Skin cleansing.

Liquid Sunshine Tan Enhancer *Arbonne, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Liquidepur mit Natriumpicosulfat *McNeil, Ger.†*
Sodium picosulfate (p. 1887·2).
Constipation.

Liquidix *Novartis, India.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Liquidorm N *Hanosan, Ger.*
Avena sativa (p. 2451·1); valeriana officinalis (p. 2640·2); natrium bromatum (p. 2461·1); ferula moschata; coffea arabica (p. 2648·2).
Homoeopathic preparation.

Liqui-Doss *Ferndale, USA.†*
Liquid paraffin (p. 2191·2).
Constipation.

Liquifilm *Allergan, Austral.; Allergan, Belg.; Allergan, Canad.†; Allergan, Fin.; Allergan, Ger.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Malaysia; Allergan, NZ; Allergan, Port.; Abdi, Turk.; Allergan, USA.†*
Polyvinyl alcohol (p. 2204·2).
Dry eyes; eye irritation; wetting solution for hard contact lenses.

Liquifilm Lagrimas *Allergan, Arg.; Allergan, Spain.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Liquifilm OK *Allergan, Ger.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Liquifilm Tears *Alvia (Αλβια), Gr.; Allergan, India; Allergan, Israel; Allergan, S.Afr.†; Allergan, Singapore; Allergan, Thai.; Allergan, UK.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes; hard contact lens lubricant.

Liquifilm Wetting *Allergan, USA.†*
Wetting solution for hard contact lenses.

Liquifresh *Allergan, Spain.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes; contact lens discomfort.

Liquigel *Thea, Ger.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Liquigen *Nutricia, Austral.; SHS, Denm.; Nutricia, Fin.; Nutricia, Fr.; Scientific Hospital Supplies, Irl.†; Nutricia, Ital.; Nutricia, NZ; SHS, UK.*
Medium-chain triglycerides (p. 2082·2).
Fat malabsorption; ketogenic diets; food for special diets.

Liquigesic Co *Paedpharm, Austral.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Liquimat *Summers, USA.*
Sulfur (p. 1721·1).
Acne; oily skin.

Liqui-Med *Praxair, Canad.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).

Liquimed *Greater Pharma, Thai.*
Ketoconazole (p. 585·3).

Liquipake *Lafayette, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Liquipom Dexa Antibiotico *Iquinosa, Spain.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye and ear disorders.

Liquipred *Transfarma, Philipp.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Liquiprin
Note: this name may be used for preparations of different composition.
HLB, Arg.
Chondroitin sulfate (p. 2476·1).
Dry eyes.

Menley & James, USA.
Paracetamol (p. 115·1).
Pain; fever.

Liquirit *Pharmachem, Ger.*
Algeldrate (p. 1817·2); magnesium carbonate (p. 1856·2); liquorice (p. 1853·2).
Gastrointestinal disorders.

Liquiron *Plus, India.*
Iron carbonyl (p. 2073·1); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); vitamin C (p. 2110·3); zinc (p. 2126·1).

Plus, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Liquisone *Uoyd, Philipp.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Liquitears *Allergan, Switz.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes; contact lens discomfort.

Liquituss GG *Capellon, USA.*
Guaifenesin (p. 1666·2).
Cough.

LiquiVent *Alliance, USA.*
⊗Perflubron (p. 2586·2).
Acute respiratory distress syndrome.

Liquivisc *Thea, Irl.; Allergan, UK.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Liracol *Medipharm, Chile.*
Tablets: Nifuroxazide (p. 331·3); phthalylsulfathiazole (p. 339·3).
Gastrointestinal infections.

Medipharm, Chile.
Oral suspension: Nifuroxazide (p. 331·3); activated attapulgite (p. 1820·1).
Bacterial gastrointestinal infections.

Liramin *Proula, Venez.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Lircapil *Medichrom, Gr.*
⊗Labetalol hydrochloride (p. 1416·2).

Lirebin *Help, Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Lirex *Silesia, Chile.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Lirgosin *Fidia, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Liroken *Kendrick, Mex.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout; inflammation; pain.

Liroken I *Kendrick, Mex.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Lirona *Pliva, Cz.†*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Lirpan *Casasco, Arg.*
Donepezil (p. 390·2).
Alzheimer's disease.

Lirra *Glenmark, Pol.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Lirtodac *Merck Serono, Arg.*
⊗Fluticasone propionate (p. 1638·1).
Asthma.

Lirtodac Plus *Merck Serono, Arg.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Lirudine *Landsteiner, Mex.*
Desloratadine (p. 625·1).
Allergic rhinitis; allergic conjunctivitis; pruritus; allergic skin disorders.

Lisa *Lisapharma, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Lisac *Bernabo, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Lisacard *Shreya, Rus.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisador *Farmasa, Braz.*
Dipyrone (p. 53·3); promethazine hydrochloride (p. 638·2); adiphenine hydrochloride (p. 2431·1).
Smooth muscle spasm.

Lisaglucon *Farmasa, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Lisak *Farmak, Ukr.*
Muramidase hydrochloride (p. 2565·1); dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Lisaler *Fortbenton, Arg.*
Loratadine (p. 633·2).

Lisaler Beta *Fortbenton, Arg.*
⊗Loratadine (p. 633·2); betamethasone valerate (p. 1624·1).

Lisalgil *Boehringer Ingelheim, Arg.*
Metamizole magnesium (p. 53·3).
Pain.

Lisalgil Compuesto *Boehringer Ingelheim, Arg.*
Metamizole magnesium (p. 53·3); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Lisanirc *Lisapharma, Ital.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

Lisantil *Bio Macro, Braz.*
Dipyrone (p. 53·3); promethazine hydrochloride (p. 638·2); adiphenine hydrochloride (p. 2431·1).

Lisapres *Libbs, Braz.*
Guanabenz acetate (p. 1395·1).
Hypertension.

Lisaspin *Grunenthal, Port.*
Lysine aspirin (p. 84·3).
Pain; fever.

Lisba *Rafarm, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Liscard *Intra-Labs, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisdene *Sandoz, Malaysia; Sandoz, Pol.†; Sandoz, Singapore; Sandoz, Thai.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisefor *Vocate, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Lisel *Madhav, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Lisel-S *Madhav, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).

Lisel-TBZ *Madhav, India.*
Ceftriaxone sodium (p. 253·3); tazobactam sodium (p. 369·3).
Bacterial infections.

Liserdol *Teofarma, Ger.; Teofarma, Ital.*
Metergoline (p. 2557·2).
Lactation inhibition; galactorrhoea; hyperprolactinaemia; migraine and vascular headache; gastric motility disorders; menstrual disorders.

Lisertil *Serral, Mex.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Lishenbao *Livzon, China.*
Urofollitropin (p. 2312·2).
Female infertility.

LiShu
Note: this name may be used for preparations of different composition.
Zhong Bao, China.
Puerarin.

Lishu
Note: this name may be used for preparations of different composition.
Suilun, China.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Lisi *Hennig, Ger.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Lisi HCT *TAD, Ger.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisi Lich *Winthrop, Ger.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Lisibal *Proula, Venez.*
Vitamin B substances (p. 2102·3).
Dietary supplement; vitamin B deficiency; neuropathies.

Lisibeta *Betapharm, Ger.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Lisibeta comp *Betapharm, Ger.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisicard *Gufic, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisicostad *Genus, UK.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisidigal *Mibe, Ger.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Lisidigal HCT *Mibe, Ger.; Mibe, Neth.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisidoc *Docpharm, Ger.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Lisifen *Cadila, India.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Lisigamma *Worwag, Cz.†; Worwag, Ger.; Worwag, Rus.; Worwag, Ukr.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Lisigamma HCT *Worwag, Ger.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisihexal *Hexal, Austria; Hexal, Ger.†; Sandoz, Pol.; Sandoz, Ukr.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Lisihexal comb *Hexal, Austria.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisihexal comp *Hexal, Ger.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisiken *Kendrick, Mex.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Lisilet *Megat, Venez.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Lisiletic *Megat, Venez.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

LisiLich comp *Winthrop, Ger.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisim *Sunward, Malaysia.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Lisinace *Alkem, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisinal *Beta, Arg.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Lisinex *XL, Philipp.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Lisinfos *Fabra, Arg.*
Vitamin B substances (p. 2102·3).

Lisino *MSD, Ger.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lisinobell *Bellwether, Austral.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Lisinocomp *Genericon, Austria.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisinol *Cipan, Port.†*
Lisinopril (p. 1420·3).

Lisinomed *Medis, Denm.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Lisinomer *Mibe, Denm.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisinoplus *Pharmacodane, Denm.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisinopril comp *Arcana, Austria; Ratiopharm, Ger.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisinopril HCT *Sandoz, Ger.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisinoratio *Ratiopharm, Pol.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisinospes *Alet, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Lisinostad *Stada, Austria.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisinotens *Stada, Denm.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisinoton *Actavis, Rus.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Lisinoton H *Actavis, Rus.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisinovil *Hexal, Braz.*
Lisinopril (p. 1420·3).

Lisinozide *Novagen, S.Afr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisipin *Cofasa, Venez.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Lisiplus *Aliud, Ger.†; Stada, Ger.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisipril *Hexal, Cz.; Orion, Fin.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Lisipril Comp *Orion, Fin.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisiprol *Richter, Pol.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Lisi-Puren *Actavis, Ger.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Lisi-Puren comp *Actavis, Ger.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisir *Kramer, India; Kopran, Thai.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisiriv *East African, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisitec *Cipla, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisi-Tos *Vannier, Arg.*
Bromhexine (p. 1656·3).
Cough.

Lisitril *Sandoz, Switz.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic microalbuminuria.

Lisitril comp *Sandoz, Switz.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Liskantin *Desitin, Cz.*
Primidone (p. 547·1).
Epilepsy.

Liskonum *GSK, UK.*
Lithium carbonate (p. 427·3).
Mania; bipolar disorder.

Lislo *Sarabhai Piramal, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lismol
Note: this name may be used for preparations of different composition.
Orchid, India.
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Lisnop *Ajanta, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisobac *Sandoz, Mex.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Lisobron *Unipharma, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Lisoclor *Neo Quimica, Braz.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisoder *Laboratorios Chile, Chile.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Lisoderma *Ivax, Arg.*
Sodium acexamate (p. 2427·3); gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Lisoderme *Belfar, Braz.*
⊗Dexamethasone (p. 1630·3).

Lisodinol *Med-One, Gr.*
Lisinopril (p. 1420·3).
Hypertension.

Lisodren *BMS, Braz.*
Mitotane (p. 832·2).
Adrenal cortex cancer; Cushing's syndrome.

Lisodur *AstraZeneca, Austral.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Lisoflu *Sanofi-Aventis, Ital.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Lisolac *Tecnimede, Port.*
Tilactase (p. 2631·2).
Lactose intolerance.

Lisolip *Gap, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lisomucil *Sanofi-Aventis, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Lisomucil Gola *Sanofi-Aventis, Ital.*
Dequalinium chloride (p. 1749·3); enoxolone (p. 54·2).
Mouth and throat disorders.

Lisomucil Tosse Sedativo *Sanofi-Aventis, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Lisomucin *Atral, Port.; Polinac, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus; cough.

Lisomyex *Proel, Gr.*
Fenofibrate (p. 1381·1).

Lisoneurin B12 *Dupomar, Arg.†*
Hydroxocobalamin (p. 2107·3).
Megaloblastic anaemia; peripheral neuropathy.

Lisonid *Plus Pharma, Pol.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Lisonid HCT *Plus Pharma, Pol.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisonin *Sons, Mex.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Lisonorm *Gedeon Richter, Hung.*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Lisopan *Azevedos, Port.*
Paracetamol (p. 115·1).
Pain; fever.

Lisoplus *Vida, Port.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).

Lisopres *Luganskii, Ukr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisopress *Gedeon Richter, Hung.; Medimpex, Irl.; Medimpex, Port.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Lisopress HCT *Gedeon Richter, Hung.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisopril *Neo Quimica, Braz.; Spirig, Switz.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic microalbuminuria.

Lisopril plus *Spirig, Switz.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisopulm *DRD, Gr.*
Ambroxol hydrochloride (p. 1654·3).

Lisoretic *Ipca, Rus.; Pharma Dynamics, S.Afr.; Ipca, Ukr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisoril *Ipca, India; Ipca, Rus.; Ipca, Singapore.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; diabetic nephropathy.

Lisoril-5HT *Ipca, India.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisotec *Sun, India; Julphar, UAE.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lisotiasid *Teva, Ukr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lisotox *Cifarma, Braz.*
Acetylmethionine (p. 1558·2); cynara (p. 2490·3); liver extract (p. 2444·1); choline citrate (p. 2055·2); cyanocobalamin (p. 2107·2).
Liver disorders.

Lisovit *Zenith, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Lisovyr *Elea, Arg.; Mintlab, Chile.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Lisozide *Austell, S.Afr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lispelin *Prati-Donaduzzi, Braz.*
Lansoprazole (p. 1851·3).

Lispor *Medipharm, Chile.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lispril *Rowex, Irl.; Siam Bheasach, Thai.*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; myocardial infarction; hypertension.

Lispril-hydrochlorothiazide *Rowex, Irl.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

List Senny *Leros, Cz.*
Senna (p. 1885·1).
Constipation; bowel evacuation.

Listab *Sotex, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Listaflex *Finadiet, Arg.*
Carisoprodol (p. 2021·3).
Skeletal muscle spasm.

Listaflex Forte *Finadiet, Arg.*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Musculoskeletal pain and spasm.

Listerfluor *Johnson & Johnson, S.Afr.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Listerine
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Canad.
Mouthwash: Cineole (p. 2479·1); thymol (p. 1772·2); menthol (p. 2553·2).
Oral hygiene; dental plaque prophylaxis.

Johnson & Johnson, Chile; Johnson & Johnson, Hong Kong; Johnson & Johnson, Singapore.
⊗Alcohol (p. 1733·1); thymol (p. 1772·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); menthol (p. 2553·2); benzoic acid (p. 1738·2).
Oral hygiene; dental plaque; gingivitis; halitosis.

Johnson & Johnson Consumer, Mex.; Pfizer Consumer, USA.
Thymol (p. 1772·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Oral hygiene; minor mouth and throat irritation.

Johnson & Johnson, NZ.
Benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2).
Oral hygiene.

Pfizer, India.
⊗Benzoic acid (p. 1738·2); alcohol (p. 1733·1); cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2).

Pfizer, Indon.†
⊗Thymol (p. 1772·2); cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); alcohol (p. 1733·1).
Oral hygiene.

Listerine Antiseptic *Johnson & Johnson, S.Afr.*
⊗Thymol (p. 1772·2); alcohol (p. 1733·1).
Mouth and throat infections; gingivitis; dental plaque prophylaxis.

Listerine Antiseptic with Fluoride *Johnson & Johnson, Canad.*
Cineole (p. 2479·1); menthol (p. 2553·2); sodium fluoride (p. 2089·2); thymol (p. 1772·2).

Listerine Antiseptic Mouthwash *Pfizer Consumer, UK.*
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Oral hygiene.

Listerine Antiseptic Tartar Control *Johnson & Johnson, Canad.*
Cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2); zinc chloride (p. 2126·1).
Dental plaque; oral hygiene.

Listerine Bright & Clean *Johnson & Johnson, Singapore.*
⊗Alcohol (p. 1733·1); propyl alcohol (p. 1768·1); poloxamer 407 (p. 2202·1); benzoic acid (p. 1738·2); cineole (p. 2479·1); zinc chloride (p. 2126·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); sodium benzoate (p. 1738·2); menthol (p. 2553·2).
Gingivitis; oral hygiene.

Listerine Citrus Fresh *Johnson & Johnson, NZ.*
Benzoic acid (p. 1738·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); menthol (p. 2553·2).
Oral hygiene.

Listerine Clasico *Interbelle, Arg.*
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Oral hygiene.

Listerine Cool Citrus *Johnson & Johnson, Singapore.*
⊗Alcohol (p. 1733·1); poloxamer 407 (p. 2202·1); benzoic acid (p. 1738·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); menthol (p. 2553·2); sodium benzoate (p. 1738·2).
Gingivitis; oral hygiene.

Listerine Cool Mint
Note: this name may be used for preparations of different composition.
Interbelle, Arg.
Thymol (p. 1772·2); cineole (p. 2479·1); methyl salicylate (p. 92·1).
Oral hygiene.

Johnson & Johnson, Hong Kong.
Thymol (p. 1772·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Halitosis.

Johnson & Johnson, S.Afr.
Thymol (p. 1772·2).
Mouth and throat disorders.

Johnson & Johnson, Singapore.
⊗Alcohol (p. 1733·1); benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); propyl alcohol (p. 1768·1).
Gingivitis; oral hygiene.

Listerine Coolmint
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Philipp.
⊗Benzoic acid (p. 1738·2); alcohol (p. 1733·1); cineole (p. 2479·1); thymol (p. 1772·2); anethole (p. 2443·3); peppermint oil (p. 1877·1); spearmint oil (p. 2621·2).
Mouth disorders; oral hygiene.

Pfizer, Indon.†
⊗Thymol (p. 1772·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); alcohol (p. 1733·1); anethole (p. 2443·3); pluronic; benzoic acid (p. 1738·2); peppermint oil (p. 1877·1); spearmint oil (p. 2621·2).
Oral hygiene.

Listerine Difesa *Johnson & Johnson, Ital.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Listerine Fresh Burst
Note: this name may be used for preparations of different composition.
Interbelle, Arg.
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Oral hygiene.

Johnson & Johnson, Singapore.
⊗Alcohol (p. 1733·1); propyl alcohol (p. 1768·1); benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Gingivitis; oral hygiene.

Listerine Fresh Citrus *Johnson & Johnson, Ital.*
Mint oil (p. 2560·1); thymol (p. 1772·2); cineole (p. 2479·1); birch oil (p. 2457·3).
Oral hygiene.

Johnson & Johnson, Philipp.
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Mouth disorders; oral hygiene.

Listerine Freshburst
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Philipp.
Benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2).
Mouth disorders; oral hygiene.

Johnson & Johnson, S.Afr.
Thymol (p. 1772·2).
Mouth and throat disorders.

Listerine Original *Johnson & Johnson, Philipp.*
⊗Benzoic acid (p. 1738·2); alcohol (p. 1733·1); cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2).
Mouth disorders; oral hygiene.

Listerine protection dents et gencives *Johnson & Johnson, Fr.*
Cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); menthol (p. 2553·2); sodium fluoride (p. 2089·2).
Oral hygiene.

Listerine Stay White *Johnson & Johnson, Fr.*
Cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); menthol (p. 2553·2); zinc chloride (p. 2126·1).
Oral hygiene.

Listerine Tartar Control
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Hong Kong.
⊗Alcohol (p. 1733·1); methyl salicylate (p. 92·1); benzoic acid (p. 1738·2); thymol (p. 1772·2); cineole (p. 2479·1); menthol (p. 2553·2); zinc chloride (p. 2126·1).
Dental plaque; dental tartar; gingivitis; halitosis.

Johnson & Johnson, Ital.
Mint oil (p. 2560·1); thymol (p. 1772·2); cineole (p. 2479·1); birch tar oil (p. 1723·2); zinc chloride (p. 2126·1).
Oral hygiene.

Johnson & Johnson, Philipp.
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2); zinc chloride (p. 2126·1).
Mouth disorders; oral hygiene.

Johnson & Johnson, NZ.†
Benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2); zinc chloride (p. 2126·1).
Oral hygiene.

Johnson & Johnson, Singapore.†
⊗Alcohol (p. 1733·1); propyl alcohol (p. 1768·1); benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); zinc chloride (p. 2126·1).
Gingivitis; oral hygiene.

Listerine Teeth Defence *Johnson & Johnson, NZ.*
Benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2); sodium fluoride (p. 2089·2).
Oral hygiene; dental caries prophylaxis.

Listerine Teeth and Gum Defence *Johnson & Johnson, Hong Kong.*
Methyl salicylate (p. 92·1); benzoic acid (p. 1738·2); thymol (p. 1772·2); cineole (p. 2479·1); menthol (p. 2553·2); sodium fluoride (p. 2089·2).
Dental caries; dental plaque; gingivitis; halitosis.

Listerine Teeth & Gum Defense *Johnson & Johnson, Philipp.*
Benzoic acid (p. 1738·2); cineole (p. 2479·1); thymol (p. 1772·2); sodium fluoride (p. 2089·2).
Mouth disorders; oral hygiene.

Johnson & Johnson, Singapore.
⊗Alcohol (p. 1733·1); benzoic acid (p. 1738·2); cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); sodium fluoride (p. 2089·2); menthol (p. 2553·2); propyl alcohol (p. 1768·1).
Gingivitis; oral hygiene.

Listerine Tooth Defense *Pfizer Consumer, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Listermint
Note: this name may be used for preparations of different composition.
Pfizer Consumer, UK.
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Pfizer, Indon.†
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis; oral hygiene.

Listermint Arctic Fresh *Pfizer, Indon.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Oral hygiene.

Listermint Arctic Mint Mouthwash *Warner-Wellcome, USA.*
⊗Glycerol (p. 2517·2).

Listermint Con Fluor *Pfizer, Chile.†*
⊗Sodium fluoride (p. 2089·2); alcohol (p. 1733·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); eugenol (p. 2501·2).
Dental caries prophylaxis; oral hygiene.

Listermint with Fluoride *Pfizer Consumer, UK.*
Sodium fluoride (p. 2089·2); cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Listn *Ind-Swift, India.*
⊗Potassium nitrate (p. 1766·2); sodium monochlorophosphate.

Listover *Biosynthesis, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Listran *Uriach, Spain.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Listril *Torrent, Braz.; Torrent, India; Torrent, Philipp.; Torrent, Rus.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Listril AM *Torrent, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Listril Plus *Torrent, India; Torrent, Rus.*
⊗Hydrochlorothiazide (p. 1403·2); lisinopril (p. 1420·3).
Hypertension.

Listril-SM *Torrent, India.*
Levamlodipine; lisinopril (p. 1420·3).

Lit-300 *Hua, Thai.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Lita *Intra-Labs, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Litace *Vir, Spain.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Litacor *Korea United, Philipp.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; rescue after high-dose methotrexate; colorectal cancer.

Litacro *Dosa, Arg.*
Tacrolimus (p. 1968·3).

LiTai *Topfond, China.*
Clindamycin phosphate (p. 269·3).

Litak *Orphan, Austral.; Lipomed, Austria; Lipomed, Cz.; Lipomed, Denm.; Lipomed, Fin.; Lipomed, Fr.; Lipomed, Ger.; Lipomed, Gr.; Lipomed, Irl.; Pharmalogic, Israel; Lipomed, Neth.; Lipomed, Norw.; Lipomed, Pol.; Lipomed, Port.; Key Oncologics, S.Afr.; Lipomed, Spain; Lipomed, Swed.; Lipomed, Switz.; Lipomed, UK.*
Cladribine (p. 769·1).
Hairy-cell leukaemia; chronic lymphocytic leukaemia; lymphoproliferative disorders; non-Hodgkin's lymphoma.

Litalgin *Leiras, Fin.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Gastrointestinal, biliary, and renal colic.

Litalir *BMS, Austria; BMS, Cz.; BMS, Ger.; BMS, Hung.; BMS, Philipp.†; BMS, Switz.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; psoriasis; myeloproliferative disorders; polycythaemia vera; thrombocythaemia.

Lita-M *Intra-Labs, India.*
Metformin (p. 489·1); pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Litamin *Christo, Hong Kong.*
Chlordiazepoxide (p. 1044·2).
Anxiety; insomnia; alcoholism; premedication.

Litan *Welman, China.*
Amoxicillin sodium (p. 216·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Litares *Aspen, S.Afr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Litarex *Actavis, Denm.; Alpharma, Neth.†; Actavis, Switz.*
Lithium citrate (p. 427·3).
Bipolar disorder; mania; depression.

Litcal *Little Greave, India.*
Syrup: Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); lysine (p. 2079·3); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1).
Little Greave, India.
Tablets: Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Litcal Forte *Little Greave, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); magnesium (p. 1786·3); zinc (p. 2126·1).

Litcoff *Little Greave, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Litcoff-DM *Little Greave, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

Litcoff-P *Little Greave, India.*
⊗Ambroxol (p. 1654·3); guaifénesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Litec *Novartis, Philipp.*
Pizotifen malate (p. 678·2).
Anorexia; depression.

Liten *Bosnalijek, Rus.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Liten H *Bosnalijek, Rus.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Literate *Hauz, India.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc gluconate (p. 2126·2).

Literate-CT *Hauz, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); zinc sulfate (p. 2126·2).

Lite-Up *Agio, India.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Hyperpigmented skin disorders.

Lithane *Erfa, Canad.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Litheum *Valdecasas, Mex.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Lithiagel *Marx, Fr.*
Basic aluminium carbonate (p. 1817·1).
Hyperphosphataemia.

Lithias-cyl L Ho-Len-Complex *Liebermann, Ger.*
Belladonna (p. 2453·3); berberis (p. 2502·1); carduus marianus (p. 1561·1); colocynthis (p. 1833·3); magnesium phosphoricum (p. 1787·3).
Homoeopathic preparation.

Lithicarb *Aspen, Austral.; Pacific, Hong Kong; Mylan, NZ.*
Lithium carbonate (p. 427·3).
Bipolar disorder; schizophrenia; depression; mania.

Lithimole *Cooper (Κοπερ), Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Lithines du Dr Gustin *Bio-Sante, Canad.†*
Sodium carbonate anhydrous (p. 2617·3); sodium chloride (p. 1795·1); dibasic sodium phosphate (p. 1791·2); sodium sulfate (p. 1888·1); tartaric acid (p. 2626·1).

Lithioderm *Labcatal, Fr.*
Lithium gluconate (p. 427·3).
Seborrhoeic dermatitis.

Lithiofor *Vifor, Ger.; Nikolakopoulos (Νικολακοπουλος), Gr.; Vifor, Hong Kong; Vifor, Switz.*
Lithium sulfate (p. 427·3).
Mania; bipolar disorder; depression; premenstrual syndrome; psychoses.

Lithionit *AstraZeneca, Norw.; AstraZeneca, Swed.*
Lithium sulfate (p. 427·3).
Bipolar disorder; mania.

Lithiorsan *Plata, Arg.†*
Thiomersal (p. 1771·3).
Antiseptic.

Lithiumeel *Ebi, Switz.*
Lithium carbonicum (p. 427·3); colchicum autumnale; ferrum phosphoricum (p. 2077·1); natrium carbonicum (p. 2617·3); strychnos nux vomica (p. 2573·3); toxicodendron quercifolium (p. 2603·3).
Homoeopathic preparation.

Lithiun *Elisium, Arg.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Lithobid *Noven, USA.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Lithocap *Intas, India.*
Lithium.
Bipolar disorder; mania; depression.

Lithocent *Crescent, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression.

Lithofalk *Falk, Ger.†; Galenica, Gr.*
Chenodeoxycholic acid (p. 2475·1); ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones.

Lithonate *Approved Prescription Services, UK.*
Lithium carbonate (p. 427·3).
Mania; bipolar disorder; depression.

Lithopik *Aarpik, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression.

Lithoril *Reliance, India.*
Lithium.
Bipolar disorder; mania; depression.

Lithostat *Mission Pharmacal, USA.*
Acetohydroxamic acid (p. 2427·1).
Adjunct in urinary-tract infection with urea-splitting organisms.

Lithosun *Sun, India.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression.

Lithuril *Kocak, Turk.*
Lithium carbonate (p. 427·3).
Mania; bipolar disorder; depression; behaviour disorders.

Lithus *Taurus, India.*
Lithium.
Bipolar disorder; mania; depression.

Litican *Sanofi-Aventis, Belg.; Sanofi-Aventis, Neth.*
Alizapride hydrochloride (p. 1815·2).
Nausea; vomiting.

Liticarb *Parma, Hung.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Litiset *Diba, Mex.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); aluminium subacetate (p. 2440·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Lit-King *Bestochem, India.*
Paracetamol (p. 115·1).
Pain; fever.

Litnim *Little Greave, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Lito *Orion, Fin.*
Lithium carbonate (p. 427·3).
Bipolar disorder.

Litocid *Labor, Pol.*
Potassium citrate (p. 1780·3).
Urinary alkalinisation.

Litocit *Apsen, Braz.*
Potassium citrate (p. 1780·3).
Renal calculi.

Litoff *Caber, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Litom *Little Greave, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Litom-D *Little Greave, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Litomik *Little Greave, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Liton *Zota, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Litonac-MR *Little Greave, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Litonac-P *Little Greave, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Litonac-SP *Little Greave, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Litonate *Biotech, Venez.*
Centella (p. 1698·3).
Burns; ulcers; wounds.

LiTong *Sailike, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Liton-Z *Zota, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Litorva *Dexcel, Israel.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Litostop *Terapeutico, Ital.*
Potassium citrate (p. 1780·3); magnesium citrate (p. 1857·1); fructose (p. 2068·2); maltodextrin (p. 2080·3); bearberry (p. 2453·2); couch-grass (p. 2487·2); cranberry (p. 2488·1); phyllanthus.
Urinary-tract disorders.

LitoZin *Lane, UK.*
Rose fruit extract (p. 2607·1).
Joint disorders.

Litrecan *Rivero, Arg.*
Linezolid (p. 317·3).
Methicillin-resistant and vancomycin-resistant Gram-positive bacterial infections.

Litron *Little Greave, India.*
Capsules: Iron carbonyl (p. 2073·1); vitamin C (p. 2110·3); zinc (p. 2126·1).

Little Greave, India.
Injection: Iron sucrose (p. 2078·1).

Little Greave, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Litron-XT *Little Greave, India.*
Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Litropina *Quim-Far, Venez.*
Homatropine methylbromide (p. 2007·3).
Gastrointestinal spasm.

Litspas *Dr Alson, India.*
Simeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2).

Little Colds Cough Formula *Vetco, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Little Colds Decongestant Plus Cough *Prestige, Canad.; Medtech, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Little Colds Multi-Symptom Cold Formula *Prestige, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Little Friend *NBTY, Ukr.†*
Vitamins; ferrous fumarate (p. 2060·3).
Dietary supplement.

Little Noses Decongestant *Prestige, Canad.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Little Tummys Gas Relief *Prestige, Canad.*
Simeticone (p. 1886·2).

Little Tummys Laxative *Vetco, USA.*
Sennosides (p. 1885·2).
Constipation.

Littlekof-DM *Biological E, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylpropanolamine hydrochloride (p. 1674·1).

Little's Chloral Syrup Paed *Little, Singapore.*
Cloral hydrate (p. 1055·2).
Sedative.

Littmox *Littman, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Litursol *Crinos, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Litusix *Dollder, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Litusix Compositum *Dollder, Venez.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol (p. 1207·2).
Respiratory-tract congestion.

Litzyme *Little Greave, India.*
Caraway oil (p. 2470·3); cardamom oil (p. 2471·1); cinnamon oil (p. 2479·3); amylase (p. 2442·1).

Liu Pu An *Kangbao, China.*
Glucosamine sulfate potassium (p. 2515·3).
Osteoarthritis.

Liv 52 *Ebi, Switz.*
Capparis spinosa; chicory (p. 2475·2); solanum nigrum; senna occidentalis; arjuna (p. 2447·2); achillea (p. 2427·3); tamarix gallica; ferrum bhasma.
Gastrointestinal disorders; tonic.

Himalaya Drug, Pol.
Achillea (p. 2427·3); capparis spinosa; cassia occidentalis; chicory (p. 2475·2); mandur bhasma calx; black nightshade (p. 2458·2); tamarix gallica; arjuna (p. 2447·2).
Liver poisoning; tonic.

Himalaya, Rus.; Himalaya, Singapore.
Oral drops: syrup: Capparis spinosa; chicory (p. 2475·2); black nightshade (p. 2458·2); arjuna (p. 2447·2); cassia occidentalis; achillea (p. 2427·3); tamarix gallica.
Liver disorders.

Himalaya Herbal, India.
Achillea (p. 2427·3); capparis spinosa.
Liver disorders.

Himalaya, Rus.; Himalaya, Ukr.
Capparis spinosa; chicory (p. 2475·2); black nightshade (p. 2458·2); arjuna (p. 2447·2); cassia occidentalis; achillea (p. 2427·3); tamarix gallica; ferric oxide (p. 2186·1).
Liver disorders; liver and biliary-tract disorders.

Himalaya, Singapore.
Tablets: Capparis spinosa; chicory (p. 2475·2); mandur bhasma; solanum nigrum (p. 2458·2); arjuna (p. 2447·2); cassia occidentalis; achillea (p. 2427·3); tamarix gallica.
Liver disorders.

Livage *Aristo, India.*
Lecithin (p. 2542·2).
Formerly contained lecithin, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine and phosphatidyl inositol.
Liver disorders.

Livalo *Kowa, China; Kowa, Jpn; Kowa, Thai.; Kowa, USA.*
Pitavastatin calcium (p. 1471·1).
Hypercholesterolaemia; hyperlipidaemias.

Livamin *Sanbe, Indon.*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition in liver disorders.

Livamine *Bioceuticals, UK.*
Vitamins; minerals.

Livari *Diba, Mex.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Livarol *Nizhfarm, Ukr.*
Ketoconazole (p. 585·3).
Fugal infections of the vagina.

Livarole *Nizpharm, Rus.*
Ketoconazole (p. 585·3).
Fungal vaginal infections.

Livasa *Ind-Swift, India.*
Capsules: Andrographis (p. 2443·2); milk thistle (p. 1561·1); phyllanthus niruri (p. 2590·1); piper longum.

Ind-Swift, India.
Syrup: Andrographis (p. 2443·2); punarnava (p. 2601·1); milk thistle (p. 1561·1); phyllanthus niruri (p. 2590·1); piper nigrum; terminalia chebula (p. 2474·3).

Livat-DS *Rose, India.*
Tricholine citrate (p. 2055·2).

Livazo *Kowa, Irl.; Kowa, Neth.; Recordati, Spain; Recordati, Ukr.*
Pitavastatin calcium (p. 1471·1).
Hypercholesterolaemia; hyperlipidaemias.

Livbel *Blubell, India.*
Capsules: Vitamin B substances (p. 2102·3); ornithine aspartate (p. 2085·2); silymarin (p. 1561·2).

Blubell, India.
Syrup: Vitamin B substances (p. 2102·3); silymarin (p. 1561·2).

Livbest *Abbott, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livbest-AM *Abbott, India.*
Ambroxol (p. 1654·3); levofloxacin (p. 315·3).

Livbid *Scoshia, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

LivCo *Mediherb, Austral.*
Schisandra (p. 2611·2); rosemary leaf (p. 2607·2); milk thistle (p. 1561·1).
Liver disorders.

Livel *Pro-Pharma, Ukr.*
Ribavirin (p. 1010·2).
Hepatitis C.

Livellin *Gedeon Richter, Cz.; Gedeon Richter, Hung.†*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Livelong *BMW, India.*
Preparation for enteral nutrition.

Livensa *Warner Chilcott, Cz.†; Procter & Gamble, Irl.†; Procter & Gamble, Neth.†; Procter & Gamble, Pol.†; Procter & Gamble, Port.†*
⊗Testosterone (p. 2305·1).
Sexual hypoactivity following oophorectomy and hysterectomy.

Liventiale *Scan Biotech, Ukr.†*
Soya phospholipids (p. 2092·3).
Liver disorders.

Livenza *Velka, Gr.*
Vincamine (p. 2645·2).

Liver Detox *Cenovis, Austral.*
Bupleurum; taraxacum (p. 2625·3); camellia sinensis (p. 2648·2); cynara (p. 2490·3); milk thistle (p. 1561·1); schisandra (p. 2611·2); taurine (p. 2626·2).
Liver disorders; digestive disorders.

Liver Plus *XL, Philipp.*
Silymarin (p. 1561·2).
Dietary supplement.

Liver Tonic Complex *Golden Glow, Austral.*
Milk thistle (p. 1561·1); cynara (p. 2490·3); schisandra (p. 2611·2); taraxacum (p. 2625·3); taurine (p. 2626·2).
Liver disorders.

Liveraide *Herbs & Nature, Philipp.*
Silymarin (p. 1561·2).
Nutritional supplement.

Livercare *Darya-Varia, Indon.*
Silibinin (p. 1561·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).
Liver disorders.

Liveril *Meyer, India.*
Choline bitartrate (p. 2055·2) ubidecarenone (p. 2637·1); vitamins; minerals; amino acids; silymarin (p. 1561·2).

Liverin *Pharmasant, Thai.*
Silymarin (p. 1561·2).
Liver disorders.

Liverine *Crisdy-Na, Philipp.*
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3); lecithin (p. 2542·2).
Liver disorders.

Live-Rite *Liverite, Canad.*
Choline bitartrate (p. 2055·2); inositol (p. 2533·2); vitamin B_{12} (p. 2107·2).

Livermate *Interchemex, Philipp.*
Silymarin (p. 1561·2).
Liver disorders.

Livermin *Korean Ginseng, Philipp.*
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3); palm oil (p. 2200·2); beeswax (p. 2170·2); soybean oil (p. 2092·3).
Liver disorders.

Liverpro *EuroHealth, Philipp.*
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).
Dietary supplement.

Liverton
Note: this name may be used for preparations of different composition.
Metrolink, Philipp.
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).
Liver disorders.

SIFFRA, Ital.
Vitamins; minerals; lactoferrin (p. 2539·3); desmodium adscendens; milk thistle (p. 1561·1); *Lactobacillus paracasei* (p. 2596·3).
Liver disorders.

Li-Verve *Cratus, India.*
Andrographis (p. 2443·2); punarnava (p. 2601·1); phyllanthus niruri (p. 2590·1).

Liver-Vite *Bioglan, Austral.†*
Milk thistle (p. 1561·1).
Liver disorders.

Livestar *Gentech, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livetan *Schwabe, Port.*
Valerian (p. 2640·2).
Insomnia; nervousness.

LiveTan DM *Centurion, USA.†*
Dextromethorphan tannate (p. 1660·1); diphenhydramine tannate (p. 626·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Livfit *Garuda, Hung.*
Tephrosia purpurea; chicory (p. 2475·2); eclipta alba; phyllanthus niruri (p. 2590·1); tinospora cordifolia; chebulic myrobalan (p. 2474·3); fumitory (p. 2508·2); andrographis (p. 2443·2); picrorhiza kurroa (p. 2590·2).
Liver disorders.

LIV-Gamma *SK, Thai.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; passive immunisation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome.

Liv-Gd *Natures Sunshine, Canad.*
Betacarotene (p. 2051·1); choline bitartrate (p. 2055·2); inositol (p. 2533·2); ferrous fumarate (p. 2060·3); vitamin C (p. 2110·3).

Natures Sunshine, Canad.
Betacarotene (p. 2051·1); choline bitartrate (p. 2055·2); inositol (p. 2533·2); ferrous gluconate (p. 2061·2); vitamin C (p. 2110·3).

Livguard *CCM, Malaysia.*
Soya lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement.

Livial *MSD, Austral.; Organon, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; MSD, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Organon, India; Schering-Plough, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; Schering-Plough, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK; Organon, Ukr.; Organon, Venez.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Livianne *Bago, Arg.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Liviel *Organon, Austria.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Liviella *MSD, Ger.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Livifem *Adcock Ingram, S.Afr.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Livifol *Biosintex, Arg.*
Folic acid (p. 2063·1).
Anaemias.

Livimex *Kowa, Jpn.*
⊗Prednisolone valeroacetate (p. 1645·2).
Skin disorders.

Livintact *Panjon, India.*
Lecithin (p. 2542·2).
Liver disorders.

Livintact-EV *Panjon, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Livipark *Sandoz, Braz.*
Pramipexole (p. 911·2).

Livipids *Delfi, Singapore.*
Phospholipids (p. 2201·2); vitamin B substances (p. 2102·3).

Livit *Affy, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Liviton *Adcock Ingram, S.Afr.*
Vitamins; minerals; caffeine (p. 1203·3); liver extract (p. 2444·1).
Tonic.

Livitrinsic-f *Goldline, USA.†*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); intrinsic factor (p. 2534·2); vitamin B_{12} substances (p. 2107·2). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Livobion *Pharma Synth, India.*
Capsules: Choline bitartrate (p. 2055·2); vitamin B substances (p. 2102·3); vitamin E acetate (p. 2119·2); lysine hydrochloride (p. 2079·3); DL-methionine (p. 1558·2).
Liver disorders.

Pharma Synth, India.
Syrup: Choline chloride (p. 2055·2); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3); DL-methionine (p. 1558·2).
Liver disorders.

Livocab *McNeil, Ger.; Janssen-Cilag, Ital.†; Janssen-Cilag, Neth.; Janssen-Cilag, Spain.†*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis; allergic rhinitis.

Livocab direkt mit Beclometason *McNeil, Ger.†*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Livocin *Nitin, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livocip *Cipla, India.*
Tricholine citrate (p. 2055·2); sorbitol (p. 2092·1).

Livodex *Ikon, India.*
Tricholine citrate (p. 2055·2).

Livogen *GSK, India.*
Syrup: Liver (p. 2444·1); yeast; vitamin B_1 (p. 2103·1); nicotinic acid (p. 2083·1).
Tonic.

Livogen Captab *Merck, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Anaemias.

Livogen Hemtonic *Merck, India.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1).
Anaemias.

Livogen-XT *Merck, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc sulfate (p. 2126·2).

Livogen-Z *Merck, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Anaemias.

Livokind *Mankind, India.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; primary biliary cirrhosis.

Livola *Landson, Indon.*
Ornithine aspartate (p. 2085·2).
Hyperammonaemia.

Livolin *Mega Lifesciences, Malaysia.*
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Mega Lifesciences, Philipp.
Vitamin B substances (p. 2102·3); *dl*-alpha tocoferil acetate (p. 2119·2); phosphatidyl choline (p. 2588·3).
Liver disorders.

Mega, Rus.
Vitamins; lecithin (p. 2542·2).
Liver disorders.

Mega WeCare, Singapore.
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); vitamin E acetate (p. 2119·2).
Liver disorders.

Livolin Forte *Mega Lifesciences, Ukr.*
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); tocoferil acetate (p. 2119·2).
Liver disorders; toxaemia of pregnancy; radiation syndrome; psoriasis.

Livolon *Biolab Sanus, Braz.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Livoluk *Panacea, India.*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Livoluk-PB *Panacea, Rus.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; salmonella enteritis.

Livomarin *Varifarma, Arg.*
Conjugated oestrogens (p. 2260·1).

Livomedrox *Varifarma, Arg.*
Medroxyprogesterone (p. 2288·1).

Livomonil *Varifarma, Arg.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Livomyn *Charak, India.*
Oral drops: Malabar nut (p. 2549·1); andrographis (p. 2443·2); Indian barberry (p. 2532·1); punarnava (p. 2601·1); coriander (p. 2486·3); zingiber officinale.

Charak, India.
Syrup; tablets: Malabar nut (p. 2549·1); aloes (p. 1816·1); andrographis (p. 2443·2); Indian barberry (p. 2532·1); punarnava (p. 2601·1); coriander (p. 2486·3); zingiber officinale.

Livoncel *Catalent, Philipp.*
Vitamins; minerals.

Livonorm *Delta Medical, Ukr.*
Milk thistle (p. 1561·1); vitamins; acetylcysteine (p. 1652·2); thioctic acid (p. 2629·1); zinc (p. 2126·1); selenium (p. 2086·3).
Liver disorders; pancreatic disorders.

Livopan *AGA, Denm.; AGA, Fin.; Linde Gas, Ger.; AGA, Swed.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Pain.

Livopill *Ordain, India.*
Folic acid (p. 2063·1); metadoxine (p. 2105·3); ornithine (p. 2085·2); pyridoxine (p. 2105·3); silymarin (p. 1561·2); thiamine (p. 2102·3).

Livoric *Syntro, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livornex *Genepharm, Gr.*
Niflumic acid (p. 101·2).

Livosil *Centaur, India.*
Silymarin (p. 1561·2).
Liver disorders.

Livosil-B *Centaur, India.*
Silymarin (p. 1561·2); thiamine nitrate (p. 2103·2); riboflavin (p. 2104·3); pyridoxine (p. 2105·3); nicotinamide (p. 2083·1); pantothenic acid (p. 2085·2); vitamin B_{12} (p. 2107·2).
Liver disorders.

Livosil-H *Centaur, India.*
Andrographis (p. 2443·2); liquorice (p. 1853·2); phyllanthus niruri (p. 2590·1); piper longum; zingiber officinale.
Liver disorders; reduced appetite; dyspepsia.

Livostin *Johnson & Johnson, Austral.; Janssen-Cilag, Austria; Johnson & Johnson Consumer, Belg.; Novartis, Braz.; Janssen, Canad.; Novartis, Canad.; Janssen-Cilag, Chile†; Johnson & Johnson, China; McNeil, Cz.; McNeil, Denm.†; McNeil, Fin.; Johnson & Johnson, Gr.; Janssen-Cilag, Israel; Johnson & Johnson, Ital.; Janssen, Jpn; Janssen-Cilag, Mex.; McNeil, Norw.; Janssen-Cilag, NZ; Johnson & Johnson, Port.; Janssen-Cilag, S.Afr.; McNeil, Swed.; Janssen-Cilag, Switz.; Novartis, Turk.†; Janssen-Cilag, Venez.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis; allergic rhinitis.

Livostor *KVZ, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Livota *Zota, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livot-MD *Trumac, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Livotone *East India Pharma, India.*
Andrographis (p. 2443·2); bile salts (p. 2457·2); cascara (p. 1826·1).

Livoven *Vensat, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livovid *Hovid, Malaysia.*
Lecithin (p. 2542·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement in liver disorders.

Livox *Zee, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Livpron *Willow, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Livren *Omega, Spain.†*
St John's wort (p. 449·1).
Asthenia.

Liv-Shreyas *Curewell, India.*
Liquorice (p. 1853·2).

Livten *Ativus, Braz.*
Polyunsaturated fatty acids.
Dietary supplement.

Livten Vit *Ativus, Braz.*
Vitamin B_6 (p. 2105·3); betacarotene (p. 2051·1); vitamin C (p. 2110·3); magnesium (p. 1786·3); borage oil (p. 2459·2).

Livto *Zimalaya, India.*
Achyranthes aspera; andrographis (p. 2443·2); Indian barberry (p. 2532·1); punarnava (p. 2601·1).

Livton Complex *Integria, Austral.*
Milk thistle (p. 1561·1); taraxacum (p. 2625·3); cynara (p. 2490·3); bupleurum; chionanthus virginica.
Liver disorders.

Livtop *Comed, India.*
⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Livzon Ganle *Livzon, China.*
⊗Terfenadine (p. 640·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Livzonphin *Livzon, China.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

LiWei *Ya Bao, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

LiWeiEr *Qi Li, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Lixacol *Tillotts, Denm.†; Tillotts, Spain.*
Mesalazine (p. 1859·2).
Ulcerative colitis; Crohn's disease.

Lixamide *Cipla-Medpro, S.Afr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Lixben *Alter, Spain.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Lixi *Biotech, Venez.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; subendocardial fibroelastosis.

Lixiana *Daiichi Sankyo, Jpn.*
Edoxaban tosilate (p. 1370·3).
Thromboembolism prophylaxis after orthopaedic surgery.

Lixiangzhu *Tong Ji Xian Dai, China.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency.

Lixiding *Lijun, China.*
Urapidil (p. 1520·2) or urapidil hydrochloride (p. 1520·2).
Hypertension.

Lixidol *Roche, Ital.*
Ketorolac trometamol (p. 80·2).
Pain.

Lixir *Abigo, Swed.*
Vitamins; caffeine (p. 1203·3).

Lixitin *Tecnofarma, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Lixocam *Med-One, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Lixtress *Pharmacare, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Liyurto *Sanify, India.*
Andrographis (p. 2443·2); punarnava (p. 2601·1); fennel (p. 2503·2); terminalia chebula (p. 2474·3).

Liz *Dey's, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Liza *Ind-Swift, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lizace *Candor, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Liza-D *Ind-Swift, India.*
Lansoprazole (p. 1851·3); domperidone (p. 1838·1).

Lizak *Farmak, Ukr.*
Muramidase hydrochloride (p. 2565·1); dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Lizam *Gedeon Richter, Neth.*
Lisinopril (p. 1420·3); amlodipine besilate (p. 1304·1).
Hypertension.

Lizamox-D *Elisa, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Lizan *Nobel, Turk.*
Diazepam (p. 1063·2).
Anxiety; insomnia; alcohol withdrawal syndrome; status epilepticus; febrile convulsions; muscle spasm; premedication.

Lizarona *Northia, Arg.*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Lizavan *Bangkok Lab & Cosmetic, Thai.*
Lorazepam (p. 1080·3).

Lizbid *Abbott, India.*
Linezolid (p. 317·3).
Bacterial infections.

Lizemox *Molekule, India.*
Linezolid (p. 317·3).
Bacterial infections.

Lizepat *Cosmopharm, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Lizhining *Changzheng-Xinkai, China.*
Etamsylate (p. 1145·2).
Haemorrhage.

Lizhishu *Hayao, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Lizhixue *C & O, China.*
Somatostatin (p. 1930·3).
Gastrointestinal haemorrhage; diabetic ketoacidosis; fistulae; prevention of complications following pancreatic surgery.

Lizhu Changle *Livzon, China.*
Bifidobacterium adolescens.
Restoration of gastrointestinal flora.

Lizhu Dele *Livzon, China.*
Bismuth potassium citrate.
Gastric hyperacidity; gastritis; peptic ulcer.

Lizhu Huanming *Livzon, China.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; auto-immune disorders.

Lizhu Qiangpai *Livzon, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Lizhu Qile *Livzon, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Lizhu Ruixin *Livzon, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Lizhu Saile *Livzon, China.*
Amino acids; low molecular weight peptides.
Brain injury; mental function impairment.

Lizhu Weike *Livzon, China.*
Valsartan (p. 1521·2).
Hypertension.

Lizhu Yindefu *Livzon, China.*
Interferon gamma (human, recombinant) (p. 999·1).
Rheumatoid arthritis; myelodysplastic syndrome; eczema.

Lizhufeng *Livzon, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Lizhukele *Livzon, China.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Lizhuling *Livzon, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lizhuwei *Livzon, China.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Lizhuxing *Livzon, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Lizidra *Jubilant, Ital.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Lizik *Aksu, Turk.*
⊗Furosemide (p. 1387·1).
Oedema.

Lizine *Akums, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lizinna *Morningside, UK.*
Ethinylestradiol (p. 2275·3); norgestimate (p. 2295·3).
Combined oral contraceptive.

Lizipadol *Boehringer Ingelheim, Spain.*
Ambroxol hydrochloride (p. 1654·3).
Sore throat.

Lizipaina *Boehringer Ingelheim, Spain.*
⊗Bacitracin (p. 225·3); muramidase (p. 2565·1); papain (p. 2582·3).
Mouth and throat inflammation.

Liz-M *Dey's, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Lizocalcio *SJA, Gr.*
Calcium folinate (p. 2066·3).
Reduction of folic acid antagonist toxicity.

Lizoforce *Mankind, India.*
Linezolid (p. 317·3).
Bacterial infections.

Lizolid *Glenmark, India.*
Linezolid (p. 317·3).
Bacterial infections.

Lizolorol *Ratiopharm, Denm.†*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Lizomed *Aglowmed, India.*
Linezolid (p. 317·3).
Bacterial infections.

Lizor *Pharos, Indon.*
Cefprozil (p. 248·2).
Bacterial infections.

Lizorolol *Ratiopharm, Neth.*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Lizovag *Novag, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Lizro *Novagen, S.Afr.*
Lisinopril (p. 1420·3).

Lizzy *Sandoz, Braz.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).

L-Kon *Laksun, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Llanol *Medifarma, Indon.†; Therapharma, Philipp.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Llanten *Ximena Polanco, Chile.†*
Plantago major (p. 2592·3).
Homoeopathic preparation.

Lloyd's Cream *Thornton & Ross, UK.*
Diethylamine salicylate (p. 51·3).
Musculoskeletal and soft-tissue disorders.

L-Lysini Aescinas *Arterium, Ukr.†*
L-lysine aescinate.
Oedema.

LM6 *AF, Mex.*
Tablets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.
Carnot, Mex.
Oral solution: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Fever; hypersensitivity; pain.

LM Dextran *Euro-Med, Philipp.*
⊗Dextran 40 (p. 1138·1).
Shock; thromboembolism prophylaxis.

L-Mato *Daffohils, India.*
Lycopene (p. 2546·2); vitamins; minerals.

LMD
Note: this name may be used for preparations of different composition.
Hospira, Canad.
⊗Dextran (p. 1138·3) in sodium chloride.
Mead Johnson, Fr.
Food for special diets.
Disorders of leucine metabolism.

L-Methyl-B6-B12 *Virtus, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).
Dietary supplement.

L-Methyl-MC *Virtus, USA.*
Vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).
Dietary supplement.

LMG *Yacca, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

L-Montus *Fourrts, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast sodium (p. 1214·3).

LMTHF/Pyridoxine HCl/Cyanocobalamin *Zerxis, USA.*
Calcium methylfolate (p. 2053·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

LMWX *Abbott, India.*
Enoxaparin (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

L-M-X *Sebela, USA.*
Lidocaine (p. 1988·1).
Anorectal disorders; topical anaesthesia.

LMX *Cadila, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

LMX4 *Ferndale, UK.*
Lidocaine (p. 1988·1).
Local anaesthesia.

LMX 4 *Eurolab, Arg.*
Lidocaine (p. 1988·1).
Local anaesthesia.

LMX Forte *Cadila, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

L-Nit *Q Check, India.*
Thioctic acid (p. 2629·1); vitamins; trace elements; acetylcysteine (p. 1652·2); levocarnitine (p. 2053·2); lycopene (p. 2546·2).

Lo *East West, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lo Loestrin Fe *Warner Chilcott, USA.*
24 Tablets, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 2 tablets, ethinylestradiol; 2 tablets, inert.
Biphasic oral contraceptive.

Lo Minastrin Fe *Warner Chilcott, USA.*
24 Tablets, ethinylestradiol (p. 2275·3); norethisterone acetate (p. 2294·3); 2 tablets, ethinylestradiol; 2 tablets, ferrous fumarate (p. 2060·3).
Sequential oral contraceptive.

Lo-Acid *Be-Tabs, S.Afr.†*
Simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Antacid; flatulence.

Loar-H *Baroda, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lo-Asomex *Actavis, Ukr.*
Levamlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; angina pectoris.

Loavel *Sanofi-Aventis, Irl.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction.

Lobac
Note: this name may be used for preparations of different composition.
Seatrace, USA.†
Salicylamide (p. 129·2); phenyltoloxamine (p. 638·1); paracetamol (p. 115·1).
Musculoskeletal pain.

Lobacin *TO-Chemicals, Thai.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Lobafen *IAE, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Lobain *DWD, India.*
Dextropropoxyphene hydrochloride (p. 43·3); ibuprofen (p. 68·2).
Pain; inflammation.

Lobak
Note: this name may be used for preparations of different composition.
Geno, India.
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Lobamine-Cystéine *Pierre Fabre, Fr.*
Methionine (p. 1558·2); cysteine hydrochloride (p. 2058·3).
Alopecia.

Lobana *Ulmer, USA.*
Soap-free skin cleanser.

Lobana Body *Ulmer, USA.*
Emollient and moisturiser.

Lobana Derm-Aide *Ulmer, USA.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Skin disorders.

Lobana Peri-Garde *Ulmer, USA.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1); chloroxylenol (p. 1748·2).
Skin disorders.

Lobarr *Pliva, Denm.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Lobate *Piramal, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Lobate-G *Piramal, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Lobate-GM *Piramal, India.*
⊗Clobetasol propionate (p. 1627·1); neomycin sulfate (p. 330·1); miconazole nitrate (p. 589·1).
Formerly contained clobetasol propionate, miconazole nitrate, and gentamicin sulfate.
Infected skin disorders.

Lobate-GN *Abbott, India.*
⊗Clobetasol propionate (p. 1627·1); neomycin sulfate (p. 330·1).

Lobate-M *Nicholas Piramal, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Lobate-S *Abbott, India.*
⊗Clobetasol propionate (p. 1627·1); lactic acid (p. 2539·1); salicylic acid (p. 1719·1); urea (p. 1727·3).

Lobazam *Sun, India.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Lobelia comp *Weleda, Ger.*
⊗Lobelia inflata (p. 2323·2); plumbum metallicum (p. 2541·3); quercus (p. 2574·1); veronica officinalis.
Homoeopathic preparation.

Lobelia Complexe No 74 *Lehning, Fr.†*
⊗Lobelia (p. 2323·2); hyoscyamus (p. 2530·2); stramonium (p. 2622·3); cuprum aceticum (p. 2486·2); ignatia (p. 2532·1).
Homoeopathic preparation.

Lobelia Med Complex *Dynamit, Austria.*
⊗Aconitum (p. 2428·3); ambra (p. 2440·3); lobelia (p. 2323·2); natrium sulfuricum (p. 1888·1).
Homoeopathic preparation.

Lobelina *Bio-Health, UK.*
⊗Lobelia (p. 2323·2).
Cough; upper respiratory-tract congestion.

Lobelo *Alapis, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Lobem *Eczacibasi, Turk.*
Moclobemide (p. 437·2).
Depression; social phobia.

Loben *Bennett, Gr.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Loben Plus *Bennett, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lobesol *Cure Quick, India; Sunward, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Lobet *Samarth, India.*
⊗Labetalol or labetalol hydrochloride (p. 1416·2).
Hypertension; controlled hypotension in anaesthesia.

Lobeta *Betapharm, Ger.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lobevat *Stiefel, Mex.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Lobibeta *Alet, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Lobiretic *Menarini, Neth.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol hydrochloride (p. 1444·2).
Hypertension.

Lobivon *Europharma, Denm.; Menarini, Gr.; Menarini, Ital.; Menarini, Neth.; Menarini, Spain.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Lobivon Plus *Menarini, Spain.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lobivon-Plus *Menarini, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lobu *Ohara, Jpn.*
Loxoprofen sodium (p. 83·3).
Inflammation; pain.

Locabase *Pierre Fabre, Fr.†*
Basis for topical preparations.

Locabiosol *Servier, Austria; Stada, Ger.; Servier, Port.*
Fusafungine (p. 302·1).
Upper respiratory-tract infection and inflammation.

Locabiotal
Note: this name may be used for preparations of different composition.
Servier, Belg.; Servier, Braz.; Servier, Gr.; Servier, Irl.; Stroder, Ital.; Servier, Malaysia; Servier, Philipp.†; Servier, S.Afr.†; Servier, Switz.; Servier, Turk.
Fusafungine (p. 302·1).
Upper respiratory-tract infection and inflammation.
Servier, Fr.
Peppermint oil (p. 1877·1).
Respiratory-tract disorders.

Locacid *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.; Pierre Fabre Dermatologie, Fr.; Pierre Fabre, Israel; Pierre Fabre Dermatologie, Pol.; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, Rus.*
Tretinoin (p. 1725·2).
Acne; keratinisation disorders; psoriasis.

Locacorten *Riemser, Ger.; Novartis, Gr.; Amdipharm, Neth.; Pro Concepta, Switz.*
⊗Flumetasone pivalate (p. 1635·2).
Skin disorders.

Locacorten with Neomycin *Novartis, Gr.*
⊗Flumetasone pivalate (p. 1635·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Locacorten Tar *Novartis, Gr.*
⊗Flumetasone pivalate (p. 1635·2); coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Skin disorders.

Locacorten Vioform *Link, Austral.; Paladin, Canad.; Amdipharm, Denm.; Amdipharm, Fin.; Riemser, Ger.; Novartis, Gr.; Amdipharm, Neth.; AFT, NZ; Novartis, S. Afr.; Amdipharm, Swed.*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Otitis externa; infected skin disorders.

Locacortene *Pharma Logistics, Belg.*
⊗Flumetasone pivalate (p. 1635·2).
Skin disorders.

Locacortene Vioform *Novartis, Turk.*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Infected skin disorders.

Locacortène Vioforme *Genopharm, Fr.†*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Infected skin disorders.

Localin *Fischer, Israel.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

LoCalnesium-C *MedChem, USA.*
Vitamin C (p. 2110·3); calcium (p. 1783·1); magnesium (p. 1786·3).
Dietary supplement.

Localone *Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo-Cosmetique, Port.*
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Skin disorders.

Localyn *Recordati, Ital.*
Ear drops: ⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Ear disorders.

Recordati, Ital.
Lotion; ointment; topical solution: ⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Recordati, Ital.
Nasal spray: ⊗Fluocinolone acetonide (p. 1636·1); clonazoline hydrochloride (p. 1659·1).
Nasal inflammation and hypersensitivity.

Localyn SV *Recordati, Ital.†*
⊗Fluocinolone acetonide (p. 1636·1).
Nasal inflammation and hypersensitivity.

Localyn-Neomicina *Recordati, Ital.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Locana *LBS, Thai.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Locanest-A *Medifarma, Turk.*
Lidocaine hydrochloride (p. 1988·2). Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Locap *Sandoz, Indon.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Locapred *Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo-Cosmetique, Port.†; Pierre Fabre, Switz.*
⊗Desonide (p. 1630·1).
Skin disorders.

Locar *Medicus, Gr.*
Levocarnitine (p. 2053·2).

Locardan *Iapharm, Gr.*
Losartan potassium (p. 1422·2).

Locardin *Ratiopharm, Denm.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Locarp *Cadila, India.*
Pilocarpine nitrate (p. 2010·3).
Production of miosis.

Locasalen *Pharma Logistics, Belg.; Riemser, Ger.; Novartis, Hong Kong; Novartis, Indon.; Amdipharm, Neth.; Sandoz, Philipp.; Pro Concepta, Switz.; Amdipharm, Thai.; Novartis, Venez.*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders; pruritus; scalp disorders.

Locasalene *Novartis, Gr.; Novartis, Turk.*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Locasalène *Genopharm, Fr.†*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Locaseptil-Neo *Drossapharm, Switz.*
⊗Prednisolone acetate (p. 1645·2); cinchocaine (p. 1983·2).
Nasal and buccal lesions.

Locasol *Nutricia, Austral.; Nutricia, Fr.*
Low-calcium enteral feed.
Calcium and vitamin D restricted diets.

Nutricia, NZ.
Infant feed.
Calcium and vitamin D restriction.

SHS, UK.
Low-calcium milk substitute.
Calcium intolerance.

Scientific Hospital Supplies, Irl.†
Low-calcium food for special diets.

Locason *Proel, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders.

Locason-N *Proel, Gr.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Locatop *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.†; Pierre Fabre Dermatologie, Fr.; Pierre Fabre, Israel; Pierre Fabre Dermatologie, Pol.; Pierre Fabre, Switz.†*
⊗Desonide (p. 1630·1).
Skin disorders.

Locekin *Gosun, China.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Locemix *Euroderm, Arg.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Loceryl *Galderma, Arg.; Galderma, Austral.; Galderma, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Chile; Galderma, China; Galderma, Cz.; Galderma, Denm.; Galderma, Fin.; Galderma, Ger.; Galderma, Gr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Taro, Israel; Galderma, Malaysia; Galderma, Mex.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Pol.; Galderma, Rus.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Swed.; Galderma, Thai.; Galderma, UK; Galderma, Venez.*
Amorolfine hydrochloride (p. 569·1).
Fungal skin and nail infections.

Galderma, India.
Amorolfine (p. 569·1).
Fungal nail infections.

Locéryl *Galderma, Fr.; Galderma, Switz.*
Amorolfine hydrochloride (p. 569·1).
Fungal skin and nail infections.

Locet *Arvincare, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Locetar *Galderma, Ital.; Galderma, Philipp.; Galderma, Port.; Galderma, Spain.*
Amorolfine hydrochloride (p. 569·1).
Fungal skin and nail infections.

Locet-P *Arvincare, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Locferon *Biomed, Rus.*
Interferon alfa (p. 989·2).

Lochol
Note: this name may be used for preparations of different composition.
Novartis, Hung.†; Clonmel, Irl.; Novartis, Jpn.
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

MG, Philipp.; Siam Bheasach, Thai.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Micro, India; Micro, Singapore.
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Locholes *TO-Chemicals, Thai.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Locholest *Warner Chilcott, USA.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; pruritus associated with biliary obstruction.

Lociaze *Ceamed, Port.†*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Locid *Psychotropics, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Locid-D *Psychotropics, India.*
Domperidone (p. 1838·1); lansoprazole (p. 1851·3).

Lociherp *Maigal, Arg.*
⊗Urea (p. 1727·3).
Skin disorders.

Lociherp Liposomas Antiage *Maigal, Arg.*
Collagen (p. 2483·2); centella (p. 1698·3).
Skin disorders.

Lociherp Liposomas Vitaminado *Maigal, Arg.*
Centella (p. 1698·3); collagen (p. 2483·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); riboflavin (p. 2104·3); panthenol (p. 2582·2); allantoin (p. 1693·1).
Skin disorders.

Locilan *Pfizer, Austral.*
Norethisterone (p. 2294·2).
Progestogen-only contraceptive.

Locin-H *Cinerea, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Locip *Forgo, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Locipil *Corona, India.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).

Locip-TZ *Forgo, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Lock-2 *Zydus, India.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; pancreatic insufficiency.

Lockesol *Dzwon, India.†*
Solution 1, sodium chloride; potassium chloride (p. 1793·2); sodium phosphate (p. 1791·2); sodium bicarbonate (p. 1781·1); solution 2, calcium chloride; magnesium chloride (p. 1787·1); glucose (p. 2068·3); glutathione disulfate.
Eye irrigation.

Lockets *Mars, UK.*
⊗Menthol (p. 2553·2); cineole (p. 2479·1); honey (p. 2072·1); glycerol (p. 2517·2).
Nasal congestion; sore throat.

Lockets Medicated Linctus *Thornton & Ross, UK.*
⊗Ipecacuanha (p. 1667·2); honey (p. 2072·1); glucose (p. 2068·3); glycerol (p. 2517·2); menthol (p. 2553·2).
Coughs; sore throats.

Locko *General Drugs, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Locobase *Astellas, Ital.; Astellas, Swed.; Astellas, Switz.*
Emollient.

Locoid *Eurolab, Arg.; Astellas, Belg.; Eurofarma, Braz.; Labomed, Chile; Zhong Hao, China; Astellas, Cz.; Astellas, Denm.; Astellas, Fin.; Astellas, Hung.; Elder, India; Astellas, Indon.†; Astellas, Irl.; Liomont, Mex.; Astellas, Neth.; Astellas, Norw.; CSL, NZ; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, S.Afr.; Astellas, Swed.; Astellas, Switz.; Santa, Turk.; Astellas, UK; Astellas, Ukr.; Onset, USA.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Loco'id *Astellas, Fr.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Locoid C *Astellas, Irl.†; CSL, NZ.*
⊗Hydrocortisone butyrate (p. 1640·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Locoidol *Astellas, Denm.†; Astellas, Norw.†*
⊗Hydrocortisone butyrate (p. 1640·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Locoidon *Astellas, Austria†; Astellas, Ital.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

LOCOL *Novartis, Ger.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia.

Locorten *Novartis, Ital.*
Cream; ointment: ⊗Flumetasone pivalate (p. 1635·2); neomycin sulfate (p. 330·1).
Skin disorders; otitis externa.

Novartis, Ital.
Ear drops; oral drops: ⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Otitis; gingivitis; oral inflammatory lesions.

Locorten Vioform *AFT, NZ; Amdipharm, UK.*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Infected ear disorders.

Locorten Vioformio *Novartis, Braz.; Novartis, Ital.†*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Skin disorders; otitis externa.

Locorten Vioformo *Novartis, Venez.*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Infected skin and ear disorders.

Locose *T Man, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Locovit *Servocare, India.*
Preparation for enteral nutrition.

Locpan *VS, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Locrim *Pharma Investi, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections with inflammation.

Locsone *Micro, Rus.*
Norfloxacin (p. 333·3).
Bacterial infections.

Loctenk *Biotenk, Arg.*
Losartan potassium (p. 1422·2).
Heart failure; hypertension.

Loctenk D *Biotenk, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; oedema.

Locula *East India Pharma, India.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Lodalès *Sanofi-Aventis, Fr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lodalis *Valeant, Canad.*
Colesevelam hydrochloride (p. 1345·1).
Hypercholesterolaemia.

Lodarin *HCS, Neth.†*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lodecon *Solas, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms; allergic disorders.

Lodem *Dexa, Indon.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Lodene *Bayer, Israel.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lodep *Sunthi Sepuri, Indon.†*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Lodeprem *Onipharm, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Loderix *Egis, Hung.†*
Setastine hydrochloride (p. 640·2).
Hypersensitivity reactions.

Loderm *Vinas, Spain.*
Erythromycin laurilsulfate (p. 291·2).
Acne.

Loderm Retinoico *Vinas, Spain.†*
Erythromycin laurilsulfate (p. 291·2); tretinoin (p. 1725·2).
Acne.

Lodesdineta *Samuel, Neth.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Lodestar *Liomont, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; cardiovascular risk reduction; heart failure; diabetic nephropathy.

Lodestar Zid *Liomont, Mex.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lodexa *LBS, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Lodi *Arvincare, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lodia
Note: this name may be used for preparations of different composition.
MSN, India.
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sanbe, Indon.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lodicap *Hizon, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Lodicord *Accord, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Lodil *Pharmahof, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lodimol *Kener, Mex.*
Dipyridamole (p. 1362·2).

Lodine *Pfizer, China; Algol, Fin.; Dexo, Fr.; Wyeth, Hong Kong†; Sigma-Tau, Switz.; Wyeth, Turk.; Shire, UK.*
Etodolac (p. 57·1).
Musculoskeletal, joint, and peri-articular disorders.

Lodip *Bosch, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Lodipen *Royton, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Lodipil *Geolab, Braz.†*
Amlodipine besilate (p. 1304·1).
Hypertension.

Lodipin *Iasis, Gr.; Roemmers, Venez.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Lodipres *Laboratorios Chile, Chile.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Lodiric *Novartis, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Lodirtrem *Serral, Mex.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lodistad *Stada, Philipp.*
Felodipine (p. 1380·3).
Hypertension.

Lodixal *Abbott, Belg.*
Verapamil hydrochloride (p. 1522·1).
Hypertension.

Lodiz *Novagen, S.Afr.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).

Lodoc *Columbia, Arg.*
Benzocaine (p. 1980·2).
Obesity.

Lodol *Symbiosis, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Lodomer *Mersifarma, Indon.*
Haloperidol (p. 1077·1).
Psychoses; behaviour disorders; alcohol withdrawal syndrome.

Lodopin *Kalbe, Indon.; Astellas, Jpn.*
Zotepine (p. 1119·1).
Schizophrenia.

Lodosyn *Valeant, USA.*
Carbidopa (p. 900·3).
Parkinsonism.

Lodotra *Merck, Austria; Mundipharma, Belg.; Norpharma, Denm.; Mundipharma, Fin.; Horizon, Ger.; Mundipharma, Ger.; Rafa, Israel; Mundipharma, Ital.; Mundipharma, Neth.; Mundipharma, Norw.; Norpharma, Pol.; Nitec, Port.; Mundipharma, Swed.; Mundipharma, Switz.; Napp, UK.*
⊗Prednisone (p. 1647·2).
Rheumatoid arthritis.

Lodoxal *Alcon, Fr.†*
Lodoxamide trometamol (p. 2545·1).
Allergic eye disorders.

Lodoz *Merck, Belg.; Merck, Cz.; Merck Serono, Fr.; Merck, Hong Kong; Merck, India; Merck, Indon.; Merck Serono, Ital.; Merck Serono, Malaysia; Merck, Norw.; Merck, Rus.; Merck, Singapore; Merck, Switz.; Merck, Thai.; Merck, Turk.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lodrane *ECR, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Allergic rhinitis; nasal congestion.

Lodrane 12 *ECR, USA.†*
Brompheniramine maleate (p. 618·1).
Allergic rhinitis.

Lodrane 24 *ECR, USA.†*
Brompheniramine maleate (p. 618·1).
Allergic rhinitis.

Lodrane D *ECR, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine tannate (p. 1676·1); brompheniramine maleate (p. 618·1) or brompheniramine tannate (p. 618·1).
Upper respiratory-tract disorders.

Lodrane 12D *ECR, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Allergic rhinitis; nasal congestion.

Lodrec *Newmed, Gr.*
Omeprazole (p. 1867·2).

Lodronat *Roche, Austria; Roche, Cz.*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; hypercalcaemia of malignancy; Paget's disease of bone.

Lodulce *Littman, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Lodyfen *Grin, Mex.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders; prevention of miosis and cystoid macular oedema in ocular surgery.

Lo-E *East West, India.*
Enalapril maleate (p. 1371·1); losartan potassium (p. 1422·2).

Loenzar *Sanovel, Rus.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Loestrin *Galen, UK; Teva, USA.*
Norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Loestrin 1.5/30 *Warner Chilcott, Canad.*
Norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3).
28-Day packs contain 7 inert tablets.
Combined oral contraceptive.

Loestrin Fe *Teva, USA.*
21 Tablets, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
Loestrin Fe 24 contains 24 tablets and 4 tablets, respectively.
Combined oral contraceptive.

Loestrol *Elfin, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Loette *Pfizer, Austria; Pfizer, Denm.; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, India; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Singapore†; Wyeth, Spain.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; acne in females.

Wyeth, Arg.; Pfizer, Austral.; Pfizer, Cz.; Wyeth, Hung.†; Pfizer, Norw.; Pfizer, NZ; Wyeth, S.Afr.†
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive; acne in women.

Loexom *IQFA, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Loexom FC *IQFA, Mex.*
Ambroxol (p. 1654·3); amoxicillin (p. 216·2).
Respiratory-tract congestion.

Loexom FS *IQFA, Mex.*
Ambroxol (p. 1654·3); amoxicillin (p. 216·2).
Respiratory-tract congestion.

Lofacol *Ferron, Indon.; Dexa, Singapore.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lofact *Medico, India.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lofarbil *Proel, Gr.*
⊗Metoprolol tartrate (p. 1434·3).

Lofecam *Sun, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lofection *Unichem, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Lofel *East African, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lofen
Note: this name may be used for preparations of different composition.
Bal, India.
Topical gel: Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Health Guard, India.
Tablets: Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Pharmaland, Thai.
Paracetamol (p. 115·1); ibuprofen (p. 68·2).

Lofenac *Chew, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Lofenalac *Mead Johnson, Israel.*
Food for special diets.
Phenylketonuria.

Lofenax *Geofman, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders; renal colic.

Lofenin *Solvang, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders congestion.

Lofenoxal *Biotech, Austral.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Loffymix *Loeffler, Mex.†*
Ketoconazole (p. 585·3); clindamycin (p. 269·3).
Vaginal infections.

Lofibra
Note: this name may be used for preparations of different composition.
OEP, Philipp.; OEP, Philipp.; Gate, USA.
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Pharos, Indon.
Ursodeoxycholic acid (p. 2638·1).
Gallstones.

Loflox *Meyer, Venez.*
Lomefloxacin (p. 319·2).
Bacterial infections of the urinary tract.

Lofo *Aronex, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lofostin *Farmedia, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia.

Lofoto *Rafarm, Gr.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections with inflammation.

Lofox *Sintez, Rus.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Lofradyk *Adamed, Cz.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Lofral *Mepha, Hong Kong; Mepha, Malaysia; Mepha, Pol.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Loft *Admac, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Loftil *Abbott, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Lofton *Abbott, Arg.; Amdipharm, Spain.†*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders; mental function impairment.

Loftyl *Amdipharm, Austria†; Pharma Logistics, Belg.†; Amdipharm, Gr.†; Abbott, Indon.; Amdipharm, Ital.†; Abbott, Neth.†; Amdipharm, Port.†; Abbott, S.Afr.; Abbott, Switz.†; Abbott, Venez.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Lofy *Biomax, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Lo-G *Euphoric, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Logadine *General Drugs, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Logafox *Meprofarm, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Logan *Ist. Chim. Inter., Ital.*
Citicoline sodium (p. 2480·2).
Parkinsonism.

Loganil *Arex, Venez.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Logascid *AstraZeneca, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; dyspepsia; heartburn.

Logastin *Osoth, Thai.*
Simeticone (p. 1886·2).
Flatulence; meteorism.

Logastric *Biothera, Belg.†*
Omeprazole magnesium (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Logat *Libbs, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Logazil *Loeffler, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Logcef *Alna, India.*
Cefixime (p. 240·3).
Bacterial infections.

Logcef-CV *Alna, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Logem *Mylan, NZ.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Logen *Goldline, USA.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Logen-MD *Gentech, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Logest *Bayer Schering, Cz.; Bayer Schering, Pol.; Bayer Schering, Rus.; Bayer, Ukr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Logflox *Alna, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Logflox-OZ *Alna, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Logic *Sienna, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Logical
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Magnesium valproate (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy.

Recalcine, Chile.
Vitamin E (p. 2119·1); ascorbic acid (p. 2110·3); ubidecarenone (p. 2637·1).
Antoxidant preparation.

Serum Institute, India.
Oral suspension: Calcium carbonate (p. 1824·3); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis; osteomalacia; rickets.

Serum Institute, India.
Tablets: Calcium carbonate (oyster shells) (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

Armstrong, Mex.†
Crospovidone (p. 2205·1).
Diarrhoea.

Logical-M *Serum Institute, India.*
Calcium carbonate (oster shells) (p. 1824·3); copper (p. 2057·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Logican *Win-Medicare, India.*
Fluconazole (p. 578·2).
Fungal infections.

Logicin Flu Strength Day & Night *Sigma, Austral.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Sigma, Hong Kong.
⊗Day-time tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night-time tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Logicin Hay Fever *Sigma, Austral.†; Treasure Mountain, Hong Kong.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Hay fever.

Logicin Rapid Relief *Sigma, Austral.; Sigma, Hong Kong; Sigma, Singapore.*
Lidocaine hydrochloride (p. 1988·2); benzydamine hydrochloride (p. 29·2); dichlorobenzyl alcohol (p. 1750·2).
Sore throat; mouth and throat disorders.

Sigma, Austral.; Sigma, Hong Kong.
Nasal spray: ⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Logicin Sinus *Sigma, Austral.; Sigma, Hong Kong.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Logiflox *Biocodex, Fr.*
Lomefloxacin hydrochloride (p. 319·2).
Cystitis in women.

Logika *Gerolymatos, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Logimat *AstraZeneca, Belg.*
⊗Felodipine (p. 1380·3); metoprolol succinate (p. 1434·3).
Hypertension.

Logimax *AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Israel†; AstraZeneca, Mex.; AstraZeneca, Philipp.; AstraZeneca, Rus.; Lailan, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.*
⊗Felodipine (p. 1380·3); metoprolol succinate (p. 1434·3).
Hypertension.

AstraZeneca, Hong Kong.
⊗Felodipine (p. 1380·3); metoprolol tartrate (p. 1434·3).
Hypertension.

Login *President Pharmagenesis, China.*
Tinidazole (p. 949·2).
Trichomoniasis; anaerobic bacterial infections.

Logiparin *Novo Nordisk, Gr.; Santa, Gr.; Medex, India.*
Tinzaparin sodium (p. 1514·2).

Logirène *Erempharma, Fr.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Heart failure.

Logista *Caprifarmindo, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Logistic *Craveri, Arg.*
Gabapentin (p. 523·3).
Epilepsy; postherpetic neuralgia; peripheral neuropathy.

Logit *Khandelwal, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Logoderm *Schering-Plough, Mex.†*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Logofren *Darci, Gr.*
Piracetam (p. 393·3).

Logout *Inga, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Logpod *Alna, India.*
Cefpodoxime.
Bacterial infections.

Logren *Intermed, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Logroton *Daiichi Sankyo, Belg.; Daiichi Sankyo, Fr.; Novartis, Malaysia; Novartis, Singapore; Daiichi Sankyo, Switz.*
⊗Metoprolol tartrate (p. 1434·3); chlortalidone (p. 1335·2).
Hypertension.

Logy *Sienna, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Logynon *Bayer, Irl.; Berlipharm, Neth.†; Bayer, Philipp.; Bayer, UK.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Logynon ED *Bayer, Austral.; Bayer Schering, S.Afr.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive; menstrual disorders.

Lo-H *East West, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lohak *TP, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

LoHist *Larken, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

LoHist D *Larken, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

LoHist PEB *Larken, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

LoHist PEB DM *Larken, USA.*
Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

LoHist PSB *Larken, USA.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

LoHist-DM *Larken, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

LOHP *HLB, Arg.*
Cystine (p. 2059·1); pyridoxine hydrochloride (p. 2105·3).
Skin, nail, and eye disorders.

Lohtone *Moraceae, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).

Lohype Plus *Ranbaxy, S.Afr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Loisan *Baliarda, Arg.*
Loratadine (p. 633·2).
Allergic disorders of the respiratory tract; allergic skin disorders; conjunctivitis.

Loisan-D *Baliarda, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).
Respiratory-tract disorders; conjunctivitis.

Loitin *Qualigen, Spain.*
Fluconazole (p. 578·2).
Fungal infections.

Loitrol *Rafarm, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).

Lojuxta *Aegerion, UK.*
Lomitapide mesilate (p. 1421·3).
Familial hypercholesterolaemia.

Lo-Kal *Cipla, India.*
Aspartame (p. 2169·2).

Lokalen *Toprak, Turk.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Lokalison-antimikrobiell Creme N *Dermapharm, Ger.†*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

LoKara *PharmaDerm, USA.†*
⊗Desonide (p. 1630·1).
Skin disorders.

Lokarin *Biotech, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Lokefar *Nafar, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Lokev *Ifars, Indon.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lok-H *Alna, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Lokilan *Ivax, Norw.†*
⊗Flunisolide (p. 1635·3).
Rhinitis.

Lokit *Kramer, India; Kopran, Philipp.; Pharmascript, S. Afr.; Kopran, Thai.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; dyspepsia; Zollinger-Ellison syndrome; acid aspiration.

Lokit-Kit *Kopran, India.*
1 Capsule, amoxicillin (p. 216·2); 1 tablet, omeprazole (p. 1867·2); 1 tablet, tinidazole (p. 949·2).

Loklor *Medikon, Indon.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lokman Kase *Lokman, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Lokoles *Corsa, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lokren *Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.*
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; angina pectoris; ischaemic heart disease.

Loksetin *Nobel, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Lol *Orchid, India.*
⊗Propranolol (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; essential tremor.

Lolergi *Mugi, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Lolergy *GPO, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic skin disorders.

Lolira-P *Zenon, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lolita *Unison, Thai.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Lomac *Cipla, Cz.; Cipla, India; Cipla, Rus.; Cipla, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Lomacin *Novartis, Mex.; Wave, Rus.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Lomaday *Reddy, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Reddy, Ukr.†
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Lomadryl *SJA, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Lomaherpan *Madaus, Austria; Lomapharm, Ger.; Lomapharm, Rus.*
Melissa (p. 2552·3).
Herpes simplex infections of the skin and mucous membranes.

Lomanor *Pharmacia, S.Afr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Lomar *Aegis, Hong Kong.†*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Lomarin
Note: this name may be used for preparations of different composition.
Geymonat, Ital.
Dimenhydrinate (p. 625·2).
Nausea; vomiting; vertigo.

Medipharm, Chile.
Lamotrigine (p. 527·2).
Bipolar disorder.

Lomatuell H *Lohmann, Ital.*
White soft paraffin (p. 2211·3).
Wound dressing.

Lomox
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Unipharma, Gr.
Nordazepam (p. 1089·3).

Lombalgina *Neo Quimica, Braz.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Lombocid *Proel, Gr.*
Povidone-iodine (p. 1767·1).
Antiseptic.

Lombriareu *Areu, Spain.†*
Pyrantel embonate (p. 165·3).
Worm infections.

L-Ombrix *Liomont, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Lomebact *Medivis, Ital.*
Lomefloxacin (p. 319·2).
Eye infections.

Lomecan V *Liferpal, Mex.†*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Lomecid *Taurus, India.*
Capsules: Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Taurus, India.
Oral gel: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Lomecid-D *Taurus, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; heartburn.

Lomecomb *Akrikhin, Rus.*
Isoniazid (p. 311·2); lomefloxacin hydrochloride (p. 319·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Lomedon *Zydus, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Lomef *Torrent, India.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lomeflon *Senju, Jpn.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye and ear infections.

Lomeflox *Aristopharma, Hong Kong.*
Lomefloxacin (p. 319·2).
Bacterial eye infections.

Lomesone *MSD, Gr.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Lomet *Microsules, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Lomet-CT *Nordic, India.*
Ciprofloxacin hydrochloride (p. 261·2); tinidazole (p. 949·2).
Bacterial infections.

Lomevel *Biohealth, Ital.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lomewon *Max, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Lomex
Note: this name may be used for preparations of different composition.
Oftalmi, Venez.
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

Saval, Chile.
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lomexel *Medley, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Lomexin *Gerot, Austria; Nycomed, Braz.; Recordati, Cz.; Effik, Fr.; Merckle Recordati, Ger.†; Galenica, Gr.; Recordati, Hung.; Recordati, Irl.; Innova, Ital.; Nycomed, Mex.; Jaba Recordati, Port.; Bouchara, Rus.; Pharmaplan, S.Afr.; Recordati, Spain; Recordati, Ukr.*
Fenticonazole nitrate (p. 578·1).
Trichomoniasis; fungal ear infections; fungal and Gram-positive bacterial nail, skin, and vulvovaginal infections.

Lomezec *Hospital Line, Gr.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer.

Lomezek *Gland, Philipp.*
Omeprazole sodium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Lomfast *Sanofi-Aventis, Fin.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Lomflox *Ipca, India; Ipca, Rus.; Ipca, Singapore.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Lomibact *Sun, India.*
Lomefloxacin (p. 319·2) or lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Lomicid *United Drug, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia; oesophagitis.

Lomidal *Silanes, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Lomide
Note: this name may be used for preparations of different composition.
Alcon, Austral.; Alcon, NZ.
Lodoxamide trometamol (p. 2545·1).
Allergic conjunctivitis; conjunctivitis.

Siam Bheasach, Thai.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lomilan *Sandoz, Rus.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; pruritus; allergic skin disorders.

Lomin *Intra-Labs, India.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lomine *Riva, Canad.†*
Dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Lomir *Novartis, Austria; Daiichi Sankyo, Belg.; Novartis, Braz.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.†; Novartis, Gr.; Novartis, Hung.; Daiichi Sankyo, Ital.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Daiichi Sankyo, Port.; Novartis, Rus.; Mizar, Spain†; Novartis, Swed.; Daiichi Sankyo, Switz.*
Isradipine (p. 1414·2).
Hypertension; angina pectoris.

Lomitas *Intas, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Lomofen *RPG, India.*
Diphenoxylate hydrochloride (p. 1835·3); furazolidone (p. 933·3).
Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Bacterial diarrhoea.

Lomoh *Emcure, Philipp.*
Enoxaparin sodium (p. 1372·3).
Thromboembolism prophylaxis; unstable angina.

Lomonox *Neiss, India.*
Enoxaparin (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

Lomont *Rosemont, UK.*
Lofepramine hydrochloride (p. 433·2).
Depression.

Lomorest *Zuventus, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Lomorin *VHB, India.*
Low-molecular-weight heparin (p. 1426·1).

Lomorin-NX *VHB, India.*
Enoxaparin sodium (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

Lomostop-MF *Wings, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Lomotil *Biotech, Austral.; Pfizer, Braz.; Pfizer, Canad.; Johnson & Johnson, Hong Kong; RPG, India; Goldshield, Irl.; Johnson & Johnson, S.Afr.; Pfizer, Thai.; Ali, Turk.; Goldshield, UK; Searle, USA.*
Diphenoxylate hydrochloride (p. 1835·3).
Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
These ingredients can be described by the British Approved Name Co-phenotrope.
Diarrhoea; ostomy management; ulcerative colitis.

Johnson & Johnson Consumer, Mex.; Johnson & Johnson, Philipp.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Lomox *Cubit, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lomox-D *Cubit, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Lomper *Dexter, Spain.*
Mebendazole (p. 158·3).
Worm infections.

Lomprax *Mintlab, Chile.*
Dimeticone (p. 2209·3).
Flatulence.

Lomtin *Reddy, India.*
Lomustine (p. 818·1).
Malignant neoplasms.

Lomudal *Sanofi-Aventis, Belg.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.*
Sodium cromoglicate (p. 1225·3).
Asthma; bronchitis; allergic conjunctivitis; allergic rhinitis; inflammatory bowel disease; food allergy; bronchial hypersensitivity.

Lomupren *Aventis, Ger.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Lomusol *Sigmapharm, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Switz.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis; allergic conjunctivitis.

Lomy *Masa, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lona *Thaipharmed, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Lonace *Pascual, Philipp.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Lonactene *Ferring, Mex.*
Carbetocin (p. 2132·3).
Uterine atony; postpartum haemorrhage.

Lonalac *Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition.

Lonalgal *Boehringer Ingelheim, Gr.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Lonarel *Tolmann, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Lonarid *Boehringer Ingelheim, Ital.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Lonarid Aplo *Boehringer Ingelheim, Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Lonarid N *Boehringer Ingelheim, Belg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Boehringer Ingelheim, Gr.
Codeine phosphate (p. 40·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Lonasen *Dainippon, Jpn.*
Blonanserin (p. 1041·2).
Schizophrenia.

Lonason *Alpharma, Mex.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Lonatec *Arlex, Mex.*
Diclofenac (p. 48·3).
Inflammation; pain.

Lonazep *Sun, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Loncarti *Inibsa, Neth.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Londer *Aenorasis, Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Londerm-N *Kinder, Braz.†*
⊗Triamcinolone acetonide (p. 1649·1); gramicidin (p. 308·3); nystatin (p. 590·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Londodact *Panvifarm, Gr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Londofis *Panvifarm, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Londofurol *Panvifarm, Gr.*
Nitrofurantoin (p. 332·1).

Londolife *Panvifarm, Gr.*
Cinoxacin (p. 261·1).
Bacterial infections.

Londoman *Panvifarm, Gr.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Londopon *Panvifarm, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Lonene *Sunthi Sepuri, Indon.†*
Etodolac (p. 57·1).
Pain; osteoarthritis; rheumatoid arthritis.

Long Ge Kang *Yu Heng, China.*
Sodium new houttuyfonate.

Long Ge Xian *Yu Heng, China.*
Aceglutamide (p. 2426·2).

Long Ge Xin *Qi Du, China.*
Clindamycin phosphate (p. 269·3).

Long Hua Su *Lianshui, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Long Ke Duo *Qinghai, China.*
Clindamycin phosphate (p. 269·3).

Long Lasting Decongestant Nasal Mist *Confab, Hong Kong.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Long Lasting Nasal Mist *Pharmascience, Canad.; Supplements Aromatik, Canad.*
⊗Oxymetazoline hydrochloride (p. 1671·3).

Long Sha *Xinjiang, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Long Sheng Tai *Duoburuifei, China.*
Aceglutamide (p. 2426·2).

Long Shu Ya *Crelord, China.*
Telmisartan (p. 1509·3).
Hypertension.

Long Tong *Shuntian, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Long Wei Xin *Chenlong, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Long Xiang *San Lian, China.*
Asarone.

Long Xin Gan *Mingxin, China.*
Matrine.

Long Xin Ning *Yu Heng, China.*
Ethylenediamine diaceturate.

Longacef
Note: this name may be used for preparations of different composition.
Leti, Venez.
Cefixime (p. 240·3).
Bacterial infections.

Longachin *Teofarma, Ital.*
Quinidine arabogalactane sulfate (p. 1481·1).
Arrhythmias.

Longacilin *Biolab Sanus, Braz.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Longacillin *Hindustan Antibiotic, India.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Longacor *Sanovel, Turk.*
Quinidine arabogalactane sulfate (p. 1481·1).
Arrhythmias.

Longactil *Cristalia, Braz.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses.

Long-Acting Cough Suppressant *Major, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Longaquin *Lavipharm, Gr.*
Quinidine arabogalactane sulfate (p. 1481·1).
Arrhythmias.

Longastatina *Italfarmaco, Ital.*
Octreotide (p. 1924·1) or octreotide acetate (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; pancreatic disorders; diarrhoea associated with immunodeficiency; gastrointestinal haemorrhage.

Longatin *Actavis, Indon.*
Noscapine (p. 1670·3).
Respiratory-tract disorders.

Longazem *De Salute, Ital.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; heart failure.

Longbalsem *Kela, Belg.†*
Ethylmorphine hydrochloride (p. 56·3); guaifenesin (p. 1666·2).
Cough.

Longcef *Kalbe, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

LongEight *Recoly, Rus.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Longes *Shionogi, Jpn.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Longevital
Note: this name may be used for preparations of different composition.
Bago, Arg.
⊗Procaine (p. 1994·3); vitamin B substances (p. 2102·3); prasterone (p. 2299·2).
Mental function impairment; cerebrovascular disorders.

Sanitalia, Ital.
Pollen (p. 2593·3); royal jelly (p. 2608·1); rose fruit (p. 2607·1); selenium (p. 2086·3).
Nutritional supplement.

Longhuanuo *Xinbao, China.*
Interferon alfa-2b (human, recombinant) (p. 989·2).
Chronic hepatitis; malignant neoplasms; viral infections.

Longidaza *Petrovax, Rus.*
Longidase hyaluronidase (p. 2527·2).
Hyperplasia of connective tissue.

Longifene *Pierre Fabre Sante, Belg.; UCB, India; GSK, S.Afr.†; UCB, Turk.*
Buclizine hydrochloride (p. 618·3).
Hypersensitivity reactions; nausea and vomiting; appetite loss; motion sickness; hay fever; urticaria; pruritus; vertigo; vestibular disorders.

Longin *Olive, India.*
Curcuminoid (p. 2489·3).

Longis *Berksam, Turk.*
Tadalafil (p. 2368·1).

Longity *Xeno, Philipp.†*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; neurosensorial ischaemia.

Longliv *Wallace, India.*
Ornithine aspartate (p. 2085·2).
Liver disorders.

Longshutong *Crelord, China.*
Bisacodyl (p. 1821·1).
Constipation.

Longtec *Qdem, UK.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Longtussin Duplex Tag und Nacht N *Tussin, Ger.*
Day capsules, guaifenesin (p. 1666·2); night capsules, codeine (p. 40·2).
Bronchitis; cough.

Loni *Solitaire, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lonicera *Betapharm, Neth.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lonikan *Merck Serono, Arg.*
⊗Fludrocortisone (p. 1634·3).
Corticosteroid.

Lonin *Chemo-Drugs, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Lonine *Wyeth, Gr.*
Etodolac (p. 57·1).
Pain; inflammation; osteoarthritis; rheumatoid arthritis.

Loni-Plus *Solitaire, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lonipril *Geolab, Braz.*
Lisinopril (p. 1420·3).
Hypertension.

Lonipril-H *Geolab, Braz.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lonita *HCS, Neth.†*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Loniten *Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Canad.; IFET (ΙΦΕΤ), Gr.; Pharmacia Upjohn, Gr.; Pfizer, Hong Kong†; Pharmacia, Irl.; Pfizer, Ital.; Pfizer, NZ; Pfizer, S.Afr.; Pharmacia, Singapore; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK.*
Minoxidil (p. 1438·3).
Hypertension.

Lonium *Apsen, Braz.*
Otilonium bromide (p. 2578·2).
Gastrointestinal spasm; aid to gastrointestinal examination.

Lonixer *Serral, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Lonlor *Synmedic, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lonna
Note: this name may be used for preparations of different composition.
Triton, India.
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Vesco, Thai.
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Lonnoten *Pfizer, Neth.*
Minoxidil (p. 1438·3).
Hypertension.

Lonol
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Boehringer Ingelheim Promeco, Mex.
Benzydamine hydrochloride (p. 29·2).
Musculoskeletal, joint and peri-articular disorders; mouth and throat disorders.

Khandelwal, India.
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Lonol Sport *Boehringer Ingelheim Promeco, Mex.*
Benzydamine hydrochloride (p. 29·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular and soft-tissue disorders.

Lonolox *Pfizer, Ger.*
Minoxidil (p. 1438·3).
Hypertension.

Lonoten *Pfizer, Fr.; IFET (ΙΦΕΤ), Gr.*
Minoxidil (p. 1438·3).
Hypertension.

Lonox *Sandoz, USA.*
Diphenoxylate hydrochloride (p. 1835·3).
Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Lonpryl *Maruko, China.*
Alfacalcidol (p. 2112·3).

Lonseren *Sanofi-Aventis, Spain.*
Pipotiazine palmitate (p. 1098·1).
Psychoses.

Lontadex *Recalcine, Chile.†*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lontax *Fidia, Neth.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Lontermin *Lek, Cz.*
⊗Procaterol hydrochloride (p. 1219·1).
Obstructive airways disease.

Lontif *Strassenburg, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Lonza *Medicine Products, Thai.*
Lorazepam (p. 1080·3).
Anxiety.

Loobid *Cachet, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Loortan *MSD, Belg.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Loortan Plus *MSD, Belg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Loosyn *Synthon, Cz.; Synthon, Port.*
⊗Letrozole (p. 817·1).
Breast cancer.

Lo-Ovral
Note: this name may be used for preparations of different composition.
Wyeth, Turk.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lo/Ovral *Akrimax, USA.*
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Looz *Intas, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Loozit *Intra-Labs, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Loozylax *Skymax, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Lop *Sons, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopa *Jean-Marie, Hong Kong.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopacut *Vitabalans, Fin.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Vitabalans, Swed.
Loperamide (p. 1854·2).
No indics.

Lopamide *Torrent, India.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loparin *Intas, India.*
Enoxaparin sodium (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

Loparine *Rivero, Arg.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders.

Lo-P-Caps *ST, Thai.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Lop-Dia *Mibe, Ger.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopecian *Cinetic, Arg.*
Amino acids; vitamin B substances (p. 2102·3); minerals; ginkgo biloba (p. 2512·3); soya protein.
Dietary supplement for hair loss.

Lopediar *Pasteur, Chile.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopedium *Sandoz, Austral.; Hexal, Ger.†; Sandoz, Hung.; Hexal, Rus.; Hexal, S.Afr.; Sandoz, Ukr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Lopela *Pharmasant, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopemid *Visufarma, Ital.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Lopep *Zynova, Philipp.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Loper *Quality, Hong Kong.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperacap *Valeant, Canad.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperam *Agio, India; Vargas, Venez.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperamil *DHA, Hong Kong; DHA, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperan *Chiesi, Spain.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperastat *Be-Tabs, S.Afr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Loperax *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopercin *Polipharm, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperdium *General Drugs, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperhoe *Betapharm, Ger.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperia *Great Eastern, Thai.†; Therapharma, Thai.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy and colostomy management.

Loperid *Vitamed, Israel.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperidol *Medley, Braz.†*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; Huntington's chorea; autism; nausea and vomiting.

Loperin *Teuto, Braz.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperium *Remedica, Hong Kong†; Remedica, Malaysia.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperiv *East African, India.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loperkey *Pharminicio, Spain.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopermid *Saba, Turk.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopermide *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopernal *Iamatica, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Loperon *Hexal, Cz.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopex *Orion, Fin.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Lopez *Intas, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy; status epilepticus.

Lophakomp-B 12 *Kohler, Ger.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Lophakomp-B 12 Depot *Kohler, Ger.*
Hydroxocobalamin acetate (p. 2107·3).
Vitamin B_{12} deficiency.

Lophakomp-Procain *Kohler, Ger.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Lophlex *Nutricia, Cz.; SHS, Irl.; Nutricia, Ital.; SHS, Pol.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Lopicard *Getz, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Lopi-Care *Rekah, Israel.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopicare *Siam Medicare, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lopid *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Philipp.; Pfizer, Port.; Pharmacia, S.Afr.; Parke, Davis, Spain; Pfizer, Swed.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Parke, Davis, USA; Pfizer, Venez.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Lopigalel *Galex, Cz.; Galex, Hung.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Lopigrel *Farmasa, Braz.; Medley, Braz.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Lopigrol *Rottapharm, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Lopil *Bangkok Lab & Cosmetic, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

T-Boma, Hong Kong.†
Loperamide (p. 1854·2).
Diarrhoea.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lopimed *Sandoz, Switz.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Lopimune *Cipla, India.*
Lopinavir (p. 1002·1); ritonavir (p. 1013·1).
HIV infection.

Lopirel *Incepta, Hong Kong; Actavis, Rus.; Actavis, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Lopiretic *BMS, Port.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lopirin *BMS, Ger.†; BMS, Switz.†*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Lopisol *Gebro, Switz.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lopiten *Guardian, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Lopitum *Medirex, Port.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loplac *Casasco, Arg.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; left-ventricular hypertrophy.

Loplac-D *Casasco, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Loplive *Pliva, Denm.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Lopol *Suphong, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lopona *Zota, India.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loporic *M & H, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Lopra *Arvincare, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Lopracil *Medicus, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Lopra-D *Arvincare, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Lopram
Note: this name may be used for preparations of different composition.
Ind-Swift, India.
Citalopram (p. 411·1).
Depression; bipolar disorder; panic disorder.

Liferpal, Mex.
Omeprazole (p. 1867·2).
Peptic ulcer.

Lopratin *Sandoz, Neth.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Loprax *Homeocan, Canad.†*
Euphorbium officinarum (p. 2501·3); gelsemium sempervirens (p. 2511·2); hypericum perforatum (p. 449·1); poison ivy.
Homoeopathic preparation.

Lopraxer *Help, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Lopraz *Pliva, Irl.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Loprazol *Teuto, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Lopred
Note: this name may be used for preparations of different composition.
Nafar, Mex.
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular hypertrophy; diabetic nephropathy; heart failure.

Phoenix, Arg.
⊗Loteprednol etabonate (p. 1642·1).
Inflammatory eye disorders.

Lopren *Mintlab, Chile.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Lopren-D *Mintlab, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lopres *Micro, India.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Lopresor *Novartis, Arg.; Novartis, Austral.; Daiichi Sankyo, Belg.; Novartis, Canad.; Recordati, Ger.; Novartis, Gr.; Novartis, Indon.; Novartis, Irl.†; Novartis, Israel; Daiichi Sankyo, Ital.; Novartis, NZ; Daiichi Sankyo, Port.; Novartis, S.Afr.; Recordati, Spain; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; hypertrophic obstructive cardiomyopathy; phaeochromocytoma; ischaemic heart disease.

Novartis, India.
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Sandoz, Mex.
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine.

Loprésor *Daiichi Sankyo, Switz.*
⊗Metoprolol fumarate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; hyperthyroidism; myocardial infarction; arrhythmias; migraine.

Lopress
Note: this name may be used for preparations of different composition.
Actavis, Hong Kong.
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Siam Bheasach, Thai.
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Lopressor *Novartis, Braz.; Daiichi Sankyo, Fr.; Novartis, USA.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; arrhythmias; myocardial infarction; angina pectoris; migraine; tremor.

Taj, India.
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Lopressor HCT *Novartis, USA.*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Loprex *Perrigo, Israel; Medirex, Port.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loprezol
Note: this name may be used for preparations of different composition.
Kimia, Indon.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Pertiwi Agung, Philipp.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Lopric *Integrated Pharmaceutical, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Lopril
Note: this name may be used for preparations of different composition.
Orion, Fin.; BMS, Fr.
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Bosnalijek, Ukr.
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Lopril H *Bosnalijek, Ukr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lopril-D *BMS, Braz.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Loprilin *Chemo, Neth.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastric hyperacidity; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Loprin *Unichem, India.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; fever; pain.

Loproc *Norma (Νορμα), Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Loprofin *Nutricia, Fr.*
Gluten-free food for special diets.
Disorders of amino-acid metabolism.

Nutricia, Ital.
Low protein foods for special diets.

Scientific Hospital Supplies, UK.
A range of low protein foods for special diets.
Low protein diets.

SHS, Irl.
A range of low-protein foods.
Inherited metabolic disorders requiring low protein diet; renal disease.

SHS Nutrition, NZ.
A range of foods for special diets.
Phenylketonuria; protein restriction.

Loprolol *Ikapharmindo, Indon.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine.

Loprox *Valeant, Canad.; Bipharma, Neth.; Sanofi-Aventis, Thai.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Mex.; Valeant, USA.
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal skin and nail infections.

Loptame *Volta, Chile.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Loptar *Aurora, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Lopurax *Sanval, Braz.*
Allopurinol (p. 600·2).
Gout.

Loquen *Pliva, Denm.†; Teva, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; mania.

Lor *Forgo, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lora
Note: this name may be used for preparations of different composition.
Atlantic, China; Orchid, India; Atlantic, Thai.; PP Lab, Thai.
Injection: Lorazepam (p. 1080·3).
Anxiety; insomnia; status epilepticus; premedication.

Phoinix Pharm (Φοινιξ Φαρμ), Gr.; Biomedica, India.
Tablets: Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; pruritus.

Lora Allergie *Mepha, Switz.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Lorabid *Aspen, S.Afr.; Actavis, Swed.†; Lilly, Turk.*
Loracarbef (p. 319·3).
Bacterial infections.

Lorabrox *Fortbenton, Arg.*
Loratadine (p. 633·2); ambroxol (p. 1654·3).

Loracalm *Torrent, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

Loracert *Galeno, Venez.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Loracid *Union Korea, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Loracin *Daehan, Singapore.*
Loratadine (p. 633·2).
Allergic disorders.

Loracine *Medicine Products, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Loraclear *AFT, NZ.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loraderm *Dermapharm, Ger.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loradex *Essex, Philipp.†*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Loradif *Sanofi Synthelabo, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loradin *Aristopharma, Hong Kong.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loradine *Teuto, Braz.; YSP, Malaysia; Yung Shin, Philipp.; Greater Pharma, Thai.*
Loratadine (p. 633·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Loradis *Stada, Denm.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorado *Sandoz, Switz.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Loradrina D *Pharlab, Braz.*
Loratadine (p. 633·2).

Loradur *Ratiopharm, Austria; Ratiopharm, Cz.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; ascites.

Lorafast *Galena, Pol.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorafem *Pierre Fabre, Ger.†*
Loracarbef (p. 319·3).
Bacterial infections.

Lorafen *Polfa Tarchomin, Pol.; Tarchomin, Rus.*
Lorazepam (p. 1080·3).
Anxiety; sleep disorders; premedication; nausea and vomiting during chemotherapy.

Loragis *TNP, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lorahexal *Hexal, Pol.†; Hexal, Rus.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; allergic conjunctivitis; urticaria; atopic eczema.

Lorahist *Unison, Philipp.; Adcock Ingram, S.Afr.*
Loratadine (p. 633·2).
Formerly known as Adco-Lorahist.
Allergic rhinitis; allergic skin disorders; urticaria; allergic conjunctivitis.

Loral *Novogen, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Loralerg *Farmasa, Braz.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Loralerg-D *Farmasa, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Lora-Lich *Winthrop, Ger.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loralin *Boniscontro & Gazzone, Ital.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Loralivio *Fada, Arg.*
Loratadine (p. 633·2).

Loram
Note: this name may be used for preparations of different composition.
Lek, Pol.
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; atopic eczema.
Unichem, India.
Losartan potassium (p. 1422·2); ramipril (p. 1483·3).
Hypertension.

Loramed *Medifive, Thai.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Loramet *Meda, Belg.; Wyeth, Gr.; Aspen, S.Afr.; Meda, Spain; Meda, Switz.; Wyeth, Thai.*
Lormetazepam (p. 1082·1).
Sedative; hypnotic; insomnia; sleep disorders.

Loram-H *Unichem, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2); ramipril (p. 1483·3).
Hypertension.

Loramide *YSP, Malaysia; Yung Shin, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loramyc *BioAlliance, Cz.; BioAlliance, Fin.†; Therabel, Fr.; BioAlliance, Ger.; Therabel, Ger.; BioAlliance, Neth.; BioAlliance, Pol.; SpePharm, UK.*
Miconazole (p. 588·3).
Candidiasis of the mouth and throat.

Loran *Guardian, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loran-D *Anglo-French Drugs, India.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).

Lorange *Panjon, India; Willore, Philipp.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; urticaria.

Loranil *Libbs, Braz.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Loranil D *Libbs, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Nasal congestion.

Loranka *SMB, Belg.*
Lormetazepam (p. 1082·1).
Insomnia.

Lorano *Sandoz, Austral.; Hexal, Austria; Hexal, Ger.†; Sandoz, Hung.; Sandoz, Philipp.; Hexal, S.Afr.; Sandoz, Ukr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; atopic eczema.

Loranol *Hexal, Cz.†*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Loranox *Deltapharm, Hong Kong†; Charoen, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Lorans *Medochemie, Hong Kong; UCB, Ital.; Medochemie, Malaysia; Medochemie, Singapore.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Loransil *Pentafarma, Port.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Loranta *Siam Bheasach, Thai.*
Losartan potassium (p. 1422·2).
Hypertension.

Lorantis *Yeni, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lora-P *PP Lab, Thai.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Lorapac *Inpac, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lorapam *Siam Bheasach, Thai.†*
Lorazepam (p. 1080·3).
Anxiety; neuroses.

Lorapan *Neo Quimica, Braz.*
Lorazepam (p. 1080·3).

Loraped *Pediatrica, Philipp.*
Loratadine (p. 633·2); phenylephrine (p. 1672·2).
Allergic rhinitis in children.

Lorapharm *Stada, Denm.; Actavis, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Lorapine *TMN Impex, Thai.*
Lorazepam (p. 1080·3).

Lora-Puren *Actavis, Ger.†*
Loratadine (p. 633·2).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; urticaria.

Lorariv *East African, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lorasifar *Siphar, Switz.*
Lorazepam (p. 1080·3).
Anxiety; sleep disorders; sedative.

Lorasliv *Vitapan, Braz.*
Loratadine (p. 633·2).

Lorastad *Stada, Neth.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorastine *Schering-Plough, Israel.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorastyne *Bellwether, Austral.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorat *Rowex, Irl.; Oftalmi, Venez.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Loratab *Biospray, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Lora-Tabs *Mylan, NZ.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Loratadine D *Major, USA.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract disorders.

Loratamed *Cimed, Braz.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Loratan *Hasco-Lek, Pol.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loratek *Biovita, Ukr.*
Desloratadine (p. 625·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Lorateva *Med, Turk.*
Loratadine (p. 633·2).

Loratia *Chemo-Drugs, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Loratin *Cipla, India; Julphar, UAE.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; pruritus; allergic skin disorders.

Loratin D *Cipla, India.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).
Allergic rhinitis.

Loratine *Investi, Arg.†; Polpharma, Pol.; Mepha, Switz.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Loraton *Quality, Hong Kong.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Loratrim *Trima, Israel.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loratyn *Yik Kwan, Hong Kong.†*
Loratadine (p. 633·2).

Loratyne *Hua Shin, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loraval *Valmor, Venez.*
Loratadine (p. 633·2).
Rhinitis; allergic conjunctivitis; urticaria; atopic eczema.

Loravan *Suphong, Thai.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Lorax
Note: this name may be used for preparations of different composition.
Wyeth, Braz.
Lorazepam (p. 1080·3).
Anxiety; premedication.

Loraxin *Vitabalans, Fin.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Loraxine *Mepha, Port.†*
Loratadine (p. 633·2).
Allergic rhinitis.

Loraxone *Exir, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Loraz *Gentech, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting associated with chemotherapy; status epilepticus.

Lorazefast *Sigma, Braz.*
Lorazepam (p. 1080·3).
Anxiety; premedication.

Lorazemed *Ranbaxy, Belg.†*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Lorazep *Asian Pharm, Thai.*
Lorazepam (p. 1080·3).
Anxiety.

Lorazetop *Apotex, Belg.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Lorazidime *Exir, Rus.*
Ceftazidime (p. 250·2).
Bacterial infections.

Lorazin *Inpac, Thai.*
Lorazepam (p. 1080·3).
Anxiety; nausea and vomiting; premedication; insomnia.

Lorbef *Lilly, Gr.*
Loracarbef (p. 319·3).
Bacterial infections.

Lorbi *GP, Arg.*
Oral solution: Bromhexine hydrochloride (p. 1656·3).
Bronchitis; obstructive airways disease.

Lorbi-Bis *GP, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Bronchitis; obstructive airways disease.

Lorbicefax *GP, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Lorbifenac *GP, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Lorbifloxacina *GP, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lorbihepatic *Bioquimico, Arg.†*
Cynara (p. 2490·3); dehydrocholic acid (p. 2492·1).
Liver disorders.

Lorbinafil *GP, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Lorbitidina *GP, Arg.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Lorbit-P *Zubit, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lorcam *Taisho, Jpn.*
Lornoxicam (p. 83·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Lorcamin *Coup, Gr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Lorcef *Metz, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Lorcet 10/650 *Forest Pharmaceuticals, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Lorcet Plus *Forest Pharmaceuticals, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Lorcet-HD *Forest Pharmaceuticals, USA.†*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Lorchek-MR *Indoco, India.*
Lornoxicam (p. 83·2); thiocolchicoside (p. 2026·2).

Lorchek-P *Indoco, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lorcin *Cinerea, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting associated with chemotherapy.

Lorcus-O *Ester, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Lordam *Surge, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lordane *Kalbe, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Lorday *Cosme, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Lordes *Nobel, Turk.*
Desloratadine (p. 625·1).

Lordestin *Gedeon Richter, Rus.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Lordin
Note: this name may be used for preparations of different composition.
Masa, Thai.
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.
Vianex (Βιανεξ), Gr.
Omeprazole (p. 1867·2).
Peptic ulcer.

Lorel *Reliance, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting associated with chemotherapy.

Lorelco *Sanofi-Aventis, Canad.†; Otsuka, Philipp.*
Probucol (p. 1475·2).
Hyperlipidaemias; hypercholesterolaemia.

Lorelin *Bergamo, Braz.; Dong Kook, Hong Kong; Cryopharma, Mex.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; uterine fibroids; endometriosis; precocious puberty; breast cancer.

Loremex Antialergico *Phoenix, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic eye disorders; allergic skin disorders.

Loremex Antigripal *Phoenix, Arg.†*
⊗Loratadine (p. 633·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; influenza symptoms.

Loremex Descongestivo *Phoenix, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms; otitis.

Loremid *Meprofarm, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loremix *Ativus, Braz.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Loremix D *Ativus, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).
Nasal congestion.

Loren *Duopharma, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorenil *Effik, Ital.*
Fenticonazole nitrate (p. 578·1).
Fungal skin and vaginal infections.

Lorenin *Pfizer, Port.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; epilepsy.

Loren-Press *Rafarm, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).

Lorentil *Neo Quimica, Braz.*
Terbinafine (p. 593·3).

Lorenzol *Rafarm, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Lorepram *Actavis, Denm.†*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Loress *Biological E, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Loreta *Zuventus, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Loretam *Meda, Ger.*
Lormetazepam (p. 1082·1).
Insomnia; premedication.

Loretsin *Best, Mex.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; atherosclerosis.

Lorex
Note: this name may be used for preparations of different composition.
Dollder, Venez.
Loratadine (p. 633·2).
Allergic eye disorders; allergic rhinitis; allergic skin disorders.

Laborate, India.
Ammonium chloride (p. 1656·1); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

Lorex-AP *Laborate, India.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).

Lorexil M *Mayo, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lorezan *Klonal, Arg.*
Lorazepam (p. 1080·3).
Anxiety.

Lorfast
Note: this name may be used for preparations of different composition.
Cadila, India; Cadila, Philipp.; Be-Tabs, S.Afr.; Cadila, Singapore.
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; hypersensitivity reactions.

Vivax, Gr.
Losartan potassium (p. 1422·2).
Hypertension.

Lorfast-AM *Cadila, India.*
Syrup: Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); loratadine (p. 633·2).

Cadila, India.
Tablets: Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2).

Lorfast-D *Cadila, India.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).

Lorflam-P *Adley, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lorhepatic *GP, Arg.*
Oral drops: Cynara (p. 2490·3).
Digestive disorder.

GP, Arg.
Tablets: Cynara (p. 2490·3); dehydrocholic acid (p. 2492·1).
Digestive disorders.

Lori *Neon, India.*
Diazepam (p. 1063·2).
Skeletal muscle spasm; premedication; alcohol withdrawal syndrome; anxiety; sedative; seizures.

Loricid *Littman, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Loricin *Sigma-Tau, Ital.*
Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Lorid *Finecure, India; Unique, Philipp.; Unique, Rus.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; urticaria.

Loridan *HCS, Neth.†*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; left-ventricular hypertrophy.

Loride *Medinfar, Port.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Loridem *Nycomed, Belg.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication.

Loriden *Giempi, Venez.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Loridin *Zydus, India; Cadila, Rus.; Zydus Cadila, Singapore; Zydus Cadila, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; urticaria; allergic skin disorders.

Loridin-D *Zydus, India.*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Lorien *Aspen, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Lorihess *Rivero, Arg.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Hypovolaemia; shock; haemodilution; leucophaeresis; extracorporeal circulation.

Lorihis *Erlimpex, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Loriken *Kendrick, Mex.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Loril *Essweil, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Loril-HT *Essweil, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorin *Stadmed, India; Great Eastern, Thai.†*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; allergic skin disorders.

Lorinden *Jelfa, Pol.†*
⊗Flumetasone pivalate (p. 1635·2).
Skin disorders.

Lorinden A *Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.; Jelfa, Ukr.*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Lorinden C *Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.; Jelfa, Ukr.*
⊗Flumetasone pivalate (p. 1635·2); clioquinol (p. 273·1).
Infected skin disorders.

Lorinden N *Jelfa, Pol.*
⊗Flumetasone pivalate (p. 1635·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Lorinden Teersalbe *Medphano, Ger.*
Coal tar (p. 1723·2).
Skin disorders.

Lorinid *Actavis, Indon.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; hepatic cirrhosis with ascites.

Lorinol *Micro, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Loripam *Triton, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy; status epilepticus; sedative.

Loris IV *Lernapharm, Canad.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).

Loris BZK *Lernapharm, Canad.*
Benzalkonium chloride (p. 1737·1).

Lorisk *Grandix, India.*
Atorvastatin calcium (p. 1309·2); fenofibrate (p. 1381·1); folic acid (p. 2063·1).
Hyperlipidaemias.

Lorispa *Sidhbali, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lorista
Note: this name may be used for preparations of different composition.
KRKA, Cz.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; cardiovascular risk reduction.

KRKA, Port.
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorista H *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorista HD *KRKA, Rus.; KRKA, Ukr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorita *T-Boma, Hong Kong†; Farmaline, Thai.*
Loratadine (p. 633·2).
Allergic skin disorders.

Loritil *Geolab, Braz.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Loritil D *Geolab, Braz.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).

Loritine *Sandoz, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lorivan *Remedica, Hong Kong; Bal, India; Dexcel, Israel.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy; mixed anxiety depressive states; obsessive-compulsive disorder; psychosomatic disorders.

Loriz *Alvartis, Mex.*
Lincomycin (p. 317·1).
Bacterial infections.

Lorizan *Arterium, Ukr.*
Loratadine (p. 633·2).
Allergic conjunctivitis; urticaria; angioedema insect bites; pruritic dermatitis; allergic rhinitis.

Lorkind *Elfin, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lorlip *Unichem, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lorlip-EZ *Unichem, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lorly *Zodley, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lormed *ProMed, Pol.*
Meloxicam (p. 86·3).
Degenerative joint disorders; rheumatoid arthritis; ankylosing spondylitis.

Lormeg *Alembic, India; Gulf Drug, S.Afr.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lormeg-D *Alembic, India.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).

Lormetamed *Ranbaxy, Belg.†*
Lormetazepam (p. 1082·1).
Insomnia.

Lormide *Westmont, Philipp.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Lormine *Northia, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Lormoto *Minova, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lormoto-P *Minova, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lormyx *Angelini, Gr.*
Rifaximin (p. 355·2).
Gastrointestinal infections.

Lornica *Micro, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lorni-S *Sidhbali, India.*
Ornithine (p. 2085·2).

Lornistar *Intra-Labs, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lornistar-P *Intra-Labs, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lornit *Zuventus, India.*
Injection; oral sachets; tablets: Ornithine aspartate (p. 2085·2).

Zuventus, India.
Syrup: Ornithine aspartate (p. 2085·2); nicotinamide (p. 2083·1); riboflavin (p. 2104·3).

Lorniz *Ritz, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lornizol *Obolenskoe, Rus.*
Ornidazole (p. 943·1).
Trichomoniasis; amoebiasis; giardiasis.

Lornofan *Emar, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lornofan-P *Emar, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lornoxi *Hetero, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lornoxi-P *Hetero, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Loromycin *Novartis, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Loron *Roche, Irl.†; Roche, UK.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis; bone pain; tumour-induced osteolysis and bone pain.

Loronet *Klar Sehen, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lorophyn *Schering-Plough, Arg.; Columbia, Mex.†; Eczacibasi, Turk.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Lorotec *Maver, Mex.*
Ketorolac (p. 80·2) or ketorolac trometamol (p. 80·2).
Pain.

Lorotens *Aurora, Gr.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure.

Lorotens Plus *Aurora, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorox *Dyota, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lorpa *Beacons, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Lorphen *Ind-Swift, India.*
Flurbiprofen (p. 65·2).
Prevention of miosis during ocular surgery; inflammation following eye surgery.

Lorpik *Aarpik, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

Lorsacor *Hexal, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Lorsaid *Piramal, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lorsaid-P *Piramal, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lorsar + HCT *Hexal, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorsedal *Prospa, Port.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; epilepsy.

Lorsedin *Siam Bheasach, Thai.*
Loratadine (p. 633·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Lorson *IPI, Indon.*
⊗Dexchlorpheniramine maleate (p. 621·1); dexamethasone (p. 1630·3).
Allergic disorders.

Lortaan *MSD, Ital.; Medinfar, Port.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Lortaan Plus *Medinfar, Port.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lortab *UCB, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Lortab ASA *UCB, USA.†*
Hydrocodone tartrate (p. 67·2); aspirin (p. 22·2).
Pain.

Lortadine *Olan-Kemed, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Lortal *Novag, Mex.*
⊗Chlortalidone (p. 1335·2).
Hypertension.

Lortan *Aronex, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Lortazil Plus *Chemica, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorter-P *Gujarat Terce, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lorthox-P *Neiss, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lortuss DM *Poly, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Lortuss EX *Poly, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Lortuss HC *Proethic, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Lortuss LQ *Poly, USA.*
⊗Doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Lorup Plus *FDC, India.*
Lornoxicam hydrochloride (p. 83·2); paracetamol (p. 115·1).

Lorvan *Cipla, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

Lorvas *Torrent, India; Torrent, Rus.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Lorvaten *Pharmex (Φαρμεξ), Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Lorwalk *Invision, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Lorwalk-P *Invision, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Loryna *Sandoz, USA.*
24 Tablets, ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1); 4 tablets, inert.
Combined oral contraceptive.

Lorzaar *MSD, Ger.*
Losartan potassium (p. 1422·2).
Heart failure; hypertension; diabetic nephropathy.

Lorzaar plus *MSD, Ger.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorzaar Protect *MSD, Ger.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure.

Lorzan *Clinbaxy, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lorzone *Vertical, USA.*
Chlorzoxazone (p. 2022·2).
Skeletal muscle spasm.

Losaar Plus *Accord, S.Afr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losab *Labochem, Port.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular hypertrophy; diabetic nephropathy.

Losacar *Zydus, India; Zydus Cadila, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Losacar-A *Cadila, India.*
Amlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Losacar-H *Zydus, India; Zydus Cadila, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losachlor *Rafarm, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Losacor *Roemmers, Arg.; Sandoz, Cz.; Biofarm, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; nephropathy; cardiovascular risk reduction.

Losacor D *Roemmers, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losaday *Invision, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losaday-H *Invision, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losaden *BMW, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Losaden-AM *BMW, India.*
Amlodipine (p. 1304·1); losartan (p. 1422·2).

Losaden-H *BMW, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Losadrac *Iasis, Gr.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Losafox *Helm, Neth.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; left-ventricular hypertrophy.

Losagard *Lupin, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Losagen *Generics, Cz.; Generics, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; stroke prophylaxis; diabetic nephropathy.

Losagen Combi *Generics, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losagen-H *Novagen, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losahelm *Helm, Neth.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; left-ventricular hypertrophy.

Losahelm/HCTZ *Helm, Neth.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losain *Sain, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losain-H *Sain, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losakare *Nitro Cadineur, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losakare-H *Nitro Cadineur, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losakind *Mankind, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losakind-H *Mankind, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losalac *T Man, Thai.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Losalen *Novartis, Braz.; Novartis, Ital.; Sandoz, Spain.†*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Losalet *Alet, Gr.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Losalet Plus *Alet, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losamater *Helm, Neth.†*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; left-ventricular hypertrophy.

Losamax *Indoco, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losamax-H *Indoco, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losamel *Clonmel, Irl.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; Helicobacter pylori *eradication in peptic ulcer.*

Losametan *AG Therapy, Gr.*
Losartan potassium (p. 1422·2).

Losamyl Comp *Mylan, Fin.†; Mylan, Swed.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losan *Kopran, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losanin *Ratiopharm, Denm.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Losanorm *Ipca, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losanorm-HR *Ipca, India.*
Losartan potassium (p. 1422·2); ramipril (p. 1483·3).
Hypertension.

Losanox *Liconsa, Neth.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; left-ventricular hypertrophy.

Losapensa Comp *Pensa, Denm.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losapol *Heumann, Irl.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Losapot *Q Check, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losapot-H *Q Check, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losapres *Pharma Investi, Chile.*
Losartan potassium (p. 1422·2).
Heart failure; hypertension.

Losapres Plus *Deva, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Losapres-D *Pharma Investi, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losaprex *Sigma-Tau, Ital.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Losaprin *Royton, Braz.*
Losartan potassium (p. 1422·2).

Losar
Note: this name may be used for preparations of different composition.
Unichem, India.
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losar-A *Unichem, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Losaratio Plus H *Ratiopharm, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Los-Arb *Sandoz, S.Afr.*
Losartan potassium (p. 1422·2).
Hypertension.

Losarb *Specifar, Gr.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Losarb Plus *Specifar, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losar-Beta *Unichem, India.*
⊗Atenolol (p. 1308·2); losartan potassium (p. 1422·2).

Losar-Beta-H *Unichem, India.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).

Losarbio *Farbio, Port.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losarbon *Bayer, Chile.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losarcomp *Genericon, Austria.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losardex *Dexcel, Israel.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Losarel *Lek, Rus.*
Losartan potassium (p. 1422·2).
Hypertension; cardiovascular risk reduction; diabetic nephropathy; heart failure.

Losarep *Invision, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losarep-H *Invision, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losarerin *Labochem, Port.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losargal *Sant Gall, Arg.*
Losartan (p. 1422·2).
Hypertension.

Losargamma *Worwag, Ger.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Losargamma HCT *Worwag, Ger.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losargard *InnoGen, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Losargard Plus *InnoGen, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losar-H *Unichem, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losariv *East African, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losarlan *Lanpharm, Arg.†*
Losartan (p. 1422·2).
Hypertension.

Losarmed *Ceamed, Port.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; stroke prophylaxis in left-ventricular hypertrophy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Losarplus *Aliud, Ger.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losarstad *Stada, Denm.; Stada, Fin.; Stada, Swed.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; left-ventricular dysfunction; diabetic nephropathy; stroke prophylaxis.

Losarstad Comp *Stada, Denm.; Stada, Fin.; Stada, Swed.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losart *Concept, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losarta *CTS, Israel.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Losartan comp *Ratiopharm, Ger.; Winthrop, Ger.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losartan Plus *Hennig, Ger.; CTS, Israel; Teva, Israel.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; stroke prophylaxis.

Losartar H *Shrrishti, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losartas *Intas, India; Intas, Singapore.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; cardiovascular risk reduction.

Losartas-HT *Intas, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losartax *Drossapharm, Switz.*
Losartan potassium (p. 1422·2).
Hypertension.

Losartec *Marjan, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Losartic *Pliva, Cz.†; Farmacom, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Losartil *Drogsan, Turk.*
Losartan potassium (p. 1422·2).

Losartil Plus *Drogsan, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Losartion *Merck, Braz.*
Losartan (p. 1422·2).

Losasun *Sunij, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losasun-HT *Sunij, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losatec *RPG, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losatec-H *RPG, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losathia *Tiefenbacher, Cz.†; Tiefenbacher, Neth.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losatrix *Ratiopharm, Denm.; Ratiopharm, Fin.; Ratiopharm, Swed.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; left-ventricular dysfunction; diabetic nephropathy; stroke prophylaxis.

Losatrix Comp *Ratiopharm, Denm.†; Ratiopharm, Fin.; Ratiopharm, Swed.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losatrust *Centaur, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Losatrust-H *Centaur, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Losavas *Orchid, Indio.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losavas-H *Orchid, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losavik *Anvik, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Losavik-H *Anvik, Indio.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losazid *Orifarm, Denm.†; Sigma-Tau, Ital.; Euro Registratie, Neth.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Losazide *Verisfield, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Löscalcon *Lilly, Ger.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Loscard *Intra-Labs, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Loscard-H *Intra-Labs, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Loscom *Comed, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Loscomb *Orion, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Loscom-H *Comed, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).
Hypertension.

Loscom-R *Comed, Indio.*
Losartan (p. 1422·2); ramipril (p. 1483·3).
Hypertension.

LoSeasonique *Teva, USA.*
84 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, ethinylestradiol.
Biphasic oral contraceptive.

Losec *AstraZeneca, Austria; AstraZeneca, Canad.; AstraZeneca, Chile; Merck, Chile; AstraZeneca, Cz.†; Boyer, Cz.†; AstraZeneca, Denm.; AstraZeneca, Gr.; AstraZeneca, Hung.; Emcure, India; AstraZeneca, Indon.; Abic, Israel; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, NZ; Bayer, NZ; AstraZeneca, Philipp.; AstraZeneco, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Venez.*
Omeprazole (p. 1867·2), omeprazole magnesium (p. 1867·2), or omeprazole sodium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; dyspepsia; heartburn; gastrointestinal haemorrhage.

AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneco, China; AstraZeneca, Fin.; Bayer, Fin.; AstraZeneca, Hong Kong; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Norw.; AstraZeneca, Singapore; Tau, Spain; AstroZeneca, Swed.; AstraZeneca, Thai.
Omeprazole magnesium (p. 1867·2) or omeprazole sodium (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Losec 1-2-3 A *AstraZeneca, Canad.*
Omeprazole magnesium (p. 1867·2); amoxicillin (p. 216·2); clarithromycin (p. 266·2).
Helicobacter pylori-associated peptic ulcer.

Losec Hp7 *AstraZeneca, NZ.*
Capsules, omeprazole (p. 1867·2); capsules, amoxicillin trihydrate (p. 216·2); tablets, clarithromycin (p. 266·2).
Helicobacter pylori-*associated peptic ulcer.*

Losec Hp 7 *AstraZeneca, Austral.†*
Tablets, omeprazole magnesium (Losec) (p. 1867·2); capsules, amoxicillin trihydrate (Amoxil) (p. 216·2); tablets, clarithromycin (Klacid) (p. 266·2).
Helicobacter pylori-*associated peptic ulcer.*

Losec 1-2-3 M *AstraZeneca, Canad.*
Omeprazole magnesium (p. 1867·2); metronidazole (p. 936·1); clarithromycin (p. 266·2).
Helicobacter pylori-associated peptic ulcer.

Losecosan *Bayer, Neth.*
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux.

LosecPro *Bayer, Cz.*
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux.

Losefan *Proel, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Losefar *Eczacibasi, Turk.*
Cefaclor (p. 232·3).
Bacterial infections.

Losepine *Pinewood, Irl.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome in peptic ulcer.

Loseprazol *ProMed, Cz.; Liconsa, Pol.; ProMed, Ukr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Losertrin *Serral, Mex.*
Clindamycin (p. 269·3).
Bacterial infections.

Losferron *Grunenthal, Belg.; SPA, Ital.; Grunenthol, Neth.; Grunenthol, Spain.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Lösferron *Meda, Austria; Meda, Cz.†; Mibe, Ger.; Ulagay, Turk.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Losforexan *Flamingo, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Losil
Note: this name may be used for preparations of different composition.
Alpharma, Mex.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Pan-Ject, Philipp.
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Losin *Zenon, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Losindia *Tiefenbacher, Denm.†*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; stroke prophylaxis; diabetic nephropathy.

Losine *IQFA, Mex.*
Povidone-iodine (p. 1767·1).
Mouth and throat disorders.

Losinon *IQFA, Mex.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Losiram *Bilim, Turk.*
Escitalopram oxalate (p. 416·2).

Losit *Orion, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Losium *Cadila, India.*
Losartan potassium (p. 1422·2).
Hypertension.

Losium-H *Cadila, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Losizopilon *Chosei, Jpn.*
Zotepine (p. 1119·1).
Schizophrenia.

Losmanin *Kleva, Gr.*
Chlorphenamine maleate (p. 620·3).

Lösnesium *Mibe, Ger.*
Magnesium carbonate (p. 1856·2); magnesium oxide (p. 1857·3).
Magnesium deficiency.

Losolvan *Canadian, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Losone *Cadila, India.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Losopil *Medipharm, Chile.*
Zopiclone (p. 1118·1).
Insomnia.

Lospi *Auspi, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lospot *Ind-Swift, Indio.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lospot-AM *Ind-Swift, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Lospotar *Cryopharma, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular hypertrophy; diabetic nephropathy; heart failure.

Lospot-H *Ind-Swift, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Loss *SaSe, Ital.*
Alendronate sodium (p. 1171·3).

Lossor *Finecure, Indio.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lostacef *Ifars, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Lostam *Temis, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Lostamucil *Temis, Arg.*
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome.

Lostankal *Arrow, Denm.; Arrow, Swed.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; left-ventricular dysfunction; diabetic nephropathy.

Lostanorm Plus *Plus Pharma, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lostapres *Temis, Arg.*
Ramipril (p. 1483·3).
Hypertension.

Lostapride *Temis, Arg.*
Mosapride citrate (p. 1865·2).
Dyspepsia; gastritis.

Lostaprolol *Temis, Arg.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Lostar *Polpharma, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

PSA, Philipp.
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lostat *Blue Cross, Indio.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lostat H *Blue Cross, Indio.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lostatin *Reddy, India; Reddy, Malaysia†; Reddy, Singapore.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction; hypercholesterolaemia.

Losterol *Gufic, Indio.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lost-HCT *Remedica, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lostin *Pharmathen, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lostradyl *Chrispa (Χριπα), Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Lostress *Mead Johnson, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Losweat *Stedman, India.*
Chlorhexidine hydrochloride (p. 1743·3); miconazole nitrate (p. 589·1).

Lot *Abbott, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lotace *Karnataka, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Lotace-H *Karnataka, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lotadine *Jean-Marie, Hong Kong; Yung Shin, Singapore.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; allergic skin disorders.

Lotal *Meyer Alian, Venez.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Lotan
Note: this name may be used for preparations of different composition.
Sandoz, Mex.
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.
Taurus, India; Trima, Israel.
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; cardiovascular risk reduction.

Lotan Plus *Trima, Israel.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; stroke prophylaxis.

Lotan-A *Taurus, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).

Lotanec *Liconsa, Denm.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; stroke prophylaxis; diabetic nephropathy.

Lotanol *Teuto, Braz.*
Losartan potassium (p. 1422·2).

Lotanos *Rowex, Irl.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Lotanos Comp *Rowex, Irl.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lotar *Biosintetica, Braz.*
Amlodipine besilate (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Lotaren *Nizphann, Rus.*
Loratadine (p. 633·2).
Hypersensitivity reactions; pruritus.

Lotasbat *Interbat, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Lotazin *HCS, Neth.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Loteak *Medirex, Port.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Loteflam *Cipla, India.*
⊗Loteprednol etabonate (p. 1642·1).
Allergic conjunctivitis.

Lotem *Adcock Ingram, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever.

Lotemax *Bausch & Lomb, Arg.; Mann, Austria; Bausch & Lomb, Canad.; Bausch & Lomb, China; Mann, Ger.; Kite (Κιτε), Gr.; Bausch & Lomb, Hong Kong; Mann, Irl.; SLE, Israel; Bausch & Lomb, Ital.; Mann, Pol.; Bausch & Lomb, Singapore; Bausch & Lomb, Thai.; Abdi, Turk.; Bausch & Lomb, UK; Bausch & Lomb, USA.*
⊗Loteprednol etabonate (p. 1642·1).
Eye inflammation and pain.

Lotemicin *Poen, Arg.*
⊗Loteprednol etabonate (p. 1642·1); tobramycin (p. 380·1).
Inflammatory eye infections.

Lotemos-HT *Genesis, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lotemp *Raptakos, India; Biolab, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Lo-Ten *Pacific, Hong Kong; Pacific, NZ.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; arrhythmias; myocardial infarction.

Loten *Alphapharm, Malaysia.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Lotencin *Pasteur, Philipp.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Lotensin
Note: this name may be used for preparations of different composition.
Kimia, Indon.
Captopril (p. 1331·2).
Hypertension; heart failure.
Novartis, Braz.; Novartis, Canad.; Novartis, China; Meda, Hung.; Novartis, Mex.; Meda, Pol.; Novartis, Rus.; Novartis, USA.
Benazepril hydrochloride (p. 1314·3).
Heart failure; hypertension; renal failure.

Lotensin H *Novartis, Braz.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lotensin HCT *Meda, Hung.; Novartis, Pol.; Novartis, USA.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lotensyl *Sun, India.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Lotensyl-AT *Sun, India.*
⊗Atenolol (p. 1308·2); lercanidipine hydrochloride (p. 1419·3).

Lotepred *Sun, India.*
⊗Loteprednol etabonate (p. 1642·1).
Allergic conjunctivitis; eye inflammation.

Loteprol *BL, Braz.*
⊗Loteprednol etabonate (p. 1642·1).
Inflammatory eye disorders.

Loterex *Bausch & Lomb, Mex.*
⊗Loteprednol etabonate (p. 1642·1).
Inflammatory eye disorders.

Lotesoft *Poen, Arg.; Poen Vision, Mex.; Roemmers Poen, Venez.*
⊗Loteprednol etabonate (p. 1642·1).
Inflammatory eye disorders.

Lotgl *Grandix, India.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Lot-H *Abbott, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Lotharson *Nufarindo, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Lotidyne *Utopian, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Lotifar *CCM, Malaysia.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Lotil *Fenton, UK.*
Emollient.
Dry skin.

Lotin
Note: this name may be used for preparations of different composition.
Intas, India.
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.
Medreich, Hong Kong.
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.
Pentafarma, Port.
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; autism.
Teva, Mex.†
Cefalotin (p. 235·1).
Bacterial infections.

Lotinex *IQFA, Mex.*
Loratadine (p. 633·2).

Lotinor *Quest, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Lotio decapans *Widmer, Switz.*
Resorcinol (p. 1718·3); salicylic acid (p. 1719·1).
Scalp disorders.

Lotio Pruni Comp cum Cupro *Weleda, S.Afr.†*
Arnica (p. 2447·2); citron fruit; copper sulfate (p. 2057·2); hamamelis (p. 2523·3); iris germanica; lappa major (p. 2540·1); silicea (p. 2208·3); blackthorn (p. 2458·2).
Varicose veins.

Lotio Zinci *Floris, Israel.*
Zinc oxide (p. 1729·1).
Skin irritation.

Lotioblanc *Panalab, Arg.*
Tretinoin (p. 1725·2).
Sun-induced skin ageing.

Lotion Calamine avec Antihistaminique *Atlas, Canad.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).

Lotion Ecran Solaire Extreme *Prodemdis, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Lotion Kleen Green *Diversey Lever, Canad.*
Triclosan (p. 1773·2).

Lotion Lubrifiante Calmante Hydratante *Prodemdis, Canad.†*
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2).

Lotion pour Feux Sauvages
Note: this name may be used for preparations of different composition.
Atlas, Canad.
Camphor (p. 2466·2); zinc salicylate (p. 1719·1).
Herpes labialis.

Lotion Sport *Confab, Canad.*
Avobenzone (p. 1695·1); ensulizole (p. 1703·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1).
Sunscreen.

Lotion Très Douce *Ombrelle, Canad.*
SPF 30: Ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Lotion Vapo *Ombrelle, Canad.†*
Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.
Ombrelle, Canad.†
Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); ecamsule (p. 1702·1).
Sunscreen.

Lotivas *Ethica, Indon.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lotoquis *Beta, Arg.*
Phenytoin calcium (p. 538·2); phenobarbital (p. 535·2).
Epilepsy.

Lotoquis Simple *Beta, Arg.*
Phenytoin calcium (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy.

Lotor *Emcure, India; Emcure, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lotorin *Unipharma, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Lotos *Alvartis, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Lotprosin *Actavis, UK.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Lotravel *LKM, Arg.*
Calcitriol (p. 2113·1).

Lotrecin *Cosmopharm, Gr.*
Butamirate citrate (p. 1657·3).

Lotrel *Novartis, USA.*
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Lotremin *MSD, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lotremine *Plough, Port.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lotrial *Roemmers, Arg.; Pharma Investi, Chile.†*
Enalapril maleate (p. 1371·1) or enalaprilat (p. 1371·1).
Heart failure; hypertension.

Lotrial D *Roemmers, Arg.; Pharma Investi, Chile.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lotricomb *Schering-Plough, Arg.; MSD, Ger.; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Skin disorders with fungal infection.

Lotriderm *MSD, Belg.; Merck, Canad.; Schering-Plough, Chile; Schering-Plough, Gr.; Fulford, India; MSD, Irl.; Schering-Plough, Pol.; Schering-Plough, S.Afr.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Skin disorders with fungal infections.
Schering-Plough, Indon.
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2).
Fungal skin infections.

Lotriga *Takeda, Jpn.*
Omega-3-acid ethyl esters (p. 1460·2).
Hyperlipidaemias.

Lotril *Gufic, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lotril-B *Gufic, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2).

Lotril-BG *Gufic, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).

Lotril-LB *Gufic, India.*
Clotrimazole (p. 576·2); lactobacillus (p. 2596·3).

Lotrim *Bal, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lotrimin
Note: this name may be used for preparations of different composition.
Assos, Turk.
Miconazole nitrate (p. 589·1).
Fungal skin infections.
Schering-Plough, Mex.; Schering, USA.
Clotrimazole (p. 576·2).
Fungal skin infections.

Lotrimin AF
Note: this name may be used for preparations of different composition.
Schering-Plough, Mex.; Schering-Plough, USA.
Miconazole nitrate (p. 589·1).
Fungal skin infections.
Schering-Plough, USA.
Cream: Clotrimazole (p. 576·2).
Fungal skin infections.

Lotrimin Ultra *Schering-Plough, USA.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Lotrisone *Schering, USA; Schering-Plough, Venez.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Skin disorders with fungal infection.

Lotronex *Prometheus, USA.*
Alosetron hydrochloride (p. 1816·2).
Irritable bowel syndrome in women.

Lotyn *Interbat, Indon.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Louten *Poen, Arg.; Poen, Chile.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Louten T *Poen, Arg.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Lova *Orchid, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovabeta *Betapharm, Ger.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovacard *Ciplo, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lovachol *Aspen, S.Afr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovacodan *Stada, Denm.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovacol *Saval, Chile; Orion, Fin.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Lovadac *Zydus, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovadrug *Med-One, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lovagamma *Worwag, Ger.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovahexal *Hexal, Ger.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovalip *Cadila, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovameg *Alembic, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovamine *Nuvia, Fr.†*
Amino acids; minerals; vitamin B substances (p. 2102·3).
Aid to weight reduction.

Lovan *Alphapharm, Austral.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Lovanil *Flupal, Venez.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lovapen *Elpen (Ελπεν), Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lovarem *Remedica, Malaysia.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovarin *Collins, Mex.†*
Loratadine (p. 633·2).
Hypersensitivity.

Lovas
Note: this name may be used for preparations of different composition.
Millimed, Thai.
Amlodipine besilate (p. 1304·1).
Hypertension; ischaemic heart disease.

Lovasa *Reliant, USA.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement.

Lovask *Bernofarm, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Lovastad *KRKA, Denm.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovastat *Torrent, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovasten *Vocate, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lovasterol *Polpharma, Pol.; Polpharma, Rus.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Lovastin *YSP, Malaysia; Richter, Pol.; Yung Shin, Singapore.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovastrol *Medley, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovatex *Gap, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovatin *Intas, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovaton *Royton, Braz.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Lovatop *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovatrol *Fahrenheit, Indon.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lovavulo *Codepharma, Fr.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Lovaza *GSK, USA.*
Omega-3-acid ethyl esters (p. 1460·2).
Hypertriglyceridaemia.

Lovecef *Medikon, Indon.†*
Cefradine (p. 249·1).
Bacterial infections.

Lovegin *Elpen (Ελπεν), Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Lovegra *PC India, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Lovelle
Note: this name may be used for preparations of different composition.
Biolab Sanus, Braz.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

MSD, Ger.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lovelle Ciclico *Silesia, Chile.*
Tablets (light green), estradiol (p. 2271·1); tablets (dark green), estradiol; trimegestone (p. 2310·3).
Menopausal disorders.

Lovelle Continuo *Silesia, Chile.*
Estradiol (p. 2271·1); trimegestone (p. 2310·3).
Menopausal disorders; osteoporosis.

Lovenox *Sanofi-Aventis, Austria; Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Port.; Aventis, USA.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders; anticoagulation during haemodialysis and haemofiltration; unstable angina; myocardial infarction.

Lovequin *Kimia, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Loveral *Royere, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Lovetel *Q Check, India.*
Telmisartan hydrochloride (p. 1509·3).
Hypertension.

Lovetel-H *Q Check, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan hydrochloride (p. 1509·3).
Hypertension.

Lovette *Pfizer, Neth.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lovex *Lupin, India.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Lovinacor *Innova, Ital.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Lovinda *Andromaco, Chile.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; androgen-induced acne.

Lovir *Ascent, Austral.; Ranboxy, Hong Kong; Lilly, India; Ranboxy, Malaysia; Douglas, NZ; Ranboxy, Rus.; Ranboxy, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Oboi, Philipp.
Aciclovir sodium (p. 964·1).
Herpesvirus infections.

Lovire *Ranboxy, S.Afr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Lovirem *Farmamust, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Loviroc *Alde Medi Impex, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Loviscol *Wyeth, Philipp.; Wyeth, Venez.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Lovorin *Biomedis, Philipp.*
Calcium folinate (p. 2066·3).
Adjunct to high-dose methotrexate therapy; methotrexate overdosage.

Lovrak *Julphar, UAE.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Low Centyl K *Leo, Irl.*
⊗Bendroflumethiazide (p. 1315·2); potassium chloride (p. 1793·2).
Hypertension.

Low Inteik *Sigma, Arg.*
Dietary fibre; protein.
Dietary supplement.

Lowasa *Mayne, Irl.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Lowater *Bio-Health, UK.*
Buchu (p. 2461·3); bearberry (p. 2453·2); taraxacum (p. 2625·3).
Premenstrual water retention.

Lowcholid *Biomedica, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Low-Deg *Invision, India.*
Paracetamol (p. 115·1).
Pain; fever.

Lowden *Saval, Chile.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Low-Dex *Syntho, India.*
⊗Dexamethasone (p. 1630·3).

Lowdol *Karnataka, India.*
Diclofenac sodium (p. 48·3); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Löwe-Komplex Nr 3 *Infirmarius, Ger.*
Rauwolfia serpentina (p. 1485·1); barium carbonicum (p. 2452·2); crataegus (p. 2488·1); nitroglycerinum (p. 1391·2); viscum album (p. 2560·2).
Homoeopathic preparation.

Löwe-Komplex Nr 6 *Infirmarius, Ger.*
Nux-vomica (p. 2573·3); acidum hydrochloricum (p. 2528·3); acidum nitricum (p. 2572·3); acidum sulfuricum (p. 2624·2); aluminium oxydatum (p. 1690·3); bryonia (p. 2461·3); carbo vegetabilis (p. 1537·3); citrullus colocynthis (p. 1833·3); lycopodium clavatum (p. 2547·1); condurango (p. 2485·3); anacardium (p. 2471·3).
Homoeopathic preparation.

Löwe-Komplex Nr 10 *Infirmarius, Ger.*
Convallaria majalis (p. 2486·2); adonis vernalis (p. 2431·1); ammi visnaga (p. 2441·2); arnica montana (p. 2447·2); crataegus (p. 2488·1); natrium tetrachloroauratum (p. 2521·2); selenicereus grandiflorus (p. 2473·2); strophanthus gratus.
Homoeopathic preparation.

Löwe-Komplex Nr 13 *Infirmarius, Ger.*
Solidago virgaurea (p. 2620·1); apis mellifica (p. 2445·2); apocynum cannabinum; convallaria majalis (p. 2486·2); digitalis purpurea (p. 1352·3); urginea maritima (p. 1677·3); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Löwe-Komplex Nr 5 Echinacea *Infirmarius, Ger.*
Echinacea ang. (p. 2498·1); apis mellifica (p. 2445·2); baptisia (p. 2647·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Lowette *Pfizer, Belg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; acne.

Lowfin *Mintlab, Chile.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Lowila *BMS, Mex.*
⊗Boric acid (p. 2459·3); urea (p. 1727·3).
Skin cleansing.

Lowila Cake *Westwood-Squibb, USA.*
Skin cleanser.

BMS, Hong Kong.†
Sodium lauril sulfoacetate (p. 2210·3).
Soap substitute.

Lowin *Duopharma, Hong Kong.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lowlip *Medikon, Indon.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lowlipid *Alapis, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Lowpres
Note: this name may be used for preparations of different composition.
Behrens, Venez.
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Lowprin *Euro-Pharm, Canad.*
Aspirin (p. 22·2).

Lowsium Plus *Rugby, USA.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Hyperacidity.

Lowtens *Aurora, Gr.; Biomedica, Gr.*
Piracetam (p. 393·3).

Lowtiyel *Italmex, Mex.*
⊗Testosterone (p. 2305·1).
Hypogonadism.

Lowvo *Simcere, China.*
Palonosetron hydrochloride.
Chemotherapy-induced nausea and vomiting.

Lox *Neon, India.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Loxalate *Alphapharm, Austral.; Mylan, NZ.*
Escitalopram oxalate (p. 416·2).
Depression.

Loxam *Hypermarcas, Braz.; Neo Quimica, Braz.; Merck, Mex.†*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Loxamet *Chemo-Drugs, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Loxamine *Mylan, NZ.*
Paroxetine hydrochloride (p. 440·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Loxanto *Sanofi-Aventis, Cz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Loxapac *Eisai, Fr.*
Loxapine (p. 1082·2) or loxapine succinate (p. 1082·2).
Psychoses.

Sandoz, Canad.; Wyeth, India.
Loxapine hydrochloride (p. 1082·2).
Psychoses.

Wyeth, Gr.
Loxapine succinate (p. 1082·2).
Schizophrenia.

Loxapin *Norma (Νορμα), Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Loxar *Taro, Israel.†*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Loxasid *Toprak, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Loxatrel *Manix, Philipp.†; Tolmann, Philipp.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Loxavit *Vitamed, Israel.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Loxazol *GSK, Neth.; Omega, Neth.; Interdelta, Switz.*
Permethrin (p. 2159·3).
Pediculosis.

Loxcam *Akesiss, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Loxcam-P *Akesiss, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Loxelza *Genepharm, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Loxen *Novartis, Fr.; Novartis, Turk.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; controlled hypotension during anaesthesia; angina pectoris.

Loxetine *March, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states.

Loxeva *Hizon, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Loxibach *Offenbach, Mex.*
Meloxicam (p. 86·3).

Loxibest *Best, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; pain.

Loxibin *Biofarma, Turk.*
Losartan potassium (p. 1422·2).
Hypertension.

Loxibin Plus *Biofarma, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Loxibrin *Merck, Mex.†*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Loxicam-P *Acekinetic, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Loxicard *Nean, India.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Loxidil *LDA, Arg.*
Glycolic acid (p. 1704·3).

Loxifan *Padro, Spain.*
⊗Letrozole (p. 817·1).
Breast cancer.

Loxiflam *Aspen, S.Afr.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Loxiflan *Farmasa, Braz.*
Meloxicam (p. 86·3).
Inflammation; pain.

Loxil *Gracia, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Loxime *Ratiopharm, Denm.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Loxin
Note: this name may be used for preparations of different composition.
Prem, India; Ildong, Philipp.
Ofloxacin (p. 334·3).
Bacterial infections.

5-Loxin
Note: this name may be used for preparations of different composition.
PLT, USA.
Indian frankincense (p. 2507·3).
Osteoarthritis.

Loxinic *Nicholas, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Loxinter *Interbat, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Loxip *Aurobindo, S.Afr.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Loxipen *Morepen, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Loxitan *Vianex (Βιανεξ), Gr.*
Meloxicam (p. 86·3).
Pain; inflammation; rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Loxitane *Watson, USA.*
Loxapine succinate (p. 1082·2).
Psychoses.

Loxitenk *Biotenk, Arg.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Loxitin *Cachet, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Loxitin-P *Cachet, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Loxmed *Westfalen, Neth.*
Oxygen (p. 1799·3).
Hypoxia; cluster headache; hyperbaric oxygen therapy.

L-Oxo *Ind-Swift, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Loxof *Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Thai.; Ranbaxy, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Loxon *Sanofi-Aventis, Pol.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Loxone *Micro, India; Micro, Singapore; Micro, Thai.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Loxone-T *Micro, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Loxonin *Sankyo, Braz.; Daiichi Sankyo, China; Daiichi Sankyo, Jpn; Rhein, Mex.; Sankyo, Philipp.†; Daiichi Sankyo, Thai.; Sankyo, Venez.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; fever.

Loxorol *Best, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Loxtev *Teva, Mex.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Loxyn *Anglo-French Drugs, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Loxzalin *Pond's, Thai.*
Cloxacillin (p. 274·3).
Gram-positive bacterial infections.

Loxzol *Sanify, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Lozaan Co *Akacia, S.Afr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Lozad *Wermar, Mex.†*
Metronidazole (p. 936·1).
Amoebiasis.

Lozadip *Alkem, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Lozan
Note: this name may be used for preparations of different composition.
Teuto, Braz.
Ketoconazole (p. 585·3).
Fungal infections.

Vysoli, Philipp.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Lozonel *Heremco, Gr.*
Losartan potassium (p. 1422·2).

Lozanoc *Stada, Denm.*
Fluconazole (p. 578·2).
Fungal infections.

Lozop
Note: this name may be used for preparations of different composition.
Zentiva, Cz.; Zentiva, Pol.; Zentivo, Rus.; Zentiva, Ukr.
Losartan potassium (p. 1422·2).
Hypertension; heart failure; cardiovascular risk reduction; diabetic nephropathy.

Lozap H *Zentiva, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lozap HCT *Zentiva, Pol.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lozap Plus *Zentiva, Rus.; Zentiva, Ukr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; cardiovascular risk reduction.

Lozapin *Torrent, India.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Lozapine *Taro, Israel.*
Clozapine (p. 1057·3).
Schizophrenia.

Lozaprin *Coup, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Lozarep *Extractum, Hung.*
Losartan potassium (p. 1422·2).

Lozaril *Gentech, India.*
Clozapine (p. 1057·3).
Schizophrenia; parkinsonism-associated psychoses.

Lozaris *Chira, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Lozartil *Novag, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Lozatan *Panagiotis, Gr.*
Losartan potassium (p. 1422·2).

Lozatin *HCS, Neth.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lozee *Apex, India.*
⊗Clobetasone butyrate (p. 1627·3); zinc sulfate (p. 2126·2).

Lozee-GM *Apex, India.*
⊗Clobetasone butyrate (p. 1627·3); miconazole (p. 588·3); zinc sulfate (p. 2126·2).

Lozee-M *Apex, India.*
⊗Clobetasone butyrate (p. 1627·3); miconazole nitrate (p. 589·1); zinc sulfate (p. 2126·2).

Lozep *Psychotropics, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Lozepam *New Life, Thai.*
Lorazepam (p. 1080·3).

Lozeprel *Multilab, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Lozic *Alde Medi Impex, India.*
Fluconazole (p. 578·2).
Fungal infections.

lozid *SoSe, Ital.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Lozide *Servier, Canad.*
⊗Indapamide (p. 1409·2).
Hypertension.

Lozil *Neo Quimica, Braz.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Lozimo *Bioresearch, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Lozione Same Urto *Savoma, Ital.*
Coltsfoot (p. 1659·2); achillea (p. 2427·3); china (p. 2478·3); ginger oil (p. 1844·1).
Hair loss.

Lozione Vittorio *Polifarma, Ital.*
Benzalkonium chloride (p. 1737·1).
Disinfection of burns, skin, and wounds.

Lozitan *Wockhardt, India; HCS, Neth.†*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; stroke prophylaxis.

Lozitar *Pinewood, Irl.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure.

Lozitar Comp *Pinewood, Irl.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Lozopin *Merck, Hong Kong.†*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Lozostun *Rottapharm, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

LP
Note: this name may be used for preparations of different composition.
Nutricia, Ital.
Low protein foods for special diets.

Waves, India.
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

LP Drink *Nutricia-Bago, Arg.; Support, Braz.*
Preparation for enteral nutrition.
Phenylketonuria and other disorders of protein metabolism.

L-Pam *Orchid, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting associated with chemotherapy.

LPD *Servocare, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

L-Peez *VHB, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

L-Peez F *VHB, India.*
Alprazolam (p. 1035·2); fluoxetine (p. 417·1).

L-Peez S *VHB, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Lpf *Milupa, Ital.*
Food for special diets.
Protein metabolism disorders; renal impairment.

LPL *Huxley, UK.*
Light liquid paraffin (p. 2191·2).
Dry skin disorders.

L-Polamidon *Sanofi-Aventis, Ger.*
⊗Levomethadone hydrochloride (p. 83·1).
Opioid withdrawal syndrome; pain.

L-Pril *Orchid, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

L-Pro *Lexus, India.*
Protein.
Dietary supplement.

L-Pro Plus *Lexus, India.*
Protein; vitamins.
Dietary supplement.

LPV *Aspen, Austral.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

LQ10 *SHS Nutricia, UK.*
Food for special diets.
Phenylketonuria.

LQ-500 *Mahakam Beta, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

LQueen *Zenacts, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

LR
Note: this name may be used for preparations of different composition.
McNeil & Argus, India.
Loratadine (p. 633·2).
Hypersensitivity reactions.

Zydus, India.
Losartan (p. 1422·2); ramipril (p. 1483·3).
Hypertension.

LS Rif *Cadila, India.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

L-Siacet *Willow, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

L-Sig *Signova, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

LSky *Pharmacon, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

LSP
Note: this name may be used for preparations of different composition.
Plus, India.
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

LSP Plus *Plus, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

LSR-H *Medihealth, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

LTA *Hospira, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

LT-AM *Nutricia, Cz.*
Food for special diets.
Glutaric aciduria type 1.

LT-Cin *Laborate, India.*
⊗Fluorometholone (p. 1637·2); tobramycin sulfate (p. 380·2).

LTC-Kit *Ind-Swift, India.*
2 Tablets, clarithromycin (p. 266·2); 2 capsules, lansoprazole (p. 1851·3); 2 tablets, tinidazole (p. 949·2).

LTD *Candor, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

L-Ther *Leben, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

L-Thro *Lexus, India.*
Azithromycin (p. 221·2).
Bacterial infections.

L-Thyrox *Hexal, Ger.†*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

L-Thyrox Jod *Hexal, Ger.†*
Levothyroxine sodium (p. 2339·1); potassium iodide (p. 2336·3).
Iodine-deficiency disorders.

L-Tine *Orchid, India.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

LTK250 *Sigma, Arg.*
Potassium citrate (p. 1780·3).
Renal calculi; urinary alkalinisation.

LTP *Sigman, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

LTP-H *Sigman, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

LTR *Sunward, Singapore.*
Codeine phosphate (p. 40·2).

LTR Cough Linctus *Beacons, Singapore.*
Codeine phosphate (p. 40·2).
Cough.

L-Trim *Leben, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

L-Triz *Invision, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

L-Triz Plus *Invision, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

L-Triz-A *Invision, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

LTT Cleanser *Shalaks, India.*
Lavender oil (p. 2541·1); melaleuca oil (p. 2551·1).

L-Tum *Lexus, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Lu Di *Lukang Chenxin, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Lu Bei *Qilu, China.*
Nedaplatin (p. 834·3).

Lu Bi An *Chaoyang Lingqiao, China.*
Gamma-aminobutyric acid (p. 2509·2).

Lu Bi Li *Aolida, China.*
Allopurinol (p. 600·2).

Lu Chang *Yangtze River, China.*
Erdosteine (p. 1665·1).
Cough.

Lu Da *Jincheng Haisi, China.*
Levofloxacin mesilate.
Bacterial infections.

Lu Ding Nuo *Fenghuang, China.*
Troxerutin (p. 2505·3).

Lu Jia Kang *Kanglong, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Lu Lin *Huaxin, China.*
Diclofenac sodium (p. 48·3).

Lu Ming Ao Xin *Renhetang, China.*
Oxaprozin (p. 112·3).

Lu Qi *Kangye, China.*
Indometacin (p. 71·2).

Lu Si Kai *Kang Yuan, China.*
Aceglutamide (p. 2426·2).

Lu Si Qi *Jinyang, China.*
Piracetam (p. 393·3).
Mental function impairment.

Lu Wei Fen *Hengda, China.*
Calcium folinate (p. 2066·3).

Lu Wei Sen *Huida, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Lu Wei Tong *Mei Da Kang Jia Le, China.*
Lysine hydrochloride (p. 2079·3).

Lu Xian Tong *Chase Sun, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Lu Xin An *Chase Sun, China.*
Norfloxacin lactate.
Bacterial infections.

Luan *Molteni, Ital.; Stada, Rus.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Luar-G *Klonal, Arg.*
Hyoscine butylbromide (p. 1845·3).

Luar-G Compositum *Klonal, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Luarprofeno *Luar, Arg.*
Flurbiprofen (p. 65·2).
Inflammatory eye disorders.

Luase *Sigma-Tau, Spain.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Lub Alvar *Alvartis, Mex.*
Hypromellose (p. 2189·2).
Dry eyes.

Lubafax *Ascent, Austral.†*
Lubricant for skin or for medical instruments.

Lubarol *Biovital, Austral.†*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Lubentyl *Sanofi-Aventis, Fr.*
Liquid paraffin (p. 2191·2).
Constipation.

Lubentyl à la Magnésie *Sanofi-Aventis, Fr.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).
Constipation.

Lubetyl *Faran, Gr.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Lubex *Phoenix, Hung.; Permamed, Switz.*
Disodium sulfosuccinated undecenoic acid monoethanolamide (p. 596·3).
Skin disorders.

Lubexyl *Phoenix, Hung.; Magnapharma, Pol.; Permamed, Switz.*
Benzoyl peroxide (p. 1696·1).
Acne.

Lub-Gel *Greenco, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Lubic *Neon, India.*
Lubricating gel.
Urogenital procedures; aid in ECGs.

Lubical *Lisapharma, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Lubire *Pyridam, Indon.*
Myrtillus (p. 2566·2); lutein (p. 2079·2); betacarotene (p. 2051·1); zinc (p. 2126·1); zeaxanthin (p. 2125·3); selenium (p. 2086·3); vitamins.
Dietary supplement.

Lubiziab *Misha, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Luborant *Antigen, UK.†*
Electrolytes (p. 1775·1); carmellose sodium (p. 2175·2); sorbitol (p. 2092·1).
Saliva substitute.

Lubrex
Note: this name may be used for preparations of different composition.
Micro, India.
Carmellose sodium (p. 2175·2).
Dry eyes.

Allerderm, Singapore.†
Sunflower oil (p. 2098·1).
Eczema of the hands.

Lubricano *Farco, Ger.*
⊗Glycerol (p. 2517·2); hyetellose (p. 2188·3).
Adjunct in radiography; catheterisation; endoscopy.

Lubricans *Vitamed, Israel.*
Emollient.
Dry skin.

Lubricante Urologico *MSD, Spain.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Lubricating Nasal Gel *Pharmascience, Canad.*
Macrogol (p. 2547·3); propylene glycol (p. 2205·2).

Lubricating Nasal Mist *Pharmascience, Canad.*
Macrogol (p. 2547·3); propylene glycol (p. 2205·2).

Lubricid *Mediphar, Venez.*
Skin cleanser.
Dry skin.

Lubrictin *Klonal, Arg.*
Chondroitin sulfate (p. 2476·1).
Dry eyes.

Lubriderm *Johnson & Johnson, Chile.*
A range of emollients.
Dry skin.

Warner-Lambert, USA.
Emollient and moisturiser.

Fortbenton, Arg.
Vitamin A (p. 2098·3); progesterone (p. 2300·2); estradiol (p. 2271·1).
Skin disorders.

Lubriderm Daily *Pfizer Consumer, USA.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Dry skin; sunscreen.

Lubriderm UV *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Lubriderm UV 15 *Johnson & Johnson, Chile.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Lubrificante Anestesico *Braun, Port.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Lubrifilm *Alcon Cusi, Spain.†*
Soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Eye irritation.

LubriFresh PM *Major, USA.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); lanolin oil (p. 2219·3).
Dry eyes.

Lubrijoint *Wallace, India.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Lubrik
Note: this name may be used for preparations of different composition.
Grin, Mex.
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Lubrilac *Zwitter, Gr.*
Hypromellose (p. 2189·2).
Dry eyes.

Lubrilag *Atlas, Arg.*
Hypromellose (p. 2189·2).
Dry eyes.

Lubrilax *Normon, Spain.*
Sodium picosulfate (p. 1887·2).
Constipation.

Lubrilin *Grin, Mex.†*
White soft paraffin (p. 2211·3).

Lubri-Mucal *Cetem, Fr.*
⊗Marine collagen (p. 2483·2) guaraprolose (p. 2187·3); methylcellulose (p. 2197·3); glycerol (p. 2517·2).
Anorectal disorders.

Lubrin *Aurora, Austral.†; Upsher Smith, Israel; Kenwood, USA.*
Vaginal lubricant.

Lubriskin *Geritrex, USA.*
Emollient.
Skin disorders.

Lubristil *Moorfields, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Lubri-Tears *Alcon, UK.†*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3); wool fat (p. 2219·3).
Eye lubrication and protection.

LubriTears *Bausch & Lomb, USA.*
Eye ointment: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Bausch & Lomb, USA.
Eye drops: ⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Lubritina Franklin *Millet-Franklin, Arg.†*
Liquid paraffin (p. 2191·2).
Constipation.

Lucai *Colon, India.*
Calcium folinate (p. 2066·3).

Lucassin *Ikaria, Austral.*
⊗Terlipressin acetate (p. 2627·1).
Hepatorenal syndrome.

Lucast *Phanna International, Ukr.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Lucebanol *Hormona, Mex.*
Idebenone (p. 392·3).
Cerebrovascular disorders; mental function disorders.

Lucen *Malesci, Ital.*
Esomeprazole magnesium (p. 1841·1) or esomeprazole sodium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lucenfal *Angelini, Spain.†*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; cerebrovascular disorders.

Lucentis *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Genentech, USA.*
Ranibizumab (p. 2602·1).
Neovascular (wet) age-related macular degeneration; macular oedema following retinal vein occlusion; diabetic macular oedema; choroidal neovascularisation secondary to pathologic myopia.

Lucetam *Egis, Hung.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Piracetam (p. 393·3).
Cerebrovascular disorders; vertigo; myoclonus; mental function impairment; dyslexia; cranial trauma; dementia; chronic alcoholism; learning disorders in children.

Lucheng *Chase Sun, China.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Luci *Ranbaxy, India.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Lucidex
Note: this name may be used for preparations of different composition.
Bago, Arg.
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Xanodyne, USA.
Caffeine (p. 1203·3).

Lucidril *Kyowa, Jpn.*
⊗Meclofenoxate hydrochloride (p. 2550·3).
Disturbed consciousness.

Lucilium *Sandoz, Switz.*
St John's wort (p. 449·1).
Depression; anxiety; insomnia.

Lucille *Organon, Ital.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Luci-N *Ranbaxy, India.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Lucipral *Balu, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Lucipro *Lupin, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lucipro-T *Lupin, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Luck *Wuhan Wujing, China.*
Diclofenac sodium (p. 48·3).
Eye pain and inflammation; inhibition of miosis in cataract surgery.

Luckcare *Epitome, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Lucold *Lupin, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Lucon *Medreich, Hong Kong.*
Fluconazole (p. 578·2).
Fungal infections.

Lucosil *Meda, Denm.*
Sulfamethizole (p. 365·1).
Urinary-tract infections.

Lucoz *Ester, India.*
Fluconazole (p. 578·2).
Fungal infections.

Lucretin *Farmasa, Braz.*
Boric acid (p. 2459·3); salicylic acid (p. 1719·1); ammonium alum (p. 2439·1).
Vulvovaginal disorders.

Lucrin *Abbott, Austral.; Abbott, Belg.; Abbott, Cz.; Abbott, Hung.; Abbott, India; Abbott, Israel; Takeda, Israel; Abbott, Malaysia; Abbott, Mex.; AbbVie, Neth.; Abbott, NZ; Abbott, Port.; Abbott, Rus.; Abbott, Singapore; AbbVie, Switz.; Abbott, Turk.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; endometriosis; breast cancer; uterine fibroids; precocious puberty; preparation for uterine surgery.

Abbott, S.Afr.†
⊗Leuprorelin (p. 2285·3) or leuprorelin acetate (p. 2285·3).
Endometriosis; prostatic cancer; precocious puberty.

Lucrin Depot *Abbott, Pol.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; uterine fibroids; endometriosis; premature puberty.

Ludea *Gedeon Richter, Hung.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ludéal *Pierre Fabre, Fr.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ludent *Sancilio, USA.*
Fluoride (p. 2089·2).
Dental caries prophylaxis.

Ludex *Grisi, Mex.†*
Famotidine (p. 1842·1).
Peptic ulcer.

Ludiomil *Amdipharm, Austria; Pharma Logistics, Belg.; Novartis, Braz.; Novartis, China; Novartis, Cz.; Amdipharm, Denm.; CSP, Fr.; Dolorgiet, Ger.; Amdipharm, Gr.; Amdipharm, Hung.; Novartis, Indon.; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; AFT, NZ; Novartis, Port.; Novartis, Rus.; Pharmaco, S.Afr.; Novartis, Singapore; Amdipharm, Spain; Amdipharm, Swed.; Novartis, Switz.; Novartis, Thai.†; Novartis, Turk.; Novartis, Ukr.; Novartis, Venez.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Novartis, Pol.†
Maprotiline (p. 433·3).
Depression.

Ludios *Soho, Indon.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Luditec *Collins, Mex.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Lueva *Organon, Belg.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Lufac-Z *Zafiro, Mex.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Lufer *Drossapharm, Switz.†*
Ferrous fumarate (p. 2060·3); ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Luffa compositum-Heel *Heel, Austria.*
⊗Aralia racemosa; arsenum jodatum (p. 2448·1); lobelia inflata (p. 2323·2); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Luffa Med Complex *Dynamit, Austria.*
Aconitum (p. 2428·3); cepa (p. 2575·2); kalium bichromicum (p. 2476·3); luffa (p. 2545·3).
Homoeopathic preparation.

Luffa Nasentropfen *DHU, Ger.*
Luffa operculata (p. 2545·3).
Homoeopathic preparation.

Luffanil *VSM, Neth.*
Luffa operculata (p. 2545·3); cardiospermum halicacabum; galphimia glauca.
Homoeopathic preparation.

Luffasan *Sanum-Kehlbeck, Ger.*
Luffa operculata (p. 2545·3).
Homoeopathic preparation.

Luffeel *Heel, Cz.; Peithner, Hung.*
Nasal spray: Luffa operculata (p. 2545·3); thryallis glauca; histaminum (p. 2525·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Cz.; Peithner, Hung.
Tablets: ⊗Aralia racemosa; arseni triiodidum (p. 2448·1); lobelia inflata (p. 2323·2); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Luffeel Comp *Heel, Ger.*
Nasal spray: Luffa operculata (p. 2545·3); thryallis glauca; histaminum (p. 2525·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Heel, Ger.
Tablets: ⊗Aralia racemosa; arsenum jodatum (p. 2448·1); lobelia inflata (p. 2323·2); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Luffeel H *Heel, Neth.*
Tablets: ⊗Aralia racemosa; arsenicum iodatum (p. 2448·1); lobelia inflata (p. 2323·2); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Heel, Neth.
Nasal spray: Luffa operculata (p. 2545·3); galphimia glauca; histaminum (p. 2525·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Luffeel Nasal Spray *Heel, Canad.*
Galphimia glauca; histaminum (p. 2525·2); luffa operculata (p. 2545·3); sulphur (p. 1721·1).
Homoeopathic preparation.

Lufi *Ipca, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lufisan *Sandoz, Braz.*
Simeticone (p. 1886·2).

Luftal *BMS, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Luften *Pharos, Indon.*
Clozapine (p. 1057·3).
Schizophrenia.

Lufyllin *Medpointe, USA.*
Diprophylline (p. 1207·3).
Asthma; reversible bronchospasm.

Lufyllin-GG *Medpointe, USA.*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Asthma; reversible bronchospasm.

Lugaxil *Bruluagsa, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Lugesteron *Leiras, Fin.*
Progesterone (p. 2300·2).
Progesterone deficiency; menstrual and menopausal disorders; female infertility.

Lugs *Vishpha, Ukr.*
Iodine (p. 2336·3); potassium iodide (p. 2336·3).
Mouth and throat inflammation.

Luiflex *Stada, Austria.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; soft-tissue injury.

Luisar *Vianex (Βιανεξ), Gr.*
Azapentacene sulfonate sodium (p. 2451·3).

Luivac *AstraZeneca, Arg.; Sankyo, Cz.; Nycomed, Mex.*
Lysates of: *Staphylococcus aureus; Streptococcus mitis; Streptococcus pyogenes; Streptococcus pneumoniae; Klebsiella pneumoniae; Moraxella catarrhalis; Haemophilus influenzae.*
Respiratory-tract infections; ear infections.

Daiichi Sankyo, Ger.; Sankyo, Pol.; Daiichi Sankyo, Port.; Daiichi Sankyo, Switz.
Lysate of: *Staphylococcus aureus; Streptococcus mitis; Streptococcus pyogenes; Streptococcus pneumoniae; Klebsiella pneumoniae; Moraxella catarrhalis; Haemophilus influenzae.*
Respiratory-tract infections.

Sankyo, Austria.
Lysate from: *Staphylococcus aureus; Streptococcus mitis; Streptococcus pyogenes; Streptococcus pneumoniae; Klebsiella pneumoniae; Moraxella (Branhamella) catarrhalis; Haemophilus influenzae.*
Respiratory-tract infections.

Sankyo, Venez.
Staphylococcus aureus; Streptococcus mitis; Streptococcus pyogenes; Streptococcus pneumoniae; Klebsiella pneumoniae; Moraxella catarrhalis; Haemophilus influenzae.
Respiratory-tract infections.

Luka *Mediez, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Lukadin *SF, Ital.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Lukair *Orifarm, Denm.; Farmasix, Port.; MSD, Switz.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Lukasm *Addenda, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Lukastang *MR Pharma, Neth.*
Montelukast sodium (p. 1214·3).
Asthma.

Lukazrol *Umut, Turk.*
Lansoprazole (p. 1851·3).

Lukol *Himalaya Herbal, India.*
Malabar nut (p. 2549·1); areca (p. 2446·3); asparagus racemosus (p. 2614·2); punarnava (p. 2601·1); cuminum cyminum; elettaria cardamomum; nutmeg (p. 2573·1); piper nigrum; rauwolfia serpentina (p. 1485·1); zingiber officinale.

Lukure *TTK, India.*
Asparagus racemosus (p. 2614·2).

Lulicon *Pola Pharma, Jpn.*
Luliconazole (p. 588·1).
Fungal skin infections.

Lullan *Sumitomo, Jpn.*
Perospirone hydrochloride (p. 1095·3).
Schizophrenia.

Luloxy-P *Aronex, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Lumalia *Pierre Fabre Dermatologie, Fr.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne in women.

Lumania *Kleva, Gr.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; acid aspiration; aid in endoscopy.

Lumaren *Elpen (Ελπεν), Gr.; Elpen, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; cacid aspiration; gastro-oesophageal reflux.

Lumbago-Gastreu S R11 *Reckeweg, Ger.*
Berberis vulgaris (p. 2502·1); calcium phosphoricum (p. 1784·2); causticum hahnemanni (p. 2595·3); dulcamara (p. 2497·3); rhododendron; rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Lumbalgine *Cooperation Pharmaceutique, Fr.*
Glycol salicylate (p. 66·2); menthol (p. 2553·2); camphor (p. 2466·2); turpentine oil (p. 2636·3); benzyl nicotinate (p. 29·3).
Muscular disorders.

Lumbax *Vargas, Venez.*
Ibuprofen (p. 68·2).
Inflammation; musculoskeletal and joint disorders; pain.

Lumbicid *Offenbach, Mex.*
Mebendazole (p. 158·3).
Amoebiasis.

Lumbolin *Jelfa, Pol.†*
Benzyl nicotinate (p. 29·3); glycol salicylate (p. 66·2); heparinoids (p. 1401·1).
Musculoskeletal, joint, and peri-articular disorders; neuralgia.

Lumboplex *Knop, Chile.*
Cedron; colocynthis (p. 1833·3); gelsemium (p. 2511·2); gnaphalium; iris vers. (p. 2534·3); magnesium phos. (p. 1787·3).
Homoeopathic preparation.

Lumbrifar *Nafar, Mex.*
Albendazole (p. 149·1).
Worm infections.

Lumbril-T *Yash, India.*
Ibuprofen (p. 68·2); tizanidine hydrochloride (p. 2026·2).

Lumeart *Armour, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Lumecap-A *Acekinetic, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Lumecare Extra Gentle *Medicom, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Lumecare Long Lasting *Medicom, UK.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Lumecare Tear Drops *Medicom, UK.*
Hypromellose (p. 2189·2).
Dry eyes.

Lumen *Nevzat, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Lumeran *Aristopharma, Hong Kong.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Lumerax *Ipca, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Lumether *Themis Medicare, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Lumewal *Prolab, Pol.*
Lupulus (p. 2546·1); lavender (p. 2541·1); motherwort (p. 2564·2); melissa (p. 2552·3); valerian (p. 2640·2).
Sleep disorders; nervous disorders.

Lumicain *Premier Dental, USA.*
Aluminium chloride (p. 1693·3).
Haemorrhage.

Lumiclar *Raymos, Arg.*
Disodium inosinate (p. 2495·2).
Eye disorders.

Lumidrops *Unipharma, Gr.*
Phenobarbital (p. 535·2).
Epilepsy.

Lumigan *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.;*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Allergan, Chile; Allergan, China; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, India; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Senju, Jpn; Allergan, Malaysia; Allergan, Mex.; Allergan, Neth.; Allergan, Norw.; Allergan, NZ; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA; Allergan, Venez.
Bimatoprost (p. 2004·2).
Glaucoma; ocular hypertension.

Lumigard *Svizera, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Lumilac *Bago, Arg.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Lumi-M *Aronex, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Lumin *Alphapharm, Austral.*
Mianserin hydrochloride (p. 434·2).
Depression.

Luminal *Bayer, Arg.; Desitin, Ger.; Bayer, India; Bayer, Port.; Kern, Spain; Merck, Switz.†; Bayer, Turk.*
Phenobarbital (p. 535·2).
Epilepsy; sedative; convulsive disorders; insomnia; excitation; adjunct in the treatment of poisoning.

Desitin, Cz.; Hospira, Philipp.; Hospira, USA.
Phenobarbital sodium (p. 535·3).
Epilepsy; anxiety disorders; premedication; tetanus; eclampsia; anxiety; insomnia; sedative.

Luminale *Bracco, Ital.*
Phenobarbital (p. 535·2) or phenobarbital sodium (p. 535·3).
Epilepsy; sedative; barbiturate withdrawal.

Luminaletas *Bayer, Arg.; Bayer, Port.; Kern, Spain.*
Phenobarbital (p. 535·2).
Epilepsy; convulsive disorders; insomnia.

Luminaletten *Desitin, Ger.; Bayer, Turk.*
Phenobarbital (p. 535·2).
Epilepsy.

Luminalum *Galenus, Pol.; GSK, Pol.; Unio, Pol.*
Phenobarbital (p. 535·2).
Epilepsy; premedication; sedative.

Luminity *Lantheus, Cz.†; BMS, Fr.†; BMS, Irl.†; BMS, Ital.†; BMS, Neth.†; BMS, Pol.†; Lantheus, Port.†; BMS, Spain†; Lantheus, Swed.†; BMS, UK.†*
⊗Perflutren-filled lipid microspheres (p. 1595·2).
Contrast medium for echocardiography.

Luminovag *Novag, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Lumirelax *Juvise, Fr.*
Cream; tablets: Methocarbamol (p. 2025·3).
Musculoskeletal and joint disorders.

Lumirem *Guerbet, Austria; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Guerbet, Ital.; Guerbet, Neth.; Martins & Fernandes, Port.; Gothia, Swed.*
Ferumoxsil (p. 1584·2).
Contrast medium for magnetic resonance imaging of the gastrointestinal tract.

Lumisol *Valuge, Arg.*
Barrier preparation.

Lumitene *Tishcon, USA.*
Betacarotene (p. 2051·1).
Dietary supplement.

Lumix *Bago, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Lumizyme *Genzyme, USA.*
Alglucosidase alfa (p. 2428·1).
Pompe disease.

Lumont *Zydus, S.Afr.*
Montelukast (p. 1214·3).

Lumox *IQFA, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Lumoxbron S *IQFA, Mex.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Bacterial infections.

Lunobell *Nobel, Jpn.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Dysmenorrhoea.

Lunadon *Vifor, Switz.†*
Tolazoline hydrochloride (p. 1516·2); drofenine hydrochloride (p. 1839·3); diphenhydramine hydrochloride (p. 626·2).
Sleep disorders; nervous disorders.

Lunafem
Note: this name may be used for preparations of different composition.
Bayer Schering, Cz.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Bayer, Spain.
Vitamins; minerals.
Dietary supplement during pregnancy and lactation.

Lunair *Genesis, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Lunaldin *Gedeon Richter, Cz.; Richter, Pol.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Lunaline *CCM, Malaysia; Duopharma, Singapore.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Lunan Beite *Lunan, China.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Musculoskeletal disorders.

Lunan Likang *Lunan, China.*
Milrinone (p. 1438·1).
Heart failure.

Lunapret *Bionorica, Pol.*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Sleep disorders.

Lunarex *Charak, India.*
Aloes (p. 1816·1); asafetida (p. 2449·3); cuminum cyminum; wild carrot (p. 2647·2); moringa pterygosperma; rubia cordifolia.
Menstrual disorders.

Lundiran *Vir, Spain.*
Naproxen (p. 98·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Lunelax *Meda, Norw.; Meda, Swed.*
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome.

Lunella *Pfizer, China.*
Medroxyprogesterone acetate (p. 2288·1); estradiol cipionate (p. 2271·1).

Lunesta *Eisai, Jpn; Sepracor, USA.*
Eszopiclone (p. 1072·3).
Insomnia.

Luneste *Microsules, Arg.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease.

Lunex *Metiska, Indon.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema; fibrinolysis.

Lung *Craveri, Arg.*
Bupropion (p. 408·2).
Depression.

Lung Diffusion Test Mix No Ne Co *Praxair, Canad.*
Carbon monoxide (p. 1797·3); neon; nitrogen (p. 1799·3); oxygen (p. 1799·3).

Lung Diffusion Test Mixture Gas *Praxair, Canad.*
Carbon monoxide (p. 1797·3); helium (p. 1798·3); nitrogen (p. 1799·3); oxygen (p. 1799·3).

Lungcaire Plus *Macropharma, Philipp.*
⊗Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); selenium yeast (p. 2125·2); calcium pantothenate (p. 2085·2); zinc oxide (p. 1729·1); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1); quercetin (p. 2505·3); acetylcysteine (p. 1652·2); dimethyl sulfone (p. 2493·3); citrus bioflavonoids (p. 2505·2); boswellia serrata; red grapeseed; green tea (p. 2648·2); elderberry; fenugreek (p. 2504·1); dimethylglycine; bromelain (p. 2460·3); verbascum (p. 2645·1); urtica (p. 2639·3); peppermint leaf (p. 1877·1).
Dietary supplement.

Lungero *Valeant, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Lungfyl *Yash, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Lung-KR *Dolmia, India.*
Drosera peltata (p. 2497·2); cephaelis ipecacuanha.

Lunibron *Valeos, Ital.*
⊗Flunisolide (p. 1635·3).
Obstructive airways disease; allergic rhinitis.

Lunis *Valeas, Ital.*
⊗Flunisolide (p. 1635·3).
Allergic rhinitis; asthma.

Luo De *Qilu, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Luo An *Tianpu, China.*
Ulinastatin (p. 2637·3).

Luo Ao Ke *Neptunus, China.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Luo Bei Er *Yong He, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Luo Bei Jing *Bei Da Gao Ke Hua Tai, China.*
Oryzanol (p. 2578·1).

Luo Da Qin *Juneng, China.*
Ligustrazine hydrochloride.

Luo Di Er *Dexin Runsheng, China.*
Terazosin hydrochloride (p. 1511·1).

Luo Fei *Sanjing, China.*
Fleroxacin (p. 298·3).

Luo Fu *Shengbaoluo, China.*
Aciclovir (p. 964·1).

Luo Ge Le *Huajin, China.*
Telmisartan (p. 1509·3).
Hypertension.

Luo Guan *Suzhou No 6, China.*
Prolonium iodide (p. 2343·3).

Luo Guon Jian *DHY, China.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Luo Jin *Wei Lun, China.*
Aldesleukin (p. 810·1).

Luo Jun Qing *Fusen, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Luo Ka Nuo *Zaozhuang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Luo Ke *Xianju, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Luo Ke Xin *Yichun, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Luo Li *Suzhou No 6, China.*
Sisomicin sulfate (p. 357·2).

Luo Li Sa *Hayao, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Luo Lie Tong *KeRui, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Luo Lin *Hengrui, China.*
Piroxicam (p. 125·3).

Luo Mei Er *Guo Feng, China.*
Lomerizine hydrochloride (p. 676·3).

Luo No *Disha, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Luo Ping *Ruixin, China.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Luo Pu *LuoXin, China.*
Sodium demethylcantharidate.

Luo Pu Jia *Tianlong, China.*
Diclofenac potassium (p. 48·3).

Luo Pu Xin *Tianlong, China.*
Fructose sodium diphosphate (p. 2507·2).

Luo Pu Xing *Tianlong, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Luo Qi *Aida, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Luo Rui *LuoXin, China.*
Fluconazole (p. 578·2).

Luo Sha Ning *Yaoyou, China.*
Telmisartan (p. 1509·3).
Hypertension.

Luo Shi Li *De Tian, China.*
Roxithromycin (p. 356·2).

Luo Shun *Suzhou No 6, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Luo Si Mei *Yabo, China.*
Roxithromycin (p. 356·2).

Luo Tang *Yinjian, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Luo Te Wei *Lanzhou Bio, China.*
A live rotavirus vaccine (p. 2416·1).
Active immunisation.

Luo Ting *LuoXin, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Luo Wei *Lanling, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Luo Wei Ke *Meijisi, China.*
Cefixime (p. 240·3).
Bacterial infections.

Luo Xi *Aimeijin, China.*
⊗Bambuterol hydrochloride (p. 1203·1).

Luo Xin Ping *Kangmei, China.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Luo Xin Wei *LuoXin, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Luo Yo *Langyi, China.*
⊗Bisoprolol fumarate (p. 1325·3).

Luo Yi *LuoXin, China.*
Tiapride hydrochloride (p. 1111·2).

Luo Zhi Da *Ruibang, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Luobang *Yangtze River, China.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Luobaomai *Atlantic, China.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Luodan *LuoXin, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Luode *Juneng, China.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Luodi *Livzon, China.*
Etidronate disodium (p. 1182·3).
Osteoporosis.

LuoHao
Note: this name may be used for preparations of different composition.
LuoXin, China.
Urapidil hydrochloride (p. 1520·2).
Hypertension.

Luohao
Note: this name may be used for preparations of different composition.
LuoXin, China.
Ceftezole sodium (p. 252·2).
Bacterial infections.

Luoheng *LuoXin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Luohuaning *NCPC, China.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Luoji *Suzhou No 6, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Luokai *Suzhou No 6, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer.

LuoLi *Hoi Yi, China.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Luoqi *LuoXin, China.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; ischaemic heart disease.

Luoqing *Suzhou No 6, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

LuoTong *Jimin, China.*
Ligustrazine phosphate.

LuoXin *Tianpu, China.*
Urokinase (p. 1520·3).

Luoxin Shoukang *LuoXin, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Luoxin Yanda *LuoXin, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Luoxu *LuoXin, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer.

Luoye *Suzhou No 6, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

LuoYi *Suzhou No 6, China.*
Micronomicin sulfate (p. 324·2).

Luoyu *LuoXin, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Lupamik *Lupin, India.*
Amikacin (p. 214·1).
Bacterial infections.

Lupan *Finadiet, Arg.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); glycerides of oleic, linoleic, palmitic, and stearic acid.
Burns; ulcers; wounds.

Lupaneta Pack *AbbVie, USA.*
⊗Injection, leuprorelin acetate (p. 2285·3); tablets, norethisterone acetate (p. 2294·3).
Endometriosis.

Lupassin *Elmor, Venez.*
Passion flower (p. 2584·1); valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders.

Lupenox *Lupin, India.*
Enoxaparin (p. 1372·3).
Deep-vein thrombosis; thromboembolism prophylaxis; prevention of coagulation during haemodialysis; unstable angina.

Lu-Peracina *Reuffer, Mex.*
Piperazine (p. 163·1).

Lupex *Yung Shin, Philipp.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Luphere *Daewoong, Philipp.*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; prostatic cancer; uterine fibroids; breast cancer; precocious puberty.

Lupibend *Lupin, India.*
Albendazole (p. 149·1).
Giardiasis; worm infections.

Lupical *Lupin, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Lupict *Lupin, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Lupiderm *Lupin, India.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Lupiderm-G *Lupin, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Lupiderm-GM *Lupin, India.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Lupiderm-M *Lupin, India.*
⊗Betamethasone dipropionate (p. 1623·3); miconazole nitrate (p. 589·1).

Lupiderm-S *Lupin, India.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Seborrhoeic dermatitis; psoriasis.

Lupidon *Seid, Spain.*
Calcium pantothenate (p. 2085·2); dimeticone (p. 1886·2); magnesium polygalacturonate (p. 2200·3).
Flatulence.

Lupidon G *Bruschettini, Ital.*
A herpes simplex type 2 vaccine (p. 2392·2).
Active immunisation.

Lupidon H *Bruschettini, Ital.*
A herpes simplex type 1 vaccine (p. 2392·2).
Active immunisation.

Lupidon H+G *Almirall, Switz.*
Lupidon H, a herpes simplex vaccine (type I); Lupidon G, a herpes simplex vaccine (type II) (p. 2392·2).
Herpes simplex infections.

Lupidox *Lupin, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Lupiflam *Lupin, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Lupiflam-C *Lupin, India.*
Caffeine (p. 1203·3); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Lupiflex *Lupin, India.*
Ketoprofen (p. 79·1); thiocolchicoside (p. 2026·2).

Lupigene *Lupin, India.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Lupigestrone *Lupin, India.*
Progesterone (p. 2300·2).
Dysfunctional uterine bleeding; recurrent miscarriage.

Lupigra *Lupin, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Lupigyl *Lupin, India.*
Metronidazole (p. 936·1).

Lupihist *Lupin, India.*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); pseudoephedrine hydrochloride (p. 1676·1).
Formerly contained diphenhydramine hydrochloride, ammonium chloride, and sodium citrate.
Cough.

Lupimeb *Lupin, India.*
Mebendazole (p. 158·3).
Worm infections.

Lupimox *Lupin, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Lupimox Forte *Lupin, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Lupinace *Lupin, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Lupinate *Lupin, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Lupipan *Lupin, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Lupipara *Lupin, India.*
Paracetamol (p. 115·1).
Pain; fever.

Lupisetron *Lupin, India.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Lupisetron Plus *Lupin, India.*
Ondansetron hydrochloride (p. 1872·1); paracetamol (p. 115·1).

Lupispas *Lupin, India.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Lupisulide *Lupin, India.*
Nimesulide (p. 101·3).
Musculoskeletal, joint and peri-articular disorders; pain.

Lupisulide MR *Lupin, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Lupisulide-D *Lupin, India.*
Diclofenac (p. 48·3); nimesulide (p. 101·3).

Lupisulide-P *Lupin, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Lupisulin-N *Shreya, India.*
⊗Isophane insulin injection (p. 475·3).
Diabetes mellitus.

Lupitaz *Lupin, India.*
Piperacillin sodium (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Lupiterra *Lupin, India.*
Tetracycline (p. 373·1).
Bacterial infections.

Lupitros *Lupin, India.*
Travoprost (p. 2012·1).
Glaucoma.

Lupivital *Lupin, India.*
Ginseng (p. 2513·3); vitamins.

Lupivon *Lupin, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Chronic pain.

Lupivon-D *Lupin, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1); diclofenac (p. 48·3).

Lupizole *Lupin, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Lupizyme *Lupin, India.*
⊗Pepsin (p. 2586·1); amylase (p. 2442·1).
Loss of appetite; digestive disorders.

Lupome *Lupin, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Lupome-D *Lupin, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Luprac *Taisho, Jpn.*
⊗Torasemide (p. 1516·3).
Oedema.

Lupram *Lundbeck, Philipp.*
Citalopram (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Luprex *Lupin, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Lupride *Sun, India.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Luprolex *Takeda, Philipp.*
⊗Leuprorelin acetate (p. 2285·3).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids; uterine myoma.

Lupron *Abbott, Arg.; Abbott, Braz.; Abbott, Canad.; Takeda, Jpn†; AbbVie, USA; Abbott, Venez.*
⊗Leuprorelin acetate (p. 2285·3).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids; precocious puberty.

Abbott, Chile.
⊗Leuprorelin (p. 2285·3) or leuprorelin acetate (p. 2285·3).
Endometriosis; prostatic cancer; uterine fibroids; breast cancer; precocious puberty.

Lupus *Biosciences Pharmakon, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Lur *Drossapharm, Switz.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Lura *Sigmar, Ital.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Luramon *Vir, Spain.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; bulimia; obsessive-compulsive disorder.

Lurantal *Astellas, Austria; Intendis, Braz.*
Isotretinoin (p. 1706·2).
Acne.

Lurdex *Liferpal, Mex.*
Albendazole (p. 149·1).
Worm infections.

Luride *Colgate Oral, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Lurispan *Romsa, Mex.*
Diphenhydramine (p. 626·1).
Insomnia.

Lurline PMS *Fielding, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); pyridoxine (p. 2105·3).
Premenstrual syndrome.

Luro *Regiomedica, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Luroxime *Admac, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Lurselle *Aventis, Thai.*
Probucol (p. 1475·2).
Hypercholesterolaemia.

Lusanoc *Meprofarm, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Lusantem *Salus, Mex.*
Meropenem (p. 321·3).
Bacterial infections.

Lusedan *Leti, Venez.*
Sertraline hydrochloride (p. 448·1).
Depression.

Lusedra *Eisai, USA.†*
Fospropofol sodium (p. 1902·1).
General anaesthesia.

Lusemin *Best, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Lusert *Pinewood, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression.

Lusimva *Balu, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Lusocef *Medilusa, Port.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Lusonal *WraSer, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Lusopress *Lusofarmaco, Cz.*
Nitrendipine (p. 1456·3).
Hypertension.

Lustec *Biofarma, Turk.*
Sertraline (p. 448·1).

Lustine *Samarth, India.*
Lomustine (p. 818·1).
Malignant neoplasms.

Lustra *Taro, Canad.; Medicis, USA.*
Hydroquinone (p. 1705·1).
Hyperpigmentation.

Lustra-AF *Taro, Canad.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Hyperpigmentation.

Lustragen *Generics, Spain.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Lustral *Pfizer, Irl.; Pfizer, Israel; Pfizer, Turk.; Pfizer, UK.*
Sertraline hydrochloride (p. 448·1).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Lustramerck *Generics, Spain.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Lustys Herbalene *Lane, UK.*
Senna leaf (p. 1885·1); frangula bark (p. 1843·3); sambucus (p. 2609·3); fennel (p. 2503·2).
Constipation.

Lutacare *Biomax, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Lutalmin *Offenbach, Mex.*
Dydrogesterone (p. 2270·1); estradiol (p. 2271·1).
Injectable contraceptive.

Lutamid *Biomedica, Ital.*
Bicalutamide (p. 749·1).

Lutamidal *Zodiac, Braz.; Tecnofarma, Chile.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Lutamin *Dewcare, India.*
Betacarotene (p. 2051·1); minerals; vitamin E acetate (p. 2119·2); mecobalamin (p. 2108·1); arginine (p. 2049·1); lutein (p. 2079·2); lycopene (p. 2546·2).

Luteina *Adamed, Pol.; Adamed, Ukr.*
Progesterone (p. 2300·2).
Menstrual disorders; endometriosis; female infertility; threatened and recurrent miscarriage; menopausal disorders; dysfunctional uterine bleeding.

Lutein-Vision *Blackmores, Austral.*
Big marigold; selenomethionine (p. 2087·1).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lutein-Vision Advanced *Blackmores, Austral.*
Big marigold; selenomethionine (p. 2087·1); zeaxanthin (p. 2125·3); omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Lutene *Herbarium, Braz.†*
⊗Agnus castus (p. 2432·2).
Menstrual disorders; female infertility; mastodynia; hyperprolactinaemia.

Lutenil *Merck, Braz.*
Nomegestrol acetate (p. 2294·1).
Menstrual disorders.

Lutenyl *Merck, Arg.; Merck, Belg.; Merck, Chile; Merck, Hong Kong; Merck, Indon.; Theramex, Ital.; Theramex, Pol.; Theramex, Port.; Merck, Turk.; Teva, Ukr.; Theramex, Ukr.*
Nomegestrol acetate (p. 2294·1).
Endometriosis; menopausal disorders; menstrual disorders; fibromas; progesterone deficiency; dysmenorrhoea; hormone replacement therapy; female infertility; recurrent miscarriage; dysfunctional uterine bleeding.

Lutényl *Theramex, Mon.*
Nomegestrol acetate (p. 2294·1).
Menopausal disorders.

Luteoliberina *Elea, Arg.*
⊗Gonadorelin (p. 2280·2).
Amenorrhoea; male and female infertility.

Lutera *Watson, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Lutéran *Sanofi-Aventis, Fr.*
Chlormadinone acetate (p. 2257·3).
Menstrual disorders; fibromas; endometriosis; menopausal disorders.

Lutevision *Ikapharmindo, Indon.†*
Myrtillus (p. 2566·2); lutein (p. 2079·2).
Dietary supplement; antoxidant.

Lutevision Extra *Ikapharmindo, Indon.*
Myrtillus (p. 2566·2); lutein (p. 2079·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement; antoxidant.

Lutevit *Otto, Indon.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); zinc (p. 2126·1).
Dietary supplement for eye health.

Lutinus *Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Neth.; Ferring, Norw.; Ferring, Swed.*
Progesterone (p. 2300·2).
Female infertility.

Lutisone *Incepta, Hong Kong.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Lutivit *Micro, India.*
Betacarotene (p. 2051·1); minerals; vitamin E (p. 2119·1); mecobalamin (p. 2108·1); arginine (p. 2049·1); lutein (p. 2079·2); lycopene (p. 2546·2); zeaxanthin (p. 2125·3).

Lutogin *Amsa, Ital.*
Progesterone (p. 2300·2).
Menstrual disorders; menopausal disorders; female infertility; threatened or habitual miscarriage.

Lutoginestryl F *Sanofi-Aventis, Mex.*
Progesterone (p. 2300·2); estradiol benzoate (p. 2271·1).
Menstrual disorders.

Lutogynestryl *Sanofi-Aventis, Arg.*
Ethisterone (p. 2277·1); ethinylestradiol (p. 2275·3).
Amenorrhoea.

Lutoral
Note: this name may be used for preparations of different composition.
Pfizer, Mex.
Chlormadinone acetate (p. 2257·3).
Menstrual disorders; uterine fibroids; uterine cancer.

Lutoral-E *Pfizer, Mex.*
Chlormadinone acetate (p. 2257·3); mestranol (p. 2291·1).
Menstrual disorders; endometriosis.

Lutorm *IFET (ΙΦΕΤ), Gr.*
Progesterone (p. 2300·2).
Menstrual disorders; hormone replacement therapy; injectable contraceptive; endometriosis; hirsutism; malignant neoplasms.

Lutrate *GP, Spain.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Lutrax *Alcon, Mex.*
Azapentacene (p. 2451·3).
Cataracts.

Lutrelef *Ferring, Austria; Ferring, Fr.; Ferring, Ger.; Ferring, Ital.; Ferring, Neth.; Ferring, Swed.†; Ferring, Switz.*
⊗Gonadorelin acetate (p. 2280·3).
Delayed puberty; male and female infertility; hypogonadal hypogonadism; polycystic ovary syndrome; investigation of hypothalamic-pituitary function; menstrual disorders; amenorrhoea.

Lutrepulse *Ferring, Canad.*
⊗Gonadorelin acetate (p. 2280·3).
Infertility.

Lutropen *Ultra, Mex.*
Pinaverium bromide (p. 2590·3).
Gastrointestinal disorders.

Lutrotam *Danpac, Indon.*
Piracetam (p. 393·3).
Cerebral infarction.

Luuf Balsam *Apomedica, Austria.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); pumilio pine oil (p. 2591·1); Scots pine oil (p. 2591·2); thymol (p. 1772·2).
Respiratory-tract disorders.

Luuf Verkoudheidsbalsem *Takeda, Neth.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); pumilio pine oil (p. 2591·1); scots pine oil (p. 2591·2); turpentine oil (p. 2636·3).

Luuf Verkoudheidsbalsem (voor baby's) *Nycomed, Neth.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); marjoram oil (p. 2550·1); turpentine oil (p. 2636·3).

Luuf Verkoudheidsbalsem (voor kinderen) *Nycomed, Neth.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); turpentine oil (p. 2636·3).

Luuf-Hustentee *Apomedica, Austria.*
Thyme (p. 2630·2); guaifenesin (p. 1666·2); menthol (p. 2553·2); camphor (p. 2466·2); fennel oil (p. 2503·3); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3).
Cough and cold symptoms.

Luuf-Nasenspray *Apomedica, Austria.*
⊗Naphazoline hydrochloride (p. 1669·3); diphenhydramine hydrochloride (p. 626·2).
Colds; hay fever; sinusitis.

Luv *Faran, Gr.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; acid aspiration; aid in endoscopy.

Luva Invisivel *Dermoteca, Port.†*
Barrier preparation.

Luvased mono *Hexal, Ger.†*
Valerian (p. 2640·2).
Anxiety disorders; sleep disorders.

Luvastix *Alchemia, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction following coronary angioplasty.

Luvatren *Yamanouchi, Jpn.†*
Moperone hydrochloride (p. 1088·3).

Luvena Prebiotic *Laclede, Singapore.*
Lactoperoxidase (p. 2539·3); muramidase (p. 2565·1); lactoferrin (p. 2539·3); glycogen (p. 2519·2); D-mannose.
Maintenance of vaginal flora and pH.

Luvenyl *AF, Mex.*
Nomegestrol acetate (p. 2294·1).
Menopausal disorders; menstrual disorders; endometriosis.

Luveris *Merck Serono, Arg.; Merck Serono, Austral.; Serono, Austria; Serono, Belg.; Merck, Braz.; Serono, Canad.; Merck, Chile; Merck Serono, China; Serono, Cz.; Merck Serono, Denm.; Serono, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Merck Serono, Hung.; Merck, Indon.; Merck Serono, Irl.; Merck Serono, Israel; Serono, Ital.; Merck Serono, Malaysia; Serono, Mex.†; Merck, Neth.; Serono, Norw.; Healthcare Logistics, NZ; Merck, Philipp.; Serono, Pol.; Serono, Port.; Serono, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Thai.; Serono, Turk.; Merck Serono, UK; Serono, USA†; Serono, Venez.*
⊗Lutropin alfa (rch) (p. 2287·1).
Female infertility.
Serum Institute, India.
⊗Luteinising hormone (p. 2287·1).

Luvier *Casasco, Arg.*
Ranitidine (p. 1882·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Luvinsta *Actavis, Denm.; Actavis, Irl.†; Actavis, UK.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Luvion
Note: this name may be used for preparations of different composition.
GiEnne, Ital.
⊗Canrenone (p. 1331·1) or potassium canrenoate (p. 1472·2).
Hyperaldosteronism; hypertension.
Intra-Labs, India.
Betacarotene (p. 2051·1); lutein (p. 2079·2); sodium selenite (p. 2087·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Luvis *Medipharm, Chile.*
Hypromellose (p. 2189·2).
Eye irritation; dry eyes.

Luvistar *Diba, Mex.*
Hypromellose (p. 2189·2).
Dry eyes; eye irritation; contact lens lubricant.

Luvmox *Medchem, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Luvos *Dunner, Switz.; Duomed, Switz.*
Clay loam.
Gastrointestinal disorders; skin disorders.

Luvox *Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Royal, Chile; Abbott, China; Solvay, Indon.; Abbott, Jpn; Solvay, Malaysia; Italmex, Mex.; Solvay, S.Afr.; Jazz, USA; Zuoz, Venez.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder; social phobia.

Luxat *Deva, Turk.*
Montelukast sodium (p. 1214·3).

Luxazone *Allergan, Ital.*
⊗Dexamethasone (p. 1630·3).
Eye disorders.

Luxazone Eparina *Tubilux, Ital.*
⊗Dexamethasone (p. 1630·3); heparin sodium (p. 1396·3).
Eye disorders.

Luxeta *Teva, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression.

Luxfen *Jelfa, Cz.; Jelfa, Pol.; Jelfa, Ukr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Luxiq *GSK, Canad.; GSK, USA.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Luxiva Changing *Norman, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Luxiva Flawless *Norman, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Luxiva Lasting *Norman, Canad.†*
SPF 12: Titanium dioxide (p. 1725·1).
Sunscreen.

Luxiva Preventage Firming *Norman, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Luxiva Preventage Hand Treatment *Norman, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Luxiva Sheer Defense *Norman, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Luxofar *Microfar, Arg.*
Coal ar (p. 1723·2).
Psoriasis.

Luxofort *Solfran, Mex.*
Vitamin B substances (p. 2102·3).
Anaemias; neuritis.

Luxomicina *Tubilux, Ital.*
Micronomicin sulfate (p. 324·2).
Eye infections.

Luxyal *AFT, Austral.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Luzamida *Alvartis, Mex.*
⊗Furosemide (p. 1387·1).

Luzamoxin *Alvartis, Mex.*
⊗Tamoxifen (p. 860·2).

Luzampil *Alvartis, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Luzapren *Alvartis, Mex.*
Naproxen (p. 98·2).

Luzarn *Emcure, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Luzei *Zenacts, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Luzei-M *Zenacts, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Luzer *Pharmacon, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Luzer-A *Pharmacon, India.*
Ambroxol hydrochloride (p. 1654·3); levocetirizine hydrochloride (p. 632·3).

Luzer-M *Pharmacon, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Luzin *Novartis, Gr.*
⊗Fluorometholone (p. 1637·2); gentamicin sulfate (p. 304·2).
Inflammatory eye disorders.

Luzina
Note: this name may be used for preparations of different composition.
ToLife, Port.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.
Helm, Port.†
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Luzolona Simple *IQFA, Mex.*
Clioquinol (p. 273·1).

Luzolona Y *IQFA, Mex.*
⊗Clioquinol (p. 273·1); fluocinolone (p. 1636·1).
Infected skin disorders.

Luzul *Baldacci, Ital.*
Lormetazepam (p. 1082·1).
Insomnia.

Lv Ding Fang *Rui Yang, China.*
Levocarnitine (p. 2053·2).

LV Flox *Entod, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lv Kang *Keruide, China.*
Tandospirone citrate (p. 1109·1).

Lv Ke *Changzhou Siyao, China.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; bronchospasm.

Lv Meng *Tian Fu, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Lv Mu An *Weiwu Guangming, China.*
Pseudomonas aeruginosa (p. 2412·3).

Lv Shu *Zhonghai, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Lv Ting Nuo *Luye, China.*
Reduced glutathione (p. 1555·2).
Alcohol liver disorders; drug toxicity; radiation trauma.

L-Vin *Intra-Labs, India.*
Levamisole (p. 157·2).
Worm infections.

L-Vist *Bayer, Gr.*
Galactose (p. 1588·1).
Adjunct to ultrasound.

L-Vit-12 *Laborate, India.*
Cyanocobalamin (p. 2107·2).

L-Vit-Z *Ankom, India.*
Betacarotene (p. 2051·1); lycopene (p. 2546·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

LVM *Laborate, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

LVX *Haledew, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

LX *Apex, India.*
Cefalexin (p. 234·1).
Bacterial infections.

LX-30 *Sigma, Arg.†*
Senna (p. 1885·1); rhubarb (p. 1884·2); magnesium oxide (p. 1857·3).
Constipation.

LXN *Siomond, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lyavinmed *Alchemia, Denm.†*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction following coronary angioplasty.

Lybella *Wassermann, Ital.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lybex *Armoxindo, Indon.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Lybrel *Wyeth, USA.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ly-Butol *Lyka, Rus.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Lycal *East African, India.*
Calcium (p. 1783·1); lysine (p. 2079·3); colecalciferol (p. 2113·1).

Lycalin *Pharmedia (Φαρμεντια), Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Lycalvit *Interbat, Indon.*
Oral syrup: Vitamins; minerals; lysine (p. 2079·3).
Dietary supplement.

Interbat, Indon.
Tablets: Vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); calcium lactate (p. 1784·1); calcium phosphate (p. 1784·2).
Dietary supplement.

Lycazid *Jagsonpal, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Lycazid-M *Jagsonpal, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Lycbound *Arunabh, India.*
Lycopene (p. 2546·2).

Lyceft *Hetero, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Lyceft Plus *Hetero, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Lycelle *Mission Pharmacal, USA.*
Citric acid (p. 2480·3); cytanyl 5; isopropyl alcohol (p. 1758·3).
Pediculosis.

Lyceplix *Pharmacare, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Lycet *Madhav, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lycin *Plus, India.*
Lincomycin (p. 317·1).
Anaerobic bacterial infections.

Lycinate *Sigma, Austral.; Healthcare Logistics, NZ.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Lycit *Uniphar, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Lycit-M *Uniphar, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Lycitrope *Cooper (Κοπερ), Gr.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Lyclear *Johnson & Johnson, Austral.; Chefaro, Irl.; GSK, Irl; GSK, Israel; GSK, S.Afr.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Lyclear Creme Rinse *Omega, UK.*
Permethrin (p. 2159·3).
Pediculosis.

Lyclear Mousse *Omega, UK.*
Dimeticone (p. 2209·3); liquid paraffin (p. 2191·2).
Pediculosis.

Lyclear Spray *Omega, UK.*
Dimeticone (p. 2209·3); liquid paraffin (p. 2191·2).
Pediculosis.

Lyclear Treatment Shampoo *Omega, UK.*
Liquid paraffin (p. 2191·2).
Pediculosis.

Lycoact *Kaizen, India.*
Vitamins; minerals; lycopene (p. 2546·2).

Lycoage *Allenge, India.*
Lycopene (p. 2546·2); minerals; vitamins.

Lycoaktin *Steigerwald, Ger.*
Injection: Lycopus virgin. (p. 2462·2); selenicereus grandiflor. (p. 2473·2); chinin. arsenicosum (p. 2601·3); coffea arab. (p. 2648·2); avena sativa (p. 2451·1).
Homoeopathic preparation.

Lycobal Forte *Fourrts, India.*
d-Alpha tocopherol (p. 2119·1); arginine (p. 2049·1); lycopene (p. 2546·2); mecobalamin (p. 2108·1); *D*-selenium monomethionine; zinc ascorbate (p. 2110·3).

Lycobel *Blubell, India.*
Capsules: Glutamic acid (p. 2070·2); lycopene (p. 2546·2); vitamins; minerals.

Blubell, India.
Syrup: Lycopene (p. 2546·2); vitamins; minerals.

Lycobeta-G *Loyal Advance, Hong Kong.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Inflammation and infection of the eye, ear, or nose.

Lycobig *Bestochem, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin E (p. 2119·1).

Lycobion *Intra-Labs, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycobond *Arunabh, India.*
Lycopene (p. 2546·2); vitamins; minerals; grape seed extract (p. 2521·3).

Lycocare *Ritz, India.*
Lycopene (p. 2546·2); vitamins; minerals; lutein (p. 2079·2); astaxanthin (p. 2170·1); zeaxanthin (p. 2125·3).

Lycocos *Symbiosis, India.*
Lycopene (p. 2546·2); vitamins.

Lycoden-M *BMW, India.*
Vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2); lysine hydrochloride (p. 2079·3).

Lycodric *Candor, India.*
Lutein (p. 2079·2); lycopene (p. 2546·2); selenium dioxide (p. 2087·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1) zinc sulfate (p. 2126·2).

Lycofact Plus *Ritz, India.*
Lutein (p. 2079·2); lycopene (p. 2546·2); vitamins; minerals; astaxanthin (p. 2170·1); zeaxanthin (p. 2125·3).

Lyco-First *Invision, India.*
Capsules: Lycopene (p. 2546·2); sodium selenite (p. 2087·1); vitamins.

Invision, India.
Syrup: Lycopene (p. 2546·2); vitamins.

Lycofit *Biomedica, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycofol *Alkem, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycofresh *PDC, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycogold *Pharmed, India.*
Carotenoids (p. 2176·2); lycopene (p. 2546·2); minerals; vitamin B_{12} (p. 2107·2); wheat-germ oil (p. 2647·1).

Lycogreen *Rapross, India.*
Lycopene (p. 2546·2); betacarotene (p. 2051·1); green tea (p. 2648·2); minerals; vitamin B substances (p. 2102·3).

Lycolar *Stellar, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycolate *Biomiicron, India.*
Glycopyrronium bromide (p. 2519·3).
Reversal of neuromuscular blockade; peptic ulcer; reduction of secretions during surgery.

Lycolife *Intra-Labs, India.*
Lycopene (p. 2546·2); sodium selenite (p. 2087·1); vitamin E (p. 2119·1).

Lycomato
Note: this name may be used for preparations of different composition.
Blossoms, India.
Lycopene (p. 2546·2); minerals.

Orchid, India.
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin E (p. 2119·1).

Lycomax *Ind-Swift, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycomin *Globus, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycomint *Mint, India.*
Lycopene (p. 2546·2); vitamins; sodium selenite (p. 2087·1).

Lycominvit *Radicura, India.*
Betacarotene (p. 2051·1); grape seed (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); minerals.

Lyconerve *Biochemix, India.*
Betacarotene (p. 2051·1); black grape seed (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); mecobalamin (p. 2108·1).

Lyconet Green *Gentech, India.*
Green tea (p. 2648·2); lycopene (p. 2546·2); vitamins.

Lyconia *Little Greave, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lyconova *Elnova, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycopol *Symbiosis, India.*
Ginseng (p. 2513·3); vitamins; minerals.

Lycoprost *Knop, Chile.*
Lycopersicum esculentum (p. 2546·2).
Antoxidant; prostatic cancer.

Lycoq *Meprofarm, Indon.†*
Lycopene (p. 2546·2); ubidecarenone (p. 2637·1); grape seed (p. 2521·3); green tea (p. 2648·2); vitamin E (p. 2119·1).
Antoxidant.

Lycor *Micro, India.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Lycoral-Z *Cubit, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycored *Jagsonpal, India.*
Lycopene (p. 2546·2); vitamins; minerals.
Antoxidant dietary supplement.

Lycorich Plus *Zee, India.*
Lycopene (p. 2546·2).

Lycortin-S *Hetero, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Lycos-CZ *Gujarat Terce, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycosel *Dr Kumars, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycoshine *Quest, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycosim *Symbiotic, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycosta *Daniel Pasteur, India.*
Capsules: Betacarotene (p. 2051·1); vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2); lysine hydrochloride (p. 2079·3).

Daniel Pasteur, India.
Syrup: Carbohydrate; lycopene (p. 2546·2); protein; vitamins; minerals; sucrose (p. 2096·3).

Lycostar *Mankind, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycostar-CM *Mankind, India.*
Calcium ascorbate (p. 2111·1); choline (p. 2055·2); lycopene (p. 2546·2); DL-methionine (p. 1558·2); selenium (p. 2086·3); wheat-germ oil (p. 2647·1); zinc sulfate (p. 2126·2).

Lycoswift *Ind-Swift, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin E (p. 2119·1).

Lycosym *Symbiosis, India.*
Capsules: Lycopene (p. 2546·2); vitamins.

Symbiosis, India.
Syrup: Lycopene (p. 2546·2); vitamins; minerals.

Lycoten *Otto, Indon.*
Lycopene (p. 2546·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Antoxidant.

Lycour *Armour, India.*
Lycopene (p. 2546·2); vitamins; trace elements.

Lycovid *Hovid, Malaysia.*
Lycopene (p. 2546·2); *d*-alpha tocopherol (p. 2119·1); carotenoids; selenium (p. 2086·3); ascorbic acid (p. 2110·3).
Dietary supplement.

Lycovit *Curex, India.*
Lycopene (p. 2546·2); vitamins.

Lycoxy
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Lutein (p. 2079·2); lycopene (p. 2546·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium yeast (p. 2125·2); zinc (p. 2126·1).
Antoxidant.

Medial, India.
Lycopene (p. 2546·2); vitamins; minerals.

Lycozin *Zodley, India.*
Betacarotene (p. 2051·1); vitamins; minerals; lycopene (p. 2546·2); lutein (p. 2079·2); lysine hydrochloride (p. 2079·3).

Lycra *Hauz, India.*
Lycopene (p. 2546·2); vitamins; minerals.

Lycyp *Brawn, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Lydase *Microgen, Rus.; Samson-Med, Rus.*
Hyaluronidase (p. 2527·2).
Burns; ulcers; wounds; musculoskeletal, joint, peri-articular, and soft-tissue disorders; myocardial infarction; hydrocephalus; tuberculosis; inflammation; improvement of drug absorption; eye disorders.

Lydenal *Biomedica, Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Lyderm
Note: this name may be used for preparations of different composition.
PSM, NZ.
Permethrin (p. 2159·3).
Scabies.

Taro, Canad.
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Lydin *Hetero, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration; dyspepsia.

Lydium *Pharos, Indon.*
Sodium hyaluronate (p. 2526·2).
Degenerative joint disorders; orthopaedic surgery.

Lydroxil *Hetero, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Lyflex *Chemidex, UK.*
Baclofen (p. 2014·3).
Spasticity.

Lyflox *Hetero, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Lyforan *Hetero, India; Lyka, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Lygal Kopfsalbe N *Taurus, Ger.†*
Salicylic acid (p. 1719·1).
Scalp disorders.

Lygal Kopftinktur N *Taurus, Ger.*
⊗Prednisolone (p. 1645·2).
Scalp disorders.

Lygnonex *Medopharm, Philipp.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias; local anaesthesia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lykocin *Lyka, Rus.*
Capreomycin sulfate (p. 231·2).
Tuberculosis.

Lyma *2M, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Lyman *Drossapharm, Switz.*
Cream; topical gel: Heparin sodium (p. 1396·3); allantoin (p. 1693·1); dexpanthenol (p. 2582·2).
Soft-tissue disorders; venous insufficiency.

Lyman Mono *Drossapharm, Switz.*
Heparin sodium (p. 1396·3).
Varices; soft-tissue injury; scars.

Lymarin *2M, Thai.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Fungal skin infections.

Lymetel *Grunenthal, Spain.†*
Fluvastatin sodium (p. 1385·1).
Hyperlipidaemias; cardiovascular risk reduction.

Lymfelite *Holland Pharma, Neth.*
Baryta carbonica (p. 2452·2); calcarea fluorica (p. 2053·1); calcarea phosphorica (p. 1784·2); juglans regia (p. 2646·1); kalium phosphoricum (p. 1790·3); natrium sulphuricum (p. 1888·1); phytolacca decandra (p. 2593·2); pinus silvestris (p. 2591·1); scrophularia nodosa; sulfur (p. 1721·1).
Homoeopathic preparation.

Lymipranil *Actavis, Rus.*
Amisulpride (p. 1036·3).
Schizophrenia.

Lymium *Ativus, Braz.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); lycopene (p. 2546·2); selenium (p. 2086·3).

Lym-MX *Natures Sunshine, Canad.*
Vitamins; magnesium (p. 1786·3).

Lympatox *Herbasante, Canad.*
Apis mellifica (p. 2445·2); arnica montana (p. 2447·2); fucus vesiculosus (p. 2612·1); goldenrod (p. 2620·1); hamamelis virginiana (p. 2523·3); new jersey tea; potassium carbonate (p. 2595·2); sodium sulfate (p. 1888·1); taraxacum officinale (p. 2625·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Lymphaden *Hevert, Ger.*
Arsenicum album (p. 2448·1); clematis; lachesis (p. 2538·3); mercurius cyanatus (p. 2555·3); phytolacca (p. 2593·2); rhus tox. (p. 2603·3); scrophularia nodosa; sulfur (p. 1721·1); thuja (p. 2629·3).
Homoeopathic preparation.

Lymphaden Complex *Hevert, Ger.*
Arsenicum album (p. 2448·1); clematis; conium (p. 2524·3); lachesis (p. 2538·3); mercurius biiodatus (p. 2555·3); phytolacca (p. 2593·2); rhus tox. (p. 2603·3); scrophularia nod.; sulfur (p. 1721·1).
Homoeopathic preparation.

Lymphaden Lymphdrusentabletten *Hevert, Ger.*
Arsenum jod. (p. 2448·1); calcium jod. (p. 1658·1); kalium jod. (p. 2336·3); lachesis (p. 2538·3); silicea (p. 2208·3).
Homoeopathic preparation.

Lymphazurin *Tyco, Canad.†; IFET (ΙΦΕΤ), Gr.; US Surgical, USA.*
Sulfan blue (p. 2624·1).
Adjunct to lymphography.

Lymphdiaral *Pascoe, Austria; Pascoe, Neth.*
Ointment: Cream: Conium (p. 2524·3); calendula (p. 2465·2); hydrargyrum bijodatum (p. 2555·3); stibium sulfuratum nigrum (p. 2445·1).
Homoeopathic preparation.

Pascoe, Austria.
Oral drops: Taraxacum officinale (p. 2625·3); calendula officinalis (p. 2465·2); acidum arsenicosum (p. 2448·1); chelidonium majus (p. 2522·2); veronica virginica; echinacea (p. 2498·1); phytolacca americana (p. 2593·2); silybum marianum (p. 1561·1); marsdenia condurango (p. 2485·3); hydrastis canadensis (p. 2528·1); lycopodium clavatum (p. 2547·1); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Pascoe, Austria.
Throat lozenges: Scrophularia nodosa; echinacea (p. 2498·1); hydrargyrum bijodatum (p. 2555·3).
Homoeopathic preparation.

Pascoe, Ger.
Injection: Conium (p. 2524·3); hydrastis (p. 2528·1); phytolacca (p. 2593·2); viscum album (p. 2560·2); scilla (p. 1677·3).
Homoeopathic preparation.

Pascoe, Ger.
Ointment: Conium (p. 2524·3); colchicum e seminibus (p. 607·1); mercurius bijodatus (p. 2555·3); stibium sulfuratum nigrum (p. 2445·1); calendula (p. 2465·2).
Homoeopathic preparation.

Pascoe, Ger.
Oral drops: Hydrastis (p. 2528·1); lycopodium (p. 2546·3); sanguinaria (p. 2610·1); phytolacca (p. 2593·2); echinacea (p. 2498·1); chelidonium (p. 2522·2); arsenicum album (p. 2448·1); calendula (p. 2465·2); taraxacum (p. 2625·3).
Homoeopathic preparation.

Pascoe, Neth.
Oral drops: Taraxacum officinale (p. 2625·3); calendula officinalis (p. 2465·2); arsenicum album (p. 2448·1); chelidonium majus (p. 2522·2); leptandra virginica; phytolacca decandra (p. 2593·2); carduus marianus (p. 1561·1); condurango (p. 2485·3); hydrastis canadensis (p. 2528·1); lycopodium clavatum (p. 2547·1); sanguinaria canadensis (p. 2610·1); echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.

Lymphdiaral Halstabletten *Pascoe, Ger.*
Scrophularia nodosa; echinacea (p. 2498·1); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Lymphdiaral sensitive N *Pascoe, Ger.*
Conium (p. 2524·3); calendula (p. 2465·2); mercurius bijodatus (p. 2555·3); stibium sulfuratum nigrum (p. 2445·1).
Homoeopathic preparation.

Lymphoglobuline *Genzyme, Fr.†; Gerolymatos, Gr.; Aventis Pasteur, India; Imtix Sangstat, Israel†; Genzyme, Neth.†; Genzyme, Pol.†; Aventis, S.Afr.†; Genzyme, Switz.†; Sanofi Pasteur, Turk.*
An antilymphocyte immunoglobulin (horse) (p. 1939·2).
Transplant rejection; graft-versus-host disease; aplastic anaemia.

Lymphomyosot *Heel, Austria.*
Myosotis arvensis; veronica officinalis; equisetum hyemale; smilax utilis; calcium phosphoricum (p. 1784·2); natrium sulfuricum (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxin (p. 2339·1); geranium robertianum; ferrum jodatum (p. 2061·3); gentiana lutea (p. 2512·1); araneus diadematus; teucrium scorodonia; pinus sylvestris (p. 2591·1); scrophularia nodosa; juglans regia (p. 2646·1); nasturtium officinale.
Homoeopathic preparation.

Peithner, Hung.
Veronica officinalis; equisetum hiemale; smilax utilis; calcium phosphoricum (p. 1784·2); natrium sulfuricum (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxin (p. 2339·1); geranium robertianum; ferrum jodatum (p. 2061·3); gentiana lutea (p. 2512·1); aranea diadema; myosotis avensis; teucrium scorodonia; pinus sylvestris (p. 2591·1); scrophularia nodosa; juglans regia (p. 2646·1); nasturtium officinale.
Homoeopathic preparation.

Heel, Cz.
Veronica officinalis; equisetum hiemale; sarsaparilla (p. 2610·3); calcii phosphas (p. 1784·2); natrii sulfas (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxinum (p. 2339·1); geranium robertianum; ferrosi iodidum (p. 2061·3); gentiana lutea (p. 2512·1); aranea diadema; myosotis arvensis; teucrium scorodonia; pinus sylvestris (p. 2591·1); scrophularia nodosa; juglans regia (p. 2646·1); nasturtium aquaticum.
Homoeopathic preparation.

Heel, Ger.
Myosotis arvensis; veronica officinalis; teucrium scorodonia; pinus silvestris (p. 2591·1); gentiana lutea (p. 2512·1); equisetum hiemale; smilax (p. 2610·3); scrophularia nodosa; juglans (p. 2646·1); calcium phosphoricum (p. 1784·2); natrium sulfuricum (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxinum (p. 2339·1); aranea diadema; geranium robertianum; nasturtium officinalis; ferrum jodatum (p. 2061·3).
Homoeopathic preparation.

Heel, Ukr.
Myosotis arvensis; veronica officinalis; teucrium scorodonia; pinus sylvestris (p. 2591·1); gentiana lutea (p. 2512·1); equisetum hyemale; sarsaparilla (p. 2610·3); scrophularia nodosa; juglans regia (p. 2646·1); calcium phosphoricum (p. 1784·2); natrium sulfuricum (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxinum (p. 2339·1); araneus diadematus; geranium robertianum; nasturtium officinale; ferrum jodatum (p. 2061·3).
Homoeopathic preparation.

Heel, Neth.
Silicea (p. 2208·3); baryta carbonica (p. 2452·2); kalium carbonicum (p. 2595·2); iris versicolor (p. 2534·3); china officinalis (p. 2478·3).
Homoeopathic preparation.

Heel, S.Afr.
Myosotis arvensis; veronica officinalis; teucrium scorodonia; pinus sylvestris (p. 2591·1); gentiana lutea (p. 2512·1); equisetum hemale; smilax (p. 2610·3); scrophularia nodosa; calcium phosphoricum (p. 1784·2); natrium sulfuricum (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxinum (p. 2339·1); araneus diadematus; geranium robertianum; nasturtium officinale; ferrum jodatum (p. 2061·3).
Homoeopathic preparation.

Lymphomyosot N *Heel, Ger.*
Myosotis arvensis; veronica; teucrium scorodon; pinus sylvestris (p. 2591·1); gentiana lutea (p. 2512·1); equisetum hiemale; smilax (p. 2610·3); scrophularia nodosa; calcium phosphoric. (p. 1784·2); natrium sulphuric. (p. 1888·1); fumaria officinal. (p. 2508·2); levothyroxin (p. 2339·1); aranea diadema; geranium robertian.; nasturtium aquatic.; ferrum jodat. (p. 2061·3).
Homoeopathic preparation.

Heel, Ukr.
Myosotis arvensis; veronica officinalis; teucrium scorodonia; pinus sylvestris (p. 2591·1); gentiana lutea (p. 2512·1); equisetum hiemale; smilax (p. 2610·3); scrophularia nodosa; calcium phosphoricum (p. 1784·2); natrium sulfuricum (p. 1888·1); fumaria officinalis (p. 2508·2); levothyroxinum (p. 2339·1); araneus diadematus; geranium robertianum; nasturtium officinale; ferrum jodatum (p. 2061·3).
Homoeopathic preparation.

Lymphoseek *Navidea, USA.*
Technetium-99m (p. 2228·1) tilmanocept.
Location of lymph nodes in breast cancer and melanoma.

Lymphozil
Note: this name may be used for preparations of different composition.
Cesra, Ger.; Cesra, Pol.
Echinaceae pallida (p. 2498·1).
Tonic; upper respiratory-tract infection.

Cesra, Cz.†
Thiamine hydrochloride (p. 2103·1); echinacea (p. 2498·1); fucus vesiculosus; lachesis mutus (p. 2538·3); silicii dioxidum; calcii carbonas (p. 1824·3); faex desenzymata.
Tonic.

Lymphozil H *Cesra, Ger.*
Echinacea purpura (p. 2498·1); lachesis mutus (p. 2538·3); phytolacca americana (p. 2593·2).
Homoeopathic preparation.

Lynamid *Lyka, Rus.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Lyncis *Savant, Arg.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Lyncis 24 *Savant, Arg.*
Omeprazole (p. 1867·2).

Lyndan *Austral, Arg.; Cassara, Arg.*
Lindane (p. 2157·1); benzocaine (p. 1980·2).
Pediculosis; scabies.

Lyndavel *Umeda, Philipp.*
Medroxyprogesterone acetate (p. 2288·1).
Adjunct in hormone replacement therapy; endometriosis; progestogen-only injectable contraceptive; menstrual disorders.

Lyndiol *Organon, Turk.*
Lynestrenol (p. 2287·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Lynet *Gentech, India.*
Lycopene (p. 2546·2); vitamins.

Lynlor *Actavis, UK.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Lynoral *Organon, India; Schering-Plough, Indon.; Organon, Neth.*
Ethinylestradiol (p. 2275·3).
Menopausal disorders; menstrual disorders; breast cancer; prostatic cancer; oestrogen deficiency; lactation inhibition; male hypersexuality.

Lynx *Wallace, India.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lyobifidus *Tradiphar, Fr.*
Bifidobacterium bifidus (*Bacillus bifidus*) (p. 2596·3).
Diarrhoea.

Lyoclar *Lyofin, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Lyo-Cortin *Vianex (Βιανεξ), Gr.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Lyoderm *Proel, Gr.*
⊗Chlorocresol (p. 1748·1); urea (p. 1727·3).
Keratolytic.

Lyo-drol *Vianex (Βιανεξ), Gr.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Lyofoam *Medlock Medical, UK.*
Polyurethane foam dressing (p. 1718·1).
Wounds; ulcers.

Lyofoam C *Medlock Medical, UK.*
Activated charcoal (p. 1537·3).
Malodorous wounds.

Lyogel *Phytopharm, Ukr.*
Heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue injury.

Lyogen *Lundbeck, Ger.*
Fluphenazine decanoate (p. 1075·1) or fluphenazine hydrochloride (p. 1075·1).
Psychoses.

Lyomer *Abdi, Turk.†*
Sea water (p. 2612·1).
Nasal congestion.

Lyomer Plus *Qualiphar, Belg.*
Sterile hypertonic sea water (p. 2612·1).
Nasal congestion.

Lyopraz *Medical Pharmaquality, Gr.*
Omeprazole (p. 1867·2).

Lyosan *Farmedia, Gr.*
Losartan potassium (p. 1422·2).

Lyostene *Synthelabo Lavipharm, Gr.*
Alizapride hydrochloride (p. 1815·2).

Lyotret *Biomedica, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Lyovac Cosmegen *Lundbeck, Belg.; Lundbeck, Neth.†; MSD, Thai.*
Dactinomycin (p. 776·3).
Malignant neoplasms.

Lyovial *Fada, Arg.*
Lorazepam (p. 1080·3).
Anxiety.

Lypestar *BMW, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Lyphe *VHB, India.*
Pralidoxime (p. 1571·1).
Organophosphorus poisoning.

Lyphen *Gracia, Indon.*
Leucoselect phytosome (oligomeric polyphenols prepared from *Vitis vinifera* (p. 2521·3)); lycopene (p. 2546·2).
Tonic.

Lyphidox *Alkem, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Lyphocin *APP, Hong Kong; American Pharmaceutical, USA.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Lypholyte *American Pharmaceutical, USA.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Lyprinol *Blackmores, Austral.; Life Plus, UK.*
Green-lipped mussel extract (p. 2522·3).
Joint disorders.

Lypro *Hetero, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Lyprovir *Biomedica, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Lyp-Sine *Blackmores, Austral.*
Lysine hydrochloride (p. 2079·3); ascorbic acid (p. 2110·3); zinc amino acid chelate (p. 2048·3).
Herpes labialis.

Lypsyl *Lornamead, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Lypsyl Cold Sore Gel *Novartis Consumer, Irl.†; Novartis Consumer, UK.*
Lidocaine hydrochloride (p. 1988·2); zinc sulfate (p. 2126·2); cetrimide (p. 1742·1).
Herpes labialis.

Lyramycin *Hetero, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Lyrase *Immunopreparat, Rus.*
Hyaluronidase (p. 2527·2).
Burns; ulcers; wounds; musculoskeletal, joint, periarticular, and soft-tissue disorders; myocardial infarction; hydrocephalus; tuberculosis; inflammation; improvement of drug absorption; eye disorders.

Lyrfhis *Farmaceutica H, Mex.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Lyrica *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain; anxiety; fibromyalgia; postherpetic neuralgia.

Lyrich *Zytras, India.*
Capsules: Lycopene (p. 2546·2); vitamins; minerals.

Zytras, India.
Syrup: Lycopene (p. 2546·2); vitamins.

Lyrich-G *Zytras, India.*
Ginseng (p. 2513·3); lycopene (p. 2546·2); vitamins; minerals.

Lyrinel *Janssen-Cilag, Ger.†; Medac, Ger.†; Janssen-Cilag, Gr.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.*
Oxybutynin hydrochloride (p. 2361·2).
Urinary incontinence; bladder instability.

Lyrinel XL *Janssen-Cilag, Irl.; Janssen-Cilag, UK.*
Oxybutynin hydrochloride (p. 2361·2).
Urinary incontinence; bladder instability.

Lyrsedin *Sons, Mex.†*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

LYS *Nutricia-Bago, Arg.; Nutricia, Ital.*
Food for special diets.
Hyperlysinaemia.

Lysadam Plus *Filadams, Philipp.*
Vitamins; taurine (p. 2626·2); chlorella extract (p. 2475·3); lysine hydrochloride (p. 2079·3).

Lysagor *Kalbe, Indon.*
Pizotifen (p. 678·2).
Vascular headache.

Lysalgo *SIT, Ital.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Lysantin *Medic, Denm.*
Orphenadrine hydrochloride (p. 909·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Lysanxia *Pfizer, Belg.; Sigma-Tau, Fr.*
Prazepam (p. 1098·2).
Anxiety; alcohol withdrawal syndrome.

Lysatox *Gerolymatos, Gr.*
Carbaryl (p. 2150·1).

Lyseen *Novartis Consumer, Ital.*
Pridinol mesilate (p. 2026·1).
Skeletal muscle spasm.

Strathmann, Ger.
Lactic-acid-producing organisms (p. 2596·3).
Vaginal infections.

Lyser *Comed, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Lyser-A Plus *Comed, India.*
⊗Amoxicillin (p. 216·2); serrapeptase (p. 2613·3).
Bacterial infections.

Lyser-D *Comed, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).
Joint disorders; post-traumatic oedema.

Lyser-DP *Comed, India.*
⊗Diclofenac (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Lysicon-V *Klar Sehen, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3).

Lysicon-V c Zinc *Klar Sehen, India.*
Vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2); lysine hydrochloride (p. 2079·3).

Lysin *Be-Tabs, S.Afr.*
Lisinopril (p. 1420·3).

Lysinevita *Frankin, Hong Kong.†*
Cyproheptadine (p. 624·1); lysine (p. 2079·3); vitamins.

Lysmin *Armoxindo, Indon.*
Vitamins; lysine (p. 2079·3).
Dietary supplement.

Lysmin Plus *Armoxindo, Indon.*
Vitamins; lysine (p. 2079·3); selenium (p. 2086·3); arachidonic acid (p. 2446·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); probiotics (p. 2596·3).
Dietary supplement.

Lysmix *Oriental, Philipp.*
Amino acids; vitamin B substances (p. 2102·3); taurine (p. 2626·2); glucose (p. 2068·3).
Nutritional supplement.

Lyso-6 *Pierre Fabre, Fr.; Galenica, Gr.*
Muramidase hydrochloride (p. 2565·1); pyridoxine hydrochloride (p. 2105·3).
Mouth disorders; mouth and throat infections.

Lysobact *Bosnalijek, Rus.; Bosnalijek, Ukr.*
Muramidase hydrochloride (p. 2565·1); pyridoxine hydrochloride (p. 2105·3).
Mouth and throat disorders.

Lysocalmspray *Pierre Fabre, Fr.†*
Cetrimide (p. 1742·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Lysocline *Teofarma, Fr.*
Methacycline hydrochloride (p. 322·3).
Bacterial infections.

Lysodren *HRA, Austria; HRA, Belg.; BMS, Canad.; HRA, Cz.; HRA, Denm.; HRA, Fin.; HRA, Fr.; HRA, Ger.†; IFET, Gr.; BMS, Hong Kong†; HRA, Hung.; HRA, Irl.; Ferlito, Ital.; HRA, Neth.; HRA, Norw.; HRA, Pol.; HRA, Port.; HRA, Spain; Medius, Switz.; HRA, UK; BMS Oncology, USA.*
Mitotane (p. 832·2).
Adrenocortical cancer.

Lysoflam *Cachet, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Cachet, India.
Tablets: Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Cachet, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Lysoform *Lysoform, Ger.*
Formaldehyde (p. 1752·2).
Surface and linen disinfection.

Lysoformin *Lysoform, Ger.*
Formaldehyde (p. 1752·2); glutaral (p. 1753·2).
Surface disinfection.

Lysoformin 3000 *Lysoform, Ger.*
Glyoxal (p. 1754·1); glutaral (p. 1753·2); didecyldimethylammonium chloride (p. 1750·3).
Disinfection of instruments and surfaces.

Lysoformin spezial *Lysoform, Ger.*
Guanidine derivative; didecyldimethylammonium chloride (p. 1750·3).
Disinfection of surfaces.

Lysomucil *Zambon, Belg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus; paracetamol overdose.

Lysonorm *Adipharm, Rus.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Lysopadol *Boehringer Ingelheim, Fr.*
Ambroxol hydrochloride (p. 1654·3).
Sore throat.

Lysopaïne
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Fr.
Muramidase hydrochloride (p. 2565·1); cetylpyridinium chloride (p. 1743·1).
Mouth and throat infections.

Boehringer Ingelheim, Switz.†
⊗Muramidase hydrochloride (p. 2565·1); papain (p. 2582·3); bacitracin (p. 225·3).
Mouth and throat disorders.

Lysopaine
Note: this name may be used for preparations of different composition.
Olvos, Gr.
⊗Muramidase hydrochloride (p. 2565·1); papain (p. 2582·3); bacitracin (p. 225·3).
Mouth disorders.

Lysopaïne dol Ambroxol *Boehringer Ingelheim, Switz.*
Ambroxol hydrochloride (p. 1654·3).
Sore throat.

Lysopaïne N *Boehringer Ingelheim, Switz.*
Muramidase hydrochloride (p. 2565·1); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Lysoplac *Pierre Fabre, Rus.†*
Chlorhexidine gluconate (p. 1743·3); sodium citrate (p. 1781·2); borax (p. 2459·2).

Lysoplex *Alna, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Lysoril *Galenica, Gr.*
Muramidase hydrochloride (p. 2565·1); pyridoxine hydrochloride (p. 2105·3).

Lysosmin *Seiko Eiyo, Hong Kong.†*
Muramidase hydrochloride (p. 2565·1).
Sinusitis; respiratory-tract congestion; haemorrhage.

Lysotossil *Zambon, Belg.*
Cloperastine fendizoate (p. 1659·2) or cloperastine hydrochloride (p. 1659·2).
Cough.

Lysovir *Alliance, UK.*
Amantadine hydrochloride (p. 890·3).
Influenza A.

Lysox *Menarini, Belg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous secretions.

Lyssavac N *Biosano, Chile; Europharma, Philipp.; Berna, Thai.†*
An inactivated rabies vaccine (p. 2413·2).
Active immunisation.

Lysteda *Ferring, USA.*
Tranexamic acid (p. 1164·2).
Menorrhagia.

Lysthenon *Nycomed, Austria; Nycomed, Ger.; Nycomed, Rus.; Takeda, Switz.; Fako, Turk.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Lysthin *Alpharma, Mex.*
Orlistat (p. 2577·1).
Obesity.

Lystin *Biolab, Hong Kong.*
Nystatin (p. 590·3).
Fungal infections.

Lytacur *Dexa, Indon.*
Lysine hydrochloride (p. 2079·3); vitamins; curcuminoid.
Nutritional supplement.

Lyteers *Fischer, Israel.*
Hyetellose (p. 2188·3).
Eye irritation; dry eyes.

Lyto *Comed, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Lytomi-C *Ultra, Mex.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Lytos *Roche, Fr.*
Clodronate disodium (p. 1180·3).
Malignant hypercalcaemia; malignant osteolysis.

Lytox *Forgo, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); arginine (p. 2049·1); lutein (p. 2079·2); lycopene (p. 2546·2); manganese (p. 2081·2); selenium (p. 2086·3); vitamin E acetate (p. 2119·2); zinc oxide (p. 1729·1).

Lyvit *Interbat, Indon.*
Vitamins; lysine (p. 2079·3).
Dietary supplement.

Lyxumia *Sanofi-Aventis, Jpn; Sanofi, UK.*
Lixisenatide (p. 489·1).
Diabetes mellitus.

Lyzip *SM, Gr.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Lyzolin *Lyka, Rus.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Lyzop *Hetero, India.*
Zopiclone (p. 1118·1).
Insomnia.

Lyzyme
Note: this name may be used for preparations of different composition.
Dr Alson, India.
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Shin Poong, Singapore.
Muramidase hydrochloride (p. 2565·1).
Haemorrhage; sinusitis; respiratory-tract congestion.

Lzen *Little Greave, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

L-Zepam *Baroda, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

L-zet *Twilight Litaka, Philipp.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

M & M *Malam, UK.*
Dressing: Cod-liver oil (p. 2056·3); purified honey (p. 2072·1).

M Trol-Z *Malar, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Maacal *Triton, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Maalox *Gerot, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Winthrop, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Philipp.; Rhone-Poulenc Rorer, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Spain; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, Venez.*
Algeldrate or aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
These ingredients can be described by the British Approved Name Co-magaldrox.
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; gastritis; antacid; dyspepsia; heartburn; hiatus hernia.

Sanofi-Aventis, Thai.
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastritis; peptic ulcer; heartburn; dyspepsia.

Maalox Advanced *Novartis Consumer, USA.*
Chewable tablets: Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).

Novartis Consumer, USA.
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Maalox Alum Milk *Sanofi-Aventis, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastritis; peptic ulcer; dyspepsia.

Maalox Antacid with Anti-gas *Novartis Consumer, Canad.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Maalox Antacid Barrier *Novartis, USA.*
Calcium carbonate (p. 1824·3).
Antacid; calcium supplement.

Maalox Ballonnements *Sanofi-Aventis, Fr.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Maalox Childrens *Novartis Consumer, USA.*
Calcium carbonate (p. 1824·3).
Antacid.

Maalox Digestion Difficile *Sanofi-Aventis, Fr.*
Boldine (p. 2458·3); sodium sulfate (p. 1888·1); monosodium phosphate (p. 1791·1).
Digestive disorders.

Maalox Extra Strength with Anti-gas *Novartis Consumer, Canad.*
Oral suspension: Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).

Novartis Consumer, Canad.
Chewable tablets: Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).

Maalox H_2 Acid Controller *Apotex, Canad.†*
Famotidine (p. 1842·1).
Gastric hyperacidity.

Maalox HRF *Novartis, Canad.†*
Calcium carbonate (p. 1824·3); sodium alginate (p. 2167·3); magnesium carbonate (p. 1856·2).
Heartburn; dyspepsia; gastro-oesophageal reflux.

Maalox Max *Novartis, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Antacid; flatulence.

Maalox Maximum Strength Multi-Symptom *Novartis Consumer, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid; flatulence.

Maalox Multi-action *Novartis Consumer, Canad.†*
Bismuth salicylate (p. 1821·3).

Maalox Plus *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Novum, Neth.†; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, UK; Sanofi-Aventis, Venez.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence; antacid; dyspepsia; heartburn; gastritis; gastro-oesophageal reflux; peptic ulcer.

Maalox Plus Antacid Junior *Novartis Consumer, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Antacid; flatulence.

Maalox Quick Dissolve with Antigas *Novartis Consumer, Canad.†*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Antacid; flatulence.

Maalox Regular Strength
Note: this name may be used for preparations of different composition.
Novartis, USA.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid; flatulence.

Maalox TC *Sanofi-Aventis, Ital.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders associated with hyperacidity.

Maalox Total Relief *Novartis, USA.*
Bismuth salicylate (p. 1821·3).
Formerly known as Maalox Total Stomach Relief.
Diarrhoea; dyspepsia; heartburn; nausea; upset stomach.

Maaloxan *Winthrop, Ger.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer.

Maalucol *Labormed, Rus.*
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastritis; peptic ulcer; gastro-oesophageal reflux; dyspepsia.

Maasol *GE Healthcare, Denm.*
⊗Albumin macroaggregates (p. 1130·2).
For radiolabelling with technetium-99m.
Radionuclide lung scanning; venoscintigraphy.

GE Healthcare, Belg.†; GE Healthcare, Fin.; GE Healthcare, Neth.; GE Healthcare, Switz.
Technetium-99m (p. 2228·1) albumin macroaggregates.
Radionuclide lung scanning; venography.

Maat *Plus, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

MabCampath *Genzyme, Austral.; Genzyme, Austria†; Genzyme, Belg.†; Genzyme, Canad.; Genzyme, Cz.†; Genzyme, Denm.†; Genzyme, Fr.†; Genzyme, Ger.†; Genzyme, Gr.†; Schering, Gr.†; Genzyme, Hong Kong; Genzyme, Hung.†; Bayer Schering, Indon.; Genzyme, Irl.†; Schering, Israel†; Genzyme, Ital.†; Genzyme, Malaysia; Bayer, Mex.; Genzyme, Neth.†; Genzyme, Norw.†; Healthcare Logistics, NZ; Genzyme, Pol.†; Genzyme, Port.†; Genzyme, S.Afr.; Genzyme, Singapore; Genzyme, Spain†; Genzyme, Swed.†; Genzyme, Switz.†; Sanofi-Aventis, Thai.; Schering, Turk.; Genzyme, UK.†*
Alemtuzumab (p. 737·1).
Chronic lymphocytic leukaemia.

Mabex *Cofasa, Venez.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Mabicrol *Boehringer Ingelheim Promeco, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Mabis *Lafedar, Arg.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); bismuth subnitrate (p. 1822·1).
Gastrointestinal hyperacidity.

MabKampat *Genzyme, Ukr.*
Alemtuzumab (p. 737·1).
Chronic lymphocytic leukaemia.

Maboclop *Mabo, Spain.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Mabogastrol *Merck, Spain.†*
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Mabron *Medochemie, Cz.; Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Medochemie, Thai.; Morningside, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

MabThera *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, India; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, Venez.*
Rituximab (p. 852·1).
Chronic lymphocytic leukaemia; rheumatoid arthritis; lymphomas; Wegener's granulomatosis; microscopic polyangiitis.

Mabuson *Polfa Pabianice, Pol.†*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Mac Azi *Sigma, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Mac Hyper Real *MAC, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Mac Lip Conditioner *MAC, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Mac Mineralize *MAC, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Mac Prep+Prime Face Protect *MAC, Canad.*
SPF 50: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Mac Select Tint *MAC, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Mac Studio Finish Concealer *MAC, Canad.*
SPF 35: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Mac Studio Moisture *MAC, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Mac Studio Sculpt *MAC, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Mac Studio Stick *MAC, Canad.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Mac Tendertone Lip Balm *MAC, Canad.†*
SPF 12: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Mac Tinted Lip Conditioner *MAC, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Maca Vibe *Rica, Hung.*
Lepidium meyenii.
Tonic.

Macaine *Adcock Ingram, S.Afr.*
Bupivacaine hydrochloride (p. 1980·3).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Macalvit
Note: this name may be used for preparations of different composition.
Novartis Consumer, Austria.
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); ascorbic acid (p. 2110·3).
Calcium and vitamin C deficiency.

Novartis Consumer, India.
Syrup: Calcium glubionate (p. 1783·2); calcium lactobionate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium supplement; tonic.

Novartis, India.
Chewable tablets; tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Novartis Consumer, Ger.†
Effervescent tablets: Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Macar *SoSe, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Macbi *Arvincare, India.*
Ivermectin (p. 155·1).
Worm infections; scabies.

Macbi Plus *Arvincare, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Worm infections.

Macbirs *Maigal, Arg.*
Pantotenyl (p. 2582·2); vitamin F (p. 2509·2).
Scalp disorders.

Macbirs Minoxidil *Maigal, Arg.*
Minoxidil (p. 1438·3).
Alopecia.

Macbirs Sulphur *Maigal, Arg.*
Sulfur (p. 1721·1).
Seborrhoea; pityriasis.

Maccabimol *Perrigo, Israel.*
Paracetamol (p. 115·1).
Pain; fever.

Maccef-LB *Admac, India.*
Cefpodoxime.
Bacterial infections.

Maccef-O *Admac, India.*
Cefpodoxime.
Bacterial infections.

Maccrol *Pharmasant, Thai.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; dyspepsia; flatulence.

Macdafen *Ifarm, Pol.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Macef *Bernofarm, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

M-Aceta *2M, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Macgel *YSP, Malaysia; Yung Shin, Singapore.*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Mach-2 *Tocogino, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Machlor *Eagle, Austral.*
Magnesium chloride (p. 1787·1); magnesium oxide (p. 1857·3); magnesium amino acid chelate (p. 2048·3); pyridoxine hydrochloride (p. 2105·3).
Magnesium and vitamin B_6 supplement.

Machto *Nakornpatana, Thai.*
Oral gel: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; flatulence; heartburn.

Nakornpatana, Thai.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); magnesium hydroxide (p. 1857·2); peppermint oil (p. 1877·1).
Peptic ulcer; gastric hyperacidity; flatulence; heartburn.

Mach-X *Hufort, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Mac-IT *Corona, India.*
Itopride hydrochloride (p. 1850·1); rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux.

Mackenzies Smelling Salts *Actavis, UK.*
Ammonia (p. 2441·2); eucalyptus oil (p. 2501·2).
Catarrh; nasal congestion.

Macladin *Target, Gr.; Guidotti, Ital.*
Clarithromycin (p. 266·2).
Bacterial infections.

Maclar *Abbott, Austria†; Abbott, Belg.; Glenmark, India; Glenmark, Malaysia; Glenmark, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Macleans Mouthguard *GSK Consumer, UK.*
Cetylpyridinium chloride (p. 1743·1); sodium fluoride (p. 2089·2).
Oral hygiene.

Macleans Sensitive *GSK Consumer, Austral.*
Sodium fluoride (p. 2089·2); strontium acetate (p. 2623·1).
Pain associated with sensitive teeth; dental caries prophylaxis.

Maclevo *Macleods, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Macliz *Admac, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Maclong *Euphoric, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Maclorex *Alpharma, Mex.†*
Chloroquine (p. 650·1).
Malaria.

Maclov *Mavi, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Macmax *Anthiea, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Macmiror *Polichem, Cz.; Polichem, Hong Kong; World Pioneer, Hong Kong; Marvecs, Ital.; Italmex, Mex.; Poli, Pol.; CSC, Rus.; Polichem, Ukr.*
Nifuratel (p. 941·2).
Genito-urinary tract infections; intestinal amoebiasis; giardiasis; genito-urinary-tract infections; Helicobacter pylori eradication.

Macmiror Complex *Polichem, Cz.; Polichem, Hong Kong; World Pioneer, Hong Kong; Marvecs, Ital.; Poli, Pol.; CSC, Rus.; Isse, Turk.; Polichem, Ukr.*
Nifuratel (p. 941·2); nystatin (p. 590·3).
Vulvovaginal infections.

Macmiror Complex V *Italmex, Mex.*
Nifuratel (p. 941·2); nystatin (p. 590·3).
Vulvovaginal infections.

Macnatal CN DHA *Macoven, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Macobal *Gramon, Arg.*
Nimodipine (p. 1455·2).
Cerebrovascular disorders; mental function impairment.

Macoderm
Note: this name may be used for preparations of different composition.
Apotex, Arg.
Zinc oxide (p. 1729·1); bismuth salicylate (p. 1821·3).
Barrier preparation.
Farmachimici, Ital.
Soap substitute.
Valuge, Arg.
Zinc oxide (p. 1729·1); soft paraffin (p. 2211·3).
Skin disorders.

Macodin *Parggon, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Maconeuron-OD *Mediez, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Macorate *Sun, India.*
Magnesium valproate (p. 553·1).

Macorel *Elpen (Ελπεν), Gr.; Ranbaxy, S.Afr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Macovan *SF, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Macox *Macleods, India; Macleods, Rus.*
Rifampicin (p. 350·3).
Bacterial infections.

Macox Plus *Macleods, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Macox-ZH *Macleods, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Macparin *Macleods, India.*
Enoxaparin sodium (p. 1372·3).
Unstable angina; myocardial infarction; thromboembolic disorders.

Mac-Pas *Macleods, Rus.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Mac-Pas Plus *Macleods, Rus.*
Sodium aminosalicylate (p. 215·2); isoniazid (p. 311·2).
Tuberculosis.

Mac-Q-Vis *Blackmores, Thai.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1).
Dietary supplement.

Macraberin *Universal Medicare, India.*
Vitamin B substances (p. 2102·3).

Macraberin-M *Universal Medicare, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Macraberin-P *Universal Medicare, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mac-RD *Corona, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Macril *Andromaco, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Macro B *Wyeth, Hong Kong.†*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Macro C *Wyeth, Hong Kong.†*
Hesperidin (p. 2505·2); rutoside (p. 2505·3); ascorbic acid (p. 2110·3).

Macro M *Wyeth, Hong Kong.†*
Vitamins; minerals; lysine (p. 2079·3).

Macro Natural Vitamin E Cream *Vitaco, Austral.*
d-Alpha tocoferil acetate (p. 2119·1); vitamin A palmitate (p. 2098·3); panthenol (p. 2582·2); allantoin (p. 1693·1); avocado oil (p. 2451·2).
Dry skin; minor skin disorders.

Macro-Albumon *Medi-Radiopharma, Cz.*
Technetium-99m (p. 2228·1) labelled human albumin macroaggregate.
Diagnosis of lung disorders; radionuclide imaging of veins.

Macrobee with Iron *Pharma Nutria, Philipp.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Macrobee with Lysine *Pharma Nutria, Philipp.*
Lysine hydrochloride (p. 2079·3); vitamins.
Nutritional supplement; tonic.

Macrobid *Warner Chilcott, Canad.; Goldshield, Irl.; Mercury, UK; Almatica, USA.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Macrocal-D *Ventaglio, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

Macroclar *East West, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Macrodantin *Pfizer, Austral.; Procter & Gamble, Canad.†; Goldshield, Irl.; Geymonat, Ital.†; Boehringer Ingelheim, Philipp.; Aspen, S.Afr.; Goldshield, UK; Almatica, USA.*
Nitrofurantoin (macrocrystalline) (p. 332·1).
Genito-urinary-tract infections.

Macrodantina *Mantecorp, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Farma, Venez.*
Nitrofurantoin (p. 332·1).
Bacterial infections of the urinary tract.

Macrodex *Meda, Denm.; Meda, Norw.; Alliance, S. Afr.†; Meda, Swed.; Eczacibasi-Baxter, Turk.; Pharmacia, USA.†*
⊗Dextran 70 (p. 1138·3) in sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis; shock; haemodilution.

Meda, Hung.
⊗Dextran 60 (p. 1138·3) in sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis.

Macrodin *Unison, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Macrofurin *Mavi, Mex.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Macrogol *Betapharm, Ger.; Ratiopharm, Ger.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Macrol
Note: this name may be used for preparations of different composition.
Sanovel, Turk.
Clarithromycin (p. 266·2).
Bacterial infections.
United American, Philipp.
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Macrolax *SIT, Ital.*
Docusate sodium (p. 1836·2); sorbitol (p. 2092·1).
Constipation.

Macroleuco *Dong-A, Philipp.*
Filgrastim (p. 1151·3).
Neutropenia.

Macrolid-S *SJA, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Macrolin
Note: this name may be used for preparations of different composition.
Standard, Philipp.
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Macromax *Investi, Arg.; Domesco, Philipp.; ICN, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Macromed *MedGen, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Macromicina *Lepetit, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Macronox *Umedica, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Macro-P *Promefarm, Ital.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Macropen
Note: this name may be used for preparations of different composition.
KRKA, Rus.; KRKA, Ukr.
Midecamycin (p. 324·3).
Bacterial infections.
Menarini, Port.
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.
Mylan, S.Afr.
Amoxicillin trihydrate (p. 216·2); flucloxacillin sodium (p. 299·2).
Bacterial infections.

Macroral *Malesci, Ital.*
Midecamycin (p. 324·3).
Bacterial infections.

Macrosafe *MSN, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Macrosalb *Draximage, Neth.†*
Technetium-99m (p. 2228·1) albumin macroaggregates.
Radionuclide lung scanning; venography.

Macrosalb Draximage *Guerbet, Ger.; Draximage, Neth.†*
Technetium-99m albumin macroaggregates (p. 2228·1).
Radionuclide imaging of the lungs; venous scintigraphy.

Macrosan *Sanitas, Chile.*
Nitrofurantoin (p. 332·1).
Bacterial urinary-tract infections.

Macrotar *Torrent, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Macrotec *GE Healthcare, Cz.; GE Healthcare, Port.; GE Healthcare, Spain.*
Technetium-99m (p. 2228·1) labelled human albumin macroaggregate.
Lung scintigraphy; radionuclide imaging of veins; diagnostic agent.

Macrotussin *Sperko, Ukr.*
Erythromycin stearate (p. 291·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Macrovit *KRKA, Ukr.*
Vitamins.
Dietary supplement.

Macrox *Indu, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Macrox-5 *Liferpal, Mex.*
Thiamine (p. 2102·3); vitamin B_{12} (p. 2107·2); pyridoxine (p. 2105·3).
Anaemias; neuritis.

Macroxam *SK, Philipp.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Macrozide *Macleods, India; Macleods, Rus.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Macrozit *Liomont, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Macrozyth *Cipla, Philipp.*
Azithromycin (p. 221·2).
Bacterial infections.

Macskakarom *Ashaninka, Hung.*
Uncaria tomentosa.
Musculoskeletal and joint disorders; immunostimulant.

Mactex *Lafi, Chile.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Macuchek *Indoco, India.*
Carotenoids (p. 2176·2); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc (p. 2126·1); glutathione (p. 1555·2); lutein (p. 2079·2).

Macugen *Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.†; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Norw.†; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.†; Pfizer, Switz.; Pfizer, Thai.†; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Eyetech, USA.*
Pegaptanib sodium (p. 2585·1).
Neovascular (wet) age-related macular degeneration.

Macugold *Ajanta, India.*
Betacarotene (p. 2051·1); carotenoids (p. 2176·2); carrot.

Macula *Horus, Fr.*
Vitamins; minerals; fish oil (p. 1460·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement; maintenance of ocular health.

Macular Vitamin Benefit *Physician Recommended Nutriceuticals, USA.*
Vitamins; copper (p. 2057·1); zinc (p. 2126·1).
Dietary supplement.

Macu Trition *Advanced Vision, USA.*
Capsules, fish oil; phytosterol (p. 1471·2); plant squalane; colecalciferol (p. 2113·1); vitamin E substances (p. 2119·1); tablets, green tea (p. 2648·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3); copper (p. 2057·1); zinc (p. 2126·1); vitamin C (p. 2110·3).
Dietary supplement.

Macu-Vision *Blackmores, Austral.*
Ascorbic acid (p. 2110·3); *d*-alpha tocoferil acid succinate (p. 2119·2); zinc oxide (p. 1729·1); copper oxide (p. 2057·1).
Dietary supplement.

Macvit *Baif, Ital.*
Vitamins; minerals; quercetin (p. 2505·3); ginkgo biloba (p. 2512·3); myrtillus (p. 2566·2); rutoside (p. 2505·3); lutein (p. 2079·2); zeaxanthin (p. 2125·3).

Madam *Panacea, India.*
Citalopram (p. 411·1).
Depression; bipolar disorder; panic disorder.

Madame Pearl's Cough Syrup *Classical Remedia, Canad.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Madame Pearl's Mucolytic *Unicorn, Hong Kong.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with thickened mucus.

Madar *Teofarma, Ital.*
Nordazepam (p. 1089·3).
Sleep disorders.

Madarat-S *Sanify, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Maddox *Pharmacon, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Maddox-AL *Pharmacon, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Made in the Shade Self-Tanner *Arbonne, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Madecassol *Bayer, Belg.; Bayer, Chile; Nikolakopoulos (Νικολακοπουλος), Gr.; Bayer, Hong Kong; Corsa, Indon.; Roche Nicholas, Indon.; Serdex, Indon.; Sanofi-Aventis, Mex.; Serdex, Thai.; Bayer, Turk.; Polinac, Venez.*
Centella (p. 1698·3).
Cicatrisation; burns; ulcers; wounds; scars; venous insufficiency; haemorrhoids; phlebitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Madécassol *Bayer Sante, Fr.; Confar, Port.*
Centella (p. 1698·3).
Ulcers; venous insufficiency; wounds; burns.

Madecassol C *Sanofi-Aventis, Mex.*
Centella (p. 1698·3); metronidazole (p. 936·1); nitrofurazone (p. 333·1).
Bacterial vaginosis; trichomoniasis.

Madecassol N *Sanofi-Aventis, Mex.*
Centella (p. 1698·3); nitrofurazone (p. 333·1).
Vaginosis.

Madelen *Rider, Chile.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Madelon *St Laurent, Canad.*
Aspirin (p. 22·2); caffeine (p. 1203·3).

Madexin *Medic+Aid, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Madiclar *Proge, Ital.*
Clarithromycin (p. 266·2).

Madicure *Johnson & Johnson, Neth.*
Mebendazole (p. 158·3).
Enterobiasis.

Madinelle *Mibe, Cz.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Madinette *Mibe, Austria; Mibe, Ger.; Sun-Farm, Pol.; Dermapharm, Switz.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Madiplot *Takeda, Thai.*
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Madiprazole *Pharmadica, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Maditez *Medipharma, Arg.*
Terbinafine (p. 593·3).
Fungal infections.

Madlexin *Meiji, Indon.*
Cefalexin (p. 234·1).
Bacterial infections.

Madol *Allenge, India.*
Tramadol (p. 139·2).
Pain.

Masa, Thai.
Tramadol hydrochloride (p. 139·2).
Pain.

Madola *Pharmaland, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Madol-P *Allenge, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Madomine *Atlantic, Malaysia.*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria.

Madonella *Kwizda, Austria.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Madonna *Biolab, Malaysia; Biolab, Thai.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Madopar *Investi, Arg.; Roche, Austral.; Roche, Austria; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, Venez.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
These ingredients can be described by the British Approved Name Co-beneldopa.
Parkinsonism; restless legs syndrome.

Madopar-F *Nicholas Piramal, India.*
Benserazide hydrochloride (p. 894·1); levodopa (p. 902·2).
Parkinsonism.

Madopark *Roche, Swed.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Madoxy *Pharmadica, Thai.*
Doxycycline (p. 288·1).
Bacterial infections.

Madrat-S *Sanify, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Madrox *Konimex, Indon.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; nausea; gastric pain; epigastric pain; flatulence; bloating.

Maelenoxyl *Foramen, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Maeve *Aamorb, India.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Mafel *Raymos, Arg.*
Progesterone (p. 2300·2).
Menstrual disorders; benign breast disorders; menopausal disorders; female infertility; threatened and habitual miscarriage.

Mafena *Maver, Mex.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Maff-D *Anthiea, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Mafia *Kaizen, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Maflo *Mapra, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Maflurell *Sanorell, Ger.*
Magnesium fluoratum (p. 2080·2).
Homoeopathic preparation.

Maforan *Sriprasit, Thai.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Maformin *Pharmadica, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mafusol *Biosynthesis, Rus.*
Sodium fumarate; sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Plasma volume expansion; extracorporeal circulation.

Mag *Cipla, India.*
Magnesium chloride (p. 1787·1).

Mag-200 *Optimox, USA.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency.

Mag 2 *Cooperation Pharmaceutique, Fr.*
Magnesium carbonate (p. 1856·2) or magnesium pidolate (p. 1787·3).
Magnesium deficiency.

Galenica, Gr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Switz.
Magnesium pidolate (p. 1787·3).
Hypomagnesaemia; magnesium deficiency; nervous disorders; muscular cramp; eclampsia; magnesium supplement.

Mag 3 *Rez, Cz.*
Technetium-99m (p. 2228·1) betiatide.
Kidney scintigraphy.

Mag 77 *Osotspa, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; gastritis; gastro-oesophageal reflux; heartburn; flatulence.

Mag 2 Junior *Cooperation Pharmaceutique, Fr.†*
Magnesium carbonate (p. 1856·2); magnesium oxide (p. 1857·3).
Magnesium supplement.

Mag Kottas Krauterexpress Abführtee *Kottas-Heldenberg, Austria.*
Frangula (p. 1843·3); senna (p. 1885·1); peppermint leaf (p. 1877·1); fennel (p. 2503·2); caraway (p. 2470·2).
Constipation.

Mag SR *Cipla-Medpro, S.Afr.*
Magnesium chloride (p. 1787·1).
Magnesium supplement.

Magacone *Shalaks, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Magadol *Alembic, India.*
Paediatric tablets; suspension: Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Alembic, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Magadol-SP *Alembic, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

Magalat *Ferron, Indon.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity.

Magalcid-S *Elfin, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Magalite *Cadifra, Fr.*
Cod-liver oil (p. 2056·3); calcium (p. 1783·1); magnesium (p. 1786·3); vitamins.
Dietary supplement; stress.

Magalphil *Queisser, Rus.*
Magaldrate (p. 1856·1).
Gastritis; peptic ulcer; gastro-oesophageal reflux; heartburn.

Magaltop *GiEnne, Ital.*
Magaldrate (p. 1856·1).
Peptic ulcer; gastro-oesophageal reflux; hyperacidity.

Magamyl *Worwag, Denm.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Magan *Savage, USA.*
Magnesium salicylate (p. 85·2).
Rheumatoid arthritis; osteoarthritis; fever; pain.

Maganol *Guardian, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Magard FA *Soho, Indon.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Magasida *Kimia, Indon.*
Aluminium magnesium hydroxide; simeticone (p. 1886·2).
Peptic ulcer; gastritis; gastro-oesophageal reflux; gastric hyperacidity; flatulence.

Magastron *1A, Ger.†; Sandoz, Ger.†*
Magaldrate (p. 1856·1).
Peptic ulcer; gastric hyperacidity.

MAG-C *Silom, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Mag-Cal Mega *Freeda, USA.*
Magnesium (p. 1786·3); calcium (p. 1783·1).
Dietary supplement.

Magcar *Deva, Turk.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).

Mag-Carb *R&D, USA.*
Magnesium carbonate (p. 1856·2).
Nutritional supplement.

Mag-CE *Asofarma, Arg.*
Magnesium (p. 1786·3); ascorbic acid (p. 2110·3).
Dietary supplement.

Magcil *Neon, India.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Magcine *Berko, Turk.*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; constipation.

Mag-Citrate *Biomed, Canad.*
Magnesium citrate (p. 1857·1).
Bowel lavage.

Magclin *Magnus, India.*
Clindamycin (p. 269·3).
Acne.

Magclo *Magnus, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Magclo-G *Magnus, India.*
⊗Clobetasol (p. 1627·1); gentamicin (p. 304·2).

Magclox-LB *Magnus, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Magcol *Pharmasant, Thai.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; gastric hyperacidity; peptic ulcer; flatulence.

Magdent-K *Magnus, India.*
⊗Potassium nitrate (p. 1766·2).

Magdent-KF *Magnus, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Magdent-R *Magnus, India.*
Sodium monofluorophosphate (p. 2091·3).

Magel-MPS *Euphoric, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Magen-700 *Marfarma, Ital.*
Magnesium (p. 1786·3); potassium (p. 1793·1); sodium (p. 1795·1); taurine (p. 2626·2).
Dietary supplement.

Magen- und Darmtee N
Note: this name may be used for preparations of different composition.
Abtswinder, Canad.†
Chamomile (p. 2474·1); cinnamon (p. 2479·2); liquorice (p. 1853·2); peppermint (p. 1877·1).

Magen-Darm-Entoxin N *Meckel, Ger.*
Artemisia absinthium (p. 2426·1); cephaelis ipecacuanha; colocynthis (p. 1833·3); cochlearia officinalis; juniperus communis (p. 2537·1).
Homoeopathic preparation.

Magen-Darmtropfen N *Heel, Ger.*
Gentiana lutea (p. 2512·1); chamomilla recutita (p. 2474·1); juniperus communis (p. 2537·1); artemisia absinthium (p. 2426·1).
Homoeopathic preparation.

Magentee St Severin *Smetana, Austria.*
Absinthium (p. 2426·1); centaury (p. 2473·2); taraxacum (p. 2625·3); sweet orange peel (p. 2576·2); St John's wort (p. 449·1).
Gastrointestinal disorders.

Magenterol *Teva, Denm.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Magerix *Pharos, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Magesto *Takeda, Hong Kong.*
Calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1); amylase (p. 2442·1); thiamine (p. 2102·3); scopolia (p. 2611·3); clove oil (p. 2481·3); fennel oil (p. 2503·3); ginger oil (p. 1844·1); cinnamon oil (p. 2479·3); orange oil (p. 2576·2); aluminium hydroxide (p. 1817·2); menthol (p. 2553·2); calcium hydrogen phosphate (p. 1783·3).
Digestive-system disorders.

Takeda, Thai.
Mamylase; amylase (p. 2442·1); vitamin B_1 (p. 2103·1); scopolia (p. 2611·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); fennel oil (p. 2503·3); ginger oil (p. 1844·1); menthol (p. 2553·2); aluminium hydroxide (p. 1817·2).
Gastrointestinal tract disorders.

Magfifty *Umeda, Thai.*
Magnesium sulfate (p. 1787·3).
Hypomagnesaemia; eclampsia; seizures.

Mag-G *Cypress, USA.*
Magnesium gluconate (p. 1787·2).
Dietary supplement.

Maghex-M *Magnus, India.*
Mouthwash: Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Magnus, India.
Topical gel: Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).

Maghora *Grands Espaces, Fr.†*
Olive oil (p. 2575·1); lavender oil (p. 2541·1); pine oil (p. 2591·1); rosemary oil (p. 2607·3).
Skin irritation.

Magic Mix *Lactalis, Fr.*
Maize starch (p. 2095·1).
Gastro-oesophageal reflux in infants; dietary aid.

Magic-M *Vensat, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Magicrem *Imvi, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); ketoconazole (p. 585·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Magicul *Alphapharm, Austral.; LCH, Hong Kong.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Maginex *Health Care Products, USA.*
Magnesium aspartate hydrochloride (p. 1786·3).
Magnesium supplement.

Maginjectable *Cooperation Pharmaceutique, Fr.*
Magnesium pidolate (p. 1787·3).
Magnesium supplement in parenteral nutrition.

Magion *Ern, Spain.*
Magaldrate (p. 1856·1).
Gastric hyperacidity.

Magium *Hexal, Ger.†*
Magnesium aspartate (p. 1787·1) or magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magium K *Hexal, Ger.†*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency.

Magix *Avon, Canad.*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Magix Tinted *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Maglax *New York Chemical, Thai.*
Magnesium sulfate (p. 1787·3).
Constipation.

Maglek B_6 *Lek-Am, Pol.*
Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Maglid
Note: this name may be used for preparations of different composition.
Melisana, Belg.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders associated with hyperacidity.
Overseas, India.
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; flatulence; peptic ulcer.

Maglucate *Pharmascience, Canad.*
Magnesium gluconate (p. 1787·2).
Hypomagnesaemia.

Mag-Mag *KB, Thai.*
Magnesium hydroxide (p. 1857·2).
Constipation.

Mag-Min *Selmag, Switz.†*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

Magmin *Blackmores, Austral.†*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

Magmix II *Professional Health, Canad.*
Magnesium carbonate (p. 1856·2).

Magna
Note: this name may be used for preparations of different composition.
Vensat, India.
Cefuroxime axetil (p. 255·2).
Bacterial infections.
Berlin-Chemie, Ger.†
Glimepiride (p. 473·2).
Diabetes mellitus.

Magnacal *Sherwood, USA.*
Lactose-free preparation for enteral nutrition.

Magnacef *Magnus, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Magnacet *Shionogi, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Magnacillin *Mapra, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Magnadrox *Zee, India.*
Dimeticone (p. 1886·2); magaldrate (p. 1856·1).

Magnal *Fecofar, Arg.*
⊗Hydrocortisone (p. 1640·1); lidocaine (p. 1988·1).
Haemorrhoids.

Magnalzia *Neckerman, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Magnamycin *Pfizer, India.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Magnapen *Wockhardt, UK.*
Capsules: Ampicillin trihydrate (p. 218·2); flucloxacillin sodium (p. 299·2) (p. 218·2).
These ingredients can be described by the British Approved Name Co-fluampicil.
Bacterial infections.
Wockhardt, UK.
Injection: Ampicillin sodium (p. 218·2); flucloxacillin sodium (p. 299·2) (p. 218·2).
These ingredients can be described by the British Approved Name Co-fluampicil.
Bacterial infections.
Wockhardt, UK.†
Syrup: Ampicillin trihydrate (p. 218·2); flucloxacillin magnesium (p. 299·2) (p. 218·2).
These ingredients can be described by the British Approved Name Co-fluampicil.
Bacterial infections.

Magnaphate *Arjun, UK.*
Magnesium glycerophosphate (p. 1787·2).
Magnesium supplement.

Magnaspart *Rosen, Ger.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Magnaspartate *Kora, UK.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Magnaspor *Ranbaxy, Mex.; Ranbaxy, Thai.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Magnatax *Ikon, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Magnatil *Tecnofarma, Chile.*
Magnesium (p. 1786·3); vitamin C (p. 2110·3).
Dietary supplement.

Magnatil Calcico *Tecnofarma, Chile.*
Ascorbic acid (p. 2110·3); magnesium (p. 1786·3); calcium (p. 1783·1).
Dietary supplement.

Magnazide *Ikon, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Magnazone *Ikon, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Magne B6 *Sanofi-Aventis, Rus.*
Tablets: Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency; asthenia.
Sanofi-Aventis, Rus.
Oral solution: Magnesium lactate (p. 1787·2); magnesium pidolate (p. 1787·3); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency; asthenia.

Magne B6 Premium *Sanofi-Aventis, Ukr.†*
Magnesium citrate (p. 1857·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency.

Magne-B6 *Sanofi-Aventis, Cz.†; Sanofi-Aventis, Hung.; Sanofi-Aventis, Ukr.*
Oral solution: Magnesium lactate (p. 1787·2); magnesium pidolate (p. 1787·3); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency.
Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Ukr.
Tablets: Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency.
Sanofi-Aventis, Pol.
Magnesium lactate (p. 1787·2); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Magné-B_6 *Sanofi-Aventis, Fr.*
Tablets: Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency.

Magne-B_6 Extra *Sanofi-Aventis, Hung.*
Magnesium citrate (p. 1857·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency.

Magne-Balans Plus *Aflofarm, Pol.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium and potassium deficiency.

Magnebe *Dominguez, Arg.*
Injection: Magnesium pidolate (p. 1787·3).
Magnesium supplement.
Dominguez, Arg.
Tablets: Magnesium citrate (p. 1857·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium supplement.

MagneBind *Nephro-Tech, USA.*
Magnesium carbonate (p. 1856·2); calcium carbonate (p. 1824·3).
Dietary phosphate binder.

Magnecyl *McNeil, Swed.*
Aspirin (p. 22·2).
Pain; fever; musculoskeletal and joint pain.

Magnecyl-koffein *McNeil, Swed.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever; musculoskeletal and joint pain.

Magnefar *Biofarm, Pol.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Magnefar B_6 *Biofarm, Pol.*
Magnesium aspartate (p. 1787·1); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Magnéginseng *Omega, Fr.†*
Magnesium lactate (p. 1787·2); ginseng (p. 2513·3); soy lethicin (p. 2542·2).
Tonic.

Magnegita *Insight, Austria; Farmaconsult, Belg.; Insight, Cz.; Insight, Denm.†; Insight, Fr.; Agfa, Ger.; Insight, Irl.; Agfa, Neth.; Insight, Port.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Magnegon *Takeda, Switz.*
Magnesium lactate (p. 1787·2); magnesium citrate (p. 1857·1).
Magnesium deficiency; magnesium supplement.

Magnelis B6 *Ufavita, Rus.*
Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency.

Magnen B6 *Marjan, Braz.*
Magnesium glycinate (p. 1786·3); pyridoxine hydrochloride (p. 2105·3).
Magnesium and vitamin B_6 supplement.

Magneon *Neon, India.*
Magnesium sulfate (p. 1787·3).

Magnerot *Worwag, Cz.; Worwag, Hung.; Worwag, Rus.; Worwag, Ukr.*
Magnesium orotate (p. 1786·3).
Magnesium deficiency; myocardial infarction; heart failure; magnesium-dependent arrhythmias; atherosclerosis; hyperlipidaemias.
Worwag, Ger.
Magnesium gluconate (p. 1787·2).
Magnesium deficiency.

Magnerot A *Worwag, Ger.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

magnerot Classic *Worwag, Ger.*
Magnesium orotate (p. 1786·3).
Magnesium deficiency.

Magnerot N *Worwag, Ger.*
Magnesium phosphate (p. 1787·3); magnesium citrate (p. 1857·1).
Magnesium deficiency.

Magnesia *Medic, Denm.; Nycomed, Denm.; Cinfa, Spain; Lainco, Spain; Charoen, Thai.*
Magnesium hydroxide (p. 1857·2).
Constipation; dyspepsia; gastro-oesophageal reflux.

Magnésia Bisurada *Wyeth Consumer, Braz.*
Magnesium carbonate (p. 1856·2); bismuth subcarbonate (p. 1822·1); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Magnesia Bisurata Aromatic *Wyeth Consumer, Ital.*
Magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Magnesia Effervescente Sella *Sella, Ital.*
Magnesium hydroxide (p. 1857·2); tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1).
Constipation; gastrointestinal hyperacidity.

Magnesia Pasteur *Pasteur, Chile.*
Magnesium hydroxide (p. 1857·2).
Antacid; constipation.

Magnesia Phosphorica I Oligoplex *Madaus, Arg.*
Magnesium phosphate (p. 1787·3); sodium sulfate (p. 1888·1); lycopodium (p. 2546·3).
Biliary-tract disorders.

Magnesia S Pellegrino *Saprochi, Israel; Sanofi-Aventis, Ital.; Actipharm, Switz.*
Magnesium hydroxide (p. 1857·2).
Constipation; digestive-system disorders; gastric hyperacidity; heartburn.

Magnesia San Pellegrino *Welt, Arg.; Santipharma, Port.†; Anotaciones, Spain; Arex, Venez.*
Magnesium hydroxide (p. 1857·2).
Constipation; dyspepsia; gastric hyperacidity.

Magnesiamaito *Orion, Fin.*
Magnesium hydroxide (p. 1857·2).
Constipation; stomach disorders associated with excess acid.

Magnesie Calcinée *Deva, Turk.*
Magnesium hydroxide (p. 1857·2).
Dyspepsia; constipation.

Magnésie Composée *Lehning, Fr.†*
Light magnesium carbonate (p. 1856·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Magnesie Plus *Omega, Belg.*
Magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Gastrointestinal disorders associated with hyperacidity.

Magnésie San Pellegrino *Auvex, Fr.*
Magnesium hydroxide (p. 1857·2).
Constipation.

Magnesio + C/Mag-CE *Asofarma, Arg.*
Magnesium carbonate (p. 1856·2); vitamin C (p. 2110·3).
Dietary supplement.

Magnesio Incaico *Incaico, Arg.*
Magnesium (p. 1786·3); calcium (p. 1783·1); ergocalciferol (p. 2113·3).
Calcium, magnesium and vitamin D supplement; osteoporosis.

Magnesio Nectar Vital *Del Sol, Arg.*
Magnesium (p. 1786·3); ascorbic acid (p. 2110·3); vitamin B_{12} (p. 2107·2).
Tonic.

Magnesio 102 Plus *ISA, Arg.*
Magnesium (p. 1786·3); iron (p. 2073·1); zinc (p. 2126·1); selenium (p. 2086·3); ginseng (p. 2513·3).
Dietary supplement.

Magnesio Vital *AM, Arg.*
Magnesium oxide (p. 1857·3); magnesium lactate (p. 1787·2).
Magnesium supplement.

Magnesioboi *Merck, Spain.*
Magnesium lactate (p. 1787·2).
Magnesium depletion.

Magnesiocard *Kwizda, Austria; Verla, Ger.; Verla, Hung.†; Tecnimede, Port.; Biomed, Switz.; Taymed, Turk.*
Magnesium aspartate hydrochloride (p. 1786·3).
Magnesium deficiency; magnesium supplement; eclampsia; premature labour.

Magnesiokatabios *SIT, Ital.*
Vitamins; magnesium (p. 1786·3).
Nutritional supplement.

Magnesiomix *Provita, Ital.*
Vitamins; magnesium (p. 1786·3).

Magnesit *Biosana, Canad.*
Magnesium citrate (p. 1857·1).
Nycomed, S.Afr.
Magnesium l-aspartate hydrochloride (p. 1786·3).
Hypomagnesaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Magnésium Biomed *Biomed, Switz.*
Effervescent tablets; granules for oral liquid: Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

Biomed, Switz.
Tablets: Magnesium hydrogen glutamate (p. 1786·3); magnesium citrate (p. 1857·1).
Magnesium deficiency; magnesium supplement.

Magnésium Complexe *Vifor, Switz.*
Magnesium chloride (p. 1787·1); magnesium hydrogen glutamate (p. 1786·3); magnesium glycerophosphate (p. 1787·2); magnesium orotate (p. 1786·3); magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

Magnesium Compound *Blackmores, Austral.*
Sodium sulfate (p. 1888·1); magnesium phosphate (p. 1787·3); dibasic potassium phosphate (p. 1791·1).
Dietary supplement.

Magnesium Diasporal *Austroplant, Austria; Protina, Ger.; Medis, Israel.*
Magnesium citrate (p. 1857·1).
Magnesium deficiency.

Magnésium Diasporal *Doetsch, Grether, Switz.*
Magnesium citrate (p. 1857·1).
Magnesium deficiency; magnesium supplement.

Magnesium Glycocolle Lafarge *SERP, Mon.*
Magnesium lactate (p. 1787·2); glycine (p. 2071·2).
Magnesium deficiency.

Magnesium Naneli Lafar *Saba, Turk.†*
Magnesium hydroxide (p. 1857·2).

Magnesium Nutrimed *Nutrimed, Switz.; Nutrifarma, Turk.*
Magnesium carbonate (p. 1856·2).
Magnesium deficiency; magnesium supplement.

Magnesium Pharmavit *Walmark, Cz.*
Magnesium oxide (p. 1857·3); ascorbic acid (p. 2110·3).
Magnesium deficiency.

Magnesium Plus
Note: this name may be used for preparations of different composition.
Natur Produkt, Rus.
Magnesium carbonate (p. 1856·2); magnesium lactate (p. 1787·2); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Magnesium deficiency.

Magnesium Powder *Blackmores, Austral.*
Magnesium citrate (p. 1857·1); levocarnitine tartrate (p. 2053·2); amino acids; vitamins; minerals.
Muscle cramps; magnesium deficiency.

Magnesium Pyre *Salvat, Spain.*
Magnesium bromide (p. 1786·3); magnesium chloride (p. 1787·1); magnesium fluoride (p. 2080·2); magnesium iodide (p. 1786·3).
Magnesium depletion.

Magnesium Sandoz *Novartis, Gr.*
Magnesium aspartate (p. 1787·1); magnesium citrate (p. 1857·1).
Magnesium deficiency.

Magnesium Tonil *APS, Ger.†*
Capsules: Heavy magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magnesium Verla *Kwizda, Austria; Verla, Ger.; Rowa, Irl.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Kwizda, Austria.
Tablets: Magnesium citrate (p. 1857·1) magnesium glutamate (p. 1786·3).
Magnesium deficiency.

Verla, Ger.
Injection: Magnesium hydrogen glutamate (p. 1786·3) or magnesium sulfate heptahydrate (p. 1787·3).
Magnesium deficiency.

Magnesium Verla N *Verla, Ger.*
Powder for oral solution: Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Verla, Ger.
Tablets: Magnesium hydrogen glutamate (p. 1786·3); magnesium citrate (p. 1857·1).
Magnesium deficiency.

Magnésium Vital *Vifor, Switz.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

Magnesium-B *Wassen, UK.*
Magnesium (p. 1786·3); vitamin B_6 (p. 2105·3); betaine hydrochloride (p. 2456·1).

Magnesium-OK *Angelini, Ital.*
Magnesium (p. 1786·3); vitamins; minerals.
Nutritional supplement.

Wassen, UK.
Magnesium oxide (p. 1857·3); minerals; vitamins.

Magnesium-Plus-Hevert *Hevert, Ger.†*
Magnesium oxide (p. 1857·3); *d*-alpha tocopherol (p. 2119·1).
Magnesium or vitamin E deficiency.

Magnesium-Sandoz *Sandoz, Switz.*
Magnesium aspartate (p. 1787·1); magnesium citrate (p. 1857·1).
Magnesium deficiency; magnesium supplement.

Sandoz, Ger.†
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Magnesium-Sandoz forte *Sandoz, Ger.†*
Magnesium aspartate (p. 1787·1); magnesium citrate (p. 1857·1).
Magnesium deficiency.

Magnesix *Douglas, Canad.†*
Vitamin B substances (p. 2102·3); magnesium (p. 1786·3); potassium (p. 1793·1).

Magnesol *KRKA, Pol.*
Magnesium citrate (p. 1857·1).
Magnesium deficiency.

Magnesona *Vitoria, Port.*
Magnesium pidolate (p. 1787·3).
Magnesium deficiency.

Magnesorot *Worwag, Ger.*
Magnesium orotate (p. 1786·3).
Magnesium deficiency.

Magnespasmil *Sanofi-Aventis, Port.*
Magnesium lactate (p. 1787·2).
Magnesium deficiency.

Magnéspasmyl *Dexo, Fr.*
Magnesium lactate (p. 1787·2).
Magnesium deficiency.

Magnespasmyl *Therabel, Belg.*
Magnesium lactate (p. 1787·2).
Magnesium deficiency.

Magnetol *Soreq, Israel.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Magnetolux *Sanochemia, Cz.; Sanochemia, Irl.; Sanochemia, Spain.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Magnetrans extra *Stada, Ger.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magnetrans forte *Stada, Ger.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magnevie B6 *Sanofi-Aventis, Fr.*
Magnesium citrate (p. 1857·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium supplement.

Magnevist *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Zydus, India; Bayer, Irl.; Bayer, Ital.; Bayer, Neth.†; Bayer Schering, Norw.; Bayer, NZ; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Schering, Turk.; Bayer, UK; Bayer, USA.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Magnevistan *Bayer, Braz.; Bayer, Chile†; Schering, Venez.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Magnevital *Teva, Hung.†*
Magnesium oxide (p. 1857·3); *d* tocopherol (p. 2119·1).
Magnesium and vitamin E deficiency.

Magnex *Pfizer, India.*
Cefoperazone (p. 243·1) or cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Magnexim *Magnus, India.*
Cefixime (p. 240·3).
Bacterial infections.

Magnexim LB *Magnus, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Magnezi Kalsine *Istanbul, Turk.*
Magnesium oxide (p. 1857·3).
Dyspepsia; gastritis; constipation; peptic ulcer.

Magnezin *Richter, Pol.*
Magnesium carbonate (p. 1856·2).
Arrhythmias; magnesium deficiency; tonic.

Magnezinc *Berko, Turk.*
Zinc sulfate (p. 2126·2); magnesium oxide (p. 1857·3).

Magnezytki *Sanofi-Aventis, Pol.†*
Magnesium lactate (p. 1787·2); wheat bran (p. 1823·3).
Constipation; obesity.

Magnezyum Diasporal *Biosel, Turk.*
Magnesium citrate (p. 1857·1).
Pre-eclampsia; eclampsia; hypomagnesaemia.

Magnical *Johnson & Johnson, India.*
Calcium carbonate (p. 1824·3); calcium hydrogen phosphate (p. 1783·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Magnicum *KVZ, Ukr.*
Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency; tonic.

Magnidicon *Tunggal Idaman, Indon.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Epigastric pain; flatulence; bloating; gastritis; peptic ulcer.

Magnidol *Streger, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Magnidol-Plus *Streger, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Magniferron *Filadams, Philipp.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Magnikor *KVZ, Ukr.*
Aspirin (p. 22·2).
Magnesium hydroxide (p. 1857·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Magnil *Sons, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Magnilek *Unique, Ukr.*
Meglumine gadopentetate (p. 1586·1).
Contrast agent for magnetic resonance imaging.

Magnine *J & J DeChane, India.*
Aluminium hydroxide (p. 1817·2); belladonna (p. 2453·3); magnesium trisilicate (p. 1858·1).

Magniton-R *Coup, Gr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Magno Sanol *Sanol, Ger.; UCB, Ger.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magnofit *Meda, Austria.*
Chewable tablets: Magnesium citrate (p. 1857·1); magnesium carbonate (p. 1856·2).
Magnesium deficiency.

Meda, Ital.
Magnesium carbonate (p. 1856·2).
Magnesium deficiency.

Magnogène *Novartis Sante, Fr.*
Magnesium chloride (p. 1787·1).
Magnesium deficiency.

Magnogene *Uriach Aquilea OTC, Spain.*
Magnesium bromide (p. 1786·3); magnesium fluoride (p. 2080·2); magnesium hydroxide (p. 1857·2).
Magnesium depletion.

Phyto-Sante, Canad.†
Magnesium chloride (p. 1787·1).

Magnograf *Bayer, Denm.; Berlipharm, Neth.†; Bayer, Spain†; Berlis, Switz.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Magnokal *Saba, Turk.*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; constipation.

Teva, Pol.
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium and potassium deficiency.

Magnol *Atlantis, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Magnolax *Pendopharm, Canad.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2).
Constipation.

Magnolonas *Technobio, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Magnonat *Naturatec, Canad.†*
Magnesium chloride (p. 1787·1).

Magnonorm *Genericon, Austria.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magnoplasm *Mayne, Austral.*
⊗Glycerol (p. 2517·2); magnesium sulfate (p. 1787·3).
Poultice for abscesses, boils, and carbuncles.

Magnopyrol *Farmasa, Braz.; Rhein, Mex.*
Metamizole magnesium (p. 53·3).
Fever; pain.

Magnoral *Medinfar, Port.*
Magnesium chloride (p. 1787·1).
Magnesium deficiency.

Magnosol *Meda, Ital.*
Magnesium carbonate (p. 1856·2); magnesium oxide (p. 1857·3); potassium bicarbonate (p. 1780·3).
Magnesium and potassium deficiency.

Magnosolv *Meda, Austria; Meda, Cz.; Meda, Hung.*
Oral granules: Precipitated magnesium carbonate (p. 1856·2); magnesium oxide (p. 1857·3).
Magnesium deficiency.

Magnostase
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Magnoston *Ariston, Braz.*
Magnesium sulfate (p. 1787·3).

Magnova *Lupin, India.*
Cefepime (p. 239·2); tazobactam (p. 369·3).
Bacterial infections.

Magnox *Lennod, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Hyperacidity.

Magnurol *Esteve, Spain.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Magnus *Sidus, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Magnus Gel *Sidus, Arg.*
Lubricating gel.

Magnyl *Nycomed, Denm.*
Aspirin (p. 22·2).
Magnesium hydroxide (p. 1857·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever; inflammation; thromboembolism prophylaxis; ischaemic heart disease.

Magnyl-E *Nycomed, Norw.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

MAG'Ocean *Nestle Proteika, Fr.†*
Magnesium oxide (p. 1857·3).
Magnesium supplement.

Magof *Magnus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Magof-OZ *Magnus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Magonate *Valeant, USA.*
Magnesium gluconate (p. 1787·2); calcium hydrogen phosphate (p. 1783·3).
Dietary supplement.

Magoral *ST, Thai.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency; gastric hyperacidity.

Mag-Oro *Eagle, Austral.*
Magnesium orotate (p. 1786·3); magnesium aspartate (p. 1787·1); magnesium amino acid chelate (p. 2048·3); potassium aspartate

(p. 1793·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium, potassium, and vitamin B_6 supplement.

Mag-Ox *Blaine, USA.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency; hyperacidity.

Magralibi *Arkadia, Ital.*
Magaldrate (p. 1856·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis; gastroduodenitis.

Magrezol *Arrow, Irl.*
Zolmitriptan (p. 682·2).
Migraine.

Magrilan *Medochemie, Cz.; Medochemie, Singapore; Medochemie, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; mixed anxiety depressive states.

Magrix *Ativus, Braz.*
Poliglusam (p. 2593·2).
Hypercholesterolaemia; slimming aid.

Mags *Plus, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Magsenum-D *Chinta, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Magsil
Note: this name may be used for preparations of different composition.
DHA, Singapore.
Magnesium trisilicate (p. 1858·1).

Magsolvit B_6 *Galenus, Pol.*
Magnesium gluconate (p. 1787·2); magnesium lactate (p. 1787·2); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Magsons *Sons, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Mag-SR *Cypress, USA.*
Magnesium chloride (p. 1787·1).
Magnesium supplement.

Mag-SR plus Calcium *Cypress, USA.*
Magnesium chloride (p. 1787·1); calcium carbonate (p. 1824·3).
Magnesium and calcium supplement.

Mag-Tab *Rider, Chile; Niche, USA.*
Magnesium lactate (p. 1787·2).
Magnesium deficiency; magnesium supplement.
Sigma, Braz.
Magnesium amino acid chelate (p. 2048·3).
Magnesium supplement.

Magtacid *Prafa, Indon.†*
Aluminium magnesium hydroxide; simeticone (p. 1886·2).
Peptic ulcer; gastritis; gastro-oesophageal reflux; gastric hyperacidity; flatulence; dyspepsia.

Magtam *Alkem, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Magtasil *ICM, Singapore.*
Magnesium trisilicate (p. 1858·1); light magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity.

Magtral *Otto, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; bloating; gastric hyperacidity; dyspepsia; peptic ulcer.

Magtrate
Note: this name may be used for preparations of different composition.
Dexter, India.
Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).
Mission Pharmacal, USA.
Magnesium gluconate (p. 1787·2).
Dietary supplement.

Magtrax *Magnus, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Maguran *Medochemie, Gr.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Magurol *Medochemie, Malaysia.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.
Medochemie, Rus.
Doxazosin (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Magvit B_6 *GSK, Ukr.*
Magnesium lactate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency; vitamin B_6 deficiency; tonic.
Medagro, Pol.
Magnesium lactate (p. 1787·2); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Magvital *Panderma, Austria.†*
Magnesium hydrogen aspartate (p. 1787·1) or magnesium sulfate (p. 1787·3).
Magnesium deficiency; premature labour; eclampsia; arrhythmias.

Mahacef *Mankind, India.*
Dispersible tablets; oral drops: Cefixime (p. 240·3).
Bacterial infections.
Mankind, India.
Syrup: Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mahacef-CV *Mankind, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mahacef-OZ *Mankind, India.*
Cefixime (p. 240·3); ornidazole (p. 943·1).

Mahacef-SB *Mankind, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Mahacef-XL *Mankind, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mahadol *Zuventus, India.*
Tablets: Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.
Zuventus, India.
Topical gel: Capsaicin (p. 35·1); diclofenac (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1).

Mahagaba-M *Mankind, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mahanac *Zuventus, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mahanac Pro *Zuventus, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Mahaquin *RPG, India.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Maicostat *ACME, Philipp.*
Nystatin (p. 590·3).
Oral candidiasis.

Mailen
Note: this name may be used for preparations of different composition.
Investi, Arg.
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); centella (p. 1698·3).
Vulvovaginal infections.
Roemmers, Chile; Roemmers, Venez.
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Mainnox *Charoen, Thai.*
Mefenamic acid (p. 85·3); dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Maintain
Note: this name may be used for preparations of different composition.
Schmid, Israel.
Benzocaine (p. 1980·2).
Premature ejaculation.

Maintane
Note: this name may be used for preparations of different composition.
Jagsonpal, India.
Injection: Hydroxyprogesterone caproate (p. 2285·1).
Threatened or recurrent miscarriage.
Jagsonpal, India.
Tablets: Allylestrenol (p. 2255·2).
Threatened miscarriage; premature labour.

Maintate *Tanabe, Indon.; Mitsubishi Tanabe, Jpn.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; arrhythmias; heart failure.

Maiorad *Rottapharm, Ital.†; Delta, Port.; Rottapharm, Thai.*
Tiropramide hydrochloride (p. 2632·2).
Smooth muscle spasm.

Maitalon *Gedeon Richter, Cz.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Maizar *Vitoria, Port.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Asthma; obstructive airways disease.

Majamil *Polpharma, Pol.*
Diclofenac (p. 48·3).
Musculoskeletal and joint disorders; neuralgia; pain; inflammation.

Majeptil *Erfa, Canad.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Rus.*
Thioproperazine mesilate (p. 1110·2).
Schizophrenia; mania; psychoses.

Majezik *Sanovel, Turk.*
Flurbiprofen (p. 65·2).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain; inflammation.

Majispa *Advik, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Major II *Pentafarma, Chile.*
Test for glucose in blood (p. 2516·3).

Major-Con *Major, USA.*
Simeticone (p. 1886·2).
Flatulence.

Major-gesic *Major, USA.*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Majorpin *Kyowa, Jpn.*
Zotepine (p. 1119·1).
Schizophrenia.

Májvédő és Detoxikáló *Naturland, Hung.*
Milk thistle (p. 1561·1); liquorice (p. 1853·2); urtica (p. 2639·3); althaea (p. 2438·3); agrimony (p. 2432·3); achillea (p. 2427·3); cichorii (p. 2475·2); taraxacum (p. 2625·3).
Liver disorders.

Makadip *CSO Pharmitalia, Ital.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Makaphyt Gouttes antitussives *Gebro, Switz.†*
Drosera (p. 2497·2); liquorice (p. 1853·2); burnet saxifrage (p. 2463·1); senega root (p. 1677·2); thyme (p. 2630·2); camphor (p. 2466·2); menthol (p. 2553·2); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2).
Cough.

Makaphyt Sirop *Gebro, Switz.†*
Drosera (p. 2497·2); liquorice (p. 1853·2); senega root (p. 1677·2); thyme (p. 2630·2).
Respiratory-tract disorders.

Ma-Ka-Ta *Nobel, Turk.*
⊗Hydrocortisone acetate (p. 1640·1); benzocaine (p. 1980·2); hydrastis (p. 2528·1).
Haemorrhoids.

Makatussin *Gebro, Switz.*
Codeine phosphate (p. 40·2).
Cough.

Makatussin Codein *Nycomed, Ger.†*
Codeine phosphate (p. 40·2).
Cough.

Makatussin Comp *Gebro, Switz.*
Dihydrocodeine hydrochloride (p. 52·2); diphenhydramine hydrochloride (p. 626·2).
Respiratory-tract disorders.

Makatussin Tropfen *Nycomed, Ger.*
Thyme (p. 2630·2); star anise oil (p. 2622·2).
Respiratory-tract congestion.

Makena *Ther-Rx, USA.*
Hydroxyprogesterone caproate (p. 2285·1).
Premature labour.

Makiren *Rafarm, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Makovan *Crocus, Gr.; Medimar, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Makro B *Tunggal Idaman, Indon.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; vitamin B supplement.

Makrovit *KRKA, Rus.*
Vitamins.

Maksipor *Fako, Turk.*
Cefalexin (p. 234·1).
Bacterial infections.

Maksiporin *Fako, Turk.; Yavuz, Turk.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

MAKU Mucolytique *Iromedica, Switz.†*
Carbocisteine (p. 1658·1).
Cough; respiratory-tract disorders with viscous mucus.

Makyokansekito *Tsumura, Jpn.*
⊗Gypsum (p. 2173·1); apricot kernel (p. 2445·3); ephedra herb (p. 1663·1); liquorice (p. 1853·2).
Traditional Kampo medicine.

Makyoyokukanto *Tsumura, Jpn.*
⊗Coix seed; ephedra herb (p. 1663·1); apricot kernel (p. 2445·3); liquorice (p. 1853·2).
Traditional Kampo medicine.

Malacin *ANB, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; rheumatoid arthritis.

Maladin *Unicure, India.*
Mepacrine hydrochloride (p. 935·2).
Malaria.

Malafene *Abbott, Belg.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Malafon *CCM, Malaysia.*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria.

Malakin *CCM, Malaysia.*
Quinine hydrochloride (p. 665·2).
Malaria.

Malamin *Purewin, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Malandil *Bohm, Spain.*
Carnitine hydrochloride (p. 2053·2); cobamamide (p. 2107·2); lysine hydrochloride (p. 2079·3).
Tonic; anaemias.

Malanil *GSK, S.Afr.; GSK, Thai.*
Atovaquone (p. 928·2); proguanil hydrochloride (p. 661·3).
Malaria.

Malaquin *PC India, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Malaracin *Malar, India.*
Amikacin (p. 214·1).
Bacterial infections.

Malarex *Actavis, Denm.; Actavis, Indon.; Danone Dumex, Singapore.*
Chloroquine phosphate (p. 650·1).
Malaria; amoebiasis; rheumatoid arthritis; photosensitivity; lupus erythematosus.

Malarin *Duopharma, Philipp.*
Quinine hydrochloride (p. 665·2).
Malaria; nocturnal leg cramps.

Malarivon *Wallace Mfg Chem., UK.*
Chloroquine phosphate (p. 650·1).
Malaria.

Malarone *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK; Glaxo Wellcome, USA.*
Atovaquone (p. 928·2); proguanil hydrochloride (p. 661·3).
Malaria.

Malarwin *Wings, India.*
Pyrimethamine (p. 662·3); sulfamethoxazole (p. 365·2).
Malaria.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Malasulf *Bombay Tablet, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Malater *Hos & Ins, India.*
Artesunate (p. 648·2).
Malaria.

Malatrit-E *Abbott, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malatrit-EL *Abbott, India.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

Malatrit-S *Abbott, India.*
Artesunate (p. 648·2).
Malaria.

Malaviron *Wallace Mfg Chem., UK.*
Chloroquine phosphate (p. 650·1).
Malaria.

Malcidal *Lark, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Malcodex *Marching, Hong Kong.†*
Vitamins.

Male + *Homeocan, Canad.*
Benzoicum acidum (p. 1738·2); berberis vulgaris (p. 2502·1); coccus cacti (p. 2179·2); colchicum autumnale; onionis spinosa (p. 2575·3); sabal serrulata (p. 2363·3); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Male Formula *Watkins, Canad.†*
Folic acid (p. 2063·1); vitamin E (p. 2119·1).

Maledrol *Bennett, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Malena
Note: this name may be used for preparations of different composition.
Juste, Spain.
Soya (p. 2092·3).
Menopausal disorders.
Sigma, Braz.
Enalapril maleate (p. 1371·1).

Malena HCT *Sigma, Braz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Malexit *Sigman, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malfin *Teva, Denm.*
⊗Morphine sulfate (p. 92·3).
Pain.

Malgacid *Ziololek, Pol.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Malgo *Finecure, India.*
Quinine sulfate (p. 665·2).
Malaria; nocturnal leg cramps.

Maliago *Cipla, India.*
Chloroquine (p. 650·1).
Malaria.

Maliaquine *Sriprasit, Thai.†*
Chloroquine phosphate (p. 650·1).
Malaria; rheumatoid arthritis.

Maliasin *Abbott, Austria; Knoll, Braz.†; Pharmalex (Φαρμαλεξ), Gr.; Abbott, Ital.; Abbott, Switz.†; Abbott, Turk.*
Barbexaclone (p. 512·1).
Epilepsy.

Malicon *Norma (Νορμα), Gr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Malidens *Piramal, India.*
Paracetamol (p. 115·1).
Fever; pain.

Maligon *Unijules, India.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Maligon-Art *Unijules, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malijet *Cachet, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malirid *Ipca, India.*
Primaquine phosphate (p. 660·2).
Malaria.

Malisoz *Sozin-Flora, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malither *Themis Medicare, India.*
Artemether (p. 648·1).
Malaria.

Malival *Silanes, Mex.*
Indometacin (p. 71·2).
Gout; inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Malival Compuesto *Silanes, Mex.*
Methocarbamol (p. 2025·3); indometacin (p. 71·2).
Inflammation; musculoskeletal, joint and peri-articular disorders; pain; skeletal muscle spasm.

Mallamint *Roberts, USA.*
Calcium carbonate (p. 1824·3).
Hyperacidity.

Mallebrin Konzentrat *Krewel, Ger.*
Aluminium chloride (p. 1693·3).
Mouth and throat inflammation.

Malnate *FDC, India.*
Artesunate (p. 648·2).
Malaria.

Malnate-R *FDC, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malocef *Pharmanel, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Malocide
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Fr.
Pyrimethamine (p. 662·3).
Toxoplasmosis.
Torrent, India.
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Malocin *M & H, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Malodip *Signova, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Malodip-AT *Signova, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Malon *CCM, Malaysia.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Malona *Acekinetic, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Malonetta *Sandoz, Denm.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Maloprim *GSK, Austral.†*
Pyrimethamine (p. 662·3); dapsone (p. 281·2).
Malaria.

Malortil *Alet, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Maloxy *Malar, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; abnormal uterine bleeding; amenorrhoea; endometrial cancer.

Malquine *Ind-Swift, India.*
Primaquine phosphate (p. 660·2).
Malaria.

Malswift *Ind-Swift, India.*
Chloroquine phosphate (p. 650·1).
Malaria.

Maltan *Masters, Pol.*
Glucose (p. 2068·3).
Nipple care.

Malther *Ind-Swift, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Maltin *Reccius, Chile.*
Malt extract (p. 2080·2).
Nutritional supplement.

Maltiron *Meprofarm, Indon.*
Vitamin B substances (p. 2102·3); ferrous gluconate (p. 2061·2).
Nutritional supplement.

Maltiron Plus *Meprofarm, Indon.*
Vitamins; minerals.
Nutritional supplement.

Maltlevol *Church & Dwight, Canad.*
Vitamins; ferric ammonium citrate (p. 2060·1).
Food supplement; iron-deficiency anaemia.

Maltocalcine *Etifar, Venez.*
Calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Maltofer *Bago, Arg.; Andromaco, Chile; Vifor, Cz.; Vifor, Fin.; Sanofi-Aventis, Hung.; Chemo-Drugs, India; Combiphar, Indon.; Vifor, Malaysia; Vifor, Port.; Vifor, Rus.; Vifor International, Switz.; Abdi, Turk.; Vifor, Ukr.; Zuoz, Venez.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.
Vifor, Malaysia.
Chewable tablets: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron deficiency; iron-deficiency anaemia.

Maltofer Fol *Bago, Arg.; Andromaco, Chile†; Vifor, Cz.; Vifor, Hong Kong; Sanofi-Aventis, Hung.; Combiphar, Indon.; Vifor, Rus.; Vifor International, Switz.; Abdi, Turk.; Vifor, Ukr.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Maltofer Fol Plus *Andromaco, Chile.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Iron, folic acid, and vitamin B_{12} deficiency.

Maltofer Vitaminado *Andromaco, Chile.*
Vitamins; minerals.
Dietary supplement.

Maltoferfol *Vifor, Port.†; Zuoz, Venez.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Anaemias; iron deficiency.

Maltogen
Note: this name may be used for preparations of different composition.
Rafarm, Gr.
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Malto-Mix *Chemo-Drugs, India.*
Iron polymaltose (p. 2077·2).

Malton E *Riemser, Ger.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Maltovis *Volchem, Ital.*
Maltodextrin (p. 2080·3).
Carbohydrate source.

Maltsupex *Wallace, USA.*
Malt extract (p. 2080·2).
Constipation.

Maltviron *P & B, India.*
Calcium gluconate (p. 1783·3); iron choline citrate (p. 2055·2); vitamins; zinc sulfate (p. 2126·2).
Tonic.

Malú *Sigma, Braz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Malugastrin *Polfa Lodz, Pol.†*
Magaldrate (p. 1856·1).
Gastric hyperacidity; peptic ulcer.

Malugel *Charoen, Thai.*
Tablets: Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Peptic ulcer; flatulence; heartburn; gastric hyperacidity.
Charoen, Thai.†
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Malugel-S *Charoen, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Malvatricin *Daudt, Braz.*
Dental gel: Sodium fluoride (p. 2089·2); tyrothricin (p. 384·1); quinosol (p. 2530·1).
Dental caries prophylaxis.

Malvatricin Antiplaca *Daudt, Braz.†*
Sodium monofluorophosphate (p. 2091·3); potassium pyrophosphate (p. 2619·3); triclosan (p. 1773·2).
Dental caries prophylaxis.

Malvatricin Antitartaro *Daudt, Braz.†*
Sodium monofluorophosphate (p. 2091·3); tetrapotassium pyrophosphate (p. 2619·3).
Dental caries prophylaxis.

Malvatricin Branqueador *Daudt, Braz.†*
Sodium fluoride (p. 2089·2) or sodium monofluorophosphate (p. 2091·3); sodium perborate (p. 1770·1); hydrogen peroxide (p. 1755·2); triclosan (p. 1773·2).
Dental caries prophylaxis; dental whitener.

Malvatricin Dentes Sensiveis *Daudt, Braz.†*
⊗Sodium monofluorophosphate (p. 2091·3); potassium nitrate (p. 1766·2); tetrapotassium pyrophosphate (p. 2619·3); triclosan (p. 1773·2).
Dental caries prophylaxis; sensitive teeth.

Malvatricin Ginecologico *Daudt, Braz.†*
Tyrothricin (p. 384·1); quinosol (p. 2530·1).
Vaginal disorders.

Malvatricin Natural *Daudt, Braz.†*
Sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3); calendula (p. 2465·2); echinacea (p. 2498·1); guaco.
Dental caries prophylaxis.

Malvatricin Natural Organic *Daudt, Braz.†*
Sodium monofluorophosphate (p. 2091·3); echinacea (p. 2498·1); propolis (p. 2597·3); rhatany (p. 2603·3); with or without hamamelis (p. 2523·3).
Dental caries prophylaxis.

Malvatricin Natural Soft *Daudt, Braz.†*
Sodium monofluorophosphate (p. 2091·3); echinacea (p. 2498·1); chamomile (p. 2474·1); aloe vera (p. 1693·2); mallow (p. 2549·2).
Dental caries prophylaxis.

Malvatricin Pastilhas *Daudt, Braz.*
Quinosol (p. 2530·1); tyrothricin (p. 384·1); benzocaine (p. 1980·2); mallow (p. 2549·2).
Mouth disorders.

Malvatricin Plus *Daudt, Braz.†*
Sodium monofluorophosphate (p. 2091·3); triclosan (p. 1773·2).
Mouth disorders.

Malvatricin Pronto *Daudt, Braz.*
Quinosol (p. 2530·1); tyrothricin (p. 384·1); mallow (p. 2549·2).
Mouth disorders.

Malvatricin Solucao para diluir *Daudt, Braz.*
Quinosol (p. 2530·1); tyrothricin (p. 384·1); mallow (p. 2549·2).
Mouth disorders.

Malvatricin Spray *Daudt, Braz.*
Quinosol (p. 2530·1); tyrothricin (p. 384·1); lidocaine hydrochloride (p. 1988·2); mallow (p. 2549·2).
Mouth disorders.

Malvatrikids Baby *Daudt, Braz.*
Mallow (p. 2549·2).
Dental caries prophylaxis.

Malvatrikids F *Daudt, Braz.*
Sodium fluoride (p. 2089·2); mallow (p. 2549·2).
Dental caries prophylaxis.

Malvatrikids Junior *Daudt, Braz.*
Sodium fluoride (p. 2089·2); mallow (p. 2549·2).
Dental caries prophylaxis.

Malvéol *Magistra, Switz.*
Althaea leaves (p. 2438·3); mallow leaves (p. 2549·2); salicylic acid (p. 1719·1); mint oil (p. 2560·1).
Mouth and throat disorders.

Malvina *Neovita, Ital.*
Mallow (p. 2549·2).
Skin disorders.

Malvinum *CCM, Malaysia.*
⊗Mesterolone (p. 2291·1).
Androgen deficiency; male infertility.

Malvit *Malar, India.*
Ginseng (p. 2513·3); vitamins.

Malvitona *Recip, Fin.; Recip, Swed.*
Vitamin B substances (p. 2102·3); caffeine (p. 1203·3).
Tonic; vitamin B deficiency.

Malvodon *IMA, Braz.†*
Mallow (p. 2549·2); poppy (p. 1675·3).
Mouth disorders.

Malvona *Daudt, Braz.*
Mouthwash: Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1); borax (p. 2459·2).
Mouth and throat disorders.

Malzix *Aamorb, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Malzix-GB *Aamorb, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mama *Pfizer, Hong Kong.*
Preparation for enteral nutrition during pregnancy and lactation.

Mama (Gold Label) *Wyeth, Malaysia.†*
Preparation for enteral nutrition.
Formerly known as Mama with DHA.
Nutritional supplement in pregnancy and lactation.

Mamacare *Mead Johnson, Philipp.*
Nutritional supplement for pregnant and breast feeding women.

Mamalak *National Enzyme, Ukr.*
Tilactase (p. 2631·2) from *Aspergillus oryzae.*
Lactase deficiency.

Mama's Best *Abbott, Indon.*
Preparation for enteral nutrition.
Nutritional supplement in pregnancy and breast feeding.

Abbott, Philipp.†
Nutritional supplement for pregnant and breast feeding women.

Mama-Whiz *Sydenham, Philipp.*
Vitamins; minerals.

Mamdew Baby Gel *Shalaks, India.*
Benzocaine (p. 1980·2).

Mamellin *Fresenius Kabi, Austria.*
Vitamin F (p. 2509·2); peru balsam (p. 2587·1); alpha tocoferil acetate (p. 2119·2).
Skin damage.

Mamex Gold HA with Immunofortis *Danone Dumex, Singapore.*
Infant feed.
Hypoallergenic infant feed.

Mamex Gold Hypoallergenic (HA) *Danone Dumex, Malaysia.*
Infant feed.
Milk protein allergy.

Mamex Gold Lactose Free *Danone Dumex, Malaysia.*
Lactose free infant feed.
Lactose intolerance.

Mamex Gold Soy *Danone Dumex, Singapore.*
Infant feed.

Mamex LF *Danone Dumex, Singapore.*
Infant feed.
Lactose intolerance.

Mami *TNP, Thai.*
Vitamins; minerals.

Mamifol *Italfarmaco, Rus.*
Folic acid (p. 2063·1).
Folic-acid-deficiency anaemia; folic acid deficiency.

Mamil Gold Soy *Danone Dumex, Singapore.*
Infant feed.

Mamil Mama *Danone Dumex, Malaysia.*
Nutritional supplement for pregnant and lactating women.

Mamil Mama with Immunoforce *Danone Dumex, Singapore.*
Nutritional supplement for pregnant and lactating women.

Mamira *Teva, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Mammol *Abbott, USA.*
Bismuth subnitrate (p. 1822·1); castor oil (p. 2472·1); peru balsam (p. 2587·1).
Nipple care.

Mammoleptin *Herbapex, Ukr.*
Deer antlers; carthamus tinctorius; ginseng (p. 2513·3); trichosanthes kirilowii root; trichosanthes rosthornii root; peony; aucklandia lappa root; forsythia; taraxacum (p. 2625·3); spatholobus suberectus; sargasso fusiform alga (p. 2612·1); figwort; Japanese kelp (p. 2612·1); echinops dahuricus; brunella vulgaris.
Fibrocystic mastopathy.

Mammosole *Gedeon Richter, Rus.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Mammozole *Gedeon Richter, Cz.; Gedeon Richter, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Mamoclam *Fitolon, Rus.*
Clam.
Benign breast disorders.

Mamofen *Khandelwal, India; Klab, Thai.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; female infertility.

Mamograf *Temis, Arg.*
Activated charcoal (p. 1537·3).
Adjunct in breast examination.

Mamomit *Pliva, Rus.*
⊗Aminoglutethimide (p. 739·2).
Malignant neoplasms; adrenal hyperplasia; hyperaldosteronism.

Mamostrol *Synthon, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Manace *CCM, Malaysia; Duopharma, Singapore.*
Haloperidol (p. 1077·1).
Psychoses; mania; Tourette syndrome; alcoholism; nausea and vomiting; neuroleptanalgesia; agitation.

Manacon *Mavi, Mex.*
Diclofenac (p. 48·3).
Inflammation; pain.

Manaderm *Wyeth, India.†*
Psoralen (p. 1711·3).
Leukoderma; psoriasis; vitiligo.

Manamin GA *Tsuruhara, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Manavite *Wyeth, India.*
Vitamins.

Mancef *Lafare, Ital.*
Cefamandole nafate (p. 236·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Mancetam *T Man, Thai.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Mancevit *T Man, Thai.†*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Manclamine *T Man, Thai.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Mandafen *Pharmachem, UK.*
Ibuprofen (p. 68·2).
Cold and influenza symptoms; fever; pain.

Mandal 425 *Gebro, Switz.*
St John's wort (p. 449·1).
Nervous disorders; insomnia.

Mandalyn Expectorant *Pharmachem, UK.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Coughs and cold symptoms.

Mandalyn Paediatric *Pharmachem, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Coughs and cold symptoms.

Mandanol *Pharmachem, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Mandelamin *Warner, India.*
Methenamine mandelate (p. 323·1).
Urinary-tract infections.

Mandelamine *Erfa, Canad.; Warner Chilcott, USA; Pfizer, Venez.*
Methenamine mandelate (p. 323·1).
Urinary-tract infections.

ManDelay *Majestic, Canad.†; Morepen, India.*
Benzocaine (p. 1980·2).
Premature ejaculation.

Mandocef *Lilly, Gr.†*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Mandofen *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Mandokef *Astro, Austria; Lilly, Gr.; Aspen, S.Afr.†; Teva, Switz.*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Mandol *Lilly, Austral.†; EuroCept, Belg.†; EuroCept, Neth.; Lilly, NZ; Lilly, Rus.*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Mandolgin *Sandoz, Denm.*
Tramadol hydrochloride (p. 139·2).
Pain.

Mandragora comp *Weleda, Ger.*
Arnica pl. tota (p. 2447·2); fol. betula (p. 2457·3); equisetum arvense (p. 2500·1); formica; mandragora; meniscus genus.
Homoeopathic preparation.

Mandragora Med Complex *Dynamit, Austria.*
Ignatia (p. 2532·1); mandragora radice; thuja (p. 2629·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Manerix *Meda, Canad.; Meda, Irl.; Meda, Spain; Roche, UK.*
Moclobemide (p. 437·2).
Depression.

Manevac
Note: this name may be used for preparations of different composition.
HFA Healthcare, UK.
Ispaghula (p. 1849·1); senna fruit (p. 1885·1).
Constipation; bowel evacuation.

Manex *T Man, Thai.†*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Manexil *Fem Care, India.*
Minoxidil (p. 1438·3).
Alopecia.

Manfenac *T Man, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Manforce *Mankind, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Manforce More *Mankind, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

Manfredol *Cantabria, Spain.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Mangimin *Key, USA.*
Manganese (p. 2081·2).
Dietary supplement.

Mangogyl *Pharma Synth, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Mangolide *DWD, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Manhaé *Nutrisanté, Fr.*
Nutritional supplement.
Menopausal disorders.

Manhae *Nutrisante, Singapore.*
Phospholipids (p. 2201·2); borage oil (p. 2459·2); gamolenic acid (p. 2509·2); citrus bioflavonoids (p. 2505·2); omega-3 fatty acids (p. 1460·1); vitamins; iron (p. 2073·1); zinc (p. 2126·1).
Menopausal disorders.

Manic *Medifive, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Manicarb *Psychotropics, India.*
Lithium.
Bipolar disorder; mania; depression.

Manidon *Abbott, Spain; Abbott, Venez.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension; myocardial infarction.

Maniglid *Bryntsalov, Rus.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Maninil *Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Maniprex *Kela, Belg.*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression.

Manivasc *Chiesi, Braz.*
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Manix *Wockhardt, India.*
⊗Cardamom (p. 2471·1); cinnamon (p. 2479·2); tribulus terrestris (p. 2633·3).
Erectile dysfunction.

Manmox *T Man, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mann *SMB, Belg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Mannex *Bioceuticals, UK.*
Vitamins; minerals.

Mannigyl *Chandra Bhagat, India.*
⊗Glycerol (p. 2517·2); mannitol (p. 1427·3).

Mannisol *Human, Cz.†; Teva, Hung.*
⊗Mannitol (p. 1427·3).
Forced diuresis; oedema; renal failure; cranial and ocular hypertension; oliguria.

Mannite *Actipharm, Switz.*
⊗Mannitol (p. 1427·3).
Constipation.

Mannit-Lösung *Serag-Wiessner, Ger.*
⊗Mannitol (p. 1427·3).
Renal failure; oedema; forced diuresis.

Mannix *Medicine Products, Thai.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Mano
Note: this name may be used for preparations of different composition.
March, Thai.
⊗Tetryzoline hydrochloride (p. 1678·3); boric acid (p. 2459·3); sodium chloride (p. 1795·1).
Allergic eye disorders.

Milano, Thai.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastric hyperacidity; heartburn; oesophagitis; peptic ulcer.

Manoane *March, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Oral contraceptive in women with androgenic symptoms.

Mano-Ap-Es *Lam Thong, Thai.*
⊗Reserpine (p. 1485·3); hydralazine hydrochloride (p. 1401·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Manobaxine *March, Thai.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm; peri-articular disorders.

Manobrozil *March, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Mano-Bruzone *March, Thai.*
Ibuprofen (p. 68·2).
Rheumatoid arthritis; pain; inflammation; fever.

Manocalm Forte *Orchid, India.*
Chlorpromazine (p. 1045·2); trifluoperazine (p. 1113·2); trihexyphenidyl (p. 917·3).

Manocalm Plus *Orchid, India.*
Trifluoperazine (p. 1113·2); trihexyphenidyl (p. 917·3).

Manocidal *March, Thai.*
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Manodepo *March, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Menstrual disorders; menopausal disorders; threatened or recurrent miscarriage; pregnancy test.

Manodextro *March, Thai.*
Dextromethorphan (p. 1660·1).
Cough.

Manodiazo *March, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; alcohol withdrawal syndrome; premedication; seizures.

Manodiol *March, Thai.*
Ethinylestradiol (p. 2275·3); norgestrel (p. 2296·1).
Menstrual disorders.

Manodol *Orchid, India.*
Haloperidol (p. 1077·1); trihexyphenidyl (p. 917·3) or trihexyphenidyl hydrochloride (p. 917·3).

Manoeidai *March, Thai.†*
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Manoflox *March, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Manogest *CMG, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Manoglucon *March, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Manohexy *Orchid, India.*
Trihexyphenidyl (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Manoketo *March, Thai.*
Ketoconazole (p. 585·3).
Scalp disorders; tinea versicolor.

Manol *Sanitas, Chile.*
Tramadol hydrochloride (p. 139·2).
Pain.

Manolium *March, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; alcohol withdrawal syndrome; premedication; seizures.

Manoll *Charak, India.*
⊗Liquorice (p. 1853·2); piper longum; tribulus terrestris (p. 2633·3); withania somnifera (p. 2450·2); zingiber officinale.

Manolone *Lam Thong, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Manomazole *March, Thai.*
Clotrimazole (p. 576·2).
Fungal and trichomonal vaginitis.

Manomet *March, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Manomic *March, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Manoprolol *Orchid, India.*
⊗Propranolol (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; essential tremor.

Manorapid Synergy *Remington, Canad.*
⊗Alcohol (p. 1733·1); butanediol (p. 2172·2); propyl alcohol (p. 1768·1); propylene glycol (p. 2205·2).

Manorest *Orchid, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Manorest Forte *Orchid, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Manorest Plus *Orchid, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Manorfen *Manor, UK.*
Ibuprofen (p. 68·2).

Manorifcin *March, Thai.*
Rifampicin (p. 350·3).
Tuberculosis; gonorrhoea.

Manoron *March, Thai.*
Cinnarizine (p. 622·1).
Vestibular disorders; cerebral and peripheral vascular disorders; migraine; motion sickness.

Manosil *March, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Manospirin *Orchid, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Manotac *Orchid, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration; dyspepsia.

Manotac Plus *Orchid, India.*
Cisapride (p. 1831·3); ranitidine (p. 1882·1).

Manoten *Orchid, India.*
⊗Atenolol (p. 1308·2).
Angina pectoris; migraine; hypertension.

Manotran *March, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Mano-Trim *Lam Thong, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Manoval *Orchid, India.*
Sodium valproate (p. 553·1).
Bipolar disorder; epilepsy; migraine.

Manoverm *March, Thai.*
Niclosamide (p. 161·2).
Taeniasis.

Manovit-C Plus *Orchid, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Manovon *March, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Obstructive airways disease.

Manoxicam *Lam Thong, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Manoxidil *March, Thai.*
Minoxidil (p. 1438·3).
Hypertension; heart failure.

Manozide *March, Thai.*
Albendazole (p. 149·1).
Worm infections.

Manpizide *T Man, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Manpower *Pidek, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Manroxin *T Man, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Mansil *Pfizer, Braz.*
Oxamniquine (p. 162·1).
Schistosomiasis.

Mantab *T Man, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Mantadan *Boehringer Ingelheim, Ital.*
Amantadine hydrochloride (p. 890·3).
Influenza A; parkinsonism; mental function impairment.

Mantadix *BMS, Fr.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza A.

Mantai *Pentafarma, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Manti *US Pharmacia, Pol.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; hiatus hernia; dyspepsia.

Manti Gastop *US Pharmacia, Pol.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; gastrointestinal procedures.

Mantidan *Eurofarma, Braz.*
Amantadine hydrochloride (p. 890·3).
Drug-induced extrapyramidal disorders; fatigue associated with multiple sclerosis; influenza A; parkinsonism.

Mantil *T Man, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Mantus *Investi, Arg.*
⊗A heparinoid (p. 1401·1); triamcinolone acetonide (p. 1649·1); hexetidine (p. 1755·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Manuia *DHU, Ger.*
Damiana (p. 2491·3); panax ginseng (p. 2513·3); acidum phosphoricum (p. 2589·1); ambra (p. 2440·3).
Homoeopathic preparation.

Manuprin *Yeni, Turk.*
Methenamine mandelate (p. 323·1).
Urinary-tract infections.

Manusept
Note: this name may be used for preparations of different composition.
Medlock Medical, Irl.; Medlock Medical, UK.
Triclosan (p. 1773·2); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Manusept basic *Bode, Ger.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Manusept viruzid *Bode, Ger.†*
⊗Propyl alcohol (p. 1768·1); alcohol (p. 1733·1).
Hand disinfection.

Manyper *Chiesi, Ger.; Chiesi, Gr.*
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Manza *Orchid, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Manzan *Gezzi, Arg.*
Camphor (p. 2466·2); phenol (p. 1763·3); thymol (p. 1772·2); hamamelis (p. 2523·3); eucalyptus oil (p. 2501·2).
Haemorrhoids.

Manzan Plus *Gezzi, Arg.*
Zinc oxide (p. 1729·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Manzer *Little Greave, India.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3).

Manzid *Admac, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Manzofen *T Man, Thai.*
Pizotifen (p. 678·2).
Migraine; cluster headache.

Maobushisaishinto *Tsumura, Jpn.*
⊗Ephedra herb (p. 1663·1); asiasarum root; aconite root (p. 2428·3).
Traditional Kampo medicine.

Maorex *Torrex Chiesi, Hung.†*
Moclobemide (p. 437·2).
Depression; social phobia.

Maosig *Aspen, Austral.*
Moclobemide (p. 437·2).
Depression.

Maoto *Tsumura, Jpn.*
⊗Apricot kernel (p. 2445·3); ephedra herb (p. 1663·1); cinnamon bark (p. 2479·2); liquorice (p. 1853·2).
Traditional Kampo medicine.

Maox *Manne, USA.*
Magnesium oxide (p. 1857·3).
Hyperacidity.

Map *Health Care, India.*
Meropenem (p. 321·3).
Bacterial infections.

Map An *Pfizer, Arg.†*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms.

Mapap *Major, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Mapap Cold Formula *Major, USA.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Mapap Sinus Congestion & Pain *Major, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Mapci *Osmed, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Mapciril *Flamingo, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Mapci-TZ *Osmed, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Mapelor *Boehringer Ingelheim, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Mapenem *Siam Bheasach, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Mapezine *Siam Bheasach, Thai.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Mapgyl *Osmed, India.*
Oral suspension: Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Osmed, India.
Tablets: Tinidazole (p. 949·2); norfloxacin (p. 333·3).

Mapime *Mapra, India.*
Cefepime (p. 239·2).
Bacterial infections.

Mapin *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression.

Mapisal *Medac, Ger.*
Emollient.
Palmar-plantar erythrodysesthesia syndrome.

Maple Melts *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals.
Tonic.

Maple Treatment *Kamins, Canad.*
SPF 20: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Mapleflex *Nutricia, Fr.; SHS, Irl.; SHS, UK.*
Food for special diets.
Maple syrup urine disease.

Mapluxin *Novartis, Mex.*
Digoxin (p. 1353·3).
Heart failure; paroxysmal supraventricular tachycardia.

Mapradrox *Mapra, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Mapratone *Mapra, India.*
Vitamin B substances (p. 2102·3).

Mapratone-Z *Mapra, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Maprazyme *Mapra, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Mapress *CCM, Malaysia.*
Haloperidol (p. 1077·1).
Psychoses; alcoholism; nausea and vomiting.

Maprilex *Liferpal, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Maprofen *Marching, Hong Kong.†*
Ibuprofen (p. 68·2).

Maprolu *Hexal, Ger.†*
Maprotiline hydrochloride (p. 433·3).
Depression.

Mapromil *Farmo Quimica, Chile.†*
Maprotiline hydrochloride (p. 433·3).
Depression.

Maprosol *LDA, Arg.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

LDA, Arg.
SPF 40: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Maprosol Autobronceante *LDA, Arg.*
Dihydroxyacetone (p. 1700·1).
Tanning agent.

Maprosol Gel *LDA, Arg.*
Aloe vera (p. 1693·2); mallow (p. 2549·2); tilia (p. 2631·3).
Sun-induced skin disorders.

Maprotibene *Ratiopharm, Cz.†*
Maprotiline hydrochloride (p. 433·3).
Depression; anxiety disorders.

Maprotil *Terra, Turk.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Maproxacin *Marching, Hong Kong.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Mapryl
Note: this name may be used for preparations of different composition.
Ikapharmindo, Indon.
Glimepiride (p. 473·2).
Diabetes mellitus.

Polfa Warszawa, Pol.
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; diabetic nephropathy.

Mapurit *Sanum-Kehlbeck, Ger.†*
dl-Alpha tocoferil acetate (p. 2119·2); magnesium oxide (p. 1857·3).
Magnesium or vitamin E deficiency.

MaQaid *Wakamoto, Jpn.*
⊗Triamcinolone acetonide (p. 1649·1).
Visualisation of the vitreous during vitrectomy; diabetic macular oedema.

Mar Plus *Stada, Hong Kong; Stada, Malaysia; Stada, Thai.*
Dexpanthenol (p. 2582·2); sea water (p. 2612·1).
Rhinitis; nasal hygiene; nasal congestion.

Mar Rhino *Stada, Cz.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis.

Maradex *Oftalmi, Venez.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Marament-N *Amino, Switz.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); benzyl nicotinate (p. 29·3); Scots pine oil (p. 2591·2).
Musculoskeletal, joint, and soft-tissue disorders.

Maranox *Dent, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Maraslavin *Sopharma, Rus.*
Artemisia pontici (p. 2426·1); clove flowers (p. 2481·2); black pepper (p. 2586·1); ginger (p. 1844·1); summer savory (p. 2625·1).
Formerly contained absinthium, clove flowers, black pepper, ginger, and thyme.
Periodontitis.

Sopharma, Ukr.
Absinthium (p. 2426·1); allspice; black pepper (p. 2586·1); ginger (p. 1844·1); thyme (p. 2630·2).
Periodontitis.

Marathon *Ivax, Arg.*
Ubidecarenone (p. 2637·1); ginseng (p. 2513·3); vitamins; minerals; trace elements.
Tonic.

Laboratorios Chile, Chile.
Vitamins; minerals; ubidecarenone (p. 2637·1); ginseng (p. 2513·3).
Dietary supplement.

Marathon Antioxidante *Ivax, Arg.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1); betacarotene (p. 2051·1); selenium (p. 2086·3).
Antoxidant preparation.

Marax
Note: this name may be used for preparations of different composition.
Nordix, Ger.; Nordmark, Ger.
Magaldrate (p. 1856·1).
Gastric hyperacidity; peptic ulcer.

Pfizer, Braz.; Pfizer, USA.
⊗Hydroxyzine hydrochloride (p. 630·3); ephedrine sulfate (p. 1663·2); theophylline (p. 1229·3).
Bronchospastic disorders; bronchospasm.

Unimed, India.
⊗Hydroxyzine hydrochloride (p. 630·3); ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3).
Asthma; bronchospasm.

Marching, Hong Kong.†
Crotamiton (p. 1699·2).
Pruritus; scabies; pediculosis.

Marbeta *Glenmark, Cz.; Disphar, Neth.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Marblen *Fleming, USA.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Hyperacidity.

Marbroxol *Marching, Hong Kong.†*
Ambroxol hydrochloride (p. 1654·3).
Cough.

Marbrozil *Marching, Hong Kong.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; primary prevention of ischaemic heart disease in men.

Marc Free *Vencare, India.*
Aloes (p. 1816·1); Indian barberry (p. 2532·1); curcuma longa; ocimum sanctum; pterocarpus santalinus; rose fruit (p. 2607·1); wheat-germ oil (p. 2647·1).
Acne.

Marcain *AstraZeneca, Austral.; Dentsply, Austral.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Rus.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, UK.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

Marcain with Fentanyl *AstraZeneca, Austral.; AstraZeneca, NZ.*
⊗Bupivacaine hydrochloride (p. 1980·3); fentanyl citrate (p. 60·1).
Epidural analgesia.

Marcaina *AstraZeneca, Braz.; AstraZeneca, Ital.; Astra, Port.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Marcaine *AstraZeneca, Belg.; Hospira, Canad.; AstraZeneca, Cz.; AstraZeneca, Gr.; AstraZeneca, Israel; AstraZeneca, Neth.; Hospira, Philipp.; AstraZeneca, Pol.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, Ukr.; Hospira, USA.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

Marcef *Glenmark, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Marcelle Essentials *Marcelle, Canad.*
SPF 15: Ensulizole (p. 1703·1); meradimate (p. 1711·2); octinoxate (p. 1715·1).
Sunscreen.

Marcelle Moisture Eye Cream *Marcelle, Canad.†*
SPF 15: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Marcelle Multi-Defense *Marcelle, Canad.*
SPF 15: Meradimate (p. 1711·2); octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Marcelle Sheer Tint *Marcelle, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Marcelle True Radiance *Marcelle, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Marcen *Vegal, Spain.†*
Ketazolam (p. 1079·2).
Anxiety; insomnia; skeletal muscle spasm.

Marcholax *Marching, Hong Kong.†*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Marclazide *Marching, Hong Kong.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Marclorhex *Cristalia, Braz.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Marco Sweet Light *Laboratorios Chile, Chile.*
Aspartame (p. 2169·2); acesulfame potassium (p. 2166·2).
Sugar substitute.

Marcocid *Willvonseder, Austria.*
Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Marcodine *Cristalia, Braz.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Marcof *Marnel, USA.†*
Hydrocodone tartrate (p. 67·2); sulfogaiacol (p. 1678·1).
Cough.

Mar-Cof BP *Marnel, USA.*
⊗Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

MAR-COF CG *Marnel, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Marcold *Zota, India.*
Oral suspension: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).

Zota, India.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Marcorodex *Rougier, Canad.*
Benzethonium chloride (p. 1738·1); phenoxyethanol (p. 1764·3).

Marcoumar *Meda, Austria; Meda, Belg.; Roche, Braz.; Meda, Denm.; Meda, Neth.; Meda, Switz.*
Phenprocoumon (p. 1468·3).
Thromboembolic disorders.

Marcumar *Meda, Ger.*
Phenprocoumon (p. 1468·3).
Thromboembolic disorders.

marcuphen *CT, Ger.*
Phenprocoumon (p. 1468·3).
Thromboembolic disorders.

Mardase-K *Zota, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Mardil Zink *Oksigon, Rus.*
Zinc chloropropionate.

Mardol *Kopran, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Marduk *S & K, Ger.*
Benzoyl peroxide (p. 1696·1).
Acne.

Mareamin *Volta, Chile.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Mareen *Krewel, Ger.*
Doxepin hydrochloride (p. 414·2).
Depression; anxiety disorders; sleep disorders; withdrawal syndromes.

Marenil *Pharmathen, Gr.*
Ibacitabine (p. 984·3).

Marenin *Berman, Mex.*
Meclozine (p. 634·3).
Vertigo.

Maresis *Farmoquimica, Braz.*
Sodium chloride (p. 1795·1).

Marevan *Aspen, Austral.; Therabel, Belg.; Farmoquimica, Braz.; Nycomed, Denm.; Orion, Fin.; IFET (ΙΦΕΤ), Gr.; Nycomed, Norw.; GSK, NZ; Orion, Rus.; GSK, Singapore; Mercury, UK.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Marex *Zota, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Marezine *Himmel, USA.*
Cyclizine hydrochloride (p. 623·2).
Motion sickness.

Marfarin *Generics, Hung.*
Warfarin sodium clathrate (p. 1527·1).
Thromboembolic disorders.

Teuto, Braz.†
Warfarin sodium (p. 1527·1).

Marfen *Scheeling, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Marfloxacin *Marching, Hong Kong.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Marflu-X *Marching, Hong Kong.†*
Paracetamol (p. 115·1); pentoxyverine citrate (p. 1672·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3); guaifenesin (p. 1666·2).
Cold symptoms.

Marga *Cooperation Pharmaceutique, Fr.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Margel *Millimed, Thai.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence.

Margesic *Marnel, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Margesic H *Marnel, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Marglucon *Marching, Hong Kong.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Margyl *Adienne, Ital.*
Phenelzine sulfate (p. 442·1).
Depression.

Marianon Hepar *Klein, Ger.*
Chelidonium majus (p. 2522·2); lycopodium clavatum (p. 2547·1); silybum marianum (p. 1561·1).
Homoeopathic preparation.

Mariastel *Pharmathen, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Mariazeller *Apotheke Gnadenmutter, Austria.*
Cinnamon (p. 2479·2); cinchona bark (p. 2478·3); dried bitter-orange peel (p. 2575·3); clove (p. 2481·2); flos aurantii (p. 2576·2); chamomile (p. 2474·1); folium aurantium; melissa (p. 2552·3); menyanthes (p. 2554·2); cardamom fruit (p. 2471·1); fructus aurantii immat; coriander (p. 2486·3); absinthium (p. 2426·1); cnicus benedictus (p. 2482·2); centaury (p. 2473·2); achillea moschata; achillea (p. 2427·3); guaiacum wood; juniper (p. 2537·1); galanga; gentian (p. 2512·1); ginger (p. 1844·1); nutmeg (p. 2573·1).
Gastrointestinal disorders.

Maricrio *SoSe, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Maridin *Pliva, Cz.†*
Rimantadine hydrochloride (p. 1012·2).
Influenza A infection.

Mariendistel Curarina *Harras-Curarina, Ger.*
Carduus marianus (p. 1561·1).
Homoeopathic preparation.

Maril *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Adjunct in gastrointestinal radiography; adjunct in duodenal intubation; gastrointestinal motility disorders; nausea and vomiting.

Marilamed *KRKA, Denm.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Marimer *Gilbert, Fr.†; Gilbert, Rus.; Gilbert, Thai.; Gilbert, Ukr.*
Sea water (p. 2612·1).
Nasopharyngeal disorders; nasal hygiene; nasal dryness; allergic rhinitis.

Marina
Note: this name may be used for preparations of different composition.
Biofarma, Venez.
Omega-3 marine triglycerides (p. 1460·3).
Hypercholesterolaemia; rheumatoid arthritis.

TMan, Thai.
Silymarin (p. 1561·2).
Liver disorders.

Marincap *Kocak, Turk.*
Omega-3 marine triglycerides (p. 1460·3).
Ischaemic heart disease; hyperlipidaemias.

Marine Lipid Concentrate *Vitaline, USA.*
Omega-3 marine triglycerides (p. 1460·3); vitamin E (p. 2119·1).
Dietary supplement.

MarinEx *Beacons, Hong Kong.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Marinol
Note: this name may be used for preparations of different composition.
Pharmadeveloppement, Fr.
Bladderwrack (p. 2612·1); laminaria (p. 2540·1); calcium carbonate (p. 1824·3); phosphoric acid (p. 2589·1); sea water (p. 2612·1).
Tonic.

Scoshia, India.
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Abbott, Canad.†; Solvay, USA.
⊗Dronabinol (p. 1840·1).
Nausea and vomiting associated with cancer chemotherapy; appetite stimulant; AIDS related anorexia.

Marching, Hong Kong.†
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Marinol Alpha *Scoshia, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Marinol Plus *Scoshia, India.*
Vitamin B substances (p. 2102·3).

Marinol-B *Scoshia, India.*
Vitamin B substances (p. 2102·3).

Marinol-GB *Scoshia, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mario *Esma, India.*
Clomipramine hydrochloride (p. 412·1).
Cataplexy associated with narcolepsy; obsessive-compulsive disorder; panic disorder; depression.

Mariomigran *Phytofarm Kleka, Pol.†*
Chrysanthemum parthenium (p. 676·1).
Migraine.

Mariosea *Teva, UK.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Maripen *Teva, Hung.*
Penamecillin.
Bacterial infections.

Mariper *KRKA, Denm.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease; cardiovascular risk reduction.

Mariprax *Farmaten, Gr.*
Pramipexole hydrochloride (p. 911·2).

RKG, Ital.
Pramipexole (p. 911·2).

Mariram *Actavis, Denm.*
Ramipril (p. 1483·3).
Hypertension; glomerular nephropathy; heart failure; myocardial infarction.

Marisil *Chemo-Drugs, India.*
Silymarin (p. 1561·2).
Liver disorders.

Mariston *Codal Synto, Thai.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Maritidine *Marching, Hong Kong.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis; Zollinger-Ellison syndrome.

Maritop *Pharmathen, Denm.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Marizine *Marching, Hong Kong.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Marlex *Neves, Port.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Marlin Salt System *Marlin, USA.†*
Sodium chloride (p. 1795·1).
Rinsing and storage solution for soft contact lenses.

Marlissa *Glenmark, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Mar-Loper *Marching, Hong Kong.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Marlora *Marching, Hong Kong.†*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Marlyn Formula 50 *Marlyn, USA.*
Amino acids; pyridoxine hydrochloride (p. 2105·3).
Nail disorders; postnatal hair-loss.

Marmodine *Marching, Hong Kong.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Marnatal-F *Marnel, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Marnif *Aamorb, India.*
Meropenem (p. 321·3).
Bacterial infections.

Marol *Morningside, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Marolderm *Dermapharm, Ger.†*
Dexpanthenol (p. 2582·2).
Skin disorders.

Maronil *Trima, Israel.*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder.

Marovilina *Atlantis, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Maroxil *Brymar, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Marozid *Liconsa, Swed.*
⊗Hydrochlorothiazide (p. 1403·2); losartan (p. 1422·2).

AGP, Denm.†
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Marpeniramine *Marching, Hong Kong.†*
Chlorphenamine (p. 620·3).

Marphage *Pasteur, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Marphazole *Marching, Hong Kong.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Marplan
Note: this name may be used for preparations of different composition.
AstraZeneca, Arg.
Levonorgestrel (p. 2296·1).
Postcoital contraceptive.

Medilink, Denm.; Validus, USA.
Isocarboxazid (p. 427·2).
Depression.

Marpram *Marvecs, Ital.*
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Marpres *Marnel, USA.*
⊗Hydrochlorothiazide (p. 1403·2); reserpine (p. 1485·3); hydralazine hydrochloride (p. 1401·2).
Hypertension.

Marpro *Zota, India.*
Preparation for enteral nutrition.

Marpro-Z *Zota, India.*
Vitamin B substances (p. 2102·3); minerals; protein hydrolysate (p. 2086·2).
Dietary supplement.

Marqibo *Talon, USA.*
Vincristine sulfate liposomal (p. 882·3).
Lymphoblastic leukaemia.

Marsedyl *Marching, Hong Kong.†*
Syrup: ⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).
Cough; upper respiratory-tract congestion.

Marching, Hong Kong.†
Tablets: ⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).
Cough; upper respiratory-tract congestion.

Marsedyl II *Marching, Hong Kong.†*
Pentoxyverine (p. 1672·1); phenylephrine (p. 1672·2); promethazine (p. 638·2).

Marsilid *Genopharm, Fr.*
Iproniazid phosphate (p. 427·2).
Depression.

Marsim *KRKA, Neth.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Mar-Spas *Marnel, USA.*
Hyoscyamine sulfate (p. 1848·1).

Marsthine *Crisdy-Na, Philipp.*
Clemastine fumarate (p. 622·3).
Allergic disorders.

Martec *Oxytech, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Martenol *Marching, Hong Kong.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; alcohol withdrawal; hyperthyroidism; migraine.

Marten-Tab *Marnel, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1).
Tension headache.

Martham *Vamsler, Philipp.*
Vitamins; minerals.

Marthritic *Marnel, USA.*
Salsalate (p. 130·1).

Martians *Walmark, Singapore.*
Vitamins; minerals.

Martidox-M *Bushnell, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Martifur *Bushnell, India.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Martindale Methadone Mixture DTF
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal.

Martis *Madhav, India.*
Artesunate (p. 648·2).
Malaria.

Martispasmol *Bushnell, India.*
Cyclandelate (p. 1347·1).
Peripheral vascular disorders.

Martiz *Meridian, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Martomide *Marching, Hong Kong.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders; adjunct in gastrointestinal procedures.

Martos *Otsuka, Indon.; Otsuka, Jpn.*
Maltose (p. 2081·1).
Carbohydrate source; diabetes mellitus.

Martulose *Marching, Hong Kong.†*
Lactulose (p. 1850·3).
Constipation; hepatic coma; hepatic encephalopathy.

Marulide *Pasteur, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Maruxa *Consilient, UK.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Mar-V *Dupomar, Arg.*
Electrolytes (p. 1775·1).
Respiratory-tract congestion.

Marvel *Orchid, India.*
Minerals; trace elements.

Marvelon *MSD, Austral.; Schering-Plough, Indon.; Organon, Philpp.; Adcock Ingram, S.Afr.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Organon, Arg.; Organon, Austria; Organon, Belg.; Merck, Canad.; Schering-Plough, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD, Ger.; Organon (Opyzvov), Gr.; MSD, Hong Kong; Organon, Hung.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Singapore; MSD, Switz.; MSD, Thai.; Organon, UK; Organon, Ukr.; Organon, Venez.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; androgen-associated skin disorders in women.

Marvil *Elisium, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Marvil D *Elisium, Arg.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Marviol *Organon, Irl.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Marvir *Lam Thong, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Marvita *Pharmed, India.*
Ferrous gluconate (p. 2061·2); lysine hydrochloride (p. 2079·3); malt extract (p. 2080·2); vitamins.

Marxide *Arrow, Ital.*
⊗Budesonide (p. 1625·1).
Asthma.

Mary Kay Lip Protector *Kay, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Mary Kay Sunscreen *Kay, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Mary Kay Timewise Sunscreen *Kay, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Mary Kay Tinted Moisturiser with Sunscreen
Kay, Canad.
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Marzine *Meda, Denm.; Meda, Fin.; Meda, Norw.; Pfizer, NZ†; GSK, Singapore; Janssen-Cilag, Switz.†*
Cyclizine hydrochloride (p. 623·2).
Motion sickness; Ménière's disease; nausea and vomiting; vertigo; vestibular disorders; dizziness.

Marzipan *Kamakshi, India.*
Meropenem (p. 321·3).
Bacterial infections.

Marzivag *Novag, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Marzolam *March, Thai.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Masa 3B *Masa, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Masabalm
Note: this name may be used for preparations of different composition.
Masa, Thai.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain.

Masafen *Masa, Thai.†*
Mefenamic acid (p. 85·3).
Pain.

Masaga *Nakornpatana, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); clove oil (p. 2481·3).
Musculoskeletal pain; neuralgia; sciatica.

Masagil *Perez Gimenez, Spain.†*
Liniment: Camphor (p. 2466·2); ammonia (p. 2441·2); methyl salicylate (p. 92·1); rosemary oil (p. 2607·3); turpentine oil (p. 2636·3).
Rheumatic and muscle pain.

Perez Gimenez, Spain.†
Topical Spray: Camphor (p. 2466·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); menthol (p. 2553·2).
Rheumatic and muscle pain.

Masai *Flamingo, India.*
Aceclofenac (p. 16·2); drotaverine (p. 2497·3).

Masapara w / Codeine *Masa, Thai.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Masaren *Masa, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Masarol *Masa, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Masaworm-1 *Masa, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Maść na Odciski *Aflofarm, Pol.; Hasco-Lek, Pol.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Corns.

Gemi, Pol.
Melilotus emplastrum (p. 2552·3); salicylic acid (p. 1719·1).
Corns.

Maść Ochronna z Witamina A *Hasco-Lek, Pol.*
Vitamin A palmitate (p. 2098·3).
Skin disorders.

Maść Przeciw Odciskom i Zgrubieniom Skóry *Farmal, Pol.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Maść Tranowa *Farmina, Pol.*
Cod-liver oil (p. 2056·3).
Skin disorders.

Maść Witaminowa Ochronna *Homeofarm, Pol.*
Vitamin A (p. 2098·3).
Skin disorders.

Mascarilla *Silesia, Chile.*
Emollient.
Drys skin; skin irritation.

Mascartil *Pharmadiet, Spain.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Masculine Herbal Complex *GNLD, Austral.*
Saw palmetto (p. 2363·3); avena (p. 2451·1); celery (p. 2472·3); damiana (p. 2491·3); achillea (p. 2427·3); St John's wort (p. 449·1); skullcap (p. 2617·1); astragalus (p. 2451·1); chillies (p. 2469·3).
Tonic.

Masdil *Lupin, India; Esteve, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; arrhythmias; hypertension.

Masedi *Serral, Mex.*
Magaldrate (p. 1856·1); dimeticone (p. 1886·2).

MAS-ER *Teva, USA.*
⊗Dexamfetamine saccharate (p. 2319·1); amfetamine aspartate (p. 2316·1); dexamfetamine sulfate (p. 2319·1); amfetamine sulfate (p. 2316·2).
Attention deficit hyperactivity disorder.

Masern-Impfstoff Mérieux *Sanofi Pasteur, Ger.*
A live measles vaccine (attenuated Schwarz strain) (p. 2398·3).
Active immunisation.

Masferol *Quimica y Farmacia, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Mashiningan *Tsumura, Jpn.*
Hemp fruit; rhubarb (p. 1884·2); immature orange; apricot kernel (p. 2445·3); magnolia bark; peony root.
Traditional Kampo medicine.

Masivol *Investi, Arg.*
Vitamin A palmitate (p. 2098·3); vitamin E acetate (p. 2119·2); allantoin (p. 1693·1).
Skin disorders.

Masivol Urea *Investi, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); vitamin A palmitate (p. 2098·3); urea (p. 1727·3).
Skin disorders.

Mass Builder *Nutrilab, Arg.*
Preparation for enteral nutrition.

Massage Balm with Arnica *Weleda, Irl.*
Arnica oil (p. 2447·2); birch leaf oil (p. 92·1); lavender oil (p. 2541·1); rosemary oil (p. 2607·3).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Massage Balm with Calendula *Weleda, UK.*
Calendula (p. 2465·2); betula alba (p. 2457·3); lavender oil (p. 2541·1).
Muscle tension.

Massageol *Neo Quimica, Braz.*
Camphor (p. 2466·2); turpentine oil (p. 2636·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Massagim *Vitoria, Port.*
Diethylamine salicylate (p. 51·3).
Musculoskeletal pain and soft-tissue injury.

Masse *Advanced Care, USA.*
Emollient and moisturiser.
Nipple care.

Janssen-Cilag, S.Afr.†
Emollient.
Nipple care.

Johnson & Johnson, India.
Allantoin (p. 1693·1).
Nipple disorders.

Massê *Johnson & Johnson, Braz.*
Emollient.
Dry skin.

Massengill *SmithKline Beecham Consumer, USA.*
Powder: Ammonium alum (p. 2439·1); phenol (p. 1763·3); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thymol (p. 1772·2); sodium chloride (p. 1795·1).
Vaginal disorders.

Massengill Disposable *SmithKline Beecham Consumer, USA.*
Vinegar (p. 2426·3).
Vaginal disorders.

Massengill Feminine Cleansing Wash *SmithKline Beecham Consumer, USA.*
Vaginal cleanser.

Massengill Medicated
Note: this name may be used for preparations of different composition.
SmithKline Beecham Consumer, USA.
Soft cloth towelette: ⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

SmithKline Beecham Consumer, USA.
Vaginal douche: Povidone-iodine (p. 1767·1).
Vaginal disorders.

Massidron *Vera, Hung.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Mastaflu *Solvay, UK.†*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Master G Formula *Natures Sunshine, Canad.*
Vitamins; minerals.

Master-Aid *Pietrasanta, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin, burns, and wounds.

Masterelax *Andromaco, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Mastical *Nycomed, Spain.*
Calcium carbonate (p. 1824·3).
Hypocalcaemia; osteoporosis.

Mastical D *Takeda, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Mastifen *East West, India.*
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Mastifen-C *East West, India.*
Cetirizine hydrochloride (p. 619·2); ketotifen (p. 631·3).

Mastifen-S *East West, India.*
⊗Ketotifen (p. 631·3); salbutamol (p. 1220·2).

Mastika *Goldshield, UK.†*
Mastic gum (p. 2550·2).
Peptic ulcer.

Mastiol *Nupel, Spain.*
Chlorhexidine acetate (p. 1743·2); benzocaine (p. 1980·2); vitamin A (p. 2098·3).
Mastitis.

Mastodynon *Bionorica, Austria; Bionorica, Cz.; Bionorica, Ger.; Bionorica, Neth.†; Bionorica, Rus.; Bionorica, Thai.†; Bionorica, Ukr.*
⊗Agnus castus (p. 2432·2); caulophyllum thalictroides (p. 2458·2); cyclamen (p. 2490·2); ignatia (p. 2532·1); iris (p. 2534·3); lilium tigrinum.
Homoeopathic preparation.

Mastofen *Pentafarma, Port.†*
⊗Tamoxifen citrate (p. 860·2).

Mastopol *Alkoy, Rus.*
Conium maculatum (p. 2524·3); thuja occidentalis (p. 2629·3); hydrastis canadensis (p. 2528·1); calcium fluoratum (p. 2053·1).
Homoeopathic preparation.

Mastoren *Farmia, Cz.; Farmia, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Mastovet *Pharmathen, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Mastrol *Synthon, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Mastroson *Darya-Varia, Indon.†*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2).
Skin disorders with bacterial infection.

Mastu *Stada, Ger.*
Bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1).
Anorectal disorders.

Mastu akut *Stada, Ger.†*
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Mastu S *Stada, Cz.†; Stada, Hong Kong†; Stada, Hung.†; Stada, Thai.†*
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders; haemorrhoids.

Masulin *Sandoz, Denm.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Masunate *Cosmas, India.*
Artesunate (p. 648·2); pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Masvitalin Ginseng *Medica, Arg.*
Ginseng (p. 2513·3); magnesium glycerophosphate (p. 1787·2); vitamins.
Tonic.

Maswin *Masa, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Masyla *Hos & Ins, India.*
Etamsylate (p. 1145·2).
Periventricular haemorrhage in neonates.

Mataren *Nizpharm, Rus.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Matase *Nufarindo, Indon.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1); ascorbic acid (p. 2110·3); vitamin B_2 (p. 2104·3).
Dietary supplement.

Matasedrin *Cosmopharm, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Matce *Aamorb, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Matce-G *Aamorb, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Matce-P *Aamorb, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Matce-PG *Aamorb, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).

Match *Mankind, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Matcine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlorpromazine hydrochloride (p. 1045·2).
Affective disorders; controlled hypotension; hypothermia induction; nausea and vomiting; premedication; schizophrenia; sedative; psychoses.

Mat-CS *Overseas, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Mate *Constant, India.*
Artesunate (p. 648·2).
Malaria.

Matenol *Unison, Hong Kong; Unison, Thai.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; Ménière's disease; vertigo; tinnitus.

Mater Test *Biosintex, Arg.*
Pregnancy test (p. 2596·1).

Materfol *Biofarma, Mex.*
Folic acid (p. 2063·1).
Prevention of neural tube defects; prevention of neonatal lip and palate defects.

Materfolic *Farmoquimica, Braz.*
Folic acid (p. 2063·1).

Matergam *ZLB, Braz.†*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Matergam-P *Zydus, India.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Materna *Wyeth, Braz.; Pfizer, Hong Kong; Emcure, India; Wyeth-Ayerst, Israel†; Wyeth, Mex.; Wyeth, Singapore; Wyeth, Turk.; Wyeth, Venez.*
Vitamins; minerals.
Dietary supplement during pregnancy and lactation.

Materna FSH *Emcure, India.*
Urofollitropin (p. 2312·2).
Female infertility.

Materna HCG *Emcure, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; prepubertal cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Materna HMG *Emcure, India.*
⊗Human menopausal gonadotrophin (p. 2284·1).
Female and male infertility.

Maternavit *Medifarm, Venez.*
Vitamins; minerals; omega-3 marine triglycerides (p. 1460·3); soya oil (p. 2092·3).
Dietary supplement.

Maternity Crema de Ordeñe *San Ceferino, Arg.*
Aloe vera (p. 1693·2); alpha tocopherol (p. 2119·1).

Maternity Sapolan Bronceador *San Ceferino, Arg.*
Coconut oil (p. 2179·3).
Tanning aid.

Matersupre *Teuto, Braz.*
Vitamins; minerals.

Matervit *Farmoquimica, Braz.; RPF, Ital.*
Vitamins; minerals.
Nutritional supplement in pregnancy.

Matever *Pharmathen, Irl.; Glenmark, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Matico Compuesto *Knop, Chile.*
Matico; calendula (p. 2465·2); salvia (p. 2608·3); platero.
Homoeopathic preparation.

Matidan *Mintlab, Chile.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Matigel *Oftalmi, Venez.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Matikomp *Knop, Chile.*
Matico; calendula (p. 2465·2); arnica (p. 2447·2).
Soft-tissue injury; ulcers; wounds.

Matil *Pharmanel, Gr.*
Amisulpride (p. 1036·3).

Matilda *Lupin, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Lupin, India.
Injection; tablets: Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Matilol *Oftalmi, Venez.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Matinor
Note: this name may be used for preparations of different composition.
FarmoQuimica, Chile.
Phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1); phenyltoloxamine citrate (p. 638·1); carbinoxamine maleate (p. 619·1).
Cold and influenza symptoms; rhinitis; otitis media; sinusitis.

Mapra, India.
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Matiz *Gentech, India.*
Mirtazapine (p. 436·1).
Depression.

Matlin *BMW, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Matmille *Ritsert, Ger.†*
Oral liquid: Chamomile (p. 2474·1).
Gastrointestinal disorders.

Matmille N *Ritsert, Ger.†*
Chamomile (p. 2474·1); chamomile oil (p. 2474·1).
Skin and mucous membrane disorders; gingivitis.

Mato *Hevert, Ger.*
Aconitum (p. 2428·3); ammon. bromat. (p. 2461·1); belladonna (p. 2453·3); bryonia (p. 2461·3); china (p. 2478·3); echinacea (p. 2498·1); mercurius cyanat. (p. 2555·3); rhus tox. (p. 2603·3).
Homoeopathic preparation.

Matofin *Sanovel, Turk.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Matoflam *Soho, Indon.*
Astaxanthin (p. 2170·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); selenium (p. 2086·3); zinc (p. 2126·1).
Eye disorders.

Matolac *Mahakam Beta, Indon.*
Ketorolac trometamol (p. 80·2).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Matovit *Soho, Indon.*
Betacarotene (p. 2051·1); myrtillus (p. 2566·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Eye disorders.

Matovit AX *Soho, Indon.*
Astaxanthin (p. 2170·1); myrtillus (p. 2566·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3); selenium (p. 2086·3); zinc (p. 2126·1).
Eye disorders.

Matovit Fifty *Soho, Indon.*
Myrtillus (p. 2566·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamin E (p. 2119·1).
Eye disorders.

Mátový *Megafyt-R, Cz.*
Peppermint leaf (p. 1877·1).
Digestive-system disorders.

Matradol *Charoon Bhesaj, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Matrex *Pfizer, UK.*
Methotrexate (p. 822·2).

Matrifen *Nycomed, Austria; Nycomed, Belg.; Nycomed, Cz.; Nycomed, Denm.; Leiras, Fin; Nycomed, Fr.; Nycomed, Ger.; Nycomed, Gr.; Nycomed, Hung.; Nycomed, Irl.; Nycomed, Ital.; Nycomed, Norw.†; Nycomed, Pol.; Nycomed, Spain; Nycomed, Swed.; Takeda, Switz.; Nycomed, UK; Nycomed, Ukr.†*
⊗Fentanyl (p. 60·1).
Pain.

Matrix
Note: this name may be used for preparations of different composition.
Macleods, India.
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

TRB, Arg.
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; fever; pain.

Wyeth Lederle, Ital.†
A heparinoid (p. 1401·1).
Osteoarthritis.

Matrix Grip *TRB, Arg.†*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Cold and influenza symptoms; allergic rhinitis and sinusitis; upper respiratory-tract congestion.

Matrix Grip Antigripal *TRB, Arg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); butetamate citrate (p. 1658·1).
Cold and influenza symptoms.

Matrix Migra *TRB, Arg.*
Caffeine (p. 1203·3); aspirin (p. 22·2); paracetamol (p. 115·1).
Cold symptoms; migraine.

Matrix-MN *Macleods, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Matro *Vannier, Arg.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; high-altitude disorders.

Matrovir *Konimex, Indon.†*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin.

Matsunaflam *Nufarindo, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Matulane *Sigma-Tau, Canad.; Sigma-Tau, USA.*
Procarbazine hydrochloride (p. 850·1).
Malignant neoplasms.

Maturity Test *Blausiegel, Braz.*
Test for the menopause.

Matzim *Watson, USA.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Maux de Gorge et de la Toux *Confab, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Mavena Anal-Gen *Mavena, Switz.*
Hamamelis (p. 2523·3).
Anorectal disorders.

Mavena Proctal-Gen *Mavena, Switz.†*
Hamamelis (p. 2523·3); diethylamine salicylate (p. 51·3).
Anorectal disorders.

Maver *Evershine, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Maveral *Bayer, Ital.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Maverex *Veropharm, Rus.*
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small-cell lung cancer.

Mavicam *Mavi, Mex.*
Meloxicam (p. 86·3).
Inflammation; pain.

Mavid *Abbott, Ger.†*
Clarithromycin (p. 266·2).
Mycobacterial infections.

Mavidol *Mavi, Mex.*
Ketorolac (p. 80·2).
Inflammation; pain.

Mavigen Sebo *Mavi, Ital.*
Cystine (p. 2059·1).
Seborrhoea.

Maviglin *Mavi, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Mavik *Abbott, Canad.; Abbott, S.Afr.; Abbott, USA.*
Trandolapril (p. 1517·2).
Hypertension; myocardial infarction; heart failure following myocardial infarction.

Mavilan *Mavi, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Mavilex *CCM, Malaysia.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Mavisid *Mavi, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Mavitalon *Help, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Mavitina *Mavi, Mex.*
Pravastatin (p. 1473·1).
Hyperlipidaemias.

Mavixan *Pharmathen, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Max
Note: this name may be used for preparations of different composition.
Pidek, India.
Amoxicillin (p. 216·2).
Bacterial infections.

Unison, Hong Kong; Unison, Singapore; Unison, Thai.†
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Valmor, Venez.
Ibuprofen (p. 68·2).
Fever; pain.

Max Pluse *BMW, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Max Repel *Eczane, Arg.*
Cream: Citronella (p. 2481·1); rue (p. 2608·2).
Insect repellent.

Eczane, Arg.
Topical spray: Citronella (p. 2481·1); bergamot; rue (p. 2608·2).
Insect repellent.

Maxaderm *Cipla-Medpro, S.Afr.*
⊗Isoconazole nitrate (p. 583·2); diflucortolone valerate (p. 1634·1).
Infected skin disorders.

Maxair *Meda, Fr.†; Medicis, USA.*
⊗Pirbuterol acetate (p. 1218·3).
Obstructive airways disease.

Maxaljin *Abdi, Turk.*
Flurbiprofen (p. 65·2).
Pain; inflammation.

Maxalt *MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Ital.; MSD, Mex.†; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Pol.; MSD, Port.; MSD, S.Afr.; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Maxaltlyo *MSD-Chibret, Fr.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Maxamaid MSUD *Nutricia, Fr.*
Food for special diets.
Leucinosis.

Maxamaid XLEU *Nutricia, Fr.*
Food for special diets.
Isovaleric acidaemia.

Maxamaid XLYS, Low Try *Nutricia, Fr.*
Food for special diets.
Glutaric aciduria.

Maxamaid XMET, Cys *Nutricia, Fr.*
Food for special diets.
Sulfite oxidase deficiency.

Maxamaid XP *Nutricia, NZ.*
Food for special diets.
Phenylketonuria.

Maxamin Forte *Oxford Laboratories, Rus.*
Vitamins; minerals.
Dietary supplement; tonic.

Maxamox *Sandoz, Austral.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Maxamp *Max, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Maxamum MSUD *Nutricia, Fr.; Nutricia, NZ.*
Food for special diets.
Maple syrup urine disease.

Maxamum XLYS, Low Try *Nutricia, Fr.*
Food for special diets.
Glutaric aciduria.

Maxamum XP *Nutricia, NZ.*
Food for special diets.
Phenylketonuria.

Maxapran *Biosintetica, Braz.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Maxaquin *Pfizer, Braz.; Pfizer, Hong Kong; Valeant, Ital.; Pfizer, Mex.; Pfizer, Port.; Pharmacare, S.Afr.†; Pfizer, Switz.†; Searle, USA†; Pfizer, Venez.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Maxartan *SJA, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Maxazi *United Biotech, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Maxbon *Gynea, Spain.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Maxcef *Merck Serono, Arg.; BMS, Braz.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Maxcep *Danlex, Philipp.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Maxcil *Triomed, S.Afr.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Maxclav *Sigman, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Maxdosa *Dosa, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Maxdrin *Hertz, Braz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).

Maxef *Salus, Mex.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Maxeftin *ACME, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Maxellax *Chanelle, Cz.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Maxen *Baliarda, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Maxen D *Baliarda, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Maxepa *Cana, Gr.; Merck, India; Seven Seas, Irl.†; Merck, Venez.*
Omega-3 fatty acids (p. 1460·1).
Hyperlipidaemias; hypertriglyceridaemia; dietary supplement.

Catalent, Austral.; Plantes et Medecines, Fr.†; Novartis Consumer, Ital.; Seven Seas, UK; Solgar, USA.
Fish oil (p. 1460·3).
Hyperlipidaemias; eczema; dietary supplement; lipid disorders; hypertriglyceridaemia.

Maxepa Evening Primrose Oil *Vitaplex, Austral.*
Marine fish oil (p. 1460·3); evening primrose oil (p. 2502·2).
Dietary supplement.

Maxeron *Wallace, India.*
Metoclopramide hydrochloride (p. 1862·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; postoperative gastric hypotonia; nausea and vomiting.

Maxflin *Labesfal, Port.†*
Fluconazole (p. 578·2).
Fungal infections.

MaxFlu *Pliva Krakow, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Maxfluor *Labesfal, Port.*
Sodium fluoride (p. 2089·2).

Maxgalin *Sun, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; epilepsy; fibromyalgia; anxiety.

Maxgalin-M *Sun, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Maxi *Sel-J, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; gout; musculoskeletal and joint disorders.

Maxi B50 Plus *Pro-Shop, Canad.†*
Vitamin B substances (p. 2102·3).

Maxibar *E-Z-EM, Irl.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Maxibat *Bilim, Ukr.†*
Cefixime (p. 240·3).
Bacterial infections.

Maxibell *Latinofarma, Braz.*
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.

Maxibiloba *Biofarma, Mex.*
Ginkgo biloba (p. 2512·3); vitamin B substances (p. 2102·3); minerals.
Mental function impairment; vitamin and mineral supplement.

Maxibiotic *Emo-Farm, Pol.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Wounds; burns; skin ulcers.

Maxibol *Sanofi-Aventis, Mex.; Sanofi-Aventis, Venez.*
Cobamamide (p. 2107·2).
Tonic.

Maxibone *Trima, Israel.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Maxibral *Demo, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Maxicain *Zee, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Maxical
Note: this name may be used for preparations of different composition.
Leti, Venez.
Calcium pidolate (p. 1784·3).

Mankind, India.
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Maxicalc *Ache, Braz.*
Calcium carbonate (p. 1824·3).

Maxicalc-D *Ache, Braz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Maxicam *Hexpharm, Indon.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Maxicardil *Northia, Arg.*
Dipyridamole (p. 1362·2).

Maxicef *Aristo, India.*
Cefepime (p. 239·2).
Bacterial infections.

Pharos, Indon.
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Maxicef-O *Aristo, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Maxichlor PEH DM *MCR, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Maxicin *Yuri, Ukr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Maxiclar *Kocak, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Maxicold *Farmstandart, Rus.; Pro-Pharma, Ukr.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract disorders.

Maxicool *Maxima Medical, Israel.*
Nitrous oxide (p. 1908·1).
General anaesthesia; pain.

Maxicort *Oftalmi, Venez.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Maxicrom *Alcon, Braz.; Alcon, Mex.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Maxid *SoSe, Ital.†*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Maxidauno *Varifarma, Arg.*
Daunorubicin (p. 778·3).
Malignant neoplasms.

Maxidex *Alcon, Austral.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Denm.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Philipp.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.; Nobel, Turk.; Alcon, UK; Alcon, Ukr.; Alcon, USA.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders; inflammatory external ear disorders.

Maxidol *Bayer Consumer, Canad.*
Naproxen sodium (p. 98·2).
Pain.

Maxidone *Watson, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Maxidrat *Talcris, Arg.*
A range of moisturisers.

Maxidrate *Libbs, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Maxidrin *Hertz, Braz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Maxidrol *Alcon, Fr.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Maxifed *MCR, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Maxifed DM *MCR, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Maxifed DMX *MCR, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; respiratory-tract congestion.

Maxifed G *MCR, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; nasal congestion.

Maxifem *Sandoz, Switz.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Maxifen *Janssen-Cilag, Braz.; Unipharm, Mex.*
Ibuprofen (p. 68·2).
Inflammation.

Maxiferon *Cipla, India.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2).

Maxiflam *Karnataka, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Maxiflam-SP *Karnataka, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Maxiflor
Note: this name may be used for preparations of different composition.
Allergan, USA.
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Maxi-Flore
Note: this name may be used for preparations of different composition.
Synergia, Fr.
Fructo-oligosaccharides (p. 2508·1); inulin (p. 2534·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium breve* (p. 2596·3).
Restoration of intestinal flora.

Maxiflox *Latinofarma, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Maxiflox D *Latinofarma, Braz.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Maxiflu DM *MCR, USA.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Maxifol *Pharma Nutria, Philipp.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Maxigan
Note: this name may be used for preparations of different composition.
Medical Pharmaquality, Gr.
Clarithromycin (p. 266·2).
Bacterial infections.

Unichem, Rus.
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Pain; fever; smooth muscle spasm.

Maxigard *ICI, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Cardiovascular risk reduction.

Maxigesic *AFT, NZ.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Pain; fever.

Shreya, India.
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Maxigesic-MR *Shreya, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders with pain and spasm.

Maxigra *Polpharma, Pol.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Maxihot *Abdi, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Maxijul *Nutricia, Fr.*
Food for special diets.

SHS, UK.
Gluten- and lactose-free preparations for enteral nutrition.

Scientific Hospital Supplies, Irl.†
Sucrose-, galactose-, lactose-, fructose-, and gluten-free food for special diets.

Scientific Hospital Supplies, Austral.†
Maltodextrin (p. 2080·3).
Carbohydrate food supplement.

Maxi-Kalz *Meda, Austria.*
Calcium monocitrate (p. 1783·2); calcium dicitrate (p. 1783·2).
Calcium supplementation.

Meda, Cz.
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis; osteomalacia; renal osteodystrophy; tetany.

Maxi-Kalz Vit D3 *Meda, Austria.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Maxilac *Ingens, Arg.†*
Povidone (p. 2204·3); sodium hyaluronate (p. 2526·2).
Dry eyes.

Maxilan *Landson, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Maxilase
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.
Alpha-amylase (p. 2442·1).
Upper respiratory-tract congestion; oedema.

Tablets, India.
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Maxilene
Note: this name may be used for preparations of different composition.
Andromaco, Mex.
Glycerol oxyester; monomethylsilanetriol potassium citrate (p. 2088·3).
Alopecia.

RGR, Canad.
Lidocaine (p. 1988·1).
Local anaesthesia.

Maxilerg *Latinofarma, Braz.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Maxilief *Clonmel, Irl.*
Caffeine (p. 1203·3); codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain; cold and influenza symptoms.

Maxilin *Anpharm (Ανφαρμ), Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Maxiliv *Ache, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Maxilube *Mission Pharmacal, USA.*
⊗Dimethicone (p. 2209·3); glycerol (p. 2517·2); carbomer 934 (p. 2173·3); trolamine (p. 2634·3); sodium laurilsulfate (p. 2210·3).
Vaginal lubricant.

Maxiluz *Valeant, Arg.*
Soap substitute.

Maxim
Note: this name may be used for preparations of different composition.
Jenapharm, Ger.
Ethinylestradiol (p. 2275·3); dienogest (p. 2267·2).
Combined oral contraceptive.

Meridian, India.
Cefuroxime (p. 255·2).
Bacterial infections.

Maxima *Bago, Arg.*
Yellow tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); red tablets, inert.
Combined oral contraceptive.

Maxima MD 24 *Bago, Arg.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Maximer *Mersifarma, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Maximicetin *Cosmopharm, Gr.*
Rifampicin (p. 350·3).
Tuberculosis; meningococcal meningitis prophylaxis; leprosy.

Maximin *Anglo-French Drugs, India.*
Vitamins; with or without minerals.

Maximiton *Varifarma, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Maximizin *Medley, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Maximo *Savant, Arg.†*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Maximum Blue Label *Vitaline, USA.*
Vitamins; minerals.

Maximum D3 *Propharma, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Maximum Green Label *Vitaline, USA.*
Vitamins; minerals.

Maximum Once A Day *Quest, Canad.†*
Vitamins; minerals.

Maximum Red Label *Vitaline, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Maximum Relief Ex-Lax *Novartis Consumer, USA.*
Senna (p. 1885·1).
Constipation.

Maximum Strength Acid Reducer *Pharmascience, Canad.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity.

Maximum Strength Allergy Drops *Bausch & Lomb, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); hypromellose (p. 2189·2).
Minor eye irritation.

Maximum Strength Anbesol *Wyeth Consumer, USA.*
⊗Benzocaine (p. 1980·2); alcohol (p. 1733·1).
Local anaesthesia.

Maximum Strength Aqua-Ban *Thompson, USA.*
Pamabrom (p. 1464·1).
Premenstrual water retention.

Maximum Strength D *21st Century, USA.*
Colecalciferol (p. 2113·1); calcium (p. 1783·1).
Vitamin D supplement.

Maximum Strength Dristan Cold *Whitehall, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Nasal congestion; cold symptoms.

Maximum Strength Flexall 454 *Chattem, USA.*
Menthol (p. 2553·2); aloe vera (p. 1693·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); thyme oil (p. 2630·3).
Pain; musculoskeletal disorders.

Maximum Strength Mucinex D *Reckitt Benckiser, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Maximum Strength Ornex *Menley & James, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Maximum Strength Sine-Aid *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Maximum Strength Sleepinal *Thompson, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Maximum Strength Sudogest Sinus *Major, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Maximum Strength Unisom SleepGels *Pfizer Consumer, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Maximus *Drogsan, Turk.*
Flurbiprofen (p. 65·2).

Maxinac *Symbiosis, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Maxinate *Biomax, India.*
Artesunate (p. 648·2).
Malaria.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Maxinem
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.
VHB, India.
Meropenem (p. 321·3).
Bacterial infections.

Maxinject *Verisfield, Gr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Maxinom *Uniao Quimica, Braz.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Maxinorm *Pharma Synth, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; gastro-oesophageal reflux; premedication.

Maxinort *Norton, Ukr.*
Cefepime (p. 239·2).
Bacterial infections.

Maxiostenil *TRB, Arg.*
Sodium hyaluronate (p. 2526·2).
Joint disorders; synovial fluid replacement.

Maxiparine *Chandra Bhagat, India.*
Enoxaparin sodium (p. 1372·3).
Unstable angina; myocardial infarction; thromboembolic disorders.

Maxiphen DM *MCR, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Maxiphen-G DM *AMBI, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Coughs.

Maxipime *BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Canad.; Merck, Chile; BMS, China; BMS, Cz.; BMS, Fin.†; BMS, Ger.; Vianex (Βιαγεξ), Gr.; BMS, Hong Kong; BMS, Hung.; BMS, India; BMS, Indon.†; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.†; BMS, Thai.; Nobel, Turk.; Hospira, USA; BMS, Venez.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Maxipiro *Gache, Venez.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; inflammation; pain.

Maxipod *Invision, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Maxipro *Scientific Hospital Supplies, UK.*
Food for special diets.
Hypoproteinaemia.

Maxirap *Sensomed, Philipp.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders; external ear disorders with infection.

Maxirex *Interbat, Indon.*
⊗Tribulus terrestris (p. 2633·3); arginine hydrochloride (p. 2049·1); muira-puama; damiana (p. 2491·3); ginseng (p. 2513·3); yohimbe; zinc (p. 2126·1); vitamin E (p. 2119·1); saw palmetto (p. 2363·3).
Tonic.

Maxirgot *Zekides, Gr.*
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Maxirich *Cipla, India.*
Vitamins; minerals.

Maxisalic *Investi, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Maxislim *Sandoz, Indon.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Maxisorb *Nutricia, Irl.*
Dietary protein supplement.
Scientific Hospital Supplies, UK.
Preparation for enteral nutrition.

Maxisteril *Germo, Ital.†*
Benzalkonium chloride (p. 1737·1).
Skin and instrument disinfection.

Maxitax *Tablets, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Maxitopir *Actavis, Rus.*
Topiramate (p. 550·3).
Epilepsy.

Maxitram *Chiesi, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Maxitratobes *Columbia, Arg.†*
⊗Mazindol (p. 2324·1); dipotassium clorazepate (p. 1056·3).
Obesity.

Maxitrin
Note: this name may be used for preparations of different composition.
Chinta, Thai.
Co-trimoxazole (p. 277·3).
Bacterial infections.
Dipa, Indon.†
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); fish oil (p. 1460·3); dimethyl sulfone (p. 2493·3); vitamin E (p. 2119·1); soya oil (p. 2092·3).
Maintenance of healthy joint function.

Maxitrol *Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile†; Alcon, Cz.; Alcon, Fin.; Alcon, Hong Kong; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.†; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.; Alcon, Thai.; Alcon, UK; Alcon, Ukr.; Alcon, USA; Alcon, Venez.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected inflammatory eye disorders.

Maxi-Tuss HCG *MCR, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Maxi-Tuss HCX *MCR, USA.†*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Coughs.

Maxius *Jaba Recordati, Port.*
Tibezonium iodide (p. 2631·2).
Mouth and throat disorders.

Maxivalet *Demo, Gr.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Maxivanil *Max Farma, Ital.*
Vancomycin hydrochloride (p. 384·2).
Antibiotic-associated colitis.

Maxivate *Westwood-Squibb, USA.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Maxivent
Note: this name may be used for preparations of different composition.
Ajanta, Philipp.
Doxofylline (p. 1208·1).
Obstructive airways disease.

Maxivision *Medical Ophthalmics, USA.*
Vitamins; minerals; nutrient supplements.

Maxivit
Note: this name may be used for preparations of different composition.
Gelcaps, Mex.
Vitamins; minerals; royal jelly (p. 2608·1).
Teguhsindo, Indon.
Betacarotene (p. 2051·1); brewer's yeast (p. 2125·2); lecithin (p. 2542·2); selenium (p. 2086·3); zinc (p. 2126·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Antioxidant; dietary supplement.

Maxivit Plus *Maneesh, India.*
Preparation for enteral nutrition.

Maxi-Vite *Goldline, USA.*
Vitamins; minerals; amino acids.

Maxmarvil *Yuyu, Thai.*
Alendronate sodium (p. 1171·3); calcitriol (p. 2113·1).
Osteoporosis.

Max-Moist *Alna, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Maxmor *Mahakam Beta, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Maxmox *Max, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Maxo-FE *Maxo, India.*
Capsules: Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).
Maxo, India.
Syrup: Copper sulfate (p. 2057·2); cyanocobalamin (p. 2107·2); ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); manganese sulfate (p. 2081·2).

Maxofen *Abbott, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Maxoflam
Note: this name may be used for preparations of different composition.
Liferpal, Mex.
Meloxicam (p. 86·3).
Fever; inflammation; pain.
Maxo, India.
Tablets: ⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).
Maxo, India.
Topical gel: Linolenic acid (p. 1460·2); diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Maxoflam-A *Maxo, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Maxoflam-D *Maxo, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Maxoflam-MR *Maxo, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Maxoflam-T *Maxo, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Maxogest *Corona, India.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Maxolic *Elnova, India.*
Docosahexaenoic acid (p. 1460·1); folic acid (p. 2063·1).

Maxolon *Valeant, Austral.; Valeant, Hong Kong†; Amdipharm, Irl.; ICN, Malaysia†; Pharmaco, S.Afr.; Amdipharm, UK.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal investigations; migraine; hiccup.
Valeant, NZ.
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Aid in gastrointestinal investigations; gastrointestinal motility disorders; nausea and vomiting.

Maxomat *Sanofi-Aventis, Fr.†*
⊗Somatropin (p. 1919·3).
Growth-hormone deficiency; Turner' syndrome.

Maxonim-P *Maxo, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Maxopem *Scoshia, India.*
Meropenem (p. 321·3).
Bacterial infections.

Maxopen *Samarth, India.*
Meropenem (p. 321·3).
Bacterial infections.

Maxoptic *Vendiz, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Inflammatory eye infections.

Maxor *Alphapharm, Austral.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Maxoral *Armstrong, Mex.†*
Tibezonium iodide (p. 2631·2).
Mouth and throat disorders.

Maxotin *Unison, Thai.†*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Maxovite *Tyson, USA.*
Vitamins; minerals.
Premenstrual syndrome.

Maxoza *Sun, India.*
Acetylcarnitine hydrochloride (p. 2053·2); citric acid (p. 2480·3); ubidecarenone (p. 2637·1); folic acid (p. 2063·1); fructose (p. 2068·2); levocarnitine (p. 2053·2); selenium (p. 2086·3); zinc (p. 2126·1); vitamin B_{12} (p. 2107·2).

Max-Pax *Biolab Sanus, Braz.*
Lorazepam (p. 1080·3).
Alcohol withdrawal syndrome; anxiety; insomnia; premedication.

Maxpil *Vinas, Spain.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Maxpro
Note: this name may be used for preparations of different composition.
Meprofarm, Indon.
Cefixime (p. 240·3).
Bacterial infections.
Themis Medicare, India.
Preparation for enteral nutrition.

Maxrel *Dey's, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Maxsoten *Meda, Belg.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Maxsulid *Farmasa, Braz.*
Nimesulide betadex (p. 101·3).
Musculoskeletal and joint disorders.

Maxtan *Simex, Indon.*
Mefenamic acid (p. 85·3).
Pain; fever; menorrhagia.

Maxtenk *Biotenk, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Maxtest *Neo Quimica, Braz.*
Pregnancy test (p. 2596·1).

Maxthio *Deva, Turk.*
Thiocolchicoside (p. 2026·2).

Maxtib *Sun, India.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Maxtol *Bausch & Lomb, Arg.*
Piroxicam (p. 125·3).
Inflammatory eye disorders.

Maxtra *Zuventus, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine (p. 1672·2) or phenylephrine hydrochloride (p. 1672·3).

Maxtra-P *Zuventus, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Maxtrex *Pharmacia, UK.*
Tablets: Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Maxtrim *BMS, Mex.; SSP, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Maxtum *Medial, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Maxudin *Menarini, Gr.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Maxulid *Verheilen, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections.

Maxulide *Max, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Maxum Multi-vite *Seroyal, Canad.†*
Vitamins; minerals.

Maxus *Bausch & Lomb, Arg.*
Chondroitin sulfate (p. 2476·1); aprotinin (p. 1133·2); sodium hyaluronate (p. 2526·2).
Dry eyes.
Bausch & Lomb, Mex.
Chondroitin sulfate (p. 2476·1).
Dry eyes.

Maxxi D3 *Myralis, Braz.*
Colecalciferol (p. 2113·1).

Maxycef *Abolmed, Rus.*
Cefepime (p. 239·2).
Bacterial infections.

Maxydol *Ascent, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain.

Maxzide *Mylan, USA.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Maybe Baby *WIN, UK.*
Fertility test (p. 2596·1).

Maycardin K *Mayrhofer, Austria.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency; digitalis poisoning.

Maydol *BMS, Venez.*
Ibuprofen (p. 68·2).
Pain.

Mayesta *Bama, Spain.*
Isotretinoin (p. 1706·2).
Acne.

Mayfex *Yeni, Turk.*
Fexofenadine hydrochloride (p. 629·1).

Maygace *BMS, Spain.*
Megestrol acetate (p. 2289·2).
Anorexia and cachexia in AIDS and cancer.

Maylox *Piramal, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Peptic ulcer; gastrointestinal hyperacidity; gastro-oesophageal reflux; flatulence; dyspepsia.

Maynar *Novag, Spain.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Mayoprina *Mayo, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Mayozest *Aristo, India.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; heart failure.

Mayul *Q Pharma, Spain.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Maz *East West, India.*
Mirtazapine (p. 436·1).
Depression.

Maze *Aarpik, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Mazepine *Valeant, Canad.; Marbiopharm, Rus.*
Carbamazepine (p. 512·2).
Epilepsy; neuropathic pain; neuralgias; alcohol withdrawal syndrome; psychoses; diabetes insipidus; polyuria; polydipsia; trigeminal neuralgia.

Mazetol *Piramal, India; Idaman, Singapore.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia.

Mazil *KRKA, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Mazitrom *Uniao Quimica, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Mazo *H & Care, India.*
Etamsylate (p. 1145·2).
Periventricular haemorrhage in neonates.

Mazon Medicated Cream *Advantage, Canad.*
Coal tar (p. 1723·2); resorcinol (p. 1718·3); salicylic acid (p. 1719·1).
Skin disorders.

Mazon Medicated Shampoo *Advantage, Canad.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Scalp disorders.

Mazon Medicated Soap *Advantage, Canad.*
Coal tar (p. 1723·2).
Skin disorders.

Mazoral *Cosme, India.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Mazzol *St Carlos, Philipp.*
⊗Mazindol (p. 2324·1).
Obesity.

M&B *Piramal, India.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

MB-12 *Mapra, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

MB Sole *Health Biotech, India.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

MBE *Hasco-Lek, Pol.*
Magnesium oxide (p. 1857·3); pyridoxine hydrochloride (p. 2105·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Dietary supplement; atherosclerosis; ischaemic heart disease.

M-beta *Betapharm, Ger.*
⊗Morphine sulfate (p. 92·3).
Pain.

MBKacin *Abbott, India.*
Amikacin (p. 214·1).
Bacterial infections.

MC 506 *Medevale, Cz.†*
Aminolevulinic acid (p. 740·1).

M C Modulo Calorico *Braun, Arg.*
Maltodextrin (p. 2080·3).
Nutritional supplement.

M-Cal
Note: this name may be used for preparations of different composition.
McNeil & Argus, India.
Oral suspension: Calcium (p. 1783·1); lysine (p. 2079·3); colecalciferol (p. 2113·1).
Stedman, India.
Tablets: Calcium carbonate (p. 1824·3); magnesium sulfate (p. 1787·3); colecalciferol (p. 2113·1).

MCalm *Globus, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

M-Cam *Unichem, India; Unichem, S.Afr.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis; juvenile idiopathic arthritis; sciatica.

M-Caps *Pal-Pak, USA.*
Methionine (p. 1558·2).
Odour, dermatitis, and ulceration in incontinent adults.

MCB *Biosans, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

MCBit *Cubit, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

MCBM *Indoco, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

MCBM 69 *Indoco, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3) or pyridoxine hydrochloride (p. 2105·3).

MCBM 69 Fe *Indoco, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); vitamin C (p. 2110·3).

M-Cet *Menarini, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

MCF *American Biocare, India.*
Vitamins; minerals.

MCFlox-OZ *McNeil & Argus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

MCF-Max *American Biocare, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).
American Biocare, India.
Injection: Vitamin B substances (p. 2102·3).

M-CIN *Macrophar, Thai.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and soft-tissue disorders.

M-Cinn *Uniphar, India.*
Amikacin (p. 214·1).
Bacterial infections.

M-Cit *Madhav, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

M-Clav *Merion, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

M-Clear *McNeil, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

MCM-Tear *Medico, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

M-Cort *Medico, India.*
⊗Hydrocortisone hydrogen succinate (p. 1640·2).
Corticosteroid.

MCP *Betapharm, Ger.; Ratiopharm, Ger.*
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Hexal, Cz.
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

MCR
Note: this name may be used for preparations of different composition.
Rafa, Israel.
⊗Morphine sulfate (p. 92·3).
Pain.

MCT *SHS, Israel; Nutricia, Ital.; Mead Johnson Nutritionals, USA.*
Medium-chain triglycerides (p. 2082·2).
Adjunct in the management of disorders of fat absorption and transport; malabsorption syndromes; disorders of lymph circulation; fat malabsorption.

Vitaflo, UK.
Preparation for enteral nutrition.
Fat malabsorption.

MCT Duocal *Scientific Hospital Supplies, Austral.†; SHS, Denm.; SHS, UK.*
Medium-chain triglycerides (p. 2082·2).
Fat malabsorption.

MCT Oil *Nutricia, Austral.; Nutricia, Cz.; SHS, Denm.; IFET (ΙΦΕΤ), Gr.; Nutricia, NZ; Mead Johnson, Port.; Nutricia, Port.; Mead Johnson Nutritionals, UK; SHS, UK.*
Medium-chain triglycerides (p. 2082·2).
Malabsorption syndromes; ketogenic diets; type I hyperlipoproteinaemia; nutritional supplement; disorders of fat absorption and digestion.

MCT Oljy *Nutricia, Fin.*
Medium-chain triglycerides (p. 2082·2).
Fat malabsorption.

MCT Pepdite *Nutricia, Austral.*
Preparation for enteral nutrition.
Fat malabsorption; short-bowel syndrome; bowel fistulae.

Scientific Hospital Supplies, Irl.†; Scientific Hospital Supplies, UK.
Infant feed.
Protein intolerance; disorders of fat absorption; bowel disorders.

MCXY *Millimed, Thai.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; rhinitis; sinusitis.

M-Cyp *McNeil & Argus, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

M-D *Milano, Thai.*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2).
Urticaria; contact dermatitis.

MD-76 *Mallinckrodt, Arg.; Mallinckrodt, Austral.†; Tyco, Canad.†; Mallinckrodt, USA.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

MD Complejo *Liferpal, Mex.*
Vitamin B substances (p. 2102·3).
Neuritis.

MD Lax *Biofarma, Mex.*
Senna (p. 1885·1); tamarind (p. 1892·2); cassia fistula (p. 1826·2); coriander (p. 2486·3); liquorice (p. 1853·2).
Constipation.

MDace-P *MDC, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

MDace-SP *MDC, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

MDas *Medico, India.*
Tobramycin sulfate (p. 380·2).
Bacterial eye infections.

MD-Cal *Combiphar, Indon.*
Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); vitamin D (p. 2112·3); zinc (p. 2126·1).
Osteoporosis; nutritional supplement.

MDCef *MDC, India.*
Cefixime (p. 240·3); lactobacillus (p. 2596·3).
Bacterial infections.

MDCef-CV *MDC, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

MDCort *MDC, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

MD-Gastroview *Mallinckrodt, Arg.; Covidien, Austral.; Mallinckrodt, USA.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for gastrointestinal radiography.

M-Divate *2M, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

MD-MF *Vensat, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

M-Dolor *Ethypharm, Austria; Hexal, Philipp.†; Salutas, Philipp.†*
⊗Morphine sulfate (p. 92·3).
Pain.

M-Dothi *Mediez, India.*
Dosulepin.
Depression.

M-Dox *Intra-Labs, India.*
Doxycycline (p. 288·1).
Bacterial infections.

6-MDP, 8-MDP *Rez, Cz.*
Technetium-99m (p. 2228·1) medronate.
Bone scanning.

MDPride *Maneesh, India.*
Protionamide (p. 345·1).
Tuberculosis.

MDR Fitness Tabs *MDR, USA.*
Vitamins; minerals.

MDS Quick *MDS Diagnostics, NZ.†*
Pregnancy test (p. 2596·1).

MDSerine *Maneesh, India.*
Cycloserine (p. 280·2).
Tuberculosis.

MDTher *Maneesh, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

MDThide *Maneesh, India.*
Ethionamide (p. 297·3).
Leprosy; tuberculosis.

Me *Famy, Malaysia.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Me-12 *Systopic, India.*
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Systopic, India.
Tablets: Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Me Plus *Systopic, India.*
Thioctic acid (p. 2629·1); chromium tripicolinate (p. 2056·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); selenium (p. 2086·3).

Mealin *Pharmasant, Thai.*
Mianserin hydrochloride (p. 434·2).
Depression.

Mealis *Pharmacypria, Gr.*
Lisinopril (p. 1420·3).
Hypertension.

Measurin *GSK, Gr.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Meaverin *Actavis, Ger.*
Injection: Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Meba *Polipharm, Thai.*
Mebendazole (p. 158·3).
Worm infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mebal-Plus *Xieon, India.*
Thioctic acid (p. 2629·1); vitamins.

Mebaral *Ovation, USA.†*
Methylphenobarbital (p. 533·1).
Epilepsy; anxiety.

Mebasap-AL *USV, India.*
Alprazolam (p. 1035·2); mebeverine hydrochloride (p. 1858·3).

Mebaspa *USV, India.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Mebaxin *Milano, Thai.*
Methocarbamol (p. 2025·3).
Musculoskeletal pain.

Mebaxol *Richmond, Arg.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; amoebiasis.

Mebazole *Torrent, India.*
Mebendazole (p. 158·3).
Worm infections.

Mebeciclol *Sanofi-Aventis, Mex.*
Mebendazole (p. 158·3); tinidazole (p. 949·2).
Nematode infections; protozoal infections.

Mebecon *Abbott, Irl.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome.

Mebelmin *Jofrain, Mex.†*
Mebendazole (p. 158·3).
Worm infections.

Meben *General Drugs, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Mebenda-P *PP Lab, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Mebendicin *Technobio, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Mebenix *Cimed, Braz.*
Albendazole (p. 149·1).
Worm infections.

Mebensole *Columbia, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Mebental *Royton, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Mebentiasis *Keton, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Mebentral *Berman, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Mebenzole *Christo, Hong Kong.†*
Mebendazole (p. 158·3).
Worm infections.

Mebetin *Sam Chun Dang, Malaysia; Sam Chun Dang, Singapore.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm; irritable bowel syndrome; irritable colon; constipation; diarrhoea; abdominal distension.

Mebex *Cipla, India.*
Mebendazole (p. 158·3).
Worm infections.

Mebex Plus *Cipla, India.*
Mebendazole (p. 158·3); pyrantel embonate (p. 165·3).
Worm infections.

Mebix *Tatkhimfarm, Rus.*
Mebikar.
Anxiety disorders; psychoses.

Mebiz *Sun, India.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

MEBO
Note: this name may be used for preparations of different composition.
Combiphar, Indon.
Skullcap root (p. 2617·1); phellodendron bark; rhizoma coptidis.
Burns.

Mebo
Note: this name may be used for preparations of different composition.
Mebo, Thai.; Julphar, UAE.
Sitosterol (p. 1471·2).
Burns; wounds; ulcers; scalds.

Mebo Scar *Julphar, UAE.*
Cactus (p. 2473·2).
Scars; dry skin.

Mebocaína *Novartis Consumer, Port.*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); oxybuprocaine hydrochloride (p. 1993·2).
Mouth and throat disorders.

Mebocatuss *Novartis Consumer, Port.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Meborilan *Sofex, Port.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Meb-Overoid *Valdecasas, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Mebrin *Psyco Remedies, India.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Mebrin-AZ *Psyco Remedies, India.*
Alprazolam (p. 1035·2); mebeverine hydrochloride (p. 1858·3).

Mebron *Daiichi Sankyo, Jpn.*
Epirizole (p. 54·3).
Pain; inflammation.

Mebronol *Farmamust, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Mebryl *GSK, India.*
Embramine hydrochloride (p. 628·2).
Hypersensitivity reactions.

Mebsin *Synmedic, Ukr.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal pain and spasm.

Mebu *Novartis, Switz.*
Cetrimonium bromide (p. 1742·3); tyrothricin (p. 384·1); lidocaine (p. 1988·1).
Mouth and throat disorders.

Mebucain
Note: this name may be used for preparations of different composition.
Novartis Consumer, Hung.
Lozenges (orange); pastilles; throat spray:
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Novartis Consumer, Hung.
Lozenges (mint): Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Mébucaïne *Novartis Consumer, Switz.*
Cetylpyridinium chloride (p. 1743·1); oxybuprocaine hydrochloride (p. 1993·2); tyrothricin (p. 384·1).
Mouth and throat disorders.

Mebucalets f *Novartis Consumer, Switz.*
Benzoxonium chloride (p. 1739·2); lidocaine (p. 1988·1).
Mouth and throat disorders.

Mebucaliquid *Novartis Consumer, Switz.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Mebuca-Orange *Novartis Consumer, Switz.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Mebucasol f *Novartis Consumer, Switz.†*
Lidocaine hydrochloride (p. 1988·2); muramidase hydrochloride (p. 2565·1); tyrothricin (p. 384·1).
Mouth and throat disorders.

Mebucaspray *Novartis Consumer, Switz.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Mebumal *NordMedica, Denm.*
Pentobarbital sodium (p. 1095·1).
Adjuvant in anaesthesia; sedative.

Mebutan *Meda, Neth.*
Nabumetone (p. 97·1).
Rheumatoid arthritis; osteoarthritis.

Mebutar *Andromaco, Arg.*
Mebendazole (p. 158·3).
Worm infections.

Mebutar Compuesto *Andromaco, Arg.*
Mebendazole (p. 158·3); tinidazole (p. 949·2).

Mebuxina *Raam, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Mebzol *Julphar, UAE.*
Mebendazole (p. 158·3).
Worm infections.

Mecain *Actavis, Ger.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mecalox *Galex, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Mecanyl *Beta, Arg.*
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Mecanyl Duo *Beta, Arg.*
Glucosamine hydrochloride (p. 2515·3) or glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Mecanyl K *Beta, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Joint disorders.

Mecanyl K Duo *Beta, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Mecap-P *Savoy, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mecatin *Haledew, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecatin-MD *Haledew, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mecaton *Norma (Νορμα), Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Mecef-S *Madhav, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Mecholyl *Gordon, USA.*
Methacholine chloride (p. 2557·3).
Iontophoresis.

Mechovit *Streuli, Switz.†*
DL-methionine (p. 1558·2); vitamins.
Liver disorders.

Mecid A *Lewison, Philipp.*
Mefenamic acid (p. 85·3).
Musculoskeletal and joint disorders; pain.

Mecir *Boehringer Ingelheim, Fr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Meclam *Gracia, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting.

Meclifar *Farcoral, Mex.*
Meclozine (p. 634·3); pyridoxine (p. 2105·3).
Nausea and vomiting; vertigo.

Meclin *Apsen, Braz.*
Meclozine hydrochloride (p. 634·3).
Nausea and vomiting; motion sickness; vertigo.

Meclison *Sons, Mex.*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting; vertigo; gastrointestinal disorders.

Meclivin *Biomedica, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Mecloderm *1x2, Ital.*
Meclocycline sulfosalicylate (p. 321·2).
Bacterial skin infections; acne; seborrhoeic dermatitis.

Mecloderm F *1x2, Ital.*
⊗Meclocycline sulfosalicylate (p. 321·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Mecloderm Ovuli *1x2, Ital.*
Meclocycline sulfosalicylate (p. 321·2).
Vulvovaginal and cervical infections.

Mecloma-F *Esma, India.*
⊗Fusidic acid (p. 302·1); mometasone furoate (p. 1644·1).

Mecloma-T *Esma, India.*
⊗Mometasone furoate (p. 1644·1); terbinafine (p. 593·3).

Meclomen *Pfizer, Chile; Galenica, Gr.*
Meclofenamate sodium (p. 85·2).
Rheumatoid arthritis; osteoarthritis; pain; inflammation; fever.

Meclomid *Randall, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal examination.

Meclon *Wassermann, Ital.*
Clotrimazole (p. 576·2); metronidazole (p. 936·1).
Vulvovaginal and cervical infections.

Meclosil *Sunward, Singapore.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); simeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2).
Gastric hyperacidity; heartburn; dyspepsia; flatulence.

Meclosorb *S & K, Ger.*
Meclocycline sulfosalicylate (p. 321·2).
Bacterial skin infections.

Mecmin *Karnataka, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecoba *Abbott, India; Sriprasit, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecoba Alpha *Abbott, India.*
Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Mecoba OD *Abbott, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Mecobal *Rapross, India; TO-Chemicals, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecobal Plus *Rapross, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Rapross, India.
Injection: Vitamin B substances (p. 2102·3).

Mecobal-GB *Uniroyal, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mecobest *Lupin, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecobex *Burgeon, India.*
Vitamin B substances (p. 2102·3).

Mecobil-OD *Vilberry, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecobil-P *Vilberry, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mecobin *Unison, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mecobion *Medley, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecobion-OD *Medley, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3); chromium tripicolinate (p. 2056·1).

Mecobion-P *Medley, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mecoblend *Akesiss, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3); minerals; vitamin E (p. 2119·1).

Mecobyte *Pharma-Tech, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecocad *Cadila, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Mecocas *Casca, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecocas-Ortho *Casca, India.*
Glucosamine sulfate (p. 2515·3); mecobalamin (p. 2108·1); dimethyl sulfone (p. 2493·3); potassium chloride (p. 1793·2); vitamin C (p. 2110·3).

Mecoday Plus *Invision, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1); chromium trichloride (p. 2055·3); selenium dioxide (p. 2087·1).

Mecoday-G *Invision, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mecoday-PG *Invision, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mecoflash *Avinash, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mecofol *Intas, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecofol-A *Meyer, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecola *Lapi, Indon.*
Thioctic acid (p. 2629·1); cyanocobalamin (p. 2107·2).
Diabetic neuropathy; antoxidant.

Mecola Forte *Lapi, Indon.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy; antoxidant.

Mecolife *Life Medicare, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecolife Plus *Life Medicare, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecolin
Note: this name may be used for preparations of different composition.
Gracia, Indon.
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Stadmed, India.
Tricholine citrate (p. 2055·2); sorbitol (p. 2092·1).
Liver disorders; biliary hypotonia; atonic constipation.

Mecomed *Medial, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecompy-Forte *Kaizen, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecona *Hauz, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecona Plus *Hauz, India.*
Mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3).

Meconerv *Micro, India.*
Injection; tablets: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Micro, India.
Syrup: Dexpanthenol (p. 2582·2); lysine hydrochloride (p. 2079·3); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Meconerv Forte *Micro, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); inositol (p. 2533·2); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Meconerv Plus *Micro, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).
Hyperhomocystinaemia; diabetic neuropathy.

Meconeuro *Novell, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Meconeuron *Pulse, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Meconeuron-HR *Pulse, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Meconovit-OD *Acto, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mecophar *Pharmaffiliates, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mecopil *Psychotropics, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Mecoriv *East African, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mecoriv Plus *EastAfrican, India.*
Thioctic acid (p. 2629·1); vitamins; trace elements.

Mecoriv-G *East African, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mecortolon *Jelfa, Pol.*
⊗Prednisolone pivalate (p. 1645·3).
Skin disorders.

Mecortolon N *Jelfa, Pol.*
⊗Prednisolone pivalate (p. 1645·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Mecosa-OD *Elisa, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); minerals.

Mecostop *Bright Future, Hong Kong.†*
Bromhexine (p. 1656·3); brompheniramine (p. 618·1); caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Mecosyn *Abdi, Turk.*
Nateglinide (p. 492·1).

Mecovit *Cipla, India; Crisdy-Na, Philipp.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; vitamin B_{12} deficiency; megaloblastic anaemia.

Mecovon *Zuventus, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Zuventus, India.
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mecox *Ferron, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Mectan *Prafa, Indon.†*
Mefenamic acid (p. 85·3).
Pain.

Mectin
Note: this name may be used for preparations of different composition.
Elea, Arg.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Meridian, India.
Ivermectin (p. 155·1).
Worm infections; scabies.

Mectizan *MSD-Chibret, Fr.†; Merck, USA.*
Ivermectin (p. 155·1).
Veterinary names include: Eqvalan; ivomec; oramec.
Onchocerciasis; lymphatic filariasis.

Mecze *Zee, India; Zee, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; neuropathies.

Mecze-FL *Zee, India.*
Folic acid (p. 2063·1); glutamic acid (p. 2070·2); mecobalamin (p. 2108·1).

Med Glybe *Medican, Canad.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Med Pass *Hormel, Hong Kong.*
Preparation for enteral nutrition.

Medabon *Sun, Neth.*
1 tablet, mifepristone (p. 2138·1); 4 vaginal tablets, misoprostol (p. 2140·3).
Termination of pregnancy.

Medacinase *Medac, Neth.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Medaclox *Sydenham, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Medacter *Angelini, Gr.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Medactin
Note: this name may be used for preparations of different composition.
Medac, Ger.†
Estramustine sodium phosphate (p. 790·1).
Prostatic cancer.

Medafein *Kocak, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Medaflox *Eurolab, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Medaflox Dol *Eurolab, Arg.*
Tablets, ciprofloxacin (p. 261·1); tablets, phenazopyridine (p. 124·3).
Urinary-tract infections.

Medal *Utopian, Thai.*
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Medalac *Medopharm, India.*
Lactobacillus sporogenes (p. 2596·3).

Medalcite *Kocak, Turk.*
Hydrotalcite (p. 1845·2).

Medalexine *IFET (ΙΦΕΤ), Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Medalginan *Medinfar, Port.*
Benzyl nicotinate (p. 29·3); capsicum (p. 2469·3); camphor (p. 2466·2); diethylamine salicylate (p. 51·3).
Musculoskeletal and joint disorders; neuritis.

Medalidon *Ethnic, Gr.*
Caffeine (p. 1203·3); ergotamine tartrate (p. 674·1).

Medalin *Meyer Alian, Venez.*
Famotidine (p. 1842·1).
Peptic ulcer.

Medamet *Caps, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Medamol *IFET (ΙΦΕΤ), Gr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Medan *Samjin, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Med-Angin *Divapharma, Fin.; Sandoz, Turk.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); levomenthol (p. 2553·2).
Sore throat.

Medani *Farmaceutica H, Mex.*
Nimesulide (p. 101·3).
Inflammation; fever.

Medarex *Medipharm, Chile.*
Cyclobenzaprine (p. 2023·1).
Skeletal muscle spasm; tension headache.

Medarum *Obolenskoe, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; vascular eye disorders.

Medaset *Kocak, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Medaspor *Cipla-Medpro, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Medatz *Bajamed, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Medaxime *Specpharm, S.Afr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Medaxol *Beijing Union, China.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Medaxone *Medochemie, Gr.; Medochemie, Rus.; Specpharm, S.Afr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Medaxonum *Medochemie, Hong Kong.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Medazine
Note: this name may be used for preparations of different composition.
Cipla, India.
Cyclizine (p. 623·2).

Cipla-Medpro, S.Afr.
Cyclizine hydrochloride (p. 623·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Medicpharma, Thai.
Medazepam (p. 1083·2).
Anxiety.

Medazol
Note: this name may be used for preparations of different composition.
Greenpharma, Braz.
Mebendazole (p. 158·3).
Worm infections.

Medipharm, Chile; Offenbach, Mex.†
Metronidazole (p. 936·1).
Anaerobic bacterial skin infections; rosacea; amoebiasis.

Medazole
Note: this name may be used for preparations of different composition.
Asian Pharm, Thai.
Mebendazole (p. 158·3).
Worm infections.

Beacons, Singapore; Picco, Thai.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; amoebiasis; giardiasis; protozoal infections.

Med-3B *PP Lab, Thai.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Medblock *Medstyle, Chile.*
SPF 50+: Titanium dioxide (p. 1725·1); alumina (p. 1817·2); zinc oxide (p. 1729·1); octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Medbufen *Medhaus, Philipp.*
Ibuprofen (p. 68·2).
Pain; fever.

Med-C *Millimed, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Medcee *Tolmann, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Medcef *Bergamo, Braz.*
Cefuroxime (p. 255·2).
Bacterial infections.

Med-Chloramp *PP Lab, Thai.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Medcin
Note: this name may be used for preparations of different composition.
Medihealth, India.
Amikacin (p. 214·1).
Bacterial infections.

Millimed, Thai.†
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Medclof *Samjin, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; gout; musculoskeletal and joint disorders.

Medcotrim *Utopian, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Meddy *Medicine Products, Thai.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Hypersensitivity disorders; nasal congestion.

Medebar *Covidien, Austral.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Medebar Plus *Tyco, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Medebiotin *Medea, Spain.*
Biotin (p. 2052·2) or biotin sodium (p. 2052·2).
Biotin deficiency.

MedEctoin *Syxyl, Ger.*
⊗Ectoine; urea (p. 1727·3).
Skin disorders.

Mededoxi *Reig Jofre, Spain.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Medelan *Medhel, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; Zollinger-Ellison syndrome; acid aspiration.

Medelox *Medhel, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Medemycin *Meiji, Hong Kong; Meiji, Jpn.*
Midecamycin (p. 324·3).
Bacterial infections.

Medene *Pharmaland, Thai.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Medenorex *Medea, Spain.†*
Cyproheptadine hydrochloride (p. 624·1); amino acids; vitamins.
Tonic.

Medent-DM *Stewart Jackson, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Medent-PE *Stewart Jackson, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Mede-Prep *Medefield, Austral.†*
⊗Mannitol (p. 1427·3).
Bowel preparation before radiography or surgery.

Mederebro *Nupel, Spain.*
Cyanocobalamin (p. 2107·2); thiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Mederma
Note: this name may be used for preparations of different composition.
Combiphar, Indon.; Merz, Indon.; Merz, Mex.
Cepalin (p. 2575·2); allantoin (p. 1693·1).
Keloid scars; scars.

Aurora, Austral.†; Merz, Israel; Merz, Malaysia; Merz, Singapore; Merz, USA.
Onion (p. 2575·2).
Scars.

Medescan *Medefield, Austral.†; Mallinckrodt, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Medeton *TP, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; endometriosis.

Medex *Sidus, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Medex Rub *Sidus, Arg.*
Adult rub: Sulfogaiacol (p. 1678·1); methyl nicotinate (p. 91·3); camphor (p. 2466·2); menthol (p. 2553·2); pine oil (p. 2591·1); eucalyptus oil (p. 2501·2).
Cold symptoms; catarrh.

Sidus, Arg.
Children's rub: Eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); niaouli oil (p. 2569·1).
Catarrh; cold symptoms.

Medexol *World Medicine, Ukr.†*
⊗Dexamethasone (p. 1630·3).
Inflammatory ear and eye disorders.

Medezol *Medea, Spain.*
Ketoconazole (p. 585·3).
Fungal skin and nail infections.

Medformin *Medopharm, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Medgenol *MedGen, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Medgesic *Medifive, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Pain; musculoskeletal disorders; tension headache.

Medgivit *MedGen, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3).

Medgyl *Medhaus, Philipp.; Taiwan Biotech, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Medhamin *Emar, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Medhamin Forte *Emar, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Medhirud *In Vitro, Hung.*
Leech (p. 1418·1); arnica (p. 2447·2).
Soft-tissue injury; varices.

Medi Creme *Pharmacare, Austral.*
Chlorhexidine acetate (p. 1743·2); cetrimide (p. 1742·1); hexamidine isetionate (p. 1754·3); allantoin (p. 1693·1); lidocaine hydrochloride (p. 1988·2).
Abrasions; cuts; minor burns; skin irritation; insect bites and stings.

Medi Pulv *Pharmacare, Austral.*
Hexamidine isetionate (p. 1754·3); chlorhexidine hydrochloride (p. 1743·3); allantoin (p. 1693·1).
Cuts; minor burns and scalds.

Mediabet *Medice, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Medialgin *IFET [ΙΦΕΤ], Gr.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain.

Medialipide *Braun, Belg.; Braun, Fr.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Medi-Alpha *Mega Lifesciences, Thai.*
Alfacalcidol (p. 2112·3).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; hyperparathyroidism; rickets; osteomalacia.

Mediamer B6 *Darya-Varia, Indon.*
Parathiazine teoclate (p. 637·1); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting; motion sickness.

Mediamik *Pantafarm, Ital.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Medianon *MedGen, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Médiatensyl *Nycomed, Fr.*
Urapidil (p. 1520·2).
Hypertension.

Mediator *Servier, Fr.†; Servier, Port.†*
⊗Benfluorex hydrochloride (p. 1315·3).
Adjunct in diabetes mellitus; hyperlipidaemias.

Mediaven *Will-Pharma, Belg.; Drossapharm, Switz.; Assos, Turk.*
Naftazone (p. 1157·1).
Venous insufficiency; diabetic retinopathy.

Mediaxal *Servier, Hong Kong; Servier, Malaysia†; Servier, Singapore.†*
⊗Benfluorex hydrochloride (p. 1315·3).
Hypertriglyceridaemia; diabetes mellitus; hyperlipidaemias.

Medibiox *Medipharm, Chile.*
Levofloxacin (p. 315·3).
Bacterial infections.

Medibron *Medi-Rx, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Médibronc *Merck Medication Familiale, Fr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Medibuse *Medi Globe, India.*
Disulfiram (p. 2495·3).
Alcoholism.

Medic *DNR, Arg.*
Salicylic acid (p. 1719·1); allantoin (p. 1693·1); coal tar (p. 1723·2).
Skin and scalp disorders.

Medic Cough *Medicpharma, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Medic Nor *Medicpharma, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Medica *Qualiphar, Belg.*
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Throat disorders.

Medica Junior *Qualiphar, Belg.*
Echinacea (p. 2498·1); vitamin C (p. 2110·3); menthol (p. 2553·2).
Sore throat.

Medicaid *LPC, UK.*
Cetrimide (p. 1742·1).
Nappy rash.

Medicaina *Cristalia, Braz.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Medicaine *Huons, Thai.*
Lidocaine hydrochloride (p. 1988·2). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Medicalm *Abtei, Austria.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome; gastrointestinal spasm.

Medicam *MMC, India.*
Piroxicam betadex (p. 126·1).
Musculoskeletal and joint disorders.

Medicament Sinus *Riva, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Medicament Sinus pour La Nuit *Confab, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); doxylamine succinate (p. 627·3).

Medicap *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore.*
Mefenamic acid (p. 85·3).
Pain; musculoskeletal, joint, and soft-tissue disorders.

Medicardin *Farmedia, Gr.*
Levocarnitine (p. 2053·2).

Medicated Acne Gel *Kamins, Canad.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Medicated Blistex DCT Lip Balm *Blistex, Canad.*
Camphor (p. 2466·2); menthol (p. 2553·2); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); phenol (p. 1763·3).
Sunscreen.

Medicated Body Powder *Major, USA.*
Menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation.

Medicated Callus Removers *Aetna Felt, Canad.†*
Salicylic acid (p. 1719·1).
Calluses.

Medicated Corn Removers *Aetna Felt, Canad.†*
Salicylic acid (p. 1719·1).
Corns.

Medicated Extract of Rosemary *Potter's, UK.*
Geranium oil (p. 2512·2); rosemary oil (p. 2607·3); methyl salicylate (p. 92·1); bay oil (p. 2453·1).
Scalp disorders.

Medicated Foot Powder *Aetna Felt, Canad.†*
Menthol (p. 2553·2).

Medicated Ointment *Golden Pride, Canad.†; Rawleigh, Canad.†*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).

Medicatex *Raymos, Arg.*
Menthol (p. 2553·2); sulfur (p. 1721·1).
Scalp disorders.

Medicebran *Medice, Spain.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder.

Mediceft *Medial, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Medicet-L *Mediez, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Medichrol *Medichrom, Gr.*
Dydrogesterone (p. 2270·1).
Menstrual disorders; hormone replacement therapy; progestogen-only oral contraceptive; endometriosis; hirsutism; malignant neoplasms.

Medichrom *Qualiphar, Belg.*
Merbromin (p. 1760·1).
Disinfection of minor wounds.

Medichronal *Darnitsa, Ukr.*
Combination product: Packet 1, glucose (p. 2068·3); low-molecular weight povidone; packet 2, glycine (p. 2071·2); sodium formate (p. 2507·1); low-molecular weight povidone.
Alcoholism.

Medicillin
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ratiopharm, Fin.
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Medicinal Gargle *Weleda, UK.*
Rhatany (p. 2603·3); myrrh (p. 2566·1); clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); geranium oil (p. 2512·2); lavender oil (p. 2541·1); peppermint oil (p. 1877·1); sage oil (p. 2609·1); aesculus (p. 2431·2); argentum nitricum (p. 2615·3); calcium fluoricum (p. 2053·1); magnesium sulfuricum (p. 1787·3).
Homoeopathic preparation.

Medicip *Mediez, India.*
Cefixime (p. 240·3).
Bacterial infections.

Mediclav *Mediez, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Mediclox Plus *Laborate, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3); lactobacillus (p. 2596·3).
Bacterial infections.

Medicol *United Laboratories, Philipp.*
Ibuprofen (p. 68·2).
Fever; pain.

Medicold *Kocak, Turk.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Medicomtrin *Medikon, Indon.†*
Pyrantel embonate (p. 165·3).
Worm infections.

Medicon *Shionogi, Jpn.*
Dextromethorphan hydrobromide (p. 1660·1); potassium cresolsulfonate.
Cough; respiratory-tract congestion.

Medicone *Dickinson, USA.†*
Ointment: Benzocaine (p. 1980·2).
Anorectal disorders.

Medicoran *Northia, Arg.*
Valsartan (p. 1521·2).
Hypertension.

Medicort
Note: this name may be used for preparations of different composition.
Surya Dermato, Indon.
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Trumac, India.
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Medicplex *Medicpharma, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Medicreme
Note: this name may be used for preparations of different composition.
Bajer, Arg.
Vitamin A palmitate (p. 2098·3); collagen (p. 2483·2).
Skin disorders.

Shreya, India.
Methyl nicotinate (p. 91·3); mephenesin (p. 2025·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Pharmabroker, NZ.†
Chlorhexidine acetate (p. 1743·2); cetrimide (p. 1742·1); hexamidine isetionate (p. 1754·3); lidocaine (p. 1988·1).
Bites; burns; insect stings; wounds.

Pharmacare, Hong Kong.†
Chlorhexidine acetate (p. 1743·2); cetrimide (p. 1742·1); hexamidine isetionate (p. 1754·3); lidocaine hydrochloride (p. 1988·2).
Burns; cuts and abrasions; skin irritation; insect bites and stings.

Medicreme-Strong *Shreya, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Medic-S *DNR, Arg.*
Collagen (p. 2483·2).
Hair disorders.

Medic-V *Medicpharma, Thai.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Medicvit *Medicpharma, Thai.*
Vitamins.

Medi-Dan *Mahdeen, Canad.*
Coal tar (p. 1723·2); benzalkonium chloride (p. 1737·1); salicylic acid (p. 1719·1).
Dandruff; seborrhoeic dermatitis.

Medident *Mediline, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disinfection.

Medi-Derm
Note: this name may be used for preparations of different composition.
Two Hip, USA.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); capsaicin (p. 35·1).

Mediderm
Note: this name may be used for preparations of different composition.
K2 Health & Wellness, Chile.†
Ivermectin (p. 155·1).

Medidine *Hands, India.*
Povidone-iodine (p. 1767·1).

Medidos *Medipharm, Chile.*
Miconazole (p. 588·3); tinidazole (p. 949·2).
Vulvovaginal anaerobic and fungal infections; trichomoniasis.

Medifam *Medichem, Philipp.*
Rifampicin (p. 350·3).
Tuberculosis.

Medifed
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Medpro, S.Afr.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Medifen
Note: this name may be used for preparations of different composition.
Grisi, Mex.
Ibuprofen (p. 68·2).
Inflammation; pain.

Medifer
Note: this name may be used for preparations of different composition.
Cassara, Arg.
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Sterling, India.
Capsules: Ascorbic acid (p. 2110·3); cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); selenium (p. 2086·3).

Sterling, India.
Syrup: Folic acid (p. 2063·1); iron choline citrate (p. 2060·2); lysine (p. 2079·3); selenium (p. 2086·3).

Medimport, Mex.†
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemia.

Mediferron-Vita *Medi-Rx, Philipp.*
Ferrous sulfate (p. 2062·2); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Iron-deficiency; iron-deficiency anaemia; tonic.

Medi-First Extra Strength Pain Relief *Medique, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); salicylamide (p. 129·2); caffeine (p. 1203·3).
Pain.

Medi-First with Lidocaine *Medique, USA.*
Lidocaine hydrochloride (p. 1988·2); benzalkonium chloride (p. 1737·1).

Medi-First Sinus Decongestant *Textilease, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Mediflex
Note: this name may be used for preparations of different composition.
Crown, S.Afr.
Indometacin (p. 71·2).
Musculoskeletal and joint disorders.

Kalbe, Indon.
Glucosamine sulfate (p. 2515·3).
Musculoskeletal and joint pain.

Medicom, Cz.†
Glucosamine sulfate sodium (p. 2515·3).
Osteoarthritis.

Mediflor
Note: this name may be used for preparations of different composition.
Merck, Indon.†
Comfrey (p. 2484·2).
Soft-tissue disorders.

Merck, Spain.†
St John's wort (p. 449·1).
Tonic; depression.

Médiflor Circulation du Sang No 12 *Merck Medication Familiale, Fr.†*
Red vine (p. 2521·3); melilot (p. 2552·3); hamamelis (p. 2523·3); melissa (p. 2552·3).
Peripheral vascular disorders.

Médiflor Tisane Contre la Constipation Passagère No 7 *Merck Medication Familiale, Fr.*
Senna (p. 1885·1); ash (p. 2450·1); fennel (p. 2503·2); liquorice (p. 1853·2); rosemary (p. 2607·2).
Constipation.

Médiflor Digestive No 3 *Merck Medication Familiale, Fr.*
Peppermint leaf (p. 1877·1); angelica (p. 2443·3); rosemary (p. 2607·2); elecampane (p. 1662·3); fennel (p. 2503·2); coriander (p. 2486·3).
Digestive disorders.

Médiflor Diuretique No 4 *Merck Medication Familiale, Fr.†*
Fennel (p. 2503·2); couch-grass (p. 2487·2); bearberry (p. 2453·2); ash (p. 2450·1); meadowsweet (p. 2550·2).
Diuresis; renal calculi.

Médiflor Douleurs Articulaires no 2 *Merck Medication Familiale, Fr.†*
Birch (p. 2457·3); ash (p. 2450·1); meadowsweet (p. 2550·2); black currant (p. 2458·1).
Joint pain.

Médiflor Hépatique No 5 *Merck Medication Familiale, Fr.*
Boldo (p. 2458·3); kinkeliba (p. 2538·2); rosemary (p. 2607·2); liquorice (p. 1853·2); mallow leaves (p. 2549·2).
Liver disorders; digestive disorders.

Médiflor no 1 *Merck Medication Familiale, Fr.*
Fucus (p. 2612·1); ash (p. 2450·1); maté (p. 2648·2); pilosella.
Slimming aid.

Médiflor Pectorale d'Alsace no 8 *Merck Medication Familiale, Fr.†*
Mallow (p. 2549·2); poppy (p. 1675·3); coltsfoot (p. 1659·2); thyme (p. 2630·2); melissa (p. 2552·3).
Respiratory-tract disorders.

Médiflor Tisane Calmante Troubles du Sommeil No 14 *Merck Medication Familiale, Fr.*
Passion flower (p. 2584·1); bitter orange (p. 2575·3); crataegus (p. 2488·1); melissa (p. 2552·3); tilia (p. 2631·3); valerian (p. 2640·2).
Nervous disorders; insomnia.

Mediflox
Note: this name may be used for preparations of different composition.
Alcon, Ital.
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Medico, India.
Moxifloxacin (p. 326·3).
Bacterial eye infections.

Medifol *Austral, Arg.*
Folic acid (p. 2063·1).
Anaemias; prevention of neural-tube defects.

Medifolin *Medinfar, Port.*
Calcium folinate (p. 2066·3).
Toxicity due to folic acid antagonists; megaloblastic anaemia; folate deficiency.

Medifome *GE Healthcare, Ger.†*
Collagen (porcine) (p. 2483·2).
Haemorrhage.

Medifon *Medinfar, Port.†*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2); dequalinium chloride (p. 1749·3); vitamin C (p. 2110·3); menthol (p. 2553·2).
Mouth and throat disorders.

Medifortan *Medi-Rx, Philipp.*
Vitamins; with or without lysine hydrochloride (p. 2079·3).

Medifortan-AS *Medi-Rx, Philipp.*
Buclizine hydrochloride (p. 618·3); vitamins.
Tonic; reduced appetite.

Medifungol *Fada, Arg.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Medigel
Note: this name may be used for preparations of different composition.
Piam, Ital.
Nutritional supplement.
Vomiting.

Medigem *Ebewe, Gr.*
Gemcitabine hydrochloride (p. 801·2).
Bladder cancer; pancreatic cancer; non-small cell lung cancer; ovarian cancer; breast cancer.

Medigesic *Maver, Chile.*
Clonixin lysine (p. 40·1).
Pain.

US Pharmaceutical, USA.†
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Medigox *Polfa Warszawa, Pol.†*
Metildigoxin (p. 1433·1).
Heart failure; supraventricular arrhythmias.

Medihaler-Iso *3M, USA.†*
⊗Isoprenaline sulfate (p. 1411·3).
Bronchospasm.

Medihoney Antibacterial Wound Gel *Comvita, Austral.; Miles, UK.*
Honey (p. 2072·1).
Burns; ulcers; wounds.

Medijel *Key, Austral.; DDD, Hong Kong; DDD, Irl.; DDD, Israel†; DDD, Malaysia; Wilson, NZ; DDD, Singapore; DDD, UK.*
Lidocaine hydrochloride (p. 1988·2); aminoacridine hydrochloride (p. 1732·3).
Oral lesions; gingivitis; denture irritation; mouth ulcers; sore gums.

Medi-Kain *Pfizer Consumer, S.Afr.*
Cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Sore throat.

Medi-Keel A *Adcock Ingram, S.Afr.*
Throat gargle: Cinchocaine hydrochloride (p. 1983·2); benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1); benzyl alcohol (p. 1739·3).
Mouth and throat disorders.

Adcock Ingram, S.Afr.
Throat spray: Phenol (p. 1763·3).
Mouth and throat infections.

Adcock Ingram, S.Afr.
Lozenges: Cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Sore throat.

Mediker *SIT, Ital.*
Phenothrin (p. 2160·1).
Pediculosis.

Medikinet *Medice, Austria; Medice, Cz.; Medice, Denm.; Medice, Fin.; Medice, Ger.; Medice, Irl.; Mediline, Israel; Medice, Neth.; Medice, Norw.; Medice, Pol.; Medice, Spain; Evolan, Swed.; Salmon, Switz.; Flynn, UK.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Mediklin
Note: this name may be used for preparations of different composition.
Maver, Chile.
Salicylic acid (p. 1719·1).
Acne.

Surya Dermato, Indon.
Clindamycin phosphate (p. 269·3).
Acne.

Medi-Klin TR *Surya Dermato, Indon.*
Clindamycin phosphate (p. 269·3); tretinoin (p. 1725·2).
Acne.

Medikol *Solvay, Norw.†; Solvay, Swed.†*
Activated charcoal (p. 1537·3).
Acute poisoning; diarrhoea.

Medikoncef *Medikon, Indon.†*
Cefaclor (p. 232·3).
Bacterial infections.

Medilac-S *Hanmi, China.*
Enterococcus faecalis (p. 2596·3); *Bacillus subtilis.*
Restoration of gastrointestinal flora.

Medilac-Vita *Hanmi, China.*
Enterococcus faecalis (p. 2596·3); *Bacillus subtilis*; vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium lactate (p. 1784·1); zinc oxide (p. 1729·1).
Gastrointestinal disorders.

Medilar *Bausch & Lomb, Ital.*
Vitamins; minerals; gamolenic acid (p. 2509·2).
Nutritional supplement.

Medilax
Note: this name may be used for preparations of different composition.
Medic, Denm.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Medilaxan *Beta, Arg.*
Ispaghula (p. 1849·1); sennosides (p. 1885·2).
Constipation.

Medilen
Note: this name may be used for preparations of different composition.
IFET (ΙΦΕΤ), Gr.
Amikacin sulfate (p. 214·2).
Bacterial infections.

Pentamedical, Ital.
Emollient.
Dry skin; skin irritation.

Medilexin *IAE, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Medilice *Wings, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Medilium *Medifive, Thai.†*
Flunarizine (p. 629·3).
Migraine; cerebrovascular disorders.

Medilop *Datla, India.*
Dicycloverine hydrochloride (p. 1834·2); loperamide (p. 1854·2); metronidazole (p. 936·1).

Medilyn *Cipla-Medpro, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Medimide *Medison, Israel.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Medimix *AGA, Denm.; AGA, Swed.; PanGas, Switz.†*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Pain; anxiety.

Medimox *Medikon, Indon.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Medimoxil *MedGen, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Medimycetin *MedGen, Philipp.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Medin G *Grisi, Mex.†*
Paracetamol (p. 115·1); chlorphenamine (p. 620·3).
Cold and influenza symptoms.

Medinac *Alde Medi Impex, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Medinait *Vicks, Spain.*
⊗Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); ephedrine sulfate (p. 1663·2); paracetamol (p. 115·1).
Cold and influenza symptoms; cough.

Medinase *Life Medicare, India.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Medinerv *Procure, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Medineuron *MMC, India.*
Vitamin B substances (p. 2102·3); glutamic acid (p. 2070·2); zinc sulfate (p. 2126·2).

Medinex
Note: this name may be used for preparations of different composition.
Mediez, India.
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Medinh-OD *Medichem, Indon.†*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Medinol *Cupal, Irl.; SSL, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Medinor *Solvay, Port.†*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Medinumm *Medial, India.*
Meropenem (p. 321·3).
Bacterial infections.

Mediol *Meprofarm, Indon.†*
⊗Normethandrone (p. 2297·3); methyloestradiol (p. 2271·1).
Amenorrhoea.

Mediolax *Medice, Ger.*
Bisacodyl (p. 1821·1).
Constipation.

Mediotic-HC *Dayton, USA.*
⊗Hydrocortisone (p. 1640·1); pramocaine hydrochloride (p. 1993·3); chloroxylenol (p. 1748·2); benzalkonium chloride (p. 1737·1).
Ear infections; pruritus.

Mediox *Medidis, Neth.*
Oxygen (p. 1799·3).
Hypoxia; cluster headache; hyperbaric oxygen therapy.

Medipam *Ratiopharm, Fin.*
Diazepam (p. 1063·2).
Anxiety disorders; pain; psychosomatic disorders; neuroses; skeletal muscle spasm; premedication; insomnia.

Medipax
Note: this name may be used for preparations of different composition.
Tecnifar, Port.
Dipotassium clorazepate (p. 1056·3).
Anxiety.

Medipekt *Orion, Fin.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Medipenam *Medihealth, India.*
Meropenem (p. 321·3).
Bacterial infections.

Medipent *Medihealth, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Medipent-D *Medihealth, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Mediphlegm *Medic+Aid, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mediphyllin Chrono *Medicus, Gr.*
Theophylline (p. 1229·3).
Bronchodilator.

Medipime *Medchem, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Medipin *Lark, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Medipip *Medihealth, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Medipirol *Medimport, Mex.†*
Metamizole magnesium (p. 53·3).
Pain.

Mediplast *Beiersdorf, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Mediplaster *Montefarmaco, Ital.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Musculoskeletal pain.

Mediplex
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.
Vitamin B substances (p. 2102·3).
Dietary supplement.

Medipo *Mediolanum, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Medipred *Medihealth, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Medi-Prep *SSL, UK.*
Cetrimide (p. 1742·1).
Skin disinfection.

Mediprim
Note: this name may be used for preparations of different composition.
Sons, Mex.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Medipro *Thorne, Canad.†*
Vitamins; minerals.

Medipulv *Pharmabroker, NZ.*
Chlorhexidine hydrochloride (p. 1743·3); hexamidine isetionate (p. 1754·3); allantoin (p. 1693·1).
Burns; wounds.

Medipyn *Caps, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain associated with tension.
Caps, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Fever; pain.

Medipyrin *Glenmark, Cz.*
Paracetamol (p. 115·1).
Fever; pain.

Medi-Quik *Mentholatum, USA.*
Topical spray: Lidocaine (p. 1988·1); benzalkonium chloride (p. 1737·1).
Skin disorders.

Mediquin *Surya Dermato, Indon.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Mediram *Mediorals, Thai.*
Ramipril (p. 1483·3).
Hypertension; myocardial infarction; heart failure; cardiovascular risk reduction.

Medirif *Medikon, Indon.†*
Rifampicin (p. 350·3).
Tuberculosis.

Mediron *Wockhardt, India.*
⊗Econazole nitrate (p. 577·3); fluocinolone acetonide (p. 1636·1); gentamicin sulfate (p. 304·2).

Medirov *Medikon, Indon.†*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis.

Medirox *Medopharm, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Medirox-A *Medopharm, India.*
Ambroxol hydrochloride (p. 1654·3); roxithromycin (p. 356·2).

Medi-Scrub *Ecolab, Canad.*
Chloroxylenol (p. 1748·2).

Mediscrub *Medikon, Indon.†; Medifarm, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; skin disinfection; hand disinfection.

Medised for Children *SSL, UK.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Cold symptoms; fever; pain.

Medisense
Note: this name may be used for preparations of different composition.
Abbott Diabetes Care, Fr.†; Abbott Diabetes Care, UK.
Test for glucose in blood (p. 2516·3).
Tripharma, Turk.
Betahistine hydrochloride (p. 2455·3).

Medisepta *Medgenix, Belg.*
Chlorhexidine acetate (p. 1743·2) or chlorhexidine gluconate (p. 1743·3).
Burns; skin disinfection; skin infections; wounds.

Medisert *Medihealth, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; premenstrual dysphoric disorder.

Medislim *British Biologicals, India.*
Preparation for enteral nutrition.

Medisnore *Naveh, Philipp.*
⊗Glycerol (p. 2517·2); eucalyptus oil (p. 2501·2); spearmint oil (p. 2621·2).
Snoring.

Medisol Bi0 *Medites, Cz.*
Sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium dihydrogen phosphate (p. 1791·1); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3).
Haemodialysis; haemofiltration.

Medisol Bi4 *Medites, Cz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium dihydrogen phosphate (p. 1791·1); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3).
Haemodialysis; haemofiltration.

Medisol K *Medites, Cz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3).
Haemodialysis; haemofiltration.

Medistat *Comed, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Medistatin *Farmellas, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Medisten *Medikon, Indon.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Medi-Swab *Smith & Nephew, Austral.; Smith & Nephew, S.Afr.†; SSL, UK.*
Isopropyl alcohol (p. 1758·3).
Skin disinfection; pre-injection swab.

Medi-Swab H *SSL, UK.*
Isopropyl alcohol (p. 1758·3); chlorhexidine acetate (p. 1743·2).
Pre-injection swab.

Medisyl *Korea United, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; labour management; puerperal bleeding.

Meditabine *Medison, Israel.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Meditam
Note: this name may be used for preparations of different composition.
Help, Gr.
Piracetam (p. 393·3).
Mental function disorders.

Meditam-6
Note: this name may be used for preparations of different composition.
Medikon, Indon.†
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Meditan
Note: this name may be used for preparations of different composition.
Farmak, Ukr.
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.
Pharmaland, Thai.
Mefenamic acid (p. 85·3).
Pain.

Meditapp *Medifive, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Hypersensitivity reactions; cough.

Meditapp Expectorant *Medifive, Thai.†*
Guaifenesin (p. 1666·2); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Hypersensitivity reactions; cough.

Medi-Test Combi 2 *BHR, UK.*
Test for glucose and protein in urine.

Medi-Test Combi 5 *Dutec, Austral.†*
Test for glucose, blood, ascorbic acid, protein, and pH in urine.

Medi-Test Combi 7 *Dutec, Austral.†*
Test for glucose, blood, ketones, ascorbic acid, nitrite, protein, and pH in urine.

Medi-Test Combi 9 *Dutec, Austral.†*
Test for glucose, ascorbic acid, ketones, blood, protein, nitrite, pH, bilirubin, and urobilinogen in urine.

Medi-Test Combi 3A *Dutec, Austral.†*
Test for glucose, protein, pH, and ascorbic acid in urine.

Medi-Test Combi 4A *Dutec, Austral.†*
Test for nitrite, blood, protein, pH, and ascorbic acid in urine.

Medi-Test Combi 6A *Dutec, Austral.†*
Test for blood, bilirubin, protein, ascorbic acid, glucose, and pH in urine.

Medi-Test Combi 5N *Dutec, Austral.†*
Test for pH, glucose, blood, ascorbic acid, protein, and nitrite in urine.

Medi-Test Glucose *Dutec, Austral.†; BHR, UK.*
Test for glucose in urine (p. 2516·3).

Medi-Test Glucose 2 *Dutec, Austral.†*
Test for glucose and ascorbic acid in urine.

Medi-Test Glucose 3 *Dutec, Austral.†*
Test for glucose, ketones, and ascorbic acid in urine.

Medi-Test Keton *Dutec, Austral.†*
Test for ketones in urine.

Medi-Test Nitrit *Dutec, Austral.†*
Test for nitrite in urine.

Medi-Test Protein 2 *Dutec, Austral.†*
Test for protein and pH in urine.

Medi-Test Urbi *Dutec, Austral.†*
Test for urobilinogen and bilirubin in urine.

Medithane *Wyeth, India.*
⊗Hydrocortisone acetate (p. 1640·1); yeast (p. 2125·2); shark-liver oil (p. 2614·2); vitamin A (p. 2098·3).
Anorectal disorders.

Medithyrox *Intermed, Gr.*
Levothyroxine sodium (p. 2339·1).

Meditic *Medicpharma, Thai.*
⊗Amiloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Diuretic.

Meditil
Note: this name may be used for preparations of different composition.
Hands, India.
Prochlorperazine (p. 1098·2).
Nausea and vomiting; psychoses; anxiety; vertigo.
Medikon, Indon.†
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Meditin *Intra-Labs, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration; dyspepsia.

Meditin Plus *Intra-Labs, India.*
Ranitidine (p. 1882·1); domperidone (p. 1838·1); simeticone (p. 1886·2).

Meditoina *Medipharm, Chile.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm.

Meditonsin *Medice, Austria; Medice, Ger.*
Aconitum (p. 2428·3); atropinum sulfuricum (p. 1310·2); mercurius cyanatus (p. 2555·3).
Homoeopathic preparation.

Meditrans *Kyowa, Jpn.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Meditrim *Medikon, Indon.†; Cipla-Medpro, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Meditrol *Mega Lifesciences, Thai.*
Calcitriol (p. 2113·1).
Renal osteodystrophy; osteoporosis; hypoparathyroidism; rickets; pseudohypoparathyroidism.

Meditussin *Pharmaland, Thai.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan (p. 1660·1).
Respiratory-tract congestion; cough.

Medivapom *Scientific Pharma, Gr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Médiveine *Elerte, Fr.*
Diosmin (p. 2505·2).
Peripheral vascular disorders; haemorrhoids.

Medivitan *Medice, Ger.*
Hydroxocobalamin (p. 2107·3); sodium folate (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Vitamin deficiency.

Medivitan IV *Medice, Ger.*
Pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Vitamin B deficiency.

Medivitan Neuro *Medice, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B_1 and B_6 deficiency.

Medi-Wipe *SSL, UK.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Hard surface disinfection.

Medix *IAE, Philipp.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Medixel *Taro, Israel.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Medixidin *Qualiphar, Belg.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gum irritation; sore throat.

Medixil *Rider, Chile.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Medixin
Note: this name may be used for preparations of different composition.
Merck Serono, Arg.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Medixon *Ferron, Indon.; Dexa, Philipp.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Medizinc *Casel, Turk.*
Zinc sulfate (p. 2126·2).

Medizol
Note: this name may be used for preparations of different composition.
Medimport, Mex.†
Metronidazole (p. 936·1).
Trichomoniasis.

Medizole *Utopian, Thai.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections; Helicobacter pylori eradication.

Medizyme
Note: this name may be used for preparations of different composition.
Utopian, Thai.
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion.
Zee, India.
⊗Activated charcoal (p. 1537·3); pancreatin (p. 2579·3); simeticone (p. 1886·2).

Medkof *Medihealth, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Medkofen *Medifive, Thai.†*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Med-Lemon Cough Syrup *Group, S.Afr.†*
Guaifenesin (p. 1666·2).
Cough.

Med-Lemon Hot Medication with Vitamin C *Group, S.Afr.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); menthol (p. 2553·2).
Cold and influenza symptoms.

Med-Lemon Hot Medication-Lemon Menthol *Group, S.Afr.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); menthol (p. 2553·2).
Cold and influenza symptoms.

Medler *Comed, India.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; rhinitis.

Med-Loral *Medhel, Gr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Mednap *Kocak, Turk.*
Naproxen (p. 98·2).

Mednil *Pharmaland, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Mednutriflex Lipide G *Braun, Fr.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipid (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)).
Contains egg lecithin.
Parenteral nutrition.

Medobeta *Medochemie, Singapore.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

Medobiotin *Medopharm, Austria; Medopharm, Ukr.*
Biotin (p. 2052·2).
Hair and nail disorders; biotin deficiency.

Medobis *Lazar, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Medobis G *Lazar, Arg.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Medocalum *Medochemie, Singapore.†*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Medocarnitin *Medosan, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; cardiac metabolic disorders.

Medocef *Medochemie, China; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Thai.†*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Medociprin *Medochemie, Hong Kong; Medochemie, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Medoclav *Medochemie, Rus.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.
Medopharm, Cz.
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Medoclazide *Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Medoclor *Medochemie, Hong Kong.*
Cefaclor (p. 232·3).
Bacterial infections.

Medocodene *Schwarz, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain; fever.

Medocor *Roemmers, Arg.*
Isosorbide dinitrate (p. 1412·2) or isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease; myocardial infarction; pulmonary hypertension; heart failure.

Medocriptine *Medochemie, Cz.; Medochemie, Hong Kong; Medochemie, Malaysia.*
Bromocriptine mesilate (p. 895·3).
Menstrual disorders; infertility; hyperprolactinaemia; acromegaly; lactation inhibition; benign breast disorders; parkinsonism; hypogonadism; galactorrhoea; prolactinomas.

Medocycline *Medochemie, Hong Kong.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Medocyl *Westmont, Indon.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Medodermone *Medochemie, Hong Kong; Medochemie, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Medofed *Medifive, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Medofer *Medopharm, India.*
Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc (p. 2126·1).

Medofloran *Medochemie, Rus.*
Terbinafine (p. 593·3).
Fungal skin, mucous membrane, and nail infections.

Medofloxine *Medochemie, Malaysia.*
Ofloxacin (p. 334·3).
Bacterial infections.

Medoflucon *Medochemie, China; Gabriel, Gr.; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Fluconazole (p. 578·2).
Fungal infections.

Medol *Mediez, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Medolexin *Medochemie, Hong Kong; Medochemie, Malaysia.*
Cefalexin (p. 234·1).
Bacterial infections.

Medolin *Medochemie, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Medomexi *Promo-Med, Rus.*
Emoxypine succinate (p. 1371·1).
Cerebrovascular disorders; mental function impairment; asthenia; withdrawal syndromes.

Medomin *Med-One, Gr.*
Glucosamine sulfate (p. 2515·3).

Medomol *Medopharm, India.*
Paracetamol (p. 115·1).
Pain; fever.

Medomycin
Note: this name may be used for preparations of different composition.
Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.†; Medochemie, Singapore; Medochemie, Thai.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Medonol *Medochemie, Hong Kong.*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3).
Pain; fever.

Medopa
Note: this name may be used for preparations of different composition.
Armoxindo, Indon.†; Atlantic, Thai.
Methyldopa (p. 1431·1).
Hypertension.
Medinfar, Port.
Dopamine hydrochloride (p. 1367·2).
Shock.

Medopal *Teva, Mex.†*
Methyldopa (p. 1431·1).
Hypertension.

Medopam *Schwulst, S.Afr.†*
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.

Medopexol *Medochemie, Cz.; Medochemie, Gr.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Medopirid *Medochemie, Cz.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Medoprazole *Medochemie, Malaysia.*
Omeprazole (p. 1867·2).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome; Helicobacter pylori *eradication.*

Medopred *Medochemie, Rus.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Medoptic *Ashford, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial eye infections; otitis externa.

Medoram *Medochemie, Cz.*
Ramipril (p. 1483·3).
Hypertension; myocardial infarction; diabetic nephropathy; cardiovascular risk reduction; heart failure.

Medoram plus H *Medochemie, Cz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Medoric *Medifive, Thai.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Medoril *Medochemie, China.*
Calcium dobesilate (p. 2464·3).
Microvascular disorders; venous insufficiency; haemorrhoids.

Medorisper *Medochemie, Cz.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Medostatin *Medochemie, Cz.; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Medotar *Medco, USA.*
Coal tar (p. 1723·2); zinc oxide (p. 1729·1).
Skin disorders.

Medovascin *Medochemie, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Medovent *Medochemie, Rus.†; Medochemie, Thai.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Medovir
Note: this name may be used for preparations of different composition.
Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.
Aciclovir (p. 964·1).
Herpesvirus infections.
Sanovel, Turk.
Lamivudine (p. 1000·2).

Medox *Zentiva, Rus.; Zentiva, Ukr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Medox ABC *Unipharm, Mex.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Medox Prenatal *Unipharm, Mex.*
Vitamins; minerals.

Medoxa *Medac, Ger.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Medoxem *Medochemie, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Medoxicam *Medochemie, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Medoxin
Note: this name may be used for preparations of different composition.
Medopharm, Cz.
Cefuroxime axetil (p. 255·2).
Bacterial infections.
Milano, Thai.†
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Medoxine *MedGen, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Medozide *Malesci, Ital.†*
⊗Methyldopa (p. 1431·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Medozine *Medochemie, Hong Kong†; Medochemie, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; migraine.

Medphlem *Medpro, S.Afr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract associated with excess and viscous mucus.

Medpramol *Schwulst, S.Afr.†*
Paracetamol (p. 115·1).
Pain; fever.

Medpro *Sterling, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Medral *Offenbach, Mex.*
Omeprazole (p. 1867·2).
Acid aspiration; gastrointestinal hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Medrigest *VHB, India.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Medrin
Note: this name may be used for preparations of different composition.
Ildong, Philipp.
Cefradine (p. 249·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zentiva, Cz.†
Embramine teoclate (p. 628·2).
Nausea and vomiting; vestibular disorders; hypersensitivity reactions.

Medrinate *Hovid, Singapore.*
Dimenhydrinate (p. 625·2).
Motion sickness; Ménière's disease.

Medripol *Virgo, Philipp.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Medrivas *Alcon Cusi, Spain.*
⊗Medroxyprogesterone acetate (p. 2288·1); tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Medrivas Antib *Alcon Cusi, Spain.*
⊗Chloramphenicol succinate (p. 257·1); medroxyprogesterone acetate (p. 2288·1); tetryzoline hydrochloride (p. 1678·3).
Infected eye disorders.

Medrocil *Fortbenton, Arg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Medrol *Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia Upjohn, India; Pfizer, Indon.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Ukr.; Pharmacia Upjohn, USA; Pfizer, Venez.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Médrol *Pfizer, Fr.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Medrol Acne Lotion *Pfizer, Canad.; Pfizer, Gr.*
⊗Methylprednisolone acetate (p. 1642·3); aluminium chlorohydrate complex (p. 1694·1); sulfur (p. 1721·1).
Acne; rosacea; seborrhoeic dermatitis.

Medronaat Draximage *Draximage, Neth.*
Technetium-99m medronate (p. 2228·1).
Bone scintigraphy.

Medronal *LKM, Arg.†*
Alprazolam (p. 1035·2).
Anxiety.

Medronate Draximage *Draximage, Irl.†*
Medronic acid (p. 1186·1).
For labelling with technetium-99m.
Bone scintigraphy.

Medrone *Pfizer, UK.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Medronorm *Obsurge, India.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Medroplex *Teva, Cz.*
Medroxyprogesterone acetate (p. 2288·1).
Breast cancer; endometrial cancer; renal cancer; cachexia associated with AIDS or cancer.

Medrosterona *Craveri, Arg.*
Medroxyprogesterone acetate (p. 2288·1).
Endometrial cancer; renal cancer.

Medrox *Pharmaceutica North America, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Medroxitest *Delta, Braz.*
Medroxyprogesterone acetate (p. 2288·1).

Medroxon *Sanval, Braz.*
Medroxyprogesterone acetate (p. 2288·1).

Medroxy *Pro Doc, Canad.*
Medroxyprogesterone acetate (p. 2288·1).
Hormone replacement therapy; menstrual disorders.

Medroxyhexal *Sandoz, Austral.†*
Medroxyprogesterone acetate (p. 2288·1).
Menstrual disorders; endometriosis; menopausal disorders.

Medsara *Asofarma, Mex.*
Cytarabine (p. 774·1).
Malignant neoplasms.

Medsatrexate *Asofarma, Mex.*
Methotrexate sodium (p. 822·2).
Malignant neoplasms.

Medsavorina *Asofarma, Mex.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; antidote to folic acid antagonists.

Medsone *Medhaus, Philipp.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Medsop *Ranbaxy, India.*
Triclosan (p. 1773·2).
Skin disinfection.

Medtax *Huons, Philipp.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility.

Medtet *Cadila, India.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Medthrocin *Utopian, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Medulac *World Medicine, Ukr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Meduňkový *Megafyt-R, Cz.*
Melissa (p. 2552·3).
Nervous disorders; sleep disorders; gastrointestinal disorders.

Medvox *Medhaus, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Medway *Mitsubishi Tanabe, Jpn.*
⊗Albumin (recombinant) (p. 1130·2).
Hypoalbuminaemia; hypovolaemic shock.

Medxil *Lark, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Medxime *Samjin, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Medyn *Medice, Ger.*
Pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Prevention of elevated homocysteine concentration; vitamin supplement.

Medzef *Union Korea, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Med-Zepam *Medical Supply, Thai.*
Diazepam (p. 1063·2).

Med-Zepoxide *Medical Supply, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).

Medzyme *Medhaus, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

ME-F *TNP, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mefa *Jean-Marie, Hong Kong; Macrophar, Thai.*
Mefenamic acid (p. 85·3).
Pain; inflammation; menorrhagia.

Mefac *P & B, India; Rowex, Irl.*
Mefenamic acid (p. 85·3).
Pain; inflammation; musculoskeletal and joint disorders.

Mefac Spas *P & B, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefacid *Floreat, India.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Mefacid Forte *Floreat, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Mefacit *Polfa Pabianice, Pol.*
Mefenamic acid (p. 85·3).
Pain.

Mefact *Medico, India.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Mefamed *Medicpharma, Thai.*
Mefenamic acid (p. 85·3).
Pain; menorrhagia.

Mefamic *APT, Hong Kong†; Patar, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain; peri-articular and soft-tissue disorders.

Mefamic-D *Plus, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefan *Lloyd, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Mefar-PD *Akums, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3); paracetamol (p. 115·1); ranitidine (p. 1882·1).

Mefast *GM P, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Mefatin-Spas *Sresan, India.*
Dicycloverine hydrochloride (p. 1834·2); famotidine (p. 1842·1); mefenamic acid (p. 85·3).

Mefax *Alkem, India.*
Mefloquine (p. 657·1).
Malaria.

Mefazil *Mayo, Mex.*
Indometacin (p. 71·2).
Inflammation; rheumatism.

Mefcil Spas *Psyco Remedies, India.*
Dicycloverine (p. 1834·2) or dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefcy *Skymax, India.*
Mefloquine (p. 657·1).
Malaria.

Mefdi *PDC, India.*
Injection: Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

PDC, India.
Tablets: Drotaverine hydrochloride (p. 2497·3); mefenamic acid (p. 85·3).

Mefdic *Chemo-Drugs, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefdol *Bal, India.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Mefdol Spas *Bal, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefegesic *UniOrange, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Mefem *Dynamit, Austria.*
Ambra (p. 2440·3); cimicifuga (p. 2478·1); lilium tigrinum; sepia (p. 2613·1).
Homoeopathic preparation.

Mefen *Pharmaniaga, Hong Kong; Milano, Thai.*
Mefenamic acid (p. 85·3).
Pain; menorrhagia.

Mefenabene *Ratiopharm, Austria.*
Mefenamic acid (p. 85·3).
Musculoskeletal and joint disorders; pain; inflammation.

Mefenac *Vickmans, Hong Kong†; United Drug, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Méfénacid *Streuli, Switz.*
Mefenamic acid (p. 85·3).
Pain; influenza symptoms.

Mefenamin *Pfizer, Switz.; Teva, Switz.*
Mefenamic acid (p. 85·3).
Pain; fever.

Mefenaminacid *Cimex, Switz.†*
Mefenamic acid (p. 85·3).
Pain; hypermenorrhoea; fever.

Mefenan *Greater Pharma, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Mefenax *One Pharma, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Mefencid *Christo, Hong Kong.†*
Mefenamic acid (p. 85·3).

Mefenix
Note: this name may be used for preparations of different composition.
Ranbaxy, Singapore.
Mefenamic acid (p. 85·3).
Pain.

Mefetil *Rafa, Israel.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Meffnex *Alna, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mefi *Constant, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mefic *Pfizer, Austral.†; Alphapharm, Hong Kong; Alphapharm, Malaysia.†*
Mefenamic acid (p. 85·3).
Menorrhagia; pain; dysmenorrhoea.

Mefinal *Sanbe, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Mefinter *Interbat, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Mefipil *Abbott, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour following foetal death; post-coital oral contraceptive.

Mefiron *Chew, Thai.*
Metronidazole (p. 936·1).
Trichomoniasis.

Mefitrax *Triton, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mef'ix *Meprofarm, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Meflam
Note: this name may be used for preparations of different composition.
Cruise, India.
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mahakam Beta, Indon.; Synergen, Philipp.
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Meflaxin *Acto, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Meflen *Diba, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Mefliam *Cipla, India; Cipla-Medpro, S.Afr.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Mefloc *Aristo, India.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Meflomax *Labesfal, Port.†*
Mefloquine hydrochloride (p. 657·1).

Meflosin *Metiska, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Meflotas *Intas, India.*
Mefloquine (p. 657·1).
Malaria.

Meflup *Lupin, India.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Meflup Forte *Lupin, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Mefmin Spas *Siomond, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3); simeticone (p. 1886·2).

Mefnasic *Sinensix, Thai.*
Mefenamic acid (p. 85·3).
Pain; menorrhagia.

Mefnex *Plus, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mefnic Spas *Yacca, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefnic-D *Yacca, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Mefol *Osmed, India.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3).

Osmed, India.
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).

Mefolex *Tolmann, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Meforal *Berlin-Chemie, Hung.; Guidotti, Hung.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Meformed *Medifive, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mefoxa *Metiska, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Mefoxil *Vianex (Βιανεξ), Gr.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Mefoxim *MSD, Turk.*
Cefoxitin sodium (p. 246·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Mefoxin *MSD, Austral.†; MSD, Braz.; MSD-Chibret, Fr.; MSD, Hong Kong†; Visufarma, Ital.; MSD, NZ; MSD, S. Afr.; Mylan, USA.*
Cefoxitin sodium (p. 246·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Mefoxitin *Infectopharm, Austria.†*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Mefpa *Pharmasant, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Mefque *Zydus, India.*
Mefloquine (p. 657·1).
Malaria.

Mefren *Novartis Consumer, Belg.*
Pastilles: Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat infections.

Novartis Consumer, Belg.
Topical solution: Chlorhexidine gluconate (p. 1743·3).
Disinfection of minor wounds; disinfection of the skin.

Me-Fresh *Scoshia, India.*
Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2); zinc chloride (p. 2126·1).

Me-Fresh Gum Paint *Scoshia, India.*
Camphor (p. 2466·2); iodine (p. 2336·3); menthol (p. 2553·2); potassium iodide (p. 2336·3); tannic acid (p. 2625·2); thymol (p. 1772·2).

Mefril *Brown & Burk, Philipp.†; Micro, Singapore.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Mefsaid *Globus, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mefsaid-D *Globus, India.*
Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).

Mefsine *Adley, India.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Mefsym-Plus *Symbiosis, India.*
Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Mefsym-Spas *Symbiosis, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3).

Mefsyn-TX *Sanify, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mef-T *Ind-Swift, India.*
Mefenamic acid (p. 85·3); tizanidine (p. 2026·2).

Meftagesic
Note: this name may be used for preparations of different composition.
Blue Cross, India.
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Indo Pacific, India.
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Meftal *Blue Cross, India.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Meftal Forte *Blue Cross, India.*
Tablets: Mefenamic acid (p. 85·3); paracetamol (p. 115·1).
Pain.

Blue Cross, India.
Cream: Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Meftal-MR *Blue Cross, India.*
Mefenamic acid (p. 85·3); tizanidine (p. 2026·2).
Back pain; sprains; strains.

Meftal-Spas *Blue Cross, India.*
Injection: Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Blue Cross, India.
Oral drops; suspension: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Blue Cross, India.
Tablets: Dicycloverine (p. 1834·2) or dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).
Smooth muscle spasm.

Meftal-TX *Blue Cross, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Meftrax *Sanify, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mefurosan *Sanbe, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mefze Spas *Zee, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3).

Mefzys *Zytras, India.*
Mefenamic acid (p. 85·3); simeticone (p. 1886·2).

Mega-3 *Reddy, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Mega Antioxidante *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Mega Antioxidante SD *New Life, Arg.*
Vitamins; minerals.

Mega AO *Usana, Canad.*
Vitamins; ubidecarenone (p. 2637·1).

Mega B
Note: this name may be used for preparations of different composition.
Alive, Canad.; Quest, UK; Arco, USA.
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Bioglan, Austral.
Vitamin B substances (p. 2102·3); minerals; vitamin C (p. 2110·3).
Vitamin B supplement.

Cenovis, Austral.
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B deficiency.

Mega B Complex *Blackmores, Austral.*
Vitamin B substances (p. 2102·3).
Tonic.

Mega C
Note: this name may be used for preparations of different composition.
Tolico, Denm.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Bioglan, Austral.†
Ascorbic acid (p. 2110·3); rose fruit (p. 2607·1); hesperidin (p. 2505·2).
Vitamin C supplement.

Mega Dole *Kripps, Canad.†*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); potassium chloride (p. 1793·2).

Mega E *Cenovis, Austral.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E supplement.

Mega Freeflex *Universal Medicare, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate potassium chloride (p. 2515·3).

Mega Gluflex *Teva, Israel.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); ascorbic acid (p. 2110·3); manganese (p. 2081·2).
Osteoarthritis.

Mega Gluflex with MSN *Teva, Israel.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis.

Mega Min *Vita Health, Canad.†*
Minerals.

Mega Swiss One *Valeant, Canad.*
Vitamins; minerals.

Mega VM *Nature's Bounty, USA.*
Vitamins; minerals.

Mega Zyme *Kripps, Canad.†*
⊗Betaine hydrochloride (p. 2456·1); bromelain (p. 2460·3); papaya.

Mega-Alpha *Aurora, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Mega-Antioxidant *Usana, Hong Kong.†*
Vitamins; inositol (p. 2533·2); rutoside (p. 2505·3); hesperidin (p. 2505·2); green tea (p. 2648·2); bilberry (p. 2566·2); choline bitartrate (p. 2055·2); L-cysteine hydrochloride; cabbage; broccoli.

Me-Gab *Sykocure, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mega-B *Charoen, Thai.*
Vitamin B_6 (p. 2105·3).
Vitamin B_6 deficiency.

Megabal *Sanbe, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; vitamin B_{12} deficiency.

Megabol *ATOZ, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Megabron *Sidus, Arg.*
Streptococcus pneumoniae; Staphylococcus aureus; Streptococcus viridans; Haemophilus influenzae; Klebsiella.
Respiratory-tract infections.

Mega-C *Kripps, Canad.*
Sodium ascorbate (p. 2111·1).

Mega-Cal *Jamieson, Hong Kong.*
Calcium (p. 1783·1).
Calcium deficiency; calcium supplement.

Megacal *Chemo-Drugs, India.*
Calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Mega-Cal with Vit D *Jamieson, Hong Kong.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; calcium supplement; vitamin D supplement.

Mega-Calcium *Sandoz, Fin.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; rickets; osteomalacia.

Mega-calcium *Novartis, Gr.*
Calcium carbonate (p. 1824·3); calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1).
Calcium deficiency.

Megace *Aspen, Austral.; BMS, Belg.; BMS, Canad.; Merck, Chile; BMS, China; BMS, Cz.; Orifarm, Denm.; BMS, Fin.†; BMS, Fr.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.†; BMS, Irl.; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, Neth.†; BMS, Norw.; Healthcare Logistics, NZ; BMS, Philipp.†; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, Swed.; BMS, Thai.; Deva, Turk.; BMS, UK; BMS Oncology, USA; Par, USA.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; anorexia or cachexia associated with AIDS or cancer.

Megacef
Note: this name may be used for preparations of different composition.
Biological E, India; Hawon, Philipp.
Cefoperazone (p. 243·1).
Bacterial infections.

Megacillin
Note: this name may be used for preparations of different composition.
Flamingo, India.
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Megacillin oral *Grunenthal, Ger.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Megacistin *Investi, Arg.*
Cystine (p. 2059·1); pyridoxine hydrochloride (p. 2105·3).
Eye disorders; skin, hair, and nail disorders.

Megaclav *Alembic, India.*
Amoxicillin (p. 216·2) potassium clavulanate (p. 268·3).
Bacterial infections.

Megaclox *Cipla, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Megaclox LB *Cipla, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Megacorp *Panalab, Arg.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer.

Megacort *Farma 1, Ital.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Musculoskeletal and joint disorders.

Megacure-DS *RND, India.*
Capsules: Andrographis (p. 2443·2); punarnava (p. 2601·1); phyllanthus niruri (p. 2590·1); terminalia chebula (p. 2474·3); tinospora cordifolia.

RND, India.
Oral drops: Punarnava (p. 2601·1); curcuma longa; tinospora cordifolia.

RND, India.
Syrup: Punarnava (p. 2601·1); curcuma longa; phyllanthus niruri (p. 2590·1); tinospora cordifolia.

Mega-CV *Aristo, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Megadase-D *Bliss, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Megadin
Note: this name may be used for preparations of different composition.
Mecom, Rus.
Vitamins; minerals.

Megadose
Note: this name may be used for preparations of different composition.
Arco, USA.
Vitamins; minerals.

Fada, Arg.
Dopamine (p. 1367·2).

Megadox *Pharmacon, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Megadoxa *Adcock Ingram, S.Afr.*
Vitamin B substances (p. 2102·3).

Megadoxa Forte *Adcock Ingram, S.Afr.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Megadyn *Abdi, Turk.; Mecom, Turk.*
Vitamins; minerals.

Megafen Plus *Jayson, Ukr.†*
Diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Musculoskeletal and joint disorders; gout; pain; inflammation.

Megafer *Boniscontro & Gazzone, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Megaferin *ABC, Ukr.†*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia; iron supplement.

Megaflox
Note: this name may be used for preparations of different composition.
Baldacci, Port.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Bliss, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Megaflox-M *Bliss, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Megaflox-TZ *Bliss, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Megafol *Alphapharm, Austral.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folic acid deficiency.

Megagin *Oxytech, India.*
Alpha tocoferil acetate (p. 2119·2); lycopene (p. 2546·2); omega-3 fatty acids (p. 1460·1);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

selenium dioxide (p. 2087·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); zinc (p. 2126·1).

Megal
Note: this name may be used for preparations of different composition.
Andromaco, Mex.
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Cough.

Megalac *Krewel, Ger.*
Almasilate (p. 1815·3) or hydrotalcite (p. 1845·2).
Gastric hyperacidity.

Megalax *Adcock Ingram, S.Afr.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Megalex *Phoenix, Arg.*
Ranitidine hydrochloride (p. 1882·1); domperidone (p. 1838·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Megalex Antiacido *Phoenix, Arg.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Megalia *Vipharm, Pol.*
Megestrol acetate (p. 2289·2).
AIDS-associated or cancer-associated cachexia.

Megalip
Note: this name may be used for preparations of different composition.
Medreich, India.
Omega-3 fatty acids (p. 1460·1); policosanol (p. 1472·1).

Megalocin *Kyorin, Jpn.†*
Fleroxacin (p. 298·3).
Bacterial infections.

Megalorat *Indeco, Arg.*
Loratadine (p. 633·2).

Megalotect *Biogam, Arg.; Biotest, Gr.; Intra Pharma, Irl.; Biotest, Israel; Biotest, Neth.; Biotest, Port.; Biotest, Singapore; Biotest, Thai.†*
A cytomegalovirus immunoglobulin (p. 2381·3).
Passive immunisation.

Mégamag *Mayoly-Spindler, Fr.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

Megamax *PGN, Arg.*
Magnesium (p. 1786·3); ginseng (p. 2513·3).
Tonic.

Megamentin *Intas, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Megamica *Mapra, India.*
Amikacin (p. 214·1).
Bacterial infections.

Megamilbedoce *Aristo, Spain.*
Hydroxocobalamin (p. 2107·3).
Vitamin B12 deficiency.

Megamin *Orchid, India.*
Vitamins; amino acids.

Megaminvit *Radicura, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); minerals; vitamins.

Megamox
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.
Dynamic, Philipp.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.
Hikma, Cz.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.
Maver, Mex.
Amoxicillin trihydrate (p. 216·2); sulbactam sodium (p. 360·1).
Bacterial infections.
Max, India.
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Mégamylase *Biocodex, Fr.*
Alpha-amylase (p. 2442·1).
Upper respiratory-tract congestion.

Meganeg *Dabur, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Meganerv *More, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuralgia; neuritis; neuropathy; hyperemesis gravidarum.

Meganerv F-A *More, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Folic acid deficiency; neuralgia; neuropathy; prevention of neural-tube defects.

Meganerv-E *More, Philipp.*
Vitamins; ferrous sulfate (p. 2062·2).
Tonic.

Meganest *Clarben, Port.; Clarben, Spain.*
Articaine hydrochloride (p. 1980·1). Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mega-Neubion *Merck, Venez.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2). Lidocaine hydrochloride (p. 1988·2) is included in some injections to alleviate the pain of injection.
Neuritis; neuralgia.

Meganeuron *Aristo, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Meganor *Alkem, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Meganox *Etex, Chile.*
Lamotrigine (p. 527·2).
Epilepsy.

Meganyl *Medicus, Gr.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Mega-Omega *Sanat, India.*
Omega-3 marine triglycerides (p. 1460·3).

Megaparin *Venus, India.*
Enoxaparin (p. 1372·3).
Thromboembolic disorders; prevention of coagulation during haemodialysis; unstable angina.

Megapen
Note: this name may be used for preparations of different composition.
Aristo, India.
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.
Aspen, S.Afr.
Amoxicillin trihydrate (p. 216·2); flucloxacillin sodium (p. 299·2).
Bacterial infections.

Megapenil *Grunenthal, Mex.†*
Injection: Clemizole penicillin (p. 269·2).
Bacterial infections.

Megapenil Forte *Grunenthal, Mex.†*
Clemizole penicillin (p. 269·2); benzylpenicillin sodium (p. 228·2). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to reduce the pain of injection.
Bacterial infections.

Megapim *Alkem, Ukr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Megapime *Alkem, India.*
Cefepime (p. 239·2).
Bacterial infections.
Ranbaxy, Malaysia; Alkem, Thai.
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Megaplatin *Genepharm, Gr.*
Carboplatin (p. 759·1).
Ovarian cancer; small-cell lung cancer.

Megaplex *Teva, Cz.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Philipp.; Teva, Rus.; Pharmachemie, Thai.; Teva, Thai.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; AIDS- and cancer-associated cachexia.

Megaplus *Investi, Arg.*
⊗Cystine (p. 2059·1); pyridoxine hydrochloride (p. 2105·3); biotin (p. 2052·2); calcium pantothenate (p. 2085·2); zinc sulfate (p. 2126·2); gelatin (p. 1154·1).
Hair and nail disorders; seborrhoea.

Megapraz *Terramedic, Philipp.†*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mega-Pred *Venus, India.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Megapress *Genepharm, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Megapril *Biomax, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Mega-Prim *Hua, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Megapyn *Aspen, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.
Aspen, S.Afr.†
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Megaril *Nodysis, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Megaril-D *Nodysis, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Megarubicin *Opus Materia, Gr.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Megase *BMS, Venez.*
Megestrol acetate (p. 2289·2).

Megashelcal *Elder, India.*
1 Capsule, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); 1 capsule, lipid; vitamin C (p. 2110·3); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Megasid *Fako, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Megasoft-E *Aristo, India.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).

Megastene *Servier, Arg.*
Sulbutiamine (p. 2103·1).
Asthenia.

Megasyn *Cipla, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Megatil *Intas, India.*
Chlorpromazine (p. 1045·2).
Psychoses; nausea and vomiting; intractable hiccup.

Mega-Tria *Biomedica, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Megatuss-D *GSK, India.*
⊗Dextromethorphan (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine (p. 642·3).
Cough.

Megatuss-P *GSK, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Megavis *Volchem, Ital.†*
Levocarnitine (p. 2053·2).
Asthenia.

Megavit
Note: this name may be used for preparations of different composition.
Diamond, Philipp.
Vitamins; lysine (p. 2079·3); lecithin (p. 2542·2); dexpanthenol (p. 2582·2); calcium carbonate (p. 1824·3); omega-3 fatty acids (p. 1460·1); chlorella growth factor (p. 2475·3).
Dietary supplement.

Megavite Fruits & Veggies *Mason, USA.*
Vitamins; minerals; choline (p. 2055·2); inositol (p. 2533·2).
Dietary supplement.

Megavitin-C *Qualiphar, Belg.*
Ascorbic acid (p. 2110·3).

Megaxin *Bayer, Israel; Perrigo, Israel.*
Moxifloxacin (p. 326·3) or moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Megazid *Mapra, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Megazing *Lapi, Indon.*
Vitamins; calcium (p. 1783·1); zinc (p. 2126·1).
Dietary supplement.

Megazol *Decomed, Port.†*
Omeprazole (p. 1867·2).

Megefren *Mylan, Spain.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; anorexia and cachexia in AIDS and cancer.

Megesin *Actavis, Hung.; Sindan, Pol.†*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer.

Megest *Uni-Sankyo, India.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Megestat *BMS, Braz.; BMS, Ger.*
Megestrol acetate (p. 2289·2).
AIDS-associated cachexia; breast cancer; endometrial cancer; prostatic cancer; benign prostatic hyperplasia; ovarian cancer; endometriosis; uterine cancer.

Mégestat *BMS, Switz.†*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer.

Megestil *Teofarma, Ital.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; AIDS-associated and cancer-associated cachexia.

Megestron *Organon, Mex.; Organon, Neth.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Meggezones *MSD, Irl.*
Levomenthol (p. 2553·2).
Nasal congestion; cough; sore throat.
Schering-Plough, UK.
Menthol (p. 2553·2).
Sore throats; coughs; catarrh; nasal congestion.

Megibal *Mitsubishi Tanabe, Jpn.*
Bemegride (p. 2318·1).
Activation of EEG abnormalities in diagnosis of epilepsy.

Megion *Biochemie, Cz.†; Sandoz, Hung.; Sandoz, Mex.; Sandoz, Philipp.; Hikma, Rus.; Sandoz, Venez.*
Ceftriaxone sodium (p. 253·3). Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Meglimid *KRKA, Rus.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Meglubet *Sandoz, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Meglucon *Sandoz, Austria; Hexal, Ger.†; Sandoz, Hung.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Meglum *Bago, Arg.*
Levamisole (p. 157·2).
Immunostimulant.

Meglyde *Chemo-Drugs, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Mego *Blue Cross, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Megox *Venus, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Mego-XL *Blue Cross, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Blue Cross, India.
Injection: Dexpanthenol (p. 2582·2); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3).

Meguanin *UCI, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Megyl-F *Indoco, India.*
Furazolidone (p. 933·3); metronidazole (p. 936·1).

Megyrina *Oncogenerika, Hung.*
Megestrol acetate (p. 2289·2).
Malignant neoplasms; cachexia.

Mehisdin-P *Synco, Singapore.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2).

Synco, Hong Kong.†
Chlorphenamine (p. 620·3); phenylephrine (p. 1672·2); sodium citrate (p. 1781·2).

Mei An *Hengrui, China.*
Mesna (p. 1557·2).

Mei Bo *Mao Xiang, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Mei Er Kai *Fang Sheng, China.*
Ornidazole (p. 943·1).
Vaginal disorders.

Mei Di Er Shu *Central, China.*
Moxonidine hydrochloride.
Hypertension.

Mei Er Tong *Yun Yang, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mei Feng *Lai Mei, China.*
Enoxacin (p. 290·2).
Bacterial infections.

Mei Fu *Lisheng, China.*
Itraconazole (p. 583·3).
Fungal infections.

Mei Fu Qiong *Huangshi FeiYun, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Mei Hong *Zhong Yi, China.*
Erythromycin (p. 291·2).
Bacterial infections.

Mei Jia Lai *Qi Li, China.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).

Mei Jia Te *Healthcare Pharma, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Mei Jia Xin *Ou Yi, China.*
Midecamycin acetate (p. 324·3).

Mei Di Ke *Si Huan Ke Bao, China.*
Fluconazole (p. 578·2).
Fungal infections.

Mei Di Lan *Si Huan Ke Bao, China.*
Oxymatrine.
Liver disorders.

Mei Lan Te *Xian Feng, China.*
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).

Mei Li Chang *Mei Lun, China.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Mei Li Neng *Kang Le, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Mei Di Lin *Si Huan Ke Bao, China.*
Oxymatrine.

Mei Ling Ge *Hengrui, China.*
Sodium (p. 1795·1); potassium (p. 1793·1); glucose (p. 2068·3).

Mei Luo Ke *Zhang Shu, China.*
Micronomicin sulfate (p. 324·2).

Mei Luo Ping *Mei Luo, China.*
Moxonidine hydrochloride.
Hypertension.

Mei Luo Qin *Pu Sheng, China.*
Ligustrazine phosphate.

Mei Nong *KunMing, China.*
Minocycline hydrochloride (p. 325·1).

Mei Nuo Xing *Yi Chuang, China.*
Minocycline hydrochloride (p. 325·1).

Mei Ou Ka *Shenyang First, China.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Mei Qu Luo *Double-Crane, China.*
Medroxyprogesterone acetate (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cancer; prostatic cancer.

Mei Si *Juneng, China.*
Telmisartan (p. 1509·3).
Hypertension.

Mei Si Bo Wei *Yookoy, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Mei Su Yu *Watson, China.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety.

Mei Ti Bo Wei *Yookoy, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Mei Tian Fu *AnJieLun, China.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Mei Wei Ning *Sine, China.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Mei De Xi *Cui Sheng, China.*
Heparin sodium (p. 1396·3).

Mei Xin Da *Tianhedi Sainuo, China.*
⊗Mazindol (p. 2324·1).
Obesity.

Mei Di Xing *Si Huan Ke Bao, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Mei Yu Ning *Huajin, China.*
Matrine.

Mei Zhen *Gui Long, China.*
Phentolamine mesilate (p. 1468·3).

Mei Zhi Quan *Fukang, China.*
Cefmetazole sodium (p. 241·3).
Bacterial infections.

Meiact *Meiji, China; Meiji, Indon.; Meiji, Jpn; Tedec Meiji, Port.; Tedec Meiji, Spain; Meiji, Thai.; Abdi, Turk.*
Cefditoren pivoxil (p. 239·1).
Bacterial infections.

Meibi *LKM, Arg.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Meibida *Zambon, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Meicelin *Meiji, China; Meiji, Jpn; Meiji, Thai.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Meiceral *Meiji, Thai.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Meiclox *Meiji, Thai.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Meidaxin *Sine, China.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; pain; fever; gout.

Meifeikang *Southwest, China.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Meifeng *Hanson, China.*
Cefalexin (p. 234·1).
Bacterial infections.

Meige *General Sanyang, China.*
Mezlocillin sodium (p. 324·1).
Gram-negative bacterial infections.

Meikewei *NCPC, China.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Meilax *Meiji, China; Meiji, Jpn.*
Ethyl loflazepate (p. 1073·1).
Anxiety; depression; sleep disorders.

Meilitai *Meiji, China.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Mei-Mei Children's Fever *Sunward, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Mei-Mei Worm *Sunward, Singapore.*
Piperazine citrate (p. 163·1).
Worm infections.

Meintein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Meinuofen *Haixin, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meinvenil Fisiologico *Fresenius Kabi, Spain.†*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Meinvenil Glucosa *Fresenius Kabi, Spain.†*
Glucose (p. 2068·3).
Fluid disorders; parenteral nutrition.

Meinvenil Glucosalina *Fresenius Kabi, Spain.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; carbohydrate source.

Meipril *Meiji, Indon.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Meisec *Meiji, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Meisusheng *Hospira, China.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis.

Meite *Hisun, China.*
Meropenem (p. 321·3).
Bacterial infections.

Meixam *Meiji, Indon.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Meixil *Meiji, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Meixinjie *Winsunny, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Mejadin *Young Il, Singapore.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris. Ménière's disease.

Mejoral
Note: this name may be used for preparations of different composition.
Elisium, Arg.; GSK, Mex.
Paracetamol (p. 115·1).
Fever; pain.

Mejoral Acti-Rapido *GSK, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Mejoral Cafeina
Note: this name may be used for preparations of different composition.
Elisium, Arg.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Omega, Spain.
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Mejoral Grip *Elisium, Arg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); butetamate citrate (p. 1658·1).
Fever; pain; respiratory-tract congestion.

Mejoral Grip T Descongestivo *Elisium, Arg.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); vitamin C (p. 2110·3).
Fever; pain; respiratory-tract congestion.

Mejoral Plus *GSK, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Mejoralito *GSK, Mex.*
Paracetamol (p. 115·1).
Fever; pain; post-vaccination reactions.

Mekan *Biomedica, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Mekinist *GSK, USA.*
Trametinib dimethyl sulfoxide (p. 875·3).
Malignant melanoma.

Meklin *Bennet, India.*
Metronidazole (p. 936·1); tetracycline hydrochloride (p. 373·2).

Mekoll *IIP, Port.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mekostest *Vitaflo, Swed.*
Allergen-impregnated patches (p. 2434·3).
Diagnosis of allergic contact dermatitis.

Meksun *Biofarma, Turk.*
Meloxicam (p. 86·3).

Mela *RPG, India.*
⊗Metolazone (p. 1434·1).
Hypertension; oedema.

Melablock *Forder, Arg.*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); melanin (p. 1711·1).
Sunscreen.

Melabon
Note: this name may be used for preparations of different composition.
Sigmapharm, Austria.
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine citrate (p. 1203·3).
Pain; fever.

Lacer, Spain.†
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Melabon K *Medice, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Melacare *Ajanta, India.*
⊗Hydroquinone (p. 1705·1); mometasone furoate (p. 1644·1); tretinoin (p. 1725·2).

Melacler *Forder, Arg.*
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3).

Melacut *Neiss, India.*
⊗Hydroquinone (p. 1705·1); mometasone furoate (p. 1644·1); tretinoin (p. 1725·2).

Meladerm
Note: this name may be used for preparations of different composition.
Inga, India.
Methoxsalen (p. 1711·3).
Psoriasis; vitiligo.

Interbat, Indon.
Hydroquinone (p. 1705·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Skin pigmentation disorders.

Meladinina *Chinoin, Mex.*
Methoxsalen (p. 1711·3).
Psoriasis; vitiligo.

Meladinine *CLS, China; Galderma, Ger.; Promedica, Singapore†; CLS, Thai.*
Methoxsalen (p. 1711·3).
Vitiligo; psoriasis; alopecia; mycosis fungoides.

Méladinine *DB, Fr.; Galderma, Switz.†*
Methoxsalen (p. 1711·3).
Skin disorders; psoriasis; vitiligo; mycosis fungoides.

Melagard *Abbott, India.*
Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Melagel *Giscard, Arg.*
Ascorbic acid (p. 2110·3); placenta extract (p. 2444·1).
Skin disorders.

Melagesic PM *Ascher, USA.*
Paracetamol (p. 115·1); melatonin (p. 2551·3).
Pain; sleep disorders.

Melaglow *Abbott, India.*
Avobenzone (p. 1695·1); curcuminoids (p. 2489·3); soya isoflavones (p. 2620·3).

Melagrião *Catarinense, Braz.*
Rorippa nasturtium-aquaticum; aconite (p. 2428·3); mikania glomerata; ipecacuanha (p. 1667·2); senega (p. 1677·2); tolu balsam (p. 1679·2); honey (p. 2072·1).
Respiratory-tract congestion.

Melalite *Nicholas Piramal, India.*
Hydroquinone (p. 1705·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Skin pigmentation disorders.

Melalite Forte *Abbott, India.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Melalite Plus *Abbott, India.*
⊗Hydrocortisone acetate (p. 1640·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).

Melalite-XL *Abbott, India.*
⊗Hydroquinone (p. 1705·1); mometasone furoate (p. 1644·1); tretinoin (p. 1725·2).

Melalong *Ajanta, India.*
Hydroquinone (p. 1705·1); tretinoin (p. 1725·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Melam *Vensat, India.*
Chlorhexidine (p. 1743·2); metronidazole (p. 936·1).

Melamil *Milte, Ital.†*
Melatonin (p. 2551·3).

Melan *Orion, India.*
Syrup: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).
Orion, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Melanasa *Vinas, Spain.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Melanda *Ali, Turk.*
Memantine hydrochloride (p. 393·1).

Melanex
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Mex.
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Melange *Seroyal, Canad.†*
Calcium fluoride (p. 2053·1); calcium phosphate tribasic (p. 1784·2); calcium sulfate (p. 2173·1); ferrum phosphoricum (p. 2077·1); magnesium phosphate dibasic (p. 1786·3); potassium chloride (p. 1793·2); potassium phosphate dibasic (p. 1791·1); potassium sulfate (p. 1793·2); silicon dioxide (p. 2208·3); sodium chloride (p. 1795·1); sodium phosphate dibasic (p. 1791·2); sodium sulfate (p. 1888·1).
Homoeopathic preparation.

Melange de Plantes Formula L1 Laxatif *Herbasante, Canad.†*
Cascara (p. 1826·1); liquorice (p. 1853·2); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Melani-D *Roche-Posay, Chile.*
SPF 15: Kojic acid (p. 1710·2); drometrizole trisiloxane (p. 1702·1).
Skin hyperpigmentation.

Melani-D Maos *Roche-Posay, Braz.*
Kojic acid (p. 1710·2); octocrilene (p. 1715·2); avobenzone (p. 1695·1); ecamsule (p. 1702·1); drometrizole trisiloxane (p. 1702·1).
Skin hyperpigmentation.

Melanocyl *Franco-Indian, India.*
Ointment: Methoxsalen (p. 1711·3); aminobenzoic acid (p. 1694·2).
Psoriasis; skin depigmentation.
Franco-Indian, India.
Solution; tablets: Methoxsalen (p. 1711·3).
Psoriasis; skin depigmentation.

Melanorm *Unimarck, India.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Melanorm-HC *Unimarck, India.*
⊗Hydrocortisone acetate (p. 1640·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).

Melanox *Surya Dermato, Indon.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Melaoline *Unipharma, Gr.*
Methoxsalen (p. 1711·3).
Psoriasis; vitiligo; atopic dermatitis.

Melart *Panion, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melarthryl *Sons, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Melartin *Ranbaxy, Malaysia.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Melascreen Dépigmentant *Ducray, Fr.*
Azelaic acid (p. 1695·1); glycolic acid (p. 1704·3).
Skin hyperpigmentation.

Melascreen solaire *Ducray, Fr.*
SPF 50+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1).
Sunscreen.

Melashine *YSP, Malaysia.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Melaskin *Roi Surya, Indon.†*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Melasmax *Dominguez, Arg.*
⊗Hydroquinone (p. 1705·1); tretinoin (p. 1725·2); dexamethasone phosphate (p. 1631·1).
Skin hyperpigmentation.

Melasoft *Forder, Arg.*
Kojic acid (p. 1710·2); arbutin (p. 1694·3).
Skin hyperpigmentation.

Melat *ATOZ, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Melatol *Elisium, Arg.*
Melatonin (p. 2551·3).
Sleep disorders.

Melatouch *Forder, Arg.*
Saxifraga sarmentosa; aminoethylphosphinic acid.
Skin hyperpigmentation.

Melavir *Australian Bodycare, UK.*
Melaleuca oil (p. 2551·1).
Herpes labialis.

Melavita *Galenium, Indon.†*
Tretinoin (p. 1725·2).
Acne; photoageing; melasma.

Melaxen *Unipharm, Rus.; Unipharm, Ukr.*
Melatonin (p. 2551·3).
Circadian rhythm disturbances; insomnia.

Melaxose *Biocodex, Fr.; Pharmasearch, Port.*
Lactulose (p. 1850·3); liquid paraffin (p. 2191·2).
Constipation.

Melbek *Nobel, Rus.; Nobel, Ukr.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders; pain.

Melbet-A *Indkus, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Melbexa *Investigacion, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Melbin *Sumitomo, Hong Kong; Sumitomo, Jpn.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mel-C *Fresenius Kabi, Austria.†*
Sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Melcam *Pharmathen, Gr.; Unison, Hong Kong; Rowex, Irl.; Unison, Thai.; Deva, Turk.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; juvenile rheumatoid arthritis.

Melcom *XL, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melcovit *Micro, India.*
Thioctic acid (p. 2629·1); vitamins; minerals.

Melcyl *East West, India.*
Methoxsalen (p. 1711·3).
Psoriasis; vitiligo.

Meldoz *Alapis, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Melenor *Medochemie, Neth.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Meleril *Roemmers, Arg.*
Thioridazine (p. 1110·2) or thioridazine hydrochloride (p. 1110·2).
Psychoses; alcohol withdrawal syndrome.

Melet *Tocagino, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Meletin *Taiwan Biotech, Malaysia.*
Mexiletine hydrochloride (p. 1436·2).
Ventricular arrhythmias.

Melex *Daiichi Sankyo, Jpn.*
Mexazolam (p. 1085·1).
Anxiety disorders; sleep disorders; psychosomatic disorders.

Melfen *PannonPharma, Hung.; Clonmel, Irl.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Melferut *Rafarm, Gr.*
Etofenamate (p. 57·2).
Inflammatory disorders.

Melfiat *Numark, USA.*
⊗Phendimetrazine tartrate (p. 2328·3).
Obesity.

Melflam *Cipla, Hong Kong; Cipla, India; Hexal, S.Afr.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; sciatica.

Melfoma *Dosa, Arg.*
Melphalan (p. 819·1).
Malignant neoplasms.

Melfor-G *Arvincare, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Melgar *Fada, Arg.*
Naproxen (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Melgib *Fada, Arg.*
Metformin (p. 489·1).
Diabetes mellitus.

Melgisorb *Molnlycke, Austral.; Molnlycke, Belg.; Molnlycke, Canad.*
Calcium alginate (p. 1136·3).
Wounds.
Molnlycke, Fr.
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Exudative wounds.
Molnlycke, Ital.
Calcium alginate (p. 1136·3); sodium alginate (p. 2167·3).
Wound dressing.

Melgisorb Ag *Molnlycke, Ger.*
Calcium alginate (p. 1136·3); carmellose (p. 2175·1); silver sodium hydrogen zirconium phosphate.
Wounds.

Melhoral *GSK Consumer, Port.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Meli Rephastasan *Repha, Ger.†*
Melilot (p. 2552·3).
Venous insufficiency; thrombophlebitis; haemorrhoids.

Meliane *Bayer, Austria; Bayer, Belg.; Bayer Schering, Fin.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer, Israel; Bayer Schering, Malaysia; Bayer, Philipp.; Bayer, Singapore; Bayer, Spain; Berlis, Switz.; Bayer, Thai.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Méliane *Bayer, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Melic
Note: this name may be used for preparations of different composition.
Pasteur, Chile.
Meloxicam (p. 86·3).
Pain; inflammation.
Pharmasant, Thai.†
⊗Methandienone (p. 2291·3).
Osteoporosis.

Melican *Teva, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Melicate *Coup, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Melice *Newmed, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melicen-FP *Psyco Remedies, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Melicide *Coup, Gr.*
Sucralfate (p. 1889·1).

Melicron *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Meliden *Mavi, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Melidox *Meprofarm, Indon.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Gastrointestinal disorders; smooth muscle spasm.

Melife-G *Life Line, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Melife-OD *Life Line, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Melimont *Antor, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Melinda *Panalab, Arg.*
Soya isoflavones (p. 2620·3).
Dietary supplement; menopausal disorders.

Melinda Plus *Panalab, Arg.*
Soya isoflavones (p. 2620·3); colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Dietary supplement; menopausal disorders.

Melinerv *Ximena Polanco, Chile.*
Melissa officinalis (p. 2552·3); tilia cordata (p. 2631·3); crataegus oxyacantha (p. 2488·1); avena sativa (p. 2451·1).
Homoeopathic preparation.

Melipass *Knop, Chile.*
Melissa (p. 2552·3); passiflora coerulea (p. 2584·1).
Anxiety; gastrointestinal disorders; sedative.

Melipramin *Egis, Cz.; Egis, Hung.; Egis, Rus.; Egis, Ukr.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis; panic disorder; obsessive-compulsive disorder.

Melipramine *Boucher & Muir, Austral.†*
Imipramine hydrochloride (p. 426·2).
Depression.

Melirgan *Coup, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Melisal *Herbapol Wrodaw, Pol.*
Chamomile (p. 2474·1); crataegus (p. 2488·1); St John's wort (p. 449·1); melissa (p. 2552·3); tilia (p. 2631·3); angelica (p. 2443·3); black currant (p. 2458·1).
Nervous disorders; sleep disorders.

Melisana
Note: this name may be used for preparations of different composition.
Klosterfrau, Canad.†
Melissa oil (p. 2553·2); cinnamon oil (p. 2479·3); nutmeg oil (p. 2573·2); orange oil (p. 2576·2).

Melisana Klosterfrau *Klosterfrau, Pol.*
Angelica (p. 2443·3); gentian (p. 2512·1); melissa (p. 2552·3); phaseolus vulgaris (p. 2587·3); ginger rhizome (p. 1844·1); black pepper (p. 2586·1); nutmeg (p. 2573·1); cinchona (p. 2478·3); senna (p. 1885·1); cardamom (p. 2471·1).
Nervous disorders; sleep disorders; gastrointestinal disorders; neuromuscular pain; gingivitis.

Meliseptol *Braun, Ger.*
Propyl alcohol (p. 1768·1); glyoxal (p. 1754·1).
Surface disinfection.

Meliseptol Rapid *Braun, Ger.*
Propyl alcohol (p. 1768·1); didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Melissa Comp. *Weleda, UK.*
Angelica root (p. 2443·3); cinnamon (p. 2479·2); melissa leaf (p. 2552·3); nutmeg (p. 2573·1); lemon oil (p. 2543·1); coriander (p. 2486·3); clove (p. 2481·2).
Nausea; stomach pain; dyspepsia; diarrhoea.

Melissed *Hasco-Lek, Pol.*
Angelica (p. 2443·3); chamomile (p. 2474·1); crataegus (p. 2488·1); St John's wort (p. 449·1); melissa (p. 2552·3); tilia (p. 2631·3); black currant (p. 2458·1).
Insomnia; nervous disorders.

Melissengeist
Note: this name may be used for preparations of different composition.
Hofmann & Sommer, Ger.
Melissa (p. 2552·3); sage (p. 2608·3); rosemary (p. 2607·2); thyme (p. 2630·2); angelica (p. 2443·3); nutmeg (p. 2573·1); cinnamon (p. 2479·2); clove (p. 2481·2);

lemon oil (p. 2543·1); menthol (p. 2553·2); citronella oil (p. 2481·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3).
Gastrointestinal disorders; superficial circulatory disorders.

Weleda, S.Afr.†
Angelica (p. 2443·3); coriander (p. 2486·3); nutmeg (p. 2573·1); clove (p. 2481·2); cinnamon (p. 2479·2); melissa (p. 2552·3); citronella oil (p. 2481·1).
Dizziness; circulatory disorders; gastrointestinal disorders; influenza symptoms; headache; migraine; neuralgia; toothache; muscle pain.

Melis-Tonic *Herbapol Krakow, Pol.*
Angelica (p. 2443·3); caraway (p. 2470·2); chamomile (p. 2474·1); crataegus (p. 2488·1); honey (p. 2072·1); peppermint leaf (p. 1877·1).
Nervous disorders; sleep disorders.

Melitase *Tecnofarma, Chile.*
Levodopa (p. 902·2); benserazide (p. 894·1).
Parkinsonism.

Melitor *Servier, Ukr.*
Agomelatine (p. 400·2).
Depression.

Melitrast *Kohler, Austria†; Kohler, Ger.*
Iosarcol (p. 1592·1).
Radiographic contrast medium.

Melitus *Abbott, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Melival
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Spain.
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; insomnia.

Melix *Lagap, Switz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Meliyos *Aarpik, India.*
Flupentixol (p. 1074·1); melitracen hydrochloride (p. 434·2).
Depression.

Melizide *Alphapharm, Austral.; LCH, Hong Kong†; Alphapharm, Malaysia†; Alphapharm, Singapore; Merck, Thai.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Mellerettes *Novartis, Turk.*
Thioridazine hydrochloride (p. 1110·2).
Anxiety disorders.

Melleril *Valeant, Braz.; AWD, Ger.; Novartis, Gr.; Novartis, India; Novartis, Indon.†; Novartis, Turk.*
Thioridazine hydrochloride (p. 1110·2).
Psychoses; schizophrenia; depression; anxiety; behaviour disorders in children; alcohol withdrawal syndrome; neuroses.

Novartis, Mex.
Thioridazine (p. 1110·2) or thioridazine hydrochloride (p. 1110·2).
Schizophrenia.

Mellihexal *Sandoz, Austral.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Mellin AD *Mellin, Ital.*
Infant feed.
Diarrhoea.

Mellin AR *Mellin, Ital.*
Infant feed.
Gastro-oesophageal reflux.

Mellin HA *Mellin, Ital.*
Infant feed.
Food intolerance.

Mellinix *Lloyd, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mellinorm *Hemofarm, Rus.†*
Pentoxifylline (p. 1465·3).

Melliora *Naturland, Hung.*
Apis mellifera (p. 2445·2); arnica (p. 2447·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Mellitron *Janssen-Cilag, Mex.*
Metformin (p. 489·1); chlorpropamide (p. 470·1).
Diabetes mellitus.

Melmet *Micro, India.*
Metformin (p. 489·1) or metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Melneurin *Hexal, Ger.†*
Melperone hydrochloride (p. 1083·2).
Alcoholism; anxiety disorders; psychoses; sleep disorders.

Melnox *Kukje, China.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Melobax *Ranbaxy, Cz.; Ranbaxy, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melobic *TO-Chemicals, Thai.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloc *T Man, Thai.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; myocardial infarction; heart failure.

Melocalm *Kleva, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melocam *YSP, Malaysia.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melocin
Note: this name may be used for preparations of different composition.
Gap, Gr.
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Melock *Santa, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melocox *Eurofarma, Braz.; Galex, Cz.; Verisfield, Gr.; Ashford, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; inflammatory disorders.

Mel-OD *Zydus, India; Cadila, Malaysia; Zydus Cadila, Philipp.; Zydus Cadila, Thai.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; juvenile arthritis.

Meloden *Bayer, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Melodene *Schering, NZ†; Bayer Schering, S.Afr.*
21 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Melodene 15 *Bayer, Spain.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Melodia
Note: this name may be used for preparations of different composition.
Bayer, Fr.
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Leon, Thai.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Melodil *Trima, Israel.*
Maprotiline hydrochloride (p. 433·3).
Depression; mixed anxiety depressive states.

Melodim *Biostam (Βιοστιμ), Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melodol
Note: this name may be used for preparations of different composition.
Aristo, India.
Meloxicam (p. 86·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Raffo, Chile.
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders.

Melodyn
Note: this name may be used for preparations of different composition.
GL Pharma, Hung.
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Meloflam *Rhiza, Philipp.; Egis, Rus.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melogen *Generics, Hung.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Melogesic *Lupin, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis; juvenile idiopathic arthritis.

Meloids *Reckitt Benckiser, Thai.*
Liquorice (p. 1853·2); menthol (p. 2553·2); cinnamon (p. 2479·2); capsicum (p. 2469·3).
Throat disorders.

Meloka *Lacer, Spain.†*
Benfotiamine (p. 2102·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain; fever.

Melokan *Kanonfarma, Rus.†*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloksam *Richter, Pol.; Gedeon Richter, Ukr.†*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; degenerative joint disorders.

Melokssia *Pliva Krakow, Pol.†*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melol
Note: this name may be used for preparations of different composition.
Globus, India.
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Pharmasant, Thai.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction.

Melomet *YSP, Malaysia.*
⊗Mometasone furoate (p. 1644·1).
Inflammatory and pruritic skin disorders.

Melonax *Biofarma, Venez.*
Meloxicam (p. 86·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Melone *Elder, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis; juvenile idiopathic arthritis.

Melonil *BMW, India.*
Lotion: Aminobenzoic acid (p. 1694·2); methoxsalen (p. 1711·3).

BMW, India.
Tablets: Methoxsalen (p. 1711·3).
Psoriasis; vitiligo.

Melophar *Julphar, UAE.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Meloprax *Mankind, India.*
Alprazolam (p. 1035·2); melatonin (p. 2551·3).
Sleep disorders; anxiety; depression.

Meloprol *Energon, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melora *Zynova, Philipp.*
Meloxicam (p. 86·3).
Inflammation; musculoskeletal and joint disorders; pain.

Melorac *Fada, Arg.†*
Meloxicam (p. 86·3).

Melorem *Mac, Gr.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melorex *Douglas, NZ.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Melorilif *Med-One, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Meloset *Aristo, India.*
Melatonin (p. 2551·3).
Sleep disorders.

Melosteral *Silanes, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Melosuganril *Sarabhai Piramal, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis; juvenile idiopathic arthritis.

Melotec *EMS, Braz.; AG Therapy, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders; osteoarthritis; rheumatoid arthritis.

Melotev *Teva, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melotop *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melovar *Zota, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Melovax *Vivax, Venez.*
Meloxicam (p. 86·3).
Inflammation; musculoskeletal and joint disorders.

Melovis *Actavis, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melox *Gry, Ger.†; Raldex, Gr.; Medochemie, Hong Kong; Extractum, Hung.; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Siam Bheasach, Thai.; Nobel, Turk.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Meloxan *Actavis, Hung.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Meloxat *Clonmel, Irl.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Meloxeron *Sandoz, Gr.*
Meloxicam (p. 86·3).

Meloxi *Bal, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Meloxibell *Bellwether, Austral.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Meloxic *Polpharma, Pol.; Polpharma, Ukr.†*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloxid *Klonal, Arg.*
Meloxicam (p. 86·3).
Inflammation; pain.

Meloxigran *Legrand, Braz.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Meloxil *Ativus, Braz.; DAST, Gr.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

MeloxiLek *Sandoz, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Meloxin *Interbat, Indon.; Yung Shin, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Meloxistad *Stada, Cz.; Steigerwald, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Meloxitor *Iator, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Melozine *Intas, India.*
Thioridazine (p. 1110·2).
Schizophrenia; depression.

Melpax *Orion, Fin.†*
Melperone hydrochloride (p. 1083·2).
Psychoses; anxiety disorders; pain; alcohol withdrawal syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Melpor *Neves, Port.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Melpred *Cipla, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Mel-Puren *Actavis, Ger.†*
Melperone hydrochloride (p. 1083·2).
Alcoholism; anxiety disorders; psychoses; sleep disorders.

Melrose *Roberts & Sheppey, UK.*
Hydrous wool fat (p. 2219·3); yellow soft paraffin (p. 2212·1); hard paraffin (p. 2188·1).
Emollient.

Melrosum Extra Sterk *Novum, Neth.*
Codeine phosphate (p. 40·2).
Cough.

Melrosum Hustensirup *Cassella-med, Ger.*
Thyme (p. 2630·2).
Catarrh; bronchitis; cough.

Melsept *Braun, Ital.*
Formaldehyde (p. 1752·2); glutaral (p. 1753·2); glyoxal (p. 1754·1).
Surface disinfection.

Melsept SF *Braun, Ger.; Braun, Ital.*
Glutaral (p. 1753·2); glyoxal (p. 1754·1); didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Melsept Spray *Braun, Ital.*
⊗Alcohol (p. 1733·1); glyoxal (p. 1754·1).
Disinfection of minor wounds and surfaces.

Melsitt *Braun, Ger.*
Formaldehyde (p. 1752·2); glutaral (p. 1753·2); didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Melsone *Psychotropics, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Melteva *Teva, Spain.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Melthix *Molekule, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Meltika *Ikapharmindo, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Meltolan *Alkem, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Meltonar *Teva Tuteur, Arg.†*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer.

Meltus Baby *SSL, UK.*
Dilute acetic acid (p. 2426·3).
Coughs.

Meltus Decongestant *Reckitt Benckiser, Irl.†; Cupal, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Catarrh; sinusitis; nasal congestion; rhinitis.

Meltus Dry Cough *SSL, UK.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Meltus Expectorant *SSL, UK.*
Guaifenesin (p. 1666·2); cetylpyridinium chloride (p. 1743·1); honey (p. 2072·1).
Coughs.

Meltus Expectorant with Decongestant *SSL, UK.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; nasal and sinus congestion.

Meltus Honey & Lemon *SSL, UK.*
⊗Guaifenesin (p. 1666·2); honey (p. 2072·1); glycerol (p. 2517·2); terpeneless lemon oil (p. 2543·1).
Coughs.

Meltus Honey and Lemon *SSL, Irl.†*
Guaifenesin (p. 1666·2).
Cough; sore throat.

Meltus Junior Expectorant *SSL, UK.*
Guaifenesin (p. 1666·2); cetylpyridinium chloride (p. 1743·1).
Coughs; catarrh.

Meltus Junior Night Time *SSL, UK.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).
Coughs; cold symptoms.

Meltus Night Time *SSL, UK.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Coughs; cold symptoms.

Melubrin *Ranbaxy, India.*
Chloroquine phosphate (p. 650·1).
Malaria; hepatic amoebiasis; rheumatoid arthritis; lupus erythematosus.

Melurjin *Drogsan, Turk.*
Meloxicam (p. 86·3).

Melus *Medichrom, Gr.*
Meloxicam (p. 86·3).

Melvit
Note: this name may be used for preparations of different composition.
Micro, India.
Thioctic acid (p. 2629·1); vitamins; minerals; trace elements.
Beta, Ital.†
Vitamins; minerals.

Melxi *Aspen, Braz.*
Pineapple; honey (p. 2072·1).
Respiratory-tract congestion.

Melyd *Stada, Cz.; Stada, Hung.; Steigerwald, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Melzap *Alkem, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Melzin *Yung Shin, Philipp.*
Clonidine hydrochloride (p. 1339·1).
Hypertension; migraine; menopausal flushing.

Mem *Elin, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.
Neon, India.
Methylergometrine (p. 2137·3).
Postpartum and postabortal haemorrhage.

Mema *Actavis, Ukr.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Memac *Orifarm, Denm.†; Paranova, Denm.†; Bracco, Ital.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Memanxa *Ascent, Austral.; Aspen, Austral.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Memanzaks *Gen, Turk.*
Memantine (p. 393·1).

Memary *Daiichi Sankyo, Jpn.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Memax *Labomed, Chile.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Membracel *Celina, Arg.*
Collagen (p. 2483·2).
Medicated dressing.

MembraneBlue *DORC, Neth.†; Dutch Ophthalmic, USA.*
Trypan blue (p. 2635·2).
Ophthalmic stain.

Memelin *Pharmacodane, Denm.†; Centrafarm, Neth.†*
⊗Exemestane (p. 792·2).
Breast cancer.

Memento *Merck, Arg.*
Pipemidic acid (p. 339·3).
Skin infections; urinary-tract infections.

Memento NF *Merck, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract.

Memi *Plus, India.*
Injection: Vitamin B substances (p. 2102·3).
Plus, India.
Tablets: Thioctic acid (p. 2629·1); vitamins; minerals.

Memi-LB *Plus, India.*
Lycopene (p. 2546·2); vitamins; zinc (p. 2126·1).

Memjet *Sterkem, India.*
Methylergometrine (p. 2137·3).
Postpartum and postabortal haemorrhage.

Memo Plus Gold *Lumen, Philipp.*
Bacopa (p. 2452·1).
Herbal supplement for memory enhancement.

Memobiotral *Bionutre, Arg.*
Vitamin B substances (p. 2102·3); amino acids.
Mental function impairment; tonic.

Memocept *Polpharma, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Memodrin *Lavipharm, Gr.*
Aniracetam (p. 389·1).
Mental function disorders.

Memo-Farmellas *Farmachrom, Gr.*
Galantamine hydrobromide (p. 391·3).

Memokit *Ximena Polanco, Chile.†*
Ginkgo biloba (p. 2512·3).
Cerebrovascular disorders; mental function impairment; peripheral vascular disorders.

Memolife *Pharmax, Hung.*
Fish oil (p. 1460·3); borage oil (p. 2459·2); soya lecithin (p. 2542·2); betacarotene (p. 2051·1).
Dietary supplement to promote mental function.

Memolos *Driburg, Arg.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Memomax-S *SJA, Gr.*
Venlafaxine hydrochloride (p. 454·2).

Memomet *Matxin, Singapore.*
Bacopa (p. 2452·1); convolvulus pluricaulis; centella (p. 1698·3).
Mental function impairment.

Memonol *Utopian, Thai.*
Pyritinol hydrochloride (p. 394·3).
Mental function disorders.

Memoplant *Schwabe, Norw.†; Schwabe, Pol.; Schwabe, Rus.; Schwabe, Ukr.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function disorders; vestibular disorders.

Memoptic *Densmore, Fr.*
Choline (p. 2055·2); ginkgo biloba (p. 2512·3); vitamins; minerals.
Dietary supplement; vision disorders; memory impairment.

Memoran *Soho, Indon.*
Phosphatidyl serine (p. 2589·1).
Memory impairment.

Memorex *Provita, Ital.*
Amino acids; vitamins; minerals.
Mental function disorders.

Memorex Compuesto *Montpellier, Arg.*
Vitamin B substances (p. 2102·3); amino acids.
Vitamin B deficiency; vitamin B supplement.

Memorex Vital *Montpellier, Arg.*
Asparagine; glutamine (p. 2070·3); pyridoxine hydrochloride (p. 2105·3); phosphoryl serine.
Tonic.

Memoria
Note: this name may be used for preparations of different composition.
AM, Arg.
Vitamin B substances (p. 2102·3); amino acids.
Tonic.
Bittner, Austria; Bittner, Rus.; Bittner, Ukr.
Hypericum (p. 449·1); ginkgo (p. 2512·3); conium (p. 2524·3); ginseng (p. 2513·3); arnica (p. 2447·2).
Homoeopathic preparation.

Memoril
Note: this name may be used for preparations of different composition.
Meditop, Hung.
Piracetam (p. 393·3).
Mental function disorders.

Memoriobutan *Bunker, Braz.*
Vitamins; minerals; amino acids.

Memoriol B6 *Baldacci, Braz.*
Glutamine (p. 2070·3); calcium glutamate; ditetraethylammonium phosphate; pyridoxine hydrochloride (p. 2105·3).
Nutritional supplement; tonic.

Memorit *Unipharm, Israel.*
Donepezil (p. 390·2).
Alzheimer's disease.

Memorix *Eczacibasi, Turk.*
Memantine (p. 393·1).

Memorx IQ Plus *Gruppo Medica, Philipp.*
Acetylcarnitine (p. 2053·2); taurine (p. 2626·2); lysine hydrochloride (p. 2079·3); vitamins; zinc (p. 2126·1).
Mental function aid; tonic.

Memory Booster
Note: this name may be used for preparations of different composition.
Healthyway, Ukr.
Ginkgo biloba (p. 2512·3); milk thistle (p. 1561·1); myrtillus (p. 2566·2); turmeric (p. 2218·1); ginger (p. 1844·1); rosemary (p. 2607·2).
Tonic.

Memory DD *Green Leaf, Philipp.†*
Centella (p. 1698·3); lecithin (p. 2542·2); camellia sinensis (p. 2648·2); bacopa (p. 2452·1); gynostemma pentaphyllum.
Mental function impairment; anxiety; stress.

Memory Plus *Green Leaf, Philipp.*
Centella (p. 1698·3); lecithin (p. 2542·2); docosahexaenoic acid (p. 1460·1).
Mental function impairment; tonic.
Life Essence, UK.
Bacopa (p. 2452·1).
Memory impairment.

Memory and Vitality Formula *Golden Glow, Austral.*
Rhodiola; ashwagandha (p. 2450·2); ginseng (p. 2513·3).
Tonic.

Memosam *Phytopharm, Ukr.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; vestibular disorders; mental function impairment; migraine; motion sickness.

Memotil *Genepharm, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Memoton Life *Medichrom, Gr.*
Galantamine hydrobromide (p. 391·3).

Memotropil *Polpharma, Pol.; Polpharma, Rus.*
Piracetam (p. 393·3).
Mental function impairment; vertigo; dyslexia; myoclonus; stroke; cerebrovascular disorders; cranial trauma; alcohol withdrawal syndrome; vestibular disorders; behaviour disorders in children; sickle-cell anaemia.

Memovigor *Euro-Pharma, Ital.*
Vitamins; minerals; phospholipids (p. 2201·2); acetylcarnitine (p. 2053·2); myrtillus (p. 2566·2); ginkgo biloba (p. 2512·3).
Mental function disorders.

Memovit B12 *Magis, Ital.*
Glutamine (p. 2070·3); DL-phosphoserine (p. 2589·1); cyanocobalamin (p. 2107·2).
Tonic.

Memovit-E *Health Saver, Philipp.†*
Lecithin (p. 2542·2); royal jelly (p. 2608·1); ginseng (p. 2513·3); rutoside (p. 2505·3); vitamins; amino acids; minerals.
Nutritional supplement; tonic.

Memox *Unipharm, Israel.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Memozan *Dielen, Fr.*
Fish oil (p. 1460·1); fish protein; vitamins.
Dietary supplement; tonic.

Mempil *General Drugs, Thai.*
Piracetam (p. 393·3).
Mental function disorders; cerebrovascular disorders.

Memtone *Aimil, India.*
Asparagus racemosus (p. 2614·2); centella (p. 1698·3); liquorice (p. 1853·2); hyoscyamus niger (p. 2530·2); rauwolfia serpentina (p. 1485·1); withania somnifera (p. 2450·2).

Memzotil *Pharmasant, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders.

Men Complex *Thompsons, Canad.†*
Ambra grisea (p. 2440·3); cimicifuga racemosa (p. 2478·1); pulsatilla (p. 2600·2); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

Men Formula *Natures Sunshine, Canad.†*
Zinc gluconate (p. 2126·2).

Men Hormone Compound *TP, Thai.*
⊗Methyltestosterone (p. 2291·3); vitamin E (p. 2119·1).
Hypogonadism.

Menabol *CFL, India.*
⊗Stanozolol (p. 2304·2).
Anabolic; osteoporosis; aplastic anaemia.

Menactra *Sanofi Pasteur, Canad.; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Singapore; Aventis Pasteur, USA.*
A meningococcal vaccine (groups A, C, W_{135}, and Y) (p. 2401·3).
Active immunisation.

Menaderm
Note: this name may be used for preparations of different composition.
Galeno, Venez.
Sulfadiazine silver (p. 362·3).
Burns.

Menarini, Ital.
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Menaderm Clio *Menarini, Spain.*
⊗Beclometasone dipropionate (p. 1621·2); clioquinol (p. 273·1).
Infected skin disorders.

Menaderm N *Menarini, Arg.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Menaderm Neomicina *Menarini, Spain.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Menaderm Otologico *Menarini, Spain.*
⊗Beclometasone dipropionate (p. 1621·2); clioquinol (p. 273·1).
External ear disorders.

Menaderm Simple *Menarini, Arg.; Menarini, Spain.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Menaderm Simplex *Menarini, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Menadion *Aspen, Braz.; Medic, Denm.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency; anticoagulant antidote.

Menadol *Rugby, USA.*
Ibuprofen (p. 68·2).

Menaelle *Theramex, Mon.*
Progesterone (p. 2300·2).
Premenstrual syndrome; menopausal disorders.

Menalcol *Orravan, Spain.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Menalgil B6 *Menarini, Spain.†*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1) pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Menalgin *DHU, Rus.*
Asculus hippocastanum (p. 2431·2); magnesium phosphoricum (p. 1787·3); potentilla anserina; chamomilla recutita (p. 2474·1); colocynthis (p. 1833·3).
Homoeopathic preparation.

Menalmina *Orravan, Spain.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Menamic *Osoth, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Menamig *Pro Farma, Switz.*
Frovatriptan succinate (p. 676·2).
Migraine.

Menamin *PP Lab, Thai.*
Prosultiamine (p. 2103·1).
Beri-beri; thiamine deficiency.

Mena-Phase Formula *Nutrifarma, Turk.*
Vitamins; minerals.

Menaril *Guidotti, Gr.*
Ketoprofen (p. 79·1).
Inflammatory disorders.

Menaven *Menarini, Spain.*
Heparin sodium (p. 1396·3).
Peripheral vascular disorders.

Menbel *Geolab, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Mencalisvit *Menarini, Spain.*
Calcium lactate (p. 1784·1); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Mencevax *GSK, Fr.; GSK, India; Litha, S.Afr.*
A meningococcal vaccine (groups A, C, W135, and Y) (p. 2401·3).
Active immunisation.

Mencevax AC *GSK, Spain.†*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Mencevax ACWY *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Fin.; GSK, Ger; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Philipp.; GSK, Rus.; GSK, Singapore; GSK, Switz.*
A meningococcal polysaccharide vaccine (groups A, C, W_{135} and Y) (p. 2401·3).
Active immunisation.

Mencip *Menarini, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Mencirax *Ativus, Braz.*
Cimicifuga (p. 2478·1).
Menopausal disorders; menstrual disorders.

Mencogrin *Raymos, Arg.*
Shampoo: Salicylic acid (p. 1719·1); climbazole (p. 576·2) coconut fatty acids; allantoin (p. 1693·1).
Scalp disorders.

Raymos, Arg.
Topical solution: ⊗Coal tar (p. 1723·2); salicylic acid (p. 1719·1); betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

Raymos, Arg.
Cream: ⊗Coal tar (p. 1723·2); allantoin (p. 1693·1); betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

Mencogrin AP *Raymos, Arg.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); cade oil (p. 1723·2); allantoin (p. 1693·1).
Scalp disorders.

Mencor *Helm, Port.†*
Felodipine (p. 1380·3).
Angina pectoris.

Mencord *Menarini, Austria.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Mencord Plus *Menarini, Austria.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

M-End Max D *McNeil, USA.*
⊗Codeine phosphate (p. 40·2); dexbrompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).

M-End PE *McNeil, USA.*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

M-END WC *McNeil, USA.*
⊗Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Mendatrex *Liptis, USA.*
Valproate semisodium (p. 553·2).

Mendazole *GSK, India.*
Mebendazole (p. 158·3).
Worm infections.

Mendicof *Sunward, Singapore.*
⊗Dexchlorpheniramine maleate (p. 621·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Mendilex *Alkaloid, Rus.*
Biperiden hydrochloride (p. 895·1).
Parkinsonism; drug-induced extrapyramidal disorders.

Mendro *Medizone, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; osteoporosis; anaemias.

Menefloks *Nevzat, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

Menegradil *Fada, Arg.*
⊗Etilefrine (p. 1379·1).
Hypotension.

Meneklin *Tum, Turk.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Menelat *Torrent, Braz.*
Mirtazapine (p. 436·1).

Menem *United Biotech, India.*
Meropenem (p. 321·3).
Bacterial infections.

Menest *Raffo, Arg.; Monarch, USA.*
Esterified oestrogens (p. 2270·3).
Menopausal vasomotor symptoms; vulval and vaginal atrophy; female hypogonadism; female castration; primary ovarian failure; breast cancer; prostatic cancer; menopausal disorders.

Menevit *Bayer, Austral.*
Vitamins; minerals; lycopene (p. 2546·2); garlic oil (p. 2510·3).
Preconceptual dietary supplement for men.

Menflixil *Solara, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Meng An Da *Nhwa, China.*
Ropivacaine mesilate.
Local anaesthesia.

Meng De Kang *Nuo Jin, China.*
⊗Metoprolol tartrate (p. 1434·3).

Meng Ling Kang *Lanzhou Bio, China.*
A meningococcal vaccine (group A and C) (p. 2401·3).
Active immunisation.

Meng Luo Ying *Baiyunshan, China.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Meng Qing *Ke Lun, China.*
Aceglutamide (p. 2426·2).

Mengaptrix *Helm, Port.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Mengdaqing *Minsheng, China.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure; oedema; ascites.

Mengdexin *Standard Chem & Pharm, China.*
Cefamandole nafate (p. 236·2).
Bacterial infections.

Mengen *Novagen, S.Afr.*
Metformin (p. 489·1).
Diabetes mellitus.

Mengy *Daksh, India.*
⊗Glycerol (p. 2517·2); mannitol (p. 1427·3).

MenHibrix *GSK, USA.*
A meningococcal (groups C and Y) and haemophilus influenzae vaccine (p. 2388·1).
Active immunisation.

Meni *FDC, India.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Meni-D *Seatrace, USA.†*
Meclozine hydrochloride (p. 634·3).
Motion sickness; vertigo.

Meni-drops *Farmex, Gr.*
Ketotifen fumarate (p. 631·3).

Meniero *Jean-Marie, Hong Kong.†*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Meniex *Fortbenton, Arg.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Menifar *Nafar, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Menin *Novell, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

MeningACon *Lu Zhu, China.*
A meningococcal vaccine (group A and C) (p. 2401·3).
Active immunisation.

Meningitec *Pfizer, Austral.; Wyeth Lederle, Austria†; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Wyeth, Gr.; Wyeth, Hung.; Pfizer, Irl.; Wyeth Lederle, Ital.; Pfizer, Neth.; Wyeth, Norw.†; Pfizer, NZ; Pfizer, Pol.; Wyeth Lederle, Port.; Wyeth, Spain; Pfizer, Switz.; Wyeth, UK.*
A meningococcal C conjugate vaccine (diphtheria CRM_{197} protein conjugate) (p. 2401·3).
Active immunisation.

Meningo A+C *Sanofi Pasteur, Chile†; Sanofi Pasteur, China; Sanofi Pasteur, Hung.*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Meningokokken-Impfstoff A + C *Sanofi Pasteur, Ger.*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Meningovax A+C *Sanofi Pasteur, Denm.†; Sanofi Pasteur, Fin.†; Sanofi Pasteur, Neth.†; Sanofi Pasteur, Norw.†; Sanofi Pasteur, Swed.†*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Meninvact *Sanofi Pasteur, Fr.†; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Neth.†*
A meningococcal C conjugate vaccine (diphtheria CRM_{197} protein conjugate) (p. 2401·3).
Active immunisation.

Menisole *Atlantic, Thai.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Menitorix *GSK, Irl.; GSK, UK.*
A haemophilus influenzae and meningococcal C conjugate vaccine (tetanus toxoid conjugate) (p. 2388·1).
Active immunisation.

Menizol *Valmor, Venez.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Menjugate *Novartis, Arg.; CSL, Austral.; Novartis, Austria; Sanofi Pasteur, Belg.; Novartis, Canad.; Novartis Vaccines, Cz.; Chiron, Denm.; Novartis Vaccines, Fin.†; Novartis Vaccines, Fr.; Novartis Vaccines, Ger.; Novartis, Gr.; Novartis Vaccines, Hung.; Novartis, Irl.; Novartis Vaccines, Ital.; Novartis Vaccines, Neth.; Novartis Vaccines, Port.; Novartis Vaccines, Spain; Novartis, Switz.; Chiron, UK.*
A meningococcal C conjugate vaccine (diphtheria CRM_{197} protein conjugate) (p. 2401·3).
Active immunisation.

Meno Support Plus *Golden Glow, Austral.*
Cimicifuga (p. 2478·1); soya isoflavones (p. 2620·3); damiana (p. 2491·3); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); colecalciferol (p. 2113·1).
Menopausal disorders.

Menobarb *Milano, Thai.†*
Phenobarbital sodium (p. 535·3).
Epilepsy; sedative; insomnia.

Menocal
Note: this name may be used for preparations of different composition.
Nutri-Source, Canad.†
Vitamins; minerals.

Menocalm *Bunker, Braz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Ménocéane *Thalgo, Fr.†*
Calciomer (marine complex containing calcium and iodine); soya isoflavones (p. 2620·3); colecalciferol (p. 2113·1).
Menopausal disorders.

Menocimed *Cimed, Braz.†*
Cimicifuga (p. 2478·1).

Menoclim
Note: this name may be used for preparations of different composition.
Beta, Arg.
Estriol (p. 2274·3).
Menopausal vulvovaginal atrophy; aid in diagnosis of cervical disorders.

Korhispana, Spain.†
Soya (p. 2092·3).
Menopausal disorders.

Menocol *Multilab, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

MenoCool *Bioplanta, UK.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Menoctyl *Menarini, India.*
Otilonium bromide (p. 2578·2).
Antispasmodic.

Meno-cyl L Ho-Len-Complex *Liebermann, Ger.*
Chamomilla (p. 2474·1); jaborandi; sanguinaria (p. 2610·1); sepia (p. 2613·1).
Homoeopathic preparation.

Menodac *Zydus, India.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Male and female infertility.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Menodoron *Weleda, Austria; Weleda, Ger.; Weleda, S. Afr.†; Weledo, Switz.*
Shepherd's purse (p. 2614·2); majorana fructus (p. 2550·1); achillea (p. 2427·3); oak bark (p. 2574·1); urtica (p. 2639·3).
Menstrual disorders.

Weleda, UK.
Shepherd's purse (p. 2614·2); majorana; achillea (p. 2427·3); oak; urtica (p. 2639·3).
Homoeopathic preparation.

Menoease *Pharmed, India.*
Vitamins; minerals; trace elements; soya isoflavones (p. 2620·3).

Menofem *Boehringer Ingelheim, Arg.; Bionorica, Cz.; Boehringer Ingelheim, Pol.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Menofit
Note: this name may be used for preparations of different composition.
Ajanta, India.
Aminobenzoic acid (p. 1694·2); carotenoids (p. 2176·2); vitamins; minerals.

Naturland, Hung.
Achillea (p. 2427·3); melissa (p. 2552·3); coriander (p. 2486·3); couch-grass (p. 2487·2); tea (p. 2648·2).
Menstrual disorders.

Menoflav *Zydus, India.*
Isoflavones (p. 2620·3).

Menoflavon *Cedar Health, UK.*
Red clover (p. 2482·1).
Menopausal disorders.

Menofloks *Nevzat, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

Menoflush *Pharmaceutical Enterprises, S.Afr.*
Ethinylestradiol (p. 2275·3); vitamins.
Menopausal disorders.

Menoforce Sage *Bioforce, UK.*
Sage (p. 2608·3).
Menopausal flushing.

Menogia *Gufic, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Menogia-MF *Gufic, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Menogon *Ferring, Cz.; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, India; Ferring, Israel; Ferring, Ital.; Ferring, Neth.†; Ferring, Philipp.; Ferring, Rus.†; Ferring, Singapore; Ferring, Thai.; Er-Kim, Turk.; Ferring, Ukr.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

Menograine *Aspen, S.Afr.*
Clonidine hydrochloride (p. 1339·1).
Migraine; menopausal flushing.

Menoguard *Ind-Swift, India.*
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Menoherb *MedicHerb, UK.*
Cimicifuga (p. 2478·1).
Menopausal symptoms.

Meno-Implant *Organon, Belg.; Organon, Neth.*
Estradiol (p. 2271·1).
Oestrogen deficiency; menopausal disorders.

Menoinfex *Sandoz, Cz.*
Meropenem (p. 321·3).
Bacterial infections.

Menol *Cyno, India.*
Vitamin B substances (p. 2102·3).

Menolia *Sunthi Sepuri, Indon.†*
Avena (p. 2451·1); saw palmetto (p. 2363·3); damiana (p. 2491·3); ginseng (p. 2513·3); arginine (p. 2049·1).
Nutritional supplement.

Menolife *Life Medicare, India.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Male and female infertility.

Menolistica *Holistica, Fr.*
Borage oil (p. 2459·2); yam (p. 2648·1); sunflower oil (p. 2098·1); fucus (p. 2612·1); fish oil (p. 1460·1); ulva lactuca; olive oil (p. 2575·1); beeswax (p. 2170·2); vitamin E (p. 2119·1).
Menopausal disorders.

Menol-Plus *Cyno, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

MenoMed *Bioforce, Switz.*
Sage (p. 2608·3).
Menopausal disorders.

Menomood *Schwabe, UK.*
St John's wort (p. 449·1); cimicifuga (p. 2478·1).
Menopausal disorders.

Menomune *Sanofi Pasteur, Arg.; Sanofi Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Fr.†; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Malaysia; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Singapore†; Sanofi Pasteur, Thai.; Sanofi Pasteur, USA.*
A meningococcal polysaccharide vaccine (groups A, C, W_{135}, and Y) (p. 2401·3).
Active immunisation.

Menonys *Uni-Sankyo, India.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Male and female infertility.

Menop *Ativus, Braz.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Menopace *Meyer, India.*
Vitamins; minerals; trace elements; aminobenzoic acid (p. 1694·2).

Vitabiotics, Hong Kong; Vitabiotics, Indon.; Nobel, Turk.; Vitabiotics, UK; Vitabiotics, Ukr.
Vitamins; minerals.
Menopausal disorders.

Vitabiotics, Cz.; Vitabiotics, Rus.
Vitamins; minerals; trace elements.
Menopausal disorders.

Menopace Iso *Meyer, India.*
Vitamins; minerals; trace elements; aminobenzoic acid (p. 1694·2); soya isoflavones (p. 2620·3).

Menopause
Note: this name may be used for preparations of different composition.
Homeocan, Canad.
Amyl nitrosum (p. 1540·2); aurum metallicum (p. 2521·1); bryonia (p. 2461·3); lachesis mutus (p. 2538·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Menopause L122 *Homeocan, Canad.*
Bryonia (p. 2461·3); cactus grandiflorus (p. 2473·2); glonoinum (p. 1391·2); potassium carb (p. 2595·2).
Homoeopathic preparation.

Menopause Relief *Herbal Concepts, UK.*
Tilia (p. 2631·3); motherwort (p. 2564·2); pulsatilla (p. 2600·2); valerian (p. 2640·2).
Menopausal disorders.

Menopause Test *Electramed, Irl.†*
Test for raised FSH in urine.

Menopause Tincture *Swiss Herbal, UK.*
Paeonia lactiflora.
Menopausal flushing.

Menopax *Ache, Braz.*
⊗Cyclofenil (p. 2261·2).
Menopausal disorders.

Menopret *Bionorica, UK.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Menoprin *Mabra, Braz.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Meno-Pro *British Biologicals, India.*
Preparation for enteral nutrition.

Menopur *Ferring, Arg.; Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Gynopharm, Chile; Ferring, China; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, India; Ferring, Irl.; Ferring, Israel; Ferring, Malaysia; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Port.; Ferring, Rus.; Ferring, S.Afr.; Ferring, Singapore; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, Thai.; Ferring, Turk.; Ferring, UK; Ferring, Ukr.; Ferring, USA.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

Menorest
Note: this name may be used for preparations of different composition.
Novartis, Austral.†; Novartis, Austria†; Novartis, Gr.
Estradiol (p. 2271·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Renata, Philipp.
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Menor-N *Evacare, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Menosan
Note: this name may be used for preparations of different composition.
Himalaya Herbal, India.
Asparagus racemosus (p. 2614·2); centella (p. 1698·3); liquorice (p. 1853·2); terminalia chebula (p. 2474·3).

Bioforce, Switz.†
⊗Agnus castus (p. 2432·2); cimicifuga racemosa (p. 2478·1); ignatia amara (p. 2532·1); lachesis muta (p. 2538·3); sanguinaria canadensis (p. 2610·1); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

Menose *Kalbe, Indon.*
Cimicifuga (p. 2478·1); lactoval; oxitriptan (p. 440·3).
Menopausal disorders; osteoporosis.

Menosoft *Elnova, India.*
Alfacalcidol (p. 2112·3); calcium citrate (p. 1783·2); copper sulfate (p. 2057·2); magnesium oxide (p. 1857·3); soya isoflavones (p. 2620·3); zinc oxide (p. 1729·1).

Menosor *TP, Thai.*
Mebeverine hydrochloride (p. 1858·3).
Smooth muscle spasm.

Menosoy
Note: this name may be used for preparations of different composition.
Midsona, Swed.
Soya isoflavone (p. 2620·3).
Menopausal disorders.

Sterling, India.
Vitamins; minerals; soya isoflavones (p. 2620·3).

Menospan-MF *Abbott, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Menostar *iNova, Singapore; Berlex, USA.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Menostat
Note: this name may be used for preparations of different composition.
East West, India.
Etamsylate (p. 1145·2); tranexamic acid (p. 1164·2).

Medifarm, Venez.
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis; dysfunctional uterine bleeding; lactation inhibition.

Menostress
Note: this name may be used for preparations of different composition.
Arrow, Braz.
Diazepam (p. 1063·2).
Anxiety.

Menotec *United Biotech, India.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Male and female infertility.

Menotensil *Abbott, Braz.*
Chlordiazepoxide (p. 1044·2); conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Menotran *East West, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Menovac *Finlay, Philipp.*
A meningococcal vaccine (p. 2401·3).
Active immunisation.

Menovalen *Borshchagovskii, Ukr.*
Lipophilic complexes of valerian (p. 2640·2) and peppermint (p. 1877·1).
Nervous disorders; sleep disorders.

Menovasan *Vishpha, Ukr.*
Menthol (p. 2553·2); procaine hydrochloride (p. 1994·3); benzocaine (p. 1980·2).
Skin disorders with itching, neuralgia, myalgia, arthralgia.

Menovasin *Yaroslavl, Rus.*
Menthol (p. 2553·2); procaine (p. 1994·3); benzocaine (p. 1980·2).
Neuralgia; myalgia; arthralgia; pruritus.

Menovis *Teofarma, Ital.*
Estradiol benzoate (p. 2271·1); progesterone (p. 2300·2).
Menstrual disorders.

Menovit
Note: this name may be used for preparations of different composition.
Chemech, India.
Vitamins; calcium carbonate (p. 1824·3); protein.

Psychotropics, India.
Vitamins; minerals; trace elements.

Menovul *Bushnell, India.*
⊗Human menopausal gonadotrophins (p. 2284·1).
Male and female infertility.

Menoxa *Soho, Indon.†*
Cimicifuga (p. 2478·1); calcium (p. 1783·1); colecalciferol (p. 2113·1).
Menopausal disorders.

Menoxiton *Royton, Braz.*
Meloxicam (p. 86·3).

Menoxy-N *Pharmatech, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Men-Phor *Geritrex, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Dry skin; pruritus.

Menpoz *Jean-Marie, Philipp.†*
Conjugated oestrogens (p. 2260·1).
Menopausal symptoms; osteoporosis; female hypogonadism; dysfunctional uterine bleeding; prostatic cancer.

Men's *Natural Factors, Canad.†*
Vitamins; minerals.

Men's 50+ *Natural Factors, Canad.†*
Vitamins; minerals.

Mens Dual-Action Multi *Bioglan, Austral.*
Vitamins; minerals; citrus bioflavonoids (p. 2505·2); tomato; bacopa (p. 2452·1); saw palmetto (p. 2363·3); Siberian ginseng (p. 2614·3); ginkgo biloba (p. 2512·3).
Dietary supplement; tonic.

Mens Performance Multi *Blackmores, Austral.*
⊗Vitamins; minerals; damiana (p. 2491·3); tribulus terrestris (p. 2633·3); ginkgo biloba (p. 2512·3); milk thistle (p. 1561·1).
Dietary supplement.

Mens Super Soy/Clover *Bioglan, Austral.†*
Red clover (p. 2482·1); soya bean (p. 2092·3); saw palmetto (p. 2363·3); damiana (p. 2491·3); calcium hydrogen phosphate (p. 1783·3).
Male menopausal disorders.

Mensalgin *Chobet, Arg.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Mensapex *Sandoz, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Mensesyl *Biropharma, Hung.*
Achillea (p. 2427·3); melissa (p. 2552·3); peppermint (p. 1877·1); betula (p. 2457·3); crataegus (p. 2488·1); fennel (p. 2503·2); St John's wort (p. 449·1).
Menstrual disorders.

Mensifem *Rhein, Mex.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Mensil-N *Biomiicron, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Mensipox *Meprofarm, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Mensoton *Berlin-Chemie, Ger.*
Ibuprofen (p. 68·2).
Pain; fever.

Menstrogen *Organon, Arg.†*
Estradiol benzoate (p. 2271·1); progesterone (p. 2300·2).
Amenorrhoea.

Menstrual Midol *Bayer Consumer, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); mepyramine maleate (p. 635·1).

Menstruasan *Bioforce, Switz.*
Aristolochia clematis (p. 2447·1); cimicifuga racemosa (p. 2478·1); lachesis mutus (p. 2538·3); potentilla anserina; pulsatilla pratensis (p. 2600·2); cyclamen europaeum (p. 2490·2).
Homoeopathic preparation.

Mentachol *Roer, Hung.*
Menthol (p. 2553·2); peppermint oil (p. 1877·1).
Digestive disorders.

Mentadem *Torrent, India.*
Memantine hydrochloride (p. 393·1).

Mental Alertness *Homeocan, Canad.*
Gelsemium sempervirens (p. 2511·2); phosphoricum acidum (p. 2589·1); picricum acidum (p. 2634·2); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Mental Fort *New Life, Arg.*
Amino acids; vitamins; trace elements.
Dietary supplement.

Mentalgina
Note: this name may be used for preparations of different composition.
Novartis, Mex.
Cetylpyridinium chloride (p. 1743·1); oxybuprocaine hydrochloride (p. 1993·2).
Mouth and throat disorders.

Mentalium *Soho, Indon.†*
Diazepam (p. 1063·2).
Anxiety; psychoses.

Mentaliv *Apsen, Braz.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome; digestive disorders.

Mentalol
Note: this name may be used for preparations of different composition.
Farmo Quimica, Chile.
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion; skin irritation.

Mentamida *Kin, Spain.†*
Benzydamine hydrochloride (p. 29·2); hexetidine (p. 1755·1).
Mouth and throat inflammation.

Mentania *Saval, Chile.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Mental function impairment.

Mentar *Hoe, Malaysia.*
Coal tar (p. 1723·2); menthol (p. 2553·2).
Scalp disorders.

Mentat *Himalaya Herbal, India.*
Centella (p. 1698·3); elettaria cardamomum; fennel (p. 2503·2); nutmeg (p. 2573·1); syzygium aromaticum; terminalia chebula (p. 2474·3); tinospora cordifolia; withania somnifera (p. 2450·2); zingiber officinale.

Mentax *Perrigo, Israel; Kaken, Jpn; Mylan, USA.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Mentha Lip Balm *Bath & Body Works, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Menthacin *Mentholatum, Canad.; Mentholatum, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2).
Arthritis; joint pain.

Menthoderm *Pharmaceutica North America, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Menthodex *Bell, UK·*
Ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Coughs.

Menthol & Wintergreen *Ovelle, Irl.*
Methyl salicylate (p. 92·1); levomenthol (p. 2553·2); capsicum oleoresin (p. 2469·3); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain.

Mentholatum *Mentholatum, Rus.*
Camphor (p. 2466·2); levomenthol (p. 2553·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2).

Vianex (Вианекс), Gr.
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Cold symptoms; respiratory-tract congestion.

Mentholatum Balm *Mentholatum, Israel.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1).
Cold symptoms; nasal congestion; hayfever.

Mentholatum Balm NF *Mentholatum, S.Afr.†*
Camphor (p. 2466·2); menthol (p. 2553·2).
Upper respiratory-tract disorders.

Mentholatum Calorub Parche *Hofmann, Chile.*
Methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Mentholatum Cherry Chest Rub *Mentholatum, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Coughs and cold symptoms.

Mentholatum Cherry Ice *Mentholatum, USA.*
SPF 11: Padimate O (p. 1716·1); dimethicone (p. 2209·3).
Dry lips; sunscreen.

Mentholatum Ibuprofen *Mentholatum, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders.

Mentholatum Inhalador *Hofmann, Chile.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); pine oil (p. 2591·1).
Upper respiratory-tract congestion.

Mentholatum Kids *Hofmann, Chile.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Upper respiratory-tract congestion; skin irritation.

Mentholatum Natural Ice *Mentholatum, USA.*
SPF 14: Padimate O (p. 1716·1); dimethicone (p. 2209·3).
Dry lips; sunscreen.

Mentholatum Natural Ice Lip Protectant *Mentholatum, USA.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Dry lips.

Mentholatum Ointment *Hofmann, Chile.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion; skin irritation.

Mentholatum, USA.
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Coughs and cold symptoms.

Mentholatum Patch *Hofmann, Chile.*
Menthol (p. 2553·2).
Musculoskeletal pain.

Mentholatum Rub *Mentholatum, Hung.*
Levomenthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); pine oil (p. 2591·1).
Cold symptoms; musculoskeletal and joint pain.

Mentholatum, UK.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1); methyl salicylate (p. 92·1).
Cold symptoms; catarrh; hay fever; musculoskeletal and joint disorders; minor skin disorders.

Mentholatum Softlips *Mentholatum, USA.*
Dimeticone (p. 2209·3).
Dry lips.

Mentholatum Softlips Lipbalm *Mentholatum, USA.*
Dimethicone (p. 2209·3); padimate O (p. 1716·1).
Dry lips.

Mentholatum Softlips Lipbalm (UV) *Mentholatum, USA.*
Octinoxate (p. 1715·1); padimate O (p. 1716·1); oxybenzone (p. 1715·3); dimethicone (p. 2209·3).
Dry lips; sunscreen.

Mentholatum Toothache Kit *Mentholatum, Israel.*
Eugenol (p. 2501·2).
Toothache.

Mentholatum Vapour Rub *Mentholatum, UK.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Nasal congestion; musculoskeletal, joint, and soft-tissue pain; skin irritation.

Mentholaxin *Farmina, Pol.*
Liquid paraffin (p. 2191·2).
Constipation.

Mentholon Original *Schoning-Berlin, Ger.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Catarrh.

Mentho-Paraffinol *Aflofarm, Pol.; Gemi, Pol.; Hasco-Lek, Pol.*
Peppermint oil (p. 1877·1); liquid paraffin (p. 2191·2).
Constipation.

Menthose *Pasteur, Chile.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); methyl salicylate (p. 92·1).
Mucous membrane inflammation; musculoskeletal pain; soft-tissue injury.

Menthosept *Polfa Lodz, Pol.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders; oral hygiene.

Menticol *Proula, Venez.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Mentidose *Faran, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Mentil *Rivan, Hung.*
Peppermint oil (p. 1877·1).
Upper respiratory-tract disorders; digestive disorders; musculoskeletal and joint pain.

Mentimol *Olgunsoy, Turk.*
Ointment: Menthol (p. 2553·2); camphor (p. 2466·2); cineole (p. 2479·1); thymol (p. 1772·2).
Musculoskeletal and joint pain.

Olgunsoy, Turk.†
Pastilles: Menthol (p. 2553·2); vitamin C (p. 2110·3); cineole (p. 2479·1).
Mouth and throat disorders; musculoskeletal and joint pain.

Mentis *Menarini, Spain.*
Pirisudanol maleate (p. 2592·2).
Cerebrovascular impairment; senile dementia.

Mentix *Royal, Chile.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Mentixa *HCS, Fin.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Mentobalsam *Farmo Quimica, Chile.†*
Methyl salicylate (p. 92·1); methyl nicotinate (p. 91·3); a macrogol lauril ether (p. 2193·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain; soft-tissue disorders.

Mentobox *Serra Pamies, Spain.*
Ointment: Camphor (p. 2466·2); cedrus deodora oil; cineole (p. 2479·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); turpentine; menthol (p. 2553·2).
Upper respiratory-tract disorders.

Mentocaina R *Azevedos, Port.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Ment-O-Cap *Rekah, Israel.†*
Turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); capsicum (p. 2469·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Cold symptoms; musculoskeletal and joint disorders.

Mentofer *Signova, India.*
Asparagus racemosus (p. 2614·2); liquorice (p. 1853·2); withania somnifera (p. 2450·2).

Mentolift *Symbiotic, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Mentolift-Plus *Symbiotic, India.*
Alprazolam (p. 1035·2); sertraline (p. 448·1).

Mentolin *Mento, Turk.*
Menthol (p. 2553·2); camphor (p. 2466·2); cineole (p. 2479·1); thymol (p. 1772·2).
Musculoskeletal and joint pain; respiratory-tract disorders; mouth and throat disorders.

Mentopas *Sin Sin, Philipp.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); thymol (p. 1772·2); borneol (p. 2460·2); zinc oxide (p. 1729·1).
Musculoskeletal and joint pain.

Mentopin
Note: this name may be used for preparations of different composition.
Genesis, Turk.
Acetylcysteine (p. 1652·2).
Respiratory disorders with increased mucus; paracetamol poisoning.

Mentoseptol *Drogsan, Turk.*
Menthol (p. 2553·2); cineole (p. 2479·1); peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Oral hygiene.

Mentowal *Polpharma, Pol.*
Menthyl isovalerate (p. 2554·1).
Gastrointestinal disorders; vertigo; migraine.

Mentra *Zydus, India.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Mentvis *Baif, Ital.*
Ginkgo biloba (p. 2512·3); myrtillus (p. 2566·2); alga klamath; rosa canina; vitamins; red wine.
Dietary supplement for maintaining mental function.

Menuvit *Finecure, India.*
Vitamins; minerals.

Menuvit-P *Finecure, India.*
Preparation for enteral nutrition.

Menveo *Novartis, Arg.; CSL Biotherapies, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis Vaccines, Cz.; Novartis, Denm.; Novartis Vaccines, Fr.; Novartis Vaccines, Ger.; Novartis, Gr.; Novartis Vaccines, Irl.; Novartis, Israel; Novartis Vaccines, Neth.; Novartis, Norw.; Novartis Vaccines, Pol.; Novartis Vaccines, Port.; Novartis Vaccines, Spain; Novartis, Swed.; Novartis, UK; Novartis Vaccines, USA.*
A meningococcal vaccine (groups A, C, W-135, and Y) (p. 2401·3).
Active immunisation.

Menwayc *Lu Zhu, China.*
A meningococcal vaccine (groups A, C, W135, and Y) (p. 2401·3).
Active immunisation.

MeNZB *Novartis, NZ.†*
A meningococcal B (outer membrane vesicle) vaccine (p. 2401·3).
Active immunisation.

Menzol
Note: this name may be used for preparations of different composition.
Menarini, India.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Menzza *Hoe, Malaysia.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Menzza Ice *Hoe, Malaysia.*
Menthol (p. 2553·2).
Musculoskeletal pain.

Menzza NP *Hoe, Malaysia.*
Capsaicin (p. 35·1).
Diabetic neuropathy; post-herpetic neuralgia.

Menzza OA *Hoe, Malaysia; Hoe, Singapore.*
Capsaicin (p. 35·1).
Osteoarthritis.

Meocil *Edol, Port.*
⊗Prednisolone acetate (p. 1645·2); neomycin sulfate (p. 330·1); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Meomel *Rafarm, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

282 MEP *Pendopharm, Canad.†*
Aspirin (p. 22·2); caffeine citrate (p. 1203·3); codeine phosphate (p. 40·2); meprobamate (p. 1083·3).
Pain; skeletal muscle spasm.

Mepa *Mega Lifesciences, Malaysia.†*
Fish oil (p. 1460·3).
Dietary supplement.

Mepact *IDM, Austria; IDM, Cz.; IDM, Denm.; Takeda, Ger.; IDM, Gr.; Takeda, Irl.; Medison, Israel; IDM, Ital.; IDM, Neth.; IDM, Norw.; IDM, Pol.; IDM, Port.; IDM, Spain; Takeda, Swed.; Takeda, Switz.; Takeda, UK.*
Mifamurtide (p. 829·1).
Osteosarcoma.

Mepacyl *Pierre Rolland, Fr.*
⊗Dexamethasone acetate (p. 1631·1); *m*-cresyl acetate (p. 1749·1); parachlorophenol (p. 1763·1).
Root canal infections.

Mepadol *Drogsan, Turk.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

Mepagyl *TNP, Thai.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; anaerobic bacterial infections.

Mepalex *Lexica, India.*
Mefloquine (p. 657·1).
Malaria.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mepar *East West, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Meparin *Medchem, Philipp.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Mepastat *Orion, Fin.†*
Medroxyprogesterone acetate (p. 2288·1).
Endometrial cancer; breast cancer; prostatic cancer.

Mepcef *Alna, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Mepcin *Alna, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mep-Con *Alna, India.*
Carmellose (p. 2175·1).
Dry eyes.

Mepebrox *Medica Pedia, Philipp.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mepef-S *Alna, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Mepem *Sumitomo, China.*
Meropenem (p. 321·3).
Bacterial infections.

Mepenam *Arterium, Ukr.*
Meropenem (p. 321·3).
Bacterial infections.

Mepenem *Pharmawealth, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Mepenox *Biochimico, Braz.*
Meropenem (p. 321·3).

Mepereost *Sandoz, Ital.; Sandoz, Neth.; Sandoz, Pol.*
Meropenem (p. 321·3).
Bacterial infections.

Meperol *LKM, Arg.*
⊗Pethidine hydrochloride (p. 121·3).
Pain.

Mep-Fluron *Alna, India.*
⊗Fluorometholone (p. 1637·2).

Mep-Fovea *Alna, India.*
Flurbiprofen sodium (p. 65·3).
Prevention of miosis during ocular surgery; inflammation following eye surgery.

Mepha B *Mepha, Israel.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Mephadolor *Mepha, Switz.*
Mefenamic acid (p. 85·3).
Pain; fever.

Mephamésone *Mepha, Switz.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Mephanol *Mepha, Switz.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Mephaquin *Nova, Braz.; IFET (ΙΦΕΤ), Gr.; Mepha, Hong Kong; Mepha, Israel†; Mepha, Malaysia; Mepha, Port.; Mepha, Singapore; Mepha, Ukr.†*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Mephaquine *Mepha, Switz.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Mepharis *Mepha, Pol.†*
Risperidone (p. 1103·2).
Schizophrenia.

Mephathiol *Mepha, Switz.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased mucus.

Mephenon *Sterop, Belg.*
⊗Methadone hydrochloride (p. 88·3).
Pain.

Mephentine *Wyeth, India.*
⊗Mephentermine sulfate (p. 1429·3).
Shock.

Mephy *Lincoln, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Mephyton *Valeant, USA.*
Phytomenadione (p. 2122·2).
Coagulation disorders due to faulty formation of factors II, VII, IX, and X.

Mepibil *Hospira, Ital.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mepicain *Monico, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepicaton *Hong Kong Medical, Hong Kong†; Gramse, Israel†; Weimer, Thai.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mepident *Cosmo, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepiforan *Baxter, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepiform *Molnlycke, Austral.; Molnlycke, Ger.; Molnlycke, Ital.; Molnlycke, UK.*
Silicone (p. 2209·2).
Hypertrophic and keloid scars.

Mepigobbi *Gobbi, Arg.*
Mepivacaine (p. 1992·2).
Local anaesthesia.

Mepihexal *Hexal, Ger.†*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mepik *Aarpik, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mepilex *Molnlycke, Belg.*
A polyurethane dressing (p. 1718·1).
Wounds.

Molnlycke, Ger.
Silicone (p. 2209·2).
Wounds; ulcers.

Mepilex Ag *Molnlycke, Ger.*
Polyurethane dressing with silver sulfate; activated charcoal (p. 1537·3).
Infected wounds.

Mepilex Border Ag *Molnlycke, Ger.*
Polyurethane dressing with silver sulfate.
Infected wounds.

Mepi-Mynol *Curaden, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepinaest *Gebro, Austria.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mepirid *Vocate, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Mepiriks *Bilim, Turk.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Mepirilid *Combiphar, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Mepiritev *Teva, Mex.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Mepisolver *AltaSelect, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepitel *Molnlycke, Belg.; Molnlycke, Ger.; Molnlycke, Ital.*
Silicone (p. 2209·2).
Wounds; ulcers; burns.

Mepivakate *Adipharm, Gr.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mepivamol *Molteni, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthetic.

Mepivastesin *3M Espe, Cz.; 3M, Ger.; 3M, Gr.; 3M, Hong Kong; 3M, Israel; Machado Malcher, Port.; 3M, Rus.; iNova, Singapore.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Mepivirgi *Fisiopharma, Ital.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthetic.

Mepi-Welk *Combustin, Ger.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Meplar *Baliarda, Arg.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Me-Plus *Systopic, India.*
Chromium tripicolinate (p. 2056·1); folic acid (p. 2063·1); thioctic acid (p. 2629·1); pyridoxine hydrochloride (p. 2105·3); selenium (p. 2086·3).

Mepodox *Globus, India.*
Cefpodoxime.
Bacterial infections.

Mepol *Taurus, India.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Mep-Orva *Alna, India.*
Ofloxacin (p. 334·3).
Bacterial conjunctivitis; corneal ulcer.

Mepracid *Nabiqasim, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mepral *Bracco, Ital.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Mepralin *Euro Generics, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; dyspepsia; Zollinger-Ellison syndrome.

Mepramida *Roemmers Rowe, Venez.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Mepramide *Pyridam, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Mepramin *UCI, Braz.*
Imipramine hydrochloride (p. 426·2).

Meprate
Note: this name may be used for preparations of different composition.
Serum Institute, India.
Medroxyprogesterone acetate (p. 2288·1).
Menstrual disorders; endometriosis.

Mepraz
Note: this name may be used for preparations of different composition.
YSS, Philipp.; Baldacci, Port.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Globus, India.
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Meprazan *Cazi, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Mepraz-D *Globus, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Meprazol *Sandoz, Austral.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mepred *Nitro Organics, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Mepresone *Dexa, Philipp.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Mepride-M *Globus, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Mepril *Kwizda, Austria.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left ventricular dysfunction.

Meprilon *Mugi, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Meprizina *Pisa, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Mepro *Rekah, Israel.*
Meprobamate (p. 1083·3).
Anxiety; insomnia.

Méprodil *Streuli, Switz.†*
Meprobamate (p. 1083·3).
Anxiety; sedative; muscle relaxant.

Meprogesic *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); meprobamate (p. 1083·3).
Pain and associated tension.

Meprolen *Vocate, Gr.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).

Meprolol
Note: this name may be used for preparations of different composition.
Adeka, Turk.
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).

TAD, Ger.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; ischaemic heart disease; myocardial infarction; arrhythmias; migraine.

Mepromaag *Meprofarm, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastro-oesophageal reflux; gastric hyperacidity; gastritis; hiatus hernia; peptic ulcer.

Mepromol *Adcock Ingram, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Adcock Ingram, S.Afr.†
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Fever; pain.

Mepron *GSK, Canad.; Glaxo Wellcome, USA.*
Atovaquone (p. 928·2).
Pneumocystis pneumonia.

Mepronet *Nycomed, Denm.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; myocardial infarction; tremor.

Mépronizine *Sanofi-Aventis, Fr.†*
Meprobamate (p. 1083·3); acepromazine maleate (p. 1035·2).
Insomnia.

Meprosetil *Meprofarm, Indon.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; behaviour disorders; vomiting; hiccups.

Meprosol *Esma, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Meproson *Meprofarm, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Meprosona-F *Sons, Mex.*
⊗Prednisone (p. 1647·2); phenylbutazone (p. 125·1).
Aluminium hydroxide (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meprotrin *Meprofarm, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Meprozin *UCI, Braz.*
Levomepromazine maleate (p. 1079·3).

Meprozine *Qualitest, USA.†*
⊗Pethidine hydrochloride (p. 121·3); promethazine hydrochloride (p. 638·2).
Pain.

Mepsonate *Gland, India.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Meptid *Riemser, Ger.; Almirall, Irl.; Monmouth, UK.*
Meptazinol hydrochloride (p. 87·3).
Pain.

Meptin *Otsuka, China; Otsuka, Hong Kong; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Malaysia; Otsuka, Philipp.; Otsuka, Singapore; Otsuka, Thai.*
⊗Procaterol hydrochloride (p. 1219·1).
Obstructive airways disease.

Meptrop *Alna, India.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Meptrop-P *Alna, India.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).

Mepusulin *Neiss, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Mepycep *Alna, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Mepyraderm *Be-Tabs, S.Afr.*
Mepyramine maleate (p. 635·1).
Allergic and pruritic skin disorders.

Mepyrimal *Adcock Ingram, S.Afr.*
Mepyramine maleate (p. 635·1).
Allergic and pruritic skin disorders.

Mepyvit-CT *Alna, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Mequin *Atlantic, Thai.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Merabin *Daewoo, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; vitamin B_{12} deficiency.

Meracilina *Ache, Braz.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Meralut *Farmila, Ital.*
Vitamin A (p. 2098·3); anthocyanosides; lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Nutritional supplement.

Meralys *Jadran, Ukr.*
⊗Xylometazoline (p. 1680·1).
Rhinitis; sinusitis; otitis media; aid in nasal investigations.

Premier Research, Neth.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Meramyl *Actavis, Hung.*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction; heart failure; myocardial infarction; nephropathy.

Meramyl HCT *Actavis, Hung.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Merankol Pastiglie *Bruno, Ital.*
Dicycloverine hydrochloride (p. 1834·2); methylcellulose (p. 2197·3); sodium laurilsulfate (p. 2210·3); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastrointestinal disorders.

Merapem *Ranbaxy, Irl.*
Meropenem (p. 321·3).
Bacterial infections.

Merapur HP *Ferring, Mex.*
⊗Menotrophin (p. 2284·1).
Female infertility.

Merasyn *AdcockIngram, S.Afr.†*
Aluminium hydroxide gel (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); methylcellulose (p. 2197·3).
Flatulence; hyperchlorhydria.

Merbenloc *Maigal, Arg.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne; seborrhoea.

Merbentyl *Adcock Ingram, S.Afr.†; Florizel, UK.†*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Merbromin *Biospray, Gr.; Mediplants, Gr.*
Merbromin (p. 1760·1).
Antiseptic.

Mercalm *Hepatoum, Fr.*
Caffeine (p. 1203·3); dimenhydrinate (p. 625·2).
Motion sickness.

Mercaptizol *Taro, Israel.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Mercapto *Chandra Bhagat, India.*
Mercaptopurine (p. 820·3).
Acute lymphocytic leukaemia; Crohn's disease.

Mercaptyl *Abbott, Switz.†*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; heavy-metal poisoning; Wilson's disease; cystinuria; biliary cirrhosis; scleroderma; pulmonary fibrosis.

Mercazolil *Akrikhin, Rus.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Merced *Menarini, Belg.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Mercide *Ranbaxy, S.Afr.*
Meropenem (p. 321·3).

Mercilon *Schering-Plough, Indon.; Organon, Norw.; Adcock Ingram, S.Afr.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Organon, Arg.; Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Organon, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Organon, Irl.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, UK; Organon, Ukr.; Organon, Venez.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Mercilon Conti *Schering-Plough, Braz.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 inert tablets.
Combined oral contraceptive.

Mercina *Merck, Chile.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Mercindol *Sanofi-Aventis, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); doxylamine succinate (p. 627·3); codeine phosphate (p. 40·2).
Pain; fever.

Merck-Cough Linctus *Merck, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Merckenzyme *Merck, India.†*
⊗Bromelains (p. 2460·3); pancreatin (p. 2579·3); ox bile (p. 2457·2).
Pancreatic insufficiency.

Merck-Expectorant *Merck, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Merck-Fed *Goldex, S.Afr.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Merck-Flu *Merck, S.Afr.†*
Capsules: Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Merck, S.Afr.†
Syrup: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Merckformin *Merck, Hung.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mercol *Exakta, Mex.†*
Policosanol (p. 1472·1).
Hypercholesterolaemia.

Mercotin *Eisai, Indon.*
Noscapine (p. 1670·3).
Cough.

Mercromina *Lainco, Spain.*
Merbromin (p. 1760·1).
Wound disinfection.

Mercryl *Menarini, Fr.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Infected skin disorders; wounds.

Mercrylsoins *NHS, Fr.*
Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3).
Skin cleansing and disinfection.

Mercrylspray *Menarini, Fr.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Wound disinfection.

Mercuchrom-Jod *Krewel, Ger.*
Povidone-iodine (p. 1767·1).
Wounds; ulcers; burns; infected skin disorders.

Mercurell *Sanorell, Ger.*
Mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Mercure-Plus *Doctor H, Rus.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); calendulae officinalis (p. 2465·2); echinacea purpurea (p. 2498·1); hamamelis virginiana (p. 2523·3); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Mercurialis zalf *Wala, Neth.*
Allium cepa (p. 2575·2); calendula officinalis (p. 2465·2); mercurialis perennis.
Homoeopathic preparation.

Mercurin *Monik, Spain.†*
Merbromin sodium (p. 1760·1).
Wound disinfection.

Mercurius Cyanatus Complexe No 43 *Lehning, Fr.†*
Echinacea (p. 2498·1); salvia (p. 2608·3); atropa belladonna (p. 2453·3); apis (p. 2445·2); spongia; acidum nitricum (p. 2572·3); kalium bichromicum (p. 2476·3); mercurius cyanatus (p. 2555·3).
Homoeopathic preparation.

Mercurius Solubilis Complexe No 39 *Lehning, Fr.*
Mercurius solubilis (p. 2555·3); aurum muraticum natronatum (p. 2521·2); kalium iodatum (p. 2336·3); natrum nitricum (p. 1769·3); natrum sulfuricum (p. 1888·1); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Mercurius-Heel *Heel, Neth.*
Ailanthus glandulosa; belladonna (p. 2453·3); echinacea angustifolia (p. 2498·1); hepar sulphur (p. 1721·3); lachesis mutus (p. 2538·3); mercurius solubilis (p. 2555·3); phytolacca decandra (p. 2593·2).
Homoeopathic preparation.

Mercurobromo *Arafarma, Spain.†*
Merbromin (p. 1760·1).
Wound disinfection.

Mercurochrome *Zarbi (Ζαρμπη), Gr.*
Merbromin (p. 1760·1).
Antiseptic.

Mercutina Brota *Escaned, Spain.†*
Merbromin (p. 1760·1).
Wound disinfection.

Merdaten *Rafarm, Gr.*
Mirtazapine (p. 436·1).

Merebral *Nycomed, Arg.*
Amino acids; cyanocobalamin (p. 2107·2); ginseng (p. 2513·3).
Mental function impairment.

Merem *Guardian, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Merendal *Biomedica, Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Merenz *Admac, India.*
Meropenem (p. 321·3).
Bacterial infections.

Mereprine
Note: this name may be used for preparations of different composition.
Cassella-med, Ger.†
Doxylamine succinate (p. 627·3).
Allergic disorders; sleep disorders; restlessness and excitement in children.

Meresa *Sanova, Austria†; Dolorgiet, Ger.; Adeka, Turk.*
Sulpiride (p. 1107·3).
Schizophrenia; depression; vestibular disorders; psychoses; Ménière's disease.

Meresasul *Sanova, Austria; Dolorgiet, Ger.*
Sulpiride (p. 1107·3).
Depression; vestibular disorders; schizophrenia.

Meretek UBT *Meretek, USA.*
Carbon-13 (p. 2470·3) labelled urea (Pranactin).
Diagnosis of Helicobacter pylori *infection.*

Merex
Note: this name may be used for preparations of different composition.
Intas, India.
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; rheumatoid arthritis; psoriasis; Crohn's disease.

Merexid *Oxford Laboratories, Rus.*
Meropenem (p. 321·3).
Bacterial infections.

Merfen *Novartis Consumer, Israel; Novartis Consumer, Switz.; Novartis, Turk.*
Chlorhexidine gluconate (p. 1743·3); benzoxonium chloride (p. 1739·2).
Wounds; burns; insect bites; skin disinfection.

Merflam *Mersifarma, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Mergexin *Mergers Drugfil, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Mergot *Solvang, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum atony; postpartum haemorrhage.

Mergotrex *Rotexmedica, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum atony; postpartum haemorrhage.

Mergox *BPL, India.*
Methylergometrine (p. 2137·3).
Postpartum and postabortal haemorrhage.

Merical *Plus, India.*
Syrup: Calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1); lysine (p. 2079·3); vitamin B substances (p. 2102·3).

Plus, India.
Tablets: Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Mericart *Merion, India.*
Glucosamine sulfate (p. 2515·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); vitamin E (p. 2119·1).

Mericip *Merion, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Mericobal *Merion, India.*
Capsules: Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Merion, India.
Injection: Dexpanthenol (p. 2582·2); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Mericobal-G *Merion, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mericof *Plus, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Mericomb *Novartis, Austria; Novartis, Braz.; Novartis, Fin.†; Novartis, Ger.; Pierre Fabre, Ger.; Novartis, Switz.†*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; norethisterone (p. 2294·2).
Menopausal disorders; hormone replacement therapy; osteoporosis.

Meriday *Servocare, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Meridia *Abbott, Canad.†; Abbott, Cz.†; Abbott, Pol.†; Abbott, Rus.; Abbott, Ukr.†; Abbott, USA.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Meridian *Roemmers, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Meridol
Note: this name may be used for preparations of different composition.
Teva, Israel.
Olaflur (p. 2085·1); stannous fluoride (p. 2094·3).
Dental caries prophylaxis; plaque prophylaxis.

Unimarck, India.
Injection: Tramadol hydrochloride (p. 139·2).
Pain.

Unimarck, India.
Tablets: Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Meridol med CHX *GABA, Ger.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Meridol Perio *GABA, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Bacterial mouth infections; oral hygiene.

Meridol Perio CHX *GABA, Fin.*
Chlorhexidine gluconate (p. 1743·3).
Mouth infections; oral hygiene.

Meridol-D
Note: this name may be used for preparations of different composition.
Unimarck, India.
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Meridone *GPO, Thai.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Meriestra *Novartis, Spain.*
Estradiol valerate (p. 2271·2).
Menopausal disorders; osteoporosis.

Meriflam *Merion, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Meriflox *Wockhardt, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Merigel *Ind-Swift, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Merigel-A *Ind-Swift, India.*
Magaldrate (p. 1856·1); oxetacaine (p. 1993·1); simeticone (p. 1886·2).

Merigest *Novartis, Austria; Novartis, Braz.; Novartis, Fin.†; Novartis, Ger.; Pierre Fabre, Ger.; Novartis, Spain†; Novartis, Switz.†*
Estradiol valerate (p. 2271·2); norethisterone (p. 2294·2).
Menopausal disorders; osteoporosis; hormone replacement therapy.

Merigest Sequi *Novartis, Spain.†*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; norethisterone (p. 2294·2).
Menopausal disorders.

Merimac *Mersifarma, Indon.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Merimono *Novartis, Braz.; Novartis, Fin.†; Novartis, Ger.*
Estradiol valerate (p. 2271·2).
Menopausal disorders; hormone replacement therapy.

Merinfec *Excalibur, Austria.*
Meropenem (p. 321·3).
Bacterial infections.

Merional *IBSA, Cz.; Angelini, Gr.; IBSA, Hong Kong†; IBSA, Hung.; CORNE, Mex.; IBSA, Pol.; IBSA, Switz.; Ali, Turk.; Pharmasure, UK; IBSA, Ukr.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

Merional-HMG *Meizler, Braz.*
⊗Gonadotrophin (p. 2284·1).
Female infertility.

Merip *Wyeth, Singapore.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Meris *Alna, India.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Meris-D *Alna, India.*
⊗Dexamethasone (p. 1630·3); gatifloxacin (p. 303·2).

Merislon *Eisai, China; Eisai, Hong Kong; Eisai, Indon.; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore; Eisai, Thai.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo; vestibular disorders.

Merisoft *Mint, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Merispas *Unimarck, India.*
Injection: Drotaverine hydrochloride (p. 2497·3).
Antispasmodic.

Unimarck, India.
Oral suspension: ⊗Cinnamon oil (p. 2479·3); citric acid monohydrate (p. 2480·3); dill oil (p. 2493·2); fennel oil (p. 2503·3); dimeticone (p. 1886·2); papain (p. 2582·3).

Meristin *Medisan, Hung.*
Tablets: Phenobarbital (p. 535·2); papaverine hydrochloride (p. 2362·3); aminophenazone (p. 21·1).
Smooth muscle spasm and pain.

Merital *Roemmers, Arg.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease; spasticity.

Meritene *Novartis, Braz.; Novartis Nutrition, USA.*
Preparation for enteral nutrition.

Meritene Protein *Nestle, Ital.*
Preparation for enteral nutrition.

Meritor *Ache, Braz.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Merix *Xeno, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Merlin *TO-Chemicals, Thai.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Merlit
Note: this name may be used for preparations of different composition.
Ebewe, Austria.
Lorazepam (p. 1080·3).
Anxiety disorders; sleep disorders.

Leovan, Gr.
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Merlopam *Mersifarma, Indon.*
Lorazepam (p. 1080·3).
Anxiety; depression.

Mermelax *Argenfarma, Arg.*
Prune (p. 1881·1); ispaghula (p. 1849·1); garcinia cambogia (p. 2510·2).
Constipation.

Mermid *Merck, Mex.†*
Dipyrone (p. 53·3).
Pain; fever.

Mero *T Man, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Merobact *Elpen (Ελπεν), Gr.; Invision, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merobat *Interbat, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Merobest *Shreshtha, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merobus *Globus, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merocad *Admac, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merocaine *SSL, Irl.; SSL, UK.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Oral pain; mouth and throat disorders.

Merocef *Mahakam Beta, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Merocets *SSL, Irl.; SSL, UK.*
Cetylpyridinium chloride (p. 1743·1).
Sore throat; mouth and throat irritation; throat infections.

Merocets Plus *SSL, Irl.; SSL, UK.*
Cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Nasal congestion; sore mouth and throat.

Merocrit *Cipla, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merod *Daksh, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meroefectil *Northia, Arg.*
Meropenem (p. 321·3).
Bacterial infections.

Merofact *Medico, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merofen *Kalbe, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Merofit *Fusion, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merokem *Taj, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meroken New *Taro, Israel.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Meromate *Baxter, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meromax *YSS, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Meromer *Orchid, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meromycin *Ratiopharm, Austria; Ratiopharm, Hung.*
Erythromycin (p. 291·2).
Acne; bacterial infections.

Meronem *AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; AstraZeneca, Venez.*
Meropenem (p. 321·3).
Bacterial infections.

Meronis *Neiss, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merop *Biomedis, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Meropam *Osper, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meropen *Sumitomo, Jpn; Swiss Parenterals, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Meropenabol *Abolmed, Rus.*
Meropenem (p. 321·3).
Bacterial infections.

Meropex *Bernofarm, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Meroplan *Abbott, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meropur *Ferring, Ital.*
⊗Menotrophin (p. 2284·1).
Female infertility.

Merosan *Arvincare, India; Sanbe, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Merosid *Kocak, Turk.*
Meropenem (p. 321·3).
Bacterial infections.

Merospect *Chandra Bhagat, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merospira *Hospira, Denm.*
Meropenem (p. 321·3).
Bacterial infections.

Merotec *Zuventus, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merotenk *Biotenk, Arg.*
Meropenem (p. 321·3).
Bacterial infections.

Merotik *Lapi, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Merotop *Sanat, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merotrol *Lupin, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merover *Evershine, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merovia *Remedina, Gr.*
Meropenem (p. 321·3).
Bacterial infections.

Merowor *Worth, India.*
Meropenem (p. 321·3).
Bacterial infections.

Meroxan *Merck, Mex.†*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Meroximer *Actavis, Irl.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Meroza *Zydus, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merozan *Demo, Gr.; Dem, Turk.*
Meropenem (p. 321·3).
Bacterial infections.

Merozen *AstraZeneca, Arg.*
Meropenem (p. 321·3).
Bacterial infections.

Merozyme-C *Plus, India.*
⊗Alpha-amylase (p. 2442·1); anise oil (p. 2444·3); caraway oil (p. 2470·3); dill oil (p. 2493·2); papain (p. 2582·3).

Merpal *Prater, Chile.*
Diclofenac diethylamine (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Inflammation; pain.

Merpem *Richmond, Arg.*
Meropenem (p. 321·3).
Bacterial infections.

Merpurin *Union Korea, Philipp.*
Mercaptopurine (p. 820·3).
Leukaemias.

Merrem *AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, NZ; Zeneca, USA.*
Meropenem (p. 321·3).
Bacterial infections.

Merron *Mersifarma, Indon.*
Cinnarizine (p. 622·1).
Vestibular disorders; cerebral and peripheral vascular disorders; motion sickness; migraine.

Mersibion *Mersifarma, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin deficiency; neuritis.

Mersidryl *Mersifarma, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; nasal congestion; rhinitis.

Mersikol *Mersifarma, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Mersisol *Sifa, Turk.*
Merbromin (p. 1760·1).
Skin disinfections; burns; wounds.

Mersitropil *Mersifarma, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; behaviour disorders in children; alcoholism.

Mersivas *Mersifarma, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Mersol
Note: this name may be used for preparations of different composition.
Merkez, Turk.
Merbromin (p. 1760·1).
Minor cuts and abrasion.

Century, USA.†
Thiomersal (p. 1771·3).
Skin disinfection.

Mersyndol *Sanofi-Aventis, Austral.; Sanofi-Aventis, NZ.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Fever; pain with tension.

Mersyndol with Codeine *Sanofi-Aventis, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Cold symptoms; pain.

Mersyndol Daystrength *Sanofi-Aventis, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Mertenil *Gedeon Richter, Cz.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias; hypercholesterolaemia; cardiovascular risk reduction.

Merthioclean *Geolab, Braz.*
Chlorhexidine gluconate (p. 1743·3).

Merthiolate
Note: this name may be used for preparations of different composition.
Gramon, Arg.; Lilly, Arg.; Aspen, S.Afr.; Srichand, Thai.; Vargas, Venez.
Thiomersal (p. 1771·3).
Skin disinfection; wounds; fungal skin infections; wound disinfection.

Merthiolate Anestesico *Gramon, Arg.*
Benzalkonium chloride (p. 1737·1); lidocaine hydrochloride (p. 1988·2).
Minor wounds; insect bites.

Merthiolate Film *Gramon, Arg.*
Acrylate copolymer.
Minor wounds.

Merthiolate Iodopovidona *Gramon, Arg.*
Povidone-iodine (p. 1767·1); nonoxinol 9 (p. 2199·1).
Skin and mucous membrane disinfection; burns; wounds.

Merthiolate Nueva Formula *Gramon, Arg.*
Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection; minor wounds.

Mertigo *Dexa, Indon.; Sriprasit, Thai.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Mertioscan *Rotop, Port.*
Technetium-99m (p. 2228·1) mertiatide.
Diagnosis of urinary-tract disorders.

Mertolok *Ratiopharm, Denm.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; heart failure.

Meruvax II *CSL Biotherapies, Austral.; Merck, USA.†*
A rubella vaccine (Wistar RA 27/3 strain) (p. 2417·1).
Active immunisation.

Merxil *Merck, Mex.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Mery *Biosans, India.*
Meropenem (p. 321·3).
Bacterial infections.

Merz Dragées Speciales *Merz, Switz.†*
Vitamins; minerals; dried yeast (p. 2125·2).
Skin, hair, and nail disorders.

Merz Special Dragees *Merz, Ukr.*
Vitamins; ferrous fumarate (p. 2060·3); *Saccharomyces cerevisiae.*
Skin, hair and nail disorders associated with vitamin and iron deficiency.

Merz Spezial *Merz, Pol.*
Iron (p. 2073·1); cystine (p. 2059·1); vitamins.
Skin, hair, and nail disorders.

Ultra, Hung.
Vitamins; cystine (p. 2059·1); ferrous fumarate (p. 2060·3).
Dietary supplement; tonic.

Medra, Austria.†
Vitamins; minerals.

Merz, Cz.†
Vitamins; dried yeast (p. 2125·2); cystine (p. 2059·1); ferrous fumarate (p. 2060·3).

Merz, Hong Kong.†
Vitamins; iron (p. 2073·1); yeast (p. 2125·2); cystine (p. 2059·1).

Merz Spezial Dragees *Merz, Rus.*
Vitamins; ferrous fumarate (p. 2060·3); yeast extract; cystine (p. 2059·1).

Merz Spezial Dragees N *Merz Consumer, Ger.†*
Vitamins; iron (p. 2073·1); acetylmethionine (p. 1558·2).

Merzbiotin *Medra, Austria.†*
Biotin (p. 2052·2).
Hair and nail disorders; biotin deficiency.

Merzen *Zee, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage; management of third-stage labour; uterine bleeding.

Mesacol *Nycomed, Braz.; Sun, India; Sun, Rus.; Sun, Thai.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Mesactol *Sandoz, Arg.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Mesadorin S *Teva Kowa, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Mesaflor *SoSe, Ital.*
Mesalazine (p. 1859·2).
Ulcerative colitis; Crohn's disease.

Mesagin *Kleva, Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Mesagran *Falk, Austria.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Mesalgin *TKS, Braz.*
Nimesulide (p. 101·3).

Mesalt *Molnlycke, Austral.; Molnlycke, Canad.*
Dressing impregnated with sodium chloride (p. 1795·1).
Wounds.

Mesasal *GSK, Austral.; GSK, Canad.; Sanofi-Aventis, Denm.; Falk, Fin.; Sanofi-Aventis, Norw.; Pharmacare, S. Afr.†; Sanofi-Aventis, Swed.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Mesaton *Ukrmedprom, Rus.*
Phenylephrine hydrochloride (p. 1672·3).
Hypotension.

Mesavancol *2care4, Denm.; Giuliani, Neth.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Mesazine *Vifor, Switz.†*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Mesconcept *Northia, Arg.†*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Mescorit *Roche, Ger.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mescryo *Cryopharma, Mex.*
Mesna (p. 1557·2).
Prevention of haemorrhagic cystitis associated with ifosfamide and cyclophosphamide.

Mesehist DM *Trigen, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Mesehist WC *Trigen, USA.*
⊗Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Mesel *Finadiet, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Měsíčkový *Megafyt-R, Cz.†*
Calendula (p. 2465·2).
Gastrointestinal disorders; biliary-tract disorders; inflammation of the skin and mucous membranes.

Mesidox *Merck, Braz.*
Doxazosin (p. 1369·1).

Mesigyna *Bayer, Arg.; Bayer, Braz.; Bayer, Chile; Bayer, Mex.; Schering, Turk.; Schering, Venez.*
Norethisterone enantate (p. 2294·3); estradiol valerate (p. 2271·2).
Combined injectable contraceptive.

Mesiken *Kener, Mex.*
Bromocriptine (p. 895·3).

Mesilex *Medarte, Gr.*
Nimesulide (p. 101·3).

Mesilon *Kolson's, India.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis; postoperative urinary retention; paralytic ileus.

Mesin *Unison, Thai.*
Albendazole (p. 149·1).
Worm infections.

Mesin-C *Unison, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Mesinib *Variforma, Arg.*
Imatinib (p. 807·3).

Mesipol *Polpharma, Rus.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mesite *Sanofi-Aventis, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mesitran *Aspen Medical, UK.*
Purified honey (p. 2072·1).
Burns; ulcers; wounds.

Meskina *Aamorb, India.*
Docosahexaenoic acid (p. 1460·1); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

Meskun *Biofarma, Turk.*
Meloxicam (p. 86·3).

M-Eslon *Ethypharm, Canad.; Grunenthal, Chile; Ethypharm, Cz.†; Ethypharm, Hong Kong†; Egis, Hung.; Multichem, NZ; Nobel, Turk.*
⊗Morphine sulfate (p. 92·3).
Pain.

Mesmerin *Sigma, Braz.*
Lorazepam (p. 1080·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; nausea and vomiting; premedication.

Mesmor *Rafarm, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Mesnex *Baxter, USA.*
Mesna (p. 1557·2).
Prevention of ifosfamide-induced haemorrhagic cystitis.

Mesnil *Asofarma, Mex.*
Mesna (p. 1557·2).
Prevention of urotoxicity due to antineoplastic therapy.

Mesocain
Note: this name may be used for preparations of different composition.
Zentiva, Cz.
Injection: Trimecaine hydrochloride (p. 1997·3).
Local anaesthesia; arrhythmias.

Zentiva, Cz.
Topical gel: Trimecaine hydrochloride (p. 1997·3); carbaethopendecinium bromide (p. 1741·3).
Catheterisation; aid in urological examination.

Mesocaine
Note: this name may be used for preparations of different composition.
Pharmy, Fr.
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Mesodal *Probiomed, Mex.*
Mesna (p. 1557·2).
Prevention of ifosfamide- and cyclophosphamide-induced haemorrhagic cystitis.

Mesoderm *Borshchagovskii, Ukr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Mesoestetic *Tylstin, Canad.*
SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Tylstin, Canad.
SPF 30: Avobenzone (p. 1695·1); ensulizole (p. 1703·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1).
Sunscreen.

Tylstin, Canad.
SPF 50: Avobenzone (p. 1695·1); ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Mesofol *Biomet, Ger.†*
Lactid-caprolactone copolymer.
Postoperative adhesions.

Mesol *Gracia, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Mesone *Pharmacore, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mesonex *Adelco, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Mesonta *Galenium, Indon.†*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Mesopil *Abbott, India.*
Misoprostol (p. 2140·3).
Peptic ulcer; termination of pregnancy.

Mesopran *Royton, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Mesorfan *Collins, Mex.†*
⊗Pseudoephedrine (p. 1676·1); chlorphenamine (p. 620·3); dextromethorphan (p. 1660·1).
Respiratory-tract congestion.

Mesotina *Rivero, Arg.*
Papaverine hydrochloride (p. 2362·3).
Vascular spasm.

Mespas *East West, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Mesporan *Mepha, Braz.†*
Ceftriaxone (p. 253·3).
Bacterial infections.

Mesporin *Mepha, Hong Kong; Mepha, Malaysia; Mepha, Port.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Mesren *Ivax, UK.†*
Mesalazine (p. 1859·2).
Crohn's disease; ulcerative colitis.

Messeldazol *Biomep, Mex.*
Metronidazole (p. 936·1).

Messelfenil *Biomep, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Messelxen *Biomep, Mex.*
Naproxen (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Messelzol *Biomep, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Mestacine *Tonipharm, Fr.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Mestamox *Metiska, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mestane *Douglas, NZ.*
⊗Exemestane (p. 792·2).
Breast cancer.

Mestian *LKM, Arg.*
Mesna (p. 1557·2).

Mestil-Ka *Fada, Arg.*
Menadione sodium bisulfite (p. 2122·2).
Vitamin K supplement.

Mestilon *Uni-Sankyo, India.*
⊗Mesterolone (p. 2291·1).
Androgen deficiency; infertility associated with hypogonadism.

Mestinon *Roemmers, Arg.; Valeant, Austral.; Meda, Austria; Meda, Belg.; Valeant, Braz.; Valeant, Canad.; Raffo, Chile; Meda, Cz.; Meda, Denm.; Meda, Fin.; Meda, Fr.; Meda, Ger.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; Invida, Hong Kong; Meda, Hung.; Transfarma, Indon.; Valeant, Indon.; Valeant, Irl.; Megapharm, Israel; Valeant, Ital.; Inovail, Malaysia; Valeant, Mex.; Meda, Neth.; Meda, Norw.; Valeant, NZ; Invida, Philipp.; Meda, Pol.; Meda,*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Port.; Pharmaco, S.Afr.†; Invida, Singapore; Meda, Spain; Meda, Swed.; Meda, Switz.; Invida, Thai.; Onko, Turk.; ICN, UK; Valeant, USA; Farma, Venez.
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis; postoperative urinary retention; atonic constipation; tachycardia; reversal of competitive neuromuscular blockade; ileus; headache; meteorism; paraesthesias.

Mesto-Of *Pond's, Thai.*
Amylase (p. 2442·1); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); thiamine nitrate (p. 2103·2); menthol (p. 2553·2); ginger oil (p. 1844·1); anise oil (p. 2444·3); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); scopolia (p. 2611·3).
Dyspepsia; hyperacidity; gastritis; heartburn; gastrointestinal motility disorders.

Mestral *Meyer Alian, Venez.*
Ibuprofen (p. 68·2).
Pain.

Mestrel *Teva, Mex.; Teva, Thai.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer.

Mestrolin *Darya-Varia, Indon.†*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Mesulid *Therabel, Belg.; CSC, Cz.; Boehringer Ingelheim, Gr.; Helsinn, Hong Kong; Schering-Plough, Hong Kong; CSC, Hung.; Stadmed, India; Helsinn Birex, Irl.†; Rafa, Israel; Novartis, Ital.; Roche, Mex.; Schering-Plough, Philipp.†; Pfizer, Turk.†*
Nimesulide (p. 101·3).
Pain; inflammation; cold and influenza symptoms; fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Mesu-P *Aamorb, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Mesupon *Alapis, Gr.; Remek, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Mesura *Andromaco, Chile.*
⊗Sibutramine (p. 2330·2).
Obesity.

Mesviron *Unigen, Thai.*
⊗Mesterolone (p. 2291·1).
Male hypogonadism; male infertility; asthenia and mental function impairment in older men.

Mesylonib *Miracalus, India.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia; myelodysplastic diseases; dermatofibrosarcoma protuberans; gastrointestinal stromal tumours; systemic mastocytosis; hypereosinophilic syndrome.

Mesyrel *Lotus, China.*
Trazodone hydrochloride (p. 451·1).
Depression.

Met
Note: this name may be used for preparations of different composition.
Betapharm, Ger.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.
Ajanta, India.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.
Ind-Swift, India.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Meta *Millimed, Thai.†*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting.

Metab Herbs *Metab, Canad.†*
Senna (p. 1885·1); taraxacum (p. 2625·3); veronica.

Metab Herbs No 1 *Metab, Canad.†*
Leptandra virginica; cascara (p. 1826·1); senna (p. 1885·1); taraxacum (p. 2625·3).
Constipation.

Metabet *Morningside, UK.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

metabiarex *Meta Fackler, Ger.*
Tuberculinum (p. 2635·3); medorrhinum; vaccininum; pyrogenium (p. 2601·1); sulfur (p. 1721·1); acid. formic. (p. 2507·1); tabacum (p. 2632·2); vincetoxicum; echinacea purp. (p. 2498·1).
Homoeopathic preparation.

Metabol
Note: this name may be used for preparations of different composition.
BodyForm, Hung.
Levocarnitine tartrate (p. 2053·2); chromium yeast (p. 2125·2); fucus (p. 2612·1).
Obesity.
Jagsonpal, India.
⊗Nandrolone phenylpropionate (p. 2293·1).
Uraemia; debility; osteoporosis; adjuvant to steroid therapy.
UB, Switz.
Gentian (p. 2512·1); red clover (p. 2482·1); absinthium (p. 2426·1); centaury (p. 2473·2); aniseed (p. 2444·2); fennel (p. 2503·2); chamomile (p. 2474·1); peppermint (p. 1877·1); rosemary (p. 2607·2); melissa (p. 2552·3); valerian (p. 2640·2); juniper (p. 2537·1); chicory (p. 2475·2).
Digestive disorders.

Metabolic *Framingham, Arg.*
Carnitine (p. 2053·2); chromium tripicolinate (p. 2056·1); garcinia cambogia (p. 2510·2).
Obesity.

Metabolic CLA *Framingham, Arg.*
Conjugated linoleic acid (p. 2509·2).
Obesity.

Metabolic Mineral Mixture *Nutricia, Austral.†; SHS, Irl.; SHS Nutrition, NZ.*
Minerals; trace elements.
Mineral supplementation for enteral diets.
SHS, UK.
Minerals.
Mineral supplementation for enteral diets.

Metabolift Fat Burner *Natures Way, Austral.*
Garcinia quaesita (p. 2510·2); guarana (p. 2648·2); caffeine (p. 1203·3); gymnema silvestre; fucus vesiculosus; maté (p. 2648·2); camellia sinensis; capsicum (p. 2469·3); bitter orange (p. 2575·3); choline bitartrate (p. 2055·2); inositol (p. 2533·2); chromium picolinate (p. 2056·1); pyridoxine hydrochloride (p. 2105·3).
Slimming aid.

Metabolimax *Molypharma, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for positron emission tomography in cardiology, neurology, and oncology.

Metabolism Advantage *Blackmores, Austral.*
Vitamins; minerals; capsicum (p. 2469·3); coleus forskohlii.
Dietary supplement.

Metabolite-A *Forder, Arg.*
Retinol (p. 2098·3).
Skin disorders.

Metabol-Mg *Pentafarma, Port.*
Magnesium aspartate (p. 1787·1).

Metacal-DMZ *Almet, India.*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Metacalmans *Chobet, Arg.*
⊗Methadone hydrochloride (p. 88·3).
Pain; opioid withdrawal.

Metacard *Ipca, India.†*
Trimetazidine hydrochloride (p. 1520·1).
Ischaemic heart disease.

Metacen *Promedica, Ital.*
Indometacin (p. 71·2).
Gout; ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Metacin *Themis, India.*
Paracetamol (p. 115·1).
Pain; fever.

Metacon *Psyco Remedies, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Metacort *Shreya, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Metacross *Pharmacross, Chile.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis.

Métacuprol *Chiesi, Fr.†*
Copper sulfate (p. 2057·2).
Skin and mucous membrane infections.

Metadate *UCB, Mex.; UCB, USA.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Metadec *Jagsonpal, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anaemia; anabolic; osteoporosis.

Metadex *Osorio de Moraes, Braz.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Metadien *Wockhardt, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metadol
Note: this name may be used for preparations of different composition.
East West, India.
Diclofenac potassium (p. 48·3); metaxalone (p. 2025·2).
Paladin, Canad.
⊗Methadone hydrochloride (p. 88·3).
Opioid dependence.

Metadon *Cristalia, Braz.; Abcur, Fin.; Extractum, Hung.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal syndrome; pain.

Metadoxil *Baldacci, Braz.; Eurodrug, Hung.; Micro, India; Baldacci, Ital.; CSC, Rus.; Eurodrug, Thai.*
Metadoxine (p. 2105·3).
Liver disorders; alcoholic liver disease; acute alcohol intoxication.

Metadoze-IPR *Biocon, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metadrate *Lupin, India.*
Magaldrate (p. 1856·1); metoclopramide hydrochloride (p. 1862·2).

Metadure *Micro, India.*
⊗Metolazone (p. 1434·1).
Hypertension; oedema.

Metafar *New Research, Ital.*
Cefmetazole sodium (p. 241·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Metafen *Polfa Lodz, Pol.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Metaflam
Note: this name may be used for preparations of different composition.
Jumont, Philipp.
Mefenamic acid (p. 85·3).
Pain.
Mahakam Beta, Indon.
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Metaflex Gesic *Montpellier, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Inflammation; pain.

Metaflex NF *Montpellier, Arg.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Metaflex Plus NF *Montpellier, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint, and peri-articular disorders.

Metafolbic *Breckenridge, USA.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Metafor *Meridian, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metagard *Ipca, India; Ipca, Malaysia†; Ipca, Rus.; Ipca, Singapore.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; vascular eye disorders; ischaemic heart disease.

Metagem *MJ Biopharm, Thai.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo; tinnitus.

metaginkgo *Metapharmaka, Switz.*
Ginkgo biloba (p. 2512·3); espeletia grandiflora; myrtillocactus geometrizans; nicotinan tabacum (p. 2632·2); plumbum metallicum (p. 2541·3); secale cornutum (p. 2137·1).
Homoeopathic preparation.
Meta Fackler, Ger.†
Ginkgo bil. (p. 2512·3); espeletia grandiflora; secale cornut. (p. 2137·1); myrtillocactus; tabacum (p. 2632·2); plumbum metall. (p. 2541·3).
Homoeopathic preparation.

Metaglez *Aristo, India.*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metaglip *BMS, USA.†*
Glipizide (p. 474·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metagon *Vital Healthcare, Philipp.*
Promethazine hydrochloride (p. 638·2).
Allergic disorders; premedication; anaphylaxis; sedative; motion sickness.

Metagyl *Ranbaxy, S.Afr.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Metaharonga *Meta Fackler, Ger.*
Asa foetida (p. 2449·3); eichhornia; haronga; nux vomica (p. 2573·3); okoubaka; syzygium jamb.; taraxacum (p. 2625·3).
Homoeopathic preparation.

metaheptachol *Metapharmaka, Switz.*
Berberis vulgaris (p. 2502·1); chelidonium majus (p. 2522·2); lophophytum leandri; quassia amara (p. 2601·1); silybum marianum (p. 1561·1).
Homoeopathic preparation.

Metajex *Cadila, India.*
Metoclopramide hydrochloride (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; premedication; gastro-oesophageal reflux.

metakaveron *Meta Fackler, Ger.*
Piper methysticum (p. 2537·3); mandragora e rad.; argentum nitricum (p. 2615·3); sumbulus mosch..
Homoeopathic preparation.

Metakelfin *Pharmacia Upjohn, India; Pfizer, Ital.*
Sulfametopyrazine (p. 367·3); pyrimethamine (p. 662·3).
Malaria.

Metalax *Leiras, Fin.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Metalcaptase *Heyl, Cz.; Heyl, Ger.; Taisho, Jpn; Abbott, S.Afr.†*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; chronic hepatitis; scleroderma; Wilson's disease; heavy-metal poisoning; cystinuria; chronic polyarthritis.

Metalgial *Ern, Spain.*
Dipyrone (p. 53·3).
Fever; pain.

Metalgin
Note: this name may be used for preparations of different composition.
Mount Mettur, India.
Paracetamol (p. 115·1).
Pain; fever.

Metalin-Z *TTK, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).
Iron-deficiency anaemia.

Metalize *Boehringer Ingelheim, Ukr.*
Tenecteplase (p. 1510·2).
Myocardial infarction.

Metalka *Mount Mettur, India.*
Sodium acid citrate (p. 1781·1).
Urinary alkalinisation; metabolic acidosis.

Metalon *Caps, S.Afr.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; vomiting.

Metalyse *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK.*
Tenecteplase (p. 1510·2).
Myocardial infarction.

Metamar *Mar, Arg.*
⊗Betamethasone (p. 1623·2), betamethasone acetate (p. 1623·2), or betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Metamax *Darnitsa, Ukr.*
Meldonium (p. 1429·3).
Cerebrovascular disorders; cardiac disorders; tonic; chronic alcoholism; obstructive airways disease; retinal disorders.

Metamide *Mylan, NZ.*
Metoclopramide hydrochloride (p. 1862·2).
Aid in gastrointestinal investigations; gastrointestinal motility disorders; nausea and vomiting.

Metamidol *Sanofi-Aventis, Port.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; febrile convulsions.

Metamol *CTS, Rus.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; gastrointestinal examination.

Metamorfoz *Sanli, Turk.*
Hydroquinone (p. 1705·1); bismuth subnitrate (p. 1822·1); almond oil (p. 2437·1); bitter almond oil.
Hyperpigmentation disorders.

Metamucil *Procter & Gamble, Arg.; Procter & Gamble, Austral.; Procter & Gamble, Braz.; Procter & Gamble, Canad.; Wick, Ger.; Pfizer, Hong Kong; Procter & Gamble, Mex.; Procter & Gamble, Neth.; Procter & Gamble, NZ; Procter & Gamble, Spain; Procter & Gamble, Switz.; Pfizer, Thai.; Procter & Gamble, USA.*
Ispaghula (p. 1849·1).
Constipation; diverticular disease; irritable bowel syndrome; stool softener; ostomy management; dietary fibre supplement; hypercholesterolaemia; diarrhoea.

Metamucil plus Calcium *Procter & Gamble, Canad.*
Ispaghula (p. 1849·1); calcium carbonate (p. 1824·3).
Dietary fibre supplement; constipation; hypercholesterolaemia.

Metanabol *Jelfa, Pol.*
⊗Methandienone (p. 2291·3).
Anabolic.

Metaneuron *Phapros, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

metaneuron N *Metapharmaka, Switz.*
Argenti nitras (p. 2615·3); mandragora e radice; petasites officinalis (p. 2463·2); piper methysticum (p. 2537·3); sumbulus moschatus.
Homoeopathic preparation.

Metanis *Biol, Arg.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Trichomoniasis; vaginal candidiasis.

Metanium *Thornton & Ross, UK.*
Titanium dioxide (p. 1725·1); titanium peroxide (p. 1725·1); titanium salicylate (p. 1725·1).
Nappy rash.

Metanium Everyday Barrier *Thornton & Ross, Singapore.*
Titanium dioxide (p. 1725·1); white soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2); dimeticone (p. 2209·3).
Nappy rash.

Metanium Nappy Rash *Thornton & Ross, Singapore.*
Titanium dioxide (p. 1725·1); titanium peroxide (p. 1725·1); titanium salicylate (p. 1725·1).
Nappy rash.

Metanor *Meda, Port.*
Flupirtine maleate (p. 65·2).
Pain.

Metanorm *Elder, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Sydenham, Philipp.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metanorm G *Elder, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Metanorm P *Elder, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Metanx *Pamlab, USA.*
Pyridoxal phosphate (p. 2105·3); mecobalamin (p. 2108·1); calcium levomefolate (p. 2053·1).
Nutritional supplement.

metaossylen N *Metapharmaka, Switz.*
Bryonia cretica (p. 2461·3); ferri chloridi (p. 2504·2) piper methysticum (p. 2537·3); stannum metallicum (p. 2632·1).
Homoeopathic preparation.

Metapio *Andromaco, Chile.*
Phenol (p. 1763·3).
Disinfection.

Metapirona *Allen, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Metaplatin *Teva Tuteur, Arg.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Metaplex *Indoco, India; Takeda, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Metaplexan *Pierre Fabre, Ger.†*
Mequitazine (p. 635·2).
Hypersensitivity disorders.

Metapride *Emar, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Metapro *Micro, India.*
⊗Metoprolol (p. 1434·3) or metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Metaprot *Antiviral, Rus.*
Ethyl thiobenzimidazole hydrobromide.
Asthenia; stress; cerebral disorders.

Metaptyl *Elpen (Ελπεν), Gr.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Metarmin *PC India, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; premedication; gastro-oesophageal reflux.

Metasedin *Esteve, Spain.*
⊗Methadone hydrochloride (p. 88·3).
Pain; opioid withdrawal.

Metasin *Teva, Mex.*
Metadoxine (p. 2105·3).
Alcohol withdrawal syndrome.

Metasinusit *Meta Fackler, Austria.*
Hydrargyrum sulfuratum rubrum (p. 2555·3); hydrastis canadensis (p. 2528·1); kalium bichromicum (p. 2476·3); verbascum densiflorum (p. 2645·1).
Homoeopathic preparation.

metasinusit *Metapharmaka, Switz.*
Hydrargyrum sulfidum rubrum (p. 2555·3); hydrastis canadensis (p. 2528·1); kali dichromas (p. 2476·3); verbascum thapsiforme (p. 2645·1).
Homoeopathic preparation.

Metaskin-N *Metiska, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

metasolidago S *Meta Fackler, Ger.†*
Serum anguillae; solidago (p. 2620·1); ononis (p. 2575·3); lespedeza; cantharis (p. 2469·2).
Homoeopathic preparation.

Metason *Fortbenton, Arg.; AG Therapy, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders; allergic rhinitis.

Métaspirine *GSK Sante, Fr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Metaspray *Cipla, India.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis.

Metastron *GE Healthcare, Austral.; GE Healthcare, Belg.†; GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Irl.; GE Healthcare, Israel; GE Healthcare, Ital.; GE Healthcare, Neth.; Satis, Port.; GE Healthcare, Spain; GE Healthcare, Switz.; GE Healthcare, UK; Amersham, USA; Medi-Physics, USA.*
Strontium-89 chloride (p. 2228·1).
Metastatic bone pain.

Metasulfin *PC India, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Metatone *Chefaro, Irl.; Chefaro, UK.*
Calcium glycerophosphate (p. 1783·3); manganese glycerophosphate (p. 2519·2); potassium glycerophosphate (p. 2519·2); sodium glycerophosphate (p. 2519·2); thiamine hydrochloride (p. 2103·1).
Tonic.

Metatop *Apotex, Belg.*
Lormetazepam (p. 1082·1).
Insomnia.

MetaTrace *Petnet, Spain.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for positron emission tomography.

Metavirulent *Meta Fackler, Austria.*
Influenzinum (p. 2393·3); acidum lacticum (p. 2539·1); aconitum napellus (p. 2428·3); ferrum phosphoricum (p. 2077·1); gelsemium sempervirens (p. 2511·2); luffa operculata (p. 2545·3); veratrum album (p. 2644·3); gentiana lutea (p. 2512·1).
Homoeopathic preparation.

metavirulent *Meta Fackler, Ger.*
Influenzinum (p. 2393·3); acid. sarcolact. (p. 2539·1); aconitum (p. 2428·3); ferrum phosph. (p. 2077·1); gelsemium (p. 2511·2); luffa (p. 2545·3); veratrum alb. (p. 2644·3); gentiana lutea (p. 2512·1).
Homoeopathic preparation.

Metapharmaka, Switz.
Acidum L-lacticum (p. 2539·1); aconitum napellus (p. 2428·3); ferri phosphas (p. 2077·1); gelsemium sempervirens (p. 2511·2); influenzinum (p. 2393·3); veratrum album (p. 2644·3).
Homoeopathic preparation.

Metax
Note: this name may be used for preparations of different composition.
C & G, Ital.
Cefmetazole sodium (p. 241·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Sons, Mex.
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Metaxide *Udomphon, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal symptoms; insomnia.

Metaxon *Ariston, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Metazidin *Pabianice, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; vascular eye disorders.

Metazine *CCM, Malaysia.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders.

Metazol
Note: this name may be used for preparations of different composition.
Thebe, S.Afr.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metazole *Captab, India.*
⊗Miconazole (p. 588·3); mometasone (p. 1644·1); nadifloxacin (p. 328·1).

Metazydyna *Polfa Pabianice, Pol.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo; tinnitus; vascular eye disorders.

Metbax *Ranbaxy, Mex.†*
Metformin (p. 489·1).
Diabetes mellitus.

Metbay *Bayer, Ital.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metcalf *Zenon, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metchek *API, NZ.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Indoco, India.
Metformin (p. 489·1).
Diabetes mellitus.

Metclam *Anthus, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Metco *Aronex, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metcor *Pharmacore, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Metcort *Delta, Braz.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Metdual *Silanes, Mex.*
Metformin hydrochloride (p. 489·1); glipizide (p. 474·1).
Diabetes mellitus.

Meted *Medicis, Canad.†; Alliance, Irl.; Alliance, UK; Sirius, USA.*
Salicylic acid (p. 1719·1); colloidal sulfur (p. 1721·1).
Scalp disorders; seborrhoea.

Metenix *IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, UK.†*
⊗Metolazone (p. 1434·1).
Hypertension; eclampsia; pre-eclampsia; oedema; ascites.

Meteor *OM, Switz.†*
Simeticone (p. 1886·2).
Flatulence; aid in gastrointestinal examination.

Meteoril *Salvat, Spain.*
Simeticone (p. 1886·2); magnesium trisilicate (p. 1858·1); aluminium glycinate (p. 1817·2).
Gastric hyperacidity; flatulence.

Meteosim *IBI, Ital.*
Simeticone (p. 1886·2).
Meteorism; aerophagia.

Meteospasmyl *Craveri, Arg.; Mayoly-Spindler, China; Mayoly-Spindler, Cz.; Teva, Hung.; Mayoly-Spindler, Malaysia; Mayoly-Spindler, Mex.; Mayoly-Spindler, Pol.; Mayoly-Spindler, Rus.; Mayoly-Spindler, Singapore; Mayoly-Spindler, Thai.†; Ali, Turk.; Mayoly-Spindler, Ukr.*
Alverine citrate (p. 1819·1); simeticone (p. 1886·2).
Meteorism; flatulence; irritable bowel syndrome; smooth muscle spasm; dyspepsia; aid in gastrointestinal examination; gastrointestinal distension.

Météospasmyl *Mayoly-Spindler, Fr.*
Alverine citrate (p. 1819·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Météoxane *Alfa Wassermann, Fr.*
Simeticone (p. 1886·2); phloroglucinol (p. 2588·2).
Gastrointestinal disorders.

Meteozym *Stegropharm, Ger.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive-system disorders.

Meterfolic *Durbin, UK.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy; neural tube defect prophylaxis.

Metermin *Cadila, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Metermine *iNova, Austral.*
⊗Phentermine (p. 2329·2).
Obesity.

Metespina *EG, Ital.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metesto *Acdhon, Thai.*
⊗Methyltestosterone (p. 2291·3).
Male hypogonadism; menopausal disorders; breast cancer in women; postpartum breast pain and engorgement.

Metex
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Medac, Denm.; Medac, Ger.; Medac, Norw.; Medac, Pol.; Medac, Port.
Methotrexate sodium (p. 822·2).
Rheumatoid arthritis; juvenile idiopathic arthritis; psoriasis; psoriatic arthritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Metfin *Sandoz, Switz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metfirex *Sanofi-Aventis, Cz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metflu *Esma, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Metfogamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.; Worwag, Ukr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metfogen *Generics, Cz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metfonorm *Abiogen, Ital.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metfor *Cipla, India; Millimed, Thai.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metforal *Menarini, Arg.; Guidotti, Ital.; Adcock Ingram, S.Afr.; Menarini, Singapore.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metforem *Orion, Fin.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metforex *United Drug, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metfor-G *Cipla, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Metforil *Menarini, Gr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metform *Brasterapica, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metformax *Menarini, Belg.; Teva, Pol.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metformdoc *Docpharm, Ger.†*
Metformin (p. 489·1).
Diabetes mellitus.

Metformed *Cimed, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metformin Duo *Temis, Arg.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Metformix *Novartis, Braz.*
Metformin (p. 489·1).
Diabetes mellitus.

Metfron *Asian Pharm, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metgli *Ordain, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metglib *Taurus, India.*
Glipizide (p. 474·1); metformin (p. 489·1).
Diabetes mellitus.

Metglucon *Investi, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metglucon Duo *Investi, Arg.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Metgol *Algol, Fin.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metgyl *Jagsonpal, India.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Methacid *Sunward, Singapore.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Methacin
Note: this name may be used for preparations of different composition.
Unicure, India.
Neomycin sulfate (p. 330·1).
Eye infections.

Hovid, Hong Kong.†
Indometacin (p. 71·2).

Methacor *Mylan, S.Afr.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Methaddict *Hexal, Ger.†*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal.

Methaderm *Taiho, Jpn.*
⊗Dexamethasone propionate (p. 1630·3).
Skin disorders.

Methadose *Rosemont, UK; Mallinckrodt, USA.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal; pain.

Methagual *Gordon, USA.*
Methyl salicylate (p. 92·1); guaiacol (p. 1666·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Metham *Promed, Indon.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); pyridoxine hydrochloride (p. 2105·3).
Tuberculosis.

Methamol *Asian Pharm, Thai.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Methandon *Acdhon, Thai.*
⊗Methandienone (p. 2291·3).
Osteoporosis; anabolic.

Methapain *Teikoku, Jpn.*
⊗Methadone hydrochloride (p. 88·3).
Pain.

Methaphyllin *Eisai, Indon.†*
Chlorophyllin copper complex sodium (p. 2178·3); propantheline bromide (p. 1880·1); magnesium trisilicate (p. 1858·1).
Peptic ulcer; gastritis.

Metharmon-F *Zoki, Thai.†*
⊗Pregnenolone; androstenedione (p. 2255·3); androstenediol; testosterone (p. 2305·1); estrone (p. 2275·2); thyroid (p. 2345·3).
Ovarian disorders; menopausal disorders.

Methatabs *PSM, NZ.*
⊗Methadone hydrochloride (p. 88·3).
Cough; opioid withdrawal syndrome; pain.

Methatropic *Goldline, USA.*
Vitamin B substances (p. 2102·3); methionine (p. 1558·2).

Methazide *Farmasintez, Rus.*
Metazide.
Tuberculosis.

Methazil *Bell, India.†*
Methyl alcohol (p. 2196·2); salicylic acid (p. 1719·1).
Fungal ear infections.

Methergin *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, India; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Sandoz, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Port.; Novartis, Spain; Novartis, Swed.; Novartis, Thai.†; Novartis, Turk.; Novartis, Venez.*
Methylergometrine maleate (p. 2137·3).
Uterine atony; postpartum haemorrhage; incomplete abortion; uterine subinvolution; third-stage labour management; lochiometra.

Méthergin *Novartis, Fr.; Novartis, Switz.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; postpartum uterine atony or subinvolution; menorrhagia.

Methergine *Validus, USA.*
Methylergometrine maleate (p. 2137·3).
Postpartum atony; postpartum haemorrhage.

Metherinal *Landson, Indon.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; third-stage labour management; uterine haemorrhage; uterine subinvolution; lochiometra; menorrhagia; metrorrhagia.

Metherlin *Taj, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Methging *JK Biochem, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Methicap *Biomax, India.*
Artemether (p. 648·1).
Malaria.

Methico *East West, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Methico Plus *East West, India.*
Vitamin B substances (p. 2102·3).

Methico-AL *East West, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Methicocid *Emcure, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Methicol *Otto, Indon.*
DL-Methionine (p. 1558·2); choline bitartrate (p. 2055·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Methiloc *Misha, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Methimez *Sun, India.*
Thiamazole (p. 2345·2).

Methin *Ind-Swift, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Methioson *Soho, Indon.*
Methionine (p. 1558·2); choline bitartrate (p. 2055·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Methiotrans *Abbott, Ger.†*
Methionine (p. 1558·2).
Urinary acidification; phosphate calculi; adjunct in antibacterial therapy.

Methiovit *Polfa Warszawa, Pol.†*
Methionine (p. 1558·2); choline citrate (p. 2055·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement; liver disorders.

Methipas-GP *Daniel Pasteur, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Methizol *Mibe, Ger.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Methnine *Medical Research, Austral.†*
Methionine (p. 1558·2).
Liver disorders; paracetamol overdosage.

Methobax *Baxter, Philipp.†*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Methobion *Medicus, Gr.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Methoblastin *Pfizer, Austral.; Pharmacia Upjohn, Gr.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Pfizer, NZ.
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis.

Methocaps *Caps, S.Afr.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Methocel
Note: this name may be used for preparations of different composition.
Celon, India.
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

OmniVision, Ger.; Novartis, Ital.; Restan, S.Afr.†; Novartis Ophthalmics, Singapore; OmniVision, Switz.
Hypromellose (p. 2189·2).
Lubricating and disinfecting drops for use with contact lenses; aid in eye examination; eye lubrication during contact lens fitting.

Methocin *TTK, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Methocip *Cipla, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; rheumatoid arthritis.

Method M *Baxter, Thai.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Methoneuron-C *Almet, India.*
Ampoule 1, vitamin C (p. 2110·3); ampoule 2, mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); folic acid (p. 2063·1).

Methopine *Burapha, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Methopt *Treasure Mountain, Hong Kong†; Sigma, NZ; Sigma, Philipp.*
Hypromellose (p. 2189·2).
Dry eyes.

Methor *Valeant, Hung.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Methor-Co *Marching, Hong Kong.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); bromhexine hydrochloride (p. 1656·3); ephedrine hydrochloride (p. 1663·2); papaverine hydrochloride (p. 2362·3); caffeine (p. 1203·3).
Cough; respiratory-tract congestion.

Methorcon *YF Chem, Thai.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); *dl*-methylephedrine hydrochloride (p. 1669·2).
Cough.

Methorex *Zydus, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Methormyl *Mugi, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Methorphan *BJ Benjaosoth, Thai.*
Dextromethorphan (p. 1660·1).
Cough.

Methorsedyl *Europharm, Hong Kong.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); promethazine hydrochloride (p. 638·2).
Cough; cold symptoms.

Methovin *Kimia, Indon.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; uterine subinvolution; lochiometra; menorrhagia; metrorrhagia.

Methovit *Glenmark, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); vitamin C (p. 2110·3).

Methovix *Zekides, Gr.*
Carbocisteine (p. 1658·1).

Methoxacet *Teva, Canad.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Musculoskeletal, joint, peri-articular and soft-tissue disorders.

Methoxacet-C *Teva, Canad.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain associated with skeletal muscle spasm.

Methoxaprim *Indian Drugs, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Methoxisal *Teva, Canad.*
Methocarbamol (p. 2025·3); aspirin (p. 22·2).
Pain associated with skeletal muscle spasm.

Methoxisal-C *Teva, Canad.*
Methocarbamol (p. 2025·3); aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain associated with skeletal muscle spasm.

Methozane *Taro, Israel.†*
Levomepromazine maleate (p. 1079·3).
Anxiety; pain; premedication; psychoses; bipolar disorder.

Methpica *Tropica Mas, Indon.*
Metformin (p. 489·1).
Diabetes mellitus.

Methuracol *Belkozin, Rus.*
Methyluracil; collagen (p. 2483·2).
Burns; ulcers; wounds.

Methycal *Indoco, India.*
Calcium citrate (p. 1783·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); colecalciferol (p. 2113·1).

Methyco *JK Biochem, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Methycobal *Eisai, China; Eisai, Hong Kong; Wockhardt, India; Eisai, Indon.; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore; Eisai, Thai.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Methyden *BMW, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Methygard *Indoco, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Methygard-OD *Indoco, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Methygin *Intas, India.*
Methylergometrine maleate (p. 2137·3).
Postpartum and postabortal haemorrhage.

Methyl Salicylate Cream, Compound *GPO, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); thymol (p. 1772·2).

Methyl Transfer *Eagle, Austral.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); pyridoxal phosphate (p. 2105·3); riboflavin (p. 2104·3); serine (p. 2088·2); zinc citrate (p. 2126·2).
Disorders of homocysteine metabolism.

Methyldronat *Darnitsa, Ukr.†*
Meldonium dihydrate (p. 1429·3).
Cerebrovascular disorders; ischaemic heart disease; tonic; alcohol withdrawal syndrome; respiratory-tract disorders; vascular eye disorders.

Methylergobrevin *Hemofarm, Rus.*
Methylergometrine maleate (p. 2137·3).
Uterine haemorrhage; maintenance of labour; metrorrhagia.

Methyl-Gag *Sanofi-Aventis, Fr.†*
Mitoguazone dihydrochloride (p. 830·2).
Leukaemias.

Methylin *AstraZeneca, Arg.; Mallinckrodt, USA.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome; minimal brain dysfunction.

Methylon *Bernofarm, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Methylpheni *TAD, Ger.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder.

Methyl-Pred *Shreshtha, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Methylpred *Aspen, Austral.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Methyneuron *Meridian, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Metibasol *Sanobia, Port.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Metica *Sarabhai Piramal, India; Ambalal Sarabhai, Thai.*
Metformin (p. 489·1).
Diabetes mellitus.

Metica-G *Sarabhai Piramal, India.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Meticel
Note: this name may be used for preparations of different composition.
Volta, Chile; Sophia, Mex.
Hypromellose (p. 2189·2).
Eye irritation; dry eyes.

MeticGlucotin *PharmaMetics, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis; rheumatoid arthritis.

Meticil *Ivax, Arg.*
Ampicillin (p. 218·2); diclofenac sodium (p. 48·3).
Mouth and throat infections.

Meticone *Elofar, Braz.†*
Dimeticone (p. 1886·2).
Flatulence.

Meticortelone *Schering-Plough, Mex.; Schering-Plough, Venez.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Meticorten *Schering-Plough, Arg.; Mantecorp, Braz.; Schering-Plough, Chile; Schering-Plough, Mex.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering, USA; Schering-Plough, Venez.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Metidrol *Medikon, Indon.†*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Metifer *Ikapharmindo, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Metifex *Cheplapharm, Ger.*
Ethacridine lactate (p. 1732·3).
Gastro-enteritis; diarrhoea.

Metifor
Note: this name may be used for preparations of different composition.
Polfarmex, Pol.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metil *Vickmans, Hong Kong.†*
Prochlorperazine (p. 1098·2).

Metilat *Metiska, Indon.*
Methylergometrine maleate (p. 2137·3).
Third-stage labour management; uterine bleeding; uterine subinvolution; lochiometra; menorrhagia; metrorrhagia.

Metilbetasone Solubile *SoSe, Ital.†*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Metilcanfor *Quim-Far, Venez.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Metil-DT *Cristalia, Braz.†*
Methyldopa (p. 1431·1).
Hypertension.

Metilenkek *Pharmamagist, Hung.*
Methylthioninium chloride (p. 1559·1).
Methaemoglobinaemia.

Metiler *Abbott, Turk.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Metilpres
Note: this name may be used for preparations of different composition.
TRB, Arg.
⊗Prednisone (p. 1647·2).
Corticosteroid.

Metilpress
Note: this name may be used for preparations of different composition.
Sigma, Braz.
Methyldopa (p. 1431·1).
Hypertension.

Metilprod *Prodotti, Braz.†*
Methyldopa (p. 1431·1).
Hypertension.

Metimyd
Note: this name may be used for preparations of different composition.
Schering, USA.†
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Eye inflammation with bacterial infection.

Metinal-Idantoina *Bayer, Ital.*
Phenytoin (p. 538·2); methylphenobarbital (p. 533·1).
Epilepsy.

Metinal-Idantoina L *Bayer, Ital.*
Phenytoin (p. 538·2); methylphenobarbital (p. 533·1); phenobarbital (p. 535·2).
Epilepsy.

Metindo *Kenyaku, Thai.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; neuritis.

Metindol *GSK, Pol.; ICN, Pol.; ICN, Rus.; ICN, Ukr.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; oedema; gout; soft-tissue disorders.

Metinox *Lennon, S.Afr.†*
Tin (p. 2632·1); tin oxide (p. 2632·1).
Acne; boils.

Metiocolin B12 *Farmasa, Braz.*
Methionine (p. 1558·2); choline chloride (p. 2055·2); inositol (p. 2533·2); vitamin B_{12} (p. 2107·2).
Liver disorders.

Metiocolin Composto *Farmasa, Braz.*
Methionine (p. 1558·2); choline citrate (p. 2055·2); betaine (p. 2456·1); cyanocobalamin (p. 2107·2).
Liver disorders.

Metiogen *Medical, Arg.*
Cynara (p. 2490·3); boldo (p. 2458·3); wild carrot (p. 2647·2); menthol (p. 2553·2).
Hepato-biliary disorders.

Metiorisan *Duncan, Arg.*
Simeticone (p. 1886·2).
Flatulence.

Metiprego *Sigillata, Denm.*
Montelukast sodium (p. 1214·3).
Asthma.

Metirel *AstraZeneca, Arg.*
Hydroxychloroquine sulfate (p. 655·2).
Lupus erythematosus; rheumatoid arthritis.

Metis *Gedeon Richter, Cz.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Metisol *Hexpharm, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Metisona *Precimex, Mex.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Metixane *Rayere, Mex.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Metixor *Landsteiner, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metixor G *Landsteiner, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Metizol
Note: this name may be used for preparations of different composition.
ICN, Pol.; Valeant, Ukr.
Thiamazole (p. 2345·2).
Hyperthyroidism.

Metkap *Karnataka, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metkor *Keshav, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metlife *Mankind, India.*
Metformin (p. 489·1) or metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metligine *Taisho, Jpn.*
⊗Midodrine hydrochloride (p. 1437·3).
Hypotension.

Metlong *Panacea, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metmin *Jenburkt, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metneed *Reliance, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Met-Neurobion *Merck, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Metnova *Generics, Neth.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metnox *Indi, India.*
Metronidazole benzoate (p. 936·1); norfloxacin (p. 333·3).

Meto *Hennig, Ger.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; ischaemic heart disease; myocardial infarction; arrhythmias; migraine.

Orchid, India.
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Meto ER HT *Orchid, India.*
⊗Hydrochlorothiazide (p. 1403·2); metoprolol succinate (p. 1434·3).
Hypertension.

Meto Zerok *Sandoz, Switz.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; heart failure; arrhythmias; migraine.

Metoart *Kocak, Turk.*
Methotrexate (p. 822·2).

Metobeta *Betapharm, Ger.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; ischaemic heart disease; myocardial infarction; arrhythmias; migraine.

Metobeta comp *Betapharm, Ger.*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metobloc *Pharma Nutria, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; ischaemic heart disease; hyperthyroidism; angina pectoris; arrhythmias.

Metoblock *Silom, Thai.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Metoc *Oriental, Arg.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Metocal *Teofarma, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis.

Metocal Vit D3 *Rotta, Malaysia; Rottapharm, Singapore.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; calcium and vitamin D supplement.

Metocal Vitamina D3 *Teofarma, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Metocalcium *Rottapharm, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Metocar *Pharmacodane, Denm.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; myocardial infarction; tremor.

Metocard *Polpharma, Pol.*
⊗Metoprolol (p. 1434·3).
Hypertension; ischaemic heart disease; arrhythmias; migraine; hyperthyroidism.

Torrent, India; Polpharma, Rus.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Metocare *Invision, India; IAE, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; heart failure.

Metoclop *Ind-Swift, India.*
Metoclopramide (p. 1862·2).
Diabetic gastroparesis; nausea and vomiting; gastro-oesophageal reflux; premedication.

Metoclop-P *Ind-Swift, India.*
Metoclopramide hydrochloride (p. 1862·2); paracetamol (p. 115·1).
Migraine.

Metoclor *Pharmaland, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Metoclosan *Sanval, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Metoclosantisa *Santisa, Braz.*
Metoclopramide (p. 1862·2).

Metocontin *Modi-Mundipharma, India.*
Metoclopramide hydrochloride (p. 1862·2).
Gastritis; gastro-oesophageal reflux; dyspepsia; duodenitis; nausea and vomiting.

Metocor *Rowex, Irl.*
⊗Metoprolol tartrate (p. 1434·3).
Myocardial infarction; arrhythmias; angina pectoris; hypertension; hyperthyroidism; migraine.

Metocris *LKM, Arg.*
Mycophenolate mofetil (p. 1961·1).

Metocyl *Rowa, Irl.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Metodik *Nova Argentia, Arg.*
Methotrexate (p. 822·2).

Metodine *Pfizer, Mex.*
Diiodohydroxyquinoline (p. 931·1); metronidazole benzoate (p. 936·1).

Metodoc *Docpharm, Ger.†*
⊗Metoprolol tartrate (p. 1434·3).
Ischaemic heart disease; arrhythmias; hypertension; migraine; myocardial infarction.

Metofin *Q Check, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Metogastron *Hexal, Austria.*
Metoclopramide hydrochloride (p. 1862·2).
Upper gastrointestinal motility disorders; nausea and vomiting.

Metogen *Yes, Pol.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; heart failure.

Metogin *Intra-Labs, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Metohexal *Hexal, Austria; Hexal, Fin.; Hexal, Ger.†; 1A, Pol.†*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; migraine; myocardial infarction; hyperthyroidism; heart failure; arrhythmias; ischaemic heart disease.

Sandoz, Austral.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; migraine; myocardial infarction.

Metohexal comp *Hexal, Ger.†*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metoject *Medac, Austria†; Medexus, Canad.; Kampar, Chile; Medac, Cz.; Medac, Denm.†; Medac, Fin.; Nordic, Fr.; Medac, Gr.; Medac, Hung.; Medac, Irl.; Tzamal, Israel; Medac, Neth.; Medac, Norw.†; Medac, Pol.; Medac, Port.; Medac, Rus.; Medac, Spain; Medac, Swed.; Gebro, Switz.; Onko, Turk.; Medac, UK.*
Methotrexate sodium (p. 822·2).
Rheumatoid arthritis; juvenile idiopathic arthritis; psoriasis; psoriatic arthritis; malignant neoplasms.

Metoklamide *Sanli, Turk.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Metolar *Cipla, India.*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Arrhythmias; angina pectoris; myocardial infarction.

Metolar-H *Cipla, India.*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metolate *Santen, Jpn.*
Methotrexate (p. 822·2).
Rheumatoid arthritis; juvenile idiopathic arthritis.

Metole *APT, Hong Kong.†*
Metronidazole (p. 936·1).
Amoebiasis; giardiasis; ulcerative gingivitis.

Metolol *Pharmaland, Thai.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris.

Metolon *Hovid, Hong Kong†; Bernofarm, Indon.†; Malaysia Chemist, Singapore.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal disorders.

Metomac *Macleods, India.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Metomax *Alphapharm, Austral.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Metomide
Note: this name may be used for preparations of different composition.
Christo, Hong Kong.†
Metoclopramide (p. 1862·2).

Metomin *Pacific, NZ.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metomylan *Mylan, Denm.; Mylan, Fin.; Mylan, Swed.*
⊗Metoprolol succinate (p. 1434·3).
Heart failure; hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; hyperthyroidism.

Metonat *VK Reagent, Ukr.*
Meldonium (p. 1429·3).
Ischaemic heart disease; cerebrovascular disorders; alcohol withdrawal syndrome.

Metonate *Otto, Indon.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Metop *Generics, Irl.*
⊗Metoprolol tartrate (p. 1434·3).
Myocardial infarction; arrhythmias; angina pectoris; hypertension; hyperthyroidism; migraine.

Metopar *Cosme, India.*
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2); paracetamol (p. 115·1).
Migraine.

Metophage *Rowex, Irl.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metophan *ICM, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Metopiron *HRA, Neth.*
Metyrapone (p. 2559·1).
Diagnosis of ACTH deficiencies or adrenocortical hyperfunction; hyperaldosteronism; Cushing's syndrome; oedema.

Metopirone *Novartis, Austral.; IFET (ΙΦΕΤ), Gr.; Novartis, Hong Kong; Novartis, Irl.; CTS, Israel; Novartis, NZ; Alliance, UK; HRA, USA.*
Metyrapone (p. 2559·1).
Cushing's syndrome; hyperaldosteronism; oedema; diagnosis of ACTH deficiency and adrenocortical hyperactivity.

Métopirone *HRA, Fr.; Medius, Switz.*
Metyrapone (p. 2559·1).
Cushing's syndrome; diagnosis of ACTH deficiencies or adrenocortical hyperfunction; hyperaldosteronism.

Metoplamin *Cifarma, Braz.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Metoplex *Jean-Marie, Hong Kong.*
⊗Dextromethorphan hydrobromide (p. 1660·1); carbinoxamine maleate (p. 619·1); bromhexine hydrochloride (p. 1656·3); ephedrine hydrochloride (p. 1663·2); caffeine (p. 1203·3); papaverine hydrochloride (p. 2362·3).
Cough; viscous bronchial secretions.

Metopresol *Tecnofarma, Mex.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; heart failure; angina pectoris; myocardial infarction; arrhythmias; hyperthyroidism; migraine.

Metopress *Sandoz, Switz.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; hyperthyroidism; arrhythmias; migraine.

Metopril *Metiska, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Metoprim
Note: this name may be used for preparations of different composition.
Munir, Turk.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Primera, Philipp.
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension.

Metoprin *Bunker, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Metoprin Balsamico *Bunker, Braz.†*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Bacterial infections.

Metoprogamma *Worwag, Ger.*
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Metoprolin *Ratiopharm, Fin.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension; myocardial infarction; heart failure; arrhythmias; hyperthyroidism; migraine.

Metoprolol comp *Ratiopharm, Ger.*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metoprolol compositum *Ratiopharm, Austria.*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metoprolol HCT *Sandoz, Ger.†*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metoprololsuccinat plus *1A, Ger.†*
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metoral
Note: this name may be used for preparations of different composition.
Reddy, India.
⊗Metolazone (p. 1434·1).
Hypertension; oedema.

Unison, Malaysia; Unison, Thai.
⊗Triamcinolone acetonide (p. 1649·1).
Oral inflammation; oral lesions; mouth disorders.

Metoratio *Ratiopharm, Denm.; Teva, Swed.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; tremor; myocardial infarction; heart failure.

Metored *Pharmaplan, S.Afr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metorex *Biological E, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; Crohn's disease.

Metorfan *Special Product's Line, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Metorfedrin *Intra, Venez.*
Dextromethorphan hydrobromide (p. 1660·1); brompheniramine (p. 618·1).
Cough; respiratory-tract congestion.

Metosafe *Zinnia, India.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Metosan
Note: this name may be used for preparations of different composition.
Lannacher, Austria.
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Metospanin *Ajanta, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metospec *Pharmaspec, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism.

Metostad *Stada, Denm.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; heart failure.

Stada, Philipp.
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Metostad Comp *Stada, Ger.†*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Meto-Succinat *Sandoz, Ger.†*
⊗Metoprolol succinate (p. 1434·3).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine.

Meto-Succinat HCT *Sandoz, Ger.†*
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Metosyn *Bioglan, Denm.; Bioglan, Norw.; GP, UK.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Metotab *Medac, Swed.*
Methotrexate sodium (p. 822·2).
Rheumatoid arthritis; psoriasis.

Meto-Tablinen *Winthrop, Ger.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; ischaemic heart disease; myocardial infarction; arrhythmias; migraine.

Metothyrin *PannonPharma, Hung.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Metoxifilin *Galeno, Venez.*
⊗Methoxyphenamine hydrochloride (p. 1669·1); theophylline (p. 1229·3).
Asthma.

Metoxim *Novartis, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Metoxiprim *Rhein, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Metoz *Centaur, India.*
⊗Metolazone (p. 1434·1).
Hypertension; oedema; ascites.

Metozolv *Salix, USA.*
Metoclopramide hydrochloride (p. 1862·2).
Gastro-oesophageal reflux; diabetic gastroparesis.

Metpamid *Sifar, Turk.; Yeni, Turk.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Metpar *Cipla, India.*
Metoclopramide (p. 1862·2); paracetamol (p. 115·1).
Migraine.

Metpata *Pharmasant, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Metper *Esma, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Metphage *Aspen, S.Afr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metphar *Novell, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metpo *Little Greave, India.*
Povidone-iodine (p. 1767·1).

Metprolol *Pharmaland, Thai.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction.

Metracin *Quimica y Farmacia, Mex.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Metracine *IFET (ΙΦΕΤ), Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; acid aspiration; pathological gastric hypersecretion.

Metracop *Copyfarm, Denm.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Metrajil *Sifar, Turk.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metral
Note: this name may be used for preparations of different composition.
Austral, Arg.; Cassara, Arg.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; rosacea.

Polfa Warszawa, Pol.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metram *APT, Hong Kong.†*
Metoclopramide hydrochloride (p. 1862·2).
Dyspepsia; flatulence; peptic ulcer; gastro-oesophageal reflux; gastritis; duodenitis; nausea and vomiting.

Metrazol *Elpen (Ελπεν), Gr.; Dinctas, Turk.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrazole *MDI, S.Afr.; General Drugs, Thai.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections; protozoal infections.

Metrecina *Liferpal, Mex.*
Oxytetracycline (p. 337·1).
Bacterial infections.

Metrelef *Ferring, Ger.*
⊗Buserelin acetate (p. 2256·2).
Endometriosis; pituitary desensitisation before ovulation induction.

Metreleptin *Shionogi, Jpn.*
Metreleptin (p. 1436·2).
Lipodystrophy.

Metren *Meyer Alian, Venez.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrergina *Biol, Arg.*
Ergometrine maleate (p. 2136·2).
Postpartum haemorrhage.

Metrex *Chandra Bhagat, India; Dae Han New, Thai.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; Crohn's disease; rheumatoid arthritis.

Metrexato *Blausiegel, Braz.*
Methotrexate sodium (p. 822·2).
Rheumatoid arthritis; psoriasis.

Metri *Libbs, Braz.*
Nicotinic acid (p. 2083·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Metricom *Apotex, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis.

Metride *Unichem, India.*
Glimepiride (p. 473·2); metformin (p. 489·1).
Diabetes mellitus.

Metride Plus *Unichem, India.*
Glimepiride (p. 473·2); metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Metrigen Fuerte *Organon, Mex.*
Estradiol benzoate (p. 2271·1); progesterone (p. 2300·2).
Menstrual disorders.

Metrim *Siam Bheasach, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Metrine *TP, Thai.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; postpartum uterine atony or subinvolution.

Metrinox *Euro-Med, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metris *Claris, India; Pharmaplan, S.Afr.; Biogalenic, Venez.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrison *Dexa, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Metrivin *Teva, Hung.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metrix *Kalbe, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Metrizol *Lafedar, Arg.; Liferpal, Mex.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrizone *The Forty-Two, Thai.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections; Helicobacter pylori *eradication.*

Metro
Note: this name may be used for preparations of different composition.
Intra-Labs, India.
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).
Braun, Hong Kong.†
Metronidazole (p. 936·1).

Metro Plus *East West, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1); zinc sulfate (p. 2126·2).

Metrobendizol *Technobio, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis.

Metrocev *Cevallos, Arg.*
Metronidazole (p. 936·1).
Rosacea; anaerobic bacterial infections; protozoal infections.

Metrocide *Pharmaland, Thai.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis.

Metrocol *Zizine, Fr.*
Metronidazole (p. 936·1).
Periodontitis.

MetroCream *Galderma, Canad.*
Metronidazole (p. 936·1).
Rosacea.

Metrocream *Galderma, Chile; Galderma, Mex.; Galderma, USA.*
Metronidazole (p. 936·1).
Rosacea.

Metrocreme *Galderma, Ger.*
Metronidazole (p. 936·1).
Rosacea.

Metrocycline *Virgo, Philipp.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Metrodal *One Pharma, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metroderme *Galderma, Port.*
Metronidazole (p. 936·1).
Rosacea.

Metrodermic *Cinetic, Arg.*
Metronidazole (p. 936·1).
Rosacea.

Metrodin *Serono, Austral.†; Serono, Braz.†; Faran, Gr.; Serono, Gr.; Serum Institute, India; Serono, Port.†; Serono, Rus.; Serono, Turk.; Serono, USA.†*
Urofollitropin (p. 2312·2).
Male and female infertility; polycystic ovary disease.

Metrodiyod *Serral, Mex.*
Diiodohydroxyquinoline (p. 931·1); metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis.

Metrofur *Sanofi-Aventis, Mex.†*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Trichomoniasis.

Metrofusin *Kalbe, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

MetroGel *Galderma, Canad.*
Metronidazole (p. 936·1).
Rosacea.

Metrogel *Galderma, Chile; Galderma, Ger.; Galderma, Irl.; Galderma, Mex.; Galderma, UK; Galderma, USA.*
Metronidazole (p. 936·1).
Rosacea; fungating malodorous tumours.

Metrogel V *iNova, S.Afr.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Metrogel Vaginal *Medicis, USA.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Metrogene *Septodont, Fr.*
Metronidazole (p. 936·1).
Periodontitis.

Metrogyl *Alphapharm, Austral.; Cooper (Κοπερ), Gr.; Fresenius Kabi, Gr.; Alphapharm, Hong Kong; JB Chemicals, India; Teva, Israel; Unique, Rus.; JB Chemicals, Thai.; Unique, Thai.; Unique, Ukr.; Unique, Venez.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; bacterial vaginosis; amoebiasis; giardiasis; rosacea; trichomoniasis; ulcers.

Metrogyl Compound *JB Chemicals, India.*
Diloxanide furoate (p. 931·2); metronidazole (p. 936·1).

Metrogyl Denta *Unique, Rus.; Unique, Ukr.*
Chlorhexidine gluconate (p. 1743·3); metronidazole benzoate (p. 936·1).
Bacterial mouth infections.

Metrogyl Plus *Unique, Rus.*
Metronidazole (p. 936·1); clotrimazole (p. 576·2).
Vaginal infections.

Metrogyl-DG *JB Chemicals, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).
Aphthous ulcer; gingivitis; mouth infections.

Metrogyl-F *JB Chemicals, India.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1); furazolidone (p. 933·3).
Amoebiasis; giardiasis; diarrhoea; dysentery; food poisoning.

Metrogyl-P *JB Chemicals, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).
Burns; ulcers; wounds; skin and vaginal infections.

Metrohex *Reddy, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).
Reddy, Rus.
Metronidazole benzoate (p. 936·1); chlorhexidine gluconate (p. 1743·3).

Metrokind-P *Mankind, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).
Burns; wounds.

Metrol *Aspen, Austral.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension; myocardial infarction; migraine.

Metrolacare *La Care, Rus.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrolag *Lagap, Switz.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrolex *Siam Bheasach, Thai.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; trichomoniasis; amoebiasis; giardiasis; ulcerative gingivitis.

Metrolocal *Paylos, Arg.*
Metronidazole (p. 936·1).
Malodorous skin lesions.

MetroLotion *Galderma, Canad.*
Metronidazole (p. 936·1).
Rosacea.

Metrolotion *Galderma, Ger.*
Metronidazole (p. 936·1).
Rosacea.

Metrolyl *Sandoz, UK·*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Metromine *Virgo, Philipp.*
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

Metron *Alkem, India; Alkem, Rus.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metron-DF *Alkem, India.*
Diloxanide furoate (p. 931·2); metronidazole (p. 936·1).

Metronide *Sanofi-Aventis, Austral.; Prodotti, Braz.†; Clonmel, Irl.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metroniflex *Baxter, Braz.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metronil *Cazi, Braz.*
Metronidazole benzoate (p. 936·1).

Metronin *Cifarma, Braz.†*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Protozoal infections.

Metronix *Cristalia, Braz.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metronol *Ain Medicare, Malaysia.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Metronor-P *PC India, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

Metronour *Organon, Ger.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metro-P *East West, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Metropast *Pasteur, Chile.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrophenicol *Virgo, Philipp.*
Chloramphenicol (p. 257·1), chloramphenicol palmitate (p. 257·1), or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Metrosa *Wallf, Ger.; Wallf, Hung.; Linderma, UK.*
Metronidazole (p. 936·1).
Rosacea.

Metrosel *Biosel, Turk.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrosept *ICN, Pol.†*
Metronidazole (p. 936·1).
Rosacea; bacterial skin infections.

Metroseptol *Jelfa, Rus.*
Metronidazole (p. 936·1).
Bacterial skin infections; rosacea.

Metroson *Sons, Mex.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis.

Metrotop *Medlock Medical, Irl.†; Medlock Medical, UK.†*
Metronidazole (p. 936·1).
Rosacea; malodorous fungating tumours; malodorous skin ulcers.

Metro-V *TO-Chemicals, Thai.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Metrovagin *Altayvitamin, Rus.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Metroval *Sanval, Braz.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).

Metrovax *Vivax, Venez.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Metrovid *Millimed, Thai.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Metrovit *Nizpharm, Rus.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Metroxid *Lakeside, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrozol *Elofar, Braz.†; Sel-J, Philipp.; Genom, Rus.; Parkfields, UK·*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Metrozole *Vickmans, Hong Kong.†*
Metronidazole (p. 936·1).

Met-Rx *Met-Rx, USA.*
Preparations for enteral nutrition.

Metsafe *MSN, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metsal *3M, Austral.†; iNova, Hong Kong; iNova, Malaysia; 3M, NZ; iNova, Philipp.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Metsal Analgesic *iNova, Austral.*
Trolamine salicylate (p. 141·2); menthol (p. 2553·2).
Muscle pain.

Metsal AR Analgesic *iNova, Austral.; iNova, Singapore.*
Trolamine salicylate (p. 141·2).
Musculoskeletal and joint pain.

Metsal AR Heat Rub *3M, Austral.*
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Metsal Heat Rub *iNova, Austral.; iNova, Singapore.*
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Metsar *Unichem, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Metsec *TP, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Metsel *Darya-Varia, Indon.*
ubidecarenone (p. 2637·1); levocarnitine fumarate (p. 2053·2); folic acid (p. 2063·1).
Dietary supplement.

Met-Sil *TP, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Metsil
Note: this name may be used for preparations of different composition.
Abbott, Turk.
Simeticone (p. 1886·2).
Flatulence.

Sinochem, Philipp.
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders.

Metsol *Orbis Consumer, UK.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Metswift *Ind-Swift, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metsyn *Synco, Hong Kong.†*
Mefenamic acid (p. 85·3).

Metta *Torrent, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Metucal *Zdorovje, Ukr.†*
Metoclopramide (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders; aid in gastrointestinal examination.

Metump *Mediez, India.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Metup *Obsurge, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Metussan *Great Eastern, Thai.†*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough.

Metvell *Novell, Indon.*
Methylergometrine maleate (p. 2137·3).
Third-stage labour management; postpartum haemorrhage; uterine subinvolution; lochiometra; puerperal bleeding.

Metvix *Galderma, Arg.; Galderma, Austral.; AB-Consult, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Canad.; Galderma, Chile; Galderma, Cz.; Galderma, Denm.; Galderma, Fin.; Galderma, Ger.; Galderma, Gr.; Galderma, Irl.; Galderma, Ital.; Galderma, Neth.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Port.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Spain; Galderma, Swed.; Galderma, Switz.; Galderma, UK.*
Methyl aminolevulinate hydrochloride (p. 740·1).
Malignant skin disorders; keratinisation disorders; basal cell carcinoma; Bowen's disease; actinic keratosis; squamous cell carcinoma; superficial malignant skin lesions.

Metvixia *Galderma, Fr.; Photocure, USA.*
Methyl aminolevulinate hydrochloride (p. 740·1).
Skin cancer; actinic keratosis.

Metxaprim *General Drugs, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Metypred *Orion, Cz.; Galen, Ger.; Orion, Hung.; Orion, Rus.; Orion, Ukr.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Orion, Pol.
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Metypresol *Intramed, S.Afr.†*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Metysolon *Dermapharm, Ger.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Metzodin *Sriprasit, Thai.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Metzok *USV, India.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Meuflox *Willow, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Meuflox-OZ *Willow, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Meva *Zydus, India.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Meva-C *Zydus, India.*
Chlordiazepoxide (p. 1044·2); mebeverine hydrochloride (p. 1858·3).

Mevac-A *Vaxines, Philipp.*
A live attenuated hepatitis A vaccine (p. 2388·3).
Active immunisation.

Mevac-Flu *Biosano, Chile.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Mevachol *Meprofarm, Indon.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Mevacor *MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, Cz.†; Vianex (Βιανεξ), Gr.; MSD, Hong Kong†; MSD, Mex.; MSD, Norw.†; MSD, Rus.; MSD, Singapore; MSD, Spain; Merck, USA; MSD, Venez.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia; coronary heart disease; hyperlipidaemias; cardiovascular risk reduction.

Mevalip *Teuto, Braz.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Mevalotin *Sankyo, Braz.; Daiichi Sankyo, China; Daiichi Sankyo, Ger.†; Daiichi Sankyo, Jpn; Daiichi Sankyo, Switz.; Daiichi Sankyo, Thai.; Sankyo, Venez.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; hypercholesterolaemia; cardiovascular risk reduction.

Mevamox *Teuto, Braz.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Mevamyst *Med-One, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Mevaren *Juste, Spain.*
Estradiol valerate (p. 2271·2); dienogest (p. 2267·2).
Menopausal disorders.

Mevasterol *Cantabria, Spain.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Mevastin *Genepharm, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Mevecan *Help, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Mevedal *Help, Gr.*
Nabumetone (p. 97·1).
Pain; inflammation; musculoskeletal and joint disorders.

Meventil *Medica Pedia, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Meverin *Arterium, Ukr.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal pain and spasm; irritable bowel syndrome.

Mevilox *Bernofarm, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Mevinacor *MSD, Ger.†; MSD, Port.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Mevinol *Vianex (Βιανεξ), Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Mevir *Guidotti, Austria.*
Brivudine (p. 970·1).
Herpes zoster infections.

Meviton *Meprofarm, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C deficiency.

Mevlor *MSD, Arg.; Chibret, Port.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Mevof *Arvincare, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Mevrabal *Medikon, Indon.†*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mewin *Winsome, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mewin Forte *Winsome, India.*
Thioctic acid (p. 2629·1); vitamins.

Mewin-GB *Winsome, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mex *Phoenix, Arg.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Mexa *Hauz, India.*
⊗Dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Mexalen *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Paracetamol (p. 115·1).
Pain; fever.

Mexam *Zydus, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis; juvenile idiopathic arthritis.

Mex-Amina *Remexa, Mex.*
Glucosamine sulfate (p. 2515·3); chondroitin (p. 2476·1); dimethyl sulfone (p. 2493·3); shark cartilage (p. 2471·3); vitamins.
Joint disorders.

Mexan
Note: this name may be used for preparations of different composition.
Mintlab, Chile; Medi-Lek, Pol.
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

TO-Chemicals, Singapore.
Gliclazide (p. 472·3).
Diabetes mellitus.

Shinyaku, Jpn.†
⊗Methoxamine hydrochloride (p. 1430·2).
Hypotension under anaesthesia; paroxysmal superventricular tachycardia.

Teva, Israel.†
Mesna (p. 1557·2).
Prevention of ifosfamide or cyclophosphamide urothelial toxicity.

Mexapin *Wandel, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Mexaquin *Konimex, Indon.†*
Chloroquine phosphate (p. 650·1).
Malaria.

Mexar *Hawthorn, USA.*
Sulfacetamide sodium (p. 361·1).
Infected skin disorders; seborrhoeic dermatitis; dandruff.

Mexaritm *Borshchagovskii, Ukr.*
Mexiletine hydrochloride (p. 1436·2).
Ventricular arrhythmias.

Mexate *Cadila, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Mexavit *Ratiopharm, Cz.†; Merckle, Rus.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Mexa-Vit C *Ratiopharm, Austria.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Mexef *Abbott, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Mexes *Aamorb, India.*
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

Mexezon *Valeant, Hung.*
⊗Exemestane (p. 792·2).
Breast cancer.

Mexia *Nobel, Turk.*
Memantine (p. 393·1).

Mexicor *Moschimfarm, Rus.; EkoFarmInvest, Ukr.*
Emoxypine succinate (p. 1371·1).
Myocardial infarction; ischaemic heart disease; hypertension; arrhythmias; hyperlipidaemias; cerebrovascular disorders; mental function impairment.

Mexicord *Polfa Grodzisk, Pol.†*
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias.

Mexidant *Mexidant, Rus.*
Emoxypine succinate (p. 1371·1).
Anxiety; cerebrovascular disorders; mental function impairment; alcohol withdrawal syndrome; neuroleptic toxicity.

Mexidin *Haledew, India.*
Chlorhexidine (p. 1743·2); metronidazole (p. 936·1).

Mexidol *Farmasoft, Rus.; Farmasoft, Ukr.*
Emoxypine succinate (p. 1371·1).
Anxiety; mental function impairment; alcohol withdrawal syndrome; cerebrovascular disorders; neuroleptic toxicity.

Mexifen *Medicus, Gr.*
Nalbuphine hydrochloride (p. 97·3).

Mexifin *Farmzaschita, Rus.*
Emoxypine succinate (p. 1371·1).
Anxiety; cerebrovascular disorders; mental function impairment; alcohol withdrawal syndrome; neuroleptic toxicity.

Mexilal *Sanitas, Chile.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders.

Mexin *Manix, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Mexinat *Chanelle, Cz.*
⊗Exemestane (p. 792·2).
Breast cancer.

Mexiprim *Farmstandart, Rus.; Mir, Rus.; Mir, Ukr.*
Emoxypine succinate (p. 1371·1).
Cerebrovascular disorders; mental function impairment; anxiety; alcohol withdrawal syndrome; neuroleptic toxicity; acute pancreatitis; peritonitis.

Mexitil *Boehringer Ingelheim, Austral.†; Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Gr.; Zydus, India; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, NZ; Eczacibasi, Turk.; Boehringer Ingelheim, USA.*
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias; diabetic neuropathy.

Mexitilen *Boehringer Ingelheim, Arg.*
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias.

Mexivit *Maneesh, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Maneesh, India.
Syrup: Biotin (p. 2052·2); copper sulfate (p. 2057·2); lysine hydrochloride (p. 2079·3); manganese (p. 2081·2); mecobalamin (p. 2108·1); selenium (p. 2086·3).

Mexochrome *Konimex, Indon.†*
Lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2); benzalkonium chloride (p. 1737·1); isopropyl alcohol (p. 1758·3).
Local anaesthesia; minor wounds; insect bites; burns.

Mexol-G *Yacca, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).

Mexomide *CCM, Malaysia.*
Metoclopramide hydrochloride (p. 1862·2).
Aid in gastrointestinal investigation; nausea and vomiting; diabetic gastroparesis.

Mexpharm *Kalbe, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Mexsana *Schering-Plough, USA.*
Kaolin (p. 1850·1); eucalyptus oil (p. 2501·2); camphor (p. 2466·2); corn starch (p. 2095·1); lemon oil (p. 2543·1); zinc oxide (p. 1729·1).
Nappy rash.

Mextran *Phoenix, Arg.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mextran Flex *Phoenix, Arg.*
Meloxicam (p. 86·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

MEXY *Millimed, Thai.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Hay fever; rhinitis.

Mexylin *Promed, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mexylor *Epifarma, Ital.*
Lormetazepam (p. 1082·1).
Insomnia.

Meylon *Otsuka, Jpn.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis; nausea; vomiting; drug intoxication.

Mezabox *Sriprasit, Thai.†*
Dipyrone (p. 53·3).
Pain.

Mezalit *Biopharm, Chile.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Mezalog *La Pharmaceuticals, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Mezapam *Organika, Rus.*
Medazepam (p. 1083·2).
Anxiety disorders; migraine; menopausal disorders; alcohol withdrawal syndrome.

Mezapin *La Pharmaceuticals, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Mezarid *Genepharm, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Mezaril *Reliance, India.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Mezatrin *Sanbe, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Mezavant *Menarini, Arg.; Shire, Austral.; Shire, Austria; Pharma Logistics, Belg.; Shire, Canad.; Shire, Denm.; Shire, Fin.; Shire, Ger.; Shire, Gr.; Shire, Irl.; Shire, Neth.; Shire, Norw.; Shire, Spain; Swedish Orphan, Swed.; Shire, UK.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Mezec *Taiyo, Jpn.*
Dextromethorphan hydrobromide (p. 1660·1); potassium cresolsulfonate.
Cough; respiratory-tract congestion.

Mezen
Note: this name may be used for preparations of different composition.
Nordic, India.
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Nordic, India.
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mezica *TTK, India.*
Ashwagandha (p. 2450·2); vitamins; minerals; ginseng (p. 2513·3).

Mezinc *Abigo, Swed.†*
Zinc oxide (p. 1729·1); zinc resin (p. 2126·1).
Wound dressing.

Mezine
Note: this name may be used for preparations of different composition.
Burapha, Thai.
Co-trimoxazole (p. 277·3).
Bacterial infections.

Phoenix, Arg.
Venlafaxine (p. 454·2).
Depression; anxiety.

Mezitan *Aramis, Hung.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders.

Mezo *Agio, India; Agio, Philipp.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mezobact-P *Globus, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Mezodin *Haledew, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Mezol *Syntho, India.*
⊗Cellulose (p. 2177·1); chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3).

Mezolam *Neon, India.*
Midazolam (p. 1085·1).
Insomnia; sedative; premedication; induction of anaesthesia.

Mezolar *Sandoz, UK.*
⊗Fentanyl (p. 60·1).
Pain.

Mezolitan *Dekaz, Gr.; Pharmathen, Gr.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mezonac *Aglowmed, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders with muscle spasm.

Mezonex *Orchid, Ukr.†*
Meropenem (p. 321·3).
Bacterial infections.

Mezophan *Milano, Thai.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

Mezo-T *Agio, India.*
⊗Mometasone (p. 1644·1); terbinafine hydrochloride (p. 593·3).

Mezym F *Berlin-Chemie, Ger.*
⊗Pancreatin (p. 2579·3).
Pancreatic disorders.

Mezym Forte *Berlin-Chemie, Hung.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Mezzoderm *Equity, S.Afr.*
⊗Hydrocortisone acetate (p. 1640·1).

Mezzopram *Sandoz, UK.*
Omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

MF *Psychotropics, India.*
Metformin (p. 489·1).
Diabetes mellitus.

MF6 *Support, Braz.*
Dietary fibre.
Formerly known as Stimulance.

M-Fact *Medico, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

MFE *Croesus, Philipp.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

MF-Kare *DKT, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; labour induction following intra-uterine fetal death; post-coital oral contraceptive.

M-Flox *Millimed, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

M-Fluk *Madhav, India.*
Fluconazole (p. 578·2).
Fungal infections.

M-Forlin *Lincoln, India.*
Metformin (p. 489·1).
Diabetes mellitus.

M-Fost *Shantha, India.*
Amifostine (p. 1539·2).
Reduction of toxicity due to cytotoxic therapy; radiotherapy-associated xerostomia.

MFresh *Hi-Tec, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).

M-Furo *Orva, Turk.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

MG400 *Triton, USA.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Seborrhoea.

MG 50 *Terapeutico, Ital.*
Magnesium proteinate (p. 1786·3).
Magnesium deficiency; magnesium supplement.

MG Cold Sore Formula *Outdoor Recreations, USA.*
Menthol (p. 2553·2); lidocaine (p. 1988·1).

Mg 5-Granoral *Vifor, Switz.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

Mg 5-Longoral *Drossapharm, Ger.; Vifor, Switz.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

MG217 Medicated *Triton, USA.*
Coal tar (p. 1723·2).
MG217 Medicated shampoo and ointment formerly contained coal tar, salicylic acid, and colloidal sulfur.
Skin disorders.

MG217 Medicated Tar-Free *Triton, USA.*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Dandruff.

Mg 5-Oraleff *Vifor, Switz.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement.

MG217 Sal-Acid *Triton, USA.*
Salicylic acid (p. 1719·1).
Psoriasis.

Mg 5-Sulfat *Drossapharm, Ger.*
Magnesium sulfate (p. 1787·3).
Magnesium deficiency.

M-Gesic *2M, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal spasm and pain.

Mg-nor *Teofarma, Ger.*
Magnesium aspartate (p. 1787·1).
Magnesium deficiency.

MGR *Inga, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

MGrox *CMG, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

MGTec-P *Oxytech, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

MHP-A *Cypress, USA.*
Hyoscyamine sulfate (p. 1848·1); methenamine (p. 322·3); salol (p. 129·3); atropine sulfate (p. 1310·2); methylthioninium chloride (p. 1559·1); benzoic acid (p. 1738·2).
Lower urinary-tract disorders.

Mi Er Ning *San Lian, China.*
Mirtazapine (p. 436·1).
Depression.

Mi Er Shen *Hai Shan, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mi Er Tuo *Guang Feng, China.*
Metronidazole (p. 936·1).

Mi Fu *Zi Fu, China.*
Mifepristone (p. 2138·1).

Mi Li Xian *Yangtze River, China.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Mi Nuo *Ao Hua, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mi Nuo Xi *Zhen Zhu, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mi Sang *Tai Ping, China.*
Clostridium butyricum.

Mi Si Long *Qing Hua Zi Guang Gu Han, China.*
Pazufloxacin mesilate (p. 338·1).

Mi Le Song *TianJin, China.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Mi Tuo Suo *Wan Lian, China.*
Megestrol acetate (p. 2289·2).

Mi Wei *Hai Kang, China.*
⊗Midodrine hydrochloride (p. 1437·3).

Mi Xi Lun *Watson, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Mi Xi Ning *Sunnyhope, China.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Mi Ying Jie *Sha Pu Ai Si, China.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Miabene *Ratiopharm, Cz.*
Mianserin hydrochloride (p. 434·2).
Depression.

Miacalcic *Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Mex.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; reflex sympathetic dystrophy; osteoporosis; bone pain; hypercalcaemia of malignancy; neurodystrophies; pancreatitis; hyperparathyroidism; vitamin D intoxication; osteolysis of malignancy; osteopenia; osteogenesis imperfecta; prevention of bone loss during immobilisation for osteoporotic fractures.

Miacalcin *Novartis, Canad.; Novartis, USA.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; hypercalcaemia; Paget's disease of bone.

Mi-Acid *Major, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Mi-Acid Gelcaps *Major, USA.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Hyperacidity.

Miadenil *Anfarm, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Miaderm Radiation Relief *Aiden, USA.*
Calendula (p. 2465·2); sodium hyaluronate (p. 2526·2); aloe vera (p. 1693·2).
Radiation dermatitis.

Miafem *Andromaco, Chile.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Miagen *Generics, Hung.*
Mianserin hydrochloride (p. 434·2).
Depression.

Miakaril *Novartis, Irl.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Mialin *Biomedica, Ital.*
Alprazolam (p. 1035·2).
Anxiety disorders.

Miambutol *Teofarma, Ital.; Kocak, Turk.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Mian Shu *Dilong, China.*
Cervus peptides; cucumis polypeptides.

Mianeurin *Hexal, Ger.†*
Mianserin hydrochloride (p. 434·2).
Depression.

Miansec *Jelfa, Pol.*
Mianserin hydrochloride (p. 434·2).
Depression.

Miansegen *Generics, Pol.*
Mianserin hydrochloride (p. 434·2).
Depression.

Miansemerck *Generics, Pol.*
Mianserin hydrochloride (p. 434·2).
Depression.

Miantrex *Pfizer, Braz.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Miao Si Ning *Pu Sheng, China.*
Aceglutamide (p. 2426·2).

Miapax *Casasco, Arg.*
Eszopiclone (p. 1072·3).
Insomnia.

Miaryl *Jin Yang, Malaysia.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Miaser *Interfarma, Ukr.*
Mianserin hydrochloride (p. 434·2).
Depression.

Miaxan *Orion, Fin.†*
Mianserin hydrochloride (p. 434·2).
Depression; insomnia.

Mibalin *Polfa Warszawa, Pol.†*
⊗Methylthioninium chloride (p. 1559·1); naphazoline nitrate (p. 1669·3).
Conjunctivitis.

Mibe *Troikaa, India.*
Ezetimibe (p. 1379·2).
Sitosterolaemia; hyperlipidaemias.

Mibeclag *Bajamed, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Miben *Celon, India.*
Midazolam hydrochloride (p. 1085·1).
Insomnia; sedative; premedication; induction of anaesthesia.

Mibesan-S *Alpharma, Mex.*
Nystatin (p. 590·3).
Oral candidiasis.

MIBG *Covidien, Belg.; Mallinckrodt, Cz.; Mallinckrodt, Fin.; MAP, Fin.; Mallinckrodt, Irl.; Mallinckrodt, Neth.; Mallinckrodt, Spain.*
Iodine-123 (p. 2225·1) iobenguane.
Radioimaging of malignant neoplasms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mibiot *Serral, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Mibiron *Faran, Gr.*
Astemizole (p. 616·1).
Allergic disorders.

Mibitec *AAA, Fr.*
Tetrakis copper tetrafluoroborate.

Mibloc FT *Andromaco, Chile.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Mibor *Celon, India.*
Bortezomib (p. 752·1).
Multiple myeloma.

Mibral *Pentafarma, Port.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Miburell *Sanorell, Ger.*
Lachesis mutus (p. 2538·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Mic
Note: this name may be used for preparations of different composition.
Alembic, India.
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.
T Man, Thai.†
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mica
Note: this name may be used for preparations of different composition.
Brawn, India.
Amikacin (p. 214·1).
Bacterial infections.

Micaden *Teuto, Braz.*
Isoconazole nitrate (p. 583·2).
Fungal vaginal infections.

Mical *Sam-On, Israel.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with viscous mucus.

Micalpha *Chrispa (Χρισπα), Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Micamin *Astellas, Rus.; Astellas, Ukr.*
Micafungin sodium (p. 588·2).
Candidiasis.

Micanol *Riemser, Austria; Riemser, Ger.; Bioglan, Israel†; AFT, NZ; CS, Port.; Bioglan, Singapore; Vinas, Spain; Bioglan, UK.*
Dithranol (p. 1701·2).
Psoriasis.

Micar *Microsules, Arg.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Micardis *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel†; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ†; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Micardis Amlo *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Switz.*
Telmisartan (p. 1509·3); amlodipine besilate (p. 1304·1).
Hypertension.

Micardis Anlo *Boehringer Ingelheim, Braz.*
Telmisartan (p. 1509·3); amlodipine (p. 1304·1).

Micardis HCT *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, USA.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Micardis Plus *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, Venez.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

MicardisPlus *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Ukr.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Micare *Servocare, India.*
Amikacin (p. 214·1).
Bacterial infections.

Micatin *Wellspring, Canad.; Advanced Care, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micaveen
Note: this name may be used for preparations of different composition.
Dermoteca, Port.†
Avena (p. 2451·1); undecenoic acid (p. 596·3); benzoic acid (p. 1738·2).
Fungal skin infections.

Micazin *Chew, Thai.*
Miconazole (p. 588·3).
Fungal skin and nail infections.

Miccil *Senosiain, Mex.*
⊗Bumetanide (p. 1329·1).
Hypertension; oedema.

Micelle A plus E *Bioglan, Austral.†*
Vitamin A (p. 2098·3); *d*-alpha tocoferil acetate (p. 2119·1).
Vitamin A and E supplement; fat malabsorption syndromes.

Micelle E *Bioglan, Austral.†; HSL, NZ.†*
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E supplement; scars; stretch marks; wounds.

Micerfin *LKM, Arg.*
Lomifylline (p. 2545·1); dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders.

Micerol *Ratiopharm, Ukr.†*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea; restoration of gastrointestinal flora; acne.

Micetal *CSC, Austria; Biosintetica, Braz.; Silesia, Chile; Medicom, Cz.; CSC, Hung.; Scharper, Ital.; Hormona, Mex.; Uriach, Pol.; Vifor, Spain.*
Flutrimazole (p. 582·1).
Fungal skin infections; pityriasis capitis; seborrhoeic dermatitis.

Micetinoftalmina *Davi, Port.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Micfox *Alde Medi Impex, India.*
Cefixime (p. 240·3).
Bacterial infections.

Michol *Boehringer Ingelheim, S.Afr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Miciclin *Reuffer, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Micifrona *Arafarma, Spain.*
Lespedeza capitata.
Uraemia.

Micin *Biosans, India.*
Amikacin (p. 214·1).
Bacterial infections.

Micitrex *Bausch & Lomb, Mex.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Miclast *Pierre Fabre, Ital.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.
Pierre Fabre, Spain.
Ciclopirox (p. 575·3).
Fungal nail infections.

Miclobet *Rayere, Mex.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Miclogenta *Yash, India.*
⊗Clobetasol butyrate (p. 1627·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Miclonazol *Cazi, Braz.*
Clotrimazole (p. 576·2).
Fungal infections.

Miclox *Multilab, Braz.*
⊗Metoprolol tartrate (p. 1434·3).

Micmat *Janssen-Cilag, S.Afr.*
Miconazole nitrate (p. 589·1).

Mico-B *Elfin, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Micoban *Genepharm, Gr.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Micobeta *Betapharm, Ger.†*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micobutina *Ariston, Arg.*
Amorolfine (p. 569·1).
Fungal nail infections.

Micocept *Sandoz, Hong Kong.*
Mycophenolate mofetil (p. 1961·1).
Cardiac, hepatic, or renal transplant rejection.

Micocert *Sidus, Arg.*
Piroctone olamine (p. 1716·3); climbazole (p. 576·2).
Scalp disorders.

Micocide *Atlas, Arg.*
Econazole nitrate (p. 577·3).
Fungal skin, nail, and vaginal infections.

Micocide A *Atlas, Arg.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Micoclin *Monserrat, Arg.*
Clotrimazole (p. 576·2).
Fungal skin and vulvovaginal infections.

Micocort-G *Themis Medicare, India.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); miconazole (p. 588·3).
Skin infections.

Micodual *Atlas, Arg.*
Climbazole (p. 576·2); piroctone olamine (p. 1716·3).
Scalp disorders.
K2 Health & Wellness, Chile.
Climbazole (p. 576·2); piroctone olamine (p. 1716·3); aloe vera (p. 1693·2).
Seborrhoeic dermatitis; dandruff.

Micoespec
Note: this name may be used for preparations of different composition.
Euroderm, Arg.
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.
Centrum, Spain.†
Econazole nitrate (p. 577·3).
Fungal skin and nail infections.

Micofeet *SM, Venez.*
Boric acid (p. 2459·3); calamine (p. 1697·2); zinc oxide (p. 1729·1); salicylic acid (p. 1719·1); camphor (p. 2466·2); menthol (p. 2553·2).
Foot hygiene.

Micoffen *Offenbach, Mex.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micofim *Elofar, Braz.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micoflup *Aivax, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Micoflux *Dollder, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Micofoot *Zeta, Ital.*
Undecenoic acid (p. 596·3); usnic acid (p. 2640·2); salicylic acid (p. 1719·1); aluminium acetate (p. 2440·1).
Fungal skin infections; disinfection of skin, burns, and wounds.

Micogal
Note: this name may be used for preparations of different composition.
Teva, Ukr.
Omoconazole nitrate (p. 591·3).
Fungal infections.

Micogel *Arterium, Ukr.*
Miconazole (p. 588·3).
Fungal skin and nail infections.
Cipla, India.
Miconazole nitrate (p. 589·1).
Fungal infections of the skin and nails; Gram-positive bacterial skin infections.

Micogel F *Cipla, India.*
⊗Miconazole nitrate (p. 589·1); fluocinolone acetonide (p. 1636·1).
Fungal skin infections.

Micogen *Genepharm, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections with inflammation.

Micogram *Glenmark, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Micogyn *Elofar, Braz.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Micogynax *Mekophar, Ukr.*
⊗Metronidazole (p. 936·1); chloramphenicol (p. 257·1); dexamethasone acetate (p. 1631·1); nystatin (p. 590·3).
Vaginal infections.

Micolamina *Theraskin, Braz.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal skin and nail infections.

Micolette *AFT, Austral.; Pinewood, Irl.; Pinewood, UK.*
⊗Sodium lauril sulfoacetate (p. 2210·3); sodium citrate (p. 1781·2); glycerol (p. 2517·2).
Constipation; bowel evacuation.

Micolis *Roemmers, Arg.; Pharma Invesi, Chile.*
Econazole nitrate (p. 577·3).
Fungal and Gram-positive skin infections; fungal vaginal infections.

Micolis Novo *Roemmers, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Micolon *Johnson & Johnson, India.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).

Micolysin *Labialfarma, Port.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Micomax
Note: this name may be used for preparations of different composition.
Plata, Arg.†
Clotrimazole (p. 576·2).
Fungal skin infections; vulvitis; balanitis.

Micomazol *Invesi, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Micomazol B *Invesi, Arg.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Micomazol Deo *Invesi, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Micomicen *Sanofi-Aventis, Ital.*
Ciclopirox olamine (p. 575·3).
Vulvovaginal candidiasis.

Micomisan *Adcock Ingram, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin infections; vaginal candidiasis.

Micon
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.
Savoy, India.
Meropenem (p. 321·3).
Bacterial infections.

Miconacina *Grin, Mex.*
Natamycin (p. 590·2).
Bacterial eye infections.

Miconal *Ecobi, Ital.; Polfa Tarchomin, Pol.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections; secondary Gram-positive bacterial infections; fungal skin and nail infections.

Miconan *Ativus, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Miconax
Note: this name may be used for preparations of different composition.
Meyer Alian, Venez.
Econazole nitrate (p. 577·3).
Fungal skin infections.

Micon-H *Beacons, Singapore.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone acetate (p. 1640·1).
Fungal skin and nail infections.

Miconihol *Avva, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Miconit *East West, India.*
Miconazole nitrate (p. 589·1).
Fungal infections.

Miconix *Genetic, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Miconol *Lafedar, Arg.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Miconorm *Ratiopharm, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Micopirox *Cassara, Arg.; D & M, Chile.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal skin, nail, and scalp infections.

Micoplex *Cazi, Braz.*
Tiabendazole (p. 166·3); neomycin sulfate (p. 330·1).
Skin infections.

Micoptic *FDC, India.*
Miconazole (p. 588·3).
Fungal infections.

Micopul *Pharmatrix, Arg.*
Miconazole nitrate (p. 589·1).
Fungal nail and skin infections.

Micoral *Investi, Arg.; Elofar, Braz.*
Ketoconazole (p. 585·3).
Fungal infections; dandruff; seborrhoeic dermatitis.

Micoral Fluco *Investi, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Micoren *Novartis Consumer, Ital.†*
⊗Prethcamide (p. 2329·3).
Respiratory insufficiency.

Micos *AGIPS, Ital.*
Econazole (p. 577·2) or econazole nitrate (p. 577·3).
Fungal infections; Gram-positive bacterial infections.

Micosbel *Belfar, Braz.*
Tiabendazole (p. 166·3).

Micosep *Cassara, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Micosep B *Cassara, Arg.*
⊗Clotrimazole (p. 576·2); betamethasone dipropionate (p. 1623·3).
Fungal skin infections with inflammation.

Micoser *Serral, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Micoset *Bago, Chile.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Micosil *Teuto, Braz.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Micoskin *Corsa, Indon.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Micosol *Cassara, Arg.*
Bifonazole (p. 573·3).
Fungal skin infections.

Micoson *Agio, India; Agio, Philipp.; Cipla, Rus.*
Miconazole nitrate (p. 589·1).
Fungal skin infections; vulvovaginal candidiasis.

Micosona *Intendis, Spain.†*
Naftifine hydrochloride (p. 590·1).
Fungal skin and nail infections.

Micosone *Christo, Hong Kong.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone acetate (p. 1640·1).
Fungal skin infections with inflammation.

Micostal *Elofar, Braz.†*
Nystatin (p. 590·3).
Candidiasis.

Micostalab *Multilab, Braz.*
Nystatin (p. 590·3).
Candidiasis.

Micostatin *Merck Serono, Arg.; BMS, Braz.; Merck, Chile; BMS, Mex.; BMS, Venez.*
Nystatin (p. 590·3).
Fungal infections.

Micostatin Baby *BMS, Mex.*
Nystatin (p. 590·3); zinc (p. 2126·1).
Fungal skin infections.

Micostyl *Stiefel, Braz.; Stiefel, Mex.*
Econazole nitrate (p. 577·3).
Fungal skin, scalp, and nail infections.

Micotar *Dermapharm, Ger.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections of the skin and mucous membranes.

Micotar ZP *Dermapharm, Ger.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Fungal skin infections.

Micotarin *Uniao Quimica, Braz.†*
Miconazole (p. 588·3).
Fungal infections.

Micotef *Teofarma, Ital.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal infections; Gram-positive bacterial infections.

Micotenk *Biotenk, Arg.*
Itraconazole (p. 583·3).
Fungal infections.

Micotex *Nycomed, Mex.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); aluminium zirconium glycine hydroxytetrachloride.
Fungal skin infections.

Sertex, Arg.
Econazole nitrate (p. 577·3).
Fungal skin infections.

Micotgez *Gezzi, Arg.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micotiazol *Cazi, Braz.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); iodine (p. 2336·3).
Fungal skin infections.

Micoticum *Mecosin, Indon.†; Domac, Spain.†*
Ketoconazole (p. 585·3).
Fungal infections.

Micotin *Sanval, Braz.*
Oxiconazole nitrate (p. 591·3).
Fungal skin infections.

Micotral *Austral, Arg.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micotran *Xeno, Philipp.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Micotrat *Delta, Braz.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Micotrim *Schering-Plough, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Micotrim P *Schering-Plough, Arg.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Micotrin *Vitapan, Braz.†*
Miconazole (p. 588·3).
Fungal skin infections.

Micoxolamina *Mastelli, Ital.*
Ciclopirox olamine (p. 575·3).
Fungal infections.

Micozen *Teuto, Braz.*
Miconazole nitrate (p. 589·1).
Fungal skin and vaginal infections.

Micozol
Note: this name may be used for preparations of different composition.
Sandoz, Mex.
Ketoconazole (p. 585·3).
Fungal infections.

Vivax Gynopharm, Venez.
Clotrimazole (p. 576·2).
Genital fungal infections.

Micozole *Taro, Canad.; AFT, NZ.*
Miconazole nitrate (p. 589·1).
Balanitis; vaginal fungal infections.

Micpro *Chandra Bhagat, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Micral Test *Roche Diagnostics, Irl.†*
Test for microalbuminuria.

Micral Test II *Roche Diagnostics, Braz.†; Roche Diagnostics, Mex.*
Test for microalbuminuria.

Roche Diagnostics, UK.
Test for microalbuminuria in diagnosis of diabetic nephropathy.

Micralax *Johnson & Johnson, Spain; Focus, UK.*
Sodium citrate (p. 1781·2); sodium alkylsulfoacetate (p. 2210·3).
Constipation; bowel evacuation; painful defaecation.

Micralax Macrogol *Johnson & Johnson, Spain.*
Macrogol 3350 (p. 2547·3).
Constipation.

Micraleve *Ivax, Arg.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Micraltest II *Roche, Chile.*
Test for microalbuminuria.

Micranex *Vamsler, Philipp.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Micranil *Phoenix, Arg.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

Micrazim *Abba, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Micrell *Gojo, Canad.*
Chloroxylenol (p. 1748·2).
Hand disinfection.

Microm *Merck, Indon.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Micreme *Mylan, NZ.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial vulvovaginal infections; balanitis.

Micreme H *Mylan, NZ.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

MICRhoGAM *Ortho Diagnostic, USA.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Micrhogam *Johnson & Johnson, India.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Micro + *Sandoz, Israel.*
Trace elements.
Parenteral nutrition.

Micro I *Sandoz, Canad.*
Sodium iodide (p. 2337·1).
Trace element additive.

Micro Clear *Woodward, Canad.*
Benzalkonium chloride (p. 1737·1).

Micro Cr *Sandoz, Canad.; Sandoz, Israel.*
Chromium trichloride (p. 2055·3).
Trace element additive; parenteral nutrition.

Micro Cu *Sandoz, Canad.; Sandoz, Israel.*
Copper sulfate (p. 2057·2).
Trace element additive; parenteral nutrition.

Micro Mn *Sandoz, Canad.; Sandoz, Israel.*
Manganese sulfate (p. 2081·2).
Trace element additive; parenteral nutrition.

Micro Mox *Micro, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Micro Plus *Sandoz, Canad.*
A range of trace element preparations.
Parenteral nutrition.

Micro Se *Sandoz, Canad.*
Selenious acid (p. 2087·1).
Trace element additive.

Micro Zn *Sandoz, Canad.; Sandoz, Israel.*
Zinc sulfate (p. 2126·2).
Trace element additive; parenteral nutrition.

Microalbustix *Bayer Diagnostics, Irl.†*
Test for albumin and creatinine in urine.

Microbamat *Sanochemia, Austria.†*
Meprobamate (p. 1083·3).
Anxiety disorders; sleep disorders.

Microbar-HD (E-Z-HD) *Bracco, Switz.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal double-contrast radiography.

Microbiane Q10 *Pileje, Fr.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1).
Tonic.

Microcal
Note: this name may be used for preparations of different composition.
Micro, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Microcal-M *Micro, India.*
Minerals; colecalciferol (p. 2113·1).

Microcef *Micro, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Microcetim *Cipan, Port.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Microcid
Note: this name may be used for preparations of different composition.
Bioglan, Denm.; Bioglan, Norw.; Bioglan, Swed.
Hydrogen peroxide (p. 1755·2).
Bacterial skin infections; impetigo.

Micro, India.
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Microcidal *Aspen, S.Afr.*
Griseofulvin (p. 582·2).
Fungal infections of the skin and nails.

Microcidum *Lvovdialik, Ukr.*
Extract of culture from *Penicillium vitale*.
Bacterial infections.

Microcilin *Sel-J, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Microcip *Ikon, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Microcip-TZ *Ikon, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Microclean *Visiontec, Arg.*
Cleaner for contact lens.

Microclismata *Farmakochimiki, Gr.†*
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Microclismi Marco Viti *Marco Viti, Ital.†*
⊗Glycerol (p. 2517·2); chamomile (p. 2474·1); mallow (p. 2549·2).
Bowel evacuation; constipation.

Microdase *Winsome, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Microdase-D *Winsome, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Microdase-DP *Winsome, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Microdep *Micro, India.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Microdine *Centaur, India.*
Povidone-iodine (p. 1767·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Microdiol *Schering-Plough, Braz.; Organon, Israel; Organon, Spain.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Kimia, Indon.
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Microdoïne *Gomenol, Fr.*
Nitrofurantoin (p. 332·1).
Cystitis.

Microdol *Sel-J, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Microdol Forte *Micro, India.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Microdox
Note: this name may be used for preparations of different composition.
Micro, India.
Capsules; dispersible tablets; dR-tablets:
Doxycycline (p. 288·1).
Bacterial infections.

Micro, India.
Tablets: Ambroxol hydrochloride (p. 1654·3); doxycycline hyclate (p. 288·2).
Respiratory-tract infections.

Micro, Singapore.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Microfem *Lafedar, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Microfer *Vianex (Βιανεξ), Gr.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Micro, India.
Iron sucrose (p. 2078·1).

Microflox *Micro, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Micro, Singapore; Micro, Thai.†
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Microflox-CT *Micro, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Microflox-DX *Micro, India.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).

Microfollin *Gedeon Richter, Rus.*
Ethinylestradiol (p. 2275·3).
Menstrual disorders; lactation inhibition; acne; prostatic cancer; menopausal disorders.

Microfulvin *Psyco Remedies, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair and nail infections.

Microgard *Stedman, India.*
⊗Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).

Microgard Tulle *Stedman, India.*
Chlorhexidine acetate (p. 1743·2); white soft paraffin (p. 2211·3).
Wounds.

Microgat *Micro, India.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Microgat-DX *Micro, India.*
⊗Dexamethasone (p. 1630·3); gatifloxacin (p. 303·2).

Microgel *Adcock Ingram, S.Afr.†*
Oral suspension: Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3); simeticone (p. 1886·2).
Peptic ulcer; gastritis; gastric hyperacidity; flatulence.

Microgen *Silesia, Chile.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Micro-Gesic *Pharma-Q, S.Afr.*
Syrup: Paracetamol (p. 115·1).
Fever; pain.

Micro, S.Afr.†
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain associated with tension.

Microgest
Note: this name may be used for preparations of different composition.
Bushnell, India.
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Bayer Schering, Thai.†
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Microgeste
Note: this name may be used for preparations of different composition.
Bayer, Port.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Microginon *Bayer, Port.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Micro-Guard
Note: this name may be used for preparations of different composition.
Coloplast, USA.†
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Microgyn *Bayer, Denm.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Microgynon *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Chile; Bayer Schering, Cz.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Israel; Bayer, Ital.; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Schering, Philipp.†; Bayer Schering, Pol.; Bayer, Rus.; Bayer, Singapore; Bayer, Spain; Bayer, Switz.; Schering, Turk.; Bayer, Ukr.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Bayer Schering, Indon.; Bayer, Thai.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Microgynon 30 *Bayer Schering, Malaysia; Bayer, UK.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Microiodid *Tatkhimfarm, Rus.*
Potassium iodide (p. 2336·3).
Goitre.

Micro-K *Paladin, Canad.; Continental Ethicals, S.Afr.†; Ther-Rx, USA.*
Potassium chloride (p. 1793·2).
Potassium depletion; potassium supplement; hypokalaemia.

Microka *Valeant, Mex.†*
Vitamin A (p. 2098·3); phytomenadione (p. 2122·2).
Periorbital hyperpigmentation; purpura; petechiae; bruising; telangiectasia.

Micro-Kalium *GL Pharma, Austria.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Microklist *Janssen-Cilag, Austria; McNeil, Ger.; Janssen-Cilag, Switz.*
Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3); sorbitol (p. 2092·1).
Constipation; bowel evacuation.

Microlac *Bal, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Microlax
Note: this name may be used for preparations of different composition.
McNeil, Denm.; McNeil Healthcare, Irl.; Johnson & Johnson Consumer, Mex.; Jaba Recordati, Port.
Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3).
Constipation; bowel evacuation.

Johnson & Johnson, Austral.; McNeil, Belg.; McNeil Consumer, Canad.; McNeil, Fin.; Johnson & Johnson, Fr.; Pfizer, Hong Kong†; McNeil, Norw.; Pharmacia, NZ; Johnson & Johnson, Rus.; Johnson & Johnson, Singapore; McNeil, Swed.; Janssen-Cilag, Switz.
Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3); sorbitol (p. 2092·1).
Bowel evacuation; constipation.

Johnson & Johnson, Neth.
Sodium lauril sulfoacetate (p. 2210·3); sorbitol (p. 2092·1).
Constipation; bowel evacuation.

Pharos, Indon.
Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3); sorbitol (p. 2092·1); macrogol 400 (p. 2547·3).
Constipation; bowel evacuation.

Microlenyn *DKT, Thai.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Microleptin *Micro, Mex.*
Gabapentin (p. 523·3).
Epilepsy.

Microlet *Dexcel, Israel.*
⊗Sodium citrate (p. 1781·2); sodium lauril sulfoacetate (p. 2210·3); glycerol (p. 2517·2).
Constipation.

Microlevlen ED *Bayer, Austral.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Microlift *Lagos, Arg.*
Marine algae; wheat germ (p. 2647·1).
Skin disorders.

Microlipid *Nestle, Canad.; Nestle, USA.*
Preparation for enteral nutrition containing safflower oil (p. 2086·3).

Microlite *Bayer, Irl.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Microlut *Bayer, Arg.; Bayer, Austral.; Bayer, Belg.; Bayer, Ger.; Bayer Schering, Indon.; Bayer, Israel; Bayer, Mex.; Bayer, NZ; Bayer Schering, Rus.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Microluton *Bayer Schering, Fin.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Micromex *Lafi, Chile.*
Omeprazole (p. 1867·2).
Gastric hyperacidity.

Micromox *Micro, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Micromycin *Darier, Mex.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Micronac *Micro, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Micro, India.
Topical gel: Aceclofenac (p. 16·2); capsicum oleoresin (p. 2469·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Micronac Plus *Micro, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Micronac-MR *Micro, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Micronase *Pharmacia Upjohn, USA.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Micronat *Ankom, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Micronazol *Hospital Line, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Micron-C *Dynamic, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias due to deficiency of iron, folic acid, or vitamin B; vitamin B_{12} deficiency.

microNefrin *Bird, USA.†*
⊗Racepinefrine hydrochloride (p. 1292·1).
Bronchospasm.

Micronema *Pfizer, Arg.*
⊗Glycerol (p. 2517·2); sodium laurilsulfate (p. 2210·3); sorbitol (p. 2092·1).
Constipation.

Micronoan *Abbott, Ital.*
Diazepam (p. 1063·2).
Epilepsy; sedative.

Micronor *Janssen-Cilag, Austral.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Singapore†; Janssen-Cilag, UK.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Micronovag *Novag, Mex.*
⊗Glycerol (p. 2517·2).
Bowel evacuation.

Micro-Novum *Janssen-Cilag, S.Afr.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Micronovum *Janssen-Cilag, Austria; Janssen-Cilag, Switz.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Micropakine *Sanofi-Aventis, Fr.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; febrile convulsions.

Micropaque *Guerbet, Austria; Codali, Belg.; Guerbet, Cz.; Guerbet, Denm.†; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; IFET (ΙΦΕΤ), Gr.; Guerbet, Hung.; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Switz.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography and computerised tomography.

Micropec *American Remedies, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Microphyllin *Sanofi-Aventis, S.Afr.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Micropil
Note: this name may be used for preparations of different composition.
Dyna, Philipp.
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
Combined oral contraceptive; dysfunctional uterine bleeding.

Sigma, Braz.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-Day packs also contains 7 inert tablets.
Combined oral contraceptive.

Micropil Plus *Dyna, Philipp.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive; dysfunctional uterine bleeding.

Micropime *Micro, India.*
Cefepime (p. 239·2).
Bacterial infections.

Micropirin *Dexcel, Israel; Ratiopharm, UK.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Micropur Forte DCCNa *Katadyn, Fr.*
Troclosene sodium (p. 1774·1); silver (p. 2615·1).
Water disinfection.

Micropyrin *Piramal, India.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain; inflammation; musculoskeletal and joint disorders.

Microret *Royal, Chile†; Darier, Mex.*
Vitamin A (p. 2098·3).
Skin hyperpigmentation; wrinkles; skin ageing.

Microret K *Royal, Chile†; Darier, Mex.*
Vitamin A (p. 2098·3); vitamin K (p. 2122·1).
Skin hyperpigmentation; wrinkles; skin ageing.

Microrgan *Liomont, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Microser *Nycomed, Arg.; Grunenthal, Chile; Formenti, Cz.; Formenti, Hung.; Formenti, Ital.; Formenti, Pol.; Formenti, Rus.; Grunenthal, Venez.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders; nausea and vomiting; nystagmus; Ménière's disease.

Microshield *Johnson & Johnson, Austral.; Johnson & Johnson, India.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Microshield Antimicrobial Hand Gel *Johnson & Johnson, Austral.†*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Microshield Antiseptic *Johnson & Johnson, Austral.†; Johnson & Johnson, India.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin, wound, burn, and instrument disinfection.

Microshield Handrub *Johnson & Johnson, Austral.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Skin disinfection.

Microshield PVP *Johnson & Johnson, Austral.; Johnson & Johnson, India.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Microshield PVP-S *Johnson & Johnson, Austral.†; Johnson & Johnson, India.*
Povidone-iodine (p. 1767·1).
Skin, wound, and burn disinfection; bacterial or fungal skin and mucous membrane infections.

Microshield T *Johnson & Johnson, Austral.; Johnson & Johnson, India.*
Triclosan (p. 1773·2).
Skin disinfection.

Microshield Tincture *Johnson & Johnson, Austral.*
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Skin, surface, and instrument disinfection.

Microsol
Note: this name may be used for preparations of different composition.
Micro, India.
⊗Chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Boiron, Fr.†
Trace elements; minerals.

Microsona *Roemmers, Arg.; Valeant, Mex.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Microsona C *Roemmers, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); ketoconazole (p. 585·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Microsona Otica *Roemmers, Arg.*
⊗Hydrocortisone (p. 1640·1); acetic acid (p. 2426·3).
Ear disorders.

Microspan-40 *Claris, India.*
⊗Dextran 40 (p. 1138·1).

Microstix-3 *Bayer, USA.*
Test for nitrite in urine and for bacterial growth.

Microsulf *Microsules, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Microsuy *Bernabo, Arg.*
Rutoside (p. 2505·3) or troxerutin (p. 2505·3); coumarin (p. 2487·2).
Venous insufficiency; haemorrhoids.

Microtaz *Micro, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Microtec *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Microterol *Microsules, Arg.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Microtid *Kener, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Microtin *Hovid, Hong Kong.†*
Miconazole (p. 588·3).

Microtina *Pyridam, Indon.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Microtrast *Codali, Belg.; Guerbet, Cz.†; Guerbet, Denm.; Guerbet, Fr.; Guerbet, Ger.; Guerbet, Hung.; Martins & Fernandes, Port.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Microvac *Dupomar, Arg.*
Streptococcus pneumoniae; Staphylococcus aureus; Streptococcus viridans; Haemophilus influenzae; Klebsiella pneumoniae.
Respiratory-tract infections.

Microvaccin
Note: this name may be used for preparations of different composition.
Prater, Chile.
Fluconazole (p. 578·2).
Fungal infections.

Microval *Wyeth, Austral.†; Wyeth, Chile; Codepharma, Fr.; Pfizer, Irl.; Aspen, S.Afr.; Wyeth, Venez.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Microvibrate *Castalia, Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Microvir *Micro, India.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Microvisc *Eco, S.Afr.*
Sodium hyaluronate (p. 2526·2).

Microvita *Valeant, Mex.†*
Vitamin A (p. 2098·3).
Acne; sun-induced skin damage; keratinisation disorders; cellulitis.

Microvlar *Bayer, Arg.; Bayer, Braz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Microxin *Rayere, Mex.*
Norfloxacin (p. 333·3).
Bacterial infections.

Microzef *Sel-J, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Microzepam *Microsules, Arg.*
Lorazepam (p. 1080·3).
Anxiety.

Microzide *Watson, USA.*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Microzol *Sel-J, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Mictasol
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Norfloxacin (p. 333·3); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Medgenix, Belg.
Camphor monobromide (p. 2467·1); methenamine (p. 322·3); mallow fruit (p. 2549·2).
Urogenital disorders; anorectal disorders.

Millet Roux, Braz.
Mallow (p. 2549·2); camphor monobromide (p. 2467·1); methylthioninium chloride (p. 1559·1).
Urinary-tract infections.

Mictasol Azul *Millet-Franklin, Arg.*
Mallow (p. 2549·2); camphor monobromide (p. 2467·1); methylthioninium chloride (p. 1559·1).
Genito-urinary tract disorders.

Mictasone *Formenti, Ital.†*
⊗Hydrocortisone acetate (p. 1640·1); tetracycline hydrochloride (p. 373·2); mallow (p. 2549·2).
Genito-urinary tract infections; haemorrhoids.

Mictonetten *Apogepha, Cz.; Apogepha, Ger.*
Propiverine hydrochloride (p. 2363·1).
Bladder disorders; urinary incontinence.

Mictonorm *Nycomed, Belg.; Apogepha, Cz.; Apogepha, Ger.; Vianex (Βιανεξ), Gr.; Apogepha, Hong Kong; Phapros, Indon.; Apogepha, Philipp.; Apogepha, Port.; Apogepha, Singapore; Apogepha, Thai.†; Sandoz, Thai.†; Frik, Turk.*
Propiverine hydrochloride (p. 2363·1).
Urinary incontinence; bladder instability; neurogenic bladder.

Mictop-F *Ind-Swift, India.*
⊗Fluocinolone acetonide (p. 1636·1); miconazole nitrate (p. 589·1).

Mictrin *Econo Med, USA.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Micturol Sedante *SIT, Spain.*
Phenazopyridine hydrochloride (p. 124·3); sulfamethizole (p. 365·1).
Urinary-tract infections.

Micyn-2 *Meyer, Venez.*
Pectin (p. 2200·3); activated attapulgite (p. 1820·1).
Diarrhoea.

Midacina *Lensa, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); gramicidin (p. 308·3); neomycin (p. 329·3).
Infected skin disorders.

Midacum *Hexal, S.Afr.*
Midazolam (p. 1085·1).
Sedative; premedication; general anaesthesia.

Midadorm *Biochimico, Braz.*
Midazolam (p. 1085·1).

Midalet *Silesia, Chile.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Midalgan Nouvelle Formule *Qualicare, Switz.†*
Glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3).
Muscle and joint disorders.

Midamor *MSD, Austral.†; AA, Canad.; MSD, NZ†; Paddock, USA.*
⊗Amiloride hydrochloride (p. 1299·1).
Oedema; hypertension; heart failure; hypokalaemia; hepatic cirrhosis with ascites.

Midane *Pelpharma, Austria.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-associated acne, alopecia, or hirsutism in women; oral contraceptive in women with androgenic symptoms.

Midanium *Polfa Warszawa, Pol.; Cipla-Medpro, S.Afr.†*
Midazolam (p. 1085·1).
Premedication; general anaesthesia; sedative.

Midapharma *Alpharma, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Midapic *Rusan, India.*
Midazolam (p. 1085·1).
Induction of anaesthesia; sedative; premedication.

Midarine *GSK, India; GSK, Ital.; GSK, Switz.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Midatenk *Biotenk, Arg.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Midaven *Merck, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Midax *Gador, Arg.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Midaz *Abbott, India.*
Midazolam (p. 1085·1).
Induction of anaesthesia; sedative; premedication.

Midazen *Halden, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Midazepin *Behrens, Venez.*
Midazolam (p. 1085·1).

Midazoject *Akacia, S.Afr.*
Midazolam (p. 1085·1).

Midazol
Note: this name may be used for preparations of different composition.
Taro, Israel.†
Midazolam (p. 1085·1).
Premedication; general anaesthesia; status epilepticus.

Midazol Ofteno
Note: this name may be used for preparations of different composition.
Sophia, Mex.
⊗Naphazoline hydrochloride (p. 1669·3); antazoline phosphate (p. 615·3).

Midecin *Farmaka, Ital.†*
Midecamycin (p. 324·3).
Bacterial infections.

Midelin *Quimica y Farmacia, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Miderizone *Meditop, Hung.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Miderlar *Chinta, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Miderm *Mendelejeff, Ital.†*
Miconazole (p. 588·3).
Fungal and Gram-positive bacterial infections.

Midermus *Biosintex, Arg.*
Range of emollient creams.

Midermus Sol *Biosintex, Arg.*
Range of sunscreens.

Midetol *Precimex, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Midexone *SM, Philipp.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Midiana *Gedeon Richter, Ital.; Richter, Pol.; Gedeon Richter, Ukr.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Midium *Teofarma, Ital.*
Vitamin A palmitate (p. 2098·3); tocoferil acetate (p. 2119·2); pyridoxine hydrochloride (p. 2105·3).
Metabolic disorders.

Midodrine *Pharos, Indon.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Midol
Note: this name may be used for preparations of different composition.
Alna, India.
Tramadol (p. 139·2).
Pain.

Invida, Philipp.
Ibuprofen (p. 68·2).
Pain.

Midol C *Hemofarm, Rus.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).

Midol Cramp & Body Aches *Bayer Consumer, USA.*
Ibuprofen (p. 68·2).
Dysmenorrhoea; musculoskeletal and joint disorders.

Midol Maximum Strength Multi-Symptom Menstrual *Sterling Health, USA.*
Paracetamol (p. 115·1); mepyramine maleate (p. 635·1).
Pain.

Midol Night-Time *Bayer Consumer, Canad.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).

Midol PM *Sterling Health, USA.*
Paracetamol (p. 115·1); diphenhydramine (p. 626·1).

Midol PMS *Bayer Consumer, Canad.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Midol Pre-Menstrual Syndrome *Bayer Consumer, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Menstrual disorders.

Midol Teen *Bayer Consumer, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); mepyramine maleate (p. 635·1).

Midol Teen Formula *Bayer Consumer, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1).
Menstrual disorders.

Midolam *Rafa, Israel.*
Midazolam (p. 1085·1).
Premedication; general anaesthesia; status epilepticus.

Midolat *Olainfarm, Rus.*
Meldonium (p. 1429·3).
Cerebrovascular disorders; ischaemic heart disease; tonic; alcohol withdrawal syndrome.

Midolen *Degorts, Mex.*
Aspirin (p. 22·2).
Pain; fever.

Midon *Nycomed, Irl.*
⊗Midodrine hydrochloride (p. 1437·3).
Orthostatic hypotension.

Midonat *Aurora, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Midosed *Sun, India.*
Midazolam (p. 1085·1).
Induction of anaesthesia; sedative; premedication.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Midotens *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim Promeco, Mex.*
Lacidipine (p. 1417·3).
Hypertension.

Midozor *Teva, Mex.*
Midazolam hydrochloride (p. 1085·1).
Premedication; sedative; general anaesthesia.

Midrat *Sandoz, Mex.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Midria Phoenix *Elea, Arg.*
Tropicamide (p. 2012·2); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis and cycloplegia.

Midriatico *Llorens, Spain.†*
Atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis; eye disorders.

Midriax-T *Klonal, Arg.*
Tropicamide (p. 2012·2); phenylephrine (p. 1672·2).
Production of mydriasis and cycloplegia.

Midric *Sanbe, Indon.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Midrid *DHP, UK.*
⊗Isometheptene mucate (p. 2535·1); paracetamol (p. 115·1).
Migraine.

Midrin *Women First, USA.*
⊗Isometheptene mucate (p. 2535·1); dichloralphenazone (p. 1071·3); paracetamol (p. 115·1).
Tension and vascular headaches.

Midriodavi *Davi, Port.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis.

Midro
Note: this name may be used for preparations of different composition.
Kela, Belg.; Midro, Switz.
Tablets: Senna (p. 1885·1).
Constipation.
Pasquali, Ital.
Senna (p. 1885·1); liquorice (p. 1853·2); peppermint leaf (p. 1877·1); caraway (p. 2470·2).
Constipation.

Midro Abfuhr *Midro, Ger.*
Senna (p. 1885·1).
Constipation.

Midro Tee *Midro, Ger.; Midro, Switz.*
Senna (p. 1885·1).
Constipation.

Sanova, Austria.
Senna (p. 1885·1); peppermint leaf (p. 1877·1); caraway (p. 2470·2); liquorice (p. 1853·2); delphinium consolida; mallow flowers (p. 2549·2).
Constipation.

Midro-Tea *Midro, Israel.*
Senna (p. 1885·1); peppermint leaf (p. 1877·1); caraway (p. 2470·2); liquorice (p. 1853·2); delphinium consolida flower; mallow flower (p. 2549·2).
Constipation.

Midu *Ebewe, China; Sandoz, China.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; auto-immune disorders.

Miduret *PP Lab, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hepatic cirrhosis with ascites; hypertension.

Midzee *Gland, India.*
Midazolam hydrochloride (p. 1085·1).
Induction of anaesthesia; sedative; premedication.

Midzol *Chandra Bhagat, India.*
Midazolam hydrochloride (p. 1085·1).
Induction of anaesthesia; sedative; premedication.

Mielastra *Veropharm, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Mielax *Valma, Chile.†*
Senna (p. 1885·1); honey (p. 2072·1).

Mielito *Ximena Polanco, Chile.*
Honey (p. 2072·1); herbal extract.
Colds and influenza; tonic.

Mielocol *Herbes Universelles, Canad.†*
Guaifenesin (p. 1666·2); aralia racemosa; cineole (p. 2479·1); honey (p. 2072·1); poplar buds (p. 2594·2); sanguinaria (p. 2610·1); white pine; wild cherry (p. 2647·2).

Mielogen *Schering-Plough, Gr.*
Molgramostim (p. 1156·2).
Neutropenia; bone marrow transplantation.

Mieteni *United Lab, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Mifebort *Taj, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; labour induction following intra-uterine fetal death; post-coital oral contraceptive.

Mifegest *Zydus, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy.

Mifegyn *Izvarino, Rus.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour.

Mifégyne *Nordic, Fr.; Cosan, Switz.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour following intra-uterine fetal death.

Mifegyne *Exelgyn, Austria; Pharma Logistics, Belg.; Exelgyn, Denm.; Exelgyn, Fin.; Nordic, Ger.; Exelgyn, Gr.; Exelgyn, Israel; Nordic, Neth.; Exelgyn, Norw.; Istar, NZ; Exelgyn, Port.; Medi Challenge, S.Afr.; Exelgyn, Spain; Nordic, Swed.; Nordic, UK.*
Mifepristone (p. 2138·1).
Termination of pregnancy.

Mifelar *Arlex, Mex.*
Metformin (p. 489·1).
Diabetes mellitus.

Mifelar-C *Arlex, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Mifenac *East West, India.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; pain.

Mifeprex *Mosfarma, Rus.; Danco, USA.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour; postcoital oral contraceptive.

Mifeprin *Sun, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; labour induction following intra-uterine fetal death; post-coital oral contraceptive.

Miferiv *East African, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; labour induction following intra-uterine fetal death; post-coital oral contraceptive.

Miflasona *Novartis, Braz.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Miflasone *Novartis, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Mifler *Velka, Gr.†*
⊗Fluprednidene (p. 1637·3); miconazole (p. 588·3).
Fungal skin disorders.

Miflexin *Adamed, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Miflo *Promedica, Ital.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Miflonid *Novartis, Cz.*
⊗Budesonide (p. 1625·1).
Asthma.

Miflonide *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Denm.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Switz.; Novartis, Turk.; Novartis, Venez.*
⊗Budesonide (p. 1625·1).
Asthma; bronchodilator; obstructive airways disease.

Miflonil *Novartis, Fr.*
⊗Budesonide (p. 1625·1).
Asthma.

Miflox-DM *Sun, India.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Mifloxin *Community Pharmacy, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Mifolian *New Hualian, China; Huan Lian, Rus.*
Mifepristone (p. 2138·1).
Termination of pregnancy; postcoital oral contraceptive; labour induction.

Miformin *GreaterPharma, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mifurol *Bayer, China; Bayer, Jpn.†*
Carmofur (p. 761·1).
Gastrointestinal cancer; breast cancer; colorectal cancer.

Mifuzide *Milano, Thai.*
Nifuroxazide (p. 331·3).
Diarrhoea.

MIG *Berlin-Chemie, Fin.; Berlin-Chemie, Pol.*
Ibuprofen (p. 68·2).
Pain; fever.

Mig *Berlin-Chemie, Rus.*
Ibuprofen (p. 68·2).
Pain; fever.

Migana *T Man, Thai.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine; vascular headache.

Migard *Menarini, Belg.; Menarini, Denm.; Menarini, Fin.; Menarini, Gr.; Menarini, Neth.; Menarini, Port.; Menarini, Swed.; Menarini, UK.*
Frovatriptan succinate (p. 676·2).
Migraine.

Migarid *Cipla, India; Cipla, Malaysia.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Migatane *Chanelle, Neth.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Migazin *Morepen, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Migea *Hexal, Cz.†; Sandoz, Denm.; Angelini, Gr.; Sandoz, Norw.; Sandoz, Pol.*
Tolfenamic acid (p. 138·3).
Migraine.

Migel *Keryos, Ital.*
Acetylcysteine (p. 1652·2); hyaluronic acid (p. 2526·2); vitamin E (p. 2119·1).
Nasal congestion.

Migentax *Geofman, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Migergot *G & W, USA.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).

Mighty *Active, India.*
Cyanocobalamin (p. 2107·2); ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2).

Mighty Plus *Active, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Mighty-SF *Active, India.*
Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2).

Miglen *Casasco, Arg.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Miglit *Biocon, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Miglucan *Roche, Fr.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Mignar *Glenmark, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Migon *Cadila, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Migprin *Sanofi Synthelabo, Turk.*
Lysine aspirin (p. 84·3); metoclopramide (p. 1862·2).

Migpriv *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fin.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Swed.†; Sanofi-Aventis, Switz.†*
Lysine aspirin (p. 84·3); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migra Dioxadol *Bago, Arg.*
Metamizole magnesium (p. 53·3); ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Migra Dorixina *Roemmers, Arg.*
Clonixin lysine (p. 40·1); ergotamine tartrate (p. 674·1).
Migraine.

Migrabeta TR *Alkem, India.*
⊗Propranolol (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; essential tremor.

Migracin *Max Farma, Ital.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Migradon *Trenka, Austria.*
Propyphenazone (p. 127·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Migradorixina *Roemmers, Venez.*
Clonixin lysine (p. 40·1); ergotamine tartrate (p. 674·1).
Migraine.

Migraeflux *Hennig, Cz.†*
Dimenhydrinate (p. 625·2); paracetamol (p. 115·1).
Migraine.

Migraeflux MCP *Hennig, Ger.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migrafen *Chatfield Laboratories, UK.*
Ibuprofen (p. 68·2).

Migrafin *Sanofi-Aventis, Neth.*
Lysine aspirin (p. 84·3); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migragesic *Andromaco, Chile.*
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Migraine and other vascular headaches.

Migragesic IDA *Acella, USA.*
⊗Isometheptene mucate (p. 2535·1); paracetamol (p. 115·1); dichloralphenazone (p. 1071·3).
Migraine; tension headache.

Migraherb *MedicHerb, UK.*
Feverfew (p. 676·1).
Migraine.

Migraine Aid *Blackmores, Austral.*
Feverfew (p. 676·1).
Migraine.

Migraine Ice *Mentholatum, UK.*
Water-based gel compress.
Migraine and other severe headache.

Migraine-Kranit
Note: this name may be used for preparations of different composition.
Lubapharm, Switz.
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Migraine and other vascular headaches.

Migral
Note: this name may be used for preparations of different composition.
Montpellier, Arg.
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); dipyrone (p. 53·3).
Migraine.

Migral II *Montpellier, Arg.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3); ergotamine tartrate (p. 674·1).
Migraine.

Migral Compositum *Montpellier, Arg.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); dipyrone (p. 53·3); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migralave + MCP *Temmler, Ger.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migraleve
Note: this name may be used for preparations of different composition.
Charwell, Israel; Llorens, Spain.
Buclizine hydrochloride (p. 618·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2); docusate sodium (p. 1836·2).
Migraine and other vascular headaches.
Johnson & Johnson, Port.; Unipharma, Switz.†
Buclizine hydrochloride (p. 618·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Migraine and other vascular headaches.
McNeil Healthcare, Irl.; McNeil, UK.
Pink tablets, buclizine hydrochloride (p. 618·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2); yellow tablets, paracetamol; codeine phosphate (p. 40·2).
Migraine.

Migralgine *Johnson & Johnson, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Migralin *Menarini, Gr.*
Frovatriptan succinate (p. 676·2).
Migraine.
Euro Generics, Philipp.
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Migraliv *Sigma, Braz.*
Caffeine (p. 1203·3); dipyrone (p. 53·3); dihydroergotamine mesilate (p. 672·2).
Migraine.

Migramax *Cephalon, UK.*
Lysine aspirin (p. 84·3); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migran *Konimex, Indon.†*
Paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain.

Migranal *Amdipharm, Austria; SteriMax, Canad.; Novartis, Neth.†; Valeant, USA.*
Dihydroergotamine mesilate (p. 672·2).
Migraine.

Migranat *Rowa, Irl.†*
Caffeine (p. 1203·3); ergotamine tartrate (p. 674·1); pipoxolan hydrochloride (p. 2591·3).
Migraine and other vascular headaches.

Migrane *Sigma, Braz.*
Aspirin (p. 22·2); ergotamine tartrate (p. 674·1); homatropine methylbromide (p. 2007·3); caffeine (p. 1203·3).
Migraine.

Migräne Hevert *Hevert, Ger.*
Oral drops: Aconitum (p. 2428·3); gelsemium (p. 2511·2); glonoinum (p. 1391·2); iris versicolor (p. 2534·3); atropin sulf. (p. 1310·2); secale cornutum (p. 2137·1).
Homoeopathic preparation.
Hevert, Ger.†
Injection: Aconitum (p. 2428·3); gelsemium (p. 2511·2); glonoinum (p. 1391·2); iris versicolor (p. 2534·3); secale cornutum (p. 2137·1); spigelia (p. 2621·3).
Homoeopathic preparation.

Migra-Nefersil *Pharma Investi, Chile.*
Clonixin lysine (p. 40·1); ergotamine tartrate (p. 674·1).
Migraine and other vascular headaches.

Migräne-Gastreu R16 *Reckeweg, Ger.*
Cimicifuga (p. 2478·1); gelsemium (p. 2511·2); iris versicolor (p. 2534·3); sanguinaria (p. 2610·1); spigelia anthelmia (p. 2621·3).
Homoeopathic preparation.

Migraneitor *Driburg, Arg.*
Sumatriptan (p. 679·2).
Migraine.

Migräne-Kranit *Krewel, Ger.*
Phenazone (p. 124·1).
Migraine.

Migräne-Neuridal *Krewel, Ger.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine and other vascular headaches.

Migranerton *Dolorgiet, Cz.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine and other vascular headaches.

Migränerton *Dolorgiet, Ger.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine and other vascular headaches.

Migranette *Sigma, Braz.*
⊗Dipyrone (p. 53·3); isometheptene mucate (p. 2535·1); caffeine (p. 1203·3).
Migraine.

Migranil *Inga, India.*
Injection: Dihydroergotamine mesilate (p. 672·2).
Migraine.
Inga, India.
Tablets: Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); belladonna (p. 2453·3); paracetamol (p. 115·1).
Migraine; cluster headache.

Migränin Ibuprofen *Reckitt Benckiser, Ger.†*
Ibuprofen (p. 68·2).
Headache including migraine.

Migränin Phenazon *Reckitt Benckiser, Ger.†*
Phenazone (p. 124·1).
Fever; pain; headache including migraine.

Migranol *Bago, Chile.*
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Migraprim *Sanofi-Aventis, Ital.*
Lysine aspirin (p. 84·3); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Migraspirina *Bayer, Port.*
Aspirin (p. 22·2).
Migraine.

Migrastat *Gerard, Irl.*
Sumatriptan succinate (p. 679·2).
Migraine.

Migrastick *Ecopharma, Chile; Arkopharma, UK.*
Lavender oil (p. 2541·1); peppermint oil (p. 1877·1).
Migraine; headache.

Migratam *Laboratorios Chile, Chile.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); dipyrone (p. 53·3).
Migraine and other vascular headaches.

Migratan *Dabur, India.*
Sumatriptan (p. 679·2).

Migratapsin *Maver, Chile.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); dihydroergotamine mesilate (p. 672·2).
Migraine.

MigraTen *Pharmelle, USA.*
⊗Isometheptene mucate (p. 2535·1); caffeine (p. 1203·3); paracetamol (p. 115·1).
Migraine; tension headache.

Migraval *Giempi, Venez.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

Migrax *Saval, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); dihydroergotamine mesilate (p. 672·2).
Vascular headache.

Migrazone *Breckenridge, USA.*
⊗Paracetamol (p. 115·1); dichloralphenazone (p. 1071·3); isometheptene mucate (p. 2535·1).
Migraine.

Migrecure *Sterkem, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Migrenol
Note: this name may be used for preparations of different composition.
Four Ventures, Rus.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.
Sanofi-Aventis, Pol.†
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); mint oil (p. 2560·1); menthol (p. 2553·2).
Migraine; neuromuscular pain.

Migrenopas *Pascoe, Austria.†*
Gelsemium (p. 2511·2); cyclamen (p. 2490·2); paris quadrifolia; asarum europaeum (p. 2449·3).
Homoeopathic preparation.

Migretil *Bial, Port.*
Belladonna (p. 2453·3); caffeine (p. 1203·3); ergotamine tartrate (p. 674·1); paracetamol (p. 115·1).
Migraine.

Migrex *Sandoz, S.Afr.*
Sumatriptan (p. 679·2).
Migraine.

Migrid *Crescent, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine.

Migril
Note: this name may be used for preparations of different composition.
GSK, India.
Caffeine (p. 1203·3); cyclizine hydrochloride (p. 623·2); ergotamine tartrate (p. 674·1).
Migraine; cluster headache.
iNova, S.Afr.; Wockhardt, UK.
Ergotamine tartrate (p. 674·1); cyclizine hydrochloride (p. 623·2); caffeine hydrate (p. 1203·3).
Migraine.

Migrin *Utopian, Thai.*
Pizotifen malate (p. 678·2).
Migraine; cluster headache.

Migristene *Aventis, Indon.†; Sanofi-Aventis, Mex.†*
Dimetotiazine mesilate (p. 626·1).
Migraine.

Migroben *Novartis, S.Afr.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Migrof *Chibret, Port.†*
Rizatriptan benzoate (p. 678·3).
Migraine.

Migset *Cipla, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Migsis *Pfizer, Jpn.*
Lomerizine hydrochloride (p. 676·3).
Migraine.

Migtal *Saval, Chile.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Migtor *Torrent, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Mihexine *Milano, Thai.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mijex *Pickles, UK.*
Gel; topical liquid; topical spray; topical stick: Diethyltoluamide (p. 2153·1).
Insect repellent.

Mijex Extra *Pickles, UK.*
Ethyl butylacetylamino propionate (p. 2154·3).
Insect repellent.

Mikabit *Cubit, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikacin *Aristo, India; Julphar, UAE.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Mikafine *Finecure, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikaject *Troikaa, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikan *Boniscontro & Gazzone, Ital.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Mikaphar *Biophar, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikapime *Alembic, India.*
Amikacin (p. 214·1); cefepime (p. 239·2).
Bacterial infections.

Mikasin *Kalbe, Indon.; Abfar, Turk.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Mikastar *Mankind, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikasul *Caplin, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Mikatax *Alkem, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Mikavir *Salus, Ital.†*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Mikazul *Ederka, Mex.†*
Amikacin (p. 214·1).
Bacterial infections.

Mikclav *Trumac, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Mikelan *Otsuka, China; Merck Serono, Fr.; Otsuka, Jpn; Otsuka, Philipp.; Otsuka, Spain.*
⊗Carteolol hydrochloride (p. 1332·3).
Hypertension; glaucoma; ocular hypertension; arrhythmias; angina pectoris.

Miker *Evershine, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikesan *Baliarda, Arg.*
Ergotamine tartrate (p. 674·1); cyproheptadine hydrochloride (p. 624·1); clonixin (p. 40·1).
Migraine.

Mi-Ke-Sons *Sons, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Mikicort *Mayoly-Spindler, Fr.*
⊗Budesonide (p. 1625·1).
Crohn's disease; diarrhoea in collagenous colitis.

Mikif *Positif, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mikilac *Servocare, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mikilac Kidtab *Servocare, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mikilac Plus *Servocare, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mikka *Syndicate, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Miklogen *Klonal, Arg.*
⊗Miconazole (p. 588·3); betamethasone valerate (p. 1624·1); gentamicin (p. 304·2).
Infected skin disorders.

Miko *Genesis, India.*
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.
Genesis, India.
Tablets: Vitamin B substances (p. 2102·3).

Miko G *Genesis, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mikoderm *Adeka, Turk.†*
Tolnaftate (p. 596·1).
Fungal skin infections.

Mikogal *Teva, Hung.; Teva, Rus.*
Omoconazole nitrate (p. 591·3).
Fungal and bacterial skin, nail, and vulvovaginal infections.

Mikonafin *Munir, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Mikonos *Investi, Arg.*
Grape (p. 2521·3).
Varicose veins.

Miko-OD *Genesis, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Miko-Penetran *Embil, Turk.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Mikorex *Bintang Toedjoe, Indon.†*
Menthol (p. 2553·2); salicylic acid (p. 1719·1); undecenoic acid (p. 596·3); benzoic acid (p. 1738·2).
Fungal skin infections.

Mikostat *Julphar, Malaysia; Julphar, UAE.*
Nystatin (p. 590·3).
Candidiasis.

Mikostat Baby Ointment *Julphar, UAE.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Nappy rash; fungal skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mikostatin *BMS, Turk.*
Nystatin (p. 590·3).
Candidiasis.

Mikozal *Julphar, UAE.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mikrazym *Avva, Rus.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive-system disorders.

Mikrex *Micro Labs, Ukr.*
Cefuroxime (p. 255·2).
Bacterial infections.

Mikrobac *Bode, Ger.*
Benzalkonium chloride (p. 1737·1); laurylamine dipropylenediamine (p. 1759·2).
Surface disinfection.

Mikrobac basic *Bode, Ger.*
Benzalkonium chloride (p. 1737·1).
Surface disinfection.

Mikrobac Tissues *Bode, Ger.*
Benzalkonium chloride (p. 1737·1); didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Mikrobiel *Verisfield, Gr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Mikrosid *BMS, Turk.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Miksor *Teva, Cz.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Miktosan *Sandoz, Gr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Mikutan N *Streuli, Switz.†*
Aluminium acetate (p. 2440·1); zinc oxide (p. 1729·1).
Burns; skin disorders.

Mil *Sun, India.*
⊗Boric acid (p. 2459·3); chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Eye strain.

3Mil *Milte, Ital.*
Colecalciferol (p. 2113·1); phytomenadione (p. 2122·2); pyridoxine (p. 2105·3).

Mila-Asma *Milano, Thai.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Mila-Cono *Milano, Thai.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Milactif *Texinfine, Fr.*
Portulaca oleracea.
Dietary supplement; age-associated neurodegenerative disorders.

Milador *Sandoz, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Milafed *Milano, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; nasal congestion; hay fever; allergic rhinitis.

Milage *Cadila, India.*
Preparation for enteral nutrition.
Nutritional supplement.

Milagin *Milano, Thai.*
Capsules: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.
Milano, Thai.
Syrup: Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.
Sperko, Ukr.
Clindamycin (p. 269·3).
Bacterial vaginosis.

Milamet *Milano, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Milamox *Milano, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Milanfore *Synthesis, Rus.*
Bortezomib (p. 752·1).
Multiple myeloma; mantle cell lymphoma.

Milanidazole *Milano, Thai.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Milano *Geno, India.*
Withania somnifera (p. 2450·2).

Milanolone *Milano, Thai.†*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth disorders.

Milanox *Diapit, Gr.*
Amino acids.
Parenteral nutrition.

Mila-Tercon *Milano, Thai.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Milavir *Sandoz, Port.*
Aciclovir (p. 964·1).
Herpes labialis.

Mila-Vita *Milano, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Milax
Note: this name may be used for preparations of different composition.
Berlin-Chemie, Ger.
⊗Glycerol (p. 2517·2).
Bowel evacuation; constipation.

Milbeta
Note: this name may be used for preparations of different composition.
Offenbach, Mex.
Cyanocobalamin (p. 2107·2); hydroxocobalamin (p. 2107·3).
Sun, India.
⊗Betamethasone (p. 1623·2).

Milbeta-N *Sun, India.*
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin (p. 329·3).
Infected eye disorders.

Milborn *Sun, India.*
Milnacipran (p. 435·3).

Milcef *Comed, India.*
Cefuroxime (p. 255·2) or cefuroxime axetil (p. 255·2).
Bacterial infections.

Milco *Piam, Ital.*
Preparation for enteral nutrition.
Phenylketonuria.

Milcobalin *Richet, Arg.*
Hydroxocobalamin (p. 2107·3); thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Neuritis; vitamin supplement.

Milcopen *Leiras, Fin.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Mild Multi-Tar Plus *Valeant, Canad.*
Coal tar (p. 1723·2); cade oil (p. 1723·2); pine tar (p. 1723·3); pyrithione zinc (p. 1718·1).
Scalp disorders.

Mildac *Merck Medication Familiale, Fr.*
St John's wort (p. 449·1).
Depression.

Milderm *Jose Lea, Singapore.*
Skin cleanser.
Dry skin; acne.

Mildex *Parggon, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin (p. 329·3).
Infected eye disorders.

Mildim *Purewin, India.*
Gliclazide (p. 472·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mildin *Orifarm, Denm.*
Loratadine (p. 633·2).
Allergic rhinitis; hay fever; urticaria.

Mildison *Astellas, Denm.; Astellas, Neth.†; Astellas, Norw.; CSL, NZ; Astellas, Swed.; Astellas, UK.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders; eczema; dermatitis.

Mildronate *Grindex, Rus.; Grindeks, Ukr.*
Meldonium (p. 1429·3).
Cardiovascular disorders; cerebrovascular disorders; retinal vascular disorders; alcohol withdrawal syndrome; tonic; ischaemic heart disease; heart failure; retinal disorders.

Mildroxyn *Makiz-Pharma, Rus.*
Meldonium (p. 1429·3).
Tonic; alcohol withdrawal syndrome; ischaemic heart disease; cerebrovascular disorders.

Milenim *Geno, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Miles Nervine *Miles, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Mileva *Elea, Arg.; Elea, Mex.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive in women with androgenic symptoms; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; polycystic ovary syndrome.

Milezzol *Randall, Mex.*
Metronidazole (p. 936·1).
Trichomoniasis.

Milfer *Velka, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Milflox Plus *Sun, India.*
Ketorolac trometamol (p. 80·2); moxifloxacin (p. 326·3).

Milgamma
Note: this name may be used for preparations of different composition.
Worwag, Cz.; Worwag, Hung.
Benfotiamine (p. 2102·3); cyanocobalamin (p. 2107·2).
Neurological symptoms associated with vitamin B deficiency; vitamin B deficiency.
Worwag, Ger.; Worwag, Hong Kong; Worwag, Pol.; Worwag, Rus.; Worwag, Ukr.
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Neurological symptoms associated with vitamin B deficiency; vitamin B deficiency; vneuritis; neuralgia; neuropathy; myalgia.
Worwag, Rus.; Worwag, Ukr.
Injection: Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuritis; neuralgia; neuropathy; myalgia.

Milgamma Compositum *Worwag, Rus.*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Neuritis; neuralgia; neuropathy; myalgia.

Milgamma mono *Worwag, Ger.*
Benfotiamine (p. 2102·3).
Vitamin B_1 deficiency.

Milgamma N *Worwag, Cz.; Worwag, Hung.*
Benfotiamine (p. 2102·3); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Neurological symptoms associated with vitamin B deficiency; myalgia; neuritis; neuralgia.
Worwag, Cz.; Worwag, Ger.
Thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Neurological symptoms associated with vitamin B deficiency; neuritis; neuralgia; polyneuropathy; myalgia.
Worwag, Pol.
Thiamine (p. 2102·3); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to reduce the pain of injection.
Neuralgia; neuropathy; neuritis.

Milgamma neuro *Worwag, Hung.*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency; neuralgia.

Milgamma protekt *Worwag, Ger.*
Benfotiamine (p. 2102·3).
Vitamin B_1 deficiency.

Milgamma-NA *Worwag, Ger.†*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Neurological symptoms associated with vitamin B deficiency.

Mili Nosik *Mili, Ukr.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; upper respiratory-tract disorders.

Milibend *Glenmark, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Milical
Note: this name may be used for preparations of different composition.
Glenmark, India; Glenmark, Malaysia.
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium supplement; dietary supplement in pregnancy and lactation; osteoporosis.
Lafi, Chile; Vivax Gynopharm, Venez.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Milical XP *Glenmark, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).
Iron-deficiency anaemia; tonic.

Milice *Mipharm, Ital.*
Piperonyl butoxide (p. 2160·2); pyrethrin (p. 2161·1).
Pediculosis.

Milicor *Samarth, India.*
Milrinone lactate (p. 1438·1).
Heart failure.

Miliom-D *Glenmark, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Miliser *Gynopharm, Chile.*
Folic acid (p. 2063·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Milistan For Children *Mili, Ukr.*
Paracetamol (p. 115·1).
Pain; fever.

Milistan Cough *Mili, Ukr.*
Ambroxol hydrochloride (p. 1654·3); carbocisteine (p. 1658·1).
Respiratory tract disorders associated with viscous bronchial secretions.

Milistan Cough Hot Tea *Mili, Ukr.*
Ambroxol hydrochloride (p. 1654·3); ascorbic acid (p. 2110·3).
Respiratory tract disorders associated with viscous bronchial secretions.

Milistan Hot Tea for Children Orange *Mili, Ukr.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Cold symptoms; rhinitis; headache; fever.

Milistan Hot Tea Lemon *Mili, Ukr.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold symptoms; rhinitis; sinusitis.

Milistan Multisymptomic *Mili, Ukr.*
Paracetamol (p. 115·1); cetirizine hydrochloride (p. 619·2); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Symptoms of influenza and other viral respiratory-tract infections; allergic upper respiratory tract disorders; pain.

Milithin *Minerva (Μινερβα), Gr.*
Lithium carbonate (p. 427·3).
Mania; bipolar disorder.

Milivo *Glenmark, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Milixim *Glenmark, India.*
Cefixime (p. 240·3).
Bacterial infections.

Milixim-CV *Glenmark, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Milixim-LX *Glenmark, India.*
Cefixime (p. 240·3); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Milk of Magnesia *Teva, Canad.; GSK, Gr.; GSK Consumer, Irl.; Humco, Israel; Charoen, Thai.; Utopian, Thai.; Omega, UK; Cypress, USA; Roxane, USA.*
Magnesium hydroxide (p. 1857·2).
Constipation; gastric hyperacidity; dyspepsia; heartburn; antacid; laxative.

Milk Thistle *Nutravite, Canad.†*
Cynara flower (p. 2490·3); milk thistle (p. 1561·1); turmeric rhizome (p. 2218·1).

Milk Thistle Complex *Bioforce, UK.*
Cynara (p. 2490·3); milk thistle (p. 1561·1); taraxacum (p. 2625·3); boldo (p. 2458·3).
Dyspepsia; flatulence.

Milk Thistle Extract Formula *Quest, Canad.*
Lappa (p. 2540·1); taraxacum root (p. 2625·3); liquorice root (p. 1853·2); milk thistle (p. 1561·1); wild yam root (p. 2648·1).
Liver disorders.

Milkal *McNeil & Argus, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Milkal-G *McNeil & Argus, India.*
Calcium (p. 1783·1).
Calcium supplement.

Milkcal *Bombay Tablet, India.*
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Milky-Rich *Invision, India.*
Syrup: Calcium (p. 1783·1); phosphorus (p. 2589·2).
Invision, India.
Tablets: Calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).

Milkytab *Speciality Meditech, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).

Milla *SIT, Ital.*
Chamomile (p. 2474·1).

Millda *Millimed, Thai.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Millefolium Complexe No 7 *Lehning, Fr.†*
Achillea millefolium (p. 2427·3); anemone pulsatilla (p. 2600·2); atropa belladonna (p. 2453·3); causticum (p. 2595·3); cinchona (p. 2478·3); equisetum arvense (p. 2500·1); nux vomica (p. 2573·3); plantago major (p. 2592·3); rubia; sulfur (p. 1721·1).
Homoeopathic preparation.

Millerspas *Aspen, S.Afr.†*
Hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); phenobarbital (p. 535·2).
Peptic ulcer; renal and biliary colic; reduction of respiratory and gastrointestinal secretions.

Millibar *Lisapharma, China; Lisapharma, Hong Kong†; Lisapharma, Ital.*
⊗Indapamide (p. 1409·2).
Hypertension.

Millicortenol *Novartis, India.*
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Millicorten-Vioform *Novartis, India.*
⊗Dexamethasone pivalate (p. 1630·3); clioquinol (p. 273·1).
Infected skin disorders; anal or vulval pruritus.

Millidol *Millimed, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Milligest *Gedeon Richter, Cz.; Sandoz, Denm.; Gedeon Richter, Hung.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Triphasic oral contraceptive.

Milligynon *Bayer, Fr.†*
Norethisterone acetate (p. 2294·3).
Progestogen-only oral contraceptive.

Millinette *Consilient, UK.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Millipred *Laser, USA.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Millisrol *Khandelwal, India†; Kayaku, Jpn.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; hypertension during surgery; controlled hypotension.

Milmor *Pharos, Indon.*
Placenta extract (p. 2444·1); vitamin B_{12} (p. 2107·2); calcium phosphate (p. 1784·2).
Lactation insufficiency.

Milmor NF *Pharos, Indon.*
Sauropus androgynus; fenugreek (p. 2504·1).
Lactation insufficiency.

Milna *Stragen, Denm.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Milnace *Torrent, India.*
Milnacipran hydrochloride (p. 435·3).

Milneuron NA *Worwag, Ger.†*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Neurological symptoms associated with vitamin B deficiency.

Milocardin *Polpharma, Pol.*
Bromisoval (p. 1041·3); mint oil (p. 2560·1); phenobarbital sodium (p. 535·3); lupulus oil.
Nervous disorders; gastrointestinal motility disorders.

Miloderme *Schering-Plough, Port.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Milopin *Baroda, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Miloride *Mylan, Fin.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; liver cirrhosis with ascites.

Milorin *Ifars, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Milorix *Gramon, Arg.†*
Pramocaine hydrochloride (p. 1993·3); phenylephrine hydrochloride (p. 1672·3); white soft paraffin (p. 2211·3).
Haemorrhoids.

Milovan *Ivax, Rus.*
Zopiclone (p. 1118·1).
Sleep disorders.

Miloz *Novell, Indon.*
Midazolam (p. 1085·1).
Premedication; anaesthesia; sedative.

Mil-Par *Sanofi-Aventis, Arg.; Merck Consumer, UK; Sanofi-Aventis, Venez.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2).
Constipation.

Milpar *Seven Seas, Irl.; Sanofi-Aventis, Mex.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2).
Constipation.

Milperinol *Pierre Fabre Sante, Belg.*
St John's wort (p. 449·1).
Depression.

Milpid *Millimed, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Milrila *Astellas, Jpn.*
Milrinone (p. 1438·1).
Heart failure.

Milron *United Biotech, India.*
Milrinone (p. 1438·1).
Heart failure.

Milrosina *Orravan, Spain.*
Resorcinol (p. 1718·3); borax (p. 2459·2).
Mouth ulcers.

Milsan *Merck, Mex.†*
Preparation for enteral nutrition.
Gastro-enteritis.

Milsana *Milte, Ital.*
Zinc oxide (p. 1729·1).
Nappy rash; barrier cream.

Miltab *Medreich, India.*
Calcium (p. 1783·1).

Miltaun *Nycomed, Austria.†*
Meprobamate (p. 1083·3).
Anxiety disorders; sleep disorders; skeletal muscle spasticity; premedication.

Miltex *Baxter, Austria; Asta Oncologia, Braz.†; Baxter, Chile; Baxter, Fin.†; Baxter Oncology, Fr.; Baxter Oncology, Ger.; Baxter, Hung.; Baxter, Israel†; Baxter, Ital.; Baxter, Philipp.†; Baxter Oncology, Singapore; Baxter, Spain†; Baxter, Swed.†; IDIS, UK.†*
Miltefosine (p. 829·3).
Skin metastases of breast cancer.

Miltina IPO *Milte, Ital.*
Infant feed.
Food intolerance.

Miltis *Millimed, Thai.*
Silymarin (p. 1561·2).
Liver disorders.

Milton *Procter & Gamble, Austral.; Ceuta, UK.*
Troclosene sodium (p. 1774·1).
Disinfection of surfaces and equipment.

SIT, Ital.; Ceuta, UK.
Sodium hypochlorite (p. 1768·3).
Disinfection; sterilisation of feeding bottles; water purification; decontamination of fruit and vegetables.

Milukant *Adamed, Ukr.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Milukante *Adamed, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Milumel AR *Milumel, Fr.*
Infant feed.
Regurgitation.

Milumel Confort *Milumel, Fr.*
Infant feed.
Infant colic; constipation.

Milumel HA *Milumel, Fr.*
Infant feed.
Milk-protein allergy.

Milupa Basic *Nutricia, Cz.*
Infant feeds.
Metabolic disorders.

Milupa Cystilac *Milupa, Pol.*
Infant feed.
Cystic fibrosis.

Milupa GA *Nutricia, Cz.*
Food for special diets.
Glutaric aciduria type 1.

Milupa GES *Milupa, Switz.†*
Oral rehydration solution (p. 1780·1).
Diarrhoea.

Milupa HN 25 *Nycomed, Mex.*
Food for special diets.
Diarrhoea; gluten intolerance.

Milupa HOM *Nutricia, Cz.*
Food for special diets.
Homocystinuria.

Milupa LEU *Nutricia, Cz.*
Food for special diets.
Disorders of leucine metabolism.

Milupa lpd *SHS, UK.*
Food for special diets.
Inherited disorders of amino-acid metabolism in childhood.

Milupa LYS *Nutricia, Cz.*
Food for special diets.
Disorders of lysine metabolism.

Milupa MSUD *Nutricia, Cz.*
Food for special diets.
Disorders of branched-chain amino-acid metabolism.

Milupa OS *Nutricia, Cz.*
Food for special diets.
Methylmalonic acidaemia; propionic acidaemia.

Milupa PKU *Milupa, Pol.*
A range of foods for special diets.
Phenylketonuria.

Nutricia, Cz.
Infant feed.
Phenylketonuria; hyperphenylalaninaemia.

Milupa PKU 2 and 3 *SHS, UK.*
Food for special diets.
Phenylketonuria.

Milupa TYR *Nutricia, Cz.*
Food for special diets.
Tyrosinaemia.

Milupa UCD *Nutricia, Cz.*
Food for special diets.
Urea cycle disorders.

Milurit *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Pol.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Milvane *Bayer, Denm.; Bayer, Ital.; Bayer Schering, Pol.; Bayer, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Milzimmunosyx *Syxyl, Ger.*
Ceanothus americanus; cinchona pubescens (p. 2478·3).
Homoeopathic preparation.

Milzone *Rubio, Spain.†*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Mim *Meyer, India.*
Vitamins; minerals.

Mima *New Life, Thai.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure.

Mimastran *Mimer, Denm.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Mimedran *Esteve, Spain.†*
Piperazine sultamate (p. 163·1).
Hyperlipidaemias.

Mimetix *Drugtech, Chile.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Mimixin *Merck Serono, Arg.*
Buflomedil (p. 1328·3); diosmin (p. 2505·2).
Peripheral vascular disorders; thromboses; venous insufficiency.

Mimor *Mac, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Mimosee *Intas, India.*
Clindamycin (p. 269·3).
Acne.

Mimpara *Amgen, Austria; Amgen, Belg.; Mantecorp, Braz.; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Amgen, Gr.; IFET (ΙΦΕΤ), Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Israel; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Rus.; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Eczacibasi, Turk.; Amgen, UK.*
Cinacalcet hydrochloride (p. 1180·1).
Hypercalcaemia in parathyroid cancer; hypercalcaemia in primary hyperparathyroidism; hyperparathyroidism in dialysis patients with end-stage renal failure.

Mimvey *Teva, USA.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Mimyx *GSK, USA.†*
⊗Betaine (p. 2456·1); olive oil (p. 2575·1); glycerol (p. 2517·2); pentylene glycol; palm glycerides; vegetable oil; squalane (p. 2213·3); hyetellose (p. 2188·3); carbomer (p. 2173·3); xanthan gum (p. 2220·1).
Burning and pruritus associated with eczema.

Min An Fen *Ke Yi, China.*
Terfenadine (p. 640·3).

Min Cough *New York Chemical, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cough; cold symptoms.

Min Da *Tian Da, China.*
Cetirizine hydrochloride (p. 619·2).

Min Huil *Neo Dermos, Arg.*
Pyrithione zinc (p. 1718·1).
Pityriasis.

Min Jie *Peiling, China.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Min Li Ke *Yellow River, China.*
Loratadine (p. 633·2).

Min Nuo Bin *Minsheng, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Min Qi *Yun Feng, China.*
Azelastine hydrochloride (p. 617·1).

Min Si Tong *Guo Feng, China.*
Pemirolast potassium (p. 1218·2).

Min Xin *Jing Xin, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Min Xing *Chang Fu Jie Jing, China.*
Pazufloxacin mesilate (p. 338·1).

Minac 50 *Spirig, Switz.*
Minocycline hydrochloride (p. 325·1).
Acne.

Minachlor *Esoform, Ital.*
Tosylchloramide sodium (p. 1773·1).
Disinfection of wounds, burns, and external genitalia.

Minadex *Abdi, Turk.*
Vitamins.

Seven Seas, Irl.
Vitamins; minerals.
Dietary supplement; tonic.

Seven Seas, UK.
Vitamins; with or without minerals.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

USP, India.
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc (p. 2126·1).

Minafen
Note: this name may be used for preparations of different composition.
Drogsan, Turk.
Paracetamol (p. 115·1).
Fever; pain.

Minakne *Galen, Ger.*
Minocycline hydrochloride (p. 325·1).
Acne.

Minalerg *Minerva (Μινερβα), Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Minalfène *Bouchara-Recordati, Fr.*
Alminoprofen (p. 20·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Minalgin *Streuli, Switz.*
Dipyrone (p. 53·3).
Pain; fever; colic.

Minalka *Cedar Health, UK.*
Minerals; vitamin D (p. 2112·3).
Musculoskeletal and joint disorders.

Minamino *Ayrton, UK.*
Vitamin B substances (p. 2102·3); amino acids; minerals.

Aspen Consumer, S.Afr.†
Amino acids; vitamin B substances (p. 2102·3); minerals; organ extracts.
Tonic.

Minamint *Grimberg, Arg.*
Xylitol (p. 2220·3); CPC; chlorophyll (p. 2178·3).
Halitosis.

Minaphlex *Nutricia, Austral.†; Nutricia, Cz.; SHS, Irl.; SHS, Pol.; SHS, UK.†*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Min-A-Pon *Minerva (Μινερβα), Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Minaral *Procure, India.*
Vitamins; minerals.

Minarex *Boniscontro & Gazzone, Ital.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis of the knee.

Minartine *Minerva (Μινερβα), Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Minastrin 24 FE *Warner Chilcott, USA.*
24 Capsules, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 4 capsules, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Minatozil *Aspen, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Minatuss *Minerva (Μινερβα), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Minax *Alphapharm, Austral.; Alphapharm, Hong Kong; Merck, Thai.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; migraine; myocardial infarction.

Minaxen *Aegis, Hong Kong.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minazol
Note: this name may be used for preparations of different composition.
Cimed, Braz.
Phenazopyridine (p. 124·3); nitroxoline (p. 333·2).
Urinary-tract infections.

Clinifood, Singapore.
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mincetam *Minova, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Mincifit *Arkopharma, Fr.†*
Black currant leaves (p. 2458·1); green tea (p. 2648·2).
Obesity.

Mincifit Body Shaper *Arkopharma, Singapore.*
9-Hydroxy-10,12-octadecadienoic acid from ivy (Hodeol); caffeine (p. 1203·3); green tea (p. 2648·2); ivy (p. 2536·2); willow (p. 129·2); hydrocitric acid from garcinia cambogia (p. 2510·2); peach extract.

Mincifit Hodeol *Arkopharma, Singapore.*
9-Hydroxy-10,12-octadecadienoic acid from ivy (Hodeol); juniper oil (p. 2537·2); vitamin E (p. 2119·1).

Mincifit Stretch Mark *Arkopharma, Singapore.*
Emollient.
Stretch marks.

Minclea *Nihon, Jpn.*
Levomenthol (p. 2553·2).
Inhibition of peristalis during upper gastrointestinal endoscopy.

Mincovit *PC India, India.*
Capsules: Vitamins; minerals.

PC India, India.
Syrup: Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Mindac *Eagle, Austral.*
Bacopa monniera (p. 2452·1); ginkgo biloba (p. 2512·3); centella asiatica (p. 1698·3); ashwagandha (p. 2450·2); schisandra chinensis (p. 2611·2); ginger (p. 1844·1); glutamine (p. 2070·3); magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1); strychnos nux vomica (p. 2573·3); pyridoxine hydrochloride (p. 2105·3).
Tonic.

Mindiab *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
Glipizide (p. 474·1).
Diabetes mellitus.

Mindol
Note: this name may be used for preparations of different composition.
Micro, India.
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

USP, India.
Diclofenac sodium (p. 48·3).
Pain.

Mindol Forte *Micro, India.*
Haloperidol (p. 1077·1); trihexyphenidyl (p. 917·3).

Mindol Plus *Micro, India.*
Haloperidol (p. 1077·1); trihexyphenidyl (p. 917·3).

Minedon *Help, Gr.*
Glucosamine sulfate (p. 2515·3).

Minelza *Bilim, Turk.*
Mirtazapine (p. 436·1).

Minera *Hua, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Minerace *Svizera, India.*
Vitamins; minerals.

Mineral *Volchem, Ital.*
Minerals.

Mineral Freez Gel *Geritrex, USA.*
Menthol (p. 2553·2).

Mineral Zinc *Mason, USA.*
Calcium (p. 1783·1); zinc (p. 2126·1).

Minerali *CTS, Israel.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); citric acid (p. 2480·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Mineralin *Doctum, Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Constipation.

Minerals+ *Homeocan, Canad.*
Natrium sulphuricum (p. 1888·1); silicea (p. 2208·3); calcarea carbonica (p. 1824·3); calcarea iodata (p. 1658·1); calcarea phosphorica (p. 1784·2); natrum phosphoricum (p. 1791·2); magnesia phosphorica (p. 1787·3); ferrum phosphoricum (p. 2077·1); rubia tinctorum; juglans regia (p. 2646·1).
Homoeopathic preparation.

Minerasol *Pharno-Wedropharm, Ger.*
Emser salts.
Nasal congestion.

Minerbon *Diba, Mex.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis; rickets; osteomalacia; renal osteodystrophy.

Minerin *Major, USA.*
Emollient.
Dry skin.

Minero
Note: this name may be used for preparations of different composition.
Daniel Pasteur, India.
Capsules: Vitamins; minerals; ginseng (p. 2513·3).

Daniel Pasteur, India.
Syrup: Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Orifarm, Denm.; Orifarm, Fin.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Minerovit *Cifarma, Braz.*
Vitamins; minerals.

Minerva
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
21 Tablets, cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Androgen-dependent acne, alopecia, and hirsutism; combined oral contraceptive.

Bayer, Austria; Bayer Schering, Cz.; Biogaran, Fr.; Bayer Schering, Hung.; Berlipharm, Neth.; Berlis, Switz.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-associated acne, alopecia, hirsutism, or seborrhoea in women; oral contraceptive in women with androgenisation.

Orchid, India.
Miglitol (p. 491·3).
Diabetes mellitus.

Minervicomplex *Provita, Ital.*
Vitamins; minerals.

Minervit *Pielle, Ital.*
Vitamins; minerals.

Minervit A-Z *Argenfarma, Arg.*
Vitamins; minerals.
Dietary supplement.

Minesol *Janssen-Cilag, Braz.*
Titanium (p. 2632·2); zinc (p. 2126·1); beta-glucan (p. 2455·2); ginkgo biloba (p. 2512·3).
Tonic.

Minesse *Wyeth, Arg.; Wyeth, Chile; Pfizer, Cz.; Pfizer, Fr.; Wyeth, Hung.†; Pfizer, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Mex.; Pfizer, Port.; Wyeth, S.Afr.; Wyeth, Spain; Pfizer, Switz.; Wyeth, Venez.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Wyeth, Braz.
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Wyeth Lederle, Austria.
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, placebo.
Combined oral contraceptive.

Minestrin *Warner Chilcott, Canad.*
Norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Minesulin *Polfa Pabianice, Pol.*
Nimesulide (p. 101·3).
Pain.

Minette *Besins, Ger.; Kade, Ger.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Minfaden *Mintlab, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Ming Jia Xin *Mingxin, China.*
Rifapentine (p. 355·1).

Ming Jie *Jiu Dian, China.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Ming Li Xin *Mingxin, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Ming Nuo *Fenghuang, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ming Qi Xin *Mingxin, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ming Sheng *Fang Ming, China.*
Adenosine cyclophosphate (p. 2430·2).

Ming Wei Xin *Hai Kang, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; ischaemic heart disease.

Ming Ze *Jin Si Li, China.*
Diammonium glycyrrhizate (p. 2520·3).

Ming Zheng *Chia Tai, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Ming Zhu Xin *Mingxin, China.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Minhavez *Melisana, Belg.*
⊗Melissa (p. 2552·3); naphazoline nitrate (p. 1669·3).
Eye irritation.

Mini *Zenacts, India.*
Amikacin (p. 214·1).
Bacterial infections.

28 mini *Jenapharm, Ger.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Mini O *Biol, Arg.*
Nystatin (p. 590·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Vaginal infections.

Mini Ovulo Lanzas *Faes, Spain.†*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Mini Pseudo *BDI, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Formerly known as Mini Thin Pseudo.
Nasal congestion.

Minian *Libbs, Braz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Minias *Bayer, Ital.*
Lormetazepam (p. 1082·1).
Insomnia.

Miniasal *Nycomed, Ger.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Miniaspi *Mersifarma, Indon.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Minibex *RND, India.*
Syrup: Vitamin B substances (p. 2102·3); minerals; ascorbic acid (p. 2110·3).

RND, India.
Tablets: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); *Lactobacillus sporogenes* (p. 2596·3).

Minibit *Polipharm, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Miniblock *USV, India.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension during surgery.

Minica S *Sato, Singapore.*
⊗Sodium citrate (p. 1781·2); sorbitol (p. 2092·1); glycerol (p. 2517·2).
Constipation.

Minicam *Sanofi-Aventis, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Minicam Carb *Sanofi-Aventis, Arg.*
Activated charcoal (p. 1537·3).
Diarrhoea; meteorism.

Miniceronal *Tunggal Idaman, Indon.†*
L-Cysteine (p. 2058·3); choline bitartrate (p. 2055·2); inositol (p. 2533·2); vitamin B_{12} (p. 2107·2).
Vitamin B_{12} and cysteine deficiency.

Minicidez *Fada, Arg.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Mini-Citizol *Aristo, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Minicycline *Shreya, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Miniderm *ACO Hud, Fin.*
⊗Glycerol (p. 2517·2).
Dry skin.

ACO Hud, Norw.; ACO Hud, Swed.
Emollient.
Dry skin.

Minidex *Alcon, Braz.*
⊗Dexamethasone (p. 1630·3).
Eye disorders.

Minidiab *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Dexo, Fr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S. Afr.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Venez.*
Glipizide (p. 474·1).
Diabetes mellitus.

Minidol *Andromaco, Chile.*
Tramadol hydrochloride (p. 139·2).
Pain.

Minidol Plus *Andromaco, Chile.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Minidolo *Winsome, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Minidoz *Recalcine, Thai.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive; acne.

Minidril *Codepharma, Fr.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Minidyne *Pedinol, USA.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Miniestrel *Andromaco, Chile.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Miniflam *Unipharma, Gr.*
Diclofenac sodium (p. 48·3).

Minifom *GSK Consumer, Fin.; GSK Consumer, Norw.; GSK Consumer, Swed.*
Dimeticone (Antifoam M) (p. 1886·2).
Adjunct to gastrointestinal endoscopy and radiography; excess gastrointestinal gas; colic.

Minigadine *Raptakos, India.*
Calcium lactobionate (p. 1784·2); ferric ammonium citrate (p. 2060·1); magnesium chloride (p. 1787·1); manganese sulfate (p. 2081·2); iodised peptone; zinc sulfate (p. 2126·2).

Minigest *Andromaco, Chile.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Minigeste *BB, Ital.; Bayer, Port.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Mini-Glynase *Julphar, UAE.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Minigrip *Kalbe, Indon.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Minigynon *Schering, Venez.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Minilactone *RPG, India.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Hypertension; ascites; oedema.

Minilase-S *Tanabe Seiyaku, China.*
Compound digestive enzymes.
Reduced appetite; bloating; abdominal pain; dyspepsia.

Minilax
Note: this name may be used for preparations of different composition.
Eurofarma, Braz.
Sorbitol (p. 2092·1).
Constipation.

Minilip
Note: this name may be used for preparations of different composition.
Teva, Hung.
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Atral, Port.†
Atorvastatin magnesium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Minima *Medley, Braz.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

MiniMax *Nestle, Denm.*
Preparation for enteral nutrition in infants.

Minimet *Micro, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Minims Artificial Tears *Chauvin, Irl.; Bausch & Lomb, UK.*
Hyetellose (p. 2188·3); sodium chloride (p. 1795·1).
Dry eyes.

Miniostenil *TRB, Arg.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Minipar-P *Servocare, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Minipar-SP *Servocare, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Minipar-TZ *Servocare, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Mini-Pe *Pfizer, Denm.; Pfizer, Swed.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Miniphase *Bayer, Fr.†*
Norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Minipil
Note: this name may be used for preparations of different composition.
Sigma, Braz.
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Minipil-2 Post *Sigma, Braz.*
Levonorgestrel (p. 2296·1).
Post-coital oral contraceptive.

Mini-Pill
Note: this name may be used for preparations of different composition.
Pfizer, Fin.
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Minipres *Pfizer, Arg.; Pfizer, Mex.; Nostrum, Spain.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; Raynaud's syndrome; benign prostatic hyperplasia; heart failure.

Minipress *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Erfa, Canad.; Dexo, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Turk.; Pfizer, USA.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; Raynaud's syndrome; benign prostatic hyperplasia.

Minipril *Alembic, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Miniprin *Time-Cap, USA.*
Aspirin (p. 22·2).

Minirin *Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Ferring, China; Ferring, Cz.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; IFET (ΙΦΕΤ), Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Israel; Ferring, Malaysia; Ferring, Mex.; Euro Registratie, Neth.†; Ferring, Norw.; Ferring, NZ; Ferring, Philipp.; Ferring, Pol.; Ferring, Port.; Ferring, Rus.; Ferring, Singapore; Ferring, Swed.; Ferring, Switz.; Er-Kim, Turk.; Ferring, Turk.; Ferring, Ukr.; Ferring, USA.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; polyuria; polydipsia; haemorrhagic disorders; test of renal concentrating capacity; stimulation of factor VIII activity; von Willebrand's disease; haemophilia A; nocturia.

Ferring, Austral.; Ferring, Denm.; Ferring, India; Ferring, Thai.
⊗Desmopressin (p. 2355·1) or desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; test of renal concentrating capacity; haemophilia A; von Willebrand's disease; platelet dysfunction; nocturia; test of fibrinolytic response.

Minirin/DDAVP *Ferring, Ital.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; renal function tests; polyuria; polydipsia; haemophilia A.

Minirinmelt *2care4, Denm.; A-Pharma, Denm.; ChemVet, Denm.; Europharma, Denm.; Orifarm, Denm.; Ferring, Fr.*
⊗Desmopressin (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

Ferring, Jpn.
⊗Desmopressin acetate (p. 2355·1).
Nocturnal enuresis; diabetes insipidus.

Minisec-AR *Pulse, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Minisem *Pik, Rus.*
Synthetic polypeptide.
Nootropic; mental function impairment; behaviour disorders in children.

Mini-Sintrom *Novartis, Fr.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Minisiston *Jenapharm, Cz.; Jenapharm, Ger.; Jenapharm, Pol.†; Bayer Schering, Rus.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive; menstrual disorders.

Minison *YSP, Malaysia.*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Ministat
Note: this name may be used for preparations of different composition.
Organon, Neth.
Lynestrenol (p. 2287·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

UniOrange, India.
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Miniten *Utopian, Thai.*
Nitrendipine (p. 1456·3).
Hypertension.

Minitic *T Man, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Diuretic.

Minitil *Helm, Port.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Minitone Plus *Universal Medikit, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Minitran
Note: this name may be used for preparations of different composition.
Adelco, Gr.
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Depression accompanied by psychosis.

3M, Arg.; iNova, Austral.; Meda, Belg.; Medicis, Canad.; Meda, Fin.; Meda, Ital.; Graceway, Mex.; Meda, Neth.; Meda, Norw.; 3M, NZ; iNova, Philipp.; Meda, Spain; Meda, Swed.; Meda, Switz.; 3M, UK; Medicis, USA.
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; maintenance of venous patency at peripheral infusion sites.

MinitranS *Meda, Ger.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Minit-Rub *Bristol-Myers Products, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Minivelle *Noven, USA.*
Estradiol (p. 2271·1).
Menopausal disorders.

Miniversol *Aguettant, UK.*
Sodium chloride (p. 1795·1) for irrigation.

Minixime *Brown & Burk, Malaysia.*
Cefixime (p. 240·3).
Bacterial infections.

Minny *Biolab, Thai.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Mino *Rhine, India.*
Paracetamol (p. 115·1).
Pain; fever.

Mino-50 *Teofarma, Belg.*
Minocycline hydrochloride (p. 325·1).
Acne.

Minoa *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Minocalve *Johnson & Johnson, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Minocin *Wyeth, Arg.†; Teofarma, Belg.; Stiefel, Canad.; Pfizer, China; Teofarma, Gr.; Wyeth, Hong Kong†; Lederle, Indon.†; Meda, Irl.; Teofarma, Ital.; Wyeth, Mex.; EU, Neth.†; Wyeth, Philipp.; Teofarma, Port.; Wyeth, Singapore; Teofarma, Spain; Drossapharm, Switz.; Wyeth-Ayerst, Thai.; Wyeth, UK; Triax, USA.*
Minocycline hydrochloride (p. 325·1).
Acne; bacterial infections; intestinal amoebiasis.

Minoclav *Minova, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Minoclin *Rekah, Israel; Ranbaxy, Malaysia.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections; intestinal amoebiasis.

Minoclir *MibeJena, Ger.*
Minocycline hydrochloride (p. 325·1).
Acne.

Minodene *Clonmel, Irl.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minoderm *Stiefel, Braz.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minodiab *Pfizer, Arg.; Europharma, Denm.; Pfizer, Gr.; Pfizer, Mex.; Pfizer, Spain; Pfizer, UK.*
Glipizide (p. 474·1).
Diabetes mellitus.

Minodil *Charoon Bhesaj, Thai.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Minodril *Kleva, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Min-O-Ear *Geritrex, USA.*
Liquid paraffin (p. 2191·2).
Ear wax removal.

Minofen *Crinos, Ital.; Liomont, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Minofer *Minova, India.*
Folic acid (p. 2063·1); iron (p. 2073·1).

Minoglen *Strides, Philipp.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Minolis *Expanscience, Fr.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minolox *Micro, India.*
Minocycline (p. 324·3).
Bacterial infections.

Minomycin *Aspen, Austral.; Healthcare Logistics, NZ.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minophyl *Neon, India.*
Aminophylline (p. 1201·2).
Bronchospasm.

Minoplus *Rosen, Ger.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minor
Note: this name may be used for preparations of different composition.
T Man, Thai.
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Minoral *Liferpal, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Minorplex *Abigo, Swed.*
Vitamins.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Minos *Minorock Mandiri, Indon.†*
Calamine (p. 1697·2); camphor (p. 2466·2); magnesium carbonate (p. 1856·2); menthol (p. 2553·2); talc (p. 1722·2); zinc oxide (p. 1729·1).
Skin irritation; pruritus.

Minoset *Bayer, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Minoset Plus *Bayer, Turk.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Fever; pain.

Minosil *Pinewood, Irl.*
Minocycline hydrochloride (p. 325·1).
Acne.

Minostad *Stada, Austria.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minotab *Teofarma, Belg.; Wyeth, Neth.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minotabs *Healthcare Logistics, NZ; Hexal, S.Afr.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minotek *Ideco, Ital.; OraPharma, Neth.*
Minocycline hydrochloride (p. 325·1).
Bacterial mouth infections.

Minoton *Ariston, Braz.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Rottapharm, Spain.
Magaldrate (p. 1856·1).
Gastric hyperacidity.

Minotrex *Medinfar, Port.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minotriyod *Adeka, Turk.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Minovag *Novag, Mex.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis; giardiasis.

Minovital *Terapeutico, Ital.*
Minoxidil (p. 1438·3).
Alopecia.

Min-Ovral *Pfizer, Canad.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Minox
Note: this name may be used for preparations of different composition.
Riva, Canad.; Edol, Port.
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Rowex, Irl.
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Minoxi *Trima, Hong Kong†; Trima, Israel; Trima, Singapore; Unipharm, Singapore.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Minoxide *BJ Benjaosoth, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; insomnia.

Minoxile *Finadiet, Arg.*
Minoxidil (p. 1438·3).
Alopecia.

Minoximen *Menarini, Ital.*
Minoxidil (p. 1438·3).
Alopecia.

Minoxitrim *Trima, Singapore†; Unipharm, Singapore.†*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Minoz *Ranbaxy, India.*
Minocycline (p. 324·3).
Bacterial infections.

Minpres *Pfizer, Venez.*
Prazosin hydrochloride (p. 1473·3).
Benign prostatic hypertrophy; heart failure; hypertension; Raynaud's syndrome.

Minprog *Pfizer, Austria; Pfizer, Ger.*
Alprostadil (p. 2352·2).
Maintenance of ductus arteriosus patency.

Minprostin *Pfizer, Denm.; Pfizer, Fin.†; IFET (ΙΦΕΤ), Gr.; Pfizer, Norw.; Pfizer, Swed.*
Dinoprostone (p. 2134·1).
Labour induction.

Minprostin E_2 *Pfizer, Ger.*
Dinoprostone (p. 2134·1).
Labour induction; production of cervical dilatation.

Minra *TNP, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Rhinitis; hay fever.

Minraam *Raam, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Minred *Orchid, India.*
Minerals; trace elements.

Minrin *Ferring, Neth.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; polyuria; polydipsia; test of renal concentrating capacity; nocturnal enuresis; uraemia; haemorrhagic disorders.

Minroset *Win-Medicare, India.*
Alfacalcidol (p. 2112·3).
Osteoporosis; renal osteodystrophy.

Minroset-C *Win-Medicare, India.*
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).
Osteoporosis.

Minscalp *East West, India.*
Minoxidil (p. 1438·3).
Alopecia.

Minsk *Anpharm (Ανφαρμ), Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Minsugar-G *Abbott, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Minsu-P *Evershine, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Min-T *Offenbach, Mex.*
⊗Atenolol (p. 1308·2).
Hypertension.

Mint *Mint, India.*
Allantoin (p. 1693·1); octinoxate (p. 1715·1); zinc oxide (p. 1729·1).

Mintaglos *Mintlab, Chile.*
Halibut oil (p. 2071·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Skin disorders; wounds.

Mintagras *Mintlab, Chile.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Mintalos *Caber, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Mintamox *Mintlab, Chile.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mintavit-C *Mintlab, Chile.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Mintayax *Reddy, Spain.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Mintcal *Mint, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Mintclav *Mint, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Mintec *Key, Austral.; Key, NZ; Almirall, UK.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome; spastic colon syndrome.

Mintezol *MSD, Austral.†; IFET (ΙΦΕΤ), Gr.; Merck, USA.†*
Tiabendazole (p. 166·3).
Worm infections.

Mintide *Venus, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).

Mintide Plus *Venus, India.*
Chromium tripicolinate (p. 2056·1); gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Mint-Lysoform *Lysoform, Ger.*
Myrrh tincture (p. 2566·1); peppermint oil (p. 1877·1).
Mouth and throat disorders.

Mintocef *Mint, India.*
Cefixime (p. 240·3).
Bacterial infections.

Mintocip *Mint, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Mintocip-TZ *Mint, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Mintodox *Mint, India.*
Cefpodoxime.
Bacterial infections.

Mintodox-CL *Mint, India.*
Cefpodoxime; clavulanic acid (p. 268·3).

Mintof *Mint, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Mintoflox *Mint, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Mintof-OZ *Mint, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Mintoil *CaDiGroup, Ital.*
Peppermint oil (p. 1877·1).
Gastrointestinal spasm.

Mintop *Reddy, India.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Mintovit *Obsurge, India.*
Vitamins; minerals.

Mintox *Major, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Hyperacidity.

Mintox Plus *Major, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Mintoxid *Orchid, India.*
Vitamins; minerals.

Mintrax *Mint, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Mintrax-S *Mint, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Mintribee *Medhaus, Philipp.*
Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; tonic.

Minulet *Pfizer, Austral.; Pfizer, NZ.*
21 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Wyeth, Arg.; Pfizer, Austria; Pfizer, Belg.; Wyeth, Braz.; Wyeth, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Wyeth, Gr.; Wyeth, Hung.; Pfizer, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Wyeth, Philipp.†; Wyeth, Pol.†; Pfizer, Port.; Wyeth, Singapore†; Wyeth, Spain; Pfizer, Switz.; Wyeth, Turk.; Wyeth, Venez.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Minulette *Pfizer, S.Afr.*
21 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Minurin *Europharma, Denm.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

Ferring, Spain.
⊗Desmopressin (p. 2355·1) or desmopressin acetate (p. 2355·1).
Diabetes insipidus; haemorrhage; nocturnal enuresis; test of renal concentrating capacity.

Minus *Tocogino, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Minuscol *Teva, Spain.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Minuslip *Ivax, Arg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Minuslip Duo *Ivax, Arg.*
Capsules, fenofibrate (p. 1381·1); tablets, ezetimibe (p. 1379·2).
Hyperlipidaemias.

Minusorb *UCI, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Minute-Gel *Oral-B, USA.*
Acidulated phosphate fluoride (p. 2089·2).
Dental caries prophylaxis.

Minvit *Radicura, India.*
Vitamins; minerals.

Minvital *Radicura, India.*
Ginseng (p. 2513·3); vitamins; minerals.

Minyak Telon *Minorock Mandiri, Indon.†*
Cajuput oil (p. 2464·1); coconut oil (p. 2179·3); fennel oil (p. 2503·3).
Emollient.

Minyak Telon Cap Tiga Anak *Berlico Mulia, Indon.†*
Cajuput oil (p. 2464·1); coconut oil (p. 2179·3); anise oil (p. 2444·3).
Muscle and joint stiffness.

Mio Aldoron *Ivax, Arg.*
Nimesulide (p. 101·3); orphenadrine citrate (p. 909·2).
Musculoskeletal pain and spasm.

Mio Aldoron NF *Ivax, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint, and peri-articular disorders.

Mio D *Kowa, Jpn.*
Vitamin B substances (p. 2102·3); oxoamidine.
Tonic.

Mioblock *Schering, Jpn.†*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Miocacin *Angelini, Gr.; Sanofi-Aventis, Port.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Miocalm *Hexa, Arg.†*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Miocalven *Chiesi, Braz.*
Calcium citrate (p. 1783·2).
Calcium supplement.

Miocalven D *Chiesi, Braz.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Osteoporosis; calcium deficiency.

Miocamen *Menarini, Gr.; Menarini, Ital.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Miocamycin *Meiji, Jpn.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Miocap *Arlex, Mex.†*
Captopril (p. 1331·2).
Hypertension.

Miocardin *Magis, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Miochol *Novartis, Austral.; Iolab, Israel; Mann, Neth.; Novartis, NZ; Novartis, Port.; Adcock Ingram, S.Afr.; Bausch & Lomb, Switz.; Novartis, UK; Novartis Ophthalmics, USA.*
Acetylcholine chloride (p. 2003·1).
Production of miosis in eye surgery.

Miochol-E *Bausch & Lomb, Canad.; Bausch & Lomb, Fin.; Novartis, Ger.; Mann, Gr.; Novartis, Hong Kong; OMJ, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.†; Bausch & Lomb, Swed.; Novartis, Turk.*
Acetylcholine chloride (p. 2003·1).
Production of miosis in eye surgery.

Miochole *Mann, Belg.; Chauvin, Fr.*
Acetylcholine chloride (p. 2003·1).
Production of miosis in eye surgery.

Miocina *Tecnofarma, Mex.*
Dopamine (p. 1367·2).
Cardiovascular disorders.

Mio-Citalgan *Merck, Braz.*
Carisoprodol (p. 2021·3); caffeine (p. 1203·3); vitamin B substances (p. 2102·3); paracetamol (p. 115·1).
Skeletal muscle spasm.

Miocor
Note: this name may be used for preparations of different composition.
Ecobi, Ital.
Levocarnitine (p. 2053·2).
Carnitine deficiency; myocardial ischaemia.

UCI, Braz.
Amiodarone hydrochloride (p. 1300·1).

Miocoron *Cristalia, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Miocrin *IFET [ΙΦΕΤ], Gr.; Rubio, Singapore; Rubio, Spain.†*
Sodium aurothiomalate (p. 130·2).
Rheumatoid arthritis; juvenile idiopathic arthritis.

Miodaren *Vitapan, Braz.*
Amiodarone (p. 1300·1).

Miodarid *Neo Quimica, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Miodaron *Biosintetica, Braz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Miodarona *Lafedar, Arg.*
Amiodarone (p. 1300·1).
Arrhythmias.

Miodom *Dominguez, Arg.*
Tolperisone hydrochloride (p. 2027·3).
Muscle relaxant.

Miodon *Biolab Sanus, Braz.*
Amiodarone (p. 1300·1).

Miodrina *Apsen, Braz.*
⊗Ritodrine hydrochloride (p. 2145·1).
Premature labour.

Miodrone *Alter, Port.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Miofibrax *Legrand, Braz.*
Cyclobenzaprine (p. 2023·1).

Mioflam *Rider, Chile.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Mioflex
Note: this name may be used for preparations of different composition.
IFET [ΙΦΕΤ], Gr.; Braun, Port.; Braun, Spain.
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Farmasa, Braz.
Carisoprodol (p. 2021·3); paracetamol (p. 115·1); phenylbutazone (p. 125·1).
Skeletal muscle spasm.

Mioflex A *Farmasa, Braz.*
Diclofenac sodium (p. 48·3); carisoprodol (p. 2021·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Miogan *Allergan, Canad.†*
Acetylcholine chloride (p. 2003·1).

Miokacin *FIRMA, Ital.*
Midecamycin (p. 324·3).
Bacterial infections.

Miokar *Sanbe, Indon.*
Pilocarpine hydrochloride (p. 2010·3).
Ocular hypertension; production of miosis.

Miol
Note: this name may be used for preparations of different composition.
DR Johns, India.
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1); glutamic acid (p. 2070·2).

Ferrer, Spain.
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Miolastan *Sanofi-Aventis, Mex.*
Tetrazepam (p. 1110·1).
Skeletal muscle spasm; spasticity.

Miolene *IFET [ΙΦΕΤ], Gr.; Menarini, India; Lusofarmaco, Ital.*
⊗Ritodrine hydrochloride (p. 2145·1).
Premature labour; threatened miscarriage.

Miolox *Baliarda, Arg.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Miol-P *DR Johns, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Mionevrasi *Teofarma, Ital.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); cocarboxylase (p. 2103·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Vitamin B deficiencies; neuritis; neuralgia.

Mionevrix *Ache, Braz.*
Carisoprodol (p. 2021·3); dipyrone (p. 53·3); vitamin B substances (p. 2102·3).
Skeletal muscle spasm.

Mionic *Richter, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Miopropan *Bernabo, Arg.*
Trimebutine (p. 2634·1) or trimebutine maleate (p. 2634·1).
Gastrointestinal spasm.

Miopropan Proctologico *Bernabo, Arg.*
Ruscogenin (p. 2608·3); trimebutine (p. 2634·1).
Haemorrhoids.

Miopropan S *Bernabo, Arg.*
Trimebutine maleate (p. 2634·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Miopropan-T *Bernabo, Arg.*
Trimebutine maleate (p. 2634·1); bromazepam (p. 1041·2).

Miorel
Note: this name may be used for preparations of different composition.
Daiichi Sankyo, Fr.
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Kleva, Gr.
Baclofen (p. 2014·3).
Spasticity.

Mio-Relax *Volta, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Miorrelax *Ducto, Braz.*
Dipyrone (p. 53·3); orphenadrine citrate (p. 909·2); caffeine (p. 1203·3).
Skeletal muscle spasm.

Miorytmil *Darnitsa, Ukr.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; myocardial infarction.

Miosan *Apsen, Braz.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Miosen
Note: this name may be used for preparations of different composition.
Teva, Spain.
Risedronate sodium (p. 1189·3).
Osteoporosis.

Mioser *Help, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Miostart *Wassermann, Ital.*
Thiocolchicoside (p. 2026·2).

Miostat *Alcon, Arg.; Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Cz.; Alcon, Fr.; Alcon, Hung.; Alcon, Israel; Alcon, Malaysia; Alcon, Neth.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Singapore; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Nobel, Turk.; Alcon, USA.*
Carbachol (p. 2005·2).
Production of miosis; reduction of intra-ocular pressure following eye surgery.

Miostein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Miostenil *Bial, Port.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).

Miotenk *Biotenk, Arg.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Miotens *Dompe, Ital.*
Thiocolchicoside (p. 2026·2).
Neuromuscular pain; parkinsonism; spasticity.

Mioticol *Farmigea, Ital.*
Carbachol (p. 2005·2).
Production of miosis in eye surgery.

Miotin
Note: this name may be used for preparations of different composition.
Captab, India.
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Meiji, Thai.
Midecamycin acetate (p. 324·3).
Bacterial infections.

Miotonachol *Fortbenton, Arg.*
Bethanechol chloride (p. 2456·2).
Prostate disorders.

Miotonal *Mylan, Ital.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Mio-Virobron *Temis, Arg.*
Nimesulide (p. 101·3); orphenadrine citrate (p. 909·2).
Musculoskeletal inflammation.

Mio-Virobron NF *Temis, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders with muscle spasm.

Miovisin *Farmigea, Ital.*
Acetylcholine chloride (p. 2003·1).
Production of miosis in eye surgery.

Miovit *Cofasa, Venez.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuralgia; neuritis; tonic.

Miozac *Fisiopharma, Ital.*
Dobutamine hydrochloride (p. 1365·3).
Cardiac inotropic.

Miozepam
Note: this name may be used for preparations of different composition.
Bernabo, Arg.†
Clonazepam (p. 519·1).
Anxiety; epilepsy.

Jelfa, Pol.†
Tetrazepam (p. 1110·1).
Painful skeletal muscle spasm.

Miozets *Uriach Aquilea OTC, Spain.*
Benzocaine (p. 1980·2); tyrothricin (p. 384·1).
Mouth and throat disorders.

Miparkan *Specifar, Ital.; Zentiva, Pol.*
Pramipexole (p. 911·2).
Parkinsonism.

Miphar *Pharmachemie, Israel.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; hepatic cirrhosis.

Miphtel *SD Healthcare, UK.*
Acetylcholine chloride (p. 2003·1).
Production of miosis in eye surgery.

Mipil *Grunenthal, Venez.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Mi-Pilo *Fischer, Israel.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of miosis.

Mipralin *Lennon, S.Afr.†*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Mipramid *IQFA, Mex.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Mipramine *Inpac, Thai.*
Imipramine hydrochloride (p. 426·2).
Depression.

Mipril H *Teva, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Mipro *Adroit, India.*
Preparation for enteral nutrition.

Miprogen *Bharat, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; premenstrual syndrome.

Miproten *PC India, India.*
Cyanocobalamin (p. 2107·2); cyclo dimethionine; iron (p. 2073·1); lysine hydrochloride (p. 2079·3); protein hydrolysate (p. 2086·2); yeast extract (p. 2125·2); zinc (p. 2126·1).

Mipyrin *CNP, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Miquimod *Lazar, Arg.*
Imiquimod (p. 985·2).
Anogenital warts; actinic keratosis; superficial basal cell carcinoma.

MIR *Rafa, Israel.*
⊗Morphine sulfate (p. 92·3).
Pain; premedication.

Mira *Chira, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Mira Klonal *Klonal, Arg.*
⊗Naphazoline (p. 1669·3); pheniramine (p. 637·2).
Eye disorders.

Mirabel *Allergan, Braz.*
⊗Tetryzoline hydrochloride (p. 1678·3); zinc sulfate (p. 2126·2).
Ocular congestion.

Mirabol *Volchem, Ital.*
Preparations for enteral nutrition.

Miracal *Mapra, India.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Miracálcio Vit D *Geolab, Braz.*
Calcium carbonate (p. 1824·3); ergocalciferol (p. 2113·3).

Miracid *Berlin Pharm, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Miraclar *Faes, Spain.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Miraclid *Mochida, Jpn.*
Ulinastatin (p. 2637·3).
Pancreatitis; shock.

Miraclin *Farmacologico Milanese, Ital.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Miracolon *Laborest, Ital.*
Rice oil; senna (p. 1885·1).
Gastrointestinal disorders.

Miradol
Note: this name may be used for preparations of different composition.
Purewin, India.
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Durbin, UK.†
Paracetamol (p. 115·1).

Mirador *Hypermarcas, Braz.*
Dipyrone (p. 53·3).

Miraflow *Ciba Vision, USA.*
Range of solutions for contact lenses.

Ciba Vision, Austral.†; Novartis, NZ.†
Cleaning solution for contact lenses.

Miraftil *Meda, Neth.*
Amlexanox (p. 1202·2).
Aphthous ulcers.

Mirafur *Orion, Fin.†*
Carmofur (p. 761·1).
Malignant neoplasms.

Miragran *Royal, Chile.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Miral
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Leiras, Fin.
Potassium chloride (p. 1793·2); magnesium hydroxide (p. 1857·2).
Potassium and magnesium deficiency.

MiraLax *Schering-Plough, USA.*
Macrogol 3350 (p. 2547·3).
Bowel evacuation.

Miraleton *Alet, Gr.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Miralgin *PannonPharma, Hung.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Miralis *Ativus, Braz.*
Myrtillus (p. 2566·2).
Retinopathy.

Miraluma *Du Pont, USA.*
Technetium-99m sestamibi (p. 2228·1).
Breast imaging.

Miralust *Adamed, Cz.; Adamed, Denm.*
Montelukast sodium (p. 1214·3).
Asthma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Miramel *Clonmel, Irl.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Miramerck *Mylan, Denm.†*
Mirtazapine (p. 436·1).
Depression.

Miramind *Torrent, India.*
Mirtazapine (p. 436·1).
Depression.

Miramycin *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Miran *Julphar, UAE.*
Meropenem (p. 321·3).
Bacterial infections.

Miranax *Grunenthal, Austria; Roche, Fin.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Miranel AF *Humco, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Miranova *Bayer, Arg.; Bayer, Braz.; Bayer, Chile; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Ital.; Bayer, Neth.; Bayer, Port.; Schering, S.Afr.†; Bayer, Switz.; Schering, Turk.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Mirap *Rowex, Irl.*
Mirtazapine (p. 436·1).
Depression.

Miraparkin *Specifar, Gr.*
Pramipexole hydrochloride (p. 911·2).

Miraper *Specifar, Ital.*
Pramipexole (p. 911·2).

Mirapex *Pharmacia, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, USA.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Mirapexin *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, UK.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Boehringer Ingelheim, Spain; Pharmacia, Spain.
Pramipexole (p. 911·2).
Parkinsonism; restless legs syndrome.

Mirapront N *Mack, Thai.*
⊗Cathine (p. 2318·2).
Obesity.

Miraqule *Alchem, India.*
Ubidecarenone (p. 2637·1).

Mirasan *Allergan, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Mira Sept *Alcon, USA.†*
Hydrogen peroxide (p. 1755·2).
Disinfecting solution for soft contact lenses.

Mirasol *KRKA, Neth.*
Mirtazapine (p. 436·1).
Depression.

Miratta *Abdi, Turk.*
Acetylcysteine (p. 1652·2).

Miravil *Orion, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; social phobia; post-traumatic stress disorder; anxiety; obsessive-compulsive disorder; panic disorder.

Mirax
Note: this name may be used for preparations of different composition.
Berlin Pharm, Singapore.
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting.

Berlin Pharm, Thai.
Domperidone maleate (p. 1838·1).
Nausea and vomiting; delayed gastric emptying.

Miraxol *Borshchagovskii, Ukr.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Miraz *Mediez, India.*
Mirtazapine (p. 436·1).
Depression.

Mirazep *Micro, India; Brown & Burk, Philipp.; Micro Labs, Ukr.*
Mirtazapine (p. 436·1).
Depression.

Mirazul *Fardi, Spain.*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Mircera *Roche, Arg.; Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, India; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.*
⊗Methoxy polyethylene glycol-epoetin beta (p. 1156·1).
Anaemia in chronic renal failure.

Mircette *Duramed, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 tablets, placebo.
Sequential oral contraceptive.

Mircol *Lafi, Chile; Medilab, Spain.*
Mequitazine (p. 635·2).
Hypersensitivity reactions; allergic conjunctivitis; allergic rhinitis; urticaria.

Mirdezel *Sandoz, Cz.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Mirelle *Bayer, Arg.; Bayer, Chile; Bayer Schering, Cz.; Bayer Schering, S.Afr.; Bayer, Switz.; Schering, Venez.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Bayer, Austria; Bayer Schering, Fin.
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, placebo.
Combined oral contraceptive.

Bayer, Belg.; Schering, Braz.; Bayer Schering, Pol.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Mirena *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Schering, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer, Cz.; Bayer Schering, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer Schering, Pol.; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Bayer, UK; Bayer, Ukr.; Bayer, USA; Schering, Venez.*
Levonorgestrel (p. 2296·1).
Menorrhagia; progestogen-releasing intra-uterine contraceptive device; prevention of endometrial hyperplasia during oestrogen replacement therapy.

Miretic *Utopian, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Mirex *Sinnex, Hung.*
Mikrorost (protekarpin) from buzakorpabol.
Digestive disorders.

Mirfulan *Ratiopharm, Austria; Recordati, Ger.*
⊗Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1); hamamelis (p. 2523·3); urea (p. 1727·3).
Skin disorders.

Mirfulan Spray N *Recordati, Ger.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1); levomenol (p. 2544·1).
Burns; skin disorders; wounds.

Miridacin *Taiho, Jpn.*
Proglumetacin maleate (p. 127·1).
Musculoskeletla, joint, and peri-articular disorders.

Miril *Teva, Cz.*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction; glomerular nephropathy; heart failure; myocardial infarction.

Miril plus H *Teva, Cz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Mirion *Pfizer, Chile.*
Estradiol valerate (p. 2271·2).

Mirip *Esma, India.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).

Miripla *Dainippon, Jpn.*
Miriplatin (p. 830·1).
Hepatocellular carcinoma.

Miriwash *Sanbe, Indon.*
Electrolytes (p. 1775·1).
Eye irrigation.

Mirlox *Gedeon Richter, Rus.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mirnite *Intas, India.*
Mirtazapine (p. 436·1).
Depression.

Miro *Unipharm, Israel.*
Mirtazapine (p. 436·1).
Depression.

Mirocef *Pliva Krakow, Pol.†*
Ceftazidime sodium (p. 250·2).
Bacterial infections.

Mirole *Niche, Irl.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Mirolut *Mir, Rus.; Stada, Ukr.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Miropriston *Stada, Ukr.*
Mifepristone (p. 2138·1).
Termination of pregnancy; induction of labour.

Miroton *Abbott, Ger.†*
Squill (p. 1677·3); convallaria (p. 2486·2); oleander (p. 2574·3); adonis vernalis (p. 2431·1).
Cardiovascular disorders.

Mirpax *Merck, Port.*
Mirtazapine (p. 436·1).
Depression.

Mirpik *Cantabria, Spain.†*
Mirtazapine (p. 436·1).
Depression.

Mirpine *Psyco Remedies, India.*
Mirtazapine (p. 436·1).
Depression.

Mirpresoc *Liconsa, Cz.; Liconsa, Irl.; Liconsa, Neth.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Mirquin *Mirren, S.Afr.*
Chloroquine sulfate (p. 650·2).
Malaria.

Mirrador *Meditrina, Gr.*
Mirtazapine (p. 436·1).

Mirstar *Sykocure, India.*
Mirtazapine (p. 436·1).
Depression.

Mirt *Panacea, India.*
Mirtazapine (p. 436·1).
Depression.

Mirta TAD *TAD, Ger.*
Mirtazapine (p. 436·1).
Depression.

Mirtabene *Ratiopharm, Austria.*
Mirtazapine (p. 436·1).
Depression.

Mirtabs *Actavis, Cz.†*
Mirtazapine (p. 436·1).
Depression.

Mirtachem *Menarini, Fin.*
Mirtazapine (p. 436·1).
Depression.

Mirtacin *Cinerea, India.*
Mirtazapine (p. 436·1).
Depression.

Mirtadep *Unichem, India.*
Mirtazapine (p. 436·1).
Depression.

Mirtadepi *Actavis, Hung.*
Mirtazapine (p. 436·1).
Depression.

Mirtagamma *Worwag, Ger.*
Mirtazapine (p. 436·1).
Depression.

Mirtagen *Generics, Pol.*
Mirtazapine (p. 436·1).
Depression.

Mirtalan *Lannacher, Rus.*
Mirtazapine (p. 436·1).
Depression.

MirtaLich *Winthrop, Ger.*
Mirtazapine (p. 436·1).
Depression.

Mirtall *Actavis, Irl.†*
Mirtazapine (p. 436·1).
Depression.

Mirtamerck *Generics, Pol.*
Mirtazapine (p. 436·1).
Depression.

Mirtamor *Specifar, Gr.*
Mirtazapine (p. 436·1).
Depression.

Mirtamylan *Mylan, Spain.*
Mirtazapine (p. 436·1).
Depression.

Mirtapil *SM, Gr.*
Mirtazapine (p. 436·1).
Depression.

Mirtaril *KRKA, Fin.*
Mirtazapine (p. 436·1).
Depression.

Mirtaron *Interpharm, Austria; Eczacibasi, Turk.*
Mirtazapine (p. 436·1).
Depression.

Mirtastad *Stada, Cz.†; Steigerwald, Pol.*
Mirtazapine (p. 436·1).
Depression.

Mirtastadin *Stada, Ukr.*
Mirtazapine (p. 436·1).
Depression.

Mirtax *Ache, Braz.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Mirtaz *Sun, India; Pinewood, Irl.†*
Mirtazapine (p. 436·1).
Depression.

Mirtazap *Mepha, Switz.*
Mirtazapine (p. 436·1).
Depression.

Mirtazelon *Krewel, Ger.*
Mirtazapine (p. 436·1).
Depression.

Mirtazon *Schering-Plough, Austral.; Imi, Denm.†; Organon, Fin.†; Aacifar, Port.*
Mirtazapine (p. 436·1).
Depression.

Mirtazonal *Actavis, Rus.*
Mirtazapine (p. 436·1).
Depression.

Mirtel *Lannacher, Austria; Gerot, Hung.†*
Mirtazapine (p. 436·1).
Depression.

Mirtex P *DMG, Ital.*
Vitamins; minerals; lipid; myrtillus (p. 2566·2).
Nutritional supplement.

Mirticam *Kameliya, Rus.*
Myrtillus (p. 2566·2); euphrasia officinalis (p. 2502·1); gelsemium (p. 2511·2); cimicifuga racemose (p. 2478·1).
Homoeopathic preparation.

Mirtilene *SIFI, Ital.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1); *dl*-alpha tocoferil acetate (p. 2119·2).
Capillary fragility.

Mirtilene Forte *SIFI, Ital.; Zambon, Rus.*
Myrtillus (p. 2566·2).
Eye disorders.

Mirtilus *Llorens, Spain.†*
Betacarotene (p. 2051·1); myrtillus (p. 2566·2).
Eye disorders.

Mirtilux *Mediwhite, Ital.*
Capsules: Vitamins; minerals; myrtillus (p. 2566·2).
Nutritional supplement.

Mediwhite, Ital.
Oral solution: Myrtillus (p. 2566·2); grape (p. 2521·3); magnesium (p. 1786·3); phosphatidyl serine (p. 2589·1); phosphatidyl choline (p. 2588·3); rhodiola rosea.
Nutritional supplement.

Mirtin *KRKA, Denm.; KRKA, Swed.*
Mirtazapine (p. 436·1).
Depression.

Mirtiros *Pharmafar, Ital.*
Hamamelis (p. 2523·3); myrtillus (p. 2566·2); crataegus (p. 2488·1).
Skin disorders.

Mirtivit
Note: this name may be used for preparations of different composition.
SIFI, Ital.
Anthocyanosides; betacarotene (p. 2051·1); vitamin E (p. 2119·1).
Dietary supplement.

Mirtor *Orion, Pol.*
Mirtazapine (p. 436·1).
Depression.

Mirubal *Zuoz, Venez.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Mirugell *Latinofarma, Braz.*
Macrogol 400 (p. 2547·3); propylene glycol (p. 2205·2); electrolytes (p. 1775·1); guaraprolose (p. 2187·3).
Dry eyes.

Mirus *Alcon, Arg.; Alcon, Mex.*
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Mirus-S *Alcon, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Mirvaso *Galderma, USA.*
Brimonidine (p. 2004·3).
Rosacea.

Mirv-HDC *Serum Institute, India.*
Rabies antisera (p. 2413·1).
Passive immunisation.

Mirzalux *Sandoz, Mex.*
Mirtazapine (p. 436·1).
Depression.

Mirzasna *KRKA, Neth.*
Mirtazapine (p. 436·1).
Depression.

Mirzaten *KRKA, Cz.; KRKA, Hung.; Niche, Irl.; KRKA, Pol.; KRKA, Rus.*
Mirtazapine (p. 436·1).
Depression.

Mirzest *La Pharmaceuticals, India.*
Mirtazapine (p. 436·1).
Depression.

Misaf *Venifer, Gr.*
Oxaprozin (p. 112·3).
Inflammatory disorders.

Misalic *Micro, India.*
⊗Betamethasone (p. 1623·2); salicylic acid (p. 1719·1).
Eczema; psoriasis; lichen planus.

Miseda *Atlantis, Mex.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic rhinoconjunctivitis; urticaria; allergic skin disorders.

Misel *Shin Poong, Singapore.*
Misoprostol (p. 2140·3).
NSAID-associated peptic ulcer.

Mishacin *Misha, India.*
Amikacin (p. 214·1).
Bacterial infections.

Mishanac *Misha, India.*
Diclofenac sodium (p. 48·3).
Pain.

Mishcal *Willow, India.*
Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Misile *Phoenix, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Misobit *Lupin, India.*
Miglitol (p. 491·3).
Diabetes mellitus.

Misobort *Taj, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Misodex *Pfizer, Ital.*
Misoprostol (p. 2140·3).
NSAID-induced peptic ulcer.

Misodine-M *Varun, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Misodomin *Kleva, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Misodron *Sons, Mex.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Misofar *Bial, Spain.*
Misoprostol (p. 2140·3).
Cervical dilatation for uterine examination; labour induction.

Misofen *Morningside, UK.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Rheumatoid arthritis; osteoarthritis.

Misofenac *Lusofarmaco, Ital.; Euro Registratie, Neth.†*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders; osteoarthritis; rheumatoid arthritis.

Misogest *Elder, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Misol *Nobel, Turk.*
Sertraline hydrochloride (p. 448·1).

Misolast *FDC, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Misolup *Lupin, India.*
Misoprostol (p. 2140·3).
Peptic ulcer; termination of pregnancy.

Misonac *Ordain, India.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; pain.

MisoOne *Exelgyn, Neth.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Misoprost *Cipla, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Misopt *Micro, India.*
⊗Dorzolamide (p. 2006·3); timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Misostol *Zodiac, Braz.; Nolver, Venez.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Misotol *Novaduo, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Misotrol *Sanofi-Aventis, Chile.*
Misoprostol (p. 2140·3).
Peptic ulcer.

Misovan *TO-Chemicals, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Missecap *Galeno, Venez.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Missilor *Pierre Fabre, Fr.*
Spiramycin (p. 358·3); metronidazole (p. 936·1).
Bacterial mouth infections.

Mission Prenatal *Mission Pharmacal, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Prenatal and postpartum supplement; iron-deficiency anaemias.

Mist *Yash, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Mist Carminative *Medicpharma, Thai.*
Capsicum tincture (p. 2469·3); compound cardamom tincture (p. 2471·1); strong ginger tincture (p. 1844·1); camphor (p. 2466·2).
Gastrointestinal disorders.

Mist Expect Stim *Christo, Hong Kong.†*
Ammonium bicarbonate (p. 1655·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); squill (p. 1677·3); senega (p. 1677·2); liquorice (p. 1853·2).
Cough; cold symptoms.

Mist Salol Menthol *PP Lab, Thai.*
Salol (p. 129·3); menthol (p. 2553·2).

Mist Scill Ammon *GPO, Thai.*
Ammonium carbonate (p. 1656·1); camphorated opium tincture; squill tincture (p. 1677·3); senega tincture (p. 1677·2).
Cough; cold symptoms.

Mist Tussis *Vidhyasom, Thai.*
Camphorated opium tincture; antimony potassium tartrate (p. 151·2); liquorice fluid extract (p. 1853·2).
Cough.

Mistabron *UCB, Austria†; UCB, Belg.; UCB, Cz.; UCB, Hong Kong†; UCB, India; UCB, Neth.†; UCB, Philipp.; GSK, Pol.†; GSK, S.Afr.; UCB, Singapore.†*
Mesna (p. 1557·2).
Respiratory-tract congestion.

Mistamine *Galderma, Mex.*
Mizolastine (p. 636·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Mistel Curarina *Harras-Curarina, Ger.*
Mistletoe (p. 2560·2).
Circulatory disorders.

Mistel-Kräutertabletten *Salushaus, Ger.*
Mistletoe (p. 2560·2).
Circulatory disorders.

Misteltropfen Hofmanns *Hofmann & Sommer, Ger.*
Mistletoe (p. 2560·2).
Circulatory disorders.

Mistick Verde *Marco Viti, Ital.*
Geranium oil (p. 2512·2); citronella oil (p. 2481·1); lavender oil (p. 2541·1).
Insect repellent.

Mistone *Novaduo, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy; labour induction following intra-uterine fetal death; post-coital oral contraceptive.

Mistra *Alna, India.*
Telmisartan (p. 1509·3).
Hypertension.

Mistral *Mediolanum, Ital.*
Dermatan sulfate sodium (p. 1350·3).
Thrombosis prophylaxis.

Mistro *Reddy, S.Afr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Misulmylan *Mylan, Spain.†*
Amisulpride (p. 1036·3).
Schizophrenia.

Misultina *Bernabo, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Misulvan
Note: this name may be used for preparations of different composition.
Drugtech, Chile.
Milnacipran hydrochloride (p. 435·3).
Depression.

Plusandex, Venez.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Misurid *Farmachimici, Ital.*
Sulfur (p. 1721·1).
Skin disorders.

Misurid Plus *Farmachimici, Ital.*
Barrier cream.

Mitab *Valeant, Hung.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Mitabor *Ratiopharm, Neth.*
Mirtazapine (p. 436·1).
Depression.

Mita-C *Milano, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Mitafar *Quimpharma, Mex.*
Nitazoxanide (p. 942·2).
Protozoal infections; anaerobic bacterial infections; worm infections.

Mitatonin *Kyorin, Hong Kong.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Mitavin *Nitro Organics, India.*
Vitamins; minerals; trace elements; lycopene (p. 2546·2).

Mitaxind *Indeco, Arg.*
Mirtazapine (p. 436·1).
Depression.

Mitayaku *Kyorin, Hong Kong.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Mite *Il-Yang, China.*
Azintamide (p. 2451·3); pancreatic enzymes (p. 2579·3); cellulase (p. 2473·1); dimeticone (p. 1886·2).
Digestive disorders.

Mitem *SpePharm, Ger.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Miten
Note: this name may be used for preparations of different composition.
Novartis, Spain.
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Miten Plus *Novartis, Spain.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Mite-X
Note: this name may be used for preparations of different composition.
Fischer, Israel.†
Permethrin (p. 2159·3).
Scabies.

Mitexan *Baxter, Braz.*
Mesna (p. 1557·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Mitforgen *Mylan, Denm.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mithen *Fidia, Ital.*
Amino acids; vitamins; minerals; St John's wort (p. 449·1).
Nutritional supplement.

Mithra-Intim *Mithra, Hong Kong.*
Lactic acid (p. 2539·1); miglyol; levomenol (p. 2544·1).
Vaginal dryness.

Nycomed, Philipp.
Lactic acid (p. 2539·1); polycarbophil (p. 1879·1); levomenol (p. 2544·1).
Vaginal dryness.

Miticoçan *Ache, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Mitil *Aspen, S.Afr.*
Prochlorperazine maleate (p. 1098·3).
Vestibular disorders; nausea and vomiting.

Mitilase *Spedrog, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Mitilor *FDC, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Mitinab *Glenmark, India.*
Imatinib (p. 807·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia; myelodysplastic diseases; dermatofibrosarcoma protuberans; gastrointestinal stromal tumours; systemic mastocytosis; hypereosinophilic syndrome.

Mitituss *Magis, Ital.*
Cloperastine fendizoate (p. 1659·2).
Cough.

Mitocent *Crescent, India.*
Mirtazapine (p. 436·1).
Depression.

Mitocin *BMS, Braz.; Cadila, India; Dae Han New, Thai.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitocin-C *BMS, Mex.†*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitocore *Mergers Drugfil, Philipp.*
Carnitine orotate (p. 2578·1); amino acids; adenine hydrochloride (p. 2430·2); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); cyanocobalamin (p. 2107·2).
Liver disorders.

Mitocortyl *Sanofi-Aventis, Fr.†*
⊗Hydrocortisone (p. 1640·1).
Insect and nettle stings; sunburn.

Mitocyna *Richmond, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitodex *Mergers Drugfil, Philipp.*
Carnitine orotate (p. 2578·1); carnitine hydrochloride (p. 2053·2); liver extract (p. 2444·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); adenosine (p. 1291·1).
Liver disorders.

Mitodus *Oncomed, India.*
Mitomycin (p. 830·3).
Malignant neoplasms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mito-extra *Medac, Ger.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitofen *Munir, Turk.*
Ketotifen fumarate (p. 631·3).

Mitog *Microsules, Arg.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Mitokebir *Aspen, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitokor *Biotenk, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Mitolem *Teva, Mex.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mito-medac *Medac, Ger.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitonco *VHB, India.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitonerb *Mergers Drugfil, Philipp.*
Carnitine orotate (p. 2578·1); amino acids; adenine hydrochloride (p. 2430·2); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); cyanocobalamin (p. 2107·2).
Liver disorders.

Mitonovag *Gobbi, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitosol *Mobius, USA.*
Mitomycin (p. 830·3).
Adjunct in glaucoma surgery.

Mitostat *Orion, Fin.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitosyl
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Belg.
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1); methyl salicylate (p. 92·1).
Skin disorders; burns; wounds.

Sanofi-Aventis, Fr.
Fish-liver oil; zinc oxide (p. 1729·1).
Skin irritation.

Sanofi-Aventis, Port.
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Burns; ulcers; wounds; skin disorders.

Sanofi-Aventis, Spain.†
Colecalciferol (p. 2113·1); vitamin A (p. 2098·3); zinc oxide (p. 1729·1).
Burns; skin disorders; wounds.

Mitosyl N *Winthrop, Ger.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1); methyl salicylate (p. 92·1).
Burns; skin disorders; wounds.

Mitotax *Reddy, India; Reddy, Malaysia; Reddy, Rus.; Reddy, Singapore; Reddy, Ukr.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Mitotie *Bioprofarma, Arg.; Armstrong, Mex.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mitoxal *Asta Oncologia, Braz.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Mitoxan *Medicamerc, Gr.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Mitoxana *Baxter, Irl.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Mitoxgen *Bioprofarma, Arg.; Armstrong, Mex.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Mitoxmar *LKM, Arg.†*
Mitoxantrone (p. 833·1).
Malignant neoplasms.

Mitozan *VHB, India.*
Mitoxantrone (p. 833·1).
Malignant neoplasms; multiple sclerosis.

Mitozytrex *SuperGen, USA.†*
Mitomycin (p. 830·3).
Adenocarcinoma of the stomach or pancreas.

Mitranax *Polipharm, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Mitrip *Teva, Pol.*
Ramipril (p. 1483·3).
Heart failure; hypertension; cardiovascular risk reduction; nephropathy.

Mitroken *Kendrick, Mex.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Mitrotan *Gap, Gr.*
Ergometrine maleate (p. 2136·2).
Postpartum haemorrhage.

Mitrotil *Lafi, Chile.*
Tenoxicam (p. 136·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders.

Mitroxene *Pharmis, Port.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Mitroxone *Columbia, Mex.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Mitryp *Baroda, India.*
Amitriptyline (p. 401·1) or amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Mitryp-10 *Baroda, India.*
Amitriptyline (p. 401·1).
Depression; neuropathic pain; migraine.

Mit's Linctus Codeine *AstraZeneca, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.

Mittavin *Sanofi-Aventis, India.*
Vitamins.
Vitamin deficiency.

Mittoval *Sanofi-Aventis, Ital.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Mituss-AX *Globus, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Mituss-BR *Globus, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Mitydec *Servocare, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Mityscab *Fem Care, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Mivacron *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; Wellcome, Port.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Spain†; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK.*
Mivacurium chloride (p. 2034·2).
Competitive neuromuscular blocker.

Mivalen *Ativus, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Mivets-G *Alembic, India.*
Vitamins.

Mivex *Mergers Drugfil, Philipp.*
Carnitine orotate (p. 2578·1); amino acids; adenine hydrochloride (p. 2430·2); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); cyanocobalamin (p. 2107·2).
Liver disorders.

Miviren *Specifar, Ital.*
Pramipexole (p. 911·2).

Mivux *Nobel, Turk.*
Lamivudine (p. 1000·2).

Mixadin *Kalbe, Indon.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms; allergic disorders.

Mixaflu *Kalbe, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Influenza symptoms; cough.

Mixagel *Naturissima, Venez.*
Thyme (p. 2630·2); chamomile (p. 2474·1); eucalyptus (p. 2501·1).
Skin cleansing.

Mixagrip *Kalbe, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; cough.

MixaLax *acaSan, Austria.†*
Macrogol 4000 (p. 2547·3).
Constipation.

Mix-Alpha 3 *Synergia, Fr.*
Vegetable oil; fish oil (p. 1460·1); natural vitamin E (p. 2119·1).
Omega-3 triglyceride supplement.

Mixamin Glucos *Fresenius Kabi, Denm.*
Amino acids; glucose (p. 2068·3); with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Mixandex *Pisa, Mex.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mixange *Tocogino, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Mixanval *Servier, Port.*
Amlodipine besilate (p. 1304·1); perindopril arginine (p. 1466·3).
Hypertension.

Mixavit *Julphar, UAE.*
Vitamins.

Mixavit C *Kalbe, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C deficiency; vitamin B and C supplement.

Mixavit-M *Julphar, UAE.*
Vitamins; minerals.

Mixcarotin *Franco-Indian, India.*
Vitamin A (p. 2098·3).

Mixcilin *Gramon, Arg.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mixed Vegetable Tablets *Dorwest, UK.*
Rorippa nasturtium-aquaticum; celery seed and plant (p. 2472·3); horseradish (p. 2526·1); parsley (p. 2583·3).
Musculoskeletal and joint disorders; cystitis; minor bladder disorders.

Mixgen *Laboratorios Chile, Chile.*
⊗Betamethasone (p. 1623·2) or betamethasone dipropionate (p. 1623·3); gentamicin (p. 304·2) or gentamicin sulfate (p. 304·2).
Infected eye disorders; infected skin disorders.

Mixigil *Virgo, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Mixobar *Bracco, Denm.; Bracco, Fin.; Bracco, Norw.; Bracco, Swed.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Mixo-EPL *Elnova, India.*
Vitamin B substances (p. 2102·3); vitamin E acetate (p. 2119·2); phospholipids (p. 2201·2).

Mixogen *Organon, India; Donmed, S.Afr.†*
Injection: ⊗Estradiol benzoate (p. 2271·1); estradiol phenylpropionate (p. 2271·2); testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2).
Menopausal disorders; oestrogen deficiency.

Organon, India.
Tablets: ⊗Ethinylestradiol (p. 2275·3); methyltestosterone (p. 2291·3).
Menopausal disorders.

Mixol *Cadila, Rus.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Mixotone *Teofarma, Ital.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); hydrocortisone sodium succinate (p. 1640·3); lidocaine hydrochloride (p. 1988·2).
Bacterial infections of the ear.

Mixovim *Orchid, India.*
Thioctic acid (p. 2629·1); vitamins; minerals; trace elements.

Mixtard 10, 20, 30, 40, and 50 *Novo Nordisk, Gr.; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Neth.; Novo Nordisk, Pol.*
⊗Mixtures of insulin injection (human, recombinant monocomponent) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human, recombinant monocomponent) 90%, 80%, 70%, 60%, and 50%, respectively (p. 475·3).
Diabetes mellitus.

Mixtard 10, 20, 30, 40, and 50 HM *Novo Nordisk, Port.*
⊗Mixtures of insulin injection (human) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human) 90%, 80%, 70%, 60%, and 50% respectively (p. 475·3).
Diabetes mellitus.

Mixtard 20, 30, and 40 *Novo Nordisk, Turk.*
⊗Mixtures of insulin injection (human) 20%, 30%, or 40 and isophane insulin injection (human) 80%, 70%, or 60%, respectively (p. 475·3).
Diabetes mellitus.

Mixtard 30 *Novo Nordisk, Belg.; Novo Nordisk, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Indon.; Novo Nordisk, NZ; Novo Nordisk, Spain; Novo Nordisk, UK.†*
⊗Mixtures of insulin injection (human, monocomponent) 30% and isophane insulin suspension (human, monocomponent) 70% respectively (p. 475·3).
Diabetes mellitus.

Mixtard 30, 40, and 50 *Novo Nordisk, Cz.*
⊗Mixtures of insulin injection (human, monocoponent) 30%, 40%, or 50% and isophane insulin suspension (human, monocomponent) 70%, 60%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Mixtard 30 and 50 *Novo Nordisk, Austria; Novo Nordisk, India; Novo Nordisk, Singapore.*
⊗Mixtures of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p. 475·3).
Formerly known as Human Mixtard.
Diabetes mellitus.

Mixtard 30/70, 50/50 *Novo Nordisk, Austral.*
⊗Mixtures of neutral insulin injection (human, pyr, monocomponent) and isophane insulin injection (human, pyr, monocomponent) respectively in the proportions indicated (p. 475·3).
Diabetes mellitus.

Mixtard HM *Novo Nordisk, Thai.*
⊗A mixture of insulin injection (human, monocomponent) 30% and isophane insulin injection (human, monocomponent) 70% (p. 475·3).
Diabetes mellitus.

Mixtard 30 HM *Novo Nordisk, Arg.†; Novo Nordisk, Chile; Novo Nordisk, Hong Kong; Novo Nordisk, Malaysia; Novo Nordisk, Philipp.; Novo Nordisk, Rus.*
⊗Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p. 475·3).
Diabetes mellitus.

Mixtard HM 30 *Novo Nordisk, Switz.*
⊗A mixture of insulin injection (human, monocomponent) 30% and isophane insulin injection (human, monocomponent) 70%, respectively (p. 475·3).
Diabetes mellitus.

Mixtard HM 30, 40, and 50 *Novo Nordisk, Israel.*
⊗Mixtures of insulin injection (human) 30%, 40%, or 50% and isophane insulin injection (human) 70%, 60%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Mixtura Pepsini *Pampa, Pol.*
⊗Pepsin (p. 2586·1); hydrochloric acid (p. 2528·3).
Gastric hypoacidity.

Mixture Conta Tussis for Adults *Mosfarma, Rus.; Vifiteh, Rus.*
Ammonium chloride (p. 1656·1); anise oil (p. 2444·3); sodium benzoate (p. 1738·2); sodium bicarbonate (p. 1781·1); liquorice (p. 1853·2); thermopsia.

Mixture Conta Tussis for Children *Mosfarma, Rus.; Vifiteh, Rus.*
Althaea (p. 2438·3); anise oil (p. 2444·3); sodium bicarbonate (p. 1781·1); liquorice (p. 1853·2).

Mixture for Inhalations *Tverskaya, Rus.; Yaroslavl, Rus.*
Menthol (p. 2553·2); eucalyptus leaf (p. 2501·1).
Respiratory-tract disorders.

Mixture Tussis *Suphong, Thai.*
Camphorated opium tincture; liquorice (p. 1853·2).
Cough.

Mixulin *Cadila, India.*
⊗A mixture of neutral insulin (porcine) 30% and isophane insulin (porcine) 70% (p. 475·3).
Diabetes mellitus.

Miya *Miyarisan, China.*
Clostridium butyricum.
Gastrointestinal disorders.

Miya-BM *Miyarisan, Jpn.*
Clostridium butyricum.
Restoration of gastrointestinal flora.

Miyadren *Fako, Turk.; Yavuz, Turk.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Miyorel *Sanofi Synthelabo, Turk.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Miz *Zytras, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Mizantrone *Vocate, Gr.*
Irinotecan hydrochloride (p. 812·2).

Mizapin *Teva, Hung.*
Mirtazapine (p. 436·1).
Depression.

Mizar *Valeant, Ital.*
Flurithromycin ethyl succinate (p. 300·2).
Bacterial infections.

Mizeco *Aamorb, India.*
Caffeine (p. 1203·3); ergotamine tartrate (p. 674·1); paracetamol (p. 115·1); prochlorperazine maleate (p. 1098·3).

Mizoco *Farmaline, Thai.*
Ketoconazole (p. 585·3).
Fungal infections of the skin, hair, and nails.

Mizodin *Unia, Pol.*
Primidone (p. 547·1).
Epilepsy.

Mizolam *CCM, Malaysia.*
Midazolam (p. 1085·1).
Insomnia; premedication.

Mizolast *FDC, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Mizole *BMW, India.*
Miconazole (p. 588·3).
Fungal skin infections.

Mizolen *Sanofi-Aventis, Spain.*
Mizolastine (p. 636·1).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Mizollen *Sanofi-Aventis, Belg.; Xian-Janssen, China; Therabel, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.†; Sanofi-Aventis, Port.; Adcock Ingram, S.Afr.; Sanofi-Aventis, Swed.†; Sanofi-Aventis, Switz.†; Sanofi-Aventis, UK.*
Mizolastine (p. 636·1).
Allergic conjunctivitis; allergic rhinitis; urticaria; allergic rhinoconjunctivitis; pruritus.

Mizoltec *Tecnofarma, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Mizonase *Gynopharm, Chile.*
Miconazole (p. 588·3); tinidazole (p. 949·2).
Fungal balanitis; trichomoniasis; vulvovaginal infections.

Mizonol *Geolab, Braz.*
Miconazole nitrate (p. 589·1).

Mizoron *Milano, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Mizosin *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; heart failure; Raynaud's disease; benign prostatic hyperplasia.

MK *Solitaire, India.*
Montelukast (p. 1214·3).
Asthma; allergic rhinitis.

M-Kast-L *Captab, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

MKCN *Medial, India.*
Amikacin (p. 214·1).
Bacterial infections.

M-Klav *Medial, India.*
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

M-Kon *Madhav, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

M-Lite *Captab, India.*
⊗Hydroquinone (p. 1705·1); mometasone (p. 1644·1); tretinoin (p. 1725·2).

MLM-Dex *Millimed, Thai.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

M-long *Grunenthal, Ger.*
⊗Morphine sulfate (p. 92·3).
Pain.

MM Expectorante *Farmasa, Braz.*
⊗Potassium iodide (p. 2336·3); lobelia (p. 2323·2); hyoscyamus (p. 2530·2).
Respiratory-tract congestion.

MMA Anamix *Nutricia, Fr.*
Food for special diets.
Methylmalonic acidaemia.

MMA PA Anamix *Nutricia, Cz.*
Food for special diets.
Methylmalonic acidaemia; propionic acidaemia.

MMA/PA *Nutricia, Ital.*
Food for special diets.
Methylmalonic aciduria; propionic aciduria.

MMA/PA Anamix *Nutricia, Austral.*
Infant feed.
Formerly known as XMTVI Analog.
Methylmalonic acidaemia; propionic acidaemia.

MMF *Ipca, India.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

MMO3 *FDC, India.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); vitamins; trace elements.

M-Moflo *Quest, India.*
Moxifloxacin (p. 326·3).
Bacterial eye infections.

M-Mox Plus *Meridian, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

M-Moxa *2M, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

MMR *Sanofi Pasteur, Denm.†*
A measles, mumps, and rubella vaccine (Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3 strains, respectively) (p. 2400·2).
Active immunisation.

MMR II *MSD, Arg.; Merck Frosst, Canad.; MSD, China; MSD, Cz.†; Sanofi Pasteur, Fin.†; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.†; MSD, Indon.; Sanofi Pasteur, Irl.†; MSD, Israel; Sanofi Pasteur, Ital.†; MSD, Malaysia; MSD, Mex.; Sanofi Pasteur, Norw.†; MSD, NZ; MSD, Pol.†; Sanofi Pasteur, Port.†; MSD, Rus.; MSD, Singapore; Sanofi Pasteur, Swed.†; MSD, Thai.; MSD, Turk.; Aventis Pasteur, UK†; Merck, USA.*
A live attenuated measles, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

MMR Triplovax *Sanofi Pasteur, Ger.†*
A measles, mumps, and rubella vaccine (More attenuated Enders', Jeryl Lynn, and Wistar RA 27/3 strains, respectively) (p. 2400·2).
Active immunisation.

MMRVaxPro *Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; Sanofi Pasteur, UK.*
A measles, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

MMS *Zydus, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mnesis *Takeda, Ital.; Takeda, Switz.†*
Idebenone (p. 392·3).
Cerebrovascular disorders; Friedreich's ataxia.

MNS *One Pharma, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Mo Ni Ka *Hailing, China; Yangtze River, China.*
Racecadotril (p. 1881·3).
Diarrhoea.

Mo Di Qi *Lukang Chenxin, China.*
Hydroxycamptothecin.

Mo Tai *Minophagen, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Mo Le Xin *Chung-Hwa, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mo Xin *Poly, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Moapar *Debioclinic, Swed.†*
⊗Triptorelin embonate (p. 2311·1).
Deviant sexual behaviour in men.

Moban *Endo, USA.†*
Molindone hydrochloride (p. 1088·3).
Psychoses.

Mobec *Boehringer Ingelheim, Ger.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Mobemid *Jelfa, Pol.*
Moclobemide (p. 437·2).
Depression; social phobia.

Mobemide *Unipharm, Israel†; Trima, Singapore; Unipharm, Singapore.*
Moclobemide (p. 437·2).
Depression; social phobia.

Moben *Elofar, Braz.†*
Mebendazole (p. 158·3).
Worm infections.

Mobex *Boehringer Ingelheim, Chile.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mobiaid *Ajanta, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Mobic *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, China; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Norw.†; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.†; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK†; Abbott, USA; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; sciatica.

Mobical *JB Chemicals, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1).

Mobicam
Note: this name may be used for preparations of different composition.
Cipla, India.
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.
Ranbaxy, Irl.
Meloxicam (p. 86·3).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Mobicox *Boehringer Ingelheim, Canad.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Switz.*
Meloxicam (p. 86·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Mobidin
Note: this name may be used for preparations of different composition.
Ascher, USA.
Magnesium salicylate (p. 85·2).
Pain; fever; inflammation.
Centaur, India.
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Mobifen *Yash, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Mobiflam *East West, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Mobiflex
Note: this name may be used for preparations of different composition.
Roche, UK.
Tenoxicam (p. 136·2).
Musculoskeletal, joint and soft-tissue disorders.
Soho, Indon.
Meloxicam (p. 86·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Mobigel
Note: this name may be used for preparations of different composition.
Yash, India.
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.
Goldshield, UK.†
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint pain.

Mobiglan *Niche, Irl.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Mobijoint *Psychotropics, India.*
Boswellia serrata (p. 2507·3); chondroitin sulfate (p. 2476·1); glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3).

Mobilat *Nycomed, Mex.; Neocare, Neth.; Ciclum, Port.; Medinova, Switz.*
A heparinoid (p. 1401·1); salicylic acid (p. 1719·1).
Joint, peri-articular and soft-tissue disorders; sports injuries.
Stada, Austria; Neocare, Belg.; Sankyo, Braz.; Silesia, Chile†; Stada, Cz.; Stada, Fin.; Medinova, Philipp.; Sankyo, Pol.; Medinova, Thai.
⊗A heparinoid (p. 1401·1); salicylic acid (p. 1719·1); suprarenal extract (p. 1648·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Mobilat DuoAktiv *Stada, Ger.*
Chondroitin sulfate (p. 2476·1); salicylic acid (p. 1719·1).
Soft-tissue injury.

Mobilat Glucosamin *Stada, Ger.†*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Mobilat Intens
Note: this name may be used for preparations of different composition.
Stada, Ger.
Flufenamic acid (p. 65·1).
Peri-articular disorders.

Mobilat Intense
Note: this name may be used for preparations of different composition.
Medinova, Switz.
A heparinoid (p. 1401·1); glycol salicylate (p. 66·2); flufenamic acid (p. 65·1).
Musculoskeletal and joint disorders.

Mobilat N *Stada, Hung.*
A heparinoid (p. 1401·1); salicylic acid (p. 1719·1).
Musculoskeletal, joint, and soft-tissue disorders.

Mobilat Schmerzspray *Stada, Ger.*
Indometacin (p. 71·2).
Peri-articular and soft-tissue disorders.

Mobilat Schmerztabletten mit Naproxen *Stada, Ger.†*
Naproxen (p. 98·2).
Pain.

Mobilis *Alphapharm, Austral.; LCH, Hong Kong.†*
Piroxicam (p. 125·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mobilisin
Note: this name may be used for preparations of different composition.
Ciclum, Port.
Cream: Flufenamic acid (p. 65·1); a heparinoid (p. 1401·1).
Musculoskeletal, joint, and peri-articular disorders.

Ciclum, Port.
Topical gel: Flufenamic acid (p. 65·1); salicylic acid (p. 1719·1); a heparinoid (p. 1401·1).
Musculoskeletal, joint, and peri-articular disorders.

Stada, Austria; Neocare, Belg.; EG, Ital.; Medinova, Switz.†
Flufenamic acid (p. 65·1); glycol salicylate (p. 66·2); a heparinoid (p. 1401·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgias.

Mobilisin Composto *Sankyo, Braz.*
Flufenamic acid (p. 65·1); a heparinoid (p. 1401·1); glycol salicylate (p. 66·2).
Musculoskeletal and joint disorders.

Mobilisin plus *Stada, Austria.*
Flufenamic acid (p. 65·1); a heparinoid (p. 1401·1); benzyl nicotinate (p. 29·3).
Musculoskeletal and joint disorders.

Mobilyzer *Omni, UK.*
Green-lipped mussel (p. 2522·3).
Nutritional supplement for joint care.

Mobi norm *Sterling, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Mobinorm-S *Sterling, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Mobisox *Sidmak, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Painful skeletal muscle spasm.

Mobiswift-D *Ranbaxy, India.*
Diclofenac potassium (p. 48·3); metaxalone (p. 2025·2).

Mobisyl *Ascher, USA.*
Trolamine salicylate (p. 141·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Mobitone *Advik, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Mobium *Orchid, India.*
Calcium dobesilate (p. 2464·3).
Peripheral vascular disorders.

Mobix *Cipla, India.*
Capsules: Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Cipla, India.
Cream: Esterified fatty acids; menthol (p. 2553·2); methyl salicylate (p. 92·1).

Mobizox *Ranbaxy, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Painful skeletal muscle spasm.

Moblo *Medizone, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Moblo-AF *Medizone, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Mobloc *AstraZeneca, Ger.*
⊗Felodipine (p. 1380·3); metoprolol succinate (p. 1434·3).
Hypertension.

Moblo-M12 *Medizone, India.*
Vitamin B substances (p. 2102·3).

Moblo-Plus *Medizone, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Mobrine-IR *Ranbaxy, India.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Mobyle *Ind-Swift, India.*
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Mobyle-V *Lincoln, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Mocef *Aamorb, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Mocef-S *Aamorb, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Mocef-TZ *Aamorb, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Mocimed *Bajamed, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moclamine *Biocodex, Fr.*
Moclobemide (p. 437·2).
Depression.

Moclav *Sandoz, Israel.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moclo A *Sandoz, Switz.*
Moclobemide (p. 437·2).
Depression; social phobia.

Moclobeta *Betapharm, Ger.*
Moclobemide (p. 437·2).
Depression.

Moclopharm *Actavis, Hung.†*
Moclobemide (p. 437·2).
Depression.

Moclostad *Pharmacodane, Denm.*
Moclobemide (p. 437·2).
Depression.

Moclox *Kopran, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Mocloxil *Anpharm, Pol.†*
Moclobemide (p. 437·2).
Depression; social phobia.

Moco *Haledew, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mocrim *Apotex, Hung.*
Moclobemide (p. 437·2).
Depression; social phobia.

Mocydone *Pharmasant, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; digestive disorders; dyspepsia.

Modaderm *Samik, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2); clotrimazole (p. 576·2).
Infected skin disorders; burns.

Modafen *Zentiva, Cz.; Zentiva, Pol.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract disorders; upper respiratory-tract symptoms in viral infections.

Modal *Rafa, Israel.*
Sulpiride (p. 1107·3).
Peptic ulcer; psychoses; vestibular disorders.

Modalert *Sun, India.*
⊗Modafinil (p. 2327·2).

Modalim *Sanofi, China; Sanofi-Aventis, Indon.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, UK.†*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Modalina *SIT, Ital.*
Trifluoperazine hydrochloride (p. 1113·2).
Psychiatric disorders.

Modamide *Gerda, Fr.*
⊗Amiloride hydrochloride (p. 1299·1).
Oedema; hypertension; ascites.

Modane
Note: this name may be used for preparations of different composition.
Bago, Chile.
Dantron (p. 1833·3); calcium pantothenate (p. 2085·2).
Constipation.

Cooperation Pharmaceutique, Fr.
Calcium pantothenate (p. 2085·2); senna (p. 1885·1).
Constipation.

Korhispana, Spain.
Calcium sennoside A (p. 1885·1); calcium sennoside B (p. 1885·1).
Constipation.

Savage, USA.
Bisacodyl (p. 1821·1).
Constipation.

Modasomil *Cephalon, Austria; Teva, Switz.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; sleep apnoea.

Modaton
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
Calcium pantothenate (p. 2085·2); dantron (p. 1833·3).
Constipation.

Montpellier, Arg.
Oral drops: Sodium picosulfate (p. 1887·2).
Constipation.

Montpellier, Arg.
Tablets: Bisacodyl (p. 1821·1).
Constipation.

Modaton Nl *Montpellier, Arg.*
Liquid paraffin (p. 2191·2).
Constipation.

Modavigil *CSL, Austral.; CSL, NZ.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; obstructive sleep apnoea-hypopnoea syndrome; shift-work sleep disorder.

Modcef *Sarabhai Piramal, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Modecate *BMS, Austral.; BMS, Canad.; Merck, Chile; BMS, Hong Kong†; BMS, Indon.†; BMS, Irl.; BMS, NZ; BMS, S.Afr.; BMS, Spain; Sanofi Synthelabo, UK.*
Fluphenazine decanoate (p. 1075·1).
Schizophrenia; psychoses.

Modécate *Sanofi-Aventis, Fr.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Moderan *Vargas, Venez.*
Lactulose (p. 1850·3).
Liver disorders; constipation.

Moderine *Uniao Quimica, Braz.*
⊗Mazindol (p. 2324·1).
Obesity.

Moderlax *Atral, Port.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Modern Herbals Cold & Catarrh *Lane, UK.*
Althaea (p. 2438·3); echinacea (p. 2498·1); sambucus (p. 2609·3).
Sinus congestion; catarrh.

Modern Herbals Cold & Congestion *Lane, UK.*
⊗Lobelia (p. 2323·2); tolu solution (p. 1679·2).
Catarrh; hay fever; congestion; rhinitis; cold symptoms.

Modern Herbals Cough Mixture *Lane, UK.*
Ipecacuanha (p. 1667·2); marrubium (p. 1668·3); squill vinegar (p. 1677·3).
Coughs; cold symptoms; sore throat; catarrh.

Modern Herbals Laxative *Lane, UK.*
Senna (p. 1885·1); aloin (p. 1816·2); cascara (p. 1826·1).
Constipation.

Modern Herbals Menopause *Lane, UK.*
Parsley (p. 2583·3); vervain (p. 2645·1); clivers (p. 2481·2); senna (p. 1885·1).
Menopausal disorders.

Modern Herbals Muscular Pain *Lane, UK.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Muscle pain.

Modern Herbals Pile *Lane, UK.*
Ointment: Hamamelis (p. 2523·3); compound benzoin tincture; zinc oxide (p. 1729·1).
Haemorrhoids.

Lane, UK.
Tablets: Cascara (p. 1826·1); slippery elm (p. 2617·1).
Haemorrhoids.

Modern Herbals Rheumatic Pain *Lane, UK.*
Celery leaf (p. 2472·3); menyanthes (p. 2554·2); cimicifuga (p. 2478·1).
Musculoskeletal and joint pain.

Modern Herbals Sleep Aid *Lane, UK.*
Passion flower (p. 2584·1).
Insomnia.

Modern Herbals Stress *Lane, UK.*
Motherwort (p. 2564·2); valerian (p. 2640·2); vervain (p. 2645·1); passion flower (p. 2584·1).
Stresses and strains; irritability.

Modern Herbals Trapped Wind & Indigestion *Lane, UK.*
Activated charcoal (p. 1537·3).
Dyspepsia; flatulence; heartburn; diarrhoea.

Modern Herbals Water Retention *Lane, UK.*
Bearberry (p. 2453·2); clivers (p. 2481·2); lappa (p. 2540·1).
Water retention.

Modet *Berksam, Turk.*
Calcium dobesilate (p. 2464·3).

Modezine *Atlantic, Philipp.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Modfil *Psyco Remedies, India.*
⊗Modafinil (p. 2327·2).

Modibloq *Zeler, Port.*
Nimodipine (p. 1455·2).

Modicon *Janssen-Cilag, Neth.; Ortho McNeil, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Modiem *Piam, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Modifenac *Actavis, Denm.†; Actavis, Norw.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders.

Modifical
Note: this name may be used for preparations of different composition.
Zodiac, Braz.; Asoforma, Mex.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Beta, Arg.
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Modifical Duo *Beta, Arg.*
1 Tablet, ibandronate sodium (p. 1184·2); 30 chewable tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Modigen *Pharma Vision, Hung.*
St John's wort (p. 449·1).
Depression.

Modigraf *Astellas, Cz.; Astellas, Denm.; Astellas, Fr.; Astellas, Ger.; Astellas, Irl.; Astellas, Neth.; Astellas, Norw.; Astellas, Pol.; Astellas, Port.; Astellas, Spain; Astellas, UK.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Modik *Germed, Braz.*
Imiquimod (p. 985·2).

Modil *General Drugs, Thai.*
Minoxidil (p. 1438·3).
Hypertension.

Modilac Expert AR *Sodilac, Fr.*
Infant feed.
Regurgitation in infants.

Modilac Expert HA *Sodilac, Fr.*
Infant feed.
Milk-protein allergy.

Modilac Expert Oéba *Sodilac, Fr.*
Infant feed.
Infant colic.

Modilac Expert Riz *Sodilac, Fr.*
Infant feed.
Cows' milk protein allergy.

Modilac Expert SL *Sodilac, Fr.*
Infant feed.
Lactose intolerance; diarrhoea.

Modilac Expert Soja *Sodilac, Fr.*
Infant feed.
Cows' milk protein allergy.

Modilac Expert Transit + *Sodilac, Fr.*
Infant feed.
Constipation.

Modimet *Ultra, Mex.†*
Dipyrone (p. 53·3).
Fever; pain.

Modin *Taisheng, Philipp.*
Famotidine (p. 1842·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Modina
Note: this name may be used for preparations of different composition.
Orifarm, Denm.; Orifarm, Fin.
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Pentafarma, Port.
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Modinexil *Lavipharm, Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Modinol *Vianex (Βιανεξ), Gr.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Modiodal *MSD, Denm.; Orifarm, Denm.; Cephalon, Fr.; Genesis, Gr.; Alfresa, Jpn; Armstrong, Mex.; Cephalon, Neth.; Teva, Norw.; Cephalon, Port.; Teva, Spain; MSD, Swed.; Gen, Turk.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; obstructive sleep apnoea; attention-deficit hyperactivity disorder; hypersomnia.

Modip *AstraZeneca, Ger.*
Felodipine (p. 1380·3).
Hypertension.

Modipas *Nafar, Mex.*
Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).

Modipin *Cadila, India.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Modisal
Note: this name may be used for preparations of different composition.
Sandoz, UK.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Moditen *Biotika, Cz.; KRKA, Hung.; BMS, Ital.; BMS, Rus.; KRKA, Rus.; KRKA, Ukr.; BMS, Venez.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Sanofi-Aventis, Fr.†
Fluphenazine hydrochloride (p. 1075·1).
Psychoses.

Modium *Pharmathen, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Modivid *Patheon, China; Sanofi-Aventis, Ital.; Sanofi-Aventis, Port.; Aventis, Turk.*
Cefodizime sodium (p. 242·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Modjul *Scientific Hospital Supplies, Irl.†*
Flavouring for use with unflavoured peptide and amino-acid preparations.

Modlip *Torrent, India.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Modlip Asp *Torrent, India.*
Aspirin (p. 22·2); atorvastatin calcium (p. 1309·2).

Modlip-AM *Torrent, India.*
Atorvastatin (p. 1309·2); levamlodipine.

Modlip-EZ *Torrent, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Mododom *Julphar, UAE.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting.

Modomed *Medifive, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; heartburn; digestive disorders; dyspepsia.

Modopar *Roche, Fr.; Eureco, Neth.†; Euro Registratie, Neth.†*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Modrasone *MSD, Irl.; Teva, UK.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Modrenal *Bioenvision, UK.†*
Trilostane (p. 2634·1).
Cushing's syndrome; hyperaldosteronism; breast cancer.

Modsenal *T Man, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Moducal *Mead Johnson, NZ; Mead Johnson Nutritionals, USA.*
Glucose polymers (p. 2080·3).
Carbohydrate source; carbohydrate supplement.

Moducren *Gerda, Fr.; MSD, Hong Kong†; MSD, Irl.†; MSD, S.Afr.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2); timolol maleate (p. 1513·2).
Hypertension.

Moducrin *MSD, Austria†; Teofarma, Ger.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2); timolol maleate (p. 1513·2).
Hypertension.

Modula *Antonetto, Ital.*
Polycarbophil calcium (p. 1879·2).
Constipation; diarrhoea.

Modulactone *Lafedar, Arg.*
⊗Spironolactone (p. 1499·3).

Modulamin *Braun, Switz.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Modulanzime *Grunenthal, Port.*
⊗Bromopride (p. 1824·2); dimeticone (p. 1886·2); pepsin (p. 2586·1); amylase (p. 2442·1); fungal lipase.
Gastrointestinal disorders.

Modulen IBD *Nestle, Braz.; Nestle, Cz.; Nestle, Fin.; Nestle, Fr.; Nestle, Israel; Nestle, Ital.; Nestle, UK.*
Preparation for enteral nutrition.
Inflammatory bowel disease.

Nestle Clinical, Irl.
Lactose- and gluten-free preparation for enteral nutrition.
Crohn's disease.

Modulo Calorico *Braun, Chile; Behrens, Venez.*
Maltodextrin (p. 2080·3).
Nutritional supplement.

Modulon *Aptalis, Canad.; Pfizer, Fr.†*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; postoperative paralytic ileus; gastrointestinal disorders.

Modupac *Inpac, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Diuretic.

Modurax *Utopian, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Moduret *Prempharm, Canad.†; MSD, Irl.; MSD, UK.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
These ingredients can be described by the British Approved Name Co-amilozide.
Hypertension; heart failure; ascites; oedema.

Moduretic *MSD, Arg.; Aspen, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Cz.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; Healthcare Logistics, NZ; MSD, Port.; MSD, S.Afr.; MSD, Swed.†; MSD, Switz.; M & H, Thai.; Abbott, Turk.; BMS, UK; Merck, USA; MSD, Venez.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
These ingredients can be described by the British Approved Name Co-amilozide.
Heart failure; oedema; hypertension; hepatic cirrhosis with ascites; hypokalaemia.

Modurétic *MSD-Chibret, Fr.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; ascites.

Moduretik *BMS, Ger.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; ascites.

Moduride *CCM, Malaysia.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis with ascites.

Modus
Note: this name may be used for preparations of different composition.
Almirall, Spain.
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

GSK, India.
Medroxyprogesterone (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders.

Modusik-A *Volta, Chile; Sophia, Mex.*
Ciclosporin (p. 1945·2).
Dry eyes.

Modustatina *Sanofi-Aventis, Ital.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery; diabetic ketoacidosis; adjunct in gastrointestinal radiography.

Modustatine *GSK, China.*
Somatostatin (p. 1930·3).
Gastrointestinal haemorrhage.

Sanofi-Aventis, Fr.†
Somatostatin acetate (p. 1930·3).
Postoperative gastrointestinal fistulae; gastrointestinal haemorrhage.

Modutrol *Gynopharm, Chile.†*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Triphasic oral contraceptive.

Moduxin *Gedeon Richter, Hung.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders.

Moex *UCB, Cz.; UCB, Fr.; Schwarz, Hong Kong†; Schwarz, Rus.; UCB, Ukr.*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Moex Plus *Schwarz, Rus.*
⊗Moexipril hydrochloride (p. 1440·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Mofacort *Surya Dermato, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mofax *Sun, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Painful skeletal muscle spasm.

Mofazt *Mega Lifesciences, Thai.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Mofcare *Madhav, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Mofcare-TZ *Madhav, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Mofecept *Kocak, Turk.*
Mycophenolate mofetil (p. 1961·1).

Mofelox *Nobel, Turk.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Mofen *Erlimpex, Indon.*
Ibuprofen (p. 68·2).
Pain; fever.

Mofetyl *RPG, India.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mofil *Zytras, India.*
Moxifloxacin (p. 326·3).
Bacterial conjunctivitis.

Mofilet *Emcure, India.*
Mycophenolic acid (p. 1961·1) or mycophenolate sodium (p. 1961·2).
Transplant rejection.

Emcure, Philipp.
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mofimutral *Valeant, Cz.; Valeant, Hung.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Moflag *Atlas, Arg.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Moflag D *Atlas, Arg.*
⊗Moxifloxacin hydrochloride (p. 326·3); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Moflo *Quest, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Moflo-OZ *Quest, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Mo-Floren *Indoco, India.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Mof-OZ *Madhav, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Mofulex *Molex Ayus, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mofur *Gabriel, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mogadan *Meda, Ger.*
Nitrazepam (p. 1089·1).
Sleep disorders.

Mogadon *Valeant, Austral.; Meda, Austria; Meda, Belg.; Valeant, Canad.; Meda, Denm.†; Meda, Fr.; Invida, Hong Kong; Meda, Irl.; Valeant, Ital.; Meda, Neth.; Meda, Norw.; Pharmaco, S.Afr.; Meda, Swed.; Meda, Switz.; ICN, UK.*
Nitrazepam (p. 1089·1).
Insomnia; sleep disorders; epilepsy; infantile spasm.

Mogasinte *Sanofi-Aventis, Port.†*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting; adjunct in gastrointestinal examinations.

Mogine *Douglas, NZ.*
Lamotrigine (p. 527·2).
Bipolar disorder; epilepsy.

Mogitob-D *Indkus, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); tobramycin (p. 380·1).
Bacterial eye infections with inflammation.

Mohexal *Sandoz, Austral.*
Moclobemide (p. 437·2).
Depression.

Mohrus *Hisamitsu, Hong Kong; Hisamitsu, Jpn.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Moira *Alna, India.*
Meropenem (p. 321·3).
Bacterial infections.

Moisderm *Interbat, Indon.*
⊗Urea (p. 1727·3).
Dry skin disorders; hyperkeratotic skin disorders.

Moiskin-AF *Helios, India.*
Emollient.

Moisol *FDC, India.*
Injection: Hypromellose (p. 2189·2).
Adjunct in ocular surgery.

FDC, India.
Eye drops: Borax (p. 2459·2); boric acid (p. 2459·3); hypromellose (p. 2189·2).
Dry eyes.

Moisol-Z *FDC, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Moist Again *Lake, USA.*
Vaginal lubricant.

Moiste *Hetero, India.*
Aloe vera (p. 1693·2); honey (p. 2072·1); melaleuca oil (p. 2551·1); wheat-germ oil (p. 2647·1).
Emollient.

Moisten *Bausch & Lomb, China.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Moi-Stir *Pharmascience, Canad.; Kingswood, USA.*
Carmellose sodium (p. 2175·2); electrolytes (p. 1775·1); sorbitol (p. 2092·1).
Dry mouth.

Moisture Drops *Bausch & Lomb, USA.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3); glycerol (p. 2517·2).
Dry eyes.

Moisture Extreme *Maybelline, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Moisture Eyes
Note: this name may be used for preparations of different composition.
Bausch & Lomb, Hong Kong; Bausch & Lomb, Mex.; Bausch & Lomb, Philipp.
⊗Glycerol (p. 2517·2); propylene glycol (p. 2205·2).
Dry eyes.

Moisture Oil-Free *Johnson & Johnson, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Moisture Rescue *Garnier, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Moisture Restore *NSE, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Moisture Rich *Johnson & Johnson, Canad.†*
SPF 20: Avobenzone (p. 1695·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Moisture Shield *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Moisture Therapy Intensive
Note: this name may be used for preparations of different composition.
Avon, Canad.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Avon, Canad.†
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Moisturel *Novartis Consumer, Canad.*
White soft paraffin (p. 2211·3); dimeticone (p. 2209·3).
Dry skin disorders.

Westwood-Squibb, USA.
Emollient.
Dry skin disorders.

Moisturex *Ranbaxy, India.*
⊗Lactic acid (p. 2539·1); liquid paraffin (p. 2191·2); propylene glycol (p. 2205·2); urea (p. 1727·3).
Dry skin disorders.

Moisturex-AF *Ranbaxy, India.*
Aloe vera (p. 1693·2); linolenic acid (p. 1460·2); lactic acid (p. 2539·1); propylene glycol (p. 2205·2); vitamin E (p. 2119·1).
Emollient.

Moisturizer *Lamas, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Moisturizing All Clear *Bausch & Lomb, Philipp.*
⊗Macrogol (p. 2547·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Moisturizing Antibacterial Hand Cleanser *Futuremed, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Moisturizing Lip Balm *Norwood, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).

Moisturizing Lip Gloss *Energizer, Canad.*
Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).

Moisturizing Sunscreen *Medical Skin Therapy, Canad.†*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Moitz *Dewcare, India.*
Cream: Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Emollient.

Dewcare, India.
Eye drops: Carmellose (p. 2175·1).
Dry eyes.

Mokbios *Mersifarma, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mokcan *Cadila, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Mokcan-C *Cadila, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Mokcan-C LB *Cadila, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Mokcell *Accord, Mex.*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphoma.

Mokelin *Rotam Reddy, China.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Mokia-G *Orion, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Moklar *Glenmark, Pol.*
Moclobemide (p. 437·2).
Depression; social phobia.

Moks *Pharmawealth, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moksilin *Sandoz, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mokuboito *Tsumura, Jpn.*
Gypsum (p. 2173·1); sinomenium stem; cinnamon bark (p. 2479·2); ginseng (p. 2513·3).
Traditional Kampo medicine.

Mol *Gufic, India.*
Paracetamol (p. 115·1).
Pain; fever.

Molacort *Molex Ayus, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Moladec *Molex Ayus, Indon.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Nutritional supplement in infants and children.

Moladerm *Molex Ayus, Indon.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Molaflam *Molex Ayus, Indon.*
Ketoprofen (p. 79·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Molagar
Note: this name may be used for preparations of different composition.
Finadiet, Arg.
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Molagit *Molex Ayus, Indon.*
Attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Molakrim *Molex Ayus, Indon.*
Menthol (p. 2553·2); eugenol (p. 2501·2); methyl salicylate (p. 92·1).
Musculoskeletal pain; soft-tissue injury; headache.

M-Olan *Mediez, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

M-Olan Plus *Mediez, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Molapect *Molex Ayus, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Molasic *Molex Ayus, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Molason *Molex Ayus, Indon.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Molat *Rowex, Irl.*
Montelukast sodium (p. 1214·3).
Asthma.

Molavir *Molex Ayus, Indon.*
Aciclovir (p. 964·1).
Herpex simplex infections of the skin and mucous membranes.

Molax *Siam Bheasach, Thai.*
Domperidone (p. 1838·1) or domperidone maleate (p. 1838·1).
Gastrointestinal disorders; hiccup.

Molaxole *Meda, Austria; Meda, Belg.; Meda, Cz.; Meda, Irl.; Meda, Ital.; Meda, Neth.; Meda, Spain; Meda, Switz.; Meda, UK.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; bowel evacuation; faecal impaction.

Molazol *Molex Ayus, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Molca *Andromaco, Chile.*
Benzethonium chloride (p. 1738·1); proflavine hydrochloride (p. 1732·3).
Disinfection of mucous membranes, skin, and wounds.

Molcass *Varifarma, Arg.*
Molgramostim (p. 1156·2).
Neutropenia.

Molcer *Wallace Mfg Chem., UK.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Mold & Smuts Extracts *Trupharm, Israel.*
Molds allergen extracts (p. 2434·3).
Skin testing; immunotherapy.

Moldep-AT *Arvincare, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Molelant *Chrispa (Χρισπα), Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Molevac *Infectopharm, Ger.*
Pyrvinium embonate (p. 166·1).
Enterobiasis.

Molexdine *Molex Ayus, Indon.*
Povidone-iodine (p. 1767·1).
Skin disinfection; wounds; oral hygiene.

Molexdryl *Molex Ayus, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Molexflu *Molex Ayus, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Molide *Helax, India.*
Magnesium (p. 1786·3); nimesulide (p. 101·3); paracetamol (p. 115·1).

Moliderm *GSK, India.*
⊗Fluticasone (p. 1638·1).
Skin disorders.

Molipaxin *Sanofi-Aventis, Irl.; Sanofi-Aventis, S.Afr.; Aventis, UK.*
Trazodone hydrochloride (p. 451·1).
Depression; mixed anxiety depressive states.

Molit *Abbott, Turk.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Molit Plus *Abbott, Turk.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm and pain.

Molival
Note: this name may be used for preparations of different composition.
Temis, Arg.
Levetiracetam (p. 531·1).
Epilepsy.

Molken *Unipharma, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mollifene *Pfeiffer, USA.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Mollipect *Biophausia, Swed.*
⊗Bromhexine hydrochloride (p. 1656·3); ephedrine hydrochloride (p. 1663·2).
Cough.

Mollome *Gedeon Richter, Cz.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Molly *Allenge, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Molly-Plus *Allenge, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Molnarux *Helm, Port.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Molnia *Maigal, Arg.*
Soap: Sulfur (p. 1721·1).
Skin disorders.

Maigal, Arg.
Shampoo: Pyrithione zinc (p. 1718·1).
Scalp disorders.

Moloco + B12 *Darya-Varia, Indon.*
Placenta extract (p. 2444·1); vitamin B_{12} (p. 2107·2).
Lactation insufficiency.

Molpireos *Helm, Port.*
Paracetamol (p. 115·1).
Pain; fever.

Molsee *Blubell, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Molsibeta *Betapharm, Ger.*
Molsidomine (p. 1441·1).
Angina pectoris.

Molsicor
Note: this name may be used for preparations of different composition.
Investi, Arg.†; Sandoz, Turk.
Molsidomine (p. 1441·1).
Angina pectoris.

Valta, Chile.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Molsidain *Sanofi-Aventis, Spain.*
Molsidomine (p. 1441·1).
Angina pectoris.

Molsidaine *Sanofi-Aventis, Arg.*
Molsidomine (p. 1441·1).
Angina pectoris.

Molsidolat *Sanofi-Aventis, Austria.*
Molsidomine (p. 1441·1).
Angina pectoris.

Molsigamma *Worwag, Ger.*
Molsidomine (p. 1441·1).
Angina pectoris.

Molsihexal *Hexal, Austria†; Hexal, Cz.; Hexal, Ger.†*
Molsidomine (p. 1441·1).
Angina pectoris.

Molsiket *UCB, Cz.*
Molsidomine (p. 1441·1).
Angina pectoris.

molsiket *UCB, Ger.*
Molsidomine (p. 1441·1).
Ischaemic heart disease.

Molsi-Puren *Actavis, Ger.†*
Molsidomine (p. 1441·1).
Ischaemic heart disease.

Molu Plus *Keshav, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Molulid *NB, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Molutrex *ACM, Fr.*
Potassium hydroxide (p. 2595·3).
Molluscum contagiosum.

Molux *Arvincare, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Molval *Dielen, Fr.*
Omega-3 fatty acids (p. 1460·1).
Dietary supplement; hyperlipidaemias.

Molvite with Iron *Pharma Nutria, Philipp.*
Ferrous sulfate (p. 2062·2); lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Vitamin and iron deficiency; nutritional supplement.

Molvite-OB *Pharma Nutria, Philipp.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Nutritional supplement for pregnancy and lactation.

Moly Kid *Stedman, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Molybdan Compositum *Heel, Canad.†*
Minerals.
Homoeopathic preparation.

Molybdène Injectable *Aguettant, Fr.†*
Ammonium molybdate (p. 2082·3).
Parenteral nutrition.

Molypen *American Pharmaceutical, USA.†*
Ammonium molybdate (p. 2082·3).
Parenteral nutrition.

Mom *Papaellinas (Παπαελληνας), Gr.*
Piperonyl butoxide (p. 2160·2); tetramethrin (p. 2162·2).

Mom Gel *Candioli, Ital.*
Phenothrin (p. 2160·1).
Pediculosis.

Mom Lozione Preventiva *Candioli, Ital.*
Benzyl benzoate (p. 2149·1).
Insect repellent.

Mom Shampoo Schiuma *Candioli, Ital.*
Phenothrin (p. 2160·1).
Pediculosis.

Mom Zanzara *Candioli, Ital.*
Benzyl benzoate (p. 2149·1); ethyl hexanediol.
Insect repellent.

Momarid *Nepentes, Pol.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momat *Glenmark, Rus.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momate *Glenmark, India; Glenmark, Malaysia; Glenmark, Philipp.*
⊗Mometasone furoate (p. 1644·1).
Skin and scalp disorders.

Momate-S *Glenmark, India.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Psoriasis.

Momat-S *Glenmark, Rus.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).

Momazol *Khandelwal, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Momecon *Bilim, Turk.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

East West, India.
⊗Mometasone (p. 1644·1).
Skin disorders.

Momecort *Mentiterm, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momederm *Jelfa, Pol.; Jelfa, Ukr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momeflo *Lupin, India.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis; nasal polyps.

Momegalen *Galen, Ger.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momegen *Generics, Hung.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momelab *Labomed, Chile.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momen *Angelini, Port.*
Benzydamine hydrochloride (p. 29·2).
Musculoskeletal and joint disorders.

Angelini, Spain.
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; fever; pain.

Momendol *Faran, Gr.; Angelini, Ital.; ACRAF, Neth.; Angelini, Port.*
Naproxen sodium (p. 98·2).
Fever; pain; musculoskeletal and joint disorders; inflammation.

Angelini, Ital.
Topical gel: Naproxen sodium (p. 98·2); a heparinoid (p. 1401·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Moment
Note: this name may be used for preparations of different composition.
Angelini, Ital.; Angelini, Port.
Ibuprofen (p. 68·2).
Pain; fever; influenza symptoms.

Apsen, Braz.
Capsaicin (p. 35·1).
Neuralgia.

Momentact *Angelini, Ital.*
Ibuprofen (p. 68·2) or ibuprofen sodium (p. 68·2).
Pain; fever; influenza symptoms.

Momento *CSC, Austria.†*
Ibuprofen (p. 68·2).
Pain.

Momentol *BMS, Spain.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Momentum
Note: this name may be used for preparations of different composition.
CSC, Austria; Pfizer, Neth.†
Paracetamol (p. 115·1).
Pain; fever.

Whitehall, USA.
Aspirin (p. 22·2); phenyltoloxamine citrate (p. 638·1).
Backache.

Momentum Muscular Backache Formula *Whitehall, USA.*
Magnesium salicylate (p. 85·2).
Pain.

Momeplus *Panalab, Arg.*
⊗Mometasone (p. 1644·1).
Skin disorders.

Momerid *Nepentes, Cz.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momesalic *Schering-Plough, Cz.; Epsilon Health, Gr.; Bilim, Turk.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Psoriasis.

Momet *Erlimpex, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mometagen *Mylan, S.Afr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mometax *Investi, Arg.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mometil *PharOS, Cz.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mometix *Drogsan, Turk.*
⊗Mometasone furoate (p. 1644·1).

Momex *Southern Cross, Austral.*
⊗Morphine sulfate (p. 92·3).
Pain.

Momexin *JSJ, USA.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momfol *Rapross, India.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Momicine *Inibsa, Spain.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Momkair *PDC, India.*
Syrup: Calcium carbonate (p. 1824·3); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).

PDC, India.
Tablets: Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).

Momordica Complexe No 109 *Lehning, Fr.†*
Rheum palmatum (p. 1884·2); momordica; belladonna (p. 2453·3); nux vomica (p. 2573·3); cinchona succirubra (p. 2478·3); colchicum (p. 607·1); cuprum aceticum (p. 2486·2); croton tiglium; phosphorus (p. 2589·2).
Homoeopathic preparation.

Momoz *Unichem, India.*
⊗Mometasone (p. 1644·1).
Skin disorders.

Momoz-F *Unichem, India.*
⊗Fusidic acid (p. 302·1); mometasone furoate (p. 1644·1).

Momoz-S *Unichem, India.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Skin disorders.

Momoz-T *Unichem, India.*
⊗Mometasone furoate (p. 1644·1); terbinafine (p. 593·3).

Momplus *Dey's, India.*
Magnesium hydroxide (p. 1857·2); liquid paraffin (p. 2191·2); sodium picosulfate (p. 1887·2).

Momtas *Cosme, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Momvita *Bionova, India.*
Docosahexaenoic acid (p. 1460·1); lycopene (p. 2546·2); vitamins; minerals.

Monace *Alphapharm, Austral.; PharmaSwiss, Cz.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Monace Combi *PharmaSwiss, Cz.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Monacef
Note: this name may be used for preparations of different composition.
Esseti, China.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zee, India.
Cefalexin (p. 234·1).
Bacterial infections.

Monafed DM *Monarch, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Monafram *Framon, Rus.*
Fragments of monoclonal antibodies.
Thrombosis prophylaxis during coronary angioplasty.

Monagyn *Theramex, Mon.*
Vulvovaginal cleanser.

Monal *Alna, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Monaless *Marjan, Braz.*
Red yeast rice (p. 2603·1).
Hyperlipidaemias.

Mona-Lisa *Hackmey, Israel.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Monamox *Zee, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Monamox-BR *Zee, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

Monamox-CL *Zee, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Monapax *Cassella-med, Ger.*
Drosera (p. 2497·2); hedera helix (p. 2536·2); china (p. 2478·3); coccus cacti (p. 2179·2); cupr. sulf. (p. 2057·2); ipecacuanha (p. 1667·2); hyoscyamus (p. 2530·2).
Homoeopathic preparation.

Monarc-M *Kamada, Israel†; Cankat, Turk.†; American Red Cross, USA.†*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A.

Monarit *Rontag, Arg.*
Naproxen sodium (p. 98·2).
Pain.

Monasan *CCM, Malaysia.*
Fluphenazine decanoate (p. 1075·1).
Schizophrenia.

Monasens *Theramex, Mon.*
Nicotinamide (p. 2083·1); sodium hyaluronate (p. 2526·2).
Vaginal lubricant.

Monast *Captab, India.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia.

Monax *Eczacibasi, Turk.*
Montelukast sodium (p. 1214·3).

Monazol *Theramex, Mon.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections; vulvovaginal candidiasis.

Moncet *Haledew, India.*
Cetirizine (p. 619·2); montelukast (p. 1214·3).

Moncycline *Am-Europharma, Philipp.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Monda *Medial, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Mondeal *Stada, Austria.*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Mondeo-LC *Invision, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Mondeslor *Sun, India.*
Desloratadine (p. 625·1); montelukast (p. 1214·3).

Mondex *S F, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Mondus *Sandoz, Arg.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Mone *Cankat, Turk.*
Meloxicam (p. 86·3).
Osteoarthritis; ankylosing spondylitis; rheumatoid arthritis.

Monecto *Fahrenheit, Indon.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monell *Novell, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Monem *Biolab, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Monet *Mapra, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Moneva *Bayer, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Mongol *Gerolymatos, Gr.*
⊗Morphine sulfate (p. 92·3).
Pain.

Monicil *Sanval, Braz.†*
Rifampicin (p. 350·3).
Tuberculosis.

Monicor *Pierre Fabre, Fr.; Wallace, India; Pharma Dynamics, S.Afr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monigen *Generics, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monilac *Chugai, Jpn.*
Lactulose (p. 1850·3).
Hyperammonaemia; constipation.

Monilen *Recip, Swed.†*
⊗Urea (p. 1727·3).
Dry skin.

Monirax *T Man, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Moni-Sanorania *Winthrop, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monisol *Hemofarm, Rus.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure.

Monistat *Johnson & Johnson, Canad.; Johnson & Johnson, NZ; Janssen, Philipp.; Janssen-Cilag, Switz.; Insight, USA.*
Miconazole nitrate (p. 589·1).
Fungal vulvovaginal infections; balanitis.

Monistat Derm *Johnson & Johnson, Canad.*
Miconazole nitrate (p. 589·1).
Fungal skin infections; vaginal candidiasis.

Monit *Intas, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monit-AS *Intas, India.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction.

Monit-Puren *Actavis, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monizol *Krolton, Arg.*
Miconazole (p. 588·3).
Vaginal candidiasis.

Monizol Cort *Krolton, Arg.*
⊗Miconazole (p. 588·3); hydrocortisone (p. 1640·1); metronidazole (p. 936·1).
Vulvovaginal infections.

Monizol Cort Crema *Krolton, Arg.*
⊗Betamethasone valerate (p. 1624·1); miconazole (p. 588·3); gentamicin sulfate (p. 304·2).

Monizole *PC India, India.*
Metronidazole (p. 936·1).
Amoebiasis; giardiasis.

Monkasta *KRKA, Cz.; KRKA, Pol.; KRKA, Spain.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

KRKA, Rus.
Montelukast (p. 1214·3).
Asthma.

Monlucare *Stada, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Monn *Natco, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monnax *Medhaus, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Monnax Plus *Medhaus, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; bloating.

5-Mono *Biochem, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

mono corax *corax, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Mono Demetrin *Pfizer, Ger.*
Prazepam (p. 1098·2).
Anxiety disorders.

Mono Mack *Pfizer, Austria; Mack, China; Mack, Cz.; Pfizer, Ger.; Pfizer, Hung.; Pfizer, Pol.; Pfizer, Rus.; Zuoz, Venez.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension; myocardial infarction.

Mono Rom *Rompharm, Rus.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Mono Tad *TAD, Pol.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Mono-A *Troikaa, India.*
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).
Angina pectoris; myocardial infarction.

Monoact *Active, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Monoalgic *Sanofi-Aventis, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Monobac *BMS, Mex.*
Aztreonam (p. 224·1).
Gram-negative bacterial infections.

Monobact *Zuventus, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Monobeta *Betapharm, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monobiotic *Ecobi, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Monobracin *Faran, Gr.*
Tobramycin (p. 380·1).
Eye infections.

Monocain *Kocak, Turk.*
Lidocaine hydrochloride (p. 1988·2).

Monocal *Mericon, USA.*
Calcium carbonate (p. 1824·3); sodium monofluorophosphate (p. 2091·3).
Dietary supplement.

Monocaps *Freeda, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Monocard *Synteza, Pol.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Mono-CC *Mint, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2); menthol (p. 2553·2).

Mono-Cedocard *Takeda, Neth.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monocef
Note: this name may be used for preparations of different composition.
Aristo, India.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Biochimico, Braz.
Cefuroxime (p. 255·2).
Bacterial infections.

Goldshield, Israel.
Cefonicid (p. 242·3).
Bacterial infections.

Monocef-O *Aristo, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Monocer *Pentafarma, Port.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Monocete *Pedinol, USA.*
Monochloroacetic acid (p. 1714·3).
Verrucae.

Monocetin *Sigma, Braz.†*
⊗Tetracycline hydrochloride (p. 373·2); bromelains (p. 2460·3).
Bacterial infections.

Monocid
Note: this name may be used for preparations of different composition.
Decomed, Port.; Rottapharm, Spain.
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Monocide *Fischer, Israel.†*
Malathion (p. 2157·2); bioallethrin (p. 2149·2).
Pediculosis.

Monocilin *Sanjivani, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Monocin *Overseas, India.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Monocinque *Menarini, Hong Kong; Lusofarmaco, Ital.; Berlin-Chemie, Rus.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Monoclair *Hennig, Ger.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monoclar *Captab, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Monoclarium *SMB, Belg.; SMB, Singapore.*
Clarithromycin (p. 266·2).
Bacterial infections.

Monoclate P *Zydus, India.*
A factor VIII preparation (p. 1148·1).

Monoclate-P *CSL, Arg.; ZLB, Braz.†; Aventis Behring, Fr.†; CSL, Gr.; Centeon, Israel†; CSL, Mex.†; Aventis Behring, UK; Centeon, USA.*
A factor VIII preparation (p. 1148·1).
Haemophilia A; haemorrhagic disorders; factor VIII deficiency.

Monoclox *Medochemie, Hong Kong†; Medochemie, Malaysia.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Monocobal-AD *Captab, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Monocontin *Win-Medicare, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monocor *Biovail, Canad.†*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Monocorat *Armstrong, Mex.*
Isosorbide mononitrate (p. 1413·3).
Heart failure; angina pectoris; pulmonary hypertension.

Monocord *Dexcel, Israel.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monocordil *Baldacci, Braz.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monocrin *Pasteur, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Monocrixo *Therabel, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Monodex *Thea, Austria.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Thea, Ger.
⊗Dexamethasone phosphate (p. 1631·1).
Inflammatory eye disorders.

Monodin *Pfizer, Port.†*
Amlodipine besilate (p. 1304·1).
Hypertension; ischaemic heart disease.

Monodoks *Deva, Turk.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Monodox *Oclassen, USA.*
Doxycycline (p. 288·1).
Bacterial infections; intestinal amoebiasis.

Monodrox *Profic Organic, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Monodur *PMC, Austral.; AstraZeneca, Turk.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Mono-Embolex *Novartis, Ger.*
Certoparin sodium (p. 1334·2).
Postoperative thrombosis prophylaxis; deep-vein thrombosis.

Monofeme *Pfizer, Austral.; Pfizer, NZ.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Monofer *Pharmacosmos, Denm.; Pharmacosmos, Fin.; Demo, Gr.; Pharmacosmos, Neth.; Pharmacosmos, Norw.; Pharmacosmos, Swed.; Vitaline, UK.*
Iron isomaltoside 1000 (p. 2077·2).
Iron-deficiency anaemia.

Monoferro *Braun, Spain.*
Iron isomaltoside (p. 2077·2).
Iron-deficiency anaemia.

Ganassini, Ital.†
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Monofin *Captab, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Monofix *CSL, NZ.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Monofix-VF *CSL, Austral.; CSL Biotherapies, Hong Kong; CSL, Singapore.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Monoflam *Winthrop, Cz.; Winthrop, Ger.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation; pain; soft-tissue disorders.

Monoflocet *Sanofi-Aventis, Fr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Monoflox
Note: this name may be used for preparations of different composition.
Captab, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Centaur, India.
Levofloxacin (p. 315·3).
Bacterial infections.

MonoGen *Nutricia, Fr.*
Food for special diets.

Monogen *Nutricia, Austral.*
Preparation for enteral nutrition in infants and children.
Disorders of lipid metabolism and absorption.

Nutricia, Denm.; SHS, Israel; SHS, UK.
Preparation for enteral nutrition.
Metabolic disorders; lipid and lymphatic disorders.

SHS, Irl.; Nutricia, Ital.
Food for special diets.
Disorders of lipid metabolism and absorption; hyperlipoproteinaemia.

Nutricia, NZ.
Gluten-free food for special diets.
Lipid and lymphatic disorders.

Monogesic *Bal, India.*
Nimesulide (p. 101·3).
Pain; sprains; tendinitis.

Monoginal *Sandoz, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

MonoGrippol *Petrovax, Rus.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Mono-Jod *Mibe, Ger.*
Potassium iodide (p. 2336·3).
Iodine deficiency.

Monoket *Sidus, Arg.; UCB, Austria; Optipharm, Gr.; Chiesi, Ital.; UCB, Norw.; Neo-Farmaceutica, Port.; UCB, Swed.; Abbott, Turk.; Adeka, Turk.; Schwarz, USA.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Mono-Latex *Wampole, USA.*
Test for infectious mononucleosis.

Monolax *Deltapharm, Hong Kong†; Charoen, Thai.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Monolin *Berlin Pharm, Thai.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monolitum *Salvat, Spain.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Monolong *Actavis, Ger.†; CTS, Israel; CTS, Rus.; Ali, Turk.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monomax *Trinity, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monomen *Menarini, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monomil *Ivax, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monomox-DX *Captab, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Mononate *Leo, India.*
Artesunate (p. 648·2).
Malaria.

Mononaxy *Cephalon, Fr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Mononine *CSL, Arg.; CSL, Austria; CSL, Belg.; ZLB, Braz.†; CSL, Canad.†; CSL, Cz.; CSL, Fr.; CSL, Ger.; Aventis, Gr.; CSL, Gr.; CSL, Israel; CSL, Ital.; CSL, Neth.; CSL, Port.; CSL, Spain; CSL, Swed.; CSL, UK; Centeon, USA.*
A factor IX preparation (p. 1149·3).
Haemophilia B; haemorrhagic disorders; factor IX deficiency.

Mononit *Perrigo, Israel; Sanofi-Aventis, Pol.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Mononitrat *Verla, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Mononitrosid *Borshchagovskii, Ukr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monopack *Bago, Chile.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monoparin *IFET{ΙΦΕΤ}, Gr.; CP Pharmaceuticals, Irl.†*
Heparin sodium (p. 1396·3).
Anticoagulant.

Wockhardt, UK.†
Heparin calcium (p. 1396·3) or heparin sodium (p. 1396·3).
Thromboembolic disorders.

Monopark *Pfizer, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monopas *Macleods, India; Farmasintez, Rus.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Monopina *Pfizer, Ital.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Monoplus *BMS, Austral.; BMS, Braz.; BMS, Gr.; BMS, Thai.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Monopost *Spectrum, UK.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Monopram *Captab, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Monopril *BMS, Austral.; BMS, Braz.; BMS, Canad.; BMS, Chile†; BMS, China; BMS, Cz.; BMS, Gr.; BMS, Hong Kong†; BMS, Hung.; BMS, Mex.; BMS, Pol.†; BMS, Rus.; BMS, S.Afr.; BMS, Swed.†; BMS, Thai.†; BMS, Turk.; BMS, USA; BMS, Venez.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Monopril Plus *BMS, Chile†; BMS, Turk.; BMS, Venez.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Monopril-HCT *BMS, USA.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Monopront *Ferraz, Lynce, Port.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monoprost *Thea, Fin.; Thea, Neth.; Thea, Switz.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Monopur *Pohl, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monorapid *Promedico, Israel.†*
Isopropyl alcohol (p. 1758·3); 1,3-butanediol (p. 2172·2).
Skin disinfection.

Monores *Valeas, Ital.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Monorythm *Santa, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monos *SF, Ital.*
Rufloxacin hydrochloride (p. 357·1).
Bacterial infections.

Monosan *ProMed, Cz.; ProMed, Pol.; Promed, Rus.; ProMed, Ukr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monoscab *Captab, India.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Monosept *Horus, Fr.*
Cethexonium bromide (p. 1742·1).
Eye infections.

Monosol *Baxter, Austria.*
Glucose (p. 2068·3); electrolytes (p. 1775·1).
Haemodialysis; haemofiltration.

Baxter, Irl.
Glucose (p. 2068·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2).
Haemodialysis; haemodiafiltration; haemofiltration.

Monosor *Vitabalans, Cz.*
Isosorbide mononitrate (p. 1413·3).
Stenocardia prophylaxis.

Monosorb *Amedius, Philipp.; GPO, Thai.; Dexcel, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monosorbitrate *Piramal, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monosordil *Elpen (Ελπεν), Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monosprin *Sun, India.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction prophylaxis.

MonoStep *Bayer, Ger.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Monosuinsulin MK *Belmed, Rus.*
⊗Soluble insulin (porcine) (p. 475·3).
Diabetes mellitus.

Monosulpa *Leti, Venez.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); kanamycin sulfate (p. 314·3).

Monotab *Zentiva, Cz.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Monotard *Novo Nordisk, Gr.; Novo Nordisk, NZ.*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Monotard HM *Novo Nordisk, Hong Kong†; Ferron, Indon.; Novo Nordisk, Indon.*
⊗Insulin zinc suspension (human) (amorphous 30%, crystalline 70%) (p. 475·3).
Diabetes mellitus.

Monotard MC *Novo Nordisk, Rus.†*
⊗Insulin zinc suspension (crystalline 70%, amorphous 30%) (porcine, monocomponent) (p. 475·3).
Diabetes mellitus.

Monotax *Biochem, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Monotax-O *Biochem, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Monotest *Aventis Pasteur, India.*
Tuberculin (p. 2635·3).
Sensitivity test.

Mono-Tildiem *Sanofi, China; Mediwin, Fr.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.†; Sanofi-Aventis, Singapore.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Monotobrin *Pharmanel, Gr.*
Tobramycin (p. 380·1).
Eye infections.

Monotop *Pharmathen, Denm.; Pharmathen, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Monotorva *USV, India.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Monotrace *East West, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monotramal *Grunenthal, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Monotrate *Sun, China; Sun, India; Sun, Thai.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Monotrean
Note: this name may be used for preparations of different composition.
Sankyo, Braz.
Papaverine (p. 2362·2); quinine hydrochloride (p. 665·2).
Vertigo.

Monotrean B6 *Sankyo, Braz.*
Papaverine (p. 2362·2); quinine hydrochloride (p. 665·2); pyridoxine hydrochloride (p. 2105·3).
Vertigo.

Monotrim *Chemidex, Irl.; Chemidex, UK.*
Trimethoprim (p. 381·2).
Bacterial infections.

Monotrin *Bago, Arg.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monovas *Nevzat, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Monover *Pharmacosmos, Irl.*
Iron isomaltoside (p. 2077·2).
Iron-deficiency anaemia.

Monovisc *Helix, Canad.; Plasmaconcept, Ger.; Anika, Singapore.*
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement; osteoarthritis.

Monovit *Sanjivani, India.*
Vitamin B substances (p. 2102·3).

Monovit-3 B *Kocak, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Monovit D3 *Kocak, Turk.*
Colecalciferol (p. 2113·1).

Monovitan C *Pliva Krakow, Pol.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Monovit-C *Kocak, Turk.*
Ascorbic acid (p. 2110·3).

Monovit-EN *Orchid, India.*
d-Alpha tocopherol (p. 2119·1).

Monovo *Almirall, Irl.; Almirall, Neth.; Almirall, Switz.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Monowel *Biolab, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Monoxar *Proge, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Monoxidil *Lamda (Λαμδα), Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Monozeclar *Abbott, Fr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Monozide
Note: this name may be used for preparations of different composition.
PD, Thai.
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; alcohol withdrawal syndrome; premedication; seizures.

BMS, S.Afr.†
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Monozol *Legrand, Braz.*
Albendazole (p. 149·1).
Worm infections.

Monsalic *Schering-Plough, Port.*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Skin disorders.

Monspes *Specifar, Denm.†*
Montelukast sodium (p. 1214·3).
Asthma.

Monstonol *Pharmacare, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Montair *Cipla, India; Metz, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montair Plus *Cipla, India.*
⊗Montelukast sodium (p. 1214·3); bambuterol hydrochloride (p. 1203·1).
Asthma.

Montair-LC *Cipla, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast sodium (p. 1214·3).

Montal *Psyco Remedies, India.*
Montelukast (p. 1214·3).
Asthma; allergic rhinitis.

Montamed *Montavit, Austria.*
Salverine hydrochloride (p. 2609·2); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain.

Montana *Agri-Pharma, Hung.*
Lupulus (p. 2546·1); gentian (p. 2512·1); cinnamon (p. 2479·2); bitter orange (p. 2575·3); caraway (p. 2470·2); taraxacum (p. 2625·3); peppermint (p. 1877·1); pterocarpus santalinus.
Gastrointestinal disorders.

Pharmonta, Austria.
Lupulus (p. 2546·1); gentian (p. 2512·1); cinnamon (p. 2479·2); bitter-orange peel (p. 2575·3); caraway (p. 2470·2); taraxacum (p. 2625·3); peppermint oil (p. 1877·1); pterocarpus santalinus.
Gastrointestinal disorders.

Montana N *Pharmonta, Ger.*
Cardamom (p. 2471·1); cinnamon (p. 2479·2); centaury (p. 2473·2); caraway (p. 2470·2); bitter-orange peel (p. 2575·3); peppermint leaf (p. 1877·1); gentian (p. 2512·1).
Gastrointestinal disorders.

Montasma *Icarus, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montasma Plus *Icarus, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Montast *Specifar, Gr.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montaz *Aristo, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Montbre *Aurel, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Montebloc *Danlex, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Montecad *Cadila, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montecon *Genericon, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Montecross *Pharmacross, Chile.*
Montelukast sodium (p. 1214·3).
Asthma.

Montefranc *MR Pharma, Neth.*
Montelukast sodium (p. 1214·3).
Asthma.

Montegen *Orifarm, Denm.; Gentili, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Montegen-L *Genesis, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast sodium (p. 1214·3).

Montek *Silom, Thai.*
Montelukast sodium (p. 1214·3).
Asthma; bronchospasm; allergic rhinitis.

Sun, India.
Montelukast (p. 1214·3).
Asthma; allergic rhinitis.

Montekast *Taiwan Biotech, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montek-LC *Sun, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast (p. 1214·3).

Montel *Ratiopharm, Cz.; Borshchagovskii, Ukr.*
Montelukast sodium (p. 1214·3).
Asthma.

Montelair *Ache, Braz.*
Montelukast (p. 1214·3).

Clonmel, Irl.
Montelukast sodium (p. 1214·3).
Asthma.

Montelak *Medreg, Pol.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montelar *Zentiva, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Montelast *Cadila, India.*
Montelukast sodium (p. 1214·3).
Asthma.

Montelubronch *Infectopharm, Ger.*
Montelukast sodium (p. 1214·3).
Asthma.

Montemax *Natrapharm, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montenorm *Plus Pharma, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Monteratio *Ratiopharm, Cz.*
Montelukast sodium (p. 1214·3).

Montero *Innovative, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Montessan *Apotex, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Montest *Genexo, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Montetrinas *Sigillata, Denm.*
Montelukast sodium (p. 1214·3).
Asthma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Montevizin *Hemofarm, Rus.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Conjunctivitis.

Montexal *Valeant, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Monthan *Specifar, Denm.; Specifar, Ital.; Specifar, Neth.*
Montelukast sodium (p. 1214·3).
Asthma.

Monti *Abbott, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Monticina *Mintlab, Chile.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Skin infections.

Montidin *Danlex, Philipp.†*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Montiget *Getz, Philipp.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montilife *MDC, India.*
Levocetirizine hydrochloride (p. 632·3); montelukast sodium (p. 1214·3).

Montisartas *Sigillata, Denm.*
Montelukast sodium (p. 1214·3).
Asthma.

Montlu-L *Shince, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Monto-2 *Shreya, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Monto-3 *Shreya, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Monto-4 *Shreya, India.*
Caplets, ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3) caplets, pyrazinamide (p. 345·2).
Tuberculosis.

Montokuf *Shreya, India.*
Codeine phosphate (p. 40·2).
Cough.

Montomycin *Shreya, India.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Montonex Forte *Shreya, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Montorip *Shreya, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Montozin *Shreya, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Montral *Micro, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Montralex *Danlex, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Montramox *Danlex, Philipp.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Montrate *Casasco, Arg.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Montulind *Sigillata, Cz.; Sigillata, Denm.*
Montelukast sodium (p. 1214·3).
Asthma.

Monty *Solitaire, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Monukast *Galeno, Venez.*
Montelukast (p. 1214·3).
Asthma.

Monural *Zambon, Hung.; Zambon, Pol.; Zambon, Rus.; Zambon, Ukr.*
Fosfomycin trometamol (p. 300·3).
Urinary-tract infections.

Monuril *Zambon, Austria; Zambon, Belg.; Zambon, Braz.; Zambon, Fr.; Pierre Fabre, Ger.; Zambon, Indon.; Zambon, Irl.; Zambon, Ital.; Zambon, Neth.; Zambon, Port.; Zambon, Switz.*
Fosfomycin trometamol (p. 300·3).
Urinary-tract infections.

Monurol *Triton, Canad.; Labomed, Chile†; Zambon, China; Zambon, Fin.†; Gerolimatos (Γερολυματος), Gr.; Zambon, Hong Kong; Rafa, Israel; Zambon, Malaysia; Sanofi-Aventis, Mex.; Zambon, Philipp.; Zambon, Singapore; Zambon, Spain; Zambon, Thai.; Bilim, Turk.; Forest Pharmaceuticals, USA.*
Fosfomycin trometamol (p. 300·3).
Urinary-tract infections.

Monway Plus *Arrowin, India.*
⊗Bambuterol (p. 1203·1); montelukast (p. 1214·3).

Mood and Anxiety Remedy *Brauer, Austral.*
Clematis vitalba; helianthemum nummularium; impatiens glandulifera; ornithogalum umbellatum; prunus cerasifera; scleranthus annuus.
Bach flower remedy.

Mood Boost *Bioplanta, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Moodeze *Thompson & Capper, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Moolpas *Pharmacare, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Moorland *Torbet Laboratories, UK.*
Bismuth aluminate (p. 1821·3); magnesium trisilicate (p. 1858·1); dried aluminium hydroxide gel (p. 1817·2); heavy magnesium carbonate (p. 1856·2); light kaolin (p. 1850·1); calcium carbonate (p. 1824·3).
Dyspepsia; heartburn; flatulence.

MOOV *Ego, Malaysia.*
Melaleuca oil (p. 2551·1).
Insect repellent.

Moov
Note: this name may be used for preparations of different composition.
Ego, Singapore.
Melaleuca oil (p. 2551·1).
Insect repellent.

Paras, Rus.
Levomenthol (p. 2553·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain; soft-tissue injury; respiratory-tract disorders; insect bites; pruritus.

MOOV Head Lice *Ego, Irl.†*
Eucalyptus oil (p. 2501·2); melaleuca oil (p. 2551·1).
Pediculosis.

Moov Head Lice Shampoo *Ego, Austral.*
Eucalyptus oil (p. 2501·2); anise oil (p. 2444·3).
Pediculosis.

Moov Head Lice Solution *Ego, Austral.*
Eucalyptus oil (p. 2501·2); melaleuca oil (p. 2551·1).
Pediculosis.

Moov Insect Repellent *Ego, Austral.*
Melaleuca oil (p. 2551·1).
Insect repellent.

Mopaday *Wockhardt, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Mopasol *Sevapharma, Cz.†*
Monobasic potassium phosphate (p. 1790·3); dibasic sodium phosphate (p. 1791·2).
Solvent for antiviral vaccines.

Mopavac *Sevapharma, Cz.†*
A measles and mumps vaccine (Schwarz and Jeryl Lynn strains, respectively) (p. 2400·1).
Active immunisation.

Mopem *Tum, Turk.*
Meropenem (p. 321·3).

Mopen *FIRMA, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Menarini, India.
Amoxicillin (p. 216·2).
Bacterial infections.

Moperidona *Sidus, Arg.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Moperidona AF *Sidus, Arg.*
Domperidone (p. 1838·1); simeticone (p. 1886·2).
Gastrointestinal disorders with excess gas.

Moperidona Enzimatica *Sidus, Arg.†*
⊗Domperidone (p. 1838·1); pancreatin (p. 2579·3); simeticone (p. 1886·2).
Gastrointestinal disorders with excess gas; pancreatic insufficiency.

Mophecen *Jelfa, Cz.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mopral *AstraZeneca, Fr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Italmex, Mex.
Omeprazole magnesium (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mopralpro *Bayer, Fr.*
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux.

Mopride *Micro, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Moprilic *Chemo, Neth.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Moprix *Sinensix, Thai.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Moproc *Ethypharm, Cz.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mopsoralen *Kela, Belg.*
Methoxsalen (p. 1711·3).
Psoriasis; vitiligo; mycosis fungoides.

Moradorm *Bouhon, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Moradorm S *Bouhon, Ger.*
Valerian (p. 2640·2); passion flower (p. 2584·1); lupulus (p. 2546·1).
Sleep disorders; nervous disorders.

Moragara *Avalanche, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Moragel *IQFA, Mex.†*
Vitamins; minerals.

Moragen *Euroderm, Arg.*
Centella (p. 1698·3); marine algae.

Moralen *Pharmanel, Gr.*
Alendronate sodium (p. 1171·3).

Morapid *Mundipharma, Austria.*
⊗Morphine sulfate (p. 92·3).
Pain.

Moraten *Faran, Gr.; Berna, Singapore; Yeni, Turk.*
A measles vaccine (attenuated Edmonston-Zagreb strain) (p. 2398·3).
Active immunisation.

Moratus *Medley, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; anxiety.

Moraxine *Fahrenheit, Indon.†*
Cefalotin (p. 235·1).
Bacterial infections.

Morazin *Moraceae, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Morband *Moraceae, India.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Morbifurb *O2, China.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Morbilvax *Biovac, S.Afr.†*
A measles vaccine (attenuated Schwarz strain) (p. 2398·3).
Active immunisation.

Morcecal *Moraceae, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Morcef *Dexa, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Morcet *Moraceae, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Morcet Plus *Moraceae, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Morcet-MR *Moraceae, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Morcontin *Modi-Mundipharma, India.*
⊗Morphine sulfate (p. 92·3).
Pain.

Morde X *Urgo, Spain.†*
Sucrose octa-acetate (p. 2215·1).
Nail biting deterrent.

Mordek *Vitalink, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

MorDHA *Shield, Irl.†*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Docosahexaenoic acid deficiency.

Mordica
Note: this name may be used for preparations of different composition.
Gruppo Medica, Philipp.
Karela; chromium polynicotinate (p. 2055·3).
Dietary supplement for blood sugar management.

Jagsonpal, India.
Injection: Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Jagsonpal, India.
Syrup; tablets: Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Morea *Sanol, Ger.; UCB, Ger.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, hirsutism, and seborrhoea in women.

Moreage *BMW, India.*
Syrup: Vitamins; minerals; lysine (p. 2079·3).

BMW, India.
Capsules: Vitamins; minerals; trace elements.

Moreal-Plus *Stada, Rus.*
Dexpanthenol (p. 2582·2).
Nasal disorders.

Morease *Reddy, India.*
Mebeverine hydrochloride (p. 1858·3).
Irritable bowel syndrome; gastrointestinal spasm.

Morease-I *Reddy, India.*
Ispaghula (p. 1849·1); mebeverine hydrochloride (p. 1858·3).

Morecalm *Moraceae, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

MoreDophilus *Freeda, USA.*
Acidophilus-carrot derivative (p. 2596·3).
Dietary supplement.

Moredrill-DX *Avalanche, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Morelac
Note: this name may be used for preparations of different composition.
Arkadia, Ital.
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Restoration of gastrointestinal flora.

Pharmacare, Philipp.
Moringa oleifera.
Nutritional supplement.

Morelax *Loeffler, Mex.*
Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).
Smooth muscle spasm; renal calculi.

Morelevo *Moraceae, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Morelin *Laboratorios Chile, Chile.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).
Mixed anxiety depressive states.

Morenazal *Sintez, Rus.*
Sea water (p. 2612·1).
Nasopharyngeal disorders; nasal hygiene.

Morep *Health Guard, India.*
Meropenem (p. 321·3).
Bacterial infections.

MorEPA *Shield, Irl.†*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Eicosapentaenoic acid deficiency.

Moret *Zytras, India.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).

Moretic *Gracia, Indon.*
Paracetamol (p. 115·1).
Pain; fever.

Morex *Micro, India.*
Moclobemide (p. 437·2).
Depression; social phobia.

Morf *Cipla, India.*
⊗Morphine sulfate (p. 92·3).
Pain.

Morfarin *Charoon Bhesaj, Thai.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Morfenil *Biochimico, Braz.*
⊗Morphine (p. 92·3).

Morfex *Tecnifar, Port.*
Flurazepam dihydrochloride (p. 1076·1).
Insomnia.

Morficontin *Lavipharm, Gr.*
⊗Morphine sulfate (p. 92·3).
Pain.

Morfozid *Kocak, Turk.*
Morinamide hydrochloride (p. 326·3).
Tuberculosis.

Morgen *Saviour, India.*
Vitamins; minerals.

Morgidox *Medimetriks, USA.*
Doxycycline hyclate (p. 288·2).

Morhulin *Actavis, Irl.; Thornton & Ross, UK.*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Superficial wounds; skin disorders.

Moriamin *Far East, Thai.*
Vitamins; amino acids.

Moriamin Forte *Europharm, Ukr.*
Vitamins; amino acids; oxyanthranillic acid.
Dietary supplement.

Morishita, Philipp.
5-Oxyanthranillic acid; vitamins; amino acids.
Nutritional supplement.

Moriamin S-2 *Ajinomoto, Philipp.*
Amino acids.
Parenteral nutrition.

Moriavit *Chunggei, Philipp.*
Capsules: Amino acids; vitamins.
Dietary supplement.

Tai Yu, Philipp.
Infusion: Amino acids.
Parenteral nutrition.

Morihepamin *Mitsubishi, China.*
Amino acids.
Hepatic encephalopathy; hyperammonaemia.

Morin *Duopharma, Philipp.*
⊗Morphine sulfate (p. 92·3).
Pain.

Morixon *Cell Pharm, Ger.†*
⊗Morphine sulfate (p. 92·3).
Pain.

Morlan *Andromaco, Mex.*
Indometacin (p. 71·2); methocarbamol (p. 2025·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Mormox *Morepen, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Morniflu *Master Pharma, Ital.*
Morniflumate (p. 92·2).
Inflammation; pain; fever.

Mornin *Sons, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Morning Sickness Formula *Blackmores, Austral.*
Pyridoxine hydrochloride (p. 2105·3); ginger (p. 1844·1).
Nausea and vomiting during pregnancy.

Moronal *Dermapharm, Ger.*
Nystatin (p. 590·3).
Fungal infections.

Moronal V *Dermapharm, Ger.†*
⊗Nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Skin disorders with fungal infection.

Morpar *Helm, Port.*
Ondansetron hydrochloride (p. 1872·1).

Morph *Sandoz, Ger.†*
⊗Morphine sulfate (p. 92·3).
Pain.

Morphanton *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Morphine sulfate (p. 92·3).
Pain.

Morpheas *Baxter, Gr.*
Propofol (p. 1909·3).
General anaesthesia; sedation in ventilated intensive care patients.

Morphgesic *Amdipharm, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

Morphitroy *Troikaa, India.*
⊗Morphine sulfate (p. 92·3).
Pain.

Morr *Intas, India.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Morrhulan *Streuli, Switz.†*
Cod-liver oil (p. 2056·3).
Minor skin lesions.

Morsi *Sigman, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Morsik-R *Intel, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Mortin *Micro, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Morton Salt Substitute *Morton Salt, USA.*
Low sodium dietary salt substitute.

Mortrin *Daffohils, India.*
Tablets: Paracetamol (p. 115·1).
Pain; fever.

Daffohils, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Mortrin Compound *Daffohils, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Mortrin-T *Daffohils, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Moruman *Faran, Gr.*
A measles immunoglobulin (p. 2398·2).
Passive immunisation.

Morupar *Sanofi-Aventis, India.*
A measles, mumps, and rubella vaccine (Schwartz, Urabe AM9, and Wistar RA 27/3 strains, respectively) (p. 2400·2).
Active immunisation.

MoRu-Viraten *Berna, Canad.†; Biosano, Chile.*
A measles and rubella vaccine (p. 2400·1).
Active immunisation.

Moruviraten *Carbel, Mex.†*
A measles and rubella vaccine (p. 2400·1).
Active immunisation.

Morvit *Aamorb, India.*
Choline bitartrate (p. 2055·2); citrus bioflavonoids (p. 2505·2); vitamins; minerals; grape (p. 2521·3); green tea (p. 2648·2).

Mor-Vita *Duopharma, Philipp.*
Pizotifen malate (p. 678·2).
Migraine; cluster headache.

MorZet *Mylan, Neth.*
Nicomorphine hydrochloride (p. 101·1).
Pain.

MOS *Valeant, Canad.*
⊗Morphine hydrochloride (p. 92·3) or morphine sulfate (p. 92·3).
Pain.

Mosadec *Zydus, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Mosafe *Glenmark, India.*
Mosapride citrate (p. 1865·2).
Gastro-oesophageal reflux; gastritis; dyspepsia; diabetic gastropathy.

Mosagen *Geno, India.*
Mosapride betadex.

Mosakind *Mankind, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Mosalan *Chrispa (Χρισπα), Gr.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Mosap *Medley, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Mosapid *Cipla, India.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Mosar *Phoenix, Arg.*
Mosapride citrate (p. 1865·2).
Dyspepsia; gastritis; gastro-oesophageal reflux.

Mosar Enzimatico *Phoenix, Arg.*
⊗Mosapride citrate (p. 1865·2); simeticone (p. 1886·2); pancreatin (p. 2579·3).
Dyspepsia; digestive disorders.

Mosar Plus *Phoenix, Arg.*
Mosapride citrate (p. 1865·2); simeticone (p. 1886·2).
Flatulence; gastroparesis; meteorism.

Mosardal *Soho, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Mosart *Cadila, India.*
Mosapride sodium (p. 1865·2).

Mosco *Medtech, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Moscontin *Mundipharma, Fr.*
⊗Morphine sulfate (p. 92·3).
Pain.

Moscut *Microsules, Arg.*
Citronella oil (p. 2481·1).
Insect repellent.

Mosec *PP Lab, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Mosegor *Novartis, Gr.; Sandoz, Philipp.; Novartis, Spain; Novartis, Thai.*
Pizotifen malate (p. 678·2).
Migraine; vascular headache; anorexia.

Moségor *Novartis, Switz.†*
Pizotifen malate (p. 678·2).
Anorexia; tonic; migraine and other vascular headaches.

Mosegor Vita *Sandoz, Philipp.*
Pizotifen malate (p. 678·2); vitamin B substances (p. 2102·3).
Reduced appetite.

Moselar *Milano, Thai.*
Pizotifen malate (p. 678·2).
Migraine.

Mosepan *Kopran, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Mosether *Cipla, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Mosgard *Cipla, India.*
Quinine sulfate (p. 665·2).

Mosha-L *Aamorb, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Mosi *FDC, India.*
Moxifloxacin (p. 326·3).
Bacterial eye infections.

Mosiba *Bennet, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Mosic *Rusan, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Mosi-D *FDC, India.*
⊗Dexamethasone (p. 1630·3); moxifloxacin (p. 326·3).
Infected eye disorders.

Mosid-MPS *Torrent, India.*
Simeticone (p. 1886·2); mosapride citrate (p. 1865·2).

Mosid-MT *Torrent, India.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Mosid-OD *Torrent, India.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Mosi-Guard *Mosi-Guard, UK.*
Citriodol.
Insect repellent.

Mosil
Note: this name may be used for preparations of different composition.
Menarini, Fr.
Midecamycin acetate (p. 324·3).
Bacterial infections.

Mosion-6 *Fortune, Hong Kong.†*
Cinnarizine (p. 622·1).

Moska *Moraceae, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Mosmass *Rafarm, Gr.*
Alendronate sodium (p. 1171·3).

Mosoile *Farmstandart, Rus.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1).
Corns.

Mosone *EON, Philipp.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Moss Eye *Syntho, India.*
Chlorobutanol (p. 1747·2); polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).

Most *Daksh, India.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mostcal *Sanat, India.*
Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Mostrafin *Teva, Cz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Mostrelan *Chrispa (Χρισπα), Gr.; Sanopharm, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Mosuolit *Help, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Mosvar *Sarthak, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Mosvit *Multicare, Philipp.*
Vitamins; minerals.

Motaderm *Bernofarm, Indon.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Motaxim *Millimed, Thai.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Moten Instab *Ranbaxy, India.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Motens *Boehringer Ingelheim, Belg.; Orifarm, Denm.; Paranova, Denm.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.†; Boehringer Ingelheim, UK.*
Lacidipine (p. 1417·3).
Hypertension.

Moteson *Konimex, Indon.†*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mother and Child Vitamin Drops *SSL, UK.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Motherwort Combination 1 *Seroyal, Canad.†*
Dioscorea villosa (p. 2648·1); helonias (p. 2524·3); motherwort common (p. 2564·2); senecio aureus (p. 2612·3).
Homoeopathic preparation.

Motherwort Combination 3 *Seroyal, Canad.†*
Alfalfa (p. 2433·1); lycopus virginicus (p. 2462·2); melissa officinalis (p. 2552·3); motherwort common (p. 2564·2).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Motiax *Neopharmed, Ital.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Moticlod *Lisapharma, Ital.*
Clodronate disodium (p. 1180·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Moticon *Condrugs, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Motid
Note: this name may be used for preparations of different composition.
Quesada, Arg.
Otilonium bromide (p. 2578·2).
Randril, Philipp.
Famotidine (p. 1842·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Motidin *Teva, Hung.*
Famotidine (p. 1842·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Motidine *Unison, Hong Kong; Unison, Singapore; Unison, Thai.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; multiple endocrine adenoma; systemic mastocytosis; gastro-oesophageal reflux.

Motidom *Ranbaxy, Mex.; TO-Chemicals, Thai.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting; gastrointestinal motility disorders.

Motidone *CCM, Malaysia.*
Domperidone (p. 1838·1).
Delayed gastric emptying; gastro-oesophageal reflux; nausea and vomiting.

Motifene *Daiichi Sankyo, Belg.; Stada, Fin.; Sankyo, UK.*
Diclofenac sodium (p. 48·3).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders.

Motilak *Veropharm, Rus.*
Domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux; abdominal distension; meteorism; heartburn; nausea and vomiting.

Motilar
Note: this name may be used for preparations of different composition.
Inpac, Thai.
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Motilaxil *Continentales, Mex.*
Sodium picosulfate (p. 1887·2).
Constipation.

Motilex
Note: this name may be used for preparations of different composition.
Almirall, Ital.
Clebopride malate (p. 1833·1).
Nausea and vomiting; aid in gastrointestinal radiography.
Kalbe, Indon.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Motilin *Inpac, Thai.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Motilium *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Johnson & Johnson Consumer, Belg.; Janssen-Cilag, Braz.; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Nycomed, Ger.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Johnson & Johnson, Neth.; Janssen-Cilag, NZ; Janssen, Philipp.; Johnson & Johnson, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Johnson & Johnson, Turk.; McNeil, UK; Winthrop, UK; McNeil, Ukr.*
Domperidone (p. 1838·1).
Dyspepsia; gastroparesis; nausea and vomiting; delayed gastric emptying; gastro-oesophageal reflux; gastrointestinal motility disorders; flatulence; abdominal distension; hiccups; meteorism; heartburn; aid in gastrointestinal examination.

Motilium-M *Johnson & Johnson, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Motinorm *Medley, India; Medley, Rus.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine; hiccups; gastrointestinal motility disorders.

Motinorm-P *Medley, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Motion *Ratiopharm, Austria.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; acne in women requiring an oral contraceptive.

Motion Plus *Solitaire, India.*
Paracetamol (p. 115·1); prochlorperazine (p. 1098·2).

Motion Sickness *Jamp, Canad.†*
Dimenhydrinate (p. 625·2).
Motion sickness.

Motional *Beta, Arg.*
Ispaghula (p. 1849·1).
Constipation; diverticular disease; irritable bowel syndrome.

Motiron *Sandoz, Denm.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Motis *Deva, Turk.*
Domperidone maleate (p. 1838·1).

Motitrel *BMS, Chile.†*
Fluphenazine hydrochloride (p. 1075·1); nortriptyline hydrochloride (p. 439·3).
Mixed anxiety depressive states.

Motival
Note: this name may be used for preparations of different composition.
Biofarma, Turk.
Nimesulide (p. 101·3).
Musculoskeletal and joint disorders; inflammation; pain.
BMS, Indon.†; BMS, Irl.†; BMS, Mex.; BMS, S.Afr.†
Fluphenazine hydrochloride (p. 1075·1); nortriptyline hydrochloride (p. 439·3).
Mixed anxiety-depressive states.

Motivan
Note: this name may be used for preparations of different composition.
GSK, Spain.
Paroxetine hydrochloride (p. 440·3).
Anxiety; depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder; panic disorder.
Union Drug, Thai.
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Motiven *Fontovit, Braz.†*
St John's wort (p. 449·1).
Depression.

Motivest *Medichem, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder.

Motivus *Gerolymatos, Gr.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Motiwin *Svizera, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Motiza *JB Chemicals, India.*
Itopride hydrochloride (p. 1850·1).

Motiza-MPS *Burgeon, India.*
Itopride hydrochloride (p. 1850·1); simeticone (p. 1886·2).

Motoblock *Talent, India.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; heart failure.

Motoblock-AM *Talent, India.*
⊗Amlodipine (p. 1304·1); metoprolol (p. 1434·3).

Motofen
Note: this name may be used for preparations of different composition.
Norma (Νορμα), Gr.
Mirtazapine (p. 436·1).
Depression.
Valeant, USA.
Difenoxin hydrochloride (p. 1835·2).
Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Motonium *Sti-Med-Sorb, Rus.*
Domperidone (p. 1838·1).
Dyspepsia; gastro-oesophageal reflux; abdominal distension; meteorism; heartburn; nausea and vomiting.

Motorix *KVZ, Ukr.*
Domperidone (p. 1838·1).
Dyspepsia; delayed gastric emptying; gastro-oesophageal reflux; nausea and vomiting.

Motoso *BMW, India.*
⊗Mometasone furoate (p. 1644·1); nadifloxacin (p. 328·1).

Motosol *Boehringer Ingelheim, Spain.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Motozina *Biomedica, Ital.†*
Dimenhydrinate (p. 625·2).
Motion sickness.

Motricord *Accord, Mex.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Motrigi *Ipca, Port.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Motrim *Lannacher, Austria.*
Trimethoprim (p. 381·2).
Bacterial infections.

Motrin *Pfizer, Braz.; McNeil Consumer, Canad.; Pfizer, Chile; Janssen-Cilag, Mex.; Pfizer, Mex.; McNeil Consumer, USA; Pfizer, Venez.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Motrin Cold & Sinus *McNeil Consumer, Canad.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Motrin GB *Apotex, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Motrin IB Sinus *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Cold symptoms; sinusitis.

Mouden *Madhav, India.*
Chlorhexidine (p. 1743·2).
Oral hygiene.

Moultons Herbal Extract *Pharmaceutical Enterprises, S.Afr.†*
Aloes (p. 1816·1); rhubarb (p. 1884·2); cascara (p. 1826·1).
Constipation.

Moultons Pain Paint *Pharmaceutical Enterprises, S. Afr.†*
Capsicum oleoresin (p. 2469·3); menthol (p. 2553·2); cassia oil (p. 2471·3); solvent ether (p. 2212·3); sassafras oil (p. 2610·3); clove oil (p. 2481·3); methyl salicylate (p. 92·1).
Muscular pain; neuralgia; digestive disorders; colic.

Mountrim *Mount Mettur, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Moure-M *Pond's, Thai.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis with ascites.

Mourinate *Charoon Bhesaj, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hepatic cirrhosis with ascites; hypertension.

Mouskito *Qualiphar, Belg.*
Ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Mouskito Sun *Qualiphar, Belg.†*
Cream SPF 15: Ethyl butylacetylaminopropionate (p. 2154·3); avobenzone (p. 1695·1); octocrilene (p. 1715·2); octinoxate (p. 1715·1).
Insect repellent; sunscreen.
Qualiphar, Belg.†
Topical spray SPF 20: Diethyltoluamide (p. 2153·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); octinoxate (p. 1715·1).
Insect repellent; sunscreen.

Mouskito Textile *Qualiphar, Belg.†*
Permethrin (p. 2159·3).
Insect repellent for textiles.

Mouskito Travel Milk *Qualiphar, Belg.†*
Diethyltoluamide (p. 2153·1); lavender oil (p. 2541·1).
Insect repellent.

Mouskito Travel Stick *Qualiphar, Belg.*
Diethyltoluamide (p. 2153·1); citronella oil (p. 2481·1).
Insect repellent.

Mouskito Tropical *Qualiphar, Belg.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Mousse Exquise Auto-Bronzante *Clarins, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Mousticologne *Omega, Fr.†*
Cream sensitive skin; lotion sensitive skin: Ethyl butylacetylaminopropionate (p. 2154·3); enoxolone (p. 54·2).
Insect repellent.
Omega, Fr.†
Diffuser: Esbiothine (p. 2149·2).
Insect repellent.
Omega, Fr.†
Lotion: Icaridin (p. 2156·3).
Insect repellent.
Omega, Fr.†
Mosquito net: Permethrin (p. 2159·3).
Insect repellent.

Mouth Kote *Parnell, Canad.*
Eriodictyon (p. 1665·2).
Dry mouth.

MouthKote *Parnell, Irl.†; Parnell, USA.*
Artificial saliva.
Dry mouth.

MouthKote F/R *Parnell, USA.*
Sodium fluoride (p. 2089·2).

MouthKote O/R *Unimed, USA.*
Topical solution: Cetylpyridinium chloride (p. 1743·1); diphenhydramine (p. 626·1).
Sore throat.
Unimed, USA.
Oral rinse: Benzyl alcohol (p. 1739·3); menthol (p. 2553·2).
Minor mouth or throat irritation.

Mouzex *Little Greave, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Mouzex-MF *Little Greave, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Mova Nitrat *Teva, Pol.*
Silver nitrate (p. 2615·3).
Bacterial eye infections in neonates.

Movac *Alkem, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Movace *Alkem, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Movace Plus *Alkem, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Movacox *Hexal, Braz.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Movalis *Aspen, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Neth.†; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Ukr.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Movasin *Sintez, Rus.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Movatec *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Gr.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Movaxin *Genepharm, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Movectro *Merck Serono, Rus.*
Cladribine (p. 769·1).
Multiple sclerosis.

Movefast *Haledew, India.*
Eucalyptus (p. 2501·1); sweet birch oil (p. 92·1).

Movelat
Note: this name may be used for preparations of different composition.
Genus, UK.
A heparinoid (p. 1401·1); salicylic acid (p. 1719·1).
Musculoskeletal and joint pain; sprains; strains.

Movelisin *Cosme, India.*
Flufenamic acid (p. 65·1); a heparinoid (p. 1401·1); glycol salicylate (p. 66·2).

Movelite Plus *Avalanche, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Movelium *Medicine Products, Thai.*
Domperidone (p. 1838·1) or domperidone maleate (p. 1838·1).
Nausea and vomiting; delayed gastric emptying.

Movens *Pharmafar, Ital.*
Meclofenamate sodium (p. 85·2).
Musculoskeletal and joint disorders; pain.

Movent *Community Pharmacy, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mover
Note: this name may be used for preparations of different composition.
Mitsubishi Tanabe, Jpn.
Actarit (p. 17·1).
Rheumatoid arthritis.

Siomond, India.
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Moverdin *Kocak, Turk.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Movere *Antula, Norw.†*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Movergan *Orion, Ger.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Movesan *Iasis, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Movespasm *Movi Health, Ukr.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Gastrointestinal spasm.

Movex
Note: this name may be used for preparations of different composition.
Rayere, Mex.
Naproxen (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Vitamed, Israel.
Bromhexine hydrochloride (p. 1656·3).
Bronchitis.

Movex Active *Movi Health, Ukr.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); diclofenac potassium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Movex Comfort *Movi Health, Ukr.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).
Musculoskeletal, joint, and peri-articular disorders.

Movex-SP *Haledew, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Movexx *Cipla, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Movexx Plus *Cipla, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Moveze *Thompson & Capper, UK.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

Movibon *Micro, India.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; dysmenorrhoea; gout; migraine.

Movicol *Norgine, Austral.; Norgine, Austria; Norgine, Belg.; Norgine, China; Norgine, Cz.†; Norgine, Denm.; Norgine, Fin.; Norgine, Fr.; Norgine, Ger.; Norgine, Gr.; Norgine, Hong Kong†; Norgine, Irl.; Norgine, Ital.; Norgine, Norw.; Norgine, NZ; Norgine, Port.; Norgine, S. Afr.; Norgine, Singapore; Norgine, Spain; Norgine, Swed.; Norgine, Switz.; PMP, Turk.; Norgine, UK.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; faecal impaction; bowel evacuation.

Movicolon *Norgine, Neth.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; faecal impaction.

Movi-Cox *Boehringer Ingelheim, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Movicox *Boehringer Ingelheim, Neth.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Movidone *Milano, Thai.†*
Povidone-iodine (p. 1767·1).
Disinfection of skin, wounds, burns, and umbilicus.

Moviflex
Note: this name may be used for preparations of different composition.
Stada, Austria.
Phenylephrine hydrochloride (p. 1672·3); a heparinoid (p. 1401·1); glycol salicylate (p. 66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Silesia, Chile.†
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Movigil *Bago, Chile.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Movigip *Youcare, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Movilat *Stada, Spain.*
A heparinoid (p. 1401·1); salicylic acid (p. 1719·1).
Rheumatic and muscular pain.

Movileps *Dexa, Indon.*
Phenytoin (p. 538·2).
Epilepsy.

Movilief *Clonmel, Irl.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Movilisin *Pharmalex (Φαρμαλεξ), Gr.; Stada, Spain.†*
Flufenamic acid (p. 65·1); a heparinoid (p. 1401·1); glycol salicylate (p. 66·2).
Myalgia; peri-articular disorders; soft-tissue disorders.

Movilor *Invision, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Movilor-P *Invision, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Movin *Neo-Farmaceutica, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Movinaza *Movi Health, Ukr.*
⊗Serrapeptase (p. 2613·3).
Soft-tissue inflammation; respiratory-tract congestion; inflammatory skin disorders; breast engorgement.

Movinella *Orifarm, Denm.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Movinim-MD *Invision, India.*
Nimesulide betadex (p. 101·3).
Pain.

Movinim-P *Invision, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Movinim-S *Invision, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

MoviPrep *Salix, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Moviprep *Norgine, Austria; Norgine, Belg.; Medical Futures, Canad.; Norgine, Denm.; Norgine, Fin.; Norgine, Fr.; Norgine, Irl.; Mediline, Israel; Norgine, Ital.; Norgine, Neth.; Norgine, Norw.; Healthcare Logistics, NZ; Norgine, Spain; Norgine, Switz.; Norgine, UK.*
Sachet A, macrogol 3350 (p. 2547·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium sulfate (p. 1888·1); sachet B, ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Bowel evacuation.

Norgine, Cz.; Norgine, Ger.
Sachet A, macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1); sachet B, ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Bowel evacuation.

Movitev *Teva, Irl.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Movithiol *Iasis, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Movivac *Sevapharma, Cz.†*
An attenuated measles vaccine (Schwarz strain) (p. 2398·3).
Active immunisation.

Movix *Lapi, Indon.; Unipharm, Rus.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Moviz *JB Chemicals, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Moviz XP *JB Chemicals, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Movizar *Youcare, Rus.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Moviz-3D *JB Chemicals, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Movmaks *Tabuk, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Movmax *Tabuk, Pol.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Movon *Ipca, India.*
Controlled-release capsules; tablets: Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders.

Ipca, India.
Capsules; dispersible tablets; topical gel: Piroxicam (p. 125·3).
Gout; dysmenorrhoea; musculoskeletal, joint, and soft-tissue disorders.

Movon-MR *Ipca, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine hydrochloride (p. 2026·2).
Muscle pain and spasm.

Movon-P *Ipca, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Movon-PT *Ipca, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).

Movoperiz *Youcare, Rus.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Movox
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Norton Waterford, Irl.
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Movoxicam *Bunker, Braz.*
Meloxicam (p. 86·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Movprep *Norgine, Swed.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Mowivit *Rodisma, Ger.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Mox
Note: this name may be used for preparations of different composition.
Elea, Arg.
Naproxen sodium (p. 98·2).
Fever; pain.

Ranbaxy, India; GPO, Thai.
Amoxicillin (p. 216·2).
Bacterial infections.

Mox P *Ranbaxy, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxacef
Note: this name may be used for preparations of different composition.
BMS, Gr.
Cefadroxil (p. 233·2).
Bacterial infections.

Moxacin
Note: this name may be used for preparations of different composition.
Aspen, Austral.†
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxadden *Roddensers, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Moxadent *Vitoria, Port.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxafav *Alna, India.*
Alfacalcidol (p. 2112·3); calcium citrate (p. 1783·2); copper sulfate (p. 2057·2); magnesium oxide (p. 1857·3); soya isoflavones (p. 2620·3); zinc oxide (p. 1729·1).

Moxafen *Taejoon, Thai.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility.

Moxai *Abdi, Turk.*
Moxifloxacin (p. 326·3).

Moxal *Julphar, UAE.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Heartburn; gastric hyperacidity.

Moxal II *Julphar, UAE.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Heartburn; gastric hyperacidity.

Moxal Plus *Julphar, UAE.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence; gastro-oesophageal reflux.

Moxalas *Solas, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Moxalid *Iasis, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Moxalole *Meda, Denm.; Meda, Fin.; Meda, Fr.; Meda, Norw.; Meda, Swed.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; faecal impaction.

Moxam *Pharos, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Moxamar *CT, Neth.*
Moxonidine (p. 1442·1).
Hypertension.

Moxan *Aspen, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxapen *Olan-Kemed, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxatag *Shionogi, USA.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxaval *Saval, Chile.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxaviv *Sandoz, Neth.†*
Moxonidine (p. 1442·1).
Hypertension.

Moxbro *DWD, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Moxcil *TP, Thai.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Gram-positive bacterial infections.

Moxcillin *Charoen, Thai.; Medicpharma, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Deltapharm, Hong Kong.†
Amoxicillin (p. 216·2).

Moxcin *T-Boma, Hong Kong†; General Drugs, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxclav *Ranbaxy, India.*
Amoxicillin (p. 216·2), amoxicillin sodium (p. 216·2), or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Moxelle *Relonchem, Irl.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Moxen
Note: this name may be used for preparations of different composition.
Xeno, Philipp.
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Universal, Hong Kong.†
Amoxicillin (p. 216·2).

Moxer *Maneesh, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxeza *Alcon, USA.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Moxflora *KanTest, India.*
Amoxicillin (p. 216·2); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Moxi *Medico, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxibact *Sun, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxibay *Bayer Schering, S.Afr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxiblu *Lupin, India.*
Moxifloxacin (p. 326·3).
Bacterial eye infections.

Moxiblu-D *Lupin, India.*
⊗Dexamethasone (p. 1630·3); moxifloxacin (p. 326·3).

Moxic *Otto, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Moxicam
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Medico Uno, Hung.
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Milano, Thai.†
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Moxicino *Andromaco, Chile.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxicip *Cipla, India.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxiclav *Southern Cross, Austral.; Medochemie, Gr.; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moxicle *Daewoong, Thai.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moxiclina *Vitae, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxiclox *Prem, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Moxidat Kid *Datla, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxiday *Chemo-Drugs, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxif *Torrent, India.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxifact *Medico, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Moxifast-CV *Hauz, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Moxifen *VHB, India.*
⊗Tamoxifen (p. 860·2).
Breast cancer; anovulatory infertility.

Moxiflox *InnoGen, Philipp.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxifor *Biofarma, Turk.*
Moxifloxacin (p. 326·3).

Moxigem *Overseas, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxigram *Micro, India.*
Moxifloxacin (p. 326·3).
Bacterial eye infections.

Moxigram-DX *Micro, India.*
⊗Dexamethasone (p. 1630·3); moxifloxacin (p. 326·3).

Moxikare *Anglo-French Drugs, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxikind *Mankind, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxikind Plus *Mankind, India.*
Amoxicillin (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Moxikind-CV *Mankind, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moxilanic *Lafi, Chile.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxilcap *Masa, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxileb *Leben, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxilen *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxilin *The Forty-Two, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxillin *United American, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxilup *Lupin, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moximac *Macleods, Rus.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moximed *Unison, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxi-Mep-D *Alna, India.*
⊗Dexamethasone (p. 1630·3); moxifloxacin (p. 326·3).

Moximet *Mount Mettur, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moximon *Cachet, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moximycin *Venus, India.*
Moxifloxacin (p. 326·3).
Bacterial infections.

Moxina *Richmond, Arg.†*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis.

Moxinax *Modern Manu, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Moxind *Indu, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxind BR *Indu, India.*
Amoxicillin (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Bacterial infections.

Moxinova *Novagen, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxinova CV *Novagen, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxinova-DT *Novagen, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxinta *Intas, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxinta-LB *Intas, India.*
Amoxicillin (p. 216·2); lactobacillus (p. 2596·3).
Bacterial infections.

Moxipal *Jagsonpal, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxiped *Wescrib, Philipp.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxipen *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Singapore.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxiphar-CV *Biophar, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxipi *Psychotropics, India.*
Amoxicillin trihydrate (p. 216·2); lactobacillus (p. 2596·3).
Bacterial infections.

Moxipil *Psychotropics, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxipil-CL *Psychotropics, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxipil-CV *Psychotropics, India.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Moxipil-L *Psychotropics, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxipil-LB *Psychotropics, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin sodium (p. 286·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxiplus *Medley, Braz.; Medico, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxiplus-CV *Medico, India.*
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxiren *Ist. Chim. Inter., Ital.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxitab *Unison, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxitec *Basel, Turk.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Moxitop *Tapgen, Belg.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxitrac *Invision, India.*
Amoxicillin (p. 216·2); or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxitrac-CV *Invision, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxitrac-DX *Invision, India.*
Amoxicillin trihydrate (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Moxitral *Austral, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxivig *Alcon, Irl.; Alcon, UK.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Moxivul *Marvecs, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moxiz CV *Ritz, India.*
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Moxklok *Laksun, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Moxl *Dewcare, India.*
Moxifloxacin (p. 326·3).
Bacterial eye infections.

Moxlin *Pacific, Hong Kong; Merck, Indon.†; Merck, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxlin CLV *Merck, Mex.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxlox *East West, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Moxlox-L *East West, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Moxnic *Medihealth, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxno *Pharmahof, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxobeta *Betapharm, Ger.*
Moxonidine (p. 1442·1).
Hypertension.

Moxocard *AWD, Ger.†*
Moxonidine (p. 1442·1).
Hypertension.

Moxodyl *PP Lab, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxof *Saval, Chile.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Moxogamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.†; Worwag, Ukr.*
Moxonidine (p. 1442·1).
Hypertension.

Moxoham *Alpharma, Neth.†*
Moxonidine (p. 1442·1).
Hypertension.

Moxon *Solvay, Belg.; Abbott, Port.; Abbott, Spain.*
Moxonidine (p. 1442·1).
Hypertension.

Moxonat *Pharmacodane, Denm.*
Moxonidine (p. 1442·1).
Hypertension.

Moxonibene *Ratiopharm, Austria.*
Moxonidine (p. 1442·1).
Hypertension.

Moxonid *Ranbaxy, Ukr.†*
Moxonidine (p. 1442·1).
Hypertension.

Moxonitex *Lek, Rus.*
Moxonidine (p. 1442·1).
Hypertension.

Moxonur *Ratiopharm, Neth.*
Moxonidine (p. 1442·1).
Hypertension.

Moxostad *Stada, Cz.; Stada, Hung.*
Moxonidine (p. 1442·1).
Hypertension.

Moxotens *Sandoz, S.Afr.*
Moxonidine (p. 1442·1).
Hypertension.

Moxovasc *AWD, Neth.†*
Moxonidine (p. 1442·1).
Hypertension.

Moxsav *Saviour, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxspen *Madhav, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxspen-CL *Madhav, India.*
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Moxtid *Allenge, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Sunthi Sepuri, Indon.†
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxtid-CS *Allenge, India.*
⊗Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3); serrapeptase (p. 2613·3).

Moxtid-D *Allenge, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).

Moxtive-Clav *Sanify, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Moxxil-Duo *Gujarat Terce, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxxo *Pharmahof, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxy Plus-CV *Yacca, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxybiotic *Karnataka, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxycarb
Note: this name may be used for preparations of different composition.
Piramal, India.
Capsules; dispersible tablets: Amoxicillin (p. 216·2); carbocisteine (p. 1658·1).
Respiratory-tract infections associated with excessive or viscous mucus.

Piramal, India.
Capsules: Amoxicillin (p. 216·2).
Bacterial infections.

Moxycare *Intag, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moxycillin *Medicpharma, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxyclav *BL, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Moxydar *Grimberg, Fr.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); aluminium phosphate (p. 1818·3); guar gum (p. 475·1).
Gastrointestinal disorders.

Moxydil *Solvay, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxylong *American Remedies, India.*
Amoxicillin (p. 216·2).
Probenecid (p. 607·3) is included in this preparation to reduce renal tubular excretion of amoxicillin.
Bacterial infections.

Moxymax *Simayla, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxynic *Abbott, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxyno *Pharmahof, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxypac *Inpac, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxypen *Teva, Israel; Aspen, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxyplus-DC *Yacca, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

Moxyplus-SL *McNeil & Argus, India.*
⊗Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); lactobacillus (p. 2596·3); serrapeptase (p. 2613·3).

Moxystat *Uniroyal, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Moxyvent *Oxytech, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Moxyvit *Vitamed, Israel.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Moxzole *Medic+Aid, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Moyzen *ICPA, India.*
Cream: Light liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Emollient.

ICPA, India.
Topical liquid: Light liquid paraffin (p. 2191·2).
Dry skin conditions.

Moz Away *Hoe, Singapore.*
Icaridin (p. 2156·3).
Insect repellent.

Moz Away Junior *Hoe, Malaysia.*
Icaridin (p. 2156·3).
Insect repellent.

Moz Away Long Hour Protection *Hoe, Malaysia.*
Icaridin (p. 2156·3).
Insect repellent.

Moza *Intas, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Moza MPS *Intas, India.*
Simeticone (p. 1886·2); mosapride citrate (p. 1865·2).

Moza Plus *Intas, India.*
Mosapride (p. 1865·2); pantoprazole (p. 1875·3).

Mozarin *Adamed, Pol.*
Escitalopram (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Mozartan *Vocate, Gr.*
Losartan potassium (p. 1422·2).
Hypertension.

Mozasef *Sun, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Mozatone *Indoco, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Moz-Away *Hoe, Malaysia.*
Citronella oil (p. 2481·1); azadirachta oil (p. 2451·2).
Insect repellent.

Mozax *Sun, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Mozax-MPS *Sun, India.*
Simeticone (p. 1886·2); mosapride (p. 1865·2).

Moz-Bite *Hoe, Malaysia; Hoe, Singapore.*
Crotamiton (p. 1699·2).
Insect bites; stings.

Mozepam
Note: this name may be used for preparations of different composition.
Elvipe, Gr.
Diazepam (p. 1063·2).

Shine, Philipp.
Nitrazepam (p. 1089·1).
Insomnia.

Mozeton *Biomedica, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Mozifen-EF *TO-Chemicals, Thai.*
Pizotifen (p. 678·2).
Migraine; cluster headache.

Mozobil *Genzyme, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Irl.; Genzyme, Israel; Sanofi-Aventis, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Sanofi-Aventis, Singapore; Genzyme, Spain; Genzyme, Swed.; Genzyme, UK; Genzyme, USA.*
Plerixafor (p. 1160·1).
Mobilisation of haematopoietic stem cells.

Mozuku *Tropica Mas, Indon.*
Fucoidan (p. 2508·1).
Peptic ulcer.

Mozzie Patch *Bioconcepts, UK.*
Citronella oil (p. 2481·1).
Insect repellent.

MozzyOff Cocktail *Sommerville, UK.*
Bog myrtle oil (p. 2458·3); azadirachta oil (p. 2451·2); eucalyptus oil (p. 2501·2).
Insect repellent.

MP Fon *Medicpharma, Thai.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

MP Next *Mediez, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

MPA
Note: this name may be used for preparations of different composition.
Chandra Bhagat, India.
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Hexal, Ger.†
Medroxyprogesterone acetate (p. 2288·1).
Breast cancer; endometrial cancer.

MPA Gyn *Hexal, Ger.†*
Medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; menstrual disorders.

MPA-beta *Betapharm, Ger.*
Medroxyprogesterone acetate (p. 2288·1).
Breast cancer; endometrial cancer.

M-P-Cil *Innovata, S.Afr.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

MPenem *United Biotech, India.*
Meropenem (p. 321·3).
Bacterial infections.

MPill *Medico, India.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

MPower *Zydus, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

M-PredniHexal *Hexal, Ger.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

M-Pride *Centaur, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

M-Pride-MPS *Centaur, India.*
Mosapride citrate (p. 1865·2); simeticone (p. 1886·2).

MPSS *Chandra Bhagat, India.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Mpx-CV *Hetero, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

MQF *Sun, India.*
Mefloquine (p. 657·1).
Malaria.

M-Quit *Elfin, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Mr. Multy *Ideal Health, UK.*
Vitamins; minerals.

Mr Nits *Botanica, NZ.*
Avocado (p. 2451·2); azadirachta (p. 2451·2); borage (p. 2459·1); canola oil (p. 2469·2); coconut oil (p. 2179·3); evening primrose oil (p. 2502·2); geranium oil (p. 2512·2); hemp; jojoba oil; melissa (p. 2552·3).
Pediculosis.

M-retard *Helvepharm, Switz.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

M-Rinse *Daffohils, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

MR-Lux *Sanochemia, Ger.; Sanochemia, Switz.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

MR-Met *Akesiss, India.*
Metformin (p. 489·1).
Diabetes mellitus.

M-Ron B *Virgo, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; vitamin B supplement.

Mrs Cullen's Powders *Cullen & Davison, UK.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Mrs Johnsons American Soothing Syrup *Adco, S.Afr.†*
Sodium chloride (p. 1795·1); chloroform (p. 1898·1).
Teething pain.

MS Contin *Mundipharma, Austral.; Mundipharma, Belg.; Purdue, Canad.; Mundipharma, China; Mundipharma, Ital.; Shionogi, Jpn; Mundipharma, Neth.; Purdue Frederick, USA; Nolver, Venez.*
⊗Morphine sulfate (p. 92·3).
Pain.

MS Direct *Mundipharma, Belg.*
⊗Morphine sulfate (p. 92·3).
Pain.

MS Mono *Mundipharma, Austral.*
⊗Morphine sulfate (p. 92·3).
Pain.

MSA *Khandelwal, India.*
Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); spirulina (p. 2622·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

MSI *Mundipharma, Cz.; Mundipharma, Ger.*
⊗Morphine sulfate (p. 92·3).
Pain.

MSIR *Purdue, Canad.; Purdue Frederick, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

MS-Kare *DKT, India.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

MSLone *Elfin, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

MSP *Rafa, Israel.†*
⊗Morphine sulfate (p. 92·3).
Pain.

MSP-Blu *Cypress, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract disorders.

MSR *Mundipharma, Ger.*
⊗Morphine sulfate (p. 92·3).
Pain.

MST
Note: this name may be used for preparations of different composition.
Cypress, USA.
Magnesium salicylate (p. 85·2).
Osteoarthritis; rheumatoid arthritis.

Mundipharma, Ger.; Mundipharma, Port.
⊗Morphine sulfate (p. 92·3) or morphine polistirex.
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

MST Continus *Raffo, Arg.; Mundipharma, Cz.†; Napp, Hong Kong; Extractum, Hung.; Mundipharma, Hung.; Mahakam Beta, Indon.; Mundipharma, Irl.; Mundipharma, Malaysia; Mundipharma, Philipp.; Norpharma, Pol.; Adcock Ingram, S.Afr.; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Switz.; Bard, Thai.; Napp, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

M-Stada *Stada, Ger.*
⊗Morphine hydrochloride (p. 92·3) or morphine sulfate (p. 92·3).
Pain.

MSUD *Nutricia-Bago, Arg.; Milupa, Ital.; Vitaflo, UK.*
Food for special diets.
Maple syrup urine disease; metabolic disorders.

MSUD 1 *Support, Braz.*
Food for special diets.

MSUD 2 *Support, Braz.*
Food for special diets.

MSUD III *SHS, Irl.*
Food for special diets.
Maple syrup urine disease.

MSUD Aid *Nutricia, Austral.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Maple syrup urine disease.

MSUD Analog *Nutricia, Fr.; SHS, UK.*
Food for special diets.
Leucinosis; maple syrup urine disease.

SHS, Israel.
Infant feed for special diets.
Maple syrup urine disease.

MSUD Anamix *Nutricia, Austral.; Nutricia, Fr.*
Food for special diets.
Formerly supplied as MSUD Analog.
Maple syrup urine disease.

MSUD Express *Vitaflo, Irl.†*
Food for special diets.
Maple syrup urine disease.

MSUD Maxamaid *Nutricia, Austral.; SHS, Irl.; Nutricia, Ital.; Nutricia, NZ.*
Food for special diets.
Maple syrup urine disease.

SHS, UK.
Leucine-, isoleucine-, and valine-free food.
Maple syrup urine disease.

MSUD Maxamum *Nutricia, Austral.; SHS, Irl.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Maple syrup urine disease.

MT Pill *Cipla, India.*
Mifepristone (p. 2138·1).
Termination of pregnancy.

MTE *APP, Hong Kong.*
Trace elements.
Additive for total parenteral nutrition solutions.

MTF *Biotenk, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

MTLac *Cosme, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

MT-Loc *Psychotropics, India.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; migraine; heart failure; myocardial infarction.

M-Toin *Medopharm, India.*
Phenytoin sodium (p. 538·2).
Epilepsy.

M2-Tone *Charak, India.*
Cyperus rotundus; withania somnifera (p. 2450·2).
Dysfunctional uterine bleeding. menstrual disorders; female infertility.

M-Trim *Milano, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

MTX *Choongwae, Singapore; Sandoz, Turk.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Ratiopharm, Ger.
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; arthritis.

MTX-2 Alf *Investigaciones Filosoficas y Cientificas, Mex.*
Thiamine nitrate (p. 2103·2).
Gastrointestinal disorders.

MTX Support *Theralogix, USA.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).

Mu Fu Xin *Yao Wang, China.*
Matrine.

Mu Xin *En Ze Jia Shi, China.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Mu Yuan *Qi Du, China.*
Matrine.

Mubonet *Best, Mex.*
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency.

Mubroxol *Chinta, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucabrox *Streuli, Switz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucaderma S *Merz, Ger.*
Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Wounds.

Mucaine *Wyeth Consumer, Austral.†; Aurium, Canad.; Wyeth, India; Aspen Consumer, S.Afr.; Wyeth, Turk.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).
Gastro-oesophageal reflux; gastritis; peptic ulcer; heartburn; dyspepsia; oesophagitis; hiatus hernia.

Lafedar, Arg.; Wyeth, Hong Kong†; Wyeth Consumer, Thai.†
Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2) or magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; hiatus hernia; heartburn; oesophagitis.

Mucalan *Bernabo, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Mucaltin Forte *Arterium, Ukr.*
Althaea (p. 2438·3).
Respiratory-tract disorders.

Mucaltin Forte c Vitamini C *Arterium, Ukr.*
Althaea (p. 2438·3); ascorbic acid (p. 2110·3).
Cough.

Mucan *Pekana, Canad.*
Agaricus muscarius; asclepias vincetoxicum; aristolochia clematis; cedron; allium sativum (p. 2510·3); hydrastis canadensis (p. 2528·1); okoubaka aubrevillei.
Homoeopathic preparation.

MucaphEd *Edwards, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).

Mucare *VHB, India.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Mucaryl-AX *Glenmark, India.*
⊗Ambroxol (p. 1654·3); terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Mucasept-A *Merz Consumer, Ger.*
⊗Isopropyl alcohol (p. 1758·3); alcohol (p. 1733·1).
Hand disinfection.

Mucedokehl *Sanum-Kehlbeck, Ger.; Ebi, Switz.*
Mucor mucedo.
Homoeopathic preparation.

Mucera *Otto, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muchan *Fada, Arg.*
⊗Ephedrine (p. 1663·1).

Mucibron *Medley, Braz.; Normon, Spain.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Novag, Mex.
Ambroxol (p. 1654·3).
Cough.

Muciclar
Note: this name may be used for preparations of different composition.
Piam, Ital.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

McNeil, Fr.†
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucil *TO-Chemicals, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucilag *Quimica y Farmacia, Mex.†*
Ispaghula (p. 1849·1).
Constipation.

Mucilar *Spirig, Switz.*
Ispaghula (p. 1849·1).
Constipation; obesity.

Mucilar Avena *Spirig, Switz.*
Ispaghula (p. 1849·1); avena (p. 2451·1).
Constipation; obesity.

Mucilax *Douglas, NZ.*
Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation.

Mucilin *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Ispaghula (p. 1849·1).
Constipation; dietary fibre supplement; stool softener.

Mucillium *Pharmascience, Canad.*
Ispaghula (p. 1849·1).
Constipation.

Mucinac *Cipla, India.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Mucine *Silom, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucinex *Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, USA.*
Guaifenesin (p. 1666·2).
Cough.

Mucinex Childrens Cold, Cough & Sore Throat *Reckitt Benckiser, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Mucinex Cold *Reckitt Benckiser, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Mucinex Cough *Reckitt Benckiser, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Mucinex DM *Reckitt Benckiser, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Mucinex Fast-Max Cold, Flu & Sore Throat *Reckitt Benckiser, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Mucinex Fast-Max Cold & Sinus *Reckitt Benckiser, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1).

Mucinex Fast-Max Severe Congestion & Cold *Reckitt Benckiser, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Mucinum
Note: this name may be used for preparations of different composition.
Confar, Port.
Cascara (p. 1826·1); senna (p. 1885·1); aniseed (p. 2444·2); boldo (p. 2458·3).
Constipation.

Pharmethic, Belg.
Bisacodyl (p. 1821·1).
Constipation.

Wing Wai, Hong Kong.†
Cascara (p. 1826·1); senna (p. 1885·1).
Constipation.

Mucinum à l'Extrait de Cascara *Innotech, Fr.*
Cascara (p. 1826·1); senna leaf (p. 1885·1); boldo (p. 2458·3); aniseed (p. 2444·2).
Constipation.

Mucipep-C *Ximena Polanco, Chile.*
Opuntia ficus-indica.

Muciplazma *Serra Pamies, Spain.*
Methylcellulose (p. 2197·3).
Constipation.

Mucipulgite *Dexo, Fr.†; Interlabo, Switz.†*
Activated attapulgite (p. 1820·1); guar gum (p. 475·1).
Constipation; gastrointestinal disorders.

Mucisol *Deca, Ital.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders.

Mucitux *E Pharma, Fr.*
Eprazinone hydrochloride (p. 1664·3).
Respiratory-tract congestion.

Mucivil *Prater, Chile.*
Terbinafine (p. 593·3).
Fungal skin infections.

Mucivital *Arkopharma, Fr.*
Ispaghula (p. 1849·1).
Constipation.

Muclear *Mega Lifesciences, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucus; paracetamol poisoning.

Muco *Patar, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muco Asthalin *Cipla, India.*
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol sulfate (p. 1220·2).

Muco Dosodos *Beta, Arg.*
Ambroxol hydrochloride (p. 1654·3); butamirate citrate (p. 1657·3); chlorphenamine maleate (p. 620·3).
Cough.

Muco Dosodos Biotic *Beta, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Muco Rhinathiol *Sanofi-Aventis, Belg.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with abnormal mucus production; otitis; sinusitis.

Mucoaliv *Cinfa, Spain.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucoangin *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Sore throat.

Mucoaricodil *Menarini, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucobar *Symbiotic, India.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).

Mucobar-S *Symbiotic, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol (p. 1220·2).

Mucobase *Defuen, Arg.*
⊗Benzocaine (p. 1980·2); dexpanthenol (p. 2582·2); aloe vera (p. 1693·2); gelatin (p. 1154·1); pectin (p. 2200·3); carmellose sodium (p. 2175·2).
Aphthous ulcers.

Mucobene *Ratiopharm, Austria; Ratiopharm, Cz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus.

Mucobrol
Note: this name may be used for preparations of different composition.
Cofasa, Venez.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Recalcine, Chile.
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1); ammonium citrate (p. 2441·3).
Cough.

Mucobron
Note: this name may be used for preparations of different composition.
Corsa, Indon.
Bromhexine (p. 1656·3).
Cough.

Elder, India.
Amoxicillin trihydrate (p. 216·2); carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess or viscous mucus.

Koz, Turk.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Medi-Rx, Philipp.
Guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough.

OFF, Ital.†
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Mucobron D *Medi-Rx, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough.

Mucobron Forte *Medi-Rx, Philipp.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).
Allergic rhinitis; cold and influenza symptoms; cough; nasal congestion; sinusitis.

Mucobrox *T-Bama, Hong Kong†; Bangkok Lab & Cosmetic, Thai.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Mucocef *Lilly, Mex.*
Cefalexin (p. 234·1); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections with excessive mucus.

Mucocef-O *Ethix, India.*
Cefpodoxime.
Bacterial infections.

Mucocetil *UCI, Braz.*
Acetylcysteine (p. 1652·2).

Mucocil
Note: this name may be used for preparations of different composition.
Utopian, Thai.
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Prafa, Indon.†
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucocin *Medicpharma, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucocis *EMS, Braz.†; SoSe, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders; respiratory-tract congestion.

Mucocistein *Neo Quimica, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucoclav *Ordain, India.*
Ambroxol hydrochloride (p. 1654·3); amoxicillin (p. 216·2); clavulanic acid (p. 268·3).

Mucoclean *Royton, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

MucoClear *Pari, UK.*
Sodium chloride (p. 1795·1).
Lower respiratory-tract congestion.

Mucoclear *Sunward, Singapore.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muco-cyl L Ho-Len-Complex *Liebermann, Ger.*
Cepa (p. 2575·2); ammonium chlor. (p. 1656·1); kalium bichrom. (p. 2476·3); cinnabaris (p. 2555·3); natrium chlor. (p. 1795·1); thuja (p. 2629·3).
Homoeopathic preparation.

Mucodic *Medicine Products, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucodin *Zorka, Rus.; Sunward, Singapore.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucodox
Note: this name may be used for preparations of different composition.
Delta, Port.
Sobrerol (p. 1677·2).
Respiratory-tract congestion.

Madaus, Belg.
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Mucodrenol *Medinfar, Port.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muco-DX *Greater Pharma, Thai.†*
Dextromethorphan hydrobromide (p. 1660·1); terpin hydrate (p. 1678·2); chlorphenamine maleate (p. 620·3).
Cough.

Mucodyne *Intermed, India; Sanofi-Aventis, Irl.; Kyorin, Jpn; Novum, Neth.; Sanofi, UK.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion; otitis media.

Mucoease Plus *Pharmaniaga, Malaysia.*
Carbocisteine (p. 1658·1); promethazine hydrochloride (p. 638·2).
Cough.

Mucofalk *Cevallos, Arg.†; Falk, Ger.; Falk, Hong Kong; Medicons, Hung.; Darya-Varia, Indon.†; Falk, Indon.†; Falk, Malaysia†; Falk, Philipp.; Falk, Pol.; Falk, Port.; Falk, Rus.; Falk, Singapore.†*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; stool softener; disorders of cholesterol metabolism; irritable bowel syndrome; inflammatory bowel disease; diverticular disease; hypercholesterolaemia; dietary fibre supplement; Crohn's disease.

Mucofalk Orange *Falk, Ukr.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea.

Mucofan *Uniao Quimica, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucofar *Quim-Far, Venez.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Muco-Fen DM *Ivax, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Mucofial *Biohealth, Ital.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders; paracetamol poisoning; cyclophosphamide-induced uropathy.

Mucoflem *Xixia, S.Afr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased, viscous mucus.

Mucofluid
Note: this name may be used for preparations of different composition.
Sanofi Pasteur, Chile†; UCB, Fr.†; UCB, Gr.; UCB, Pol.; UCB, Spain.
Mesna (p. 1557·2).
Nasal congestion; respiratory-tract disorders; respiratory-tract congestion.

Spirig, Switz.
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucoflux
Note: this name may be used for preparations of different composition.
Liomont, Mex.
⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Merck, Braz.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Rottapharm, Hong Kong; Rotta, Malaysia; Rotta, Philipp.; Rottapharm, Singapore; Rottapharm, Thai.
Sobrerol (p. 1677·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucofor *Vifor, Switz.*
Erdosteine (p. 1665·1).
Respiratory-tract disorders associated with viscous mucus.

Mucofrin *Epifarma, Ital.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning; cyclophosphamide-induced uropathy.

Mucogel
Note: this name may be used for preparations of different composition.
Ebi, Switz.
Mucor racemosus.
Homoeopathic preparation.

Forest Laboratories, UK.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
These ingredients can be described by the British Approved Name Co-magaldrox.
Dyspepsia; gastro-oesophageal reflux; heartburn.

Mucogen *Antigen, Irl.†*
Carbocisteine (p. 1658·1).
Lower respiratory-tract disorders with excessive or viscous mucus.

Mucogeran *Grossmann, Switz.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucogyne *IPRAD, Fr.*
Mallow (p. 2549·2); chamomile (p. 2474·1); sodium hyaluronate (p. 2526·2).
Menopausal vaginal disorders.

Mucohelp *Neiss, India.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Mucohex *ProMed, Cz.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucohexin *Sanbe, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucokehl *Sanum-Kehlbeck, Ger.*
Mucor racemosus.
Homoeopathic preparation.

Mucola *Union Drug, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucolab *Multilab, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Mucolan *Milano, Thai.†*
Ambroxol hydrochloride (p. 1654·3).
Bronchitis; asthma.

Mucolase *Lampugnani, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Mucolate *Pharmasant, Thai.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough; nasal congestion.

Mucolator *Abbott, Fr.†; Abbott, Malaysia; Abbott, Port.†; Abbott, S.Afr.; Kocak, Turk.*
Acetylcysteine (p. 1652·2).
Paracetamol overdose; respiratory-tract congestion.

Mucolax *Burapha, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucoless
Note: this name may be used for preparations of different composition.
Pfizer, S.Afr.
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased, viscous mucus.

Rekah, Israel; Vitamed, Israel.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucolex
Note: this name may be used for preparations of different composition.
CCM, Malaysia.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Pfizer Consumer, Irl.†; Johnson & Johnson, Port.†; Pharmahof, Thai.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Marching, Hong Kong.†
Guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Mucolexin *United Lab, Malaysia; Pediatrica, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2).
Cough.

Mucolica *Ikapharmindo, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucolid
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with increased or viscous mucus.

Greater Pharma, Thai.
Ambroxol hydrochloride (p. 1654·3).
Bronchitis; asthma.

Mucolin
Note: this name may be used for preparations of different composition.
Abbott, Braz.; Cooper (Копер), Gr.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Sanofi-Aventis, Mex.
Ampicillin (p. 218·2); carbocisteine (p. 1658·1).
Respiratory-tract infections.

Zuoz, Venez.
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Mucolin Pediatrico *Sanofi-Aventis, Mex.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucolinc *Cipla, India.*
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Mucolinct *Adcock Ingram, S.Afr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excess mucus.

Mucolise *T Man, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Mucolisil *Sanofi-Aventis, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucolit *CTS, Israel.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with excessive or viscous mucus.

Mucolite *American Remedies, India; Reddy, India.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucolitic *Nova Argentia, Arg.; Nycomed, Braz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucolitic Antitusivo *Nova Argentia, Arg.*
Carbocisteine (p. 1658·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; respiratory-tract congestion.

Mucolitico *Sanitas, Chile.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucolix
Note: this name may be used for preparations of different composition.
Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion; cough.

Ciforma, Braz.†
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucolyptus *Medi-Rx, Philipp.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucolyse *Utopian, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucolysin
Note: this name may be used for preparations of different composition.
Sandoz, Denm.
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucolyte
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with viscous mucus.

Mucomed
Note: this name may be used for preparations of different composition.
Medifive, Thai.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mediline, Israel.
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with excessive or viscous mucus.

Spirig, Switz.
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mucomelt *Venus, India.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Mucomelt Forte *Venus, India.*
Acetylcysteine (p. 1652·2); cefixime (p. 240·3).

Mucomelt-A *Venus, India.*
Acetylcysteine (p. 1652·2); ambroxol (p. 1654·3).

Mucomelt-XP *Venus, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Muco-Mepha *Mepha, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucomex
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucomix *Samarth, India.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders; paracetamol poisoning.

Mucomox *Stedman, India.*
Ambroxol hydrochloride (p. 1654·3); amoxicillin trihydrate (p. 216·2).

Mucomyst *Wellspring, Canad.; Meda, Denm.; Meda, Fin.; BMS, Fr.; BMS, Gr.; Meda, Norw.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

BMS, Austral.†; Apothecon, USA.†
Acetylcysteine sodium (p. 1652·2).
Mucolytic in bronchopulmonary disorders; respiratory-tract disorders associated with viscous mucus.

Mucomystendo *BMS, Fr.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion in tracheotomised patients.

Mucon *ICM, Singapore.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Muconal *Osmed, India.*
Amoxicillin (p. 216·2); carbocisteine (p. 1658·1); *Lactobacillus sporogenes* (p. 2596·3).

Muconasal Plus *Boehringer Ingelheim, Cz.*
⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Muconase *Pharma Nutria, Philipp.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Muconex *Tripharma, Rus.; Abdi, Turk.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucus; paracetamol overdosage.

Muconix *Jumont, Philipp.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Mucopac *Inpac, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucopain *ICPA, India.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Mucopan *Adcock Ingram, S.Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Mucopec *Macrophar, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucopect *Boehringer Ingelheim, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucopen *Peerage, India.*
Syrup: ⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Peerage, India.
Tablets: Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Mucophylline *Medi-Rx, Philipp.*
Guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); theophylline (p. 1229·3).
Respiratory-tract disorders.

Mucoplant Eukalyptový *Naturwaren, Cz.*
Eucalyptus oil (p. 2501·2); Scots pine oil (p. 2591·2); camphor (p. 2466·2).
Respiratory-tract disorders.

Mucoplant Jitrocelový *Naturwaren, Cz.*
Plantaginis (p. 2604·2); peppermint oil (p. 1877·1).
Respiratory-tract disorders.

Mucoporetta *ACO Hud, Fin.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucoprednibron *Pfizer, Arg.*
Ambroxol hydrochloride (p. 1654·3); butetamate citrate (p. 1658·1).
Respiratory-tract disorders.

Mucoprom *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia.*
Carbocisteine (p. 1658·1); promethazine hydrochloride (p. 638·2).
Cough.

Mucopront *Olvos, Gr.; PharmaSwiss, Hung.*
Carbocisteine (p. 1658·1) or carbocisteine sodium (p. 1658·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Zuoz, Venez.
Carbocisteine sodium (p. 1658·2).
Respiratory-tract congestion.

Mucorama
Note: this name may be used for preparations of different composition.
Zuoz, Venez.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucoreg *Acekinetic, India.*
Ambroxol acefyllinate (p. 1201·2).

Mucorem *Remek, Gr.*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Mucoresp *Azine, India.*
Oral drops: Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Azine, India.
Tablets: ⊗Ambroxol (p. 1654·3) or ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2); theophylline (p. 1229·3).

Mucoresp Plus *Azine, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Mucoresp-CT *Azine, India.*
⊗Ambroxol hydrochloride (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Mucoresp-CZ *Azine, India.*
Ambroxol hydrochloride (p. 1654·3); cetirizine (p. 619·2).

Mucoresp-3D *Azine, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Mucorespiral *Sanofi-Aventis, Port.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucorhinathiol Infantil *Sanofi-Aventis, Port.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Mucorhinathiol Mucoral *Sanofi-Aventis, Port.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucorhinyl
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Neth.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Mucorid *Meridian, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Mucoris *FDC, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Mucos *Meprofarm, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucosa comp H *Heel, Neth.*
Anacardium orientale (p. 2471·3); hydrastis canadensis (p. 2528·1); ipecacuanha (p. 1667·2); kalium bichromicum (p. 2476·3); kreosotum (p. 1659·3); nux vomica (p. 2573·3); phosphorus (p. 2589·2); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Mucosa compositum *Heel, Ger.*
Mucosa naris suis; mucosa oris suis; mucosa pulmonis suis; mucosa oculi suis; mucosa vesicae felleae suis; mucosa vesicae urinariae suis; mucosa pylori suis; mucosa duodeni suis; mucosa oesophagi suis; mucosa jejuni suis; mucosa ilei suis; mucosa coli suis; mucosa recti suis; mucosa ductus choledochi suis; ventriculus suis; pankreas suis (p. 2444·1); argentum nitricum (p. 2615·3); belladonna (p. 2453·3); oxalis acetosella; anacardium (p. 2471·3); phosphorus (p. 2589·2); lachesis (p. 2538·3); ipecacuanha (p. 1667·2); nux vomica (p. 2573·3); veratrum; pulsatilla (p. 2600·2); kreosotum (p. 1659·3); sulfur (p. 1721·1); natrium oxalaceticum (p. 2578·3); colibacillinum; condurango (p. 2485·3); kalium bichromicum (p. 2476·3); hydrastis (p. 2528·1); mandragora; momordica balsamina; ceanothus.
Homoeopathic preparation.

Mucosal *Boehringer Ingelheim, Jpn; Suphong, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucosan
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Austria; Boehringer Ingelheim, Spain.
Ambroxol hydrochloride (p. 1654·3).
Neonatal respiratory distress syndrome; respiratory-tract disorders.

Resinag, Switz.†
Aluminium formate (p. 1817·1); aluminium hydroxide (p. 1817·2); cineole (p. 2479·1); chamomile (p. 2474·1); sage (p. 2608·3); arnica (p. 2447·2); tetracaine hydrochloride (p. 1996·3).
Mouth disorders.

Mucosat *SSRI, Rus.*
Chondroitin sulfate (p. 2476·1).
Osteoporosis; parodontopathy; fractures; degenerative joint and spinal disorders.

Mucosat Neo *Belmed, Ukr.*
Chondroitin sulfate (p. 2476·1).
Joint disorders.

Mucoseptal *Actipharm, Switz.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Mucosform *Lejal, Philipp.*
Elixir: Bromhexine hydrochloride (p. 1656·3).
Cough.

Lejal, Philipp.
Tablets: Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3).
Cough; hypersensitivity reactions.

Mucosin
Note: this name may be used for preparations of different composition.
Europharm, Hong Kong.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Zentiva, Cz.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucosis *Drogsan, Turk.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucosit *Herbapol Poznan, Pol.*
Allantoin (p. 1693·1); calendula (p. 2465·2); chamomile oil (p. 2474·1); chamomile (p. 2474·1); mint oil (p. 2560·1); oak bark (p. 2574·1); sage (p. 2608·3); thyme (p. 2630·2); coltsfoot (p. 1659·2).
Mouth disorders.

Mucosma *Azine, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Mucosma-T *Azine, India.*
⊗Doxofylline (p. 1208·1); terbutaline (p. 1228·1).

Mucosof *Atlantic, China.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucosol
Note: this name may be used for preparations of different composition.
CTS, Israel†; CTS, Rus.; Adcock Ingram, S.Afr.
Carbocisteine (p. 1658·1).
Aid in bronchial examination; respiratory-tract congestion.

AstraZeneca, India.
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3).
Cough associated with obstructive airways disease.

Malaysia Chemist, Singapore.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucosolin *Terramedic, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Mucosolvan *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Ital.; Teijin, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Neonatal respiratory distress syndrome; respiratory-tract congestion.

Hexpharm, Indon.
Bromhexine hydrochloride (p. 1656·3).
Cough.

Mucoso lvan Compositum *Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Mucosolvon *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Switz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucosolvon Compositum *Boehringer Ingelheim, Arg.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Mucospas *Boehringer Ingelheim, Austria; Unilfarma, Port.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Mucospect *Universal, Hong Kong; Aspen Consumer, S. Afr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucospire *Rosa-Phytopharma, Fr.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders.

Mucosta *Otsuka, China; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Malaysia; Otsuka, Philipp.; Otsuka, Thai.*
Rebamipide (p. 1884·1).
Gastritis; gastric ulcer; dry eyes.

Mucostar *Krugher, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucostein
Note: this name may be used for preparations of different composition.
Kleva, Gr.
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).

Mucostop *Mepha, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus.

Mucosys *United Biotech, India.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Mucotein *Combiphar, Indon.*
Erdosteine (p. 1665·1).
Respiratory-tract disorders.

Mucotherm *Lannacher, Austria.*
Ethyl nicotinate (p. 56·3).
Prostatitis; anorectal disorders.

Mucothiol *Jolly-Jatel, Fr.*
Methyl dacisteine (p. 1669·2).
Respiratory-tract congestion.

Sanofi-Aventis, Gr.
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Mucotic *Hua, Thai.*
Acetylcysteine (p. 1652·2).
Bronchitis associated with increased or viscous mucus.

Mucotoss
Note: this name may be used for preparations of different composition.
Sigma, Braz.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucotosse
Note: this name may be used for preparations of different composition.
Labialfarma, Port.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muco-Treat *Mediline, Israel.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mucotreis *Ecobi, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Mucotrol *Edwards, USA.*
Acesulfame potassium (p. 2166·2); aloe (p. 1693·2); angelica (p. 2443·3); camellia sinensis; centella (p. 1698·3); cyamopsis psoraloides; liquorice (p. 1853·2); fallopia japonica.

Mucotuss *Terramedic, Philipp.*
Capsules: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Terramedic, Philipp.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Mucotussan *Medikon, Indon.†*
Dextromethorphan (p. 1660·1); phenylpropanolamine (p. 1674·1); diphenhydramine (p. 626·1); bromhexine (p. 1656·3).
Cough.

Mucotyle *Shree Ganesh, India.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Mucovent
Note: this name may be used for preparations of different composition.
Daffohils, India.
Ambroxol (p. 1654·3); acetylcysteine (p. 1652·2).

Mucovibrol *Liomont, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucovibrol Amoxi *Liomont, Mex.*
Ambroxol hydrochloride (p. 1654·3); amoxicillin trihydrate (p. 216·2).
Respiratory-tract infections.

Mucovibrol C *Liomont, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract congestion.

Mucovin *Leiras, Fin.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mucovis *Pharma Nutria, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucovital *Rottapharm, Spain.*
Carbocisteine lysine (p. 1658·2).
Respiratory-tract congestion.

Mucovix *SM, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucovon *Heromycin, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muco-X *Axapharm, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucoxan *IBSA, Ital.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucoxin
Note: this name may be used for preparations of different composition.
CCM, Malaysia; Pharmasant, Thai.†
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion; respiratory-tract disorders associated with increased or viscous mucus.

Mucoxina *Bruluagsa, Mex.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Mucoxine *Pharmasant, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Mucoxol
Note: this name may be used for preparations of different composition.
Montpellier, Arg.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Serral, Mex.
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Tempo Scan Pacific, Indon.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucoxolan *Teuto, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucoza *Pond's, Thai.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucozan *Pond's, Thai.†*
Ambroxol hydrochloride (p. 1654·3).
Bronchitis; asthma.

Mucozym *Mucos, Ger.†*
⊗Bromelains (p. 2460·3).
Nasal inflammation.

Mucum *Julphar, UAE.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Mucus Relief DM *Major, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

MucusRelief *Major, USA.*
Guaifenesin (p. 1666·2).
Cough.

MucusRelief DM *Major, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Mucusurf *Healthprime, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mucylin *Yarindo, Indon.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Mucyst *Neon, India.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

Mud *Eurofarma, Braz.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); nystatin (p. 590·3).
Infected skin disorders.

Mudagrip *Lafedar, Arg.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Fever; pain.

Mudantil L *Geminis, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Mudot *Alna, India.*
Drotaverine (p. 2497·3).

Muelita *Cabuchi, Arg.*
Benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1); peppermint oil (p. 1877·1); methylthioninium chloride (p. 1559·1).

Mueller Gesic *Mueller, Canad.†*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).

Mufe *Aamorb, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Aamorb, India.
Oral suspension: Iron carbonyl (p. 2073·1); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Mufect *Sun, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Muflex *TO-Chemicals, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Muforan *Pfizer, Arg.*
Fotemustine (p. 799·3).
Cerebral cancer; malignant melanoma.

MuGard *Access, USA.*
⊗Benzyl alcohol (p. 1739·3); carbomer homopolymer A; glycerol (p. 2517·2).

Speciality European Pharma, Ger.
Carbomer 971P (p. 2173·3).
Oral mucositis.

Mugasin *Apotex, Mex.*
Ispaghula (p. 1849·1).
Constipation.

Mugisept *Mugi, Indon.*
Povidone-iodine (p. 1767·1).
Wounds.

Muistin *Verisfield, Gr.*
Risperidone (p. 1103·2).
Schizophrenia.

Mujonal *Hanmi, China.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Mukobron *Aflofarm, Pol.†*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Mukolatin *Atabay, Turk.*
Acetylcysteine (p. 1652·2).

Mukolina *Pliva Krakow, Pol.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Mukoliz *Terra, Turk.*
Carbocisteine (p. 1658·1).
Respiratory disorders with increased mucus.

Mukoral *Biofarma, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mukoseptonex *Teva, Cz.*
Carbaethopendecinium bromide (p. 1741·3).
Nose disorders.

Mukoseptonex E *Teva, Cz.*
⊗Carbaethopendecinium bromide (p. 1741·3); ephedrine hydrochloride (p. 1663·2).
Nose disorders.

Mukosetil *Sandoz, Turk.*
Acetylcysteine (p. 1652·2).

Mukotik *Kocak, Turk.*
Carbocisteine (p. 1658·1).
Respiratory disorders with increased mucus.

Mulade *Sriprasit, Thai.*
Guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mulax *Fahrenheit, Indon.*
Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation; irritable bowel syndrome.

Mulcatel *Maver, Chile.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Mulch *Pharmaffiliates, India.*
Preparation for enteral nutrition.

Muli *O2, China.*
Diclofenac (p. 48·3); gentamicin sulfate (p. 304·2).
Bacterial eye infection with inflammation.

Mulimen H *Heel, Neth.*
⊗Agnus castus (p. 2432·2); cimicifuga racemosa (p. 2478·1); gelsemium sempervirens (p. 2511·2); hypericum perforatum (p. 449·1); sepia officinalis (p. 2613·1).
Homoeopathic preparation.

Mulitmix
Note: this name may be used for preparations of different composition.
Indo French, India.
Tablets: ⊗Bromhexine (p. 1656·3); ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3).

Mulkine *Dexo, Fr.†*
Montmorillonite; guar gum (p. 475·1).
Constipation.

Müller'sche Tabletten *Muller Goppingen, Ger.*
Ammon. bromat. (p. 2461·1); belladonna (p. 2453·3); calc. jodat. (p. 1658·1); echinacea (p. 2498·1); mentholum (p. 2553·2); merc. cyanat (p. 2555·3).
Homoeopathic preparation.

Mulmicor *Scheffler, Ger.†*
Camphor (p. 2466·2).
Hypotension.

Mulmin *Juggat, India.*
Vitamins; ferrous gluconate (p. 2061·2); zinc sulfate (p. 2126·2).

Mulmin Plus *Juggat, India.*
Vitamins; ferrous gluconate (p. 2061·2); zinc sulfate (p. 2126·2) centella (p. 1698·3).

Mulmin Pro *Juggat, India.*
Preparation for enteral nutrition.

Mulmin-F *Juggat, India.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).

Mulsanol *Ifars, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3); arachidonic acid (p. 2446·1); fructo-oligosaccharides (p. 2508·1); docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Multanzim *Fako, Turk.†*
⊗Pancreatin (p. 2579·3); bile extract (p. 2457·2).

Multaq *Sanofi-Aventis, Austria; Sanofi-Aventis, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, USA.*
Dronedarone hydrochloride (p. 1369·3).
Atrial fibrillation; atrial flutter.

Multe-Pak *SoloPak, USA.†*
Trace elements.
Parenteral nutrition.

Multi *Lafarmen, Arg.*
Vitamins; minerals.
Dietary supplement; tonic.

Multi-11 *Sandoz, Canad.*
Vitamins.
Parenteral nutrition.

Multi-12 *Bayer, Canad.†; Baxter, Singapore.*
Vitamins.
Parenteral nutrition.

Multi 2 *Vitazan, Canad.†*
Vitamins; minerals.

Multi II *Solgar, UK.*
Amino acids; vitamins; minerals.

Multi 75 *Fibertone, USA.*
Vitamins; minerals.

Multi 1000 *Sandoz, Canad.*
Vitamins.
Parenteral nutrition.

Multi B *Seroyal, Canad.†; Thorne, Canad.†*
Vitamin B substances (p. 2102·3).

Multi B Complex *Quest, UK.*
Vitamin B (p. 2102·3); vitamin C (p. 2110·3).

Multi B+C *Elvipe, Gr.*
Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3).

Multi B-Plex *Future, Canad.*
Vitamin B substances (p. 2102·3).

Multi Cal-Mag *Seroyal, Canad.†*
Vitamins; minerals.

Multi Caps *Flora, Canad.*
Vitamins; minerals.

Multi Enzyme *Natural Factors, Canad.†*
⊗Enzymes from *Aspergillus niger*; *Aspergillus oryzae*; *Bacillus subtilis*; *Saccharomyces cerevisiae* (p. 2125·2); and *Trichoderma reesei*; bromelain (p. 2460·3); papain (p. 2582·3).
Digestive disorders.

Multi + Ginkgo for 55+ *Blackmores, Austral.†*
Vitamins; minerals; ginkgo biloba (p. 2512·3).

Multi Glyco *Seroyal, Canad.*
Vitamins; minerals.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Multi Min Chelate with Vitamin C *Metagenics, Canad.†*
Mineral; vitamin C (p. 2110·3).

Multi Mineral *Swiss Herbal, Canad.†*
Minerals.

Multi Minerals *Nutri-Cology, Canad.†*
Minerals.

Multi Recharge *Biotherm, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); ecamsule (p. 1702·1).
Sunscreen.

Multi Up *Fher, Ital.*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic.

Multi Vi Min *Sisu, Canad.*
Vitamins; minerals.

Multi Vit Drops with Iron *Barre-National, USA.*
Vitamins; iron (p. 2073·1).

Multi-Action Actifed *Pfizer Consumer, UK.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; rhinitis.

Multi-Action Actifed Chesty Coughs Expectorant
Note: this name may be used for preparations of different composition.
Pfizer Consumer, UK.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; upper respiratory-tract congestion.

Multi-Action Actifed Dry Coughs *Pfizer Consumer, UK.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs; upper respiratory-tract congestion.

Multi-Age Correction *Sanofi Consumer, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Multi-Aid *Bestochem, India.*
Vitamins; minerals; trace elements.

Multi-B Complex *Integrative, USA.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Multi-B Forte *Johnson & Johnson, Austral.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Multibay *Bayer, India.*
Vitamins.

Multiberry *Laborate, India.*
Vitamin B substances (p. 2102·3).

Multibic *Fresenius Medical, Ital.; Fresenius Kabi, Turk.*
A range of haemofiltration solutions (p. 1778·2).

Fresenius Medical, Cz.; Fresenius Medical, Neth.; Fresenius Medical, Switz.
Glucose monohydrate (p. 2069·1); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); with or without potassium chloride (p. 1793·2).
Haemofiltration.

Fresenius Medical, Denm.; Fresenius Medical, Fin.; Fresenius Medical, Fr.; Fresenius Medical, Hung.; Fresenius Medical, Israel; Fresenius Medical, Norw.; Fresenius Medical, Port.; Fresenius Medical, Spain; Fresenius Medical, Swed.
Glucose (p. 2068·3); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); with or without potassium chloride (p. 1793·2) (p. 1778·2).
Haemofiltration; haemodialysis.

Multibionta *Merck, Mex.*
Vitamins; minerals; probiotics (p. 2596·3).

Merck, Austria†; Merck, Ger.†; Seven Seas, UK.
Vitamins.
Parenteral nutrition.

Multibionta N *Merck, Cz.†*
Vitamins.
Parenteral nutrition.

Multibionta plus Mineralien und Spurenelemente *Merck, Austria.†*
Vitamins; minerals; trace elements.

Multibionta Probiotic *Seven Seas, Irl.†*
Vitamins; minerals; *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).

Multibiotic *Chema-Elektromet, Pol.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Multical *Symbiosis, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Multicap *Sriprasit, Thai.*
Vitamins; minerals.

Multicentrum *Wyeth Consumer, Ital.*
Vitamins; minerals; trace elements.
Nutritional supplement.

Multichew *Chew, Thai.*
Vitamins.

Multico *Sunward, Hong Kong.*
Vitamins.
Dietary supplement.

Multicomp *Naturland, Hung.*
Magnesium (p. 1786·3); iron (p. 2073·1); manganese (p. 2081·2); zinc (p. 2126·1); copper (p. 2057·1).

Multicor *Multilab, Braz.†*
Verapamil hydrochloride (p. 1522·1).
Hypertension.

Multicort *Chandra Bhagat, India.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Multicrom *Menarini, Fr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Multi-Day *Nature's Bounty, USA.*
Vitamins; with or without minerals.

Multiderm
Note: this name may be used for preparations of different composition.
Perrigo, Israel.
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Skin disorders.

Multiderme
Note: this name may be used for preparations of different composition.
Multilab, Braz.
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Skin disorders.

Multidex *Medifarm, Venez.*
Maltodextrin (p. 2080·3); ascorbic acid (p. 2110·3).
Wounds; burns; ulcers.

Multidyn *Nutri-Dyn, Canad.†*
Vitamins; minerals.

Multi-Encap *Thorne, Canad.†*
Vitamins; minerals.

Multiferon *Swedish Orphan, Cz.; Swedish Orphan, Denm.; Swedish Orphan, Fin.; Swedish Orphan, Norw.; Key Oncologics, S.Afr.†; Swedish Orphan, Swed.*
Interferon alfa (p. 989·2).
Viral infections; malignant neoplasms.

Multiferrum *Medicus, Gr.*
Iron dextran (p. 2075·3).

Multiflow *Natural Factors, Canad.†*
Vitamins; minerals.

Multifluorid *DMG, Ger.†*
Sodium fluoride (p. 2089·2); olaflur (p. 2085·1); dectaflur (p. 2059·1).
Dental caries prophylaxis; hypersensitive teeth.

Multifol *Breckenridge, USA.*
Ferrous fumarate (p. 2060·3); calcium carbonate (p. 1824·3) vitamins.

Multi-Force *Prairie Naturals, Canad.†*
Vitamins; minerals.

Multiformil *Farmedia, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Multifung *Rider, Chile.*
Bifonazole (p. 573·3).
Fungal and Gram-positive bacterial skin infections.

Multifungin H *Piramal, India.*
⊗Bamipine (p. 617·2); hydrocortisone acetate (p. 1640·1).
Inflamed fungal skin infections.

Multigain *Torrent, India.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Multigam *CAF-DCF, Belg.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia.

Multigat *Laborate, India.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Multigen
Note: this name may be used for preparations of different composition.
Breckenridge, USA.
Vitamin B_{12} (p. 2107·2); dessicated stomach (p. 2444·1); iron (p. 2073·1).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.

Medhaus, Philipp.
Vitamins; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Multigen Plus *Medhaus, Philipp.*
Vitamins; amino acids; chlorella (p. 2475·3).
Nutritional supplement.

Multigenics *Metagenics, Canad.*
Vitamins; minerals.

Multigesic
Note: this name may be used for preparations of different composition.
Piramal, India.
Diethylamine salicylate (p. 51·3).
Lumbago; sciatica; sprains; fibrositis.

Multiging *Hauz, India.*
Vitamins; minerals; trace elements; ginseng (p. 2513·3).

Multigotas *Gobbi, Arg.*
Vitamins.

Multigrip *Multilab, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Multigrow *Lloyd, Philipp.*
Vitamins; chlorella (p. 2475·3); taurine (p. 2626·2); with or without lysine (p. 2079·3).
Dietary supplement.

MultiHance *Bracco, Austral.; Bracco, Austria; Bracco, Belg.; Bracco, Canad.; Bracco, China; Bracco, Cz.; Bracco, Denm.; Bracco, Fin.; Bracco, Fr.; Bracco, Ger.; Bracco, Gr.; Bracco, Hung.; Bracco, Irl.; Bracco, Israel; Bracco, Ital.; Bracco, Neth.; Bracco, Norw.; Regional Health, NZ; Bracco, Port.; Bracco, Singapore; Bracco, Spain; Bracco, Swed.; Bracco, Switz.; Gurel, Turk.; Bracco, UK; Bracco, USA.*
Meglumine gadobenate (p. 1584·3).
Contrast medium for magnetic resonance imaging.

Multi-HTM *Laborate, India.*
⊗Hydroquinone (p. 1705·1); mometasone furoate (p. 1644·1); tretinoin (p. 1725·2).

Multi-12/K1 *Baxter, Chile; Sandoz, Israel.*
Vitamins.

Sandoz, Canad.
Vitamins for infusion.

Multi-Kid *Maccabi Care, Israel.*
Vitamins; minerals.
Nutritional supplement.

MultiLac
Note: this name may be used for preparations of different composition.
Fresenius, Switz.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1778·2).
Haemofiltration.

Multilac
Note: this name may be used for preparations of different composition.
Fresenius Medical, Cz.; Fresenius Medical, Neth.; Fresenius Medical, Port.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3).
Haemofiltration; haemodialysis.

Multilarm *Thea, Fr.†*
Sodium chloride (p. 1795·1).

Multilex *Rugby, USA.*
Vitamins; with or without minerals.

Multilim *Atlantic, Hong Kong†; Atlantic, Thai.*
Vitamins.
Tonic; vitamin supplement.

Multilim RG *Atlantic, Thai.*
Ginseng (p. 2513·3); royal jelly (p. 2608·1); vitamins; minerals.

Multilind *Merck, Chile; Stada, Ger.; Dermapharm, Switz.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Fungal skin infections.

Dermapharm, Switz.
Oral suspension: Nystatin (p. 590·3).
Fungal infections.

Multilipius *Asclepius, India.*
Lycopene (p. 2546·2); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Multiload *Schering-Plough, Austral.†; Schering-Plough, Braz.; Schering-Plough, Chile; Organon, China; MSD-Chibret, Fr.; Organon, Ger.†; MSD, Hong Kong; Organon, India; Organon, Ital.; Schering-Plough, Malaysia; MSD, NZ; MSD, Singapore; MSD, Switz.; MSD, Thai.; Organon, Turk.†; Organon, UK; Organon, Venez.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Multilyte *American Pharmaceutical, USA.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Multima *Beres, Hung.*
Vitamins; minerals.

Multimax *Unipharm, Rus.*
Vitamins; minerals; trace elements; with or without lutein (p. 2079·2).

Unipharm, Ukr.
Vitamins; minerals; lutein (p. 2079·2).
Dietary supplement.

Multimax for Eyes *Unipharm, Rus.*
Vitamins; minerals; bioflavonoids (p. 2505·2); lutein (p. 2079·2); royal jelly (p. 2608·1); myrtillus (p. 2566·2).

Multi-Mega *Natural Life, Arg.*
Vitamins; minerals; medicinal herbs.

Multimel *Baxter, Gr.*
Amino acids; glucose (p. 2068·3); soya oil (p. 2092·3); olive oil (p. 2575·1).
Parenteral nutrition.

Multi-Min *GNLD, Austral.*
Minerals; trace elements; colecalciferol (p. 2113·1).

Multi-Mineral *Super Nutrition, Canad.†*
Minerals; ergocalciferol (p. 2113·3).

MultiMineral *Usana, Canad.†*
Minerals.

Multi-Mineral Complex *Golden Neo-Life, Canad.*
Minerals.

Multi-Mins *Seroyal, Canad.†*
Minerals.

Multimix
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Vitamins.

Indo French, India.
Oral liquid: ⊗Ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3).

Indo French, India.
Syrup: ⊗Bromhexine hydrochloride (p. 1656·3); ephedrine hydrochloride (p. 1663·2); sodium iodide (p. 2337·1); theophylline (p. 1229·3).

Multin *Lazar, Arg.*
Paracetamol (p. 115·1); dipyrone (p. 53·3).
Fever; pain.

Multinat *Naturatec, Canad.†*
Vitamins; minerals.

Multinatal Plus *Brookstone, USA.*
Vitamins; minerals.

Multi-ND *Laborate, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Multinebulgen *Caber, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; allergic rhinitis.

Multio *Genomma, Arg.*
Arginine (p. 2049·1).
Vaginal lubricant.

Multipan-D *Laborate, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Multiparin *IFET (ΙΦΕΤ), Gr.; LCH, Hong Kong†; Technopharm, Irl.†; Artex, NZ; Wockhardt, UK.†*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Multiphar *Pharmaffiliates, India.*
Capsules: Vitamins; zinc sulfate (p. 2126·2); ginseng (p. 2513·3).

Pharmaffiliates, India.
Syrup: Vitamin B substances (p. 2102·3); zinc (p. 2126·1); lysine (p. 2079·3).

Multiplex *Kevin, India.*
Vitamin B substances (p. 2102·3).

Pharmasant, Thai.
Vitamins.

Multiplex 1 *Alpinamed, Switz.*
Cyclamen europaeum (p. 2490·2); echinacea angustifolia (p. 2498·1); iris versicolor (p. 2534·3); pulsatilla pratensis (p. 2600·2); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Multipressim *Multilab, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Multipretten *Midsona, Swed.*
Peppermint leaf (p. 1877·1); achillea (p. 2427·3); aniseed (p. 2444·2); fennel (p. 2503·2); caraway (p. 2470·2); imperatoria; coriander (p. 2486·3); caraway oil (p. 2470·3); fennel oil (p. 2503·3); star anise oil (p. 2622·2); peppermint oil (p. 1877·1); coriander oil (p. 2487·1).
Gastrointestinal disorders.

Multi-Pro
Note: this name may be used for preparations of different composition.
Professional Health, Canad.
Vitamins minerals.

Multiprodukt *Natur Produkt, Rus.*
Vitamins; minerals.

Multiron *Vitabiotics, UK.*
Vitamins; minerals; ginseng (p. 2513·3).

Multisal *Polfa Kutno, Pol.†*
Minerals.

Multi-Sanostol *Nycomed, Cz.*
Vitamins; calcium (p. 1783·1).

Nycomed, Ger.
Vitamins.

Nycomed, Mex.
Vitamins; calcium (p. 1783·1); phosphorus (p. 2589·2).

Nycomed, Pol.
Calcium gluconate (p. 1783·3); calcium phosphorolactate; vitamins.
Tonic.

Multisedil *Andromaco, Chile.*
Diazepam (p. 1063·2); chlormezanone (p. 1045·1).
Anxiety; sleep disorders; skeletal muscle spasm.

Multisef *Nevzat, Turk.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Multisoro *Multilab, Braz.*
Adult: ⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Multilab, Braz.
Infant: Sodium chloride (p. 1795·1).
Nasal congestion.

Multispec-E *Pharmaspec, Philipp.*
Ferrous fumarate (p. 2060·3); vitamins.
Nutritional supplement; iron-deficiency anaemia; vitamin B deficiency.

Multistix *Bayer, Austral.; Siemens, USA.*
Test for glucose, protein, blood, ketones, bilirubin, urobilinogen, and pH in urine.

Multistix 2 *Siemens, USA.*
Test for nitrites and leucocytes in urine.

Multistix 5 *Bayer, Austral.*
Test for glucose, blood, protein, nitrite, and leucocytes in urine.

Multistix 7 *Siemens, USA.*
Test for glucose, protein, blood, ketones, nitrites, leucocytes, and pH in urine.

Multistix 9 *Siemens, S.Afr.†; Siemens, USA.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, and leucocytes in urine.

Multistix GP *Bayer Diagnostics, UK.*
Test for specific gravity, pH, protein, glucose, ketones, blood, nitrites, and leucocytes in urine.

Bayer Diagnostics, Irl.†
Test for pH, protein, glucose, ketones, leucocytes, blood, nitrites, and specific gravity in urine.

Multistix SG *Bayer Diagnostics, Irl.†; Bayer Diagnostics, UK.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, and specific gravity in urine.

Multistix 8 SG *Bayer, Arg.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, and specific gravity in urine.

Bayer, Austral.; Siemens, Fr.†; Siemens, Ital.; Bayer Diagnostics, UK; Siemens, USA.
Test for glucose, protein, blood, ketones, nitrites, leucocytes, pH, and specific gravity in urine.

Bayer Diagnostics, Irl.†
Test for pH, protein, glucose, ketones, leucocytes, blood, nitrites, and specific gravity in urine.

Multistix 9 SG *Siemens, USA.*
Test for glucose, protein, blood, ketones, bilirubin, nitrites, leucocytes, pH, and specific gravity in urine.

Multistix 10 SG *Bayer, Arg.; Bayer, Austral.; Bayer Diagnostics, Irl.†*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leucocytes, and specific gravity in urine.

Siemens, Fr.†; Siemens, Ital.; Siemens, S.Afr.; Bayer Diagnostics, UK; Siemens, USA.
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, leucocytes, and specific gravity in urine.

Multi-Symptom PMS Relief *Jamp, Canad.; Pendopharm, Canad.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).

Multi-Symptom Tylenol Cough *McNeil Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Formerly known as Maximum Strength Tylenol Cough.
Coughs.

Multi-Symptom Tylenol Cough with Decongestant *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Formerly known as Maximum Strength Tylenol Cough with Decongestant.
Coughs and cold symptoms.

Multi-Tabs *Ferrosan, Cz.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Vitamin deficiency.

Ferrosan, Rus.; Nutriforma, Turk.
Vitamins; minerals.

Ferrosan, Pol.†; Ferrosan, Ukr.
Vitamins; with or without minerals.
Dietary supplement.

Multitabs ACD *Ferrosan, Denm.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1).
Vitamin deficiency.

Multi-Tabs B-Complex *Ferrosan, Rus.*
Thiamine nitrate (p. 2103·2); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); nicotinamide (p. 2083·1); calcium pantothenate (p. 2085·2); folic acid (p. 2063·1).
Vitamin B deficiency; tonic; neuritis; neuralgia.

Multi-Tabs Immuno *Ferrosan, Hung.*
Lactobacillus GG (p. 2596·3); vitamins; minerals.

Multi-Tabs Neo *Ferrosan, Fin.†*
Vitamins; minerals.

Multi-Tar *Valeant, Hong Kong.†*
Pyrithione zinc (p. 1718·1); tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2).
Scalp disorders.

Multi-Tar Plus *Valeant, Canad.†*
Cade oil (p. 1723·2); tar (p. 1723·3); coal tar (p. 1723·2); pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis.

Multitest *Gerolymatos, Gr.*
Tetanus antigen; diphtheria antigen; streptococcus group C antigen; tuberculin antigen (p. 2635·3); candida albicans antigen; trichophyton mentagrophytes antigen (p. 2634·1); proteus mirabilis antigen; tuberculin antigen (p. 2635·3).
Assessment of cell-mediated immunity.

Multitest CMI *CSL, Austral.†*
Tetanus toxoid; diphtheria toxoid; streptococcus group C antigen; tuberculin (p. 2635·3); candida antigen; trichophyton antigen (p. 2634·1); proteus antigen.
Assessment of cell-mediated immunity.

Multiton *Biochimici, Ital.*
Vitamins; minerals.

Multitrace-5 *Luitpold, Singapore.*
Chromium (p. 2055·3); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc (p. 2126·1).
Parenteral nutrition.

Multi-Unibion *Proel, Gr.*
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Multi-Vi-Min *Sisu, Canad.†*
Vitamins; minerals.

Multiviral *Meyer, Venez.*
Vitamins; minerals.
Dietary supplement.

Multi+Vision *Bioglan, Austral.*
Lutein (p. 2079·2); vitamins; minerals.
Dietary supplement for maintenance of eye health.

Multi-Vit *Laformen, Arg.*
Vitamins; minerals.

Multivit *T Man, Thai.*
Vitamins.

Multivit Natura *Meyer Nature, Venez.*
Ginseng (p. 2513·3); acerola; wheat germ (p. 2647·1); vitamins; minerals.
Dietary supplement; tonic.

Multivit Perinatal *Meyer, Venez.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Multivitamin *Maccabi Care, Israel.*
Vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2).
Nutritional supplement.

Multivitamin M *Maccabi Care, Israel.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Multivitaminas Isamax *ISA, Arg.*
Vitamins; minerals.
Dietary supplement.

Multivitamol *Natur Produkt, Pol.*
Ferrous lactate (p. 2062·1); vitamins.
Tonic.

Multivitamol Dr Theiss *Naturwaren, Ukr.*
Ferrous lactate (p. 2062·1); vitamins.
Dietary supplement.

Multivitaplex *Actavis, Indon.*
Vitamins.

Multivit-B *Lannacher, Austria.*
Vitamin B substances (p. 2102·3).

Multi-Vite *Seroyal, Canad.†*
Vitamins; minerals.

Multivite Gold *Universal Medicare, India.*
Vitamins; minerals; trace elements; amino acids; carotenoids (p. 2176·2); choline bitartrate (p. 2055·2); citrus bioflavonoids (p. 2505·2); garlic (p. 2510·3); ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); green tea (p. 2648·2); lycopene (p. 2546·2).

Multivite Vision *Universal Medicare, India.*
Carotenoids (p. 2176·2); vitamins; trace elements; docosahexaenoic acid (p. 1460·1); lutein (p. 2079·2); lycopene (p. 2546·2).

Multivite Woman *Universal Medicare, India.*
Vitamins; minerals; trace elements; amino acids; choline bitartrate (p. 2055·2); carotenoids (p. 2176·2); citrus bioflavonoids (p. 2505·2); evening primrose oil (p. 2502·2); ginkgo biloba (p. 2512·3); green tea (p. 2648·2); lycopene (p. 2546·2).

Multivite-FM *Universal Medicare, India.*
Vitamins; minerals.

Multivite-FM Omega *Universal Medicare, India.*
Carotenoids (p. 2176·2); vitamins; minerals; omega-3 fatty acids (p. 1460·1).

Multivox *Psyco Remedies, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Multi-Woman *Sisu, Canad.†*
Vitamins; minerals.

Multi-Xone *Laborate, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Multizac *Psychotropics, India.*
Vitamins; trace elements; amino acids; lutein (p. 2079·2).

Multizol *Multilab, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Multi-Zyme *Foodscience, Canad.†*
⊗Amylase (p. 2442·1); betaine hydrochloride (p. 2456·1); bromelain (p. 2460·3); cellulase (p. 2473·1); lipase (p. 2579·3); ox bile (p. 2457·2); papain (p. 2582·3); pepsin (p. 2586·1); protease (p. 2598·1).
Digestive disorders.

Multodrin *Montavit, Austria.*
⊗Dexamethasone (p. 1630·3); diphenhydramine hydrochloride (p. 626·2).
Skin disorders.

Multosin *Takeda, Ger.*
Estramustine sodium phosphate (p. 790·1).
Prostatic cancer.

Multoxid *CMG, India.*
Vitamins; lycopene (p. 2546·2); zinc (p. 2126·1).

Multra *WN, Canad.†*
Vitamins; minerals.

Multramin *Catalent, Philipp.*
Vitamins; minerals; citrus bioflavonoids (p. 2505·2); lecithin (p. 2542·2).
Nutritional supplement.

Multum
Note: this name may be used for preparations of different composition.
Rosen, Ger.†
Chlordiazepoxide (p. 1044·2).
Anxiety disorders; sleep disorders.

Mulvidren-F Softab *Stuart, USA.*
Sodium fluoride (p. 2089·2) with vitamins.
Dental caries prophylaxis in children.

Mulvitron *Wescrib, Philipp.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Mumaten *Yeni, Turk.*
A mumps vaccine (Rubini strain) (p. 2402·3).
Active immunisation.

Mum-2-B *Sunpab, Singapore.*
Vitamins; minerals; fish oil (p. 1460·1).
Dietary supplement in pregnancy and breast feeding.

Mumcal *Aamorb, India.*
Syrup: Calcium gluconate (p. 1783·3); calcium lactate (p. 1784·1); cyanocobalamin (p. 2107·2); colecalciferol (p. 2113·1); lysine hydrochloride (p. 2079·3).

Aamorb, India.
Tablets: Calcium citrate (p. 1783·2); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).

Mumfer *Glenmark, India.*
Chewable tablets: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron and folic acid deficiency in pregnancy.

Glenmark, India.
Oral drops; syrup: Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia.

Mumfer-Z *Glenmark, India.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1); zinc (p. 2126·1).
Iron-deficiency anaemia; iron, zinc, and folic acid deficiency in pregnancy.

Mummin *Pharmasant, Thai.†*
Vitamins; minerals; iron (p. 2073·1).
Nutritional supplement during and after pregnancy.

Mummum *FDC, India.*
Preparation for enteral nutrition.

Mumo *Serum Institute, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Mumomega *Equazen, Hong Kong.*
Marine fish oil (p. 1460·3); evening primrose oil (p. 2502·2).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mumomega Equazen *Vifor, Singapore.†*
Marine fish oil (p. 1460·3); evening primrose oil (p. 2502·2); arachidonic acid (p. 2446·1); vitamin E (p. 2119·1).
Dietary fatty acid supplement.

Mumpsvax *Vianex (Βιανεξ), Gr.; Merck, USA.†*
A mumps vaccine (p. 2402·3).
Active immunisation.

Mumzyme *Aamorb, India.*
⊗Simeticone (p. 1886·2); bile (p. 2457·2); pancreatin (p. 2579·3).

Mundidol *Mundipharma, Austria.*
⊗Morphine sulfate (p. 92·3).
Pain.

Mundisal *Lavipharm, Gr.; Extractum, Hung.; Mundipharma, Hung.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Nasal and oropharyngeal pain and inflammation; mouth disorders.

Mundipharma, Austria; Mundipharma, Cz.; Mundipharma, Rus.; Mundipharma, Switz.
Choline salicylate (p. 39·2).
Nasal and oropharyngeal pain and inflammation; mouth disorders.

Muni *Robugen, Ger.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Munipyrin *Garuda, Hung.*
⊗Ashwagandha (p. 2450·2); commiphora wightii; pluchea lanceolata; asparagus racemosae (p. 2614·2); tinospora cordifolia; curcuma longa (p. 2218·1); Indian gooseberry (p. 2532·2); minerals; beleric myrobalan (p. 2453·2); chebulic myrobalan (p. 2474·3); black pepper (p. 2586·1); picrorhiza kurroa (p. 2590·2); plumbago zeylanica; hordeum vulgare; plantanum; ginger (p. 1844·1); sida cordifolia; liquorice (p. 1853·2); tribulus terrestris (p. 2633·3); ricinus communis.
Musculoskeletal and joint disorders.

Munitren *Robugen, Ger.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Munobal *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austria; Sanofi-Aventis, Ger.; Sanofi-Aventis, Mex.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension; heart failure.

Munorm *Flamingo, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Munotras *Monte Verde, Arg.†*
Mycophenolate mofetil (p. 1961·1).

Muntel *UCB, Irl.; Lacer, Spain.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Munti-Vim *Hua, Thai.*
Vitamins.

Mu-Oint *Ind-Swift, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupaten *Bayer, Arg.*
Isoconazole (p. 583·2) or isoconazole nitrate (p. 583·2).
Fungal skin infections; fungal or Gram-positive bacterial vaginal infections.

Mupax
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Mupirocin (p. 327·2) or mupirocin calcium (p. 327·2).
Bacterial skin infections; elimination of nasal staphylococci.

Arrow, Fr.†
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Antacid.

Muphoran *Servier, Austral.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, China; Servier, Fr.; Servier, Gr.†; Servier, Israel; Italfarmaco, Ital.; Servier, NZ; Servier, Port.; Servier, Turk.*
Fotemustine (p. 799·3).
Disseminated malignant melanoma; brain tumours.

Mupiban *Agio, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupicin *Amherst, Philipp.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupider *Kleva, Gr.; Kleva, Singapore.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupiderm *Almirall, Fr.; EON, Philipp.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupimet *Fourrts, India.*
Mupirocin (p. 327·2); metronidazole (p. 936·1).

Mupinova *Zuventus, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupiran *Vocate, Gr.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupirax *Micro, India; Micro, Singapore.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Mupirox
Note: this name may be used for preparations of different composition.
Fortbenton, Arg.; Blau, Pol.
Mupirocin (p. 327·2).
Bacterial skin infections; elimination of nasal staphylococci.

EMS, Braz.
Ciclopirox (p. 575·3).

Mupiskin *Mastelli, Ital.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Muporin *TO-Chemicals, Thai.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Muprin *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Muralion *Socofar, Port.†*
Flavonoids (p. 2505·2).
Vascular disorders.

Murazyme *Grunenthal, Belg.*
Muramidase hydrochloride (p. 2565·1).
Herpesvirus infections; minor wounds.

Murelax *Sigma, Austral.*
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.

Murhinol *Farmaline, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Muricalm *Novartis, Braz.*
Pimethixene (p. 638·1).
Respiratory-tract disorders in children.

Murine
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Berberine chloride (p. 2455·1).
Eye cleansing; eye irritation.

Prestige, Canad.; Ross, USA.†
Eye drops: Povidone (p. 2204·3); polyvinyl alcohol (p. 2204·2).
Dry eyes.

Ross, USA.
Ear drops: Urea hydrogen peroxide (p. 1774·2).
Removal of ear wax.

Murine Allergy *Aspen, Austral.*
⊗Antazoline sulfate (p. 616·1); xylometazoline hydrochloride (p. 1680·1).
Allergic eye disorders.

Murine Bright & Moist Eyes *Prestige, UK.*
⊗Hypromellose (p. 2189·2); naphazoline hydrochloride (p. 1669·3).
Dry eyes; eye irritation.

Murine Clear Eyes *Aspen, Austral.; Aspen Consumer, S.Afr.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Murine Contacts *Prestige, UK.*
Carmellose sodium (p. 2175·2).
Comfort drops for contact lenses.

Murine Dry & Tired Eyes *Prestige, UK.*
⊗Carmellose sodium (p. 2175·2); glycerol (p. 2517·2).
Dry eyes; eye irritation.

Murine Hayfever *Prestige, UK.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Murine Irritation and Redness Relief *Prestige, Irl.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Murine Irritation & Redness Relief *Prestige, UK.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Murine Natural Tears *Zuellig, Hong Kong.†*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Murine Plus *Abbott, Singapore; Ross, USA.*
⊗Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3); tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Zuellig, Hong Kong.†
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Murine Plus Natural *Zuellig, Hong Kong.†*
⊗Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3); tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Murine Revital Eyes *Aspen, Austral.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes; eye cleansing; eye irritation.

Murine Sore Eyes *Aspen, Austral.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Murine Tears *Aspen, Austral.†*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes; eye irritation.

Muro 128 *Bausch & Lomb, Arg.; Bausch & Lomb, Canad.; Bausch & Lomb, Mex.; Bausch & Lomb, USA.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Murocel *Bausch & Lomb, USA.†*
Methylcellulose (p. 2197·3).
Dry eyes.

Muroci *BMW, India.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Murocoll-2 *Bausch & Lomb, USA.†*
Hyoscine hydrobromide (p. 1845·3); phenylephrine hydrochloride (p. 1672·3).
Induction of mydriasis and cycloplegia; uveitis.

Murode *Teofarma, Spain.*
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Muroptic *Optopics, USA.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Musaldox *Continentales, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Musalten *Continentales, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Musapam *Krewel, Ger.†*
Tetrazepam (p. 1110·1).
Skeletal muscle tension and spasm.

Musapro *Emcure, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Musaral *T Man, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Musaril *Sanofi-Aventis, Ger.†*
Tetrazepam (p. 1110·1).
Skeletal muscle spasm.

Muscadol *Julphar, UAE.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain.

Muscalax *Polipharm, Singapore; Polipharm, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain; respiratory-tract congestion; sprains; strains.

Muscalm *Kayaku, Jpn.*
Tolperisone hydrochloride (p. 2027·3).
Spasticity; skeletal muscle tension.

Muscarin *Sipra, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Muscarsan *Sanum-Kehlbeck, Ger.*
Amanita muscaria e thallo.
Homoeopathic preparation.

Muscelax *Hua, Thai.†*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; skeletal muscle spasm.

Muscle & Back Pain Relief *Jamp, Canad.; Pendopharm, Canad.; Pharmetics, Canad.; Rougier, Canad.; Vita Health, Canad.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).

Muscle & Back Pain Relief-8 *Pharmascience, Canad.; Pharmetics, Canad.; Vita Health, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); methocarbamol (p. 2025·3).

Muscle & Back Pain Relief Extra Strength *Pendopharm, Canad.; Pharmetics, Canad.*
Aspirin (p. 22·2); methocarbamol (p. 2025·3).

Muscle Care *Kiwi, Neth.*
Arnica montana (p. 2447·2); ruta graveolens (p. 2608·2); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Muscle & Joint Cream *Bayer, USA.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Muscle Mist *Country Connections, Canad.*
Clove oil (p. 2481·3); menthol (p. 2553·2).

Muscle Rub
Note: this name may be used for preparations of different composition.
Weleda, S.Afr.†
Copper (p. 2057·1); camphor (p. 2466·2); capsicum (p. 2469·3); arnica (p. 2447·2); clove oil (p. 2481·3); menthol (p. 2553·2); cajuput oil (p. 2464·1).
Musculoskeletal pain and stiffness.

Musclide *Kleva, Gr.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Muscodac *Ind-Chemie, India.*
Tablets: Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Ind-Chemie, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Muscodol *Obsurge, India.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Muscoflex *Epifarma, Ital.; Bilim, Turk.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm; spasticity; parkinsonism; neuromuscular pain.

Muscol *Teva, Israel; Teva, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; musculoskeletal pain.

Muscolic *Osoth, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Musco-ril *Sanofi-Aventis, Gr.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Muscoril *Sigma, Braz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Pol.†; Sanofi Synthelabo, Turk.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm; soft-tissue pain; muscle spasticity; parkinsonism; neuromuscular pain; oedema.

Muscoril Trauma *Sanofi-Aventis, Ital.*
Thiocolchicoside (p. 2026·2); aescin (p. 2431·2).
Soft-tissue injury.

Muscort *LBS, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and soft-tissue pain.

Musculare *Eurofarma, Braz.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Musculax *MSD, Jpn.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Muscunor *Fada, Arg.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Muscuprina *Sigma, Braz.*
Cyclobenzaprine hydrochloride (p. 2023·1).

Muscuron *Pharmaplan, S.Afr.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Muse *Paladin, Canad.; Meda, Cz.†; Meda, Denm.; Meda, Fin.; Meda, Fr.; Meda, Ger.; Meda, Gr.; Meda, Irl.; Meda, Ital.; Meda, Neth.; Meda, Port.; Janssen-Cilag, S. Afr.†; Meda, Spain; Meda, Switz.; Meda, UK; Meda, USA.*
Alprostadil (p. 2352·2).
Erectile dysfunction; adjunct to ultrasound examination of penile function.

Musilaks *Sanofi Synthelabo, Turk.*
Phenolphthalein (p. 1877·3); vanillin (p. 2218·3).
Constipation.

Musilax *Trophic, Canad.*
Ispaghula (p. 1849·1).
Constipation.

Musin *Otto, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Muskazon *Kurtsan, Turk.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

Muskel *Svizera, India.*
Tablets: Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Svizera, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Muskelax *United American, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Muskol *Schering-Plough, Canad.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Muslax *Biological E, India.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Muslexac *Inpac, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle spasm and pain.

Musocalm *Medicine Products, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Musocan *Sriprasit, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Musol *Teva, Mex.*
Diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Musolax *Daewoo, Thai.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Musovon *Medicine Products, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Mustargen *Ovation, Canad.†; MSD, Israel; Pro Concepta, Switz.†; Lundbeck, USA.*
Chlormethine hydrochloride (p. 765·1).
Malignant neoplasms; polycythaemia vera; mycosis fungoides.

Mus-TC *Interpharma, Chile.*
Clarithromycin (p. 266·2).
Bacterial infections.

Musterole *Schering-Plough, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); methyl nicotinate (p. 91·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Musterole Extra *Schering-Plough, USA.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); mustard oil (p. 2646·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Mustoforan *Servier, Spain.*
Fotemustine (p. 799·3).
Malignant melanoma.

Mustone *Chandra Bhagat, India.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis; paralytic ileus; postoperative urinary retention.

Mustong *TTK, India.*
⊗Liquorice (p. 1853·2); nutmeg (p. 2573·1); tinospora cordifolia; tribulus terrestris (p. 2633·3); withania somnifera (p. 2450·2).

Mustophoran *Servier, Cz.; Servier, Hung.; Servier, Pol.; Servier, Rus.; Servier, Ukr.*
Fotemustine (p. 799·3).
Malignant melanoma; brain tumours.

Mustopic *Systopic, India.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Musvan *Parggon, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Musxan *Pharmasant, Thai.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Mutabase *MSD, Spain.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Depression.

Mutabon *Schering-Plough, Ital.; Schering-Plough, Port.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Psychiatric disorders; anxiety; mixed anxiety-depressive disorders.

Mutabon-D *Schering-Plough, Indon.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Depression; mixed anxiety-depressive disorders.

Mutabon-M *Schering-Plough, Indon.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Mixed anxiety-depressive states.

Mutaflor *Emonta, Austria; Ardeypharm, Cz.; Sabora, Fin.; Ardeypharm, Ger.; Ardeypharm, Hung.†; Vifor, Switz.; Ardeypharm, Ukr.*
Escherichia coli.
Gastrointestinal disorders; constipation; ulcerative colitis; irritable colon; diarrhoea.

Mutagrip *Sanofi Pasteur, Arg.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fr.†; Sanofi Pasteur, Ger.; IFET [ΙΦΕΤ], Gr.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Aventis, S.Afr.†; Sanofi-Aventis, Spain; Sanofi Pasteur, Switz.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Mutamso *Europharm, Hong Kong.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus.

Mutamycin *BMS Oncology, USA.†*
Mitomycin (p. 830·3).
Disseminated carcinoma of the stomach or pancreas.

Mutan *GL Pharma, Austria.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Mutax *Chandra Bhagat, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Mutax Plus *Chandra Bhagat, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Mutech *Pharma-Tech, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Mutésa *Genopharm, Fr.†*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3); oxetacaine (p. 1993·1).
Gastro-oesophageal pain.

Mutharsin *Finadiet, Arg.*
Ricinoleic acid triglyceride; arachidic acid triglyceride; palmitic acid glyceride; stearic acid glyceride.
Squamous skin disorders.

Muttifen *Offenbach, Mex.*
Trimebutine (p. 2634·1).

Mutum *Raffo, Arg.; Nolver, Venez.*
Fluconazole (p. 578·2).
Fungal infections.

Muvar *Pharmatrix, Arg.*
Hyaluronic acid (p. 2526·2); lactic acid (p. 2539·1).
Dry skin.

Muvease *Matxin, Singapore.*
Boswellia serrata (p. 2507·3); commiphora wightii; curcuma longa; moringa pterygosperma; vitex negundo.
Joint disorders.

Muvera *Sun, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Muveron *Solas, Indon.*
Vitamins; calcium gluconate (p. 1783·3); lysine hydrochloride (p. 2079·3); ferrous gluconate (p. 2061·2); zinc sulphate (p. 2126·2).
Anaemias; nutritional supplement in pregnancy and lactation.

Muvidina *LKM, Arg.*
Zidovudine (p. 1024·2); lamivudine (p. 1000·2).
HIV infection.

Muvik *Cadila, India.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; rheumatoid arthritis; osteoarthritis.

Muvinlax *Libbs, Braz.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Muvinor *Libbs, Braz.*
Polycarbophil calcium (p. 1879·2).
Constipation.

Muvito *Rafarm, Gr.*
Tetracycline hydrochloride (p. 373·2).
Acne.

Muxelix *Saval, Chile.*
Ivy (p. 2536·2).
Respiratory-tract congestion; cough.

Muxen *Meyer Alian, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Muxol
Note: this name may be used for preparations of different composition.
Saval, Chile.
Ambroxol (p. 1654·3).
Respiratory-tract disorders.

Biocodex, Fr.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Vifor, Switz.
Bisacodyl (p. 1821·1).
Constipation.

Muzic *Alkem, India.*
Mosapride (p. 1865·2).
Gastrointestinal motility disorders.

Muzoral *Mugi, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Muzox *Stedman, India.*
Chlorzoxazone (p. 2022·2); tramadol hydrochloride (p. 139·2).

MV Poly *Pharmasant, Thai.*
Vitamins.

M-Vac *Serum Institute, India.*
A measles vaccine (attenuated Edmonston Zagreb strain) (p. 2398·3).
Active immunisation.

MVI *USV, India; Grossman, Mex.; Hospira, USA.*
Vitamins.
Parenteral nutrition.

Mvimin *Gujarat Terce, India.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3); lactoferrin (p. 2539·3).

MVM *Tyson, USA.*
Vitamins; minerals.

MXL *Napp, Gr.; Napp, Irl.†; Napp, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

My Caps *Pharos, Indon.*
Betacarotene (p. 2051·1); vitamin B_2 (p. 2104·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); copper (p. 2057·1); selenium (p. 2086·3); zinc (p. 2126·1).
Antoxidant; tonic.

My Way *Gavis, USA.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Myaccord *Douglas, NZ.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Myacyne *Schur, Ger.*
Ointment: Neomycin sulfate (p. 330·1).
Infected skin disorders; infected wounds.

Myadec *Myadec, Austral.*
Vitamins; minerals.

Pfizer Consumer, USA.
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Myal *Tripharma, Turk.*
Thiocolchicoside (p. 2026·2).

Myalgesic *Pharmanik (Φαρμανικ), Gr.*
Salicylamide (p. 129·2); benzocaine (p. 1980·2).

Myambutol *Aspen, Austral.; Max Pharma, Austria; Teofarma, Belg.; Orifarm, Denm.; Genopharm, Fr.; Riemser, Ger.; Wyeth, Gr.; Wyeth, India; Teofarma, Neth.; Healthcare Logistics, NZ; Teofarma, Spain; Labatec, Switz.; Labatec, Switz.; X-Gen, USA.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis and other mycobacterial infections.

Myambutol-INH *Wyeth, Gr.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Myamlo *Mandar, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Myamlo-AT *Mandar, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Myamolite *Holland Pharma, Neth.*
Arnica montana (p. 2447·2); belladonna (p. 2453·3); baryta carbonica (p. 2452·2); calcarea fluorica (p. 2053·1); calcarea carbonica ostrearum (p. 1824·3); mercurius solubilis (p. 2555·3); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

My-B *Greater Pharma, Thai.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3); polymyxin B sulfate (p. 342·3).
Infected skin disorders; burns; wounds.

Mybacin *Greater Pharma, Thai.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Mybacin Dermic *Greater Pharma, Thai.*
Bacitracin (p. 225·3); neomycin (p. 329·3).
Infected skin disorders.

Mybroxol *Greater Pharma, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Mybu *Neon, India.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Mybucod *Aspen, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; inflammation; fever.

Mybulen *Aspen, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; inflammation; fever.

Mycalcin *Greater Pharma, Thai.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; bone pain; Paget's disease of bone; hypercalcaemia.

Mycalcium *Bombay Tablet, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Mycamine *Astellas, Austria; Astellas, Braz.; Astellas, Canad.; Astellas, China; Astellas, Cz.; Astellas, Denm.; Astellas, Fr.; Astellas, Ger.; Astellas, Gr.; Astellas, Hong Kong; Astellas, Hung.; Astellas, Indon.; Astellas, Irl.; Astellas, Ital.; Astellas, Neth.; Astellas, Norw.; Astellas, Philipp.; Astellas, Pol.; Astellas, Port.; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Astellas, Thai.; Astellas, UK; Astellas, USA.*
Micafungin sodium (p. 588·2).
Candidiasis; prophylaxis of aspergillosis and candidiasis following haematopoietic stem-cell transplantation.

Mycanden
Note: this name may be used for preparations of different composition.
Ronnet, Arg.
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycarzem *Pharmanel, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Mycazole *Verisfield, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Mycef *Unique, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Mycel Gyno *Biolab Sanus, Braz.†*
Isoconazole nitrate (p. 583·2).
Fungal vaginal infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Mycelex
Note: this name may be used for preparations of different composition.
Ortho McNeil, USA.
Clotrimazole (p. 576·2).
Oral candidiasis.

Mycelex-3
Note: this name may be used for preparations of different composition.
Ortho McNeil, USA.†
Butoconazole nitrate (p. 574·2).
Vaginal candidiasis.

Mycelex-7
Note: this name may be used for preparations of different composition.
Ortho McNeil, USA.
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Mycella *Silom, Thai.*
Ketoconazole (p. 585·3).
Fungal infections of the skin, nails, and mucous membranes.

Mycelvan *Liomont, Mex.*
Terbinafine (p. 593·3).
Fungal infections.

Mycept *Panacea, India; Panacea, Philipp.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mycer *Arlak, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Mycer G *Arlak, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Mycetin *Farmigea, Ital.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Mycifor *Forum, UK.*
Clarithromycin citrate (p. 266·2).
Bacterial infections.

Myci-GC *Misemer, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Mycil *Reckitt Benckiser, Irl.; Crookes Healthcare, UK.*
Ointment: Tolnaftate (p. 596·1); benzalkonium chloride (p. 1737·1).
Fungal skin infections.

Reckitt Benckiser, Irl.; Crookes Healthcare, UK.
Topical powder: Tolnaftate (p. 596·1); chlorhexidine hydrochloride (p. 1743·3).
Fungal skin infections; prickly heat.

Reckitt Benckiser, Irl.; Crookes Healthcare, UK.
Topical spray: Tolnaftate (p. 596·1).
Fungal skin infections; prickly heat.

Boots, Hong Kong.†
Tolnaftate (p. 596·1); benzalkonium chloride (p. 1737·1); chlorhexidine hydrochloride (p. 1743·3).
Fungal skin infections.

Mycil Healthy Feet
Note: this name may be used for preparations of different composition.
Boots Healthcare, Austral.
Cream: Tolnaftate (p. 596·1); benzalkonium chloride (p. 1737·1).
Fungal skin infections.

Reckitt Benckiser, Austral.
Topical powder: Tolnaftate (p. 596·1); chlorhexidine hydrochloride (p. 1743·3).
Fungal skin infections.

Mycin
Note: this name may be used for preparations of different composition.
Neon, India; Neon, Philipp.
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Syntho, India.
Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Mycinadol *Sons, Mex.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint pain; inflammation.

Mycinette *Pfeiffer, USA.*
Phenol (p. 1763·3); alum (p. 2439·1).
Sore throat.

Mycinettes *Pfeiffer, USA.*
Benzocaine (p. 1980·2).
Sore throat.

Mycinil *Gerolymatos, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Mycinopred *Allergan, Switz.†*
⊗Prednisolone acetate (p. 1645·2); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Infected eye disorders.

Myci-Spray *Misemer, USA.*
Phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Nasal congestion.

Myclausen *Passauer, Cz.; Passauer, Denm.; Passauer, Irl.; Navamedic, Neth.; Passauer, Pol.; Passauer, Port.; Vitaflo, Swed.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Myclav *Solitaire, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Unichem, Malaysia.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Myclin *Sanbe, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Stragen, Denm.†; Stragen, Fin.†
Clindamycin phosphate (p. 269·3).
Acne.

Myclopir *Bevo, Gr.*
Ciclopirox (p. 575·3).
Fungal vaginal infections.

Myclovear *Gerard, Irl.†*
Famciclovir (p. 979·1).
Herpesvirus infections.

Myco *T Man, Thai.*
Ketoconazole (p. 585·3).
Scalp disorders.

Myco-Aid *Pharmaniaga, Malaysia.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Mycoapaisyl *Merck Medication Familiale, Fr.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Mycoback *Cipla, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Mycobact *Cipla, India.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Mycobacter *Mentiterm, Gr.; Zekides, Gr.*
Econazole nitrate (p. 577·3).
Fungal skin and vaginal infections.

Mycobal *Ind-Swift, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mycoban
Note: this name may be used for preparations of different composition.
ICM, Singapore.
Miconazole nitrate (p. 589·1).
Fungal infections of skin, nails, or scalp.

Sandoz, S.Afr.
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Myco-Biotic ‖ *Moore, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Skin disorders.

Mycobutin *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Neth.; Pfizer, NZ; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pharmacia Upjohn, USA.*
Rifabutin (p. 348·3).
Mycobacterial infections.

Mycobutol *Cadila, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Mycochlorin *Sermmitr, Thai.†; SM, Thai.†*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Mycochlorin-T *SM, Thai.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Mycocid *Intermed, India.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Mycocide NS *Woodward, USA.*
Tolnaftate (p. 596·1).
Formerly contained benzalkonium chloride.
Fungal skin infections.

Mycocil *Landsteiner, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Mycocin *Cosme, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

Mycoclear *Zydus, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycocox *Cadila, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Mycocox-4 *Cadila, India.*
1 Tablet, ethambutol (p. 296·1); isoniazid (p. 311·2); 2 tablets, pyrazinamide (p. 345·2); 1 tablet, rifampicin (p. 350·3).
Tuberculosis.

Mycocox-E *Cadila, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Mycocox-Z *Cadila, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Mycocur
Note: this name may be used for preparations of different composition.
Nobel, Turk.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Mycoda *T Man, Thai.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Myco-Decidin *Teva, Cz.*
2-Aminotridecane undecenoate.
Fungal skin infections.

Mycodécyl *H2 Pharma, Fr.*
Cream: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

H2 Pharma, Fr.
Topical powder: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); calcium undecenoate (p. 596·3).
Fungal skin infections.

H2 Pharma, Fr.
Topical solution: Undecenoic acid (p. 596·3).
Fungal skin infections.

Mycodekan *Teva, Cz.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Mycoderm
Note: this name may be used for preparations of different composition.
Ego, Austral.; Ego, Malaysia.†
Salicylic acid (p. 1719·1); sodium propionate (p. 593·1); butyl hydroxybenzoate (p. 1757·1).
Fungal skin infections.

FDC, India.
Topical powder: Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); menthol (p. 2553·2).
Fungal skin infections; seborrhoeic dermatitis; hyperhidrosis; bromhidrosis.

FDC, India.
Cream: ⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Otto, Indon.
Ketoconazole (p. 585·3).
Fungal infections.

Ego, Hong Kong.†
Dusting powder: Salicylic acid (p. 1719·1); sodium propionate (p. 593·1).
Fungal skin infections.

Mycoderm-C *FDC, India; FDC, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycodib *Diba, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Mycodot-4 *Cadila, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Mycodot Kit *Cadila, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Mycodot-E *Cadila, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Mycodot-Z *Cadila, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Mycodril *BMW, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Mycodrox *DAST, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Mycofebrin *Coup, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Mycofem *Fem Care, India.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Mycofen
Note: this name may be used for preparations of different composition.
Nexus, Gr.
Mycophenolate mofetil (p. 1961·1).

Nycomed, Denm.
Ciclopirox (p. 575·3).
Fungal nail infections.

Mycofenor *Orion, Cz.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mycofentin *Elmor, Venez.*
Fenticonazole nitrate (p. 578·1).
Fungal skin, nail, and vaginal infections.

Mycofin *Nobel, Ukr.*
Terbinafine (p. 593·3) or terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Mycofit *Intas, India.*
Mycophenolic acid (p. 1961·1).
Transplant rejection.

Mycoflucan *Reddy, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Myco-flusemidon *Anfarm, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Mycofug *Almirall Hermal, Ger.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycogel *Biorga, Fr.†; Biorga, Hong Kong.†*
Copper pidolate (p. 1720·3); zinc pidolate (p. 1720·3); melaleuca oil (p. 2551·1).
Skin and scalp cleanser; skin and scalp disorders.

Mycogen ‖ *Goldline, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Skin disorders.

Myco-Hermal *Hermal, Israel; Hermal, Singapore.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycohexal *Hexal, S.Afr.†*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

MycoHydralin *Bayer, Fr.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Mycoket *Sintez, Rus.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Myco-L *Mediez, India.*
Vitamins; minerals; lycopene (p. 2546·2).

Mycol
Note: this name may be used for preparations of different composition.
Anglo-French Drugs, India.
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Greater Pharma, Thai.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

VHB, India.
Amphotericin B (p. 569·2).
Fungal infections.

Mycolacil *Frezyderm, Gr.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Mycolat *Rowex, Irl.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mycoldosa *Dosa, Arg.*
Mycophenolate mofetil (p. 1961·1).

Mycolog *Sanofi-Aventis, Belg.; Sanofi-Aventis, Neth.†*
⊗Triamcinolone acetonide (p. 1649·1); gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Mycolog N *Sanofi-Aventis, Switz.*
⊗Fluocinonide (p. 1636·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Mycolog-II *Westwood-Squibb, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Cutaneous candidiasis.

Mycomax *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.*
Fluconazole (p. 578·2).
Fungal infections.

Mycomycen *Verisfield, Gr.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal nail and vaginal infections.

Myconaf *Kocak, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Myconafin *1A, Austria.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Myconafine *PharmaSwiss, Hung.; Actavis, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Myconel *Marnel, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Skin disorders.

Myconex *Cadila, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Myconip *Uni-Sankyo, India.*
Lactobacillus sporogenes (p. 2596·3).
Vaginitis; leucorrhoea.

Myconip-C *Uni-Sankyo, India.*
Clotrimazole (p. 576·2); *Lactobacillus acidophilus* (p. 2596·3).

Myconor-4 *Psychotropics, India.*
Azithromycin (p. 221·2); fluconazole (p. 578·2); ornidazole (p. 943·1).

Myconorm
Note: this name may be used for preparations of different composition.
Psychotropics, India.
Tablets: Griseofulvin (p. 582·2).
Fungal hair, skin, and nail infections.

Psychotropics, India.
Topical powder: Chlorhexidine hydrochloride (p. 1743·3); clotrimazole (p. 576·2).

Ratiopharm, Ukr.†
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Myconorm-F *Psychotropics, India.*
Fluconazole (p. 578·2).
Fungal infections.

Myconormin *Hermal, Austria; Almirall Hermal, Ger.; Almirall, Switz.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail, scalp, and skin infections.

Myconova *Bionova, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Mycophen *Micro, India.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejections.

Mycopheno-cell *Cell Pharm, Ger.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mycopol *Nycomed, Austria.*
Undecenoic acid (p. 596·3); benzoic acid (p. 1738·2); isopropyl alcohol (p. 1758·3).
Fungal skin and nail infections.

Mycoral *Kalbe, Indon.; Kalbe, Singapore; T Man, Thai.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis; dandruff.

Mycoress *CCD, Fr.*
Sodium hyaluronate (p. 2526·2); burdock (p. 2540·1); *Lactobacillus crispatus*; *Lactobacillus reuteri* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Maintenance of vaginal flora.

Mycorest *Zydus, India; Zydus, S.Afr.; Wintac, Singapore.*
Fluconazole (p. 578·2).
Fungal infections.

Mycoril *Remedica, Hong Kong; Remedica, Singapore; Remedica, Thai.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Mycorine *Galenium, Indon.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mycosamthong *Sermmitr, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Mycosedermyl *Cooperation Pharmaceutique, Fr.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Myco-shampoo *T Man, Thai.*
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Mycosid *Meditop, Hung.*
Sodium parachlorobenzoate (p. 593·2); zinc oxide (p. 1729·1).
Fungal skin infections.

Mycosin *Prodotti, Braz.†*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mycosolon *Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.†*
⊗Mazipredone hydrochloride (p. 1642·2); miconazole (p. 588·3).
Fungal and Gram-positive bacterial skin and nail infections.

Richter, Pol.
⊗Mazipredone hydrochloride (p. 1642·2); miconazole nitrate (p. 589·1).
Fungal skin infections.

Mycosone-B *Utopian, Thai.*
⊗Betamethasone valerate (p. 1624·1); clotrimazole (p. 576·2).
Fungal skin infections.

Mycosoral *Akrikhin, Rus.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Mycospas *Macleods, India.*
Isoniazid (p. 311·2); sodium aminosalicylate (p. 215·2).
Tuberculosis.

Mycospor *Bayer, Austral.; Bayer, Braz.; Bayer, China; Bayer, Cz.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong†; Bayer, Hung.†; Bayer, India; Bayer Schering, Indon.; Bayer, Mex.; Bayer, Neth.; Bayer, Pol.; Bayer, Port.; Bayer, Rus.; Bayer Consumer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Turk.; Bayer, Ukr.; Bayer, Venez.*
Bifonazole (p. 573·3).
Fungal skin and nail infections; corynebacterial erythrasma; dandruff.

Bayer, Rus.; Bayer, Turk.
Ointment: ⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Mycospor Kit *Bayer, Ukr.†*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal skin and nail infections.

Mycospor Onicoset *Bayer, Mex.; Bayer, Spain; Bayer, Venez.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Mycospor Onycho-set *Bayer, S.Afr.†*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Mycospor Onychoset *Bayer, Pol.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Mycospor Sada na Nehty *Bayer, Cz.*
⊗Bifonazole (p. 573·3); urea (p. 1727·3).
Fungal nail infections.

Mycosporan *Bayer, Chile; Bayer, Swed.†*
Bifonazole (p. 573·3).
Fungal skin infections.

Mycosquam *Pierre Fabre, Fr.†*
Ciclopirox olamine (p. 575·3).
Scalp disorders.

Mycostar *Gentech, India.*
Citicoline (p. 2480·1).
Parkinsonism; cerebrovascular disorders; head injury.

Mycostat *Overseas, India.*
Ethambutol (p. 296·1).
Tuberculosis.

Mycostatin *BMS, Austral.; Dermapharm, Austria; Convatec, Canad.†; BMS, China; BMS, Denm.; BMS, Fin.; BMS, Gr.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong†; Sarabhai Piramal, India; Taisho, Indon.; BMS, Irl.; BMS, Ital.; BMS, Malaysia; BMS, Norw.; Healthcare Logistics, NZ; BMS, Philipp.†; BMS, Port.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Thai.†; BMS, USA.*
Nystatin (p. 590·3).
Candidiasis.

Mycostatine *BMS, Fr.; Sanofi-Aventis, Switz.*
Nystatin (p. 590·3).
Candidiasis.

Mycostatin-Zinkoxid *Dermapharm, Austria.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Candidiasis.

Mycosten *Pierre Fabre Dermo-Cosmetique, Arg.†; Pierre Fabre, Belg.*
Ciclopirox (p. 575·3).
Fungal skin and nail infections.

Pierre Fabre Dermatologie, Pol.
Ciclopirox olamine (p. 575·3).
Fungal and bacterial skin infections.

Mycoster *Pierre Fabre Dermatologie, Fr.; Pierre Fabre, Israel; Pierre Fabre Dermo-Cosmetique, Port.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal infections of the skin and nails.

Pierre Fabre, Switz.
Ciclopirox olamine (p. 575·3).
Fungal skin infections; seborrhoeic dermatitis.

Mycostop
Note: this name may be used for preparations of different composition.
Galenium, Indon.†
Griseofulvin (micronized) (p. 582·2).
Fungal infections of the skin, hair, and nails.

Marching, Hong Kong.†
Chlorphenamine (p. 620·3); tolnaftate (p. 596·1).

Mycosure *Lupin, India.*
Fluconazole (p. 578·2).
Fungal infections.

Mycosyl *ACME, Philipp.*
Nystatin (p. 590·3).
Oral candidiasis.

Myco-Synalar *Minerva (Μινερβα), Gr.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Mycosyst *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Polfa Grodzisk, Pol.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Fluconazole (p. 578·2).
Fungal infections.

Mycota
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, S.Afr.; Thornton & Ross, UK.
Cream; topical powder: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections; tinea pedis.

Thornton & Ross, UK.
Topical spray: Undecenoic acid (p. 596·3); dichlorophen (p. 152·3).
Tinea pedis.

Mycotel *SM, Thai.†*
Albendazole (p. 149·1).
Worm infections.

Mycoterb *Gerolymatos, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Mycothambin-INH *UAP, Indon.†*
Ethambutol (p. 296·1); isoniazid (p. 311·2). Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Mycotic *Pharma Synth, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).
Ear infections.

Mycotop *Solitaire, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Solitaire, India.
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mycotopic *Utopian, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycotrazol *Golenium, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Myco-Triacet II *Lemmon, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Skin disorders.

Mycotricide *SM, Thai.†*
Praziquantel (p. 164·1).
Trematode infections.

Mycotuf *Cadila, India.*
Ethionamide (p. 297·3).
Tuberculosis; leprosy.

Mycotuf P *Cadila, India.*
Protionamide (p. 345·1).
Tuberculosis.

Mycovin *Community Pharmacy, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Mycovit *Solitaire, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Mycovit-GB *Solitaire, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Mycovit-OD *Solitaire, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Mycoxyl *Bangkok Lab & Cosmetic, Thai.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Myco-Z *Taisho, Indon.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Fungal skin infections.

Mycozid *Soho, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Mycozole *Osoth, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Mycozole-B *Osoth, Thai.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2).
Fungal skin infections.

Mycurit-3 *Cadila, India.*
Ethambutol (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Mycurit-4 *Cadila, India.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Mycurit-Z *Cadila, India.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Mycurium *Taro, Israel.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Mycutol *Mediapharm, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Myda *T Man, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Myda-B *T Man, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone valerate (p. 1624·1).
Fungal skin infections.

Myderison *Meditop, Hung.†*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Mydeton *Gedeon Richter, Hung.*
Tolperisone hydrochloride (p. 2027·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Skeletal muscle spasm and spasticity.

Mydexin *Optaderm, Philipp.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Inflammatory eye disorders with infection.

Mydfrin *Alcon, Canad.; Alcon, Chile; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Philipp.; Alcon, Singapore†; Alcon, Turk.; Alcon, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis without cycloplegia; ophthalmic examination; uveitis; open-angle glaucoma.

Mydiatab *Hainan, Hong Kong.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mydic-MR *Solitaire, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Mydic-S *Solitaire, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Mydocalm *Wabosan, Austria; Gedeon Richter, Cz.; Strathmann, Ger.; Gedeon Richter, Hong Kong; Richter, Pol.; Gedeon Richter, Rus.; Labatec, Switz.; Gedeon Richter, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Skeletal muscle spasm; spasticity; movement disorders; obliterative vascular disorders; peripheral vascular disease.

Gedeon Richter, Ukr.
Tolperisone (p. 2027·3) or tolperisone hydrochloride (p. 2027·3).
Lidocaine hydrochloride is included in the intramuscular injection to alleviate the pain of injection.
Skeletal muscle spasm; spasticity; obliterative vascular disease.

Mydocalm-A *Chinoin, Mex.*
Tolperisone hydrochloride (p. 2027·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Mydolen *Miracalus, India.*
Lenalidomide (p. 816·1).

Mydono *Milano, Thai.†*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm and spasticity; obliterative vascular diseases.

Mydosone *Condrugs, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Mydral *Bausch & Lomb, USA.*
Tropicamide (p. 2012·2).
Production of cycloplegia and mydriasis.

Mydramide *Fischer, Israel.*
Tropicamide (p. 2012·2).
Production of mydriasis.

Mydriacil *Alcon, Irl.†; Alcon, Ukr.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Mydriacyl *Alcon, Austral.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Denm.; Alcon, Hong Kong; Alcon, Malaysia; Alcon, NZ; Alcon, Philipp.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore†; Alcon, Swed.; Alcon, Thai.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Mydriasert *Thea, Belg.; Thea, Denm.; Thea, Fin.; Thea, Fr.; Thea, Ger.; Zeiss Meditec, Ital.; Thea, Neth.; Thea, Port.; Thea, Spain; Thea, Swed.; Thea, Switz.; Spectrum, UK.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).
Production of mydriasis.

Mydriaticum *Agepha, Austria; Thea, Fr.; Stulln, Ger.; AdcockIngram, S.Afr.; OmniVision, Switz.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Mydril *Alcon, Arg.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Mydrilate *Intrapharm, Irl.; Intrapharm, UK.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Mydrin-M *Santen, China.*
Tropicamide (p. 2012·2).

Mydrin-P *Santen, China.*
Tropicamide (p. 2012·2); phenylephrine (p. 1672·2).

Santen, Hong Kong.
Tropicamide (p. 2012·2); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis and cycloplegia.

Mydrox
Note: this name may be used for preparations of different composition.
Solitaire, India.
Cefadroxil (p. 233·2).
Probenecid (p. 607·3) is included in this preparation to reduce renal tubular excretion of cefadroxil.
Bacterial infections.

Mydrum *Chauvin Ankerpharm, Cz.†; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.†; Bausch & Lomb, Rus.*
Tropicamide (p. 2012·2).
Production of cycloplegia and mydriasis.

Mydula *Gentech, India.*
Duloxetine.
Depression; diabetic neuropathy; stress urinary incontinence in women.

Myelobromol *Durbin, UK.*
Mitobronitol (p. 830·2).
Chronic myeloid leukaemia.

Myelogen *Panacea, India.*
Mecobalamin (p. 2108·1).
Vitamin B_{12} deficiency; peripheral neuropathy.

Myelostat *Zydus, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms; sickle-cell disease; essential thrombocythaemia.

Myelostim *Italfarmaco, Ital.*
Lenograstim (p. 1155·2).
Neutropenia induced by bone-marrow transplantation or cytotoxic chemotherapy; mobilisation of autologous peripheral blood progenitor cells.

Myestin *VHB, India.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis; paralytic ileus; postoperative urinary retention.

Myfenax
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Teva, Belg.; Teva, Cz.; Teva, Denm.; Teva, Gr.; Teva, Hung.; Teva, Irl.; Teva, Norw.; Teva, Pol.; Teva, Port.; Teva, Spain; Teva, Swed.; Teva, Ukr.
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Myfene *Mac, Gr.*
⊗Fentanyl (p. 60·1).
Pain.

Myferon *ME Pharmaceuticals, USA.*
Polysaccharide-iron complex (p. 2086·2).

Myfetil *Specifar, Gr.; Intas, Philipp.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Myfloxin *Greater Pharma, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Myfortic *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S. Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Mycophenolate sodium (p. 1961·2).
Transplant rejection.

Myfungar *Zentiva, Cz.; Taurus, Ger.†; Medihealth, Mex.; Zentiva, Rus.; Zentiva, Ukr.†*
Oxiconazole nitrate (p. 591·3).
Fungal and Gram-positive bacterial skin and vaginal infections.

Mygaba *Gentech, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Mygale compositum *Weleda, Austria.†*
Agaricus muscarius; stramonium herba (p. 2622·3); mygale avicularis.
Homoeopathic preparation.

Mygalin *Gentech, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Mygel *Geneva, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Mygenta *Elfin, India.*
Gentamicin (p. 304·2).
Bacterial infections.

Mygesal *Greater Pharma, Thai.*
Methyl salicylate (p. 92·1).
Musculoskeletal and joint pain; sprains; strains.

MyggA *Midsona, Swed.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

MyggA Natural *Midsona, Swed.*
Menthoglycol.
Insect repellent.

Myglo *Aarpik, India.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Aarpik, India.
Syrup: Vitamin B substances (p. 2102·3); ferrous gluconate (p. 2061·2).

Myglo-CS *Aarpik, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Myglyc *Pinewood, Irl.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Mygraft *Claris, India.*
Mycophenolic acid (p. 1961·1).
Transplant rejection.

MyGran
Note: this name may be used for preparations of different composition.
Arrow, NZ.
Sumatriptan succinate (p. 679·2).
Migraine.

Mygran
Note: this name may be used for preparations of different composition.
Ultramark, India.
Domperidone (p. 1838·1); flunarizine hydrochloride (p. 629·3); paracetamol (p. 115·1).

Mygref *Medis, Cz.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Mygrepam *Obolenskoe, Rus.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

MyHist-DM *Larken, USA.*
Dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

MyHist-PD *Larken, USA.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Myk *Jolly-Jatel, Fr.†*
Sulconazole nitrate (p. 593·3).
Fungal skin infections.

Myk-1 *Will-Pharma, Belg.; Will-Pharma, Neth.*
Sulconazole nitrate (p. 593·3).
Fungal skin infections.

Myko Cordes *Ichthyol, Austria†; Ichthyol, Ger.*
Clotrimazole (p. 576·2).
Fungal and corynebacterial skin infections.

Ichthyol, Austria.†
Paste: Clotrimazole (p. 576·2); zinc oxide (p. 1729·1).
Fungal skin infections.

Myko Cordes Plus *Ichthyol, Ger.*
Clotrimazole (p. 576·2); zinc oxide (p. 1729·1).
Fungal skin infections.

Mykoderm *Engelhard, Ger.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Mykoderm Heilsalbe *Engelhard, Ger.*
Nystatin (p. 590·3).
Fungal skin infections.

Mykoderm Mund-Gel *Engelhard, Ger.*
Miconazole (p. 588·3).
Fungal mouth infections.

Mykodermina *Pampa, Pol.*
Ointment; topical liquid: Undecenoic acid monoethanolamide (p. 596·3).
Fungal skin infections.

Pampa, Pol.
Topical powder: Undecenoic acid monoethanolamide (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Mykofungin *Riemser, Ger.*
Clotrimazole (p. 576·2).
Fungal and bacterial infections of skin and genito-urinary tract.

Mykohaug *Betapharm, Ger.*
Clotrimazole (p. 576·2).
Fungal and bacterial infections of skin and vagina.

Mykohexal *Hexal, Cz.*
Fluconazole (p. 578·2).
Fungal infections.

Mykontral *Riemser, Ger.*
Tioconazole (p. 595·3).
Fungal skin infections.

Mykoproct sine *Stegropharm, Ger.†*
⊗Nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections.

Mykoseptin *Zentiva, Cz.; Zentiva, Rus.; Zentiva, Ukr.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Mykosert *Pfleger, Ger.*
Sertaconazole (p. 593·2) or sertaconazole nitrate (p. 593·2).
Fungal skin infections.

Mykotin *Ardeypharm, Ger.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal skin and mouth infections.

Mykrox *Celltech, USA.*
⊗Metolazone (p. 1434·1).
Formerly known as Microx.
Hypertension.

Mykundex *Riemser, Ger.*
Nystatin (p. 590·3).
Fungal infections.

Mykundex Heilsalbe *Riemser, Ger.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Fungal skin infections.

Mykundex mono *Riemser, Ger.*
Nystatin (p. 590·3).
Fungal skin infections.

Mylagen *Goldline, USA.*
Capsules: Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Hyperacidity.

Goldline, USA.
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Mylan-Beclo *Mylan, Canad.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Mylan-Combo *Mylan, Canad.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).

Mylan-Eti-Cal *Mylan, Canad.*
14 Tablets, disodium etidronate (p. 1550·3); 76 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Mylan-Glybe *Mylan, Canad.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Mylan-Nitro *Mylan, Canad.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Mylanta
Note: this name may be used for preparations of different composition.
Elea, Arg.; Pfizer, Philipp.†
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; heartburn.

Johnson & Johnson, Austral.; McNeil Consumer, Canad.†; Johnson & Johnson, Chile; Pfizer, Indon.†; Johnson & Johnson, NZ; McNeil Consumer, USA.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; heartburn; flatulence; peptic ulcer; gastritis; hiatus hernia; gastric hyperacidity; gastro-oesophageal reflux.

Johnson & Johnson, China; J&J-Merck, USA.†
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; gastro-oesophageal reflux; heartburn; hyperacidity.

Mylanta II *Elea, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastrointestinal hyperacidity.

Mylanta de Bolso *Johnson & Johnson, Braz.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Mylanta DS *Johnson & Johnson, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Heartburn; dyspepsia; flatulence.

Mylanta Extra *Elea, Arg.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); famotidine (p. 1842·1).
Gastric hyperacidity.

Mylanta Gas *Elea, Arg.; McNeil Consumer, USA.*
Simeticone (p. 1886·2).
Gastrointestinal disorders with excess gas; flatulence.

Mylanta Gelcaps *J&J-Merck, USA.†*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Hyperacidity.

Mylanta Heartburn Relief *Pfizer Consumer, Austral.; Johnson & Johnson, NZ.*
Alginic acid (p. 2167·2); calcium carbonate (p. 1824·3); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); sodium bicarbonate (p. 1781·1).
Antacid; gastro-oesophageal reflux; dyspepsia.

Pfizer Consumer, Austral.
Tablets: Magaldrate (p. 1856·1); alginic acid (p. 2167·2); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux; dyspepsia.

Mylanta 12 Hour Action *Johnson & Johnson, Austral.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; heartburn.

Mylanta Max *Elea, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastrointestinal hyperacidity; flatulence.

Mylanta Plus
Note: this name may be used for preparations of different composition.
Elea, Arg.; Johnson & Johnson, Braz.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastrointestinal hyperacidity.

Mylanta Reflux *Elea, Arg.*
Oral liquid: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); calcium alginate (p. 1136·3); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1).
Gastric hyperacidity; gastro-oesophageal reflux.

Elea, Arg.
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); alginic acid (p. 2167·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Mylanta Rolltabs *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.*
Magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Dyspepsia; heartburn; antacid.

Mylanta Simple *Elea, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Mylanta Supreme *McNeil Consumer, USA.*
Magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Antacid.

Mylanta Ultimate Strength *McNeil Consumer, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Heartburn; dyspepsia.

Mylaquel *Generics, Denm.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Mylcer *Flexopharm, Irl.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Mylefan *Cadila, India.*
Busulfan (p. 754·3).
Bone marrow transplantation; chronic myeloid leukaemia; polycythaemia vera; essential thrombocythaemia.

Mylenamylan *Mylan, Belg.†*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Mylepsinum *AWD, Ger.*
Primidone (p. 547·1).
Epilepsy.

Myleran *GSK, Arg.; Aspen, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Triton, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; Aspen, Hong Kong; GSK, India; Aspen, Irl.; Perrigo, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; Aspen, Neth.; Healthcare Logistics, NZ; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; Aspen, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.*
Busulfan (p. 754·3).
Chronic myeloid leukaemia; polycythaemia vera; essential thrombocythaemia; myelofibrosis; haematopoietic stem-cell transplantation; thrombocytopenia.

Myléran *Genopharm, Fr.*
Busulfan (p. 754·3).
Chronic myeloid leukaemia; haematopoietic stem cell transplantation.

Myleuca *IPRAD, Fr.*
Melaleuca oil (p. 2551·1).
Skin cleansing; adjunct in fungal skin infections.

Myleugyn *IPRAD, Fr.*
Econazole nitrate (p. 577·3).
Vulvovaginal fungal infections.

Mylformet *Vale, Pol.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Mylicon *Janssen-Cilag, Braz.; McNeil, Denm.; Johnson & Johnson, Ital.; J&J-Merck, USA.*
Dimeticone (p. 1886·2).
Dyspepsia; flatulence; infant colic; aerophagia; adjunct in gastrointestinal investigations; meteorism.

Mylicongas *Johnson & Johnson, Ital.*
Simeticone (p. 1886·2).
Meteorism; aerophagia.

Myllacid *Novell, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence.

Myloc *Mylan, NZ.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; heart failure; arrhythmias; myocardial infarction; migraine; hyperthyroidism.

Mylocort *Aspen Consumer, S.Afr.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders; anogenital pruritus.

Mylom *Ranbaxy, Thai.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas.

Mylopram *Mylan, Denm.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Mylotarg *Wyeth, Arg.; IFET (ΙΦΕΤ), Gr.; Wyeth, Israel; Wyeth, Singapore†; Wyeth-Ayerst, USA†; Wyeth, Venez.*
Gemtuzumab ozogamicin (p. 802·2).
Acute myeloid leukaemia.

My-Marvel *Herbs & Nature, Philipp.*
Taheebo tree bark.
Nutritional supplement.

Mymin C *Greater Pharma, Thai.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Mymol *Burapha, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Mymox *Goldex, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Mynatal *ME Pharmaceuticals, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Mynate 90 Plus *ME Pharmaceuticals, USA.*
Vitamins; minerals.

Mynberrys Compound *Juggat, India.*
Creosote (p. 1659·3); ferrous gluconate (p. 2061·2); guaiacol (p. 1666·1); egg lecithin (p. 2542·2); liver extract (p. 2444·1).

Myneocin *Greater Pharma, Thai.*
Neomycin (p. 329·3).
Diarrhoea; gastrointestinal infections.

Myneuron *Indkus, India.*
Vitamin B substances (p. 2102·3).

Mynocine *Tonipharm, Fr.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Mynuron *Aglowmed, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Myo-24 *Wockhardt, India.*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Myoace *Merck, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Myobat *Interbat, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Myobid *Panacea, India; Panacea, Rus.*
Ethionamide (p. 297·3).
Tuberculosis; mycobacterial infections including tuberculosis and leprosy.

Myobloc
Note: this name may be used for preparations of different composition.
Genepharm, Gr.
Diacerein (p. 45·3).
Osteoarthritis.

Solstice, USA.
Botulinum B toxin (p. 2017·1).
It is also described as containing rimabotulinumtoxinB.
Spasmodic torticollis.

Myobolin *Troikaa, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Myocal *Remedina, Gr.*
Calcitonin (salmon) (p. 1178·1).

Myocalm *UCB, Jpn.*
Piracetam (p. 393·3).
Cortical myoclonus.

Myocard
Note: this name may be used for preparations of different composition.
Korea United, Philipp.
Dopamine hydrochloride (p. 1367·2).
Shock.

Teva, Denm.
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Myocardon mono *Altana, Austria.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure.

Myocet *Cephalon, Austria; Cephalon, Cz.; Elan, Irl.; Elan, Neth.; Cephalon, Port.; Teva, Spain; Teva, Swed.*
Liposomal doxorubicin citrate (p. 783·1).
Breast cancer.

Cephalon, Belg.; Sopherion, Canad.; Cephalon, Denm.; Zeneus, Fr.; Cephalon, Ger.; Cephalon, Gr.; Cephalon, Hung.; Medison, Israel; Cephalon, Ital.; Teva, Norw.; Cephalon, Pol.; Cephalon, UK.
Liposomal doxorubicin hydrochloride (p. 783·1).
Breast cancer.

Myocholine *Glenwood, Austria; Glenwood, Belg.; Glenwood, Ger.; Vifor, Switz.*
Bethanechol chloride (p. 2456·2).
Bladder disorders; urinary retention; bladder atony.

Myochrysine *Sanofi-Aventis, Canad.; Akorn, USA.†*
Sodium aurothiomalate (p. 130·2).
Rheumatoid arthritis; psoriatic arthritis; juvenile idiopathic arthritis.

MyoCIT *Citrage, Fr.*
L-Citrulline (p. 2056·3).
Dietary supplement.

Myocord *Ivax, Arg.*
⊗Atenolol (p. 1308·2).
Arrhythmias; hypertension; ischaemic heart disease.

Myocrisin *Sanofi-Aventis, Austral.; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.†; Sanofi-Aventis, NZ; Sanofi-Aventis, Swed.; Sanofi-Aventis, Thai.; JHC Healthcare, UK.*
Sodium aurothiomalate (p. 130·2).
Rheumatoid arthritis; juvenile idiopathic arthritis; Still's disease; psoriatic arthritis; lupus erythematosus.

Myodial *Beximco, Philipp.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Myodin *Kocak, Turk.*
Thiocolchicoside (p. 2026·2).

Myodipine *Help, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Myodrine *Deltapharm, Hong Kong†; Charoen, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Muscle pain; tension headache; rheumatism.

Myodura *Wockhardt, India.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Myofan *Emar, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Myofen *NuLife, India.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Myoflex
Note: this name may be used for preparations of different composition.
Bayer Consumer, Canad.; Armstrong, Mex.†; Novartis Consumer, USA.
Trolamine salicylate (p. 141·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Siam Bheasach, Thai.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal and joint pain; neuralgia.

Pharmacare, S.Afr.†
Paracetamol (p. 115·1); chlormezanone (p. 1045·1).
Pain and associated tension.

Myoflexin *Zentiva, Hung.*
Chlorzoxazone (p. 2022·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Myogard *RPG, India.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Myogit *Pfleger, Cz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation; pain.

Myograf *Bergamo, Braz.*
Filgrastim (p. 1151·3).

Myogrel-AP *Macleods, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thromboembolism prophylaxis.

Myokinase *Biocon, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Myolastan *Sanofi-Aventis, Austria†; Sanofi-Aventis, Belg.†; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Fr.†; Sanofi-Aventis, Pol.†; Sanofi-Aventis, Spain.†*
Tetrazepam (p. 1110·1).
Skeletal muscle spasm and spasticity.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Myolaxin *Geno, India.*
Camphor (p. 2466·2); capsicum (p. 2469·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Myolaxin-D *Geno, India.*
Camphor (p. 2466·2); capsaicin (p. 35·1); diclofenac diethylamine (p. 48·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Myolong *VHB, India.*
Milrinone lactate (p. 1438·1).
Heart failure.

Myoman *Metiska, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Myomergin *Ethica, Indon.*
Methylergometrine maleate (p. 2137·3).
Third-stage labour management; postpartum haemorrhage.

Myomethol *RX, Hong Kong; RX, Thai.†*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm; cramps.

Myometril *Oriental, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Myonac *M & H, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation.

Myonal
Note: this name may be used for preparations of different composition.
Eisai, China; Eisai, Indon.; Eisai, Ital.; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore; Eisai, Thai.
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm; spasticity; myotonias.

Uni-Sankyo, India.
Nimesulide (p. 101·3).
Pain.

Myonasan *Hanosan, Ger.*
Spigelia anthelmia (p. 2621·3); camphora (p. 2466·2); aurum chloratum (p. 2521·1); kalmia latifloria (p. 2537·2); veratrum album (p. 2644·3); arnica montana (p. 2447·2); melissa officinalis (p. 2552·3); cactus (p. 2473·2); strophanthus gratus (p. 1507·2); ignatia (p. 2532·1).
Homoeopathic preparation.

Myonep *Lapi, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Myonil *Ferrosan, Denm.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Myonit *Troikaa, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; hypertension and controlled hypotension during surgery.

Myo-Oil *Berko, Turk.*
Almond oil (p. 2437·1); lavender oil (p. 2541·1); chamomile oil (p. 2474·1); anise oil (p. 2444·3); orange oil (p. 2576·2); camphor (p. 2466·2); bitter apple oil.
Muscle spasm.

Myopa *Charoen, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle spasm and pain.

Myopam *MIP, Pol.†*
Tetrazepam (p. 1110·1).
Skeletal muscle spasm; spasticity.

Myopan *Servocare, India.*
Meropenem (p. 321·3).
Bacterial infections.

Myopas *T Man, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle spasm and pain.

Myophen *Charoen, Thai.†*
Carisoprodol (p. 2021·3); phenylbutazone (p. 125·1).
Musculoskeletal, joint, and peri-articular disorders.

Myoplège *Genevrier, Fr.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Myoplex *Metagenics, Canad.†*
Lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).

Myopril *Unique, Rus.†; Unique, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Myoprin *Biotech, S.Afr.*
Aspirin (p. 22·2).
Pain; fever; thromboembolism prophylaxis.

Myo-Pyrolate *Neon, India.*
Glycopyrronium bromide (p. 2519·3); neostigmine metilsulfate (p. 687·2).

Myoqinon *Pharma Nord, Hung.*
Ubidecarenone (p. 2637·1).
Coenzyme deficiency.

Myora *Bangkok Lab & Cosmetic, Thai.†*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Myorelex *Neon, India.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Myores *Meprofarm, Indon.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm.

Myori *Tempo Scan Pacific, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Myoril *Sanofi-Aventis, India.*
Thiocolchicoside (p. 2026·2).
Painful skeletal muscle spasm.

Myorisan *Versapharm, USA.*
Isotretinoin (p. 1706·2).
Acne.

Myosic *M & H, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain.

Myoskelet *Biomedica, Gr.*
Niflumic acid (p. 101·2).

Myoson *Strathmann, Ger.*
Pridinol mesilate (p. 2026·1).
Skeletal muscle spasm.

Myosotis Complexe No 63 *Lehning, Fr.†*
Myosotis; anemone pulsatilla (p. 2600·2); arsenicum iodatum (p. 2448·1); lycopodium (p. 2546·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Myospa *Hua, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain.

Myospasmal *TAD, Ger.†*
Tetrazepam (p. 1110·1).
Skeletal muscle tension and spasm.

Myospaz *Win-Medicare, India.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Pain; muscle spasm.

Myospaz Forte *Win-Medicare, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Pain; muscle spasm.

Myostigmin *Neon, India.*
Neostigmine metilsulfate (p. 687·2).
Myasthenia gravis; reversal of competitive neuromuscular blockade; paralytic ileus; postoperative urinary retention.

Myostin *Ivax, Irl.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Myotan *Unique, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Myotec *United Biotech, India.*
Mycophenolate mofetil (p. 1961·1) or mycophenolate sodium (p. 1961·2).
Transplant rejection.

Myotonachol *Glenwood, Canad.†; Glenwood, USA.*
Bethanechol chloride (p. 2456·2).
Urinary retention; neurogenic bladder; gastro-oesophageal reflux.

Myotonic *Meprofarm, Indon.†*
Methylergometrine maleate (p. 2137·3).
Uterine bleeding; third-stage labour management.

Myotonine *Glenwood, UK.*
Bethanechol chloride (p. 2456·2).
Gastro-oesophageal reflux; urinary retention.

Myovedon *Aurobindo, India.*
Trimetazidine (p. 1520·1).
Angina pectoris; Ménière's disease.

Myovek *Faran, Gr.*
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias.

Myoview *GE Healthcare, Austral.; GE Healthcare, Belg.†; GE Healthcare, Cz.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Irl.; GE Healthcare, Israel; GE Healthcare, Ital.; GE Healthcare, Neth.; GE Healthcare, Port.; GE Healthcare, Rus.; GE Healthcare, Spain; GE Healthcare, Switz.; GE Healthcare, UK.*
Technetium-99m tetrofosmin (p. 2228·1).
Myocardial perfusion imaging; breast imaging.

GE Healthcare, Denm.
Tetrofosmin.
For radiolabelling with technetium-99m.
Myocardial perfusion imaging; breast imaging.

Myovin *Cadila, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Myoviton
Note: this name may be used for preparations of different composition.
Pharos, Indon.
Pyridoxine hydrochloride (p. 2105·3); adenosine triphosphate, disodium salt (p. 2430·3).
Muscle weakness; myocardial disorders.

Myoxam *Menarini, Spain.*
Midecamycin acetate (p. 324·3).
Bacterial infections.

Myoxan *TO-Chemicals, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm; parkinsonism.

Myozar *Wockhardt, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Myozyme *Genzyme, Austria; Genzyme, Belg.; Genzyme, Braz.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Irl.; Genzyme, Israel; Genzyme, Ital.; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Norw.; Healthcare Logistics, NZ; Genzyme, Pol.; Genzyme, Port.; Genzyme, Spain; Genzyme, Swed.; Genzyme, Switz.; Genzyme, UK; Genzyme, USA.*
Alglucosidase alfa (p. 2428·1).
Pompe disease.

Mypaid *Adcock Ingram, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever; inflammation.

Mypara *Greater Pharma, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Mypara Plus *Greater Pharma, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Muscular pain; tension headache; rheumatism.

Myphetane DX *Morton Grove, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Mypred *Samarth, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Mypride *Meridian, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Myprodol *Adcock Ingram, S.Afr.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; inflammation; fever.

Myproflam *Adcock Ingram, S.Afr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders.

Myprox *Solitaire, India.*
Isoxsuprine (p. 2535·2).
Peripheral vascular disorders.

Myquine *Elfin, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Myra *Innovitelle, Philipp.*
Vitamin E (p. 2119·1).

Myra 300-E *Myra, Hong Kong.†*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Myrac *Glades, USA.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Myracof *Amherst, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Myracof-AF *General Drug, Philipp.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Myracof-T *General Drug, Philipp.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Myrafer *Myralis, Braz.*
Iron (p. 2073·1).

Myrafort F *Myralis, Braz.*
Vitamins.

Myrall *Stada, Hung.*
St John's wort (p. 449·1).
Depression.

Myralon *Organon, Turk.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Myramydez *Infamed, Ukr.*
Miramistin (p. 1761·2).
Otitis media; skin disinfection.

Myran *VHB, India; Korea United, Singapore.*
Busulfan (p. 754·3).
Chronic myeloid leukaemia; essential thrombocytopenia; polycythaemia vera; bone marrow transplantation; essential thrombocythaemia.

Myrazole-B *T Man, Thai.*
⊗Betamethasone valerate (p. 1624·1); clotrimazole (p. 576·2).
Infected skin disorders.

Myrbetriq *Astellas, USA.*
Mirabegron (p. 2360·3).
Bladder hyperactivity.

Myremol *Myrex Ethica, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Myrevit *Myrex Ethica, Philipp.*
Vitamins.
Dietary supplement.

Myrevit-C *Myrex Ethica, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Myriacyl *Alcon, Mex.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Myrin *Wyeth, Philipp.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Myrin-P *Wyeth, Philipp.; Wyeth-Ayerst, Thai.†*
Ethambutol hydrochloride (p. 296·1); rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Myrol *Polichem, Ital.*
Dihydroergocryptine mesilate (p. 390·2).
Dementia; vascular headache; parkinsonism; hyperprolactinaemia; lactation inhibition.

Myron *Alarsin, India.*
Malabar nut (p. 2549·1); commiphora wightii.

Myronin *Kyorin, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Myrox *Almet, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Myroxine *Sandoz, Gr.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Myrrhinil-Intest *Repha, Ger.*
Myrrh (p. 2566·1); carbo coffeae (p. 2648·2); chamomile (p. 2474·1).
Gastrointestinal disorders.

Myrtaven *IBSA, Switz.*
Myrtillus (p. 2566·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Myrtine *Lehning, Fr.*
Myrtle oil (p. 2566·3).
Respiratory-tract disorders.

Myrtoplex *Darou Pakhsh, Rus.*
Myrrh (p. 2566·1).
Herpes simplex infections of skin and mucous membranes.

Mysept *Panacea, Rus.*
Mycophenolate mofetil (p. 1961·1).
Renal transplant rejection.

Myser
Note: this name may be used for preparations of different composition.
Mitsubishi Tanabe, Jpn.
⊗Difluprednate (p. 1634·2).
Skin disorders.
Panacea, India.
Cycloserine (p. 280·2).
Tuberculosis.

Myset *Novogen, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Myskin *CellTran, UK.*
Bioengineered autologous human skin substitute (p. 1720·2).
Burns; diabetic foot ulcers; wounds.

Myslee *Astellas, Jpn.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Mysocort *Greater Pharma, Thai.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Mysoline *HLB, Arg.; Link, Austral.; Sanova, Austria; Fagron, Belg.; AstraZeneca, Braz.; SERB, Fr.; Cana, Gr.; IFET (ΙΦΕΤ), Gr.; Piramal, India; SERB, Irl.; SIT, Ital.; Columbia, Mex.; Fagron, Neth.; Azevedos, Port.; Pharmaplan, S.Afr.; AstraZeneca, Singapore; SERB, Spain; Proreo, Switz.; AstraZeneca, Turk.; SERB, UK†; Valeant, USA.*
Primidone (p. 547·1).
Epilepsy; essential tremor.

Mysolone-N *Greater Pharma, Thai.*
⊗Prednisolone (p. 1645·2); neomycin sulfate (p. 330·1).
Skin disorders; burns; wounds.

Mysoven *Greater Pharma, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Myspa *Greater Pharma, Thai.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm.

Myspec *Neon, India.*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea.

Mysteclin
Note: this name may be used for preparations of different composition.
Dermapharm, Austria; Dermapharm, Ger.
Tetracycline (p. 373·1); amphotericin B (p. 569·2).
Vaginal infections.

Mystika *Penn, Arg.*
Pregabalin (p. 545·3).

Mysulfan *Chandra Bhagat, India.*
Busulfan (p. 754·3).
Bone marrow transplantation; chronic myeloid leukaemia; polycythaemia vera; essential thrombocythaemia.

Mytaderm *GMP, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Skin disorders with bacterial infection.

Mytancid *Synco, Hong Kong†; Synco, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Flatulence; gastric hyperacidity.

Mytanyl *Lavipharm, Irl.*
⊗Fentanyl (p. 60·1).
Pain.

Mytax-O *Solitaire, India.*
Cefixime (p. 240·3).
Bacterial infections.

Mytedom *Cristalia, Braz.*
⊗Methadone hydrochloride (p. 88·3).

Mytel *Rhine, India.*
Telmisartan (p. 1509·3).
Hypertension.

Mytelase *Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Swed.; Sanofi-Aventis, USA.*
Ambenonium chloride (p. 684·3).
Myasthenia gravis; postoperative ileus; postoperative bladder atony.

Mytel-H *Rhine, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan (p. 1509·3).

Mythro *Biochemix, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Mythrocin *Farmamprant, Gr.; Esma, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Mytic *Venus, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Mytic 810 *Piam, Ital.*
Medium-chain triglycerides (p. 2082·2).
Obesity.

Myticef *Panacea, India.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Mytifer *Ethix, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc (p. 2126·1).

Mytimox *Panacea, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Mytob *H & Care, India.*
Tobramycin (p. 380·1).
Bacterial infections.

Mytobra *Elfin, India.*
Tobramycin (p. 380·1).
Bacterial infections.

Mytodex *Ashford, Philipp.*
⊗Tobramycin (p. 380·1); dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders with infection.

Mytoxid *Korea United, Philipp.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Mytra *Novagen, S.Afr.*
Mirtazapine (p. 436·1).

Mytrocin *Greater Pharma, Thai.*
Nitrofurazone (p. 333·1).
Bacterial skin, burn, and wound infections.

Mytusan DM *Am-Europharma, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Mytussin AC *Morton Grove, USA.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Mytussin DAC *Morton Grove, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Mytussin DM *Morton Grove, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Mytussin PE *Morton Grove, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Myval *Gerard, Irl.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

My-Vitalife *ME Pharmaceuticals, USA.*
Vitamins; minerals.

Myvlar *Berlis, Switz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Myxina *Norma (Νορμα), Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Myxofat *Riemser, Ger.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Myza *Esma, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Myzaar *Gerard, Irl.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Myzaar Comp *Gerard, Irl.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Myzar *Intas, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; stroke prophylaxis; diabetic nephropathy.

Myzer *Panacea, Rus.*
Cycloserine (p. 280·2).
Mycobacterial infections including tuberculosis.

Myzilra *Qualitest, USA.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Myzole *Admac, India.*
Fluconazole (p. 578·2).
Fungal infections.

MZ1 *Medix, Mex.*
⊗Mazindol (p. 2324·1).
Obesity.

M-Zavir *2M, Thai.*
Aciclovir (p. 964·1).
Herpes simplex skin infections.

M-Zole *Alpharma, USA.†*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

M-Zyme *Medizone, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

4-N-1 *DermaRite, USA.*
Dimeticone (p. 2209·3).

N B *Phapros, Indon.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Infected skin disorders.

N D Clear *Seatrace, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Na Chuan *Jiu Dian, China.*
Sumatriptan succinate (p. 679·2).
Migraine.

Na Ke Jia *Sheng Bao Kang, China.*
Nocardia rubra cell wall skeleton.

Na Ke Si *Saida, China.*
Tumour necrosis factor (human, recombinant) (p. 878·1).

Na De Lai *Hua Lu, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Na Neng *Double-Crane, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

NA Neurocard *Max Biocare, Austral.*
Fish oil (p. 1460·3); folic acid (p. 2063·1); magnesium oxide (p. 1857·3); calcium carbonate (p. 1824·3); bacopa (p. 2452·1).
Dietary supplement.

Na Nuo Ka *Sanjiu Aidefu, China.*
Calcium carbonate (p. 1824·3).

Na Pu Xing *Jin Yuan, China.*
Naproxen sodium (p. 98·2).

Na Qi *Pu Luo Kang Yu, China.*
Azithromycin sodium citrate.
Bacterial infections.

Na Le Shu *Lai Mei, China.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced sedation; opioid overdose.

Na Si Li Tuo *Jiang Kang, China.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Na Tuo *Meirui, China.*
Naftopidil (p. 2361·1).

Na Xin De *Qilu, China.*
Zidovudine (p. 1024·2).
HIV infection.

Na Xin Tong *Tailison, China.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Na Xun *Ya Bang Ai Pu Sen, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Na Zhi *ZhongNuo, China.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Naabak *Pfizer, Arg.; Allergan, Braz.; Thea, Fr.; Pfizer, Singapore; Thea, Switz.; Pfizer, Venez.*
Sodium isospaglumate (p. 2535·2).
Allergic conjunctivitis; allergic eye disorders.
Thea, Port.
Spaglumic acid (p. 2535·2).
Allergic conjunctivitis.

Naaxia *Allergan, Braz.; Pfizer, Chile†; Thea, Fr.; Thea, Ital.; Thea, Spain.*
Sodium isospaglumate (p. 2535·2).
Allergic conjunctivitis; blepharoconjunctivitis.
Thea, Hong Kong; Thea, Philipp.
Isospaglumic acid (p. 2535·2).
Allergic conjunctivitis.
Novartis, Gr.
Spaglumic acid (p. 2535·2); isospaglumate (p. 2535·2).
Allergic conjunctivitis.
Novartis, Hung.†; Novartis, Turk.
Sodium isospaglumate (p. 2535·2); sodium spaglumate (p. 2535·2).
Allergic conjunctivitis.

Naaxiafree *Thea, Fr.†*
Sodium isospaglumate (p. 2535·2).
Allergic conjunctivitis.

Nabal *Win-Medicare, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Nab-DT *Bennet, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Nabelon *Help, Gr.*
Ambroxol hydrochloride (p. 1654·3).

Nabesac *Masa, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain.

Nabian-K *Ultra, Mex.†*
Topiramate (p. 550·3).
Epilepsy; neuropathic pain; migraine.

Nabicortin *Help, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Nabigem *Microsules, Arg.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Nabi-HB *Biotest, USA.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Nabila *Raffo, Arg.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension.

Nabolin Dec *BMW, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nabone *TO-Chemicals, Thai.*
Nabumetone (p. 97·1).
Rheumatoid arthritis; osteoarthritis.

Nabonet *M & H, Thai.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Naborel *Elpen (Ελπεν), Gr.*
Nimodipine (p. 1455·2).
Prophylaxis and prevention of ischaemic neurological findings.

Nabratin *Raffo, Arg.*
Clopidogrel bisulfate (p. 1342·3).

Nabuco *Trima, Israel.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders.

Nabucox *Mayoly-Spindler, Fr.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders.

Nabuflam *Micro, India.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Nabuser *Geymonat, Ital.*
Nabumetone (p. 97·1).
Musculoskeletal, joint, and peri-articular disorders.

Nabuton *Medichrom, Gr.; ICN, Pol.*
Nabumetone (p. 97·1).
Pain; inflammation; musculoskeletal and joint disorders.

NAC
Note: this name may be used for preparations of different composition.
Sigma, Braz.; Aliud, Cz.; Ratiopharm, Ger.; Stada, Ger.; Aliud, Hung.†; Ratiopharm, Rus.; Temmler, Thai.; Basel, Turk.; Med, Turk.
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Nac
Note: this name may be used for preparations of different composition.
Klonal, Arg.
Piroxicam (p. 125·3).
Inflammation; pain.
Systopic, India.
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders.

Nac Gel *Systopic, India.*
Diclofenac diethylamine (p. 48·3).
Soft-tissue disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nac Plus *Systopic, India.*
Paracetamol (p. 115·1); diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Nacef *Abolmed, Rus.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Nacel *Celon, India.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Nacfil *Fourrts, India.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Nacku *Rishab, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Nacku-P *Rishab, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Naclens *Visiontec, Arg.*
⊗Subtilisin A (p. 2624·1).
Cleansing of contact lenses.

Naclex *Pharos, Indon.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Naclo *Natco, India.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Naclodin *Valmor, Venez.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Naclof *Thea, Neth.; Novartis, Pol.; Novartis, Rus.†; Novartis, Thai.†; Excelvision, Ukr.*
Diclofenac sodium (p. 48·3).
Eye inflammation and pain; inhibition of intra-operative miosis; prevention of cystoid macular oedema following eye surgery.

Naclomol *Yacca, India.*
Tablets: Diclofenac sodium (p. 48·3) or diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Yacca, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Naclomol-MR *Yacca, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Naclomol-S *Yacca, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Naclor *Claris, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).

Naclyte *Claris, India.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).

Nacmol Plus *Nestor, India.*
Benzyl alcohol (p. 1739·3); diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Nacoflar *Phapros, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Nacom *MSD, Ger.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Nacomic *Alpharma, Mex.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin and nail infections.

Nacon *Cypress, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1); hyoscine methonitrate (p. 1846·1).
Rhinitis.

Nacpo *Helax, India.*
Tablets: Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Helax, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Nacrez *Teva, Denm.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Nacro *Investigaciones Filosoficas y Cientificas, Mex.*
Nicotinamide (p. 2083·1).
Vitamin B_3 deficiency; neurodermatitis.

Nacser *Merion, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Nacser D *Merion, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Nactop *Apotex, Belg.*
Acetylcysteine (p. 1652·2).

Nad *Medical, Spain.†*
Nadide (p. 2567·1).
Vertigo.

Nadamen *Medochemie, Singapore.†*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nadem *Ivax, Arg.*
Aesculus (p. 2431·2).
Haemorrhoids; venous insufficiency.

Nadenel *Geminis, Arg.*
Clopidogrel (p. 1342·3).

Naderm *Cristalia, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Naderm RF *Piramal, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).

Nadetos *Raymos, Arg.*
Oxeladin citrate (p. 1671·2).
Cough.

Nadexen *Novartis, Gr.*
Pirisudanol maleate (p. 2592·2).

Nadibact *Cipla, India.*
Nadifloxacin (p. 328·1).
Bacterial skin infections.

Nadib-M *Diba, Mex.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Nadicin *Psyco Remedies, India.*
Nadifloxacin (p. 328·1).
Bacterial skin infections.

Nadicin-C *Psyco Remedies, India.*
⊗Clobetasol propionate (p. 1627·1); nadifloxacin (p. 328·1).
Infected skin disorders.

Nadiclopht *Konpharma, Ital.*
Diclofenac (p. 48·3).

Nadiclox *Medinfar, Port.*
Fusidic acid (p. 302·1) or sodium fusidate (p. 302·1).
Bacterial skin infections.

Nadiderm *Abbott, India.*
Nadifloxacin (p. 328·1).
Bacterial skin infections.

Nadifen *GMP, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation following cataract surgery.

Nadiflox *Cipla, India.*
Nadifloxacin (p. 328·1).
Bacterial infections.

Nadim *Hetero, India.*
Nadifloxacin (p. 328·1).
Bacterial skin infections.

Nadione *DMG, Ital.*
Bioflavonoids (p. 2505·2); vitamin C (p. 2110·3); phytomenadione (p. 2122·2).
Nutritional supplement.

Nadipinia *Cardinal, Hong Kong.*
Nifedipine (p. 1447·2).
Heart failure; hypertension.

Nadiskin *Hetero, India.*
Nadifloxacin (p. 328·1).
Bacterial skin infections.

Naditone *Kleva, Gr.*
Nabumetone (p. 97·1).
Pain; inflammation; musculoskeletal and joint disorders.

Nadix *Troikaa, India.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Nadixa *Pfleger, Ger.; Ferrer, Gr.; Geymonat, Ital.; Ferrer-Novag, Mex.; Ferrer, Port.; Ferrer, Spain; Adeka, Turk.*
Nadifloxacin (p. 328·1).
Acne.

Nadona *Medea, Spain.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Nadoxin *Wockhardt, India; Wockhardt, Philipp.; Wockhardt, Ukr.*
Nadifloxacin (p. 328·1).
Bacterial skin infections; acne; folliculitis.

Nadoxin-C *Wockhardt, India.*
⊗Clobetasol propionate (p. 1627·1); nadifloxacin (p. 328·1).
Infected skin disorders.

Nadrifor *Kleva, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Nadrohep *Gland, India.*
Nadroparin calcium (p. 1443·2).
Thromboembolic disorders; prevention of coagulation during haemodialysis; unstable angina.

Nadrone *Keshav, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nadryl *Riva, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Nadyak *Sanovel, Turk.*
⊗Sibutramine hydrochloride (p. 2330·2).

Naeltjie-Olie *Aspen Consumer, S.Afr.*
Clove oil (p. 2481·3).
Toothache; colic.

Naemis *Teva, Belg.; Merck Serono, Irl.†; Theramex, Ital.; Theramex, Mon.; Merck, Neth.†; Theramex, Port.*
10 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; nomegestrol acetate (p. 2294·1).
Menopausal disorders.

Naetene *Novartis, Braz.*
Vitamins; minerals.

Naf *Ordain, India.*
Sodium fluoride (p. 2089·2).

Naf Buches *Naf, Arg.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Nafacil *Tecnofarma, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Nafadren *Nafar, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Nafapin *Nafar, Mex.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Nafarin *Medifarma, Indon.†; UAP, Indon.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; nasal congestion; sinusitis; allergic disorders.

Nafarin A (Reformulated) *United American, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine (p. 620·3) or chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Nafartol *Nafar, Mex.*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Nafasol *Aspen, S.Afr.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Nafatab *Nafar, Mex.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Nafatosin *Nafar, Mex.*
Benzonatate (p. 1656·2).
Cough.

Nafavine *Roemmers Osmoph, Venez.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nafavir *GPO, Thai.*
Nelfinavir mesilate (p. 1004·1).
HIV infection.

Nafazol *Hemofarm, Rus.*
⊗Naphazoline (p. 1669·3).
Nasopharyngeal inflammation.

Nafazolex *Biosintex, Arg.*
⊗Naphazoline (p. 1669·3).
Nasal congestion.

Nafendol *Nafar, Mex.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal, joint, and soft-tissue disorders.

Nafin
Note: this name may be used for preparations of different composition.
Ranbaxy, S.Afr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Nafina *Giempi, Venez.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Nafiset *Pizzard, Mex.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; polydipsia; test of renal function; nocturnal enuresis.

Naflam *Collins, Mex.*
Nabumetone (p. 97·1).
Musculoskeletal, joint, and soft-tissue disorders.

Naflapen *Collins, Mex.†*
Naproxen (p. 98·2).
Inflammation; pain.

Naflax *Gold Coast, Philipp.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Naflex *Seven Stars, Thai.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Naflin *Globus, India.*
⊗Boric acid (p. 2459·3); chlorphenamine maleate (p. 620·3); hypromellose (p. 2189·2); naphazoline (p. 1669·3); zinc sulfate (p. 2126·2).

naFlora *Invida, Philipp.*
Lactic acid (p. 2539·1).
Vaginal irritation; maintenance of normal vaginal flora.

Naflox *Farmigea, Ital.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Nafloxin *Cooper (Κοπερ), Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Naflucen *Nafar, Mex.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Nafluryl *Atlantis, Mex.*
Flunarizine (p. 629·3).
Migraine; peripheral vascular disorders.

Nafluvent *Fada, Arg.*
⊗Fentanyl (p. 60·1).
Pain.

Nafordyl *Kleva, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Nafoxal *Sandoz, Indon.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders.

Nafpin *Nafar, Mex.*
Felodipine (p. 1380·3).

Nafrinse *Medical Products, Canad.†*
Sodium fluoride (p. 2089·2).

Naftate *Apex, Indon.†; Sunward, Singapore.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Naftazolina *Bruschettini, Ital.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye congestion; eye irritation; nasal congestion.

Naftex *Elvipe, Gr.*
Hyoscine hydrobromide (p. 1845·3).

Nafti *Ratiopharm, Ger.*
Naftidrofuryl oxalate (p. 1443·3).
Peripheral vascular disorders.

Naftilong *Hexal, Ger.†; Hexal, Hung.*
Naftidrofuryl oxalate (p. 1443·3).
Peripheral vascular disorders.

Naftilux *Therabel, Fr.*
Naftidrofuryl oxalate (p. 1443·3).
Mental function impairment in the elderly; peripheral vascular and cerebrovascular disorders.

Naftin *Allergan, Canad.†; Merz, USA.*
Naftifine hydrochloride (p. 590·1).
Fungal skin infections.

Nagel Batrafen *Sanofi-Aventis, Ger.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Nagelin *IAE, Philipp.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; nasal congestion; cold symptoms.

Naglazym *BioMarin, Rus.*
Galsulfase (p. 2509·1).
Mucopolysaccharidosis VI.

Naglazyme *LCA, Belg.; BioMarin, Cz.; BioMarin, Denm.; BioMarin, Fr.; BioMarin, Ger.; IFET (ΙΦΕΤ), Gr.; BioMarin, Irl.; Medison, Israel; BioMarin, Ital.; Stendhal, Mex.; BioMarin, Neth.; BioMarin, Pol.; BioMarin, Port.; BioMarin, Spain; BioMarin, Swed.; Drac, Switz.; BioMarin, USA.*
Galsulfase (p. 2509·1).
Mucopolysaccharidosis VI.

Nagun *Dosa, Arg.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Nai Di *Pu Luo Kang Yu, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nai De *San Ai, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Nai Bang *Ya Bang Ai Pu Sen, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Nai Er *Bai Yang, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Nai Ge *HuaXia, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Nai Kang *ZhenYuan, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nai Neng *Mei Da Kang Jia Le, China.*
Glucose (p. 2068·3); fructose (p. 2068·2).

Nai Ping *Hui Feng, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Nai Pu Tong *JiCheng, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Nai Te *Bai Yang, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nai Xing Long *Beisheng Hansheng, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nai Yi *Shenlong, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

NaiBang *Ya Bang Sheng Yuan, China.*
Ambroxol hydrochloride (p. 1654·3).

Naid *Winsome, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Naidi *Hisun, China.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Naid-P *Winsome, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Naidufuxing *Changzheng-Xinkai, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nail Nutrition *Cantassium Co., UK.*
Vitamins; minerals; amino acids.

Nailderm *Gerard, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

4 Nails *Marlyn, USA.*
Vitamins; minerals; amino acids.

Nails Hair and Skin *Blackmores, Austral.*
Silicon dioxide (p. 2208·3); equisetum (p. 2500·1); vitamins; minerals.
Dietary supplement.

NailVit *Pharmadass, UK.*
Vitamins; minerals; amino acids.

Nairet *Otto, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Najatox *Mekophar, Rus.*
Cobra venom; camphor (p. 2466·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Nakaron *Vamsler, Philipp.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); vitamin B_2 (p. 2104·3).
Iron-deficiency anaemia.

Naklofen *KRKA, Cz.; KRKA, Rus.; KRKA, Ukr.*
Diclofenac sodium (p. 48·3).
Pain; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

KRKA, Pol.
Diclofenac (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Naklofen Duo *KRKA, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; gout; fever.

Nakom *Lek, Cz.; Sandoz, Pol.; Lek, Rus.; Sandoz, Ukr.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Nakozap *AMPDR, Port.†*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Naksojin *Deva, Turk.*
Nimorazole (p. 942·1).
Vaginal trichomoniasis; giardiasis; amoebiasis; ulcerative gingivitis.

Nalabest *Best, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; ischaemic heart disease.

Nal-acid *Pharmanik (Φαρμανικ), Gr.*
Nalidixic acid (p. 328·3).
Genito-urinary tract infections.

Nalador *Bayer, Austria; Bayer, Fr.; Bayer, Ger.; Schering, Hong Kong†; Bayer Schering, Hung.; Bayer, Ital.; Bayer, Neth.; Bayer, Port.; Bayer, Switz.; Bayer, Thai.*
Sulprostone (p. 2145·3).
Termination of pregnancy; postpartum haemorrhage; facilitate intra-uterine manipulation; labour induction following fetal death.

Nalapres *Mediolanum, Ital.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nalapril *Klonal, Arg.*
Enalapril (p. 1371·1).
Hypertension.

Nalator *Plus, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Nalbix *Azevedos, Port.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Nalcrom *Sanofi-Aventis, Canad.; Italchimici, Cz.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Irl.; Italchimici, Ital.; Sanofi-Aventis, Neth.; Douglas, NZ; Rhone-Poulenc Rorer, Pol.†; Italchimici, Rus.; Proreo, Switz.; Sanofi-Aventis, UK.*
Sodium cromoglicate (p. 1225·3).
Food allergies; inflammatory bowel disease; hypersensitivity reactions.

Nalcryn *Cryopharma, Mex.*
Nalbuphine (p. 97·3).
Pain.

Naldec *IAE, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Naldecol *BMS, Chile.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms.

Naldecol Compuesto *BMS, Chile.†*
Tablets: ⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Naldecon
Note: this name may be used for preparations of different composition.
BMS, Braz.
Oral solution: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1).
Pain; fever; nasal congestion; cold symptoms.

BMS, Braz.
Tablets: Yellow tablets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); orange tablets, paracetamol; carbinoxamine maleate (p. 619·1).
Meridian, India.
⊗Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Naldecon Bebê *BMS, Braz.†*
Paracetamol (p. 115·1); carbinoxamine maleate (p. 619·1).

Naldecon Dia *BMS, Braz.*
Yellow tablets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); white tablets, paracetamol.
Cold symptoms.

Naldecon Noite *BMS, Braz.*
Yellow tablets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); orange tablets, paracetamol; carbinoxamine maleate (p. 619·1).
Cold symptoms.

Naldecon Senior EX *Sandoz, USA.*
Guaifenesin (p. 1666·2).
Coughs and cold symptoms.

NalDex *Blansett, USA.†*
Dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Nalecol *Casasco, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Nalergine *BMS, Pol.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Nalerona *Silesia, Chile.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol withdrawal syndrome; opioid withdrawal.

Naletal *Guardian, Indon.*
Cilostazol (p. 1337·1).
Arterial occlusion; intermittent claudication.

Nalex *Blansett, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

Nalex A C *Great Southern, USA.*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Nalex DH *Blansett, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3).

Nalex Expectorant *Blansett, USA.*
⊗Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Nalex-A *Blansett, USA.†*
Chlorphenamine maleate (p. 620·3); phenyltoloxamine citrate (p. 638·1); phenylephrine hydrochloride (p. 1672·3).

Nalex-A 12 *Blansett, USA.†*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Upper respiratory-tract disorders.

Nalfina *Cristalia, Braz.*
Nalbuphine hydrochloride (p. 97·3).

Nalfon *Xspire, USA.*
Fenoprofen calcium (p. 59·2).
Rheumatoid arthritis; osteoarthritis; pain.

Nalfrx *Blansett, USA.†*
⊗Dexchlorpheniramine tannate (p. 620·3); pseudoephedrine tannate (p. 1676·1); mepyramine tannate (p. 635·1).
Upper respiratory-tract disorders.

Nalgesic
Note: this name may be used for preparations of different composition.
Hexa, Arg.
Piroxicam (p. 125·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Nalgésic *Sciencex, Fr.*
Fenoprofen calcium (p. 59·2).
Pain.

Nalgesin
Note: this name may be used for preparations of different composition.
KRKA, Cz.; KRKA, Rus.; KRKA, Ukr.
Naproxen sodium (p. 98·2).
Gout; inflammation; pain; fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Suphong, Thai.
Mefenamic acid (p. 85·3).
Inflammation; pain.

Nalgestan *Medifarma, Indon.; UAP, Indon.*
Phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Nasal congestion; rhinitis; sinusitis; cold symptoms.

Nalgiflex *Ronnet, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Nalgiflex Relax *Ronnet, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Nalgin-P *PP Lab, Thai.*
Dipyrone (p. 53·3); lidocaine hydrochloride (p. 1988·2).
Pain.

Nalidin *TAD, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Nalidys *Biological E, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Naline
Note: this name may be used for preparations of different composition.
Biostan, India.
⊗Adrenaline (p. 1292·1).

Pharmaland, Thai.
Codergocrine mesilate (p. 389·2).
Cerebral and peripheral vascular disorders.

Nalion
Note: this name may be used for preparations of different composition.
Medochemie, Hong Kong.†
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Sandoz, Spain.†
Norfloxacin (p. 333·3).
Bacterial infections.

Nalisen *Cryopharma, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Nalix *Reuffer, Mex.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Nalixone *Sons, Mex.*
Nalidixic acid (p. 328·3); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections and pain.

Nalle *Nikkho, Braz.*
⊗Vitex agnus castus (p. 2432·2).
Menopausal disorders.

Nallian *Gedeon Richter, Denm.†; Gedeon Richter, Hung.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Nal-M *Madhav, India.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Nalol *Sunward, Singapore.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor; migraine.

Nalomet *Schering-Plough, Gr.*
Azatadine maleate (p. 616·3).

Nalomet-D *Schering-Plough, Gr.*
⊗Azatadine maleate (p. 616·3); pseudoephedrine sulfate (p. 1676·1).

Nalomin *Nafar, Mex.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Nalone
Note: this name may be used for preparations of different composition.
SERB, Fr.†
Naloxone hydrochloride (p. 1562·3).
Opioid-induced respiratory depression; diagnosis of toxic coma; opioid overdosage; diagnosis of opioid dependence.

Nalopril *Siam Bheasach, Thai.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Nalorex *BMS, Belg.; MSD-Chibret, Fr.†; Vianex (Βιανεξ), Gr.; BMS, Irl.; Molteni, Ital.; BMS, Neth.†; BMS, Port.†; BMS, UK.*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal; alcohol withdrawal.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nalox
Note: this name may be used for preparations of different composition.
Omega, Arg.
Metronidazole (p. 936·1).
Bacterial infections; trichomoniasis.

Samarth, India.
Naloxone (p. 1562·3).
Opioid overdosage; reversal of opioid depression.

Naloxon *Warsaw-Polfa, Rus.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression; diagnosis of opioid dependence.

Nalpain *Orpha-Devel, Denm.; Orpha-Devel, Fin.; Stragen, Ger.; Orpha-Devel, Port.; Vitaflo, Swed.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Nal-PM *Madhav, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Naltima *Intas, India.*
Naltrexone hydrochloride (p. 1565·1).
Opioid dependence.

Naltraccord *Arrow, NZ.*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal; alcohol withdrawal.

Naltrexin *Orpha-Devel, Austria†; OrPha, Switz.*
Naltrexone hydrochloride (p. 1565·1).
Opioid overdosage; opioid withdrawal.

Naltrox *Richmond, Arg.†*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Naluril *Cazi, Braz.*
Nalidixic acid (p. 328·3).
Bacterial infections.

Nalvir *Richmond, Arg.*
Nelfinavir (p. 1004·1).
HIV infection.

Nam *Lincoln, India.*
Tablets: Nimesulide (p. 101·3).
Pain.

Lincoln, India.
Topical gel: Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); nimesulide (p. 101·3).

Nam Cold *Lincoln, India.*
Oral drops; syrup: ⊗Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Lincoln, India.
Tablets: ⊗Cetirizine hydrochloride (p. 619·2); nimesulide (p. 101·3); pseudoephedrine hydrochloride (p. 1676·1).

Nam Cold Nasal *Lincoln, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nam Cold-L *Lincoln, India.*
⊗Levocetirizine (p. 632·3); nimesulide (p. 101·3); pseudoephedrine hydrochloride (p. 1676·1).

Nam Cold-NS *Lincoln, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nam Cold-SR *Lincoln, India.*
Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2); nimesulide (p. 101·3); phenylephrine hydrochloride (p. 1672·3).

Nam Cold-Z *Lincoln, India.*
⊗Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); zinc (p. 2126·1).

Nambrol *Baldacci, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; allergic rhinitis.

Namedia *Pharmasant, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Namenda *Forest Laboratories, USA.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Nametone *Pharmasant, Thai.*
Nabumetone (p. 97·1).
Rheumatoid arthritis; osteoarthritis.

Namgem *Dewcare, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Namic *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Mefenamic acid (p. 85·3).
Pain; fever.

Namifen *Novag, Mex.*
Mefenamic acid (p. 85·3).
Pain; peri-articular disorders.

Namir *Duncan, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Namitace *Farmaceutica H, Mex.*
Cetirizine (p. 619·2).

Namosid *Taj, India.*
Nimesulide (p. 101·3).
Pain.

Nam-P *Lincoln, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Namplus *Lincoln, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3).

Namsafe *Lincoln, India.*
Nimesulide (p. 101·3); DL-methionine (p. 1558·2).
Pain; inflammation.

Nan AL *Nestle, Malaysia.*
Infant feed.
Lactose intolerance; diarrhoea.

Nan AL 110 *Nestle, Singapore.*
Infant feed.
Lactose intolerance; diarrhoea.

Nan al 110 *Nestle, Thai.*
Infant feed.

Nan AR *Nestle, Arg.; Nestle, Braz.; Nestle, Mex.; Nestle, Venez.*
Infant feed.
Gastro-oesophageal reflux.

Nan Bo *Topfond, China.*
Imiquimod (p. 985·2).

Nan HA *Nestle, Arg.; Nestle, Hong Kong; Nestle, Malaysia; Nestle, Mex.; Nestle, Port.; Nestle, Singapore; Nestle, Thai.; Nestle, Venez.*
Infant feed.
Cows' milk allergy; soya allergy; allergic disorders; colic; regurgitation.

Nestle, Braz.; Nestle, Indon.
Hypoallergenic infant feed.

Nan HA with Protect Start *Nestle, Philipp.†*
Hypoallergenic infant feed.

Nan Lactose Free *Nestle, Indon.†; Nestle, Thai.†*
Infant feed.
Lactose intolerance; diarrhoea; infant colic.

Nan sem Lactose *Nestle, Braz.*
Infant feed.
Lactose intolerance.

Nan sin Lactosa *Nestle, Arg.; Nestle, Mex.; Nestle, Venez.*
Infant feed.
Lactose intolerance; diarrhoea; gastroenteritis.

Nan Soy *Nestle, Braz.; Nestle, Thai.†*
Infant feed.
Cow's milk intolerance; lactose intolerance; galactosaemia; diarrhoea.

Nan Soya *Nestle, Mex.; Nestle, Venez.*
Infant feed.
Lactose intolerance; gastroenteritis; diarrhoea; galactosaemia.

Nandodel *Ankom, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nandro *Nitin, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Unigen, Thai.
⊗Nandrolone decanoate (p. 2293·1).
Breast cancer in women; osteoporosis in men.

Nandrobol *Cadila, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nandrodec *Radicura, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nandrosande *Sanderson, Chile.†*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic.

Nandy *Siomond, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Naneson *Sano, Turk.*
Anise (p. 2444·2); menheae.
Gastrointestinal pain.

Nani Pre Dental *Alter, Spain.*
Benzocaine (p. 1980·2).
Toothache.

Naniprus *Sopharma, Rus.*
Sodium nitroprusside (p. 1497·1).
Hypertensive crisis; controlled hypotension; acute heart failure.

Nankair *PDC, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nano-Albumon *Medi-Radiopharma, Cz.*
Technetium-99m (p. 2228·1) labelled human albumin macroaggregate.
Imaging of bone marrow and lymphatic system.

Nanocef *Hauz, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Nanocis *CIS, Cz.; CIS, Port.*
Technetium-99m rhenium sulfide (p. 2228·1).
Imaging of the lymphatic system; gastro-oesophageal scintigraphy.

CIS, Fr.; CIS, Irl.
Rhenium-186 (p. 2227·2) colloidal sulfide.
Imaging of the lymphatic system; gastro-oesophageal scintigraphy.

Nanocoll *GE Healthcare, Belg.†; GE Healthcare, Cz.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Neth.; GE Healthcare, Port.; GE Healthcare, Spain; GE Healthcare, Switz.; GE Healthcare, UK.*
Technetium-99m (p. 2228·1) labelled albumin colloid.
Imaging of bone marrow and lymphatic system; scanning for abdominal inflammation.

GE Healthcare, Denm.; GE Healthcare, Ital.
⊗Albumin colloidal particles (p. 1130·2).
For radiolabelling with technetium-99m.
Radioimaging of bone marrow and lymphatic system.

Nanofix *Octapharma, Denm.; Octapharma, Irl.; Octapharma, Swed.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Nanogam *CAF-DCF, Belg.; Sanquin, Fin.; Sanquin, Irl.; Sanquin, Neth.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; passive immunisation; Kawasaki disease; Guillain-Barré syndrome; immunodeficiency; bone-marrow transplantation.

Nanotiv *Octapharma, Denm.†; Octapharma, Irl.†; Octapharma, Israel†; Octapharma, Neth.†; Octapharma, Norw.†; Octapharma, Port.; Octapharma, Spain†; Octapharma, Swed.†*
A factor IX preparation (p. 1149·3).
Haemophilia B; factor IX deficiency; haemorrhagic disorders.

Nanovert *Daffohils, India.*
Betahistine (p. 2455·3).
Ménière's disease.

NanoVM 1-3 Years *Solace, USA.*
Vitamins; minerals.
Dietary supplement.

NanoVM 4-8 Years *Solace, USA.*
Vitamins; minerals.
Dietary supplement.

Nanoxel *Dabur, India; Fresenius Kabi, Philipp.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Nansen *D&G, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Nantarid *Gedeon Richter, Cz.; Gedeon Richter, Denm.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; psychoses.

Nanyuan *Simcere, China.*
Ribavirin (p. 1010·2).
Viral respiratory-tract infections; herpesvirus skin infections.

Nanzon *JK Biochem, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nao Man Ning *Xiang Rui, China.*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Nao Rui An *Da Heng, China.*
Zolmitriptan (p. 682·2).
Migraine.

Nao Tai *Biochem, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Naofid *Velka, Gr.*
Nimesulide (p. 101·3).
Pain.

Naos *Mediolanum, Ital.*
⊗Salbutamol sulfate (p. 1220·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Naox *Eurofarma, Braz.*
Oxytocin (p. 2143·1).

Nap
Note: this name may be used for preparations of different composition.
Cubit, India.
Nimesulide (p. 101·3).
Pain.

Roomi, Philipp.
Zinc oxide (p. 1729·1); alpha-bisabolol (p. 2544·1); aloe vera (p. 1693·2).
Skin irritation; nappy rash; burns; abrasions.

Nap Plus *Cubit, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Napa *Beximco, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Napacod *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Napageln *Pfizer, Jpn.*
Felbinac (p. 58·3).
Musculoskeletal, joint, and peri-articular disorders.

Napalgin *Doctors, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Napamide *Ascent, Austral.; Niche, Irl.; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore; Douglas, Thai.*
⊗Indapamide (p. 1409·2).
Hypertension.

Napamol *AdcockIngram, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Napan *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Mefenamic acid (p. 85·3).
Pain; fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Napexar *RPG, India.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Napflam *Aspen, S.Afr.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; dysmenorrhoea; gout.

Napha A *CCM, Malaysia.*
⊗Antazoline phosphate (p. 615·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Napha Forte *Medical Ophthalmics, USA.*
⊗Naphazoline hydrochloride (p. 1669·3).

Naphacel *Sophia, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3); hypromellose (p. 2189·2).
Eye irritation.

Naphazoline Plus *Parmed, USA.†*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Minor eye irritation.

Naphcon *Alcon, Austral.; Alcon, Belg.; Pharmex (Φαρμεξ), Gr.; Alcon, NZ; Alcon, Thai.†; Alcon, USA; Alcon, Venez.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye congestion; eye irritation.

Naphcon Forte *Alcon, Canad.; Alcon, Israel.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation; conjunctivitis; eye congestion.

Naphcon-A *Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Hong Kong; Alcon, Indon.; Alcon, Malaysia; Alcon, NZ; Alcon, Philipp.; Alcon, Singapore; Alcon, Thai.; Alcon, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Allergic eye disorders; eye congestion or irritation.

Naphensyl *Adcock Ingram, S.Afr.*
Phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Naphoptic-A *Optopics, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye irritation.

Naphtears *Alcon, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); dextran 70 (p. 1138·3).
Eye disorders.

Alcon, Mex.
⊗Naphazoline hydrochloride (p. 1669·3); hypromellose (p. 2189·2) and dextran 70 (Duasorb) (p. 1138·3).
Allergic conjunctivitis; eye irritation; dry eyes.

Napi-D *Biomax, India.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Napiers Elixir of Echinacea Complex *Napiers, UK.*
Echinacea angustifolia (p. 2498·1); wild indigo (p. 2647·2); fumitory (p. 2508·2).
Cold and influenza symptoms; skin disorders.

Napiers Herbal Slimming Aid *Rickard Lanes, UK.*
Fucus vesiculosus; clivers (p. 2481·2).
Slimming aid.

Napiers Herbal Stress & Sleep Aid *Rickard Lanes, UK.*
Vervain (p. 2645·1); skullcap (p. 2617·1); passion flower (p. 2584·1); avena (p. 2451·1).
Anxiety; insomnia.

Napiers Oral Skin Soother Herbal Relief *Rickard Lanes, UK.*
Lappa (p. 2540·1); sarsaparilla (p. 2610·3); red clover (p. 2482·1); queen's delight; cascara (p. 1826·1); pokeroot (p. 2593·2); zanthoxylum americanum.
Skin irritation.

Napilene *Chinta, Thai.*
Benzalkonium chloride (p. 1737·1); cetrimide (p. 1742·1).
Napkin rash; minor burns and wounds.

Napitol *Carringtons, Singapore.*
Cetrimide (p. 1742·1); benzalkonium chloride (p. 1737·1).
Nappy rash; minor burns and wounds.

Napmel *PannonPharma, Hung.*
Naproxen (p. 98·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Napolit *Biomedica, Gr.*
⊗Carteolol (p. 1332·3).
Glaucoma.

Naponal *Munir, Turk.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Napoxen *Sel-J, Philipp.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Napoxol *Ultra, Mex.*
Naproxen (p. 98·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nappy Rash Relief Cream *Brauer, Austral.*
Calendula (p. 2465·2); clematis recta; St John's wort (p. 449·1); chamomile (p. 2474·1); mezereum.
Nappy rash.

Nappy-Hippo *Sriprasit, Thai.*
Zinc oxide (p. 1729·1).
Nappy rash.

Napradol *Fako, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Napran *Orchid, Philipp.*
Paracetamol (p. 115·1).
Pain.

Napratec *Pharmacia, UK.*
Naproxen (p. 98·2).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Napreben *Merqurio, Ital.*
Naproxen betainate sodium (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Naprelan *Sunovion, Canad.; Alkermes, Neth.†; OEP, Philipp.†; Victory, USA.*
Naproxen sodium (p. 98·2).
Pain; musculoskeletal, joint, and peri-articular disorders; gout; soft-tissue disorders.

Napren *Nycomed, Norw.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Sandoz, Turk.
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Naprex
Note: this name may be used for preparations of different composition.
Medifarma, Indon.; Pediatrica, Indon.; Pediatrica, Philipp.
Paracetamol (p. 115·1).
Fever; pain.

Naprilate *Taiwan Biotech, Philipp.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Naprilene *Sigma-Tau, Ital.; Sigma-Tau, Spain.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Napris *Symbiosis, India.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Naprius *Aesculapius, Ital.*
Naproxen (p. 98·2).
Pain; fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Naprix *Libbs, Braz.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; primary prophylaxis of atherosclerotic complications.

Naprix A *Libbs, Braz.*
Ramipril (p. 1483·3); amlodipine besilate (p. 1304·1).
Hypertension.

Naprix D *Libbs, Braz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Naprizide *Taro, Israel.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Naprobene *Ratiopharm, Austria.*
Naproxen (p. 98·2).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Naprobin *Miracalus, India.*
Fludarabine phosphate (p. 794·1).

Naprobleo *Miracalus, India.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Naprocap *Miracalus, India.*
Capecitabine (p. 757·3).
Malignant neoplasms.

Naprocet *Boniscontro & Gazzone, Ital.; Tecnifar, Port.*
Naproxen cetrimonium (p. 98·2).
Mouth and throat disorders; vaginal infections.

Naprodev *Deva, Turk.*
Naproxen (p. 98·2).
Musculoskeletal and joint pain.

Naprodex *Ilacsan, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; inflammation.

Naprodil *Diba, Mex.†*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Naprodil Plus *Diba, Mex.†*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Naprodom *Crescent, India.*
Domperidone (p. 1838·1); naproxen (p. 98·2).

Naprodox *Miracalus, India.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Naprofidex *Fidex, Arg.*
Naproxen (p. 98·2).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Naproflam *Socabom, Belg.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Naproflex *Pharmasant, Thai.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; inflammation; pain; fever.

Naprofos *Miracalus, India.*
Amifostine (p. 1539·2).
Reduction of toxicity due to cytotoxic therapy; radiotherapy-associated xerostomia.

Naprogen *Klonal, Arg.*
Naproxen (p. 98·2).
Fever; pain.

Naprogesic *Bayer Consumer, Austral.; Bayer, Chile; Bayer, NZ.*
Naproxen sodium (p. 98·2).
Fever; inflammation; pain; dysmenorrhoea.

Naprometin *Roche, Fin.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation; fever.

Napromex *Ratiopharm, Fin.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation; fever.

Napronax *Neo Quimica, Braz.*
Naproxen sodium (p. 98·2).
Pain; fever; inflammation.

Naprontag *AstraZeneca, Arg.*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Naprontag Flex *AstraZeneca, Arg.*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Musculoskeletal pain and spasm.

Napro-Pac *Abdi, Turk.*
Naproxen (p. 98·2).
Lansoprazole (p. 1851·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Naproplat *Miracalus, India; Naprod, Philipp.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Naprorex *Aegis, Hong Kong.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Naproscript *Pharmachem, S.Afr.; Ranbaxy, S.Afr.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Naprosian *Asian Pharm, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout.

Naprossene *EG, Ital.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Naprosyn *Roche, Austral.; Roche, Canad.; Minerva (Μινερβα), Gr.; Roche, Hong Kong†; Valeant, Hung.; RPG, India; Roche, Irl.; Recordati, Ital.; Roche, Norw.†; Roche, NZ; Roche, Philipp.; Roche, Port.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Thai.; Abdi, Turk.; Roche, UK; Roche, USA.*
Naproxen (p. 98·2).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; fever.

Bayer, Braz.
Naproxen sodium (p. 98·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Naprosyne *Roche, Belg.; Grunenthal, Fr.*
Naproxen (p. 98·2).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Naprotab *Sanli, Turk.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Napro-Tax *Miracalus, India; Naprod, Philipp.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Naprovite *Roche, Neth.†*
Naproxen sodium (p. 98·2).
Pain; fever; inflammation; musculoskeletal and joint disorders; gout.

Naprox *Teuto, Braz.*
Naproxen (p. 98·2).
Inflammation; pain.

Naproxi *Gerard, Israel.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Naprux *Andromaco, Arg.*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Naprux Disten *Andromaco, Arg.*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Musculoskeletal and joint disorders.

Napryn *Themis, India.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Napsen *Sriprasit, Thai.†*
Naproxen (p. 98·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Naptizer *Baroda, India.*
Cuminum cyminum; fennel (p. 2503·2); piper longum; tinospora cordifolia.

Napton *Bao Ling Fu Jin, China.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Napxen *APT, Hong Kong.†*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout.

Naqua
Note: this name may be used for preparations of different composition.
CNW, Hong Kong†; Bial, Port.†
⊗Furosemide (p. 1387·1).
Forced diuresis; nephrotic syndrome; oedema; renal failure; hypertension.

Naragran *GSK, Denm.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Naramerg *Teva, Irl.†*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Naramig *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; Paranova, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; UCB, Ger.; GSK, Gr.; GSK, Irl.; GSK, Israel; GSK, Mex.†; GSK, Neth.; GSK, Norw.; GSK, NZ; Glaxo Wellcome, Port.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Naranocor HM *Pfluger, Ger.*
Convalleria majalus (p. 2486·2); crataegus (p. 2488·1); iberis amara; kalmia latifolia (p. 2537·2); nitroglycerinum (p. 1391·2); selenicereus grandiflorus (p. 2473·2).
Homoeopathic preparation.

Naranofem *Pfluger, Ger.†*
Cimicifuga racemosa (p. 2478·1); potentilla anserina; hypericum perforatum (p. 449·1); caulophyllum thalictroides (p. 2458·2); chamaelirium luteum (p. 2524·3); anamirta cocculus (p. 2483·1).
Homoeopathic preparation.

Naranotox *Pfluger, Ger.*
Echinacea angustifolia (p. 2498·1); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Naranotox comp *Pfluger, Ger.*
Acid. silicicum (p. 2208·3); ferrum phosphoricum (p. 2077·1); calendula officinalis (p. 2465·2); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Narapril *Julphar, UAE.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Naratrex *Sun, India.*
Naratriptan (p. 677·3).
Migraine.

Naratrin *EMS, Braz.*
Naratriptan (p. 677·3).

Naraverg *Teva, Irl.*
Naratriptan hydrochloride (p. 677·3).
Migraine.

Naraya *Temapharm, Pol.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Narbel *Nitto, Jpn.*
⊗Tetryzoline nitrate (p. 1678·3).
Nasal congestion; eye congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Narbon *Buxton, Arg.*
Hydroxychloroquine sulfate (p. 655·2).
Malaria; rheumatoid arthritis; juvenile idiopathic arthritis; lupus erythematosus; porphyria cutanea tarda; sun-induced skin disorders; amoebiasis.

Narcan *Reckitt Benckiser, Austral.†; Cristalia, Braz.; SERB, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; BMS, Irl.†; Sirton, Ital.; AFT, NZ; Sanofi-Aventis, S.Afr.; BMS, Singapore; BMS, Thai.; BMS, Venez.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression; diagnosis of toxic coma; diagnosis of opioid dependence.

Narcanti *AstraZeneca, Arg.†*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression.

Narcaricin *Rotam Reddy, China.*
Benzbromarone (p. 603·3).
Hyperuricaemia; gout.

Narcaricina *Evolabis, Braz.*
Benzbromarone (p. 603·3).
Gout; hyperuricaemia.

Narcodon *Adipharm, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Noradrenaline acid tartrate (p. 1458·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.

Narcof *Cypress, USA.*
Guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Cough.

Narcoral *Sirton, China; Sirton, Ital.*
Naltrexone hydrochloride (p. 1565·1).
Opioid dependence; alcohol dependence; opioid overdosage; opioid withdrawal.

Narcotan
Note: this name may be used for preparations of different composition.
Zentiva, Cz.†; Zentiva, Hung.†; Zentiva, Pol.†; Leciva, Rus.
Halothane (p. 1902·1).
General anaesthesia.

Troikaa, India; Troikaa, Philipp.
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression.

Narcotest *ID Pharma, Fr.*
Range of tests for detection of drugs in urine, saliva, or sweat.

Narcotuss *Legrand, Braz.*
Guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Respiratory-tract disorders.

Narcozep *Roche, Fr.*
Flunitrazepam (p. 1073·3).
Premedication; general anaesthesia.

Nardelzine *Pfizer, Belg.*
Phenelzine sulfate (p. 442·1).
Depression.

Nardil *Link, Austral.; Erfa, Canad.; Hansam, Irl.†; Link, NZ; Archimedes, UK; Parke, Davis, USA.*
Phenelzine sulfate (p. 442·1).
Depression; mixed anxiety depressive states; phobic states.

Nardyl Sommeil *Vifor, Switz.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Narebox *Zydus, India.*
Reboxetine (p. 447·1).
Depression.

Nareel *Heel, Canad.†*
Ammonium carbonate (p. 1656·1); calcium sulfide crude (p. 1721·3); cistus canadensis; common arum; euphorbium officinarum; hydrastis canadensis (p. 2528·1); lemna minor; melilot (p. 2552·3); periwinkle; phosphorus (p. 2589·2); potassium dichromate (p. 2476·3); sticta pulmonaria (p. 2546·1); veronica officinalis.
Homoeopathic preparation.

Narfen *Alter, Spain.†*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal, joint, and peri-articular disorders.

Narfoz *Pharos, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Narhinel *Novartis Consumer, Ital.*
Sodium chloride (p. 1795·1).
Nasal hygiene.

Narhinel Balsamico Adulti *Novartis Consumer, Ital.*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2); menthol (p. 2553·2).
Nasal congestion.

Narhinel Balsamico Bambini *Novartis Consumer, Ital.*
Eucalyptus oil (p. 2501·2); Scots pine oil (p. 2591·2); lavender oil (p. 2541·1).
Nasal congestion.

Naricin
Note: this name may be used for preparations of different composition.
Inpac, Thai.
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders; Ménière's disease.

Naridrin *EMS, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); mepyramine maleate (p. 635·1); dexpanthenol (p. 2582·2).
Nasal congestion.

Naridrin Bebe *EMS, Braz.*
Sodium chloride (p. 1795·1).

Naridrin H *EMS, Braz.*
Sodium chloride (p. 1795·1).

Nariflux *Cifarma, Braz.*
⊗Dexpanthenol (p. 2582·2); naphazoline hydrochloride (p. 1669·3); mepyramine maleate (p. 635·1).
Nasal congestion.

Narifont *Rappai, Switz.*
Electrolytes (p. 1775·1).
Nasal dryness; nasal irrigation.

Narifresh *Rappai, Switz.*
Sea salt (p. 2612·1); chamomile (p. 2474·1).
Nasal disorders.

Narigen *Vocate, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Narimed *Regiomedica, Neth.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Narine *MSD, Spain.*
⊗Pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Allergic rhinitis.

Narish *Symbiosis, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Narisoro *Legrand, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Naristar *UCB, Ital.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; conjunctivitis.

Naritec *TO-Chemicals, Thai.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Narium *Hamilton, Austral.; Hamilton, NZ.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal irritation and inflammation.

Narix *Cimed, Braz.*
⊗Naphazoline (p. 1669·3).
Nasal congestion.

Narixan *Wasserm̈ann, Ital.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; upper respiratory-tract congestion.

Nariz
Note: this name may be used for preparations of different composition.
Cadila, India.
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Tempo Scan Pacific, Indon.
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness.

Hawthorn, USA.†
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Nariz HC *Hawthorn, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); hydrocodone tartrate (p. 67·2).
Cough.

Narizima *Baldacci, Port.*
Muramidase hydrochloride (p. 2565·1); thonzylamine hydrochloride (p. 642·1); isobenzidrine iodide.
Rhinitis; sinusitis.

Narizine
Note: this name may be used for preparations of different composition.
BMW, India; Beacons, Singapore.
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders; vertigo.

Charoon Bhesaj, Thai.
Cinnarizine (p. 622·1).
Vertigo; cerebral and peripheral vascular disorders; migraine; motion sickness.

Narkamon *VUAB, Cz.*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia; pain; bronchospasm.

Narlecin *Mersifarma, Indon.*
Erythromycin (p. 291·2).
Bacterial infections.

Narlisim *Baldacci, Ital.*
Muramidase hydrochloride (p. 2565·1); phenolpropamine iodide; thonzylamine hydrochloride (p. 642·1).
Nasal congestion.

Narlox *Duopharma, Philipp.*
Naloxone hydrochloride (p. 1562·3).
Diagnosis of opioid overdosage; reversal of opioid depression.

Narmo *Kevin, India.*
Paracetamol (p. 115·1).
Pain; fever.

Narobic *Thebe, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Narocin *Teva, Israel.*
Naproxen sodium (p. 98·2).
Fever; musculoskeletal and joint disorders; pain.

Narol
Note: this name may be used for preparations of different composition.
Minerva (Μινερβα), Gr.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Narop *AstraZeneca, Swed.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

Naropeine *AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Port.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

Naropin *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, China; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; Rimsa, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; APP, USA.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia; pain.

Naropin with Fentanyl *AstraZeneca, Austral.; AstraZeneca, NZ.*
⊗Ropivacaine hydrochloride (p. 1996·1); fentanyl citrate (p. 60·1).
Epidural analgesia.

Naropina *AstraZeneca, Ital.*
Ropivacaine hydrochloride (p. 1996·1).
Epidural anaesthesia; local anaesthesia; pain.

Narpan *CCM, Malaysia.*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal.

Nartap *Condrugs, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion; cold symptoms; rhinitis.

Naruyd *Gedeon Richter, Cz.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Narva *Gedeon Richter, Hung.*
⊗Indapamide (p. 1409·2).
Hypertension.

Narvin *TO-Chemicals, Thai.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Narvox *Vindex, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Narxona *Scott-Cassara, Arg.*
Naloxone (p. 1562·3).

Narzine *Psyco Remedies, India.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Nas *Oftalmi, Venez.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Nasa *Millimed, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Nasa Rhinathiol *Sanofi-Aventis, Belg.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasa W/ Codeine *Millimed, Thai.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Nasabid *Jones, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Nasal congestion; cough.

Nasaclear *Pacific, NZ.†*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Nasacor *Sanofi-Aventis, S.Afr.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Nasacort *Sanofi-Aventis, Arg.; Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Nasacort AQ *Sanofi-Aventis, Malaysia.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Nasadec *Medlink, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion; sinusitis.

Nasadur *Premier Research, Neth.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasafed *Medikon, Indon.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; sinusitis; allergic disorders.

Nasafed Plus *Medikon, Indon.†*
⊗Triprolidine (p. 642·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Cold and influenza symptoms; sinusitis; nasopharyngitis.

Nasaflam *Fahrenheit, Indon.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal and joint disorders; inflammation; pain.

Nasagesic *More, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Nasair *Oftalmi, Venez.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

NaSal *Bayer, USA.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nasal Decongestant *Confab, Canad.*
⊗Xylometazoline hydrochloride (p. 1680·1).

Nasal Jelly
Note: this name may be used for preparations of different composition.
Kondon, USA.
Phenol (p. 1763·3); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1).
Nasal congestion.

Nasal Moist *Blairex, USA.*
Sodium chloride (p. 1795·1).
Inflammation and dryness of nasal membranes.

Nasal Physiological Solution *Confab, Hong Kong.*
Sodium chloride (p. 1795·1).
Nasal hygiene.

Nasal Relief *Rugby, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nasal & Sinus Cold Formula *Vita Health, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Nasal Spray *Reese, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).

Nasalate *Paedpharm, Austral.*
Chlorhexidine gluconate (p. 1743·3); phenylephrine hydrochloride (p. 1672·3).
Nasal vestibulitis; nasal surgery.

Nasalcrom *Medtech, USA.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Nasal-Ease *Health Care Products, USA.*
Nasal gel: Zinc acetate (p. 2126·1); aloe vera (p. 1693·2); calendula (p. 2465·2).
Inflammation and dryness of nasal membranes.

Health Care Products, USA.
Nasal spray: Zinc gluconate (p. 2126·2); sodium chloride (p. 1795·1).
Inflammation and dryness of nasal membranes.

Nasalex *Fabop, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Nasaleze *Mantecorp, Braz.*
Cellulose (p. 2177·2).

Nasalide *Teva, Fr.†*
⊗Flunisolide (p. 1635·3).
Allergic rhinitis.

Nasaliv *Uniao Quimica, Braz.*
Oral solution: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1).
Influenza symptoms.

Uniao Quimica, Braz.
Tablets: Yellow tablets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); orange tablets, paracetamol; carbinoxamine maleate (p. 619·1).
Influenza symptoms.

Nasalong *Mikrofarm, Ukr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; otitis media; aid in rhinoscopy and nasal procedures.

Nasalt *Greenco, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nasaltropfen axcount *Axcount, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasalub *Quimica y Farmacia, Mex.*
⊗Sodium chloride (p. 1795·1); glycerol (p. 2517·2).
Nasal dryness.

Nasamet *Verisfield, Gr.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis.

Nasamex *Konimex, Indon.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; sinusitis.

Nasamol *Nicholas, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Nasan *Sandoz, Hung.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis.

Nasanal *Brady, Austria.*
Aluminium acetotartrate (p. 2440·1); pumilio pine oil (p. 2591·1).
Nasal disorders.

Nasaphen *Prohealth, Philipp.†*
Phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Nasarel
Note: this name may be used for preparations of different composition.
Dabur, India.
⊗Nafarelin acetate (p. 2292·2).
Endometriosis; pituitary desensitisation in controlled ovarian stimulation; precocious puberty.

Ivax, USA.
⊗Flunisolide (p. 1635·3).
Rhinitis.

Nasarox *Plough, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nasasinutab *McNeil, Belg.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasatab LA *ECR, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Nasatapp *Prohealth, Philipp.*
Brompheniramine maleate (p. 618·1); phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Nasathera *Morishita, Philipp.*
Paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1) or phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion; cold and influenza symptoms.

Nasathera CPM *Morishita, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; sinusitis; rhinitis.

Nasathera P *Morishita, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Nasatrim *Verisfield, Gr.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Nasben *Vifor, Switz.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasciodine *Pharmadass, UK.*
Iodine (p. 2336·3); menthol (p. 2553·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); rectified camphor oil (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders.

Nascobal *Par, USA.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Nasea *Astellas, China; Astellas, Indon.; Astellas, Jpn; Astellas, Philipp.; Astellas, Thai.*
Ramosetron hydrochloride (p. 1881·3).
Nausea and vomiting associated with cancer chemotherapy; postoperative nausea and vomiting.

Nased *VS, Thai.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Naselin *Cipla, India.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nasen *Polfarmex, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Nasengel *Ratiopharm, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis; catarrh.

Nasengel AL *Aliud, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; catarrh.

Nasenöl *Weleda, Austria.*
Calendulae (p. 2465·2); hydrargyrum sulfuratum rubrum (p. 2555·3); matricariae (p. 2474·1); camphora (p. 2466·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Rhinitis; nasal dryness and crusting.

Nasenspray *Ratiopharm, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; catarrh; rhinitis; sinusitis.

Nasenspray AL *Aliud, Cz.; Aliud, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; catarrh.

Nasenspray E *Hexal, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasenspray K *Hexal, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

NasenSpray Panthenol *Ratiopharm, Ger.*
Dexpanthenol (p. 2582·2).
Nasal congestion.

Nasentropfen AL *Aliud, Cz.†; Aliud, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; catarrh.

Nasentropfen Stada *Stada, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasentropfen-ratiopharm
Note: this name may be used for preparations of different composition.
Ratiopharm, Ger.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Naseptin *Alliance, Irl.; Glenmark, S.Afr.; Alliance, UK.*
Chlorhexidine hydrochloride (p. 1743·3); neomycin sulfate (p. 330·1).
Nasal carriage of staphylococci.

Naset *Esoform, Ital.*
Sodium chloride (p. 1795·1); sodium hyaluronate (p. 2526·2).
Nasal dryness; nasal hygiene.

Nasex
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Port.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Felton, Austral.†
⊗Oxymetazoline hydrochloride (p. 1671·3); cineole (p. 2479·1); menthol (p. 2553·2).
Nasal congestion.

Nasiben *Merck, Austria.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis.

Nasic *Klosterfrau, Austria; Cassella-med, Cz.; Artesan, Ger.; Cassella-med, Ger.; Melisana, Switz.*
⊗Xylometazoline hydrochloride (p. 1680·1); dexpanthenol (p. 2582·2).
Nasal congestion; rhinitis.

Nasic-cur *Artesan, Ger.; Cassella-med, Ger.*
Dexpanthenol (p. 2582·2).
Rhinitis sicca.

Nasifed *Burapha, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis; cold and influenza symptoms.

Nasilex *Lafi, Chile.*
⊗Pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; hypersensitivity reactions.

Nasin
Note: this name may be used for preparations of different composition.
GSK Consumer, Swed.; Leti, Venez.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; nasal congestion.

Medicpharma, Thai.
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Nasiral *Istanbul, Turk.*
Salicylic acid (p. 1719·1).
Calluses.

Nasivin
Note: this name may be used for preparations of different composition.
Merck, Austria; Merck, Braz.; Merck, Cz.; Merck, Ger.; Merck, Hung.; Merck, Israel; Sato, Jpn; Merck, Neth.; Merck, Philipp.; Merck, Pol.; Nycomed, Rus.; Julphar, UAE; Seven Seas, UK; Merck, Ukr.; Takeda, Ukr.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; otitis media; rhinitis; sinusitis; catarrh; Eustachian tube congestion; ocular congestion.

Merck, Chile.
⊗Sodium chloride (p. 1795·1); glycerol (p. 2517·2).
Nasal hygiene; nasal congestion.

Nasivin Sanft *Merck, Ger.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Catarrh; nasal congestion; rhinitis; sinusitis; otitis media.

Nasivin Zink *Merck, Ger.†*
⊗Oxymetazoline hydrochloride (p. 1671·3); zinc gluconate (p. 2126·2).
Rhinitis; sinusitis; catarrh.

Nasivine *Iromedica, Switz.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; catarrh.

Nasivion *Merck, India.*
⊗Oxymetazoline (p. 1671·3) or oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nasivion-S *Merck, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nasmer free *Vifor, Switz.*
Dead Sea salt (p. 2612·1); dexpanthenol (p. 2582·2); sodium hyaluronate (p. 2526·2); eucalyptus oil (p. 2501·2); neroli oil (p. 2568·3); peppermint oil (p. 1877·1); pine oil (p. 2591·1); thyme oil (p. 2630·3).
Nasal dryness; nasal congestion.

Nasmer 3plus *Vifor, Switz.*
Dead Sea salt (p. 2612·1); dexpanthenol (p. 2582·2); sodium hyaluronate (p. 2526·2).
Nasal dryness; nasal congestion.

Naso
Note: this name may be used for preparations of different composition.
Ratiopharm, Norw.
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis.

T Man, Thai.
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Naso Pekamin *Medical, Spain.†*
⊗Phenylephrine hydrochloride (p. 1672·3); kanamycin sulfate (p. 314·3); trypsin (p. 2635·2).
Nose and throat disorders.

Naso Wikoryl *Alembic, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Nasobec *Teva, Cz.; Teva, Hong Kong; Norton Waterford, Irl.; Norton, Pol.†; Teva, Rus.; Ivax, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Nasobol Inhalo *Sanofi, Switz.*
Cineole (p. 2479·1); menthol (p. 2553·2); rosemary oil (p. 2607·3); thyme oil (p. 2630·3).
Respiratory-tract disorders.

Nasobol Xylo *Sanofi, Switz.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis.

Nasocare Plus *Glenmark, India.*
Syrup: ⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Glenmark, India.
Tablets: ⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Nasoclean *Terme di Tabiano, Ital.*
Thermal water.
Nasal cleansing.

Nasoclear *Zydus, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nasoclear Aloegel *Zydus, India.*
Aloe vera (p. 1693·2); geranium oil (p. 2512·2); sodium chloride (p. 1795·1).

Nasocort *AstraZeneca, Israel.*
⊗Budesonide (p. 1625·1).
Nasal polyps; rhinitis.

Nasodren *Trommsdorff, Ger.*
Cyclamen (p. 2490·2).
Nasal congestion.

Nasofan *Ivax, Cz.; Teva, Fin.; Teva, Gr.; Teva, Hong Kong; Ivax, Irl.; Teva, Ital.; Cantabria, Spain†; Mepha, Switz.; Ivax, UK; Teva, Ukr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Nasofed *Hawthorn, USA.†*
⊗Pseudoephedrine tannate (p. 1676·1).
Nasal congestion.

Nasofelin *Neo Quimica, Braz.*
⊗Fenoxazoline hydrochloride (p. 1665·3).
Nasal congestion.

Nasoferm *Nordic, Swed.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis.

Nasoflo *UnitedAmerican, Philipp.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Nasogrip *Cazi, Braz.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); mepyramine maleate (p. 635·1); caffeine (p. 1203·3).
Cold and influenza symptoms.

Naso-Heel S *Peithner, Hung.*
Helianthemum canadense; arum maculatum; melilotus officinalis (p. 2552·3); lobaria pulmonaria (p. 2546·1); hydrastis canadensis (p. 2528·1); phosphorus (p. 2589·2); vinca minor (p. 2645·2); veronica officinalis; hydrargyrum biiodatum (p. 2555·3); ammonium carbonicum (p. 1656·1); lemna minor; hydrargyrum sulfuratum rubrum

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2555·3); kalium bichromicum (p. 2476·3); aurum chloratum natronatum (p. 2521·2).
Homoeopathic preparation.

Nasohist *Hawthorn, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; cold symptoms.

Nasohist-DM *Hawthorn, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; allergic rhinitis.

Nasojol *Lafedar, Arg.*
⊗Naphazoline (p. 1669·3); neomycin (p. 329·3).
Nasal congestion.

Nasol Baby *Bayer Consumer, Ukr.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; rhinitis; sinusitis; otitis media; adjunct to nasal investigation.

Nasol Kids *Bayer Consumer, Ukr.*
Phenylephrine hydrochloride (p. 1672·3); cineole (p. 2479·1).
Nasal congestion; rhinitis; sinusitis; otitis media; adjunct to nasal investigation.

Nasolin
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Sodium chloride (p. 1795·1); benzalkonium chloride (p. 1737·1).
Nasal disorders.

Orion, Fin.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

TNP, Thai.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Darnitsa, Ukr.†
⊗Naphazoline nitrate (p. 1669·3).
Rhinitis; sinusitis; otitis media; eustachitis; nasal haemorrhage; adjunct to nasal procedures.

Nasolina *Salvat, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nasolver *Mintlab, Chile.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough.

Nasomaris *Premier Research, Neth.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasomed *Spirig, Switz.*
Peppermint oil (p. 1877·1); camphor oil (p. 2466·2); lanolin (p. 2219·3).
Dryness of the nasal mucosa.

Nasomet
Note: this name may be used for preparations of different composition.
Orifarm, Denm.; Schering-Plough, Port.
⊗Mometasone furoate (p. 1644·1).
Rhinitis; nasal polyps.

Sun, India.
⊗Xylometazoline hydrochloride (p. 1680·1).
Eye congestion.

Nasomicina *Northia, Arg.; Sanofi-Aventis, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Nose and throat infections with congestion.

Nasomil *Multilab, Braz.*
⊗Diphenhydramine (p. 626·1); naphazoline (p. 1669·3).

Nasomin *Medipharm, Chile.*
⊗Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); xylometazoline hydrochloride (p. 1680·1); antazoline phosphate (p. 615·3).
Upper respiratory-tract disorders.

Nasomixin CM *Teofarma, Ital.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Nasonal *Premier Research, Neth.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nasonex *Schering-Plough, Arg.; MSD, Austral.; Aesca, Austria; MSD, Belg.; Schering-Plough, Braz.; Merck, Canad.; Schering-Plough, Chile; MSD, China; Schering-Plough, Cz.; Schering-Plough, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; MSD, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; MSD, Jpn; Schering-Plough, Malaysia; MSD, Neth.; Schering-Plough, Norw.; MSD, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.; Schering, USA; Schering-Plough, Venez.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis; sinusitis; nasal polyps; rhinosinusitis.

Nasop *Hawthorn, USA.†*
Phenylephrine hydrochloride (p. 1672·3) or phenylephrine tannate (p. 1672·2).
Nasal congestion.

Nasopax *Meditop, Hung.*
⊗Bromhexine hydrochloride (p. 1656·3); oxymetazoline hydrochloride (p. 1671·3).
Influenza symptoms; rhinitis; sinusitis.

NasOpen *GM, USA.*
⊗Chlorcyclizine hydrochloride (p. 620·2); pseudoephedrine hydrochloride (p. 1676·1).

NasOpen PE *GM, USA.*
Phenylephrine hydrochloride (p. 1672·3); thonzylamine hydrochloride (p. 642·1).
Upper respiratory-tract disorders.

Nasopomada *Medical, Spain.†*
⊗Bismuth subgallate (p. 1822·1); prednisolone (p. 1645·2); rutoside (p. 2505·3); sulfanilamide (p. 368·1); tetracycline hydrochloride (p. 373·2); urea (p. 1727·3); benzocaine (p. 1980·2).
Nasal polyps; sinusitis.

Naso-Ratiopharm *Ratiopharm, Fin.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis.

Nasorest *Community Pharmacy, Thai.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; cold symptoms.

Nasorest Expectorant *Community Pharmacy, Thai.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract disorders.

Nasorhinathiol *Sanofi-Aventis, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nasoryl *Glenmark, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Nasosal *DDD, UK.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Naso-Spray *GNCLS, Ukr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinitis; sinusitis; otitis media; aid in nasal procedures.

Nasosyn *Farmasyn, Gr.*
⊗Xylometazoline hydrochloride (p. 1680·1); dexpanthenol (p. 2582·2).

Nasotane *Community Pharmacy, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Allergic rhinitis; nasal congestion; cough.

Nasotapp *Community Pharmacy, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Nasotuss *Hawthorn, USA.*
Chlorcyclizine hydrochloride (p. 620·2); codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough; allergic rhinitis symptoms.

Naspor *Genepharm, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Naspro *Nicholas, Indon.*
Aspirin (p. 22·2).
Aluminium hydroxide (p. 1817·2) and magnesium hydroxide (p. 1857·2) are included in Naspro Forte in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Nasrea *Cinerea, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Nassa *Triton, India.*
Mirtazapine (p. 436·1).
Depression.

Nasterid *Ativus, Braz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Nasterid A *Ativus, Braz.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Nasteril *Asofarma, Arg.*
Finasteride (p. 2358·3).
Prostate disorders.

Nasterol *Nolver, Venez.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Nastifrin *Laboratorios Chile, Chile.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract disorders; otitis; eye congestion.

Nastifrin Compuesto *Laboratorios Chile, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold symptoms.

Nastifrin Compuesto DN *Laboratorios Chile, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); night tablets, paracetamol; pseudoephedrine sulfate; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Nastil *Best, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Nastilox *Pharmathen, Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Nastizol *Bago, Arg.*
Nose drops: ⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Bago, Arg.; Bago, Chile.
Syrup; tablets: ⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Nasal congestion; rhinitis; upper respiratory-tract disorders.

Nastizol Compositum *Bago, Arg.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3); bromhexine hydrochloride (p. 1656·3); paracetamol (p. 115·1).
Influenza symptoms.

Bago, Chile.
⊗Pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cough and cold symptoms; rhinitis; sinusitis.

Nastizol Dia-Noche *Bago, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); night tablets, paracetamol; pseudoephedrine sulfate; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; nasal congestion.

Nastizol Ex *Armstrong, Mex.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Nastizol Expectorante *Bago, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with excess or viscous mucus.

Nastizol Hidrospray *Bago, Arg.*
⊗Budesonide (p. 1625·1).
Rhinitis.

Nastizol-L *Bago, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Nastoren *Lepetit, Ital.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; prevention of postoperative complications following pancreatic surgery.

Nastul *Chemopharma, Chile.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Nastul Compuesto *Chemopharma, Chile.*
⊗Pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Nastul Dia y Noche *Chemopharma, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); night tablets, paracetamol; pseudoephedrine sulfate; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Nasulind *Steierl, Ger.†*
Peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Nasal congestion.

Nasvical *Savio, Ital.*
Ketorolac trometamol (p. 80·2).

Nat B *Mega Lifesciences, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; dietary supplement.

Nat C *Mega Lifesciences, Thai.*
Vitamin C (p. 2110·3); bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); rutoside (p. 2505·3); acerola; rose hips (p. 2607·1).
Vitamin C deficiency.

Nat E *Mega Lifesciences, Thai.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Nať Jmelí *Megafyt-R, Cz.†*
Mistletoe (p. 2560·2).
Hypertension; presclerotic disorders.

Nať Máty Peprné *Megafyt-R, Cz.†*
Peppermint leaf (p. 1877·1).
Digestive-system disorders.

Nať Pelyňku Pravého *Leros, Cz.†*
Absinthium (p. 2426·1).
Digestive-system disorders.

Nať Řebříčku *Leros, Cz.†*
Achillea (p. 2427·3).
Loss of appetite; dyspepsia; wounds; pelvic pain.

Nať Šalvěje Lékařské *Leros, Cz.†*
Sage (p. 2608·3).
Mouth disorders; dyspepsia; diarrhoea.

Nať Třezalky *Leros, Cz.†*
St John's wort (p. 449·1).
Depression.

Nata Komplete *WH Nutritionals, USA.*
Vitamins; minerals.
Dietary supplement.

Natabec *Silesia, Chile.*
Vitamins; minerals.
Dietary supplement.

Pfizer, Turk.†
Ferrous sulfate (p. 2062·2); calcium carbonate (p. 1824·3); vitamins.

Natabion *Pyridam, Indon.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias in pregnancy and lactation.

NataBoost *Hyphens, Singapore.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); arachidonic acid (p. 2446·1).
Fatty acid supplement in pregnancy and lactation.

NataChew *Eckson, USA.*
Vitamins; iron (p. 2073·1).

Nataclox *Sun, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Natacyn *Alcon, Arg.; Alcon, Hong Kong†; Alcon, Malaysia; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, USA.*
Natamycin (p. 590·2).
Fungal eye infections.

Natadrops *Cipla, India.*
Natamycin (p. 590·2).
Fungal eye infections.

Natafort *Mission Pharmacal, USA.*
Vitamins; iron (p. 2073·1).

Natal Care
Note: this name may be used for preparations of different composition.
Dalmia, India.
Preparation for enteral nutrition.

Jose Lea, Singapore.
Omega-3 marine triglycerides (p. 1460·3); arachidonic acid (p. 2446·1); oleic acid (p. 2200·1); *d*-alpha tocopherol (p. 2119·1).
Dietary supplement in pregnancy and lactation.

Natal Plus *Eagle, Austral.*
Vitamins; minerals; bioflavonoids (p. 2505·2); ginger (p. 1844·1); cysteine (p. 2058·3); inositol (p. 2533·2); lecithin (p. 2542·2).
Dietary supplement in pregnancy and lactation.

Natalac *Gruppo Medica, Philipp.*
Moringa oleifera.
Nutritional supplement for breastfeeding women.

Natalac FeFol *Gruppo Medica, Philipp.*
Moringa oleifera; ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Dietary supplement for breastfeeding women.

Natalben *Italfarmaco, Ital.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); iodine (p. 2336·3); docosahexaenoic acid (p. 1460·1).
Dietary supplement in pregnancy and lactation.

Natalbes *Catalent, Philipp.*
Ferrous fumarate (p. 2060·3); sodium fluoride (p. 2089·2); folic acid (p. 2063·1); vitamins; minerals.
Nutritional supplement for pre- and post-natal women.

NatalCare *Ethex, USA.*
Vitamins; minerals.

Natalie *Orchid, Philipp.*
Vitamins; minerals; folic acid (p. 2063·1).
Dietary supplement for preconception and pregnancy.

Natalience *Lero, Fr.*
Vitamins; minerals; fish oil (p. 1460·1).
Dietary supplement during pregnancy and lactation.

Natalin *Mead Johnson Nutritionals, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Dietary supplement during pregnancy and lactation.

Natalins com Flúor *Mead Johnson, Braz.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1); fluoride (p. 2089·2).

Natalins Fólico *Mead Johnson, Braz.*
Vitamins; minerals.

Natalins-M *Mead Johnson, Philipp.*
Vitamins; minerals; with or without fluoride (p. 2089·2).
Dietary supplement for pre- and post-natal women.

Natalsid *Nizpharm, Rus.*
Sodium alginate (p. 2167·3).
Anorectal disorders.

Natalsure *Wharton, Philipp.*
Vitamins; minerals; taurine (p. 2626·2).
Dietary supplement for pre- and postnatal women.

Natalvirt CA *Virtus, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.
Dietary supplement.

Natalvirt DHA *Virtus, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.
Dietary supplement.

Natalwiz *Metro, Philipp.*
Vitamins; minerals; taurine (p. 2626·2).
Dietary supplement for pregnant and breast-feeding women.

Natalya *Stragen, Cz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Natam *Alna, India.*
Natamycin (p. 590·2).
Bacterial eye infections.

Natamet *Sun, India.*
Natamycin (p. 590·2).
Bacterial eye infections.

Natamin C *Hind Wing, Hong Kong.†*
Dimeticone (p. 2209·3); folic acid (p. 2063·1); minerals; vitamins.

Natamox *Natco, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Nataral *Kenyaku, Thai.*
Vitamins; minerals; iron (p. 2073·1).
Dietary supplement during pregnancy and lactation.

Natarex Prenatal *Major, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Natasadol *Cosmopharm, Gr.*
Diltiazem hydrochloride (p. 1359·2).

NataTab *Ethex, USA.*
Vitamins; minerals.

Natavit *Bernofarm, Indon.*
Docosahexaenoic acid (p. 1460·1); arachidonic acid (p. 2446·1); folic acid (p. 2063·1).
Dietary supplement in pregnancy and lactation.

Natax *Poen, Arg.*
Bromfenac sodium (p. 30·1).
Eye inflammation.

Natazia *Bayer, USA.*
4 Tablets, estradiol valerate (p. 2271·2); 22 tablets, estradiol valerate; dienogest (p. 2267·2); 2 tablets, inert.
Four-phase oral contraceptive; menorrhagia.

Natberry *CCM, Malaysia.*
Myrtillus (p. 2566·2).
Tired eyes.

Natberry Extra *CCM, Malaysia.*
Myrtillus (p. 2566·2); calendula (p. 2465·2).
Tired eyes.

Natberry Plus *CCM, Malaysia.*
Myrtillus (p. 2566·2); wolfberry.
Tired eyes.

Nat-C *Mega Lifesciences, Malaysia†; Mega We Care, Singapore.*
Vitamin C (p. 2110·3); bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); rutoside (p. 2505·3); rose fruit (p. 2607·1); acerola.
Vitamin C deficiency; dietary supplement.

Natcal *Reddy, India.*
Hydroxyapatite (p. 2529·3).
Osteoporosis.

Natcal-D3 *Reddy, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Natcardine *Franco-Indian, India.*
Quinidine phenylethylbarbiturate (p. 1481·1).
Arrhythmias.

Natclovir *Natco, India.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infections.

Natcocillin *Natco, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Natcold Plus *Natco, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Nat-E *Biofarma, Venez.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; vitamin E supplement.

Natear *Silom, Thai.*
Hypromellose (p. 2189·2).
Eye irritation; dry eyes.

Natecal *Italfarmaco, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

ITF, Chile; Italfarmaco, Port.; Italfarmaco, Spain.
Calcium carbonate (p. 1824·3).
Calcium deficiency; hypocalcaemia; osteoporosis.

Natecal D *ITF, Chile; Italfarmaco, Port.; Italfarmaco, Spain; Effik, Switz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; fractures.

Natecal D3 *ITF, Gr.; ITF, Neth.; ITF, Pol.; Italfarmaco, Rus.; Trinity, UK.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteoporosis.

Nateglin *Phoenix, Arg.†*
Nateglinide (p. 492·1).
Diabetes mellitus.

Natele *Bayer, Braz.; Bayer, Mex.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Natele Easygels *Bayer, Chile.*
Vitamins; minerals.
Dietary supplement.

Natelide *Alembic, India.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Natelle-EZ *Tiber, USA.*
Vitamins; minerals.

Natenol *Willow, India.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; migraine.

Natenol-AM *Willow, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Nateran *Synthon, Neth.*
⊗Exemestane (p. 792·2).
Breast cancer.

Natezhen *Alcon, China.*
Natamycin (p. 590·2).

Natfer *Biomedica, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc methionine sulfate.

Natibo *Norma (Νορμα), Gr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Naticare *Labomed, Chile.*
Vitamins; minerals; fibre (p. 1823·3); fish oil (p. 1460·3).
Nutritional supplement.

Natifa *Libbs, Braz.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Natifa Pro *Libbs, Braz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Natifar *Bial, Spain.*
Folic acid (p. 2063·1); potassium iodide (p. 2336·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Natigesta *Farmalab, Braz.*
Vitamins; minerals.

Nati-K *DB, Fr.*
Potassium tartrate (p. 1793·3).
Hypokalaemia.

Natil-N *Hormosan, Ger.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders.

Natimed *Bial, Spain.*
Folic acid (p. 2063·1); potassium iodide (p. 2336·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Natisedine
Note: this name may be used for preparations of different composition.
Sanovel, Turk.
Quinidine phenylethylbarbiturate (p. 1481·1).
Arrhythmias.

Natisfar *Nafar, Mex.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Natispray *Teofarma, Fr.; Teofarma, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; pulmonary oedema.

Nativa *Natural San, Arg.*
A range of herbal preparations and dietary supplements.

Nativit *Sigma, Braz.*
Vitamins; minerals; iron (p. 2073·1).

Nativit Flúor *Sigma, Braz.*
Vitamins; minerals; fluoride (p. 2089·2).

Nativit Minerais *Sigma, Braz.*
Vitamins; minerals.

Nato *Natco, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Natolac *Medreich, India.*
Docosahexaenoic acid (p. 1460·1).

Natopherol *Abbott, Hong Kong†; Abbott, Indon.; Abbott, Singapore.*
Vitamin E (p. 2119·1).
Nutritional supplement; antoxidant; vitamin E supplement.

Abbott, Malaysia.
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency; scars; wounds; inflammation.

Natoptic *FDC, India.*
Natamycin (p. 590·2).
Bacterial eye infections.

Nat'Os *Monin, Fr.*
Soya; vitamin C (p. 2110·3); calcium carbonate (p. 1824·3); selenium (p. 2086·3).
Dietary supplement.

Natovit *Bruno, Ital.*
Tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Natoz *Medreich, India.*
Betacarotene (p. 2051·1); *d*-alpha tocopherol (p. 2119·1); grape (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); ascorbate (p. 2110·3).

Natpreg *Genesis, India.*
Progesterone (p. 2300·2).
Menopausal disorders; dysfunctional uterine bleeding; amenorrhoea.

Natracalm *Chefaro, UK.*
Passion flower (p. 2584·1).
Tension.

NatraFlex *Nutralife, UK.*
Capsaicin (p. 35·1); dimethyl sulfone (p. 2493·3); boswellia serrata (p. 2507·3).
Joint pain.

Natralgin *Elvipe, Gr.*
Dipyrone (p. 53·3).
Pain; fever.

Natrapel *Ardern, UK.*
Citronella oil (p. 2481·1).
Insect repellent.

Natrapel Plus *Tender, Canad.*
Citronella oil (p. 2481·1); geraniol (p. 2512·2).
Insect repellent.

Natrasleep *Chefaro, UK.*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Insomnia.

Natravene *Chefaro, UK.*
Frangula bark (p. 1843·3); taraxacum (p. 2625·3).
Constipation.

Natravox *Natrapharm, Philipp.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Natraway Sport 1 & 2 *Northern Naturals, Canad.†*
Achillea (p. 2427·3); borage (p. 2459·1); lappa (p. 2540·1); chickweed; comfrey (p. 2484·2); erechtites hieracifolia; hydrastis (p. 2528·1); melilot (p. 2552·3); plantain (p. 2592·3); sambucus (p. 2609·3); brunella vulgaris.

Natraway Sport 3 *Northern Naturals, Canad.†*
Achillea (p. 2427·3); borage (p. 2459·1); lappa (p. 2540·1); capsicum (p. 2469·3); chickweed; comfrey (p. 2484·2); erechtites hieracifolia; hydrastis (p. 2528·1); plantain (p. 2592·3); sambucus (p. 2609·3); self heal; trifolium.

Natrax *Polfa Pabianice, Pol.*
Naproxen (p. 98·2).
Fever; pain.

Natrecor *Janssen-Cilag, Arg.; Janssen-Ortho, Canad.; Janssen-Cilag, Indon.†; Scios, Singapore†; Scios, USA; Janssen-Cilag, Venez.*
⊗Nesiritide citrate (p. 1444·3).
Heart failure.

Natribic *Pharmacobel, Belg.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis; hyperkalaemia; alkalinisation of the urine.

Natricin *Natrapharm, Philipp.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy; neisseria meningitidis carriers.

Natriclo *Pharmacobel, Belg.*
Sodium chloride (p. 1795·1).
Hyponatraemia; fluid disorders.

Natrilix *Servier, Arg.; Servier, Austral.; Servier, Braz.; Grunenthal, Chile; Servier, China; Servier, Denm.; Servier, Fin.; Cheplapharm, Ger.; Servier, Hong Kong; Serdia, India; Servier, Indon.; Servier, Irl.; Servier, Ital.; Servier, Malaysia; Servier, Mex.; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Singapore; Servier, Thai.; Servier, UK; Servier, Venez.*
⊗Indapamide (p. 1409·2).
Hypertension.

Natriofoline *Medac, Rus.*
Sodium folinate (p. 2067·1).
Antidote to folic acid antagonists; adjunct to fluorouracil therapy.

Natroba *ParaPRO, USA; Pernix, USA.*
Spinosad (p. 2161·3).
Pediculosis.

Natrofen *Vocate, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Natrol C *Nefa, Turk.*
Vitamin C (p. 2110·3).

Natrol Ester C *Nefa, Turk.*
Citrus bioflavanoid complex (p. 2505·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Natrolip *Stedman, India.*
Chromium tripicolinate (p. 2056·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); policosanol (p. 1472·1); vitamin E (p. 2119·1).

Natron
Note: this name may be used for preparations of different composition.
Panjon, India.
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Natropas *Finadiet, Arg.*
Cinnarizine (p. 622·1).
Vestibular disorders.

Natrophylline Compound *Lennon, S.Afr.†*
⊗Aminophylline (p. 1201·2); ephedrine hydrochloride (p. 1663·2); phenobarbital (p. 535·2).
Obstructive airways disease.

Natrossil *Natiris, Venez.*
Rhubarb (p. 1884·2); boldo (p. 2458·3); achyranthes aspera; phyllanthus niruri (p. 2590·1).
Liver disorders.

Natrosteril *Baxter, Fin.†*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Natrum Carbonicum Complexe No 10 *Lehning, Fr.†*
Acide benzoicum (p. 1738·2); arnica (p. 2447·2); lithium carbonicum (p. 427·3); berberis vulgaris (p. 2502·1); natrum phosphoricum (p. 1791·2); natrum carbonicum (p. 2617·3); arsenicum album (p. 2448·1); lycopodium (p. 2546·3); apis (p. 2445·2); terebenthina.
Homoeopathic preparation.

Natterman Melrosum *Novum, Neth.*
Honey (p. 2072·1).
Cough.

Natterman Noscasan *Novum, Neth.*
Noscapine hydrochloride (p. 1670·3).
Cough.

Natterman Streptofree *Novum, Neth.*
Dequalinium chloride (p. 1749·3).
Sore throat.

Natubiotin *Rodisma, Ger.*
Biotin (p. 2052·2).
Biotin deficiency.

Natubrown *Natufarma, Arg.*
Betacarotene (p. 2051·1); lycopene (p. 2546·2).
Dietary supplement; tanning aid.

Natucor *Rodisma, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Natudophilus *Cantassium Co., UK.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3).

Natudor *Pierre Fabre, Fr.*
Crataegus (p. 2488·1); passion flower (p. 2584·1).
Palpitations; insomnia; anxiety.
Pierre Fabre Sante, Belg.
Valerian (p. 2640·2); crataegus (p. 2488·1); tilia (p. 2631·3).
Anxiety; insomnia.

Natu-fem *Rodisma, Ger.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Natu-Hepa *Rodisma, Ger.; Vita Health, Switz.*
Cynara (p. 2490·3).
Dyspepsia; biliary-tract disorders; digestive-system disorders.

Natuimmun *Hevert, Ger.†*
Echinacea ang. (p. 2498·1); aconitum (p. 2428·3); lachesis (p. 2538·3).
Homoeopathic preparation.

Natulan *Link, Austral.†; Sigma-Tau, Fr.; Sigma-Tau, Ger.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Sigma-Tau, Ital.; Sigma-Tau, Neth.; Sigma-Tau, Rus.; Yugosun, S.Afr.; Roche, Singapore; Sigma-Tau, Spain†; Sigma-Tau, Switz.*
Procarbazine hydrochloride (p. 850·1).
Malignant neoplasms.

Natulax
Note: this name may be used for preparations of different composition.
Natufarma, Arg.†
Cascara (p. 1826·1).
Constipation.

Natulax Plus *Natufarma, Arg.*
Cascara (p. 1826·1); sodium picosulfate (p. 1887·2).
Constipation.

Natu-lind *Rodisma, Ger.*
Urtica leaf (p. 2639·3).
Rheumatism; urinary-tract disorders.

Natu-prosta *Rodisma, Ger.*
Urtica root (p. 2639·3).
Benign prostatic hyperplasia.

Natura 10 *Maurino, Arg.*
Cleansing, disinfecting, storage, and wetting solution for soft contact lenses.

Natura Clean *Biotech, Arg.*
Cleansing solution for contact lenses.

Natura Clens *Biotech, Arg.*
Cleansing, wetting, and protein-removal solution for hard and gas-permeable contact lenses.

Natura Confort *Biotech, Arg.*
Sodium hyaluronate (p. 2526·2); poloxamer 407 (p. 2202·1).
Contact lens care.

Natura Express *Biotech, Arg.*
Cleansing and wetting solution for soft contact lenses.

Natura Fenac *Amhof, Arg.*
Diclofenac sodium (p. 48·3).
Eye disorders.

Natura Fresh *Biotech, Arg.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Natura Lagrimas *Amhof, Arg.*
Hypromellose (p. 2189·2).
Dry eyes.

Natura Perflex *Biotech, Arg.*
Ethoxylated propylene glycol.
Cleansing solution for flexible and gas permeable contact lenses.

Natura Plus *Biotech, Arg.*
Poloxamine.
Cleansing, disinfecting, storage, and wetting solution for soft contact lenses.

Natura Wet *Biotech, Arg.*
Polyvinyl alcohol (p. 2204·2).
Wetting solution for flexible and gas permeable contact lenses.

Natural Balance Tears *Major, USA.*
Hypromellose (p. 2189·2).
Dry eyes.

Natural Deep Sleep *Naturopathica, Austral.†*
Valerian (p. 2640·2); lupulus (p. 2546·1); passion flower (p. 2584·1) melissa (p. 2552·3).
Sleep disorders.

Natural Diet *AM, Arg.*
Bladderwrack (p. 2612·1); centella (p. 1698·3); equisetum (p. 2500·1); carnitine (p. 2053·2); vitamin E (p. 2119·1).
Dietary supplement.

Natural E *Bioglan, Austral.†; Nutrifarma, Turk.†; Mason, USA.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; vitamin E supplement.

Natural FX *Cover FX, Canad.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Natural Herb Tablets *Dorwest, UK.*
Senna (p. 1885·1); aloes (p. 1816·1); cascara (p. 1826·1); valerian (p. 2640·2); taraxacum (p. 2625·3).
Constipation.

Natural HRT *Swiss Herbal, Canad.*
⊗Dong quai (p. 2497·1); agnus castus (p. 2432·2); cimicifuga (p. 2478·1); wild yam (p. 2648·1); soya isoflavones (p. 2620·3); lappa (p. 2540·1).
Menopausal disorders.

Natural HRT Nightime *Swiss Herbal, Canad.*
Cimicifuga (p. 2478·1); passion flower (p. 2584·1); melissa (p. 2552·3).
Sleep disorders associated with the menopause.

Natural Ice Lipbalm *Mentholatum, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Natural Sweet *PGN, Arg.*
Stevia rebaudiana (p. 2214·2).
Sugar substitute.

Natural Wealth *Nefa, Turk.*
Vitamins; minerals.

Naturalag *Alcon, Mex.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes; eye irritation.

Naturalass *Naturmed, Ital.*
⊗Lactulose (p. 1850·3); mannitol (p. 1427·3); glycerol (p. 2517·2); inulin (p. 2534·3); plant fibre; minerals.
Gastrointestinal disorders.

Naturalist *Prater, Chile.*
Aspartame (p. 2169·2).
Sugar substitute.

Naturals Antibacterial Liquid Soap *Avon, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Naturalyte *Unico, USA.*
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Naturalyte H *Fresenius Medical, Canad.*
Acetic acid (p. 2426·3); calcium chloride (p. 1783·1); glucose (p. 2068·3); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); with or without potassium chloride (p. 1793·2) (p. 1778·2).
Haemodialysis solution.

Naturapia Calcium Complex *US Pharmacia, Pol.†*
Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Dietary supplement; osteoporosis; osteomalacia.

Naturapia Menopauza *US Pharmacia, Pol.*
Calcium citrate (p. 1783·2); calcium phosphate (p. 1784·2); magnesium oxide (p. 1857·3); colecalciferol (p. 2113·1); cimicifuga (p. 2478·1); soya (p. 2092·3).
Menopausal disorders.

Naturapia Prostata *US Pharmacia, Pol.†*
Alanine (p. 2048·3); glutamic acid (p. 2070·2); glycine (p. 2071·2); pyridoxine (p. 2105·3); zinc picolinate (p. 2126·1); saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Naturbotic *Kolson's, India.*
Valerian (p. 2640·2).

Naturcarsevt *Bulgarian Rose, Rus.*
Silibinin (p. 1561·2).
Liver disorders.

Natur-E *Darya-Varia, Indon.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E supplement.

Nature Care *Garuda, Hung.*
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome.

Nature Complex Reduct-Te *Prater, Chile.*
Boldo (p. 2458·3); trique; equisetum (p. 2500·1); tilia (p. 2631·3); stevia rebaudiana (p. 2214·2).

Nature Made Oyster Shell Calcium *Abdi, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Nature Throid *RLC, USA.*
Thyroid (p. 2345·3).
Hypothyroidism.

Naturee *Saimirra, Singapore.*
d-alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Naturel Kalsiyum Vit *Sandoz, Turk.*
Calcium from oyster shell (p. 1783·1); colecalciferol (p. 2113·1).
Nutritional supplement.

Naturema *Bernofarm, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); selenium (p. 2086·3); manganese (p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1); vitamin C (p. 2110·3).
Dietary supplement for healthy joints; osteoarthritis.

Nature's Cure Acne *Natures Cure, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Nature's Gate *Levlad, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Nature's Gate Aquablock *Levlad, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Natures Own Acidophilus Plus *Natures Own, Austral.†*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium animalis* ssp lactis *(p. 2596·3).*
Maintenance of normal gastrointestinal flora.

Nature's Tears *Rugby, USA.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Nature's Wash Plus *Geritrex, USA.*
Soap substitute.

Nature's Way Mega B *Roche, Hong Kong.†*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement.

Nature's Way Women's All-In-One *Roche, Hong Kong.†*
Vitamins; minerals.

Naturest
Note: this name may be used for preparations of different composition.
Lane, Hung.; Lane, UK.
Passion flower (p. 2584·1).
Insomnia.

Naturetti *Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.*
Senna (p. 1885·1); cassia pulp (p. 1826·2); tamarind (p. 1892·2); coriander (p. 2486·3); liquorice (p. 1853·2).
Constipation.

Natureyes *Bernofarm, Indon.*
Myrtillus (p. 2566·2); lutein (p. 2079·2); vitamin E (p. 2119·1).
Dietary supplement.

Naturfibr *Bratch, Canad.†*
Ispaghula (p. 1849·1).

Naturkaps Tran *Hasco-Lek, Pol.*
Cod-liver oil (p. 2056·3).
Dietary supplement.

Naturlax
Note: this name may be used for preparations of different composition.
Maver, Chile.
Tea: Senna (p. 1885·1).
Constipation.
Newport, Hong Kong.
Ispaghula (p. 1849·1).
Constipation.
Maver, Chile.†
Jelly: Senna (p. 1885·1); liquorice (p. 1853·2); plum.
Constipation.

Naturlesterol *Bernofarm, Indon.*
Garlic (p. 2510·3); poliglusam (p. 2593·2); green tea (p. 2648·2).
Dietary supplement.

Naturliver *Bernofarm, Indon.*
Schisandra chinensis (p. 2611·2); soya isoflavone (p. 2620·3); milk thistle (p. 1561·1); curcuma.
Liver disorders.

Naturocil *Peter, Ital.*
Melaleuca oil (p. 2551·1); thyme oil (p. 2630·3).
Vaginal disorders.

Naturogest *Zydus, India.*
Progesterone (p. 2300·2).
Premenstrual syndrome; puerperal depression.

Naturol *Prafa, Indon.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E supplement.

Naturolax *Organon, India; Organon, Rus.*
Ispaghula (p. 1849·1).
Constipation; diverticular disease; irritable bowel syndrome.

Naturophta Macula *Horus, Fr.*
⊗Black capsules, fish oil (p. 1460·1); big marigold; lutein (p. 2079·2); silica (p. 2208·3); vitamin E (p. 2119·1); vitamin A (p. 2098·3); Haematococcus pluvialis; brown capsules, fish oil; vitamin C (p. 2110·3); glycerol (p. 2517·2); vitamin B substances (p. 2102·3); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); sodium selenite (p. 2087·1).
Dietary supplement; retinal disorders.

Naturpep-C *Ximena Polanco, Chile.*
Opuntia ficus-indica.
Gastrointestinal disorders.

Natursel-C *Ximena Polanco, Chile.*
Rosa mosqueta (p. 2607·1); wild carrot (p. 2647·2); spirulina (p. 2622·1); vitamin E (p. 2119·1); selenium (p. 2086·3).
Antoxidant.

Naturub *Le Naturiste, Canad.*
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal pain; cough.

Natur-Zin *Ximena Polanco, Chile.*
Wild carrot (p. 2647·2); spirulina (p. 2622·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Dietary supplement.

Natus Gerin *Legrand, Braz.*
Vitamins; minerals; amino acids; ginseng (p. 2513·3).

Natusan *Johnson & Johnson, Spain.*
Glyceroborate complex; boric acid (p. 2459·3); borax (p. 2459·2).
Skin irritation.

Natu-Seda *Vita Health, Switz.*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Natvie C *Franco-Indian, India.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Naucet *Brussels, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Naucid *Abbott, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Naudicelle *Bio-Oil Research, Irl.†*
Evening primrose oil (p. 2502·2).
Dietary supplement.

Nausamine *Sriprasit, Thai.†*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; motion sickness; vertigo.

Nausatrol *Medique, USA.*
Glucose (p. 2068·3); fructose (p. 2068·2); phosphoric acid (p. 2589·1).
Nausea.

Nauseatol *Sandoz, Canad.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting.

Nausedron *Cristalia, Braz.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Nausefe *Inibsa, Port.*
Dicycloverine hydrochloride (p. 1834·2); doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting.

Nausetil *Aspen, Austral.; Intas, India.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; psychoses; anxiety; vertigo.

Nausetrol *Walsh, USA.*
Glucose (p. 2068·3); fructose (p. 2068·2); phosphoric acid (p. 2589·1).
Nausea and vomiting.

Nausetron *Aspen, S.Afr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Nausetum *Ferrier, Fr.*
Cocculus indicus (p. 2483·1); nux vomica (p. 2573·3); tabacum (p. 2632·2).
Homoeopathic preparation.

Naushi *Bestochem, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Nausicalm
Note: this name may be used for preparations of different composition.
AFT, NZ.
Cyclizine hydrochloride (p. 623·2) or cyclizine lactate (p. 623·2).
Nausea and vomiting; vestibular disorders.
Nogues, Fr.
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting.
Uniao Quimica, Braz.
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting; vertigo.

Nausidome *Abbott, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Nausidone *Sofex, Port.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting.

Nausiend *Pharmis, Port.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Nausifar MPS *Infar, India.*
Metoclopramide (p. 1862·2); simeticone (p. 1886·2).

Nausik *MMC, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Nausil *Siam Bheasach, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Dyspepsia; flatulence; peptic ulcer; gastro-oesophageal reflux; nausea and vomiting.

Nausilon B6 *Cifarma, Braz.*
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting; vertigo.

Nausin *T Man, Thai.†*
Metoclopramide hydrochloride (p. 1862·2).
Delayed gastric emptying; nausea and vomiting; gastro-oesophageal reflux.

Nausyn *Weleda, Austria.*
Cocculus fructus (p. 2483·1); ipecacuanha radix (p. 1667·2); petroleum (p. 2587·2).
Homoeopathic preparation.
Weleda, UK.
Absinthium (p. 2426·1); cocculus (p. 2483·1); ipecacuanha (p. 1667·2); nux vomica (p. 2573·3); petroleum (p. 2587·2).
Homoeopathic preparation.

Nautamine *Sanofi-Aventis, Fr.*
Diphenhydramine di(acefyllinate) (p. 626·2).
Motion sickness.

Nautigo *Bell, India.†*
Domperidone (p. 1838·1).
Nausea and vomiting; meteorism; gastroparesis; gastro-oesophageal reflux.

Nautisol *Medochemie, Malaysia.*
Prochlorperazine mesilate (p. 1098·3).
Anxiety; mania; nausea and vomiting; schizophrenia; vertigo.

Nautrol *Precimex, Mex.*
Difenidol hydrochloride (p. 1835·1).
Vertigo; nausea and vomiting.

Nauzelin *Kyowa, Jpn.*
Domperidone (p. 1838·1).
Nausea; vomiting; abdominal discomfort; heartburn.

Nauzine *Be-Tabs, S.Afr.*
Cyclizine hydrochloride (p. 623·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Navalin *Molekule, India.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder; migraine.

Navamin *Greater Pharma, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; vomiting in pregnancy.

Navane *Pfizer, Austral.†; Erfa, Canad.; Pfizer, Hong Kong†; Pfizer, USA.*
Tiotixene (p. 1112·1).
Psychoses; depression.

Navelbine *Rovafarm, Arg.; Pierre Fabre, Austral.; Boehringer Ingelheim, Austria; Pierre Fabre, Belg.; Darrow, Braz.; Pierre Fabre, Canad.; Baxter, Chile; Pierre Fabre, China; Pierre Fabre, Cz.; Pierre Fabre, Denm.; Pierre Fabre, Fin.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Hong Kong; Pierre Fabre, Hung.; Abbott, India; Transfarma, Indon.; Pierre Fabre, Irl.; Pierre Fabre, Israel; Pierre Fabre, Ital.; Kyowa, Jpn; Pierre Fabre, Malaysia; Pierre Fabre, Mex.; Pierre Fabre, Neth.; Pierre Fabre, Norw.; NZ Medical & Scientific, NZ; Baxter, Philipp.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Tema, S.Afr.; Pierre Fabre, Singapore; Pierre Fabre, Spain; Pierre Fabre, Swed.; Robapharm, Switz.; Pierre Fabre, Thai.; Pierre Fabre, Turk.; Pierre Fabre, UK; Pierre Fabre, Ukr.; Pierre Fabre, USA.*
Vinorelbine tartrate (p. 885·3).
Cervical cancer; breast cancer; ovarian cancer; non-small cell lung cancer; prostatic cancer.

Navi Blef *Navi, Fr.*
Chamomile (p. 2474·1); melaleuca (p. 2551·1); pantothenic acid (p. 2085·2).
Eyelid hygiene; blepharitis.

Navicalm
Note: this name may be used for preparations of different composition.
Cavalheiro, Port.†; Arafarma, Spain.
Meclozine hydrochloride (p. 634·3).
Motion sickness; vestibular disorders.

Navidoxine *UCB, Hong Kong.†*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting.

Navidrex *Goldshield, UK.*
⊗Cyclopenthiazide (p. 1347·2).
Hypertension; heart failure; oedema.

Navildez *Cryopharma, Mex.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Navin *Cancernova, Ger.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Navirel *Medac, Cz.; Medac, Denm.; Medac, Fin.; Medac, Ger.; Medac, Neth.; Medac, Norw.; Medac, Pol.; Medac, Port.; Medac, Swed.*
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small cell lung cancer.

Navispare *Novartis, Hong Kong; Goldshield, UK.*
⊗Cyclopenthiazide (p. 1347·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Navitae *Navi, Fr.*
Sodium hyaluronate (p. 2526·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Eye irritation.

Naviten *Solvay, Rus.*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Navixen
Note: this name may be used for preparations of different composition.
Ferrer, Spain.
Eprosartan mesilate (p. 1376·2).
Hypertension.
Mavi, Mex.†
Naproxen (p. 98·2).
Fever; inflammation; pain.

Navixen Plus *Ferrer, Spain.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Navizan *Caber, Ital.*
Tizanidine hydrochloride (p. 2026·2).

Navoban *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Chile†; Novartis, China; Genopharm, Denm.; Novartis, Fr.†; Novartis, Ger.†; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Alkopharma, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.†; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.†; Novartis, Spain†; Alkopharma, Swed.; Genopharm, Swed.; Alkopharma, Switz.; Novartis, Thai.†; Novartis, Turk.; Novartis, Ukr.; Novartis, Venez.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Navotrax *Neo Quimica, Braz.*
Clonazepam (p. 519·1).
Epilepsy.

Naxan *Hikma, Port.*
Naloxone hydrochloride (p. 1562·3).
Diagnosis of opioid overdosage; reversal of opioid-induced depression.

Naxar-P *Nafar, Mex.*
Ispaghula (p. 1849·1).
Constipation.

Naxdom *Sun, India.*
Domperidone (p. 1838·1); naproxen sodium (p. 98·2).

Naxelan *Labomed, Chile.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Naxen *Elder, India; Darya-Varia, Indon.†; Syntex, Indon.†; Syntex, Mex.†; Douglas, NZ.*
Naproxen (p. 98·2).
Gout; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Naxene *Suphong, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Naxidin *Zelion, Hung.*
Nizatidine (p. 1866·1).
Gastro-oesophageal reflux; peptic ulcer.

Naxifelar *Pisa, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Naxii *US Pharmacia, Pol.*
Naproxen sodium (p. 98·2).
Pain; fever.

Naxilan-Plus *Rayere, Mex.*
Nalidixic acid (p. 328·3); phenazopyridine (p. 124·3).
Urinary-tract infections.

Naxo *Sons, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Naxo C *AstraZeneca, Arg.*
Fluconazole (p. 578·2).
Vaginal candidiasis.

Naxo TV *AstraZeneca, Arg.*
⊗Metronidazole (p. 936·1); nystatin (p. 590·3); dexamethasone (p. 1630·3); lidocaine (p. 1988·1); neomycin sulfate (p. 330·1).
Vaginal and cervical infections.

Naxocina *AstraZeneca, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Naxoclinda *Rontag, Arg.*
Clindamycin phosphate (p. 269·3).
Vaginal infections.

Naxodol
Note: this name may be used for preparations of different composition.
Mintlab, Chile.
Tramadol hydrochloride (p. 139·2).
Pain.
Syntex, Mex.†
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Musculoskeletal, joint, and peri-articular disorders.

Naxodol Plus *Mintlab, Chile.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Naxogin *Rontag, Arg.; Pfizer, Belg.†; Pfizer, Braz.; Pfizer, Gr.; Pfizer, Rus.; Pfizer, Ukr.*
Nimorazole (p. 942·1).
Protozoal infections; anaerobic bacterial infections; trichomoniasis; giardiasis; amoebiasis; bacterial vaginosis; ulcerative gingivitis.

Naxogin Complex *Kalbe, Indon.; Pfizer, Indon.*
Nimorazole (p. 942·1); chloramphenicol (p. 257·1); nystatin (p. 590·3).
Vaginal infections.

Naxogin Compositum *Pfizer, Chile.†*
Nimorazole (p. 942·1); nystatin (p. 590·3); chloramphenicol (p. 257·1).
Vaginal infections.

Naxogin Composto *Pfizer, Braz.*
Nimorazole (p. 942·1); chloramphenicol (p. 257·1); nystatin (p. 590·3).
Vulvovaginal infections.

Naxolan *Hospira, Port.*
Naloxone hydrochloride (p. 1562·3).

Naxopaar *Parggon, Mex.*
Naproxen (p. 98·2).
Inflammation.

Naxopren *Mylan, Fin.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; fever; inflammation.

Naxotec *Uniao Quimica, Braz.*
Naproxen (p. 98·2).

Naxpa *Ferrer, Spain.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Naxuril *Vianex (Βιανεξ), Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Naxy *Cephalon, Fr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Naxyl *FGK, Cz.*
Dequalinium chloride (p. 1749·3).
Bacterial vaginosis.

Naxyn *Teva, Israel.*
Naproxen (p. 98·2).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Naya-AB *BMW, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Nayacal *BMW, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Nayacef *BMW, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nayacip *BMW, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Nayaclav *BMW, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Nayaclor *BMW, India.*
Cefaclor (p. 232·3).
Bacterial infections.

Nayacort *BMW, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Nayafix *BMW, India.*
Cefixime (p. 240·3).
Bacterial infections.

Nayanim *BMW, India.*
Nimesulide (p. 101·3).
Pain.

Nayapred *BMW, India.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Nayawax *BMW, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).

Nazal Spray *Sato, Singapore.*
⊗Naphazoline hydrochloride (p. 1669·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Nazalet *Stanley, Israel.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nazalin *Bell, India.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nazamit *Mintlab, Chile.†*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Nazarel *Teva, Rus.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Nazaren *Weifa, Norw.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis.

Nazcare *Mint, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Naze *Abbott, Turk.; Yenisehir, Turk.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nazene Z *Adcock Ingram, S.Afr.*
⊗Oxymetazoline hydrochloride (p. 1671·3); zinc sulfate (p. 2126·2).
Nasal congestion; allergic rhinitis; sinusitis.

Nazicol *Kinder, Braz.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Nazil *Sophia, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye congestion.

Nazin
Note: this name may be used for preparations of different composition.
Aristopharma, Hong Kong.
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.
CCM, Malaysia; Duopharma, Singapore.
Cinnarizine (p. 622·1).
Peripheral vascular disorders; vestibular disorders; cerebral and peripheral vascular disorders; motion sickness.

Nazine *Vesco, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders; Ménière's disease.

Nazinette du Docteur Gilbert *Pharmadeveloppement, Fr.*
Wild thyme oil (p. 2648·1); Scots pine oil (p. 2591·2); eucalyptus oil (p. 2501·2); myrtle oil (p. 2566·3); clove oil (p. 2481·3); thyme oil (p. 2630·3); terpineol (p. 2627·2).
Rhinopharyngeal disorders.

Nazipons *Rafarm, Gr.*
Fenoprofen calcium (p. 59·2).

Nazle *Servocare, India.*
⊗Xylometazoline (p. 1680·1).
Eye congestion; nasal congestion.

Nazo *Pharma Dynamics, S.Afr.†*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2).
Nasal congestion.

Nazoden *Laborate, India.*
⊗Oxymetazoline (p. 1671·3).
Nasal congestion.

Nazo-F *Candor, India.*
⊗Fluocinolone acetonide (p. 1636·1); miconazole nitrate (p. 589·1).

Nazoferon *Farmak, Ukr.*
Interferon alfa-2b (p. 989·2).
Viral infections of the respiratory tract.

Nazofix *Frik, Turk.*
⊗Mometasone furoate (p. 1644·1).

Nazol
Note: this name may be used for preparations of different composition.
Bayer Schering, Rus.; Bayer Consumer, Ukr.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinitis; sinusitis; otitis media; adjunct to nasal investigation.
CCM, Malaysia; Duopharma, Singapore.
⊗Danazol (p. 2263·2).
Endometriosis; fibrocystic breast disease; hereditary angioedema; menorrhagia; benign breast disorders; gynaecomastia; pre-operative thinning of the endometrium.

Nazol Advance *Bayer Schering, Rus.*
⊗Oxymetazoline hydrochloride (p. 1671·3); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1).
Rhinitis; sinusitis; nasal congestion.

Nazol Advans *Bayer Consumer, Ukr.*
⊗Oxymetazoline hydrochloride (p. 1671·3); menthol (p. 2553·2); cineole (p. 2479·1); camphor (p. 2466·2).
Nasal congestion; rhinitis; sinusitis; otitis media; adjunct to nasal investigation.

Nazol Baby *Bayer Schering, Rus.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Nazol Kids *Bayer Schering, Rus.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Nazole *Medicpharma, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Nazolfarm *Continentales, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Nazolin
Note: this name may be used for preparations of different composition.
Beximco, Singapore.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; otitis media.
BMW, India.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nazoltec *Tecnofarma, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Nazoster *Berksam, Turk.*
⊗Mometasone furoate (p. 1644·1).

Nazovell *Novell, Indon.*
Ketoprofen (p. 79·1).
Osteoarthritis; rheumatoid arthritis; pain.

Naztril *Quimica y Farmacia, Mex.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nazz *USP, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

NB-3 *Sigma, Arg.*
Nicotinamide (p. 2083·1).
Depression; anxiety; obesity; alcoholism; migraine; headache.

NBace-P *NB, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

NBal-AT *NB, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

NBCal *NB, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

NBCef *NB, India.*
Cefixime (p. 240·3).
Bacterial infections.

NBCid *NB, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

NBCin *NB, India.*
Amikacin (p. 214·1).
Bacterial infections.

N-Bend *Elfin, India.*
Albendazole (p. 149·1).
Protozoal infections; worm infections.

NBGest *NB, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1); vitamin B substances (p. 2102·3).

NBLcet *NB, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

NBLcet Plus *NB, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

NBLox *NB, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

NBMox-DC *NB, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).
Bacterial infections.

NBox *NB, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

NBOxid *NB, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); lycopene (p. 2546·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

NBox-OZ *NB, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

NBOzole *NB, India.*
Fluconazole (p. 578·2).
Fungal infections.

NBTone *NB, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

NBWorm *NB, India.*
Albendazole (p. 149·1).
Worm infections.

NC Derm *Kee, India.*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1); clotrimazole (p. 576·2).
Infected skin disorders.

NCA *Troikaa, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastritis; gastric hyperacidity; heartburn.

N-Care *BMW, India.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3).

N-Care Forte *BMW, India.*
Capsules: Thioctic acid (p. 2629·1); inositol (p. 2533·2); trace elements; vitamins; evening primrose oil (p. 2502·2); arginine (p. 2049·1).
BMW, India.
Injection: Vitamin B substances (p. 2102·3).

NCH *Novartis Consumer, Irl.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

N-Cid *Willow, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

N-Ciz *Nortech, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

N-Cobal *Advance, Malaysia.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

N-Cool *Adley, India.*
⊗Camphor (p. 2466·2); menthol (p. 2553·2); naphazoline hydrochloride (p. 1669·3); phenylephrine hydrochloride (p. 1672·3).

NCZ *Laborate, India.*
⊗Chlorphenamine maleate (p. 620·3); methylcellulose (p. 2197·3); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).

2nd Skin ScarGel *Spenco, Hong Kong.*
Silicone (p. 2209·2).
Hypertrophic and keloid scars.

ND-Gesic *Hyrex, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract symptoms.

N-Dip *Taurus, India.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

NDMas *Cosmas, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

NDN *Finecure, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

NE *Cachet, India.*
Levocarnitine (p. 2053·2); vitamin E acetate (p. 2119·2).

NE Plus *Cachet, India.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Neaclear Liquid Oxygen *Neaclear, Singapore.†*
Salicylic acid (p. 1719·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Acne; soap substitute.

Neagel *Poen, Arg.*
Ganciclovir (p. 982·3).
Viral eye infections.

Nealorin *Probios, Port.†*
Carboplatin (p. 759·1).

Neasyn *Torrent, India.*
Nicotinic acid (p. 2083·1).

Neat Effect *Neat Feat, NZ.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Neat Feat *Neat Feat, NZ.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Neat One *Neat Feat, NZ.*
Aluminium-zirconium tetrachlorohydrex glycine (p. 1694·1).
Hyperhidrosis.

Neat Touch *Neat Feat, NZ.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Neatenol *Rottapharm, Spain.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; myocardial infarction; hypertension.

Neatenol Diu *Rottapharm, Spain.*
⊗Bendroflumethiazide (p. 1315·2); atenolol (p. 1308·2).
Hypertension.

Neatenol Diuvas *Rottapharm, Spain.†*
⊗Bendroflumethiazide (p. 1315·2); hydralazine hydrochloride (p. 1401·2); atenolol (p. 1308·2).
Hypertension.

Neatin *Jelfa, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Nebacetin *Sandoz, Austria; Nycomed, Braz.; Astellas, Ger.†; Nycomed, Gr.; Pharos, Indon.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial eye infections; bacterial infections of the skin and mucous membranes.

Nebacetina *Nycomed, Mex.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial skin infections; infected burns, wounds, and ulcers.

Nebaciderme *Multilab, Braz.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Bacterial skin infections.

Nebacimed *Cimed, Braz.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial skin infections.

Nebacop *Medico Uno, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebal *Reuffer, Mex.*
Hydroxocobalamin (p. 2107·3).
Neuritis.

Nebaletor *Plus Pharma, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebalgan *Ipca, Rus.*
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Smooth muscle spasm; pain.

Nebapul *Royal, Chile.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Nebasulf *Pfizer, India.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3); sulfacetamide (p. 361·1) or sulfacetamide sodium (p. 361·1).
Bacterial skin infections.

Nebcin *Aspen, Austral.†; Lilly, Gr.; Lilly, NZ; Lilly, Rus.; Aspen, S.Afr.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Lilly, Turk.
Tobramycin (p. 380·1).
Bacterial infections.

Nebcina *NordMedica, Denm.; EuroCept, Norw.; Meda, Swed.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Nebcine *Erempharma, Fr.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Nebect *Elfin, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Nebenhohlen-Tropfen Nr 26 *Doskar, Austria.†*
Kalium bichromicum (p. 2476·3); hydrastis canadensis (p. 2528·1); hepar sulfuris (p. 1721·3); mercurius bijodatus (p. 2555·3); calcium fluoratum (p. 2053·1); acidum silicicum (p. 2208·3).
Homoeopathic preparation.

Nebest *USV, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebest-H *USV, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol hydrochloride (p. 1444·2).
Hypertension.

Nebibeta *Gedeon Richter, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebicar *OEP, Philipp.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension.

Nebicard *Torrent, Philipp.; Biofarm, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Torrent, India.
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebicard-H *Torrent, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nebicard-SM *Torrent, India.*
⊗Nebivolol (p. 1444·2); levamlodipine.
Hypertension.

Nebicard-V *Torrent, India.*
⊗Nebivolol (p. 1444·2); valsartan (p. 1521·2).

Nebicina *Teofarma, Ital.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Nebicon *Plus Pharma, Denm.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebicur *Bennett, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2).

Nebid *Bayer, Ital.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Nebidelta *Pensa, Denm.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebido *Bayer, Arg.; Bayer, Austria; Bayer, Belg.; Schering, Braz.; Bayer, Chile; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Jenapharm, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, Philipp.; Bayer Schering, Pol.; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Schering, Ukr.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Nebilan *Lannacher, Austria; Lannacher, Cz.†*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebilenin *Adamed, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebilet *Menarini, Arg.; CSL, Austral.; Biolab Sanus, Braz.; Labomed, Chile; Berlin-Chemie, Cz.; Menarini, Fin.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.; Menarini, Irl.; Menarini, Malaysia; Menarini, Neth.; Berlin-Chemie, Pol.; Menarini, Pol.; Menarini, Port.; Berlin-Chemie, Rus.; Adcock Ingram, S.Afr.; Menarini, Singapore; Menarini, Switz.; Menarini, Thai.; Menarini, UK; Berlin-Chemie, Ukr.; Leti, Venez.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure; ischaemic heart disease.

Nebilet Comp *Menarini, Denm.†*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nebilet Plus *Menarini, Irl.; Menarini, Switz.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nebilet Plus H *Menarini, Cz.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nebiloc *Menarini, Neth.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebilol *JB Chemicals, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebilol-H *JB Chemicals, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nebilong *Micro, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Micro Labs, Ukr.
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension.

Nebilong-AM *Micro, India.*
⊗Amlodipine (p. 1304·1); nebivolol (p. 1444·2).

Nebilong-H *Micro, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nebilostad *Stada, Neth.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebilox *GSK, Ital.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nébilox *Negma, Fr.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebimac *Macleods, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebimac-H *Macleods, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nebimarin *Labochem, Port.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebimel *Clonmel, Irl.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebinad *Farma-Projekt, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebinex *Glenmark, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebinex-AM *Glenmark, India.*
⊗Amlodipine (p. 1304·1); nebivolol (p. 1444·2).

Nebinorm *Glenmark, Cz.; Sandoz, Turk.*
⊗Nebivolol hydrochloride (p. 1444·2).

Nebiotin *SF, Ital.*
Biotin (p. 2052·2).
Biotin deficiency.

Nebipil *Alkem, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebipril-SA *Alkem, India.*
⊗Nebivolol (p. 1444·2); levamlodipine.
Hypertension.

Nebiretic *Menarini, Neth.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nebiscal *Plus Pharma, Cz.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebispes *Galex, Cz.†; Galex, Hung.; Galex, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebistar *Lupin, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebistar-SA *Lupin, India.*
⊗Nebivolol (p. 1444·2); levamlodipine.
Hypertension.

Nebiten *Anthus, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebiten-H *Anthus, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nebithan *Worwag, Denm.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebitrix *Glenmark, Cz.; Glenmark, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebival *KVZ, Ukr.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebivas *Intra-Labs, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebivas-H *Intra-Labs, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nebivas-SA *Intra-Labs, India.*
⊗Nebivolol (p. 1444·2); levamlodipine.
Hypertension.

Nebivator *Torrent, Rus.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; ischaemic heart disease.

Nebivep *Extractum, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebivogen *Generics, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebivor *Orion, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Neblic
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Azithromycin (p. 221·2).
Bacterial infections.

Neblik
Note: this name may be used for preparations of different composition.
Astellas, Spain.
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Nebol *Rowex, Irl.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebris
Note: this name may be used for preparations of different composition.
Pharmafar, Ital.
Olax dissitiflora; chamomile (p. 2474·1).
Dry skin.

Teva, Neth.
Tobramycin (p. 380·1).
Pseudomonal lung infections in cystic fibrosis.

Nebtev *Teva, Irl.†*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nebufurd *Fabra, Arg.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Nebu-Iprasal *Teva, Belg.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Nebula *Zydus, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nebulasma *Urbion, Spain.†*
Sodium cromoglicate (p. 1225·3).
Asthma; bronchospasm.

Nebulcort *Italchimici, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; allergic rhinitis.

Nebulcrom *Sanofi-Aventis, Spain.*
Sodium cromoglicate (p. 1225·3).
Asthma; bronchospasm.

Nebulex *Laboratorios Chile, Chile.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Nebulgen *Athena, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; allergic rhinitis.

Nebulicina
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Spain.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Boehringer Ingelheim, Arg.
⊗Fenoxazoline hydrochloride (p. 1665·3).
Nasal congestion.

NebuPent *American Pharmaceutical, USA.*
Pentamidine isetionate (p. 944·3).
Pneumocystis pneumonia.

Nebusal *SteriMax, Canad.; Forest Laboratories, UK.*
Hypertonic sodium chloride (p. 1795·1).
Respiratory-tract congestion.

Nebusun *Tatsumi, Jpn.†*
Oxazolam (p. 1093·1).
Anxiety states; premedication; sleep disorders.

Nebutrax *Vannier, Arg.*
⊗Salbutamol (p. 1220·2).

Nebu-Trop *Teva, Belg.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

NEC *Piam, Ital.*
Protein-free preparation for enteral nutrition.
Renal disease.

Necamin *Ache, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Necare *Meridian, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate (p. 2515·3); manganese sulfate (p. 2081·2); dimethyl sulfone (p. 2493·3); vitamin E (p. 2119·1).

Necaxime *Nectar, Thai.*
Cefotaxime sodium (p. 244·1).
Bacterial infection.

Neceft *Nitin, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Neciblok *Kalbe, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Necid *New Research, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Neck + Chest Perfector *Avon, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neclav
Note: this name may be used for preparations of different composition.
Elfin, India.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Farmalider, Port.
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorders; behaviour disorders; autism.

Neclor *New Research, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Neclovir *ITA, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Necob *Nitin, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Necob Plus *Nitin, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).
Nitin, India.
Injection: Vitamin B substances (p. 2102·3).

Necon 0.5/35, 1/35 *Watson, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Necon 1/50 *Watson, USA.*
Norethisterone (p. 2294·2); mestranol (p. 2291·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Necon 10/11 *Watson, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Biphasic oral contraceptive.

Necopen *Esteve, Spain.†*
Cefixime (p. 240·3).
Bacterial infections.

Necro B6 *Bunker, Braz.*
Adenosine (p. 1291·1); methionine (p. 1558·2); betaine (p. 2456·1); choline citrate (p. 2055·2); pyridoxine hydrochloride (p. 2105·3).
Liver disorders.

Necta C *Maver, Chile.*
Sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Nectaday *Maver, Chile.†*
Vitamins; minerals; with or without ginseng (p. 2513·3).
Dietary supplement.

Nectadon-C *Intermed, Gr.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Nectadyn H *Heel, Neth.*
Baptisia tinctoria (p. 2647·2); drosera rotundifolia (p. 2497·2); hydrastis canadensis (p. 2528·1); ipecacuanha (p. 1667·2); rumex crispus (p. 2649·3); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Nectar G *Del Sol, Arg.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3); glucosamine (p. 2515·3).
Degenerative joint disorders; antoxidant.

Nectarmicin *Biomedica, Gr.*
Econazole nitrate (p. 577·3).
Fungal infections.

Nectozyme *Symbiosis, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Nécyrane *Pierre Fabre, Fr.*
Ritiometan magnesium (p. 1768·2).
Nose and throat infections.

Ned *Charak, India.*
Liquorice (p. 1853·2).

Neda-Früchtewürfel *Novartis Consumer, Austria.*
Senna (p. 1885·1); fig (p. 1843·2); liquid paraffin (p. 2191·2).
Formerly contained senna, fig, tamarind, and liquid paraffin
Constipation.

Neda Früchtewürfel *Novartis Consumer, Ger.†*
Senna (p. 1885·1).
Constipation.

Nedal *Polfa Warszawa, Pol.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nedax *Stiefel, Braz.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Nedax Plus *Stiefel, Braz.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Nedeltran *Sanofi-Aventis, Neth.*
Alimemazine tartrate (p. 615·1).
Hypersensitivity reactions.

Nedep *Biochemix, India.*
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Nedge *Elder, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Nediclon *Bruluart, Mex.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Nedios *Takeda, Neth.*
Acipimox (p. 1290·2).
Hyperlipidaemias.

Nedis *Omega, Arg.*
Miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Neditol *Aspire, UK.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Nedolon P *Merck Serono, Ger.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Nedopron *Euroned, Gr.*
Omeprazole sodium (p. 1867·2).

Nedoxal *Quimica y Farmacia, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Nee *Bennet, India.*
Doxycycline (p. 288·1).
Bacterial infections.

NEE 1/35 *Lexis, USA.*
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Need *Daksh, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Needin *Stadmed, India.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

Neem-MD *Biochemix, India.*
Nimesulide (p. 101·3).
Pain.

Neeri *Aimil, India.*
⊗Punarnava (p. 2601·1); tribulus terrestris (p. 2633·3).

Neet *Madhav, India.*
Nimesulide (p. 101·3).
Pain.

Neet Plus *Madhav, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Neet-S *Madhav, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

NeevoDHA *Pamlab, USA.*
Vitamins; minerals; algal oil; soy lecithin (p. 2542·2).
Dietary supplement.

Nefacool *Mankind, India.*
⊗Chlorphenamine maleate (p. 620·3); methylcellulose (p. 2197·3); naphazoline hydrochloride (p. 1669·3).

Nefadon
Note: this name may be used for preparations of different composition.
Ad-Drugstel, Philipp.
Cefalexin (p. 234·1).
Bacterial infections.
Mead Johnson, Gr.
Nefazodone hydrochloride (p. 438·2).
Depression.

Nefagrel *Phoenix, Arg.*
Prasugrel (p. 1472·3).

Nefalox *Lamda (Λαμδα), Gr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Nefazan *Phoenix, Arg.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Nefazan Compuesto *Phoenix, Arg.*
Tablets, clopidogrel bisulfate (Nefazan) (p. 1342·3); tablets, aspirin (p. 22·2).
Thromboembolic disorders.

Nefazol *New Research, Ital.*
Cefazolin sodium (p. 237·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Nefelid *Farmamust, Gr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nefersil *Pharma Investi, Chile.*
Clonixin lysine (p. 40·1).
Pain.

Nefersil B *Pharma Investi, Chile.*
Clonixin lysine (p. 40·1); thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin acetate (p. 2107·3).
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

Nefid *Dalmia, India.*
⊗Euphorbia microphylla (p. 2501·3); tribulus terrestris (p. 2633·3).
Renal calculi.

Nefirel *BMS, Gr.*
Nefazodone hydrochloride (p. 438·2).
Depression.

Neflo *Evershine, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Neflo-P *Evershine, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Neflox *Lamsa, Arg.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Neflox-TZ *Bactolac, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Nefluan *Molteni, Ital.; Stada, Rus.*
⊗Lidocaine hydrochloride (p. 1988·2); neomycin sulfate (p. 330·1); fluocinolone acetonide (p. 1636·1).
Endoscopy; catheterisation; urinary-tract inflammation; rectal disorders.

Nefoben *Ivax, Arg.*
Theophylline (p. 1229·3) or theophylline sodium glycinate (p. 1229·3).
Obstructive airways disease.

Nefoxef *Mylan, Denm.; Mylan, Fin.; Mylan, Swed.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Nefrecil *Labor, Pol.†*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Nefrin
Note: this name may be used for preparations of different composition.
Sophia, Mex.
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

Nefrisol *Shree Ganesh, India.*
Phenylephrine hydrochloride (p. 1672·3).

Nefroamino *Braun, Chile.*
Amino acids.
Parenteral nutrition in renal failure.

Nefrobonisol *Bonimed, Pol.*
Achillea (p. 2427·3); birch leaf (p. 2457·3); equisetum (p. 2500·1); solidago (p. 2620·1); taraxacum (p. 2625·3); urtica (p. 2639·3).
Renal calculi; hyperuricaemia.

Nefrocarnit *Medice, Austria; Medice, Ger.; Medice, Neth.*
Levocarnitine (p. 2053·2).
Carnitine deficiency.

Nefro-Carnitin *Assos, Turk.*
Levocarnitine (p. 2053·2).

Nefrodial *Abbott, Braz.*
Preparation for enteral nutrition in renal disease.

Nefrofer *Kalbe, Indon.*
Iron sucrose (p. 2078·1).
Adjunct to erythropoietin in haemodialysis-induced iron-deficiency anaemia.

Nefrol *Herbapol Krakow, Pol.*
Ammi visnaga (p. 2441·2); petroselinum sativum; phaseolus vulgaris (p. 2587·3); solidago (p. 2620·1); taraxacum (p. 2625·3).
Renal calculi.

Nefronet *Ronnet, Arg.*
Norfloxacin (p. 333·3).
Genito-urinary infections.

Nefrosave *Fourrts, India.*
Acetylcysteine (p. 1652·2); taurine (p. 2626·2).

Nefroselamin *Biosel, Turk.†*
Amino acids.
Parenteral nutrition.

Nefrosept *Afloform, Pol.*
Bearberry (p. 2453·2); solidago (p. 2620·1).
Urinary-tract disorders.

Nefrotal *Roemmers Rowe, Venez.*
Losartan potassium (p. 1422·2).
Heart failure; hypertension.

Nefrotal H *Roemmers Rowe, Venez.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nefrotect *Fresenius Kabi, Ukr.*
Amino acids.
Parenteral nutrition in renal failure.

Nefro-Zinc *Medice, Ger.†*
Zinc chloride (p. 2126·1).
Zinc deficiency in dialysis patients.

Nefryl *Armstrong, Mex.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Nefsul *Nitin, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Nefter *Neiss, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Neftum-AXT *Nutramedica, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Neftum-SB *Nutramedica, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Nefzon *Nitin, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Negaban *Eumedica, Belg.; Eumedica, UK.*
Temocillin sodium (p. 372·3).
Gram-negative bacterial infections.

Negacef *Julphar, UAE.*
Ceftazidime (p. 250·2).
Bacterial infections.

Negacne *Wierham, Arg.*
Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); zinc sulfate (p. 2126·2); coltsfoot (p. 1659·2); aloe vera (p. 1693·2).
Acne.

Negadix *CFL, India.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Negadix-M *Cosme, India.*
Metronidazole (p. 936·1); nalidixic acid (p. 328·3).

Negafen *Julphar, UAE.*
Terbinafine hydrochloride (p. 593·3).

Negaflox *Zydus, India; Cadila, Rus.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Negaplus *Orchid, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Negaporosis *Bajer, Arg.*
Calcium carbonate (p. 1824·3); sodium monofluorophosphate (p. 2091·3).
Osteoporosis.

Negatol *Nycomed, Ital.*
Policresulen (p. 1160·2).
Gynaecological disorders; wounds; furunculosis; chilblains.

Négatol Dental *Wild, Switz.*
Policresulen (p. 1160·2).
Gingival haemorrhage; aphthous stomatitis.

Negazole *Julphar, UAE.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Protozoal infections; anaerobic bacterial infections; bacterial vaginosis; dracunculiasis; inflammatory bowel disease.

NegGram *Sanofi-Aventis, USA.†*
Nalidixic acid (p. 328·3).
Gram-negative urinary-tract infections.

Negortire *Armstrong, Mex.*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Negram *Sanofi, Irl.†; KRKA, Rus.*
Nalidixic acid (p. 328·3).
Bacterial infections.

Negrustin *Hexal, Rus.*
St John's wort (p. 449·1).
Depression; anxiety.

Neholis *Procesos Farmaceuticos Industriales, Spain.*
Senna (p. 1885·1).
Constipation.

Nehydrin *Sanochemia, Austria.†*
Dihydroergocristine mesilate (p. 390·1).
Cerebrovascular disorders.

Nei Zhang Qing *Wuhan Wujing, China.*
Thyroxine sodium (p. 2339·1); liothyronine (p. 2342·3).

Nei De Zi *Jinyu, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Neipilept *Soteks, Rus.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

NeiQing *Hisun, China.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Neirispin *Zdorovje, Ukr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Neiromet *Veropharm, Rus.*
Idebenone (p. 392·3).
Cerebrovascular disorders; mental function disorders; vestibular disorders.

Neiromidin *Olainfarm, Rus.*
Ipidacrine (p. 687·1).
Nervous system disorders.

Neiromidinum *Olainfarm, Ukr.*
Ipidacrine (p. 687·1) or ipidacrine hydrochloride (p. 687·1).
Peripheral nervous system disorders; mental function impairment; myasthenia; multiple sclerosis; gastrointestinal atony.

Neiron *Mili, Ukr.*
Thiamine nitrate (p. 2103·2); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Disorders associated with vitamin B deficiency.

NeisVac *Baxter, Fr.*
A meningococcal group C conjugate vaccine (tetanus toxoid protein conjugate) (p. 2401·3).
Active immunisation.

NeisVac-C *Baxter Immuno, Arg.; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; GSK, Canad.; Baxter, Chile; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK.*
A meningococcal group C conjugate vaccine (tetanus toxoid protein conjugate) (p. 2401·3).
Active immunisation.

Neitrostim *Vector, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Neivex *Aurobindo, India.*
Nelfinavir (p. 1004·1).
HIV infection.

Nekacin *New Research, Ital.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Neko *Pfizer, India.*
Triclocarban (p. 1773·2).

Neksium *AstraZeneca, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Nektol *Vamsler, Philipp.†*
Paracetamol (p. 115·1).
Fever; pain.

Nel *McNeil & Argus, India.*
Nelfinavir (p. 1004·1).
HIV infection.

Nelabocin *Pharmathen, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Neladex *World Medicine, Ukr.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Inflammatory eye disorders; otitis media.

Neladryl DMP *Galenium, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); paracetamol (p. 115·1).
Fever; cough; respiratory-tract congestion.

Neladryl Expectorant *Galenium, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Nelapine *Littman, Philipp.; Berlin Pharm, Thai.*
Nifedipine (p. 1447·2).
Cardiac disorders; hypertension; angina pectoris; Raynaud's syndrome.

Nelbinex *Pharmathen, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Nelconil *SJA, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Neldim *Vilco, Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Nelet *Gerard, Irl.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nelex *Nycomed, Port.*
Policresulen (p. 1160·2).
Cervical erosion; cervicitis; vaginal disorders.

Nelfigen *Vitarum, Arg.†*
Diphenhydramine (p. 626·1).

Nelfilea *Elea, Arg.*
Nelfinavir mesilate (p. 1004·1).
HIV infection.

Neliacan *Pharmathen, Gr.*
Flurbiprofen (p. 65·2).

Nelicort *GMP, Indon.*
⊗Fludrocortisone acetate (p. 1634·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Otitis externa; inflammatory ear disorders.

Nelin *Biolab, Thai.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Neliprax *Pharmathen, Denm.†; Arti, Pol.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Neloren *Lek, Cz.; Sandoz, Pol.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Lek, Rus.†
Lincomycin (p. 317·1).
Bacterial infections.

Nelorpin *Ferrer, Spain.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Nelsid *Ind-Swift, India.*
Tablets: Nimesulide (p. 101·3).
Pain.

Ind-Swift, India.
Topical gel: Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); nimesulide (p. 101·3).

Nelsid Fort *Ind-Swift, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nelsid Plus *Ind-Swift, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nelsid-MR *Ind-Swift, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nelsid-S *Ind-Swift, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nelsons Clikpak Series *Nelson, UK.*
A range of homoeopathic remedies.
Homoeopathic preparation.

Nelsons Noctura *Hanseler, Switz.†*
Alfalfa (p. 2433·1); avena sativa (p. 2451·1); coffea arabica (p. 2648·2); humulus lupulus (p. 2546·1); kalii bromidum (p. 2461·1); passiflora incarnata (p. 2584·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Nelsons Pollenna *Hanseler, Switz.†*
Allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); schoenocaulon officinale (p. 2611·2).
Homoeopathic preparation.

Nelsons Sinusit *Hanseler, Switz.†*
Hydrastis canadensis (p. 2528·1); kalii dichromas (p. 2476·3); pulsatilla pratensis (p. 2600·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Nelsons Traumatica *Hanseler, Switz.†*
Arnica montana (p. 2447·2); hypericum perforatum (p. 449·1); rhus toxicodendron (p. 2603·3); ruta graveolens (p. 2608·2); symphytum officinale (p. 2484·2).
Homoeopathic preparation.

Nelsons Travella *Hanseler, Switz.†*
Anamirta cocculus (p. 2483·1); apomorphini hydrochloridum (p. 892·3); delphinium staphisagria; nicotiana tabacum (p. 2632·2); petroleum (p. 2587·2); strychnos nux-vomica (p. 2573·3); theridion curassavicum.
Homoeopathic preparation.

Neltolon *Pharmathen, Gr.*
Bifonazole (p. 573·3).

Nelvir *Cipla, India; Cipla, Venez.*
Nelfinavir mesilate (p. 1004·1).
HIV infection.

Nelya *Phagecon, Cz.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Nemaban *Yacca, India.*
Albendazole (p. 149·1).
Worm infections.

Nemacina *LKM, Arg.*
Nelfinavir mesilate (p. 1004·1).
HIV infection.

Nemactil *IFET [ΙΦΕΤ], Gr.; Sanofi-Aventis, Spain.*
Pericyazine (p. 1095·2).
Psychoses; behaviour disorders; anxiety.

Nemalin *Valetudo, Ital.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Nemapres *Kener, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Nemasole *Janssen-Cilag, Arg.*
Mebendazole (p. 158·3).
Worm infections.

Nembutal *Ovation, USA.*
Pentobarbital sodium (p. 1095·1).
Sedative; insomnia; premedication; epilepsy.

Nemdatine *Actavis, UK.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Nemdyn *Valeant, Austral.*
Neomycin undecenoate (p. 330·1); bacitracin zinc (p. 225·3).
Fungal or bacterial ear infections.

Nemea *Adamed, Spain.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses in parkinsonism.

Nemegel *Medica, Arg.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3); zinc oxide (p. 1729·1); vitamin A palmitate (p. 2098·3).
Acne.

Nemeriv *East African, India.*
Nimesulide (p. 101·3).
Pain.

Nemeriv-P *East African, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nemerop *Hospital Line, Gr.*
Meropenem (p. 321·3).
Bacterial infections.

Nemestran *Sanofi-Aventis, Arg.; Sanofi, China; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.†; Sanofi-Aventis, Rus.; Sanofi-Aventis, Switz.†*
⊗Gestrinone (p. 2280·2).
Endometriosis.

Nemexin *Torrex, Austria†; Torrex Chiesi, Cz.†; BMS, Ger.; Torrex, Hung.†; BMS, Switz.†*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal.

Nemicina *Bunker, Braz.*
Neomycin sulfate (p. 330·1).
Bacterial skin infections.

Nemil *Kramer, India.*
Nimesulide (p. 101·3).
Pain.

Nemil-Os *Kopran, Thai.†*
Nimesulide (p. 101·3).
Inflammation; musculoskeletal and joint disorders; fever.

Nemocebral *Ivax, Arg.*
Idebenone (p. 392·3).
Cerebrovascular disorders.

Nemocebral Plus *Ivax, Arg.*
Idebenone (p. 392·3); nimodipine (p. 1455·2).
Cerebrovascular disorders; mental function impairment.

Nemocid *Ipca, India; Ipca, Rus.*
Pyrantel embonate (p. 165·3).
Worm infections.

Nemodine
Note: this name may be used for preparations of different composition.
Dollder, Venez.
Nimodipine (p. 1455·2).
Mental function impairment; ischaemic neurological deficit.

Kener, Mex.
Ketotifen fumarate (p. 631·3).
Hypersensitivity reactions.

Nemofex *Pharma Synth, India.*
Albendazole (p. 149·1).
Worm infections.

Nemon *Chemo-Drugs, India.*
Nimesulide (p. 101·3).
Pain.

Nemoril *Gelpharma, Mex.*
Ginkgo biloba (p. 2512·3).
Dietary supplement.

Nemotan *Medochemie, Rus.†*
Nimodipine (p. 1455·2).

Nemozole *Ipca, India; Ipca, Rus.*
Albendazole (p. 149·1).
Worm infections; hydatid cyst.

Nems *Helm, Port.*
Omeprazole (p. 1867·2).
Gastric hyperacidity; dyspepsia.

Nency-P *Zenon, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nene Dent
Note: this name may be used for preparations of different composition.
Nycomed, Arg.
Benzocaine (p. 1980·2); ethacridine lactate (p. 1732·3); acriflavinium chloride (p. 1732·3).
Mouth disorders.

Nycomed, Mex.
Lidocaine hydrochloride (p. 1988·2); lauromacrogol 400 (p. 2194·1).
Teething pain.

Nenê Dent N *Nycomed, Braz.*
Lidocaine hydrochloride (p. 1988·2); lauromacrogol 400 (p. 2194·1); chamomile (p. 2474·1).
Teething disorders.

Nene Dent NF *Nycomed, Arg.*
Chamomile (p. 2474·1); lidocaine hydrochloride (p. 1988·2); lauromacrogol 400 (p. 2194·1).
Gingivitis.

Nenedent
Note: this name may be used for preparations of different composition.
Zuoz, Venez.
Lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Nenegloss *Maver, Chile.†*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3); allantoin (p. 1693·1); with or without aloe vera (p. 1693·2).
Cicatrisation.

Nenegloss Z *Maver, Chile.*
Zinc oxide (p. 1729·1).
Barrier preparation.

Nene-Lax *Dentinox, Ger.*
⊗Glycerol (p. 2517·2).
Bowel evacuation; constipation.

Neo *Charak, India.*
Liquorice (p. 1853·2).
Nocturnal enuresis; premature ejaculation.

Neo Akmine *Elvipe, Gr.*
Resorcinol (p. 1718·3); sulfur (p. 1721·1).

Neo Alertop *Laboratorios Chile, Chile.*
Levocetirizine (p. 632·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Neo A-V *Neo Dermos, Arg.*
Salicylic acid (p. 1719·1).
Astringent.

Neo Axedil *Norma [Νορμα], Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neo Baby Cream *Neo Laboratories, UK.*
Cetrimide (p. 1742·1); benzalkonium chloride (p. 1737·1).
Nappy rash; skin irritation.

Neo Baby Gripe Mixture *Neo Laboratories, UK.*
Dill oil (p. 2493·2); Strong Ginger Tincture BP (p. 1844·1); sodium bicarbonate (p. 1781·1).
Infant colic.

Neo Bacitrin *Rottapharm, Spain.†*
Ointment: Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); zinc oxide (p. 1729·1).
Burns; skin infections; ulcers; wounds.

Neo Bendazol *Neo Química, Braz.*
Albendazole (p. 149·1).
Worm infections.

Neo Borocillina *Wassermann, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); sodium benzoate (p. 1738·2).
Mouth and throat disinfection.

Neo Borocillina Ant Oro *Wassermann, Ital.*
Benzyl alcohol (p. 1739·3); sodium benzoate (p. 1738·2).
Mouth and throat disorders.

Neo Borocillina Balsamica *Wassermann, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); terpin hydrate (p. 1678·2); menglytate (p. 1669·1).
Mouth and throat disinfection; respiratory-tract infections.

Neo Borocillina C *Wassermann, Ital.*
Dichlorobenzyl alcohol (p. 1750·2); ascorbic acid (p. 2110·3).
Mouth and throat disinfection.

Neo Borocillina Collutorio *Wassermann, Ital.*
Dichlorobenzyl alcohol (p. 1750·2).
Mouth and throat disinfection.

Neo Borocillina Decong *Wassermann, Ital.*
Camphor (p. 2466·2); cineole (p. 2479·1); menglytate (p. 1669·1).

Neo Borocillina Spray *Wassermann, Ital.*
Dichlorobenzyl alcohol (p. 1750·2).
Mouth and throat disinfection.

Neo Borocillina Tosse Compresse *Wassermann, Ital.*
Dextromethorphan hydrobromide (p. 1660·1); dichlorobenzyl alcohol (p. 1750·2).
Cough; mouth and throat disinfection.

Neo Butartrol *Sanitas, Chile.*
Ibuprofen (p. 68·2); dipyrone (p. 53·3); chlormezanone (p. 1045·1).
Headache; musculoskeletal and joint disorders.

Neo Butazol *Neo Química, Braz.*
Phenylbutazone calcium (p. 125·1).

Neo C *GNLD, Austral.*
Ascorbic acid (p. 2110·3); Neo-Plex Concentrate (orange juice; orange peel; orange bioflavonoid complex); acerola; rose fruit (p. 2607·1); rutoside (p. 2505·3); hesperidin (p. 2505·2); lemon bioflavonoid complex.
Vitamin C deficiency.

Neo Cal
Note: this name may be used for preparations of different composition.
Golden Neo-Life, Canad.
Vitamins; minerals.
Neolab, Canad.†
Calcium carbonate (p. 1824·3).

Neo Cal D *Neolab, Canad.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).

Neo Cardiol *Francia, Ital.†*
Levocarnitine (p. 2053·2).
Carnitine deficiency; myocardial ischaemia.

Neo Cebetil *Uniao Química, Braz.*
Ampoule A, vitamin B substances (p. 2102·3); ampoule B, vitamin C (p. 2110·3); fructose (p. 2068·2).

Neo Cefadril *Neo Química, Braz.*
Cefadroxil (p. 233·2).
Bacterial infections.

Neo Cefix *Neo Química, Braz.*
Cefixime (p. 240·3).
Bacterial infections.

Neo Ceflex *Neo Química, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Neo Cepacol Pastiglie *Sanofi-Aventis, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disinfection.

Neo Citran *Novartis, Austria; Novartis Consumer, Hung.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Neo Citran Chest Congestion & Cough *Novartis, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).

Neo Citran Colds & Flu *Novartis Consumer, Canad.*
Oral powder: Pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Neo Citran Coughs Colds & Flu *Novartis Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Neo Citran D M *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); dextromethorphan hydrobromide (p. 1660·1).

Neo Citran Extra Strength Cold & Sinus *Novartis Consumer, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Neo Citran Grippe/refroidissement *Novartis Consumer, Switz.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Neo Citran Non Drowsy Cold & Flu *Novartis Consumer, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Neo Citran Sinus *Novartis Consumer, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Neo Citran Sore Throat & Cough *Novartis Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Neo Citran Total *Novartis Consumer, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Neo Clotrimazyl *Neo Química, Braz.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Neo Coltirot *Roux-Ocefa, Arg.*
Topical spray: Neomycin sulfate (p. 330·1); gramicidin (p. 308·3); benzalkonium chloride (p. 1737·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Neo Davenol *Sunthi Sepuri, Indon.†; Wyeth, Indon.†*
Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms; allergic disorders.

Neo Decapeptyl *Ache, Braz.*
⊗Triptorelin embonate (p. 2311·1).
Prostatic cancer.

Neo Diaform *Corsa, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Neo Diastop *Armoxindo, Indon.*
Attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Neo DM
Note: this name may be used for preparations of different composition.
Laser, USA.
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Cough; cold symptoms.

Neo Doxicilin *Neo Química, Braz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Neo Durasina *GSK Consumer, Spain.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Neo Eblimon *Guidotti, Ital.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; inflammation.

Neo Emocicatrol *Bouty, Ital.*
Tannic acid (p. 2625·2); benzalkonium chloride (p. 1737·1).
Disinfection of the nasal mucosa.

Neo Emoform *Polifarma Benessere, Ital.*
Sodium monofluorophosphate (p. 2091·3); hexetidine (p. 1755·1).
Oral hygiene; gingivitis.

Neo Entrostop *Kalbe, Indon.*
Activated attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Neo Esoformolo *Esoform, Ital.*
Sodium *o*-phenylphenol (p. 1762·3).
Surface disinfection.

Neo Fedipina *Neo Química, Braz.*
Nifedipine (p. 1447·2).
Hypertension.

Neo Fenicol *Neo Química, Braz.*
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Neo Fluostomygen *Stomygen, Ital.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Neo Fólico *Neo Química, Braz.*
Folic acid (p. 2063·1).
Anaemias.

Neo Formitrol *Mipharm, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Mouth disinfection.

Neo Fulvigal *Anfarm, Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Neo Furasil *Neo Química, Braz.*
Furazolidone (p. 933·3).
Gastrointestinal infections.

Neo Gripe Mixture *Neo Laboratories, UK.*
Dill oil (p. 2493·2); ginger (p. 1844·1); sodium bicarbonate (p. 1781·1).
Colic; teething.

Neo Gynoxa *Kalbe, Indon.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Neo H2 *Boniscontro & Gazzone, Ital.*
Roxatidine acetate hydrochloride (p. 1884·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neo HC
Note: this name may be used for preparations of different composition.
Laser, USA.
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Neo Hidroclor *Neo Química, Braz.*
⊗Hydrochlorothiazide (p. 1403·2).
Diuretic.

Neo Hormoviton *Tempo Scan Pacific, Indon.*
Oral liquid: Arginine (p. 2049·1); yohimbe; ginseng (p. 2513·3); royal jelly (p. 2608·1); vitamin B substances (p. 2102·3).
Tonic for males.

Tempo Scan Pacific, Indon.
Capsules: Yohimbe; damiana (p. 2491·3); ginseng (p. 2513·3); zinc (p. 2126·1); vitamin B substances (p. 2102·3); royal jelly (p. 2608·1).
Tonic for males.

Neo Hormoviton Greng *Tempo Scan Pacific, Indon.*
Arginine (p. 2049·1); yohimbe; ginseng (p. 2513·3); vitamin B substances (p. 2102·3); royal jelly (p. 2608·1).
Tonic for males.

Neo Hubber *Teofarma, Spain.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Ear disorders; rhinitis.

Neo Iodine *Combiphar, Indon.*
Povidone-iodine (p. 1767·1).
Mouth and throat disorders; skin disinfection; skin and wound infections.

Neo Isocaden *Neo Química, Braz.*
Isoconazole nitrate (p. 583·2).
Vaginal infections.

Neo Itrax *Neo Química, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Neo Kaocitin *Erlimpex, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Neo Kaolana *Sanbe, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Neo Kaominal *MolexAyus, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Neo Kef *Phoenix, Arg.*
Loperamide hydrochloride (p. 1854·2); neomycin sulfate (p. 330·1).
Diarrhoea.

Neo Koniform *Konimex, Indon.†*
Activated attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Neo Lactoflorene *Montefarmaco, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins.
Nutritional supplement.

Neo Larmax *Andromaco, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Neo Linco *Neo Química, Braz.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Neo Loratadin *Neo Química, Braz.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Neo Mebend *Neo Química, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Neo Melubrina *Sanofi-Aventis, Spain.†*
Dipyrone (p. 53·3).
Pain; fever.

Neo Metrodazol *Neo Química, Braz.*
Metronidazole (p. 936·1).

Neo Mistatin *Neo Química, Braz.*
Nystatin (p. 590·3).
Candidiasis.

Neo Mom *Candioli, Ital.*
Shampoo: Phenothrin (p. 2160·1).
Pediculosis.

Candioli, Ital.
Topical powder: Tetramethrin (p. 2162·2); phenothrin (p. 2160·1).
Pediculosis.

Neo Moxicilin *Neo Química, Braz.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Neo Moxilin *Neo Química, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Neo Multigrin *Grin, Mex.†*
Vitamins; minerals.

Neo Napacin *Konimex, Indon.†*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2).
Asthma.

Neo Nifalium *Pharmanik (Φαρμανικ), Gr.*
Flunitrazepam (p. 1073·3).
Insomnia.

Neo Nisidina *Boehringer Ingelheim, Ital.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever; cold symptoms.

Neo Novapon *Tanabe, Indon.*
⊗Paracetamol (p. 115·1); tipepidine hibenzate (p. 1679·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); alcohol (p. 1733·1).
Cold and influenza symptoms; cough.

Neo Novapon Plus *Tanabe, Indon.*
Paracetamol (p. 115·1); ethenzamide (p. 56·2); tipepidine hibenzate (p. 1679·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

neo OPT *Optimed, Ger.†*
Bromazepam (p. 1041·2).
Anxiety; sleep disorders.

Neo Pelvicillin *Temis, Arg.*
Metronidazole (p. 936·1); miconazole (p. 588·3); neomycin sulfate (p. 330·1);

polymyxin B sulfate (p. 342·3); centella (p. 1698·3).
Vulvovaginal infections.

Neo Prodiar *Erlimpex, Indon.*
Furazolidone (p. 933·3).
Gastrointestinal infections.

Neo Química Colírio *Neo Quimica, Braz.†*
⊗Naphazoline hydrochloride (p. 1669·3); zinc phenolsulfonate (p. 1729·3); berberine sulfate (p. 2455·1).
Eye congestion.

Neo Resiguard *Nicholas, Indon.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Hand disinfection; skin infections; wounds.

Neo Rheumacyl *Bode, Indon.; Tempo Scan Pacific, Indon.*
Cream: Menthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain; sprains.

Bode, Indon.; Tempo Scan Pacific, Indon.
Tablets: Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Neo Rheumacyl Neck and Shoulder *Bode, Indon.; Tempo Scan Pacific, Indon.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus (p. 2501·1).
Neck and shoulder pain.

Neo Rheumacyl Neuro *Bode, Indon.; Tempo Scan Pacific, Indon.*
Ibuprofen (p. 68·2); vitamin B_1 (p. 2102·3) vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain with numbness and cramp.

Neo Rhinovit *Menarini, Gr.*
⊗Ephedrine hydrochloride (p. 1663·2).
Nasal congestion.

Neo Rinactive *Alcon, Port.†; M4, Spain†; Alcon, Turk.*
⊗Budesonide (p. 1625·1).
Rhinitis; nasal polyps.

Neo Rinoleina *Sanofi-Aventis, Ital.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Neo Sampoon *Eisai, Hong Kong†; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore.†*
Menfegol (p. 2553·2).
Spermicidal contraceptive.

Neo Sedeks *Sistas, Turk.*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2); potassium iodide (p. 2336·3).
Respiratory-tract congestion.

Neo Stress *Bioglan, Austral.†*
Vitamins; minerals; amino acids.

Neo Tionazol *Neo Quimica, Braz.*
Tioconazole (p. 595·3).
Fungal infections.

Neo Tomizol *Ferrer, Spain.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Neo Triaminic *Novartis, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Neo Tusilan *Landson, Indon.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough; cold symptoms; allergic disorders.

Neo Urgenin *Neo-Farmaceutica, Port.; Rottapharm, Spain.†*
Echinacea angustifolia (p. 2498·1); pygeum africanum (p. 2363·2); saw palmetto (p. 2363·3).
Prostatic disorders.

Neo Verpamil *Neo Quimica, Braz.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; hypertension.

Neo-Active Antirheumatic *Christo, Hong Kong.†*
Phenazone (p. 124·1); vitamin B substances (p. 2102·3).

Neo-Active Vit B-1 *Christo, Hong Kong.†*
Thiamine (p. 2102·3).

Neo-Active Vit B-12 *Christo, Hong Kong.†*
Cyanocobalamin (p. 2107·2).

Neo-Adinal *Norma (Νορμα), Gr.*
Carbocisteine (p. 1658·1).

Neo-adlibamin *Norma (Νορμα), Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Neo-Aesculan *Herbapol Poznan, Pol.*
Esculoside (p. 2431·2); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

NeoAfrin *Schering-Plough, Pol.*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Rhinitis; sinusitis.

Neoalexil *Diba, Mex.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Neo-Alledryl *Prater, Chile.*
Desloratadine (p. 625·1).

Neoamiyu *Mitsubishi, China; Ajinomoto, Thai.*
Amino acids.
Parenteral nutrition in renal failure; parenteral nutrition in renal insufficiency.

Neoamox *Tum, Turk.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Neo-Angin
Note: this name may be used for preparations of different composition.
Klosterfrau, Austria; Divapharma, Cz.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2); anise oil (p. 2444·3); peppermint oil (p. 1877·1).
Mouth and throat disorders.

Divapharma, Ger.; Divapharma, Hung.; Divapharma, Pol.; Divapharma, Ukr.
Dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Divapharma, Rus.
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2) levomenthol (p. 2553·2).
Mouth and throat disorders.

Doetsch, Grether, Switz.
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Neo-Angin avec lidocaine et chlorhexidine *Doetsch, Grether, Switz.*
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Neo-Antiasthman *Minerva (Μινερβα), Gr.*
Theophylline (p. 1229·3).

Neo-antiperstam *Biostam (Βιοσταμ), Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Neo-Anusol *Nizhpharm, Rus.*
Bismuth subnitrate (p. 1822·1); zinc oxide (p. 1729·1); tannic acid (p. 2625·2); resorcinol (p. 1718·3); iodine (p. 2336·3); methylthioninium chloride (p. 1559·1).
Anorectal disorders.

Neo-Argicilline *Petsiavas, Gr.*
Gramicidin (p. 308·3).

Neoasma *Tarmac, USA.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Neoastrin *Lafedar, Arg.*
Neomycin sulfate (p. 330·1); bismuth subcarbonate (p. 1822·1); activated charcoal (p. 1537·3); papaverine hydrochloride (p. 2362·3); atropine sulfate (p. 1310·2); vitamins.
Gastrointestinal disorders.

Neoate *APT, Hong Kong.†*
Neomycin sulfate (p. 330·1).
Bowel preparation before abdominal surgery.

Neoazarina *Herbapol Wroclaw, Pol.*
Greater celandine (p. 2522·2); codeine phosphate (p. 40·2); thyme (p. 2630·2).
Catarrh; cough.

Neo-B12 *Hospira, Austral.; Hospira, NZ.*
Hydroxocobalamin chloride (p. 2107·3).
Vitamin B_{12} deficiency anaemias; optic neuropathy.

Neobac *Dermapharm, Ger.†*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Burns; wounds; skin and nose infections.

Neobacigrin *Grin, Mex.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Infected inflammatory eye disorders.

Neobacipan *Royton, Braz.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Skin infections.

Neobacitracine *Erfa, Belg.*
Drops; inhalation: Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial eye, ear, nose, and skin infections.

Erfa, Belg.
Ointment: Bacitracin (p. 225·3); polymyxin b sulfate (p. 342·3).
Skin infections.

Neobate *Alna, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin (p. 329·3).

Neobefol *Italfarmaco, Port.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Folic acid and vitamin B_{12} deficiency; prevention of neural tube defects.

NeoBenz *SkinMedica, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Neobes *Medix, Mex.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Neobet *Medicpharma, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neo-Betasone *Hovid, Singapore.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neo-Bex *Brostel, Canad.*
Vitamin B substances (p. 2102·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.

Neo-Bex Forte *Neolab, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Neobid *Brussels, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Neo-Bilagit *Sanofi-Aventis, Hung.*
Papaverine hydrochloride (p. 2362·3); homatropine methylbromide (p. 2007·3); dehydrocholic acid (p. 2492·1).

Neobitiol *Fortbenton, Arg.*
Aluminium chlorohydrate (p. 1694·1); neomycin (p. 329·3).
Hyperhidrosis.

Neoblanc *Fortbenton, Arg.*
⊗Fluocinolone (p. 1636·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).
Melasma.

Neobloc *Trima, Israel; GX, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension; migraine; myocardial infarction; arrhythmias.

Neobol *Unipharm, Mex.*
⊗Neomycin sulfate (p. 330·1); clostebol acetate (p. 2260·1).
Infected skin disorders; infected burns, wounds, and ulcers.

Neobonsen *Salus, Ger.*
Evening primrose oil (p. 2502·2).
Eczema.

Neoboost *Darya-Varia, Indon.*
Echinacea purpurea (p. 2498·1); andrographis (p. 2443·2); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Immunostimulant; cold symptoms.

Neoboost Kids *Darya-Varia, Indon.*
Echinacea purpurea (p. 2498·1); propolis (p. 2597·3); ascorbic acid (p. 2110·3); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Immunostimulant; cold symptoms.

Neo-botacreme *Target, Gr.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Neobradoral *Novartis Consumer, Port.*
Domiphen bromide (p. 1751·1).
Mouth and throat infections.

Neo-Bromexan *Medi-Rx, Philipp.*
Chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; nasal congestion.

Neo-Bromexan Forte *Medi-Rx, Philipp.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Fever; nasal congestion; pain.

Neo-Bronchol
Note: this name may be used for preparations of different composition.
Divapharma, Cz.; Divapharma, Rus.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Neo-Bronchoton-R *Elvipe, Gr.*
⊗Ipecacuanha (p. 1667·2); racephedrine hydrochloride (p. 1663·2).

Neo-Brontyl *Collins, Mex.†*
Guaifenesin (p. 1666·2); sodium dibunate (p. 1677·3); dipyrone (p. 53·3).
Cough.

NeoBros *Fidia, Ital.*
Phosphatidyl serine (p. 2589·1); vitamin E (p. 2119·1).
Mental function disorders.

NeoBros 10 *Fidia, Ital.*
Phosphatidyl serine (p. 2589·1); vitamins; minerals.
Mental function disorders.

NeoBros C *Fidia, Ital.*
Phosphatidyl serine (p. 2589·1); creatine (p. 2488·3); vitamins; minerals.
Nutritional supplement.

Neobrufen *Abbott, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; fever.

Neobrufen con Codeina *Abbott, Spain.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Neobutamina *Neo Quimica, Braz.*
Dobutamine hydrochloride (p. 1365·3).

Neo-C
Note: this name may be used for preparations of different composition.
Jumont, Philipp.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Neocaína *Cristalia, Braz.*
Bupivacaine hydrochloride (p. 1980·3).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Neocalcit *DAST, Gr.*
Calcium phosphate (p. 1784·2).
Prevention and treatment of calcium deficiency.

Neocalm *Intas, India.*
Trifluoperazine (p. 1113·2).
Psychoses; nausea and vomiting; anxiety.

Neocalm Forte *Intas, India.*
Chlorpromazine (p. 1045·2); trifluoperazine hydrochloride (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).

Neocalm Plus *Intas, India.*
Trifluoperazine (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).

Neocalmans *Chobet, Arg.*
⊗Morphine hydrochloride (p. 92·3) or morphine sulfate (p. 92·3).
Pain.

Neo-Candimyk *Viofar, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Neocapil *Spirig, Cz.; Medicine & Business, Hung.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Néocapil *Spirig, Switz.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Neo-Capsiderm *Herbapol Poznan, Pol.*
Camphor (p. 2466·2); capsaicin (p. 35·1); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Neuromuscular pain.

Neocarb *Biological E, India.*
Carboplatin (p. 759·1).
Ovarian cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neocarbo *Neocorp, Ger.†*
Carboplatin (p. 759·1).
Malignant neoplasms.

Neocard-Atn *Neon, India; Neon, Ukr.†*
⊗Amlodipine besilate (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Neocardina *Herbapol Wroclaw, Pol.*
Convallaria (p. 2486·2); crataegus (p. 2488·1); valerian (p. 2640·2).
Cardiovascular disorders.

Neocard-Lis *Neon, India; Neon, Ukr.†*
Amlodipine besilate (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Neocardon *Gap, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Neocare
Note: this name may be used for preparations of different composition.
Cantabria, Spain.
Tretinoin (p. 1725·2).
Acne.

VHB, India.
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Neocate *Nutricia, Austral.; Support, Braz.; Nutricia, China; SHS, Cz.; SHS, Denm.; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Hong Kong; Nutricia, Indon.; Nutricia, Irl.; SHS, Israel; Nutricia, Ital.; SHS, Malaysia; Nutricia, NZ; Nutricia, Port.; Nutricia, Singapore; SHS, Singapore; Scientific Hospital Supplies, UK.*
Infant feed.
Elemental diet; whole protein intolerance; bowel disorders; malabsorption; cows' milk allergy.

Neocate Advance *SHS, Israel.*
Preparation for enteral nutrition.
Food allergy.

Neocate One + *SHS, USA.*
Preparation for enteral nutrition.

Neocef
Note: this name may be used for preparations of different composition.
Atral, Port.
Cefixime (p. 240·3).
Bacterial infections.

GSK, India.
Cefalexin (p. 234·1).
Bacterial infections.

Neoceflex *Neo Quimica, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Neoceftriona *Neo Quimica, Braz.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Neocenta *Ifars, Indon.*
Neomycin sulfate (p. 330·1); placenta extract (p. 2444·1).
Burns; ulcers; wounds; infected skin disorders.

Neo-Cephyl *Boiron, Cz.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Neoceptin-R *Beximco, Singapore.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Neocetrin *Bunker, Braz.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial skin infections.

Neoceuticals Clear Skin *Q-Med, Ital.†*
Salicylic acid (p. 1719·1); acetyl mandelic acid (p. 320·3).
Acne.

Neoceuticals Gel de Limpieza Facial *HLB, Arg.*
Gluconolactone (p. 2515·2); triclosan (p. 1773·2).
Skin cleanser; seborrhoea.

Neoceuticals PDS *Q-Med, Ital.*
Emollient.
Dry skin conditions.

Neoceuticals Spot Treatment *Q-Med, Ital.†*
Glycolic acid (p. 1704·3); acetyl mandelic acid (p. 320·3); vitamin A (p. 2098·3).
Acne.

Neochinosol *Dermapharm, Ger.*
Ethacridine lactate (p. 1732·3).
Mouth and throat disorders.

Neocibalena *Novartis Consumer, Spain.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Neo-Cibalgina *Novartis Consumer, Ital.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Neocillin *Neon, India.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Neocin
Note: this name may be used for preparations of different composition.
Fischer, Israel.
Neomycin sulfate (p. 330·1).
Bacterial eye infections.

Ocusoft, USA.
Polymyxin B (p. 342·3); neomycin (p. 329·3); bacitracin (p. 225·3).
Bacterial eye infections.

Neocina
Note: this name may be used for preparations of different composition.
Elofar, Braz.†
Neomycin sulfate (p. 330·1).

Neocinolon *Teuto, Braz.*
⊗Neomycin sulfate (p. 330·1); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Neocip *Cipla, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Neocip FC *Cipla, India.*
⊗Ciprofloxacin (p. 261·1); fluocinolone acetonide (p. 1636·1); clotrimazole (p. 576·2).
Infected skin disorders.

Neocip M *Cipla, India.*
Ciprofloxacin (p. 261·1); metronidazole (p. 936·1).

Neocit *Daksh, India.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism; head injury.

Neocitec *Sandoz, Arg.; Novartis, Braz.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

NeoCitran Antitussif *Novartis Consumer, Switz.*
Butamirate citrate (p. 1657·3).
Cough.

NeoCitran Antitussive *Novartis Consumer, Hung.†*
Butamirate citrate (p. 1657·3).
Cough.

Neocitran Cough *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

NeoCitran Expectorant
Note: this name may be used for preparations of different composition.
Novartis Consumer, Switz.
Acetylcysteine (p. 1652·2).
Cough.

Novartis, Hung.†
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Neocitran Extra Stength Daytime Total *Novartis Consumer, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Neocitran Extra Stength Daytime Total Plus Mucus Relief *Novartis Consumer, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Neocitran Extra Strength Chest Congestion Cold & Mucous Relief *Novartis Consumer, Canad.†*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Formerly known as Neocitran Extra Strength Chest Congestion & Cold.

Neocitran Extra Strength Cold and Flu *Novartis Consumer, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); paracetamol (p. 115·1).

Neocitran Extra Strength Nighttime Total *Novartis Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Neocitran Nighttime Cough *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Neocitran Nighttime Total Cold & Flu *Novartis Consumer, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).

Neocitran Thin Strips Daytime Cough and Cold *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Neocitran Thin Strips Nighttime Cough and Cold *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Neoclaritine *Schering-Plough, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Neoclarityn *Schering-Plough, Cz.; MSD, Gr.; MSD, Irl.; MSD, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, UK.*
Desloratadine (p. 625·1).
Hypersensitivity reactions; allergic rhinitis; urticaria.

Neo-Clarosip *Grunenthal, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Neo-Cleanse *GNLD, Austral.*
Senna leaf (p. 1885·1); buckthorn bark (p. 1824·2); liquorice (p. 1853·2); prune (p. 1881·1); rhubarb (p. 1884·2); leptandra virginica root; mallow flower (p. 2549·2); asparagus (p. 2450·2); aniseed (p. 2444·2).
Constipation.

Neoclobet *Marching, Hong Kong.†*
⊗Clobetasol (p. 1627·1); neomycin (p. 329·3); nystatin (p. 590·3).
Infected skin disorders.

Neoclox *Neon, India.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Neoclym *Marvecs, Ital.*
⊗Cyclofenil (p. 2261·2).
Menstrual disorders; menopausal disorders; anovulatory infertility.

Neocodin
Note: this name may be used for preparations of different composition.
Sanli, Turk.
Codeine (p. 40·2); ethylmorphine (p. 56·3).
Cough.

Néo-Codion *Bouchara-Recordati, Fr.*
Infant syrup: Sodium benzoate (p. 1738·2); grindelia (p. 2522·3); senega (p. 1677·2).
Respiratory-tract congestion.

Bouchara-Recordati, Fr.
Paediatric syrup: Codeine camsilate (p. 40·2); sodium benzoate (p. 1738·2).
Cough.

Bouchara-Recordati, Fr.
Syrup: Codeine camsilate (p. 40·2).
Cough.

Bouchara-Recordati, Fr.
Tablets: Codeine camsilate (p. 40·2); sulfogaiacol (p. 1678·1); grindelia (p. 2522·3).
Cough.

Neo-Codion *Bouchara, Rus.†*
Tablets: Codeine camsilate (p. 40·2); sulfogaiacol (p. 1678·1); grindelia (p. 2522·3).
Cough.

Bouchara, Rus.†
Syrup: Codeine camsilate (p. 40·2).
Cough.

Neo-Codion Babies *Bouchara, Rus.†*
Senega root (p. 1677·2); grindelia (p. 2522·3); sodium benzoate (p. 1738·2).
Respiratory-tract disorders with viscous mucus.

Néo-Codion N *Interdelta, Switz.*
Syrup: Codeine camsilate (p. 40·2); ascorbic acid (p. 2110·3); ipecacuanha (p. 1667·2); tolu balsam (p. 1679·2).
Cough.

Interdelta, Switz.
Tablets: Codeine camsilate (p. 40·2); sulfogaiacol (p. 1678·1); grindelia (p. 2522·3).
Cough.

Neocof
Note: this name may be used for preparations of different composition.
Norma (Νορμα), Gr.
Acetylcysteine (p. 1652·2).
Mucolytic.

Neocoflan *Neo Quimica, Braz.*
Diclofenac diethylamine (p. 48·3).
Inflammation.

Neocol *Gunsa, Turk.†*
Oxytetracycline (p. 337·1).
Bacterial skin infections.

Neocolan *Seid, Spain.†*
Dicycloverine hydrochloride (p. 1834·2); metochalcone (p. 2558·3); procaine hydrochloride (p. 1994·3).
Hepatobiliary disorders.

Neo-Coldan *Ad-Drugstel, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Neocon
Note: this name may be used for preparations of different composition.
Acto, India.
Fluconazole (p. 578·2).
Fungal infections.

Janssen-Cilag, Neth.
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Neocones
Note: this name may be used for preparations of different composition.
Septodont, Fr.; Septodont, Spain.
Neomycin sulfate (p. 330·1); benzocaine (p. 1980·2).
Dental disorders.

Néocônes *Wild, Switz.*
Neomycin sulfate (p. 330·1); benzocaine (p. 1980·2).
Dental disorders.

Neocopan *Ducto, Braz.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Skeletal muscle spasm; pain.

Neocophen *Millimed, Thai.†*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Neo-Cordial *Universal Drug, India.*
⊗Alcohol (p. 1733·1); alpha tocoferil acetate (p. 2119·2); hyoscyamus (p. 2530·2); liquorice (p. 1853·2); valerian (p. 2640·2).

Neocorten *Sanli, Turk.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Neocortic *Ferron, Indon.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone sodium sulfate (p. 1630·3).
Infected eye disorders.

Neocortin *Legrand, Braz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Neo-Cortisone *Hovid, Singapore.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neocortizul *Lersan, Arg.†*
⊗Chloramphenicol succinate (p. 257·1); prednisolone (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).

Neocristin *GSK, India.†*
Vincristine sulfate (p. 882·3).
Lymphomas; leukaemias.

Neo-Cromaton Bicomplesso *Menarini, Ital.*
Vitamin B substances (p. 2102·3).
Macrocytic anaemias; deficiency states.

Neocrystepin *Zentiva, Cz.†*
⊗Chlortalidone (p. 1335·2); dihydroergocristine mesilate (p. 390·1); reserpine (p. 1485·3).
Hypertension.

Neocuron *Neon, India.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Neo-Currino *Fabra, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1).
Nasal congestion.

Neocutan *Mediline, Israel.*
Dexpanthenol (p. 2582·2).
Skin irritation; dry lips.

Neocutan Silver *Mediline, Israel.*
Dexpanthenol (p. 2582·2); chlorhexidine gluconate (p. 1743·3); silver chloride (p. 2615·1); vitamin A (p. 2098·3).
Minor burns.

Neo-Cutigenol *Takeda, Belg.*
Chlorhexidine acetate (p. 1743·2); vitamin A palmitate (p. 2098·3).
Wounds; burns; ulcers; skin disorders.

Neocutis *Pentaderm, Ital.*
Azelaic acid (p. 1695·1); jaluramina.
Seborrhoea; acne.

Neo-Cystine *Sofex, Port.*
Cystine (p. 2059·1); vitamin A acetate (p. 2098·3).
Hair and nail disorders.

Neo-Cytamen *Mayne, Austral.†; UCB, Irl.; Teofarma, Ital.; GSK, NZ; Focus, UK.*
Hydroxocobalamin (p. 2107·3).
Macrocytic anaemias; tobacco amblyopia; Leber's optic atrophy; neuritis; neuralgia; pernicious anaemia; vitamin B_{12} deficiency; optic neuropathies.

Neocyte *Biomedis, Philipp.*
Recombinant human granulocyte colony-stimulating factor.
Chemotherapy-induced neutropenia.

Neo-Davisolona *Davi, Port.*
⊗Neomycin sulfate (p. 330·1); prednisolone sodium phosphate (p. 1645·3).
Infected eye disorders.

Neodazol *Neo Quimica, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis.

Neodec *Nitin, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Neo-Deca *CCM, Malaysia.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Allergic and inflammatory eye and ear disorders.

Néo-Décongestine *Melisana, Switz.*
⊗Kaolin (p. 1850·1); glycerol (p. 2517·2); salicylic acid (p. 1719·1); methyl salicylate (p. 92·1).
Soft-tissue disorders; sore throat.

Neoderm
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Skin disorders.

Tai Guk, Singapore.
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected inflammatory skin disorders.

Neoderma 47 *Neovita, Ital.*
Mallow (p. 2549·2); vervain (p. 2645·1); pansy (p. 2647·3).
Barrier preparation.

Neoderm-F *Sons, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neodermicina *Greenpharma, Braz.*
Neomycin (p. 329·3).

Neo-Desogen *Teleflex, Ital.*
Benzalkonium chloride (p. 1737·1).
Skin, burn, and wound disinfection; instrument disinfection.

Neo-Destomygen *Stomygen, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Neodetoxergon *Baldacci, Ital.*
Amino acids; vitamins; minerals.
Nutritional supplement.

Neodex *Neo Quimica, Braz.*
Cream: ⊗Dexamethasone acetate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neo Quimica, Braz.; CTRS, Fr.
Tablets: ⊗Dexamethasone acetate (p. 1631·1).
Corticosteroid.

Osoth, Thai.
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neo-Dex (Improved) *Jean-Marie, Hong Kong.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Inflammatory eye infections.

Neodexa *Llorens, Spain.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected eye disorders.

Neodexa Plus *Novartis Ophthalmics, Arg.†*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); naphazoline hydrochloride (p. 1669·3).

Neo-Dexacanol *Norma (Νορμα), Gr.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Neodexasone *Medical Ophthalmics, USA.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin (p. 329·3).
Infected eye disorders.

Neodextril *IFET (ΙΦΕΤ), Gr.*
⊗Dextran 40 (p. 1138·1) in glucose or sodium chloride.

Neodextril 40 *Fresenius Kabi, Port.*
⊗Dextran 40 (p. 1138·1) in glucose or sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis.

Neodextril 70 *Fresenius Kabi, Port.*
⊗Dextran 70 (p. 1138·3) in glucose or sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis.

Neodex-V *Vista, Philipp.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Bacterial ear infections.

Neodia *Hypermarcas, Braz.*
Levonorgestrel (p. 2296·1).

Neodiab *Seven Stars, Thai.†*
Glipizide (p. 474·1).
Diabetes mellitus.

Neo-Diaral *Roberts, USA.*
Loperamide (p. 1854·2).
Diarrhoea.

Neo-Diphenamine *Vickmans, Hong Kong.†*
Dimenhydrinate (p. 625·2).

Neo-Disterin *Norma (Νορμα), Gr.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Neodol
Note: this name may be used for preparations of different composition.
Brown & Burk, Rus.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diba, Mex.
Paracetamol (p. 115·1).
Pain; fever.

Micro, India; Micro, Singapore.
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal and joint disorders.

Neo-Dolaren *Carnot, Mex.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Neodolpasse *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Hung.*
Diclofenac sodium (p. 48·3); orphenadrine citrate (p. 909·2).
Musculoskeletal and joint disorders; pain; inflammation.

Neodor *Neo-Farmaceutica, Port.*
Capsicum oleoresin (p. 2469·3).
Joint pain.

Neodrea *VHB, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms.

Neodrin *Neo Quimica, Braz.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo.

Neo-Drol *Neon, India.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Neodrol-AS *Neon, India.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Neodrox *Cipla, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Neoduplamox *Valeas, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Neodur *Laborterapia, Port.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Neo-Durabolic *Hauck, USA.*
⊗Nandrolone decanoate (p. 2293·1).
Anaemia in renal disease.

Neoefodil *Lanpharm, Arg.*
⊗Naphazoline nitrate (p. 1669·3); sodium citrate (p. 1781·2); ephedrine sulfate (p. 1663·2).
Nasal congestion.

Neo-egmol *Target, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Neo-Elcosal *Elvipe, Gr.*
Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).

Neo-Elixir *Nikolakopoulos, Gr.†*
⊗Isoprenaline sulfate (p. 1411·3).

Neo-Emedyl *Montavit, Austria.*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Motion sickness.

Neo-endusix *Anfarm, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Neo-Enteroseptol *Specifar, Gr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Neo-Eparbiol *Ecobi, Ital.*
Inosine (p. 2533·1); cyanocobalamin (p. 2107·2).
Neuralgia; neuritis; pernicious anaemia.

Neo-Epinine *GSK, India.*
⊗Isoprenaline sulfate (p. 1411·3).

Neo-Eunomin *Gedeon Richter, Ger.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Biphasic oral contraceptive; acne; seborrhoea; alopecia; hirsutism.

Neofam *Silesia, Chile.†*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Neofarmiz *Neo-Farmaceutica, Port.*
Azithromycin (p. 221·2).
Bacterial infections.

Neofatrim *Technobio, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Neofebrin *USV, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); paracetamol (p. 115·1).

Neofedrin
Note: this name may be used for preparations of different composition.
Akdeniz, Turk.
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Neo Quimica, Braz.
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).

Neofel *Neolab, UK.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Neofen
Note: this name may be used for preparations of different composition.
Ferron, Indon.
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Bacterial eye infections.

Neofenox Naphazoline *Reckitt Benckiser, Belg.†*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Neo-Fer *Neolab, Canad.*
Ferrous fumarate (p. 2060·3).
Iron deficiency.

Neofer *Mahakam Beta, Indon.*
Cyanocobalamin (p. 2107·2); thioctic acid (p. 2629·1); biotin (p. 2052·2).
Antoxidant; diabetic neuropathy.

Neo-Fer CF *Neolab, Canad.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency.

Neo-Ferro Folgamma *Worwag, Hung.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Anaemia during pregnancy.

Neofex *GX, Philipp.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Neofilin *Damitsa, Ukr.*
Theophylline (p. 1229·3).
Asthma; obstructive airways disease; pulmonary hypertension; apnoea.

NeoFitolizyna *Herbapol Pruszkow, Pol.†*
Couch-grass (p. 2487·2); birch leaf (p. 2457·3); equisetum (p. 2500·1); petroselinum sativum; solidago (p. 2620·1).
Urinary-tract disorders.

Neoflogin *Neo Quimica, Braz.*
Benzydamine hydrochloride (p. 29·2).
Fever; inflammation; pain.

Neoflor *Nycomed, Mex.*
Enterococcus faecium (p. 2596·3).
Restoration of intestinal flora; diarrhoea; irritable bowel syndrome; hepatic encephalopathy.

Neoflox *Neon, India.*
Flucloxacillin sodium (p. 299·2).
Staphylococcal infections.

Neofloxin *Beximco, Singapore.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Neo Quimica, Braz.
Norfloxacin (p. 333·3).
Bacterial infections.

Neoflu *Olainfarm, Rus.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Neoflubin *Ebewe, Austria; Neocorp, Ger.†*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Neofluor *Neocorp, Ger.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Neofol *Neon, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prophylaxis of neural tube defects in pregnancy.

Neofolin
Note: this name may be used for preparations of different composition.
Neocorp, Ger.†
Calcium folinate (p. 2066·3).
Folic acid deficiency; prevention of methotrexate toxicity; adjunct to fluorouracil in colorectal cancer.

Neofollin
Note: this name may be used for preparations of different composition.
Biotika, Cz.
Estradiol valerate (p. 2271·2).
Oestrogen deficiency; menstrual disorders; menopausal disorders.

Neofomiral *Silanes, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Neofon *Seven Stars, Thai.†*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

Neoform
Note: this name may be used for preparations of different composition.
GX, Philipp.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Neo-fradin *Pharma Tek, USA.*
Neomycin sulfate (p. 330·1).

Neofrin *Ocusoft, USA.*
Phenylephrine hydrochloride (p. 1672·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neoftalm *Raymos, Arg.*
Trimethoprim (p. 381·2); polymyxin B sulfate (p. 342·3).
Eye infections.

Neoftalm Dexa *Raymos, Arg.*
⊗Trimethoprim (p. 381·2); polymyxin B sulfate (p. 342·3); dexamethasone sodium phosphate (p. 1631·2).
Eye infections.

Neofulvin *Chew, Thai.*
Griseofulvin (p. 582·2).
Fungal infections.

Neofungin *Ivax, Rus.*
2-Aminotridecane undecenoate.
Fungal skin infections.

Neo-Furadantin *Formenti, Ital.*
Nitrofurantoin (p. 332·1).
Bacterial infections of the genito-urinary tract.

Neogaba *Symbiosis, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neogadine *Raptakos, India.*
⊗Iodised peptone; calcium phosphate (p. 1784·2); magnesium chloride (p. 1787·1); phosphoric acid (p. 2589·1); sodium metavanadate; vitamin B_1 (p. 2103·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); alcohol (p. 1733·1).
Asthenia; tonic; digestive disorders.

Neogadine SG *Raptakos, India.*
⊗Peptone (p. 2086·2); magnesium chloride (p. 1787·1); manganese sulfate (p. 2081·2); zinc sulfate (p. 2126·2); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); nicotinamide (p. 2083·1); alcohol (p. 1733·1).

neogama *Hormosan, Ger.†*
Sulpiride (p. 1107·3).
Vestibular disorders; depression; schizophrenia.

Neogasol *Lafi, Chile.*
Dimeticones (p. 2209·3).
Aerophagia.

Neogel *Masa, Thai.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Neogentin *Svizera, India.*
Urofollitropin (p. 2312·2).
Female infertility.

Neogest
Note: this name may be used for preparations of different composition.
VHB, India.
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Neo-Gilurytmal *Teofarma, Austria; Pharmaselect, Cz.; Teofarma, Ger.; Pharmaselect, Hung.; Solvay, Indon.*
Prajmalium bitartrate (p. 1472·2).
Arrhythmias.

Neoglandyna *Tymofarm, Pol.*
Borage oil (p. 2459·2).
Premenstrual syndrome; atopic eczema; metabolic disorders; hepatitis.

Neoglim *Dynamic, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Neogobion *Pharos, Indon.; Pharos, Singapore.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; nutritional supplement.

Neo-Golaseptine *SMB, Belg.*
Chlorhexidine (p. 1743·2); benzethonium chloride (p. 1738·1).
Mouth and throat disorders.

Neogra *Taj, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Neogranormon *Teva, Hung.*
Ergocalciferol (p. 2113·3); vitamin A (p. 2098·3); pancreas extract (p. 2444·1); zinc oxide (p. 1729·1).
Skin disorders.

Neogrein *Neo Quimica, Braz.*
Paracetamol (p. 115·1); ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2).
Migraine.

Neogrip
Note: this name may be used for preparations of different composition.
Neo-Farmaceutica, Port.
Paracetamol (p. 115·1).
Fever; pain.
Rider, Chile.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; rhinitis.

Neogyn *Ecobi, Ital.*
Lysates of lactobacilli (p. 2596·3); chlorhexidine (p. 1743·2).
Personal hygiene.

Neogynon *Bayer, Arg.; Bayer, Denm.†; Bayer, Gr.; Bayer, Mex.; Schering, Venez.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Neogynona *Bayer, Spain.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Neo-HC
Note: this name may be used for preparations of different composition.
Neolab, Canad.†
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Neo-Healar *Arab, Malaysia.†*
Lupinus albus; vateria indica; peppermint (p. 1877·1); aloe vera (p. 1693·2).
Haemorrhoids.

Neohemodes *Sintez, Rus.*
Povidone (p. 2204·3); electrolytes (p. 1775·1).
Shock; intoxication.

NeoHepatect *Biotest, Cz.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Neohepatect *Biotest, Ital.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Neo-Hepatex *Biological E, India.*
Liver extract (p. 2444·1); vitamin B_{12} (p. 2107·2).
Liver disorders.

Neo-Hesna *Takeda, Thai.†*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhagic disorders.

Neo-Hydro *Beacons, Singapore.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Né0-Hydro *Streuli, Switz.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Inflammation and infection of the eye; rhinitis; sinusitis; otitis externa.

Neohysticlar *Mintlab, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Neoimmun *Kwizda, Austria.*
Ciclosporin (p. 1945·2).
Transplant rejection; auto-immune disorders; nephrotic syndrome; rheumatoid arthritis; atopic dermatitis.

Neointestopan *Novartis, Rus.*
Attapulgite (p. 1820·1).
Diarrhoea; food intolerance or poisoning.

Neo-Intol *Carlo Erba Reagents, Ital.*
Cetrimonium tosilate (p. 1742·3).
External genital disinfection.

Neoiodarsolo *Baldacci, Ital.*
Amino acids; vitamin B substances (p. 2102·3).
Tonic.

Neo-Ipertas *Norma (Νορμα), Gr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Neo-K
Note: this name may be used for preparations of different composition.
Combiphar, Indon.
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding.

Neo-Kalmol *Specifar (Σπεσιφαρ), Gr.*
Paracetamol (p. 115·1).
Fever; pain.

Neokanyn *Neon, India.*
Kanamycin acid sulfate (p. 314·3).
Bacterial infections.

Neokap *Degorts, Mex.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Gastrointestinal infections.

Neokardil *Pro-Pharma, Ukr.*
Crataegus (p. 2488·1); ginkgo biloba (p. 2512·3); pueraria.
Ischaemic heart disease; cerebral and peripheral vascular disorders.

Neokatall *Medimpex, Ital.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Neokay *Neoceuticals, UK.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding.

Neo-Kiddielets *United Laboratories, Philipp.†*
Paracetamol (p. 115·1).
Fever; pain.

Neo-klar *Pasteur, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Neolag *Atlas, Arg.*
⊗Trimethoprim (p. 381·2); polymyxin B sulfate (p. 342·3); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Neolaikan *Farmasa, Mex.*
Valerian (p. 2640·2).
Anxiety; sleep disorders.

Neolanta *Supra Ferbindo, Indon.*
Simeticone (p. 1886·2).
Flatulence.

Neo-Laryngobis *Teva, Canad.*
Bismuth dipropylacetate (p. 1821·3).
Sore throat.

Neolasil *Neo Quimica, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Neolecsin *Jumont, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Neolefrin *Neo Quimica, Braz.*
Tablets: Yellow tablets, phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); orange tablets, carbinoxamine maleate (p. 619·1); paracetamol.
Neo Quimica, Braz.
Syrup: Phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1); paracetamol (p. 115·1).

Neolefrin Baby *Neo Quimica, Braz.*
Carbinoxamine maleate (p. 619·1); paracetamol (p. 115·1).

Neo-Lemesil *Anpharm (Ανφαρμ), Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; fever.

Neolet
Note: this name may be used for preparations of different composition.
Eczacibasi, Turk.
Tyrothricin (p. 384·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1).
Mouth and throat disorders.

Neolette
Note: this name may be used for preparations of different composition.
Silesia, Chile.
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 tablets, inert.
Sequential oral contraceptive.

Neolexin *Seven Stars, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Neolid *Seven Stars, Thai.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Neo-Lidocaton *Dentomarket, Gr.*
Lidocaine hydrochloride (p. 1988·2). Lypressin (p. 2643·1) and noradrenaline (p. 1458·2) are included in this preparation to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Neolidona *Neo Quimica, Braz.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema.

Neolin-Entoxin *Meckel, Ger.*
⊗Drosera (p. 2497·2); euphrasia (p. 2502·1); grindelia robusta (p. 2522·3); lobelia inflata (p. 2323·2).
Homoeopathic preparation.

Neoloid *Kenwood, USA.†*
Castor oil (p. 2472·1).
Constipation.

Neolon D *Neo Quimica, Braz.*
⊗Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Neoloridin *Zydus, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Neoloridin-D *Cadila, India.*
⊗Desloratadine (p. 625·1); pseudoephedrine sulfate (p. 1676·1).

Neo-Lotan *Neopharmed, Ital.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; stoke prophylaxis.

Neo-Lotan Plus *Neopharmed, Ital.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Neolucid *SMB, Chile.*
Soap substitute.

Neolucid Ultra HR *SMB, Chile.*
Hyaluronic acid (p. 2526·2).
Dry skin.

Neolucid-C *SMB, Chile.†*
Ascorbyl palmitate (p. 1737·1).
Skin ageing; sun-induced skin damage.

Neolucid-pH5 *SMB, Chile.*
A moisturiser.

Neolut *Adelco, Gr.*
Medroxyprogesterone acetate (p. 2288·1).
Menstrual disorders; hormone replacement therapy; progestogen-only contraceptive; endometriosis; hirsutism; malignant neoplasms; female infertility.

Neolutin Forte *VUAB, Cz.*
Hydroxyprogesterone caproate (p. 2285·1).
Menstrual disorders; progesterone deficiency.

Neomagnol *Valeant, Hung.*
Tosylchloramide sodium B (p. 1773·1).
Disinfection.

Neomas *Temis, Arg.*
Neomycin sulfate (p. 330·1).
Gastrointestinal infections.

Neomas L *Temis, Arg.*
Neomycin sulfate (p. 330·1); loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Neomed *Cimed, Braz.*
Neomycin (p. 329·3).

Neomedil *Nuova Farmec, Ital.*
⊗Benzalkonium chloride (p. 1737·1); alcohol (p. 1733·1).
Skin, burn, and wound disinfection.

Neo-Medrol *Pharmacia, Austral.†; Pfizer, Gr.; Pfizer, Israel; Pharmacia, S.Afr.†; Pfizer, Singapore.*
Lotion: ⊗Methylprednisolone acetate (p. 1642·3); neomycin sulfate (p. 330·1); aluminium chlorohydrate (p. 1694·1); sulfur (p. 1721·1).
Acne; rosacea; seborrhoeic dermatitis; infected skin disorders.
Pfizer, Malaysia; Pfizer, Thai.
⊗Methylprednisolone acetate (p. 1642·3); neomycin sulfate (p. 330·1); alcloxa (p. 1692·2); sulfur (p. 1721·1).
Acne; rosacea; seborrhoeic dermatitis.

Neo-Medrol Acne *Pfizer, Canad.; Pfizer, Hong Kong.*
⊗Methylprednisolone acetate (p. 1642·3); neomycin sulfate (p. 330·1); aluminium chlorohydrate (p. 1694·1); sulfur (p. 1721·1).
Acne; rosacea; seborrhoeic dermatitis.

Neomelin *Collins, Mex.†*
Dipyrone (p. 53·3).
Fever; pain.

Neo-Melubrina *Sanofi-Aventis, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Neo-Mercazole *Link, Austral.; Amdipharm, Denm.; Amdipharma, Hong Kong; Piramal, India; Nicholas, Indon.; Amdipharm, Irl.; Amdipharm, Norw.; AFT, NZ; Aspen, S.Afr.; Amdipharm, UK.†*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Néo-Mercazole *CSP, Fr.; Pro Concepta, Switz.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Neomercazole *Abbott, Philipp.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Neomercurocromo *SIT, Ital.*
Ointment; topical powder: Chlorhexidine gluconate (p. 1743·3).
Wound disinfection.

SIT, Ital.
Topical solution: Chloroxylenol (p. 1748·2).
Wound disinfection.

Neomerdin *MedChoice, Philipp.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Neomet *Littman, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Neometho *Boryung, Thai.*
Methotrexate (p. 822·2).
Malignant neoplasms; rheumatoid arthritis; psoriasis.

Neomex *Neon, India.*
Mebendazole (p. 158·3).
Worm infections.

Neomicol *Medix, Mex.*
Miconazole nitrate (p. 589·1).
Fungal infections.

Neomicon *Cifarma, Braz.*
Neomycin sulfate (p. 330·1).
Bacterial skin infections.

Neomidantan *Olainfarm, Ukr.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza type A; postherpetic neuralgia.

Neo-Milanox *Diapit, Gr.*
Amino acids.
Parenteral nutrition.

Neo-Minophagen C *Dexa, Indon.; Minophagen, Jpn.†*
Ammonium glycyrrhizate (p. 2520·3).
Liver disorders; skin disorders.

Eisai, China.
Injection: Glycyrrhizic acid (p. 2520·2); glycine (p. 2071·2); cysteine hydrochloride (p. 2058·3).
Liver disorders; skin disorders.

Eisai, China.
Tablets: Glycyrrhizic acid (p. 2520·2); glycine (p. 2071·2); methionine (p. 1558·2).
Liver disorders; skin disorders.

Neomit *Neon, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Neomixen *Pisa, Mex.*
Neomycin (p. 329·3).
Bacterial infections.

Neomodex *Sophia, Mex.*
⊗Neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Neomol *Neon, India.*
Paracetamol (p. 115·1).
Pain; fever.

Neomol-MR *Sozin-Flora, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Neomol-XP *Sozin-Flora, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Neomox *Danlex, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Neo-Multi-B *Elvipe, Gr.*
Vitamin B substances (p. 2102·3).

Neo-Mune *Otsuka, Indon.; Thai Otsuka, Thai.*
Preparation for enteral nutrition.

Neo-mycodermol *Adelco, Gr.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Neomycol *Lavipharm, Gr.†*
Fluconazole (p. 578·2).
Fungal infections.

Neomyrt Plus *Baif, Ital.*
Myrtillus (p. 2566·2); bioflavonoids (p. 2505·2); centella (p. 1698·3); selenium (p. 2086·3); vitamin C (p. 2110·3); rutoside (p. 2505·3).
Nutritional supplement.

Neo-NaClex *GSK, NZ; Goldshield, UK.†*
⊗Bendroflumethiazide (p. 1315·2).
Hypertension; oedema.

Neo-NaClex-K *Goldshield, UK.*
⊗Bendroflumethiazide (p. 1315·2); potassium chloride (p. 1793·2).
Hypertension; oedema.

Neonaxil *Probiomed, Mex.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Neo-Nevral *Bruno, Ital.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Neonutrin *Fresenius Kabi, Cz.*
Amino acids.
Parenteral nutrition.

Neo-omnipen *Norma (Νορμα), Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Neo-Optal *Olan-Kemed, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Neo-Optalidon *Novartis Consumer, Ital.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Neo-Otil *Elvipe, Gr.*
⊗Hydrocortisone (p. 1640·1); chloramphenicol (p. 257·1); benzocaine (p. 1980·2).

Neopam *Troikaa, India.*
Pralidoxime iodide (p. 1571·1).
Organophosphorus poisoning.

Neopan *Adcock Ingram, S.Afr.*
Neomycin sulfate (p. 330·1); sodium propionate (p. 593·1).
Ear infections.

Neo-Pancreatinum *Jelfa, Pol.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Neopankreoflat *Royal, Chile.*
⊗Pancreatin (p. 2579·3); dimeticones (p. 2209·3).
Digestive disorders; flatulence.

Neo-Panlacticos *Italmex, Mex.*
Lactic-acid-producing organisms (p. 2596·3); vitamin B substances (p. 2102·3).
Restoration of normal gastrointestinal flora.

Neo-Panlacticos Plus *Italmex, Mex.*
Lactic-acid-producing organisms (p. 2596·3); vitamin B substances (p. 2102·3); dimeticone (p. 1886·2).
Restoration of normal gastrointestinal flora; flatulence.

Neo-Panpur *Egis, Hung.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Neopantol *Hypermarcas, Braz.*
Panthenol (p. 2582·2).

Neo-Parmecal *Geymonat, Ital.†*
Food for special diets.
Gastrointestinal disorders.

Neo-Pasmonal *Technobio, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Neopecsul *Parggon, Mex.*
Neomycin (p. 329·3); homatropine (p. 2007·3); sulfaguanidine (p. 364·3).

Neopect *Masa, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Neo-Penotran *Embil, Malaysia; Embil, Philipp.; Bayer Schering, Rus.; Bayer, Singapore; Embil, Singapore; Embil, Turk.; Bayer, Ukr.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1).
Vaginal candidiasis; vaginal trichomoniasis; bacterial vaginosis.

Neopeptine *Raptakos, India.*
Capsules: ⊗Amylase (p. 2442·1); papain (p. 2582·3); simeticone (p. 1886·2).
Dyspepsia; flatulence; anorexia; meteorism; heartburn.

Raptakos, India.
Oral drops: ⊗Amylase (p. 2442·1); papain (p. 2582·3); dill oil (p. 2493·2); anise oil (p. 2444·3); caraway oil (p. 2470·3).
Dyspepsia; flatulence; anorexia; meteorism.

Raptakos, India.
Oral liquid: ⊗Amylase (p. 2442·1); papain (p. 2582·3).
Dyspepsia; flatulence; anorexia; meteorism.

Neoperazona *Neo Quimica, Braz.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Neo-Percodan *Sanofi-Aventis, Mex.*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3).
Fever; pain.

Neophagen C *Taiho, Jpn.*
Ammonium glycyrrhizate (p. 2520·3).
Liver disorders.

Neophe *Noos, Ital.*
Amino acids.
Nutritional supplement.

Neophedan *Aspen, S.Afr.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Neophenicol *Westmont, Indon.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Neophos *Cipla, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Neophyllin *Eisai, Jpn.*
Aminophylline (p. 1201·2).
Obstructive airways disease; congestive heart failure.

Neophyr *Sol, Neth.*
Nitric oxide (p. 1457·1).
Neonatal respiratory distress syndrome; pulmonary hypertension.

Neopiram *Neon, India.*
Piracetam (p. 393·3).
Mental function impairment.

Neopiridin *Neo Quimica, Braz.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).

Neopirome *Neon, India.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Neoplat *Biological E, India.*
Cisplatin (p. 766·1).
Ovarian cancer; testicular cancer; bladder cancer.

Neoplatin
Note: this name may be used for preparations of different composition.
Oncomed, India; Boryung, Thai.
Carboplatin (p. 759·1).
Ovarian cancer; lung cancer.

BMS, Spain.†
Cisplatin (p. 766·1).
Malignant neoplasms.

Neoplaxol *Richmond, Arg.*
Etoposide (p. 790·2).
Malignant neoplasms.

Neoplex *Medicopharm, Austria.*
Albumin tannate (p. 1815·1); liquorice (p. 1853·2); magnesium trisilicate (p. 1858·1).
Gastrointestinal disorders.

Neoplus *Terapeutico, Ital.*
Royal jelly (p. 2608·1); pollen (p. 2593·3); ginseng (p. 2513·3).
Nutritional supplement.

Neopoldanen *Herbapol Poznan, Pol.†*
Pygeum africanum (p. 2363·2); maize (p. 2487·1).
Benign prostatic hyperplasia.

Neopolydex *Medical Ophthalmics, USA.*
⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3); polymyxin B (p. 342·3).
Infected eye disorders.

Neopolymyx *Genepharm, Gr.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Neoposid *Neocorp, Ger.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Neoprazol *Neo Quimica, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Neopresol *Bago, Chile.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia.

Neopress *Neo Quimica, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Neoprex *Sigma-Tau, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Neoprim *Stadmed, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Neo-Priphen *Minerva (Μινερβα), Gr.*
⊗Neomycin sulfate (p. 330·1); gramicidin (p. 308·3); naphazoline nitrate (p. 1669·3); phenylephrine hydrochloride (p. 1672·3).

Neoprobal *Mayo, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Neoproct *Intendis, Fin.*
⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

NeoProfen *Ovation, USA.*
Ibuprofen lysine (p. 68·3).
Closure of patent ductus arteriosus.

Neoprost
Note: this name may be used for preparations of different composition.
Bausch & Lomb, Arg.
Travoprost (p. 2012·1); sodium hyaluronate (p. 2526·2).
Glaucoma.

Ranbaxy, Pol.
Bicalutamide (p. 749·1).
Prostatic cancer.

Neoproxil *Teva, Mex.†*
Cyproterone acetate (p. 2261·2).
Male sexual deviation; prostatic cancer; androgenisation in females; precocious puberty.

Neo-Pruristam *Biostam (Βιοσταμ), Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Neo-Pulmolysine *Unipharma, Gr.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Neopulmonier *Quimica y Farmacia, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Neo-Pyodron N *Cassella-med, Ger.†*
Zinc oxide (p. 1729·1); almasilate (p. 1815·3).
Skin disorders.

Neo-Pyrazol *Bonapace, Thai.†*
Phenylbutazone sodium (p. 125·1). Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Musculoskeletal, joint, and soft-tissue disorders.

Neo-Pyrazon *United American, Malaysia†; United American, Philipp.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Neopyrin *Riemser, Ger.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Neopyrin ASA *Biofarm, Pol.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Neoquabin *Korea United, Philipp.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Neoquin *Cassara, Arg.*
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3); kojic acid (p. 1710·2); titanium dioxide (p. 1725·1).
Skin hyperpigmentation.

Neoquin Forte *Cassara, Arg.*
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3).
Skin hyperpigmentation.

Neoquine *Neon, India.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Neoral *Novartis, Austral.; Novartis, Canad.; Novartis, China; IFET (ΙΦΕΤ), Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, NZ; Novartis, UK; Novartis, USA.*
Ciclosporin (p. 1945·2).
Transplant rejection; nephrotic syndrome; rheumatoid arthritis; psoriasis; atopic dermatitis; graft-versus-host disease; uveitis.

Néoral *Novartis, Fr.*
Ciclosporin (p. 1945·2).
Atopic dermatitis; medullary aplasia; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neoral-Sandimmun *Novartis, Belg.*
Ciclosporin (p. 1945·2).
Transplant rejection; uveitis; psoriasis; nephrotic syndrome; rheumatoid arthritis; atopic eczema.

NeoRecormon *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche Diagnostics, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, India; Roche, Irl.; Roche, Ital.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Pol.; Roche, Port.; Roche, Spain; Roche, Swed.; Roche, Turk.; Roche, UK.*
⊗Epoetin beta (p. 1141·1).
Anaemias; autologous blood transfusions.

Neorelium *Polfa Tarchomin, Pol.*
Diazepam (p. 1063·2).
Anxiety disorders; sleep disorders; alcohol withdrawal syndrome; skeletal muscle spasm; premedication.

Neoren *Medipharm, Chile.*
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Neoren-D *Indoco, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).

Neorex *GSK, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); salbutamol sulfate (p. 1220·2).

Neo-Rinactive *Alcon, Turk.*
⊗Budesonide (p. 1625·1).

Neorino *Hipolabor, Braz.*
Sodium chloride (p. 1795·1).

Neo-Rowachol *Rowa Wagner, Hong Kong.*
Menthol (p. 2553·2); menthone (p. 2554·2); α-pinene (p. 2591·3); β-pinene (p. 2591·3); borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1).
Biliary disorders; gallstones; liver disorders.

Neo-Rowatinex *Rowa Wagner, Hong Kong.*
Camphene (p. 2466·2); borneol (p. 2460·2); fenchone (p. 2503·1); cineole (p. 2479·1); α-pinene (p. 2591·3); β-pinene (p. 2591·3); anethole (p. 2443·3).
Urinary-tract disorders.

Neorpan Plus *Quimica y Farmacia, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Neo-Sabenyl *Qualiphar, Belg.*
Clorophene (p. 1748·3); trolamine laurilsulfate (p. 2210·3).
Disinfection of skin, hands, mucous membranes, instruments, and materials; skin disorders; wound irrigation; irrigation in ear, nose, and throat procedures.

Neosac *Neo Quimica, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Neosaldina *Nycomed, Braz.*
⊗Dipyrone (p. 53·3); isometheptene mucate (p. 2535·1); caffeine (p. 1203·3).
Smooth muscle spasm.

Neosalus *Quinnova, USA.*
⊗Dimeticone (p. 2209·3); glycerol (p. 2517·2); trolamine (p. 2634·3); parabens (p. 1756·3).
Barrier cream.

Neosanmag *Sanbe, Indon.*
Calcium carbonate (p. 1824·3); famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; flatulence.

Neo-Sarkol *Remek, Gr.*
Vitamin B substances (p. 2102·3).

Neosartan *GX, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Neosartan Plus *GX, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Neosayomol *Cinfa, Spain.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic skin reactions.

Neosec *Masa, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Pain.

Neosed *Advance, China.*
Salicylamide (p. 129·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1); caffeine (p. 1203·3).
Cold and influenza symptoms; allergic rhinitis.

Neosedal *Loeffler, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Neosemid *Neo Quimica, Braz.*
⊗Furosemide (p. 1387·1).
Hypertension.

Neo-Septol *Specifar (Σπεσιφαρ), Gr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Neoseptolete *KRKA, Cz.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Neoseptolete Duo *KRKA, Cz.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Neoset *Deva, Turk.*
Granisetron (p. 1844·3).

Neosilin *Sanli, Turk.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Neosine *Aflofarm, Pol.*
Inosine pranobex (p. 988·3).
Viral infections.

Neo-Sinedol *Wild, Switz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Neo-Sinefrina *GSK Consumer, Port.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Neosinol *Interbat, Indon.*
⊗Neomycin sulfate (p. 330·1); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Neo-Sintrom *Novartis, Chile.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Neoskabi *Vita Kimya, Turk.*
Benzyl benzoate (p. 2149·1).
Scabies; pediculosis.

Neosma *Ifars, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Neosmektine *Farmstandart, Rus.*
Dioctahedral smectite (p. 1887·1).
Gastrointestinal disorders.

Neosol *Breckenridge, USA.†*
Hyoscyamine sulfate (p. 1848·1).

Neosoldan *Medichrom, Gr.*
Lactulose (p. 1850·3).

Neosolets *SMB, Chile.*
Glycolic acid (p. 1704·3).
Acne; keratinisation disorders.

Neosolone *Chew, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Neosona *Amhof, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); naphazoline hydrochloride (p. 1669·3).

Neosone *Christo, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neosoro *Neo Quimica, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Neosoro H *Neo Quimica, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Neosoro Infantil *Neo Quimica, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Neospasmina *Herbapol Lublin, Pol.*
Crataegus (p. 2488·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Neospasmol *Herbapol Lublin, Pol.†*
Crataegus (p. 2488·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

NeoSpect *CIS, Cz.†; Amersham, Fr.†; GE Healthcare, Irl.†; CIS, Ital.†; GE Healthcare, Neth.†; CIS, Port.†; GE Healthcare, Rus.; CIS, Spain.†*
Technetium-99m deprotide trifluoroacetate (p. 2228·1).
Radionuclide imaging for pulmonary malignancy.

Neospir *Elvipe, Gr.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Neosporin
Note: this name may be used for preparations of different composition.
GSK, Canad.
Bladder irrigation: Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial urinary-tract infections.

Pfizer Consumer, Austral.†; GSK, Canad.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong; GSK, India; GSK, Mex.; GSK, Philipp.; GSK, Switz.; GSK, Turk.; Pliva, UK†; Monarch, USA.
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Bacterial skin infections; bacterial eye and ear infections.

Pfizer Consumer, Austral.†; GSK, Canad.; GSK, India; GSK, Mex.
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Bacterial skin infections; eye infections.

Neosporin AF *Pfizer Consumer, USA.†*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Neosporin GU *Glaxo Wellcome, USA.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Prevention of catheter-associated urinary-tract infections.

Neosporin + Pain Relief *Warner-Lambert, USA.*
Cream: Neomycin (p. 329·3); polymyxin B sulfate (p. 342·3); pramocaine hydrochloride (p. 1993·3).

Warner-Lambert, USA.
Ointment: Neomycin (p. 329·3); polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); pramocaine hydrochloride (p. 1993·3).

Neosporin-H *GSK, India.*
Ear drops: ⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); hydrocortisone (p. 1640·1).
Otitis externa.

GSK, India.
Ointment: ⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3); hydrocortisone (p. 1640·1).
Infected skin disorders.

Neossolvan *Neo Quimica, Braz.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Neostan *Danlex, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Neostatin *Cassara, Arg.; Delta, Braz.*
Nystatin (p. 590·3).
Candidiasis; fungal infections.

Neostesin *Nycomed, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Neostig *Carinopharm, Ger.*
Neostigmine metilsulfate (p. 687·2).
Myasthenia gravis; reversal of competitive neuromuscular blockade.

Neostigmine Min-I-Mix *IMS, USA.*
Neostigmine metilsulfate (p. 687·2).
Atropine sulfate (p. 1310·2) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Neostil *Novartis Consumer, Port.†*
Dimetindene maleate (p. 626·1).
Hypersensitivity reactions.

Neo-Stomygen *Stomygen, Ital.*
Mouthwash: Chlorhexidine gluconate (p. 1743·3); cetylpyridinium chloride (p. 1743·1).
Oral hygiene; oral disinfection.

Stomygen, Ital.
Toothpaste: Sodium monofluorophosphate (p. 2091·3); propolis (p. 2597·3); enoxolone (p. 54·2); cetylpyridinium chloride (p. 1743·1).
Oral hygiene; oral disinfection.

NeoStrata *HLB, Arg.; Hamilton, Austral.; Canderm, Canad.†; Medstyle, Chile; Q-Med, Ital.; Assos, Turk.*
A range of preparations containing glycolic acid (p. 1704·3) or gluconolactone (p. 2515·2).
Keratinisation disorders; emollient; skin care; skin disorders.

Medstyle, Chile.
Depigmenting gel forte: Gluconolactone (p. 2515·2); lactobionic acid (p. 2539·2); kojic acid (p. 1710·2); hydroquinone (p. 1705·1); liquorice (p. 1853·2).
Skin pigmentation disorders.

Medstyle, Chile.
Shampoo: Gluconolactone (p. 2515·2); mandelic acid (p. 320·3); piroctone olamine (p. 1716·3).
Dandruff.

NeoStrata Akne *Assos, Turk.*
Chlorhexidine (p. 1743·2); glycolic acid (p. 1704·3).
Acne.

NeoStrata Blemish Spot Gel *Canderm, Canad.†*
Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3).
Acne.

NeoStrata Daytime *Canderm, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).

NeoStrata Daytime Protection Cream *Hamilton, Austral.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Emollient; sunscreen.

NeoStrata Gel Despigmentante *HLB, Arg.*
Hydroquinone (p. 1705·1); glycolic acid (p. 1704·3).
Skin hyperpigmentation.

NeoStrata Hiperpigmentasyon *Assos, Turk.*
Glycolic acid (p. 1704·3); hydroquinone (p. 1705·1).
Skin hyperpigmentation disorders.

NeoStrata HQ *Sanofi, Canad.†*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

NeoStrata HQ Plus *Sanofi Consumer, Canad.*
SPF 20: Hydroquinone (p. 1705·1); padimate O (p. 1716·1); oxybenzone (p. 1715·3); octocrilene (p. 1715·2).

NeoStrata Lip Conditioner *Hamilton, Austral.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Dry lips; sunscreen.

NeoStrata Sunblock *Canderm, Canad.†*
Lotion SPF 30: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Canderm, Canad.†
Spray SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); octisalate (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

NeoStrata Sunshield *Canderm, Canad.†*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

NeoStrata Ultra-Smoothing *Canderm, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).

Neo-Strata Uplifting *Canderm, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Neosulf *Alphapharm, Austral.*
Neomycin sulfate (p. 330·1).
Bowel sterilisation before surgery.

Neosulfur *Laborest, Ital.†*
Dimethyl sulfone (Lignisul) (p. 2493·3); zinc (p. 2126·1); copper (p. 2057·1); grape (p. 2521·3); vitamin B substances (p. 2102·3).
Musculoskeletal, joint, and peri-articular pain.

Neosulida *Neo Quimica, Braz.*
Nimesulide (p. 101·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Neosulide Plus *Aaron, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Neosurf *Docpharm, Ukr.*
Phospholipid surfactant.
Neonatal respiratory distress syndrome.

Neo-Suxigal *Anfarm, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Neosyd *GMP, Indon.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Eye infections.

Neo-Synalar
Note: this name may be used for preparations of different composition.
Roche, Venez.
Ointment: ⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Stiefel, Philipp.
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Neo-Synalar con Neomicina *Roche, Venez.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected ear and skin disorders.

Neosynephrin *Ursapharm, Pol.*
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

Neo-Synephrine *Hospira, Austral.; Hospira, Canad.; Ursapharm, Cz.; Sanofi Winthrop, Israel†; Teofarma, Ital.; Hospira, Philipp.; Ospedalia, Switz.; Bayer, USA; Hospira, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; paroxysmal supraventricular tachycardia; maintenance of blood pressure during surgery; hypotension; shock; eye congestion; production of mydriasis; adjunct in spinal or regional anaesthesia; vascular failure in shock, drug-induced hypotension, or hypersensitivity.

Néosynéphrine *AGEPS, Fr.; Europhta, Mon.*
Phenylephrine hydrochloride (p. 1672·3).
Hypotension; production of mydriasis.

Neosynephrine *Hospira, NZ.*
Phenylephrine hydrochloride (p. 1672·3).

Neo-Synephrine 12 Hour *Bayer, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Neosynephrin-POS *Ursapharm, Ger.*
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis; uveitis.

Neotab *Deva, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neotach *Neon, India.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension.

Neotaflan *Neo Quimica, Braz.*
Diclofenac potassium (p. 48·3) or diclofenac resinate (p. 48·3).
Inflammation; pain.

Neotalem *Teva, Mex.; Lemery, Thai.; Atafarm, Turk.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Neotam *Biological E, India.*
⊗Tamoxifen (p. 860·2).
Breast cancer; anovulatory infertility.

Neotaren *Neo Quimica, Braz.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

NeoTaxan *Neocorp, Ger.†*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Neotaxl *VHB, India.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

NeoTect *Diatide, USA.*
Technetium-99m depreotide (p. 2228·1).
Scintigraphic imaging for pulmonary malignancy.

Neotensin *UCB, Spain.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Neotensin Diu *UCB, Spain.†*
⊗Hydrochlorothiazide (p. 1403·2); enalapril maleate (p. 1371·1).
Hypertension.

Neotetranase *Rottapharm, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Neotiapim *Sandoz, Braz.*
Quetiapine (p. 1101·1).

Neotibi *Pyridam, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Neotic *Arbor, USA.†*
⊗Benzocaine (p. 1980·2); phenazone (p. 124·1); glycerol (p. 2517·2); zinc acetate (p. 2126·1).
Ear wax removal; otitis media.

Neotica *TNP, Thai.*
Balm; mild gel: Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); eugenol (p. 2501·2).
Muscle pain and inflammation; sprains; sports injuries; insect bites.

TNP, Thai.
Capsules; topical gel: Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Neotigason *Sandoz, Arg.; Actavis, Austral.; Roche, Austria; Actavis, Belg.; Roche, Braz.; Roche, Chile; Roche, China; Actavis, Cz.; Actavis, Denm.; Actavis, Fin.; Actavis, Ger.; Actavis, Gr.; Actavis, Hong Kong; Actavis, Hung.; Actavis, Irl.; Devries, Israel; Actavis, Ital.; Roche, Malaysia; Roche, Mex.; Actavis, Neth.; Actavis, Norw.; Healthcare Logistics, NZ; Pascual, Philipp.; Roche, Pol.; Actavis, Port.; Actavis, Rus.; Akacia, S.Afr.; Roche, Singapore; Actavis, Spain; Actavis, Swed.; Actavis, Switz.; Actavis, Thai.; Roche, Turk.; Roche, UK; Roche, Venez.*
Acitretin (p. 1690·3).
Keratinisation disorders; psoriasis; hyperkeratotic disorders.

Neo-Tinic *Neolab, Canad.†*
Vitamins; iron (p. 2073·1).

Neo-Tiroimade *Neves, Port.*
Liothyronine sodium (p. 2342·3).
Thyroid disorders.

Neotomic *USV, India.*
⊗Glycerol (p. 2517·2); sodium chloride (p. 1795·1).
Constipation; bowel evacuation.

Neoton *Alfa Wassermann, China; Alfa Wassermann, Cz.; CSC, Rus.*
Creatine phosphate sodium (p. 2488·3).
Cardioplegia; myocardial ischaemia; cardiac disorders; cerebral and peripheral vascular disorders.

Alfa Wassermann, Pol.
Creatine phosphate (p. 2489·1).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Cardiac disorders.

Neotop
Note: this name may be used for preparations of different composition.
Ind-Swift, India.
Neomycin sulfate (p. 330·1); sulfacetamide (p. 361·1); bacitracin zinc (p. 225·3).

Medley, Braz.†
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Bacterial skin infections.

Neotopic *Technilab, Pol.†*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected wounds.

Neo-Tormentil *Galenowe Olsztyn, Pol.*
Borax (p. 2459·2); ichthammol (p. 1705·3); tormentil (p. 2633·2); zinc oxide (p. 1729·1).
Wounds.

Neotoss *Neo Quimica, Braz.*
Dropropizine (p. 1662·2).
Cough.

Neotrace *American Pharmaceutical, USA.†*
Trace elements.
Additive for intravenous total parenteral nutrition solutions.

Neotrace-4 *LCH, Hong Kong.†*
Trace elements.

Neotracin
Note: this name may be used for preparations of different composition.
OmniVision, Switz.
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial eye infections.

Neotren *Apotex, UK.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disease.

Neotretin *Cassara, Arg.*
Tretinoin (p. 1725·2).
Acne; keratinisation disorders.

Neotrex *Advaita, Mex.*
Isotretinoin (p. 1706·2).
Acne.

Neotrexat *Neocorp, Ger.†*
Methotrexate (p. 822·2).
Malignant neoplasms.

Neotrexate *GSK, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Neotri *Mibe, Ger.*
⊗Xipamide (p. 1536·1); triamterene (p. 1518·3).
Oedema; hypertension.

Neotricin
Note: this name may be used for preparations of different composition.
Legrand, Braz.
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Eye infections.

Neotricin HC *Bausch & Lomb, USA.†*
⊗Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3); polymyxin B sulfate (p. 342·3); hydrocortisone acetate (p. 1640·1).
Eye inflammation with bacterial infection.

Neotrim *Danlex, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Neotrin *Neo Quimica, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Neotrizol *Synmedic, Ukr.*
⊗Ornidazole (p. 943·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); prednisolone (p. 1645·2).
Vulvovaginal infections.

NeoTuss *Marin, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

NeoTussan *Novartis Consumer, Ger.†*
Dextromethorphan polistirex (p. 1660·1).
Cough.

NeoTuss-D *Marin, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Neo-Tussin
Note: this name may be used for preparations of different composition.
Marching, Hong Kong.†
⊗Chlorphenamine (p. 620·3); codeine (p. 40·2); ephedrine (p. 1663·1).

Neotussin
Note: this name may be used for preparations of different composition.
Vickmans, Hong Kong.†
Guaifenesin (p. 1666·2).
Cough.

Neo-Ulcoid *Valdecasas, Mex.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Neo-Up *GX, Philipp.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Neourizine *Adelco, Gr.*
⊗Reserpine (p. 1485·3); chlorothiazide (p. 1334·3).
Hypertension.

Neo-Ustiol *INTES, Ital.*
Sodium citrate (p. 1781·2); sodium aminobenzoate (p. 2617·2); procaine (p. 1994·3); cod-liver oil (p. 2056·3).
Ophthalmic burns.

Neovaxitol *Bouty, Ital.†*
Bacillus coagulans; vitamin B substances (p. 2102·3).
Restoration of gastrointestinal flora.

Neovec *Neon, India.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Neovent
Note: this name may be used for preparations of different composition.
Neolab, UK.
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Interhealthcare, Philipp.†
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Neovermin *Neo Quimica, Braz.*
Mebendazole (p. 158·3); tiabendazole (p. 166·3).
Worm infections.

Neovir *Pharmasynthez, Ukr.*
Oxodihydroacridinyl sodium acetate.
Viral infections; radiation immunodeficiency; chlamydial infections; venereal lymphogranuloma; multiple sclerosis; candidiasis of skin and mucous membranes.

Pharmsintez, Rus.
Cridanimod.
Viral infections; radiation immunodeficiency; chlamydial infections; venereal lymphogranuloma; multiple sclerosis; candidiasis of the skin and mucous membranes.

Neovis *Pfizer, Ital.*
Vitamins; carbohydrate; minerals; creatine (p. 2488·3).
Nutritional supplement.

NeoVisc *Stellar, Canad.*
Sodium hyaluronate (p. 2526·2).
Replacement of synovial fluid following arthrocentesis.

Neo-Vita *Christo, Hong Kong.†*
Vitamin B substances (p. 2102·3).

Neovita *Savoy, Singapore.*
Syrup: Ginseng (p. 2513·3); vitamins.
Tonic.

Savoy, Singapore.
Capsules: Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2).
Tonic.

Wallace Mfg Chem., UK.
Vitamins; ginseng (p. 2513·3); with or without minerals and lecithin (p. 2542·2).

Neovitam *KVZ, Ukr.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuralgia; neuritis; neuropathy.

Neovlar *Bayer, Braz.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Neovletta *Bayer, Swed.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Neoxene *Finderm, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin, wounds, burns, and vagina.

Neoxicam *GX, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Neoxidil *Galderma, Belg.; Galderma, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Neoxil
Note: this name may be used for preparations of different composition.
Offenbach, Mex.
Neomycin (p. 329·3); kaolin (p. 1850·1); pectin (p. 2200·3); homatropine (p. 2007·3).
Diarrhoea.

Neoxinal *Nuova Farmec, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin, wounds, and burns.

Neoxy *Hisamitsu, Jpn.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity.

Neo-Xylestesin *3M Espe, Austria.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

NeOxyn *Gedeon Richter, Philipp.*
Oxytocin (p. 2143·1).
Third-stage labour; uterine atony; incomplete abortion; uterine curettage.

Neozentius *Pharma Investi, Chile.*
Escitalopram (p. 416·2).
Depression.

Neozep
Note: this name may be used for preparations of different composition.
United American, Hong Kong; Medifarma, Indon.
Phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1); salicylamide (p. 129·2); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; rhinitis; sinusitis; nasopharyngeal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

United Laboratories, Philipp.
Oral drops: Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; nasal congestion.
United Laboratories, Philipp.
Syrup; tablets: Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms; nasal congestion.
Great Eastern, Thai.†
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Neozep Non-Drowsy *United Laboratories, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms; nasal congestion.

Neozimina *Neo Quimica, Braz.*
Clofazimine (p. 273·3).
Leprosy.

Neozine
Note: this name may be used for preparations of different composition.
Alkem, India.
Procarbazine.
Sanofi-Aventis, Braz.
Levomepromazine hydrochloride (p. 1079·3) or levomepromazine maleate (p. 1079·3).
Adjunct in general anaesthesia; pain; premedication; psychoses.

Neozol
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neozolam *Neo Quimica, Braz.*
Alprazolam (p. 1035·2).
Anxiety.

Neozolone *British Dispensary, Thai.*
⊗Prednisolone (p. 1645·2); neomycin (p. 329·3).
Infected skin disorders; seborrhoeic dermatitis; eczema.

Nepar *Rusan, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nepatic *Kalbe, Indon.*
Gabapentin (p. 523·3).
Epilepsy.

Nepecef *Aspen, Braz.*
Cefepime (p. 239·2).
Bacterial infections.

Nepenic *New Research, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Nepenthe
Note: this name may be used for preparations of different composition.
Hexal, Philipp.†
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Neper *Ivax, Arg.*
Mesna (p. 1557·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Neperlan *Terramedic, Philipp.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Nepezil *Vianex (Βιανεξ), Gr.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

NephPlex RX *Nephro-Tech, USA.*
Vitamins.
For dialysis patients.

Nephral *Pfleger, Ger.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

NephrAmine *Eczacibasi-Baxter, Turk.*
Amino acids.
Parenteral nutrition.

Nephramine *Braun, Canad.; Fresenius Kabi, Fr.†; Braun, Hong Kong; Braun, Spain; R&D, USA.*
Amino acids.
Parenteral nutrition in renal impairment.

Nephrisol
Note: this name may be used for preparations of different composition.
Kalbe, Indon.; Sanghiang, Indon.
Preparation for enteral nutrition in renal failure.

Nephrisol mono *Cesra, Ger.†*
Solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Nephro-Calci *R&D, USA.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; dietary supplement.

Nephrocaps *Elder, India; Valeant, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin deficiency in renal dialysis.

Nephrocaps QT *Fleming, USA.*
Vitamins.
Dietary supplement.

Nephrocare
Note: this name may be used for preparations of different composition.
Abbott, Israel; Ross, Israel.
Preparation for enteral nutrition.
Complete nutrition or food supplement in renal disease.
Delta Medical, Ukr.
Cranberry (p. 2488·1); celery seed (p. 2472·3); rorippa nasturtium-aquaticum; parsley (p. 2583·3); vitamin C (p. 2110·3); vitamin B_6 (p. 2105·3); potassium citrate (p. 1780·3).
Urinary-tract disorders.

Nephro-Fer *Watson, USA.†*
Ferrous fumarate (p. 2060·3).
Iron-deficiency anaemias.

Nephroferol *Verisfield, Gr.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Nephrogesic *Johnson & Johnson, India.*
Phenazopyridine hydrochloride (p. 124·3); nitrofurantoin (p. 332·1).
Urinary-tract infections.

NephroMAG *Rotop, Fin.; Rotop, Neth.; Rotop, Spain.*
Mertiatide.
For radiolabelling with technetium-99m.
Urinary-tract imaging; assessment of renal function.

Nephron *Nephron, USA.†*
⊗Racepinefrine hydrochloride (p. 1292·1).
Bronchospasm.

Nephron FA *Nephro-Tech, USA.*
Vitamins; iron (p. 2073·1); folic acid (p. 2063·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Nephronex
Note: this name may be used for preparations of different composition.
Llorens, USA.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Nephronorm med *ProStrakan, Ger.*
Tablets: Java tea (p. 2536·3).
Urinary-tract disorders.

Nephroplex *Steierl, Ger.*
Apocynum cannabinum; equisetum arvense (p. 2500·1); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Nephroselect M *Dreluso, Ger.*
Solidago virgaurea (p. 2620·1); equisetum (p. 2500·1); birch leaf (p. 2457·3); ononis (p. 2575·3); lovage (p. 2545·3); tropaeolum majus (p. 2454·3); saw palmetto (p. 2363·3).
Urinary-tract disorders.

Nephrosolid *Bioforce, Switz.*
Solidago virgaurea (p. 2620·1); silver birch (p. 2457·3); ononis (p. 2575·3); equisetum (p. 2500·1).
Urinary-tract disorders.

Nephrosteril *Fresenius Kabi, Hong Kong; Fresenius Kabi, India; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.†; Fresenius Kabi, Philipp.; Fresenius Kabi, Singapore†; Fresenius Kabi, Thai.*
Amino acids.
Parenteral nutrition in renal disease.

Nephrotect *Fresenius Kabi, Cz.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Spain; Fresenius Kabi, Switz.†; Fresenius Kabi, Turk.*
Amino acids.
Parenteral nutrition in renal failure.

Nephrotrans *Medice, Ger.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis.

Néphrotrans *Salmon, Switz.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis.

Nephro-Vite *Rugby, USA; Watson, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Nephrovit-Fe *Fahrenheit, Indon.*
Vitamins; iron (p. 2073·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Nutritional supplement in haemodialysis.

Nephrox *Fleming, USA.*
Aluminium hydroxide (p. 1817·2).
Hyperacidity.

N-Epi *Novell, Indon.; Novell, Thai.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; shock.

Nepiros *SIFFRA, Ital.*
Vitamin B substances (p. 2102·3); propolis (p. 2597·3); *Lactobacillus paracasei* (p. 2596·3); acacia honey (p. 2072·1); black currant (p. 2458·1); lactoferrin (p. 2539·3); rose fruit (p. 2607·1); echinacea angustifolia (p. 2498·1); salix alba.
Inflammation; fever.

Nepitin *Ali, Turk.*
Gabapentin (p. 523·3).

Nepituss *Bioindustria, Ital.*
Nepinalone hydrochloride (p. 1670·2).
Cough.

Nepla *KRKA, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Neplit *Orion, Hung.†; Menarini, Pol.*
⊗Budesonide (p. 1625·1).
Asthma.

Nepocef *TTK, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Nepocil *TTK, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Nepoclox *TTK, India.*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Nepodex *Latinofarma, Braz.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Nepomox *TTK, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Nepotax *TTK, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Nepramel *Clonmel, Irl.*
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neprazol *Neckerman, Braz.*
Omeprazole (p. 1867·2).

Nepresol *Cristalia, Braz.*
Hydralazine hydrochloride (p. 1401·2).
Heart failure; hypertension.
Novartis, Austria†; Teofarma, Ger.; IFET(ΙΦΕΤ), Gr.; Novartis, Gr.; Novartis, Thai.†
Dihydralazine mesilate (p. 1358·3) or dihydralazine sulfate (p. 1358·3).
Hypertension; eclampsia; heart failure.
Novartis, India.
Dihydralazine sulfate (p. 1358·3).
Hypertension.

Nepressol *Genopharm, Fr.*
Dihydralazine mesilate (p. 1358·3).
Pre-eclampsia.

Nepro *Abbott, Arg.; Abbott Nutrition, Singapore; Ross, USA.*
Preparation for enteral nutrition in renal dialysis patients.
Abbott, Austral.; Abbott, Chile; Abbott, Indon.†; Abbott, Malaysia; Abbott, Philipp.; Abbott, Thai.; Abbott, Turk.
Preparation for enteral nutrition in renal failure.
Abbott, Canad.
Preparation for enteral nutrition in renal dialysis patient.
Abbott, Cz.
Preparation for enteral nutrition in renal insufficiency.
Abbott, Hong Kong; Abbott, NZ.
Preparation for enteral nutrition in dialysis patients.
Abbott, Irl.
Preparation for enteral nutrition.
Abbott Nutrition, UK.
Preparation for enteral nutrition in renal failure or cirrhosis.

Neptalip *Rayere, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Neptazane *Wyeth-Ayerst, Thai.; Fera, USA.*
⊗Methazolamide (p. 2009·1).
Glaucoma.

Neptide *Bangkok Lab & Cosmetic, Thai.*
Nimesulide (p. 101·3).
Inflammation; pain.

Neptoin *Mankind, India.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Neptolin *Santa, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Neradin *Collins, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Nerapin *LKM, Arg.*
Nevirapine (p. 1005·1).
HIV infection.

Neravir *GPO, Thai.*
Nevirapine (p. 1005·1).
HIV infection.

Nerbet *Interpharma, Chile.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

NerBloc *Eisai, Jpn.*
Botulinum B toxin (p. 2017·1).
Cervical dystonia.

Ner-B-Vite *Lloyd, Philipp.*
Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Nerdipina *OM, Port.; Ferrer, Spain.*
Nicardipine hydrochloride (p. 1445·2).
Cerebrovascular disorders; hypertension; angina pectoris.

Nereflun *New Research, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchostenosis; allergic rhinitis.

Nerelid *New Research, Ital.*
Nimesulide (p. 101·3).
Pain.

Nerex *Farmanova, Ital.*
Royal jelly (p. 2608·1); honey (p. 2072·1); myrtillus (p. 2566·2); fructose (p. 2068·2).
Nutritional supplement.

Nerfalex *Generics Pharmacal, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Nerfeco *Ferron, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nerfit *Nitro Organics, India.*
Alanine (p. 2048·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Nergadan *Vifor, Spain.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Nergyform *Clinique, Canad.*
Minerals.

Neribase *Intendis, Denm.; Intendis, Ital.; Intendis, Port.†*
Emollient.
Dry skin; skin disorders.

Néribase *Intendis, Fr.*
Basis for topical preparations; emollient.

Neriderm *Perrigo, Israel.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Neriforte *Intendis, Austria.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Nerilon *Interbat, Indon.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Neripros *Pharos, Indon.*
Risperidone (p. 1103·2).
Psychoses.

Nérisalic *Bayer, Fr.*
⊗Diflucortolone valerate (p. 1634·1); salicylic acid (p. 1719·1).
Skin disorders.

Nerisalic *Stiefel, Canad.†; Intendis, Ital.*
⊗Diflucortolone valerate (p. 1634·1); salicylic acid (p. 1719·1).
Skin disorders.

Nerisona *Bayer, Arg.; Intendis, Austria; Bayer, Belg.; Intendis, Braz.; Intendis, Ger.; Bayer, Gr.; Transfarma, Indon.; Intendis, Ital.; Intendis, Mex.; Intendis, Neth.; Intendis, Philipp.; Bayer, Port.*
⊗Diflucortolone valerate (p. 1634·1).
Skin and scalp disorders.

Nerisona C *Bayer, Arg.; Bayer, Gr.; Intendis, Ital.; Bayer, Port.; Schering, Turk.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infested skin disorders.

Nerisona Combi *Transfarma, Indon.; Intendis, Philipp.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Nérisone *Bayer, Fr.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Nerisone *Stiefel, Canad.; Intendis, Hong Kong; CSL, NZ; Bayer Schering, S.Afr.; Meadow, UK.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Nérisone C *Bayer, Fr.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Nerisone C *Intendis, Hong Kong; Schering, NZ.*
⊗Diflucortolone valerate (p. 1634·1); chlorquinaldol (p. 260·1).
Infected skin disorders.

Nerita *Delegant, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Nerixia *Abiogen, Ital.*
Neridronate sodium (p. 1186·2).
Osteogenesis imperfecta; Paget's disease of bone.

Nerjuwin *Aurel, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Nerjuwin-P *Aurel, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nero *Elea, Arg.*
Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).
Smooth muscle spasm.

Nerox-B *Abdi, Turk.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Neroxim *Nitin, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Neruda *Sanovel, Turk.*
Gabapentin (p. 523·3).

Nerva *Gracia, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Nerva Plus *Gracia, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Vitamin B and folic acid deficiency.

Nervafil *Filadams, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency; neurological pain; neuropathies.

Nervamin *Prati-Donaduzzi, Braz.*
Thiamine (p. 2102·3).

Nervan
Note: this name may be used for preparations of different composition.
Meyer, Venez.
Bromazepam (p. 1041·2).
Anxiety.

Rosch & Handel, Austria.
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine citrate (p. 1203·3).
Pain; fever.

Nervatona Calm *Brauer, Austral.*
Oral liquid: oral spray; tablets: Cocculus (p. 2483·1); helonias (p. 2524·3); passion flower (p. 2584·1); ignatia (p. 2532·1); nux vomica (p. 2573·3); phosphoricum acidum (p. 2589·1); sepia (p. 2613·1); zincum metallicum (p. 2126·1).
Anxiety; homoeopathic preparation.

Nervatona Focus *Brauer, Austral.*
Oral spray: oral liquid: Argentum nitricum (p. 2615·3); cocculus (p. 2483·1); helonias (p. 2524·3); ignatia (p. 2532·1); kali phosphoricum (p. 1790·3); magnesia phosphorica (p. 1787·3); nux vomica (p. 2573·3); panax ginseng (p. 2513·3); passiflora (p. 2584·1); phosphoricum acidum (p. 2589·1); sepia (p. 2613·1); valeriana (p. 2640·2); zincum met. (p. 2126·1).
Homoeopathic preparation; anxiety; stress.

Nervaxon *Schwabe, Ital.*
St John's wort (p. 449·1).
Depression.

Nerve *Med-One, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Nerve Agent Antidote L4A1 *Ministry of Defence, UK.*
Pralidoxime mesilate (p. 1571·1); avizafone (p. 1040·3); atropine sulfate (p. 1310·2).
Nerve agent exposure.

Nerve Agent Pre-Treatment Tablet Set L1A1 *Ministry of Defence, UK.*
Pyridostigmine bromide (p. 689·2).
Risk of poisoning by organophosphorus cholinesterase inhibitors.

Nerve Tonic *Hylands, Canad.*
Calcarea phosphorica (p. 1784·2); ferrum phosphorica (p. 2077·1); kali phosphoricum (p. 1790·3); magnesia phosphoricum (p. 1787·3); natrum phosphoricum (p. 1791·2).
Homoeopathic preparation.

Nervelin-M *Zodley, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nerven *Uniao Quimica, Braz.*
Thiamine hydrochloride (p. 2103·1).

Nerven-Dragees
Note: this name may be used for preparations of different composition.
Zeller, Israel.
Crataegus (p. 2488·1); passion flower (p. 2584·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Insomnia; nervous disorders.

Nervendragees
Note: this name may be used for preparations of different composition.
Ratiopharm, Pol.
Lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Nervenkapseln *Ratiopharm, Ger.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders; sleep disorders.

Nervenruh *Klosterfrau, Austria.*
Valerian (p. 2640·2); passion flower (p. 2584·1); lupulus (p. 2546·1).
Anxiety disorders; sleep disorders.

Nerventee St Severin *Smetana, Austria.*
Valerian (p. 2640·2); lupulus (p. 2546·1); St John's wort (p. 449·1); peppermint leaf (p. 1877·1); calluna vulgaris; delphinium consolida.
Anxiety disorders; sleep disorders.

Nerve-O-Fitt *Hanburys, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Nerveplex *IAE, Philipp.*
Capsules: Vitamins; minerals; taurine (p. 2626·2).
Nutritional supplement.
IAE, Philipp.
Oral drops; syrup: Vitamins; minerals; chlorella (p. 2475·3); lysine (p. 2079·3); taurine (p. 2626·2).
Nutritional supplement.

Nervex
Note: this name may be used for preparations of different composition.
Prosel, Philipp.
Vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).

Nervic *Unimarck, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).
Unimarck, India.
Injection; tablets: Vitamin B substances (p. 2102·3).
Unimarck, India.
Syrup: Lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3).

Nervic-1500 *Unimarck, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nervic Plus *Unimarck, India.*
Vitamins; trace elements; lycopene (p. 2546·2).

Nervic-G *Unimarck, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nervicin *Cinerea, India.*
Capsules: Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).
Cinerea, India.
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nervicin-G *Cinerea, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nervifène *Interdelta, Switz.*
Cloral hydrate (p. 1055·2).
Agitation; insomnia.

Nervijen *Jenburkt, India.*
Capsules: Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).
Jenburkt, India.
Injection: Vitamin B substances (p. 2102·3).

Nervijen-CT *Jenburkt, India.*
Citicoline (p. 2480·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Nervijen-D *Jenburkt, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3); chromium tripicolinate (p. 2056·1); zinc oxide (p. 1729·1); inositol (p. 2533·2); lutein (p. 2079·2).

Nervijen-P *Jenburkt, India.*
Benfotiamine (p. 2102·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pregabalin (p. 545·3); vitamin B_6 (p. 2105·3).

Nervikan *Schwabe, Spain; Abdi, Turk.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; insomnia; anxiety.

Nervilan *Jumont, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Neuritis; neuralgia; neuropathy; encephalopathy.

Nervimax Plus *Cruise, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Nervimax-G *Cruise, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nervim-P *Dewcare, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nervinat *St Laurent, Canad.*
Tilia (p. 2631·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders.

Nervinetas *Novum, Mex.; Grunenthal, Venez.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Anxiety; sleep disorders; insomnia.

Nervinetten *Zellaforte, Switz.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Agitation; sleep disorders.

Nervinex *Guidotti, Spain.*
Brivudine (p. 970·1).
Herpes zoster infections.

Nervinolum *Herbapol Krakow, Pol.*
Lupulus (p. 2546·1); lavender (p. 2541·1); motherwort (p. 2564·2); melissa (p. 2552·3).
Nervous disorders; sleep disorders.

Nervinum *Herbapol Lublin, Pol.†*
Lupulus (p. 2546·1); lavender (p. 2541·1); melissa (p. 2552·3).
Sleep disorders; nervous disorders.

Nervion *Zytras, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); minerals.
Zytras, India.
Injection: Vitamins.
Zytras, India.
Syrup: Vitamins; lysine (p. 2079·3).

Nerviplant *Schwabe, Neth.†*
Valerian (p. 2640·2).
Sleep disorders.

Nerviplex *Jayson, Ukr.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuropathy; neuralgia; neuritis.

Nervisatis *Gezzi, Arg.*
Valerian (p. 2640·2).
Sedative.

Nervistop *Lafedar, Arg.*
Lorazepam (p. 1080·3).
Anxiety; muscle spasm.

Nervit B-Plus *Evapharm, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency.

Nervita *Boiron, Canad.*
Anacardium orientale (p. 2471·3); cina; coffea cruda (p. 2648·2); gelsemium sempervirens (p. 2511·2); kalium bromatum (p. 2461·1); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Nervite *JRalph, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency.

Nervitone
Note: this name may be used for preparations of different composition.
Alembic, India.
Peptone (p. 2086·2); calcium gluconate (p. 1783·3); magnesium chloride (p. 1787·1); manganese sulfate (p. 2081·2); yeast extract.
Tonic.
Combiphar, Indon.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; facial paresis; ischialgia; vitamin B deficiency.

Nervitone E *Combiphar, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Neuralgia; neuritis; facial paresis; ischialgia; vitamin B deficiency.

Nervium
Note: this name may be used for preparations of different composition.
Saba, Turk.
Diazepam (p. 1063·2).
Anxiety; insomnia; alcohol withdrawal syndrome; status epilepticus; febrile convulsions; muscle spasm; premedication.
De Mayo, Braz.†
Bromazepam (p. 1041·2).
Anxiety; insomnia.

Nervival *VSM, Neth.*
Aconitum napellus (p. 2428·3); asa foetida (p. 2449·3); coffea cruda (p. 2648·2); ignatia amara (p. 2532·1); kalium phosphoricum (p. 1790·3); leonurus cardiaca (p. 2564·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Nervix *Bago, Chile.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

nervo OPT N *Optimed, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Nervobion *Merck, Spain.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2).
Vitamin B deficiency.

Nervobion Fuerte *Merck Serono, Arg.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

Nervocaine *Keene, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Nervocalm *Garden House, Arg.*
Passion flower (p. 2584·1); melissa (p. 2552·3); valerian (p. 2640·2); tilia (p. 2631·3).
Nervous disorders.

Nervocel *Amnol, Ital.†*
Choline (p. 2055·2); melatonin (p. 2551·3).
Dietary supplement to aid mental function.

Nervocur *Fabra, Arg.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Nervocuril *Fabra, Arg.*
Flunitrazepam (p. 1073·3).

Nervofleur *Bloem Beheer, Neth.*
Gelsemium sempervirens (p. 2511·2); sepia officinalis (p. 2613·1); anacardium orientale (p. 2471·3); ignatia amara (p. 2532·1); pulsatilla pratensis (p. 2600·2); crataegus oxyacantha (p. 2488·1).
Homoeopathic preparation.

Nervoheel
Note: this name may be used for preparations of different composition.
Heel, Neth.; Ebi, Switz.
Acidum phosphoricum (p. 2589·1); strychnos ignatii (p. 2532·1); sepia officinalis (p. 2613·1); kalium bromatum (p. 2461·1); zincum isovalerianicum (p. 2641·2).
Homoeopathic preparation.

Heel, Austria.
Acidum phosphoricum (p. 2589·1); strychnos ignatii (p. 2532·1); sepia officinalis (p. 2613·1); psorinum nosode; kalium bromatum (p. 2461·1); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Peithner, Hung.
Acidum phosphoricum (p. 2589·1); strychnos ignatii (p. 2532·1); sepia officinalis (p. 2613·1); psorinum-nosode; kalium bromatum (p. 2461·1); zincum isovalerianicum (p. 2641·2).
Homoeopathic preparation.

Nervoid N *Hanosan, Ger.*
Avena sativa (p. 2451·1); valeriana officinalis (p. 2640·2); passiflora incarnata (p. 2584·1); cimicifuga racemosa (p. 2478·1); ambra grisea (p. 2440·3); semecarpus anacardium (p. 2471·3).
Homoeopathic preparation.

Nervoject F *Syxyl, Ger.*
Hypericum perforatum (p. 449·1); valeriana officinalis (p. 2640·2); strychnos ignatii (p. 2532·1).
Homoeopathic preparation.

Nervolta *Volta, Chile.†*
Calcium bromolactobionate (p. 1044·1).
Sedative.

Nervomag *Herbapol Lublin, Pol.*
Valerian (p. 2640·2); melissa (p. 2552·3); magnesium oxide (p. 1857·3); vitamin B_6 (p. 2105·3).
Nervous disorders; sleep disorders.

Nervomax TB12 *TRB, Arg.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); thioctic acid (p. 2629·1).
Neuropathy.

Nervomix *Adamed, Pol.*
Lupulus (p. 2546·1); St John's wort (p. 449·1); melissa (p. 2552·3); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Nervon-GM *Laksun, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nervonic *Medihealth, India.*
Syrup: Vitamins.

Medihealth, India.
Tablets: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Nervonic-P *Medihealth, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nervon-M *Laksun, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nervon-PM *Laksun, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nervopax *Lehning, Fr.*
⊗Corallium rubrum; atropinum sulfuricum (p. 1310·2); cuprum aceticum (p. 2486·2); magnesia phosphorica (p. 1787·3); arsenicum album (p. 2448·1); zincum valerianicum (p. 2641·2); agnus castus (p. 2432·2); silicea (p. 2208·3).
Homoeopathic preparation.

Nervo-Plantin *Infirmarius, Ger.†*
Acidum phosphoricum (p. 2589·1); ambra grisea (p. 2440·3); avena sativa (p. 2451·1); coffea arabica (p. 2648·2); passiflora incarnata (p. 2584·1); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Nervoptin *Abbott, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nervoregin *Pfluger, Ger.*
Acidum phosphoricum (p. 2589·1); avena sativa (p. 2451·1); humulus lupulus (p. 2546·1); passiflora incarnata (p. 2584·1).
Homoeopathic preparation.

Nervoregin comp *Pfluger, Ger.*
Agaricus; valeriana officinalis (p. 2640·2); asa foetida (p. 2449·3); strychnos ignatii (p. 2532·1); zincum isovalerianicum (p. 2641·2).
Homoeopathic preparation.

Nervoregin H *Pfluger, Ger.*
Tablets: Acidum phosphoricum (p. 2589·1); anamirta cocculus (p. 2483·1); avena sativa (p. 2451·1); hypericum perforatum (p. 449·1); passiflora incarnata (p. 2584·1).
Homoeopathic preparation.

Nervosal *Neuropharma, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Nervosan
Note: this name may be used for preparations of different composition.
Herbapol Lublin, Pol.†
Valerian (p. 2640·2); achillea (p. 2427·3); peppermint (p. 1877·1); melissa (p. 2552·3); chamomile (p. 2474·1).
Nervous disorders; sleep disorders.

Nervosol *Herbapol Wroclaw, Pol.*
Angelica (p. 2443·3); lupulus (p. 2546·1); melissa (p. 2552·3); valerian (p. 2640·2); lavender (p. 2541·1).
Insomnia; nervous disorders.

Nervostal *Pharmanik (Φαρμανικ), Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Nervoton *Farmo Quimica, Chile.*
Vitamin B substances (p. 2102·3).
Tonic.

Nervová Čajová Směs *Megafyt-R, Cz.*
Valerian (p. 2640·2); peppermint leaf (p. 1877·1); melissa (p. 2552·3); fennel (p. 2503·2).
Nervous disorders.

Nervpin *Schoning-Berlin, Ger.*
Menthol (p. 2553·2); Norway spruce oil.
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; superficial vascular disorders.

Nervrite *Vitality, Canad.*
Dried yeast (p. 2125·2); phosphatidyl choline (p. 2588·3); skullcap (p. 2617·1); valerian (p. 2640·2); vitamin B substances (p. 2102·3).

Nervup *Abbott, India.*
Capsules: Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Abbott, India.
Injection: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nervup Forte *Abbott, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Nervup-ER *Abbott, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Nervup-OD *Abbott, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Nervup-PG *Abbott, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nervuptin *Piramal, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nervz *Intas, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Nervz-B *Intas, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); inositol (p. 2533·2); chromium polynicotinate (p. 2055·3).

Nervz-G *Intas, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nerwin-GT *Arrowin, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nerwin-MD *Arrowin, India.*
Thioctic acid (p. 2629·1); vitamins; selenium dioxide (p. 2087·1); zinc sulfate (p. 2126·2).

Nerwobonisol *Bonimed, Pol.*
Chamomile (p. 2474·1); crataegus (p. 2488·1); lupulus (p. 2546·1); motherwort (p. 2564·2); melissa (p. 2552·3); valerian (p. 2640·2).
Insomnia; nervous disorders.

Nerwonal *Pampa, Pol.*
Crataegus (p. 2488·1); passion flower (p. 2584·1).
Arrhythmias; nervous disorders; sleep disorders.

Nesacaine *AstraZeneca, Canad.; APP, USA.*
Chloroprocaine hydrochloride (p. 1983·1).
Local anaesthesia.

Nesbiler *Klonal, Arg.*
⊗Fluorometholone (p. 1637·2); neomycin (p. 329·3).
Infected eye disorders.

Nescon-PD *Cypress, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Nesfare *Rottapharm, Spain.*
⊗Framycetin sulfate (p. 301·2); triamcinolone acetonide (p. 1649·1); centella (p. 1698·3).
Infected skin disorders.

Nesgarin *Somyurek, Turk.*
Benzoic acid (p. 1738·2); sodium fluoride (p. 2089·2); cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Oral hygiene.

Nesina *Takeda, Jpn; Takeda, USA.*
Alogliptin benzoate (p. 467·2).
Diabetes mellitus.

Nesivine *Merck, Belg.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; otitis media; sinusitis; Eustachian-tube inflammation.

Nesopin *Sintez, Rus.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis.

Nesp *Taiyo, Singapore; Kyowa Hakko Kirin, Thai.*
⊗Darbepoetin alfa (p. 1137·1).
Anaemias.

Nespo *Dompe, Cz.†; Dompe Biotec, Ital.†*
⊗Darbepoetin alfa (p. 1137·1).
Anaemias.

Nessiol *Pyridam, Indon.*
Phospholipids (p. 2201·2); vitamin B complex (p. 2102·3); vitamin E (p. 2119·1).
Dietary supplement for liver disorders.

Nestabs *Womens Choice, USA.*
Vitamins; minerals.
Dietary supplement.

Nestabs ABC *Womens Choice, USA.*
Tablets, minerals; vitamins; capsules, eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).

Nestabs DHA *Womens Choice, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).
Dietary supplement.

Nestan *Farmanic, Gr.*
Meptazinol (p. 87·3).

Nestargel *Nestle, Switz.†; Nestle, UK.*
Ceratonia (p. 2178·1).
Infant feed thickener; vomiting.

Nestic *Asian Pharm, Thai.*
Clotrimazole (p. 576·2).
Vaginal fungal infections; trichomoniasis.

Nestilo *Nitro Organics, India.*
Escitalopram (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Nestle VHC *Nestle, USA.*
Preparation for enteral nutrition.

Nestosule-MV *Nestor, India.*
Oral drops: Vitamins; minerals; lysine hydrochloride (p. 2079·3).

Nestor, India.
Syrup: Vitamins; minerals; trace elements.

Nestor, India.
Tablets: Vitamins; minerals; trace elements; silicon (p. 2209·2).

Nestosyl
Note: this name may be used for preparations of different composition.
H2 Pharma, Fr.
Ointment: Benzocaine (p. 1980·2); butyl aminobenzoate (p. 1982·3); resorcinol (p. 1718·3); hydroxyquinoline (p. 2530·1); zinc oxide (p. 1729·1).
Insect stings.

Pharmacobel, Belg.
Pramocaine hydrochloride (p. 1993·3); chlorhexidine hydrochloride (p. 1743·3); zinc oxide (p. 1729·1).
Skin disorders; minor wounds.

Remark, Neth.
Pramocaine hydrochloride (p. 1993·3); zinc oxide (p. 1729·1).
Skin disorders.

H2 Pharma, Fr.†
Topical solution: Benzocaine (p. 1980·2); butyl aminobenzoate (p. 1982·3); hydroxyquinoline (p. 2530·1).
Local anaesthesia; catheterisation.

Nestrolan *3DDD, Belg.*
Trazodone hydrochloride (p. 451·1).
Depression.

Nestum *Nestle, Port.*
Preparations for enteral nutrition.

Netaf *Chemopharma, Chile.*
Ketorolac (p. 80·2).
Pain.

Netamise *Chanelle, Cz.*
⊗Exemestane (p. 792·2).

Netan *Almirall, Neth.*
Ebastine (p. 628·1).
Allergic rhinitis.

Netazox *Ind-Swift, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Netazox-OF *Ind-Swift, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Netclav *Bionet, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Netfer *Bionet, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Netflox-OZ *Bionet, India.*
Potassium clavulanate (p. 268·3); ofloxacin (p. 334·3).
Bacterial infections.

Nethaprin Dospan *Adcock Ingram, S.Afr.†*
⊗Bufylline (p. 1203·3); doxylamine succinate (p. 627·3); etafedrine hydrochloride (p. 1665·2); phenylephrine hydrochloride (p. 1672·3).
Obstructive airways disease; allergic cough.

Nethaprin Expectorant *Adcock Ingram, S.Afr.†*
⊗Bufylline (p. 1203·3); doxylamine succinate (p. 627·3); etafedrine hydrochloride (p. 1665·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Neticin *Samarth, India.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netil *Siam Bheasach, Thai.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netilcin *Excella, India; Medica Korea, Philipp.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netildex *SIFI, Ital.; Teka, Turk.*
⊗Dexamethasone sodium phosphate (p. 1631·2); netilmicin sulfate (p. 331·1).
Infected eye disorders.

Netilyn *Schering-Plough, Fin.†; MSD, Swed.†*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netira *SIFI, Mex.; Teka, Turk.*
Netilmicin sulfate (p. 331·1).
Bacterial eye infections.

Netisum *Phergal, Spain.*
Valerian (p. 2640·2); passion flower (p. 2584·1).
Insomnia; nervous disorders.

Netmicin *United Biotech, India.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netocur *Duncan, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Netocur Balsamico *Duncan, Arg.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Bacterial infections.

Netom-D *Bionet, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Netracin *Pyridam, Indon.†*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Skin infections.

Netran *Farmakon, Rus.*
Chloramphenicol (p. 257·1); methyluracil.
Wounds.

Netrasol Co *Specpharm, S.Afr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Netrocid *Symbiosis, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Netrolex *Sanovel, Turk.*
Levetiracetam (p. 531·1).

Netromax *Zuventus, India.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netromicina *Mantecorp, Braz.; Schering-Plough, Mex.; Schering-Plough, Port.; Schering-Plough, Venez.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nétromicine *MSD-Chibret, Fr.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netromycin *MSD, China; MSD, Gr.; MSD, Hong Kong; Fulford, India; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Philipp.†; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; MSD, Thai.; Schering-Plough, Turk.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netromycine *Schering-Plough, Cz.; Schering-Plough, Hung.†; Schering-Plough, Pol.; Essex, Switz.†*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netrozin *Duopharma, Philipp.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Netspan *Cipla, India.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nettacin *SIFI, Cz.†; SIFI, Ital.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Nettavisc *SIFI, Ital.*
Netilmicin sulfate (p. 331·1).
Bacterial eye infections.

Nettle Leaf Capsules *Solgar, UK.*
Urtica (p. 2639·3).
Joint pain.

Nettoyant Essilor *Ocular Sciences, Fr.†*
Sodium perborate (p. 1770·1).

Netunal *Merck Serono, Arg.*
Sucralfate (p. 1889·1).
Gastro-oesophageal reflux; peptic ulcer.

Neturone *Schering-Plough, Turk.*
Methenamine (p. 322·3).
Urinary-tract infections.

Networm *Venus, India.*
Albendazole (p. 149·1); ivermectin (p. 155·1).
Nematode infections.

Neu Viplex *Siam Bheasach, Thai.†*
Vitamin B substances (p. 2102·3).
Vitamin deficiency; neurological disorders; joint disorders; pernicious anaemia.

Neuart *Benesis, Jpn.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Neubee *Medifive, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuropathy; vitamin B deficiency; vitamin supplement; toxaemia of pregnancy; tonic.

Neubion *Merck, Venez.*
Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Nuritis; neuralgia.

Neucam *Lupin, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Neucam-P *Lupin, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Neucare *Hoe, Singapore.*
Barrier preparation.

Neuciti *Lapi, Indon.*
Citicoline (p. 2480·1).
Head injury; stroke; hemiplegia.

Neuclar *Sarabhai Piramal, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Neucobal *Sun, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Neucobal-Forte *Sun, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Neucomox *Health Biotech, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Neuer *Daiichi, Jpn.*
Cetraxate hydrochloride (p. 1826·3).
Peptic ulcer; gastritis.

Neufer-Z *Embiotic, India.*
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); zinc sulfate (p. 2126·2).
Embiotic, India.
Syrup: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Neufil *Bial, Port.*
Diprophylline (p. 1207·3).
Obstructive airways disease.

Neuflo *Yung Shin, Singapore.*
Muramidase hydrochloride (p. 2565·1).
Sinusitis; haemorrhage.

Neugaba *Sun, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Neugabin *Mepro, Chile.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neugal *Diba, Mex.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Neugel *Oxytech, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Neugeron *Armstrong, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias.

Neugrast *Accord, Braz.*
Fluorouracil (p. 795·2).

Neukan *Apivita, Gr.†*
St John's wort (p. 449·1).
Depression.

Neukine *Intas, India; Accord, Mex.; Intas, Thai.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Neukob *Behrens, Venez.*
Ginkgo biloba (p. 2512·3).

Neulab *Laborate, India.*
Nimesulide (p. 101·3).
Pain.

Neulab Active *Laborate, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Neulab D *Laborate, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Neulab-MR *Laborate, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3).

Neulactil *Sanofi-Aventis, Austral.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, NZ; JHC Healthcare, UK.*
Pericyazine (p. 1095·2).
Psychoses; anxiety; aggression; behaviour disorders.

Neulamin *Sandoz, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Neulasta *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Amgen, Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Amgen, UK; Amgen, USA.*
Pegfilgrastim (p. 1152·1).
Neutropenia.

Neulastim *Roche, Arg.; Roche, Braz.; Roche, Chile; Roche, Hong Kong; Roche, India; Roche, Indon.; Roche, Israel; Roche, Mex.; Roche, NZ; Roche, Rus.; Roche, Singapore; Roche, Thai.; Roche, Ukr.*
Pegfilgrastim (p. 1152·1).
Neutropenia.

Neulastyl *Roche, Philipp.*
Pegfilgrastim (p. 1152·1).
Neutropenia.

Neuleptil *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Erfa, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Fr.; IFET (ΜΦΕΤ), Gr.; Sanofi-Aventis, Israel; Teofarma, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Venez.*
Pericyazine (p. 1095·2).
Psychoses; behaviour disorders; schizophrenia.

Neulide *East West, India.*
Nimesulide (p. 101·3).
Pain.

Neulin *Ferron, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebrovascular disorders.

Neumantine *Millimed, Thai.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Neumax *Dabur, India.*
Filgrastim (p. 1151·3).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Neumega *Wyeth, Braz.; Wyeth, Israel†; Pfizer, Rus.; Genetics Institute, USA; Wyeth, Venez.*
Oprelvekin (p. 1157·2).
Thrombocytopenia.

Neumer *H & Care, India.*
Meropenem (p. 321·3).
Bacterial infections.

Neumobacticel *Bago, Arg.*
Co-trimoxazole (p. 277·3); bromhexine hydrochloride (p. 1656·3).
Bacterial infections.

Neumocort *Cassara, Arg.; D & M, Chile.*
⊗Budesonide (p. 1625·1).
Asthma.

Neumotein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Neumoterol *Phoenix, Arg.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Neumotex *Phoenix, Arg.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; asthma.

Neumotide *Phoenix, Arg.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Neumyn-AS *Rayere, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2).
Asthma; bronchitis.

Neupax
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.
Bago, Arg.
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder; panic attacks.

Neupax Duo-S *Armstrong, Mex.*
Alprazolam (p. 1035·2); sulpiride (p. 1107·3).
Psychosomatic disorders.

Neupeg *Intas, India.*
Pegfilgrastim (p. 1152·1).

Neupent AF *Ranbaxy, India.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neupogen *Roche, Arg.; Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Roche, Chile; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Roche, Hong Kong; Amgen, Hung.; Piramal, India; Roche, Indon.; Amgen, Irl.; Roche, Israel; Dompe Biotec, Ital.†; Roche, Malaysia; Roche, Mex.; Amgen, Neth.; Amgen, Norw.; Roche, NZ; Amgen, Pol.; Amgen, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Roche, Thai.; Roche, Turk.; Amgen, UK; Roche, Ukr.; Amgen, USA; Roche, Venez.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of autologous peripheral blood progenitor cells.

Neupomax *Farmstandart, Rus.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Neupopeg *Dompe Biotec, Ital.†*
Pegfilgrastim (p. 1152·1).
Neutropenia.

Neupram *Neuropharma, Arg.*
Haloperidol (p. 1077·1).

Neupreg *Intra-Labs, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Neupreg Forte *Intra-Labs, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Neupro *UCB, Austral.; Schwarz, Austria; UCB, Belg.; Schwarz, Cz.; UCB, Denm.; UCB, Fr.; Schwarz, Ger.; UCB, Ger.; UCB, Gr.; UCB, Hong Kong; Schwarz, Hung.; Schwarz, Irl.; UCB, Israel; UCB, Ital.; Otsuka, Jpn; UCB, Neth.; UCB, Norw.; Schwarz, Pol.; UCB, Port.; UCB, Spain; UCB, Swed.; UCB, Switz.; Abbott, Thai.; UCB, UK; UCB, Ukr.; UCB, USA.*
Rotigotine (p. 914·1).
Parkinsonism; restless legs syndrome.

Neuquinon *Eisai, China; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.*
Ubidecarenone (p. 2637·1).
Cardiovascular disorders; hepatitis; heart failure; angina pectoris.

Neuraben *Pfizer, Ital.*
Thiamine bezomil (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis.

Neurabol *Zydus, India.*
Capsules: ⊗Stanozolol (p. 2304·2).
Anabolic; osteoporosis.
Zydus, India.
Injection: ⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis.

Neuractin
Note: this name may be used for preparations of different composition.
Drugtech, Chile.
Valproate semisodium (p. 553·2).
Epilepsy; migraine.
Overseas, India.
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Neuractin Forte *Overseas, India.*
Thioctic acid (p. 2629·1); inositol (p. 2533·2); vitamin B substances (p. 2102·3); chromium (p. 2055·3); selenium (p. 2086·3); zinc (p. 2126·1).

Neuradapt *Monin, Fr.*
Magnesium glycerophosphate (p. 1787·2); rhodiola rosea; vitamin B_6 (p. 2105·3).
Dietary supplement; stress.

Neuragel-D *Adcock Ingram, S.Afr.†*
Dicycloverine hydrochloride (p. 1834·2); aluminium hydroxide (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastric hyperacidity.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neuragen *Indo French, India.*
Vitamin B substances (p. 2102·3); minerals; lysine hydrochloride (p. 2079·3).

Neuragon *Sriprasit, Thai.†*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Mixed anxiety depressive states.

Neural *Cristalia, Braz.*
Lamotrigine (p. 527·2).
Epilepsy.

Neural-B *EuroHealth, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Neuritis; neuralgia; lumbago; neuropathy; vitamin B deficiency.

Neuralfa *Amnol, Ital.*
Thioctic acid (p. 2629·1); linoleic acid (p. 2509·2); asparagine (p. 2050·3); vitamins; minerals.
Nutritional supplement.

Neuralgie-Gastreu R70 *Reckeweg, Ger.*
Aconitum (p. 2428·3); cedron; colocynthis (p. 1833·3); kalmia (p. 2537·2); verbascum (p. 2645·1).
Homoeopathic preparation.

Neuralgie-Injektopas SL *Pascoe, Ger.*
Mezereum; gnaphalium polycephalum; ranunculus bulbosus; asclepias tuberosa (p. 2593·2); gelsemium (p. 2511·2).
Homoeopathic preparation.

Neuralgin
Note: this name may be used for preparations of different composition.
Pfleger, Ger.
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Kalbe, Indon.
Paracetamol (p. 115·1); ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain.

Neuralgin extra *Pfleger, Ger.*
Ibuprofen lysine (p. 68·3).
Pain; fever.

Neuralgin RX *Kalbe, Indon.*
Dipyrone (p. 53·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); caffeine (p. 1203·3).
Pain; neuralgia.

Neuralgina *Cifarma, Braz.*
⊗Isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).

Neuralin *Chinoin, Mex.*
⊗1 Ampoule, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin (p. 2107·3); 1 ampoule, dexamethasone sodium phosphate (p. 1631·2); lidocaine hydrochloride (p. 1988·2).
Neuritis; neuralgias; inflammation; rheumatism.

Neuralprona *Bioquimico, Arg.†*
Naproxen (p. 98·2).
Fever; inflammation; pain.

Neuralta Migren *Alta Care, Ital.*
Ginkgo biloba (p. 2512·3); meadowsweet (p. 2550·2); feverfew (p. 676·1); peppermint oil (p. 1877·1); melissa oil (p. 2553·2); rosemary oil (p. 2607·3).
Migraine; headaches; mental function impairment.

Neuramide *Difa, Ital.*
Neuramide.
Herpesvirus infections.

Neuramin *Orion, Fin.*
Thiamine hydrochloride (p. 2103·1).
Thiamine deficiency.

Neuramizone *Sriprasit, Thai.*
Belladonna alkaloids (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).
Sedative; migraine; menopausal disorders.

Neuran *Ranbaxy, Pol.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neuranidal *Stada, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Neurap *Torrent, India.*
Pimozide (p. 1096·3).
Schizophrenia; monosymptomatic hypochondria; paranoid states; Tourette's syndrome.

Neurapas *Pascoe, Austria; Pascoe, Ger.; Pascoe, Spain.*
St John's wort (p. 449·1); valerian (p. 2640·2); passion flower (p. 2584·1).
Depression; sleep disorders; neuropathy; neuroses; insomnia.

Neuratab B6 *Waves, India.*
Vitamin B substances (p. 2102·3); *Lactobacillus sporogenes* (p. 2596·3); glutamic acid (p. 2070·2); magnesium oxide (p. 1857·3).

Neuratab-M Forte *Waves, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Neurax
Note: this name may be used for preparations of different composition.
Mylan, S.Afr.†
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; hypersensitivity disorders; pruritus.

Neuraxon *Pyridam, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B1, B6 and B12 deficiencies.

NeuRecover *NeuroGenesis, USA.*
Vitamins; minerals; amino acids.

Neurex
Note: this name may be used for preparations of different composition.
Beta, Arg.
Acetylcarnitine hydrochloride (p. 2053·2).
Cerebral vasculopathy; peripheral neuropathy.

Euro-Pharma, Ital.
Citicoline sodium (p. 2480·2).
Parkinsonism.

Hexal, Pol.†
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Neurexal *Sandoz, S.Afr.*
Gabapentin (p. 523·3).
Epilepsy.

Neurexan *Heel, Ger.*
Passiflora incarnata (p. 2584·1); avena sativa (p. 2451·1); coffea arabica (p. 2648·2); zincum isovalerianicum (p. 2641·2).
Homoeopathic preparation.

Neuri B6 *Cazi, Braz.*
Pyridoxine hydrochloride (p. 2105·3).
Neuritis.

Neuribe *Vivax, Venez.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Vitamin B deficiency neurological disorders.

Neurica-M *Micro, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Neuri-cyl N Ho-Len-Complex *Liebermann, Ger.*
Aesculus (p. 2431·2); ars. alb. (p. 2448·1); colocynthis (p. 1833·3); ginseng (p. 2513·3); kalium jod. (p. 2336·3); nux moschata (p. 2573·1); rhus tox. (p. 2603·3).
Homoeopathic preparation.

Neuril
Note: this name may be used for preparations of different composition.
Alternova, Denm.
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neurilan *Gross, Braz.*
Bromazepam (p. 1041·2).
Anxiety.

Neurindo *Yarindo, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Neuriplège Sport *Genevrier, Fr.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); isopropyl myristate (p. 2190·3); cineole (p. 2479·1); menthol (p. 2553·2).
Skeletal muscle pain.

Neuris *NeuPharma, Thai.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders in children; behaviour disorders in dementia.

Neuristan *Casasco, Arg.*
Pregabalin (p. 545·3).
Neuropathic pain; epilepsy; anxiety; fibromyalgia rheumatica.

Neuritis *Hovid, Hong Kong.†*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Neurium
Note: this name may be used for preparations of different composition.
Abbott, Braz.
Lamotrigine (p. 527·2).
Epilepsy.

Hexal, Ger.†
Thioctic acid (p. 2629·1) or ethylenediamine thioctate (p. 2629·1).
Diabetic polyneuropathy.

Neurivit *Cazi, Braz.*
Thiamine hydrochloride (p. 2103·1).

Neuro *Stada, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neuro Laz *Lazar, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Neuro Nutrients *Solgar, UK.*
Amino acids; vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); ginkgo biloba (p. 2512·3).

Neuro Panstop *Armoxindo, Indon.*
Dipyrone (p. 53·3); thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia.

Neuro uno *Stada, Ger.†*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neuro-Ace *Ace, Philipp.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Neuro-Act *PC India, India.*
Vitamin B substances (p. 2102·3).

Neuroactil *Bago, Arg.*
Acetylcarnitine hydrochloride (p. 2053·2).

Neuroage *Allenge, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); vitamin E (p. 2119·1).

Allenge, India.
Injection; tablets: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Allenge, India.
Syrup: Vitamins.

Neuroage GF *Allenge, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neuroage Plus *Allenge, India.*
Capsules: Ascorbic acid (p. 2110·3); lycopene (p. 2546·2); mecobalamin (p. 2108·1); spirulina (p. 2622·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1).

Allenge, India.
Syrup: Lycopene (p. 2546·2); mecobalamin (p. 2108·1).

Neuroage-B *Allenge, India.*
Benfotiamine (p. 2102·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

NeuroAid *Moleac, Malaysia.*
Astragalus (p. 2451·1); danshen (p. 2491·3); red peony; ligusticum sinense; ginseng (p. 2513·3); moutan bark; leech (p. 1418·1); eupolyphaga seu steleophaga; lignum dalbergiae odoriferae; calculus bovis artifactus; uncaria hook; buthus martensii; radix polygalae tenuifolia; rhizoma acori tatarinowii.
Tonic.

Moleac, Singapore.
Huang qi (p. 2451·1); danshen (p. 2491·3); red peony; chuanxiong; senega root (p. 1677·2); calamus (p. 2464·2); dong quai (p. 2497·1); carthamus tinctorius; prunus persica; leech (p. 1418·1); eupolyphaga seu steleophaga; buthus martensii Karsch; calculus bovis artifactus; saigae tartaricae cornu.
Post-stroke rehabilitation.

Neuro-B *Sunward, Singapore.*
Thiamine nitrate (p. 2103·2); pyridoxine (p. 2105·3); cyanocobalamin (p. 2107·2).

neuro-B forte *Biomo, Ger.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neurological system disorders.

Neuroba *Medico Uno, Hung.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neurobase *Sydenham, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Neurobat *Interbat, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; tonic; nausea and vomiting of pregnancy; vitamin B deficiency.

Neurobat A *Interbat, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; lumbago; ischialgia.

Neurobene *Ratiopharm, Cz.*
Cyanocobalamin (p. 2107·2).
Megaloblastic anaemia; vitamin B_{12} deficiency; neuritis; neuralgias.

Neuro-Beston *Tanabe, Indon.*
Bisbentiamine (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; myalgia; arthralgia; neuritis; vitamin B deficiency; vitamin B supplement; anaemias.

Neurobex *Actavis, Ukr.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neurological disorders; vitamin B deficiency.

British Dispensary, Thai.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Anaemias; neurological disorders.

Ind-Swift, India.
Capsules; tablets: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); *Lactobacillus acidophilus* (p. 2596·3).

Ind-Swift, India.
Injection; oral drops: Vitamin B substances (p. 2102·3).

Ind-Swift, India.
Syrup: Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Neurobex Neo *Actavis, Ukr.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Neurobex-B *Ind-Swift, India.*
Vitamin B substances (p. 2102·3).

Neurobexol *EuroHealth, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency; vitamin B supplement; neuritis; neuralgia; neuropathy; encephalopathy.

Neurobex-Z *Ind-Swift, India.*
Vitamin B substances (p. 2102·3); zinc (p. 2126·1).

Neurobiane *Pileje, Fr.*
Tryptophan (p. 453·2); magnesium (p. 1786·3); vitamin B_6 (p. 2105·3).
Dietary supplement; stress.

Neurobine *YSP, Malaysia.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuropathy; neuralgia; neuritis; vitamin B deficiency.

Neurobion *Merck, Austria; Merck, Belg.; Merck, Ger.; Merck, Gr.; Merck, Hung.; Merck, Mex.; Merck, Neth.†; Merck, Port.; Merck, Swed.*
Thiamine hydrochloride (p. 2103·1) or thiamine disulfide (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency; joint disorders; alcoholism; polyneuropathy.

Merck, Fin.; Nycomed, Rus.; Merck, Ukr.
Thiamine disulfide (p. 2102·3) or thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; neuritis; neuralgia.

Merck, Hong Kong; Merck Serono, Malaysia; Merck, Singapore; Merck, Thai.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuropathies; facial paresis; neuralgia; neuritis; vitamin B deficiency; toxaemia of pregnancy.

Merck, India.
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Merck, Indon.; Merck, Philipp.; Merck, S.Afr.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuropathy; asthenia; neuralgia; hyperemesis gravidarum; vitamin B deficiency.

Neurobion N *Merck, Ger.*
Octotiamine (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neurobionta *Merck, Chile.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Lidocaine (p. 1988·1) is included in some injections to alleviate the pain of injection.
Musculoskeletal and joint pain; neuralgia; neuritis; vitamin B deficiency.

Neurobiovit *Prafa, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuralgia; neuritis; asthenia; vomiting of pregnancy; vitamin B supplement.

NeuroBloc *Eisai, Austria; Eisai, Cz.; Eisai, Denm.; Eisai, Fr.; Eisai, Ger.; Eisai, Gr.; Eisai, Hung.; Elan, Irl.; Eisai, Ital.; Eisai, Neth.; Eisai, Norw.; Eisai, Pol.; Eisai, Port.; Eisai, Spain; Eisai, Swed.; Eisai, UK.*
Botulinum B toxin (p. 2017·1).
Spasmodic torticollis.

Neuro-B's *Dynamic, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Neuritis; neuralgia; neuropathy; vitamin B deficiency.

Neurocalme *Geistlich, Switz.*
Vitamin B substances (p. 2102·3); calcium carbonate (p. 1824·3); magnesium glycerophosphate (p. 1787·2); magnesium oxide (p. 1857·3).
Tonic.

Neurocam *Recalcine, Chile.*
Clonixin lysine (p. 40·1); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Neurocap-G *Biosync, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neurocap-OD *Biosync, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_6 (p. 2105·3).

Neurocet *Hexpharm, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; alcoholism.

Neurocetam *Micro, India; Brown & Burk, Philipp.; Micro, Singapore.*
Piracetam (p. 393·3).
Myoclonus; mental function impairment.

Neurochek *Indoco, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Neurochol *Landson, Indon.*
Lecithin (p. 2542·2); vitamin B substances; vitamin E (p. 2119·1).
Brain function supplement.

Neurocil *Bayer, Ger.*
Levomepromazine hydrochloride (p. 1079·3) or levomepromazine maleate (p. 1079·3).
Bipolar disorder; psychoses; pain.

Neurocine *Ivax, Arg.*
Bifemelane hydrochloride (p. 389·2).
Cerebrovascular disorders; mental function impairment.

Neurocit *Elnova, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium oxide (p. 1857·3); mecobalamin (p. 2108·1); zinc oxide (p. 1729·1).

Neurocynesine *Boiron, Fr.†; Boiron, Neth.†*
Acetanilidum (p. 17·1); cedron; ignatia (p. 2532·1); iris versicolor (p. 2534·3); spigelia anthelmia (p. 2621·3); usnea barbata (p. 2640·2).
Homoeopathic preparation.

Neurodavur *Davur, Spain.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Neurodavur Plus *Davur, Spain.*
⊗Vitamin B substances (p. 2102·3); dexamethasone sodium phosphate (p. 1631·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuralgia; neuritis; myalgia.

Neurodep *Med. Prod. Panam., USA.*
Injection: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Med. Prod. Panam., USA.
Capsules: Vitamin B substances (p. 2102·3).

Neuroderm *Infectopharm, Ger.*
Bath additive: Almond oil (p. 2437·1); light liquid paraffin (p. 2191·2).
Skin disorders.

Neuroderm Akut *Infectopharm, Ger.*
⊗Hydrocortisone buteprate (p. 1640·1).
Skin disorders.

Neuroderm Pflegecreme *Infectopharm, Ger.*
Emollient.
Dry skin.

Neurodex *Dexa, Indon.; Dexa, Singapore.†*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neurological disorders; morning sickness; vitamin B deficiency; vitamin B supplement; nausea; anaemias; tonic.

Neurodial *Kimia, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Neurodiclovit *Lannacher, Rus.*
Diclofenac sodium (p. 48·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Pain; inflammation; neuritis; neuralgia; gout; musculoskeletal, joint, and soft-tissue disorders.

Neuro-Do *Grasler, Ger.*
Cyclamen (p. 2490·2); gelsemium (p. 2511·2); glonoinum (p. 1391·2); melilotus officinalis (p. 2552·3); paris quadrifolia.
Homoeopathic preparation.

Neurodol Tissugel *IBSA, Switz.*
Lidocaine (p. 1988·1).
Post-herpetic neuralgia.

Neurodoron *Weleda, Ger.*
Aurum metallicum (p. 2521·1); kalium phosphoricum (p. 1790·3); ferrum-quarz.
Homoeopathic preparation.

Neuro-Effekton B *Teofarma, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous system disorders.

Neurofenac *Merck, Austria.*
Diclofenac sodium (p. 48·3); vitamin B substances (p. 2102·3).
Musculoskeletal and joint disorders; neuralgia; neuritis; gout; pain.

Merck, Indon.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Merck, Philipp.
Diclofenac sodium (p. 48·3); vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Musculoskeletal and joint pain; neuropathy; neuralgia; fibromyalgia.

Neuroflax *Sanofi-Aventis, Mex.*
Cobamamide (p. 2107·2); thiocolchicoside (p. 2026·2).
Musculoskeletal and joint disorders.

Neuroflorine *Hepatoum, Fr.†*
Passion flower (p. 2584·1); crataegus (p. 2488·1); valerian (p. 2640·2).
Insomnia; anxiety; palpitations.

Neurofor *Sanofi-Aventis, Mex.*
Cobamamide (p. 2107·2).
Neuritis; anaemias.

Neuroforte
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Polyneuritis; neuralgia; diabetic neuropathy.

Meridian, India.
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); vitamin E (p. 2119·1).

Neuroforte-E *Medi-Rx, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1).
Degenerative nerve disorders; neuritis; neuralgia.

Neurogab *Emgen, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neurogabaf *Richmond, Arg.†*
Phenobarbital (p. 535·2).
Epilepsy; sedative; insomnia.

Neurogamma *Worwag, Rus.*
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Neurogard *Vanguard, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); glutamic acid (p. 2070·2); zinc sulfate (p. 2126·2).

Neurogen *Bernofarm, Indon.†*
Dipyrone (p. 53·3); chlordiazepoxide (p. 1044·2); vitamin B_1 (p. 2102·3).
Pain.

Neurogen-E *Imperial, Hong Kong; Imperial, Malaysia; Imperial, Singapore.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Vitamin supplement.

Neuro-Ginsan N *Hanosan, Ger.*
Valeriana officinalis (p. 2640·2); avena sativa (p. 2451·1); sumbulus moschatus; humulus lupulus (p. 2546·1); passiflora incarnata (p. 2584·1); panax ginseng (p. 2513·3); cimicifuga racemosa (p. 2478·1); gelsemium sempervirens (p. 2511·2); acidim picrinicum (p. 2634·2).
Homoeopathic preparation.

Neuroglow *Symbiosis, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2).

Neuroglow-B *Symbiosis, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); inositol (p. 2533·2); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Neuroglutamin *Pharmonta, Austria.*
Glutamic acid (p. 2070·2).
Memory and concentration disorders.

Neuro-GM *Cyno, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neurogriseovit *Deva, Turk.*
Ampoule I, vitamin B_{12} (p. 2107·2); ampoule II, vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Vitamin B deficiency.

Neurohax *Guardian, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Peripheral nervous system disorders; vitamin B deficiency.

Neurokab-OD *Lancer, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2).

Neurokair *PDC, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

PDC, India.
Injection: Vitamin B substances (p. 2102·3).

Neurokan *Midsona, Denm.; Midsona, Swed.*
St John's wort (p. 449·1).
Depression; low mood; anxiety; insomnia.

Neurokomplit *Farmstandart, Rus.*
Vitamins; minerals; rutoside (p. 2505·3); thioctic acid (p. 2629·1).

Neurol
Note: this name may be used for preparations of different composition.
Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety-depressive states.

Abigo, Swed.
Valerian (p. 2640·2).
Anxiety; insomnia.

SIT, Ital.
Sodium valerate (p. 2641·2); sodium glycerophosphate (p. 2519·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Tonic.

Neuro-Kranit *Kleva, Gr.*
Vincamine (p. 2645·2).

Neurolab *Laborate, India.*
Vitamin B substances (p. 2102·3).

Neurolac-MD *Laclin, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Neurolax *Helax, India.*
Vitamin B substances (p. 2102·3).

Neurolax-OD *Helax, India.*
Thioctic acid (p. 2629·1); vitamin B substances (p. 2102·3).

Neurolep *Sandoz, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; alcohol withdrawal syndrome; neuralgias; diabetic neuropathy; diabetes insipidus; polyuria; polydipsia.

Neurolepsin *Wabosan, Austria.*
Lithium carbonate (p. 427·3).
Mania; depression.

Neuro-Lichtenstein N *Winthrop, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neurolin *Fahrenheit, Indon.*
Citicoline (p. 2480·1).
Head injury; stroke; hemiplegia.

Neurolink *Biolink, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; neurological disorders.

Neurolipon *MIP, Pol.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Neurolite *Lantheus, Austral.; Lantheus, Cz.; Lantheus, Denm.; Lantheus, Fin.; BMS, Fr.; Lantheus, Israel; BMS, Ital.; BMS, Neth.†; Lantheus, Port.; Lantheus, Spain.†*
Technetium-99m bicisate (p. 2228·1).
Cerebral perfusion imaging.

Neurolithium *Cristalia, Braz.*
Lithium carbonate (p. 427·3).
Depression; mania; bipolar disorder; alcoholism; psychoses; headache.

Labcatal, Fr.†
Lithium gluconate (p. 427·3).
Bipolar disorder; mania.

Neurologico *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Neuromade *Teofarma, Spain.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Vitamin B deficiency.

Neuromas-G *Cosmas, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neuromax *Vitabalans, Cz.; Vitabalans, Fin.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Neuromed
Note: this name may be used for preparations of different composition.
Daksh, India.
Capsules: Folic acid (p. 2063·1); thioctic acid (p. 2629·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); vitamin E (p. 2119·1).

Daksh, India.
Injection; tablets: Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Daksh, India.
Oral powder: Mecobalamin (p. 2108·1); protein.

Daksh, India.
Oral sachets: Calcium (p. 1783·1); glucosamine (p. 2515·3); mecobalamin (p. 2108·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Promed, Indon.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B1, B6 and B12 deficiencies.

Neuromed-GF *Daksh, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neuromet
Note: this name may be used for preparations of different composition.
Merck, Thai.
Mecobalamin (p. 2108·1).
Peripheral neuropathies; vitamin B_{12} deficiency.

Neuromethyn *Sam Chun Dang, Malaysia; Sam Chun Dang, Singapore.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Neuromin
Note: this name may be used for preparations of different composition.
Ordain, India.
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Quality, Hong Kong.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Facial paresis; neuralgias; neuritis; neuropathies; vitamin B deficiency.

Neuromin-3 *Beacons, Singapore.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Neuromin-EA *Ordain, India.*
Vitamin B substances (p. 2102·3); amino acids; zinc (p. 2126·1); chromium tripicolinate (p. 2056·1).

Neuromin-M *Ordain, India.*
Mecobalamin (p. 2108·1); piracetam (p. 393·3).

Neuromol *Ultramark, India.*
Paracetamol (p. 115·1); prochlorperazine maleate (p. 1098·3).

Neuromol-MR *Ultramark, India.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).

Neuromultivit *Lannacher, Austria; GL Pharma, Cz.; Extractum, Hung.; Lannacher, Rus.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuropathy; neuralgia; neuritis.

Neuron *Uniao Quimica, Braz.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Neuro-Norm *Darnitsa, Ukr.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; cranial trauma; vestibular disorders; mental function impairment; migraine.

Neurontin
Note: this name may be used for preparations of different composition.
Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Parke, Davis, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Parke, Davis, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Parke, Davis, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain; postherpetic neuralgia.
United Lifecare, India.
Thioctic acid (p. 2629·1); vitamins.

Neurop *Worwag, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Neuropax *ASD Pharma, Fr.†*
Passion flower (p. 2584·1); crataegus (p. 2488·1).
Insomnia; palpitations.

Neurophen *Ind-Swift, India.*
Cream: Chlorphenamine maleate (p. 620·3); diethylamine salicylate (p. 51·3); menthol (p. 2553·2); mephenesin (p. 2025·2); methyl nicotinate (p. 91·3); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).

Ind-Swift, India.
Injection: ⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Ind-Swift, India.
Tablets: Chlorphenamine maleate (p. 620·3); diclofenac sodium (p. 48·3); magnesium trisilicate (p. 1858·1); paracetamol (p. 115·1).

Neurophen-Compound *Ind-Swift, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Neurophil *Ethica, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuritis; neuralgia; vomiting of pregnancy; circulatory disorders.

Neurophosphates *GSK, India.†*
Vitamin B_1 (p. 2103·1); vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); nicotinamide (p. 2083·1).
Tonic; vitamin B supplement.

Neurophosphates-Iron *GSK, India.*
⊗Alcohol (p. 1733·1); calcium glycerophosphate (p. 1783·3); ferric ammonium citrate (p. 2060·1); glycerophosphoric acid (p. 2519·2); sodium glycerophosphate (p. 2519·2); vitamin B substances (p. 2102·3).

Neuropil *Psyco Remedies, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Neuropill *Ordain, India.*
Thioctic acid (p. 2629·1); gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neuroplant *Schwabe, Ger.; Schwabe, Ukr.*
St John's wort (p. 449·1).
Anxiety; depression.

Neuroplex *Cubit, India.*
Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3).

NeuroPlus
Note: this name may be used for preparations of different composition.
Hovid, Malaysia.
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); phosphatidyl choline (p. 2588·3); *d*-alpha tocopherol (p. 2119·1).
Dietary supplement.

Neuroplus
Note: this name may be used for preparations of different composition.
Baliarda, Arg.
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Neuropret *Bionorica, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

Neuroptic *Progen, Ital.*
Thioctic acid (p. 2629·1); vitamins.
Nutritional supplement.

Neuropyramin *Pyridam, Indon.†*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; vitamin B deficiency; tonic.

Neuroquick *Marching, Hong Kong.†*
Ibuprofen (p. 68·2); vitamin B substances (p. 2102·3).

Neurorace *Pentafarma, Port.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Neuro-ratiopharm N *Ratiopharm, Ger.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neurorubin *Acino, Switz.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neuropathy; neuritis; neuralgias.

Neurorubine *Mepha, Hong Kong; Mepha, Malaysia; Mepha, Singapore.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; musculoskeletal, joint, and peri-articular disorders; migraine; drug-induced vitamin B_6 deficiency.

Mepha, Ukr.
Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; neuropathy; Wernicke-Korsakoff syndrome; beri-beri.

Neuros *Santa, Gr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Neurosan *Geoprodukt, Hung.*
Clinoptilolite; minerals.
Gastrointestinal disorders.

Neurosanbe *Sanbe, Indon.; Sanbe, Singapore.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Peripheral nervous system disorders; vitamin B deficiency.

Neurosanbe Plus *Sanbe, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.

Neurosande *Sanderson, Chile.*
Pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1).
Vitamin B supplement.

Neuroscan *Rotop, Cz.*
Technetium-99m (p. 2228·1) exametazime.
Radionuclide imaging.

Neurosedine *Adelco, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Neuroselect *Dreluso, Ger.*
Lycopus virg. (p. 2462·2); pulsatilla (p. 2600·2); passifl. incarn. (p. 2584·1); gelsemium (p. 2511·2).
Homoeopathic preparation.

Neuroset *Plus, India.*
Vitamin B substances (p. 2102·3).

NeuroSlim *Matrix, USA; NeuroGenesis, USA.*
Vitamins minerals; amino acids.

Neurosmart *Pediapharma, Philipp.*
Docosahexaenoic acid (p. 1460·1); taurine (p. 2626·2); zinc gluconate (p. 2126·2); magnesium gluconate (p. 1787·2); glucose (p. 2068·3).
Dietary supplement to improve mental function.

Neurosomat *Beta, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Neurosoz-MC *Sozin-Flora, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); inositol (p. 2533·2); mecobalamin (p. 2108·1).

Neurospark *Venus, India.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism; head injuries.

Neurospas
Note: this name may be used for preparations of different composition.
Ind-Swift, India.
Capsules: Paracetamol (p. 115·1); dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm and pain.

Ind-Swift, India.
Oral drops: Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).

Neurospas-CD *Ind-Swift, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2); dicycloverine hydrochloride (p. 1834·2).
Irritable bowel syndrome; smooth muscle spasm.

Neurospas-MF *Ind-Swift, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Neurostil *Ivax, Irl.*
Gabapentin (p. 523·3).
Epilepsy; seizures; neuropathic pain.

Neurostop Complex *Lacer, Spain.†*
Benfotiamine (p. 2102·3); hydroxocobalamin acetate (p. 2107·3); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency.

Neuroswift *Ind-Swift, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Neurotam *Kalbe, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; learning difficulties in children; alcoholism.

Neurotioct *TRB, Arg.*
Thioctic acid (p. 2629·1).
Neuropathy.

Neurotol
Note: this name may be used for preparations of different composition.
Orion, Fin.
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; alcohol withdrawal syndrome; bipolar disorder.

Venus, India.
⊗Glycerol (p. 2517·2); mannitol (p. 1427·3).
Raised intracranial pressure; cerebral oedema.

Neurotol-M *Venus, India.*
⊗Mannitol (p. 1427·3).
Renal failure; cerebral oedema; raised intra-ocular pressure; raised intracranial pressure; test of renal function.

Neuroton
Note: this name may be used for preparations of different composition.
Darvys, Philipp.
Piracetam (p. 393·3).
Mental function disorders; myoclonus; cerebrovascular disorders.

NCSN, Ital.
Citicoline sodium (p. 2480·2).
Parkinsonism.

PGN, Arg.†
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).

Neurotone
Note: this name may be used for preparations of different composition.
Bio-Health, UK.
Lupulus (p. 2546·1); skullcap (p. 2617·1); valerian (p. 2640·2).
Stress.

PC India, India.
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Pharmaceutical Enterprises, S.Afr.
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); lecithin (p. 2542·2); choline bitartrate (p. 2055·2); calcium glycerophosphate (p. 1783·3); zinc gluconate (p. 2126·2); ferrous fumarate (p. 2060·3).
Tonic.

Neurotônico *EMS, Braz.*
Minerals; vitamin B substances (p. 2102·3).

Neurotop *Gerot, Austria; GL Pharma, Cz.; GL Pharma, Hung.; GL Pharma, Pol.; Gerot, Singapore; Orion, Switz.†*
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; trigeminal neuralgia; diabetic neuropathy; diabetes insipidus; alcohol withdrawal syndrome; glossopharyngeal neuralgia; nocturia; migraine; dysarthria.

Neurotop Plus *Laborate, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Neurotop-G *Novaduo, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Neurotop-M *Laborate, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Neurotrat *Nordmark, Indon.; Tunggal Idaman, Indon.*
Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Neuritis; neuralgia.

Zydus, India.
Capsules: Ascorbic acid (p. 2110·3); calcium pantothenate (p. 2085·2); chromium (p. 2055·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); thiamine nitrate (p. 2103·2); zinc sulfate (p. 2126·2).
Neuritis; neuralgia; neuropathy; migraine; nausea and vomiting.

Zydus, India.
Injection: 1 Vial, ascorbic acid; 1 vial, cyanocobalamin; folic acid (p. 2063·1); nicotinamide (p. 2083·1).
Neuritis; neuralgia; neuropathy; migraine; nausea and vomiting.

Neurotrat S *Abbott, Ger.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neurotropic *GMP, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Neurotropic Plus *GMP, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Neurotrox *Elea, Arg.*
Paroxetine (p. 440·3) or paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Neurotrypt *Sigma, Braz.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Neuroval *GMP, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Neurovasculaire Sérocytol *Serolab, Switz.†*
An immunoglobulin (equine).
Musculoskeletal, joint and peri-articular disorders; circulatory disorders; skin disorders.

Neurovegetalin *Verla, Ger.*
St John's wort (p. 449·1).
Depression.

Neuro-Vibolex *CNP, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Nervous-system disorders.

Neurovig-M *Madhav, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Neurovig-MD *Madhav, India.*
Vitamin B substances (p. 2102·3).

Neurovin *Micro, India.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Neuro-Vit *Marching, Hong Kong.†*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Neurovit *Bilim, Turk.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Vitamin B deficiency.

GL Pharma, Pol.
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Neuropathy; neuralgia; neuritis.

Hovid, Singapore.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Peripheral neuropathy; neuralgia.

Hovid, Hong Kong.†
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Neurovit E *Kimia, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Neuritis; neuralgia; neuropathy; tonic.

Neurovita *Rubimed, Neth.*
Ambra grisea (p. 2440·3); cerebrum suis (p. 2444·1); china officinalis (p. 2478·3); cuprum aceticum (p. 2486·2); melissa officinalis (p. 2552·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Neuro-Vital *Ind-Swift, India.*
Vitamins; minerals.

Neurovitan *Astellas, Jpn; Hikma, Ukr.*
Octotiamine (p. 2103·1); riboflavin (p. 2104·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; vitamin B supplement; neuritis; neuralgia; neuropathy; arthralgia; myalgia.

Orion, Fin.†
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); nicotinamide (p. 2083·1); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Neurovitol *Kator, Fr.*
Minerals; vitamin B substances (p. 2102·3); marine algae (p. 2612·1); lecithin (p. 2542·2); linseed oil (p. 2544·2); fish oil (p. 1460·1).
Dietary supplement for memory and concentration.

Neurovon *Ind-Swift, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Neuro-Wied Novo *Wiedemann, Ger.†*
Vitamin B substances (p. 2102·3).
Tonic.

Neurox
Note: this name may be used for preparations of different composition.
Nectar, Thai.
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Soteks, Rus.
Emoxypine succinate (p. 1371·1).
Cerebrovascular disorders; mental function impairment; alcohol withdrawal syndrome; anxiety.

Neuroxel *PrimeDrug, Philipp.; DHA, Singapore.*
Thiamine nitrate (p. 2103·2); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Neuritis; neuralgia; neuropathy; vitamin B deficiency.

Neuroxin *Age D'or, Singapore.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Neuroxin-12 *Zydus, India.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Neuroxon *Arterium, Ukr.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; head trauma; neurological disorders.

Neurozan *Vitabiotics, UK.*
Phosphatidyl serine (p. 2589·1); ubidecarenone (p. 2637·1); glutathione (p. 1555·2); omega-3 docosahexaenoic acid; arginine (p. 2049·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Neurozen *AstraZeneca, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Neurozepam *Nova Argentia, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Neurozine *Ultramark, India.*
Cinnarizine (p. 622·1); paracetamol (p. 115·1).

Neurum *Saval, Chile.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain.

Neuryl *Bago, Arg.; Bago, Chile.*
Clonazepam (p. 519·1).
Anxiety; epilepsy; panic disorder.

Neusalus *Quinnova, USA.*
Emollient.

Neusilin *Soho, Indon.†*
Aluminium magnesium silicate (p. 2168·2).
Peptic ulcer; gastric hyperacidity.

Neusinol *Labima, Belg.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Neustim *FDS, Rus.*
Molgramostim (p. 1156·2).
Neutropenia.

Neut *Abbott, USA.*
Sodium bicarbonate (p. 1781·1).
Neutralising additive solution for acidic intravenous infusions.

Neutapin *Kenyaku, Thai.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Neutar *Johnson & Johnson, Port.†*
Coal tar (p. 1723·2).
Dandruff; seborrhoeic dermatitis of the scalp.

Neuthione *Senju, China.*
Glutathione (p. 1555·2).
Eye disorders.

Neutop *Elea, Arg.*
Topiramate (p. 550·3).
Epilepsy.

Neutoss *Belfar, Braz.*
⊗Salbutamol (p. 1220·2).

Neutracaine *Stedman, India.*
Famotidine (p. 1842·1); magaldrate (p. 1856·1).

Neutracid *Vivax, Venez.*
Famotidine (p. 1842·1).
Heartburn.

Neutracide *CPH, Port.†*
Calcium carbonate (p. 1824·3); glycocolic acid.
Gastric hyperacidity.

Neutracol *Beta, Arg.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

NeutraFluor *Colgate-Palmolive, Austral.*
Sodium fluoride (p. 2089·2).
Fluoride supplement; sensitive teeth.

Neutraflux *Stedman, India.*
Domperidone (p. 1838·1); esomeprazole magnesium (p. 1841·1).

NeutraGard Advanced *Pascal, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Neutrahep *Gland, India.*
Protamine sulfate (p. 1572·1).

Neutrahist *Cypress, USA.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms.

Neutrahist PDX *Cypress, USA.†*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; upper respiratory-tract symptoms.

NeutraLice *Key, Austral.*
Melaleuca oil (p. 2551·1); lavender oil (p. 2541·1).
Pediculosis.

NeutraLice Advance *Key, Austral.*
Benzyl alcohol (p. 1739·3).
Pediculosis.

Neutralite *Canadian Custom Packaging, Canad.*
Chlorobutanol (p. 1747·2); monobasic potassium phosphate (p. 1790·3); dibasic sodium phosphate (p. 1791·2).

Neutral-O *Skymax, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Neutram *East West, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Neutram-P *East West, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Neutran *Prodotti, Braz.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

NeutrapHor Skin Protectant *pH R&D, USA.*
Emollient.

Neutra-Phos-K *Alza, USA.*
Monobasic and dibasic potassium phosphates (p. 1790·3) (p. 1791·1).
Phosphorus supplement.

Neutrapime *Alpha Aromatic, India.*
Cefepime (p. 239·2).
Bacterial infections.

NeutraSal *Invado, USA.*
Calcium chloride (p. 1783·1); dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1); silicon dioxide (p. 2208·3); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1).
Saliva substitute.

Neutravera Glucose Calcium *Fresenius Medical, Fr.*
Sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); glucose (p. 2068·3) (p. 1778·2).
Peritoneal dialysis.

Neutrazid
Note: this name may be used for preparations of different composition.
Idaman, Singapore.
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium trisilicate (p. 1858·1).

OPC, Philipp.
Sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1); sodium hydrogen phosphate (p. 1791·1).
Gastric hyperacidity.

Neutrexin *Ipsen, Gr.; Schering-Plough, Thai.*
Trimetrexate glucuronate (p. 596·2).
Pneumocystis pneumonia.

Neutrobar *Darier, Mex.*
⊗Glycerol (p. 2517·2).
Skin disorders; soap substitute.

Neutrofer *Sigma, Braz.*
Ferrous glycinate (p. 2061·3).
Iron-deficiency anaemia; iron deficiency.

Neutrofer Fólico *Sigma, Braz.*
Ferrous glycinate (p. 2061·3); folic acid (p. 2063·1).
Anaemias.

Neutrofer Neonatal *Sigma, Braz.*
Ferrous glycine chelate (p. 2061·3).

Neutrofil *Varifarma, Arg.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Neutrogena *Johnson & Johnson, Arg.*
A range of skincare preparations.

Johnson & Johnson, Austral.
A range of skin cleansers and moisturisers.

Johnson & Johnson, Braz.
A range of soap substitutes, shampoos, and skin care preparations.

Johnson & Johnson, Chile.
A range of emollients.
Skin disorders.

Johnson & Johnson, NZ.
A range of skin cleansers and emollients.

Johnson & Johnson, Venez.
A range of skin cleansing and moisturising preparations.

Neutrogena Dermatologicals, USA.
Skin cleanser; emollient and moisturiser.

Neutrogena, Philipp.
A range of skin cleansing preparations.

Neutrogena, USA.
SPF 8: Octinoxate (p. 1715·1); meradimate (p. 1711·2); titanium dioxide (p. 1725·1).
Sunscreen.

Neutrogena, USA.
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); meradimate (p. 1711·2); titanium dioxide (p. 1725·1).
Sunscreen.

Neutrogena, USA.
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); meradimate (p. 1711·2); zinc oxide (p. 1729·1).
Sunscreen.

Neutrogena, USA.
SPF 25: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Neutrogena Acne Mask *Johnson & Johnson, Turk.*
Benzoyl peroxide (p. 1696·1).
Acne.

Neutrogena Acne Skin Cleanser *Johnson & Johnson, Austral.*
Triclosan (p. 1773·2).
Acne; oily skin.

Neutrogena Acne Wash *Johnson & Johnson, Canad.*
Salicylic acid (p. 1719·1).
Acne.

Neutrogena Antiacne *Johnson & Johnson, Braz.*
Salicylic acid (p. 1719·1).
Acne.

Neutrogena Antiseptic *Neutrogena, USA.*
Skin cleanser.

Neutrogena Anti-Wrinkle *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Neutrogena Barra *Johnson & Johnson, Chile.*
SPF 15: Octinoxate (p. 1715·1); ethylhexyl palmitate; oxybenzone (p. 1715·3).
Sunscreen; chapped lips.

Neutrogena Bloqueador Solar *Key, Chile.†*
SPF 30; SPF 45: Methoxycinnamic acid esters; benzimidazole; homosalate (p. 1705·1).
Sunscreen.

Neutrogena Bloqueador Solar Piel Sensible *Key, Chile.†*
SPF 30: Titanium dioxide (p. 1725·1).
Sunscreen.

Neutrogena Build a Tan *Johnson & Johnson, Chile.*
SPF 15: Dihydroxyacetone (p. 1700·1); octinoxate (p. 1715·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3).
Sunscreen; suntanning agent.

Johnson & Johnson, Chile.
Dihydroxyacetone (p. 1700·1).
Formerly known as Neutrogena Bronceador.
Suntanning agent.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neutrogena Chemical-Free *Neutrogena, USA.*
SPF 17: Titanium dioxide (p. 1725·1).
Sunscreen.

Neutrogena Clear Pore *Johnson & Johnson, Canad.†*
Salicylic acid (p. 1719·1).
Acne.

Neutrogena Colour Boosting Sunscreen *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Crema Humectante *Johnson & Johnson, Chile.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Formerly contained octinoxate and titanium dioxide.
Sunscreen.

Neutrogena Day Moisture *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Neutrogena Deep Clean Limpiador Facial *Johnson & Johnson, Chile.*
Salicylic acid (p. 1719·1).
Skin cleansing.

Neutrogena Drying *Neutrogena Dermatologicals, USA.*
Hamamelis (p. 2523·3).

Neutrogena Fairness UV Block *Neutrogena, Philipp.†*
SPF 30: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1).
Sunscreen.

Neutrogena Fresh Cooling Sunscreen *Johnson & Johnson, Canad.*
SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Gel Control Brillo *Key, Chile.†*
Salicylic acid (p. 1719·1).
Seborrhoea.

Neutrogena Glow *Neutrogena, USA.*
SPF 8: Octinoxate (p. 1715·1).
Sunscreen.

Neutrogena Healthy Defense *Johnson & Johnson, Canad.†; Johnson & Johnson, Chile.*
SPF 30: SPF 30: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.

Neutrogena Healthy Skin *Johnson & Johnson, Braz.; Johnson & Johnson, Canad.*
SPF 15: SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Johnson & Johnson, Chile.
Cream SPF 15: Octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Johnson & Johnson, Chile.
Lotion SPF 15: Glycolic acid (p. 1704·3); octinoxate (p. 1715·1).
Skin disorders; sunscreen.

Key, Chile.†
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); glycolic acid (p. 1704·3).
Skin pigmentation disorders; sunscreen.

Neutrogena Healthy Skin Anti-rugas com FPS 15 *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Neutrogena Healthy Skin Intensive *Johnson & Johnson, Chile.*
SPF 15: Oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

Neutrogena Illuminating *Johnson & Johnson, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2).
Sunscreen.

Neutrogena Intensified *Neutrogena, USA.*
SPF 15: Octinoxate (p. 1715·1); ensulizole (p. 1703·1); titanium dioxide (p. 1725·1).
Sunscreen.

Neutrogena Limpiadora *Key, Chile.†*
Glycolic acid (p. 1704·3); salicylic acid (p. 1719·1).
Skin cleansing.

Neutrogena Linea Acne *Key, Chile.†*
Salicylic acid (p. 1719·1).
Acne; seborrhoea.

Neutrogena Lip *Neutrogena, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Lip Moisturizer *Johnson & Johnson, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Locion Humectante *Key, Chile.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Men Sensitive Skin *Johnson & Johnson, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Moisture *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena, USA.
SPF 5: Octinoxate (p. 1715·1).
Sunscreen.

Neutrogena, USA.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena New Hands *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Norwegian Formula Dermatological Cream *Neutrogena, UK.*
⊗Glycerol (p. 2517·2).
Dry skin.

Neutrogena No-Stick *Neutrogena, USA.*
Octinoxate (p. 1715·1); homosalate (p. 1705·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Neutrogena OnSpot *Johnson & Johnson, Venez.*
Benzoyl peroxide (p. 1696·1).
Acne.

Neutrogena Pore Refining *Johnson & Johnson, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Neutrogena Sensitive Skin *Johnson & Johnson, Canad.†*
SPF 30: Titanium dioxide (p. 1725·1).
Sunscreen.

Neutrogena Shampoo Neutar *Key, Chile.†*
Coal tar (p. 1723·2).
Scalp disorders.

Neutrogena SPF 30 *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena SPF 30 Healthy Defense *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Neutrogena SPF 45 Healthy Defense *Johnson & Johnson, Canad.†*
SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Stick *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Neutrogena T-Gel *Johnson & Johnson, Venez.*
Coal tar (p. 1723·2).
Scalp disorders.

Neutrogena T/Gel *Johnson & Johnson, Austral.; Johnson & Johnson, Canad.†; Johnson & Johnson, Gr.; Johnson & Johnson, Irl.; Neutrogena, USA.*
Shampoo: Coal tar (p. 1723·2).
Scalp disorders; dandruff; seborrhoeic dermatitis.

Neutrogena T/Gel Acondicionador *Johnson & Johnson, Chile.*
Salicylic acid (p. 1719·1).
Formerly known as Neutrogena Acondicionador Neutar Gel.
Scalp disorders.

Neutrogena T/Gel Conditioner *Johnson & Johnson, Canad.†*
Salicylic acid (p. 1719·1).
Scalp disorders.

Neutrogena T/Gel Therapeutic *Johnson & Johnson, Canad.*
Shampoo: Coal tar (p. 1723·2).
Scalp disorders.

Neutrogena T-Sal
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Venez.
Salicylic acid (p. 1719·1).
Seborrhoeic dermatitis of the scalp.

Neutrogena T/Sal
Note: this name may be used for preparations of different composition.
Neutrogena Dermatologicals, USA.
Salicylic acid (p. 1719·1); coal tar (p. 1723·2).

Neutrogena T/Scalp *Neutrogena Dermatologicals, USA.*
⊗Hydrocortisone (p. 1640·1).
Pruritus of the scalp.

Neutrogena Ultra Sheer *Johnson & Johnson, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Johnson & Johnson, Venez.
SPF 30; SPF 45: Cinoxate (p. 1699·2); octisalate (p. 1715·2); oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

Neutrogena Ultra Sheer Dry-Touch Sunblock *Neutrogena, USA.*
SPF 70: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogena Ultra Sheer Sunscreen *Johnson & Johnson, Canad.*
SPF 30; SPF 45; SPF 60; SPF 70; SPF 85: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Neutrogin *Chugai, Jpn.*
Lenograstim (p. 1155·2).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Neutrolac *SIT, Ital.*
Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Neutromax *Sidus, Arg.; Pentafarma, Chile; Bio Sidus, Thai.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Neutromed *Wabosan, Austria.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; gastrointestinal erosions; acid aspiration; gastrointestinal haemorrhage; Zollinger-Ellison syndrome.

Neutron *Icarus, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Neutron-OD *Icarus, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Neutronorm *Ebewe, Austria.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; gastrointestinal erosions; gastrointestinal haemorrhage; Zollinger-Ellison syndrome.

Neutropain *HPP, Hong Kong.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders.

Neutrose S Pellegrino *Sanofi-Aventis, Ital.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); kaolin (p. 1850·1); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Neutrosec *Tablets, India.*
DL-Methionine (p. 1558·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Liver disorders.

Neutroses *Pharmacobel, Belg.; DB, Fr.; Uhlmann-Eyraud, Switz.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); kaolin (p. 1850·1); magnesium trisilicate (p. 1858·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; gastric hyperacidity; flatulence; meteorism.

Neutrosol *Behrens, Venez.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Neu-Up *Yakult, Jpn.*
Nartograstim (p. 1157·2).
Neutropenia.

Neuvert *East West, India.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Neuvesca *USV, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Neuviplex *Siam Bheasach, Thai.*
Vitamin B_1 (p. 2102·3); Vitamin B_2 (p. 2104·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neurological disorders; rheumatoid arthritis; beriberi; pernicious anaemia.

Neuvita *Irom, Jpn.*
Octotiamine (p. 2103·1).
Vitamin B_1 deficiency; vitamin B_1 supplement.

Neuvital *Bennet, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Neuvitan *Eczacibasi, Turk.*
Octotiamine (p. 2103·1); vitamin B_2 (p. 2104·3).
Vitamin B deficiency.

Neuxetin *Korea United, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Neuzym *Eisai, Hong Kong; Eisai, Jpn; Eisai, Malaysia; Eisai, Singapore.*
Muramidase hydrochloride (p. 2565·1).
Haemorrhage; respiratory-tract congestion and inflammation; sinusitis.

Nev *McNeil & Argus, India.*
Nevirapine (p. 1005·1).
HIV infection.

Neva *Novogen, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Nevacort *Finderm, Ital.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1).
Bacterial vaginal infections.

Nevakson *Nevzat, Turk.*
Ceftriaxone (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Neval *Hela, Swed.*
Valerian (p. 2640·2).
Anxiety; sleep disorders.

Nevanac *Alcon, Arg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Gr.; Alcon, India; Alcon, Irl.; Alcon, Israel; Alcon, Jpn; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA.*
Nepafenac (p. 101·1).
Pain and inflammation associated with cataract surgery.

Neva-OZ *Novogen, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Nevaton *Mediherb, Austral.*
St John's wort (p. 449·1); skullcap (p. 2617·1); damiana (p. 2491·3); schisandra (p. 2611·2).
Nervous disorders.

Nevdep *Constant, India.*
Citalopram (p. 411·1).
Depression; bipolar disorder; panic disorder.

Neve *Cadila, India.*
Nevirapine (p. 1005·1).
HIV infection.

Neverpentin *Daewoong, Thai.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Nevexitin *Hexal, Philipp.†; Salutas, Philipp.†*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Nevigarmon *Sanofi-Aventis, Rus.*
Nalidixic acid (p. 328·3).
Bacterial infections.

Nevigramon *Sanofi-Aventis, Hung.; Chinoin, Pol.†*
Nalidixic acid (p. 328·3).
Gram-negative bacterial infections.

Nevimune *Cipla, India; Cipla, Venez.*
Nevirapine (p. 1005·1).
HIV infection.

Nevipan *Ranbaxy, India; Ranbaxy, Malaysia.*
Nevirapine (p. 1005·1).
HIV infection.

Nevir *Emcure, India.*
Nevirapine (p. 1005·1).
HIV infection.

Neviral *Cristalia, Braz.*
Nevirapine (p. 1005·1).
HIV infection.

Neviran *SF, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Neviretro *Alkem, India.*
Nevirapine (p. 1005·1).
HIV infection.

Nevirz *Guardian, Indon.†*
Aciclovir (p. 964·1).
Herpes virus infections.

Nevis-P *Orion, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nevivir *Bliss, S.Afr.*
Nevirapine (p. 1005·1).

Nevofam *Nevzat, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nevol *Medley, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nevol-H *Medley, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nevotek *Biofarma, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Nevotens *Aramis, Hung.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nevox *Kalbe, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Nevparin *Nevzat, Turk.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Nevradin *Bernofarm, Indon.†*
Capsules: Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); adenosine monophosphate (p. 2430·2).
Neuritis; neuralgia; megaloblastic anaemia.
Bernofarm, Indon.†
Injection: Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; megaloblastic anaemia.

Nevradin E *Bernofarm, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Vitamin B and E deficiency.

Nevralgex *Cimed, Braz.*
Dipyrone (p. 53·3); orphenadrine citrate (p. 909·2); caffeine (p. 1203·3).
Pain; smooth muscle spasm.

Nevramin *Takeda, Hong Kong.*
Fursultiamine hydrochloride (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; musculoskeletal and joint pain; vitamin B1, B6 and B12 supplement; anaemia.
Takeda, Indon.; Takeda, Philipp.
Fursultiamine (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; vitamin B supplement; anaemias; neural disorders.
Takeda, Malaysia.
Tablets: Fursultiamine (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Anaemias; neuralgia; rheumatic disorders.
Takeda, Singapore; Takeda, Thai.
Fursultiamine (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2). Mepivacaine hydrochloride (p. 1992·2) is included in the intramuscular injection to alleviate the pain of injection.
Neuralgia; neuritis; paresis; diabetic neuropathy; polyneuritis; anaemias.

Nevril *Amnol, Ital.*
Cream: Hamamelis (p. 2523·3); devil's claw root (p. 42·3); chamomile (p. 2474·1); mallow (p. 2549·2); calendula (p. 2465·2); salix (p. 129·2); copper (p. 2057·1); zinc (p. 2126·1); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Nevril Crono *Amnol, Ital.*
Vitamins; minerals; plant extracts.
Nutritional supplement; musculoskeletal and joint disorders.

Nevrine Codeine *Pharmacobel, Belg.*
Paracetamol (p. 115·1); caffeine hydrate (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Nevrix *Arese, Braz.; Ativus, Braz.*
Cyanocobalamin (p. 2107·2); pyridoxine (p. 2105·3); thiamine (p. 2102·3).

Nevrogamma *Medichrom, Gr.*
Lorazepam (p. 1080·3).

Nevrol *Prodotti, Braz.†*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); lavender oil (p. 2541·1); rosemary oil (p. 2607·3); mustard oil (p. 2646·1).
Musculoskeletal and joint disorders.

Nevrol Cemal *Vita Kimya, Turk.*
Orange peel (p. 2575·3); lemon oil (p. 2543·1); orange oil (p. 2576·2); neroli oil (p. 2568·3); menthol (p. 2553·2); valerian (p. 2640·2); melissa (p. 2552·3).
Agitation.

Nevromine *Franco-Indian, India.*
Piper longum; rauwolfia serpentina (p. 1485·1); withania somnifera (p. 2450·2).

Nevrorestol *Bros, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Nevrovit *Menarini, Gr.*
Vitamin B substances (p. 2102·3).

New Allerin *United American, Singapore.*
Guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; allergic rhinitis; sinusitis.

New Artifen Plus *Aglowmed, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

New BCool *Julphar, UAE.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

New Coldin *Medikon, Indon.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

New Dettol *Reckitt Benckiser, Hong Kong.†*
Chloroxylenol (p. 1748·2).
Skin disinfection.

New Diatabs *Medifarma, Indon.*
Activated attapulgite (p. 1820·1).
Diarrhoea.

New Era Biochemic Tissue Salts *Seven Seas, UK.*
Minerals.
Homoeopathic preparation.

New Era Combination Remedy *Seven Seas, UK.*
A range of multimineral preparations.
Homoeopathic preparation.

New Era Elasto *Seven Seas, UK.*
Calcium fluoride (p. 2053·1); calcium phosphate (p. 1784·2); iron phosphate (p. 2077·1); magnesium phosphate (p. 1787·3).
Homoeopathic preparation.

New Era Nervone *Seven Seas, UK.*
Calcium phosphate (p. 1784·2); magnesium phosphate (p. 1787·3); potassium chloride (p. 1793·2); sodium phosphate (p. 1791·2); potassium phosphate (p. 1791·1).
Homoeopathic preparation.

New Eye Lotion *Optrex, India.†*
Boric acid (p. 2459·3); borax (p. 2459·2); allantoin (p. 1693·1); salicylic acid (p. 1719·1); zinc sulfate (p. 2126·2).
Eye irritation; tired eyes.

New Gel *New York Chemical, Thai.*
Oral suspension: Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity.
New York Chemical, Thai.
Tablets: Aluminium glycinate (p. 1817·2); belladonna (p. 2453·3).
Gastric hyperacidity.

New Gel-D *New York Chemical, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

New Iteol-3 *AstraZeneca, India.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

New Kenacomb *BMS, Indon.†*
⊗Nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Skin disorders with fungal infection.

New Mezonac *Aglowmed, India.*
Chlorzoxazone (p. 2022·2); diclofenac (p. 48·3); paracetamol (p. 115·1).

New Mixavit *Julphar, UAE.*
Vitamins.

New Nicip *Cipla, India.*
Nimesulide (p. 101·3).
Pain.

New O Tone *New York Chemical, Thai.*
Vitamin B substances (p. 2102·3); minerals.
Dietary supplement.

New Panazox *Cadila, India.*
Chlorzoxazone (p. 2022·2).
Formerly contained diclofenac potassium, paracetamol, and chlorzoxazone.
Painful skeletal muscle spasm.

New Patecs A *Daiichi, Hong Kong.†*
Arnica (p. 2447·2); glycol salicylate (p. 66·2).
Musculoskeletal and joint disorders.

New Premisol *Molekule, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

New Probiza *Swiss Biotech, India.*
Bifodobacterium bifidum (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

New Skelan *Medifarma, Indon.; UAP, Indon.*
Phenylbutazone calcium (p. 125·1); carisoprodol (p. 2021·3).
Musculoskeletal and joint pain and spasm.

New Skin *Beiersdorf, Chile.†*
Barrier preparation.

New Terocin *Alexso, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); lidocaine (p. 1988·1).

New Tonin Troche *Sato, Singapore.*
Apricot kernel extract (p. 2445·3); liquorice (p. 1853·2); noscapine (p. 1670·3).

New Una Cool *Kowa, Jpn.*
Diphenhydramine hydrochloride (p. 626·2); lidocaine (p. 1988·1); levomenthol (p. 2553·2); camphor (p. 2466·2).
Pruritus.

New Viminta *Molekule, India.*
Vitamins; minerals; trace elements; lysine hydrochloride (p. 2079·3).

New Zephrol *Elder, India.*
⊗Ammonium chloride (p. 1656·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

NewAce
Note: this name may be used for preparations of different composition.
BMS, Neth.†
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Newace
Note: this name may be used for preparations of different composition.
Max, India.
Enalapril (p. 1371·1).
Hypertension; heart failure.

Newanti *Simcere, China.*
Biapenem (p. 231·1).
Bacterial infections.

Newart *Ufsa, Turk.*
Frovatriptan succinate (p. 676·2).

Newbolin *Zenon, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Newcain *Intra-Labs, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Newcid *BMW, India.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).

Newclar *Raymos, Arg.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Conjunctivitis.

Newdizime *Daewoong, China.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Newfactan *Yuhan, Philipp.*
Bovine lung surfactant (p. 2599·2).
Neonatal respiratory distress syndrome.

New-Feripro *Cachet, India.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

New-Fill *Sanofi-Aventis, Fr.*
Poly L-lactic acid.
Lipoatrophy in HIV infection.

Newflox *Raymos, Arg.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Newilrene *New York Chemical, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cough; cold symptoms.

New-Livfit *Dabur, India.*
Punarnava (p. 2601·1); terminalia chebula (p. 2474·3).

New-Nok *Meditrend, Israel.*
Permethrin (p. 2159·3).
Pediculosis.

Newpan *Ferring, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Newpharvit *Newcharoen, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Newrelax *Potter's, UK.*
Lupulus (p. 2546·1); skullcap (p. 2617·1); valerian (p. 2640·2); vervain (p. 2645·1).
Tension.

Newsicam *Shin Poong, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

New-Skin *Medtech, USA.*
Topical barrier preparation.

Newspar *Interbat, Indon.*
Sparfloxacin (p. 357·3).
Bacterial infections of the respiratory tract.

Newtain *Chandra Bhagat, India.*
Protamine sulfate (p. 1572·1).
Heparin overdose.

Newtel *Systopic, India.*
Telmisartan (p. 1509·3).
Hypertension.

Newtel-H *Systopic, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan (p. 1509·3).
Hypertension.

Newtol *New York Chemical, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Newtrolax *Newtramax, India.*
Vitamins; minerals; protein hydrolysate (p. 2086·2).

Newtromin-Z *Newtramax, India.*
Ascorbic acid (p. 2110·3); glucose (p. 2068·3); zinc sulfate (p. 2126·2).

New-um *New York Chemical, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Newvit-S *Newtramax, India.*
Vitamins; minerals; spirulina (p. 2622·1).

Nex *Neon, India.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression.

Nexa *Hexpharm, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemorrhage.

Nexa Plus *Upsher-Smith, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1). Docusate calcium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Nexa Select *Upsher-Smith, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Nexadron *Klonal, Arg.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Nexadron Compuesto *Klonal, Arg.*
Eye drops: ⊗Dexamethasone (p. 1630·3); naphazoline (p. 1669·3); neomycin (p. 329·3).
Eye disorders.

Nexadron Plus *Klonal, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1).
Nasal disorders.

Nexavar *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer Schering, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.; Bayer Schering, Port.; Bayer, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, USA.*
Sorafenib tosilate (p. 857·3).
Renal cell carcinoma; hepatocellular carcinoma; thyroid cancer.

Nexcip *Invision, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Nexcip-TZ *Invision, India.*
Ciprofloxacin hydrochloride (p. 261·2); tinidazole (p. 949·2).

Nexcob Plus *Nitro Cadineur, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); thiamine (p. 2102·3).

Nexcob-G *Nitro Cadineur, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nexef-O *Invision, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Nexef-SB *Invision, India.*
Ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Nexef-TBZ *Invision, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Nexen *Therabel, Fr.*
Nimesulide (p. 101·3).
Musculoskeletal and joint disorders; pain.

Nexiam *AstraZeneca, Belg.; AstraZeneca, S.Afr.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nexiclon *NextWave, USA.†*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Nexilav *Cosar, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Nexim *H & Care, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Nexipram *Maver, Chile.*
Escitalopram oxalate (p. 416·2).

Nexipride *Sun, India.*
Levosulpiride (p. 1108·1).
Gastro-oesophageal reflux; irritable bowel syndrome; dyspepsia.

Nexito *Sun, India.*
Escitalopram oxalate (p. 416·2).
Depression; obsessive-compulsive disorder; anxiety; panic disorder.

Nexito Forte *Sun, India.*
Clonazepam (p. 519·1); escitalopram oxalate (p. 416·2).

Nexito-Plus *Sun, India.*
Clonazepam (p. 519·1); escitalopram oxalate (p. 416·2).

Nexitra *Ifars, Indon.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema; menorrhagia.

Nexium *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; AstraZeneca, USA.*
Esomeprazole magnesium (p. 1841·1) or esomeprazole sodium (p. 1841·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; prevention of rebleeding in peptic ulcer; dyspepsia.

AstraZeneca, Philipp.; AstraZeneca, Singapore; AstraZeneca, Venez.
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nexium 1-2-3 A *AstraZeneca, Canad.*
Esomeprazole magnesium (p. 1841·1); amoxicillin (p. 216·2); clarithromycin (p. 266·2).
Eradication of Helicobacter pylori.

Nexium Hp *AstraZeneca, Austral.; AstraZeneca, Swed.*
Tablets, esomeprazole magnesium (Nexium) (p. 1841·1); capsules, amoxicillin trihydrate (Amoxil) (p. 216·2); tablets, clarithromycin (Klacid) (p. 266·2).
Peptic ulcer; eradication of Helicobacter pylori.

Nexivol *Abdi, Turk.*
⊗Nebivolol hydrochloride (p. 1444·2).

Nex-M *D R Johns, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).

NexoBrid *Teva, Neth.*
⊗Bromelains (p. 2460·3).
Burns.

Nexocardil *Nexo, Arg.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; hypertension.

Nexodal *Orpha-Devel, Cz.; Orpha-Devel, Denm.; Orpha-Devel, Fin.; Orpha-Devel, Irl.†; Orpha-Devel, Neth.†; Orpha-Devel, Norw.; Orpha-Devel, Port.; Vitaflo, Swed.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced respiratory depression; diagnosis of opioid overdosage.

Nexofil *Nexo, Arg.†*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Nexofloxacin *Nexo, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Nexogrip *Nexo, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); bromhexine (p. 1656·3).
Influenza symptoms.

Nexomist *Cipla-Medpro, S.Afr.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis.

Nexoprazol *Nexo, Arg.*
Omeprazole (p. 1867·2).

Nexotensil *Nexo, Arg.*
Amlodipine (p. 1304·1).
Hypertension.

Nexovital Folico *Andromaco, Arg.*
Folic acid (p. 2063·1).
Anaemias; folic acid supplement.

Nexpan *Zuventus, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Nexplanon *Europharma, Denm.; Paranova, Denm.; Organon, Fin.; MSD-Chibret, Fr.; Organon, Norw.; MSD, Swed.; Organon, UK; Organon, USA.*
Etonogestrel (p. 2277·2).
Progestogen-releasing implantable contraceptive.

Nexpro *Torrent, India.*
Esomeprazole (p. 1841·1) or esomeprazole magnesium (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Nexpro-RD *Torrent, India.*
Domperidone (p. 1838·1) or domperidone maleate (p. 1838·1); esomeprazole (p. 1841·1) or esomeprazole magnesium (p. 1841·1).

Nexproxyn *Medopharm, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Next Choice *Watson, USA.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Next Step *Francelab, Arg.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Nextcam *Armour, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Nextcam-P *Armour, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Nexterone *Prism, USA.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Nextin *Biochemix, India.*
Isotretinoin (p. 1706·2).
Acne.

Nextop *Torrent, India.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Nextrim Aktiv *Polpharma, Rus.*
Aspirin (p. 22·2); ethenzamide (p. 56·2); caffeine (p. 1203·3).
Fever; pain.

Nextrim Fast *Polpharma, Rus.*
Aspirin (p. 22·2).
Fever; pain; thromboembolism prophylaxis.

Nextrim Plus *Polpharma, Rus.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Nexus *Senosiain, Mex.*
Amlodipine (p. 1304·1).
Hypertension.

Nexvep *BMS, Braz.*
Etoposide phosphate (p. 790·3).
Malignant neoplasms.

Nexx *Anthiea, India.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Ney Opin Nr 58 *Vitorgan, Ger.*
Bulb oculi lysat bovis fetal (p. 2444·1).
Homoeopathic preparation.

NeyArthros Nr 43-Sol *Vitorgan, Ger.†*
Articuli fet; cartilago (p. 2471·3); synovia (p. 2444·1).
Homoeopathic preparation.

NeyArthros-Liposome (Revitorgan Lp Nr 83) *Vitorgan, Ger.†*
⊗Cartilago articuli (p. 2471·3); synovia; articuli fet.; thymus fet. (p. 2631·1); funicul. umbilical. (p. 2444·1); metenolonum aceticum (p. 2291·2); prednisolonum aceticum (p. 1645·2); zincum sulfuricum (p. 2126·2); manganum sulfuricum (p. 2081·2); magnesium chloratum (p. 1787·1); kalium chloratum (p. 1793·2); calcium chloratum (p. 1783·1); columna vertebralis fet.; musculi fet.; gland. suprarenal.
Homoeopathic preparation.

NeyArthrosome (Revitorgan-Dilution) *Vitorgan, Ger.†*
⊗Cartilago articuli (p. 2471·3); synovia; articuli fet.; thymus fet. (p. 2631·1); funicul. umbilical. (p. 2444·1); columna vertebralis fet.; capsul articuli fet; musculi fet.; gland. suprarenal (p. 2444·1); metenolonum aceticum (p. 2291·2); prednisolonum aceticum (p. 1645·2); glucosum monohydricum (p. 2069·1); zincum sulfuricum (p. 2126·2); manganum sulfuricum (p. 2081·2); magnesium chloratum (p. 1787·1); kalium chloratum (p. 1793·2); calcium chloratum (p. 1783·1); lecithinum (p. 2542·2); cholesterolum (p. 2179·1).
Homoeopathic preparation.

NeyAthos Nr 43 *Vitorgan, Ger.*
Articuli fetal; cartilago fetal (p. 2471·3); synovia fetal (p. 2444·1).
Homoeopathic preparation.

NeyChon Nr 68 *Vitorgan, Ger.*
⊗Thymus (p. 2631·1); hypophysis (p. 2444·1); diencephal. (p. 2444·1); medull. spinal.; gland. suprarenal. (p. 2444·1); testes (p. 2304·3); hepar (p. 2444·1); pancreas (p. 2444·1); muscul.; columna vertebral.; articul.; ren (p. 2444·1); placenta (p. 2444·1); nucleus pulp. (p. 2444·1); with or without tocopherolum aceticum (p. 2119·2); procainum hydrochloridum (p. 1994·3).
Homoeopathic preparation.

NeyChondrin Nr 68-Sol *Vitorgan, Ger.†*
⊗Thymus fet. (p. 2631·1); hypophysis (p. 2444·1); diencephalon (p. 2444·1); medulla spinal.; gland. suprarenal. (p. 2444·1); testes juv. (p. 2304·3); hepar (p. 2444·1); pancreas (p. 2444·1); musculi; columna vertebral. fet.; articuli fet.; ren (p. 2444·1); placenta (p. 2444·1); nucleus pulp. (p. 2444·1).
Homoeopathic preparation.

NeyDesib Nr 78 *Vitorgan, Ger.*
Thymus fet. (p. 2631·1); lien fet. (p. 2444·1); lymphonodi; gland. suprarenal. (p. 2444·1).
Allergies; auto-immune disorders.

NeyDil Nr 66 *Vitorgan, Ger.†*
⊗Diencephal. (p. 2444·1); placenta mat. (p. 2444·1); funicul. umbilical. (p. 2444·1); thymus juv. (p. 2631·1); epiphys.; testes juv. (p. 2304·3); gland. suprarenal. (p. 2444·1); gland. thyreoid. (p. 2345·3); medull. oss.; pulmo; hepar (p. 2444·1); pancreas (p. 2444·1); ren (p. 2444·1); lien (p. 2444·1); mucosa intestinal. (p. 2444·1); with or without tocopherolum aceticum (p. 2119·2); cyanocobalaminum (p. 2107·2).
Homoeopathic preparation.

NeyDIL Nr 70 *Vitorgan, Ger.*
Placenta lysat bovis mat (p. 2444·1).
Homoeopathic preparation.

Neydin-F *Vitorgan, Ger.†*
Placenta fet. (p. 2444·1); ovar (p. 2298·2); cutis fet.; amnion (p. 2442·1); hepar (p. 2444·1); gland. suprarenal. (p. 2444·1); liquor amnii; faecis (p. 2444·1).
Homoeopathic preparation.

Neydin-M *Vitorgan, Ger.†*
⊗Placenta mat. (p. 2444·1); testes (p. 2304·3); cutis fet.; hepar (p. 2444·1); gland. suprarenal. (p. 2444·1); liquor amnii; faecis (p. 2444·1); amnion (p. 2442·1).
Homoeopathic preparation.

NeyDop Nr 97 *Vitorgan, Ger.*
Cortex cerebri; diencephalon (p. 2444·1); cerebellum (p. 2444·1); placenat fet. (p. 2444·1).
Homoeopathic preparation.

NeyFaexan Nr 55 *Vitorgan, Ger.*
Mucosa intestinal. (p. 2444·1); muc. vesicae urinar.; mucosa vesicae felleae; muc. nasopharyngea (p. 2444·1).
Homoeopathic preparation.

NeyFegan Nr 26 *Vitorgan, Ger.*
Liver extract (p. 2444·1).
Homoeopathic preparation.

NeyFoc Nr 69 *Vitorgan, Ger.*
Dienceph. (p. 2444·1); cerebellum (p. 2444·1); cort. cerebri; cerebrum; medull. spinal; hepar (p. 2444·1); pancreas (p. 2444·1); lien (p. 2444·1); gland. thyreoid. (p. 2345·3); thym. (p. 2631·1); placenta (p. 2444·1); mucos. misc. (p. 2444·1); with or without pyridoxinum hydrochloricum (p. 2105·3); cyanocobalaminum (p. 2107·2).
Homoeopathic preparation.

NeyGero Nr 64 *Vitorgan, Ger.*
⊗Embryo tot. (p. 2444·1); placenta (p. 2444·1); funicul. umbilical. (p. 2444·1); cor; ren (p. 2444·1); pancreas (p. 2444·1); mucos. intestinal.; lien (p. 2444·1); thym. (p. 2631·1); gland. suprarenal. (p. 2444·1); gland. parathyreoid. (p. 2444·1); testes (p. 2304·3); hypophys. (p. 2444·1); diencephalon (p. 2444·1); cort. cerebri (p. 2444·1); amnion (p. 2442·1); with or without tocopherolum aceticum (p. 2119·2); cyanocobalaminum (p. 2107·2); pyridoxinum hydrochloricum (p. 2105·3); procainum hydrochloricum (p. 1994·3).
Homoeopathic preparation.

NeyGeront Nr 64-Sol L *Vitorgan, Ger.†*
⊗Embryo tot. (p. 2444·1); placenta (p. 2444·1); funicul. umbilical. (p. 2444·1); cor; ren (p. 2444·1); pancreas (p. 2444·1); mucos. intestinal.; lien (p. 2444·1); thym. (p. 2631·1); gland. suprarenal. (p. 2444·1); gland. parathyreoid. (p. 2444·1); testes (p. 2304·3); hypophys. (p. 2444·1); diencephalon (p. 2444·1); cort. cerebri (p. 2444·1); amnion (p. 2442·1).
Homoeopathic preparation.

NeyGeront Vitalkapsein A *Vitorgan, Ger.*
⊗Embryo tot. (p. 2444·1); placenta (p. 2444·1); funicul. umbilical. (p. 2444·1); cor; pancreas (p. 2444·1); mucos. intestinal.; lien (p. 2444·1); thym. (p. 2631·1); gland. suprarenal. (p. 2444·1); gland. parathyreoid. (p. 2444·1); testes (p. 2304·3); ovar (p. 2298·2); hypophys. (p. 2444·1); diencephalon (p. 2444·1); cort. cerebri; hepar (p. 2444·1); amnion (p. 2442·1); heparinum (p. 1396·3); procaini hydrochloridum (p. 1994·3); lecithinum (p. 2542·2); liothyroninum hydrochloridum (p. 2342·3); tocopherolum aceticum (p. 2119·2); cyanocobalaminum (p. 2107·2); pyridoxinum hydrochloricum (p. 2105·3); triglycerida mediocatenalia; acidum glutamicum (p. 2070·2).
Homoeopathic preparation.

NeyIm Nr 73 pro injectione *Vitorgan, Ger.*
Placenta mat. (p. 2444·1); funiculus umbilical. (p. 2444·1); thymus juv. (p. 2631·1).
Homoeopathic preparation.

NeyImmun Nr 73-Sol *Vitorgan, Ger.†*
Placenta mat. (p. 2444·1); funiculus umbilical. (p. 2444·1); thymus juv. (p. 2631·1).
Homoeopathic preparation.

NeyLing Nr 66 *Vitorgan, Ger.*
⊗Diencephal. (p. 2444·1); placenta mat. (p. 2444·1); funicul. umbilical. (p. 2444·1); thym. (p. 2631·1); epiphys.; testes (p. 2304·3); gland. suprarenal. (p. 2444·1); gland; thyreoid. (p. 2345·3); medull. oss.; pulmo; hepar (p. 2444·1); pancreas (p. 2444·1); ren (p. 2444·1); lien (p. 2444·1); mucos. intestinal. (p. 2444·1); tocopherolum aceticum (p. 2119·2); cyanocobalaminum (p. 2107·2).
Homoeopathic preparation.

NeyNormin Nr 65 *Vitorgan, Ger.*
Thymus fet. (p. 2631·1); gland. suprarenal. (p. 2444·1); lymphonodi; gland. parathyreoidea; hepar (p. 2444·1); ren (p. 2444·1); pancreas (p. 2444·1); lien (p. 2444·1); vasa fet.; funiculus umbilical. (p. 2444·1); hypophysis (p. 2444·1); diencephalon (p. 2444·1); mucosae miscae; cutis; medulla ossium (p. 2444·1).
Homoeopathic preparation.

NeyPson Nr 5 *Vitorgan, Ger.*
Cut lysat bovis fetal (p. 2444·1).
Homoeopathic preparation.

NeySol L 66 *Vitorgan, Ger.†*
⊗Diencephalon (p. 2444·1); placenta mat. (p. 2444·1); funiculus umbilical. (p. 2444·1); thymus juv. (p. 2631·1); epiphysis; testes juv. (p. 2304·3); gland. suprarenal. (p. 2444·1); gland. thyreoidea (p. 2345·3); medulla ossium; pulmo; hepar (p. 2444·1); pancreas (p. 2444·1); ren (p. 2444·1); lien (p. 2444·1); mucosa intestinal. (p. 2444·1).
Homoeopathic preparation.

Neythymun *Vitorgan, Ger.†*
Extractum thymus (p. 2631·1).
Homoeopathic preparation.

NeyTroph Nr 96 oral *Vitorgan, Ger.†*
Musculi juv.; musculi fet.; cor fet.; thymus (p. 2631·1); medulla spinal.; cort. cerebri; epiphysis; diencephalon (p. 2444·1).
Homoeopathic preparation.

NeyTroph Nr 96 pro injectione *Vitorgan, Ger.*
Musculi juv.; musculi fet.; cor fet.; thymus (p. 2631·1); medulla spinal.; cort. cerebri; epiphysis; diencephalon (p. 2444·1).
Homoeopathic preparation.

NeyTroph Nr96-Sol *Vitorgan, Ger.†*
Musculi juv.; musculi fet.; cor fet.; thymus (p. 2631·1); medulla spinal.; cort. cerebri; epiphysis; diencephalon (p. 2444·1).
Homoeopathic preparation.

Nezaflo *Sun, India.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Nezalast *Sun, India.*
⊗Azelastine hydrochloride (p. 617·1); fluticasone propionate (p. 1638·1).

Nezatin *Heremco, Gr.*
Simvastatin (p. 1489·2).

Nezefib *Rafarm, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Bacterial eye infections with inflammation.

Nezeril *GSK Consumer, Swed.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; nasal congestion.

NF *Sunij, India.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

NF Formulas Childrens *Integrative, USA.*
Vitamins; minerals.
Dietary supplement.

N-Fess *Frik, Turk.*
Montelukast sodium (p. 1214·3).

NFil *Miracalus, India.*
Filgrastim (p. 1151·3).
Mobilisation of peripheral blood progenitor cells; neutropenia.

N-Flox *Laborate, India.*
Norfloxacin (p. 333·3).
Bacterial ear or eye infections.

N-Flox D *Laborate, India.*
⊗Dexamethasone (p. 1630·3); norfloxacin (p. 333·3).

N-Flox TZ *Laborate, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

NG-Care *Systocare, India.*
Glyceryl trinitrate (p. 1391·2).

NGLong *Novartis, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

N-Gra *Willow, India.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

NGT *Geneva, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Skin disorders.

NGTel *Intel, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

NH4 Silhouette *ISA, Arg.*
Chromium (p. 2055·3).
Dietary supplement.

Nherea *Zwitter, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Ni Chang *Hua Yuan Zhong Sheng, China.*
⊗Bumetanide (p. 1329·1).
Oedema; hypertension.

Ni Da Er *Central, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Ni Di Duo *Ao Dong, China.*
Levocarnitine (p. 2053·2).

Ni Er *Song He, China.*
Levocarnitine (p. 2053·2).

Ni Er Ping *Lunan, China.*
Pemirolast potassium (p. 1218·2).
Allergic conjunctivitis.

Ni Er Xin *Xincat, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Ni Fen Sa *Jiangxi, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Ni Fu Ping *Mei Luo, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Ni Ji *Kang Ji Er, China.*
Etamsylate (p. 1145·2).

Ni Ke *Shouhe Jinhai, China.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; pseudoephedrine hydrochloride; diphenhydramine (p. 626·1).
Cold and influenza symptoms.

Ni Li An *Huanghai, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Ni Mei Xin *Qing Hua Zi Guang, China.*
Metronidazole (p. 936·1).

Ni Meng Shu *TianJing, China.*
Pipotiazine palmitate (p. 1098·1).
Schizophrenia.

Ni Mu Ke Si *Aoyipollen, China.*
⊗Methazolamide (p. 2009·1).
Glaucoma.

Ni Sai Xin *Sanhome, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Ni Song *XinShiDai, China.*
Ketorolac trometamol (p. 80·2).
Pain.

Ni Ting *Nhwa, China.*
Nizatidine (p. 1866·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Ni Wei Fu *Ang Li Kang, China.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; gastritis.

Niacef
Note: this name may be used for preparations of different composition.
Surya Dermato, Indon.
Nicotinamide (p. 2083·1).
Acne.

Niacex *Isdin, Chile.†*
Nicotinamide (p. 2083·1).
Acne.

Niacifort-6 *Ikapharmindo, Indon.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Niaclop *Neiadas (Νειαδας), Gr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Niagra *Pure Health, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Nialbumin *Remek, Gr.*
⊗Albumin (p. 1130·2).

Nialip *Reddy, India.*
Nicotinic acid (p. 2083·1).
Hyperlipidaemias.

Niamycetine *Neiadas (Νειαδας), Gr.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Nianate *Kripps, Canad.*
Inositol nicotinate (p. 1410·3).

Niap *Reddy, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nia-Plex *Future, Canad.*
Inositol (p. 2533·2); nicotinamide (p. 2083·1); nicotinic acid (p. 2083·1).

Niar *Abbott, Braz.; Knoll, Braz.; Abbott, Cz.†; Abbott, Mex.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism; psychiatric disorders.

Niascor *Kocak, Turk.*
Nicotinic acid (p. 2083·1).

Niaspan *Abbott, Arg.; Abbott, Austria; Sunovion, Canad.; Abbott, Chile; Merck Serono, China; Abbott, Fin.†; Abbott, Fr.†; Abbott, Ger.†; Abbott, Hong Kong; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Mex.; Abbott, Neth.†; Abbott, Norw.†; Abbott, Philipp.; Abbott, Port.; Abbott, Singapore; Abbott, Swed.†; Abbott, Switz.†; Abbott, Thai.; Abbott, Turk.; Abbott, UK†; Abbott, USA; Merck, Venez.*
Nicotinic acid (p. 2083·1).
Hyperlipidaemias; hypercholesterolaemia; cardiovascular risk reduction.

Niaspanor *Abbott, Ital.*
Nicotinic acid (p. 2083·1).

NiaStase *Novo Nordisk, Canad.*
Eptacog alfa (activated) (p. 1147·2).
Haemophilia.

Niavas *Ranbaxy, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Niavas-D *Ranbaxy, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Niazitol *GMP, Indon.*
Ethambutol (p. 296·1); isoniazid (p. 311·2). Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Niazol *Arex, Venez.*
⊗Naphazoline nitrate (p. 1669·3).
Rhinitis; sinusitis; sore throat.

Nibentan *Lens, Rus.*
(RS)-4-Nitro-N-{1-phenyl-5-(diethylamino) pentyl}benzamide hydrochloride.
Arrhythmias.

Niberan *Balu, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Niblet *Fecofar, Arg.*
⊗Salbutamol (p. 1220·2).

Nibocin *Biospray, Gr.; Zekides, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Nibren *Coup, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Nibrevin *Ingers, Cz.†*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Nibulen *Aventis, Turk.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections; vaginal candidiasis.

Nica *Yung Shin, Philipp.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Nicabate *GSK Consumer, Austral.; GSK, NZ.†*
Nicotine (p. 2569·3) or nicotine polacrilex (p. 2569·3).
Aid to smoking withdrawal.

Nicam *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Nicotinamide (p. 2083·1).
Acne.

Nican
Note: this name may be used for preparations of different composition.
Raptakos, India.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Uhlmann-Eyraud, Switz.†
Codeine (p. 40·2); belladonna (p. 2453·3); drosera (p. 2497·2); grindelia (p. 2522·3); ribwort plantain (p. 2604·2); thyme (p. 2630·2); sodium benzoate (p. 1738·2).
Cough.

Nicapress *Pliva, Ital.†*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

Nicardal *Italfarmaco, Ital.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

Nicardia *JB Chemicals, India; Unique, Rus.; JB Chemicals, Thai.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; heart failure; Raynaud's syndrome.

Nicaro *Nicholas, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin deficiency.

Nicarpin *SF, Ital.†*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension.

Nicaven *Farma 1, Ital.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

NicAzel Forte *Elorac, USA.*
Vitamin B_6 (p. 2105·3); folic acid (p. 2063·1); copper (p. 2057·1); zinc (p. 2126·1); Azerizin (nicotinamide (p. 2083·1); azelaic acid (p. 1695·1); quercetin (p. 2505·3); curcumin (p. 2180·1)).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

N'ice *SmithKline Beecham Consumer, USA.*
Lozenges: Menthol (p. 2553·2).
Sore throat.

SmithKline Beecham Consumer, USA.
Throat spray: ⊗Menthol (p. 2553·2); glycerol (p. 2517·2).
Sore throat.

Nice 'n Clear
Note: this name may be used for preparations of different composition.
Nelson, UK.
Azadirachta oil (p. 2451·2).
Pediculosis.

N'ice 'n Clear
Note: this name may be used for preparations of different composition.
SmithKline Beecham Consumer, USA.
Menthol (p. 2553·2).

N'ice Vitamin C *Insight, USA.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; scurvy.

Nicef *Galen, UK.*
Cefradine (p. 249·1).
Bacterial infections.

Nicene N
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.†
Nitroxoline (p. 333·2).
Urinary-tract infections.

Nicerbium *Micro, India; Brown & Burk, Philipp.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Nicergin *Rosch & Handel, Austria.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Nicergobeta *Betapharm, Ger.†*
Nicergoline (p. 2569·1).
Mental function disorders.

Nicerin *Glenmark, Pol.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Nicerium *Hexal, Ger.†; Sandoz, Ukr.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders; hypertension; mental function impairment.

Nicet *Bennet, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nicetal *Sandoz, Philipp.†*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Nicetam *Reliance, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Nicetile *Sigma-Tau, Ital.*
Acetylcarnitine hydrochloride (p. 2053·2).
Cerebrovascular disorders; nerve disorders.

Nichinto *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; citrus unshiu peel; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Nichlorgin *GPP, Rus.*
Chloronitrophenol.
Fungal skin infections.

Nichobion *Nicholas, Indon.*
Ferrous fumarate (p. 2060·3); magnesium sulfate (p. 1787·3); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); intrinsic factor (p. 2534·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Nichodryl *Nicholas, Indon.*
⊗Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2); alcohol (p. 1733·1).
Cough due to allergy.

Nichofed *Nicholas, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine (p. 1676·1).
Cold symptoms; sinusitis; allergic rhinitis.

Nichoflam *Nicholas, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Nichogencin *Nicholas, Indon.*
Gentamicin sulfate (p. 304·2).
Skin infections.

Nicholin *Takeda, China; Takeda, Indon.; Wyeth Lederle, Ital.†; Takeda, Jpn; Takeda, Philipp.*
Citicoline (p. 2480·1).
Pancreatitis; head injury; cerebrovascular disorders; neurological disorders; parkinsonism.

Nichomedson *Nicholas, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Nichomycin *Nicholas, Indon.*
Lincomycin (p. 317·1).
Bacterial infections.

Nichorizin *Nicholas, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Nichospor *Nicholas, Indon.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Nichostan *Nicholas, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain; menorrhagia.

Nichoviton *Nicholas, Indon.*
Adenosine triphosphate (p. 2430·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Asthenia; fatigue.

Nicid *Dr Alson, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Niciflex-T *Cipla, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1); tizanidine hydrochloride (p. 2026·2).

Nicin *Nitin, India.*
Amikacin (p. 214·1).
Bacterial infections.

Nicinal *Cipla, India.*
Nicotinic acid (p. 2083·1); vitamin B_6 (p. 2105·3).

Nicip *Cipla, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain; sprains; tendinitis.

Nicip Cold *Cipla, India.*
Nimesulide (p. 101·3); phenylpropanolamine (p. 1674·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms.

Nicip D *Cipla, India.*
Nimesulide (p. 101·3); diclofenac sodium (p. 48·3).
Pain; inflammation.

Nicip MR *Cipla, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).

Nicip Plus *Cipla, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Inflammation; pain.

Nicip Supergel *Cipla, India.*
Nimesulide (p. 101·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); linseed oil (p. 2544·2).

Nicip T *Cipla, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Nicispas *Cipla, India.*
Nimesulide (p. 101·3); dicycloverine hydrochloride (p. 1834·2).

Niclofen *Nitin, India.*
Benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Niclofen-S *Nitin, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Niclopar-S *Nitin, India.*
⊗Diclofenac potassium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Niclosan *GSK, India.*
Niclosamide (p. 161·2).
Diphyllobothriasis; hymenolepiasis; taeniasis.

Nico Drops *Saval, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Eye irritation; dry eyes.

Nico Hepatocyn *Uriach Aquilea OTC, Spain.*
Cynara (p. 2490·3); aloes (p. 1816·1); boldo (p. 2458·3); cascara (p. 1826·1).
Constipation.

Nicobion *Teofarma, Fr.; Merck, Ger.†*
Nicotinamide (p. 2083·1).
Pellagra; nicotinamide deficiency.

NicoBloc *Galpharm, UK.*
Aid to smoking withdrawal.

Nicobrevin *Medimpex, Hung.; Aspar, Irl.†; Pro-Health, NZ; Aspar, UK.*
Menthyl valerate (p. 2554·1); quinine (p. 665·1); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Aid to smoking withdrawal.

Nicocin *Universal, Hong Kong†; Ordain, India.*
Nicotinic acid (p. 2083·1).

Nicoderm *McNeil Consumer, Canad.; SmithKline Beecham Consumer, USA.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicodose *Pierre Fabre, Denm.*
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Nicoduce *Abbott, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

Nicofer *Abbott, India.*
Injection: Iron sucrose (p. 2078·1).

Abbott, India.
Syrup: Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Abbott, India.
Tablets: Folic acid (p. 2063·1); iron (p. 2073·1).

Nicofer-F *Abbott, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prophylaxis of neural tube defects in pregnancy.

Nicofer-XT *Abbott, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Nicoflex *Reanal, Hung.; Reanal, Rus.*
Capsaicin (p. 35·1); ethyl nicotinate (p. 56·3); glycol salicylate (p. 66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nicogum *Pierre Fabre, Fr.†*
Nicotine resin complex (p. 2569·3).
Aid to smoking withdrawal.

Nicol
Note: this name may be used for preparations of different composition.
Avalanche, India.
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

CCM, Malaysia.
Chloramphenicol (p. 257·1).
Bacterial eye and ear infections.

Nicol-AT *Avalanche, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Nicolin *Affy, India.*
Clindamycin (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Nicol-LS *Avalanche, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Nicolsint *EG, Ital.*
Citicoline (p. 2480·1).
Parkinsonism.

Nicomide *Sirius, USA.†*
Nicotinamide (p. 2083·1); zinc oxide (p. 1729·1); copper oxide (p. 2057·1); folic acid (p. 2063·1).

Nicomild *Millimed, Thai.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicopass *Pierre Fabre Dermo-Cosmetique, Port.*
Nicotine polacrilex (p. 2569·3).
Aid to smoking withdrawal.

Pierre Fabre, Cz.†; Pierre Fabre, Fin.; Pierre Fabre, Fr.; Pierre Fabre, Gr.; Pierre Fabre, Hung.†; Pierre Fabre, Neth.
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Pierre Fabre, Irl.; Wockhardt, UK.†
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicopatch *Pierre Fabre Sante, Belg.; Pierre Fabre, Cz.†; Pierre Fabre, Fin.; Pierre Fabre, Fr.; Pierre Fabre, Gr.; Pierre Fabre, Neth.†; Pierre Fabre Dermo-Cosmetique, Port.; Wockhardt, UK.†*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicoprive
Note: this name may be used for preparations of different composition.
DB, Fr.
Ascorbic acid (p. 2110·3); crataegus (p. 2488·1); vitamin B substances (p. 2102·3).
Aid to smoking withdrawal.

Nicord
Note: this name may be used for preparations of different composition.
Evershine, India.
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Marjan, Braz.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Nicordilen *Gap, Gr.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

NicoRelief *Major, USA.*
Nicotine polacrilex (p. 2569·3).
Smoking cessation.

Nicorette *Johnson & Johnson, Arg.; Johnson & Johnson, S.Afr.; Johnson & Johnson, Thai.; GSK, USA.*
Nicotine polacrilex (p. 2569·3).
Aid to smoking withdrawal.

Johnson & Johnson, Austral.; Janssen-Cilag, Austria; McNeil, Belg.; McNeil Consumer, Canad.; Johnson & Johnson, Chile; Johnson & Johnson, China; McNeil, Cz.; Pfizer, Cz.; McNeil, Denm.; McNeil, Fin.; Johnson & Johnson, Fr.; McNeil, Ger.; Johnson & Johnson, Gr.; Johnson & Johnson, Hong Kong; McNeil, Hung.; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Johnson & Johnson, Ital.; Johnson & Johnson, Malaysia; Johnson & Johnson Consumer, Mex.; Johnson & Johnson, Neth.; McNeil, Norw.; Johnson & Johnson, NZ; Johnson & Johnson, Philipp.; McNeil, Pol.; Johnson & Johnson, Port.; Johnson & Johnson, Rus.; Johnson & Johnson, Singapore; Johnson & Johnson, Spain; McNeil, Swed.; Janssen-Cilag, Switz.; Pfizer Consumer, UK; McNeil, Ukr.
Nicotine (p. 2569·3), nicotine betadex (p. 2570·2), nicotine resinate (p. 2569·3), or nicotine tartrate (p. 2569·3).
Aid to smoking withdrawal.

Johnson & Johnson, Braz.
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Nicorol *Actavis, Neth.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicort *Abbott, India.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Nicospan *Chinoin, Rus.*
Nicotinic acid (p. 2083·1); drotaverine hydrochloride (p. 2497·3).
Cerebral and peripheral vascular spasm.

Nicostat *Greenpharma, Braz.*
Nystatin (p. 590·3).
Candidiasis.

Nicosyn *Sirius, USA.*
Sulfur (p. 1721·1); sulfacetamide sodium (p. 361·1).
Acne.

Nicotabs *Thaipharmed, Thai.*
Nicotinic acid (p. 2083·1).
Vascular disorders; nicotinic acid deficiency; hyperlipidaemias.

Nicotears *Saval, Chile.*
Eye drops: ⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Saval, Chile.
Eye gel: Carbomer 940 (p. 2173·3).
Dry eyes.

Nicotex *Cipla, India.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Nicotex-2 *Cipla, India.*
Nicotine polacrilex (p. 2569·3).
Aid to smoking withdrawal.

Nicotibina *Sanofi-Aventis, Arg.*
Isoniazid (p. 311·2).
Tuberculosis.

Nicotibine *Econophar, Belg.*
Isoniazid (p. 311·2).
Tuberculosis.

Nicotinell *Novartis Consumer, Austral.; Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Chile; Novartis, China; Novartis Consumer, Cz.†; Novartis, Denm.; Novartis, Fin.; Novartis Sante, Fr.; Novartis Consumer, Ger.†; Novartis, Gr.; Novartis Consumer, Hong Kong; Novartis Consumer, Hung.; Novartis Consumer, Irl.;*

Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Malaysia; Novartis Consumer, Neth.; Novartis, Norw.; Novartis Consumer, NZ; Novartis, Philipp.; Novartis Consumer, Pol.†; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis OTC, Singapore; Novartis Consumer, Spain; Novartis, Swed.; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis Consumer, UK.
Nicotine (p. 2569·3), nicotine betadex (p. 2570·2), nicotine polacrilex, nicotine resinate (p. 2569·3), or nicotine tartrate (p. 2569·3).
Aid to smoking withdrawal.

Nicotinell TTS *Novartis Consumer, Arg.; Novartis, Braz.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicotivit *Elvipe, Gr.*
Nicotinamide (p. 2083·1).

Nicotrol *Janssen-Cilag, Austria; McNeil Consumer, Canad.†; McNeil, Fin.†; Pfizer Consumer, NZ; Pharmacia, USA.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nicovas *Micro, India.*
Inositol nicotinate (p. 1410·3).

Nicovel *Orifarm, Denm.; Orifarm, Norw.*
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Nicox *Novell, Indon.†*
Nimesulide (p. 101·3).
Osteoarthritis; peri-articular disorders; pain; inflammation.

Nicozid *IFET(ΙΦΕΤ), Gr.†; Piam, Ital.*
Isoniazid (p. 311·2).
Tuberculosis.

Nicozinc *Chobet, Arg.*
Tablets: Zinc pidolate (p. 1720·3).
Peripheral vascular disorders.

Chobet, Arg.
Topical solution: Zinc pidolate (p. 1720·3); lincomycin hydrochloride (p. 317·1).
Skin infections.

Nicozone
Note: this name may be used for preparations of different composition.
Helm, Irl.
Nicorandil (p. 1446·2).
Angina pectoris.

Nida, Singapore.
Ketoconazole (p. 585·3).
Fungal infections.

Nicpime-AM *Abbott, India.*
Amikacin (p. 214·1); cefepime (p. 239·2).
Bacterial infections.

Nictram *Nitin, India.*
Tramadol (p. 139·2) or tramadol hydrochloride (p. 139·2).
Pain.

Nictram Plus *Nitin, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Nicy Days *Bionova, India.*
Vitamin B substances (p. 2102·3); ginger (p. 1844·1); magnesium (p. 1786·3); manganese (p. 2081·2); valerian (p. 2640·2).

Nida *Unicure, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

NidaGel *Graceway, Canad.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Nidagen *Systopic, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; menopausal disorders.

Nidagest *Systopic, India.*
Allylestrenol (p. 2255·2).
Threatened miscarriage.

Nidal al 110 *Nestle, Fr.*
Infant feed.
Lactose intolerance; diarrhoea.

Nidal AR *Nestle, Fr.*
Infant feed.
Regurgitation in infants.

Nidal Excel HA *Nestle, Fr.*
Infant feed.
Potential hypersensitivity to cows milk.

Nidal Pélargon *Nestle, Fr.*
Infant feed.
Digestive disorders.

Nidatar *Apotex, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Nidazea *Widmer, Austria; Widmer, Belg.; Widmer, Neth.; Widmer, Switz.*
Metronidazole (p. 936·1).
Rosacea.

Nidazol *Ulagay, Turk.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Nida-Zole *Medicine Products, Thai.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Nidazole
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Sipra, India.
Ornidazole (p. 943·1).
Protozoal infections; anaerobic bacterial infections.

Nidazolin *Bunker, Braz.*
Nystatin (p. 590·3).
Fungal infections.

Nidazol-M *Ulagay, Turk.*
Miconazole nitrate (p. 589·1); metronidazole (p. 936·1).
Vulvovaginal candidiasis.

Nidazone *T Man, Thai.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections; Helicobacter pylori *eradication.*

Nidcal-AF *Newtramax, India.*
Calcium citrate (p. 1783·2); vitamin D (p. 2112·3).

Nidcor *Pharma Nutria, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Niddafin *CT, Neth.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Niddaryl *Dee, UK·*
Glimepiride (p. 473·2).
Diabetes mellitus.

Niddastig *Centrafarm, Neth.†*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Niddavita *Gedeon Richter, Neth.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Niddazol *Stada, Denm.*
Itraconazole (p. 583·3).
Fungal infections.

Nidem *Aspen, Austral.; Arrow, Hong Kong; Sigma, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Nideshu *Huashan, China.*
Telmisartan (p. 1509·3).
Hypertension.

Nidex *Nestle, Braz.; Nestle, Ital.*
Maltodextrin (p. 2080·3).
Nutritional supplement.

Nidi Spas *Sunshine, India.*
Diclofenac sodium (p. 48·3); fenpiverinium bromide (p. 2504·1); pitofenone hydrochloride (p. 2592·2).

Nidic *Meridian, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Nidicard *Kocak, Turk.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nidilat *Sanofi Synthelabo, Turk.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nidim *Nitro Organics, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Nidina Active *Nestle, Ital.*
Infant feed.
Lactose intolerance.

Nidina Confort *Nestle, Ital.*
Infant feed.
Regurgitation.

Nidina HA *Nestle, Ital.; Nestle, Port.*
Infant feed.
Food hypersensitivity; protein intolerance.

Nidina Probiotico *Nestle, Ital.*
Infant feed.
Gastrointestinal disorders.

Nidoba *Klar Sehen, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Nidol
Note: this name may be used for preparations of different composition.
Cantabria, Spain.
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain.

Eurodrug, Hong Kong; Eurodrug, Hung.; Eurodrug, Thai.
Nimesulide (p. 101·3).
Fever; inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nidolid *Eurodrug, Philipp.*
Nimesulide (p. 101·3).
Musculoskeletal and joint pain.

Nidolin *Eurodrug, Mex.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nidra *Jagsonpal, India.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Nidralon-V *Liferpal, Mex.*
Metronidazole (p. 936·1).
Vaginal infections.

Nidran *Daiichi Sankyo, China; Daiichi Sankyo, Jpn.*
Nimustine hydrochloride (p. 836·3).
Malignant neoplasms.

Nidrazid *Zentiva, Cz.; Zentiva, Pol.*
Isoniazid (p. 311·2).
Tuberculosis.

Nidrel *UCB, Fr.*
Nitrendipine (p. 1456·3).
Hypertension.

Nidrozol *Teva, Mex.†*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis.

Nid-XT *Vilberry, India.*
Syrup: Cyanocobalamin (p. 2107·2); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Vilberry, India.
Tablets: Ferrous ascorbate (p. 2060·3); folic acid (p. 2063·1).

Nieral *Schuck, Ger.*
Solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Nierentee St Severin *Smetana, Austria.*
Ononis (p. 2575·3); equisetum (p. 2500·1); herb. polygonii.
Urinary-tract disorders.

Nierentropfen Cosmochema *Heel, Ger.*
Berberis vulgaris (p. 2502·1); solidago virgaurea (p. 2620·1); lytta vesicatoria.
Homoeopathic preparation.

Niereston *Otsuka, Indon.*
Electrolytes (p. 1775·1); carbohydrates.
Renal insufficiency.

Nieron E *UCB, Ger.*
Equisetum (p. 2500·1).
Urinary-tract disorders.

Nifabol *Elfin, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nifadil *Sanval, Braz.*
Nifedipine (p. 1447·2).
Angina pectoris.

Nifal *Meyer, Venez.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifalin *Pharmanik (Φαρμανικ), Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Nifangin *Orion, Fin.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifar *Nafar, Mex.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; myocardial infarction; Raynaud's syndrome.

Nifatenol *Hexal, Ger.†*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension.

Nifazyme *Elfin, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Nifcard *Intra-Labs, India.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

Nifdec *Elfin, India.*
Diclofenac (p. 48·3).
Inflammation; pain.

Nife *AbZ, Ger.†; CT, Ger.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifebene *Ratiopharm, Austria.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifecard
Note: this name may be used for preparations of different composition.
Bros, Gr.
Nitrendipine (p. 1456·3).
Hypertension.

Sigma, Austral.†; Lek, Cz.; Lek, Hong Kong; Sandoz, Hong Kong; Teva, Hung.†; Lek, Rus.; Sandoz, Singapore; Lek, Thai.†; Sandoz, Ukr.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifecip *Cipla, Malaysia.*
Nifedipine (p. 1447·2).
Hypertension.

Nifeclair *Hennig, Ger.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifecor *Betapharm, Ger.†*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Nifed *Rowex, Irl.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifed Sol *Phoenix, Arg.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifedalat *Sandoz, S.Afr.*
Nifedipine (p. 1447·2).
Angina pectoris; Raynaud's syndrome; hypertension.

Nifedax *Royton, Braz.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifedel *Klonal, Arg.*
Nifedipine (p. 1447·2).
Angina pectoris.

Nifediac *Teva, USA.*
Nifedipine (p. 1447·2).
Hypertension.

Nifedical *Teva, USA.*
Nifedipine (p. 1447·2).
Hypertension.

Nifedicard *Kinder, Braz.†*
Nifedipine (p. 1447·2).
Angina pectoris.

Nifedicor *Nikolakopoulos, Gr.; Valeant, Ital.; Streuli, Switz.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome; ischaemic heart disease.

Nifedi-Denk *Denk, Singapore; Denk, Thai.*
Nifedipine (p. 1447·2).
Ischaemic heart disease; hypertension; Raynaud's syndrome; angina pectoris.

Nifedigel *Gelcaps, Mex.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Nifedilong *CTS, Israel.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifedin *Sanbe, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; myocardial infarction; hypertension; Raynaud's syndrome.

Nifedine *Piramal, India.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifedipat *Hexal, Gr.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nifedipres *Cryopharma, Mex.*
Nifedipine (p. 1447·2).
Heart failure; angina pectoris; hypertension.

Nifedipress *Dexcel, UK.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Nifehexal *Sandoz, Austral.; Hexal, Austria; Hexal, Ger.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifelat
Note: this name may be used for preparations of different composition.
Biosintetica, Braz.
⊗Nifedipine (p. 1447·2); atenolol (p. 1308·2).
Angina pectoris; hypertension.
TAD, Ger.†; Cipla, Hong Kong; Cipla, India; Remedica, Malaysia; Zdravlje, Rus.; Remedica, Singapore; Remedica, Thai.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; heart failure; Raynaud's disease.

Nifen *Meridian, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nifen MR *Meridian, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nifen Plus *Meridian, India.*
⊗Paracetamol (p. 115·1); nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Niferex *UCB, Denm.; UCB, Ital.; UCB, Norw.; UCB, Port.; Erol, Swed.*
Ferrous glycine sulfate (p. 2061·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency.
UCB, China; GSK, Hong Kong; Tillomed, UK; Ther-Rx, USA.
Polysaccharide-iron complex (p. 2086·2).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Niferex Forte *Ther-Rx, USA.*
Polysaccharide-iron complex (p. 2086·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; megaloblastic anaemia.

Niferex-PN *Ther-Rx, USA.†*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Niferil *USV, India.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris; Raynaud's syndrome.

Nifesal *Germed, Ital.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifestad *Stada, Philipp.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifetex *Wintac, Singapore.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifetolol *Anglo-French Drugs, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension.

Nifezzard *Pizzard, Mex.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifgel *Elfin, India.*
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1).

Nifical *Winthrop, Ger.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Niflactol *BMS, Spain.*
Morniflumate (p. 92·2) or niflumic acid (p. 101·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Niflam
Note: this name may be used for preparations of different composition.
BMS, Ital.
Capsules; topical gel: Niflumic acid (p. 101·2).
Pain; inflammation.
BMS, Ital.
Suppositories: Morniflumate (p. 92·2).
Pain; inflammation.

Niflamol *BMS, Gr.*
Niflumic acid (p. 101·2) or morniflumate (p. 92·2).
Inflammatory joint disorders; spondyloarthropathies.

Niflan *Senju, Jpn; SIFI, Mex.*
Pranoprofen (p. 127·1).
Inflammatory eye disorders.

Niflec *Meiji, Indon.; Meiji, Thai.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Niflucan *Duncan, Arg.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders.

Niflugel *BMS, Belg.; BMS, Cz.†; BMS, Fr.*
Niflumic acid (p. 101·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nifluril
Note: this name may be used for preparations of different composition.
BMS, Cz.†; BMS, Fr.; BMS, Port.
Capsules: Niflumic acid (p. 101·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.
BMS, Fr.
Suppositories: Morniflumate (p. 92·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Niflux *Alter, Port.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Respiratory-tract congestion.

Nifopress *Goldshield, UK.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Niformina *Tiefenbacher, Neth.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Nifostin *Penn, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Nifoxime *Sanify, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Nifret *Apothecon, Neth.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifser *Serral, Mex.*
Nifedipine (p. 1447·2).
Hypertension.

Niftas *Intas, India.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nif-Ten *AstraZeneca, Austria; AstraZeneca, Fin.†; AstraZeneca, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Philipp.†; AstraZeneca, Singapore; AstraZeneca, Switz.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Niftran *Abbott, India.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nifuda *Huanghai, China.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nifudiar *Meprofarm, Indon.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Nifugal *GSK, India; Zydus, India.*
Clotrimazole (p. 576·2).
Fungal mouth infections.

Nifugal-B *GSK, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2).
Fungal skin infections.

Nifural *Medifarma, Indon.; Pediatrica, Indon.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Nifuran
Note: this name may be used for preparations of different composition.
Bamford, NZ.
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nifurantin *Apogepha, Ger.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nifurantin B 6 *Apogepha, Ger.*
Nitrofurantoin (p. 332·1); pyridoxine hydrochloride (p. 2105·3).
Urinary-tract infections.

Nifurat *Bago, Chile.*
Nifuroxazide (p. 331·3); activated attapulgite (p. 1820·1).
Diarrhoea.

Nifuretten *Apogepha, Ger.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nifurol *Reuffer, Mex.*
Nitrofurazone (p. 333·1).

Nifurtox *Richmond, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Nifuryl *Gunsa, Turk.†*
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Nig *Neon, India; VHB, India.*
Glyceryl trinitrate (p. 1391·2).
Unstable angina; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nigalax *Sanofi-Aventis, Arg.*
Suppositories: Bisacodyl (p. 1821·1); docusate sodium (p. 1836·2); sodium lauril sulfoacetate (p. 2210·3).
Bowel evacuation.
Sanofi-Aventis, Arg.
Tablets: Bisacodyl (p. 1821·1); docusate sodium (p. 1836·2).
Bowel evacuation.

Nigap *Psychotropics, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nigepan *Nizpharm, Rus.*
Benzocaine (p. 1980·2); heparin sodium (p. 1396·3).
Haemorrhoids.

Nigersan *Sanum-Kehlbeck, Ger.*
Aspergillus niger.
Homoeopathic preparation.

Night Cough *Vita Health, Canad.*
Diphenhydramine hydrochloride (p. 626·2).
Cough.

Night Nurse *GSK Consumer, Irl.; GSK Consumer, UK.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Night Peel *Lierac, Fr.†*
⊗Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); urea (p. 1727·3); enoxolone (p. 54·2).
Sun-induced skin damage.

Night Relief Cold & Flu *Banner, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Night Time Cold/Flu Relief *Prometic, USA.*
⊗Doxylamine succinate (p. 627·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Nightcalm *Galpharm, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Nighttime *Jamp, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Nighttime Cold & Flu *Pharmetics, Canad.; Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Nighttime Cold & Flu Relief *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nighttime Cold and Flu-In-One *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nighttime Cold Relief *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Nighttime Contac Cold & Sore Throat *GSK Consumer, Canad.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; sore throat.

Nighttime Contac Complete Cough, Cold & Flu *GSK Consumer, Canad.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; cough.

Nighttime Extra Strength Contac Cold & Sore Throat *Meda, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; sore throat.

Nighttime Extra Strength Contac Complete Cough, Cold & Flu *Meda, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Could and influenza symptoms; coughs.

Nighttime Pamprin *Chattem, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Insomnia.

Nighttime Super Strength Contac Complete *GSK Consumer, Canad.†*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nighttime Total Cold and Flu *Vita Health, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Niglinar *Rivero, Arg.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; hypertension; induction of intra-operative hypotension.

Niglostin *Hasco-Lek, Pol.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Nigroids *Ernest Jackson, UK.*
Liquorice (p. 1853·2); menthol (p. 2553·2).

Nigvisal B *Nizpharm, Rus.*
Common viper venom; salicylic acid (p. 1719·1); camphor (p. 2466·2); turpentine oil (p. 2636·3).
Arthralgia; neuralgia; myalgia; sciatica.

Nijutsuto *Tsumura, Jpn.*
Pinellia tuber; atractylodes lancea rhizome; clematis root; skullcap root (p. 2617·1); cyperus rhizome; citrus unshiu peel; atractylodes rhizome; poria sclerotium; liquorice (p. 1853·2); ginger (p. 1844·1); arisaema tuber; aralia cordata root.
Traditional Kampo medicine.

Nik + Aid *Leib, Canad.†*
Hamamelis (p. 2523·3).

Nikableomicina *Pfizer, Chile.*
Bleomycin hydrochloride (p. 749·3).
Malignant neoplasms.

Nikaloz *Actavis, Denm.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nikarin *TO-Chemicals, Thai.*
Miconazole nitrate (p. 589·1).
Oral and gastrointestinal candidiasis.

Nikavir *AZT, Rus.*
Phosphazide.
HIV infection.

Nikee *Kee, India.*
Nimesulide (p. 101·3).
Pain.

Nikekang *Southwest, China.*
Codeine phosphate (p. 40·2).
Cough; pain.

Nikidac *Novogen, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nikkho Vac *Nikkho, Braz.*
Allergen extracts (airborne proteins, food proteins, and respiratory-tract bacterial antigens) (p. 2434·3).
Allergen immunotherapy.

Niklod *Savio, Ital.*
Clodronate disodium (p. 1180·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Hyperparathyroidism; osteoporosis; osteolysis of malignancy; multiple myeloma.

nikofrenon *Riemser, Ger.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nikolam *Meprofarm, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Nikomox-CV *Eris, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Nikor *Indeco, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Nikoran *Torrent, India; Torrent, Philipp.*
Nicorandil (p. 1446·2).
Angina pectoris.

Nikoril *Medinfar, Port.†*
Nicorandil (p. 1446·2).
Angina pectoris.

Nikotriol *Eris, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium (p. 1786·3); zinc (p. 2126·1).

Nikotugg *ACO, Swed.†*
Nicotine resin (p. 2569·3).
Aid to smoking withdrawal.

Nikron *Zentiva, Hung.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Niksen *Toprak, Turk.†*
Permethrin (p. 2159·3).
Pediculosis.

Niksin *Scoshia, India.*
Amikacin (p. 214·1).
Bacterial infections.

Nilacelin *Nicholas, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Nilacid *Zentiva, Hung.*
Magnesium trisilicate (p. 1858·1); magnesium oxide (p. 1857·3); monobasic sodium phosphate (p. 1791·1); bismuth subnitrate (p. 1822·1).
Gastritis; gastric hyperacidity; peptic ulcer.

Nilacol *Nicholas, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Niladacin *Nicholas, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Nilaflox *Nicholas, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Nilandron *Hoechst Marion Roussel, USA.*
Nilutamide (p. 836·2).
Prostatic cancer.

Nilapur *Nicholas, Indon.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Nilaren *Nicholas, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Nilatika *Nicholas, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Nilavid *Nicholas, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Nilcer *Khandelwal, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Nilcid-MPS *Pharmacia Upjohn, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Nilclamida *Belfar, Braz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Nilden *IQFA, Mex.*
Nimesulide (p. 101·3).

Nile
Note: this name may be used for preparations of different composition.
Honghui, China.
Mizolastine (p. 636·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.
Intra-Labs, India.
Nimesulide (p. 101·3).
Pain.

Nile Plus *Intra-Labs, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nile-CZ *Intra-Labs, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nile-P *Nordic, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nile-S *Nordic, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nile-SP *Nordic, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nile-TZ *Intra-Labs, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Nilevar *Codepharma, Fr.*
⊗Norethandrolone (p. 2294·2).
Medullary aplasia.

Nilfene *Pharmis, Port.*
⊗Fentanyl citrate (p. 60·1).
Pain; neuroleptanalagesia.

Nilflux *Biol, Arg.*
Staphylococcus aureus; haemolytic Streptococcus; *Streptococcus pyogenes*; non-haemolytic Streptococcus; *Enterococcus faecalis* (p. 2596·3); *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Micrococcus roseus*; *Moraxella catarrhalis*; *Haemophilus influenzae*; hyaluronidase (p. 2527·2); ox bile (p. 2457·2); ascorbic acid (p. 2110·3).
Respiratory-tract infections.

Nilgar *Mega Lifesciences, Ukr.†*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Nilgrip *Biol, Arg.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Nilhist *JB Chemicals, India.*
⊗Chlorphenamine maleate (p. 620·3); naphazoline (p. 1669·3).

Nilid *Aspen, Mex.*
Nimesulide (p. 101·3).
Peri-articular and soft-tissue disorders; pain; fever; inflammation.

Nilide *Cadila, India; Pharmasant, Thai.*
Nimesulide (p. 101·3).
Pain; inflammation; fever.

Nilisu *Xinhua, China.*
Nimodipine (p. 1455·2).
Cerebral vasospasm following subarachnoid haemorrhage.

Nilitis *Ipca, India.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders.

Nilium *Help, Gr.*
Flunitrazepam (p. 1073·3).
Insomnia.

Nilken *Kener, Mex.*
⊗Buphenine hydrochloride (p. 2462·3).

Nill-O-Wax *Hanburys, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).

Nilmadin *Norma (Νορμα), Gr.*
Glyceryl trinitrate (p. 1391·2).

Nilmide *Labesfal, Port.*
Nimesulide (p. 101·3).
Pain.

Nilogrin *Polfa Pabianice, Pol.; Pabianice, Rus.†*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders; retinopathy; circulatory ear disorders; vascular eye disorders; vestibular disorders; migraine.

Nilol *Intas, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nilox *CNP, Ger.*
Nitroxoline (p. 333·2).
Urinary-tract infections.

Niloxid *Overseas, India.*
Vitamins; minerals; amino acids; lycopene (p. 2546·2).

Nilperidol *Cristalia, Braz.*
⊗Fentanyl citrate (p. 60·1); droperidol (p. 1072·1).

Nilsec *Max, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Nilson *Pantafarm, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Nilstat *Aspen, Austral.; Teofarma, Belg.; Healthcare Logistics, NZ; Lederle, USA.*
Nystatin (p. 590·3).
Candidiasis.

Niltan *Reddy, India.*
Arbutin (p. 1694·3); boswellia serrata (p. 2507·3); coriander oil (p. 2487·1); liquorice (p. 1853·2).

Niltro *Duncan, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Nilup *Lupin, India.*
Nimesulide (p. 101·3).
Pain.

Nilup-P *Lupin, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nilvadis *Eczacibasi, Turk.*
Nilvadipine (p. 1455·2).
Hypertension.

Nilvo *Elpen (Ελπεν), Gr.*
Piroxicam (p. 125·3).

Nilwart *Reddy, India.*
Imiquimod (p. 985·2).

Nimace-MD *Wintech, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis; dysmenorrhoea.

Nimace-P *Wintech, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimace-SP *Wintech, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimact *Indu, India.*
Nimesulide (p. 101·3).
Pain.

Nimadorm *Sandoz, Denm.†*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Nimagyl *Akums, India.*
Nimesulide (p. 101·3).
Pain.

Nimagyl-PC *Akums, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimaid *Winsome, India.*
Nimesulide (p. 101·3).
Pain.

Nimaid-P *Winsome, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimalge *Labesfal, Port.†*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Nimalgex *Hexal, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Nimartin *Vida, Port.†*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Nimat *ATOZ, India.*
Nimesulide (p. 101·3).
Pain.

Nimat-MR *ATOZ, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimat-Plus *ATOZ, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimbasit *Biosana, Canad.*
Minerals.

Nimbex *GSK, Austral.; GSK, Austria; GSK, Belg.; Abbott, Canad.; GSK, Chile; Abbott, China; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Malaysia†; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Spain; GSK, Swed.†; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Abbott, USA.*
Cisatracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Nimbid *AstraZeneca, India.*
Nimesulide (p. 101·3).
Pain.

Nimbisan *Caber, Ital.†*
Brotizolam (p. 1042·1).
Insomnia.

Nimbium *GSK, Arg.; GSK, Braz.*
Cisatracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Nimbra Plus *Indkus, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimbu *Sienna, India.*
Nimesulide (p. 101·3).
Pain.

Nimbus
Note: this name may be used for preparations of different composition.
Biomerica, USA.
Pregnancy test (p. 2596·1).
Moraceae, India.
Nimesulide (p. 101·3).
Pain.

Nimbus Plus *Moraceae, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimcare-A *Alde Medi Impex, India.*
Paracetamol (p. 115·1); nimesulide (p. 101·3).

Nimcet *Svizera, India.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nimcet Plus *Svizera, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Pain.

Nimcin-P *Cinerea, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimcom *Comed, India.*
Tizanidine (p. 2026·2).
Spasticity; skeletal muscle spasm.

Ni-MD *Meridian, India.*
Nimesulide (p. 101·3).
Pain.

Nimdal *Datla, India.*
Nimesulide (p. 101·3).
Pain.

Nimdard *Moraceae, India.*
Nimesulide (p. 101·3).
Pain.

Nimdard Plus *Moraceae, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimdase *Akums, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Nimdase-P *Obsurge, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nimdin *Siomond, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimeb *Taurus, India.*
Nimesulide (p. 101·3).
Pain.

Nimeb-P *Taurus, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimeb-T *Taurus, India.*
Tizanidine (p. 2026·2).
Spasticity; skeletal muscle spasm.

Nimecox *Leti, Venez.*
Nimesulide betadex (p. 101·3).
Inflammation; pain.

Nimed *Medicom, Cz.; Helsinn Birex, Indon.; Schering-Plough, Indon.; Helsinn Birex, Port.*
Nimesulide (p. 101·3).
Osteoarthritis; peri-articular disorders; pain; inflammation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nimedex *Italformaco, Ital.*
Nimesulide betadex (p. 101·3).
Pain.

Nimedine *Anfarm, Gr.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Nimegel *Alapis, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Nimegen *Medica Korea, Malaysia; Medica Korea, Singapore.*
Isotretinoin (p. 1706·2).
Acne.

Nimegesic *Alembic, India; Alembic, Ukr.*
Nimesulide (p. 101·3).
Pain.

Nimegesic-P *Alembic, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimel
Note: this name may be used for preparations of different composition.
Acto, India.
Nimesulide (p. 101·3).
Pain.

Nimelid *PannonPharma, Hung.; Deva, Turk.; SM, Venez.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Nimelide *Genepharm, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Nimelide Fen *Cadila, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Nimenol *Krugher, Ital.†*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nimenrix *GSK, Belg.; GSK, Denm.; GSK, Neth.; GSK, Norw.; GSK, Spain; GSK, UK.*
A meningococcal conjugate vaccine (groups A, C, W135, and Y) (p. 2401·3).
Active immunisation.

Nimepast *Pasteur, Chile.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nimepis *Pisa, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nimeril *David, India.*
Nimesulide (p. 101·3).
Pain.

Nimeril-T *David, India.*
Nimesulide betadex (p. 101·3); tizanidine (p. 2026·2).
Musculoskeletal and joint disorders.

Nimes *Sanovel, Turk.*
Nimesulide (p. 101·3).
Musculoskeletal and joint disorders; inflammation; pain.

Nimesel *Waves, India.*
Nimesulide (p. 101·3).
Pain.

Nimesel-P *Waves, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimesil *Guidotti, Cz.; Guidotti, Pol.; Menarini, Rus.; Guidotti, Ukr.*
Nimesulide (p. 101·3).
Pain; inflammation; osteoarthritis.

Nimesilam *Sigma, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Nimesis-MD *Cruise, India.*
Nimesulide (p. 101·3).
Pain.

Nimesis-P *Cruise, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimesubal *Baldacci, Braz.*
Nimesulide (p. 101·3).

Nimesul *Medichrom, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Nimesulene *Guidotti, Ital.; Menarini, Port.*
Nimesulide (p. 101·3).
Pain.

Nimesulin *Cifarma, Braz.*
Nimesulide (p. 101·3).
Fever; pain; inflammation.

Nimesulix *Teuto, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Nimesulon *Sanval, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Nimesyl *Rider, Chile.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nimeter-A *Gujarat Terce, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimeth *Nitin, India.*
Methylergometrine (p. 2137·3).
Postpartum and postabortal haemorrhage.

Nimetiz *Ajanta, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Nimfast *Zydus, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Nimi *Shreya, India.*
Nimesulide (p. 101·3).
Pain.

Nimic *Geminis, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Nimica *Ipca, India; Ipca, Rus.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nimica Plus *Ipca, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).
Fever, inflammation; pain.

Nimicin *Emcure, India.*
Amikacin (p. 214·1).
Bacterial infections.

Nimicon *Precimex, Mex.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Nimicor *Recalcine, Chile.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Nimika *Elfin, India.*
Amikacin (p. 214·1).
Bacterial infections.

Nimi-LB *Shreya, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Nimill *Millimed, Thai.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Nimind *Indoco, Thai.†*
Nimesulide (p. 101·3).
Inflammation; pain; musculoskeletal and joint disorders.

Nimind CT *Indoco, India.*
Nimesulide (p. 101·3).
Pain.

Nimitiz *East West, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Nimiz *Zota, India.*
Nimesulide (p. 101·3).
Pain.

Nimiz-Plus *Zota, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimkair *PDC, India.*
Nimesulide (p. 101·3).
Pain.

Nimkair-F *PDC, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Nimkair-P *PDC, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimkul *Finecure, India.*
Nimesulide (p. 101·3).
Pain.

Nimkul DCM *Finecure, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Nimkul Para *Finecure, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimkul SP *Finecure, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimkul-CZ *Finecure, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3).

Nimkul-MR *Finecure, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimlak-MD *Laksun, India.*
Nimesulide (p. 101·3).
Pain.

Nimlak-Plus *Laksun, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimley-MD *Zodley, India.*
Nimesulide (p. 101·3).
Pain.

Nimley-P *Zodley, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimley-S *Zodley, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimlide *Zydus Cadila, Thai.*
Nimesulide (p. 101·3).
Pain; joint inflammation.

Nimlid-MD *Wintech, India.*
Nimesulide (p. 101·3).
Pain.

Nimlid-P *Wintech, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimli-P *Aronex, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimlodi *Ajanta, India.*
Nimesulide (p. 101·3).
Pain.

Nimm *Codal Synto, Hong Kong.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Nim-MR *Varun, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3).

Nimnil-P *Biosync, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimo *TO-Chemicals, Thai.†*
Nimesulide (p. 101·3).
Pain; inflammation; fever.

Nimobal *Baldacci, Braz.*
Nimodipine (p. 1455·2).

Nimobid *Mapra, India.*
Nimesulide (p. 101·3).
Pain.

Nimobrain *Benedetti, Ital.*
Nimodipine (p. 1455·2).
Neurological deficit following cerebral vasospasm.

Nimocard *Medicon, India.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Nimocer *Micro, India.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Nimodec *United Biotech, India.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Nimodex *Psychotropics, India.*
Dextropropoxyphene (p. 43·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimodia-P *Positif, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimodil *Remedina, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Nimodilat *Lazar, Arg.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Nimodilat Plus *Lazar, Arg.*
Nimodipine (p. 1455·2); citicoline sodium (p. 2480·2).
Cerebrovascular disorders.

Nimodip *USV, India.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Nimodiphexal *Sandoz, Ukr.†*
Nimodipine (p. 1455·2).
Cerebrovascular disorders; mental function impairment.

Nimodol *Aristo, India.*
Nimesulide (p. 101·3).
Inflammation; pain.

Nimofen *Haledew, India.*
Nimesulide (p. 101·3).
Pain.

Nimofen-P *Haledew, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimofen-T *Haledew, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimogem *Intas, India.*
Nimesulide (p. 101·3).
Pain.

Nimopace *Arunabh, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimopace A *Arunabh, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).

Nimopax *Cifarma, Braz.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage; mental function disorders.

Nimopect *Hevert, Ger.*
Thyme (p. 2630·2).
Bronchitis; catarrh.

Nimopine *Simpex, Rus.*
Nimodipine (p. 1455·2).
Cerebrovascular disorders.

Nimoreagin *Baliarda, Arg.*
Nimodipine (p. 1455·2); citicoline (p. 2480·1).
Cerebrovascular disorders; mental function impairment.

Nimoril *Brussels, India.*
Nimesulide (p. 101·3).
Pain.

Nimo-Somazina *Temis, Arg.*
Citicoline (p. 2480·1); nimodipine (p. 1455·2).
Cerebrovascular disorders.

Nimost *Sanbe, Indon.†*
Nimesulide (p. 101·3).
Osteoarthritis; peri-articular disorders; pain.

Nimotas-CD *Intas, India.*
Nimesulide (p. 101·3).
Pain.

Nimotas-P *Intas, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimotide *Torrent, India.*
Nimodipine (p. 1455·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Nimotiz MR *Mandar, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimotop *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.; Bayer, Port.; Bayer, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, Ukr.; Bayer, USA†; Bayer, Venez.*
Nimodipine (p. 1455·2).
Mental function impairment; neurological deficit following cerebral vasospasm with or without subarachnoid haemorrhage; vertigo; stroke prophylaxis.

Nimovac-V *Pharmathen, Gr.*
Nimodipine (p. 1455·2).
Subarachnoid haemorrhage.

Nimoven *Vencare, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimpa *Globus, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimpain P *Prompt Cure, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimpain PS *Prompt Cure, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nimpain T *Prompt Cure, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimpain-MD *Prompt Cure, India.*
Nimesulide (p. 101·3).
Pain.

Nimpar *Active, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimpara *DWD, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimpep *Intra-Labs, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimpic *Parenteral Drugs, India.*
Nimesulide (p. 101·3).
Pain.

Nimpure-MD *Purewin, India.*
Nimesulide (p. 101·3).
Pain.

Nimpure-P *Purewin, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimpure-PS *Purewin, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nimras-MD *Rass, India.*
Nimesulide (p. 101·3).
Pain.

Nimriz *Ritz, India.*
Nimesulide (p. 101·3).
Pain.

Nimriz Plus *Ritz, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nims *Caber, Ital.*
Nimesulide (p. 101·3).
Pain; fever; inflammation.

Nimsaid *Medley, India.*
Nimesulide (p. 101·3).
Pain.

Nimsaid-P *Medley, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimsaid-S *Medley, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimsaid-T *Medley, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimsol Plus *Keshav, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nims-P *Shreshtha, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimspa *Obsurge, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Nimspas *Zota, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Nimsutech *Pharma-Tech, India.*
Nimesulide (p. 101·3).
Pain.

Nimtech *Macleods, India.*
Nimesulide betadex (p. 101·3).
Pain.

Nimtiz-MR *Chemo-Drugs, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimtop *Reliance, India.*
Nimesulide (p. 101·3).
Pain.

Nimucare *Medico, India.*
Nimesulide (p. 101·3).
Pain.

Nimucare-P *Medico, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimucet *Intas, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimucet-Fen *Intas, India.*
Diclofenac (p. 48·3); nimesulide (p. 101·3).

Nimucet-MR *Intas, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimucold *Symbiosis, India.*
⊗Cetirizine hydrochloride (p. 619·2); nimesulide (p. 101·3); pseudoephedrine hydrochloride (p. 1676·1).

Nimuda *Almet, India.*
Nimesulide (p. 101·3).
Pain.

Nimudin *Osper, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Nimuflex *Sarabhai Piramal, India.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Nimuflex-MR *Abbott, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimuflex-P *Abbott, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimuflex-T *Sarabhai Piramal, India.*
Tizanidine (p. 2026·2).
Spasticity; skeletal muscle spasm.

Nimulase-D *TTK, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Nimulex-FD *Pharmed, India.*
Nimesulide (p. 101·3).
Pain.

Nimulid *Panacea, India; Panacea, Rus.; Panacea, Thai.*
Nimesulide (p. 101·3).
Inflammation; pain; musculoskeletal, joint and peri-articular disorders.

Nimulid MR *Panacea, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).
Muscle spasm; pain; osteoarthritis.

Nimulid Nugel *Panacea, India.*
Nimesulide (p. 101·3); menthol (p. 2553·2); methyl salicylate (p. 92·1); capsaicin (p. 35·1); linoleic acid (p. 2509·2).
Musculoskeletal, joint, and peri-articular disorders.

Nimulid SP *Panacea, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).
Inflammation; haematoma.

Nimumol-P *Glories, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimupain *Cipla, India.*
Nimesulide (p. 101·3).
Pain.

Nimupain Plus *Cipla, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimupet *Vista, India.*
Nimesulide (p. 101·3).
Pain.

Nimuris-Plus *Symbiosis, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimus *Tecnofarma, Chile.*
Bezafibrate (p. 1323·2).
Atherosclerosis; hyperlipidaemias.

Nimuspas *Stedman, India.*
Dicycloverine hydrochloride (p. 1834·2); nimesulide (p. 101·3).

Nimustar *Invision, India.*
Nimesulide (p. 101·3).
Pain.

Nimustar-P *Invision, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimustar-S *Invision, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimusym *Symbiosis, India.*
Nimesulide (p. 101·3).
Pain.

Nimusym-Plus *Symbiosis, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimusyp *Centaur, India.*
Nimesulide (p. 101·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain; fever.

Nimutab *Centaur, India.*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Nimutal *Symbiosis, India.*
Nimesulide (p. 101·3).
Pain.

Nimutal-Plus *Symbiosis, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimvar Plus *ATOZ, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimvar-MD *Zota, India.*
Nimesulide (p. 101·3).
Pain.

Nimvar-MR *Zota, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimvastid *KRKA, Cz.; KRKA, Denm.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.; KRKA, Swed.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Nimven Plus *Vensat, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimven-MD *Vensat, India.*
Nimesulide (p. 101·3).
Pain.

Nimven-S *Vensat, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nimven-T *Vensat, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nimvista *Cadila, India.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Nimvista Plus *Cadila, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimvista-D *Cadila, India.*
Diclofenac sodium (p. 48·3); nimesulide (p. 101·3).

Nimvista-MR *Cadila, India.*
Chlorzoxazone (p. 2022·2); nimesulide (p. 101·3); paracetamol (p. 115·1).

Nimvon-S *Ajanta, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Ninazo *Gache, Venez.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Ninazol *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis; fungal infections.

Nincort *Xinghui, China.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Ninderm *Maigal, Arg.*
Topical powder: Azulene (p. 2452·1); zinc oxide (p. 1729·1); starch (p. 2095·1).
Skin disorders.

Maigal, Arg.
Shampoo: Poloxyl lanolin (p. 2219·3); trolamine laurilsulfate (p. 2210·3).
Scalp disorders.

Nindral *Torrent, India.*
Flurazepam hydrochloride (p. 1076·1).
Insomnia.

Nine *Skymax, India.*
Quinine (p. 665·1) or quinine dihydrochloride (p. 665·1).

Nine Rubbing Oils *Potter's, UK.*
Amber oil (p. 2440·3); clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); linseed oil (p. 2544·2); methyl salicylate (p. 92·1); volatile mustard oil (p. 2646·1); turpentine oil (p. 2636·3); thyme oil (p. 2630·3); peppermint oil (p. 1877·1).
Musculoskeletal, joint, and soft-tissue disorders.

Nineka *Novag, Mex.*
Neomycin sulfate (p. 330·1); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Ninfagin *RPF, Ital.*
Grapefruit; lactic-acid-producing organisms (p. 2596·3); chlorhexidine gluconate (p. 1743·3); mallow (p. 2549·2); aloe vera (p. 1693·2).
Restoration of vaginal mucosa.

Ning Dan Xin *Qi Li, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Ning Fen *Lunan, China.*
Isoflurane (p. 1903·2).
General anaesthesia.

Ning Gan Xin *Tong Yong Tong Meng, China.*
Matrine.

Ning Hu Shu Xin *Sha Pu Ai Si, China.*
Diflunisal (p. 51·3).
Osteoarthritis; rheumatoid arthritis; pain.

Ning Lan Xin *Chang An, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Ning Li Ping *Simcere, China.*
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Ning Luo Xin *Qi Li, China.*
Levofloxacin mesilate.
Bacterial infections.

Ning Mai Xin *Chang An, China.*
Sodium new houttuyfonate.

Ning Sha *LuoXin, China.*
Levofloxacin mesilate.
Bacterial infections.

Ning Sheng Xin *Chang An, China.*
Lappaconitine hydrobromide (p. 1418·1).

Ning Tong *Lunan, China.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Ning Wei Shu *Guo Feng, China.*
Lafutidine (p. 1851·3).
Peptic ulcer; gastritis; acid aspiration.

Ning Xiu Xin *Qi Li, China.*
Piracetam (p. 393·3).
Mental function impairment.

Ning Xu Xin *Yang Jiang, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Ning Xue Xin *Tong Yong Tong Meng, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Ning Ye *Zhongsheng Haitian, China.*
Ethylenediamine diaceturate.

Ning Yu Xin *Chang An, China.*
Enoxacin gluconate.
Bacterial infections.

Ninghongxin *Huaxin, China.*
⊗Erythropoietin (human, recombinant) (p. 1141·1).
Anaemia in renal failure.

Ninivet *Gedeon Richter, Cz.; Gedeon Richter, Hung.*
⊗Letrozole (p. 817·1).
Breast cancer.

Ninjinto *Tsumura, Jpn.*
Liquorice (p. 1853·2); atractylodes lancea rhizome; ginseng (p. 2513·3); ginger (p. 1844·1).
Traditional Kampo medicine.

Ninjin'yoeito *Kracie, Jpn; Tsumura, Jpn.*
Ginseng (p. 2513·3); angelica acutiloba root (p. 2443·3); peony root; rehmannia root; atractyloides rhizome; poria sclerotium; cinnamon bark (p. 2479·2); astragalus root (p. 2451·1); citrus unshiu peel; polygala root; schisandra fruit; liquorice (p. 1853·2).
Traditional Kampo medicine.

Ninlium *Chinta, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; delayed gastric emptying; dyspepsia.

Ninza *Hauz, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nio Marine *Lagos, Arg.*
Rhodysterol; fucus (p. 2612·1); centella (p. 1698·3); ivy (p. 2536·2); caffeine (p. 1203·3).
Cellulite.

Niocitran *Novartis Consumer, Belg.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Ni-Odan *Odan, Canad.*
Nicotinic acid (p. 2083·1).

Niofen
Note: this name may be used for preparations of different composition.
Investi, Arg.
Capsules: Fluconazole (p. 578·2).
Candidiasis.

Investi, Arg.
Pessaries: Tioconazole (p. 595·3).
Vulvovaginal fungal infections.

K2 Health & Wellness, Chile.
Ibuprofen (p. 68·2).
Fever; pain.

Niofen Cold HBP *K2 Health & Wellness, Chile.*
Ibuprofen (p. 68·2); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Niofen Flu *K2 Health & Wellness, Chile.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

Niolib *Santa, Gr.*
Olanzapine (p. 1089·3).

Niolox *Nitro Organics, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Niolox-D *Nitro Organics, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Niolox-OZ *Nitro Organics, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Niontix *Linde Gas, Cz.; AGA, Denm.; AGA, Fin.; Linde Gas, Ger.; Linde Gas, Neth.; AGA, Norw.; AGA, Swed.*
Nitrous oxide (p. 1908·1).
General anaesthesia; pain; sedative.

Niopam *Bracco, Irl.; Bracco, UK.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Niosilin *Medigivor, Venez.*
Benzoic acid (p. 1738·2); precipitated sulfur (p. 1721·1); salicylic acid (p. 1719·1); menthol (p. 2553·2); titanium dioxide (p. 1725·1); kaolin (p. 1850·1).
Fungal skin infections.

Niostal *Spefar, Venez.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Nioxil *Geolab, Braz.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Nipam *La Pharmaceuticals, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nipartan *Micro, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Nipartan-H *Micro, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nipas *Galena, Pol.*
Aspirin (p. 22·2).
Dental pain.

Nipatra *Amdipharm, UK.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Nipaxon *McNeil, Swed.*
Noscapine (p. 1670·3).
Cough.

Nipcan *Ipca, India.*
Fluconazole (p. 578·2).
Fungal infections.

Nipcare *Neon, India.*
Wool fat (p. 2219·3).
Nipple care in pregnancy and breast feeding.

Nipe
Note: this name may be used for preparations of different composition.
Transfarma, Indon.
Isothipendyl (p. 631·2) or isothipendyl hydrochloride (p. 631·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.
Vargas, Venez.
Capsules; oral powder; syrup: Paracetamol (p. 115·1); chlorphenamine (p. 620·3); caffeine (p. 1203·3).
Influenza symptoms.
Vargas, Venez.
Oral drops; oral powder (sin cafeina): Paracetamol (p. 115·1); chlorphenamine (p. 620·3).
Influenza symptoms.

Nipent *Hospira, Denm.; Hospira, Fr.; Hospira, Ger.; Hospira, Gr.; IFET (ΙΦΕΤ), Gr.; Hospira, Irl.; Hospira, Ital.; Hospira, Neth.; Hospira, Port.; Hospira, Spain; Eurogen, UK; Hospira, USA.*
Pentostatin (p. 845·3).
Hairy-cell leukaemia.

Niperten *KRKA, Rus.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; heart failure.

Niphex *Nitin, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Nipidol *Biofarma, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Nipin *Lisapharma, Ital.; Lisapharma, Singapore.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Nipit *Anthiea, India.*
Sodium chloride (p. 1795·1).

Niplonac *Abbott, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Niplonac-MR *Abbott, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Niplonac-P *Abbott, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Nipodur *Anfarm, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Nipogalin *Anfarm, Gr.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Nipolen *Mintlab, Chile.*
Chlorphenamine maleate (p. 620·3).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Nipolept *Astellas, Austria†; Sanofi-Aventis, Ger.†*
Zotepine (p. 1119·1).
Schizophrenia.

Niponeurin *Lacer, Port.†*
⊗Selegiline hydrochloride (p. 914·2).

Nipp *Aamorb, India.*
Cefpodoxime.
Bacterial infections.

Nipp-CA *Aamorb, India.*
Cefpodoxime; clavulanic acid (p. 268·3).

Nipredin *Proel, Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Nipress
Note: this name may be used for preparations of different composition.
Rider, Chile.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.
Samarth, India.
Sodium nitroprusside (p. 1497·1).
Hypertensive crisis; controlled hypotension; heart failure.

Nipride *Biolab Sanus, Braz.; Hospira, Canad.*
Sodium nitroprusside (p. 1497·1).
Controlled hypotension; ergot intoxication; heart failure; hypertensive crisis.

Niprina *Esteve, Spain.†*
Nitrendipine (p. 1456·3).
Hypertension; angina pectoris; Raynaud's syndrome.

Niprusodio *Fada, Arg.*
Sodium nitroprusside (p. 1497·1).
Hypertension.

Nipruss *UCB, Cz.; UCB, Ger.; Schwarz, Israel; Biofarma, Turk.*
Sodium nitroprusside (p. 1497·1).
Hypertension; controlled hypotension; heart failure; hypertensive crisis.

Niqero *Stasisport, Neth.*
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

NiQuitin *GSK, Arg.; GSK Consumer, Austria; GSK Consumer, Belg.; GSK, Braz.; Alza, China; GSK Consumer, Cz.; GSK Sante, Fr.; GSK Consumer, Ger.; GSK Consumer, Hung.; GSK Consumer, Irl.; GSK, Israel†; GSK Consumer, Ital.; GSK Consumer, Malaysia; GSK, Mex.; GSK Consumer, Neth.; GSK Consumer, Pol.; GSK Consumer, Port.; GSK Consumer, Rus.; GSK Consumer, Spain; GSK Consumer, Swed.; GSK Consumer, UK.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Niquitin *GSK, Singapore.*
Nicotine polacrilex (p. 2569·3).
Aid to smoking cessation.

NiQuitinminis *GSK Sante, Fr.*
Nicotine resinate (p. 2569·3).
Aid to smoking withdrawal.

Niraben *Samchully, Singapore.*
Nifuroxazide (p. 331·3).
Bacterial diarrhoea.

Nirapel *Ivax, Arg.*
Nitrendipine (p. 1456·3).
Hypertension.

Nirason N *Ravensberg, Ger.†*
Pentaerithrityl tetranitrate (p. 1465·1).
Ischaemic heart disease; myocardial infarction.

Niravam *Azur, USA.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Nircadel *Ratiopharm, Denm.†; Ratiopharm, Fin.†*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Nirmadil *Fahrenheit, Indon.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Nirmin *Zorka, Rus.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; controlled hypotension; pulmonary oedema.

Nirocef *Sel-J, Philipp.*
Cefdinir (p. 238·3).
Bacterial infections.

Nirolex Chesty Cough and Decongestant *Boots Healthcare, Irl.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion; catarrh.

Nirolex Chesty Coughs with Decongestant *Boots, UK.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Nirolex Day Cold & Flu *Boots Healthcare, Irl.; Boots, UK.*
⊗Paracetamol (p. 115·1); pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nirolex Dry Cough *Boots, UK.*
⊗Glycerol (p. 2517·2).
Coughs.

Nirolex Dry Cough and Decongestant *Boots Healthcare, Irl.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Nirolex Dry Coughs with Decongestant *Boots, UK.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Nirolex Night Cold & Flu *Boots, UK.*
⊗Paracetamol (p. 115·1); pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Niromylan *Mylan, Spain.†*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Niron Komplete *Eckson, USA.*
Iron (p. 2073·1); vitamins.
Dietary supplement.

Nirox
Note: this name may be used for preparations of different composition.
Gabriel, Gr.
Roxithromycin (p. 356·2).
Bacterial infections.

Nirvaxal *Teva, Israel.†*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Nervous gastrointestinal disorders.

Nisacalm *Mayoly-Spindler, Fr.†*
Thymol (p. 1772·2); salol (p. 129·3); menthol (p. 2553·2).
Minor burns.

Nisacne *Neiss, India.*
Clindamycin (p. 269·3); nicotinamide (p. 2083·1).
Acne.

Nisagon *Ifars, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Nisaid
Note: this name may be used for preparations of different composition.
Thebe, S.Afr.
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; inflammation; pain; gout.
Zwitter, Gr.
Oxaprozin (p. 112·3).
Inflammatory disorders.

Nisalgen *UCI, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Nisapulvol
Note: this name may be used for preparations of different composition.
Mayoly-Spindler, Fr.†; Mayoly-Spindler, Malaysia.
Benzyl hydroxybenzoate (p. 1756·3).
Pruritus.
Wing Wai, Hong Kong.†
Benzyl hydroxybenzoate (p. 1756·3); zinc oxide (p. 1729·1).

Nisaseptol *Mayoly-Spindler, Fr.†*
Benzyl hydroxybenzoate (p. 1756·3).
Pruritus.

Nisasol *Mayoly-Spindler, Fr.†*
Benzyl hydroxybenzoate (p. 1756·3).
Burn and wound disinfection.

Nisaxin *Tabuk, Cz.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia.

Nisba *Osmed, India.*
Nimesulide (p. 101·3).
Pain.

Nisba Plus *Osmed, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Niscamil *Loeffler, Mex.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Niscobal *Neiss, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Niscort *Neiss, India.*
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Nisdrol *Neiss, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nise *Reddy, India; Reddy, Rus.; Reddy, Ukr.*
Tablets: Nimesulide (p. 101·3).
Osteoarthritis; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nise Gel *Reddy, India.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); nimesulide (p. 101·3).

Nise-MR *Reddy, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Niser *Meridian, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Nisfollic *Neiss, India.*
Follicle-stimulating hormone (p. 2278·2).

Nisis *Ipsen, Fr.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Nisisco *Ipsen, Fr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nisita *Engelhard, Singapore.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1).
Nasal congestion; nasal dryness.

Nisivir *Neiss, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Niskacin *Neiss, India.*
Amikacin (p. 214·1).
Bacterial infections.

Niskinase *Neiss, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Nislev *Pharos, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Nislevo *Neiss, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Nislevo-MK *Neiss, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Nisley *Zodley, India.*
Granisetron (p. 1844·3).
Nausea and vomiting.

Nislutin *Neiss, India.*
Grape seed (p. 2521·3); green tea (p. 2648·2); lutein (p. 2079·2); lycopene (p. 2546·2).

Nismentin *Neiss, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Nismol *Neiss, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Nismol-S *Neiss, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nisoflan *Geolab, Braz.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Nisoftat *Armstrong, Mex.†*
Interferon alfa-2a (p. 989·2).
Hepatitis C; hairy-cell leukaemia; Kaposi's sarcoma; chronic myeloid leukaemia.

Nisolid *Chiesi, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; rhinitis.

Nisolon *CCM, Malaysia.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Nisolone *Psychotropics, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Nisoran *Aesculapius, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Nispam *Neiss, India.*
Pralidoxime chloride (p. 1571·1).
Organophosphorus poisoning.

Nispil *Sons, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Infected eye disorders.

Nispirome *Neiss, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Nispred *Neiss, India.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Nisshin Seirogan *Eng An, Hong Kong.†*
Creosote (p. 1659·3); phellodendron; geranium.
Cough.

Nistaglos *Andromaco, Chile.*
Halibut-liver oil (p. 2071·3); nystatin (p. 590·3); zinc oxide (p. 1729·1).
Fungal skin infections; nappy rash.

Nistagrand *Ahimsa, Arg.*
Nystatin (p. 590·3).
Fungal infections.

Nistagyn *Medley, Braz.†*
Nystatin (p. 590·3).
Vaginal candidiasis.

Nistaken *Kendrick, Mex.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Nistamed *Omedir, Arg.*
Nystatin (p. 590·3).
Fungal infections.

Nistan *Apotex, Mex.*
Nystatin (p. 590·3).
Fungal infections.

Nistaquim *Quimica y Farmacia, Mex.*
Nystatin (p. 590·3).
Fungal infections.

Nistat *Cevallos, Arg.*
Nystatin (p. 590·3).
Bacterial and fungal infections.

Nistatec *Royton, Braz.*
Nystatin (p. 590·3).
Vaginal candidiasis.

Nistatin *Prodotti, Braz.†*
Nystatin (p. 590·3).
Candidiasis.

Nistaval *Sanval, Braz.*
Nystatin (p. 590·3).
Candidiasis.

Nistear *Neiss, India.*
Carmellose (p. 2175·1).

Nistinol *Luar, Arg.†*
Nystatin (p. 590·3); tinidazole (p. 949·2).
Vaginal infections.

Nistomic *Cifarma, Braz.*
Nystatin (p. 590·3).
Vaginal candidiasis.

Nistoral *Laboratorios Chile, Chile.*
Nystatin (p. 590·3).
Candidiasis.

Nistrazin *Geolab, Braz.*
Nystatin (p. 590·3).
Vaginal candidiasis.

Nistrom *Neiss, India.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Nisufar *Elofar, Braz.*
Nimesulide (p. 101·3).

Nisuflex *Cazi, Braz.*
Nimesulide (p. 101·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nisulid *Ache, Braz.; Grunenthal, Chile; Psyco Remedies, India; Robapharm, Switz.*
Nimesulide (p. 101·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nisunate *Neiss, India.*
Artesunate (p. 648·2).
Malaria.

Nisural *Laboratorios Chile, Chile.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Nisyleen *VSM, Neth.*
Aconitum napellus (p. 2428·3); gelsemium sempervirens (p. 2511·2); ipecacuanha (p. 1667·2); phosphorus (p. 2589·2); bryonia alba; eupatorium perfoliatum (p. 2459·1); eucalyptus globulus (p. 2501·1).
Homoeopathic preparation.

Nisylen *DHU, Austria†; DHU, Ger.*
Aconitum (p. 2428·3); gelsemium (p. 2511·2); ipecacuanha (p. 1667·2); phosphorus (p. 2589·2); bryonia (p. 2461·3); eupatorium perfol. (p. 2459·1).
Homoeopathic preparation.

Nisyspray *VSM, Neth.*
Allium cepa (p. 2575·2); kalium iodatum (p. 2336·3); luffa operculata (p. 2545·3); pulsatilla pratensis (p. 2600·2); silicea (p. 2208·3).
Homoeopathic preparation.

Niszol *Neiss, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Nitacal *Nitin, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Nitacid *Darnitsa, Ukr.*
Sulfanilamide (p. 368·1); aminitrozole (p. 926·2).
Wounds; ulcers; burns; abscesses.

Nitacure *Alembic, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Nitagon *Cipla-Medpro, S.Afr.*
Permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2).
Pediculosis.

NiTaiMei *Si Bao, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Nitan *Rekah, Israel.†*
⊗Pemoline (p. 2328·2).
Attention deficit hyperactivity disorder; depression; fatigue.

Nita-O *Alembic, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Nitaquin *Utopian, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; rheumatoid arthritis; amoebiasis.

Nitarid *Cipla, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Nitastin *Novis, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Nitavan *Stadmed, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitaxim *Nitin, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Nitaxim-O *Nitin, India.*
Cefixime (p. 240·3).
Bacterial infections.

Nitazet *Glenmark, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Nitazet-O *Glenmark, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).
Diarrhoea.

Nitdin *Lupin, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Nitdin-TZ *Lupin, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).

Nite Time Cold Formula *Barre-National, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Coughs and cold symptoms.

Nitecall *Adcock Ingram, S.Afr.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Niteherb *MedicHerb, UK.*
Valerian (p. 2640·2).
Sleep disturbances.

Niteherb Plus *MedicHerb, UK.*
Valerian (p. 2640·2); passion flower (p. 2584·1).
Sleep disturbances.

Niten *Ivax, Arg.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Niten D *Ivax, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nitens *Crinos, Ital.*
Naproxen cetrimonium (p. 98·2).
Mouth and throat disorders.

Nitepax *Aspen Consumer, S.Afr.*
Noscapine resin complex (p. 1670·3).
Cough.

Niterey *Pharmatrix, Arg.*
Tretinoin (p. 1725·2).
Light-induced skin damage; keratinisation disorders; rosacea.

Nitetime Cold Medicine *Jamp, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Nitexol *Andromaco, Chile.*
Duloxetine hydrochloride (p. 415·1).
Depression.

Nithiodote *Hope, USA.*
Sodium nitrite (p. 1574·3); sodium thiosulfate (p. 1576·1).
Cyanide poisoning.

Nithra *East West, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitical *Nitin, India.*
Calcium (p. 1783·1); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).

Nitidex *Ivax, Arg.*
Duloxetine.
Depression; neuropathic pain; anxiety; fibromyalgia.

Nitigraf *Juste, Spain.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Nitin *Profic Organic, India.*
Ranitidine (p. 1882·1),.
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; acid aspiration; dyspepsia.

Nitipime *Nitin, India.*
Cefepime (p. 239·2).
Bacterial infections.

Nitised *Petsiavas [Πετσιαβας], Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Nitizest *Nitin, India.*
Capsules: Folic acid (p. 2063·1); iron (p. 2073·1); zinc (p. 2126·1).

Nitin, India.
Syrup: Iron (p. 2073·1); selenium (p. 2086·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); zinc (p. 2126·1).

Nitlor *BMW, India.*
Ornithine aspartate (p. 2085·2).

Nitlor Plus *BMW, India.*
Ornithine aspartate (p. 2085·2); silymarin (p. 1561·2).

Nitlotion *Shantys, UK.*
Coconut oil (p. 2179·3).
Pediculosis.

Nit-N-Mite *Ipca, India.†*
Lotion: Lindane (p. 2157·1).
Pediculosis; scabies.

Nitocin *Nitin, India.*
Oxytocin (p. 2143·1).
Postpartum haemorrhage; labour induction; evaluation of fetal distress; termination of pregnancy.

Nitoliv *Biomax, India.*
Ornithine aspartate (p. 2085·2); silymarin (p. 1561·2).

Nitoman *Valeant, Canad.; Medilink, Denm.; Temmler, Ger.; Lundbeck, Irl.; UCB, Port.; UCB, Spain.*
Tetrabenazine (p. 2627·3).
Chorea; drug-induced extrapyramidal disorders; hyperkinetic movement disorders; Huntington's chorea.

Niton *Labesfal, Port.*
Nimodipine (p. 1455·2).

Nitopro *Maruishi, Jpn.*
Sodium nitroprusside (p. 1497·1).
Hypertension.

Nitorol *Eisai, Jpn.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction; ischaemic heart disease.

Nitossil *Novartis Consumer, Ital.*
Cloperastine fendizoate (p. 1659·2).
Cough.

Nitozol *Korea Pharma, Singapore.*
Ketoconazole (p. 585·3).
Dandruff.

Nitpep *Nitin, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Nitpep-D *Nitin, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).

Nitpirome *Nitin, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Nitra *Micro, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Nitracor *Pliva Krakow, Pol.*
Glyceryl trinitrate (p. 1391·2).
Unstable angina; myocardial infarction; pulmonary oedema; hypertensive crisis; controlled hypotension.

Nitra-Dent *Micro, India.*
Benzalkonium chloride (p. 1737·1); choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).

Nitradisc *Pfizer, Arg.; Pfizer, Braz.; Pfizer, Mex.; Pfizer, Port.; Pfizer, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrados *Douglas, NZ; Douglas, Singapore; Douglas, Thai.*
Nitrazepam (p. 1089·1).
Epilepsy; insomnia; infantile spasm.

Nitra-Hex *Micro, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Nitraket *Chiesi, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitra-Met *Micro, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).

Nitramin *Coup, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Nitrangin *Actavis, Ger.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; coronary spasm.

Nitra-OR *Micro, India.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).

Nitrapan *Cristalia, Braz.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitravet *Anglo-French Drugs, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitraz *Triton, India.*
Nitrazepam (p. 1089·1).
Insomnia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nitrazadon *Valeant, Canad.*
Nitrazepam (p. 1089·1).
Insomnia; epilepsy.

Nitrazepol *Farmasa, Braz.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitregamma *Worwag, Ger.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrek *Bertek, USA.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitren
Note: this name may be used for preparations of different composition.
Wockhardt, India.
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction.

Nitren Lich *Winthrop, Ger.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrencord *Biosintetica, Braz.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrendidoc *Docpharm, Ger.†*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrendil *Bago, Arg.; Elmor, Venez.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrendilat *SM, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrensal *TAD, Ger.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrepin *USV, India.*
Nitrendipine (p. 1456·3).

Nitrepress *Hexal, Cz.; Hexal, Ger.†*
Nitrendipine (p. 1456·3).
Hypertension.

Nitre-Puren *Actavis, Ger.†*
Nitrendipine (p. 1456·3).
Hypertension.

Nitresan *ProMed, Cz.*
Nitrendipine (p. 1456·3).
Hypertension.

Nitrest *Sun, India; Sun, Mex.; Sun, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia; sleep disorders.

Nit-Ret *Zentiva, Cz.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; coronary spasm; heart failure.

Nitriate *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Sodium nitroprusside (p. 1497·1).
Hypertensive crisis; controlled hypotension; heart failure.

Nitridazol *HLB, Arg.*
Itraconazole (p. 583·3).
Fungal infections.

Nitriderm TTS *Novartis, Fr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitriga *Indo French, India.*
Arginine (p. 2049·1).

Nitril *Claris, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Nitrilan *Biomedica, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Nitrileno *Libbs, Braz.*
⊗Nitrofurazone (p. 333·1); naphazoline hydrochloride (p. 1669·3).
Nasal disorders.

Nitro
Note: this name may be used for preparations of different composition.
AstraZeneca, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Orion, Fin.; Orion, Rus.; Orion, Ukr.
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; heart failure; controlled hypotension; left ventricular dysfunction; pulmonary oedema; hypertension.

Nitro Carino *Carinopharm, Ger.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; heart failure.

Nitro Mack *Pfizer, Austria†; Galenica, Gr.; Mack, Hong Kong†; Zuoz, Venez.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; pulmonary hypertension; myocardial infarction.

Nitro Pohl *Pohl, Austria; Pohl, Cz.; Merck Serono, Hung.; Pohl-Boskamp, Hung.; Pohl, Neth.*
Glyceryl trinitrate (p. 1391·2).
Myocardial infarction; heart failure; angina pectoris; hypertension; controlled hypotension; hypertensive crisis.

Nitro-Bid
Note: this name may be used for preparations of different composition.
Savage, USA.
Glyceryl trinitrate (p. 1391·2).
Perioperative hypertension; heart failure; angina pectoris; controlled hypotension.

Nitrocalm *Symbiosis, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitrocard *Chema-Elektromet, Pol.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; peripheral vascular disorders.

Nitrocerin *Elvipe, Gr.; Intra-Labs, India.*
Glyceryl trinitrate (p. 1391·2).
Heart failure; angina pectoris.

Nitrocin *Samarth, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nitrocine *Jenahexal, China; GSK, Hong Kong; Pharos, Indon.†; UCB, Indon.†; UCB, Irl.; Schwarz, Israel; GSK, Malaysia; GSK, S.Afr.; GSK, Singapore; Schwarz, Thai.†; UCB, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; controlled hypotension; heart failure; unstable angina; control of blood pressure and myocardial ischaemia during cardiovascular surgery; pulmonary oedema; hypertension.

Nitrocontin *Modi-Mundipharma, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrocor *3M, Chile†; Recordati, Ital.; Farmstandart, Rus.; Troika, Venez.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; hypertensive crisis; myocardial infarction.

Nitrocure *Panacea, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nitroday *Invision, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Nitrodent-K *Nitro Organics, India.*
⊗Potassium nitrate (p. 1766·2).

Nitrodent-KF *Nitro Organics, India.*
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).

Nitrodent-R *Nitro Organics, India.*
Sodium monofluorophosphate (p. 2091·3); zinc sulfate (p. 2126·2).

Nitroder *Keton, Mex.*
Glyceryl trinitrate (p. 1391·2).

Nitro-Derm *Revabuen, USA.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitroderm *Novartis, Austria; Novartis, Belg.; Novartis, Chile; Novartis, Malaysia; Novartis, NZ; Novartis, Pol.; Novartis, Spain; Novartis, Thai.; Novartis, Venez.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; prophylaxis of phlebitis and extravasation.

Nitroderm TTS *Novartis, Arg.; Novartis, Braz.; Novartis, Ger.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Port.; Novartis, Switz.; Novartis, Turk.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; prevention of phlebitis and extravasation.

Nitrodisc *Roberts, USA.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrodom *Dominguez, Arg.*
Glyceryl trinitrate (p. 1391·2).
Anal fissure; haemorrhoids.

Nitro-Dur *Schering-Plough, Arg.; MSD, Austral.; Ebewe, Austria†; Merck, Canad.; Schering-Plough, Hong Kong†; Schering-Plough, Hung.; MSD, Irl.; Sigma-Tau, Ital.; Schering-Plough, Mex.; MSD, Neth.; Schering-Plough, Norw.; Schering-Plough, Port.; MSD, Spain; MSD, Switz.; Schering-Plough, UK; Key, USA.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Nitrodyl *Lavipharm, Gr.; MSD, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Nitrofast *Taj, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nitrofen *Teuto, Braz.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nitrofix
Note: this name may be used for preparations of different composition.
Arafarma, Spain.
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Micro, India.
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Nobel, Turk.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Nitrofix-AS *Micro, India.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction.

Nitrofungin *Ivax, Rus.*
Chloronitrophenol.
Fungal skin infections.

Nitrofungin Neo *Teva, Ukr.†*
2-Aminotridecane undecenoate.
Fungal skin infections.

Nitrofur-C *Leiras, Fin.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Nitrogard *Forest Pharmaceuticals, USA.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrogesic *Troikaa, India.*
Glyceryl trinitrate (p. 1391·2).
Anal fissures.

Nitroglyn *United Biotech, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nitrogranulong *Farmstandart, Rus.; Shchelkovskii, Rus.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction.

Nitrogray *Gray, Arg.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitroina *Teofarma, Spain.*
Acetic acid (p. 2426·3); greater celandine (p. 2522·2); salicylic acid (p. 1719·1); iodine tincture (p. 2336·3); thuja (p. 2629·3).
Warts.

Nitroject *Omega, Canad.; Sun, India; Sun, Rus.; Sun, Thai.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; unstable angina; pulmonary oedema; hypertension; controlled hypotension.

Nitrokaf *Kimia, Indon.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrol
Note: this name may be used for preparations of different composition.
Paladin, Canad.
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

GSK Sante, Fr.†
Celandine (p. 2522·2); thuja (p. 2629·3); iodine (p. 2336·3); salicylic acid (p. 1719·1); glacial acetic acid (p. 2426·3).
Warts.

Nitrolife *Life Medicare, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Nitrolingual *Sanofi-Aventis, Austral.; Pohl, Austria; Tramedico, Belg.; Sanofi-Aventis, Canad.; Health Vision, China; Pohl, Denm.; Pohl, Ger.; IFET (ΙΦΕΤ), Gr.; Lavipharm, Gr.; Niadas, Gr.; Pohl, Hong Kong; Merck Serono, Hung.; Pohl-Boskamp, Hung.; Modi-Mundipharma, India†; Merck Serono, Irl.; Pohl, Israel; Pohl, Neth.; Pohl, Norw.; Douglas, NZ; Pohl-Boskamp, Philipp.; Merck, S. Afr.; Pohl-Boskamp, Singapore; Pohl-Boskamp, Swed.; Lubapharm, Switz.; Farma-Tek, Turk.†; Merck, UK; Sciele, USA.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; heart failure; ischaemic heart disease; hypertensive crisis; biliary colic; pulmonary oedema; smooth muscle spasm; coronary spasm; controlled hypotension.

Nitrolingual protect *Pohl, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

NitroMed *Omedir, Arg.*
Nitrofurazone (p. 333·1).
Bacterial skin infections.

Nitromex *Actavis, Denm.†; Actavis, Fin.†; Actavis, Norw.†; Actavis, Swed.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitromidager *Streger, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis.

Nitromin *Egis, Irl.†; Teva, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitromint *Egis, Cz.; Egis, Hung.; Egis, Pol.; Quilaban, Port.; Egis, Rus.; Egis, Thai.; Egis, Ukr.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; coronary artery spasm.

NitroMist *Akrimax, USA.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitron *Nitin, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Nitronal *Pohl-Boskamp, Fr.; IFET (ΙΦΕΤ), Gr.; Merck, Irl.†; Douglas, NZ; Pohl-Boskamp, Philipp.; Lubapharm, Switz.†; Farma-Tek, Turk.; Merck, UK.*
Glyceryl trinitrate (p. 1391·2).
Heart failure; myocardial infarction; controlled hypotension; coronary artery spasm; angina pectoris; hypertensive crisis; hypertension and myocardial ischaemia during and after cardiac surgery.

Nitrong *Lavipharm, Gr.; KRKA, Rus.; KRKA, Ukr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; heart failure.

Nitropenton *Egis, Hung.†*
Pentaerithrityl tetranitrate (p. 1465·1).
Angina pectoris.

Nitroplast *Lacer, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitroplus *Neon, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nitropohl *Tramedico, Belg.†*
Glyceryl trinitrate (p. 1391·2).

Nitropresabbott *Abbott, Braz.*
Sodium nitroprusside (p. 1497·1).
Hypertension.

Nitropress *Hospira, USA.*
Sodium nitroprusside (p. 1497·1).
Hypertensive crisis; controlled hypotension.

Nitroprin *Life Medicare, India.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction.

Nitro-pro *Elan, USA.*
Lactose-free, gluten-free preparation for enteral nutrition.

Nitroprus *Scott-Cassara, Arg.; Cristalia, Braz.*
Sodium nitroprusside (p. 1497·1).
Hypertension.

Nitroprussiat *Rottapharm, Spain.*
Sodium nitroprusside (p. 1497·1).
Hypertension; controlled hypotension.

NitroQuick *Ethex, USA.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitroretard *Faran, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Nitrosid *Orion, Fin.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction; heart failure.

Nitrosol *Shree Ganesh, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

Nitrosorbide *Lusofarmaco, Ital.*
Isosorbide dinitrate (p. 1412·2).
Cardiac disorders.

Nitrosorbon *Pohl, Ger.†; Pohl-Boskamp, Philipp.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Nitrospray *Farmstandart, Rus.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrostat *Pfizer, Canad.; Pfizer, China; Pfizer, Philipp.; Parke, Davis, USA.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrosun *Sun, India; Sun, Rus.*
Nitrazepam (p. 1089·1).
Insomnia; sleep disorders; premedication; encephalopathy.

Nitrosylon *Lavipharm, Gr.; Abbott, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrosym *Symbiosis, India.*
Nitrazepam (p. 1089·1).
Insomnia.

Nitro-Time *Time-Cap, USA.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Nitrotoin *Faran, Gr.*
Nitrofurantoin (p. 332·1).

Nitrovas *Aurobindo, India.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Nitroven *Pohl, Norw.*
Glyceryl trinitrate (p. 1391·2).
Unstable angina; heart failure; blood pressure control during cardiac surgery.

Nitrovir *Chandra Bhagat, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; hypertension and induction of hypotension during surgery.

5-Nitrox *Balkanpharma, Rus.†*
Nitroxoline (p. 333·2).
Urinary antiseptic.

Nitrumon *IFET (ΙΦΕΤ), Gr.; Cetin, Turk.*
Carmustine (p. 761·2).
Malignant neoplasms.

Nittyfor *Teva, Rus.; Teva, Ukr.*
Permethrin (p. 2159·3).
Pediculosis.

Nitux *Zambon, Switz.*
Morclofone (p. 1669·2).
Cough.

Nitzix *Aamorb, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Nitzix-O *Aamorb, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Nitzole *Nitin, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Nitzole-D *Nitin, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Niu Ke Te *Wanze, China.*
Aspirin zinc.

Niu Quan Li *Nutricia, China.*
Preparation for enteral nutrition.

Niuliva *Grifols, Spain.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Niux *Cassara, Arg.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Nivabétol *Dexo, Fr.†*
Betaine (p. 2456·1); acetylmethionine (p. 1558·2); sorbitol (p. 2092·1).
Dyspepsia; constipation.

Nivadil *Dolorgiet, Ger.; Astellas, Irl.; Astellas, Jpn; Menarini, Port.*
Nilvadipine (p. 1455·2).
Hypertension.

Nivador *Wellcome, Spain.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Nivagin *TP, Thai.†*
Dipyrone (p. 53·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Pain; fever.

Nivalen *Help, Gr.*
Diazepam (p. 1063·2).

Nivalin *Sopharma, Pol.; Sopharma, Rus.; Sopharma, Ukr.*
Galantamine hydrobromide (p. 391·3).
Reversal of competitive neuromuscular blockade; smooth muscle atony; neuromuscular disorders; Alzheimer's disease; nocturnal enuresis; impotence.

Nivant *Zydus, India.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Nivaquine *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Neth.; Aventis, NZ†; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Switz.; Beacon, UK.*
Chloroquine sulfate (p. 650·2).
Malaria; rheumatoid arthritis; lupus erythematosus; light-sensitive skin conditions; hepatic amoebiasis; giardiasis.

Sanofi-Aventis, Arg.
Chloroquine (p. 650·1).
Lupus erythematosus; malaria; rheumatoid arthritis; light-sensitive skin disorders.

Nivaquine-P *Piramal, India.*
Chloroquine phosphate (p. 650·1).
Malaria; hepatic amoebiasis; rheumatoid arthritis; lupus erythematosus.

Nivas
Note: this name may be used for preparations of different composition.
Raffo, Arg.
Nimodipine (p. 1455·2).
Cerebrovascular disorders; neurological deficit following subarachnoid haemorrhage; Alzheimer's disease.

Tecnofarma, Chile.†
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Nivas Plus *Raffo, Arg.*
Nimodipine (p. 1455·2); citicoline (p. 2480·1).
Cerebrovascular disorders.

Nivate-NC *Nitin, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).

Nivea *Beiersdorf, USA.*
A range of emollient, cleansing, and moisturising preparations.

Nivea Lip Care *Beiersdorf, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Nivea Sun *Beiersdorf, USA.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); ensulizole (p. 1703·1).
Sunscreen.

Nivea Visage Q10 Advanced Wrinkle Reducer *Beiersdorf, Canad.†*
Avobenzone (p. 1695·1); ensulizole (p. 1703·1).
Sunscreen.

Nivelan N *Lafedar, Arg.*
Alprazolam (p. 1035·2).
Anxiety.

Nivelipol *Temis, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Nivemycin *IFET (ΙΦΕΤ), Gr.; Sovereign, UK.*
Neomycin sulfate (p. 330·1).
Bacterial infections; bowel preparation; hepatic coma.

Nivestim *Hospira, Austral.; Hospira, Austria; Hospira, Cz.; Hospira, Denm.; Hospira, Fr.; Hospira, Ger.; Hospira, Gr.; Hospira, Irl.; Hospira, Neth.; Hospira, Norw.; Hospira, Pol.; Hospira, Port.; Hospira, Spain; Hospira, Swed.; Hospira, UK.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Nivetril *Nafar, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Nivicof *Medhaus, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Nivitron *Coup, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Nivoflox *Grunenthal, Port.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Nix *Omega, Belg.; GSK Consumer, Canad.; Insight, Canad.; ACO Hud, Denm.; ACO Hud, Fin.; Omega, Gr.; Chefaro, Ital.; ACO Hud, Norw.; Chefaro, Port.; GSK, Rus.; ACO Hud, Swed.; Insight, USA.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Nixacid *Sandoz, Swed.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Nixcort *Biochemix, India.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Nixelaf-C *Bruluagsa, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Nixema *Mekos, Denm.†; Mekos, Neth.†*
A range of allergen extracts (p. 2434·3).
Diagnosis of allergic contact dermatitis.

Nixia *Wanbury, India.*
Tizanidine (p. 2026·2).
Spasticity; skeletal muscle spasm.

Nixin *Mepha, Braz.†; Mepha, Port.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Nixo *Huashin, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Nixoderm *Nixoderm, Malaysia; Royce, Singapore.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Skin disorders; ringworm.

Nixol *Filaxis, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Nixoran *Roemmers, Arg.*
Nitazoxanide (p. 942·2).
Worm infections; protozoal infections.

Nixotinex *Homeocan, Canad.*
⊗Capsules, tabacum (p. 2632·2); nicotinum (p. 2569·3); ignatia (p. 2532·1); lobelia (p. 2323·2); caladium; gelsemium (p. 2511·2); argentum nitricum (p. 2615·3); cocculus (p. 2483·1); oral drops, thuja (p. 2629·3); carduus marianus (p. 1561·1); juniperus communis (p. 2537·1); betula alba (p. 2457·3).
Homoeopathic preparation.

Nixtensyn *Kramer, Philipp.*
Diazepam (p. 1063·2).
Anxiety; delirium tremens; musculoskeletal spasm; spasticity.

Nixyn *Teofarma, Spain.*
Capsules; suppositories: Isonixin (p. 78·3).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

Teofarma, Spain.
Cream: Isonixin (p. 78·3); methyl salicylate (p. 92·1).
Peri-articular and soft-tissue disorders.

Niyat *Abbott, India.*
Atorvastatin (p. 1309·2); nicotinic acid (p. 2083·1).

Nizac *Aspen, Austral.*
Nizatidine (p. 1866·1).
Gastro-oesophageal reflux; peptic ulcer.

Nizacol *PS, Ital.*
Miconazole (p. 588·3).
Fungal infections.

Nizale *Janssen, Port.*
Ketoconazole (p. 585·3).
Fungal infections.

Nizamyl *Novag, Mex.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Nizapas-MD *Daniel Pasteur, India.*
Nimesulide (p. 101·3).
Pain.

Nizapas-MR *Daniel Pasteur, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Nizapas-P *Daniel Pasteur, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nizapas-SP *Daniel Pasteur, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Niza-Spas *Daniel Pasteur, India.*
Dicycloverine (p. 1834·2); nimesulide (p. 101·3).

Nizax *Teofarma, Ital.*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Nizaxid *Lafi, Chile; Norgine, Fr.; Prospa, Port.†*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Nizcreme *Janssen-Cilag, S.Afr.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Nizer *USV, India.*
Nimesulide (p. 101·3) or nimesulide betadex (p. 101·3).
Osteoarthritis; pain; sprains; tendinitis.

USV, Ukr.†
Nimesulide (p. 101·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); capsaicin (p. 35·1).
Musculoskeletal, joint, soft tissue, and peri-articular disorders; painful disorders.

Nizi *FDC, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).
Musculoskeletal and joint disorders.

Nizin-V *Andromaco, Mex.*
Nystatin (p. 590·3).
Vulvovaginal candidiasis.

Niziran *Crisdy-Na, Philipp.*
Cinnarizine (p. 622·1).
Atherosclerosis; cerebrovascular disorders; Ménière's disease; motion sickness.

Nizithro *Neiss, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Nizla *Scoshia, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Nizla Plus *Scoshia, India.*
Ambroxol (p. 1654·3); levocetirizine hydrochloride (p. 632·3); paracetamol (p. 115·1).

Nizo *Daksh, India.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Nizocef *USP, India.*
Cefixime (p. 240·3).
Bacterial infections.

Nizoclav *USP, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Nizod *Acekinetic, India.*
Hydroxyzine (p. 630·3).
Anxiety; pruritus; premedication; sedative.

Nizodox *USP, India.*
Cefpodoxime.
Bacterial infections.

Nizol *Intas, India; Pyridam, Indon.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; fungal infections.

Nizole *Hovid, Hong Kong†; Hovid, Singapore.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Nizolex *Yung Shin, Philipp.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Nizonazol *Hertz, Braz.*
Ketoconazole (p. 585·3).

Nizonide *Lupin, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Nizonide-O *Lupin, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Nizoral *Janssen-Cilag, Austral.; Johnson & Johnson, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Johnson & Johnson, Canad.; Xian-*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Janssen, China; Janssen-Cilag, Cz.; McNeil, Denm.; Janssen-Cilag, Fin.; Orion, Fin.; Janssen-Cilag, Fr.†; McNeil, Ger.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Johnson & Johnson, Hung.; Janssen-Cilag, Indon.; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Johnson & Johnson, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Johnson & Johnson, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Johnson & Johnson, Thai.; Johnson & Johnson, Turk.; Janssen-Cilag, UK; McNeil, UK; McNeil, Ukr.; McNeil Consumer, USA; Janssen-Cilag, Venez.
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis; dandruff.

Nizoral Cool *Janssen-Cilag, Thai.*
Ketoconazole (p. 585·3); menthol (p. 2553·2).
Fungal skin infections; seborrhoeic dermatitis.

Nizorelle *Janssen-Cilag, S.Afr.†*
Ketoconazole (p. 585·3).
Dandruff.

Nizoretic *Kinder, Braz.†*
Ketoconazole (p. 585·3).
Fungal infections.

Nizotrax *USP, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Nizotrax-S *USP, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Nizovules *Janssen-Cilag, S.Afr.†*
Ketoconazole (p. 585·3).
Vaginal candidiasis.

Nizox *Grandix, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Nizox-MR *Grandix, India.*
Tizanidine (p. 2026·2); valdecoxib (p. 141·3).

Nizral *Johnson & Johnson, India.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Nizshampoo *Johnson & Johnson, S.Afr.*
Ketoconazole (p. 585·3).
Pityriasis versicolor; pityriasis capitis; seborrhoeic dermatitis.

Nizuil *Multilab, Braz.*
Nimesulide (p. 101·3).

Nizurin *Collins, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

NKCef *NK, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

NKCef+S *NK, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

NKCefta *NK, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

NKH Anamix *Nutricia, Cz.*
Food for special diets.
Hyperglycinaemia.

NKZone *NK, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

NL-33 *Morinaga, Indon.*
Infant feed.
Lactose intolerance; galactosaemia.

N-Labstix *Bayer Diagnostics, UK.*
Test for glucose, protein, pH, ketones, blood, and nitrites in urine.

Bayer Diagnostics, Irl.†
Test for glucose, protein, pH, ketones, blood, and nitrite in urine.

N-Lid *Orchid, India.*
Nimesulide (p. 101·3).
Pain.

NM Power *Cadila, India.*
Norfloxacin (p. 333·3); metronidazole (p. 936·1).
Bacterial infections; protozoal infections.

NMD *Grandix, India.*
Nimesulide (p. 101·3).
Pain.

N-Meedia *Nortech, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); vitamin C (p. 2110·3).

N-Multistix SG *Bayer Diagnostics, Irl.†; Bayer Diagnostics, UK.*
Test for specific gravity, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and pH in urine.

NMX *Biomax, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

No 0 *Double-Crane, China.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3); dihydralazine sulfate (p. 1358·3); reserpine (p. 1485·3).
Hypertension.

No 440 *Herbes Universelles, Canad.†*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

No Blos For *Akums, India.*
Etamsylate (p. 1145·2); mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

No Doz *Key, Austral.*
Caffeine (p. 1203·3).
Fatigue.

No Doz Plus *Key, Austral.*
Caffeine (p. 1203·3); vitamin B substances (p. 2102·3); glucose (p. 2068·3).
Fatigue.

No Drowsiness Sinarest *Ciba, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

No Gas Enzimi *Giuliani, Ital.*
Alpha galactosidase (p. 2437·2); tilactase (p. 2631·2); ginger (p. 1844·1); passion flower (p. 2584·1); chamomile (p. 2474·1).
Gastrointestinal gas.

No Pain-HP *Young Again Nutrients, USA.*
Capsaicin (p. 35·1).
Pain.

No Pic *Gebro, Switz.*
Lidocaine hydrochloride (p. 1988·2); diphenhydramine hydrochloride (p. 626·2); benzalkonium chloride (p. 1737·1); levomenthol (p. 2553·2); dexpanthenol (p. 2582·2).
Insect bites; skin irritation; burns; allergic skin disorders.

No Shot *Kolex, Hung.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Noacid
Note: this name may be used for preparations of different composition.
Egis, Hung.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Egis, Pol.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

OBA, Denm.
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Gastro-oesophageal reflux.

Noacid Diates *Provefarma, Arg.†*
Liquorice (p. 1853·2); calcium (p. 1783·1); magnesium (p. 1786·3).
Dietary supplement.

Noah Smearing Film *Nipro, China.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Noal-LC *Intel, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Noal-LM *Intel, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Noalzy *NB, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Noalzy Plus *NB, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Noameba-DS *Ipca, India.†*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis.

Noan *Farmasa, Braz.; Teofarma, Ital.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Noax *CSC, Cz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Noax 3 *AF, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Noax Uno *CSC, Austria; CSC, Pol.*
Tramadol hydrochloride (p. 139·2).
Pain.

Nobactam *Microsules, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Nobactam Bronquial *Microsules, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Nobactam Clavulanico *Microsules, Arg.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Nobacter *Eucerin, Fr.*
A range of skin cleansers containing triclocarban (p. 1773·2) or triclosan (p. 1773·2).

Nobateks *Nobel, Turk.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Nobaxin *Lek-Am, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Nobecid *Nobel, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Nobel, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Nobel *Mankind, India.*
Tablets: Nimesulide betadex (p. 101·3).
Pain.

Mankind, India.
Topical gel: Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Nobel Plus *Mankind, India.*
Paracetamol (p. 115·1); nimesulide betadex (p. 101·3).
Pain.

Nobel Spas *Mankind, India.*
Injection: Diclofenac sodium (p. 48·3); fenpiverinium bromide (p. 2504·1); pitofenone hydrochloride (p. 2592·2).

Mankind, India.
Tablets: Nimesulide (p. 101·3); drotaverine (p. 2497·3).
Smooth muscle spasm and pain.

Nobel-MR *Mankind, India.*
Nimesulide betadex (p. 101·3); paracetamol (p. 115·1); tizanidine (p. 2026·2).

Noben *Binnofarm, Rus.*
Idebenone (p. 392·3).
Cerebrovascular disorders; mental function disorders.

Nobese
Note: this name may be used for preparations of different composition.
Benmoon, India.
Punarnava (p. 2601·1); fenugreek (p. 2504·1).

Getz, Philipp.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Nobese No. 1 *Adcock Ingram, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Nobex *Bioway, China.*
Mouse nerve growth factor.
N-Hexane induced peripheral neuropathy.

Nobiretic *Menarini, Belg.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nobiten *Menarini, Belg.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Noble Formula *Ontos, USA.*
Pyrithione zinc (p. 1718·1).
Hyperkeratotic skin disorders.

Noble Formula HC *Ontos, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Noblifen *Mint, India.*
Mefenamic acid (p. 85·3); tranexamic acid (p. 1164·2).

Nobligan *Nycomed, Arg.; Grunenthal, Austria; Grunenthal, Denm.; Abbott, India; Janssen-Cilag, Mex.; Pisa, Mex.; Grunenthal, Norw.; Grunenthal, Port.; Janssen-Cilag, S.Afr.; Andromaco, Spain†; Grunenthal, Swed.; Grunenthal, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Noboyle *Neiss, India.*
Fusidic acid (p. 302·1).
Skin infections.

Nobrec *Medico Uno, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Nobritol *Kern, Spain.*
Amitriptyline hydrochloride (p. 401·1); medazepam (p. 1083·2).
Anxiety; depression.

Nobrium *Teva, Hung.†*
Medazepam (p. 1083·2).
Anxiety disorders.

Nobucaine *LBS, Philipp.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; ventricular arrhythmias.

Noc
Note: this name may be used for preparations of different composition.
Lafi, Chile.
Apomorphine hydrochloride (p. 892·3).
Erectile dysfunction.

Orchid, India.
Fluoxetine (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Nocad *Abbott, India.*
Thioctic acid (p. 2629·1); chromium (p. 2055·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); selenium (p. 2086·3).

No-Calm *Ni-The, Gr.*
Levomepromazine maleate (p. 1079·3).

Nocarex *Pisa, Mex.†*
Nalmefene hydrochloride (p. 1562·1).
Opioid antagonist.

Nocasio *Nitec, Port.†*
⊗Prednisone (p. 1647·2).
Rheumatoid arthritis.

Nocazin *Alpharma, Mex.*
Isoconazole nitrate (p. 583·2).
Fungal skin and nail infections.

Nocedan *Avansor, Fin.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Nocertone *Sanofi-Aventis, Belg.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.*
Oxetorone fumarate (p. 678·1).
Migraine; cluster headache.

Nociclin *EMS, Braz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Nocid
Note: this name may be used for preparations of different composition.
Biolink, Philipp.; Farmaline, Thai.
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kalbe, Indon.
Amino acids.
Dietary supplement in protein restriction.

Noclog *Neiss, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Noclog-EZ *Neiss, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

No-Clot *Elfin, India.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Nocold *Cipla, India.*
Oral drops; sustained-release capsules; syrup: Phenylpropanolamine (p. 1674·1); chlorphenamine (p. 620·3).
Cold symptoms.

Cipla, India.
Tablets: Paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms.

Nocold Plus *Cipla, India.*
Syrup: Paracetamol (p. 115·1); sodium citrate (p. 1781·2); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Cipla, India.
Tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms.

Nocovit *Neiss, India.*
Vitamins.

Nocpaz *Sanitas, Chile.†*
Doxylamine succinate (p. 627·3).
Insomnia.

Noctacalm *Socobom, Belg.†*
Lormetazepam (p. 1082·1).
Sleep disorders.

Noctaderm *Ranbaxy, India.*
Doxepin (p. 414·2).

Noctal
Note: this name may be used for preparations of different composition.
Abbott, Braz.
Estazolam (p. 1072·2).
Insomnia.

Noctamid *Bayer, Austria; Bayer, Belg.; Bayer, Ger.; Bayer, Gr.; Bayer, Irl.; Bayer, Neth.; Bayer, NZ; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Switz.*
Lormetazepam (p. 1082·1).
Sleep disorders; premedication; insomnia.

Noctamide *Bayer, Fr.*
Lormetazepam (p. 1082·1).
Insomnia.

Noctaval *Sigma, Braz.; Biomedica, Ital.*
Valerian (p. 2640·2).
Nervous disorders; insomnia; anxiety.

Nocte *Bago, Arg.; Armstrong, Mex.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Noctel *Intel, India.*
Injection: Diclofenac (p. 48·3).
Inflammation; pain.

Intel, India.
Ointment: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Noctiden *Biolab Sanus, Braz.*
Zolpidem (p. 1116·2).
Insomnia.

Noctilan *Boehringer Ingelheim, Chile.*
Brotizolam (p. 1042·1).
Insomnia.

Noctin *PC India, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Noctis *Bouty, Ital.*
Valerian (p. 2640·2); passion flower (p. 2584·1); crataegus (p. 2488·1).
Sleep disorders.

Noctissin *Actavis, Pol.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

Noctium *Ferrier, Fr.*
Coffea cruda (p. 2648·2); cypripedium pubescens; jalapa (p. 1850·1); stramonium (p. 2622·3).
Homoeopathic preparation.

Noctofer *Polfa Tarchomin, Pol.*
Lormetazepam (p. 1082·1).
Sleep disorders.

Nocton *Saval, Chile.*
Lormetazepam (p. 1082·1).
Sleep disorders.

Noctor *Torrex, Austria.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; sedative.

Noctran *Menarini, Fr.†*
Dipotassium clorazepate (p. 1056·3); acepromazine (p. 1035·1); acepromet azine (p. 1035·2).
Insomnia.

Noctura
Note: this name may be used for preparations of different composition.
Nelson, UK.
Kali brom (p. 2461·1); coffea (p. 2648·2); passiflora (p. 2584·1); avena sativa (p. 2451·1); alfalfa (p. 2433·1); valeriana (p. 2640·2).
Homoeopathic preparation.

Recalcine, Chile.
Midazolam (p. 1085·1).
Hypnotic.

Nocturin
Note: this name may be used for preparations of different composition.
Elder, India.
Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity.

Ferring, Ger.
⊗Desmopressin acetate (p. 2355·1).
Polyuria; polydipsia; nocturnal enuresis; diabetes insipidus.

Nocturno *Trima, Israel.*
Zopiclone (p. 1118·1).
Insomnia.

Noctyl *Merck Medication Familiale, Fr.*
Doxylamine succinate (p. 627·3).
Insomnia.

Noculi *Ranbaxy, India.*
Magnesium citrate (p. 1857·1); potassium citrate (p. 1780·3).

Nocutil *Gebro, Austria; Gebro, Denm.; Apogepha, Ger.; Gebro, Hung.; Medac, Swed.; Gebro, Switz.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; polyuria; nocturia; polydipsia.

Nocvalène *Arkomedika, Fr.†*
Crataegus (p. 2488·1); red-poppy petal (p. 2207·3); passion flower (p. 2584·1).
Insomnia.

Nodanton *Loeffler, Mex.†*
Ondansetron (p. 1872·1).

Nodard *Cipla, India.*
Nimesulide (p. 101·3).
Pain.

Nodard Plus *Cipla, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nodasic *Rafarm, Gr.*
Amisulpride (p. 1036·3).

Nodé DS *Bioderma, Fr.*
Ichthammol (p. 1705·3); cade oil (p. 1723·2); salicylic acid (p. 1719·1); climbazole (p. 576·2); pyrithione zinc (p. 1718·1); piroctone olamine (p. 1716·3).
Scalp disorders.

Node DS
Note: this name may be used for preparations of different composition.
Bioderma, Venez.
Piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1); ichthammol (p. 1705·3); pyrithione zinc (p. 1718·1); climbazole (p. 576·2).
Scalp disorders.

Dispolab, Chile.†
Climbazole (p. 576·2); salicylic acid (p. 1719·1); piroctone olamine (p. 1716·3); lactic acid (p. 2539·1); pyrithione zinc (p. 1718·1); castor oil (p. 2472·1).
Seborrhoeic dermatitis; dandruff.

Nodé DS+ *Bioderma, Fr.*
Piroctone olamine (p. 1716·3); pyrithione zinc (p. 1718·1); vitamin B_6 (p. 2105·3); salicylic acid (p. 1719·1); ictasol (p. 1706·1); cade hydrolate (p. 1723·2); zanthalene; laminaria (p. 2540·1).
Dandruff; hair loss.

Nodé G *Bioderma, Fr.†*
Sage oil (p. 2609·1).
Scalp disorders.

Nodé K *Bioderma, Fr.*
Shampoo: Salicylic acid (p. 1719·1); cade hydrolate (p. 1723·2); zanthoxylum (p. 2650·1); coleus barbatus.
Dandruff.

Bioderma, Fr.
Topical emulsion: Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); shea butter (p. 2208·2); vaseline; zanthalene.
Dandruff; psoriasis.

Nodé P *Bioderma, Fr.†*
Cade oil (p. 1723·2); salicylic acid (p. 1719·1); climbazole (p. 576·2); pyrithione zinc (p. 1718·1); piroctone olamine (p. 1716·3).
Scalp disorders.

Nodescron *Pisa, Mex.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Nodex *Brothier, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Nodi *Comed, India.*
Racecadotril (p. 1881·3).
Diarrhoea.

Nodia
Note: this name may be used for preparations of different composition.
Marvecs, Ital.
Diosmectite (p. 1887·1).
Gastrointestinal disorders.

Multichem, NZ.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Nodiamex *IQFA, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Nodiar *Duncan, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Nodict *Sun, India.*
Naltrexone hydrochloride (p. 1565·1).
Opioid withdrawal syndrome; alcohol withdrawal syndrome.

Nodimox Plus *Alkem, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); *Lactobacillus acidophilus* (p. 2596·3).
Bacterial infections.

Nodimox Plus-LB *Alkem, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Nodimox-LB *Alkem, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Nodine *Cipla, India.*
Ketorolac trometamol (p. 80·2).
Pain.

Nodipir *Klonal, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Nodir *Polfarmex, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Nodirep *Bio-Gen, Turk.*
Risperidone (p. 1103·2).

Nodiril *Actavis, Indon.*
Risperidone (p. 1103·2).
Psychoses.

Nodis *Temis, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Nodiz *Pascual, Philipp.*
Meclozine hydrochloride (p. 634·3).
Motion sickness; nausea; vomiting; vestibular disorders.

Nodoff *Potter's, UK.*
Oral liquid: Passion flower (p. 2584·1); skullcap (p. 2617·1); lupulus (p. 2546·1); valerian (p. 2640·2); Jamaica dogwood (p. 2536·3).
Insomnia.

Potter's, UK.
Tablets: Passion flower (p. 2584·1).
Insomnia.

Nodolfen *Lacer, Spain.*
Ibuprofen (p. 68·2).
Fever; pain.

Nodolip *Rayere, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Nodolor *Macoven, USA.*
⊗Isometheptene mucate (p. 2535·1); paracetamol (p. 115·1); dichloralphenazone (p. 1071·3).
Migraine; tension headache.

Nodon *Cadila, India.*
⊗Nebivolol (p. 1444·2).
Hypertension.

Nodon-AM *Cadila, India.*
⊗Amlodipine (p. 1304·1); nebivolol (p. 1444·2).

Nodon-H *Cadila, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

NoDoz *Novartis, USA.*
Caffeine (p. 1203·3).
Fatigue.

Nodresol *Shree Ganesh, India.*
⊗Noradrenaline (p. 1458·2).

Nodrix *Biomep, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Nodrof *Tempo Scan Pacific, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms; cough.

No-Drowsiness Allerest *Ciba, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Noducil *Andromaco, Chile.†*
⊗Sibutramine (p. 2330·2).
Obesity.

Nodycin *Nodysis, India.*
Azithromycin (p. 221·2).
Bacterial infections.

Nodyfer *Nodysis, India.*
Capsules: Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); trace elements; protein hydrolysate (p. 2086·2).

Nodysis, India.
Syrup: Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); ferric ammonium citrate (p. 2060·1).

Noebra *Meditrina, Gr.*
Choline alfoscerate (p. 389·2).

Noell *Polfarmex, Pol.*
Ketoconazole (p. 585·3).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Noex *Eurofarma, Braz.*
⊗Budesonide (p. 1625·1).

Nofail *Pharmex (Φαρμεξ), Gr.*
Ondansetron hydrochloride (p. 1872·1).
Postoperative nausea and vomiting; chemotherapy-induced nausea and vomiting.

Nofardom *Adamed, Cz.; Aramis, Hung.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Nofear-72 *Solitaire, India.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Nofebrin *Legrand, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Nofena *Konimex, Indon.†*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Noff *Nitin, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Noff-OR *Nitin, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Nofiva *Agio, India.*
Paracetamol (p. 115·1).
Pain; fever.

Noflam
Note: this name may be used for preparations of different composition.
Gracia, Indon.
Ketoprofen (p. 79·1).
Rheumatoid arthritis; ankylosing spondylitis; gout; osteoarthritis.

Mylan, NZ.
Naproxen (p. 98·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Noflam P *Euphoric, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Noflamen *Egis, Cz.; Egis, Hung.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Noflam-N *Pacific, Hong Kong.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Noflexin *Novell, Indon.*
Pefloxacin (p. 338·1).
Bacterial infections.

Noflo *Global, India.*
Etamsylate (p. 1145·2).
Menorrhagia; haemorrhage.

Noflorox *Merck, Mex.*
Norfloxacin (p. 333·3).
Bacterial infections.

No-Flu
Note: this name may be used for preparations of different composition.
Maver, Chile.
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); noscapine hydrochloride (p. 1670·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Noflux *YSP, Malaysia.*
Muramidase hydrochloride (p. 2565·1).
Haemorrhage; sinusitis.

Nofoklam *Nufarindo, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Noforit *Arriani, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Nofrattil *SF, Ital.*
Alendronate sodium (p. 1171·3).

Nofro *Winsome, India.*
Copper (p. 2057·1); manganese sulfate (p. 2081·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Nofrozic *Fortune, Hong Kong.†*
Dequalinium (p. 1749·3).

Nofung
Note: this name may be used for preparations of different composition.
Egis, Hong Kong; Egis, Hung.; Egis, Rus.
Fluconazole (p. 578·2).
Fungal infections.

Nufarindo, Indon.
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Nogacid *Cadila, India.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Nogacid D *Cadila, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

No-Gas
Note: this name may be used for preparations of different composition.
Giuliani, Ital.
Dimeticone (p. 1886·2); activated charcoal (p. 1537·3).
Aerophagia; meteorism.

Nogastra *Andromaco, Chile.*
Oral suspension: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer; flatulence; gastro-oesophageal reflux.

Andromaco, Chile.
Tablets: Simeticone (p. 1886·2); magnesium carbonate (p. 1856·2); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; peptic ulcer; flatulence; gastro-oesophageal reflux.

Nogesic *Kocak, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Nogest *Mithra, Belg.*
Nomegestrol acetate (p. 2294·1).
Menopausal disorders; menstrual disorders.

Nogesta *Laboratorios Chile, Chile.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Noginox *Galeno, Venez.*
Isoconazole nitrate (p. 583·2).
Vulvovaginal infections.

Nogit-M *Alde Medi Impex, India.*
Metronidazole benzoate (p. 936·1); norfloxacin (p. 333·3).

No-Gras *Medica, Arg.*
Centella (p. 1698·3); spirulina (p. 2622·1); lecithin (p. 2542·2).
Slimming aid; cellulite.

No-Gravid *Irmed, Ital.*
Copper (p. 2057·1).
Intra-uterine contraceptive device.

Nogren *Pyridam, Indon.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Migraine.

Nogripe *Teuto, Braz.*
Orange tablets, dipyrone (p. 53·3); chlorphenamine maleate (p. 620·3); green tablets, dipyrone; caffeine (p. 1203·3).
Influenza symptoms.

Nogron *Egis, Neth.*
Temozolomide (p. 865·2).
Malignant glioma.

Nogryp *Volta, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

NoHist *Larken, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

NoHist DMX *Larken, USA.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

NoHist LQ *Larken, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

NoHist Plus *Larken, USA.*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

NoHist-PDX *Larken, USA.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Noiafren *Sanofi-Aventis, Spain.*
Clobazam (p. 518·2).
Alcohol withdrawal syndrome; anxiety; epilepsy.

Noir *Arlak, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Noitron *Help, Gr.*
Isotretinoin (p. 1706·2).
Acne.

5-NOK *Lek, Ukr.*
Nitroxoline (p. 333·2).
Urinary-tract infections.

5-Nok *Lek, Rus.*
Nitroxoline (p. 333·2).
Urogenital infections.

Nokatar *Prater, Chile.*
Ginkgo biloba (p. 2512·3).

Nokid *Aurobindo, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Noklot *Zydus, India; Zydus Cadila, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; atherosclerosis; myocardial infarction; peripheral arterial disease.

Noklot Plus *Zydus, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3).
Thrombosis prophylaxis; acute coronary syndrome.

Noklot-CV *Zydus, India.*
Aspirin (p. 22·2); clopidogrel (p. 1342·3); atorvastatin (p. 1309·2).

Nokoba *Fahrenheit, Indon.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage.

Nokole *Union Drug, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Noksprey *Sperko, Rus.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nokturn *Sanovel, Turk.*
Paroxetine hydrochloride (p. 440·3).

Nolac *Nestle, Ital.*
Infant feed.
Intolerance to cow's milk, soya, egg, and gluten.

Nolahist *Carnrick, USA.†*
Phenindamine tartrate (p. 637·1).
Allergic rhinitis.

Nolaid *Medice, Neth.*
Lidocaine hydrochloride (p. 1988·2).
Sore throat.

Nolais *Medipharm, Chile.*
Permethrin (p. 2159·3).
Pediculosis.

Nolarmin *Coup, Gr.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nolasque *Ultra, Mex.*
⊗Spironolactone (p. 1499·3).
Heart failure; hypertension; oedema; ascites; nephrotic syndrome.

Nolcer *Euro-Med, Philipp.*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Nolder *Pfizer, Ital.†*
Amino acids; carbohydrate; phospholipids (p. 2201·2); vitamins; selenium (p. 2086·3).
Nutritional supplement.

Nolen *Craveri, Arg.*
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Venous insufficiency; haemorrhoids.

Noleptan *Boehringer Ingelheim Promeco, Mex.*
Fominoben (p. 1665·3) or fominoben hydrochloride (p. 1665·3).
Cough.

Boehringer Ingelheim, Jpn.†
Fominoben hydrochloride (p. 1665·3).

Nolia *Shinto, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Nolian *Pentaforma, Port.†*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

Nolicin *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Norfloxacin (p. 333·3).
Bacterial infections.

Nolil *Offenbach, Mex.*
Clioquinol (p. 273·1).
Fungal skin infections.

Nolipax *Salus, Ital.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias; diabetic retinopathy; xanthomatosis.

Nolipo
Note: this name may be used for preparations of different composition.
Sanbe, Indon.
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Teuto, Braz.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Noliprel *Anpharm, Pol.; Servier, Pol.; Servier, Rus.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Servier, Cz.; Servier, Ukr.
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Noliprel A *Servier, Rus.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Nolisim *Fada, Arg.*
Colistin (p. 275·3).
Bacterial infections.

Noliterax *Servier, Cz.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).

Servier, Fin.; Servier, Neth.
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Nolofene *Distrifarma, Port.*
Ibuprofen (p. 68·2).
Pain; fever.

Nolol
Note: this name may be used for preparations of different composition.
Pharmaland, Thai.†
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Nolotil *Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain.*
Metamizole magnesium (p. 53·3).
Pain; fever.

Nolpaza *KRKA, Cz.; KRKA, Hung.; KRKA, Irl.; KRKA, Neth.†; KRKA, Rus.; KRKA, Spain; KRKA, Ukr.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

KRKA, Pol.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nolvac *Pharmathen, Gr.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Nolvadex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.†; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, India; AstraZeneca, Indon.†; AstraZeneca, Irl.; AstraZeneca, Israel†; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.†; AstraZeneca, Norw.; AstraZeneca, NZ†; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK†; AstraZeneca, Venez.*
⊗Tamoxifen citrate (p. 860·2).
Anovulatory infertility; breast cancer; endometrial cancer.

Nom *Cyno, India.*
Nimesulide (p. 101·3).
Pain.

Nomafen *Fidia, Ital.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Nomexor *Menarini, Austria.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nomexor plus HCT *Menarini, Austria.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nomicon *Casasco, Arg.*
Econazole nitrate (p. 577·3).
Fungal skin and nail infections.

Nomigrain *Torrent, India.*
Flunarizine hydrochloride (p. 629·3).
Migraine.

Nomigren *Bosnalijek, Ukr.*
Propyphenazone (p. 127·3); caffeine (p. 1203·3); camylofin hydrochloride (p. 2467·1); mecloxamine citrate (p. 1859·1); ergotamine tartrate (p. 674·1).
Migraine.

Nomit *Speciality Meditech, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3).
Nausea and vomiting in pregnancy.

Nomkof *Cadila, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).

Nomkof-B NF *Cadila, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Nomocon *Cadila, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nomokof *Cadila, India.†*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Nomokof BNF *Cadila, India.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Nomon mono *Maxmedic, Ger.*
Cucurbita (p. 2489·2).
Urinary-tract disorders.

Nomopain *Aventis, S.Afr.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); doxylamine succinate (p. 627·3); codeine phosphate (p. 40·2).
Pain and associated tension.

Nomorcid-MPS *Acto, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Nomorcuf *Sarthak, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Nomotec *Tecnofarma, Mex.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; atopic eczema.

Nom-P *Cyno, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Noms *Plus, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Non Drowsy Contac Cold 12 Hour *GSK Consumer, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Non Drowsy Contac Complete *GSK Consumer, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Non Drowsy Regular Strength Contac Cold 12 Hour *GSK Consumer, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Non Drowsy Super Strength Contac Complete *GSK Consumer, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; cough.

Nona *Arlak, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Nonafact *CAF-DCF, Belg.; Sanquin, Cz.; Sanquin, Fin.; Sanquin, Irl.; Sanquin, Neth.; Sanquin, Pol.; Sanquin, Port.; Centurion, Turk.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Nonak *Pentamedical, Ital.*
Potassium azeloyl diglycinate; sulfosalicylic acid; piroctone olamine (p. 1716·3).
Skin disorders.

Nonak Detergente *Pentamedical, Ital.*
Soap substitute.

Nonaler *Esan, Chile.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; conjunctivitis.

Nonalges *Tempo Scan Pacific, Indon.*
Tramadol (p. 139·2).
Pain.

Nonan *Baxter, Belg.*
Trace elements.
Parenteral nutrition.

Aguettant, Fr.†
Minerals.
Parenteral nutrition.

Nonavit *De Mayo, Braz.†*
Vitamins; amino acids; minerals.

Non-Drowsy Allergy *Major, USA.*
Loratadine (p. 633·2).
Formerly known as Clear-Atadine.
Allergic rhinitis.

Non-Drowsy Sinutab *McNeil Healthcare, Irl.; Pfizer Consumer, UK.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion with pain or fever; nasal and sinus congestion with pain.

Non-Drowsy Sudafed Congestion Cold & Flu *Pfizer Consumer, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Non-Drowsy Sudafed Congestion Relief *Pfizer Consumer, UK.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Non-Drowsy Sudafed Decongestant *Pfizer Consumer, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; hay fever.

Non-Drowsy Sudafed Decongestant Nasal Spray *McNeil, UK.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Non-Drowsy Sudafed Dual Relief *Pfizer Consumer, UK.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Non-Drowsy Sudafed Dual Relief Max *Pfizer Consumer, UK.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion with pain or fever.

Non-Drowsy Sudafed Expectorant *Pfizer Consumer, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs; upper respiratory-tract congestion.

Non-Drowsy Sudafed Linctus *Pfizer Consumer, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; upper respiratory-tract congestion.

Nonemi *Lapi, Indon.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); calcium phosphate (p. 1784·2); cobalt sulfate (p. 2482·2); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; vitamin B deficiency.

Noneston *Help, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Nonflamin *Takeda, Indon.*
Tinoridine hydrochloride (p. 138·1).
Inflammation; pain.

Non-Ovlon *Jenapharm, Rus.†*
Ethinylestradiol (p. 2275·3); norethisterone acetate (p. 2294·3).
Combined oral contraceptive.

Non-Preg *LBS, Malaysia.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; endometriosis.

Nontoss *Cooper (Κοπερ), Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Noobut *Interchem, Ukr.*
4-Amino-3-phenylbutyric acid hydrochloride.
Mental function impairment; anxiety; obsessive-compulsive disorder; insomnia; premedication; alcohol withdrawal syndrome; vestibular disorders; motion sickness.

NooCam *Kamelia, Rus.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; mental function disorders; migraine; vestibular disorders; motion sickness.

Noocephal *Pyridam, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; learning difficulties in children; cerebrovascular disorders.

Noocetam *Tropica Mas, Indon.; Pharmasant, Thai.*
Piracetam (p. 393·3).
Mental function impairment; cerebrovascular disorders; chronic alcoholism; cerebral trauma.

Nooclerin *Pik, Rus.*
⊗Deanol aceglumate (p. 2319·1).
Mental function impairment; cerebrovascular disorders; asthenia; alcohol withdrawal syndrome.

Noodipina *Apsen, Braz.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage; mental function impairment.

Noodis *UCB, Belg.*
Piracetam (p. 393·3).
Childhood learning difficulties.

Noojerone *Pliva, Rus.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Noopept *Masterfarm, Rus.*
N-Phenylaxetil-L-prolylglycine ethyl ester.
Mental function impairment; brain trauma; asthenia.

Noophen *Olainfarm, Ukr.*
4-Amino-3-phenylbutyric acid hydrochloride.
Mental function impairment; asthenia; anxiety; neuroses; stammer; tics; insomnia; premedication; alcohol withdrawal syndrome; vestibular disorders; motion sickness.

Noostan *HLB, Arg.; UCB, Port.*
Piracetam (p. 393·3).
Cerebrovascular disorders; mental function impairment; myoclonus.

Nootrocet *Oriental, Philipp.*
Piracetam (p. 393·3).
Mental function disorders; myoclonus.

Nootron *Biosintetica, Braz.*
Piracetam (p. 393·3).
Cerebrovascular disorders; senile dementia.

Nootrop *UCB, Ger.; UCB, Gr.†*
Piracetam (p. 393·3).
Mental function disorders.

Nootropil *UCB, Austria; UCB, Belg.; Sanofi-Aventis, Braz.; UCB, Cz.; UCB, Fin.; GSK, Hong Kong; UCB, Hung.; UCB, India; UCB, Indon.; UCB, Irl.†; UCB, Ital.; UCB, Jpn†; GSK, Malaysia; UCB, Mex.; UCB, Neth.; UCB, Norw.; GSK, Philipp.; Jelfa, Pol.; UCB, Pol.; Vedim, Port.†; UCB, Rus.; GSK, S.Afr.†; GSK, Singapore; UCB, Spain; UCB, Swed.; UCB, Switz.; GSK, Thai.; UCB, Turk.; UCB, UK; UCB, Ukr.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment; alcoholism; vertigo; coma; organic brain disorders; cerebrovascular disorders; dyslexia; behaviour disorders; sickle-cell crisis; dementia; cerebral trauma; learning difficulties in children; vestibular disorders.

Nootropyl *HLB, Chile; UCB, Fr.*
Piracetam (p. 393·3).
Alcoholism; childhood behaviour disorders; cerebrovascular disorders; mental function impairment; senile dementia; vertigo; myoclonus; dyslexia in children.

Nopain *Krewel, Ger.†*
Dipyrone (p. 53·3).
Fever; pain.

Nopain Plus *Casel, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Nopal *Eurodrug, Hong Kong; Eurodrug, Malaysia; Eurodrug, Singapore.*
Opuntia streptacantha; opuntia ficus-indica; opuntia robusta.
Dietary supplement.

Nopalu *Pharmacie Centrale des Armees, Fr.*
Proguanil hydrochloride (p. 661·3); chloroquine sulfate (p. 650·2).
Malaria.

Nopan *CTI, Israel†; CTS, Rus.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Nopar
Note: this name may be used for preparations of different composition.
Lilly, Ital.
Pergolide mesilate (p. 910·2).
Parkinsonism.

Unipharma, Gr.
Homatropine methylbromide (p. 2007·3).
Gastrointestinal disorders characterised by smooth muscle spasm.

Nopatic *Rayere, Mex.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Nopause *Mega We Care, Singapore.*
Cimicifuga (p. 2478·1).
Premenstrual syndrome; menopausal disorders.

Nopekar *Labormed, Cz.; Labormed, Denm.; Labormed, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; panic disorder; anxiety.

Noperten *Dexa, Indon.; Dexa, Singapore.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Nopez *Nevzat, Turk.*
Donepezil hydrochloride (p. 390·2).

Nopil *Mepha, Switz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Noplak *Daudt, Braz.†*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Noplak Max *Daudt, Braz.*
Cetylpyridinium chloride (p. 1743·1); chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2).

Noplaq *Alkem, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Nopral *Richmond, Arg.*
⊗Modafinil (p. 2327·2).

Nopremin *Minerva (Μινερβα), Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Nopres *Dexa, Hong Kong.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Ferron, Indon.
Fluoxetine (p. 417·1).
Depression.

Nopretens *Valeant, Cz.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Nopretens Plus H *Valeant, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nopril *Kimia, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Noprilam *Bial, Port.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Noprilex *Cosmopharm, Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Nopron *Genopharm, Fr.†; Sanofi-Aventis, Ital.*
Niaprazine (p. 636·2).
Insomnia.

Vianex (Βιανεξ), Gr.
Naproxen (p. 98·2).

Noprostol *Novell, Indon.*
Misoprostol (p. 2140·3).
NSAID-induced gastric ulcer.

Noptic *Andromaco, Chile.*
Eszopiclone (p. 1072·3).
Insomnia.

Nopucid
Note: this name may be used for preparations of different composition.
Dalider, Venez.
Deltamethrin (p. 2152·1).
Pediculosis; scabies.

Elea, Arg.
Permethrin (p. 2159·3).
Pediculosis.

Nopucid Bio II *Elea, Arg.*
Cyclomethicone 5; dimeticone (p. 2209·3); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1).
Pediculosis.

Nopucid Bio Citrus *Elea, Arg.*
Cyclomethicone 5; dimeticone (p. 2209·3); bergamot oil (p. 2455·1).
Pediculosis.

Nopucid Compuesto *Elea, Arg.*
Deltamethrin (p. 2152·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Nopucid MC *Elea, Arg.*
Phenothrin (p. 2160·1).
Pediculosis.

Nopucid Rapida *Elea, Arg.*
Deltamethrin (p. 2152·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Nor 2 *Raffo, Arg.*
Norfloxacin (p. 333·3); phenazopyridine (p. 124·3).
Urinary-tract infections.

Nor T *Cipla, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nora
Note: this name may be used for preparations of different composition.
TNP, Thai.
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Nora-30
Note: this name may be used for preparations of different composition.
Mithra, Belg.
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Norace *Hormona, Mex.*
14 Tablets, mestranol (p. 2291·1); 7 tablets, mestranol; norethisterone (p. 2294·2).
Sequential oral contraceptive; menstrual disorders; menopausal disorders.

Noracin *Chew, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norad *Neon, India.*
⊗Noradrenaline (p. 1458·2).

Noradox *Benedetti, Ital.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Noradran *Norma, UK.*
⊗Diphenhydramine hydrochloride (p. 626·2); diprophylline (p. 1207·3); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Coughs.

Noradren *Demo, Gr.; IFET (ΙΦΕΤ), Gr.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Noradria *Troikaa, India.*
⊗Noradrenaline (p. 1458·2).

Norafexine *Pharmanel, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Norages
Note: this name may be used for preparations of different composition.
GES, Spain.
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; cardiac arrest.

Meprofarm, Indon.
Dipyrone (p. 53·3).
Pain.

Noragyl *Mankind, India.*
Suspension: Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Mankind, India.
Tablets: Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Noragyl-OZ *Mankind, India.*
Norfloxacin (p. 333·3); ornidazole (p. 943·1).
Diarrhoea; dysentery.

Noral *Ulagay, Turk.†*
Paracetamol (p. 115·1).
Fever; pain.

Noralin *United Biotech, India.*
⊗Noradrenaline acid tartrate (p. 1458·2).

Noralox *Jagsonpal, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Noranat *Nova Argentia, Arg.*
⊗Indapamide (p. 1409·2).
Hypertension.

Noraphen *Bangkok Lab & Cosmetic, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle spasm and pain.

Norapred *Bruluart, Mex.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Norapril *Finmedical, Ital.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction.

Norash *Raptakos, Malaysia; Raptakos, Singapore.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1); calamine (p. 1697·2); cetrimide (p. 1742·1).
Skin disorders.

Noratak *Scios, Israel; Janssen-Cilag, Switz.†*
⊗Nesiritide citrate (p. 1444·3).
Heart failure.

Norate *Dewcare, India.*
Norethisterone (p. 2294·2) or norethisterone acetate (p. 2294·3).
Menorrhagia; endometriosis; premenstrual syndrome; breast cancer.

Noratoquin *Quimpharma, Mex.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; cold symptoms.

Noravid *IFET (ΙΦΕΤ), Gr.; Crinos, Ital.†*
Defibrotide (p. 1350·1).
Thromboembolic disorders.

Noraxon *Norton, Ukr.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Norazol *Ranbaxy, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Nor-B *Moraceae, India.*
Capsules; tablets: Vitamin B substances (p. 2102·3); *Lactobacillus* (p. 2596·3).

Moraceae, India.
Syrup: Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Norbactin *Ranbaxy, India; Ranbaxy, Mex.†; Ranbaxy, Philipp.†; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.; Ranbaxy, Ukr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norbactin-Z *Ranbaxy, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norbal *AVI, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Norbid *Alembic, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norbit *Cubit, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Norbloc *Pascual, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Norboral *Silanes, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Norcalcin *Chemica, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Norcard *Akacia, S.Afr.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Norcephin *Alkem, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Norcin *Utopian, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norco *Watson, China; Watson, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Norcolut *Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Gedeon Richter, Rus.; Gedeon Richter, Singapore; Gedeon Richter, Ukr.*
Norethisterone (p. 2294·2).
Endometriosis; menstrual disorders; benign breast disorders; dysfunctional uterine bleeding; lactation inhibition; menopausal disorders; female infertility; uterine fibroids; endometrial cancer; progestogen-only oral contraceptive.

Norcuron *MSD, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.†; Organon, Canad.†; Schering-Plough, Chile; MSD, China; Organon, Cz.; Organon, Fin.; MSD-Chibret, Fr.; Essex, Ger.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Organon, India; Schering-Plough, Indon.; Organon Teknika, Irl.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Pisa, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Sanofi-Aventis, S.Afr.; MSD, Singapore†; Organon, Spain; MSD, Swed.†; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK; Organon, Ukr.†; Organon, USA.†*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Norcutin *CCM, Malaysia; Duopharma, Singapore.*
Norethisterone (p. 2294·2).
Dysfunctional uterine bleeding; amenorrhoea; endometriosis; premenstrual syndrome; mastopathy; menorrhagia; breast cancer.

Norcynt *Royal, Chile; Italmex, Mex.*
Moxonidine (p. 1442·1).
Hypertension.

Nordaz *Bouchara-Recordati, Fr.; Bouchara-Recordati, Singapore.*
Nordazepam (p. 1089·3).
Anxiety; alcohol withdrawal syndrome.

Nordep *Orchid, India.*
Nortriptyline.
Depression.

Nordet *Wyeth, Mex.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Nordette *Pfizer, Austral.; Aspen, S.Afr.; Teva, USA.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive; menstrual disorders.

Wyeth, Arg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, Israel; Wyeth, Malaysia; Pfizer, NZ; Wyeth, Philipp.; Wyeth, Singapore†; Pfizer, Thai.; Wyeth, Venez.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders; endometriosis; dysfunctional uterine bleeding.

Nordex
Note: this name may be used for preparations of different composition.
Ashford, Philipp.
Paracetamol (p. 115·1).
Pain; fever.

Nexus, Gr.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Nordibela *Nordin, Mex.*
Centella (p. 1698·3); fucus vesiculosus; equisetum (p. 2500·1).
Cellulite.

Nordimenty *Nordin, Mex.*
St John's wort (p. 449·1); melissa (p. 2552·3); chamomile (p. 2474·1).

Nordinet Adulto *Nordin, Mex.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Nordinet Infantil *Nordin, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Nordiol *Aspen, S.Afr.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive; menstrual disorders.

Wyeth, Chile; Wyeth, Gr.; Wyeth, Mex.†; Wyeth, Philipp.; Wyeth, Venez.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; endometriosis; dysfunctional uterine bleeding; menstrual disorders; dysmenorrhoea.

Nordip *Alphapharm, Austral.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Nordipine *CCM, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Norditopin *Novo Nordisk, Pol.*
⊗Somatropin (p. 1919·3).
Growth disorders in renal failure; growth hormone deficiency; Turner' syndrome; short children born small for gestational age.

Norditropin *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Canad.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong†; Novo Nordisk, Hung.; Novo Nordisk, India; Ferron, Indon.; Novo Nordisk, Indon.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, Ukr.; Novo Nordisk, USA.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure; Prader-Willi syndrome; short children born small for gestational age; cachexia or wasting in AIDS; short bowel syndrome; SHOX deficiency; Noonan syndrome.

Norditropine *Novo Nordisk, Fr.; Novo Nordisk, Switz.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure.

Nordolce *Vegetal, Ital.*
Acero canadese.
Nutritional supplement.

Nordox *Tecnofarma, Chile.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain and irritation.

Nordurine *Ferring, Irl.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis; nocturia.

Nordyl *Rosemont, Thai.†*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough.

Nordys *Micro, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norebox *Pfizer, Spain.*
Reboxetine mesilate (p. 447·1).
Depression.

Norecil *Maver, Mex.*
Metronidazole (p. 936·1); diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Norecsero *Micro, Mex.*
Citalopram (p. 411·1).
Depression.

No-Ref *Sanitas, Chile.*
Simeticone (p. 1886·2); metoclopramide (p. 1862·2); chlordiazepoxide (p. 1044·2).
Gastrointestinal disorders.

Noregyna *Mabra, Braz.*
Norethisterone enantate (p. 2294·3); estradiol valerate (p. 2271·2).
Combined injectable contraceptive.

Norel AD *US Pharmaceutical, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Norel DM *US Pharmaceutical, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Nasal congestion; cough.

Norel EX *US Pharmaceutical, USA.†*
Phenylephrine (p. 1672·2); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Norel LA *US Pharmaceutical, USA.†*
Phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract disorders.

Norel SD *US Pharmaceutical, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Norel SR *US Pharmaceutical, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); phenyltoloxamine citrate (p. 638·1).
Allergic rhinitis.

Norelbin *Eurofarma, Braz.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Norelut *Hovid, Hong Kong†; Dexa, Indon.*
Norethisterone (p. 2294·2).
Amenorrhoea; abnormal uterine bleeding; endometriosis.

Noremifa *DMG, Ital.*
Magnesium alginate (p. 2167·2); simeticone (p. 1886·2); xanthan gum (p. 2220·1).
Gastro-oesophageal reflux.

Noremine *Maver, Chile.*
Bromhexine hydrochloride (p. 1656·3).

Norep *Mankind, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Norepin *Delex, Philipp.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Norepine *Sterop, Belg.*
⊗Noradrenaline acid tartrate (p. 1458·2).

Norepirin *Chandra Bhagat, India.*
⊗Noradrenaline acid tartrate (p. 1458·2).

Noreskin *Genepharm, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Norestin *Biolab Sanus, Braz.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Noreta HRT *Zydus, India.*
Norethisterone (p. 2294·2).
Menopausal disorders.

Norex
Note: this name may be used for preparations of different composition.
Huons, Philipp.
Norfloxacin (p. 333·3).
Urinary-tract infections.

Nordic, India.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Superlife, Mex.
Arnica (p. 2447·2); rosemary (p. 2607·2).
Musculoskeletal and joint pain.

Norexan *Baxter, Indon.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Norezor *Help, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Norf *Sigma, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfa *Suphong, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfaben M *Pisa, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Norfacin *Shreya, Rus.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfagyl *Life Line, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Norfan
Note: this name may be used for preparations of different composition.
Suphong, Thai.
Norfloxacin (p. 333·3).
Bacterial infections.

Vocate, Gr.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Norfass *Pharmahof, Thai.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfast *Intra-Labs, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Norfazole *Wings, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Norfcin *SM, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfem *Unicure, Philipp.*
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Norfen *Bago, Arg.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Norfen TZ *Cadila, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norfenazin *Nupel, Spain.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Norfenon *Abbott, Mex.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Norflacil *Inpac, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norflam
Note: this name may be used for preparations of different composition.
Solas, Indon.
Echinacea (p. 2498·1); vitamin B substances (p. 2102·3); javanese turmeric (p. 2636·2); acacia (p. 2166·1).
Inflammation.

Norflam T
Note: this name may be used for preparations of different composition.
3M, S.Afr.
Ibuprofen (p. 68·2).
Pain; fever.

Norflen *Raam, Mex.*
Phenazopyridine hydrochloride (p. 124·3); norfloxacin (p. 333·3).
Urinary-tract infections.

Norflex *iNova, Austral.; Medicis, Canad.; Meda, Fin.; Meda, Ger.; Meda, Gr.; iNova, Malaysia; Graceway, Mex.; iNova, NZ; iNova, S.Afr.; Meda, Swed.; iNova, Thai.; Graceway, USA; Zuoz, Venez.*
Orphenadrine citrate (p. 909·2).
Prolapsed intervertebral disc; torticollis; musculoskeletal and joint injury; hiccups; tension headache; skeletal muscle spasm and pain; peri-articular and soft-tissue disorders.

Norflex Co *iNova, S.Afr.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Pain; skeletal muscle spasm.

Norflex Plus *Graceway, Mex.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

Norflo *Medifive, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norflocin *Mepha, Switz.; Polipharm, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norflohexal *Sandoz, Austral.†; Hexal, Ger.†; Sandoz, Ukr.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Norflok *Teva, Spain.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Norflol *Oriental, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norflosal *TAD, Ger.†*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Norflox *Biomedica, Ital.*
Norfloxacin pivoxil (p. 333·3).
Urinary-tract infections.

Prodotti, Braz.†; 1A, Ger.†; CT, Ger.†; Sandoz, Ger.†; Cipla, India; Osoth, Thai.; RX, Thai.
Norfloxacin (p. 333·3).
Bacterial infections.

Norflox TZ *Cipla, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Gastrointestinal infections.

Norfloxasan *Sanval, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfloxil *Greenpharma, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfloxin *Cipla, Malaysia; TO-Chemicals, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfloxmed *Cimed, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfloxpac *Inpac, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfloxyl *Bangkok Lab & Cosmetic, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norfluxx *Ruhrpharm, Ger.*
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract.

Norforms
Note: this name may be used for preparations of different composition.
Fleet, USA.
Pessaries: Vaginal deodorant.

Norfox *United Drug, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norgalax *Norgine, Belg.; Norgine, Fr.; Norgine, Neth.; Norgine, Port.; Norgine, Switz.; Norgine, UK; Norgine, Ukr.*
Docusate sodium (p. 1836·2).
Constipation; bowel evacuation.

Norgalax Miniklistier *Norgine, Ger.†*
⊗Docusate sodium (p. 1836·2); glycerol (p. 2517·2).
Bowel evacuation; constipation.

Norgalax Rektalgel *Norgine, Ger.*
⊗Docusate sodium (p. 1836·2); glycerol (p. 2517·2).
Bowel evacuation; constipation.

Norgesic
Note: this name may be used for preparations of different composition.
iNova, Austral.; Meda, Austria; 3M, Chile†; Meda, Fin.; Meda, Gr.; iNova, Hong Kong; 3M, Israel†; iNova, Malaysia; 3M, NZ; iNova, Philipp.; iNova, Singapore; Meda, Swed.; iNova, Thai.; Zuoz, Venez.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Soft-tissue disorders; musculoskeletal and joint injury; prolapsed intervertebral disc; torticollis; tension headache; skeletal muscle pain and spasm; dysmenorrhoea.

3M, USA.†
Orphenadrine citrate (p. 909·2); aspirin (p. 22·2); caffeine (p. 1203·3).
Musculoskeletal pain.

Norgest *Micro, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Norgeston *Schering, UK.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Norgestrel Cex *Biotenk, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Norgestrel Continuo *Biotenk, Arg.*
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Norgestrel Max *Biotenk, Arg.*
Levonorgestrel (p. 2296·1).
Progestogen-only post-coital oral contraceptive.

Norgestrel Minor *Biotenk, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Norgestrel Plus *Biotenk, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Norgetex *United Drug, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle spasm and pain.

Norgic *Pond's, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle spasm.

Norglen *Glenmark, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Norglicem *Rottapharm, Spain.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Norglobin *Claris, India.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immune thrombocytopenia; immunodeficiency; Guillain-Barré syndrome; Kawasaki disease; bone marrow transplantation.

Norgrade *Globus, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Norica Plus *Polifarma Benessere, Ital.*
Spray: Orthophenylphenol (p. 1762·3); benzalkonium chloride (p. 1737·1).
Surface disinfection.

Noricaven *Bionorica, Ger.*
Aesculus (p. 2431·2).
Venous insufficiency.

Noriday *Pfizer, Austral.; 2care4, Denm.; Europharma, Denm.; Pharmacia, Irl.; Pfizer, Malaysia; Pfizer, NZ; Pharmacia, UK.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Noriderm *EMS, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Norifaz *Adamed, Cz.; Adamed, Pol.; Azevedos, Port.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Norifaz Trio *Aramis, Hung.*
4 Tablet, risedronate sodium (Norifaz) (p. 1189·3); 56 tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1) (Calcichew D3).
Osteoporosis.

Norigyl *Medley, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Noril *Ranbaxy, Mex.†*
Lisinopril (p. 1420·3).

Norilafin *Leontik, Gr.*
Sulindac (p. 134·2).

Norilet *Reddy, India; Reddy, Rus.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norilet-A *Reddy, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Noriline *Quatromed, S.Afr.†*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Norimin *Pfizer, Austral.; Pfizer, NZ.*
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Pharmacia, UK.
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Norimko *NRIM, Neth.*
Vancomycin hydrochloride (p. 384·2).
Gram-positive bacterial infections.

Norimode *Aspen, S.Afr.; Tillomed, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Norin *Intra-Labs, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norincol *Volchem, Ital.*
Carbohydrate; lipids; amino acids; fibre.
Nutritional supplement.

Norin-MZ *Intra-Labs, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Norin-TD *Intra-Labs, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norinyl *Pfizer, Mex.*
Norethisterone (p. 2294·2); mestranol (p. 2291·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menopausal disorders.

Norinyl-1 *Pfizer, Austral.; Pfizer, Hong Kong†; Pfizer, NZ; Pharmacia, UK.*
Norethisterone (p. 2294·2); mestranol (p. 2291·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Norinyl-1/28 *Pfizer, S.Afr.*
21 Tablets, norethisterone (p. 2294·2); mestranol (p. 2291·1); 7 tablets, inert.
Combined oral contraceptive.

Norinyl 1 + 35 *Searle, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Norinyl 1 + 50 *Searle, USA.*
Norethisterone (p. 2294·2); mestranol (p. 2291·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Noripam *Brainware, S.Afr.†*
Oxazepam (p. 1092·2).
Anxiety disorders; alcohol withdrawal syndrome.

Noripurum *Nycomed, Braz.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemias.

Noripurum Fólico *Nycomed, Braz.*
Folic acid (p. 2063·1); iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemias.

Noripurum Vitaminado *Nycomed, Braz.*
Iron polymaltose (p. 2077·2); vitamins.
Iron-deficiency anaemia.

Norisodrine with Calcium Iodide *Abbott, USA.*
⊗Isoprenaline sulfate (p. 1411·3); calcium iodide (p. 1658·1).
Coughs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Noristerat *Bayer, Ger.; Zydus, India; Bayer Schering, Malaysia; Bayer, Mex.; Schering, Philipp.†; Bayer, UK.*
Norethisterone enantate (p. 2294·3).
Progestogen-only injectable contraceptive.

Norit *Norit, Austria; Kela, Belg.; Norit, Cz.†; Norit, Gr.; Norit, Israel; Norit, Neth.; Norit, Port.; Apotheca, Singapore†; Tanner, Switz.; Galpharm, UK.*
Activated charcoal (p. 1537·3).
Diarrhoea; treatment of poisoning; flatulence.

Norit Carbomix *Norit, Denm.*
Activated charcoal (p. 1537·3).
Treatment of poisoning.

Noritate *Valeant, Canad.; Sanofi, China; Dermik, Hong Kong†; Mediline, Israel; Aventis, UK; Valeant, USA.*
Metronidazole (p. 936·1).
Rosacea; acne.

Norit-Carbomix *Norit, Austria; Kela, Belg.*
Activated charcoal (p. 1537·3).
Treatment of poisoning; diarrhoea.

Noritet *Quatromed, S.Afr.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Noritis *Cadila, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Noritren *Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ital.; Lundbeck, Norw.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Norizec *Medifarma, Indon.; UAP, Indon.; Therapharma, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Norlamine *Biotech, Venez.*
Ofloxacin (p. 334·3).
Bacterial infections.

NorLevo *HRA, Denm.; Aska, Jpn; Nycomed, Swed.; Sandoz, Switz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Norlevo *Sandoz, Austral.; Besins, Belg.; HRA, Canad.; HRA, Fin.; HRA, Fr.; Gerolymatos, Gr.; Win-Medicare, India; Ferring, Irl.; CTS, Israel; Angelini, Ital.; HRA, Neth.; HRA, Norw.; Fargin, Port.; Actor, S.Afr.; Chiesi, Spain; Abdi, Turk.; Polinac, Venez.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Norlex-TZ *Lexus, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norlidine *Biotech, Venez.*
Povidone-iodine (p. 1767·1).
Vulvovaginal and cervical infections.

Norline *Pharmaland, Thai.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Norlip *Unipharm, Israel.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Norlon *Ranbaxy, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norlopin *Saba, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Norlut N *Cipla, India.*
Norethisterone acetate (p. 2294·3).

Norlutate *Erfa, Canad.*
Norethisterone acetate (p. 2294·3).
Abnormal uterine bleeding; endometriosis; amenorrhoea.

Normabrain *Torrent, India; Torrent, Philipp.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment; mental function disorders.

Normabraïn *UCB, Ger.†*
Piracetam (p. 393·3).
Mental function disorders.

Normace *Unichem, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Normace-D *Unichem, India.*
⊗Enalapril (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Normaclin *Aflofarm, Pol.*
Clindamycin phosphate (p. 269·3).
Acne.

Normacol *Norgine, Belg.; Helix, Canad.; Norgine, Fr.; Norgine, Hong Kong†; Norgine, Irl.; Norgine, Ital.; Norgine, Neth.; Norgine, NZ; Norgine, S.Afr.; Norgine, Singapore; Norgine, Switz.; Norgine, UK.*
Sterculia (p. 1888·3).
Constipation; ostomy management; diverticular disease; ingestion of foreign bodies; irritable bowel syndrome.

Normacol Lavement *Norgine, Fr.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Normacol Plus *Norgine, Austral.; IFET (ΙΦΕΤ), Gr.; Norgine, Hong Kong†; Norgine, Irl.; Norgine, NZ; Norgine, Port.; Norgine, S.Afr.; Norgine, Singapore; Norgine, UK.*
Sterculia (p. 1888·3); frangula (p. 1843·3).
Constipation; bowel evacuation; diverticular disease; ostomy management.

Normadate *GSK, India.*
Labetalol.
Hypertension.

Normaderm Barra de Limpieza *Vichy, Chile.*
Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); hamamelis (p. 2523·3); zinc pidolate (p. 1720·3).
Soap substitute; seborrhoea.

Normaderm Concentrado Activo *Vichy, Chile.*
Salicylic acid (p. 1719·1); silica (p. 2208·3); kaolin (p. 1850·1); hamamelis (p. 2523·3).
Skin disorders.

Normaderm Exfoliante *Vichy, Chile.*
Salicylic acid (p. 1719·1); glicacil (p. 2156·3); glycolic acid (p. 1704·3); jojoba esters; zinc polysaccharides (p. 2126·1).
Skin cleansing; seborrhoea.

Normaderm Gel de Limpieza *Vichy, Chile.*
Glicacil (p. 2156·3); salicylic acid (p. 1719·1); glycolic acid (p. 1704·3); hamamelis (p. 2523·3).
Acne; seborrhoea.

Normaderm Stick Secante Camufu Imperfecciones *Vichy, Chile.*
Aluminium chlorohydrate (p. 1694·1); salicylic acid (p. 1719·1); triclosan (p. 1773·2).
Skin disorders.

Normaderm Tonico Astringente *Vichy, Chile.*
Glicacil (p. 2156·3); salicylic acid (p. 1719·1); glycolic acid (p. 1704·3).
Skin disorders.

Normadiab *Actavis, Hung.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Normadil *GX, Philipp.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's disease.

Normafenac *Norma (Νορμα), Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Normafibe *Norgine, Austral.*
Sterculia (p. 1888·3).
Constipation; fibre supplement.

Normafilus *Codifra, Fr.*
Lactobacillus acidophilus (p. 2596·3).
Gastrointestinal discomfort.

Normaflore *Sanofi-Aventis, Hung.*
Bacillus clausii.
Maintenance of gastrointestinal flora.

Normaflu *Ratiopharm, Ital.*
Paracetamol (p. 115·1).
Fever; cold and influenza symptoms; pain.

Normagan *Gujarat Terce, India.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; motion sickness; insomnia.

Normaglyc *Jelfa, Cz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Normagut
Note: this name may be used for preparations of different composition.
Wockhardt, India; Mega Lifesciences, Ukr.
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; gastrointestinal motility disorders.

Normakut *Gebro, Austria.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Normal *Helios, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Normal Dandruff Treatment *Apollo, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Normalac
Note: this name may be used for preparations of different composition.
Gynopharm, Chile; Vivax Gynopharm, Venez.
Lynestrenol (p. 2287·3).
Progestogen-only oral contraceptive.

Mankind, India; Molteni, Pol.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Normalax
Note: this name may be used for preparations of different composition.
Taro, Israel.
Macrogol 3350 (p. 2547·3).
Constipation.

Normalene *Montefarmaco, Ital.*
Bisacodyl (p. 1821·1).
Constipation.

NormaLine
Note: this name may be used for preparations of different composition.
Antonetto, Ital.
Glucomannan (p. 2515·2).
Obesity; dietary supplement in diabetes mellitus and hyperlipidaemias.

Normaline
Note: this name may be used for preparations of different composition.
Julphar, UAE; Apothecary, USA.
Sodium chloride (p. 1795·1).
Sodium depletion; nasal congestion.

Normaline Plus *Mankind, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Normaline-H *Mankind, India.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide (p. 1044·2).

Normalip *Quesada, Arg.*
Atorvastatin (p. 1309·2).
Hypercholesteroloaemia.

Normalip pro *Abbott, Ger.†*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Normalite 1000 *Codifra, Fr.*
Vitamins; minerals; with or without ginseng (p. 2513·3).

Normaloe *Tillomed, UK.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Normalol *Dexcel, Israel.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; migraine; myocardial infarction.

Normamor *Uniao Quimica, Braz.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Normanomin *Norma (Νορμα), Gr.*
Codergocrine mesilate (p. 389·2).

Normapril *Cazi, Braz.*
Captopril (p. 1331·2).
Hypertension.

Normarit *Sigma-Tau, Ital.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Normase *Bioavenir, Israel; Molteni, Ital.; Molteni, Pol.†; Reddy, Rus.; Molteni, Ukr.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; hepatic cirrhosis; hyperammonaemia; gastroenteritis.

Normasec *Ronnet, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Normasol *Seton, Israel; SSL, Singapore; Medlock Medical, UK.*
Sodium chloride (p. 1795·1).
Irrigation solution.

Normason *Astraform, Ukr.*
Zopiclone (p. 1118·1).
Insomnia.

Normastig *Uniao Quimica, Braz.*
Neostigmine metilsulfate (p. 687·2).

Normastigmin *Sigmapharm, Austria; IFET (ΙΦΕΤ), Gr.*
Neostigmine metilsulfate (p. 687·2).
Reversal of competitive neuromuscular blockade; myasthenia gravis; gastrointestinal atony; urinary retention.

Normastigmin mit Pilocarpin *Sigmapharm, Austria.*
Neostigmine bromide (p. 687·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma; pre- and post-operative lowering of intra-ocular pressure; reversal of mydriasis and cycloplegia.

Normastin
Note: this name may be used for preparations of different composition.
Metro, Philipp.
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Hexpharm, Indon.†
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Normaten
Note: this name may be used for preparations of different composition.
Bago, Chile.
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Normaten Plus *Bago, Chile.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Normatens
Note: this name may be used for preparations of different composition.
ICN, Pol.
⊗Clopamide (p. 1342·3); dihydroergocristine (p. 390·1); reserpine (p. 1485·3).
Hypertension.

Meda, Rus.; Meda, Ukr.
⊗Dihydroergocristine mesilate (p. 390·1); clopamide (p. 1342·3); reserpine (p. 1485·3).
Hypertension.

Normatens Plus *Pharmanel, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Normatin *World Medicine, Ukr.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Normatol *Pfizer, Chile.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Normavix *Norma (Νορμα), Gr.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).

Normavom *Cryopharma, Mex.*
Difenidol hydrochloride (p. 1835·1).
Nausea and vomiting; vertigo.

Normax
Note: this name may be used for preparations of different composition.
Galen, UK; United Drug, UK.
Dantron (p. 1833·3); docusate sodium (p. 1836·2).
These ingredients can be described by the British Approved Name Co-danthrusate.
Constipation.

Ipca, India; Ipca, Rus.
Norfloxacin (p. 333·3).
Bacterial infections.

Normax TZ *Ipca, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Normaxid *Stallion, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Normaxin *Systopic, India.*
Clidinium bromide (p. 1833·2); chlordiazepoxide (p. 1044·2); dicycloverine hydrochloride (p. 1834·2).
Irritable bowel syndrome.

Normaxin-RT *Systopic, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2); dicycloverine hydrochloride (p. 1834·2); ranitidine (p. 1882·1).

Normazidol *Olainfarm, Rus.*
Pirlindole hydrochloride (p. 446·3).
Depression; alcohol withdrawal syndrome.

Olainfarm, Ukr.†
Pirlindole (p. 446·3).
Bipolar disorder; schizophrenia; depression; anxiety; alcohol and nicotine withdrawal syndrome; senile dementia.

Normell *Sanofi-Aventis, Gr.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Normenta *Ipca, India.†*
Piracetam (p. 393·3).
Myoclonus.

Normet *Emcure, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Normetec *Pfizer, Philipp.; Pfizer, Thai.*
Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2).
Hypertension; angina pectoris.

Normetic
Note: this name may be used for preparations of different composition.
Lupin, India.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Nor-Metrogyl *JB Chemicals, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Normex Plus *Quimica y Farmacia, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Normhydral *Gebro, Austria.*
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Normide
Note: this name may be used for preparations of different composition.
Morepen, India.
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Normide-CZ *Morepen, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Normigel *Molnlycke, Canad.*
Sodium chloride hydrogel (p. 1795·1).
Wounds.

Normil *Torrent, Philipp.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Normini *Pfizer, Philipp.*
Betahistine hydrochloride (p. 2455·3).
Meniere's disease.

Normint *Mint, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Normison *Aspen, Austral.; Genopharm, Fr.; Meda, Gr.; Meda, Ital.; EuroCept, Neth.; Healthcare Logistics, NZ; Teofarma, Port.; Aspen, S.Afr.; Meda, Switz.*
Temazepam (p. 1109·1).
Insomnia; sleep disorders; premedication.

Normital *Phoenix, Arg.*
⊗Spironolactone (p. 1499·3).
Oedema; heart failure; cirrhosis; nephrotic syndrome; hyperaldosteronism; hypertension.

Normiten *Teva, Israel.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

Normix *Alfa Wassermann, Cz.; Alfa Wassermann, Hung.; Wassermann, Ital.; Gurel, Turk.*
Rifaximin (p. 355·2).
Gastrointestinal bacterial infections; hepatic encephalopathy; infection prophylaxis in colorectal surgery; hyperammonaemia.

Normlgel *Molnlycke, Austral.; Molnlycke, Fr.*
Sodium chloride (p. 1795·1).
Burns; ulcers; wounds.

Molnlycke, Belg.
A hydrogel dressing.
Wounds.

Normo Gastryl *Sabex, Canad.†*
Sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1); sodium phosphate (p. 1791·2).
Gastric hyperacidity.

Normobren *Medosan, Ital.*
Acetylcarnitine hydrochloride (p. 2053·2).
Cerebrovascular disorders.

Normobron *Chiesi, Gr.*
⊗Salbutamol (p. 1220·2).
Bronchodilator.

Normoc *Recordati, Ger.†*
Bromazepam (p. 1041·2).
Anxiety; insomnia.

Normocarb *Dialysis Solutions, Canad.*
Magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1778·2).
Haemodialysis.

Normocard *Polfa Warszawa, Pol.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Normocedon *Biospray, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Normocid
Note: this name may be used for preparations of different composition.
Flamingo, India.
Injection: Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Ultramark, India.
Oral liquid: Domperidone (p. 1838·1); magaldrate (p. 1856·1); simeticone (p. 1886·2).

Normodiab *Actavis, Cz.; Actavis, Denm.; Actavis, Pol.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Normodin *Genepharm, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Normodipin *Gedeon Richter, Ukr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Normodipine *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Normodol *Normon, Spain.*
Ibuprofen arginine (p. 68·2).
Pain; fever.

Normoenzym Forte *Farmstandart, Rus.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders; adjunct in abdominal examination.

Normofat *Soho, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Normoflex *Degorts, Mex.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Normofundin *Braun, Fin.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Normofundin G-5 *Braun, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Normofundin OP *Braun, Ger.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Normofundina *Braun, Spain.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Carbohydrate source; fluid and electrolyte disorders.

Normofusin *Fresenius Kabi, Fin.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Normogastrol *Normon, Spain.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Normogin *Baldacci, Ital.*
Bacilli vaginalis culture.
Vaginal bacterial infections.

Normoginkgo *Normon, Spain.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Normoglaucon *Tramedico, Belg.†; Mann, China; Mann, Ger.; Tramedico, Neth.†; Mann, Pol.; Lepori, Port.†*
⊗Pilocarpine hydrochloride (p. 2010·3); metipranolol hydrochloride (p. 2009·2).
Glaucoma; ocular hypertension.

Normoglucon *Wabosan, Austria.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Normohex *Hexal, Austria.*
Moxonidine (p. 1442·1).
Hypertension.

Normolact *Borshchagovskii, Ukr.*
Lactulose (p. 1850·3).
Constipation; hypercholesterolaemia; hepatic encephalopathy; hepatic coma.

Normolax
Note: this name may be used for preparations of different composition.
EMS, Braz.
Lactulose (p. 1850·3).

Herbapol Lublin, Pol.
Frangula bark (p. 1843·3).
Constipation.

Normolaxil *Trenker, Belg.†*
Lactitol (p. 1850·3).
Constipation.

Normolem *Teva, Mex.*
Melatonin (p. 2551·3).
Sleep disorders.

Normolip *Sun, India.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Normolipol *Austral, Arg.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Normolose *Adelco, Gr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Normolose-H *Adelco, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Normolyt *Gebro, Austria; Gebro, Hung.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Normolytoral *Gebro, Switz.*
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Normomale *Arafarma, Spain.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Normonal *Eisai, Jpn; Eisai, Thai.*
⊗Tripamide (p. 1520·2).
Hypertension.

Normoparin *Caber, Ital.†*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Normopres
Note: this name may be used for preparations of different composition.
Ali, Turk.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Delta, Braz.
Nifedipine (p. 1447·2).
Hypertension.

KVZ, Ukr.
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vista, Philipp.
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Normopresan *Rafa, Israel.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Normopresil *Sanofi-Aventis, Spain.*
⊗Chlortalidone (p. 1335·2); atenolol (p. 1308·2).
Hypertension.

Normopress
Note: this name may be used for preparations of different composition.
Caber, Ital.
⊗Atenolol (p. 1308·2); indapamide (p. 1409·2).
Hypertension.

Alliance, S.Afr.†
Methyldopa (p. 1431·1).
Hypertension.

Normopril *Aristo, India.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Normoprost Compuesto *Temis, Arg.*
Pygeum africanum (p. 2363·2); glutamic acid (p. 2070·2); alanine (p. 2048·3); glycine (p. 2071·2).
Prostate disorders.

Normoprost Plus *Temis, Arg.*
Pygeum africanum (p. 2363·2); saw palmetto (p. 2363·3).
Prostate disorders.

Normoreum *Normon, Spain.*
Devil's claw root (p. 42·3).
Joint pain.

Normorix *Nycomed, Norw.; Nycomed, Swed.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Oedema; hypertension; liver cirrhosis with ascites.

Normorytmin *Abbott, Arg.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Normosan *Herbapol Lublin, Pol.†*
Caraway (p. 2470·2); frangula bark (p. 1843·3); peppermint leaf (p. 1877·1); sambucus (p. 2609·3); senna (p. 1885·1).
Constipation.

Normosang *Orphan, Austria; Orphan, Belg.; Orphan, Cz.; Orphan, Denm.; Orphan, Fin.; Orphan, Fr.; Orphan, Ger.; IFET [ΙΦΕΤ], Gr.; Orphan, Irl.; Orphan, Ital.; Orphan Pacific, Jpn; Orphan, Neth.; Orphan Europe, Port.; Orphan, Spain; Orphan Europe, Swed.; Stauffacher, Switz.; Orphan, UK.*
Haem arginate (p. 1555·3).
Porphyria.

Normosept *Normon, Spain.*
Chlorhexidine gluconate (p. 1743·3).

Normoskin *Hautel, Arg.*
Aluminium chlorohydrate (p. 1694·1).

Normosol *Hospira, Canad.*
A range of electrolyte infusions with or without glucose (p. 1775·1).
Fluid and electrolyte disorders.

Hospira, Ital.; Hospira, USA.
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Normosoy *Normon, Spain.*
Soya bean (p. 2092·3).
Menopausal disorders.

Normospas *Systopic, India.*
Dicycloverine (p. 1834·2); mefenamic acid (p. 85·3).

Normospor *Adcock Ingram, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal fungal infections.

Normoten
Note: this name may be used for preparations of different composition.
Soho, Indon.
Amlodipine besilate (p. 1304·1).
Hypertension.

Torrent, Philipp.
Losartan potassium (p. 1422·2).
Hypertension.

Normothen *Bioindustria, Ital.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Normotherin *Unipharma, Gr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Normotil
Note: this name may be used for preparations of different composition.
Novell, Indon.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Normoton *Fitapharm, Ukr.*
Crataegus (p. 2488·1); peppermint leaf (p. 1877·1); melissa (p. 2552·3); motherwort (p. 2564·2); clove (p. 2481·2).
Cardiovascular disorders.

Normotride *Arafarma, Spain.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris.

Normotus *Normon, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Normovagil *Arafarma, Spain.*
⊗Glycerol (p. 2517·2).
Vaginal dryness.

Normoval *Normon, Spain.*
Valerian (p. 2640·2).
Nervous disorders; insomnia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Normoven *KVZ, Ukr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Normovidona *Normon, Spain.*
Povidone-iodine (p. 1767·1).

Normovite Antianemico *Normon, Spain.*
Folic acid (p. 2063·1); ferrous gluceptate (p. 2061·2).
Iron and folic acid deficiency.

Normozin *Psychotropics, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine (p. 1113·2).

Normpress *Greater Pharma, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; myocardial infarction.

Normudal *Combiphar, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Normulen *Euro Registratie, Neth.†; Pfizer, Spain.†*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis.

Nornij *Sunij, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Nornij-TZ *Sunij, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norocin *Vianex (Βιανεξ), Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Norodol *Ali, Turk.*
Haloperidol (p. 1077·1).
Psychoses; agitation; behaviour disorders; anxiety; hiccups; nausea and vomiting.

Norofren *Sanofi Synthelabo, Turk.*
Pimozide (p. 1096·3).
Psychoses.

Norogil *Sanofi-Aventis, Braz.*
Dihydroergocristine mesilate (p. 390·1); lomifylline (p. 2545·1).
Thrombosis prophylaxis; orthostatic hypotension; migraine and other vascular headaches; impaired mental function.

Noroid *Soho, Indon.*
Emollient.
Atopic eczema; dry skin.

Noromat *Biofarma, Turk.*
Topiramate (p. 550·3).

Noronal *Ducto, Braz.*
Ketoconazole (p. 585·3).
Fungal infections.

Noros *Kalbe, Indon.*
Grapeseed extract (p. 2521·3); lycopene (p. 2546·2); vitamin E (p. 2119·1); vitamin C (p. 2110·3); vitamin B substances (p. 2102·3); selenium (p. 2086·3); zinc (p. 2126·1).
Antoxidant; dietary supplement.

Noroseptan *Bros, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Nörotrop *Sandoz, Turk.*
Piracetam (p. 393·3).
Mental function disorders; behaviour disorders; cerebrovascular disorders; alcoholism.

Noroxin *MSD, Arg.; MSD, Austral.; MSD, Ital.; MSD, Mex.; MSD, Neth.†; MSD, NZ†; MSD, Port.; MSD, S.Afr.†; MSD, Spain†; MSD, Switz.; Abbott, Turk.; Merck, USA; Roberts, USA; MSD, Venez.*
Norfloxacin (p. 333·3).
Bacterial infections.

Noroxine *MSD-Chibret, Fr.*
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract; gonococcal urethritis; gonococcal cervicitis.

Norpace *RPG, India; Searle, S.Afr.; Ali, Turk.; Searle, USA.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Norpen Oro *Norma (Νορμα), Gr.*
Olanzapine (p. 1089·3).

Norper *DWD, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Norphed *Huons, Philipp.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; gastrointestinal haemorrhage.

Norphen
Note: this name may be used for preparations of different composition.
Atlantic, Singapore; Atlantic, Thai.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain; tension headache; dysmenorrhoea.

Norphin *Unichem, India.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Norpid *Greater Pharma, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Norpilen *Andromaco, Chile.*
Venlafaxine (p. 454·2).
Depression; anxiety.

Norpin *Dalim, Thai.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; shock.

Norpin A *Hanmi, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); methylephedrine hydrochloride (p. 1669·2); sulfogaiacol (p. 1678·1); riboflavine sodium phosphate (p. 2104·3); caffeine (p. 1203·3).
Cold symptoms; cough.

Norplant *Djaya Bima Agung, Indon.†; Leiras, Indon.†; Bayer, Thai.*
Levonorgestrel (p. 2296·1).
Progestogen-releasing implantable contraceptive.

Norplat *Getz, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Norpled *Cryopharma, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Norplus *Imperial, Philipp.*
⊗Imidapril hydrochloride (p. 1409·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Norpramin
Note: this name may be used for preparations of different composition.
Hoechst Marion Roussel, USA.
Desipramine hydrochloride (p. 413·1).
Depression.

Labesfal, Port.
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

UCB, Spain.†
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Norpress
Note: this name may be used for preparations of different composition.
Atral, Port.
⊗Indapamide (p. 1409·2).
Hypertension.

Mylan, NZ.
Nortriptyline hydrochloride (p. 439·3).
Depression; aid to smoking withdrawal.

Norpril *Teva, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Norprolac *Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Israel; Ferring, Mex.; Ferring, Neth.; Ferring, Norw.; Pharmaco, NZ; Ferring, Pol.; Ferring, Port.; Ferring, Rus.; Ferring, S. Afr.; Ferring, Singapore; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, Turk.; Ferring, UK; Ferring, Ukr.*
Quinagolide hydrochloride (p. 2601·2).
Hyperprolactinaemia; acromegaly; lactation inhibition.

Norpy *Hos & Ins, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nor-QD *Watson, USA.*
Norethisterone (p. 2294·2).
Progestogen-only oral contraceptive.

Norquinol
Note: this name may be used for preparations of different composition.
Mavi, Mex.
Norfloxacin (p. 333·3).
Bacterial infections.

Norrit *Ind-Swift, India.*
Eye/ear drops: Norfloxacin (p. 333·3).
Eye and ear infections.
Ind-Swift, India.
Oral suspension: Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Norrit-Ord *Ind-Swift, India.*
Norfloxacin (p. 333·3); ornidazole (p. 943·1).

Nor-S *Systacare, India.*
⊗Noradrenaline acid tartrate (p. 1458·2).

Norsec *Guardian, Indon.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Norsed *Sanofi-Aventis, Cz.†; Sanofi-Aventis, Port.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Norsept *Polfa Pabianice, Pol.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Norserin *Norton, Pol.†*
Mianserin hydrochloride (p. 434·2).
Depression.

Norset *MSD-Chibret, Fr.*
Mirtazapine (p. 436·1).
Depression.

Norsic *Andromaco, Chile.*
Quetiapine (p. 1101·1).
Schizophrenia.

Norsica *Suphong, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle spasm and pain.

Norsol
Note: this name may be used for preparations of different composition.
Finadiet, Arg.; Sandoz, Switz.
Norfloxacin (p. 333·3).
Bacterial infections.

Bilim, Turk.
⊗Prednisolone sodium phosphate (p. 1645·3).
Inflammatory eye disorders.

Norspan *Mundipharma, Austral.; Mundipharma, Cz.; Norpharma, Denm.; Mundipharma, Fin.; Grunenthal, Ger.; Mundipharma, Jpn; Mundipharma, Norw.; Pharmaco, NZ; Mundipharma, Philipp.; Napp, Port.†; Mundipharma, Swed.*
⊗Buprenorphine (p. 30·2).
Pain.

Norspor *Pond's, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Norstene *Rotexmedica, Philipp.; Atral, Port.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Norsulfazol *Moschimfarm, Rus.; Obolenskoe, Rus.*
Sulfathiazole (p. 368·3).
Bacterial infections.

Norsulin
Note: this name may be used for preparations of different composition.
Therapharma, Philipp.
Metformin hydrochloride (p. 489·1); glipizide (p. 474·1).
Diabetes mellitus.

Polfa Pabianice, Pol.†
Gliclazide (p. 472·3).
Diabetes mellitus.

Norswel *Zydus, India.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Nor-T *Cipla, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Nort *Klar Sehen, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Nortafen *Norton, Ukr.†*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nortan *Sanofi Synthelabo, Turk.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Nortase *Repha, Ger.*
Rizolipase; protease and amylase from *Aspergillus oryzae.*
Pancreatic insufficiency.

Nortec *Ativus, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Norteic *Zdorovje, Ukr.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Nortelol *Atlantic, Hong Kong; Atlantic, Thai.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Nortem *Ivax, Irl.*
Temazepam (p. 1109·1).
Insomnia; premedication.

Nortemp *Ballay, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Norten
Note: this name may be used for preparations of different composition.
Baroda, India.
⊗Propranolol (p. 1479·1).
Hypertension; phaeochromocytoma; myocardial infarction; arrhythmias; migraine; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; essential tremor.

Imperial, Philipp.
Imidapril hydrochloride (p. 1409·1).
Hypertension; heart failure; diabetic nephropathy.

Nortenolol *Tillomed, Irl.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Nor-Tenz *Grin, Mex.*
Brimonidine (p. 2004·3).
Glaucoma; ocular hypertension.

Norterol *Tecnifar, Port.*
Nortriptyline hydrochloride (p. 439·3).
Anxiety; depression.

Norterone *Acdhon, Thai.*
Norethisterone acetate (p. 2294·3).
Menstrual disorders; endometriosis; progestogen-only oral contraceptive; menopausal disorders; breast cancer.

North Sunx Sunscreen *Coretex, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Northicalm *Northia, Arg.*
Diphenhydramine (p. 626·1); calamine (p. 1697·2).

Northiron *Norma (Νορμα), Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Northyx *Centrix, USA.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Nortifen *Otto, Indon.*
Ketotifen fumarate (p. 631·3).
Asthma.

Nortimil *Chiesi, Ital.*
Desipramine hydrochloride (p. 413·1).
Depression; psychoses.

Nortin *La Pharmaceuticals, India.*
Nortriptyline.
Depression.

Nortivan *Gedeon Richter, Hung.; Polfa Grodzisk, Pol.; Gedeon Richter, Rus.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Nortivan HCT *Gedeon Richter, Hung.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Nortolan *Anfarm, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Nortram *Shin Poong, Philipp.†*
Norfloxacin (p. 333·3).
Urinary-tract infections; gonorrhoea.

Nortrel
Note: this name may be used for preparations of different composition.
Barr, USA.
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Wyeth, Braz.†
Levonorgestrel (p. 2296·1).
Progestogen-only oral contraceptive.

Nortrigin *Meizler, Braz.*
Lamotrigine (p. 527·2).

Nortrilen *Lundbeck, Belg.; Lundbeck, Cz.; Lundbeck, Ger.; Gerolimatos (Γερολυματος), Gr.; Lundbeck, Hong Kong; Lundbeck, Neth.; Lundbeck, Switz.; Lundbeck, Thai.†*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Nortrip *Teuto, Braz.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Nortuss *Rosemont, Thai.†*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough.

Nortussine *Norgine, Belg.*
Dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cough.

Norgine, Fr.†
Paediatric syrup: Dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1); guaifenesin (p. 1666·2).
Cough.

Norgine, Fr.†
Syrup: Dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1).
Cough.

Nortussine Mono *Norgine, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Nortylin *Rekah, Israel.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Nortyline *Condrugs, Thai.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Nor-U *Hindustan Antibiotic, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norubin *Cadila, India.*
Daunorubicin (p. 778·3).
Malignant neoplasms.

Norum *Chew, Thai.*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Noruvec *Huons, Philipp.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Noruxol *Smith & Nephew, Ital.*
⊗Collagenase (p. 2484·1).
Necrotic wounds and ulcers.

Norvadin *Bryntsalov, Rus.; Abdi, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Abdi, Ukr.†
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Norvagen *Stargen, Gr.*
Amlodipine besilate (p. 1304·1).

Norvalet *Alet, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Norvapine *Ascent, Austral.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Norvas *Pfizer, Mex.; Pfizer, Spain.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Norvasc *Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris; Raynaud's syndrome; ischaemic heart disease; cardiovascular risk reduction.

Norvask *Pfizer, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Norvate *Taj, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Norvectan *Atral, Port.; Fardi, Spain.*
Ibuprofen lysine (p. 68·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Norvent *Ind-Chemie, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

Norvent-D *Ind-Chemie, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Norventyl *Valeant, Canad.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Norvetal *Gynopharm, Chile.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Norviken *Vent-3, Arg.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Norvipren *Sandoz, Denm.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Norvir *Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, China; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; AbbVie, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Jpn; Abbott, Malaysia; Abbott, Mex.; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK; Abbott, USA; Abbott, Venez.*
Ritonavir (p. 1013·1).
HIV infection.

Norvit *Prohealth, India.*
Norfloxacin (p. 333·3).
Ear or eye infections.

Norvomin *Saga, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Norwegian Formula Ageless Handcream *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Norwegian Formula Lip Moisturizer *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Norwich Extra Strength *Procter & Gamble, USA.*
Aspirin (p. 22·2).
Pain; fever; inflammation; transient ischaemic attacks; myocardial infarction.

Norwich Regular Strength *Lee, USA.*
Aspirin (p. 22·2).
Fever; pain.

Norxacin *Siam Bheasach, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norxia *Asian Pharm, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Norxin *Cazi, Braz.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Norzac *Ivax, Irl.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Norzee-TZ *Wings, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Norzen *FDC, India.*
Norfloxacin (p. 333·3).
Ear infections.

Norzol *Rosemont, UK.*
Metronidazole benzoate (p. 936·1).
Bacterial infections.

Norzyme *Nordmark, Singapore.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Nos *Dermofarm, Spain.†*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Nos-Air *Invision, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nos-Air Saline *Invision, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Nosatel *Guidotti, Gr.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Nosazine *Universal, Hong Kong.†*
Noscapine (p. 1670·3); phenylephrine (p. 1672·2); promethazine (p. 638·2).

Nosbal *Merck, Mex.*
⊗Atenolol (p. 1308·2).
Hypertension.

Nos-Bra *Bryntsalov, Rus.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Nosbrom *Frankin, Hong Kong.†*
Bromhexine (p. 1656·3); noscapine (p. 1670·3).
Cough.

Noscaflex *Kela, Belg.*
Syrup: Noscapine hydrochloride (p. 1670·3); guaifenesin (p. 1666·2).
Cough.

Kela, Belg.
Tablets: Noscapine hydrochloride (p. 1670·3).
Cough.

Nosca-Mereprine *Novum, Belg.*
Noscapine hydrochloride (p. 1670·3).
Cough.

Noscapax *Nicholas, Indon.*
⊗Noscapine (p. 1670·3); pseudoephedrine (p. 1676·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Cough.

Noscaphylline *Marching, Hong Kong.†*
Noscapine (p. 1670·3); theophylline (p. 1229·3).

Nose Fresh *Rappai, Switz.*
Nasal spray: Sea salt (p. 2612·1).
Nasal dryness.

Rappai, Switz.
Nasal oil: Sesame oil (p. 2614·1).
Nasal dryness.

Rappai, Switz.
Nasal ointment: Sea salt (p. 2612·1); macrogol 400 (p. 2547·3).
Nasal dryness.

Nose Fresh au D-panthenol *Rappai, Switz.*
Sea salt (p. 2612·1); dexpanthenol (p. 2582·2).
Nasal dryness.

Nosedin *Combiphar, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Noseeze *Goldshield, UK.*
Sesame oil (p. 2614·1).
Inflammation and dryness of the nasal mucosa.

Nosic *Indoco, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Nosirid *Plus, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Nosirid-P *Plus, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).
Migraine.

Nositrol *Cryopharma, Mex.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Nosoap *Investi, Arg.*
Soap substitute.

Percos, India.
Cetyl alcohol (p. 2178·2).

Nosobac *Aglowmed, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Nosocef *Wockhardt, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

No-Sol *Farmak, Ukr.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal dryness.

Nosomik *Aglowmed, India.*
Amikacin (p. 214·1).
Bacterial infections.

No-Sor Nose Balm *Pickles, UK.*
Dibrompropamidine isetionate (p. 1750·1); wheat-germ oil (p. 2647·1); menthol (p. 2553·2); eucalyptus (p. 2501·1).

No-Sor Vapour Rub *Pickles, UK.*
Camphor (p. 2466·2); turpentine; menthol (p. 2553·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar wood oil (p. 2472·3); thymol (p. 1772·2).
Upper respiratory-tract congestion.

Nosox *Hasco-Lek, Pol.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

No-Spa *Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.†; Chinoin, Pol.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi Synthelabo, Thai.†; Sanofi-Aventis, Ukr.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm; pain.

No-Spalgin *Sanofi-Aventis, Hung.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Ukr.†*
Codeine phosphate (p. 40·2); drotaverine hydrochloride (p. 2497·3); paracetamol (p. 115·1).
Pain; headache.

Nospan *YSP, Malaysia; Yung Shin, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

No-Spasma *Nabros, Ukr.†*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1); mefenamic acid (p. 85·3).
Colic pain; dysmenorrhoea.

Nospasmin *Sanitas, Chile.*
Pipethanate (p. 1878·2).
Smooth muscle spasm.

Nospasmin Compuesto *Sanitas, Chile.*
Metamizole magnesium (p. 53·3); pipethanate hydrochloride (p. 1878·2).
Nausea and vomiting; smooth muscle spasm.

Nostaden *Mintlab, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Nostel *Pyridam, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Nostero *Tolmann, Philipp.†*
Phenylpropanolamine hydrochloride (p. 1674·1); brompheniramine maleate (p. 618·1).
Nasal congestion.

Nosterol *Lamsa, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Nosteron *Gedeon Richter, Denm.†; Richter, Pol.*
⊗Exemestane (p. 792·2).
Breast cancer.

Nostidyn *Farmaceutica H, Mex.*
Norethisterone enantate (p. 2294·3); estradiol valerate (p. 2271·2).
Injectable contraceptive.

Nostil
Note: this name may be used for preparations of different composition.
Deva, Turk.
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Nasal congestion.

Latinofarma, Braz.
Ofloxacin (p. 334·3).
Bacterial eye infections.

Nostimex *Rafarm, Gr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Nostipan *Micro, India.*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Nostra *Corona, India.*
Norethisterone acetate (p. 2294·3).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Nostren *Meprofarm, Indon.*
Capsaicin (p. 35·1); methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain; sprains.

Nostril
Note: this name may be used for preparations of different composition.
Ciba, USA.
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Boehringer Ingelheim, Fr.†
Chlorhexidine gluconate (p. 1743·3); cetrimonium bromide (p. 1742·3).
Nose and throat infections.

Nostrilet *Osoth, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; hay fever; nasal congestion; cold symptoms.

Nostrilla *Insight, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nostrilla Complete Congestion Relief *Insight, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nostrilla Conditioning Double Moisture *Insight, USA.*
Cineole (p. 2479·1); sodium chloride (p. 1795·1); spearmint oil (p. 2621·2); sweet birch oil (p. 92·1).
Nasal dryness.

Nostroline *Co-Pharma, UK.*
Menthol (p. 2553·2); cineole (p. 2479·1); geranium oil (p. 2512·2).
Nasal congestion.

Nosulin *Dey's, India.*
Guar gum (p. 475·1).

Nosweat *Madaus, Austria; Biokraft, Norw.†*
Sage (p. 2608·3).
Hyperhidrosis.

Notakehl *Sanum-Kehlbeck, Ger.; Ebi, Switz.*
Penicillium chrysogenum.
Homoeopathic preparation.

Notem *Teva, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Noten *Alphapharm, Austral.; ICH, Hong Kong†; Alphapharm, Malaysia†; Alphapharm, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Notence *Crescent, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Notensyl *CTI, Israel.*
Dicycloverine hydrochloride (p. 1834·2).
Irritable bowel syndrome; neurogenic intestinal disorders.

Noteron *Little Greave, India.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; menopausal disorders; premenstrual syndrome; breast cancer.

Notezine *Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.*
Diethylcarbamazine citrate (p. 153·1).
Filariasis.

Notgaz *Automedic, Fr.†*
Activated charcoal (p. 1537·3); simeticone (p. 1886·2).
Dyspepsia; meteorism.

Notiabolfen *Accord, Irl.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Notidin *Nobel, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Notirol *Actavis, Rus.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Notis *Toll, Pol.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Notisym-LB *Symbiosis, India.*
Lactic acid bacillus (p. 2596·3); norfloxacin (p. 333·3); tinidazole (p. 949·2).

Notolac *Farma, Venez.*
Ketorolac trometamol (p. 80·2).
Pain.

Notorium *Adelco, Gr.*
Bromazepam (p. 1041·2).
Anxiety disorders.

No-Tos Adultos *Medical, Arg.; Sanofi-Aventis, Arg.*
Lozenges: Hexylresorcinol (p. 1755·1); senega (p. 1677·2); liquorice (p. 1853·2); tolu balsam (p. 1679·2); cineole (p. 2479·1).
Cough.

Medical, Arg.
Syrup: ⊗Sodium benzoate (p. 1738·2); ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); senega (p. 1677·2); aconite (p. 2428·3); niaouli oil (p. 2569·1); tolu (p. 1679·2); liquorice (p. 1853·2).
Cough.

No-Tos Biotic *Medical, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

No-Tos Hedera *Sanofi-Aventis, Arg.*
Ivy (p. 2536·2).
Bronchial catarrh.

No-Tos Infantil *Medical, Arg.; Sanofi-Aventis, Arg.*
Lozenges: Sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1); senega (p. 1677·2); liquorice (p. 1853·2); ipecacuanha (p. 1667·2); tolu balsam (p. 1679·2).
Cough.

Medical, Arg.; Sanofi-Aventis, Arg.
Syrup: Sodium benzoate (p. 1738·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); senega (p. 1677·2); liquorice (p. 1853·2); tolu balsam (p. 1679·2); Desessartz syrup (p. 1667·2).
Cough.

No-Tos Mucolitico *Medical, Arg.; Sanofi-Aventis, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Cough; catarrh.

No-Tos NF *Sanofi-Aventis, Arg.*
Bromhexine hydrochloride (p. 1656·3); butetamate citrate (p. 1658·1).
Cough.

No-Tos Pocket *Sanofi-Aventis, Arg.*
Noscapine (p. 1670·3); guaifenesin (p. 1666·2); benzocaine (p. 1980·2); hexylresorcinol (p. 1755·1).
Cough.

Notoxin *Szama, Arg.*
Cholesterol; chlorophyll (p. 2178·3); turpentine oil (p. 2636·3); zinc oxide (p. 1729·1).
Burns; skin cleansing; skin infections; ulcers; wounds.

Notozen *Bouzen, Arg.†*
Bromhexine (p. 1656·3); clofedanol (p. 1659·1).
Cough.

Notpel *Leovan, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Notrab *Microsules, Arg.*
Ranitidine (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Nötras *Liba, Turk.*
Aspirin (p. 22·2).
Fever; pain.

Notril *Winsome, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Notrino *Grimberg, Fr.†*
Cysteine (p. 2058·3); precipitated sulfur (p. 1721·1); vitamin A acetate (p. 2098·3); dried yeast (p. 2125·2).
Rhinitis; rhinopharyngitis.

Notritis *Caprifarmindo, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Notrix *Sanitas, Chile.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Notrixum *Novell, Indon.; Novell, Thai.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Notrotam *Landson, Indon.*
Piracetam (p. 393·3).
Cerebrovascular disorders; alcoholism; mental function impairment.

Notta
Note: this name may be used for preparations of different composition.
Bittner, Austria; Bittner, Rus.; Bittner, Ukr.
Avena sativa (p. 2451·1); phosphorus (p. 2589·2); chamomilla (p. 2474·1); coffea (p. 2648·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Sanovel, Turk.
Montelukast sodium (p. 1214·3).
Asthma.

Nottem *Sanofi-Aventis, Ital.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Notty *East African, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Notus
Note: this name may be used for preparations of different composition.
Rimafar, Spain.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Notusin *Medea, Spain.*
Codeine phosphate (p. 40·2).
Cough.

Notuss
Note: this name may be used for preparations of different composition.
Ache, Braz.
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1); dropropizine (p. 1662·2).
Cough.

Notuss PD *Stewart Jackson, USA.*
Hydrocodone tartrate (p. 67·2); dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Notuss-AC *SJ Pharm, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Notuss-DC *SJ Pharm, USA.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Notuss-Forte *SJ Pharm, USA.*
⊗Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Notuss-NX *SJ Pharm, USA.†*
Codeine phosphate (p. 40·2); chlorcyclizine hydrochloride (p. 620·2).
Upper respiratory-tract disorders.

Notuss-NXD *SJ Pharm, USA.†*
⊗Codeine phosphate (p. 40·2); chlorcyclizine hydrochloride (p. 620·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Notuss-PE *SJ Pharm, USA.*
Codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Nouriast *Kyowa Hakko Kirin, Jpn.*
Istradefylline (p. 902·2).
Parkinsonism.

Nourifusion Multi-Vitamin Moisturizer *Herbalife, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Nourilax *Omega, Neth.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Nourish *Claris, India.*
A range of preparations for enteral nutrition.

Nourishake *GNLD, Austral.*
Nutritional supplement.

Nouriva Repair *Ferndale, USA.*
Emollient.

Nova Derm
Note: this name may be used for preparations of different composition.
Darier, Mex.
Glycolic acid (p. 1704·3).
Dry skin disorders; acne.

Nova Derm Facial Lightening *Darier, Mex.*
Glycolic acid (p. 1704·3); hydroquinone (p. 1705·1); kojic acid (p. 1710·2).
Hyperpigmentation disorders.

Nova Paratropina *Lazar, Arg.*
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm.

Nova Paratropina Compositum *Lazar, Arg.*
Pargeverine hydrochloride (p. 1877·1); clonixin lysine (p. 40·1).
Colic; dyskinesia; menstrual disorders.

Nova T *Bayer, China.*
Copper-wound plastic (p. 2057·1) with a silver core (p. 2615·1).
Intra-uterine contraceptive device.

Nova Vizol *Bell, India.†*
Hypromellose (p. 2189·2).
Dry eyes.

Novaban *Genopharm, Belg.; Alkopharma, Neth.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Novabupi *Cristalia, Braz.*
Levobupivacaine hydrochloride (p. 1987·3). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Novacard *Elnova, India.*
Nifedipine (p. 1447·2).
Angina pectoris; Raynaud's syndrome.

NovaCare *Fielding, USA.*
Vitamins; minerals.

Novacef
Note: this name may be used for preparations of different composition.
Gador, Arg.; Saga, India.
Cefixime (p. 240·3).
Bacterial infections.

Novaceft *Radicura, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Novaceft-S *Radicura, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Novacétol *Pharmastra, Fr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); codeine hydrochloride (p. 40·2).
Pain; fever.

Novacetol *Prater, Chile.*
Clotrimazole (p. 576·2).
Fungal skin infections; trichomoniasis.

Novacid *Willow, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Novacid-D *Willow, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Novacilina *Tecnofarma, Chile.*
Levofloxacin (p. 315·3).
Bacterial infections.

Novacin *TO-Chemicals, Thai.*
Neomycin (p. 329·3); bacitracin (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Throat disorders.

Novacip *Radicura, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Novacip-S *Radicura, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Novaclar *Novagen, India.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Novaclav *Cipla, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Novacler *Monserrat, Arg.*
Dipyrone (p. 53·3).
Colic; fever; pain.

Novaclox *Cipla, India.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Novaclox LB *Cipla, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Novacloxab *Relyo, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Novacne *Novofarm (Νοβοφαρμ), Gr.*
Isotretinoin (p. 1706·2).
Acne.

Novacodin *Vargas, Venez.*
⊗Ethylmorphine (p. 56·3); lobelia (p. 2323·2); grindelia (p. 2522·3); althaea (p. 2438·3); Desessartz (p. 1667·2); senega (p. 1677·2); ammonium acetate (p. 1655·3).
Cough.

Novacor *Tri Medical, Thai.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; heart failure.

Novacort
Note: this name may be used for preparations of different composition.
Ache, Braz.
⊗Ketoconazole (p. 585·3); neomycin sulfate (p. 330·1); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Primus, USA.
⊗Hydrocortisone acetate (p. 1640·1); pramocaine (p. 1993·3).
Skin disorders.

Radicura, India.
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Novade *Eczacibasi, Turk.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Nova-Dec *Rugby, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Novadep-AT *Novagen, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Novadepot *Radicura, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

Novaderm *Zambon, Braz.*
⊗Clostebol acetate (p. 2260·1); neomycin sulfate (p. 330·1).
Infected wounds, burns, and ulcers.

Novadiol *Vichy, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Novadol *Radicura, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Novadol-P *Radicura, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Novador *Novartis, Mex.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Novadox *Pure Health, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Novadral *Pfizer, Austria†; Pfizer, Switz.†; Eczacibasi, Turk.*
⊗Norfenefrine hydrochloride (p. 1459·1).
Hypotension; shock.

Novadrel *Prater, Chile.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections with inflammation.

Novadryl *Elnova, India.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions; motion sickness.

Novafac *Silesia, Chile.†*
10 Tablets, conjugated oestrogens (p. 2260·1); 11 tablets conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Novafac 30 *Silesia, Chile.*
17 Tablets, conjugated oestrogens (p. 2260·1); 13 tablets conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Novafac CC *Silesia, Chile.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Novafed A *Hoechst Marion Roussel, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Novafem *Silesia, Chile.*
Medroxyprogesterone acetate (p. 2288·1); estradiol cipionate (p. 2271·1).
Combined injectable contraceptive.

NovaFerrum 50 *Gensavis, USA.*
Polysaccharide-iron complex (p. 2086·2).
Iron deficiency.

Novaferrum 125 *Gensavis, USA.*
Polysaccharide-iron complex (p. 2086·2); colecalciferol (p. 2113·1).
Dietary supplement.

NovaFerrum Pediatric *Gensavis, USA.*
Polysaccharide-iron complex (p. 2086·2).
Iron deficiency.

Novafex *Radicura, India.*
Cefixime (p. 240·3).
Bacterial infections.

Novafibra *Novartis Consumer, Ital.†*
Guar gum (p. 475·1).
Gastrointestinal disorders.

Novafix *Mucos, Venez.*
Dental adhesive: Carmellose (p. 2175·1); vinyl copolymer.
Denture fixative.

Mucos, Venez.
Effervescent tablets: Sodium bicarbonate (p. 1781·1); potassium peroxomonosulfate; sodium perborate (p. 1770·1); sodium lauril ether sulfate (p. 2210·3).
Denture cleanser.

Novafix Extra Fuerte *Biotoscana, Chile.*
Vinyl copolymer; carmellose (p. 2175·1).
Dental fixative.

Novafix Ultra Fuerte *Biotoscana, Chile.*
Vinyl copolymer; carmellose (p. 2175·1).
Dental fixative.

Romsa, Mex.
Carmellose sodium (p. 2175·2).
Dental fixative.

Novaflox
Note: this name may be used for preparations of different composition.
Ashford, Singapore.
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

Novagen, India.
Levofloxacin (p. 315·3).
Bacterial infections.

Novaflox-OZ *Novagen, India.*
Levofloxacin (p. 315·3); ornidazole (p. 943·1).

Novag Grip *Novag, Spain.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms; pain; fever.

Novag Grip Fenilefrina *Novag, Spain.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

Novag Rino *Ferrer, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Novag Tuss *Ferrer, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Novagel *Osper, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); carmellose sodium (p. 2175·2).

Novagel-D *Osper, India.*
Domperidone (p. 1838·1); magaldrate (p. 1856·1); simeticone (p. 1886·2).

Novageon *Liferpal, Mex.*
Benzalkonium chloride (p. 1737·1); nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1).
Vaginal infections.

Novagest Expectorant with Codeine *Major, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Coughs.

Novaglow *Novagen, India.*
⊗Glycerol (p. 2517·2); titanium dioxide (p. 1725·1); vitamin E acetate (p. 2119·2).

Novagon *Novag, Mex.*
Ispaghula (p. 1849·1).
Constipation.

Novagreen *Greenpharma, Braz.*
Dipyrone (p. 53·3).
Pain; fever.

Novahaler
Note: this name may be used for preparations of different composition.
Lavipharm, Gr.
⊗Salbutamol sulfate (p. 1220·2).

Novahistex DH *Sanofi-Aventis, Canad.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Novahistine DH
Note: this name may be used for preparations of different composition.
Deston, USA.
Dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Coughs and cold symptoms; respiratory allergies.

Sanofi-Aventis, Canad.
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Novahistine DMX *SmithKline Beecham Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs; nasal congestion.

Novain *Agepha, Austria.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Novakom-S *Nobel, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Novakuf *Lupin, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).

Noval *Demo, Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Novalac AC *Bayer, Austral.; NHS, Fr.; Novalac, Malaysia.*
Infant feed.
Colic; digestive disorders; infant colic.

Novalac AD *Bayer, Austral.; Novalac, Malaysia.*
Infant feed.
Diarrhoea.

Novalac Allernova AR *NHS, Fr.*
Infant feed.
Cows' milk allergy; regurgitation.

Novalac AR *Bayer, Austral.; NHS, Fr.; Novalac, Malaysia.*
Infant feed.
Regurgitation; gastro-oesophageal reflux in infants.

Novalac Diarinova *NHS, Fr.*
Infant feed.
Diarrhoea.

Novalac HA *Bayer, Austral.; NHS, Fr.*
Infant feed.
Hypoallergenic feed; infants with a family history of allergy.

Novalac Hydranova *NHS, Fr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium citrate (p. 1780·3); citric acid (p. 2480·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Novalac IT *Bayer, Austral.; Novalac, Malaysia.*
Infant feed.
Constipation.

Novalac Riz *NHS, Fr.*
Infant feed.
Cow's milk intolerance; lactose intolerance.

Novalac Transit+ *NHS, Fr.*
Infant feed.
Constipation.

Novalak *Zytras, India.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Novalax *Willow, India.*
Liquid paraffin (p. 2191·2); magnesium hydroxide (p. 1857·2).

Novalax Plus *Willow, India.*
Sodium picosulfate (p. 1887·2).

Novalcina *Sanofi-Aventis, Venez.*
Dipyrone (p. 53·3).
Fever; pain.

Novaldon *Terra, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Novale *Psychotropics, India.*
Ketoconazole (p. 585·3).

Novales *Gulf Drug, S.Afr.*
Pravastatin (p. 1473·1).
Hyperlipidaemias.

Novell, Indon.
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Novalexin *Hexa, Arg.†*
Cefalexin (p. 234·1).
Bacterial infections.

Novalfem *Sanofi-Aventis, Braz.*
Ibuprofen (p. 68·2).
Fever; pain.

Novalgin
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Hung.†; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Switz.; Aventis, Thai.†; Aventis, Turk.
Dipyrone (p. 53·3).
Pain; fever.

Stirol, Ukr.
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Novalgina *Sanofi-Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Ital.*
Dipyrone (p. 53·3).
Fever; pain.

Novalgine *Sanofi-Aventis, Belg.*
Dipyrone (p. 53·3).
Pain; fever.

Novalif *Pharmavita, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Novalina *Bionova, India.*
Spirulina (p. 2622·1).

Novalini *Willow, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Novalket *Zdorovje, Ukr.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Novalona *Andromaco, Chile.*
Hyoscine butylbromide (p. 1845·3); oxazepam (p. 1092·2).
Smooth muscle spasm.

Novalox *Gerolymatos, Gr.*
Aluminium glycinate (p. 1817·2); magnesium oxide (p. 1857·3).
Antacid.

Novalucol
Note: this name may be used for preparations of different composition.
Meda, Swed.
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Heartburn; epigastric pain.

Novaluzid *Meda, Denm.; Meda, Fin.; Meda, Norw.; AstraZeneca, Philipp.†; Meda, Swed.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium carbonate (p. 1856·2).
Gastro-oesophageal reflux; peptic ulcer; gastritis; heartburn; dyspepsia; epigastric pain; gastric hyperacidity.

Novamet
Note: this name may be used for preparations of different composition.
Claris, Thai.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Novamil AR *Bayer, Mex.*
Infant feed.
Gastro-oesophageal reflux.

Novamilor *Novopharm, Canad.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Novamin
Note: this name may be used for preparations of different composition.
BMS, Braz.
Amikacin sulfate (p. 214·2).
Bacterial infections.

SSPC, China.
Amino acids.
Parenteral nutrition.

Novamine *Clintec, USA.*
Amino acids.
Parenteral nutrition.

Novaminsulfon *Ratiopharm, Ger.*
Dipyrone (p. 53·3).
Fever; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Novamir *Aledicine, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Novamox
Note: this name may be used for preparations of different composition.
Ache, Braz.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.
Cipla, India; Multicare, Philipp.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.
Sandoz, Pol.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Novamox AX *Cipla, India.*
Amoxicillin (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections with increased mucus.

Novamox LB *Cipla, India.*
Amoxicillin (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Novamox-CV *Cipla, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Novamoxin *Novopharm, Canad.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Novanaest *Gebro, Austria.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Novanox *Pfleger, Ger.*
Nitrazepam (p. 1089·1).
Sleep disorders.

Novantron *Meda, Ger.; Meda, Switz.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Novantrone *Sigma, Austral.†; Pfizer, China; Meda, Fin.; Meda, Fr.; Meda, Gr.; Wyeth, Hong Kong†; Wyeth, Hung.†; Wyeth, Irl.†; Wyeth Lederle, Israel; Meda, Ital.; Meda, Norw.; Zuellig, NZ; Meda, Port.†; Wyeth, S.Afr.†; Meda, Spain; Meda, Swed.; Er-Kim, Turk.; Serono, USA.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms; multiple sclerosis.

Novapam
Note: this name may be used for preparations of different composition.
Douglas, NZ.
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; skeletal muscle spasm; premedication.
Cancernova, Ger.
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; bone metastases in breast cancer; multiple myeloma.
Asian Pharm, Thai.†
Dipyrone (p. 53·3); paracetamol (p. 115·1).
Fever; pain.

Novapen
Note: this name may be used for preparations of different composition.
Pinewood, Irl.†
Ampicillin (p. 218·2).
Bacterial infections.

Novaphylline *Cooper (Κοπερ), Gr.*
Theophylline (p. 1229·3).
Asthma; obstructive airways disease; neonatal apnoea and bradycardia.

Novapime *Lupin, India.*
Cefepime (p. 239·2).
Bacterial infections.

Novapirina *Novartis Consumer, Ital.*
Diclofenac sodium (p. 48·3).
Pain; fever.

Novapress *Novag, Mex.*
Captopril (p. 1331·2).
Hypertension.

Novaprin
Note: this name may be used for preparations of different composition.
Novag, Mex.
⊗Danazol (p. 2263·2).
Mastalgia; endometriosis; gynaecomastia; menorrhagia; precocious puberty; breast cancer; hereditary angioedema.
Pharmexco, UK.
Ibuprofen (p. 68·2).

Novapsyl *Novag, Mex.*
Benzonatate (p. 1656·2).
Cough.

Novaquasol-A *Minerva (Μινερβα), Gr.*
Vitamin A palmitate (p. 2098·3); dexpanthenol (p. 2582·2).

Novarel *Ferring, USA.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility.

Novaride *Radicura, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Novaril *Renata, Philipp.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Novarnela *Andromaco, Chile.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2).
Fungal skin infections with inflammation.

Novarona *Dollder, Venez.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Novaroxim *Radicura, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Novarrutina *Zurita, Braz.*
Rutoside (p. 2505·3); aesculus (p. 2431·2); polygonum punctatum; smilax japicanga.
Venous insufficiency.

Novas *Innoderm, Philipp.*
⊗Glycerol (p. 2517·2).
Skin cleansing; soap substitute.

Novascab *Invision, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).
Scabies.

Novascabin *PannonPharma, Hung.*
Benzyl benzoate (p. 2149·1); dimethyl phthalate (p. 2153·3).
Scabies.

Novasen *Novopharm, Canad.*
Aspirin (p. 22·2).
Inflammation; pain.

Novasone *Schering-Plough, Arg.; MSD, Austral.; Schering-Plough, Thai.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Novasorin *Vendiz, Philipp.*
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Novasource *Novartis, Braz.; Novartis Consumer, Cz.; Nestle, Denm.; Novartis Nutrition, Fr.†; Nestle, Ital.; Novartis, Turk.†; Nestle, UK.*
A range of preparations for enteral nutrition.
Nestle, Fin.
Preparation for enteral nutrition in renal impairment.
Novartis Nutrition, Singapore.
Preparation for enteral nutrition.

Novasource Renal *Nestle, Canad.; Nestle, Hong Kong.*
Preparation for enteral nutrition.
Renal failure.
Novartis Nutrition, Singapore; Novartis Nutrition, USA.
Preparation for enteral nutrition in renal failure.

Novaspas
Note: this name may be used for preparations of different composition.
Novagen, India.
Tablets: Drotaverine (p. 2497·3); mefenamic acid (p. 85·3).
Ultramark, India.
Injection; tablets: Diclofenac potassium (p. 48·3); fenpiverinium bromide (p. 2504·1); pitofenone hydrochloride (p. 2592·2).

Novastan *Mitsubishi, China; Mitsubishi, Denm.; Mitsubishi, Fin.; Mitsubishi, Ital.; Mitsubishi Tanabe, Jpn; Mitsubishi, Norw.; Biovitrum, Swed.*
Argatroban (p. 1307·2).
Heparin-induced thrombocytopenia; arterial occlusive disease; thromboembolic disorders.

Novastat *Lupin, India.*
Rosuvastatin (p. 1488·2).
Hyperlipidaemias.

Novasten *Novag, Mex.*
Astemizole (p. 616·1).
Hypersensitivity.

NovaStep *Bayer, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Novasus *SJ Pharm, USA.*
Chlorphenamine tannate (p. 620·3); hydrocodone tannate (p. 67·2).
Upper respiratory-tract disorders.

Novasutin *Blausiegel, Braz.*
Tetracycline hydrochloride (p. 373·2); amphotericin B (p. 569·2).
Vaginal infections.

Nova-T *Bayer, Arg.; Bayer, Canad.; Bayer, Ger.; Schering, Hong Kong†; Bayer Schering, Indon.; Schering, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Schering, NZ†; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Switz.; Schering, Turk.†; Schering, UK; Schering, Venez.*
Copper-wound plastic (p. 2057·1) with a silver core (p. 2615·1).
Intra-uterine contraceptive device.

Novatax *Cipla, India; Cipla, Venez.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Novate *Blau, Pol.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Novaten *Ajanta, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Novativ *Ativus, Braz.*
Sertraline hydrochloride (p. 448·1).
Depression.

Novatrax *Novagen, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Novatretin *Douglas, NZ.*
Acitretin (p. 1690·3).
Psoriasis; keratinisation disorders.

Novatrex
Note: this name may be used for preparations of different composition.
Ache, Braz.
Azithromycin (p. 221·2).
Bacterial infections.
Pfizer, Fr.
Methotrexate (p. 822·2).
Psoriasis; rheumatoid arthritis.

Novatron *Radicura, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Novatropina *Uniao Quimica, Braz.*
Homatropine methylbromide (p. 2007·3).
Smooth muscle spasm.

Novavir *Novag, Mex.*
Zidovudine (p. 1024·2).
HIV infection.

Novax *Gracia, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Novaxen *Novag, Mex.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; pain; inflammation.

Novazef *China Chem & Pharma, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Novazidim *Radicura, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Novazidine *Help, Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Novazolam *Monserrat, Arg.*
Alprazolam (p. 1035·2).
Anxiety; depression.

Novazyme Elachi *Lupin, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Novee *Elnova, India.*
Vitamin E acetate (p. 2119·2).
Vitamin E supplement.

Novegam *Chinoin, Mex.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Novek *Ethypharm, China; Santa, Gr.; Ethypharm, Neth.†; Ethypharm, Port.†; Agen, Spain.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Novelas *Solas, Indon.*
Moisturiser.

Noveldexis *Pisa, Mex.*
Cisplatin (p. 766·1).
Bladder cancer; ovarian cancer; testicular cancer.

Novelio *Gerolymatos, Gr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Novelmin *Bunker, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Novelon *Organon, India.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Novemina *Lazar, Arg.*
Dipyrone (p. 53·3).
Fever; pain.

Noventa *Intra-Labs, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Noverban *Prolab, Pol.*
Verbascum (p. 2645·1).
Upper respiratory-tract disorders.

Novergo *Elvipe, Gr.*
Ergometrine maleate (p. 2136·2).

Noveril *Novartis, Austria†; Novartis, Cz.; Novartis, Hung.†; Novartis, Israel†; Novartis, Pol.†*
Dibenzepin hydrochloride (p. 413·3).
Depression; nocturnal enuresis.

Novéril *Novartis, Switz.*
Dibenzepin hydrochloride (p. 413·3).
Depression.

Noverty *Novell, Indon.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Novesin *Novartis Ophthalmics, Cz.†; Restan, S.Afr.; OmniVision, Switz.; Novartis, Thai.†; Novartis, Turk.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Novesina *Novartis, Ital.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Novesine *OmniVision, Ger.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Novetron *Noventis, Cz.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Novgos *Genus, UK.†*
⊗Goserelin acetate (p. 2282·3).
Prostatic cancer.

Novhepar *Coup, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Nov'Hepar B-12 *Vincenti, Venez.*
Vitamin B substances (p. 2102·3); gentian (p. 2512·1); CNA syrup.

Novial *Sigma, Braz.; MSD, Ger.; Organon, Mex.; Organon, Venez.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive; acne.

Noviana *Novo Nordisk, Cz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders.

Noviblock *Medicamerc, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2).

Novicarbon *CTI, Israel.†*
Activated charcoal (p. 1537·3); senna (p. 1885·1); rhubarb (p. 1884·2); fennel oil (p. 2503·3).
Constipation; dyspepsia; flatulence.

Novicrit *Novartis, Austral.*
⊗Epoetin lambda (p. 1141·2).
Anaemias; autologous blood transfusion.

Novidat
Note: this name may be used for preparations of different composition.
Diffucap, Braz.
Venlafaxine hydrochloride (p. 454·2).
Depression.
Temis, Arg.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Novidrine *Northia, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Noviform
Note: this name may be used for preparations of different composition.
Novartis, Ger.†; Meda, Swed.
Bibrocathol (p. 2457·1).
Eye disorders.

Teva, Hung.
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

Noviform Plusz *Teva, Hung.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Novigan *Reddy, Rus.; Reddy, Ukr.*
Ibuprofen (p. 68·2); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Pain; fever; smooth muscle spasm.

Novigan-M *Reddy, India.*
Nimesulide (p. 101·3).
Pain.

Novigrel *Novendia, Gr.*
Clopidogrel (p. 1342·3).

Noviken *Kendrick, Mex.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Novil *Zydus, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Novilax *Eurospital, Ital.*
⊗Sodium lauril sulfoacetate (p. 2210·3); sodium citrate (p. 1781·2); glycerol (p. 2517·2); sorbitol (p. 2092·1).
Constipation.

Novimax *Anfarm, Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Novimol *CTS, Israel.*
Paracetamol (p. 115·1).
Pain; fever.

Novimol Tsinun *CTS, Israel.†*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).
Cold symptoms.

Novina *Novag, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Novipec *Montavit, Austria.†*
⊗Salverine (p. 2609·2); ephedrine (p. 1663·1); spike lavender oil (p. 2621·3).
Respiratory-tract disorders.

Novirell B_1 *Sanorell, Ger.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Novirell B_6 *Sanorell, Ger.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Novirell B_{12} *Sanorell, Ger.*
Cyanocobalamin (p. 2107·2).
Megaloblastic anaemia; vitamin B_{12} deficiency.

Novisor *Interhealthcare, Philipp.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Novital *Zambon, Switz.*
Eucalyptus oil (p. 2501·2); japanese mint oil (p. 2560·1); pine cone oil; citronella oil (p. 2481·1); rosemary oil (p. 2607·3); cajuput oil (p. 2464·1); pine oil (p. 2591·1); cypress oil (p. 2491·1).
Cough and colds.

Novitropan *CTS, Israel; CTS, Rus.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder; nocturnal enuresis.

Novix *Grifols, Spain.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Novizet *Microsules, Arg.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Novo *Novogen, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Novo AC and C *Novopharm, Canad.*
Aspirin (p. 22·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain.

Novo Alerpriv *Montpellier, Arg.*
Desloratadine (p. 625·1).
Allergic rhinitis; pruritus; urticaria.

Novo Asat *Gezzi, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Novo B *Novopharm, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Novo Benitol *Benitol, Arg.*
Calcium carbonate (p. 1824·3); glycine (p. 2071·2).
Antacid.

Novo E *Novopharm, Canad.†*
d-Alpha tocoferil acetate (p. 2119·1) or *dl*-alpha tocoferil acetate (p. 2119·2).

Novo Fosfostilben *Sandoz, Arg.†*
Diethylstilbestrol (p. 2267·3).
Prostatic cancer.

Novo Geniol *GSK, Arg.*
Ibuprofen (p. 68·2).
Pain; fever.

Novo Humorap *Bago, Arg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Novo Insomnium *Gador, Arg.*
Eszopiclone (p. 1072·3).
Insomnia.

Novo Meprazine *Novopharm, Canad.*
Levomepromazine maleate (p. 1079·3).
Psychoses; pain; nausea; vomiting; insomnia.

Novo Miconol *Fabra, Arg.†*
Zinc undecenoate (p. 596·3); zinc oxide (p. 1729·1); sodium propionate (p. 593·1); salicylic acid (p. 1719·1).
Skin disorders.

Novo Paramicon *Northia, Arg.*
Econazole (p. 577·2).
Fungal infections.

Novo Petrin Novum *OTW, Ger.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Novo Prostasan *Biokosma, Arg.*
Urtica (p. 2639·3); pollen (p. 2593·3); saw palmetto (p. 2363·3); echinacea (p. 2498·1).
Benign prostatic hyperplasia.

Novo Rino *Bunker, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); sodium chloride (p. 1795·1).
Nasal congestion.

Novo Rino-S *Bunker, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Novo-Alprazol *Novopharm, Canad.†*
Alprazolam (p. 1035·2).
Anxiety; sedative.

Novo-Atenol *Novopharm, Canad.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Novo-Atenolthalidone *Novopharm, Canad.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Novo-AZT *Novopharm, Canad.*
Zidovudine (p. 1024·2).
HIV infection.

Novobroncol
Note: this name may be used for preparations of different composition.
Lanpharm, Arg.
Camphor (p. 2466·2); pine oil (p. 2591·1); turpentine oil (p. 2636·3); peru balsam (p. 2587·1); cinnamic acid (p. 1748·3); menthol (p. 2553·2); paramethylisopropylphenol.
Respiratory-tract disorders.

Novocain *Hospira, Canad.†; Hospira, USA.†*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Novo-Captoril *Novopharm, Canad.†; Novopharm, Hong Kong.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Novo-Carbamaz *Novopharm, Canad.†*
Carbamazepine (p. 512·2).
Epilepsy.

Novocebrin *Meda, Port.†*
Flupirtine maleate (p. 65·2).
Fever; pain.

Novocef *PharmaSwiss, Pol.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Novocephal *Fresenius Kabi, Austria.*
Piracetam (p. 393·3).
Mental function disorders; cortical myoclonus.

Novocetrin *Teva, Hung.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Novo-Cholamine *Novopharm, Canad.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; bile-acid induced diarrhoea; pruritus associated with partial biliary obstruction.

Novocilin
Note: this name may be used for preparations of different composition.
Ache, Braz.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Novo-Cimetine *Novopharm, Canad.*
Cimetidine (p. 1827·1).
Histamine H_2 receptor antagonist.

Novocin *Captab, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Novo-Clavamoxin *Novopharm, Canad.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Novo-Clopamine *Novopharm, Canad.*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder.

Novo-Clopate *Novopharm, Canad.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; sedative.

Novo-Cloxin *Novopharm, Canad.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Novocral *Help, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Novo-Cycloprine *Novopharm, Canad.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Novodase *Novogen, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Novo-Dermoquinona *Ulorente, Spain.*
Mequinol (p. 1711·1).
Hyperpigmentation.

Novodex *Novogen, India.*
Dextropropoxyphene (p. 43·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Novo-Difenac *Novopharm, Canad.†*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Osteoarthritis; rheumatoid arthritis; inflammation; pain.

Novodigal *Meda, Austria†; Mibe, Ger.*
β-Acetyldigoxin (p. 1290·2).
Heart failure; arrhythmias.

Novodil
Note: this name may be used for preparations of different composition.
OFF, Ital.†
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Novo-Diltazem *Novopharm, Canad.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Novo-Dimenate *Novopharm, Canad.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo.

Novo-Dipam *Novopharm, Canad.*
Diazepam (p. 1063·2).

Novodol *UniOrange, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Novodoxim *Captab, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Novo-Doxylin *Novopharm, Canad.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Novo-Etidronatecal *Novopharm, Canad.*
14 Tablets, etidronate disodium (p. 1182·3); 76 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Novofarma *Novofarma, Arg.*
Shampoo: Coal tar (p. 1723·2); menthol (p. 2553·2).
Dandruff; seborrhoea.

Novofarma, Arg.
Cream: ⊗Allantoin (p. 1693·1); sulfur (p. 1721·1); coal tar (p. 1723·2); urea (p. 1727·3).
Keratinisation disorders; dry skin.

Novofarma, Arg.
Lotion: Sulfur (p. 1721·1); coal tar (p. 1723·2); dexpanthenol (p. 2582·2).
Scalp disorders.

Novofem *Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Neth.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Swed.; Novo Nordisk, Switz.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Novo Nordisk, Israel; Novo Nordisk, Norw.; Novo Nordisk, UK.
12 Tablets, estradiol (p. 2271·1); norethisterone acetate (p. 2294·3); 16 tablets, estradiol.
Menopausal disorders; osteoporosis.

Novo Nordisk, China; Novo Nordisk, Ger.
Red tablets, estradiol (p. 2271·1); white tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novofemme *Novo Nordisk, Fr.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novofen
Note: this name may be used for preparations of different composition.
Mandar, India.
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Remedica, Hong Kong†; Remedica, Malaysia; Remedica, Singapore; Remedica, Thai.
⊗Tamoxifen citrate (p. 860·2).
Anovulatory infertility; breast cancer.

Novofer *Ache, Braz.*
Ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemias.

Novo-Ferrogluc *Novopharm, Canad.†*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Novo-Ferrosulfate *Novopharm, Canad.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Novo-Fiber *Novopharm, Canad.†*
Grain and citrus fibre.
Constipation; fibre supplement.

Novoflam *Novogen, India.*
Dispersible tablets: Diclofenac (p. 48·3).
Inflammation; pain.

Novogen, India.
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Novoflam-Plus *Novogen, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Pain; inflammation.

Novoflon *Novofarm (Νοβοφαρμ), Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Novo-Flupam *Novopharm, Canad.†*
Flurazepam hydrochloride (p. 1076·1).
Insomnia.

Novo-Flurprofen *Novopharm, Canad.*
Flurbiprofen (p. 65·2).
Inflammation; pain.

Novo-Folacid *Novopharm, Canad.*
Folic acid (p. 2063·1).
Anaemias.

NovoFormin *Novo Nordisk, Rus.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Novofran *Seagull, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Novo-Furantoin *Novopharm, Canad.†*
Nitrofurantoin (p. 332·1).
Bacterial infections of the urinary tract.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Novogard *Novo Nordisk, Israel.*
Metformin hydrochloride (p. 489·1); repaglinide (p. 495·2).
Diabetes mellitus.

Novogel
Note: this name may be used for preparations of different composition.
Captab, India.
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Ford Medical, UK.
Hydrogel dressing.
Wounds.

Novo-Gesic *Novopharm, Canad.; Novopharm, Pol.†*
Paracetamol (p. 115·1).
Pain; fever.

Novo-Gesic C *Novopharm, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Novogumil *Fernandez y Canivel, Spain.*
Amino acids; honey (p. 2072·1); minerals; quillaia (p. 2207·1); cyproheptadine hydrochloride (p. 624·1).

Novogyl-MPS *Mandar, India.*
Diloxanide furoate (p. 931·2); dimeticone (p. 1886·2); metronidazole (p. 936·1).

Novogyn *Bayer, Ital.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Novo-Helisen *Allergopharma, China; Allergopharma, Ger.; Allergopharma, Pol.; Allergo, Turk.*
A range of allergen extracts (p. 2434·3).
Allergen immunotherapy; hyposensitisation.
ACM, Neth.†
House-dust mite extract (p. 2434·3).

Novo-Hélisen *Allergopharma, Switz.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Novo-Herklin 2000 *Armstrong, Mex.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Novo-Hydrazide *Novopharm, Canad.†*
⊗Hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Novo-Hydrocort *Novopharm, Canad.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Novo-Hylazin *Novopharm, Canad.†*
Hydralazine hydrochloride (p. 1401·2).
Hypertension.

Novoinhalipt *Mikrofarm, Rus.*
Sulfanilamide (p. 368·1); sulfathiazole sodium (p. 368·3); thymol (p. 1772·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1).
Mouth and throat disorders.

Novo-Ipramide *Novopharm, Canad.*
Ipratropium bromide (p. 1211·3).
Bronchodilator.

Novo-Keto *Novopharm, Canad.†*
Ketoprofen (p. 79·1).
Pain; fever.

Novolax
Note: this name may be used for preparations of different composition.
Trima, Israel.
Lactitol (p. 1850·3).
Constipation; hepatic encephalopathy.

Novolev *Captab, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Novo-Levocarbidopa *Novopharm, Canad.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Novo-Lexin *Novopharm, Canad.*
Cefalexin (p. 234·1).
Bacterial infections.

Novolid *Micro, India.*
Nimesulide (p. 101·3).
Pain.

Novolid-MR *Micro, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Novolid-S *Micro, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Novolin 30/70 *Novo Nordisk, Mex.*
⊗Mixture of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p. 475·3).
Diabetes mellitus.

Novolin 30/70, 40/60, 50/50 *Novo Nordisk, Canad.*
⊗Mixtures of insulin injection (human, pyr) and isophane insulin injection (human) in the proportions indicated (p. 475·3).
Diabetes mellitus.

Novolin 70/30 *Novo Nordisk, Braz.; Novo Nordisk, USA.*
⊗A mixture of isophane insulin injection (human) and insulin injection (human) (p. 475·3), respectively, in the proportions indicated.
Diabetes mellitus.

Novolin N *Novo Nordisk, Arg.; Novo Nordisk, Braz.; Novo Nordisk, China; Novo Nordisk, Jpn; Novo Nordisk, Mex.; Novo Nordisk, USA.*
⊗Isophane insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

Novolin NPH *Novo Nordisk, Canad.*
⊗Isophane insulin injection (human, pyr) (p. 475·3).
Diabetes mellitus.

Novolin R *Novo Nordisk, Arg.; Novo Nordisk, Braz.; Novo Nordisk, China; Novo Nordisk, Jpn; Novo Nordisk, Mex.; Novo Nordisk, USA.*
⊗Insulin injection (human,recombinant) (p. 475·3).
Diabetes mellitus.

Novolin 30R, 40R, and 50R *Novo Nordisk, Jpn.*
⊗Mixtures of insulin injection (human, recombinant) 30%, 40%, or 50% and isophane insulin (human, recombinant) 70%, 60%, or 50% respectively (p. 475·3).
Diabetes mellitus.

Novolin 30R, 50R *Novo Nordisk, China.*
⊗Mixtures of neutral insulin (human) 30% or 50% and isophane insulin (human) 70% or 50% (p. 475·3).
Diabetes insulin.

Novolin Toronto *Novo Nordisk, Canad.*
⊗Neutral insulin injection (human, pyr) (p. 475·3).
Diabetes mellitus.

NovoLog *Novo Nordisk, USA.*
⊗Insulin aspart (p. 475·3).
Diabetes mellitus.

Novo-Lorazem *Novopharm, Canad.*
Lorazepam (p. 1080·3).
Anxiety; sedative.

Novolten *Poly, China.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Novom *Aldril, Philipp.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; gastrointestinal intubation and radiography; nausea and vomiting.

Novo-Medopa *Novopharm, Canad.*
Methyldopa (p. 1431·1).
Hypertension.

Novo-Medrone *Novopharm, Canad.†*
Medroxyprogesterone acetate (p. 2288·1).

Novomet *Novo Nordisk, Austral.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Novo-Methacin *Novopharm, Canad.*
Indometacin (p. 71·2).
Inflammation; pain.

Novo-Metoprol *Novopharm, Canad.†; Novopharm, Hong Kong.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris.

Novomin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; gastrointestinal disorders; Ménière's disease.

Novomine *Novogen, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Novomine-AD *Novogen, India.*
Cobamamide (p. 2107·2); iron carbonyl (p. 2073·1); folic acid (p. 2063·1).

Novomine-GB *Novogen, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Novomine-OD *Novogen, India.*
Vitamins.

No-Vomit
Note: this name may be used for preparations of different composition.
IMA, Braz.†
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Novomit
Note: this name may be used for preparations of different composition.
Klonal, Arg.
Metoclopramide (p. 1862·2).
Dyspepsia; nausea and vomiting.
Milte, Ital.
Ginger (p. 1844·1).
Motion sickness.

NovoMix *Novo Nordisk, Braz.; Novo Nordisk, Malaysia.*
⊗A mixture of insulin aspart 30% and protamine insulin aspart 70% (p. 475·3).
Diabetes mellitus.

NovoMix 30 *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Canad.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, India; Novo Nordisk, Indon.; Novo Nordisk, Mex.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, S. Afr.; Novo Nordisk, Singapore; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, UK; Novo Nordisk, Ukr.*
⊗A mixture of insulin aspart 30% and protamine insulin aspart 70% (p. 475·3).
Diabetes mellitus.

NovoMix 30, 50, 70 *Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, Spain; Novo Nordisk, Turk.*
⊗Mixtures of insulin aspart 30%, 50%, or 70% and protamine insulin aspart 70%, 50%, or 30% (p. 475·3).
Diabetes mellitus.

NovoMix 30 or 70 *Novo Nordisk, Austria.*
⊗Mixtures of soluble insulin aspart 30% or 70% and protamine insulin aspart 70% or 30% respectively (p. 475·3).
Diabetes mellitus.

Novo-Mucilax *Novopharm, Canad.†*
Ispaghula (p. 1849·1).
Constipation.

Novonac *UniOrange, India.*
Diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Novonac-P *UniOrange, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Novo-Naprox *Novopharm, Canad.†*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Inflammation; pain.

Novoneural *Mugi, Indon.†*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; vitamin B supplement.

Novo-Nidazol *Novopharm, Canad.*
Metronidazole (p. 936·1).
Trichomoniasis.

NovoNorm *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, India; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, Ukr.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Novopac *Lafedar, Arg.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Novopasmil Compuesto *Lafedar, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Novo-Passit *Teva, Cz.; Ivax, Rus.; Teva, Ukr.*
Valerian (p. 2640·2); melissa (p. 2552·3); St John's wort (p. 449·1); crataegus (p. 2488·1); passion flower (p. 2584·1); lupulus (p. 2546·1); sambucus (p. 2609·3); guaifenesin (p. 1666·2).
Anxiety disorders; insomnia; migraine; gastrointestinal disorders; irritability; pruritus; nervous-system disorders; neurasthenia; sleep disorders; stress headache; menopausal syndrome; neurocirculatory dystonia; eczema; urticaria.

Novo-Pen-VK *Novopharm, Canad.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Novo-Peridol *Novopharm, Canad.*
Haloperidol (p. 1077·1).
Psychoses; nausea and vomiting.

Novo-Phane *Wockhardt, India.*
Vitamins; minerals; amino acids.

Novophane DS *ACM, Fr.*
Piroctone olamine (p. 1716·3); pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1); sodium lactate (p. 1781·2); lactic acid (p. 2539·1); enoxolone (p. 54·2).
Dandruff.

Novophane K *ACM, Fr.*
Piroctone olamine (p. 1716·3); pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1); cade oil (p. 1723·2); sodium lactate (p. 1781·2); lactic acid (p. 2539·1); enoxolone (p. 54·2).
Dandruff.

Novo-Pheniram *Novopharm, Canad.*
Chlorphenamine maleate (p. 620·3).

Novopin MIG neu *Schoning-Berlin, Ger.*
Mint oil (p. 2560·1).
Muscle pain; neuralgia; respiratory-tract congestion; gastrointestinal disorders.

Novo-Pindol *Novopharm, Canad.†*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris.

Novo-Pirocam *Novopharm, Canad.*
Piroxicam (p. 125·3).
Inflammation; pain.

Novo-Plan *Polifarma, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Novoplas *Octapharma, Port.*
Plasma (p. 1158·2).
Haemorrhagic disorders; immune thrombocytopenia.

Novoplatinum *Hospira, Port.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Novo-Plus
Note: this name may be used for preparations of different composition.
Novogen, India.
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.
Novopharm, Canad.†
Lactose (p. 2078·3).
Placebo.

Novopone *Gerolymatos, Gr.*
Niflumic acid (p. 101·2).
Inflammatory disorders.

Novo-Pramine *Novopharm, Canad.*
Imipramine hydrochloride (p. 426·2).
Depression.

Novo-Pranol *Novopharm, Canad.†*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; cardiac disorders; migraine headache; phaeochromocytoma.

Novo-Prazin *Novopharm, Canad.†*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Novopressan *Ethypharm, China.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; arrhythmias; hypertrophic cardiomyopathy.

Novopressina-V *Biol, Arg.*
⊗Vasopressin (p. 2642·3).
Abdominal distension associated with abdominal surgery or radiography; diabetes insipidus.

Novo-Profen *Novopharm, Canad.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Novo-Propamide *Novopharm, Canad.†*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Novoptine *Gifrer Barbezat, Fr.*
Cetylpyridinium chloride (p. 1743·1).
Eye infections.

Novopulm *Meda, Spain.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Novopulmon *Meda, Fin.; Meda, Fr.; Meda, Ger.; Meda, Swed.; Meda, Ukr.*
⊗Budesonide (p. 1625·1).
Asthma; obstructive airways disease.

Novo-Purol *Novopharm, Canad.*
Allopurinol (p. 600·2).

Novopyrin *Sanofi-Aventis, Hung.†*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Novopyrine *Haver, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Novoquin *Rayere, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Novorab *Novogen, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Novorab-D *Novogen, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Novo-Ranidine *Novopharm, Canad.†; Novopharm, Hong Kong†; Novopharm, Pol.†*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal disorders; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

NovoRapid *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Canad.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, India; Novo Nordisk, Indon.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, Ukr.*
⊗Insulin aspart (p. 475·3).
Diabetes mellitus.

NovoRapid 30 Mix *Novo Nordisk, Jpn.*
⊗A mixture of soluble insulin aspart 30% and protamine insulin aspart 70% (p. 475·3).
Diabetes mellitus.

Novo-Renal *Novopharm, Canad.†*
Vitamin and mineral preparation for dialysis patients.

Novorin *Polfa, Hung.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis media.

Novoris *Novofarm (Νοβοφαρμ), Gr.*
Risperidone (p. 1103·2).
Psychoses.

Novo-Rythro *Novopharm, Canad.*
Erythromycin estolate (p. 291·2) or erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Novosal *Perfetti, Ital.*
Low sodium dietary salt substitute.

Novoscabin *Polon, Pol.*
Benzyl benzoate (p. 2149·1).
Scabies.

Novosef *Eczacibasi, Philipp.; Eczacibasi, Rus.; Eczacibasi, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Novo-Semide *Novopharm, Canad.†*
⊗Furosemide (p. 1387·1).
Oedema.

Novosept *Natur Produkt, Rus.*
Tetracaine hydrochloride (p. 1996·3); cetylpyridinium chloride (p. 1743·1); zinc sulfate (p. 2126·2).

NovoSeven *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, India; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, Ukr.; Novo Nordisk, USA.*
Eptacog alfa (activated) (p. 1147·2).
Haemorrhagic disorders; haemophilia.

Novo-Sorbide *Novopharm, Canad.†*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Novospar *Zydus, India.*
Sparfloxacin (p. 357·3).
Community-acquired pneumonia; chronic bronchitis.

Novo-Spiroton *Novopharm, Canad.†*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism.

Novo-Spirozine *Novopharm, Canad.†*
⊗Hydrochlorothiazide (p. 1403·2); spironolactone (p. 1499·3).
Oedema; hypertension.

Novosta *Novell, Indon.*
30 Tablets, pravastatin sodium (p. 1473·1); 30 tablets, aspirin (p. 22·2).
Cardiovascular risk reduction.

Novostatin *Progen, Ital.*
Red rice; policosanol (p. 1472·1); taurine (p. 2626·2); zinc (p. 2126·1); nicotinic acid (p. 2083·1).
Nutritional supplement.

Novo-Sucralate *Novopharm, Canad.†*
Sucralfate (p. 1889·1).
Peptic ulcer.

Novo-Sundac *Novopharm, Canad.†*
Sulindac (p. 134·2).
Inflammation; pain.

Novo-Tears *Saval, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); hypromellose (p. 2189·2); dextran (p. 1138·3).
Eye congestion; eye irritation.

Novoter
Note: this name may be used for preparations of different composition.
Gujarat Terce, India.
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.
Teofarma, Spain.
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Novoter Gentamicina *Teofarma, Spain.*
⊗Fluocinonide (p. 1636·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Novo-Theophyl *Novopharm, Canad.†*
Theophylline (p. 1229·3).

Novothirteen *Novo Nordisk, Denm.; Novo Nordisk, Switz.*
Catridecacog (p. 1150·3).
Factor XIII A-subunit deficiency.

Novothyral *Merck, Austria; Merck, Belg.; Merck, Chile; Merck Serono, Ger.; Merck, Pol.; Merck, Rus.; Merck, Switz.*
Liothyronine sodium (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroiditis; adjunct to antithyroid therapy; goitre; thyrotoxicosis; thyroid cancer.

Novothyrox *Genpharm, USA.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Novotil
Note: this name may be used for preparations of different composition.
Sandoz, Indon.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.
Zydus, India.
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders.

Novo-Timol *Novopharm, Canad.*
⊗Timolol maleate (p. 1513·2).
Angina pectoris; hypertension.

Novotiral *Merck, Mex.*
Liothyronine sodium (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism; euthyroid goitre; adjunct to antithyroid therapy.

Novotossil *Zambon, Ital.*
Cloperastine fendizoate (p. 1659·2).
Cough.

Novo-Triamzide *Novopharm, Canad.†*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Novo-Trimel *Novopharm, Canad.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Novo-Tripramine *Novopharm, Canad.*
Trimipramine maleate (p. 453·1).
Depression.

Novo-Triptyn *Novopharm, Canad.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Novovate *Bilim, Turk.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Novo-Veramil *Novopharm, Canad.; Novopharm, Pol.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Novo-Vites *Novopharm, Canad.†*
Vitamins; with or without iron (p. 2073·1).

Novoxapam *Novopharm, Canad.*
Oxazepam (p. 1092·2).

Novoxit *Novogen, India.*
Flupentixol (p. 1074·1); melitracen (p. 434·2).
Depression.

Novozid *Captab, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Novozithron *Novofarm (Νοβοφαρμ), Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Novozitron *Fada, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Novozox *Novogen, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Novralflex *Medquimica, Braz.*
Dipyrone (p. 53·3); caffeine (p. 1203·3); orphenadrine (p. 909·2).

Novumtrax *Pisa, Mex.†*
Cytarabine (p. 774·1).
Leukaemias; non-Hodgkin's lymphoma.

Novuxol
Note: this name may be used for preparations of different composition.
Smith & Nephew, Neth.; Abbott, Turk.
⊗Collagenase (p. 2484·1).
Wound debridement.

nový P-AM *Nutricia, Cz.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Novygra *Nabros, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Novynette *Gedeon Richter, Cz.; Sandoz, Denm.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Finderm, Ital.; Gedeon Richter, Malaysia; Richter, Pol.; Grunenthal, Port.; Gedeon Richter, Rus.; Gedeon Richter, Thai.; Gedeon Richter, Ukr.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Nowax *Bell, UK.*
Cineole (p. 2479·1); nutmeg oil (p. 2573·2); terpineol (p. 2627·2); arachis oil (p. 2446·1).
Ear wax removal.

Noworm *Alkem, India.*
Albendazole (p. 149·1).
Worm infections.

Nox *Finecure, India.*
Norfloxacin (p. 333·3).
Bacterial infections.

Noxa *Indoco, India.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Noxacorn
Note: this name may be used for preparations of different composition.
Dexxon, Israel.
Salicylic acid (p. 1719·1); benzocaine (p. 1980·2).
Corns; calluses.

Noxadif *Adipharm, Gr.*
Pantoprazole sodium (p. 1875·3).

Noxafil *Schering-Plough, Arg.; MSD, Austral.; Schering-Plough, Austria; MSD, Belg.; Schering-Plough, Chile; Schering-Plough, Cz.; MSD, Denm.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; Schering-Plough, Hung.; MSD, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; Schering-Plough, Pol.; Schering-Plough, Port.; Merck, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.; Schering, USA.*
Posaconazole (p. 592·1).
Fungal infections.

Noxap *Air Products, Belg.; Air Products, Cz.; Air Products, Fr.; Air Products, Neth.; Carburos Metalicos, Spain.*
Nitric oxide (p. 1457·1).
Neonatal respiratory distress syndrome.

Noxarel *Genepharm, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Capillary disorders.

Noxebron *Am-Europharma, Philipp.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Noxeprom *Grisi, Mex.*
Alprazolam (p. 1035·2).
Anxiety; insomnia; panic disorder; alcohol withdrawal syndrome.

Noxetine *Novell, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Noxetol *Ivax, Arg.*
⊗Exemestane (p. 792·2).
Breast cancer.

Noxi *Allenge, India.*
Lornoxicam (p. 83·2).
Pain; osteoarthritis; rheumatoid arthritis.

Noxibel *Bago, Arg.; Bago, Rus.*
Mirtazapine (p. 436·1).
Depression.

Noxicam-MD *Nitro Organics, India.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Noxidem *Cipla-Medpro, S.Afr.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Noxidil *Perrigo, Israel; TO-Chemicals, Thai.*
Minoxidil (p. 1438·3).
Alopecia androgenetica; hypertension; heart failure.

Noxifen *Interhealthcare, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Nasal congestion.

Noxigyl *Medley, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Noxine *Sriprasit, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Noxinor *Masa, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Noxi-P *Allenge, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Noxivid *Biofarma, Mex.†*
Camelia sinensis (p. 2648·2); bearberry (p. 2453·2); ascorbic acid (p. 2110·3).
Antoxidant.

Noxobran *Biomedica, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Noxon *Formenti, Ital.*
Lornoxicam (p. 83·2).
Pain; inflammation.

Noxopran *Casasco, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Noxoram *Alkem, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Noxorin *Orion, Denm.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nox-Pain *TMan, Thai.*
Methyl salicylate (p. 92·1); eugenol (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Noxprey *Sperko, Ukr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; eustachitis; otitis media; aid to nasopharyngeal procedures; nasal congestion.

Noxraxin *Osoth, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Noxtor *Rafarm, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Nox-TZ *Finecure, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Noxyflex *Innotech, Fr.†*
Noxytiolin (p. 1762·1).
Intraperitoneal infections.

Noxyflex S *Geistlich, Irl.†; Geistlich, UK.*
Noxytiolin (p. 1762·1).
Fungal and bacterial infections; infections in body cavities.

Noxylen *Tylid, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Noxzema Triple Clean *Culver, Canad.*
Cleanser: Triclosan (p. 1773·2).
Procter & Gamble, Canad.†
Pads: Salicylic acid (p. 1719·1).

Nozac *Farmazak, Gr.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Nozat *Baldacci, Port.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Nozee *Fem Care, India.*
Syrup: Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Fem Care, India.
Tablets: Cetirizine hydrochloride (p. 619·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Nozepam *Leksredstva, Rus.; Organika, Rus.*
Oxazepam (p. 1092·2).
Anxiety disorders; depression.

Nozer *Be-Tabs, S.Afr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Nozi *Miklos, Hung.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); bornyl acetate (p. 2460·2).
Nasal congestion.

Nozik *Candor, India.*
Ambroxol (p. 1654·3); cetirizine (p. 619·2).

Nozik-P *Candor, India.*
⊗Cetirizine (p. 619·2); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Nozil *Mankind, India.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Nozin *Intra-Labs, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Nozinan *Gerot, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.†; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Recip, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, UK.*
Levomepromazine hydrochloride (p. 1079·3) or levomepromazine maleate (p. 1079·3).
Psychoses; mania; depression; sleep disorders; pain; alcohol withdrawal syndrome; psychomotor disorders; adjunct in general anaesthesia; disturbed behaviour; schizophrenia; anxiety disorders; premedication; nausea and vomiting; insomnia; sedative.
Sanofi-Aventis, Arg.; Patriot, Philipp.; Vitoria, Port.
Levomepromazine (p. 1079·3).
Nausea and vomiting; pain; psychoses; schizophrenia; anxiety; depression; behaviour disorders in children.

Nozlen *Eisai, Jpn.*
Sodium gualenate (p. 1887·1).
Peptic ulcer; mouth and throat disorders; gastritis.

Nozoa *Micro, India.*
Nitazoxanide (p. 942·2).
Giardiasis; cryptosporidiosis.

Nozoil *ENT Technologies, Austral.*
Sesame oil (p. 2614·1); vitamin E substances (p. 2119·1).
Nasal dryness.

Nozol *Sinochem, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Nozuca *Darvys, Philipp.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Nozy *Ind-Swift, India.*
⊗Xylometazoline (p. 1680·1).
Nasal congestion.

Nozy Cold *Ind-Swift, India.*
⊗Nimesulide (p. 101·3); pseudoephedrine (p. 1676·1).

NP-27 *Farmo Quimica, Chile.*
Topical powder: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.
Farmo Quimica, Chile.
Topical solution: Undecenoic acid (p. 596·3); isopropyl alcohol (p. 1758·3).
Fungal skin infections.

NP2 AP-HP *Fresenius Kabi, Fr.*
Glucose (p. 2068·3); amino acids; electrolytes (p. 1775·1).
Parenteral nutrition in infants.

NP100 Prématurés AP-HP *Fresenius Kabi, Fr.*
Glucose (p. 2068·3); amino acids; electrolytes (p. 1775·1).
Parenteral nutrition in premature neonates.

N-Pain Relief *Willow, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

NPBor *Sanify, India.*
⊗Boric acid (p. 2459·3); chlorphenamine (p. 620·3); naphazoline (p. 1669·3).

NPCom *Profic Organic, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nplate *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fr.; Amgen, Ger.; Amgen, Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Israel; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Spain; Amgen, Swed.; Amgen, UK; Amgen, USA.*
Romiplostim (p. 1162·2).
Immune thrombocytopenia.

N-Plus *Mediez, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

NPM *Laborate, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

N-Rich
Note: this name may be used for preparations of different composition.
Biomedica, India.
Vitamins; lysine hydrochloride (p. 2079·3); zinc sulfate (p. 2126·2).
Willow, India.
Vitamins; trace elements; lycopene (p. 2546·2).

N-Rich Baby *Biomedica, India.*
Coconut oil (p. 2179·3); vitamin E (p. 2119·1).

N-Rox *Willow, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

NRX *Cadila, Philipp.*
Norfloxacin (p. 333·3).
Bacterial infections.

NS *Filorga, Fr.†*
Nutritional supplements.

NSA *CSL Biotherapies, Hong Kong†; CSL, Singapore.*
⊗Albumin (p. 1130·2).
Shock; hypoproteinaemia; burns; adult respiratory distress syndrome; haemodialysis; plasma exchange.

NSAID Eye *Syntho, India.*
Diclofenac (p. 48·3).
Prevention of intra-operative miosis; eye inflammation and pain; allergic conjunctivitis.

N-Sanigest *Sanify, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; menopausal disorders.

N-Side *Cosme, India.*
Nimesulide (p. 101·3) or nimesulide betadex (p. 101·3).
Pain.

NSI-Dryl *Willow, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

NSI-Kuff *Willow, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan (p. 1660·1); phenylephrine (p. 1672·2).

NSI-Ril *Willow, India.*
⊗Bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

N-S-Plus *Symbiosis, India.*
⊗Nimesulide (p. 101·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

NT-Addict *Willow, India.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

NTBec *Neon, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

NTD *Euphoric, India.*
Suspension: Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.
Euphoric, India.
Tablets: Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

NT-Diorea *Fortune, Hong Kong.†*
Loperamide (p. 1854·2).
Diarrhoea.

N-Tiz *Bio-Drug, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

NT-Kuf *Hauz, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).

NT-Kuf-AM *Hauz, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline sulfate (p. 1228·1).

NTKuf-D *Hauz, India.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

NT-Kuf-M *Hauz, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

NT-Natal *Kee, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Threatened and recurrent miscarriage.

NT-Natal MP *Kee, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

NTOmec-G *Sanify, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

NTR *Teofarma, Ital.*
Phenylephrine hydrochloride (p. 1672·3); thenyldiamine hydrochloride (p. 641·3).
Cold symptoms.

N-Trip *Medicine Products, Thai.*
Nortriptyline hydrochloride (p. 439·3).

NT-Scab *Intas, India.*
Cetrimide (p. 1742·1); lindane (p. 2157·1).
Scabies.

NT-Spas *Intas, India.*
Injection: Dicycloverine (p. 1834·2).
Gastrointestinal spasm.
Intas, India.
Tablets: Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

NTSpass *Cratus, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

N-TZ *Avalanche, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

NT-Z *East West, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

NTZ Long Acting Nasal *Sterling Health, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Nu Axiom *Panjon, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

nu Qten Com *Novell, Indon.*
Ubidecarenone (p. 2637·1); thioctic acid (p. 2629·1); carnitine (p. 2053·2).
Dietary supplement in diabetes mellitus.

Nuage Bioplasma *Standard Homeopathic, Canad.†*
Calcium fluoride (p. 2053·1); calcium phosphate triphasic (p. 1784·2); calcium sulfate (p. 2173·1); ferrum phosphoricum (p. 2077·1); magnesium phosphate dibasic (p. 1786·3); potassium chloride (p. 1793·2); potassium phosphate dibasic (p. 1791·1); potassium sulfate (p. 1793·2); silica marina (p. 2208·3); sodium chloride (p. 1795·1); sodium phosphate dibasic (p. 1791·2); sodium sulfate (p. 1888·1).
Homoeopathic preparation.

Nuage Tissue *Hylands, Canad.*
A range of mineral preparations.
Homoeopathic preparation.

Nu-Alpraz *Nu-Pharm, Canad.*
Alprazolam (p. 1035·2).
Anxiety; sedative.

Nu-Amilzide *Nu-Pharm, Canad.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Oedema; hypertension.

Nu-Amoxi *Nu-Pharm, Canad.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Nu-Ampi *Nu-Pharm, Canad.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Nuardin *Tramedico, Belg.*
Cimetidine (p. 1827·1).
Gastrointestinal disorders associated with hyperacidity.

Nuasa *Uniphar, Irl.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; unstable angina; myocardial infarction.

Nu-Atenol *Nu-Pharm, Canad.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Nu-Baclo *Nu-Pharm, Canad.*
Baclofen (p. 2014·3).
Muscle relaxation; skeletal muscle spasticity.

Nubact *Aareen, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Nubain *Cristalia, Braz.; Sandoz, Canad.; BMS, Cz.†; Du Pont, Cz.†; Vianex (Βιανεξ), Gr.; Torrex, Hung.†; Invida, Philipp.; BMS, Singapore; BMS, Thai.; Endo, USA.†*
Nalbuphine hydrochloride (p. 97·3).
Adjunct to general anaesthesia; pain; premedication.

Nubaina *AstraZeneca, Arg.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Nubase *Biomiicron, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Nubelium *BMW, India.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; vertigo; migraine.

Nubend *Kramer, India.*
Albendazole (p. 149·1).
Worm infections.

Nubeta *Abbott, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

Nubeta-H *Abbott, India.*
⊗Hydrochlorothiazide (p. 1403·2); nebivolol (p. 1444·2).
Hypertension.

Nubeta-SM *Abbott, India.*
⊗Levamlodipine; nebivolol (p. 1444·2).
Hypertension.

Nubevital BB *GSK, Arg.*
SPF 24: Oxybenzone (p. 1715·3); sulisobenzone (p. 1722·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Nubevital P *GSK, Arg.*
SPF 8: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Nubevital Sunblock Ultra *GSK, Arg.*
SPF 55: Oxybenzone (p. 1715·3); sulisobenzone (p. 1722·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Nubolin *Dr Alson, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Nubral *Galderma, Ger.*
⊗Urea (p. 1727·3).
Dry skin.

Nubrex *Sandoz, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Nu-Cal *Odan, Canad.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Nucal *Dr Alson, India.*
Calcium carbonate (p. 1824·3); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).

Nu-Cal D *Odan, Canad.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).

Nu-Capto *Nu-Pharm, Canad.*
Captopril (p. 1331·2).
ACE inhibitor.

Nucarnit *Nucron, India.*
Levocarnitine (p. 2053·2).

Nucart-OA *Gufic, India.*
Boswellia serrata (p. 2507·3); glucosamine sulfate (p. 2515·3).

Nucaza *Nucleus, Neth.†*
Azithromycin ethanolate (p. 221·2).
Bacterial infections.

Nucef *Guardian, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Nu-Cephalex *Nu-Pharm, Canad.*
Cefalexin (p. 234·1).
Bacterial infections.

Nucerin *Novagen, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Nucet *Helax, India.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Nucez *Little Greave, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Nucez Plus *Little Greave, India.*
Syrup: Chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); paracetamol (p. 115·1); phenylephrine (p. 1672·2); sodium citrate (p. 1781·2).
Little Greave, India.
Tablets: ⊗Levocetirizine (p. 632·3); paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Nucid-D *Dr Alson, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Nu-Cimet *Nu-Pharm, Canad.*
Cimetidine (p. 1827·1).
Histamine H_2-receptor inhibitor.

Nucip *Armour, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Nucip-TZ *Armour, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Nuclav *Abbott, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Nuclear *Zenon, India.*
Cefixime (p. 240·3).
Bacterial infections.

Nucleinas *Arterium, Ukr.*
Ribonucleic acid (p. 2604·1).
Immunostimulant.

Nucleo CMF Forte *Ferrer, Ukr.*
Disodium cytidine phosphate (p. 2491·1); trisodium uridine triphosphate (p. 2638·1); disodium uridine diphosphate (p. 2495·2); disodium uridine monophosphate (p. 2495·2).
Neuralgias; neuritis; neuropathy.

Nucleo CMP
Note: this name may be used for preparations of different composition.
Ferrer, Spain.
Sodium cytidine monophosphate (p. 2491·1); disodium uridine diphosphate (p. 2495·2); disodium uridilic acid; sodium uridine triphosphate (p. 2638·1).
Neuralgias; neuritis.
Ferrer-Novag, Mex.
Disodium cytidine phosphate (p. 2491·1); trisodium uridine triphosphate (p. 2638·1).
Peripheral neuropathies; neuralgia.

Núcleo CMP *Gross, Braz.*
Disodium cytidine phosphate (p. 2491·1); trisodium uridine triphosphate (p. 2638·1); hydroxocobalamin (p. 2107·3).
Neuritis.

Nucleserina *Medea, Spain.*
Pyridoxine hydrochloride (p. 2105·3); ribonucleic acid (p. 2604·1); phosphoserine (p. 2589·1); glutamine (p. 2070·3).
Mental function disorders; tonic.

Nucleus
Note: this name may be used for preparations of different composition.
Actavis, Port.†
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.
Actavis, Port.†
⊗Letrozole (p. 817·1).
Breast cancer.

Nuclevit B_{12} *Robert & Carriere, Canad.*
Minerals; vitamin B_{12} (p. 2107·2); nucleotides.
Tonic.

Nuclina *Mapra, India.*
Spirulina (p. 2622·1).

Nuclosina *Meda, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Nuclox *Zytras, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Nu-Cloxi *Nu-Pharm, Canad.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Nucoa *Llorente, Spain.†*
Isopropyl myristate (p. 2190·3).
Skin irritation; ulcers; wounds.

Nucobrox *Bangkok Lab & Cosmetic, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Nucofed *Roberts, USA.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Nucold *Dr Alson, India.*
Oral drops; syrup: ⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Dr Alson, India.
Tablets: ⊗Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Nucolox *Sigma, Austral.†*
Ispaghula (p. 1849·1); starch (p. 2095·1).
Constipation.

Nu-COPD *Carwin, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Nucope *Mankind, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Nucope-AD *Mankind, India.*
⊗Ambroxol (p. 1654·3); desloratadine (p. 625·1); pseudoephedrine (p. 1676·1).
Allergic rhinitis; cold symptoms; sinusitis.

Nucoril *Nucron, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

NuCort
Note: this name may be used for preparations of different composition.
WraSer, USA.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Nucort
Note: this name may be used for preparations of different composition.
Mankind, India.
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Nucort-P *Mankind, India.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Nucosef *Johnson & Johnson, Austral.†*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; upper respiratory-tract congestion.

Nucotet *Gulf Drug, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).

Nucotrim *Gulf Drug, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis; nocardiosis.

Nu-Cotrimox *Nu-Pharm, Canad.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Nucotuss Expectorant *Barre-National, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Coughs.

Nucoxia *Zydus, India.*
Etoricoxib (p. 57·3).
Pain.

Nucoxia-MR *Zydus, India.*
Etoricoxib (p. 57·3); thiocolchicoside (p. 2026·2).

Nucoxia-P *Zydus, India.*
Etoricoxib (p. 57·3); paracetamol (p. 115·1).

Nucoxia-SP *Zydus, India.*
⊗Etoricoxib (p. 57·3); serrapeptase (p. 2613·3).

Nuctalon *Takeda, Fr.*
Estazolam (p. 1072·2).
Insomnia.

Nucul *Koutsoumani, Gr.*
Nifedipine (p. 1447·2).

Nucynta *Janssen, Canad.; Janssen, USA.*
Tapentadol hydrochloride (p. 136·1).
Pain.

Nudep
Note: this name may be used for preparations of different composition.
Guardian, Indon.
Sertraline (p. 448·1).
Depression.
Mankind, India.
Duloxetine hydrochloride (p. 415·1).
Depression; diabetic neuropathy; stress urinary incontinence in women.

Nu-Derm
Note: this name may be used for preparations of different composition.
Johnson & Johnson Consumer, Belg.
A hydrocolloid dressing.
Wounds.
Obagi, Indon.
A range of skin cleansers and moisturisers.
Systagenix, Ital.
Hydrocolloid dressing.
Wounds; ulcers.

Nuderm *Obagi, Canad.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Nu-Derm Action *Obagi, Singapore.*
Emollient.
Dry skin.

Nu-Derm Alginato *Johnson & Johnson Medical, Arg.*
Calcium alginate (p. 1136·3).
Wounds.

Nu-Derm Blender *Obagi, Singapore.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Nu-Derm Clear *Obagi, Singapore.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Nu-Derm Exfoderm *Obagi, Singapore.*
Fytic acid (p. 1553·3).
Skin disorders; adjunct to hydroquinone and tretinoin therapy.

Nu-Derm Exfoderm Forte *Obagi, Singapore.*
Glycolic acid (p. 1704·3); lactic acid (p. 2539·1).
Skin disorders; adjunct to hydroquinone and tretinoin therapy.

Nu-Derm Healthy Skin *Obagi, Singapore.*
SPF 35: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Nu-Derm Healthy Skin Protection *Obagi, Indon.*
SPF 35: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Nu-Derm Hidrocoloide *Johnson & Johnson Medical, Arg.*
Carmellose sodium (p. 2175·2).
Wounds.

Nu-Derm Physical UV Block *Obagi, Singapore.*
SPF 32: Zinc oxide (p. 1729·1).
Sunscreen.

Nu-Derm Sunblock *Obagi, Indon.†*
SPF 15: Padimate O (p. 1716·1); hydroquinone (p. 1705·1).
Sunscreen; skin pigmentation disorders.
Obagi, Indon.†
SPF 24: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); betacarotene (p. 2051·1).
Sunscreen.

Nu-Derm Sunfader *Obagi, Singapore.†*
SPF 15: Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Skin hyperpigmentation.

Nuderm Sunfader *Obagi, Canad.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Skin pigmentation disorders.

Nu-Derm Tolereen *Obagi, Singapore.†*
⊗Hydrocortisone (p. 1640·1).
Skin irritation.

Nu-Derm Toner *Obagi, Singapore.*
Aloe barbadensis (p. 1816·1); hamamelis (p. 2523·3); allantoin (p. 1693·1); sage (p. 2608·3); calendula (p. 2465·2).
Skin cleanser.

Nu-Diclo *Nu-Pharm, Canad.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Nudiclo *Macleods, India.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Nu-Diltiaz *Nu-Pharm, Canad.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Nudopa *Medicine Products, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Nudoth *Gentech, India.*
Dosulepin.
Depression.

Nudoxim *Zenon, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Nudoxy *NuLife, India.*
Doxycycline (p. 288·1).
Bacterial infections.

Nudramag *Nufarindo, Indon.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; peptic ulcer; flatulence; bloating.

Nuedexta *Avanir, USA.*
Dextromethorphan hydrobromide (p. 1660·1); quinidine sulfate (p. 1481·2).
Pseudobulbar affect.

Nuelin *iNova, Austral.; Meda, Denm.; Meda, Fin.; iNova, Hong Kong; Meda, Irl.; iNova, Malaysia; Meda, Norw.; iNova, NZ; iNova, Philipp.; iNova, S.Afr.; iNova, Singapore; iNova, Thai.; 3M, UK; Zuoz, Venez.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Nuerel *Salvat, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinitis; sinusitis.

Nuevapina *Fabop, Arg.*
Aspirin (p. 22·2).
Fever; pain.

Nueve Lunas *Fada, Arg.*
Pregnancy test (p. 2596·1).

Nuface
Note: this name may be used for preparations of different composition.
Fem Care, India.
Avobenzone (p. 1695·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Guardian, Indon.
Tretinoin (p. 1725·2).
Acne.

Nufacetam *Nufarindo, Indon.*
Piracetam (p. 393·3).
Cerebral infarction.

Nufaclapide *Nufarindo, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Nufaclav *Nufarindo, Indon.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Nufaclind *Nufarindo, Indon.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Nufacobal *Nufarindo, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nufacort *Nufarindo, Indon.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Nufadex *Nufarindo, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Nufadipect *Nufarindo, Indon.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Nufadol *Nufarindo, Indon.*
Paracetamol (p. 115·1).
Pain; cold symptoms.

Nufadoxin *Nufarindo, Indon.*
Isoniazid (p. 311·2).
Vitamin B_1 (p. 2102·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Nufadryl Expectorant *Nufarindo, Indon.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Nufafloqo *Nufarindo, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Nufagrabion *Nufarindo, Indon.*
Ferrous fumarate (p. 2060·3); vitamins; minerals.
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement in pregnancy.

Nufagrabion-GM *Nufarindo, Indon.*
Ferrous fumarate (p. 2060·3); docosahexaenoic acid (p. 1460·1); vitamins; minerals.
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement in pregnancy.

Nufalemzil *Nufarindo, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Nufalev *Nufarindo, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Nufalora *Nufarindo, Indon.*
Loratadine (p. 633·2).
Allergic skin disorders; urticaria; allergic rhinitis.

Nufamicron *Nufarindo, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Nufamox *Nufarindo, Indon.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Nufanibrox *Nufarindo, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Nufapolar *Nufarindo, Indon.*
⊗Desonide (p. 1630·1).
Skin disorders.

Nufapotram *Nufarindo, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Nufaprazol *Nufarindo, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Nufapredson *Nufarindo, Indon.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Nufapreg *Nufarindo, Indon.*
Promethazine teoclate (p. 638·2).
Nausea and vomiting; vestibular disorders; motion sickness.

Nufaprim *Nufarindo, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Nufarol *Rafarm, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Nufasic *Nufarindo, Indon.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain; respiratory-tract congestion.

Nufathiam *Nufarindo, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Nufatrac *Nufarindo, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Nufemic *New York Chemical, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Nufenac *Karnataka, India.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Nufervit *Elisa, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).

Nufex *RPG, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Nufex Beta *RPG, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Nufil-Safe *Biocon, India.*
Filgrastim (p. 1151·3).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Nufirom *Guardian, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Nufit *Guardian, Indon.*
Caplets: Echinacea purpurea (p. 2498·1); pink rock rose; selenium (p. 2086·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Guardian, Indon.
Oral syrup: Echinacea purpurea (p. 2498·1); pink rock rose; zinc picolinate (p. 2126·1).
Immunostimulant.

Nufix *Captab, India.*
Cefixime (p. 240·3).
Bacterial infections.

Nufloxib *Alphapharm, Austral.*
Norfloxacin (p. 333·3).
Bacterial infections.

Nufolic *Nufarindo, Indon.*
Folic acid (p. 2063·1).
Folic acid supplement.

Nuforce *Mankind, India.*
Fluconazole (p. 578·2).
Fungal infections.

Nuforce Dust Powder *Mankind, India.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Nuforce Kit *Mankind, India.*
1 Capsule, fluconazole (p. 578·2); 2 tablets, tinidazole (p. 949·2).

Nuforce-3 Kit *Mankind, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, ornidazole (p. 943·1).
Vulvovaginal infections.

Nuforce Mouth Paint *Mankind, India.*
Clotrimazole (p. 576·2).

Nuforce Shampoo *Mankind, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

Nuforce V 6 *Mankind, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Nuforce-CD *Mankind, India.*
Clindamycin (p. 269·3); clotrimazole (p. 576·2).

Nuforce-GM *Mankind, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).

Nüfro *Munir, Turk.*
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Nufulvin *NuLife, India.*
Griseofulvin (p. 582·2).
Fungal skin, hair, and nail infections.

Nugatex *Rafarm, Gr.*
Calcium dobesilate (p. 2464·3).
Capillary disorders.

Nu-Gel
Note: this name may be used for preparations of different composition.
Johnson & Johnson Consumer, Belg.
A hydrogel dressing.
Wounds.

Johnson & Johnson, Irl.
Hydrogel dressing.
Wounds.

Johnson & Johnson, Israel; Systagenix, Ital.
Sodium alginate (p. 2167·3).
Wounds.

Systagenix, Ital.
Dressing: Povidone (p. 2204·3).
Burns; wounds.

Nu-Gel Hidrogel con Alginato *Johnson & Johnson Medical, Arg.†*
Sodium alginate (p. 2167·3).
Ulcers.

Nu-Gel Hidrogel en Placa *Johnson & Johnson Medical, Arg.†*
Povidone-iodine (p. 1767·1).
Wounds.

Nugen Eye/Ear *Syntho, India.*
Ciprofloxacin lactate (p. 261·2); phenylephrine hydrochloride (p. 1672·3).

Nugen-XL *Anglo-French Drugs, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1); lactobacillus (p. 2596·3).

Nugesia *Elisa, India.*
Tablets: Paracetamol (p. 115·1); nimesulide (p. 101·3).

Elisa, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Nugesia-SP *Elisa, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Nugesic *Unimarck, India.*
Nimesulide (p. 101·3).
Pain.

Nugit-M *Dr Alson, India.*
Metronidazole benzoate (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Nugrel *Micro, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Nugrel Plus *Micro, India.*
Clopidogrel (p. 1342·3); aspirin (p. 22·2).
Thrombosis prophylaxis; acute coronary syndrome.

Nuhair *Polipharm, Thai.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Nuhist *Dayton, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Nu-Hydral *Nu-Pharm, Canad.*
Hydralazine hydrochloride (p. 1401·2).
Hypertension.

Nu-Hydro *Nu-Pharm, Canad.*
⊗Hydrochlorothiazide (p. 1403·2).

Nu-Indo *Nu-Pharm, Canad.*
Indometacin (p. 71·2).
Inflammation; pain.

Nu-Iron V *Merz, USA.*
Polysaccharide-iron complex (p. 2086·2); folic acid (p. 2063·1); vitamins; calcium (p. 1783·1).
Iron-deficiency anaemias.

Nujol *Mantecorp, Braz.; MSD, Gr.*
Liquid paraffin (p. 2191·2).
Constipation.

Nukaine *Duopharma, Philipp.*
Nalbuphine hydrochloride (p. 97·3).
Pain.

Nukast *Zuventus, India.*
Levocetirizine (p. 632·3); montelukast (p. 1214·3).

Nu-Ketocon *Nu-Pharm, Canad.†*
Ketoconazole (p. 585·3).
Fungal infections.

Nüklofer *Radyum, Turk.*
Ferric ammonium citrate (p. 2060·1).
Iron deficiency; iron-deficiency anaemia.

Nulacin Fermentos *Seid, Spain.†*
⊗Amylolytic enzymes; proteolytic enzymes; lipolytic enzymes (p. 2579·3); dehydrocholic acid (p. 2492·1); procaine (p. 1994·3).
Digestive enzyme deficiency.

Nulacta *Guardian, Indon.*
Fish oil (p. 1460·3); peppermint oil (p. 1877·1).
Nutritional supplement for pregnancy and lactation.

Nulacta Plus *Guardian, Indon.*
Fish oil (p. 1460·3); peppermint oil (p. 1877·1); folic acid (p. 2063·1).
Nutritional supplement for pregnancy and lactation.

Nulagrip C *Medical, Arg.*
Ascorbic acid (p. 2110·3); aspirin (p. 22·2); caffeine (p. 1203·3).
Cold and influenza symptoms.

Nularef *Lafedar, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Nularef Cort *Lafedar, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Allergic rhinitis; allergic skin disorders.

Nularef-D *Lafedar, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Cold and influenza symptoms; otitis; rhinitis; sinusitis.

Nulartrin *Ivax, Arg.*
Diacerein (p. 45·3).
Degenerative joint disorders.

Nulasta *Misha, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Nulastres *Duncan, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Nulcefam *Armoxindo, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Nulcer *Armoxindo, Indon.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Nulcerin *Docta, Spain.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Nulcex *Biomedipharma, Spain.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nuleb *Leben, India.*
Nimesulide (p. 101·3).
Pain.

Nulecit *Watson, USA.†*
Sodium ferric gluconate complex (p. 2089·1).
Iron-deficiency anaemia.

Nuleron *Teofarma, Ital.*
Magnesium polygalacturonate (p. 2200·3); calcium pantothenate (p. 2085·2); promethazine hydrochloride (p. 638·2); dimeticone (p. 1886·2).
Gastrointestinal disorders associated with excess gas.

NuLev *Alaven, USA.*
Hyoscyamine sulfate (p. 1848·1).

Nu-Levocarb *Nu-Pharm, Canad.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Nulide *Neon, India.*
Nimesulide (p. 101·3).
Pain.

Nulife *Elder, India.*
Nicotine polacrilex (p. 2569·3).
Aid to smoking cessation.

Nulin *Velka, Gr.*
Codergocrine mesilate (p. 389·2).

Nulip *Gufic, India.†*
Nucleic acid (p. 2573·1).
Viral infections.

Nulipar *Baliarda, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Nulite *Dominguez, Arg.*
Pinaverium bromide (p. 2590·3).
Gastrointestinal disorders; adjunct in bowel examination.

Nullo *Monticello, USA.*
Chlorophyllin copper complex (p. 2178·3).
Control of body odour.

Nulobes *Columbia, Arg.*
Tiratricol (p. 2346·3).
Obesity.

Nuloc *Alkem, India.*
Esomeprazole (p. 1841·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Nuloc-D *Alkem, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Nulojix *BMS, Denm.; BMS, Fr.; BMS, Ger.; BMS, Irl.; BMS, Israel; BMS, Ital.; BMS, Neth.; BMS, Norw.; BMS, Swed.; BMS, Switz.; BMS, UK; BMS, USA.*
Belatacept (p. 1944·3).
Renal transplant rejection.

Nu-Look *Intra-Labs, India.*
Levocarnitine (p. 2053·2); vitamin E (p. 2119·1).

Nu-Loraz *Nu-Pharm, Canad.*
Lorazepam (p. 1080·3).
Anxiety; sedative.

Nu-Lotan *MSD, Jpn.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Nulox *Nufarindo, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

NuLytely *Zodiac, Braz.; Asofarma, Mex.; Braintree, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Numanis *Bayer, Spain.†*
⊗Testosterone undecylate (p. 2305·2).
Hypogonadism.

Numark *Boehringer Ingelheim Promeco, Mex.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Numark Flu Relief *Numark, UK.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2).
Cold and influenza symptoms.

Numark Max Strength Cold & Flu *Numark, UK.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2).
Cold and influenza symptoms.

Numark Muscle Rub *Numark, UK.*
Methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Numark Muscle Spray *Numark, UK.†*
Glycerol mono salicylate; methyl salicylate (p. 92·1); ethyl salicylate (p. 56·3).
Musculoskeletal and joint disorders.

Numatol *Decrox, Spain.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; head injury.

Numbon *Teva, Israel.*
Nitrazepam (p. 1089·1).
Insomnia.

Nu-Medopa *Nu-Pharm, Canad.*
Methyldopa (p. 1431·1).
Hypertension.

Numeg *Dr Alson, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Numel *Savoy, India.*
Nimesulide (p. 101·3).
Pain.

Numen *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa.

Numencial
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
Sulpiride (p. 1107·3); diazepam (p. 1063·2).
Mixed anxiety depressive states.
Ivax, Arg.
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Numeta *Baxter, Switz.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3) and olive oil (p. 2575·1)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Numeta GE *Baxter, Denm.; Baxter, Fin.; Baxter, Ger.; Baxter, Irl.; Baxter, Norw.; Baxter, Swed.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3) and olive oil (p. 2575·1)); electrolytes (p. 1775·1).
Contains egg phosphatide.
Parenteral nutrition.
Baxter, Neth.
Amino acids; glucose (p. 1780·1); lipid (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg phospholipids.
Parenteral nutrition.

Numeth *Genesis, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); thiamine (p. 2102·3).

Nu-Metop *Nu-Pharm, Canad.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; hypertension.

Numis *Nobel, Turk.*
Liquid soap pH 4.2: Soap substitute.
Genital hygiene in women.
Nobel, Turk.
Shampoo: Piroctone olamine (p. 1716·3); levomenol (p. 2544·1); dexpanthenol (p. 2582·2).
Dandruff.

Numlo *Emcure, India.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Numlo-AT *Emcure, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Hypertension; angina pectoris.

Numlo-D *Emcure, India.*
⊗Hydrochlorothiazide (p. 1403·2); levamlodipine.

Numlo-L *Emcure, India.*
Amlodipine (p. 1304·1); lisinopril (p. 1420·3).
Hypertension.

Nummit *Ipca, India.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Numoisyn *Align, USA.*
Sorbitol (p. 2092·1); linseed (p. 2544·2); chondrus (p. 2176·3).
Formerly contained sorbitol, macrogol, malic acid, and electrolytes.
Saliva substitute.

Numol *Karnataka, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Numol-MR *Karnataka, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Numonyl C *Sanofi Synthelabo, Mex.†*
Chlorphenamine (p. 620·3); paracetamol (p. 115·1); caffeine (p. 1203·3).

Numonyl Jarabe *Sanofi Synthelabo, Mex.†*
Phenylpropanolamine (p. 1674·1); chlorphenamine (p. 620·3); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Numorphan *Endo, USA.*
⊗Oxymorphone hydrochloride (p. 114·2).
Pain; premedication; adjunct to general anaesthesia; anxiety in dyspnoea associated with left ventricular failure and pulmonary oedema.

Numosol *Medipharm, Chile.*
Oxolamine citrate (p. 1671·2).
Respiratory-tract disorders.

Numox *Jenburkt, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Numox-LB *Jenburkt, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Numoxx *Cipla-Medpro, S.Afr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Num-Zit
Note: this name may be used for preparations of different composition.
Silesia, Chile.
Zinc sulfate (p. 2126·2).
Dietary supplement.

Nu-Naprox *Nu-Pharm, Canad.*
Naproxen (p. 98·2).
Inflammation; pain.

Nu-Natal Advanced *Rising Pharmaceuticals, USA.*
Vitamins; minerals; docusate sodium (p. 1836·2).

Nunest *Servocare, India.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; amenorrhoea; dysfunctional uterine bleeding; endometrial cancer.

Nu-Nifed *Nu-Pharm, Canad.*
Nifedipine (p. 1447·2).
Angina pectoris.

Nuo An Ping *Pude, China.*
Aceglutamide (p. 2426·2).

Nuo Bai Li *Limin, China.*
Tiopronin (p. 1578·1).

Nuo Bang *Hengrui, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Nuo Bei Qi *Limin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Nuo Bi Song *Baike Hengdi, China.*
Oxaprozin (p. 112·3).
Osteoarthritis; rheumatoid arthritis.

Nuo Bin *Hanson, China.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Nuo Chen *Lukang Chenxin, China.*
Potassium dehydroandrographolide succinate.

Nuo Chong *Shengjitang, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Nuo Da Ming *Dongbao, China.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Nuo Er *Yang Zhou, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Nuo Er Ma *Winsunny, China.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Nuo Fei *Ke Lun, China.*
Lafutidine (p. 1851·3).
Peptic ulcer; gastritis; acid aspiration.

Nuo Hao *WeiKang, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Nuo He *Baike Hengdi, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Nuo Jia Nan *ZhongNuo, China.*
Biapenem (p. 231·1).
Bacterial infections.

Nuo Jian *WeiKang, China.*
Ambroxol hydrochloride (p. 1654·3).

Nuo Jin Ping *Jinliyuan, China.*
Telmisartan (p. 1509·3).
Hypertension.

Nuo Jun Xin *KangNing, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Nuo Ke *Shenwei, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Nuo Ke Da *Hui Yin Bi, China.*
Isosorbide mononitrate (p. 1413·3).

Nuo Lai Xin *Rhodiola, China.*
Lysine hydrochloride (p. 2079·3).
Cerebral ischaemia; head injury.

Nuo Lan Pin *Rotam Reddy, China.*
Nevirapine (p. 1005·1).
HIV infection.

Nuo Li Er *Zhen Zhu, China.*
Gatifloxacin (p. 303·2).

Nuo Li Si *Wanze, China.*
Tosufloxacin tosilate (p. 381·2).

Nuo Ling Dun *Baijingyu, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Nuo De Lun *Guo Ao, China.*
Oxaprozin (p. 112·3).
Osteoarthritis; rheumatoid arthritis.

Nuo Lv Ting *Zizhu, China.*
Mifepristone (p. 2138·1).
Termination of pregnancy.

Nuo Mei Shu *Yaoyou, China.*
Cimetidine (p. 1827·1).

Nuo Qing *Zhenshiming, China.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Nuo Sha *Kangmei, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Nuo Shi *Xinchang, China.*
⊗Testosterone undecylate (p. 2305·2).

Nuo Shi Mei *Suzhong Haixin, China.*
Telmisartan (p. 1509·3).
Hypertension.

Nuo Shu An *ZhongNuo, China.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Nuo Si Da *Lunan, China.*
Levocetirizine hydrochloride (p. 632·3).

Nuo Su Lin *Yaoyou, China.*
Huperzine A.

Nuo Tong *Huaren, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Nuo Xiang *Mao Xiang, China.*
Matrine.

Nuo Xin *Hanson, China.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Nuo Xin Sheng *Si Huan, China; Wellso, China.*
Naltrexone hydrochloride (p. 1565·1).
Opioid dependence.

Nuo Yang *Hengrui, China.*
Butorphanol tartrate (p. 33·2).
Pain.

Nuo Zhen *Grand, China.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Nuo Zheng *Xinzhongzheng, China.*
Nimesulide (p. 101·3).
Pain.

Nuo Zhi Lin *Ke Lun, China.*
Ethylenediamine diaceturate.

Nuo Zhi Su *Daying, China.*
⊗Erythropoietin (human, recombinant) (p. 1141·1).

NuoHao *Wei Kang, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Nuojia *Grand, China.*
Enoxacin (p. 290·2).
Bacterial infections.

Nuoke *WeiKang, China.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Nuomei *WeiKang, China.*
Mezlocillin sodium (p. 324·1).
Bacterial infections.

Nuoning *Grand, China.*
Tiopronin (p. 1578·1).
Liver disorders.

Nuopulun *Neptunus, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Nuosen *Luye, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer.

Nuosic *Millimed, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle pain; tension headache; dysmenorrhoea.

Nuosong *Baike Hengdi, China.*
Oxaprozin (p. 112·3).
Musculoskeletal and joint disorders; pain; inflammation.

Nuovodox *Bergamo, Braz.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Nuowei *Kawin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

NuOx *Gentex, USA.*
Benzoyl peroxide (p. 1696·1); sulfur (p. 1721·1).
Acne.

Nu-Oxybutyn *Nu-Pharm, Canad.*
Oxybutynin hydrochloride (p. 2361·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nuoyi *Wei Kang, China.*
Aceglutamide (p. 2426·2).

Nupan *Novogen, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Nupan-D *Novogen, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Nupar *Savoy, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Nuparin *Troikaa, India.*
Heparin (p. 1396·3).
Thromboembolic disorders.

Troikaa, Philipp.
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Nupatch *Zydus, India.*
Diclofenac diethylamine (p. 48·3).

Nupeldol *Nupel, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Nupentin *Alphapharm, Austral.; Mylan, NZ; Alphapharm, Singapore.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Nu-Pen-VK *Nu-Pharm, Canad.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Nuperazone *Chandra Bhagat, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Nuperazone Plus *Chandra Bhagat, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Nupercainal
Note: this name may be used for preparations of different composition.
Novartis Consumer, Canad.; Ciba, USA.
Ointment: Cinchocaine (p. 1983·2).
Pain; haemorrhoids; pruritus.

Novartis, Braz.; Novartis, Gr.; Novartis, India†; Materforma, Port.; LPC, UK.
Cinchocaine hydrochloride (p. 1983·2).
Pain; haemorrhoids; anorectal disorders; skin irritation.

Novartis Consumer, Canad.
Cream: Cinchocaine (p. 1983·2); domiphen bromide (p. 1751·1).
Pain; pruritus.

Nupic *La Pharmaceuticals, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Nu-Pindol *Nu-Pharm, Canad.*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris.

Nu-Pirox *Nu-Pharm, Canad.*
Piroxicam (p. 125·3).
Inflammation; pain.

Nupod *Abbott, India.*
Cefpodoxime.
Bacterial infections.

Nupod-CV *Abbott, India.*
Cefpodoxime proxetil (p. 248·1); clavulanic acid (p. 268·3).

Nuprafen *Beximco, Singapore.*
Naproxen (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Nu-Prazo *Nu-Pharm, Canad.*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Nuprin
Note: this name may be used for preparations of different composition.
Actavis, Irl.
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Nu-Prochlor *Nu-Pharm, Canad.*
Prochlorperazine maleate (p. 1098·3).
Psychoses; vomiting.

Nuprosan *Sanbe, Indon.*
Amino acids.
Parenteral nutrition.

Nura *Genesis, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Nurabax *Ranbaxy, Cz.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Nura-D *Genesis, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Nuradef *Alna, India.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

NurAiD *Moleac, Fr.*
Astragalus; sage root (p. 2608·3); peony root; lovage root (p. 2545·3); angelica (p. 2443·3); carthamus; peach; senega root (p. 1677·2); calamus (p. 2464·2).
Dietary supplement; tonic.

Nura-IT *Genesis, India.*
Itopride hydrochloride (p. 1850·1); rabeprazole (p. 1881·1).
Gastro-oesophageal reflux.

Nuramed *Zydus, India.*
Pregabalin (p. 545·3).
Postherpetic neuralgia; partial seizures; fibromyalgia; anxiety.

Nu-Ranit *Nu-Pharm, Canad.*
Ranitidine hydrochloride (p. 1882·1).
Histamine H_2-receptor antagonist.

Nurasic *TO-Chemicals, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain.

Nuravon *Abbott, India.*
Edaravone (p. 1370·2).

Nureflex *Reckitt Benckiser, Austria; Reckitt Benckiser, Fr.; Reckitt Benckiser, Ital.†*
Ibuprofen (p. 68·2).
Fever; pain; juvenile idiopathic arthritis.

Nuren *Dabur, India.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Nuren-Ace *Dabur, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Nurest *Aarpik, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Nurezan *Rafarm, Gr.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic.

Nuriban *Roux-Ocefa, Arg.*
⊗Furosemide diethylaminoethanol (p. 1387·1).
Diuretic.

Nuriban A *Roux-Ocefa, Arg.*
⊗Furosemide (p. 1387·1); amiloride hydrochloride (p. 1299·1).
Oedema.

Nuricon *Revifar, Gr.*
Indometacin (p. 71·2).

Nurifier *Ajanta, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Nuri-Kapseln *Sanochemia, Austria.†*
Halibut-liver oil (p. 2071·3); cod-liver oil (p. 2056·3).
Vitamin A and D deficiency.

Nuril
Note: this name may be used for preparations of different composition.
Almirall, Spain.
Pipemidic acid (p. 339·3).
Urinary-tract infections.

USV, India.
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Nur-Isterate *Bayer Schering, S.Afr.*
Norethisterone enantate (p. 2294·3).
Injectable contraceptive.

Nurite *Afexa, Canad.*
Ginseng (p. 2513·3).
Mental fatigue.

Nuritrex B12 *Organon, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Nuro-B
Note: this name may be used for preparations of different composition.
Rimsa, Mex.
Meloxicam (p. 86·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuralgias; neuropathies; neuritis.

TO-Chemicals, Thai.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuromuscular pain; neuralgia.

Nurobest *TTK, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Nurobex *Biochemix, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nurocain *Dentsply, Austral.†*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Nurocare-PG *Armour, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nurocer *Aldril, Philipp.*
Piracetam (p. 393·3).
Mental function disorders; cortical myoclonus.

Nuroclad *Symbiotic, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nuroclad-GB *Symbiotic, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nuroclad-Plus *Symbiotic, India.*
Thioctic acid (p. 2629·1); chromium (p. 2055·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Nuroday *Wockhardt, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nurofast *Reckitt Benckiser, Ital.†*
Ibuprofen (p. 68·2).
Pain; fever.

Nurofen *Reckitt Benckiser, Austral.; Reckitt Benckiser, Austria; Reckitt Benckiser, Belg.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Denm.; Reckitt Benckiser, Fr.; Reckitt Benckiser, Ger.; Reckitt Benckiser, Gr.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Hung.; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Reckitt Benckiser, Ital.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Neth.; Boots Healthcare, NZ; Reckitt Benckiser, Pol.; Reckitt Benckiser, Port.; Reckitt Benckiser, Rus.; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Spain; Reckitt Benckiser, Swed.; Reckitt Benckiser, Switz.; Reckitt Benckiser, Thai.; Abdi, Turk.; Reckitt Benckiser, UK; Reckitt Benckiser, Ukr.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Nurofen Advance *Reckitt Benckiser, Cz.†; Reckitt Benckiser, Irl.*
Ibuprofen lysine (p. 68·3).
Pain; fever; inflammation; cold and influenza symptoms.

Nurofen All Night Cold & Flu *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Nurofen All Night Flu Relief *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Nurofen Antigrip *Reckitt Benckiser, Pol.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nurofen Cold & Flu *Reckitt Benckiser, Austral.; Reckitt Benckiser, Gr.; Reckitt Benckiser, Hung.; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Boots Healthcare, NZ†; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Abdi, Turk.; Reckitt Benckiser, UK.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sore throat.

Nurofen Cold & Flu Relief *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Nurofen Influenza e Raffreddore *Reckitt Benckiser, Ital.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nurofen Migraine *Reckitt Benckiser, Austral.; Reckitt Benckiser, NZ; Reckitt Benckiser, UK.*
Ibuprofen lysine (p. 68·3).
Migraine; headache.

Nurofen Migrenol *Reckitt Benckiser, Pol.†*
Ibuprofen lysine (p. 68·3).
Migraine.

Nurofen Plus *Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Reckitt Benckiser, NZ; Reckitt Benckiser, Pol.; Reckitt Benckiser, Rus.; Reckitt Benckiser, S.Afr.†; Reckitt Benckiser, Turk.; Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain; inflammation; musculoskeletal and joint disorders; fever; cold and influenza symptoms.

Nurofen Rhume *Reckitt Benckiser, Fr.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Nurofen Sinus *Crookes Healthcare, UK.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Nurofen Stopgrip *Reckitt Benckiser, Cz.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Nurofen Tension Headache *Reckitt Benckiser, NZ.*
Ibuprofen lysine (p. 68·3).
Tension headache.

Nurofen Zavance *Reckitt Benckiser, Austral.*
Ibuprofen sodium (p. 68·2).
Fever; pain.

Nurofenfem *Reckitt Benckiser, Fr.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Nurofenflash *Reckitt Benckiser, Fr.*
Ibuprofen (p. 68·2).
Formerly known as Nuroflash.
Fever; pain.

Nurofenpro *Reckitt Benckiser, Fr.*
Ibuprofen (p. 68·2).
Pain; fever.

Nurofentabs *Reckitt Benckiser, Fr.*
Ibuprofen (p. 68·2).
Fever; pain.

Nuroflash *Reckitt Benckiser, Ital.*
Ibuprofen lysine (p. 68·3).

Nuroflow *Symbiotic, India.*
Paracetamol (p. 115·1); prochlorperazine (p. 1098·2).

Nurokind *Mankind, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nurokind Hart *Mankind, India.*
Atorvastatin (p. 1309·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Nurokind Ortho *Mankind, India.*
Glucosamine sulfate (p. 2515·3); mecobalamin (p. 2108·1); dimethyl sulfone (p. 2493·3).
Joint disorders.

Nurokind Plus *Mankind, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Mankind, India.
Injection: Dexpanthenol (p. 2582·2); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Nurokind-G *Mankind, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nurokind-More *Mankind, India.*
Calcium pantothenate (p. 2085·2); chromium tripicolinate (p. 2056·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); zinc sulfate (p. 2126·2).

Nuro-M *Moraceae, India.*
Capsules: Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Moraceae, India.
Syrup: Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Nuro-M Plus *Moraceae, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); thiamine nitrate (p. 2103·2).

Nuromas *Cosmas, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nuromas-PG *Cosmas, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nuromax
Note: this name may be used for preparations of different composition.
Active, India.
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nuromax-OD *Active, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); thiamine (p. 2102·3).

Nuromax-PG *Active, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nuromin *Nodysis, India.*
Thioctic acid (p. 2629·1); vitamins; selenium dioxide (p. 2087·1).

Nuromol *Reckitt Benckiser, UK.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Nuron-E *Icon, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Neuritis; neuralgia; neuropathy; vitamin B deficiency; chronic hepatitis.

Nurosenz *Abbott, India.*
Thioctic acid (p. 2629·1); benfotiamine (p. 2102·3); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Nurosolv *Reckitt Benckiser, Ital.*
Ibuprofen (p. 68·2).
Pain; fever.

Nurovir *East African, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).

Nurovole *Alpha Aromatic, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nurovole Plus *Alpha Aromatic, India.*
Thioctic acid (p. 2629·1); mecobalamin (p. 2108·1).

Nurovole-PG *Alpha Aromatic, India.*
Mecobalamin (p. 2108·1); pregabalin (p. 545·3).

Nu-Rox *Laboratorios Chile, Chile.*
Enoxaparin sodium (p. 1372·3).
Thromboembolism prophylaxis; venous thrombosis; unstable angina; myocardial infarction; extracorporeal circulation.

Nuroxy *Dr Alson, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Nurozac-OD *Agio, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Nuroz-OD *Zydus, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Nurrid *Gedeon Richter, Cz.†; Gedeon Richter, Denm.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Nurrish *GSK, India.*
Nutritional supplement.

Nurse Harvey's Gripe Mixture *Harvey Scruton, Israel.*
Dill oil (p. 2493·2); sodium bicarbonate (p. 1781·1).
Infant colic.

Harvey-Scruton, UK.
Dill oil (p. 2493·2); caraway oil (p. 2470·3); sodium bicarbonate (p. 1781·1).
Infant colic.

Nurse Sykes Powders *Anglian, UK.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever; cold and influenza symptoms.

Nursoy *Pfizer, Hong Kong; Wyeth Nutrition, Indon.; Wyeth, Malaysia; Wyeth, Philipp.*
Infant feed.
Lactose intolerance; galactokinase deficiency; cows' milk allergy.

Wyeth, Braz.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Singapore; Wyeth, Venez.
Soy protein infant feed.
Cows' milk intolerance; lactose intolerance; galactokinase deficiency.

Nusaid *Molekule, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Nusaid-MR *Molekule, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Nusaid-P *Molekule, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Nusaid-SP *Molekule, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Nu-Salt *Cumberland, USA.*
Low sodium dietary salt substitute.

Nusar *Emcure, India.*
Losartan (p. 1422·2).
Hypertension; diabetic nephropathy.

Nusar-AM *Emcure, India.*
Amlodipine (p. 1304·1).
Hypertension.

Nusar-AM Low *Emcure, India.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Nusar-ATN *Emcure, India.*
⊗Atenolol (p. 1308·2); losartan potassium (p. 1422·2).

Nusar-H *Emcure, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Nu-Seals *Alliance, Irl.; Alliance, UK.*
Aspirin (p. 22·2).
Pain; thrombosis prophylaxis; fever; inflammation; thromboembolic disorders.

Nu-Seng *Intra-Labs, India.*
Ginseng (p. 2513·3); vitamin E (p. 2119·1).

Nusept *BMW, India.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Nuset *Sun, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Nusobee *Wockhardt, India.*
Infant feeds.

Nuso-San *Takeda, Belg.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis.

Nusprin *Emcure, India.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Nussidex *Teva, Israel.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms.

Nustasium *Labima, Belg.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Nustat *Ordain, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Nuta *Osotspa, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Nutacold *Osotspa, Thai.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Nutam *Molekule, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Nutam Plus *Molekule, India.*
Citicoline (p. 2480·1); piracetam (p. 393·3).

Nutaphake *Sensomed, Philipp.*
Adenosine triphosphate (p. 2430·3).
Cataract.

Nutarzol *New York Chemical, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Nutaxin *Aglowmed, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Nutaxin-S *Aglowmed, India.*
Cefotaxime sodium (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Nutaz *Mankind, India.*
Mirtazapine (p. 436·1).
Depression.

Nu-Tears *Optopics, USA.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Nu-Tears II *Optopics, USA.*
Polyvinyl alcohol (p. 2204·2); macrogol 400 (p. 2547·3).
Dry eyes.

Nutec MPS *Zee, India.*
Domperidone (p. 1838·1); magaldrate (p. 1856·1).

Nu-Tetra *Nu-Pharm, Canad.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Nuthyal Plus *Zubit, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy; megaloblastic anaemia.

Nuthyl-AL *Zubit, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3).

Nuthyl-GB *Zubit, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Nutilis *Nutricia, Irl.; Baxter, NZ; Nutricia, NZ.*
Food and fluid thickener.
Dysphagia.

Nutricia, Austral.; Support, Braz.; Nutricia, Cz.; Nutricia, Fr.; Nutricia, Ital.; Nutricia, Port.
Food thickener.
Dysphagia.

Nutricia Clinical, UK.
Preparation for enteral nutrition.

Nutitionist Regenerating Moisturizer *Garnier, Canad.†*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Nutiva *Genesis, India.*
Vitamins; minerals; trace elements.

Nutiva-Lyco *Genesis, India.*
Vitamins; minerals; citrus bioflavonoids (p. 2505·2); green tea (p. 2648·2); crataegus (p. 2488·1); lycopene (p. 2546·2); parsley leaf (p. 2583·3).

Nutiva-Pro *Genesis, India.*
Nutritional supplement.

Nutizym Compositum *Merck, Venez.*
⊗Bromelains (p. 2460·3); pancreatin (p. 2579·3); ox bile (p. 2457·2); dimeticone (p. 1886·2).
Digestive disorders.

Nutlevo *Positif, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Nutob *Zytras, India.*
Tobramycin (p. 380·1).
Eye infections.

Nutob-F *Zytras, India.*
⊗Fluorometholone (p. 1637·2); tobramycin (p. 380·1).

Nutoin *Minova, India.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Nutra *Stalwart, India.*
Iron choline citrate (p. 2060·2); lysine hydrochloride (p. 2079·3); magnesium chloride (p. 1787·1); manganese chloride (p. 2081·2); nicotinamide (p. 2083·1); zinc sulfate (p. 2126·2).

Nutra Fibra *Investigacion, Mex.†*
Vitamins; minerals; fibre.

Nutra-Cee *Manix, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Nutracel
Note: this name may be used for preparations of different composition.
Baxter, UK.
Glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Isdin, Spain.
Guanosine (p. 2523·2); inosine (p. 2533·1); miconazole nitrate (p. 589·1); vitamin F (p. 2509·2).
Skin disorders.

Nutracip *Nutramedica, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Nutracip-SB *Nutramedica, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Nutracort *Galderma, Braz.; Galderma, Chile; Galderma, Gr.; Galderma, Mex.; Healthpoint, USA; Galderma, Venez.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Nutra'Crème *Beaubour Nutrition, Fr.†*
Preparation for enteral nutrition.

Nutradab-SF *Sanify, India.*
Preparation for enteral nutrition.

Nutraderm *Galderma, Arg.; Galderma, Braz.; Galderma, Canad.†; Galderma, Chile; Orion, Fin.†; Galderma, Mex.; Galderma, Philipp.; Galderma, USA.*
Emollient.
Dry skin; moisturiser; vehicle for topical drugs.

Nutraderm Advanced Formula *Valeant, USA.*
Emollient.

Nutradex *Fresenius Kabi, Swed.*
Carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Nutradyn *Rhine, India.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1).

Nutrafem
Note: this name may be used for preparations of different composition.
Bionutra, Singapore.
Eucommia ulmoides; vigna radiata.
Menopausal disorders.

Nutrascience, Philipp.
Calcium citrate (p. 1783·2); magnesium citrate (p. 1857·1); zinc gluconate (p. 2126·2); cissus quadrangularis; oligofructose; withania somnifera; red clover (p. 2482·1); trikatu.
Menopausal disorders; osteoporosis.

Nutrafilm *Giscard, Arg.*
Ammonium lactate (p. 1694·3).
Dry skin.

Nutrafit *Northfield, Philipp.*
Green tea (p. 2648·2); levocarnitine (p. 2053·2); guarana (p. 2648·2); chromium tripicolinate (p. 2056·1).
Nutritional supplement.

Nutraisdin *Isdin, Chile.*
SPF 30: Octocrilene (p. 1715·2); ensulizole (p. 1703·1); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); octil triazone (p. 1715·1); bisoctrizole (p. 1697·1); iscotrizinol (p. 1706·1).
Moisturiser with sunscreens.

Isdin, Port.
Cream: Dexpanthenol (p. 2582·2); zinc oxide (p. 1729·1); borage oil (p. 2459·2); vitamin E (p. 2119·1).
Napkin rash.

Isdin, Port.
Lotion: ⊗Dexpanthenol (p. 2582·2); glycerol (p. 2517·2); borage oil (p. 2459·2); avocado oil (p. 2451·2).
Nappy rash.

Nutraisdin ZN *Isdin, Chile.*
Barrier preparation with zinc oxide (p. 1729·1).
Nappy rash.

Nutral *Bionutre, Arg.*
Amino acids; minerals; vitamins.
Dietary supplement; tonic.

Nutralcon *Galderma, Arg.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Nutraloric *Nutraloric, USA.*
Preparation for enteral nutrition.

Nutramedix *Interhealth, Hung.*
Uncaria tomentosa.
Musculoskeletal and joint disorders; immunostimulant.

Nutrament *Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition.

Nutramigen *BMS, Pol.; Mead Johnson, Pol.*
A range of infant feeds.
Food allergy.

Mead Johnson, Denm.; Mead Johnson, Israel.
Food for special diets.
Milk protein sensitivity; soy-protein sensitivity; digestive disorders; lactose intolerance; eczema.

Mead Johnson, Fr.; Mead Johnson, Irl.; Mead Johnson, Ital.; Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.
Infant feed.
Atopic dermatitis; galactosaemia; enteral nutrition; cows' milk allergy; milk protein sensitivity; lactose intolerance; sucrose intolerance; protein intolerance; diarrhoea; abdominal colic; food allergies; digestive disorders.

Mead Johnson, Austral.†; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.
Lactose- and sucrose-free protein hydrolysate (p. 2086·2) preparation.
Protein sensitivity; malabsorption disorders; disaccharide intolerance; galactosaemia; homocystinuria; gastro-enteritis.

Nutramigen AA *Mead Johnson, Ital.*
Amino-acid based infant feed.
Cows' milk allergy; food allergies.

Mead Johnson Nutritionals, UK.
Infant feed.
Cows' milk protein allergy; food allergies.

Nutramigen Premium *Mead Johnson, Mex.*
Infant feed.
Protein sensitivity.

Nutramin *Fresenius Kabi, Cz.; Behrens, Venez.*
Amino acids.
Parenteral nutrition.

Nutra'Mix *Lactalis, Fr.*
Preparation for enteral nutrition.

NutraMX *Vita Health, Singapore.*
Vitamins; minerals; ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); glutamine (p. 2070·3); inositol (p. 2533·2); lysine (p. 2079·3).

Nutraplus *Galderma, Austral.; Galderma, Braz.; Galderma, Fr.†; Galderma, Irl.; Galderma, Malaysia; Galderma, Mex.; Galderma, NZ; Galderma, Philipp.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Switz.; Galderma, Thai.; Atabay, Turk.; Taymed, Turk.; Galderma, UK; Valeant, USA.*
⊗Urea (p. 1727·3).
Dry skin disorders; hyperkeratotic skin disorders.

Nutrared *Nutramedica, India.*
Dexpanthenol (p. 2582·2); mecobalamin (p. 2108·1); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).

Nutrasendi *Mersifarma, Indon.*
⊗Vitamins; minerals; gelatin (p. 1154·1).
Dietary supplement for healthy joints and bones.

Nutrasona *Isdin, Spain.*
⊗Hydrocortisone buteprate (p. 1640·1).
Skin disorders.

Nutra-Soothe
Note: this name may be used for preparations of different composition.
Pertussin, USA.
Emollient.

Nutrasorb *Galderma, Mex.*
⊗Acrylate copolymer; glycerol (p. 2517·2).
Acne; seborrhoea.

Nutra-Tat *Atabay, Turk.*
Aspartame (p. 2169·2).
Sugar substitute.

Nutratopic Gel *Isdin, Chile.*
Soap substitute.

Nutratopic Locion *Isdin, Arg.; Isdin, Chile.*
Emollient.

Nutratopic Rx *Isdin, Chile.*
Emollient.

Nutravance *Breckenridge, USA.*
Vitamins; minerals; thioctic acid; lutein (p. 2079·2).

Nutravit Light *Investigacion, Mex.†*
Proteina; vitamins; minerals.
Obesity.

Nutrazinc *EuroHealth, Philipp.*
Vitamin A (p. 2098·3); lysine (p. 2079·3); chlorella growth factor (p. 2475·3) taurine (p. 2626·2); zinc sulfate (p. 2126·2); vitamin B substances (p. 2102·3).
Dietary supplement; tonic.

Nutrem *Medihealth, Mex.*
Vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); vitamin A palmitate (p. 2098·3); dexpanthenol (p. 2582·2); gamolenic acid (p. 2509·2); linoleic acid (p. 2509·2).
Sun-induced skin damage; wrinkles.

Nutren *Nestle, Braz.; Nestle, Canad.; Nestle, Hong Kong; Nestle, Indon.; Nestle, Philipp.; Nestle, Singapore; Nestle, Thai.*
A range of preparations for enteral nutrition.

Nestle, China.
Preparation for enteral nutrition.

Nestle, Israel.
A range of lactose-free and gluten-free preparations for enteral nutrition.

Nestle, Malaysia.
Range of preparations for enteral nutrition.

Nestle, USA.
Lactose-free, gluten-free preparation for enteral nutrition.

Nutrena *Abbott, Turk.*
Preparation for enteral nutrition.
Renal failure.

Nutr-E-Sol *Advanced Nutritional Technology, USA.*
Tocofersolan (p. 2119·1).
Vitamin E supplement.

NutreStore *Emmaus, USA.*
Glutamine (p. 2070·3).
Short bowel syndrome.

Nutre-T *Nucitec, Mex.*
Preparation for enteral nutrition.

Nutrex
Note: this name may be used for preparations of different composition.
JK Biochem, India.
Capsules: Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

JK Biochem, India.
Oral drops: Folic acid (p. 2063·1); iron (p. 2073·1).

Nutrexon *Nufarindo, Indon.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol dependence; opioid dependence.

Nutri 10 *Medisys, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2).
Nutritional supplement.

Nutri 10 Excel *Medisys, Philipp.*
Vitamins; iron (p. 2073·1).
Nutritional supplement.

Nutri Yin-Nutri Yang *Pronutri, Fr.†*
Nutri Yin, magnesium chloride (p. 1787·1); magnesium carbonate (p. 1856·2); calcium phosphate (p. 1784·2); Nutri Yang, calcium chloride (p. 1783·1); zinc gluconate (p. 2126·2); magnesium phosphate (p. 1787·3); calcium phosphate (p. 1784·2).
Tonic.

Nutria *Lifestyles, Canad.†*
Vitamins; minerals.

Nutri-Aid *Martek, Philipp.*
Docosahexaenoic acid (p. 1460·1); sunflower oil (p. 2098·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Dietary supplement.

Nu-Triazide *Nu-Pharm, Canad.†*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Nutribén APLV *Nutriben, Fr.*
Infant feed.
Allergy to cows' milk protein.

Nutribén AR *Nutriben, Fr.*
Infant feed.
Regurgitation.

Nutribén Caliben *Nutriben, Fr.*
Infant feed.
Infant colic.

Nutribén HA *Nutriben, Fr.*
Infant feed.
Risk of allergy.

Nutribén sans Lactose *Nutriben, Fr.*
Infant feed.
Diarrhoea.

Nutribén Transiben *Nutriben, Fr.*
Infant feed.
Constipation.

Nutribone *Aus Biomed, Austral.*
Calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1); phytomenadione (p. 2122·2); manganese (p. 2081·2); magnesium (p. 1786·3); ascorbic acid (p. 2110·3); folic acid (p. 2063·1); zinc (p. 2126·1); pyridoxine hydrochloride (p. 2105·3).
Calcium supplement; osteoporosis.

Nutribone Plus *Abbott, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Nutribone-Kid *Abbott, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Nutribraun *Braun, Port.*
Amino acids; electrolytes (p. 1775·1); lipids (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)).
Parenteral nutrition.

Nutrica *Duckbill, India.*
Vitamins; minerals; trace elements.

Nutricaire *PediaCare, Philipp.*
Vitamins; zinc (p. 2126·1); chlorella (p. 2475·3); taurine (p. 2626·2); lysine (p. 2079·3).
Dietary supplement for children.

Nutrical *Nutricia, Ital.*
Preparation for enteral nutrition.

Nutricap
Note: this name may be used for preparations of different composition.
More, Philipp.
Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2); rutoside (p. 2505·3); ginkgo biloba (p. 2512·3); lycopene (p. 2546·2); lutein (p. 2079·2); selenium yeast (p. 2125·2); zeaxanthin (p. 2125·3).
Nutritional supplement.

Nutrisante, Fr.
Amino acids; vitamins; zinc oxide (p. 1729·1); bambusa arundinacea.
Hair and nail disorders.

Polinac, Venez.
Nut oil (p. 2446·1); litothamne; milk protein; yeast (p. 2125·2); acerola; lecithin (p. 2542·2); beeswax (p. 2170·2).
Dietary supplement.

Nutricard *Raptakos, India.*
Preparation for enteral nutrition.

Nutricare *Scott-Cassara, Arg.*
Amino acids; carbohydrate.
Parenteral nutrition.

Nutricee *Pharma Nutria, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Nutrichol *Landson, Indon.*
Preparation for enteral nutrition with vitamins.
Nutritional supplement.

Nutricobal Plus *Avinash, India.*
Thioctic acid (p. 2629·1); chromium polynicotinate (p. 2055·3); mecobalamin (p. 2108·1).

Nutricom *Panjon, India.*
Vitamins; minerals; trace elements.

Nutricom-NB *Panjon, India.*
Benfotiamine (p. 2102·3); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3).

Nutricomp *Braun, Cz.; Braun, Indon.†*
A range of preparations for enteral nutrition.

Nutricomp Fiber *Braun, Singapore.†*
Preparation for enteral nutrition with fibre.
Dietary supplement.

Nutricomp Protein *Braun, Singapore.†*
Amino acids.
Dietary protein supplement.

Nutricon *Pasadena, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Nutrideen *Bioceuticals, UK.*
Marine protein extract; vitamin C (p. 2110·3); zinc (p. 2126·1).

NutriDox *Advanced Vision, USA.†*
Doxycycline (p. 288·1).

Nutridrink *Support, Braz.; Nutricia, Cz.*
A range of preparations for enteral nutrition.

Nutricia, Denm.; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Indon.†; Nutricia, Ital.; Nutricia, Port.†
Preparation for enteral nutrition.

Nutrifac *Rising Pharmaceuticals, USA.*
Vitamins; minerals.

Nutrifar *Ifars, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Nutrifil *Pfizer, India.*
Capsules: Vitamins; zinc (p. 2126·1).

Pfizer, India.
Oral liquid: Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Nutriflam *Tropica Mas, Indon.*
⊗Serrapeptase (p. 2613·3); pancreatin (p. 2579·3); lecithin (p. 2542·2).
Inflammation.

Nutriflex *Braun, Arg.; Braun, Belg.; Braun, Chile; Braun, Cz.; Braun, Denm.; Braun, Ger.; Bioser (Biosep), Gr.; Braun, Hung.; Braun, Irl.; Braun, Neth.; Braun, Norw.; Braun, Pol.; Braun, Rus.; Braun, Swed.; Braun, UK; Braun, Ukr.†*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Braun, Austria; Braun, Fin.; Braun, Hong Kong; Braun, Port.; Braun, Switz.
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Braun, Turk.
Amino acids; carbohydrate; electrolytes (p. 1775·1); with or without lipids.
Parenteral nutrition.

Nutriflex Lipid *Braun, Austria; Braun, Belg.; Braun, Cz.; Braun, Ger.; Bioser (Biosep), Gr.; Braun, Hong Kong; Braun, Irl.; Braun, Neth.; Braun, Norw.; Braun, Spain; Braun, Swed.; Braun, Switz.; Braun, Thai.; Braun, UK.*
Amino acids; glucose (p. 2068·3); lipids (p. 2092·3); with or without electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Braun, Arg.
Amino acids; glucose (p. 2068·3); lipids; electrolytes (p. 1775·1).
Parenteral nutrition.

Braun, Denm.
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3) and medim-chain triglycerides (p. 2082·2)) electrolytes (p. 1775·1).
Parenteral nutrition.

Braun, Fin.
Amino acids; carbohydrates; electrolytes (p. 1775·1); lipid (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)).
Parenteral nutrition.

Braun, Port.
Amino acids; carbohydrates; lipids; electrolytes (p. 1775·1).
Parenteral nutrition.

Nutriflex Lipide *Braun, Fr.†*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1); lipid (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)).
Parenteral nutrition.

NuTRIflex Omega *Braun, Cz.; Braun, Ger.; Braun, Norw.; Braun, Spain; Braun, UK.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3), medium-chain triglycerides (p. 2082·2), and omega-3 triglycerides (p. 1460·3)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

NutriFocus *Abbott, USA.*
Preparation for enteral nutrition.

Nutrifol
Note: this name may be used for preparations of different composition.
Pentamedical, Ital.
Vitamin; amino acids.
Prevention of hair loss.

Rhine, India.
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Nutrigel *Farbo, Ital.*
Fructose (p. 2068·2); soya lecithin (p. 2542·2); honey (p. 2072·1); royal jelly (p. 2608·1).

Nutrigen *Mead Johnson, Ital.†*
Infant feed.
Food allergies; milk intolerance.

Nutrigrow *Medisys, Philipp.*
Syrup: Chlorella growth factor (p. 2475·3); taurine (p. 2626·2); lysine hydrochloride (p. 2079·3); vitamins.
Nutritional supplement.

Medisys, Philipp.†
Capsules: Chlorella growth factor (p. 2475·3); taurine (p. 2626·2); lysine hydrochloride (p. 2079·3); vitamins; minerals; selenium yeast (p. 2125·2).
Nutritional supplement.

Nutrigrow Plus *Medisys, Philipp.*
Chlorella growth factor (p. 2475·3); taurine (p. 2626·2); lysine hydrochloride (p. 2079·3); vitamins; zinc (p. 2126·1).
Dietary supplement.

Nutrihar *Taurus, India.*
Vitamins; minerals.

NutriHeal *Nestle, USA.*
Preparation for enteral nutrition.

Nutrihelper *Nutricional, Arg.†*
Preparation for enteral nutrition.

Nutrijoint *Darya-Varia, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); turmeric (p. 2218·1); javanese turmeric (p. 2636·2).
Joint disorders.

Nutrilac *Bohusovicka Mlekarna, Cz.*
A range of preparations for enteral nutrition.

Nutrilamine *Braun, Fr.*
Amino acids.
Parenteral nutrition.

Nutrilan *Galagen, USA.*
Lactose-free preparation for enteral nutrition.

Nutrilarm *Thea, Fr.*
Omega-3 fatty acids (p. 1460·1); omega-6 fatty acids (p. 2575·2); vitamins; zinc oxide (p. 1729·1).
Dietary supplement for dry eyes.

Nutrilex Lipid Peri *Braun, India.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipids (from medium-chain triglycerides (p. 2082·2) and soya oil (p. 2092·3)).
Parenteral nutrition.

Nutrilex Peri *Braun, India.*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Nutrilic *Chemech, India.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; prophylaxis of neural tube defects in pregnancy.

Nutrilin *Medifarma, Indon.; Pediatrica, Indon.; Pediatrica, Thai.*
Vitamins; with or without iron (p. 2073·1).
Nutritional supplement.

Pediatrica, Philipp.
Oral drops: Vitamins; taurine (p. 2626·2).
Nutritional supplement.

Pediatrica, Philipp.
Syrup: Vitamins; minerals with taurine.
Nutritional supplement.

Nutrilogie *Vichy, Chile.*
Range of emollients.
Dry skin.

Nutrilon Allergy Care *Nutricia, Cz.*
Infant feed.
Cow's milk intolerance.

Nutrilon Anti-Regurgitasi *Nutricia, Indon.*
Infant feed.
Gastro-oesophageal reflux in infants.

Nutrilon AR *Nutricia-Bago, Arg.; Nutricia, Cz.; Nutricia, Port.†*
Infant feed.
Gastro-oesophageal reflux in infants; regurgitation.

Nutrilon Hypo-Allergenic *Nutricia, Indon.*
Hypoallergenic infant feed.

Nutrilon Lactomin *Nutricia, Port.†*
Infant feed.
Lactose intolerance.

Nutrilon Low Lactose *Nutricia, Indon.†*
Infant feed.
Diarrhoea.

Nutrilon Omneo *Nutricia, Mex.†*
Infant feed.
Digestive disorders.

Nutrilon Pepti *Nutricia-Bago, Arg.; Nutricia, Cz.; Cow & Gate, Irl.†; Nutricia, Ital.; Nutricia, Port.†*
Infant feed.
Cows' milk intolerance; food hypersensitivity.

Nutrilon Pepti-Junior *Nutricia, Indon.; Nutricia, Mex.†*
Infant feed.
Cows' milk allergy; malabsorption syndrome; gastrointestinal disorders.

Nutrilon sin Lactosa *Nutricia-Bago, Arg.*
Infant feed.
Lactose intolerance; diarrhoea.

Nutrilon S/Lactosa *Andromaco, Chile.*
Infant feed.
Lactose intolerance.

Nutrilon Soya *Nutricia-Bago, Arg.; Andromaco, Chile; Nutricia, Cz.; Nutricia, Venez.*
Infant feed.
Lactose intolerance; galactosaemia; cows' milk intolerance.

Nutricia, Indon.
A range of infant feeds.
Lactose intolerance; cows' milk allergy.

Cow & Gate, Israel†; Nutricia, Mex.†
Soya-based infant feed.
Cows' milk protein allergy; lactose intolerance.

Nutrilyte *American Regent, USA.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Nutrimaiz SM *Uniao Quimica, Braz.*
Vitamin B substances (p. 2102·3); glutamic acid (p. 2070·2); ferric ammonium citrate or ferrous sulfate; magnesium chloride or magnesium sulfate; calcium phosphate (p. 1784·2); buclizine hydrochloride (p. 618·3); carnitine hydrochloride (p. 2053·2).
Tonic; reduced appetite.

Nutrimeal *Usana, Hong Kong†; Usana, Singapore.†*
Preparation for enteral nutrition.

Nutrimen C RE9 Reality Moisturizing Sunscreen *Arbonne, Canad.†*
SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Nutriminc RE9 Reality Day Cream *Arbonne, Canad.†*
SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Nutrimon *Raptakos, India.*
Nutritional supplement.

NutriMulti *Blackmores, Austral.*
Vitamins; minerals; dunaliella salina; wheat grass; ganoderma lucidum; spirulina (p. 2622·1); camellia sinensis.

Nutrineal *Baxter, Belg.; Baxter, Fr.; Baxter, Neth.; Baxter, Port.*
Amino acids; sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2) (p. 1778·2).
Peritoneal dialysis.

Nutrineal PD4 *Baxter, Canad.; Baxter, Denm.; Baxter, Ital.; Baxter, Spain; Baxter, Switz.*
Sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); amino acids (p. 1778·2).
Peritoneal dialysis.

Baxter, Cz.; Baxter, Fin.; Baxter, Irl.; Baxter, Norw.; Baxter, Rus.; Adcock Ingram Critical Care, S.Afr.†; Baxter, Swed.; Eczacibasi-Baxter, Turk.
Amino acids; sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2) (p. 1778·2).
Peritoneal dialysis.

Baxter, Israel.
Amino acids; electrolytes (p. 1775·1) (p. 1778·2).
Peritoneal dialysis.

Baxter, UK.
Electrolytes (p. 1775·1); amino acids (p. 1778·2).
Peritoneal dialysis.

Nutrini *Nutricia, Austral.*
A range of preparations for enteral nutrition in children.

Support, Braz.; Nutricia, Denm.; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia Clinical, UK.
A range of preparations for enteral nutrition.

Nutricia, Cz.
Preparation for enteral nutrition in children.

Nutricia, NZ.
Preparations for enteral nutrition in children.

Nutricia, Pol.†; Nutricia, Port.
Preparation for enteral nutrition.

NutriniKid *Nutricia, Denm.*
A range of preparations for enteral nutrition.

NutriniMax *Nutricia, Denm.*
A range of preparations for enteral nutrition.

Nutriperi Lipid *Braun, Ital.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)); electrolytes (p. 1775·1).
Parenteral nutrition.

Nutriplasmal *Braun, Port.†*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Parenteral nutrition.

Nutri-Plex *Future, Canad.*
Vitamins; minerals.

NutriPlus *Nutricia Clinical, UK.*
Preparation for enteral nutrition.

Nutriplus Lipid *Braun, Ital.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)); with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Nutripods *Nutri Start, Canad.†*
Vitamins; minerals.

Nutrir Nutricion Parenteral Total *Fresenius Kabi, Arg.*
Preparation for parenteral nutrition.

Nutrisan *Novartis, India.*
Vitamins; minerals.
Vitamin and mineral deficiency.

NutriScience *Wassen, UK.*
Selenium (p. 2086·3); antoxidant vitamins; ubidecarenone (p. 2637·1); plant extracts.

Nutrisil *Darier, Mex.*
Arachis oil (p. 2446·1).
Skin disorders; soap substitute.

Nutrisol *Mitsubishi, Philipp.; Mitsubishi Guangzhou, Singapore.*
Amino acids.
Parenteral nutrition.

Nutrisol-S *Mitsubishi, China; Mitsubishi Guangzhou, Hong Kong.*
Amino acids.
Parenteral nutrition.

Mitsubishi, Indon.
Amino acids; sorbitol (p. 2092·1).
Parenteral nutrition.

Nutrison *Nutricia-Bago, Arg.; Nutricia, Austral.; Support, Braz.; Nutricia, Cz.; Nutricia, Denm.; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Ital.; Nutricia, NZ; Nutricia, Pol.; Nutricia, Port.; Nutricia Clinical, UK.*
A range of preparations for enteral nutrition.

Nutricia, China; Nutricia, Irl.
Preparations for enteral nutrition.

Nutricia, Indon.†
Preparation for enteral nutrition.

Nutrison MCT *Nutricia Clinical, UK.*
Gluten- and fructose-free, low-lactose preparation for enteral nutrition.
Fat malabsorption.

Nutrispecial Lipid *Braun, Ital.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)); with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Nutri-Tab OB *WH Nutritionals, USA.*
Vitamins; minerals.
Dietary supplement.

Nutritein *Teingro, Arg.*
Proteins; vitamins; minerals.
Dietary supplement.

Nutritime *General Topics, Ital.*
Emollient.
Dry skin.

Nutritrace *Braun, Fin.; Braun, Neth.*
Trace elements.
Parenteral nutrition.

Nutrivance *Avon, Canad.*
Vitamins; minerals.

Nutrivisc *Alcon, Fr.*
Povidone (p. 2204·3).
Dry eyes.

Nutrivision *Kalbe, Singapore.†*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); vitamin B_2 (p. 2104·3); zinc (p. 2126·1); selenomethionine (p. 2087·1); chromium (p. 2055·3); superoxide dismutase (p. 135·2); citrus bioflavonoids (p. 2505·2); taurine (p. 2626·2); carrot root; quercetin (p. 2505·3); rutoside (p. 2505·3); lutein (p. 2079·2); myrtillus (p. 2566·2); glutathione (p. 1555·2); zeaxanthin (p. 2125·3); astaxanthin (p. 2170·1); zanthin; futurebiotics bioaccelerators.
Dietary supplement.

nutrivision *Kalbe, Indon.*
Superoxide dismutase (Glisodin) (p. 135·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); vitamin B_2 (p. 2104·3); selenium (p. 2086·3); chromium (p. 2055·3); lutein (p. 2079·2); quercetin (p. 2505·3); taurine (p. 2626·2); citrus bioflavonoids (p. 2505·2); acetylcysteine (p. 1652·2); myrtillus (p. 2566·2); glutathione (p. 1555·2); zeaxanthin (p. 2125·3); astaxanthin (p. 2170·1); xanthine; carrot root; rutoside (p. 2505·3); seng; futurebiotics bioaccelerators.
Antioxidant; dietary supplement.

Nutrivita *Lloyd, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Nutrizest *Zinnia, India.*
Vitamins; minerals; amino acids; *Lactobacillus sporogenes* (p. 2596·3).

Nutrizima *Merck, Chile.*
⊗Pancreatin (p. 2579·3); dimeticone (p. 1886·2).
Digestive disorders.

Nutri-Zinc *Nutrifarma, Turk.*
Zinc sulfate (p. 2126·2).

Nutrizinc *Healthprime, Philipp.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Nutri-ZYM *Future, Canad.*
Vitamins; minerals.

Nutrizym
Note: this name may be used for preparations of different composition.
Merck, Irl.†; Merck, UK.
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Nutrocal *Wockhardt, India.*
Preparation for enteral nutrition.

Nutrocal DM *Wockhardt, India.†*
Preparation for enteral nutrition.

Nutrodrip *Novartis, Irl.†; Novartis Consumer, UK.*
A range of preparations for enteral nutrition.

Nutrof *Thea, Philipp.†*
Vitamins; zinc (p. 2126·1); selenium (p. 2086·3); glutathione (p. 1555·2); lutein (p. 2079·2).
Nutritional supplement.

Nutrof Total *Thea, Fr.*
Vitamins; minerals; fish oil (p. 1460·1); tagetes erecta; grape (p. 2521·3).
Dietary supplement.

Nutrolin-B *Cipla, India.*
Lactobacillus (p. 2596·3); vitamin B substances (p. 2102·3).
Adjunct to antibiotic therapy; aphthous ulcers; diarrhoea; acne.

Nutropin *Roche, Canad.; Ipsen, Gr.; Ipsen, Irl.; Medison, Israel; Ipsen, Neth.; Ipsen, Spain; Ipsen, UK; Beaufour-Ipsen, Ukr.; Genentech, USA.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner's syndrome; growth disorders in renal failure; idiopathic short stature.

NutropinAq *Ipsen, Austral.; Ipsen, Austria; Ipsen, Belg.; Ipsen, Cz.; Ipsen, Denm.; Ipsen, Fin.; Ipsen, Fr.; Ipsen, Ger.; Ipsen, Hung.; Ipsen, Ital.; Ipsen, Norw.; Ipsen, Pol.; Ipsen, Port.; Ipsen, Swed.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner's syndrome; growth disorders in renal failure; Prader-Willi syndrome.

Nutroplex *Great Eastern, Thai.*
Vitamins; minerals; iron (p. 2073·1).
Nutritional supplement; iron-deficiency anaemia.

United American, Hong Kong.†
Ferric ammonium citrate (p. 2060·1); vitamins; minerals.
Dietary supplement; iron-deficiency anaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Nutroplex with Iron & Lysine *United American, Hong Kong; United American, Malaysia.†*
Vitamins; minerals; iron (p. 2073·1); lysine (p. 2079·3).
Tonic; nutritional supplement.

United American, Singapore.
Vitamins; minerals; iron (p. 2073·1).
Tonic.

United Laboratories, Philipp.
Vitamins; minerals; lysine (p. 2079·3).
Nutritional supplement.

Nutroplex Lysine *Great Eastern, Thai.*
Vitamins; minerals; iron (p. 2073·1); lysine (p. 2079·3).
Nutritional supplement; iron-deficiency anaemia.

Nutros *Labrha, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Nutrosa *Nutricia-Bago, Arg.*
Glucose (p. 2068·3).
Dietary supplement.

Nutrotal *Metro, Philipp.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); ubidecarenone (p. 2637·1); lycopene (p. 2546·2); lutein (p. 2079·2); minerals; vitamins; garlic (p. 2510·3); taurine (p. 2626·2).
Nutritional supplement.

Nutrox *Tyson, USA.*
Vitamins minerals; amino acids.

Nutro-Z *Zodley, India.*
Nutritional supplement.

Nutrozyme *Cipla, India.*
Capsules: ⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Cipla, India.
Oral liquid: ⊗Amylase (p. 2442·1); papain (p. 2582·3).

Cipla, India.
Tablets: ⊗Amylase (p. 2442·1); papain (p. 2582·3); simeticone (p. 1886·2); nicotinamide (p. 2083·1); charcoal (p. 1537·3).

Nutuss-A *Dr Alson, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Nutuss-BR *Dr Alson, India.*
⊗Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Nuvacthen *IFET (ΙΦΕΤ), Gr.*
⊗Tetracosactide (p. 1648·1).
Adrenocorticotrophic hormone.

Nuvacthen Depot *Defiante, Spain.*
⊗Tetracosactide hexa-acetate (p. 1648·1).
Adrenocorticotrophic hormone.

Nuvail *Innocutis, USA.*
Poly-ureaurethane.
Nail disorders.

NuvaRing *MSD, Austral.; Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Merck, Canad.; Schering-Plough, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Organon (Οργανον), Gr.; Organon, Hung.; Organon, Irl.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Organon, Neth.; Organon, Norw.; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; Essex, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Organon, Ukr.; Organon, USA.*
Etonogestrel (p. 2277·2); ethinylestradiol (p. 2275·3).
Contraceptive vaginal ring.

Nuvelle *Bayer, Denm.†; Bayer, NZ; Bayer, Port.; Bayer, Spain†; Bayer, UK.†*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders; osteoporosis.

Schering, Gr.
Estradiol valerate (p. 2271·2); levonorgestrel (p. 2296·1).
Menopausal disorders.

Nuvelle Continuous *Bayer, UK.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Nu-Verap *Nu-Pharm, Canad.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Nuvigil *Cephalon, USA.*
⊗Armodafinil (p. 2316·3).
Narcoleptic syndrome; obstructive sleep apnoea; shift-work sleep disorder.

Nuvir *Organon, India.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism; osteoporosis.

Nuvision *Guardian, Indon.*
Myrtillus (p. 2566·2); vitamin A (p. 2098·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); selenium (p. 2086·3); zinc (p. 2126·1).
Supplement for healthy eyes.

Nuvit *Pharmaland, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neurological disorders; neuropathy; toxaemia of pregnancy; anorexia; neurasthenia.

Nuvoclav *Mugi, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Nuvolax *Orion, Denm.*
Macrogol 4000 (p. 2547·3).
Constipation.

Nuvoneural *Mugi, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B supplement; neuritis; neuralgia.

Nuvorell *Sanorell, Ger.*
Strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Nux Med Complex *Dynamit, Austria.*
Belladonna (p. 2453·3); coffea (p. 2648·2); nux vomica (p. 2573·3); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Nux Vomica Complexe No 49 *Lehning, Fr.*
Nux vomica (p. 2573·3); bryonia (p. 2461·3); cinchona (p. 2478·3); ipeca (p. 1667·2); sulfur (p. 1721·1); arsenicum album (p. 2448·1); anemone pulsatilla (p. 2600·2); robinia.
Homoeopathic preparation.

Nux Vomica Composé *Boiron, Fr.*
Nux vomica (p. 2573·3); bryonia (p. 2461·3); argentum nitricum (p. 2615·3); condurango (p. 2485·3); abies nigra; robinia pseudo acacia; solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Nux Vomica N Oligoplex *Madaus, Ger.*
Nux vomica (p. 2573·3); allium sativum (p. 2510·3); bryonia (p. 2461·3); china (p. 2478·3); phosphorus (p. 2589·2).
Homoeopathic preparation.

Nux Vomica-Homaccord *Heel, Austria.*
Strychnos nux-vomica (p. 2573·3); bryonia cretica; lycopodium clavatum (p. 2547·1); citrullus colocynthis.
Homoeopathic preparation.

Heel, Neth.
Bryonia cretica; colocynthis (p. 1833·3); lycopodium clavatum (p. 2547·1); nux vomica (p. 2573·3).
Homoeopathic preparation.

Nux Vom-Plus *Doctor H, Rus.*
Artemesia absinthium (p. 2426·1); asarum europaeum (p. 2449·3); acidum sulfuricum (p. 2624·2); cinchona pubescens (p. 2478·3); passiflora incarnata (p. 2584·1); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Nuxal comp *Pfluger, Ger.*
Bismutum subnitricum (p. 1822·1); carbo vegetabilis (p. 1537·3); ferrum metallicum (p. 2073·1); lycopodium clavulatum (p. 2547·1); natrium chloratum (p. 1795·1); stibium sulfuratum nigrum (p. 2445·1); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Nuxal H *Pfluger, Ger.*
Carbo vegetabilis (p. 1537·3); colocynthis (p. 1833·3); lycopodium clavatum (p. 2547·1); momordica balsamina; stibium sulfuratum nigrum (p. 2445·1); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Nuzac *Cipla, India.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Nuzak *Cipla-Medpro, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Nuzide *Intas, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Nuzide-M *Intas, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).

Nuzym *Guardian, Indon.*
Ubidecarenone (p. 2637·1).
Tonic.

NVDP *Solitaire, India.*
Doxylamine (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Nyaderm *Taro, Canad.*
Nystatin (p. 590·3).
Fungal and bacterial skin and vaginal infections.

Nyal Allergy + Hayfever Relief *Valeant, Austral.*
Albizia; skullcap (p. 2617·1).
Hypersensitivity reactions; allergic rhinitis.

Nyal Antiviral Cold Sore *Valeant, Austral.*
Aciclovir (p. 964·1).
Herpes labialis.

Nyal Bronchitis Cough *Valeant, Austral.*
Ammonium chloride (p. 1656·1).
Cough.

Nyal Chesty Cough *Valeant, Austral.*
Guaifenesin (p. 1666·2); glucose (p. 2068·3); treacle (p. 2096·3).
Cough; upper respiratory-tract congestion.

Nyal Cold + Flu *Valeant, Austral.*
Phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion.

Nyal Cold + Flu Fighter *Valeant, Austral.*
Salix (p. 129·2); sambucus (p. 2609·3); horseradish (p. 2526·1).
Cold and influenza symptoms.

Nyal Cold + Flu Fighter Day + Night *Valeant, Austral.*
Day tablets, salix (p. 129·2); sambucus (p. 2609·3); horseradish (p. 2526·1); night tablets, sambucus; horseradish; valerian (p. 2640·2).
Cold and influenza symptoms.

Nyal Cold Sore *Valeant, Austral.*
Cream: Menthol (p. 2553·2); camphor (p. 2466·2).
Herpes labialis; cracked lips.

Nyal Cough, Cold & Flu Day + Night *Valeant, Austral.*
Day tablets, echinacea (p. 2498·1); salix (p. 129·2); garlic (p. 2510·3); horseradish (p. 2526·1); liquorice (p. 1853·2); ascorbic acid (p. 2110·3); zinc gluconate (p. 2126·2); night tablets, echinacea; salix; garlic; horseradish; liquorice; zinc gluconate; valerian (p. 2640·2).
Cold and influenza symptoms.

Nyal Decongestant
Note: this name may be used for preparations of different composition.
Valeant, Austral.
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Nyal Dry Cough *Valeant, Austral.*
Pentoxyverine citrate (p. 1672·1).
Cough.

Nyal Eczema Relief *Valeant, Austral.*
Colloidal oatmeal (p. 2451·1).
Eczema; skin irritation; burns.

Nyal Head Cold Fighter Day + Night *Valeant, Austral.*
Day tablets, salix (p. 129·2); garlic (p. 2510·3); echinacea (p. 2498·1); night tablets, salix; garlic; valerian (p. 2640·2).
Cold symptoms.

Nyal Medithroat Gargle *Valeant, Austral.*
Povidone-iodine (p. 1767·1).
Sore throat.

Nyal Nasal Decongestant + Pain Relief PE *Valeant, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinusitis.

Nyal Nasal Decongestant PE *Valeant, Austral.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinusitis.

Nyal Nasal Spray *Valeant, Austral.*
Zinc gluconate (p. 2126·2); eucalyptus oil (p. 2501·2); melaleuca oil (p. 2551·1).
Nasal congestion.

Nyal Night-Time Cough *Valeant, Austral.*
Squill (p. 1677·3); liquorice (p. 1853·2); senega root (p. 1677·2); melissa (p. 2552·3).
Cough.

Nyal Sinus + Pain Relief PE *Valeant, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion; sinusitis.

Nyal Sinus Relief *Valeant, Austral.*
Horseradish (p. 2526·1); sambucus (p. 2609·3); salix (p. 129·2).
Sinusitis.

Nyal Sinus Relief Day + Night *Valeant, Austral.*
Day tablets, horseradish (p. 2526·1); sambucus (p. 2609·3); salix (p. 129·2); night tablets, horseradish; sambucus; salix; skullcap (p. 2617·1).
Sinusitis.

Nyal Sinus Relief PE *Valeant, Austral.*
Phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion.

Nyal Sleep Aid *Valeant, Austral.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Insomnia.

Nyal Toothache Drops *Valeant, Austral.*
Benzocaine (p. 1980·2); phenol (p. 1763·3).
Toothache.

Nycolutamid *Nycomed, Denm.; Nycomed, Swed.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Nycoplus B-Tonin *Nycomed, Norw.*
Vitamin B substances (p. 2102·3); caffeine (p. 1203·3).
Vitamin B deficiency; tonic.

Nycoplus B-Total *Nycomed, Norw.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Nycoplus Calcigran *Nycomed, Norw.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Nycoplus C-vitamin *Nycomed, Norw.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Nycoplus E-vitamin *Nycomed, Norw.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Nycoplus Ferro-Retard *Nycomed, Norw.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Nycoplus Folsyre *Nycomed, Norw.*
Folic acid (p. 2063·1).
Folic acid deficiency.

Nycoplus Magnesium *Nycomed, Norw.*
Magnesium lactate (p. 1787·2); magnesium citrate (p. 1857·1).
Magnesium deficiency.

Nycoplus Neo-Fer *Nycomed, Norw.*
Ferrous fumarate (p. 2060·3).
Iron deficiency; iron-deficiency anaemia.

Nycopren *Nycomed, Gr.*
Naproxen (p. 98·2).
Pain; inflammation; musculoskeletal and joint disorders.

Nycovir *Nycomed, Austria.†*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpes simplex infections; varicella-zoster infections.

NYDA *Brauer, Austral.; Pohl, UK.*
Dimeticone (p. 2209·3).
Pediculosis.

Nyda L *Pohl, Ger.*
Dimeticone (p. 2209·3).
Pediculosis.

Nydase *Imbio, Rus.*
Hyaluronidase (p. 2527·2).
Burns; ulcers; wounds; musculoskeletal, joint, periarticular, and soft-tissue disorders.

Nydral *Demo, Gr.*
Nifedipine (p. 1447·2).

Nydrazid *Apothecon, USA.*
Isoniazid (p. 311·2).
Tuberculosis.

Nyefax *Ascent, Austral.; Douglas, NZ; Douglas, Thai.†*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Nyepzyl *Ultra, Mex.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

NYFE *Aamorb, India.*
⊗Nebivolol (p. 1444·2).
Hypertension; heart failure.

NYFE-SA *Aamorb, India.*
⊗Nebivolol (p. 1444·2); levamlodipine.
Hypertension.

Nykob *SVUS, Cz.; MA, Denm.; MA, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; mania; bipolar disorder.

Nylax with Senna *Crookes Healthcare, UK.*
Senna (p. 1885·1).
Constipation.

Nylex *Novendia, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Nylichlor *Farmanic, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Nylipark *Pharmanik (Φαρμανικ), Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Nylsanuc *Nucleus, Denm.*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

Nymalize *Arbor, USA.*
Nimodipine (p. 1455·2).
Reduction of ischaemic neurological deficit following subarachnoid haemorrhage.

Nymiko *Sanbe, Indon.*
Nystatin (p. 590·3).
Candidiasis.

Nyogel *Novartis, Austral.; Novartis, Belg.; 2care4, Denm.; Orifarm, Denm.; Novartis, Fr.; Novartis, Ger.†; Alcon, Gr.; Novartis, Irl.; Novartis, Ital.; Novartis, Neth.; Novartis, Port.; Adcock Ingram, S.Afr.; Novartis, UK.†*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Nyolol *Alcon, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.†; Novartis, India; Novartis, Indon.; Novartis, Israel; Novartis, Mex.; Europhta, Mon.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Alcon, Thai.†; Novartis, Turk.; Novartis, Ukr.†; Novartis, Venez.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Nyoshinsan *Tsumura, Jpn.*
Cyperus rhizome; cnidium rhizome; atractylodes lancea rhizome; angelica acutiloba root (p. 2443·3); skullcap root (p. 2617·1); cinnamon bark (p. 2479·2); ginseng (p. 2513·3); areca (p. 2446·3); coptis rhizome; liquorice (p. 1853·2); clove (p. 2481·2); saussurea root.
Traditional Kampo medicine.

Nyoxep *Medimar, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp disorders.

Nypine *Arrow, Austral.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

NyQuil Hot Therapy *Richardson-Vicks, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Coughs and cold symptoms.

NyQuil Nighttime Cold/Flu *Richardson-Vicks, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Coughs and cold symptoms.

Nyrin *Korea United, Singapore.*
Calcium levofolinate (p. 2067·1).
Reduction of methotrexate toxicity; megaloblastic anaemia.

VHB, India.
Folinic acid (p. 2066·3).
Methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil in colorectal cancer.

Korean United, Malaysia.†
Calcium folinate (p. 2066·3).
Megaloblastic anaemia; rescue after high-dose methotrexate; adjunct to fluorouracil in colorectal cancer.

Nysconitrine *Therabel, Belg.†*
Glyceryl trinitrate (p. 1391·2).
Heart failure; angina pectoris.

Nyserin *Swiss Parenterals, Philipp.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction.

Nyskin *Saval, Chile.*
Adapalene (p. 1692·1).
Acne.

Nysmosons-V *Sons, Mex.*
⊗Metronidazole (p. 936·1); nystatin (p. 590·3); fluocinolone acetonide (p. 1636·1).
Vaginal infections.

Nystacid *Aspen, S.Afr.*
Nystatin (p. 590·3).
Candidiasis.

Nystaderm *Dermapharm, Austria†; Dermapharm, Ger.*
Nystatin (p. 590·3).
Fungal infections.

Nystaderm comp *Dermapharm, Ger.*
⊗Nystatin (p. 590·3); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Nystaform *Typharm, Irl.†; Typharm, UK.*
Nystatin (p. 590·3); chlorhexidine hydrochloride (p. 1743·3).
Fungal and bacterial skin infections.

Nystaform-HC *Typharm, UK.*
⊗Nystatin (p. 590·3); chlorhexidine acetate (p. 1743·2) or chlorhexidine hydrochloride (p. 1743·3); hydrocortisone (p. 1640·1).
Infected skin disorders.

Nystalocal *Pierre Fabre, Ger.; Medinova, Switz.*
⊗Dexamethasone (p. 1630·3); chlorhexidine hydrochloride (p. 1743·3); nystatin (p. 590·3).
Infected skin disorders.

Nystamysyn *Farmasyn, Gr.*
Nystatin (p. 590·3).
Fungal infections.

Nystan *BMS, UK.*
Nystatin (p. 590·3).
Fungal infections.

Nystatin Softpaste *Holsten, Ger.*
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Fungal skin infections.

Nystetrin *Help, Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Nystin
Note: this name may be used for preparations of different composition.
Lapi, Indon.
Nystatin (p. 590·3).
Oral candidiasis.

Polipharm, Thai.
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Vaginal infections.

Nystop *Paddock, USA.*
Nystatin (p. 590·3).
Candidiasis.

Nytamel *Clonmel, Irl.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Ny-Tannic *Allegis, USA.†*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Nytcold Medicine *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Coughs and cold symptoms.

Nyte *Kopran, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Nytex *Pharos, Indon.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Nytol *Prestige, Canad.; GSK, Israel; GSK, Mex.; GSK Consumer, UK; Block, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Nytol Herbal *GSK Consumer, UK.*
Lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Formerly contained lupulus, Jamaica dogwood, passion flower, pulsatilla, and wild lettuce.
Insomnia.

Nytol Natural Source *GSK Consumer, Canad.*
Valerian (p. 2640·2).
Insomnia.

Nyzoc *Nycomed, Austria.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease.

Nyzol *Gerolymatos, Gr.*
Olanzapine (p. 1089·3).

N-Zarevet *Perrigo, Israel.*
Calcium carbonate (p. 1824·3).
Antacid; calcium supplement.

N-Zen *TC Pharma-Chem, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

N-Zol *DR Johns, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

N-Zolin *Plus, India.*
⊗Chlorphenamine maleate (p. 620·3); methylcellulose (p. 2197·3); naphazoline hydrochloride (p. 1669·3).

O2 *Medley, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

O-4 Cycline *Aspen, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

O & D *Hy-Gro, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

O & O *Glenmark, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

OA
Note: this name may be used for preparations of different composition.
Aaron, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Interbat, Indon.
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1).
Osteoarthritis; dietary supplement to maintain healthy joints.

Mead Johnson, Fr.
Food for special diets.
Propionic acidaemia; methylmalonic acidaemia.

OA Forte *Interbat, Indon.*
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1); vitamin E (p. 2119·1).
Osteoarthritis; dietary supplement to maintain healthy joints.

OA Plus
Note: this name may be used for preparations of different composition.
Interbat, Indon.
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1); vitamin E (p. 2119·1); dimethyl sulfone (p. 2493·3); boron (p. 2052·3); collagen (p. 2483·2).
Osteoarthritis; dietary supplement to maintain healthy joints.

Solitaire, India.
Diacerein (p. 45·3); glucosamine sulfate (p. 2515·3); mecobalamin (p. 2108·1); dimethyl sulfone (p. 2493·3).

OAC Hp7 *AstraZeneca, Philipp.†*
Clarithromycin (p. 266·2); amoxicillin (p. 216·2); omeprazole (p. 1867·2).
Helicobacter pylori *eradication in peptic ulcer disease.*

OAM *Daffohils, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

O-AP *Alpha Aromatic, India.*
Cyproheptadine (p. 624·1); tricholine citrate (p. 2055·2).

Oasil *Gap, Gr.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety disorders.

Oass *Syntho, India.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Oaxen *Rafarm, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

OB-12 *Obsurge, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

OB Cal *PP Lab, Thai.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity.

OB Complete *Vertical, USA.*
Vitamins; minerals; with or without docosahexaenoic (p. 1460·1).

OB Max *Gruppo Medica, Philipp.*
Vitamins; minerals; taurine (p. 2626·2).
Pre- and post-natal nutritional supplement.

OB Smart SG *Gruppo Medica, Philipp.*
Vitamins; minerals; taurine (p. 2626·2); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Pre-natal nutritional supplement.

Obactin *Meridian, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Obactin-OZ *Meridian, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Obactin-TZ *Meridian, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Obalix *Faes, Spain.*
Bilastine (p. 617·3).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Obat Kutu Rambut Cap Dua Jempol *Konimex, Indon.†*
Lindane (p. 2157·1).
Pediculosis.

Obax *Wockhardt, India.*
Gliclazide (p. 472·3); metformin (p. 489·1).
Diabetes mellitus.

Obbekjaers *Bennett, UK.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome.

Ob-Cal *Obsurge, India.*
Oral suspension: Calcium citrate (p. 1783·2); lysine hydrochloride (p. 2079·3); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc gluconate (p. 2126·2).

Obsurge, India.
Tablets: Calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Ob-Cal A *Obsurge, India.*
Alfacalcidol (p. 2112·3); calcium citrate (p. 1783·2).

Obcin *Oriental, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage.

Obdhamin *Solas, Indon.*
Vitamins; minerals; rofufa (docosahexaenoic acid); omega-3; lecithin (p. 2542·2).
Nutritional supplement for pregnancy and lactation.

Obecirol *Farmedia, Gr.*
⊗Budesonide (p. 1625·1).
Allergic disorders.

Obeclox *Medix, Mex.*
⊗Clobenzorex hydrochloride (p. 2318·3).
Obesity.

Obectiv *Probiomed, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Obedeuce *Intra-Labs, India.*
Chromium tripicolinate (p. 2056·1); garcinia cambogia (p. 2510·2); green tea (p. 2648·2); vitamin E (p. 2119·1).
Obesity.

Obéflorine *Lehning, Fr.†*
Bladderwrack (p. 2612·1); chicory (p. 2475·2); couch-grass (p. 2487·2); equisetum (p. 2500·1); ash leaves (p. 2450·1).
Obesity.

Obegyn Prenatal *Fleming, USA.*
Vitamins.

Obelit *Intas, India.*
Orlistat (p. 2577·1).
Obesity.

Oben *Armour, India.*
Albendazole (p. 149·1).
Worm infections.

Obendol *Vitae, Mex.*
⊗Mazindol (p. 2324·1).
Obesity.

Obenyl *Charak, India.*
Punarnava (p. 2601·1); cuminum cyminum.
Obesity.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Oberdol
Note: this name may be used for preparations of different composition.
Diafarm, Spain.†
Ibuprofen (p. 68·2).
Gout; musculoskeletal, joint, and peri-articular disorders; fever; pain.

Obergan *Demo, Gr.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Obesan-X *Technikon, S.Afr.*
⊗Phendimetrazine tartrate (p. 2328·3).
Obesity.

Obesmin *Fahrvitex, Hung.*
Borage oil (p. 2459·2); evening primrose oil (p. 2502·2); ammonium metavanadate; manganese chloride (p. 2081·2); nicotinamide (p. 2083·1); pyridoxine hydrochloride (p. 2105·3).
Obesity.

Obestal *Stallion, Philipp.*
Orlistat (p. 2577·1).
Obesity.

Obestat *Cipla, India.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

O-Beta *Intas, India.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; migraine.

Obex-LA *Adcock Ingram, S.Afr.*
⊗Phendimetrazine tartrate (p. 2328·3).
Obesity.

OBH *Berlico Mulia, Indon.*
Liquorice (p. 1853·2); ammonium chloride (p. 1656·1); anise oil (p. 2444·3); peppermint oil (p. 1877·1).
Cough.

OBHdryl *Ikapharmindo, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); liquorice (p. 1853·2); SASA.
Cough.

Obical *Medifarma, Indon.*
Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); phosphorus (p. 2589·2); colecalciferol (p. 2113·1); fructo-oligosaccharides (p. 2508·1).
Calcium deficiency; calcium supplement; osteoporosis.

Westmont, Malaysia; Westmont, Singapore.
Calcium (p. 1783·1); magnesium oxide (p. 1857·3); phosphorus (p. 2589·2); colecalciferol (p. 2113·1); fructo-oligosaccharides (p. 2508·1).
Dietary supplement.

Obid *Radicura, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Obid-ER *Ordain, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Obid-OZ *Radicura, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Obifen *Ayrton, UK.*
Ibuprofen (p. 68·2).

Obiless *Solitaire, India.*
Orlistat (p. 2577·1).
Obesity.

Obimet *Abbott, India.*
Metformin (p. 489·1) or metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Obimet-GX *Abbott, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Obimin *Westmont, Hong Kong; Westmont, Malaysia; BioFemme, Philipp.; Westmont, Singapore.*
Vitamins; minerals.
Dietary supplement during pregnancy and lactation.

Obimin Pluz *Westmont, Singapore.*
Fish oil (p. 1460·1); omega-3 fatty acids (p. 1460·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamins; minerals; trace elements.
Dietary supplement in pregnancy and lactation.

Obimin-AF *Medifarma, Indon.; Great Eastern, Thai.†*
Vitamins; minerals.
Nutritional supplement during pregnancy and lactation.

Obimin-AZ *Great Eastern, Thai.*
Ferrous fumarate (p. 2060·3); vitamins; minerals.
Nutritional supplement during pregnancy and lactation.

Obimol *Ayrton, UK.*
Paracetamol (p. 115·1).

Obinese *Pfizer, Mex.*
Chlorpropamide (p. 470·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

O-Biol *Biol, Arg.*
Nystatin (p. 590·3); neomycin sulfate (p. 330·1); nitrofurazone (p. 333·1); vitamin A (p. 2098·3).
Vaginal infections.

O-Biol P *Biol, Arg.†*
Nystatin (p. 590·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Vaginal infections.

O-Biotic *Zwitter, Gr.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Obipluz *Darya-Varia, Indon.*
Vitamins; minerals; fish oil (p. 1460·1); omega-3 fish oil (p. 1460·3).
Nutritional supplement for pregnancy and lactation.

O-Bit *Zubit, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Obit *Malar, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Obitane *Pharmasol, Thai.*
Chlorhexidine gluconate (p. 1743·3).

O-Bit-DM *Zubit, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Obit-M *Malar, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Obit-OZ *Malar, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Obitrol *Micro, India.*
Orlistat (p. 2577·1).
Obesity.

Obit-TZ *Malar, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oblant *Degorts, Mex.*
Cinnarizine (p. 622·1).
Vestibular disorders; motion sickness; cerebral and peripheral vascular disorders.

Oblax A-1-1 *Knop, Chile.*
Phenolphthalein (p. 1877·3); magnesium oxide (p. 1857·3); marine algae.
Bowel evacuation; constipation.

Obleas Chinas *Maver, Chile.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Cold symptoms.

Oblisec *Microsules, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

OB-Mom *Dynamic, Philipp.*
Vitamins; minerals.
Dietary supplement during pregnancy and lactation.

Obocil *Oboi, Philipp.; Samarth, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Obogen *Oboi, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Oboliz *Rafarm, Gr.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Obosan *Rafarm, Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Obra *Syntho, India.*
Tobramycin sulfate (p. 380·2).
Eye infections.

Obracin *EuroCept, Belg.; EuroCept, Neth.; Teva, Switz.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Obra-D *Syntho, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); tobramycin sulfate (p. 380·2).
Eye inflammation with bacterial infection.

Obradon *CP Pharma, Hung.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Obra-F *Syntho, India.*
⊗Fluorometholone (p. 1637·2); tobramycin (p. 380·1).

Obrase *Cadila, India.*
Folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Obrasone *Cadila, India.*
⊗Tobramycin sulfate (p. 380·2); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Obron-6 *Pfizer, Indon.†*
Vitamins; minerals.
Nutritional supplement for pregnancy and lactation.

Obruman *Oxbridge, UK.*
⊗Albumin (p. 1130·2).
Plasma volume expansion.

Obry *Grin, Mex.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Obrydex *Grin, Mex.*
⊗Tobramycin (p. 380·1); dexamethasone phosphate (p. 1631·1) or dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections with inflammation.

Obrypre *Grin, Mex.*
⊗Tobramycin (p. 380·1); prednisolone acetate (p. 1645·2).
Bacterial eye infections with inflammation.

Obsidan
Note: this name may be used for preparations of different composition.
Actavis, Ger.; Actavis, Rus.
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; tremor; migraine; hyperthyroidism; hypertrophic cardiomyopathy; anxiety.

UCB, Fin.
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency; iron-deficiency anaemia.

Obsidan comp *UCB, Fin.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Obstetric Care *Orion, Singapore.*
Chlorhexidine gluconate (p. 1743·3).

Obstetrix *Seyer, USA.*
Vitamins; iron (p. 2073·1); calcium (p. 1783·1); zinc (p. 2126·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Obstinol M *UCB, Ger.*
Liquid paraffin (p. 2191·2).
Bowel regulation.

Obstipar *Tecnifar, Port.†*
Lactulose (p. 1850·3).
Constipation.

Obteran *Prafa, Indon.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Obtrex *Pronova, USA.*
Vitamins; minerals.

Obtrin *Tai Yu, Philipp.†*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; postpartum atony.

Obucort *Otsuka, Indon.; Otsuka, Philipp.; Otsuka, Thai.*
⊗Budesonide (p. 1625·1).
Asthma.

Obusonid *Velka, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Obutin *Hanlim, Singapore.*
Oxybutynin hydrochloride (p. 2361·2).
Urinary-tract disorders.

Obynal-M *Medi-Rx, Philipp.*
Vitamins; minerals.
Pre- and post-natal nutritional supplement.

Obzin *DR Johns, India.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; premenstrual dysphoric disorder.

Oc *Cadila, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

OC8 *Sebela, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

OC-35 *Polfarmex, Pol.; Helm, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women; oral contraceptive in women with androgenic symptoms.

Ocacin *Novartis, Spain.†*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

O-Cal
Note: this name may be used for preparations of different composition.
Pharmics, USA.
Vitamins; minerals.

Ocal
Note: this name may be used for preparations of different composition.
Helios, India.
Calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).
Calcium supplement; osteoporosis; osteomalacia.

Occidal *Ranbaxy, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Occlusal *Medicis, Canad.†; Alliance, Irl.; Alliance, UK; Medicis, USA.*
Salicylic acid (p. 1719·1).
Warts.

Ocean *Valeant, USA.*
Sodium chloride (p. 1795·1).
Nasal irritation.

Ocean Nasal Moisturizer *Valeant, USA.*
⊗Hyaluronan (p. 2526·2); glycerol (p. 2517·2).

Ocean Spray *Kivema, Israel.*
Sodium chloride (p. 1795·1).
Nasal dryness.

Oceantone *Cantassium Co., UK.*
Green-lipped mussel (p. 2522·3).

O-Cebran *Blue Cross, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

O-Cebran-O *Blue Cross, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

O-Cebran-OZ *Blue Cross, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ocecor *Syncom, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

O-Cef *Plus, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ocef *Gujarat Terce, India.*
Cefuroxime (p. 255·2) or cefuroxime axetil (p. 255·2).
Bacterial infections.

Ocefa-SB *Osmed, India.*
Cefoperazone (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Ocefax *Roux-Ocefa, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Ocef-CV *Gujarat Terce, India.*
Cefuroxime axetil (p. 255·2); clavulanic acid (p. 268·3).

Ocella *Barr, USA.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Oceph *Zuventus, India.*
Cefdinir (p. 238·3).
Bacterial infections.

Ocepred *Sun, India.*
⊗Ofloxacin (p. 334·3); prednisolone acetate (p. 1645·2).

Oceral *Bayer, Braz.; Roche, Braz.; Teva, Switz.; Roche, Turk.*
Oxiconazole nitrate (p. 591·3).
Mixed fungal and Gram-positive bacterial infections.

Ochozim *Italmex, Mex.*
⊗Pepsin (p. 2586·1); trypsin (p. 2635·2); chymotrypsin (p. 2477·3); amylase (p. 2442·1); lipase (p. 2579·3); cellulase (p. 2473·1); rennet; ox bile extract (p. 2457·2); dimeticone (p. 1886·2).
Gastrointestinal disorders.

Ocid *Zydus, India; Cadila, Rus.; Zydus Cadila, Singapore; Zydus Cadila, Thai.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; heartburn; epigastric pain.

Ocid-D *Cadila, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ociderm-N *Pyridam, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Ocifril *La Pharmaceuticals, India.*
Clomipramine (p. 412·1) or clomipramine hydrochloride (p. 412·1).
Cataplexy associated with narcolepsy; phobias; obsessive-compulsive disorder; panic disorder; depression.

Ocimax *Pidek, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ocimix *Panacea, India.*
Ornidazole (p. 943·1); ciprofloxacin (p. 261·1).
Gastrointestinal infections.

Ocin *Grandix, India; Macrophar, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ocinil *Quest, India.*
Capsules: Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Quest, India.
Syrup: Magaldrate (p. 1856·1); simeticone (p. 1886·2).

Ocinil-D *Quest, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Ocitoc *Biochimico, Braz.*
Oxytocin (p. 2143·1).

Ocium *Bal, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ocium-M *Bal, India.*
Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Ociz *Ritz, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ociz-OR *Ritz, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

OCL *Abbott, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Oclam *Rishab, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

O'Clean *Cosme, India.*
⊗Timolol (p. 1513·2).
Glaucoma; ocular hypertension.

OCM *Gobbi, Arg.*
Chlordiazepoxide hydrochloride (p. 1044·2).

Ocobar *PC India, India.*
⊗Timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Ocona *Shalaks, India.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Ocona-CT *Sarabhai Piramal, India.*
Coal tar (p. 1723·2); ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Ocona-Z *Sarabhai Piramal, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).

O-Cox *Captab, India.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Ocoxin *SM, Venez.*
Arginine (p. 2049·1); cysteine (p. 2058·3); ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2); green tea (p. 2648·2); manganese sulfate (p. 2081·2); cinnamon (p. 2479·2); pyridoxal (p. 2105·3).

Ocplex *Octapharma, Cz.; Octapharma, Swed.*
Factor VIII inhibitor bypassing fraction (p. 1149·2).
Haemorrhagic disorders.

Ocrix *Biomep, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Ocsaar *MSD, Israel.*
Losartan potassium (p. 1422·2).
Diabetic nephropathy; heart failure; hypertension; cardiovascular risk reduction.

Ocsaar Plus *MSD, Israel.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; stroke prophylaxis.

Octacosanol *Cantassium Co., UK.*
Vitamin E (p. 2119·1); octacosanol (p. 1472·1).

Octadon P *UCB, Ger.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Octafil *Octapharma, Fin.*
A factor VIII preparation (p. 1148·1).
Haemophilia A.

Octafix *Octapharma, Fr.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Octagam *Octapharma, Austral.; Octapharma, Austria; Octapharma, Belg.; Octapharma, Braz.; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Fr.; Octapharma, Ger.; IFET (ΙΦΕΤ), Gr.; Octapharma, Gr.; Octapharma, Hong Kong†; Octapharma, Hung.; Medispan, India; Octapharma, Israel; Octapharma, Mex.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, NZ; Octapharma, Port.; Octapharma, Rus.; Octapharma, Singapore†; Octapharma, Swed.; Octapharma, Switz.; Octapharma, Thai.; Farmapek, Turk.; Octapharma, UK; Octapharma, USA.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome; immunodeficiency; agammaglobulinaemia; bone marrow transplantation.

Octagamocta *Octapharma, Spain.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immunodeficiency; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone-marrow transplantation.

Octaglob D *Octapharma, Mex.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Octalbin *Octapharma, Braz.; Octapharma, Denm.†; Octapharma, Fin.; Kalbe, Indon.; Octapharma, Ital.; Octapharma, Mex.; Octapharma, NZ; Octapharma, Spain.†*
⊗Albumin (p. 1130·2).
Plasma volume expansion; hypoalbuminaemia; hypoproteinaemia; hypovolaemia.

Octalbine *Octapharma, Belg.; Octapharma, Fr.†; Octapharma, Neth.*
⊗Albumin (p. 1130·2).
Hypovolaemia.

Octamide *Adria, USA.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Octamox *Medispan, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Octanate *Varifarma, Arg.; Octapharma, Austria; Octapharma, Belg.; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fr.; Octapharma, Ger.; Octapharma, Gr.; Octapharma, Hung.; Octapharma, Irl.; Octapharma, Israel; Octapharma, Ital.; Octapharma, Mex.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, NZ; Octapharma, Port.; Octapharma, Rus.; Octapharma, Spain; Octapharma, Swed.; Octapharma, Switz.; Octapharma, Thai.; Berk, Turk.; Octapharma, UK.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders; haemophilia A; factor VIII deficiency.

Octanine *Varifarma, Arg.; Octapharma, Austria; Octapharma, Belg.; Octapharma, Cz.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Norw.; Octapharma, Rus.; Octapharma, Spain; Octapharma, Thai.*
A factor IX preparation (p. 1149·3).
Haemophilia B; haemorrhagic disorders.

Octanine F *Octapharma, Hung.; Octapharma, Mex.; Octapharma, Switz.; Berk, Turk.*
A factor IX preparation (p. 1149·3).
Haemophilia B; haemorrhagic disorders.

Octaninef *Octapharma, Port.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Octanorm *Octapharma, Ital.*
A normal immunoglobulin (p. 2403·3).

Octanyl *Bago, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Octanyne *Berk, Turk.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Octapharma *Octapharma, China.*
⊗Albumin (p. 1130·2).

Octaplas *Octapharma, Austria; Octapharma, Belg.; Octapharma, Cz.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Hung.; Octapharma, Irl.; Octapharma, Ital.; Octapharma, Mex.; Octapharma, Neth.†; Octapharma, Norw.; Octapharma, NZ; Octapharma, Port.; Octapharma, Swed.; Octapharma, Switz.; Octapharma, UK; Octapharma, USA.*
Plasma (p. 1158·2).
Haemorrhagic disorders; reversal of oral anticoagulant effects; thrombocytopenic purpura.

Octaplex *Octapharma, Austria; Octapharma, Belg.; Octapharma, Braz.; Octapharma, Canad.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Fr.; Octapharma, Ger.; Octapharma, Irl.; Octapharma, Israel; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Port.; Octapharma, Spain; Octapharma, Switz.; Octapharma, UK.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Octasa *Tillotts, UK.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Octate *VHB, India.*
Octreotide acetate (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; postoperative pancreatic complications; variceal haemorrhage; AIDS-associated diarrhoea.

Octati *Octapharma, Mex.*
An antithrombin III preparation (p. 1132·3).
Antithrombin III deficiency.

Octatron *Errelife, Ital.*
Amino acids; vitamins; trace elements.

Octavi *Berk, Turk.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Octavital *Silanes, Mex.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals.
Nutritional supplement.

Octegra *Bayer, Austria; Elpen (Ελπεν), Gr.; Bayer, Hung.†; Bayer, Ital.; Bayer, Neth.†; Bayer, Spain.†*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Octeniderm *Schulke & Mayr, Austria; Farmex, Gr.; Schulke & Mayr, Switz.*
Octenidine hydrochloride (p. 1762·2); propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Octenisan *Schulke & Mayr, Singapore.*
Octenidine hydrochloride (p. 1762·2); lactic acid (p. 2539·1); allantoin (p. 1693·1).
Skin disinfection.

Octenisept *Schulke & Mayr, Austria; Schulke & Mayr, Cz.; Schulke & Mayr, Ger.; Farmex, Gr.; Schulke, Pol.; Schulke, Rus.; Schulke & Mayr, Singapore; Schulke & Mayr, Switz.; Schulke & Mayr, Ukr.*
Octenidine hydrochloride (p. 1762·2); phenoxyethanol (p. 1764·3).
Disinfection of burns, mucous membranes, skin, and wounds; fungal skin infections.

Octenisept Wound Gel *Schulke & Mayr, Singapore.*
Octenidine hydrochloride (p. 1762·2); propylene glycol (p. 2205·2).
Wound healing.

Octex *Degorts, Mex.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Octiban *Degorts, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Octide *United Biotech, India.*
Octreotide (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; postoperative pancreatic complications; variceal haemorrhage; AIDS-associated diarrhoea.

Octifen *Uniao Quimica, Braz.*
Ketotifen fumarate (p. 631·3).

Octilia *Pharmalex (Φαρμαλεξ), Gr.; Bouty, Ital.; Zambon, Rus.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation and congestion.

Octim *Ferring, Fr.; Ferring, UK.*
⊗Desmopressin acetate (p. 2355·1).
Haemorrhage.

Octin *Cipla-Medpro, S.Afr.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Octinum *Abbott, Turk.*
⊗Isometheptene hydrochloride (p. 2535·1).
Smooth muscle spasm.

Octinum-D *Pharmalex (Φαρμαλεξ), Gr.*
Octamylamine hydrochloride (p. 2574·2).
Smooth muscle spasm.

Octiveran *Rafarm, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Octobolin *Symbiotic, India.*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Octocaine *Novocol, Canad.; Novocol, Israel; Clarben, Port.; Clarben, Spain; Septodont, USA.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Octocin *LBS, Thai.*
Oxytocin (p. 2143·1).
Labour induction; uterine inertia; incomplete abortion; postpartum haemorrhage.

Octodec *Symbiotic, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Octodiol *Servier, Cz.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Octolipen *Farmstandart, Rus.*
Thioctic acid (p. 2629·1).
Polyneuropathy.

Octomol *Diasa, Spain.†*
Paracetamol (p. 115·1).
Pain; fever.

Octonativ-M *Octapharma, Swed.†*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Octonox *Pharmacobel, Belg.†*
Lormetazepam (p. 1082·1).
Insomnia.

Octorax *Demo, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Octoret *Demo, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Octosan *Sanofi-Aventis, Ger.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Octostim *Ferring, Arg.; Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Gynopharm, Chile; Ferring, Denm.; Ferring, Fin.; CSL, Ger.; Ferring, Ger.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Israel; Ferring, Mex.; Ferring, Neth.; Ferring, Norw.; Ferring, NZ; Ferring, Philipp.; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Er-Kim, Turk.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; haemorrhage; haemophilia A; von Willebrand's disease; platelet dysfunction.

Octra *Farmak, Ukr.*
Octreotide acetate (p. 1924·1).
Acromegaly; pancreatic and gastrointestinal endocrine tumours; AIDS-associated diarrhoea; complications following pancreatic surgery; variceal haemorrhage.

Octralin *Raam, Mex.*
Tacrolimus (p. 1968·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Octrayne *Hospira, Port.*
Octreotide acetate (p. 1924·1).
Gastrointestinal endocrine tumours; pancreatic fistulas; acromegaly; AIDS-associated refactory diarrhoea; variceal haemorrhage; prevention of complications following pancreatic surgery.

Octrene *Pierre Fabre, Gr.*
Chlorhexidine (p. 1743·2); chlorocresol (p. 1748·1); hexamidine (p. 1754·3).
Disinfection.

OctreoScan *BSM, Austria; Covidien, Belg.; Mallinckrodt, Cz.; Mallinckrodt, Denm.; Mallinckrodt, Fin.; Mallinckrodt, Irl.; Covidien, Ital.; Mallinckrodt, Neth.; Mallinckrodt, Port.; Mallinckrodt, Spain; Mallinckrodt, USA.*
Indium-111 pentetreotide (p. 2224·3).
Diagnosis and location of neuroendocrine and carcinoid tumours.

Octrestatin *Farm-Synthesis, Ukr.*
Octreotide (p. 1924·1).
Prevention of pancreatic complications following abdominal surgery; variceal haemorrhage.

Octride *Sun, Braz.; Sun, India.*
Octreotide (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; prevention of complications following pancreatic surgery; variceal haemorrhage; AIDS-associated diarrhoea.

Sun, China; Sun, Rus.; Sun, Thai.
Octreotide acetate (p. 1924·1).
Acromegaly; gastrointestinal endocrine tumours; prevention of complications following pancreatic surgery; variceal haemorrhage; carcinoid tumours.

Octrin *Biopharma, Ukr.*
Octreotide (p. 1924·1).
Acromegaly; gastropancreatic endocrine tumours; AIDS-associated diarrhoea; variceal haemorrhage; complications following pancreatic surgery.

Octronis *Neiss, India.*
Octreotide (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; postoperative pancreatic complications; variceal haemorrhage; AIDS-associated diarrhoea.

Ocubeta *Cadila, India.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Ocubrax *Alcon, Belg.; Alcon Cusi, Spain; Liba, Turk.; Alcon, Ukr.†*
Diclofenac sodium (p. 48·3); tobramycin (p. 380·1).
Ocular inflammation and infection following cataract surgery.

Ocu-Caine *Ocumed, USA.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

OcuCaps *Akorn, USA.*
Antoxidants; vitamins; minerals.

Ocu-Carpine *Ocumed, USA.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Ocucel *FDC, India.*
⊗Naphazoline (p. 1669·3).
Eye congestion.

Ocucel-A *FDC, India.*
⊗Chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3).

Ocucer *La Care, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocuchlor *Elder, India.*
Chloramphenicol (p. 257·1).
Eye infections.

Ocucin *Sun, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ocuclear
Note: this name may be used for preparations of different composition.
Elder, India.
⊗Boric acid (p. 2459·3); chlorphenamine maleate (p. 620·3); hypromellose (p. 2189·2); naphazoline hydrochloride (p. 1669·3); sodium chloride (p. 1795·1); zinc sulfate (p. 2126·2).

Ocucoat *Storz, Fr.†; Storz, Israel†; Bausch & Lomb, USA.*
Hypromellose (p. 2189·2).
Adjunct in ocular surgery.

Bausch & Lomb, USA.†
Eye drops: ⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Ocudecon *Cadila, India.*
⊗Naphazoline hydrochloride (p. 1669·3); phenylephrine hydrochloride (p. 1672·3).

Ocudiafan *Biosintex, Arg.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye congestion.

Ocudol *Oftalmi, Venez.*
Ketorolac trometamol (p. 80·2).
Inflammatory eye disorders.

Ocudor *FDC, India.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Ocular hypertension; glaucoma.

Ocudor-T *FDC, India.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).

Ocudox *Ocusoft, USA.*
Doxycycline hyclate (p. 288·2).

Ocufen *Allergan, Austral.; Allergan, Braz.; Allergan, Canad.†; Allergan, Chile; Allergan, China; Horus, Fr.; Allergan, Ital.; Allergan, Mex.; Allergan, NZ; Allergan, S. Afr.†; Allergan, Singapore†; Abdi, Turk.; Allergan, UK; Allergan, USA.*
Flurbiprofen sodium (p. 65·3).
Maintenance of mydriasis during cataract extraction; prevention of cystoid macular oedema; anterior eye inflammation.

Ocuflam *Sanbe, Indon.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Ocuflox *Allergan, Austral.; Allergan, Canad.; Allergan, Mex.; Allergan, USA.*
Ofloxacin (p. 334·3).
Bacterial eye infections; bacterial conjunctivitis.

Ocuflur *OmniVision, Ger.; Alvia (Αλβια), Gr.; FDC, India.*
Flurbiprofen sodium (p. 65·3).
Prevention of miosis in ophthalmic surgery; anterior eye inflammation.

Ocu-Force *Prairie Naturals, Canad.†*
Vitamins; minerals.

Ocufree *Centaur, India.*
Carotenoids (p. 2176·2); selenium dioxide (p. 2087·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zeaxanthin (p. 2125·3); zinc sulfate (p. 2126·2).
Eye disorders.

Ocufri *Allergan, Norw.†*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Ocugard *Phapros, Indon.*
Lutein (p. 2079·2); myrtillus (p. 2566·2).
Dietary supplement for healthy eyes.

Ocugel *Meda, Belg.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Ocugold *Ajanta, India.*
Betacarotene (p. 2051·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3).

Ocuhist *Pfizer Consumer, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye irritation and pruritus.

Oculac
Note: this name may be used for preparations of different composition.
Alcon, Denm.; Alcon, Fin.; Thea, Norw.; Novartis Ophthalmics, Swed.; Alcon, Switz.
Povidone (p. 2204·3).
Dry eyes; contact lens wetting solution.

Svizera, India.
Ketorolac trometamol (p. 80·2).
Allergic conjunctivitis; pain, inflammation and photophobia following eye surgery; cystoid macular oedema.

Oculan *Bal, India.*
⊗Timolol (p. 1513·2).
Ocular hypertension; glaucoma.

Oculast *Centaur, India.*
Azelastine hydrochloride (p. 617·1).
Conjunctivitis.

Oculastin *Meda, Fin.; Meda, Neth.; Meda, Port.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Oculerge *Aspen, S.Afr.*
⊗Antazoline hydrochloride (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Allergic conjunctivitis.

Oculex *Interbat, Indon.*
Capsules: Myrtillus (p. 2566·2); lutein (p. 2079·2); betacarotene (p. 2051·1); vitamin A (p. 2098·3); vitamin B_2 (p. 2104·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Eye disorders.

Interbat, Indon.
Syrup: Myrtillus (p. 2566·2); lutein (p. 2079·2); betacarotene (p. 2051·1); vitamin A (p. 2098·3); vitamin B_2 (p. 2104·3); vitamin E (p. 2119·1).
Eye disorders.

Oculix *Sanitas, Chile.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Oculoheel *Heel, Austria; Heel, Neth.*
Euphrasia officinalis (p. 2502·1); cochlearia officinalis; jaborandi; echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.

Peithner, Hung.
Euphrasia officinalis (p. 2502·1); cochlearia officinalis; pilocarpus; echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.

Ocu-Lol *Laborate, India.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Oculone *Yash, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oculor *Parenteral Drugs, India.*
Chloramphenicol (p. 257·1).
Eye infections.

Oculosan
Note: this name may be used for preparations of different composition.
Novartis, Chile†; Thea, Gr.; Thea, Hong Kong; Novartis, Philipp.; Novartis, Pol.; Adcock Ingram, S.Afr.; Excelvision, Thai.
⊗Zinc sulfate (p. 2126·2); naphazoline nitrate (p. 1669·3).
Eye irritation; conjunctivitis; irrigation of tear ducts.

Novartis, Indon.
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2); hamamelis (p. 2523·3); orange flower water; lavender water; euphrasia (p. 2502·1).
Eye irritation.

Thea, Switz.
⊗Zinc sulfate (p. 2126·2); naphazoline nitrate (p. 1669·3); hamamelis (p. 2523·3); euphrasia (p. 2502·1); neroli oil (p. 2568·3); lavender oil (p. 2541·1).
Eye irritation.

Oculosan N *Novartis, Ger.†*
⊗Zinc sulfate (p. 2126·2); naphazoline nitrate (p. 1669·3).
Conjunctivitis.

Oculotec *Novartis, Chile.†*
Povidone (p. 2204·3).
Dry eyes.

Oculotect
Note: this name may be used for preparations of different composition.
Novartis, Austria; Alcon, Belg.; Thea, Gr.; Novartis Ophthalmics, Hung.; Novartis, Irl.†; Novartis, Malaysia†; Thea, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis Ophthalmics, Singapore; Alcon Cusi, Spain; Novartis, Turk.; Novartis, UK.†
Povidone (p. 2204·3).
Dry eyes; wetting solution for contact lenses.

Novartis, China; Novartis, Ger.†; Novartis Ophthalmics, Hung.; Alcon, Switz.
Vitamin A palmitate (p. 2098·3).
Dry eyes; corneal damage.

Novartis, Ger.
Eye drops: Vitamin A palmitate (p. 2098·3); hypromellose (p. 2189·2).
Dry eyes.

Novartis, Indon.; Novartis, Pol.
Vitamin A palmitate (p. 2098·3); carbomer 980 (p. 2173·3).
Dry eyes.

Oculotect Fluid *Novartis, Ger.*
Povidone (p. 2204·3).
Dry eyes.

Ocu-Lube *Ocumed, USA.*
White soft paraffin (p. 2211·3).
Dry eyes.

Ocumed *Promed, Rus.; ProMed, Ukr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocumer *Farma-Projekt, Pol.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Ocumethyl *Alexandria, Rus.*
⊗Diphenhydramine hydrochloride (p. 626·2); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Conjunctivitis; eye irritation.

Ocumol *Wave, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocu-Mycin *Ocumed, USA.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Ocu-Pentolate *Ocumed, USA.*
Cyclopentolate hydrochloride (p. 2005·3).

Ocuper *Ashford, Philipp.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocu-Phrin *Ocumed, USA.*
Phenylephrine hydrochloride (p. 1672·3).

Ocupol *Centaur, India.*
Polymyxin B sulfate (p. 342·3); chloramphenicol (p. 257·1).
Bacterial ear or eye infections.

Ocupol-D *Centaur, India.*
⊗Polymyxin B sulfate (p. 342·3); chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Infected inflammatory ear or eye disorders.

Ocupred *Oftalmi, Venez.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Ocupres
Note: this name may be used for preparations of different composition.
Cadila, India.
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocupres-E *Cadila, Rus.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Ocupress
Note: this name may be used for preparations of different composition.
Uniao Quimica, Braz.
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma.

Ocuprost *Bausch & Lomb, Arg.; Arrow, S.Afr.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Ocuprostim *Bausch & Lomb, Arg.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocurax *Ipca, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ocurest *Centaur, India.*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline hydrochloride (p. 1669·3); menthol (p. 2553·2); camphor (p. 2466·2).
Eye irritation.

Ocurest-AH *Centaur, India.*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline hydrochloride (p. 1669·3); menthol (p. 2553·2); camphor (p. 2466·2); chlorphenamine maleate (p. 620·3).
Conjunctivitis; allergic eye disorders; eye irritation.

Ocurest-Z *Centaur, India.*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2); menthol (p. 2553·2); camphor (p. 2466·2).
Eye congestion.

Ocurins *Vista, Philipp.*
Electrolytes (p. 1775·1).
Eye wash.

Ocuroid *Parenteral Drugs, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).

Ocusan *Agepha, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Ocusert *Allergan, NZ.†*
Pilocarpine (p. 2010·2).
Glaucoma; ocular hypertension.

Ocusoft VMS *Ocusoft, USA.*
Vitamins; minerals.

Ocusol *ANB, Malaysia; ANB, Singapore; ANB, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1);

sodium acetate (p. 1781·1); sodium citrate (p. 1781·2).
Irrigation during eye, ear, nose, and throat surgery.

Ocuson *Sanbe, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Ocusone *Parenteral Drugs, India.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory eye disorders.

Ocu-Spor-B *Ocumed, USA.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Eye infections.

Ocu-Spor-G *Ocumed, USA.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Eye infections.

Ocustress *Farmila, Ital.*
Vitamins; ubidecarenone (p. 2637·1); ginseng (p. 2513·3).
Dietary supplement.

Cipla, India.
⊗Naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Ocu-Sulf *Cipla, India.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Ocusulf *Optopics, USA.†*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Ocusun *Apotex, Arg.*
Hyaluronic acid (p. 2526·2); bisoctrizole (p. 1697·1); aloe vera (p. 1693·2).
Sunscreen.

Ocusyn *Ashford, Singapore.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Ocu-Tears
Note: this name may be used for preparations of different composition.
Ocumed, USA.
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Ocutears
Note: this name may be used for preparations of different composition.
Lafedar, Arg.
Hypromellose (p. 2189·2).
Dry eyes.

Santen, Ger.†
Soya lecithin (p. 2542·2).
Dry eyes.

Ocutim *Cipla, India.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ocutob *Centaur, India.*
Tobramycin sulfate (p. 380·2).
Bacterial eye infections.

Ocutob-D *Centaur, India.*
⊗Tobramycin sulfate (p. 380·2); dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Ocuton *Ritter, Hong Kong.†*
Oxedrine hydrochloride (p. 1463·2).
Eye irritation.

Ocutone *Cadila, India.*
Sodium chloride (p. 1795·1).

Ocutricin *Bausch & Lomb, USA.*
Eye drops: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Eye infections.

Bausch & Lomb, USA.
Eye ointment: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Eye infections.

Ocutrien *Cantassium Co., UK.*
Vitamins; minerals.

Ocu-Trol *Ocumed, USA.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Ocu-Tropic *Ocumed, USA.*
Tropicamide (p. 2012·2).

Ocu-Tropine *Ocumed, USA.†*
Atropine sulfate (p. 1310·2).

Ocu-V *Mahakam Beta, Indon.*
Lutein (p. 2079·2); lycopene (p. 2546·2); myrtillus (p. 2566·2); echinacea (p. 2498·1); betacarotene (p. 2051·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).
Eye disorders.

Ocuvir *FDC, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ocuvit *Cadila, India.*
Vitamin E (p. 2119·1).

Ocuvite *Bausch & Lomb, Hong Kong; Mann, Irl.†; Bausch & Lomb, Thai.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Nutritional supplement for healthy eyes.

Bausch & Lomb, Canad.†; Bausch & Lomb, Ital.; Bausch & Lomb, Mex.; Bausch & Lomb, Philipp.; Intrapharm, UK.
Vitamins; minerals.
Nutritional supplement; age-related macular degeneration.

Bausch & Lomb, Singapore.
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc oxide (p. 1729·1); cupric oxide.
Nutritional supplement for healthy eyes.

Ocuvite Adult 50+ *Bausch & Lomb, Singapore.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper gluconate (p. 2057·2); lutein (p. 2079·2); omega-3 fatty acids (p. 1460·1); zeaxanthin (p. 2125·3).
Dietary supplement for healthy eyes.

Ocuvite Complete *Bausch & Lomb, Ukr.*
Omega-3 triglycerides (p. 1460·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); lutein (p. 2079·2); zeaxanthin (p. 2125·3); zinc (p. 2126·1).
Dietary supplement for eye health.

Ocuvite DM *Bausch & Lomb, Arg.*
Vitamins; minerals; lutein (p. 2079·2).

Ocuvite Eye + Multi *Bausch & Lomb, USA.*
Vitamins; minerals; lutein (p. 2079·2); lycopene (p. 2546·2); zeaxanthin (p. 2125·3).
Dietary supplement.

Ocuvite Lutein *Bausch & Lomb, Braz.*
Ascorbic acid (p. 2110·3); tocopherol (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).

Bausch & Lomb, Singapore.
Vitamins; minerals; lutein (p. 2079·2).
Nutritional supplement for healthy eyes.

Ocuvite Lutein Forte *Bausch & Lomb, Ukr.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); zinc (p. 2126·1); selenium (from yeast) (p. 2086·3).
Dietary supplement for eye health.

Ocuvite Omega3 *Bausch & Lomb, Arg.*
Omega-3 (p. 1460·1); vitamins; minerals; lutein (p. 2079·2).
Dietary supplement.

Ocuvite PreserVision *Bausch & Lomb, Braz.*
Betacarotene (p. 2051·1); ascorbic acid (p. 2110·3); *dl*-alpha tocoferil acetate (p. 2119·2); copper oxide (p. 2057·1); zinc oxide (p. 1729·1).

Bausch & Lomb, Hong Kong.
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc oxide (p. 1729·1); cupric oxide.
Nutritional supplement for healthy eyes.

Bausch & Lomb, Austral.†
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc oxide (p. 1729·1); copper (p. 2057·1).
Age-related macular degeneration.

Ocuwet *Centaur, India.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Ocylin *Multilab, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Od *Brawn, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Odaban *Bracey, UK.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Odace *Zydus, India; Darya-Varia, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Odacet *Mapra, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Odaft *Plethico, Malaysia; Sel-J, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Odal *Klar Sehen, India.*
Albendazole (p. 149·1).
Worm infections.

Odamesol *Iasis, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Odamida *Pelayo, Spain.*
Benzalkonium chloride (p. 1737·1); zinc chloride (p. 2126·1).
Mouth disorders.

Odan K-20 *Odan, Canad.*
Potassium chloride (p. 1793·2).
Potassium supplement.

Odanet *Pharmanik (Φαρμανικ), Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Odanex *Saval, Chile.†*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Odanostin *Ifars, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Odanse *Ind-Chemie, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Odaril *Moraceae, India.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).

Odaril-XP *Moraceae, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Odasen *Lyofin, Gr.*
Ondansetron hydrochloride (p. 1872·1).

Odasol *Genepharm, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Odasyl *Twilight Litaka, Philipp.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Oddibil *Gerot, Austria; Sanofi-Aventis, Braz.; Cooperation Pharmaceutique, Fr.*
Fumitory (p. 2508·2).
Digestive and renal disorders; biliary-tract disorders.

Ödemin *Santen, Fin.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; epilepsy; oedema.

Odenil *Galderma, Spain.*
Amorolfine hydrochloride (p. 569·1).
Fungal skin and nail infections.

Odeoxil *Demo, Gr.†*
Buflomedil (p. 1328·3).

Odep *Crescent, India.*
Amitriptyline (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain; migraine.

Odeston *Pabianice, Rus.*
Hymecromone (p. 2530·2).
Biliary-tract disorders.

Odetol *Medichem, Philipp.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

O-Dex *Hanburys, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); hypromellose (p. 2189·2); ofloxacin (p. 334·3).

Odexan *Sons, Mex.*
⊗Ampoule I, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin acetate (p. 2107·3); ampoule II, dexamethasone sodium phosphate (p. 1631·2); lidocaine hydrochloride (p. 1988·2).
Neuritis; neuralgias.

Odiazine *Chew, Thai.*
Sulfadiazine (p. 361·3).
Bacterial infections.

Odical *Procure, India.*
Hydroxyapatite (p. 2529·3); colecalciferol (p. 2113·1).

Odicip-OZ *Solitaire, India.*
Ciprofloxacin (p. 261·1); ornidazole (p. 943·1).

Odicoba *Traikaa, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Odicon *Rapross, India.*
Fluconazole (p. 578·2).
Fungal infections.

Odicoza *Bright Future, Hong Kong.*
Dicloxacillin (p. 286·1).
Staphylococcal infections.

Odifam *Dynamic, Philipp.†*
Rifampicin (p. 350·3).
Tuberculosis; meningococcal carriers.

Odifex *Biochem, India.*
Fexofenadine hydrochloride (p. 629·1).
Hypersensitivity reactions.

Odiglim *Zinnia, India.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Odiglim-M *Zinnia, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Odimont *Zydus, India.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Odimont Plus *Zydus, India.*
⊗Bambuterol hydrochloride (p. 1203·1); montelukast (p. 1214·3).
Asthma; allergic rhinitis.

Odimox-DL *Solitaire, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1); lactobacillus (p. 2596·3).

O-Din *Grace, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Odinah *Medichem, Philipp.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Odinol *Alembic, India.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Odinol-AM *Alembic, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Odipan-D *Solitaire, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Odipep *Panacea, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Odipin *Sustime, Philipp.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Odipril *Blue Cross, India.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Odipril-H *Blue Cross, India.*
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

Odirab *Biochem, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Odiron *Medichem, Philipp.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).
Iron-deficiency anaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Odiron-C *Medichem, Indon.†; Medichem, Singapore.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Medichem, Philipp.†
Vitamin B substances (p. 2102·3); iron (p. 2073·1); vitamin E (p. 2119·1). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Odirox *Cipla, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Odisulfan *Raam, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Oditel *Zinnia, India.*
Telmisartan (p. 1509·3).
Hypertension.

Oditel-H *Zinnia, India.*
⊗Hydrochlorothiazide (p. 1403·2); telmisartan (p. 1509·3).
Hypertension.

Odiven *Zydus, S.Afr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; mixed anxiety depressive states.

Odivir Kit *Cipla, India.*
Efavirenz (p. 975·1); lamivudine (p. 1000·2); didanosine (p. 972·3).
HIV infection.

Odix *Pentafarma, Port.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Odizol *Solitaire, India.*
Omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Od-Kit *VHB, India.*
1 Tablet, azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2); 2 tablets, secnidazole (p. 947·3).

Odnatron *Kleva, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Odo-fre *Self-Care Products, UK.*
Parsley seed oil (p. 2583·3).

Odoman *Maan, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Odonac *Klar Sehen, India.*
Diclofenac (p. 48·3).
Prevention of intra-operative miosis; eye inflammation and pain; allergic conjunctivitis.

Odongel *Mintlab, Chile.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Odongi *Candioli, Ital.*
Benzalkonium chloride (p. 1737·1); eugenol (p. 2501·2); tetracaine (p. 1996·3).
Dental caries.

Odonid *Daudt, Braz.†*
Metronidazole (p. 936·1).

Odontal *Streuli, Switz.*
Mint oil (p. 2560·1); star anise oil (p. 2622·2); clove (p. 2481·2); cinnamon (p. 2479·2); anise oil (p. 2444·3).
Mouth and throat disorders.

Odontalgico Dr. Knapp *Montefarmaco, Ital.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); thiamine hydrochloride (p. 2103·1); caffeine (p. 1203·3).
Pain.

Odonticina *Pentafarma, Port.*
Roxithromycin (p. 356·2).
Bacterial infections.

Odontis-Rx *Daudt, Braz.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Odontobiotic
Note: this name may be used for preparations of different composition.
Reig Jofre, Spain.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Odonton-Echtroplex *Weber & Weber, Ger.*
Arnica mont. (p. 2447·2); calendula offic. (p. 2465·2); delphinium staph.; echinacea purp. (p. 2498·1); hepar sulf. (p. 1721·3); kalium bichrom. (p. 2476·3); kalium sulf. (p. 1793·2); symphytum offic. (p. 2484·2).
Homoeopathic preparation.

Odop *Hos & Ins, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Odospi *Auspi, India.*
Cefpodoxime; *Lactobacillus sporogenes* (p. 2596·3).

Odospi-S *Auspi, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Odourless Garlic
Note: this name may be used for preparations of different composition.
Blackmores, Austral.
Garlic (p. 2510·3); parsley (p. 2583·3).
Cold and influenza symptoms.

Odoxil *Lupin, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Od-Phyllin *Sun, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Od-Prin *Ordain, India.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Odranal
Note: this name may be used for preparations of different composition.
Raffo, Chile.
Oxybutynin (p. 2361·2).
Neurogenic bladder.

Raffo, Arg.†
Bupropion hydrochloride (p. 408·2).
Depression; aid to smoking withdrawal.

Odric *Shinyaku, Jpn.*
Trandolapril (p. 1517·2).
Hypertension.

Odrik *Abbott, Austral.; Abbott, Denm.; Abbott, Fr.; Abbott, Gr.; Abbott, Irl.; Abbott, NZ†; Vitoria, Port.; Alter, Spain.†*
Trandolapril (p. 1517·2).
Hypertension; left ventricular dysfunction following myocardial infarction; heart failure; diabetic nephropathy.

Odrinol *Viofar, Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).

O-Due *Teofarma, Ital.*
Taurine (p. 2626·2).
Vascular disorders.

Odupril *Pharmanik (Φαρμανικ), Gr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Odven SBK *Bioquimed, Mex.*
Venlafaxine hydrochloride (p. 454·2).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; social phobia; panic disorder.

Odycin *Velka, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Oecotrim *Fresenius Kabi, Austria.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Oedemex *Mepha, Switz.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; forced diuresis.

OeKolp *Kade, Ger.*
Estriol (p. 2274·3).
Vaginal disorders; menopausal disorders.

Oekolp *Kade, Pol.*
Estriol (p. 2274·3).
Vulvovaginal disorders associated with oestrogen deficiency.

Oemine *Phytobiolab, Fr.*
Nutritional supplements.

Oenanthe Crocata Complexe No 78 *Lehning, Fr.*
Oenanthe crocata; stramonium (p. 2622·3); nux vomica (p. 2573·3); cuprum aceticum (p. 2486·2); hyoscyamus (p. 2530·2); arsenicum album (p. 2448·1); atropinum sulfuricum (p. 1310·2); cocculus (p. 2483·1); arnica (p. 2447·2); stannum muriaticum.
Homoeopathic preparation.

Oenobiol *Oenobiol, Fr.*
Nutritional supplements.

Oeparol *Agropharm, Pol.†*
Evening primrose oil (p. 2502·2).
Dietary supplement.

Oesclim *Triton, Canad.; Abbott, Fr.; Fournier, Gr.; Fournier, Pol.; Solvay, Swed.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Oesto-Mins *Tyson, USA.*
Vitamins; minerals.

Oestraclin *Seid, Spain.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Oestring *Pfizer, Swed.*
Estradiol (p. 2271·1).
Vaginal disorders due to oestrogen deficiency.

Oestro Gel *Rontag, Arg.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Oestrodose *Besins, Fr.; Besins International, Israel†; Besins, Port.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Oestrogel *Besins, Belg.; Farmoquimica, Braz.; Besins, China; Besins, Cz.; Besins, Fr.; Angelini, Gr.; Besins, Hong Kong; Besins, Hung.†; Chemech, India; Besins, Irl.; Besins International, Israel; Besins, Malaysia; CORNE, Mex.; Besins, Rus.; Besins, Singapore; Vifor, Switz.; Besins, Thai.; Marlborough Pharmaceuticals, UK; Besins, Ukr.*
Estradiol (p. 2271·1).
Vaginal atrophy after menopause; menopausal disorders; osteoporosis.

Oestro-Gynaedron *Drossapharm, Switz.*
Estriol (p. 2274·3).
Oestrogen deficiency; adjunct in vaginal surgery.

Oestro-Gynaedron M *Drossapharm, Ger.*
Estriol (p. 2274·3).
Vaginal disorders; oestrogen deficiency.

Of *JB Chemicals, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Of Plus *Plus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofac *Savoy, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofacin *Indu, India; Nakornpatana, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofacin-M *Nordic, India.*
Metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

Ofacin-O *Nordic, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofacin-TZ *Indu, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofac-O *Savoy, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

O-Fact *Esma, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofac-T *Savoy, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

O-Fact-OZ *Esma, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofal
Note: this name may be used for preparations of different composition.
Hi-Tec, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Novartis, Arg.
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ofal-M *Hi-Tec, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofal-OZ *Hi-Tec, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofal-TZ *Hi-Tec, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofarsin *Bausch & Lomb, Spain.*
Carbomer (p. 2173·3).
Dry eyes.

Ofax *Hetero, India; McNeil & Argus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofax-TZ *Hetero, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofbeat *Synergen, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofbid *Aarpik, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofbid-OZ *Aarpik, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofcare *Medico, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofcare-NT *Medico, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Ofcare-OD *Medico, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofcin *YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofcura *Daniel Pasteur, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofcura-OZ *Daniel Pasteur, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofdaz *Helios, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofdex *Leben, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Ofee *Masa, Thai.*
Orphenadrine citrate (p. 909·2).

Ofel *East African, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofelder *Elder, India.*
Ofloxacin (p. 334·3).

Ofelder-D *Elder, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Ofelder-PA *Elder, India.*
⊗Ofloxacin (p. 334·3); prednisolone (p. 1645·2).

Oferin *Unipharma, Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Oferta *Sanovel, Turk.*
Olanzapine (p. 1089·3).

Ofertil *Bernofarm, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Ofet *Adley, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofetaxim *Alkem, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ofet-D *Adley, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Ofet-H *Adley, India.*
Methylcellulose (p. 2197·3); ofloxacin (p. 334·3).

Ofet-O *Adley, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofet-T *Adley, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Off *Johnson, Canad.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Off Skintastic *Johnson, Canad.†*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Offentina *Offenbach, Mex.†*
Ranitidine (p. 1882·1).
Peptic ulcer.

Off-Ezy *Del, USA.*
Salicylic acid (p. 1719·1).
Corns; calluses; warts.

Off-Ten *Medipharm, Chile.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Offy *Solitaire, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofia *Biosync, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofia-OZ *Biosync, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofirex *Worth, India.*
Cefoperazone (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Ofirmev *Cadence, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Ofkab *Lancer, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofkab-OZ *Lancer, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofkair *PDC, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofkair-OZ *PDC, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofkozin *Kocak, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

OFL *Bewell, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofla *Khandelwal, India; Khandelwal, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflab *Concept, India.*
Ofloxacin (p. 334·3); *Lactobacillus sporogenes* (p. 2596·3).

Oflabin *Medispan, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflabin+LB *Medispan, India.*
Ofloxacin (p. 334·3); *Lactobacillus sporogenes* (p. 2596·3).

Oflabin-TZ *Medispan, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflab-OZ *Concept, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflacin *Micro, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflacin-DX *Micro, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Oflacin-P *Micro, India.*
⊗Ofloxacin (p. 334·3); prednisolone acetate (p. 1645·2).

Oflact *Health Care, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflact-M *Health Care, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oflact-OZ *Health Care, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflador *Khandelwal, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflagard *Biomax, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflagard-O *Biomax, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflagard-OL *Biomax, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1); lactobacillus (p. 2596·3).

Oflage *Peerage, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflage-OZ *Peerage, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflahill *Daffohils, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflak *Laksun, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflamed *Aglowmed, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflamed-MN *Aglowmed, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oflamed-OZ *Aglowmed, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflamed-TZ *Aglowmed, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofla-OZ *Khandelwal, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflaquin *Nodysis, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflaquin-M *Nodysis, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oflaquin-OZ *Nodysis, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflark-O *RK Medicare, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflas *Shreshtha, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflaset *Wintech, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflaset-OZ *Wintech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflas-OZ *Shreshtha, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflatoon *Zydus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflatoon-MZ *Zydus, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oflatoon-OZ *Zydus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).
Diarrhoea; dysentery.

Ofla-TZ *Khandelwal, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflavid *Trigenesis, India.*
Oral suspension: Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Trigenesis, India.
Tablets: Ofloxacin (p. 334·3).
Bacterial infections.

Oflavid-TZ *Trigenesis, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflawin *Wintech, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflawin-OZ *Wintech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflawin-TZ *Wintech, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflazet *SM, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Oflee *Leemed, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflee-M *Leemed, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oflee-NT *Leemed, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Oflee-OZ *Leemed, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflem *Laborate, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflem-D *Laborate, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin (p. 329·3); ofloxacin (p. 334·3).

Oflem-OZ *Laborate, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofler *Aristo, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofler-TZ *Aristo, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflex *Finecure, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflict *Active, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflict-OZ *Active, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflin *Zydus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflina-OZ *Core Gestra, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflin-TZ *Zydus, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflo *Nordic, India; Unique, Rus.; Unique, Thai.; Unique, Ukr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflobac *Chinta, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflobay *Nestor, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Oflocain *Darnitsa, Ukr.*
Ofloxacin (p. 334·3); lidocaine (p. 1988·1).
Infected burns, ulcers, and wounds; infected skin disorders.

Oflocee *Farmaline, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflocet *Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflocide *Tripharma, Rus.; Abdi, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflocin
Note: this name may be used for preparations of different composition.
GSK, Ital.
Ofloxacin (p. 334·3).
Respiratory-tract infections; urinary-tract infections.

Farmedia, Gr.
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Oflocollyre *Biospray, Gr.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Oflocos *Symbiosis, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflocos-OZ *Symbiosis, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflocos-TZ *Symbiosis, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflo-D *Nordic, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Ofloday *Invision, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloday-OZ *Invision, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofloden *BMW, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloden-O *BMW, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofloden-T *BMW, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflodex *Dexcel, Israel.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflo-DT *Nordic, India.*
Ofloxacin (p. 334·3); *Lactobacillus sporogenes* (p. 2596·3).

Oflog *Stalwart, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflogen *Generics, Hung.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflohexal *Hexal, Ger.†; Sandoz, Ukr.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloine *Sunshine, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloine-OZ *Sunshine, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofloks *Eczacibasi, Turk.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflo-M *Nordic, India.*
Metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

Oflomac *Macleods, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflomac-TZ *Macleods, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflomelid *Sintez, Rus.*
Ofloxacin (p. 334·3); methyluracil; lidocaine hydrochloride (p. 1988·2).
Burns; ulcers; wounds.

Oflomet
Note: this name may be used for preparations of different composition.
Ikon, India.
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Pond's, Thai.
Ofloxacin (p. 334·3).
Bacterial infections.

Oflomil *Glenmark, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflomil-OZ *Glenmark, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflomits *Mits, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflomix *Orion, India.*
Cefixime (p. 240·3).
Bacterial infections.

Oflon *Hy-Gro, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflono *SMB, Chile.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Oflono-D *SMB, Chile.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Inflammatory eye disorders with infection.

Oflon-OZ *Medinova, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflon-TZ *Hy-Gro, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflo-OZ *Nordic, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflopar *Pardys, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflopar-OR *Pardys, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflopip *BMW, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflopip-O *BMW, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofloren *Indoco, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloren-OZ *Indoco, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofloren-TZ *Indoco, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflostar *Cadila, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflostar-D *Cadila, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Oflostar-M *Cadila, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oflostar-OZ *Cadila, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflostar-TZ *Cadila, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflosyn *Medlink, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflotas *Intas, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflotas-OZ *Intas, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oflotec *Acto, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Oflotec-OZ *Acto, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofloter *Gujarat Terce, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflo-TZ *Nordic, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oflovid *Trigenesis, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflovir *Vir, Spain.*
Ofloxacin (p. 334·3).
Bacterial infections.

O-Flox *Silom, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflox *Allergan, Arg.; Stada, Austria†; Allergan, Braz.; Allergan, Chile; CT, Ger.†; Sandoz, Ger.†; Cipla, India; Allergan, Israel; RX, Thai.; Allergan, Venez.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflox D *Cipla, India.*
⊗Ofloxacin (p. 334·3); dexamethasone (p. 1630·3).
Infected eye disorders.

Oflox TZ *Cipla, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofloxa *LBS, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloxabol *Abolmed, Rus.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloxacina *Braun, Israel.*
Ofloxacin hydrochloride (p. 334·3).
Bacterial infections.

Ofloxbeta *Betapharm, Ger.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloxcin *Siam Bheasach, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofloxin *Zentiva, Cz.; Zentiva, Rus.; Zentiva, Ukr.*
Ofloxacin (p. 334·3) or ofloxacin hydrochloride (p. 334·3).
Bacterial infections.

Ofloxol *Ain Medicare, Malaysia.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflozen *Klar Sehen, India.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Oflozen-D *Klar Sehen, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Oflxcin *Bombay Tablet, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oflxcin-TZ *Bombay Tablet, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofly *Zodley, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofly-OZ *Zodley, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

OFM *JB Chemicals, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Of-M *JB Chemicals, India.*
Metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

Ofmed *Mediez, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofmed-OZ *Mediez, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofnet *Gentech, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofnet-OZ *Gentech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofnida *Waves, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofnida-LB *Waves, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1); *Lactobacillus sporogenes* (p. 2596·3).

Ofnifenil *SJA, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Ofniforte *Medinova (Μεντινοβα), Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Ofnij *Sunij, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofnimarex *DAST, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ofnis *Neiss, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofniskel *Zekides, Gr.*
Etodolac (p. 57·1).

Ofnis-OZ *Neiss, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofo *Osmed, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofodex *Atlantis, Mex.*
Ear drops: ⊗Hydrocortisone (p. 1640·1); chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Otitis externa; otitis media.

Atlantis, Mex.
Eye drops: ⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Inflammatory eye disorders with infection.

Ofo-OZ *Osmed, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofor
Note: this name may be used for preparations of different composition.
Symmedic, Ukr.
Ofloxacin (p. 334·3); ornidazole (p. 943·1).
Bacterial infections; trichomoniasis.

Worth, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Ofor-OZ *Worth, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oforta *Sanofi-Aventis, USA.†*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Ofo-TZ *Osmed, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofoxin
Note: this name may be used for preparations of different composition.
Medley, India.
Ofloxacin (p. 334·3).

Zambon, Braz.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Ofpil *Psychotropics, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofpil-O *Psychotropics, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofpil-TZ *Psychotropics, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofral *Hiral, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofral-OZ *Hiral, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofral-TZ *Hiral, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oframax *Nanxin, China; Ranbaxy, India; Ranbaxy, Mex.; Ranbaxy, Pol.; Ranbaxy, Rus.; Ranbaxy, S.Afr.; Ranbaxy, Singapore; Ranbaxy, Thai.; Ranbaxy, Ukr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Oframax Forte *Ranbaxy, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).

Ofran *Sienna, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofran-OZ *Sienna, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofras *Rass, India.*
Ofloxacin (p. 334·3).
Bacterial eye infections; ear infections.

O2-Fresh *Genesis, India.*
Mouthwash: Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Genesis, India.
Toothpaste: ⊗Potassium nitrate (p. 1766·2).

O2-Fresh-GP *Genesis, India.*
Cetrimide (p. 1742·1); tannic acid (p. 2625·2); zinc chloride (p. 2126·1).

Ofsis *Intel, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofsis-OZ *Intel, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofspan *Pharmatech, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofspan-OZ *Pharmatech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofspan-TZ *Pharmatech, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofspin *Blossoms, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofspin-OZ *Blossoms, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oft *JB Chemicals, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oftabiotico *Saval, Chile.*
Eye drops: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial eye infections.

Saval, Chile.
Eye ointment: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial eye infections.

Oftaboril *Alcon, Mex.*
Boric acid (p. 2459·3); borax (p. 2459·2); phenylephrine (p. 1672·2).
Eye disorders.

Oftacilox *Alcon, Ital.; Alcon, Port.; Alcon Cusi, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Oftacin *Intag, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oftacin-OZ *Intag, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oftaciprox *Laboratorios Chile, Chile.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Oftacon *Saval, Chile.†*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Oftadek *Ukrmedprom, Rus.*
Decamethoxine (p. 1749·2).
Conjunctivitis.

Oftadil *Diba, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Oftagel *Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Hung.; Santen, Norw.; Santen, Pol.; Santen, Rus.; Santen, Swed.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Oftagen
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Latanoprost (p. 2008·1).

Saval, Chile.
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Oftagen Compuesto *Saval, Chile.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).
Bacterial eye infections with inflammation.

Oftaial *INTES, Ital.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Oftalar *Alcon, Ital.; Alcon, Port.†; Alcon Cusi, Spain†; Alcon, Turk.*
Pranoprofen (p. 127·1).
Postoperative eye inflammation; inflammatory eye disorders.

Oftalblu *Alfa Intes, Ital.†*
Trypan blue (p. 2635·2).
Aid in cataract surgery.

Oftalbrax *Biosintex, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Oftal-D *Drawer, Arg.*
Neomycin sulfate (p. 330·1); chloramphenicol (p. 257·1); phenylephrine hydrochloride (p. 1672·3).
Eye infections.

Oftaldrop *Denver, Arg.*
⊗Prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Eye inflammation.

Oftaler *Saval, Chile.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Oftalirio *Saval, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); antazoline phosphate (p. 615·3).
Eye congestion.

Oftalmil *Bruschettini, Ital.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc phenolsulfonate (p. 1729·3).
Eye irritation.

Oftal-Mix *Fada, Arg.*
Latanoprost (p. 2008·1).
Ocular hypertension.

Oftalmol *Firn M, Rus.*
Boric acid (p. 2459·3); diphenhydramine (p. 626·1); zinc sulfate (p. 2126·2).
Conjunctivitis.

Oftalmol Ocular *Nupel, Spain.*
⊗Boric acid (p. 2459·3); mercuric cyanide (p. 2555·3); naphazoline nitrate (p. 1669·3); trinitrophenol (p. 2634·2); procaine hydrochloride (p. 1994·3).
Infected eye disorders; eye congestion.

Oftalmolets *Alcon, Arg.*
Erythromycin lactobionate (p. 291·3).
Bacterial eye infections.

Oftalmolosa Cusi *Alcon Cusi, Malaysia.*
Erythromycin (p. 291·2).
Bacterial eye infections.

Oftalmolosa Cusi Antiedema *Alcon Cusi, Singapore.†*
Sodium chloride (p. 1795·1).
Corneal oedema.

Oftalmotonil *Bausch & Lomb, Arg.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Oftalmotrim *Alcon Cusi, Malaysia; Alcon, Port.; Alcon Cusi, Spain; Alcon, Turk.†*
Polymyxin B sulfate (p. 342·3); trimethoprim (p. 381·2).
Bacterial eye infections.

Oftalmowell *UCB, Spain.*
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Oftalook *Denver, Arg.*
Sodium chloride (p. 1795·1).
Dry eyes.

Oftalook Plus *Denver, Arg.*
Hypromellose (p. 2189·2).
Dry eyes.

Oftaltein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Oftamirin *Darnitsa, Ukr.*
Miramistin (p. 1761·2).
Eye and ear infections; rhinitis.

Oftan
Note: this name may be used for preparations of different composition.
Santen, Cz.; Santen, Hong Kong; Santen, Norw.; Santen, Philipp.; Santen, Pol.†
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Santen, Fin.†
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Oftan Akvakol *Santen, Fin.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Oftan A-Pant *Santen, Fin.*
Vitamin A palmitate (p. 2098·3); dexpanthenol (p. 2582·2).
Eye disorders.

Oftan Catachrom *Santen, Rus.*
Cytochrome C (p. 2491·2); adenosine (p. 1291·1); nicotinamide (p. 2083·1).
Cataract.

Oftan C-C *Santen, Fin.*
⊗Hydrocortisone caproate (p. 1640·1); chloramphenicol (p. 257·1).
Eye disorders.

Oftan Chlora *Santen, Fin.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Oftan Dexa *Santen, Fin.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Oftan Dexa-Chlora *Santen, Fin.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Eye disorders.

Oftan Dexamethason *Santen, Rus.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Oftan Flurekain *Santen, Fin.*
Oxybuprocaine hydrochloride (p. 1993·2); fluorescein sodium (p. 2506·2).
Adjunct in eye examination.

Oftan IDU *Santen, Rus.*
Idoxuridine (p. 985·1).
Viral eye infections.

Oftan Metaoksedrin *Santen, Fin.*
Phenylephrine hydrochloride (p. 1672·3).
Uveitis; production of mydriasis.

Oftan Obucain *Santen, Fin.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Oftan Pilocarpin *Santen, Rus.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; reversal of mydriasis.

Oftan Starine *Santen, Fin.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Oftan Syklo *Santen, Fin.*
Cyclopentolate hydrochloride (p. 2005·3).
Aid in eye examination.

Oftan Timolol *Santen, Hung.; Santen, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Oftaquix *Santen, Austria; Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Ger.; Santen, Hung.; Tubilux, Ital.; Santen, Neth.†; Santen, Philipp.; Santen, Pol.; Santen, Port.; Santen, Rus.; Santen, Swed.; Kestrel, UK.*
Levofloxacin (p. 315·3).
Bacterial infections.

Oftar *Varun, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oftarinol *Polpharma, Pol.*
Sodium chloride (p. 1795·1).
Eye cleansing.

Oftarx *Sanify, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oftaseptik *Kener, Mex.*
⊗Naphazoline (p. 1669·3).

Oftasona N *Saval, Chile.*
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).
Eye infections with inflammation.

Oftasona P *Saval, Chile.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory eye disorders.

Oftastad *Stada, Fin.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Oftastad Comp *Stada, Fin.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Oftasteril *Alfa Intes, Ital.*
Povidone-iodine (p. 1767·1).
Skin disinfection; eye irrigation.

Oftavir *Saval, Chile.*
Aciclovir (p. 964·1).
Herpesvirus eye infections.

Oftavit *Kener, Mex.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Oftec *Technica, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oftech-OZ *Pharma-Tech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oftec-M *Technica, India.*
Metronidazole (p. 936·1); ofloxacin (p. 334·3).

Oftensin *Polpharma, Pol.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension.

Ofterra *Oftalmi, Venez.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Oftic *Saval, Chile.*
Diclofenac sodium (p. 48·3).
Eye inflammation following cataract surgery.

Officlin *Grin, Mex.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial eye infections.

Oftidor *Jelfa, Cz.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Oftimolo *Farmila, Ital.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Oftinal *Schering-Plough, Spain.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye irritation.

Oftini *P & B, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oftipan *Jelfa, Pol.*
Carbomer (p. 2173·3).
Dry eyes.

Oftol *Saval, Chile.*
⊗Loteprednol etabonate (p. 1642·1).
Inflammatory eye disorders.

Oftophenazol *Polfa Warszawa, Pol.*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic conjunctivitis; eye irritation.

Oftpred *Latinofarma, Braz.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Oftum *Profic Organic, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oftum-OZ *Profic Organic, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oftum-TZ *Profic Organic, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oftwo *Dexter, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofus *Sam Chun Dang, Hong Kong.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Ofuxal *Specifar (Σπεσιφαρ), Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Ofven *Vensat, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofven-TZ *Vensat, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ofwin *Purewin, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofwin-OZ *Purewin, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofzac *Trumac, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofzac-OZ *Trumac, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofzen *Zentis, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ofzen-OZ *Zentis, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ofzim *Investigaciones Filosoficas y Cientificas, Mex.*
Cocarboxylase (p. 2103·1); ribonuclease (p. 2604·1).
Bacterial and viral infections.

Ofzo *Comed, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ogast *Takeda, Fr.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ogasto *Lusomedicamenta, Port.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Ogastoro *Takeda, Fr.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ogastro *Abbott, Braz.; Abbott, Mex.; Abbott, Turk.; Abbott, Venez.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Ogen *Pfizer, Austral.†; Pfizer, Canad.; Pfizer, Indon.†; Pharmacia, USA.*
Estropipate (p. 2275·2).
Menopausal disorders; vulval and vaginal atrophy; female hypogonadism; female castration; primary ovarian failure; osteoporosis; oestrogen deficiency.

Ogerol *Help, Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Ogest *Comed, India.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Ogestrel *Scoshia, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ogestrel-D *Scoshia, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ogiflegon *Zekides, Gr.*
Lysine aspirin (p. 84·3).

Ogikenchuto *Tsumura, Jpn.*
Peony root; astragalus root (p. 2451·1); cinnamon bark (p. 2479·2); jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Og-Lac *Life Line, India.*
Fructo-oligosaccharides (p. 2508·1); *Lactobacillus sporogenes* (p. 2596·3); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).

Oglo *Panacea, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Ogmen *Intermed, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ogyline *Effik, Fr.†*
Norgestrienone (p. 2297·3).
Progestogen-only oral contraceptive.

O2H *Medley, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

OH B12 *Jaba Recordati, Port.*
Hydroxocobalamin acetate (p. 2107·3).
Neuralgias; neuritis.

Pfizer, Ital.
Hydroxocobalamin (p. 2107·3).
Anaemias; neuralgia; neuritis; liver disorders.

Oh God *Neiss, India.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Ohexine *Greater Pharma, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ohrentropfen Similasan *Jacoby, Austria.*
Chamomilla recutita (p. 2474·1); mercurius solubilis (p. 2555·3); sulfur (p. 1721·1).
Homoeopathic preparation.

OIF *Otsuka, Jpn.*
Interferon alfa (p. 989·2).
Hepatitis; renal cancer; chronic myeloid leukaemia.

Oikamid *Teva, Cz.*
Piracetam (p. 393·3).
Cerebrovascular disorders; mental function impairment; dementia; vertigo.

Oil Bleo *Khandelwal, India.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Oil Free Defense *Dermalogica, Canad.*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Oil Free Faces Sunscreen *Tanning Research, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Oil of Olay *Procter & Gamble, Canad.*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Procter & Gamble, USA.
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); ensulizole (p. 1703·1).
Sunscreen.

Oil of Olay Total Effects *Procter & Gamble, Canad.†*
Avobenzone (p. 1695·1); ensulizole (p. 1703·1); octocrilene (p. 1715·2); octisalate (p. 1715·2).
Sunscreen.

Oilalfo Compuesto *Investi, Arg.; Valeant, Arg.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders.

Oilatum
Note: this name may be used for preparations of different composition.
GSK, Arg.; GSK, India; Stiefel, Pol.
Liquid paraffin (p. 2191·2).
Soap substitute; dry skin disorders.

GSK, India.
Cream; lotion: Light liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry skin disorders.

Stiefel, Canad.; Stiefel, Malaysia; Stiefel, NZ†; Stiefel, Philipp.
Light liquid paraffin (p. 2191·2) or liquid paraffin (p. 2191·2).
Dry skin; skin irritation; soap substitute.

Stiefel, Israel.
Soap substitute.
Dry skin disorders.

Stiefel, Ital.
Emollient.

Stiefel, Malaysia; Stiefel, Philipp.
Cream: Light liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry skin disorders.

Stiefel, Chile†; Stiefel, Mex.
Arachis oil (p. 2446·1).
Dry skin disorders.

Oilatum Bar *Stiefel, Austral.†; Stiefel, Hong Kong; Stiefel, Indon.†; Stiefel, S.Afr.†; Stiefel, Singapore; Stiefel, Thai.†*
Liquid paraffin (p. 2191·2).
Soap substitute.

Oilatum Bath Formula *Stiefel, UK.*
Light liquid paraffin (p. 2191·2).
Dry skin disorders.

Oilatum Cream
Note: this name may be used for preparations of different composition.
Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Singapore; Stiefel, Thai.†; Stiefel, UK.
Light liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry skin; skin irritation.

Stiefel, Indon.†; Stiefel, S.Afr.†
Arachis oil (p. 2446·1).
Dry skin disorders.

Oilatum Emollient *Stiefel, Fr.; Stiefel, S.Afr.†; Stiefel, Singapore.*
Liquid paraffin (p. 2191·2).
Dry skin.

Stiefel, Austral.†; GSK, Cz.; Stiefel, Hong Kong; Stiefel, Thai.†
Light liquid paraffin (p. 2191·2).
Dry skin disorders; bath additive; pruritus.

Stiefel, Irl.
Light liquid paraffin (p. 2191·2); acetylated wool alcohols (p. 2219·2).
Skin irritation; dry skin.

Stiefel, UK.
Liquid paraffin (p. 2191·2); acetylated wool alcohols (p. 2219·2).
Dry skin conditions.

Oilatum Fragrance Free *Stiefel, UK.*
Light liquid paraffin (p. 2191·2).
Dry skin disorders.

Oilatum Gel *GSK, Cz.; Stiefel, Hong Kong; Stiefel, Indon.†; Stiefel, Irl.; Stiefel, Thai.†; Stiefel, UK.*
Light liquid paraffin (p. 2191·2).
Dry skin disorders; skin irritation; eczema.

Stiefel, Singapore.
Liquid paraffin (p. 2191·2).
Dry skin disorders.

Oilatum Hypoallergenic Wash *Stiefel, Hong Kong.*
Skin cleanser.

Oilatum Junior *Stiefel, Irl.; Stiefel, UK.*
Bath additive: Light liquid paraffin (p. 2191·2).
Dry skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Stiefel, UK.
Cream: Light liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry skin; pruritus.

Oilatum Junior Flare-Up *Stiefel, Irl.*
Light liquid paraffin (p. 2191·2); triclosan (p. 1773·2); benzalkonium chloride (p. 1737·1).
Infected eczema.

Oilatum Plus *Stiefel, Austral.; GSK, Cz.; Stiefel, Hong Kong; Stiefel, Indon.†; Stiefel, Irl.; Stiefel, NZ; Stiefel, Philipp.; GSK, S.Afr.; Stiefel, Singapore; Stiefel, Thai.†; Stiefel, UK.*
Light liquid paraffin (p. 2191·2); triclosan (p. 1773·2); benzalkonium chloride (p. 1737·1).
Eczema; bath additive; infected eczema.

GSK, India; Stiefel, Pol.
Benzalkonium chloride (p. 1737·1); light liquid paraffin (p. 2191·2); triclosan (p. 1773·2).
Infected eczema.

Oilatum Plus Antibacterial *Stiefel, Malaysia.*
Light liquid paraffin (p. 2191·2); triclosan (p. 1773·2); benzalkonium chloride (p. 1737·1).
Eczema.

Oilatum Scalp Intensive *Stiefel, UK.*
Ciclopirox olamine (p. 575·3); salicylic acid (p. 1719·1); panthenol (p. 2582·2); menthol (p. 2553·2).
Scalp disorders.

Oilatum Scalp Treatment *Stiefel, Irl.†; Stiefel, UK.*
Ciclopirox olamine (p. 575·3).
Dry scalp disorders.

Oilatum Shower Gel *Stiefel, Austral.†*
Light liquid paraffin (p. 2191·2).
Dry skin.

Oilatum Soap *GSK, USA.*
Skin cleanser.

Stiefel, UK.
Liquid paraffin (p. 2191·2).
Dry skin disorders.

Stiefel, Irl.
Light liquid paraffin (p. 2191·2).
Dry skin disorders.

Oilezz *MSD, Thai.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive; acne.

Oil-Free Sunscreen *Balley, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Oiltopic *D & M, Chile.*
Emollient.
Dry skin.

Oilum Body Scrub and Whitening *Galenium, Indon.†*
Soap substitute.

Oilum Soap *Galenium, Indon.†*
Moisturising soap.

Oiz *Aamorb, India.*
Betacarotene (p. 2051·1); folic acid (p. 2063·1); minerals; omega-3 fatty acids (p. 1460·1); proanthocyanidins.

Ojen *Jenburkt, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ojen-OZ *Jenburkt, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Øjensalve Neutral *Ophtha, Denm.; SAD, Denm.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Blepharitis; protection of eyelid and cornea.

Ojen-TZ *Jenburkt, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Ojosbel *Dermofarm, Spain.*
⊗Hamamelis water (p. 2523·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Ojosbel Azul *Dermofarm, Spain.†*
⊗Hamamelis water (p. 2523·3); methylthioninium chloride (p. 1559·1); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Ojus *Charak, India.*
Celery (p. 2472·3); cuminum cyminum; liquorice (p. 1853·2); piper longum; piper nigrum; syzygium aromaticum; withania somnifera (p. 2450·2); zingiber officinale.

Oka Mentol *Kurtsan, Turk.*
Cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2); camphor (p. 2466·2).
Cold and influenza symptoms; cough; sinusitis; sore throat.

Okacet *Cipla, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Okacet-L *Cipla, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Okacid *Cipla, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Okacid D *Cipla, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Okacin *Novartis Ophthalmics, Arg.; Novartis, Austria; Novartis, Belg.†; Novartis Ophthalmics, Cz.†; Novartis, Ger.†; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.†; Novartis, India; Novartis, Israel†; Novartis, Ital.; Novartis, Philipp.; Novartis, Pol.†; Novartis, Port.; Ciba Vision, Rus.†; Novartis Ophthalmics, Singapore; Novartis, Switz.†; Novartis, Thai.†; Novartis, Turk.; Novartis, Ukr.†; Novartis, Venez.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

Okacyn *Adcock Ingram, S.Afr.†*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

Okaflox *Cipla, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Okaflox M *Cipla, India.*
Ofloxacin (p. 334·3); metronidazole benzoate (p. 936·1).
Bacterial infections.

Okaflox-TZ *Cipla, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Okagyl *Cipla, India.*
Metronidazole (p. 936·1); norfloxacin (p. 333·3).
Diarrhoea.

Okal *PuertoGaliano, Spain.†*
Chewable tablets: Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Puerto Galiano, Spain.†
Tablets: Aspirin (p. 22·2).
Pain; fever; musculoskeletal, joint and peri-articular disorders.

Okalan *Cipla, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Okalan D *Cipla, India.*
Lansoprazole (p. 1851·3); domperidone (p. 1838·1).

Okaldol *Puerto Galiano, Spain.*
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever.

Okaldol con Cafeina *Puerto Galiano, Spain.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever.

Okalgrip *Puerto Galiano, Spain.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Okaltus *Puerto Galiano, Spain.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Okamet *Cipla, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Okamycin *Cipla, India.*
Erythromycin (p. 291·2).
Acne.

Okanorm Plus *Cipla, India.*
Metoclopramide hydrochloride (p. 1862·2); paracetamol (p. 115·1).

Okaril *Cipla, India.*
⊗Salbutamol sulfate (p. 1220·2); bromhexine (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Respiratory-tract disorders.

Okaril Plus *Cipla, India.*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Respiratory-tract disorders.

Okasma *Sigman, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

Okatrim DS *Cipla, India.*
Co-trimoxazole (p. 277·3).

Okavax *Sanofi Pasteur, Hong Kong; Aventis Pasteur, India; Sanofi Pasteur, Indon.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Mex.; Research Foundation, Philipp.; Osaka University, Rus.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
A varicella-zoster vaccine (Oka strain) (p. 2423·3).
Active immunisation.

Okavir *Cipla, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Okeron *Wockhardt, India.*
Octreotide (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; postoperative pancreatic complications; variceal haemorrhage; AIDS-associated diarrhoea.

Okeye *Tedec Meiji, Spain.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Oki *Dompe, Ital.; Dompe, Rus.*
Ketoprofen lysine (p. 79·1).
Inflammation; pain; musculoskeletal, joint, and peri-articular disorders.

Oki 3A *Armstrong, Mex.*
Ketoprofen lysine (p. 79·1).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Okil *Maxo, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Okil-OZ *Maxo, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Okimus *Biocodex, Fr.*
Quinine benzoate (p. 665·1); crataegus (p. 2488·1).
Nocturnal muscle cramps.

Oko-Health *Healthyway, Ukr.*
Vitamins; thioctic acid (p. 2629·1); myrtillus (p. 2566·2); euphrasia (p. 2502·1); lutein (p. 2079·2); lycopene (p. 2546·2); glycine (p. 2071·2); taurine (p. 2626·2); cysteine (p. 2058·3); quercetin (p. 2505·3); zeaxanthin (p. 2125·3).
Dietary supplement for eye health.

Okomistin *Infamed, Rus.*
Miramistin (p. 1761·2).
Inflammatory eye disorders.

Okoubarell *Sanorell, Ger.*
Okoubaka aubrevillei.
Homoeopathic preparation.

Okoubasan *Sanum-Kehlbeck, Ger.*
Okoubaka aubrevillei.
Homoeopathic preparation.

Okovidit *Dioptra, Rus.*
Laminaria (p. 2540·1).
Eye disorders.

Oks *Unimarck, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oksabron *Deva, Turk.*
Oxolamine phosphate (p. 1671·2).
Cough.

Oksalamin *Berko, Turk.*
Oxolamine phosphate (p. 1671·2).
Cough.

Oksamen *Nevzat, Turk.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Oksiaskaril *Aroma, Turk.*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Oksijenli *Oro, Turk.*
Hydrogen peroxide (p. 1755·2).
Wounds; skin infections; gargle; minor haemorrhage.

Oksikam *Sanofi Synthelabo, Turk.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Oksinazal *Eczacibasi, Turk.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Oksitin *ProMed, Turk.*
Barrier cream.

Oksna *Unison, Philipp.†*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Oksolin *Med-Care, Turk.*
Oxolinic acid (p. 336·3).
Urinary-tract infections.

Oks-OZ *Unimarck, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

OKT3 *Janssen-Cilag, Venez.*
Muromonab-CD3 (p. 1960·1).
Transplant rejection.

Oktenisept *Schulke & Mayr, Ukr.*
Octenidine hydrochloride (p. 1762·2); phenoxyethanol (p. 1764·3).
Skin and mucous membrane disinfection; wounds; burns; ulcers.

Oktidel *Italfarmaco, Spain.*
Octreotide acetate (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; prevention of complications following pancreatic surgery; variceal haemorrhage.

Okugest *VSM, Neth.*
Arsenicum album (p. 2448·1); carbo vegetabilis (p. 1537·3); croton tiglium; okoubaka aubrevillei; veratrum album (p. 2644·3).
Homoeopathic preparation.

Okuzell *Pharmaselect, Austria.†*
Hypromellose (p. 2189·2).
Eye irritation.

OI *Leben, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

O-Lac *Mead Johnson, Braz.†; Mead Johnson, Indon.; Mead Johnson Nutritionals, Thai.†*
Infant feed.
Lactose intolerance; galactosaemia; sucrose intolerance.

Olace *La Pharmaceuticals, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Oladay *Invision, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Oladay-F *Invision, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Oladin *Collins, Mex.†*
⊗Salbutamol (p. 1220·2).

Olafid *Fidia, Ital.*
Olanzapine benzoate (p. 1089·3).
Schizophrenia; bipolar disorder.

Olam *Valdecasas, Mex.†*
Kaolin (p. 1850·1); pectin (p. 2200·3).

Olamin *Micro, India.*
Ciclopirox (p. 575·3) or ciclopirox olamine (p. 575·3).
Fungal skin and scalp infections.

Olamin P *Delta BKB, Ital.†*
Piroctone olamine (p. 1716·3).
Seborrhoeic dermatitis.

Ol-Amine
Note: this name may be used for preparations of different composition.
Therabel, Belg.
Vitamins; minerals.

Olamine
Note: this name may be used for preparations of different composition.
Pharmatrix, Arg.
Aloe vera (p. 1693·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1); provitamin C.
Skin disorders.

Olamin-F *Micro, India.*
⊗Ciclopirox olamine (p. 575·3); fluocinolone acetonide (p. 1636·1).
Fungal skin infections with inflammation.

Olamyc *Sanofi-Aventis, Gr.*
⊗Salicylic acid (p. 1719·1); triamcinolone acetonide (p. 1649·1); benzalkonium chloride (p. 1737·1).
Skin disorders.

Olan
Note: this name may be used for preparations of different composition.
Micro, India; Brown & Burk, Philipp.; Alter, Port.
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Andromaco, Mex.
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Olandic *Atral, Port.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Olandoz *Sandoz, Indon.*
Olanzapine (p. 1089·3).
Schizophrenia.

Olandus *Zydus, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olane *Phoenix, Arg.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Olanex *Ranbaxy, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olanex-F *Ranbaxy, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Olan-Gin *Olan-Kemed, Thai.†*
Dipyrone (p. 53·3).
Lidocaine (p. 1988·1) is included in some injections to alleviate the pain of injection.
Pain; fever.

Olanzalet *Alet, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olanzapik *Aarpik, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olanzapro *Aldril, Philipp.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olanzaran *Ranbaxy, Neth.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olanzep *Extractum, Hung.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Olanzin *Actavis, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olanzine *Mylan, NZ.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olapax *Reliance, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olapin *Psyco Remedies, India; Merck, Port.†; Unison, Thai.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder; psychoses.

Olapin Forte *Crescent, India.*
Fluoxetine hydrochloride (p. 417·1); olanzapine (p. 1089·3).

Olapin Plus *Crescent, India.*
Fluoxetine hydrochloride (p. 417·1); olanzapine (p. 1089·3).

Olapine *Kleva, Gr.*
Olanzapine (p. 1089·3).

Olark *Leovan, Gr.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Olartan *Menarini, Gr.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olartan Plus *Menarini, Gr.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olasol *Altayvitamin, Rus.*
Benzocaine (p. 1980·2); boric acid (p. 2459·3); sea buckthorn oil (p. 2612·1); chloramphenicol (p. 257·1).
Wounds; burns; pruritus.

Olasyn *Synthon, Neth.; Synthon, Port.*
Olanzapine benzoate (p. 1089·3).
Schizophrenia; bipolar disorder.

Synthon, Pol.
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olatin *Lotus, China; Sandoz, Denm.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Olatropil *Olainfarm, Ukr.*
Gamma-aminobutyric acid (p. 2509·2); piracetam (p. 393·3).
Mental function disorders; cerebrovascular disorders; cerebral metabolic disorders; neuroses; asthenia; disturbed behaviour; schizophrenia; alcoholic polyneuritis; dementia; motion sickness.

Olavac *Raam, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Olazax *Glenmark, Cz.; Glenmark, Irl.; Glenmark, Neth.; Glenmark, Pol.; Glenmark, Port.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olazofren *Legrand, Braz.*
Olanzapine (p. 1089·3).

Ölbad Cordes *Ichthyol, Austria†; Ichthyol, Ger.†*
Soya oil (p. 2092·3).
Bath additive; skin disorders.

Ölbad Cordes F *Ichthyol, Ger.†*
Arachis oil (p. 2446·1).
Bath additive; skin disorders.

Olban *Indoco, India.*
Albendazole (p. 149·1).
Worm infections.

Olbas *Hanseler, Switz.*
Oil: Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1); sweet birch oil (p. 92·1); juniper oil (p. 2537·2); clove oil (p. 2481·3).
Cold symptoms.

Hanseler, Switz.
Ointment: Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1); sweet birch oil (p. 92·1); juniper oil (p. 2537·2); poppy-seed oil (p. 2594·3).
Cold symptoms; nasal congestion.

Lane, Irl.
Nasal inhaler: Cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); levomenthol (p. 2553·2); peppermint oil (p. 1877·1).
Sinus congestion; catarrh; hay fever; cold and influenza symptoms.

Lane, Pol.; Hanseler, Switz.†; Lane, UK.
Inhaler: Cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); menthol (p. 2553·2).
Nasal congestion; sinusitis.

Lane, Irl.
Oil: Cajuput oil (p. 2464·1); clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); menthol (p. 2553·2); mint oil, partly dementholised (p. 2560·1); methyl salicylate (p. 92·1).
Nasal congestion; mouth and throat inflammation; muscular pain.

Lane, Irl.
Pastilles: Eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); levomenthol (p. 2553·2); juniper oil (p. 2537·2); methyl salicylate (p. 92·1); clove oil (p. 2481·3).
Nasal congestion; mouth and throat inflammation.

Lane, Pol.
Oil: Cajuput oil (p. 2464·1); clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); peppermint oil (p. 1877·1); menthol (p. 2553·2); birch oil (p. 92·1).
Nasal congestion; musculoskeletal and joint pain.

Lane, Pol.; Lane, UK.
Pastilles: Eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); peppermint oil (p. 1877·1); menthol (p. 2553·2); birch oil (p. 92·1); clove oil (p. 2481·3).
Sore throat; cold symptoms; coughs.

Lane, UK.
Oil: Cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); clove oil (p. 2481·3); juniper oil (p. 2537·2); menthol (p. 2553·2); dementholised mint oil (p. 2560·1).
Nasal congestion.

Tramedico, Neth.†
Eucalyptus oil (p. 2501·2); clove oil (p. 2481·3); juniper oil (p. 2537·2); dementholised mint oil (p. 2560·1); levomenthol (p. 2553·2); methyl salicylate (p. 92·1); cajuput oil (p. 2464·1).
Respiratory-tract congestion.

Novyphar, Belg.
Peppermint oil (p. 1877·1); eugenol (p. 2501·2); cajuput oil (p. 2464·1); sweet birch oil (p. 92·1); juniper oil (p. 2537·2); cineole (p. 2479·1); menthol (p. 2553·2).
Upper respiratory-tract disorders.

Olbas, Ger.
Drops: Peppermint oil (p. 1877·1); cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); sweet birch oil (p. 92·1).
Cold symptoms; gastrointestinal disorders; headache; neuralgia; rheumatism; pain.

Olbas, Ger.
Topical spray: Propane (p. 1802·3); isopropyl alcohol (p. 1758·3).
Soft-tissue disorders.

Olbas for Children *Lane, UK.*
Cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); clove oil (p. 2481·3); juniper oil (p. 2537·2); menthol (p. 2553·2); dementholised mint oil (p. 2560·1); methyl salicylate (p. 92·1).
Respiratory-tract congestion.

Olbas Powerflu plus Vitamin C *Lane, UK.*
Tablets, paracetamol (p. 115·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); tablets, sodium ascorbate (p. 2111·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Olbendital *Italmex, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Olbenorm *Norma (Νορμα), Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Olbetam *Pfizer, Austria; Pfizer, Belg.; Pfizer, Chile; Pfizer, China; Pfizer, Denm.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Neth.; Pfizer, NZ; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK.*
Acipimox (p. 1290·2).
Hyperlipidaemias.

Olcadil *Novartis, Braz.; Novartis, Port.*
Cloxazolam (p. 1057·2).
Anxiety; sleep disorders; premedication.

Olcenon *Pola Pharma, Jpn.*
Tretinoin tocoferil (p. 1725·2).
Skin ulcers.

Oldamin *Fuji, Jpn.*
Monoethanolamine oleate (p. 2562·3).
Oesophageal varices.

Oldaram *Ranbaxy, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Oldinot *Elea, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Oldren *Roemmers, Arg.*
⊗Eplerenone (p. 1374·2).
Heart failure following myocardial infarction; hypertension.

Oleanz *Maver, Chile; Sun, India; Pharmaplan, S.Afr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Oleclox *Shalaks, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Oledro *Drogsan, Turk.*
Oral powder; tablets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); oxolamine citrate (p. 1671·2).
Fever; pain.

Drogsan, Turk.
Paediatric syrup: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Fever; pain.

Olekast *Specifar, Denm.†*
Montelukast sodium (p. 1214·3).
Asthma.

Olenxa *Target, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Oleo Calcarea *NewFaDem, Ital.; Nova Argentia, Ital.*
Aluminium acetate (p. 2440·1); glacial acetic acid (p. 2426·3); zinc oxide (p. 1729·1); calcium oxide (p. 2465·2); levomenthol (p. 2553·2).

Óleo de Prímula *Catarinense, Braz.; Fontovit, Braz.*
Gamolenic acid (p. 2509·2); linoleic acid (p. 2509·2).

Oleo Tüll *Sanofi-Aventis, Ger.*
Soft paraffin (p. 2211·3); wool fat (p. 2219·3).
Wounds.

Oleobal *Pierre Fabre Dermo Kosmetik, Ger.*
Soya oil (p. 2092·3); light liquid paraffin (p. 2191·2).
Bath additive; skin disorders.

Oleoderm
Note: this name may be used for preparations of different composition.
Remexa, Mex.
Calcium hydroxide (p. 2465·1).
Skin disorders.

Vita, Venez.
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2).
Emollient.

Oleoderm Plus *Remexa, Mex.*
Calcium hydroxide (p. 2465·1); avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Oleofin *Casasco, Arg.*
Orlistat (p. 2577·1).
Obesity.

Oleo-Lax *Fada, Arg.*
Propofol (p. 1909·3).
General anaesthesia.

Oleomycetin *Agepha, Austria.†*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Oleomycetin-Prednison *Agepha, Austria.†*
⊗Chloramphenicol (p. 257·1); prednisone (p. 1647·2).
Infected eye disorders.

Oleosorbate *Eumedica, Belg.†*
Polysorbate 80 (p. 2203·3).
Rhinitis; ear wax removal.

Oleovit *Fresenius Kabi, Austria.*
Vitamin A palmitate (p. 2098·3); dexpanthenol (p. 2582·2).
Eye disorders.

Oleovit D_3 *Fresenius Kabi, Austria.*
Colecalciferol (p. 2113·1).
Rickets; hypoparathyroidism.

Oleptal *Torrent, Braz.; Torrent, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oleptro *Labopharm, USA.*
Trazodone hydrochloride (p. 451·1).
Depression.

Oles *Esma, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olesan *Ranbaxy, Ukr.*
Pastilles: Malabar nut (p. 2549·1); clove (p. 2481·2); eucalyptus oil (p. 2501·2).
Sore throat; cough; cold symptoms.

Ranbaxy, Ukr.†
Syrup: Malabar nut (p. 2549·1); turmeric (p. 2218·1); hedychium spicatum.
Cough; respiratory-tract congestion.

Ranbaxy, Ukr.†
Topical gel: Methyl salicylate (p. 92·1); cade oil (p. 1723·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); menthol (p. 2553·2).
Cough and cold symptoms.

Olesan Oil *Ranbaxy, India.*
Eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); clove oil (p. 2481·3).

Olestesin *Altayvitamin, Rus.*
Sea buckthorn oil (p. 2612·1); sulfaethidole; benzocaine (p. 1980·2).
Anorectal disorders.

Olestyr *Pendopharm, Canad.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; short bowel syndrome; pruritus in biliary obstruction.

Oletetrin *Biosintez, Rus.*
Oleandomycin phosphate (p. 335·3); tetracycline (p. 373·1).
Bacterial infections.

Oleum Basileum *Atoma, Swed.*
Eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1); peppermint oil (p. 1877·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Oleum Rhinale *Weleda, UK.*
Calendula (p. 2465·2); merc. sulph. (p. 2555·3); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2).
Homoeopathic preparation.

Oleum Rhinale Nasal Oil *Weleda, S.Afr.†*
Camphor (p. 2466·2); mercurius sulfuratus ruber; calendula (p. 2465·2); chamomile (p. 2474·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Nasal congestion; sinusitis; rhinitis.

Oleum Salviae Comp *Weleda, S.Afr.†*
Eucalyptus oil (p. 2501·2); fennel oil (p. 2503·3); juniper oil (p. 2537·2); peppermint oil (p. 1877·1); Scots pine oil (p. 2591·2); rosemary oil (p. 2607·3); sage oil (p. 2609·1); labdanum oil.
Respiratory-tract disorders.

Oleum Salvum *Atoma, Swed.*
Eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1); peppermint oil (p. 1877·1).

Olevo *Lincoln, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Olevon *Alkem, India.*
Vitamins; trace elements; docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Olex Tab *Lexus, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Olexar *Cipla, India; Cipla-Medpro, S.Afr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder; psychoses.

Olexin *Rayere, Mex.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Oley-OZ *AstraZeneca, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Olez *DR Johns, India.*
Lansoprazole (p. 1851·3).
Peptic ulcer; hypersecretory disorders; dyspepsia; gastro-oesophageal reflux.

Olf *GNLD, Austral.†*
Ganoderma lucidum; celery (p. 2472·3); avena (p. 2451·1); salvia officinalis (p. 2608·3); damiana (p. 2491·3); St John's wort (p. 449·1); astragalus membranaceus (p. 2451·1); angelica polymorpha root (p. 2497·1) cinnamon (p. 2479·2); liquorice (p. 1853·2).
Tonic.

Olfen *Mepha, Braz.†; Mepha, China; Mepha, Cz.; Mepha, Hong Kong; Mepha, Israel; Mepha, Malaysia; Mepha, Port.; Mepha, Singapore.*
Diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; musculoskeletal, joint, and peri-articular disorders; renal and biliary colic.

Mepha, Pol.; Mepha, Switz.; Mepha, Ukr.
Diclofenac (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; gout.

Olfex *Bial, Spain.*
⊗Budesonide (p. 1625·1).
Asthma.

Olfi *Ipca, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Olfi TZ *Ipca, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Olfic *Keshav, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Olfic-OZ *Keshav, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Olfi-O *Ipca, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Olfo
Note: this name may be used for preparations of different composition.
Iasis, Gr.
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Alpic, India.
Ofloxacin (p. 334·3).
Bacterial infections.

Olfon-OR *Hy-Gro, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Olfosonide *Novis, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Olfovel *TO-Chemicals, Thai.*
Levofloxacin (p. 315·3).
Bacterial infections.

Olfrex *Nobel, Turk.*
Olanzapine (p. 1089·3).

Olgacal *Servocare, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Olgeria *Neiss, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Oliade Bath *Ind-Swift, India.*
Arachis oil (p. 2446·1); vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).

Olibanum RA *Zilly, Ger.*
Indian frankincense (p. 2507·3).
Homoeopathic preparation.

Olicap *Acekinetic, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Olicap-D *Acekinetic, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Olicard *Abbott, Cz.; Solvay, Ger.†; Solvay, Hung.; Solvay, Pol.; Solvay, Rus.; Solvay, Ukr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Olicardin *Medicopharm, Austria.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; pulmonary hypertension; heart failure.

OliClinomel *Baxter, Arg.*
Amino acids; glucose (p. 2068·3); lipid; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Clintec, Austria; Baxter, Chile; Baxter, Cz.; Baxter, Fin.; Baxter, Hung.; Baxter, Irl.; Clintec, Israel; Baxter, Ital.; Baxter, Norw.; Baxter, NZ; Baxter, Port.; Clintec, Spain; Baxter, Swed.; Baxter, UK.
Amino acids; glucose (p. 2068·3); lipids (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Clintec, Belg.; Baxter, Denm.†; Baxter, Fr.; Baxter, Ger.†; Baxter, Gr.; Clintec, Neth.; Baxter, Switz.†; Baxter, Thai.
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3) and olive oil (p. 2575·1)); with or without electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Eczacibasi-Baxter, Turk.
Amino acids; glucose (p. 2068·3); lipids; electrolytes (p. 1775·1).
Parenteral nutrition.

Oliclinomel *Baxter, Rus.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipids (from olive oil (p. 2575·1) and soya oil (p. 2092·3)).
Contains egg lecithin.
Parenteral nutrition.

Olidermil *Edol, Port.*
Zinc oxide (p. 1729·1); almond oil (p. 2437·1).
Dry skin.

Olie *SAD, Denm.†*
Arachis oil (p. 2446·1).
Constipation; bowel evacuation.

Olife *Life Line, India.*
Oral suspension: Ofloxacin (p. 334·3).
Bacterial infections.

Life Line, India.
Tablets: Lactobacillus sporogenes (p. 2596·3); ofloxacin (p. 334·3).

Olife-M *Life Line, India.*
Metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

Olife-OZ *Life Line, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Olife-TZ *Life Line, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oliflox *Delta, Port.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Oligel *Karnataka, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Oligobiane Fe-Cu *Pileje, Fr.*
Ferrous sulfate (p. 2062·2); copper sulfate (p. 2057·2).
Iron deficiency.

Oligobs *CCD, Fr.*
Vitamins; minerals.
A range of dietary supplements.

Oligocomplesso *Chimicor, Fr.†*
Trace elements.

Oligocure *Labcatal, Fr.*
Manganese gluconate (p. 2081·2); copper gluconate (p. 2057·2); colloidal gold (p. 2521·1).
Asthenia.

Oligoderm *Labcatal, Fr.†*
Manganese gluconate (p. 2081·2); copper gluconate (p. 2057·2).
Cracked nipples.

Oligoelementos *Biosano, Chile; Braun, Port.*
Trace elements.
Parenteral nutrition.

Oligo-elements Aguettant *Aguettant, Fr.*
Trace elements.
Parenteral nutrition.

Oligogranul *Boiron, Fr.†*
Trace elements; minerals.

Oligophytum *Holistica, Fr.*
A range of mineral-rich plant extracts.

Oligoplex *Natural Touch, UK.*
A range of homoeopathic remedies.
Homoeopathic preparation.

OligoPlus *Braun, Spain.*
Trace elements.
Parenteral nutrition.

Oligorhine *Monin, Fr.*
Copper (p. 2057·1); silver (p. 2615·1).
Nasal hygiene.

Oligosol *Labcatal, Fr.*
Trace elements; minerals.

Pharmafactory, Switz.†
Minerals.

Oligossac *Support, Braz.*
Maltodextrin (p. 2080·3).
Preparation for enteral nutrition.

Oligostandard *Braun, Spain.*
Trace elements.
Parenteral nutrition.

Oligostim *Boiron, Fr.*
Trace elements; minerals.

Oligotide *Hiteck Bio, China.*
Anti-hepatitis B transfer factor (p. 2633·2).
Hepatitis B.

Oligovit *Ativus, Braz.; Farmstandart, Rus.; Galenika, Ukr.*
Vitamins; minerals.

Olig-Trat *Citopharma, Braz.*
Zinc sulfate (p. 2126·2); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); chromium trichloride (p. 2055·3).

Olima *Mankind, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olimag *Marforma, Ital.*
Magnesium (p. 1786·3); iodine (p. 2336·3); vitamin B_6 (p. 2105·3).
Nutritional supplement.

Olimel *Baxter, Belg.; Baxter, Ger.; Baxter, Norw.; Baxter, Swed.; Baxter, Switz.*
Amino acids; glucose (p. 2068·3); lipid (from olive oil (p. 2092·3) and soya oil (p. 2575·1)); with or without electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Neth.; Baxter, Spain.
Amino acids; lipids (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); glucose (p. 2068·3); with or without electrolytes (p. 1775·1).
Contains egg phosphatides.
Parenteral nutrition.

Baxter, Fr.
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3) and olive oil (p. 2575·1)).
Contains egg phospholipids.
Parenteral nutrition.

Olimer *Rontag, Arg.†*
Clonazepam (p. 519·1).
Panic disorder; epilepsy.

Olimestra *Miklich, Pol.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olin *Gufic, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Oliseptil Gorge-Larynx *Ineldea, Fr.*
Oral spray: Eucalyptus (p. 2501·1); calendula (p. 2465·2); honey (p. 2072·1); propolis (p. 2597·3); melaleuca oil (p. 2551·1); peppermint oil (p. 1877·1).
Respiratory-tract congestion; sore throat.

Ineldea, Fr.
Syrup: Honey (p. 2072·1); scots pine (p. 2591·1); echinacea (p. 2498·1); peppermint leaf (p. 1877·1); propolis (p. 2597·3); acerola; lemon oil (p. 2543·1); scots pine oil (p. 2591·2).
Cold symptoms; sore throat.

Oliseptil Nez-Gorge *Ineldea, Fr.*
Ravensara oil; eucalyptus oil (p. 2501·2); cypress oil (p. 2491·1); rosemary oil (p. 2607·3); niaouli oil (p. 2569·1); melaleuca oil (p. 2551·1); cinnamon oil (p. 2479·3).
Nasal congestion.

Olipazix *Medico Uno, Cz.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olipcis *Sanfer, Mex.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Oliphenicol *Am-Europharma, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Olisat *Biocon, India.*
Orlistat (p. 2577·1).
Obesity.

Olisir *Menarini, Ital.*
Bilastine (p. 617·3).

Olit *Cadila, India; Cadila, Singapore; Cadila, Thai.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Oliten *Alapis, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Olitrace *Braun, Ital.*
Trace elements.
Parenteral nutrition.

Olivalax *Tisane Provencale, Fr.*
Senna (p. 1885·1); olive oil (p. 2575·1).
Constipation.

Olive Leaf Plus *Golden Glow, Austral.*
Olive leaf (p. 2574·3); tabebuia avellanedae; garlic (p. 2510·3); echinacea (p. 2498·1); sambucus (p. 2609·3); zinc gluconate (p. 2126·2); thyme oil (p. 2630·3).
Tonic.

Olivenol *CreAgri, Malaysia.*
Olive oil (p. 2575·1).
Dietary supplement.

Olivenol Livin' Active *10B International, Singapore.*
Olive oil (p. 2575·1); glucosamine hydrochloride (p. 2515·3).
Dietary supplement.

Olivenol Livin' Begin *10B International, Singapore.*
Olive oil (p. 2575·1).
Dietary supplement.

Olivenol livin' Begin *10B International, Malaysia.†*
Olive oil (p. 2575·1).
Dietary supplement.

Olivenol Livin' Vigor *10B International, Singapore.*
Olive oil (p. 2575·1); Levocarnitine tartrate (p. 2053·2).
Dietary supplement.

Olivenol livin' Vigor *10B International, Malaysia.†*
Levocarnitine tartrate (p. 2053·2); olive oil (p. 2575·1).
Dietary supplement.

Olivenol Livin' Youthful *10B International, Singapore.*
Olive oil (p. 2575·1); thioctic acid (p. 2629·1).
Dietary supplement.

Olivenol livin' Youthful *10B International, Malaysia.†*
Thioctic acid (p. 2629·1); olive oil (p. 2575·1).
Dietary supplement.

Olivevital *Blackmores, Austral.†*
Olive leaf (p. 2574·3).
Tonic.

Olivin *Royal, Chile.*
Olanzapine (p. 1089·3).
Psychoses.

Olivysat *Ysatfabrik, Ger.†*
Olive leaves (p. 2574·3).
Prevention of atherosclerosis.

Oliza *Intas, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olkingo *KRKA, Denm.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olkreso *KRKA, Denm.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olla-D *Sienna, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ollafax *Frik, Turk.*
Olanzapine (p. 1089·3).

Olla-MT *Sienna, India.*
Omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ollantay *Higate, Arg.*
Maté (p. 2648·2).

Olmar *Helm, Port.*
Ondansetron hydrochloride (p. 1872·1).

Olmat *Micro, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmat-AM *Micro, India.*
Amlodipine (p. 1304·1); olmesartan medoxomil (p. 1459·2).

Olmat-AMH *Micro, India.*
⊗Amlodipine (p. 1304·1); hydrochlorothiazide (p. 1403·2); olmesartan medoxomil (p. 1459·2).

Olmat-H *Micro, India.*
⊗Hydrochlorothiazide (p. 1403·2); olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmax *Glenmark, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmax-H *Glenmark, India.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmec *Phoenix, Arg.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmecip *Cipla, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmefast *Intra-Labs, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmefast-H *Intra-Labs, India.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmegan *Daiichi Sankyo, Ital.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmesar *Macleods, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmesar-A *Macleods, India.*
Amlodipine (p. 1304·1); olmesartan medoxomil (p. 1459·2).

Olmesar-H *Macleods, India.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetec *Schering-Plough, Arg.; MSD, Austral.; Sankyo, Austria; Daiichi Sankyo, Belg.; Pfizer, Braz.; Merck, Canad.; Schering-Plough, Chile; Daiichi Sankyo, China; Menarini, Cz.; Daiichi, Denm.; Daiichi Sankyo, Fin.; Daiichi Sankyo, Fr.; Daiichi Sankyo, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Sankyo, Israel†; Daiichi Sankyo, Ital.; Daiichi Sankyo, Jpn; Pfizer, Malaysia; Daiichi Sankyo, Neth.; Nycomed, Norw.; Pfizer, Philipp.; Sankyo, Port.; Pfizer, Singapore; Daiichi Sankyo, Spain; Daiichi Sankyo, Switz.; Pfizer, Thai.; Pfizer, Turk.; Daiichi Sankyo, UK; Schering-Plough, Venez.*
Olmesartan medoxomil (p. 1459·2).
Hypertension; heart failure; diabetic nephropathy.

Olmetec Anlo *Pfizer, Braz.*
Olmesartan; amlodipine (p. 1304·1).

Olmetec Comp *Nycomed, Norw.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetec D *Schering-Plough, Arg.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetec HCT *Pfizer, Braz.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetec HCTZ *Daiichi Sankyo, Neth.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetec Plus *MSD, Austral.; Daiichi Sankyo, Austria; Daiichi Sankyo, Belg.; Merck, Canad.; Schering-Plough, Chile; Daiichi Sankyo, China; Daiichi, Denm.; Daiichi Sankyo, Fin.; Daiichi Sankyo, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Malaysia; Pfizer, Philipp.; Daiichi Sankyo, Port.; Pfizer, Singapore; Daiichi Sankyo, Spain; Daiichi Sankyo, Switz.; Pfizer, Thai.; Pfizer, Turk.; Daiichi Sankyo, UK.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetec Plus H *Menarini, Cz.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmetor *Torrent, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmetor-H *Torrent, India.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmezar *OEP, Philipp.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmezest *Sun, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmezest-H *Sun, India.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmifon *Cephalon, Fr.†*
⊗Adrafinil (p. 2315·3).
Mental function impairment in the elderly.

Olmighty *Merck, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmighty-H *Merck, India.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmis *Unichem, India.*
Tacrolimus (p. 1968·3).
Transplant rejection; Crohn's disease; atopic eczema.

Olmoran *AstraZeneca, Spain.*
Zafirlukast (p. 1239·3).
Asthma.

Olmy *Zydus, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olmy-A *Zydus, India.*
Amlodipine (p. 1304·1); olmesartan.

Olmy-H *Zydus, India.*
⊗Olmesartan; hydrochlorothiazide (p. 1403·2).
Hypertension.

Olmy-R *Zydus, India.*
Olmesartan; ramipril (p. 1483·3).

Olmysar *Bilim, Turk.*
Olmesartan medoxomil (p. 1459·2).

Olmysar Plus *Bilim, Turk.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).

Olmyzem *Farmazak, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olo *Ind-Swift, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Oloblu *Lupin, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Olodin *FDC, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Ologyn *Labatec, Switz.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Olopat *Elea, Arg.*
Olopatadine hydrochloride (p. 636·2).
Allergic conjunctivitis.

Olopeg *MIP, Fin.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Constipation; bowel evacuation.

MIP, Pol.
Macrogol 4000 (p. 2547·3).
Constipation; bowel evacuation.

Olorest-F *Solitaire, India.*
Fluoxetine (p. 417·1); olanzapine (p. 1089·3).

Olotic *Zytras, India.*
⊗Beclometasone (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).

Olpin *East West, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olpinat *Vipharm, Cz.; Vipharm, Hung.; Vipharm, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder; psychoses.

Olpine-AT *Uniroyal, India.*
⊗Amlodipine (p. 1304·1); atenolol (p. 1308·2).
Angina pectoris; hypertension.

Olpira *Helm, Port.†*
Paracetamol (p. 115·1).
Pain; fever.

Olpit *Epitome, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Olpit-NZ *Epitome, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Olpit-OZ *Epitome, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Olpitric *Cubit, India.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Olpress *Malesci, Ital.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olprezide *Malesci, Ital.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olsar *Unichem, India; Menarini, Port.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Olsar Plus *Menarini, Port.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Olsar-A *Unichem, India.*
Amlodipine (p. 1304·1); olmesartan medoxomil (p. 1459·2).

Olsar-H *Unichem, India.*
⊗Hydrochlorothiazide (p. 1403·2); olmesartan medoxomil (p. 1459·2).
Hypertension.

Olsar-M *Unichem, India.*
⊗Metoprolol succinate (p. 1434·3); olmesartan medoxomil (p. 1459·2).

Olson *Zytras, India.*
Ornithine aspartate (p. 2085·2).

Olstadryn *Centrafarm, Neth.†*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

Oltal *Talent, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Oltar *Berlin-Chemie, Cz.; Menarini, Fin.; Berlin-Chemie, Pol.†; Menarini, Pol.†; Berlin-Chemie, Ukr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Oltaur *Taurus, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oltaur-TZH *Taurus, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oltril *Myung, Thai.*
Sodium valproate (p. 553·1).
Epilepsy.

Olumpil *Misha, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Olux *Mipharm, Ital.; GSK, USA.*
⊗Clobetasol propionate (p. 1627·1).
Psoriasis; skin and scalp disorders.

Olwexya *KRKA, Cz.; KRKA, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Olworm *Biochem, India.*
Albendazole (p. 149·1).
Worm infections.

Olyco Plus *Rishab, India.*
Lycopene (p. 2546·2); vitamins; trace elements.

Olymox *Shalaks, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Olynth *McNeil, Cz.; McNeil, Ger.; Pfizer, Rus.†; McNeil, Swed.; Janssen-Cilag, Switz.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Olynth salin *McNeil, Ger.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Olypan *Hennig, Denm.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer Zollinger-Ellison syndrome.

Olysio *Janssen, USA.*
Simeprevir (p. 1015·2).
Chronic hepatitis C.

Olyspal *Cosmopharm, Gr.*
⊗Budesonide (p. 1625·1).
Asthma.

Olyster *Zydus, India.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Olzamed *Medis, Denm.†*
Olanzapine (p. 1089·3).
Schizophrenia; mania; bipolar disorder.

Olzap *Baroda, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olzapin *Lek-Am, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Olzin *Egis, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

OM3 *Isodisnatura, Fr.†*
Fish oil (p. 1460·1).
Dietary supplement.

Omaato *Bionova, India.*
Lycopene (p. 2546·2); vitamins; trace elements.

Omaclopil *Lafedar, Arg.*
Pilocarpine (p. 2010·2).
Glaucoma; production of miosis.

Omacor *Abbott, Austral.; Solvay, Austria; Solvay, Belg.; Pronova, Cz.; Pierre Fabre, Fr.; Abbott, Ger.; Abbott, Gr.; Pronova, Hung.; Pronova, Irl.; Abbott, Israel; Pronova, Neth; Pronova, Norw.; Pronova, Philipp.; Pronova Biocare, Pol.; Pronova, Port.; Solvay, Rus.; Pronova, Spain; Abbott, Thai.; Solvay, UK; Abbott, Ukr.*
Omega-3-acid ethyl esters (p. 1460·2).
Hyperlipidaemias; hypertriglyceridaemia; myocardial infarction prophylaxis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Omaflaxina *Biosintex, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Omaflaxina D *Biosintex, Arg.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Omag *Ordain, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omaha *Velka, Gr.*
Sulpiride (p. 1107·3).

Omalcer *Wockhardt, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omapin *Brawn, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omapren *Qualigen, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcers; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Omar *Hexal, Pol.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omaron *Nizpharm, Rus.; Nizhfarm, Ukr.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Asthenia; vestibular disorders; Ménière's disease; migraine; cerebrovascular disorders; mental function disorders.

Omastin *Beximco, Singapore.*
Fluconazole (p. 578·2).
Fungal infections.

Omatex *Phoenix, Arg.*
Enoxaparin sodium (p. 1372·3).
Thromboembolic disorders.

Ombel *Blubell, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ombel-D *Blubell, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ombest *BMW, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ombest-D *BMW, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ombrelle Cream *Ombrelle, Canad.*
SPF 60: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle Kids *Ombrelle, Canad.*
SPF 60: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle L'Oreal Suncare Research Kids *Ombrelle, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle Lotion *Ombrelle, Canad.*
SPF 15; SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); ensulizole (p. 1703·1).
Sunscreen.

Ombrelle, Canad.
SPF 45: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle Lotion Extreme
Note: this name may be used for preparations of different composition.
Ombrelle, Canad.
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle Sport *Ombrelle, Canad.*
Gel; spray: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ombrelle Sport Lotion *Ombrelle, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle Stick *Ombrelle, Canad.*
SPF 60: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Ombrelle Vapo Sport *Ombrelle, Canad.*
SPF 15: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); octisalate (p. 1715·2).
Sunscreen.

Omcare *Medico, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omcare Gel *Medico, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Omcare-D *Medico, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omcid *Indu, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omcilon-A M *BMS, Braz.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); nystatin (p. 590·3).
Infected skin disorders.

Omcilon-A Orabase *BMS, Braz.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth ulceration.

Omcure *Finecure, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omcure-D *Finecure, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omdom *Bestochem, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ome TAD *TAD, Ger.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omebeta *Betapharm, Ger.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omebloc *Zee, Philipp.; Behrens, Venez.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omec *Hexal, Austria.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; acid aspiration; Zollinger-Ellison syndrome.

Omecaps *Mayo, Mex.; Ajanta, Rus.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omecat *Pensa, Swed.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omecer *East West, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omecer-D *East West, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omecid *Saga, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omecid-D *Saga, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omecid-RD *Saga, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omecip *Cipla, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omecip-D *Cipla, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omeclamox-Pak *Pernix, USA.*
Capsules, omeprazole (p. 1867·2); tablets, clarithromycin (p. 266·2); capsules, amoxicillin (p. 216·2).
Eradication of Helicobacter pylori.

Omecos *Symbiosis, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omecos-D *Symbiosis, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omed *Medhaus, Philipp.; Sandoz, Switz.*
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omediprol *Actavis, Fr.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Omedoc *Docpharm, Ger.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omeezol-D *RK Medicare, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omefar *Wunderpharm, Arg.*
Omeprazole (p. 1867·2).

Omeflox *Entod, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Omeflox-KT *Entod, India.*
Ketorolac trometamol (p. 80·2); ofloxacin (p. 334·3).

Omega
Note: this name may be used for preparations of different composition.
Bactolac, India.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omega-3 *Knop, Chile; Lysi, Pol.*
Omega-3 marine triglycerides (p. 1460·3).
Hyperlipidaemias; arrhythmias; atherosclerosis; hypertension; rheumatic disorders.

Omega III *Nutrifarma, Turk.*
Omega-3 marine triglycerides (p. 1460·3).
Ischaemic heart disease; hyperlipidaemias.

Omega 7 *Pharma Nord, UK.*
Sea buckthorn oil (p. 2612·1).
Dietary supplement.

Omega 100 *Omega, Arg.*
Carbinoxamine maleate (p. 619·1).
Hypersensitivity reactions.

Omega 100 Bronquial *Omega, Arg.*
Guaifenesin (p. 1666·2).
Cough.

Omega Essentials with Vitamin D-3 *Physician Recommended Nutriceuticals, USA.*
Omega-3 fatty acids (p. 1460·1); vitamin D (p. 2112·3).

Omega 100 Expectorante *Omega, Arg.*
Carbinoxamine maleate (p. 619·1); ammonium chloride (p. 1656·1).
Hypersensitivity reactions.

Omega Gold *Bell Kenz, Philipp.*
Fish oil (p. 1460·3).
Cardiovascular risk reduction; hypertriglyceridaemia.

Omega 100 L *Omega, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Omega 1-step *Omega, Irl.†*
Pregnancy test (p. 2596·1).

Omegabiane *Pileje, Fr.*
Fish oil (p. 1460·1).
Dietary supplement.

Omegabloc *Trianon, Philipp.*
Fish oil (p. 1460·3); vitamin E (p. 2119·1).
Cardiovascular risk reduction.

Omegacand *Egis, Neth.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Omegacand HCT *Egis, Neth.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Omegachek *Indoco, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); selenium (p. 2086·3); zinc sulfate (p. 2126·2).

Omegacin *Meiji, Jpn.*
Biapenem (p. 231·1).
Bacterial infections.

Oméga cœur *Holistica, Fr.*
Omega-3 marine triglycerides (p. 1460·3); omega-6 triglycerides (p. 2575·2); omega-9 triglycerides.
Dietary supplement.

Omegadin Plus *GD, Ital.*
Fatty acids; glycine (p. 2071·2); selenium (p. 2086·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3).

OmegaGen Cardio *Invida, Philipp.*
Krill oil.
Hypercholesterolaemia.

Omega-H3 *Vitabiotics, UK.*
Vitamins; minerals; nutritional supplements.

Oméga line *Holistica, Fr.*
Borage oil (p. 2459·2).
Dietary supplement.

Oméga line Solaire *Holistica, Fr.*
Borage oil (p. 2459·2); carotene; wheat-germ oil (p. 2647·1); grape-seed oil (p. 2521·3); vitamin E (p. 2119·1).
Photoageing of the skin.

Omegamma *Worwag, Ger.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeganorm *Novamen, Arg.†*
Linolenic acid (p. 1460·2); linoleic acid (p. 2509·2); alpha tocopherol (p. 2119·1).
Dietary supplement.

Omegast *Nobel, Turk.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omegastrol *Ducto, Braz.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omegaven *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Port.*
Omega-3 marine triglycerides (p. 1460·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Chile; SSPC, China; Fresenius Kabi, Denm.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, India; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.; Fresenius Kabi, UK; Fresenius Kabi, Ukr.
Fish oil (p. 1460·1).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Omegavite *Novum, Mex.*
Omega-3 fatty acids (p. 1460·1).
Nutritional supplement.

Omegen *Generics, Hung.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omegic *Intra-Labs, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).

Omegold *Cadila, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omegord *Medispan, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omegrim *AMPDR, Port.†*
Omeprazole (p. 1867·2).

OmeHennig *Hennig, Ger.†*
Omeprazole (p. 1867·2).
Heartburn; acid reflux.

Omejel *Akums, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omejel-DM *Akums, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omel *Jagsonpal, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omelar Cardio *Obolenskoe, Rus.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Omelax *Zytras, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omelax-D *Zytras, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

OmeLich *Winthrop, Ger.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omelina *Gelpharma, Mex.*
Linseed oil (p. 2544·2).
Dietary supplement.

Omelix *Ratiopharm, Denm.†*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration.

Omelon *YSP, Malaysia; Yung Shin, Philipp.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; Helicobacter pylori eradication; acid aspiration; dyspepsia.

Omeman *T Man, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omen *Adroit, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omenat *Natco, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omenax *Geolab, Braz.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omen-D *Adroit, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ome-nerton *Dolorgiet, Ger.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omenole *Korea United, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omentum *Kamakshi, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; hypersecretory disorders.

Omentum-D *Kamakshi, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Omep *UCI, Braz.; Hexal, Ger.†; Hexal, Hung.; Bal, India; Sandoz, Ukr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia; gastrointestinal hyperacidity.

Omepac *Inpac, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omepirex *Winthrop, Cz.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastrointestinal hyperacidity; Zollinger-Ellison syndrome.

Omeplus *Plus, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ome-PPI *Blue Cross, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omepra *Rafa, Israel; BA Farma, Port.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Omepradex *Dexcel, Israel.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepral *AstraZeneca, Austral.*
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

FDC, India; AstraZeneca, Jpn.
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omepralan *GL Pharma, Austria.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; acid aspiration.

Omepramed *Cimed, Braz.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepramix *Ache, Braz.*
Capsules, omeprazole (p. 1867·2); tablets, clarithromycin (p. 266·2); capsules, amoxicillin trihydrate (p. 216·2).
Helicobacter pylori*-associated peptic ulcer.*

Omeprasec *HLB, Arg.*
Omeprazole magnesium (p. 1867·2) or omeprazole sodium (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprawin *Chinoin, Hung.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprax *Sanitas, Chile; Drossapharm, Switz.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omepraz *Alkem, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omeprazen *Malesci, Ital.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omepraz-HP Kit *Alkem, India.*
1 Tablet, amoxicillin (p. 216·2); 1 capsule, omeprazole (p. 1867·2); 1 tablet, tinidazole (p. 949·2).

Omeprazid *Nobel, Turk.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Omeprazin *EMS, Braz.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).

Omepren *Blue Cross, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omeprix *Rafa, Israel.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Omeprol *Hexal, Cz.†; Medichrom, Gr.; Sinensix, Thai.; Sandoz, Turk.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omepromp *PromptCure, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omepron *Westmont, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprotec *Hexal, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Omeptas *Zim, Philipp.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ome-Puren *Actavis, Ger.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ome-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omerane *Medicus, Gr.*
Omeprazole (p. 1867·2).

Omeratio *Ratiopharm, Port.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Omerax *Farbio, Port.*
Omeprazole (p. 1867·2).

Omeraze *Invision, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omeraze-D *Invision, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omeria *Mediolanum, Ital.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Omeris *Symbiosis, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omeris-D *Symbiosis, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omesar *Menarini, Irl.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Omesar Plus *Menarini, Irl.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Omesec *CCM, Malaysia; Upha, Singapore; Natco, Thai.; United Drug, Thai.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; Helicobacter pylori eradication; acid aspiration; dyspepsia.

Omesek *Terra, Turk.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omestad *Stada, Denm.; Stada, Fin.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Omesun *Sunrise, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omesun-D *Sunrise, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omesym *Symbiosis, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omesym-D *Symbiosis, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omet *Hufort, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Ometab *Intas, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ometec *Technobio, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Ometon *Labesfal, Port.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Ometrix *Biotech Naturis, Venez.*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement; hyperlipidaemias.

Omevar *ATOZ, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omevar-D *ATOZ, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omevax *Vivax, Venez.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omevell *Novell, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omexel *Astellas, Fr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omey *Intas, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omez *Reddy, India; Reddy, Philipp.; Reddy, Rus.; Reddy, S.Afr.; Reddy, Thai.†; Reddy, Ukr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia; heartburn; pancreatitis; systemic mast-cell disease; gastric hyperacidity.

Reddy, Malaysia.
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omez D *Reddy, Rus.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux.

Omez Insta *Reddy, India.*
Omeprazole (p. 1867·2); sodium bicarbonate (p. 1781·1).

Omezalin *Ferakon, Gr.*
Omeprazole (p. 1867·2).

Omez-D *Reddy, India; Reddy, Ukr.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia; gastroparesis; peptic ulcer.

Omezelis *Biocodex, Fr.*
Crataegus (p. 2488·1); melissa (p. 2552·3); calcium (p. 1783·1); magnesium (p. 1786·3).
Nervous disorders; sleep disorders.

Omez-FF *Reddy, India.*
Omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omezol *Alembic, India; Standard Chem, Malaysia; Mylan, NZ; Mepha, Switz.; Standard Chem & Pharm, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; ulcerative oesophagitis; acid aspiration.

Standard, Singapore.
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omezolan *Grunenthal, Port.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Omezole *Psyco Remedies, India; Hovid, Malaysia; Hovid, Singapore; Millimed, Thai.*
Omeprazole (p. 1867·2).
Gastric hypersecretory disorders; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omezolon *Hipolabor, Braz.*
Omeprazole (p. 1867·2).

Omezul *Roemmers-Klinos, Venez.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omfact *Medico, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omfact-D *Medico, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

OM3flex *Isodisnatura, Fr.†*
Fish oil (p. 1460·1); devil's claw root (p. 42·3); meadowsweet (p. 2550·2); zinc sulfate (p. 2126·2).
Joint disorders.

OMG 3 *Nutrilab, Arg.*
Omega-3 (p. 1460·1).
Dietary supplement.

Omibact *Osper, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Omibact-TZ *Osper, India.*
Ciprofloxacin hydrochloride (p. 261·2); tinidazole (p. 949·2).

Omibase-D *Arunabh, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omic *Astellas, Belg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omicap *Micro, India; Micro, Singapore; Micro, Thai.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omicas *Casca, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omicas-D *Casca, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omic-D *Mediez, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omicef *Sel-J, Philipp.*
Cefdinir (p. 238·3).
Bacterial infections.

Omicite *Torrent, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Omicohol A *Omicron, Arg.*
⊗Alcohol (p. 1733·1); aloe vera (p. 1693·2).

Omicool *Invision, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omicool-D *Invision, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omicral *Medico Uno, Hung.*
Itraconazole (p. 583·3).
Fungal infections.

Omicur *Morningside, UK.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Omida comprimes homeopathiques pour la gorge *Omida, Switz.*
Ailanthus glandulosa; carbo vegetabilis (p. 1537·3); ferrum phosphoricum (p. 2077·1); selenium (p. 2086·3).
Homoeopathic preparation.

Omida Gel Antirhumatismal *Omida, Switz.*
Rhus toxicodendron (p. 2603·3); ledum (p. 2550·1); symphytum (p. 2484·2).
Homoeopathic preparation.

Omida Rubiderm *Omida, Switz.*
Mahonia aquifolium (p. 2577·1).
Homoeopathic preparation.

Omidec *Daksh, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omidec-ES *Daksh, India.*
Domperidone (p. 1838·1); esomeprazole (p. 1841·1).

Omidip *Indu, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omidom *Mankind, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omidrox *Osper, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Omifin *Sanofi-Aventis, Mex.; Effik, Spain.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Omiflu *CCM, Malaysia.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Omiflux *Micro, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omig *Rass, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omig-DM *Rass, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omilcal *Franco-Indian, India.*
Chewable tablets: Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).
Calcium deficiency; osteoporosis.

Franco-Indian, India.
Oral suspension: Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1); calcium lactate (p. 1784·1); vitamin B_{12} (p. 2107·2).
Calcium deficiency; osteoporosis.

Omilee *Wintech, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omilee-D *Wintech, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omilipis *Richmond, Arg.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Omiloc *Hexal, S.Afr.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ominax *Mapra, India.*
Cefotaxime (p. 244·1).
Bacterial infections.

Omind *Indoco, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ominil *Laborate, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Omipix *Biopharm, Rus.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omipro *Jelfa, Hung.; Jelfa, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omipure *Mankind, India.*
Esomeprazole (p. 1841·1).
Oesophagitis; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omiryl *Erfar, Gr.*
Sulpiride (p. 1107·3).

Omisafe *Innovative, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Omistat *AGIPS, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Omit *Finecure, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Omitive *Sanify, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omitive-D *Sanify, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omitop *Ultramark, India.*
Domperidone (p. 1838·1); omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omitop-DM *Ultramark, India.*
Domperidone (p. 1838·1); omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omitox *Shreya, Rus.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omix *Astellas, Fr.; Astellas, Switz.; Tekhnolog, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omizac *Torrent, India; Torrent, Philipp.; Torrent, Rus.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omizol *Blossoms, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omizol-D *Blossoms, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

OM3junior *Isodisnatura, Fr.†*
Fish oil (p. 1460·1); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Dietary supplement.

Omkair *PDC, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omkair-D *PDC, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omlar-CV *Stellar, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Omlek *Unique, Philipp.; Unique, Thai.*
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omlink *Lincoln, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omlink-D *Lincoln, India.*
Domperidone hydrochloride (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omlo *Globus, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omlo-D *Globus, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ommac *McNeil & Argus, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ommac Plus *McNeil & Argus, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

OM3memory *Isodisnatura, Fr.†*
Fish oil (p. 1460·1); curcuma longa; ginkgo biloba (p. 2512·3).
Dietary supplement for memory impairment.

Ommunal *Nycomed, Arg.; Angelini, Ital.; Leti, Venez.*
Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae; Klebsiella ozaenae; Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Moraxella catarrhalis.
Respiratory-tract infections.

Omna One *Abbott, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Omnacefpo *Abbott, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Omnacortil *Macleods, India.*
Cream: ⊗Methylprednisolone (p. 1642·2).
Skin disorders.

Macleods, India.
Dispersible tablets; suspension: ⊗Prednisolone (p. 1645·2).
Corticosteroid.

Omnadren *Jelfa, Pol.*
⊗Testosterone phenylpropionate (p. 2305·2); testosterone propionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism; breast cancer; endometrial cancer.

Jelfa, Rus.; Jelfa, Ukr.
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone caproate (p. 2305·1); testosterone isocaproate (p. 2305·2).
Male infertility; testosterone deficiency; osteoporosis; breast cancer; ovarian cancer; dysfunctional uterine bleeding; endometriosis; uterine fibroids; premenstrual syndrome; menopausal disorders; female virilization; male hypogonadism; prostatitis.

Omnalio *Estedi, Spain.†*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; insomnia; alcohol withdrawal syndrome; skeletal muscle spasm.

Omnapil *Psychotropics, India.*
Cefixime (p. 240·3).
Bacterial infections.

Omnapil-CV *Psychotropics, India.*
Cefixime (p. 240·3); potassium clavulanate (p. 268·3).
Bacterial infections.

Omnaris *Nycomed, Arg.; Nycomed, Austral.; Nycomed, Braz.; Nycomed, Canad.; Nycomed, Hong Kong; Nycomed, Malaysia; Nycomed, Mex.; Nycomed, Philipp.; Sepracor, USA.*
⊗Ciclesonide (p. 1626·3).
Allergic rhinitis; sinusitis; nasal polyps.

Omnatax *Piramal, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Omnatax-CV *Abbott, India.*
Cefixime (p. 240·3); clavulanic acid (p. 268·3).
Bacterial infections.

Omnatax-O *Abbott, India.*
Cefixime (p. 240·3).
Bacterial infections.

Omnazide *Innovative, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Omneo *Nutricia, Port.†*
A range of infant feeds.
Gastrointestinal disorders.

Omnexel *Astellas, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omni
Note: this name may be used for preparations of different composition.
Ciplo, India.
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Foodscience, Canad.†
Vitamins; minerals.

Omnibionta *Merck, Austria.†*
Vitamins.

Omnibus *Polychronus, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Omnic *Eurolab, Arg.; Eurofarma, Braz.; Labomed, Chile; Astellas, Cz.; Astellas, Denm.; Astellas, Fin.; Astellas, Ger.; Astellas, Gr.; Astellas, Hung.; Astellas, Irl.; Astellas, Israel; Astellas, Ital.; Astellas, Neth.; Astellas, Norw.; Astellas,*

Pol.; Astellas, Port.; Astellas, Rus.; Astellas, Spain; Astellas, Ukr.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omnicare Daily Cleaner *Allergan, Austral.†*
Cleaning solution for soft contact lenses.
Allergan, NZ.†
Cleansing solution for soft contact lenses.

Omnicef
Note: this name may be used for preparations of different composition.
Astellas, Indon.; Janssen-Cilag, Mex.; Pfizer, Thai.; Abbott, USA.
Cefdinir (p. 238·3).
Bacterial infections.

Aristo, India.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Omnicol *Omnia, Swed.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Omniderm *Face, Ital.*
⊗Fluocinolone acetonide (p. 1636·1).
Inflammatory skin disorders.

Omniflora *Novartis Consumer, Austria.*
Lactobacillus gasseri (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3).
Gastrointestinal disorders.

Omniflora Akut *Novartis Consumer, Ger.†*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea.

Omniflora N *Novartis Consumer, Ger.†*
Lactobacillus gasseri (p. 2596·3); *Bifidobacterium longum* (p. 2596·3).
Gastrointestinal disorders.

Omniflox
Note: this name may be used for preparations of different composition.
Embiotic, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Omniflox-CT *Embiotic, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Omnigel *Cipla, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1); linseed oil (p. 2544·2).

Omnigen Forte *Emar, India.*
Vitamins; minerals; trace elements; amino acids; ginseng (p. 2513·3).

Omnigeriat *Fabra, Arg.*
Cyproterone acetate (p. 2261·2).

OmniHIB *SmithKline Beecham, USA.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (p. 2387·2).
Active immunisation.

Omnihist LA *WE, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract symptoms.

Omnikain *Jayson, Ukr.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Omnilax *Omnia, Swed.*
Macrogol (p. 2547·3); sorbitol (p. 2092·1).
Constipation.

Omnilite *Holland Pharma, Neth.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); chamomilla (p. 2474·1); conium maculatum (p. 2524·3); dulcamara (p. 2497·3); echinacea purpurea (p. 2498·1); hamamelis virginiana (p. 2523·3); hydrastis canadensis (p. 2528·1); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Omnilup *Lupin, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omnimax *Intas, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omnimune *Pediapharma, Philipp.*
Omega-3 fatty acids (p. 1460·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc gluconate (p. 2126·2); sodium selenite (p. 2087·1).
Vitamin and mineral supplement.

Omnipaque *HLB, Arg.; GE Healthcare, Austral.; Bayer, Austria; GE Healthcare, Belg.; GE Healthcare, Canad.; General Electric, Chile; GE Healthcare, China; GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Fr.; Bayer, Ger.; GE Healthcare, Gr.; Amersham, Hung.; GE Healthcare, Irl.; GE Healthcare, Israel; GE Healthcare, Ital.; GE Healthcare, Neth.; GE Healthcare, Norw.; GE Healthcare, NZ; Satis, Port.; GE Healthcare, Rus.; GE Healthcare, Spain; GE Healthcare, Swed.; Bayer, Switz.†; Yurtoglu, Turk.; GE Healthcare, UK; Nycomed, Ukr.; GE Healthcare, USA.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Omnipen
Note: this name may be used for preparations of different composition.
Pharmed, India.
Ampicillin (p. 218·2); cloxacillin (p. 274·3).

Sandoz, Mex.
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Omniplasma *Octapharma, Neth.*
Plasma (p. 1158·2).
Haemorrhagic disorders.

Omnipred *Alcon, USA.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Omnirom *Cipla, India.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Omniscan *HLB, Arg.; GE Healthcare, Austral.; GE Healthcare, Austria; GE Healthcare, Belg.; GE Healthcare, Canad.; General Electric, Chile; GE Healthcare, China; GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Ger.; GE Healthcare, Gr.; GE Healthcare, Hung.; GE Healthcare, Irl.; Nycomed, Israel; GE Healthcare, Ital.; Daiichi Sankyo, Jpn; GE Healthcare, Neth.; GE Healthcare, Norw.; GE Healthcare, NZ; Satis, Port.; GE Healthcare, Rus.; GE Healthcare, Spain; GE Healthcare, Swed.; GE Healthcare, Switz.; Yurtoglu, Turk.; GE Healthcare, UK; Nycomed, Ukr.; Sanofi Winthrop, USA.*
Gadodiamide (p. 1585·2).
Contrast medium for magnetic resonance imaging.

Omni-Sorb *OmniVision, Ger.*
Sodium chloride (p. 1795·1).
Corneal disorders.

Omnistad *Stada, Denm.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omnitan H *Macleods, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Omnitel *Pharmed, India.*
Albendazole (p. 149·1).
Worm infections.

Omnitest *Braun, Austral.*
Test for glucose in blood (p. 2516·3).

Omnitor *Cipla, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Omnitor-EZ *Cipla, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Omnitrast *Bayer, Spain.†*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Omnitrope *Sandoz, Austral.; Sandoz, Austria; Sandoz, Belg.; Sandoz, Braz.; Sandoz, Canad.; Sandoz, Cz.; Sandoz, Denm.; Sandoz, Fr.; Sandoz, Ger.; Sandoz, Irl.; Sandoz, Ital.; Sandoz, Neth.; Sandoz, Norw.; Sandoz, Pol.; Sandoz, Port.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Switz.; Sandoz, UK; Sandoz, USA.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; growth disorders in renal failure; Turner's syndrome; Prader-Willi syndrome; short children born small for gestational age.

Omnitus
Note: this name may be used for preparations of different composition.
Hemofarm, Rus.
Butamirate citrate (p. 1657·3).
Cough.

Pharmed, India.
Dextromethorphan (p. 1660·1).
Cough.

Omnivit with Minerals *Allied, S.Afr.†*
Vitamins; minerals.

Omnivox *ACME, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Omnixim *Cipla, India.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Omnopon *Bodene, S.Afr.*
Papaveretum (p. 112·2) (containing morphine hydrochloride, codeine hydrochloride, and papaverine hydrochloride).
Pain.

Moscow Endocrine, Rus.
Mixed opium alkaloids (p. 112·2) (codeine, morphine hydrochloride, noscapine, papaverine hydrochloride, thebaine).
Pain; smooth muscle spasm.

Omodol *Solitaire, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Omolin *Gedeon Richter, Cz.†; Bioethical, Ital.; Chemo, Neth.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Omontys *Affymax, USA.*
⊗Peginesatide acetate (p. 1158·1).
Anaemia in renal dialysis.

Omoprel *Belfar, Braz.*
Omeprazole (p. 1867·2).

Omoquis *Chemo, Neth.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omore *Biomax, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omore-D *Biomax, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omotrip *Solitaire, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Omoxitin *USV, India.*
2 Tablets, amoxicillin (p. 216·2); 2 tablets, omeprazole (p. 1867·2); 2 tablets, tinidazole (p. 949·2).

O-Moxy *Zubit, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

O-Moxy-CL *Zubit, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

O-Moxy-DC *Zubit, India.*
Amoxicillin (p. 216·2); dicloxacillin (p. 286·1).

Omozin *Rubio, Spain.†*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ompep *Chemo-Drugs, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ompirol *Biochemix, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ompli *Medial, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ompli-D *Medial, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ompranyt *Bial, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Ompraz *Laksun, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ompraz-D *Laksun, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omprest-D *Ester, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omracap *Nectar, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omracap-DM *Nectar, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omr-IgG *IFET (ΙΦΕΤ), Gr.; Omrix, Israel.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; immune thrombocytopenia; passive immunisation; Kawasaki disease; Guillain-Barré syndrome; bone marrow transplantation.

Omri-Hep-B *Omrix, Israel.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Omriz *Ritz, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omriz-D *Ritz, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omron *Gujarat Terce, India.*
Iron sucrose (p. 2078·1).

Omron Plus *Gujarat Terce, India.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); iron (p. 2073·1).

Omsal *Richter, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omsil *Pliva, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omsulosin *Ranbaxy, Rus.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Omsy *Indu, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omtec *Technica, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omuro *Sanfer, Mex.*
Otilonium bromide (p. 2578·2).
Irritable bowel syndrome.

Omven *Vensat, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omven-D *Vensat, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Omybal *Keshav, India.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Omycet *Collins, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

OMZ *Ferron, Indon.; Schwarz, Philipp.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Omzee *Zenon, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Omzee-D *Zenon, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Onabet *Glenmark, India.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections; seborrhoeic dermatitis; vaginal candidiasis.

Onadrine *Sunward, Singapore.*
Orphenadrine citrate (p. 909·2).
Skeletal muscle spasm; parkinsonism.

Onadron *Yurtoglu, Turk.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Onafen *Zota, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

Zota, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Onafen-CZ *Zota, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Onafen-Gel *Zota, India.*
Diclofenac diethylamine (p. 48·3); diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Onagris *Sperko, Ukr.*
Soya bean (p. 2092·3).
Menopausal disorders.

Onaka *Max Farma, Ital.*
Pidotimod (p. 2590·2).
Immunostimulant.

Onalide-MD *Zota, India.*
Nimesulide (p. 101·3).
Pain.

Onalide-MR *Zota, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Onamox *Zota, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Onamox-CL *Zota, India.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Onancen *Ultra, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Onapan *Alpharma, Mex.†*
Diazepam (p. 1063·2).

Onapract *Zota, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Onastrone *Zota, India.*
Progesterone (p. 2300·2).
Amenorrhoea; dysfunctional uterine bleeding; recurrent miscarriage.

Onat *Zota, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting in pregnancy.

Onazole *Zota, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Onazole-DP *Zota, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Onazole-RD *Zota, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Onazyme *Zota, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Onbact *Plus, India.*
Ceftriaxone (p. 253·3); sulbactam sodium (p. 360·1).

Onbit *Cubit, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onbrez *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Jpn; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.*
⊗Indacaterol maleate (p. 1211·2).
Obstructive airways disease.

Onbrize *Novartis, Arg.*
⊗Indacaterol maleate (p. 1211·2).
Obstructive airways disease.

Oncare *Medico, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Oncaspar *Filaxis, Arg.; Medac, Ger.; IFET (ΙΦΕΤ), Gr.; Medac, Pol.; Medac, Rus.; Sigma-Tau, USA.*
Pegaspargase (p. 743·3).
Acute leukaemias.

Once *Shreshtha, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Once a Day *Purity Life, Canad.*
Vitamins; minerals.

Once Daily Mens Multi *Cenovis, Austral.*
Vitamins; minerals; trace elements; citrus bioflavonoids (p. 2505·2); lysine hydrochloride (p. 2079·3); fish oil (p. 1460·1).
Dietary supplement.

Once Daily 50+ Multi *Cenovis, Austral.*
Vitamins; minerals; trace elements; citrus bioflavonoids (p. 2505·2); linseed oil (p. 2544·2).
Dietary supplement.

Once Daily Womens Multi *Cenovis, Austral.*
Vitamins; minerals; trace elements; citrus bioflavonoids (p. 2505·2) lysine hydrochloride (p. 2079·3); evening primrose oil (p. 2502·2).
Dietary supplement.

Onceair *Abdi, Turk.*
Montelukast sodium (p. 1214·3).
Asthma.

Once-D *Shreshtha, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Oncef *Plus, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Oncet
Note: this name may be used for preparations of different composition.
Medley, India.
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Wakefield, USA.
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Cough and cold symptoms.

Oncibel *Belfar, Braz.*
⊗Triamcinolone (p. 1648·3); neomycin (p. 329·3); gramicidin (p. 308·3); nystatin (p. 590·3).

Oncicrem-A *Geolab, Braz.*
⊗Triamcinolone acetonide (p. 1649·1).

Oncileg *Legrand, Braz.*
⊗Triamcinolone (p. 1648·3); neomycin (p. 329·3); gramicidin (p. 308·3); nystatin (p. 590·3).

Oncileg A *Legrand, Braz.*
⊗Triamcinolone (p. 1648·3).

Onciplus *Prodotti, Braz.†*
⊗Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Onco-BCG *Serum Institute, India; Biomed, Ukr.*
A BCG vaccine (p. 2378·1).
Bladder cancer.

Oncobine *Meizler, Braz.; Cipla, Cz.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Oncobleo *Sun, India.*
Bleomycin (p. 749·3).
Malignant neoplasms.

Oncobleocin *Biotoscana, Chile.†*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Oncocarb *Biotoscana, Chile.†*
Carboplatin (p. 759·1).
Malignant neoplasms.

Onco-Carbide *Teofarma, Ital.*
Hydroxycarbamide (p. 803·1).
Chronic myeloid leukaemia.

Oncocarbil *LKM, Arg.*
Dacarbazine (p. 776·1).
Malignant neoplasms.

Oncocarbin
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Mitoxantrone (p. 833·1).

Sun, India.
Carboplatin (p. 759·1).
Ovarian cancer.

Oncocin *Chandra Bhagat, India.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Oncocristin *Sun, India.*
Vincristine (p. 882·3).
Malignant neoplasms.

Kocak, Turk.†
Vincristine sulfate (p. 882·3).

Oncodac *United Biotech, India.*
Dacarbazine (p. 776·1).
Metastatic melanoma; Hodgkin's disease; soft-tissue sarcoma.

Oncodaunotec *Biotoscana, Chile.†*
Daunorubicin hydrochloride (p. 778·3).
Leukaemias.

Oncoden *Torrent, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Oncodocel *Zodiac, Braz.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Oncodox *Cipla, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Meizler, Braz.
Doxorubicin hydrochloride (p. 783·1).

Oncodria *Sun, India.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Oncoemet *Biotoscana, Chile.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

OncoFem *Helvetia, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Oncofluor *United Biotech, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Oncofolic *Medac, Ger.*
Sodium folinate (p. 2067·1).
Prevention of methotrexate toxicity; adjunct to fluorouracil in colorectal cancer.

Oncofu *Gobbi, Arg.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Oncogem *Cipla, India.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Oncoginase *Chandra Bhagat, India.*
Asparaginase (p. 743·3).
Acute lymphoblastic leukaemia.

Oncolet *Biochem, India.*
⊗Letrozole (p. 817·1).
Malignant neoplasms.

Oncomide *Khandelwal, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; bone marrow transplantation.

Oncomox *Sun, India.*
⊗Tamoxifen (p. 860·2).
Breast cancer; anovulatory infertility.

Oncon *Zubit, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onconase *United Biotech, India.*
Asparaginase (p. 743·3).
Acute lymphoblastic leukaemia.

Oncophage *Agenus, Rus.*
Vitespen (p. 887·1).

Oncophos *Cadila, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Oncoplat *Medicus, Gr.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Oncoplatin
Note: this name may be used for preparations of different composition.
Bergamo, Braz.
Carboplatin (p. 759·1).
Malignant neoplasms.

Sun, India; Kocak, Turk.†
Cisplatin (p. 766·1).
Ovarian cancer; testicular cancer; bladder cancer.

Oncoplaxel *Biotoscana, Chile.†*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Oncoplus *GP, Arg.*
Gemcitabine (p. 801·2).
Malignant neoplasms.

Oncoril *Naprod, Philipp.*
Gemcitabine hydrochloride (p. 801·2).
Pancreatic cancer; non-small cell lung cancer.

Oncosal *Inibsa, Spain.†*
Flutamide (p. 798·2).
Prostatic cancer.

OncoSeeds *Amersham, Austral.†*
Iodine-125 (p. 2225·2) titanium capsules.
Prostatic cancer.

Oncosid *United Biotech, India.*
Etoposide (p. 790·2).
Testicular cancer; small cell lung cancer.

Oncosil *Fako, Turk.*
Fluorouracil (p. 795·2).

Oncostin *Cipla, Philipp.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Oncotam *Zydus, India.*
⊗Tamoxifen (p. 860·2).
Breast cancer; anovulatory infertility.

Oncotamox *Biotoscana, Chile.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Oncotar *United Biotech, India.*
Cytarabine (p. 774·1).
Acute leukaemias; leukaemic meningitis.

OncoTax *Helvetia, Cz.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Oncotaxel
Note: this name may be used for preparations of different composition.
Actavis, Austral.
Docetaxel (p. 780·3).
Malignant neoplasms.

Sun, India; Sun, Thai.†
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Oncotaxen *Sambrook, Gr.*
Paclitaxel (p. 839·3).

Oncothal *Cadila, India.*
Thalidomide (p. 867·3).
Erythema nodosum leprosum; multiple myeloma.

OncoTICE *MSD, Austral.; Organon, Austria; Organon, Belg.; Merck, Canad.; Organon, Fin.†; Apogepha, Ger.†; Organon (Οργανον), Gr.; Infar, India; Organon, Israel; Organon, Ital.; Organon, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Schering-Plough, Pol.; Organon, Port.; Organon, Spain; MSD, Swed.; MSD, Switz.; Organon, Turk.; Organon, UK; Organon, Venez.*
A BCG vaccine (p. 2378·1).
Bladder and urethral cancer.

Oncotin *Cipla, Philipp.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Oncotrex *Sun, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

Oncotron *Sun, India; Kocak, Turk.*
Mitoxantrone (p. 833·1).
Malignant neoplasms.

Oncotrone *Baxter, Rus.*
Mitoxantrone (p. 833·1).
Malignant neoplasms.

Oncouracil *Kocak, Turk.†*
Fluorouracil (p. 795·2).

Oncourcil *Sun, India.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Oncovin *Aspen, Austral.†; Stada, Austria; Eurogenerics, Belg.†; ABL, Braz.; Pharmacodane, Denm.; Pharmacodane, Fin.; EG, Fr.; Lilly, Gr.; Sandoz, Mex.; Stada, Swed.; Teva, Switz.; Lilly, Turk.; Genus, UK; Lilly, USA.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms; immune thrombocytopenia.

Oncovit *Feron, India.*
Vitamins; trace elements; lycopene (p. 2546·2).

Oncovite *Mission Pharmacal, USA.*
Vitamins; zinc (p. 2126·1).

Oncoxan *Chandra Bhagat, India.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Oncoxin *Tobbest Busindo, Indon.*
Vitamins; minerals; green tea (p. 2648·2); cinnamon (p. 2479·2); amino acids.
Dietary supplement.

OncoZol *Helvetia, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Onctose *Merck Medication Familiale, Fr.*
Diphenhydramine metilsulfate (p. 626·1); lidocaine hydrochloride (p. 1988·2).
Pruritus.

Onctose a l'Hydrocortisone *Denolin, Belg.†*
⊗Hydrocortisone acetate (p. 1640·1); diphenhydramine metilsulfate (p. 626·1); lidocaine hydrochloride (p. 1988·2).
Pruritus; insect stings; cutaneous hypersensitivity Reactions.

Onctose Hydrocortisone *Merck Medication Familiale, Fr.*
⊗Diphenhydramine metilsulfate (p. 626·1); lidocaine hydrochloride (p. 1988·2); hydrocortisone acetate (p. 1640·1).
Pruritus.

Ond *Bestochem, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onda *Vianex (Βιανεξ), Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondace *Cosme, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondagen *Generics, Hung.; Generics, Pol.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondai *Sinkhai, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondal *Silanes, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

OndaLEK *Sandoz, Pol.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondameton *Medicina, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondanaccord *Arrow, NZ.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondansetran *Gland, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondantril *Sigma, Braz.*
Ondansetron (p. 1872·1).

Ondanz *Elder, India.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondar *Zota, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondaren *Pharmanel, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondarom *Allenge, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondas *Biosans, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondaseprol *Novendia, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Ondasol *Ufavita, Rus.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondatab *Arrow, Irl.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondavell *Novell, Indon.; Novell, Thai.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondavom *Global, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondax
Note: this name may be used for preparations of different composition.
Acekinetic, India.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Saval, Chile.
Cisapride (p. 1831·3).
Gastro-oesophageal reflux.

Ondaz *Sandoz, Austral.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondem *Alkem, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondemet *Alliance, UK.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Zentiva, Cz.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondemet-MD *Invision, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondensan *GL Pharma, Austria.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.

Onderm *Obsurge, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).

Ondet *Intas, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondeton *Biospray, Gr.*
Ondansetron hydrochloride (p. 1872·1).

Ondigo *Lancer, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onditron *Wockhardt, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondocil *H & Care, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondocos *Symbiosis, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondolen *Menarini, Port.*
⊗Hydrochlorothiazide (p. 1403·2); spironolactone (p. 1499·3).
Oedema; ascites; hypertension; nephrotic syndrome.

Ondorise *Sunrise, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondosia *Willow, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondosym *Symbiosis, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondot *Siomond, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ond-R *Bestochem, India.*
2 Tablets, ondansetron (p. 1872·1); 1 tablet, rabeprazole (p. 1881·1).
Nausea and vomiting; peptic ulcer; gastro-oesophageal reflux.

Ondran *Pinewood, Irl.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ondrea *Cinerea, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondřejova Mast *Herbacos Recordati, Cz.*
Salicylic acid (p. 1719·1); lavender oil (p. 2541·1).
Skin disorders; ulcers.

Ondron *Amrit, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondrovit *Alna, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ondrox *LSI, USA.*
Vitamins; minerals; amino acids.

Onduarp *Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Neth.*
Telmisartan (p. 1509·3); amlodipine besilate (p. 1304·1).
Hypertension.

O-NE *Cachet, India.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin E (p. 2119·1).
Cardiovascular risk reduction.

One *Natural Life, Arg.*
Vitamins; minerals.

One A Day *Bayer, Braz.; Bayer, USA.*
Vitamins; with or without minerals.

Bayer Consumer, Canad.
A range of vitamin and mineral preparations.

Bayer, Turk.
Vitamins; minerals.

One A Day Energy *Bayer Consumer, Canad.*
Vitamins; minerals.

One A Day Men's Health Formula *Bayer, USA.*
Vitamins; minerals; lycopene (p. 2546·2).
Dietary supplement.

One A Day Vitacraves *Bayer, USA.*
Vitamins; iodine (p. 2336·3); zinc (p. 2126·1); choline (p. 2055·2); inositol (p. 2533·2).
Dietary supplement.

One All Caps *Taurus, India.*
Withania somnifera (p. 2450·2).

One Alpha C *Ranbaxy, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

One For Baby Bums *PDN, Hong Kong.*
Barrier preparation.
Nappy rash.

One BE *Lupin, India.*
Withania somnifera (p. 2450·2).

One Can *Wallace, India.*
Fluconazole (p. 578·2).
Fungal infections.

One Clav *Lupin, India.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

One Daily Adults 50+ *21st Century, USA.*
Vitamins; minerals; trace elements.
Dietary supplement.

One Dia *Q Check, India.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).

One And Only *Nutri-Chem, Canad.†*
Vitamins; minerals.

One Step Foaming Antiseptic Wash *Belvedere, Canad.*
Benzalkonium chloride (p. 1737·1).

One Step Foaming Hand Sanitizer *Belvedere, Canad.*
Benzalkonium chloride (p. 1737·1).
Hand disinfection.

One Step Hand Sanitizer *Belvedere, Canad.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

One Touch
Note: this name may be used for preparations of different composition.
ABJ, Canad.
Benzocaine (p. 1980·2); tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Johnson & Johnson Medical, Arg.; Lifescan, Canad.†; Lifescan, Fr.; Lifescan, Irl.†; Lifescan, Ital.; Lifescan, Port.; Lifescan, USA.
Test for glucose in blood (p. 2516·3).

One-A-Day Kids Scooby-Doo *Bayer, USA.*
Vitamins; minerals; trace elements.

One-A-Day Men's *Bayer, Hong Kong.†*
Calcium (p. 1783·1); vitamins.

One-A-Day Special Wellness Formula for Men *Bayer, Philipp.*
Vitamins; minerals.
Nutritional supplement.

One-A-Day Special Wellness Formula for Women *Bayer, Philipp.*
Vitamins; minerals.
Nutritional supplement.

One-A-Day WeightSmart *Bayer, USA.*
Vitamins; minerals; trace elements.

One-A-Day-Men *Bayer, Singapore.*
Vitamins; minerals.

One-A-Day-Women *Bayer, Singapore.*
Vitamins; minerals.

Oneaid *BMW, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

One-Alfa *Teijin, Rus.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia; osteoporosis.

Onealfa *Teijin, Jpn.*
Alfacalcidol (p. 2112·3).
Osteoporosis; disorders of vitamin D metabolism.

One-Alpha *Leo, Canad.; Europharma, Denm.; Leo (Λεο), Gr.; Leo, Hong Kong; Ranbaxy, India; Darya-Varia, Indon.; Leo, Indon.; Leo, Irl.; Leo, Israel; Leo, Malaysia; CSL, NZ; Leo, Philipp.; Leo, Pol.; Adcock Ingram Critical Care, S.Afr.; Leo, Singapore†; Leo, Thai.; Abdi, Turk.; Leo, UK.*
Alfacalcidol (p. 2112·3).
Hypoparathyroidism; hyperparathyroidism; hypophosphataemia; rickets; osteomalacia; hypocalcaemia; osteoporosis; renal osteodystrophy; vitamin D deficiency disorders; neonatal hypocalcaemia.

Oned *Health Care, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

OneDuro *Janssen, Jpn.*
⊗Fentanyl (p. 60·1).
Pain.

Onefin *LKM, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Oneflex *One Pharma, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Onelacne *DNR, Arg.*
Amino acids; vitamin B substances (p. 2102·3); sulfurated peptides (p. 1721·1).
Acne.

Onelaxant-R *Apotex, Philipp.*
Baclofen (p. 2014·3).
Muscle spasticity.

Onemer *Pisa, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Onemin *Apotex, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Onerve *Shield, India.*
Thioctic acid (p. 2629·1); gamolenic acid (p. 2509·2); mecobalamin (p. 2108·1); pyridoxal phosphate (p. 2105·3).

One-Six-Twelve *Cathay, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

M & H, Thai.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Metabolic disorders; neuritis; neuralgias.

Onespar *Euphoric, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Onest *Ester, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

One-Tablet-Daily *Goldline, USA.*
Vitamins; with or without minerals.

Onetazid *One Pharma, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Onetic *Fahrenheit, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

One-Trex *Burapha, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Onetrim *One Pharma, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

One-Up *Torrent, India.*
Vitamins; minerals; trace elements; lutein (p. 2079·2); silicon dioxide (p. 2208·3).

One-Up Gold *Torrent, India.*
Vitamins.

Onevit *One Pharma, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2).
Nutritional supplement.

Onexacin *Apotex, Philipp.*
Ofloxacin (p. 334·3).
Chlamydial infection; mycobacterial infection.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Onexid *Korea United, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections.

Onexmol *Best, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Oneza *KRKA, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Onfi *Lundbeck, USA.*
Clobazam (p. 518·2).
Lennox-Gastaut syndrome.

Onfor *Fada, Arg.*
Nalbuphine (p. 97·3).
Pain.

Ongecin *Jodas, Rus.*
Gemcitabine hydrochloride (p. 801·2).
Non-small cell lung cancer; pancreatic cancer.

Ongicil *Mavi, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Onglinex *Medinfar, Port.*
Cystine (p. 2059·1); pyridoxine hydrochloride (p. 2105·3).
Hair and nail disorders.

Ongliza *AstraZeneca, Ukr.*
Saxagliptin hydrochloride (p. 499·2).
Diabetes mellitus.

Onglyza *BMS, Arg.; AstraZeneca, Austral.; BMS, Austral.; AstraZeneca, Austria; BMS, Austria; AstraZeneca, Belg.; BMS, Braz.; AstraZeneca, Canad.; BMS, Canad.; BMS, Chile; BMS, China; BMS, Cz.; BMS, Denm.; BMS, Fr.; AstraZeneca, Ger.; BMS, Ger.; AstraZeneca, Gr.; BMS, Gr.; BMS, Hong Kong; AstraZeneca, Hung.; BMS, Hung.; BMS, India; AstraZeneca, Israel; BMS, Ital.; Kyowa Hakko Kirin, Jpn; AstraZeneca, Malaysia; BMS, Mex.; AstraZeneca, Neth.; BMS, Neth.; BMS, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, Singapore; BMS, Spain; BMS, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS, USA.*
Saxagliptin hydrochloride (p. 499·2).
Diabetes mellitus.

Ongone *Hiral, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onguent aux herbes Keller *UB, Switz.*
Arnica (p. 2447·2); calendula (p. 2465·2); cineole (p. 2479·1); benzoic acid (p. 1738·2).
Wounds.

Onguent Hemorrhoidal *Confab, Canad.†*
Pramocaine hydrochloride (p. 1993·3); zinc sulfate (p. 2126·2).
Haemorrhoids.

Onguent nasal Rüedi *Spirig, Switz.*
Mint oil (p. 2560·1); camphor oil (p. 2466·2).
Nasal dryness.

Onguent Vaporisant *Confab, Canad.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Upper respiratory-tract congestion; musculoskeletal pain.

Onic *Nicholas, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Onicef *Sel-J, Philipp.*
Cefdinir (p. 238·3).
Bacterial infections.

Onicit *Schering-Plough, Braz.; Schering-Plough, Chile; Schering-Plough, Mex.; Pfizer, S.Afr.; Schering-Plough, Venez.*
Palonosetron hydrochloride (p. 1875·1).
Nausea and vomiting.

Onicozol *Reig Jofre, Spain.†*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Onidaz *Medley, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Oniflox *Acme, India.*
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Diarrhoea; dysentery.

Onim-MD *Shreya, India.*
Nimesulide betadex (p. 101·3).
Pain.

Onirema *Biotech, Venez.*
Nitrazepam (p. 1089·1).
Insomnia; premedication.

Onirex *Orion, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Oniz
Note: this name may be used for preparations of different composition.
Birz, India.
Ondansetron (p. 1872·1).
Nausea and vomiting.
Stadmed, India.
Ornidazole (p. 943·1).
Trichomoniasis; anaerobic bacterial infections; amoebiasis; giardiasis.

Onizef *Taisheng, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Oniz-O *Stadmed, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Onkam *Kamron, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onkmoeck *Stada, Cz.; Pharmacodane, Denm.*
Temozolomide (p. 865·2).
Malignant glioma.

Onko BCG *Biomed Lublin, Pol.*
A BCG vaccine (p. 2378·1).
Bladder cancer.

Onkocristin *Onkoworks, Ger.†*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Onkofluor *Hospira, Ger.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Onkomet *Klab, Thai.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Onkostatil *Microsules, Arg.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Onkotrone *Baxter, Austral.; Baxter Oncology, Cz.†; Baxter Oncology, Ger.; Baxter, Hung.; Baxter, Ital.; Baxter, NZ; Baxter, Philipp.†; Baxter, UK.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Onkovertin *Braun, Singapore; Braun, Thai.†*
⊗Dextran 40 (p. 1138·1) in sodium chloride or glucose.
Plasma volume expansion; thromboembolism prophylaxis; shock.

Onlex *Lexus, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onli-2 *Kopran, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Onlipeg *Promefarm, Ital.*
Macrogol 4000 (p. 2547·3).
Constipation.

Only Minerals *Sisu, Canad.†*
Minerals.

Only One *Sisu, Canad.†*
Vitamins; minerals.

Onlyciti *Solitaire, India.*
Citicoline (p. 2480·1).
Head injury; cerebrovascular disorders; parkinsonism.

Onmel *Merz, USA.*
Itraconazole (p. 583·3).
Fungal infections.

Onmero *Rishab, India.*
Meropenem (p. 321·3).
Bacterial infections.

Ono *Samarth, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onoact *Ono, Jpn.*
⊗Landiolol hydrochloride (p. 1418·1).
Intra-operative tachyarrhythmias.

Onocalman *Schwarzwalder, Ger.*
Acidum nitricum (p. 2572·3).
Homoeopathic preparation.

Onofin-K *Rayere, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Onon *Ono, Jpn.*
Pranlukast (p. 1218·3).
Asthma; allergic rhinitis.

Onopordon Comp B *Weleda, UK.*
Onopordon; cowslip (p. 2596·2); hyoscyamus (p. 2530·2).
Cardiac disorders.

Onoton *Sanofi-Aventis, Mex.*
⊗Pancreatin (p. 2579·3); hemicellulase (p. 2473·1); simeticone (p. 1886·2).
Pancreatic disorders; digestive disorders; adjunct in abdominal radiography.

Onotrex *Sun, India.*
Methotrexate (p. 822·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis; Crohn's disease.

On-OZ *Oxytech, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Onprelen *Genericon, Cz.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Onquevit *Sandoz, Mex.*
Citicoline sodium (p. 2480·2).
Cerebral disorders.

Onrectal *Herbes Universelles, Canad.†*
⊗Benzocaine (p. 1980·2); bismuth subcarbonate (p. 1822·1); bismuth subgallate (p. 1822·1); hamamelis (p. 2523·3); naphazoline hydrochloride (p. 1669·3); zinc oxide (p. 1729·1).
Haemorrhoids.

Onristat *Mili, Ukr.†*
2 yellow tablets, rabeprazole (p. 1881·1); 2 white tablets, ornidazole (p. 943·1); 2 rose tablets, clarithromycin (p. 266·2).
Eradication of Helicobacter pylori.

Onriz *Ritz, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onsat *Aamorb, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onsenal *Pfizer, Austria†; Pfizer, Belg.†; Pfizer, Cz.†; Pfizer, Denm.†; Pfizer, Ger.†; Pfizer, Irl.†; Pfizer, Neth.†; Pfizer, Port.†; Pfizer, Spain†; Pfizer, Swed.†; Pfizer, UK.†*
Celecoxib (p. 36·3).
Familial adenomatous polyposis.

Onsénal *Pfizer, Fr.†*
Celecoxib (p. 36·3).
Familial adenomatous polyposis.

Onset *ATOZ, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.
Pharmedic, Philipp.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Onsetron *Arrow, Austral.; Pacific, NZ.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Onsett *Cadila, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onsia *Siam Bheasach, Thai.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.

Onsolis *Meda, Canad.†; Meda, USA.†*
⊗Fentanyl citrate (p. 60·1).
Pain.

Onspot *Plus, India.*
Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Onstal *Anthus, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onstar *Celon, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Onsudil *Jaba Recordati, Port.*
⊗Procaterol hydrochloride (p. 1219·1).
Obstructive airways disease.

Ontac *Elder, India.*
Diclofenac (p. 48·3); or diclofenac sodium (p. 48·3).
Inflammation; pain.

Ontac Plus *Elder, India.*
Chlorzoxazone (p. 2022·2).
Skeletal muscle spasm.

Ontact Forte *Elder, India.*
Chlormezanone (p. 1045·1); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Ontak *IFET (ΙΦΕΤ), Gr.; Eisai, USA.*
Denileukin diftitox (p. 780·2).
T-cell lymphoma.

Ontax *Libbs, Braz.*
Paclitaxel (p. 839·3).

Ontek *Zentis, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ontelio-L *Zenon, India.*
Levocetirizine (p. 632·3); montelukast sodium (p. 1214·3).

On-the-Spot Acne Treatment *Neutrogena, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Ontic *Corona, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ontil *Health Guard, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ontin *BMW, India.*
Tretinoin (p. 1725·2).
Acne; photodamaged skin.

Ontiz *Zytras, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onto-D *Aronex, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ontome *Epitome, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Ontop *Systopic, India.†*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Ontracel *Raam, Mex.*
Paroxetine (p. 440·3).
Depression.

Ontrax *Blausiegel, Braz.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Onufrid *Rafarm, Gr.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Onv *Sigman, India.*
Ondansetron (p. 1872·1); or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Onvin *Cadila, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Onxel *Darrow, Braz.*
Paclitaxel (p. 839·3).
Ovarian cancer.

Onxol *Ivax, Cz.†; Zenith Goldline, USA.†*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Onychomal *Almirall Hermal, Ger.*
⊗Urea (p. 1727·3).
Nail disorders.

Onychon *Zentiva, Cz.†; Leciva, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Onykoleïne *Asepta, Mon.*
Melaleuca oil (p. 2551·1).
Fungal nail infections.

Onylac *Cipla, India.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Onylaq *Galderma, Mex.*
Amorolfine hydrochloride (p. 569·1).
Fungal nail infections.

Onymax *Galderma, Ital.; Galderma, Pol.; Galderma, Switz.†*
Terbinafine hydrochloride (p. 593·3).
Fungal nail, scalp, and skin infections.
Galderma, Ger.†
Terbinafine (p. 593·3).
Fungal nail and skin infections.

Onypso *Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Switz.*
⊗Urea (p. 1727·3).
Nail thickening associated with psoriasis.

Onyric *Ferrer-Novag, Mex.*
Magnesium glutamate hydrobromide (p. 2549·1).
Attention-deficit hyperactivity disorder; sleep disorders; anxiety.

Onyster *Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Switz.*
⊗Urea (p. 1727·3).
Fungal nail infections.

Ony-Tec *Medea, Spain.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Onytec *Bailleul, Fr.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Onz *Symbiosis, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Onza *Abbott, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Onzapin *Actavis, Singapore.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Onzem *Novartis, India.*
Diltiazem (p. 1359·2).
Angina pectoris; hypertension.

Onzet *M & H, Thai.*
Azithromycin (p. 221·2).
Bacterial infections.

Onzy *Hauz, India.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Oox *Aamorb, India.*
⊗Ambroxol (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Oox-DM *Aamorb, India.*
Dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylephrine (p. 1672·2); triprolidine hydrochloride (p. 642·3).

Oox-LC *Aamorb, India.*
Ambroxol (p. 1654·3); levocetirizine (p. 632·3).

Oox-P *Aamorb, India.*
Ambroxol (p. 1654·3); dextromethorphan (p. 1660·1); menthol (p. 2553·2); phenylephrine (p. 1672·2).

Opacite *Justesa Imagen, Arg.*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Opacorden *Polpharma, Pol.*
Amiodarone (p. 1300·1).
Arrhythmias.

Opacout *HLB, Arg.*
Disodium inosinate (p. 2495·2).
Cataracts.

Opacrile *Bacon, Arg.*
Iopamidol (p. 1590·3).
Radiographic contrast agent.

Opagis *Nevzat, Turk.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opak *Merkez, Turk.†*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Opalescence *Grimberg, Arg.*
Sodium fluoride (p. 2089·2).
Tooth whitener.

Opalgyne *Innotech, Fr.*
Benzydamine hydrochloride (p. 29·2).
Vaginitis.

Opalino *Weltrap, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Opalmon *Ono, Jpn.*
Limaprost alfadex (p. 1420·3).
Thromboangiitis obliterans; intermittent claudication.

Opam *Wockhardt, India.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Opamid *Orion, Pol.*
⊗Indapamide (p. 1409·2).
Hypertension.

Opamox *Orion, Fin.*
Oxazepam (p. 1092·2).
Anxiety disorders; psychoses; depression; insomnia.

Opana *Endo, USA.*
⊗Oxymorphone hydrochloride (p. 114·2).
Pain.

Oparsan Con Lisina y L-Glutamina *Sanitas, Chile.*
Vitamins; minerals; amino acids.
Dietary supplement.

Opas *Co-Pharma, UK.*
Sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity; heartburn; flatulence; dyspepsia.

Opat *Dewcare, India.*
Olopatadine (p. 636·2).
Allergic conjunctivitis.

Opatanol *Alcon, Belg.; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hung.; Alcon, Irl.; Alcon, Ital.; Alcon, Neth.; Alcon, Norw.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, UK; Alcon, Ukr.*
Olopatadine hydrochloride (p. 636·2).
Allergic conjunctivitis.

Opaz *Aglowmed, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Opaz-DM *Aglowmed, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Opazimes *Co-Pharma, UK.*
⊗Aluminium hydroxide (p. 1817·2); light kaolin (p. 1850·1); belladonna (p. 2453·3); morphine hydrochloride (p. 92·3).
Dyspepsia; diarrhoea; gastro-enteritis.

Opcon-A *Bausch & Lomb, Canad.; Bausch & Lomb, Hong Kong; Bausch & Lomb, Mex.; Bausch & Lomb, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye irritation or congestion; allergic or inflammatory disorders of the eye.

Opebrin *Coup, Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Opehex *Hexal, Philipp.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opel *Medopharm, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Opel Plus *Mission Happiness, India.*
Paracetamol (p. 115·1); nimesulide (p. 101·3).

Opel-D *Medopharm, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Opel-MR *Mission Happiness, India.*
Nimesulide (p. 101·3); tizanidine hydrochloride (p. 2026·2).

Open *Zee, India.*
Meropenem (p. 321·3).
Bacterial infections.

Openvas
Note: this name may be used for preparations of different composition.
LKM, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Pfizer, Spain.
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Openvas Plus *Pfizer, Spain.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Opep *Shantha, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Opeq *Hanburys, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Opeq-OZ *Hanburys, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Opera *Newtramax, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Opera-D *Newtramax, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Operand *Redi-Products, USA.*
Povidone-iodine (p. 1767·1).
Skin disinfection; vaginal disorders.

Operaz *Protech, Rus.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Operium *PP Lab, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Opex *Vista, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Opgenra *Howmedica, Cz.; Olympus, Denm.; Olympus, Ger.; Howmedica, Irl.; Olympus, Neth.; Howmedica, Pol.; Howmedica, Port.*
Eptotermin alfa (p. 1177·3).
Lumbar spine fusion.

Opglucon *Lotus, Malaysia.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Ophan *Chew, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cough; nasal congestion.

Ophar *Biophar, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ophar-OZ *Biophar, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ophidus *Motima, Fr.*
Lactobacillus acidophilus (p. 2596·3); bifidobacterium.
Maintenance of intestinal flora.

Ophtacalm *Chauvin, Fr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Ophtacalmfree *Chauvin, Fr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Ophtagram *Bausch & Lomb, Port.; Bausch & Lomb, Switz.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Ophtaguttal *Agepha, Austria.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2); boric acid (p. 2459·3).
Conjunctival irritation.

Ophtal
Note: this name may be used for preparations of different composition.
Teva, Cz.
Boric acid (p. 2459·3); benzododecinium bromide (p. 1739·2).
Eye disorders.

Ophtal Z *Winzer, Ger.†*
Zinc sulfate (p. 2126·2).
Eye irritation.

Ophtalin Plus *Novartis, Turk.†*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Ophtalmin N *Winzer, Ger.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Ophtalmine *Cooperation Pharmaceutique, Fr.†*
Boric acid (p. 2459·3); borax (p. 2459·2); red vine (p. 2521·3); rose water; peppermint water (p. 1877·1); hamamelis (p. 2523·3).
Eye irritation.

Ophtalmoferon *Firn M, Rus.*
Interferon alfa-2a (p. 989·2); diphenhydramine (p. 626·1).
Viral eye infections.

Ophtamedine *Thea, Belg.; IFET [ΙΦΕΤ], Gr.*
Hexamidine isetionate (p. 1754·3).
Eye disorders; otitis; rhinitis.

Ophtamolol *Dar Al Dawa, Hong Kong.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Ophtasiloxane *Alcon, Fr.*
Dimeticone (p. 2209·3).
Prevention of corneal adhesions; corneal burns.

Ophtasone *Bausch & Lomb, Philipp.; Bausch & Lomb, Switz.*
⊗Betamethasone sodium phosphate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Ophtaxia *Chauvin, Fr.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1).
Eye irrigation.

Ophtergine *Horus, Fr.*
Yellow mercuric oxide (p. 2555·2).
Blepharitis.

Ophthacare *Himalaya Herbal, India.*
Curcuma longa; ocimum sanctum; rosa damascena (p. 2607·1).
Conjunctivitis; dry eyes.

Ophthalin *Ciba Vision, Austral.†; Zeiss, NZ†; Ciba Vision, Thai.†; Iocom, UK.*
Sodium hyaluronate (p. 2526·2).
Adjunct in ocular surgery.

Ophthalmo-Azulen *Zentiva, Cz.*
Guaiazulene (p. 2523·1).
Eye trauma.

Ophthalmo-Evercil *Teva, Cz.*
Phenylephrine hydrochloride (p. 1672·3); esculoside (p. 2431·2).
Eye irritation.

Ophthalmoferon *Zdravo, Ukr.*
Interferon alfa-2b (p. 989·2).
Inflammatory eye disorders.

Ophthalmo-Framykoin *Zentiva, Cz.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial eye infections.

Ophthalmo-Framykoin Compositum *Zentiva, Cz.*
⊗Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); hydrocortisone acetate (p. 1640·1).
Eye disorders.

Ophthalmo-Septonex *Teva, Cz.*
Eye drops: Carbaethopendecinium bromide (p. 1741·3); boric acid (p. 2459·3); borax (p. 2459·2); guaiazulene (p. 2523·1); fennel oil (p. 2503·3).
Eye disorders.

Zentiva, Cz.
Eye ointment: Carbaethopendecinium bromide (p. 1741·3).
Eye disorders.

Ophthalmo-Timogal *Ivax, Cz.†*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Ophthetic *Allergan, Canad.†; Allergan, NZ†; Allergan, USA.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

Ophthifluor *Deklerkt, USA.*
Fluorescein sodium (p. 2506·2).
Ophthalmic diagnostic agent.

Ophtholique *Promed, Rus.; ProMed, Ukr.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Eye irritation; dry eyes.

Ophtim *Thea, Fr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ophtocain N *Winzer, Ger.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia for ophthalmic procedures.

Ophtopur-Z *Winzer, Ger.†*
Zinc sulfate (p. 2126·2).
Eye disorders.

Opiate *Sanify, India.*
Tramadol (p. 139·2).
Pain.

Opiate-P *Sanify, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Opiate-PD *Sanify, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1); tramadol (p. 139·2).

Opibion *Otto, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemia; nutritional supplement.

Otto, Malaysia; Otto, Singapore.
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron; Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement in pregnancy and lactation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Opibright *Otto, Indon.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Eye disorders.

Opicef *Otto, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Opicel *Otto, Indon.*
Barrier preparation.
Dry skin.

Opicillin *Otto, Indon.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Opiclam *Otto, Indon.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Gram-positive bacterial infections.

Opidiar *Otto, Indon.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Opigesic *Bayer, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Opii Simplex *Rekah, Israel.*
Opium (p. 111·3).
Pain.

Opilax *Otto, Indon.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Opilet *Rafarm, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Opilina *Arex, Venez.*
Oxolamine (p. 1671·2).
Cough.

Opilina Compuesta *Arex, Venez.*
Oxolamine phosphate (p. 1671·2); bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Opilon *Hansam, Irl.†; Archimedes, UK.*
Moxisylyte hydrochloride (p. 1441·3).
Raynaud's syndrome; menière's disease; peripheral vascular disorders.

Opimox *Otto, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Opin
Note: this name may be used for preparations of different composition.
Triton, India.
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Weiao, China.
Interferon alfa-2a (p. 989·2).
Gynaecological viral infections.

Opinac *Plus, India.*
Aceclofenac (p. 16·2); benzyl alcohol (p. 1739·3); capsaicin (p. 35·1); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Opinacea *Otto, Indon.*
Caplets: Echinacea purpurea (p. 2498·1); bee propolis (p. 2597·3); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Otto, Indon.
Oral syrup: Echinacea purpurea (p. 2498·1); bee propolis (p. 2597·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Opineuron *Otto, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Opino *Wabosan, Austria; Menarini, Gr.*
Topical gel: ⊗Buphenine hydrochloride (p. 2462·3); aescin (p. 2431·2); melissa oil (p. 2553·2); pumilio pine oil (p. 2591·1); rosemary oil (p. 2607·3).
Varicose veins; thrombophlebitis; muscle injuries; vascular disorders.

Wabosan, Austria.
Tablets: ⊗Buphenine hydrochloride (p. 2462·3); aescin (p. 2431·2).
Vascular disorders.

Soho, Indon.†
⊗Buphenine hydrochloride (p. 2462·3); aescin (p. 2431·2); rosemary oil (p. 2607·3); turpentine oil (p. 2636·3); melissa oil (p. 2553·2).
Varicose veins; thrombophlebitis; phlebitis; venous insufficiency; soft-tissue injury.

Opiodur *Pfizer, UK.*
⊗Fentanyl (p. 60·1).

Opi-OT *Elder, India.*
Injection: Tramadol (p. 139·2).
Pain.

Elder, India.
Tablets: Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Opiphen *Otto, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Opipra *TAD, Ger.†*
Opipramol hydrochloride (p. 440·2).
Anxiety.

Opipram *Krewel, Ger.*
Opipramol hydrochloride (p. 440·2).
Anxiety.

Opirap *Triton, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Opirel *Ali, Turk.*
Clopidogrel bisulfate (p. 1342·3).

Opiren *Takeda, Spain.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Opirom *Osper, India.*
Cefpirome (p. 247·2).
Bacterial infections.

Opisial *Bausch & Lomb, Ital.†*
Sodium hyaluronate (p. 2526·2).
Aid in eye surgery.

Opistan *Otto, Indon.*
Mefenamic acid (p. 85·3).
Fever; menorrhagia; pain.

Opithrocin *Otto, Indon.*
Erythromycin ethyl succinate (p. 291·2); erythromycin stearate (p. 291·3).
Bacterial infections.

Opixime *Otto, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Opizole *Myung In, Singapore.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Opizone *Britannia Pharmaceuticals, UK.*
Naltrexone hydrochloride (p. 1565·1).

O-Plat
Note: this name may be used for preparations of different composition.
Raffo, Arg.; Zodiac, Braz.; Tecnofarma, Chile.
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Oplat
Note: this name may be used for preparations of different composition.
Nolver, Venez.
Carboplatin (p. 759·1).
Malignant neoplasms.

Oplatin *United Biotech, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Opliphon *Fada, Arg.*
Phenytoin (p. 538·2).
Epilepsy.

Opm *Meprofarm, Indon.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opnol *CCS, Swed.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Opobyl
Note: this name may be used for preparations of different composition.
Spedrog, Arg.
Bile salts (p. 2457·2); boldo (p. 2458·3); belladonna (p. 2453·3).
Hepatobiliary disorders; dyspepsia.

Bailly, Fr.†; Uriach Aquilea OTC, Spain.
Aloes (p. 1816·1); boldo (p. 2458·3).
Constipation.

Opocarbon *Monserrat, Arg.*
Phthalylsulfathiazole (p. 339·3); neomycin sulfate (p. 330·1); activated charcoal (p. 1537·3); kaolin (p. 1850·1).
Bowel sterilisation; diarrhoea; gastrointestinal infections.

Opoenterol *Lanpharm, Arg.*
⊗Lactic acid (p. 2539·1); homatropine methylbromide (p. 2007·3); papain (p. 2582·3); pepsin (p. 2586·1).
Gastrointestinal spasm; digestive disorders.

Opokan *Alfafarm, Pol.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis; juvenile idiopathic arthritis.

Opon *Gripin, Turk.*
Aspirin (p. 22·2).
Fever; pain.

Oponaf *Angelini, Spain.*
Lactitol (p. 1850·3).
Constipation; hepatic encephalopathy.

Opoplex *Valeant, Braz.*
Vitamins.

Oposim *Richet, Arg.*
⊗Propranolol hydrochloride (p. 1479·1).

Opostibac *Farmaceutica H, Mex.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Opo-Veinogène *H2 Pharma, Fr.*
Red vine (p. 2521·3); aesculus (p. 2431·2); esculoside (p. 2431·2).
Peripheral vascular disorders; haemorrhoids.

Opovital B12 *Roux-Ocefa, Arg.*
Vitamin B substances (p. 2102·3); minerals.
Tonic.

O-Powercef *Wockhardt, India.*
Cefixime (p. 240·3).
Bacterial infections.

Opox
Note: this name may be used for preparations of different composition.
Guardian, Indon.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Hetero, India.
Cefpodoxime.
Bacterial infections.

Opox-CV *Hetero, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Oppi-R *Aqualife, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Opplin *TNP, Thai.*
Boric acid (p. 2459·3); borax (p. 2459·2); allantoin (p. 1693·1); chlorobutanol (p. 1747·2); salicylic acid (p. 1719·1); zinc sulfate (p. 2126·2); hamamelis (p. 2523·3).
Eye irritation.

Opra *Actavis, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Oprad *Cryopharma, Mex.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Opraks *Toprak, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Opralix *Intermed, Gr.*
Lidocaine hydrochloride (p. 1988·2); prilocaine hydrochloride (p. 1994·1).

Opram *Armoxindo, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Opramed *Charoon Bhesaj, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Opramid *IQFA, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Oprane *Vifor, Switz.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Opraz *Littman, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Oprazium *Farmedia, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Oprazol *Spirig, Switz.†; Hikma, Ukr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Oprazole *Atlantic, Thai.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Oprazon *Ariston, Braz.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opredsone *Greater Pharma, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Oprex *Psyco Remedies, India.*
Haloperidol (p. 1077·1).
Psychoses; Tourette's syndrome; tics; anxiety; behaviour disorders; intractable hiccup; restlessness; confusion.

Oprezol *Kimia, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Opridan
Note: this name may be used for preparations of different composition.
Farmedia, Gr.
Isotretinoin (p. 1706·2).
Acne.

Opridon *Deva, Turk.*
Opipramol hydrochloride (p. 440·2).
Depression.

Oprimol *Taro, Israelt†; Foko, Turk.†*
Opipramol hydrochloride (p. 440·2).
Depression.

Oprizole *Essenpharma, Philipp.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Oprymea *KRKA, Cz.; KRKA, Denm.; KRKA, Ger.; TAD, Ger.; KRKA, Hung.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.; KRKA, Swed.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Opsar Tears *Charoon Bhesaj, Thai.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Eye irritation; dry eyes.

Opsartimol *Charoon Bhesaj, Thai.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Opsil *Silom, Thai.*
Boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irritation.

Opsil Tears *Silom, Thai.*
Hypromellose (p. 2189·2).
Dry eye; wetting solution for hard contact lenses.

Opsil-A *Silom, Thai.*
⊗Tetryzoline hydrochloride (p. 1678·3); antazoline hydrochloride (p. 615·3).
Allergic eye disorders.

Opsite *Smith & Nephew, Austral.; Smith & Nephew, Fr.; Smith & Nephew, Ger.; Smith & Nephew, S.Afr.; Smith & Nephew Healthcare, UK.*
Polyurethane dressing (p. 1718·1).
Wounds; burns; protection of cannula sites.

Opsite Flexigrid *Smith & Nephew, Ital.*
Polyurethane dressing (p. 1718·1).
Wounds; ulcers.

Opsonat *Pekana, Neth.*
Nitricum acidum (p. 2572·3); sulphuricum acidum (p. 2624·2); bellis perennis (p. 2454·2); cantharis vesicatoria (p. 2469·2); glechoma hederacea (p. 2523·1); gratiola officinalis; hydrastis canadensis (p. 2528·1); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Opsor *Medimar, Gr.*
Salicylic acid (p. 1719·1).

Opsorad *Alapis, Gr.*
Salicylic acid (p. 1719·1).

Opstres *Multicare, Philipp.*
Vitamins.
Nutritional supplement.

Opsumit *Actelion, UK; Actelion, USA.*
Macitentan (p. 1427·2).
Pulmonary hypertension.

Optacd *Dey's, India.*
Sulfacetamide (p. 361·1).
Eye infections.

Optacid *Meditop, Hung.*
Sodium hydrogen sulfate (p. 2619·1); monobasic sodium phosphate (p. 1791·1).
Gastrointestinal disorders.

Optacilin *Nycomed, Braz.*
Ampicillin benzathine (p. 218·2); ampicillin sodium (p. 218·2).
Bacterial infections.

Optaflox *Optaderm, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Optaflu *Novartis Vaccines, Cz.; Novartis Vaccines, Irl.; Novartis Vaccines, Neth.; Novartis Vaccines, Pol.; Novartis Vaccines, Port.; Novartis Vaccines, UK.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Optajun *F5 Profas, Spain.†*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Optal *Olan-Kemed, Thai.*
Eye drops: Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Olan-Kemed, Thai.
Eye lotion: Boric acid (p. 2459·3); borax (p. 2459·2); chlorobutanol (p. 1747·2); salicylic acid (p. 1719·1).
Eye irritation.

Optalgin *Teva, Israel.*
Dipyrone (p. 53·3).
Fever; pain.

Optalia *Boiron, Canad.†*
Calcarea fluorica (p. 2053·1); calendula officinalis (p. 2465·2); cineraria maritima; euphrasia officinalis (p. 2502·1); kalium muriaticum (p. 1793·2); magnesia carbonica (p. 1856·2); silicea (p. 2208·3).
Homoeopathic preparation.

Optalidon
Note: this name may be used for preparations of different composition.
Novartis Consumer, Ital.
Propyphenazone (p. 127·3); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain.

Novartis Consumer, Port.; Omega, Spain; Novartis, Turk.
Propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain.

Optalidon Ibu
Note: this name may be used for preparations of different composition.
Novartis Consumer, Ger.†
Ibuprofen (p. 68·2).
Pain; fever.

Optalidon N *Novartis Consumer, Ger.†*
Propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain.

Optalidon Nieuwe Formule *Novartis Consumer, Belg.*
Ibuprofen (p. 68·2).
Pain; fever.

Optalidon Zahnschmerz mit Diclofenac *Novartis Consumer, Ger.†*
Diclofenac potassium (p. 48·3).
Fever; pain.

Optal-Pro *Olan-Kemed, Thai.*
Ciprofloxacin hydrochloride (p. 261·2).
Infected corneal ulcers; bacterial conjunctivitis.

Optal-Tears *Olan-Kemed, Thai.*
Hypromellose (p. 2189·2).
Dry eye; wetting solution for contact lenses.

Optamid *Novartis, Turk.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Optamide
Note: this name may be used for preparations of different composition.
Optaderm, Philipp.
⊗Acetazolamide (p. 2001·1).
Glaucoma; epilepsy; heart failure; oedema.

Optamol *Marck Biosciences, Philipp.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Optamox *Pharma Investi, Chile.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Roemmers, Arg.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Optamox Duo *Roemmers, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Optaphen *Pascual, Philipp.*
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Allergic eye disorders; eye irritation.

Optase
Note: this name may be used for preparations of different composition.
Onset, USA.
⊗Peru balsam (p. 2587·1); castor oil (p. 2472·1); trypsin (p. 2635·2).

Osper, India.
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Optase-D *Osper, India.*
⊗Diclofenac sodium (p. 48·3); serrapeptase (p. 2613·3).

Optase-DC *Osper, India.*
⊗Chymotrypsin (p. 2477·3); diclofenac (p. 48·3); trypsin (p. 2635·2).

Optavite *Akorn, Canad.†; Dioptic, Canad.†*
Vitamins; minerals.

Optaz *Shreya, India.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Optazol *Hormona, Mex.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Optear *Micro, India.*
Hypromellose (p. 2189·2).
Dry eyes.

Opteron *GiEnne, Ital.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Optex *Acme, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guanethidine (p. 1395·2).

Optex-AT *Acme, India.*
⊗Ambroxol hydrochloride (p. 1654·3); guaifenesin (p. 1666·2); menthol (p. 2553·2); terbutaline (p. 1228·1).

Opthaflox *Grin, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Opthagen *Pascual, Philipp.*
Gentamicin sulfate (p. 304·2).
Conjunctivitis.

Optha-LL *Landson, Indon.*
Lutein (p. 2079·2); lycopene (p. 2546·2); vitamin E (p. 2119·1); zinc (p. 2126·1); betacarotene (p. 2051·1); vitamin A (p. 2098·3); myrtillus (p. 2566·2).
Supplement for healthy eyes.

Opthavir *Grin, Mex.*
Aciclovir (p. 964·1).
Herpes simplex keratitis.

Opthil *GMP, Indon.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Opti *Eclectic Institute, Canad.†; Metagenics, Canad.†*
Vitamins; minerals.

Optibet *Sanbe, Indon.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Optibetol *Polfa Warszawa, Pol.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Optibiol
Note: this name may be used for preparations of different composition.
Nutrisante, Fr.
Fish oil (p. 1460·1); tagetes; retinophospholipids (p. 2201·2); zinc sulfate (p. 2126·2); chromium (p. 2055·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Visual disorders.

Polinac, Venez.
Betacarotene (p. 2051·1); chromium yeast (p. 2125·2); zinc yeast (p. 2125·2); cranberry (p. 2488·1); egg phospholipids; vegetable oil; fish oil (p. 1460·1).
Dietary supplement.

Yves Ponroy, Singapore.
Omega-3 triglycerides (p. 1460·1); phospholipids (p. 2201·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3); cryptoxanthin; vitamin E (p. 2119·1); vitamin C (p. 2110·3); zinc (p. 2126·1); chromium (p. 2055·3).
Nutritional supplement for maintenance of eye health.

Yves Ponroy, Canad.†
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); chromium yeast (p. 2125·2); zinc sulfate (p. 2126·2).

Opti-Biostim *Eclectic Institute, Canad.*
Pyridoxine hydrochloride (p. 2105·3); vitamin A palmitate (p. 2098·3); vitamin C (p. 2110·3); zinc gluconate (p. 2126·2).

Optic *TP, Thai.*
Boric acid (p. 2459·3); chlorobutanol (p. 1747·2); borax (p. 2459·2).
Eye irritation.

Opticaine *Biocel, Turk.†*
Proxymetacaine (p. 1995·3).
Local anaesthesia.

Optical Illusion *Dempsey, Canad.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Optican *Hauz, India.*
Fluconazole (p. 578·2).

Opticar *Ashford, Singapore.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Opticare PMS *Standard Drug, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Opticef
Note: this name may be used for preparations of different composition.
Acme, India.
Ceftriaxone (p. 253·3).
Bacterial infections.

Opticef-S *Acme, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Optichlor *Ashford, Singapore.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Opticide *Pharmaland, Thai.*
Praziquantel (p. 164·1).
Trematode infections.

Opti-Clean *Alcon, Braz.*
Cleaning solution for contact lenses.

Alcon, USA.
Range of solutions for contact lenses.

Opti-Clean II *Alcon, Canad.†*
Cleaning solution for hard and soft contact lenses.

Opticort *Sandoz, Canad.*
⊗Framycetin sulfate (p. 301·2); gramicidin (p. 308·3); dexamethasone sodium metasulfobenzoate (p. 1631·1).
Infected eye and ear disorders.

Opticrom *Sanofi-Aventis, Austral.; Melisana, Belg.; Allergan, Canad.; Aventis, Ger.†; Teva, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Aventis, NZ†; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.; Aventis, Thai.; Eczacibasi, Turk.†; Sanofi-Aventis, UK; Allergan, USA.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; keratitis; vernal keratoconjunctivitis; keratoconjunctivitis.

Opticron *Cooperation Pharmaceutique, Fr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Opticul *FDC, Philipp.*
Hypromellose (p. 2189·2).
Dry eyes.

Opticyl *Optopics, USA.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Optiday GQ *Biofarma, Mex.*
Vitamins; minerals.

Optiderm *Hermal, Austria; Almirall Hermal, Ger.; Almirall, Ital.; Herrmann, Pol.†; Almirall, Switz.*
⊗Urea (p. 1727·3); lauromacrogol 400 (p. 2194·1).
Dry and pruritic skin disorders.

Optidorm *Dolorgiet, Ger.*
Zopiclone (p. 1118·1).
Sleep disorders.

Optidox *Acme, India.*
Doxylamine succinate (p. 627·3); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Optifast *Novartis Nutrition, Singapore.*
Food for special diets.
Obesity.

Optifast VLCD *Nestle, Austral.*
Food for special diets.
Obesity.

Optifen
Note: this name may be used for preparations of different composition.
Spirig, Switz.
Ibuprofen (p. 68·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; fever.

Zuventus, India.
Flurbiprofen (p. 65·2).
Prevention of miosis during eye surgery; inflammation following eye surgery.

Optifer *Gufic, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc (p. 2126·1).

Optifit *Acme, India.*
Capsules: Vitamins; minerals; trace elements; spirulina (p. 2622·1).

Acme, India.
Oral drops: Vitamins; minerals; trace elements; choline chloride (p. 2055·2).

Optiflam-P *Acme, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Optifluor *Diba, Mex.†*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Optiflur *Intra-Labs, India.*
Flurbiprofen (p. 65·2).
Prevention of miosis during eye surgery; inflammation following eye surgery.

Opti-Free *Alcon, Braz.; Alcon, Fr.†; Alcon, NZ; Alcon, S.Afr.; Alcon, Turk.; Alcon, USA.*
A range of preparations for contact lens care.

Alcon, Canad.
Cleaning, rinsing, disinfecting, and storage solution, cleaning tablets, and rewetting drops for soft contact lenses.

Alcon, UK.
A range of solution for contact lens care.

Alcon, Mex.
⊗Pancreatin (p. 2579·3).
Cleansing solution for contact lenses.

Opti-Free Daily *Alcon, Austral.†*
Cleansing solution for soft contact lenses.

Opti-Free Express *Alcon, Austral.*
Cleaning, disinfecting, rinsing, and storage solution for soft and disposable contact lenses.

Alcon, Mex.
A range of solutions for soft contact lens care.

Opti-Free Multiaccion *Alcon, Mex.*
Cleansing, disinfecting, and lubricating solution for contact lenses.

Opti-Free Replenish *Alcon, Austral.*
Disinfecting, rinsing, and storage solution for contact lenses.

Opti-Free Supra Clens *Alcon, Mex.*
⊗Pancreatin (p. 2579·3).
Cleansing solution for contact lenses.

OptiFresh *Vivax Optipharm, Venez.*
⊗Dextran (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Optifresh *Konimex, Indon.†*
Polyvinyl alcohol (p. 2204·2).
Eye irritation; dry eyes.

Optigen *Xepa-Soul Pattinson, Singapore.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Optigene *Pfeiffer, USA.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Optigene 3 *Pfeiffer, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Minor eye irritation.

Opti-Genta *Vitamed, Israel.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Optigrel *Optipharm, Gr.*
Clopidogrel (p. 1342·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Optigrow *Rhiza, Philipp.*
Vitamins; levocarnitine (p. 2053·2); lysine hydrochloride (p. 2079·3); zinc sulfate (p. 2126·2); biotin (p. 2052·2); inositol (p. 2533·2); taurine (p. 2626·2); chlorella growth factor (p. 2475·3).
Dietary supplement for children.

Optihist-Plus *Entod, India.*
⊗Chlorphenamine maleate (p. 620·3); tetryzoline hydrochloride (p. 1678·3).

Optiject *Guerbet, Belg.; Guerbet, Fr.*
Ioversol (p. 1593·1).
Radiographic contrast medium.

Optil *Opus, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Optilac *Raymos, Arg.*
Chondroitin sulfate sodium (p. 2476·1); aprotinin (p. 1133·2).
Dry eyes.

Optilar *Geolab, Braz.*
Ketorolac trometamol (p. 80·2).

Optilast *Meda, Irl.; Megapharm, Israel; Adcock Ingram, S.Afr.; Viatris, UK.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Optilax
Note: this name may be used for preparations of different composition.
Zuventus, India.
⊗Timolol (p. 1513·2).
Glaucoma; ocular hypertension.

Optilets *Abbott, USA.*
Vitamins.

Optilets-M *Abbott, Indon.*
Vitamins; minerals.

Abbott, USA.
Vitamins; minerals; iron (p. 2073·1).

Optilube
Note: this name may be used for preparations of different composition.
Dioptic, Canad.
Wool fat (p. 2219·3); liquid paraffin (p. 2191·2); soft paraffin (p. 2211·3).

Zuventus, India.
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).

Optilube PVA *Dioptic, Canad.*
Polyvinyl alcohol (p. 2204·2).

Optima *Stanley, Israel.†*
Vitamins; minerals.

Optima IFX *Usana, Mex.*
Vitamin C (p. 2110·3); zinc (p. 2126·1); carotenoids (p. 2176·2).

Optimark *Mallinckrodt, Arg.; Covidien, Austral.; Covidien, Austria; Covidien, Belg.; Tyco, Canad.; Covidien, Cz.; Covidien, Denm.†; Covidien, Gr.; Covidien, Hung.; Covidien, Irl.; Covidien, Neth.; Covidien, Norw.; Covidien, Pol.; Tyco, Port.; Covidien, Rus.; Mallinckrodt, Spain; Covidien, Swed.; Mallinckrodt, USA.*
Gadoversetamide (p. 1587·3).
Contrast medium for magnetic resonance imaging.

Optimax
Note: this name may be used for preparations of different composition.
Ferron, Indon.
Lutein (p. 2079·2); lycopene (p. 2546·2); vitamin E (p. 2119·1); ascorbic acid (p. 2110·3); zinc (p. 2126·1); betacarotene (p. 2051·1); myrtillus (p. 2566·2).
Supplement for healthy eyes.

Merck, UK.†
Tryptophan (p. 453·2).
Depression.

Optimax Plus
Note: this name may be used for preparations of different composition.
Ferron, Indon.
Lutein (p. 2079·2); lycopene (p. 2546·2); zeaxanthin (p. 2125·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3); zinc (p. 2126·1); betacarotene (p. 2051·1); myrtillus (p. 2566·2).
Dietary supplement for healthy eyes.

Optimental *Abbott, Canad.†*
Preparation for enteral nutrition.

Optimide *Micro, India.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Optimide Plus *Micro, India.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).

Optimin
Note: this name may be used for preparations of different composition.
Abbott, Mex.
Vitamins; minerals.

Optimina Fem *Temis, Arg.*
Pollen (p. 2593·3); ginseng (p. 2513·3); vitamins.
Tonic.

Optimina Plus *Temis, Arg.*
Yohimbine hydrochloride (p. 2372·3); pollen (p. 2593·3); ginseng (p. 2513·3); vitamin E acetate (p. 2119·2).
Erectile dysfunction.

Optimine *Schering-Plough, Canad.†*
Azatadine maleate (p. 616·3).
Hypersensitivity reactions.

Optimoist *Colgate-Palmolive, USA.*
Hyetellose (p. 2188·3); electrolytes (p. 1775·1); sodium monofluorophosphate (p. 2091·3); xylitol (p. 2220·3).
Dry mouth.

Optimol *Santen, Denm.; Duopharma, Hong Kong†; CCM, Malaysia; Sun, Rus.; Santen, Swed.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Optimox *Troikaa, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Optimus *Gerolymatos, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections.

Optimyxin *Sandoz, Canad.*
Eye ointment: Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Eye infections.

Sandoz, Canad.
Eye/ear drops: Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Eye or ear infections.

Optimyxin Plus *Sandoz, Canad.*
Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Eye or ear infections.

Optinate *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Lepetit, Ital.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Optinate Combi *Sanofi-Aventis, Denm.; Sanofi-Aventis, Swed.†*
Orange tablets, risedronate sodium (p. 1189·3); blue tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Optinate Combi D *Sanofi-Aventis, Fin.†*
Tablets, risedronate sodium (p. 1189·3); effervescent granules, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Optinate Omega-3 *First Horizon, USA.*
Tablets, vitamins; minerals; iron (p. 2073·1); capsules, docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.
Dietary supplement.

Optinem *AstraZeneca, Austria.*
Meropenem (p. 321·3).
Bacterial infections.

Optinesse *Codepharma, Fr.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Optineuron *Lupin, India.*
Injection: Vitamin B substances (p. 2102·3); dexpanthenol (p. 2582·2).
Neuropathies; vitamin B deficiency; vitamin B supplement for parenteral nutrition.

Lupin, India.
Tablets: Vitamin B substances (p. 2102·3).
Neuropathies; vitamin B deficiency.

Optineuron Forte *Lupin, India.*
Vitamins.

Optipar *Hexal, Denm.; Hexal, Fin.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Optipect Kodein *UCB, Ger.*
Codeine (p. 40·2).
Cough.

OptiPranolol *Bausch & Lomb, USA.*
⊗Metipranolol hydrochloride (p. 2009·2).
Glaucoma; ocular hypertension.

Optipred *Prohealth, Philipp.*
⊗Prednisolone (p. 1645·2) or prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Optipres *Cipla, India.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Optipyrin *Pfleger, Ger.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Optiray *Mallinckrodt, Arg.; Covidien, Austral.; Covidien, Austria; Guerbet, Belg.; Tyco, Canad.; Covidien, Cz.; Covidien, Denm.; Covidien, Fin.; Guerbet, Fr.; Alfa Medis, Gr.; Covidien, Hung.; Covidien, Irl.; Covidien, Ital.; Mallinckrodt, Neth.; Tyco, Norw.; Tyco, Port.; Covidien, Rus.; Covidien, Spain; Covidien, Swed.; Guerbet, Switz.; Mallinckrodt, Switz.; Tyco, UK; Mallinckrodt, USA.*
Ioversol (p. 1593·1).
Radiographic contrast medium.

Optirifa Plus *Troikaa, India.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Opti-Safe *Fischer, Israel.†*
Flavonoid compounds (p. 2505·2); lutein (p. 2079·2); betacarotene (p. 2051·1); myrtillus (p. 2566·2); rutoside (p. 2505·3); vitamins; minerals.
Nutritional supplement; eye disorders.

Opti-Safe Areds *Fischer, Israel.*
Lutein (p. 2079·2); betacarotene (p. 2051·1); vitamins; minerals.
Age-related macular degeneration; eye disorders.

Optisedine *Pharmacobel, Belg.*
Lorazepam (p. 1080·3).
Anxiety.

Optiskin *Urgo, Fr.†*
Polyurethane dressing (p. 1718·1).
Wounds.

Opti-Soak *Alcon, Mex.*
Polidronium chloride.
Wetting, disinfecting and storage of gas-permeable and hard contact lenses.

Alcon, Canad.†
Conditioning and disinfecting solution for hard and gas permeable contact lenses.

Alcon, NZ†; Alcon, S.Afr.†
Wetting, soaking, and disinfecting solution for hard and gas-permeable contact lenses.

Opti-Soft *Alcon, USA.†*
Rinsing and storage solution for soft contact lenses.

Optisol *Fischer, Israel.†*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Optison *Amersham, Austria; GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Ger.; Amersham, Gr.; GE Healthcare, Hung.; GE Healthcare, Irl.; GE Healthcare, Ital.; GE Healthcare, Neth.; GE Healthcare, Norw.; GE Healthcare, Port.; GE Healthcare, Swed.; GE Healthcare, UK; GE Healthcare, USA.*
⊗Perflutren-filled (p. 1595·2) albumin microspheres.
Contrast medium for echocardiography.

Optisulin
Note: this name may be used for preparations of different composition.
Reddy, India.
Chromium tripicolinate (p. 2056·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); zinc sulfate (p. 2126·2).

Sanofi-Aventis, Cz.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.
⊗Insulin glargine (p. 475·3).
Diabetes mellitus.

Opti-Tears *Alcon, Braz.*
⊗Dextran (p. 1138·3); hypromellose (p. 2189·2).
Comfort drops for contact lenses.

Alcon, S.Afr.†; Alcon, UK; Alcon, USA.†
Rewetting drops for contact lenses.

Alcon, Canad.†
Comfort drops for contact lenses.

Optium
Note: this name may be used for preparations of different composition.
Abbott, Arg.
Test for glucose and ketones in blood.

Abbott Diabetes Care, UK.
Test for ketones in blood.

Abbott Diabetes Care, Austral.
Test for glucose in blood (p. 2516·3).

Columbia, Mex.
Clonixin lysine (p. 40·1); caffeine (p. 1203·3); ergotamine tartrate (p. 674·1).
Vascular headache.

Optium B Ketone *Abbott Diagnostics, Ital.*
Test for glucose and ketones in blood.

Optium Plus *Abbott Diagnostics, Ital.; Abbott, UK.*
Test for glucose in blood (p. 2516·3).

Optium Xceed *Abbott, Irl.†*
Test for glucose and ketones in blood.

Opti-Up *Variforma, Arg.; Abbott, Turk.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Optivar *Medpointe, USA.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis.

Optivate *GP, Arg.; BPL, Israel; Landsteiner, Mex.; BPL, Singapore; BPL, UK.*
A factor VIII preparation (p. 1148·1).
Haemophilia A; haemorrhagic disorders.

Optive *Abbott, India; Allergan, USA.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Allergan, Arg.; Allergan, Austral.; Allergan, Braz.; Allergan, Chile; Allergan, Ger.; Allergan, Hong Kong; Allergan, Israel; Allergan, Mex.; Allergan, Philipp.; Allergan, Singapore; Allergan, Switz.; Allergan, Thai.; Allergan, UK; Allergan, Ukr.
⊗Carmellose sodium (p. 2175·2); glycerol (p. 2517·2).
Dry eyes; eye irritation.

Optivis *United Drugs, Hong Kong.*
Chloramphenicol (p. 257·1).
Eye infections.

Optivision *Pharmed, India.*
Chromium tripicolinate (p. 2056·1); lutein (p. 2079·2); selenium (p. 2086·3); vitamins; zinc (p. 2126·1).

Sophia, Mex.
Linseed oil (p. 2544·2); vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement.

Optivita Plus *Konsuma, Venez.*
Vitamins; minerals.

Optivite *Psychotropics, India.*
Vitamins; lutein (p. 2079·2).

Optivite PMT *Optimox, USA.*
Vitamins; minerals.
Premenstrual syndrome.

Optix *KVZ, Ukr.*
Betacarotene (p. 2051·1); lutein (p. 2079·2); vitamin E (p. 2119·1); ascorbic acid (p. 2110·3); zinc (p. 2126·1); copper (p. 2057·1); zeaxanthin (p. 2125·3).
Dietary supplement for eye health.

Optix Forte *KVZ, Ukr.*
Omega-3-acid ethyl esters (p. 1460·2); betacarotene (p. 2051·1); lutein (p. 2079·2); vitamin E (p. 2119·1); zeaxanthin (p. 2125·3).
Dietary supplement for eye health.

OptiZen *InnoZen, USA.*
Polysorbate 80 (p. 2203·3).
Dry eyes.

Optizen-D *Acme, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Optizoline *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Opti-Zyme *Alcon, USA.†*
⊗Pancreatin (p. 2579·3).
Range of cleansing solutions for contact lenses.

Optizyme *Acme, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Optobet *Vilco, Gr.*
Diclofenac sodium (p. 48·3).
Prevention of miosis in ophthalmic surgery.

Optocain *Dentapharm, Gr.; Molteni, Ital.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Optocef *Bayer, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Optocin *Prem, India.*
Gentamicin (p. 304·2).
Eye infections.

Optocol *Prem, India.*
Chloramphenicol (p. 257·1).
Eye infections.

Optodrop *Rafarm, Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3).

Optodrop-Co *Rafarm, Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).

Optoflox *Alkem, India.*
Norfloxacin (p. 333·3).
Eye infections.

Optomega *Usana, Canad.*
Cucurbita (p. 2489·2); turmeric (p. 2218·1); helianthus annuus; linseed (p. 2544·2); olive oil (p. 2574·3); rosemary (p. 2607·2).

Optomicin
Note: this name may be used for preparations of different composition.
Grin, Mex.
Erythromycin stearate (p. 291·3).
Bacterial eye infections.

Optomycin
Note: this name may be used for preparations of different composition.
Vendiz, Philipp.
Chloramphenicol (p. 257·1).
Bacterial ear infections.

Optopress *NTC, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Optosol *Otsuka, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium acetate (p. 1781·1); sodium citrate (p. 1781·2).
Eye irritation.

Optovisc *Ashford, Singapore.*
Hypromellose (p. 2189·2).
Dry eyes.

Optovit *Hermes, Ger.; Vifor, Switz.†*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency; vitamin E supplement.

Optovit actiflex *Hermes, Ger.*
Salix (p. 129·2).
Musculoskeletal and joint disorders.

Optovit E *Qualiphar, Belg.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency; vitamin E supplement.

Optovite B12 *Normon, Spain.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Optrex *Reckitt Benckiser, Austral.; Schering-Plough, Canad.; Pierre Fabre, Fr.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Irl.; Reckitt Benckiser, Ital.; Optrex, Malaysia; Boots Healthcare, NZ; Reckitt Benckiser, Port.; Optrex, Singapore; Reckitt Benckiser, Spain; Reckitt Benckiser, Switz.; Reckitt Benckiser, Thai.; Crookes Healthcare, UK.*
Hamamelis (p. 2523·3).
Eye wash; eye irritation, inflammation, and congestion; dry eyes.

Optrex Allergy *Crookes Healthcare, UK.*
Sodium cromoglicate (p. 1225·3).
Formerly known as Optrex Hayfever Allergy.
Allergic conjunctivitis.

Optrex Clear Eyes *Reckitt Benckiser, Irl.*
⊗Hamamelis (p. 2523·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Optrex compresses *Reckitt Benckiser, Switz.†*
Hamamelis (p. 2523·3); allantoin (p. 1693·1).
Eye irritation.

Optrex Contact Lens Friendly Eye Drops *Reckitt Benckiser, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Optrex Hayfever Allergy *Boots Healthcare, NZ.†*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Optrex Infected Eyes *Reckitt Benckiser, UK.*
Chloramphenicol (p. 257·1).
Bacterial conjunctivitis.

Optrex Medicated *Reckitt & Colman, Austral.†*
⊗Hamamelis (p. 2523·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Optrex Red Eyes *Crookes Healthcare, UK.*
⊗Hamamelis (p. 2523·3); naphazoline hydrochloride (p. 1669·3).
Formerly known as Optrex Clear Eyes.
Eye irritation.

Optrex Red-Eye Relief *Boots Healthcare, NZ.*
⊗Hamamelis (p. 2523·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Optrine *Konimex, Indon.†*
⊗Naphazoline (p. 1669·3).

Optruma *Lilly, Cz.; Pierre Fabre, Fr.; Daiichi Sankyo, Ger.; Lilly, Irl.; Menarini, Ital.; Lilly, Neth.; Lilly, Pol.; Lilly, Port.; Esteve, Spain.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Optryl
Note: this name may be used for preparations of different composition.
Ashford, Philipp.
Erythromycin (p. 291·2).
Bacterial eye infections.

Teva, Israel.
⊗Naphazoline hydrochloride (p. 1669·3); diphenhydramine hydrochloride (p. 626·2).
Eye disorders.

Opturem *Kade, Ger.†*
Ibuprofen (p. 68·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Opumyk *Medimar, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Opun *Nitro Organics, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Opus *Guardian, Indon.*
Soya isoflavone (p. 2620·3); calcium glycerophosphate (p. 1783·3); colecalciferol (p. 2113·1).
Dietary supplement; menopausal symptoms.

OPV
Note: this name may be used for preparations of different composition.
Aventis Pasteur, India; GSK, Turk.
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Opvero *Sanofi Pasteur, Arg.; Sanofi Pasteur, Thai.*
An oral poliomyelitis vaccine (trivalent) (p. 2411·1).
Active immunisation.

OPV-Merieux
Note: this name may be used for preparations of different composition.
Sanofi Pasteur, S.Afr.
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Opyrin *Taisho, Jpn.*
Flufenamate aluminium (p. 65·1).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Op-Zole *United Lifecare, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Op-Zole D *United Lifecare, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

OQN *Sigman, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

OQN-O *Sigman, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oqueen *Zenacts, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oqueen-OZ *Zenacts, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

O-Quin *Burgeon, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

OR *Sinopharm, Thai.*
Chlorhexidine gluconate (p. 1743·3).

Ora *Masa, Thai.*
Lorazepam (p. 1080·3).
Anxiety; neuroses.

ORA5 *McHenry, USA.*
Copper sulfate (p. 2057·2); potassium iodide (p. 2336·3); iodine (p. 2336·3).
Minor mouth or throat irritation.

Orabase *Aspen, Austral.; Convatec, Canad.; BMS, Irl.†; BMS, NZ; BMS, S.Afr.†; Convatec, UK.*
⊗Carmellose sodium (p. 2175·2); pectin (p. 2200·3); gelatin (p. 1154·1).
Stoma care; oral and perioral lesions; skin lesions.

Orabase Baby *Colgate-Hoyt, USA.*
Benzocaine (p. 1980·2).
Mouth disorders.

Orabase Dental *Colgate Oral, USA.*
Benzocaine (p. 1980·2).
Mouth pain.

Orabase HCA *Colgate-Hoyt, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Oral inflammatory and ulcerative lesions.

Orabase Lip *Colgate-Hoyt, USA.*
Benzocaine (p. 1980·2); allantoin (p. 1693·1); menthol (p. 2553·2); camphor (p. 2466·2); phenol (p. 1763·3).
Minor irritation.

Orabase-B *Colgate-Palmolive, USA.*
Benzocaine (p. 1980·2).
Oral lesions.

Orabet
Note: this name may be used for preparations of different composition.
Hexal, Denm.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Orabetic *Biolab, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Orabloc *Pierrel, USA.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ora-C *Vickmans, Hong Kong.†*
Cefalexin (p. 234·1).
Bacterial infections.

Oracalcid-B12 *Ind-Swift, India.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).

Oracare *Pascual, Philipp.*
Chlorine dioxide (p. 1747·1).
Halitosis.

Oracea *Galderma, Denm.; Galderma, Fin.; Galderma, Swed.; Galderma, Switz.; Galderma, USA.*
Doxycycline (p. 288·1).
Rosacea.

Oracéfal *BMS, Fr.*
Cefadroxil (p. 233·2).
Bacterial infections.

Oraceftin *Fako, Turk.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Oracid *More, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Oracilin *Legrand, Braz.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Oracilline *UCB, Fr.*
Phenoxymethylpenicillin (p. 338·3) or benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Oracin *Bright Future, Hong Kong.†*
Erythromycin (p. 291·2).
Bacterial infections.

Oracit *Carolina, USA.*
Sodium citrate (p. 1781·2); citric acid (p. 2480·3).
Urine alkalinising agent; chronic metabolic acidosis.

Oracort
Note: this name may be used for preparations of different composition.
Taro, Canad.; Taro, Israel; AFT, NZ.
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Brel, Philipp.†
⊗Prednisone (p. 1647·2).
Corticosteroid.

Oracort E *Taro, Israel; Taro, Singapore.*
⊗Triamcinolone acetonide (p. 1649·1); lidocaine hydrochloride (p. 1988·2).
Oral lesions; mouth disorders.

Oracortia *TNP, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth ulcers.

Oraday *Biolab, Hong Kong†; Biolab, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Oradekan *Streger, Mex.*
Vitamins.

Oradex *Cavico, Malaysia.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; mouth ulcers; oral hygiene.

Oradexon *Organon, Fin.; Organon (Орухоу), Gr.; Organon, Hung.†; Organon, Port.; MSD, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Schering-Plough, Chile; Schering-Plough, Indon.; Organon, Neth.; Organon, Philipp.
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Oradiet *Sanitas, Chile.*
Orlistat (p. 2577·1).
Obesity.

Oradin *Adelco, Gr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Oradroxil *Lampugnani, Ital.*
Cefadroxil (p. 233·2).
Bacterial infections.

Orafate *McCullough, USA.*
Sucralfate (p. 1889·1).
Mouth lesions.

Orafer Comp *Rhein, Mex.*
Ferrous sulfate (p. 2062·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Iron deficiency; iron-deficiency anaemia.

Oraflora *McW, India.*
Folic acid (p. 2063·1); *Lactobacillus acidophilus* (p. 2596·3); nicotinamide (p. 2083·1); vitamin B_2 (p. 2104·3).

Oraflora Gel *McW, India.*
Choline salicylate (p. 39·2).
Mouth lesions.

Ora-G *Pharma Synth, India.*
Cetrimide (p. 1742·1); choline salicylate (p. 39·2); menthol (p. 2553·2); tannic acid (p. 2625·2).
Mouth disorders.

Oragalin Espasmolitico *Lacer, Spain.*
Azintamide (p. 2451·3); hyoscine methobromide (p. 1846·1).
Hepatobiliary disorders.

Oragard
Note: this name may be used for preparations of different composition.
Colgate-Palmolive, Ital.†
Hydrogen peroxide (p. 1755·2).
Mouth disorders.

Oragard-B *Colgate-Palmolive, Canad.*
Benzocaine (p. 1980·2).
Mouth pain.

Oragesic
Note: this name may be used for preparations of different composition.
Jean-Marie, Hong Kong.
⊗Triamcinolone acetonide (p. 1649·1); lidocaine hydrochloride (p. 1988·2); chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Parnell, USA.
Benzyl alcohol (p. 1739·3); menthol (p. 2553·2).
Formerly known as TiSol.
Minor mouth or throat irritation.

Orahesive *Convatec, Canad.; Convatec, UK.*
⊗Carmellose sodium (p. 2175·2); pectin (p. 2200·3); gelatin (p. 1154·1).
Dental adhesive; oral and perioral lesions; stoma care.

Orahex *Abbott, India; Pharmahex, Philipp.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene; halitosis.

Abbott, India.
Oral gel: Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).

Orajel *Church & Dwight, Canad.; Hand-Prod, Pol.†; Church & Dwight, UK; Church & Dwight, USA; Del, USA.*
Benzocaine (p. 1980·2).
Oral pain; toothache; minor mouth or throat irritation; mouth disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Orajel Denture Plus *Church & Dwight, Canad.†*
Benzocaine (p. 1980·2); menthol (p. 2553·2).

Orajel Mouth Aid *Del, USA.*
Topical gel: Benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1); zinc chloride (p. 2126·1).
Mouth and lip sores.

Del, USA.
Topical liquid: Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Orajel Mouth Sore Medicine *Church & Dwight, Canad.*
Benzocaine (p. 1980·2); zinc chloride (p. 2126·1).
Oral pain.

Orajel Perioseptic *Del, USA.*
Urea hydrogen peroxide (p. 1774·2).
Oral inflammation; oral hygiene.

Del, Canad.†
Hydrogen peroxide (p. 1755·2).
Mouth disorders.

Orajel PM *Del, USA.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Toothache.

Orajel Ultra Canker Sore *Church & Dwight, Canad.*
Benzocaine (p. 1980·2); levomenthol (p. 2553·2).
Mouth pain.

Orakit *Fada, Arg.*
Potassium chloride (p. 1793·2).
Potassium supplement.

Oral Aid *Beacons, Singapore.*
⊗Chlorhexidine hydrochloride (p. 1743·3); triamcinolone acetonide (p. 1649·1); lidocaine (p. 1988·1).
Mouth ulcers; sore gums; toothache.

Oral Impact *Nestle, Fr.; Nestle, Hong Kong.*
Preparation for enteral nutrition.

Nestle, Thai.
Preparation for pre-operative enteral nutrition.

Oral Infant Cold Drops *Tanta, Canad.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Oral Pain Relief *Major, USA.*
Benzocaine (p. 1980·2).

Oral Rehydration Salts *DHA, Hong Kong; DHA, Malaysia.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

DHA, Singapore.
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Oral Spray *Gemno, Ital.†*
Propolis (p. 2597·3).

Oral Wound Rinse *Carrington, USA.*
Acemannan hydrogel (p. 2426·3).
Mouth disorders.

Oral-Aid *CCM, Malaysia.*
⊗Chlorhexidine hydrochloride (p. 1743·3); lidocaine (p. 1988·1); triamcinolone acetonide (p. 1649·1).
Mouth ulcers; sore gums; toothache; denture irritation.

Oralair *Stallergenes, Austria; Stallergenes, Belg.; Paladin, Canad.; Stallergenes, Cz.; Stallergenes, Ger.; Stallergenes, Neth.; Stallergenes, Spain; Stallergenes, Switz.*
Grass pollen allergen extracts (p. 2434·3) (p. 2593·3).
Allergic rhinitis; allergen immunotherapy; hyposensitisation.

Oralav *Braun, Ger.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Oral-B Anti-Bacterial with Fluoride *Oral-B, Canad.*
Cetylpyridinium chloride (p. 1743·1); sodium fluoride (p. 2089·2).

Oral-B Collutorio Denti Gengive *Procter & Gamble, Ital.*
Cetylpyridinium chloride (p. 1743·1); sodium fluoride (p. 2089·2).
Prevention of dental disorders.

Oral-B Denti Sensibili *Procter & Gamble, Ital.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Sensitive teeth.

Oral-B Pasta Dentifricia Denti e Gengive *Procter & Gamble, Ital.†*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Oralbiotico *Sanofi-Aventis, Port.†*
Oral liquid: Tyrothricin (p. 384·1); zinc chloride (p. 2126·1).
Mouth and throat infections.

Oral-Blue *Concept, Israel.†*
Troclosene potassium (p. 1774·1).
Oral hygiene.

Oralcam *Landsteiner, Mex.*
Amlodipine camsilate (p. 1304·1).
Hypertension; angina pectoris.

Oralcef *Geymonat, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Oralcon
Note: this name may be used for preparations of different composition.
Famy, Malaysia; Famy, Neth.; Famy, Norw.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Oralcon-F *Famy, Thai.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Oraldene *McNeil Healthcare, Irl.; Pfizer Consumer, UK.*
Hexetidine (p. 1755·1).
Mouth and throat infections; oral hygiene.

Oraldine *Johnson & Johnson, S.Afr.*
Hexetidine (p. 1755·1).
Mouth and throat infections.

Oralet *Hikma, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Oralex *Eva, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Oral-Eze *Petrus, Austral.*
Benzocaine (p. 1980·2); clove oil (p. 2481·3).
Toothache.

Oralfresh *Maver, Chile.*
Mouthwash: ⊗Cetylpyridinium chloride (p. 1743·1); alcohol (p. 1733·1); domiphen bromide (p. 1751·1).
Oral hygiene.

Oralfresh Citrus *Maver, Chile.†*
⊗Alcohol (p. 1733·1); cineole (p. 2479·1); zinc chloride (p. 2126·1); methyl salicylate (p. 92·1); thymol (p. 1772·2).
Oral hygiene.

Oralfresh Clasico *Maver, Chile.†*
Mouthwash: ⊗Alcohol (p. 1733·1); methyl salicylate (p. 92·1); cineole (p. 2479·1); thymol (p. 1772·2); menthol (p. 2553·2).
Oral hygiene.

Oralfresh Proteccion *Maver, Chile.*
Toothpaste: Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Oralgen *Artu, Neth.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Oralgene *Maver, Chile.*
Dental gel: Chlorhexidine gluconate (p. 1743·3); sodium fluoride (p. 2089·2).
Oral hygiene.

Maver, Chile.
Mouthwash: Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Maver, Chile.
Tablets: Chlorhexidine gluconate (p. 1743·3); xylitol (p. 2220·3).
Oral hygiene.

Oralife Peppermint *Orion, Austral.*
Peppermint oil (p. 1877·1); chlorhexidine gluconate (p. 1743·3).
Dry lips and mouth.

Orion, NZ.
Peppermint oil (p. 1877·1); chlorhexidine gluconate (p. 1743·3); wool fat (p. 2219·3).
Dry, cracked lips.

Oralin *Orion, Swed.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Oralipin *Roche, Chile.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Oralis *Health Biotech, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Oralit *Kimia, Indon.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); calcium chloride (p. 1783·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Oralite *Domesco, Philipp.; Zuoz, Venez.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration.

Oralka-K *Haledew, India.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3).

Oralmedic *Paracelsia, Ger.; Ceuta, UK.*
HybenX (hydroxybenzenesulfonic acid; hydromethoxybenzenesulfonic acid; sulfuric acid (p. 2624·2)).
Mouth ulcers.

Oralmox *Boniscontro & Gazzone, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Oralmuv *LKM, Arg.*
Lamivudine (p. 1000·2).
HIV infection.

Oralog *Pharmasant, Thai.†*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Oralone Dental *Taro, USA.†*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Oralovite *Meda, Swed.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin deficiency; alcoholism; polyneuropathy.

Oraloz *Alkem, India.*
Clotrimazole (p. 576·2).

Oralpac *Inpac, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth ulcers.

Oralpädon *Stada, Ger.; Stada, Hung.†*
Potassium chloride (p. 1793·2); glucose monohydrate (p. 2069·1); sodium chloride (p. 1795·1); sodium acid citrate (p. 1781·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Oralpaedon *Helvepharm, Switz.*
Glucose monohydrate (p. 2069·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium acid citrate (p. 1781·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Oralpred *Biolab Sanus, Braz.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

OralSeven *Oral 7, Singapore.*
Mouth gel: Lactoperoxidase (p. 2539·3); muramidase (p. 2565·1); lactoferrin (p. 2539·3); glucose oxidase (p. 2516·3).
Mouth disorders; dry mouth.

Oral 7, Singapore.
Mouthwash: Lactoferrin (p. 2539·3); muramidase (p. 2565·1); lactoperoxidase (p. 2539·3); glucose oxidase (p. 2516·3); calcium lactate (p. 1784·1).
Mouth disorders; dry mouth.

Oral7, Singapore.
Toothpaste: Lactoferrin (p. 2539·3); muramidase (p. 2565·1); lactoperoxidase (p. 2539·3); glucose oxidase (p. 2516·3); sodium monofluorophosphate (p. 2091·3); calcium lactate (p. 1784·1).
Mouth disorders; dry mouth.

Oralsone *Gramon, Arg.; Vinas, Spain.*
⊗Hydrocortisone hydrogen succinate (p. 1640·2).
Mouth ulcers.

Oralsone C *Gramon, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Oralsone Herpes *Gramon, Arg.*
Aciclovir (p. 964·1).
Herpes simplex infections of the face and lips.

Oralsone Topic *Gramon, Arg.*
Rhubarb (p. 1884·2); salicylic acid (p. 1719·1).
Oral lesions.

Oral-T *Silom, Singapore; Silom, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Oralten *Perrigo, Israel.*
Clotrimazole (p. 576·2).
Oropharyngeal candidiasis.

Oralube *Orion, NZ.*
Electrolytes (p. 1775·1).
Saliva substitute.

Oralvac *Bencard, Ger.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Oralyte *Rugby, USA.*
Electrolytes (p. 1775·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration solution.

Sanofi-Aventis, UK.
Glucose (p. 2068·3); citric acid (p. 2480·3); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration solution.

OraMagic Plus *MPM, USA.*
Benzocaine (p. 1980·2).
Mouth and throat disorders.

OraMagicRx *MPM, USA.*
Aloemannon Plus (p. 1693·2).
Mouth and throat disorders.

Oramax
Note: this name may be used for preparations of different composition.
Alpha Aromatic, India.
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Julphar, UAE.
Fluconazole (p. 578·2).
Genital candidiasis.

Oramed *Mediline, Israel.†*
Benzocaine (p. 1980·2).
Dental pain; mouth pain.

Oramedy *Dong Kook, Hong Kong; Dong Kook, Singapore.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral inflammatory disorders; oral lesions.

Oramellox *Alpex, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Oramet *Hexal, Fin.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Oramide *UAP, Indon.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Oramikron *Kocak, Turk.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Oramil *Ganassini, Ital.*
Rose honey (p. 2072·1).
Oral disinfection.

Oraminax *BA Farma, Port.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Oramin-G *Molex Ayus, Indon.*
Vitamins; minerals; ginseng (p. 2513·3); aloe vera (p. 1693·2); lecithin (p. 2542·2).
Tonic.

Oraminic II *Vortech, USA.*
Brompheniramine maleate (p. 618·1).
Hypersensitivity reactions.

Oramorph *Molteni, Austria; Norgine, Belg.; Molteni, Denm.; Molteni, Fin.; Norgine, Fr.; Archimedes, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Irl.; Molteni, Ital.; Molteni, Neth.; Molteni, Norw.; Molteni, Pol.; Molteni, Port.; Molteni, Spain; Abcur, Swed.; Norgine, Switz.; Boehringer Ingelheim, UK; aai, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Oramox *Athlone, Irl.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Oran *Nordic, India.*
Chlorhexidine gluconate (p. 1743·3); menthol (p. 2553·2).

Oranerv *More, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Oranex *Farmacom, Pol.*
Azithromycin (p. 221·2).
Bacterial infections.

Orano *Unison, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain; tension headache.

Oranol *Bayer, Switz.*
Vitamins.

Oranor *Carnot, Mex.*
Norfloxacin (p. 333·3).
Bacterial infections.

Orap *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.†; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Pharmascience, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen, Hong Kong; Johnson & Johnson, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Astellas, Jpn; Janssen-Cilag, Neth.; Janssen-Cilag, NZ†; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Thai.†; Janssen-Cilag, UK; Gate, USA; Lemmon, USA; Janssen-Cilag, Venez.*
Pimozide (p. 1096·3).
Schizophrenia; behaviour disorders in children; Tourette syndrome; paranoia; psychoses; anxiety disorders; personality disorders; dyskinesias; tics; choreas; anxiety.

Orapa *The Forty-Two, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Orapan *Novaduo, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Orapan-D *Novaduo, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Orapaste *Atlantic, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth ulcers; mouth inflammation.

Oraphen-PD *Great Southern, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Orapred *Sciele, USA.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Oraqix *Dentsply, Austria; Dentsply, Denm.; Dentsply, Fin.; Dentsply, Fr.; Dentsply, Ger.; Dentsply, Irl.; Dentsply, Ital.; Dentsply, Neth.; Dentsply, Norw.; Dentsply, NZ; Dentsply, Port.; Dentsply, Spain; Dentsply, Swed.; Oraltek, Switz.; Dentsply, UK; Dentsply, USA.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Orascreen *Zila, Gr.; Stafford-Miller, NZ.*
Tolonium chloride (p. 2632·3).
Diagnosis of oral cancer.

Ora-Sed *Hamilton, Hong Kong; Hamilton, Malaysia; Pfizer, NZ; Valeant, Singapore.*
Choline salicylate (p. 39·2).
Mouth ulcers; sore gums; teething pain; denture irritation.

Ora-Sed Jel *Hamilton, Austral.*
Choline salicylate (p. 39·2).
Mouth lesions; infant teething.

Orasep *Llorens, USA.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2).

Orasept
Note: this name may be used for preparations of different composition.
Bayer, Ukr.
Phenol (p. 1763·3).
Mouth and throat disorders.
Silom, Thai.
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.
Pharmakon, USA.†
Oral liquid: Tannic acid (p. 2625·2); methylbenzethonium chloride (p. 1760·3).
Sore throat.
Pharmakon, USA.†
Throat spray: Benzocaine (p. 1980·2); methylbenzethonium chloride (p. 1760·3); menthol (p. 2553·2).
Sore throat.

Orasia *Willow, India.*
Choline salicylate (p. 39·2); lidocaine (p. 1988·1).
Mouth lesions.

Orasic *Otto, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Orasol *Goldline, USA.*
⊗Benzocaine (p. 1980·2); phenol (p. 1763·3); alcohol (p. 1733·1); povidone-iodine (p. 1767·1).

Orasone *Phoenix, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Orasorbil *Delta, Port.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ora-Sore *Wings, India.*
Choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).
Mouth disorders.

Orastin *ACME, Philipp.*
Nystatin (p. 590·3).
Oral candidiasis.

Orastina *Sanofi-Aventis, Braz.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; diagnosis of placental insufficiency or fetal distress; lactation deficiency.

Oratane *Ascent, Austral.; Douglas, Malaysia; Darier, Mex.; Douglas, NZ; Pharmaplan, S.Afr.; Douglas, Singapore.*
Isotretinoin (p. 1706·2).
Acne.

Orate *Arvincare, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3).

OraTest *Chrisopoulos, Gr.; Zila, Neth.†; Zila, Port.*
Tolonium chloride (p. 2632·3).
Diagnosis of malignant neoplasms.

Oratol *Codilab, Port.*
Salicylic acid (p. 1719·1); zinc chloride (p. 2126·1).
Mouth and throat disorders.

Oratram *Molteni, Pol.*
Tramadol hydrochloride (p. 139·2).
Pain.

Oratric *Cubit, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

Oratrol *Alkon (Αλκον), Gr.*
⊗Diclofenamide (p. 2006·3).
Glaucoma.

Oratuss *Virdex, USA.*
Pentoxyverine citrate (p. 1672·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).

Oravacs *United Cell Biotech, China.*
An oral cholera vaccine (p. 2381·1).
Active immunisation.

OraVerse *Septodont, USA.*
Phentolamine mesilate (p. 1468·3).
Reversal of local anaesthesia.

Oravig *Vestiq, USA.*
Miconazole (p. 588·3).
Oral candidiasis.

Oravil
Note: this name may be used for preparations of different composition.
TRB, Arg.
Colecalciferol (p. 2113·1).
Vitamin D deficiency; rickets; osteomalacia; osteoporosis.
Streuli, Switz.†
Vitamin A acetate (p. 2098·3); *d*-alpha tocoferil acetate (p. 2119·1).
Dietary supplement.

Oravir *Novartis, Fr.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Orawin *Svizera, India.*
Choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).
Mouth lesions.

Orawis *Merck, India.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Oraxim *Malesci, Ital.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Oraxin *Centaur, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Oraxyl *e5, USA.†*
Doxycycline hyclate (p. 288·2).
Periodontitis.

Oraycea *Galderma, Ger.*
Doxycycline (p. 288·1).
Rosacea.

Oraz *Osper, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Oraz-D *Osper, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Orazep *Crescent, India.*
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication; nausea and vomiting induced by cytotoxic therapy.

Orazinc *Medhaus, Philipp.*
Zinc gluconate (p. 2126·2).
Zinc deficiency.
Mericon, USA.
Zinc sulfate (p. 2126·2).
Dietary supplement.

Orbenil *Sandoz, Israel.*
Cloxacillin sodium (p. 275·1).
Gram-positive bacterial infections.

Orbenin *IFET (ΙΦΕΤ), Gr.; SmithKline Beecham, Gr.; SmithKline Beecham, Philipp.; GSK, S.Afr.†; GSK, Spain; GSK, Thai.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Orbénine *Astellas, Fr.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Orbeos *Pfizer, Fin.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Orbest *Biochemix, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Orbical D3 *Zwitter, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Orbifen *Orbis Consumer, UK.*
Ibuprofen (p. 68·2).
Fever; pain.

Orbifen Cold & Flu *Orbis Consumer, UK.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Orbipront *Galenica, Gr.; Persos, Gr.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Orbits *Pharmed, India.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Orbivan *ECR, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3); caffeine (p. 1203·3).
Pain.

Orbivan CF *ECR, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).

Orbiz *Ritz, India.*
Chlorhexidine (p. 1743·2).
Oral hygiene; gingivitis.

Orbone *Ordain, India.*
Boron (p. 2052·3); calcium (p. 1783·1) or calcium carbonate (p. 1824·3); chondroitin sulfate (p. 2476·1); copper (p. 2057·1); glucosamine sulfate (p. 2515·3); manganese (p. 2081·2); dimethyl sulfone (p. 2493·3); silicon (p. 2088·3) or silicon dioxide (p. 2208·3); colecalciferol (p. 2113·1).

Orbone Forte *Ordain, India.*
Boron (p. 2052·3); copper (p. 2057·1); glucosamine sulfate (p. 2515·3); manganese (p. 2081·2); silicon dioxide (p. 2208·3).

Orbone Tab *Rapross, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).

Orcal *Lek, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Orcef *Rishab, India.*
Cefixime (p. 240·3).
Bacterial infections.

Orcel *Ortec, USA.*
Bioengineered human skin equivalent (p. 1720·2).
Wounds.

Orcerin *Macleods, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Orchidol *Orchid, India.*
Tramadol (p. 139·2).
Pain.

Orcigesic *Sunward, Singapore.*
Orphenadrine citrate (p. 909·2); mefenamic acid (p. 85·3).
Skeletal muscle pain and spasm.

Orcilone *Chew, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Orcinol *Julphar, UAE.†*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3); ammonium chloride (p. 1656·1).
Bronchitis; cough.

Orcipol *World Medicine, Ukr.*
Ciprofloxacin (p. 261·1); ornidazole (p. 943·1).
Bacterial infections; protozoal infections.

Orcl *Shinyaku, Jpn.*
Actarit (p. 17·1).
Rheumatoid arthritis.

Ord *Ind-Swift, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Ordi *Hos & Ins, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ordi-G *Hos & Ins, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Ordine *Mundipharma, Austral.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Ordipha *Tonipharm, Fr.*
Azithromycin (p. 221·2).
Bacterial infections.

Orecil NF *Senosiain, Mex.*
⊗Lidocaine hydrochloride (p. 1988·2); ofloxacin (p. 334·3); hydrocortisone hydrogen succinate (p. 1640·2).
Bacterial ear infections.

Oreda *Hua, Thai.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Oregan *GMP, Indon.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Oreges *Metro, Philipp.†*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration; vomiting; diarrhoea.

Oregra *Rishab, India.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Orelox *Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; Daiichi Sankyo, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Port.†; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Switz.; Sanofi Pasteur, Turk.; Aventis, UK.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Oren *Natco, India.*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Orencia *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Irl.; BMS, Israel; BMS, Ital.; BMS, Jpn; BMS, Neth.; BMS, Norw.; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Turk.; BMS, UK; BMS, USA.*
Abatacept (p. 15·2).
Rheumatoid arthritis; juvenile idiopathic arthritis.

Orengedokuto *Tsumura, Jpn.*
Skullcap root (p. 2617·1); coptis rhizome; gardenia fruit; phellodendron bark.
Traditional Kampo medicine.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Orento *Tsumura, Jpn.*
Pinellia tuber; coptis rhizome; ginger (p. 1844·1); liquorice (p. 1853·2); cinnamon bark (p. 2479·2); jujube; ginseng (p. 2513·3).
Traditional Kampo medicine.

Orenzym *Noventis, Cz.*
Takadiastase (p. 2442·1).
Digestive-system disorders.

Oreta *Reddy, India.*
⊗Letrozole (p. 817·1).
Breast cancer.

Oretes *Brown & Burk, Philipp.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; premenstrual syndrome.

Orex *Yash, India.*
Benzalkonium chloride (p. 1737·1); choline salicylate (p. 39·2); menthol (p. 2553·2); tannic acid (p. 2625·2).

Orexene *Azevedos, Port.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Orexin *Roberts, USA.*
Vitamin B (p. 2102·3).

Orex-Lo *Yash, India.*
Choline salicylate (p. 39·2); lidocaine hydrochloride (p. 1988·2).

Orex-M *Yash, India.*
Chlorhexidine gluconate (p. 1743·3); metronidazole (p. 936·1).

Orezinc *Novell, Indon.*
Zinc sulfate (p. 2126·2).
Adjunct to oral rehydration therapy for diarrhoea in children.

Orfadin *Orphan, Austral.; Orphan, Austral.; Orphan, Belg.; Swedish Orphan, Cz.; Swedish Orphan, Denm.; Swedish Orphan, Fin.; Orphan, Fr.; Swedish Orphan, Ger.; Swedish Orphan, Gr.; Swedish Orphan, Irl.; Megapharm, Israel; Orphan, Neth.; Swedish Orphan, Norw.; Swedish Orphan, Pol.; Swedish Orphan, Port.; Swedish Orphan, Rus.; Orphan, Spain; Swedish Orphan, Swed.; Swedish Orphan, USA.*
Nitisinone (p. 2572·2).
Tyrosinaemia type 1.

Orfarin *Orion, Malaysia; Orion, Singapore†; Orion, Thai.; Drogsan, Turk.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Orfenace *SteriMax, Canad.*
Orphenadrine citrate (p. 909·2).
Skeletal muscle spasm.

Orfenal *Remedica, Thai.*
Orphenadrine hydrochloride (p. 909·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Orfidal *Europharma, Denm.; Pfizer, Spain.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Orfiril *Desitin, Cz.; Desitin, Denm.; Desitin, Fin.; Desitin, Ger.; Desitin, Hung.; Desitin, Israel; Ranbaxy, Malaysia; Pharmachemie, Neth.; Desitin, Norw.; Desitin, Pol.; Ranbaxy, Singapore; Desitin, Swed.; Desitin, Switz.*
Sodium valproate (p. 553·1).
Epilepsy; mania; bipolar disorder; migraine.

Orfix *Orchid, India.*
Capsules; dispersible tablets: Cefixime (p. 240·3).
Bacterial infections.

Orchid, India.
Oral powder: Anhydrous citric acid (p. 2480·3); anhydrous glucose (p. 2069·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1).

Orflaz Kit *Aristo, India.*
Ornidazole (p. 943·1); fluconazole (p. 578·2); azithromycin (p. 221·2).

Orflex *Chew, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Pain; skeletal muscle spasm.

Orflo *Sresan, India.*
Suspension: Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Sresan, India.
Tablets: Lactobacillus sporogenes (p. 2596·3); ofloxacin (p. 334·3); ornidazole (p. 943·1).

Orgacal *Osper, India.*
Hydroxyapatite (p. 2529·3).
Osteoporosis.

Orgafem *HWS OTC, Austria.*
Cimicifuga (p. 2478·1); crocus (p. 2208·2); damiana (p. 2491·3); ginseng (p. 2513·3); sepia (p. 2613·1).
Homoeopathic preparation.

Orgalutran *Schering-Plough, Austral.; Schering-Plough, Braz.; Merck, Canad.; MSD, Hong Kong; Organon, Hung.; Organon, Irl.; Organon, Philipp.†*
Ganirelix acetate (p. 2279·2).
Controlled ovarian stimulation.

Organon, Arg.; Organon, Austria; Schering-Plough, Belg.; Schering-Plough, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Organon (Οργανον), Gr.; Organon, India; Schering-Plough, Indon.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; MSD, Neth.; Organon, Norw.; MSD, NZ; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Singapore; Organon, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK; Schering-Plough, Ukr.; Organon, Venez.
Ganirelix (p. 2279·2).
Controlled ovarian stimulation.

Orgamed *Organon, India.*
Medroxyprogesterone (p. 2288·1).
Menorrhagia; endometriosis; menopausal disorders; breast cancer; endometrial cancer; renal cell carcinoma; prostatic cancer; amenorrhoea.

Orgametril *Organon, Austria; Organon, Belg.; Organon, Cz.; Organon, Denm.†; Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hung.†; Organon, Neth.; Organon, Pol.; Organon, Rus.; MSD, Spain; MSD, Swed.; Organon, Turk.; Schering-Plough, Ukr.*
Lynestrenol (p. 2287·3).
Benign breast disorders; endometrial cancer; endometriosis; menstrual disorders; dysfunctional uterine bleeding; progestogen-only oral contraceptive; functional uterine bleeding; uterine hyperplasia; secondary amenorrhoea; hormone replacement therapy; menopausal disorders; malignant neoplasms; endometrial hyperplasia.

Orgamétril *Organon, Fr.†*
Lynestrenol (p. 2287·3).
Menstrual disorders; endometriosis; progestogen-only oral contraceptive.

Orgamox-CL *Shinto, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3); *Lactobacillus sporogenes* (p. 2596·3).

Orgamox-CL BD *Shinto, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).

Organ-I NR *Qualitest, USA.*
Guaifenesin (p. 1666·2).
Cough.

Organic Mineral *Bioglan, Austral.†*
Minerals.

Organidin NR
Note: this name may be used for preparations of different composition.
Wallace, USA.
Guaifenesin (p. 1666·2).
Formerly contained iodinated glycerol.
Coughs.

Organoneuro Cerebral *Gross, Braz.*
Gamma-aminobutyric acid (p. 2509·2); glutamic acid (p. 2070·2); calcium phosphate (p. 1784·2); vitamin B substances (p. 2102·3).
Nutritional supplement.

Organoneuro Optico *Gross, Braz.*
Tryptophan (p. 453·2); vitamin A (p. 2098·3); thiamine (p. 2102·3); riboflavin (p. 2104·3); ascorbic acid (p. 2110·3); tocopherol (p. 2119·1).
Nutritional supplement.

Orgaplasma *Ardeypharm, Ger.*
Ginseng (p. 2513·3).
Tonic.

Orgaran *MSD, Austral.; Organon, Austria; Organon, Belg.; Merck, Canad.; MSD-Chibret, Fr.; Essex, Ger.; IFET (ΙΦΕΤ), Gr.; Organon (Οργανον), Gr.; Organon, Irl.; Organon, Neth.; Schering-Plough, NZ†; Organon, Port.; MSD, Swed.; MSD, Switz.; Organon, UK.*
Danaparoid sodium (p. 1349·2).
Thromboembolism prophylaxis; deep-vein thrombosis; heparin-induced thrombocytopenia.

Orgasporin *Mir, Rus.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; autoimmune disorders.

Orgasulin Mix 30/70 *Organon, Turk.†*
⊗A mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p. 475·3).
Diabetes mellitus.

Orgasulin NPH *Organon, Turk.*
⊗Isophane insulin injection (p. 475·3).
Diabetes mellitus.

Orgesic *Burapha, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Orgestriol *Organon, Arg.*
Estriol (p. 2274·3).
Urogenital disorders in women associated with oestrogen deficiency; aid in cervical smear diagnosis; female infertility.

Orginal E *Pyridam, Indon.*
Tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Orgran *Crombie, NZ.*
Gluten-free pasta.
Dermatitis herpetiformis; gluten-sensitive enteropathies.

Orhydrate *Pediapharma, Philipp.†*
Sodium (p. 1795·1); chloride; potassium (p. 1793·1); citrate; magnesium (p. 1786·3); gluconate; glucose (p. 2068·3); sucrose (p. 2096·3) (p. 1780·1).
Oral rehydration; diarrhoea.

Oributol *Orion, Fin.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Oricar *Abbott, India.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure; left-ventricular dysfunction following myocardial infarction.

Oricitral *TTK, India.*
Sodium acid citrate (p. 1781·1).
Urinary alkaliniser.

Oricyclin *Orion, Fin.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Oridip *Orion, Fin.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Oriel *Intas, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Oriens *Galenica, Gr.*
Mizolastine (p. 636·1).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Orifungal *Janssen-Cilag, Arg.*
Ketoconazole (p. 585·3).
Fungal infections.

Origin *Uni-Sankyo, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Original Alka-Seltzer Effervescent Tablets *Bayer, USA.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); aspirin (p. 22·2).
Hyperacidity.

Original Antiseptic Mouthwash *Trillium, Canad.†*
Cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2).
Mouth disorders.

Original Cabdrivers Expectorant *Merck Consumer, UK.*
Dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); terpin hydrate (p. 1678·2); pumilio pine oil (p. 2591·1); eucalyptus oil (p. 2501·2).
Coughs.

Original Eye Drops
Note: this name may be used for preparations of different composition.
Arrow, Canad.
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Bausch & Lomb, Canad.
⊗Naphazoline hydrochloride (p. 1669·3).
Eye disorders.

Original Grosser Bittner Balsam *Bittner, Rus.*
Cnicus benedictus (p. 2482·2); carlina; gentian (p. 2512·1); liquorice (p. 1853·2); nutmeg (p. 2573·1); teriak (peppermint, sage, angelica, ginger); menyanthes (p. 2554·2); aniseed (p. 2444·2); sweet orange peel (p. 2576·2); clove (p. 2481·2); bitter orange peel (p. 2575·3); centaury (p. 2473·2); cubeb (p. 2489·2); verbascum (p. 2645·1); ginger (p. 1844·1); white ash; curcuma; angelica root (p. 2443·3); myrrh (p. 2566·1); elecampane (p. 1662·3); tormentil (p. 2633·2); achillea (p. 2427·3); iris germanica; calamus (p. 2464·2); Curacao rind; absinthium (p. 2426·1); camphor (p. 2466·2).
Nervous disorders; sleep disorders; gastrointestinal disorders; lipid disorders; musculoskeletal, joint, and soft-tissue disorders; mouth and throat disorders.

Original Herb Cough Drops *Ricola, Canad.†*
Achillea (p. 2427·3); althaea (p. 2438·3); cowslip (p. 2596·2); horehound (p. 1668·3); mallow (p. 2549·2); peppermint leaf (p. 1877·1); greater burnet saxifrage (p. 2463·1); ribwort plantain (p. 2604·2); sage (p. 2608·3); sambucus (p. 2609·3); thyme (p. 2630·2); veronica officinalis.

Original Schwedenbitter *Riviera, Cz.*
Gentian (p. 2512·1); absinthium (p. 2426·1); angelica (p. 2443·3); calamus (p. 2464·2); tormentil (p. 2633·2); myrrh (p. 2566·1); taraxacum (p. 2625·3); marrubium (p. 1668·3); zedoary; nutmeg (p. 2573·1); mace (p. 2547·3); English walnut (p. 2646·1); theriaca electuarium sine opio.
Appetite loss; digestive disorders.

Original Sensodyne *Block, USA.*
⊗Potassium nitrate (p. 1766·2).
Hypersensitive teeth.

Originalsweet *Rider, Chile.*
Aspartame (p. 2169·2).
Sugar substitute.

Original-Tinktur N Truw *Truw, Ger.*
Aconitum napellus (p. 2428·3); atropa belladonna (p. 2453·3); bryonia cretica; cephaelis ipecacuanha; echinacea angustifolia (p. 2498·1).
Homoeopathic preparation.

Origins IBS Relief *Blackmores, Austral.*
Peppermint oil (p. 1877·1).
Irritable bowel syndrome.

Origlucon *Orion, Fin.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Orilox-P *Orion, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Orimed *Oriental, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Orimetene *Novartis, Gr.; Novartis, Hong Kong.†*
⊗Aminoglutethimide (p. 739·2).
Breast cancer; Cushing's syndrome; prostatic cancer.

Orimol *Orion, India.*
Paracetamol (p. 115·1).
Pain; fever.

Orinase *Upjohn, USA.†*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Orinase Diagnostic *Upjohn, USA.†*
Tolbutamide sodium (p. 504·2).
Diagnosis of pancreatic adenoma.

Orinate *Forgo, India.*
Artesunate (p. 648·2).
Malaria.

Orin-O *Shince, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Orinol Plus *Sagmel, Rus.*
Phenyltoloxamine citrate (p. 638·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Rhinitis.

Orinse *Centaur, India.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Orio-DT *Sienna, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Oripeg *Orion, Cz.*
Macrogol 4000 (p. 2547·3).
Constipation.

Oriphage *Orion, India.*
Metformin (p. 489·1).
Diabetes mellitus.

Oriphex *Zydus, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Oripod *Orion, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Oriprim *Zydus, India; Cadila, Rus.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Oriprim-P *Zydus, India.*
Polymyxin B sulfate (p. 342·3); trimethoprim (p. 381·2).
Bacterial eye infections.

Oriptan *Orion, Denm.; Orion, Fin.; Orion, Swed.*
Sumatriptan succinate (p. 679·2).
Migraine.

Oriro *Orion, India.*
Oral suspension: Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc gluconate (p. 2126·2).
Orion, India.
Tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Oris *SM, Thai.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Orisantin *Orion, Fin.*
Dipyridamole (p. 1362·2); aspirin (p. 22·2).
Stroke prophylaxis.

Oris-gel *Marching, Hong Kong.†*
Benzalkonium chloride (p. 1737·1); choline salicylate (p. 39·2).

Oritax *Jodas, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Oritaxim *Cadila, Rus.; Alliance, S.Afr.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Oritaximax *Cadila, India.*
Cefotaxime sodium (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Oritaxime *Cadila, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Oritaxim-O *Cadila, India.*
Cefixime (p. 240·3).
Bacterial infections.

Oritiz *Orion, India.*
Ceftriaxone (p. 253·3); tazobactam (p. 369·3).
Bacterial infections.

Oritop *Orion, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Oritop-D *Orion, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Oriven *Orion, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Orivid *Pharmasant, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Orix *Remedina, Gr.*
Nifedipine (p. 1447·2).

Orixa *Orion, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Orixal *Ifars, Indon.*
Clarithromycin (p. 266·2).

Orizal *Menarini, Gr.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).

Orizole *Medopharm, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Orizolin *Cadila, Rus.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zydus, India.
Cefazolin (p. 237·2).
Bacterial infections.

Orizon *Orion, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Orkacin *Orchid, India.*
Amikacin (p. 214·1).
Bacterial infections.

Orkid-S *Ind-Chemie, India.*
⊗Halcinonide (p. 1639·3); salicylic acid (p. 1719·1).

Orlasil *Bright Future, Hong Kong.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Orlawax *Alcon, Mex.*
Trolamine (p. 2634·3).
Ear wax removal.

Orlept *LCH, Hong Kong†; Wockhardt, UK.*
Sodium valproate (p. 553·1).
Epilepsy.

Orlica *Torrent, India.*
Orlistat (p. 2577·1).
Obesity.

Orlidox *Rishab, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Orlidox-D *Rishab, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2); dicycloverine (p. 1834·2).

Orlimac *Macleods, India.*
Orlistat (p. 2577·1).
Obesity.

Orlitroy *Troikaa, India.*
Orlistat (p. 2577·1).
Obesity.

Orliv *Intag, India.*
Cyproheptadine hydrochloride (p. 624·1); tricholine citrate (p. 2055·2).

Orlobin *Help, Gr.; Medicus, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Orloc *Orion, Fin.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; migraine; heart failure.

Orloc Comp *Orion, Fin.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Orlon *Gynopharm, Chile.*
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Orlu *Hos & Ins, India.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; calcium oxalate calculi; uric acid nephropathy.

Ormandyl *Pierre Fabre, Cz.†; Pierre Fabre, Fr.; Pierre Fabre, Gr.; Pierre Fabre, Port.; Pierre Fabre, Spain.†*
Bicalutamide (p. 749·1).
Prostatic cancer.

Ormax *Sperko, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Ormigrein *Schering-Plough, Braz.*
Paracetamol (p. 115·1); ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); hyoscyamine sulfate (p. 1848·1); atropine sulfate (p. 1310·2).
Migraine.

Ormil *Atabay, Turk.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Ormist *TNP, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Ormitac *Intermed, Gr.*
Calcium phosphate (p. 1784·2).

Ormodon *Pharmaceutical Enterprises, S.Afr.†*
Nitrazepam (p. 1089·1).
Insomnia.

Ormox *Orion, Fin.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ornacol *GSK, S.Afr.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; nasal congestion.

Ornade-2 *Vianex (Βιανεξ), Gr.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Ornadine *Vesco, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Ornex
Note: this name may be used for preparations of different composition.
Ascher, USA.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms.
SmithKline Beecham, Philipp.
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion; sinusitis; cold and influenza symptoms.

Orni *Zydus, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Ornicef *Aristo, India.*
Cefixime (p. 240·3); ornidazole (p. 943·1).

Ornicetil *Alkaloid, Rus.*
Ornithine oxoglurate (p. 2085·2).
Liver disorders; test of pituitary function; protein deficiency.

Ornicétil *Chiesi, Fr.†*
Ornithine oxoglurate (p. 2085·2).
Parenteral nutrition; pituitary function testing; hepatic encephalopathy.

Ornida *Aristo, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Orniden *Denis, India.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; amoebiasis.

Ornidone *Tripharma, Turk.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Ornidox *Symbiotic, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ornidyl *Sanofi-Aventis, USA.†*
Eflornithine hydrochloride (p. 932·1).
African trypanosomiasis.

Orniflox *Ajanta, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

OrniFlu *Microgen, Rus.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Ornigil *Yuri, Ukr.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; amoebiasis; giardiasis.

Orniject *Tum, Turk.*
Ornidazole (p. 943·1).

Ornil *Volchem, Ital.*
L-Ornithine (p. 2085·2).
Adjunct in dietary management of hypercholesterolaemia.

Ornil KGF *Volchem, Ital.*
L-Ornithine oxoglurate (p. 2085·2).
Stress.

Orniliv *Life Medicare, India.*
⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Ornilox *Micro, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ornimax *Obsurge, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Orni-O *Zydus, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Orniona *Vertex, Rus.*
Ornidazole (p. 943·1).
Protozoal infections.

Ornipan *Moraceae, India.*
Syrup: Ornithine aspartate (p. 2085·2); nicotinamide (p. 2083·1); riboflavin sodium phosphate (p. 2104·3).
Moraceae, India.
Tablets: ⊗Ornithine aspartate (p. 2085·2); pancreatin (p. 2579·3).

Ornisid *Tripharma, Rus.; Abdi, Turk.; Abdi, Ukr.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections; trichomoniasis; amoebiasis; giardiasis.

Ornitaine
Note: this name may be used for preparations of different composition.
Bernabo, Arg.
Amino acids; vitamin B substances (p. 2102·3).
Liver disorders.

Ornitargin *Baldacci, Braz.*
Arginine (p. 2049·1); ornithine (p. 2085·2); citrulline (p. 2056·3).
Parenteral nutrition.

Ornitop *Toprak, Turk.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Ornivir *East African, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Ornizen *Sun, India.*
Ornidazole (p. 943·1).
Protozoal infections.

Ornizol *Arterium, Ukr.*
Ornidazole (p. 943·1).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Ornof *Aristo, India.*
Ornidazole (p. 943·1); ofloxacin (p. 334·3).

Oroacid *Rosch & Handel, Austria.†*
⊗Betaine hydrochloride (p. 2456·1); pepsin (p. 2586·1).
Hypochlorhydria; loss of appetite.

Orobicin *Fulton, Ital.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Gastrointestinal infections; pre-operative bowel preparation.

Orobiotic *Fortbenton, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Orocaine *Thebe, S.Afr.*
Cetrimide (p. 1742·1); benzocaine (p. 1980·2).
Mouth and throat infections.

Orocal
Note: this name may be used for preparations of different composition.
Medihealth, India.
Alfacalcidol (p. 2112·3); calcium carbonate (p. 1824·3).
Theramex, Mon.
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Orocal D_3 *Nycomed, Pol.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Orocal Vitamine D3 *Theramex, Mon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Orochlor *Aspen Consumer, S.Afr.*
Benzocaine (p. 1980·2); chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Orochol *Scott-Cassara, Arg.; Berna, Philipp.†*
An oral cholera vaccine (p. 2381·1).
Active immunisation.

Orocil *Novartis, Gr.*
Benzoxonium chloride (p. 1739·2).
Mouth infections.

Orocil Lido *Novartis, Gr.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Oro-Clense *Germiphene, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis.

Orodin *Meiji, Indon.*
Povidone-iodine (p. 1767·1).
Mouth and throat disorders.

Orodina *Laboratorios Chile, Chile.*
Cyproheptadine hydrochloride (p. 624·1); vitamins; lysine hydrochloride (p. 2079·3).
Reduced appetite.

Orodrops *Orion, Fin.*
Cinchocaine hydrochloride (p. 1983·2).
Earache.

Orofact *Medico, India.*
Dental paste: ⊗Potassium nitrate (p. 1766·2).
Medico, India.
Mouthwash: Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Orofar
Note: this name may be used for preparations of different composition.
Novartis Consumer, Belg.
Benzoxonium chloride (p. 1739·2).
Mouth and throat disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Novartis Consumer, Cz.; Novartis Consumer, Pol.; Novartis Consumer, Switz.
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders; mouth and throat infections.

Orofar Lidocaine *Novartis Consumer, Belg.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Orofar Max *Novartis Consumer, Pol.*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Orofar-L *Novartis, Philipp.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Orofen *Sandoz, Denm.†*
Ketoprofen (p. 79·1).
Dysmenorrhoea; gout; inflammation; musculoskeletal and joint disorders.

Orofeno *Megat, Venez.*
Ketoprofen (p. 79·1).
Inflammation; pain.

Orofer *Emcure, India.*
Capsules; suspension; tablets: Folic acid (p. 2063·1); iron (p. 2073·1).

Emcure, India.
Oral drops: Iron (p. 2073·1) or iron polymaltose (p. 2077·2).

Emcure, India.
Syrup: Cyanocobalamin (p. 2107·2); iron (p. 2073·1).

Emcure, Philipp.; Emcure, Thai.
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron deficiency; iron-deficiency anaemia.

Orofer Kit *Emcure, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); folic acid (p. 2063·1); iron polymaltose (p. 2077·2).

Oroferon *Kocak, Turk.*
Ferrous sulfate (p. 2062·2); mucoproteose (p. 2564·3).
Iron deficiency; iron-deficiency anaemia.

Oroflocina *Jelfa, Pol.*
Levofloxacin (p. 315·3).
Bacterial infections.

Oroflox-OZ *Ethix, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Orogab-M *Rishab, India.*
Gabapentin (p. 523·3); mecobalamin (p. 2108·1).

Orogyn *CCD, Fr.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3); *Lactobacillus crispatus.*
Restoration of vaginal flora.

Oroheks *Abdi, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Oroheks Plus *Abdi, Turk.; Tripharma, Turk.*
Chlorhexidine gluconate (p. 1743·3); benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Oroken *Sanofi-Aventis, Fr.*
Cefixime (p. 240·3).
Respiratory-tract infections; otitis media; pyelonephritis; urinary-tract infections.

Orole *Kaizen, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Orole-D *Kaizen, India.*
Omeprazole (p. 1867·2); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Oromag *Theramex, Mon.*
Magnesium lactate (p. 1787·2); magnesium citrate (p. 1857·1).
Magnesium deficiency.

Oromic *Janssen-Cilag, Spain.†*
Itraconazole (p. 583·3).
Fungal infections.

Oromone *Abbott, Fr.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Oromylase *Biogaran, Fr.†*
Amylase (p. 2442·1).
Throat inflammation.

Oronac *Embiotic, India.*
Tablets; injection: Diclofenac sodium (p. 48·3).
Inflammation; pain.

Embiotic, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Oronac Plus *Embiotic, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Oro-NaF *Germiphene, Canad.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Oronazol *KRKA, Rus.*
Ketoconazole (p. 585·3).
Fungal infections.

Oronime *Aurobindo, Ital.*
Nimesulide (p. 101·3).
Pain.

Oronine H *Classical Remedia, Canad.†*
Chlorhexidine gluconate (p. 1743·3).

Oroperidys *Pierre Fabre Sante, Belg.; Pierre Fabre, Cz.; Pierre Fabre, Gr.; Pierre Fabre, Port.*
Domperidone (p. 1838·1).
Nausea and vomiting; bloating; gastro-oesophageal reflux.

Oropéridys *Pierre Fabre, Fr.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastrointestinal motility disorders.

Oropigma Gel *Dermoprog, Ital.*
Ubidecarenone (p. 2637·1).

Oropram *Pharmaco, Hung.†; Plus Pharma, Pol.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Oropur *NHS, Fr.*
Parsley oil (p. 2583·3); sunflower oil (p. 2098·1).
Halitosis.

Ororhinathiol *Sanofi-Aventis, Belg.*
Dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Orosept
Note: this name may be used for preparations of different composition.
Triomed, S.Afr.†
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Orosprevent *Bayer, Braz.*
Nifedipine (p. 1447·2); aspirin (p. 22·2).

Orotam *Rishab, India.*
Piracetam (p. 393·3).
Cortical myoclonus; mental function impairment.

Orotate *Akesiss, India.*
Calcium orotate (p. 2578·1).
Calcium supplement; osteoporosis.

Orotral *SM, Gr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Orotre *Theramex, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Orotrex *Medinfar, Port.*
Isotretinoin (p. 1706·2).
Acne.

Orovas *Pharma Nutria, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Orovit *Biomiicron, India.*
Oral drops: Vitamins; minerals; trace elements; glutamic acid (p. 2070·2); choline bitartrate (p. 2055·2).

Biomiicron, India.
Syrup: Vitamins; minerals; trace elements; glutamic acid (p. 2070·2); lysine hydrochloride (p. 2079·3).

Biomiicron, India.
Tablets: Vitamins; minerals; trace elements; glutamic acid (p. 2070·2).

Orovital-G *Forgo, India.*
Vitamins; minerals; trace elements; ginseng (p. 2513·3).

Orovite *Thornton & Ross, Irl.†; Thornton & Ross, UK.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Orovite '7' *Thornton & Ross, UK.*
Vitamins.

Oroxadin *Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Oroxin *Pharos, Indon.*
Oxomemazine (p. 637·1); guaifenesin (p. 1666·2).
Cough.

Oroxine *Aspen, Austral.; Aspen, Malaysia; GSK, Singapore.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer; thyroiditis; suppression of thyrotrophin.

Orozamudol *Meda, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Orozim *Arex, Venez.*
⊗Pancreatin (p. 2579·3).
Digestive disorders.

Orozone-SB *Solitaire, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Orpar *Pharmasant, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Muscle pain.

Orphamol *Torrent, India.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).

Orphen *Solas, Indon.*
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

Orphenadol *YSP, Malaysia; Yung Shin, Singapore.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain and spasm.

Orphenadrine Compound *Sandoz, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3); orphenadrine citrate (p. 909·2).
Painful musculoskeletal disorders.

Orphengesic
Note: this name may be used for preparations of different composition.
Bangkok Lab & Cosmetic, Thai.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain; tension headache.

Par, USA.†
Orphenadrine citrate (p. 909·2); aspirin (p. 22·2); caffeine (p. 1203·3).
Musculoskeletal pain.

Orphensic *General Drugs, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm; tension headache; rheumatism.

Orphipal *GSK, India.*
Orphenadrine hydrochloride (p. 909·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Orphol *Madaus, Ger.†; Opfermann, Ger.†; Rottapharm, Ger.†*
Codergocrine mesilate (p. 389·2).
Mental function disorders.

Orpic *Aspen, S.Afr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Dey's, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Orpic-T *Dey's, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).
Bacterial infections.

Orpidix *Proel, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis; allergic eye disorders; asthma.

Orpime *Orchid, India; Orchid, Thai.†*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Orpin *Orchid, Rus.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Orpro *Ordain, India.*
Rabeprazole (p. 1881·1).
Gastro-oesophageal reflux; hypersecretory disorders; peptic ulcer.

Orprozil *Orchid, India.*
Cefprozil (p. 248·2).
Bacterial infections.

Orra-D *Orion, India.*
⊗Diclofenac potassium (p. 48·3); serrapeptase (p. 2613·3).

Orregel *Hoe, Malaysia.*
Cetylpyridinium chloride (p. 1743·1); choline salicylate (p. 39·2).
Teething pain; mouth ulcers; oral pain.

Orrepaste *Hoe, Malaysia; Hoe, Singapore.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

ORS *GPO, Thai.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Oral rehydration therapy.

O.R.S. *Clinova, UK.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); riboflavin-5-phosphate; glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1) (p. 1780·1).
Oral rehydration.

ORS Bicarbonate *Pharmaniaga, Malaysia.*
Sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Orset *Servipharm, Israel.*
Oral rehydration solution (p. 1780·1).
Oral rehydration therapy.

Orsinon *Rekah, Israel.†*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Ors-L *Juggat, India.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2).

Orsoten *KRKA, Rus.*
Orlistat (p. 2577·1).
Obesity.

Orstanorm *Amdipharm, Fin.; Amdipharm, Swed.*
Dihydroergotamine mesilate (p. 672·2).
Orthostatic hypotension; migraine; hypotension.

Ortakehl *Sanum-Kehlbeck, Cz.*
Penicillium roquefortii.
Homoeopathic preparation.

Ortanol *Lek, Cz.; Sandoz, Cz.; Sandoz, Gr.; Sandoz, Pol.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Sandoz, Denm.
Omeprazole magnesium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Orthal Forte *Cipla, India.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Digestive disorders.

Orthangin novo *Nycomed, Ger.†*
Crataegus (p. 2488·1).
Heart failure.

Ortho 0.5/35 *Janssen-Ortho, Canad.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho 1/35 *Janssen-Ortho, Canad.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho 7/7/7 *Janssen-Ortho, Canad.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Ortho 777 *Mochida, Jpn.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Ortho Applicator *Johnson & Johnson, India.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Ortho Cyclen *Janssen-Cilag, Israel; Janssen, USA.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho Evra *Janssen, USA.*
Norelgestromin (p. 2294·1); ethinylestradiol (p. 2275·3).
Combined transdermal contraceptive.

Ortho Gynest Depot *Janssen-Cilag, Ital.*
Estriol (p. 2274·3).
Menopausal disorders.

Ortho Micronor *Ortho McNeil, USA.*
Norethisterone (p. 2294·2).
Formerly known as Micronor.
Progestogen-only oral contraceptive.

Ortho Tri-Cyclen *Janssen, USA.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Orthobact *Arvincare, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Orthobid *Abbott, India.*
Nimesulide (p. 101·3).
Pain; inflammation.

Orthobid Plus *Abbott, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Orthobid-MR *Abbott, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Orthocel *Biochem, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis.

Ortho-Cept *Janssen-Ortho, Canad.; Ortho McNeil, USA.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Orthocerin-G *Mediez, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3).

Orthoclone *Janssen-Cilag, Gr.; Janssen-Cilag, S.Afr.†*
Muromonab-CD3 (p. 1960·1).
Immunosuppressant; acute renal, cardiac, or hepatic allograft rejection.

Orthoclone OKT3 *Janssen-Cilag, Austral.†; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Fin.†; Janssen-Cilag, Fr.†; Janssen-Cilag, Ger.†; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.†; Janssen-Cilag, Norw.†; Janssen-Cilag, NZ; Janssen-Cilag, Port.; Janssen-Cilag, Singapore; Janssen-Cilag, Swed.†; Janssen-Cilag, Switz.†; Gurel, Turk.†; Ortho Biotech, USA.†*
Muromonab-CD3 (p. 1960·1).
Transplant rejection.

Orthocos *Symbiosis, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Ortho-Creme *Janssen-Cilag, Irl.†*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Orthocure *Symbiosis, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Orthodac *Pharmatech, India.*
Tablets: Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Pharmatech, India.
Topical gel: Benzyl alcohol (p. 1739·3); diclofenac sodium (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Orthodac MR *Pharmatech, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Orthodex *Psychotropics, India.*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3); ibuprofen (p. 68·2).

Orthodex Plus *Psychotropics, India.*
Dextropropoxyphene hydrochloride (p. 43·3); ibuprofen (p. 68·2).

Orthodex-MR *Psychotropics, India.*
Nimesulide (p. 101·3); tizanidine (p. 2026·2).

Ortho-Dienestrol *Ortho McNeil, USA.†*
Dienestrol (p. 2267·2).
Atrophic vaginitis; kraurosis vulvae.

Ortho-Est *Janssen-Cilag, S.Afr.*
Estropipate (p. 2275·2).
Menopausal disorders; osteoporosis.

Ortho-Gynest *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.†; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.; Janssen-Cilag, UK†; Janssen-Cilag, Venez.*
Estriol (p. 2274·3).
Menopausal disorders; vulvovaginal disorders due to oestrogen deficiency; oestrogen deficiency; pruritus vulvae; dyspareunia.

Ortho-Gynol *Janssen-Cilag, Austral.†; Janssen-Cilag, NZ.†*
An octoxinol (p. 2199·3).
Contraceptive.

Johnson & Johnson, Canad.†
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Orthokin *Pharma Investi, Chile.*
Chlorhexidine gluconate (p. 1743·3); zinc acetate (p. 2126·1); sodium fluoride (p. 2089·2).
Oral hygiene.

Ortho-Maren retard *Lubapharm, Switz.†*
⊗Pholedrine sulfate (p. 1469·3); norfenefrine hydrochloride (p. 1459·1).
Hypotension.

Orthon *Remedina, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Orthonett Novum *Janssen-Cilag, Swed.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ortho-Novum 1/35 *Codepharma, Fr.†; Janssen-Cilag, Mex.; Ortho McNeil, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho-Novum 1/50 *Ortho McNeil, USA.†*
Norethisterone (p. 2294·2); mestranol (p. 2291·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho-Novum 7/7/7 *Ortho McNeil, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Ortho-Novum 10/11 *Ortho McNeil, USA.†*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Biphasic oral contraceptive.

Orthoris *Symbiosis, India.*
Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Orthorub *Clinique Lafontaine, Canad.†*
Cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Orthotime *Solitaire, India.*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2).

Orthovisc *Helix, Canad.; Plasmaconcept, Ger.; Anika, Israel†; Anika, Singapore; Biomeks, Turk.; Surgicraft, UK; Ortho Biotech, USA.*
Sodium hyaluronate (p. 2526·2).
Oosteoarthritis.

OrthoWash *Omnii, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Orthoxicol Cold & Flu *Johnson & Johnson, NZ.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Orthoxicol Day & Night *Johnson & Johnson, NZ.†*
⊗Day caplets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); night caplets, paracetamol; chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Orti C *Seroyal, Canad.†*
Vitamin C (p. 2110·3).

Ortinase *Osper, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Ortinose *Laborate, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Ortisan *Cedar Health, UK.*
Fruit; fibre.
Constipation.

Ortis, Ital.
Senna (p. 1885·1); tamarind (p. 1892·2).
Constipation.

Ortitruw *Truw, Ger.*
Echinacea angust. (p. 2498·1).
Homoeopathic preparation.

Orto Dermo P *Normon, Spain.†*
Povidone-iodine (p. 1767·1).
Burns; skin disinfection; wounds.

Ortocal-CT *Biomax, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Ortocer *Evershine, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ortocol *Mavi, Mex.*
Diclofenac (p. 48·3); vitamin B substances (p. 2102·3).
Inflammation; neuritis; pain.

Ortodermina *Sofar, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Surface anaesthesia of skin and mucous membranes.

Ortofen *Tatkhimfarm, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Ortofer *Bryntsalov, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain.

Ortoflan *Medley, Braz.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Ortoflex *Tallinn, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ortophen *Biochimic, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Ortopsique *Psicofarma, Mex.*
Diazepam (p. 1063·2).
Anxiety disorders; epilepsy; alcohol withdrawal syndrome; insomnia; skeletal muscle spasm.

Ortosamin *Germed, Braz.*
Glucosamine (p. 2515·3).

Ortosol P *Galderma, Braz.*
Piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1).
Scalp disorders.

Ortoton *Recordati, Ger.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm and tension.

Ortoxine *Volta, Chile.*
Chlorhexidine hydrochloride (p. 1743·3).
Oral hygiene.

Ortrel *Janssen-Cilag, Venez.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ortrip *Pharmasant, Thai.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Ortrizol *Farcoral, Mex.*
Metronidazole (p. 936·1).
Trichomoniasis; giardiasis; ascariasis.

Or-Tyl *Ortega, USA.†*
Dicycloverine hydrochloride (p. 1834·2).
Functional bowel/irritable bowel syndrome.

Orudis *Sanofi-Aventis, Austral.; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Aventis, NZ†; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Hawgreen, UK.*
Ketoprofen (p. 79·1).
Pain; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; oedema; renal colic.

Oruf *Arvincare, India.*
Cefuroxime (p. 255·2).
Bacterial infections.

Orugesic *Sanofi-Aventis, Irl.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Orungal *Janssen-Cilag, Hung.; Janssen-Cilag, Pol.; Janssen-Cilag, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Orungamin *Ozon, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Orunit *Obolenskoe, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Orunzol *Tekhnolog, Ukr.†*
Itraconazole (p. 583·3).
Fungal infections.

Oruvail *Sanofi-Aventis, Austral.; Sanofi-Aventis, Gr.; Aventis, Hong Kong†; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Aventis, S.Afr.†; Sanofi-Aventis, Singapore; Aventis, Thai.; Sanofi-Aventis, UK.*
Ketoprofen (p. 79·1).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Orvas *Systopic, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Orvaz-EZ *Systopic, India.*
Atorvastatin (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Orvaz-FT *Systopic, India.*
Atorvastatin (p. 1309·2); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Orvirem *Olifen, Rus.*
Rimantadine hydrochloride (p. 1012·2).
Influenza.

Oryant *CKD, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Orymax *Evershine, India.*
Capsules: Betacarotene (p. 2051·1); grape (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); mecobalamin (p. 2108·1).

Evershine, India.
Soft gel capsules: Grape (p. 2521·3); lutein (p. 2079·2); lycopene (p. 2546·2); vitamins.

Orzid *Orchid, India; Orchid, Rus.; Orchid, S.Afr.; Orchid, Ukr.†*
Ceftazidime (p. 250·2).
Bacterial infections.

OS *Nutricia, Ital.*
Foods for special diets.
Propionic acidaemia; methylmalonic aciduria.

Os *Nutricia-Bago, Arg.*
Food for special diets.
Metabolic disorders.

Osa Gel de dentition *Iromedica, Switz.*
Salicylamide (p. 129·2); lidocaine hydrochloride (p. 1988·2); dexpanthenol (p. 2582·2).
Teething pain.

Osadrox *Sandoz, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Osaflexan *Rottapharm, Fr.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Osagel *Farmanic, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Osalen *Anpharm, Pol.†; Eczacibasi, Turk.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osamin *Erlimpex, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1).
Osteoarthritis; dietary supplement for healthy joints.

Osamine *Unison, Thai.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Osangin *Antonetto, Ital.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disinfection.

Osani *Sanify, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Osani-D *Sanify, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Osani-DS *Sanify, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Osani-M *Sanify, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Osani-NT *Sanify, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Osani-O *Sanify, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Osani-T *Sanify, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Osanit
Note: this name may be used for preparations of different composition.
Iasis, Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.
Zepperfeldt, Ger.
Magnesium phosphoricum (p. 1787·3); calcium carbonicum (p. 1824·3); ferrum phosphoricum (p. 2077·1); matricaria recutita (p. 2474·1); calcium phosphoricum (p. 1784·2).
Homoeopathic preparation.

Osanit Chamomilla *Schmidgall, Austria.*
Chamomilla recutita (p. 2474·1).
Homoeopathic preparation.

Osanit Zahnungskügelchen *Schmidgall, Austria.*
Chamomilla recutita (p. 2474·1); calcium phosphoricum (p. 1784·2); magnesium phosphoricum (p. 1787·3); calcium carbonicum (p. 1824·3); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Osarbon *Nizhpharm, Rus.*
Acetarsol (p. 926·2); boric acid (p. 2459·3).
Trichomoniasis.

Osarcid *Nizpharm, Rus.*
Acetarsol (p. 926·2); sulfanilamide (p. 368·1).
Trichomoniasis.

Osart *Invision, India.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Osart-H *Invision, India.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Osaston *Angelini, Gr.; Faran, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osaten *Offenbach, Mex.*
Ketotifen (p. 631·3).
Hypersensitivity.

Osatrol *Darya-Varia, Indon.†*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Osbonelle *Actavis, Irl.; Actavis, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis; bone metastases.

Os-Cal *Sanofi-Aventis, Braz.; Wyeth, Canad.†; Sanofi-Aventis, Hong Kong; SmithKline Beecham Consumer, USA.*
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency.
Sanofi-Aventis, Singapore.
Calcium (p. 1783·1).
Calcium deficiency; calcium supplement.

Oscal
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.
Osper, India.
Calcium carbonate (p. 1824·3).
Hyperphosphataemia in renal failure; gastric hyperacidity.

Oscal-12 *P & B, India.*
Injection: Calcium glubionate (p. 1783·2); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).
Osteomalacia; osteoporosis; calcium supplement.
P & B, India.
Tablets: Calcium gluconate (p. 1783·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); colecalciferol (p. 2113·1).
Dietary supplement.

Os-Cal D *Wyeth, Canad.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Oscal D *Sanofi-Aventis, Venez.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium and vitamin D supplement.

Os-Cal + D *Sanofi-Aventis, Hong Kong; GSK Consumer, USA.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium supplement; calcium deficiency.
Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.
Sanofi-Aventis, Singapore.
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

OsCal Extra D *GSK, USA.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).

Os-Cal Forte *SmithKline Beecham Consumer, USA.*
Vitamins; minerals; iron (p. 2073·1).

Os-Cal Fortified *GSK Consumer, USA.*
Vitamins; minerals; calcium (p. 1783·1); iron (p. 2073·1).

Os-Cal Plus *SmithKline Beecham, USA.*
Vitamins; minerals; iron (p. 2073·1).

Os-Cal Ultra *GSK Consumer, USA.*
Vitamins; minerals.

Oscale *Gache, Venez.*
Calcium from oyster shells (p. 1783·1).
Calcium supplement; osteoporosis.

Oscap *Thorne, Canad.†*
Vitamins; minerals.

Oscart *Mayoly-Spindler, Fr.†*
Glucosamine (p. 2515·3).
Joint disorders.

Oscillococcinum *Key Sun, Austral.; Boiron, Canad.; Boiron, Fr.; Boiron, Hung.; Boiron, Neth.; Boiron, Port.; Boiron, Rus.; Boiron, Switz.; Boiron, Ukr.*
Anas barbariae hepatis et cordis (p. 2444·1).
Homoeopathic preparation.

Oscimin *Larken, USA.*
Hyoscyamine sulfate (p. 1848·1).

Osclav *Osper, India.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Oscob Forte *Auspi, India.*
Thioctic acid (p. 2629·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine (p. 2105·3); thiamine nitrate (p. 2103·2); vitamin E (p. 2119·1).

Oscodin *Osper, India.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); menthol (p. 2553·2).

Oscorel *Sanofi-Aventis, Neth.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders.

Osdil *Troikaa, India.*
Valethamate bromide (p. 1895·2).
Dysmenorrhoea; smooth muscle spasm.

Osdip *Auspi, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Osdip-MR *Auspi, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Osdoril *Osmed, India.*
⊗Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); ephedrine (p. 1663·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Osdren *Mintlab, Chile.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osdryl *Auspi, India.*
Ammonium chloride (p. 1656·1); diphenhydramine (p. 626·1); menthol (p. 2553·2); sodium citrate (p. 1781·2).

Osec *Crescent, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Oseflox *Osper, India.*
Ofloxacin (p. 334·3).
Ear infections.

Osel *Koutsoumani, Gr.*
⊗Atenolol (p. 1308·2).

Osemin *Degorts, Mex.*
⊗Furosemide (p. 1387·1).

Oseni *Takeda, USA.*
Alogliptin benzoate (p. 467·2); pioglitazone (p. 493·1).
Diabetes mellitus.

Oseo Total *New Life, Arg.*
Amino acids; trace elements; vitamins.
Dietary supplement.

Oseofem *Biotenk, Arg.†*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Oseofort *Silesia, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Hypocalcaemia; osteoporosis.

Oseotal *Chemopharma, Chile.*
Alendronic acid (p. 1171·3).
Osteoporosis.

Oseotenk *Biotenk, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Oseototal *Novartis, Spain.†*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis.

O-Set *United Biotech, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Oset *Medley, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Osetron *Reddy, India; Reddy, Ukr.*
Ondansetron (p. 1872·1).
Nausea and vomiting.
Reddy, Malaysia; Reddy, Rus.; Reddy, Singapore.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Oseum
Note: this name may be used for preparations of different composition.
Grossman, Mex.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; osteolysis of malignancy; Paget's disease of bone; reflex sympathetic dystrophy; hypercalcaemia.
Raffo, Chile.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osex *Comed, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2).

Osex Forte *Comed, India.*
Calcium (p. 1783·1); phosphorus (p. 2589·2); zinc sulfate (p. 2126·2).

Osfer *Auspi, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); selenium dioxide (p. 2087·1); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Osfit *Kalbe, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); boron citrate; zinc sulfate (p. 2126·2); copper sulfate (p. 2057·2); chromium picolinate (p. 2056·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); silica.
Osteoporosis; dietary supplement for healthy bones.

Osfit DHA *Kalbe, Indon.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); tuna fish oil.
Dietary supplement in pregnancy and lactation.

Osflex *Novell, Indon.*
Sodium hyaluronate (p. 2526·2).
Degenerative joint disorders; orthopaedic surgery.

Osflox *Auspi, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Osflox-OR *Auspi, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Osfo *Gap, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Osfolate *Baxter Oncology, Fr.†*
Calcium folinate (p. 2066·3).
Drug-induced megaloblastic anaemias; prevention of methotrexate toxicity.

Osfolato *Mayoly-Spindler, Ital.*
Calcium folinate (p. 2066·3).
Folate deficiency; reversal of methotrexate toxicity.

Oshdol *Mystico, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Oshell Forte *Lancer, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Oshflox *Mystico, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oshrid *Mystico, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Oshvert *Mystico, India.*
Betahistine (p. 2455·3).
Ménière's disease.

Oshzol-D *Mystico, India.*
Domperidone (p. 1838·1); rabeprazole (p. 1881·1).

Osibact *Osper, India.*
Levofloxacin (p. 315·3).
Bacterial infections.

Osiban *Kocak, Turk.*
Ibandronate sodium (p. 1184·2).

Osicare *Systopic, India.*
Glucosamine sulfate (p. 2515·3); dimethyl sulfone (p. 2493·3).

Osicare-DS *Systopic, India.*
Glucosamine sulfate potassium chloride (p. 2515·3).

O-Sid *Siam Bheasach, Thai.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Osidec *Osmed, India.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; osteoporosis; breast cancer; anaemias.

Osiflox *Osper, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Osiflox-OZ *Osper, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Osiflox-TZ *Osper, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Osigilatin *Sigillata, Neth.†*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Osigraft *Howmedica, Cz.; Olympus, Denm.; Howmedica, Fr.; Olympus, Ger.; Olympus, Gr.; Olympus, Irl.; Howmedica, Ital.; Olympus, Neth.; Howmedica, Pol.; Howmedica, Port.; Olympus, Spain; Olympus, Swed.; Stryker, Switz.*
Eptotermin alfa (p. 1177·3).
Fracture of tibia; promotion of bone formation in fractures.

Osihex *Osper, India.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Osimax *Tempo Scan Pacific, Indon.*
Syrup: Calcium hydrogen phosphate (p. 1783·3); calcium lactate (p. 1784·1); vitamins; lysine hydrochloride (p. 2079·3); turmeric (p. 2218·1).
Nutritional supplement.
Tempo Scan Pacific, Indon.
Tablets: Calcium hydrogen phosphate (p. 1783·3); calcium lactate (p. 1784·1); vitamins.
Calcium supplement.

Osimol *Biomedica, Gr.*
Calcium folinate (p. 2066·3).

Osin *Osmed, India.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Osipine *Astellas, Ital.*
Barnidipine hydrochloride (p. 1314·1).
Hypertension.

Osiren
Note: this name may be used for preparations of different composition.
Lafedar, Arg.
⊗Spironolactone (p. 1499·3).
Hypertension.
Probiomed, Mex.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Osiron *Osmed, India.*
Folic acid (p. 2063·1); iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Ositin *Gracia, Indon.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); turmeric (p. 2218·1); Indian frankincense (p. 2507·3); salix (p. 129·2).
Osteoarthritis; joint disorders.

Ositron *Leovan, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Osivan *Leovan, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Osivit-D3 *Kocak, Turk.*
Alfacalcidol (p. 2112·3).

Oskadon *Supra Ferbindo, Indon.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Oskadon Flu & Batuk Berdahak *Supra Ferbindo, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Influenza symptoms; cough.

Oskadon Migra *Supra Ferbindo, Indon.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Migraine.

Oskadon SP *Supra Ferbindo, Indon.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Myalgia.

Oskadryl *Supra Ferbindo, Indon.*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2).
Formerly contained dextromethorphan hydrobromide, guaifenesin, ephedrine hydrochloride, and chlorphenamine maleate.
Cough; influenza symptoms.

Oskamag *Supra Ferbindo, Indon.†*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence; dyspepsia.

Oskana *Velka, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Oskar *Mankind, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Oskept *Charoon Bhesaj, Thai.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; calcium supplement.

Oskoval *Demo, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; pathological gastric hypersecretion; acid aspiration.

Oslax *Obsurge, India.*
Sodium picosulfate (p. 1887·2).

Oslif *Novartis, Cz.; Pierre Fabre, Fr.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Ferrer, Spain.*
⊗Indacaterol maleate (p. 1211·2).
Obstructive airways disease.

Osmach *Ratiopharm, UK.*
⊗Fentanyl (p. 60·1).
Pain.

Osmanil *Winthrop, UK.*
⊗Fentanyl (p. 60·1).
Pain.

Osmetin 3 *Novell, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); omega-3 fatty acids (p. 1460·1).
Osteoarthritis; joint disorders.

Osmil
Note: this name may be used for preparations of different composition.
Opfermann, Ger.†
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Osmitrol *Baxter, Austral.; Baxter, Canad.; Baxter, Hong Kong†; Baxter, India; Baxter, Israel; Baxter, Singapore; Baxter, USA.*
⊗Mannitol (p. 1427·3).
Acute renal failure; cerebral oedema; forced diuresis; raised intra-ocular pressure; osmotic diuretic; oliguria.

Osmo *TNP, Thai.*
Vitamins; lysine (p. 2079·3).

Osmo Soft *Cooperation Pharmaceutique, Fr.*
Hydrogel dressing.
Burns.

Osmo-Adalat *Bayer, Israel; Bayer, Rus.; Bayer, Ukr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; ischaemic heart disease.

Osmofundin *Braun, Hong Kong†; Braun, Singapore.*
⊗Mannitol (p. 1427·3); sorbitol (p. 2092·1).

Osmofundin 15% N *Braun, Ger.*
⊗Mannitol (p. 1427·3).
Renal failure; forced diuresis.

Osmofundina *Braun, Port.*
⊗Mannitol (p. 1427·3).
Renal failure; ocular hypertension; raised intracranial pressure; oedema; forced diuresis.

Braun, Spain.
⊗Sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); mannitol (p. 1427·3).

Osmofundina Concentrada *Braun, Spain.*
⊗Mannitol (p. 1427·3).
Ascites; cranial hypertension; glaucoma; oedema; oliguria.

Osmogel
Note: this name may be used for preparations of different composition.
Alphrema, Ital.
Suleparoid (p. 1507·2); hyaluronic acid (p. 2526·2); centella (p. 1698·3); aescin (p. 2431·2).
Venous insufficiency.

Merck Medication Familiale, Fr.
Magnesium sulfate (p. 1787·3); lidocaine hydrochloride (p. 1988·2).
Soft-tissue disorders.

Micro, India.
Sodium chloride (p. 1795·1).
Eye irrigation.

Osmoglyn *Alcon, USA.†*
⊗Glycerol (p. 2517·2).
Glaucoma; raised intra-ocular pressure before ophthalmic surgery.

Osmogol *Promed, Rus.*
Macrogol 4000 (p. 2547·3).
Constipation.

Osmohale *Pharmaxis, Denm.; Pharmaxis, Irl.; Pharmaxis, Ital.; Pharmaxis, Neth.; Aldo, Spain; Pharmaxis, UK.*
⊗Mannitol (p. 1427·3).
Diagnosis of bronchial hyperresponsiveness.

Osmolac
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Ital.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; hepatic cirrhosis.

Gilbert, Fr.
Infant feed.
Diarrhoea.

Osmolagrimas *Elea, Arg.*
Sodium hyaluronate (p. 2526·2); macrogol 400 (p. 2547·3).
Dry eye.

Osmolak *Biofarma, Turk.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

OsmoLax
Note: this name may be used for preparations of different composition.
Key, Austral.
Macrogol 3350 (p. 2547·3).
Constipation.

Osmolite *Abbott, Austral.; Abbott, Chile; Abbott, Israel; Abbott, Ital.*
Preparations for enteral nutrition.

Abbott, Braz.; Abbott, Hong Kong; Abbott, NZ.
A range of preparations for enteral nutrition.

Abbott, Canad.; Abbott, Cz.; Abbott, Irl.; Abbott Nutrition, Singapore; Abbott, Turk.
Preparation for enteral nutrition.

Abbott Nutrition, UK.
Gluten- and lactose-free preparations for enteral nutrition.

Ross, USA.
A range of isotonic lactose-free preparations for enteral nutrition.

Osmolite HN *Abbott, Arg.; Abbott, Mex.†; Abbott, Philipp.; Abbott, Venez.*
Preparation for enteral nutrition.

Osmonagre *Motima, Fr.*
Evening primrose oil (p. 2502·2).
Premenstrual syndrome; dry skin.

Osmopak-Plus *Teva, Canad.*
Hydrated magnesium sulfate (p. 1787·3); benzocaine (p. 1980·2).
Superficial inflammatory conditions.

OsmoPrep *TMC, UK; Salix, USA.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Osmoran *Rafarm, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Osmorich *Abbott, Ital.*
Preparation for enteral nutrition.

Osmorol *Pisa, Mex.†*
⊗Mannitol (p. 1427·3).

Osmosal *Leiras, Fin.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration solution.

Osmosia *Floxia, Singapore.*
Barrier cream.

Osmosteril *Fresenius Kabi, Ger.; Fresenius Kabi, Neth.*
⊗Mannitol (p. 1427·3).
Forced diuresis; renal failure; intra-ocular hypertension; intracranial hypertension.

Osmotan G *Aguettant, Fr.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Osmotic-6 *Greenco, India.*
Borax (p. 2459·2); boric acid (p. 2459·3); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).

Osmotol *Chauvin, Fr.*
⊗Resorcinol (p. 1718·3); ephedrine hydrochloride (p. 1663·2).
Otitis externa.

Osmovist *Bayer, Canad.†*
Iotrolan (p. 1592·3).
Radiographic contrast medium.

Osmowin *Win-Medicare, India.*
Galactose (p. 1588·1); lactose (p. 2078·3); lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Osmycin *Pharos, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Osnervan *Aspen, Ger.*
Procyclidine hydrochloride (p. 912·2).
Parkinsonism; drug-induced extrapyramidal disorders.

Osnip *Auspi, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Osocillin *Osper, India.*
Ampicillin (p. 218·2).
Bacterial infections.

Osocillin-S *Osper, India.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Osoclox *Osper, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3).
Bacterial infections.

Osoferon *Osper, India.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Osomol *Pierre Rolland, Fr.*
Guaiacol (p. 1666·1); formaldehyde (p. 1752·2).
Root canal infections.

Osomox *Osper, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Osonide *Ranbaxy, India.†*
⊗Ciclesonide (p. 1626·3).
Asthma.

Osonim *Osper, India.*
Nimesulide (p. 101·3).
Pain.

Osonim-P *Osper, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Osotax *Osper, India.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Osotax-S *Osper, India.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Ospamox *Sandoz, Austria; Sandoz, Cz.; Sandoz, Gr.; Sandoz, Hong Kong; Sandoz, Hung.; Sandoz, Indon.; Sandoz, Malaysia; Novartis, NZ; Sandoz, Pol.; Sandoz, Port.; Sandoz, Rus.; Sandoz, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sandoz, Ukr.; Sandoz, Venez.
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ospar *Osper, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Ospas *Auspi, India.*
Drotaverine (p. 2497·3); nimesulide (p. 101·3).

Ospen *Sandoz, Austria; KRKA, Cz.; Sandoz, Cz.; Sandoz, Hung.; Sandoz, Pol.; KRKA, Rus.; Sandoz, Rus.; Sandoz, Switz.; KRKA, Ukr.†; Sandoz, Venez.*
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Sandoz, Gr.; Sandoz, Indon.; Sandoz, Malaysia; Sandoz, Singapore.†
Phenoxymethylpenicillin (p. 338·3) or benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Ospexin *Sandoz, Arg.; Sandoz, Austria; Sandoz, Cz.†; Sandoz, Hong Kong; Sandoz, Indon.; Sandoz, Malaysia; Sandoz, Singapore; Sandoz, Ukr.†*
Cefalexin (p. 234·1).
Bacterial infections.

Osphena *Shionogi, USA.*
⊗Ospemifene (p. 2298·1).
Menopausal vulvovaginal atrophy.

Ospical *Auspi, India.*
Calcium carbonate (p. 1824·3); lysine hydrochloride (p. 2079·3); colecalciferol (p. 2113·1).

Ospical-M *Auspi, India.*
Boron (p. 2052·3); calcium (p. 1783·1); copper (p. 2057·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).

Ospical-OP *Auspi, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1).

Ospicid *Auspi, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ospicid-D *Auspi, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ospidol *Osper, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ospidyne *Osper, India.*
Codeine phosphate (p. 40·2); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Ospil *IQFA, Mex.*
Captopril (p. 1331·2).

Ospocard *Unipack, Austria.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Ospolot *Teva Tuteur, Arg.; Phebra, Austral.; AOP Orphan, Austria; Desitin, Cz.; Desitin, Ger.; IFET (ΙΦΕΤ), Gr.; Desitin, Hung.; Desitin, Israel; Desitin, Switz.*
Sultiame (p. 549·2).
Epilepsy.

Ospol-OZ *Symbiosis, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ospor *Merck, Spain.†*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis.

Osporin
Note: this name may be used for preparations of different composition.
Olive Healthcare, Philipp.
Ciclosporin (p. 1945·2).
Transplant rejection; rheumatoid arthritis; psoriasis; atopic dermatitis; nephrotic syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ospronim *Intramed, S.Afr.†*
⊗Pentazocine lactate (p. 120·3).
Pain.

Osprovit *Osper, India.*
Vitamin B substances (p. 2102·3); iron choline citrate (p. 2060·2); magnesium sulfate (p. 1787·3); protein hydrosylate (p. 2086·2).

Osprovit-Z *Osper, India.*
Preparation for enteral nutrition.

Ospur Ca *Sanofi-Aventis, Ger.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Ospur D_3 *Sanofi Synthelabo, Ger.†*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; osteoporosis; osteomalacia; rickets.

Osra
Note: this name may be used for preparations of different composition.
Bennet, India.
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Hua, Thai.
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Osral *Panacea, India.*
⊗Raloxifene (p. 2303·1).
Osteoporosis.

Osrex *Osmed, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).

Osséans D3 *Sciencex, Fr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osseocalcina *Normal, Port.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Osseopor *Greenpharma, Braz.*
Calcium carbonate (p. 1824·3).

Osseor *Servier, China; Servier, Cz.; Servier, Irl.; Stroder, Ital.; Servier, Neth.; Servier, Pol.; Servier, Port.; Rovi, Spain.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Ossica *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.*
Ibandronate sodium (p. 1184·2).
Osteoporosis; bone metastases.

Ossidal *Truw, Ger.*
Apis mellifica (p. 2445·2); lachesis mutus (p. 2538·3); arnica montana (p. 2447·2); silybum marianum (p. 1561·1).
Homoeopathic preparation.

Ossidoss *Wockhardt, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ossidos-T *Wockhardt, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Ossidrol *Alapis, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Ossimet *Mylan, Ital.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Ossin
Note: this name may be used for preparations of different composition.
Basi, Port.
Chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Grunenthal, Ger.†
Sodium fluoride (p. 2089·2).
Osteoporosis.

Ossiplex *Gebro, Austria†; Henning, Ger.†; Sanofi-Aventis, Ger.†; Pharmacare, S.Afr.†*
Sodium fluoride (p. 2089·2); ascorbic acid (p. 2110·3).
Osteoporosis.

Ossivite *Wyeth, India.*
Colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Formerly contained vitamin A. colecalciferol, calcium carbonate, and calcium hydrogen phosphate.
Calcium and vitamin D deficiency.

Ossmax *Ranbaxy, Austral.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osso *Grisi, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Ossocal-D *Delta, Braz.†*
Calcium carbonate (p. 1824·3); ergocalciferol (p. 2113·3).
Calcium and vitamin D supplement.

Ossofez *TTK, India.*
Calcium (p. 1783·1); ferrous fumarate (p. 2060·3); magnesium carbonate (p. 1856·2); phosphorus (p. 2589·2); zinc sulfate (p. 2126·2).

Ossofortin D *Strathmann, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D_3 deficiency; osteoporosis.

Ossofortin forte *Strathmann, Ger.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D_3 deficiency; osteoporosis.

Ossofortin Plus *Strathmann, Ger.*
Effervescent tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); slow-release tablets, sodium fluoride (p. 2089·2).
Osteoporosis.

Ossopan *Germania, Austria; Ache, Braz.; Pierre Fabre, Fr.; TTK, India; Darya-Varia, Indon.; Pierre Fabre, Indon.; Sanofi, Irl.†; Pierre Fabre, Mex.; Pierre Fabre, Pol.; Pierre Fabre, Port.†; Robapharm, Switz.; Pierre Fabre, Thai.*
Hydroxyapatite (p. 2529·3).
Calcium and phosphorus deficiency; osteoporosis; bone fractures; calcium and phosphorus supplement; bone disorders; delayed callus formation; osteomalacia; mineral deficiency; growth disorders in children; dental caries prophylaxis; rickets.

Ossopan Alfa *TTK, India.*
Alfacalcidol (p. 2112·3); calcium (p. 1783·1); magnesium (p. 1786·3); phosphorus (p. 2589·2).

Ossoral *Dexa, Indon.*
Hydroxyapatite (p. 2529·3).
Osteoporosis; calcium supplement.

Ossotrat D *Delta, Braz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Ossovit *Interbat, Indon.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); magnesium (p. 1786·3); zinc (p. 2126·1); with or without vitamin K_1 (p. 2122·2).
Osteoporosis; calcium supplement.

Ossovit Plus *Interbat, Indon.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); phytomenadione (p. 2122·2); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2); copper (p. 2057·1); soya isoflavones (p. 2620·3).
Dietary supplement for healthy bones.

Osspulvit D_3 *Madaus, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Ossum *Zenacts, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ossum-D *Zenacts, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

OST *BJ Benjaosoth, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

OST Vit *Greater Pharma, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Ostac *Roche, Braz.†; Roche, Ger.; Roche, Gr.; Roche, Hong Kong†; Riemser, Neth.; Roche, Port.; Roche, Singapore; Roche, Swed.†; Roche, Switz.†*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Ostadil *Mibe, Neth.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostaham *Tiefenbacher, Neth.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostakair *PDC, India.*
Glucosamine sulfate (p. 2515·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); vitamin E (p. 2119·1).

Ostakair-D *PDC, India.*
Diacerein (p. 45·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); vitamin E (p. 2119·1).

Ostalert *Medarte, Gr.; Verisfield, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostalon *Gedeon Richter, Rus.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Gedeon Richter, Ukr.
Alendronic acid (p. 1171·3).
Osteoporosis.

Ostalon Calcium-D *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
4 Tablets, alendronate sodium (p. 1171·3); 28 tablets, colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Osteoporosis.

Ostaren *Utopian, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Ostarin *Otto, Indon.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Ostatac *Spedrog, Arg.*
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Ostatac Duo *Spedrog, Arg.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate (p. 2515·3).
Joint disorders.

Ostaven *Velka, Gr.*
Alendronate sodium (p. 1171·3).

Ostawin *Novaduo, India.*
Diacerein (p. 45·3); dimethyl sulfone (p. 2493·3); glucosamine sulfate potassium chloride (p. 2515·3).

Oste *Soho, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); zinc (p. 2126·1); magnesium (p. 1786·3).
Osteoarthritis; dietary supplement.

Oste OD *Soho, Indon.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; joint disorders.

Ostebon *Aristo, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Ostebon-M *Aristo, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium oxide (p. 1857·3); copper sulfate (p. 2057·2); manganese sulfate (p. 2081·2); sodium boron; selenium dioxide (p. 2087·1); chromium picolinate (p. 2056·1).

Ostedron *Kleva, Gr.; ICN, Pol.†*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis; hypercalcaemia of malignancy.

Osteel *Heel, Canad.†*
Arnica montana (p. 2447·2); asafetida (p. 2449·3); calcium phosphate tribasic (p. 1784·2); diadem spider; hecla lava; potassium iodide (p. 2336·3); sodium sulfate (p. 1888·1); stillingia.
Homoeopathic preparation.

Ostela *Coronet, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1).
Osteoarthritis; dietary supplement.

Ostelin *Roemmers, Arg.; IFET (ΙΦΕΤ), Gr.; Teofarma, Ital.*
Ergocalciferol (p. 2113·3).
Vitamin D supplement; vitamin D_2 deficiency.

Sanofi-Aventis, Austral.
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Ostelin ACD *Roemmers, Arg.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); ergocalciferol (p. 2113·3).
Dietary supplement.

Ostelin F *Roemmers, Arg.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3); sodium fluoride (p. 2089·2).
Vitamin supplement; dental caries prophylaxis.

Ostelox *Sanbe, Indon.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ostemax *Polpharma, Pol.; Polpharma, Ukr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osten *Takeda, Jpn.*
Ipriflavone (p. 1185·3).
Osteoporosis.

Ostena *Accord, S.Afr.*
Alendronate sodium (p. 1171·3).

Ostenan *Marjan, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostenil
Note: this name may be used for preparations of different composition.
Chemedica, Fr.; Chemedica, Ger.; Chemedica, Switz.; Bio-Gen, Turk.; Chemedica, UK.
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee; joint disorders.

Teva, Pol.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteo
Note: this name may be used for preparations of different composition.
Biomedica, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Healtheries, NZ.
Calcium carbonate (p. 1824·3).
Calcium supplement.

Osteo-4 *Manix, Philipp.*
Calcium gluconate (p. 1783·3); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Osteoporosis.

Osteo Bi-Flex *Bago, Chile.†*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Joint disorders.

Osteo Complex *Peter, Ital.*
Calcium (p. 1783·1); vitamin D (p. 2112·3); boron (p. 2052·3); fluoride (p. 2089·2); zinc (p. 2126·1); copper (p. 2057·1); equisetum (p. 2500·1); lupulus (p. 2546·1).
Nutritional supplement for healthy bones.

Osteo D *Teva, Hung.†; Teva, Thai.*
Calcitriol (p. 2113·1).
Renal osteodystrophy; osteoporosis; osteopathy.

Osteo Formula *Sisu, Canad.†*
Vitamin D (p. 2112·3); minerals.

Osteo Regime *Regime, Canad.†*
Vitamins; minerals.

Osteo Support *Pharmagenics, UK.*
Hydroxyapatite (p. 2529·3).
Bone disorders.

Osteoaid *Trianon, Philipp.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis.

Osteoartisi Active *Kapharma, Ukr.*
Glucosamine hydrochloride (p. 2515·3); celery (p. 2472·3); salix alba (p. 129·2); ginger (p. 1844·1).
Musculoskeletal and joint pain; gout.

Osteoartisi Active Plus *Kapharma, Ukr.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); celery (p. 2472·3); salix alba (p. 129·2); ginger (p. 1844·1).
Musculoskeletal and joint pain; gout.

Osteoartisi Max *Kapharma, Ukr.*
Glucosamine hydrochloride (p. 2515·3); calcium (p. 1783·1); phytomenadione (p. 2122·2); rutoside (p. 2505·3); colecalciferol (p. 2113·1); salix alba (p. 129·2); bacopa (p. 2452·1); ginkgo biloba (p. 2512·3); myrtillus (p. 2566·2); centella (p. 1698·3).
Osteoarthritis; rheumatoid arthritis; varicose veins; myositis.

Osteobel *Blubell, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); magnesium (p. 1786·3); zinc (p. 2126·1).

Osteobion *Centrum, Spain.†*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis.

Osteobon
Note: this name may be used for preparations of different composition.
Bago, Arg.; Cipla-Medpro, S.Afr.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteocal *TRB, Fr.†; Nicholas, Indon.; Farmalider, Spain.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement; osteoporosis; hyperphosphataemia.

Osteocal D3 *Genopharm, Fr.†; Doetsch, Grether, Switz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osteocal Plus *Nicholas, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium (p. 1786·3); manganese (p. 2081·2); zinc (p. 2126·1); sodium fluoride (p. 2089·2).
Calcium deficiency; calcium supplement; dietary supplement for healthy bones and teeth.

Osteocalcin *Arcola, USA.*
Calcitonin (salmon) (p. 1178·1).

Osteocalcio *Biofarma, Mex.*
Calcium (p. 1783·1); ergocalciferol (p. 2113·3).
Osteoporosis.

Osteocalm *Dielen, Fr.*
Collagen (p. 2483·2); colecalciferol (p. 2113·1); vitamin C (p. 2110·3); calcium (p. 1783·1); zinc (p. 2126·1).
Bone and cartilage disorders.

Osteocalmine *Oriental, Arg.*
Piroxicam (p. 125·3).
Inflammation; pain.

Osteocap *Mega Lifesciences, Malaysia.*
Calcitriol (p. 2113·1).
Osteoporosis; hypoparathyroidism; renal osteodystrophy; rickets.

Osteocaps *Merck, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osteocare *Vitabiotics, Hong Kong; Nobel, Turk.*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); vitamin D (p. 2112·3).
Calcium deficiency; calcium supplement.

Vitabiotics, Cz.; Vitabiotics, Rus.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2); magnesium hydroxide (p. 1857·2).
Osteoporosis; osteomalacia; dietary supplement.

Vitabiotics, Indon.; Vitabiotics, Philipp.†; Vitabiotics, Ukr.†
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).
Calcium and magnesium supplement; osteoporosis; nutritional supplement; calcium and vitamin D deficiency.

Vitabiotics, UK.
Calcium carbonate (p. 1824·3); calcium lactate (p. 1784·1); calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2); colecalciferol (p. 2113·1).

Vitabiotics, Hung.†
Calcium carbonate (p. 1824·3); magnesium (p. 1786·3); zinc (p. 2126·1); colecalciferol (p. 2113·1).
Calcium supplement.

Osteochek *Indoco, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1); pyridoxine hydrochloride (p. 2105·3); zinc sulfate (p. 2126·2).

Osteochondrin S *Dyckerhoff, Ger.†*
Ribonucleic acids from cattle and yeast (p. 2604·1).
Bone disorders.

Osteocip *Cipla, India.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1).

Osteocis *CIS, Fin.; CIS, Fr.; CIS, Irl.; CIS, Neth.; CIS, Port.; CIS, Spain; Schering, UK.*
Technetium-99m (p. 2228·1) oxidronate.
Bone scintigraphy; bone scanning; bone imaging.

Osteocit *Seaford, Canad.*
Calcium citrate (p. 1783·2).
Calcium supplement.

Osteocit-D *Seaford, Canad.*
Calcium citrate (p. 1783·2); vitamin D (p. 2112·3).

Osteoclar *Amnol, Ital.*
Dimethyl sulfone (p. 2493·3); green-lipped mussel (p. 2522·3); glucosamine (p. 2515·3); collagen (p. 2483·2); trace elements.
Nutritional supplement.

Osteocynesine *Boiron, Fr.; Boiron, Neth.†*
Calcarea carbonica (p. 1824·3); calcarea phosphorica (p. 1784·2); calcarea fluorica (p. 2053·1); sulfur iodatum (p. 2624·2).
Homoeopathic preparation.

Ostéocynésine *Boiron, Port.*
Calcarea carbonica ostreica (p. 1824·3); calcarea fluorica (p. 2053·1); calcarea phosphorica (p. 1784·2); sulfur iodatum (p. 2624·2).
Homoeopathic preparation.

Osteo-D
Note: this name may be used for preparations of different composition.
Med, Turk.
Calcitriol (p. 2113·1).
Renal osteodystrophy; osteoporosis.

Solvang, Philipp.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); simeticone (p. 1886·2).
Hyperacidity; calcium supplement.

OsteoD *Teva, Cz.*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Osteodidronel *Warner Chilcott, Belg.*
Etidronate disodium (p. 1182·3).
Postmenopausal osteoporosis.

Osteodol *Fem Care, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Osteodon *Zentiva, Cz.†; BioSaude, Port.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; Paget's disease of bone; osteoporosis.

Osteodrug *Med-One, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Osteodur *Vivax Gynopharm, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis; hypercalcaemia of malignancy; Paget's disease of bone.

Osteoeze *Galen, Irl.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

OsteoEze Active *Herron, Austral.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine hydrochloride (p. 2515·3).
Joint disorders.

OsteoEze Active + MSM *Herron, Austral.*
Chondroitin sulfate sodium (p. 2476·1); dimethyl sulfone (p. 2493·3); glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

OsteoEze Bone & Joint *Aspen, Austral.*
Glucosamine hydrochloride (p. 2515·3); calcium carbonate (p. 1824·3); vitamin D (p. 2112·3); vitamin K_1 (p. 2122·2).
Osteoarthritis.

Osteofar *Elofar, Braz.; Fahrenheit, Indon.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Osteofem
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets; hypocalcaemia.

Osteofene *AstraZeneca, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteofix
Note: this name may be used for preparations of different composition.
Knop, Chile.
Symphytum officinale (p. 2484·2).
Homoeopathic preparation.

Promedica, Ital.
Ipriflavone (p. 1185·3).
Postmenopausal osteoporosis.

Osteoflam
Note: this name may be used for preparations of different composition.
Indoco, India.
Injection; tablets: Diclofenac sodium (p. 48·3).
Inflammation; pain.

Indoco, India.
Topical gel: Diclofenac diethylamine (p. 48·3); linseed oil (p. 2544·2); methyl salicylate (p. 92·1).

Soho, Indon.
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2).
Osteoarthritis; dietary supplement for healthy joints.

Osteoflam-MR *Indoco, India.*
Diclofenac sodium (p. 48·3); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Painful muscle spasm.

Osteoflex *Aristo, India.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese sulfate (p. 2081·2); vitamin E (p. 2119·1).
Osteoarthritis.

Osteoform
Note: this name may be used for preparations of different composition.
Sigma, Braz.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Weiao, China.
Minerals; calcium ascorbate (p. 2111·1); colecalciferol (p. 2113·1).
Dietary supplement.

Osteofos
Note: this name may be used for preparations of different composition.
Cipla, Hong Kong; Cipla, India; Cipla, Ukr.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Dynamic, Philipp.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Menarini, Austria.
Colecalciferol (p. 2113·1); calcium phosphate (p. 1784·2).
Calcium and vitamin D deficiency; osteoporosis.

Osteofos D3 *Menarini, Irl.; Menarini, Ital.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osteofree *Pertiwi Agung, Malaysia; Pertiwi Agung, Singapore.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Osteo-G *Biomedica, India.*
Boron (p. 2052·3); calcium citrate (p. 1783·2); copper (p. 2057·1); magnesium (p. 1786·3); manganese (p. 2081·2); colecalciferol (p. 2113·1); zinc (p. 2126·1); soya isoflavones (p. 2620·3).

Osteogel *Pampa, Pol.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium sulfate (p. 1787·3).
Calcium and magnesium deficiency; osteoporosis; osteomalacia; hypoparathyroidism; tetany; long-term immobility; fractures.

Osteogen
Note: this name may be used for preparations of different composition.
Watkins, Canad.
Calcium citrate (p. 1783·2); silicon dioxide (p. 2208·3); vitamin C (p. 2110·3).

Richard, Fr.†
Pyridoxine phosphate (p. 2105·3); calcium ascorbate (p. 2111·1); magnesium deoxyribonucleinate (p. 2492·2); deoxyribonucleic acid (p. 2492·2).
Osteopathies; asthenia.

Osteogenon *Pierre Fabre, Cz.; Pierre Fabre, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Rus.; Pierre Fabre, Ukr.*
Hydroxyapatite (p. 2529·3).
Osteoporosis; fractures; osteopenia; calcium and phosphate deficiency; bone and joint disorders.

Osteo-Guard *Douglas, Canad.†*
Colecalciferol (p. 2113·1); hydroxyapatite (p. 2529·3); magnesium HVP chelate (p. 2048·3).

Osteoheel *Peithner, Hung.; Ebi, Switz.*
Hekla lava; kalium iodatum (p. 2336·3); asa foetida (p. 2449·3); stillingia sylvatica; araneus diadematus; natrium sulfuricum (p. 1888·1); mercurius praecipitatus ruber (p. 2555·3); calcium phosphoricum (p. 1784·2).
Homoeopathic preparation.

Osteojoin-D *Oxytech, India.*
Diacerein (p. 45·3); dimethyl sulfone (p. 2493·3); glucosamine sulfate potassium chloride (p. 2515·3).

Osteokom *Lapi, Indon.*
Cream: Glucosamine sulfate (p. 2515·3); chondroitin (p. 2476·1); camphor (p. 2466·2).
Osteoarthritis; joint disorders.

Lapi, Indon.
Caplets: Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1); manganese (p. 2081·2); magnesium glycerophosphate (p. 1787·2).
Osteoarthritis; dietary supplement for healthy joints.

Osteokom Forte *Lapi, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); selenium (p. 2086·3); zinc (p. 2126·1); manganese (p. 2081·2); magnesium glycerophosphate (p. 1787·2).
Osteoarthritis; dietary supplement for healthy joints.

Osteolax *Dynamic, Philipp.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Osteole *Pinewood, Irl.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Osteo-Life
Note: this name may be used for preparations of different composition.
Viatris, UK.
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium supplement.

Viva, Canad.†
Calcium HVP chelate (p. 2048·3); magnesium HVP chelate (p. 2048·3); colecalciferol (p. 2113·1).

Osteoligo *Clinique Lafontaine, Canad.†*
Calcium proteinate (p. 1783·1); calcium carbonate (p. 1824·3); magnesium proteinate (p. 1786·3); magnesium hydroxide (p. 1857·2).

Osteolip *Amnol, Ital.*
Thioctic acid (p. 2629·1); linoleic acid (p. 2509·2); asparagine; vitamins; minerals.
Nutritional supplement.

Osteolip Crema *Amnol, Ital.*
Thioctic acid (p. 2629·1); dimethyl sulfone (p. 2493·3); aescin (p. 2431·2).
Skin disorders.

Osteo-Logic *Quest, Canad.†*
Vitamin C (p. 2110·3); vitamin D (p. 2112·3); calcium (p. 1783·1); magnesium (p. 1786·3); silicon; zinc (p. 2126·1).

OsteoMax *Oftalmi, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteomax *Abdi, Turk.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteomed *Wallace, Singapore.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Osteomeg *Mega Lifesciences, Philipp.†*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Osteomel *Clonmel, Irl.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteomerck *Merck, Spain.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osteomin *Nycomed, Mex.*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis.

Osteomin Art *New Life, Arg.*
Vitamins; minerals.
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Osteomin D *Nycomed, Mex.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis; rickets; osteomalacia; tetany.

Osteonat *Pharmanel, Gr.*
Alendronate sodium (p. 1171·3).

Osteonate
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Risedronate sodium (p. 1189·3).
Osteoporosis.

Raffo, Arg.; Pharma Dynamics, S.Afr.
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Osteonic *Nicholas, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); zinc (p. 2126·1); magnesium (p. 1786·3).
Osteoarthritis; dietary supplement for healthy joints.

Osteonorm
Note: this name may be used for preparations of different composition.
Acis, Neth.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Caber, Ital.
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; multiple myeloma; hyperparathyroidism; osteoporosis.

Chrispa (Χριστα), Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

OsteoNutri *Medley, Braz.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Osteoporosis; osteomalacia; rickets; calcium and vitamin D supplement.

Osteoplex
Note: this name may be used for preparations of different composition.
Steierl, Austria.
Acidum silicicum (p. 2208·3); calcium carbonicum (p. 1824·3); calcium phosphoricum (p. 1784·2); symphytum (p. 2484·2).
Homoeopathic preparation.

Steierl, Ger.
Acidum silicicum (p. 2208·3); calcium carbonicum (p. 1824·3); calcium phosphoricum (p. 1784·2); symphytum (p. 2484·2).
Homoeopathic preparation.

Osteoplus
Note: this name may be used for preparations of different composition.
Chiesi, Braz.
Ipriflavone (p. 1185·3).
Osteoporosis.

Recordati, Ger.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osteopor
Note: this name may be used for preparations of different composition.
Pierre Fabre, Spain.
Hydroxyapatite (p. 2529·3).
Osteoporosis.

Combiphar, Indon.
Cimicifuga (p. 2478·1); red clover (p. 2482·1); calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Osteoporosis; menopausal disorders.

Osteoprevix D *Airela, Braz.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Osteopro
Note: this name may be used for preparations of different composition.
Health Perception, UK.
Ipriflavone (p. 1185·3); calcium (p. 1783·1); vitamins; minerals.
Osteoporosis.

Osteoprocare *Lifeforce, Canad.*
Minerals; vitamin D (p. 2112·3).

Osteor *Pyridam, Indon.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1); selenium (p. 2086·3).
Joint disorders.

Osteor Plus *Pyridam, Indon.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); ascorbic acid (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1); dimethyl sulfone (p. 2493·3).
Supplement for healthy joints; osteoarthritis.

Osteoral *Ache, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteor-C *Pyridam, Indon.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); capsicum (p. 2469·3); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Osteorel *Intermed, Gr.*
Calcium phosphate (p. 1784·2).
Calcium deficiency.

Osteo-Relief *Cenovis, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); capsicum (p. 2469·3).
Osteoarthritis; rheumatoid arthritis.

Osteo-Relief Plus MSM *Cenovis, Austral.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis.

Osteos
Note: this name may be used for preparations of different composition.
Help, Gr.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteosan *Silesia, Chile.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Osteosense Plus *Preferred Nutrition, Canad.†*
Vitamin C (p. 2110·3); vitamin D (p. 2112·3); minerals.

Osteoshield *FDC, India.*
Soya (p. 2092·3); calcium (p. 1783·1).
Dietary supplement in osteoporosis.

Osteosil Calcium *Ghimas, Ital.*
Calcium (p. 1783·1); equisetum (p. 2500·1).
Nutritional supplement.

Osteosol *Amersham, Fin.†*
Technetium-99m (p. 2228·1) medronate.
Radionuclide bone imaging.

Osteostab *Rottapharm, Ital.*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; multiple myeloma; hyperparathyroidism; osteoporosis.

Osteotin *Phapros, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2).
Joint disorders.

Osteoton
Note: this name may be used for preparations of different composition.
Gerolymatos, Gr.
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Osteotriol *Teva, Ger.; Teva, Rus.*
Calcitriol (p. 2113·1).
Renal osteodystrophy; osteoporosis; hypoparathyroidism.

Osteover *Veropharm, Rus.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis; hypercalcaemia.

Osteovile *Pharmanel, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Osteovit
Note: this name may be used for preparations of different composition.
Pharmadass, UK.
Vitamins; minerals; trace elements.

Sintexline, Spain.†
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osteovital *Investi, Arg.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Osteovital Plus *Investi, Arg.*
Powders, strontium ranelate (p. 1190·3); tablets, calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Osteoporosis.

Osteoz *Zodak, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Osteoz Plus *Zodak, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium hydroxide (p. 1857·2); zinc (p. 2126·1).

Osteoz-FR *Zodak, India.*
Calcium gluconate (p. 1783·3); cyanocobalamin (p. 2107·2); ferrous gluconate (p. 2061·2); folic acid (p. 2063·1).

Ostepam *Nordic, Fr.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; myeloma; osteolytic bone lesions; Paget's disease of bone.

Osteral *Silanes, Mex.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Osterepar *Polpharma, Rus.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Ostetan *Bama, Spain.†*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis.

Osteum *Vinas, Spain.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis; ectopic ossification.

Osteus *Farmanic, Gr.*
Calcium phosphate (p. 1784·2).
Calcium deficiency.

OsteVit-D *Key, Austral.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

OsteVit-D + Calcium *Key, Austral.*
Colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Calcium and vitamin D supplement.

Ostezolen *Frik, Turk.*
Zoledronic acid (p. 1192·3).

Ostical *GSK, Pol.†*
Calcium carbonate (p. 1824·3); calcium lactate gluconate (p. 1784·2).
Calcium deficiency; osteoporosis.

Osticalcin *Biomedica, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Osticer *Sanat, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ostiderm *Pedinol, USA.*
Roll-on: Aluminium chlorohydrate (p. 1694·1); camphor (p. 2466·2).
Hyperhidrosis; foot odour.

Pedinol, USA.
Lotion: Aluminium sulfate (p. 2440·2); zinc oxide (p. 1729·1).
Formerly contained aluminium sulfate and phenol.
Hyperhidrosis; foot odour.

Ostidil-D3 *SoSe, Ital.*
Alfacalcidol (p. 2112·3).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Ostifin-G *Zytras, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Ostifix *Farmedia, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

OstiGen *US Food & Pharmaceuticals, USA.*
Vitamin D (p. 2112·3); vitamin K (p. 2122·1); minerals.

Ostin *Osper, India.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Ostinate *Grunenthal, Port.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Ostine
Note: this name may be used for preparations of different composition.
Angelini, Spain.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Graha, Indon.
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); zinc (p. 2126·1).
Supplement for healthy joints.

Ostion *Lusoterapia, Port.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease.

Ostirein *Farmedia, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Osti-Rich *Akesiss, India.*
Calcitriol (p. 2113·1); calcium citrate (p. 1783·2); magnesium (p. 1786·3); zinc (p. 2126·1).

Ostisave *Zydus, India.*
Ademetionine (p. 2429·3).

Ostitriol *Farmedia, Gr.*
Calcitriol (p. 2113·1).
Vitamin D deficiency.

Ostium *Medley, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).

Ostiwel *Sanat, India.*
Chondroitin sulfate (p. 2476·1); glucosamine sulfate potassium chloride (p. 2515·3).

Ostiwel Forte *Sanat, India.*
Glucosamine hydrochloride (p. 2515·3); dimethyl sulfone (p. 2493·3).

Ostizox *Acme, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Osto-3 *Dewcare, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc (p. 2126·1).

Ostobon *Coloplast, UK.*
A deodorant powder for use with ostomies.

Ostocalcium *GSK, India.*
Syrup: Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1); vitamin B_{12} (p. 2107·2).
Calcium and vitamin D deficiency; rickets.

GSK, India.
Tablets: Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Ostocare *Cure & Care, India.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1); zinc (p. 2126·1); magnesium hydroxide (p. 1857·2).

Ostocavid *Sudmedica, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Ostocrat *Cratus, India.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); colecalciferol (p. 2113·1); zinc sulfate (p. 2126·2).

Osto-D2 *Triton, Canad.*
Ergocalciferol (p. 2113·3).

Ostodia-G *Zenon, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3).

Ostodronic *Apotex, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostofen
Note: this name may be used for preparations of different composition.
Torrent, India.
Ketoprofen (p. 79·1).
Rheumatic disorders; pain; inflammation.

Ostofit *Torrent, India.*
Chondroitin (p. 2476·1); glucosamine (p. 2515·3).

Ostogard *Micro, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ostogene *Genepharm, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Ostokind *Solitaire, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ostolek *Lek-Am, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostomax *Unipharma, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ostonat *Natco, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ostone-B12 *TP, Thai.*
Calcium (p. 1783·1); ergocalciferol (p. 2113·3); vitamin B_{12} (p. 2107·2).
Rickets; osteomalacia; pernicious anaemia.

Ostonex *Micro, India.*
Calcitriol (p. 2113·1); calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).
Osteoporosis; osteomalacia; hypocalcaemia.

Ostop *Abbott, India.*
10 Capsules, chondroitin sulfate (p. 2476·1); manganese (p. 2081·2); 10 capsules, glucosamine sulfate (p. 2515·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Osteoarthritis.

Ostoplus *Meditrina, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Ostopor *Unipharma, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Ostorel *Adroit, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ostorin *Active, India.*
Diacerein (p. 45·3).
Osteoarthritis.

Ostosalm *Pfizer, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Ostospray *Sun, India.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Ostotab *Dewcare, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ostovell *Novell, Indon.*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Ostovit *Geno, India.*
1 Capsule chondroitin sulfate (p. 2476·1); manganese (p. 2081·2); 2 capsules, glucosamine sulfate (p. 2515·3); vitamin C; vitamin E (p. 2119·1).
Osteoarthritis.

Ostovit-G *Geno, India.*
Glucosamine sulfate (p. 2515·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Ostowap D$_3$ *Lek-Am, Pol.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency; osteoporosis; osteomalacia; tetany.

Ostram *Merck, Arg.; Merck, Chile†; Merck Serono, Fr.; Galenica, Gr.; Merck Lipha Sante, Pol.; Merck Sante, Spain; Bracco, UK.*
Calcium phosphate (p. 1784·2).
Osteoporosis; calcium deficiency; calcium supplement.

Merck, Turk.
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Ostram D3 *Merck, Arg.; Merck, Chile; Bracco, Ital.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Ostram Vitamine D$_3$ *Merck Serono, Fr.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiencies; osteoporosis.

Ostramont *Chrispa (Χρισπα), Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Ostri *Osmed, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Ostrid *Otto, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ostril *Auspi, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Ostrimix *Dipa, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); zinc sulfate (p. 2126·2); magnesium hydroxide (p. 1857·2); dimethyl sulfone (p. 2493·3).
Supplement for healthy joints.

Ostrin Q10 *Qualiphar, Belg.*
Oyster extract; taurine (p. 2626·2); zinc orotate (p. 2126·1); ginseng (p. 2513·3); vitamin B substances (p. 2102·3); ubidecarenone (p. 2637·1); microencapsulated melon juice (Extramel).
Tonic.

Ostriol *Aristo, India; Fahrenheit, Indon.*
Calcitriol (p. 2113·1).
Hyperparathyroidism; hypoparathyroidism; rickets; hypocalcaemia; osteoporosis; renal osteodystrophy.

Ostriol Forte *Aristo, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc (p. 2126·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia.

Ostrobit *Cubit, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Ostrobit-CZ *Cubit, India.*
Calcitriol (p. 2113·1); calcium (p. 1783·1); zinc sulfate (p. 2126·2).

Ostron *Lifeplan, UK.*
Vitamin D (p. 2112·3); vitamin B_6 (p. 2105·3); folic acid (p. 2063·1); calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1); boron (p. 2052·3); copper (p. 2057·1); manganese (p. 2081·2).
Dietary supplement for healthy bones.

Östronara *Besins, Ger.; Kade, Ger.*
16 Tablets, estradiol valerate (p. 2271·2); 12 tablets, estradiol valerate; levonorgestrel (p. 2296·1).
Menopausal disorders; osteoporosis.

Ostulex *Novartis, Irl.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Osul-S *Biomax, India.*
Cefoperazone sodium (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

OsvaRen *Fresenius Medical, Austria; Fresenius Medical, Cz.; Fresenius Medical, Denm.; Fresenius Medical, Fin.; Fresenius Medical, Ger.; Fresenius Medical, Gr.; Fresenius Medical, Irl.; Fresenius Medical, Neth.; Fresenius Medical, Norw.; Fresenius Medical, Port.; Fresenius Medical, Spain; Fresenius Medical, Swed.; Fresenius Medical, UK.*
Calcium acetate (p. 1783·1); heavy magnesium carbonate (p. 1856·2).
Hyperphosphataemia in dialysis patients.

Osvical
Note: this name may be used for preparations of different composition.
Alodial, Port.†
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Osvical D *Alter, Spain.*
Calcium pidolate (p. 1784·3); colecalciferol (p. 2113·1).
Osteoporosis; calcium and vitamin D deficiency.

Osvion Plus *Solas, Indon.*
Ascorbic acid (p. 2110·3); vitamin E (p. 2119·1); vitamin D (p. 2112·3); manganese sulfate (p. 2081·2); zinc sulfate (p. 2126·2); selenium (p. 2086·3); glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3); chondroitin sulfate (p. 2476·1).
Osteoarthritis; maintenance of healthy joints.

Osvit *Baif, Ital.*
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1); fish oil (p. 1460·1).
Nutritional supplement for healthy bones.

Osyfen Plus *Pharma Synth, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1). Magnesium trisilicate (p. 1858·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Osynec-K *Pharma Synth, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Osyra *Astellas, Ital.*
Emollient.

Osyrol *Sanofi-Aventis, Ger.†*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; liver cirrhosis and ascites; oedema.

Osyrol Lasix *Sanofi-Aventis, Ger.†*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Oedema; ascites; hyperaldosteronism; liver cirrhosis.

Oszid *Osper, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ot *Panjon, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

O-Tab *Procure, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Otaci Diyet Life Psyllium Plus *Kurtsan, Turk.†*
Ispaghula (p. 1849·1); vitamin B substances (p. 2102·3).

Otacii Meyanbali *Kurtsan, Turk.*
Menthol (p. 2553·2); thymol (p. 1772·2); camphor (p. 2466·2).
Mouth and throat disorders.

Otaci Musillium *Kurtsan, Turk.†*
Ispaghula (p. 1849·1).

Otacii Oka Mentol *Kurtsan, Turk.*
Cineole (p. 2479·1); menthol (p. 2553·2); thymol (p. 1772·2); camphor (p. 2466·2).
Mouth and throat disorders.

Otacii Salvia *Kurtsan, Turk.*
Thymol (p. 1772·2); menthol (p. 2553·2); cineole (p. 2479·1); camphor (p. 2466·2).
Mouth and throat disorders.

Otago *Pharmacon, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Otago-O *Pharmacon, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Otalex
Note: this name may be used for preparations of different composition.
Roemmers, Venez.
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Otitis externa.

Otalex G
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Phenazone (p. 124·1); gentamicin sulfate (p. 304·2); procaine hydrochloride (p. 1994·3).
Otitis externa.

Otalgan
Note: this name may be used for preparations of different composition.
Exakta, Mex.
⊗Chloramphenicol (p. 257·1); prednisolone (p. 1645·2); lidocaine (p. 1988·1).
Earache.

Sudmedica, Ger.; Vifor, Ital.; Vifor, Switz.
Procaine hydrochloride (p. 1994·3); phenazone (p. 124·1).
Otitis media; earache.

Vifor, Austria.
Lidocaine hydrochloride (p. 1988·2); phenazone (p. 124·1).
Otitis media; earache.

Vifor, Belg.; Vifor, Neth.
Lidocaine hydrochloride (p. 1988·2).
Earache.

Otamina *Gache, Venez.*
Phenazone (p. 124·1).
Earache.

Otan *Vincenti, Venez.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2); phenazone (p. 124·1).
Ear infections.

Otandrol
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
⊗Chloramphenicol (p. 257·1); benzocaine (p. 1980·2); betamethasone dipropionate (p. 1623·3).
Infected ear disorders.

Otanol
Note: this name may be used for preparations of different composition.
Gebro, Austria.
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa; otitis media.

Otarex *Teva, Israel.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; premedication; pruritus; behaviour disorders in children.

Otari *Rafarm, Gr.*
Calcitriol (p. 2113·1).
Vitamin D deficiency.

Otaspirin *Natco, India.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Otaxem *Best, Mex.*
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

OTC HP Kit *Biochem, India.*
2 Capsules, omeprazole (p. 1867·2); 2 tablets, tinidazole (p. 949·2); 2 tablets, clarithromycin (p. 266·2).
Peptic ulcer.

Otede *Sanbe, Indon.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Otedram *Psicofarma, Mex.*
Bromazepam (p. 1041·2).
Nervous disorders.

Oteel H *Heel, Neth.*
Capsicum annuum (p. 2469·3); chamomilla (p. 2474·1); ferrum phosphoricum (p. 2077·1); mercurius dulcis (p. 2555·3); mercurius solubilis (p. 2555·3); plantago major (p. 2592·3); pulsatilla pratensis (p. 2600·2); silicea (p. 2208·3).
Homoeopathic preparation.

Otek-AC Plus *FDC, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); chloramphenicol (p. 257·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Otek-O *FDC, India.*
Glacial acetic acid (p. 2426·3); lidocaine hydrochloride (p. 1988·2); ofloxacin (p. 334·3).

Otelus *Specifar, Denm.†; Specifar, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Otenor *Rafarm, Gr.*
Sulfacetamide sodium (p. 361·1); chloramphenicol (p. 257·1).
Bacterial eye infections.

O-Tetra *PP Lab, Thai.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Otex *Dendron, UK.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Otex HC *Cassara, Arg.; D & M, Chile.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

OTG *Misha, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

OTG-D *Misha, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Othtric *Cubit, India.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Otiborin *Santen, Fin.*
⊗Boric acid (p. 2459·3); alcohol (p. 1733·1).
Ear infections.

Otic *Haledew, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Otic Domeboro *Bayer, USA.*
Acetic acid (p. 2426·3); aluminium acetate (p. 2440·1).
Superficial infections of the external auditory canal.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Otic Edge *Rivers Edge, USA.†*
⊗Phenazone (p. 124·1); benzocaine (p. 1980·2); policosanol (p. 1472·1); acetic acid (p. 2426·3); glycerol (p. 2517·2).
Acute otitis media; ear wax removal.

Otic-Care *Parmed, USA.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial ear infections.

Oticerim *Daudt, Braz.*
⊗Sodium perborate (p. 1770·1); urea (p. 1727·3).
Ear wax removal.

Otichek *Indoco, India.*
⊗Beclometasone (p. 1621·2); clotrimazole (p. 576·2); lidocaine (p. 1988·1); ofloxacin (p. 334·3).

Oticin *Teral, USA.*
Chloroxylenol (p. 1748·2); pramocaine hydrochloride (p. 1993·3).
Ear ache.

Oticin HC *Teral, USA.*
⊗Hydrocortisone (p. 1640·1); chloroxylenol (p. 1748·2); pramocaine hydrochloride (p. 1993·3).

Otic-O *Haledew, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oticom *Ashford, Philipp.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); nystatin (p. 590·3).
Otitis externa.

Oticum *Saval, Chile.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); betamethasone sodium phosphate (p. 1623·3); lidocaine hydrochloride (p. 1988·2).
Infected ear disorders.

Otide *United Biotech, India.*
Octreotide (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; prevention of complications following pancreatic surgery; variceal haemorrhage; HIV-associated diarrhoea.

Otiden *BMW, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).

Otiderm *BMW, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine (p. 1988·1).

Otidin *Teva, Israel.*
Phenazone (p. 124·1); tetracaine hydrochloride (p. 1996·3).
Otitis media.

Otidrop *Alembic, India.*
Lidocaine hydrochloride (p. 1988·2).

Otidrops *Hexa, Arg.*
⊗Lidocaine hydrochloride (p. 1988·2); cetrimide (p. 1742·1); prednisolone (p. 1645·2).
Earache.

Otifar *Farmaceutica H, Mex.*
⊗Benzocaine (p. 1980·2); chloramphenicol (p. 257·1); hydrocortisone (p. 1640·1).
External ear disorders.

Otiflox
Note: this name may be used for preparations of different composition.
Centaur, India.
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2); ofloxacin (p. 334·3).
Tramedico, Neth.
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa.

Otil *Elvipe, Gr.*
⊗Phenazone (p. 124·1); benzocaine (p. 1980·2); ephedrine sulfate (p. 1663·2).

Otilax *Epsilon Health, Gr.*
Otilonium bromide (p. 2578·2).

Otilin *Collins, Mex.†*
Lidocaine (p. 1988·1); neomycin (p. 329·3).

Otilon *Sanbe, Indon.*
⊗Fludrocortisone acetate (p. 1634·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Otitis externa.

Otimed
Note: this name may be used for preparations of different composition.
Steierl, Ger.
Pulsatilla pratensis (p. 2600·2); calcium jodatum (p. 1658·1).
Homoeopathic preparation.

Otimisin *Bilim, Turk.*
⊗Prednisolone metasulfobenzoate (p. 1645·2); tetracaine hydrochloride (p. 1996·3).
Otitis externa.

Otina *GSK, India.*
⊗Betamethasone valerate (p. 1624·1); chloramphenicol (p. 257·1); lidocaine hydrochloride (p. 1988·2).

Otinum *ICN, Pol.; Meda, Rus.; ICN, Ukr.; Meda, Ukr.*
Choline salicylate (p. 39·2).
Earache; removal of ear wax; otitis media; tympanitis.

Otio-cyl Ho-Len-Complex *Liebermann, Ger.*
Cocculus (p. 2483·1); calcium carb (p. 1824·3); chininum sulfuricum (p. 665·2); conium maculatum (p. 2524·3); tabacum (p. 2632·2); nitroglycerinum (p. 1391·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Otipax *Biocodex, Cz.; Biocodex, Fr.; Biocodex, Hung.; Biocodex, Rus.; Zambon, Switz.; Biocodex, Ukr.*
Lidocaine hydrochloride (p. 1988·2); phenazone (p. 124·1).
Otitis; earache.

Biocodex, Belg.
Lidocaine hydrochloride (p. 1988·2).
Otitis.

Otirelax *Rompharm, Rus.*
Phenazone (p. 124·1); lidocaine hydrochloride (p. 1988·2).
Otitis.

Otirilin *Grunenthal, Venez.*
Phenazone (p. 124·1); lidocaine hydrochloride (p. 1988·2).
Earache.

Otiser *Serral, Mex.*
⊗Benzocaine (p. 1980·2); chloramphenicol (p. 257·1); hydrocortisone (p. 1640·1).
Ear disorders.

Otisol *Bayer Consumer, Ukr.*
Phenazone (p. 124·1); benzocaine (p. 1980·2); phenylephrine hydrochloride (p. 1672·3).
Otitis media.

Otitex *Sudmedica, Ger.*
Docusate sodium (p. 1836·2).
Removal of ear wax.

OtiTricin *Bausch & Lomb, USA.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B (p. 342·3).
Bacterial ear infections.

Otix *M4, Spain.*
⊗Dexamethasone phosphate (p. 1631·1); polymyxin B sulfate (p. 342·3); trimethoprim (p. 381·2).
Otitis externa.

Oto Biotaer *Investi, Arg.†*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Otitis externa.

Oto Eni *Grossman, Mex.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1); lidocaine hydrochloride (p. 1988·2).
Infected external ear disorders.

Otobacid N *Torrex Chiesi, Cz.; Chiesi, Ger.*
⊗Dexamethasone (p. 1630·3); cinchocaine hydrochloride (p. 1983·2).
Ear disorders.

Oto-Betnovate *Farmoquimica, Braz.*
⊗Betamethasone valerate (p. 1624·1); chlorphenesin (p. 575·3); tetracaine hydrochloride (p. 1996·3).
Ear disorders.

Otobiotic
Note: this name may be used for preparations of different composition.
Denver, Arg.
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Ear disorders.
Schering, USA.
⊗Polymyxin B sulfate (p. 342·3); hydrocortisone (p. 1640·1).
Bacterial ear infections.

Otobrain *Farmila, Ital.*
Vitamins; glycerophospholipids; ginkgo biloba (p. 2512·3).
Nutritional supplement; vertigo; tinnitus.

Otobrol *Farmoz, Port.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Otocain *Abana, USA.*
Benzocaine (p. 1980·2).
Earache.

Otocalmia *Medical, Arg.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); turpentine oil (p. 2636·3).
Ear wax removal; earache.

Otocalmia Biotic *Medical, Arg.; Sanofi-Aventis, Arg.*
Neomycin sulfate (p. 330·1); phenazone (p. 124·1); sodium carbonate (p. 2617·3); cetrimide (p. 1742·1).
Otitis externa.

Otocalmine *Pharmacobel, Belg.*
Lidocaine hydrochloride (p. 1988·2).
Earache.

Otoceril *Menarini, Port.*
Paradichlorobenzene (p. 2583·2); benzocaine (p. 1980·2); chlorobutanol (p. 1747·2).
Removal of ear wax.

Otocerol *Lafedar, Arg.*
Phenazone (p. 124·1); sodium carbonate (p. 2618·1).
Ear disorders.

Otocerum *Reig Jofre, Spain.*
Phenol (p. 1763·3); chlorobutanol (p. 1747·2); benzocaine (p. 1980·2); turpentine oil (p. 2636·3); castor oil (p. 2472·1).
Removal of ear wax.

Otocin *Mankind, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Otocin-O *Mankind, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); lidocaine (p. 1988·1); ofloxacin (p. 334·3).

Otociprin *Fardi, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa.

Otocipro *Fortbenton, Arg.*
⊗Hydrocortisone (p. 1640·1); ciprofloxacin (p. 261·1).
Ear infections.

Otociriax *Farmoquimica, Braz.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Otoclean *Pharma Synth, India.*
Chlorobutanol (p. 1747·2); lidocaine (p. 1988·1); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).
Ear wax removal.

Otoclean Gotas Oticas *Cassara, Arg.*
Sodium carbonate (p. 2617·3); polysorbate 80 (p. 2203·3).
Ear wax removal; earache.

Otocomb Otic *Aspen, Austral.*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3); gramicidin (p. 308·3).
Otitis externa.

Otocort
Note: this name may be used for preparations of different composition.
Epsilon Health, Gr.
⊗Neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3); acetic acid (p. 2426·3).
Otitis externa.
Lemmon, USA.
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B (p. 342·3).
Bacterial ear infections.
Oftalmi, Venez.
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Otitis externa.

Otocos *Symbiosis, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Otocuril *Fabra, Arg.*
Phenazone (p. 124·1); sulfathiazole sodium (p. 368·3); ethacridine lactate (p. 1732·3).
Ear disorders.

Oto-cyl Ho-Len-Complex *Liebermann, Ger.*
Calcium carb. (p. 1824·3); chininum sulf. (p. 665·2); cocculus (p. 2483·1); conium (p. 2524·3); crataegus (p. 2488·1); glonoinum (p. 1391·2); sabadilla (p. 2611·2); tabacum (p. 2632·2).
Homoeopathic preparation.

Otodex *Sanofi-Aventis, Austral.*
⊗Framycetin sulfate (p. 301·2); gramicidin (p. 308·3); dexamethasone (p. 1630·3).
Ear disorders.

Otodolor
Note: this name may be used for preparations of different composition.
Peithner, Austria.
Capsicum annuum (p. 2469·3); chamomilla recutita (p. 2474·1); pulsatilla pratensis (p. 2600·2); acidum silicicum (p. 2208·3); acidum boricum (p. 2459·3).
Homoeopathic preparation.
Ursapharm, Ger.
⊗Glycerol (p. 2517·2); lidocaine hydrochloride (p. 1988·2).
Earache.

Otodolor Soft *Ursapharm, Ger.*
⊗Glycerol (p. 2517·2).
Removal of ear wax.

Otodril *Solitaire, India.*
Chlorphenamine maleate (p. 620·3); codeine (p. 40·2).

Oto-End *Larken, USA.*
⊗Chloroxylenol (p. 1748·2); hydrocortisone (p. 1640·1); pramocaine hydrochloride (p. 1993·3).

Otofa *Bouchara-Recordati, Fr.; Bouchara, Rus.; Interdelta, Switz.; Bouchara-Recordati, Ukr.*
Rifamycin sodium (p. 354·3).
Otitis.

Otofen *Arlex, Mex.*
Guaifenesin (p. 1666·2); oxolamine (p. 1671·2).
Cough.

Otoflour *Bell, India.*
Sodium fluoride (p. 2089·2).
Otosclerosis; conductive deafness.

Otoflox *Cassara, Arg.; Sensomed, Philipp.*
Ofloxacin (p. 334·3).
Otitis externa; otitis media; bacterial ear infections.

Otofluor *SIT, Ital.*
Sodium fluoride (p. 2089·2); calcium gluconate (p. 1783·3).
Otosclerosis; osteoporosis.

Otofoxin *Zambon, Braz.*
Ciprofloxacin (p. 261·1).

Otofren *Pfluger, Ger.*
Aconitum napellus (p. 2428·3); arsenum iodatum (p. 2448·1); aurum metallicum (p. 2521·1); graphites (p. 2522·1); hepar sulfuris calcarea (p. 1721·3); phytolacca americana (p. 2593·2); thuja occidentalis (p. 2629·3); viola odorata.
Homoeopathic preparation.

Otogen Calmante *Ern, Spain.*
Benzalkonium chloride (p. 1737·1); clove oil (p. 2481·3); phenol (p. 1763·3); tetracaine hydrochloride (p. 1996·3); menthol (p. 2553·2).
Ear disorders.

Otogesic *Johnson & Johnson, India.*
⊗Oxymethurea (p. 1762·3); cinchocaine (p. 1983·2); glycerol (p. 2517·2).
Formerly contained acediasulfone, oxymethurea, cinchocaine, and glycerol.
Ear infections; earache.

Otolef HC *Biosintex, Arg.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Otitis externa.

Otolin
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3); benzocaine (p. 1980·2); nipagin.
Otitis.

Otolisan *Pharma Investi, Chile.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); betamethasone sodium

phosphate (p. 1623·3); lidocaine hydrochloride (p. 1988·2).
Infected ear disorders.

Otolóide *Cimed, Braz.*
Phenol (p. 1763·3); procaine hydrochloride (p. 1994·3).
Ear disorders.

Otomar-HC *Marnel, USA.*
⊗Chloroxylenol (p. 1748·2); hydrocortisone (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Ear disorders.

Otomicina *Medley, Braz.*
Chloramphenicol (p. 257·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Otomide *Aelslife, Fr.†*
Hexamidine isetionate (p. 1754·3); lidocaine hydrochloride (p. 1988·2).
Otitis.

Otomidone *SIT, Ital.*
Phenazone (p. 124·1); procaine hydrochloride (p. 1994·3).
Earache.

Otomidrin *Fardi, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); framycetin sulfate (p. 301·2); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Otomixyn *EMS, Braz.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Otomize *Kite (Κιτε), Gr.; GSK Consumer, Irl.†; GSK Consumer, UK.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1).
Otitis externa.

Otomycin *Taro, Israel.*
Neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3); sodium propionate (p. 593·1); benzocaine (p. 1980·2); benzyl alcohol (p. 1739·3).
Ear infections.

Otomycin-HPN *Misemer, USA.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B (p. 342·3).
Bacterial ear infections.

Otonac *Solitaire, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Otonac-P *Solitaire, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Otonorthia *Northia, Arg.*
Phenazone (p. 124·1); procaine (p. 1994·3); gentamicin (p. 304·2).
Ear disorders.

Otopain *Interbat, Indon.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); fludrocortisone acetate (p. 1634·3); lidocaine hydrochloride (p. 1988·2).
Otitis.

Otopax *Bruschettini, Ital.*
Procaine hydrochloride (p. 1994·3); phenazone (p. 124·1).
Earache.

Oto-Phen Forte *Adcock Ingram, S.Afr.†*
⊗Benzocaine (p. 1980·2); ephedrine hydrochloride (p. 1663·2); phenazone (p. 124·1); potassium hydroxyquinoline sulfate (p. 2530·1).
Otitis; earache.

Otopraf *Prafa, Indon.*
⊗Fludrocortisone acetate (p. 1634·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Otopreven *Fortbenton, Arg.*
Acetic acid (p. 2426·3).
Ear infections.

Otorex *Indoco, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).

Otoryl *Otto, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Otosal *Coup, Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Otosamthong *SM, Thai.†*
⊗Furaltadone hydrochloride (p. 301·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); fludrocortisone acetate (p. 1634·3); lidocaine hydrochloride (p. 1988·2).
Otitis media; otitis externa.

Otosan *Streuli, Switz.*
Procaine hydrochloride (p. 1994·3); phenazone (p. 124·1).
Ear disorders; earache.

Otosat *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa.

Otosedol *Pensa, Spain.†*
Phenazone (p. 124·1); procaine hydrochloride (p. 1994·3).
Earache.

Otoseptil
Note: this name may be used for preparations of different composition.
Roux-Ocefa, Arg.
⊗Neomycin sulfate (p. 330·1); hydrocortisone (p. 1640·1); benzocaine (p. 1980·2).
Ear disorders.

Sanitas, Chile.
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Infected ear disorders.

Otosoft *Yash, India.*
Docusate sodium (p. 1836·2).

Otosol *Norgine, Philipp.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Otospon *Vianex (Βιανεξ), Gr.*
⊗Ciprofloxacin hydrochloride (p. 261·2); fluocinolone acetonide (p. 1636·1).
Otitis externa.

Otosporin *Investi, Arg.; GSK, Austria; Farmoquimica, Braz.; GSK, Cz.†; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Neth.; Wellcome, Port.; Aspen, S.Afr.; GSK, Singapore; GSK, Switz.†; GSK, UK†; Calmic, USA.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial ear infections.

Otosporin C *Investi, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Otosporin Dexa *Investi, Arg.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Otitis media; otitis externa.

Otosporin L *Investi, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); lidocaine hydrochloride (p. 1988·2).
Bacterial ear infections.

Otosym *Symbiosis, India.*
⊗Beclometasone dipropionate (p. 1621·2); chloramphenicol (p. 257·1); clotrimazole (p. 576·2); lidocaine hydrochloride (p. 1988·2).

Otosynalar *Roche, Braz.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Oto-Synalar N *Lusomedicamenta, Port.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).

Otothricinol *Plan, Switz.*
Tyrothricin (p. 384·1); phenazone (p. 124·1); cetylpyridinium chloride (p. 1743·1).
Ear disorders.

Otovowen *Weber & Weber, Austria; Weber & Weber, Ger.*
Aconitum napellus (p. 2428·3); capsicum annuum (p. 2469·3); chamomilla recutita (p. 2474·1); echinacea purpurea (p. 2498·1); hydrargyrum bicyanatum (p. 2555·3); hydrastis canadensis (p. 2528·1); iodum (p. 2336·3); natrium tetraboracicum (p. 2459·2); sambucus nigra (p. 2609·3); sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Otowax *Sensomed, Philipp.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Otowaxol *Norgine, Ger.†*
Docusate sodium (p. 1836·2).
Removal of ear wax.

Oto-Xilodase *Apsen, Braz.*
Lidocaine hydrochloride (p. 1988·2); neomycin sulfate (p. 330·1); hyaluronidase (p. 2527·2).
Ear disorders.

Otoxin *Gland, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; lactation promotion.

Otozambon
Note: this name may be used for preparations of different composition.
Zambon, Hong Kong.
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Otitis externa; otitis media; suppurative complications following ear and mastoid surgery.

Zambon, Indon.
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); betamethasone (p. 1623·2); lidocaine hydrochloride (p. 1988·2).
Formerly contained neomycin sulfate, polymyxin B sulfate, furaltadone hydrochloride, fludrocortisone acetate, and lidocaine hydrochloride.
Ear disorders.

Otozin *Allegis, USA.*
⊗Phenazone (p. 124·1); benzocaine (p. 1980·2); glycerol (p. 2517·2); zinc acetate (p. 2126·1).

Otradrops *Manx, UK.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Otram *Elfin, India.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Otrasel *Cephalon, Fr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Otraspray *Manx, UK.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Otrębuski *Sanofi-Aventis, Pol.†*
Ispaghula (p. 1849·1); wheat bran (p. 1823·3).
Constipation; hypercholesterolaemia; obesity; dietary fibre supplement.

Otredil *Med-One, Gr.*
Ondansetron hydrochloride (p. 1872·1).

Otreon
Note: this name may be used for preparations of different composition.
Sankyo, Austria; Daiichi Sankyo, Ital.; Sankyo, Neth.†; Daiichi Sankyo, Spain.†
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Otrex *Stragen, Pol.*
Diosmin (p. 2505·2).
Venous insufficiency.

Otrexup *Antares, USA.*
Methotrexate (p. 822·2).
Rheumatoid arthritis; juvenile idiopathic arthritis; psoriasis.

Otriduo *Novartis Consumer, Spain.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Nasal congestion.

Otriduo Rhume *Novartis Consumer, Switz.*
Dimetindene maleate (p. 626·1); phenylephrine (p. 1672·2).
Cold symptoms; rhinitis; sinusitis.

Otrifar *Novartis Consumer, Port.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Nasal congestion.

Otriflu *Novartis Consumer, Neth.; Novartis, Norw.†; Novartis Consumer, Port.*
Diclofenac potassium (p. 48·3).
Pain; fever.

Otrim *Biochem, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Otrinol *Zambon, Switz.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Otrinoz *Novartis, India.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Otrisalin *Novartis, Gr.; Novartis, Turk.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Otriven *Novartis, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Conjunctival disorders.

Otriven Baby *Novartis Consumer, Ger.†*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Otriven gegen Schnupfen *Novartis Consumer, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Otriven mit Dexpanthenol *Novartis Consumer, Ger.†*
Dexpanthenol (p. 2582·2).
Nasal disorders.

Otrivin *Novartis Consumer, Austral.; Novartis Consumer, Austria; Novartis Consumer, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Gr.; Novartis Consumer, Hong Kong; Novartis Consumer, Hung.; Novartis, India; Novartis, Indon.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Malaysia; Novartis Consumer, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis Consumer, Pol.; Novartis Consumer, Rus.; Novartis Consumer, S.Afr.; Novartis OTC, Singapore; Novartis Consumer, Spain†; Novartis, Swed.; Novartis Consumer, Switz.; Novartis, Thai.; Novartis Consumer, Ukr.; Ciba Consumer, USA.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; otitis media; aid in rhinoscopy; rhinitis; sinusitis; cold symptoms; upper respiratory-tract congestion.

Novartis Consumer, Neth.
Oral liquid: Bromhexine hydrochloride (p. 1656·3).
Cough.

Novartis Consumer, Neth.
Syrup: Noscapine hydrochloride (p. 1670·3).
Cough.

Otrivin Advance *Novartis, Gr.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Nasal congestion.

Otrivin Allergia *Novartis Consumer, Hung.*
Dimetindene maleate (p. 626·1); phenylephrine (p. 1672·2).
Allergic rhinitis; nasal congestion.

Otrivin Allergy *Novartis Consumer, Pol.*
Dimetindene maleate (p. 626·1); phenylephrine hydrochloride (p. 1672·3).
Rhinitis; nasal congestion; sinusitis; otitis media.

Otrivin Baby *Novartis Consumer, Ital.†*
Sodium chloride (p. 1795·1).
Nasal cleansing; nasal dryness.

Otrivin Comp *Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Nasal congestion; rhinitis; rhinorrhoea.

Otrivin Complete *Novartis Consumer, Israel.*
⊗Ipratropium bromide (p. 1211·3); xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinorrhoea.

Otrivin Duo *Novartis Consumer, Hung.; Novartis Consumer, Neth.; Novartis Consumer, Pol.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Nasal congestion.

Otrivin med mentol *Novartis, Norw.*
⊗Xylometazoline hydrochloride (p. 1680·1); menthol (p. 2553·2); cineole (p. 2479·1).
Rhinitis; sinusitis; aid in rhinoscopy.

Otrivin Menthol *Novartis, Denm.; Novartis, Fin.; Novartis Consumer, Neth.; Novartis, Swed.*
⊗Xylometazoline hydrochloride (p. 1680·1); menthol (p. 2553·2); cineole (p. 2479·1).
Nasal congestion; rhinitis; sinusitis; upper respiratory-tract congestion; aid in rhinoscopy.

Otrivin Mer *Novartis Consumer, Switz.*
Sea water (p. 2612·1).
Nasal congestion.

Otrivin neusallergie azelastine *Novartis Consumer, Neth.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Otrivin neusallergie loratadine *Novartis Consumer, Neth.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Otrivin rhume des foins *Novartis Consumer, Switz.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Otrivin Saline Baby *Novartis Consumer, Austral.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Otrivin Saline Nasal Spray *Novartis OTC, Singapore.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal dryness.

Otrivin Saline Plus *Novartis, Austral.*
Pantothenic acid (p. 2085·2); sea water (p. 2612·1).
Nasal congestion; nasal dryness.

Otrivin Sea Water *Novartis, Austral.*
Sea water (p. 2612·1).
Nasal congestion; nasal dryness.

Otrivina *Novartis Consumer, Arg.; Novartis, Braz.; Novartis Consumer, Port.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; aid in rhinoscopy; otitis media.

Otrivin-Alert *Novartis, India.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Otrivin-C *Novartis, India.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; nasal polyps.

Otrivine *Novartis Consumer, Irl.; Novartis, NZ; Novartis, Turk.; Novartis Consumer, UK.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinitis; sinusitis.

Otrivine Anti-Allergie *Novartis Consumer, Belg.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Otrivine Anti-Rhinitis *Novartis Consumer, Belg.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis; otitis.

Otrivine Duo *Novartis Consumer, Belg.*
⊗Ipratropium bromide (p. 1211·3); xylometazoline hydrochloride (p. 1680·1).

Otrivine Menthol *Novartis, NZ.*
⊗Xylometazoline hydrochloride (p. 1680·1); menthol (p. 2553·2); eucalyptus (p. 2501·1).
Nasal congestion.

Otrivine Mentol *Novartis, Turk.*
⊗Xylometazoline hydrochloride (p. 1680·1); menthol (p. 2553·2); cineole (p. 2479·1).
Nasal congestion.

Otrivine Mu-Cron *Novartis Consumer, UK.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Otrivine Nasa-Tab *Novartis Consumer, Belg.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Otrivine-Antistin *Novartis, Irl.; Novartis, NZ†; Novartis Consumer, UK.*
⊗Xylometazoline hydrochloride (p. 1680·1); antazoline sulfate (p. 616·1).
Allergic conjunctivitis; eye irritation.

Otrivini *Novartis Consumer, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Otrivin-Menthol *Novartis, Gr.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Otrivin-S *Novartis, India.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Otrix *Indeco, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Otron *Daffohils, India.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Otron-D *Daffohils, India.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Otrozol *Pisa, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; anaerobic bacterial infections.

Otsu-D5 *Otsuka, Indon.*
Glucose (p. 2068·3).
Carbohydrate source; fluid depletion.

Otsujito *Tsumura, Jpn.*
Angelica acutiloba root (p. 2443·3); bupleurum root; skullcap root (p. 2617·1); liquorice (p. 1853·2); cimicifuga rhizome (p. 2478·1); rhubarb (p. 1884·2).
Traditional Kampo medicine.

Otsuka Cez *Otsuka, Jpn.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Otsuka MV *Otsuka, Jpn; Otsuka, Thai.*
Vitamins.
Parenteral nutrition.

Otsu-NS *Otsuka, Indon.*
Sodium chloride (p. 1795·1).
Sodium and chloride replacement.

Otsutran *Otsuka, Indon.*
⊗Dextran 40 (p. 1138·1); electrolytes (p. 1775·1).
Plasma volume expansion; extracorporeal circulation.

Otto *Pharmacon, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ottocid *Polifarma Benessere, Ital.*
Phenothrin (p. 2160·1).
Acaricide.

Otto-D *Pharmacon, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; omeprazole.

Ottogenta *Otto, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Ottopan *Otto, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Ottoprim *Otto, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ottoslavin *Slavic, Rus.*
Boric acid (p. 2459·3); procaine (p. 1994·3).
Otitis media.

Ottovis *Fitolife, Ital.*
Royal jelly (p. 2608·1); ginseng (p. 2513·3); wheat-germ oil (p. 2647·1); soya lecithin (p. 2542·2); pollen (p. 2593·3).
Tonic.

Oturga *Legrand, Braz.*
Tyrothricin (p. 384·1); salicylic acid (p. 1719·1); boric acid (p. 2459·3); procaine hydrochloride (p. 1994·3).
Ear disorders.

Otylol *Bridoux, Fr.*
⊗Procaine hydrochloride (p. 1994·3); tetracaine hydrochloride (p. 1996·3); phenol (p. 1763·3); ephedrine hydrochloride (p. 1663·2); thyme oil (p. 2630·3).
Ear disorders.

Otymox *Solitaire, India.*
Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

Otymox-MF *Solitaire, India.*
Moxifloxacin (p. 326·3).
Bacterial eye infections.

Ou Di Bei *CSPC, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Ou Bei *Qilu, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Ou Hua Da *Ouhua, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; dyspepsia; acid aspiration.

Ou Ji *Hengrui, China.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Ou Jia *Ou Yi, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Ou Di Jia *Simcere, China.*
Aldioxa (p. 1692·2).

Ou Jian *Ou Yi, China.*
Cefixime (p. 240·3).
Bacterial infections.

Ou Kai *Luye, China.*
Sodium aescinate (p. 2431·2).

Ou Ke Ning *Dongbao, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ou Ke Shuang *Bai Li, China.*
Rifaximin (p. 355·2).

Ou Lai *Luye, China.*
Sodium aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Inflammation; soft-tissue disorders; phlebitis.

Ou Lai Ning *Ou Yi, China.*
Oxiracetam (p. 393·3).
Dementia; organic brain syndrome.

Ou Lan Ning *Hanson, China.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ou Lan Tong *San Lian, China.*
Oxiracetam (p. 393·3).
Dementia; organic brain syndrome.

Ou Li *Wanma, China.*
Calcium folinate (p. 2066·3).
Folic acid antagonist antidote; high-dose methotrexate toxicity; megaloblastic anaemia; adjunct to fluorouracil.

Ou Li Kang Ding *Yaojiang, China.*
Azasetron hydrochloride (p. 1820·2).

Ou Lin *Nanchang, China.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Ou Mai *Xinhua, China.*
Citicoline sodium (p. 2480·2).
Head injury.

Ou De Man *Huasen, China.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Ou Mei Ning *ChangJiang, China.*
Telmisartan (p. 1509·3).
Hypertension.

Ou Mei Te *Double-Crane, China.*
Matrine.

Ou Nai Te *Ruide Hetong, China.*
Interleukin-2 (human recombinant) (p. 810·1).

Ou Ning *SL Pharm, China.*
Thymopentin (p. 2631·1).
Chronic hepatitis B; immune function disorders.

Ou Nuo *Sanye, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Ou Pu Ding *Hua Shen, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ou Rui Si *ChangJiang, China.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Ou Shuang *Ou Yi, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Ou Su *Yangtze River, China.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Ou Te Luo Kang *Huakang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Ou Ting *Xia Du, China.*
Azasetron hydrochloride (p. 1820·2).

Ou Tong *Luye, China.*
Capsaicin (p. 35·1).
Musculoskeletal, joint, and soft-tissue disorders.

Ou Zhi *Qilu, China.*
Indinavir sulfate (p. 986·1).
HIV infection.

Ou Zhi Ning *Beijing Union, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ouch *Savoy, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Oukat *Aamorb, India.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Oukat-H *Aamorb, India.*
⊗Hydrochlorothiazide (p. 1403·2); olmesartan medoxomil (p. 1459·2).
Hypertension.

Oular *Cosmas, India.*
Bacillus mesentericus; Clostridium butyricum; Lactobacillus sporogenes (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).

Ouliting *Huayuan Century, China; Shennong, China.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Oulogram *Ni-The, Gr.*
Tyrothricin (p. 384·1); borax (p. 2459·2); tannic acid (p. 2625·2); thymol (p. 1772·2).
Gum disorders.

Out of Africa *Sutton, Canad.†*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Outgro
Note: this name may be used for preparations of different composition.
Whitehall, USA.
Tannic acid (p. 2625·2); chlorobutanol (p. 1747·2).
Ingrown toenails.

Outlook *Lifeplan, UK.*
St John's wort (p. 449·1); rosemary (p. 2607·2); avena (p. 2451·1); vitamin B substances (p. 2102·3).

Out-of-Sorts *Potter's, UK.*
Senna (p. 1885·1); aloes (p. 1816·1); cascara (p. 1826·1); taraxacum (p. 2625·3); fennel (p. 2503·2).
Constipation.

Ouvidonal *Neo Quimica, Braz.*
Chloramphenicol (p. 257·1); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Ouwei *CSPC, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Ouyi *CSPC, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Ovabion *Berlico Mulia, Indon.*
Vitamins; minerals; iron (p. 2073·1). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Nutritional supplement for pregnancy and lactation.

Ovacare *Meyer, India.*
Nutritional supplement.

Ovace *Mission Pharmacal, USA.*
Sulfacetamide sodium (p. 361·1).

Ovadril *Toprak, Turk.*
Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1); lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2).
Pruritus.

Ovagen *Bushnell, India.*
Clomifene.
Anovulatory infertility.

Oval *Cubit, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Ova-Mit *Remedica, Hong Kong†; Remedica, Malaysia; Remedica, Philipp.; Remedica, Singapore; Remedica, Thai.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ovapac *Pharmathen, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Ovarell *Sanorell, Ger.*
Cimicifuga racemosa (p. 2478·1).
Homoeopathic preparation.

Ovartein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Ovastat *Medac, Ger.*
Treosulfan (p. 877·3).
Ovarian cancer.

Ovazol-V *Gelcaps, Mex.†*
Metronidazole (p. 936·1).
Vaginal trichomoniasis.

Ovcon 35 *BMS, USA.*
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Ovcon 50 *BMS, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Over *Solitaire, India.*
Cefoperazone (p. 243·1).
Bacterial infections.

Overal *Lusofarmaco, Ital.*
Roxithromycin (p. 356·2).
Bacterial infections.

Overdrive *Nu Skin, Canad.*
Vitamins; minerals.

Overnight Acne Control *Johnson & Johnson, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Overoid *Valdecasas, Mex.†*
Niclosamide (p. 161·2).
Worm infections.

Overpon *Valdecasas, Mex.*
Piperazine citrate (p. 163·1).
Worm infections.

Over-SB *Solitaire, India.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Ovestal *Hexal, Neth.†*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Ovesterin *Organon, Norw.; MSD, Swed.*
Estriol (p. 2274·3).
Vulvovaginal disorders due to oestrogen deficiency.

Ovestin *Schering-Plough, Austral.; Organon, Austria; Schering-Plough, Chile; MSD, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD, Ger.; Organon (Οργανον), Gr.; Organon, Hung.; Schering-Plough, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.†; Organon, Mex.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.; Organon, Venez.*
Estriol (p. 2274·3).
Oestrogen deficiency; menopausal disorders; adjunct in cervical smear tests; adjunct in vaginal surgery; atrophic vaginitis; female infertility; genito-urinary disorders due to oestrogen deficiency; vaginal disorders; female incontinence; prostatic dysplasia.

Ovestinon *MSD, Spain.*
Estriol (p. 2274·3).
Oestrogen deficiency; menopausal disorders.

Ovestrion *Schering-Plough, Braz.*
Estriol (p. 2274·3).
Menopausal disorders; female infertility.

Ovex *Johnson & Johnson MSD Consumer, UK.*
Mebendazole (p. 158·3).
Enterobiasis.

Oviala *Ratiopharm, Ger.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Ovicalm *Hoch Wertig, Arg.*
Ovi putamen.
Dietary supplement.

Ovidac *Zydus, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Ovide *Medicis, USA.*
Malathion (p. 2157·2).
Pediculosis.

Ovidine *Ind-Swift, India.*
Povidone-iodine (p. 1767·1).
Disinfection; wounds; skin infections.

Ovidine-M *Ind-Swift, India.*
Metronidazole (p. 936·1); povidone-iodine (p. 1767·1).

Ovidol *Organon, Belg.; Organon, Neth.†*
7 Tablets, ethinylestradiol (p. 2275·3); 15 tablets, ethinylestradiol; desogestrel (p. 2266·3).
Sequential-type oral contraceptive.

Ovidon *Gedeon Richter, Hung.†; Gedeon Richter, Rus.†; Gedeon Richter, Ukr.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Ovidrel *Merck Serono, Arg.; Merck Serono, Austral.; Merck, Braz.; Serono, Canad.; Merck, Chile; Merck Serono, China; Serono, Hong Kong; Serum Institute, India; Merck, Indon.; Merck Serono, Malaysia; Merck, Mex.; Healthcare Logistics, NZ; Merck, Philipp.; Merck, S.Afr.; Merck, Singapore; Merck, Thai.; Serono, USA; Serono, Venez.*
⊗Choriogonadotropin alfa (rch) (p. 2258·1).
Female infertility.

Ovilow *Svizera, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ovimed *Medico, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ovinol *Norma (Νορμα), Gr.*
Norfloxacin (p. 333·3).
Urinary tract infections.

Ovinum *Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Oviol *Organon, Ger.†*
7 Tablets, ethinylestradiol (p. 2275·3); 15 tablets, ethinylestradiol; desogestrel (p. 2266·3).
28-Day packs also contain 6 inert tablets.
Sequential-type oral contraceptive.

Ovipauz-L *Svizera, India.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ovipreg *Win-Medicare, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ovipro-MF *Grandix, India.*
⊗Clomifene citrate (p. 2259·1); folic acid (p. 2063·1); mecobalamin (p. 2108·1).

Ovir *Osper, India.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ovisen *Biomep, Mex.*
Fluoxetine (p. 417·1).
Depression.

Ovisil *Zee, India.*
⊗Chlorphenamine maleate (p. 620·3); naphazoline (p. 1669·3).

Oviskin *Kalbe, Indon.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Ovista *Reddy, India.*
Selenium (p. 2086·3); vitamins; zinc gluconate (p. 2126·2).

Ovitec *Biomax, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ovitrelle *Serono, Austria; Merck Serono, Belg.; Serono, Cz.; Merck Serono, Denm.; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Merck Serono, Gr.; Merck Serono, Hung.; Merck Serono, Irl.; Merck Serono, Israel; Serono, Ital.; Merck, Neth.; Serono, Norw.; Serono, Pol.; Serono, Port.; Merck Serono, Rus.; Merck, Spain; Merck, Swed.; Merck, Switz.; Serono, Turk.; Serono, UK.*
⊗Choriogonadotropin alfa (p. 2258·1).
Female infertility.

Ovitrop *Sun, India.*
Urofollitropin (p. 2312·2).
Male and female infertility.

Ovobel *Blubell, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ovocterol *Rafarm, Gr.*
Haloperidol (p. 1077·1).

Ovoctil *Rafarm, Gr.*
Acetylcysteine (p. 1652·2).
Mucolytic.

Ovofar *Organon, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ovogin *Valeant, Arg.*
Ketoconazole (p. 585·3); clindamycin phosphate (p. 269·3).
Vaginal bacterial and fungal infections.

Ovogrel *Leon, Irl.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ovol *Church & Dwight, Canad.; Carter Horner, Hong Kong†; Church & Dwight, Thai.†*
Simeticone (p. 1886·2).
Flatulence; infant colic; bloating.

Ovoplex *Wyeth, Spain.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive; menstrual disorders.

Ovoresta *Organon, Braz.†*
Lynestrenol (p. 2287·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Ovoresta M *Organon, Ger.†*
Lynestrenol (p. 2287·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Ovral *Aspen, S.Afr.*
21 Tablets, norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive; menstrual disorders.

Pfizer, Canad.; Wyeth, Gr.; Wyeth, Mex.; Wyeth-Ayerst, USA†; Wyeth, Venez.
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Wyeth, India.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; dysfunctional uterine bleeding; endometriosis; menstrual disorders.

Ovran *Pfizer, Irl.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ovran 30 *Wyeth, UK.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Ovranette *Eurim, Austria; Pfizer, Irl.; Wyeth, UK.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive; endometriosis; menstrual disorders.

Ovuclom *VHB, India.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Ovucript *VHB, India.*
Bromocriptine (p. 895·3).
Parkinsonism; galactorrhoea; infertility; acromegaly; lactation inhibition; benign breast disorders; menstrual disorders.

Ovufem *Bernabo, Arg.*
Pessaries: Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); centella (p. 1698·3); polymyxin B sulfate (p. 342·3).
Vulvovaginal infections.

Bernabo, Arg.
Tablets: Metronidazole (p. 936·1).
Amoebiasis; giardiasis; bacterial infections.

Ovufol-HP *VHB, India.*
Urofollitropin (p. 2312·2).
Male and female infertility.

Ovugraf-HP *VHB, India.*
⊗Human menopausal gonadotrophin (p. 2284·1).
Female and male infertility.

Ovukalen *Knop, Chile.*
Calendula (p. 2465·2); echinacea (p. 2498·1); helonias (p. 2524·3); hydrastis (p. 2528·1).
Homoeopathic preparation.

Ovulate-C *VHB, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Ovulate-M *VHB, India.*
⊗Human menopausal gonadotrophin (p. 2284·1).
Female and male infertility.

Ovulet *Renata, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Ovulin *Euro Generics, Philipp.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Ovulobact *Sanopharma, Hung.*
Lactobacillus (p. 2596·3).
Restoration of vaginal flora.

Ovulol *Microsules, Arg.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Ovumax-HP *VHB, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Ovumix *Elea, Arg.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); centella (p. 1698·3); polymyxin B sulfate (p. 342·3).
Vulvovaginal infections.

OvuPlan *Key, Austral.*
Fertility test (p. 2596·1).

Ovuquick *MediMar, UK.*
Fertility test (p. 2596·1).

Ovurelix *Sun, India.*
Cetrorelix acetate (p. 2257·2).
Female infertility.

Ovurila *Nufarindo, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation.

Ovutrig-HP *VHB, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Anovulatory infertility; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism.

Ovysmen *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, UK.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Oxa
Note: this name may be used for preparations of different composition.
Beta, Arg.
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

CT, Ger.
Oxazepam (p. 1092·2).
Anxiety disorders; sleep disorders.

Oxa B12 *Beta, Arg.*
⊗Diclofenac potassium (p. 48·3); betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Oxa Forte *Beta, Arg.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Pain.

Oxa Sport *Beta, Arg.*
Diclofenac diethylamine (p. 48·3); pridinol mesilate (p. 2026·1); benzyl nicotinate (p. 29·3); menthol (p. 2553·2); lidocaine hydrochloride (p. 1988·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and peri-articular disorders with muscle spasm.

Oxabenz *Actavis, Denm.*
Oxazepam (p. 1092·2).
Anxiety.

Oxacant-mono *Klein, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Oxacant-sedativ *Klein, Ger.*
Crataegus (p. 2488·1); motherwort (p. 2564·2); melissa (p. 2552·3); valerian (p. 2640·2).
Nervous cardiac disorders.

Oxacatin *Taro, Israel.*
Oxomemazine (p. 637·1); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Cough.

Oxacin-OZ *Maan, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxaclen *MedGen, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Oxacycle *Specifar (Σπεσιφαρ), Gr.*
Oxytetracycline hydrochloride (p. 337·2).

Oxacycle-P *Specifar, Gr.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Skin infections.

Oxadisten *Beta, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Inflammation; muscle spasm; pain.

Oxadol *Kedrion, Rus.*
Nefopam hydrochloride (p. 100·2).
Pain.

Oxafem *Beta, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Dysmenorrhoea; migraine.

Oxaflam *Fahrenheit, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Oxaflox *Coronet, Indon.*
Pefloxacin (p. 338·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Oxagesic *Beta, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Fever; pain.

Oxaine-M *Wyeth, Gr.*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3); oxetacaine (p. 1993·1).
Antacid.

Oxal
Note: this name may be used for preparations of different composition.
Anvik, India.
Ofloxacin (p. 334·3).
Columbia, Mex.
Albendazole (p. 149·1); quinfamide (p. 947·1).
Parasitic infections.
Taisheng, Philipp.
Oxacillin sodium (p. 336·2).
Staphylococcal infections.

Oxalatin *Spirit, Austral.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxalcor *Corsalud, Venez.*
Oxolamine phosphate (p. 1671·2).
Cough.

Oxalem *Pharmachemie, Philipp.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxalgin *Zydus, India.*
Diclofenac sodium (p. 48·3).
Prevention of intra-operative miosis; eye inflammation; corneal trauma; allergic conjunctivitis; pain; inflammation.

Oxalgin Nanogel *Zydus, India.*
Diclofenac sodium (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Oxalgin-D *Zydus, India.*
Diclofenac sodium (p. 48·3).
Pain; renal colic.

Oxalgin-DP *Zydus, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Oxalgin-SR *Zydus, India.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Oxalibbs *Libbs, Braz.*
Oxaliplatin (p. 838·1).

Oxalic *Aronex, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxaliccord *Arrow, NZ.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxalic-NZ *Aronex, India.*
Nitazoxanide (p. 942·2); ofloxacin (p. 334·3).

Oxalimedac *Biem, Turk.*
Oxaliplatin (p. 838·1).

Oxalin *Polfa Warszawa, Pol.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Oxalip *American Taiwan, Thai.*
Oxaliplatin (p. 838·1).
Colorectal cancer; gastric cancer.

Oxaliplan *Cancernova, Ger.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxaliprol *Novendia, Gr.*
Oxaliplatin (p. 838·1).

Oxaliquid *Ebewe, Cz.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxalisin *Pharmachemie, Neth.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxaliwin *Sanofi-Aventis, S.Afr.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxalix *Ratiopharm, Port.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxalpin *Deva, Turk.*
Oxaliplatin (p. 838·1).

Oxaltie *Bioprofarma, Arg.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxaltina *Farmaten, Gr.*
Oxaliplatin (p. 838·1).

Oxam *Genexo, Pol.†*
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.

Oxamed *Medac, Irl.†*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxamet *Teva, Cz.; Teva, Ukr.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; otitis media; rhinitis; sinusitis.

Oxamil *Merck, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxamin *Ratiopharm, Fin.*
Oxazepam (p. 1092·2).
Anxiety disorders; depression; insomnia.

Oxamine *Psyco Remedies, India.*
Amoxapine (p. 407·3).
Depression.

Oxamp *Sintez, Rus.*
Ampicillin sodium (p. 218·2); oxacillin sodium (p. 336·2).
Bacterial infections.

Oxampicine *Krasfarma, Rus.*
Ampicillin sodium (p. 218·2); oxacillin sodium (p. 336·2).
Bacterial infections.

Oxamsar *Biochimic, Rus.*
Ampicillin sodium (p. 218·2); oxacillin sodium (p. 336·2).
Bacterial infections.

Oxan *Gracia, Indon.*
Grape seed extract (p. 2521·3); green tea extract (p. 2648·2); citrus bioflavonoids (p. 2505·2); pine extract.
Tonic.

Oxana *Psyco Remedies, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxandrin *CSL, Austral.†; Savient, USA.*
⊗Oxandrolone (p. 2298·2).
Weight loss; protein catabolism; bone pain associated with osteoporosis; delayed puberty in boys; growth retardation in boys; Turner's syndrome in girls.

Oxanest *Leiras, Fin.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxanon *Ariston, Braz.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Oxantil *BB, Cz.*
Etofylline (p. 1208·2); theophylline (p. 1229·3).
Cerebrovascular disorders; ischaemic heart disease; obstructive airways disease.

Oxapax *Sandoz, Denm.*
Oxazepam (p. 1092·2).
Anxiety.

Oxapen *Biolab Sanus, Braz.; Pharmawealth, Philipp.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Oxapron *AG Therapy, Gr.*
Oxaprozin (p. 112·3).
Inflammatory disorders.

Oxaprost *Beta, Arg.*
Diclofenac sodium (p. 48·3).
Misoprostol (p. 2140·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal, joint, and peri-articular disorders.

Oxaqual *Lilly, Turk.*
Oxaliplatin (p. 838·1).

Oxarol *Chugai, Jpn; Maruho, Jpn.*
Maxacalcitol (p. 2113·3).
Hyperparathyroidism; psoriasis.

Oxascand *Teva, Swed.*
Oxazepam (p. 1092·2).
Anxiety; sleep disorders; alcohol withdrawal syndrome.

Oxatalis *Vitalis, Philipp.*
Oxacillin (p. 336·2).
Bacterial infections.

Oxatera *Teva, Rus.*
Oxaliplatin (p. 838·1).
Colorectal cancer; ovarian cancer.

Oxathos *Medix, Mex.*
Oxolamine citrate (p. 1671·2).
Cough.

Oxatokey *Inkeysa, Spain.†*
Oxatomide (p. 636·3).
Hypersensitivity reactions.

OxBipp *Masters, UK.*
Bismuth subnitrate (p. 1822·1); iodoform (p. 1758·2).

Oxca *Bouzen, Arg.†*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxcal *Solas, Indon.*
Calcium hydrogen phosphate (p. 1783·3); alpha tocoferil acetate (p. 2119·2); selenium (p. 2086·3); betacarotene (p. 2051·1); vitamin D (p. 2112·3); zinc sulfate (p. 2126·2).
Osteoporosis; calcium supplement.

Oxcap *Sunrise, India.*
Amoxapine (p. 407·3).
Depression.

Oxcarb *Uniao Quimica, Braz.; Cipla, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxcarmylan *Mylan, Spain.†*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxcazo *Unichem, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxcin-Ord *Uniroyal, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxcord *Biosintetica, Braz.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Oxcq *Wallace, India.*
Hydroxychloroquine (p. 655·2).
Rheumatoid arthritis; systemic lupus erythematosus; malaria.

Oxdrin *Scoshia, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxdrin-D *Scoshia, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Oxdrin-Ord *Scoshia, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxebewe *Liba, Turk.*
Oxaliplatin (p. 838·1).

Oxecta *King, USA.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxeda *Lavipharm, Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Oxedep *Torrent, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder.

Oxefate-O *BMW, India.*
Oxetacaine (p. 1993·1); sucralfate (p. 1889·1).

Oxelio *Jaldes, Fr.*
Betacarotene (p. 2051·1); palm oil carotenoids (p. 2200·2); natural tocopherols (p. 2119·1); ascorbic acid (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1); soya oil (p. 2092·3).
Nutritional supplement for protection against sun-induced skin damage.

Oxelio Topique *Jaldes, Fr.*
Lycopene (p. 2546·2); betacarotene (p. 2051·1); jojoba oil; almond oil; apricot oil; vitamins.
Protection against sun-induced skin damage.

Oxema Improved *Jean-Marie, Hong Kong.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1); oxetacaine (p. 1993·1).
Gastrointestinal disorders.

Oxemet *GSK, Arg.*
Metformin (p. 489·1).
Diabetes mellitus.
GSK, Chile.
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Oxeno *Bernabo, Arg.*
Loxoprofen sodium (p. 83·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Oxens *CCD, Fr.*
Sodium hyaluronate (p. 2526·2).
Vaginal lubricant.

Oxéol *AstraZeneca, Fr.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Oxeol *Paranova, Denm.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Oxep *Abbott, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxepa *Abbott, Braz.; Abbott, Hong Kong†; Abbott, Israel; Abbott, Ital.; Abbott, Singapore†; Abbott, Turk.; Abbott Nutrition, UK.*
Preparation for enteral nutrition.
Nutritional support in ventilated patients.

Oxeptal *Zydus, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxerol *Eczacibasi, Turk.*
Oxaliplatin (p. 838·1).

Oxetine
Note: this name may be used for preparations of different composition.
Minerva (Μινερβα), Gr.
Roxithromycin (p. 356·2).
Bacterial infections.
Pharmaland, Thai.
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.
Hexal, Austral.†
Paroxetine hydrochloride (p. 440·3).
Depression; social phobia; panic disorder; obsessive-compulsive disorder.

Oxetol *Sun, India; Sun, Mex.*
Oxcarbazepine (p. 533·2).
Epilepsy; neuropathic pain.

Oxez *Orifarm, Denm.; AstraZeneca, Gr.*
⊗Formoterol fumarate (p. 1209·2).
Asthma; obstructive pulmonary disease.

Oxeze *AstraZeneca, Canad.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Oxian *Barrenne, Braz.†*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; vertigo.

Oxiber *Zee, India.*
Flurbiprofen sodium (p. 65·3).
Prevention of intra-operative miosis; postoperative eye inflammation.

Oxibet *Orchid, India.*
Vitamins; selenium (p. 2086·3); zinc (p. 2126·1).

Oxibran *Prospa, Port.*
Piracetam (p. 393·3).
Mental function impairment.

Oxibron *Montpellier, Arg.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Oxibron NF *Montpellier, Arg.*
⊗Clenbuterol hydrochloride (p. 1207·2); ambroxol hydrochloride (p. 1654·3).
Obstructive airways disease.

Oxibut *Bernabo, Arg.*
Ibuprofen (p. 68·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Oxicalmans *Chobet, Arg.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxicanol *Teva, Mex.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Oxicobal *Ifars, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Oxicodal *Drugtech, Chile.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxid *Bactolac, India.*
Vitamins; minerals; trace elements.

Oxiderma *Galderma, Spain.*
Benzoyl peroxide (p. 1696·1).
Acne.

Oxidermos *Neo Dermos, Arg.*
⊗Lactic acid (p. 2539·1); urea (p. 1727·3); alpha tocopherol (p. 2119·1); octinoxate (p. 1715·1).

Oxidevit *Echo, Rus.*
Alfacalcidol (p. 2112·3).
Osteodystrophy; hypoparathyroidism; pseudohypoparathyroidism; rickets; osteomalacia; osteoporosis; renal acidosis.

Oxidon *Micro, India.*
Copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Oxidox *Focus, India.*
Doxylamine succinate (p. 627·3); folic acid (p. 2063·1); pyridoxine (p. 2105·3).
Nausea and vomiting in pregnancy.

Oxifast *Shionogi, Jpn.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxiflox *Akums, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxiflox-OZ *Akums, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxiflox-TZ *Akums, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oxi-Freeda *Freeda, USA.*
Vitamins; minerals; amino acids.

Oxifrin *Teuto, Braz.*
⊗Oxymetazoline (p. 1671·3).
Nasal congestion.

Oxifungol *Armstrong, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Oxigat *Indoco, India.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Oxigen *Biosintetica, Braz.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Oxigon *Panagiotis, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Oxiken *Kendrick, Mex.†*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; shock.

Oxiklorin *Orion, Fin.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus; light-sensitive skin disorders.

Oxilan *Guerbet, Turk.; Guerbet, USA.*
Ioxilan (p. 1593·3).
Radiographic contrast medium.

Oxilepsi *Eczacibasi, Turk.*
Oxcarbazepine (p. 533·2).

Oxiler D *Cassara, Arg.*
Oxymetazoline carbonate.
Nasal congestion.

Oxilin *Pasteur, Chile; Allergan, Ital.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Conjunctivitis; eye congestion; nasal congestion; rhinitis.

Oximar *Dupomar, Arg.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Oximar Respiratorio *Dupomar, Arg.†*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Oximax *Mantecorp, Braz.*
⊗Mometasone furoate (p. 1644·1).

Oximen *Orravan, Spain.*
Hydrogen peroxide (p. 1755·2); phosphoric acid (p. 2589·1).
Skin and mucous membrane disinfection; haemostasis.

Oximet *Orchid, India.*
Acetylcysteine (p. 1652·2); vitamins; minerals.

Oximezin *Demo, Gr.*
Piroxicam (p. 125·3).

Oximino *Orchid, India.*
Vitamins; minerals; trace elements; amino acids; spirulina (p. 2622·1).

Oximum *Q Pharma, Spain.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Oxin *Sons, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1).
Cough.

Oxin Plus *Synokem, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Oxine
Note: this name may be used for preparations of different composition.
Sykocure, India.
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxinest *Latinofarma, Braz.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Oxinorm
Note: this name may be used for preparations of different composition.
Medifarm, Venez.
Vitamins; minerals.

Oxinovag *Gobbi, Arg.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxinovag Complex *Gobbi, Arg.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Oxipelle *Valeant, Braz.*
Oxiconazole nitrate (p. 591·3).
Fungal skin infections.

OxiPen *Behrens, Venez.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Oxiplasol *Sigillata, Neth.†*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxiplat *Medac, Cz.†; Sun, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxipod *Indoco, India.*
Cefpodoxime.
Bacterial infections.

Oxipod-CV *Indoco, India.*
Cefpodoxime; clavulanic acid (p. 268·3).
Bacterial infections.

Oxipor *Medtech, Canad.†*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); benzocaine (p. 1980·2).
Skin disorders.

Oxipor VHC *Whitehall, USA.*
Coal tar (p. 1723·2).
Formerly contained coal tar, salicylic acid, and benzocaine.
Psoriasis.

SA Druggists Self Med, S.Afr.†
⊗Salicylic acid (p. 1719·1); benzocaine (p. 1980·2); alcohol (p. 1733·1); coal tar (p. 1723·2).
Psoriasis.

Oxipre *Taurus, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc (p. 2126·1).

Oxipres *Sandoz, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Oxi-Q *Ariston, Arg.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability; neurogenic bladder; nocturnal enuresis.

Oxi-Red *Intra-Labs, India.*
Syrup: Vitamin B substances (p. 2102·3); ferric ammonium citrate (p. 2060·1); potassium iodide (p. 2336·3); copper (p. 2057·1); selenium (p. 2086·3); zinc (p. 2126·1).
Intra-Labs, India.
Tablets: Folic acid (p. 2063·1); sodium feredetate (p. 2088·3); vitamin B_{12} (p. 2107·2); zinc sulfate (p. 2126·2).

Oxired *Intra-Labs, India.*
Vitamins; lysine hydrochloride (p. 2079·3); zinc (p. 2126·1).

Oxired-L *Intra-Labs, India.*
Vitamins; trace elements; lutein esters (p. 2079·2).

Oxired-M *Intra-Labs, India.*
Vitamins; minerals; trace elements.

Oxi-Reul *Ultra, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

Oxirich *Hy-Gro, India.*
Vitamins; trace elements.

Oxis *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, China; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Irl.; Teva, Israel; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.†; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore†; Tau, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease; asthma.

Oxisafe *Orchid, India.*
Vitamins; trace elements.

Oxisept *Demo, Gr.*
Povidone-iodine (p. 1767·1).
Mouth infections; skin disinfection.

Oxisoma *Ecofarm, Ital.†*
Soap substitute.

Oxistat *Investi, Arg.†; GSK, Mex.; PharmaDerm, USA.*
Oxiconazole nitrate (p. 591·3).
Fungal skin infections.

Oxi-T *Collins, Mex.†*
Tetracycline (p. 373·1).
Bacterial infections.

Oxit *Reddy, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxitab *Cubit, India.*
Vitamins; minerals.

Oxital C *Serral, Mex.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Oxitan *Dabur, India; Alternavida, Mex.; Fresenius Kabi, Thai.*
Oxaliplatin (p. 838·1).
Colorectal cancer; ovarian cancer; neuroblastoma.

Oxitard *Himalaya Herbal, India.*
Wild carrot (p. 2647·2); liquorice (p. 1853·2); mangifera indica; syzygium aromaticum; grape (p. 2521·3); withania somnifera.

Oxitel *Fresenius Kabi, Philipp.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxitina *LKM, Arg.*
Oxybutynin hydrochloride (p. 2361·2).

Oxitine *Psyco Remedies, India.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Oxiton *Uniao Quimica, Braz.*
Oxytocin (p. 2143·1).

Oxitone *Harson, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; missed or incomplete abortion; postpartum haemorrhage.

Oxitopisa *Pisa, Mex.*
Oxytocin (p. 2143·1).
Labour induction; hydatidiform mole; incomplete abortion.

Oxit-OZ *Reddy, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxitra *Zytras, India.*
Capsules: Vitamins; chromium (p. 2055·3); selenium (p. 2086·3); zinc (p. 2126·1).
Zytras, India.
Syrup: Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).

Oxitraklin *Atlantis, Mex.*
Oxytetracycline (p. 337·1).
Bacterial infections.

Oxitropic *Ebewe, Fin.†; Ebewe, Spain.†*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxivent *Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.*
Oxitropium bromide (p. 1218·1).
Obstructive airways disease.

Oxivim *Orchid, India.*
Vitamins; minerals; trace elements.

Oxivit *Intra-Labs, India.*
Vitamins; trace elements.

Oxizinco *Elofar, Braz.†*
Zinc oxide (p. 1729·1); benzalkonium chloride (p. 1737·1); cod-liver oil (p. 2056·3).
Skin disorders.

Oxken *Kendrick, Mex.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxmazetol *Abbott, India.*
Oxcarbazepine (p. 533·2).
Seizures.

Oxo *Ind-Swift, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxobron *Diba, Mex.†*
Oxolamine citrate (p. 1671·2).
Cough.

Oxo-D *Ind-Swift, India.*
⊗Dexamethasone (p. 1630·3); ofloxacin (p. 334·3).

Oxodil *Polpharma, Pol.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Oxodoline *Organika, Rus.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema.

Oxofenil *DAST, Gr.; Zekides, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Oxoferin *Elder, India; Oxochemie, Indon.; Pharos, Indon.; Oxo, Port.; Oxo, Thai.; Vargas, Venez.*
Tetrachlorodecaoxide (p. 2628·2).
Cicatrisation; wounds; burns; ulcers.

Oxogina *Flupal, Venez.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid effects; diagnosis of opioid overdosage.

Oxoism *Arlak, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxoism-OZ *Arlak, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxokool Plus *Solitaire, India.*
Domperidone (p. 1838·1); flunarizine (p. 629·3); paracetamol (p. 115·1).

Oxol *Venus, Thai.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Duopharma, Philipp.
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Oxolavin Compuesto *Vincenti, Venez.*
Oxolamine citrate (p. 1671·2); bromhexine hydrochloride (p. 1656·3).
Cough.

Oxolvan *Bruluart, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Oxo-M *Ind-Swift, India.*
Metronidazole benzoate (p. 936·1); ofloxacin (p. 334·3).

Oxomar *Offenbach, Mex.*
Oxolamine (p. 1671·2).
Cough.

Oxomifer *Reuffer, Mex.*
Oxolamine (p. 1671·2).
Cough.

Oxo-Ord *Ind-Swift, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxop *Centaur, India.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Oxop-D *Centaur, India.*
⊗Dexamethasone sodium phosphate (p. 1631·2); ofloxacin (p. 334·3).

Oxopect *Mahakam Beta, Indon.*
Oxomemazine (p. 637·1); guaifenesin (p. 1666·2).
Cough.

Oxoplan *Samarth, India.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Oxopurin *Dexcel, Israel.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Oxotil *Vargas, Venez.*
Oxolamine phosphate (p. 1671·2).
Cough.

Oxotus *Jofrain, Mex.†*
Oxolamine (p. 1671·2).
Cough.

Oxotusin *Allen, Mex.*
Oxolamine (p. 1671·2).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Oxotuss *Berksam, Turk.*
Oxolamine phosphate (p. 1671·2).

Oxo-TZ *Ind-Swift, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oxo-Val *Saval, Chile.*
Vitamins; minerals.
Dietary supplement.

Oxowin *Arrowin, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Ox-Pam *Douglas, NZ.*
Oxazepam (p. 1092·2).
Alcohol withdrawal syndrome; anxiety.

Oxplatin *Daewoong, Thai.*
Oxaliplatin (p. 838·1).

Oxrate *Wockhardt, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxsac *Masa, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Oxsoralen *Valeant, Austral.†; Gerot, Austria; Valeant, Braz.; Valeant, Canad.; Raffo, Chile; GL Pharma, Cz.; Invida, Hong Kong; GL Pharma, Hung.; Surya Dermato, Indon.; Taisho, Jpn; ICN, Malaysia†; Valeant, Mex.; ICN, NZ†; Gerot, Pol.; Gerot, Rus.; Pharmaco, S.Afr.†; Invida, Singapore; Galderma, Spain; ICN, USA.*
Methoxsalen (p. 1711·3).
Photosensitivity; vitiligo; psoriasis; skin pigmentation disorders; mycosis fungoides; lichen planus; atopic dermatitis.

Oxsoralen Ultra *Investi, Arg.*
Methoxsalen (p. 1711·3).
Psoriasis.

Oxsule *Lexus, India.*
Vitamins; minerals.

Oxtellar *Supernus, USA.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Oxter *Ind-Swift, India.*
Oxytetracycline (p. 337·1).

Oxtercid *Interbat, Indon.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Oxtimon *Rotexmedica, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; missed abortion.

Oxtin
Note: this name may be used for preparations of different composition.
Guardian, Indon.
Oxatomide (p. 636·3).
Allergic disorders.

Merck, Venez.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Oxwal *Wallace, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxwal-OZ *Wallace, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxwal-TZ *Wallace, India.*
Ofloxacin (p. 334·3); tinidazole (p. 949·2).

Oxxa *Toprak, Turk.*
Acetylcysteine (p. 1652·2).
Respiratory disorders with increased mucus; paracetamol poisoning.

Oxxalgan *Meditrina, Gr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Oxy
Note: this name may be used for preparations of different composition.
DR Johns, India.
Ceftriaxone (p. 253·3).
Bacterial infections.

Mentholatum, Austral.; Mentholatum, Canad.†; Mentholatum, Cz.†; GSK, Hong Kong†; Mentholatum, Israel; Mentholatum, Neth.†; GSK Consumer, UK; SmithKline Beecham Consumer, USA.
Benzoyl peroxide (p. 1696·1).
Acne.

Oxy Clean Facial Scrub *GSK Consumer, UK.*
Borax (p. 2459·2); triclosan (p. 1773·2).
Acne.

Oxy Cleanser *GSK Consumer, UK.*
Regular: ⊗Triclosan (p. 1773·2); salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Formerly called Oxy Clean Medicated Cleanser.
Acne.

GSK Consumer, UK.
Sensitive: ⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Acne.

Oxy Daily Moisturizer *Mentholatum, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Oxy Daily Wash *GSK, Hong Kong.†*
Triclosan (p. 1773·2).
Skin disorders.

Oxy Dots *GSK Consumer, UK.*
Salicylic acid (p. 1719·1); triclosan (p. 1773·2).
Spots.

Oxy Duo Pads *GSK Consumer, UK.*
Regular: ⊗Triclosan (p. 1773·2); salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Acne.

GSK Consumer, UK.
Sensitive: ⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Acne.

Oxy Facial Wash *GSK Consumer, UK.*
Triclosan (p. 1773·2).
Skin disorders.

Oxy IR *Purdue, Canad.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxy Medicated Skin Wash *Mentholatum, Austral.†*
Triclosan (p. 1773·2).
Acne; skin cleanser.

Oxy Medicated Soap *SmithKline Beecham, USA.*
Triclosan (p. 1773·2).

Oxy Night Watch *SmithKline Beecham Consumer, USA.*
Salicylic acid (p. 1719·1).

Oxyace *JB Chemicals, India; Unique, Rus.; Unique, Thai.*
Vitamins; minerals.

Oxyal *Santen, Ger.; Tubilux, Ital.; Europhta, Mon.†; Kestrel, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Oxyban *Medley, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc (p. 2126·1).

Oxybase *Sandoz, Gr.*
Oxybutynin hydrochloride (p. 2361·2).
Incontinence.

Oxyben *Santen, Philipp.†*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Oxyboldine *Cooperation Pharmaceutique, Fr.*
Boldine (p. 2458·3); anhydrous sodium sulfate (p. 1888·1); monobasic sodium phosphate (p. 1791·1).
Dyspepsia.

Oxybral *GSK, Ukr.*
Vincamine (p. 2645·2).
Disorders of cerebral, ocular, and vestibular circulation.

Oxybro
Note: this name may be used for preparations of different composition.
Cadila, India.
Injection: Oxytocin (p. 2143·1).
Termination of pregnancy; postpartum haemorrhage; labour induction; evaluation of fetal distress.

Cadila, India.
Tablets: Amoxicillin (p. 216·2); bromhexine (p. 1656·3).
Respiratory-tract infections.

Oxybugamma *Worwag, Ger.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability; urinary incontinence.

Oxybuta *Medopharm, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Oxybutin *Holsten, Ger.; Troikaa, India.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability; urinary incontinence.

Oxycane *Invision, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).

Oxycardil *Vedim, Pol.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Oxycel *Associated Hospital Supply, UK; Becton Dickinson, USA.*
Oxidised cellulose (p. 1157·3).
Bleeding in surgical procedures.

Oxycet *Oxytech, India.*
Levocetirizine (p. 632·3).
Hypersensitivity reactions.

Oxycide *PP Lab, Thai.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Oxycline *General Drugs, Thai.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Oxycod *Rafa, Israel.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxycontin *Raffo, Arg.; Mundipharma, Austral.; Mundipharma, Austria; Mundipharma, Belg.; Zodiac, Braz.; Purdue, Canad.†; Tecnofarma, Chile; Mundipharma, China; Mundipharma, Cz.; Norpharma, Denm.; Mundipharma, Fin.; Mundipharma, Fr.; Extractum, Hung.; Mundipharma, Hung.; Mundipharma, Irl.; Rafa, Israel; Mundipharma, Ital.; Shionogi, Jpn; Mundipharma, Malaysia; Mundipharma, Neth.; Mundipharma, Norw.; Pharmaco, NZ; Mundipharma, Philipp.; Norpharma, Pol.; Mundipharma, Port.†; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Swed.; Mundipharma, Switz.; Napp, UK; Purdue Frederick, USA; Nolver, Venez.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxycort *Jelfa, Pol.; Polfa Tarchomin, Pol.; Jelfa, Ukr.*
⊗Hydrocortisone acetate (p. 1640·1); oxytetracycline hydrochloride (p. 337·2).
Infected ear, eye, and skin disorders.

Tarchomin, Hung.; Jelfa, Rus.; Tarchomin, Rus.
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1); oxytetracycline hydrochloride (p. 337·2).
Infected skin disorders.

Oxyderm
Note: this name may be used for preparations of different composition.
Valeant, Canad.; Hind Wing, Hong Kong.†
Benzoyl peroxide (p. 1696·1).
Acne.

Oxyderme
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Nystatin (p. 590·3); zinc oxide (p. 1729·1).
Prickly heat.

Oxydermine *Wild, Switz.*
Zinc oxide (p. 1729·1); lauromacrogol 400 (p. 2194·1).
Wounds; skin disorders; burns.

Oxydex *Apex, India.*
Acetylcysteine (p. 1652·2); alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); zinc (p. 2126·1).

Oxydon *Rowex, Irl.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxyeye *Eyekare, India.*
Betacarotene (p. 2051·1); copper sulfate (p. 2057·2); glutathione (p. 1555·2); lutein (p. 2079·2); manganese chloride (p. 2081·2); selenious acid (p. 2087·1); zinc oxide (p. 1729·1).

Oxyfast *Purdue Frederick, USA.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxyflox *Cipla, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Oxyflux *Rayere, Mex.*
⊗Clenbuterol hydrochloride (p. 1207·2).

OxyGal *CT, Cz.†*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Oxygéron *Drossapharm, Switz.†*
Vincamine (p. 2645·2).
Cerebrovascular disease; circulatory eye disorders.

Oxygesic *Mundipharma, Ger.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxyglobin *Glorious, India.*
Chromium trichloride (p. 2055·3); ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); protein hydrolysate (p. 2086·2); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).

Oxy-Grape *Intra-Labs, India.*
Grape (p. 2521·3); vitamin E (p. 2119·1).

OxyIR *Purdue Frederick, USA.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxyla *Novell, Indon.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; pre-eclampsia; caesarian section.

Oxyla-AL *Alna, India.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).

Oxylac *Genesis, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3); lactic acid (p. 2539·1).

OxyLic *Worwag, Ukr.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3); lycopene (p. 2546·2); betacarotene (p. 2051·1); selenium yeast (p. 2125·2).
Tonic.

Oxylim *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Atlantic, Singapore.
Oxytetracycline (p. 337·1).
Bacterial infections.

Oxylin *Allergan, China; Allergan, India; Allergan, Irl.†; Allergan, Mex.; Allergan, Neth.; Allergan, Port.; Allergan, S.Afr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Conjunctivitis; eye irritation; allergic conjunctivitis; conjunctival irritation.

Oxylone *CCM, Malaysia; Duopharma, Singapore.*
⊗Oxymetholone (p. 2298·3).
Anaemias.

Oxylyco *Sanify, India.*
Lycopene (p. 2546·2); vitamin A (p. 2098·3).

Oxyma *Mankind, India.*
Betacarotene (p. 2051·1).

Oxymark *Unimarck, India.*
Dextropropoxyphene hydrochloride (p. 43·3); ibuprofen (p. 68·2); paracetamol (p. 115·1).

Oxymed *Medlink, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; lactation promotion; missed or incomplete abortion.

Oxymedin *Kade, Ger.†*
Oxybutynin hydrochloride (p. 2361·2).
Urinary incontinence; bladder instability.

Oxymet *Greater Pharma, Thai.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; nasopharyngitis; sinusitis; nasal congestion.

Oxymycin *DDSA Pharmaceuticals, UK.*
Oxytetracycline (p. 337·1).
Bacterial infections.

SA Druggists, S.Afr.†
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Oxyna *Sapco, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Oxynal *Euphoric, India.*
Diclofenac sodium (p. 48·3).
Pain.

Oxynal-P *Euphoric, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Oxy-Nase *Hoe, Singapore.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Oxynase *Hoe, Malaysia.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Oxynate-AR *Oxytech, India.*
Artesunate (p. 648·2).
Malaria.

Oxyneo *Purdue, Canad.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxynium *Unipharma, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Oxyno *Milano, Thai.†*
Oxyphencyclimine hydrochloride (p. 1875·1).
Gastrointestinal disorders; genito-urinary disorders.

Oxynorm *Mundipharma, Austral.; Mundipharma, Austria; Mundipharma, Belg.; Norpharma, Denm.; Mundipharma, Fin.; Mundipharma, Fr.; Mundipharma, Irl.; Mundipharma, Neth.; Mundipharma, Norw.; Pharmaco, NZ; Mundipharma, Philipp.; Norpharma, Pol.; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Swed.; Mundipharma, Switz.; Napp, UK.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxynormoro *Mundipharma, Fr.; Mundipharma, Port.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Oxynox *Air Products, Fr.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Analgesia in anaesthesia and painful procedures.

Oxynutra *PP Lab, Thai.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Oxypamol-D *Shalaks, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Oxypan *Oxytech, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Oxypan-D *Oxytech, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Oxypen *Dexa, Indon.*
Lutein (p. 2079·2); lycopene (p. 2546·2); vitamin E (p. 2119·1); vitamin C (p. 2110·3); zinc (p. 2126·1); betacarotene (p. 2051·1); selenium yeast (p. 2125·2).
Antoxidant; tonic.

Oxyperazine *Coup, Gr.*
Trifluoperazine hydrochloride (p. 1113·2).

Oxypérol *Chiesi, Fr.†*
Peru balsam (p. 2587·1); zinc oxide (p. 1729·1).
Skin irritation.

Oxyphar *Mediphar, Venez.*
Zinc oxide (p. 1729·1).
Burns; ulcers; wounds; skin irritation.

Oxyphyllin *Noventis, Cz.*
Etofylline (p. 1208·2).
Cerebrovascular disorders; ischaemic heart disease; obstructive airways disease.

Oxyplastine *Sinclair, Fr.; Wild, Switz.*
Zinc oxide (p. 1729·1).
Skin irritation; skin disorders.

Oxyprem *ModHike, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1). Magnesium trisilicate (p. 1858·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Oxypur *Mars, India.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Oxy-Q *Daffohils, India.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; systemic lupus erythematosus; malaria.

Oxyrea *Cadila, India.*
Hydroxycarbamide (p. 803·1).
Malignant neoplasms.

Oxy-S *DR Johns, India.*
Ceftriaxone (p. 253·3); sulbactam (p. 360·1).
Bacterial infections.

Oxysept *AMO, Canad.*
Hydrogen peroxide (p. 1755·2).
Cleaning and disinfecting solution for soft contact lenses.

Allergan, Braz.†; Allergan, USA.†
Hydrogen peroxide (p. 1755·2).
Disinfecting solution for contact lenses.

Oxysept Comfort *AMO, Arg.*
Hydrogen peroxide 3% (p. 1755·2).
Disinfecting and lubricating solution for soft contact lenses.

Oxysept 1 Step *Advanced Medical Optics, NZ.*
Solution, hydrogen peroxide (p. 1755·2); tablets, catalase (p. 2472·2).
Formerly known as Omnicare 1 Step.
Disinfecting and neutralising system for soft contact lenses.

AMO, Austral.
Hydrogen peroxide (p. 1755·2).
Formerly known as Omnicare 1 Step.
Disinfecting and neutralising system for soft contact lenses.

Oxyspas *Cipla, India; Cipla-Medpro, S.Afr.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder; urinary incontinence; nocturnal enuresis.

Oxystar *Cadila, India.*
Oxytocin (p. 2143·1).
Termination of pregnancy; postpartum haemorrhage; labour induction; evaluation of fetal distress.

Oxytel *Coup, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Oxyten *Choongwae, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; uterine atony; lactation promotion.

Oxyteracin *Jagsonpal, India.*
Oxytetracycline (p. 337·1).

Oxytetra *Abbott, India.*
Oxytetracycline (p. 337·1).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.

Oxytetral *Actavis, Denm.†; Actavis, Norw.†; Actavis, Swed.†*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections; acne.

Oxythyol *Richard, Fr.*
Zinc oxide (p. 1729·1); ichthammol (p. 1705·3).
Skin irritation.

Oxyton *Inga, India.*
Oxytocin (p. 2143·1).
Termination of pregnancy; postpartum haemorrhage; labour induction; evaluation of fetal distress.

Oxytret *Active, India.*
Betacarotene (p. 2051·1); copper (p. 2057·1); manganese (p. 2081·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Oxy-Triactin *Pharmed, India.*
Oxyphenbutazone (p. 114·3).

Oxytrol *Hospira, Austral.; Watson, Canad.; Hospira, NZ; Watson, USA.*
Oxybutynin (p. 2361·2).
Bladder hyperactivity; bladder instability.

Oxyuran *Elvipe, Gr.*
Piperazine hydrate (p. 163·1).

Oxyurin *Klonal, Arg.*
Oxybutynin (p. 2361·2).
Neurogenic bladder.

Oxy-V *Greenco, India.*
Copper (p. 2057·1); lutein (p. 2079·2); manganese (p. 2081·2); mecobalamin (p. 2108·1); selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zeaxanthin (p. 2125·3); zinc (p. 2126·1).

Oxyvit
Note: this name may be used for preparations of different composition.
AstraZeneca, India.
Betacarotene (p. 2051·1); manganese (p. 2081·2); selenium (p. 2086·3); vitamin A palmitate (p. 2098·3); vitamin C (p. 2110·3); vitamin E acetate (p. 2119·2); zinc sulfate (p. 2126·2).

Ferron, Indon.
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin deficiency.

Oxyzal *Gordon, USA.*
Hydroxyquinoline sulfate (p. 2530·1); benzalkonium chloride (p. 1737·1).
Minor skin infections.

Oxzey *Sunrise, India.*
Oxcarbazepine (p. 533·2).
Epilepsy.

O'Yes *Hovid, Malaysia.*
Tocotrienols (p. 2119·1); carotenoids (p. 2098·3); squalene (p. 2213·3); phytosterol complex (p. 1471·2).
Skin ageing; protection against skin cancer.

O'Yes Feminine Hygiene Wash *Hovid, Singapore.*
Lactic acid (p. 2539·1); tocoferil acetate (p. 2119·2).
Vaginal irritation; feminine hygiene.

Oysco *Rugby, USA.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; dietary supplement.

Oysco D *Rugby, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Oyst-Cal *Goldline, USA.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; dietary supplement.

Oyst-Cal-D *Goldline, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Oyster Calcium *Cypress, USA.*
Calcium (oyster shells) (p. 1783·1).
Calcium supplement.

Nature's Bounty, USA.
Calcium (p. 1783·1); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Oyster Calcium with Vitamin D *Cypress, USA.*
Calcium (oyster shells) (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Nion, USA.
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Oyster Shell Calcium with Vitamin D *Major, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Oystercal-D *Winsor, Hong Kong†; Nature's Bounty, USA.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; dietary supplement.

Oyst-O-Cal *Cadila, India.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Oyup *Unikid, India.*
Paracetamol (p. 115·1).
Pain; fever.

Oz *Pharmatre, Ital.*
Zinc oxide (p. 1729·1).
Skin disorders.

Oz Crema *Apotex, Mex.*
Miconazole (p. 588·3).
Fungal skin infections.

Oza *Sienna, India.*
Ofloxacin (p. 334·3).
Bacterial infections.

Ozace *Psychotropics, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Oza-O *Sienna, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).

Ozap *Finecure, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ozapex *Pharmathen, Gr.; Pharmathen, Neth.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ozapim *Labesfal, Port.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Ozapin *Ipca, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ozaprin *Ali, Turk.*
Olanzapine (p. 1089·3).

Ozarium *Anpharm (Ανφαρμ), Gr.*
Losartan potassium (p. 1422·2).

Ozcef *Ranbaxy, Austral.*
Cefaclor (p. 232·3).
Bacterial infections.

Ozed *Biosans, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ozed-D *Biosans, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ozeltan *Help, Gr.*
Nizatidine (p. 1866·1).
Peptic ulcer.

Ozen *Pharos, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Ozepal *Demo, Gr.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Ozepam *Ipca, India.*
Clonazepam (p. 519·1).
Epilepsy.

Ozepran *Sandoz, Gr.*
Pantoprazole sodium (p. 1875·3).

Ozex *Otsuka, Jpn; Toyama, Jpn.*
Tosufloxacin tosilate (p. 381·2).
Bacterial infections.

Oziclide *Ranbaxy, Austral.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Ozid *Darya-Varia, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ozidal *Ranbaxy, Austral.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Ozidia *Pfizer, Fr.*
Glipizide (p. 474·1).
Diabetes mellitus.

Oziklid *Ranbaxy, Ukr.*
Gliclazide (p. 472·3).
Diabetes mellitus.

OZL *Nordic, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ozlodip *Ranbaxy, Austral.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ozmep *Spirit, Austral.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ozo *Ind-Swift, India.*
Omeprazole (p. 1867·2) or omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ozo-D *Ind-Swift, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ozoderpin *Demo, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Ozodom *Chemo-Drugs, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ozoken *Kener, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ozol *NB, India.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ozol-D *NB, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Ozole *Ranbaxy, Austral.*
Fluconazole (p. 578·2).
Fungal infections.

Ozolin *Osper, India.*
Cefazolin (p. 237·2).
Bacterial infections.

Ozonol
Note: this name may be used for preparations of different composition.
Bayer Consumer, Canad.
Phenol (p. 1763·3); zinc oxide (p. 1729·1).
Cuts; burns; bites and stings; skin irritation.

GSK Consumer, Port.
Ibuprofen (p. 68·2).
Fever; pain.

Ozonol Antibiotic Plus *Bayer Consumer, Canad.*
Polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3); lidocaine hydrochloride (p. 1988·2).
Minor cuts and burns; skin irritation.

Ozonosol *Lagos, Arg.*
SPF 34: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Lagos, Arg.
SPF 11; SPF 20: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); ensulizole (p. 1703·1).
Sunscreen.

Lagos, Arg.
SPF 55+: Titanium dioxide (p. 1725·1); amiloxate (p. 1694·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); enzulizole (p. 1703·1).
Sunscreen.

Ozonyl *Gross, Braz.*
Injection: Menthol (p. 2553·2); guaiacol (p. 1666·1); terpin hydrate (p. 1678·2); cineole (p. 2479·1); niaouli oil (p. 2569·1); camphor (p. 2466·2); benzyl cinnamate (p. 2454·3).
Respiratory-tract congestion.

Ozonyl Aquoso *Gross, Braz.*
Cineole (p. 2479·1); niaouli oil (p. 2569·1); guaifenesin (p. 1666·2); sodium camsilate (p. 2617·3); lidocaine hydrochloride (p. 1988·2).
Respiratory-tract congestion.

Ozonyl Expectorante *Gross, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium camsilate (p. 2617·3); guaifenesin (p. 1666·2); cineole (p. 2479·1); niaouli oil (p. 2569·1); menthol (p. 2553·2).
Respiratory-tract congestion.

Ozopulmin *Geymonat, Ital.*
Injection: Verbenone (p. 2645·1).
Respiratory-system disorders.

Geymonat, Ital.
Suppositories: Verbenone (p. 2645·1); pine oil (p. 2591·1).
Respiratory-system disorders.

Ozopulmin G *Geymonat, Ital.*
Suppositories: Verbenone (p. 2645·1); pine oil (p. 2591·1).
Cough; catarrh.

Geymonat, Ital.
Syrup: Verbenone (p. 2645·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; catarrh.

Geymonat, Ital.†
Topical gel: Verbenone (p. 2645·1).
Cough; catarrh.

Ozothine *Zambon, Fr.*
Suppositories: Oxidation products of turpentine oil (p. 2636·3).
Respiratory-tract disorders.

Zambon, Fr.†
Syrup: Oxidation products of turpentine oil (p. 2636·3); sodium benzoate (p. 1738·2).
Respiratory-tract disorders.

Ozotine à la Diprophylline *Zambon, Fr.*
Oxidation products of turpentine oil (p. 2636·3); diprophylline (p. 1207·3).
Respiratory-tract disorders.

Ozovit *Pascoe, Ger.*
Magnesium peroxide (p. 1759·3).
Constipation; dyspepsia; meteorism.

Ozpan *Ranbaxy, Austral.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ozurdex *Allergan, Canad.; Neomed, Cz.; Allergan, Denm.; Allergan, Fr.; Allergan, Ger.; Allergan, Irl.; Allergan, Israel; Allergan, Neth.; Allergan, Norw.; Allergan, Pol.; Allergan, Port.; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, UK; Allergan, Ukr.; Allergan, USA.*
⊗Dexamethasone (p. 1630·3).
Macular oedema; uveitis.

Ozus *Mission Happiness, India.*
Fluconazole (p. 578·2).
Fungal infections.

Ozvir *Ranbaxy, Austral.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ozym *Trommsdorff, Ger.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

P-37 *Moraceae, India.*
Paracetamol (p. 115·1).
Pain; fever.

P-125 *Apex, India.*
Paracetamol (p. 115·1).
Pain; fever.

P Chlor DM *SDA, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

P & S *Aero, USA.*
Shampoo: Salicylic acid (p. 1719·1).
Seborrhoea.

Pharmascience, Canad.; Baker Cummins, USA.
Phenol (p. 1763·3).
Scalp disorders; psoriasis; seborrhoeic dermatitis.

Pharmascience, Canad.
Shampoo: Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Psoriasis; seborrhoea.

P & S Plus *Pendopharm, Canad.†*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Psoriasis; seborrhoeic dermatitis.

Pa Fu Lin *SanJiu, China.*
Peony glycosides.

Pa Lai Xin *Haochuang, China.*
Folic acid (p. 2063·1).

Pa Rui Da *Baike Hengdi, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Pa Te La *Yaoyou, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Pa La Xin *Sine, China.*
Paracetamol (p. 115·1).
Fever; pain.

Pa Di Xing *Dikang Changjiang, China.*
Pazufloxacin mesilate (p. 338·1).

Paar *Finecure, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Pabafilm *Galderma, Mex.†*
Aminobenzoic acid (p. 1694·2); oxybenzone (p. 1715·3).
Sunscreen.

Pabal *Ferring, Austria; Ferring, Belg.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Hung.; Ferring, Irl.; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Port.; Ferring, Swed.; Ferring, Switz.; Ferring, UK; Ferring, Ukr.*
Carbetocin (p. 2132·3).
Uterine atony and haemorrhage following Caesarean section.

Pabalak *Sarabhai Piramal, India.*
Aminobenzoic acid (p. 1694·2).
Sunscreen.

Pabanox
Note: this name may be used for preparations of different composition.
Surya Dermato, Indon.
Oxybenzone (p. 1715·3); padimate O (p. 1716·1); titanium dioxide (p. 1725·1).
Sunscreen.

Pabasol *Galderma, Mex.†*
Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Pabasun *Dexo, Fr.*
Aminobenzoic acid (p. 1694·2).
Sunscreen.

Pabatab *Shalaks, India.*
Aminobenzoic acid (p. 1694·2).

Pabatab-BZ *Shalaks, India.*
Biotin (p. 2052·2); calcium pantothenate (p. 2085·2); nicotinamide (p. 2083·1); aminobenzoic acid (p. 1694·2); zinc (p. 2126·1).

Pabialgin P *Polfa Pabianice, Pol.†*
Propyphenazone (p. 127·3); allobarbital (p. 1035·2).
Pain.

Pabiprofen *Polfa, Cz.†*
Ibuprofen (p. 68·2).
Inflammation; pain.

Pabitan *Polfa Pabianice, Pol.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Pabrinex *Archimedes, Irl.; Archimedes, UK.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin supplement; alcoholism; vitamin deficiency.

Pabron Cold & Flu *Taisho, Malaysia.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Allergic rhinitis; sinus congestion; cold and influenza symptoms.

Pabron Cough
Note: this name may be used for preparations of different composition.
Taisho, Malaysia.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion; cough.

Taisho, Thai.
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pabron Cough & Aches *Taisho, Malaysia.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cough; nasal congestion; cold symptoms.

Pabron Cough & Sinus *Taisho, Malaysia.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders with cough.

Pabron Cough-D *Taisho, Malaysia.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Pabron SN *Taisho, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; cold symptoms; nasal and sinus congestion.

Pabron XT *Taisho, Thai.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms; cough.

P-A-C *Upjohn, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Pacamic *Inpac, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Pacaps *Lunsco, USA.*
Butalbital (p. 1043·3); caffeine (p. 1203·3); paracetamol (p. 115·1).

Paceco *Malaysia Chemist, Singapore.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Fever; pain.

Pacemol *Malaysia Chemist, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Pacerone *Upsher-Smith, USA.*
Amiodarone hydrochloride (p. 1300·1).
Ventricular arrhythmias.

Pacetaker *Little Greave, India.*
Meropenem (p. 321·3).
Bacterial infections.

Pacetin *Choongwae, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Paceum *Orion, Switz.*
Diazepam (p. 1063·2).
Non-psychotic mental disorders; sleep disorders; skeletal muscle spasm; convulsions; premedication.

Pacid *Procure, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pacidol *Biocodex, Fr.*
Sucrose (p. 2096·3).
Adjunct in painful procedures in infants.

Pacidom-C *Indo Pacific, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Pacidom-O *Indo Pacific, India.*
Domperidone (p. 1838·1); omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia.

Pacidom-P *Indo Pacific, India.*
Domperidone (p. 1838·1); paracetamol (p. 115·1).

Pacifed *Inpac, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Pacifen *Mylan, NZ.*
Baclofen (p. 2014·3).
Skeletal muscle spasm and spasticity.

Pacifene *Sussex, UK.*
Ibuprofen (p. 68·2).
Pain; fever.

Pacilia *Biogaran, Fr.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Pacimol *Ipca, India; Multichem, NZ†; Nat Druggists, S. Afr.†*
Paracetamol (p. 115·1).
Fever; pain.

Pacimol Plus *Ipca, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Pacimol-M *Ipca, India.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Pacinac *Gentech, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Gentech, India.
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Pacinac-NP *Gentech, India.*
Domperidone (p. 1838·1); naproxen sodium (p. 98·2).

Pacinax *Silesia, Chile.†*
Diazepam (p. 1063·2).
Epilepsy.

Pacinone *Schering-Plough, Port.*
Halazepam (p. 1077·1).
Anxiety.

Paciquil *Stadmed, India.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; muscle spasm; seizures; alcohol withdrawal syndrome.

Pacisyn *DLF, Denm.*
Nitrazepam (p. 1089·1).
Insomnia.

Pacitane *Wyeth, India.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Pacium *Biomed, Spain.†*
Diazepam (p. 1063·2).
Contains pyridoxine hydrochloride.
Anxiety; insomnia; febrile convulsions; skeletal muscle spasm; alcohol withdrawal syndrome.

Pacizox *Ipca, India.*
Paracetamol (p. 115·1); diclofenac sodium (p. 48·3); chlorzoxazone (p. 2022·2).
Skeletal muscle spasm and pain.

Pacliavenir *Bioavenir, Israel.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclicad *Cadila, India.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Paclikebir *Aspen, Arg.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclimedac *Medac, Cz.; Medac, Denm.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer; non-small cell lung cancer; Kaposi's sarcoma.

Pacline *Heaton, Cz.; PharmaSwiss, Gr.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer; non-small cell lung cancer; Kaposi's sarcoma.

Pacliron *Feron, India.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Paclisan *Sanfer, Mex.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer.

Paclit *Cancernova, Ger.; Alvia (Αλβια), Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclitax *Eurofarma, Braz.; Cipla, India; Cipla, Rus.; Cipla, Venez.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclitaxin *Teva, Belg.; Pharmachemie, Fin.; Chemipharm, Gr.; Pharmachemie, Neth.; Pharmachemie, Philipp.; Pharmachemie, Singapore; Pharmachemie, Thai.; Teva, Thai.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclitec *United Biotech, India.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Paclitera *Stragen, Rus.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Pacliteva *Teva Tuteur, Arg.*
Paclitaxel (p. 839·3).
Ovarian cancer.

Paclitol *Pharmanel, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclitrust *Panacea, India.*
Paclitaxel (p. 839·3).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Paclixel *Novagen, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paclo-GMD *Daksh, India.*
Diacerein (p. 45·3); glucosamine (p. 2515·3); dimethyl sulfone (p. 2493·3).

Paclo-MR *Daksh, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Pacmadol *Inpac, Thai.*
Tramadol (p. 139·2).
Pain.

Pacnex *Medimetriks, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Pacofen *DHA, Singapore; Sanli, Turk.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Pacofen-S *Sanli, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Pacogen *Chinta, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Pacogesic *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Pacopan *Pharmasant, Thai.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm with pain.

Pacroma *Biocon, India.*
Pimecrolimus (p. 1716·1).
Atopic eczema.

Pactadine *Inpac, Thai.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Pactens
Note: this name may be used for preparations of different composition.
Merck, Gr.
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; hypertrophic obstructive cardiomyopathy; arrhythmias; hyperthyroidism; phaeochromocytoma; myocardial infarction.
Merck, Mex.
Naproxen sodium (p. 98·2).
Pain; inflammation.

Pactum *Alembic, India.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Pacyl *Jagsonpal, India.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Pädamin *Fresenius Kabi, Austria.*
Amino acids.
Parenteral nutrition.

Padax *Adcock Ingram, S.Afr.*
Piperazine citrate (p. 163·1).
Worm infections.

Padéryl *Gerda, Fr.*
Codeine phosphate (p. 40·2).
Cough.

Padet *Pharmatrix, Arg.*
Metronidazole (p. 936·1).
Rosacea.

Pädiacrom *Padia, Ger.†*
Sodium cromoglicate (p. 1225·3).
Asthma.

Pädiafusin *Baxter, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Pädiafusin OP *Baxter, Ger.*
Potassium-free electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Pädiamol *Padia, Ger.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Pädiamuc *Padia, Ger.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Pädiatifen *Padia, Ger.†*
Ketotifen fumarate (p. 631·3).
Asthma; bronchitis; allergic rhinitis; allergic skin disorders.

Paditex *Fada, Arg.*
Clonazepam (p. 519·1).

Padma 28 *Cedar Health, UK.*
Aegle sepiar fructus; allspice; aquilegiae herba; calendula flos; cardamomi fructus; caryophylli flos (p. 2481·2); costi amari radix; hedychii rhizoma; lactucae sativae folium; lichen islandicus (p. 2531·2); liquiritiae radix (p. 1853·2); meliae tousend fructus; myrobalani fructus; plantaginis herba; polygoni herba; potentillae aureae herba; santali rubri lignum; sidae cordifoliae herba; aconiti tuber (p. 2428·3); valerianae radix (p. 2640·2); calcium sulfate (p. 2173·1); camphor (p. 2466·2).
Circulatory disorders.

Padma, Switz.
Aegle sepiar fructus; allspice; aquilegiae vulgaris herba; calcii sulfas (p. 2173·1); calendulae flos cum calycibus; cardamomi fructus; caryophylli flos.; costi amari radix; dextrocamphora (p. 2466·2); hedychii rhizoma; lactucae sativae folium; lichen islandicus (p. 2531·2); liquiritiae radix (p. 1853·2); meliae tousend fructus; myrobalani fructus; plantaginis herba; polygoni avicularis herba (p. 2538·2); potentillae aureae herba; santali rubri lignum; sidae cordifoliae herba; aconiti tuber (p. 2428·3); valerianae radix (p. 2640·2).
Circulatory disorders.

Tymofarm, Pol.
Aconite (p. 2428·3); aegle sepiar; allspice; aquilegia; calendula (p. 2465·2); camphor (p. 2466·2); cardamom (p. 2471·1); clove (p. 2481·2); costus root; hedychii rhizome; lettuce; Iceland moss (p. 2531·2); liquorice (p. 1853·2); meliae tausend; myrobalani; ribwort plantain (p. 2604·2); knotgrass (p. 2538·2); golden potentilla; sandalwood bark; sidae cordifoliae; valerian (p. 2640·2); calcium sulfate (p. 2173·1).
Peripheral vascular disorders.

Padma Circosan *World Foods, UK.*
Saussurea costus; Iceland moss (p. 2531·2); azadirachta (p. 2451·2); cardamom (p. 2471·1); chebulic myrobalan (p. 2474·3); pterocarpus santalinus; pimenta officinalis; aegle marmelos; aquilegia vulgaris; liquorice (p. 1853·2); ribwort plantain (p. 2604·2); knotgrass (p. 2538·2); potentilla aurea; clove (p. 2481·2); kaempferia galanga; sida; valerian (p. 2640·2); lactuca sativa; calendula (p. 2465·2); cinnamomum camphora oil; calcium sulfate (p. 2173·1).
Peripheral vascular disorders.

Padma Digestin *Padma, Switz.*
Punicae granati (p. 164·1); galanga; piperis longae; cardamomi semen (p. 2471·1); cinnamomi cassiae (p. 2479·2).
Digestive disorders.

Padma-Lax *Padma, Switz.*
Aloes (p. 1816·1); kaolin (p. 1850·1); calumba radix (p. 2466·1); condurango (p. 2485·3); enulae radix; gentian (p. 2512·1); myrobalan (p. 2474·3); sodium bicarbonate (p. 1781·1); anhydrous sodium sulfate (p. 1888·1); piper longum; frangula bark (p. 1843·3); cascara (p. 1826·1); rhubarb (p. 1884·2); nux vomica (p. 2573·3); ginger (p. 1844·1).
Constipation.

Padmed Circosan *Padma, Switz.*
Aegle sepiar fructus; allspice; aquilegiae vulgaris herba; calcii sulfas (p. 2173·1); calendulae flos cum calycibus; cardamomi fructus; caryophylli flos (p. 2481·2); costi amari radix; dextrocamphora (p. 2466·2); hedychii rhizoma; lactucae sativae folium; lichen islandicus (p. 2531·2); liquirtiae radix; meliae tousend fructus; myrobalani fructus; plantaginis herba; polygoni avicularis herba (p. 2538·2); potentillae aureae herba; santali rubri lignum; sidae cordifoliae herba; aconiti tuber (p. 2428·3); valerianae radix (p. 2640·2).
Circulatory disorders.

Padmed Laxan *Padma, Switz.*
Aloes (p. 1816·1); calumba radix (p. 2466·1); condurango (p. 2485·3); frangula bark (p. 1843·3); gentian (p. 2512·1); elecampane (p. 1662·3); kaolin (p. 1850·1); myrobalan (p. 2474·3); sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1); piper longum; cascara (p. 1826·1); rhubarb (p. 1884·2); nux vomica (p. 2573·3); ginger (p. 1844·1).
Constipation.

Padolten *Billev, Pol.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Padomil *Kleva, Gr.*
Mefenamic acid (p. 85·3).

Padonil *Phapros, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Padovan Ton *Rayere, Mex.*
Nitazoxanide (p. 942·2).
Amoebiasis; giardiasis; trichomoniasis; worm infections.

Padrasen *Kyowa, Jpn.*
Clocapramine hydrochloride (p. 1054·2).
Schizophrenia.

Padrin *Irom, Jpn.*
Prifinium bromide (p. 1879·3).
Smooth muscle spasm; pancreatitis; adjunct in gastrointestinal examination.

Padutin *Wabosan, Austria.*
Kallidinogenase (p. 2537·2).
Male infertility.

Paedamin *Care, Austral.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion; cold symptoms; allergic rhinitis.

Paedialgon *Rosen, Ger.†*
Paracetamol (p. 115·1).
Fever; pain.

Paediasure *Abbott, Irl.*
Preparation for enteral nutrition.

Abbott Nutrition, UK.
A range of preparations for enteral nutrition.

Paediathrocin *Amdipharm, Ger.†*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Paediatric Seravit *Nutricia, NZ.*
Vitamins; minerals trace elements.
Dietary supplement.

Scientific Hospital Supplies, Austral.
Vitamins; minerals; trace elements.
Metabolic disorders; dietary supplement.

SHS, UK.
Vitamins; minerals.

Paedicof *Sunward, Singapore.*
⊗Dexchlorpheniramine maleate (p. 621·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinusitis; rhinitis; cough; post nasal drip.

Paedritone *Charak, India.*
Aloes (p. 1816·1); Indian barberry (p. 2532·1); cardamom (p. 2471·1); curcuma longa; cyperus scariosus; fennel (p. 2503·2); liquorice (p. 1853·2); piper longum; terminalia chebula (p. 2474·3); zingiber officinale.
Infant colic.

Paeonia-Plus *Doctor H, Rus.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); acidum nitricum (p. 2572·3); hamamelis virginiana (p. 2523·3); krameria triandra (p. 2603·3); paeonia officinalis.
Homoeopathic preparation.

Paf *Lofarma, Ital.*
Bucarbetene.
Scabies.

Pafenon *Gedeon Richter, Hung.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; gastritis; Zollinger-Ellison syndrome.

Paferxin *Liferpal, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Pafinur *Rottapharm, Ital.*
Rupatadine fumarate (p. 640·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Page *Orchid, India.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Pagero *Sarabhai Piramal, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Paglitaz *Focus Care, Neth.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pagluferal *Mosfarma, Rus.*
Bromisoval (p. 1041·3); calcium gluconate (p. 1783·3); caffeine sodium benzoate (p. 1203·3); papaverine hydrochloride (p. 2362·3); phenobarbital (p. 535·2).
Epilepsy.

Pagyn *Patar, Thai.*
Tinidazole (p. 949·2).
Bacterial infections; protozoal infections; Helicobacter pylori eradication.

Pai De *Fu He Hua Xing, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Pai Di *Youbo, China.*
Sodium new houttuyfonate.

Pai Da Yi Er *SSPC, China.*
Trace elements.
Parenteral nutrition.

Pai Fen *Wanjie High Tech, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Pai Fu *Double-Crane, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Pai Ke Xin *Tailong, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Pai Meng *Xinhua, China.*
Oxymatrine.

Pai Nai Xin *Yongning, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Pai Sheng *Lijun, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Pai Shu *Asia Pioneer, China.*
Piperacillin sodium (p. 340·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Pai Shu Ke *Guangji, China.*
Pazufloxacin mesilate (p. 338·1).

Pai Si Ke *Huinan Tiantai, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Pai Si Xin *Bai Li, China.*
Pazufloxacin mesilate (p. 338·1).

Pai Su *Qilu, China.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Pai Ting *Hengrui, China.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Pai Tong Xin *IND, China.*
Reteplase (p. 1486·2).
Myocardial infarction.

Pai Wei Xin *Yongning, China.*
Cefuroxime (p. 255·2).
Bacterial infections.

Pai Xin *Enhua Saide, China.*
Benproperine phosphate (p. 1656·2).

Paiazym *Homeosyn, Ital.*
Carica papaya.
Dietary supplement.

Paidisheng *Huayu, China.*
Mirtazapine (p. 436·1).
Depression.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Paidocin *Promedica, Ital.*
Rokitamycin (p. 356·1).
Bacterial infections.

Paidofebril *Aldo, Spain.*
Ibuprofen (p. 68·2).
Juvenile idiopathic arthritis; pain; fever.

Paidoflor *Ardeypharm, Ger.*
Lactobacillus acidophilus (p. 2596·3).
Gastrointestinal disorders.

Paidolax *Casen Fleet, Spain.*
⊗Glycerol (p. 2517·2).
Constipation.

Paidoterin Descongestivo *Aldo, Spain.*
Chlorphenamine maleate (p. 620·3); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper-respiratory-tract congestion.

Paidovit *Andromaco, Chile.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3).
Vitamin A, D, and C deficiency.

Pailuo *Yimin, China.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Pain Aid *Zee, Canad.†*
Aspirin (p. 22·2); caffeine (p. 1203·3).

Pain Buster *Confab, Canad.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).

Pain Bust-R II *Continental, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Pain Doctor *Fougera, USA.*
Capsaicin (p. 35·1); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Pain.

Pain & Fever Relief *Brauer, Austral.*
Aconitum nap. (p. 2428·3); belladonna (p. 2453·3); cimicifuga (p. 2478·1); euphorbium; ferrum phos. (p. 2077·1); gelsemium (p. 2511·2); merc. sol. (p. 2555·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Pain Relief Balm *Boots, UK.†*
Glycol monosalicylate (p. 66·2); ethyl nicotinate (p. 56·3); nonivamide (p. 102·3).
Musculoskeletal and joint pain; stiffness; sciatica; lumbago; fibrositis.

Pain Relieving Rub *G & W, USA.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).

Painadol *FDC, India.*
Tramadol (p. 139·2).
Pain.

Painadol-P *FDC, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Painagon *Be-Tabs, S.Afr.*
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Be-Tabs, S.Afr.
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); meprobamate (p. 1083·3); caffeine (p. 1203·3).
Pain; pain associated with tension.

Painaid *Zee, USA.*
Aspirin (p. 22·2); salicylamide (p. 129·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Painaid Back Relief *Zee, USA.*
Paracetamol (p. 115·1); magnesium salicylate (p. 85·2).
Pain.

Painaid BRF Back Relief Formula *Zee, USA.*
Magnesium salicylate (p. 85·2); paracetamol (p. 115·1).
Pain.

Painaid ESF Extra-Strength Formula *Zee, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Painaid Free *Zee, Canad.*
Paracetamol (p. 115·1).
Fever; pain.

Painaid PMF *Zee, Canad.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1).

Painaid PMF Premenstrual Formula *Zee, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1).
Pain.

Painamol *Be-Tabs, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Painamol Plus *Be-Tabs, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Painblok *Gulf Drug, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Painbreak *Riemser, Ger.*
⊗Morphine sulfate (p. 92·3).
Pain.

Paincodein *Austell, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).

Paindol *Polipharm, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Painease *Future, Canad.*
Dioscorea villosa (p. 2648·1); frankincense (p. 2507·3); turmeric (p. 2218·1); valerian (p. 2640·2).

PainEaze *Blue Ocean, UK.*
Frankincense (p. 2507·3); peppermint (p. 1877·1); menthol (p. 2553·2); dimethyl sulfone (p. 2493·3); eucalyptus (p. 2501·1).
Musculoskeletal, joint, and soft-tissue disorders.

Painelief *British Dispensary, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Painex
Note: this name may be used for preparations of different composition.
Confar, Port.
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Lagap, UK.
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain.

Mint, India.
Tramadol (p. 139·2).
Pain.

Toprak, Turk.
Etofenamate (p. 57·2).
Musculoskeletal and joint pain.

Pain-Flex *Perrigo, Israel.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue disorders.

Painfort *Nolver, Venez.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Pain.

Pain-gesic *Mason, USA.*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1).
Pain.

Painkair *PDC, India.*
Injection: Diclofenac sodium (p. 48·3).
Pain.

PDC, India.
Tablets: Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Painkair-MR *PDC, India.*
Chlorzoxazone (p. 2022·2); diclofenac potassium (p. 48·3); paracetamol (p. 115·1).

Painkila *Mugi, Indon.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Painnox *Deltapharm, Hong Kong†; Charoen, Thai.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Painoff
Note: this name may be used for preparations of different composition.
Rafarm, Gr.
Glucosamine sulfate (p. 2515·3).

Marching, Hong Kong.†
Diclofenac (p. 48·3).

Painogesic *Innovata, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Painol *The Forty-Two, Thai.*
Syrup: Paracetamol (p. 115·1); salicylamide (p. 129·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

The Forty-Two, Thai.
Tablets: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Painon *Haibin, China.*
Meropenem (p. 321·3).
Bacterial infections.

Pai-Noren *2M, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Painout *Ethix, India.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Painrelipt-D *Biostam (Βιοσταμ), Gr.*
Piroxicam (p. 125·3).
Inflammatory disorders.

Painrite *Columbia, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Painrite SA *Columbia, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Painsik *Best, Mex.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

Painstop Day-Time Pain Reliever *Care, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Painstop Night-Time Pain Reliever *Care, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain.

Painza *Siam Bheasach, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal pain.

Painza Cool *Siam Bheasach, Thai.*
Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Paiqi *Lijun, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Pakab *Wermar, Mex.*
Pinaverium bromide (p. 2590·3).

Pakinase *Finadiet, Arg.*
⊗Metoclopramide (p. 1862·2); amylase (p. 2442·1); cellulase (p. 2473·1); pancreatin (p. 2579·3); dehydrocholic acid (p. 2492·1).
Digestive disorders.

Paklitaxfil *Filaxis, Arg.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

Pakurat *Oriental, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Palacimol *Spyfarma, Spain.†*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Palacos *Soll, Gr.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2).

Palacos E with Garamycin *Schering-Plough, Austral.†*
Methylmethacrylate/methyl acrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos E con Gentamicina *Schering-Plough, Chile.†*
Methylmethacrylate-methylacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos with Garamycin *Schering-Plough, NZ.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos LV with Gentamicin *Schering-Plough, UK.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos R *Schering-Plough, Chile†; Merck, Singapore; Merck, Thai.†; Schering-Plough, UK.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2).
Bone cement for orthopaedic surgery.

Palacos R with Garamycin *Schering-Plough, Austral.†; Trinity, S.Afr.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos R with Gentamicin *Schering-Plough, UK.*
Methylmethacrylate/methylacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos R con Gentamicina *Schering-Plough, Chile.†*
Methylmethacrylate-methylacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Palacos R with Gentamycin *Schering-Plough, Gr.*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methacrylate copolymer (p. 2558·2).
Bacterial infections.

Paladac *Pfizer, Turk.*
Vitamins.

Paladin *Pal Midwest, USA.*
Soft paraffin (p. 2211·3); starch (p. 2095·1); wool fat (p. 2219·3); zinc oxide (p. 1729·1); liquid paraffin (p. 2191·2); boric acid (p. 2459·3); beeswax (p. 2170·2); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Nappy rash.

Palafer *Meda, Canad.*
Ferrous fumarate (p. 2060·3).
Iron supplement; iron-deficiency anaemia; iron deficiency.

Palafer CF *Meda, Canad.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Prenatal supplement.

Palan *Lafedar, Arg.*
Vitamin A (p. 2098·3); neomycin sulfate (p. 330·1).
Wounds.

Palandra *Bayer, Denm.; Bayer, Fin.; Bayer, Irl.; Bayer, Neth.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Palane *Cryopharma, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Palasept G *Heraeus, Ger.†*
Gentamicin sulfate (p. 304·2); polymethylmethacrylate (p. 2558·2).
Bone and soft-tissue infection.

Palat *Ebewe, Irl.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Palatrin *Degorts, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Palatrobil *Monserrat, Arg.*
Oral drops: Cynara (p. 2490·3); wild carrot (p. 2647·2); menthol (p. 2553·2); boldo (p. 2458·3).
Digestive disorders.

Monserrat, Arg.
Tablets: Dehydrocholic acid (p. 2492·1); cynara (p. 2490·3).
Digestive disorders.

Palcaps *Breckenridge, USA.†*
Pancreatic enzymes (porcine) (p. 2579·3).
Pancreatic deficiency.

Palcid *Pharmadica, Thai.*
Cisapride (p. 1831·3).
Dyspepsia; gastroparesis; gastro-oesophageal reflux.

Palcol *Jofrain, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Paldar *Investi, Arg.; Raffo, Chile.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Paldesic *Rosemont, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Palentin *Phapros, Indon.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Paleodina *Liferpal, Mex.†*
Dipyrone (p. 53·3).
Pain.

Paleo-ISR *Malody, India.*
Itopride; pantoprazole (p. 1875·3).

Palexia *Grunenthal, Cz.; Grunenthal, Denm.; Grunenthal, Ger.; Grunenthal, Irl.; Grunenthal, Neth.; Grunenthal, Norw.; Grunenthal, Spain; Grunenthal, Swed.; Grunenthal, Switz.; Grunenthal, UK.*
Tapentadol hydrochloride (p. 136·1).
Pain.

Palexil *Kocak, Turk.*
Adapalene (p. 1692·1).

Palface *ACE, Neth.†*
⊗Dextromoramide tartrate (p. 43·2).
Pain.

Palfium *Antigen, Irl.†; ACE, Neth.*
⊗Dextromoramide tartrate (p. 43·2).
Pain.

Palgic
Note: this name may be used for preparations of different composition.
Pamlab, USA.
Carbinoxamine maleate (p. 619·1).
Allergic rhinitis.
Scoshia, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Palgic DS *Pan American, USA.*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Palgic-D
Note: this name may be used for preparations of different composition.
Pan American, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract disorders.
Scoshia, India.
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Paliatil *Medifarma, Mex.*
⊗Aminophylline (p. 1201·2); atropine (p. 1310·2); ephedrine (p. 1663·1); phenobarbital (p. 535·2).

Palimodon *Pharmathen, Gr.†*
Buflomedil hydrochloride (p. 1328·3).

Palin
Note: this name may be used for preparations of different composition.
Genesis, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.
Sandoz, Pol.; Lek, Rus.; Lek, Ukr.
Pipemidic acid (p. 339·3).
Bacterial infections.

Palin-D *Genesis, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Palio *DWD, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Palio-D *DWD, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Paliris *Sun, India.*
Paliperidone (p. 1093·1).
Schizophrenia.

Palistop *Gap, Gr.*
Flutamide (p. 798·2).
Prostatic cancer.

Palitax *Pharmedic, Philipp.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; Kaposi's sarcoma.

Palitenox *Pharmathen, Gr.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular pain; gout; pain.

Paliuryl *Merck Medication Familiale, Fr.†*
Rhamnus paliurus.
Stimulation of renal water excretion.

Palixid *Gedeon Richter, Hung.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Palladon *Norpharma, Denm.; Mundipharma, Fin.; Mundipharma, Ger.; Mundipharma, Neth.; Mundipharma, Norw.; Mundipharma, Swed.; Mundipharma, Switz.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Palladon Comp *Mundipharma, Swed.†*
⊗Atropine sulfate (p. 1310·2); hydromorphone hydrochloride (p. 67·3).
Pain with smooth muscle spasm.

Palladone *Mundipharma, Belg.; Mundipharma, Cz.; IFET (ΙΦΕΤ), Gr.; Extractum, Hung.; Mundipharma, Hung.; Mundipharma, Irl.; Rafa, Israel; Napp, Port.†; Mundipharma, Spain; Napp, UK.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Pallagicin *Baxter, Indon.†*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Pallidone *Douglas, NZ.*
⊗Methadone hydrochloride (p. 88·3).
Opioid dependence; pain; cough.

Pallohyman *Remedina, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Pallopikeron *Remedina, Gr.*
Nefopam hydrochloride (p. 100·2).

Pallosixanet *Remedina, Gr.*
Cimetidine (p. 1827·1).

Pallotrinate *Remedina, Gr.*
Codergocrine mesilate (p. 389·2).

Pallrywyn Forte *Charak, India.*
⊗Clove (p. 2481·2); piper longum; tribulus terrestris (p. 2633·3); withania somnifera.

Palmer's Cocoa Butter Formula *Palmer, Malaysia.*
A range of cocoa butter (p. 2216·1) preparations.
Dry skin; skin care.

Palmer's Cocoa Butter Formula Nappy Rash Ointment *Palmer, Malaysia.*
Theobroma oil (p. 2216·1); panthenol (p. 2582·2); soft paraffin (p. 2211·3); vitamin A (p. 2098·3).
Skin irritation; nappy rash.

Palmer's Cocoa Butter Formula Nursing Cream *Palmer, Malaysia.*
Theobroma oil (p. 2216·1); panthenol (p. 2582·2); soft paraffin (p. 2211·3).
Sore or cracked nipples.

Palmer's Cocoa Butter Formula Scar Serum *Palmer, Malaysia.*
Theobroma oil (p. 2216·1); vitamin E (p. 2119·1); shark-liver oil (p. 2614·2); silicone (p. 2209·2); onion (p. 2575·2).
Scars; stretch marks.

Palmer's Skin Success *ET Browne, Canad.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Palmer's Skin Success Acne Medication *Palmer, Malaysia.*
Salicylic acid (p. 1719·1).
Acne; skin cleanser.

Palmetto Plus *Usana, Hong Kong†; Usana, Singapore.†*
Saw palmetto (p. 2363·3); lycopene (p. 2546·2); soya isoflavones (p. 2620·3).
Nutritional supplement.

Pal-MF *Vensat, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).

Palmiclor *Mayo, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Palmicol
Note: this name may be used for preparations of different composition.
Otto, Indon.
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.
Cheplapharm, Ger.†
Heavy magnesium carbonate (p. 1856·2).
Gastrointestinal disorders; magnesium deficiency.

Palmifer *Reuffer, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Palmisol *Parggon, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Palmitate-A *Akorn, USA.†*
Vitamin A (p. 2098·3).

Palmoxan *Gelcaps, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Palmyforte *Nafar, Mex.*
Vitamin A palmitate (p. 2098·3).
Vitamin A supplement.

Palnox *Glenmark, India.*
Palonosetron (p. 1875·1).
Nausea and vomiting.

Paloc *Patar, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders; mouth ulcers.

Palocit *Triton, India.*
Citalopram hydrobromide (p. 411·1).
Depression; bipolar disorder; panic disorder.

Palomar E *Pal Midwest, USA.*
Vitamin E (p. 2119·1); boric acid (p. 2459·3); beeswax (p. 2170·2); wool fat (p. 2219·3); liquid paraffin (p. 2191·2); soft paraffin (p. 2211·3); starch (p. 2095·1); zinc oxide (p. 1729·1).
Skin disorders.

Palon *Unison, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; tremor.

Palonew *Sun, India.*
Palonosetron (p. 1875·1).
Nausea and vomiting.

Palovir *Pharmacore, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Paloxi *Helsinn, Israel.*
Palonosetron hydrochloride (p. 1875·1).
Nausea and vomiting associated with cancer chemotherapy.
Kalbe, Indon.
Palonosetron (p. 1875·1).
Nausea and vomiting induced by cancer chemotherapy.

Palpasin *Crisdy-Na, Philipp.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Palpitin-PP *PannonPharma, Hung.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Palron *Aamorb, India.*
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).

Pals *Glenwood, USA.*
Chlorophyllin copper complex (p. 2178·3).
Odour control in ostomy and incontinent patients.

Palser *Meditrina, Gr.*
Omeprazole (p. 1867·2).

Palther *Health Biotech, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Paltomiel *Knop, Chile.*
Adult syrup: Eucalyptus (p. 2501·1); avocado (p. 2451·2); aniseed (p. 2444·2); honey (p. 2072·1).
Respiratory-tract congestion.
Knop, Chile.
Infant syrup: Eucalyptus (p. 2501·1); avocado (p. 2451·2); honey (p. 2072·1).
Respiratory-tract congestion.

Paltomiel Plus *Knop, Chile.*
⊗Eucalyptus (p. 2501·1); avocado (p. 2451·2); honey (p. 2072·1); lobelia (p. 2323·2); echinacea (p. 2498·1).
Respiratory-tract disorders.

Paludrine *AstraZeneca, Austral.†; AstraZeneca, Austria†; AstraZeneca, Belg.; AstraZeneca, Fr.; AstraZeneca, Ger.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Irl.†; AstraZeneca, Ital.†; AstraZeneca, Neth.; AstraZeneca, Singapore; AstraZeneca, Swed.†; AstraZeneca, UK.*
Proguanil hydrochloride (p. 661·3).
Malaria.

Palukin *Kinder, Braz.†*
Quinine hydrochloride (p. 665·2) or quinine sulfate (p. 665·2).
Malaria.

Paluther *Sanofi-Aventis, Braz.; Abbott, India.*
Artemether (p. 648·1).
Malaria.

Palux
Note: this name may be used for preparations of different composition.
Taisho, Jpn.
Alprostadil (p. 2352·2).
Peripheral vascular disorders; skin ulcers; patent ductus arteriosus; mesenteric arterial portography.

Palzen *Reddy, India.*
Palonosetron (p. 1875·1).
Nausea and vomiting.

Palzic-D *Scoshia, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pam
Note: this name may be used for preparations of different composition.
East West, India.
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.
TV Pharm, Thai.
Diazepam (p. 1063·2).

Pam-A *Choongwae, Singapore.*
Pralidoxime chloride (p. 1571·1).
Organophosphate poisoning.

Pam-A Korea *Shree Ganesh, India.*
Pralidoxime (p. 1571·1).
Organophosphate poisoning.

Pamacid *Alphapharm, Austral.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pamagin C *Cachet, India.*
Syrup: Paracetamol (p. 115·1); cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2); phenylephrine (p. 1672·2); zinc gluconate (p. 2126·2).
Cachet, India.
Tablets: Paracetamol (p. 115·1); cetirizine hydrochloride (p. 619·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine (p. 1672·2); zinc gluconate (p. 2126·2).

Pamagin Plus *Cachet, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Pamax *Sanitas, Chile.*
Paroxetine (p. 440·3).
Depression; panic disorder; obsessive-compulsive disorder; anxiety; social phobia.

Pamba *Nycomed, Cz.; Nycomed, Ger.*
Aminomethylbenzoic acid (p. 1132·2).
Haemorrhage.

Pamclav *Pardys, India.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Pamdosa *Dosa, Arg.*
Pamidronate disodium (p. 1186·3).

Pamecil *Medochemie, Hong Kong; Medochemie, Malaysia.*
Ampicillin sodium (p. 218·2).
Bacterial infections.
Medochemie, Singapore.†
Ampicillin (p. 218·2).
Bacterial infections.

Pamedox *Medochemie, Hong Kong.†*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Pamela *Geno, India.*
Paracetamol (p. 115·1); DL-methionine (p. 1558·2).
Fever; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pamelor *Novartis, Braz.; Mallinckrodt, USA.*
Nortriptyline hydrochloride (p. 439·3).
Depression; panic disorder; pain; narcoleptic syndrome.

Pamergan
Note: this name may be used for preparations of different composition.
Cristalia, Braz.
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; insomnia; sedative; pain; premedication.

Pamergan P100
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
⊗Pethidine hydrochloride (p. 121·3); promethazine hydrochloride (p. 638·2).
Pain; premedication.

Pamerit *Alapis, Gr.*
Pamidronate disodium (p. 1186·3).
Paget's disease of bone; hypercalcaemia of malignancy.

Pamex *Deva, Turk.*
Pamidronate disodium (p. 1186·3).

Pamid *CTS, Israel.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Pamidem *Dem, Turk.*
Pamidronate disodium (p. 1186·3).

Pamidia *Farmacom, Pol.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; Paget's disease of bone.

Pamidran *Hospira, Port.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; bone metastases.

Pamidria *Cipla, India.*
Pamidronate disodium (p. 1186·3).
Bone metastases.

Pamidrin *Teva, Belg.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Pamidro *Medicon, India.*
Pamidronate disodium (p. 1186·3).

Pamidro-Cell *Stada, Austria.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolytic metastases of breast cancer; multiple myeloma.

Pamidro-cell *Cell Pharm, Ger.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; multiple myeloma; osteolytic metastases in breast cancer.

Pamidrom *Cristalia, Braz.*
Pamidronate disodium (p. 1186·3).

Pamidron *Hexal, Ger.†; Sandoz, Switz.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; multiple myeloma.

Pamidrone *Medicus, Gr.*
Pamidronate disodium (p. 1186·3).

Pamifect *Natco, India.*
Pemetrexed disodium (p. 844·3).
Non-small cell lung cancer; malignant pleural mesothelioma.

Pamifos *Kampar, Chile; Medac, Denm.; Medac, Fin.; Medac, Ger.; Medac, Hung.; Dabur, India; Vipharm, Pol.; Medac, Spain†; Medac, Swed.; Opopharma, Switz.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; Paget's disease of bone; osteolytic bone metastases; osteogenesis imperfecta; fibrous dysplasia of bone; metastatic bone disease.

Pamine *Kenwood, USA.*
Hyoscine methobromide (p. 1846·1).
Peptic ulcer (adjunct).

Pamine FQ Kit *Kenwood, USA.*
Tablets, hyoscine methobromide (p. 1846·1); capsules, *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); *Bifidobacterium; Streptococcus thermophilus* (p. 2596·3) (Flora-Q).

Paminject *EG, Fr.†*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy.

Pamipro *Medac, Neth.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; multiple myeloma.

Pamir *Helm, Port.†*
⊗Indapamide (p. 1409·2).
Hypertension.

Pamiray *Landsteiner, Mex.†; Hemat, Turk.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Pamired *Ferron, Indon.*
Pamidronic acid (p. 1186·3).
Osteolysis of malignancy; hypercalcaemia of malignancy.

Reddy, Braz.; Reddy, Malaysia; Reddy, Singapore; Reddy, Ukr.
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; Paget's disease of bone; osteolytic bone metastases.

Pamisol *Hospira, Austral.; Hospira, Hong Kong; Hospira, Malaysia; Mayne, Mex.; Hospira, NZ; Mayne, Pol.; Hospira, Singapore; Hospira, Thai.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; Paget's disease of bone; osteolysis of malignancy.

Pamitor *Torrex, Austria; Torrex Chiesi, Cz.; Torrex Chiesi, Hung.; Torrex Chiesi, Pol.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; Paget's disease of bone.

Pamizep *Shine, Philipp.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; epilepsy; alcohol withdrawal syndrome; skeletal muscle spasm.

Pamocil *Farma 1, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pamocombi *Pharma-Regist, Cz.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Pamol *Nycomed, Denm.; Leiras, Fin.; Finecure, India; Interbat, Indon.; Nycomed, Norw.; Johnson & Johnson, NZ; Nycomed, Swed.; Patar, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Pamol DCM *Finecure, India.*
Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).

Pamol F *Leiras, Fin.*
Paracetamol (p. 115·1).
Fever; pain.

Pamonova *Miklich, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Pamorelin *Ipsen, Austria; Ipsen, Denm.; Ipsen, Fin.; Ipsen, Ger.; Rowfarma, Mex.; Ipsen, Neth.; Ipsen, Norw.; Ipsen, Swed.; Debio, Switz.*
⊗Triptorelin embonate (p. 2311·1).
Prostatic cancer; endometriosis; female infertility; breast cancer; precocious puberty.

Pamoseo *LKM, Arg.*
Alendronate (p. 1171·3).
Osteoporosis.

Pamoxet *LKM, Arg.*
Paroxetine (p. 440·3).
Depression.

Pampar *Finadiet, Arg.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer.

Pampara *Siu Guan, Malaysia.*
Pralidoxime chloride (p. 1571·1).
Organophosphorus pesticide poisoning; anticholinesterase overdose.

Pampe *Azevedos, Port.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Pamprin *Chattem, Canad.; Chattem, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome; pain.

Pamprin Ibuprofen *Chattem, Canad.*
Ibuprofen (p. 68·2).
Pain; fever.

Pamserine *Samarth, India.*
Cycloserine (p. 280·2).
Tuberculosis.

Pamycon *Biotika, Cz.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial infections.

Pan
Note: this name may be used for preparations of different composition.
Alkem, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

PAN-2400 *Bio-Tech, USA.†*
Lipase (p. 2579·3); protease (p. 2598·1); amylase (p. 2579·3).
Pancreatic insufficiency.

Pan Amin G *Otsuka, Indon.*
Amino acids; sorbitol (p. 2092·1).
Parenteral nutrition.

Otsuka, Hong Kong.†
Amino acids.
Parenteral nutrition.

Pan C *Freeda, USA.*
Hesperidin (p. 2505·2); citrus bioflavonoids complex (p. 2505·2); vitamin C (p. 2110·3).
Capillary bleeding.

Pan Duo Xi Lai *Jiangxi, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Pan Ke Fu Lin *Fenghuang, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Pan Limpiador AL *Pierre Fabre Dermo-Cosmetique, Arg.*
Soap substitute.

Pan Nuo *Aida, China.*
Etimicin sulfate (p. 298·2).
Bacterial infections.

Pan De Xin *Lisheng, China.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Panabiotin *Panalab, Arg.*
Biotin (p. 2052·2).
Alopecia.

Panac *BMS, Mex.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Panac K *BMS, Mex.†*
Ampicillin potassium (p. 218·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Panace *Psyco Remedies, India.*
Tablets: Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Psyco Remedies, India.
Topical gel: Aceclofenac (p. 16·2); linseed oil (p. 2544·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Panacef *Valeas, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Panace-P *Psyco Remedies, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Panaco *Beacons, Singapore.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Panacod *Sanofi-Aventis, Fin.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Panact *DWD, India.*
Paracetamol (p. 115·1).
Pain; fever.

Panacta *Panpharma, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Panadal Pain Relief Patch *GSK, Hong Kong.†*
Glycol salicylate (p. 66·2); levomenthol (p. 2553·2); camphor (p. 2466·2); *dl*-alpha tocoferil acetate (p. 2119·2).
Musculoskeletal and joint pain.

Panadeine
Note: this name may be used for preparations of different composition.
GSK Consumer, Austral.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Hong Kong; GSK Consumer, Irl.; Sanofi-Aventis, Malaysia; GSK, NZ†; Sanofi-Aventis, Singapore.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever; cold and influenza symptoms.

Panadeine Plus *GSK Consumer, Austral.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain; fever.

Panado *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Panado Medsip *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Panado Plus *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).

Panado-Co *Pharmacon, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Panadol *GSK Consumer, Austral.; GSK Consumer, Belg.; GSK Consumer, Canad.; GSK, Chile; GSK, China; GSK Consumer, Cz.; GSK Consumer, Fin.; GSK Sante, Fr.; GSK, Gr.; GSK, Hong Kong; GSK Consumer, Hung.; Sterling, Indon.; GSK Consumer, Irl.; GSK, Israel; GSK Consumer, Ital.; GSK Consumer, Malaysia; GSK Consumer, Neth.; GSK Consumer, NZ; GSK Consumer, Pol.; GSK Consumer, Port.; GSK Consumer, Rus.; GSK, Singapore; GSK Consumer, Spain; GSK Consumer, Switz.; GSK, Thai.; GSK, Turk.; GSK Consumer, UK; GSK Consumer, Ukr.; GSK Consumer, USA.*
Paracetamol (p. 115·1).
Fever; pain; cold and influenza symptoms.

Panadol Antigrippine *GSK Consumer, Switz.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Panadol C *GSK Consumer, Switz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Panadol Codeine *GSK Consumer, Belg.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Panadol Cold *GSK Consumer, Malaysia.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; nasal congestion.

Panadol Cold & Cough *GSK, Hong Kong.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; cough.

Panadol Cold Flu *GSK Consumer, Malaysia.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; nasal congestion; cold symptoms.

Panadol Cold & Flu
Note: this name may be used for preparations of different composition.
GSK Consumer, Austral.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

GSK Consumer, Irl.
Sachets: Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; pain; fever; musculoskeletal disorders.

GSK, Gr.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

GSK, Hong Kong.
Paracetamol (p. 115·1); vitamin C (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); terpin hydrate (p. 1678·2).
Cold and influenza symptoms.

Panadol Cold & Flu Day *GSK, Hong Kong.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); terpin hydrate (p. 1678·2).
Cough; cold symptoms.

Panadol Cold & Flu Extra *GSK, Hong Kong.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); noscapine (p. 1670·3); caffeine (p. 1203·3); ascorbic acid (p. 2110·3); terpin hydrate (p. 1678·2).
Cough; cold symptoms.

Panadol Cold & Flu Hot Remedy *GSK, Hong Kong; GSK, Singapore.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Panadol Cold & Flu Nasal *GSK, Hong Kong.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Panadol Cold & Flu Night *GSK, Hong Kong.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Panadol Cold & Flu Plus *GSK, Hong Kong.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Panadol Cold & Flu Relief *GSK Consumer, Irl.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Cold and influenza symptoms; pain; fever.

Panadol Cold & Flu Relief PE *GSK Consumer, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Panadol for Cold Relief *GSK, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Panadol For Cold Relief Extra *GSK, Singapore.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Panadol Comp *GSK Consumer, Fin.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Panadol Compuesto *GSK, Chile.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Panadol For Cough and Cold *GSK, Singapore.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine (p. 1676·1).
Cold and influenza symptoms; cough.

Panadol Extend *GSK Consumer, Switz.*
Paracetamol (p. 115·1).
Pain; fever.

Panadol Extra *GSK Consumer, Austral.; GSK Consumer, Cz.; GSK, Gr.; GSK, Hong Kong; GSK Consumer, Hung.; Sterling, Indon.; GSK Consumer, Irl.; GSK Consumer, Pol.; GSK Consumer, Port.; GSK Consumer, Rus.; GSK, Singapore; GSK Consumer, Switz.; GSK, Turk.; GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain; cold and influenza symptoms.

Panadol Fever & Congestion *GSK Consumer, Irl.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Panadol Flu Strength Day & Night PE *GSK Consumer, Austral.*
Day caplets, paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); night caplets, paracetamol; phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Panadol Flumax *GSK, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Panadol Head Cold *GSK Consumer, Irl.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; pain; fever.

Panadol Hot *GSK Consumer, Fin.*
Paracetamol (p. 115·1); menthol (p. 2553·2).
Fever; pain; cold and influenza symptoms.

Panadol Max Strength Cold & Flu *GSK Consumer, Irl.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Panadol Menstrual
Note: this name may be used for preparations of different composition.
GSK Consumer, Malaysia; GSK, Singapore.
Paracetamol (p. 115·1); pamabrom (p. 1464·1).
Premenstrual and menstrual pain and discomfort; menstrual disorders.

GSK, Hong Kong.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Dysmenorrhoea.

Panadol Night *GSK Consumer, Irl.; GSK, NZ; GSK Consumer, UK.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms; pain; insomnia; fever.

Panadol Pain Relief *GSK, Hong Kong.*
Glycol salicylate (p. 66·2); levomenthol (p. 2553·2); camphor (p. 2466·2); *dl*-alpha tocoferil acetate (p. 2119·2).
Musculoskeletal and joint pain.

Panadol Plus *GSK Consumer, Belg.; GSK, Chile; GSK Consumer, Neth.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Panadol Plus Grip *GSK Consumer, Cz.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Panadol Sinus *GSK Consumer, Austral.; GSK, Hong Kong†; GSK Consumer, Port.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinus congestion; pain; cold and influenza symptoms.

Panadol Sinus Day & Night *GSK Consumer, Austral.*
⊗Day caplets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night caplets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Sinus congestion; pain; fever.

Panadol Sinus Max *GSK, Singapore.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinusitis.

Panadol Sinus Relief PE *GSK Consumer, Austral.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Headache; sinus pain; nasal congestion.

Panadol Ultra
Note: this name may be used for preparations of different composition.
GSK Consumer, Cz.; GSK Consumer, Hung.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain; fever.

GSK, Hong Kong; GSK Consumer, UK.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol.
Fever; pain.

Panadol Vitamin C *GSK, Gr.*
Paracetamol (p. 115·1); vitamin C (p. 2110·3).
Pain; fever.

Panadox *Shijiazhuang, Philipp.*
Oxacillin sodium (p. 336·2).
Staphylococcal infections.

Panafcort *Aspen, Austral.; Adcock Ingram, S.Afr.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Panafcortelone *Aspen, Austral.; Aspen, Hong Kong.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Panafen
Note: this name may be used for preparations of different composition.
GSK Consumer, Cz.; GSK, NZ.
Ibuprofen (p. 68·2).
Pain; fever; inflammation; musculoskeletal and joint disorders.

Leontik, Gr.
Cinoxacin (p. 261·1).

Panafen Plus *GSK Consumer, Austral.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Fever; inflammation; pain.

Panafil *Healthpoint, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3); chlorophyllin copper complex (p. 2178·3) or chlorophyllin copper complex sodium (p. 2178·3).
Wounds; ulcers; burns.

Panafil-White *Rystan, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3).
Wounds; ulcers; burns.

Panaflex
Note: this name may be used for preparations of different composition.
GSK Consumer, Malaysia.
Glycol salicylate (p. 66·2); menthol (p. 2553·2); camphor (p. 2466·2); tocoferil acetate (p. 2119·2).
Muscle and joint pain.

GSK, Hong Kong.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint pain.

Panaflex Extra *GSK Consumer, Malaysia; GSK, Singapore.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Panaflu Plus *Malaysia Chemist, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Panafox *Panpharma, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Panagesic *Chemopharma, Chile.*
Paracetamol (p. 115·1).
Fever; pain.

Panagesic Con Cafeina *Chemopharma, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Panagesic Periodo Menstrual *Chemopharma, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Panagram Max *GSK Consumer, Irl.*
Paracetamol (p. 115·1).
Pain; fever.

Panalba *Help, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Panaldine *Sanofi-Aventis, Jpn.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Panalene *Panalab, Arg.*
Adapalene (p. 1692·1).
Acne.

Panalene Duo *Panalab, Arg.*
Adapalene (p. 1692·1); benzoyl peroxide (p. 1696·1).
Acne.

Panaleve *Pinewood, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Panalgan *Staufen, Ger.*
Acid. sulfuricum (p. 2624·2); viscum album (p. 2560·2).
Homoeopathic preparation.

Panalgesic *Sanofi-Aventis, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain with tension.

Panalgesic Gold *ECR, USA.*
Liniment: Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Panalgine *Atabay, Turk.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Fever; pain.

Panalgorin *PannonPharma, Hung.*
Dipyrone (p. 53·3).
Fever; pain.

Pañaline *Darier, Mex.*
Topical powder: Maize starch (p. 2095·1).
Nappy rash.

Darier, Mex.
Cream: Vitamin E (p. 2119·1); zinc oxide (p. 1729·1).
Nappy rash.

Panam *Sandoz, Denm.†*
Paracetamol (p. 115·1).
Fever; pain.

Panama *Mint, India.*
Injection: Diclofenac potassium (p. 48·3).
Pain.

Mint, India.
Ointment: Diclofenac (p. 48·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Panama Plus *Mint, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Panama-D *Mint, India.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Panama-SP *Mint, India.*
⊗Aceclofenac (p. 16·2); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Panamax
Note: this name may be used for preparations of different composition.
GSK, Singapore.
Diclofenac sodium (p. 48·3).
Formerly contained ibuprofen.
Musculoskeletal and joint pain.

Sanofi-Aventis, Austral.
Paracetamol (p. 115·1).
Pain; fever.

Panamax Co *Sanofi-Aventis, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Panamic *TO-Chemicals, Thai.†*
Mefenamic acid (p. 85·3).
Pain.

Pan-Amin *LCH, Hong Kong†; Thai Otsuka, Thai.*
Amino acids.
Parenteral nutrition.

Panamir *DMG, Ital.*
Simeticone (p. 1886·2); xanthan gum (p. 2220·1).

Panamol *Beacons, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Panamor *Aspen, S.Afr.*
Diclofenac sodium (p. 48·3) or diclofenac epolamine (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Panangin *Gedeon Richter, China; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Hypokalaemia; heart failure; myocardial infarction; arrhythmias; potassium and magnesium deficiency.

Gedeon Richter, Ukr.
Potassium asparaginate; magnesium asparaginate.
Heart failure; myocardial infarction; arrhythmias; hypokalaemia; hypomagnesaemia.

Panaprost *Panalab, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Panaron *Khandelwal, India.*
Amiodarone hydrochloride (p. 1300·1).
Ventricular arrhythmias.

Panasol-S *Seatrace, USA.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Panasorbe *Sanofi-Aventis, Port.*
Paracetamol (p. 115·1).
Pain; fever.

Panastat *Panalab, Arg.*
Itraconazole (p. 583·3).
Fungal infections.

Pan-Asténico R *Vitoria, Port.*
Arginine aspartate (p. 2049·1).

Panataxel *Bioprofarma, Arg.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Panatrix *Boniscontro & Gazzone, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Panatus *KRKA, Rus.*
Butamirate citrate (p. 1657·3).
Cough.

Panatuss DX *Seyer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); dexchlorpheniramine maleate (p. 621·1).
Upper respiratory-tract disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Panatuss DXP *Seyer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); dexbrompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Panau Salap *Sunward, Singapore.*
Salicylic acid (p. 1719·1).
Keratinisation disorders; acne.

Panavir *Moschimfarm, Ukr.*
Solanum tuberosum.
Viral infections.

Panaxan *Phytofarm Kleka, Pol.†*
Ginseng (p. 2513·3).
Tonic.

Panaxim *Panpharma, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Panazeclox *Pisa, Mex.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Panazole *Shijiazhuang, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Panazyme *Bioglan, Austral.†*
⊗Pancreatin (p. 2579·3).
Digestive enzyme supplement.

Pan-Benzathine G *Panpharma, Hong Kong.*
Benzathine benzylpenicillin (p. 227·2).

Panbesy *Eurodrug, Hong Kong; Eurodrug, Singapore; Eurodrug, Thai.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Panbloc *Tablets, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panbrabene *Ratiopharm, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panbro *Synco, Hong Kong†; Synco, Singapore.*
Propantheline bromide (p. 1880·1).
Gastrointestinal spasm; adjunct in peptic ulcer; enuresis; hyperhidrosis; urinary incontinence.

Pancas *Casca, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pancas-D *Casca, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pancebrin *Lilly, Thai.*
Vitamins.

Pancef
Note: this name may be used for preparations of different composition.
Aglowmed, India.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.
Alkaloid, Rus.
Cefixime (p. 240·3).
Bacterial infections.

Pan-Cefazolin *Pharmalogic, Israel.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Pancef-O *Aglowmed, India.*
Cefixime (p. 240·3).
Bacterial infections.

Pancef-O LB *Aglowmed, India.*
Cefixime (p. 240·3); *Lactobacillus sporogenes* (p. 2596·3).

Pancef-S *Aglowmed, India.*
Ceftriaxone (p. 253·3) or ceftriaxone sodium (p. 253·3); sulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Pan-Ceftriaxone *Pharmalogic, Israel.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Pan-Cefuroxime *Pharmalogic, Israel.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Pancet *Panjon, India.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Panchol *GL Pharma, Austria.*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Pancillin *Sandoz, Denm.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Panciol *Rosunifarm, Rus.*
Reindeer antler (pantocrinum).
Asthenia.

Panclasa *Atlantis, Mex.*
Injection; capsules: Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).
Smooth muscle spasm.
Atlantis, Mex.
Oral solution: Phloroglucinol (p. 2588·2).
Infantile colic and dyspepsia.

Panclasa Fem *Atlantis, Mex.*
Phloroglucinol (p. 2588·2).
Premenstrual syndrome; dysmenorrhoea.

Panclav *Hemofarm, Ukr.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Panclo B12 *Denver, Arg.*
⊗Betamethasone (p. 1623·2); diclofenac sodium (p. 48·3); hydroxocobalamin (p. 2107·3).

Pancloflex *Denver, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).

Panclogesic *Denver, Arg.*
Paracetamol (p. 115·1); diclofenac potassium (p. 48·3).
Inflammation; pain.

Panclor *Elpen (Ελπεν), Gr.; Polfa Grodzisk, Pol.†*
Cefaclor (p. 232·3).
Bacterial infections.

Pancof *Pan American, USA.†*
⊗Dihydrocodeine tartrate (p. 52·3); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Pancof PD *Pan American, USA.†*
Dihydrocodeine tartrate (p. 52·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pancof XP *Pan American, USA.†*
⊗Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Pancof-EXP *Pan American, USA.†*
⊗Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2); pseudoephedrine (p. 1676·1).
Cough.

Pancof-HC *Pan American, USA.†*
⊗Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Pancof-XL *Pan American, USA.†*
⊗Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Panconium *Khandelwal, India.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Pancoran *Novartis, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Pancre Zyme *Kripps, Canad.†*
Amylase (p. 2442·1); lipase (p. 2579·3); protease (p. 2579·3).

Pancrearell *Sanorell, Ger.*
Eichhornia crassipes.
Homoeopathic preparation.

Pancrease *Orifarm, Denm.; IFET (ΙΦΕΤ), Gr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Janssen-Cilag, Austral.†; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Invest Impex, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.†; Janssen-Cilag, Norw.†; Janssen-Cilag, NZ; Janssen-Cilag, Swed.†; Ortho McNeil, USA.†
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Pancrease HL *Janssen-Cilag, Neth.; Janssen-Cilag, UK.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Pancreas-Gastreu N *Reckeweg, Ger.*
Colocynthis (p. 1833·3); lycopodium (p. 2546·3); momordica balsamina; phosphorus (p. 2589·2).
Homoeopathic preparation.

Pancreasim *Tekhnolog, Ukr.†*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Pancreatein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Pancreaze *Janssen, USA.*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Pancrecura *HLB, Arg.*
⊗Pancreatin (p. 2579·3).
Pancreatin insufficiency.

Pancrélase *DB, Fr.*
Fungal cellulase (p. 2473·1).
Dyspepsia.

Pancreolan *Zentiva, Cz.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Pancrex *Mipharm, Ital.; Paines & Byrne, NZ; Paines & Byrne, UK.*
⊗Pancreatin (p. 2579·3).
Malabsorption syndromes; cystic fibrosis; pancreatic insufficiency.

Pancrin *Abbott, Austria.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Pancrit *Andromaco, Chile.*
Cetylpyridinium chloride (p. 1743·1); allantoin (p. 1693·1).
Mouth and throat disorders.

Pancuron *Scott-Cassara, Arg.; Cristalia, Braz.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Pancurox *Hospira, Port.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Pancutan *Purissimus, Arg.*
Halibut oil (p. 2071·3); gentamicin embonate (p. 304·2).
Burns; skin infections; ulcers; wounds.

Pancutan Base *Purissimus, Arg.†*
Halibut oil (p. 2071·3).
Skin disorders.

Pan-D *Alkem, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pandat *Datla, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pandat-D *Datla, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pandeflu *Microgen, Rus.*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Pandel *Silesia, Chile; Galderma, Ger.†; Taisho, Jpn; Medinfar, Port.; CollaGenex, USA.*
⊗Hydrocortisone buteprate (p. 1640·1).
Skin disorders.

Pandemrix *GSK, Belg.; GSK, Cz.; GSK, Denm.†; GSK, Fr.†; GSK, Irl.; GSK, Israel; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Swed.; GSK, UK.†*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Panderm
Note: this name may be used for preparations of different composition.
Julphar, UAE.
⊗Nystatin (p. 590·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.
SJA, Gr.
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Pandermil *Edol, Port.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Pandev *Deva, Turk.*
Pantoprazole sodium (p. 1875·3).

Pandiff *Abbott, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pandigal *DAST, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Pandom *Osper, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pandon *Osper, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pandostal *Galpha, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pandosun *Sunrise, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pandosun-D *Sunrise, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pandox *Aglowmed, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Pandrat *LKM, Arg.*
Pamidronate disodium (p. 1186·3).
Osteoporosis.

Pandry *Dr Kumars, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pandry D *Dr Kumars, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pane Free *Vencare, India.*
Capsicum (p. 2469·3); eucalyptus oil (p. 2501·2); mentha arvensis; sweet birch oil (p. 92·1).

Panectyl *Erfa, Canad.*
Alimemazine tartrate (p. 615·1).
Pruritus; cough; dyspnoea.

Pan-Enteral *Otsuka, Indon.; Thai Otsuka, Thai.*
Preparation for enteral nutrition.

Panenza *Sanofi Pasteur, Fr.†*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Panex
Note: this name may be used for preparations of different composition.
Brown & Burk, Philipp.
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual syndrome.
Micro, India.
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Panfaco *Zekides, Gr.*
Acetylcysteine (p. 1652·2).

Panfast *Sanat, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panfast-D *Sanat, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panfil G *Pan American, USA.*
Diprophylline (p. 1207·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Panflu 1 *Sinovac, China.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Panfor *Mega Lifesciences, Philipp.; Mega Lifesciences, Ukr.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Pan-Fort Procaine *Universal, Hong Kong.†*
Benzylpenicillin (p. 228·1); procaine benzylpenicillin (p. 344·2).

Panfugan *Nycomed, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Pan-Fungex *Sanofi-Aventis, Port.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Panfungol *Esteve, Spain.*
Ketoconazole (p. 585·3).
Fungal infections.

Panfurex *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong.*
Nifuroxazide (p. 331·3).
Infectious diarrhoea.

Pangamil *Biotech, Venez.*
Tinidazole (p. 949·2).
Protozoal infections.

Pangastren *Laboratorios Chile, Chile.*
Metoclopramide (p. 1862·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastro-oesophageal reflux.

Pangavit B *Church, Mex.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neuritis; neuropathies; neuralgias; vitamin B deficiency.

Pangavit Hypak *Church, Mex.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neuralgias; neuritis; neuropathy; vitamin B deficiency.

Pangavit Pediatrico *Church, Mex.*
Cyproheptadine hydrochloride (p. 624·1); cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); riboflavin sodium phosphate (p. 2104·3).
Appetite loss; megaloblastic anaemia; vitamin deficiency.

Pangel *Pannoc, Belg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Pangest
Note: this name may be used for preparations of different composition.
Beta, Arg.
Pantoprazole sodium (p. 1875·3).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.
Farmasa, Braz.
Bromopride (p. 1824·2).
Gastro-oesophageal reflux; gastroparesis.

Pangestyme *Ethex, USA.†*
Lipase (p. 2579·3); protease (p. 2598·1); amylase (p. 2579·3).
Pancreatic insufficiency.

Pangon *LBS, Thai.*
⊗Pentazocine lactate (p. 120·3).
Pain.

PanGraf *Panacea, India.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Pangramin *ALK, Cz.; ALK, Hung.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Pangrol *Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.; Berlin-Chemie, Pol.; Menarini, Pol.; Berlin-Chemie, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Pangy *Indu, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pangy-DM *Indu, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panhematin *Invida, Austral.; Ovation, USA.*
Haematin (p. 1555·3).
Porphyria.

Panik *Sunrise, India.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Panim *Panjon, India.*
Nimesulide (p. 101·3).
Pain; peri-articular disorders.

Panimun Bioral *Panacea, India; Panacea, Rus.; Panacea, Thai.†*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; rheumatoid arthritis; psoriasis; eczema; nephrotic syndrome; aplastic anaemia.

Panimycin *Meiji, Jpn.*
Dibekacin sulfate (p. 286·1).
Bacterial infections.

Panion *Kowa, Jpn.*
Adenosine triphosphate, disodium salt (p. 2430·3); vitamin B substances (p. 2102·3).

Panitol
Note: this name may be used for preparations of different composition.
Cryopharma, Mex.
Propanidid (p. 1909·3).
General anaesthesia.
Pharmaland, Thai.†
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Panitone *Wesley, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Paniverin *Sanofi-Aventis, Hung.†*
Nicotinic acid (p. 2083·1); drotaverine hydrochloride (p. 2497·3).
Atherosclerosis; cerebrovascular disorders; migraine.

Panjecxime *Bharat, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Panjecxone *Bharat, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Panka *Microsules, Arg.*
Abacavir (p. 962·3).
HIV infection.

Pankai *Sinkhai, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pankai-D *Sinkhai, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panklav *Hemofarm, Rus.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Pankreaplex mono *Schaper & Brummer, Ger.*
Javanese turmeric (p. 2636·2).
Dyspepsia.

Pankrease *Janssen-Cilag, S.Afr.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic disorders.

Pankreatan *Nordix, Ger.; Nordmark, Ger.*
⊗Pancreatin (p. 2579·3).
Digestive system disorders.

Pankreaticum *Hevert, Ger.*
Injection: oral drops: Eichhornia; okoubaka; quassia (p. 2601·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Pankreoflat *Raffo, Arg.; Pharmaselect, Austria; Apsen, Braz.; Solvay, Ger.†; Pharmaselect, Hung.; Solvay, India; Solvay, Indon.; Solvay, Israel†; Nycomed, Mex.; Solvay, Philipp.; Vitoria, Port.; Solvay, Rus.; Solvay, S.Afr.; Faes, Spain; Frik, Turk.*
⊗Pancreatin (p. 2579·3); dimeticone (p. 1886·2).
Digestive disorders; aerophagia; meteorism; flatulence; excess gastrointestinal gas; pancreatic insufficiency; preparation for gastrointestinal examination.

Pankreon *Zuoz, Venez.*
⊗Pancreatin (p. 2579·3).
Digestive disorders.

Pankreon for Children *Solvay, Indon.*
⊗Pancreatin (p. 2579·3); vitamin A (p. 2098·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Gastrointestinal disorders.

Pankreon Comp *Solvay, Indon.; Frik, Turk.*
⊗Pancreatin (p. 2579·3); ox bile extract (p. 2457·2).
Pancreatic insufficiency; digestive disorders; pancreatic disorders.

Pankreon Compositum *Infinity, Venez.*
Pancreatic enzymes (p. 2579·3); bile extract (p. 2457·2).
Digestive disorders.

Pankreon Total *Raffo, Arg.*
⊗Pancreatin (p. 2579·3); papain (p. 2582·3); cellulase (p. 2473·1); dehydrocholic acid (p. 2492·1); simeticone (p. 1886·2); metoclopramide hydrochloride (p. 1862·2).
Digestive disorders.

Pankreosil *Zuoz, Venez.*
⊗Pancreatin (p. 2579·3); dimeticone (p. 1886·2).
Digestive disorders; flatulence.

Pankreozym *Raffo, Arg.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Pankrodigest *Desra, Turk.†*
⊗Pancreatin (p. 2579·3); cholic acid (p. 2457·2).

Panlactam *Darnitsa, Ukr.*
Meropenem (p. 321·3).
Bacterial infections.

Panlee-D *Indkus, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panlem *Teva, Mex.†*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Panlid *Funke, Cz.†*
Lidocaine hydrochloride (p. 1988·2); allantoin (p. 1693·1); dexpanthenol (p. 2582·2); cetylpyridinium chloride (p. 1743·1).
Burns; wounds.

Panlipase *Sun, India.*
Amylase; lipase; protease (p. 2579·3).

Panlipol *Mead Johnson, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Panlisu *Huadong, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Panloc *Glenmark, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panlor *Pan American, USA.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3); dihydrocodeine tartrate (p. 52·3).
Pain.

Panmeilu *Aosaikang, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; acid aspiration.

Panmicid *Merck, Mex.*
Pantoprazole (p. 1875·3).

Panmicol *Purissimus, Arg.*
Clotrimazole (p. 576·2).
Fungal skin, scalp, and mucous membrane infections.

Panmikin *Eczacibasi, Philipp.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Panmint *USP, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panmint-D *USP, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panmist LA *Pan American, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Panmist JR *Pan American, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

PanMist-DM *Pan American, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Panmist-S *Pan American, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Panmyk *Bros, Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Skin disorders with fungal infection.

Pannaz *Pan American, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Formerly contained phenylpropanolamine, chlorphenamine, and hyoscine.
Upper respiratory-tract disorders.

Pannocort *Pannoc, Belg.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Pannogel *Sinclair, Fr.*
Benzoyl peroxide (p. 1696·1).
Acne.

Pannox *Panpharma, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Pano *Medial, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panocaps *Breckenridge, USA.†*
Pancreatic enzymes (porcine) (p. 2579·3).
Pancreatic deficiency.

Panocid *Indkus, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panocod *Sanofi-Aventis, Swed.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Pan-OD *Burgeon, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pano-D *Medial, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panodil *GSK Consumer, Denm.; GSK, Norw.; GSK Consumer, Swed.*
Paracetamol (p. 115·1).
Pain; fever.

Panofen
Note: this name may be used for preparations of different composition.
Liferpal, Mex.
Paracetamol (p. 115·1).
Fever; pain.
Pharmathen, Denm.
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.
VS, Thai.
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Inflammation; pain.

Panoff *Hoe, Malaysia; Hoe, Singapore.*
⊗Sulfur (p. 1721·1); glycerol (p. 2517·2).
Soap substitute.

Panogastin *Jelfa, Cz.; Jelfa, Hung.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.
Jelfa, Pol.
Pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panopaz *Aglowmed, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panopaz-D *Aglowmed, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pan-Ophtal *Winzer, Ger.*
Dexpanthenol (p. 2582·2).
Eye disorders.

Panoptic *Bausch & Lomb, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); diphenhydramine hydrochloride (p. 626·2).
Eye disorders.

Panoptic Lagrimas *Bausch & Lomb, Arg.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Panoptic NF *Bausch & Lomb, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Panor *Trumac, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Panoral *Eberth, Ger.*
Cefaclor (p. 232·3).
Bacterial infections.

Panor-D *Trumac, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panore *MR Pharma, Neth.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Panoric *Haledew, India.*
Dill oil (p. 2493·2); fennel oil (p. 2503·3); simeticone (p. 1886·2).

Panorox *Ultramark, India.*
Piroxicam (p. 125·3).

Panos *Daiichi Sankyo, Fr.†*
Tetrazepam (p. 1110·1).
Skeletal muscle spasm.

Panotil *Zambon, Braz.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); fludrocortisone acetate (p. 1634·3); lidocaine hydrochloride (p. 1988·2).
Ear disorders.

Panotile *Zambon, Belg.; Zambon, Fr.; Zambon, Neth.; Zambon, Spain†; Zambon, Switz.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); fludrocortisone acetate (p. 1634·3); lidocaine hydrochloride (p. 1988·2).
Ear disorders; otitis externa; infected ear disorders.

Panotile cipro *Pierre Fabre, Ger.*
Ciprofloxacin hydrochloride (p. 261·2).
Otitis externa; otitis media.

Panoto-S *Rhein, Mex.*
Ivy (p. 2536·2).
Cold symptoms.

Panotos *Ivax, Arg.*
Dextromethorphan hydrobromide (p. 1660·1); bromhexine hydrochloride (p. 1656·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Respiratory-tract disorders.

Panotos NF *Ivax, Arg.*
⊗Bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1).
Respiratory-tract disorders.

Panoxen *Oxford Laboratories, Rus.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Panoxi *Bausch & Lomb, Arg.*
⊗Oxymetazoline hydrochloride (p. 1671·3); sodium hyaluronate (p. 2526·2).
Eye disorders.

Panoxilin *Siam Medicare, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

PanOxyl *Stiefel, Austral.; Stiefel, Braz.; Stiefel, Canad.; GSK, Fr.; Stiefel, Ger.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Israel; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Norw.†; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Port.; GSK, S. Afr.; Stiefel, Singapore; Stiefel, Spain†; Stiefel, Thai.; Stiefel, UK; GSK, USA.*
Benzoyl peroxide (p. 1696·1).
Acne; skin disinfection.

PanOxyl Clear Acne *Stiefel, Canad.†*
Salicylic acid (p. 1719·1); triclosan (p. 1773·2).
Acne.

Panpac *Acto, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panpac-D *Acto, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia.

Panpari *Elisa, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panpari-D *Elisa, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panpiryna *Cyntfarm, Pol.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Panplex 2-Phase *Integrative, USA.*
⊗Betaine hydrochloride (p. 2456·1); pepsin (p. 2586·1); glutamic acid hydrochloride (p. 2070·3); pancreatin (p. 2579·3); ox bile extract (p. 2457·2).
Digestive disorders.

Panpra *Shinto, India; Stalwart, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panprabene *Ratiopharm, Austria.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panpra-D *Stalwart, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panprax *Drossapharm, Switz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Panprazox *Polpharma, Pol.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panpro *Biosync, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panpro-D *Biosync, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal; dyspepsia.

Panproton *Cantabria, Spain.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panprozole *Chandra Bhagat, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panpur *Axcan, Ger.*
⊗Porcine pancreatin (p. 2579·3).
Pancreatic insufficiency.

Panpure *Emcure, India.*
S-Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panquil *Pfizer Consumer, Austral.†*
Promethazine hydrochloride (p. 638·2); paracetamol (p. 115·1).
Fever; pain.

Panrazol *Actavis, Denm.; Actavis, Hong Kong; Actavis, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panref *Bioforma, Turk.*
Pantoprazole (p. 1875·3).

Panretin *Bioprofarma, Arg.; Ligand, Austria; Eisai, Cz.; Cephalon, Fr.; Cephalon, Ger.; Eisai, Gr.; Eisai, Irl.; Ligand, Neth.; Eisai, Pol.; Eisai, Port.; Eisai, Spain; Eisai, USA.*
Alitretinoin (p. 738·2).
Skin lesions in Kaposi's sarcoma.

Panrole-D *Brawn, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pansa *Zuventus, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pansa-D *Zuventus, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pansafe *UniOrange, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pansafe-D *UniOrange, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pansaul *Auspi, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pansaul-D *Auspi, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panscol *Baker Cummins, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Pansebase *Sofex, Port.*
Lecithin (p. 2542·2); lactic acid (p. 2539·1).
Seborrhoeic dermatitis.

Pansebase Composto *Sofex, Port.*
Lecithin (p. 2542·2); lactic acid (p. 2539·1); ichthammol (p. 1705·3).
Psoriasis; seborrhoeic dermatitis; pruritus.

Pansement Mag *Pharmamag, Canad.†*
Magnesium sulfate (p. 1787·3).

Panseptil *Gedis, Ital.†*
⊗Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1); alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Surface disinfection.

Pansi-SD *Sidhbali, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panso *Soho, Indon.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; gastric hyperacidity; Zollinger-Ellison syndrome.

Pansoft *Mint, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pansoft-D *Mint, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pansoral *Rovafarm, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Rus.; Pierre Fabre, Switz.†*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Mouth disorders; inflammation and ulcers of the mouth.

Pansoral Premières Dents *Pierre Fabre, Fr.*
Althaea (p. 2438·3); chamomile (p. 2474·1).
Teething pain.

Pansoral Primeros Dientes *Rovafarm, Arg.*
Chamomile (p. 2474·1); althaea (p. 2438·3); saffron (p. 2208·2).
Teething pain.

Pansoral Teething *Pierre Fabre, Rus.*
Chamomile (p. 2474·1); althaea (p. 2438·3); saffron (p. 2208·2).
Teething pain.

Pierre Fabre, Singapore.†
Chamomile (p. 2474·1); althaea (p. 2438·3).
Teething pain.

Pansporin *Takeda, Jpn.*
Cefotiam hydrochloride (p. 246·1) or cefotiam hexetil hydrochloride (p. 246·1).
Mepivacaine hydrochloride (p. 1992·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Panstal N *Cipla, India.*
⊗Pancreatin (p. 2579·3).
Digestive disorders.

Panstop *Armoxindo, Indon.*
Dipyrone (p. 53·3).
Pain.

Panstrike *Maxo, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panstrike-D *Maxo, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pansulfox *Stiefel, Chile.*
Benzoyl peroxide (p. 1696·1).
Acne.

Pansulide RD *Rusan, India.*
Nimesulide (p. 101·3).
Pain.

Pansure *David, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantab *Reliance, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantabit *Cubit, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantabit-D *Cubit, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantabol-D *Meridian, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantacid
Note: this name may be used for preparations of different composition.
Aramis, Hung.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantacin *Cinerea, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantact *Active, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantact-D *Active, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantadal *Dallas, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantadal-D *Dallas, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantadolor *Labialfarma, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Pantadom *Mankind, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantaflux *Pantafarm, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Pantagen *Picco, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Pantagon *Ordain, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantagon-DM *Ordain, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantakind *Mankind, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantaltius *Altius, Arg.†*
Pantoprazole (p. 1875·3).

Pantamax *Pidek, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantamep *Alna, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantamep-D *Alna, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantames *Pantafarm, Ital.*
Nimesulide (p. 101·3).
Pain.

Pantamin MV *Marching, Hong Kong.†*
Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement; tonic.

Pantanib *Acekinetic, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantanib-D *Acekinetic, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantanib-IT *Acekinetic, India.*
Itopride; pantoprazole (p. 1875·3).

Pantapil-D *Psychotropics, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantasun *Sun, Braz.*
Pantoprazole (p. 1875·3).

Pantaxin *Panpharma, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Pantaz *Medley, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantazol *Synergen, Philipp.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

United Biotech, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantazone *Picco, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

Pantebiol *Ulagay, Turk.*
Dexpanthenol (p. 2582·2).

Pantec
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Fluconazole (p. 578·2).
Fungal infections.

Concept, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantec Plus *Concept, India.*
Mosapride (p. 1865·2); pantoprazole (p. 1875·3).

Pantec-D *Concept, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantecta *Nycomed, Cz.; Nycomed, Irl.; Nycomed, Ital.; Nycomed, Neth.; Nycomed, Pol.; Nycomed, Port.; Nycomed, Spain.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantelmin *Janssen-Cilag, Austria; Janssen-Cilag, Braz.; Johnson & Johnson, Port.*
Mebendazole (p. 158·3).
Worm infections.

Pantene Anti-Dandruff *Procter & Gamble, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Pantenol *Ratiopharm, Rus.; Saba, Turk.†*
Dexpanthenol (p. 2582·2).
Wounds; burns; ulcers; skin disorders.

Pantenol Plus *Saba, Turk.*
Dexpanthenol (p. 2582·2); chlorhexidine hydrochloride (p. 1743·3).
Infected skin disorders.

Pantest *Ester, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantest-D *Ester, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panteston *Organon, Fin.; Schering-Plough, NZ.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism; male infertility; osteoporosis in men; testosterone deficiency in men.

Pantestone
Note: this name may be used for preparations of different composition.
Filaxis, Arg.
⊗Anastrozole (p. 742·1).
Malignant neoplasms.

MSD-Chibret, Fr.
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Pantetina *Pharmafar, Ital.*
Pantethine (p. 1464·2).
Hypertriglyceridaemia.

Pantevit *EMS, Braz.*
Pantothenic acid (p. 2085·2); vitamin B_6 (p. 2105·3); resorcinol (p. 1718·3).
Alopecia.

Panthec *Sanovel, Turk.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Panthecream *Phytopharm, Ukr.*
Dexpanthenol (p. 2582·2).
Skin irritation; skin damage.

Panthenol *Chauvin Ankerpharm, Cz.; Quintesence, Cz.; Chauvin ankerpharm, Ger.; Mibe, Ger.; Ratiopharm, Ger.; Riemser, Ger.; Chauvin, Hung.; Jenapharm, Hung.; Chauvin, Rus.; Farmstandart, Rus.; Mikrofarm, Rus.; Bausch & Lomb, Ukr.*
Dexpanthenol (p. 2582·2).
Skin and mucous membrane injury; postoperative gastrointestinal atony; respiratory-tract disorders; paraesthesias; polyneuropathy; skin irritation; wounds; burns; inflammatory disorders of the gastrointestinal tract; pantothenic acid deficiency; mouth and throat disorders; eye disorders; sensation of burning in feet; ulcers.

Panthestin *Darnitsa, Ukr.*
Dexpanthenol (p. 2582·2); miramistin (p. 1761·2).
Infected skin disorders; wounds; ulcers; burns; vulvovaginal injury.

Panthevenol *Borshchagovskii, Ukr.*
Troxerutin (p. 2505·3); dexpanthenol (p. 2582·2).
Varicose veins; haemorrhoids; thromboses; skin ulcers; soft-tissue injury; scars; abscesses; furunculosis; intertrigo; cracked nipples during breast-feeding.

Panthisone *Rekah, Israel.†*
⊗Panthenol (p. 2582·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders; skin disorders; wounds.

Panthoderm *Akrikhin, Rus.; Jones, USA.*
Dexpanthenol (p. 2582·2).
Skin disorders; burns; ulcers; wounds.

Panthoderm-A *Sanofi Pasteur, Chile.†*
Vitamin A palmitate (p. 2098·3); panthenol (p. 2582·2).
Skin disorders.

Panthor *Juggat, India.*
Ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2).

Pantiban *Royal, Chile.*
Syrup: Amino acids; vitamins; minerals.
Dietary supplement.

Royal, Chile.†
Capsules: Vitamins; minerals; rutoside (p. 2505·3); ginseng (p. 2513·3); procaine hydrochloride (p. 1994·3).
Dietary supplement.

Pantif *Positif, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantin *Hetero, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantin-D *Hetero, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantin-RD *Hetero, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantip *GL Pharma, Austria.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantium
Note: this name may be used for preparations of different composition.
Win Medica, Gr.; Clonmel, Irl.
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; pathological hypersecretory disorders.

Accord, Braz.
Paclitaxel (p. 839·3).

Intas, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantium-D *Intas, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panto *Nycomed, Canad.; Sandoz, Turk.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer.

Sienna, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panto B+C *Adelco, Gr.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Panto Liquid *Pharmaselect, Austria.*
Panthenol (p. 2582·2).
Liver disorders; neuropathies; sweating; skin disorders; upper respiratory-tract inflammation.

Pantoavenir *Bioavenir, Israel.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pantobamin *Medix, Spain.*
Cyproheptadine (p. 624·1); amino acids; vitamins.
Anorexia; tonic.

Pantobron *Abbott, Mex.*
Erythromycin (p. 291·2) or erythromycin ethyl succinate (p. 291·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Pantoc *Nycomed, Port.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pantocaf *Knoll, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantocal *Eurofarma, Braz.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer.

Pantocalcin *Valenta, Rus.; Shchelkovskii, Ukr.*
Calcium hopantenate (p. 2465·1).
Mental function disorders; extrapyramidal disorders; epilepsy; Huntington's chorea; hepatolenticular degeneration; parkinsonism; micturition disorders.

Pantocar *Micro, India; Brown & Burk, Philipp.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantocar-D *Micro, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantocas *Casasco, Arg.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Pantocid *API, NZ; Sun, Thai.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; hypersecretory disorders.

Sun, India; Pharmaplan, S.Afr.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; pathological hypersecretory disorders.

Pantocid-D *Sun, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantocid-HP *Sun, India.*
Amoxicillin (p. 216·2); clarithromycin (p. 266·2); pantoprazole (p. 1875·3).

Pantocid-IT *Sun, India.*
Itopride hydrochloride (p. 1850·1); pantoprazole (p. 1875·3).

Pantocip *Cipla, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantocos *Symbiosis, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantocos-D *Symbiosis, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantocycline *Chew, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Panto-D *Sienna, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantodac *Zydus, India.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pantodac-D *Zydus, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantoday *Invision, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantoday-D *Invision, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantodex *Geolab, Braz.*
Dexpanthenol (p. 2582·2).

Pantofer *Biophar, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantofer-D *Biophar, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantofin *Q Check, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantoflux
Note: this name may be used for preparations of different composition.
Actavis, Irl.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Micro, India.
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantogam *Pik, Rus.; Pik, Ukr.†*
Calcium hopantenate (p. 2465·1).
Cerebrovascular disorders; paediatric cerebral palsy; mental function impairment; extrapyramidal disorders; micturition disorders; epilepsy; psychoses; neurogenic bladder disorders.

Pantogar *Assos, Turk.*
Cystine (p. 2059·1); aminobenzoic acid (p. 1694·2); keratin (p. 2538·1); thiamine (p. 2102·3); calcium pantothenate (p. 2085·2); medicinal yeast (p. 2125·2).
Hair and nail disorders.

Biolab Sanus, Braz.; Combiphar, Indon.; Merz, Singapore; Merz, Switz.; Merz, Ukr.
Calcium pantothenate (p. 2085·2); cystine (p. 2059·1); thiamine nitrate (p. 2103·2); medicinal yeast (p. 2125·2); keratin (p. 2538·1); aminobenzoic acid (p. 1694·2).
Hair and nail disorders; hair loss.

Merz, Austria.
Calcium pantothenate (p. 2085·2); cystine (p. 2059·1).
Hair and nail disorders.

Merz, Hong Kong.
Vitamins; medicinal yeast (p. 2125·2); keratin (p. 2538·1); aminobenzoic acid (p. 1694·2); cystine (p. 2059·1).
Hair and nail disorders.

Merz, Mex.
Saccharomyces cerevisiae; thiamine nitrate (p. 2103·2); calcium pantothenate (p. 2085·2); cystine (p. 2059·1); aminobenzoic acid (p. 1694·2); keratin (p. 2538·1).
Alopecia; hair disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pantogen *Generics, Pol.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantogerolan *GL Pharma, Neth.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Pantok *Lacer, Spain.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Pantokar *Micro Labs, Ukr.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantol
Note: this name may be used for preparations of different composition.
Pharmaland, Thai.
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Siomond, India.
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantolax *Actavis, Ger.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Pantol-D *Siomond, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantolex *Adley, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantolex-D *Adley, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantoloc *Nycomed, China; Avinash, India; Ikon, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Nycomed, Austria; Nycomed, Canad.; Nycomed, Cz.; Nycomed, Denm.; Nycomed, Hong Kong; Nycomed, Irl.; Nycomed, Philipp.; Nycomed, S.Afr.; Novartis Consumer, Spain; Novartis, Swed.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Pantoloc Control *Nycomed, Neth.; Nycomed, Norw.; Novartis Consumer, UK.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Pantolup *Lupin, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantom *Grandix, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantomas *Cosmas, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantomas-D *Cosmas, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal; dyspepsia.

Pantomax *Cure Quick, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantom-D *Grandix, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantomed
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Dexpanthenol (p. 2582·2).

Sanitas, Arg.; Takeda, Belg.; Ratiopharm, Hung.†
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; NSAID-induced peptic ulcer.

Pantomed-D *Mediez, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantometil *Lersan, Arg.†*
Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1).
Eye infections.

Pantomicina *Abbott, Arg.; Abbott, Mex.; Amdipharm, Spain; Abbott, Venez.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Abbott, Braz.
Erythromycin (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Abbott, Chile.
Erythromycin lactobionate (p. 291·3).
Bacterial infections.

Pantomore *Avalanche, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantomore-D *Avalanche, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantomyl *Generics, Cz.; Polpharma, Denm.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantonate *Eagle, Austral.†*
Calcium pantothenate (p. 2085·2).
Vitamin B_5 supplement.

Pantonic *Mediphar, Venez.*
⊗Urea (p. 1727·3); panthenol (p. 2582·2).
Scalp disorders.

Pantonid *Syntro, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantonid-D *Syntro, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantonis *Neiss, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

PantoNyco *Nycomed, Denm.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

PantoNycomed *Nycomed, Denm.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantop *Aristo, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Nycomed, Arg.; Zuoz, Venez.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia; hiatus hernia.

PantoPAC *Takeda, Neth.*
Tablets, pantoprazole sodium (p. 1875·3); tablets, clarithromycin (p. 266·2); tablets, amoxicillin trihydrate (p. 216·2).
Peptic ulcer.

Pantopan *EG, Fr.†; Almirall, Ital.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Taj, India.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantopaz *Hexal, Braz.*
Pantoprazole (p. 1875·3).
Peptic ulcer.

Pantop-D *Aristo, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantopep *Hetero, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantop-HP *Aristo, India.*
Clarithromycin (p. 266·2); metronidazole (p. 936·1); pantoprazole sodium (p. 1875·3).

Pantop-HP Kit *Aristo, India.*
2 Tablets, amoxicillin (p. 216·2); 2 tablets, clarithromycin (p. 266·2); 2 tablets, pantoprazole (p. 1875·3).

Pantopik *Aarpik, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantopik-D *Aarpik, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantopraz *Domesco, Philipp.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia; peptic ulcer; Zollinger-Ellison syndrome.

Pantoprem *Meda, Ger.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantopril *Ultramark, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantoprix *Shou Chan, Philipp.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantoprol *Sinensix, Thai.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; pathological hypersecretory disorders.

Pantor *Torrent, Philipp.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; dyspepsia; acid aspiration; Zollinger-Ellison syndrome.

Pantorc *Nycomed, Ital.; Eureco, Neth.†; Euro Registratie, Neth.†; Medcor, Neth.†*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pantosandoz *Sandoz, Ukr.†*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastritis; dyspepsia.

Pantosec *Cipla, India.*
Pantoprazole (p. 1875·3) or pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Medicina, Gr.; Ranbaxy, Irl.
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux.

Pantosec D *Cipla, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux.

Pantosh *Keshav, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantosh D *Keshav, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantosig *Signova, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantosig-D *Signova, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantosin *Daiichi, Jpn.*
Pantethine (p. 1464·2).
Pantothenic acid deficiency; pantothenic acid supplement; hyperlipidaemias; constipation; streptomycin and kanamycin toxicity; eczema; blood disorders.

Pantosol *Vista, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantostin *Simons, Ger.*
Alfatradiol (p. 2255·2).
Alopecia androgenetica.

Pantosym-D *Symbiosis, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantotab *Micro, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantothen *Pharmaselect, Austria.*
Panthenol (p. 2582·2).
Liver disorders; respiratory-tract disorders; neuropathies; alcoholism; muscle cramps; sweating; skin disorders; gastrointestinal tract disorders.

Streuli, Switz.
Calcium pantothenate (p. 2085·2).
Skin and mucous membrane disorders; respiratory-tract disorders.

Pantotive *Sanify, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantotive-D *Sanify, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantovar *ATOZ, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantovar-D *ATOZ, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantovigar *Merz, Rus.*
Thiamine nitrate (p. 2103·2); calcium pantothenate (p. 2085·2); cystine (p. 2059·1); aminobenzoic acid (p. 1694·2); keratin (p. 2538·1); yeast (p. 2125·2).
Hair and nail disorders.

Simons, Ger.
Thiamine nitrate (p. 2103·2); calcium pantothenate (p. 2085·2); medicinal yeast (p. 2125·2); cystine (p. 2059·1); keratin (p. 2538·1).
Disorders of the hair and nails.

Pantovit *Pharmed, India.*
Capsules: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Pharmed, India.
Injection: Vitamin B substances (p. 2102·3).

Sanova, Austria.†
Vitamins.

Pantovom *Acme, India.*
Domperidone (p. 1838·1); pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantox *Pharma-Tech, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Teuto, Braz.
Pantoprazole sodium (p. 1875·3).

Pantox-D *Pharma-Tech, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantoxon *Aesculapius, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Pantoz *Osmed, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantoz-D *Osmed, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantozim *Intas, Philipp.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantozol *Aronex, India; Pharos, Indon.; Nycomed, Mex.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration.

Nycomed, Austria; Takeda, Belg.; Nycomed, Braz.; Nycomed, Cz.; Nycomed, Fr.; Nycomed, Ger.; Nycomed, Neth.; Shine, Philipp.; Takeda, Switz.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantozol Control *Nycomed, Irl.; Nycomed, Pol.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Pantozol-D *Aronex, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantpas *Bayer, Turk.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Pantra *Nutramedica, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantra-D *Nutramedica, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantrat *Cifarma, Braz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Pantrex *Ying Yuan, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Pantric *Synmedic, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantrim *Picco, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pantrixon *Panpharma, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Pantroz *Celon, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantry *Vensat, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantry-D *Vensat, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantul *GL Pharma, Cz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantup *Rowex, Irl.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantus *Baliarda, Arg.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantyson *Orion, Fin.*
⊗Hydrocortisone (p. 1640·1); dexpanthenol (p. 2582·2).
Skin disorders.

Pantz *Ritz, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pantz-D *Ritz, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Pantz-DM *Ritz, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panum *JB Chemicals, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Unique, Rus.
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastritis.

Panum-D *JB Chemicals, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panum-P *Nordic, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Panum-SP *Nordic, India.*
⊗Nimesulide (p. 101·3); serrapeptase (p. 2613·3).

Panuron *Troikaa, India; Troika, Venez.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Pan-Vasin *Theodoridis, Gr.†*
Benzethonium chloride (p. 1738·1).

Panvax *CSL Biotherapies, Austral.; CSL, NZ.*
An influenza vaccine (H1N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Panvermin *Andromaco, Mex.†*
Mebendazole (p. 158·3).
Worm infections.

Panvid *Picco, Thai.*
Vitamins.

Pan-Vision *OmniVision, Ger.*
Hypromellose (p. 2189·2).
Dry eyes.

Panvit *Teuto, Braz.*
Vitamins; with or without minerals.

Panvitan *Takeda, Jpn.*
Vitamins.

Panvitan-M *Takeda, Singapore; Takeda, Thai.†*
Vitamins; minerals.

Panvitrop *Nycomed, Braz.*
Methionine (p. 1558·2); choline tartrate (p. 2055·2); sodium phenylethylacetate; liver extract (p. 2444·1); vitamin B substances (p. 2102·3); tocopherol (p. 2119·1); rutoside (p. 2505·3).
Liver disorders.

Panwarfin *Abbott, Gr.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Panwell *Genesis, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panxeol *Monin, Fr.†*
California poppy (p. 2466·1); passion flower (p. 2584·1).
Nervous disorders; insomnia.

Panz *Glories, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panzac *Agio, India.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Panzac-D *Agio, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panzat *Atral, Port.*
Pantoprazole sodium (p. 1875·3).

Panz-D *Glories, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panzer
Note: this name may be used for preparations of different composition.
Medispan, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Wermar, Mex.
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Panzer-TZ *Medispan, India.*
Ciprofloxacin (p. 261·1); tinidazole (p. 949·2).

Panzid *Glaxo Allen, Ital.*
Ceftazidime (p. 250·2).
Bacterial infections.

Panzim *Bryntsalov, Rus.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders; abdominal examination.

Panzo-D *H & Care, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panzol *Apotex, Pol.*
Pantoprazole (p. 1875·3).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panzor *Orion, Fin.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panz-SR *Glories, India.*
Domperidone (p. 1838·1); pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; dyspepsia.

Panzyme *Radicura, India.*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Panzynorm *Medicopharm, Austria; KRKA, Cz.; KRKA, Rus.; KRKA, Ukr.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders.

Panzynorm forte-N *Axcan, Ger.*
⊗Porcine pancreatin (p. 2579·3).
Pancreatic insufficiency.

Panzynorm-N *Zydus, India.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Panzytrat *Abbott, Braz.; Axcan, Cz.; Axcan, Ger.; Vianex (Bizvež), Gr.; Axcan, Hung.; Aptalis, Neth.; Axcan, Pol.; Ipsen, Rus.; Sigma-Tau, Switz.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders; aid in abdominal examination.

Technipro, Austral.; Pharmaco, NZ.
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Pa-Pa *Euphoric, India.*
Pyrantel embonate (p. 165·3).
Worm infections.

Papaine *DB, Fr.*
Carica papaya.
Dyspepsia.

Paparin *Troikaa, India.*
Papaverine hydrochloride (p. 2362·3).

Papasine *Bernabo, Arg.*
Naproxen (p. 98·2); tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Papaven *Medikon, Indon.†*
⊗Graptophyllum pictum; troxerutin (p. 2505·3); papain (p. 2582·3).
Haemorrhoids; phlebitis; venous insufficiency.

Papaveryl *Vincenti, Venez.*
Papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Papaya Enzyme *Nature's Bounty, USA.*
⊗Papain (p. 2582·3); amylase (p. 2442·1).
Gastrointestinal disorders.

Papazol *Dalkhimfarm, Rus.*
Bendazol hydrochloride (p. 2454·3); papaverine hydrochloride (p. 2362·3).
Hypertension; smooth muscle spasm; vascular spasm; facial nerve palsy.

Papcef *Alna, India.*
Cefpodoxime.
Bacterial infections.

Papcef-CV *Alna, India.*
Cefpodoxime or cefpodoxime proxetil (p. 248·1); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Papenzima *Pfizer, Chile.*
⊗Papain (p. 2582·3).
Soft-tissue injury.

Papfyll *Onset, USA.*
⊗Chlorophyllin copper complex (p. 2178·3); papain (p. 2582·3).
Burns; ulcers; wounds.

Papilock *Santen, Jpn.*
Ciclosporin (p. 1945·2).
Vernal keratoconjunctivitis.

Papine *Duphar Nezel, Spain.†*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Paps *Richard, Fr.†*
Sulfur (p. 1721·1); zinc undecenoate (p. 596·3); bismuth subgallate (p. 1822·1); menthol (p. 2553·2); camphor (p. 2466·2); salicylic acid (p. 1719·1); zinc oxide (p. 1729·1); boric acid (p. 2459·3); lavender oil (p. 2541·1).
Pruritus.

Papuless *Theraskin, Braz.*
Nicotinamide (p. 2083·1).

Papulex *Sinclair, Austral.; Sinclair, Fr.; Invida, Singapore.*
Nicotinamide (p. 2083·1).
Acne; skin cleansing.

Sinclair, Austral.; Sinclair, Fr.
Cream: Nicotinamide (p. 2083·1); zinc pidolate (p. 1720·3).
Acne.

Papulex Isocorrexion *Invida, Singapore.*
Nicotinamide (p. 2083·1); zinc pidolate (p. 1720·3).
Acne; dry skin.

Papulex Oil-Free *Invida, Singapore.*
Cream: Nicotinamide (p. 2083·1); zinc pidolate (p. 1720·3).
Acne.

Papytazyme *Anglo-French Drugs, India.*
Syrup: ⊗Amylase (p. 2442·1); papain (p. 2582·3).
Digestive disorders.

Anglo-French Drugs, India.
Tablets: ⊗Pancreatin (p. 2579·3); ox bile extract (p. 2457·2); ginger oleoresin (p. 1844·1); activated charcoal (p. 1537·3).
Formerly contained amylase, papain, pancreatin, ox bile extract, pepsin, ginger oleoresin, and activated charcoal.
Digestive disorders.

Par
Note: this name may be used for preparations of different composition.
Angelini, Gr.
Paracetamol (p. 115·1).
Pain; fever.

Daudt, Braz.
Paracetamol (p. 115·1); dipyrone (p. 53·3).
Fever; pain.

Par Glycerol *Par, USA.*
Iodinated glycerol (p. 1667·2).
Coughs.

Para *ANH, Thai.; Charoen, Thai.; GPO, Thai.; United Drug, Thai.; Utopian, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Medgenix, Belg.
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Royal, Chile.†
Dimeticone (p. 2209·3).
Barrier preparation.

Para Iop *HLB, Chile.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Para Lentes *Omega, Fr.†*
Acetic acid (p. 2426·3).
Pediculosis.

Para Piojicida *Raymos, Arg.*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Para Plus *Raymos, Arg.; Medgenix, Belg.; Omega, Fr.; Rafa, Israel; Pacific, NZ; Omega, Rus.; Omega, Ukr.*
Malathion (p. 2157·2); permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2).
Pediculosis.

Para Répulsif *Omega, Fr.†*
Ethyl butylacetylaminopropionate (p. 2154·3).
Head lice repellent.

Para Sol SD *New Life, Arg.*
Vitamins; betacarotene (p. 2051·1).

Para Spécial Poux *Omega, Fr.*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Para Z Mol *Cabuchi, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Parabact
Note: this name may be used for preparations of different composition.
Grace, India.
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Cadila, India.†
Norfloxacin (p. 333·3); tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Parabec *Adley, India.*
Benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); paradichlorobenzene (p. 2583·2); turpentine oil (p. 2636·3).

Parabig *Winsome, India.*
Paracetamol (p. 115·1).
Pain; fever.

Parabutol *Prafa, Indon.†*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Paracain *Sunways, India.*
Proxymetacaine hydrochloride (p. 1995·3).

Paracamf *Zizine, Fr.*
Amylocaine hydrochloride (p. 1979·3); benzocaine (p. 1980·2); resorcinol (p. 1718·3).
Dental disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Paracap *Masa, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Paracare *PSM, NZ.*
Paracetamol (p. 115·1).
Fever; pain.

Paracef *SPM, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Paracefan *Boehringer Ingelheim, Ger.*
Clonidine hydrochloride (p. 1339·1).
Alcohol withdrawal syndrome 406 in ROTE.08, only HCl inj for alcohol withdrawal.

Paracen *Greenpharma, Braz.*
Paracetamol (p. 115·1).
Pain; fever.

Paraceon *Verman, Fin.*
Paracetamol (p. 115·1).
Pain; fever.

Paracet *Vickmans, Hong Kong†; Vitamed, Israel; Weifa, Norw.; Be-Tabs, S.Afr.; Osotspa, Thai.; United Drug, Thai.; Gripin, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Paracetacod *Adcock Ingram, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); ascorbic acid (p. 2110·3).
Pain.

Paracetal *Bright Future, Hong Kong.†*
Paracetamol (p. 115·1).
Fever; pain.

Paracetamol C & F *Pharmaniaga, Hong Kong†; Pharmaniaga, Malaysia.†*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; cough; nasal congestion.

Paracetamol comp
Note: this name may be used for preparations of different composition.
Apotex, Neth.
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.
Aliud, Ger.†; Stada, Ger.†
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Paracetamol Grip NF *Raffo, Arg.*
⊗Paracetamol (p. 115·1); bromhexine hydrochloride (p. 1656·3); pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Cold and influenza symptoms.

Paracetamol-C *Hemofarm, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Paracetanal *Zydus, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paracetol *Prafa, Indon.†; Alliance, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Paracetrex *Royton, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Paracets *Sussex, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Paracets Cold Relief *Sussex, UK.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Paracets Plus *Sussex, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Parachoc *Care, Austral.*
Liquid paraffin (p. 2191·2).
Constipation.

Paracin
Note: this name may be used for preparations of different composition.
Chinta, Thai.
Paracetamol (p. 115·1); potassium citrate (p. 1780·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cough; cold and influenza symptoms.
Stadmed, India.
Paracetamol (p. 115·1).
Fever; pain.

Paracip *Cipla, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paracip CPM *Cipla, India.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).

Paracip Plus *Cipla, India.*
Paracetamol (p. 115·1); diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Paraclear *Roche Consumer, UK.*
Paracetamol (p. 115·1).

Paraclim *Elea, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Paraclo *BMW, India.*
Dicycloverine (p. 1834·2); paracetamol (p. 115·1).

Paracne *Panalab, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Para-Co *Medicpharma, Thai.*
Codeine phosphate (p. 40·2).

Paracod *Cipla, India.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Paracodamol *Balkanpharma, Rus.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Paracode *Arrow, NZ.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Paracodin *Abbott, Austral.†; Teofarma, Austria; Teofarma, Ger.; Teofarma, Irl.; Abbott, S.Afr.*
Dihydrocodeine tartrate (p. 52·3).
Cough.
Teofarma, Austria; Teofarma, Switz.
Dihydrocodeine thiocyanate (p. 52·2).
Cough; diarrhoea.

Paracodin N *Teofarma, Ger.*
Dihydrocodeine tartrate (p. 52·3) or dihydrocodeine thiocyanate (p. 52·2).
Cough.

Paracodina *Teofarma, Ital.*
Syrup: Dihydrocodeine tartrate (p. 52·3); benzoic acid (p. 1738·2).
Cough.
Teofarma, Ital.
Oral drops: Dihydrocodeine thiocyanate (p. 52·2).
Cough.
Teofarma, Spain.
Dihydrocodeine tartrate (p. 52·3).
Cough.

Paracodine *Teofarma, Belg.*
Syrup; tablets: Dihydrocodeine tartrate (p. 52·3).
Cough.

Paracodol *Roche Consumer, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain; fever.

Paracodrate *Unijules, India.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine (p. 1672·2).

Paracol *T Man, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Paracol-Dex *T Man, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Paracor *Corsalud, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Paract *Actavis, Rus.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Paractol *Zydus, India.*
Oral liquid: Simeticone (p. 1886·2); ried aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders with excess gas; abdominal radiography; gastric hyperacidity.
Zydus, India.
Tablets: Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2).
Gastrointestinal disorders with excess gas; abdominal radiography; gastric hyperacidity.

Paracut *Vitabalans, Swed.*
Paracetamol (p. 115·1).
Fever; pain.

Paradco *Adco, S.Afr.†*
Paracetamol (p. 115·1).
Fever; pain.

Paradeine *Charoen, Thai.*
Paracetamol (p. 115·1); codeine (p. 40·2).
Pain.

Paradentose *Dentsply, Fr.†*
Resorcinol (p. 1718·3); camphor (p. 2466·2).
Periodontitis.

Paraderm Plus *Pfizer Consumer, Austral.†; Wyeth Consumer, NZ.†*
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2); bufexamac (p. 30·2).
Burns; insect bites; minor skin lesions; stings; sunburn.

Paradex *Aspen, Austral.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.
PSM, NZ.†
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Paradic *Osper, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Paradic-C *Osper, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Paradic-MR *Nordic, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Paradine
Note: this name may be used for preparations of different composition.
Hakay, Turk.
Paracetamol (p. 115·1).
Pain; fever.
Medicpharma, Thai.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Paradis *Biomedica, Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Paradise *Torrent, India.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Para-don *Healthypharm, Neth.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); propyphenazone (p. 127·3).
Pain; fever.

Paradote *Sinclair, UK.†*
Paracetamol (p. 115·1); DL-methionine (p. 1558·2).
These ingredients can be described by the British Approved Name Co-methiamol.
Pain; fever.

Paradrine *DHA, Hong Kong; DHA, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Paradroxil *BMS, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Paradryl *Prafa, Indon.*
Injection: Diphenhydramine hydrochloride (p. 626·2).
Cough.
Prafa, Indon.
Syrup: ⊗Ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2); alcohol (p. 1733·1); diphenhydramine (p. 626·1).
Cough.

Parafen *Pharmahof, Thai.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2).

Parafizz *Cipla, India; Cipla, Malaysia.*
Paracetamol (p. 115·1).
Pain; fever.

Paraflan *Pharlab, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Paraflax *Johnson & Johnson, India.*
Chlorzoxazone (p. 2022·2); ibuprofen (p. 68·2).
Skeletal muscle spasm and pain.

Paraflex *Janssen-Cilag, S.Afr.†; Biophausia, Swed.; Gurel, Turk.; McNeil Pharmaceutical, USA.*
Chlorzoxazone (p. 2022·2).
Skeletal muscle spasm; premedication; headache; musculoskeletal pain.

Paraflex AN *Janssen-Cilag, Arg.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Paraflex Plus *Janssen-Cilag, Arg.*
⊗Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1); dexamethasone (p. 1630·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Parafludeten *Alter, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Parafon *Janssen-Cilag, Gr.; Johnson & Johnson, India; Janssen, Philipp.†; Johnson & Johnson, S.Afr.†; Janssen-Cilag, Thai.; Gurel, Turk.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Parafon DSC *Johnson & Johnson, India.*
Baclofen (p. 2014·3).
Formerly contained chlorzoxazone.
Spasticity.

Parafon Forte *Janssen-Cilag, Mex.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Parafon Forte DSC *Janssen, USA.*
Chlorzoxazone (p. 2022·2).
Musculoskeletal pain.

Parafort *Auspi, India.*
Paracetamol (p. 115·1).
Pain; fever.

Parafortan
Note: this name may be used for preparations of different composition.
Khandelwal, India; Khandelwal, Philipp.
Diclofenac sodium (p. 48·3).
Pain; gout; inflammation; musculoskeletal and joint disorders; renal and biliary colic.
Khandelwal, India.
Tablets: Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Para-G *Millimed, Thai.†*
Paracetamol (p. 115·1).
Fever; pain.

Paragar *Spirig, Switz.*
Liquid paraffin (p. 2191·2); agar (p. 2167·2); phenolphthalein (p. 1877·3).
Constipation.

Para-Gard *Future, Canad.*
Absinthium (p. 2426·1); barberry (p. 2502·1); gentian (p. 2512·1); hydrastis (p. 2528·1); butternut (p. 2463·2); quassia (p. 2601·1).
Digestive disorders.

Paragard T380A *Ortho McNeil, USA.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Parage *Allenge, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paragel *Omega, Gr.*
Liquid paraffin (p. 2191·2).
Constipation.

Parageniol *GSK, Arg.*
Paracetamol (p. 115·1).
Pain; fever.

Parageniol Caff *GSK, Arg.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Parageniol Grip Caliente *GSK, Arg.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Paragesic *CCM, Malaysia.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Smooth muscle spasm and pain.

Paraghurt *Actavis, Denm.*
Enterococcus faecium (p. 2596·3).
Diarrhoea.

Paragin *Pharmasant, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Paraglow *Aglowmed, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paragol N *Streuli, Switz.*
Liquid paraffin (p. 2191·2).
Constipation.

Para-Gone *Future, Canad.*
Barberry (p. 2502·1); clove (p. 2481·2); garlic (p. 2510·3); gentian (p. 2512·1); hydrastis (p. 2528·1); milk thistle (p. 1561·1); oregano (p. 2576·3); quassia (p. 2601·1).
Digestive disorders.

Paragoriese-Elikser *Lennon, S.Afr.†*
Opium (p. 111·3); anise oil (p. 2444·3); camphor (p. 2466·2).
Diarrhoea; abdominal pain; cough.

Paragram *Vickmans, Hong Kong.†*
Paracetamol (p. 115·1).
Fever; pain.

Paragrippe *Boiron, Cz.; Boiron, Fr.; Boiron, Neth.†; Boiron, Port.*
Arnica montana (p. 2447·2); belladonna (p. 2453·3); eupatorium perfoliatum (p. 2459·1); gelsemium (p. 2511·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Parahexal *Hexal, Austral.†*
Paracetamol (p. 115·1).
Fever; pain.

Para-Hist HD *Pharmics, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

Para-Hot *Orion, Fin.*
Paracetamol (p. 115·1).
Fever; pain.

Paraiop *Ingens, Arg.†*
Latanoprost (p. 2008·1).
Ocular hypertension.

Para-IV *Jiangsu Sihuan, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Parakapton *Rosch & Handel, Austria†; Strallhofer, Austria.†*
Paracetamol (p. 115·1).
Pain, fever.

Para-4-Kids *Blue Sky, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Parakodin *Atabay, Turk.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).

Parakol *CCM, Malaysia.*
⊗Dexchlorpheniramine maleate (p. 621·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; allergic disorders.

Paraks *Abbott, Turk.*
Levamisole (p. 157·2).
Ascariasis; trichostrongyliasis.

Paral
Note: this name may be used for preparations of different composition.
Hauz, India.
Paracetamol (p. 115·1).
Pain; fever.

Paraldim *Fourrts, India.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

Paralen *Zentiva, Cz.*
Paracetamol (p. 115·1).
Fever; pain.

Paralen Extra *Zentiva, Cz.; Zentiva, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Paralen Grip *Zentiva, Cz.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms; cough.

Paralen Hot Drink *Zentiva, Cz.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Paralen Plus *Zentiva, Cz.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract disorders; fever.

Parales *Psyco Remedies, India.*
Trihexyphenidyl hydrochloride (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Paralgen *Legrand, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Paralgesic Gold *ECR, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Paralgin
Note: this name may be used for preparations of different composition.
Sigma, Austral.
Paracetamol (p. 115·1).
Pain; fever.

Weifa, Norw.
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Paralice *Omega, Austral.*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Paralide *Plus, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Paralief *Clonmel, Irl.*
Paracetamol (p. 115·1).
Pain; fever.

Paralife *Lifeon, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paralink *Rice Steele, Irl.*
Paracetamol (p. 115·1).
Pain; fever.

Paralon *Janssen-Cilag, Braz.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Pain; smooth muscle spasm.

Paral-P *Hauz, India.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2).

Paralymphine *Andromaco, Chile.*
Iodine (p. 2336·3); manganese glycerophosphate (p. 2519·2); tannin (p. 2625·2); calcium phosphate (p. 1784·2); ferrous phosphate.
Tonic.

Paralyoc *Cephalon, Fr.*
Paracetamol (p. 115·1).
Pain; fever.

Paraman *T Man, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Paramax *Sanofi-Aventis, Irl.; GSK, NZ; Sanofi Synthelabo, UK.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Gastric stasis; migraine; nausea and vomiting.
Vitabalans, Fin.
Paracetamol (p. 115·1).
Pain; fever.

Paramax Combi *Vitabalans, Cz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Paramax Comp *Vitabalans, Fin.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Paramax Rapid *Vitabalans, Cz.; Vitabalans, Hung.*
Paracetamol (p. 115·1).
Pain; fever.

Paramax-Cod *Vitabalans, Fin.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Paramed *GSK, S.Afr.; Medicpharma, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Paramed-Co *Medicpharma, Thai.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Paramegal *Glenmark, Cz.*
Paracetamol (p. 115·1).
Fever; pain.

Paramen *Vent-3, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Paramet *Wallace, India.*
Paracetamol (p. 115·1); metoclopramide (p. 1862·2).
Migraine.

Parameter *Invision, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paramex *Konimex, Indon.†*
Propyphenazone (p. 127·3); paracetamol (p. 115·1); dexchlorpheniramine maleate (p. 621·1); caffeine (p. 1203·3).
Pain; fever.

Paramidon *Abbott, Turk.; Biokem, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Paramin *Elvipe, Gr.*
Paracetamol (p. 115·1).
Fever; pain.

Paraminan *Dexo, Fr.*
Aminobenzoic acid (p. 1694·2).
Photodamage of the skin.

Paramino-Corazida *Basi, Port.*
Aminosalicylic acid (p. 215·2).
Tuberculosis.

Paraminol *Franco-Indian, India.*
Aminobenzoic acid (p. 1694·2).
Sunscreen.

Paramix *Liomont, Mex.*
Nitazoxanide (p. 942·2).
Protozoal infections; worm infections.

Paramol
Note: this name may be used for preparations of different composition.
Belfar, Braz.; Dexcel, Israel; Perrigo, Israel; General Drugs, Thai.
Paracetamol (p. 115·1).
Fever; pain.

Galen, Irl.; SSL, UK.
Paracetamol (p. 115·1); dihydrocodeine tartrate (p. 52·3).
Pain; fever; cough.

Paramol AF Day *Dexcel, Israel.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; nasal congestion.

Paramol AF Night *Dexcel, Israel.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; nasal congestion.

Paramol AF & Shiul Day *Dexcel, Israel.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms; nasal congestion.

Paramol AF & Shiul Night *Dexcel, Israel.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms; nasal congestion.

Paramol Forte *APT, Hong Kong.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Paramol Plus *Dexcel, Israel.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Paramol Target *Perrigo, Israel.*
Aspirin (p. 22·2); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain.

Paramol TP *TP, Thai.*
Paracetamol (p. 115·1).
Lidocaine hydrochloride (p. 1988·2) is included in some injections to alleviate the pain of injection.
Pain; fever.

Paramolan *Medinfar, Port.*
Paracetamol (p. 115·1).
Pain; fever.

Paramolan C *Medinfar, Port.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Paramol-F *Beacons, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Paranal *Siam Bheasach, Thai.†*
Paracetamol (p. 115·1).
Pain; fever.

Paranal-L *Siam Bheasach, Thai.†*
Paracetamol (p. 115·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Pain; fever.

Paranausine *Eurogenerics, Belg.†*
Dimenhydrinate (p. 625·2).

Paranix *Cinetic, Arg.; Paracelsia, Ger.; Interdelta, Switz.*
Anise oil (p. 2444·3); coconut oil (p. 2179·3); ylang ylang oil (p. 2649·3).
Pediculosis.

Parano *Milano, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Paranol *Utopian, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Paranomin *Combiphar, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine (p. 1674·1).
Cold and influenza symptoms; upper respiratory-tract disorders.

Paranorm
Note: this name may be used for preparations of different composition.
Cipla, India.
Metoclopramide (p. 1862·2); paracetamol (p. 115·1).
Migraine.

Wallace Mfg Chem., UK.
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Coughs.

Para-Nox
Note: this name may be used for preparations of different composition.
Sanofi Synthelabo, Turk.
Forte suppositories; paediatric syrup; s suppositories; tablets: Paracetamol (p. 115·1).
Fever; pain.

Sanofi Synthelabo, Turk.
Suppositories: Paracetamol (p. 115·1); phenobarbital (p. 535·2).
Fever; pain.

Paranox
Note: this name may be used for preparations of different composition.
Roi Surya, Indon.†
SPF 33: Enzacamene (p. 1703·2); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Paranox F *Roi Surya, Indon.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Parapaed *Ritsert, Ger.†; Pinewood, Irl.; AFT, NZ; Pinewood, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Parapane *Pharma-Q, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Parapic *Biomed, Switz.*
Roll-on; topical solution; topical spray:
Levomenthol (p. 2553·2); mepyramine maleate (p. 635·1); cineole (p. 2479·1); lauromacrogol 400 (p. 2194·1); isopropyl alcohol (p. 1758·3).
Insect bites and stings.

Biomed, Switz.†
Topical gel: Lidocaine hydrochloride (p. 1988·2); diphenhydramine hydrochloride (p. 626·2); benzalkonium chloride (p. 1737·1); menthol (p. 2553·2); dexpanthenol (p. 2582·2).
Insect stings; skin irritation.

Paraplatin *BMS, Braz.; BMS, Chile†; BMS, China; BMS, Fin.†; BMS, Gr.; BMS, Hong Kong; BMS, Hung.†; BMS, India; BMS, Indon.†; BMS, Irl.†; BMS, Ital.; BMS, Mex.;*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

BMS, NZ†; BMS, Philipp.†; BMS, Pol.†; BMS, Rus.; BMS, S.Afr.†; BMS, Singapore; BMS, Spain; BMS, Swed.†; BMS, Switz.; BMS, Thai.; BMS, Turk.†; BMS, UK; BMS, USA.
Carboplatin (p. 759·1).
Malignant neoplasms.

Paraplatine *BMS, Fr.†*
Carboplatin (p. 759·1).
Malignant neoplasms.

Para-plus *Olvos, Gr.*
Permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2); malathion (p. 2157·2).
Pediculosis.

ParaPlus *Pfizer Consumer, Irl.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Parapoux *Omega, Fr.†*
Permethrin (p. 2159·3).
Pediculosis.

Parapres *Almirall, Spain.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Parapres Plus *Almirall, Spain.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Parapro *Medicine Products, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Parapsyl *Barrenne, Braz.*
Liquid paraffin (p. 2191·2); ispaghula (p. 1849·1).
Constipation.

Parapsyllium *Alfa Wassermann, Fr.*
Ispaghula (p. 1849·1); liquid paraffin (p. 2191·2); sorbitol (p. 2092·1).
Constipation.

Paraqueimol *Ache, Braz.*
Sulfacetamide sodium (p. 361·1); trolamine (p. 2634·3).
Skin infections.

Paraquin *Shreya, India.*
Chloroquine (p. 650·1).
Malaria; lupus erythematosus; hepatic amoebiasis; rheumatoid arthritis.

Pararegl *Dompe, Cz.†; Dompe, Ital.†*
Cinacalcet hydrochloride (p. 1180·1).
Hyperparathyroidism in dialysis patients with end-stage renal disease; hypercalcaemia in parathyroid cancer.

Parartrin *Cazi, Braz.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Paras *YSP, Malaysia.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Parasafe *Strassenburg, India.*
Methionine (p. 1558·2); paracetamol (p. 115·1).
Fever; pain.

Para-schmerz *Abdi-Med, Switz.†*
Paracetamol (p. 115·1).
Pain; fever.

Parasedol *Kocak, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Parasidose
Note: this name may be used for preparations of different composition.
Gilbert, Cz.; Gilbert, Fr.; Multichem, NZ; Expanscience, Port.; Gilbert, Rus.
Phenothrin (p. 2160·1).
Pediculosis.

Parasimed *Cimed, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Parasin
Note: this name may be used for preparations of different composition.
Ache, Braz.
Albendazole (p. 149·1).
Worm infections.

Parasinus *Kocak, Turk.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Parasol
Note: this name may be used for preparations of different composition.
Surya Dermato, Indon.
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); oxybenzone (p. 1715·3).
Sunscreen.

Parasone *Vida, Hong Kong.†*
⊗Dexamethasone (p. 1630·3); paracetamol (p. 115·1); vitamin B substances (p. 2102·3).
Musculoskeletal, joint, and peri-articular disorders.

Paraspas *Cadila, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).

Para-Speciaal *Chefaro, Neth.†*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Paraspeed *Nycomed, Austria.†*
Paracetamol (p. 115·1).
Pain; fever.

Para-Suppo *Orion, Fin.*
Paracetamol (p. 115·1).
Fever; pain.

Parasym *Symbiosis, India.*
Paracetamol (p. 115·1).
Pain; fever.

Parat *Asian Pharm, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Paratab *Sunward, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Para-Tabs *Orion, Fin.*
Paracetamol (p. 115·1).
Fever; pain.

Paratabs *Actavis, Denm.†; Pinewood, Irl.*
Paracetamol (p. 115·1).
Cold and influenza symptoms; pain; musculoskeletal disorders; fever.

Paratel *Intel, India.*
Paracetamol (p. 115·1).
Pain; fever.

Paratel Plus *Intel, India.*
Paracetamol (p. 115·1); promethazine (p. 638·2).

Paratel-AC *Intel, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Paratel-ACP *Intel, India.*
Aceclofenac (p. 16·2); chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).

Paratel-DS *Intel, India.*
⊗Diclofenac sodium (p. 48·3); paracetamol (p. 115·1); serrapeptase (p. 2613·3).

Paratel-LC *Intel, India.*
Lornoxicam (p. 83·2); paracetamol (p. 115·1).

Paratel-NP *Intel, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Paratel-T *Intel, India.*
Paracetamol (p. 115·1); tramadol (p. 139·2).
Pain.

Paraterax *Servier, Cz.; Servier, Denm.; Servier, Fr.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Paraterol *Vachon, Canad.†*
Chamomile (p. 2474·1).

Paratol *Chew, Thai.†*
Paracetamol (p. 115·1).
Pain; fever.

Paratônico *Multilab, Braz.†*
Ferrous sulfate (p. 2062·2); phosphoric acid (p. 2589·1); aloes (p. 1816·1); myrrh (p. 2566·1); cinnamon (p. 2479·2); nutmeg (p. 2573·1).
Reduced appetite.

Paratonina *Angelini, Spain.†*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Paratral *Austral, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Paratram *Zodiac, Braz.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).

Paratropina *Lazar, Arg.*
Homatropine methylbromide (p. 2007·3).
Habitual vomiting in infants; hyperchlorhydria; smooth muscle spasm.

Paratropina Antigas *Lazar, Arg.*
Simeticone (p. 1886·2); homatropine methylbromide (p. 2007·3).
Gastrointestinal spasm.

Paratropina Compuesta *Lazar, Arg.*
Homatropine methylbromide (p. 2007·3); metamizole magnesium (p. 53·3).
Colic; dysmenorrhoea.

Para-Tulle *Cotton Craft, Philipp.*
Chlorhexidine acetate (p. 1743·2).
Wounds.

Paratusin *Prafa, Indon.*
Syrup: ⊗Noscapine (p. 1670·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); succus liquid; pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.
Prafa, Indon.
Tablets: Noscapine (p. 1670·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold symptoms.

Parax *Sandoz, S.Afr.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Paraxin *Abbott, India.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Parazid *Psyco Remedies, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Parazin-C *Psyco Remedies, India.*
Chlordiazepoxide (p. 1044·2); trifluoperazine (p. 1113·2).

Parazine *David, India.*
Paracetamol (p. 115·1).
Pain; fever.

Parazobid *Abbott, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Parazol *Cazi, Braz.*
Albendazole (p. 149·1).
Worm infections.

Parazolandin *Sarabhai Piramal, India.*
Nimesulide (p. 101·3); paracetamol (p. 115·1).

Parazone *Quality, Hong Kong.*
Paracetamol (p. 115·1); chlormezanone (p. 1045·1).
Pain; skeletal muscle spasm; premenstrual syndrome; dysmenorrhoea.

Parazox-D *Chemo-Drugs, India.*
Chlorzoxazone (p. 2022·2); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Parcaine *Ocusoft, USA.*
Proxymetacaine hydrochloride (p. 1995·3).

Parcar *Zydus, India.*
Cabergoline (p. 899·3).
Parkinsonism; lactation inhibition; hyperprolactinaemia.

Parcef *East West, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.
Jayson, Ukr.†
Ceftriaxone (p. 253·3).
Bacterial infections.

Parcel *Novartis, Braz.*
Paracetamol (p. 115·1); dihydroergotamine mesilate (p. 672·2); caffeine (p. 1203·3).
Migraine.

Parcemol *Synco, Hong Kong†; Synco, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Parcet *Pharmahof, Thai.†*
Paracetamol (p. 115·1).
Fever; pain.

Parcetin *Denver, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Parcetol *Abbott, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Parche Leon Fortificante *Beiersdorf, Chile.†*
Capsicum (p. 2469·3).
Musculoskeletal and joint disorders.

Parche Negro Belladona *Quimica y Farmacia, Mex.*
Capsicum (p. 2469·3); methyl salicylate (p. 92·1); colophony (p. 2484·2); zinc oxide (p. 1729·1); calcium carbonate (p. 1824·3); belladonna (p. 2453·3); negro de humo.
Musculoskeletal disorders.

Parclen *Lepetit, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Parclo-AP *Candor, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Parco-D *Patar, Thai.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Parcode *Troth, Ukr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Parcono *Milano, Thai.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Parcopa *Azur, USA.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Parcoten *Aegis, Hong Kong.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Parcy *Chemo-Drugs, India.*
Sparfloxacin (p. 357·3).
Chronic bronchitis; community-acquired pneumonia.

Pardelprin *Alpharma, UK.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Pardex
Note: this name may be used for preparations of different composition.
Parggon, Mex.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.
Sriprasit, Thai.
Dextropropoxyphene napsilate (p. 43·3).
Pain.

Pardix *Arlex, Mex.*
Dicloxacillin (p. 286·1).
Bacterial infections.

Pardon *Acdhon, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Pardoz *Hexpharm, Indon.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Pa-Real *Lampugnani, Ital.*
Royal jelly (p. 2608·1).
Nutritional supplement.

Parégorique *Lafran, Fr.†*
Prepared opium (p. 111·3); benzoic acid (p. 1738·2); anise oil (p. 2444·3); camphor (p. 2466·2).
Diarrhoea.

Pareira Brava Composé *Boiron, Fr.*
Pareira brava; berberis vulgaris (p. 2502·1); arsenicum album (p. 2448·1); terebenthina; mercurius corrosivus (p. 2555·2); sarsaparilla (p. 2610·3); solidago virga aurea (p. 2620·1); apocynum cannabinum; uva ursi (p. 2453·2).
Homoeopathic preparation.

Paremyd *Akorn, USA.*
⊗Hydroxyamfetamine hydrobromide (p. 2529·3); tropicamide (p. 2012·2).
Induction of mydriasis with partial cycloplegia.

Parentamin *Serag-Wiessner, Ger.†; Fresenius Kabi, Ital.*
Amino acids.
Parenteral nutrition.

Parentamin E *Serag-Wiessner, Ger.†*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Parentamin X-E *Serag-Wiessner, Ger.†*
Amino acids; electrolytes (p. 1775·1); xylitol (p. 2220·3).
Parenteral nutrition.

Parentamin Hepa *Serag-Wiessner, Ger.†*
Amino acids.
Parenteral nutrition in liver disease.

Parenterin *Legrand, Braz.*
Neomycin sulfate (p. 330·1); phthalylsulfathiazole (p. 339·3); aluminium hydroxide (p. 1817·2); pectin (p. 2200·3).
Diarrhoea.

Parenzyme *Medley, Braz.†*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Inflammation.

Parenzyme Ampicilina *Medley, Braz.*
Ampicillin (p. 218·2).
Bacterial infections; inflammation.

Parenzyme Analgesico *Medley, Braz.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3); paracetamol (p. 115·1).
Inflammation; pain.

Parenzyme Tetraciclina *Medley, Braz.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections; inflammation.

Paretin *Sandoz, Hung.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; anxiety.

Parexat *Spirig, Switz.†*
Paroxetine hydrochloride (p. 440·3).
Depression; anxiety; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder.

Parexel *Zodiac, Braz.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer.

Par-F *Pharmics, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Parfenac *Dermapharm, Austria; Wyeth, Fr.†; Riemser, Ger.†; Home, Port.†; Dermapharm, Switz.*
Bufexamac (p. 30·2).
Skin disorders; burns; insect stings.

Parfeno *LKM, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Pargine *Meda, Fr.*
Arginine aspartate (p. 2049·1).
Retarded growth.

Pargitan *Nevada, Swed.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; spasms in children; drug-induced extrapyramidal disorders.

Pari *Ipca, India.*
Paroxetine hydrochloride (p. 440·3).
Depression; anxiety disorders; obsessive-compulsive disorder; social phobia; premenstrual dysphoric disorder.

Paride *Pharos, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Pariet *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Eisai, China; Eisai, Denm.; Eisai, Fin.; Janssen-Cilag, Fr.; Eisai, Ger.; Janssen-Cilag, Gr.; Eisai, Hong Kong; Janssen-Cilag, Hung.; Eisai, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Ital.; Eisai, Jpn; Eisai, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Eisai, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Eisai, Singapore; Janssen-Cilag, Spain; Eisai, Swed.; Eisai, Switz.; Eisai, Thai.; Janssen-Cilag, Turk.; Eisai, UK; Janssen-Cilag, Venez.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; pathological hypersecretory disorders; gastritis.

Parilac *Teva, Israel.†*
Bromocriptine mesilate (p. 895·3).
Acromegaly; amenorrhoea; galactorrhoea; male and female infertility; parkinsonism; pituitary prolactinoma.

Parina *Pharmasant, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain; peri-articular disorders; tension headache.

Parinix *Richmond, Arg.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Parin-POS *Ursapharm, Ger.*
Heparin sodium (p. 1396·3).
Eye irritation.

Parinvenza *Bruno, Ital.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Paritrel *Trima, Israel.†*
Amantadine hydrochloride (p. 890·3).
Drug-induced extrapyramidal disorders; influenza A; parkinsonism.

Parixam *Apotex, Philipp.†*
Piroxicam (p. 125·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Parizac *Lacer, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcers; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Parkadina *Basi, Port.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza A; Creutzfeldt-Jakob disease.

Parkemed *Pfizer, Austria.*
Mefenamic acid (p. 85·3).
Musculoskeletal and joint disorders; pain; inflammation; fever.

Parkexin *Teuto, Braz.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Parkidopa *Cristalia, Braz.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Parkilyne *Aspen, S.Afr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Parkinane *Eisai, Fr.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Parkinel *Bago, Arg.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Parkinsan *Lundbeck, Ger.*
Budipine hydrochloride (p. 899·2).
Parkinsonism.

Parkinsol *Teuto, Braz.*
Biperiden hydrochloride (p. 895·1).
Parkinsonism.

Parklen *Neo Quimica, Braz.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Parkon *Parkinpharm, Rus.*
Hydrogen peroxide (p. 1755·2).
Epistaxis.

Parkopan *Hexal, Ger.; Hexal, Pol.†; Sandoz, Ukr.†*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Parkotil *Lilly, Ger.†*
Pergolide mesilate (p. 910·2).
Parkinsonism.

Parkyn *Abdi, Turk.*
Pramipexole (p. 911·2).

Parlatos *Perez Gimenez, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Parlax *SERP, Mon.*
Liquid paraffin (p. 2191·2).
Constipation.

Parlazin *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Rus.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria; angioedema.

Parlodel *Novartis, Arg.; Novartis, Austral.; Meda, Austria; Meda, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, China; Meda, Cz.; Paranova, Denm.; Meda, Fin.; Meda, Fr.; Meda, Gr.; Novartis, Hong Kong; Novartis, Indon.; Meda, Irl.; Novartis, Israel†; Meda, Ital.; Novartis, Jpn; Novartis, Malaysia; Sandoz, Mex.; Meda, Neth.; Meda, Norw.; Novartis, Philipp.; Meda, Pol.; Meda, Port.; Meda, Rus.; Novartis, S.Afr.; Novartis, Singapore; Meda, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Meda, UK; Novartis, Ukr.†; Novartis, USA; Novartis, Venez.*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; benign breast disorders; premenstrual disorders; lactation inhibition; polycystic ovary syndrome; acromegaly; menstrual disorders; female infertility; mastalgia; prolactinomas; parkinsonism; male hypogonadism; male infertility; neuroleptic malignant syndrome; galactorrhoea; gynaecomastia; adenomas.

Parmid
Note: this name may be used for preparations of different composition.
Sandoz, UK.
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Parmital *Raffo, Arg.*
Pramipexole (p. 911·2).
Parkinsonism.

Parmodalin *SIT, Ital.*
Tranylcypromine sulfate (p. 450·3); trifluoperazine hydrochloride (p. 1113·2).
Depression.

Parmol *Hovid, Hong Kong; Hovid, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Parnassan *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Polfa Grodzisk, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Par-Natal Plus 1 Improved *Parmed, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Parnate *Link, Austral.; GSK, Braz.; GSK, Canad.; Goldshield, Irl.; Boucher & Muir, NZ; Pharmafrica, S.Afr.; Goldshield, Spain; Covis, USA.*
Tranylcypromine sulfate (p. 450·3).
Depression; anxiety disorders.

Parnavel *Ozone, Rus.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Parnirol *Glenmark, Pol.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Parnon *Svizera, India.*
Trihexyphenidyl hydrochloride (p. 917·3).
Extrapyramidal disorders.

Parnoxil *Biospray, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Paro aux fluorures d'amines Gelee *Esro, Switz.*
Sodium fluoride (p. 2089·2); olaflur (p. 2085·1); dectaflur (p. 2059·1).
Dental caries prophylaxis.

Paro Fluor *Esro, Switz.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Paroc *Hexal, Denm.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Parocetan *Stada, Austria.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; post-traumatic stress disorder; social phobia.

Parocin *Boehringer Ingelheim, Spain.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Parocline *CSP, Fr.*
Minocycline hydrochloride (p. 325·1).
Periodontal infections.

Parodium *K2 Health & Wellness, Chile.*
Chlorhexidine gluconate (p. 1743·3); rhubarb (p. 1884·2); eugenol (p. 2501·2); formaldehyde (p. 1752·2).
Gingivitis; periodontitis.

Rovafarm, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Rus.
Chlorhexidine gluconate (p. 1743·3); rhubarb (p. 1884·2); formaldehyde (p. 1752·2).
Sensitive gums; gum disorders.

Parodontal *Serum-Werk Bernburg, Ger.*
Chamomile (p. 2474·1); sage (p. 2608·3); lidocaine (p. 1988·1).
Mouth inflammation.

Parodontax
Note: this name may be used for preparations of different composition.
Ali, Turk.
Chamomile (p. 2474·1); echinacea (p. 2498·1); sage (p. 2608·3); rhatany (p. 2603·3); sodium bicarbonate (p. 1781·1).
Dental caries prophylaxis.

GSK Consumer, Ital.
Chlorhexidine (p. 1743·2).
Oral hygiene.

Stafford-Miller, Braz.†
Echinacea purpurea (p. 2498·1); sodium bicarbonate (p. 1781·1); chamomile (p. 2474·1); myrrh (p. 2566·1); rhatany root (p. 2603·3); sage (p. 2608·3).
Oral hygiene.

GSK Consumer, Austria.†
Mouthwash: Echinacea purpurea (p. 2498·1); chamomile (p. 2474·1); myrrh (p. 2566·1); menthol (p. 2553·2); clove oil (p. 2481·3); caraway oil (p. 2470·3); sage oil (p. 2609·1); peppermint oil (p. 1877·1); mint oil (p. 2560·1).
Inflammation of the mouth and gums; bleeding gums; oral hygiene.

GSK Consumer, Austria.†
Toothpaste: Echinacea purpurea (p. 2498·1); sodium bicarbonate (p. 1781·1); chamomile (p. 2474·1); myrrh (p. 2566·1); rhatany root (p. 2603·3); sage oil (p. 2609·1); peppermint oil (p. 1877·1).
Dental caries prophylaxis; oral hygiene.

Parodontax Fluor *GSK, Arg.*
Echinacea purpura (p. 2498·1); chamomile (p. 2474·1); sage (p. 2608·3); myrrh (p. 2566·1); rhatany (p. 2603·3); sodium bicarbonate (p. 1781·1); sodium fluoride (p. 2089·2).
Gum disorders.

Parodontocide *Mosfarma, Rus.*
Carnation oil; peppermint oil (p. 1877·1); sage oil (p. 2609·1); sodium fluoride (p. 2089·2); thymol (p. 1772·2); eugenol (p. 2501·2); salol (p. 129·3).
Gingivitis; stomatitis; periodontitis.

Paroex *CSP, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Bacterial mouth infections.

Parogal *Galenus, Gr.*
Meloxicam (p. 86·3).

ParoGen *Generics, Pol.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; anxiety; panic disorder; social phobia; post-traumatic stress disorder.

Parogen *Generics, Hung.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Parogencyl *Procter & Gamble, Ital.*
Metesculetol sodium (p. 2557·3); dexpanthenol (p. 2582·2).
Gum disorders.

Parogencyl Bi-Actif *Rider, Chile.†*
Metesculetol sodium (p. 2557·3); provitamin B.
Gum disorders.

Parogencyl prévention gencives *Procter & Gamble, Fr.†*
Sodium fluoride (p. 2089·2); cetylpyridinium chloride (p. 1743·1); metesculetol sodium (p. 2557·3).
Gum disorders.

Parogencyl sensibilité gencives *Procter & Gamble, Fr.†*
Chlorhexidine gluconate (p. 1743·3); metesculetol sodium (p. 2557·3).
Gum disorders.

Parol
Note: this name may be used for preparations of different composition.
Atabay, Turk.
Paracetamol (p. 115·1).
Fever; pain.

Parol Cold *Atabay, Turk.*
Paracetamol (p. 115·1); phenylpropanolamine (p. 1674·1).
Fever; pain.

Parol Hot *Atabay, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Parolet *Alet, Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Parolex *Hexal, Cz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

ParoLich *Winthrop, Ger.†*
Paroxetine hydrochloride (p. 440·3).
Depression; anxiety disorders; panic attacks; social phobias; post-traumatic stress disorder; obsessive-compulsive disorder.

Paroma *Sanovel, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Paromerck *Generics, Pol.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; anxiety; social phobia; post-traumatic stress disorder; panic disorder.

Paronal *Takeda, Belg.; Takeda, Neth.*
Asparaginase (p. 743·3).
Acute leukaemia; acute lymphocytic leukaemia.

Paronex *Sandoz, Switz.*
Paroxetine hydrochloride (p. 440·3).
Depression; social phobia; panic disorder; obsessive-compulsive disorder; anxiety; post-traumatic stress disorder.

Paroplak *Procter & Gamble, Fr.†*
Chlorhexidine gluconate (p. 1743·3); polysorbate 20 (p. 2203·2); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Parosat *Specifar (Σπεσιφαρ), Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paroser *Apotex, Irl.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder.

Paroteva *Med, Turk.*
Paroxetine (p. 440·3).

Paroticin *Adelco, Gr.*
⊗Fludrocortisone acetate (p. 1634·3); lidocaine hydrochloride (p. 1988·2); polymyxin B sulfate (p. 342·3).
Ear infections.

Parotin *Cipla, Hong Kong; Cipla, India; CTS, Israel.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; mixed anxiety depressive states; post-traumatic stress disorder.

Paroven *Novartis Consumer, Austral.; Novartis Consumer, NZ; Novartis Consumer, S.Afr.†; Novartis Consumer, UK.*
Oxerutins (p. 2505·3).
Chronic venous insufficiency; prevention of skin and mucosal reactions to radiotherapy; haemorrhoids.

Parox
Note: this name may be used for preparations of different composition.
Teuto, Braz.; Rowex, Irl.
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; post-traumatic stress disorder.

Parox Meltab
Note: this name may be used for preparations of different composition.
Saval, Chile.
Paracetamol (p. 115·1).
Fever; pain.

Paroxalon *Krewel, Ger.*
Paroxetine hydrochloride (p. 440·3).
Depression; anxiety; obsessive-compulsive disorder; panic disorder.

Paroxat *Hexal, Austria; Hexal, Ger.†; GSK, Hung.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder; anxiety; panic disorder.

Paroxegen *Ratiopharm, Denm.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paroxetop *Streuli, Switz.†*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paroxia *Medochemie, Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paroxiflex *Stada, Swed.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social anxiety disorder; post-traumatic stress disorder; anxiety.

Paroxin *Pharma Start, Ukr.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paroxinor *Orion, Pol.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Parpicillin *Prafa, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Parsel
Note: this name may be used for preparations of different composition.
Novartis Consumer, Port.
Paracetamol (p. 115·1).
Pain; fever.
Novartis, Mex.; Novartis, Venez.
Dihydroergotamine mesilate (p. 672·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Migraine and other vascular headaches; migraine.

Parselenium E *Nutrilite, Arg.*
Vitamin E succinate (p. 2119·3); selenium yeast (p. 2086·3); parsley (p. 2583·3).
Dietary supplement.

Parsenida *Raam, Mex.*
Nitazoxanide (p. 942·2).
Protozoal infections; worm infections.

Parsenn Crème pour herpès *Parsenn, Switz.*
Rhubarb (p. 1884·2); sage (p. 2608·3).
Herpes labialis.

Parsitan *Erfa, Canad.*
Profenamine hydrochloride (p. 912·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Parsolen *Giempi, Venez.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Parson *Nobel, Turk.*
Pramipexole (p. 911·2).

Partamol *Atlantic, Malaysia; Atlantic, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Partane *Taro, Israel.*
Trihexyphenidyl hydrochloride (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Partial *Vocate, Gr.; Anfarm, Hong Kong.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; inflammatory disorders.

Particol *Prafa, Indon.†*
⊗Hydrocortisone acetate (p. 1640·1); chloramphenicol (p. 257·1).
Infected skin disorders.

Partoben *Purissimus, Arg.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation; immune thrombocytopenic purpura.

Partobulin *Baxter, Austria; Immuno, Austria; Baxter, Cz.; Baxter BioScience, Ger.†; Baxter, Hong Kong; Baxter, Ital.; Baxter, Pol.; Baxter, Rus.; Eczacibasi-Baxter, Turk.; Baxter, UK.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Partogama *Baxter, Braz.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Partogamma *Baxter, Arg.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Partramec *Polpharma, Cz.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Partusisten *Boehringer Ingelheim, Ger.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Rus.*
⊗Fenoterol hydrobromide (p. 1208·2).
Premature labour; fetal distress; obstructive airways disease.

Paruman *Faran, Gr.*
A mumps immunoglobulin (p. 2402·3).
Passive immunisation.

Parvemaxol *Chefaro, Neth.†*
Clotrimazole (p. 576·2).
Tinea pedis.

Parvid *Genesis, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Parvilox *Virgo, Philipp.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Parvisedil *SIT, Ital.*
Aminohydroxybutyric acid (p. 512·1); valerian (p. 2640·2); passion flower (p. 2584·1); chamomile (p. 2474·1); crataegus (p. 2488·1).
Restlessness and insomnia in infants.

Parvlex *Freeda, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals.
Iron-deficiency anaemia.

Parvodex *Jagsonpal, India.*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Parvolex *Mayne, Austral.†; Bioniche, Canad.; IFET (ΙΦΕΤ), Gr.; Mayne, Hong Kong†; UCB, Irl.; Mayne, Malaysia†; Mayne, NZ; Aspen, S.Afr.; Hospira, Singapore†; UCB, UK.*
Acetylcysteine (p. 1652·2).
Paracetamol overdosage; respiratory-tract congestion.

Parvon *Jagsonpal, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Parvon Forte *Jagsonpal, India.*
Dextropropoxyphene hydrochloride (p. 43·3); ibuprofen (p. 68·2).
Formerly contained dextropropoxyphene hydrochloride, diclofenac sodium, and paracetamol.
Musculoskeletal and joint disorders; pain.

Parvon Spas *Jagsonpal, India.*
Dextropropoxyphene hydrochloride (p. 43·3); dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).
Smooth muscle spasm and pain.

Parvon-N *Jagsonpal, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Parxium *Monte Verde, Arg.†*
Pramipexole (p. 911·2).
Parkinsonism.

Parzidim *Sandoz, Singapore.*
Ceftazidime (p. 250·2).
Bacterial infections.

PAS *Kocak, Turk.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

PAS Sodium *Atlantic, Thai.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Pasaden
Note: this name may be used for preparations of different composition.
Bayer, Ital.
Etizolam (p. 1073·2).
Anxiety; insomnia.

Pasalen *Pharmaland, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Pasalix *Marjan, Braz.*
Passion flower (p. 2584·1); salix (p. 129·2); crataegus (p. 2488·1).
Insomnia; anxiety.

Pasang *Pascoe, Spain.*
Passion flower (p. 2584·1).
Insomnia.

Pascalium *Pharmathen, Gr.*
Bromazepam (p. 1041·2).
Anxiety disorders.

Pascallerg *Pascoe, Ger.*
Alumen chromic. (p. 2476·2); acid. formic. (p. 2507·1); gelsemium (p. 2511·2).
Homoeopathic preparation.

Pascodem *Pascoe, Ger.*
Ononis spinosa (p. 2575·3); apis mellifica (p. 2445·2); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Pascoe Calm *Pascoe, UK.*
Passion flower (p. 2584·1).
Anxiety; insomnia.

Pascoe-Agil *Pascoe, Ger.; Globopharm, Switz.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

Pascoe-Agil HOM *Pascoe, Ger.*
Harpagophytum (p. 42·3); arnica (p. 2447·2); bryonia (p. 2461·3); calcium phosphoricum (p. 1784·2); silicea (p. 2208·3).
Homoeopathic preparation.

Pascofemin *Pascoe, Austria.*
⊗Agnus castus (p. 2432·2); cimicifuga (p. 2478·1); caulophyllum thalictroides (p. 2458·2); fraxinus americana; senecio aureus (p. 2612·3); pulsatilla (p. 2600·2); lilium tigrinum; ignatia (p. 2532·1); aletris farinosa; helonias dioica (p. 2524·3).
Homoeopathic preparation.
Pascoe, Ger.
⊗Agnus castus (p. 2432·2); cimicifuga (p. 2478·1); pulsatilla (p. 2600·2); aletris farinosa; helonias dioica (p. 2524·3); lilium tigrinum; ignatia (p. 2532·1); senecio aureus (p. 2612·3); caulophyllum thalictroides (p. 2458·2).
Homoeopathic preparation.

Pascofemin spasmo *Pascoe, Ger.*
Caulophyllum thalictroides (p. 2458·2); viburnum prunifolium (p. 2458·1); colocynthis (p. 1833·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Pascoflair *Pascoe, Austria; Pascoe, Ger.*
Passion flower (p. 2584·1).
Nervous disorders.

Pascoleucyn *Pascoe, Ger.*
Injection: Echinacea (p. 2498·1); aconitum (p. 2428·3); bryonia (p. 2461·3); lachesis (p. 2538·3); sulphur jodatum (p. 2624·2).
Homoeopathic preparation.
Pascoe, Ger.
Tablets: Baptisia (p. 2647·2); bryonia (p. 2461·3); eupatorium perfoliatum (p. 2459·1); thuja (p. 2629·3); lachesis (p. 2538·3).
Homoeopathic preparation.

Pascoleucyn N *Pascoe, Ger.*
Echinacea (p. 2498·1); baptisia (p. 2647·2); eupatorium perfoliatum (p. 2459·1); thuja (p. 2629·3); lachesis (p. 2538·3).
Homoeopathic preparation.

Pascolibrin *Pascoe, Ger.*
Passiflora incarnata (p. 2584·1); ignatia (p. 2532·1); cocculus (p. 2483·1); ambra (p. 2440·3); cimicifuga (p. 2478·1).
Homoeopathic preparation.

Pascomucil *Pascoe, Ger.*
Ispaghula (p. 1849·1).
Constipation.

Pasconal *Pascoe, Austria.*
Avena sativa (p. 2451·1); valeriana officinalis (p. 2640·2); strychnos ignatii (p. 2532·1); tarantula hispanica.
Homoeopathic preparation.

Pasconal Nerventropfen *Pascoe, Ger.*
Avena sativa (p. 2451·1); valeriana (p. 2640·2); ignatia (p. 2532·1); tarantula.
Homoeopathic preparation.

Pasconat *Yuriya-Farm, Rus.; Yuri, Ukr.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Pasconeural-Injektopas *Pascoe, Ger.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Pascopankreat *Pascoe, Ger.*
Combination pack: ⊗Yellow tablets, absinthium (p. 2426·1); condurango (p. 2485·3); red tablets, pancreatin (porcine) (p. 2579·3).
Digestive system disorders.

Pascorbin *Pascoe, Ger.; Optipharm, Gr.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Pascorenal N *Pascoe, Ger.*
Apis mellifica (p. 2445·2); balsam. copaivae; apocynum; equisetum hiem.; helleborus; petroselinum (p. 2583·3); sarsaparilla (p. 2610·3).
Homoeopathic preparation.

Pascorenal-Injektopas *Pascoe, Ger.*
Apis mellifica (p. 2445·2); belladonna (p. 2453·3); cantharis (p. 2469·2); mercurius sublimatus corrosivus (p. 2555·2).
Homoeopathic preparation.

Pascosabal *Pascoe, Ger.*
Sabal serrulatum (p. 2363·3); belladonna (p. 2453·3); colocynthis (p. 1833·3); hydrangea arborescens (p. 2528·1).
Homoeopathic preparation.

Pascosedon *Pascoe, Ger.*
Valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3).
Anxiety; sleep disorders.

Pascosedon Baldrian *Pascoe, Ger.†*
Valerian (p. 2640·2).
Restlessness; sleep disorders.

Pascotox Purpurea *Pascoe, Ger.†*
Echinacea purpurea (p. 2498·1).
Respiratory- and urinary-tract infections.

Pascoventral *Pascoe, Ger.*
Peppermint leaf (p. 1877·1); chamomile (p. 2474·1); caraway (p. 2470·2).
Gastrointestinal disorders.

Pasedon *Lensa, Spain.†*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Pasem *Monserrat, Arg.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Verrucas; warts; callosities.

Paser *Sciencex, Fr.; IFET (ΙΦΕΤ), Gr.; Jacobus, USA.*
Aminosalicylic acid (p. 215·2).
Tuberculosis.

Jacobus, Rus.
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Pasetocin *Kyowa, Jpn.*
Amoxicillin (p. 216·2).
Bacterial infections.

Pas-Fatol N *Riemser, Ger.; Fatol, Rus.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Pasgram *Salvat, Spain.†*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pasic *Cristalia, Braz.*
Passion flower (p. 2584·1); salix (p. 129·2); crataegus (p. 2488·1).
Anxiety.

Pasidor *Cafar, Venez.*
Passion flower (p. 2584·1); valerian (p. 2640·2); crataegus (p. 2488·1).
Anxiety; sleep disorders.

Pasifluidina *Gache, Venez.*
Passion flower (p. 2584·1); valerian (p. 2640·2); crataegus (p. 2488·1).
Nervous disorders; insomnia.

Pasil *Taisho Toyama, Jpn.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Pasilopram *Sandoz, Turk.*
Citalopram (p. 411·1).

Pasinordin *Nordin, Mex.*
Chamomile (p. 2474·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders.

Pask *Farmasintez, Rus.; Skopinski, Rus.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Pask-Akri *Akrikhin, Rus.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Pasminox *Beta, Arg.*
Otilonium bromide (p. 2578·2).
Smooth muscle spasm.

Pasminox Somatico *Beta, Arg.*
Otilonium bromide (p. 2578·2); diazepam (p. 1063·2).
Muscle spasm.

Pasmodil *Collins, Mex.†*
Dipyrone (p. 53·3); butylhyoscine (p. 1845·3).
Fever; pain.

Pasmodina *Drawer, Arg.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Pasmodina Compuesta *Drawer, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Pasmolit *Jofrain, Mex.†*
Homatropine (p. 2007·3).

Pasmovit *Finadiet, Arg.*
Phloroglucinol (p. 2588·2).
Smooth muscle spasm and pain.

Pasodol *Chinta, Thai.†*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Skeletal muscle spasm.

Pasodron *Rider, Chile.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Pasorex *Ratiopharm, Denm.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paspat *Daiichi Sankyo, Ital.*
Lysate of *Staphylococcus aureus*; *Streptococcus mitis*; *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae.*
Respiratory-tract infections.

Nycomed, Mex.
Lysate of *Staphylococcus aureus*; *Staphylococcus albus*; *Streptococcus viridans*; *Streptococcus haemolyticus*; *Streptococcus pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*; *Candida albicans.*
Respiratory-tract infections.

Paspat Oral *Sankyo, Port.*
Staphylococcus aureus; *Streptococcus mitis*; *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae.*
Respiratory-tract infections.

Paspertin *Solvay, Austria; Abbott, Ger.; Abbott, Switz.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; gastro-oesophageal reflux; preparation for gastrointestinal radiography.

Pasport *Sandoz, Turk.*
Tadalafil (p. 2368·1).

Pasquam *Sanbe, Indon.*
Dexpanthenol (p. 2582·2).
Wounds.

Pasrin *Aspen, S.Afr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders; mixed anxiety depressive states.

Passacanthine *Lanpharm, Arg.*
Belladonna (p. 2453·3); convallaria (p. 2486·2); crataegus (p. 2488·1); passion flower (p. 2584·1).
Muscle spasm; nervous disorders.

Passagen *Sandoz, Denm.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Passagix *Obolenskoe, Rus.*
Domperidone (p. 1838·1).
Nausea and vomiting; hiccups; gastrointestinal disorders.

Passaneuro *Bunker, Braz.*
Tablets: Passion flower (p. 2584·1); erythrina mulungu (p. 2564·3); chamomile (p. 2474·1).
Sedative; anxiety.

Bunker, Braz.
Oral suspension: Passion flower (p. 2584·1); erythrina mulungu (p. 2564·3); melissa (p. 2552·3).
Sedative; anxiety.

Passedan *Austroplant, Austria.*
Passion flower (p. 2584·1); melissa leaf (p. 2552·3).
Dystonias; menopausal disorders; sleep disorders.

Austroplant, Cz.†
Passion flower (p. 2584·1); melissa (p. 2552·3); sweet orange peel (p. 2576·2); cinnamon (p. 2479·2).
Nervous-system disorders.

Passédyl *Urgo, Fr.*
Sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1).
Respiratory-tract congestion.

Passibil *Hasco-Lek, Pol.*
Crataegus (p. 2488·1); ginkgo biloba (p. 2512·3); passion flower (p. 2584·1).
Cerebrovascular disorders; mental function impairment; vertigo; nervous disorders.

Passidon *Ardeypharm, Ger.*
Passion flower (p. 2584·1).
Nervous disorders.

Passidorm *DHU, Rus.*
Passiflora incarnata (p. 2584·1); zincum metallicum (p. 2126·1); lupulus (p. 2546·1); eschscholzia californica (p. 2466·1).
Homoeopathic preparation.

Passifit *Farmstandart, Rus.*
Valerian (p. 2640·2); lupulus (p. 2546·1); thyme (p. 2630·2); crataegus (p. 2488·1); mint (p. 1877·1).
Insomnia; nervous disorders.

Passiflor
Note: this name may be used for preparations of different composition.
Phytofarm Kleka, Pol.
Passion flower (p. 2584·1).
Nervous disorders; insomnia.

Sidroga, Switz.
Passion flower (p. 2584·1); crataegus (p. 2488·1).
Sleep disorders.

Passiflora *Tamar, Israel.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); valerian (p. 2640·2); orange flower (p. 2575·3).
Insomnia; nervousness; tension.

Passiflora Complex *Dolisos, Canad.†*
Acidum phosphoricum (p. 2589·1); coffea cruda (p. 2648·2); iamara (p. 2573·3); magnesium (p. 1786·3); nyckterinia; palladium (p. 2579·3); passiflora (p. 2584·1); tellurium.
Homoeopathic preparation.

Hevert, Ger.†
Avena sativa (p. 2451·1); chamomilla (p. 2474·1); cocculus (p. 2483·1); hyoscyamus (p. 2530·2); lupulus (p. 2546·1); passiflora incarnata (p. 2584·1); valeriana (p. 2640·2).
Homoeopathic preparation.

Passiflora Composé *Boiron, Fr.*
Passiflora incarnata (p. 2584·1); ignatia amara (p. 2532·1); coffea cruda (p. 2648·2); nyckterinia; tellurium metallicum; phosphoricum acidum (p. 2589·1); palladium metallicum (p. 2579·3); magnesium metallicum (p. 1786·3).
Homoeopathic preparation.

Passiflora Compound *Vitamed, Israel.†*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Anxiety; insomnia; tension.

Passiflora Curarina *Harras-Curarina, Ger.*
Passion flower (p. 2584·1).
Agitation.

Passiflora GHL *Lehning, Fr.*
Passiflora incarnata (p. 2584·1); avena sativa (p. 2451·1); belladonna (p. 2453·3); secale cornutum (p. 2137·1); valeriana (p. 2640·2).
Homoeopathic preparation.

Passiflorin *Austroplant, Austria.*
Passion flower (p. 2584·1).
Sleep disorders; nervous disorders.

Passiflorine
Note: this name may be used for preparations of different composition.
Karousatos, Gr.; Chiesi, Spain.
Passion flower (p. 2584·1); crataegus (p. 2488·1); salix alba (p. 129·2).
Anxiety; insomnia.

Jolly-Jatel, Fr.
Passion flower (p. 2584·1); crataegus (p. 2488·1).
Insomnia; nervous disorders.

Millet Roux, Braz.; Teofarma, Ital.
Passion flower (p. 2584·1); crataegus (p. 2488·1); salix alba.
Sedative; anxiety; insomnia.

Passiflorum *Zuoz, Venez.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); willow (p. 129·2).
Sleep disorders.

Passifuril *Millet Roux, Braz.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Passin *Simons, Ger.*
Crataegus (p. 2488·1); passion flower (p. 2584·1).
Nervous cardiovascular disorders.

Passinevrol *Elvipe, Gr.*
Valerian (p. 2640·2); passion flower (p. 2584·1); crataegus (p. 2488·1).

Passinevryl *Clement Thionville, Fr.†*
Passion flower (p. 2584·1); crataegus (p. 2488·1); valerian (p. 2640·2).
Insomnia; nervous disorders.

Passionflower Plus *Eagle, Austral.†*
Passion flower (p. 2584·1); valerian (p. 2640·2); skullcap (p. 2617·1); lupulus (p. 2546·1).
Anxiety; insomnia.

Passispasmin *Herbapol Lublin, Pol.*
Crataegus (p. 2488·1); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Passispasmol *Herbapol Lublin, Pol.†*
Crataegus (p. 2488·1); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Passit *Megafyt-R, Cz.*
Valerian (p. 2640·2); melissa (p. 2552·3); passion flower (p. 2584·1).
Nervous disorders.

Pasta Arsenicale *Ogna, Ital.*
⊗Arsenic trioxide (p. 2448·1); lidocaine (p. 1988·1); ephedrine hydrochloride (p. 1663·2).
Dental disorders.

Pasta boli *Spirig, Switz.*
Salicylic acid (p. 1719·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); methyl salicylate (p. 92·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Pasta Cool
Note: this name may be used for preparations of different composition.
Apomedica, Austria.
Heparin sodium (p. 1396·3); salicylic acid (p. 1719·1).
Soft-tissue injury; musculoskeletal and joint disorders; peri-articular disorders.

Volmix, Hung.
Heparin sodium (p. 1396·3); salicylic acid (p. 1719·1); bolus rubra; kaolin (p. 1850·1); melissa oil (p. 2553·2); rosemary oil (p. 2607·3); pumilio pine oil (p. 2591·1).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Pasta Devitalizzante *Ogna, Ital.*
Paraformaldehyde (p. 1763·1); lidocaine (p. 1988·1).
Dental disorders.

Pasta Dicofarm *Dicofarm, Ital.*
Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); vitamin E (p. 2119·1); vitamin F (p. 2509·2).
Skin irritation.

Pasta Di Hoffmann *Sella, Ital.*
Olive oil (p. 2575·1); zinc oxide (p. 1729·1).
Skin disorders.

Pasta Iodoformica Radiopaca *Ogna, Ital.*
Iodoform (p. 1758·2); parachlorophenol (p. 1763·1); camphor (p. 2466·2); menthol (p. 2553·2).
Dental root canal infections.

Pasta Kappa *Italzama, Ital.*
Barrier preparation.

Pasta de Lassar *Andromaco, Mex.; IQFA, Mex.; Quimica y Farmacia, Mex.*
Zinc oxide (p. 1729·1).
Skin disorders; wounds; burns; barrier preparation.

Pasta Lassar *Valma, Chile; Volta, Chile.*
Zinc oxide (p. 1729·1); wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Skin disorders.

Pasta Lassar Imba *Perez Gimenez, Spain.*
Almond oil (p. 2437·1); lanolin (p. 2219·3); zinc oxide (p. 1729·1).
Burns; skin disorders; wounds.

Pastilhas Valda *Canonne, Braz.†*
Menthol (p. 2553·2); cineole (p. 2479·1).
Mouth disorders.

Pastillas De Ambay *Weltrap, Arg.*
Ambay; sulfogaiacol (p. 1678·1).
Cough.

Pastillas Dr Andreu *Bayer, Spain.*
Dextromethorphan hydrobromide (p. 1660·1); sodium benzoate (p. 1738·2).
Cough.

Pastillas Koki Mentol Tirotricina *Perez Gimenez, Spain.*
Benzocaine (p. 1980·2); tyrothricin (p. 384·1); menthol (p. 2553·2).
Mouth and throat disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pastillas Lorbi *GP, Arg.†*
Allantoin (p. 1693·1); benzocaine (p. 1980·2); sulfadiazine (p. 361·3).
Mouth and throat disorders.

Pastillas Medex *Sidus, Arg.*
Tolu balsam (p. 1679·2); benzocaine (p. 1980·2); hexylresorcinol (p. 1755·1); allantoin (p. 1693·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Cough; sore throat.

Pastillas Pagliano *Lafedar, Arg.*
Menthol (p. 2553·2); camphor (p. 2466·2); benzyl alcohol (p. 1739·3); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); tolu balsam (p. 1679·2).
Cough; sore throat.

Pastillas Pectorales Kely *Reckitt Benckiser, Spain.†*
Cineole (p. 2479·1); niaouli oil (p. 2569·1); senega (p. 1677·2); liquorice (p. 1853·2); sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1); terpin monohydrate (p. 1678·2).
Respiratory-tract disorders.

Pastilles bronchiques S *Hanseler, Switz.*
Drosera (p. 2497·2); liquorice (p. 1853·2); ribwort plantain (p. 2604·2); menthol (p. 2553·2); anise oil (p. 2444·3).
Respiratory-tract congestion.

Pastilles contre le mal de gorge *Medibudget, Switz.†*
Cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2); levomenthol (p. 2553·2).
Mouth and throat disorders.

Pastilles Médicinales Vicks *Procter & Gamble, Fr.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); tolu balsam (p. 1679·2); benzyl alcohol (p. 1739·3).
Sore throat.

Pastilles Monléon *Toulade, Fr.†*
Methylthioninium chloride (p. 1559·1); tolu balsam (p. 1679·2); drosera (p. 2497·2); hamamelis (p. 2523·3).
Mouth and throat disorders.

Pastilles pectorales du Dr. Welti *Welti, Switz.*
⊗Benzoic acid (p. 1738·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); lidocaine (p. 1988·1); ipecacuanha (p. 1667·2); senega (p. 1677·2); levomenthol (p. 2553·2); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); liquorice (p. 1853·2).
Cough.

Pastiséról *Bailly, Fr.†*
Guaiacol (p. 1666·1); benzoic acid (p. 1738·2).
Throat irritation.

Pastrizol *DNA, Mex.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Pastylki Wykrztuśne *Medagro, Pol.*
Liquorice (p. 1853·2); sulfogaiacol (p. 1678·1).
Respiratory-tract congestion.

Pasuchaca Vibe *Rička, Hung.*
Geranium dielsianum.
Aid in diabetes mellitus.

Pat *TNP, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Pataday *Alcon, Canad.; Alcon, Hong Kong; Alcon, Israel; Alcon, Malaysia; Alcon, Philipp.; Alcon, USA.*
Olopatadine hydrochloride (p. 636·2).
Allergic conjunctivitis.

Patanase *Alcon, USA.*
Olopatadine hydrochloride (p. 636·2).
Allergic rhinitis.

Patanol *Alcon, Arg.; Alcon, Austral.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Hong Kong; Alcon, Indon.; Alcon, Israel; Kyowa, Jpn; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.; Alcon, USA; Alcon, Venez.*
Olopatadine hydrochloride (p. 636·2).
Allergic conjunctivitis.

Patar Com *Patar, Thai.*
Vitamin B substances (p. 2102·3).

Patar 3 B *Patar, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Patar Cough Capsule *Patar, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Patar E-400 *Patar, Thai.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; vitamin E supplement.

Patar Enema *Patar, Thai.*
Sodium chloride (p. 1795·1).
Constipation.

Patar 88 Enema *Patar, Thai.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

Patar Kal *Patar, Thai.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Patar lotion *Patar, Thai.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); camphor (p. 2466·2).
Pruritus.

Patar-B-Fer *Patar, Thai.*
Vitamins; minerals; iron (p. 2073·1).

Patar-cap *Patar, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Patarcolate *Patar, Thai.*
Ox bile salts (p. 2457·2); cascara (p. 1826·1); phenolphthalein (p. 1877·3); capsicum (p. 2469·3).
Constipation.

Patardium *Patar, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Patargesic *Patar, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Patarlin *Patar, Thai.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Patarpain *Patar, Thai.*
Methyl salicylate (p. 92·1); eugenol (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Patarphen *Patar, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Patarsul *Patar, Thai.*
Cascara (p. 1826·1); nux vomica (p. 2573·3); asafetida (p. 2449·3); ginger (p. 1844·1); capsicum (p. 2469·3); amylase (p. 2442·1).
Constipation.

Patartim *Patar, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Patarvate-C *Patar, Thai.*
⊗Betamethasone valerate (p. 1624·1); clioquinol (p. 273·1).
Infected skin disorders.

Patarvate-N *Patar, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin (p. 329·3).
Infected skin disorders.

Patarver *Patar, Thai.*
Diiodohydroxyquinoline (p. 931·1); catechu (p. 2472·3); thymol (p. 1772·2).
Diarrhoea.

Patarvit *Patar, Thai.*
Vitamins; with or without lysine (p. 2079·3).

Pataxel *Vianex (Βιανεξ), Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Pat-Chobet *Chobet, Arg.*
Animal tissue extracts (brain, spleen, liver, and skin) (p. 2444·1).
Liver disorders.

Pâte Suisse *Lehning, Fr.†*
Levomenthol (p. 2553·2); sodium benzoate (p. 1738·2).
Throat irritation.

Patecs *Nipro, China.*
Indometacin (p. 71·2).

Patector *Techsphere, Arg.; Carnot, Mex.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Endometriosis; menstrual disorders; female infertility; injectable contraceptive; endometrial hyperplasia.

Patentex *Merz, Austria; Merz, Fin.; Diapharm, Gr.; Merz, Hong Kong†; Merz, Hung.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Patentex Oval *Merz Consumer, Ger.; Riemser, Ger.; Merz, Pol.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Patentex Oval N *Merz, Cz.†; Merz, Rus.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Pâtes Pectorales *Boiron, Fr.*
Aconitum (p. 2428·3); drosera (p. 2497·2); bryonia (p. 2461·3); ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Patiox *MDM, Ital.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Patir *Rafa, Israel.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Patox *Wermar, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Patral *Mahakam Beta, Indon.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Patrex *Pfizer, Mex.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Patriflex *Largen, Philipp.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Patrol *Wassermann, Ital.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Patroxin *Patar, Thai.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer; goitre.

Patryl *Biolink, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Patum *Picco, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Patuxan *Collins, Mex.†*
Vitamins.

Pauly *Nutricia, Ital.*
Gluten-free foods for special diets.

Pausafren T *Finadiet, Arg.*
Oxazepam (p. 1092·2).
Menopausal disorders.

Pausanil *Sofar, Ital.*
Pomegranate (p. 164·1); cimicifuga (p. 2478·1).
Menopausal disorders.

Pausanol *Leiras, Fin.*
Estriol (p. 2274·3).
Oestrogen deficiency; menopausal vaginal disorders.

Pausedal
Note: this name may be used for preparations of different composition.
Alter, Port.
Colecalciferol (p. 2113·1); calcium pidolate (p. 1784·3).
No indics.
Alter, Spain.
Levosulpiride (p. 1108·1).
Dyspepsia.

Pausene *Theramex, Ital.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; cyproterone acetate (p. 2261·2).
Menopausal disorders; osteoporosis.

Pausigin *Angelini, Port.*
Estriol (p. 2274·3).
Vulvovaginal disorders.

Pausogest *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.†*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Pavacol-D *Alliance, UK.*
Pholcodine (p. 1675·1).
Cough.

Pavedal *Pharma Investi, Chile.*
⊗Metolazone (p. 1434·1).
Ascites; heart failure; hypertension; nephrotic syndrome; oedema.

Paver *Wermar, Mex.*
Pravastatin (p. 1473·1).
Hyperlipidaemias.

Pavertrin *Duncan, Arg.*
Idebenone (p. 392·3).
Cerebrovascular disorders.

Paverysat forte N *Ysatfabrik, Ger.†*
Greater celandine (p. 2522·2).
Biliary-tract and gastrointestinal spasm.

Paverysat L *Ysatfabrik, Ger.*
Taraxacum (p. 2625·3).
Reduced appetite; biliary-tract disorders.

Paviria *TNP, Thai.*
Aciclovir (p. 964·1).
Herpes simplex skin infections.

Pavivac *Sevapharma, Cz.*
A mumps vaccine (Jeryl Lynn strain) (p. 2402·3).
Active immunisation.

Pavlinox *Medicus, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Pavulon *Organon, Arg.; Organon, Austral.†; Organon, Braz.†; Schering-Plough, Chile; MSD, China; Organon, Cz.; Organon, Fin.†; MSD-Chibret, Fr.†; Organon (Οργανον), Gr.; MSD, Hong Kong; Schering-Plough, Indon.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Neth.†; Organon, Philipp.†; Organon, Rus.; Sanofi-Aventis, S.Afr.†; MSD, Singapore†; MSD, Swed.†; Essex, Switz.†; MSD, Thai.†; Organon, Turk.; Schering-Plough, Turk.; Organon, Venez.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Pax *Aspen, S.Afr.*
Diazepam (p. 1063·2).
Anxiety; premedication; alcohol withdrawal syndrome; status epilepticus; skeletal muscle spasm.

Paxabel *Marvecs, Ital.*
Macrogol 4000 (p. 2547·3).
Constipation.

Paxadorm *Thebe, S.Afr.*
Nitrazepam (p. 1089·1).
Insomnia.

Paxam *Alphapharm, Austral.; Mylan, NZ.*
Clonazepam (p. 519·1).
Epilepsy.

Paxan *Biosintetica, Braz.*
Paroxetine (p. 440·3).
Depression.

Paxapride *Sandoz, Arg.*
Cinitapride (p. 1831·3).
Dyspepsia; gastrointestinal motility disorders; gastro-oesophageal reflux.

Paxel
Note: this name may be used for preparations of different composition.
Intas, Philipp.
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell cancer.
Ceapharma, Port.†
Donepezil hydrochloride (p. 390·2).
Alzheimer's dementia.

Paxeladin *Beaufour-Ipsen, Ukr.*
Oxeladin citrate (p. 1671·2).
Cough.

Paxéladine *Ipsen, Fr.*
Oxeladin citrate (p. 1671·2).
Cough.

Paxene *Mayne, Belg.†; Norton, Cz.†; Faulding, Fr.†; Norton, Gr.; Pharmachemie, Gr.; Norton, Hung.†; Ivax, Irl.†; Norton, Neth.†; Mayne, Port.†; Ivax, Rus.; Combino, Spain†; Mayne, Swed.†; Mayne, UK.†*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paxera *Ali, Turk.*
Paroxetine hydrochloride (p. 440·3).

Paxeratio *Ratiopharm, Pol.†*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia.

Paxetil *Medibial, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; post-traumatic stress disorder.

Paxical *Intramed, S.Afr.†*
Droperidol (p. 1072·1).
Premedication; neuroleptanalgesia; nausea and vomiting.

Paxicam *Danpac, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Paxidal
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.†
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain and associated tension.
Wallace Mfg Chem., UK.†
Caffeine (p. 1203·3); meprobamate (p. 1083·3); paracetamol (p. 115·1).

Paxidorm *Pharmaserve, Singapore; Norma, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Paxil *GSK, Arg.; GSK, Braz.; GSK, Canad.; GSK, Jpn; GSK, Mex.; GSK, Rus.; GSK, S.Afr.; GSK, Turk.; Apotex, USA; GSK, Venez.*
Paroxetine hydrochloride (p. 440·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; premenstrual dysphoric disorder.

Paxilfar *Tecnifar, Port.*
Tramadol hydrochloride (p. 139·2).
Pain.

Paximol *ICM, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Paxinol *GSK, Gr.*
Paroxetine hydrochloride (p. 440·3).

Paxiprid *Fako, Turk.*
Amisulpride (p. 1036·3).

Paxirasol *Egis, Cz.; Egis, Hung.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Paxital *Medicamerc, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Paxitas *Accord, S.Afr.*
Paclitaxel (p. 839·3).

Paxium *Jaba Recordati, Port.*
Chlordiazepoxide (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; muscle spasm.

Paxoll *Venus, Thai.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; AIDS-related Kaposi's sarcoma; non-small cell lung cancer.

Paxon
Note: this name may be used for preparations of different composition.
Gador, Arg.
Losartan potassium (p. 1422·2).
Hypertension; heart failure.
Saval, Chile.
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Paxon D *Gador, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Paxoral *Farmasa, Braz.*
Lysate of: *Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Diplococcus pneumoniae; Klebsiella pneumoniae; Klebsiella ozaenae; Moraxella catarrhalis; Haemophilus influenzae.*
Respiratory-tract infections.

Paxotin *Adeka, Turk.*
Paroxetine hydrochloride (p. 440·3).

Paxpar *Merck, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Paxt *WPR, Irl.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety disorders; post-traumatic stress disorder.

Paxtibi *Biomed, Spain.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Paxtin *Sandoz, Pol.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Paxtine *Alphapharm, Austral.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Paxtrat *Uniao Quimica, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Paxum *East India Pharma, India.*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal syndrome; muscle spasm; insomnia; premedication; status epilepticus; tetanus.

Paxus *Kalbe, Indon.*
Paclitaxel (p. 839·3).
Ovarian cancer; non-small cell lung cancer; breast cancer.

Paxxet *Trima, Israel.*
Paroxetine hydrochloride (p. 440·3).
Depression; mixed anxiety depressive states; panic disorders; obsessive-compulsive disorder; social phobia.

Paxyl
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Austral.
Lidocaine hydrochloride (p. 1988·2); benzalkonium chloride (p. 1737·1); allantoin (p. 1693·1).
Burns; insect bites; sunburn; windburn; chapped skin.

Pazbronquial *Cinfa, Spain.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); sodium benzoate (p. 1738·2); sodium citrate (p. 1781·2); sulfogaiacol (p. 1678·1); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); menthol (p. 2553·2); drosera (p. 2497·2); lobelia inflata (p. 2323·2); oregano (p. 2576·3); grindelia (p. 2522·3).
Cough.

Pazergicel *Proel, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Pazeril *Novendia, Gr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Pazital *Gebro, Spain.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Pazo *Bristol-Myers Products, USA.*
⊗Benzocaine (p. 1980·2); ephedrine sulfate (p. 1663·2); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Haemorrhoids.

Pazol XS *Stratus, USA.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Scalp disorders.

Pazolam *Atral, Port.*
Alprazolam (p. 1035·2).
Anxiety disorders; mixed anxiety depressive states; panic disorder.

Pazolexa *Medico Uno, Hung.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pazolini *Faria, Braz.†*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Pazucross *Mitsubishi Tanabe, Jpn.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

PB Gel *Lagos, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

PB-Hyos *Kylemore, USA.*
Phenobarbital (p. 535·2); atropine sulfate (p. 1310·2); hyoscyamine sulfate (p. 1848·1); hyoscine hydrobromide (p. 1845·3).

PBM Allergy *Boca, USA.†*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

PC *Grin, Mex.*
⊗Glycerol (p. 2517·2).
Dry eyes.

PC-20 *Millimed, Thai.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

PC 30 V *Cheplapharm, Ger.*
Aesculus (p. 2431·2); dexpanthenol (p. 2582·2); chamomile (p. 2474·1).
Skin disorders; wounds; ulcers.
Proreo, Switz.
Allantoin (p. 1693·1); dexpanthenol (p. 2582·2); chamomile (p. 2474·1); aesculus (p. 2431·2).
Skin ulcers; barrier preparation.

PC 30 N *Terra-Bio, Ger.†*
Chamomile (p. 2474·1).
Burns; skin disorders.

PCA (18F) *PET, Denm.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide agent for assessment of regional glucose metabolism by positron emission tomography.

P-Canyl *Osoth, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

PC-Cap *Alra, USA.†*
Dextropropoxyphene hydrochloride (p. 43·3); aspirin (p. 22·2); caffeine (p. 1203·3).

PCE *Methapharm, Canad.; Abbott, USA.*
Erythromycin (p. 291·2).
Bacterial infections.

P-Cillin V *PP Lab, Thai.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

PCM
Note: this name may be used for preparations of different composition.
Cypress, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Rhinitis.

PCP *Xepa-Soul Pattinson, Singapore.*
Prochlorperazine maleate (p. 1098·3).
Vertigo; nausea and vomiting; anxiety; psychoses.
Tack Fung, Hong Kong.†
Prochlorperazine (p. 1098·2).

PC-Tar *Geritrex, USA.*
Coal tar (p. 1723·2).
Scalp disorders.

PDF *Pharmascience, Canad.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

PDP Liquid Protein *Wesley, USA.*
Tryptophan (p. 453·2); hydrolysed animal collagen (p. 2483·2).
Dietary supplement.

PE Tann/CP Tann *Brighton, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Peace *YSP, Malaysia.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Peacef *Yung Shin, Singapore.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Pearinda *Pharma Dynamics, S.Afr.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Pearinda Plus *Pharma Dynamics, S.Afr.*
⊗Perindopril (p. 1466·3); indapamide (p. 1409·2).

Pearls IC *Enzymatic Therapy, USA.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium breve* (p. 2596·3).
Maintenance of gastrointestinal flora.

Pearsol *Pearson, Ital.*
Pyrethrum (p. 2161·1).
Insecticide.

Pebegal *Probiomed, Mex.*
Benzonatate (p. 1656·2).
Cough.

Pebiot *Mavi, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

PEC *Universal, Hong Kong.*
⊗Promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2); codeine phosphate (p. 40·2).
Cough.

Pecasolin *Rafarm, Gr.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Pe-Ce *Gebro, Austria.†*
Turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar leaf oil (p. 2629·3); camphor (p. 2466·2); thymol (p. 1772·2).
Cough and cold symptoms.

Peceve *Ipex, Swed.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

PecFent *Archimedes, Cz.; Archimedes, Fr.; Archimedes, Ger.; Archimedes, Irl.; Archimedes, Neth.; Archimedes, Port.; Archimedes, Spain; Archimedes, UK.*
⊗Fentanyl citrate (p. 60·1).
Pain.
Molteni, Pol.
⊗Fentanyl (p. 60·1).
Pain.

Pecivax *Farmaceutica H, Mex.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Pecof *Glenmark, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with bronchospasm.

Pecol *Casen Fleet, Port.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Pecolin *Universal, Hong Kong.†*
⊗Codeine (p. 40·2); ephedrine (p. 1663·1); promethazine (p. 638·2).

PE-CPM-MSN *Kylemore, USA.*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pectapas *Pascoe, Ger.*
Crataegus (p. 2488·1); cactus (p. 2473·2); spigelia (p. 2621·3); valeriana (p. 2640·2).
Homoeopathic preparation.

Pectapas CPL *Pascoe, Ger.*
Crataegus (p. 2488·1); cactus (p. 2473·2); spigelia (p. 2621·3); cuprum (p. 2057·1).
Homoeopathic preparation.

Pectapas SL *Pascoe, Ger.*
Crataegus (p. 2488·1); cactus (p. 2473·2); spigelia (p. 2621·3); glonoinum (p. 1391·2); magnesium phosphoricum (p. 1787·3).
Homoeopathic preparation.

Pectin-K *MDI, S.Afr.†*
Kaolin (p. 1850·1); apple pectin (p. 2200·3).
Diarrhoea.

Pecto-Baby *Vifor, Switz.†*
Guaifenesin (p. 1666·2); pholcodine (p. 1675·1); chlorphenamine maleate (p. 620·3).
Cough.

Pectobonisol *Bonimed, Pol.*
Echinacea purpurea (p. 2498·1); liquorice (p. 1853·2); peppermint leaf (p. 1877·1); ribwort plantain (p. 2604·2); thyme (p. 2630·2); tilia (p. 2631·3).
Respiratory-tract disorders.

Pectobron *Sidus, Arg.*
Sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2); calcium hypophosphite (p. 2530·3); sodium hypophosphite (p. 2530·3); potassium hypophosphite (p. 2530·3); senega (p. 1677·2); tolu balsam (p. 1679·2).
Bronchitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pectobronc *Lafi, Chile.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pectobronc Plus *Lafi, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Pectocalmine Junior N *Vifor, Switz.*
Codeine phosphate (p. 40·2).
Cough.

Pectocalmine N *Vifor, Switz.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); ephedrine hydrochloride (p. 1663·2); opium (p. 111·3); senega (p. 1677·2).
Cough and associated respiratory-tract disorders.

Pectocil *Ethica, Indon.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Pectocor N *Riemser, Ger.*
Camphor (p. 2466·2).
Cardiac disorders.

Pectoderme *Plantes et Medecines, Fr.†*
α-Pinene (p. 2591·3); β-pinene (p. 2591·3); terpineol (p. 2627·2); eugenol (p. 2501·2); cineole (p. 2479·1).
Respiratory-tract congestion.

PectoDrill *Pierre Fabre, Irl.; Pierre Fabre, Pol.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Pectodrill *Pierre Fabre, Cz.; Pierre Fabre, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Pectoflorine *Lehning, Fr.†*
Mallow (p. 2549·2); erysimum (p. 2524·2); grindelia (p. 2522·3); althaea (p. 2438·3); thyme (p. 2630·2); verbascum (p. 2645·1); Scots pine (p. 2591·1).
Respiratory-tract disorders.

Pectofree *Novum, Neth.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pectokast *Knop, Chile.*
⊗Sodium salicylate (p. 132·2); sodium bromide (p. 2461·1); alcohol (p. 1733·1); thyme (p. 2630·2); liquorice (p. 1853·2); aesculus (p. 2431·2); ipecacuanha (p. 1667·2).
Cough.

Pectolin *Synco, Hong Kong†; Synco, Singapore.*
Light kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Pectolvan C *Farmak, Ukr.*
Ambroxol hydrochloride (p. 1654·3); carbocisteine (p. 1658·1).
Respiratory-tract disorders with viscous mucus.

Pectolvan Hedera *Farmak, Ukr.*
Ivy (p. 2536·2).
Inflammatory disorders of the respiratory tract.

Pectolvan Phyto *Farmak, Ukr.*
Elecampane (p. 1662·3); Iceland moss (p. 2531·2); soapwort (p. 2617·2); hyssop (p. 2530·3); thyme (p. 2630·2).
Respiratory-tract disorders.

Pectolvan Stop *Farmak, Ukr.*
Butamirate citrate (p. 1657·3); guaifenesin (p. 1666·2).
Cough.

Pectomucil *Qualiphar, Belg.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous secretions; paracetamol poisoning.

Pectoral
Note: this name may be used for preparations of different composition.
Mepha, Ukr.
Plantain (p. 2592·3); thyme (p. 2630·2); primula (p. 2596·2); senega (p. 1677·2).
Respiratory-tract congestion.

Pectoral Hebert *Fecofar, Arg.*
Clofedanol hydrochloride (p. 1659·1); bromhexine hydrochloride (p. 1656·3).
Cough.

Pectoral Lafedar *Lafedar, Arg.*
Sulfogaiacol (p. 1678·1); oxeladin (p. 1671·2).
Cough.

Pectoral Lafedar Niños *Lafedar, Arg.*
Sulfogaiacol (p. 1678·1).
Cough.

Pectoral N *Mepha, Switz.*
Plantain (p. 2592·3); cowslip (p. 2596·2); senega (p. 1677·2); thyme (p. 2630·2).
Cough; cold symptoms.

Pectoral Pasteur *Pasteur, Chile.*
Sodium benzoate (p. 1738·2); ammonium chloride (p. 1656·1); drosera (p. 2497·2); liquorice (p. 1853·2).
Respiratory-tract disorders.

Pectorales Elixir *Biosintez, Rus.*
Ammonia (p. 2441·2); anise oil (p. 2444·3); liquorice (p. 1853·2).
Respiratory-tract disorders.

Pectorales Species No 1 *Microgen, Rus.; Zdorovje, Rus.*
Althaea (p. 2438·3); oregano (p. 2576·3); coltsfoot (p. 1659·2).
Respiratory-tract disorders.

Pectorales Species No 2 *Microgen, Rus.; Zdorovje, Rus.*
Coltsfoot (p. 1659·2); plantain (p. 2592·3); liquorice (p. 1853·2).
Respiratory-tract disorders.

Pectorales Species No 3 *Lek, Rus.; Zdorovje, Rus.*
Althaea (p. 2438·3); aniseed (p. 2444·2); liquorice (p. 1853·2); pine buds; sage (p. 2608·3).
Respiratory-tract disorders.

Pectorales Species No 4 *Krasnogorskleksredstva, Rus.; Zdorovje, Rus.*
Rhododendron tomentosum (p. 2550·1); calendula (p. 2465·2); peppermint leaf (p. 1877·1); chamomile (p. 2474·1); liquorice (p. 1853·2); viola tricolor.
Respiratory-tract disorders.

Pectorex Mucolytique *Iromedica, Switz.*
Carbocisteine (p. 1658·1).
Cough; bronchitis with viscous mucous.

Pectosan Toux Sèche *Cooperation Pharmaceutique, Fr.†*
Syrup: Ethylmorphine hydrochloride (p. 56·3).
Cough.

Pectosol *Herbapol Pruszkow, Pol.*
Hyssop (p. 2530·3); elecampane (p. 1662·3); Iceland moss (p. 2531·2); soapwort (p. 2617·2); thyme (p. 2630·2).
Cough; respiratory-tract congestion.

Pectosorin *Richter, Austria.†*
Sulfogaiacol (p. 1678·1).
Cough; catarrh; bronchitis.

Pectox *Sanofi-Aventis, Arg.; Italfarmaco, Spain; Iromedica, Switz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Knop, Chile.
Ivy (p. 2536·2); eucalyptus (p. 2501·1).
Respiratory-tract disorders.

Pectramin *Streuli, Switz.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Pectrolyte *Adcock Ingram, S.Afr.*
⊗Kaolin (p. 1850·1); pectin (p. 2200·3); chloroform and morphine tincture (p. 92·3); sodium lactate (p. 1781·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Diarrhoea.

Pectum *Solas, Indon.*
Cimicifuga (p. 2478·1); grindelia (p. 2522·3); ginger (p. 1844·1); betel; liquorice (p. 1853·2); thyme (p. 2630·2); honey (p. 2072·1).
Cough.

Pectusin *Farmstandart, Rus.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders.

Pectyl *Nycomed, Denm.*
⊗Opium (p. 111·3); benzoic acid (p. 1738·2); camphor (p. 2466·2); glycerol (p. 2517·2).
Coughs.

P.E.D. *Universal, Hong Kong.†*
⊗Dextromethorphan (p. 1660·1); ephedrine (p. 1663·1); promethazine (p. 638·2).

Pedab *Otto, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Pedamed *Rice Steele, Irl.*
Zinc undecenoate (p. 596·3); zinc oxide (p. 1729·1); alum (p. 2439·1); allantoin (p. 1693·1); chlorhexidine hydrochloride (p. 1743·3).
Fungal infections.

Pedcee *Medica Pedia, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Pedea *Orphan, Austria; Orphan, Belg.; Orphan, Cz.; Orphan, Denm.; Orphan, Fr.; Orphan, Ger.; IFET (ΙΦΕΤ), Gr.; Orphan, Irl.; Orphan, Ital.; Orphan, Neth.; Orphan Europe, Norw.; Orphan, Pol.; Orphan Europe, Port.; Nycomed, Rus.; Tema, S.Afr.; Orphan, Spain; Orphan Europe, Swed.; Orphan, UK; Merckle, Ukr.*
Ibuprofen (p. 68·2).
Closure of patent ductus arteriosus.

Ped-Element *Darrow, Braz.†*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

Pedia Care Childrens Decongestant *Pfizer Consumer, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Pedia Relief Cough-Cold *Major, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

PediaCare Allergy Formula *McNeil Consumer, USA.*
Chlorphenamine maleate (p. 620·3).

PediaCare Childrens Cold & Allergy *Pfizer Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold symptoms.

PediaCare Childrens Cough & Congestion *Medtech, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

PediaCare Childrens Cough & Sore Throat *Medtech, USA.*
Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

PediaCare Childrens Long-Acting Cough *Pfizer Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

PediaCare Childrens Long-Acting Cough Plus Cold *Pfizer Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

PediaCare Childrens Multi-Symptom Cold *Pfizer Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

PediaCare Childrens Pain Reliever Fever Reducer IB *Medtech, USA.*
Ibuprofen (p. 68·2).
Fever; pain.

PediaCare Cold & Flu Hydration *Medtech, USA.*
Vitamin C (p. 2110·3); electrolytes (p. 1775·1).

PediaCare Cough-Cold *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

PediaCare Infant's Decongestant *McNeil Consumer, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

PediaCare Infants Long-Acting Cough *Pfizer Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

PediaCare Infants Pain Reliever Fever Reducer *Medtech, USA.*
Ibuprofen (p. 68·2).
Fever; pain.

PediaCare NightRest Cough-Cold Formula *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Pediacel *Sanofi Pasteur, Austral.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Israel; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Mex.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Port.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.; Sanofi Pasteur, UK.*
A diphtheria, tetanus, pertussis (acellular), poliomyelitis (inactivated), and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Pediachlor *Pediatrica, Philipp.*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Pediacof *Sanofi Winthrop, USA.*
Codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); potassium iodide (p. 2336·3).
Coughs.

Pedia-Col
Note: this name may be used for preparations of different composition.
Greater Pharma, Thai.
Syrup: Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Greater Pharma, Thai.
Tablets: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Pediacol
Note: this name may be used for preparations of different composition.
Euro-Pharm, Canad.
Simeticone (p. 1886·2).
Infant colic.

Pediaderm *Andromaco, Chile.*
Cod-liver oil (p. 2056·3); vitamin A (p. 2098·3); colecalciferol (p. 2113·1); boric acid (p. 2459·3); zinc oxide (p. 1729·1).
Burns; skin irritation; wounds.

pediaderm AF *Arbor, USA.*
Nystatin (p. 590·3).
Fungal skin infections.

pediaderm TA *Arbor, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Pediaflex *Flamingo, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Pediaflor *Ross, USA.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis in children.

Pediafortan *Medi-Rx, Philipp.*
Vitamins.
Nutritional supplement.

Pediafortan Forte *Medi-Rx, Philipp.*
Lysine hydrochloride (p. 2079·3); taurine (p. 2626·2); vitamins.
Nutritional supplement.

Pediafortan Forte-GE *Medi-Rx, Philipp.*
Lysine hydrochloride (p. 2079·3); taurine (p. 2626·2); chlorella (p. 2475·3); vitamins.
Nutritional supplement.

Pediafortan-AS *Medi-Rx, Philipp.*
Buclizine hydrochloride (p. 618·3); vitamins.
Appetite stimulant; tonic.

Pediafortan-C *Medi-Rx, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Pediagrow *Ethica, Indon.*
Vitamins; glutamic acid (p. 2070·2); lysine hydrochloride (p. 2079·3); fatty acids.
Nutritional supplement.

Pediahist DM *Boca, USA.*
Syrup: ⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).

Boca, USA.†
Oral drops: ⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pedia-Lax *Fleet, Hong Kong; Fleet, USA.*
Chewable tablets: Magnesium hydroxide (p. 1857·2).
Constipation.

Fleet, Hong Kong; Fleet, USA.
Oral liquid: Docusate sodium (p. 1836·2).
Constipation.

Fleet, USA.
Enema: Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

Fleet, USA.
Oral strips: Senna (p. 1885·1).
Constipation.

Fleet, USA.
Suppositories: ⊗Glycerol (p. 2517·2).
Constipation.

Pedialyte *Abbott, Austral.; Abbott, Canad.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium citrate (p. 1780·3); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Abbott, Braz.; Abbott, Indon.; Abbott, Philipp.; Abbott Nutrition, Singapore†; Abbott, USA; Abbott, Venez.
Electrolytes (p. 1775·1); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy; vomiting.

Abbott, Chile.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Abbott, Hong Kong†; Abbott, NZ.
Glucose (p. 2068·3); sodium (p. 1795·1); potassium (p. 1793·1); chloride; citrate (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Abbott, Turk.†
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Pedialyte FOS *Abbott, Mex.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); fructo-oligosaccharides (p. 2508·1) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Pedialyte Mild *Abbott, Philipp.*
Electrolytes (p. 1775·1).
Oral rehydration therapy.

Pedialyte SR *Abbott, Mex.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium citrate (p. 1780·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Pediamin *Liferpal, Mex.*
Vitamins.

Pediamino PLM *Braun, Chile.*
Amino acids.
Parenteral nutrition.

Pediamox *Pediatrica, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pediaphen *Euro-Pharm, Canad.*
Paracetamol (p. 115·1).
Pain; fever.

Pediaplex *Medica Pedia, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion; sinusitis; otitis media.

Pediapred *Sanofi-Aventis, Canad.; UCB, USA.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Pediaprofen *Laboratorios Chile, Chile.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Pediarix *GSK, USA.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and recombinant hepatitis B vaccine (p. 2386·1).
Active immunisation.

Pediasea *Recalcine, Chile.*
Sodium chloride (p. 1795·1).
Nasal cleansing.

PediaSure *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Indon.; Abbott, Israel; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Pol.†; Abbott, Venez.*
Preparation for enteral nutrition in children.

Abbott, Canad.; Abbott, Hong Kong; Abbott, Ital.; Abbott Nutrition, Singapore; Abbott, Thai.; Abbott, Turk.
Preparation for enteral nutrition.

Abbott Nutrition, USA.
Lactose-free preparation for enteral nutrition in children.

Pediatan *Proethic, USA.†*
Chlorphenamine tannate (p. 620·3).

Pediatan D *Proethic, USA.†*
Chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Pediatapp *PediaCare, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); brompheniramine maleate (p. 618·1).
Nasal congestion; rhinitis.

Pediatex *Zyber, USA.*
Carbinoxamine maleate (p. 619·1) or carbinoxamine tannate.
Allergic rhinitis.

Pediatex-D *Zyber, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract disorders.

Pediatex-DM *Zyber, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs; upper respiratory-tract disorders.

Pediatric Electrolyte *Pendopharm, Canad.*
Glucose (p. 2068·3); fructose (p. 2068·2); potassium citrate (p. 1780·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2) (p. 1780·1).
Diarrhoea; oral rehydration solution.

Pediatrim *PediaCare, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pediatrivite *Seroyal, Canad.†*
Vitamins; minerals.

Pediatrix *Teva, Canad.*
Paracetamol (p. 115·1).
Pain; fever.

Pediaven *AGEPS, Fr.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Pediavent *PediaCare, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders with excess mucus and bronchospasm.

Pediavit *Euro-Pharm, Canad.*
Vitamins; with or without minerals.

Pediavit 3 *Farcoral, Mex.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); ascorbic acid (p. 2110·3).
Nutritional supplement.

Pediavit Select *Euro-Pharm, Canad.*
Vitamins; ferrous sulfate (p. 2062·2).

Pediaxil *Flamingo, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pediazole *Methapharm, Canad.; Abbott, Gr.; Amdipharm, Gr.; IFET (ΙΦΕΤ), Gr.; Abbott, Israel†; Abbott, Mex.; Ross, USA.†*
Erythromycin ethyl succinate (p. 291·2); acetyl sulfafurazole (p. 364·1).
Otitis media.

Pédiazole *Bioprojet, Fr.*
Erythromycin ethyl succinate (p. 291·2); acetyl sulfafurazole (p. 364·1).
Otitis media.

Pedibene *Ratiopharm, Austria.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Pedi-Boro Soak Paks *Pedinol, USA.†*
Aluminium sulfate (p. 2440·2); calcium acetate (p. 1783·1).
Skin irritation.

Pedibu *Zuoz, Venez.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Pedic *Stadmed, India.*
Vitamins; lysine (p. 2079·3); zinc (p. 2126·1).
Vitamin deficiency in infants and children.

Pedicrem *Prieto, Arg.*
Permethrin (p. 2159·3).
Scabies.

Pediderm
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Deltamethrin (p. 2152·1).
Pediculosis; scabies.

Pedi-Dri *Pedinol, USA.*
Nystatin (p. 590·3).
Candidiasis.

Pedifan *Vilco, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Pedifen *Atabay, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Pedikurol *Ratiopharm, Austria.*
Clotrimazole (p. 576·2).
Fungal skin and nail infections.

Pediletan *Cimed, Braz.*
Lindane (p. 2157·1).
Pediculosis.

Pediletan Permetrina *Cimed, Braz.*
Permethrin (p. 2159·3).

Pedilin
Note: this name may be used for preparations of different composition.
KRKA, Rus.†; KRKA, Ukr.
Malathion (p. 2157·2).
Pediculosis.

Mecom, Turk.
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Respiratory-tract congestion.

Pedilin Ko *KRKA, Rus.†; KRKA, Ukr.†*
Tetramethrin (p. 2162·2); piperonyl butoxide (p. 2160·2).
Pediculosis.

Pedilis *Metiska, Indon.*
Syrup: Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Pedi-Lotion *Mediphar, Venez.*
Lotion: Benzalkonium chloride (p. 1737·1); menthol (p. 2553·2).
Hyperhidrosis.

Mediphar, Venez.
Topical powder: Benzalkonium chloride (p. 1737·1); menthol (p. 2553·2); camphor (p. 2466·2); zinc oxide (p. 1729·1).
Hyperhidrosis.

Pedimat *Sandoz, Turk.*
Paracetamol (p. 115·1); phenobarbital (p. 535·2).
Fever; pain.

Pedimed
Note: this name may be used for preparations of different composition.
Flora, Hung.
MEA, disodium undecylenamido sulfosuccinate (p. 596·3); irgasan DP-100; benzoxonium chloride (p. 1739·2).
Fungal nail infections.

Adcock Ingram, S.Afr.†
Aluminium oxide (p. 1690·3); magnesium oxide (p. 1857·3); methylpolysiloxane (p. 1886·2).
Flatulence associated with hyperacidity.

Pedimed Foot Care Cream *Pierre Fabre Sante, Singapore.*
Piroctone olamine (p. 1716·3); tocoferil nicotinate (p. 1516·1); ruscus (p. 2463·1).
Foot care in diabetes.

Pedimin *Metiska, Indon.*
Vitamins.
Nutritional supplement.

Pediotic *Monarch, USA.†*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial ear infections.

Pediox *Atley, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Pediox-S *Atley, USA.†*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Pedipar *Adeka, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Pedipirox *Hi-Tech, USA.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Pedi-Pro *Pedinol, USA.*
Benzalkonium chloride (p. 1737·1); menthol (p. 2553·2).
Formerly contained aluminium chlorohydrate, chloroxylenol, menthol, and zinc undecenoate.
Skin infections.

Pedipur *Prolab, Pol.*
Methenamine (p. 322·3); zinc oxide (p. 1729·1); talc (p. 1722·2).
Hyperhidrosis.

Pediron *ST, Thai.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia in infants and children; iron supplement.

Pedisol *Fischer, Israel.†*
Cream: Triclosan (p. 1773·2); panthenol (p. 2582·2); chamomile (p. 2474·1); wool fat (p. 2219·3).
Dry skin; hard skin.

Fischer, Israel.†
Topical spray: Undecenoic acid (p. 596·3); aluminium chlorohydrate (p. 1694·1); menthol (p. 2553·2); purified talc (p. 1722·2).
Foot odour and perspiration.

Peditrace *Fresenius Kabi, Austria; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Baxter, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Irl.; Pharmacia, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Singapore; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK.*
Trace elements.
Parenteral nutrition.

Peditral *RPG, India.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Oral rehydration therapy.

Peditus *Sandoz, Turk.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Pedituss Cough *Major, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); potassium iodide (p. 2336·3).
Coughs.

Pediur *Lyofin, Gr.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).

Pedivit *Unique, Rus.†*
Vitamins; minerals.

Pedi-Vit-A *Pedinol, USA.*
Vitamin A (p. 2098·3).
Irritated or dry skin.

Pedopur *Jacoby, Austria.*
Grape (p. 2521·3).
Peripheral vascular disorders.

Pedoz *Hamilton, Austral.*
Tetrabromocresol (p. 1771·3); undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); zinc oxide (p. 1729·1).
Tinea pedis; foot odour.

Pedpain *Columbia, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Pedrin *Aroma, Turk.*
⊗Guaifenesin (p. 1666·2); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract congestion.

Pedryl *Gap, Gr.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; lambliasis; anaerobic bacterial infections.

PedTE-PAK *SoloPak, USA.†*
Trace elements.
Parenteral nutrition.

Pedtrace *American Pharmaceutical, USA.†*
Trace elements.
Parenteral nutrition.

PedvaxHIB *MSD, Austral.; MSD, Braz.; Merck Frosst, Canad.; MSD, China; MSD, Hong Kong†; MSD, Indon.;*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

MSD, Mex.; MSD, Pol.; MSD, Thai.; MSD, Turk.; Merck, USA.
A haemophilus influenzae conjugate vaccine (meningococcal protein conjugate) (p. 2387·2).
Active immunisation.

Pedvitin *Greater Pharma, Thai.*
Vitamins.

Pedzinc Plus C *Gruppo Medica, Philipp.*
Vitamin C (p. 2110·3); zinc (p. 2126·1).
Dietary supplement.

Peerless Composition Essence *Potter's, UK.*
Oak bark (p. 2574·1); pinus canadensis; poplar bark (p. 2450·3); prickly ash bark (p. 2650·1); bayberry bark (p. 2453·1).
Colds.

Pefamic *PP Lab, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Pefbid *Alembic, India.*
Pefloxacin (p. 338·1).
Bacterial infections.

Peflacin *Sanofi-Aventis, Braz.; Sanofi-Aventis, Ital.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Peflacina *Aventis, Mex.†*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Peflacine *Sanofi-Aventis, Gr.; Egis, Hung.†; Sanofi-Aventis, Indon.; Egis, Pol.; Sanofi-Aventis, Port.†; Aventis, Thai.; Eczacibasi, Turk.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Péflacine *Sanofi-Aventis, Fr.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Peflocin *Darnitsa, Ukr.†*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Peflox *Formenti, Ital.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Pefloxabol *Abolmed, Rus.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Pefrakehl *Sanum-Kehlbeck, Ger.*
Candida parapsilosis.
Homoeopathic preparation.

Péga *Bailleul, Fr.†*
Potassium and arginine phosphocitroglutamate.
Asthenia.

Pegalax *Medical Futures, Canad.*
Macrogol 3350 (p. 2547·3).
Constipation.

Peganix *Baliarda, Arg.*
⊗Piroxicam (p. 125·3); prednisone (p. 1647·2).
Musculoskeletal and joint disorders.

Peganone *Lundbeck, USA.*
Ethotoin (p. 521·3).
Epilepsy.

Pegasys *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, USA; Roche, Venez.*
Peginterferon alfa-2a (p. 989·2).
Chronic hepatitis C; chronic hepatitis B.

Pegasys RBV *Roche, Austral.; Roche, Canad.; Roche, NZ; Roche, Philipp.*
Injection, peginterferon alfa-2a (Pegasys) (p. 989·2); tablets, ribavirin (Copegus) (p. 1010·2).
Chronic hepatitis C.

Pegatron *MSD, Austral.; MSD, NZ.*
Capsules, ribavirin (Rebetol) (p. 1010·2); injection, peginterferon alfa-2b (PEG-Intron) (p. 989·2).
Chronic hepatitis C.

Pegetron *Merck, Canad.*
Capsules, ribavirin (p. 1010·2); injection, peginterferon alfa-2b (p. 989·2).
Chronic hepatitis C.

PE/GG *Kylemore, USA.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pegicol *Norgine, S.Afr.; Norgine, Switz.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Pegina *Potter's, UK.*
Calumba (p. 2466·1); calamus (p. 2464·2); compound cardamom tincture (p. 2471·1); magnesium sulfate (p. 1787·3); magnesium trisilicate (p. 1858·1); rhubarb (p. 1884·2).
Dyspepsia; flatulence.

PegIntron *MSD, Austral.; Schering-Plough, Austria; MSD, Belg.; Schering-Plough, Braz.; Schering-Plough, Chile; MSD, China; Schering-Plough, Cz.; MSD, Denm.; Schering-Plough, Fin.; MSD, Ger.; Schering-Plough, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.; Schering, USA; Schering-Plough, Venez.*
Peginterferon alfa-2b (p. 989·2).
Chronic hepatitis C; chronic hepatitis B.

MSD, Jpn.
Interferon alfa-2b (p. 989·2).
Chronic hepatitis C.

Peglasta *Roche, Malaysia; Kyowa Hakko, Philipp.; Kyowa, Singapore; Kyowa Hakko Kirin, Thai.*
Pegfilgrastim (p. 1152·1).
Neutropenia.

PegLax *Casen Fleet, UK.*
Macrogol 4000 (p. 2547·3).
Constipation.

Peglax *Floris, Israel.*
Macrogol 3350 (p. 2547·3).
Constipation; haemorrhoids; anal fissure.

Peglyte
Note: this name may be used for preparations of different composition.
Pendopharm, Canad.; Pharmascience, Singapore.
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Pharmascience, Hong Kong.
Electrolytes (p. 1775·1).
Gastrointestinal lavage.

Pegorion *Orion, Fin.*
Macrogol 4000 (p. 2547·3).
Constipation.

Pegtron *Schering-Plough, Mex.*
Peginterferon alfa-2b (p. 989·2).
Chronic hepatitis C.

Pegtron Cotronak Kit *Schering-Plough, Mex.*
Injection, peginterferon alfa-2b (p. 989·2); capsules, ribavirin (p. 1010·2).
Chronic hepatitis C.

Pehacain *Phapros, Indon.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Pehachlor *Phapros, Indon.*
Chlorphenamine maleate (p. 620·3).
Allergic disorders.

Pehacort *Phapros, Indon.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Pehadoxin *Phapros, Indon.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pehamoxil *Phapros, Indon.*
Amoxicillin (p. 216·2).
Bacterial infections.

Pehastan *Phapros, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Pehatrim *Phapros, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pehavask *Phapros, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Pehavral *Phapros, Indon.*
Vitamins; minerals.

PE-HCL-CPM-MSN *Kylemore, USA.*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

PE-Hist DM *Larken, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pei Bi Jia *Guojia, China.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).

Pei Er Ji *Chang An, China.*
L-Alanyl-L-glutamine (p. 2070·2).
Parenteral nutrition.

Pei Xin *Baotou, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Peidolax *Casen Fleet, Ukr.*
⊗Glycerol (p. 2517·2).
Constipation.

Peifeikang *Sine, China.*
Bifidobacteria; *Lactobacillus acidophilus* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).
Restoration of intestinal flora; diarrhoea.

Peifu *Hailing, China.*
Faropenem sodium (p. 298·2).
Bacterial infections.

Peifuren *Unicorn, China.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Peindol *Giempi, Venez.*
Ketoprofen (p. 79·1).
Inflammation; pain.

PeiNing *Kangmei, China.*
Propiverine hydrochloride (p. 2363·1).
Neurogenic bladder.

Peitel *Ferrer, Spain.*
⊗Prednicarbate (p. 1645·1).
Skin disorders.

Peitil *Peili, China.*
Glucosamine sulfate (p. 2515·3).

Peitoral Martel *Hertz, Braz.*
Guaifenesin (p. 1666·2); pinho (p. 2591·1); honey (p. 2072·1); agriao; guaco.

PeiXin *Xinlibang, China.*
Octreotide acetate (p. 1924·1).

Pekaso *Kenyaku, Hong Kong.†*
Mefenamic acid (p. 85·3).
Pain.

Pekiron *Kyorin, Jpn.*
Amorolfine hydrochloride (p. 569·1).
Fungal skin infections.

Pektodin *Pasifik, Turk.†*
⊗Ephedrine hydrochloride (p. 1663·2); sulfogaiacol (p. 1678·1).
Respiratory-tract congestion.

Pektrol *KRKA, Rus.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Pelargon *Nestle, Ital.*
Infant feed.
Gastrointestinal disorders.

Pelastin *Sanbe, Indon.*
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Peledox *Novartis Consumer, Spain.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Pelethrocin *Help, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Help, Pol.
Diosmin (p. 2505·2).
Venous insufficiency.

PeleVerus Clear *CellEra, USA.*
Zinc acetate (p. 2126·1).

Pelidren *Actavis, Denm.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Pelikair *Nycomed, Belg.†*
Ketoconazole (p. 585·3).
Fungal scalp disorders.

Pellexeme *Coup, Gr.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Pelmec *Casasco, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Pelmec Duo *Casasco, Arg.*
Amlodipine besilate (p. 1304·1); benazepril hydrochloride (p. 1314·3).
Hypertension.

Pelmec Max *Casasco, Arg.*
Tablets, amlodipine besilate (p. 1304·1); tablets, losartan potassium (p. 1422·2).
Hypertension.

Pelmec Max D *Casasco, Arg.*
⊗Tablets, amlodipine besilate (p. 1304·1) (Pelmec); tablets, losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2) (Loplac-D).
Hypertension.

Pelmec Plus *Casasco, Arg.*
Amlodipine besilate (p. 1304·1); atorvastatin (p. 1309·2).
Angina pectoris; hypertension; hyperlipidaemias.

Pelo Libre *GSK, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Pelo Libre Protectora *GSK, Arg.*
Acetic acid (p. 2426·3).
Pediculosis.

Pelogel *Sulphur Zdroj, Pol.*
Myrtillus (p. 2566·2); peppermint oil (p. 1877·1).
Periodontitis; gingivitis.

Pelox *Wockhardt, India; Wockhardt, Ukr.†*
Pefloxacin (p. 338·1).
Bacterial infections.

Wockhardt, Rus.
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Pelsana Med *Schmidgall, Austria.*
Bath oil: Sunflower oil (p. 2098·1); undecenoic acid (p. 596·3).
Skin disorders.

Schmidgall, Austria.
Topical powder: Zinc undecenoate (p. 596·3).
Skin disorders.

Pelsano *Iromedica, Switz.*
Bath additive: Sunflower oil (p. 2098·1); undecenoic acid (p. 596·3).
Skin disorders.

Iromedica, Switz.
Ointment: Sunflower oil (p. 2098·1); dexpanthenol (p. 2582·2).
Skin disorders.

Pelsano Med *Penta, Hung.*
Bath additive: Sunflower oil (p. 2098·1); undecenoic acid (p. 596·3).
Dry skin disorders.

Penta, Hung.
Ointment: Sunflower oil (p. 2098·1); dexpanthenol (p. 2582·2).
Dry skin disorders.

Pelset Plus *Muskus, Venez.*
⊗Pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1); urea (p. 1727·3).
Scalp disorders.

Peltazon *Aska, Jpn.*
⊗Pentazocine hydrochloride (p. 120·3). Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Pelusarl *Isei, Jpn.*
Oxazolam (p. 1093·1).
Anxiety states; premedication; sleep disorders.

Pelvichthol N *Ichthyol, Ger.†*
Ictasol (p. 1706·1); benzyl nicotinate (p. 29·3).
General pelvic symptoms.

Pelvicillin NF *Temis, Arg.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Pelvimag *Code, Fr.*
Onion (p. 2575·2); magnesium carbonate (p. 1856·2); maltodextrin (p. 2080·3); aesculus (p. 2431·2).
Urinary-tract disorders; pelvic disorders.

Pelzont *MSD, Austria†; MSD, Cz.†; MSD, Irl.†; MSD, Neth.†; MSD, Pol.†; MSD, Port.†*
Nicotinic acid (p. 2083·1); laropiprant (p. 2540·3).
Hyperlipidaemias.

Pemar *Medipharm, Chile.*
Piroxicam (p. 125·3).
Inflammation; pain.

Pemidal *Polfa Pabianice, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Pemine *Lilly, Ital.*
Penicillamine hydrochloride (p. 1567·1).
Wilson's disease; lead poisoning; gold poisoning; cystinuria; rheumatoid arthritis.

Pemirox *Santen, Hong Kong; Santen, Thai.*
Pemirolast potassium (p. 1218·2).
Allergic eye disorders.

PE-Mix *Fresenius Kabi, Austria.†*
Amino acids; carbohydrates; electrolytes (p. 1775·1); lipids (as soya oil (p. 2092·3)).
Contains egg lecithin.
Parenteral nutrition.

Pemix
Note: this name may be used for preparations of different composition.
Almirall, Mex.
Cinitapride acid tartrate (p. 1831·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Pemol *Chinta, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Pemtrex *Kocak, Turk.*
Pemetrexed disodium (p. 844·3).

Pemzek *AstraZeneca, Switz.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Pemzek Plus *AstraZeneca, Switz.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pemzo *Aspen, Austral.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pen di Ben *Bago, Arg.*
Benzathine benzylpenicillin (p. 227·2). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pen Mega *1A, Ger.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Pen Oral *Sanofi-Aventis, Arg.*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Penachlor *Dynamic, Philipp.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Penadur *Vesale, Belg.; Wyeth, Gr.; Wyeth, Philipp.†; Wyeth, Turk.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Penadur 6.3.3 *Wyeth, Turk.*
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Penagon *Metiska, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Peñagrande *Ahimsa, Arg.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penam *Jeil, Philipp.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Penamox *Sanfer, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Penamox M *Sanfer, Mex.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Penaten
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Ger.
Thyme oil (p. 2630·3).
Respiratory-tract disorders.

Penatone *CCM, Malaysia.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Penbak *Eczacibasi, Turk.*
Bacampicillin (p. 225·2).
Bacterial infections.

Penbene *Ratiopharm, Austria; Ratiopharm, Cz.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penbeta *Betapharm, Ger.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penbiosyn *Medi-Rx, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Penbiotic *Bernofarm, Indon.†*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Penbisin *Ulagay, Turk.†*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Penbritin *GSK, Indon.†; GSK, Irl.†; Hormona, Mex.; GSK, S.Afr.†; Chemidex, UK.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.
SmithKline Beecham, Philipp.
Ampicillin trihydrate (p. 218·2).
Bacterial infections.
GSK, Thai.†
Ampicillin (p. 218·2).
Bacterial infections.

Penbritin Ex *Hormona, Mex.*
Ampicillin trihydrate (p. 218·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Penbrosol *Solvang, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); brompheniramine maleate (p. 618·1).
Nasal congestion; rhinitis.

Pencain K *Bilim, Turk.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).

Pencarv *General Drugs House, Philipp.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Pencial *Biomed, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Pencid *Zentiva, Cz.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Pencil 400 *Prodotti, Braz.†*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pencil B *Prodotti, Braz.†*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Pencil P *Prodotti, Braz.†*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pencilin-V *Teuto, Braz.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Pencip *Cipla, India.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pencla *Penmix, Thai.†*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Penclen *Zentiva, Cz.*
Penamecillin.
Bacterial infections.

Penclox *Pisa, Mex.*
Dicloxacillin sodium (p. 286·1).
Bacterial infections.

Pencom *Alembic, India.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Pencor *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Pencotrex *Hua, Thai.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

PENcream *Humco, USA.*
Pharmaceutical base.

Pencrist *Fako, Turk.†*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pencroftonum *Farmsintez, Rus.*
Mifepristone (p. 2138·1).
Termination of pregnancy.

Pendepon Compositum *Biotika, Cz.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Pendex *Cypress, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pendiben Compuesto *Pisa, Mex.†*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2); benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Pendiben L-A *Pisa, Mex.†*
Benzylpenicillin (p. 228·1).
Bacterial infections.

Pendine *Alphapharm, Austral.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Pendium *Galenus, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Pendrex *Rowex, Irl.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Pendrex Plus *Rowex, Irl.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Pendrox *Intas, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Pendysin *Infectopharm, Ger.*
Benzathine benzylpenicillin (p. 227·2). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Chronic streptococcal infections; syphilis.

Penecare *Reed & Carnrick, USA.*
Emollient.

Penecort *Allergan, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Penedil *Teva, Israel.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Penegra *Zydus, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Penem *M & H, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Pener *Unison, Thai.*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Penester *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Penetaat DraxImage *Draximage, Neth.†*
Technetium-99m pentetate (p. 2228·1).
Radionuclide imaging agent.

Penetrating Rub *Golden Pride, Canad.†; Rawleigh, Canad.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1); expressed mustard oil (p. 2646·1).

Penetro *Daudt, Braz.*
Inhalation: Terpineol (p. 2627·2); cineole (p. 2479·1); menthol (p. 2553·2); benzoic acid (p. 1738·2).
Respiratory-tract congestion.

Penezil *Lyofin, Gr.*
Donepezil hydrochloride (p. 390·2).

Penfantil *Klonal, Arg.*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Penfill N *Novo Nordisk, Jpn.†*
⊗Isophane insulin (human, recombinant) (p. 475·3).
Diabetes mellitus.

Penfill R *Novo Nordisk, Jpn.†*
⊗Insulin injection (human, recombinant) (p. 475·3).
Diabetes mellitus.

Penfill 10R, 20R, 30R, 40R, 50R *Novo Nordisk, Jpn.†*
⊗Mixtures of insulin injection (human, recombinant) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human, recombinant) 90%, 80%, 70%, 60%, and 50% respectively (p. 475·3).
Diabetes mellitus.

Penfixteva *Med, Turk.*
Pentoxifylline (p. 1465·3).

Penfri *Ethica, Indon.*
Ginseng (p. 2513·3); borneol (p. 2460·2); dioscorea rhizome; geranium herb; herba erodii; rhizoma menispermi.
Musculoskeletal and soft-tissue pain and inflammation.

Pen-G *PP Lab, Thai.*
Benzylpenicillin (p. 228·1).
Bacterial infections.

Pengesic *Hovid, Malaysia; Hovid, Philipp.; Hovid, Singapore.*
Tramadol hydrochloride (p. 139·2).
Pain.

Pengesod *Grunenthal, Mex.†*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Penglobe *AstraZeneca, India; AstraZeneca, Philipp.†; AstraZeneca, Thai.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Pengon *Elpen (Ελπεν), Gr.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Penhance *Sel-J, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Penhexal *Hexal, Ger.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penhexal VK *Sandoz, Austral.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penibiot *Normon, Spain.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Penibrin *Sandoz, Israel; SLE, Israel.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Penicigran *Legrand, Braz.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penicil *Rimsa, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Penicillin G Procaine Fortified *Panpharma, Hong Kong.†*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Penicina *Epicaris, Arg.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penicomb *Chrispa (Χρισπα), Gr.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Penidural *Astellas, Neth.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Penidure *Wyeth, India.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Penigra *Hasco-Lek, Pol.*
Guarana (p. 2648·2); muira-puama; schisandra (p. 2611·2); saw palmetto (p. 2363·3); zinc monomethionine.
Male impotence.

Penikin *Radyum, Turk.†*
⊗Caffeine (p. 1203·3); metamizole (p. 53·3); ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Penilan *Vitoria, Port.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Penilente LA *Biotech, S.Afr.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Penilevel *Ern, Spain.*
Capsules; oral sachets: Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Ern, Spain.
Injection: Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Penilevel Retard *Ern, Spain.*
Benzylpenicillin sodium (p. 228·2); benzathine benzylpenicillin (p. 227·2); phenoxymethylpenicillin calcium (p. 338·3).
Bacterial infections; rheumatic fever.

Penilfedrin P *Lersan, Arg.†*
Benzylpenicillin potassium (p. 228·2).
Bacterial eye infections.

Penimex *Unique, Ukr.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Peni-Oral *Vesale, Belg.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penipastil *Casel, Turk.*
Cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Penipot *Antibioticos, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Penisodina *Pisa, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Penisol *Teva, Mex.†*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Penkain-K *Bilim, Turk.†*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Penkaron *Ariston, Braz.*
Benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Pen-Kera *Ascher, USA.*
Emollient and moisturiser.

Penlac *Valeant, Canad.; Valeant, USA.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Penles *Nitto Denko, Jpn.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Penlol *Pose, Thai.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

PenMix 10, 20, 30, 40, or 50 *Novo Nordisk, NZ.*
⊗Mixtures of insulin injection (human) 10%, 20%, 30%, 40%, or 50% and isophane insulin (human) 90%, 80%, 70%, 60% or 50% respectively (p. 475·3).
Diabetes mellitus.

Penmox *Coronet, Indon.*
Amoxicillin (p. 216·2).
Bacterial infections.

Pennsaid *Paladin, Canad.; Vianex (Βιανεξ), Gr.; Italchimici, Ital.; Dimethaid, Port.; Dimethaid, UK.*
Diclofenac sodium (p. 48·3).
Osteoarthritis.

Nuvo, USA.
Diclofenac (p. 48·3).
Osteoarthritis.

Penodex *Rotexmedica, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Penodil *Remedica, Hong Kong.†*
Ampicillin (p. 218·2).
Bacterial infections.

Penoksil *Akdeniz, Turk.*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Penomax *Orion, Denm.; Orion, Fin.; Orion, Norw.; Orion, Swed.*
Pivmecillinam hydrochloride (p. 342·2).
Urinary-tract infections; salmonellosis.

Penomor *Blooming Fields, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Penopen *Remedica, Singapore.*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Penopril *Elpen (Ελπεν), Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pen-Os *Eczacibasi, Turk.; Sandoz, Turk.*
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Penoza *Elpen (Ελπεν), Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Penprocilina *Lakeside, Mex.†*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Penpurin *Elpen (Ελπεν), Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Pen-Rafa VK *Rafa, Israel.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penrazol *Elpen (Ελπεν), Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Penrazole *Elpen, Singapore.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; gastrointestinal hypersecretion.

Penrite *Columbia, S.Afr.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Pensilina *Tum, Turk.†*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pensiral *Serral, Mex.*
Pentoxifylline (p. 1465·3).
Cerebrovascular disorders.

Pensodil *Loeffler, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Pensordil *Elpen (Ελπεν), Gr.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Penstad *Stada, Austria.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penstapho *BMS, Belg.; BMS, Ital.*
Oxacillin sodium (p. 336·2).
Gram-positive bacterial infections.

Pensulan *Andromaco, Chile.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); zinc oxide (p. 1729·1); aluminium hydroxide (p. 1817·2).
Skin infections.

Pensulvit *SIFI, Ital.*
Tetracycline (p. 373·1); sulfamethylthiazole (p. 367·3).
Bacterial eye infections.

Penta
Note: this name may be used for preparations of different composition.
Elpen (Ελπεν), Gr.
Mefenamic acid (p. 85·3).

Fonte, Switz.†
Salol (p. 129·3); thymol (p. 1772·2); menthol (p. 2553·2); peppermint oil (p. 1877·1); anise oil (p. 2444·3).
Mouth and throat disorders; oral hygiene.

Tulip, Ukr.†
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger Ellison syndrome; gastritis; dyspepsia.

Penta-3B *Sandoz, Canad.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; alcoholism; vitamin B supplement.

Penta-3B + C *Sandoz, Canad.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ascorbic acid (p. 2110·3).
Neuritis; alcoholism; vitamin supplement.

Penta-3B Plus *Sandoz, Canad.*
Vitamins.

Pentabufen *Mosfarma, Rus.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3); dipyrone (p. 53·3); phenobarbital (p. 535·2).
Pain.

Pentacard *Altana, China; Darya-Varia, Indon.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Pentacarinat *Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Aventis, Gr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; JHC Healthcare, UK; Armour, USA.*
Pentamidine isetionate (p. 944·3).
Pneumocystis pneumonia; leishmaniasis; African trypanosomiasis.

Pentacel *Sanofi Pasteur, Canad.*
Vial, a haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate)(Act-HIB); ampoule, a diphtheria, tetanus, pertussis, and poliomyelitis vaccine (Quadracel) (p. 2385·3).
Active immunisation.

Sanofi Pasteur, USA.
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Pentacin
Note: this name may be used for preparations of different composition.
Darya-Varia, Indon.†
Azapentacene sulfonate sodium (p. 2451·3).
Cataract.

Pentacis *CIS, Fin.; CIS, Fr.; CIS, Irl.; CIS, Port.; CIS, Spain; Schering, UK.*
Technetium-99m (p. 2228·1) pentetate trisodium and calcium.
Radionuclide imaging agent.

Pentacol *Sofar, Ital.*
Mesalazine (p. 1859·2).
Crohn's disease; ulcerative colitis.

Pentacrin *Elpen (Ελπεν), Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Pentact-HIB *Sanofi Pasteur, Hong Kong†; Aventis Pasteur, Israel; Aventis Pasteur, Philipp.†; Medatek, Turk.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Sanofi Pasteur, Chile.†
Vial, a haemophilus influenzae conjugate vaccine (Act-HIB); syringe diphtheria, tetanus, pertussis, and poliomyelitis vaccine (Tetracoq) (p. 2385·3).
Active immunisation.

Pentaderm *Crawford, UK.*
5-Methoxypsoralen (p. 1714·1).
Vitiligo; psoriasis; eczema; mycosis fungoides; polymorphic light eruption; solar urticaria.

Pentaerythritol Compositum *Galena, Pol.*
Pentaerithrityl tetranitrate (p. 1465·1); glyceryl trinitrate (p. 1391·2).
Heart failure.

Pentaferr *Pentafarma, Chile.*
Sodium ferric gluconate complex (p. 2089·1).
Iron-deficiency anaemia.

Pentaflucin *Uralbiopharm, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); diphenhydramine (p. 626·1); rutoside (p. 2505·3).
Cold symptoms.

Pentagab *Generics, Denm.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Pentagin *Daiichi Sankyo, Jpn.*
⊗Pentazocine (p. 120·3) or pentazocine hydrochloride (p. 120·3).
Naloxone hydrochloride (p. 1562·3) is included in the tablets to discourage abuse.
Pain.

Pentaglobin *Biogam, Arg.; Biotest, Austria; Pentafarma, Chile; Biotest, Cz.†; Biotest, Ger.; Biotest, Gr.; Biotest, Hong Kong; Biotest, Hung.; Biotest, Ital.; Pisa, Mex.; Biotest, Pol.; Biotest, Rus.; Mednostica, S.Afr.†; Biotest, Singapore; Biotest, Thai.; Kansuk, Turk.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immunodeficiency; hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome; thrombocytopenia.

Pentaker *Pentamedical, Ital.*
Amino acids; vitamins; minerals; linseed oil (p. 2544·2); astaxanthin (p. 2170·1); pine.
Dietary supplement for hair and nails.

Pental *Kansuk, Turk.*
Thiopental sodium (p. 1915·1).
General anaesthesia; raised intracranial pressure in ventilated patients.

Pentalac *UCI, Braz.*
Lactulose (p. 1850·3).

Pentalgin
Note: this name may be used for preparations of different composition.
Leksredstva, Rus.
Paracetamol (p. 115·1); naproxen (p. 98·2); caffeine (p. 1203·3); drotaverine hydrochloride (p. 2497·3); pheniramine maleate (p. 637·2).
Pain; cold symptoms; smooth muscle spasm.

Pentalgin Plus *Leksredstva, Rus.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); phenobarbital (p. 535·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain; fever.

Pentalgin-N *Farmstandart, Rus.*
Dipyrone (p. 53·3); naproxen (p. 98·2); phenobarbital (p. 535·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Pentaloc *Cadila, India.*
Pantoprazole (p. 1875·3).
Peptic ulcer.

Pentalong *Actavis, Cz.; Actavis, Ger.†*
Pentaerithrityl tetranitrate (p. 1465·1).
Angina pectoris.

Pentalox *Delta, Braz.*
Pentoxifylline (p. 1465·3).

Pentam *IFET (ΙΦΕΤ), Gr.; American Pharmaceutical, USA.*
Pentamidine isetionate (p. 944·3).
Pneumocystis pneumonia.

Pentamin *Dalkhimfarm, Rus.*
Azamethonium bromide (p. 1313·1).
Peripheral vascular disorders; hypertension; oedema; controlled hypotension; aid in cystoscopy.

Pentamina *Hospira, Port.†*
Pentamidine isetionate (p. 944·3).
Pneumocystis pneumonia; trypanosomiasis; leishmaniasis.

Pentamol *Penta, Ger.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Pentamycetin *Sandoz, Canad.*
Chloramphenicol (p. 257·1).
Eye infections.

Pentamycetin-HC *Sandoz, Canad.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Eye and ear infections.

Pentarim *Rimsa, Mex.*
Thiopental (p. 1915·1).
General anaesthesia.

Pentasa *Ferring, Arg.; Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Ferring, Chile; Gynopharm, Chile; Ferring, China; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Gerolymatos, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Irl.; Ferring, Israel; Ferring, Ital.; Kyorin, Jpn; Ferring, Malaysia; Ferring, Mex.; Ferring, Neth.; Ferring,*

Norw.; Pharmaco, NZ; Ferring, Philipp.; Ferring, Pol.; Ferring, Port.; Ferring, Rus.; Ferring, S.Afr.; Ferring, Singapore; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, Thai.; Ferring, Turk.; Ferring, UK; Ferring, Ukr.; Shire, USA.
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Pentased *Kharkov, Ukr.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3); phenobarbital (p. 535·2); codeine phosphate (p. 40·2).
Pain; fever.

Pentasone *Sandoz, Canad.*
⊗Gentamicin sulfate (p. 304·2); betamethasone sodium phosphate (p. 1623·3).

Pentaspan *BMS, Canad.; Du Pont, USA.*
⊗Pentastarch (p. 1146·1).
Plasma volume expansion; leucapheresis.

Pentatec *Elpen (Ελπεν), Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pentatop *Pentatop, Ger.*
Sodium cromoglicate (p. 1225·3).
Hypersensitivity reactions.

Pentavac *Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Port.; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Pentavir *Fortbenton, Arg.*
Cream: Penciclovir (p. 1008·2).

Fortbenton, Arg.
Tablets: Famciclovir (p. 979·1).

Penta-Vite Chewable *Bayer Consumer, Austral.*
Vitamins; minerals.

Penta-Vite Infant Vitamins *Bayer Consumer, Austral.*
Vitamins.

Penta-Vite Liquid *Bayer Consumer, Austral.*
Vitamins.
Dietary supplement.

Penta-Vite Multi Vitamins with Iron *Bayer Consumer, Austral.*
Vitamins; iron (p. 2073·1).

Pentawin *Biochem, India.*
⊗Pentazocine lactate (p. 120·3).
Pain; premedication.

Pentaxim *Sanofi Pasteur, Arg.; Sanofi Pasteur, China; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and Haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Pentazine VC with Codeine *Century, USA.*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Pentazol *Swiss Parenterals, Philipp.*
Thiopental sodium (p. 1915·1).
General anaesthesia; convulsive states.

Pentcillin *Taisho Toyama, Jpn.*
Piperacillin sodium (p. 340·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Penthal *Oboi, Philipp.*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Penthrox *Medical Developments, Austral.; NZ Medical & Scientific, NZ.*
Methoxyflurane (p. 1907·3).
Pain.

Pentibrom *Maver, Mex.*
Ampicillin trihydrate (p. 218·2); bromhexine hydrochloride (p. 1656·3).
Bacterial infections.

Pentibroxil *Maver, Mex.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Penticlox *Maver, Mex.*
Amoxicillin (p. 216·2).
Bacterial infections.

Penticort *Pharmadeveloppement, Fr.†*
⊗Amcinonide (p. 1621·1).
Skin disorders.

Pentidix *Maver, Mex.*
Ampicillin (p. 218·2); dicloxacillin (p. 286·1).
Bacterial infections.

Pentids *Piramal, India.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pentila *Biomedica, Gr.*
⊗Levobunolol hydrochloride (p. 2008·3).

Pentilin *KRKA, Cz.†; KRKA, Pol.†; KRKA, Rus.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye and ear disorders.

Pentiline *Charoon Bhesaj, Thai.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Pentin
Note: this name may be used for preparations of different composition.
Bilim, Turk.
Benzathine benzylpenicillin (p. 227·2).

Specifar, Gr.
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Pentiver *Maver, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Pentobrim *Rotexmedica, Philipp.*
Thiopental sodium (p. 1915·1).
General anaesthesia; convulsions.

Pentoclave *Defuen, Arg.*
Erythromycin (p. 291·2).
Acne.

Pentoclave Combi *Defuen, Arg.*
Erythromycin (p. 291·2); benzoyl peroxide (p. 1696·1).
Acne.

Pentocur *Abcur, Fin.*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Pentofin *Apotex, UK.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Pentoflux *Bouchara-Recordati, Fr.*
Pentoxifylline (p. 1465·3).
Intermittent claudication; mental function impairment in the elderly.

Pentohexal *Hexal, Austria; Hexal, Ger.†; Sandoz, Pol.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Pentol *Sidus, Arg.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); centella (p. 1698·3).
Vulvovaginal infections.

Pentolab *Lamsa, Arg.*
Pentoxifylline (p. 1465·3).

Pentolair *Bausch & Lomb, USA.†*
Cyclopentolate hydrochloride (p. 2005·3).

Pentomer *Ratiopharm, Austria; Merckle, China; Ratiopharm, China; Ratiopharm, Cz.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular disorders of the ear and eye.

Pentong *HPP, Hong Kong.†*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Pento-Puren *Actavis, Ger.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Pentorel *Khandelwal, India.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Pentostam *GSK, Israel; GSK, UK.*
Sodium stibogluconate (p. 926·3).
Leishmaniasis.

Pentotex *Rotexmedica, Malaysia.*
Thiopental sodium (p. 1915·1).
General anaesthesia; convulsions.

Pentothal *Abbott, Austral.†; Hospira, Belg.†; Hospira, Canad.†; Hospira, Denm.; Hospira, Fin.; Hospira, Fr.†; Hospira, Gr.; Abbott, Hong Kong†; Transfarma, Indon.; Hospira, Ital.; Abbott, Mex.; Hospira, Mex.; Hospira, Neth.; Hospira, Norw.†; Hospira, Philipp.; Abbott, Singapore; Hospira, Spain; Hospira, Swed.†; Ospedalia, Switz.; Hospira, Thai.†; Abbott, Turk.†; Abbott, USA.†*
Thiopental sodium (p. 1915·1).
General anaesthesia; convulsions; sedative; epilepsy; raised intracranial pressure; regional anaesthesia.

Pentovit *Altayvitamin, Rus.; Valenta, Rus.; Veropharm, Rus.*
Vitamin B substances (p. 2102·3).

Pentowin *XL, Philipp.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pentox *Farmasa, Braz.; CT, Ger.†; Littman, Philipp.; Abdi, Turk.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Pentoxal *Huons, Philipp.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Pentoxi *Genericon, Austria; Mepha, Switz.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Pentoxifillene *Dexa, Indon.†*
Pentoxifylline (p. 1465·3).
Intermittent claudication.

Pentoximed *S Med, Austria.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Pentoxin *Teuto, Braz.; Ratiopharm, Fin.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Pentoxyl-EP *Extractum, Hung.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Pentoz *Reddy, S.Afr.*
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pentral *Bunker, Braz.*
Pentoxifylline (p. 1465·3).

Pentrat *Pharlab, Braz.*
Pentoxifylline (p. 1465·3).

Pentrax *Medicis, Canad.; Alliance, Irl.; Alliance, UK; GenDerm, USA.*
Coal tar (Fractar) (p. 1723·2).
Scalp disorders.

Johnson & Johnson, Ital.
Coal tar (Fractar) (p. 1723·2); salicylic acid (p. 1719·1).
Seborrhoeic dermatitis.

Pentren *Pisa, Mex.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pentrexyl *BMS, Belg.*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

BMS, Denm.; BMS, Gr.; BMS, Ital.; BMS, Mex.; BMS, Norw.; BMS, Philipp.†
Ampicillin sodium (p. 218·2).
Bacterial infections.

BMS, Hong Kong†; BMS, Thai.†
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Pentrexyl Expec *BMS, Mex.*
Ampicillin trihydrate (p. 218·2); bromhexine hydrochloride (p. 1656·3).
Bacterial infections of the respiratory tract.

Pentrexyl-S12-H *BMS, Mex.*
Sultamicillin (p. 369·1).
Bacterial infections.

Pentrox *Medical Developments, Ukr.*
Methoxyflurane (p. 1907·3).
Pain.

Pen-V *Atlantic, Thai.; General Drugs, Thai.; Utopian, Thai.*
Phenoxymethylpenicillin (p. 338·3) or phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Genericon, Austria.
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penvasc *Drogsan, Turk.*
Amlodipine (p. 1304·1).

Pen-V-Cil *Cifarma, Braz.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penvedon *Acdhon, Thai.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Pen-Vee *Pendopharm, Canad.†*
Benzathine phenoxymethylpenicillin (p. 228·1).
Bacterial infections.

Pen-Vee K *Wyeth-Ayerst, USA.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penvelin *The Forty-Two, Thai.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penveno *Milano, Thai.*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Pen-Ve-Oral *Eurofarma, Braz.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Pen-Vi-K *Sandoz, Mex.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Penvir *Sigma, Braz.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Penvir Lábia *Sigma, Braz.*
Penciclovir (p. 1008·2).
Herpes labialis.

Penzital *Shreya, Rus.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency; digestive disorders; aid in abdominal examination.

PEP *Galpharm, UK.*
Glucose (p. 2069·1); caffeine (p. 1203·3).
Fatigue.

Pepar *Glenmark, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pep-Back *Alva, Canad.*
Caffeine (p. 1203·3).
Fatigue.

Pep-Bloc *Sanbe, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepcid *Merck, Canad.; McNeil, Fin.; MSD, Irl.; Pfizer Consumer, Neth.†; McNeil, Norw.; Johnson & Johnson, Spain; McNeil, Swed.; Johnson & Johnson MSD Consumer, UK†; MSD, UK†; Marathon, USA.*
Famotidine (p. 1842·1).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn.

Pepcid Complete *McNeil Consumer, Canad.; McNeil Consumer, USA.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Dyspepsia; heartburn.

Pepcid Duo *McNeil, Fin.; McNeil, Swed.*
Famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Dyspepsia; heartburn; gastrointestinal disorders associated with hyperacidity.

Pepcidac *Johnson & Johnson, Fr.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux.

Pepciddual *McNeil, Ger.†; Johnson & Johnson, Ital.*
Famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; gastric hyperacidity; heartburn.

Pepcidduo *Johnson & Johnson, Fr.; McNeil, Norw.*
Famotidine (p. 1842·1); magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; heartburn.

Pepcidin *MSD, Fin.†; MSD, Neth.†; MSD, Norw.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Pepcidina *MSD, Port.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux.

Pepcidine *MSD, Austral.; MSD, Hong Kong; MSD, Malaysia†; MSD, Mex.; MSD, Philipp.†; MSD, Singapore; M & H, Thai.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; pathological hypersecretory conditions.

Pepcidtwo *McNeilHealthcare, Irl.; Johnson & Johnson MSD Consumer, UK.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); famotidine (p. 1842·1).
Dyspepsia; heartburn.

Pepcine *Masa, Thai.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Pepdenal *Macrophar, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pepdif *Sanofi Synthelabo, Turk.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepdine *MSD-Chibret, Fr.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Pepdite *Nutricia, Austral.*
Preparation for enteral nutrition.
Milk protein intolerance; bowel disorders.

Scientific Hospital Supplies, Irl.†; SHS, UK.
Infant feed.
Protein or lactose intolerance; bowel disorders; malabsorption syndromes.

Pepdual *Johnson & Johnson, Spain.†*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Pepdul *Teofarma, Ger.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepermentdruppels *Pharmacare, S.Afr.†*
Peppermint oil (p. 1877·1).
Colic; flatulence.

Pepevit *Diba, Mex.†*
Nicotinic acid (p. 2083·1).
Pellagra; hypercholesterolaemia.

Pepfamin *Siam Bheasach, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepfiz *Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Thai.*
⊗Amylase (p. 2442·1); papain (p. 2582·3); simeticone (p. 1886·2).
Flatulence; dyspepsia; pancreatitis; liver disorders; excess gastrointestinal gas; aid in abdominal examination.

Pepgastrin *Pharlab, Braz.†*
Aluminium hydroxide (p. 1817·2).

Pepleo *Kayaku, Jpn.*
Peplomycin sulfate (p. 846·1).
Malignant neoplasms.

Peploc *Pharma Dynamics, S.Afr.*
Pantoprazole (p. 1875·3).

Peponen *Teva, Hung.; Biogal, Pol.; Teva, Rus.; Teva, Ukr.*
Cucurbita oil (p. 2489·2).
Benign prostatic hyperplasia; cardiovascular disorders; gastrointestinal disorders.

Peposterol *Herbapol Poznan, Pol.*
Cucurbita oil (p. 2489·2).
Benign prostatic hyperplasia.

Peppermint Field *Bertram, Thai.*
Balm stick: Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); peppermint oil (p. 1877·1).
Musculoskeletal and joint pain.

Bertram, Thai.
Topical gel: Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1).
Musculoskeletal and joint pain.

Pep-Rani *Medinfar, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Peprasan-T *Sel-J, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Peprazol *Libbs, Braz.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepridon *Xeno, Philipp.*
Domperidone (p. 1838·1).
Nausea; vomiting; dyspepsia.

Pepsa-lax *Angelfarma, Port.*
Ispaghula (p. 1849·1).
Constipation; adjuvant in hypercholesterolaemia; dietary fibre supplement; colostomy regulation.

Pepsaletten N *Cheplapharm, Ger.†*
Glutamic acid hydrochloride (p. 2070·3).
Gastrointestinal disorders.

Pepsamar *Gador, Arg.; Sanofi-Aventis, Braz.; GSK, Gr.; Angelini, Port.; Sanofi-Aventis, Spain.†*
Aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; dyspepsia; gastritis; peptic ulcer.

Pepsamar Duo *Gador, Arg.*
Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Pepsane *Rosa-Phytopharma, Fr.; Mayoly-Spindler, Mex.; Rosa-Phytopharma, Ukr.*
Guaiazulene (p. 2523·1); dimeticone (p. 1886·2).
Gastro-oesophageal pain; gastric hyperacidity; heartburn.

Pepsane-R *Rosa-Phytopharma, Rus.*
Dimeticone (p. 1886·2); guaiazulene (p. 2523·1).
Gastrointestinal disorders; aid in abdominal examination.

Pepsaplus *Sanofi-Aventis, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity.

Pepsicaps *Hertz, Braz.†*
Omeprazole (p. 1867·2).
Peptic ulcer.

Pepsitase *Hua, Thai.*
⊗Pepsin (p. 2586·1); amylase (p. 2442·1); papain (p. 2582·3); gentian (p. 2512·1); pancreatin (p. 2579·3); activated charcoal (p. 1537·3); vitamin B_1 (p. 2103·1).
Digestive disorders.

Pepsogel *Legrand, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Pepsotol *Herbes Universelles, Canad.†*
⊗Peppermint oil (p. 1877·1); pepsin (p. 2586·1); sodium bicarbonate (p. 1781·1).

Pepsytoin *Pond's, Thai.*
Phenytoin sodium (p. 538·2).
Epilepsy.

Peptab *Sanofi-Aventis, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage.

Peptac *Ivax, UK.*
Sodium alginate (p. 2167·3); sodium bicarbonate (p. 1781·1); calcium carbonate (p. 1824·3).
Heartburn; gastro-oesophageal reflux; hiatus hernia.

Peptamen *Nestle, Braz.; Nestle, Hong Kong; Nestle, Indon.; Nestle Clinical, Irl.†; Nestle, Israel; Nestle, Ital.; Nestle, Malaysia; Nestle, Philipp.; Nestle, Rus.; Carnation, USA.*
Preparation for enteral nutrition.
Gastrointestinal disorders.

Nestle, Canad.; Nestle, Fr.; Nestle, Thai.; Nestle, UK.
A range of preparations for enteral nutrition.
Gastrointestinal disorders.

Peptan *Vianex (Βιανεξ), Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Peptavlon *SERB, Fr.†*
Pentagastrin (p. 2585·3).
Test of gastric secretory function.

Peptazol *Montpellier, Arg.; Recordati, Ital.; Montpellier, Rus.; Bago, Singapore.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Peptgel *Teuto, Braz.*
Aluminium hydroxide (p. 1817·2).
Antacid.

Pepti-2000 *Nutricia, Indon.†*
Preparation for enteral nutrition.

Peptic Guard *Mylan, Canad.*
Famotidine (p. 1842·1).
Dyspepsia; gastro-oesophageal reflux.

Peptic Relief
Note: this name may be used for preparations of different composition.
Rugby, USA.
Bismuth salicylate (p. 1821·3).
Gastrointestinal disorders.

Peptica
Note: this name may be used for preparations of different composition.
Littman, Philipp.
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Unison, Thai.†
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepticaine *Pfizer, India.*
Oxetacaine (p. 1993·1); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer; hiatus hernia.

Peptical *LHT-TEN, Israel.*
Fructose (p. 2068·2); glucose (p. 2068·3); phosphoric acid (p. 2589·1).
Nausea and vomiting.

Pepticate *Nutricia, Denm.*
Infant feed.
Cow's milk intolerance; soya intolerance.

Pepticum *Aristo, Spain; Medinsa, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Pepticus *Montpellier, Arg.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptidine *ANH, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Peptifar *Tecnimede, Port.†*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepti-Junior *Lactalis, Fr.; Cow & Gate, Irl.; Nutricia, NZ.*
Infant feed.
Malabsorption; food intolerance; gastrointestinal disorders; cows' milk intolerance; diarrhoea; food allergy.

Nutricia, China; Cow & Gate, Israel†; Nutricia, Port.†; Cow & Gate, UK.
Food for special diets.
Malabsorption; diarrhoea; food intolerance; digestive disorders; milk protein intolerance.

Nutricia, Austral.†
Preparation for enteral nutrition.
Food hypersensitivity; malabsorption syndromes.

Pepti-Max
Note: this name may be used for preparations of different composition.
Columbia, Mex.
Bismuth salicylate (p. 1821·3); ranitidine (p. 1882·1).

Peptinal *Laboratorios Chile, Chile.†*
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastritis; gastro-oesophageal reflux; hyperphosphataemia; peptic ulcer.

Laboratorios Chile, Chile.†
Tablets: Aluminium hydroxide (p. 1817·2); magnesium carbonate (p. 1856·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastritis; gastro-oesophageal reflux; hyperphosphataemia; peptic ulcer.

Peptinal Forte *Laboratorios Chile, Chile.†*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium carbonate (p. 1856·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux.

Peptinex *Nestle, Hong Kong; Novartis Nutrition, USA.*
Preparation for enteral nutrition.

Peptirex *Segix, Ital.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Peptisol *Kalbe, Indon.; Sanghiang, Indon.*
High-protein preparation for enteral nutrition.

Peptisolv *Unison, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptison *Nutricia, Turk.†*
Preparation for enteral nutrition.

Peptisoothe *AFT, NZ.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; gastrointestinal haemorrhage; acid aspiration.

Peptisorb *Nutricia, Austral.†; Nutricia, China; Nutricia, Cz.; Nutricia, Denm.†; Nutricia, Fin.; Nutricia, Ital.; Nutricia, NZ; Nutricia, Pol.*
Preparation for enteral nutrition.

Nutricia Clinical, UK.
Fructose- and gluten-free, low-lactose preparation for enteral nutrition.

Nutricia, Port.
Range of preparations for enteral nutrition.

Pepto Children's *Procter & Gamble, USA.*
Calcium carbonate (p. 1824·3).

Pepto Diarrhea Control *Procter & Gamble, USA.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Pepto-Bismol *Procter & Gamble, Canad.*
Chewable tablets: Calcium carbonate (p. 1824·3); bismuth salicylate (p. 1821·3).
Diarrhoea; nausea; dyspepsia; upset stomach.

Procter & Gamble, Braz.†; Procter & Gamble, Canad.; Procter & Gamble, China; Zuellig, Hong Kong†; Procter & Gamble, Mex.; Procter & Gamble (H&B Care), UK; Procter & Gamble, USA.
Bismuth salicylate (p. 1821·3).
Diarrhoea; nausea; dyspepsia; adjunct in peptic ulcer; heartburn; gastric hyperacidity.

Peptochol *Grossman, Mex.*
Magnesium sulfate (p. 1787·3); boldo (p. 2458·3); peptone (p. 2086·2).
Biliary-tract disorders.

Peptoci *Pharmasant, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Peptodin
Note: this name may be used for preparations of different composition.
Kleva, Gr.
Nizatidine (p. 1866·1).

Mustafa, Philipp.
Famotidine (p. 1842·1).
Dyspepsia; acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptolite *Perrigo, Israel.*
Bismuth salicylate (p. 1821·3).
Gastrointestinal disorders.

Peptomet *Remedica, Singapore.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; migraine.

Peptonorm *Unipharma, Gr.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Peptonum *Linfar, Arg.*
Retinal amino acids and polypeptides (bovine) (p. 2444·1).
Dietary supplement.

Peptopancreasi *Arrow, Braz.†*
⊗Pepsin (p. 2586·1); pancreatin (p. 2579·3); amylase (p. 2442·1).
Digestive system disorders.

Peptozil *Hypermarcas, Braz.*
Bismuth salicylate (p. 1821·3).

Peptrad *Shin Poong, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Peptulan *Farmasa, Braz.*
Bismuth citrate (p. 1821·3).
Gastrointestinal hyperacidity; gastritis; peptic ulcer.

Peptyl *Monin, Fr.*
Deglycyrrhizinised liquorice (p. 1853·2); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Pepzan
Note: this name may be used for preparations of different composition.
Ascent, Austral.; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore.
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Frik, Turk.
⊗Pepsin (p. 2586·1); glutamic acid hydrochloride (p. 2070·3).
Gastrointestinal disorders.

Pepzitrat *Berlin-Chemie, Ger.†*
⊗Pepsin (p. 2586·1); citric acid (p. 2480·3).
Gastrointestinal disorders.

Pepzol
Note: this name may be used for preparations of different composition.
Mahakam Beta, Indon.
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Pequisy *Ultra, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Perabacticel *Merck Medication Familiale, Fr.*
Nifuroxazide (p. 331·3).
Diarrhoea.

Peracel *Merck Medication Familiale, Fr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Peracil *Boniscontro & Gazzone, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Peracin *Pharmadica, Thai.†*
Piperacillin sodium (p. 340·1).
Bacterial infections.

Peracon
Note: this name may be used for preparations of different composition.
Frik, Turk.
Isoaminile cyclamate (p. 1668·2).
Cough.

Lafi, Chile.
Cyproheptadine hydrochloride (p. 624·1); carnitine hydrochloride (p. 2053·2); lysine hydrochloride (p. 2079·3).
Reduced appetite.

Solvay, Gr.; Solvay, Indon.
Isoaminile (p. 1668·2).
Cough.

Peragal *Galena, Pol.*
Perazine dimaleate (p. 1095·2).
Schizophrenia.

Peraljin
Note: this name may be used for preparations of different composition.
Aroma, Turk.
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

Aroma, Turk.†
Caffeine (p. 1203·3); dipyrone (p. 53·3).
Fever; pain.

PeraSafe *Antec Dupont, Singapore; Du Pont, Singapore.*
Peroxygen-generating system (p. 1763·1).
Instrument sterilisation.

Perasian *Asian Pharm, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Peratil *Synco, Singapore.*
Prochlorperazine maleate (p. 1098·3).
Vertigo; nausea and vomiting.

Synco, Hong Kong.†
Prochlorperazine (p. 1098·2).

Perative
Note: this name may be used for preparations of different composition.
Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Cz.; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Mex.†; Abbott, Philipp.; Abbott, Turk.; Abbott Nutrition, UK; Abbott, Venez.
Preparation for enteral nutrition.

Giscard, Arg.
Ketoconazole (p. 585·3).
Fungal infections.

Peratsin *Orion, Fin.*
Perphenazine (p. 1095·3) or perphenazine decanoate (p. 1096·1).
Psychoses; nausea and vomiting.

Peraxin *Korea United, Philipp.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Perazin *Hasco-Lek, Pol.*
Perazine dimaleate (p. 1095·2).
Schizophrenia.

Perazodin *Remedica, Singapore.*
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

Perazole *Beijing Kawin, Philipp.; Medchem, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Perazolin *Zenyaku, Jpn.*
Sobuzoxane (p. 857·2).
Leukaemia; lymphoma.

Perazyna *Galena, Pol.†*
Perazine dimaleate (p. 1095·2).
Psychoses.

Perbel *Medipharma, Arg.*
Benzyl benzoate (p. 2149·1); permethrin (p. 2159·3).
Pediculosis.

Perbilen *Sanofi-Aventis, Spain.*
⊗Piretanide (p. 1470·3).
Oedema; hypertension.

Perbrons *Casel, Turk.*
Oxolamine phosphate (p. 1671·2).
Cough.

Percamf *Yaroslavl, Rus.*
Camphor (p. 2466·2); capsicum (p. 2469·3).
Neuralgia; myalgia.

Percarnil *Actavis, Denm.; Actavis, Irl.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Percas *Ivax, Arg.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Perchloracap *Tyco, Canad.†*
Potassium perchlorate (p. 2343·2).

Percitale *Piam, Ital.*
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Perclin *Fortbenton, Arg.*
Clindamycin phosphate (p. 269·3); benzoyl peroxide (p. 1696·1).
Acne.

Perclod *IWA, Cz.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Percocet *BMS, Canad.; Taro, Israel; Endo, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain; fever.

Percocyn *Landson, Indon.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Percodan
Note: this name may be used for preparations of different composition.
Taro, Israel†; Endo, USA.
⊗Oxycodone hydrochloride (p. 113·1); oxycodone terephthalate (p. 113·2); aspirin (p. 22·2).
Pain.

BMS, Canad.†
⊗Oxycodone hydrochloride (p. 113·1); aspirin (p. 22·2).
Pain; fever; inflammation.

Percof *Eurofarma, Braz.*
Levodropropizine (p. 1662·3).
Cough.

Percogesic *Medtech, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Formerly contained paracetamol and phenyltoloxamine citrate.
Pain; fever.

Percogesic Extra Strength *Medtech, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Pain.

Percutafeine *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.*
Caffeine (p. 1203·3).
Cellulite.

Percutaféine *Pierre Fabre Sante, Fr.*
Caffeine (p. 1203·3).
Localised subcutaneous adiposity.

Percutalfa *Pierre Fabre Sante, Singapore.*
Glycolic acid (p. 1704·3); fatty acids.
Prevention of stretch marks.

Rovafarm, Arg.
Alfa hydroxy acids (p. 1704·3); omega 3 (p. 1460·1); liquid paraffin (p. 2191·2).
Stretch marks.

Percutalgine
Note: this name may be used for preparations of different composition.
Besins, Belg.
⊗Dexamethasone acetate (p. 1631·1); salicylamide (p. 129·2); glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3).
Musculoskeletal, peri-articular, and soft-tissue disorders.

Besins, Fr.
⊗Dexamethasone (p. 1630·3) or dexamethasone acetate (p. 1631·1); salicylamide (p. 129·2); glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3).
Peri-articular and soft-tissue disorders.

Besins, Ukr.†
⊗Dexamethasone (p. 1630·3); salicylamide (p. 129·2).
Musculoskeletal, joint, and peri-articular disorders.

Percutalgin'Phyto *Besins, Fr.*
Clove oil (p. 2481·3); bay oil (p. 2453·1); myrtle oil (p. 2566·3).
Musculoskeletal pain.

Percutane *Genepharm, Austral.†*
Capsicum oleoresin (p. 2469·3); lappa (p. 2540·1); arnica (p. 2447·2); aloe vera (p. 1693·2).
Musculoskeletal and joint disorders.

Percutol *Aspire, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Perdamel *Clonmel, Irl.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; aggressive behaviour in Alzheimer's disease; behaviour disorders in autistic disorder.

Perderm *Schering-Plough, Hong Kong†; Schering-Plough, Indon.*
⊗Alclometasone dipropionate (p. 1621·1).
Skin disorders.

Perdiem *Novartis Consumer, USA.†*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation.

Perdiem Fiber *Novartis Consumer, USA.*
Ispaghula (p. 1849·1).
Constipation.

Perdin *Merck, Port.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Perdipina *Astellas, Ital.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

Perdipine *Astellas, China; Astellas, Indon.; Astellas, Jpn; Astellas, Philipp.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; heart failure.

Perdix *Schwarz, Israel; Omnimed, S.Afr.†; UCB, UK.*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Perdofemina *Johnson & Johnson Consumer, Belg.*
Ibuprofen (p. 68·2).
Pain; fever.

Perdofen *Johnson & Johnson, Port.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Perdolan *Johnson & Johnson Consumer, Belg.*
Paracetamol (p. 115·1).
Fever; pain.

Perdolan Codeine *Johnson & Johnson Consumer, Belg.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Perdolan Compositum *Johnson & Johnson Consumer, Belg.*
Tablets; suppositories (adult): Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Janssen-Cilag, Belg.†
Suppositories (infant and child): Aspirin (p. 22·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Perdophen *Johnson & Johnson Consumer, Belg.*
Ibuprofen (p. 68·2).
Pain; fever.

Perdox *Vera, Hung.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Perduretas Codeina *Nupel, Spain.*
Codeine phosphate (p. 40·2).
Cough.

Perebron *Cinay, Turk.*
Oxolamine phosphate (p. 1671·2).
Cough.

Laboratorios Chile, Chile; Faran, Gr.; Elmor, Venez.
Oxolamine citrate (p. 1671·2) or oxolamine phosphate (p. 1671·2).
Cough.

Pereks *Kurtsan, Turk.*
⊗Ephedrine hydrochloride (p. 1663·2); diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2).
Respiratory-tract disorders.

Perenal *Help, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Perenan *Sanofi, China.*
Co-dergocrine mesilate (p. 389·2).
Cerebral and peripheral vascular disorders.

Perenterol *UCB, Ger.; Zambon, Switz.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; acne.

Perenteryl *Merck, Chile.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea.

Peresal *Ecolab, Ital.†*
Hydrogen peroxide (p. 1755·2); peracetic acid (p. 1763·1).
Disinfection of dialysis equipment.

Perfadex *Vitrolife, Swed.*
⊗Dextran 40 (p. 1138·1); glucose monohydrate (p. 2069·1); electrolytes (p. 1775·1).
Organ perfusion before transplantation.

Perfalgan *BMS, Austral.; BMS, Austria; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; IFET (ΙΦΕΤ), Gr.; BMS, Hung.; BMS, Irl.; BMS, Israel; BMS, Ital.; BMS, Neth.†; BMS, Norw.; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Spain; BMS, Swed.; BMS, Switz.; Byk Gulden, Turk.; BMS, UK.*
Paracetamol (p. 115·1).
Pain; fever.

Perfan *Belpharma, Belg.†; Carinopharm, Ger.; Inca, Irl.; Inca, Ital.; Carinopharm, Neth.; Aventis, UK.*
Enoximone (p. 1373·3).
Heart failure.

Perfane *ProStrakan, Fr.*
Enoximone (p. 1373·3).
Heart failure.

Perfect Body *Knop, Chile.*
Centella (p. 1698·3); equisetum (p. 2500·1); fucus; ginkgo biloba (p. 2512·3); melissa (p. 2552·3); spirulina (p. 2622·1).
Cellulite; stretch marks.

Perfect Solutions *Perfect Solutions, Canad.†*
Sodium fluoride (p. 2089·2).

Perfect Solutions 1-Minute *Perfect Solutions, Canad.†*
Hydrogen fluoride (p. 2529·1); phosphoric acid (p. 2589·1); sodium fluoride (p. 2089·2).

Perfect Solutions In Office Rinse
Note: this name may be used for preparations of different composition.
Perfect Solutions, Canad.†
Hydrogen fluoride (p. 2529·1); sodium fluoride (p. 2089·2); monobasic sodium phosphate (p. 1791·1).

Perfect Solutions in Office Rinse
Note: this name may be used for preparations of different composition.
Perfect Solutions, Canad.†
Stannous fluoride (p. 2094·3).

Perfect Sun *Biokosma, Arg.*
Urucum; alpha tocopherol (p. 2119·1); betacarotene (p. 2051·1).
Dietary supplement.

Perfectil *Vitabiotics, Hong Kong; Vitabiotics, Rus.; Vitabiotics, Ukr.*
Vitamins; minerals; cystine (p. 2059·1); echinacea (p. 2498·1); lappa (p. 2540·1).
Nutritional supplement for skin, hair, and nails.

Vitabiotics, UK.
Vitamins; amino acids; minerals; herbs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Perfectil Plus *Vitabiotics, Ukr.*
Tablets, vitamins; minerals; carotenoids (p. 2176·2); cystine (p. 2059·1); grape seed (p. 2521·3); capsules, omega-3 triglycerides (p. 1460·3); lutein esters (p. 2079·2); comfrey oil (p. 2484·2); black currant seed oil (p. 2458·1); ubidecarenone (p. 2637·1).
Dietary supplement for skin, hair, and nails.

Perfecting Day Cream *Balley, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Perfenol *Uniao Quimica, Braz.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).

Perfluoron *Alcon, USA.*
⊗Perfluorooctane (p. 2587·1).
Ophthalmic tamponade.

Perflux *Fresenius Kabi, Austria.*
Electrolytes (p. 1775·1).
Forced diuresis.

Perfluxi *Amnol, Ital.*
Grape (p. 2521·3).
Circulatory disorders.

Perfluxi Cremagel *Amnol, Ital.*
⊗Capsaicin (p. 35·1); ginkgolide (p. 2513·3); camphor (p. 2466·2); ruscogenin (p. 2608·3); 18 beta glycyrrhecetic acid (p. 54·2); mallow (p. 2549·2); urea (p. 1727·3); zinc oxide (p. 1729·1); silicone.
Raynaud's syndrome.

Perfocrat *Phytofarm Kleka, Pol.†*
Crataegus (p. 2488·1); St John's wort (p. 449·1); melissa (p. 2552·3).
Anxiety.

Perfocyn *Bell, India.†*
⊗Prednisolone (p. 1645·2); chloramphenicol (p. 257·1); benzocaine (p. 1980·2); acetic acid (p. 2426·3).
Ear infections.

Perform
Note: this name may be used for preparations of different composition.
FinestHealth Products, Canad.†
Camphor (p. 2466·2); menthol (p. 2553·2).

Performance Bodycare Sunscreen *Kinesys, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Performance Moisturizer *Kinesys, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Performance Sunscreen *Kinesys, Canad.*
SPF 45: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kinesys, Canad.
Cream SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Kinesys, Canad.
Spray SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Performer *Piam, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Perforomist *Dey, USA.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Perfracort *Fortbenton, Arg.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Perftoran *Perftoran, Rus.*
⊗Perflunafene (p. 2586·3); perfluoromethylcyclohexylpiperidine; poloxamer (p. 2201·3); electrolytes (p. 1775·1).
Plasma volume expansion.

Perfudal *Odin, Spain.†*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Perfungol *Bago, Chile.*
Topical powder: Chlorocresol (p. 1748·1); zinc oxide (p. 1729·1); boric acid (p. 2459·3).
Fungal skin infections.

Bago, Chile.†
Ointment: Chlorocresol (p. 1748·1); nicotinamide (p. 2083·1); cholesterol (p. 2179·1).
Fungal skin infections.

Perfus Multivitaminico *Rius, Spain.†*
Carbazochrome (p. 1137·1); vitamins; electrolytes (p. 1775·1).
Haemorrhage; skeletal muscle disorders.

Perfusalgan *BMS, Belg.*
Paracetamol (p. 115·1).
Fever; pain.

Perfusion mixte *Streuli, Switz.†*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Dehydration.

Pergalen *Millet-Franklin, Arg.*
Sodium apolate (p. 1497·1); benzyl nicotinate (p. 29·3).
Skin ulcers; thrombophlebitis; haematomas; superficial thrombosis.

Pergamid *Pfizer, Arg.*
Aniracetam (p. 389·1).
Mental function impairment.

Perganit *AstraZeneca, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; pulmonary oedema; hypertension.

Pergastid *AGIPS, Ital.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pergidal *Valeas, Ital.*
Macrogol 4000 (p. 2547·3).
Constipation.

Pergogreen *Faran, Gr.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

Pergonal *Serono, Braz.†; Faran, Gr.; Serono, Hong Kong†; Serum Institute, India; Serono, Rus.; Serono, Turk.*
⊗Menotrophin (p. 2284·1).
Male and female infertility.

Pergotime *Merck, Belg.; Merck, Denm.; Merck Serono, Fr.; Merck, Norw.; Merck, Swed.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Pergoveris *Merck Serono, Arg.; Merck Serono, Austria; Merck Serono, Belg.; Merck, Braz.; Merck, Cz.; Merck Serono, Denm.; Merck Serono, Fr.; Merck Serono, Ger.; Merck Serono, Gr.; Merck Serono, Hung.; Merck Serono, Irl.; Merck Serono, Israel; Serono, Ital.; Merck, Neth.; Merck Serono, Norw.; Serono, Pol.; Serono, Port.; Merck, Singapore; Merck, Spain; Serono, Swed.†; Merck, Switz.; Merck Serono, UK.*
⊗Follitropin alfa (p. 2278·2); lutropin alfa (p. 2287·1).
Female infertility.

Perhip *Hasco-Lek. Pol.*
St John's wort (p. 449·1).
Depression.

Peri Solution *Otsuka, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Renal insufficiency.

Periactin *Aspen, Austral.; MSD, Austria; MSD, Belg.; IFET (ΙΦΕΤ), Gr.†; MSD, Irl.†; Avantgarde, Ital.; Auden McKenzie, Neth.; MSD, NZ; MSD, S.Afr.; MSD, Singaporet; Sigma-Tau, Spain; MSD, Swed.†; M & H, Thai.; MSD, UK.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; pruritus; migraine; vascular headache; reduced appetite; urticaria; allergic rhinitis.

Périactine *Teofarma, Fr.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions.

Periagna *Bio-Health, UK.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Periamin G *Baxter, Ger.†*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Periatin *MSD, Braz.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine and other vascular headaches; reduced appetite.

Pericaina *Senese, Ital.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Pérical *Besins, Fr.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis.

Pericam *Clonmel, Irl.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Pericate *Unipharm, Israel.*
Haloperidol decanoate (p. 1077·2).
Psychoses.

Pericephal *Arcana, Austria.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Perichlor *Pharmascience, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Perichol *Pharmacodane, Denm.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Peri-Colace *Purdue, USA.*
Sennosides (p. 1885·2); docusate sodium (p. 1836·2).
Constipation.

Pericor *Torrent, Braz.*
Perindopril (p. 1466·3).

Perida *Codal Synto, Thai.†*
Haloperidol (p. 1077·1).
Psychoses; behaviour disorders in children; tics; stuttering.

Peridal *Medley, Braz.*
Domperidone (p. 1838·1).
Gastrointestinal motility disorders; nausea and vomiting.

Peridane *Columbia, Mex.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; thrombosis prophylaxis.

Peridex *3M, Canad.; Procter & Gamble, USA.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis.

Peridializ *Ulagay, Turk.*
Glucose (p. 2068·3); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
Peritoneal dialysis.

Peridil *Cryopharma, Mex.*
Azapetine phosphate (p. 1313·1).
Peripheral vascular disorders.

Peridin-C *Beutlich, USA.*
Hesperidin methyl chalcone (p. 2505·2); hesperidin complex (p. 2505·2); ascorbic acid (p. 2110·3).
Capillary bleeding.

Peridom-M *Masa, Thai.*
Domperidone maleate (p. 1838·1).
Delayed gastric emptying; nausea; vomiting.

Peridon *Lafedar, Arg.; Italchimici, Ital.*
Domperidone (p. 1838·1).
Gastrointestinal disorders; gastrointestinal motility disorders.

Peridona *UCI, Braz.*
Domperidone (p. 1838·1).

Peridonium *Norton, Ukr.†*
Domperidone (p. 1838·1).
Delayed gastric emptying; gastro-oesophageal reflux; nausea; vomiting.

Peridont *Oftalmi, Venez.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis.

Peridor *Trima, Israel.†*
Haloperidol (p. 1077·1).
Psychoses; Tourette syndrome; behaviour disorders in children.

Péridys *Pierre Fabre, Fr.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia; gastro-oesophageal reflux.

Perifas *Otto, Indon.*
Cinnarizine (p. 622·1).
Peripheral vascular disorders; vestibular disorders; motion sickness.

Perifem *Orion, Spain.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Periflex
Note: this name may be used for preparations of different composition.
Braun, Ital.
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Perifusin *Fresenius Kabi, Gr.*
Amino acids.
Parenteral nutrition.

Perifusin-N *Fresenius Kabi, Gr.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3).
Parenteral nutrition.

Perigard *Glenmark, India.*
Perindopril (p. 1466·3).
Heart failure; hypertension.

Glenmark, Malaysia; Glenmark, Philipp.
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Perigard-D *Glenmark, India.*
⊗Perindopril (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Perigard-DF *Glenmark, India.*
⊗Perindopril (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Perigona *MIP, Denm.; MIP, Fin.; MIP, Norw.; MIP, Swed.*
Glucosamine hydrochloride magnesium sulfate (p. 2515·3).
Osteoarthritis.

Periguard *DermaRite, USA.*
Barrier preparation.

Perika *VSM, Belg.; Schwabe, Norw.†; Schwabe, Spain.†*
St John's wort (p. 449·1).
Depression; anxiety; insomnia; tonic.

Périkaviben *Fresenius Kabi, Fr.*
Amino acids; carbohydrate; lipid (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Perikan *Austroplant, Austria.†*
St John's wort (p. 449·1).
Depression.

Perikliman *Kwizda, Austria.*
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Perilax
Note: this name may be used for preparations of different composition.
Crisdy-Na, Philipp.
Domperidone (p. 1838·1).
Dyspepsia; nausea; vomiting.

Nordic Drugs, Denm.; Pharmacare, S.Afr.†
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Perilife *Frik, Turk.*
Risperidone (p. 1103·2).

Périlox *Drossapharm, Switz.*
Metronidazole (p. 936·1).
Rosacea.

Perinace *CCM, Malaysia; Upha, Singapore.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension.

Perinal
Note: this name may be used for preparations of different composition.
Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.
⊗Hydrocortisone (p. 1640·1); lidocaine hydrochloride (p. 1988·2).
Anal and perianal pain, inflammation and pruritus.

Tempo Scan Pacific, Indon.
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Perinalon *Sandoz, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Perinauz *Medinfar, Port.†*
Domperidone maleate (p. 1838·1).
Gastrointestinal disorders.

Perindan *Medico Uno, Hung.†*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension.

Perindo *Alphapharm, Austral.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension; cardiovascular risk reduction.

Perindo Combi *Alphapharm, Austral.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Perindocyl *Servier, Belg.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; myocardial infarction.

Perindoran *Ranbaxy, Pol.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Perineva *KRKA, Denm.; Pharma-Regist, Hung.; KRKA, Rus.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction; myocardial infarction.

Perinorm *Ipca, India; Ipca, Rus.; Nat Druggists, S.Afr.†*
Metoclopramide hydrochloride (p. 1862·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; postoperative gastric hypotonia; nausea and vomiting.

Perinpa *Ratiopharm, Cz.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Perinpress *Obolenskoe, Rus.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension.

Perinutriflex Lipide *Braun, Fr.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipids.
Contains egg lecithin.
Parenteral nutrition.

Perio-Aid *Dentaid, Chile.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene.

Perio-Aid c Cloruro de Cetilpiridinio *Dentaid, Chile.*
Chlorhexidine gluconate (p. 1743·3); cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Periobacter *Naf, Arg.*
Chlorhexidine (p. 1743·2); xylitol (p. 2220·3).
Mouth infections.

Periobacter Prof Avio *Naf, Arg.*
Chlorhexidine acetate (p. 1743·2); thymol (p. 1772·2).

Periochip *Dexcel, Denm.; Dexcel, Fin.; Arriani, Gr.; Dexcel, Irl.; Dexcel, Israel; Curaden, Ital.; Dexcel, Neth.; Dexcel, Norw.; Dexcel, Port.; Dexcel, Singapore†; Dexcel, Swed.; Karr, Switz.; Adria, USA.*
Chlorhexidine gluconate (p. 1743·3).
Periodontal disease.

Periocline *Sunstar, China.*
Minocycline (p. 324·3).

Sunstar, Gr.; Sunstar, Jpn.
Minocycline hydrochloride (p. 325·1).
Periodontitis.

Period Pain Relief
Note: this name may be used for preparations of different composition.
Boots, UK.
Naproxen (p. 98·2).
Dysmenorrhoea.

Herbal Concepts, UK.
Alchemilla; motherwort (p. 2564·2); valerian (p. 2640·2); pulsatilla (p. 2600·2); vervain (p. 2645·1); helonias (p. 2524·3).
Premenstrual syndrome; dysmenorrhoea.

Periodent *Grimberg, Arg.*
Chlorhexidine gluconate (p. 1743·3); xylitol (p. 2220·3).
Mouth disorders.

Periodentyl *GSK, Mex.*
Mouthwash: Triclosan (p. 1773·2); zinc chloride (p. 2126·1); vitamin E acetate (p. 2119·2); xylitol (p. 2220·3).
Oral hygiene.

GSK, Mex.
Toothpaste: Triclosan (p. 1773·2); zinc citrate (p. 2126·2); enoxolone (p. 54·2); sodium monofluorophosphate (p. 2091·3).
Oral hygiene.

Periodil *Pharmatrix, Arg.*
Dental gel: Chlorhexidine gluconate (p. 1743·3).
Periodontal disorders; oral hygiene.

Pharmatrix, Arg.
Mouth spray; mouthwash: Chlorhexidine gluconate (p. 1743·3); cetylpyridinium chloride (p. 1743·1).
Periodontal disorders; oral hygiene.

Periodontil *Sanofi-Aventis, Braz.*
Spiramycin (p. 358·3); metronidazole (p. 936·1).
Bacterial infections; protozoal infections.

Periogard
Note: this name may be used for preparations of different composition.
Colgate-Palmolive, Canad.; GABA, Gr.; Colgate-Palmolive, UK†; Colgate Oral, USA.
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Periogard Chlorohex *Colgate Oral Care, Austral.†; Colgate-Palmolive, Ital.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; mouth disorders.

Periogard Plus *Colgate-Palmolive, Ital.*
Oral drops: Cetylpyridinium chloride (p. 1743·1).
Gum disorders.

Colgate-Palmolive, Ital.
Toothpaste: Zinc citrate (p. 2126·2); sodium monofluorophosphate (p. 2091·3).
Gingivitis.

Periokin *Pasteur, Chile.†*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; dental caries prophylaxis.

PeriOlimel *Baxter, Austria; Baxter, Canad.; Baxter, Cz.*
Glucose (p. 2068·3); amino acids; lipid (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg phosphatides.
Parenteral nutrition.

Baxter, Belg.; Baxter, Switz.
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1); lipids (from soya oil (p. 2092·3) and olive oil (p. 2575·1)).
Contains egg lecithin.
Parenteral nutrition.

Périolimel *Baxter, Fr.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipid (from olive oil (p. 2575·1) and soya oil (p. 2092·3)).
Contains egg phosphatides.
Parenteral nutrition.

PerioMed *Omnii, USA.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Periosan *Vitae, Mex.*
Doxycycline (p. 288·1).
Bacterial infections.

Periostat *Pendopharm, Canad.; Alliance, Irl.; Taro, Israel†; Ideco, Ital.; Alliance, Neth.; Alliance, Port.; Karr, Switz.†; Alliance, UK; Galderma, USA.*
Doxycycline hyclate (p. 288·2).
Periodontitis; bacterial infections.

Periotret *Verisfield, Gr.*
Metronidazole benzoate (p. 936·1).
Bacterial mouth infections.

Perioxidin *GSK, Mex.†*
Dental gel: Chlorhexidine gluconate (p. 1743·3).
Mouth infections.

GSK, Mex.†
Mouthwash: Chlorhexidine gluconate (p. 1743·3); xylitol (p. 2220·3).
Gingivitis; periodontitis.

Peripan *Mepha, Braz.†*
Pentoxifylline (p. 1465·3).

Periphramine *Braun, Spain.†*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

Periplasmal *Braun, Ger.†; Braun, Pol.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Periplasmal G *Braun, Spain.†*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Periplasmal XE *Braun, Ger.*
Amino acids; xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Periplum
Note: this name may be used for preparations of different composition.
Fortbenton, Arg.
Fluconazole (p. 578·2).
Fungal infections.

Italfarmaco, Ital.
Nimodipine (p. 1455·2).
Neurological deficit following cerebral vasospasm.

Peripride *Ipca, India.†*
Mosapride citrate (p. 1865·2).
Gastro-oesophageal reflux; dyspepsia; gastroparesis.

Periset *Ipca, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

PeriShield *Ameriderm, USA.*
Barrier ointment.

Perismofven *Fresenius Kabi, Ital.*
Amino acids; glucose (p. 2068·3); lipid (p. 2092·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Perisom *Somex, Irl.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Perison *Strathmann, Ger.*
Escherichia coli; Morganella morganii; Proteus mirabilis; Klebsiella pneumoniae; Enterococcus faecalis (p. 2596·3).
Urinary-tract infections.

Perispa *Platinum, Philipp.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm; spasticity.

Péristaltine *Novartis Sante, Fr.†*
Cascara (p. 1826·1).
Constipation.

Peritofundina *Braun, Port.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); with or without potassium chloride (p. 1793·2) (p. 1778·2).
Peritoneal dialysis.

Peritol *Egis, Cz.; Infectopharm, Ger.; Egis, Hung.; Themis Medicare, India; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; carcinoid syndrome; allergic skin disorders; angioedema; reduced appetite; insect bites; rhinitis; vascular headache; urticaria; migraine.

Peritone *Blackmores, Austral.*
Aloes (p. 1816·1); cascara (p. 1826·1); ginger (p. 1844·1); cardamom fruit (p. 2471·1); peppermint oil (p. 1877·1).
Constipation.

Peritoneal Lactate *ANB, Thai.†*
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium metabisulfite (p. 1770·3) (p. 1778·2).
Peritoneal dialysis.

Peritrast *Kohler, Austria; Kohler, Ger.; Kohler, Hung.*
Lysine amidotrizoate (p. 1581·2).
Radiographic contrast medium.

Peritrate *Warner, India; Teofarma, Ital.; Pfizer, Thai.*
Pentaerithrityl tetranitrate (p. 1465·1).
Angina pectoris; coronary insufficiency.

Peritrol *OraPharma, Neth.†*
Minocycline hydrochloride (p. 325·1).
Periodontitis.

Perivasc *Alphapharm, Austral.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Perivel Plus *Nevzat, Turk.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).

Periven *Fresenius Kabi, Ital.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg phospholipids.
Parenteral nutrition.

Peri-Wash II *Coloplast, Canad.; Zuellig, Hong Kong.†*
Benzethonium chloride (p. 1738·1).
Skin cleansing.

Perixis *Accord, UK.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Perizal *Specpharm, S.Afr.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorder.

Perjeta *Roche, Israel; Chugai, Jpn; Roche, Switz.; Roche, UK; Genentech, USA.*
Pertuzumab (p. 846·2).
Breast cancer.

Perkapil *Kurtsan, Turk.*
Dipyrithione (p. 1701·1).
Seborrhoeic dermatitis of the scalp.

Perkhotal *Gepach, Rus.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Perlane *Medicis, USA.*
Hyaluronic acid (p. 2526·2).
Lidocaine (p. 1988·1) is included in some injections to reduce the pain of injection.
Facial wrinkles.

Perlas De PMMA con Gentamicina *Merck, Chile.†*
Methylmethacrylate methacrylate copolymer (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone and soft-tissue infections.

Perlatos *Quesada, Arg.*
Levodropropizine (p. 1662·3).
Cough.

Perle + Antiseptic *Avmor, Canad.*
Triclosan (p. 1773·2).

Perlea *Elea, Arg.*
Vitamins; minerals.
Dietary supplement.

Perléane *Biogaran, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Perlic *Menarini, Spain.*
Frovatriptan succinate (p. 676·2).
Migraine.

Perlice *Galderma, India.*
Permethrin (p. 2159·3).
Pediculosis.

Perlinganit *UCB, Austria; UCB, Cz.; UCB, Fin.; Schwarz, Ger.†; Schwarz, Philipp.; UCB, Pol.; Schwarz, Rus.; UCB, Switz.; Kurtsan, Turk.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; controlled hypotension; myocardial infarction; hypertensive crisis; hypertension; ischaemic heart disease.

Perlol *Asian Pharm, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris.

Perloxx *Athlon, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Perludil *Collins, Mex.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive; menstrual disorders.

Perlutal *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive; endometriosis; female infertility; menstrual disorders.

Perlutan *Boehringer Ingelheim, Braz.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive.

Perlutex *Leo, Denm.†; Leo, Norw.†*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen; endometriosis; test of ovarian function; menopausal disorders; uterine cancer.

Permadoze *Actavis, Port.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency; iron-deficiency anaemia.

Permafoam *Hartmann, Belg.; Hartmann, Fr.*
A polurethane dressing (p. 1718·1).
Wounds.

Permapen *Roerig, USA.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Permasol *Munir, Turk.*
Potassium permanganate (p. 1766·3).
Suppurating eczematous reactions; wounds.

Permax *Aspen, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Cz.; Lilly, Mex.; Lilly, Neth.†; Healthcare Logistics, NZ; Lilly, Port.; Lilly, S.Afr.†; Lilly, Switz.†; Munir, Turk.*
Pergolide mesilate (p. 910·2).
Parkinsonism.

Permecil *Prieto, Arg.*
Benzyl benzoate (p. 2149·1); permethrin (p. 2159·3).
Pediculosis.

Perme-Cure *Ferrer, Spain.*
Permethrin (p. 2159·3).
Scabies.

Permetor *Egis, Neth.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Permicaps *Bago, Arg.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Permid *Hizon, Philipp.†*
Loperamide (p. 1854·2).
Diarrhoea; ostomy management.

Permidal *Liferpal, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Permin *Tekhnolog, Ukr.*
Permethrin (p. 2159·3).
Pediculosis.

Permitabs *Centrapharm, UK.*
Potassium permanganate (p. 1766·3).
Wound cleansing.

Permite *Galderma, India.*
Permethrin (p. 2159·3).
Pediculosis.

Permitil
Note: this name may be used for preparations of different composition.
Panalab, Arg.
Sildenafil (p. 2364·1).
Erectile dysfunction.

Permixon *Rovafarm, Arg.; Germania, Austria; Mediwin, Fr.; Pierre Fabre, Hong Kong; Pierre Fabre, Israel; Pierre Fabre, Ital.; Pierre Fabre, Mex.; Pierre Fabre, Pol.†; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Singapore; Pierre Fabre, Spain; Robapharm, Switz.; Pierre Fabre, Thai.*
Saw palmetto (p. 2363·3).
Prostatic adenoma; benign prostatic hyperplasia; prostatitis.

Permotil *Sofar, Ital.*
Domperidone maleate (p. 1838·1).
Gastrointestinal disorders.

Permucal *Sankyo, Venez.*
⊗A heparinoid (p. 1401·1); prednisolone (p. 1645·2); oxypolyethoxidodecane; hexachlorophene (p. 1754·1).
Anorectal disorders.

Permut *Eurofarma, Braz.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Permvastat *Permatec, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Permykot *Indeco, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Permyo *Ferron, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Pernamed *Medifive, Thai.*
Perphenazine (p. 1095·3).
Psychoses; nausea and vomiting.

Pernazène *Jolly-Jatel, Fr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Pernazene *Sanofi Synthelabo, Thai.†*
⊗Tymazoline hydrochloride (p. 1679·3).
Nasal congestion.

Pernazene Oxy *Sanofi-Aventis, Thai.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis.

Pernazine *Atlantic, Thai.*
Perphenazine (p. 1095·3).
Schizophrenia; nausea and vomiting.

Pernazinum *Labor, Pol.*
Perazine dimaleate (p. 1095·2).
Psychoses; anxiety disorders.

Pernexin *Bayer, Ital.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; anaemias.

Pernionin Thermo Teilbad *Krewel, Ger.*
Benzyl nicotinate (p. 29·3).
Bath additive; musculoskeletal and joint disorders; peripheral vascular disorders.

Pernionin Thermo Vollbad *Krewel, Ger.*
Benzyl nicotinate (p. 29·3).
Bath additive; musculoskeletal and joint disorders.

Pernox *Ranbaxy, USA.*
Polyethylene granules (abrasive) (p. 1690·3); sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Acne.

Pero Vap *Rougier, Canad.*
Hydrogen peroxide (3 per cent) (p. 1755·2).
Wounds.

Perocur *Hexal, Ger.†; Sandoz, Turk.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; acne.

Perofen *Remedica, Hong Kong; Remedica, Malaysia†; Remedica, Singapore.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Perohid *Munir, Turk.*
Hydrogen peroxide (3 percent) (p. 1755·2).
Skin and mucous membrane disinfection; wounds.

Peroma *Vianex (Βιανεξ), Gr.*
Nilvadipine (p. 1455·2).
Hypertension.

Peromyces *1A, Ger.†*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea; acne.

Peronten *Pharmathen, Gr.*
Gabapentin (p. 523·3).

Perosall *Biomed Krakow, Pol.*
Pollen allergen extracts (p. 2593·3) (p. 2434·3).
Hyposensitisation.

Peroxacne *Arafarma, Spain.*
Benzoyl peroxide (p. 1696·1).
Acne.

Perox-A-Mint *Sage, Canad.†*
Hydrogen peroxide (1.5 per cent) (p. 1755·2).

Peroxiben *Isdin, Port.; Isdin, Spain.*
Benzoyl peroxide (p. 1696·1).
Acne.

Peroxiben Plus *Isdin, Chile.*
Benzoyl peroxide (p. 1696·1).
Acne; seborrhoea.

Peroxiclin Duo *LKM, Arg.*
Benzoyl peroxide (p. 1696·1); clindamycin (p. 269·3).
Acne.

Peroximicina *LKM, Arg.*
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

Peroxx *Vianex (Βιανεξ), Gr.*
Rofecoxib (p. 128·3).
Osteoarthritis; rheumatoid arthritis.

Peroxy-Dental *Gemi, Pol.*
Hydrogen peroxide 30% (p. 1755·3).
Periodontitis.

Peroxygel *Gemi, Pol.*
Hydrogen peroxide 30% (p. 1755·3).
Wound disinfection.

Peroxyl *Colgate-Palmolive, Austral.; Colgate-Palmolive, Canad.; Colgate-Palmolive, Gr.; Colgate-Palmolive, UK; Colgate-Palmolive, USA.*
Hydrogen peroxide (p. 1755·2).
Mouth disorders; oral hygiene; oral wounds; mouth and gum irritation.

Perphenan *Taro, Israel.*
Perphenazine (p. 1095·3).
Anxiety; nervous states; vomiting.

Perry Medical Prenatal *Kirkman, USA.*
Vitamins; minerals.
Dietary supplement.

Persantin *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Gr.; IFET (ΙΦΕΤ), Gr.; Boehringer Ingelheim, Hong Kong; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Venez.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders; angina pectoris; nephrotic syndrome; ischaemic heart disease; cardiac stress testing; cerebrovascular disorders; placental insufficiency; microcirculatory disorders; secondary prevention of stroke and transient ischaemic attacks; myocardial infarction.

Boehringer Ingelheim, Spain.
Dipyridamole hydrochloride (p. 1362·2).
Thrombosis prophylaxis; stress testing in myocardial perfusion imaging.

Persantine *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Orifarm, Denm.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, USA.*
Dipyridamole (p. 1362·2).
Ischaemic heart disease; thromboembolic disorders; vasodilator in myocardial perfusion imaging; ischaemic stroke prophylaxis.

Persatina *2M, Thai.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Persen *Lek, Cz.; Sandoz, Pol.; Lek, Rus.; Sandoz, Ukr.*
Valerian (p. 2640·2); melissa (p. 2552·3); peppermint leaf (p. 1877·1).
Nervous disorders; sleep disorders; insomnia.

Persen Cardio *Sandoz, Ukr.*
Passion flower (p. 2584·1); crataegus (p. 2488·1).
Nervous disorders; cardiac disorders.

Persidal *Mersifarma, Indon.*
Risperidone (p. 1103·2).
Psychoses.

Persivate *Aspen, S.Afr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Perskindol Classic
Note: this name may be used for preparations of different composition.
Interpharma, Hung.
Levomenthol (p. 2553·2); scots pine oil (p. 2591·2); sweet orange oil (p. 2576·2); sweet birch oil (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain; headache.

Vifor, Switz.
Bath additive: Pine-needle oil (p. 2591·1); orange oil (p. 2576·2); lavender oil (p. 2541·1); rosemary oil (p. 2607·3); lemon oil (p. 2543·1); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); jojoba oil.
Muscle and joint pain; cold symptoms; superficial circulatory disorders; bath additive.

Vifor, Switz.
Topical fluid; topical gel; topical spray; wipes: Menthol (p. 2553·2); sweet birch oil (p. 92·1); pine-needle oil (p. 2591·1); lemon oil (p. 2543·1); orange oil (p. 2576·2); bergamot oil (p. 2455·1); rosemary oil (p. 2607·3); lavender oil (p. 2541·1); terpineol (p. 2627·2); isobornyl acetate (p. 2460·2).
Muscle and joint pain.

Perskindol Cool *Vifor, Switz.*
Menthol (p. 2553·2).
Soft-tissue injury.

Perskindol Cool Arnica *Vifor, Switz.*
Arnica (p. 2447·2); menthol (p. 2553·2).
Soft-tissue disorders.

Perskindol Cool Consoude *Vifor, Switz.*
Comfrey (p. 2484·2); levomenthol (p. 2553·2).
Joint and soft-tissue disorders.

Perskindol Dolo *Vifor, Switz.*
Sweet birch oil (p. 92·1); pine needle oil (p. 2591·1).
Musculoskeletal, joint, and soft-tissue disorders.

Perskindol Ibuprofen acute *Vifor, Switz.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Pers-Mant *Orva, Turk.*
Miconazole (p. 588·3); aluminium chlorohydrate (p. 1694·1).

Persol
Note: this name may be used for preparations of different composition.
Wallace, India.
Benzoyl peroxide (p. 1696·1).
Acne.

Persol Forte *Wallace, India.*
Benzoyl peroxide (p. 1696·1); sulfur (p. 1721·1).
Acne.

Perspi *Szama, Arg.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Pert Plus *Idelle, Canad.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis.

Pertacilon *Elpen (Ελπεν), Gr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Pertaxol *Kleva, Gr.*
⊗Betaxolol hydrochloride (p. 1322·3).
Hypertension; glaucoma; ocular hypertension.

Pertensal *Bayer, Spain.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Pertenso *Ivax, Arg.*
⊗Clonidine (p. 1339·1); bendroflumethiazide (p. 1315·2).
Hypertension.

Pertenso N *Sanol, Ger.; UCB, Ger.*
⊗Propranolol hydrochloride (p. 1479·1); hydralazine hydrochloride (p. 1401·2); bendroflumethiazide (p. 1315·2).
Hypertension.

Perti *Reddy, Rus.†*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Pertil *AstraZeneca, Spain.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Pertinar *Ivax, Arg.*
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Pertiroid *Piam, Ital.*
Potassium perchlorate (p. 2343·2).
Hyperthyroidism.

Pertium *Saval, Chile.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Pertlenon *Filofarm, Pol.*
Urea hydrogen peroxide (p. 1774·2).
Wound disinfection; mouth and throat disorders.

Pertriptyl *Orion, Fin.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Anxiety disorders; depression; schizophrenia.

Pertrosom *Alvartis, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Pertudoron *Weleda, Austria†; Weleda, Fr.*
Atropa belladonna (p. 2453·3); cinchona rubra (p. 2478·3); coccus cacti (p. 2179·2); drosera rotundifolia (p. 2497·2); ipecacuanha (p. 1667·2); mephitis putorius; veratrum album (p. 2644·3).
Homoeopathic preparation.

Pertudoron 1 *Weleda, Ger.*
Belladonna (p. 2453·3); china (p. 2478·3); coccus cacti (p. 2179·2); drosera (p. 2497·2); ipecacuanha (p. 1667·2); mephitis putorius; veratrum album (p. 2644·3).
Homoeopathic preparation.

Weleda, Canad.†
Belladonna (p. 2453·3); cochineal (p. 2179·2); drosera rotundifolia (p. 2497·2); ipecac (p. 1667·2); mephitis mephitica; quinine (p. 665·1); white hellebore root (p. 2644·3).
Homoeopathic preparation.

Pertudoron 2 *Weleda, Canad.†; Weleda, Ger.*
Cuprum acetic. (p. 2486·2).
Homoeopathic preparation.

Pertudoron Drops *Weleda, S.Afr.†*
Drosera (p. 2497·2); china cortex (p. 2478·3); veratrum album (p. 2644·3); coccus cacti (p. 2179·2); belladonna (p. 2453·3); ipecacuanha (p. 1667·2); mephites putorius.
Homoeopathic preparation.

Pertusan *Argenfarma, Arg.*
Centella (p. 1698·3).
Venous disorders; haemorrhoids.

Pertussin
Note: this name may be used for preparations of different composition.
Knop, Chile.
Rumex (p. 2649·3); ipecacuanha (p. 1667·2); drosera (p. 2497·2).
Homoeopathic preparation.

Lewison, Philipp.
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Medphano, Ger.
Syrup: Thyme (p. 2630·2).
Cough.

Phytopharm, Rus.
Wild thyme (p. 2648·1); potassium bromide (p. 2461·1).
Cough.

Pertussol *Rekah, Israel.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1).
Cough.

Pertustat *Flamingo, Philipp.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Pertzye *Digestive Care, USA.*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Peru Stick *Tentan, Switz.*
Lidocaine hydrochloride (p. 1988·2); peru balsam (p. 2587·1); camphor (p. 2466·2); castor oil (p. 2472·1).
Chapped and cracked skin; frostbite.

Pérubore *Mayoly-Spindler, Fr.*
Thyme oil (p. 2630·3); rosemary oil (p. 2607·3); lavender oil (p. 2541·1); thymol (p. 1772·2).
Formerly contained thyme oil, rosemary oil, lavender oil, thymol, and peru balsam.
Upper respiratory-tract congestion.

Perubore *ACP, Belg.†*
Peru balsam (p. 2587·1); thyme oil (p. 2630·3); rosemary oil (p. 2607·3); thymol (p. 1772·2).
Sinusitis; rhinitis.

Perusliuos-K *Fresenius Kabi, Fin.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Perviam *Johnson & Johnson Consumer, Belg.†*
Ibuprofen lysine (p. 68·3).
Pain; fever.

Pervicol *Phoenix, Arg.*
⊗Alcohol (p. 1733·1); aloe vera (p. 1693·2).
Hand cleanser.

Pervicol Toallas *Phoenix, Arg.*
⊗Alcohol (p. 1733·1); aloe vera (p. 1693·2); chlorhexidine (p. 1743·2).

Pervil *Vianex (Βιανεξ), Gr.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Pervinox *Phoenix, Arg.*
Povidone-iodine (p. 1767·1).
Skin, wound, and ulcer disinfection.

Pervinox Clorhexidina *Phoenix, Arg.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Pervinox D *Phoenix, Arg.*
Povidone-iodine (p. 1767·1).
Genital-tract infections.

Pervinox Extra Mint *Phoenix, Arg.*
Cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); sodium fluoride (p. 2089·2); peppermint oil (p. 1877·1); spearmint oil (p. 2621·2).
Oral hygiene; dental caries prophylaxis.

Pervinox Fresh Mint *Phoenix, Arg.*
Cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); sodium fluoride (p. 2089·2).
Oral hygiene; dental caries prophylaxis.

Pervinox Fruit *Phoenix, Arg.*
Cineole (p. 2479·1); thymol (p. 1772·2); methyl salicylate (p. 92·1); menthol (p. 2553·2); sodium fluoride (p. 2089·2).
Oral hygiene; dental caries prophylaxis.

Pervinox Incoloro *Phoenix, Arg.*
Chlorhexidine gluconate (p. 1743·3).
Wound disinfection.

Pervinox Jabon *Phoenix, Arg.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).
Hand cleansing.

Pervioral *Royal, Chile.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Pervisept *Phoenix, Arg.*
Cymbopogon.
Insect repellent.

Pervita
Note: this name may be used for preparations of different composition.
Sanbe, Indon.
Vitamins; minerals.

Per-Vital *Munir, Turk.*
Vitamins; lutein (p. 2079·2).

Pervivo *Bittner, Austria.*
Manna (p. 1858·2); camphor (p. 2466·2); zedoary; angelica (p. 2443·3); myrrh (p. 2566·1); gentian (p. 2512·1); carlina acaulis; nutmeg (p. 2573·1); liquorice (p. 1853·2); elecampane (p. 1662·3) centaury (p. 2473·2); clove (p. 2481·2); galanga; ginger (p. 1844·1); cnicus benedictus (p. 2482·2); achillea moschata; theriac; iris florentina; verbascum (p. 2645·1); bitter orange peel (p. 2575·3); calamus (p. 2464·2); absinthium (p. 2426·1); curacao peel; cubeb (p. 2489·2); star anise (p. 2622·1); sweet orange peel (p. 2576·2); menyanthes (p. 2554·2).
Gastrointestinal disorders; tonic.

Bittner, Pol.
Manna (p. 1858·2); camphor (p. 2466·2); angelica (p. 2443·3); myrrh (p. 2566·1); gentian (p. 2512·1); nutmeg (p. 2573·1); liquorice (p. 1853·2); centaury (p. 2473·2); clove (p. 2481·2); galanga; cnicus benedictus (p. 2482·2); achillea moschata; bitter-orange peel (p. 2575·3); verbascum (p. 2645·1); calamus (p. 2464·2); absinthium (p. 2426·1); curacao peel; star anise (p. 2622·1); menyanthes leaf (p. 2554·2); sweet-orange peel (p. 2576·2); cubeb (p. 2489·2); elecampane (p. 1662·3); iris florentina; theriac; zedoary; ginger (p. 1844·1).
Dyspepsia; gallbladder disorders; infections; musculoskeletal and joint disorders.

Pervone *Sanofi-Aventis, Gr.*
Dihydroergotamine mesilate (p. 672·2).
Migraine; vascular headache.

Perycit *Sanwa, Jpn.*
Niceritrol (p. 1446·1).
Hyperlipidaemias; peripheral vascular disorders.

Perzine *PP Lab, Thai.*
Perphenazine (p. 1095·3).
Psychoses; nausea and vomiting.

Pesendorfer *Iso, Ger.*
Berberis (p. 2502·1); conium (p. 2524·3); echinacea (p. 2498·1); hamamelis (p. 2523·3); populus.
Homoeopathic preparation.

Pesium *Flupal, Venez.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Pespire *Berman, Mex.*
Vitamin B substances (p. 2102·3).

Pestarin *Provit, Mex.†*
Rifampicin (p. 350·3).
Bacterial infections.

Petadolex *Weber & Weber, Ger.†*
Butterbur (p. 2463·2).
Smooth muscle spasms.

Pe-Tam *Qualiphar, Belg.*
Paracetamol (p. 115·1).
Fever; pain.

Petaxel *Biochem, India.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Peteha *Riemser, Ger.; Fatol, Hong Kong; Fatol, Rus.*
Tablets: Protionamide (p. 345·1).
Tuberculosis.

Petercillin *Aspen, S.Afr.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Peterkaïen *Intramed, S.Afr.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; arrhythmias.

Peterphyllin *Intramed, S.Afr.†*
Injection: Aminophylline (p. 1201·2).
Obstructive airways disease.

Peter's Sirop *Merck Medication Familiale, Fr.*
Ethylmorphine hydrochloride (p. 56·3).
Cough.

Peteyu *Charoon Bhesaj, Thai.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Petezam *Rivero, Arg.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Petibelle *Jenapharm, Ger.; Lusal, Port.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Petimid *Tems, Turk.*
Ethosuximide (p. 521·1).
Epilepsy.

Petina Compound *Jean-Marie, Hong Kong.*
Cyproheptadine hydrochloride (p. 624·1); vitamins.
Appetite loss; tonic.

Petinan *Biochimico, Braz.*
⊗Pethidine (p. 121·3).

Petinimid *Gerot, Austria; GL Pharma, Cz.; IFET (ΙΦΕΤ), Gr.; Gerot, Pol.*
Ethosuximide (p. 521·1).
Absence seizures.

Pétinimid *Orion, Switz.*
Ethosuximide (p. 521·1).
Absence seizures.

Petinutin *Pfizer, Ger.; Pfizer, Switz.*
Mesuximide (p. 533·1).
Absence seizures; epilepsy.

Petites Pilules Carters *Sofibel, Fr.†*
Boldine (p. 2458·3); aloes (p. 1816·1).
Constipation.

Petivit BC *Brasterapica, Braz.*
Cyproheptadine hydrochloride (p. 624·1); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).

Petnidan *Desitin, Ger.; Desitin, Hung.*
Ethosuximide (p. 521·1).
Absence seizures.

Petogen *Fresenius Kabi, S.Afr.*
Medroxyprogesterone acetate (p. 2288·1).
Injectable contraceptive.

Petrazole *Pharos, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Petrazyc *Petsiavas, Gr.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Petylyl *Temmler, Ger.†; AWD, Pol.†*
Desipramine hydrochloride (p. 413·1).
Depression.

Peucetol *Serral, Mex.*
Pantoprazole (p. 1875·3).

Pevaryl *ICN, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Cz.; McNeil, Denm.†; McNeil, Fin.†; Johnson & Johnson, Fr.; Janssen-Cilag, Gr.; Janssen-Cilag, Hung.; Johnson & Johnson, Hung.; Janssen-Cilag, Israel†; Johnson & Johnson, Neth.; McNeil, Norw.; Pacific, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Johnson & Johnson, Port.; Janssen-Cilag, Singapore; McNeil, Swed.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Econazole nitrate (p. 577·3).
Fungal and Gram-positive bacterial infections.

Johnson & Johnson Consumer, Belg.†; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Roche, S.Afr.; Janssen-Cilag, Switz.
Econazole (p. 577·2) or econazole nitrate (p. 577·3).
Fungal infections; Gram-positive bacterial infections.

Pevaryl HP *Janssen, Philipp.†*
Econazole nitrate (p. 577·3); zinc oxide (p. 1729·1).
Fungal skin infections.

Pevazol *Chema-Elektromet, Pol.*
Econazole nitrate (p. 577·3).
Fungal skin, nail, and ear infections; mixed fungal and Gram-positive bacterial skin infections.

Pevison *Europharma, Denm.; Janssen-Cilag, Gr.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections with inflammation.

Pevisone *Janssen-Cilag, Austria; Johnson & Johnson Consumer, Belg.†; Xian-Janssen, China; Janssen-Cilag, Denm.†; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Cilag, Hong Kong; Janssen-Cilag, Israel†; Janssen-Cilag, Ital.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin and nail infections with inflammation.

Pexeva *Noven, USA.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder.

Pexogies *Synthon, Cz.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Pexola *Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Turk.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Pexopaul *Synthon, Cz.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Pexsig *Aspen, Austral.; Healthcare Logistics, NZ.*
Perhexiline maleate (p. 1466·3).
Angina pectoris.

Peyona *Torrex Chiesi, Cz.; Chiesi, Gr.; Chiesi, Irl.; Chiesi, Neth.; Chiesi, Pol.; Chiesi, Port.; Chiesi, Spain; Chiesi, UK.*
Caffeine citrate (p. 1203·3).
Formerly known as Nymusa.
Apnoea of prematurity.

Pezale *Sandoz, Gr.*
Donepezil hydrochloride (p. 390·2).

Pezeta-Ciba *Sandoz, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pezide *Greater Pharma, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

PF Drops *Candor, India.*
Paracetamol (p. 115·1).
Pain; fever.

PFD *Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Ital.†*
Preparation for enteral nutrition.
Amino-acid metabolic disorders.

Pfeiffer's Cold Sore *Pfeiffer, USA.*
Sumatra benzoin (p. 2624·3); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1).
Oral lesions.

Pfeil *Stada, Ger.*
Ibuprofen (p. 68·2).
Pain.

P-Fen *Millimed, Thai.†*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; gout; fever; pain.

Pfizer Obstetric Lotion *Pfizer Consumer, Singapore.†*
Chlorhexidine gluconate (p. 1743·3).
Disinfection and lubrication during gynaecological or obstetric procedures.

Pfizerpen *Pfizer, USA.*
Benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Pflügerplex Gelsemium *Pfluger, Ger.*
Cyclamen purpurascens (p. 2490·2); gelsemium sempervirens (p. 2511·2); melilotus officinalis (p. 2552·3); primula veris (p. 2596·2); sanguinaria canadensis (p. 2610·1); strychnos nux-vomica (p. 2573·3); thea chinensis (p. 2648·2).
Homoeopathic preparation.

Pflügerplex Lemna *Pfluger, Ger.*
⊗Acid. silicicum (p. 2208·3); calcium carbonicum (p. 1824·3); kalium nitricum (p. 1766·2); lemna minor; sanguinaria canadensis (p. 2610·1); teucrium marum; thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

PFT *Reckitt Benckiser, India.*
Simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2).
Flatulence; dyspepsia; gastric hyperacidity; gastritis; peptic ulcer; hiatus hernia; aerophagia; oesophagitis.

PG/53 *Raymos, Arg.*
Fertility test (p. 2596·1).

P-Glitz *Cipla, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

P-Glitz M *Cipla, India.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

P-Gyzole *Osoth, Thai.*
Clotrimazole (p. 576·2).
Vaginal candidiasis; trichomoniasis.

pH4 *Biological E, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; peptic ulcer; heartburn.

pH Care *Biomedis, Malaysia.*
⊗Glycerol (p. 2517·2); panthenol (p. 2582·2); cocamidopropyl betaine; bisabolol (p. 2544·1); chamomile (p. 2474·1); citric acid (p. 2480·3); sodium lauril ether sulfate (p. 2210·3).
Vaginal hygiene.

Biomedis, Philipp.
⊗Dexpanthenol (p. 2582·2); glycerol (p. 2517·2); chamomile (p. 2474·1).
Feminine hygiene.

pH Care Intimate Wash *Biomedis, Singapore.*
⊗Dexpanthenol (p. 2582·2); glycerol (p. 2517·2); chamomile (p. 2474·1).
Feminine hygiene.

Phacebonate *Synthon, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis; bone metastases in breast cancer.

Phaclor *Bright Future, Hong Kong.†*
Cefaclor (p. 232·3).
Bacterial infections.

Phacobiotic *Bros, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Phacocef *Bros, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Phacolysin *Liye, China.*
Phacolysin.
Cataract.

Phacotrex *Bros, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Phacovit *Bros, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Phadilon *Phapros, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Phadryl *Burapha, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Phaeva *Bayer, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Phakan *Chauvin, Fr.†*
Combination pack: Oral solution, glycine (p. 2071·2); glutamic acid (p. 2070·2); pyridoxine hydrochloride (p. 2105·3); capsules, cysteine hydrochloride (p. 2058·3); ascorbic acid (p. 2110·3).
Cataracts.

Phalol *Phapros, Indon.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Phaltrexia *Pharos, Indon.†*
Naltrexone hydrochloride (p. 1565·1).
Opioid dependence.

Phanalgin *Rekah, Israel.†*
Dipyrone (p. 53·3).
Fever; pain.

Phanate *Pharmaland, Thai.†*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression.

Phanatuss Cough *Pharmakon, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Phanères *Lero, Fr.*
Evening primrose oil (p. 2502·2); cystine (p. 2059·1); vitamins; zinc (p. 2126·1).
Hair and nail disorders.

Phanerol *Apotex, Philipp.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; migraine; hypertrophic subaortic stenosis; phaeochromocytoma.

Phapax *Lehning, Fr.*
Cyclamen europaeum (p. 2490·2); gelsemium sempervirens (p. 2511·2); chelidonium majus (p. 2522·2); ruta graveolens (p. 2608·2); iris versicolor (p. 2534·3); sanguinaria canadensis (p. 2610·1); argentum nitricum (p. 2615·3); cimicifuga (p. 2478·1); digitalis purpurea (p. 1352·3); melilotus officinalis (p. 2552·3).
Homoeopathic preparation.

Phapin *Phapros, Indon.*
Ampicillin (p. 218·2).
Bacterial infections.

Phaproxin *Phapros, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Pharbechlor *Pharbest, USA.*
Chlorphenamine maleate (p. 620·3).
Antihistamine.

Pharben *Gelpharma, Mex.*
Benzonatate (p. 1656·2).
Cough.

Pharbetol *Pharbest, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Pharbrix *Sons, Mex.*
1 Ampoule, tetracycline hydrochloride (p. 373·2); 1 ampoule, lidocaine hydrochloride (p. 1988·2); chlorphenamine maleate (p. 620·3); sodium ascorbate (p. 2111·1); guaifenesin (p. 1666·2).
Bacterial infections.

Pharcal *Community Pharmacy, Thai.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Pharcetil *Teva, Philipp.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Pharcina *Exakta, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Pharcold *Community Pharmacy, Thai.*
⊗Paracetamol (p. 115·1); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Phardiab *Burapha, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Phardol Schmerz *Kreussler, Ger.*
Ketoprofen (p. 79·1).
Peri-articular and soft-tissue disorders.

Pharemin *Pacific, Philipp.*
Vitamins; iron (p. 2073·1).

Pharepa *Pharmatex, Ital.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Pharfed *Pharmaland, Thai.*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine (p. 1676·1).
Respiratory-tract congestion.

Pharflox *Pharos, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Pharicid *Pharmanel, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Pharken *Lilly, Spain.†*
Pergolide mesilate (p. 910·2).
Parkinsonism.

Pharlecon *Stargen, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Pharlemyron *Konstantinos, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Pharlinde *Main Life, Hong Kong.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Pharmacaine *Quimpharma, Mex.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Pharma-Cal D *Pharmascience, Canad.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement.

Pharmacen *Alpharma, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Pharmacetin *Olan-Kemed, Thai.*
Chloramphenicol (p. 257·1).
Bacterial ear infections.

Pharmachem *GruppoMedica, Philipp.*
Guaifenesin (p. 1666·2).
Cough.

Pharmacists Creme *Reese, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); capsicum oleoresin (p. 2469·3).

Pharmacists Lotion *Reese, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); capsicum oleoresin (p. 2469·3).

Pharmacist's Own Pain Relief *API, NZ.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Pharmacist's Own Pain Relief Plus *API, NZ.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain.

Pharmacort *Teva, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Pharma-Dentix *Germiphene, Israel.†*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders; oral hygiene.

Pharmadine *TP, Thai.*
Povidone-iodine (p. 1767·1).
Disinfection of burns and wounds.

Pharmadol
Note: this name may be used for preparations of different composition.
Pharmaland, Thai.
Tramadol hydrochloride (p. 139·2).
Pain.

Bright Future, Hong Kong†; Sodhan, Turk.
Paracetamol (p. 115·1).
Pain; fever.

Pharmadose alcool *Gilbert, Fr.*
⊗Alcohol (p. 1733·1).
Skin and wound disinfection.

Pharmadose teinture d'arnica *Gilbert, Fr.*
Arnica (p. 2447·2).
Ecchymoses.

Pharmafet *Alpharma, Mex.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Pharmafil *Alpharma, Mex.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Pharmaflam *Quimpharma, Mex.*
Diclofenac resinate (p. 48·3).
Inflammation; fever; pain.

Pharmaflur *Pharmics, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Pharmafort *Boehringer Ingelheim, Arg.*
Ginseng (p. 2513·3); rutoside (p. 2505·3); vitamins; minerals.
Tonic.

Pharmagin
Note: this name may be used for preparations of different composition.
New Century, Thai.
Ginsenosides (p. 2513·3).

Pharmasant, Thai.†
Metamizole.
Pain; fever.

Pharmagrip *Cinfa, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms; pain; fever.

Pharmagrip Duo *Cinfa, Spain.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Pharmakod expectorant *Sanofi-Aventis, Fr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Pharmakod toux sèche *Sanofi-Aventis, Fr.†*
Pholcodine (p. 1675·1).
Cough.

Pharmalatum *Medipharm, Chile.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Nasal congestion.

Pharmalgen *ALK, Belg.; ALK, Denm.; ALK, Neth.; ALK, Pol.; ALK, Switz.; ALK, UK; ALK, USA.*
Venom of bee (p. 2434·3), wasp (p. 2434·3), hornet, yellow jacket, or mixed vespids.
Allergen immunotherapy.

Western Allergy, Canad.†
A range of allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity; allergen immunotherapy.

Pharmalgen Albumin *ALK, Denm.*
⊗Human albumin (p. 1130·2); mannitol (p. 1427·3).
Diluent for allergen extracts.

Pharmamox *Doctors, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pharmapress *Aspen, S.Afr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Pharmapress Co *Aspen, S.Afr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pharmaprol *Cosmopharm, Gr.*
Ambroxol hydrochloride (p. 1654·3).

Pharmarin *Pharmaland, Thai.*
Silymarin (p. 1561·2).
Liver disorders.

Pharmaskin *Pharmaskin, Rus.*
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Pharmaspirin *Sodhan, Turk.*
Aspirin (p. 22·2).

Pharmatet *Pharmachem, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).

Pharmatex *Raymos, Arg.; Innotech, Cz.; Innotech, Fr.; Innotech, Hong Kong; Innotech, Hung.; Innothera, Irl.; Sidefarma, Port.†; Innotech, Rus.; Innotech, Ukr.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Pharmaton *Boehringer Ingelheim, Hong Kong; Pharmaton, Israel; Boehringer Ingelheim, Mex.; Boehringer Ingelheim, S.Afr.†; Abdi, Turk.; Boehringer Ingelheim Self Medication, UK.*
Ginseng (p. 2513·3); vitamins; minerals; lecithin (p. 2542·2).
Age-related disorders; tonic; dietary supplement.

Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Fr.†; Boehringer Ingelheim, Irl.
Ginseng (p. 2513·3); vitamins; minerals.
Tonic; age-related disorders.

Boehringer Ingelheim, Ger.
Vitamins; minerals; ginseng (p. 2513·3); essential fatty acids.

Boehringer Ingelheim, Philipp.
⊗Vitamins; minerals; ginseng (p. 2513·3); deanol tartrate (p. 2319·1); rutoside (p. 2505·3); choline (p. 2055·2); inositol (p. 2533·2); linoleic acid (p. 2509·2); linolenic acid (p. 1460·2).
Nutritional supplement.

Boehringer Ingelheim, Thai.
⊗Ginseng (p. 2513·3); deanol tartrate (p. 2319·1); rutoside (p. 2505·3); lecithin (p. 2542·2); vitamins; minerals.
Tonic.

Pharmaton, Malaysia.†
Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2); choline (p. 2055·2); inositol (p. 2533·2); linoleic acid (p. 2509·2); linolenic acid (p. 1460·2).
Tonic.

Pharmaton, Singapore.†
Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2); rutoside (p. 2505·3).

Pharmaton Activit *Boehringer Ingelheim, Cz.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Pharmaton Complex *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Spain.†*
⊗Ginseng (p. 2513·3); deanol tartrate (p. 2319·1); rutoside (p. 2505·3); vitamins; minerals.
Tonic.

Boehringer Ingelheim, Mex.
⊗Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); lecithin (p. 2542·2); deanol tartrate (p. 2319·1).

Pharmaton Fizzi *Boehringer Ingelheim, Thai.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Pharmaton Formula *Boehringer Ingelheim, Indon.; Pharmaton, Indon.*
⊗Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2); rutoside (p. 2505·3); deanol tartrate (p. 2319·1).
Tonic.

Pharmaton Geriatric *Boehringer Ingelheim, Gr.*
⊗Vitamins; minerals; deanol tartrate (p. 2319·1); rutoside (p. 2505·3); ginseng (p. 2513·3).

Pharmaton Kiddi *Boehringer Ingelheim, Braz.*
Lysine hydrochloride (p. 2079·3); vitamins; minerals.

Boehringer Ingelheim, Singapore.
Vitamins; minerals; lysine (p. 2079·3).

Pharmaton, Switz.
Vitamins; minerals.

Pharmaton Kiddi Vita *Pharmaton, Switz.*
Lysine hydrochloride (p. 2079·3); vitamins; calcium (p. 1783·1).

Pharmaton Matruelle *Boehringer Ingelheim, Indon.; Pharmaton, Indon.; Boehringer Ingelheim, Mex.*
Vitamins; minerals; omega-3 fatty acids (p. 1460·1).
Dietary supplement in pregnancy and breast feeding.

Pharmaton with Selenium *Boehringer Ingelheim, Malaysia.*
Ginseng (p. 2513·3); vitamins; minerals; selenium (p. 2086·3).
Dietary supplement.

Boehringer Ingelheim, Singapore.
Vitamins; minerals; trace elements; ginseng (p. 2513·3); with or without lecithin (p. 2542·2).
Dietary supplement.

Pharmaton Vit *Boehringer Ingelheim, Indon.; Pharmaton, Indon.*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic.

Pharmaton Vital *Boehringer Ingelheim, Hung.*
⊗Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); lecithin (p. 2542·2); deanol tartrate (p. 2319·1).
Tonic.

Pharmaton Vital Geriavit *Pharmaton, Switz.*
⊗Ginseng (p. 2513·3); deanol tartrate (p. 2319·1); vitamins; minerals; rutoside (p. 2505·3); lecithin (p. 2542·2).
Tonic.

Pharmatovit Ginseng *Pharmaton, Switz.*
Vitamins; minerals; ginseng (p. 2513·3).

Pharmavoyage Moustiquaires *Katadyn, Fr.*
Mosquito net impregnated with permethrin (Peripel) (p. 2159·3) or deltamethrin (p. 2152·1).
Insect repellent.

Pharmazolin *Farmak, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Allergic rhinitis; nasal congestion; sinusitis.

Pharmecort *Pharmex (Φαρμεξ), Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Pharmexin *Pharmex (Φαρμεξ), Gr.*
Brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Pharmix *Apotex, Philipp.†*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Pharmorat *Leti, Venez.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Pharmorubicin *Pfizer, Austral.; Pfizer, Canad.; Pfizer, China; Pfizer, Hong Kong; Pharmacia, Irl.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Pharmotidine *Community Pharmacy, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Pharmox *Greenpharma, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

Pharmtina *Stada, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Pharmyork *Bros, Gr.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; gastrointestinal investigations; acid aspiration.

Pharnax *Pharmaland, Thai.*
Alprazolam (p. 1035·2).
Mixed anxiety depressive states.

Pharnazine *Pharmaland, Thai.*
Fluphenazine decanoate (p. 1075·1).
Schizophrenia.

Pharnolol *Pharlab, Braz.*
⊗Propranolol (p. 1479·1).

Pharodime *Pharos, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Pharothrocin *Pharos, Indon.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Pharo-Tus *Nakornpatana, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough.

Pharproxin *Community Pharmacy, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Phartidine *Quimpharma, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Pharyndol *Bioethic, Fr.*
Adult spray: ⊗Glycerol (p. 2517·2); honey (p. 2072·1); grape (p. 2521·3); sambucus (p. 2609·3).
Sore throat.
Bioethic, Fr.
Paediatric spray: ⊗Glycerol (p. 2517·2); honey (p. 2072·1); grape (p. 2521·3); sambucus (p. 2609·3); soya (p. 2092·3).
Sore throat.

Pharyngomed *Materia Medica, Rus.*
Atropa belladonna (p. 2453·3); acidum silicicum (p. 2209·1); hepar sulfuris (p. 1721·3); phytolacca americana (p. 2593·2).
Homoeopathic preparation.

Pharyngor *Rappai, Switz.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1).
Dry mouth and throat.

Pharynx *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Cetylpyridinium chloride (p. 1743·1); benzocaine (p. 1980·2).
Mouth and throat infections.

Pharzil *Pharmaland, Thai.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Phazyme *GSK Consumer, Canad.; GSK Consumer, USA.*
Simeticone (p. 1886·2).
Flatulence.

pH-Derm *Mediphar, Venez.*
A range of barrier preparations, emollients, and skin cleansers.

Phelics *Humana, Ital.*
Phenylalanine-free preparations for enteral nutrition.
Phenylketonuria.
Markdistri, Cz.
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Phemax *Pharmasant, Thai.*
Orphenadrine (p. 909·2).
Musculoskeletal pain and spasm.

Phemine *T Man, Thai.*
Guaifenesin (p. 1666·2); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cough and cold symptoms.

Phenacold *Caprifarmindo, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2).
Cough.

Phenadex *Dexa, Indon.*
⊗Promethazine hydrochloride (p. 638·2); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ascorbic acid (p. 2110·3).
Cough.

Phenadine *Quality, Hong Kong.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain and irritation.

Phenadoz *Watson, USA.*
Promethazine hydrochloride (p. 638·2).

Phenaemal *Desitin, Cz.*
Phenobarbital (p. 535·2).
Epilepsy; psychomotor disorders.

Phenaemaletten *Desitin, Cz.*
Phenobarbital (p. 535·2).
Epilepsy; psychomotor disorders.

Phenahist *Universal, Hong Kong.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); diphenylpyraline hydrochloride (p. 627·2).
Cold and influenza symptoms.

Phenameth DM *Major, USA.*
Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Phenamin *Nycomed, Norw.†*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; pruritus.

Phenapap *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Phenapap Sinus Headache & Congestion *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Phenasen *Phebra, Austral.*
Arsenic trioxide (p. 2448·1).
Acute promyelocytic leukaemia.

Phenaseptic *Rugby, USA.*
Phenol (p. 1763·3).
Minor mouth or throat irritation.

Phenate
Note: this name may be used for preparations of different composition.
Alphapharm, Malaysia; Pacific, NZ†; Pacific, Singapore.
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

PhenaVent *Ethex, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Phenazin *Mayne, Port.†*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Phenazo *Valeant, Canad.; Valeant, Hong Kong.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain; lower urinary-tract irritation.

PhenazoForte Plus *Creekwood, USA.*
Butalbital (p. 1043·3); hyoscyamine hydrobromide (p. 1848·1); phenazopyridine hydrochloride (p. 124·3).
Interstitial cystitis.

Phenazone *Chinta, Thai.*
Phenylbutazone (p. 125·1).
Musculoskeletal and joint disorders; gout.

Phenazopyridine Plus *Breckenridge, USA.*
Phenazopyridine hydrochloride (p. 124·3); hyoscyamine hydrobromide (p. 1848·1); secbutabarbital (p. 1106·2).

Phencarol *Olainfarm, Rus.; Olainfarm, Ukr.*
Quifenadine hydrochloride (p. 640·1).
Hypersensitivity; allergic disorders.

Phenchlormine-D *SSP, Thai.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Phencodin *Neopharm, Thai.†*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Cough.

Phencol *Christo, Hong Kong.†*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1).
Respiratory-tract disorders.

Phendiridine *TP, Thai.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain; dysuria.

Phenedrine *Medichem, Philipp.*
Theophylline (p. 1229·3).
Asthma.

Phenerbel-S *Rugby, USA.*
Phenobarbital (p. 535·2); ergotamine tartrate (p. 674·1); belladonna (p. 2453·3).

Phenergan *Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Gr.; Piramal, India; Aventis, Indon.†; Sanofi-Aventis, Irl.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Aventis, UK; Westward, USA.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; insomnia; motion sickness; nausea and vomiting; premedication; sedative; anaphylaxis; allergic rhinitis; urticaria; sleep disorders; adjunct to anaesthesia; parkinsonism; postoperative pain (adjunct); pruritus.

Phénergan *UCB, Fr.*
Promethazine (p. 638·2) or promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; pruritus; insomnia.

Phenerine *Pharmacare, S.Afr.†*
Orphenadrine hydrochloride (p. 909·3).
Parkinsonism.

Phenerzin *Nestor, Philipp.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea; vomiting; anaphylaxis.

Phenetone *Cipla, India.*
Phenobarbital (p. 535·2).

Phenex *Abbott, Austral.*
Phenylalanine-free preparation for enteral nutrition.
Hyperphenylalaninaemia; phenylketonuria.
Ross, USA.
A range of phenylalanine-free preparations for enteral nutrition including an infant feed.
Phenylketonuria; hyperphenylalaninaemia.

Phenexpect *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Phenexpect CD *DHA, Singapore.*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1).
Cough.

Phenexpect DM *DHA, Singapore.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Phenhist DH with Codeine *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Phenhist Expectorant *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Coughs.

Phenhydan *Desitin, Ger.; Desitin, Switz.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy; neuropathic pain; seizures associated with neurosurgery or head injury; trigeminal neuralgia.
Medsan, Turk.
Phenytoin sodium (p. 538·2).
Epilepsy; trigeminal neuralgia.

Phenicol *Vitamed, Israel.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Phenihidin *Belmed, Rus.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; Raynaud's disease.

Phenilep *Prafa, Indon.†*
Phenytoin sodium (p. 538·2).
Epilepsy.

Phenimixin *Vitamed, Israel.*
Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Phenobarb *PP Lab, Thai.*
Phenobarbital sodium (p. 535·3).
Epilepsy; insomnia; sedative.

Phenobiotic *Bernofarm, Indon.†*
Thiamphenicol (p. 376·3).
Bacterial infections.

Phenocillin *Streuli, Switz.†*
Phenoxymethylpenicillin (p. 338·3).
Bacterial infections.

Phenoco *TO-Chemicals, Thai.†*
Phenobarbital (p. 535·2).
Epilepsy; sedative.

Phenodex *Vesco, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Phenokinon-F *Vesco, Thai.*
Progesterone (p. 2300·2); estradiol benzoate (p. 2271·1).
Menstrual disorders.

Phenolax *ANH, Thai.*
Phenolphthalein (p. 1877·3).
Constipation.

Pheno-M *Vesco, Thai.†*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive; dysfunctional uterine bleeding; endometriosis.

Phenorelaxan *Moschimfarm, Rus.*
Phenazepam (p. 1096·3).
Anxiety disorders; epilepsy; psychoses; movement disorders.

Phenotal *Asian Pharm, Thai.*
Phenobarbital sodium (p. 535·3).
Epilepsy; sedative; insomnia.

Phenotropil *Valenta, Rus.; Valenta, Ukr.*
⊗Fonturacetam (p. 391·3).
Metabolic and vascular cerebral disorders; mental function disorders; depression; obesity; convulsions; chronic alcoholism.

Phenpro *AbZ, Ger.; Ratiopharm, Ger.*
Phenprocoumon (p. 1468·3).
Thromboembolic disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Phenprogamma *Worwag, Ger.*
Phenprocoumon (p. 1468·3).
Thromboembolic disorders.

Phenrex *Imrex, Canad.*
Chloroxylenol (p. 1748·2).

Phensedyl
Note: this name may be used for preparations of different composition.
Nicholas Piramal, India.
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Cough.

Sanofi-Aventis, Singapore; Olic, Thai.
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough; cold symptoms.

Sanofi-Aventis, S.Afr.
⊗Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Phensedyl Dry Cough *Sanofi-Aventis, Malaysia.*
⊗Promethazine hydrochloride (p. 638·2); pholcodine (p. 1675·1); ephedrine hydrochloride (p. 1663·2).
Cough.

Phensedyn *Quality, Hong Kong.*
⊗Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough; nasal congestion.

Phensic *Seven Seas, Irl.†; Merck Consumer, UK.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Phenybut-Anvi *Antiviral, Rus.*
4-Amino-3-phenylbutyric acid hydrochloride.
Anxiety disorders; obsessive-compulsive disorder; stammer; tics; insomnia; premedication; alcohol withdrawal syndrome; vestibular disorders; motion sickness.

Phenylephrine Complex *Breckenridge, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Phenyl-Free *Mead Johnson, Chile; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Israel; Mead Johnson, Ital.; Mead Johnson, NZ; Mead Johnson, Pol.; Mead Johnson Nutritionals, USA.*
Food for special diets.
Phenylketonuria; disorders of phenylalanine metabolism.

Phenylgesic *Goldline, USA.*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Phenylhistine DH *Qualitest, USA.*
⊗Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Phenylin *Zdorovje, Rus.*
Phenindione (p. 1467·3).
Thromboembolic disorders.

Phenyl-T *Boca, USA.†*
Phenylephrine tannate (p. 1672·2).
Nasal congestion.

Phenyltrope *Sandoz, Canad.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Phenyphrine-Azol *Vitamed, Israel.†*
⊗Mepyramine maleate (p. 635·1); naphazoline hydrochloride (p. 1669·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Phenyramon *Faran, Gr.*
Codergocrine mesilate (p. 389·2).

Phenytek *Bertek, USA.*
Phenytoin (p. 538·2).
Epilepsy.

Pheoronex *Medopharm, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Pherazine with Codeine *Halsey, USA.*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Pherazine DM *Halsey, USA.*
Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Pherazine VC *Halsey, USA.*
Promethazine hydrochloride (p. 638·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract symptoms.

Pherazine VC with Codeine *Halsey, USA.*
Promethazine hydrochloride (p. 638·2); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Pherazone *Chinta, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Pheresthal *Bryntsalov, Rus.*
⊗Pancreatin (p. 2579·3); hemicellulase (p. 2473·1); ox bile (p. 2457·2).
Pancreatic insufficiency; digestive disorders; abdominal examination.

pH5-Eucerin *Beiersdorf, Venez.*
A range of barrier preparations, emollients, and skin cleansers.

Beiersdorf, Thai.†
A range of skin cleansing and emollient preparations.

Phexin *GSK, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Phezam *Balkanpharma, Rus.; Actavis, Ukr.*
Cinnarizine (p. 622·1); piracetam (p. 393·3).
Cerebrovascular disorders; mental function impairment; vestibular disorders; migraine; eye disorders; motion sickness.

Phezipam *Tatkhimfarm, Rus.*
Phenazepam (p. 1096·3).
Anxiety disorders; withdrawal syndromes; epilepsy; schizophrenia; movement disorders; premedication.

Phicon *Williams, USA.*
Pramocaine hydrochloride (p. 1993·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Local anaesthesia.

Phicon-F *Williams, USA.*
Pramocaine hydrochloride (p. 1993·3); undecenoic acid (p. 596·3).
Fungal skin infections.

Philenterol *Ipsen, Port.†*
Macrogol 4000 (p. 2547·3).

Philinal *Rekah, Israel.†*
Suppositories: Diprophylline (p. 1207·3); phenobarbital (p. 535·2).
Obstructive airways disease.

Philinet *Rekah, Israel.†*
Diprophylline (p. 1207·3); phenobarbital (p. 535·2).
Obstructive airways disease.

Philipon-S *SJA, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Philips Leche de Magnesia *GSK Consumer, Venez.*
Magnesium hydroxide (p. 1857·2).
Constipation; gastric hyperacidity.

Phillips *GSK, Arg.*
Docusate sodium (p. 1836·2).
Constipation.

Phillips' Chewable *Bayer, USA.*
Magnesium hydroxide (p. 1857·2).
Hyperacidity.

Phillips' Magnesia Tablets *Bayer Consumer, Canad.*
Magnesium hydroxide (p. 1857·2).
Hyperchlorhydria; peptic ulcer; constipation.

Phillips' Milk of Magnesia *Bayer Consumer, Canad.; Bayer, USA.*
Magnesium hydroxide (p. 1857·2).
Constipation; gastric hyperacidity; dyspepsia.

pHisoDerm *Chattem, USA.*
Skin cleanser.

pHisoDerm Acne Mask *Mentholatum, Canad.†*
Salicylic acid (p. 1719·1).
Acne.

pHisoHex
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Canad.; Sanofi Winthrop, USA.
Entsufon sodium (p. 2500·1); hexachlorophene (p. 1754·1).
Skin disinfection; skin cleansing.

pHisoHex Face Wash *Aspen, Austral.*
Triclosan (p. 1773·2).
Acne.

pHisoHex Reformulated *PHC, Indon.*
Triclosan (p. 1773·2).
Skin cleansing; minor skin infections; acne.

P-Hist *Midlothian, USA.*
Dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1); dexchlorpheniramine maleate (p. 621·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

P-Hist DM *Midlothian, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Phlébocrème *Merck Medication Familiale, Fr.*
Benzocaine (p. 1980·2); dodeclonium bromide (p. 1750·3); esculoside (p. 2431·2); enoxolone (p. 54·2).
Anorectal disorders.

Phlebodia *IFA, Mex.; Innothera, Pol.; Innothera, Rus.*
Diosmin (p. 2505·2).
Haemorrhoids; capillary fragility; venous insufficiency.

Phlebodril *Robapharm, Switz.*
Cream: Butcher's broom (p. 2463·1); melilot (p. 2552·3).
Venous insufficiency.

Pierre Fabre, Ger.†
Butcher's broom (p. 2463·1); trimethylhesperidin chalcone (p. 2505·2).
Vascular disorders.

Phlebodril N
Note: this name may be used for preparations of different composition.
Robapharm, Switz.
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2).
Haemorrhoids; venous insufficiency.

Phlebodril Venenkapsein *Pierre Fabre, Ger.*
Butcher's broom (p. 2463·1).
Formerly known as Phlebodril mono.
Haemorrhoids; venous insufficiency.

Phlébogel *Merck Serono, Fr.†*
⊗Aescin (p. 2431·2); buphenine hydrochloride (p. 2462·3).
Chronic venous insufficiency.

Phlébosédol *Lehning, Fr.†*
Aesculus (p. 2431·2); hamamelis (p. 2523·3); viburnum (p. 2458·1); alchemilla; red vine (p. 2521·3).
Haemorrhoids; venous insufficiency.

Phlebostasin *Takeda, Switz.*
Aesculus (p. 2431·2).
Venous insufficiency.

Phlebosup *Merck Medication Familiale, Fr.*
Benzocaine (p. 1980·2); dodeclonium bromide (p. 1750·3); esculoside (p. 2431·2); enoxolone (p. 54·2).
Anorectal disorders.

Phlegmol *MedGen, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Phlemasol *Littman, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Phlemex-PE *Cypress, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Phlexy *Nutricia, Austral.; Nutricia, Cz.; Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.; Nutricia, NZ; SHS Nutrition, NZ.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

SHS, UK.
Amino acids.
Phenylketonuria.

Phlexy Vits *SHS, Irl.*
Vitamins; minerals; trace elements.
Nutritional supplement for restricted therapeutic diets.

Phlexy-Vits *Nutricia, Fr.*
Vitamins; minerals; trace elements.

Phlexyvits *SHS, UK.*
Vitamins; minerals.

Phloderm *Herbapol Poznan, Pol.†*
Hamamelis (p. 2523·3).
Skin disorders.

Phlogantin *Streuli, Switz.†*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); mint oil (p. 2560·1); kaolin (p. 1850·1).
Musculoskeletal and soft-tissue disorders; burns; wounds.

Phlogenzym *Mucos, Austria; Mucos, Cz.; Mucos, Ger.†; Mucos, Hung.; Romsa, Mex.; Mucos, Rus.; Mucos, Ukr.; Mucos, Venez.*
⊗Bromelains (p. 2460·3); trypsin (p. 2635·2); rutoside (p. 2505·3).
Pain; inflammation; oedema; wounds; thrombophlebitis; musculoskeletal, joint, periarticular, and soft-tissue disorders; burns.

Phlogenzym mono *Mucos, Ger.*
⊗Bromelain (p. 2460·3).
Nasal congestion.

Phlogosam *PannonPharma, Hung.*
Ointment: Sodium sulfosalicylate samarate.
Skin disorders; thrombophlebitis; burns.

PannonPharma, Hung.
Topical foam: Dexpanthenol (p. 2582·2) lidocaine (p. 1988·1); sodium sulfosalicylate samarate.
Skin disorders; thrombophlebitis; wounds.

Phlogosol *PannonPharma, Hung.*
Sodium sulfosalicylate samarate; hexachlorophene (p. 1754·1).
Mouth and throat disorders.

Phocium *Pharmasant, Thai.*
Calcium phosphate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium supplement.

Phocytan *Aguettant, Fr.*
Glucose-1-phosphate disodium, tetrahydrate (p. 2070·2).
Parenteral nutrition; hypophosphataemia.

Phoenix Lagrimas *Elea, Arg.*
Eye gel: Carbomer 974P (p. 2173·3).
Dry eyes.

Elea, Arg.; Phoenix, Arg.
Eye drops: ⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Eye irritation; dry eyes.

Pholcodex *Pinewood, Irl.*
Pholcodine (p. 1675·1).
Cough.

Pholcodyl *Zambon, Fr.†*
Pholcodine (p. 1675·1); erysimum (p. 2524·2).
Cough.

Pholcolin *Antigen, Irl.†*
Pholcodine (p. 1675·1).
Cough.

Pholcolinct *Adcock Ingram, S.Afr.†*
Pholcodine (p. 1675·1).
Cough.

Pholco-Mereprine *OJG, Belg.*
Doxylamine succinate (p. 627·3); pholcodine (p. 1675·1); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Respiratory-tract disorders.

Pholcones Bismuth *Cooperation Pharmaceutique, Fr.*
Guaifenesin (p. 1666·2); bismuth succinate (p. 1821·3); cineole (p. 2479·1).
Respiratory-tract congestion.

Pholcotussin *Europharm, China.*
Pholcodine (p. 1675·1).
Cough.

Pholdyston *Krewel, Ger.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Pholix *Vickmans, Hong Kong.†*
Phenylpropanolamine (p. 1674·1); pholcodine (p. 1675·1); promethazine (p. 638·2).

Pholtex *iNova, S.Afr.*
Pholcodine (p. 1675·1).
Cough.

Pholtex Linctus *iNova, S.Afr.*
Pholcodine resin complex (p. 1675·1); phenyltoloxamine resin complex (p. 638·1).
Cough.

Phol-Tussil *Interdelta, Switz.*
Pholcodine (p. 1675·1); tolu balsam (p. 1679·2).
Cough.

Phol-Tux *Interdelta, Switz.*
Pholcodine (p. 1675·1); ethylmorphine hydrochloride (p. 56·3); sulfogaiacol (p. 1678·1); belladonna (p. 2453·3); senega root (p. 1677·2); sodium benzoate (p. 1738·2).
Cough.

Phonal *Reig Jofre, Spain.*
Lozenges: Bacitracin (p. 225·3); benzocaine (p. 1980·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Mouth and throat disorders.

Reig Jofre, Spain.
Throat spray: ⊗Benzalkonium chloride (p. 1737·1); dexamethasone sodium phosphate (p. 1631·2).
Mouth and throat disorders.

Phönix Hydrargyrum *Phonix, Neth.*
Antimonium crudum (p. 2445·1); arnica montana flos (p. 2447·2); cuprum sulphuricum (p. 2057·2); kaolin (p. 1850·1); mercuric chloride (p. 2555·2).
Homoeopathic preparation.

Phönix Silybum spag *Phonix, Ger.*
⊗Acidum arsenicum (p. 2448·1); aesculus hippocastanum (p. 2431·2); arnica (p. 2447·2); atropa belladonna (p. 2453·3); bolus alba (p. 1850·1); chelidonium majus (p. 2522·2); crataegus (p. 2488·1); cuprum sulfuricum (p. 2057·2); digitalis purpurea (p. 1352·3); filipendula ulmaria (p. 2550·2); hydrargyrum bichloratum (p. 2555·2); juniperus communis (p. 2537·1); kalium nitricum (p. 1766·2); orthosiphon stamineus (p. 2536·3); paeonia officinalis; silybum marianum (p. 1561·1); solidago virgaurea (p. 2620·1); stibium sulfuratum nigrum (p. 2445·1); tartarus depuratus (p. 1879·2); camphor (p. 2466·2); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Phönix Solidago comp *Phonix, Neth.*
Aluminium silicicum (p. 1818·3); antimonium crudum (p. 2445·1); arnica montana flos (p. 2447·2); aurum muriaticum (p. 2521·1); cuprum sulfuricum (p. 2057·2); D-camphora (p. 2466·2); digitalis purpurea (p. 1352·3); juniperus communis (p. 2537·1); mercurius corrosivus (p. 2555·2); solidago virgaurea (p. 2620·1); spirea ulmaria (p. 2550·2); urtica urens (p. 2639·3).
Homoeopathic preparation.

Phönix Solidago spag *Phonix, Ger.*
Arnica (p. 2447·2); aurum chloratum (p. 2521·1); bolus alba (p. 1850·1); cuprum sulfuricum (p. 2057·2); digitalis purpurea (p. 1352·3); filipendula ulmaria (p. 2550·2); hydrargyrum bichloratum (p. 2555·2); juniperus communis (p. 2537·1); solidaga virgaurea (p. 2620·1); stibium sulfuratum nigrum (p. 2445·1); urtica urens (p. 2639·3); camphora (p. 2466·2).
Homoeopathic preparation.

Phönix Thuja-Lachesis spag *Phonix, Ger.*
Arnica (p. 2447·2); bolus alba (p. 1850·1); cuprum sulfuricum (p. 2057·2); dryopteris filix-mas (p. 158·3); echinacea (p. 2498·1); hydrargyrum bichloratum (p. 2555·2); iodum (p. 2336·3); lachesis mutus (p. 2538·3); stibium sulfuratum nigrum (p. 2445·1); thuja occidentalis (p. 2629·3); verbena officinalis (p. 2645·1); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Phönix Urtica-Arsenicum spag *Phonix, Ger.*
⊗Acidum arsenicosum (p. 2448·1); arnica (p. 2447·2); aurum chloratum (p. 2521·1); bolus alba (p. 1850·1); cuprum sulfuricum (p. 2057·2); digitalis purpurea (p. 1352·3); dryopteris filix-mas (p. 158·3); euspongia officinalis; filipendula ulmaria (p. 2550·2); hydrargyrum bichloratum (p. 2555·2); hypericum perforatum (p. 449·1); juniperus communis (p. 2537·1); kalium nitricum (p. 1766·2); orthosiphon stamineus (p. 2536·3); solidago virgaurea (p. 2620·1); stibium sulfuratum nigrum (p. 2445·1); tartarus depuratus (p. 1879·2); urtica urens (p. 2639·3); camphora (p. 2466·2); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

phöno Gripp *Phonix, Ger.*
Aconitum napellus (p. 2428·3); echinacea angustifolia (p. 2498·1); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

phöno Ven *Phonix, Ger.*
Aesculus hippocatanum (p. 2431·2); hamamelis virginiana (p. 2523·3); silybum marianum (p. 1561·1).
Homoeopathic preparation.

Phor Pain *Goldshield, UK.*
Ibuprofen (p. 68·2).
Muscle pain.

Phorpain *Goldshield, Irl.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Phos-Bind *Fako, Turk.*
Calcium acetate (p. 1783·1).

Phosblock *Kyowa, Jpn.*
Sevelamer hydrochloride (p. 1573·1).
Hyperphosphataemia.

Phoscal *Armoxindo, Indon.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); vitamin K_1 (p. 2122·2); magnesium (p. 1786·3); phosphorus (p. 2589·2).
Nutritional supplement.

PhosChol *American Lecithin, USA.*
Phosphatidyl choline (p. 2588·3).
Nutritional supplement.

Phosetamin *Kohler-Pharma, Ger.†*
Calcium, magnesium, and potassium salts of phosphorylcolamine (p. 2589·3).
Electrolyte disorders.

Phos-Ex *Gry, Austria; Nordiatech, Denm.; Baltian, Fin.; Gry, Ger.†; Cablon, Neth.†; Vitaline, Norw.; Renapharma, Swed.; Vitaline, Swed.; Say, Turk.; Vitaline, UK.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Phosex *Vitaline, Irl.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia in dialysis patients.

Phos-Flur *ColgateOral, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Phosfoenema *Cristalia, Braz.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Phosfomin *Sarabhai Piramal, India.*
Vitamin B substances (p. 2102·3); yeast; lysine hydrochloride (p. 2079·3).
Vitamin B deficiency; tonic.

Phosfomin Iron *Piramal, India.*
Iron (p. 2073·1).

Phosforid *Sun, India.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Phosgel *Boryung, China.*
Colloidal aluminium phosphate (p. 1818·3).

Phoslax *Odan, Canad.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation.

PhosLo *Fresenius Medical, Belg.; Fresenius Medical, Canad.; Pasteur, Chile; Fresenius Medical, Neth.; Fresenius Medical, Spain; Fresenius Medical, UK; Fresenius Medical, USA.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Phos-NaK *Cypress, USA.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2); monobasic potassium phosphate (p. 1790·3); dibasic potassium phosphate (p. 1791·1).
Nutritional supplement.

Phos-Out *Dincsa, Turk.*
Calcium acetate (p. 1783·1).

Phospha 250 Neutral *Rising Pharmaceuticals, USA.*
Dibasic sodium phosphate (p. 1791·2); monobasic potassium phosphate (p. 1790·3); monobasic sodium phosphate (p. 1791·1).

Phosphaden *Moschimfarm, Rus.; Vifiteh, Rus.*
Adenosine phosphate (p. 2430·2).
Vascular disorders; wounds; ulcers; nervous system disorders.

Phosphalugel *Astellas, Fr.; Astellas, Ger.; Astellas, Port.; Astellas, Rus.; Astellas, Ukr.*
Aluminium phosphate (p. 1818·3).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; gastritis; dyspepsia.

Phosphasal *BioComp, USA.*
Methenamine (p. 322·3); salol (p. 129·3); methylthioninium chloride (p. 1559·1); monobasic sodium phosphate (p. 1791·1); hyoscyamine sulfate (p. 1848·1).

Phosphate-Novartis *Novartis, Canad.*
Monobasic sodium phosphate (p. 1791·1); potassium bicarbonate (p. 1780·3).
Hypercalciuria; electrolyte supplement.

Phosphates *Pendopharm, Canad.; Pendopharm, Singapore; Pharmascience, Singapore.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Phosphate-Sandoz *Novartis, NZ; Novartis, S.Afr.; HK Pharma, UK.*
Monobasic sodium phosphate (p. 1791·1); sodium bicarbonate (p. 1781·1); potassium bicarbonate (p. 1780·3).
Hypercalcaemia; hypophosphataemia; rickets.

Novartis, Austral.
Monobasic sodium phosphate (p. 1791·1).
Hypophosphataemia; hypercalcaemia.

Phosphoclean *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Constipation.

Phosphocol *Mallinckrodt, USA.†*
Phosphorus-32 (p. 2227·1) in the form of chromic phosphate.
Malignant neoplasms.

Phosphogliv *Farmstandart, Rus.; Farmstandart, Ukr.*
Phospholipids (p. 2201·2); sodium glycyrrhizate.
Liver disorders; skin disorders.

Phospho-Lax *Sofar, Ital.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Phospho-Laxat *Hospital Line, Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Constipation.

Phospho-Laxative *RiC, Pol.†*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation; constipation.

Phospholine Iodide *Wyeth-Ayerst, USA.*
Ecothiopate iodide (p. 2007·2).
Glaucoma; convergent strabismus.

Phosphonciale *Kanonfarma, Rus.*
Phospholipids (p. 2201·2); milk thistle (p. 1561·1).

Phosphoneuros *Bouchara-Recordati, Fr.*
Phosphoric acid (p. 2589·1); calcium dihydrogen phosphate (p. 2464·2); dibasic sodium phosphate (p. 1791·2); magnesium glycerophosphate (p. 1787·2).
Hypercalciuria; hypophosphataemic rickets.

Phosphonorm *Medice, Ger.; Salmon, Switz.*
Aluminium chlorohydrate (p. 1694·1).
Hyperphosphataemia.

Phosphoprep *Pharmatel, Austral.†*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Phosphor *Herbapol Lodz, Pol.†*
⊗Ammonium phosphate (p. 2442·1); monobasic potassium phosphate (p. 1790·3); dibasic sodium phosphate (p. 1791·2).
Renal calculi; osteoporosis; fractures; hypercalciuria; hypercalcaemia; hypophosphataemia.

Phosphoral *Casen Fleet, Denm.; Casen Fleet, Fin.; Fleet, Neth.; Casen Fleet, Norw.; CCS, Swed.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

Phosphore Alko *Genopharm, Fr.*
⊗Manganese glycerophosphate (p. 2519·2); monobasic potassium phosphate (p. 1790·3); ammonium phosphate (p. 2442·1).
Hypercalciuria; rickets.

Phosphor-Homaccord *Peithner, Austria; Heel, Canad.†*
Phosphorus (p. 2589·2); argentum nitricum (p. 2615·3); paris quadrifolia.
Homoeopathic preparation.

Phosphorus Med Complex *Dynamit, Austria.*
Acidum phosphoricum (p. 2589·1); acidum picrinicum (p. 2634·2); phosphorus (p. 2589·2).
Homoeopathic preparation.

Phospho-Soda *Fleet, Philipp.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Phosphosorb *Fresenius Medical, Cz.; Fresenius Medical, Fr.; Fresenius Medical, Ger.; Fresenius Medical, Gr.; Fresenius Medical, Neth.; Fresenius Medical, Port.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Phosphovitam *Gap, Gr.*
Calcium (p. 1783·1); vitamins.

Phosribbon *Zeria, Jpn.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Hypophosphataemia.

Phostal *Stallergenes, Cz.; Stallergenes, Ger.; Stallergenes, Ital.†; Stallergenes, Pol.; Stallergenes, Switz.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy; hyposensitisation.

Photerpès *Bioderma, Fr.*
SPF 50+: Glycyrrhizic acid (p. 2520·2); lactoferrin (p. 2539·3).
Sunscreen; herpes labialis.

Photifed-M *Bright Future, China.*
⊗Pholcodine (p. 1675·1); triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms; cough.

Photo Finish *Smashbox, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

PhotoBarr *Axcan, Cz.; Axcan, Pol.*
Porfimer sodium (p. 848·3).
Barrett's oesophagus.

Photobarr *Axcan, Fr.†; Axcan, Hung.; Axcan, Irl.; Axcan, Neth.†; Axcan, Port.*
Porfimer sodium (p. 848·3).
Barrett's oesophagus.

Photoderm
Note: this name may be used for preparations of different composition.
Bioderma, Fr.
Capsules: Betacarotene (p. 2051·1); tomato oleoresin; copper oxide (p. 2057·1); green tea (p. 2648·2); vitamin C (p. 2110·3); fish oil (p. 1460·1); vitamin E (p. 2119·1).
Tanning aid.

Bioderma, Venez.
SPF 20: Bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); octil triazone (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Dispolab, Arg.
A range of sunscreens.

Photoderm AKN *Bioderma, Venez.*
SPF 20: Glycolic acid (p. 1704·3); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); dehydroacetic acid (p. 1749·2); phenoxyethanol (p. 1764·3).
Sunscreen for patients with acne.

Dispolab, Chile.†
SPF 40: Bisoctrizole (p. 1697·1); parsol; octocrilene (p. 1715·2); salicylic acid esters (p. 1719·1); glycolic acid (p. 1704·3).
Sunscreen for greasy skin.

Photoderm AR *Dispolab, Chile.†*
SPF 50: Bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1).
Sunscreen.

Photoderm Kid *Dispolab, Chile.†*
SPF 40: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1).
Sunscreen.

Photoderm Max
Note: this name may be used for preparations of different composition.
Bioderma, Ital.
Cream: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2).
Sunscreen.

Bioderma, Ital.
Topical milk: Octil octanoate; octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.

Bioderma, Venez.
SPF 60+: Bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

Dispolab, Chile†; Bioderma, Venez.
SPF 100: Bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); octil triazone (p. 1715·1); enzacamene (p. 1703·2).
Sunscreen.

Photoderm Spot *Dispolab, Chile.†*
SPF 100: Bisoctrizole (p. 1697·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1).
Sunscreen.

Photofrin *Techsphere, Arg.; Axcan, Canad.; Bioprojet, Fr.; Meduna, Ger.†; Galenica, Gr.; Axcan, Hung.; Axcan,*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Irl.; Axcan, Israel†; AF, Mex.; Axcan, Port.; Axcan, UK; Pinnacle, USA.
Porfimer sodium (p. 848·3).
Bladder cancer; oesophageal cancer; non-small cell lung cancer; dysplasia associated with Barrett's oesophagus; malignant mesotheliomna; endobronchial cancer.

Photogenic Concealer *Lancome, Canad.†*
SPF 15: Titanium dioxide (p. 1725·1).
Sunscreen.

Photogenic Lumessence *Lancome, Canad.*
Octinoxate (p. 1715·1).
Sunscreen.

Photoplex *Allergan, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Photoscreen *Silesia, Chile.*
SPF 50: Bisoctrizole (p. 1697·1); cinnamate (p. 1699·2); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Silesia, Chile.†
SPF 30 spray: Bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); cinnamate (p. 1699·2); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Phototrop *Tubilux, Ital.*
Acetylcarnitine (p. 2053·2); omega-3 marine triglycerides (p. 1460·3); ubidecarenone (p. 2637·1).
Nutritional supplement.

Phoxilium *Gambro, Cz.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2); monobasic sodium phosphate (p. 1791·1) (p. 1778·2).
Haemodialysis; haemofiltration.

Gambro, Denm.; Hospal, Fr.; Gambro, Irl.; Gambro, Neth.; Gambro, Norw.; Gambro, Port.; Gambro, Spain; Gambro, Swed.
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2); dibasic sodium phosphate (p. 1791·2) (p. 1778·2).
Haemodialysis; haemofiltration.

Gambro, Fin.
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); calcium chloride; dibasic sodium phosphate (p. 1791·2) (p. 1778·2).
Haemodialysis; haemofiltration.

Phrachedi *Millimed, Thai.†*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting in pregnancy; radiation sickness.

Phrachedi Balm *Millimed, Thai.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal pain; sprains; insect bites; pruritus.

Phrenilin *Valeant, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1).
Tension headache.

Phrenilin w Caffeine and Codeine *Valeant, USA.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain.

Phthizoetham *Akrikhin, Rus.*
Isoniazid (p. 311·2); ethambutol (p. 296·1).
Tuberculosis.

Phthizopiram *Akrikhin, Rus.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Phudicin *Bright Future, China.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Phygelin *Ivax, Mex.†*
⊗Polygeline (p. 1160·3).
Plasma volume expansion.

PhyLarm *LCA, Fr.*
Sodium chloride (p. 1795·1); borax (p. 2459·2); boric acid (p. 2459·3).
Eye irrigation.

Phylarm *Poen, Arg.*
Sodium chloride (p. 1795·1); borax (p. 2459·2); boric acid (p. 2459·3).
Dry eyes; eye irritation.

Poen Vision, Mex.
Sodium chloride (p. 1795·1).
Dry eyes.

Phyllan *Sanofi-Aventis, Gr.*
Veralipride (p. 1114·2).

Phyllocontin *Purdue, Canad.†; Mahakam Beta, Indon.; Mundipharma, Indon.; Mundipharma, Irl.*
Aminophylline (p. 1201·2).
Obstructive airways disease; heart failure; bronchospasm.

Pharmafrica, S.Afr.; Napp, UK.
Aminophylline hydrate (p. 1201·3).
Asthma; emphysema; chronic bronchitis; heart failure; obstructive airways disease.

Phyllotemp *Remek, Gr.*
Aminophylline (p. 1201·2).

Phylobid *Wockhardt, India.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Phyloday *Wockhardt, India.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Phylorinol *Schaffer, USA.*
Topical solution: Phenol (p. 1763·3); boric acid (p. 2459·3); strong iodine solution (p. 2336·3).
Oral wounds and infections.

Schaffer, USA.
Mouthwash: Phenol (p. 1763·3); methyl salicylate (p. 92·1).
Minor mouth or throat irritation.

Phytalzéal *Phythea, Fr.*
Fish oil (p. 1460·1); vitamin B substances (p. 2102·3); myrtillus (p. 2566·2).
Dietary supplement.

Phymet DTF *GSK, Irl.*
⊗Methadone hydrochloride (p. 88·3).
Opioid addiction; pain.

Phymorax *Medica Korea, Singapore.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; premedication; skin disorders; nausea and vomiting; alcohol withdrawal syndrome.

Phy-O *Biospray, Gr.*
Sodium chloride (p. 1795·1).

Physeptone *Aspen, Austral.; Aspen, S.Afr.; Martindale Pharmaceuticals, UK.*
⊗Methadone hydrochloride (p. 88·3).
Pain; cough; opioid withdrawal syndrome.

Physical *Perrigo, Israel.†*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Physicare Gel *Vitamed, Israel.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation.

Physioattivo *Esoform, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Genital hygiene.

Physiodese *Tripharma, Turk.*
Sodium chloride (p. 1795·1).
Nasal cleansing; eyewash.

Physiodose *Gilbert, Hong Kong; Batteur, Ital.*
Sodium chloride (p. 1795·1).
Eye and nose cleansing; eye and nose hygiene.

Physiogel
Note: this name may be used for preparations of different composition.
Braun, Switz.
⊗Modified gelatin (p. 1154·1); electrolytes (p. 1775·1).
Hypovolaemia.

GSK, Singapore.
A range of emollients and cleansers.

Stiefel, Fr.
A range of emollients and humectants.
Dry skin disorders.

Stiefel, Hong Kong.
Shampoo: Hypoallergenic shampoo.
Sensitive scalp.

Stiefel, Malaysia.
A range of emollients and skin cleansers.

Stiefel, Hong Kong; Stiefel, Indon.†; Stiefel, Ital.; Stiefel, Philipp.; Stiefel, Thai.†
Skin cleanser: Sodium cocoyl isetionate (p. 2210·3).
Soap substitute; soap-free cleanser.

Stiefel, Hong Kong.
Cream; lotion: Phytosterols (p. 1471·2); ceramide (p. 1699·1); squalane (p. 2213·3); phospholipids (p. 2201·2); triglycerides.
Emollient.

Physiogel AI *Stiefel, Hong Kong; Stiefel, Indon.*
Emollient.
Dry skin; skin irritation.

Physiogesic *Hebert, Canad.*
Diethylamine salicylate (p. 51·3).

Physiogine *MSD-Chibret, Fr.*
Estriol (p. 2274·3).
Vulvovaginal disorders due to oestrogen deficiency.

Physioglau *Bausch & Lomb, Port.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Physiologic *Vifor, Switz.*
Sodium chloride (p. 1795·1).
Nasal irrigation.

Physiologica *Qualiphar, Belg.; Gifrer Barbezat, Fr.†*
Sodium chloride (p. 1795·1).
Nasal irrigation; eye wash.

Physiologica Gifrer *Abdi, Turk.*
Sodium chloride (p. 1795·1).
Eye irrigation; nasal congestion.

Physiologica Nasal *Qualiphar, Belg.*
Sodium chloride (p. 1795·1); sodium hyaluronate (p. 2526·2).
Nasal congestion; nasal hygiene.

Physiolyte *McGaw, USA.*
Electrolytes (p. 1775·1).
Irrigation solution.

Physiomag *Alphapole, Fr.*
Rare earths.
Joint and muscle pain.

Physiomer *Sanofi-Aventis, Fr.; Gerolymatos, Gr.; Sanofi-Aventis OTC, Ital.; Goemar, Philipp.; Goemar, Rus.*
Sea water (p. 2612·1).
Nasal congestion; nasal hygiene; nasal disorders; nasal irrigation.

Physiomycine *Dexo, Fr.*
Methacycline hydrochloride (p. 322·3).
Bacterial infections.

Physioneal *Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Irl.; Baxter, Israel; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Port.; Adcock Ingram Critical Care, S.Afr.†; Baxter, Swed.; Baxter, Switz.*
Glucose (p. 2068·3); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); sodium lactate (p. 1781·2) (p. 1778·2).
Peritoneal dialysis.

Eczacibasi-Baxter, Turk.; Baxter, UK.
A range of peritoneal dialysis solutions (p. 1778·2).

Physioneal Glucosa *Baxter, Spain.*
Glucose monohydrate (p. 2069·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); sodium lactate (p. 1781·2) (p. 1778·2).
Peritoneal dialysis.

Physiorhine *Melisana, Belg.*
Sodium chloride (p. 1795·1).
Cleansing of eyelids; nasal irrigation.

Physiosoin *Bausch & Lomb, Switz.†*
Sodium chloride (p. 1795·1).
Eye wash; nasal irrigation; wound irrigation.

PhysioSol *Abbott, USA.*
Electrolytes (p. 1775·1).
Irrigation solution.

Physiotears *Alcon, Irl.†*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Physiotens *Abbott, Austral.; Solvay, Cz.†; Solvay, Denm.†; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Solvay, Hong Kong†; Abbott, Hung.; Solvay, Indon.; Solvay, Malaysia; Abbott, Norw.; Solvay, Philipp.; Solvay, Pol.; Solvay, Rus.; Solvay, S.Afr.; Solvay, Singapore†; Abbott, Swed.; Abbott, Switz.; Solvay, Turk.; Solvay, UK; Solvay, Ukr.*
Moxonidine (p. 1442·1).
Hypertension.

Physiotulle *Coloplast, Fr.; Coloplast, Ger.*
Carmellose (p. 2175·1).
Wounds; burns; ulcers.

Coloplast, UK.
Carmellose sodium (p. 2175·2).
Wounds.

Physiotulle-Ag *Coloplast, Ger.; Coloplast, UK.*
Sulfadiazine silver (p. 362·3); carmellose (p. 2175·1).
Wounds; burns; ulcers.

P-Hysplan *Raam, Mex.*
Sirolimus (p. 1966·2).

Physuline *Otsuka, Jpn.*
⊗Mozavaptan hydrochloride (p. 2564·3).
Hyponatraemia in cancer-related syndrome of inappropriate antidiuretic hormone secretion.

Phytacis *CIS, Fr.; CIS, Neth.; CIS, Port.*
Technetium-99m (p. 2228·1) fytate.
Liver scintigraphy.

Phytalgic *Phythea, Fr.*
Fish oil (p. 1460·1); urtica (p. 2639·3); zinc (p. 2126·1); vitamin E (p. 2119·1).
Dietary supplement; joint discomfort and stiffness.

Phytat DB *Marx, Fr.†*
Sodium fytate (p. 1553·3).
Hypercalciuria.

Phytémag *Lesourd, Fr.*
Magnesium glycerophosphate (p. 1787·2); apium root; buchu leaf (p. 2461·3); equisetum (p. 2500·1); ginger (p. 1844·1).
Tonic.

Phytex *Forest Laboratories, UK.*
Borotannic complex (p. 2625·2) (p. 2459·3); salicylic acid (p. 1719·1); methyl salicylate (p. 92·1); acetic acid (p. 2426·3).
Fungal skin and nail infections.

Wynlit, Irl.†
Tannic acid (p. 2625·2); boric acid (p. 2459·3); salicylic acid (p. 1719·1); methyl salicylate (p. 92·1); acetic acid (p. 2426·3).
Fungal skin and nail infections.

Phythéol *Phytosolba, Fr.†*
Zanthoxylum (p. 2650·1); fenugreek (p. 2504·1); shiitake; salix (p. 129·2); piroctone olamine (p. 1716·3); salicylic acid (p. 1719·1); ichthammol (p. 1705·3).
Dandruff.

Phytic Acid *Mac, Ital.*
Fytic acid (p. 1553·3); glycolic acid (p. 1704·3).
Hyperpigmentation disorders.

Phyto Corrective Gel *Dispolab, Chile.†*
Arbutin (p. 1694·3); pepino; thyme (p. 2630·2); bioflavonoids (p. 2505·2).
Skin pigmentation disorders.

Phyto Novo-Sed *Vilar, Rus.*
Echinacea (p. 2498·1); melissa (p. 2552·3); rose fruit (p. 2607·1); crataegus (p. 2488·1); motherwort (p. 2564·2).
Nervous disorders.

Phyto Soya *Arkomedika, Fr.; Arkopharma, Spain.*
Soya (p. 2092·3).
Menopausal disorders; hyperlipidaemia.

Dispolab, Chile; Arkopharma, Hong Kong; Arkopharma, Singapore.
Soya isoflavones (p. 2620·3).
Menopausal disorders; vaginal dryness.

Phyto Spot *Dispolab, Chile.*
Arbutin (p. 1694·3); kojic acid (p. 1710·2); thyme (p. 2630·2); cucurbitacin.
Skin pigmentation disorders.

Phytobene *Phytopharm, Ukr.*
Dimethyl sulfoxide (p. 2182·2); heparin sodium (p. 1396·3); dexpanthenol (p. 2582·2).
Joint, peri-articular, and soft-tissue disorders; neuralgia; phlebitis; varicose veins.

Phytobronchin *Steigerwald, Ger.*
Cowslip rhizome (p. 2596·2); thyme (p. 2630·2).
Cold symptoms.

Phyto-C *Steierl, Ger.*
Viscum album (p. 2560·2); basilicum (p. 2453·1); juniperus sabina.
Homoeopathic preparation.

Phyto-Cal *Phyto-Sante, Canad.*
Calcarea carbonica (p. 1824·3); calcarea fluorica (p. 2053·1); calcarea phosphorica (p. 1784·2); silicea (p. 2208·3); sulfur iodatum (p. 2624·2).
Homoeopathic preparation.

Phytocalm
Note: this name may be used for preparations of different composition.
Arkopharma, UK.
Passion flower (p. 2584·1).
Stress and strain; insomnia.

Wierhom, Arg.
Passion flower (p. 2584·1); valerian (p. 2640·2); tilia (p. 2631·3).
Insomnia; nervous disorders.

Douglas, Canad.†
Passion flower (p. 2584·1); valerian (p. 2640·2).

Phyto-Care *Marlyn, Hong Kong.*
Soya isoflavones (p. 2620·3).
Menopausal disorders; osteoporosis.

Phytocine *Marching, Hong Kong.†*
Cetrimide (p. 1742·1); diphenhydramine (p. 626·1); zinc oxide (p. 1729·1).

Phytocleanse *Arkopharma, UK.*
Cynara (p. 2490·3).
Digestive disorders.

Phytocold *Arkopharma, UK.*
Echinacea (p. 2498·1).
Colds.

Phytocor *Pharma Dynamics, S.Afr.*
Policosanol (p. 1472·1).
Hypercholesterolaemia.

Phytocortal *Steierl, Ger.*
Dioscorea (p. 2648·1); bellis perennis (p. 2454·2); chelidonium (p. 2522·2).
Homoeopathic preparation.

Phytoderm Compositum *Teva, Israel.*
Tolnaftate (p. 596·1); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Fungal skin infections.

Phytodiet *Phytodiet, Fr.†*
High protein food for special diets.

Phytodolor *Flordis, Austral.; Madaus, Austria; Steigerwald, Cz.†; Steigerwald, Ger.*
Populus tremula (p. 2450·3); ash (p. 2450·1); solidago (p. 2620·1).
Musculoskeletal and joint disorders; rheumatism; neuralgia.

Phyto-Ease *Marlyn, Hong Kong.*
Soya isoflavones (p. 2620·3); saw palmetto (p. 2363·3); lycopersicon lycopersicum.
Benign prostatic hyperplasia; nutritional supplement.

Phytoestrin *Usana, Canad.; Usana, Hong Kong†; Usana, Singapore.†*
⊗Agnus castus (p. 2432·2); liquorice (p. 1853·2); soya isoflavones (p. 2620·3); cimicifuga (p. 2478·1); dong quai (p. 2497·1).
Dietary supplement; menstrual disorders; menopausal disorders.

Phytofibre *Plantes et Medecines, Fr.†*
Ispaghula (p. 1849·1).
Constipation.

Phytogargarisme *Boiron, Fr.†*
Sabadilla (p. 2611·2); phytolacca decandra (p. 2593·2); anemone pulsatilla (p. 2600·2); baryta carbonica (p. 2452·2); mercurius solubilis (p. 2555·3); populus candicans.
Homoeopathic preparation.

Phytogastrol *Krasnogorskleksredstva, Rus.*
Calamus (p. 2464·2); peppermint leaf (p. 1877·1); chamomile (p. 2474·1); liquorice (p. 1853·2); fennel (p. 2503·2).

Phytohepar *Steigerwald, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Phytohepatol No 2 *Krasnogorskleksredstva, Rus.*
Helichrysum; coriander (p. 2486·3); peppermint leaf (p. 1877·1); achillea (p. 2427·3).
Liver disorders.

Phytohustil *Steigerwald, Ger.*
Althaea (p. 2438·3).
Cough.

Phyto-L *Steierl, Ger.*
⊗Silybum marianum (p. 1561·1); vitex agnus castus (p. 2432·2); chelidonium majus (p. 2522·2).
Homoeopathic preparation.

Phytolacca-Plus *Doctor H, Rus.*
Atropa belladonna (p. 2453·3); barium carbonicum (p. 2452·2); eucalyptus globulus (p. 2501·1); hepar sulfuris (p. 1721·3); phytolacca americana (p. 2593·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Phyto-Laxia *Phytopharma, Switz.†*
Frangula bark (p. 1843·3); senna (p. 1885·1).
Constipation.

PhytoLife *Blackmores, Austral.*
Soya bean (p. 2092·3); calcium hydrogen phosphate (p. 1783·3).
Osteoporosis; menopausal disorders.

Phytolife Plus *Blackmores, UK.*
Calcium (p. 1783·1); soya (p. 2092·3).
Menopausal disorders.

Phytolysin Plus *Farmak, Ukr.*
Sage oil (p. 2609·1); mint oil (p. 2560·1); pumilio pine oil (p. 2591·1).
Pyelonephritis; cystitis; prostatitis; urethritis; urolithiasis.

Phytolyt *Zdorovje, Ukr.*
Knotgrass (p. 2538·2); St John's wort (p. 449·1); equisetum (p. 2500·1); ammi visnaga extract (Avisan) (p. 2441·2).
Urolithiasis.

Phyto-Marinex *Phyto-Sante, Canad.*
Boldo (p. 2458·3); choline citrate (p. 2055·2); cynara (p. 2490·3); rosemary (p. 2607·2); taraxacum (p. 2625·3).

Phytomélis *Lehning, Fr.*
Hamamelis (p. 2523·3); aesculus (p. 2431·2).
Peripheral vascular disorders; haemorrhoids.

Phytonefrol *Krasnogorskleksredstva, Rus.*
Calendula (p. 2465·2); peppermint leaf (p. 1877·1); bearberry (p. 2453·2); fennel (p. 2503·2); eleutherococcus (p. 2614·3).

Phytonoctu *Steigerwald, Ger.*
Melissa (p. 2552·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Phytopause *Pharma Dynamics, S.Afr.†*
Soya isoflavones (p. 2620·3).
Dietary supplement; menopausal disorders.

Phytopause BSF *Pharma Dynamics, S.Afr.†*
Soya isoflavones (p. 2620·3); calcium (p. 1783·1); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Calcium supplement; osteoporosis.

Phytophanère *Phytosolba, Fr.†*
Wheat-germ oil (p. 2647·1); carrot oil; borage oil (p. 2459·2); rice-bran oil; salmon oil (p. 1460·1); yeast (p. 2125·2); acerola; fish roe.
Fragile hair and nails.

Phytopharma Calcium *Phytopharma, Switz.*
Calcium hydrogen phosphate (p. 1783·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Phytopro *Metagenics, Canad.†*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); *d*-alpha tocoferil acid succinate (p. 2119·2); zinc chelate (p. 2048·3).

Phytoral *Micro, Singapore.*
Ketoconazole (p. 585·3).
Fungal infections.

Phytorelax
Note: this name may be used for preparations of different composition.
Arkopharma, UK.
Valerian (p. 2640·2).
Stress; tension.
Natur Produkt, Rus.
Valerian (p. 2640·2); crataegus (p. 2488·1).
Nervous disorders; insomnia.

Phytoslim *World Foods, UK.*
Fucus vesiculosus.
Slimming aid.

Phytosolaire *Phytosolba, Fr.†*
Borage oil (p. 2459·2); olive oil (p. 2575·1); selenium (p. 2086·3); palm oil (p. 2200·2); tomato oleoresin; vitamin E (p. 2119·1); lycopene (p. 2546·2); lutein (p. 2079·2).
Tanning aid.

Phytospray *Asepta, Mon.*
Enoxolone (p. 54·2); ginkgo biloba (p. 2512·3); aesculus (p. 2431·2); menthol (p. 2553·2).
Heavy legs.

Phytosquame *Phytosolba, Fr.†*
Hydnocarpus oil; melaleuca oil (p. 2551·1); piroctone olamine (p. 1716·3).
Dandruff.

Phyto-Strol *Loges, Ger.; Muller Goppingen, Ger.*
Rhapontic rhubarb (p. 1884·2).
Menopausal disorders.

Phytotux *Lehning, Fr.*
Tolu balsam (p. 1679·2); Desessartz syrup (p. 1667·2).
Cough.

Phytotux H *Homeocan, Canad.*
Arnica (p. 2447·2); belladonna (p. 2453·3); bryonia (p. 2461·3); cetraria (p. 2531·2); coccus cacti (p. 2179·2); corallium rubrum; drosera (p. 2497·2); ipeca (p. 1667·2); stannum metallicum (p. 2632·1).
Homoeopathic preparation.

Phytovein *Catarinense, Braz.*
Aesculus (p. 2431·2).
Vascular disorders.
Arkopharma, UK.
Butcher's broom (p. 2463·1).
Venous insufficiency; haemorrhoids.

Phytovir *Jacoby, Austria; Parsenn, Switz.*
Rhubarb (p. 1884·2); sage (p. 2608·3).
Herpes labialis.

Phytozac *Synapsya, Fr.*
Capsules for men: Morning capsules, taurine (p. 2626·2); tyrosine (p. 2098·3); magnesium (p. 1786·3); potassium (p. 1793·1); vitamin B substances (p. 2102·3); evening capsules, magnesium; melissa (p. 2552·3); valerian (p. 2640·2).
Nervous disorders.
Synapsya, Fr.
Capsules for women: Morning capsules, magnesium (p. 1786·3); royal jelly (p. 2608·1); california poppy (p. 2466·1); potassium (p. 1793·1); vitamin B substances (p. 2102·3); evening capsules, magnesium; tryptophan (p. 453·2); rhodiola; melissa (p. 2552·3).
Nervous disorders.

Phyzidine *Europharm, Hong Kong.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pi Fu Ping *Hengrui, China.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Pi Fu Te *Pidi, China.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Pi Jin *BSPC, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Pi Ke *Nuo De, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Pi Luo Tong *Pidi, China.*
Lysine hydrochloride (p. 2079·3).
Cerebral ischaemia; head injury.

Pi Lv *BSPC, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Pi Mai Le *Pidi, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder.

Pi Nuo *Pidi, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Pi Si Ke *Pidi, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Piam *Denver, Arg.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Piaojiamei *Zizhu, China.*
Aspartic acid (p. 2050·3); magnesium oxide (p. 1857·3); potassium hydroxide (p. 2595·3).
Hypokalaemia; heart failure.

Piascledine *Abbott, Braz.; Pharma Investi, Chile; Medicom, Cz.; ABC, Ital.; Expanscience, Pol.; Expanscience, Rus.*
Avocado oil (p. 2451·2); soya oil (p. 2092·3).
Musculoskeletal and joint disorders; mouth disorders; skin disorders; phlebitis; skin ulceration; gum disorders; degenerative joint disorders.
Bernabo, Arg.
Avocado (p. 2451·2); soya (p. 2092·3).
Arthroses.
Rhein, Mex.
Avocado oil (p. 2451·2); soya (p. 2092·3).
Osteoarthritis.

Piasclédine *Expanscience, Fr.*
Avocado oil (p. 2451·2); soya oil (p. 2092·3).
Periodontal disease; osteoarthritis of the hip and knee.

Piax *Alphapharm, Austral.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Pibaksin *Sanbe, Indon.*
Mupirocin (p. 327·2).
Skin infections.

Picalm *Grunenthal, Port.*
Piketoprofen (p. 125·3) or piketoprofen hydrochloride (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Picamic *Tropica Mas, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Picamilon *Akrikhin, Rus.; Farmstandart, Rus.*
Sodium N-nicotinyl-gamma-aminobutyrate.
Cerebrovascular disorders; depression; asthenia; anxiety; chronic alcoholism; migraine; glaucoma; urological disorders.

Picanoil *Echo, Rus.*
Sodium N-nicotinyl-gamma-aminobutyrate.
Cerebrovascular disorders; asthenia; depression; nervous disorders; chronic alcoholism; migraine; glaucoma; urological disorders.

Pica pan *DHA, Hong Kong; DHA, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Picaplin *Medic-Aid, Philipp.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Picasum *Cantabria, Spain.*
Capsaicin (p. 35·1).
Neuropathic pain; musculoskeletal pain.

Picato *Leo, Neth.; Leo, UK; Leo, USA.*
Ingenol mebutate (p. 809·3).
Actinic keratosis.

Picavit *Tropica Mas, Indon.*
Vitamins; lysine (p. 2079·3).
Vitamin and amino acid deficiency.

Piccadilly Foot Ointment *Adco, S.Afr.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Piccomycin *Picco, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Pician *Altfarm, Rus.*
Pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Picibanil *Chugai, Jpn.*
Picibanil (p. 2590·2).
Malignant neoplasms.

Picilin *Elvipe, Gr.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Picillin *CT, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pickles *Ransom, Irl.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Pickles Antiseptic Cream *Pickles, UK.*
Dibrompropamidine isetionate (p. 1750·1).
Burns; scalds; sunburn.

Pickles Chilblain Cream *Pickles, UK.*
Methyl nicotinate (p. 91·3).
Chilblains.

Pickles Corn Caps *Pickles, UK.*
Salicylic acid (p. 1719·1); colophony (p. 2484·2).
Corns.

Pickles Foot Ointment *Ransom, UK.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Pickles Smelling Salts *Pickles, UK.*
Strong ammonia solution (p. 2441·2); eucalyptus oil (p. 2501·2); pine oil (p. 2591·1).
Headache; nasal congestion.

Piclodin *Pharos, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Piclodorm *Moschimfarm, Rus.*
Zopiclone (p. 1118·1).
Insomnia.

Picodan *Odan, Canad.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).

Picolax *Ferring, Hong Kong; Ferring, Irl.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).
Bowel evacuation.
Neo-Farmaceutica, Port.; Farmak, Ukr.
Sodium picosulfate (p. 1887·2).
Bowel evacuation; constipation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ferring, UK.
Sodium picosulfate (p. 1887·2); magnesium citrate (p. 1857·1).
Bowel evacuation.

Picolaxine *Pharmacobel, Belg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Picolite *Lactalis, Fr.*
Maltodextrin (p. 2080·3); sucrose (p. 2096·3); sodium chloride (p. 1795·1); potassium citrate (p. 1780·3); citric acid (p. 2480·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Picolon *Medic, Denm.*
Sodium picosulfate (p. 1887·2).
Constipation.

PicoPrep *Fresenius Kabi, Austral.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).
Bowel evacuation.

Picoprep *Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Hung.; Pharmatel, Malaysia†; Ferring, Neth.; Ferring, Norw.; Fresenius Kabi, NZ; Beta, S.Afr.†; Ferring, Swed.; Ferring, Switz.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).
Bowel evacuation; constipation.

Pico's Children's Cough *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha tincture (p. 1667·2).
Cough.

Pico's Cough *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); liquorice (p. 1853·2).
Cough.

Pico-Salax
Note: this name may be used for preparations of different composition.
Ferring, Canad.; Ferring, Israel.
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).
Bowel evacuation.

Ferring, Neth.
Sodium picosulfate (p. 1887·2).
Constipation.

Picosen *Vishpha, Ukr.*
Sodium picosulfate (p. 1887·2); senna (p. 1885·1).
Constipation.

Picot AR *Lactalis, Fr.*
Infant feed.
Regurgitation.

Picozone *Stada, Hung.*
⊗Letrozole (p. 817·1).
Breast cancer.

Picturlop *MVA, Cz.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Picula *Ethica, Indon.*
Soya lecithin (p. 2542·2); phyllanthus niruri (p. 2590·1); Javanese turmeric (p. 2636·2).
Liver disorders.

Picutex *Sertex, Arg.*
Quassia (p. 2601·1).
Pediculosis.

Picyn *Bernofarm, Indon.*
Sultamicillin (p. 369·1).
Bacterial infections.

PiDaNa *HRA, Ger.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Pidef *Landsteiner, Mex.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Pidezol *Egis, Hung.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

PiDi Gan *Pidi, China.*
Inosine (p. 2533·1).
Neutropenia; thrombocytopenia; heart failure; angina pectoris; hepatitis; optic atrophy; retinitis.

PiDi Ming *Pidi, China.*
Citicoline sodium (p. 2480·2).
Loss of consciousness in head injury and brain surgery.

Pidilat *Solvay, Ger.†*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Pidogen *Silom, Thai.†*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Pidolen *Pharmex (Φαρμεξ), Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Pidomag *Baldacci, Braz.*
Magnesium pidolate (p. 1787·3).
Magnesium deficiency.

Pidovix *Lapi, Indon.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Pidoxam *Patar, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Pidoxina *Parggon, Mex.*
Meclozine (p. 634·3); pyridoxine (p. 2105·3).
Nausea and vomiting; vertigo.

Pidrol *Gache, Venez.*
⊗Ammonium acetate (p. 1655·3); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract congestion.

Piecidex NF *Andromaco, Arg.*
Cream: Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Andromaco, Arg.
Lotion: Bifonazole (p. 573·3); diphenhydramine hydrochloride (p. 626·2).
Fungal skin infections.

Piel Vital *AM, Arg.*
Betacarotene (p. 2051·1); vitamins; minerals; methionine (p. 1558·2).
Dietary supplement.

Pielograf *Juste, Spain.†*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Piesital *Demo, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Piextane *Helm, Ital.*
⊗Exemestane (p. 792·2).

Pi-Fedrin *Flupal, Venez.*
⊗Sodium benzoate (p. 1738·2); ammonium acetate (p. 1655·3); drosera (p. 2497·2); ephedrine hydrochloride (p. 1663·2); mepyramine maleate (p. 635·1).
Respiratory-tract congestion.

Piflaxan *Pisa, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pifrol *Arlex, Mex.†*
Dipyrone (p. 53·3).
Fever; pain.

Pigenil *Pharmafar, Ital.*
Pygeum africanum (p. 2363·2).
Prostatic hyperplasia.

Pigitil *Dorom, Ital.*
Pidotimod (p. 2590·2).
Immunostimulant.

Pigloss *Bajamed, Mex.*
Glipizide (p. 474·1).
Diabetes mellitus.

Pigmal *Gramon, Arg.*
Pirolenoso acid.
Pediculosis.

Pigmanorm
Note: this name may be used for preparations of different composition.
Widmer, Ger.
⊗Hydroquinone (p. 1705·1); tretinoin (p. 1725·2); hydrocortisone (p. 1640·1).
Skin hyperpigmentation.

Widmer, Switz.
⊗Hydroquinone (p. 1705·1); tretinoin (p. 1725·2); dexamethasone (p. 1630·3); dexpanthenol (p. 2582·2); octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Skin hyperpigmentation.

Pigmentasa *Zeler, Port.; Vinas, Spain.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Pigmet *Sandoz, Indon.†*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Pik Gel *Amnol, Ital.*
Centella (p. 1698·3); ginkgo biloba (p. 2512·3); peppermint (p. 1877·1); devil's claw root (p. 42·3); menthol (p. 2553·2); aesculus (p. 2431·2); pineapple; equisetum (p. 2500·1); achillea (p. 2427·3); ginger (p. 1844·1); meadowsweet (p. 2550·2); sesamum indicum; myrtillus (p. 2566·2).
Circulatory disorders.

Pikangwang *Dihon, China.*
Ketoconazole (p. 585·3).

Pikasol *Axellus, Swed.*
Fish oil (p. 1460·1).

Pikcef *Nevzat, Ukr.*
Cefepime (p. 239·2).
Bacterial infections.

Pikefi *Erfar, Gr.*
⊗Glycerol (p. 2517·2).

Piklon *KVZ, Ukr.*
Zopiclone (p. 1118·1).
Insomnia.

Pikogam *North Star, Rus.*
Sodium N-nicotinyl-gamma-aminobutyrate.
Cerebrovascular disorders; asthenia; depression; nervous disorders; chronic alcoholism; migraine; glaucoma; urological disorders.

Pikovit *KRKA, Pol.; KRKA, Rus.; Sandoz, Turk.; KRKA, Ukr.*
Vitamins; with or without minerals.
Nutritional supplement; vitamin and mineral preparation.

KRKA, Cz.†
Vitamins.

Piky *Sanofi-Aventis, Port.*
Dimeticone (p. 2209·3).
Pediculosis.

Pil *Sophia, Mex.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Pil Keluarga Berencana *Schering, Indon.†*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Pilamin *Obolenskoe, Rus.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Pilder *Quimifar, Spain.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Pildoras Zeninas *Puerto Galiano, Spain.*
Aloes (p. 1816·1); cascara (p. 1826·1).
Constipation.

Pileabs *Lane, UK.*
Slippery elm bark (p. 2617·1); cascara sagrada (p. 1826·1).
Haemorrhoids.

Pilelife *Yung Shin, Hong Kong.†*
⊗Lidocaine (p. 1988·1); prednisolone acetate (p. 1645·2); chlorhexidine hydrochloride (p. 1743·3); tocoferil acetate (p. 2119·2); alcloxa (p. 1692·2).
Anorectal disorders.

Pilem *Uniao Quimica, Braz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Pilensar *IMA, Braz.†*
Lindane (p. 2157·1).
Pediculosis; scabies.

Piletabs *Potter's, UK.*
Pilewort (p. 2590·3); agrimony (p. 2432·3); cascara (p. 1826·1); stone root (p. 2622·2).
Haemorrhoids.

Pilex *Himalaya, Ukr.*
Mimosa pudica; eclipta alba; vitex negundo; calendula (p. 2465·2); cinnamomum camphora; borax (tankana) (p. 2459·2); yashad bhasma; azadirachta (p. 2451·2); ailanthus excelsa; blumea balsamifera; allium ascalonicum; calamus (p. 2464·2); black nightshade (p. 2458·2).
Haemorrhoids; varicose veins.

Himalaya, Rus.
Guggul (p. 2523·2); azadirachta (p. 2451·2); shilajeet; berberis aristata (p. 2532·1); emblica (p. 2532·2); terminalia chebula (p. 2474·3); terminalia belerica (p. 2453·2); cassia pulp (p. 1826·2); bauhinia variegata; mesua ferrea.
Haemorrhoids.

Pilexal *Apex, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; influenza symptoms.

Pil-Food *Serra Pamies, Spain.*
Vitamins; amino acids; millet.
Hair, scalp, and nail disorders.

Vifor, Switz.
Vitamins; amino acids; protein hydrolysate (p. 2086·2); millet.
Hair and nail disorders.

Pilfood *Cedar Health, UK.*
Vitamin E (p. 2119·1); riboflavin (p. 2104·3); vitamin B_6 (p. 2105·3); biotin (p. 2052·2); pantothenic acid (p. 2085·2); methionine (p. 1558·2); cystine (p. 2059·1).
Dietary supplement for healthy hair.

Serra Pamies, Hong Kong.
Vitamins; methionine (p. 1558·2); cystine (p. 2059·1); protein hydrolysate (p. 2086·2); millet.
Dietary supplement for healthy hair.

Pilfud *Bosnalijek, Ukr.*
Minoxidil (p. 1438·3).
Alopecia.

Pilian *Yung Shin, Singapore.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions.

Pilison *Intendis, Austria.*
⊗Fluocortolone pivalate (p. 1637·1); salicylic acid (p. 1719·1).
Skin disorders.

Pilka *Novartis Consumer, Austria; Ferrer, Spain.*
Drosera (p. 2497·2); thyme (p. 2630·2).
Cough.

Novartis Consumer, Israel; Novartis Consumer, Switz.
Drosera (p. 2497·2); thyme (p. 2630·2); pinguiculae.
Cough.

Pilka Forte *Novartis Consumer, Austria.*
⊗Drosera (p. 2497·2); thyme (p. 2630·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Pill 72 *Cipla, Hong Kong; Cipla, India.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Pilo *Meda, Belg.; Chauvin, Fr.; Grin, Mex.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; induction of miosis; hernia of the iris; reversal of mydriasis and cycloplegia.

Pilo Cura *Lokman, Turk.*
Resorcinol (p. 1718·3); salicylic acid (p. 1719·1); sodium pantothenate (p. 2085·2).
Scalp disorders.

Pilobloc *Farmila, Ital.*
⊗Pilocarpine hydrochloride (p. 2010·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Piloblog *Thea, Fr.†*
⊗Pilocarpine hydrochloride (p. 2010·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Pilocan *Latinofarma, Braz.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of miosis.

Pilocar *FDC, India.*
Pilocarpine nitrate (p. 2010·3).
Glaucoma; production of miosis.

Novartis Ophthalmics, USA†; Oftalmi, Venez.
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of miosis; raised intra-ocular pressure; reversal of mydriasis.

Pilocarpol *Lersan, Arg.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of miosis.

Pilocollyre *Cooper (Κοπερ), Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of mydriasis.

Pilofar *Farmedia, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Xerostomia.

Pilogel *Alcon, Chile; Alcon, Cz.; Alcon, Gr.; Alcon, Irl.†; Alcon, Neth.†; Alcon, S.Afr.; Alcon, Singapore†; Alcon, Turk.; Alcon, UK.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

Pilokarsol *Sanovel, Turk.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Pilomann *Mann, Ger.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; reversal of drug-induced mydriasis.

Pilomann-Ol *Mann, Ger.*
Pilocarpine (p. 2010·2).
Glaucoma; reversal of drug-induced mydriasis.

Pilomed
Note: this name may be used for preparations of different composition.
Bausch & Lomb, Arg.†
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; production of miosis.

Pilopil *Guardian, Indon.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Pilopine HS *Alcon, Canad.; Alcon, USA.*
Pilocarpine hydrochloride (p. 2010·3).
Production of miosis; glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Pilopos *Ursapharm, Cz.†; Ursapharm, Ger.†*
Pilocarpine nitrate (p. 2010·3).
Glaucoma; reversal of drug-induced mydriasis.

Pilopt *Allergan, Austral.†; Healthcare Logistics, NZ.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

Piloptic *Optopics, USA.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; reversal of mydriasis.

Pilopto-Carpine *Lebeh, USA.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Pilorcarpin Puroptal *Agepha, Austria.*
Pilocarpine hydrochloride (p. 2010·3).
Intra-ocular hypertension.

Pilosed *Bilim, Turk.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Pilosol *Ophthalmos, Braz.*
Pilocarpine (p. 2010·2).

Pilostat *Bausch & Lomb, USA.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Pilosuryl *Pierre Fabre, Fr.*
Pilosella; phyllanthus (p. 2590·1).
Water retention.

Pilotim *Alcon, Arg.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

Pilotimol *Sintez, Rus.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

Pilotina *Genepharm, Gr.*
Pilocarpine nitrate (p. 2010·3).
Glaucoma; production of mydriasis.

Pilovate *Cipla, India.*
⊗Beclometasone dipropionate (p. 1621·2); phenylephrine hydrochloride (p. 1672·3); lidocaine hydrochloride (p. 1988·2).
Skin disorders.

Piloxidil *Chemical Research, Pol.*
Minoxidil (p. 1438·3).
Alopecia.

Pilsinic *Nichi-Iko, Jpn.*
Pilsicainide hydrochloride (p. 1470·1).
Arrhythmias.

Pilulas Ross *GSK, Braz.*
Aloin (p. 1816·2); capsicum (p. 2469·3); ipecacuanha (p. 1667·2); belladonna (p. 2453·3).
Constipation.

Pilules de Vichy *Omega, Belg.†*
Sodium picosulfate (p. 1887·2); electrolytes (p. 1775·1).
Constipation.

Pilus *Gentili, Ital.*
Finasteride (p. 2358·3).

Pilzcin *Shionogi, Jpn.†*
Croconazole hydrochloride (p. 577·2).
Fungal skin infections.

Pima *Fleming, USA.*
Potassium iodide (p. 2336·3).
Respiratory-tract congestion.

Pima Biciron N *S & K, Ger.†*
Natamycin (p. 590·2).
Fungal eye infections.

Pimafucin *Astellas, Cz.; Astellas, Fin.; Galderma, Ger.†; Astellas, Hung.; Astellas, Neth.; Astellas, Pol.; Astellas, Rus.; Santa, Turk.; Astellas, Ukr.*
Natamycin (p. 590·2).
Fungal nail, skin, and vaginal infections; trichomoniasis.

Pimafucort *Astellas, Cz.; Astellas, Fin.; Astellas, Hung.; Astellas, Neth.; CSL, NZ; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, Ukr.*
⊗Hydrocortisone (p. 1640·1); natamycin (p. 590·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Pimalev *Mikart, USA.*
⊗Paracetamol (p. 115·1); oxycodone hydrochloride (p. 113·1).
Pain.

Pimax *Unicure, Philipp.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Pimcep *PSA, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Pime
Note: this name may be used for preparations of different composition.
Macrophar, Thai.
Cefepime (p. 239·2).
Bacterial infections.

Raam, Mex.
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Pimenol *Pfizer, Jpn.*
Pirmenol (p. 1471·1).
Arrhythmias.

Pimidel *KRKA, Rus.; KRKA, Ukr.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Pimiken *Kendrick, Mex.*
Magnesium valproate (p. 553·1).
Epilepsy.

Pimoftal *Gerolimatos (Γερολυματος), Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Pimple *Ingens, Arg.†*
Minocycline (p. 324·3).
Acne.

Pimplex *Konimex, Indon.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Pin Chuan *Lisheng, China.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Pinaclav *Pinewood, Irl.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Pinaclor *Ranbaxy, Irl.*
Cefaclor (p. 232·3).
Bacterial infections.

Pinadone *Pinewood, Neth.†*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal.

Pinadone DTF *Pinewood, Irl.*
⊗Methadone hydrochloride (p. 88·3).
Opioid addiction.

Pinadrina *Pisa, Mex.†*
⊗Adrenaline (p. 1292·1).

Pinafor *Medicus, Gr.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Pin-Alcol *Schoning-Berlin, Ger.*
Menthol (p. 2553·2); Norway spruce oil.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pruritus; neuritis; neuralgia.

Pinaloid *Ferring, S.Afr.*
Cyclizine (p. 623·2).

Pinam *Meyer Alian, Venez.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Pinamet *Pinewood, Irl.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity.

Pinamox *Athlone, Irl.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pinapaz *Merck, Port.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Pinarsina *Medea, Spain.†*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Pinaspor *Ferring, S.Afr.*
Clotrimazole (p. 576·2).

Pinaval-T *Nycomed, Mex.*
Ebastine (p. 628·1).
Allergic rhinitis; allergic skin disorders.

Pinazan *Cristalia, Braz.*
Clozapine (p. 1057·3).

Pinazo *Gache, Venez.*
⊗Naphazoline nitrate (p. 1669·3); mepyramine maleate (p. 635·1).
Nasal congestion.

Pinbarix *Ranbaxy, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Pinden *Trima, Israel.†*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris; arrhythmias.

Pindol *Mylan, NZ.†*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris; arrhythmias.

Pineal *Laborest, Ital.*
Magnesium (p. 1786·3); nicotinic acid (p. 2083·1); tryptophan (p. 453·2).
Depression.

Pineal Notte *Laborest, Ital.*
Melatonin (p. 2551·3); valerian (p. 2640·2).
Sleep disorders.

Laborest, Ital.
Oxitriptan (p. 440·3); melatonin (p. 2551·3).
Sleep-wake cycle disorders.

Pinealtein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Pineapple Brand Ear Drop *Beacons, Singapore.*
Hydrogen peroxide (p. 1755·2).
Ear wax removal.

Pineapple Brand Lotion *Beacons, Singapore.*
Salicylic acid (p. 1719·1).
Acne; keratinisation disorders.

Pinetarsol *Ego, Austral.*
Bath oil: Pine tar (p. 1723·3); light liquid paraffin (p. 2191·2).
Skin disorders.

Ego, Austral.
Solution: Pine tar (p. 1723·3); trolamine laurilsulfate (p. 2210·3).
Skin disorders.

Ego, Austral.; Ego, Hong Kong; Ego, Irl.†; Ego, Malaysia; Ego, NZ; Ego, Singapore; Crawford, UK.†
Pine tar (p. 1723·3).
Skin disorders; eczema; psoriasis.

Pinex *Actavis, Denm.; Actavis, Norw.; Actavis, Swed.*
Paracetamol (p. 115·1).
Pain; fever.

Pinex Comp *Actavis, Denm.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Pinex Forte *Actavis, Norw.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Pinex Major *Actavis, Norw.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Pinfetil *Novell, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Ping An *Tianshun, China.*
Zinc gluconate (p. 2126·2).

Ping Da Er *Pdy, China.*
Nimodipine (p. 1455·2).
Cerebral vasospasm.

Ping Fang Shu *Kangdini, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ping Fu *Rui Yang, China.*
Isosorbide mononitrate (p. 1413·3).

Ping Ke Ya Xin *Kangerwei, China.*
Telmisartan (p. 1509·3).
Hypertension.

Ping Li Da *Si Bao, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Ping Neng *Huashan, China.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ping Te *Lunan, China.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Ping Xin *Lunan, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Ping Zhi *Gaohua, China.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Pingel *Eczacibasi, Turk.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Sanofi-Aventis, Ukr.
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Pingfu *Xuebao, China.*
Nadifloxacin (p. 328·1).

Pingtan *Taiyang, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

PiniHelix *Apipol, Pol.*
Ivy (p. 2536·2); liquorice (p. 1853·2); thyme (p. 2630·2); pine.
Respiratory-tract disorders.

Pinikehl *Sanum-Kehlbeck, Ger.*
Fomitopsis pinicola e mycelio.
Homoeopathic preparation.

Piniment *Austroplant, Austria.*
Balsam: Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); Scots pine oil (p. 2591·2); pumilio pine oil (p. 2591·1); turpentine oil (p. 2636·3); guaiazulene (p. 2523·1).
Cough; respiratory-tract disorders; gastrointestinal spasm; musculoskeletal and joint disorders.

Austroplant, Austria.
Nasal ointment: ⊗Ephedrine hydrochloride (p. 1663·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); Scots pine oil (p. 2591·2); pumilio pine oil (p. 2591·1); turpentine oil (p. 2636·3); sage oil (p. 2609·1); sunflower oil (p. 2098·1).
Nasal congestion.

Austroplant, Austria.
Ointment: Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); Scots pine oil (p. 2591·2); pumilio pine oil (p. 2591·1); turpentine oil (p. 2636·3).
Cold and influenza symptoms; cough; catarrh.

Pinimenthol *Apivita, Gr.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); scots pine oil (p. 2591·2); pumilio pine oil (p. 2591·1); turpentine oil (p. 2636·3); menthol (p. 2553·2).

Pinimenthol Erkältungsbad *Spitzner, Ger.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Bath additive; cold symptoms.

Pinimenthol Erkältungsbad für Kinder *Spitzner, Ger.*
Eucalyptus oil (p. 2501·2).
Bath additive; cold symptoms.

Pinimenthol Erkältungsbalsam mild *Spitzner, Ger.*
Eucalyptus oil (p. 2501·2); Norway spruce oil.
Respiratory-tract congestion.

Pinimenthol Erkältungsinhalat *Spitzner, Ger.*
Eucalyptus oil (p. 2501·2); pine needle oil (p. 2591·1).
Cold symptoms.

Pinimenthol Erkältungssalbe *Spitzner, Ger.*
Eucalyptus oil (p. 2501·2); pine needle oil (p. 2591·1); menthol (p. 2553·2).
Cold symptoms.

Pinimentol *Apotheca Pacis, Pol.*
Eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); peppermint oil (p. 1877·1); pine oil (p. 2591·1).
Respiratory-tract congestion; skeletal muscle pain; neuralgia.

Pink Bismuth *Perrigo, Israel.*
Bismuth salicylate (p. 1821·3).
Abdominal cramps; diarrhoea; dyspepsia; flatulence; nausea.

Pink Luna *Stada, Ger.*
Ethinylestradiol (p. 2275·3); chlormadinone acetate (p. 2257·3).
Combined oral contraceptive.

Pinklot *Stiefel, Arg.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3); salicylic acid (p. 1719·1); calamine (p. 1697·2).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pinloc *Orion, Fin.*
⊗Pindolol (p. 1470·1).
Angina pectoris; hypertension; arrhythmias.

Pinnacaine *Sircle, USA.*
Benzocaine (p. 1980·2).
Ear ache.

Pino-Cort *Bell, India.†*
⊗Atropine sulfate (p. 1310·2); hydrocortisone acetate (p. 1640·1).
Allergic conjunctivitis; corneal burns; pre- and postmedication in ocular surgery.

Pinorax *AFT, NZ.*
Dantron (p. 1833·3); poloxamer 188 (p. 2202·1).
Constipation.

Pinorec *Novell, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Pinosol *Zentiva, Cz.; Slovakofarma, Hung.; Zentiva, Pol.†; Zentiva, Rus.; Zentiva, Ukr.†*
Pine oil (p. 2591·1); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); guaiazulene (p. 2523·1); tocoferil acetate (p. 2119·2).
Nasal congestion; rhinitis; nasopharyngeal inflammation; adjunct in surgery of nasal cavities; upper respiratory-tract congestion; upper respiratory-tract inflammation.

Slovakofarma, Hung.; Zentiva, Pol.†; Zentiva, Rus.; Zentiva, Ukr.
Nasal ointment: Pine oil (p. 2591·1); eucalyptus oil (p. 2501·2); tocoferil acetate (p. 2119·2); menthol (p. 2553·2); thymol (p. 1772·2).
Nasal congestion; adjunct in surgery of nasal cavities; upper respiratory-tract inflammation; upper respiratory-tract congestion.

Zentiva, Pol.†; Zentiva, Rus.; Zentiva, Ukr.
Nasal cream: Cream: Eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); thymol (p. 1772·2); tocoferil acetate (p. 2119·2).
Nasal congestion; adjunct in surgery of nasal cavities; upper respiratory-tract inflammation; upper respiratory-tract congestion.

Zentiva, Cz.†
Nasal cream: Scots pine oil (p. 2591·2); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); alpha tocoferil acetate (p. 2119·2).
Cold symptoms; nasal congestion; postoperative nasal packing.

Zentiva, Cz.†
Nasal ointment: Menthol (p. 2553·2); Scots pine oil (p. 2591·2); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); alpha tocoferil acetate (p. 2119·2).
Cold symptoms; nasal congestion; postoperative nasal packing.

Pinovit *Farmak, Ukr.*
Pumilio pine oil (p. 2591·1); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); *dl*-alpha tocoferil acetate (p. 2119·2); thymol (p. 1772·2).
Rhinitis; rhinopharyngitis; nasal and throat infections and inflammation.

Pinovitum *Farmak, Rus.*
Eucalyptus oil (p. 2501·2); pine oil (p. 2591·1); peppermint oil (p. 1877·1); thymol (p. 1772·2); guaiazulene (p. 2523·1); alpha tocoferil acetate (p. 2119·2).
Rhinitis; throat disorders.

Pinral *Sanovel, Turk.*
Lamotrigine (p. 527·2).

Pin-Rid *Apothecary, USA.*
Pyrantel embonate (p. 165·3).

Pinselina Knapp *Montefarmaco, Ital.*
Benzocaine (p. 1980·2); phenol (p. 1763·3); thymol (p. 1772·2); menthol (p. 2553·2).
Mouth disorders.

Pinsheng *Xincat, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Pintal *Alet, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Pinup *Watsin Genetech, China.*
Voriconazole (p. 597·1).
Fungal infections.

Pinvex *Cofasa, Venez.*
Anthraquinone oxymethyl glycosides (p. 1884·2); salicylic acid (p. 1719·1).
Mouth and throat disorders.

Pin-X *Penn, USA.*
Pyrantel embonate (p. 165·3).
Worm infections.

Pin-Xol *Hoe, Malaysia.*
Tar (p. 1723·3).
Skin irritation; pruritus; cleanser for scaly skin.

Piobaj *Grin, Mex.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Ocular hypertension; glaucoma.

Piodermina *Farmachimici, Ital.*
Sodium fusidate (p. 302·1); thyme (p. 2630·2); mallow (p. 2549·2).
Bacterial skin infections.

Piodrex *Bunker, Braz.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Pioforce *Biofarma, Turk.*
Pioglitazone hydrochloride (p. 493·1).

Pioglar *Ranbaxy, Rus.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Ranbaxy, Ukr.
Pioglitazone (p. 493·1).
Diabetes mellitus.

Pioglit *Phoenix, Arg.; Sun, Rus.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piogtan *Eczacibasi, Turk.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piokil Plus *Novapharm, Venez.*
Permethrin (p. 2159·3).
Pediculosis.

Pioktanina *Hasco-Lek, Pol.*
Methylrosanilinium chloride (p. 1761·1).
Skin infections.

Pioletal *Delta, Braz.*
Permethrin (p. 2159·3).
Pediculosis.

Piomed *Comed, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piomed M *Ipca, India.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Piondia *Sandoz, Turk.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pionix *Kalbe, Indon.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pionix-M *Kalbe, Indon.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Pioprost *Poen Vision, Mex.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Pioral Pasta *Teofarma, Ital.*
Chlorothymol (p. 1748·2).
Oral disinfection.

Piorlis *Uriach Aquilea OTC, Spain.†*
Eugenol (p. 2501·2); peppermint oil (p. 1877·1); methyl salicylate (p. 92·1); thymol (p. 1772·2); tyrothricin (p. 384·1).
Pyorrhoea; gingivitis; gum disinfection; mouth ulcers.

Piosafe *Aristo, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piosafe MF *Aristo, India.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Piosan *Belfar, Braz.*
Permethrin (p. 2159·3).

Piotamax *Francelab, Arg.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Piotaz *Germed, Braz.*
Pioglitazone (p. 493·1).

Umedica, Philipp.
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piouno *Wockhardt, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piovalen *Chrispa (Χρισπα), Gr.*
Cimetidine (p. 1827·1).

Pioz *USV, Ukr.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Piozar *Shou Chan, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piozil *Almus, Port.†*
Benzyl benzoate (p. 2149·1).

Piozone *Imperial, Philipp.; M & H, Thai.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Piozulin *Cadila, India.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pip Acid *Iasis, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Pipedic *Pharmasant, Thai.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Pipefort *Lampugnani, Ital.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Pipegal *Galenika, Rus.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Pipelin *Skopinski, Rus.*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Pipemid *Visufarma, Ital.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Pipemidin *Stirol, Ukr.*
Pipemidic acid (p. 339·3).
Genito-urinary-tract infections.

Piperacyl *Bode, Indon.; Tempo Scan Pacific, Indon.*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Piperato *Ronava, Venez.*
Piperazine adipate (p. 163·1); piperazine hydrate (p. 163·1).
Worm infections.

Piperazil *Allen, Mex.*
Piperazine (p. 163·1).
Ascariasis; enterobiasis.

SM, Venez.
Piperazine hydrate (p. 163·1).
Ascariasis; enterobiasis.

Pipercin *Clonmel, Irl.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Piperdin *Etifar, Venez.*
Piperazine hydrate (p. 163·1).
Worm infections.

Pipergress *Parggon, Mex.*
Piperazine (p. 163·1).
Worm infections.

Piperin *Rowex, Irl.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Piperital *IBI, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pipermel *Basi, Port.*
Piperazine (p. 163·1).
Enterobiasis; ascariasis.

Pipersal *Farma 1, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

PiperTaz *Sandoz, Austral.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Pipertaz *Great Eastern, Thai.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Pipertex *Pharmatex, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pipertox *Codilab, Port.*
Piperazine (p. 163·1).
Worm infections.

Piperzan *Quim-Far, Venez.*
Piperazine hydrate (p. 163·1).
Worm infections.

Pipetecan *Richmond, Arg.*
Irinotecan (p. 812·2).
Malignant neoplasms.

Pipetexina *Richmond, Arg.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Pipitaz *Astro, Austria.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Piplex *Mediderm, Chile.*
Isotretinoin (p. 1706·2).
Acne.

Pipolphen *Egis, Hung.; Egis, Rus.; Egis, Ukr.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; sedative; motion sickness; vertigo; pain.

Pipolzine *Bryntsalov, Rus.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; sedative; premedication; nausea and vomiting.

Piportil *Sanofi-Aventis, Irl.†; Sanofi-Aventis, NZ; Sanofi-Aventis, Singapore; JHC Healthcare, UK.*
Pipotiazine palmitate (p. 1098·1).
Psychoses.

Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.†; Sanofi-Aventis, Rus.†
Pipotiazine (p. 1098·1) or pipotiazine palmitate (p. 1098·1).
Psychoses.

Piportil L4 *Sanofi-Aventis, Arg.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Mex.*
Pipotiazine palmitate (p. 1098·1).
Psychoses; schizophrenia.

Piportyl *Sanofi-Aventis, Chile.*
Pipotiazine palmitate (p. 1098·1).
Psychoses.

Pippen *Pharmaland, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Pipracil *Wyeth, India; Wyeth, Thai.*
Piperacillin sodium (p. 340·1).
Bacterial infections.

Pipracin *Vitamed, Israel.*
Piperacillin sodium (p. 340·1).
Bacterial infections.

Pipraks *Eczacibasi, Turk.*
Piperacillin sodium (p. 340·1).
Bacterial infections.

Pipralen *Lennon, S.Afr.†*
Piperazine citrate (p. 163·1).
Ascariasis; enterobiasis.

Pipram *Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; Nikolakopoulos, Gr.; Teofarma, Ital.; Sanofi-Aventis, Neth.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Pipril *Wyeth, Gr.*
Piperacillin sodium (p. 340·1).
Bacterial infections.

Piprine *Be-Tabs, S.Afr.*
Piperazine citrate (p. 163·1).
Ascariasis; enterobiasis.

Piprol *Biomed, Spain.†*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Piptal
Note: this name may be used for preparations of different composition.
Nicholas, Indon.
Pipenzolate bromide (p. 1878·1); phenobarbital sodium (p. 535·3).
Colic; smooth muscle spasm; regurgitation; vomiting.

Piptalin *Deva, Turk.*
Pipenzolate bromide (p. 1878·1).
Smooth muscle spasm.

Piptaz *United American, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Piptazira *Hospira, Norw.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Pipurin *NCSN, Ital.*
Pipemidic acid (p. 339·3).
Genitourinary-tract infections.

Pipurol *Zambon, Braz.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Pipzen *Degorts, Mex.*
Pipenzolate bromide (p. 1878·1).

Piquet *Abdi, Turk.*
Quetiapine (p. 1101·1).

Pir-05 *Rafarm, Gr.*
Lysates of *Streptococcus pyogenes; Streptococcus viridans; Klebsiella pneumoniae; Haemophilus influenzae; Moraxella catarrhalis; Streptococcus pneumoniae; Klebsiella ozaenae.*

Pir Hot D *Deva, Turk.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Pira *Omega, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Pirabene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Piracetam (p. 393·3).
Organic brain disorders; cortical myoclonus; mental function impairment; cerebrovascular disorders; vertigo; alcohol withdrawal syndrome; mental function disorders.

Piracalamina *Szama, Arg.*
Phenol (p. 1763·3); mepyramine maleate (p. 635·1); calamine (p. 1697·2); zinc oxide (p. 1729·1).
Contact dermatitis; lichen; pruritus; sunburn.

Piracebral *Hexal, Ger.†*
Piracetam (p. 393·3).
Mental function disorders.

Piracem *Alet, Gr.; Specifar, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Piracemed *Ranbaxy, Belg.†*
Piracetam (p. 393·3).
Mental function disorders.

Piracetop *Apotex, Belg.†*
Piracetam (p. 393·3).
Mental function disorders.

Piracetrop *Holsten, Ger.†*
Piracetam (p. 393·3).
Mental function disorders.

Piracezine *Minskinterkaps, Rus.*
Piracetam (p. 393·3); cinnarizine (p. 622·1).
Cerebrovascular disorders; cranial trauma; mental function disorders; vestibular disorders; motion sickness; migraine.

Piracross *Pharmacross, Chile.*
Topiramate (p. 550·3).
Epilepsy.

Pirafrin *Diba, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Pain; fever; nasal congestion; rhinitis; conjunctival congestion.

Piraldina *Bracco, Ital.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Piraldyne *Dentoral, Turk.*
Rhubarb (p. 1884·2); salicylic acid (p. 1719·1).
Mouth disorders.

Piralen *Otto, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Piralgin *SoSe, Ital.*
Dipyrone (p. 53·3).
Fever; pain.

Piralgina *Diba, Mex.*
Tablets: Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Pain; fever; respiratory-tract congestion.

Diba, Mex.
Oral solution: Paracetamol (p. 115·1).
Fever; pain.

Piralgina 650 *Diba, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Piralgina C *Diba, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Piralyn *Kener, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Piram *General Drugs, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Piramax *Cipla-Medpro, S.Afr.*
Topiramate (p. 550·3).
Epilepsy.

Piram-D *LCH, Hong Kong†; Pacific, NZ.†*
Piroxicam (p. 125·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders; pain.

Pirament *Ipca, India.*
Piracetam (p. 393·3).
Myoclonus.

Piramil *Sandoz, Cz.; Sandoz, Gr.; Sandoz, Hung.†; Sandoz, Pol.; Lek, Rus.; Sandoz, Thai.†; Sandoz, Venez.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction; diabetic nephropathy; myocardial infarction.

Piramil Plus *Sandoz, Gr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Piramin *Elofar, Braz.†*
Paracetamol (p. 115·1).
Fever; pain.

Pirandall *Randall, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Pirantal *Pharmanel, Gr.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Pirantrim *Keton, Mex.*
Pyrantel embonate (p. 165·3).
Worm infections.

Pirantrin *Koz, Turk.*
Pyrantel embonate (p. 165·3).
Worm infections.

Pirasam *SRS, Philipp.†*
Piracetam (p. 393·3).
Myoclonus.

Piraska *Supra Ferbindo, Indon.†*
Pyrantel embonate (p. 165·3).
Worm infections.

Pirasmin *Deva, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Pirasod *Parggon, Mex.*
Dipyrone (p. 53·3).

Piratam *GSK, India; Beacons, Singapore.*
Piracetam (p. 393·3).
Alcoholism; cerebrovascular disorders; cerebral trauma; vertigo; senile dementia; behaviour disorders in children; sickle-cell disease; mental function impairment.

Piratin *Quality, Hong Kong.*
Piracetam (p. 393·3).
Dementia.

Piratrof *Novell, Indon.*
Piracetam (p. 393·3).
Cerebral infarction.

Piratropil *Jelfa, Rus.*
Piracetam (p. 393·3).
Mental function impairment; cerebrovascular disorders; alcohol withdrawal syndrome; learning disorders in children; sickle-cell anaemia.

Pirax *Pharmaland, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Sandoz, Switz.†
Piracetam (p. 393·3).
Mental function impairment; myoclonus; dyslexia.

Piraxil *Suphong, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Pirazinid *Kocak, Turk.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pirazinon *Sanval, Braz.†*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pirazmen *Deva, Turk.*
Theophylline (p. 1229·3).

Pircam *Newcharoen, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Pirdolin *Dermadolin, Turk.*
Pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1).
Seborrhoeic dermatitis of the scalp.

Piremol *Loeffler, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Pirepil *Decomed, Port.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Pirespa *Shionogi, Jpn.*
Pirfenidone (p. 2592·1).
Idiopathic pulmonary fibrosis.

Pirestop *Epifarma, Ital.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Piretanyl *Pasteur, Chile.*
Syrup: Chlorphenamine maleate (p. 620·3); dipyrone (p. 53·3).
Cold and influenza symptoms.

Pasteur, Chile.
Tablets: Chlorphenamine maleate (p. 620·3); dipyrone (p. 53·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Pirexin *Juventus, Spain.*
Ibuprofen (p. 68·2).
Gout; musculoskeletal, joint, and peri-articular disorders; fever; pain.

Pirexyl *Pasteur, Chile.*
Diclofenac sodium (p. 48·3).
Fever; musculoskeletal and joint disorders; pain.

Pirfalin *Farmigea, Ital.*
Pirenoxine sodium (p. 2591·3).
Cataracts.

Piridos *Omedir, Arg.†*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis.

Pirifur *Sanofi-Aventis, Mex.*
Phenazopyridine hydrochloride (p. 124·3); nalidixic acid (p. 328·3).
Urinary-tract infections.

Pirigrip *Biosintex, Arg.*
⊗Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

Pirilène *Sanofi-Aventis, Fr.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pirimat *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions; anaphylaxis.

Pirimed *Medihealth, Mex.; Roemmers Medihe, Venez.*
Pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis; psoriasis; scalp disorders.

Pirimetan *Richmond, Arg.*
⊗Propranolol hydrochloride (p. 1479·1).

Pirimir *Sanofi-Aventis, Mex.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Pirin *Patar, Thai.*
Aspirin (p. 22·2).
Fever; thromboembolism prophylaxis; pain.

Pirinace *Sidus, Arg.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Influenza symptoms.

Pirinase *GSK Consumer, UK.*
⊗Fluticasone propionate (p. 1638·1).
Formerly known as Flixonase.
Allergic rhinitis.

Pirinovag *Novag, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Piriteze *GSK Consumer, UK.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis.

Piriton *GSK Consumer, Irl.; GSK, Singapore; GSK Consumer, UK.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Piriton Expectorant *GSK, India.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cold symptoms; cough.

Piritos *Biosintex, Arg.*
Bromhexine (p. 1656·3); butetamate (p. 1658·1).
Respiratory-tract congestion.

Pirium *Janssen-Cilag, Gr.*
Pimozide (p. 1096·3).
Psychoses.

Pirmella 1/35 *Lupin, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Combined oral contraceptive.

Pirmella 7/7/7 *Lupin, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Triphasic oral contraceptive.

Piroalgin *Lafedar, Arg.*
Piroxicam (p. 125·3).
Inflammation; pain.

Pirobac *Koni-Cofarm, Chile.*
Benzoyl peroxide (p. 1696·1).
Acne.

Pirobec *MDM, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular pain and inflammation.

Pirobeta *Betapharm, Ger.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Pirobutil *Degorts, Mex.*
Dipyrone (p. 53·3); butylhyoscine (p. 1845·3).
Pain; muscle spasm.

Pirocam *Ratiopharm, Austria; Dexa, Indon.; Spirig, Switz.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Pi-rock *SSP, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Piroctol *Valuge, Arg.*
Ciclopirox (p. 575·3); collagen (p. 2483·2).
Scalp disorders.

Pirodax *Teva, Mex.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Pirodene *Medikon, Indon.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Pirofel *Sanbe, Indon.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Pirofen *Deva, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Piroflam *Medipharm, Chile.*
Diclofenac diethylamine (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Inflammation; pain.

Winthrop, Ger.
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Piroflan *Belfar, Braz.*
Piroxicam (p. 125·3).

Piroftal *Bruschettini, Ital.*
Piroxicam (p. 125·3).
Eye inflammation; ocular oedema.

Pirogina *Teuto, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Pirogreen *Greenpharma, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; dysmenorrhoea.

Pirohexal-D *Hexal, Austral.†; Hexal, NZ.†*
Piroxicam (p. 125·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Pirok *Abbott, Turk.*
Pyrvinium embonate (p. 166·1).
Oxyuriasis.

Pirolam *Medana, Pol.*
Ciclopirox olamine (p. 575·3).
Fungal and bacterial skin infections; fungal nail infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pirom
Note: this name may be used for preparations of different composition.
Sandoz, Denm.
Piroxicam (p. 125·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.
Solmer, Switz.
Balm: Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); cinnamon oil (p. 2479·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.
Solmer, Switz.
Embrocation: Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); lemon oil (p. 2543·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Piromebrina *Degorts, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Piromed *3DDD, Belg.*
Piroxicam (p. 125·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Pironal
Note: this name may be used for preparations of different composition.
Bago, Chile.
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Pironal Flu *Bago, Chile.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; nasal congestion.

Pirophen *Pfizer, NZ.*
Aspirin (p. 22·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Pirorheum *Hexal, Austria†; Sandoz, Hung.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Piros *Menarini, Ital.*
Paracetamol (p. 115·1).
Fever; pain.

Pirosal
Note: this name may be used for preparations of different composition.
Saba, Turk.
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Fever; pain.

Pirosol *Sandoz, Switz.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Pirostad *Stada, Philipp.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Pirox *CT, Ger.; Cipla, India; Sandoz, Mex.; Medicine Products, Thai.*
Piroxicam (p. 125·3).
Gout; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Piroxal *Medicpharma, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Piroxam *PP Lab, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Piroxan *Diba, Mex.†*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal, joint and peri-articular disorders; gout.

Piroxcin *Polipharm, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Piroxen *Codal Synto, Thai.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Piroxene *Abbott, Braz.*
Piroxicam (p. 125·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxgel *Isdin, Spain.*
Coal tar (p. 1723·2).
Scalp disorders.

Piroxica *Stada, Hong Kong.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and soft-tissue disorders.

Piroxidon *Acdhon, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Piroxifar *Elofar, Braz.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; dysmenorrhoea.

Piroxil *Sanval, Braz.*
Piroxicam (p. 125·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxin *Cifarma, Braz.; Ratiopharm, Fin.*
Piroxicam (p. 125·3).
Gout; dysmenorrhoea; musculoskeletal, peri-articular and soft-tissue disorders.

Piroxinid *Ducto, Braz.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; dysmenorrhoea.

Piroxistad *Stada, Austria.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation; pain.

Piroxitop *Topgen, Belg.†*
Piroxicam (p. 125·3).

Pirox-Man *T Man, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Piroxone *Burapha, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Piroxsil *Silom, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Pirtad *TAD, Fin.†*
Glimepiride (p. 473·2).
Diabetes mellitus.

Pirucin *Saba, Turk.*
Epirubicin hydrochloride (p. 787·1).

Pirval *Fada, Arg.*
Alprazolam (p. 1035·2).

Pirzinol *Solfran, Mex.*
Piperazine (p. 163·1).
Worm infections.

Pisacaina *Pisa, Mex.†*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; ventricular arrhythmias.

Pisalin *2M, Thai.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Pisalpra *Pisa, Mex.*
Alprazolam (p. 1035·2).
Anxiety.

Pisamor *Flamingo, Philipp.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Pisapem *Pisa, Mex.*
Meropenem (p. 321·3).
Bacterial infections.

Pisatrina *Pisa, Mex.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pisaurit *Pisa, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; anxiety; obsessive-compulsive disorder.

Pisaveril *Demo, Gr.*
Allantoin (p. 1693·1); coal tar (p. 1723·2).

Pisavit AD-15 *Pisa, Mex.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamin A and D supplement.

Piscis 3 *Vargas, Venez.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Pisdeno *Pisa, Mex.*
Adenosine (p. 1291·1).
Paroxysmal supraventricular tachycardia; diagnosis of arrhythmias.

Pisono *Finadiet, Arg.*
Solifenacin.
Bladder hyperactivity.

Pistofil *Rafarm, Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Pitiren *Savoma, Ital.*
Climbazole (p. 576·2); strontium chloride (p. 2623·1); lauromacrogol 400 (p. 2194·1); levomenol (p. 2544·1); menthyl lactate (p. 2554·1); benzyl alcohol (p. 1739·3); vitamin E (p. 2119·1).
Seborrhoeic dermatitis.

Pitiriax *Cassara, Arg.*
Salicylic acid (p. 1719·1); piroctone olamine (p. 1716·3).
Dandruff.

Pitocin *Pfizer, India; JHP, USA.*
Oxytocin (p. 2143·1).
Induction of labour; postpartum haemorrhage; incomplete or inevitable abortion; uterine inertia.

Pitogin *Ethica, Indon.*
Oxytocin (p. 2143·1).
Labour induction and enhancement; incomplete abortion; postpartum haemorrhage; caesarian section.

Piton-S *Schering-Plough, Indon.*
Oxytocin (p. 2143·1).
Labour induction; uterine haemorrhage; incomplete abortion; lactation stimulation.

Pitoxil *Sanovel, Turk.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Pitressin *Link, Austral.; IFET (ΙΦΕΤ), Gr.; Goldshield, Irl.; Link, NZ; Goldshield, UK.†*
⊗Argipressin (p. 2643·1).
Diabetes insipidus; adjunct in abdominal radiography; postoperative abdominal distension; variceal haemorrhage.

Pitressin Synthetic *JHP, USA.*
⊗Vasopressin (p. 2642·3).
Abdominal distension; abdominal radiography; diabetes insipidus.

Pitrex *Taro, Canad.; Teva, Israel.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Pitrion *Rafa, Israel.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Pitrisan *Rekah, Israel.†*
Ointment: Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.
Rekah, Israel.†
Topical solution: Undecenoic acid (p. 596·3); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); chlorobutanol (p. 1747·2); resorcinol (p. 1718·3).
Fungal skin infections.

Pitrisol *Rekah, Israel.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); lidocaine hydrochloride (p. 1988·2).
Fungal infections.

Pitunal *Menarini, Gr.*
Frovatriptan succinate (p. 676·2).
Migraine.

Pituo *Pidi, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Pitylis *Raymos, Arg.*
Ketoconazole (p. 585·3).
Scalp disorders.

Pityol *Zentiva, Cz.*
Ichthammol (p. 1705·3); boric acid (p. 2459·3); zinc oxide (p. 1729·1); guaiazulene (p. 2523·1).
Skin disorders.

Pityrum *Apotex, Arg.*
Ciclopirox (p. 575·3); collagen (p. 2483·2).
Dandruff.

Pityval *Roche-Posay, Braz.*
Piroctone olamine (p. 1716·3); iodopropynyl butyl carbamate (p. 2156·3).
Seborrhoeic dermatitis.
Roche-Posay, Fr.†
Piroctone olamine (p. 1716·3); iodopropynyl butyl carbamate (Glycacil) (p. 2156·3); thermal water.
Skin irritation.
Roche-Posay, Chile.
Piroctone olamine (p. 1716·3); iodopropynyl butyl carbamate (Glycacil); thermal water.
Seborrhoeic dermatitis.

Pivalephrine *Santen, Jpn.*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma; ocular hypertension.

Pivalone *Pfizer, Fr.; Pfizer, Singapore; Uhlmann-Eyraud, Switz.†*
⊗Tixocortol pivalate (p. 1648·3).
Rhinitis; nasal polyps.

Pivalone compositum *Uhlmann-Eyraud, Switz.*
⊗Tixocortol pivalate (p. 1648·3); neomycin sulfate (p. 330·1).
Infected nasal disorders.

Pivefrin *Kleva, Gr.*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Pixacor *Synmedic, Philipp.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Pixeta *Accord, S.Afr.*
Pravastatin (p. 1473·1).
Hyperlipidaemias.
Accord, S.Afr.
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pixian *Pidi, China.*
Cefalexin (p. 234·1); trimethoprim (p. 381·2).
Bacterial infections.

Pixicam *Sandoz, S.Afr.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Pixidin *Sanico, Belg.*
Chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disorders.

Pixin *Pidi, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Pixor Stick Anti-acne N *Doetsch, Grether, Switz.*
Salicylic acid (p. 1719·1); triclosan (p. 1773·2).
Acne.

Pixorid *Roemmers-Klinos, Venez.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; pain.

Pixuvri *CTI, Denm.; CTI, Neth.; CTI, Norw.; CTI, Spain; CTI, UK.*
Pixantrone maleate (p. 847·2).
Non-Hodgkin's lymphoma.

999 Piyanping *SanJiu, China.*
⊗Dexamethasone acetate (p. 1631·1).
Skin disorders.

Piyavit *Girud, Rus.*
Powdered leech (p. 1418·1).
Superficial vascular disorders; oedema.

Piyeloseptyl *Biofarma, Turk.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Piyraleks *Berko, Turk.*
Liquorice (p. 1853·2); zinc sulfate (p. 2126·2); salicylic acid (p. 1719·1); clove oil (p. 2481·3); peppermint oil (p. 1877·1).
Mouth disorders.

Pizaccord *Douglas, NZ.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pizar *Kleva, Gr.*
Flurbiprofen (p. 65·2).

Pizide *Pharmasant, Thai.*
Pimozide (p. 1096·3).
Psychoses.

Pizobac *One Pharma, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Pizomed *Medifive, Thai.*
Pizotifen malate (p. 678·2).
Anorexia; migraine; reduced appetite.

PK Aid *Scientific Hospital Supplies, Austral.†; SHS, Irl.; SHS, UK.*
Amino acids without phenylalanine.
Phenylketonuria.

PK Max *Scientific Hospital Supplies, Irl.†*
Food for special diets.
Phenylketonuria.

PK-Levo *Merz, Ger.†*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

PK-Merz *Merz, Austria; Merz, Cz.; Merz, Ger.; Pharmacare, Gr.; Merz, Hong Kong; Merz, Hung.; Megapharm, Israel; Merz, Malaysia; Merz, Mex.; Merz,*

Philipp.; Medinfar, Port.; Merz, Switz.; Assos, Turk.; Merz, Ukr.
Amantadine sulfate (p. 890·3).
Parkinsonism; influenza; coma; postherpetic neuralgia; drug-induced extrapyramidal disorders; neuralgia.

PKU *Nutricia, Ital.; Vitaflo, UK.*
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

Nutricia-Bago, Arg.; Support, Braz.
A range of foods for special diets.
Phenylketonuria.

PKU Anamix *Nutricia, Austral.*
Infant feed.
Formerly known as XP Analog.
Phenylketonuria.

Nutricia, Cz.; SHS, Irl.
Food for special diets.
Phenylketonuria; hyperphenylalaninaemia.

PKU Anamix Junior *SHS, UK.*
Food for special diets.
Phenylketonuria.

PKU Lophlex *SHS, UK.*
Food for special diets.
Phenylketonuria.

Plabel *Belfar, Braz.*
Metoclopramide (p. 1862·2).

Plac Out *Bernabo, Arg.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat infections; oral hygiene.

Placatus *Noos, Ital.*
Nepinalone hydrochloride (p. 1670·2).
Cough.

Placentex *Mastelli, Ital.*
Polydeoxyribonucleotide (p. 2492·2).
Inflammatory and degenerative disorders.

Placentrex *David, India.*
Injection; topical gel: Placenta extract (human) (p. 2444·1).
Vitiligo; burns; wounds; rheumatoid arthritis; osteoarthritis; pelvic inflammatory disease.

David, India.
Topical lotion: Deoxyribonucleic acid (p. 2492·2); ribonucleic acid (p. 2604·1); tyrosine (p. 2098·3).
Vitiligo.

Placidiax *Richmond, Arg.†*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Placidox *Lupin, India.*
Diazepam (p. 1063·2).
Anxiety disorders; alcohol withdrawal syndrome; skeletal muscle spasm.

Placil *Alphapharm, Austral.*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; phobic states; narcoleptic syndrome.

Placinoral *Brainpharma, Spain.*
Lorazepam pivalate (p. 1080·3).
Anxiety; insomnia.

Placis *Boryung, Thai.; Farma-Tek, Turk.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Placitin *Pharmedic, Philipp.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Placol *Bennett, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Placor *Rottapharm, Hung.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Placta *Actavis, Indon.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Actavis, Singapore.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Plactidil *Teofarma, Ital.*
Picotamide (p. 1469·3).
Thromboembolic disorders.

Pladel *Phapros, Indon.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Pladogrel *Fahrenheit, Indon.*
Clopidogrel (p. 1342·3).
Cardiovascular risk reduction; unstable angina.

Plagerine *Brown & Burk, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Plagex *Teuto, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Plagon *De Mayo, Braz.†*
Metoclopramide (p. 1862·2); vitamin B_6 (p. 2105·3).
Nausea and vomiting.

Plagrel *Sandoz, Braz.*
Clopidogrel (p. 1342·3).

Toronto, Hung.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Plagril *Reddy, Rus.; Reddy, Singapore; Reddy, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; myocardial infarction; cerebrovascular ischaemia; atherosclerosis.

Plagrol *Adcock Ingram, S.Afr.*
Clopidogrel (p. 1342·3).

Plak *Polifarma Benessere, Ital.*
Chlorhexidine (p. 1743·2).
Dental plaque prophylaxis.

Plak Out *Gerolymatos, Gr.; Polifarma Benessere, Ital.; KerrHawe, Switz.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; mouth disorders; oral disinfection.

Plaketar *Biolab Sanus, Braz.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Plaksat *Actavis, Rus.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Plamet *Libbs, Braz.*
Bromopride (p. 1824·2).
Nausea and vomiting; aid in endoscopy; gastrointestinal disorders.

Plamida *Prodotti, Braz.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Plamidasil *Delta, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Plamide *Utopian, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Delayed gastric emptying; nausea and vomiting; gastro-oesophageal reflux; aid in gastrointestinal examination.

Plamine *Picco, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Delayed gastric emptying; nausea and vomiting; gastro-oesophageal reflux; aid in gastrointestinal examination.

Plamivon *Bunker, Braz.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Plamox *Vitarum, Arg.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Plan *Craveri, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Plan B *Paladin, Canad.; Teva, USA.*
Levonorgestrel (p. 2296·1).
Progestogen-only postcoital oral contraceptive.

Plan Duo *Craveri, Arg.*
Tablets, ezetimibe (p. 1379·2); tablets, atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Planak *Fahrenheit, Indon.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Plander *Fresenius Kabi, Ital.*
⊗Dextran 70 (p. 1138·3) in sodium chloride.
Plasma volume expansion.

Plander R *Fresenius Kabi, Ital.*
⊗Dextran 40 (p. 1138·1) in sodium chloride.
Plasma volume expansion; thrombosis prophylaxis; extracorporeal perfusion.

Planibu *Fahrenheit, Indon.*
Medroxyprogesterone acetate (p. 2288·1).
Injectable contraceptive.

Planitrix *Bros, Gr.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Planizol *Solfran, Mex.*
Metronidazole (p. 936·1).
Amoebiasis.

Planor
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Clopidogrel bisulfate (p. 1342·3).

Plant Spray *Dolisos, Canad.†*
Plantago; echinacea (p. 2498·1).
Homoeopathic preparation.

Planta Lax *Hoeveler, Austria.*
Senna leaf and pod (p. 1885·1); frangula bark (p. 1843·3); blackberry leaf; chamomile flowers (p. 2474·1); coriander (p. 2486·3); fennel (p. 2503·2).
Constipation.

Plantaben *Nycomed, Arg.; Madaus, Austria; Nycomed, Braz.; Biotoscana, Chile; Madaus, Hong Kong; Nycomed, Mex.; Rottapharm, Spain; Rottapharm, Thai.*
Ispaghula (p. 1849·1).
Constipation; diarrhoea; diverticular disease; hypercholesterolaemia; irritable bowel syndrome; dietary fibre supplement; metabolic disorders; hyperlipidaemias.

Plantacard N *Madaus, Ger.*
Arnica (p. 2447·2); crataegus (p. 2488·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Plantacid
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Epigastric pain; gastric hyperacidity; gastritis; peptic ulcer.

Zdorovje, Rus.
Plantain (p. 2592·3).
Gastritis; peptic ulcer; colitis.

Plantagen *Gemi, Pol.*
Ribwort plantain (p. 2604·2).
Respiratory-tract disorders.

Plantaglucid *Vifiteh, Rus.; Zdorovje, Rus.*
Plantain (p. 2592·3).
Gastritis; peptic ulcer; colitis.

Plantago-Plus *Doctor H, Rus.*
Delphinium staphisagria; kreosotum (p. 1659·3); mercurius solubilis (p. 2555·3); plantago major (p. 2592·3).
Homoeopathic preparation.

Plantalax *Sofar, Ital.*
Ispaghula (p. 1849·1).
Constipation.

Plantasor *Soria, Spain.*
Ispaghula (p. 1849·1).
Constipation; dietary fibre supplement.

Plantax
Note: this name may be used for preparations of different composition.
Cinfa, Spain.
Ispaghula (p. 1849·1).
Constipation.

Planten *Wyeth Consumer, Ital.*
Ispaghula (p. 1849·1).
Constipation.

Plantex *Lek, Pol.; Lek, Rus.; Sandoz, Ukr.*
Fennel (p. 2503·2); fennel oil (p. 2503·3).
Flatulence; colic; meteorism.

Plantifort *Hasco-Lek, Pol.*
Echinacea purpurea (p. 2498·1); ribwort plantain (p. 2604·2).
Upper respiratory-tract infections.

Plantigmin *Polifarma, Turk.*
Neostigmine metilsulfate (p. 687·2).

Plantival
Note: this name may be used for preparations of different composition.
Farmasa, Mex.
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; insomnia.

VSM, Neth.
Passion flower (p. 2584·1); avena (p. 2451·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Nervous excitement and unrest.

Plantival forte *Schwabe, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; agitation.

Plantival Mono *Schwabe, Switz.*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Plantival novo *Schwabe, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; agitation.

Planum
Note: this name may be used for preparations of different composition.
Menarini, Ital.
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Pfizer, Ger.
Temazepam (p. 1109·1).
Sleep disorders.

Plaqacide *Oral-B, Austral.*
Chlorhexidine gluconate (p. 1743·3).
Oral disorders; prevention of dental plaque.

Plaquemax *Bergamo, Braz.*
Oprelvekin (p. 1157·2).

Plaquenil *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Canad.; Abbott, China; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi Pasteur, Turk.; Sanofi Synthelabo, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, USA.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus; juvenile idiopathic arthritis; photodermatoses; malaria; arthropathies; Sjögren's syndrome.

Plaquetal *Menarini, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Plaquetil *Rider, Chile.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Plaquevix *EMS, Braz.*
Clopidogrel (p. 1342·3).

Plaquinol *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; BioSaude, Port.; Sanofi-Aventis, Venez.*
Hydroxychloroquine sulfate (p. 655·2).
Malaria; rheumatoid arthritis; juvenile idiopathic arthritis; lupus erythematosus; photodermatoses; amoebiasis.

Plardox *Lafedar, Arg.*
Oxeladin citrate (p. 1671·2).
Cough.

Plas-Amino *Otsuka, Jpn.*
Amino acids; glucose (p. 2068·3).
Parenteral nutrition.

Plasbumin *Cristalia, Braz.; Grifols, Canad.; Bayer, Chile†; Talecris, China; Talecris, Ger.; Demo, Gr.; Talecris, Hong Kong; Dipa, Indon.; Kedrion, Ital.; Bayer, Philipp.; Talecris, Rus.; Grifols, Spain; Biem, Turk.; Talecris, USA.*
⊗Albumin (p. 1130·2).
Shock; burns; hypoproteinaemia; cerebral oedema; plasma volume expansion; hypoalbuminaemia; hypovolaemia; extracorporeal circulation; adult respiratory distress syndrome; haemolytic disease of the newborn; hepatic failure; haemodialysis; haemodilution; neonatal hyperbilirubinaemia.

Plasbutein *German Red Cross, Philipp.*
⊗Albumin (p. 1130·2).
Plasma volume expansion.

Plasedan *Quesada, Arg.†*
Alprazolam (p. 1035·2).

Plasil *Duncan, Philipp.; Sanofi-Aventis, Thai.*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; gastrointestinal investigations; nausea and vomiting.

Sanofi-Aventis, Braz.; Kimia, Indon.; Lepetit, Ital.; Sanofi-Aventis, Mex.
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; gastrointestinal examination.

Plasil Enzimático *Sanofi-Aventis, Braz.*
⊗Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2); pancreatin (p. 2579·3); sodium dehydrocholate (p. 2492·1); bromelains (p. 2460·3).
Digestive disorders.

Plasil Enzimatico *Sanofi-Aventis, Mex.*
⊗Metoclopramide hydrochloride (p. 1862·2); bromelains (p. 2460·3); pancreatin (p. 2579·3); sodium dehydrocholate (p. 2492·1); simeticone (p. 1886·2).
Gastrointestinal, biliary-tract, and pancreatic disorders.

Plasimine *Stiefel, Spain.*
Mupirocin (p. 327·2).
Bacterial skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Plasiver *Medochemie, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Plasma du Dr Quinton *Chimicor, Fr.†*
Sea water (p. 2612·1).

Plasma Volume *Baxter, Cz.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion.

Baxter, Irl.
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion.

PlasmaHES *Baxter, Austria.*
⊗An etherified starch (p. 1146·1) in electrolytes.
Plasma volume expansion.

Plasmaline *Krasfarma, Rus.*
⊗Pentastarch (p. 1146·1).
Plasma volume expansion; haemodilution.

Plasmalyt *Baxter, Austria.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Plasma-Lyte *Baxter, Austral.; Baxter, Belg.; Baxter, Cz.; Baxter, Hong Kong†; Baxter, Irl.; Baxter, Port.; Baxter, Rus.; Baxter, Swed.; Baxter, UK; Baxter, USA.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Baxter, Canad.; Baxter, Singapore; Baxter, Spain.†
Electrolyte infusions with glucose (p. 1775·1).
Fluid and electrolyte disorders.

Plasmalyte *Baxter, Denm.; Baxter, Fin.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Baxter, Fr.
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); with or without calcium gluconate (p. 1783·3).
Fluid and electrolyte disorders.

Baxter, Norw.
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Plasma-Lyte IV *Baxter, NZ.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders.

Plasma-Lyte A *Baxter, Israel; Baxter, Switz.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Plasma-Lyte Oral *Baxter, NZ.†*
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1780·1).
Diarrhoea; oral rehydration solution.

Plasmanate *Bayer, Gr.†; Bayer Biological, Hong Kong†; Dipa, Indon.; Bayer, Israel; Bayer, Philipp.†; GenAsia, Philipp.†; Bayer, Singapore; Talecris, USA.*
⊗Plasma protein fraction (human) (p. 1159·2).
Hypoproteinaemia; hypovolaemia; plasma volume expansion; shock.

Plasma-Plex *Armour, USA.*
⊗Plasma protein fraction (p. 1159·2).
Hypoproteinaemia; hypovolaemia.

Plasmarine *Pharmadeveloppement, Fr.*
Minerals.
Tonic.

Plasmasafe *Kedrion, Ital.*
Plasma (p. 1158·2).
Haemorrhagic disorders; reversal of oral anticoagulant effects; thrombocytopenic purpura.

Plasmasteril *Fresenius Kabi, Turk.†*
⊗Hetastarch (p. 1146·1).
Plasma volume expansion.

PlasmaVolume *Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Spain.*
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Hypovolaemia; shock; haemodilution.

Baxter, Ital.; Baxter, Neth.
⊗An etherified starch (p. 1146·1) in electrolytes.
Hypovolaemia.

Plasmax *Sel-J, Philipp.*
⊗Polygeline (p. 1160·3).
Shock; plasma volume expansion.

Ranbaxy, Thai.†
⊗Polygeline (p. 1160·3); electrolytes (p. 1775·1).
Shock; maintenance of fluid volume during surgery; extracorporeal circulation.

Plasmin *Landson, Indon.; Sea Pharmacom, Philipp.*
⊗Collagenase (p. 2484·1); fibrinolysin (p. 1382·3); profibrinolysin activator.
Occlusive vascular disorders.

Plasminex *Sanbe, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; dental extraction in haemophiliacs; hereditary angioedema.

Plasmion *Fresenius Kabi, Fr.*
⊗Gelatin (p. 1154·1).
Shock; hypotension.

Plasmodex *Meda, Norw.*
⊗Dextran 60 (p. 1138·3).
Plasma volume expansion.

Meda, Swed.
⊗Dextran 60 (p. 1138·3); electrolytes (p. 1775·1).
Plasma volume expansion.

Plasmodin *Ifars, Indon.*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria.

Plasmohes *Aguettant, Fr.*
⊗Etherified starch in sodium chloride (p. 1146·1).

Plasmoquine *Medchem, S.Afr.*
Chloroquine sulfate (p. 650·2).
Malaria; lupus erythematosus; rheumatoid arthritis.

Plasmotrim *Nova, Braz.*
Sodium artesunate (p. 648·2).
Malaria.

Plast Apyr Fisiologico *Fresenius Kabi, Spain.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Plast Apyr Glucosado *Fresenius Kabi, Spain.*
Glucose (p. 2068·3).
Carbohydrate source; fluid and electrolyte disorders.

Plast Apyr Glucosalino *Fresenius Kabi, Spain.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1).
Carbohydrate source; fluid and electrolyte disorders.

Plasténan *Horus, Fr.*
Sodium acexamate (p. 2427·3).
Skin ulcers.

Plastenan *Sanofi-Aventis, Arg.*
Sodium acexamate (p. 2427·3).
Wounds; burns; ulcers.

Plastenan con Neomicina *Sanofi-Aventis, Arg.*
Sodium acexamate (p. 2427·3); neomycin sulfate (p. 330·1).
Ulcers.

Plastin *Taiwan Biotech, Philipp.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Plastranit *UCB, Port.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Plastufer *Meda, Ger.†*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Plastulen *Stada, Ger.†*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Plastulen Duo *Stada, Ger.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Plastules B-12 *Wyeth, India.*
Ferrous sulfate (p. 2062·2); yeast (p. 2125·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); liver extract (p. 2444·1).
Anaemias; iron deficiency.

Plasvit *Collins, Mex.†*
Vitamins; minerals.

Platamine
Note: this name may be used for preparations of different composition.
Pfizer, Braz.
Carboplatin (p. 759·1).
Malignant neoplasms.

Pfizer, Arg.†; Pfizer, Gr.; Pfizer, Ital.; Pfizer, Philipp.†
Cisplatin (p. 766·1).
Malignant neoplasms.

Platanovag *Gobbi, Arg.*
Cisplatin (p. 766·1).

Platarex *Medochemie, Cz.; Pliva, Denm.†*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Platel *Proton, Gr.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Platet *Nicholas, Singapore.†*
Aspirin (p. 22·2).
Thromboembolic disorders.

Platexan *Apotex, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Platiblastin-S *Pfizer, Switz.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platicad *Biocad, Rus.*
Oxaliplatin (p. 838·1).
Colorectal cancer; ovarian cancer.

Platidiam *Teva, Cz.; Pliva, Hung.; Pliva Lachema, Pol.; Pliva, Rus.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platidine *Quamed, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Platin
Note: this name may be used for preparations of different composition.
Cadila, India; Intas, Philipp.
Cisplatin (p. 766·1).
Malignant neoplasms.

Wockhardt, India.
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Platina *Boiron, Cz.*
Platinum metallicum (p. 2593·1).
Homoeopathic preparation.

Platinex *BMS, Ger.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platino II *Filaxis, Arg.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platinol *BMS, Fin.†; BMS, Gr.; BMS, Mex.; BMS, NZ†; BMS, Philipp.†; BMS, Rus.; BMS, Switz.†; BMS, Thai.†; BMS Oncology, USA.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platinostyl *Ivax, Arg.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Platinox
Note: this name may be used for preparations of different composition.
Korea United, Philipp.
Oxaliplatin (p. 838·1).
Colorectal cancer.

Sandoz, Indon.
Cisplatin (p. 766·1).
Malignant neoplasms.

Platinoxan *Baxter, Philipp.†*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platinum *Colgate-Palmolive, Ital.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Platinwas *Farma-Tek, Turk.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Platiran *BMS, Braz.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platistine *Pfizer, Braz.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platium *Rider, Chile.†*
Vitamins; minerals.
Dietary supplement.

Plato *Aspen, S.Afr.*
Dipyridamole (p. 1362·2).
Thromboembolism prophylaxis.

Platof *Sanbe, Indon.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disease.

Platosin *Teva, Belg.†; Teva, Cz.†; Chemipharm, Gr.; Combiphar, Indon.; Pharmachemie, Indon.; Pfizer, Jpn; Pharmachemie, Malaysia; Pharmachemie, Neth.; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platosin-S *Er-Kim, Turk.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Platox *Hospira, Cz.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Platsul A
Note: this name may be used for preparations of different composition.
Chobet, Arg.
Sulfadiazine silver (p. 362·3); vitamin A (p. 2098·3); lidocaine (p. 1988·1).
Infected skin disorders; wounds; ulcers; burns.

Grunenthal, Chile.
Sulfadiazine silver (p. 362·3); lidocaine (p. 1988·1); vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Infected burns and wounds.

Plaudit *SoSe, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Plaunac *Guidotti, Ital.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Plaunazide *Guidotti, Ital.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Plavasc *Teuto, Braz.*
Ticlopidine hydrochloride (p. 1512·1).

Plavelate *Win Medica, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Plavidosa *Specifar, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Plavihex *Pasteur, Philipp.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Plavix *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; BMS, Austria; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; BMS, Fin.; Sanofi-Aventis, Fin.; BMS, Fr.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; BMS, Hong Kong; Sanofi-Aventis, Hong Kong; BMS, Hung.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Jpn; BMS, Malaysia; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; BMS, Neth.; Sanofi-Aventis, Neth.; Sanofi BMS, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; BMS, Pol.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; BMS, Swed.; Sanofi-Aventis, Swed.; BMS, Switz.; Sanofi, Switz.; Sanofi-Aventis, Thai.; Sanofi Synthelabo, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; BMS, USA; Sanofi-Aventis, Venez.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis; thromboembolism prophylaxis; unstable angina; myocardial infarction; acute coronary syndrome; stroke prophylaxis; cardiovascular risk reduction; thromboembolic disorders.

Plavocorin *Sandoz, Cz.; Sandoz, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Plavogrel *Alet, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Plax
Note: this name may be used for preparations of different composition.
Colgate-Palmolive, Ital.
Triclosan (p. 1773·2); sodium fluoride (p. 2089·2).
Dental plaque prevention.

Pfizer Consumer, USA.
Sodium pyrophosphate (p. 2619·3); sorbitol (p. 2092·1).
Formerly known as Advanced Formula Plax.

Johnson & Johnson, Canad.†
Sodium benzoate (p. 1738·2); sodium laurilsulfate (p. 2210·3); sodium salicylate (p. 132·2).

Plaxitin *Ebewe, Gr.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Plazadol *Sel-J, Philipp.; Plethico, Rus.*
Tramadol hydrochloride (p. 139·2).
Pain.

Plazolit
Note: this name may be used for preparations of different composition.
Mintlab, Chile.
Pargeverine hydrochloride (p. 1877·1).

PledgaClin *JSJ, USA.*
Clindamycin phosphate (p. 269·3); isopropyl alcohol (p. 1758·3).
Acne.

Plegh *Grin, Mex.*
Phenylephrine (p. 1672·2).

Plegicil *Pharmaxim, Denm.; Sanofi Synthelabo, Turk.*
Acepromazine maleate (p. 1035·1).
Anxiety disorders; hiccup; nausea and vomiting; agitation; psychoses.

Pleginer *Angenerico, Spain.*
Soya (p. 2092·3).
Menopausal disorders.

Plegisol *Hospira, Canad.; Hospira, Fr.; Hospira, Neth.; Hospira, NZ†; Hospira, Port.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1).
Cardioplegic solution.

Sanofi Synthelabo, Turk.; Hospira, USA.
Electrolytes (p. 1775·1).
Cardioplegic solution.

Plegomazin *Egis, Cz.*
Chlorpromazine hydrochloride (p. 1045·2).
Schizophrenia; bipolar disorder; nausea and vomiting; pain; premedication; tetany; porphyria.

Plegomazine *Chew, Thai.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; anxiety.

Plegrin *Specifar, Denm.†; Alet, Neth.†*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis; unstable angina; myocardial infarction.

Pleiamide *Sanofi-Aventis, Ital.*
Chlorpropamide (p. 470·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Plemerid *Essenpharma, Philipp.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine (p. 1674·1); sodium citrate (p. 1781·2).
Respiratory-tract disorders.

Plemex
Note: this name may be used for preparations of different composition.
Trevenodd, Philipp.
Vitex negundo.
Cough; obstructive airways disease.

Bright Future, Hong Kong.†
Doxycycline (p. 288·1).
Bacterial infections.

Plenacor
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Bago, Arg.; Bago, Braz.
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; arrhythmias.

Plenacor D *Bago, Arg.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Plenactol *3M, Chile.†*
Orphenadrine citrate (p. 909·2).
Musculoskeletal pain.

Plenadren *DuoCort, Denm.; DuoCort, Irl.; ViroPharma, Neth.; ViroPharma, Norw.; ViroPharma, UK.*
⊗Hydrocortisone (p. 1640·1).
Adrenal insufficiency.

Plenaer *Valeas, Ital.*
⊗Salbutamol sulfate (p. 1220·2); flunisolide (p. 1635·3).
Obstructive airways disease.

Plenalgin *Rezlov, Rus.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Smooth muscle spasm; fever; pain.

Plenaxis *Speciality European Pharma, Denm.; Speciality European Pharma, Ger.; EuroCept, Neth.*
Abarelix (p. 2255·1).
Prostatic cancer.

Plendil *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; Novastra, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; Beta, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Venez.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension; ischaemic heart disease.

Plendur *Sandoz, Denm.†*
Felodipine (p. 1380·3).
Hypertension.

Plenesia *Merck Medication Familiale, Fr.*
California poppy (p. 2466·1); passion flower (p. 2584·1).
Insomnia.

Plenica *Roemmers, Arg.*
Pregabalin (p. 545·3).
Epilepsy; anxiety; neuropathic pain; fibromyalgia.

Plenidon *Lafi, Chile.*
Zaleplon (p. 1114·3).
Insomnia.

Plenigell *Latinofarma, Braz.*
Carmellose sodium (p. 2175·2).
Eye irritation; dry eyes; contact lens lubricant.

Plenigraf *Juste, Spain.*
Calcium amidotrizoate (p. 1581·2); meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Justesa Imagen, Arg.
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Plenish-K *Aspen, S.Afr.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Plenobiotic Duo *Fecofar, Arg.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Plenosol *Madaus, Ger.*
Viscum album (p. 2560·2).
Homoeopathic preparation.

Plenovid *Tecnofarma, Chile.†*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Plenovit *Phoenix, Arg.*
Vitamins; minerals; with or without ginseng (p. 2513·3).

Plenovit Melatonina *Phoenix, Arg.*
Melatonin (p. 2551·3); vitamin B_6 (p. 2105·3).
Insomnia.

Plenty *Medley, Braz.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Plenum *Duncan, Arg.*
Guaifenesin (p. 1666·2).
Cough.

Plenur *Faes, Spain.*
Lithium carbonate (p. 427·3).
Bipolar disorder; depression.

Pleo Vitamin *Inibsa, Spain.†*
Vitamins; minerals; orotic acid diethylaminoethanol salt; adenosine phosphate (p. 2430·2).
Tonic.

Pleom *Sel-J, Philipp.; Rezlov, Rus.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Pleomix-Alpha *MIT, Ger.*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy.

Pleon *Lacer, Spain.†*
Adenine (p. 2430·2); vitamin B substances (p. 2102·3); carnitine orotate (p. 2578·1); fructose diphosphate magnesium; potassium orotate (p. 2578·1); xanthine.
Tonic.

Pleon RA *Sanofi-Aventis, Ger.*
Sulfasalazine (p. 1890·1).
Polyarthritis.

Plepat *Solfran, Mex.*
Vitamin B substances (p. 2102·3).
Anaemias.

Plerico *In Vitro, Hung.*
Calendula (p. 2465·2).
Skin disorders.

Plerozef *Sel-J, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Plerudin *In Vitro, Hung.*
Leech (p. 1418·1); calendula (p. 2465·2).
Varicose veins; soft-tissue inflammation.

Plesmet *Link, Irl.†*
Ferrous glycine sulfate (p. 2061·3).
Iron-deficiency anaemia.

Plesonax *Neo Quimica, Braz.*
Bisacodyl (p. 1821·1).
Constipation.

Plessir *Medipharm, Chile.*
Eszopiclone (p. 1072·3).
Insomnia.

Pletaal *Janssen-Cilag, Arg.; Otsuka, China; Otsuka, Hong Kong; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Malaysia; Otsuka, Philipp.; Otsuka, Thai.*
Cilostazol (p. 1337·1).
Arterial occlusion; stroke prophylaxis; intermittent claudication; peripheral vascular disorders; stroke.

Pletal *Invida, Austral.; Otsuka, Fr.†; Otsuka, Ger.; UCB, Ger.; Otsuka, Irl.†; Italfarmaco, Ital.; Otsuka, Spain; Otsuka, Swed.; Abdi, Turk.; Otsuka, UK; Otsuka, USA.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Plethirox *Sel-J, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Pletil *Pfizer, Braz.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Pletoz *Cipla, India.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Pletzolyn *Sel-J, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Pleumolysin *Teva, Cz.*
Codeine phosphate (p. 40·2); thyme (p. 2630·2); gypsophila saponin (p. 2610·2); aconite (p. 2428·3); sweet orange oil (p. 2576·2).
Cough; respiratory-tract inflammation.

Plevilox *Farmasintez, Rus.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Plex B *Delta, Braz.*
Vitamin B substances (p. 2102·3).

Plexicodim *Pisa, Mex.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Plexion
Note: this name may be used for preparations of different composition.
Medicis, USA.
Sulfur (p. 1721·1); sulfacetamide sodium (p. 361·1).
Acne.

Pharos, Indon.
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Plexol *Sandoz, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Plexoton B12 *SoSe, Ital.*
Vitamin B substances (p. 2102·3).
Liver disorders; anaemias; tonic.

Plexus
Note: this name may be used for preparations of different composition.
Recalcine, Chile.
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Senosiain, Mex.
Ambroxol (p. 1654·3); dextromethorphan (p. 1660·1).
Cough.

Plexxo *Desitin, Cz.; Desitin, Hung.†; Desitin, Pol.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Pleyar *Casasco, Arg.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Plezolin *Sel-J, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Pliagel *Alcon, S.Afr.†*
Poloxamer 407 (p. 2202·1).
Cleaning solution for contact lenses.

Pliaglis *Galderma, Neth.; Galderma, Spain; Galderma, UK; Galderma, USA.*
Lidocaine (p. 1988·1); tetracaine (p. 1996·3).
Local anaesthesia.

Plidan
Note: this name may be used for preparations of different composition.
Rhein, Mex.; Roemmers, Venez.
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm.

Roemmers, Arg.
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome; epilepsy.

Plidan Compuesto *Rhein, Mex.; Roemmers, Venez.*
Pargeverine hydrochloride (p. 1877·1); clonixin lysine (p. 40·1).
Smooth muscle pain and spasm.

Plidex *Roemmers, Arg.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Plidex T *Roemmers, Arg.*
Diazepam (p. 1063·2); trimebutine (p. 2634·1) or trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Plimage *TS, Ital.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Plinzene *Douglas, NZ.†*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Plisil *Pliva, Rus.*
Paroxetine mesilate (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Plissamur *Ardeypharm, Ger.*
Aesculus (p. 2431·2).
Venous insufficiency.

Plitican *Sanofi-Aventis, Fr.*
Alizapride hydrochloride (p. 1815·2).
Nausea; vomiting.

Plivamol *Pliva, Spain.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Plixym *Pliva Krakow, Pol.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Plofed *Polfa Warszawa, Pol.*
Propofol (p. 1909·3).
General anaesthesia.

Plogovis *Amnol, Ital.†*
⊗Aescin (p. 2431·2); bromelains (p. 2460·3).
Skin disorders.

Plogrel *Therapharma, Philipp.; Oxford Laboratories, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Plokim *Solara, Mex.†*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Plokon *Shinyaku, Thai.†*
Piprinhydrinate (p. 638·1).
Hypersensitivity reactions; asthma; cold symptoms.

Plomurol *Valma, Chile.*
Lindane (p. 2157·1).
Pediculosis.

Plorinoc *Klonal, Arg.*
Loperamide (p. 1854·2).
Diarrhoea.

Plosek *Pasteur, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Plostim *Alcon, Arg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Plovacal *Medipharma, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ploxal *Kocak, Turk.*
Oxaliplatin (p. 838·1).

Plumarol *Lacer, Spain.*
Miglitol (p. 491·3).
Diabetes mellitus.

Plumger *Fada, Arg.*
Pancuronium bromide (p. 2035·1).
Competitive neuromuscular blocker.

Plurair *Libbs, Braz.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Pluralais *Alter, Spain.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Pluravit *Bayer, NZ.†*
Vitamins; minerals.

Plurexid *UCB, Fr.†*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin and mucous membranes.

Pluriamin *Gynopharm, Chile.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Pluribios *Madariaga, Spain.†*
Vitamins; cocarboxylase (p. 2103·1).
Eye disorders.

Pluridoxina *Sidefarma, Port.*
Doxycycline fosfatex (p. 288·2).
Bacterial infections.

Plurilac *Alphrema, Ital.*
⊗Acacia (p. 2166·1); inulin (p. 2534·3); lactulose (p. 1850·3); mannitol (p. 1427·3); dimeticone (p. 2209·3); fennel (p. 2503·2); mallow (p. 2549·2); peppermint (p. 1877·1).
Dietary fibre supplement; gastrointestinal disorders.

Plurimec *Biolab Sanus, Braz.*
Ivermectin (p. 155·1).

Plurimen *Orion, Spain.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Plurimineral *Support, Braz.*
Minerals.

Plurisemina *Northia, Arg.*
Gentamicin (p. 304·2).
Bacterial infections.

Pluriverm *Medley, Braz.†*
Mebendazole (p. 158·3).
Worm infections.

Plurivitamin *Support, Braz.*
Vitamins.

Pluryl *Leo, Gr.*
⊗Bendroflumethiazide (p. 1315·2).

30 Plus
Note: this name may be used for preparations of different composition.
Ajantha, Malaysia.†
Ginseng (p. 2513·3); ashwagandha (p. 2450·2).
Tonic.

Tanning Research, Canad.†
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

45 Plus *Tanning Research, Canad.†*
SPF 45: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Plus Kalium retard *Amino, Switz.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Plus & Plus *Wierhom, Arg.*
Copper oleate (p. 2151·2); coconut diethanolamides; sodium laurilsulfate (p. 2210·3).
Pediculosis.

Plusabcir *Dosa, Arg.*
Abacavir sulfate (p. 963·1).
HIV infection.

Plusage *Biosintetica, Braz.†*
Soap substitute.
Seborrhoea.

Pluscal *Cassara, Arg.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Pluscloran *Sintesina, Arg.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Pluscor
Note: this name may be used for preparations of different composition.
Merck Serono, Ital.
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Sandoz, Arg.
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

Plusefec *Chemopharma, Chile.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Pluseptic *Duncan, Arg.*
Ceftazidime (p. 250·2).
Bacterial infections.

Pluserix *Vianex (Βιανεξ), Gr.*
A measles, mumps and rubella vaccine (Schwarz, Urabe AM 9, and Wistar RA27/3 strains, respectively) (p. 2400·2).
Active immunisation.

Plus-Fer *Gerolymatos, Gr.*
Iron polymaltose (p. 2077·2).
Iron-deficiency anaemia; iron supplement.

Plusflex *Braun, Ital.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3).
Parenteral nutrition.

Plusgel
Note: this name may be used for preparations of different composition.
Collins, Mex.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastritis; peptic ulcer; dyspepsia; meteorism; aerophagia.

Lagos, Arg.†
Piroctone olamine (p. 1716·3).
Scalp disorders.

Plusgin *Raffo, Chile.*
Fluconazole (p. 578·2).
Fungal infections.

Plusindol *Randall, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Pluspen *Cevallos, Arg.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Pluspiryna *Polpharma, Pol.†*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Plusplatin *Dosa, Arg.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Plustaxano *Dosa, Arg.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Pluston *Ferakon, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Plus-Tos *Medipharm, Chile.*
Clofedanol hydrochloride (p. 1659·1); bromhexine hydrochloride (p. 1656·3).
Cough.

Plusvent *Almirall, Spain.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Asthma.

Plusvisol *IQFA, Mex.*
Cyanocobalamin (p. 2107·2).

Plusvit *Ecofarm, Ital.*
Octacosanol (p. 1472·1); royal jelly (p. 2608·1).
Tonic.

Pluvio *Lampugnani, Ital.*
Soya oil (p. 2092·3); urtica (p. 2639·3); avocado oil (p. 2451·2); saw palmetto (p. 2363·3); vitamins.
Nutritional supplement.

Pluviton *Sam-On, Israel.*
Vitamins; minerals.

pM
Note: this name may be used for preparations of different composition.
Chiesi, Fr.†
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

P&M *Khandelwal, India.*
Metformin (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

9PM *Cipla, India.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

PM Auscolos *PharmaMetics, Austral.*
Bovine colostrum (p. 2380·3).
Digestive disorders.

PM Ausphyllo *PharmaMetics, Austral.*
Phytomenadione (p. 2122·2).
Vitamin K supplement.

PM Branin *PharmaMetics, Austral.*
Bacopa (p. 2452·1).
Mental function disorders; nervous disorders.

PM Bright Kids *PharmaMetics, Austral.*
Omega-3 triglycerides (p. 1460·1).
Tonic.

PM Cartisak *Max Biocare, Austral.*
Shark cartilage (p. 2471·3).
Joint inflammation.

PM Dreamtime *PharmaMetics, Austral.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Insomnia; nervous disorders; anxiety.

PM Eye Tonic *PharmaMetics, Austral.*
Myrtillus (p. 2566·2); fish oil (p. 1460·3); thiamine hydrochloride (p. 2103·1); vitamin A palmitate (p. 2098·3); riboflavin (p. 2104·3).
Dietary supplement for healthy eyes.

A Max Biocare, Hong Kong.†
Myrtillus (p. 2566·2); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); vitamin A (p. 2098·3); vitamin B_1 (p. 2103·1); vitamin B_2 (p. 2104·3).
Dietary supplement for healthy eye function.

PM Golbimac *PharmaMetics, Austral.*
Bacopa (p. 2452·1).
Memory and concentration enhancement.

PM H-Regulator *PharmaMetics, Austral.*
⊗Soya (p. 2092·3); agnus castus (p. 2432·2).
Premenstrual syndrome; menopausal disorders; osteoporosis.

PM IQShield *PharmaMetics, Austral.*
Fish oil (p. 1460·3); bovine colostrum (p. 2380·3); zinc amino acid chelate (p. 2048·3); potassium iodide (p. 2336·3); cyanocobalamin (p. 2107·2); vitamin B_1 (p. 2103·1); vitamin B_2 (p. 2104·3).
Dietary supplement.

PM Joint-Aid *PharmaMetics, Austral.†*
Glucosamine sulfate potassium chloride (p. 2515·3).
Joint disorders.

PM Joint-Care *PharmaMetics, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); grape (p. 2521·3); green tea (p. 2648·2); lecithin (p. 2542·2).
Osteoarthritis; rheumatoid arthritis.

PM Kiddiecal *PharmaMetics, Austral.*
Calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1); phytomenadione (p. 2122·2).
Calcium supplement; osteoporosis.

PM Kids Intelligent *PharmaMetics, Austral.*
Acetylcarnitine (p. 2053·2); fish oil (p. 1460·3); folic acid (p. 2063·1); zinc amino acid chelate (p. 2048·3); bacopa (p. 2452·1).
Dietary supplement.

PM LifeBrain *PharmaMetics, Austral.*
Ginkgo biloba (p. 2512·3); bacopa (p. 2452·1).
Tonic.

PM LifePro Max for Men *PharmaMetics, Austral.*
Epimedium sagittatum; ginkgo biloba (p. 2512·3); tyrosine (p. 2098·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Dietary supplement for men.

PM LifePro Max for Women *PharmaMetics, Austral.*
⊗Epimedium sagittatum; agnus castus (p. 2432·2); ginseng (p. 2513·3); tyrosine (p. 2098·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Premenstrual syndrome; dietary supplement for women.

PM Meno-Care *PharmaMetics, Austral.*
Cimicifuga (p. 2478·1); red clover (p. 2482·1); dong quai (p. 2497·1); ginger (p. 1844·1); sage (p. 2608·3).
Menopausal disorders; menstrual disorders.

PM Metic-Glucotin *PharmaMetics, Austral.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate (p. 2476·1).
Musculoskeletal and joint disorders.

PM NextG Cal *PharmaMetics, Austral.*
Hydroxyapatite (p. 2529·3); colecalciferol (p. 2113·1); phytomenadione (p. 2122·2).
Calcium supplement; osteoporosis.

PM Procare *PharmaMetics, Austral.*
Fish oil (p. 1460·1); vitamins; minerals.
Dietary supplement in preconception, pregnancy, and breast feeding.

PM Remem *PharmaMetics, Austral.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function impairment.

PM Sirin *Kapharma, Ukr.*
Milk thistle (p. 1561·1); schisandra chinensis (p. 2611·2); cynara (p. 2490·3); inositol (p. 2533·2); choline bitartrate (p. 2055·2); methionine (p. 1558·2) taurine (p. 2626·2).
Liver disorders.

PM Syrin *PharmaMetics, Austral.*
Milk thistle (p. 1561·1); schisandra (p. 2611·2); cynara (p. 2490·3); inositol (p. 2533·2); choline bitartrate (p. 2055·2); methionine (p. 1558·2); taurine (p. 2626·2).
Liver disorders; digestive disorders.

P-Mega-Tablinen *Winthrop, Ger.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

PML Crono *SIFI, Ital.*
Nicotinamide (p. 2083·1); vitamin E (p. 2119·1); lutein (p. 2079·2).

PMQ-INGA *Inga, India.*
Primaquine phosphate (p. 660·2).
Malaria.

PMS *Homeocan, Canad.*
Cimicifuga racemosa (p. 2478·1); hydrastis canadensis (p. 2528·1); hyoscyamus niger (p. 2530·2); lycopodium clavatum (p. 2547·1); mercurius corrosivus (p. 2555·2); nitricum acidum (p. 2572·3); sabina; secale cornutum (p. 2137·1); aurum metallicum (p. 2521·1).
Homoeopathic preparation.

PMS-Artificial Tears *Pharmascience, Hong Kong.†*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

PMS-ASA *Pharmascience, Canad.*
Aspirin (p. 22·2).

PMS-Dopazide *Pharmascience, Canad.*
⊗Methyldopa (p. 1431·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

PMS-ISMN *Pharmascience, Canad.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

PMS-Levazine *Pharmascience, Canad.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Depression; psychoses.

PMS-Polytrimethoprim *Pharmascience, Canad.*
Trimethoprim sulfate (p. 381·3); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

PMT Formula *Vitalia, UK.*
Evening primrose oil (p. 2502·2); vitamins; minerals; valerian (p. 2640·2); passion flower (p. 2584·1).
Premenstrual syndrome.

PMT-Eze *Bioglan, Austral.†*
⊗Vitamins; minerals; bladderwrack (p. 2612·1); juniper (p. 2537·1); alchemilla; bearberry (p. 2453·2); viburnum opulus; vitex agnus castus (p. 2432·2).
Menstrual disorders.

Pneucid *Scipharm, S.Afr.†*
Sodium citrate (p. 1781·2); citric acid monohydrate (p. 2480·3).
Buffering agent for increasing gastric pH before anaesthesia.

Pneumaseptic *Tradiphar, Fr.†*
Sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Respiratory-tract congestion.

Pneumo 23 *Sanofi Pasteur, Arg.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, China; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Indon.; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.†; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Neth.; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.†; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Pneumocal *Hizon, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Pneumodoron 1 *Weleda, Ger.; Weleda, S.Afr.†*
Aconitum napellus (p. 2428·3); bryonia (p. 2461·3).
Homoeopathic preparation.

Pneumodoron 2 *Weleda, Ger.; Weleda, S.Afr.†*
Phosphorus (p. 2589·2); tartarus stibiatus (p. 151·2).
Homoeopathic preparation.

Pneumodoron Nr 1 *Weleda, Austria.*
Aconitum nap. (p. 2428·3); bryonia rad. (p. 2461·3).
Homoeopathic preparation.

Pneumodoron Nr 2 *Weleda, Austria.*
Phosphorus (p. 2589·2); tartarus stibiatus (p. 151·2).
Homoeopathic preparation.

Pneumogéine *SERP, Mon.†*
Theophylline and sodium acetate (p. 1229·3).
Asthma; obstructive airways disease.

Pneumo-Kast *SM, Gr.*
Montelukast sodium (p. 1214·3).
Asthma.

Pneumol *Gerolymatos, Gr.*
Carbocisteine (p. 1658·1).
Mucolytic.

Pneumol Plus *Gerolymatos, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

Pneumopan
Note: this name may be used for preparations of different composition.
Gebro, Austria.†
Thyme (p. 2630·2); equisetum (p. 2500·1); ribwort plantain (p. 2604·2); sulfogaiacol (p. 1678·1).
Cough.

Pneumorel *Servier, Fr.; Servier, Hong Kong†; Stroder, Ital.; Servier, Port.*
Fenspiride hydrochloride (p. 1209·2).
Cough; respiratory-tract disorders.

Pneumosolv *Utopian, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Pneumotussin *ECR, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Pneumovax *MSD, China; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.†; Sanofi Pasteur, Ital.; Sanofi Pasteur, Norw.; MSD, Philipp.; Sanofi Pasteur, Swed.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Pneumovax II *Sanofi Pasteur, Irl.; Sanofi Pasteur, UK.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Pneumovax 23 *MSD, Arg.; CSL Biotherapies, Austral.; Merck Frosst, Canad.; MSD, Chile; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Israel; Sanofi Pasteur, Neth.; MSD, NZ; MSD, Pol.; Sanofi Pasteur, Port.; MSD, S.Afr.; MSD, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Switz.; MSD, Thai.; Merck, USA.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Pnu-Imune 23 *Wyeth, Gr.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

PNV OB+DHA *PharmaPure, USA.*
Tablets, vitamins; trace elements; capsules, docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.

PNV-DHA *Acella, USA.*
Minerals; vitamins; docosahexaenoic acid (p. 1460·1).

PNV-Iron *Acella, USA.†*
Biotin (p. 2052·2); calcium levomefolate (p. 2053·1); folic acid (p. 2063·1); calcium (p. 1783·1); copper (p. 2057·1); iron (p. 2073·1); magnesium (p. 1786·3); zinc (p. 2126·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); colecalciferol (p. 2113·1); vitamin E substances (p. 2119·1).
Dietary supplement.

PO 12 *Boehringer Ingelheim, Fr.*
Enoxolone (p. 54·2).
Skin irritation.

Pó Antisséptico *Bunker, Braz.†*
Boric acid (p. 2459·3); salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Skin disorders.

Po Sum On Medicated Oil *Zen, Israel.†*
Peppermint oil (p. 1877·1).
Musculoskeletal, joint, and soft-tissue disorders; cough.

Pobrax *Pharmasant, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Peptic ulcer; dyspepsia; biliary dyskinesia; irritable colon; ureteric spasm; dysmenorrhoea.

Pocin *Polipharm, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Pocin G *CCM, Malaysia.†*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial eye infections.

Pocin H *CCM, Malaysia.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Otitis.

PocketScan *Lifescan, Irl.†*
Test for glucose in blood (p. 2516·3).

Poconéol no 1 *Pierre Fabre, Fr.*
Costus spicatus; croton campestris; anchieta salutaris; robinia coccinea.
Homoeopathic preparation.

Poconéol no 2 *Pierre Fabre, Fr.*
Carica papaya; acanthus volubilis; dorstenia multiformis; mimosa virginalis.
Homoeopathic preparation.

Poconéol no 3 *Pierre Fabre, Fr.*
Cinnamodendron axillare; ferdinandusa elliptica; mimosa virginalis.
Homoeopathic preparation.

Poconéol no 4 *Pierre Fabre, Fr.*
Franciscea uniflora; gomphrena officinal; jacaranda caroba; scoparia dulcis.
Homoeopathic preparation.

Poconéol no 5 *Pierre Fabre, Fr.*
Myristica bicuiba; mespilodaphne pretiosa; echinodorus macrophyllus; viscum album (p. 2560·2); schinus molle; cereus grandiflorus (p. 2473·2).
Homoeopathic preparation.

Poconéol no 6 *Pierre Fabre, Fr.*
Bignonia copaia; croton campestris; sennebiera pinnatifida.
Homoeopathic preparation.

Poconéol no 7 *Pierre Fabre, Fr.*
Laurus persea (p. 2451·2); ruizia fragrans (p. 2458·3); cassia occidentalis; piper umbellatum; achras sapota.
Homoeopathic preparation.

Poconéol no 8 *Pierre Fabre, Fr.*
Psidium pomiferum; smilax officinalis; cayaponia tayuya; sapindus esculentus.
Homoeopathic preparation.

Poconéol no 9 *Pierre Fabre, Fr.*
Mikania guaco; caesalpinia ferrea; bixa orellana; scoparia dulcis; origanum vulgare (p. 2576·3); phellandrium aquaticum.
Homoeopathic preparation.

Poconéol no 10 *Pierre Fabre, Fr.*
Bignonia quinquefolia; coumarouna odorata; gomphrena officinal; kordelestris syphilitica.
Homoeopathic preparation.

Poconéol no 11 *Pierre Fabre, Fr.*
Chrysophyllum glycypheleum; maytenus ilicifolia; psidium pomiferum; trianosperma ficifolium.
Homoeopathic preparation.

Poconéol no 12 *Pierre Fabre, Fr.*
Bignonia copaia; iacaranda caroba; maytenus ilicifolia.
Homoeopathic preparation.

Poconéol no 13 *Pierre Fabre, Fr.*
Drymis granatensis; ferdinandusa elliptica; scoparia dulcis; smilax officinalis.
Homoeopathic preparation.

Poconéol no 14 *Pierre Fabre, Fr.*
Plumeria lancifolia; chondodenron tomentosum; solanum paniculatum; acanthus volubilis; mimosa pudica.
Homoeopathic preparation.

Poconéol no 15 *Naturactive, Fr.†*
Chiococca brachiata; gesneria grandis; scoparia dulcis.
Homoeopathic preparation.

Poconéol no 16 *Pierre Fabre, Fr.*
Meibomia triflora; cochlospermum insigne; leonurus globusus; mikania guaco.
Homoeopathic preparation.

Poconéol no 17 *Pierre Fabre, Fr.*
Verbena jamaicensis; drymis granatensis; carica papaya.
Homoeopathic preparation.

Poconéol no 18 *Pierre Fabre, Fr.*
Echinodorus macrophyllus; psidium pomiferum; rosa gallica (p. 2207·3).
Homoeopathic preparation.

Poconéol no 19 *Naturactive, Fr.†*
Gesneria nitida; lindernia crustacea; scoparia dulcis.
Homoeopathic preparation.

Poconéol no 20 *Pierre Fabre, Fr.*
Cecropia palmata; cuscuta racemosa; anacardium occidentalis.
Homoeopathic preparation.

Poconéol no 21 *Pierre Fabre, Fr.*
Astronium fraxinifolium; croton campestris; erythrina corallodendron.
Homoeopathic preparation.

Poconéol no 22 *Pierre Fabre, Fr.*
Guettarda uruquensis; piper nigrum (p. 2586·1); citrus medica.
Homoeopathic preparation.

Poconéol no 23 *Naturactive, Fr.†*
Boerhavia hirsuta (p. 2601·1); ferdinandusa elliptica; mikania hirsutissima.
Homoeopathic preparation.

Poconéol no 24 *Pierre Fabre, Fr.*
Ageratum conyzoides; tussilago farfara (p. 1659·2); viola littoralis.
Homoeopathic preparation.

Poconéol no 25 *Pierre Fabre, Fr.*
Laurus persea (p. 2451·2); plumeria lancifolia.
Homoeopathic preparation.

Poconéol no 26 *Pierre Fabre, Fr.*
Lindernia crustacea; robinia coccinea; schinus molle.
Homoeopathic preparation.

Poconéol no 27 *Pierre Fabre, Fr.*
Coriandrum sativum (p. 2486·3); dorstenia multiformis; laurus nobilis.
Homoeopathic preparation.

Poconéol no 28 *Pierre Fabre, Fr.*
Carica papaya; hymenaea courbaril; mespilodaphne pretiosa.
Homoeopathic preparation.

Poconéol no 31 *Pierre Fabre, Fr.*
Cactus grandiflorus (p. 2473·2); coumarouna odorata; cucumis colocynthis.
Homoeopathic preparation.

Poconéol no 32 *Naturactive, Fr.†*
Dictamnus albus; indigofera tinctoria; valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Poconéol no 34 *Pierre Fabre, Fr.*
Mespilodaphne pretiosa; punica granatum (p. 164·1); cochlearia armoracia (p. 2526·1).
Homoeopathic preparation.

Poconéol no 35 *Pierre Fabre, Fr.*
Hymenaea courbaril; tilia europaea (p. 2631·3); vaccinium myrtillus (p. 2566·2).
Homoeopathic preparation.

Poconéol no 37 *Pierre Fabre, Fr.*
Althaea officinal (p. 2438·3); anthemis nobilis (p. 2474·1); baccharis trimera (p. 2471·2); juglans regia (p. 2646·1).
Homoeopathic preparation.

Poconéol no 43 *Pierre Fabre, Fr.*
Matricaria parthenium (p. 676·1); polygonum acre; pulchea quitoc; viscum album (p. 2560·2); tanacetum balsamita.
Homoeopathic preparation.

Poconéol no 44 *Pierre Fabre, Fr.*
Juniperus communis (p. 2537·1); linum usitatissimum; psidium pomiferum.
Homoeopathic preparation.

Poconéol no 48 *Pierre Fabre, Fr.*
Cecropia palmata; ipecacuanha (p. 1667·2); verbena officinalis (p. 2645·1).
Homoeopathic preparation.

Poconéol no 50 *Pierre Fabre, Fr.*
Piptadenia colubrina; polygonum acre; plumeria lancifolia.
Homoeopathic preparation.

Poconéol no 51 *Pierre Fabre, Fr.*
Boehmeria caudata; perianthopodus tomba; hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Poconéol no 53 *Pierre Fabre, Fr.*
Argemone mexicana; trianosperma ficifolium.
Homoeopathic preparation.

Poconéol no 54 *Pierre Fabre, Fr.*
Anethum foeniculum (p. 2503·2); cochlospermum insigne; ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Poconéol no 55 *Pierre Fabre, Fr.*
Anona coriacea; croton campestris; teucrium chamaepytis; tussilago farfara (p. 1659·2).
Homoeopathic preparation.

Poconéol no 56 *Pierre Fabre, Fr.*
Equisetum arvense (p. 2500·1); ferdinandusa elliptica; sium augustifolium.
Homoeopathic preparation.

Poconéol no 57 *Pierre Fabre, Fr.*
Agrimonia eupatoria (p. 2432·3); agropyrum repens (p. 2487·2); moracea aphylla; populus nigra.
Homoeopathic preparation.

Poconéol no 58 *Pierre Fabre, Fr.*
Citrus aurantium (p. 2575·3); ferdinandusa elliptica; lepidium latifolium.
Homoeopathic preparation.

Poconéol no 59 *Naturactive, Fr.†*
Coumarouna odorata; mentha piperita (p. 1877·1); solanum cernuum.
Homoeopathic preparation.

Poconéol no 61 *Naturactive, Fr.†*
Arnica montana (p. 2447·2); lycopus europaeus (p. 2462·2); mikania hirsutissima; myristica bicuiba.
Homoeopathic preparation.

Poconéol no 63 *Pierre Fabre, Fr.*
Anchieta salutaris; anacardium occidentalis.
Homoeopathic preparation.

Poconéol no 65 *Naturactive, Fr.†*
Artemisia vulgaris; viscum album (p. 2560·2).
Homoeopathic preparation.

Poconéol no 66 *Pierre Fabre, Fr.*
Acanthus volubilis; laurus nobilis; salvia (p. 2608·3).
Homoeopathic preparation.

Poconéol no 67 *Pierre Fabre, Fr.*
Acimum incanescens; asparagus officinal (p. 2450·2); cichorium intybus (p. 2475·2); gomphrena officinal.
Homoeopathic preparation.

Poconéol no 69 *Pierre Fabre, Fr.*
Citrus medica; erythrina corallodendron; papaver rhoeas.
Homoeopathic preparation.

Poconéol no 71 *Pierre Fabre, Fr.*
Meibomia triflora; scandix cerofolium; solanum nigrum (p. 2458·2).
Homoeopathic preparation.

Poconéol no 73 *Pierre Fabre, Fr.*
Erythrina corallodendron; spondias lutea; chiococca anguifuga.
Homoeopathic preparation.

Poconéol no 74 *Naturactive, Fr.†*
Baccharis trimera (p. 2471·2); hydrocotyle umbellata; plumeria lancifolia.
Homoeopathic preparation.

Poconéol no 75 *Pierre Fabre, Fr.*
Coffea arabica (p. 2648·2); pulchea quitoc.
Homoeopathic preparation.

Poconéol no 76 *Pierre Fabre, Fr.*
Laurus persea (p. 2451·2); plumeria lancifolia; brunella vulgaris.
Homoeopathic preparation.

Poconéol no 77 *Pierre Fabre, Fr.*
Boehmeria caudata; macchaerium incorruptibile; spondias lutea.
Homoeopathic preparation.

Poconéol no 79 *Pierre Fabre, Fr.*
Agropyrum repens (p. 2487·2); costus spicatus; ficus carica (p. 1843·2).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Poconéol no 81 *Naturactive, Fr.†*
Agrimonia eupatoria (p. 2432·3); caesalpinia ferrea; geum urbanum.
Homoeopathic preparation.

Poconéol no 82 *Naturactive, Fr.†*
Acide borique (p. 2459·3); aloes (p. 1816·1); alun (p. 2439·1); asa foetida (p. 2449·3).
Homoeopathic preparation.

Pocophage *Pharmasant, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Podactin *Reese, USA.*
Cream: Miconazole (p. 588·3).
Fungal skin infections.

Reese, USA.
Topical powder: Tolnaftate (p. 596·1).
Fungal skin infections.

Podakrin *Pharmasant, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Pod-Ben-25 *C & M, USA.*
Podophyllum resin (p. 1717·1).
Warts.

Podertonic *Inkeysa, Spain.*
Ferrocholinate (p. 2060·2).
Iron deficiency; iron-deficiency anaemia.

Podexine Anti-Transpirante *Vichy, Chile.*
Glycacil (p. 2156·3); aluminium salts (p. 2439·2).
Hyperhidrosis of the feet.

Podexine Durezas y Callosidades *Vichy, Chile.*
Salicylic acid (p. 1719·1); polyethylene miscrospheres (p. 1690·3).
Calluses.

Podexine Exfoliante *Vichy, Chile.*
Aluminium microcrystals (p. 2439·2) (p. 1690·3).
Calluses on feet.

Podexine Pie Diabetico *Vichy, Chile.*
Nutralipids; LHA; biotique E; ginkgo biloba (p. 2512·3).
Dryness, fissures and diabetic foot problems.

Podine *Aspen Consumer, S.Afr.*
Povidone-iodine (p. 1767·1).
Skin infections; wounds; burns; mouth and throat disorders.

Podocon *Paddock, USA.*
Podophyllum resin (p. 1717·1).
Genital warts.

Podofilia *Bustillos, Mex.*
Podophyllum resin (p. 1717·1).
Warts; verrucas; keratosis.

Podofilm *Paladin, Canad.; Entreprises, China; Pharmascience, Hong Kong; Pharmascience, Singapore; Assos, Turk.*
Podophyllum resin (p. 1717·1).
Anogenital warts; warts.

Podofilox *Pharmalex (Φαρμαλεξ), Gr.*
Podophyllotoxin (p. 1717·1).
Anogenital warts.

Podofin *Syosset, USA.*
Podophyllum resin (p. 1717·1).
Genital warts; epitheliomatosis; keratoses.

Podomexef *Daiichi Sankyo, Ger.; Daiichi Sankyo, Switz.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Podonin-S *Teva, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Podoxin *Cassara, Arg.*
Podophyllotoxin (p. 1717·1).
Anogenital warts.

Poen Efrina *Poen, Arg.*
Phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis; eye inflammation.

Poenbioptal *Poen, Arg.*
Chloramphenicol (p. 257·1); neomycin (p. 329·3); phenylephrine (p. 1672·2).
Eye disorders.

Poenbioptal NF *Poen, Arg.*
Polymyxin B (p. 342·3); neomycin (p. 329·3); phenylephrine (p. 1672·2).
Eye disorders.

Poencaina *Poen, Arg.; Roemmers Poen, Venez.*
Proxymetacaine (p. 1995·3).
Local anaesthesia.

Poenfenicol *Poen, Arg.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Poenflox *Poen, Chile†; Roemmers Poen, Venez.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Poenglaucol *Poen, Arg.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Poenkerat *Poen, Arg.; Poen, Chile†; Poen Vision, Mex.; Roemmers Poen, Venez.*
Ketorolac trometamol (p. 80·2).
Cystoid macular oedema; eye inflammation; prevention of intra-operative miosis; uveitis.

Poentimol *Poen, Arg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Poentobral *Poen Vision, Mex.; Roemmers Poen, Venez.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Poentobral D *Poen Vision, Mex.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3); naphazoline hydrochloride (p. 1669·3).
Bacterial eye infections with inflammation.

Poentobral F *Poen Vision, Mex.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Poentobral Plus *Poen, Chile; Roemmers Poen, Venez.*
⊗Dexamethasone (p. 1630·3); tobramycin (p. 380·1).
Bacterial eye infections with inflammation; infected eye disorders.

Poetra *GSK, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Pofol *Dong Kook, Thai.; Sandoz, Turk.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Pogetol *Pharmasant, Thai.*
Chlorpromazine (p. 1045·2).
Psychoses; nausea and vomiting.

PO-HO bleu *Hanseler, Switz.*
Camphor oil (p. 2466·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); turpentine oil (p. 2636·3).
Headache; respiratory-tract disorders.

Poietam *Materia Medica, Rus.*
Human erythropoietin antibodies.

Point *Trima, Israel.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and soft-tissue disorders.

Point-Two *Colgate Oral, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Poison Antidote Kit *Bowman, USA.*
Combination pack: Syrup, ipecacuanha (p. 1667·2); suspension, charcoal (p. 1537·3).
Emergency treatment of poisoning.

Poison Ivy/Oak *Hylands, Canad.*
Croton tiglium; rhus toxicodendron (p. 2603·3); xerophyllum asphodeloides.
Homoeopathic preparation.

Polacel *Medikon, Indon.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Polamec *Mecosin, Indon.†*
Dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Polamine
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; rhinorrhoea.

Polantac *Polinac, Venez.*
Magnesium trisilicate (p. 1858·1); magnesium oxide (p. 1857·3); monobasic sodium phosphate (p. 1791·1); carmellose sodium (p. 2175·2); bismuth subcarbonate (p. 1822·1).
Peptic ulcer; gastritis; oesophagitis.

Polapril *Polpharma, Ukr.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction.

Polar Ice *Scott, Canad.†*
Menthol (p. 2553·2).
Musculoskeletal and joint pain.

Polaramex *Schering-Plough, Venez.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1).
Allergic respiratory-tract disorders.

Polaramin *Aesca, Austria†; Schering-Plough, Denm.†; Schering-Plough, Ital.; Schering-Plough, Norw.; Schering-Plough, Swed.†*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; pruritus; insect bites; urticaria; sunburn; allergic rhinitis; hay fever.

Polaramin Espettorante *Schering-Plough, Ital.*
⊗Dexchlorpheniramine maleate (p. 621·1); guaifenesin (p. 1666·2); pseudoephedrine sulfate (p. 1676·1).
Cough; colds.

Polaramine *MSD, Austral.; MSD, Belg.; Mantecorp, Braz.; MSD-Chibret, Fr.; Schering-Plough, Gr.; MSD, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Neth.; MSD, NZ; MSD, Singapore; MSD, Spain; Essex, Switz.†*
Dexchlorpheniramine maleate (p. 621·1).
Urticaria; pruritus; allergic rhinitis; insect bites; allergic conjunctivitis; eczema; hypersensitivity reactions; allergic skin disorders.

Polaramine Crema *MSD, Spain.*
Allantoin (p. 1693·1); dexchlorpheniramine maleate (p. 621·1).
Cutaneous hypersensitivity reactions.

Polaramine Expectorant *Schering-Plough, Hong Kong†; Schering-Plough, Indon.; MSD, Singapore; Schering, USA.*
⊗Dexchlorpheniramine maleate (p. 621·1); guaifenesin (p. 1666·2); pseudoephedrine sulfate (p. 1676·1).
Cough; hypersensitivity reactions with respiratory-tract symptoms; hay fever; rhinitis; asthma.

Polaramine Expectorante *Mantecorp, Braz.; MSD, Spain.†*
⊗Dexchlorpheniramine maleate (p. 621·1); guaifenesin (p. 1666·2); pseudoephedrine sulfate (p. 1676·1).
Respiratory-tract disorders.

Polaramine Reformulado *Schering-Plough, Venez.*
Loratadine (p. 633·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Polaratin *Globo, Braz.*
Dexchlorpheniramine (p. 620·3).

Polarax *Sunward, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Allergic conditions.

Polaren *Cifarma, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Polarine *Sunward, Singapore.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms; sinusitis; allergic rhinitis.

Polarist *Bernofarm, Indon.†*
Dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Polaronil
Note: this name may be used for preparations of different composition.
Essex, Ger.†
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Polaryn *Teuto, Braz.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Polase *Wyeth Consumer, Ital.; Home, Port.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).
Magnesium and potassium supplement; potassium and magnesium deficiency.

Polase Sport *Wyeth Consumer, Ital.*
Potassium (p. 1793·1); magnesium (p. 1786·3); vitamins.
Nutritional supplement.

Polbax novo *Strathmann, Ger.*
Solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Polcortolon *Jelfa, Rus.*
Ointment: ⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Polfa Pabianice, Pol.; Pabianice, Rus.; Pabianice, Ukr.
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Polcortolon N *Medphano, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Polcortolon TC *Tarchomin, Hung.†; Polfa Tarchomin, Pol.; Tarchomin, Rus.*
⊗Triamcinolone acetonide (p. 1649·1); tetracycline hydrochloride (p. 373·2).
Infected skin disorders.

Polcortolone *Pabianice, Hung.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Polcotec *Best, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; acid aspiration; aid in gastrointestinal examination; nausea and vomiting.

Polcrom *Polfa Warszawa, Pol.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Poldan *Sanbe, Indon.*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Migraine.

Poldanen *Herbapol Poznan, Pol.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Polenat *Natufarma, Arg.*
Pollen (p. 2593·3).
Dietary supplement.

Poléry *Pierre Fabre, Fr.*
Paediatric syrup: Pholcodine (p. 1675·1); erysimum (p. 2524·2).
Cough.

Pierre Fabre, Fr.
Syrup: Codeine (p. 40·2); erysimum (p. 2524·2).
Cough.

Polet *Wermar, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Polfenon *Polpharma, Pol.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Polfergan *Polfarmex, Pol.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions.

Polfilin *Polpharma, Pol.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular ear and eye disorders.

Polfungicid *ICN, Pol.*
Chlormidazole hydrochloride (p. 575·3); salicylic acid (p. 1719·1).
Skin and nail infections.

Polhumin Mix -2, -3, -4, -5 *Polfa Tarchomin, Pol.*
⊗Mixtures of insulin injection (human) 20%, 30%, 40%, or 50% and isophane insulin (human) 80%, 70%, 60%, or 50%, respectively (p. 475·3).
Diabetes mellitus.

Polhumin N *Polfa Tarchomin, Pol.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Polhumin R *Polfa Tarchomin, Pol.*
⊗Neutral insulin injection (human) (p. 475·3).
Diabetes mellitus.

Poli ABE *Qualigen, Spain.*
Pyridoxine hydrochloride (p. 2105·3); vitamin A palmitate (p. 2098·3); tocoferil acetate (p. 2119·2).
Vitamin A, B, and E deficiency.

Poli B Fuerte *Lepetit, Arg.*
Vitamin B substances (p. 2102·3).

Poliacel *Aventis Pasteur, Austral.†; Sanofi-Aventis, Braz.; Sanofi-Aventis, NZ†; Sanofi Pasteur, Turk.*
An adsorbed diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Poliacel-Act-Hib *Sanofi Pasteur, Israel.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Polial *Ultrapharm, UK.*
Gluten- and lactose-free food for special diets.
Gluten sensitivity.

Poliamin *Behrens, Venez.*
Amino acids.
Parenteral nutrition.

Polibar *Bracco, Belg.; Bracco, Cz.; Bracco, Hung.; Bracco, Irl.; Bracco, Neth.; Bracco, Port.; Opakim, Turk.; E-Z-EM, UK; E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Polibar ACB *Esco, Gr.; E-Z-EM, Israel; Bracco, Switz.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Polibar Liquid *Therapex, Canad.†*
Barium sulfate (p. 1583·2).
Simeticone (p. 1886·2) is included in this preparation to eliminate gas from the gastrointestinal tract before radiography.
Radiographic contrast medium.

Polibar Plus *Therapex, Canad.†; E-Z-EM, Israel.†*
Barium sulfate (p. 1583·2).
Simeticone (p. 1886·2) is included in this preparation to eliminate gas from the gastrointestinal tract before radiography.
Contrast medium for gastrointestinal radiography.

Polibar Rapid *Therapex, Canad.†; E-Z-EM, Hung.†; E-Z-EM, UK.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Polibatrin *Teva, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Polibeta B12 *Ceccarelli, Ital.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Polibetic *Rimsa, Mex.*
Vitamins; minerals.

Polibroxol *Polipharm, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Polibutin *Desma, Spain.*
Trimebutine (p. 2634·1) or trimebutine maleate (p. 2634·1).
Gastrointestinal spasm; nausea and vomiting.

Policano *Alapis, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Poli-Cifloxin *Polipharm, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Policitra *Flupal, Venez.*
Sodium citrate (p. 1781·2); potassium citrate (p. 1780·3); citric acid (p. 2480·3).
Urinary alkalinisation.

Policlavumoxil *EMS, Braz.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Policol *Polipharm, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis; cold symptoms.

Policold *Polipharm, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Nasal congestion; hypersensitivity reactions; hay fever; cold symptoms.

Policolinosil *Nupel, Spain.*
Amino acids; liver extract (p. 2444·1); pangamic acid (p. 2582·1); ribonucleic acid (p. 2604·1); thioctic acid (p. 2629·1); inositol (p. 2533·2); vitamin B substances (p. 2102·3).
Liver disorders; tonic.

Policor
Note: this name may be used for preparations of different composition.
Gador, Arg.
Cilostazol (p. 1337·1).
Peripheral vascular disorders.
Herron, Austral.
Policosanol (p. 1472·1).
Hypercholesterolaemia.

Poli-Cycline *Polipharm, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Polidan *Polydan, Rus.*
Sodium nucleospermate.
Leucopenia; thrombocytopenia.

Polideltaxin NF *Exakta, Mex.*
⊗Dexamethasone (p. 1630·3); neomycin (p. 329·3).
Infected eye disorders.

Polidemisin *Sanbe, Indon.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Poliderms *Uniao Quimica, Braz.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Polidoc *Concept, Israel.†*
Lauromacrogol 400 (p. 2194·1).
Varices.

Polienzim *Sanitas, Arg.*
Lipase (p. 2579·3); protease (p. 2598·1); cellulase (p. 2473·1); amylase (p. 2442·1); simeticone (p. 1886·2).
Digestive disorders; flatulence.

Poli-Fibrozil *Polipharm, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Poliflorin *Soylu, Turk.*
Passion flower (p. 2584·1).
Insomnia; nervous disorders.

Poli-Flunarin *Polipharm, Thai.*
Flunarizine (p. 629·3).
Migraine; cerebral and peripheral vascular disorders; memory impairment; irritability; sleep disorders.

Poli-Formin *Polipharm, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Polifrisin *Sanbe, Indon.*
Polymyxin B (p. 342·3); neomycin (p. 329·3); phenylephrine hydrochloride (p. 1672·3).
Bacterial eye infections.

Poliginax *Abbott, Braz.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); nystatin (p. 590·3); tinidazole (p. 949·2).
Vulvovaginal infections.

Poligot *Polipharm, Thai.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; migraine and other vascular headache.

Poligot-CF *Polipharm, Thai.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Poligram *Puebla, Arg.*
Polysaccharides from *Pseudomonas aeruginosa.*
Immunostimulant.

Polijodurato *Farmigea, Ital.*
Sodium iodide (p. 2337·1); potassium iodide (p. 2336·3); rubidium iodide (p. 2608·2); calcium chloride (p. 1783·1).
Cataracts.

Polik
Note: this name may be used for preparations of different composition.
Leti, Venez.
Clotrimazole (p. 576·2).
Fungal infections.
Meiji, Indon.†
Haloprogin; enoxolone (p. 54·2).
Fungal skin infections.

Polikos *Landson, Indon.†*
Policosanol (p. 1472·1).
Hypercholesterolaemia; platelet aggregation; intermittent claudication.

Polimerosa *Nutricia-Bago, Arg.*
Maltodextrin (p. 2080·3).
Dietary supplement; pancreatic disorders; gastrointestinal disorders.

Polimisin *Kocak, Turk.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial eye and skin infections.

Polimod *Doppel, China; Pharmanel, Gr.; Marvecs, Ital.*
Pidotimod (p. 2590·2).
Immunostimulant.

Polimoxil *Legrand, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Polimucil *Pharmanel, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.
SIT, Ital.
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Polinail *Polichem, Cz.; Polichem, Pol.*
Ciclopirox (p. 575·3).
Fungal nail infections.

Polinazolo *Rottapharm, Ital.*
Econazole nitrate (p. 577·3).
Vulvovaginal candidiasis; fungal balanitis.

Polinevrit *Gap, Gr.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin (p. 2107·3).

Polinorm *AstraZeneca, Austria.†*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2); hydralazine hydrochloride (p. 1401·2).
Hypertension.

Polins Cough *Malaysia Chemist, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Cough.

Polio Sabin *GSK, Israel; GSK, Malaysia; GSK, Mex.†; GSK, Philipp.; GSK, Pol.†; GSK, Singapore; GSK, Thai.; GSK, Turk.†*
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

PolioBoostrix *GSK, Ital.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Poliodine *Gifrer Barbezat, Fr.†*
Povidone-iodine (p. 1767·1).
Wound and skin disinfection.

polio-elan *Feldhoff, Ger.†*
Pumilio pine oil (p. 2591·1); rosemary oil (p. 2607·3).
Musculoskeletal and joint disorders; bronchitis.

Polioftal *Raymos, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

PolioInfanrix *GSK, Ital.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Polioral *Novartis, Arg.; Teva, Mex.†; Novartis Vaccines, Philipp.; Litha, S.Afr.; Novartis Vaccines, Thai.*
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Poliorix *IFET (ΙΦΕΤ), Gr.; GSK, Philipp.†; GSK, Rus.; GSK, Switz.; GSK, Turk.†*
An inactivated poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Poli-Otico *Roemmers Osmoph, Venez.*
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); dexamethasone sodium phosphate (p. 1631·2).
Infected ear disorders.

Poliovax-IN *Novartis Vaccines, Ital.†*
An inactivated poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Poliplex *BMS, Braz.*
Vitamins; minerals.

Polipred *Allergan, Braz.*
⊗Prednisolone acetate (p. 1645·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Poli-Relaxane *Polipharm, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Musculoskeletal pain; tension headache.

Polireumin *TRB, Braz.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Poliroxin *Polipharm, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Polirreumin *TRB, Arg.*
Hydroxychloroquine sulfate (p. 655·2).
Lupus erythematosus; malaria; rheumatoid arthritis.

Polisan *Milana, Ital.†*
Benzalkonium chloride (p. 1737·1).
Surface disinfection.

Polised *SIT, Ital.*
Sulfogaiacol (p. 1678·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Poliseng *Teuto, Braz.*
Amino acids; minerals; vitamins; ginseng (p. 2513·3).
Tonic.

Polisorb
Note: this name may be used for preparations of different composition.
Polisorb, Rus.
Silicon dioxide (p. 2208·3).
Poisoning; intestinal infections; food and drug allergy.

Polisulfade *Sanobia, Port.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Skin infections.

Politid *Actavis, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Politifen *Polipharm, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; bronchitis; hypersensitivity reactions.

Politosse *Marvecs, Ital.*
Levocloperastine fendizoate (p. 1659·1).
Cough.

Poli-Uretic *Polipharm, Thai.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hepatic cirrhosis.

Polivit *Abdi Ibrahim, Indon.†; Abdi, Turk.*
Vitamins.
Nutritional supplement.

Polivit C *Abdi, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Polivitaplex con Minerales *Gache, Venez.*
Vitamins; minerals.

Polivitaplex Simple *Gache, Venez.*
Vitamins.

Poliwit *Fisiopharma, Ital.*
Vitamins; minerals.

Polixan *Polipharm, Thai.†*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Muscle pain and spasm.

Polixin *Sophia, Mex.*
Eye drops: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial eye infections.
Sophia, Mex.
Eye ointment: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Bacterial eye infections.

Polizep *Polipharm, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Polizine *Polipharm, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

Pollen Plus *Homeocan, Canad.*
Ambrosia artemisia; phleum pratense (p. 2593·3); grass pollen; taraxacum (p. 2625·3); tree pollen; alium cepa (p. 2575·2); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Pollenase Allergy *Peach, UK.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Pollenase Antihistamine *Peach, UK.*
Chlorphenamine (p. 620·3).
Hypersensitivity reactions.

Pollenase Nasal *Peach, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Formerly known as Pollenase Hayfever.
Hypersensitivity reactions.

Pollenna *Nelson, UK.*
Allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); sabadilla officinarum (p. 2611·2).
Homoeopathic preparation.

Pollenshield *Actavis, UK.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Pollentyme *Pharma Dynamics, S.Afr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Pollinex *Allergy Therapeutics, Cz.; Allergy Therapeutics, Neth.; Allergy Therapeutics, Pol.; Allergy Therapeutics, UK.*
Grass or tree pollen allergen extracts (p. 2593·3) (p. 2434·3).
Allergen immunotherapy; diagnosis of allergy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pollinex Quattro *Bencard, Ger.*
Pollen extracts (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

Pollinex-R *Nycomed, Canad.*
Aqueous extract of short ragweed pollen (p. 2593·3) (p. 2434·3).
Allergen immunotherapy of ragweed pollen.

Pollingel *Bracco, Ital.*
Pollen (p. 2593·3); royal jelly (p. 2608·1).
Nutritional supplement.

Pollingel Ginseng *Bracco, Ital.*
Pollen (p. 2593·3); ginseng (p. 2513·3).
Nutritional supplement.

Pollinosan *Bioforce, Ger.†*
Ammi visnaga (p. 2441·2); aralia racemosa; cardiospermum; galphimia glauca; luffa operculata (p. 2545·3); okoubaka aubrevillei; larrea mexicana (p. 2474·3).
Homoeopathic preparation.

Bioforce, Switz.†
Ammi visnaga (p. 2441·2); aralia racemosa; cardiospermum; luffa operculata (p. 2545·3); okoubaka; paloondo (p. 2474·3); thryallis glauca.
Homoeopathic preparation.

Pollivita *Permamed, Switz.*
Butterbur (p. 2463·2).
Allergic rhinitis.

Pollstimol *Strathmann, Ger.; Strathmann, Hung.*
Grass pollen extracts (p. 2593·3).
Benign prostatic hyperplasia; prostatic disorders; urethritis.

Pollyferm *Nordic, Swed.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Polmesilat *Polon, Pol.*
Pridinol mesilate (p. 2026·1).
Skeletal muscle spasm; spasticity.

Polmofen *Yeni, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Polmonin *Farmanic, Gr.*
Tolfenamic acid (p. 138·3).
Pain; inflammation; musculoskeletal and joint disorders.

Polocaine *Dentsply, Canad.; APP, USA.*
Mepivacaine hydrochloride (p. 1992·2). Corbadrine hydrochloride (p. 2486·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Polocard *Polpharma, Pol.; Polpharma, Ukr.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis; myocardial infarction; angina pectoris.

Polodina-R *Polon, Pol.*
Povidone-iodine (p. 1767·1).
Disinfection of skin and wounds; skin and mucous membrane infections.

Polofar *Ifars, Indon.†*
Dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Polol *Geolab, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; pain; tremor; phaeochromocytoma; subaortic hypertrophic stenosis.

Polol-H *Geolab, Braz.*
⊗Propranolol hydrochloride (p. 1479·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Polomigran *Polon, Pol.*
Pizotifen malate (p. 678·2).
Migraine.

Polopiryna *Polpharma, Pol.*
Aspirin (p. 22·2).
Fever; pain.

Polopiryna C *Polpharma, Pol.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Polopiryna C Plus *Polpharma, Pol.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3). Calcium lactate gluconate (p. 1784·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; fever; cold and influenza symptoms.

Polopiryna S *Polpharma, Pol.*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa
Fever; pain; thromboembolism prophylaxis.

Poloxane *Armoxindo, Indon.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastro-oesophageal reflux; pyrosis; hiatus hernia; gastritis; gastralgia; heartburn; gastric hyperacidity; meteorism; flatulence.

Pol-Pala *Lektravy, Ukr.*
Aerva lanata.
Urolithiasis.

Polper B12 *Casasco, Arg.*
Amino acids; hydroxocobalamin hydrochloride (p. 2107·2).
Dietary supplement; tonic.

Polper Calcio-Magnesio *Casasco, Arg.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Tonic.

Polper Ginseng *Casasco, Arg.†*
Amino acids; cyanocobalamin (p. 2107·2); ginseng (p. 2513·3).
Tonic.

Polper Vascular *Casasco, Arg.*
Dihydroergotamine mesilate (p. 672·2); amino acids; vitamin B_{12} (p. 2107·2).
Cerebrovascular disorders; vestibular disorders; vascular eye disorders.

Polprazol *Polpharma, Pol.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Polpril *Polpharma, Pol.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction; diabetic nephropathy.

Polsen *Polfa Pabianice, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Polseptol *GSK, Pol.†*
Povidone-iodine (p. 1767·1).
Skin and vaginal infections; ulcers; wounds.

Polstigminum *Teva, Pol.*
Neostigmine metilsulfate (p. 687·2).
Myasthenia gravis; postoperative ileus; postoperative urinary retention; reversal of competitive neuromuscular blockade.

Poltax *Geolab, Braz.*
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3), or diclofenac potassium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Poltaxel *Polfa Tarchomin, Pol.†*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer; non small-cell lung cancer.

Poltram *Polpharma, Pol.*
Tramadol hydrochloride (p. 139·2).
Pain.

Poltram Combo *Polpharma, Pol.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Poltroon *Pisa, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Poludan *Veropharm, Rus.*
Potassium polyriboadenylate-potassium polyribouridylate (p. 2594·1).
Viral eye diseases.

Polvac *Teomed, Switz.*
Pollen allergen extracts (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

Polvertic *Medana, Cz.; Medana, Hung.; Medana, Neth.; Medana, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Polviderm NF *Bajer, Arg.*
Zinc oxide (p. 1729·1); benzalkonium chloride (p. 1737·1); phenoxyethanol (p. 1764·3).
Skin disorders.

Polvir *ICN, Pol.†*
Denotivir (p. 972·3).
Herpes labialis; genital herpes.

Polvo Roge *Casasco, Arg.*
Magnesium oxide (p. 1857·3); magnesium carbonate (p. 1856·2).
Bowel evacuation; constipation.

Polvos Alcalinos *Volta, Chile.*
Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); sodium bicarbonate (p. 1781·1); spearmint oil (p. 2621·2).
Antacid.

Poly C *Usana, Canad.; Usana, Hong Kong†; Usana, Singapore.†*
Citrus bioflavonoids complex (p. 2505·2); vitamin C (p. 2110·3).
Vitamin C supplement; antoxidant.

Usana, Mex.
Vitamin C (p. 2110·3).
Dietary supplement.

Poly Gel *Alcon, Austral.*
Carbomer (p. 2173·3).
Dry eyes; eye irritation.

Poly Hist DHC *Poly, USA.*
Dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Cough.

Poly Hist DM *Poly, USA.*
Dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Poly Hist NC *Poly, USA.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract disorders.

Poly Pred *Allergan, China; Allergan, Spain.*
⊗Prednisolone acetate (p. 1645·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Inflammatory eye disorders with infection.

Poly Visc *Alcon, Austral.*
Paraffin (p. 2211·3); wool fat (p. 2219·3).
Dry eyes.

Poly-Alkohol *Merz, Ger.†*
Isopropyl alcohol (p. 1758·3); 1,3-butanediol (p. 2172·2).
Skin disinfection.

Polyanion *Sigmapharm, Austria.†*
Pentosan polysulfate sodium (p. 1465·1).
Thromboembolic disorders; hyperlipidaemias.

Poly-Arthrisan M *Hanosan, Ger.*
Colchicum autumnale (p. 607·1); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Polyasma *Pharmasant, Thai.*
Theophylline (p. 1229·3).

Poly-B con Vitamina C *Grossman, Mex.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Polybamycin *Shin Poong, Singapore.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Polybé *Gedeon Richter, Hung.†*
Vitamin B substances (p. 2102·3).

Polybee *Chew, Thai.*
Vitamin B substances (p. 2102·3); yeast (p. 2125·2).

Polybion *Merck, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3) or lysine (p. 2079·3).
Vitamin B and C deficiency.

Oro, Turk.†
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Polybon *Pharmasant, Thai.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).
Anxiety; depression; agitation.

Polycal *Nutricia Clinical, UK.*
Food for special diets.

Nutricia, Austral.†; Nutricia, Hong Kong; Nutricia, Irl.
Carbohydrates.

Nutricia, NZ.
Preparation for enteral nutrition.

Polycapran *Borisov, Rus.*
Aminocaproic acid (p. 1131·3).
Haemorrhage.

Polycilline *Mecom, Turk.†*
Trimethoprim sulfate (p. 381·3); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Polycin
Note: this name may be used for preparations of different composition.
Nakornpatana, Thai.
Nitrofurazone (p. 333·1).
Burns; wound infections; skin ulcers.

CNW, Hong Kong.†
Bacitracin (p. 225·3); neomycin (p. 329·3); polymyxin B (p. 342·3).
Skin infections.

Polycin-B *Ocusoft, USA.*
Bacitracin zinc (p. 225·3); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Polycitra-K *Janssen-Ortho, Canad.†*
Potassium citrate (p. 1780·3).
Hypokalaemia.

Polyclens *Alcon, Austral.†; Alcon, Mex.*
Cleaning liquid for contact lenses.

Alcon, NZ†; Alcon, S.Afr.†
Cleaning solution for contact lenses.

Poly-Cof *Millimed, Thai.†*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough.

Polycolvit *Pharmasant, Thai.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium phosphate (p. 1784·2).
Vitamin B and C deficiency; anaemias.

Polycose *Abbott, Austral.; Abbott, Canad.; Abbott, Hong Kong†; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, NZ†; Abbott, Singapore; Abbott Nutrition, UK†; Ross, USA.*
Glucose polymers.
Nutritional carbohydrate supplement.

Abbott, Philipp.
Preparation for enteral nutrition.
High-calorie supplement.

Polycrol *Reckitt Benckiser, India; Nicholas, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; flatulence; dyspepsia; heartburn; gastritis; aerophagia; oesophagitis; hiatus hernia.

Nicholas, Indon.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; flatulence; dyspepsia; heartburn.

Polycrol 400 *Nicholas, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; flatulence; dyspepsia; heartburn.

Polycutan *Perrigo, Israel.*
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Polydene *Socobom, Belg.*
Piroxicam (p. 125·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Polyderm
Note: this name may be used for preparations of different composition.
Taro, Canad.
Bacitracin zinc (p. 225·3); polymyxin B sulfate (p. 342·3).
Minor wounds; burns.

Poly-Dex
Note: this name may be used for preparations of different composition.
Ocusoft, USA.
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Polydex
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Polydexa
Note: this name may be used for preparations of different composition.
Therabel, Belg.; Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Neo-Farmaceutica, Port.; Bouchara, Rus.; Bouchara-Recordati, Singapore; Interdelta, Switz.; Bouchara-Recordati, Ukr.
Ear drops: ⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); dexamethasone sodium metasulfobenzoate (p. 1631·1).
Otitis externa; otitis media; infected ear disorders.

Polydexa with Phenylephrine *Bouchara, Rus.; Bouchara-Recordati, Ukr.*
⊗Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); dexamethasone sodium metasulfobenzoate (p. 1631·1); phenylephrine hydrochloride (p. 1672·3).
Rhinopharyngitis; sinusitis; nasal inflammation and infection; rhinitis.

Polydex-N *Aristopharma, Hong Kong.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Inflammatory eye disorders.

Polydine
Note: this name may be used for preparations of different composition.
Fischer, Israel; Century, USA.
Povidone-iodine (p. 1767·1).
Skin disinfection; disinfection of burns, skin, and wounds; skin and vaginal infections.

Pharmasant, Thai.
Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1).
Cough.

Polydine CD *Pharmasant, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).

Polydol *Pharmasant, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Muscle pain; tension headache; dysmenorrhoea.

Polydona *Riemser, Ger.*
Povidone-iodine (p. 1767·1).
Wounds; burns; skin ulcers.

Polydrop *Pharmasant, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; rhinorrhoea.

Polydryl *Pharmasant, Thai.*
Diphenhydramine (p. 626·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cold symptoms; cough; nasal congestion.

Poly-elan *Feldhoff, Ger.*
Pumilio pine oil (p. 2591·1); rosemary oil (p. 2607·3).
Musculoskeletal and joint disorders; bronchitis.

Polyenzyme-I *Chew, Thai.†*
⊗Amylase (p. 2442·1); papain (p. 2582·3); pancreatin (p. 2579·3); vitamin B substances (p. 2102·3); diphenhydramine hydrochloride (p. 626·2); homatropine methylbromide (p. 2007·3); simeticone (p. 1886·2); activated charcoal (p. 1537·3).
Digestive disorders.

Polyenzyme-N *Chew, Thai.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Digestive disorders.

Polyerga *HorFerVit, Ger.*
Polypeptides derived from spleen.
Adjuvant tumour therapy.

Polyfax *Pliva, Irl.; Teva, UK.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Eye and skin infections; bacterial skin infections.

Polyfed *Biolab, Thai.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; hay fever; nasal congestion; cold symptoms.

Polyflam *Socobom, Belg.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Polyfra *Alcon, Fr.†*
Eye drops: Framycetin sulfate (p. 301·2); polymyxin B sulfate (p. 342·3); oxedrine tartrate (p. 1463·2).
Bacterial eye infections.

Alcon, Fr.†
Eye ointment: Framycetin sulfate (p. 301·2); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Polygam *NBI, S.Afr.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome; bone marrow transplantation.

Polygemostat *Technopark, Rus.*
Aminocaproic acid (p. 1131·3); oak bark (p. 2574·1); St John's wort (p. 449·1); calcium alginate (p. 1136·3); urtica (p. 2639·3); achillea (p. 2427·3); equisetum (p. 2500·1); chlorhexidine gluconate (p. 1743·3).
Capillary and venous haemorrhage.

Polygot *Pharmasant, Thai.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Polygynax *Innotech, Cz.*
Neomycin sulfate (p. 330·1); nystatin (p. 590·3) polymyxin B sulfate (p. 342·3).
Vulvovaginal infections.

Raymos, Arg.; Innotech, Fr.; Innotech, Hong Kong; Innotech, Rus.; Innotech, Singapore; Innotech, Ukr.
Neomycin sulfate (p. 330·1); nystatin (p. 590·3); polymyxin B sulfate (p. 342·3).
Vulvovaginal and cervical infections.

Polygynax Virgo *Innotech, Fr.*
Neomycin sulfate (p. 330·1); nystatin (p. 590·3); polymyxin B sulfate (p. 342·3).
Vulvovaginitis.

Polyhadon *Pharmasant, Thai.*
Haloperidol (p. 1077·1).
Schizophrenia; alcoholism.

PolyHES *Intasol, Rus.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; haemodilution.

Polyionique *AGEPS, Fr.; Baxter, Fr.; Fresenius Kabi, Fr.; Maco-Pharma, Fr.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Poly-Iron *Cypress, USA.*
Polysaccharide-iron complex (p. 2086·2).
Iron deficiency.

Poly-Iron Forte *Cypress, USA.*
Polysaccharide-iron complex (p. 2086·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron-deficiency anaemia; megaloblastic anaemia.

Poly-Joule *Nutricia, Austral.*
Dextrin (p. 2059·1).
Nutritional supplement.

Poly-Karaya *Sanofi-Aventis, Fr.*
Sterculia (p. 1888·3); crospovidone (p. 2205·1).
Diarrhoea; constipation; meteorism.

Polymagma *Wyeth, Philipp.†*
Attapulgite (p. 1820·1).
Diarrhoea.

Poly-Micron *Alcon, Mex.*
Neomycin (p. 329·3); gramicidin (p. 308·3); polymyxin B (p. 342·3).
Bacterial eye infections.

Polyminerol *Lavena, Rus.*
Electrolytes (from Pomeranian lakes) (p. 1775·1).
Periodontitis; gingivitis.

Polymox *Hormona, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Polymycin *Medical Ophthalmics, USA.*
Eye drops: Neomycin (p. 329·3); polymyxin B (p. 342·3); gramicidin (p. 308·3).
Eye infections.

Medical Ophthalmics, USA.
Eye ointment: Neomycin (p. 329·3); polymyxin B (p. 342·3); bacitracin (p. 225·3).
Eye infections.

Poly-N *Beacons, Singapore.*
Salicylic acid (p. 1719·1); titanium dioxide (p. 1725·1); benzoic acid (p. 1738·2); sulfur (p. 1721·1).
Acne.

Polynadim *Synthesis, Rus.*
⊗Diphenhydramine (p. 626·1); naphazoline (p. 1669·3).
Allergic eye disorders.

Poly-Nag *Pascual, Philipp.†*
Poly-N-acetyl-D-glucosamine (p. 2515·3).
Osteoarthritis.

Polynase *YSP, Malaysia.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; sinusitis; upper respiratory-tract congestion.

Polyneospin *Hovid, Hong Kong.†*
Gramicidin (p. 308·3); neomycin (p. 329·3); polymyxin B (p. 342·3).
Eye infections.

Polynerv *More, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Vitamin B deficiency; neuritis; neuropathy; hyperemesis gravidarum; neuralgia.

Polynerv-E with lecithin *More, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2); betacarotene (p. 2051·1); lutein (p. 2079·2); lycopene (p. 2546·2); linolenic acid (p. 1460·2); ubidecarenone (p. 2637·1).
Nutritional supplement; tonic.

Polynovate *Pharmasant, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Polyod *Drogsan, Turk.*
Povidone-iodine (p. 1767·1).
Oral hygiene; skin disinfection.

Polyoph *Seng, Hong Kong; Seng, Thai.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Bacterial eye infections.

Polyoxidin *Krasfarma, Rus.*
Macrogol 20 000 (p. 2547·3).
Hypovolaemia.

Polyoxidonium *Petrovax, Rus.*
Azoximer bromide.
Inflammation; infections; rheumatoid arthritis; hypersensitivity reactions; reduction of antineoplastic toxicity; burns; ulcers; secondary immunodeficiency.

Polypen *Combiphar, Indon.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

YSS, Philipp.
Ampicillin sodium (p. 218·2).
Bacterial infections.

Polyphan *Sti-Med-Sorb, Rus.*
Lignin (p. 2544·1).
Gastrointestinal disorders; intoxication; hypersensitivity disorders; gynaecological disorders; dental disorders.

Polyphed *Pharmasant, Thai.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Polyphepan *Sayntek, Rus.*
Lignin (p. 2544·1).
Acute poisoning; renal failure; hepatic failure; disorders of lipid metabolism; food and drug allergies.

Polypictine *Adelco, Gr.*
Polymyxin B sulfate (p. 342·3); streptomycin sulfate (p. 359·1); kaolin (p. 1850·1); pectin (p. 2200·3).

Polyplex *Elea, Arg.; Phoenix, Arg.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin b sulfate (p. 342·3).
Inflammatory eye infections.

Poly-Pred
Note: this name may be used for preparations of different composition.
Allergan, USA.†
⊗Prednisolone acetate (p. 1645·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye inflammation with bacterial infection.

Polypred
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
⊗Prednisolone (p. 1645·2).
Skin disorders.

Polypress
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Polyquin *Tai Guk, Singapore.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Polyrhinium *Ferrier, Fr.; Arko Diffusion, Switz.*
Allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); histaminum dihydrochloridum (p. 2525·2); strychnos nux vomica (p. 2573·3).
Homoeopathic preparation.

Polyrinse *Alcon, Fr.†; Alcon, S.Afr.†*
Sodium chloride (p. 1795·1).
Rinsing and soaking solution for contact lenses.

Polysept *Dermapharm, Ger.; Rekah, Israel.*
Povidone-iodine (p. 1767·1).
Burns; skin and mucous membrane disinfection; skin ulcers; wounds; skin infections; vaginal cleansing.

Polyseptol *Qualiphar, Belg.*
Filtrate from culture of: *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa,* and *Escherichia coli*; sulfanilamide (p. 368·1); cod-liver oil (p. 2056·3).
Infected skin and mucous membrane disorders.

Polysianes *Pierre Fabre Dermo-Cosmetique, Arg.*
SPF 40: Bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); octocrilene (p. 1715·2); cinnamate; titanium dioxide (p. 1725·1); morinda citrifolia.
Sunscreen.

Pierre Fabre Dermo-Cosmetique, Arg.
SPF 10; SPF 15; SPF 20: Bisoctrizole (p. 1697·1); octocrilene (p. 1715·2); cinnamate; morinda citrifolia.
Sunscreen.

Polysianes Autobronceante *Pierre Fabre Dermo-Cosmetique, Arg.*
Titanium dioxide (p. 1725·1); octocrilene (p. 1715·2); cinnamate; dihydroxyacetone (p. 1700·1).
Sunscreen; tanning aid.

Polysilane
Note: this name may be used for preparations of different composition.
Pharos, Indon.
Oral granules: Dimeticone (p. 1886·2); ceratonia (p. 2178·1).
Heartburn; pyrosis; gastritis; flatulence.

Pharos, Indon.
Oral suspension; tablets: Magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2).
Heartburn; pyrosis; gastritis; flatulence.

UPSA, Fr.; BMS, Switz.†
Dimeticone (p. 1886·2).
Gastrointestinal disorders; flatulence; meteorism.

Sanofi Synthelabo, Thai.†
Aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2).
Heartburn; dyspepsia; pyrosis; gastritis; flatulence.

Polysilane Delalande *Sanofi-Aventis, Fr.*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Polysilane Max *Pharos, Indon.*
Magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3); famotidine (p. 1842·1).
Gastric hyperacidity.

Polysilic *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Dyspepsia; peptic ulcer; gastritis; meteorism; flatulence; gastro-oesophageal reflux.

Polyskin *Floris, Israel.*
Povidone-iodine (p. 1767·1).
Disinfection of burns, skin, and wounds.

Polysorb
Note: this name may be used for preparations of different composition.
Fougera, USA.†
Emollient and moisturiser.

Polyspectran *Alcon, Ger.; Alcon, Hong Kong.†*
Eye and ear drops: Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial infections of the eye and ear.

Alcon, Ger.; Alcon, Hong Kong.†
Ointment: eye ointment: Polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial infections of the eye, ear, and nose.

Polyspectran Gramicidine *Alcon, Belg.†*
Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Polyspectran HC *Alcon, Ger.*
⊗Polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3); hydrocortisone acetate (p. 1640·1).
Bacterial and inflammatory eye, ear and nose disorders; skin disorders.

Polyspor *Teva, Hung.†*
Polymyxin b sulfate (p. 342·3); gramicidin (p. 308·3).

Polysporin
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Canad.
Cream; eye/ear drops: Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Infected skin disorders; bacterial contamination prophylaxis; eye and ear infections.
Johnson & Johnson, Canad.; Johnson & Johnson, S.Afr.†; Pfizer, USA.
Eye ointment; ointment: Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3).
Eye and ear infections; skin infections; wounds; burns; ulcers.
Pfizer, Braz.†
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Skin infections.
GSK, Fin.†
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Eye infections.

Polysporin Complete *Johnson & Johnson, Canad.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); gramicidin (p. 308·3); lidocaine (p. 1988·1).
Wounds; burns; itching.

Polysporin Itch Relief *Johnson & Johnson, Canad.*
Pramocaine hydrochloride (p. 1993·3); zinc acetate (p. 2126·1).
Insect bites; skin irritation; minor cuts and abrasions.

Polysporin For Kids *Johnson & Johnson, Canad.*
Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3); lidocaine hydrochloride (p. 1988·2).
Wounds; burns.

Polysporin Lip Protectant *Johnson & Johnson, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Polysporin Lip Treatment *Johnson & Johnson, Canad.*
Allantoin (p. 1693·1); pramocaine hydrochloride (p. 1993·3).

Polysporin Plus Pain Relief *Johnson & Johnson, Canad.*
Cream: Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3); lidocaine hydrochloride (p. 1988·2).
Infected burns and wounds; skin pain.
Johnson & Johnson, Canad.
Ear drops: Lidocaine hydrochloride (p. 1988·2); polymyxin B sulfate (p. 342·3).

Polysporin Triple Antibiotic *Johnson & Johnson, Canad.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); gramicidin (p. 308·3).
Minor wounds; burns.

Polystafana *Sevapharma, Cz.†*
A staphylococcal vaccine (p. 2420·2).
Active immunisation.

Polysteron 250 *Organon, Venez.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism; osteoporosis.

Polytab *Pharmasant, Thai.*
Cyproheptadine hydrochloride (p. 624·1).
Reduced appetite; hypersensitivity reactions; pruritus.

Polytabs-F *Major, USA.*
Vitamins; fluoride (p. 2089·2).
Dental caries prophylaxis; dietary supplement.

Polytanol *Pharmasant, Thai.*
Amitriptyline hydrochloride (p. 401·1).
Depression; mixed anxiety depressive states.

Polytar *Stiefel, Austral.; Stiefel, Braz.; Stiefel, Canad.; GSK, Cz.; Stiefel, Hong Kong; Stiefel, Hung.†; Stiefel, Indon.†; Stiefel, Israel; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Port.; Stiefel, S.Afr.; GSK, Singapore; Stiefel, Thai.*
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2).
Seborrhoeic dermatitis; skin disorders; scalp disorders.
GSK, USA.
Coal tar solution; crude coal tar (p. 1723·2).
Scalp and skin disorders.
Stiefel, Pol.
Coal tar (p. 1723·2).
Scalp disorders.
Stiefel, Irl.
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2); arachis oil (p. 2446·1).
Scalp disorders.
Stiefel, Spain.†
Tar (p. 1723·3); juniper oil (p. 2537·2); coal tar (p. 1723·2).
Skin and scalp disorders.

Polytar AF
Note: this name may be used for preparations of different composition.
GSK, Cz.; Stiefel, Hung.†; Stiefel, UK.†
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2); pyrithione zinc (p. 1718·1).
Scalp disorders.
Stiefel, Canad.
Coal tar (p. 1723·2); dipyrithione (p. 1701·1); salicylic acid (p. 1719·1); menthol (p. 2553·2).
Scalp disorders.
Stiefel, Pol.
Coal tar (p. 1723·2); pyrithione zinc (p. 1718·1).
Scalp disorders.

Polytar Emollient *Stiefel, Hong Kong; Stiefel, NZ†; Stiefel, UK.*
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2); liquid paraffin (p. 2191·2).
Skin disorders; aid to ointment and paste removal in psoriasis.
Stiefel, Irl.
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2); liquid paraffin (p. 2191·2); arachis oil (p. 2446·1).
Skin disorders.

Polytar Liquid *Stiefel, UK.*
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2).
Scalp disorders; aid to ointment and paste removal in psoriasis.

Polytar Plus *Stiefel, Austral.; Stiefel, Singapore.*
Coal tar (p. 1723·2).
Scalp disorders.
Stiefel, NZ; Stiefel, UK.
Tar (p. 1723·3); cade oil (p. 1723·2); coal tar (p. 1723·2).
Scalp disorders; aid to ointment removal in psoriasis.

Poly-Tears *Alcon, Austral.; Alcon, NZ.*
⊗Hypromellose (p. 2189·2); dextran 70 (p. 1138·3).
Dry eyes.

Polytopic *Sandoz, Canad.*
Cream: Polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).
Sandoz, Canad.
Ointment: Polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3).
Infected lesions.

Polytracin *Medical Ophthalmics, USA.*
Bacitracin (p. 225·3); polymyxin B (p. 342·3).
Eye infections.

Polytrim *Allergan, Canad.; GSK, Turk.*
Trimethoprim sulfate (p. 381·3); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.
GSK, Belg.; GSK, Neth.; Allergan, USA.
Trimethoprim (p. 381·2); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Poly-Tussin *Poly, USA.*
Codeine phosphate (p. 40·2); chlorcyclizine hydrochloride (p. 620·2).
Cough.
Pharmakon, USA.†
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Poly-Tussin AC *Poly, USA.*
Brompheniramine maleate (p. 618·1); codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Poly-Tussin D *Poly, USA.*
⊗Codeine phosphate (p. 40·2); chlorcyclizine hydrochloride (p. 620·2); pseudoephedrine (p. 1676·1).
Cough.

Poly-Tussin DHC *Poly, USA.*
Brompheniramine maleate (p. 618·1); dihydrocodeine tartrate (p. 52·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Poly-Tussin EX *Poly, USA.*
Dihydrocodeine tartrate (p. 52·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Polyvaccinum *Biomed Krakow, Pol.*
Staphylococcus aureus; Staphylococcus epidermidis; Streptococcus pyogenes; Streptococcus salivarius; Streptococcus pneumoniae; Escherichia coli; Klebsiella pneumoniae; Haemophilus influenzae; Corynebacterium pseudodiphtheriticum; Moraxella catarrhalis.
Respiratory-tract inflammation; catarrh; neuralgia; urogenital inflammation.

Polyvalent Snake Antivenom *CSL, Austral.; CSL, Singapore.*
A snake antiserum of king brown snake, tiger snake, brown snake, death adder and taipan (p. 2419·1).
Passive immunisation.

Poly-Vent DM *Poly, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Poly-Vent IR *Poly, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Poly-Vent Plus *Poly, USA.†*
⊗Paracetamol (p. 115·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Poly-Vi-Flor *Mead Johnson, Philipp.*
Fluoride (p. 2089·2); vitamins; with or without iron (p. 2073·1).
Nutritional supplement; dental caries prophylaxis.
Mead Johnson Nutritionals, Thai.†; Zylera, USA.
Vitamins; fluoride (p. 2089·2).
Dietary supplement; dental caries prophylaxis.

Poly-Vi-Flor with Iron *Zylera, USA.*
Fluoride (p. 2089·2); ferrous bisglycinate hydrochloride (p. 2048·3); vitamins.
Dietary supplement.

Poly-Vi-Flúor *Mead Johnson, Braz.*
Vitamins; fluoride (p. 2089·2).
Dietary supplement.

Poly-Visc *Alcon, NZ.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Eye lubrication and protection.

Poly-Vi-Sol *BMS, Arg.; Mead Johnson Nutritionals, Canad.; Mead Johnson, Hong Kong; BMS, Mex.; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.*
Vitamins.
Vitamin deficiency; dietary supplement.
Mead Johnson, Philipp.
Vitamins; with or without iron (p. 2073·1).
Nutritional supplement.

Polyvit *Pharmasant, Thai.*
Ferrous fumarate (p. 2060·3); riboflavin (p. 2104·3); vitamin C (p. 2110·3); folic acid (p. 2063·1); citric acid (p. 2480·3).
Anaemias; vitamin supplement.
Taro, Israel.
Oral drops: Vitamins.

Polyvit 30 Plus *Taro, Israel.*
Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3).

Poly-Vita *Major, USA.*
Vitamins.
Dietary supplement.

Poly-Vita with Iron *Major, USA.*
Iron (p. 2073·1); vitamins.
Dietary supplement.

Polyvitamins *Pharmetics, Canad.†*
Vitamins.

Polyvitaplex *Sanofi-Aventis, Hung.*
Vitamins.
Vitamin deficiency.

Polyxan *Utopian, Thai.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Polyxen *Pharmasant, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout.

Polyxicam *Pharmasant, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Polyxit *Pharmasant, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Polyzalip *Pharmasant, Thai.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Polyzym *Alcon, Braz.; Alcon, S.Afr.†*
⊗Pancreatin (p. 2579·3).
Contact lens cleanser; contact lens cleaner.
Alcon, NZ.†
Cleaning of soft and gas-permeable contact lenses.

Pomada Amarilla *Saval, Chile.*
Yellow mercuric oxide (p. 2555·2).
Eye infections.

Pomada Antibiotica *SIT, Spain.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Burns; skin infections; ulcers; wounds.

Pomada Minancora *Minancora, Braz.*
Benzalkonium chloride (p. 1737·1); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Skin disorders.

Pomada Vitaminica *Pasteur, Chile.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); dexpanthenol (p. 2582·2); zinc oxide (p. 1729·1).
Skin disorders; wounds.

Pomaderme *Legrand, Braz.*
Theobroma oil (p. 2216·1); boric acid (p. 2459·3); zinc oxide (p. 1729·1); talc (p. 1722·2).
Skin disorders.

Pomadom *Pharmasant, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; epilepsy.

Pomag *KG, Ital.*
Magnesium citrate (p. 1857·1); potassium aspartate (p. 1793·1); potassium phosphate (p. 1791·1).
Magnesium and potassium supplement.

Pomalyst *Celgene, USA.*
Pomalidomide (p. 847·3).
Multiple myeloma.

Pomat Ichthyole *Aroma, Turk.†*
Ichthammol (p. 1705·3).
Eczema.

Pomegara *AstraZeneca, Rus.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone.

Pomicina *Belfar, Braz.*
Neomycin (p. 329·3).

Pommade au Baume *Zeller, Switz.*
Baume Zeller (sumatra benzoin (p. 2624·3), tolu balsam (p. 1679·2), myrrh (p. 2566·1), red-poppy petal (p. 2207·3), absinthium (p. 2426·1), achillea (p. 2427·3), guaiacum resin (p. 2523·1), tormentil (p. 2633·2), incense); peru balsam (p. 2587·1); camphor (p. 2466·2); zinc oxide (p. 1729·1); turpentine oil (p. 2636·3).
Minor burns and abrasions; skin irritation.

Pommade Ichthyole *Gunsa, Turk.†*
Ichthammol (p. 1705·3).
Eczema.

Pommade Maurice *Cooperation Pharmaceutique, Fr.†*
Yellow mercuric oxide (p. 2555·2).
Eye infections.

Pommade Mo Cochon *Tradiphar, Fr.*
Salicylic acid (p. 1719·1).
Corns; callus; verrucae.

Pommade nasale de Nager *Streuli, Switz.†*
Camphor oil (p. 2466·2); mint oil (p. 2560·1).
Nasal congestion.

Pommade nasale de Ruedi *Streuli, Switz.†*
Camphor oil (p. 2466·2); mint oil (p. 2560·1).
Nasal dryness; nasal congestion.

Pompaton *Nufarindo, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Ponac *Aspen Consumer, S.Afr.*
Mefenamic acid (p. 85·3).
Pain; musculoskeletal, joint, and soft-tissue disorders.

Ponacap *KB, Thai.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Ponalar *Coronet, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Ponalgic *Antigen, Irl.*
Mefenamic acid (p. 85·3).
Pain; musculoskeletal and joint disorders; menorrhagia; dysmenorrhoea.

Ponaris *Panalab, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Ponatap *KB, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Poncobex *Armoxindo, Indon.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and vitamin C deficiencies.

Poncodryl *Armoxindo, Indon.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough.

Poncodryl DMP *Armoxindo, Indon.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cold symptoms; cough.

Poncofen *Armoxindo, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Poncoflox *Armoxindo, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Poncohist *Armoxindo, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Rhinitis; allergic skin disorders.

Poncolin *Armoxindo, Indon.*
⊗Chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); sodium citrate (p. 1781·2); guaifenesin (p. 1666·2).
Cough; asthma.

Poncolin D *Armoxindo, Indon.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); sodium citrate (p. 1781·2).
Cough; respiratory-tract congestion.

Ponconeuron *Armoxindo, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuritis; neuralgia.

Poncoquin *Armoxindo, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Poncosolvon *Armoxindo, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Pondactil *Pond's, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; hay fever; nasal congestion; cold symptoms.

Pondactone *Pond's, Thai.*
⊗Spironolactone (p. 1499·3).
Ascites; hypertension; oedema; aldosteronism.

Pondarmett *Pond's, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pondeal *Lero, Fr.*
Konjac root.
Slimming aid.

Pondera *Eurofarma, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Pondex *Dexa, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Pondicilina *Nycomed, Braz.*
Cetalkonium chloride (p. 1741·3); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Pondnacef *Pond's, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Pondnadysmen *Pond's, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Pondnoxcill *Pond's, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pondocillin *Pharmacodane, Denm.*
Pivampicillin (p. 341·3).
Bacterial infections.

Pondoxcycline *Pond's, Thai.*
Doxycycline (p. 288·1).
Bacterial infections.

Pondperdone *Pond's, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; gastrointestinal disorders; dyspepsia.

Pondtroxin *Pond's, Thai.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Pondusvitam *IQB, Braz.*
Buclizine (p. 618·3); vitamin B substances (p. 2102·3).
Tonic; reduced appetite.

Ponebac *Ashford, Philipp.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Ponesta *Simesa, Ital.*
Zolmitriptan (p. 682·2).
Migraine.

Ponflu *Armoxindo, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2).
Influenza symptoms; cough.

Pongesic *Pharmaniaga, Hong Kong.*
Mefenamic acid (p. 85·3).
Pain; musculoskeletal and joint disorders.

Pongesics *General Drugs, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Ponmel *PannonPharma, Hung.; Clonmel, Irl.†*
Mefenamic acid (p. 85·3).
Pain; inflammation; fever; musculoskeletal and joint disorders; dysmenorrhoea.

Ponnac *Sriprasit, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Ponnesia *Asian Pharm, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Ponostop *Ni-The, Gr.*
Diethylamine salicylate (p. 51·3); camphor (p. 2466·2); capsaicin (p. 35·1).
Musculoskeletal and joint pain.

Ponotex *Adelco, Gr.*
Aspirin (p. 22·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Pain.

Ponsamic *Guardian, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Ponsdril *Legrand, Braz.*
Mefenamic acid (p. 85·3).

Ponser *Medhaus, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Ponsis *Vickmans, Hong Kong.†*
Mefenamic acid (p. 85·3).

Ponsolit *Biomedica, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Ponstan *Pfizer, Austral.; Pfizer, Braz.; Erfa, Canad.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Chemidex, Irl.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer Consumer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S. Afr.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Chemidex, UK; Pfizer, Venez.*
Mefenamic acid (p. 85·3).
Pain; fever; menorrhagia; dysmenorrhoea; premenstrual syndrome; inflammation; dysfunctional uterine bleeding; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ponstel *Adcock Ingram, S.Afr.; Sciele, USA.*
Mefenamic acid (p. 85·3).
Pain; fever; musculoskeletal and joint disorders; menorrhagia.

Ponstelax *Combiphar, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Ponstil *Elea, Arg.*
Mefenamic acid (p. 85·3).
Fever; inflammation; pain.

Ponstil Mujer *Elea, Arg.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ponstin *Elea, Arg.*
Ibuprofen (p. 68·2).
Fever; pain.

Ponstinetas *Elea, Arg.*
Ibuprofen (p. 68·2).
Fever; pain; inflammation.

Ponstyl *Pfizer, Fr.*
Mefenamic acid (p. 85·3).
Pain.

Pontacid *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Mefenamic acid (p. 85·3).
Pain; menorrhagia; inflammation.

Pontalon *YSP, Malaysia; Yung Shin, Singapore; YSP, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Pontalsic *Grunenthal, Belg.; Bayer, Spain.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Pontaser *Roddensers, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Pontef *Tolmann, Philipp.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Pontefix *Fimo, Ital.*
Zinc phosphate (p. 2126·1).
Cement in dentistry.

Ponti *Sophia, Mex.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Pontin *Hexal, Braz.*
Mefenamic acid (p. 85·3).
Fever; inflammation; pain.

Pontiride *Psicofarma, Mex.*
Sulpiride (p. 1107·3).
Anxiety disorders; obsessive-compulsive disorder; schizophrenia; vertigo; movement disorders; peptic ulcer; depression; lactation disorders.

Pontizoc *Nufarindo, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Pontocaine *Hospira, Canad.; Hospira, Philipp.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia; spinal anaesthesia.

Hospira, USA.
Tetracaine (p. 1996·3) or tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Pontrex *Delta, Braz.*
Mefenamic acid (p. 85·3).

Pontyl *Malaysia Chemist, Singapore.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Ponuric *Armoxindo, Indon.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Pool 8 *Fiori, Ital.*
Amino acids.
Nutritional supplement.

Popam *Pharmasant, Thai.*
Diazepam (p. 1063·2).

Pophen *Asian Union, Thai.*
Chlorphenamine (p. 620·3).
Hypersensitivity disorders.

Popiş *Med-Care, Turk.†*
Barrier cream.

Po-Pon-S *Shionogi, USA.*
Vitamins; minerals.

Popscaine *Maruishi, Jpn.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia; pain.

POR 8 *Ferring, Austral.; Pharmaco, NZ; Ferring, S.Afr.*
Ornipressin (p. 2577·3).
Reduction of bleeding during surgery; variceal haemorrhage.

Poral *Sons, Mex.*
⊗Chloramphenicol (p. 257·1); hydrocortisone (p. 1640·1).
Infected eye disorders.

Porazine *Pharmasant, Thai.*
Perphenazine (p. 1095·3).
Anxiety; tension; agitation; nausea and vomiting.

Porcerösítö *Beres, Hung.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Poremax-C *Orion, Fin.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Porfirin 12 *Teofarma, Ital.*
Oral liquid: Haematoporphyrin dihydrochloride (p. 2523·3); cyanocobalamin (p. 2107·2); inositol (p. 2533·2).
Tonic.

Pormus *Unison, Hong Kong; Unison, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Painful musculoskeletal spasm; skeletal muscle pain; peri-articular disorders; tension headache.

Poro *YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore; YSP, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Porocalm *Pharmathen, Gr.*
Alendronate sodium (p. 1171·3).

Porodron *Benedetti, Ital.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Porosal *Meyer Alian, Venez.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Porphin *Crawford, UK.*
5-Aminolevulinic acid (p. 740·1).
Available only on a named patient basis.
Precancerous skin disorders; skin cancer.

Porpovan *Cristalia, Braz.†*
Propofol (p. 1909·3).
General anaesthesia.

Portagen *Mead Johnson, Austral.†; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Ital.; BMS, Pol.†; Mead Johnson, Pol.†; BMS, S.Afr.†*
Preparation for enteral nutrition.
Disorders of fat absorption and digestion.

Mead Johnson Nutritionals, USA.
Lactose-free preparation for enteral nutrition.

Mead Johnson Nutritionals, Canad.†
Gluten-free preparation for enteral nutrition.
Disorders of fat digestion and absorption.

Portal *Lek, Cz.†; Lek, Hung.; Lek, Rus.; Lek, Ukr.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia; panic disorder; anorexia nervosa.

Portalac *Belupo, Rus.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Portamin *Darrow, Braz.*
Amino acids.
Parenteral nutrition.

Portia *Apotex, Canad.; Barr, USA.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Portiron *Gedeon Richter, Hung.*
Losartan potassium (p. 1422·2).
Hypertension; stroke prophylaxis; diabetic nephropathy; heart failure.

Portiron HCT *Gedeon Richter, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Portiv *Buxton, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Portolac *Novartis Consumer, Belg.†; Novartis Consumer, Ital.; Shinyaku, Jpn.*
Lactitol (p. 1850·3).
Liver disorders; constipation; hyperammonaemia; hepatic encephalopathy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Portonal *Demo, Gr.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Portora *Glenmark, Cz.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Poruxin *Vianex (Βιανεξ), Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Posalfilin *Norgine, Austral.†; Norgine, Irl.; Norgine, NZ; Norgine, S.Afr.†; Norgine, UK.†*
Podophyllum resin (p. 1717·1); salicylic acid (p. 1719·1).
Warts.

Posanin *Pose, Thai.†*
Dipyridamole (p. 1362·2).
Thrombosis prophylaxis; ischaemic heart disease.

Posanol *Merck, Canad.*
Posaconazole (p. 592·1).
Aspergillosis; candidiasis.

Posdrink *Catarinense, Braz.†*
Aspirin (p. 22·2); mepyramine maleate (p. 635·1); caffeine (p. 1203·3).
Aluminium hydroxide (p. 1817·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Pose-Bac *Pose, Thai.†*
Benzalkonium chloride (p. 1737·1).
Disinfection.

Pose-Crequat *Pose, Thai.†*
Phenolic compound; quaternary ammonium compound.
Disinfection.

Pose-Cresol *Pose, Thai.†*
Phenolic compound (p. 1763·3).
Hand disinfectant.

Posedene *Pose, Thai.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Pose-Iodophore *Pose, Thai.†*
Iodine (p. 2336·3).
Disinfection.

Posene *Pose, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Posequat *Pose, Thai.†*
Quaternary ammonium compound.
Disinfection.

Posequat with GA *Pose, Thai.†*
Glutaral (p. 1753·2); quaternary ammonium compound.
Disinfection.

Posid *Cadila, India; Pharmachemie, Philipp.*
Etoposide (p. 790·2).
Malignant neoplasms.

Posidol *Pharmaland, Thai.*
Mebhydrolin napadisilate (p. 634·2).
Hypersensitivity reactions.

Posidon *Darrow, Braz.*
Etoposide (p. 790·2).
Malignant neoplasms.

Posifenicol C *Ursapharm, Ger.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Posiformin *Ursapharm, Ger.; Ursapharm, Switz.*
Bibrocathol (p. 2457·1).
Inflammatory eye disorders.

Posiject *Primex, Irl.*
Dobutamine hydrochloride (p. 1365·3).
Heart failure; cardiac stress testing.

Posinova *Orion, Fin.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Posipen *Sanfer, Mex.*
Dicloxacillin sodium (p. 286·1).
Gram-positive bacterial infections.

Positiva *Gerolymatos, Gr.*
Sertraline hydrochloride (p. 448·1).

Positively Ageless Sunscreen *Johnson & Johnson, Canad.*
SPF 45; SPF 60: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Positively Radiant *Johnson & Johnson, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Positivum *Sanova, Austria.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Positon *Faes, Spain.*
⊗Neomycin sulfate (p. 330·1); nystatin (p. 590·3); triamcinolone (p. 1648·3) or triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Posivyl *Laboratorios Chile, Chile.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Poslov *Mabra, Braz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Posmox *Pharmacare, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Posnac *Pose, Thai.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation.

Posorutin *Ursapharm, Ger.†; Ursapharm, Pol.*
Troxerutin (p. 2505·3).
Vascular eye disorders; venous insufficiency; haemorrhoids; ophthalmic disorders.

Pospargin *Kalbe, Indon.*
Methylergometrine maleate (p. 2137·3).
Third-stage labour management; uterine atony; postpartum haemorrhage; lochiometra; caesarian section.

Posprand *Glenmark, Braz.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Possia *AstraZeneca, Irl.; AstraZeneca, Pol.; AstraZeneca, Port.*
Ticagrelor (p. 1511·3).
Thromboembolism prophylaxis in acute coronary syndrome.

Post Solar Nort *Nolt, Arg.*
Aloe vera (p. 1693·2); alpha tocopherol (p. 2119·1).

Postadoxine
Note: this name may be used for preparations of different composition.
GSK, Philipp.
Meclozine hydrochloride (p. 634·3).
Nausea and vomiting.
UCB, Turk.
Meclozine hydrochloride (p. 634·3); vitamin B_6 (p. 2105·3).
Motion sickness; nausea and vomiting.

Postafen
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Braz.
Buclizine hydrochloride (p. 618·3).
Reduced appetite.
UCB, Denm.; UCB, Fin.; UCB, Norw.; UCB, Swed.
Meclozine hydrochloride (p. 634·3).
Allergic rhinitis; urticaria; motion sickness; nausea and vomiting.

Postafene *Pierre Fabre Sante, Belg.; UCB, Gr.; UCB, Hong Kong.†*
Meclozine hydrochloride (p. 634·3).
Motion sickness; nausea and vomiting; vertigo.

Postap *Pose, Thai.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; hypersensitivity reactions; cough.

Postap Expectorant *Pose, Thai.†*
Guaifenesin (p. 1666·2); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Hypersensitivity reactions; nasal congestion; cough.

Post-Day *Investigacion, Mex.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Postec *Apsen, Braz.*
⊗Hyaluronidase (p. 2527·2); betamethasone valerate (p. 1624·1).

Posterine *Kade, Ger.*
Hamamelis (p. 2523·3).
Anorectal disorders.

Posterisan
Note: this name may be used for preparations of different composition.
Kade, Hong Kong; Kade, Philipp.; Kade, Rus.
Cell contents and metabolic products of *Escherichia coli*.
Anorectal disorders.
Kade, Pol.
Escherichia coli.
Anorectal disorders.
Kade, Ger.†
Cell components and metabolic products of *Escherichia coli*.
Anorectal disorders.
Nycomed, China.
⊗Inactivated *Escherichia coli*; hydrocortisone (p. 1640·1); phenol (p. 1763·3).
Anorectal disorders.

Posterisan akut *Kade, Ger.*
Lidocaine (p. 1988·1).
Anorectal disorders.

Posterisan cort *Kade, Ger.*
⊗Hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Posterisan Forte *Kade, Hong Kong.*
⊗Inactivated *Escherichia coli*; hydrocortisone (p. 1640·1).
Anorectal disorders.
Kade, Hung.; Kade, Rus.
⊗Cell contents and metabolic products of *Escherichia coli*; hydrocortisone (p. 1640·1).
Anorectal disorders.

Posterisan H *Kade, Pol.*
⊗*Escherichia coli*; hydrocortisone (p. 1640·1).
Anorectal disorders.

Posterisan protect *Kade, Ger.*
Jojoba; yellow beeswax; cetylstearylisononanoate.
Haemorrhoids.

Postinor *Bayer, Austral.; Medimpex, Austria; Mithra, Belg.; Gedeon Richter, China; Gedeon Richter, Cz.; Medimpex, Gr.; Gedeon Richter, Israel; Gedeon Richter, Malaysia; Medimpex, Neth.; Medimpex, Norw.; Bayer, NZ; Medimpex, Port.; Gedeon Richter, Rus.; Gedeon Richter, Singapore; Bayer, Spain; Bayer, Swed.; Gedeon Richter, Thai.; Gedeon Richter, Ukr.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Postinor-2 *Gobbi, Arg.; Ache, Braz.; Gedeon Richter, Hong Kong; Tunggal Idaman, Indon.; DNA, Mex.; Medimpex, UK; Aciprosalud, Venez.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Postinor Uno *Ache, Braz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Postinor-Duo *Richter, Pol.†*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Postmenop *Recalcine, Thai.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Postop *Sensomed, Philipp.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Postotic *Sensomed, Philipp.*
⊗Dexamethasone (p. 1630·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected ear disorders.

Postoval *Aspen, S.Afr.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; norgestrel (p. 2296·1); 7 tablets, inert.
Menstrual disorders; menopausal disorders.

Post-Pengha *Zizine, Fr.*
Lidocaine (p. 1988·1); eugenol (p. 2501·2).
Dental disorders.

Postuitrin *Ulagay, Turk.*
Oxytocin (p. 2143·1).
Labour induction; caesarean section; postpartum haemorrhage; incomplete abortion.

Posture *Whitehall, USA.*
Calcium phosphate (p. 1784·2).
Calcium supplement.

Posture D *Wyeth, Mex.*
Tribasic calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis; rickets; osteomalacia; tetanus.

Posture-D *Whitehall, USA.*
Calcium phosphate (p. 1784·2); vitamin D (p. 2112·3).
Calcium supplement.

Posyd *Combiphar, Indon.; Pharmachemie, Indon.*
Etoposide (p. 790·2).
Malignant neoplasms.

Potaba *Glenwood, Austria; Glenwood, Canad.; Glenwood, Ger.; IFET (ΙΦΕΤ), Gr.; Glenwood, UK; Glenwood, USA.*
Potassium aminobenzoate (p. 2594·3).
Peyronie's disease; scleroderma; dermatomyositis; morphoea; pemphigus.

Potable Aqua *IBIS, UK; Wisconsin Pharmacal, USA.*
Tetraglycine hydroperiodide (p. 1771·3).
Disinfection of drinking water.

Potacol-R *Otsuka, Indon.; Otsuka, Jpn.*
Electrolytes (p. 1775·1); maltose (p. 2081·1).
Carbohydrate source; fluid and electrolyte disorders; metabolic acidosis.

Potactasol *Actavis, Cz.; Actavis, Fr.; Actavis, Irl.; Devries, Israel; Actavis, Neth.; Actavis, Norw.; Actavis, Port.; Actavis, UK.*
Topotecan hydrochloride (p. 872·3).
Malignant neoplasms.
Actavis, Pol.
Topotecan (p. 872·3).
Ovarian cancer; small-cell lung cancer; cervical cancer.

Potamkim *Kilab, Arg.*
Potassium gluconate (p. 1793·2).
Potassium supplement.

Potant *Sanovel, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Potasalan *Lannett, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Potasi *Eagle, Austral.*
Dibasic potassium phosphate (p. 1791·1); potassium citrate (p. 1780·3); potassium aspartate (p. 1793·1); potassium orotate (p. 2578·1).
Potassium supplement.

Potasio C *Dominguez, Arg.*
Potassium chloride (p. 1793·2); sodium ascorbate (p. 2111·1).
Hypokalaemia.

Potasion *Sanofi-Aventis, Spain.*
Potassium chloride (p. 1793·2).
Potassium depletion.

Potasion Solucion *Sanofi-Aventis, Spain.*
Potassium gluceptate (p. 1793·1).
Hypokalaemia.

Potasoral *Armstrong, Mex.†*
Potassium gluconate (p. 1793·2).
Hypokalaemia.

Potassion *Miba, Ital.*
Potassium succinate (p. 1793·1); potassium malate (p. 1793·1); potassium citrate (p. 1780·3); potassium acid tartrate (p. 1879·2); potassium bicarbonate (p. 1780·3).
Potassium deficiency; acidosis.

Potassride *General Drugs, Thai.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Pota-Vi-Kin *Collins, Mex.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Potazen *Medikon, Indon.†*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Potcit *CCM, Malaysia; Beacons, Singapore.*
Potassium citrate (p. 1780·3); citric acid (p. 2480·3).
Inflammatory bladder disorders; potassium supplement; alkalinisation of urine; urinary-tract infections.

Pot-Citra *Hoe, Malaysia.*
Potassium salts (p. 1793·1).
Alkalinisation of urine; gout; acidosis; potassium supplement.

Potecin *Flamingo, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Potekam *Dosa, Arg.*
Topotecan (p. 872·3).
Malignant neoplasms.

Poteligeo *Kyowa Hakko Kirin, Jpn.*
Mogamulizumab (p. 834·2).
T-cell leukaemia/lymphoma.

Poten-C with Potassium *Da Vinci, Canad.†*
Potassium citrate (p. 1780·3); calcium ascorbate (p. 2111·1).

Poten-Cee *Yik Kwan, Hong Kong†; Pascual, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Potenciator *Faes, Spain.*
Arginine aspartate (p. 2049·1).
Tonic.

Potencil *Sanitas, Arg.*
Cyproheptadine hydrochloride (p. 624·1); arginine hydrochloride (p. 2049·1); cobamamide (p. 2107·2).
Anabolic; reduced appetite.

Potencort *Julphar, UAE.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Potensik *Pyridam, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Potentiale *Tekhnolog, Ukr.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Potenvit *Interhealthcare, Philipp.*
Vitamins.
Dietary supplement.

Potenzia *Lifeplan, UK.*
Vitamins; minerals; saw palmetto (p. 2363·3); pygeum africanum (p. 2363·2); urticaria; bearberry (p. 2453·2); curcumin (p. 2180·1); tomato.
Dietary supplement for men.

Potiga *GSK, USA.*
Retigabine (p. 547·3).
Epilepsy.

Potional *Kleva, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Potklor *Bushnell, India.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Po-Trim *Polipharm, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Potter's Catarrh Pastilles *Ernest Jackson, UK.*
Pine silvestris oil (p. 2591·2); pumilio pine oil (p. 2591·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thymol (p. 1772·2); althaea (p. 2438·3).
Cough and cold symptoms.

Potters Children's Cough Pastilles *Ernest Jackson, UK.*
Ipecacuanha (p. 1667·2); squill (p. 1677·3); citric acid (p. 2480·3); honey (p. 2072·1).
Formerly known as Jacksons Childrens Cough Pastilles.
Coughs.

Potters Decongestant Pastilles *Ernest Jackson, UK.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Coughs; nasal congestion.

Potters Elixir of Echinacea Plus *Potter's, UK.*
Echinacea (p. 2498·1); wild indigo (p. 2647·2); fumitory (p. 2508·2).
Cold and influenza symptoms; skin disorders.

Potters Gees Linctus *Ernest Jackson, UK.*
Camphorated opium tincture; squill (p. 1677·3); cinnamic acid (p. 1748·3); benzoic acid (p. 1738·2); glacial acetic acid (p. 2426·3); honey (p. 2072·1).
Coughs.

Potters Strong Bronchial Catarrh Pastilles *Ernest Jackson, UK.*
Menthol (p. 2553·2); benzoin tincture (p. 2624·3); anise oil (p. 2444·3); peppermint oil (p. 1877·1); capsicum oleoresin (p. 2469·3).
Coughs and cold symptoms; catarrh.

Potters Sugar Free Cough Pastilles *Ernest Jackson, UK.*
Liquorice (p. 1853·2); menthol (p. 2553·2); benzoin tincture (p. 2624·3); anise oil (p. 2444·3); clove oil (p. 2481·3); peppermint oil (p. 1877·1); capsicum oleoresin (p. 2469·3).
Coughs; cold symptoms; catarrh.

Potussan *Pharmasant, Thai.*
Dextromethorphan (p. 1660·1).
Cough.

Poudre du Marcheur *Laphi, Fr.†*
Irgasan (p. 1773·2); lavender oil (p. 2541·1); lemon oil (p. 2543·1); pine oil (p. 2591·1); zinc oxide (p. 1729·1); talc (p. 1722·2); starch (p. 2095·1).
Foot hygiene; hyperhidrosis.

Poudre Velours *Eurogenerics, Belg.†*
Ichthammol (p. 1705·3).
Skin disorders.

Poulmycin *Demo, Gr.*
Bifonazole (p. 573·3).

Povadine *Hua, Thai.*
Povidone-iodine (p. 1767·1).
Wound disinfection; burns.

Povanil *Pharmasant, Thai.*
Clonazepam (p. 519·1).
Epilepsy; status epilepticus.

Povanyl *Omega, Fr.*
Pyrvinium embonate (p. 166·1).
Enterobiasis.

PovEyeOdine *Concept, Israel.*
Povidone-iodine (p. 1767·1).
Disinfection in ophthalmic procedures.

Povi Complex *Fada, Arg.*
Povidone-iodine (p. 1767·1).
Skin, mucous membrane, and instrument disinfection.

Povibac *Sertex, Arg.*
Povidone-iodine (p. 1767·1).
Skin, mucous membrane, wound, and burn disinfection; skin infections.

Povicler *Monserrat, Arg.*
Povidone-iodine (p. 1767·1).
Disinfection.

Poviderm *Nuova Farmec, Ital.; Hoe, Malaysia.*
Povidone-iodine (p. 1767·1).
Burns; wounds; skin infections; skin and wound disinfection.

Povidine *Stadmed, India; Phoenix, Philipp.; T Man, Thai.*
Povidone-iodine (p. 1767·1).
Burns; mouth and throat inflammation; wounds; skin infections; skin and mucous membrane disinfection; disinfection of burns and wounds.

Poviiodex *Kocak, Turk.*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane disinfection; wounds; burns; skin infections.

Povin *Andromaco, Chile.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); pantothenilic alcohol; zinc oxide (p. 1729·1).
Skin disorders.

Poviod *Saba, Turk.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Povi-odine *Seng, Thai.*
Povidone-iodine (p. 1767·1).
Disinfection of burns and wounds.

Poviodine *Alapis, Gr.; Minerva (Μινερβα), Gr.*
Povidone-iodine (p. 1767·1).

Poviral *Roemmers, Arg.; Hexpharm, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Povisep *Jayson, Ukr.*
Povidone-iodine (p. 1767·1).
Eye infections.

Poviseptin *Mertsel, Turk.*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane disinfection; burns; wounds.

Povitiol *Biosintex, Arg.*
Povidone-iodine (p. 1767·1).
Disinfection.

PO-V-SU *Malaysia Chemist, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2).

Powdered C *GNLD, Austral.†*
Ascorbic acid (p. 2110·3) and other vitamin C substances (p. 2110·3).
Vitamin C deficiency.

Power B *Maccabi Care, Israel.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Power C with Potassium *Foodscience, Canad.†*
Potassium citrate (p. 1780·3); vitamin C substances (p. 2110·3).

Power Clear *L'Oreal, Canad.†*
Pyrithione zinc (p. 1718·1).

Power Orot *Worwag, Ger.†*
Magnesium orotate (p. 1786·3).
Magnesium deficiency.

Powercef *Wockhardt, India.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Powercort *Glenmark, Rus.; Glenmark, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Powergel *Menarini, UK.*
Ketoprofen (p. 79·1).
Soft-tissue injury.

Powergyl *Cipla, India.*
Norfloxacin (p. 333·3); metronidazole (p. 936·1).
Diarrhoea.

PowerMate *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; green tea extract (p. 2648·2); ginkgo biloba extract (p. 2512·3); glutathione (p. 1555·2); acetylcysteine (p. 1652·2); echinacea (p. 2498·1); golden seal root; pine bark extract.
Tonic.

PowerSleep *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; passion flower (p. 2584·1); valerian (p. 2640·2); oxitriptan (p. 440·3); melatonin (p. 2551·3).
Tonic.

Powervit *Interhealthcare, Philipp.*
Vitamins.
Dietary supplement.

PowerVites *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; aminobenzoic acid (p. 1694·2); inositol (p. 2533·2); bioflavonoids (p. 2505·2); bee pollen (p. 2593·3); folic acid (p. 2063·1).
Tonic.

PoxClin *Chefaro, Ger.†*
Aloe vera (p. 1693·2).
Skin lesions in varicella infection.

Poxkare *Bioethic, Fr.*
Potassium hydroxide (p. 2595·3).
Molluscum contagiosum.

Pozapam *Pharmasant, Thai.*
Prazepam (p. 1098·2).
Anxiety.

Pozato *Libbs, Braz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Pozhexol *Pharmasant, Thai.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Pozineg *Aurobindo, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Biosano, Chile.
Cefepime (p. 239·2).
Bacterial infections.

Pozitron-Scan-FDG *Pozitron, Hung.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for detection of malignant neoplasms by positron-emission tomography.

PP Bio *Plus, India.*
Amylase (p. 2442·1); fructo-oligosaccharides (p. 2508·1); *Bifidobacterium bifidium* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); lactobacillus (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

PP Tage *Plus, India.*
Amylase (p. 2442·1); fructo-oligosaccharides (p. 2508·1); *Bifidobacterium bifidium* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); lactobacillus (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).

Ppar *Beximco, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

P-Parol *Osoth, Thai.*
⊗Propranolol (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; tremor.

PPB *Medisys, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Nasal congestion.

PPG *Bago, Chile; Dalmer, China.*
Policosanol (p. 1472·1).
Hypercholesterolaemia.

PPS *Baxter, Ital.*
⊗Plasma protein fraction (p. 1159·2).
Hypovolaemia; shock; burns.

PPSB Conc SD *CAF-DCF, Belg.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

PPSB Konzentrat S-TIM *Baxter BioScience, Ger.†*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

PPSB-human *Octapharma, Ger.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

PR *PruGen, USA.*
Emollient.

PR21 *Sigma, Arg.*
Saw palmetto (p. 2363·3); pollen (p. 2593·3); tomato.
Benign prostatic hyperplasia.

PR Freeze Spray *Crookes Healthcare, UK.*
Dimethyl ether (p. 1798·3); dimethoxymethane (p. 2493·2).
Muscular pain and stiffness.

PR Heat Spray *Crookes Healthcare, UK.†*
Methyl salicylate (p. 92·1); ethyl nicotinate (p. 56·3); camphor (p. 2466·2).
Muscular and rheumatic pain; sprains; bruises.

PR Natal *PruGen, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Praber *KRKA, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Prabex *Sandoz, Turk.*
Rabeprazole (p. 1881·1).

Prabexol *Chemo, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Pracap *Darrow, Braz.†*
Finasteride (p. 2358·3).
Alopecia.

Pracem *Novag, Mex.*
Dipyridamole (p. 1362·2).

Pracet *UCB, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Pracne *Grunenthal, Chile.*
Minocycline (p. 324·3).
Bacterial infections.

Practazin *Pfizer, Fr.†*
⊗Spironolactone (p. 1499·3); altizide (p. 1298·2).
Hypertension; oedema.

Practil *Organon, Ital.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Practin *Wockhardt, India.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity disorders; migraine.

Practiser *Serral, Mex.*
Diclofenac (p. 48·3).
Inflammation; pain.

Practizol *Collins, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Practogen *Genepharm, Gr.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Practomil *Braun, Switz.*
⊗Glycerol (p. 2517·2).
Bowel evacuation; constipation.

Practon *Pfizer, Fr.†*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; oedema; hypertension; myasthenia.

Pradax *Boehringer Ingelheim, Canad.*
Dabigatran etexilate mesilate (p. 1347·3).
Thromboembolism prophylaxis following orthopaedic surgery.

Pradaxa *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fr.;*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, USA.
Dabigatran etexilate mesilate (p. 1347·3).
Thromboembolism prophylaxis following orthopaedic surgery; stroke and systemic embolism prophylaxis in atrial fibrillation.

Pradex *Merck, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal examination.

Pradif *Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Switz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Pradinolol *Ducto, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension.

Prafamoc *Prafa, Indon.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Pragesol *Novell, Indon.*
Dipyrone (p. 53·3).
Pain; fever.

Pragmatar
Note: this name may be used for preparations of different composition.
GSK, India.
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); menthol (p. 2553·2); camphor (p. 2466·2).
Fungal skin infections.
Alliance, Irl.†
Coal tar (p. 1723·2); sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Dandruff; skin disorders.

Pragmaten *Sanofi-Aventis, Chile.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states.

Prairie Gold *Larkhall Laboratories, UK.*
Vitamin E (p. 2119·1).

Praize *Ipca, India.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Praize-D *Ipca, India.*
Pantoprazole (p. 1875·3); domperidone (p. 1838·1).
Gastro-oesophageal reflux.

Prakten *Sandoz, Turk.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions.

Pralax *Fahrenheit, Indon.*
Lactulose (p. 1850·3).
Constipation.

Pralexin *Prafa, Indon.†*
Cefalexin (p. 234·1).
Bacterial infections.

Pralia *Daiichi Sankyo, Jpn.*
Denosumab (p. 1182·1).
Osteoporosis.

Pralifan *Inibsa, Spain.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Pralol *Pharmasant, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; anxiety; tremor; myocardial infarction; migraine.

Pralotam *Mediapharm, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Pram *Lannacher, Austria; GL Pharma, Cz.; Lannacher, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder; anxiety.

Pramalon *Merck, S.Afr.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastric hypomotility; aid to gastrointestinal examination.

Pramatis *Sandoz, Pol.*
Escitalopram oxalate (p. 416·2).
Depression.

Pramaxima *Teva, Pol.*
Ziprasidone hydrochloride (p. 1115·2).
Schizophrenia; bipolar disorder.

Pramcil *Medipharm, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

PramCort *Rochester, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Skin disorders.

PrameGel *Medicis, Canad.; Bioglan, USA.*
Pramocaine hydrochloride (p. 1993·3); menthol (p. 2553·2).
Pruritus.

Pramexyl *Epifarma, Ital.†*
Citalopram hydrobromide (p. 411·1).
Depression; anxiety disorders.

Pram-HCA *Acella, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Pramidal *Probiomed, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Pramidalin *Ducto, Braz.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Pramide
Note: this name may be used for preparations of different composition.
Galeno, Venez.
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.
Sanofi-Aventis, Port.
Pyrazinamide (p. 345·2).
Tuberculosis.

Pramidin *Sirton, Ital.; Crinos, Pol.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders; cytostatic induced nausea and vomiting.

Pramigel *Carnot, Mex.*
Metoclopramide hydrochloride (p. 1862·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastrointestinal disorders; migraine.

Pramigen *Mylan, Cz.; Mylan, Ital.*
Pramipexole (p. 911·2).
Parkinsonism.
Mylan, Fin.
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Pramil *Greenpharma, Braz.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders; nausea and vomiting.

Pramilem *Teva, Mex.†*
Metoclopramide (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Pramilet *Abbott, Malaysia.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Dietary supplement during pregnancy and lactation.

Pramilets FA *Abbott, Singapore.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Dietary supplement in pregnancy.

Pramin *Alphapharm, Austral.; ICH, Hong Kong.†*
Metoclopramide hydrochloride (p. 1862·2).
Adjunct in gastrointestinal examination; gastroparesis; nausea and vomiting.
Rafa, Israel.
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; gastro-oesophageal reflux.

Pramina *Elea, Arg.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety disorders.

Praminal *Merck, Indon.†*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Praminan *Cazi, Braz.*
Imipramine hydrochloride (p. 426·2).
Depression.

Pramino *Janssen-Cilag, Cz.; Janssen-Cilag, Ger.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive; acne.

Pramip *Mibe, Ger.*
Pramipexole (p. 911·2).
Parkinsonism.

Pramipexolane *Disphar, Neth.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Pramistar *Berlin-Chemie, Ukr.*
Pramiracetam (p. 394·2).
Mental function impairment.

Pramital *Anpharm (Ανφαρμ), Gr.*
Citalopram hydrobromide (p. 411·1).

Pramitenorm *Plus Pharma, Hung.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Pramithan *Mylan, Cz.*
Pramipexole (p. 911·2).

Pramithon *Synthon, Denm.; Synthon, Neth.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Pramixil *CSC, Cz.; CSC, Pol.*
Pramipexole (p. 911·2).
Parkinsonism; restless legs syndrome.

Pramiz *Zim, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Pramol *Silesia, Chile.†*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Pramolan *Polpharma, Pol.*
Opipramol hydrochloride (p. 440·2).
Depression; sleep disorders; neurosis; menopausal disorders.

Pramosone *Sebela, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Skin disorders.

PramOtic *Hawthorn, USA.*
Chloroxylenol (p. 1748·2); pramocaine hydrochloride (p. 1993·3).
Bacterial infections of the external ear.

Pramox *Hawthorn, USA.*
Pramocaine hydrochloride (p. 1993·3).
Pruritus; skin irritation.

Pramox HC *Dermtek, Canad.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Skin disorders.

Pramur *Prafa, Indon.†*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; liver disorders; hypercholesterolaemia.

Pranadox *Pisa, Mex.†*
Zidovudine (p. 1024·2).
HIV infection.

Pranalip *Hexal, S.Afr.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Prandase *Bayer, Canad.†; Bayer, Israel.*
Acarbose (p. 466·2).
Diabetes mellitus.

PrandiMet *Novo Nordisk, USA.*
Repaglinide (p. 495·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Prandin *Medley, Braz.; Novo Nordisk, Cz.; Novo Nordisk, Irl.; Sanfer, Mex.; Novo Nordisk, Neth.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Spain; Daiichi Sankyo, UK; Novo Nordisk, USA.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Prandin E_2 *Pfizer, S.Afr.*
Dinoprostone (p. 2134·1).
Labour induction.

Pranex *Bayer, Venez.*
Acemetacin (p. 16·3).
Pain; inflammation.

Pranix *Liferpal, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Pranofen *Alcon, Gr.*
Pranoprofen (p. 127·1).
Inflammatory eye disorders.

Pranoflog *SIFI, Ital.*
Pranoprofen (p. 127·1).
Anterior eye inflammation.

Pranolal *Cazi, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension.

Pranolol *Actavis, Norw.; Darnitsa, Ukr.†*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; hypertension; arrhythmias; myocardial infarction; migraine; tremor; hyperthyroidism; phaeochromocytoma.

Pranopulin *Senju, China.*
Pranoprofen (p. 127·1).
Eye inflammation.

Pranosine *Sanfer, Mex.*
Inosine pranobex (p. 988·3).
Viral infections.

Pranox *Meda, Belg.*
Pranoprofen (p. 127·1).
Eye inflammation.

Prantal *MSD, Austral.; Schering-Plough, NZ.†*
Diphemanil metilsulfate (p. 2494·3).
Hyperhidrosis.

Pranzo *Vinas, Spain.*
Cyproheptadine hydrochloride (p. 624·1); carnitine hydrochloride (p. 2053·2); lysine hydrochloride (p. 2079·3).
Anorexia; tonic.

Pranzol *Ranbaxy, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Praol *Elvipe, Gr.†*
Meprobamate (p. 1083·3).

Praoz *Actavis, Port.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Praquantel *Atlantic, Thai.*
Praziquantel (p. 164·1).
Trematode infections.

Prareduct *Daiichi Sankyo, Belg.; Daiichi Sankyo, Spain.*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Prascolend *Teva, Mex.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; atherosclerosis.

Prasepine *Pfizer, Thai.†*
Prazepam (p. 1098·2).
Anxiety; skeletal muscle spasm.

Prasikon *Polipharm, Thai.*
Praziquantel (p. 164·1).
Trematode infections.

Prasiver *Maver, Mex.*
Pravastatin (p. 1473·1).

Prasterol *Lusofarmaco, Ital.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Prastin *Teva, Hung.†*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; atherosclerosis; hypercholesterolaemia.

Praten *Prafa, Indon.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Praticef *Caber, Ital.†*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Pratiderm *Prati-Donaduzzi, Braz.*
Nystatin (p. 590·3); zinc (p. 2126·1).

Pratifar *Ifars, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Pratiflip *Tiefenbacher, Neth.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pratigel *Prati-Donaduzzi, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); turpentine oil (p. 2636·3).

Pratin *Taiwan Biotech, Malaysia.*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Prati-Sal *Prati-Donaduzzi, Braz.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3).

Pratium *Mantecorp, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Pratonil *Help, Gr.*
Dibekacin sulfate (p. 286·1).
Bacterial infections.

Pratropil *Fahrenheit, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma; intellectual improvement in children.

Pratsiol *Douglas, Austral.†; Orion, Fin.; Douglas, NZ†; Aspen, S.Afr.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; benign prostatic hyperplasia; heart failure; Raynaud's syndrome.

Pratsorin *Prati-Donaduzzi, Braz.*
Sodium chloride (p. 1795·1).

Praux *Fabop, Arg.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Prava
Note: this name may be used for preparations of different composition.
BMS, S.Afr.
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.
IFET (ΙΦΕΤ), Gr.
Lomustine (p. 818·1).

Pravabeta *Betapharm, Ger.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravachol *Aspen, Austral.; BMS, Canad.; BMS, China; BMS, Denm.†; BMS, Fin.†; BMS, Gr.; BMS, Hong Kong†; BMS, Indon.†; BMS, Malaysia; BMS, Norw.; Healthcare Logistics, NZ; BMS, Singapore; BMS, Swed.†; BMS, Turk.; Deva, Turk.; BMS, USA.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; unstable angina pectoris; cardiovascular risk reduction; atherosclerosis; reduction in hyperlipidaemia after organ transplantation.

Pravacol *Merck Serono, Arg.; BMS, Braz.; Merck, Chile; BMS, Mex.; BMS, Port.; BMS, Venez.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Pravacor *Accord, S.Afr.*
Pravastatin sodium (p. 1473·1).

Pravadium *Plus, Gr.*
Pravastatin sodium (p. 1473·1).

Pravadual *BMS, Fr.*
Aspirin (p. 22·2); pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction.

Pravafact *AG Therapy, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pravafenix *SMB, Cz.; SMB, Irl.*
Pravastatin sodium (p. 1473·1); fenofibrate (p. 1381·1).
Hyperlipidaemias.

Pravagamma *Worwag, Ger.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravahelp *Help, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pravalen *Nexus, Gr.*
Pravastatin sodium (p. 1473·1).

PravaLich *Winthrop, Ger.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravalip *Lavipharm, Gr.; Trima, Israel.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction.
Mibe, Ger.†
Pravastatin (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravalo *Ratiopharm, Irl.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravalong *Angelini, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pravalotin *Mepha, Switz.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; myocardial infarction; unstable angina pectoris.

Pravamel *Clonmel, Irl.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction; post-transplant hyperlipidaemia in patients on immunosuppressive therapy.

Pravandrea *Tiefenbacher, Neth.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravanox *Verisfield, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Prava-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

PravASA *Paladin, Canad.†*
30 Tablets, pravastatin sodium (p. 1473·1); 30 tablets, aspirin (p. 22·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravaselect *Menarini, Ital.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravasin *BMS, Ger.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravasine *BMS, Belg.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravasta eco *Sandoz, Switz.†*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; myocardial infarction; unstable angina pectoris.

Pravastar *Apotex, Hung.†*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravastat *Pharmacor, Austral.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravastax *Drossapharm, Switz.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Pravat *Apotex, Irl.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravatine *Spirig, Switz.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; coronary heart disease.

Pravator *Ranbaxy, India.*
Pravastatin (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction.
Ranbaxy, Pol.
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction.

Pravaxis *Genepharm, Gr.*
Pravastatin sodium (p. 1473·1).

Pravaz *Amherst, Philipp.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction.

Pravedol *Biomedica, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pravenor *Pro-Pharma, Ukr.*
Urtica (p. 2639·3); selenomethionine (p. 2087·1); avena (p. 2451·1); fenugreek (p. 2504·1); Japanese mountain plant; melilot (p. 2552·3).
Prostatitis.

Pravid *Hovid, Malaysia.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pravidel *Meda, Ger.; Meda, Swed.*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; lactation inhibition; galactorrhoea; amenorrhoea; female infertility; acromegaly; parkinsonism.

Pravidine *Arlex, Mex.†*
Stavudine (p. 1015·3).
HIV infection.

Pravil *Duncan, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Pravin *Iasis, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pravinat *Interbat, Indon.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravitin *Rowex, Irl.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction; post-transplant hyperlipidaemia in patients on immunosuppressive therapy.

Pravlon *Prafa, Indon.†*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin disinfection.

Pravostin *Minerva (Μινερβα), Gr.*
Pravastatin (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pravox *Hizon, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Prax *Sebela, USA.*
Pramocaine hydrochloride (p. 1993·3).
Local anaesthesia.

Praxal *Sandoz, Turk.*
Pravastatin sodium (p. 1473·1).

Praxedol *Probiomed, Mex.*
Naproxen (p. 98·2).
Inflammation; pain.

Praxel *Laboratorios Chile, Chile; Teva, Mex.; Teva, Thai.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Praxilene *Merck, Belg.; Alapis, Gr.; Remek, Gr.; Merck, Hong Kong; Merck, Indon.; Merck Serono, Irl.; Formenti, Ital.; Merck, Philipp.; Merck, Port.; Merck, Singapore; Faes, Spain; Merck, Thai.; Merck, UK.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders; chronic venous ulcer; senile dementia.

Praxilène *Merck Serono, Fr.; Merck, Switz.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders.

Praxinor *Merck Serono, Fr.*
⊗Theodrenaline hydrochloride (p. 2629·1); cafedrine hydrochloride (p. 1330·1).
Hypotension.

Praxion *Pharos, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Praxis
Note: this name may be used for preparations of different composition.
Ivax, Arg.
⊗Simeticone (p. 1886·2); domperidone (p. 1838·1); pancreatin (p. 2579·3).
Digestive disorders; flatulence.
Lisapharma, Ital.
Bicalutamide (p. 749·1).
Prostatic cancer.

Praxiten *Meda, Austria; Teofarma, Ger.*
Oxazepam (p. 1092·2).
Anxiety disorders; sleep disorders.

Praxona *Roemmers Rowe, Venez.*
Carisoprodol (p. 2021·3); dipyrone (p. 53·3); salicylamide (p. 129·2).
Pain; muscle spasm.

Prayanol *Sanitas, Chile.*
Amantadine hydrochloride (p. 890·3).
Influenza; parkinsonism.

Prazam *Royal, Chile; Grunenthal, Port.*
Alprazolam (p. 1035·2).
Mixed anxiety-depressive states; panic disorder; anxiety; sleep disorders; premenstrual syndrome.

Prazaxa *Boehringer Ingelheim, Jpn.*
Dabigatran etexilate mesilate (p. 1347·3).
Thromboembolism prophylaxis in atrial fibrillation.

Prazectol *Zentiva, Cz.*
Esomeprazole magnesium (p. 1841·1).

Prazen *Delta, Braz.*
St John's wort (p. 449·1).
Depression.

Prazene *Pfizer, Ital.*
Prazepam (p. 1098·2).
Anxiety disorders; psychoneurotic disorders.

Prazentol *Tecnimede, Port.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Prazex *Safex, Port.*
Omeprazole (p. 1867·2).

Prazidec *Tecnofarma, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Prazigast *Jelfa, Pol.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.
Jelfa, Neth.†
Omeprazole sodium (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazina *Armoxindo, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Prazine *IFET (ΙΦΕΤ), Gr.; Tentan, Switz.*
Promazine hydrochloride (p. 1100·1).
Psychoses; sedative; nausea; vomiting.

Prazinil *Pierre Fabre, Fr.*
Carpipramine hydrochloride (p. 1044·2).
Anxiety; psychoses.

Prazipar *Rubio, Spain.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazite *Asian Pharm, Thai.*
Praziquantel (p. 164·1).
Trematode infections.

Prazitral *LA, Arg.*
Praziquantel (p. 164·1).
Worm infections.

Prazocip *Cipla, India.*
Prazosin hydrochloride (p. 1473·3).

Prazol
Note: this name may be used for preparations of different composition.
Kenyaku, Thai.
Alprazolam (p. 1035·2).
Anxiety; panic disorder.
Medley, Braz.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.
Polfa Pabianice, Pol.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolan *Liomont, Mex.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Prazole *Renata, Thai.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolene *Tecnimede, Port.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Prazolex *Greenpharma, Braz.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolin *Boehringer Ingelheim, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Prazolit *Teva, Mex.*
Omeprazole (p. 1867·2).
Acid aspiration; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Prazolol *Geolab, Braz.*
Omeprazole (p. 1867·2).

Prazomyl *Actavis, Denm.; Labesfal, Port.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazone-S *Norton, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.
Venus, Thai.
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Prazonil *Sanval, Braz.†*
Omeprazole (p. 1867·2).
Peptic ulcer.

Prazopant *Actavis, Austria.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Prazotec *Fahrenheit, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Prazovex *Avex, Malaysia.*
Alprazolam (p. 1035·2).
Anxiety.

Praz-Up *Balu, Gr.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

PRC *Croesus, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Pre Calent *Wierhom, Arg.*
Pine oil (p. 2591·1); eucalyptus (p. 2501·1); methyl salicylate (p. 92·1); camphor (p. 2466·2).
Musculoskeletal disorders.

Pre Clean Mom *Candioli, Ital.*
Permethrin (p. 2159·3).
Pediculosis.

Pre Clor *Grin, Mex.*
⊗Chloramphenicol (p. 257·1); prednisone (p. 1647·2).
Infected eye disorders.

Pre Mat *Rider, Chile.*
Ferrous glycine sulfate (p. 2061·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; folic acid-deficiency anaemia.

Pre Nutrison *Nutricia, Ital.*
Preparation for enteral nutrition.

Preabor *Caprifarmindo, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Preastig *Alfa Intes, Ital.*
Vitamins; minerals; glutathione (p. 1555·2).
Nutritional supplement.

Preattached *Hospira, Canad.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Pre-Attain *Sherwood, USA.*
Lactose-free preparation for enteral nutrition.

Pre-Baby *Esteripharma, Mex.*
Pregnancy test (p. 2596·1).

Prebanal *LKM, Arg.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain; anxiety; fibromyalgia.

Prebictal *Tecnofarma, Chile.*
Pregabalin (p. 545·3).
Neuropathic pain; epilepsy; fibromyalgia.

Preblacon *Actavis, UK.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Prebructal *Bryntsalov, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; chorioretinal vascular disorders.

Prébutix *Pierre Fabre Sante, Fr.*
Ethyl butylacetylaminopropionate (p. 2154·3).
Insect repellent.

Precaptil *Tecnofarma, Mex.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Precarbay *CCM, Malaysia.*
Acarbose (p. 466·2).
Diabetes mellitus.

Precardin *Farmedia, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

PreCare *Ther-Rx, USA.*
Vitamins; minerals.

Precedex *Bago, Arg.; Hospira, Austral.; Abbott, Braz.; Hospira, Canad.; Orion, Cz.†; Hospira, Hong Kong; Transfarma, Indon.; Hospira, Jpn; Hospira, Malaysia; Abbott, Mex.†; Hospira, NZ; Hospira, Philipp.; Abbott, Pol.†; Abbott, S.Afr.; Hospira, Singapore; Hospira, Thai.; Abbott, Turk.†; Hospira, USA.*
Dexmedetomidine hydrochloride (p. 1063·1).
Sedation in mechanically ventilated patients; postoperative sedation.

Precenid *Mintlab, Chile.*
Ibuprofen (p. 68·2); dipyrone (p. 53·3); chlormezanone (p. 1045·1).

Precicol *Liferpal, Mex.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm and pain.

Precidona *Precimex, Mex.*
Dipyrone (p. 53·3).
Fever; inflammation; pain.

Precifen *Precimex, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Precifenac *Precimex, Mex.*
Diclofenac (p. 48·3).
Inflammation; pain.

Precileucin *Precimex, Mex.*
Calcium folinate (p. 2066·3).
Reduction of folic acid antagonist toxicity; megaloblastic anaemia.

Precipitan *Target, Gr.*
Sumatriptan succinate (p. 679·2).
Migraine.

Precirux *Nafar, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Precision *Sandoz Nutrition, USA.*
A range of lactose-free preparations for enteral nutrition.

Precision Plus *Abbott, Arg.; Abbott Diabetes Care, Austral.†*
Test for glucose in blood (p. 2516·3).

Pre-Clar *Laboratorios Chile, Chile.*
Clarithromycin (p. 266·2).
Bacterial infections; peptic ulcer.

Preclint *Medinfar, Port.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation.

Preconceive *Lane, Irl.; Lane, UK.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Precopar *Sanbe, Indon.*
Amino acids; xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition in liver disease.

Precort *Kocak, Turk.*
⊗Methylprednisolone (p. 1642·2).

Precortalon aquosum *MSD, Swed.*
⊗Prednisolone sodium succinate (p. 1646·1).
Corticosteroid.

Precortil *Cazi, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Precortisyl *Aventis, UK.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Precortivit *Menarini, Gr.*
⊗Prednisolone (p. 1645·2); neomycin sulfate (p. 330·1); vitamin A acetate (p. 2098·3).
Infected skin disorders.

Precosa *Biocodex, Fin.; Algol, Norw.; Algol, Swed.*
Saccharomyces boulardii (p. 2596·3).
Antibiotic-associated diarrhoea; antibiotic-associated colitis; diarrhoea.

Precose *CCM, Malaysia†; Bayer, USA.*
Acarbose (p. 466·2).
Diabetes mellitus.

Precosol *Kela, Belg.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Precoxi *CCM, Malaysia.*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Precten *Savio, Ital.*
Losartan potassium (p. 1422·2).

Précyclan *Lisapharm, Fr.†*
⊗Meprobamate (p. 1083·3); bendroflumethiazide (p. 1315·2); medroxyprogesterone acetate (p. 2288·1).
Premenstrual syndrome.

Pred
Note: this name may be used for preparations of different composition.
Grin, Mex.; Allergan, Singapore; Alcon, USA.
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Prosel, Philipp.
⊗Prednisone (p. 1647·2).
Corticosteroid.

Pred Fort *Allergan, Braz.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Pred Forte *Allergan, Belg.; Allergan, Canad.; Allergan, Chile; Allergan, China; Allergan, Fin.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Israel; Allergan, Malaysia; Allergan, Neth.; Allergan, NZ; Allergan, Philipp.; Allergan, S.Afr.; Allergan, Spain; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Pred G *Allergan, USA.*
⊗Prednisolone acetate (p. 1645·2); gentamicin sulfate (p. 304·2).
Infected eye disorders.

Pred Mild *Allergan, Braz.; Allergan, Canad.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Malaysia; Allergan, NZ; Allergan, S.Afr.; Allergan, Thai.; Allergan, USA.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Pred Oph *Seng, Thai.*
⊗Prednisolone sodium phosphate (p. 1645·3); gentamicin sulfate (p. 304·2).
Infected eye and ear disorders.

Preda *Kalbe, Indon.; Sanghiang, Indon.*
Infant feed.
Malabsorption.

Predalon *Essex, Ger.*
⊗Chorionic gonadotrophin (p. 2258·1).
Cryptorchidism; delayed puberty; hypogonadism; female infertility.

Predcap *Bangkok Lab & Cosmetic, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Pred-Clysma *Bayer, Denm.; Bayer Schering, Norw.; Bayer, Swed.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Crohn's disease; ulcerative colitis; proctosigmoiditis.

Predcor *Hauck, USA.*
⊗Prednisolone acetate (p. 1645·2).
Corticosteroid.

Predeltin *Quatromed, S.Afr.†*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Predenema *Forest Laboratories, Hong Kong†; Forest, Irl.†; Chemidex, UK.†*
⊗Prednisolone metasulfobenzoate sodium (p. 1645·3).
Ulcerative colitis.

Predfoam *Forest Laboratories, Hong Kong; Forest, Irl.†; Forest Laboratories, UK.†*
⊗Prednisolone metasulfobenzoate sodium (p. 1645·3).
Proctitis; ulcerative colitis.

Predi *KB, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Pre-Dial *Silanes, Mex.*
Metformin (p. 489·1).
Diabetes mellitus.

Predictor *Omega, Austral.; Organon, Braz.†; Omega, Fr.†; Chefaro, Israel; Chefaro, Ital.; Genesis, Turk.; Chefaro, UK.*
Pregnancy test (p. 2596·1).

Predi-Medrol *Uniao Quimica, Braz.*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Predisole *PP Lab, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Predison *Cristalia, Braz.†*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Predisyr *Phoenix, Philipp.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Predizin *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic vestibular disorders; ischaemic eye disorders.

Predman *T Man, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Predmetil *Eurofarma, Braz.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Predmicin
Note: this name may be used for preparations of different composition.
EMS, Braz.
⊗Polymyxin B sulfate (p. 342·3); prednisolone (p. 1645·2); benzocaine (p. 1980·2); clioquinol (p. 273·1).
Skin disorders.

Predmix *Lennon, Austral.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Predmycin P *Allergan, Belg.; Allergan, Thai.*
⊗Prednisolone acetate (p. 1645·2); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Infected eye disorders.

Predmycin-P *Allergan, Irl.; Allergan, Philipp.; Allergan, Singapore.†*
⊗Prednisolone acetate (p. 1645·2); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Infected eye disorders.

Prednax *Geolab, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Prednecort *Yung Shin, Philipp.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Prednefrin
Note: this name may be used for preparations of different composition.
Allergan, Arg.; Allergan, Austral.
⊗Prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Inflammatory eye disorders.

Prednefrin SF *Allergan, Mex.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Prednersone *General Drugs, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Prednesol *Phoenix, Irl.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Pred-NF *Grin, Mex.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Predni *Winthrop, Ger.*
⊗Prednisolone acetate (p. 1645·2).
Parenteral corticosteroid.

Predni H *Winthrop, Ger.*
⊗Prednisolone (p. 1645·2) or prednisolone acetate (p. 1645·2).
Corticosteroid.

Predni M *Winthrop, Ger.*
⊗Methylprednisolone (p. 1642·2).
Oral corticosteroid.

Predni Tablinen *Winthrop, Ger.*
⊗Prednisone (p. 1647·2).
Oral corticosteroid.

Prednicarb *Darnitsa, Ukr.*
⊗Prednisolone (p. 1645·2); urea (p. 1727·3).
Inflammatory skin disorders.

Prednicort
Note: this name may be used for preparations of different composition.
Behrens, Venez.
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Otto, Indon.
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Prednicutan *Dermapharm, Switz.*
⊗Prednicarbate (p. 1645·1).
Skin disorders.

Prednidib *Diba, Mex.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Prednifarma
Note: this name may be used for preparations of different composition.
Raymos, Arg.
⊗Solution A, phenylephrine hydrochloride (p. 1672·3); phenazone (p. 124·1); hypromellose (p. 2189·2); powder B, prednisolone sodium phosphate (p. 1645·3).
Inflammatory eye disorders.

Valeant, Arg.
⊗Prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Inflammatory eye disorders.

Predniftalmina *Davi, Port.*
⊗Chloramphenicol (p. 257·1); prednisolone (p. 1645·2).
Infected eye disorders.

Prednigalen *Galen, Ger.*
⊗Prednisolone acetate (p. 1645·2).
Corticosteroid.

Prednihexal *Hexal, Ger.†*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Prednilem *Teva, Mex.†*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Prednicil *Edol, Port.*
⊗Prednisolone acetate (p. 1645·2).
Eye disorders.

Predni-Ophtal *Winzer, Ger.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Prednipirine *Lanpharm, Arg.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Predni-POS *Ursapharm, Cz.; Ursapharm, Ger.; Biem, Turk.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Prednis *Legrand, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Prednisil *Silom, Thai.†*
Cream: ⊗Prednisolone (p. 1645·2).
Skin disorders.

Prednisil-N *Silom, Thai.†*
⊗Prednisolone (p. 1645·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Prednisol *Pasadena, USA.†*
⊗Prednisolone tebutate (p. 1646·1).
Corticosteroid.

Prednisolon J *Gedeon Richter, Hung.†*
⊗Prednisolone (p. 1645·2); clioquinol (p. 273·1).
Infected skin disorders.

Prednisolone-N *GPO, Thai.*
⊗Prednisolone (p. 1645·2); neomycin (p. 329·3).
Infected skin disorders.

Prednisolut *Mibe, Ger.*
⊗Prednisolone hydrogen succinate (p. 1645·3).
Parenteral corticosteroid.

Prednisona Neomicina *Alcon Cusi, Spain.*
⊗Neomycin sulfate (p. 330·1); prednisone (p. 1647·2).
Infected eye disorders.

Prednisonal *Klonal, Arg.*
⊗Meprednisone (p. 1642·2).
Corticosteroid.

Prednitop *Sanofi-Aventis, Austria; Dermapharm, Ger.; Abbott, Switz.*
⊗Prednicarbate (p. 1645·1).
Inflammatory skin disorders; eczema; scalp psoriasis.

Prednocris *LKM, Arg.*
Ranitidine (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; dyspepsia; acid aspiration.

Prednol *Nevzat, Turk.*
Cream; ointment: ⊗Prednisolone (p. 1645·2).
Skin disorders.

Nevzat, Turk.
Injection; tablets: ⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Prednol-A *Nevzat, Turk.*
⊗Prednisolone (p. 1645·2); clioquinol (p. 273·1).
Skin disorders.

Prednox *Pyridam, Indon.; One Pharma, Philipp.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Predon *LBS, Malaysia.*
⊗Prednisolone acetate (p. 1645·2).
Corticosteroid.

Predone *Cipla, India.*
⊗Prednisolone (p. 1645·2) or prednisolone acetate (p. 1645·2).
Corticosteroid.

Predonema *Kyorin, Jpn.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Ulcerative colitis; regional enteritis.

Predonium *Servier, Hong Kong; Servier, Neth.†; Servier, NZ; Servier, Port.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

PReDopa *Kyowa, Jpn.*
Dopamine hydrochloride (p. 1367·2).
Shock.

Predopam *Dem, Turk.*
Dopamine hydrochloride (p. 1367·2).

Predoral *Blue Sky, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Pred-Phosphate *Medical Ophthalmics, USA.*
⊗Prednisolone phosphate (p. 1645·2).
Eye disorders.

Predsim *Mantecorp, Braz.*
⊗Prednisolone (p. 1645·2) or prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Predsol *Aspen, Austral.; UCB, Irl.; Focus, UK.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Proctitis; ulcerative colitis; Crohn's disease; inflammatory disorders of the ear or eye.

Predsolets *SMB, Chile.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Predsol-N *Focus, UK.†*
⊗Prednisolone sodium phosphate (p. 1645·3); neomycin sulfate (p. 330·1).
Inflammatory disorders of the ear or eye with bacterial infection.

Predsolone *Lennon, Austral.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Predsomed *Medicpharma, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Predson *Cristalia, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Predsone *Lennon, Austral.; Jiangsu Pengyao, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Predual
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Pamabrom (p. 1464·1); paracetamol (p. 115·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Andromaco, Chile.
Paracetamol (p. 115·1); ibuprofen (p. 68·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Predualergin *Nova Argentia, Arg.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Preductal *Servier, Cz.; Servier, Hung.; Anpharm, Pol.; Servier, Pol.; Servier, Rus.; Servier, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic eye and ear disorders; vestibular disorders; chorioretinal vascular disorders.

Predval *Sanval, Braz.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Predxal *Armstrong, Mex.*
Telmisartan (p. 1509·3).
Hypertension.

Predxal Plus *Armstrong, Mex.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Preema *Delta Medical, Ukr.*
Lactobacillus rhamnosus (p. 2596·3).
Restoration of normal gastrointestinal flora.

Preface *Centaur, India.*
Ramipril (p. 1483·3).
Heart failure; hypertension; myocardial infarction.

Prefamone *Dexo, Thai.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Prefaxil *Royal, Chile.*
Pregabalin (p. 545·3).
Neuropathic pain; epilepsy.

Prefaxine *Polpharma, Cz.†; Polpharma, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Prefem *Labomed, Chile.†*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Premenstrual syndrome.

Prefemine *Zeller, Switz.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Preferred Remedies Aches & Pains *Reese, USA.*
Hypericum perforatum (p. 449·1); agaricus musc.; arnica mont. (p. 2447·2); nux vomica (p. 2573·3); rhus tox. (p. 2603·3); rhododendron.
Homoeopathic preparation.

Preferred Remedies Allergy *Reese, USA.*
Allium cepa (p. 2575·2); ambrosia artemisae; euphrasia officinalis (p. 2502·1); sabadilla (p. 2611·2); sticta pulmonaria (p. 2546·1); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Preferred Remedies Antacid *Reese, USA.*
Solidago virga. (p. 2620·1); albies nig.; argentum nit. (p. 2615·3); bryonia alba; condurango (p. 2485·3); nux vomica (p. 2573·3); robinia.
Homoeopathic preparation.

Preferred Remedies Cold & Flu *Reese, USA.*
Aconitum napellus (p. 2428·3); belladonna (p. 2453·3); echinacea angustifolia (p. 2498·1); eupatorium perfoliatum (p. 2459·1); ferrum phosphoricum (p. 2077·1); gelsemium sempervirens (p. 2511·2).
Homoeopathic preparation.

Preferred Remedies Detoxin *Reese, USA.*
Berberis; bryonia alba; chelidonium majus (p. 2522·2); nux vomica (p. 2573·3); carduus benedictus (p. 2482·2); carduus marianus (p. 1561·1); cynaria scolimus (p. 2490·3); juniperus; solidago (p. 2620·1); taraxacum (p. 2625·3).
Homoeopathic preparation.

Preferred Remedies Fatigue *Reese, USA.*
Ignatia (p. 2532·1); phosphoric acid (p. 2589·1); picric acid (p. 2634·2); rhus tox. (p. 2603·3); selenium (p. 2086·3).
Homoeopathic preparation.

Preferred Remedies Sinus *Reese, USA.*
Allium cepa (p. 2575·2); hydrastis canadensis (p. 2528·1); sticta pulmonaria (p. 2546·1); kali bichromicum (p. 2476·3).
Homoeopathic preparation.

Preferred Remedies Sleep *Reese, USA.*
Avena sativa (p. 2451·1); chamomilla (p. 2474·1); coffea (p. 2648·2); humulus lup. (p. 2546·1); ignatia (p. 2532·1); passiflora (p. 2584·1).
Homoeopathic preparation.

Preferred Remedies Stress *Reese, USA.*
Ambra grisea (p. 2440·3); chamomilla (p. 2474·1); lycopodium clavatum (p. 2547·1); staphysagria; stramonium (p. 2622·3).
Homoeopathic preparation.

Prefest *Janssen-Cilag, Arg.; Janssen-Cilag, Mex.; Teva, USA.*
15 Tablets, estradiol (p. 2271·1); 15 tablets, estradiol; norgestimate (p. 2295·3).
Menopausal disorders; osteoporosis.

Janssen-Cilag, Braz.
Pink tablets, estradiol (p. 2271·1); white tablets, estradiol; norgestimate (p. 2295·3).
Menopausal disorders.

Prefesta *Janssen-Cilag, S.Afr.†*
Pink tablets, estradiol (p. 2271·1); white tablets, estradiol; norgestimate (p. 2295·3).
Menopausal disorders.

Prefit *Sandoz, Indon.*
Vitamin B substances (p. 2102·3); minerals; glutamic acid (p. 2070·2); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Prefix *Nobel, Turk.*
Cefprozil (p. 248·2).
Bacterial infections.

Preflam *Cipla-Medpro, S.Afr.*
⊗Prednisolone (p. 1645·2).
Inflammation.

Preflex Daily Cleaner *Alcon, USA.*
Cleansing solution for soft contact lenses.

Preflucel *Baxter, Cz.; Baxter, Fin.; Baxter, Ger.; Baxter, Irl.; Baxter, Neth.; Baxter, Norw.; Baxter, Swed.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Pré-Folic *Elofar, Braz.*
Folic acid (p. 2063·1).

Prefolic *Zambon, Ital.*
Calcium methylfolate (p. 2053·1).
Folate deficiency; antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity.

Prefrin *Allergan, Arg.; Allergan, Austral.; Allergan, Canad.†; Genepharm, Gr.; Allergan, Hong Kong†; Allergan, Malaysia; Allergan, NZ; Allergan, S.Afr.; Allergan, Singapore.*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation; eye congestion.

Prefrin A *Allergan, Canad.†; Alvia (Αλβία), Gr.*
Mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Prefucet *Rafarm, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Pregab *Torrent, India.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain.

Pregaday *Focus, UK.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Prophylaxis of iron and folic acid deficiency in pregnancy.

Pregalex *Andromaco, Chile.*
Pregabalin (p. 545·3).
Neuropathic pain; epilepsy.

Pregamal *GSK, S.Afr.*
Folic acid (p. 2063·1); ferrous fumarate (p. 2060·3).
Anaemias in pregnancy.

Pregamed *Ameda, Ukr.*
Pregabalin (p. 545·3).
Epilepsy; neuropathic pain; anxiety; fibromyalgia.

Pregestimil *Mead Johnson, Austral.†; Mead Johnson, Braz.†; Mead Johnson, Denm.; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Indon.; Mead Johnson, Irl.; Mead Johnson, Israel; Mead Johnson, Ital.; BMS, Pol.†; Mead Johnson, Pol.†; Mead Johnson, Singapore; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, USA.*
Infant feed.
Galactosaemia; fat malabsorption; diarrhoea; food intolerances and allergies; inflammatory bowel disease; malabsorption syndromes; carbohydrate intolerance; galactokinase deficiency; lactose or sucrose and protein intolerance; cows' milk allergy; steatorrhoea; malnutrition; disaccharidase deficiency.

Mead Johnson Nutritionals, UK.
Lactose- and sucrose-free infant feed.
Protein intolerance; impaired fat absorption.

Pregestimil Premium *Mead Johnson, Mex.*
Infant feed.
Malabsorption.

Preglandin *Ono, Jpn.*
Gemeprost (p. 2137·2).
Termination of pregnancy.

Preg-Less *Sigma, Braz.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Combined injectable contraceptive.

Pregmag *ICN, Hung.†*
Magnesium citrate (p. 1857·1); folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium and folic acid supplement.

Pregnacare *Vitabiotics, Cz.†; Vitabiotics, Hong Kong; Vitabiotics, Hung.†; Vitabiotics, Indon.; Vitabiotics, Irl.†; Vitabiotics, Rus.; Nobel, Turk.; Vitabiotics, UK; Vitabiotics, Ukr.*
Vitamins; minerals.
Dietary supplement in pregnancy and breast feeding; vitamin and mineral deficiency.

Vitabiotics, Hong Kong.
Cream: Calendula (p. 2465·2); evening primrose oil (p. 2502·2); aloe vera (p. 1693·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); carotenoids; dexpanthenol (p. 2582·2).
Skin care during and after pregnancy.

Pregnacare Plus *Vitabiotics, UK.*
Vitamins; minerals; omega-3 DHA (p. 1460·1).
Dietary supplement in pregnancy and lactation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pregnalac *NBTY, Ukr.†*
Vitamins; calcium sulfate (p. 2173·1); ferrous fumarate (p. 2060·3); zinc oxide (p. 1729·1).
Dietary supplement in pregnancy and lactation.

Pregnamin *Blooming Fields, Philipp.*
Vitamins; minerals.
Nutritional supplement for pregnant and breast-feeding women.

Pregnancy & Breastfeeding Formula *Cenovis, Austral.*
Tuna oil (p. 1460·3); vitamins; minerals.
Dietary supplement.

Pregnancy & Breast-Feeding Gold *Blackmores, Austral.*
Omega-3 marine triglycerides (p. 1460·3); vitamins; minerals.
Dietary supplement during pregnancy and lactation.

Pregnasea *Kalbe, Indon.*
Ginger (p. 1844·1); vitamin B_6 (p. 2105·3).
Nausea and vomiting.

Pregnatal *Scanpharm, Hong Kong.†*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Pregnavit *Ratiopharm, Austria.*
Vitamins; iron (p. 2073·1).

Ratiopharm, Hung.; Ratiopharm, Rus.
Vitamins; minerals.

Ratiopharm, Ukr.
Vitamins; ferrous fumarate (p. 2060·3); calcium lactate (p. 1784·1); calcium dihydrogen phosphate (p. 2464·2).
Dietary supplement.

Ratiopharm, Cz.†
Vitamins; calcium (p. 1783·1); iron (p. 2073·1).

Pregnavit F *Ratiopharm, Rus.*
Vitamins.

Pregnazon *Pharmadass, UK.*
Vitamins; minerals; trace elements.

Pregnidoxin *UCB, India.*
Meclozine hydrochloride (p. 634·3); caffeine (p. 1203·3).
Nausea and vomiting; Ménière's syndrome.

Pregnolan *Mabra, Braz.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive.

Pregnolin *Dexa, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Pregnorm *Win-Medicare, India.*
⊗Menotrophin (p. 2284·1).
Male and female infertility; cryptorchidism; delayed puberty; male hypogonadism; threatened or recurrent miscarriage; premature labour.

Pregnosis *Key, Austral.; Roche, USA.*
Pregnancy test (p. 2596·1).

Pregnosticon *Organon, Israel.*
Pregnancy test (p. 2596·1).

Pregnyl *Organon, Arg.; MSD, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Merck, Canad.; Schering-Plough, Chile; Organon, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Schering-Plough, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Adcock Ingram, S.Afr.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK; Schering-Plough, Ukr.; Organon, USA; Organon, Venez.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility; cryptorchidism; hypogonadotrophic hypogonadism; delayed puberty; metrorrhagia.

Pregobin *Drugtech, Chile.*
Pregabalin (p. 545·3).
Epilepsy; neuralgia; neuropathic pain.

Pregomin *Support, Braz.†*
Infant feed.
Carbohydrate malabsorption syndromes; cow's-milk-protein intolerance; digestive system disorders; soya-milk-protein intolerance.

Pregomin Pepti *Milupa, Switz.*
Infant feed.
Cow's-milk-protein intolerance; soya-milk-protein intolerance; carbohydrate malabsorption syndromes; digestive system disorders.

Prégomine *SD, Fr.†*
Infant feed.
Cows' milk protein allergy; diarrhoea.

Pregtenol *Fahrenheit, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

PregVit *Duchesnay, Canad.*
Vitamins; minerals.
Nutritional supplement during pregnancy and lactation.

Pregvit *Science Pharma, UK.*
Vitamins; minerals; folic acid (p. 2063·1).
Dietary supplement during pregnancy and lactation.

Pregvomit *Fahrenheit, Indon.*
Parathiazine teoclate (p. 637·1); pyridoxine hydrochloride (p. 2105·3).
Vomiting; motion sickness.

Prehist *Marnel, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Prehist D *Marnel, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract symptoms.

Prejomin *Milupa, UK.†*
Gluten-free preparation for special diets.
Lactose, sucrose and fructose intolerance; protein sensitivity; galactokinase deficiency.

Preko *Abdi, Turk.*
Metformin hydrochloride (p. 489·1); pioglitazone (p. 493·1).
Diabetes mellitus.

Prekunil *Noos, Ital.*
Amino acids.
Nutritional supplement.

Prelactic *Frezyderm, Malaysia.*
⊗Lactic acid (p. 2539·1); prebiotic oligosaccharides; hyaluronic acid (p. 2526·2); glycerol (p. 2517·2).
Regulation of vaginal pH and flora.

Prelafal *Akromed, S.Afr.†*
Vitamins; minerals.

Prelar *Teva, Mex.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; endometriosis; uterine fibroids.

Prelat *Yung Shin, Philipp.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Prelectal *Stroder, Ital.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Prelief *AkPharma, USA.*
Calcium glycerophosphate (p. 1783·3).
Dyspepsia.

Prelis *Mibe, Ger.*
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Prelis comp *Mibe, Ger.*
⊗Metoprolol tartrate (p. 1434·3); chlortalidone (p. 1335·2).
Hypertension.

Prelisin *Cosmopharm, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Preloc *Unison, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Prelon *Angelini, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Prelone *Ache, Braz.; Adcock Ingram, S.Afr.; Aero, USA.*
⊗Prednisolone (p. 1645·2) or prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Prelone-3 *Sunward, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Prelow *Glenmark, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Medico Uno, Hung.
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Prelow Plus *Liconsa, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prelu-2 *Boehringer Ingelheim, USA; Roxane, USA.*
⊗Phendimetrazine tartrate (p. 2328·3).
Obesity.

Prelude *Rendell, UK.*
Nonoxinol 9 (p. 2199·1).
Spermicidal contraceptive.

Prem *Sigma, Braz.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders.

Premalex *Lundbeck, Swed.*
Escitalopram oxalate (p. 416·2).
Premenstrual dysphoric disorder.

Premandol *Spirig, Switz.*
⊗Prednisolone acetate (p. 1645·2).
Skin disorders.

Premarin *Wyeth, Arg.; Pfizer, Austral.; Wyeth, Braz.; Pfizer, Canad.; Pfizer, China; IFET (ΙΦΕΤ), Gr.; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, India; Pfizer, Irl.; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, NZ; Wyeth, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK; Wyeth-Ayerst, USA; Wyeth, Venez.*
Conjugated oestrogens (p. 2260·1).
Oestrogen deficiency; menopausal disorders; osteoporosis; prostatic cancer; breast cancer; dysfunctional uterine bleeding; vaginal and vulvar atrophy; female hypogonadism; primary ovarian failure.

Premastan *CORNE, Mex.*
Progesterone (p. 2300·2).
Benign breast disorders.

Premaston *Kalbe, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Preme *TNP, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Premelle *Wyeth, Braz.; Pfizer, China; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, Philipp.; Pfizer, S.Afr.; Wyeth, Singapore; Wyeth, Turk.†*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; vaginal and vulval atrophy; hormone replacement therapy; oestrogen deficiency.

Premelle Ciclo *Wyeth, Braz.*
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; vaginal and vulval atrophy.

Premelle Combinato *Wyeth Lederle, Ital.†*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Premelle Continuo *Wyeth, Venez.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Premelle Cycle *Wyeth, Gr.; Wyeth, Hong Kong†; Wyeth, Philipp.; Pfizer, S.Afr.; Wyeth, Singapore; Wyeth, Turk.*
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Premence *Vitabiotics, Hong Kong; Vitabiotics, UK.*
Vitamins; minerals.
Premenstrual syndrome.

Pré-Mens *Sigma, Braz.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1).

PreMens
Note: this name may be used for preparations of different composition.
Phytotec, Hung.; Zeller, Switz.
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Prementaid *Potter's, UK.*
Vervain (p. 2645·1); motherwort (p. 2564·2); pulsatilla (p. 2600·2); bearberry (p. 2453·2); valerian (p. 2640·2).
Premenstrual syndrome.

PremesisRx *Ther-Rx, USA.†*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); calcium (p. 1783·1).
Nausea.

Premherb *MedicHerb, UK.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Premia *Wyeth Lederle, Ital.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Wyeth, Austral.†
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Premia Continuous *Pfizer, Austral.; Pfizer, NZ.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Premid
Note: this name may be used for preparations of different composition.
Grin, Mex.
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Meda, Denm.
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Premig *Sanofi-Aventis, Gr.*
Lysine aspirin (p. 84·3); metoclopramide hydrochloride (p. 1862·2).
Migraine.

Premio *Bosch, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Premique *Pfizer, Irl.; Pfizer, UK.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Premique Cycle *Pfizer, Irl.; Pfizer, UK.†*
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Premium
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Valsartan (p. 1521·2).

Quest, Canad.†
A range of vitamin and mineral preparations.

Premium Memori Plus *Green Leaf, Philipp.*
Centella (p. 1698·3); bacopa (p. 2452·1); lecithin (p. 2542·2); docosahexaenoic acid (p. 1460·1).
Nutritional supplement.

Premium Plus *Abdi, Turk.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Premium Sunscreen *Norwood, Canad.*
SPF 15: Avobenzone (p. 1695·1); ensulizole (p. 1703·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Premject *Pound International, UK.*
Lidocaine (p. 1988·1).
Premature ejaculation.

Premosan *Julphar, UAE.*
Metoclopramide hydrochloride (p. 1862·2).
Gastro-oesophageal reflux; gastrointestinal motility disorders; nausea and vomiting; hiccup; gastrointestinal procedures; migraine.

Prempak N *Wyeth, S.Afr.†*
21 Tablets, conjugated oestrogens (p. 2260·1); 10 tablets, medrogestone (p. 2287·3).
28-Day packs also contain 7 inert tablets.
Menopausal disorders; osteoporosis.

Prempak-C *Pfizer, Irl.; Wyeth, Singapore†; Pfizer, UK.*
28 Tablets, conjugated oestrogens (p. 2260·1); 12 tablets, norgestrel (p. 2296·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Premphase *Wyeth-Ayerst, USA.*
Maroon tablets, conjugated oestrogens (p. 2260·1); blue tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Premplus
Note: this name may be used for preparations of different composition.
Pfizer, Canad.
14 Tablets, conjugated oestrogens (Premarin) (p. 2260·1); 14 tablets, medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Prempro *Wyeth-Ayerst, USA.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Prempro Bifasico *Sigma, Braz.*
14 Blue tablets, conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1); 14 red tablets, conjugated oestrogens.
Menopausal disorders.

Prempro Monofasico *Sigma, Braz.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Premsyn PMS *Chattem, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Pain.

Premular *Flordis, Austral.*
⊗Agnus castus (p. 2432·2).
Premenstrual syndrome.

Prémunil *Lero, Fr.*
Vitamins; *Lactobacillus casei* (p. 2596·3); minerals.
Dietary supplement.

Prena 1 Chew with Quatrefolic *BocaGreenMD, USA.*
Vitamins.

Prena 1 Plus with Quatrefolic *BocaGreenMD, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1).

Prena1 with Quatrefolic *BocaGreenMD, USA.*
Vitamins; iron (p. 2073·1); zinc (p. 2126·1); docosahexaenoic acid (p. 1460·1).
Dietary supplement.

PrenaCare *Cypress, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Prenacid *SIFI, Ital.; Zambon, Rus.; Teka, Turk.*
⊗Desonide sodium phosphate (p. 1630·1).
Inflammatory eye disorders.

Prenadona *Ariston, Arg.†*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Prenafirst *Cypress, USA.*
Vitamins; minerals.

Prenafort *Cypress, USA.*
Vitamins; iron (p. 2073·1).

Prenaforte *Nutriforce, Singapore.*
Vitamins; minerals.
Nutritional supplement during pregnancy and lactation.

Prenagen *Kalbe, Indon.; Sanghiang, Indon.*
A range of preparations for enteral nutrition.

Prenaissance *Acella, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Prenaissance DHA *Acella, USA.*
Tablets, minerals; vitamins; capsules, eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.

Prenaissance Harmony DHA *Acella, USA.*
Tablets, vitamins; minerals; capsules, omega-3 fatty acids (p. 1460·1).
Dietary supplement.

Prenaissance Promise *Acella, USA.*
Tablets, minerals; vitamins; capsules, eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Docusate sodium (p. 1836·2) is included in the tablets to reduce the constipating effects of iron.

Prenal *Tempo Scan Pacific, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Prenalon *Degorts, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Prenamed *Medicpharma, Thai.*
Vitamins; minerals.

Prenamia *Sanbe, Indon.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Vitamin and mineral supplement in anaemia.

Prenamin *Gynopharm, Chile.*
Docosahexaenoic acid (p. 1460·1).
Dietary supplement in pregnancy and lactation.

PrenaPlus *Cypress, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Prenarex Plus *Pascual, Philipp.*
Iron (p. 2073·1); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Prenarpil *Medicpharma, Thai.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Prenase *Nufarindo, Indon.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

PreNata *Sancilio, USA.*
Iron (p. 2073·1); vitamins.

Prenatabs *Cypress, USA.*
Vitamins; minerals.

Pre-Natal *Be-Tabs, S.Afr.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Prenatal *Cypress, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Docusate sodium (p. 1836·2) may be included in this preparation to reduce the constipating effects of iron.

Manon, Israel.
Vitamins; minerals; trace elements; iron (p. 2073·1); folic acid (p. 2063·1).
Nutritional supplement during pregnancy and lactation.

Jamp, Canad.; Nutricorp, Canad.; Pharmetics, Canad.; VitaHealth, Canad.; WN, Canad.; Wyeth, India; Erlimpex, Indon.; Wyeth Consumer, Mex.; Teofarma, Port.
Vitamins; minerals.
Nutritional supplement.

Ethex, USA.
Vitamins; with or without minerals.

Plus Pharma, USA.
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); zinc (p. 2126·1).
Dietary supplement.

Prenatal 1 *VitaMed, USA.*
Vitamins; iron (p. 2073·1); docosahexaenoic acid (p. 1460·1); zinc (p. 2126·1).
Dietary supplement.

Prenatal DHA *Erlimpex, Indon.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Prenatal EM *Erlimpex, Indon.*
Ginger (p. 1844·1); vitamin B_6 (p. 2105·3).
Nausea and vomiting during pregnancy.

Prenatal with Folic Acid *Geneva, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Prenatal Hematinic with Folic Acid *Cypress, USA.*
Folic acid (p. 2063·1); iron (p. 2073·1).
Dietary supplement.

Prenatal Nutrients *Solgar, UK.*
Vitamins; minerals.

Prenatal PC *Integrity, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Prenatal Plus *Boca, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); zinc (p. 2126·1); copper (p. 2057·1).

Zenith Goldline, USA.
Vitamins; minerals; calcium (p. 1783·1); iron (p. 2073·1).

Prenatal Plus Iron *Major, USA.*
Vitamins; minerals; iron (p. 2073·1).

Prenatal-S *Goldline, USA.†*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Prenate *First Horizon, USA; Sciele, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Prenate AM with Quatrefolic *Avion, USA.*
Folic acid (p. 2063·1); calcium (p. 1783·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); ginger (p. 1844·1); cowberry (p. 2487·3).

Prenate Chewable with Quatrefolic *Avion, USA.*
Folate (p. 2063·1); calcium (p. 1783·1); boron (p. 2052·3); magnesium (p. 1786·3); vitamins; blueberry.
Dietary supplement.

Prenate Elite with Quatrefolic *Avion, USA.*
Vitamins; minerals.
Dietary supplement.

Prenate Essential *Shionogi, USA.*
Vitamins; iron (p. 2073·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Prenate Mini *Avion, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1); blueberry.
Dietary supplement.

Prenatex *Medix, Mex.*
Vitamins; minerals.

Prenatin Plus *Soho, Indon.*
Vitamins; minerals.
Nutritional supplement; tonic.

Prenatin-DF *Soho, Indon.*
Vitamins; minerals with ferrous fumarate (p. 2060·3) and docosahexaenoic acid (p. 1460·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Nutritional supplement in pregnancy and lactation; anaemia.

Prenatol *Wyeth, Hong Kong.†*
Amino acids; proteins.
Prevention of stretch marks during pregnancy.

Prenavit *Gynopharm, Chile.*
Vitamins; calcium phosphate (p. 1784·2); ferrous gluconate (p. 2061·2).
Dietary supplement.

Vivax Gynopharm, Venez.
Vitamins; minerals.

Prenesa *KRKA, Ukr.*
Perindopril (p. 1466·3).
Hypertension; heart failure.

Prenessa *KRKA, Cz.; 2care4, Denm.†; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction; stroke prophylaxis.

Prenewel *KRKA, Cz.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

PreNexa *Upsher-Smith, USA.*
Folic acid (p. 2063·1); calcium (p. 1783·1); vitamin B_6 (p. 2105·3); carbon; colecalciferol (p. 2113·1); vitamin E substances (p. 2119·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1); docusate sodium (p. 1836·2).
Dietary supplement.

Prenolin *Dexa, Indon.†*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Prenolol *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Prenolone *Bago, Arg.*
⊗Meprednisone hemisuccinate (p. 1642·2).
Corticosteroid.

Prenoretic *AstraZeneca, Arg.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Prenormine *AstraZeneca, Arg.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Prenorvine *Rafarm, Gr.*
⊗Buprenorphine hydrochloride (p. 30·3).

Prenoxad
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced respiratory depression; diagnosis of opioid overdose.

Prent *Gepepharm, Ger.†; Bayer, Ital.; Bayer, Port.; Bayer, Turk.*
⊗Acebutolol hydrochloride (p. 1289·2).
Hypertension; ischaemic heart disease; arrhythmias; angina pectoris.

Pre-Op *Nutricia, NZ.*
Preparation for pre-operative enteral nutrition.

PreOp *Nutricia, Austral.*
Preparation for enteral nutrition.
Pre-operative dietary management of surgical patients.

Preorbotic *MedChem, USA.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); inulin (p. 2534·3); glucomannan oligosaccharides.

Preotact *Nycomed, Austria; Nycomed, Cz.; Nycomed, Denm.†; Nycomed, Fr.†; Nycomed, Ger.; Nycomed, Gr.; Nycomed, Irl.; Nycomed, Ital.; Nycomed, Neth.; Nycomed, Norw.; Nycomed, Pol.; Nycomed, Port.; Nycomed, Spain; Nycomed, Swed.†; Nycomed, UK.*
Parathyroid hormone (recombinant) (p. 1188·3).
Osteoporosis.

Prep *Lennon, S.Afr.†*
Borax (p. 2459·2); menthol (p. 2553·2); thymol (p. 1772·2); camphor (p. 2466·2); clove oil (p. 2481·3); phenol (p. 1763·3).
Skin disorders; burns; insect bites; ulcers.

Prep Kit-C *Pharmatel, Austral.*
One sachet, macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1) (Glycoprep-C); two sachets, sodium picosulfate (p. 1887·2) (Picoprep).
Bowel evacuation.

Prepacol *Guerbet, Austria; Guerbet, Belg.; Guerbet, Cz.; Guerbet, Ger.*
Combination pack: Combination pack: Combination pack: Combination pack: 1 Tablet, bisacodyl (p. 1821·1); oral solution, dibasic sodium phosphate dodecahydrate (p. 1791·2); monobasic sodium phosphate dihydrate (p. 1791·1).
Bowel evacuation.

Prépacol *Guerbet, Fr.*
Combination pack: 4 Tablets, bisacodyl (p. 1821·1); oral solution, dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation.

Prepacort H *Wyeth Consumer, Ital.*
⊗Hydrocortisone acetate (p. 1640·1); benzocaine (p. 1980·2).
Haemorrhoids.

Prepadine *Berk, UK.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Prepagel *Frik, Turk.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Musculoskeletal and joint pain.

Prepandemic Influenza Vaccine *GSK, Irl.*
An inactivated influenza vaccine (H5N1) (split virion) (p. 2393·3).
Pandemic influenza prophylaxis.

Prepandrix *GSK, Cz.; GSK, Irl.; GSK, Neth.; GSK, Port.*
An influenza vaccine (H5N1) (split virion) (p. 2393·3).
Pandemic influenza prophylaxis.

Pre-Par *Eumedica, Belg.; IFET (ΙΦΕΤ), Gr.; Reig Jofre, Spain; Eczacibasi, Turk.*
⊗Ritodrine hydrochloride (p. 2145·1).
Premature labour; prevention of uterine contractions during surgery in pregnancy;

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

prevention of uterine hypermotility in labour; production of uterine relaxation; fetal asphyxia.

Preparacion H *Wyeth, Spain.†*
Yeast extract (p. 2125·2); shark-liver oil (p. 2614·2).
Haemorrhoids.

Preparation H
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Canad.; Pfizer, Cz.; Pfizer, Gr.; Wyeth, Gr.; Wyeth Consumer, Irl.†; Whitehall, Israel; Wyeth, Rus.†; SA Druggists Self Med, S.Afr.†; Wyeth Consumer, UK; Whitehall, USA.
Suppositories: Live yeast cell derivative (Bio-Dyne) (p. 2125·2); shark-liver oil (p. 2614·2).
Haemorrhoids.

Pfizer Consumer, Singapore.
Rectal ointment: Shark-liver oil (p. 2614·2); fish-liver oil; hydrolysed yeast (p. 2125·2).
Formerly contained phenylephrine hydrochloride and shark-liver oil.
Haemorrhoids.

Pfizer Consumer, Hong Kong; Wyeth Consumer, Mex.; Wyeth Consumer, Thai.†
Shark-liver oil (p. 2614·2); phenylephrine hydrochloride (p. 1672·3).
Haemorrhoids.

Pfizer Consumer, Singapore.
Rectal gel: Hamamelis (p. 2523·3).
Haemorrhoids.

Wyeth Consumer, USA.
Cream: ⊗Phenylephrine hydrochloride (p. 1672·3); pramocaine hydrochloride (p. 1993·3); glycerol (p. 2517·2).
Formerly contained shark-liver oil and phenylephrine hydrochloride.
Anorectal disorders.

Preparation H Clear Gel *Wyeth Consumer, UK.*
Hamamelis (p. 2523·3).
Haemorrhoids.

Preparation H Cooling Gel *Whitehall-Robins, USA.*
Hamamelis (p. 2523·3); phenylephrine hydrochloride (p. 1672·3).
Anorectal disorders.

Préparation H Veinotonic *Wyeth Sante, Fr.†*
Diosmin (p. 2505·2).
Haemorrhoids.

Preparation H-PE Gel *Pfizer Consumer, Canad.*
Hamamelis (p. 2523·3); phenylephrine hydrochloride (p. 1672·3).
Haemorrhoids.

Preparazione H
Note: this name may be used for preparations of different composition.
Wyeth Consumer, Ital.
Yeast cell extract (p. 2125·2); shark-liver oil (p. 2614·2).
Anorectal disorders.

Prepcat *Tyco, Canad.†; Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography; radiographic contrast medium.

Pre-Pen *Hollister-Stier, Canad.†*
Penicilloyl-polylysine (p. 2585·2).
Diagnosis of penicillin hypersensitivity.

Prepenem *Choongwae, China; Choongwae, Thai.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Choongwae, Hong Kong.
Imipenem (p. 309·2); cilastatin (p. 260·3).
Bacterial infections.

Prephen *Orion, NZ.†*
Substituted phenols.
Disinfection.

Prepidil *Pfizer, Austria; Pfizer, Belg.; Paladin, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Ger.; Pharmacia Upjohn, Gr.; Pfizer, Hung.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Spain; Pharmacia Upjohn, USA.*
Dinoprostone (p. 2134·1).
Labour induction.

Prepkit-C *Fresenius Kabi, NZ.*
1 Sachet, macrogol 3350 (p. 2547·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium sulfate (p. 1888·1)(Glycoprep-C); 2 sachets, sodium picosulfate (p. 1887·2) (Picoprep).
Bowel evacuation.

Prepodyne *West Penetone, Canad.†*
Poloxamer iodine complex.

Prepopik *Ferring, USA.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).
Bowel evacuation.

Prepram *Medix, Mex.*
Citalopram hydrobromide (p. 411·1).
Depression; post-traumatic stress disorder; panic disorder.

Prepulsid *Janssen-Cilag, Belg.†; Janssen-Cilag, Braz.; Xian-Janssen, China; Janssen-Cilag, Fr.†; Janssen-Cilag, Israel†; Janssen-Cilag, Neth.†; Janssen, Port.†; Janssen-Cilag, S.Afr.†; Janssen-Cilag, Singapore.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; impaired gastric motility; gastroparesis; dyspepsia; gastrointestinal motility disorders; regurgitation and vomiting in infants; gastro-oesophageal reflux in infants; upper-gastrointestinal discomfort.

PreQue 10 *Watson, USA.*
Vitamins; minerals; ubidecarenone (p. 2637·1); docosahexaenoic acid (p. 1460·1); lycopene (p. 2546·2).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Preran *Sanofi-Aventis, Jpn.*
Trandolapril (p. 1517·2).
Hypertension.

Preridon *Alapis, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Presartan *ICN, Pol.; Ipca, Rus.; Ipca, Ukr.; Giempi, Venez.*
Losartan potassium (p. 1422·2).
Heart failure; hypertension; diabetic nephropathy; cardiovascular risk reduction.

Presartan H *ICN, Pol.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prescaina *Llorens, Spain.*
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Prescal *Novartis, UK.†*
Isradipine (p. 1414·2).
Hypertension.

Preschol *Promed, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Presco *Polipharm, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Prescol *Atlantis, Mex.*
Trimebutine (p. 2634·1).
Gastrointestinal motility disorders.

Prescription Strength Desenex *Novartis Consumer, USA.†*
Topical spray: Miconazole nitrate (p. 589·1).
Fungal infections.

Prescriptives All You Need *Prescriptives, Canad.*
SPF 15 for drier skins: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Prescriptives, Canad.
SPF 15 for normal skins; SPF 15 for oiler skins: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1).
Sunscreen.

Prescriptives Anti-Age *Prescriptives, Canad.†*
SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Prescriptives Anywhere *Prescriptives, Canad.*
SPF 12; SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Prescriptives Flawless *Prescriptives, Canad.*
Liquid SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Prescriptives, Canad.
Powder SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Prescriptives Incredible *Prescriptives, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Prescriptives Site Unseen *Prescriptives, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Prescriptives Sunsheen *Prescriptives, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Prescriptives Virtually Fresh *Prescriptives, Canad.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Presdeten *Alter, Spain.†*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Pre-Seed *INGfertility, Singapore.*
Arabinogalactan.
Vaginal lubricant.

Presentil *Coup, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Presept *Johnson & Johnson Medical, UK.*
Troclosene sodium (p. 1774·1).
Instrument and surface disinfection.

Presera *Quinnova, USA.*
Emollient.
Dry skin.

Preserv Nonoxinol-9 *Blausiegel, Braz.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Préservation *Texinfine, Fr.*
Fig (p. 1843·2); maize oil (p. 2080·2).
Tonic.

Preservex *Movianto, UK.*
Aceclofenac (p. 16·2).
Musculoskeletal and joint disorders.

PreserVision *Bausch & Lomb, Singapore.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc oxide (p. 1729·1); cupric oxide; lutein (p. 2079·2).
Dietary supplement to promote healthy eyes.

Chauvin, Fr.
Fish oil (p. 1460·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc sulfate (p. 2126·2).
Dietary supplement; eye disorders.

Preservision *Bausch & Lomb, USA.*
Vitamins; minerals.
Formerly known as Ocuvite Preservision.

Preservision Eye Vitamin *Bausch & Lomb, USA.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); omega-3 (p. 1460·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); zinc (p. 2126·1); copper (p. 2057·1); fish oil (p. 1460·1).
Dietary supplement.

Preservision Lutein *Bausch & Lomb, USA.*
Vitamins; minerals; lutein (p. 2079·2).

Preservision Luteina *Bausch & Lomb, Ital.*
Vitamins; minerals; lutein (p. 2079·2).

Presi Regul *Fabra, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension.

Presi Regul D *Fabra, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Presid *Teva, Cz.; Teva, Hung.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

President's Choice Hand Sanitizer *Belvedere, Canad.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

President's Choice Sport Sunblock *Fruit of the Earth, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

President's Choice Sunblock *Fruit of the Earth, Canad.*
Lotion SPF 30: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Fruit of the Earth, Canad.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Fruit of the Earth, Canad.
Spray SPF 30: Diolamine methoxycinnamate (p. 1700·2); octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

President's Choice Sunblock for Babies *Fruit of the Earth, Canad.*
SPF 45: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

President's Choice Sunblock for Children *Fruit of the Earth, Canad.*
SPF 30: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

President's Choice Sunless Tanning Cream *Fruit of the Earth, Canad.*
SPF 15: Octocrilene (p. 1715·2); octinoxate (p. 1715·1).
Sunscreen.

President's Choice Sunscreen *Fruit of the Earth, Canad.*
SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Presilam *Pasteur, Chile.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Presinex *Pfizer, Arg.; Fariberica, Port.; Ferring, Rus.; Pliva, UK.†*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; polyuria; polydipsia; nocturnal enuresis; test of renal concentrating capacity; haemophilia A.

Presinol *Teofarma, Ger.*
Tablets: Methyldopa (p. 1431·1).
Hypertension.

Presinor *Lafedar, Arg.*
Losartan potassium (p. 1422·2).
Hypertension.

Presinor D *Lafedar, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Presistin *Maver, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; gastro-oesophageal reflux.

Přesličkа *Leros, Cz.†*
Equisetum (p. 2500·1).
Urinary-tract disorders; wounds.

Přesličková *Megafyt-R, Cz.†*
Equisetum (p. 2500·1).
Urinary-tract disorders; wounds.

Preslopin *Raam, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Preslow *AstraZeneca, Port.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Presmin *Latinofarma, Braz.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma.

Preso *Soho, Indon.†*
St John's wort (p. 449·1).
Depression.

Presocor *Rider, Chile.†*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Presoga *Utopian, Thai.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Presokin *Chemopharma, Chile.†*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Presolar *Cipla, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Presolin *Unison, Thai.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Presolol *Alphapharm, Austral.; LCH, Hong Kong.†*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Presomen *Abbott, Ger.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Presomen Compositum *Abbott, Ger.*
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, medrogestone (p. 2287·3); conjugated oestrogens.
Menopausal disorders; osteoporosis.

Presomen conti *Abbott, Ger.*
Conjugated oestrogens (p. 2260·1); medrogestone (p. 2287·3).
Menopausal disorders; osteoporosis.

Presone-1 *Liomont, Mex.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Presoquin *Dollder, Venez.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; arrhythmias; hypertension.

Presovasc *Pharmavita, Chile.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Prespir *Remexa, Mex.*
Aluminium chloride (p. 1693·3); triclosan (p. 1773·2); hamamelis (p. 2523·3).
Hyperhidrosis.

Press-12 *Genepharm, Gr.; PannonPharma, Hung.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Press Plus *Biolab Sanus, Braz.*
Amlodipine (p. 1304·1); benazepril (p. 1314·3).

Pressac *Damor, Ital.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Pressamea *Verisfield, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Pressat *Biolab Sanus, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Press-Down *Veltipharm, Gr.*
Losartan potassium (p. 1422·2).

Press-Down-Plus *Veltipharm, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Pressel *Legrand, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Presselin All *Combustin, Ger.*
⊗Acidum formicicum (p. 2507·1); aralia racemosa; acid. arsenicosum (p. 2448·1); cuprum aceticum (p. 2486·2); lobelia inflata (p. 2323·2).
Homoeopathic preparation.

Presselin Nervenkomplex *Combustin, Ger.*
Acidum phosphor. (p. 2589·1); acidum picrinicum (p. 2634·2); ambra grisea (p. 2440·3); zincum aceticum (p. 2126·1); zincum phosphor. (p. 2126·1); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Presselin Nervennahrung N *Combustin, Ger.†*
Zincum aceticum (p. 2126·1); zincum phosphoricum (p. 2126·1); zincum valerianicum (p. 2641·2); acid. phosphoricum (p. 2589·1); acid. picrinicum (p. 2634·2); ambra grisea (p. 2440·3).
Homoeopathic preparation.

Pressicaine *Dentsply, Fr.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Pressicaine N *Dentsply, Fr.†*
Lidocaine hydrochloride (p. 1988·2). Noradrenaline acid tartrate (p. 1458·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Pressil *Farbio, Port.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Pressin *Alphapharm, Austral.†; Utopian, Thai.*
Prazosin hydrochloride (p. 1473·3).
Hypertension; Raynaud's syndrome; benign prostatic hyperplasia; heart failure.

Pressitan *Iquinosa, Spain.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Pressitan Plus *Iquinosa, Spain.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pressodipin *Genepharm, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Pressolat *Bayer, Israel.*
Nifedipine (p. 1447·2).
Hypertension.

Pressomax *Kinder, Braz.†*
Captopril (p. 1331·2).
Hypertension.

Pressotec *Teuto, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Pressural *Polifarma, Ital.*
⊗Indapamide (p. 1409·2).
Hypertension.

Pressuril *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Pressyn *Ferring, Canad.*
⊗Vasopressin (p. 2642·3).
Postoperative abdominal distension; adjunct in abdominal radiography; diabetes insipidus.

Prestance *Servier, Cz.; Servier, Rus.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Prestarium *Europharma, Denm.; Servier, Pol.; Servier, Rus.; Servier, Ukr.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; cardiovascular risk reduction; stroke prophylaxis.

Servier, Cz.
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Prestarium Combi *Servier, Cz.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Servier, Ukr.
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Prestarium Neo *Servier, Cz.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure; cardiovascular risk reduction.

Prestarium Neo Combi *Servier, Cz.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Prestarium Plus *Servier, Pol.†*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Presterin *Roux-Ocefa, Arg.*
Pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); calcium carbonate (p. 1824·3).
Nausea and vomiting in pregnancy; vitamin and mineral supplement.

Prestige *Alvear, Arg.*
Test for glucose in blood (p. 2516·3).

Prestige Light Response *Prestige, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Prestim *Meda, Irl.; ICN, UK.*
⊗Timolol maleate (p. 1513·2); bendroflumethiazide (p. 1315·2).
Hypertension.

Prestodol *Rayere, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Prestodol Compuesto *Rayere, Mex.*
Clonixin lysine (p. 40·1); hyoscine butylbromide (p. 1845·3).
Smooth muscle pain.

Prestoflam *Rayere, Mex.*
Clonixin lysine (p. 40·1); diclofenac sodium (p. 48·3).
Pain; inflammation.

Prestole *Almirall, Fr.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prestrenol *Interbat, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Prestylon *Teva, UK.*
Omega-3-acid ethyl esters (p. 1460·2).
Hyperlipidaemias; cardiovascular risk reduction.

Presumin *Gedeon Richter, Hung.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Presun *Westwood, USA.*
Cream SPF 15; SPF 8; SPF 39: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Presun Active *Bristol-Myers Products, USA.*
SPF 15; SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Presun Facial *Westwood, USA.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Presun for Kids *Bristol-Myers Products, USA; Westwood, USA.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Presun Lip Stick *Westwood, USA.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Presun Moisturizing *Bristol-Myers Products, USA.*
SPF 46: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Presun Moisturizing with Keri *Bristol-Myers Products, USA.*
SPF 25: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Bristol-Myers Products, USA.
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Presun Sensitive Skin *Bristol-Myers Products, USA; Westwood, USA.*
SPF 15; SPF 29: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Presun Spray Mist *Bristol-Myers Products, USA.*
SPF 23: Octinoxate (p. 1715·1); padimate O (p. 1716·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Presun Ultra *Westwood-Squibb, USA.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Presyc *Pasteur, Chile.*
Capsaicin (p. 35·1).
Diabetic neuropathy; musculoskeletal and joint pain; postherpetic neuralgia; pruritus; phantom-limb pain.

Pretal *Jaapharm, Canad.†*
Vitamins; minerals.

Pretanix *Servier, Hung.*
⊗Indapamide (p. 1409·2).
Hypertension.

Pretanix Komb *Anpharm, Hung.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Pretenol *Duopharma, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Pretenol C *CCM, Malaysia; Duopharma, Singapore.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Preterax *Servier, Arg.; Servier, Austria; Servier, Belg.; Servier, Canad.†; Servier, Gr.; Servier, Mex.; Servier, Neth.; Servier, Philipp.; Servier, Port.; Servier, S.Afr.; Servier, Singapore†; Servier, Spain; Servier, Switz.†; Servier, Turk.; Servier, Venez.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Servier, Fr.; Servier, Ger.; Servier, Irl.; Servier, Ital.
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Preterian *Servier, Neth.*
⊗Indapamide (p. 1409·2); perindopril arginine (p. 1466·3).
Hypertension.

Pretifen *Unipharm, Mex.*
Ketotifen (p. 631·3).
Asthma.

Pretilon *Sandoz, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Pretts Diet Aid *Milance, USA.*
Alginic acid (p. 2167·2); carmellose sodium (p. 2175·2); sodium bicarbonate (p. 1781·1).

Pretuval *Bayer, Switz.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms; cough.

Pretuval C *Bayer, Switz.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; cough.

Pretz
Note: this name may be used for preparations of different composition.
Parnell, USA.
Sodium chloride (p. 1795·1).
Inflammation and dryness of nasal membranes.

Parnell, Irl.†
Moisturising nasal spray.
Nasal dryness.

Prevacid *Takeda, Canad.; Takeda, China; IFET (ΙΦΕΤ), Gr.; Takeda, Jpn†; Takeda, Malaysia; Takeda, Philipp.; Takeda, Singapore; Takeda, Thai.; Takeda, USA.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; Helicobacter pylori eradication; dyspepsia.

Prevacid NapraPAC *TAP, USA.†*
Naproxen (p. 98·2).
Lansoprazole (p. 1851·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Prevage
Note: this name may be used for preparations of different composition.
Allergan, USA.
Idebenone (p. 392·3).
Skin wrinkles.

Arden, Canad.
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Prevahist *Nabros, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Prevalin *Omega, UK.*
Impermeable microgel nasal barrier.
Allergic rhinitis.

Interdelta, Switz.
Bentonite (p. 2170·3); xanthan gum (p. 2220·1); sesame oil (p. 2614·1); peppermint oil (p. 1877·1).
Allergic rhinitis.

Omega, Neth.
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Prevalin Allerstop *Omega, Neth.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Prevalina *Andromaco, Chile.*
Mianserin hydrochloride (p. 434·2).
Depression.

Prevalite *Upsher-Smith, USA.*
Colestyramine (p. 1346·1).

Prevas *Soho, Indon.†*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis.

Prevasal *Remedina, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Prevax *Biosintetica, Braz.*
Calcium folinate (p. 2066·3).

Prevefem Complex *Rimsa, Mex.*
Soya (p. 2092·3); calcium saccharate (p. 2172·3); alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); vitamin A palmitate (p. 2098·3).
Menopausal disorders.

Prevegyne *Duchesnay, Canad.; Theramex, Mon.*
Ascorbic acid (p. 2110·3).
Bacterial vaginosis; restoration of vaginal flora.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Preven *Biomeks, Turk.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Postcoital oral contraceptive.

Prevenar *Wyeth, Arg.; Pfizer, Austral.; Wyeth Lederle, Austria; Pfizer, Belg.; Wyeth, Chile; Pfizer, China; Wyeth Lederle, Cz.; Wyeth, Denm.; Pfizer, Fin.; Wyeth, Fr.†; Wyeth, Ger.; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth Lederle, Hung.; Wyeth, Indon.; Wyeth, Irl.; Neopharm, Israel; Wyeth Lederle, Ital.; Pfizer, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Wyeth, Norw.†; Pfizer, NZ; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Rus.; Pfizer, S. Afr.; Pfizer, Singapore†; Pfizer, Spain; Wyeth, Swed.; Pfizer, Switz.†; Wyeth, Turk.; Wyeth, UK; Wyeth, Venez.*
A pneumococcal conjugate vaccine (7-valent) (p. 2410·1).
Active immunisation.

Prevenar 13 *Pfizer, Austral.; Wyeth Lederle, Austria; Wyeth, Chile; Pfizer, Fr.; Wyeth Lederle, Hung.; Wyeth, Israel; Pfizer, Neth.; Pfizer, Norw.; Wyeth Lederle, Pol.; Wyeth Lederle, Port.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Ukr.*
A pneumococcal conjugate vaccine (13-valent) (p. 2410·1).
Active immunisation.

Prevencor
Note: this name may be used for preparations of different composition.
Medley, Braz.
Aspirin (p. 22·2); simvastatin (p. 1489·2).
Atherosclerosis.

Paranova, Denm.; Euro Registratie, Neth.†; Stephar, Neth.†; Pfizer, Spain.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Prevent *Agropharm, UK.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Insect repellent.

Prevent X *Jedmon, Canad.†*
Alkyldimethylethylbenzyl ammonium chloride (p. 1736·2); benzalkonium chloride (p. 1737·1).
Skin disinfection.

Preventex *Aromapharm, Irl.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Preventor *Sant Gall, Arg.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Preventus *Yalacta, Fr.*
Organ extracts.
Tonic.

Prevepen *Grunenthal, Chile.†*
Clemizole penicillin (p. 269·2).
Bacterial infections.

Prevepen Forte *Grunenthal, Chile.*
Benzylpenicillin sodium (p. 228·2); clemizole penicillin (p. 269·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Preveral con Codeina *Vargas, Venez.*
Promethazine hydrochloride (p. 638·2); codeine phosphate (p. 40·2).
Cough and cold symptoms; allergic rhinitis.

Preveral con Dextrometorfano *Vargas, Venez.*
Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms; allergic rhinitis.

Prevex
Note: this name may be used for preparations of different composition.
Simesa, Ital.
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Stiefel, Canad.
Cream: Yellow soft paraffin (p. 2212·1).
Barrier cream.

Stiefel, Thai.†
Barrier gel.

Trans Canaderm, Canad.†
Lotion: Moisturiser.

Prevex B *Stiefel, Canad.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Prevex HC *Stiefel, Canad.; Stiefel, Thai.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Previane *Legrand, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Previdент *Colgate Oral, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Previdez-2 *EMS, Braz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Previfect *Novartis Consumer, Neth.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Previfem *Qualitest, USA.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Prévigrip *Novartis Vaccines, Fr.†*
Inactivated influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Previnfec *Lafedar, Arg.*
Chloroxylenol (p. 1748·2); terpineol (p. 2627·2); ammonium dodecylsulfonate.
Disinfection.

Previscan
Note: this name may be used for preparations of different composition.
Investi, Arg.
Pentoxifylline (p. 1465·3).
Intermittent claudication.

Préviscan *Merck Serono, Fr.*
Fluindione (p. 1385·1).
Thromboembolic disorders.

Previta *Sofex, Port.*
Ticlopidine hydrochloride (p. 1512·1).

Prevnar *Pfizer, Canad.; Pfizer, Thai.†; Pfizer, USA.*
A pneumococcal conjugate vaccine (7-valent) (p. 2410·1).
Active immunisation.

Prevnar 13 *Pfizer, Canad.; Pfizer, Thai.*
A pneumococcal conjugate vaccine (13-valent) (p. 2410·1).
Active immunisation.

Prevolac *Cosmopharm, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Prevora 1 *CHX, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Dental root caries.

Prevora Stage 1 *CHX, Irl.*
Chlorhexidine acetate (p. 1743·2).
Dental caries.

Prevpac *Takeda, USA.*
Capsules, lansoprazole (Prevacid) (p. 1851·3); capsules, amoxicillin trihydrate (Trimox) (p. 216·2); tablets, clarithromycin (Biaxin) (p. 266·2).
Duodenal ulcer associated with Helicobacter pylori *infection.*

Prevyol *Legrand, Braz.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Pre-Wax *Product Excellence, Canad.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Prexan *New Research, Ital.*
Naproxen (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgias.

Prexanil *Servier, Cz.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Prexat *ITF, Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Prexaton *Alphapharm, Austral.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Prexidine *Expanscience, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Mouth infections.

Prexige *Novartis, Arg.; Novartis, Austria†; Novartis, Braz.; Novartis, Chile†; Novartis, Gr.; Novartis, Hung.†; Novartis, Indon.†; Novartis, NZ†; Novartis, Swed.†; Novartis, Turk.*
Lumiracoxib (p. 84·1).
Osteoarthritis; pain; rheumatoid arthritis.

Prexon *YSS, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Prexulid *Cifarma, Braz.*
Nimesulide (p. 101·3).

Prexum *Sermedica, Port.†; Biogaran, S.Afr.*
Perindopril erbumine (p. 1467·1).
Heart failure; hypertension; cardiovascular risk reduction; myocardial infarction.

Servier, Indon.†
Perindopril (p. 1466·3).
Hypertension; heart failure; stroke prophylaxis.

Prexum Plus *Biogaran, S.Afr.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Prezal *Sanofi-Aventis, Neth.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Prezista *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, UK; Janssen, USA.*
Darunavir ethanolate (p. 971·2).
HIV infection.

Janssen-Cilag, Arg.; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Gr.; Janssen-Cilag, Malaysia; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Johnson & Johnson, Turk.
Darunavir (p. 971·2).
HIV infection.

Prezolon *Nycomed, Gr.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Priacin *Medochemie, Gr.; Medochemie, Singapore.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Priadel *Sanofi-Aventis, Belg.; Petsiavas, Gr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Bamford, NZ; Sanofi-Aventis, Port.; Sanofi-Aventis, Switz.; Sanofi, UK.*
Lithium carbonate (p. 427·3).
Bipolar disorder; mania; depression; hypomania; aggressive or self-harming behaviour.

Prialt *Eisai, Austria; Eisai, Cz.; Eisai, Denm.; Eisai, Fr.; Eisai, Ger.; Eisai, Gr.; Eisai, Hung.; Eisai, Irl.; Eisai, Ital.; Eisai, Neth.; Eisai, Norw.†; Eisai, Pol.; Eisai, Port.; Eisai, Spain; Eisai, Swed.; Eisai, Switz.; Eisai, UK; Azur, USA.*
Ziconotide acetate (p. 142·2).
Pain.

Prialta *OEP, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Prialta-Met *OEP, Philipp.*
Pioglitazone hydrochloride (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Pribac *Liferpal, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pribercor *Ranbaxy, Hung.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Pricam *Mintlab, Chile.*
Piroxicam (p. 125·3).
Inflammation; pain.

Pricefil *Vianex (Biuvex), Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Priciasol *Labima, Belg.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Pricital *Lavipharm, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression; panic disorder.

Prickly Heat Powder *Church & Dwight, Austral.*
Zinc oxide (p. 1729·1).
Prickly heat; heat rash; chafed skin; eczema.

Pricoron *Zentiva, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Pridam *Pisa, Mex.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension.

Pridamiral Pack *Almirall, Mex.*
Cinitapride (p. 1831·3); omeprazole (p. 1867·2).

Pridana *Novartis, Port.*
Pirisudanol maleate (p. 2592·2).
Mental function disorders.

Pridax *Gebro, Austria; Pharmore, Ger.*
Alprostadil (p. 2352·2).
Peripheral arterial disease.

Pridecil *Chiesi, Braz.*
Bromopride (p. 1824·2).
Nausea and vomiting.

Pridesia *Sanbe, Indon.*
Cisapride (p. 1831·3).
Gastrointestinal disorders.

Pri-De-Sid *Polipharm, Thai.*
Cisapride (p. 1831·3).
Dyspepsia; gastroparesis; gastro-oesophageal reflux; gastrointestinal motility disorders.

Pridio *Quimifar, Spain.†*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); salicylamide (p. 129·2).
Fever; nasal congestion; pain.

Prifec *Indeco, Arg.*
Diclofenac (p. 48·3); pridinol (p. 2026·1).

Prifen *Soho, Indon.†*
Ibuprofen (p. 68·2).
Osteoarthritis; rheumatoid arthritis; pain; fever.

Priftin *Hoechst Marion Roussel, USA.*
Rifapentine (p. 355·1).
Tuberculosis.

Priglide *Menarini, Fin.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Prigost *Rider, Chile.*
Bromocriptine mesilate (p. 895·3).
Hyperprolactinaemia; parkinsonism.

Prikap *Elea, Arg.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism; carbon monoxide poisoning; manganese poisoning.

Prilace
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Ramipril (p. 1483·3).
Heart failure; hypertension; diabetic nephropathy; cardiovascular risk reduction.

Farma, Venez.
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; asymptomatic left-ventricular dysfunction.

Sanofi-Aventis, Ital.
⊗Ramipril (p. 1483·3); piretanide (p. 1470·3).
Hypertension.

Prilagin *Sofar, Ital.*
Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Candidiasis; Gram-positive bacterial infections.

Prilamil *Decomed, Port.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; nephropathy; cardiovascular risk reduction.

Prilan *Sofex, Port.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Prilanil *KRKA, Neth.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Prilarem *Iliafarm, Gr.*
Amisulpride (p. 1036·3).

Prilben *Richmond, Arg.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease; mental function impairment; spasticity.

Prilcor *Sigma, Braz.*
Lisinopril (p. 1420·3).
Hypertension.

Prilenap *Hemofarm, Rus.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prilenor *Mediolanum, Ital.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Priligy *Janssen-Cilag, Austria; Janssen-Cilag, Fin.; Janssen-Cilag, Ger.; Janssen-Cilag, Irl.; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Menarini, Neth.; Janssen-Cilag,*

NZ; Janssen-Cilag, Port.; Janssen-Cilag, Singapore; Menarini, Spain; Janssen-Cilag, Swed.; Menarini, UK.
Dapoxetine hydrochloride (p. 2354·2).
Premature ejaculation.

Prilitab-HCT *Tiefenbacher, Neth.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prilitaril-HCT *Egis, Neth.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prilkenzide *Kendrick, Mex.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Prillana *KRKA, Denm.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Prilos *Pyridam, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Prilosec *AstraZeneca, USA.*
Omeprazole (p. 1867·2) or omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; heartburn.

Prilotekal *Goldshield, UK.*
Prilocaine hydrochloride (p. 1994·1).
Spinal anaesthesia.

Prilotrand *Generics, Denm.*
Trandolapril (p. 1517·2).
Hypertension; left ventricular dysfunction following myocardial infarction.

Prilovase *Pentafarma, Port.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Prilpa *Teva, Port.*
⊗Indapamide (p. 1409·2); perindopril erbumine (p. 1467·1).
Hypertension.

Prilpressin *Legrand, Braz.*
Captopril (p. 1331·2).
Hypertension.

Priltenk *Biotenk, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; myocardial infarction; atherosclerosis.

Prim E *Mega Lifesciences, Malaysia.*
Evening primrose oil (p. 2502·2); vitamin E (p. 2119·1).
Premenstrual syndrome; skin disorders.

Primabion *Sandoz, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuropathy; peripheral circulatory disorders; vomiting of pregnancy; migraine; asthenia.

Primacaine *Pierre Rolland, Fr.*
Articaine hydrochloride (p. 1980·1). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Primacaine Adrenaline *Pierre Rolland, China; Pierre Rolland, Rus.*
Articaine hydrochloride (p. 1980·1). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Prima-Cal *Nupharma, Thai.*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Prima-Cal Plus Vit D *Nupharma, Thai.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium and vitamin D supplement.

Primace *Pascual, Philipp.*
Captopril (p. 1331·2).
Hypertension.

Primacef *Bergamo, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

Primacillin *Medikon, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Primacin *Boucher & Muir, Austral.*
Primaquine phosphate (p. 660·2).
Malaria.

Primacine *Pinewood, Irl.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Primacip *Cipla, India.*
Primaquine phosphate (p. 660·2).
Malaria.

Primacor *Sanofi-Aventis, Austral.; Sanofi-Aventis, Braz.; Sanofi, China; Sanofi-Aventis, Hong Kong; Sanofi Winthrop, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, NZ; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Sanofi Synthelabo, UK; Sanofi Winthrop, USA.†*
Milrinone lactate (p. 1438·1).
Heart failure.

Primacort *Sel-J, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Primactam *Meditrina, Gr.*
Tolfenamic acid (p. 138·3).
Inflammatory disorders.

Primacton *Streuli, Switz.†*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; cirrhosis with ascites; nephrotic syndrome; hyperaldosteronism.

PrimaDerm *Metanoia, Fr.*
Barrier preparation.

Primaderm
Note: this name may be used for preparations of different composition.
Farmachimici, Ital.
Barrier cream.
Roi Surya, Indon.†
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Primadex *Dexa, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Primadol *Soho, Indon.*
Paracetamol (p. 115·1); metoclopramide hydrochloride (p. 1862·2).
Fever; migraine; pain.

Primadrill *Pierre Fabre Sante, Fr.†*
Althaea (p. 2438·3).
Mouth and throat disorders.

Primadryl Plus *Sandoz, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Prima-E *Sandoz, Indon.*
d-Alpha tocopherol (p. 2119·1).
Antoxidant.

Primagal *Demo, Gr.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Primakinder *Kinder, Braz.†*
Primaquine phosphate (p. 660·2).
Malaria.

Primalan *Rovafarm, Arg.; Pierre Fabre, Fr.; Pierre Fabre, Mex.; Natrapharm, Philipp.; Pierre Fabre, Port.; Pierre Fabre, Rus.*
Mequitazine (p. 635·2).
Hypersensitivity reactions; pruritus; allergic rhinitis; urticaria; allergic conjunctivitis; atopic eczema.

Primalix *Demo, Gr.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Primamet *Lek, Cz.†*
Cimetidine (p. 1827·1) or cimetidine hydrochloride (p. 1827·1).
Gastrointestinal haemorrhage; peptic ulcer; acid aspiration; Zollinger-Ellison syndrome; gastro-oesophageal reflux; dyspepsia; gastric hyperacidity; acute pancreatitis.

Primanol Borage Oil *Jamieson, Canad.†*
Evening primrose oil (p. 2502·2); borage oil (p. 2459·2).

Primaquin *Gynopharm, Chile.*
Estradiol (p. 2271·1).
Menopausal disorders.

Primaquin MP *Gynopharm, Chile.†*
18 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Primaquin MP Continuo *Gynopharm, Chile.†*
Estradiol (p. 2271·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Primarocin *Genepharm, Gr.*
Codergocrine mesilate (p. 389·2).

Primasef *Nevzat, Turk.†*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Primasept Med *Schulke & Mayr, Singapore.*
Propyl alcohol (p. 1768·1); isopropyl alcohol (p. 1758·3); orthophenylphenol (p. 1762·3).
Hand disinfection.

Primaspan *Orion, Fin.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Primastick *Omega, Fr.†*
Pregnancy test (p. 2596·1).

Primatam *Sandoz, Indon.*
Piracetam (p. 393·3).
Mental function impairment; chronic alcoholism; cerebral trauma.

Primatene *Pfizer Consumer, USA.*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Asthma.

Primatene Mist *Wyeth Consumer, USA.†*
⊗Adrenaline (p. 1292·1).
Bronchial asthma.

Primatene Mist Suspension *Wyeth Consumer, USA.†*
⊗Adrenaline acid tartrate (p. 1292·2).
Bronchial asthma.

Primatour *Meda, Neth.*
Chlorcyclizine hydrochloride (p. 620·2); cinnarizine (p. 622·1).
Motion sickness.

Primatuss Cough Mixture 4 *Rugby, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Primatuss Cough Mixture 4D *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Primavent *Boehringer Ingelheim, Philipp.*
⊗Budesonide (p. 1625·1).
Asthma.

Primavera-N *Fabra, Arg.*
Metoclopramide hydrochloride (p. 1862·2).
Dyspepsia; nausea and vomiting.

Primax
Note: this name may be used for preparations of different composition.
Ashford, Singapore.
Proxymetacaine (p. 1995·3).
Local anaesthetic.
Elder, Philipp.
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; prostatic cancer; breast cancer.

Primaxin *MSD, Austral.; Merck Frosst, Canad.; Vianex (Βιανεξ), Gr.; MSD, NZ; MSD, UK; Merck, USA.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Primazole *Kalbe, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Primbactam *Menarini, Ital.*
Aztreonam (p. 224·1).
Gram-negative bacterial infections.

Primcillin *Meda, Denm.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Prime *Muscle Marketing, Canad.†*
Cyanocobalamin (p. 2107·2).

Prime Source *Gojo, Canad.*
Triclosan (p. 1773·2).
Skin disinfection.

Prime Source with Chloroxylenol *Gojo, Canad.*
Chloroxylenol (p. 1748·2).
Skin disinfection.

Primene *Baxter, Arg.; Baxter, Austral.; Baxter, Austria; Clintec, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Gr.; Kalbe, Indon.; Baxter, Irl.; Baxter, Israel; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Clintec, Spain; Eczacibasi-Baxter, Turk.; Baxter, UK.*
Amino acids.
Parenteral nutrition in neonates and children.

Primène *Baxter, Fr.*
Amino acids.
Parenteral nutrition in neonates and infants.

Prime-ORS *Healthprime, Philipp.*
Electrolytes (p. 1775·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration; diarrhoea.

Primera *Eurofarma, Braz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Primeral
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Braz.
⊗Bromopride (p. 1824·2); dimeticone (p. 1886·2); pepsin (p. 2586·1); α-amylase (p. 2442·1); lipase (p. 2579·3).
Nausea and vomiting; digestive disorders.

Primeravinte *Eurofarma, Braz.†*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Primesin *Novartis, Ital.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia.

Primid *Apsen, Braz.*
Primidone (p. 547·1).
Epilepsy; essential tremor.

Primil *Francia, Ital.†*
Magnesium (p. 1786·3); potassium (p. 1793·1); vitamins.
Nutritional supplement.

Primiprost *AstraZeneca, India.*
Dinoprostone (p. 2134·1).
Labour induction.

Primlev *Akrimax, USA.*
⊗Paracetamol (p. 115·1); oxycodone hydrochloride (p. 113·1).
Formerly known as Primalev.
Pain.

Primobolan *Bayer, Mex.; Bayer Schering, S.Afr.*
⊗Metenolone acetate (p. 2291·2) or metenolone enantate (p. 2291·2).
Anabolic; aplastic anaemia.
Schering, Austral.†; Panagakis, Gr.; Schering, Turk.
⊗Metenolone enantate (p. 2291·2).
Anabolic; breast cancer; aplastic anaemia; osteoporosis.

Primobolan Depot *Bayer, Spain.*
⊗Metenolone enantate (p. 2291·2).
Anabolic.

Primocef *Julphar, UAE.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Primocid *Genepharm, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Primodian Depot *Schering, S.Afr.†; Bayer Schering, Thai.†*
⊗Estradiol valerate (p. 2271·2); testosterone enantate (p. 2305·1).
Menopausal disorders; osteoporosis.

Primodium *Ikapharmindo, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.
Janssen-Cilag, Swed.
Loperamide oxide (p. 1854·2).
Diarrhoea.

Primofénac *Streuli, Switz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Primogyn *Bayer, Mex.*
Estradiol valerate (p. 2271·2).
Amenorrhoea; uterine hypoplasia; oestrogen deficiency; menorrhagia; menopausal disorders; osteoporosis.

Primogyn Depot *Schering, Austral.†; Schering, S.Afr.†*
Estradiol valerate (p. 2271·2).
Amenorrhoea; oestrogen deficiency; menorrhagia; uterine hypoplasia; dysfunctional uterine bleeding.

Primogyna *Bayer, Braz.*
Estradiol valerate (p. 2271·2).
Menopausal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Primolin *Tribest, S.Afr.†*
Evening primrose oil (p. 2502·2).
Dietary supplement.

Primolut Depot *Bayer, Mex.*
Hydroxyprogesterone caproate (p. 2285·1).
Recurrent miscarriage; female infertility; amenorrhoea; uterine hypoplasia.

Primolut N *Bayer, Austral.; Bayer Schering, Fin.; Schering, Hong Kong†; German Remedies, India; Bayer Schering, Indon.; Bayer, Irl.; Bayer Schering, Malaysia†; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Schering, UK.*
Norethisterone (p. 2294·2).
Menorrhagia; menstrual disorders; endometriosis; benign breast disorders; adjunct to oestrogen replacement therapy; dysfunctional uterine bleeding; mastopathy; postponement of menstruation; amenorrhoea; premenstrual syndrome; menopausal disorders; progestogen-only oral contraceptive; malignant neoplasms.

Primolut-Nor *Bayer, Arg.; Bayer, Belg.; Bayer, Braz.; Schering, Chile†; Bayer Schering, Fin.; Bayer, Ger.†; Bayer, Gr.; Schering, Israel; Bayer, Ital.; Bayer, Mex.; Bayer Schering, Pol.; Bayer, Port.; Schering, Rus.†; Bayer, Spain; Bayer, Swed.; Bayer, Ukr.*
Norethisterone acetate (p. 2294·3).
Dysfunctional uterine bleeding; endometriosis; menstrual disorders; amenorrhoea; progestogen-only oral contraceptive; hormone replacement therapy; breast or endometrial cancer; female infertility; uterine hypoplasia; mastopathy; mastalgia; postponement of menstruation; benign breast disorders.

Primoly *General Drugs, Thai.*
Pramocaine hydrochloride (p. 1993·3).
Skin irritation; burns; pruritus; insect bites.

Primoniat Depot *Bayer, Chile.*
⊗Testosterone propionate (p. 2305·2); testosterone enantate (p. 2305·1).
Some injections contain only testosterone enantate.
Aplastic anaemia; breast cancer; male hypogonadism.

Primonil *Teva, Israel.†*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Primordiale *Lancome, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Primoris *Herbarium, Braz.†*
Borage oil (p. 2459·2); wheat-germ oil (p. 2647·1); evening primrose oil (p. 2502·2).

Primorix *Medipharm, Chile.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Primosiston
Note: this name may be used for preparations of different composition.
Bayer, Arg.
Injection: Hydroxyprogesterone caproate (p. 2285·1); estradiol benzoate (p. 2271·1).
Dysfunctional uterine bleeding.
Bayer, Arg.; Bayer, Austria; Bayer, Braz.; Bayer, Chile; Bayer, Switz.†
Tablets: Norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3).
Dysfunctional uterine bleeding; menstrual disorders; menorrhagia; polymenorrhoea.

Primoson-F *Sons, Mex.*
Progesterone (p. 2300·2); estradiol benzoate (p. 2271·1).
Menstrual disorders.

Primostat *Bayer, Mex.*
Gestonorone caproate (p. 2280·1).
Benign prostatic hyperplasia; endometrial cancer.

Primoteston Depot *Bayer, Austral.; Bayer, Mex.; Schering, NZ.†*
⊗Testosterone enantate (p. 2305·1).
Testosterone deficiency in men; hypogonadism in males; aplastic anaemia; breast cancer.

Primotox *Vitae, Mex.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Primotren *Lek, Cz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Primovist *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer, China; Bayer Schering, Cz.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer, Irl.; Bayer, Ital.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, Port.; Bayer Schering, Rus.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Turk.; Bayer, UK.*
Sodium gadoxetate (p. 1588·1).
Contrast medium for magnetic resonance imaging of the liver.

Primovit *Wharton, Philipp.*
Vitamins; minerals.
Dietary supplement.

Primoxil
Note: this name may be used for preparations of different composition.
Sandoz, Indon.†
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Primperan *Sanofi-Aventis, Belg.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Gr.; Astellas, Jpn; Sanofi-Aventis, Neth.; Sanofi-Aventis, Swed.; Biofarma, Turk.*
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Gaastrointestinal motility disorders; nausea and vomiting; aid in gastrointestinal examination; gastro-oesophageal reflux.
Sanofi-Aventis, Hong Kong; Delagrange, Indon.; Soho, Indon.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.†; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Berk, UK; Sanofi-Aventis, Venez.
Metoclopramide hydrochloride (p. 1862·2).
Migraine; nausea; vomiting; gastrointestinal motility disorders; aid in gastrointestinal examination; gastroparesis; gastro-oesophageal reflux; dyspepsia.

Primpéran *Sanofi-Aventis, Fr.; Sanofi-Aventis, Switz.*
Metoclopramide (p. 1862·2) or metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal disorders.

Primperan Compositum *Delagrange, Indon.; Soho, Indon.*
⊗Metoclopramide hydrochloride (p. 1862·2); pancreatin (p. 2579·3).
Gastrointestinal disorders.

Primperil *Lafedar, Arg.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Primpesasy *Sanofi Synthelabo, Mex.†*
Metoclopramide hydrochloride (p. 1862·2); dimeticone (p. 1886·2).
Oesophagitis; hiatus hernia; gastritis; peptic ulcer; aid to gastrointestinal examination; nausea and vomiting.

Primrose Micelle *Bioglan, Austral.†*
Evening primrose oil (p. 2502·2).
Eczema; mastalgia.

Primrose-E *Bioglan, Austral.†*
Evening primrose oil (p. 2502·2); *d*-alpha tocopherol (p. 2119·1).
Premenstrual syndrome.

Primsoja *Gayoso, Spain.†*
Soya (p. 2092·3).
Menopausal disorders.

Primsol *FSC, Hong Kong; Ascent, USA.*
Trimethoprim hydrochloride (p. 381·2).
Otitis media; urinary-tract infections.

Primsulfon *Novell, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Primum *Sandoz, Arg.*
Flunitrazepam (p. 1073·3).
Insomnia.

Primunox *Solas, Indon.*
Echinacea purpurea (p. 2498·1); phyllanty.
Immunomodulator.

Primzole *Sunward, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Prinac Ac *Collins, Mex.†*
Folic acid (p. 2063·1).
Anaemias.

Prinachol *Zurita, Braz.*
Boldo (p. 2458·3).
Liver disorders.

Prinarten *Liferpal, Mex.*
Captopril (p. 1331·2).
Hypertension.

Prinasma *Medikon, Indon.†*
⊗Ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3).
Asthma.

Princi B1 + B6 *Sanofi-Aventis, Neth.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency associated with alcoholism.

Princi-B *Sanofi-Aventis, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; beri-beri.

SERP, Mon.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3).
Asthenia.

Princi-B Fort *Sanofi Synthelabo, Hong Kong†; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Singapore.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neurological disorders; neuritis; neuralgias; vitamin B deficiency; tonic; diabetic neuropathy.

Princimox *BMS, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Principen *Apothecon, USA.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Princol *Provit, Mex.†*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Prindace *Servier, Irl.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease.

Prindavam *Arrow, Irl.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Prindex
Note: this name may be used for preparations of different composition.
Glenmark, Irl.
Perindopril erbumine (p. 1467·1).
Hypertension; coronary artery disease; heart failure.
Armstrong, Mex.†
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1).
Upper respiratory-tract congestion.

Prinex *Intermed, Gr.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Prinil
Note: this name may be used for preparations of different composition.
Mepha, Switz.
Lisinopril (p. 1420·3).
Hypertension; heart failure.
TRB, Arg.
Pridinol mesilate (p. 2026·1).
Muscle spasm.

Priniser *Serral, Mex.*
Lisinopril (p. 1420·3).
Hypertension.

Prinivil *MSD, Austral.; MSD, Braz.; Merck Frosst, Canad.; MSD, Cz.†; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; Mediolanum, Ital.; MSD, Mex.; MSD, NZ; MSD, Pol.; MSD, Port.; MSD, S.Afr.†; MSD, Singapore; Frosst, Spain; Merck, USA; MSD, Venez.*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Prinivil Plus *Frosst, Spain.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prinol *Hizon, Philipp.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Prinol Plus *Rivero, Arg.*
Preparation for enteral nutrition.

Prinopril *Cifarma, Braz.*
Lisinopril (p. 1420·3).
Hypertension.

Prinorm *Valeant, Hung.; Galenika, Rus.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; tremor; hypertrophic obstructive cardiomyopathy; hyperthyroidism; migraine.

Prinox *Andromaco, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Printan *Raffo, Chile.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal hygiene.

Prinzide *MSD, Braz.; Merck Frosst, Canad.; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; Mediolanum, Ital.; MSD, Mex.; MSD, Port.; Mepha, Switz.; Merck, USA.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prioderm *Meda, Belg.; Norpharma, Denm.; Mundipharma, Fin.; Meda, Fr.; Seton, Irl.†; Rafa, Israel; Meda, Neth.; Mundipharma, Norw.; SSL, NZ†; Mundipharma, Swed.; Mundipharma, Switz.; SSL, UK.†*
Malathion (p. 2157·2).
Pediculosis; scabies.

Prionelle *Campus, Swed.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Combined oral contraceptive.

Priora *Delta Medical, Ukr.*
Docosanol (p. 974·3).
Herpes simplex infections.

Priorin *Bayer, Austria.*
Millet; calcium pantothenate (p. 2085·2); cystine (p. 2059·1).
Hair and nail disorders.
Bayer, Turk.
Calcium pantothenate (p. 2085·2); millet; wheat-germ oil (p. 2647·1); cystine (p. 2059·1).
Supplement for healthy hair and nails.

Priorin N *Bayer, Switz.*
Millet; calcium pantothenate (p. 2085·2); cystine (p. 2059·1); wheat-germ oil (p. 2647·1).
Hair and nail disorders.

Priorix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; Litha, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
A measles, mumps, and rubella vaccine (attenuated Schwarz, RIT 4385, and Wistar RA 27/3 strains, respectively) (p. 2400·2).
Active immunisation.

Priorix-Tetra *GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.†; GSK, Ger.; GSK, Gr.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, NZ; GSK, Port.; GSK, Singapore; GSK, Switz.; GSK, Thai.*
A measles, mumps, rubella, and varicella-zoster vaccine (attenuated Schwarz, Jeryl Lynn, Wistar RA 27/3, and OKA strains respectively) (p. 2401·2).
Active immunisation.

Priosol *Braun, Spain.*
Calcium chloride (p. 1783·1); glucose (p. 2068·3); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); with or without potassium chloride (p. 1793·2).
Haemofiltration solution.

Priovit 12 *SIT, Ital.*
Vitamins.

Piper *Ivax, Arg.*
Pipemidic acid (p. 339·3).
Bacterial infections.

Piper Plus *Ivax, Arg.*
Pipemidic acid (p. 339·3); phenazopyridine (p. 124·3).
Urinary-tract infections.

Pripsen *Thornton & Ross, UK.†*
Oral powder: Piperazine phosphate (p. 163·2); senna (p. 1885·1).
Enterobiasis; ascariasis.
Thornton & Ross, UK.†
Tablets: Mebendazole (p. 158·3).
Enterobiasis.

Prisdal *Lundbeck, Spain.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Prisma *Pasteur, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression.
Mediolanum, Ital.; Medinfar, Port.
Mesoglycan sodium (p. 2557·2).
Peripheral vascular disorders; phlebitis; thrombophlebitis; thromboembolic disorders; haematoma.

Prismasol *Gambro, Austria; Gambro, Canad.; Gambro, Denm.; Hospal, Fr.; Gambro, Irl.; Gambro, Neth.; Gambro, Norw.; Gambro, Port.; Gambro, Spain; Gambro, Switz.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); lactic acid (p. 2539·1);

sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3) (p. 1778·2).
Haemofiltration; haemodialysis; haemodiafiltration.

Gambro, Swed.
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); anhydrous glucose (p. 2069·1); lactic acid (p. 2539·1).
Haemofiltration; haemodialysis.

Prismasol Kalium *Gambro, Fin.*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3); lactic acid (p. 2539·1) (p. 1778·2).
Haemofiltration; haemodialysis.

Prismasol O *Gambro, Canad.*
Calcium chloride (p. 1783·1); lactic acid (p. 2539·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1778·2).
Haemodialysis.

Prismocal *Gambro, Canad.*
Lactic acid (p. 2539·1); magnesium chloride (p. 1787·1); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1) (p. 1778·2).
Haemodialysis.

Prisonil *Austral, Arg.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Prisonil D *Austral, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pristesin F *Unipharm, Mex.*
Prilocaine hydrochloride (p. 1994·1). Felypressin (p. 2502·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Pristine *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Ketoconazole (p. 585·3).
Fungal scalp disorders; dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Pristinex *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Ketoconazole (p. 585·3).
Fungal skin and scalp disorders; fungal infections.

Pristiq *Wyeth, Arg.; Pfizer, Austral.; Wyeth, Braz.; Pfizer, Canad.; Wyeth, Chile; Pfizer, Hong Kong; Wyeth, Israel; Wyeth, Malaysia; Pfizer, Singapore; Pfizer, Thai.; Wyeth, USA.*
Desvenlafaxine succinate (p. 413·2).
Depression; menopausal disorders.

Pristonal *Cifarma, Braz.*
Cimetidine (p. 1827·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pritacort *Molex Ayus, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Pritadol *Alter, Spain.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Pritagesic *Molex Ayus, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.

Pritalinc *Molex Ayus, Indon.*
Lincomycin (p. 317·1).
Bacterial infections.

Pritamox *Molex Ayus, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pritanol
Note: this name may be used for preparations of different composition.
Alter, Port.
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Molex Ayus, Indon.
Allopurinol (p. 600·2).
Hyperuricaemia.

Pritaren *Prime, Singapore.*
Diclofenac sodium (p. 48·3).
Juvenile idiopathic arthritis.

Pritasma *Molex Ayus, Indon.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Pritavit *Molex Ayus, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C deficiency; tonic.

Pritor *GSK, Braz.; Bayer Schering, Cz.; Pharmacodane, Denm.†; Bayer, Fr.; Bayer, Gr.; Bayer Schering, Hung.; Bayer Schering, Irl.; Bayer, Ital.; Bayer, Neth.; GSK, Philipp.; Bayer, Pol.; Bayer Schering, Port.; Bayer, Rus.; Boehringer Ingelheim, S.Afr.; Bayer, Spain; GSK, Turk.; Bayer, Ukr.; GSK, Venez.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction; diabetic nephropathy.

Pritor HCT *GSK, Braz.†*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Pritor Plus *Bayer, Gr.; Bayer, Pol.; Bayer, Spain; GSK, Turk.; GSK, Venez.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

PritorPlus *Bayer Schering, Cz.; Bayer, Denm.; Bayer, Fr.; Bayer Schering, Hung.; Bayer Schering, Irl.; Bayer, Ital.; Bayer, Neth.; GSK, Philipp.; Bayer Schering, Port.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Privast *Aurora, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Privigen *CSL, Austria; CSL, Belg.; CSL, Canad.; CSL, Cz.; CSL, Denm.; CSL, Fr.; CSL, Ger.; CSL, Gr.; CSL, Irl.; CSL, Israel; CSL, Neth.; CSL, Norw.; CSL, NZ; CSL, Pol.; CSL, Port.; CSL, Spain; CSL, Swed.; CSL, Switz.; CSL, UK; CSL, USA.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; immune thrombocytopenia; Guillain-Barré syndrome; Kawasaki disease; bone marrow transplantation; hypogammaglobulinaemia; passive immunisation; toxic shock syndrome.

Privin *Novartis Consumer, Ger.†*
⊗Naphazoline nitrate (p. 1669·3).
Aid to cystoscopy and rhinoscopy.

Privina *Novartis Consumer, Arg.; Novartis, Braz.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Privine *Insight, USA.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Privituss *Aesculapius, Ital.; Alpharma, Mex.*
Levocloperastine fendizoate (p. 1659·1).
Cough.

Prixar *Chiesi, Ital.; Medcor, Neth.†*
Levofloxacin (p. 315·3).
Bacterial infections.

Prixin
Note: this name may be used for preparations of different composition.
IQFA, Mex.
Cisapride (p. 1831·3).

Richmond, Arg.
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Prixina *Faran, Gr.; Medagro, Pol.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Prixlae *Center, Philipp.; Shou Chan, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Prizelip *Ferakon, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Prizma *Trima, Israel.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Prizogen *Vonnace, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pro-4 *MD, Singapore.*
Bifidobacterium; *Lactobacillus acidophilus* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); fructo-oligosaccharides (p. 2508·1); wheat dextrin (p. 2647·1).
Maintenance of gastrointestinal flora.

Pro ABS *Medicine Products, Thai.*
Activated charcoal (p. 1537·3); magnesium hydroxide (p. 1857·2); belladonna (p. 2453·3); peppermint oil (p. 1877·1).
Flatulence.

Pro Amox *Pro Doc, Canad.*
Amoxicillin (p. 216·2).
Bacterial infections.

Pro ATP *Graha, Indon.*
Adenosine triphosphate (p. 2430·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Dietary supplement.

Pro Chlorax *Pro Doc, Canad.†*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).

Pro HDL *Wockhardt, India.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Pro Kalk *Graha, Indon.*
Calcium lactate (p. 1784·1).
Calcium supplement.

Pro Lertus *Tecnofarma, Chile.*
Diclofenac colestyramine (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Pro Lumière *Chanel, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Pro Ulco *Abbott, Spain.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pro-AAS *Pro Doc, Canad.*
Aspirin (p. 22·2).

Proacid
Note: this name may be used for preparations of different composition.
Ziololek, Pol.†
Aluminium glycinate (p. 1817·2); magnesium carbonate (p. 1856·2).
Hyperacidity; peptic ulcer; gastritis.

Proacne *T Man, Thai.*
Isotretinoin (p. 1706·2).
Acne.

ProActive *Pharmaton, Switz.*
Vitamins; minerals; ginseng (p. 2513·3).
Tonic; dietary supplement.

Proactive Multi for 50+ *Blackmores, Austral.*
Vitamins; minerals; big marigold; ubidecarenone (p. 2637·1).
Dietary supplement; tonic.

Proaf *Teva, Israel.†*
⊗Isoflupredone acetate (p. 1642·1); ephedrine hydrochloride (p. 1663·2); naphazoline nitrate (p. 1669·3).
Rhinitis; sinusitis.

Proagil *HWS OTC, Austria.*
Causticum (p. 2595·3); ferrum phosphoricum (p. 2077·1); ledum (p. 2550·1); rhododendron.
Homoeopathic preparation.

ProAir
Note: this name may be used for preparations of different composition.
Ivax, USA.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Proair
Note: this name may be used for preparations of different composition.
Montpellier, Arg.
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Proair Bronquial *Montpellier, Arg.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

ProAktiv
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Austria.
Vitamins; minerals with ginseng (p. 2513·3).
Tonic.

Proaktiv
Note: this name may be used for preparations of different composition.
Steigerwald, Ger.
Salix (p. 129·2).
Rheumatism; headache.

Proalid *Darier, Mex.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Pro-Aller *Pekana, Hung.*
Ailanthus altissima; comocladia dentata; euphrasia officinalis (p. 2502·1); gratiola officinalis; juglans regia (p. 2646·1); okoubaka aubrevillei; smilax utilis (p. 2610·3); taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Proallergodil *Meda, Fr.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Proalor *Zdorovje, Ukr.†*
Propolis (p. 2597·3); ascorbic acid (p. 2110·3).
Inflammation of the ear, nose, and throat.

Pro-Alusin-L *Gap, Gr.*
Propantheline bromide (p. 1880·1); chlordiazepoxide hydrochloride (p. 1044·2).

ProAmatine *Shire Richwood, USA.*
⊗Midodrine hydrochloride (p. 1437·3).
Orthostatic hypotension.

Proampi *GSK Sante, Fr.†*
Pivampicillin (p. 341·3).
Bacterial infections.

Proanes *Sanbe, Indon.*
Propofol (p. 1909·3).
General anaesthesia.

Proartinal *Provit, Mex.†*
Ibuprofen (p. 68·2).
Pain; inflammation.

Proasma-T *Medicine Products, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease; premature labour.

Proats *Richmond, Arg.*
Pramipexole (p. 911·2).
Parkinsonism.

Proaven *Royal, Chile.*
Avena (p. 2451·1); linoleic acid (p. 2509·2); nicotinamide (p. 2083·1).
Dry skin.

Proavenal H *Panalab, Arg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Proavenal Omegatopic *Panalab, Arg.*
Avena (p. 2451·1); linoleic acid (p. 2509·2); nicotinamide (p. 2083·1).
Emollient; moisturiser.

Proaxen *Pentafarma, Port.*
Oxcarbazepine (p. 533·2).
Epilepsy; trigeminal neuralgia.

Probact *Ethical, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Pro-Banthine *Aspen, Austral.; Wellspring, Canad.†; Searle, Gr.; RPG, India; Soho, Indon.†; Archimedes, Irl.; Healthcare Logistics, NZ; Aspen, S.Afr.; Pharmacia, Singapore; Archimedes, UK; Schiapparelli Searle, USA.†*
Propantheline bromide (p. 1880·1).
Irritable bowel syndrome; peptic ulcer; nocturnal enuresis; gastrointestinal spasm; hyperhidrosis; neurogenic bladder; urinary incontinence; adjunct in gastrointestinal diagnostic procedures; gastritis; renal colic.

Probase 3 *Schering-Plough, UK.*
Emollient.
Dry skin.

Probat *Tanabe, Indon.*
Guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Probax *Fischer, USA.*
Propolis (p. 2597·3).
Skin disorders.

Probecid *Biophausia, Norw.; Biophausia, Swed.*
⊗Probenecid (p. 607·3).
Gout; adjunct to beta-lactam antibacterials; gouty arthritis.

Probec-T *J&J-Merck, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Probelin *Euro Generics, Philipp.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Proben *Aspen, S.Afr.*
⊗Probenecid (p. 607·3).
Gout.

Probena *IBSA, Ital.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Probendazol *Prodotti, Braz.†*
Mebendazole (p. 158·3).
Worm infections.

Probenil *Elofar, Braz.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Probenxil *Cimed, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Inflammation.

Probeta
Note: this name may be used for preparations of different composition.
Allergan, Canad.†
⊗Levobunolol hydrochloride (p. 2008·3); dipivefrine hydrochloride (p. 2495·1).
Ocular hypertension; glaucoma.

Pro-Bextra *Pfizer, Chile.*
Parecoxib sodium (p. 119·3).
Postoperative pain.

ProBi *Medifarma, Indon.; Pediatrica, Indon.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); selenium yeast (p. 2125·2).
Nutritional supplement for digestive function in children.

Probic *Q Pharma, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Probicid *Kocak, Turk.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Probien *Teguhsindo, Indon.*
Oxerutins (p. 2505·3).
Venous insufficiency; haemorrhoids.

Probifor *Partner, Rus.*
Bifidibacterium bifidum (p. 2596·3).
Gastrointestinal disorders.

Probigol *Omeofarma, Ital.*
Propolis (p. 2597·3); echinacea (p. 2498·1).
Oral hygiene.

Probinul *CaDiGroup, Ital.*
Lactic-acid-producing organisms (p. 2596·3).

Pro-bio *Bharat, Philipp.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea.

Probio HP+ *Mayoly-Spindler, Mex.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3).
Dietary supplement.

Probio Lact Active Formula *Medipharm, Malaysia.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3)*Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3) *Bifidobacterium lactis* (p. 2596·3); inulin (p. 2534·3).
Maintenance of gastrointestinal flora.

Probio-C *Ikapharmindo, Indon.*
Ascorbic acid (p. 2110·3) or sodium ascorbyl phosphate (p. 1720·3).
Vitamin C supplement.

Probiolog *Mayoly-Spindler, Fr.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3).
Dietary supplement; gastrointestinal disorders.

ProbiomaX
Note: this name may be used for preparations of different composition.
Bioglan, Austral.
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3).
Maintenance of gastro-intestinal flora.

Probiomax
Note: this name may be used for preparations of different composition.
Midsona, Swed.
Lactobacillus reuteri (p. 2596·3).
Maintenance of gastrointestinal flora.

Pro-Bionate *Natren, USA.*
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement.

Probiotic Formula *Rugby, USA.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Bifidobacterium lactis* (p. 2596·3).

Probiotin *Tropica Mas, Indon.*
Clindamycin (p. 269·3).
Gram-positive bacterial infections.

Pro-BIS *Rosell Lallemand, Singapore.*
Lactobacillus plantarum (p. 2596·3).
Gastrointestinal discomfort.

Probitor *Sandoz, Austral.; Sandoz, Gr.; Sandoz, Malaysia; Sandoz, Thai.†; Sandoz, Venez.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Probitor Hp7 *Sandoz, Austral.*
Tablets, clarithromycin (p. 266·2); capsules, amoxicillin trihydrate (p. 216·2); capsules, omeprazole (p. 1867·2).
Helicobacter pylori-associated peptic ulcer.

Probivac-B *Probiomed, Mex.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Probizal *Loeffler, Mex.*
Nitrofurazone (p. 333·1).
Bacterial vulvovaginal infections.

Problok
Note: this name may be used for preparations of different composition.
Terra, Turk.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; migraine; myocardial infarction; hyperthyroidism.

Probofex Caps *Wockhardt, India.*
Ferrous aminoate (p. 2048·3); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Iron-deficiency anaemia; iron supplement.

ProBrain
Note: this name may be used for preparations of different composition.
Seven Seas, UK.
Omega-3 triglycerides (p. 1460·1) ginkgo biloba (p. 2512·3).
Dietary supplement.

Probrain
Note: this name may be used for preparations of different composition.
Royal, Chile.
Rivastigmine (p. 394·3).
Alzheimer's disease.

Probrom *Medicine Products, Thai.*
Brompheniramine maleate (p. 618·1).
Allergic conditions.

Probue *Vesco, Thai.†*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Probufen *Nakornpatana, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders.

Probuxil *Quimica y Farmacia, Mex.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Procadax *Fulford, India.*
Ceftibuten (p. 252·2).
Bacterial infections.

Procaine Penicillin *Kapl, Malaysia.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Pro-Cal
Note: this name may be used for preparations of different composition.
Pro-Biotiks, USA.
Calcium (p. 1783·1); magnesium (p. 1786·3); phosphorus (p. 2589·2); vitamin D (p. 2112·3); vitamin C (p. 2110·3).
Vitaflo, UK.
Nutritional supplement.
Disease-related malnutrition.
Vitaflo, Irl.†
Preparation for enteral nutrition.

ProcAlamine *McGaw, Singapore.*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.

ProcalAmine *Eczacibasi-Baxter, Turk.*
Amino acids.
Parenteral nutrition.
McGaw, USA.
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition.
Victus, Venez.
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.
Pisa, Mex.
⊗Amino acids; glycerol (p. 2517·2); electrolytes (p. 1775·1).
Parenteral nutrition.

Procalcio *Finadiet, Arg.†*
Calcium citrate (p. 1783·2).
Calcium deficiency; osteoporosis.

Procalm
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; vertigo.
Atlas, Arg.
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Procalma *Meprofarm, Indon.*
Fish oil (p. 1460·3); vitamin E (p. 2119·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement in pregnancy and lactation.

Procalmil *Arkopharma, Fr.; Arkopharma, Port.*
St John's wort (p. 449·1).
Depression.

Procalut *Kocak, Turk.*
Bicalutamide (p. 749·1).

Procamide *Zambon, Braz.†*
Procainamide hydrochloride (p. 1475·3).
Arrhythmias.

Procan *Erfa, Canad.*
Procainamide hydrochloride (p. 1475·3).
Arrhythmias.

Procanazol
Note: this name may be used for preparations of different composition.
Protech, Rus.
Fluconazole (p. 578·2).
Fungal infections.

Procanbid *Monarch, USA.†*
Procainamide hydrochloride (p. 1475·3).
Ventricular arrhythmias.

Procanest *Gray, Arg.*
Procaine hydrochloride (p. 1994·3).
Local anaesthesia.

Procanol *ICM, Singapore.*
Procaine hydrochloride (p. 1994·3).
Local anaesthetic.

Procap-C *Xepa-Soul Pattinson, Singapore.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Procaptan *Stroder, Ital.*
Perindopril arginine (p. 1466·3).
Hypertension; heart failure.

Procard *Cyathus, Cz.*
Dexrazoxane hydrochloride (p. 1548·1).

Procardia
Note: this name may be used for preparations of different composition.
Pfizer, USA.
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.
Roemmers, Arg.
Prasugrel hydrochloride (p. 1472·3).
Thromboembolism prophylaxis during percutaneous coronary intervention.

Procardin
Note: this name may be used for preparations of different composition.
Medochemie, Hong Kong†; Medochemie, Singapore.
Dipyridamole (p. 1362·2).
Thromboembolic disorders.
Medikon, Indon.†
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Procardio *Meprofarm, Indon.†*
Crataegus (p. 2488·1); salviae miltiorrhizae (p. 2491·3); notoginseng; levocarnitine (p. 2053·2); levocarnitine tartrate (p. 2053·2); vitamin B_6 (p. 2105·3).
Cardiac disorders.

Procardol *Adelco, Gr.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Pro-Cas *Milk Industries, Israel.†*
Protein supplement.

Procasol *Solfran, Mex.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Procavit *EMS, Braz.*
Vitamins; minerals; amino acids.

Procéane Hypertonique *Nestle Proteika, Fr.†*
Sea water (p. 2612·1).
Nutritional supplement; tonic.

Procef *PharmaSwiss, Gr.; BMS, Hong Kong†; Dompe, Ital.†; BMS, Mex.; BMS, Philipp.†; BMS, Port.; BMS, Singapore; BMS, Switz.; BMS, Thai.†; BMS, Venez.*
Cefprozil (p. 248·2).
Bacterial infections.

Procefa *Promed, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Procelac *Ivax, Arg.*
Omeprazole (p. 1867·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Proceli *Ambe Medical, UK.*
A range of gluten-free foods.
Gluten sensitivity.

ProCentra *FSC, USA.*
⊗Dexamfetamine sulfate (p. 2319·1).

Procephal *Provit, Mex.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Procepim *Meprofarm, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Proceptin *Beximco, Singapore.*
Omeprazole (p. 1867·2).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Procere *Pyridam, Indon.*
Codergocrine mesilate (p. 389·2).
Mental function impairment in the elderly.

Procet *Pro Doc, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).

Procetalette *Vickmans, Hong Kong.†*
Paracetamol (p. 115·1); dextropropoxyphene (p. 43·2).
Pain.

Procetam *Meprofarm, Indon.*
Piracetam (p. 393·3).
Mental function impairment; chronic alcoholism; cerebral trauma.

Procetamol *Vickmans, Hong Kong.†*
Paracetamol (p. 115·1); dextropropoxyphene (p. 43·2).
Pain.

Procetoken *Bernabo, Arg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Prochic *Millimed, Thai.*
Colchicine (p. 604·1).
Gout.

Prochieve *Columbia, USA.†*
Progesterone (p. 2300·2).
Amenorrhoea; female infertility.

Prochlor *CCM, Malaysia; Beacons, Singapore.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; psychoses.

Procicar *Medihealth, Mex.*
Zinc oxide (p. 1729·1); calamine (p. 1697·2).
Wounds.

Prociclide *Crinos, Ital.†*
Defibrotide (p. 1350·1).
Thrombosis prophylaxis.

Prociclina *Prodotti, Braz.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Pro-Cid *Phebra, Austral.*
⊗Probenecid (p. 607·3).
Adjunct to beta-lactam antibacterials; gout; reduction of cidofovir-associated nephrotoxicity.

Prociflor *Epifarma, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Procilin *IQFA, Mex.†*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Procilina *Mayo, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Procillin *Caps, S.Afr.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Fako, Turk.†
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Procimax *Libbs, Braz.*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Procimeti *Provit, Mex.†*
Cimetidine (p. 1827·1).
Peptic ulcer.

Procinet *Quesada, Arg.*
Tegaserod maleate (p. 1893·1).

Procion *Medipharm, Chile.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Procipro *Protech, Rus.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Procirex *KG, Ital.*
Bromopride hydrochloride (p. 1824·2).
Digestive disorders.

Pro-Clear *Propharma, USA.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Proclearz *Profoot, Canad.*
Tolnaftate (p. 596·1).

Proclimine *Medicine Products, Thai.*
Oxyphencyclimine hydrochloride (p. 1875·1).
Gastrointestinal disorders; genito-urinary disorders.

Proclor *Pentafarma, Port.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Procloril *Provit, Mex.†*
Chloramphenicol (p. 257·1).
Bacterial infections.

Proclose *Probiomed, Mex.*
Octreotide (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; AIDS-associated diarrhoea; postoperative pancreatic complications; variceal haemorrhage.

Procloxin *Inpac, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Proclozam *Meprofarm, Indon.*
Clobazam (p. 518·2).
Anxiety; psychosomatic disorders.

Proclozine *Pharmasant, Thai.*
Prochlorperazine maleate (p. 1098·3).
Schizophrenia; mania; alcoholism; anxiety.

Procodin *DHA, Singapore.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Cough.

Procodyl *Bangkok Lab & Cosmetic, Thai.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; vestibular disorders; insomnia; motion sickness.

Procof *Aspen, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); pholcodine (p. 1675·1); guaifenesin (p. 1666·2).
Cough.

Procold
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza and cold symptoms; allergic rhinitis.

Procolic *Meprofarm, Indon.*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Procomvax *Sanofi Pasteur, Cz.†; Sanofi Pasteur, Gr.; Pasteur Merieux, Irl.†; Sanofi Pasteur, Neth.†; Sanofi Pasteur, Pol.†; Sanofi Pasteur, Port.†*
A Haemophilus influenzae and hepatitis B vaccine (p. 2388·1).
Active immunisation.

ProCoMycin *Physicians Science & Nature, USA.*
Polymyxin B sulfate (p. 342·3); neomycin (p. 329·3); bacitracin zinc (p. 225·3); lidocaine (p. 1988·1).
Skin infections.

Procor
Note: this name may be used for preparations of different composition.
Prosel, Philipp.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Unipharm, Israel.
Amiodarone hydrochloride (p. 1300·1).
Angina pectoris; arrhythmias; heart failure; myocardial infarction.

Procoralan *Servier, Arg.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, Cz.; Servier, Denm.; Servier, Fr.; Servier, Ger.; Servier, Gr.; Servier, Hung.; Servier, Irl.; Servier, Ital.; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, Spain; Servier, Swed.; Servier, Switz.; Servier, UK.*
Ivabradine hydrochloride (p. 1415·1).
Angina pectoris; heart failure.

Procordal *Muller Goppingen, Ger.*
Camphora (p. 2466·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Procordal vertigo *Muller Goppingen, Ger.*
Cocculus (p. 2483·1); ipecacuanha (p. 1667·2); petroleum rectificatum (p. 2201·2); tabacum (p. 2632·2).
Homoeopathic preparation.

ProCort
Note: this name may be used for preparations of different composition.
Womens Choice, USA.
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Procort
Note: this name may be used for preparations of different composition.
Roberts, USA.†
⊗Hydrocortisone (p. 1640·1).
Corticosteroid.

Procortin *Homeofarm, Pol.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Procorum *Abbott, Austria; Abbott, China; Abbott, Ger.; Teva, Hung.†; Abbott, Ital.; Knoll, Mex.†; Abbott, Philipp.†; Abbott, Thai.†*
Gallopamil hydrochloride (p. 1390·3).
Angina pectoris; hypertension; arrhythmias; atherosclerosis; ischaemic heart disease; myocardial infarction.

Procosa
Note: this name may be used for preparations of different composition.
Usana, Canad.
Glucosamine hydrochloride (p. 2515·3); manganese (p. 2081·2); potassium (p. 1793·1); vitamin C (p. 2110·3).

Usana, Malaysia.†
Glucosamine (p. 2515·3).
Osteoarthritis.

Procosa II *Usana, Mex.*
Glucosamine sulfate (p. 2515·3); turmeric (p. 2218·1); vitamins; minerals.

Usana, Hong Kong.†
Glucosamine sulfate (p. 2515·3); calcium ascorbate (p. 2111·1); manganese gluconate (p. 2081·2); silicon (p. 2088·3); turmeric (p. 2218·1).
Osteoarthritis.

Usana, Singapore.†
Vitamin C (p. 2110·3); manganese (p. 2081·2); glucosamine sulfate (p. 2515·3); silicon (p. 2088·3); turmeric (p. 2218·1).
Dietary supplement.

Procoutol *Spirig, Switz.*
Triclosan (p. 1773·2).
Skin disorders.

Procozin *Professional Health, Canad.*
Copper citrate; zinc citrate (p. 2126·2).

Procren *Abbott, Denm.; AbbVie, Fin.; Abbott, Norw.; Abbott, Swed.*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; prostatic cancer; uterine fibroma.

Procrin *AbbVie, Spain.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; female infertility.

Procrit *Ortho Biotech, USA.*
⊗Epoetin alfa (p. 1141·1).
Anaemia of chronic renal failure; anaemia in zidovudine-treated HIV-infected patients; anaemia in cancer patients on chemotherapy; pre-operative anaemias.

Proctasacol *Giuliani, Ital.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Proctase-P *Meiji, Thai.*
⊗Proctase; pancreatin (p. 2579·3).
Inflammation; oedema; haematoma; respiratory-tract congestion.

Procto Synalar-N *Minerva (Μινερβα), Gr.*
⊗Fluocinolone acetonide (p. 1636·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Procto Venart *Casasco, Arg.*
⊗Ruscogenin (p. 2608·3); prednisolone (p. 1645·2); cinchocaine hydrochloride (p. 1983·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Haemorrhoids.

Proctoacid *Nycomed, Mex.*
Policresulen (p. 1160·2); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Proctocella Complex *Peter, Ital.*
Centella (p. 1698·3); arnica (p. 2447·2); devil's claw (p. 42·3); aloe vera (p. 1693·2); beta-glucan (p. 2455·2); menthol (p. 2553·2).

Proctocort
Note: this name may be used for preparations of different composition.
Salix, USA.
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Proctocream HC 2.5% *Schwarz, USA.†*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Proctocrem *Ronnet, Arg.*
⊗Lidocaine (p. 1988·1); hydrocortisone (p. 1640·1); menthol (p. 2553·2).
Anorectal disorders.

Proctodan-HC *Odan, Canad.*
⊗Pramocaine hydrochloride (p. 1993·3); hydrocortisone acetate (p. 1640·1); zinc sulfate (p. 2126·2).
Anorectal disorders.

Proctofoam *Alaven, USA.*
Pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Proctofoam-HC *Duchesnay, Canad.; Meda, Irl.; Megapharm, Israel; Meda, Ital.; Meda, UK; Meda, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Proctogel *Maver, Chile.*
Tribenoside (p. 2633·3); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Procto-Glyvenol
Note: this name may be used for preparations of different composition.
Novartis Consumer, Arg.; Herbacos Recordati, Cz.; Novartis, Gr.; Novartis, Philipp.; Novartis Consumer, Port.; Novartis Consumer, Rus.
Tribenoside (p. 2633·3); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Novartis, Braz.; Novartis, Chile; Novartis Consumer, Israel; Novartis, Mex.; Novartis Consumer, Pol.; Novartis Consumer, Switz.; Novartis, Turk.; Recordati, Ukr.; Novartis, Venez.
Tribenoside (p. 2633·3); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Haemorrhoids; anorectal disorders.

Procto-Hemolan *Aflofarm, Pol.*
Tribenoside (p. 2633·3); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Procto-Hemolan Control *Aflofarm, Pol.*
Diosmin (p. 2505·2).
Haemorrhoids.

Procto-Ikatral *Baliarda, Arg.*
⊗Oligomeric proanthocyanidins (p. 2521·3); lidocaine hydrochloride (p. 1988·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Proctol *Odan, Canad.*
⊗Hydrocortisone (p. 1640·1); cinchocaine hydrochloride (p. 1983·2); framycetin sulfate (p. 301·2); esculoside (p. 2431·2).
Anorectal disorders.

Proctolog *Pfizer, Fr.; Menarini, Port.; Pfizer, Singapore; Desma, Spain; Abdi, Turk.*
Ruscogenin (p. 2608·3); trimebutine (p. 2634·1).
Haemorrhoids; anorectal disorders.

Proctolyn *Recordati, Ital.*
⊗Fluocinolone acetonide (p. 1636·1); ketocaine hydrochloride (p. 1987·2).
Anorectal disorders.

Procto-Metadyne *Fada, Arg.*
⊗Lidocaine hydrochloride (p. 1988·2); phenylephrine hydrochloride (p. 1672·3); betamethasone valerate (p. 1624·1).
Haemorrhoids.

Proctomyxin HC *Sandoz, Canad.*
⊗Hydrocortisone (p. 1640·1); framycetin sulfate (p. 301·2); cinchocaine hydrochloride (p. 1983·2); esculoside (p. 2431·2).
Anorectal disorders.

Proctophytol *Krasnogorskleksredstva, Rus.*
Coriander (p. 2486·3); buckthorn (p. 1824·2); senna (p. 1885·1); liquorice (p. 1853·2); achillea (p. 2427·3).

Proctoplex *Knop, Chile.*
Hamamelis (p. 2523·3); aesculus (p. 2431·2); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Proctopure *Dermofarma, Ital.*
Aescin (p. 2431·2); aesculus (p. 2431·2); hamamelis (p. 2523·3); calendula (p. 2465·2); liquorice (p. 1853·2); melaleuca.
Anorectal disorders.

Proctor's Pinelyptus *Ernest Jackson, UK.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); pine silvestris oil (p. 2591·2); siberian fir oil.
Throat irritation; coughs.

Proctosan
Note: this name may be used for preparations of different composition.
Hertz, Braz.
Azulene (p. 2452·1); hamamelis (p. 2523·3); lidocaine (p. 1988·1); menthol (p. 2553·2); aesculus (p. 2431·2).
Haemorrhoids.

Stada, Rus.; Stada, Ukr.
Bufexamac (p. 30·2); bismuth subgallate (p. 1822·1); titanium dioxide (p. 1725·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Proctosedyl
Note: this name may be used for preparations of different composition.
Aptalis, Canad.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Norw.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.†; Sanofi-Aventis, Thai.
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone (p. 1640·1); framycetin sulfate (p. 301·2); esculoside (p. 2431·2).
Anorectal disorders.

Sanofi-Aventis, Austral.; Sanofi-Aventis, NZ; Aventis, UK.
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone (p. 1640·1).
Haemorrhoids; pruritus ani; anorectal disorders.

Bayer, Ital.
Cream: ⊗Amylocaine (p. 1979·3); benzocaine (p. 1980·2); hydrocortisone acetate (p. 1640·1); esculoside (p. 2431·2).
Haemorrhoids; anal pruritus.

Bayer, Ital.
Suppositories: ⊗Benzocaine (p. 1980·2); hydrocortisone acetate (p. 1640·1); esculoside (p. 2431·2).
Haemorrhoids; anal pruritus.

Sanofi-Aventis, India.
⊗Hydrocortisone acetate (p. 1640·1); heparin (p. 1396·3); framycetin sulfate (p. 301·2); esculoside (p. 2431·2); benzocaine (p. 1980·2); butyl aminobenzoate (p. 1982·3).
Haemorrhoids.

Sanofi-Aventis, Neth.
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone (p. 1640·1); framycetin sulfate (p. 301·2).
Haemorrhoids.

Sanofi-Aventis, Rus.
⊗Hydrocortisone acetate (p. 1640·1); framycetin sulfate (p. 301·2); heparin sodium (p. 1396·3); esculoside (p. 2431·2); benzocaine (p. 1980·2); butyl aminobenzoate (p. 1982·3).
Anorectal disorders.

Sanofi-Aventis, Ukr.
⊗Hydrocortisone acetate (p. 1640·1); framycetin sulfate (p. 301·2); heparin sodium (p. 1396·3); esculoside (p. 2431·2).
Anorectal disorders.

Proctosedyl M *Sanofi-Aventis, Rus.*
⊗Framycetin sulfate (p. 301·2); hydrocortisone acetate (p. 1640·1); esculoside (p. 2431·2); benzocaine (p. 1980·2); butyl aminobenzoate (p. 1982·3).
Haemorrhoids.

Proctosedyl-N *Sanofi-Aventis, Gr.*
⊗Hydrocortisone (p. 1640·1); cinchocaine hydrochloride (p. 1983·2).

Proctosoll *Wassermann, Ital.*
⊗Benzocaine (p. 1980·2); hydrocortisone acetate (p. 1640·1); heparin sodium (p. 1396·3).
Haemorrhoids.

Proctosone *Technilab, Pol.†*
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1); esculoside (p. 2431·2).
Anorectal disorders.

Proctosteroid *Aldo, Spain.*
⊗Triamcinolone diacetate (p. 1649·1).
Ulcerative colitis; proctosigmoiditis; proctitis.

Procto-Synalar *Astellas, Belg.*
⊗Fluocinolone acetonide (p. 1636·1); lidocaine hydrochloride (p. 1988·2); bismuth subgallate (p. 1822·1); menthol (p. 2553·2).
Anorectal disorders.

Procto-Synalar N *Minerva (Μινερβα), Gr.; Teofarma, Switz.*
⊗Fluocinolone acetonide (p. 1636·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Proctox-H *Multilab, Braz.*
Policresulen (p. 1160·2); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Proctozorin-N *Teva, Israel.*
⊗Hydrocortisone (p. 1640·1); allantoin (p. 1693·1); benzocaine (p. 1980·2); aluminium acetotartrate (p. 2440·1); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Anorectal disorders.

Proctyl *Nycomed, Arg.; Nycomed, Braz.*
Policresulen (p. 1160·2); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Proctyl HC *Nycomed, Arg.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Proculin *Chauvin ankerpharm, Ger.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Conjunctivitis.

Procur *Ascent, Austral.; Douglas, NZ; Douglas, Singapore.*
Cyproterone acetate (p. 2261·2).
Androgenisation in females; prostatic cancer; sexual deviation in males.

Procur Plus *Guardian, Indon.*
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); ginseng (p. 2513·3); turmeric (p. 2218·1).
Nutritional supplement.

Pro-Cure
Note: this name may be used for preparations of different composition.
MSD, Israel.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Procure
Note: this name may be used for preparations of different composition.
Pharmathen, Gr.
Bicalutamide (p. 749·1).

Procuta *Expanscience, Fr.*
Isotretinoin (p. 1706·2).
Acne.

Procutan *Schering-Plough, S.Afr.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Pro-Cute *Ferndale, USA.*
Emollient and moisturiser.

Procylin *Kaken, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Procysbi *Raptor, USA.*
Mercaptamine bitartrate (p. 2554·3).
Nephropathic cystinosis.

Procythol *Sanofi-Aventis, Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Procytox *Baxter, Canad.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Pro-Dafalgan *IFET (ΙΦΕΤ), Gr.†*
Propacetamol hydrochloride (p. 127·2).
Fever; pain.

Prodafem *Pfizer, Austria; Pfizer, Switz.*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; menorrhagia; menopausal disorders; endometriosis; diagnosis of amenorrhoea.

Prodaril-N *Medicine Products, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Prodasone *Pfizer, Chile.*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; dysfunctional uterine bleeding; endometrial hyperplasia.

Prodazole *Inpac, Thai.*
Albendazole (p. 149·1).
Worm infections.

ProDefinition *Blackmores, Austral.*
Nutritional supplement.

Prodeine *Sanofi-Aventis, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Prodel *Pasteur, Chile.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Prodel B *Pasteur, Chile.*
⊗Betamethasone (p. 1623·2); chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Prodep *Sun, Rus.; Sun, Thai.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Pro-Derm *Pro-Derma, Canad.*
SPF 60: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Proderm
Note: this name may be used for preparations of different composition.
Dow, USA.
Castor oil (p. 2472·1); peru balsam (p. 2587·1).
Decubitus ulcers.
Galderma, Braz.
Emollient.
Chefaro, Irl.†
Barrier preparation.

Pro-Derm Creme de Jour *Pro-Derma, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Proderma *Cantabria, Spain.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Prodermal *Meprofarm, Indon.*
Tioconazole (p. 595·3).
Fungal skin infections.

Prodetoxon *Echo, Rus.*
Naltrexone hydrochloride (p. 1565·1). Triamcinolone acetonide (p. 1649·1) is also included in this preparation to prevent local inflammatory reaction in the area of implantation.
Opioid dependence.

Prodexon *Meprofarm, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Prodiabet *Bernofarm, Indon.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Prodiabin-N *Probiomed, Mex.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Prodiamel *Corsa, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Pro-Diclo *Pro Doc, Canad.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Prodiem Bulk Fibre *Novartis Consumer, Canad.*
Polycarbophil calcium (p. 1879·2).

Prodif *Pfizer, Jpn.*
Fosfluconazole (p. 582·2).
Fungal infections.

Prodifer *Provit, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Prodigy Autocode *Alvear, Arg.*
Test for glucose in blood (p. 2516·3).

Prodilantin *Pfizer, Fr.*
Fosphenytoin sodium (p. 523·1).
Epilepsy.

Prodin *MedChoice, Philipp.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; panic disorder.

Prodinam *AstraZeneca, Arg.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Prodinan *Therabel, Fr.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prodisan *Embil, Turk.*
Azapropazone (p. 28·3).
Gout; musculoskeletal and joint disorders.

Prodium
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.
Breckenridge, USA.
Phenazopyridine hydrochloride (p. 124·3).
Irritation of the lower urinary tract.

Prodofenaco *Prodotti, Braz.†*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Fever; inflammation; pain.

Prodol *Technikon, S.Afr.†*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and gum pain.

Prodolina *Boehringer Ingelheim Promeco, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Prodomix *Loeffler, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Prodoner *Sawai, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Prodopa *Mylan, NZ.*
Methyldopa (p. 1431·1).
Hypertension.

Prodopina *Prodotti, Braz.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Prodopirona *Prodotti, Braz.†*
Dipyrone (p. 53·3).
Fever; pain.

Prodopressin *Prodotti, Braz.†*
Enalapril maleate (p. 1371·1).
Hypertension.

Prodorol *Be-Tabs, S.Afr.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension; anxiety; hyperthyroidism; phaeochromocytoma.

Prodotamol *Prodotti, Braz.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Prodoxacilina *Prodotti, Braz.†*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Prodoxican *Prodotti, Braz.†*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint and peri-articular disorders.

Prodoxidil *Prodotti, Braz.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Prodoxifilina *Prodotti, Braz.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Prodoxil *Prodotti, Braz.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Prodoxin *Prodotti, Braz.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Prodren *Alkon (Αλκον), Gr.*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Prodrin *Gentex, USA.*
⊗Paracetamol (p. 115·1); caffeine (p. 1203·3); isometheptene mucate (p. 2535·1).
Migraine.

Produvir *Prodotti, Braz.†*
Zidovudine (p. 1024·2).
HIV infection.

Proelsartan *Novendia, Gr.*
Losartan potassium (p. 1422·2).

Proemend *Ono, Jpn.*
Fosaprepitant meglumine (p. 1843·3).
Nausea and vomiting associated with cancer chemotherapy.

Proendotel *Bausch & Lomb, Ital.*
Cloricromen hydrochloride (p. 1345·1).
Thrombotic disorders.

Proepa *MSD, Braz.*
Polyunsaturated fatty acids.
Thrombosis prophylaxis.

Pro-Epanutin *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Norw.; Pfizer, Swed.; Pfizer, UK.*
Fosphenytoin sodium (p. 523·1).
Epilepsy; seizures associated with neurosurgery or head trauma; status epilepticus.

Proetzonide *Dallas, Arg.*
⊗Budesonide (p. 1625·1).
Asthma.

Proetztotal *Dallas, Arg.*
Nasal spray: Phenylephrine hydrochloride (p. 1672·3); neomycin sulfate (p. 330·1); chlorphenamine maleate (p. 620·3); gramicidin (p. 308·3).
Dallas, Arg.
Nebuliser solution: ⊗Phenylephrine hydrochloride (p. 1672·3); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).

Prof *Ivax, Arg.†*
Chondroitin sulfate A (p. 2476·1).
Degenerative joint disorders.

Profact *Sanofi-Aventis, Ger.*
⊗Buserelin acetate (p. 2256·2).
Prostatic cancer.

Profadine *Sanmenxia Sinoway, China.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Profal *Actavis, Irl.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Profalexina *Prodotti, Braz.†*
Cefalexin (p. 234·1).
Bacterial infections.

Profalin CPS *Mayo, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Profamid *Orion, Denm.; Orion, Fin.*
Flutamide (p. 798·2).
Prostatic cancer.

Profar *Organon, India.*
Allylestrenol (p. 2255·2).
Benign prostatic hyperplasia.

Profasi *Serono, Austral.†; Serono, Gr.; Serono, Hong Kong†; Serum Institute, India; Serono, Irl.†; Healthcare Logistics, NZ; Serono, S.Afr.; Serono, Singapore; Serono, Turk.; Serono, USA.†*
⊗Chorionic gonadotrophin (p. 2258·1).
Cryptorchidism; hypogonadotrophic hypogonadism; male and female infertility; threatened or recurrent miscarriage; delayed puberty; pituitary dwarfism.

Profasi HP *Serono, Braz.†; Pharmascience, Canad.†*
⊗Chorionic gonadotrophin (p. 2258·1).
Recurrent miscarriage; menstrual disorders; male and female infertility; delayed puberty; hypogonadotrophic hypogonadism.

Profat *Promed, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Profaxen *Nafar, Mex.*
Naproxen (p. 98·2).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

ProFe *Pro-Pharma, USA.*
Iron (p. 2073·1).
Dietary supplement.

ProFe Forte *Propharma, USA.*
Vitamins; iron (p. 2073·1).
Dietary supplement.

Profecom *Combiphar, Indon.*
Ketoprofen (p. 79·1).
Gout; rheumatoid arthritis; osteoarthritis; pain.

Profed *Medicine Products, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; hay fever; nasal congestion; cold symptoms.

Profelan *Pharmachem, UK.*
Arnica (p. 2447·2); zinc oxide (p. 1729·1); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); spearmint oil (p. 2621·2).
Musculoskeletal, joint, and soft-tissue injury.

Profémigr *Sanofi-Aventis, Fr.*
Ketoprofen (p. 79·1).
Migraine.

Profemina *Laboratorios Chile, Chile.†*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Profemina MP *Laboratorios Chile, Chile.†*
18 Tablets, conjugated oestrogens (p. 2260·1); 12 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis.

Profen
Note: this name may be used for preparations of different composition.
Christo, Hong Kong; Guardian, Indon.; KB, Thai.; Dincsa, Turk.
Ibuprofen (p. 68·2).
Pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; fever; inflammation.

Profen II *Ivax, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Formerly contained phenylpropanolamine hydrochloride and guaifenesin.
Coughs.

Profen II DM *Ivax, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Formerly contained phenylpropanolamine hydrochloride, guaifenesin, and dextromethorphan hydrobromide.
Coughs.

Profen Forte DM *Ivax, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Formerly contained phenylpropanolamine hydrochloride, dextromethorphan hydrobromide, and guaifenesin.
Coughs.

Profenac *Cipla, India.*
Diclofenac sodium (p. 48·3).
Prevention of intra-operative miosis; eye pain and inflammation; allergic conjunctivitis.

Profenal
Note: this name may be used for preparations of different composition.
Yarindo, Indon.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Profenicol *Prodotti, Braz.†*
Ear drops: Chloramphenicol (p. 257·1); lidocaine (p. 1988·1).
Ear infections.
Prodotti, Braz.†
Tablets; eye drops; injection: Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Profenid *Sanofi-Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Israel; Sanofi-Aventis, Mex.; Sanofi-Aventis, Pol.; Vitoria, Port.; Sanofi-Aventis, Thai.†; Eczacibasi, Turk.; Sanofi-Aventis, Venez.*
Ketoprofen (p. 79·1).
Inflammation; pain; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Profénid *Sanofi-Aventis, Fr.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Profenil
Note: this name may be used for preparations of different composition.
Pascual, Hong Kong.
Alverine citrate (p. 1819·1).
Gastrointestinal spasm.

Profenil Complex *Faran, Gr.*
Ketoprofen (p. 79·1); sucralfate (p. 1889·1).
Inflammatory disorders.

Profenlax *Grisi, Mex.†*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).

Pro-Feno *Pro Doc, Canad.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Profeno *Milano, Thai.*
Ibuprofen (p. 68·2).
Pain.

Profenox *Tecnimede, Port.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Profenzol *Farcoral, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Profer *Tedec Meiji, Port.; Tedec Meiji, Spain.*
Ferritin (p. 2060·2).
Iron-deficiency anaemia; iron deficiency.
Aesculapius, Ital.
Iron acetylaspartilate-protein complex (p. 2073·1).
Iron deficiency; iron-deficiency anaemias.

Profercol *Best, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders; migraine.

Profergan *Teuto, Braz.*
Promethazine hydrochloride (p. 638·2).
Nausea and vomiting; sedative; vertigo.

Proferrin *Medical Futures, Canad.*
Haem iron polypeptide (p. 1555·3).
Iron deficiency.

Profertil *Kalbe, Indon.; Kalbe, Singapore.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility; anovulatory infertility.

Profetal *Institute of New Medical Technology, Rus.*
Alpha fetoprotein (p. 2437·1).
Ulcerative colitis; thyroiditis; occlusive vascular disease.

Profex *Taro, Israel.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Profiben *Sandoz, Mex.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Profiber *Sherwood, USA.*
Lactose-free preparation for enteral nutrition.

Profibrat *Pharos, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Proficar *Polfarmex, Pol.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Profidox *Rimsa, Mex.*
Finasteride (p. 2358·3); alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Profika *Ikapharmindo, Indon.*
Ketoprofen (p. 79·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Profilas *Kalbe, Indon.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic rhinitis; allergic conjunctivitis.

Profile B Plus Fat Burner *Roche, Hong Kong.†*
Arginine aspartate (p. 2049·1); lecithin (p. 2542·2); ornithine aspartate (p. 2085·2); vitamin B_6 (p. 2105·3).

Profilnine *Grifols, Hong Kong; Grifols, Malaysia; Grifols, Philipp.; Grifols, Singapore; Grifols, Thai.; Grifols, USA.*
A factor IX complex (p. 1149·3).
Haemophilia B; haemorrhagic disorders.

Profilox *Filadams, Philipp.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Profim *Promed, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Profin *Nexus, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Profinal *Julphar, UAE.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular and soft-tissue disorders; pain; fever; inflammation.

Profinal Cold & Sinus *Julphar, UAE.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Profinal FM *Julphar, UAE.†*
Ibuprofen (p. 68·2); caffeine (p. 1203·3); mepyramine maleate (p. 635·1).
Dysmenorrhoea.

Profinal XP *Julphar, UAE.*
Ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain.

Profinject *Faran, Gr.*
Ketoprofen (p. 79·1).
Inflammatory disorders.

Profinosa *Alet, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Profisin *Sanitas, Chile.*
Dicycloverine hydrochloride (p. 1834·2); chlordiazepoxide hydrochloride (p. 1044·2).
Smooth muscle spasm.

Profiten *Perrigo, Israel.*
Ketotifen fumarate (p. 631·3).
Hypersensitivity reactions; asthma.

Profium *De Mayo, Braz.†*
Mebendazole (p. 158·3); tiabendazole (p. 166·3).
Worm infections.

Profium Plus *Duncan, Arg.*
Dextropropoxyphene (p. 43·2); dipyrone (p. 53·3).
Pain.

Proflam
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Ketoprofen (p. 79·1).
Eurofarma, Braz.
Aceclofenac (p. 16·2).
Inflammation; pain.

Proflavanol *Usana, Mex.*
Grape seed (p. 2521·3); vitamin C (p. 2110·3).
Dietary supplement.
USANA, USA.
Vitamin C (p. 2110·3); flavonoids from grape seed (p. 2505·2).
Nutritional supplement.
Usana, Hong Kong.†
Vitamin C (p. 2110·3) grape seed (p. 2521·3); ascorbyl palmitate (p. 1737·1).
Vitamin C supplement; antoxidant.
Usana, Malaysia†; Usana, Singapore.†
Ascorbyl palmitate (p. 1737·1); grape seed (p. 2521·3); vitamin C (p. 2110·3).
Dietary supplement; vitamin C and antoxidant supplement.

Proflavanol 90 *Usana, Canad.†*
Calcium ascorbate (p. 2111·1); magnesium ascorbate (p. 1787·1); potassium ascorbate (p. 1793·1); zinc ascorbate (p. 2110·3); grape seed (p. 2521·3).
Nutritional supplement.

Proflavanol C *Usana, Canad.†*
Calcium ascorbate (p. 2111·1); potassium ascorbate (p. 1793·1); magnesium ascorbate (p. 1787·1); zinc ascorbate (p. 2110·3).
Vitamin C supplement.

Proflax *Sidus, Arg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

ProFLEX
Note: this name may be used for preparations of different composition.
MZL, S.Afr.†
Glucosamine hydrochloride (p. 2515·3); calcium carbonate (p. 1824·3); vitamin C (p. 2110·3); manganese sulfate (p. 2081·2).
Dietary supplement.

Proflex
Note: this name may be used for preparations of different composition.
Morishita, Philipp.
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; inflammation; fever.
Novartis Consumer, Irl.†; Novartis Consumer, UK.†
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

ProFLEX 750
Note: this name may be used for preparations of different composition.
MZL, S.Afr.†
Glucosamine hydrochloride (p. 2515·3); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3).
Dietary supplement.

Proflex Plus *Beximco, Singapore.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Proflor *Leti, Venez.*
Lactobacillus acidophilus (p. 2596·3).
Diarrhoea.

Proflox
Note: this name may be used for preparations of different composition.
Therabel, Belg.; Bayer, Gr.; Bialfar, Port.; Esteve, Spain.
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.
Cipla, India.
Pefloxacin mesilate (p. 338·1).
Bacterial infections.
Sigma, Braz.; Pharmasant, Thai.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Profloxin *Sandoz, Austral.; Clonmel, Irl.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Proflusak *Akrikhin, Rus.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Profluxol *Ultra, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Profol
Note: this name may be used for preparations of different composition.
Claris, Thai.; Biogalenic, Venez.
Propofol (p. 1909·3).
General anaesthesia; sedative.
Medley, Braz.
Buclizine hydrochloride (p. 618·3); lysine (p. 2079·3); tryptophan (p. 453·2); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Tonic.

Profolen *Blausiegel, Braz.*
Propofol (p. 1909·3).
General anaesthesia.

Profort *Abbott, Braz.*
Preparation for enteral nutrition.

ProFree *Allergan, USA.†*
⊗Papain (p. 2582·3).
Cleansing solution for contact lenses.

Profungal *Kalbe, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Profura *Medicine Products, Thai.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Profurex *Biolab, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Profut *Mecosin, Indon.†*
Cyproheptadine hydrochloride (p. 624·1).
Allergic rhinitis; allergic skin disorders.

Profuzosin *Sandoz, Philipp.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Profylac *Semper, Denm.*
Infant feed.
Milk allergy; lactose intolerance.

Progandol *Almirall, Spain.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Progastim *Labormed, Pol.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; gastric hyperacidity.

Progastric *Combiphar, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Bloating; gastric hyperacidity; peptic ulcer.

Progastrit *Hexal, Ger.†*
Chewable tablets: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1).
Gastrointestinal disorders.
Hexal, Ger.†
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Progeffik *Effik, Ital.; Effik, Spain.*
Progesterone (p. 2300·2).
Menstrual disorders; menopausal disorders; female infertility; threatened or habitual miscarriage.

Progemzal *Sandoz, Indon.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Progen *Mayo, Mex.†*
Gentamicin (p. 304·2).
Bacterial infections.

Progence *Kimia, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin supplement.

Progendo *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Progesterone (p. 2300·2).
Dysfunctional uterine bleeding; recurrent miscarriage; premenstrual syndrome; menopausal disorders; female infertility.

Proger-F *Streger, Mex.*
Progesterone (p. 2300·2); estradiol benzoate (p. 2271·1).
Menstrual disorders.

Progering *Silesia, Chile.*
Progesterone (p. 2300·2).
Vaginal ring contraceptive.

Progesic
Note: this name may be used for preparations of different composition.
Xepa-Soul Pattinson, Hong Kong; Metiska, Indon.; Xepa-Soul Pattinson, Singapore.
Paracetamol (p. 115·1).
Fever; pain.

Progest
Note: this name may be used for preparations of different composition.
Elea, Arg.
Progesterone (p. 2300·2).
Benign breast disorders; female infertility; menopausal disorders; menstrual disorders; recurrent and threatened miscarriage; prevention of endometrial hyperplasia during oestrogen replacement therapy.

Progestan *Besins, Fr.; Kocak, Turk.*
Progesterone (p. 2300·2).
Menstrual disorders; menopausal disorders; progesterone deficiency; female infertility; threatened and recurrent miscarriage; benign breast disorders.

Progesteron-Depot *Jenapharm, Ger.†*
Hydroxyprogesterone caproate (p. 2285·1).
Female infertility; threatened or recurrent miscarriage; menstrual disorders.

Progestérone-retard Pharlon *Bayer, Fr.*
Hydroxyprogesterone caproate (p. 2285·1).
Progestogen; female infertility; threatened or recurrent miscarriage; premature labour; menstrual disorders.

Progestogel *Besins, Belg.; Besins, Fr.; Besins, Ger.; Kade, Ger.; Besins, Hong Kong; Azevedos, Port.; Besins, Rus.; Vifor, Switz.; Besins, Thai.†; Besins, Ukr.; Biopas, Venez.*
Progesterone (p. 2300·2).
Benign breast disorders.

Progeston *Meprofarm, Indon.*
Allylestrenol (p. 2255·2).
Threatened and recurrent miscarriage; premature labour.

Progestosol *Seid, Spain.†*
Progesterone (p. 2300·2).
Seborrhoeic dermatitis and associated alopecia; acne.

Progevera *IFET (ΙΦΕΤ), Gr.; Pfizer, Spain.*
Medroxyprogesterone acetate (p. 2288·1).
Contraception; endometriosis; cancer of breast, kidney, and endometrium; menstrual disorders; menometrorrhagia; female infertility; menopausal disorders.

Progevera 250 *Pfizer, Spain.*
Medroxyprogesterone acetate (p. 2288·1).
Breast cancer; endometrial cancer.

Progis *Tripharma, Turk.*
Lansoprazole (p. 1851·3).

Proglau *Edol, Port.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Proglicem *Schering-Plough, Arg.; MSD-Chibret, Fr.; MSD, Ger.; IFET (ΙΦΕΤ), Gr.; Schering-Plough, Ital.; MSD, Neth.; Schering-Plough, Singapore; MSD, Switz.*
Diazoxide (p. 1351·3).
Hypertensive episodes in nephropathy; hypoglycaemia; hypertension.

Proglycem *Merck, Canad.; Baker Norton, USA.*
Diazoxide (p. 1351·3).
Hypoglycaemia.

Pro-Gola *Sixtem, Ital.*
Propolis (p. 2597·3).

Progona *MIP, Austria; CNP, Ger.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis of the knee.

Progor *SMB, Belg.; SMB, Thai.; Galephar, Turk.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Progout *Alphapharm, Austral.; Pacific, Hong Kong; Mylan, NZ†; Alphapharm, Singapore.*
Allopurinol (p. 600·2).
Hyperuricaemia; renal calculi; gout.

Prograf *Gador, Arg.; Janssen-Cilag, Austral.; Astellas, Austria; Janssen-Cilag, Braz.; Astellas, Canad.; Pharma Investi, Chile; Astellas, China; Astellas, Cz.; Astellas, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Ger.; Astellas, Gr.; Astellas, Hong Kong; Astellas, Hung.; Astellas, Indon.; Astellas, Irl.; Astellas, Israel; Astellas, Ital.; Astellas, Jpn; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Delphi, Neth.; Euro Registratie, Neth.; Fisher, Neth.; Astellas, Norw.; Janssen-Cilag, NZ; Astellas, Philipp.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, S.Afr.; Janssen-Cilag, Singapore; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Astellas, Thai.; Eczacibasi, Turk.; Astellas, UK; Astellas, Ukr.; Astellas, USA; Janssen-Cilag, Venez.*
Tacrolimus (p. 1968·3).
Rheumatoid arthritis; transplant rejection; graft-versus-host disease; lupus nephritis; myasthenia gravis; ulcerative colitis; interstitial lung disease; atopic eczema.

Prograft *Astellas, Belg.; Astellas, Neth.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Progray *Gray, Arg.*
Propanidid (p. 1909·3).
General anaesthesia.

Progresse
Note: this name may be used for preparations of different composition.
Biosintetica, Braz.
Gabapentin (p. 523·3).
Epilepsy.

Progtolog *Abdi, Turk.*
Ruscogenin (p. 2608·3); trimebutine (p. 2634·1).

Pro-Guard *Bioglan, Austral.†*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Pro-Gut *MD, Singapore.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus lactis* (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); soya (p. 2092·3); papaya; fructo-oligosaccharides (p. 2508·1).
Maintenance of gastrointestinal flora.

Progut *Galmed, Cz.†*
Sodium picosulfate (p. 1887·2).
Constipation.

Progutt *Protherapix, Malaysia.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Nutritional supplement.

Progyluton *Bayer, Chile; Schering, Israel; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Port.; Bayer, Singapore; Bayer, Spain; Schering, Venez.*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; norgestrel (p. 2296·1).
Menopausal disorders; osteoporosis; menstrual disorders; oestrogen deficiency.

Progynex *Kocak, Turk.*
Progesterone (p. 2300·2).

Progynon *Bayer, Arg.; Bayer, Austria†; Bayer, Denm.; Panagakis, Gr.; Bayer, Swed.; Schering, Thai.†*
Estradiol valerate (p. 2271·2).
Menstrual disorders; oestrogen deficiency; menopausal disorders; osteoporosis; amenorrhoea; menorrhagia; dysfunctional uterine bleeding.

Progynova *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Chile; Bayer, China; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Hong Kong†; Bayer Schering, Indon.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer Schering, Pol.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Switz.; Bayer, Thai.; Bayer, Ukr.; Schering, Venez.*
Estradiol valerate (p. 2271·2).
Menopausal disorders; osteoporosis; oestrogen deficiency; female hypogonadism.
Bayer, Spain; Bayer, UK.
Estradiol (p. 2271·1) or estradiol valerate (p. 2271·2).
Menopausal disorders; osteoporosis.

Prohair *MSD, Chile.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

ProHance *Bracco, Canad.*
Gadoteridol (p. 1587·2).
Contrast medium for magnetic resonance imaging.

Prohance *Regional Health, Austral.; Bracco, Austria; Bracco, Belg.; Bracco, Cz.; Bracco, Denm.; Bracco, Fin.; Bracco, Fr.; Bracco, Ger.; Bracco, Irl.; Bracco, Ital.; Eisai, Jpn; Bracco, Neth.; Bracco, Norw.; Bracco, Spain; Bracco, Swed.; Bracco, Switz.; Bracco, UK; Bracco, USA.*
Gadoteridol (p. 1587·2).
Contrast medium for magnetic resonance imaging.

Prohelic *Promed, Indon.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); fish oil (p. 1460·1).
Dietary supplement in pregnancy and breast feeding.

Prohep *Aventis, S.Afr.†*
Liver hydrolysate (p. 2444·1); vitamin B_{12} (p. 2107·2); choline bitartrate (p. 2055·2); cysteine (p. 2058·3); inositol (p. 2533·2).
Liver disorders.

Prohepar *Nordmark, Rus.*
Inositol (p. 2533·2); liver extract (p. 2444·1); cyanocobalamin (p. 2107·2); choline bitartrate (p. 2055·2); cysteine hydrochloride (p. 2058·3).

Prohessen *Pharos, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic disorders.

ProHexal *Sandoz, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Prohibit
Note: this name may be used for preparations of different composition.
Sandoz, Indon.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prohiper *Mersifarma, Indon.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcolepsy.

Prohist *Be-Tabs, S.Afr.*
Promethazine hydrochloride (p. 638·2).
Sedative; premedication; hypersensitivity reactions.

Prohist CF *Pdy, USA.*
Clofedanol hydrochloride (p. 1659·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract disorders.

Prohistam *Materia Medica, Rus.*
Histamine antibodies.

Prohistin *Meprofarm, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Pro-Hydroxyquine *Pro Doc, Canad.*
Hydroxychloroquine sulfate (p. 655·2).
Lupus erythematosus; rheumatoid arthritis; malaria.

Prohype *Pharmathen, Gr.*
Finasteride (p. 2358·3).

Proimbus *Meprofarm, Indon.†*
Echinacea (p. 2498·1); ganoderma lucidum; calcium pantothenate (p. 2085·2).
Immunostimulant.

Pro-Indo *Pro Doc, Canad.*
Indometacin (p. 71·2).

Proinfark *Phapros, Indon.*
Dopamine hydrochloride (p. 1367·2).
Shock.

Projímavá *Megafyt-R, Cz.*
Senna (p. 1885·1); achillea (p. 2427·3); fennel (p. 2503·2); peppermint leaf (p. 1877·1); liquorice (p. 1853·2).
Constipation; bowel evacuation.

Pro-600K *Pro Doc, Canad.*
Potassium chloride (p. 1793·2).
Potassium supplement.

Prokanazol *ProMed, Cz.*
Itraconazole (p. 583·3).
Fungal infections.

Proken M *Kendrick, Mex.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; myocardial infarction; angina pectoris.

Prokids
Note: this name may be used for preparations of different composition.
Mahakam Beta, Indon.
Vitamins; docosahexaenoic acid (p. 1460·1); arachidonic acid (p. 2446·1); curcuminoid (p. 2489·3); bovine colostrum (p. 2380·3); lysine hydrochloride (p. 2079·3).
Dietary supplement for infants and children.

Proking *Cetus, Arg.*
Clobutinol hydrochloride (p. 1658·3).
Cough.

Proking NF *Cetus, Arg.*
Butamirate citrate (p. 1657·3).
Cough.

Prokinyl *Techni-Pharma, Mon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Proklot *Torrent, Philipp.*
Tranexamic acid (p. 1164·2).
Angioedema; fibrinolytic haemorrhage.

Proktosedon *Polmex, Pol.*
⊗Cinchocaine hydrochloride (p. 1983·2); esculoside (p. 2431·2); hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Anorectal disorders.

Pro-Lacta *Pascual, Philipp.*
Moringa oleifera.
Nutritional supplement.

Prolacta with DHA for Baby *Novell, Indon.*
Fish oil (p. 1460·3).
Nutritional supplement for the developing foetus.

Prolacta with DHA for Mother *Novell, Indon.*
Fish oil (p. 1460·3).
Nutritional supplement in pregnancy.

Prolactase *Pharmascience, Canad.*
Tilactase from *Aspergillus oryzae* or *Kluyveromyces lactis* (p. 2631·2).
Lactase insufficiency.

Proladone *Phebra, Austral.*
⊗Oxycodone pectinate (p. 113·1).
Pain.

Prolaken *Teva, Mex.†*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias.

Prolanz *Sunthi Sepuri, Indon.†*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Prolasol *Premier Research, Neth.†*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Prolastin *Teva Tuteur, Arg.; Talecris, Austria; Grifols, Canad.; Grifols, Ger.; Demo, Gr.; IFET (ΙΦΕΤ), Gr.; Talecris, Irl.; Grifols, Neth.; Bayer, Port.; Crucell, Switz.; Talecris, USA.*
$Alpha_1$-proteinase inhibitor (p. 2438·1).
$Alpha_1$ antitrypsin deficiency.

Prolastina *Grifols, Denm.; Grifols, Fin.; Kedrion, Ital.; Grifols, Spain; Grifols, Swed.*
$Alpha_1$-proteinase inhibitor (p. 2438·1).
$Alpha_1$ antitrypsin deficiency.

Prolaxatan *Polfa Lodz, Pol.†*
Macrogol 4000 (p. 2547·3).
Constipation.

Proldin *Sons, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Prolecin *Promed, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Prolekofen *Lek, Cz.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Prolene *Fonterra, Indon.†*
Preparation for enteral nutrition.

Prolensa *Bausch & Lomb, USA.*
Bromfenac sodium (p. 30·1).
Eye pain and inflammation following cataract surgery.

Prolepsi *Mersifarma, Indon.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Proleukin *Raffo, Arg.†; Novartis, Austria; Novartis, Belg.; Zodiac, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Chiron, Hong Kong†; Novartis, Hung.;*

Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Asofarma, Mex.; Novartis, Neth.; Novartis, NZ; Novartis, Pol.†; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Roche, Turk.; Novartis, UK; Prometheus, USA.
Aldesleukin (p. 810·1).
Malignant melanoma; acute megaloblastic leukaemia; bone marrow transplantation; renal-cell carcinoma.

Pro-Levocarb *Pro Doc, Canad.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Prolevox *Meprofarm, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Prolex DM *Blansett, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1).
Cough.

Prolex DMX *Blansett, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1).
Cough.

Prolia *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fr.; Amgen, Ger.; Amgen, Gr.; Amgen, Hung.; Amgen, Irl.; GSK, Israel; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; GSK, Singapore; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Amgen, UK; GSK, Ukr.; Amgen, USA.*
Denosumab (p. 1182·1).
Osteoporosis; bone-loss associated with chemotherapy in breast cancer or prostatic cancer.

Prolic *Sanbe, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Prolid *Protech, Rus.*
Nimesulide (p. 101·3).
Fever; pain; inflammation.

Prolief *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Prolifed *Quality, Hong Kong.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Prolifen *Effik, Ital.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Prolift *Pfizer, Braz.; Pfizer, Chile.*
Reboxetine mesilate (p. 447·1).
Depression.

Proligon *Kee, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Induction of ovulation; hypogonadotrophic hypogonadism; male infertility.

Prolipase *Janssen-Cilag, Arg.*
⊗Pancrelipase (p. 2580·1).
Dyspepsia; pancreatic insufficiency.

Prolipid
Note: this name may be used for preparations of different composition.
Cowik, Pol.
Guazuma ulmifolia; murraya; sonchus arvensis.
Hypercholesterolaemia.
Unipharma, Gr.
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Prolisina E2 *Pfizer, Arg.*
Dinoprostone (p. 2134·1).
Labour induction.

Prolisina VR *Pfizer, Arg.*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus.

Proliva *Gracia, Indon.*
Selenium (p. 2086·3); milk thistle (p. 1561·1); citrus bioflavonoids (p. 2505·2); myrtillus (p. 2566·2); thioctic acid (p. 2629·1); quercetin (p. 2505·3); turmeric (p. 2218·1); liquorice (p. 1853·2); taraxacum (p. 2625·3).
Dietary supplement for liver function.

Proliver *Simex, Indon.*
Curcuminoid (p. 2489·3); silymarin phytosome (p. 1561·2); choline bitartrate (p. 2055·2); vitamin B_6 (p. 2105·3).
Liver disorders.

Prolivit *Erlimpex, Indon.*
Phospholipids (p. 2201·2); vitamin B substances (p. 2102·3).
Nutritional supplement.

Prolix *Pharma Nutria, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Prolixan *Unipharma, Gr.*
Azapropazone (p. 28·3).
Rheumatoid arthritis; ankylosing spondylitis.

Prolixin *BMS, Turk.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Prolohex *Hexal, Philipp.†*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Prolol *Dexcel, Israel; Atlantic, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension; angina pectoris; myocardial infarction; migraine; hyperthyroidism; hypertrophic obstructive cardiomyopathy; phaeochromocytoma; tremor.

Prolon 8 *Promed, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Prolong *Maver, Chile.*
Lidocaine (p. 1988·1).
Erectile dysfunction.

Prolopa *Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Proloprim *Glaxo Wellcome, USA.*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Proloscan *Teva, Mex.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prolosin *Niche, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prolubrin *Mayo, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Prolung *Galenium, Indon.†*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Proluton *Bayer, Arg.; Schering, Austral.†*
Progesterone (p. 2300·2).
Amenorrhoea; progesterone test in secondary amenorrhoea.
Bayer, Ital.
Hydroxyprogesterone caproate (p. 2285·1).
Threatened or recurrent miscarriage; progestogen deficiency; amenorrhoea; female infertility; uterine hypoplasia; metrorrhagia.

Proluton Depot *Bayer, Arg.; Bayer, Austria; Bayer, Ger.†; IFET (ΙΦΕΤ), Gr.; Zydus, India; Bayer Schering, Malaysia; Schering, Philipp.†; Bayer, Thai.; Bayer, Turk.*
Hydroxyprogesterone caproate (p. 2285·1).
Amenorrhoea; female infertility; threatened or recurrent miscarriage; endometriosis; hormone replacement therapy; cancer of breast, uterus, or kidney.

Proma *Doctors, Philipp.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses.

Promac *Provit, Mex.†*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Promacet *MCR, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).
Pain.

Promacta *GSK, USA.*
Eltrombopag olamine (p. 1140·1).
Immune thrombocytopenia; hepatitis C-associated thrombocytopenia.

Promactil *Combiphar, Indon.*
Chlorpromazine (p. 1045·2).
Psychoses; nausea and vomiting.

Promag *Kalbe, Indon.*
Hydrotalcite (p. 1845·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Epigastric pain; bloating; peptic ulcer; gastric hyperacidity.

Promag Double Action *Kalbe, Indon.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Promagen *ICM, Singapore.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; insomnia.

Promanum *Braun, Port.†*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Promanum N *Braun, Cz.; Braun, Ger.; Braun, Switz.†*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Hand disinfection.

Promavit *Lapi, Indon.*
Vitamins; minerals; omega-3 fatty acids (p. 1460·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); tuna fish oil.
Dietary supplement for for pregnant and breast-feeding women.

Promax
Note: this name may be used for preparations of different composition.
Hikma, Ukr.
Naproxen sodium (p. 98·2).
Pain; musculoskeletal and joint disorders; gout.
Gerolymatos, Gr.†
Alendronate sodium (p. 1171·3).
Osteoporosis.

Promazine *Atlantic, Philipp.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses.

Prome *Interbat, Indon.*
Promethazine hydrochloride (p. 638·2); ipecacuanha (p. 1667·2); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Promeal *Volchem, Ital.*
Preparation for enteral nutrition.

Promecilina *Sandoz, Mex.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Promedex *Interbat, Indon.*
Syrup: Promethazine hydrochloride (p. 638·2); dextromethorphan (p. 1660·1); ipecacuanha (p. 1667·2); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Respiratory-tract disorders with cough.
Interbat, Indon.
Tablets: Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders with cough.

Promedin *Vargas, Venez.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Promedina *Vargas, Venez.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Promedyl
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
⊗Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2).
Hypersensitivity disorders; cough; respiratory-tract congestion.

Promedyl DM *CCM, Malaysia.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough; nasal congestion.

Promedyl Plus *CCM, Malaysia.*
Chlorphenamine maleate (p. 620·3); pholcodine (p. 1675·1).
Cough.

Promega *Parke, Davis, USA.*
Omega-3 marine triglycerides (p. 1460·3); vitamin E (p. 2119·1).
Dietary supplement.

Promel *Quim-Far, Venez.*
Dipyrone (p. 53·3).
Fever; pain.

Promelix *Sunward, Singapore.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).

Promemore *SVUS, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Promeno *Interbat, Indon.*
Red clover (p. 2482·1).
Menopausal disorders.

Promenorea *Verisfield, Gr.*
Progesterone (p. 2300·2).
Menstrual disorders.

Promensil *Novogen, Austral.; Farmoquimica, Braz.; Pharmacare, Canad.; Novogen, UK.*
Red clover (p. 2482·1).
Menopausal disorders.
Ikapharmindo, Indon.
Isoflavone (p. 2620·3).
Menopausal disorders.

Promergan *Belfar, Braz.*
Promethazine (p. 638·2).

Promes *Protech, Rus.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Promesec *Mars, Philipp.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Promesin *Kocak, Turk.*
Tobramycin (p. 380·1).

Promet
Note: this name may be used for preparations of different composition.
Oriental, Philipp.
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions.
Millimed, Thai.†
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; mastocytosis.

Prometax *Biosintetica, Braz.; Novartis, Cz.; Novartis, Denm.; Novartis, Gr.; Novartis, Irl.; Biofutura, Ital.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Esteve, Spain.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Prometazol *Sanval, Braz.*
Promethazine (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; sedative.

Promeths with Dextromethorphan *Barre-National, USA.*
Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Prometh VC Plain *Barre-National, USA†; Goldline, USA†; Warner Chilcott, USA.†*
Promethazine hydrochloride (p. 638·2); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis; nasal congestion.

Promethazine comp *Ratiopharm, Neth.†*
Promethazine (p. 638·2); potassium sulphoguaiacolate; ipecacuanha (p. 1667·2).
Cough.

Promethazine Compound Linctus *Marching, Hong Kong.†*
⊗Promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2).
Cold and influenza symptoms.

Promethazine Expectorants *Vitamed, Israel.*
Promethazine hydrochloride (p. 638·2); ipecacuanha (p. 1667·2); sulfogaiacol (p. 1678·1).
Cough.

Promethazine Ikapharmindo *Ikapharmindo, Indon.*
Promethazine hydrochloride (p. 638·2); sulfogaiacol (p. 1678·1); citric acid (p. 2480·3); sodium citrate (p. 1781·2); ipecacuanha (p. 1667·2).
Cough.

Promethazine VC with Codeine *Warner Chilcott, USA.*
Promethazine hydrochloride (p. 638·2); phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2).

Promethegan *G & W, USA.*
Promethazine hydrochloride (p. 638·2).

Prometidine *Cazi, Braz.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Prometrium *Merck, Canad.; Rottapharm, Ital.; Solvay, USA.*
Progesterone (p. 2300·2).
Adjunct to oestrogen replacement therapy; menopausal disorders; menstrual disorders; female infertility; threatened or habitual miscarriage; amenorrhoea.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Promezal *Landsteiner, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Promezin *Jinling, Philipp.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; premedication.

Promezol *Promed, Indon.; Vargas, Venez.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Promibasol *Rayere, Mex.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Promibasol-Plus *Rayere, Mex.†*
⊗Fluocinolone acetonide (p. 1636·1); metronidazole (p. 936·1); nystatin (p. 590·3).
Vulvovaginal infections.

Promiced *IQFA, Mex.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Promicin *Mayo, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Promictan *Avansor, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Promid *Biofarma, Turk.†*
Protionamide (p. 345·1).
Tuberculosis.

Promidan *Mintlab, Chile.*
Chlormezanone (p. 1045·1); diazepam (p. 1063·2).
Skeletal muscle spasm; anxiety.

Promil Lactose-free *Wyeth, Philipp.*
Infant feed.
Lactose intolerance.

Promin *Vickmans, Hong Kong.†*
Promethazine (p. 638·2).

Prominol *MCR, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1).
Pain.

Prominox *Alet, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Promise
Note: this name may be used for preparations of different composition.
Wyeth, Singapore.
Nutritional supplement for children.

Promiseb *Promius, USA.*
Emollient.

Promisec *Aristo, India.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; gastritis; peptic ulcer.

Pro-Misil *Veltipharm, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections.

Pro-Miss *Kato, Pol.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); mepyramine (p. 635·1).
Premenstrual syndrome.

Promit *Medical Specialties, Austral.; Pharmacia, S.Afr.†; Pharmacia, USA.†*
⊗Dextran 1 (p. 1137·3).
Prevention of anaphylactic reactions to infusions of dextran.

Promiten *Meda, Denm.; Meda, Hung.; Meda, Norw.; Meda, Swed.*
⊗Dextran 1 (p. 1137·3).
Prevention of anaphylactic reactions to infusions of dextrans.

Promix 3 *Capo Sole, Ital.*
Propolis (p. 2597·3); myrtillus (p. 2566·2); echinacea (p. 2498·1); agrumi oil.

Promixin
Note: this name may be used for preparations of different composition.
Profile, Denm.; Swedish Orphan, Ger.; Profile, Irl.; Profile, Norw.; Profile, Spain; Profile, UK.
Colistimethate sodium (p. 275·3).
Pseudomonal lung infections in cystic fibrosis; Gram-negative bacterial infections.
Pyridam, Indon.
Thiamphenicol (p. 376·3).
Bacterial infections.

Promizol *Senosiain, Mex.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Promnix *Taro, Israel.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Promocard *AstraZeneca, Neth.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Promocid *Mugi, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

ProMod *Abbott, Austral.†; Abbott, Chile; Abbott, Ital.†; Abbott, Malaysia; Abbott, NZ; Abbott, Philipp.*
Dietary protein supplement.
Abbott Nutrition, Singapore.
Nutritional supplement.

Promofort *Amnol, Ital.*
Acai; magnesium chelate; potassium aspartate (p. 1793·1); citrulline malate (p. 2056·3); SunActive iron; zinc chelate.
Asthenia.

Promogran *Systagenix, Ital.*
Oxidised cellulose (p. 1157·3); collagen (p. 2483·2).
Skin ulcers.

Promogran Prisma *Systagenix, Ital.*
Oxidised cellulose (p. 1157·3); collagen (p. 2483·2); silver (p. 2615·1).
Wounds; skin ulcers.

Promolan *Sarabhai Piramal, India.*
High-protein dietary supplement.

Promolax *Amnol, Ital.*
Psyllium (p. 1849·1); tryptophan (p. 453·2); fennel (p. 2503·2).
Gastrointestinal disorders; obesity.

Promonta *Nycomed, Pol.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Promotion *Rayere, Mex.*
Meloxicam (p. 86·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and soft-tissue disorders.

Promox *Medreich, Hong Kong; Prosel, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Promoxil *Cipla-Medpro, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Promoxy *Inpac, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Promptcillin Forte *Teva, Hung.*
Benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Promuba *Meprofarm, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Promuxol *Gracia, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Promyrtil *Schering-Plough, Chile.*
Mirtazapine (p. 436·1).
Depression.

Pronadrine *Inpac, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle pain and spasm.

Pronal *Pro Doc, Canad.*
Aspirin (p. 22·2); butalbital (p. 1043·3); caffeine (p. 1203·3).

Pronal Dix *Mayo, Mex.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Pronal-C *Pro Doc, Canad.*
Aspirin (p. 22·2); butalbital (p. 1043·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).

Pronalges *Dexa, Indon.; Dexa, Singapore.*
Ketoprofen (p. 79·1).
Osteoarthritis; rheumatoid arthritis; pain; musculoskeletal and joint disorders; inflammation.

Pronalol *Burapha, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; arrhythmias; migraine; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; anxiety; tremor; hyperthyroidism.

Pronamic *Inpac, Thai.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Pronapen *Pfizer, Turk.; Pfizer, Venez.*
Benzylpenicillin potassium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Pronasteron *Sanval, Braz.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Pronat
Note: this name may be used for preparations of different composition.
Solfran, Mex.†
Naproxen (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Pronatal *Ginsana, Switz.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Pronativ *Octapharma, NZ.*
Human prothrombin complex (p. 1149·3).
Haemorrhagic disorders.

Pronax *Intas, Philipp.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia androgenetica.

Pronaxen *Orion, Fin.; Orion, Swed.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; inflammation; pain; fever.

Pronaxil *Streger, Mex.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Pronemia Hematinic *Lederle, USA.*
Ferrous fumarate (p. 2060·3); intrinsic factor concentrate (p. 2534·2); vitamin B_{12} substances (p. 2107·2); folic acid (p. 2063·1). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Pronenen *Cifarma, Braz.*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1); zinc oxide (p. 1729·1).
Skin disorders.

Pronerv *Gerot, Austria.*
Thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuropathies; neuralgia; neuritis.

Pronervon *Ivax, Arg.*
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Pronervon T *Scheffler, Ger.†*
Temazepam (p. 1109·1).
Sleep disorders.

Pronestin *Rekah, Israel.*
Benzocaine (p. 1980·2); methylthioninium chloride (p. 1559·1); thymol (p. 1772·2).
Gingivitis; mouth hygiene; stomatitis.

Pronestyl *BMS, Austral.†; IFET (ΙΦΕΤ), Gr.; BMS, India; BMS, Irl.†; BMS, NZ; BMS, S.Afr.†; BMS, Singapore.*
Procainamide hydrochloride (p. 1475·3).
Arrhythmias.

Proneurax *Janssen-Cilag, Venez.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Proneurin *Hexal, Ger.†*
Promethazine hydrochloride (p. 638·2).
Anxiety; hypersensitivity reactions; sleep disorders; vomiting.

Proneurit *Demo, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Proneuron *Meprofarm, Indon.*
Dipyrone (p. 53·3); diazepam (p. 1063·2).
Pain.

Pronicid *Themis, Rus.*
Protionamide (p. 345·1).
Tuberculosis.

Pronicol *Bioresearch, Mex.*
Chloramphenicol (p. 257·1).
Gastrointestinal infections.

Pronicy *Kalbe, Indon.*
Cyproheptadine hydrochloride (p. 624·1).
Allergic rhinitis; allergic skin disorders.

Pronita *Bufa, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); sorbitol (p. 2092·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Iron-deficiency anaemia.

Pronitol *Abbott, Spain.†*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Pronivel *Elea, Arg.*
⊗Epoetin (p. 1141·1).
Anaemias.

Pronix *Vannier, Arg.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Pronizol *Kocak, Turk.*
Ornidazole (p. 943·1).

Pronoctan *Bayer, Denm.*
Lormetazepam (p. 1082·1).
Insomnia; premedication.

Pronoran *Servier, Pol.; Servier, Rus.; Servier, Ukr.*
Piribedil (p. 911·1).
Parkinsonism; intermittent claudication; ischaemic eye disorders; mental function impairment.

Pronoxen *Farcoral, Mex.*
Naproxen (p. 98·2).
Inflammation; pain.

Prontalgin
Note: this name may be used for preparations of different composition.
GiEnne, Ital.
Tramadol hydrochloride (p. 139·2).
Pain.

Prontalgine *Boehringer Ingelheim, Fr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Prontinal *Dompe, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Obstructive airways disease; rhinitis.

Pronto *Church & Dwight, Canad.*
Pyrethrum flower (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.
Del, USA.
Shampoo: Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.
Del, USA.
Surface spray: Phenothrin (p. 2160·1).
Lice infestation.

Pronto Digest *New Life, Arg.*
Amino acids; pancreatic enzymes (p. 2579·3).
Dietary supplement.

Pronto Platamine *Pfizer, Ital.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Prontobario *Gerot, Austria; Bracco, Ital.*
Barium sulfate (p. 1583·2).
Simeticone (p. 1886·2) is included in some preparations to eliminate gas from the gastrointestinal tract before radiography.
Contrast medium for gastrointestinal radiography.

Prontoferro *Amsa, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Prontoflex *Cyathus, Cz.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue disorders.

Prontofort *Medix, Mex.*
Tramadol hydrochloride (p. 139·2).
Pain.

Prontogest *Amsa, Ital.*
Progesterone (p. 2300·2).
Threatened or recurrent miscarriage; menstrual disorders; postnatal depression; adjunct in gynaecological surgery.

Prontoket *Medicom, Cz.†; CSC, Hung.†*
Ketoprofen (p. 79·1).
Inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Prontol *Novag, Mex.*
⊗Metoprolol (p. 1434·3).
Hypertension.

Prontolax
Note: this name may be used for preparations of different composition.
Generis, Port.
Ispaghula (p. 1849·1).
Constipation; dietary fibre supplement; colostomy management; irritable bowel syndrome; hypercholesterolaemia.

Streuli, Switz.
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Prontonema *Biosintex, Arg.*
Sodium phosphate (p. 1791·2).
Bowel evacuation.

Prontopyrin plus *McNeil, Ger.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Prontosan *Braun, UK.*
Polihexanide (p. 1766·1).
Wounds.

Pron-X *Farcoral, Mex.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Influenza symptoms.

Prootocipro *Fortbenton, Arg.*
⊗Ciprofloxacin (p. 261·1); hydrocortisone (p. 1640·1).
Infected eye disorders.

Propa *Jean-Marie, Hong Kong.*
⊗Propranolol (p. 1479·1).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; migraine; myocardial infarction.

Xepa-Soul Pattinson, Singapore.
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; anxiety; migraine; tremor; arrhythmias; hypertrophic obstructive cardiomyopathy; hyperthyroidism; myocardial infarction.

Propac *Sherwood, USA.*
Dietary protein supplement.

Propace *Apotex, Mex.*
Metoclopramide (p. 1862·2).

Propacet *Lemmon, USA.†*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Propacor *Bunker, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).

Propaderm *Paladin, Canad.; Kyowa, Jpn.*
⊗Beclometasone dipropionate (p. 1621·2).
Skin disorders.

Propain *Adcock Ingram, S.Afr.; Sankyo, UK.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); caffeine (p. 1203·3).
Pain; tension headache; fever; cold and influenza symptoms.

Propain Forte *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); caffeine (p. 1203·3); phenobarbital (p. 535·2).
Pain and associated tension.

Propain Plus *Sankyo, UK.*
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain.

Propal *Sandoz, Denm.; Svizera, India.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; migraine; myocardial infarction; hyperthyroidism; tremor; variceal haemorrhage; arrhythmias; hypertrophic subaortic stenosis.

Propalem *Teva, Mex.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hypertrophic obstructive cardiomyopathy; hyperthyroidism; phaeochromocytoma.

Propalgin
Note: this name may be used for preparations of different composition.
Montpellier, Arg.
Pargeverine hydrochloride (p. 1877·1); clonixin lysine (p. 40·1).
Pain; muscle spasm.

Propalgina Plus *Bayer, Spain.*
Ascorbic acid (p. 2110·3); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Propam *Pacific, NZ.†*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; premedication; skeletal muscle spasm; sleep disorders; spasticity.

Propamide *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Propan *ADP, Philipp.*
Buclizine hydrochloride (p. 618·3); vitamins.
Nutritional supplement.

UCI, Braz.
Buclizine hydrochloride (p. 618·3); vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Reduced appetite; tonic.

Propan Gel-S *Adcock Ingram, S.Afr.*
Aluminium hydroxide (p. 1817·2); magnesium oxide (p. 1857·3); dicycloverine hydrochloride (p. 1834·2); dimeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis; heartburn; flatulence.

Propan with Iron *ADP, Philipp.*
Buclizine hydrochloride (p. 618·3); ferrous sulfate (p. 2062·2); vitamin B substances (p. 2102·3).
Anorexia; tonic.

Propan TLC *ADP, Philipp.*
Vitamins; chlorella (p. 2475·3); taurine (p. 2626·2).
Dietary supplement.

Propaneitor *Driburg, Arg.*
⊗Propranolol (p. 1479·1).
Migraine.

Propanol *Beacons, Singapore; Utopian, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; angina pectoris; arrhythmias; anxiety; migraine; tremor; phaeochromocytoma; myocardial infarction; hypertrophic cardiomyopathy; hyperthyroidism.

Propanolon *Brasterapica, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).

Propanorm *ProMed, Cz.; ProMed, Rus.; ProMed, Ukr.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Propanox *Royton, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension.

PropapH *Del, USA.*
Salicylic acid (p. 1719·1).
Acne.

Proparakain-POS *Ursapharm, Ger.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

Propargile *Holistica, Fr.*
Propolis (p. 2597·3); pollen (p. 2593·3); clay.
Digestive disorders.

Proparin *Probiomed, Mex.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders; anticoagulation in blood transfusion, extracorporeal circulation, and dialysis.

Propark *Uniao Quimica, Braz.*
Biperiden hydrochloride (p. 895·1).

Propass *Hormel, Hong Kong; Hormel, Singapore.*
Dietary protein supplement.
Preparation for enteral nutrition.

Propast *CaDiGroup, Ital.*
Zinc oxide (p. 1729·1); propolis (p. 2597·3); undecenoic acid (p. 596·3).
Skin disorders.

Propavan *Sanofi-Aventis, Swed.*
Propiomazine maleate (p. 640·1).
Sleep disorders.

Propavent
Note: this name may be used for preparations of different composition.
GSK, Arg.
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; allergic rhinitis; nasal polyps.

Propavente
Note: this name may be used for preparations of different composition.
Glaxo Wellcome, Port.
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Cough.

Propazine *Tatkhimfarm, Rus.*
Promazine (p. 1099·3).
Agitation.

Propecia *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Biavéz), Gr.; MSD, Hong Kong; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Neth.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Propel *Intersect ENT, USA.*
⊗Mometasone furoate (p. 1644·1).
Nasal congestion following sinus surgery.

Propenem *Promed, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Propepsa *Gracia, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Properazine *Sunward, Singapore.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; psychoses; vertigo.

Properil *Royal, Chile.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Propes *NIR, Ukr.*
Peptide extract from embryo tissue of large horned cattle (p. 2444·1).
Malignant neoplasms; immunodeficiency.

Propeshia *MSD, Mex.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Propess *Craveri, Arg.; Ferring, Austria; Ferring, Belg.; Ferring, Braz.; CSC, Cz.†; Ferring, Denm.; Ferring, Fin.†; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Israel; Ferring, Ital.; Ferring, Mex.; Ferring, Neth.; Controlled Therapeutics, Pol.; Ferring, Port.; Ferring, S.Afr.; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, UK.*
Dinoprostone (p. 2134·1).
Induction and maintenance of labour; termination of pregnancy.

Prophage *Medicine Products, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Prophedin *Siam Bheasach, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; hay fever; upper respiratory-tract congestion; cold symptoms.

Pro-Phree *Abbott, Austral.†; Ross, USA.*
Protein-free infant feed supplement.

Prophylactin C *GSK, Rus.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Vitamin C deficiency.

Prophyllin *Rystan, USA.*
Sodium propionate (p. 593·1); chlorophyllin copper complex (p. 2178·3).
Dermatophytosis; contact dermatoses; eczemas; minor burns.

Prophylux *Hennig, Ger.†*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; myocardial infarction; migraine; anxiety; essential tremor.

Propiden *Sandoz, Denm.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Propil *Pfizer, Braz.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Propilan *Glenmark, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Propilracil *Biolab Sanus, Braz.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Propimedac *Medac, Ger.*
Propiverine hydrochloride (p. 2363·1).
Bladder hyperactivity.

Propimex *Ross, USA.*
A range of methionine- and valine-free preparations for enteral nutrition including an infant feed.
Propionic acidaemia; methylmalonic acidaemia.

Propine *Allergan, Austral.†; Allergan, Belg.†; Allergan, Braz.; Allergan, Canad.†; Allergan, Denm.†; Allergan, Fin.†; Allergan, Fr.†; Allergan, Hong Kong†; Allergan, Irl.†; Allergan, Ital.; Allergan, Norw.†; Allergan, NZ†; Allergan, Singapore†; Allergan, Swed.†; Allergan, Thai.; Allergan, UK†; Allergan, USA.*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma; ocular hypertension.

Propinorm *Amdipharm, Irl.*
Propiverine hydrochloride (p. 2363·1).
Urinary incontinence; bladder instability.

Propiochrone *IFET (ΙΦΕΤ), Gr.; MSD, Gr.*
⊗Betamethasone sodium phosphate (p. 1623·3); betamethasone dipropionate (p. 1623·3).
Corticosteroid.

Propioform *Schering-Plough, Gr.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Propiogenta *Schering-Plough, Gr.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin (p. 304·2).
Infected skin disorders.

Propional *Silanes, Mex.*
Naproxen (p. 98·2).
Pain; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders.

Propionat *Farmigea, Ital.*
Sodium propionate (p. 593·1).
Eye disorders.

Propiosalic *Paranova, Denm.; MSD, Gr.*
⊗Salicylic acid (p. 1719·1); betamethasone dipropionate (p. 1623·3).
Skin disorders.

Propiosol *Neo Química, Braz.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Propirin *Christo, Hong Kong.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Propiver *Mibe, Ger.*
Propiverine hydrochloride (p. 2363·1).
Bladder hyperactivity.

Proplasia *Anabiosis, Gr.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Proplex *Baxter, Israel.†*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Proplex T *Baxter, Hong Kong†; Baxter, USA.†*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Proplexo *Prodotti, Braz.†*
Vitamin B substances (p. 2102·3).

Proplexo C *Prodotti, Braz.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Pro-Plus *Roche Consumer, Irl.†; Roche Consumer, UK.*
Caffeine (p. 1203·3).
Fatigue.

Propoabbott *Abbott, Braz.†*
Propofol (p. 1909·3).
General anaesthesia.

Propociclina *Actimex, Ital.*
Propolis bioflavonoid (p. 2597·3).
Mouth infections.

Propofan *Sanofi-Aventis, Fr.†*
Tablets: Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Propofol Lipuro *Lapidot, Israel.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Propogen *Genepharm, Gr.*
Propofol (p. 1909·3).

Propolan *Herbapol Wroclaw, Pol.†*
Propolis (p. 2597·3).
Gingivitis; sore throat; burns; chilblains; wounds; skin infections.

Propolcream *Bucaneve, Ital.†*
Propolis (p. 2597·3).

Propoleos *Natufarma, Arg.*
Propolis (p. 2597·3).
Mouth and throat disorders.

Propolgel *Princeps, Ital.*
Propolis (p. 2597·3).
Skin irritation.

Propolipid *Fresenius, Belg.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Propofol (p. 1909·3).
General anaesthesia; sedative; sedation in ventilated patients.

Propolis C *Knop, Chile.*
Propolis (p. 2597·3); eucalyptus (p. 2501·1); ascorbic acid (p. 2110·3).
Immunostimulant.

Propolisan *Apipol, Pol.*
Propolis (p. 2597·3).
Burns; wounds; fungal skin infections; foot hyperhidrosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Propolisept Urtinktur *Johanser, Ger.*
Propolis (p. 2597·3).
Homoeopathic preparation.

Propolisept-Salbe *Johanser, Ger.†*
Propolis (p. 2597·3).
Skin disorders.

Propolisol *Apipol, Pol.*
Propolis (p. 2597·3).
Skin disorders; mouth and throat disorders.

Propolkit *Ximena Polanco, Chile.*
Oral drops; capsules: Propolis (p. 2597·3).
Immunostimulant.

Ximena Polanco, Chile.
Spray: Honey (p. 2072·1); plantain (p. 2592·3); propolis (p. 2597·3); eucalyptus (p. 2501·1); bitter orange (p. 2575·3); menthol (p. 2553·2).

Ximena Polanco, Chile.
Syrup: Honey (p. 2072·1); propolis (p. 2597·3); rose hip (p. 2607·1); plantain (p. 2592·3); eucalyptus (p. 2501·1).

Proponol *Help, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Proposol *Altayvitamin, Rus.*
Propolis (p. 2597·3).
Skin disorders.

Proposol-N *Mikrofarm, Rus.*
⊗Glycerol (p. 2517·2); propolis (p. 2597·3).
Inflammatory mouth disorders.

Propotil *Biochimico, Braz.*
Propofol (p. 1909·3).

Propovan *Cristalia, Braz.; Bharat, Rus.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Propoven *Fresenius Kabi, Irl.; Fresenius Kabi, UK; APP, USA.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

ProPower *Blackmores, Austral.*
Nutritional supplement.

Propoxymol *Christo, Hong Kong.†*
Paracetamol (p. 115·1); dextropropoxyphene (p. 43·2).
Pain.

Propra comp *Ratiopharm, Ger.*
⊗Propranolol hydrochloride (p. 1479·1); triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Propral *Orion, Fin.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hyperthyroidism; phaeochromocytoma; digitalis toxicity; migraine and cluster headache; essential tremor; myocardial infarction; hypertension.

Propramed *Cimed, Braz.*
⊗Propranolol (p. 1479·1).

Propra-ratiopharm *Ratiopharm, Ger.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias; angina pectoris; tremor; hyperthyroidism.

Proproten *Materia Medica, Rus.*
Antibodies to brain-specific proteins S-100.
Alcohol withdrawal syndrome.

Propur *Five Coop, Hung.*
Propolis (p. 2597·3).
Inflammation; immunostimulant.

Propycil *Admeda, Cz.; Admeda, Ger.; Admeda, Hung.; Admeda, Port.; Livron, Rus.; Pro Concepta, Switz.; Frik, Turk.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Propyderm *ACO Hud, Swed.*
Emollient.
Dry skin.

Propyfenazon comp *MAE, Neth.*
Propyphenazone (p. 127·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Propyl *Sriprasit, Singapore; Sriprasit, Thai.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Propy-Lacticare *Stiefel, Fr.†*
Lactic acid (p. 2539·1); propylene glycol (p. 2205·2).
Dry skin disorders.

Propyless *MSD, Swed.*
Emollient.
Dry skin.

Propylthiocil *Teva, Israel.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Propyl-Thyracil *Paladin, Canad.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Propymal *Apotex, Neth.*
Valproic acid (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Propyretic *Combiphar, Indon.*
Paracetamol (p. 115·1).
Fever.

Propysal *CCS, Swed.†*
Emollient.
Dry skin.

Pro-Q *CollaGenex, USA.*
Dimeticone (p. 2209·3).
Barrier preparation.

ProQuad *Sanofi Pasteur, Cz.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; MSD, NZ; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Merck, USA.*
A measles, mumps, rubella, and varicella-zoster vaccine (Enders Edmonston, Jeryl Lynn, RA 27/3, and Oka/Merck strains respectively) (p. 2401·2).
Active immunisation.

Proquiferon *Probiomed, Mex.*
Interferon alfa-2a (p. 989·2).
Malignant neoplasms; chronic hepatitis B; chronic hepatitis C.

Proquin *Genepharm, Austral.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

P-Roquine *PP Lab, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria.

Proracyl *Genopharm, Fr.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Proral *Utopian, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; phaeochromocytoma; arrhythmias; migraine; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; anxiety; tremor; hyperthyroidism.

Pro-Red *Pro-Pharma, USA.†*
Hydrocodone tartrate (p. 67·2); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pro-Red AC *Pro-Pharma, USA.*
Codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Cough.

Prorelax *Behrens, Venez.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Prorelief *HLB, Arg.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Prorenal *Novell, Indon.*
DL-3-Methyl-2-oxo-valeric acid; 4-methyl-2-oxo-valeric acid; 2-oxo-3-phenyl-propionic acid; 3-methyl-2-oxo-butyric acid; DL-2-hydroxy-4-methylthio-butyric acid; amino acids.
Renal insufficiency.

Prorhinel *Interdelta, Switz.*
Benzododecinium bromide (p. 1739·2); sodium chloride (p. 1795·1); polysorbate 80 (p. 2203·3).
Nasal disorders.

Novartis Sante, Fr.
Benzododecinium bromide (p. 1739·2); polysorbate 80 (p. 2203·3).
Rhinopharyngeal infections.

Prorhinite *Novartis Sante, Fr.†*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Proris *Pharos, Indon.*
Ibuprofen (p. 68·2).
Fever; pain.

Prorner *Nichi-Iko, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Prosal N *Welti, Switz.*
Chamomile (p. 2474·1); rhatany (p. 2603·3); sage (p. 2608·3).
Mouth and throat inflammation.

Proscal *Protherapix, Malaysia.*
Minerals; trace elements; colecalciferol (p. 2113·1).
Dietary supplement for healthy bones.

Proscar *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.†; MSD, Denm.; MSD, Fin.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; Chibret, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Proscope *Alfresa, Jpn.*
Iopromide (p. 1591·3).
Radiographic contrast medium.

Prosdina *Biotech, Venez.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prosdox Duo *Lafedar, Arg.*
30 Tablets, finasteride (p. 2358·3); 30 tablets, doxazosin (p. 1369·1).
Benign prostatic hyperplasia.

Prosec *ACME, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; dyspepsia.

Proseda F *Szama, Arg.*
Fluconazole (p. 578·2).
Fungal infections.

Prosedal *Loeffler, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Prosed/DS *Ferring, USA.*
Methenamine (p. 322·3); salol (p. 129·3); methylthioninium chloride (p. 1559·1); benzoic acid (p. 1738·2); hyoscyamine sulfate (p. 1848·1).
Formerly contained methenamine, salol, methylthioninium chloride, benzoic acid, atropine sulfate, and hyoscyamine sulfate.
Pain and discomfort of the urinary tract.

Prosedyl
Note: this name may be used for preparations of different composition.
Marching, Hong Kong.†
⊗Codeine (p. 40·2); ephedrine (p. 1663·1); promethazine (p. 638·2).

Prosek *Eczacibasi, Turk.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Proselamin *Biosel, Turk.†*
Amino acids.
Parenteral nutrition.

Proselem *Vita Api, Fr.*
Spirulina (p. 2622·1); selenium (p. 2086·3); vitamin E (p. 2119·1); superoxide dismutase (p. 135·2).
Dietary supplement.

Proseloc *Sel-J, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Prosense for Men *Aus Biomed, Austral.†*
Epimedium sagittatum; ginkgo biloba (p. 2512·3); calcium (p. 1783·1); tyrosine (p. 2098·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Erectile dysfunction; stress.

Prosense for Women *Aus Biomed, Austral.†*
⊗Epimedium sagittatum; agnus castus (p. 2432·2); ginseng (p. 2513·3); calcium (p. 1783·1); tyrosine (p. 2098·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Premenstrual syndrome; reduced libido; stress.

Proseptine *Qualiphar, Belg.†*
Ether (p. 2212·3).
Skin cleansing.

Proseptine-Plus *Qualiphar, Belg.†*
Butylated hydroxytoluene (p. 1741·1).
Adhesive plaster remover.

Proserem *Arkofarm, Ital.†*
St John's wort (p. 449·1).
Depression.

Proserine *Hawon, Thai.†*
Cycloserine (p. 280·2).
Tuberculosis.

Prosertin *Probiomed, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder; panic disorder.

Proseval *Solas, Indon.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); glutamic acid (p. 2070·2); vitamin B substances (p. 2102·3); calcium phosphate (p. 1784·2).
Cerebral and peripheral vascular disorders.

Prosfortil *Hecht, Austria.*
Serenoa repens (p. 2363·3); lytta vesicatoria.
Homoeopathic preparation.

Prosgutt *Farmasa, Mex.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia; urinary-tract disorders.

Proshield Plus *Healthpoint, Canad.*
Dimeticone (p. 2209·3).

Prosic *Galenium, Indon.*
Ibuprofen (p. 68·2).
Pain; fever.

Prosicca *Agepha, Austria.*
Hypromellose (p. 2189·2).
Eye irritation.

ProSight Lutein *Major, USA.*
Vitamins; minerals.

Prosigne *Cristalia, Braz.*
Botulinum A toxin (p. 2017·1).

Pro-Sil *Amred, UK.*
Silicone gel (p. 2209·2).
Scars; burns.

Prosimed *3DDD, Belg.†*
Fluoxetine (p. 417·1).
Depression.

Prosinal *Gracia, Indon.*
Ibuprofen (p. 68·2).
Fever; pain.

Prosium *Protherapix, Malaysia.†*
Mineral preparation high in calcium, magnesium, and phosphorus.
Nutritional supplement.

Prosix *Inpac, Thai.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Proskin
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Zinc oxide (p. 1729·1).
Nappy rash; skin irritation.

Teofarma, Spain.
Dimeticone (p. 2209·3); thiomersal (p. 1771·3); zinc oxide (p. 1729·1).
Skin disorders.

Prosmin *Biotenk, Arg.; Apogepha, Ger.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prosneo *Farmoz, Port.*
Flutamide (p. 798·2).
Prostatic cancer.

Prosner *Towa, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Prosobee *Mead Johnson, Braz.†; Mead Johnson, Hong Kong†; Mead Johnson, Indon.; Mead Johnson, Irl.†; Mead Johnson, Ital.†; BMS, Pol.†; Mead Johnson, Pol.†; Mead Johnson, Singapore; Mead Johnson Nutritionals, UK; Mead Johnson, Venez.*
Infant feed.
Galactosaemia; galactokinase deficiency; diarrhoea; lactose and sucrose intolerance; cows' milk intolerance.

Mead Johnson Nutritionals, USA.
Soy protein infant feed.
For infants with a family history of hypersensitivity.

Prosodina *Liferpal, Mex.*
Benzylpenicillin (p. 228·1).
Bacterial infections.

Prosoft *R & D, Mon.*
St John's wort (p. 449·1).
Depression.

Prosogan *Takeda, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Prosolmin *Roemmers Osmoph, Venez.*
Vitamins; minerals.

Prosolvin *Pharmanel, Gr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prosolvit *Roemmers Osmoph, Venez.*
Vitamins.

Proson *Bernofarm, Indon.†*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Proson N *Bernofarm, Indon.†*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Prosoyal *FDC, India.*
Infant feed.
Lactose intolerance; intolerance to animal milk.

Prospa *Medicine Products, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle pain; dysmenorrhoea.

Prospan *Sanova, Austria; Engelhard, Cz.; Merck Medication Familiale, Fr.; Engelhard, Ger.; Farmasyn, Gr.; Engelhard, Hung.; Transfarma, Indon.; Engelhard, Malaysia; Engelhard, Neth.; Engelhard, Norw.; Engelhard, Pol.; Engelhard, Singapore; Medhouse, Swed.; Zeller, Switz.; Engelhard, Ukr.; Roemmers, Venez.*
Ivy (p. 2536·2).
Cough and associated respiratory-tract disorders; respiratory-tract congestion.

Prospanex *Zeller, Switz.*
Ivy (p. 2536·2).
Cough.

Prospantus *Engelhard, Spain.*
Ivy (p. 2536·2).
Cough.

Prospaxid *Prospa, Port.*
Nizatidine (p. 1866·1).

Prospec *Apotex, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Prosphere *Carnot, Mex.*
Progesterone (p. 2300·2).
Menstrual disorders; endometriosis; premenstrual syndrome; hirsutism; female infertility; threatened or recurrent miscarriage; menopausal disorders; endometrial hyperplasia.

Prospiril *Schering-Plough, Gr.; Schering-Plough, Port.*
⊗Mometasone furoate (p. 1644·1).
Asthma.

Prosta Balance *Eagle, Austral.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3); tomato; quercetin (p. 2505·3); zinc citrate (p. 2126·2); selenomethionine (p. 2087·1); ferrous phosphate (p. 2077·1); nickel.
Benign prostatic hyperplasia.

Prosta Ease *Valeant, Canad.*
Cucurbita seed oil (p. 2489·2); pygeum africanum (p. 2363·2); linseed oil (p. 2544·2); saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prosta Fink forte *GSK Consumer, Ger.†*
Cucurbita (p. 2489·2).
Prostatic disorders.

Prosta Urgenin Uno *Madaus, Ger.; Rottapharm, Ger.; Madaus, Ukr.†*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostab *Unicure, Philipp.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia; alopecia androgenetica.

Prostabiol *Nutrisante, Fr.*
Cucurbita oil (p. 2489·2); acerola; pollen (p. 2593·3); zinc gluconate (p. 2126·2); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Urinary-tract disorders in men.

Prostacaps *Hasco-Lek, Fin.†*
Saw palmetto (p. 2363·3).
Prostatic disorders.

Prostacare *Mega Lifesciences, Philipp.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostacer *Mega Lifesciences, Ukr.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostacide *Vida, Port.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

ProstaCo *Mediherb, Austral.*
Urtica (p. 2639·3); saw palmetto (p. 2363·3); crataeva nurvala; cucurbita oil (p. 2489·2).
Prostate disorders.

Prostacom *Combiphar, Indon.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prostacor *Microgen, Rus.*
Prostate extract (bovine) (p. 2444·1).
Prostate disorders.

ProstActive *Pascual, Philipp.*
Saw palmetto (p. 2363·3).
Prostatic disorders.

Prostacur
Note: this name may be used for preparations of different composition.
Mylan, Spain.
Flutamide (p. 798·2).
Prostatic cancer.

Finadiet, Arg.
Sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Prostacure *Mibe, Denm.; Mibe, Ger.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prostadil *UCB, Ger.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prostadilat *Pfizer, Austria.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Prostadirex *Sanofi-Aventis, Fr.*
Flutamide (p. 798·2).
Prostatic cancer.

Prostadyn *Dunner, China; Dunner, Switz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostafilina *BMS, Venez.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Prostafin *Santa, Gr.; Atral, Port.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prostafit *Biokosma, Arg.*
Urtica (p. 2639·3); cucurbita (p. 2489·2); pollen (p. 2593·3); tomato; zinc (p. 2126·1).
Dietary supplement.

Prostaflo *Akacia, S.Afr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prostaflor *Sanova, Austria; Bayer, Switz.†*
Pollen extract (Cernitin T, Cernitin GBX) (p. 2593·3).
Prostatic disorders; benign prostatic hyperplasia.

Prostaflux *Teuto, Braz.*
Doxazosin mesilate (p. 1369·1).

Prostaforce *Vogel, Fin.; Magnapharma, Pol.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostaform *LRN, Fr.*
Day tablets, cranberry (p. 2488·1); night tablets, phytosterols (p. 1471·2); boswellia (p. 2507·3); zinc citrate (p. 2126·2); vitamin E (p. 2119·1).
Prostatic disorders.

Prostafort *Knop, Chile.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostaforton *Hexal, Ger.†*
Urtica root (p. 2639·3).
Benign prostatic hyperplasia.

Prostagood *Abdi, Turk.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostagutt *Austroplant, Austria.*
Saw palmetto (p. 2363·3); populi trem. (p. 2450·3); urtica dioica (p. 2639·3).
Prostatic disorders; bladder disorders.

Prostagutt Forte *Schwabe, Rus.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostagutt forte *Schwabe, Ger.*
Saw palmetto (p. 2363·3); urtica root (p. 2639·3).
Benign prostatic hyperplasia.

Prostagutt mono *Schwabe, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostagutt uno *Schwabe, Ger.; Schwabe, Switz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostagutt-F *Schwabe, Switz.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostaherb N *Cesra, Ger.; Cesra, Pol.; Centocor, Rus.*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostakan
Note: this name may be used for preparations of different composition.
Schwabe, Singapore.
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostakan Forte *Schwabe, Cz.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Prostatic disorders.

Prostakan Mono *Schwabe, Cz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostakur *Medikon, Indon.†*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostal
Note: this name may be used for preparations of different composition.
Motima, Fr.
Pollen (p. 2593·3).
Urinary-tract disorders in men.

Teikoku, Jpn.
Chlormadinone acetate (p. 2257·3).
Prostatic hyperplasia; prostatic cancer.

Prostalane *VSM, Belg.†*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostalin
Note: this name may be used for preparations of different composition.
Kyowa, Jpn.
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Pharco, Ukr.
Ichthammol (p. 1705·3); potassium iodide (p. 2336·3); chamomile (p. 2474·1).
Benign prostatic hyperplasia; anorectal disorders.

Prostalizyna *Herbapol Pruszkow, Pol.*
Sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Prostall *Drugtech, Chile.*
Tamsulosin hydrochloride (p. 2369·1).
Prostatic disorders.

ProstaMed
Note: this name may be used for preparations of different composition.
Bioforce, Switz.
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostamed
Note: this name may be used for preparations of different composition.
Dr Klein, Ukr.
Cucurbita (p. 2489·2); solidago (p. 2620·1); green quaking aspen (p. 2450·3).
Benign prostatic hyperplasia; prostatitis.

Klein, Ger.
Cucurbita (p. 2489·2); solidago virgaurea (p. 2620·1); populus tremula leaves (p. 2450·3).
Prostatic disorders; urinary-tract disorders.

Prostamed Mikto *Klein, Ger.*
Chimaphila umbellata; populus tremuloides (p. 2450·3); serenoa repens (p. 2363·3).
Homoeopathic preparation.

Prostamed Urtica *Klein, Ger.*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostamen *Kocak, Turk.*
Lycopene (p. 2546·2); selenium (p. 2086·3); vitamin E (p. 2119·1).
Antoxidant.

Lafarmen, Arg.
Alpha tocopherol (p. 2119·1); lycopene (p. 2546·2); bearberry (p. 2453·2); zinc (p. 2126·1).
Dietary supplement.

Prostamid *BDH, India.*
Flutamide (p. 798·2).
Prostatic cancer.

Prostamide *Gerolymatos, Gr.*
Flutamide (p. 798·2).
Prostatic cancer.

Prostamnic *Schwarz, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prostamol Uno *Berlin-Chemie, Cz.; Berlin-Chemie, Hung.; Menarini, Hung.; Berlin-Chemie, Pol.; Menarini, Pol.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia; prostatitis.

Prostan *Medicine Products, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Prostanac *Pyridam, Indon.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Prostandin *Ono, Jpn.*
Alprostadil alfadex (p. 2352·2).
Chronic arterial occlusion; controlled hypotension in surgery; maintenance of patent ductus arteriosus; peripheral vascular disorders; diagnosis of erectil dysfunction.

Prostandril *Pliva, Cz.†; Pliva Krakow, Pol.†*
Flutamide (p. 798·2).
Prostatic cancer.

Prostanil *Lepetit, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prostanon *Pharmachemie, Philipp.*
Flutamide (p. 798·2).
Prostatic cancer.

Prostanorm *Vilar, Rus.*
St John's wort (p. 449·1); solidago (p. 2620·1); liquorice (p. 1853·2); echinacea purpurea (p. 2498·1).
Prostatitis.

Prostanovag *Gobbi, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prostanus *Sandoz, Philipp.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prostap *Orifarm, Denm.†; Takeda, Irl.; Takeda, UK·*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; endometriosis; uterine fibroids.

Prostaphilin-A *BMS, Philipp.†*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Prostaphlin *BMS, Cz.; BMS, Philipp.†*
Oxacillin sodium (p. 336·2).
Staphylococcal infections.

Prostaphlin-A *BMS, Hong Kong.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Prostaplant *Marvecs, Ital.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Micturition disorders; benign prostatic hyperplasia.

Schwabe, Pol.; Schwabe, Rus.; Schwabe, Ukr.
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostaplant Forte *Schwabe, Ukr.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostaplex *Douglas, Canad.*
Vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1).

Prostapol *Herbapol Krakow, Pol.*
Arnica (p. 2447·2); shepherd's purse (p. 2614·2); St John's wort (p. 449·1); solidago (p. 2620·1); valerian (p. 2640·2); rapeseed.
Benign prostatic hyperplasia.

Prostarell *Sanorell, Ger.*
Populus tremuloides (p. 2450·3).
Homoeopathic preparation.

Prostarmon.F *Ono, Jpn.*
Dinoprost (p. 2133·3).
Induction and augmentation of labour; intestinal paralysis following surgery; ileus; termination of pregnancy.

Prostasabal *Hevert, Ger.*
Sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Prostasan *Aponova, Austria; Biofarma, Mex.; Bioforce, Switz.; Bioforce, UK.*
Saw palmetto (p. 2363·3).
Prostatic disorders; benign prostatic hyperplasia.

Prostascint Kit *Cytogen, Israel.*
Indium-111 capromab pendetide (p. 2224·3).
Localisation of prostatic cancer.

ProstaSecurA *Vitalco, Fr.*
Prosta-Reductase, cucurbita (p. 2489·2); saw palmetto (p. 2363·3); pygeum africanum (p. 2363·2); urtica (p. 2639·3); Prosta-Immun, glutamic acid (p. 2070·2); echinacea (p. 2498·1); zinc (p. 2126·1); selenium (p. 2086·3); vitamin B_6 (p. 2105·3); Prosta-Antiox, ginkgo biloba (p. 2512·3); garlic (p. 2510·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); glycine (p. 2071·2); alanine (p. 2048·3).
Urinary-tract disorders; prostatic disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Prostaserene *Therabel, Belg.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Pro-Stat
Note: this name may be used for preparations of different composition.
Medical Nutrition, USA.
Preparation for enteral nutrition.

Prostat
Note: this name may be used for preparations of different composition.
GSK, China.
Pollen extract (p. 2593·3).
Benign prostatic hyperplasia; prostatitis.

Marjan, Braz.
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostata *Stada, Ger.†*
Urtica root (p. 2639·3).
Benign prostatic hyperplasia.

Prostata-Entoxin N *Meckel, Ger.*
Kreosotum (p. 1659·3); populus tremuloides (p. 2450·3); sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Prostata-Gastreu N R25 *Reckeweg, Ger.*
Chimaphila umbellata; conium (p. 2524·3); ferrum picrinicum (p. 2634·2); pareira brava; populus tremuloides (p. 2450·3); pulsatilla (p. 2600·2); sabal serrulatum (p. 2363·3).
Homoeopathic preparation.

Prostata-Komplex L Ho-Fu-Complex *Liebermann, Ger.*
Chimaph. umb.; ferrum picrinic. (p. 2634·2); magnes. carb. (p. 1856·2); sabal serr. (p. 2363·3); staphisagria.
Homoeopathic preparation.

Prostata-Komplex N Ho-Fu-Complex *Liebermann, Ger.†*
Chimaph. umb.; clematis; ferrum picri. (p. 2634·2); magnes. carb. (p. 1856·2); sabal serr. (p. 2363·3); staphisagria; thuja (p. 2629·3).
Homoeopathic preparation.

Prostatal *Herbarium, Braz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostate Care *Golden Glow, Austral.*
d-Alpha tocopherol (p. 2119·1); lycopene (p. 2546·2); selenomethionine (p. 2087·1); zinc amino acid chelate (p. 2048·3); epilobium parviflorum; urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostate Defence *Golden Glow, Austral.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostate Health Formula *Blackmores, Austral.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3); tomato; *d*-alpha tocopherol (p. 2119·1); selenomethionine (p. 2087·1); zinc sulfate (p. 2126·2).
Prostatic disorders.

Prostate Support *Reese, USA.*
Sitosterol (p. 1471·2); zinc citrate (p. 2126·2).

Prostatein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Prostatic *UCB, Pol.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Prostatil *Boniscontro & Gazzone, Ital.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Prostatilen *Tsitomed, Rus.*
Prostate extract (bovine) (p. 2444·1); glycine (p. 2071·2); dimethyl sulfoxide (p. 2182·2).
Prostatitis.

Prostatonin *Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Hung.; Ginsana, Switz.*
Pygeum africanum (p. 2363·2); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prosta-Truw *Truw, Ger.*
Urtica root (p. 2639·3).
Benign prostatic hyperplasia.

Prosta-Urgenin *Madaus, Austria; Madaus, Belg.; Madaus, Cz.; Madaus, Thai.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prosta-Urgenine *Zeller Madaus, Switz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostavasin *Sidus, Arg.; UCB, Austria; Biosintetica, Braz.; UCB, China; UCB, Cz.; UCB, Ger.; IFET (ΙΦΕΤ), Gr.; Schwarz, Hong Kong†; UCB, Hung.; Schwarz, Ital.; UCB, Pol.*
Alprostadil alfadex (p. 2352·2).
Intermittent claudication; peripheral arterial occlusion; thromboangiitis obliterans; chronic obstructive arterial disease.

Prostazid *Madaus, Ger.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prostazocin *Ceutical, Hong Kong.†*
Doxazosin (p. 1369·1).

Prostazosin *Teva, Denm.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Prostazosina *LKM, Arg.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia.

Prostazyn *Beres, Hung.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3); solidago (p. 2620·1).
Benign prostatic hyperplasia.

Prostease *Jamieson, Canad.; Jamieson, Hong Kong.*
Cranberry (p. 2488·1); cucurbita seed oil (p. 2489·2); pygeum bark (p. 2363·2); saw palmetto berry (p. 2363·3).
Prostate disorders; urinary-tract disorders; nutritional supplement.

Prostem *Baldacci, Braz.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Prostem Plus *Baldacci, Braz.*
Pygeum africanum (p. 2363·2); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Prostene *Ivax, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prostenongel *Kevelt, Rus.*
Dinoprostone (p. 2134·1).
Labour induction.

Prosteon *Theralogix, USA.*
Vitamins; minerals.
Dietary supplement.

Prostep *Aveva, Canad.†; Lederle, USA.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Prosteren *Cornelli, Ital.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prosterid *Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prosteride *Yoo Young, Philipp.; Atlantic, Thai.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prosterit *Kocak, Turk.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Prosterol *Herbapol Poznan, Pol.*
Sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Prostess *TAD, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostex *Medix, Mex.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Prostica *TAD, Ger.†*
Flutamide (p. 798·2).
Prostatic cancer.

Prostide
Note: this name may be used for preparations of different composition.
ICN, Pol.
Bicalutamide (p. 749·1).
Prostatic cancer.

Libbs, Braz.; Pharos, Indon.; Sigma-Tau, Ital.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Probiomed, Mex.
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Prostig *Duopharma, Philipp.*
Neostigmine metilsulfate (p. 687·2).
Myasthenia gravis; reversal of competitive neuromuscular blockade; ileus.

Prostigmin *Valeant, Arg.; Valeant, Austral.†; Valeant, Austria†; Transfarma, Indon.; Meda, Neth.; Invida, Philipp.; Roche, Singapore; Meda, Switz.*
Neostigmine metilsulfate (p. 687·2).
Meteorism; myasthenia gravis; paroxysmal supraventricular tachycardia; postoperative urinary retention; ileus; reversal of competitive neuromuscular blockade; postoperative intestinal atony; constipation; flatulence.

Invida, Thai.
Neostigmine (p. 687·1).
Meteorism; atonic constipation; paroxysmal tachycardia; myasthenia gravis; migraine; postoperative intestinal atony and urinary retention; reversal of competitive neuromuscular blockade; heartburn and flatulence in pregnancy; tinnitus; deafness; Ménière's disease.

Valeant, Canad.; Valeant, USA.
Neostigmine bromide (p. 687·2).
Myasthenia gravis; postoperative distension and urinary retention; reversal of competitive neuromuscular blockade.

Prostigmina *Valeant, Ital.*
Neostigmine metilsulfate (p. 687·2).
Gastrointestinal atony; myasthenia gravis; reversal of competitive neuromuscular blockade.

Prostigmine *IFET (ΙΦΕΤ), Gr.; Roche, Gr.*
Neostigmine bromide (p. 687·2).
Myasthenia gravis.

Meda, Belg.; Valeant, Braz.; Meda, Fr.; Valeant, Mex.; Meda, Spain.†
Neostigmine metilsulfate (p. 687·2).
Reversal of competitive neuromuscular blockade; myasthenia gravis; constipation; meteorism; postoperative urinary retention; paralytic ileus.

Prostin E2 *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Paladin, Canad.; Pfizer, Cz.; 2care4, Denm.; Abacus, Denm.; Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; IFET (ΙΦΕΤ), Gr.; Pfizer, Gr.; Pharmacia Upjohn, Gr.; Vianex (Βιανέξ), Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.†; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, NZ; Pfizer, Port; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Pharmacia Upjohn, USA.*
Dinoprostone (p. 2134·1).
Labour induction; termination of pregnancy; intra-uterine death; hydatidiform mole; missed abortion; gestational trophoblastic tumours.

Prostin F2 *IFET (ΙΦΕΤ), Gr.*
Dinoprost trometamol (p. 2133·3).

Prostin F2 Alfa *Pfizer, Rus.*
Dinoprost trometamol (p. 2133·3).
Termination of pregnancy; labour induction.

Prostin F2 Alpha *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Israel; Pharmacia, NZ; Pfizer, S.Afr.*
Dinoprost trometamol (p. 2133·3).
Hydatidiform moles; fetal death in-utero; termination of pregnancy; labour induction.

Prostin 15M *Pfizer, Cz.; Pfizer, NZ.*
Carboprost trometamol (p. 2133·1).
Termination of pregnancy; postpartum haemorrhage.

Prostin Pediatrico *Pfizer, Chile.*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus.

Prostin VR *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Max, India; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S. Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Upjohn, USA.*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus; congenital heart defects in neonates.

Prostine E_2 *Pfizer, Fr.*
Dinoprostone (p. 2134·1).
Labour induction; termination of pregnancy; hydatidiform mole.

Prostine VR *Pfizer, Fr.*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus.

Prostinfenem *Pfizer, Denm.; Pfizer, Swed.*
Carboprost trometamol (p. 2133·1).
Postpartum haemorrhage; termination of pregnancy.

Prostin/15M *Pfizer, Belg.; Pfizer, Neth.†*
Carboprost trometamol (p. 2133·1).
Postpartum haemorrhage; termination of pregnancy; intra-uterine death.

Prostivas *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
Alprostadil (p. 2352·2).
Maintenance of patent ductus arteriosus.

Prostman *Uniao Quimica, Braz.*
Cyproterone acetate (p. 2261·2).

Prostodin *AstraZeneca, India; AstraZeneca, Philipp.*
Carboprost trometamol (p. 2133·1).
Postpartum haemorrhage; termination of pregnancy.

Prostoklar *Baliarda, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prostopine *Alform, Rus.*
Royal jelly (p. 2608·1); honey (p. 2072·1); ambrosia; propolis (p. 2597·3); pollen (p. 2593·3).

Prostudox *Sintez, Rus.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Prosturol *Farmasierra, Spain.*
Benzydamine hydrochloride (p. 29·2); pygeum africanum (p. 2363·2).
Prostatic adenoma.

Prosulf
Note: this name may be used for preparations of different composition.
Advance, Thai.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

CP Pharmaceuticals, Hong Kong; CP, Israel; Wockhardt, UK.†
Protamine sulfate (p. 1572·1).
Neutralisation of heparin activity; heparin overdosage.

Prosulpin *ProMed, Cz.; Promed, Rus.*
Sulpiride (p. 1107·3).
Depression; behaviour disorders; psychoses; psychosomatic gastrointestinal disorders; premenstrual dysphoric disorder; anxiety; migraine; vertigo.

ProSure *Abbott, Cz.*
Preparation for enteral nutrition.

Prosure *Abbott, Hong Kong; Abbott, Indon.; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Philipp.; Abbott Nutrition, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott, UK.*
Preparation for enteral nutrition.
Cancer-associated cachexia.

Prosxaflo *Farmaceutica H, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Pro-Symbioflor *Ebi, Switz.*
Enterococcus faecalis (p. 2596·3); *Escherichia coli.*
Gastrointestinal disorders.

Symbiopharm, Ger.
Autolysates of: *Escherichia coli*; *Enterococcus faecalis* (p. 2596·3).
Gastrointestinal disorders.

Prosztika *Phace, Hung.*
Flutamide (p. 798·2).
Prostatic cancer.

Prota *Samarth, India.*
Protamine sulfate (p. 1572·1).
Antidote to heparin.

Protab *Eczacibasi, Turk.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); methylpolysiloxane (p. 1886·2).

Protagens *Alcon, Neth.*
Povidone (p. 2204·3).
Dry eyes.

Protagent *Alcon, Austria; Alcon, Ger.; Farmex, Gr.; Alcon, Hong Kong; Alcon, Switz.; Liba, Turk.*
Povidone (p. 2204·3).
Dry eyes; wetting drops for contact lenses; eye irritation.

Protal *Aurora, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension.

Protal complex *Medilat, Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Protalgine *Probiomed, Mex.*
Lamotrigine (p. 527·2).
Epilepsy.

protAlgon *Lavipharm, Gr.*
Paracetamol (p. 115·1).
Pain.

Protam *Synthon, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Protamox *Armoxindo, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Protan *Apotex, Mex.*
Dextromethorphan (p. 1660·1).
Cough.

Protanol *Teuto, Braz.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Protaphane *Novo Nordisk, Austral.; Novo Nordisk, Cz.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Irl.; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, NZ; Novo Nordisk, Pol.; Novo Nordisk, Port.*
⊗Neutral isophane insulin injection (human, pyr, monocomponent) (p. 475·3).
Diabetes mellitus.

Protaphane HM *Novo Nordisk, Hong Kong; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.*
⊗Neutral isophane insulin injection (human, monocomponent) (p. 475·3).
Diabetes mellitus.

Protat *Potter's, UK.*
Corn silk (p. 2487·1).
Formerly contained corn silk and kava.
Bladder discomfort.

Protaxil *Delta, Port.*
Proglumetacin maleate (p. 127·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Protaxol *Provit, Mex.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Protaxon *Madaus, Ger.; Rottapharm, Ger.*
Proglumetacin maleate (p. 127·1).
Musculoskeletal, joint, and soft-tissue disorders; gout.

Protaxos *Servier, Malaysia; Servier, Thai.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Protazine *CCM, Malaysia.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; vestibular disorders; sedative.

Proteamin *Terumo, Jpn.*
Amino acids; with or without xylitol (p. 2220·3).
Parenteral nutrition.

Protease *Richmond, Arg.*
Nevirapine (p. 1005·1).
HIV infection.

Protec
Note: this name may be used for preparations of different composition.
ACP, UK.
Di-(2-ethylhexyl)adipate (p. 2153·1).
Insect repellent.

AGIPS, Ital.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Pro-Tec Sport *Allergan, Canad.†*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Protecadin *Taiho, Jpn.*
Lafutidine (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; gastritis; premedication.

Proteccion Ultra *Rider, Chile.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); meradimate (p. 1711·2); homosalate (p. 1705·1).
Sunscreen.

ProTech *Triton, USA.*
Povidone-iodine (p. 1767·1); lidocaine hydrochloride (p. 1988·2).
Cuts; burns.

Protech
Note: this name may be used for preparations of different composition.
Drogsan, Turk.
Pantoprazole (p. 1875·3).

Protecor *Salus, Ger.*
Crataegus (p. 2488·1); magnesium complex with acid hydrolysate of corn starch; alpha tocoferil acetate (p. 2119·2).
Cardiovascular disorders.

Protecor Herz-Schutz *Duopharm, Ger.†*
Crataegus (p. 2488·1).
Cardiovascular disorders.

Protecor novo *Duopharm, Ger.†*
Crataegus (p. 2488·1).
Heart failure.

Protect *EHN, Canad.†*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); ubidecarenone (p. 2637·1); selenium (p. 2086·3).

Protectaid *Pirri, Hong Kong; Tree of Life, Israel; Sinclair, UK.*
Nonoxinol 9 (p. 2199·1); sodium cholate (p. 2457·2); benzalkonium chloride (p. 1737·1).
Contraceptive.

Protectina *Gross, Braz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Protective Gel *Vichy, Canad.†*
SPF 20: Avobenzone (p. 1695·1); ensulizole (p. 1703·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1).
Sunscreen.

Protective Lip Care *Biotherm, Canad.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Protective Lotion *Stroms, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Protective Ointment *Smith & Nephew, Canad.*
Soft paraffin (p. 2212·1).

Protective Sport Sunscreen *Energizer, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Protective Sunscreen *Energizer, Canad.†*
SPF 10: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

ProtectNatal *Gil, USA.*
Vitamins; minerals; trace elements; ubidecarenone (p. 2637·1); eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); omega-3 fish oil (p. 1460·1).
Dietary supplement.

Protectol *Daniels, USA.*
Calcium undecenoate (p. 596·3).
Fungal skin infections; nappy rash; minor skin irritation; hyperhidrosis; bromhidrosis.

Protector *Quimifar, Spain.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Protector Labial Extrem *Isdin, Arg.; Isdin, Chile.†*
SPF 45: SPF 45: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); bemotrizinol (p. 1695·3); avobenzone (p. 1695·1).
Sunscreen.

Protectura *Faran, Gr.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Protectyl Sunscreen High Protection *Yves Rocher, Canad.†*
Lotion SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Protectyl Sunscreen Minimal Protection *Yves Rocher, Canad.†*
Lotion SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Protectyl Sunscreen Moderate Protection *Yves Rocher, Canad.†*
Lotion SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Yves Rocher, Canad.†
Spray SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Protectyl Suntan *Yves Rocher, Canad.†*
SPF 4: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Proteflazid *Ecofarm, Rus.*
Calamagrostis epigeios; deschampsia caespitosa.
Herpes simplex infections of the skin and mucous membranes.

Ecofarm, Ukr.
Calamagrostis epigejos; deschampsia caespitosa.
Viral infections.

Protegra *Inverness, USA.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); minerals; grape seed extract (p. 2521·3).

Protegra Antioxid *Wyeth-Whitehall, Arg.*
Vitamins; minerals.

Proteigeno *Lafedar, Arg.*
β-Aminoethanol phosphoric acid; amino acids; pyridoxine (p. 2105·3).
Parenteral nutrition; dietary supplement.

Protéika PRO'gram *Nestle Proteika, Fr.†*
Dietary supplement.
Obesity.

Protein Blend *K-PAX, USA.*
Preparation for enteral nutrition.

Proteina 100 *Survival, Arg.*
Calcium caseinate (p. 2055·2).
Dietary supplement.

Proteinex *Victus, Venez.*
Preparation for enteral nutrition.
Protein supplement.

Proteinex Victus *Droser, Arg.*
Calcium caseinate (p. 2055·2).
Dietary supplement.

Protelium *Fada, Arg.†*
Isoxsuprine (p. 2535·2).

Protelos *Servier, Austria; Servier, Belg.; Grunenthal, Chile; Servier, Cz.; Servier, Denm.; Servier, Fr.; Servier, Ger.; Servier, Gr.; Servier, Hung.; Servier, Irl.; Servier, Israel; Servier, Ital.; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, Spain; Servier, Swed.; Servier, Turk.; Servier, UK.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Proten *Otsuka, Indon.*
Preparation for enteral nutrition.

Protenate *Hyland, USA.*
⊗Plasma protein fraction (p. 1159·2).
Hypoproteinaemia; hypovolaemia.

Prote-Neu *Biotenk, Arg.*
A pneumococcal vaccine (14 valent) (p. 2410·1).
Active immunisation.

Protensin-M *BMS, S.Afr.†*
⊗Hydroflumethiazide (p. 1406·3); reserpine (p. 1485·3).
Hypertension.

Proteobil *Neckerman, Braz.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).

Proteoferrina *Bayer, Ital.†*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Proteovir *Richmond, Arg.*
Saquinavir (p. 1014·2).
HIV infection.

Proteozym *Wiedemann, Ger.*
⊗Bromelains (p. 2460·3).
Inflammation.

Proteozyme Forte *Douglas, Canad.*
⊗Vitamins; minerals; papain (p. 2582·3); pepsin (p. 2586·1).

Proterine *Novell, Indon.*
Isoxsuprine hydrochloride (p. 2535·2).
Premature labour; peripheral vascular disorders.

Proternol-L *Kowa, Jpn.*
Levisoprenaline hydrochloride.
Stokes-Adams syndrome; heart failure; postoperative low cardiac output; asthma.

Protevasc *Richter, Pol.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders.

Protevis *Allergan, Arg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Protexel *LFB, Fr.*
Protein C (p. 1161·1).
Thromboembolic disorders.

Protexin *Vitaminkosar, Hung.*
Lactobacillus casei (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Bifidobacterium breve* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3) or *B. infantis* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3).
Restoration of gastrointestinal flora.

Combiphar, Indon.
Capsules: Lactobacillus acidophilus (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Bifidobacterium breve* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Diarrhoea; lactose intolerance; constipation; flatulence; candidiasis.

Probiotics, Singapore.
Lactic-acid-producing organisms (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Maintenance of gastrointestinal health.

Protexin Balance *Probiotics International, Hong Kong.*
Fructo-oligosaccharides (p. 2508·1); lactic-acid-producing organisms (p. 2596·3).
Digestive system disorders.

Protexin Balance+ *Probiotics International, Hong Kong.*
Fructo-oligosaccharides (p. 2508·1); lactic-acid-producing organisms (p. 2596·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Digestive system disorders.

Protexin Restore *Probiotics International, Hong Kong.*
Fructo-oligosaccharides (p. 2508·1); lactic-acid-producing organisms (p. 2596·3).
Digestive system disorders.

Protexin Vitality *Probiotics International, Hong Kong.*
Fructo-oligosaccharides (p. 2508·1); lactic-acid-producing organisms (p. 2596·3); vitamin C (p. 2110·3).
Digestive system disorders.

Protexio *Floxia, Singapore.*
SPF 50+: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Pro-T-Flor *Columbia, Mex.*
Bifidobacterium longum (p. 2596·3); *Enterococcus faecium* (p. 2596·3).
Diarrhoea.

Prothanon *Riemser, Ger.†*
Topical gel: Dioxopromethazine hydrochloride (p. 638·2).
Itching; pruritus.

Prothazin *UCB, Cz.; UCB, Ger.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; motion sickness; sedative; insomnia; anxiety; premedication; vomiting; allergic disorders.

ProThelial *McCullough, USA.*
Sucralfate (p. 1889·1).
Mouth lesions.

Prothenol *Zwitter, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Xerostomia.

Protheo *MSD, China.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Prothiaden *Abbott, Austral.; Teofarma, Belg.; Zentiva, Cz.; Teofarma, Denm.; Teofarma, Fr.; Abbott, Hong Kong†; Abbott, India; Teofarma, Irl.; Abbott, Malaysia; Teofarma, Neth.; Abbott, NZ†; Abbott, Philipp.†; Abbott, S.Afr.; Abbott, Singapore; Alter, Spain†; Movianto, UK.*
Dosulepin hydrochloride (p. 414·1).
Depression; mixed anxiety depressive states; nocturnal enuresis; urinary incontinence; post-traumatic stress disorder; pain; premedication.

Prothiazine *CTS, Israel; Rafa, Israel.*
Promethazine hydrochloride (p. 638·2).
Anaphylaxis; hypersensitivity reactions; nausea and vomiting; premedication.

Prothiazine Expectorant *CTS, Israel; CTS, Rus.*
Promethazine hydrochloride (p. 638·2); guaifenesin (p. 1666·2); ipecacuanha (p. 1667·2).
Cough.

Prothicid *Themis Medicare, India.*
Protionamide (p. 345·1).
Tuberculosis.

Prothin *Quality, Hong Kong.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Prothiucil *Phafag, Austria.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism; ulcerative colitis.

Prothrombinex *CSL Biotherapies, Hong Kong; CSL, NZ.*
Prothrombin complex (coagulation factors II, IX, X) (p. 1149·3).
Haemorrhagic disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Prothromplex *Baxter, Cz.; Baxter, Hung.; Baxter, Norw.; Baxter, Pol.; Baxter, Spain; Baxter, Switz.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Prothromplex Partiell *Baxter, Austria.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Prothromplex S-TIM 4 *Immuno, Austria.†*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Prothromplex TOTAL *Baxter, Austria.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Prothromplex-T *Baxter, Braz.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Prothromplex-T TIM 4 *Adcock Ingram Critical Care, S.Afr.†*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Prothuril *Unipharma, Gr.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Prothyl *Septodont, Fr.†*
Benzocaine (p. 1980·2).
Dental disorders.

Prothyra *Sunthi Sepuri, Indon.†*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; dysfunctional uterine bleeding; endometriosis.

Prothyrid *Henning, Ger.; Sanofi-Aventis, Ger.*
Levothyroxine sodium (p. 2339·1); liothyronine hydrochloride (p. 2342·3).
Hypothyroidism; thyroiditis.

Protiaden *Teofarma, Ital.*
Dosulepin hydrochloride (p. 414·1).
Depression; mixed anxiety depressive states.

Protiadene *Teofarma, Port.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Protica *Ethica, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Protid *Lunsco, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Protiderm *Panalab, Arg.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Fungal nappy rash.

Protifar *Nutricia, Austral.; Nutricia, Cz.; Nutricia, Hong Kong; Nutricia, Irl.; Nutricia, NZ.*
Dietary protein supplement.

Nutricia Clinical, UK.
Low-lactose, gluten- and sucrose-free food for special diets.
Hypoproteinaemia.

Nutricia, Fin.; Nutricia, Indon.†; Nutricia, Ital.; Nutricia, Pol.; Nutricia, Venez.
Preparation for enteral nutrition.
Hypoproteinaemia; protein supplement.

Nutricia, Fr.
Nutritional protein supplement.

Nutricia, Port.
High protein nutritional supplement.

Protifast *Protifast, Fr.*
Protein enriched nutritional supplement.

Protifed *Graha, Indon.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms; allergic rhinitis.

Protiferron *Eumedica, Neth.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Protifortifiant *Omega, Fr.*
Protein enriched nutritional supplement.

Protina G *Fresenius Kabi, Ital.*
Preparation for enteral nutrition.

Protinex *Pfizer, India.*
High-protein dietary supplement.

Protinules *Alembic, India.*
High-protein dietary supplement.

Protinum *Ali, Turk.*
Pantoprazole (p. 1875·3).

Protiocomb *Akrikhin, Rus.*
Lomefloxacin hydrochloride (p. 319·2); protionamide (p. 345·1); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Protitus *Mayo, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Protium *Altana, Irl.; Nycomed, Irl.; Nycomed, UK.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders; Zollinger-Ellison syndrome.

Protizole *Gerard, Irl.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Protobex *Centaur, India.*
Nutritional supplement.

Proto-Boric *Bell, India.†*
⊗Boric acid (p. 2459·3); borax (p. 2459·2); naphazoline hydrochloride (p. 1669·3); camphor (p. 2466·2); menthol (p. 2553·2).
Corneal ulcer; inflammatory eye infections.

Protocide *Trima, Israel.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Protocord *Accord, Mex.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Protocort *Pharos, Indon.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Protofen *Kimia, Indon.*
Ketoprofen (p. 79·1).
Rheumatoid arthritis; ankylosing spondylitis; gout; osteoarthritis.

Protogyl *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Metronidazole (p. 936·1).
Amoebiasis; genito-urinary-tract infections; vaginal trichomoniasis.

Proto-Itecan *ABL, Braz.*
Irinotecan (p. 812·2).

Proton
Note: this name may be used for preparations of different composition.
Medinfar, Port.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Protone *Aristo, India.*
Oral drops: Casein (p. 2055·2); lysine hydrochloride (p. 2079·3); carbohydrates; vitamin B substances (p. 2102·3).
Tonic.

Aristo, India.
Oral liquid: Ferrous sulfate (p. 2062·2); casein (p. 2055·2); carbohydrates; vitamin B substances (p. 2102·3); yeast extract; zinc (p. 2126·1).
Tonic; dietary supplement.

Protoner *Pharminicio, Spain.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protonex *Abdi, Turk.*
Pantoprazole (p. 1875·3).

Protonexa *Medico Uno, Hung.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protonis *Royal, Chile.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Protonix
Note: this name may be used for preparations of different composition.
Hizon, Philipp.
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Wyeth-Ayerst, USA.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Protop *Interbat, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Protopam *Wyeth-Ayerst, USA.*
Pralidoxime chloride (p. 1571·1).
Organophosphorus insecticide poisoning; anticholinesterase antagonist.

Protopic *Roche, Arg.; Astellas, Austria; Astellas, Belg.; Roche, Braz.; Astellas, Canad.; Roche, Chile; Astellas, China; Astellas, Cz.; Astellas, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Ger.; Astellas, Gr.; Astellas, Hong Kong; Astellas, Hung.; Astellas, Indon.; Janssen-Cilag, Indon.; Astellas, Irl.; Astellas, Israel; Astellas, Ital.; Astellas, Jpn; Janssen-Cilag, Malaysia; Roche, Mex.; Astellas, Neth.; Astellas, Norw.; Janssen, Philipp.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, S.Afr.; Janssen-Cilag, Singapore; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Janssen-Cilag, Thai.; Eczacibasi, Turk.; Astellas, UK; Astellas, Ukr.; Astellas, USA.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Protos *Servier, Arg.; Servier, Austral.; Servier, Braz.; Servier, Hong Kong; Servier, Indon.; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Singapore.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Protosin *Streger, Mex.*
Quinfamide (p. 947·1).
Intestinal amoebiasis.

Protosol *Kamada, Israel.*
Aprotinin (p. 1133·2).
Reduction of blood loss in cardiopulmonary bypass; shock.

Protostat *Ortho Pharmaceutical, USA.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; anaerobic bacterial infections.

Protosulfil *Roemmers Osmoph, Venez.*
Sulfadiazine silver (p. 362·3).
Burns; wounds.

Protovit *Bayer, Belg.; Bayer, Ital.; Bayer, Spain.*
Vitamins.

Bayer, Fr.†
Vitamins; minerals.

Protovit N *Bayer, Port.*
Vitamins.

Protovit Plus *Bayer, Braz.; Roche, Braz.*
Vitamins.

Protozole *Claris, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Protphenolosid *Ecofarm, Ukr.*
Calamagrostis epigejos; deschampsia caespitosa.
Viral infections; immunodeficiency disorders.

ProTract *Probiomics, Austral.*
Lactobacillus fermentum (p. 2596·3).
Irritable bowel syndrome; atopic eczema in infants.

Protradon *ProMed, Cz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Pro-Triazide *Pro Doc, Canad.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).

Protrim *Mayo, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Protrin *Pro Doc, Canad.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Protromplex *Baxter, Arg.; Baxter, Rus.*
A factor IX preparation (p. 1149·3).
Haemorrhagic disorders.

Protromplex TIM 3 *Baxter, Ital.*
Factor IX (p. 1149·3).
Deficiency of factors II, IX, and X.

Protub-2 *Farmasintez, Rus.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Protub-3 *Farmasintez, Rus.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Protub-4 *Farmasintez, Rus.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2); ethambutol (p. 296·1).
Tuberculosis.

Protub-5 *Farmasintez, Rus.*
Lomefloxacin hydrochloride (p. 319·2); pyrazinamide (p. 345·2); protionamide (p. 345·1); ethambutol (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.

Protubetham *Farmasintez, Rus.*
Isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Protub-Lome *Farmasintez, Rus.*
Isoniazid (p. 311·2); lomefloxacin hydrochloride (p. 319·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Protubpira *Farmasintez, Rus.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2).

Protubvita *Farmasintez, Rus.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Protusif *Pyridam, Indon.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2).
Cough; nasal congestion.

Protussa *Abbott, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Protylol *Pro Doc, Canad.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal disorders.

Pro-Uro
Note: this name may be used for preparations of different composition.
CHR Hansen, Singapore.
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3).
Maintenance of vaginal flora.

Proursan *ProMed, Pol.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; biliary cirrhosis; biliary reflux.

Prova *Cadila, India.*
Protein hydrolysate (p. 2086·2); carbohydrates; minerals.
Tonic.

Provacsin Nasal *Inmunolab, Arg.*
⊗Neomycin sulfate (p. 330·1); naphazoline hydrochloride (p. 1669·3); *Staphylococcus aureus*; non-haemolytic streptococcus; *Moraxella catarrhalis*; *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Pseudomonas aeruginosa*; fungal extracts.
Upper respiratory-tract congestion.

Provacsin Oral *Wierhom, Arg.*
Corynebacterium acnes; *Staphylococcus aureus*; *Staphylococcus albus*; haemolytic streptococcus; enterococcus; *Escherichia coli*; *Proteus mirabilis*; *Pseudomonas aeruginosa*; ascorbic acid (p. 2110·3).

Provag *Geymonat, Ital.†*
Lactobacillus acidophilus (p. 2596·3).
Vaginal disorders.

Provagin *Meprofarm, Indon.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Provamed *Promed, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Provames *Sanofi-Aventis, Fr.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Provamicina *Sanofi-Aventis, Mex.; Sanofi-Aventis, Venez.*
Spiramycin (p. 358·3).
Toxoplasmosis; bacterial infections.

Provarivax *Sanofi Pasteur, Belg.; Sanofi Pasteur, Neth.*
A varicella-zoster vaccine (OKA strain) (p. 2423·3).
Active immunisation.

Provas
Note: this name may be used for preparations of different composition.
Protherapix, Malaysia.
Omega-3-acid ethyl esters (p. 1460·2); vitamin E substances (p. 2119·1).
Nutritional supplement.

UCB, Ger.
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Provas comp *UCB, Ger.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Provasc *ACME, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Provasyn *Gedeon Richter, Philipp.*
Bromocriptine mesilate (p. 895·3).
Acromegaly; benign breast disorders; female infertility; lactation inhibition; menstrual disorders; parkinsonism; prolactinomas; puerperal mastitis.

Provax
Note: this name may be used for preparations of different composition.
Almirall, Port.
Lysates of *Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Klebsiella pneumoniae; Klebsiella ozaenae; Streptococcus pneumoniae; Haemophilus influenzae; Moraxella catarrhalis.*
Respiratory-tract infections.

Vivax, Venez.
Vitamins; fish oil (p. 1460·1); soya lecithin (p. 2542·2).

Provay *Hormona, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Proveblue
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
Methylthioninium chloride (p. 1559·1).
Chemical- and drug-induced methaemoglobinaemia.

Provella *Upsher-Smith, USA.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Lactobacillus fermentum* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).

Proven *Ascent, Austral.*
Ibuprofen (p. 68·2).
Fever; pain.

Proven Plus *Ascent, Austral.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain; inflammation.

Provenal *Antrivex, Ital.*
Sulodexide (p. 1507·3).
Chronic venous ulcer.

Provençale No 2 *Tisane Provencale, Fr.†*
Equisetum (p. 2500·1); ash leaf (p. 2450·1); fucus (p. 2612·1).
Obesity.

Provençale No 4 *Tisane Provencale, Fr.†*
Passion flower (p. 2584·1); crataegus (p. 2488·1); tilia (p. 2631·3).
Nervous disorders.

Provenen *HWS OTC, Austria.†*
Aesculus (p. 2431·2).
Venous insufficiency.

Provenge *Dendreon, USA.*
Sipuleucel-T (p. 857·1).
Prostatic cancer.

Proventil *Schering, USA.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Bronchospasm.

Proventol Expectorant *Sandoz, Indon.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Provera *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile†; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; IFET (ΙΦΕΤ), Gr.; Pharmacia Upjohn, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Grunenthal, Mex.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Thai.; Pfizer, UK; Pharmacia Upjohn, USA; Pfizer, Venez.*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; menorrhagia; endometriosis; menopausal disorders; malignant neoplasms; metrorrhagia; adjunct in oestrogen replacement therapy; menstrual disorders; dysfunctional uterine bleeding; endometrial hyperplasia; progesterone supplement; anorexia and cachexia associated with cancer or AIDS; female infertility; injectable contraceptive.

Provertin-UM TIM 3 *Baxter, Ital.*
Factor VII (p. 1147·1).
Factor VII deficiency.

Provestin *LBS, Philipp.*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; endometriosis; malignant neoplasms; injectable contraceptive.

Provexel NS *Multicare, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Provicar *Teva, Mex.; Elmor, Venez.*
Levocarnitine (p. 2053·2).
Carnitine deficiency; levocarnitine deficiency.

Provida OB *US Pharmaceutical, USA.*
Vitamins; minerals; *Lactobacillus casei* KE-99 (p. 2596·3).

ProvideXtra *Fresenius Kabi, Denm.†; Fresenius Kabi, Fin.; Fresenius Kabi, Philipp.; Fresenius Kabi, UK.*
Preparation for enteral nutrition.
Milk protein intolerance; gastrointestinal disorders.

Fresenius Kabi, Irl.
Dietary protein supplement.

Proview *Pharos, Indon.*
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3); myrtillus (p. 2566·2); grape seed (p. 2521·3); acetylcysteine (p. 1652·2); taurine (p. 2626·2); ginkgo biloba (p. 2512·3); citrus bioflavonoids (p. 2505·2); euphrasia (p. 2502·1); raspberry (p. 2207·2).
Antoxidant; dietary supplement for healthy eye function and cerebral and peripheral circulation.

Proviflox *SMHP, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Provigil
Note: this name may be used for preparations of different composition.
Schering-Plough, Belg.; Paranova, Denm.†; Cephalon, Irl.; Cephalon, Israel; Cephalon, Ital.; Pharmaplan, S.Afr.; Cephalon, UK; Cephalon, USA.
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; sleep apnoea; shift-work sleep disorder; idiopathic hypersomnia.

Svizera, India.
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility.

Provigor *Meprofarm, Indon.†*
Cistanchis herba; epimedii folium; fenugreek (p. 2504·1); sarsaparilla (p. 2610·3); cuscutae semen; calcium pantothenate (p. 2085·2).
Tonic.

Provimin *Ross, USA.*
Proteins; vitamins; minerals.
For enteral nutrition.

Provin
Note: this name may be used for preparations of different composition.
McNeil Healthcare, Irl.
Ibuprofen (p. 68·2).
Pain; fever.

Plusandex, Venez.
Vitamins; minerals.

Provinace *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Provindol *E-Pharma, Ital.*
Naproxen sodium (p. 98·2).
Pain; fever.

Provinerv *Ad-Drugstel, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Proviodine *Rougier, Canad.; Rougier, Hong Kong.†*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane disinfection; mouth infections; vaginal infections; wounds; burns; skin disorders.

Provir *Bio-Kem, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Proviron
Note: this name may be used for preparations of different composition.
Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Chile; Bayer Schering, Cz.; Bayer, Gr.; Bayer Schering, Hung.; Bayer Schering, Indon.; Schering, Israel; Bayer, Ital.; Bayer, Mex.; Bayer, Philipp.; Bayer Schering, Pol.; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S. Afr.; Bayer, Spain; Schering, Turk.; Schering, UK; Schering, Ukr.; Schering, Venez.
⊗Mesterolone (p. 2291·1).
Erectile dysfunction; male infertility; male hypogonadism; androgen deficiency; aplastic anaemia.

Proviron Depot
Note: this name may be used for preparations of different composition.
Schering, Venez.
⊗Testosterone enantate (p. 2305·1).
Androgen deficiency; hypogonadism; male infertility.

Provironum *Zydus, India; Bayer Schering, Malaysia; Bayer, Singapore; Bayer, Thai.*
⊗Mesterolone (p. 2291·1).
Androgen deficiency; erectile dysfunction; hypogonadism; male infertility.

Provirsan *ProMed, Cz.; Promed, Rus.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Provisacor *Orifarm, Denm.; AstraZeneca, Ital.; AstraZeneca, Neth.; AstraZeneca, Spain.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

ProVisc *Alcon, USA.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Provisc *Alcon, Arg.†; Alcon, Austral.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Ital.; Alcon, Malaysia†; Alcon, NZ; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore†; Alcon, Thai.; Alcon, Turk.†*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Provisual *Poen, Arg.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Provisual Compuesto *Poen, Arg.*
⊗Gentamicin sulfate (p. 304·2); dexamethasone (p. 1630·3); tetryzoline hydrochloride (p. 1678·3).
Infected eye disorders.

Provita *Scherer, Thai.*
Vitamins; minerals; amino acids.

Provital *Pertiwi Agung, Singapore.*
Ginseng (p. 2513·3); vitamins; minerals; lysine hydrochloride (p. 2079·3); glutamic acid (p. 2070·2).
Nutritional supplement.

Landson, Indon.
Ginseng (p. 2513·3); vitamins; lysine (p. 2079·3); glutamic acid (p. 2070·2); minerals.
Mental function impairment.

Prohealth, Philipp.
Vitamins; minerals; lysine (p. 2079·3).
Nutritional supplement.

Provital Plus *Landson, Indon.*
Ginseng (p. 2513·3); vitamins; lysine (p. 2079·3); glutamic acid (p. 2070·2); minerals; lecithin (p. 2542·2).
Immunostimulant.

Provitamin A-E *Cielle, Ital.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); royal jelly (p. 2608·1).
Nutritional supplement.

Provit-Cee *Vitalink, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Proviton *CCM, Malaysia.*
Vitamins; minerals; ginseng (p. 2513·3); lecithin (p. 2542·2); lysine (p. 2079·3).

Provit, Mex.†
Vitamins.

Provive *Antibioticos, Mex.†; AFT, NZ; Claris, Port.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Provixen-N *DAST, Gr.; Zekides, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Provizar *SMHP, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Provocholine *Methapharm, Canad.; Biotis, Israel; Diater, Spain; Methapharm, USA.*
Methacholine chloride (p. 2557·3).
Diagnosis of bronchial hyperresponsiveness.

Provoltar *Sandoz, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Provomer *Meprofarm, Indon.*
Parathiazine teoclate (p. 637·1); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting; motion sickness.

Provon Antimicrobial *Gojo, Canad.*
Chloroxylenol (p. 1748·2).
Skin disinfection.

Provon Antiseptic *Gojo, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Provon Medicated *Gojo, Canad.*
Triclosan (p. 1773·2).
Skin disinfection.

Provon Medicated with Chloroxylenol *Gojo, Canad.*
Chloroxylenol (p. 1748·2).
Skin disinfection.

Provosal *GL Pharma, Hung.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Provula *Dexa, Indon.*
⊗Clomifene citrate (p. 2259·1).
Male and female infertility.

Prowess *Harley Street Supplies, UK.*
⊗Yohimbine hydrochloride (p. 2372·3); pemoline (p. 2328·2); methyltestosterone (p. 2291·3).
Erectile dysfunction.

Prowess Plain *Harley Street Supplies, UK.*
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction.

Pro-Whey *Milk Industries, Israel.†*
Protein supplement.

Proworm *Hexpharm, Indon.†*
Pyrantel embonate (p. 165·3).
Worm infections.

Proxacin
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.; Medreich, Hong Kong; Polfa Warszawa, Pol.; Fako, Turk.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Inpac, Thai.
Norfloxacin (p. 333·3).
Bacterial infections.

Proxagol *Union Health, Ital.*
Naproxen cetrimonium (p. 98·2).
Mouth and throat inflammation.

Proxal *Arrow, Irl.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Proxalin *Degorts, Mex.*
Naproxen (p. 98·2).
Gout; pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Proxalin Plus *Degorts, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Proxalyoc *Cephalon, Fr.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Proxatan *Investi, Arg.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Proxazin *Metz, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Pro-XB *Biomep, Mex.*
Ibuprofen (p. 68·2).
Pain.

Proxcip *Mugi, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Proxco *Unimex, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Proxen *Macarthur, Austral.; Grunenthal, Austria; Roche, Ger.; Grunenthal, Switz.; Pharmaland, Thai.*
Naproxen (p. 98·2).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Proxiclav *Prohealth, Philipp.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3) or clavulanic acid (p. 268·3).
Bacterial infections.

Proxidan *Meprofarm, Indon.*
d-Alpha tocopherol (p. 2119·1).
Antioxidant.

Proxidin
Note: this name may be used for preparations of different composition.
Novell, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Proxil *Rottapharm, Ital.*
Proglumetacin maleate (p. 127·1).
Inflammation; pain.

Proximax *Integrated Pharmaceutical, Philipp.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Proxime
Note: this name may be used for preparations of different composition.
Leti, Venez.
Levofloxacin (p. 315·3).
Bacterial infections.
Protech, Rus.
Cefuroxime sodium (p. 255·3).
Bacterial infections.
Sanbe, Indon.
Aspirin (p. 22·2).
Glycine (p. 2071·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Proximic *Polpharma, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Proxinor *Medicine Products, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Proxitor *Combiphar, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Proxium *Pro-Pharma, Ukr.*
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Proxivex *Blue Sky, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Proxocarpine *Moscow Endocrine, Rus.*
Proxodolol; pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Proxofeline *Moscow Endocrine, Rus.*
Clonidine hydrochloride (p. 1339·1); proxodolol.
Glaucoma.

Proxol *Sam-On, Israel.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Fever; pain.

Prox-S *Prosel, Philipp.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Proxytab *Wockhardt, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Proxyvon *Wockhardt, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Proza *Landson, Indon.*
Oral syrup: Echinacea angustifolia extract (Polinacea) (p. 2498·1); zinc picolinate (p. 2126·1).
Respiratory-tract infections; immunostimulant.
Landson, Indon.; Landson, Singapore.
Echinacea angustifolia extract (Polinacea) (p. 2498·1); ascorbic acid (p. 2110·3); zinc picolinate (p. 2126·1).
Respiratory-tract infections; immunostimulant; tonic.

Prozac *Lilly, Arg.; Lilly, Austral.; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Fr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, NZ; Lilly, Philipp.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder; mixed anxiety depressive states.

Prozaids *Protherapix, Malaysia.*
Curcumin betadex.
Tonic.

Prozamel *Clonmel, Irl.*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Prozatan *UCB, Irl.†*
Fluoxetine hydrochloride (p. 417·1).
Bulimia; depression; obsessive-compulsive disorder.

Prozef *BMS, S.Afr.*
Cefprozil (p. 248·2).
Bacterial infections.

Prozelax *Biomedis, Philipp.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Prozen *Teuto, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Prozep *Chemidex, UK.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Prozidil *Pharmanel, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Prozin
Note: this name may be used for preparations of different composition.
Basic, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.
Lusofarmaco, Ital.
Chlorpromazine hydrochloride (p. 1045·2).
Psychiatric disorders; vomiting; hiccups; pain; premedication.

Prozinc *Prohealth, Philipp.*
Zinc sulfate (p. 2126·2).
Nutritional supplement.

Prozine
Note: this name may be used for preparations of different composition.
Hauck, USA.
Promazine hydrochloride (p. 1100·1).
Psychoses.
Pharmacor, Austral.
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting.
Sunward, Singapore.
Promethazine hydrochloride (p. 638·2).
Allergic conditions; nausea and vomiting; insomnia.
Utopian, Thai.
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses.

Prozit *Niche, Irl.; Pinewood, UK.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Prozma *Healthy Body Services, Canad.†*
Pyridoxine hydrochloride (p. 2105·3); magnesium (p. 1786·3); zinc (p. 2126·1).

Prozolin *Liferpal, Mex.*
Metronidazole benzoate (p. 936·1).

Prozolon *Berko, Turk.*
⊗Prednisolone (p. 1645·2).
Skin disorders.

ProZone Baby *Darier, Mex.*
SPF 34: Melanin (p. 1711·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

ProZone Block *Royal, Chile.*
SPF 50+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); phenethyl benzoate; povidone; hexadecene coplymer; titanium dioxide (p. 1725·1); isocetyl stearoyl stearate.
Sunscreen.

ProZone Body *Darier, Mex.*
SPF 25: Melanin (p. 1711·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

ProZone Face *Darier, Mex.*
SPF 25: Melanin (p. 1711·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.
Royal, Chile.†
Melanin (p. 1711·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); homosalate (p. 1705·1); titanium dioxide (p. 1725·1).
Sunscreen.

ProZone Gel *Royal, Chile; Darier, Mex.*
SPF 30: Melanin (p. 1711·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); homosalate (p. 1705·1).
Sunscreen.

ProZone Ultra *Darier, Mex.*
SPF 80: Melanin (p. 1711·1); octocrilene (p. 1715·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1).
Sunscreen.

ProZone Ultra Fluido *Darier, Mex.*
SPF 60: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); melanin (p. 1711·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Prozu *Brown & Burk, Philipp.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Prozylex *Norma (Νορμα), Gr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Prozyn *Adcock Ingram, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states; bulimia nervosa; obsessive-compulsive disorder.

Prrrikweg *VSM, Neth.*
Echinacea angustifolia (p. 2498·1); ledum palustre (p. 2550·1); urtica urens (p. 2639·3).
Homoeopathic preparation.

Prubagen *Liferpal, Mex.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

PruClair *PruGen, USA.*
Enoxolone (p. 54·2).
Pruritus; skin irritation.

Pruderm *Apotex, Arg.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Pruritus.

Prudoxin *Healthpoint, USA.*
Doxepin hydrochloride (p. 414·2).
Pruritus.

Průdušková *Megafyt-R, Cz.*
Plantain (p. 2604·2); wild thyme (p. 2648·1); althaea (p. 2438·3); liquorice (p. 1853·2); tilia (p. 2631·3); rose fruit without seeds (p. 2607·1).
Respiratory-tract inflammation; cough.

Prugal *Silanes, Mex.*
Glipizide (p. 474·1).
Diabetes mellitus.

Pruina *Faes, Spain.*
Senna (p. 1885·1); cassia fistula (p. 1826·2); coriander (p. 2486·3); tamarind (p. 1892·2).
Constipation.

Prulit *Vinas, Spain.†*
Menthol (p. 2553·2).
Muscle sprains and strains; pruritus; insect stings.

PruMyx *PruGen, USA.*
Barrier preparation.

Prunacolon *Takeda, Neth.*
Senna (p. 1885·1); dexpanthenol (p. 2582·2).
Bowel evacuation; constipation.

Prunasine *Nycomed, Neth.*
Senna (p. 1885·1); dexpanthenol (p. 2582·2).
Bowel evacuation; constipation.
Takeda, Belg.
Senna fruit (p. 1885·1).
Constipation.

Prurex
Note: this name may be used for preparations of different composition.
Pentamedical, Ital.
Piroctone olamine (p. 1716·3); enoxolone (p. 54·2); butyl aminobenzoate (p. 1982·3); benzyl alcohol (p. 1739·3); benzyl benzoate (p. 2149·1).
Skin irritation.

Pruriced *D & M, Chile.*
Calamine (p. 1697·2); raspberry seed oil; Uriage thermal water.
Pruritus; skin irritation.
Uriage, Fr.
Cream: Calamine (p. 1697·2); raspberry seed oil (p. 2207·2); Uriage thermal water.
Skin irritation.
Uriage, Fr.
Topical gel: Calamine (p. 1697·2); glycine (p. 2071·2); Uriage thermal water.
Skin irritation.

Pruriderm *Infectopharm, Ger.*
Lauromacrogol 400 (p. 2194·1).
Pruritus.

Pruridol *Cazi, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Prurifen *Neo Química, Braz.*
Ketotifen fumarate (p. 631·3).

Prurigel *Fortbenton, Arg.*
Triclosan (p. 1773·2); mallow (p. 2549·2); chamomile (p. 2474·1).
Scalp disorders.

Pruri-Gran *Legrand, Braz.*
Hydroxyzine hydrochloride (p. 630·3).

Prurilite *Holland Pharma, Neth.*
Apis mellifica (p. 2445·2); clematis erecta; dulcamara (p. 2497·3); hepar sulphur (p. 1721·3); ledum palustre (p. 2550·1); rhus toxicodendron (p. 2603·3); sulphur (p. 1721·1); urtica urens (p. 2639·3); histaminum muriaticum (p. 2525·2); calcarea carbonica ostrearum (p. 1824·3).
Homoeopathic preparation.

Pruri-med *Permamed, Switz.*
Disodium sulfosuccinated undecenoic acid monoethanolamide (p. 596·3); lauromacrogol 400 (p. 2194·1).
Skin disorders.

Pruri-med Lipolotion *Permamed, Switz.*
⊗Lauromacrogol 400 (p. 2194·1); urea (p. 1727·3).
Skin disorders.

Prurimix *Metochem, Austria.*
Talc (p. 1722·2); zinc oxide (p. 1729·1); lauromacrogol 400 (p. 2194·1); menthol (p. 2553·2); diphenylpyraline hydrochloride (p. 627·2).
Skin disorders.

Prurisedan *Andromaco, Arg.*
Topical powder: Phenol (p. 1763·3); camphor (p. 2466·2); boric acid (p. 2459·3); zinc stearate (p. 2221·2); zinc oxide (p. 1729·1).
Allergic skin disorders; insect bites; pruritus; sunburn; urticaria.
Andromaco, Arg.
Cream: Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2).
Allergic skin disorders; pruritus; insect bites; sunburn.

Prurisedan Incolora *Andromaco, Arg.*
Lotion: Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1).
Pruritus; skin irritation.

Prurisedan Rosa *Andromaco, Arg.*
Lotion: Phenol (p. 1763·3); camphor (p. 2466·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2); neocalamine (p. 1697·2).
Allergic skin disorders; insect bites; pruritus; sunburn; urticaria.

Prurisedine *Eurogenerics, Belg.†*
Albichtyol; chlorobutanol (p. 1747·2).
Skin disorders.

Prurix *GSK, Arg.; Stiefel, Chile; Stiefel, Mex.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Pruritus; skin irritation.

Prurizin *Darrow, Braz.*
Hydroxyzine hydrochloride (p. 630·3).
Hypersensitivity reactions.

Pryce-Kidz *Interhealthcare, Philipp.*
Vitamins; taurine (p. 2626·2); lysine hydrochloride (p. 2079·3); chlorella growth factor (p. 2475·3).
Dietary supplement.

Pryleugan *Temmler, Ger.†*
Imipramine hydrochloride (p. 426·2).
Depression; pain; nocturnal enuresis.

Pryltec *Geolab, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Pryltec-H *Geolab, Braz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Prysma *Ariston, Arg.; Q Pharma, Spain.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prysoline *Rekah, Israel.*
Primidone (p. 547·1).
Epilepsy.

PSE CPM *Boca, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

PSE MSC *Cypress, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); hyoscine methonitrate (p. 1846·1).
Cold symptoms; rhinitis; sinusitis.

Pseudo *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Pseudo-Car DM *Geneva, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); carbinoxamine maleate (p. 619·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Pseudo-Chlor *Geneva, USA; Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Pseudoephedrine T *Pharmaniaga, Malaysia.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Nasal congestion.

Pseudofrin *Trianon, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Congestion.

Pseudo-Gest *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Pseudo-Gest Plus *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Pseudophage *Servier, Fr.*
Sodium alginate (p. 2167·3); agar (p. 2167·2).
Obesity.

Pseudorine *Sunward, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal and bronchial congestion.

Pseudovac *Biomed Krakow, Pol.*
A pseudomonal vaccine (7-valent) (p. 2412·3).
Active immunisation.

Psibeter *BA Farma, Port.†*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Psicardiol *Pfizer, Philipp.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Psico Blocan *Estedi, Spain.†*
Chlordiazepoxide hydrochloride (p. 1044·2); hyoscine methobromide (p. 1846·1).
Gastrointestinal spasm.

Psicoasten *Beta, Arg.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder; premenstrual dysphoric disorder.

Psicocen *Centrum, Spain.*
Sulpiride (p. 1107·3).
Anxiety disorders; psychoses; vertigo.

Psicolit *Farmo Quimica, Chile.*
Lithium carbonate (p. 427·3).
Mania.

Psiconor *Ivax, Arg.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Psicosedin *Farmasa, Braz.*
Chlordiazepoxide (p. 1044·2).
Alcohol withdrawal syndrome; adjuvant in general anaesthesia; anxiety.

Psicosedol *Spedrog, Arg.†*
Alprazolam (p. 1035·2).

Psicosoma *Ferrer, Spain.*
Oral liquid: Magnesium glutamate hydrobromide (p. 2549·1); promethazine hydrochloride (p. 638·2).
Insomnia; night terrors; sedative.

Ferrer, Spain.
Tablets: Magnesium glutamate hydrobromide (p. 2549·1).
Insomnia; anxiety; behaviour disorders; nervous disorders associated with magnesium deficiency.

Psicotil *Azevedos, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia.

Psicotop *Fabop, Arg.*
Diazepam (p. 1063·2).

Psicotric *Qualigen, Spain.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Psidep *Atral, Port.*
Mirtazapine (p. 436·1).
Depression.

Psilo-Balsam *Stada, Cz.; Stada, Hung.; Stada, Rus.; Stada, Ukr.*
Diphenhydramine hydrochloride (p. 626·2).
Skin irritation; allergic skin disorders; pruritus; urticaria; sunburn; first-degree burns; insect stings; eczema.

Psilumax *Columbia, Mex.†*
Psyllium seed (p. 1849·1); wheat fibre (p. 1823·3).
Bowel evacuation; constipation.

Psipax *Merck, Port.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Psiquial *Merck, Braz.; Merck, Venez.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Psiu *Teuto, Braz.*
Cetylpyridinium chloride (p. 1743·1); ammonium chloride (p. 1656·1).
Respiratory-tract congestion.

PSO *CS, Fr.†*
Cream: ⊗Kokum butter; urea (p. 1727·3).
Seborrhoea.

CS, Fr.†
Mousse: ⊗Kokum butter; glycerol (p. 2517·2).
Soap substitute.

CS, Fr.†
Shampoo: ⊗Kokum butter; urea (p. 1727·3); piroctone olamine (p. 1716·3).
Dandruff.

Psocortene *Genopharm, Fr.†*
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Skin disorders.

Psoderm *Sandoz, Turk.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Psodermil *Edol, Port.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin and scalp disorders.

Psoradexan *Almirall Hermal, Ger.*
⊗Dithranol (p. 1701·2); urea (p. 1727·3).
Psoriasis.

Psoraffect *Verisfield, Gr.*
Calcipotriol (p. 1697·2).
Psoriasis.

Psoraks *Kurtsan, Turk.*
Dithranol (p. 1701·2); salicylic acid (p. 1719·1).
Psoriasis.

Psoralon MT *Almirall Hermal, Ger.*
Dithranol (p. 1701·2); salicylic acid (p. 1719·1).
Psoriasis.

Psor-a-set *Hogil, USA.*
Salicylic acid (p. 1719·1).

Psor-Asist *Plunkett, Austral.*
Cream: ⊗Sulfur (p. 1721·1); salicylic acid (p. 1719·1); coal tar (p. 1723·2); urea (p. 1727·3); vitamin A palmitate (p. 2098·3).
Psoriasis.

Plunkett, Austral.
Lotion: ⊗Sulfur (p. 1721·1); salicylic acid (p. 1719·1); aloe vera (p. 1693·2); urea (p. 1727·3); vitamin A palmitate (p. 2098·3).
Psoriasis of the scalp.

Psorasolv *Potter's, UK.*
Starch (p. 2095·1); sublimed sulfur (p. 1721·1); zinc oxide (p. 1729·1); pokeroot (p. 2593·2); clivers (p. 2481·2).
Psoriasis.

Psorcon *Dermik, USA.*
⊗Diflorasone diacetate (p. 1633·3).
Skin disorders.

Psorcutan *Intendis, Austria; Leo, Ger.; Intendis, Ital.; Schering, Turk.*
Calcipotriol (p. 1697·2).
Psoriasis.

Psorcutan Beta *Intendis, Austria; Leo, Ger.; Schering, Turk.*
⊗Calcipotriol (p. 1697·2); betamethasone dipropionate (p. 1623·3).
Psoriasis.

Psorent *NeoStrata, USA.*
Coal tar (p. 1723·2).
Psoriasis.

Psorex *GSK, Braz.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Psoriacalm *Phytobiolab, Fr.*
Marine phospholipids (p. 1460·3).
Psoriasis; ichthyosis.

Psoriasin *Alva, Canad.*
Coal tar (p. 1723·2).

Psoriasin Medicated Wash *Alva, USA.*
Salicylic acid (p. 1719·1).
Skin disorders.

Psoriatec *Sirius, USA.*
Dithranol (p. 1701·2).
Formerly known as Micanol.
Psoriasis.

Psoriaten *DHU, Rus.; DHU, Ukr.*
Mahonia aquifolium (p. 2577·1).
Homoeopathic preparation.

Psoricap *Arterium, Ukr.*
Pyrithione zinc (p. 1718·1).
Skin disorders.

Psoriderm
Note: this name may be used for preparations of different composition.
Dermal Laboratories, Irl.; Dermal Laboratories, UK.
Coal tar (p. 1723·2).
Psoriasis.

Erlimpex, Indon.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Mipharm, Ital.†
Dithranol (p. 1701·2).
Psoriasis.

Psorilom *Alkoy, Rus.*
Berberis vulgaris (p. 2502·1); fumaria officinalis (p. 2508·2); graphites (p. 2522·1); kalium bromatum (p. 2461·1); solidago virgaurea (p. 2620·1); toxicodendron quercifolium (p. 2603·3).
Homoeopathic preparation.

Psorimed *Wolff, Ger.; Wolff, Gr.; Wolff, Neth.†*
Salicylic acid (p. 1719·1).
Scalp psoriasis.

Psorin
Note: this name may be used for preparations of different composition.
LPC, UK.
Ointment: Dithranol (p. 1701·2); salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Psoriasis.

LPC, UK.
Scalp gel: Dithranol (p. 1701·2); salicylic acid (p. 1719·1); methyl salicylate (p. 92·1).
Psoriasis.

Kinder, Braz.†
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Psorinol *Ipca, India.†*
Dithranol (p. 1701·2).
Psoriasis.

Psorisan *RiC, Pol.†*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); zinc oxide (p. 1729·1).
Skin disorders.

Psovate *Kurtsan, Turk.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

PsP *Sahabat, Indon.*
Polysaccharide peptide from *Ganoderma lucidum.*
Immunostimulant.

Psycholanz *Ipca, India.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Psychoneuroticum N *Asconex, Ger.*
Amanita muscaria; asa foetida (p. 2449·3); myristica fragrans (p. 2573·1); strychnos ignatii (p. 2532·1); valeriana officinalis (p. 2640·2); zincum isovalerianicum (p. 2641·2).
Homoeopathic preparation.

Psychoneuroticum (Röwo-578) *Asconex, Ger.†*
Agaricus; asa foetida (p. 2449·3); anacardium occ.; coffea arabic. (p. 2648·2); ignatia (p. 2532·1); nux moschata (p. 2573·1); sabadilla (p. 2611·2); sumbulus moschatus; valeriana (p. 2640·2); zincum valerianicum (p. 2641·2); calcium hypophosphorosum (p. 2530·3).
Homoeopathic preparation.

Psychopax *Sigmapharm, Austria; Proreo, Switz.*
Diazepam (p. 1063·2).
Anxiety disorders; sleep disorders; skeletal muscle spasm; epilepsy; febrile convulsions; premedication.

Psychordal *Viofar, Gr.*
Risperidone (p. 1103·2).

Psychotonin *Madaus, Austria; Steigerwald, Ger.*
St John's wort (p. 449·1).
Depression; anxiety.

Psychotonin-sed *Steigerwald, Ger.†*
St John's wort (p. 449·1); valerian (p. 2640·2).
Anxiety; depression; sleep disorders.

Psychotonisol *Phytofarm Kleka, Pol.†*
St John's wort (p. 449·1); melissa (p. 2552·3); passion flower (p. 2584·1).
Nervous disorders.

Psycoton *DRD, Gr.; Biomedica, Ital.*
Piracetam (p. 393·3).
Mental function impairment.

Psylia *Techni-Pharma, Mon.*
Psyllium (p. 1849·1).
Constipation.

Psylli-Mucil Plus *Bioglan, Austral.†*
Ispaghula (p. 1849·1); slippery elm (p. 2617·1); peppermint leaf (p. 1877·1); ginger (p. 1844·1); pectin (p. 2200·3).
Bowel cleanser.

Psyllogel *Nathura, Ital.*
Psyllium (p. 1849·1).
Dietary fibre supplement.

Psyllogel Fermenti *Nathura, Ital.*
Psyllium (p. 1849·1); lactic-acid-producing organisms (p. 2596·3).
Dietary fibre supplement.

Psynor *Swiss Pharma, Philipp.*
Chlorpromazine hydrochloride (p. 1045·2).
Anxiety; intractable hiccup; nausea and vomiting; porphyria; psychoses; tetanus.

Psyrazine *Condrugs, Thai.*
Trifluoperazine (p. 1113·2).
Anxiety; psychoses; nausea and vomiting.

PSY-Stabil *Pekana, Hung.*
Acidum phosphoricum (p. 2589·1); agaricus muscarius; semecarpus anacardium (p. 2471·3); avena sativa (p. 2451·1); juglans regia (p. 2646·1); cinchona succirubra (p. 2478·3); strychnos ignatii (p. 2532·1); piper methysticum (p. 2537·3); schoenocaulon officinale (p. 2611·2).
Homoeopathic preparation.

PSY-stabil *Pekana, Neth.*
Phosphoricum acidum (p. 2589·1); agaricus muscarius; anacardium orientale (p. 2471·3); avena sativa (p. 2451·1); china officinalis (p. 2478·3); ignatia amara (p. 2532·1); sabadilla (p. 2611·2); piper methysticum (p. 2537·3).
Homoeopathic preparation.

PTA *Neuropharma, Arg.*
Alprazolam (p. 1035·2).
Anxiety; depression.

PT-AM *Nutricia, Cz.*
Food for special diets.
Tyrosinaemia.

P-Tanna *Prasco, USA.*
Phenylephrine tannate (p. 1672·2); mepyramine tannate (p. 635·1).
Upper respiratory-tract disorders.

PTE *Fujisawa, USA.†*
Trace elements.
Parenteral nutrition.

Pterin *Korea United, Philipp.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

P-Tex *Poly, USA.†*
Brompheniramine tannate (p. 618·1).
Hypersensitivity reactions.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ptinolin *Help, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

P-Trovite *Rotexmedica, Malaysia.*
Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); riboflavin (p. 2104·3); ampoule 2, sodium pantothenate; glucose (p. 2068·3); nicotinamide (p. 2083·1); ascorbic acid (p. 2110·3).
Vitamin deficiency.

PTU *TO-Chemicals, Thai.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Pu Le *Junan, China.*
Lappaconitine hydrobromide (p. 1418·1).

Pu An Kang Shang *SanJiu JiShi, China.*
Enoxacin gluconate.
Bacterial infections.

Pu Chang *Shyndec, China.*
Naftopidil (p. 2361·1).
Benign prostatic hyperplasia.

Pu Ding Yang *Tang Ren, China.*
Phentolamine mesilate (p. 1468·3).

Pu En Fu *Guoda, China.*
Lumbrokinase.

Pu Le Er *Lu Yin, China.*
Paracetamol (p. 115·1).
Fever; pain.

Pu Er Tai *Chang Fu Jie Jing, China.*
Ranitidine hydrochloride (p. 1882·1).
Pathological hypersecretory disorders; peptic ulcer; acid aspiration; gastro-oesophageal reflux.

Pu Fei Te *Xincat, China.*
Nimesulide (p. 101·3).
Pain.

Pu Feng Qing *Yake, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Pu Fu *Wu Zhou Tong, China.*
Inosine (p. 2533·1).

Pu Fu Lin *Duoburuifei, China.*
Nicotinamide (p. 2083·1).

Pu Gan Jing *Pu Sheng, China.*
Diammonium glycyrrhizate (p. 2520·3).

Pu Gen Xin *Dadongfang, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Pu Guang *Ke Lun, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Pu He *Chang Fu Jie Jing, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Pu Hong *Shyndec, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Pu Hui Zhi *Shyndec, China.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Pu Le Kang *Aiwei, China.*
Lysine hydrochloride (p. 2079·3).

Pu Le Kang Ni *Ji Sheng, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Pu Ke *Ke Lun, China.*
⊗Mannitol (p. 1427·3).

Pu Kuai *Baiyunshan, China.*
Cefaclor (p. 232·3); bromhexine (p. 1656·3).

Pu Lai Le *Hanson, China.*
Pemetrexed disodium (p. 844·3).
Non-small cell lung cancer; malignant pleural mesothelioma.

Pu Li De *Hengli, China.*
Glucosamine hydrochloride (p. 2515·3).

Pu Li *Zhongyuanwei, China.*
Glucosamine hydrochloride (p. 2515·3).
Joint disorders.

Pu Li Da *Yao Wang, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Pu Li Duo *Simcere, China.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Pu Li Kang *Fengyuan, China.*
Fructose (p. 2068·2).

Pu Li Ning *Hayao, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Pu Lie An *Shyndec, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Pu Lin *Hansen, China.*
Adenosine cyclophosphate meglumine.

Pu Le Lin *Lu Yin, China.*
Puerarin.

Pu Luo *Qi Li, China.*
Enoxacin gluconate.
Bacterial infections.

Pu Luo Bi Da *Ou Yi, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine (p. 1676·1).

Pu Luo Chuan *Chang Fu Jie Jing, China.*
Arginine hydrochloride (p. 2049·1).

Pu Luo Lin *Yang Zhou, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Pu Luo Ping *Yuansen, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Pu Luo Shi *Huakang, China.*
Tinidazole (p. 949·2).

Pu Luo Si Tai *Bafeng, China.*
Glutamic acid (p. 2070·2); alanine (p. 2048·3); glycine (p. 2071·2).

Pu Mai *Puzhong, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Pu Mei La Tai *Ke Lun, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; head injury; parkinsonism.

Pu Mei Te *Shyndec, China.*
Telmisartan (p. 1509·3).
Hypertension.

Pu Nai Tong *Chang Fu Jie Jing, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Pu Nai Xin *Pu Sheng, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Pu Ni Ke Si *Haixin, China.*
Bromhexine hydrochloride (p. 1656·3).

Pu Le Ning *Lu Yin, China.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Pu Le Qi *Shyndec, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Pu Qi Ao *San Lian, China.*
Dipyridamole (p. 1362·2).

Pu Ren Ping *Pudu, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Pu Run *Chia Tai, China.*
Puerarin.

Pu Sen Ou Ke *Hui Pu Sen, China.*
⊗Naproxen sodium (p. 98·2); pseudoephedrine hydrochloride (p. 1676·1).

Pu Sha Tong *Minsheng, China.*
Matrine.

Pu Shu *Mao Xiang, China.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Pu Su Xin *Haochuang, China.*
⊗Propranolol hydrochloride (p. 1479·1).

Pu Ta Ning *Peili, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Pu Wei *TianJing, China.*
Nimesulide (p. 101·3).
Pain.

Pu Xi Ding *Shyndec, China.*
Zidovudine (p. 1024·2).
HIV infection.

Pu Le Xin *Lu Yin, China.*
⊗Propranolol hydrochloride (p. 1479·1).

Pu Xin Qing *Chang Fu Jie Jing, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Pu Ya Te *Wu Zhou Tong, China.*
Levofloxacin mesilate.
Bacterial infections.

Pu Yang *Xin Ma, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Pu Yi *Puzhong, China.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Pu Le Yi *Xianju, China.*
Pidotimod (p. 2590·2).
Immunostimulant.

Pu Yi Ge *Shuai Ke, China.*
Puerarin.

Pu You Ke *Tasly, China.*
Prourokinase.

Pu Yuan Xin *Yuyuan, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Pubergen *Uni-Sankyo, India.*
⊗Chorionic gonadotrophin (p. 2258·1).
Male and female infertility; recurrent miscarriage; cryptorchidism; hypogonadotrophic hypogonadism; delayed puberty; oligospermia; pituitary dwarfism.

Pubex *Tafarm, Gr.*
Phenothrin (p. 2160·1).
Pediculosis.

Pucker Up *Aztex, Canad.†*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Pudan-Lebertran-Zinksalbe *Bano, Austria.*
Zinc oxide (p. 1729·1); peru balsam (p. 2587·1); cod-liver oil (p. 2056·3).
Wounds; burns; nappy rash; decubitus ulcer.

Puder Płynny *Aflofarm, Pol.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation.

Farmina, Pol.
Menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation.

Puder Płynny wysuszający *Hasco-Lek, Pol.*
Menthol (p. 2553·2); zinc oxide (p. 1729·1).
Pruritus.

Puder Płynny z Anestezyną *Hasco-Lek, Pol.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Pruritus.

Pudin Haran *Garuda, Hung.*
Peppermint oil (p. 1877·1); spearmint oil (p. 2621·2).
Digestive disorders.

Pudroderm *Pampa, Pol.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation.

Pudrospan *Gemi, Pol.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Pruritus.

Pugritex *Davur, Irl.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Puiritol *HPP, Hong Kong.*
Ofloxacin (p. 334·3).
Bacterial infections.

Pulbronc *Recalcine, Chile.*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3); ammonium chloride (p. 1656·1).
Cough.

Pulbronc Simple *Recalcine, Chile.*
Clobutinol hydrochloride (p. 1658·3).
Cough.

Pulbronkal *Permatec, Arg.*
Tobramycin (p. 380·1).

Pulcet *Nobel, Turk.; Nobel, Ukr.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastritis; dyspepsia.

Pulibex *Medinova (Μεντινοβα), Gr.*
Aciclovir (p. 964·1).
Labial and genital herpes simplex infections.

PuLiLuo *Feima, China.*
Meloxicam (p. 86·3).

PuLiMin *Feima, China.*
Pemirolast potassium (p. 1218·2).

Pulin *YSP, Malaysia; Yung Shin, Singapore.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; adjunct in radiography of the gastrointestinal tract.

Pulkrin *Kinder, Braz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

PulmaCo *Mediherb, Austral.*
Skullcap (p. 2617·1); malabar nut (p. 2549·1); grindelia (p. 2522·3); turmeric (p. 2218·1); ginkgo biloba (p. 2512·3); fennel oil (p. 2503·3).
Respiratory-tract disorders.

Pulmagol *Pasteur, Chile.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); sodium benzoate (p. 1738·2); drosera (p. 2497·2); lobelia (p. 2323·2).
Respiratory-tract disorders.

Pulmax
Note: this name may be used for preparations of different composition.
Ivax, Cz.†; Ivax, Ger.†; Teva, Hung.†; Teva, Port.†
⊗Budesonide (p. 1625·1).
Obstructive airways disease; asthma.

Pulmaxan *AstraZeneca, Ital.*
⊗Budesonide (p. 1625·1).
Asthma.

Pulm-Cod (C & G) *Stadmed, India.*
Vitamins; calcium (p. 1783·1); creosote (p. 1659·3); sulfoguaiacol (p. 1678·1).
Respiratory-tract disorders.

Pulmeno *Artis, Spain.*
Theophylline (p. 1229·3).
Obstructive airways disease; paroxysmal dyspnoea; heart failure.

Pulmex
Note: this name may be used for preparations of different composition.
Novartis Consumer, Hung.; Novartis Consumer, Rus.†; Novartis Consumer, Switz.
Camphor (p. 2466·2); peru balsam (p. 2587·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3).
Respiratory-tract disorders; cough; cold symptoms.

Novartis Consumer, Israel.
Peru balsam (p. 2587·1); camphor (p. 2466·2).
Bronchitis; catarrh; cold symptoms; cough.

Novartis Consumer, Switz.
Bath additive: Thyme oil (p. 2630·3); pine needle oil (p. 2591·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3); lavender oil (p. 2541·1); niaouli oil (p. 2569·1).
Cough; cold symptoms.

Novartis Consumer, Belg.†
Benzyl benzoate (p. 2149·1); benzyl cinnamate (p. 2454·3); camphor (p. 2466·2); rosemary oil (p. 2607·3); cineole (p. 2479·1); vanillin (p. 2218·3).
Upper respiratory-tract disorders.

Pulmex Baby
Note: this name may be used for preparations of different composition.
Novartis Consumer, Belg.
Benzyl benzoate (p. 2149·1); benzyl cinnamate (p. 2454·3); rosemary oil (p. 2607·3); cineole (p. 2479·1); vanillin (p. 2218·3).
Upper respiratory-tract disorders.

Novartis Consumer, Hung.; Novartis Consumer, Pol.; Novartis Consumer, Rus.; Novartis Consumer, Switz.
Peru balsam (p. 2587·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3).
Respiratory-tract congestion; cough; cold symptoms.

Pulmiben *Italfarmaco, Port.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Pulmicort *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, China; AstraZeneca, Cz.; 2care4, Denm.; ChemVet, Denm.; Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; Pharmacodane, Denm.; SinGad, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Pol.; AstraZeneca, Port.; Stuart, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; AstraZeneca, USA; AstraZeneca, Venez.*
⊗Budesonide (p. 1625·1).
Asthma; croup; bronchitis; obstructive airways disease; allergic rhinitis; nasal polyps.

Pulmictan *Reig Jofre, Spain.*
⊗Budesonide (p. 1625·1).
Asthma.

Pulmin-CMC *Doctors, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Pulminetta *In Vitro, Hung.*
Menthol (p. 2553·2); thymol (p. 1772·2); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3); sodium chloride (p. 1795·1).
Respiratory-tract congestion.

Pulmison *Boehringer Ingelheim, S.Afr.*
⊗Prednisone (p. 1647·2).
Obstructive airways disease.

Pulmist *SoSe, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Pulmitac *Platinum, Philipp.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Pulmiver *Bio-synthesis, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; allergic skin disorders.

Pulmo Bailly *Bailly, Fr.; DDD, UK.*
Codeine (p. 40·2); guaiacol (p. 1666·1).
Cough.

Pulmo Borbalan *Spyfarma, Spain.†*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Pulmo Bronchialcomplex *Hevert, Ger.*
Oral drops: ⊗Ammi visnaga (p. 2441·2); belladonna (p. 2453·3); coralium rubrum; cuprum metall. (p. 2057·1); grindelia rob. (p. 2522·3); lobelia infl. (p. 2323·2); sticta (p. 2546·1).
Homoeopathic preparation.

Hevert, Ger.
Tablets: Drosera (p. 2497·2); grindelia rob. (p. 2522·3); kalium jod. (p. 2336·3); naphthalinum (p. 2158·2); spongia; sticta (p. 2546·1); teucrium scor.; verbascum (p. 2645·1); jerba santa (p. 1665·2).
Homoeopathic preparation.

Pulmo Lisoflam *Pfizer, Arg.*
⊗Budesonide (p. 1625·1).
Asthma; allergic rhinitis.

Pulmobrol *Transfarma, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Pulmobron *Mugi, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Pulmocare *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, China; Abbott, Cz.; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.†; Abbott, NZ; Abbott, Philipp.; Abbott Nutrition, Singapore; AstraZeneca, Turk.; Abbott Nutrition, UK; Abbott, Venez.*
Preparation for enteral nutrition.
Respiratory system disorders.

Abbott Nutrition, USA.
Lactose-free preparation for enteral nutrition.
Respiratory system disorders.

Pulmocis *CIS, Cz.; CIS, Fin.; CIS, Fr.; CIS, Irl.; CIS, Neth.; Schering, UK.*
Technetium-99m (p. 2228·1) labelled human albumin macroaggregates.
Lung perfusion scintigraphy; venoscintigraphy.

Pulmoclase *Olvos, Gr.; UCB, Irl.†*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Pulmocler *Monserrat, Arg.*
Bromhexine hydrochloride (p. 1656·3); butetamate citrate (p. 1658·1).
Respiratory-tract disorders.

Pulmo-Cod
Note: this name may be used for preparations of different composition.
Stadmed, India.
Vitamins; calcium (p. 1783·1).

Pulmo-cyl Ho-Len-Complex *Liebermann, Ger.*
⊗Bryonia (p. 2461·3); cuprum met. (p. 2057·1); drosera (p. 2497·2); kalium jod. (p. 2336·3); laurocerasus (p. 2475·2); lobelia (p. 2323·2); stannum jod..
Homoeopathic preparation.

Pulmodex *Multicare, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pulmodexane *Bailly, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pulmodilat *Greenpharma, Braz.†*
Aminophylline (p. 1201·2).

Pulmo-Drainol *Boiron, Fr.†*
Ipecacuanha (p. 1667·2); antimonium tartaricum (p. 151·2); baryta muriatica (p. 2452·3); sanguinaria canadensis (p. 2610·1); phosphorus (p. 2589·2); anemone pulsatilla (p. 2600·2); bryonia dioica (p. 2461·3); silicea (p. 2208·3); spongia tosta; stannum (p. 2632·1); kermes mineralis.
Homoeopathic preparation.

Pulmodrin *More, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pulmodual *Cathay, Philipp.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Pulmofasa *Sabater, Spain.*
Ammonium camphocarbonate diaminopyridine carboxylate (p. 2316·2); calcium pantothenate (p. 2085·2); cineole (p. 2479·1); senega (p. 1677·2); sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1); tolu balsam (p. 1679·2); Scots pine oil (p. 2591·2); anethole (p. 2443·3).
Respiratory-tract disorders.

Pulmofluide Simple *AIM, Fr.*
Terpin (p. 1678·2); cineole (p. 2479·1); sodium benzoate (p. 1738·2); guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Pulmoflux *Neo Quimica, Braz.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Pulmofor *Vifor, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Pulmolet *Leti, Venez.*
⊗Budesonide (p. 1625·1).
Asthma.

Pulmolin
Note: this name may be used for preparations of different composition.
Taiwan Biotech, Philipp.
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Pharos, Indon.†
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pulmoll *GSK Sante, Fr.†*
Terpin (p. 1678·2); menthol (p. 2553·2); amylocaine hydrochloride (p. 1979·3).
Throat disorders.

Pulmoll Menthol Eucalyptus *GSK Sante, Fr.†*
Menthol (p. 2553·2); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2).
Cold symptoms; sore throat.

Pulmolor *Movi Health, Ukr.*
Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2).
Respiratory-tract disorders.

Pulmonar *OM, Port.*
Lysates of *Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae; Staphylococcus aureus; Streptococcus pyogenes; Moraxella catarrhalis.*
Respiratory-tract infections.

Pulmonarom *Sanofi-Aventis, Mex.*
Lysate of *Haemophilus influenzae; Staphylococcus aureus; Moraxella catarrhalis; Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus agalactiae; Streptococcus dysgalactiae; Streptococcus anginosus.*
Respiratory-tract infections.

Pulmo-Neural Serocytol *Serolab, Switz.†*
An immunoglobulin (equine).
Cold and influenza symptoms.

Pulmonil *Pampa, Pol.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); menthol (p. 2553·2); pine oil (p. 2591·1); thymol (p. 1772·2); turpentine oil (p. 2636·3).
Cold symptoms.

Pulmonix
Note: this name may be used for preparations of different composition.
Biotenk, Arg.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Pulmonix Grip *Biotenk, Arg.*
⊗Bromhexine hydrochloride (p. 1656·3); paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Influenza symptoms.

Pulmonix Plus *Biotenk, Arg.*
Ambroxol hydrochloride (p. 1654·3); loratadine (p. 633·2).
Respiratory-tract disorders.

Pulmonox *Woikoski, Fin.*
Nitric oxide (p. 1457·1).
Neonatal respiratory distress syndrome.

Pulmonyl *Euro-Med, Philipp.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Pulmophyllin *Adcock Ingram, S.Afr.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Pulmophylline *Riva, Canad.*
Theophylline (p. 1229·3).
Bronchoconstriction.

Pulmor *Drogsan, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Pulmoran *Leros, Cz.*
Sage (p. 2608·3); althaea (p. 2438·3); knotgrass (p. 2538·2); thyme (p. 2630·2); urtica (p. 2639·3); sambucus (p. 2609·3); plantain (p. 2604·2); liquorice (p. 1853·2); fennel (p. 2503·2).
Upper respiratory-tract disorders.

Pulmorell *Sanorell, Ger.*
Grindelia robusta (p. 2522·3).
Homoeopathic preparation.

Pulmo-Rest
Note: this name may be used for preparations of different composition.
Stadmed, India.
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol (p. 1220·2); guaifenesin (p. 1666·2).
Cough associated with obstructive airways disease.

Pulmorest
Note: this name may be used for preparations of different composition.
Santa, Turk.
Levodropropizine (p. 1662·3).

Pulmo-Rest Expectorant *Stadmed, India.†*
⊗Bromhexine hydrochloride (p. 1656·3); salbutamol (p. 1220·2); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough associated with obstructive airways disease.

Pulmorex DM *Prodemdis, Canad.†*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1).

Pulmorphan *Riva, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Pulmorphan Pediatrique *Riva, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Pulmosal *Azevedos, Port.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with excessive mucus.

Pulmosan
Note: this name may be used for preparations of different composition.
Gezzi, Arg.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Steierl, Ger.
Atropa belladonna (p. 2453·3); cephaelis ipecacuanha; cuprum aceticum (p. 2486·2); drosera (p. 2497·2).
Homoeopathic preparation.

Pulmosan Aller *Gezzi, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Pulmosan Caramelos *Gezzi, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Pulmosan Infekt *Steierl, Ger.*
Apis mellifica (p. 2445·2); echinacea (p. 2498·1); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Pulmosérum *Bailly, Fr.*
Codeine (p. 40·2); guaiacol (p. 1666·1).
Cough.

Pulmosina *Labomed, Chile.*
Eucalyptus (p. 2501·1); avocado (p. 2451·2); pectoral flowers; tolu balsam (p. 1679·2); honey (p. 2072·1).
Cough.

Pulmosodyl *Bridoux, Fr.*
Pholcodine (p. 1675·1); sodium benzoate (p. 1738·2); tolu balsam (p. 1679·2).
Cough.

Pulmotabs *Sanofi-Aventis, Mex.*
Lysates of *Streptococcus pneumoniae; Klebsiella pneumoniae; Streptococcus haemolyticus; Staphylococcus aureus; Moraxella catarrhalis; Haemophilus influenzae.*
Respiratory-tract infections.

Pulmotec *Cyclomedica, Denm.; Cyclomedica, Fin.; Cydopharma, Fr.; Cyclomedica, Irl.; Cyclomedica, Neth.; Cyclomedica, Port.; Cyclomedica, Spain.*
Technetium-99m (p. 2228·1) labelled carbon microparticles (Technegas).
Diagnosis of pulmonary embolism.

Pulmoterol *Lek-Am, Pol.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Pulmotin *Serum-Werk Bernburg, Ger.*
Ointment: Anise oil (p. 2444·3); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3); conifer oil; thymol (p. 1772·2).
Respiratory-tract disorders.

Pulmotin Inhalat *Serum-Werk Bernburg, Ger.*
Eucalyptus oil (p. 2501·2).
Cold symptoms.

Pulmotosse *Delta, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Pulmovance *Meditrina, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Pulmovax *MSD, Mex.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Pulmovent
Note: this name may be used for preparations of different composition.
Prohealth, Philipp.
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Pulmovital *Ifusa, Mex.*
Sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Cough.

Pulmoxcel *GX, Philipp.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Pulmoxy *Micro, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pulmoxyl *Micro, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pulmozyme *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Turk.; Roche, UK; Roche, Ukr.; Genentech, USA.*
Dornase alfa (p. 1662·1).
Cystic fibrosis; respiratory-tract congestion.

Pulmus *Merck, Port.*
Sobrerol (p. 1677·2).
Respiratory-tract disorders with excessive mucus.

Pulna *Landson, Indon.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pulneo *Aflofarm, Pol.*
Fenspiride hydrochloride (p. 1209·2).
Respiratory-tract disorders.

Pulparthrol *Pierre Rolland, Fr.*
Eugenol (p. 2501·2); lidocaine (p. 1988·1).
Root canal infections.

Pulperyl *Septodont, Fr.*
Lidocaine hydrochloride (p. 1988·2); creosote (p. 1659·3); phenol (p. 1763·3); eugenol (p. 2501·2).
Root canal infections.

Pulpomixine *Septodont, Cz.†; Septodont, Fr.*
⊗Dexamethasone acetate (p. 1631·1); framycetin sulfate (p. 301·2); polymyxin B sulfate (p. 342·3).
Root canal infections; dental disorders.

Pulsalux *Novartis, Ital.*
Soya oil (p. 2092·3); ginkgo biloba (p. 2512·3); melilot (p. 2552·3); rutoside (p. 2505·3).
Circulatory disorders.

Pulsar
Note: this name may be used for preparations of different composition.
Medosan, Ital.
Colextran hydrochloride (p. 1347·1).
Hyperlipidaemias.

Phoenix, Arg.
Cisapride (p. 1831·3).
Gastro-oesophageal reflux.

Pulsar-AT Dual *Liomont, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Pulsaren *Biofarm, Pol.*
Quinapril (p. 1480·2).
Hypertension; heart failure.

Pulsatilla comp *Heel, Neth.*
⊗Pulsatilla pratensis (p. 2600·2); sulphur (p. 1721·1); cortisonum (p. 1629·2).
Homoeopathic preparation.

Pulsatilla Complexe No 60 *Lehning, Fr.†*
Anemone pulsatilla (p. 2600·2); atropa belladonna (p. 2453·3); aconitum (p. 2428·3); bryonia (p. 2461·3); cuprum aceticum (p. 2486·2); mercurius corrosivus (p. 2555·2); sulfur (p. 1721·1); natrum muriaticum (p. 1795·1); lamium album.
Homoeopathic preparation.

Pulsatilla Med Complex *Dynamit, Austria.*
Arsenicum album (p. 2448·1); colchicum (p. 607·1); ipecacuanha (p. 1667·2); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Pulsatirell *Sanorell, Ger.*
Pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Pulsit *Precimex, Mex.*
Haloperidol (p. 1077·1).
Psychoses; behaviour disorders in children.

Pulsol *Probiomed, Mex.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Pulsor *Tecnimede, Port.*
Calcium pangamate (p. 2582·1).

Pultex *Permatec, Arg.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Pulvinal Beclometasone Dipropionate *Trinity, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Pulvinal Salbutamol *Trinity, UK.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Pulviplasmine *Boiron, Fr.†*
Thuya occidentalis (p. 2629·3); hydrastis canadensis (p. 2528·1); erysimum (p. 2524·2); atropa belladonna (p. 2453·3); hamamelis virginiana (p. 2523·3); phytolacca decandra (p. 2593·2).
Homoeopathic preparation.

Pulvo 47
Note: this name may be used for preparations of different composition.
Abbott, Gr.
Catalase (p. 2472·2); neomycin sulfate (p. 330·1).
Wound healing.

Abbott, Thai.†; Genesis, Turk.
Catalase (p. 2472·2); hexamidine isetionate (p. 1754·3).
Wound debridement; burns; wounds; ulcers; skin irritation.

Pulvo-Hexa *Fournier-Gerolymatos, Gr.*
Catalase (p. 2472·2); hexamidine isetionate (p. 1754·3).

Puma Balm *Aspen, S.Afr.*
Clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); amber oil (p. 2440·3); turpentine oil (p. 2636·3); camphor (p. 2466·2); menthol (p. 2553·2).
Cold symptoms; musculoskeletal and joint pain; nasal congestion.

Puma Cough Balsam *SA Druggists Self Med, S.Afr.†*
Camphor (p. 2466·2); anise oil (p. 2444·3); menthol (p. 2553·2); ammonium chloride (p. 1656·1); liquorice (p. 1853·2); tolu balsam (p. 1679·2).
Cough; respiratory-tract congestion.

Pumarix *GSK, Cz.; GSK, Irl.; GSK, Neth.*
An influenza vaccine (H5N1) (p. 2393·3).
Pandemic influenza prophylaxis.

Pumilene Vapo *Montefarmaco, Ital.*
Pumilio pine oil (p. 2591·1); cineole (p. 2479·1); peppermint oil (p. 1877·1).

Pumilsan *Montefarmaco, Ital.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disinfection.

Pumpan *Bittner, Austria; Bittner, Rus.; Bittner, Ukr.*
Crataegus (p. 2488·1); arnica (p. 2447·2); kalium carbonicum (p. 2595·2); digitalis (p. 1352·3); convallaria (p. 2486·2).
Homoeopathic preparation.

Pumpitor *Sanbe, Indon.; Sanbe, Singapore.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Punab *Wermar, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; cardiovascular risk reduction.

Puncto Digest *PlantaPhile, UK.*
Ginger (p. 1844·1).
Digestive disorders.

Puncto Rub *PlantaPhile, UK.*
Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3).
Nasal congestion; musculoskeletal pain and stiffness.

Puncto SleepTight *PlantaPhile, UK.*
Valerian (p. 2640·2); melissa (p. 2552·3); lupulus (p. 2546·1).
Sleep disorders.

Puncto Travel *PlantaPhile, UK.*
Ginger (p. 1844·1).
Motion sickness.

Pungino *Wyeth Consumer, Ital.*
Vitamin B_1 (p. 2102·3); citronella oil (p. 2481·1).
Insect repellent.

Punol *Biolab, Thai.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Punto G *Mi Flora, Arg.†*
Propylene glycol (p. 2205·2); hypromellose (p. 2189·2); lactic acid (p. 2539·1).
Vaginal lubricant.

Puntol *Velka, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Puntual *Lainco, Spain.*
Calcium sennoside A (p. 1885·1); calcium sennoside B (p. 1885·1).
Constipation.

Puntualex *Lainco, Spain.*
Calcium sennoside A (p. 1885·1); calcium sennoside B (p. 1885·1).
Bowel evacuation.

Pupilek *Gemi, Pol.†*
Allantoin (p. 1693·1); zinc oxide (p. 1729·1).
Skin irritation.

Pupilla *Wassermann, Ital.*
⊗Naphazoline nitrate (p. 1669·3).
Inflammatory and allergic eye disorders.

Pupilla Antistaminico *Wassermann, Ital.*
⊗Naphazoline nitrate (p. 1669·3); thonzylamine hydrochloride (p. 642·1).
Inflammatory and allergic eye disorders.

Pupilla Light *Wassermann, Ital.*
Benzalkonium chloride (p. 1737·1); hypromellose (p. 2189·2); chamomile water; hyssop water; rose water; plantaginis water; mallow water; myrtillus water.
Eye disinfection; eye irritation.

Puqi *Qianjiang, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Puraclin *Neo Dermos, Arg.*
Skin cleanser.

Puraclin Exfoliante *Neo Dermos, Arg.*
Polyethylene and silica granules (p. 1690·3).
Abrasive skin cleanser.

Puraflor *Wyeth Consumer, Ital.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); minerals; glutathione (p. 1555·2); lactoferrin (p. 2539·3).
Restoration of gastrointestinal flora.

Puraloe *Eurolab, Arg.*
Aloe vera (p. 1693·2); tretinoin (p. 1725·2).
Keratinisation disorders; acne.

Puraloe Nutritiva *Eurolab, Arg.*
Aloe vera (p. 1693·2); vitamin A (p. 2098·3); collagen (p. 2483·2); elastin (p. 2483·2).
Skin disorders.

Puraloe Post Solar *Eurolab, Arg.*
Aloe vera (p. 1693·2).
Sunburn.

Puralube *Fera, USA.*
Eye ointment: White soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2).
Dry eyes.

Fougera, USA.
Eye drops: Polyvinyl alcohol (p. 2204·2).

Puran T4 *Sanofi-Aventis, Braz.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Puraplus *Neo Dermos, Arg.*
Brassica napus; soya (p. 2092·3); vitamin E (p. 2119·1); glycolic acid (p. 1704·3).
Skin hyperpigmentation.

Purasoft *Neo Dermos, Arg.*
Glycolic acid (p. 1704·3); avena (p. 2451·1).
Skin disorders.

Purasol *APT, Hong Kong.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Purata *Aspen, S.Afr.*
Oxazepam (p. 1092·2).
Anxiety; tension; alcohol withdrawal syndrome.

Puravit A/D/E *Myralis, Braz.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); vitamin E (p. 2119·1).

Puravit Multi *Myralis, Braz.*
Ascorbic acid (p. 2110·3); vitamin E (p. 2119·1); cyanocobalamin (p. 2107·2); pyridoxine (p. 2105·3).

Purazine *Pharmacare, S.Afr.†*
Cinnarizine (p. 622·1).
Nausea; vomiting; vertigo.

Purbac *Aspen, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Pur-Bloka *Aspen, S.Afr.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; phaeochromocytoma; migraine.

Purbloka *Aspen, S.Afr.*
⊗Propranolol hydrochloride (p. 1479·1).

Purcelina *Aulo Gelio, Arg.*
Range of moisturisers and emollients.

Purderal *Pharmacare, S.Afr.†*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Pure Gardens *Awareness, Canad.*
Apple oil; vitamin C (p. 2110·3); vitamin E (p. 2119·1); aloe vera (p. 1693·2); almond oil (p. 2437·1); olive oil (p. 2575·1); sesame oil (p. 2614·1); chamomile (p. 2474·1); calendula (p. 2465·2); beeswax (p. 2170·2); jojoba oil; linseed oil (p. 2544·2).
Skin disorders.

Pure Health *Lexon, UK.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Pure Omega *BritHealth, UK.*
Fish oil concentrate (p. 1460·1).

Pure Perfection Classic *Koolatron, Canad.*
Benzoyl peroxide (p. 1696·1).

Pure Perfection Moisturizer *Koolatron, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Pure Plan *Cedar Health, UK.*
Birch; meadowsweet (p. 2550·2); cynara (p. 2490·3); taraxacum (p. 2625·3); lappa (p. 2540·1); wild pansy (p. 2647·3); fennel (p. 2503·2); bladderwrack (p. 2612·1); tamarind (p. 1892·2); prune (p. 1881·1); green tea (p. 2648·2).

PureFe OB Plus *PharmaPure, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); trace elements.

PureFe Plus *PharmaPure, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); trace elements.

Puregon *Organon, Arg.; MSD, Austral.; Organon, Austria; Organon, Belg.; Schering-Plough, Braz.; Merck, Canad.; Schering-Plough, Chile; MSD, China; Organon, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Organon (Οργανον), Gr.; MSD, Hong Kong; Organon, Hung.; Schering-Plough, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; MSD, Neth.; Organon, Norw.; MSD, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; MSD, Singapore; Organon, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, UK; Schering-Plough, Ukr.; Organon, Venez.*
Follitropin beta (p. 2278·2).
Male and female infertility.

PureLan *Medela, Canad.*
Wool fat (p. 2219·3).
Nipple care.

Purell *Gojo, Canad.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Puresis *Aspen, S.Afr.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Puretam *Biotrends, Gr.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Purete *L'Oreal, Canad.†*
Pyrithione zinc (p. 1718·1).

Purethal *Hal, Hung.; Haarlems Allergenen, Pol.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Hal, Ger.; Hal, Neth.
Modified allergen extracts of grass, tree, cereals, and plant pollen (p. 2593·3) and house dust mite (p. 2434·3).
Allergen immunotherapy.

PureTrim *Awareness, Canad.*
Preparation for enteral nutrition.

PureVit DualFe Plus *PharmaPure, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); trace elements.

Purex *Hasco-Lek, Pol.†*
Echinacea purpurea (p. 2498·1).
Ulcers; wounds.

Purfalox *Kleva, Gr.*
Tolfenamic acid (p. 138·3).
Pain; inflammation; musculoskeletal and joint disorders.

Purfilx *Filaxis, Arg.*
Cyproterone acetate (p. 2261·2).

Purgazen *Agepha, Austria.†*
Bisacodyl (p. 1821·1); dimeticone (p. 1886·2).
Constipation; bowel evacuation.

Purg-Odan *Odan, Canad.*
Sodium picosulfate (p. 1887·2); magnesium oxide (p. 1857·3); citric acid (p. 2480·3).

Purgolac *Pharmanel, Gr.*
Lactulose (p. 1850·3).
Constipation.

Purgo-Pil *Qualiphar, Belg.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Purgoxin *Aspen, S.Afr.*
Digoxin (p. 1353·3).
Atrial fibrillation; heart failure.

Purgyl *Istanbul, Turk.*
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Bowel evacuation; constipation.

Puricap *Richmond, Arg.*
⊗Anastrozole (p. 742·1).

Puricemia *Sanbe, Indon.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Puriclav *Polifarma, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Puricos *Aspen, S.Afr.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Purid *Sanofi-Aventis, Chile.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Puride *Polipharm, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Purifam *Sunthi Sepuri, Indon.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; endocrine adenoma.

Purifol *Metro, Philipp.*
Folic acid (p. 2063·1).
Folate deficiency.

Purifying Gel *Floxia, Singapore.*
Sage (p. 2608·3); lappa (p. 2540·1); melaleuca oil (p. 2551·1); allantoin (p. 1693·1); glycolic acid (p. 1704·3).
Acne.

Purigan *Elpen (Ελπεν), Gr.*
Allopurinol (p. 600·2).

Purigel Crisp *Qualiphar, Belg.†*
Hamamelis (p. 2523·3); benzyl alcohol (p. 1739·3); levomenol (p. 2544·1); arnica (p. 2447·2); menthol (p. 2553·2); menthyl acetate (p. 2554·1).
Soft-tissue injury.

Purigel NF *Qualiphar, Belg.*
Chamomile (p. 2474·1); arnica (p. 2447·2); dexpanthenol (p. 2582·2); menthol (p. 2553·2); menthyl lactate (p. 2554·1); benzyl alcohol (p. 1739·3).
Pruritus; skin irritation; bruising; inflammation.

Purilon *Coloplast, Belg.*
A hydrogel dressing.
Wounds.

Coloplast, Fr.
Carmellose sodium (p. 2175·2); calcium alginate (p. 1136·3).
Wounds; ulcers.

Coloplast, Arg.†; Coloplast, Ger.
Carmellose (p. 2175·1); calcium alginate (p. 1136·3).
Ulcers; wounds.

Purinase *Imperial, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Puri-Nethol *GSK, Arg.; Aspen, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; Excella, Cz.; Aspen, Ger.; GSK, Gr.; Aspen, Hong Kong; GSK, India; GSK, Irl.; Perrigo, Israel; GSK, Ital.; GSK, Mex.; Aspen, Neth.; Aspen, Norw.; Healthcare Logistics, NZ; GSK, Philipp.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Swed.; Pro Concepta, Switz.; Aspen, Thai.; GSK, Turk.; GSK, UK.†*
Mercaptopurine (p. 820·3).
Leukaemias; auto-immune disorders; non-Hodgkin's lymphoma.

Puri-Néthol *Genopharm, Fr.*
Mercaptopurine (p. 820·3).
Leukaemias.

Purinethol *Teva, Canad.; Gate, USA.*
Mercaptopurine (p. 820·3).
Leukaemias.

Purinetone *Korea United, Singapore.*
Mercaptopurine (p. 820·3).
Acute lymphatic leukaemia; Crohn's disease.

Purinol
Note: this name may be used for preparations of different composition.
Ratiopharm, Austria; Ratiopharm, Cz.; Tack Fung, Hong Kong†; Pinewood, Irl.; Ratiopharm, Rus.
Allopurinol (p. 600·2).
Gout; renal calculi; hyperuricaemia; prophylaxis of uric acid and calcium oxalate stones.

Yeni, Turk.
Methenamine (p. 322·3); methenamine anhydromethylenecitrate (p. 322·3).
Urinary-tract infections.

Purisole *Fresenius Kabi, Port.*
⊗Sorbitol (p. 2092·1); mannitol (p. 1427·3).
Bladder irrigation.

Purisole SM *Fresenius Kabi, Pol.†*
⊗Sorbitol (p. 2092·1); mannitol (p. 1427·3).
Bladder irrigation.

Purispec *Pharmaspec, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Puristen *Dynamic, Philipp.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Puritabs *Balmar, NZ.*
Troclosene sodium (p. 1774·1).
Water disinfection.

Puritenk *Biotenk, Arg.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Purium *Lennon, S.Afr.†*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Purivist *Allergan, Cz.; Allergan, Fr.*
Epinastine hydrochloride (p. 628·3).
Allergic conjunctivitis.

Purmist *MKR, Canad.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).

Purmycin *Aspen, S.Afr.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Purolase *Roszdrava, Rus.*
Saruplase (p. 1489·2).
Myocardial infarction.

Puromylon *Aspen, S.Afr.*
Nalidixic acid (p. 328·3).
Gram-negative bacterial urinary-tract infections.

Puroxan *Kent Union, Philipp.; Eurodrug, Thai.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Puroxel *Vitalink, Philipp.*
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Purpose *Johnson & Johnson, USA; Merck, USA.*
A range of emollient, cleansing, and moisturising preparations.

Purpumicina *Microsules, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Pur-Rutin *Andreabal, Switz.*
Troxerutin (p. 2505·3).
Haemorrhoids; venous insufficiency.

Pursana *Zeller, Switz.*
Sorbitol (p. 2092·1); fig (p. 1843·2).
Constipation.

Purselect *Kleva, Gr.*
Lactulose (p. 1850·3).

Pursenid *Novartis Consumer, Spain.*
Calcium sennoside A (p. 1885·1); calcium sennoside B (p. 1885·1).
Constipation.

Pursennid *Novartis Consumer, Austria; Novartis Consumer, Ital.; Novartis, Norw.*
Calcium sennoside A (p. 1885·1); calcium sennoside B (p. 1885·1).
Constipation; bowel evacuation.

Novartis, Fin.; Novartis, Swed.; Novartis, Turk.
Senna (p. 1885·1).
Constipation.

Novartis, Gr.
Calcium sennosides (p. 1885·1).
Constipation; bowel evacuation.

Pursennide *Novartis Sante, Fr.; Novartis Consumer, Port.; Novartis Consumer, Switz.*
Calcium sennosides (p. 1885·1).
Constipation.

Purubex *Eisai, Indon.*
Teprenone (p. 1893·3).
Gastric ulcer; gastropathy.

Pushijie *Qi Li, China.*
Thiamphenicol glycinate hydrochloride (p. 377·1).

Pushu Laishi *RAAS, China.*
Prothrombin complex (p. 1149·3).
Haemorrhagic disorders.

Pusili *Pude, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Pusiran *Atlantic, China; Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Puvasoralen *Crawford, UK.*
Methoxsalen (p. 1711·3).
Available on a named-patient basis only.
Psoriasis; vitiligo; mycosis fungoides.

PV Carpine *Allergan, Austral.†*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

PV Jod *Hasco-Lek, Pol.*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane infections; disinfection of burns, skin, mucous membranes, ulcers, and wounds.

PV7 Polivitamin *Sanli, Turk.*
Vitamins.

PVA *Allergan, Austral.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

P-Vate *Osoth, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

P-Vidine *PP Lab, Thai.*
Povidone-iodine (p. 1767·1).
Skin, mucous membrane, and wound disinfection.

PVP-Jod *Ratiopharm, Ger.*
Povidone-iodine (p. 1767·1).
Skin disinfection; skin infections; ulcers; wounds.

P-V-Tussin *Numark, USA.†*
Syrup: ⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough and cold symptoms.

Numark, USA.†
Tablets: Hydrocodone tartrate (p. 67·2); phenindamine tartrate (p. 637·1); guaifenesin (p. 1666·2).
Cough.

Pyassan *Sanofi-Aventis, Hung.*
Cefalexin (p. 234·1).
Bacterial infections.

Pycameth *Tropica Mas, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Pycnogenol Plus *Reese, USA.*
Bioflavonoids (p. 2505·2); grape seed (p. 2521·3); pycnogenol (p. 2590·3).

Pyderma *Pyridam, Indon.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Pygno-Vite *Bioglan, Austral.†*
Vitis vinifera (p. 2521·3); myrtillus (p. 2566·2).
Peripheral circulatory disorders.

Pylaquin *Roi Surya, Indon.†*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Pylera *Axcan, Irl.; Aptalis, USA.*
Bismuth subcitrate potassium (p. 1822·1); metronidazole (p. 936·1); tetracycline hydrochloride (p. 373·2).
Duodenal ulcer; Helicobacter pylori eradication in peptic ulcer.

Pylison *Brown & Burk, Philipp.*
Lansoprazole (p. 1851·3).
Barrett's oesophagus; gastro-oesophageal reflux; peptic ulcer.

Pylobact *Ranbaxy, Rus.*
Capsules, omeprazole (p. 1867·2); tablets, clarithromycin (p. 266·2); tablets, tinidazole (p. 949·2).
Peptic ulcer.

Pylobact Combi *Ranbaxy, Malaysia.*
Tablets, clarithromycin (p. 266·2); capsules, omeprazole (p. 1867·2); tablets, tinidazole (p. 949·2).
Peptic ulcer.

Pylobact Neo *Ranbaxy, Ukr.*
Combination product: Tablets, amoxicillin (p. 216·2); tablets, clarithromycin (p. 266·2); capsules, omeprazole (p. 1867·2).
Peptic ulcer.

Pylobactell *Torbet, Cz.; BSIA, Gr.; Torbet, Irl.; Torbet, Neth.; Torbet, Pol.; Torbet, Port.; Torbet Laboratories, UK.*
Carbon-13 (p. 2470·3) labelled urea.
Diagnosis of Helicobacter pylori infection.

Pylokit *Cipla, India.*
2 Capsules, lansoprazole (p. 1851·3); 2 tablets, tinidazole (p. 949·2); 2 tablets, clarithromycin (p. 266·2).
Helicobacter pylori *eradication.*

Pylopac *Merck, Chile; Medix, Mex.*
Capsules, lansoprazole (p. 1851·3); tablets, clarithromycin (p. 266·2); capsules, amoxicillin (p. 216·2).
Helicobacter pylori-associated peptic ulcer.

Pylor *Pyridam, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Pylori 13 *Proreo, Switz.*
Carbon-13 labelled urea (p. 2470·3).
Test for Helicobacter pylori *infection.*

Pylorid *GSK, Braz.; GSK, Fin.†; GSK, Gr.; GSK, Philipp.; GSK, Singapore; GSK, Thai.†; GSK, Turk.; GSK, Venez.*
Ranitidine bismuth citrate (p. 1883·3).
Peptic ulcer.

Pylorid-KA *GSK, Austral.†*
Combination pack: Tablets, ranitidine bismuth citrate (Pylorid) (p. 1883·3); tablets, clarithromycin (p. 266·2); capsules, amoxicillin trihydrate (p. 216·2).
Helicobacter pylori*-associated peptic ulcer.*

Pylorikit *Neo Quimica, Braz.*
Capsules, lansoprazole (p. 1851·3); capsules, amoxicillin trihydrate (p. 216·2); tablets, clarithromycin (p. 266·2).
Helicobacter pylori-associated peptic ulcer.

Pyloripac *Medley, Braz.*
Capsules, amoxicillin (p. 216·2); tablets, clarithromycin (p. 266·2); capsules, lansoprazole (p. 1851·3).
Helicobacter pylori-associated peptic ulcer.

Pyloripac Retrat *Medley, Braz.*
Capsules, lansoprazole (p. 1851·3); tablets, levofloxacin (p. 315·3); capsules, amoxicillin trihydrate (p. 216·2).
Helicobacter pylori eradication.

Pyloriset
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.
Lansoprazole (p. 1851·3); clarithromycin (p. 266·2).

Orion, USA.
Test for gastrointestinal disorders.

Pylorisin *GSK, Austria.†*
Ranitidine bismuth citrate (p. 1883·3).
Peptic ulcer.

Pyloritrat *Teuto, Braz.*
Capsules, lansoprazole (p. 1851·3); capsules, amoxicillin trihydrate (p. 216·2); tablets, clarithromycin (p. 266·2).
Helicobacter pylori*-associated peptic ulcer.*

Pynamic *Condrugs, Thai.*
Mefenamic acid (p. 85·3).
Pain.

Pyndale *Crisdy-Na, Philipp.*
⊗Pindolol (p. 1470·1).
Angina pectoris; hypertension.

Pynmed *Medpro, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Medpro, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain with tension.

Pynocare *Mega Lifesciences, Malaysia.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3).
Dietary supplement.

Pynocare 40 Actisome *Mega Lifesciences, Philipp.*
Procyanidin (p. 2590·3); ascorbic acid (p. 2110·3); betacarotene (p. 2051·1); *d*-alpha tocoferil acetate (p. 2119·1).
Melasma.

Pynocarewhite *Mega Lifesciences, Malaysia.*
Maritime pine (p. 2590·3); vitamin C (p. 2110·3); dunaliella salina; vitamin E (p. 2119·1); lycopene (p. 2546·2); ceramide (p. 1699·1).
Dietary supplement.

Pynstop *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); doxylamine succinate (p. 627·3).
Pain.

Pyodontyl *Sanofi-Aventis, Hong Kong.†*
Metesculetol sodium (p. 2557·3); allantoin (p. 1693·1).
Gum disorders; dental hygiene.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Pyoglit *Intas, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Pyolysin *Serum-Werk Bernburg, Ger.*
Extract of: staphylococci; streptococci; *Escherichia coli*; *Pseudomonas aeruginosa*; *Micrococcus ovis*-Bouillon; zinc oxide (p. 1729·1); salicylic acid (p. 1719·1).
Burns; infected skin disorders; skin ulcers; wounds.

Serum-Werk Bernburg, Rus.
Extract of *Escherichia coli*; *Pseudomonas aeruginosa*; *Streptococcus pyogenes*; *Enterococcus faecalis* (p. 2596·3); *Staphylococcus aureus*; salicylic acid (p. 1719·1); zinc oxide (p. 1729·1).
Burns; ulcers; wounds; skin infections.

Pyorex *Bailly, Fr.*
Ethacridine lactate (p. 1732·3); sodium ricinoleate (p. 2215·1).
Oral hygiene.

Pyostacine *Sanofi-Aventis, Fr.*
Pristinamycin (p. 344·1).
Bacterial infections.

Pyracon *Hua, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Pyrad Thimero Sahakarn *United Drug, Thai.*
Thiomersal (p. 1771·3).
Skin disinfection.

Pyradexon *Pyridam, Indon.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Pyradol
Note: this name may be used for preparations of different composition.
Xixia, S.Afr.†
Paracetamol (p. 115·1).
Pain; fever.

Pyrad-Povidone *United Drug, Thai.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Pyrad-Violet *United Drug, Thai.*
Methylrosanilinium chloride (p. 1761·1).
Skin disinfection.

Pyrafat *Riemser, Austria; Riemser, Ger.; Fatol, Hong Kong; Fatol, Rus.*
Pyrazinamide (p. 345·2).
Mycobacterial infections.

Pyrahexal *Hexal, Pol.*
Dipyrone (p. 53·3).
Fever; pain.

Pyralen *Thebe, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Pyralfin *Lupin, India.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Pyralgin *Polpharma, Pol.*
Dipyrone (p. 53·3).
Fever; pain.

Belmed, Rus.
Dipyrone (p. 53·3); codeine (p. 40·2); caffeine (p. 1203·3); naproxen (p. 98·2); phenobarbital (p. 535·2).
Pain; fever.

Pyralgina *Polpharma, Pol.*
Dipyrone (p. 53·3).
Pain; fever.

Pyralginum *GSK, Pol.†*
Dipyrone (p. 53·3).
Fever; pain.

Pyralin *Pfizer, Austral.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; Crohn's disease; rheumatoid arthritis.

Pyralvex *Lazar, Arg.; Norgine, Austria; Norgine, Belg.; Norgine, Cz.†; Meda, Fr.; Norgine, Ger.†; Meda, Gr.; Norgine, Hong Kong†; Alpharma, Indon.†; Norgine, Ital.; Meda, Neth.; Norgine, Philipp.; Norgine, Port.; Norgine, S.Afr.; Norgine, Singapore; Meda, Spain; Meda, Switz.; Norgine, Thai.; PMP, Turk.; Norgine, UK.*
Anthraquinone glycosides (p. 1884·2); salicylic acid (p. 1719·1).
Mouth and throat disorders; gingivitis; denture irritation.

Pyramax *Shin Poong, Kor.*
Pyronaridine phosphate (p. 664·3); artesunate (p. 648·2).
Malaria.

Pyramer *Combiphar, Indon.*
Parathiazine teoclate (p. 637·1); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting; motion sickness.

Pyramet *Cipla, India.*
Pyrimethamine (p. 662·3); sulfamethoxazole (p. 365·2).
Malaria.

Pyramide *Pharmasant, Thai.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pyramin *Terramedic, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pyramox *RX, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Pyranol *Solfran, Mex.*
Dipyrone (p. 53·3).
Fever; pain.

Pyrantin *Vickmans, Hong Kong.†*
Pyrantel embonate (p. 165·3).
Worm infections.

Pyrapam *General Drugs, Thai.*
Pyrantel embonate (p. 165·3).
Worm infections.

Pyrasol *Dynamic, Philipp.†*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pyravit *Galenium, Indon.*
Isoniazid (p. 311·2).
Pyridoxine (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pyrazide *Sanofi-Aventis, S.Afr.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pyrazidol *Dalkhimfarm, Rus.*
Pirlindole hydrochloride (p. 446·3).
Depression; alcohol withdrawal syndrome; Alzheimer's disease.

Pyrazin *Concept, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Pyrazolone *Utopian, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

Pyrcon *Krewel, Ger.*
Pyrvinium embonate (p. 166·1).
Enterobiasis.

Pyrcost *Kleva, Gr.*
Piroxicam (p. 125·3).

Pyrecol *Polipharm, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; hay fever.

Pyréflor *Leurquin, Fr.*
Shampoo: Permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2).
Pediculosis.

Leurquin, Fr.†
Lotion: Permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2); enoxolone (p. 54·2).
Pediculosis.

Pyrelle HB *Pharmelle, USA.†*
Secbutabarbital (p. 1106·2); hyoscyamine hydrobromide (p. 1848·1); phenazopyridine hydrochloride (p. 124·3).
Interstitial cystitis.

Pyrethrum Spray *Nelson, UK.*
Arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); echinacea angustifolia (p. 2498·1); hypericum perforatum (p. 449·1); ledum palustre (p. 2550·1); rumex crispus (p. 2649·3); pyrethrum pale.
Homoeopathic preparation.

Pyrex *Novell, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Pyrexin *Meprofarm, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Pyrexon *Wockhardt, India.*
Paracetamol (p. 115·1).
Fever; pain.

Pyrflox *Pyridam, Indon.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Pyribion *Universal, Hong Kong.†*
Pyridoxine (p. 2105·3).

Pyricar *S t Carlos, Philipp.*
Pyridoxine (p. 2105·3).
Dietary supplement.

Pyricef *Pyridam, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Pyrichlor PE *Breckenridge, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Pyricontin *Modi-Mundipharma, India.*
Pyridoxine (p. 2105·3).
Vitamin B_6 deficiency.

Pyridin *Vickmans, Hong Kong.†*
Phenazopyridine (p. 124·3).

Pyridium *Zodiac, Braz.; Zodiac, Braz.; Erfa, Canad.; Pfizer, Hong Kong; Pharmalink, India; Pfizer, Indon.†; Biotech, S.Afr.†; Warner Chilcott, USA.*
Phenazopyridine hydrochloride (p. 124·3).
Pain and irritation of the urinary tract.

Pyridium Plus *Warner Chilcott, USA.*
Phenazopyridine hydrochloride (p. 124·3); hyoscyamine hydrobromide (p. 1848·1); butalbital (p. 1043·3).
Urinary-tract pain and spasm, with apprehension.

Pyridol *Pyridam, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Pyridryl *Pyridam, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; allergic symptoms.

Pyridryl Plus *Pyridam, Indon.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; allergic symptoms.

Pyrifoam *Dermatech, Austral.; Balmar, NZ; Dermatech, Philipp.*
Permethrin (p. 2159·3).
Pediculosis.

Pyrifort *UAP, Indon.†*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pyrigesic *East India Pharma, India.*
Paracetamol (p. 115·1).
Fever; pain.

Pyril D *Macoven, USA.*
Mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Pyril DM *Macoven, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Pyrilax *Berlin-Chemie, Ger.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Pyrimed *Utopian, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Pyrimel *Catarinense, Braz.†*
Paracetamol (p. 115·1).
Fever; pain.

Pyrimine *Sriprasit, Thai.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis; ileus; postoperative urinary retention; constipation.

Pyrimon *FDC, India.*
⊗Dexamethasone (p. 1630·3); chloramphenicol (p. 257·1).
Eye infections; allergic eye disorders; eye trauma.

Pyrinon *Hana, Philipp.*
Pyridostigmine bromide (p. 689·2).
Myasthenia gravis.

Pyrinyl II *Barre-National, USA.*
Pyrethrins (p. 2161·1); piperonyl butoxide technical (p. 2160·2).
Pediculosis.

Pyrinyl Plus *Rugby, USA.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Pyriped
Note: this name may be used for preparations of different composition.
Mintlab, Chile.
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Pyrisept
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Phenazopyridine hydrochloride (p. 124·3).
Pain and irritation of the urinary tract.

Weifa, Norw.
Cetylpyridinium chloride (p. 1743·1).
Minor wounds; mouth and throat disorders.

Pyrisone *Beacons, Singapore.*
Pyrimethamine (p. 662·3); dapsone (p. 281·2).
Malaria.

Pyritil *Biolab, Malaysia; Biolab, Thai.*
Pyritinol hydrochloride (p. 394·3).
Organic brain disorders.

Pyrixin *Synco, Hong Kong.†*
Pyridoxine (p. 2105·3).

Pyrizole *BJ Benjaosoth, Thai.*
Phenazopyridine hydrochloride (p. 124·3); sulfafurazole (p. 364·1).
Urinary-tract disorders.

Pyrlex *Athlon, USA.†*
Mepyramine tannate (p. 635·1).
Coryza; nasal congestion.

Pyrlex CB *Athlon, USA.*
Pentoxyverine tannate (p. 1672·1); mepyramine tannate (p. 635·1).
Cough.

Pyrocaps *Be-Tabs, S.Afr.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Pyrogallic *Gordon, USA.*
Pyrogallol (p. 1718·2).
Calluses; verrucas.

Pyrogastrone *Sanofi, Irl.†*
Carbenoxolone sodium (p. 1825·3); alginic acid (p. 2167·2); aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux; hiatus hernia; peptic ulcer; heartburn; flatulence.

Pyrogenal *Medgamal, Rus.*
Salmonella typhi lipopolysaccharide.
Immunomodulator.

Pyrogenium *Hanosan, Ger.*
Pyrogenium nosode (p. 2601·1); echinacea (p. 2498·1); bryonia (p. 2461·3); kalium chloricum (p. 1793·2); toxicodendron quercifolium (p. 2603·3); hydrargyrum bicyanatum (p. 2555·3); lachesis mutus (p. 2538·3); crotalus horridus.
Homoeopathic preparation.

Pyron *Reuffer, Mex.*
Dipyrone (p. 53·3).
Pain.

Pyronal *Tanabe, Indon.*
Dipyrone (p. 53·3).
Fever.

Pyronpac *Inpac, Thai.*
Dipyrone (p. 53·3).
Fever; pain.

Pyrosal *Herbapol Wroclaw, Pol.*
Salix (p. 129·2); sambucus (p. 2609·3); tilia (p. 2631·3); coltsfoot leaf (p. 1659·2).
Upper respiratory-tract disorders.

Pyroxin *Sanofi-Aventis, Austral.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency disorders.

Pyr-Pam *UCI, Braz.*
Pyrvinium embonate (p. 166·1).
Enterobiasis.

Pyrvin *Orion, Fin.*
Pyrvinium embonate (p. 166·1).
Worm infections.

Pysolan *Pyridam, Indon.; One Pharma, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Pytazen *Douglas, NZ.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders; myocardial infarction.

Pyteldon *Acdhon, Thai.*
Pyrantel embonate (p. 165·3).
Worm infections.

Pytest *Kimberley-Clark, USA.*
Carbon-14 (p. 2223·2) labelled urea.
Diagnosis of Helicobacter pylori infection.

Pytramic *Pyridam, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemorrhage.

Pyverm *Cifarma, Braz.*
Pyrvinium embonate (p. 166·1).
Worm infections.

Pyxime *Pyridam, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Pyzina *Lupin, India; Lupin, Rus.*
Pyrazinamide (p. 345·2).
Tuberculosis.

PZA *Sandoz, Malaysia; Sandoz, Singapore; Sandoz, Thai.†*
Pyrazinamide (p. 345·2).
Tuberculosis.

PZA-Ciba *Novartis, India; Sandoz, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

PZC *Mitsubishi Tanabe, Jpn.*
Perphenazine fendizoate (p. 1095·3), perphenazine hydrochloride, or perphenazine maleate.
Schizophrenia; nausea and vomiting; Ménière's disease.

P-Zide *Cadila, India.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Q10
Note: this name may be used for preparations of different composition.
Pharma Nord, Fr.
Ubidecarenone (p. 2637·1).
Tonic.

Beres, Hung.
Ubidecarenone (p. 2637·1); vitamins; trace elements.
Tonic.

Q200 *LCH, Hong Kong†; Mylan, NZ.*
Quinine sulfate (p. 665·2).
Malaria; myotonia; nocturnal cramps.

Q300 *LCH, Hong Kong†; Mylan, NZ.*
Quinine sulfate (p. 665·2).
Malaria; myotonia; nocturnal cramps.

Q 10 *Sidefarma, Port.*
Ubidecarenone (p. 2637·1).
Cardiomyopathy; encephalopathy.

Q Cef *Guardian, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Q & P *Kowa, Jpn.*
Vitamins; oryzanol (p. 2578·1); oxoamidine.
Tonic.

Q & P Gold *Kowa, Jpn.*
Vitamins; ginseng (p. 2513·3); astragari radix; oxoamidine; arginine hydrochloride (p. 2049·1); caffeine (p. 1203·3).
Tonic.

Qari *Leurquin, China; Mediolanum, Ital.*
Rufloxacin hydrochloride (p. 357·1).
Bacterial infections.

Q-Bac *Pose, Thai.†*
Chlorhexidine gluconate (p. 1743·3).
Disinfection.

QDALL *Atley, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

QDALL AR *Atley, USA.†*
Chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Q-dryl *Qualitest, USA.*
Diphenhydramine hydrochloride (p. 626·2).

QED *Omega, Irl.†*
Test for alcohol in saliva.

QED A-150 *Prieto, Arg.†*
Test for alcohol in blood.

Q-Gel *Interhealth, Hung.*
Ubidecarenone (p. 2637·1).
Tonic.

Qi Di *Tiantaishan, China.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders; acid aspiration; gastro-oesophageal reflux; dyspepsia.

Qi An *Qilu, China.*
Cefixime (p. 240·3).
Bacterial infections.

Qi Bei *Lananqi, China.*
Granulocyte-macrophage colony-stimulating factor (recombinant, human).

Qi Cun *Qi Li, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Qi Er Neng *Livzon, China.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Qi Er Su *Huaren, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Qi Fang Neng *Shuang Cheng, China.*
Inosine (p. 2533·1).

Qi Fu *Hailing, China; Yangtze River, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Qi Gu Le *Huang Long, China.*
Sodium glucuronate (p. 2517·1).

Qi Gu Ke *Huang Long, China.*
Naproxen sodium (p. 98·2).

Qi Gu Mei *Huang Long, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Qi Hao *Zichuan, China.*
Isosorbide mononitrate (p. 1413·3).

Qi Hong *Hayao, China.*
Azithromycin lactobionate.
Bacterial infections.

Qi Ji *Qi Du, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Qi Ke *Hailing, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Qi Ke Ou *Southwest Synthetic, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Qi Li *Treeful, China.*
Troxerutin (p. 2505·3).

Qi Li Qing *Tongyong, China; Xinzhongzheng, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Qi Li Tuo *Qiyunsheng, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Qi Luo *Hengrui, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Qi Luo Ke *Meijisi, China.*
Zidovudine (p. 1024·2).
HIV infection.

Qi Luo Shu *Youhua, China.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Qi Mai Xing *Yatai, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Qi Mi Gao *Team, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Qi Ming *Kangnuo, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Qi Ming Lei Ao *Tiancheng, China.*
Ozagrel (p. 2579·1).

Qi Ning *Ai Sheng, China.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Qi Nuo *Double-Crane, China.*
Azithromycin lactobionate.
Bacterial infections.

Qi Nuo Bi Tong *Wanjie High Tech, China.*
Doxifluridine (p. 782·3).

Qi Ping *Hengrui, China.*
Levocetirizine hydrochloride (p. 632·3).

Qi Qi *Hui Yin Bi, China.*
Setastine hydrochloride (p. 640·2).

Qi Qin *Qi Du, China.*
Ligustrazine hydrochloride.

Qi Qiong *Qi Du, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Qi Rui Hong Yuan *Duoburuifei, China.*
Ethylenediamine diaceturate.

Qi Ruo Da *Ke Lun, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Qi Sheng *Hacon, China.*
Levofloxacin mesilate.
Bacterial infections.

Qi Shi *Weierkang, China.*
Aceglutamide (p. 2426·2).

Qi Shu *Neptunus, China.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Qi Si Ding *Qinba, China.*
Levofloxacin (p. 315·3).
Bacterial infections.

Qi Suo *Hailisheng, China.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Qi Tai *Jiu Tai, China.*
Azithromycin fumarate.
Bacterial infections.

Qi Ting *Qi Du, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Qi Wei
Note: this name may be used for preparations of different composition.
Lanling, China.
Roxithromycin (p. 356·2).
Bacterial infections.

Qi Xian *Shenyang First, China.*
Azithromycin (p. 221·2) or azithromycin lactobionate.
Bacterial infections.

Qi Xin *Hailing, China; Yangtze River, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Qi Xing *Hua Lu, China.*
Tegafur (p. 864·2).
Malignant neoplasms.

Qi Zheng *Qilu, China.*
A low-molecular-weight heparin (p. 1426·1).

Qi Zhi *Tiantaishan, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Qi Zhi Ping *Longhua, China.*
Metformin hydrochloride (p. 489·1); gliclazide (p. 472·3).
Diabetes mellitus.

Qia Ke *Song He, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Qian De *Global, China.*
Fluconazole (p. 578·2).
Fungal infections.

Qian Di *Jiekang, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Qian Le An *Lukang Chenxin, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Qian Bai *Renrenkang, China.*
Hydroquinone (p. 1705·1).
Hyperpigmented skin disorders.

Qian Er *Jinlong, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Qian Er Fen *Yangzhou No 3, China.*
Rifaximin (p. 355·2).
Gastrointestinal infections.

Qian Ke *Bai Ao, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Qian Li Xin *New Asiatic, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Qian Nuo Lin *Qian Jin Xiang Jiang, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Qian Tong *Bei Shi, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Qian Xin *Fengyuan, China.*
Isosorbide mononitrate (p. 1413·3).

Qian Yi *Jinqilin, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Qianbao *HongQi, China.*
Chlorophyllin copper complex sodium (p. 2178·3).

Qiang Ni *Qi Du, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Qiang Pu Jin *Jin Lan, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Qiang Pu Xin *Jin Lan, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Qiang Le Su *Zizhu, China.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Qiang Yi *Hailisheng, China.*
Levocetirizine hydrochloride (p. 632·3).

QianYi *Weifang, China.*
Fluconazole (p. 578·2).
Fungal infections.

Qibite *Southwest Synthetic, China.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Qidrox *Soho, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Qie Er *Jiuhe, China.*
Tremella polysaccharide.

Qie Ling Bao *Tianhedi Sainuo, China.*
Tiopronin (p. 1578·1).

Qie Nuo *Jiuhe, China.*
Cineole (p. 2479·1); pinene (p. 2591·3).

Qiflon *Nabiqasim, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Qiftrim *Hexal, Braz.*
Co-trimoxazole (p. 277·3).

QiFuMei *Baxter, China.*
Sevoflurane (p. 1912·3).
General anaesthesia.

QiKe *Jiqi Huakang, China.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

QiLi *Zhong Bao, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Qiluoxian *Southwest Synthetic, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Qimaite *CSPC, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Qimoxin *White Swan, China.*
Thymosin (p. 2631·1).

Qin Er Kang *Baiyunshan, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Qin Fu *Yuekang Kaiyue, China.*
Ibuprofen (p. 68·2).

Qin Ke Ao *Sanjing Hailing, China.*
Cefixime (p. 240·3).
Bacterial infections.

Qin Ke Xi *Ou Yi, China.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Qin Lin *Lifeshine, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Qin Su *Yangtze River, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Qinda *Lifeshine, China.*
Lornoxicam (p. 83·2).
Pain.

Qing Chang *Yixin, China.*
Sodium demethylcantharidate.

Qing Da *Lunan, China.*
Piracetam (p. 393·3).
Cerebrovascular disorders; head injury; mental function impairment.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Qing Dian *QiLi, China.*
Matrine.

Qing Er *Bikai, China.*
Ozagrel sodium (p. 2579·1).

Qing Er Qi *Huajin, China.*
Zopiclone (p. 1118·1).
Insomnia.

Qing Fen *Hui Ren, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Qing Feng *United Lab, China.*
Methyl salicylate (p. 92·1).

Qing Fu *Wanqing, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Qing He *Chang Fu Jie Jing, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Qing Jian *Tongyong, China; Xinzhongzheng, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Qing Kang *Kangnaike, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Qing Ke Long *Huana, China.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).

Qing Ke Yi *Huajin, China.*
Cefixime (p. 240·3).
Bacterial infections.

Qing Kuang *Tianciu, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Qing Lang *Double-Crane, China.*
Paracetamol (p. 115·1); amantadine hydrochloride (p. 890·3); caffeine (p. 1203·3); bezoar bovis; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Qing Lin *Haixin, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Qing Qing *Renrenkang, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Qing Shi Ge *Pude, China.*
Asarone.

Qing Tian *Yongli, China.*
Lomerizine hydrochloride (p. 676·3).

Qing Tong *Changlong, China.*
Lappaconitine hydrobromide (p. 1418·1).

Qing Xing *Ke Lun, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Qing Zhi Wei *Beifang, China.*
Tocoferil nicotinate (p. 1516·1).

Qingdi *NCPC, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Qingkun *LuoXin, China.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Qingli *Double-Crane, China.*
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Qinolon *United American, Philipp.; Great Eastern, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Qinosyn *Pasteur, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Qinox *Solas, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Qiong Sha Ao *Hua Lu, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Qipro *Meprofarm, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Qipu *Yangtze River, China.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Qiquan *Hiteck Bio, China.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular disorders of the ear and eye.

Qitai *Sine, China.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Qital *Ethica, Indon.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Qiu Lu *Zhongqi, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

QiWei *ErYe, China.*
Phentolamine mesilate (p. 1468·3).

Dongting, China.
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Qiyu *HongQi, China.*
Gentamicin sulfate (p. 304·2); bismuth subcarbonate (p. 1822·1).
Gastrointestinal infections.

Qiyue *Jiqi Huakang, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Qizol *Ethica, Indon.*
Cefmetazole sodium (p. 241·3).
Bacterial infections.

Qlair *Bayer, Israel.*
4 Tablets, estradiol valerate (p. 2271·2); 22 tablets, dienogest (p. 2267·2); estradiol valerate; 2 tablets, inert.
Sequential oral contraceptive.

Qlaira *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer, Irl.; Bayer, Neth.; Bayer, Norw.; Bayer Schering, Pol.; Berlifarma, Port.; Bayer, Singapore.; Bayer, Spain; Bayer, Swed.; Bayer, UK.*
4 Tablets, estradiol valerate (p. 2271·2); 22 tablets, estradiol valerate; dienogest (p. 2267·2); 2 tablets, inert.
Sequential oral contraceptive; menstrual disorders.

Qnasl *Teva, USA.*
⊗Beclometasone dipropionate (p. 1621·2).
Allergic rhinitis.

Qpime *Julphar, UAE.*
Cefepime (p. 239·2).
Bacterial infections.

Q-Pril *Polpharma, Pol.*
Quinapril (p. 1480·2).
Hypertension; heart failure.

Qpril *Alphapharm, Austral.*
Quinapril hydrochloride (p. 1480·2).
Heart failure; hypertension.

Q-Prost *Ariston, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Q-Prost Alopex *Ariston, Arg.*
Finasteride (p. 2358·3).
Alopecia.

Q-Roxin *Choongwae, Kor.*
Balofloxacin (p. 226·3).
Urinary-tract infections.

Qsymia *Vivus, USA.*
⊗Phentermine (p. 2329·2); topiramate (p. 550·3).
Obesity.

QT *Schering-Plough, USA.*
SPF 2: Octinoxate (p. 1715·1); dihydroxyacetone (p. 1700·1).
Sunscreen.

Q-Tapp DM *Qualitest, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Q-Ten *Novell, Indon.*
Ubidecarenone (p. 2637·1).
Antoxidant; tonic.

QTest *Quidel, USA.*
Pregnancy test (p. 2596·1).

Q-Tussin CF *Qualitest, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Qu Ao *San Lian, China.*
Amino acids.

Qu Er Man Duo *Yaojiang, China.*
Fluconazole (p. 578·2).
Fungal infections.

Qu Feng *Huali, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Qu Li *Yaoyou, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Qu Ming *Chang Fu Jie Jing, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Qu Ning *SL Pharm, China.*
Zaleplon (p. 1114·3).
Insomnia.

Qu Tan *Chung-Hwa, China.*
⊗Serrapeptase (p. 2613·3).

Qu Teng *Longgui, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Qu Tong Kang *Southwest, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Qu Ya *Wanjie High Tech, China.*
Telmisartan (p. 1509·3).
Hypertension.

Quadevit *Farmstandart, Rus.*
Vitamins; minerals.

KVZ, Ukr.
Vitamins; rutoside (p. 2505·3); glutamic acid (p. 2070·2); methionine (p. 1558·2); phytin (p. 1553·3); potassium chloride (p. 1793·2); copper sulfate (p. 2057·2).
Vitamin and mineral supplement.

Quadezyme *Pascual, Hong Kong.*
Muramidase hydrochloride (p. 2565·1); dequalinium chloride (p. 1749·3).
Allergic rhinitis; mouth and throat disorders; sinusitis.

Quadion *Fortbenton, Arg.*
Ketoconazole (p. 585·3).
Dandruff; fungal skin and scalp infections.

Quadmax *Multicare, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Quadracel *Sanofi Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi-Aventis, NZ.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Quadramet *CIS, Cz.; CIS, Fr.; CIS, Irl.; CIS, Ital.; CIS, Neth.; CIS, Pol.; CIS, Port.; CIS, Spain; CBI, Switz.; CIS, UK; EUSA, USA.*
Samarium-153 lexidronam pentasodium (p. 2227·3).
Metastatic bone pain.

Quadrapax *Acella, USA.*
Atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); hyoscyamine sulfate (p. 1848·1); phenobarbital (p. 535·2).

Quadrasa *Norgine, Fr.*
Sodium p-aminosalicylate (p. 215·2).
Ulcerative colitis.

Quadrax *Boehringer Ingelheim Promeco, Mex.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Quadribeta *Belfar, Braz.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).

Quadriderm
Note: this name may be used for preparations of different composition.
Schering-Plough, Arg.
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Mantecorp, Braz.; MSD, Hong Kong; Essex, Philipp.; Schering-Plough, S.Afr.; MSD, Thai.
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Schering-Plough, Venez.
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1).
Infected skin disorders.

Quadriderm NF *Schering-Plough, Mex.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Quadriderme *Schering-Plough, Port.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Quadrihexal *Hexal, Braz.*
⊗Tolnaftate (p. 596·1); clioquinol (p. 273·1); gentamicin (p. 304·2); betamethasone (p. 1623·2).
Infected skin disorders.

Quadrikin *Kinder, Braz.†*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Quadrilon *Neo Quimica, Braz.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Quadrinal *Knoll, USA.*
⊗Ephedrine hydrochloride (p. 1663·2); phenobarbital (p. 535·2); theophylline calcium salicylate (p. 1229·3); potassium iodide (p. 2336·3).
Chronic respiratory disease.

Quadriplus *Delta, Braz.†*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Quadrocef *Arterium, Ukr.*
Cefepime (p. 239·2).
Bacterial infections.

Quadropril *Meda, Austria; AWD, Ger.; AWD, Hung.†; AWD, Rus.; Teva, Ukr.*
Spirapril hydrochloride (p. 1499·3).
Hypertension; heart failure.

Quadrotopic *Vendiz, Philipp.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Quadtab *United American, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Quagu-Test *Fada, Arg.*
Aprotinin (p. 1133·2).

Qual *Silanes, Mex.*
Paracetamol (p. 115·1); dextropropoxyphene hydrochloride (p. 43·3); diazepam (p. 1063·2).
Pain; painful muscle spasm.

Qualaquin *AR Scientific, USA.*
Quinine sulfate (p. 665·2).
Malaria.

Quali-A *Quality, Hong Kong.*
Tretinoin (p. 1725·2).
Acne; photodamaged skin.

Qualiaden *Quality, Hong Kong.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Qualiceclor *Quality, Hong Kong.*
Cefaclor (p. 232·3).
Bacterial infections.

Quali-Cefurnat *Quality, Hong Kong.*
Cefuroxime (p. 255·2).
Bacterial infections.

Qualiclinda *Quality, Hong Kong.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Qualiclovir *Quality, Hong Kong.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Qualicor *Quality, Hong Kong.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Qualicren *Quality, Hong Kong.*
Azelaic acid (p. 1695·1).
Acne; skin pigmentation disorders.

Qualiderm *Greenpharma, Braz.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Quali-Docalm *Quality, Hong Kong.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm; spasticity.

Qualidom *Quality, Hong Kong.*
Domperidone (p. 1838·1).
Delayed gastric emptying; gastro-oesophageal reflux; nausea and vomiting.

Qualidrox *Quality, Hong Kong.*
Cefadroxil (p. 233·2).
Bacterial infections.

Qualidrozine *Quality, Hong Kong.*
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; urticaria.

Quali-Flon *Quality, Hong Kong.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Qualifutin *Quality, Hong Kong.*
Fusidic acid (p. 302·1).
Gram-positive bacterial skin infections.

Qualigoline *Quality, Hong Kong.*
Nicergoline (p. 2569·1).
Cerebral and peripheral circulatory disorders.

Qualigyl *Quality, Hong Kong.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Quali-itrazole *Quality, Hong Kong.*
Itraconazole (p. 583·3).
Fungal infections.

Qualikin *Quality, Hong Kong.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders; oral hygiene.

Qualilaic *Quality, Hong Kong.*
Azelaic acid (p. 1695·1).
Acne; skin pigmentation disorders.

Quali-Mentin *Quality, Hong Kong.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Qualipantyl *Quality, Hong Kong.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Qualiphor *Quality, Hong Kong.*
Cefaclor (p. 232·3).
Bacterial infections.

Qualipid *Quality, Hong Kong.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; primary prevention of ischaemic heart disease.

Qualiprinol *Quality, Hong Kong.*
Inosine pranobex (p. 988·3).
Viral infections.

Qualiquan *Quality, Hong Kong.*
Doxepin hydrochloride (p. 414·2).
Depression.

Qualisac *Quality, Hong Kong.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder.

Qualisef *Quality, Hong Kong.*
Cefradine (p. 249·1).
Bacterial infections.

Qualisolvon *Quality, Hong Kong.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Qualisone *GX, Philipp.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Qualistat *Terramedic, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Qualiton *TO-Chemicals, Thai.*
Guaifenesin (p. 1666·2); theophylline (p. 1229·3).
Bronchospasm; cough.

Qualitriptine *Quality, Hong Kong.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Qualixamin *Quality, Hong Kong.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Quali-Xit *Quality, Hong Kong.*
Flupentixol hydrochloride (p. 1074·2); melitracen hydrochloride (p. 434·2).
Anxiety; depression; psychosomatic disorders.

Qualizep *Quality, Hong Kong.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1); salicylamide (p. 129·2).
Cold and influenza symptoms; rhinitis; sinusitis.

Qualizide *Quality, Hong Kong.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Qualizindol *Quality, Hong Kong.*
⊗Mazindol (p. 2324·1).
Obesity.

Qualizyme *Quality, Hong Kong.*
Muramidase (p. 2565·1).
Sinusitis; respiratory-tract disorders with viscous mucus; sore throat; minor haemorrhage.

Quamatel *Gedeon Richter, Cz.; Gedeon Richter, Hong Kong†; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Famotidine (p. 1842·1).
Gastrointestinal haemorrhage; peptic ulcer; acid aspiration; acute pancreatitis; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; gastric hyperacidity; gastralgia.

Quamiprox *Nufarindo, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Quan Bo *Jinquan Baoshan, China.*
Nedaplatin (p. 834·3).

Quan Kang Nuo *Lukang Medicine, China.*
Seratrodast (p. 1225·3).

Quan Qi *Quangang, China.*
Interleukin-2 (human, recombinant) (p. 810·1).

Quan Sheng *Quangang, China.*
Granulocyte-macrophage colony-stimulating factor.

Quan Ying *Jiang Kang, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Quan Zhu *HaiWang Fuyao, China.*
Inosine (p. 2533·1).

Quanil *Teofarma, Ital.†*
Meprobamate (p. 1083·3).
Anxiety disorders.

Quanilene *Vitae, Mex.*
Fluoxetine (p. 417·1).
Depression.

Quantaffirm *Organon Teknika, USA.*
Test for infectious mononucleosis.

Quantalan *BMS, Austria; BMS, Ger.; BMS, Port.; BMS, Switz.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; diarrhoea; pruritus associated with biliary obstruction; biliary-tract disorders; poisoning with phenprocoumon.

Quantia *Unison, Thai.*
Quetiapine (p. 1101·1).
Schizophrenia; bipolar disorder.

Quantidex *Ifars, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Quantrel *Pfizer, Indon.†; Johnson & Johnson, Philipp.; Pfizer, Venez.*
Oxantel embonate (p. 162·2); pyrantel embonate (p. 165·3).
Worm infections.

Quantrim Herbal Slimming Tablets *Rickard Lanes, UK.*
Fucus vesiculosus; clivers (p. 2481·2).
Slimming aid.

Quantum *Perrigo, Israel.*
Vitamins; minerals; lycopene (p. 2546·2); lutein (p. 2079·2).

Quarelin *Sanofi-Aventis, Hung.*
Dipyrone (p. 53·3); caffeine (p. 1203·3); drotaverine hydrochloride (p. 2497·3).
Migraine.

Quark *Polifarma, Ital.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; renal insufficiency.

Quarlintan *Medis, Ital.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Quartacef *Cipla, Ukr.†*
Cefepime (p. 239·2).
Bacterial infections.

Quartette *Teva, USA.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, ethinylestradiol.
Combined oral contraceptive.

Quasense *Watson, USA.*
84 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Quatrofen *Nycomed, Ital.*
⊗Fentanyl (p. 60·1).
Pain.

Quatro-Soda *Aspen, S.Afr.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); citric acid (p. 2480·3).
Urinary alkalinisation.

Quattrovac *Astellas, Jpn.*
An adsorbed diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Quavir *Soho, Indon.†*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Qubi *Ethica, Indon.*
Ubidecarenone (p. 2637·1).
Antoxidant; tonic.

Qucin *Aristo, India.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Qudermin *Serral, Mex.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Qudesan *Akvion, Rus.*
Ubidecarenone (p. 2637·1).
Cardiovascular disorders; digestive disorders; renal disorders; nervous disorders; asthenia.

Qudix *Adamed, Spain.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Que Wei *Huabang, China.*
Tazarotene (p. 1724·2).
Psoriasis.

Que Zhi Du *Tianxin, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Quecor *Labofarm, Pol.*
Oak bark (p. 2574·1).
Diarrhoea.

Quedox
Note: this name may be used for preparations of different composition.
Ajanta, Philipp.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Rayere, Mex.
Clarithromycin (p. 266·2).
Bacterial infections.

Quefuli *Ebewe, China; Sandoz, China.*
Calcium folinate (p. 2066·3).
Antidote to methotrexate; adjunct to fluorouracil in colorectal cancer.

Queimalive *Cifarma, Braz.*
Sulfacetamide sodium (p. 361·1).
Bacterial skin infections.

Queimax *Farlab, Port.*
Camphor (p. 2466·2); potassium hydroxyquinoline sulfate (p. 2530·1).
Skin disorders.

Quel *Ipca, India.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; psychoses associated with parkinsonism.

Quelan *Lannacher, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Quelesu *Zizhu, China.*
Theophylline (p. 1229·3).
Asthma.

Quelicin *Abbott, Braz.; Hospira, Canad.; Hospira, Indon.; Transfarma, Indon.; Hospira, Philipp.; Hospira, USA.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Quelidrine *Abbott, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); ephedrine hydrochloride (p. 1663·2); phenylephrine hydrochloride (p. 1672·3); ammonium chloride (p. 1656·1); ipecac fluidextract (p. 1667·2).
Coughs.

Quellada *Aspen, Austral.; GSK, Hong Kong.*
Permethrin (p. 2159·3).
Scabies; pediculosis.

Quellada M *Stafford-Miller, Irl.†; GSK Consumer, UK.†*
Malathion (p. 2157·2).
Pediculosis; scabies.

Quelodin F *Ariston, Arg.*
Greater celandine (p. 2522·2); taraxacum (p. 2625·3); milk thistle (p. 1561·1); linoleic acid (p. 2509·2) or magnesium linoleate.
Biliary-tract disorders.

Quelor *Actavis, Irl.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Quemagrasas *Teingro, Arg.*
Amino acids; vitamins; minerals.
Dietary supplement.

Quemed *Actavis, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Quemicetina *Pfizer, Braz.*
Chloramphenicol palmitate (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Rontag, Arg.†; Pfizer, Mex.
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Quemicetina con Hidrocortisona *AstraZeneca, Arg.*
⊗Chloramphenicol (p. 257·1); hydrocortisone acetate (p. 1640·1).
Infected skin and eye disorders.

Quemicetina Nasal Compuesta *Rontag, Arg.*
⊗Chloramphenicol (p. 257·1); ephedrine hydrochloride (p. 1663·2); tripelennamine hydrochloride (p. 642·3).
Nasal infections.

Quemicetina Nasal NF *AstraZeneca, Arg.*
Mupirocin calcium (p. 327·2).
Elimination of nasal staphylococci.

Quemox *YSP, Malaysia; YSP, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Quemyl *Generics, Denm.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Quensyl *Sanofi-Aventis, Ger.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus; malaria.

Quentakehl *Sanum-Kehlbeck, Ger.*
Penicillium glabrum.
Homoeopathic preparation.

Quentapil *ICN, Neth.; ICN, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quentiax *KRKA, Spain.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quepaz *Phoenix, Arg.*
Quetiapine (p. 1101·1).
Psychoses.

Quepin *Specifar (Σπεσιφαρ), Gr.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Quepita *Ingers, Cz.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quepsan *ProMed, Cz.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Queratal *Liferpal, Mex.*
Tretinoin (p. 1725·2).

Queratopil *Pharma Investi, Chile.*
Ammonium lactate (p. 1694·3); panthenol (p. 2582·2); allantoin (p. 1693·1); levomenol (p. 2544·1).
Hyperkeratinisation.

Querok *Legrand, Braz.*
Quetiapine (p. 1101·1).

Queropax *Sigma, Braz.*
Quetiapine (p. 1101·1).

Quer-Out *Atlas, Arg.*
Diclofenac sodium (p. 48·3).
Actinic keratosis.

Quertin *Borshchagovskii, Ukr.*
Quercetin (p. 2505·3).
Peptic ulcer; soft-tissue inflammation; glomerulonephritis; circulatory disorders.

Querto *Nycomed, Ger.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Quest Gamma EPA Plus *Banner Pharmacaps, Malaysia.*
Fish oil concentrate (p. 1460·3).
Dietary supplement.

Questax *SVUS, Cz.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Questran *BMS, Arg.; Aspen, Austral.; BMS, Belg.; BMS, Braz.; BMS, Cz.†; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Gr.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong†; BMS, Indon.†; BMS, Irl.; BMS, Mex.; BMS, Neth.; BMS, Norw.; Healthcare Logistics, NZ.; BMS, S.Afr.; BMS, Swed.; BMS, Thai.; BMS, UK; Par, USA.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; diarrhoea; adjunct in organophosphorus pesticide poisoning; hyperlipidaemias; hyperoxaluria; diarrhoea and pruritus associated with biliary-tract disorders; pruritus; rehydration; Crohn's disease.

BMS, Ital.
Colestyramine hydrochloride.
Hypercholesterolaemia; biliary obstruction and associated pruritus.

Quetanex *Medopharm, Philipp.†*
Ketamine hydrochloride (p. 1905·1).
General anaesthesia.

Quetapel *Mylan, NZ.*
Quetiapine fumarate (p. 1101·1).
Psychoses; bipolar disorder.

Quetastad *Stada, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Queteper *Actavis, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Medis, Ital.
Quetiapine (p. 1101·1).

Quetex *Rowex, Irl.; Apotex, Neth.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetiafair *Fair-Med, Neth.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetialan *Gerot, Austria.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Quetiamylan *Mylan, Spain.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetiaros *Rospaw, Arg.*
Quetiapine (p. 1101·1).
Psychoses.

Quetiazic *Raffo, Arg.*
Quetiapine (p. 1101·1).
Psychoses.

Tecnofarma, Chile.
Quetiapine fumarate (p. 1101·1).
Bipolar disorder.

Quetidin *Drugtech, Chile.*
Quetiapine (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetifi *Tiefenbacher, Cz.†*
Quetiapine fumarate (p. 1101·1).

Quetilis *Actavis, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Quetin *Zentiva, Cz.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetipin *Cristalia, Braz.*
Quetiapine (p. 1101·1).

Quetiratio *Ratiopharm, Denm.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetiron *Pharma Start, Ukr.*
Quetiapine fumarate (p. 1101·1).
Psychoses; bipolar disorder.

Quetiser *Sun-Farm, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetoser *Cipla-Medpro, S.Afr.*
Quetiapine (p. 1101·1).

Quetrop *Glenmark, Cz.; Glenmark, Neth.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Quetros *Ache, Braz.*
Quetiapine (p. 1101·1).

Quetzal *Smaller, Spain.†*
St John's wort (p. 449·1).
Tonic.

Quexel *Sanofi-Aventis, Arg.*
Metformin (p. 489·1).
Diabetes mellitus.

Qugyl *RPG, India.*
Diloxanide furoate (p. 931·2); metronidazole (p. 936·1).
Amoebiasis; giardiasis.

Quiacort *Euroderm, Arg.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Quiacort G *Euroderm, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Quiacort G Plus *Euroderm, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2); clotrimazole (p. 576·2).
Infected skin disorders.

Quiagen *Generics, Hung.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quibron-R *BMS, Gr.*
Theophylline (p. 1229·3).

Quibron-T *BMS, Indon.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Quibus *CSO Pharmitalia, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Quick N Easy *KK, UK.*
Pregnancy test (p. 2596·1).

QuickCal *Vitaflo, UK.*
High energy food fortifier.

Vitaflo, Irl.†
Preparation for enteral nutrition.

QuicKlean *Hovid, Malaysia.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

QuickVue *Quidel, USA.*
Pregnancy test (p. 2596·1).

Quidex
Note: this name may be used for preparations of different composition.
Ferron, Indon.; Ferron, Philipp.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Poen, Arg.
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Health Alliance, Hong Kong.†
Ciprofloxacin (p. 261·1).
Bacterial infections.

Quidofril *Serral, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Quidorfen *Nycomed, Spain.†*
⊗Fentanyl (p. 60·1).
Pain.

Quiedorm *Menarini, Spain.*
Quazepam (p. 1100·3).
Insomnia.

Quiens *Antonetto, Ital.*
St John's wort (p. 449·1).
Depression.

Quies auriculaire *Quies, Fr.†*
Sea water (p. 2612·1).
Irrigation solution for ear canal hygiene.

Quiet Days *Cantassium Co., UK.*
Skullcap (p. 2617·1); lupulus (p. 2546·1); valerian (p. 2640·2).

Quiet Life *Lane, Irl.*
Motherwort (p. 2564·2); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2); thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); nicotinamide (p. 2083·1).
Irritability; stress.

Lane, UK.
Motherwort (p. 2564·2); wild lettuce (p. 2647·3); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2); thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); nicotinamide (p. 2083·1).
Stresses and strains; insomnia.

Quiet Nite *Cantassium Co., UK.*
Valerian (p. 2640·2); lupulus (p. 2546·1); lettuce (p. 2647·3); passion flower (p. 2584·1).
Insomnia.

Quiet Tyme *Cantassium Co., UK.*
Skullcap (p. 2617·1); lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2); gentian (p. 2512·1); vitamin B substances (p. 2102·3).

Quiétiline *Sciencex, Fr.*
Bromazepam (p. 1041·2).
Anxiety; alcohol withdrawal syndrome.

Quiétude *Boiron, Canad.; Boiron, Fr.; Boiron, Switz.*
Chamomilla vulgaris (p. 2474·1); gelsemium sempervirens (p. 2511·2); hyoscyamus niger (p. 2530·2); kalium bromatum (p. 2461·1); passiflora incarnata (p. 2584·1); stramonium (p. 2622·3).
Homoeopathic preparation.

Quietude *Boiron, Neth.†*
Chamomilla (p. 2474·1); gelsemium sempervirans (p. 2511·2); hyoscyamus niger (p. 2530·2); kalium bromatum (p. 2461·1); passiflora incarnata (p. 2584·1); stramonium (p. 2622·3).
Homoeopathic preparation.

Quiflox *Teuto, Braz.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Quiflural *Rayere, Mex.*
Ofloxacin (p. 334·3).
Bacterial infections.

Quik *Valeas, Ital.*
Cloperastine fendizoate (p. 1659·2).
Cough.

Quik-Check *Farmaceutica H, Mex.†*
Pregnancy test (p. 2596·1).

Quilagen *Randall, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Quilarex *Ariston, Arg.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder; obsessive-compulsive disorder.

Quilaxin *CCM, Malaysia.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Qui-Lea *Elea, Arg.*
Quinestrol (p. 2303·1).
Menopausal disorders.

Quilla simplex *ACO Hud, Swed.*
Ammonium chloride (p. 1656·1); quillaia (p. 2207·1).
Cough.

Quillivant *Next Wave, USA.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention deficit hyperactivity disorder.

Quilonium-R *GSK, Philipp.*
Lithium carbonate (p. 427·3).
Mania.

Quilonorm *Doetsch, Grether, Switz.*
Lithium acetate (p. 427·3) or lithium carbonate (p. 427·3).
Bipolar disorder; depression; mania.

GSK, Austria.
Lithium carbonate (p. 427·3).
Bipolar disorder; mania.

Quilonum *GSK, Austral.; Cephalon, Ger.; GSK, Ger.; GSK, S.Afr.*
Lithium carbonate (p. 427·3).
Bipolar disorder; cluster headache; depression; mania.

Quilox *Cipla, Philipp.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Quimbo *Trommsdorff, Ger.*
Levodropropizine (p. 1662·3).
Cough.

Quimea *Kleva, Gr.*
⊗Quinapril (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quimefuran *IQFA, Mex.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Quimobrom *Maver, Mex.*
Erythromycin (p. 291·2); bromhexine (p. 1656·3).
Bacterial infections.

Quimocyclar *Grossman, Mex.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Quimodril *Italfarmaco, Spain.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3); teclothiazide potassium (p. 1509·2).
Oedema.

Quimofan *Quimica y Farmacia, Mex.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Quimofeina *Quimica y Farmacia, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Quimolauril *Maver, Mex.*
Erythromycin (p. 291·2).
Bacterial infections.

Quimosporina *Quimica y Farmacia, Mex.*
Cefalexin (p. 234·1).
Bacterial infections.

Quimotrip *Collins, Mex.†*
⊗Tetracycline (p. 373·1); trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Bacterial infections.

Quimpe Antibiotico *Quimpe, Spain.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Quimpedor *Quimpe, Spain.*
Caffeine (p. 1203·3); phenazone (p. 124·1); pyridoxine hydrochloride (p. 2105·3); propyphenazone (p. 127·3); thiamine hydrochloride (p. 2103·1).
Pain; fever.

Quimtadine *Quimpharma, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Quimtadine DSQ *Quimpharma, Mex.†*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; rhinitis; pruritus; urticaria.

Quimtafriol *Quimpharma, Mex.†*
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; rhinitis; pruritus; urticaria.

Quimtatil *Quimpharma, Mex.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Quimtulac *Quimpharma, Mex.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Quinace *Pharma Dynamics, S.Afr.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinace Co *Pharma Dynamics, S.Afr.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinacid *Sigillata, Denm.†*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinacris *Cristalia, Braz.*
Chloroquine hydrochloride (p. 650·1).
Malaria.

Quinagen *Mylan, S.Afr.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinaglute *Schering, S.Afr.†*
Quinidine gluconate (p. 1481·2).
Arrhythmias.

Quinalar *Leti Gentek, Venez.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

QuinaLich comp *Winthrop, Ger.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinanorm Kombi *Plus Pharma, Hung.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinaphar *Teva, Rus.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinaplus *Aliud, Ger.†; Stada, Ger.†*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinapril comp *Betapharm, Ger.†; Hexal, Ger.†*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinapril plus *1A, Ger.†*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinapril-HCT *Sandoz, Hung.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinapro *Biex, Irl.†*
Quinapril hydrochloride (p. 1480·2).
Heart failure; hypertension.

Quinard *Actavis, Ukr.†*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinaretic *Amide, USA; Leti Gentek, Venez.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinaril *Biolab, Thai.†*
Quinapril (p. 1480·2).
Hypertension; heart failure.

Quinarsol *Cipla, India.*
Quinine dihydrochloride (p. 665·1) or quinine sulfate (p. 665·2).
Malaria.

Quinaspen *Aspen, S.Afr.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinate *Aspen, Austral.*
Quinine sulfate (p. 665·2).
Malaria.

Quinax *Alcon, Hong Kong; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, Singapore; Alcon, Thai.; Alcon, Ukr.*
Azapentacene polysulfonate sodium (p. 2451·3).
Cataract.

Quinazide *Malesci, Ital.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quinazil *Malesci, Ital.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinbisul *Aspen, Austral.; LCH, Hong Kong.†*
Quinine bisulfate (p. 665·1).
Malaria.

Quinfaval *Valdecasas, Mex.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Quinicardine *Barrenne, Braz.; Adilna, Turk.*
Quinidine sulfate (p. 1481·2).
Arrhythmias.

Quinil *Tillomed, UK.*
Quinapril (p. 1480·2).
Heart failure; hypertension.

Quinilan *LKM, Arg.*
Imiquimod (p. 985·2).
Anogenital warts.

Quinimax *Sanofi-Aventis, Fr.*
Quinine gluconate (p. 665·1) or quinine hydrochloride (p. 665·2); quinidine gluconate (p. 1481·2) or quinidine hydrochloride (p. 1481·1); cinchonine hydrochloride (p. 2478·3); cinchonidine hydrochloride (p. 2478·3).
Malaria.

Quininga *Inga, India.*
Quinine dihydrochloride (p. 665·1) or quinine sulfate (p. 665·2).
Malaria.

Quinobact *Allergan, India; Piramal, India.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Quinobiot *Andromaco, Chile.*
Levofloxacin (p. 315·3).
Bacterial infections.

Quinobiotic *Pharos, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Quinocin *Vida, Hong Kong.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Quinocip *IE Medica, Philipp.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Quinocort
Note: this name may be used for preparations of different composition.
Oftalmi, Venez.
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Quinoderm *Ferndale, Irl.; Winthrop, S.Afr.†; Ferndale, UK.*
Benzoyl peroxide (p. 1696·1); potassium hydroxyquinoline sulfate (p. 2530·1).
Acne; folliculitis; skin disorders.

Quinoderm Antibacterial Face Wash *Ferndale, UK.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1); detergents.
Skin cleanser; soap substitute.

Quinodermil-AS *Edol, Port.*
Salicylic acid (p. 1719·1); clioquinol (p. 273·1).
Infected skin disorders.

Quinoflox *Biolab Sanus, Braz.; Diba, Mex.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Quinoflox Otico *Diba, Mex.*
Ciprofloxacin hydrochloride (p. 261·2); lidocaine hydrochloride (p. 1988·2).
Bacterial ear infections.

Quinoform
Note: this name may be used for preparations of different composition.
EMS, Braz.
Norfloxacin (p. 333·3).
Bacterial infections.

Quinoforme
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Fr.†
Basic quinine formate (p. 665·1).
Malaria.

Quinoftal *Oftalmi, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial eye infections.

Quinolev *Ahlcon, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Quinomed *Bausch & Lomb, Arg.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Quinomed L *Bausch & Lomb, Arg.*
Levofloxacin (p. 315·3).
Bacterial eye infections.

Quinoret *Darier, Mex.*
Hydroquinone (p. 1705·1); vitamin A (p. 2098·3).
Skin pigmentation disorders; sun-induced skin damage.

Quinoret Forte *Darier, Mex.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Quinoryl *ACME, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Quinosul *Parggon, Mex.*
Diiodohydroxyquinoline (p. 931·1).
Diarrhoea.

Quinotic *Oftalmi, Venez.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Quinotic HC *Oftalmi, Venez.*
⊗Ciprofloxacin hydrochloride (p. 261·2); hydrocortisone (p. 1640·1).
Otitis externa.

Quinovid *Mugi, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Quinox *Labesfal, Port.*
Ciprofloxacin (p. 261·1) or ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Quinradon-N *Hua, Thai.†*
Diiodohydroxyquinoline (p. 931·1); nystatin (p. 590·3); boric acid (p. 2459·3); phosphoric acid (p. 2589·1).
Vaginal infections.

Quinsana Plus *Mennen, USA.†*
Tolnaftate (p. 596·1).
Fungal skin infections.

Quinsil *Silom, Thai.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quinsul *Lennon, Austral.†*
Quinine sulfate (p. 665·2).
Malaria; nocturnal leg cramps.

Quintabs *Freeda, USA.*
Vitamins; with or without minerals.

Quintalgine *Interhim, Rus.*
Dipyrone (p. 53·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); phenobarbital (p. 535·2).
Pain; fever.

Quintanrix *GSK, Cz.†; GSK, Neth.†*
A diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenzae vaccine (p. 2384·3).
Active immunisation.

Quintasa *Ferring, Denm.*
Mesalazine (p. 1859·2).
Ulcerative colitis.

Quintasol *Biosynthesis, Rus.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium acetate (p. 1781·1).
Fluid and electrolyte disorders.

Quintonine *GSK Sante, Fr.†*
Cinnamon (p. 2479·2); kola (p. 2648·2); dried bitter-orange peel (p. 2575·3); cinchona bark (p. 2478·3); quassia (p. 2601·1); gentian (p. 2512·1).
Asthenia.

Quintor *Torrent, Rus.*
Ciprofloxacin (p. 261·1) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Quinvaxem *Novartis, Chile; Novartis, Philipp.; Novartis Vaccines, Thai.*
A diphtheria, tetanus, pertussis, haemophilus influenzae, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Quiprime *Zynova, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Quiralam *Retrain, Spain.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Quirgel *Retrain, Spain.*
Dexketoprofen trometamol (p. 79·1).
Pain; inflammation.

Quiril *Sandoz, Switz.*
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Quiril comp. *Sandoz, Switz.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Quirocaine *Abbott, Mex.†*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Quisegen *Lafedar, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Quiss *Jagsonpal, India.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Quit
Note: this name may be used for preparations of different composition.
Aspen Consumer, S.Afr.
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Quitacallos *Farmo Quimica, Chile.*
Salicylic acid (p. 1719·1) in amyl acetate.
Keratoses; warts; callouses.

Quitacoff *Rutland Biodynamics, UK.*
⊗Lobelia (p. 2323·2); squill (p. 1677·3).
Cough.

Quitadol *Biomep, Mex.*
Paracetamol (p. 115·1).
Pain.

Quitadrill *Pierre Fabre Sante, Fr.†*
Mequitazine (p. 635·2).
Hypersensitivity.

Quitaxon *Nepalm, Fr.*
Doxepin hydrochloride (p. 414·2).
Depression.

Quitoso *Angelini, Port.*
Permethrin (p. 2159·3).
Pediculosis.

Quitoso NF *Elisium, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

QuitX
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Quixidar *GSK, Neth.†*
Fondaparinux sodium (p. 1385·3).
Thromboembolic disorders.

Quixil *Omrix, Belg.†; Omrix, Denm.; Omrix, Fin.; Omrix, Ger.†; Johnson & Johnson, Ital.; Omrix, Neth.†; Omrix, Swed.†; Janssen-Cilag, Switz.*
Solution 1, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); tranexamic acid (p. 1164·2); solution 2, thrombin (p. 1163·2); calcium chloride (p. 1783·1).
Haemorrhage.

Ethicon, Fr.†
Solution I, human clottable proteins; tranexamic acid (p. 1164·2); solution II, thrombin (p. 1163·2); calcium chloride (p. 1783·1).
Haemorrhage.

Omrix, Israel.†
Human clottable proteins; human alpha thrombin (p. 1163·2); calcium chloride (p. 1783·1).
Haemorrhage.

Omrix, Port.†
Thrombin (p. 1163·2); calcium chloride (p. 1783·1); plasma (p. 1158·2); tranexamic acid (p. 1164·2).
Haemorrhage.

Quixin *Santen, USA.*
Levofloxacin (p. 315·3).
Bacterial conjunctivitis.

Quixx *Berlin-Chemie, Ukr.*
Sea water (p. 2612·1).
Nasal disorders.

Qumic *Bosch, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Quocel *Rayere, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Quocin *Isdin, Spain.*
Acetic acid (p. 2426·3); salicylic acid (p. 1719·1).
Callosities.

Quodixor *Pharmathen, Cz.; Pharmathen, Neth.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Quomem *GSK, Neth.; GSK, Spain†; GSK, Thai.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Quool *Allmi-Care, UK.*
Menthol (p. 2553·2).
Musculoskeletal pain.

Quorum *Progen, Ital.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Quotal *Nova Argentia, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections; helicobacter pylori eradication.

Quotane *Zambon, Fr.*
Quinisocaine hydrochloride (p. 1996·1).
Pruritus.

Quotavil *Quality, Hong Kong.*
Ofloxacin (p. 334·3).
Bacterial infections.

Qupron *Shin Poong, Singapore.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Qura *Bernabo, Arg.*
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine sulfate (p. 1676·1); paracetamol (p. 115·1).
Influenza symptoms.

Qura Nasal *Bernabo, Arg.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Qura Plus *Bernabo, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Qura Tos *Bernabo, Arg.*
Ivy (p. 2536·2).
Respiratory-tract congestion.

Qutan-10 *Ikapharmindo, Indon.*
Ubidecarenone (p. 2637·1); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc gluconate (p. 2126·2).
Tonic.

Qutenza *Astellas, Austria; Astellas, Cz.; Astellas, Denm.; Astellas, Fr.; Astellas, Ger.; Astellas, Gr.; Astellas, Irl.; Astellas, Neth.; Astellas, Norw.; Astellas, Pol.; NeurogesX, Port.; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Astellas, UK; NeurogesX, USA.*
Capsaicin (p. 35·1).
Neuropathic pain.

Qutifar *Ifars, Indon.†*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Qutipin *Maver, Chile.*
Quetiapine fumarate (p. 1101·1).

Qutong *Simcere, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

QV *Ego, Malaysia; Crawford, UK.*
A range of emollients and soap substitutes.
Dry skin disorders.

Ego, Austral.
Soap substitute; bath additive; emollient.
Skin disorders.

Ego, Hong Kong.
A range of soap substitutes, bath additives, and emollients.
Skin disorders.

Ego, NZ.
A range of emollient and cleansing skin preparations.
Dry skin disorders.

Ego, Singapore.
A range of emollients, soap substitutes, and skin and scalp cleansers.
Skin disorders.

Ego, Malaysia.
Face Moisturising Cream SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Emollient; sunscreen.

QV Feet Heel Balm *Ego, Austral.*
Emollient.
Dry, cracked heels.

QV Flare Up *Ego, Austral.*
Cream: ⊗Liquid paraffin (p. 2191·2); glycerol (p. 2517·2); white soft paraffin (p. 2211·3); phenoxyethanol (p. 1764·3); povidone (p. 2204·3).
Eczema.

Ego, Austral.
Skin wash: Skin cleanser.
Eczema.

Ego, Austral.; Ego, Malaysia†; Ego, Singapore.
Light liquid paraffin (p. 2191·2); benzalkonium chloride (p. 1737·1); triclosan (p. 1773·2).
Eczema.

QV Lip Balm *Ego, Austral.; Ego, Hong Kong; Ego, NZ; Ego, Singapore.*
SPF 30+: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Dry, cracked, or chapped lips; sunscreen.

Ego, Malaysia.
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); white soft paraffin (p. 2211·3); dimeticone (p. 2209·3).
Dry, cracked, or chapped lips; sunscreen.

QV Naked Anti-Perspirant Deodorant *Ego, Austral.*
Aluminium zirconium tetrachlorohydrex gly (p. 1694·1).
Hyperhidrosis.

Qvar *iNova, Austral.; UCB, Belg.; Graceway, Canad.; Teva, Fr.; Lavipharm, Gr.; 3M, Hong Kong†; Norton Waterford, Irl.; 3M, Israel; iNova, Malaysia; Teva, Neth.; 3M, NZ; 3M, Philipp.†; Teva, Port.; iNova, S.Afr.; Teva, Switz.; iNova, Thai.; Ivax, UK; Ivax, USA.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

Qvarspray *Teva, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Formerly known as Nexxair.
Asthma.

Q-Vax *CSL Biotherapies, Austral.*
An inactivated Q fever vaccine (p. 2412·3).
Active immunisation.

Q-win *Brown & Burk, Philipp.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia.

QX 10 *Sigma, Arg.*
Folic acid (p. 2063·1); pyridoxine (p. 2105·3); cobalamin; ubidecarenone (p. 2637·1).
Hyperhomocysteinaemia; folic acid deficiency anaemias; tonic.

QX 100 *Sigma, Arg.*
Ubidecarenone (p. 2637·1).
Chronic fatigue syndrome; mental function impairment.

Qxar *QX, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

R & C *GSK Consumer, Canad.†; Prestige, Canad.*
Shampoo: spray: Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis; surface and textile insecticide.

R Calm *Labima, Belg.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic conjunctivitis; allergic rhinitis; urticaria; pruritus.

RA Bloc *Euro-Med, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; peptic ulcer.

RA Lotion *Medco, USA.*
Resorcinol (p. 1718·3); calamine (p. 1697·2); borax (p. 2459·2).
Acne.

RA Morph *Pfizer, NZ.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Raamcap *Raam, Mex.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Raamcinet *Raam, Mex.*
Cetirizine hydrochloride (p. 619·2).
Allergic skin disorders; allergic rhinitis; urticaria.

Raamfen *Raam, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

RabAvert *Novartis, Canad.; Chiron, USA.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Rabbit Balm *Millimed, Thai.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal pain and inflammation; insect bites.

Rabebir *Plus Pharma, Cz.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rabec *Phoenix, Arg.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer.

Rabecole *Apotex, Cz.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rabeloc *Cadila, India.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rabeman *Aramis, Hung.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rabemylon *Rafarm, Gr.*
⊗Methyldopa (p. 1431·1); hydrochlorothiazide (p. 1403·2).

Rabesat *Genetic, Ital.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Rabicip *Cipla, India.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer.

Rabiclon *Clonmel, Irl.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux disease.

Rabies-Imovax *Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Norw.; Sanofi Pasteur, Swed.*
A rabies vaccine (human diploid cell culture) (p. 2413·2).
Active immunisation.

Rabiesvax *Juventis, Philipp.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Rabigam *NBI, S.Afr.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Rabipor *Litha, S.Afr.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Rabipur *CSL Biotherapies, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, China; Novartis Vaccines, Cz.; Novartis, Denm.; Novartis Vaccines, Fr.; Novartis Vaccines, Ger.; Sanofi-Aventis, India; Novartis, Israel; Novartis Vaccines, Ital.; Novartis Vaccines, Neth.; Novartis, Norw.; Novartis Vaccines, Philipp.; Novartis Vaccines, Port.; Novartis, Rus.; Novartis Vaccines, Singapore; Novartis Vaccines, Spain; Novartis, Switz.; Novartis Vaccines, Thai.; Chiron Vaccines, UK.*
A rabies vaccine (Flury LEP strain) (p. 2413·2).
Active immunisation.

RabirEP *Extractum, Hung.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rabiril *Ananta, Ukr.*
Rabeprazole sodium (p. 1881·1); domperidone maleate (p. 1838·1).
Gastro-oesophageal reflux; dyspepsia; nausea and vomiting; flatulence.

Rabivac *Berk, Turk.*
A rabies vaccine (Pitman Moore strain) (p. 2413·2).
Active immunisation.

Rabivax *Serum Institute, India; Serum Institute, Thai.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Rablas *Medichrom, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Rabolan *Rafarm, Gr.*
Losartan potassium (p. 1422·2).
Hypertension.

Rabro N *Teoforma, Ger.*
Calcium carbonate (p. 1824·3); liquorice (p. 1853·2); magnesium oxide (p. 1857·3).
Gastric hyperacidity; heartburn.

Rabufen *Medicpharma, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain.

Rabugen *Unison, Hong Kong; Unison, Malaysia.*
Domperidone (p. 1838·1) or domperidone maleate (p. 1838·1).
Gastrointestinal motility disorders; nausea and vomiting; dyspepsia; flatulence; gastrointestinal disorders.

Rabugen-M *Unison, Thai.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; delayed gastric emptying.

Rabyprex *Vera, Hung.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Race *Ali, Turk.*
Ramipril (p. 1483·3).

Race Plus *Ali, Turk.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).

Racep *Samjin, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Racestyptine *Septodont, Canad.*
Aluminium chloride (p. 1693·3); hydroxyquinoline sulfate (p. 2530·1).

Wild, Switz.†
Solution: Aluminium chloride (p. 1693·3).
Dental and gum disorders.

Racetam *Samjin, Singapore.*
Piracetam (p. 393·3).
Cerebrovascular disorders; cerebral trauma.

Racidrix *CT, Denm.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Raciper *Ranbaxy, Hung.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Raclonid *Actavis, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Racol *Otsuka, Jpn.*
Preparation for enteral nutrition.

Racorval *Nova Argentia, Arg.*
Valsartan (p. 1521·2).
Hypertension; heart failure; left-ventricular dysfunction.

Racorval D *Nova Argentia, Arg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Racovel *Cryopharma, Mex.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Radacef *Vianex (Βιανεξ), Gr.*
Ceforanide (p. 243·3).
Bacterial infections.

Radacefe *BMS, Port.*
Cefprozil (p. 248·2).
Bacterial infections.

Radahlorin *Rada, Rus.*
Spirulina (p. 2622·1).

Radalgin *Streuli, Switz.†*
Nonivamide (p. 102·3); methyl nicotinate (p. 91·3); glycol salicylate (p. 66·2); histamine hydrochloride (p. 2525·2).
Musculoskeletal pain; sports injuries.

Radanil *Masters, Arg.*
Benznidazole (p. 929·3).
American trypanosomiasis.

Radblock *KI, Canad.*
Potassium iodide (p. 2336·3).
Thyroid blocking agent.

Radedorm *AWD, Ger.†; CT, Ger.†; AWD, Rus.*
Nitrazepam (p. 1089·1).
Sleep disorders; premedication; epilepsy.

Radepur *AWD, Ger.*
Chlordiazepoxide (p. 1044·2).
Anxiety disorders; insomnia.

Radermin *Viofar, Gr.*
Etofenamate (p. 57·2).
Inflammatory disorders.

Radevit *Retinoids, Rus.*
Alpha tocoferil acetate (p. 2119·2); vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Skin disorders; burns; skin lesions.

RadiaGel *Carrington, USA.*
Acemannan (p. 2426·3).
Radiation wounds.

Radialar 280 *Juste, Spain.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Radian-B *Devries, Israel.*
Cream: Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3).
Musculoskeletal, joint, and soft-tissue disorders.

Devries, Israel.
Liniment; topical spray: Aspirin (p. 22·2); menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue disorders.

Ransom, UK.
Liniment; topical spray: Menthol (p. 2553·2); camphor (p. 2466·2); ammonium salicylate (p. 21·1); salicylic acid (p. 1719·1); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Ransom, UK.
Topical rub: Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3); camphor oil (p. 2466·2).
Musculoskeletal and joint disorders.

Radian-B Ibuprofen *Ransom, UK.*
Ibuprofen (p. 68·2).
Musculoskeletal pain; sports injuries.

Radian-B Red Oils *Roche Consumer, UK.*
Methyl nicotinate (p. 91·3); expressed mustard oil (p. 2646·1).
Musculoskeletal and joint pain.

Radiance
Note: this name may be used for preparations of different composition.
Blackmores, Austral.
Day capsules, tomato; lutein (p. 2079·2); ascorbic acid (p. 2110·3); *d*-alpha tocopherol (p. 2119·1); night capsules, marine protein; ubidecarenone (p. 2637·1); camelia sinensis; grape seed (p. 2521·3); maritime pine (p. 2590·3); citrus bioflavonoids (p. 2505·2); *d*-alpha tocoferil acetate (p. 2119·1); betacarotene (p. 2051·1); selenomethionine

(p. 2087·1); zinc amino acid chelate (p. 2048·3).
Dietary supplement for healthy skin.

Elea, Mex.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Radiant C *Herbalife, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

RadiaPlex Rx *MPM, USA.*
Aloe vera (p. 1693·2); sodium hyaluronate (p. 2526·2).
Hydrogel dressing; wounds; burns.

Radiavit *Viofar, Gr.*
Diosmin (p. 2505·2).
Capillary disorders.

Radiblock *Sandoz, Indon.*
Green tea (p. 2648·2); vitamins; zinc (p. 2126·1); selenium (p. 2086·3).
Antoxidant.

Radibrax *Pharmasant, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).

Radicacine *Panalab, Arg.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis.

Radicura *Walker, Arg.*
Boldo (p. 2458·3); carqueja (p. 2471·2); canchalagua.
Digestive disorders.

Radicut
Note: this name may be used for preparations of different composition.
Mitsubishi, Jpn.
Edaravone (p. 1370·2).
Cerebral infarction.

Peseri, Cz.†
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Radiesse *BioForm, USA.*
Calcium hydroxyapatite (p. 2529·3).
Facial lipoatrophy; facial wrinkles and folds.

Radifree *Nikkho, Braz.*
Grape seed (p. 2521·3).
Cardiovascular disorders.

Radigen *Medipharm, Chile.*
Risperidone (p. 1103·2).
Psychoses.

Radikal
Note: this name may be used for preparations of different composition.
Takeda, Belg.
Malathion (p. 2157·2).
Pediculosis.

Radilem *Teva, Mex.†*
⊗Methylprednisolone acetate (p. 1642·3).
Corticosteroid.

Radin *Dexa, Hong Kong†; Dexa, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; Zollinger-Ellison syndrome.

Radina *Amhof, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Radina Dex *Amhof, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Radio Salil *Vinas, Spain.*
Cream: Camphor (p. 2466·2); methyl nicotinate (p. 91·3); methyl salicylate (p. 92·1); salicylic acid (p. 1719·1); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Vinas, Spain.
Spray: Camphor (p. 2466·2); diethylamine salicylate (p. 51·3); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Radiocare *Cantabria, Indon.; Combiphar, Indon.*
Helix aspersa.
Antoxidant; skin disorders.

Radiogardase *Heyl, USA.*
Prussian blue (p. 1572·3).
Exposure to caesium-137 or thallium.

Radiogardase-Cs *Haupt, Cz.; Heyl, Ger.*
Prussian blue (p. 1572·3).
Reduction in body-half-life of radiocaesium.

Radiogen *Medichrom, Gr.*
Niflumic acid (p. 101·2).

Radiomiron *Bayer, Chile.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Radiopaque *Dabur, India.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Radiosélectan *Bayer, Fr.*
Sodium amidotrizoate (p. 1581·3); meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Radipon *Teva, Hung.†*
Emetine hydrochloride (p. 932·3); phenobarbital (p. 535·2); codeine (p. 40·2); ammonium chloride (p. 1656·1).
Bronchitis.

Radirex *Herbapol Wroclaw, Pol.*
Rhubarb (p. 1884·2).
Constipation; obesity.

Radite *Walker, Arg.*
Camellia sinensis (p. 2648·2).
Antoxidant.

Radite Plus *Walker, Arg.*
Camelia sinensis (p. 2648·2); vitamin E (p. 2119·1); vitamin C (p. 2110·3); selenium (p. 2086·3).
Dietary supplement.

Radivit *Molex Ayus, Indon.*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1).
Nutritional supplement.

Radix *Streuli, Switz.†*
Poultice: Aspirin (p. 22·2); ichthammol (p. 1705·3); chamomile (p. 2474·1); methyl salicylate (p. 92·1); mint oil (p. 2560·1); iodine (p. 2336·3).
Cold symptoms; musculoskeletal, joint, and soft-tissue disorders; burns; skin disorders.

Radol
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Dichloroxylenol (p. 1750·2); clorophene (p. 1748·3).
Disinfectant.

Pyridam, Indon.; One Pharma, Philipp.
Tramadol hydrochloride (p. 139·2).
Pain.

Rado-Salil *Will-Pharma, Belg.*
Ethyl salicylate (p. 56·3); methyl salicylate (p. 92·1); glycol salicylate (p. 66·2); salicylic acid (p. 1719·1); camphor (p. 2466·2); menthol (p. 2553·2); capsicum oleoresin (p. 2469·3).
Lumbago; musculoskeletal, joint, and soft-tissue disorders.

Radoso *Alapis, Gr.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Raductil *Abbott, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Radycodin *Yeni, Turk.*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); ephedrine (p. 1663·1).
Respiratory-tract congestion.

Radyn *Arlex, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastric hyperacidity.

Radyobarit *Yeni, Turk.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Radyobarit-Double Contrast *Yeni, Turk.*
Barium sulfate (p. 1583·2); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); simeticone (p. 1886·2).
Double contrast radiography.

Radyokodin *Radyum, Turk.*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); ephedrine (p. 1663·1).
Respiratory-tract disorders.

Rafacalcin *Rafarm, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Rafapen V-K *Rafa, Israel.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Rafapen Mega *Rafa, Israel.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial endocarditis prophylaxis; upper respiratory-tract infections.

Rafassal *Rafa, Israel.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Rafathricin with Benzocaine *Rafa, Israel.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Rafen *Alphapharm, Austral.; LCH, Hong Kong.†*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Rafen Plus *Alphapharm, Austral.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Inflammation; pain.

Rafex *Medley, Braz.*
Fexofenadine (p. 629·1).

Raffo-Ca *Raffo, Arg.*
Calcium citrate (p. 1783·2).
Osteoporosis.

Raffolutil *Raffo, Arg.*
Bicalutamide (p. 749·1).

Raffonin *Raffo, Chile.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis.

Raffreddoremed *Iodosan, Ital.*
⊗Paracetamol (p. 115·1); isopropamide iodide (p. 1848·3); dimetofrine hydrochloride (p. 1362·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Rafocilina *Raffo, Arg.*
Ofloxacin (p. 334·3).
Bacterial ear infections.

Rafofer *Raffo, Chile.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Rafonex *Steinbach, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Rafree *Reddy, Malaysia; Reddy, Philipp.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Raftace *Wockhardt, India.*
Oral liquid: Sodium alginate (p. 2167·3); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastro-oesophageal reflux; hiatus hernia; dyspepsia.

Wockhardt, India.
Tablets: Alginic acid (p. 2167·2); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux; hiatus hernia; dyspepsia.

Raft-Eze *Pinewood, UK.*
Sodium bicarbonate (p. 1781·1); sodium alginate (p. 2167·3); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux.

Rafton
Note: this name may be used for preparations of different composition.
Ferring, Fr.; Ferring, Ital.
⊗Budesonide (p. 1625·1).
Chronic diarrhoea associated with collagenous colitis; inflammatory bowel disease.

Ragaden *Ganassini, Ital.*
Cetylpyridinium chloride (p. 1743·1).
Nipple disinfection.

Ragex *AGIPS, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Ragonil *Masters, Ecuad.*
Benznidazole (p. 929·3).
Protozoal infections.

Rahistin *Kimia, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Raikar *Baldacci, Port.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Raikocef *Mediolanum, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Rain-LY *LKM, Arg.*
Biotin (p. 2052·2); dexpanthenol (p. 2582·2); salicylic acid (p. 1719·1).
Hair tonic.

Raivas *Dexa, Indon.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; cardiac arrest.

Raklam *Sigillata, Denm.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Ralcidin *Shreya, India.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold symptoms.

Ralenost *Ranbaxy, Cz.†; Ranbaxy, Thai.; Ranbaxy, Ukr.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ralenova *Meda, Ger.*
Mitoxantrone hydrochloride (p. 833·1).
Multiple sclerosis.

Ralexa *Platinum, Thai.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Ralfeen *Synthon, Cz.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Ralgec *IAE, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Ralgen *Zentiva, Hung.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ralgex *SSL, Irl.; SSL, UK.†*
Cream: Glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3); capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint disorders.

SSL, Irl.
Topical spray: Glycol salicylate (p. 66·2); ethyl salicylate (p. 56·3); methyl salicylate (p. 92·1); methyl nicotinate (p. 91·3).
Musculoskeletal and joint disorders.

SSL, UK.†
Topical stick: Glycol salicylate (p. 66·2); ethyl salicylate (p. 56·3); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3); menthol (p. 2553·2).
Musculoskeletal and joint disorders.

Ralgex Freeze Spray *SSL, UK.†*
Isopentane; dimethyl ether (p. 1798·3); glycol monosalicylate (p. 66·2).
Musculoskeletal and joint disorders.

Ralgex Heat Spray *SSL, Irl.*
Glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3).
Musculoskeletal and joint pain and stiffness.

Ralgex Heat Spray (low-odour) *SSL, UK.†*
Glycol monosalicylate (p. 66·2); methyl nicotinate (p. 91·3).
Musculoskeletal and joint disorders.

Raliks *Saba, Turk.*
Ramipril (p. 1483·3).

Ralinet *Coup, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Ralista *Cipla, India.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Ralivia *Valeant, Canad.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ralix *Cypress, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Ralizon *Panagiotis, Gr.*
Cetirizine hydrochloride (p. 619·2).

Ralnea *TAD, Ger.; Pharma-Regist, Hung.; Consilient, UK.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ralofekt *Temmler, Ger.†*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders; vascular disorders of the eye or ear.

RaloMeer *Synthon, Neth.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Ralopar *Sanofi-Aventis, Port.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Ralover *Synthon, Neth.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Ralovera *Pfizer, Austral.*
Medroxyprogesterone acetate (p. 2288·1).
Abnormal uterine bleeding; amenorrhoea; adjunct to oestrogen therapy; endometriosis; malignant neoplasms.

Raloxa *Synthon, Neth.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Raloxiep *Synthon, Irl.; Synthon, Neth.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

RaloxStar *Synthon, Neth.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Raloxten *Synthon, Neth.*
⊗Raloxifene hydrochloride (p. 2303·1).
Osteoporosis.

Ralozam *Pfizer, Austral.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Ralser *Serral, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Ralsifen-X *Serral, Mex.*
⊗Tamoxifen (p. 860·2).
Breast cancer.

Ralsin *CCM, Malaysia.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Raltiva *Rotam Reddy, China.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Raltone *Medochemie, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ralydan *EuroCept, Denm.; EuroCept, Ital.*
Lidocaine (p. 1988·1); tetracaine (p. 1996·3).
Local anaesthesia.

Ramace *Sanofi-Aventis, Austral.; Teva, Hung.; AstraZeneca, Mex.; AstraZeneca, S.Afr.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction; heart failure following myocardial infarction; diabetic nephropathy; myocardial infarction.

Ramace Plusz *Vera, Hung.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramadine *Apotex, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Ramadol *VS, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ramag *TP, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Zollinger-Ellison syndrome; gastro-oesophageal reflux; peptic ulcer.

Ramavit
Note: this name may be used for preparations of different composition.
Lumar, Philipp.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Ramazid H *Actavis, Rus.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramcor *Ipca, India.*
Ramipril (p. 1483·3).
Heart failure; hypertension.

Ramcor H *Ipca, India.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramend *Queisser, Ger.*
Senna (p. 1885·1).
Constipation.

Ramet Dalibour *Tradiphar, Fr.*
Copper sulfate (p. 2057·2); zinc sulfate (p. 2126·2).
Skin cleaning and disinfection.

Ramezol *Hanmi, China; Hanmi, Singapore.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ramgen *Bluepharma, Port.†*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy; cardiovascular risk reduction.

Rami *Sandoz, Ukr.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction.

Rami Compositum *Sandoz, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Rami Slijmoplossende *Chefaro, Neth.†*
Carbocisteine (p. 1658·1).
Cough.

Ramiad *Hexal, Denm.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Rami-Asomex *Actavis, Ukr.*
Levamlodipine besilate (p. 1304·1); ramipril (p. 1483·3).
Hypertension; diabetic nephropathy.

Ramic *Pinewood, Irl.*
Ramipril (p. 1483·3).
Nephropathy; heart failure; hypertension; myocardial infarction; cardiovascular risk reduction.

Ramicard *Stada, Cz.; AWD, Ger.†; Stada, Hung.; JB Chemicals, Thai.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction; nephropathy.

Ramicard Plus *AWD, Ger.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramicin *Westmont, Indon.†*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Ramicin-ISO *Westmont, Indon.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis; leprosy.

Ramiclair *Hennig, Ger.*
Ramipril (p. 1483·3).
Hypertension.

Ramiclair Plus *Hennig, Ger.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramicomp *Genericon, Austria.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramicor *Ranbaxy, Pol.*
Ramipril (p. 1483·3).
Heart failure; hypertension; myocardial infarction.

Ramicor Comb *Ranbaxy, Pol.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramicor D *Sanofi-Aventis, Port.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramicort *GMP, Indon.*
⊗Hydrocortisone (p. 1640·1); chloramphenicol (p. 257·1).
Ear disorders.

Rami-Dextromethorfan *Chefaro, Neth.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Ramieca *Biomedica, Ital.*
Ramipril (p. 1483·3).

Ramigamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.*
Ramipril (p. 1483·3).
Hypertension.

Ramigamma HCT *Worwag, Ger.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramihexal *Sandoz, Ukr.†*
Ramipril (p. 1483·3).
Hypertension; heart failure; diabetic nephropathy.

Ramihexal Compositum *Sandoz, Ukr.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramil *Zentiva, Cz.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction; nephropathy.

Ramil H *Zentiva, Cz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

RamiLich *Winthrop, Ger.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction; nephropathy.

RamiLich comp *Winthrop, Ger.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramilo *Rowex, Irl.*
Ramipril (p. 1483·3).
Heart failure; hypertension.

Ramiplus *Aliud, Ger.†; Stada, Ger.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipres *Pasteur, Chile; Cipla, India.*
Ramipril (p. 1483·3).
Heart failure; hypertension.

Ramipres H *Cipla, India.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipress HCT *Sigma, Braz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).

Ramipril comp *Betapharm, Ger.; Hexal, Ger.; Ratiopharm, Ger.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipril H *Actavis, Cz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipril HCT *Sandoz, Ger.†; Sanofi-Aventis, Switz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipril HCTad *TAD, Ger.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipril Plus *1A, Ger.†; Teva, Israel.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramipro *EuroHealth, Philipp.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction.

Rami-Q comp *Juta, Ger.†; Q-Pharm, Ger.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramiril *Micro, Thai.†*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Ramistada *Stada, Cz.†*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction.

Ramistos *Pasteur, Chile.*
⊗Codeine (p. 40·2); bromoform (p. 2460·3); belladonna (p. 2453·3); lobelia (p. 2323·2); drosera (p. 2497·2); grindelia (p. 2522·3).
Respiratory-tract disorders.

Ramitab-HCT *Generis, Neth.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramitace *Clonmel, Irl.*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction.

Ramitanid *Aliud, Ger.†*
⊗Ramipril (p. 1483·3); piretanide (p. 1470·3).
Hypertension.

Ramitens *Rafa, Israel.*
Ramipril (p. 1483·3).
Heart failure; hypertension; cardiovascular risk reduction.

Ramitens Plus *Rafa, Israel.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramitop *Pascual, Philipp.*
Tobramycin (p. 380·1).
Eye infections.

Ramitren *Ozone, Cz.†; GSK, Rus.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction; nephropathy.

Ramitrine *Ranbaxy, Mex.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Ramivan *Medipharm, Chile.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ramiwin *Zentiva, Hung.†; Sanofi-Aventis, S.Afr.*
Ramipril (p. 1483·3).
Hypertension; heart failure following myocardial infarction; diabetic nephropathy; heart failure; myocardial infarction; cardiovascular risk reduction.

Ramiwin HCT *Zentiva, Hung.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramixa Plus H *Ingers, Cz.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramixal *Sandoz, Indon.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction.

Ramixole *Actavis, Ital.*
Pramipexole (p. 911·2).

Ramizes Com *Farmak, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ramizes *Farmak, Ukr.*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction.

Ramlet *Rafarm, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ramno Fix *Piam, Ital.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus casei casei* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3) (p. 2596·3); zinc (p. 2126·1); vitamin B substances (p. 2102·3).
Digestive disorders.

Ramnoflor Plus *Piam, Ital.*
Lactic-acid-producing organisms (p. 2596·3); zinc (p. 2126·1); fructo-oligosaccharides (p. 2508·1); vitamin B substances (p. 2102·3).
Restoration of gastrointestinal flora.

Ramoclav *Ranbaxy, Pol.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ramol *Nakornpatana, Thai.*
Paracetamol (p. 115·1).
Pain.

Rampil *Aspen, S.Afr.*
Ramipril (p. 1483·3).
Hypertension; heart failure following myocardial infarction; diabetic nephropathy; cardiovascular risk reduction.

Ramses *Durex, Canad.†*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Ramtace *Unison, Thai.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; nephropathy; cardiovascular risk reduction.

Ramtrex *Ashford, Philipp.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections.

Ramve *Farma-Projekt, Pol.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Ramy CE *Grin, Mex.*
Ascorbic acid (p. 2110·3).

Ramyte *Actavis, Irl.†*
Ramipril (p. 1483·3).
Hypertension; heart failure; nephropathy; cardiovascular risk reduction.

Ran Lich *Winthrop, Ger.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranacox *MSD, Belg.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; gout; pain.

Ranae *Umedica, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranamp *Ranbaxy, S.Afr.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Ranbapril *Ranbaxy, Hung.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Rancef *Ranbaxy, Austral.*
Cefalexin (p. 234·1).
Bacterial infections.

Ranceph *Ranbaxy, S.Afr.*
Cefalexin (p. 234·1).
Bacterial infections.

Rancif *Daiichi Sankyo, Mex.; Sel-J, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Rancil *Ranbaxy, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ran-Citalo *Ranbaxy, Canad.*
Citalopram hydrobromide (p. 411·1).
Depression.

Ranclav *Ranbaxy, Rus.; Ranbaxy, S.Afr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ranbaxy, Thai.
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ranclazide *Ranbaxy, Thai.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Ranclor *Daiichi Sankyo, Mex.*
Cefaclor (p. 232·3).
Bacterial infections.

Rancor *Ranbaxy, Cz.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Rancotrim *Ranbaxy, Rus.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Rancus *Mersifarma, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Randa *Kayaku, Jpn.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Randac *Bright Future, Hong Kong.†*
Ranitidine (p. 1882·1).

Randex *Randall, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Randin *Pasteur, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Randine *Greenpharma, Braz.*
Ranitidine (p. 1882·1).

Randism *Ranbaxy, Mex.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Randronate *Ranbaxy, Neth.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Randum *Teofarma, Ital.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Raneks *Bilim, Turk.*
Rabeprazole sodium (p. 1881·1).

Ranepal *Liferpal, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Ranexa *Menarini, Austria; Menarini, Cz.; Berlin-Chemie, Ger.; Menarini, Gr.; Menarini, Irl.; Neopharm, Israel; Menarini, Neth.; Menarini, Pol.; Menarini, Port.; Menarini, Spain; Menarini, Switz.; Menarini, UK; Gilead, USA.*
Ranolazine (p. 1484·3).
Angina pectoris.

Ranfast *Ranbaxy, Mex.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Ranfaxiran *Ranbaxy, Cz.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Ranfen *Ranbaxy, S.Afr.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; fever; pain.

Ranferon-12 *Ranbaxy, Ukr.*
Capsules: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2).
Iron-deficiency anaemia; iron and folic acid deficiency.

Ranbaxy, Ukr.†
Elixir: Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron-deficiency anaemia; iron and folic acid deficiency.

Ranflocs *Ranbaxy, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Ranflu *Ranbaxy, Mex.†*
Fluconazole (p. 578·2).
Fungal infections.

Rangabax *Ranbaxy, Irl.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Rangimet G *Ranbaxy, Mex.*
Metformin (p. 489·1); glimepiride (p. 473·2).
Diabetes mellitus.

Rangin *Novartis, Hung.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Rangyn *Ranbaxy, Mex.†*
Clotrimazole (p. 576·2).

Rani 2 *Alphapharm, Austral.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Raniben *FIRMA, Ital.*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Raniberl *Berlin-Chemie, Ger.†; Berlin-Chemie, Pol.; Menarini, Pol.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Ranibeta *Betapharm, Ger.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; gastrointestinal haemorrhage.

Ranibloc *Glaxo Allen, Ital.; Behrens, Venez.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastrointestinal hyperacidity; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Raniblok *Hexal, Braz.*
Ranitidine (p. 1882·1).

Ranic *Hexal, Austria; Sandoz, Pol.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Ranicare *Nicholas, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Ranicel *Laboratorios Chile, Chile.†*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastric hyperacidity.

Ranicid *M & H, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Raniclon *Sandoz, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Raniclor
Note: this name may be used for preparations of different composition.
Cifarma, Braz.†
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranbaxy, USA.†
Cefaclor (p. 232·3).
Bacterial infections.

Ranicodan *Pharmacodane, Denm.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer.

Ranicur *Merck, Fin.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ranicux *TAD, Ger.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage.

Ranid
Note: this name may be used for preparations of different composition.
Stada, Denm.
⊗Hydrochlorothiazide (p. 1403·2); ramipril (p. 1483·3).
Hypertension.

TMan, Thai.
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ranidex *OFF, Ital.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Ranidil *Menarini, Ital.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; peptic ulcer gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ranidin *Uniao Quimica, Braz.; Faes, Spain.†*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration; gastric hyperacidity.

Ranidina *Bunker, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranidine *Greenpharma, Braz.†; Christo, Hong Kong†; Biolab, Singapore.*
Ranitidine (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration.

Biolab, Thai.
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranifarm *Continentales, Mex.*
Ranitidine (p. 1882·1).
Gastric hyperacidity; peptic ulcer.

Raniflex *Royton, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranifur *Teva, Mex.*
Ranitidine (p. 1882·1) or ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Ranigast *Polpharma, Pol.; Polpharma, Rus.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; gastrointestinal haemorrhage; Zollinger-Ellison syndrome; dyspepsia; heartburn.

Raniger *Streger, Mex.*
Ranitidine (p. 1882·1).

Ranihexal *Sandoz, Austral.†; Hexal, S.Afr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ranil
Note: this name may be used for preparations of different composition.
Faran, Gr.
Verapamil hydrochloride (p. 1522·1).

Ranilex *Molex Ayus, Indon.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Ranimax *Teva, Pol.*
Ranitidine (p. 1882·1).
Dyspepsia; heartburn; hyperacidity.

Ranimed *Lamsa, Arg.; Sandoz, Switz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hyperacidity; gastrointestinal haemorrhage; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ranimex *Orion, Fin.†*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ranin *Pharos, Indon.; Umeda, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders; Zollinger-Ellison syndrome; acid aspiration.

Rani-nerton *Dolorgiet, Ger.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; gastrointestinal haemorrhage.

Raninorm *Genericon, Austria.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal bleeding.

Raniplex *Abbott, Fr.; Remedica, Hong Kong.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastrointestinal haemorrhage; acid aspiration.

Raniprotect *Riemser, Ger.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; gastrointestinal haemorrhage.

Rani-Puren *Actavis, Ger.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; gastrointestinal haemorrhage.

Rani-Q *Mylan, Swed.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; heartburn.

Ranisan *ProMed, Cz.; Sandoz, Fin.; Kopran, Philipp.; ProMed, Pol.; Promed, Rus.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; dyspepsia; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; gastric hyperacidity.

Ranisen *Senosiain, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Ranit *Be-Tabs, S.Afr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration.

Ranitab *Sel-J, Philipp.; Deva, Turk.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Ranitac *Sinochem, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranital *Lek, Cz.; Sandoz, Hong Kong.*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ranitalis *Pan-Ject, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitax *Saval, Chile.†*
Ranitidine (p. 1882·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitein *Steinbach, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ranitic *Investi, Arg.†; Hexal, Austral.†; Hexal, Ger.†; Hexal, Hung.; Rowex, Irl.; Tillomed, UK.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; heartburn; gastrointestinal haemorrhage.

Ranitidoc *Docpharm, Ger.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastrointestinal haemorrhage.

Ranitil *EMS, Braz.; Tillomed, UK.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Ranitimed *Ranbaxy, Belg.†*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pyrosis.

Ranitin *Prodotti, Braz.†; Torrent, Pol.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitine *Azevedos, Port.; Torrent, Rus.; Biofarma, Turk.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Ranitinol *Ducto, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranition *Sanval, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranitral *Austral, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Ranitrat *Cazi, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranitul *Oriental, Arg.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Ranit-VC *Vesco, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Ranivell *Novell, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Raniver *Biosel, Turk.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranivint *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranixal *Ratiopharm, Fin.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ranizac *Pharmanel, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ranketo *Ranbaxy, Mex.†*
Ketorolac (p. 80·2).

Ran-Levo *Ranbaxy, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Ranloc *Ranbaxy, Pol.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranlol *Ranbaxy, Malaysia.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ranlosin *Lek, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Ranmark *Daiichi Sankyo, Jpn.*
Denosumab (p. 1182·1).
Bone metastases.

Ranmino *Ranbaxy, Mex.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Ranmoxy *Ranbaxy, Austral.; Ranbaxy, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ranobel *Nobel, Turk.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranocalcin HM *Pfluger, Ger.*
Acid. silicium (p. 2208·3); calcium carbonicum (p. 1824·3); calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); ferrum phosphoricum (p. 2077·1); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Ranofren *Adamed, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ranolta *Jean-Marie, Hong Kong.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranomax *Apotex, Belg.; Ranbaxy, Denm.; Biogen, Gr.; Labormed, Hung.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Ranopine *Ranbaxy, Irl.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranopril *Ranbaxy, Malaysia; Ranbaxy, Pol.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Ranoprin *Ratiopharm, Fin.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hyperthyroidism; essential tremor; migraine; hypertension; myocardial infarction; hypertrophic obstructive cardiomyopathy; glaucoma; phaeochromocytoma; portal hypertension.

Ranoprost *Ranbaxy, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Ranostop *Phytopharm, Ukr.*
Povidone-iodine (p. 1767·1).
Skin and wound disinfection; fungal and bacterial skin infections.

RanoTroc *ST, Thai.†*
Clotrimazole (p. 576·2).
Oropharyngeal candidiasis.

Ranoxyl
Note: this name may be used for preparations of different composition.
Ascent, Austral.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Ranbaxy, Hong Kong†; Ranbaxy, Rus.; Ranbaxy, Thai.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ranozol *ST, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Ranperidon *Ranbaxy, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Ranplasia *Rowfarma, Mex.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Ranpres *Ranbaxy, Mex.*
Captopril (p. 1331·2).

Ranselex *Ranbaxy, Ukr.*
Celecoxib (p. 36·3).
Rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Ransetron *Ranbaxy, Pol.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Ransim *Ranbaxy, Austral.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Ranstar *Ranbaxy, Mex.†*
Stavudine (p. 1015·3).
HIV infection.

Ransulin 70/30 *Tonghua Dongbao, Philipp.*
⊗Mixture of isophane insulin 70% (human) and insulin injection 30% (human) (p. 475·3).
Diabetes mellitus.

Ransulin-N *Tonghua Dongbao, Philipp.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Ransulin-R *Tonghua Dongbao, Philipp.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Rantac *JB Chemicals, India; Unique, Rus.; Medicine Products, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity; dyspepsia; gastrointestinal haemorrhage; acid aspiration.

Rantag *Julphar, UAE.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; pathological hypersecretory disorders; gastrointestinal haemorrhage; acid aspiration.

Rantaksym *Ranbaxy, Pol.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Rantec *Berk, UK.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; dyspepsia; acid aspiration; gastrointestinal haemorrhage.

Rantex *Biotech, Venez.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Ranthrocin *Ranbaxy, Singapore.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections of the respiratory tract.

Ranticid *Kimia, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Pathological hypersecretory disorders; peptic ulcer.

Rantin *Kalbe, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders; gastro-oesophageal reflux.

Rantizec *Ildong, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rantodine *Utopian, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Rantopir *Ranbaxy, Ukr.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Rantral *Ranbaxy, S.Afr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Rantudal *Meda, Gr.*
Acemetacin (p. 16·3).
Pain; inflammation; musculoskeletal disorders; spondyloarthritis; gout.

Rantudil *Bayer, China; Meda, Cz.†; Meda, Ger.; Meda, Hung.; Kowa, Jpn; Bayer, Mex.; Bayer, Philipp.†; Bayer, Pol.; Bialfar, Port.; Bayer, Turk.*
Acemetacin (p. 16·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; gout; thrombophlebitis; vasculitis; pain; fever.

Ranuber *Meda, Spain.†*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranulin *Pisa, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ranunculus Complexe No 79 *Lehning, Fr.*
Ranunculus; rhododendron ferrugineum; ruta graveolens (p. 2608·2); aconitum (p. 2428·3); bryonia (p. 2461·3); gelsemium (p. 2511·2); colocynthis (p. 1833·3); terebinthina; gnaphalium dioicum.
Homoeopathic preparation.

Ranvir *Ranbaxy, Cz.†; Ranbaxy, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ranvor *Ranbaxy, Mex.†*
Simvastatin (p. 1489·2).

Ranzac *LPC, UK.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastric hyperacidity; heartburn.

Ranzepam *Ranbaxy, Austral.*
Diazepam (p. 1063·2).
Anxiety disorders; skeletal muscle spasm; alcohol withdrawal syndrome.

Ranzol *Ranbaxy, S.Afr.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Raoloz *Genetic, Ital.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Rap Phyto *IPRAD, Fr.*
Cream: Scoparium (p. 2611·3); arnica (p. 2447·2); lavandula angustifolia; aesculus (p. 2431·2).
Venous insufficiency.

IPRAD, Fr.
Topical gel: Empetrum nigrum; butcher's broom (p. 2463·1); aesculus (p. 2431·2).
Venous insufficiency.

Rapacholin AC *Herbapol Wroclaw, Pol.†*
Activated charcoal (p. 1537·3); cynara (p. 2490·3); raphanus sativum; artemisia abrotanum.
Gallbladder and liver disorders; constipation.

Rapacholin C *Herbapol Wroclaw, Pol.*
Activated charcoal (p. 1537·3); cynara (p. 2490·3); dehydrocholic acid (p. 2492·1); mint oil (p. 2560·1); raphanus sativum.
Gallbladder and liver disorders; digestive disorders.

Rapacholin Forte *Herbapol Wroclaw, Pol.*
Dehydrocholic acid (p. 2492·1); raphanus sativum; mint oil (p. 2560·1).
Bile deficiency; dyspepsia; constipation.

Rapaflo *Watson, Canad.; Watson, USA.*
Silodosin (p. 2367·2).
Benign prostatic hyperplasia.

Rapaid *Rye, Singapore.*
Cream; topical spray: Melaleuca oil (p. 2551·1).
Skin irritation.

Rye, Singapore.
Topical powder: Melaleuca oil (p. 2551·1); corn starch; zinc oxide (p. 1729·1).
Skin irritation.

Rapaid Itch Relief *McGloins, Austral.*
Melaleuca oil (p. 2551·1).
Bites; minor wounds; skin infections; skin irritation; stings.

Rapaid Rash-Relief *McGloins, Austral.*
Melaleuca oil (p. 2551·1); aloe vera (p. 1693·2).
Skin irritation.

Rapako comp *Truw, Ger.*
Teucrium marum; hydrastis canadensis (p. 2528·1); chamomilla recutita (p. 2474·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Rapako xylo *Truw, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis.

Rapamune *Wyeth, Arg.; Pfizer, Austral.; Wyeth Lederle, Austria; Pfizer, Belg.; Wyeth, Braz.; Pfizer, Canad.; Wyeth, Chile; Pfizer, China; Wyeth, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Wyeth, Gr.; Pfizer, Hong Kong; Wyeth, Hung.; Wyeth, India; Wyeth, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Rus.; Pfizer, S. Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK; Wyeth-Ayerst, USA; Wyeth, Venez.*
Sirolimus (p. 1966·2).
Renal transplant rejection.

Rapesples *Specifar, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rap-eze *Roche Consumer, UK.*
Calcium carbonate (p. 1824·3).
Dyspepsia; heartburn.

Raphachol *Parma, Hung.*
Raphanus sativus.
Digestive disorders.

Rapiacta *Shionogi, Jpn.*
Peramivir (p. 1009·1).
Influenza.

Rapi-Betacort *Cassara, Arg.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Rapiclav *Aspen, Mex.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ipca, Rus.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ipca, Thai.
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Rapicort *Pharmis, Port.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Rapid Action *Arrow, Canad.*
Paracetamol (p. 115·1).
Fever; pain.

Rapid B-12 Energy *Mason, USA.*
Cyanocobalamin (p. 2107·2).

Rapid Strand *Amersham, Austral.†*
Iodine-125 (p. 2225·2) titanium capsules welded into a silver rod.
Prostatic cancer.

Rapidax *Ashford, Philipp.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Infected ear disorders.

Rapidex *Medilife, Philipp.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Rapi-Dexacort *Cassara, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Rapidica *Piramal, India.*
⊗Neutral insulin injection (porcine, highly purified) (p. 475·3).
Diabetes mellitus.

Rapidin *Danlex, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Rapido *Sedico, Rus.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Rapidocaine *Sintetica, Switz.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline hydrochloride (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Arrhythmias; local anaesthesia.

Rapidol
Note: this name may be used for preparations of different composition.
Pfizer, Chile; Ranbaxy, Malaysia; Pasteur, Philipp.; Ranbaxy, Singapore; Actavis, Ukr.
Paracetamol (p. 115·1).
Pain; fever.
Pharmonta, Austria.
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

RapidVue *Quidel, USA.*
Pregnancy test (p. 2596·1).

Rapifast *Innovact, Gr.*
Losartan potassium (p. 1422·2).
Hypertension.

Rapifen *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.†; Janssen-Cilag, Irl.; Janssen-Cilag, Israel†; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Johnson & Johnson, Turk.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
⊗Alfentanil hydrochloride (p. 18·2).
Induction of general anaesthesia; adjuvant in anaesthesia; general anaesthesia; pain in ventilated patients; analgesia during anaesthesia.

Rapignost Basic Screen Plus *Advance Diagnostic, Irl.†*
Test for ascorbic acid, glucose, protein, blood, pH, and nitrites in urine.

Rapignost Diabetes Profile *Advance Diagnostic, Irl.†*
Test for ketones, ascorbic acid, and glucose in urine.

Rapignost Total Screen LSG *Advance Diagnostic, Irl.†*
Test for bilirubin, urobilinogen, pH, glucose, protein, ketones, blood, nitrite, ascorbic acid, leucocytes, and specific gravity in urine.

Rapilax *Merck Serono, Arg.; Hertz, Braz.*
Sodium picosulfate (p. 1887·2).
Constipation.

Rapilax Fibras *Merck, Arg.*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation.

Rapilazole *Actavis, Pol.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rapilin *Sun, India.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Rapilose *Aspire, UK.*
Glucose (p. 2068·3).
Hypoglycaemia; glucose tolerance test.

Rapilysin *Actavis, Austral.; Actavis, Austria; Roche, Belg.; Actavis, Cz.; Actavis, Denm.; Actavis, Fin.; Actavis, Fr; Actavis, Ger.; Actavis, Gr.; Actavis, Hong Kong; Actavis, Irl.; Actavis, Ital.; Actavis, Neth.; Actavis, Norw.; Healthcare Logistics, NZ; Roche, Pol.; Actavis, Port.; Roche, Singapore; Actavis, Spain; Actavis, Swed.; Actavis, Switz.; Fako, Turk.; Roche, UK.*
Reteplase (p. 1486·2).
Myocardial infarction; thrombosis; pulmonary embolism.

Rapime *Fahrenheit, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Rapimig *Actavis, Ukr.*
Zolmitriptan (p. 682·2).
Migraine.

Rapimix *Piramal, India.*
⊗A mixture of insulin injection (porcine, highly purified) 30% and isophane insulin (porcine, highly purified) 70% (p. 475·3).
Diabetes mellitus.

Rapiqure *Brown & Burk, Philipp.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Rapiscan *Rapidscan, Denm.; Rapidscan, Irl.; Rapidscan, Neth.; Gilead, Pol.; Gilead, Port.; Rapidscan, UK.*
Regadenoson (p. 1485·2).
Stress testing in myocardial perfusion imaging.

Rapither-AB *Ipca, India.*
Alpha-beta arteether (p. 648·1).
Malaria.

Rapitil *Sanofi-Aventis, UK.*
Nedocromil sodium (p. 1216·2).
Allergic conjunctivitis; keratoconjunctivitis.

Rapitram *Sun, Braz.*
Tramadol (p. 139·2).
Pain.

Rapivir *GSK, Mex.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Rapix *Senosiain, Mex.*
Ketorolac (p. 80·2).
Pain.

Rapolyte *Helsinn Birex, Irl.†; koGen, UK.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Raponer *Actavis, UK.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Raporsin *Actavis, Irl.; Actavis, UK.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Rapoxol *Sandoz, Cz.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rappell *Chefaro, UK.*
Piperonal (p. 2160·2).
Head lice repellent.

Rapten *Hemofarm, Ukr.*
Diclofenac (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rapten Duo *Hemofarm, Rus.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Rapten Rapid *Hemofarm, Rus.*
Diclofenac potassium (p. 48·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Raptiva *Serono, Arg.; Serono, Austral.†; Serono, Austria†; Serono, Braz.†; Serono, Canad.†; Serono, Cz.†; Serono, Denm.†; Serono, Fin.†; Merck-Lipha, Fr.†; Serono, Ger.†; Serono, Gr.†; Serono, Hong Kong†; Serono, Irl.†; Serono, Israel; Serono, Ital.†; Serono, Malaysia†; Serono, Mex.†; Serono, Neth.†; Serono, Norw.†; Healthcare Logistics, NZ; Serono, Port.†; Serono, Rus.; Merck, Singapore†; Merck, Spain†; Serono, Swed.†; Merck, Switz.†; Serono, Turk.; Serono, UK†; Genentech, USA.†*
Efalizumab (p. 1702·2).
Psoriasis.

Raptor *Meditrina, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Rapura *Tentan, Switz.*
Peru balsam (p. 2587·1); camphor (p. 2466·2); thymol (p. 1772·2); zinc oxide (p. 1729·1).
Minor skin lesions.

Rapydan *OPi, Fr.†; EuroCept, Gr.; EuroCept, Irl.; EuroCept, Neth.; EuroCept, Norw.; EUSA, Port.; EuroCept, Swed.; EUSA, UK.†*
Lidocaine (p. 1988·1); tetracaine (p. 1996·3).
Local anaesthesia.

Rapyden *EuroCept, Cz.*
Lidocaine (p. 1988·1); tetracaine (p. 1996·3).
Local anaesthesia.

Raquiferol *Roemmers, Arg.*
Ergocalciferol (p. 2113·3).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; vitamin D deficiency; rickets; hypophosphataemia.

Raquiferol D3 *Roemmers, Arg.*
Calcitriol (p. 2113·1).
Hypocalcaemia.

Raquitriol *Spedrog, Arg.*
Calcitriol (p. 2113·1).
Osteomalacia; renal osteodystrophy; hypoparathyroidism; pseudohypoparathyroidism; rickets.

Rarical *Janssen-Cilag, Braz.*
Vitamins; minerals.

Raricap *Haldane, Singapore.*
Calcium ferrous citrate (p. 2053·1); folic acid (p. 2063·1).
Iron-deficiency anaemia.
Johnson & Johnson, India.
Calcium (p. 1783·1); folic acid (p. 2063·1); iron (p. 2073·1).
Formerly contained calcium ferrous citrate, folic acid, vitamin B2, vitamin B6, and vitamin B12.
Iron-deficiency anaemia.

Raricap Combi *Haldane, Singapore.*
Red tablets, calcium ferrous citrate (p. 2053·1); folic acid (p. 2063·1); pink tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); magnesium hydroxide (p. 1857·2); zinc sulfate (p. 2126·2).
Calcium supplement in pregnancy and lactation; iron-deficiency anaemia.

Raricap L *Johnson & Johnson, India.*
Calcium (p. 1783·1); folic acid (p. 2063·1); iron (p. 2073·1).
Formerly contained calcium ferrous citrate, vitamin A palmitate, colecalciferol, vitamin B1, vitamin B2, nicotinamide, and lysine hydrochloride.
Iron-deficiency anaemia.

Rarozol *AMPDR, Port.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Rasax *AstraZeneca, Arg.*
Rasagiline mesilate (p. 912·3).
Parkinson's disease.

Rasec
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.
Pentafarma, Port.†
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Raset *Unison, Thai.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Rashfree *Pediatrica, Philipp.*
Zinc oxide (p. 1729·1).
Skin irritation; haemorrhoids.
Pfizer, India.
Benzalkonium chloride (p. 1737·1); zinc oxide (p. 1729·1).
Skin disinfection; nappy rash.

Rasilamlo *Novartis, Cz.; Novartis, Irl.; Novartis, Neth.*
Amlodipine besilate (p. 1304·1); aliskiren fumarate (p. 1295·3).
Hypertension.

Rasilez *Novartis, Arg.; Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.; Novartis, Fr.; Novartis, Ger.; Novartis, Hung.; Novartis, Irl.; Novartis, Ital.; Novartis, Neth.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, UK.*
Aliskiren fumarate (p. 1295·3).
Hypertension.
Novartis, Braz.; Novartis, Chile; Novartis, China; Novartis, Denm.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Israel; Novartis, Malaysia; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.; Novartis, Ukr.
Aliskiren (p. 1295·3).
Hypertension.

Rasilez D *Novartis, Arg.; Novartis, Chile.*
⊗Aliskiren (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Rasilez HCT *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.†; Novartis, Fr.; Novartis, Ger.; Novartis, Irl.; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.*
⊗Aliskiren fumarate (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.
Novartis, Gr.
⊗Aliskiren (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Rasilles *Novartis, Mex.*
Aliskiren (p. 1295·3).
Hypertension.

Rasine *Q-Pharma, Arg.*
Polypodium leucotomos.
Psoriasis; vitiligo.

Rasitol *YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema; oliguria.

Rasitrio *Novartis, Irl.; Novartis, Neth.; Novartis, Swed.†*
⊗Aliskiren fumarate (p. 1295·3); hydrochlorothiazide (p. 1403·2); amlodipine besilate (p. 1304·1).
Hypertension.

Rasoltan *Actavis, Hung.; Actavis, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure.

Raspberry-Lemonade Blast *Blistex, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Raspisons *Sons, Mex.*
Neomycin (p. 329·3); vitamin A (p. 2098·3).
Bacterial skin infections.

Raspon *Diapit, Gr.*
Isopropamide iodide (p. 1848·3).

Rasputin *Young Il, Singapore.*
Calcitriol (p. 2113·1).
Hyperparathyroidism; rickets; hypoparathyroidism.

Rastan *Farmstandart, Rus.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure.

Rastinon *Aspen, Austral.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Mex.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Rastocin *Pliva Krakow, Pol.†; Pliva, Rus.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Ratacand *AstraZeneca, Ital.; Euro Registratie, Neth.†*
Candesartan cilexetil (p. 1330·2).
Hypertension; left-ventricular dysfunction; heart failure.

Ratacand Plus *SinGad, Denm.; AstraZeneca, Ital.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ratacand Zid *Orifarm, Denm.†*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ratan *Ethica, Indon.*
Ranitidine (p. 1882·1).
Duodenal ulcer; pathological hypersecretory disorders.

Ratanhia comp *Weleda, Ger.†*
Myrrh (p. 2566·1); rhatany root (p. 2603·3); aesculus (p. 2431·2); argentum nitricum (p. 2615·3); fluorit; kieserit; ol fl. caryophylli; ol eucalypti; ol lavandulae; ol menthae pip; ol salviae off.
Mouth disorders.

Ratax *Pyridam, Indon.*
Ginseng (p. 2513·3); cordyceps sinensis; epimedii; vitamin E acetate (p. 2119·2); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).
Tonic.

Rati Salil Crema *Gramon, Arg.; Sanofi-Aventis, Arg.*
Amyl salicylate (p. 21·2); camphor (p. 2466·2); turpentine oil (p. 2636·3); salicylic acid (p. 1719·1); capsaicin (p. 35·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rati Salil D *Gramon, Arg.; Sanofi-Aventis, Arg.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rati Salil Flex *Gramon, Arg.; Sanofi-Aventis, Arg.*
Salicylic acid (p. 1719·1); diethylamine salicylate (p. 51·3); capsaicin (p. 35·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Rati Salil Gel *Gramon, Arg.; Sanofi-Aventis, Arg.*
Methyl salicylate (p. 92·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Rati Salil Ice *Gramon, Arg.; Sanofi-Aventis, Arg.*
Menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rati Salil Pro *Gramon, Arg.; Sanofi-Aventis, Arg.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ratic *Atlantic, Singapore; Atlantic, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ratica *LBS, Thai.*
Ranitidine (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer.

Raticina *Bernabo, Arg.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ratinal *Gracia, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

ratio-Aclavulanate *Ratiopharm, Canad.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ratioalerg *Ratiopharm, Spain.†*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

ratioAllerg
Note: this name may be used for preparations of different composition.
Ratiopharm, Ger.
Nasal spray: ⊗Beclometasone dipropionate (p. 1621·2).
Hay fever.
Ratiopharm, Austria.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

ratio-Calmydone *Teva, Canad.*
⊗Hydrocodone tartrate (p. 67·2); etafedrine hydrochloride (p. 1665·2); doxylamine succinate (p. 627·3).
Cough.

ratio-Coristex-DH *Ratiopharm, Canad.*
Phenylephrine hydrochloride (p. 1672·3); hydrocodone tartrate (p. 67·2).
Cough.

ratio-Cotridin *Teva, Canad.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

ratio-Cotridin Expectorant *Teva, Canad.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Ratiodol *Ratiopharm, Spain.†*
Ibuprofen (p. 68·2).
Pain; fever; inflammation; musculoskeletal, joint, and soft-tissue disorders.

ratioDolor *Ratiopharm, Austria.*
Ibuprofen lysine (p. 68·3).
Pain.

ratio-Ectosone *Teva, Canad.*
⊗Betamethasone valerate (p. 1624·1).
Skin and scalp disorders.

ratio-Emtec *Teva, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; cold symptoms; upper respiratory-tract disorders.

Ratiofemin *Ratiopharm, Spain.†*
Soya (p. 2092·3).
Menopausal disorders.

Ratiogel *Ratiopharm, Pol.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ratiograstim *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Denm.†; Ratiopharm, Fr.; Ratiopharm, Ger.; Ratiopharm, Hung.; Ratiopharm, Irl.; Ratiopharm, Ital.; Ratiopharm, Neth.; Ratiopharm, Norw.; Ratiopharm, Pol.; Ratiopharm, Port.; Ratiopharm, Spain; Ratiopharm, Swed.; Ratiopharm, UK.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Ratiogrip *Ratiopharm, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

ratio-Hemcort-HC *Teva, Canad.*
⊗Hydrocortisone acetate (p. 1640·1); zinc sulfate (p. 2126·2).
Anorectal disorders.

ratio-Ipra Sal *Teva, Canad.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

ratio-Lenoltec No 4 *Teva, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

ratio-Lenoltec No 1, No 2, No 3 *Teva, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Fever; pain.

Ratiomir *Ratiopharm, Spain.†*
Valerian (p. 2640·2).
Nervous disorders; insomnia.

Ratiomucol *Ratiopharm, Spain.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Rationale *Manetti Roberts, Ital.*
Colextran hydrochloride (p. 1347·1).
Hyperlipidaemias.

ratio-Oxycocet *Teva, Canad.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

ratio-Oxycodan *Teva, Canad.*
⊗Oxycodone hydrochloride (p. 113·1); aspirin (p. 22·2).
Pain.

Ratioparch *Ratiopharm, Spain.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, peri-articular, and soft-tissue pain.

Ratiopharmeva *Ratiopharm, Belg.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgenisation in females.

ratio-Proctosone
Note: this name may be used for preparations of different composition.
Teva, Canad.
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone acetate (p. 1640·1); framycetin sulfate (p. 301·2); esculoside (p. 2431·2).
Anorectal disorders.

Ratiopyrin *Ratiopharm, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

RatioSoft *Ratiopharm, Austria.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis.

ratio-Tecnal *Teva, Canad.*
Butalbital (p. 1043·3); caffeine (p. 1203·3); aspirin (p. 22·2).
Tension; pain.

ratio-Tecnal C *Teva, Canad.*
Butalbital (p. 1043·3); caffeine (p. 1203·3); aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; tension.

ratio-Theo-Bronc *Ratiopharm, Canad.*
Guaifenesin (p. 1666·2); potassium iodide (p. 2336·3); theophylline (p. 1229·3); mepyramine maleate (p. 635·1).
Obstructive airways disease.

ratio-Topilene *Teva, Canad.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

ratio-Topisalic *Teva, Canad.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders; keratinisation disorders.

ratio-Topisone *Teva, Canad.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

ratio-Triacomb *Teva, Canad.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Infected skin disorders.

Raudil *Novag, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastrointestinal haemorrhage; acid aspiration; dyspepsia.

Raunatine *Tomskhimfarm, Rus.*
Rauwolfia serpentina (p. 1485·1).
Hypertension.

RauwolfiaViscomp *Schuck, Ger.*
Rauwolfia serpentina (p. 1485·1); viscum album (p. 2560·2); allium sativum (p. 2510·3); barium chloratum (p. 2452·3); crataegus (p. 2488·1); equisetum arvense (p. 2500·1).
Homoeopathic preparation.

Ravalgen
Note: this name may be used for preparations of different composition.
Tecnofarma, Chile.
Clopidogrel (p. 1342·3).
Atherosclerosis.

Ravalton *Rafarm, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ravamil *Merck, S.Afr.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; arrhythmias.

Ravata *Heaton, Cz.*
⊗Buprenorphine hydrochloride (p. 30·3).
Opioid withdrawal syndrome.

Ravel *KRKA, Ukr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Ravenol *Mylan, Ital.*
Sulodexide (p. 1507·3).
Thrombotic disorders.

Ravicti *Hyperion, USA.*
Glycerol phenylbutyrate (p. 2518·3).
Urea cycle disorders.

Ravimed *CCM, Malaysia.*
Medroxyprogesterone acetate (p. 2288·1).
Amenorrhoea; dysfunctional uterine bleeding; breast cancer; hormone replacement therapy; renal cell carcinoma; endometriosis; endometrial cancer.

RaVita *Combiphar, Indon.*
Vitamin C (p. 2110·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); L-lysine (p. 2079·3).
Appetite supplement for children.

Ravivo *Drogsan, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Ravona *Mitsubishi Tanabe, Jpn.*
Pentobarbital calcium (p. 1095·1).
Sedative; insomnia; premedication.

Ravostan *Santa, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Ravotaf *Mayo, Mex.*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract disorders.

Ravotril *Roche, Chile.*
Clonazepam (p. 519·1).
Anxiety; epilepsy; panic attacks; social phobia.

Raw Prostate *NaturalLife, Arg.*
Prostate extract (p. 2444·1).
Dietary supplement.

Rawel *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Port.; KRKA, Rus.*
⊗Indapamide (p. 1409·2).
Hypertension.

Raxenol *Mavi, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Inflammation; pain; fever.

Raxeto *Dosa, Arg.*
⊗Raloxifene (p. 2303·1).
Osteoporosis.

Raxibacumab Injection *GSK, USA.*
Raxibacumab (p. 2415·1).
Anthrax.

Raxicam *Unison, Philipp.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Raxide *GX, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Raxim *Nanxin, China.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Raxsoma *SSP, Thai.†*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Skeletal muscle spasm.

Raxtan *Sanovel, Rus.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Raxtane *Sanovel, Turk.*
Rofecoxib (p. 128·3).
Osteoarthritis; rheumatoid arthritis; pain.

Ray Block *Del-Ray, USA.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Raycept *Zambon, Port.*
Calcium levofolinate (p. 2067·1).
Anaemias; methotrexate toxicity.

Raylis *Promo-Med, Rus.*
Ginseng (p. 2513·3); false ginseng; codonopsis pilosula; astragalus (p. 2451·1); epimedium.
Erectile dysfunction.

Rayonfur *Materforma, Port.*
Nitrofurazone (p. 333·1).
Infected burns, ulcers, and wounds; skin disinfection.

Rayos *Horizon, USA.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Raypid *Rayere, Mex.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Rayzon *Pfizer, S.Afr.*
Parecoxib sodium (p. 119·3).
Postoperative pain.

Razadyne *Janssen, USA.*
Galantamine hydrobromide (p. 391·3).
Formerly known as Reminyl.
Alzheimer's disease.

Razapina *Sandoz, Braz.*
Mirtazapine (p. 436·1).
Depression.

Razel *Glenmark, India.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Razene *Mylan, NZ.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; insect bites; urticaria.

Razepam *TNP, Thai.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Razil *Rafarm, Gr.*
Donepezil hydrochloride (p. 390·2).

Razimax *Rafarm, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Razin *CTI, Israel.*
⊗Phentermine resinate (p. 2329·2).
Obesity.

Razo *Reddy, Ukr.†*
Rabeprazole (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; gastritis.

Razolager *Gerard, Irl.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Razolam *Fabop, Arg.*
Alprazolam (p. 1035·2).
Anxiety; depression.

Razole *Rowex, Irl.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Razylfin *Help, Gr.*
Pentoxifylline (p. 1465·3).

RBC *Co-Pharma, UK.*
Calamine (p. 1697·2); dibrompropamidine isetionate (p. 1750·1).
Formerly contained antazoline hydrochloride, calamine, and cetrimide.
Insect bites and stings.

Rybar, Irl.†
Antazoline hydrochloride (p. 615·3); calamine (p. 1697·2); cetrimide (p. 1742·1).
Pruritus; skin irritation.

RBC-Kit *Soreq, Israel.*
Stannous chloride for labelling with technetium-99m (p. 2228·1).
Red blood cell labelling.

RCF *Ross, USA.*
Carbohydrate-free soy protein feed.
Carbohydrate intolerance; ketogenic diet.

R-Cin *Lupin, India.*
Rifampicin (p. 350·3).
Tuberculosis.

R-Cinex *Lupin, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

R-Cinex Z *Lupin, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

R-Den *TNP, Thai.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

RE DCP *Rivers Edge, USA.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Reabilan *Galagen, USA.*
A range of lactose-free, gluten-free preparations for enteral nutrition.

Reacel-A *Offenbach, Mex.*
Tretinoin (p. 1725·2).
Acne; keratinisation disorders.

Reactidiem *Johnson & Johnson, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Reactine
Note: this name may be used for preparations of different composition.
Cipla, India.
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

McNeil, Belg.; McNeil Consumer, Canad.; McNeil, Cz.; McNeil, Ger.; McNeil Healthcare, Irl.; Johnson & Johnson Consumer, Mex.; Johnson & Johnson, Neth.; McNeil, Norw.†; McNeil, Spain.†
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria; pruritus; allergic eye disorders.

Johnson & Johnson, Ital.
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Réactine *McNeil, Fr.†*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Reactine Allergy & Sinus *McNeil Consumer, Canad.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Reactine duo *McNeil, Ger.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Reactine Forte *Cipla, India.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1); diclofenac (p. 48·3).
Pain; inflammation.

Reactine Levocabastina *Johnson & Johnson, Spain.*
Levocabastine hydrochloride (p. 632·2).
Allergic conjunctivitis.

Reactine Plus
Note: this name may be used for preparations of different composition.
Cipla, India.
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

McNeil, Spain.†
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Reactine Pseudoephedrine *McNeil, Belg.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Reactivan *Merck, S.Afr.†*
⊗Fencamfamin hydrochloride (p. 2322·2); vitamins.
Tonic.

Readi-Cat *E-Z-EM, Canad.†; E-Z-EM, USA.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Ready Bath
Note: this name may be used for preparations of different composition.
Medline, Canad.
Benzalkonium chloride (p. 1737·1).
Skin cleansing.

Readybath
Note: this name may be used for preparations of different composition.
Medline, Canad.
Dimeticone (p. 2209·3).

Readycleanse *Medline, Canad.*
Dimeticone (p. 2209·3).

Reaferon Lipint *Vector, Rus.*
Interferon alfa-2a (p. 989·2).
Hepatitis B; hypersensitivity reactions; chlamydial infections; respiratory-tract infections.

Reagin *Baliarda, Arg.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders.

Reagin Vascular *Baliarda, Arg.*
Citicoline (p. 2480·1); codergocrine mesilate (p. 389·2).
Mental function impairment in the elderly.

Real One *Piramal, India.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Realaxan *Unique, Rus.*
Macrogol 4000 (p. 2547·3).
Constipation.

Realderm *Reall, Switz.*
⊗Zinc oxide (p. 1729·1); glycerol (p. 2517·2); aluminium acetotartrate (p. 2440·1).
Nappy rash; skin irritation.

Realdiet Renal *Lactalis, Fr.*
Preparation for enteral nutrition.
Dialysis patients.

Realdiron *Teva, Rus.; Teva, Ukr.*
Interferon alfa-2b (p. 989·2).
Hepatitis B; hepatitis C; encephalitis; malignant neoplasms.

Realdrax *Liferpal, Mex.*
Ibuprofen (p. 68·2).
Fever; pain.

Realen *Ist. Chim. Inter., Ital.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Real-Vit *Solfran, Mex.†*
Vitamins.

Reamberin *Polisan, Rus.*
Meglumine sodium succinate; sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Detoxification.

Reambisar *Biochimic, Rus.*
N-(1-Desoxy-D-glucitol-1-yl)-N-methylammonium sodium succinate.

Reandron *Bayer, Austral.; Bayer, NZ; Bayer, Spain.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Reanima *Benitol, Arg.*
Caffeine (p. 1203·3); paracetamol (p. 115·1).
Fever; pain.

Reanimat *Unipharma, Gr.*
Nifedipine (p. 1447·2).

Reanutriflex Lipide *Braun, Fr.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3) and medium-chain triglycerides (p. 2082·2)); with or without electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Reanutriflex Omega *Braun, Fr.*
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3), medium-chain triglycerides (p. 2082·2), and omega-3 triglycerides (p. 1460·1)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Reapam *Pfizer, Neth.*
Prazepam (p. 1098·2).
Anxiety.

Reaphirm Plant Source DHA *Everett, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).

Reaptan *Servier, Austral.; Servier, Fin.; Servier, Irl.*
Perindopril arginine (p. 1466·3); amlodipine besilate (p. 1304·1).
Coronary heart disease; hypertension.

Stroder, Ital.
Perindopril (p. 1466·3); amlodipine besilate (p. 1304·1).

Reasec *Gedeon Richter, Cz.; Janssen-Cilag, Gr.; Gedeon Richter, Hung.; Richter, Pol.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Re-Azo *Reese, USA.*
Phenazopyridine hydrochloride (p. 124·3).

Re-B *Unison, Malaysia.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neurological disorders.

Re-B Forte *Unison, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; vitamin B deficiency.

Rebakol *Ecopharma, Chile.*
Phytosterols (p. 1471·2); vitamin E (p. 2119·1).
Hypercholesterolaemia.

Rebal Plus *Fahrenheit, Indon.*
Mecobalamin (p. 2108·1); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).
Peripheral neuropathy.

ReBalance *Zeller, Switz.*
St John's wort (p. 449·1).
Anxiety disorders; insomnia.

Rebasin *Sanovel, Turk.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Rebaten *Sigma, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias.

Rebetol *MSD, Austral.; Schering-Plough, Austria; MSD, Belg.; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; MSD, Jpn; Schering-Plough, Malaysia; MSD, Neth.; MSD, Norw.; MSD, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.; Schering-Plough, USA; Schering-Plough, Venez.*
Ribavirin (p. 1010·2).
For use in combination with interferon alfa-2b or peginterferon alfa-2b.
Chronic hepatitis C.

Rebetron *Schering-Plough, Austral.†; Schering-Plough, Hong Kong†; Schering-Plough, NZ.†*
Injection, interferon alfa-2b (Intron A) (p. 989·2); capsules, ribavirin (Rebetol) (p. 1010·2).
Chronic hepatitis C.

Rebif *Merck Serono, Arg.; Merck Serono, Austral.; Serono, Austria; Merck Serono, Belg.; Merck, Braz.; EMD, Canad.; Merck Serono, China; Merck, Cz.; Merck Serono, Denm.; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Merck Serono, Hung.; Serum Institute, India; Merck, Indon.; Merck Serono, Irl.; Merck Serono, Israel; Serono, Ital.; Merck Serono, Malaysia; Merck, Mex.; Merck, Neth.; Merck Serono, Norw.; Healthcare Logistics, NZ†; Merck, Philipp.; Serono, Pol.; Merck, Port.; Merck Serono, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Thai.; Serono, Turk.; Merck Serono, UK; Serono, USA; Serono, Venez.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

Reblenine *Sodhan, Turk.*
A factor IX preparation (p. 1149·3).

Re-Bone
Note: this name may be used for preparations of different composition.
Mallinckrodt, Cz.†
Rhenium-186 (p. 2227·2) etidronate.
Painful bone metastases; prostatic cancer.

Rebone
Note: this name may be used for preparations of different composition.
Ache, Braz.
Ipriflavone (p. 1185·3).
Osteoporosis.

Puspa, Indon.
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); manganese sulfate (p. 2081·2); magnesium glycerophosphate (p. 1787·2); zinc (p. 2126·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Joint disorders.

Řebříčkový Čaj; Řebříčková Nať *Megafyt-R, Cz.†*
Achillea (p. 2427·3).
Appetite loss; dyspepsia; skin disorders; wounds; pelvic pain.

Reca *Cantabria, Spain.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Recaflex *Recalcine, Chile.†*
Tenoxicam (p. 136·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Recaflux *Copernico, Ital.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Recain *Mahakam Beta, Indon.*
Bupivacaine (p. 1980·3).
Local anaesthesia.

Recal *New Farma, Ital.*
Calcium carbonate (p. 1824·3).
Calcium deficiency.

Recal D *Rivers Edge, USA.*
Vitamin B substances (p. 2102·3); calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Dietary supplement.

Recalbon *Ono, Jpn.*
Minodronic acid (p. 1186·2).
Osteoporosis.

Recalcin *Hasco-Lek, Pol.*
Chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis.

Recalm *Herbarium, Braz.*
Valerian (p. 2640·2).
Anxiety; insomnia.

Sanofi-Aventis, Chile.†
Valerian (p. 2640·2); passion flower (p. 2584·1); melissa (p. 2552·3); tilia (p. 2631·3).
Insomnia; anxiety; irritability.

Recalplex *Cazi, Braz.*
Vitamin B substances (p. 2102·3).
Nutritional supplement.

Recalvit D *Biofarm, Pol.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Recamicina *Recalcine, Chile.*
Levofloxacin (p. 315·3).
Bacterial infections.

Recatol Algin *Riemser, Ger.*
Alginic acid (p. 2167·2); carmellose sodium (p. 2175·2).
Obesity.

Recatol mono *Riemser, Ger.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Obesity.

Recaxin *Gynopharm, Chile.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Rec-DZ *Hetero, India.*
Diazepam (p. 1063·2).
Anxiety; epilepsy; febrile convulsions; tetanus; premedication; sedative.

Receant *Remedina, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Recef *Farma 1, Ital.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Recephin *Sel-J, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Receptozine *Be-Tabs, S.Afr.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity.

Recessan *Kreussler, Ger.*
Lauromacrogol 400 (p. 2194·1).
Mouth inflammation.

Rechol *Pharos, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Recikalc-D *Recip, Fin.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Recipect *Orion, Fin.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Recit *Gador, Arg.*
Atomoxetine hydrochloride (p. 2316·3).
Attention-deficit hyperactivity disorder.

Recita *Ipca, India.*
Escitalopram oxalate (p. 416·2).
Depression.

Recital *Trima, Israel.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorders.

Reclast *Novartis, USA.*
Zoledronic acid (p. 1192·3).
Paget's disease of bone; osteoporosis.

Reclide *Reddy, Malaysia; Reddy, Rus.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Reclipsen *Watson, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3); 7 tablets, inert.
Combined oral contraceptive.

Reclofen *Combiphar, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Reclomide *Major, USA.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Reclor *Piramal, India.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Reclovax *Remedica, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Reclusmyn *Bioclon, Mex.*
Spider venom antisera (p. 2419·3).
Spider bite.

RECO
Note: this name may be used for preparations of different composition.
GMP, Indon.
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Reco
Note: this name may be used for preparations of different composition.
TRB, Arg.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; gastro-oesophageal reflux; acid aspiration.

Recocef *Julphar, UAE.*
Cefaclor (p. 232·3).
Bacterial infections.

Recodryl *GMP, Indon.*
Diphenhydramine hydrochloride (p. 626·2).
Allergic rhinitis; urticaria; motion sickness.

Recofen *Reese, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).

Recofen-D *Reese, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).

Recofluid *Recordati, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Recofol *Alphapharm, Austral.†; Bayer, China; Bayer Schering, Cz.†; Bayer, Denm.; Primex, Fin.†; Bayer Schering, Gr.; Dexa, Indon.; Leiras, Indon.; Bayer, Israel; Pisa, Mex.; Primex, Neth.; Bayer Schering, Rus.; Mylan, S. Afr.†; Bayer Schering, Singapore; Primex, Singapore; Primex, Spain; Bayer Schering, Thai.†; Er-Kim, Turk.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Recolfar *Fahrenheit, Indon.*
Colchicine (p. 604·1).
Gout.

Recolin *Pyridam, Indon.*
Citicoline sodium (p. 2480·2).
Mental function impairment in the elderly.

Recoma *Marching, Hong Kong.†*
Noscapine (p. 1670·3).
Cough.

Recombicyte *Beijing Four Rings, Philipp.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Recombinant H-B Vax II *MSD, Israel.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Recombinate *Baxter, Arg.; Baxter, Austral.; Baxter, Austria†; Baxter, Belg.; Baxter, Braz.; Baxter, Canad.†; Baxter, Cz.; Baxter, Fr.†; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Baxter, Israel; Baxter, Ital.; Baxter, Jpn; Baxter, Neth.; Baxter, NZ; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter BioScience, UK; Baxter, USA.*
A factor VIII preparation (recombinant) (p. 1148·1).
Haemorrhagic disorders; haemophilia A.

Baxter, Fin.; Baxter, Port.; Baxter, Spain.
Octocog alfa (p. 1148·2).
Haemophilia A.

Recombivax *Vianex (Βιανεξ), Gr.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Recombivax HB *Merck Frosst, Canad.; Merck, USA.*
A hepatitis B vaccine (recombinant DNA) (p. 2389·3).
Active immunisation.

Recomint *GMP, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold symptoms.

Recomvax B *Sanofi Pasteur, Chile; Aventis Pasteur, Philipp.†; LG, Philipp.†*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Reconter *Libbs, Braz.*
Escitalopram (p. 416·2).
Depression; panic disorder; anxiety; obsessive-compulsive disorder; social phobia.

Reconvan *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.†; Fresenius Kabi, UK.*
Preparation for enteral nutrition.

Recormon *Roche, Arg.; Roche, Braz.; Roche, Chile; Roche, China; Roche, Gr.; Roche, Hong Kong; Roche, Indon.; Roche Diagnostics, Israel; Roche, Malaysia; Roche, Mex.; Roche, NZ†; Roche, Philipp.; Roche, Rus.; Roche, S. Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Serono, Turk.; Roche, Ukr.; Roche, Venez.*
⊗Epoetin beta (p. 1141·1).
Anaemias; autologous blood transfusion.

Recort Plus *Reese, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Recoside *Ali, Turk.*
Thiocolchicoside (p. 2026·2).

Recosine *Pharmanel, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Recosyn *Recordati, Ger.*
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement.

Recotens *Valeant, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Recothrom *Bayer, Canad.*
Thrombin alfa (recombinant) (p. 1163·2).
Haemorrhage.

Zymo, USA.
Thrombin (recombinant) (p. 1163·2).
Haemorrhage.

Recover *Pharmatrix, Arg.*
A barrier preparation.

Recover Ol *Dispolab, Chile.*
CEA Oleuropein Complex; vitamins; kojic acid (p. 1710·2); arbutin (p. 1694·3).
Skin disorders.

Recover Whitening *Pharmatrix, Arg.*
Glycolic acid (p. 1704·3); octinoxate (p. 1715·1); Indian gooseberry (p. 2532·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); aloe vera (p. 1693·2).
Skin hyperpigmentation; sun-induced skin damage.

Recoveron *Armstrong, Mex.*
Calcium acexamate (p. 2427·3) or sodium acexamate (p. 2427·3).
Burns; ulcers; wounds; osteoporosis; hypocalcaemia.

Recoveron N *Armstrong, Mex.*
Sodium acexamate (p. 2427·3); neomycin sulfate (p. 330·1).
Infected burns, ulcers, and wounds; skin infections.

Recoveron NC *Armstrong, Mex.*
Sodium acexamate (p. 2427·3); neomycin sulfate (p. 330·1).
Infected burns, ulcers, and wounds; skin infections.

Recovit *GMP, Indon.*
Vitamins.
Dietary supplement.

Recovit Plus *GMP, Indon.*
Vitamins; minerals.
Dietary supplement.

Recoxa *Zentiva, Cz.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Recozil *Recon, Singapore.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Recozin *Sel-J, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Recrea *Meda, Fin.; Meda, Norw.; Antula, Swed.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Rectacaine *Reese, USA.*
Ointment: Phenylephrine hydrochloride (p. 1672·3); shark-liver oil (p. 2614·2).

Reese, USA.
Suppositories: Phenylephrine hydrochloride (p. 1672·3).

Rectacort-HC *Acino, USA.*
⊗Hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Rectagene Medicated Balm *Pfeiffer, USA.*
Yeast (p. 2125·2); shark-liver oil (p. 2614·2).
Haemorrhoids.

Rectagene Medicated Rectal Balm *Pfeiffer, USA.*
Benzocaine (p. 1980·2); phenylephrine hydrochloride (p. 1672·3); bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1); mepyramine maleate (p. 635·1).
Anorectal disorders.

Rectaktiv *Altfarm, Rus.*
Aesculus (p. 2431·2).
Constipation.

Rectalad *Church & Dwight, Austral.†*
Docusate sodium (p. 1836·2).
Bowel evacuation; constipation.

Rectamigdol *Uriach, Spain.†*
Bismuth camphocarbonate (p. 1821·3).
Sore throat.

Rectanal *Galenus, Pol.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation; constipation.

RectiCare *Ferndale, USA.*
Lidocaine (p. 1988·1).
Anorectal disorders.

Rectifiance Intense *Chanel, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Rectinol *Pfizer Consumer, Austral.*
⊗Adrenaline (p. 1292·1); benzocaine (p. 1980·2); cinchocaine hydrochloride (p. 1983·2); zinc oxide (p. 1729·1).
Anorectal disorders.

Rectinol HC *Pfizer Consumer, Austral.†*
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone (p. 1640·1).
Anorectal disorders.

Rectiole *Caldeira & Metelo, Port.*
⊗Glycerol (p. 2517·2).
Constipation; bowel evacuation.

Rectiv *Aptalis, USA.*
Glyceryl trinitrate (p. 1391·2).
Anal fissure.

Recto Menaderm NF *Menarini, Spain.*
⊗Beclometasone dipropionate (p. 1621·2).
Anorectal disorders.

Rectocalm *Sanitas, Arg.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Rectodelt *Trommsdorff, Cz.; Trommsdorff, Ger.; Trommsdorf, Hung.; Trommsdorff, Ukr.*
⊗Prednisone (p. 1647·2).
Rectal corticosteroid.

Rectogel *Riva, Canad.*
Benzocaine (p. 1980·2); zinc sulfate (p. 2126·2).
Anorectal disorders.

Rectogel HC *Riva, Canad.*
⊗Benzocaine (p. 1980·2); zinc sulfate (p. 2126·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Rectogesic *Care, Austral.*
Topical powder: Zinc oxide (p. 1729·1).
Anorectal disorders.

Care, Austral.; ProStrakan, Belg.; ProStrakan, Cz.; ProStrakan, Denm.; ProStrakan, Fin.; ProStrakan, Fr.; ProStrakan, Ger.; ProStrakan, Gr.; ProStrakan, Hung.; ProStrakan, Irl.; Perrigo, Israel; ProStrakan, Ital.; ProStrakan, Neth.†; ProStrakan, Norw.; HSL, NZ; Ferring, Pol.†; ProStrakan, Port.; Care, Singapore; ProStrakan, Spain; ProStrakan, Swed.; Strakan, UK.
Glyceryl trinitrate (p. 1391·2).
Anal fissure; haemorrhoids; anorectal disorders.

Rectomenaderm *Menarini, Arg.*
⊗Beclometasone dipropionate (p. 1621·2).
Anorectal disorders.

Rectopanbiline *Meda, Fr.*
⊗Bile extract (p. 2457·2); gelatin (p. 1154·1); glycerol (p. 2517·2).
Constipation; bowel evacuation.

Rectopred *Jacoby, Austria.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Croup.

Rectoquotane *Zambon, Fr.*
Quinisocaine hydrochloride (p. 1996·1); cetrimide (p. 1742·1).
Anorectal disorders.

Recto-Reparil *Madaus, Ital.*
Aescin (p. 2431·2); tetracaine hydrochloride (p. 1996·3).
Anorectal disorders.

Rectosec *SecFarm, Pol.*
Benzocaine (p. 1980·2); Peru balsam (p. 2587·1); zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3).
Anorectal disorders.

Rectoseptal-Néo bismuthé *Actipharm, Switz.*
Bismuth succinate (p. 1821·3); cineole (p. 2479·1); terpin hydrate (p. 1678·2); potassium hydroxyquinoline sulfate hydrate (p. 2530·1).
Pharyngeal disorders.

Rectoseptal-Néo simple *Actipharm, Switz.*
Cineole (p. 2479·1); terpin hydrate (p. 1678·2); potassium hydroxyquinoline sulfate (p. 2530·1).
Respiratory-tract disorders.

Rectovasol *Qualiphar, Belg.*
Bismuth subgallate (p. 1822·1); bismuth oxyiodogallate (p. 1821·3); zinc oxide (p. 1729·1); aesculus (p. 2431·2); hamamelis (p. 2523·3); amylocaine (p. 1979·3); peru balsam (p. 2587·1).
Haemorrhoids.

Rectoxal *Ariti, Gr.*
Oxaliplatin (p. 838·1).

Rectozorin *Teva, Israel.*
Ointment: Bismuth oxychloride (p. 1821·3); thymol iodide (p. 1772·2); zinc oxide (p. 1729·1); benzocaine (p. 1980·2); menthol (p. 2553·2).
Anorectal disorders.

Teva, Israel.
Suppositories: Bismuth subgallate (p. 1822·1); thymol iodide (p. 1772·2); zinc oxide

(p. 1729·1); benzocaine (p. 1980·2); menthol (p. 2553·2); tannic acid (p. 2625·2).
Haemorrhoids.

Recugel
Note: this name may be used for preparations of different composition.
Bausch & Lomb, Arg.
Dexpanthenol (p. 2582·2).
Corneal lesions.

Bausch & Lomb, Ital.
Carbomer (p. 2173·3); dexpanthenol (p. 2582·2).
Dry eyes.

Recuperin-B *Atlantic, Philipp.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; neuritis.

Recupex *Wockhardt, India.*
Lactose-free nutritional preparation.
Enteral nutritional.

Recur *Menarini, Cz.*
Frovatriptan succinate (p. 676·2).
Migraine.

Recustein *Landson, Indon.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Recycline *Rekah, Israel.*
Tetracycline hydrochloride (p. 373·2).
Bacterial eye and skin infections.

Red Cross Toothache *Mentholatum, USA.*
Eugenol (p. 2501·2).
Toothache.

Red Kooga *Peter Black, UK.*
Ginseng (p. 2513·3).
Tonic.

Red Kooga Co-Q-10 and Ginseng *Peter Black, UK.*
Ginseng (p. 2513·3); ubidecarenone (p. 2637·1).
Tonic.

Red Off *Laboratorios Chile, Chile.*
⊗Naphazoline (p. 1669·3).
Eye irritation.

Red Off Aqua *Laboratorios Chile, Chile.*
⊗Naphazoline hydrochloride (p. 1669·3); polyvinyl alcohol (p. 2204·2).
Eye irritation.

Red Off Plus *Laboratorios Chile, Chile.*
⊗Antazoline (p. 615·3); naphazoline (p. 1669·3).
Eye irritation.

Red Oil *Nella, UK.*
Methyl nicotinate (p. 91·3); volatile mustard oil (p. 2646·1); clove oil (p. 2481·3); arachis oil (p. 2446·1).
Muscle pain.

Red Sage Catarrh Remedy *Rickard Lanes, UK.*
Sage (p. 2608·3); liquorice (p. 1853·2).
Respiratory-tract congestion.

Red Seal *Quatromed, S.Afr.†*
Merbromin (p. 1760·1).
Wounds; skin cleansing; bacterial infections of mucous membranes.

Red Skin *Dossier, Neth.*
Atropa belladonna (p. 2453·3); rhus toxicodendron (p. 2603·3); urtica dioica (p. 2639·3).
Homoeopathic preparation.

Red Throat Spray *Clay Park, USA.*
Phenol (p. 1763·3).
Sore throat.

Redac *Gerolymatos, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Redacid *Maver, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Redactiv *Wassermann, Ital.*
Rifaximin (p. 355·2).
Bacterial skin infections.

Redaflam *Maver, Mex.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Redalip *Maver, Mex.*
Bezafibrate (p. 1323·2).
Hypercholesterolaemia.

Redantai *Southwest, China.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Redap *Galderma, Denm.*
Adapalene (p. 1692·1).
Acne.

Redaxa fit *Riemser, Ger.†*
Equisetum (p. 2500·1).
Water retention.

Redaxin *Konimex, Indon.†*
Red yeast rice (p. 2603·1).
Hyperlipidaemias.

Reddyvit *Reddy, Rus.*
Vitamins; zinc sulfate (p. 2126·2).

Redecil *Retinoids, Rus.*
Vitamin A palmitate (p. 2098·3); methyluracil.
Skin disorders.

Redepra *Nevzat, Turk.*
Mirtazapine (p. 436·1).

Rederm *Orchard, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Vertex, Rus.
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Redermic Piel *Roche-Posay, Chile.*
Madecassoside (p. 1698·3); hyaluronic acid (p. 2526·2); vitamin C (p. 2110·3).
Skin disorders.

Redermic XL *Roche-Posay, Chile.*
SPF 15: Madecassoside (p. 1698·3); hyaluronic acid (p. 2526·2); vitamin C (p. 2110·3); drometrizole trisiloxane (p. 1702·1); ecamsule (p. 1702·1).
Skin disorders.

Rediarin *Maver, Mex.*
Loperamide (p. 1854·2).
Diarrhoea.

Rediazine *Chew, Thai.*
Sulfadiazine (p. 361·3).
Bacterial infections.

Redicalcin *Vianex (Βιανεξ), Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Redicor *Reddy, S.Afr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Redicres *Columbia, Mex.*
⊗Clobenzorex hydrochloride (p. 2318·3).
Obesity.

Redilanz *Reddy, S.Afr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Redilev *Reddy, S.Afr.*
Levetiracetam (p. 531·1).
Epilepsy.

Redimune *CSL, Switz.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; bone marrow transplantation; immune thrombocytopenia; Guillain-Barŕe syndrome; Kawasaki disease.

Redinac *Polfarmex, Pol.†*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Redipred *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Redisol *MSD, Thai.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency; schilling test.

Rediun-E *Baliarda, Arg.*
⊗Spironolactone (p. 1499·3).
Heart failure; cirrhosis with ascites; hyperaldosteronism; hypertension; oedema; nephrotic syndrome.

Redol Comp *Orion, Fin.*
⊗Dextromethorphan hydrobromide (p. 1660·1); salbutamol sulfate (p. 1220·2).
Respiratory-tract disorders.

Redomex *Lundbeck, Belg.*
Amitriptyline hydrochloride (p. 401·1).
Depression; pain.

Redopril *Sandoz, Venez.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; myocardial infarction.

ReDormin *Flordis, Austral.; Beres, Hung.; Zeller, Switz.*
Tablets: Valerian (p. 2640·2); lupulus (p. 2546·1).
Sleep disorders.

Zeller, Switz.†
Syrup: Valerian (p. 2640·2).
Sleep disorders.

Redormin Night *Neopharm, Israel.*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Sleep disorders.

Redotex *Medix, Mex.*
⊗Cathine hydrochloride (p. 2318·2); liothyronine (p. 2342·3); atropine sulfate (p. 1310·2); aloin (p. 1816·2); diazepam (p. 1063·2).
Obesity.

Redotex NF *Medix, Mex.*
⊗Cathine hydrochloride (p. 2318·2); atropine sulfate (p. 1310·2); aloin (p. 1816·2).
Obesity.

Redotrin *Coup, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Redoxc *Bayer, Spain.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Redoxon *Bayer, Belg.*
Tablets: Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Bayer Consumer, Arg.; Bayer Consumer, Austral.†; Bayer, Belg.†; Bayer, Braz.; Roche, Braz.; Bayer Consumer, Canad.; Bayer, China; Roche, Gr.; Bayer, Hong Kong†; Bayer, Irl.†; Bayer, Israel; Bayer, Ital.; Bayer Consumer, Mex.; Roche, NZ; Bayer, Port.; Bayer, Singapore†; Bayer, Spain†; Bayer, Switz.; Bayer, Turk.; Roche Consumer, UK.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement; idiopathic methaemoglobinaemia; dietary supplement; urine acidification; adjunct in iron supplementation; methaemoglobinaemia; malabsorption syndromes.

Bayer, Belg.†
Injection: Sodium ascorbate (p. 2111·1).
Vitamin C deficiency; vitamin C supplement.

Redoxon A *Bayer Consumer, Arg.*
Ascorbic acid (p. 2110·3); vitamin A palmitate (p. 2098·3).
Vitamin A and C deficiency.

Redoxon All Day Defence *Bayer, Singapore.*
Vitamin C (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc supplement.

Redoxon Calciovit *Bayer, Spain.†*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); pyridoxine hydrochloride (p. 2105·3).
Calcium deficiency; rickets; osteomalacia; bone and dental disorders.

Redoxon Complex *Bayer, Spain.†*
Vitamins; minerals.

Redoxon Doble Accion *Bayer Consumer, Arg.; Bayer, Chile.*
Ascorbic acid (p. 2110·3); zinc citrate (p. 2126·2).
Vitamin C and zinc supplement; vitamin C and zinc deficiency.

Redoxon Double Action *Bayer Consumer, Austral.; Bayer, Hong Kong†; Bayer Consumer, Indon.; Roche, NZ†; Bayer, Singapore; Roche Consumer, UK.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Dietary supplement; vitamin C and zinc deficiency; vitamin C and zinc supplement.

Bayer, Cz.†; Bayer, Irl.
Ascorbic acid (p. 2110·3); zinc citrate (p. 2126·2).
Vitamin C and zinc deficiency.

Redoxon Fortimun *Bayer Consumer, Indon.*
Vitamins; minerals.
Dietary supplement.

Redoxon Kids *Bayer, Singapore.*
Vitamin C (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc supplement.

Redoxon Vita Immune *Bayer, Singapore.*
Vitamins; minerals.
Dietary supplement.

Redoxon Zinc *Bayer Consumer, Thai.*
Vitamin C (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc deficiency.

Redoxon + Zinc *Bayer, Switz.*
Ascorbic acid (p. 2110·3) or sodium ascorbate (p. 2111·1); zinc citrate (p. 2126·2).
Vitamin C and zinc supplement.

Redoxon Zinco *Bayer, Braz.; Roche, Braz.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).

Redoxon + Zinc *Bayer, Belg.*
Ascorbic acid (p. 2110·3); zinc (p. 2126·1).
Vitamin C and zinc supplement.

Redoxon-B *Bayer Consumer, Canad.*
Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3); magnesium salts (p. 1786·3).
Nutritional supplement.

Redras *Miklich, Denm.*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Redrate *Sanofi-Aventis, Port.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Redrocin *Unison, Thai.†*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Redsai Stress *Bunker, Braz.*
Vitamins; minerals.

Redseng *Korhispana, Spain.*
Ginseng (p. 2513·3).
Tonic.

Redseng Polivit *Korhispana, Spain.†*
Vitamins; ginseng (p. 2513·3).
Tonic.

Redualgas *Sigma, Arg.*
Poliglusam (p. 2593·2); bladderwrack (p. 2612·1).
Slimming aid.

Reduben *Cofasa, Venez.*
Nimesulide (p. 101·3).
Pain.

Reducar *Gap, Gr.; GA Pharmaceuticals, Hong Kong.*
Isotretinoin (p. 1706·2).
Acne.

Reducel *GX, Philipp.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Reducform-F *Ximena Polanco, Chile.*
Lessonia nigrescens; carmellose (p. 2175·1); fabiana imbricata; spirulina (p. 2622·1); inulin (p. 2534·3).
Obesity; digestive disorders.

Reducin *Finadiet, Arg.†*
Soya lecithin (p. 2542·2).
Dietary supplement.

Reducin-A *JB Chemicals, India.*
Diclofenac (p. 48·3); paracetamol (p. 115·1).
Musculoskeletal and joint disorders.

Reduclim *Farmoquimica, Braz.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Reducofen *Germed, Braz.*
Fenofibrate (p. 1381·1).

Reducol
Note: this name may be used for preparations of different composition.
MSD, Braz.
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Reductase *Natufarma, Arg.*
Garcinia cambogia (p. 2510·2); levocarnitine (p. 2053·2).
Dietary supplement; slimming aid.

Reduc-Te *Ximena Polanco, Chile.*
Boldo (p. 2458·3); inulin (p. 2534·3); fennel (p. 2503·2); rosa mosqueta (p. 2607·1); equisetum (p. 2500·1); tilia (p. 2631·3).
Obesity.

Reductel *Degorts, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Reductil *Abbott, Austral.†; Abbott, Austria†; Abbott, Belg.†; Abbott, Braz.†; Abbott, Chile†; Abbott, Denm.†; Abbott, Fin.†; Abbott, Ger.†; Abbott, Gr.†; Abbott, Hong Kong†; Abbott, Hung.†; Abbott, Indon.†; Abbott, Irl.†; Teva, Israel†; Abbott, Ital.†; Abbott, Malaysia†; Abbott, Neth.†; Abbott, Norw.†; Abbott, NZ†; Abbott, Philipp.†; Abbott, Port.†; Abbott, S.Afr.†; Abbott, Singapore†; Abbott, Spain†; Abbott, Swed.†; Abbott, Switz.†; Abbott, Thai.†; Abbott, Turk.†; Abbott, UK†; Abbott, Venez.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Reducto *Sanova, Austria.†*
Monobasic potassium phosphate (p. 1790·3); dibasic sodium phosphate (p. 1791·2).
Calcium oxalate stones; hypercalcaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Reducto-spezial *Temmler, Ger.*
Monobasic potassium phosphate (p. 1790·3); dibasic sodium phosphate dihydrate (p. 1791·2).
Calcium oxalate stones; phosphate supplement; hypercalcaemia.

Redudiet *AM, Arg.*
Garcinia cambogia (p. 2510·2); centella (p. 1698·3); alginic acid (p. 2167·2); vitamin E (p. 2119·1).
Slimming aid.

Redufat *Catarinense, Braz.†*
Bladderwrack (p. 2612·1).
Obesity; hypothyroidism.

Reduff *Hoe, Philipp.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Redugluc *Microsules, Arg.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Reduksin *Promo-Med, Rus.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Reduktan *Leros, Cz.*
Bladderwrack (p. 2612·1); frangula bark (p. 1843·3); sambucus (p. 2609·3); senna (p. 1885·1); fennel (p. 2503·2); petroselinum root; birch leaf (p. 2457·3); liquorice (p. 1853·2).
Slimming aid.

Redulip
Note: this name may be used for preparations of different composition.
Umedica, Philipp.
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Redumas *Teva, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Redumax *Sivaderm, Arg.*
Coaxel (caffeine (p. 1203·3); levocarnitine (p. 2053·2); coenzyme A (p. 2483·2)); plant extracts.
Cellulite.

Redumed *Rimsa, Mex.*
⊗Sibutramine (p. 2330·2); carnitine (p. 2053·2).
Obesity.

Reduprec *Ultra, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Reduprost *Raffo, Arg.*
Tamsulosin (p. 2369·1).
Benign prostatic hyperplasia.

Redurate *Thebe, S.Afr.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Redur-PCM *Rivers Edge, USA.†*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Redusa *Jean-Marie, Hong Kong.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Reduscole *Unison, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Redusec *Solas, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Redu-ST *Silanes, Mex.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Redustat *Liomont, Mex.*
Orlistat (p. 2577·1).
Obesity.

Redustatin *Uniao Quimica, Braz.*
Lovastatin (p. 1425·2).

Redusterol *Raffo, Arg.; Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; hypercholesterolaemia.

Redusterol Duo *Raffo, Arg.*
Simvastatin (p. 1489·2); ezetimibe (p. 1379·2).
Hyperlipidaemias.

Redutemp *International Ethical, USA.*
Paracetamol (p. 115·1).

Reduten *Sanitas, Chile.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Redutens *Kalbe, Indon.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction.

Redutona *Faes, Spain.†*
Phenytoin (p. 538·2); phenobarbital (p. 535·2); aminohydroxybutyric acid (p. 512·1); pyridoxine hydrochloride (p. 2105·3).
Epilepsy.

Reduvit *Technikon, S.Afr.*
Vitamins; minerals.

Re-Dux *Bernabo, Arg.*
Bismuth citrate (p. 1821·3).
Peptic ulcer.

Reduxpain *Kenyaku, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal, joint, and soft-tissue disorders.

Redvit *Bunker, Braz.*
Vitamins; minerals; amino acids.

Reedvit *Lafedar, Arg.*
Cyanocobalamin (p. 2107·2).
Anaemia; neuralgia; neuritis.

Reef Deep Sun Tan Oil *Boots Healthcare, Austral.†*
SPF 6: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Reef Sun Tan Oil *Reckitt Benckiser, Austral.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Reergin *Naturland, Hung.*
Glutamic acid (p. 2070·2); aspartic acid (p. 2050·3).
Tonic.

Reese's OneTab Congestion & Cough *Reese, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Reese's Pinworm *Reese, USA.*
Pyrantel embonate (p. 165·3).
Worm infections.

ReFacto *Wyeth, Austral.†; Wyeth Lederle, Austria; Pfizer, Belg.; Wyeth, Canad.†; Wyeth, Cz.; Wyeth, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Wyeth, Hung.; Pfizer, Irl.; Wyeth, Israel†; Wyeth Lederle, Ital.; Pfizer, Neth.; Pfizer, Norw.; Wyeth, Norw.; Wyeth, NZ†; Wyeth, Pol.; Wyeth Lederle, Port.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK; Pfizer, Ukr.; Genetics Institute, USA.*
Moroctocog alfa (p. 1148·2).
Haemophilia A; haemorrhagic disorders.

Refador *Teva, Cz.†; Pliva, Hung.†*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Refagan
Note: this name may be used for preparations of different composition.
Bayer Consumer, Indon.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; allergic rhinitis.

Refam *Terramedic, Philipp.†*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and leprosy.

Refam Duo *Terramedic, Philipp.†*
Oral suspension, rifampicin (Refam) (p. 350·3); syrup, isoniazid (p. 311·2) (Terozid Forte).
Vitamin B_6 (p. 2105·3) is included in the Terozid Forte preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Refam Pedia Kit *Terramedic, Philipp.†*
Oral suspension, rifampicin (Refam) (p. 350·3); syrup, isoniazid (p. 311·2) (Terozid Forte); oral suspension, pyrazinamide (p. 345·2) (Pyramin).
Pyridoxine hydrochloride (p. 2105·3) is included in the Terozid Forte preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Refaquin *Surya Dermato, Indon.*
⊗Hydroquinone (p. 1705·1); tretinoin (p. 1725·2); fluocinolone acetonide (p. 1636·1).
Melasma.

Refastin *Medana, Pol.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

Refaz *Pharmathen, Irl.*
Levofloxacin (p. 315·3).
Bacterial infections.

Refenax Caramelos Expectorantes *Monserrat, Arg.*
Tolu balsam (p. 1679·2); niaouli oil (p. 2569·1); lidocaine (p. 1988·1); hexylresorcinol (p. 1755·1); cineole (p. 2479·1); menthol (p. 2553·2).
Cough; mouth and throat disorders.

Refenax Colirio *Monserrat, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye disorders.

Refenax Gotas Nasales *Monserrat, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); diphenhydramine hydrochloride (p. 626·2).
Nasal congestion.

Refenax Jarabe *Monserrat, Arg.*
⊗Butetamate citrate (p. 1658·1); ammonium chloride (p. 1656·1); guaifenesin (p. 1666·2); pseudoephedrine (p. 1676·1); sodium benzoate (p. 1738·2); sodium citrate (p. 1781·2).
Cough.

Refenax Lagrimas *Monserrat, Arg.*
⊗Glycerol (p. 2517·2).
Dry eyes; eye irritation.

Refenesen *Reese, USA.*
Guaifenesin (p. 1666·2).

Refenesen Plus *Reese, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Referan *Iasis, Gr.*
Aniracetam (p. 389·1).
Mental function disorders.

Referen *Fresenius Medical, Port.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Refesan T *Hanosan, Ger.*
Calcium phosphoricum (p. 1784·2); ferrum phosphoricum (p. 2077·1); magnesium phosphoricum (p. 1787·3); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Refinish *L'Oreal, Canad.†*
Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Refissa *Suneva, USA.*
Tretinoin (p. 1725·2).

Refixime *XL, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Reflex
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Spain.
Camphor (p. 2466·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); menthol (p. 2553·2).
Rheumatic and muscle pain.

Uniao Quimica, Braz.
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).

Reflexan *Pharma Invesi, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

ReflexGel *Reckitt Benckiser, Belg.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2).
Musculoskeletal, joint, peri-articular, and soft-tissue pain and inflammation.

Reflexor *Combiphar, Indon.*
Glucosamine (p. 2515·3) or glucosamine sulfate potassium chloride (p. 2515·3).
Osteoarthritis.

Reflexpatch *Reckitt Benckiser, Belg.†*
Camphor (p. 2466·2); methyl salicylate (p. 92·1).
Pain; inflammation.

Reflexspray *Reckitt Benckiser, Belg.*
Methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal, joint, peri-articular, and soft-tissue pain and inflammation.

Reflin *Ranbaxy, India; Ranbaxy, Rus.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Reflor *Sanova, Austria; Sanofi Synthelabo, Turk.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; gastrointestinal disorders.

Reflotron *Roche Diagnostics, Irl.*
Test for a range of cardiac risk factors in blood, serum, or plasma.

Reflucan *Sel-J, Philipp.*
Fluconazole (p. 578·2).
Fungal infections.

Refludan *Celgene, Austral.; Celgene, Austria†; Celgene, Belg.†; Bayer, Canad.; Celgene, Cz.†; Celgene, Fr.†; Pharmion, Ger.†; Schering, Ger.†; Celgene, Gr.†; Celgene, Hung.†; Pharmion, Irl.†; Celgene, Ital.†; Pharmion, Neth.†; Pharmion, Norw.†; Hoechst Marion Roussel, NZ†; Celgene, Pol.†; Celgene, Port.†; Celgene, Swed.†; Celgene, Switz.†; Pharmion, UK†; Bayer, USA.†*
Lepirudin (p. 1418·2).
Acute coronary syndromes; thromboembolic disorders in patients with heparin-associated thrombocytopenia.

Refludin *Key Oncologics, S.Afr.; Celgene, Spain.†*
Lepirudin (p. 1418·2).
Thromboembolic disorders.

Reflumox *Sanofi-Aventis, Chile.*
Magnesium alginate (p. 2167·2); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium carbonate (p. 1856·2); potassium bicarbonate (p. 1780·3).
Gastric hyperacidity; oesophagitis.

Reflux
Note: this name may be used for preparations of different composition.
ACE, Neth.
Methenamine mandelate (p. 323·1).
Urinary-tract infections.

Monte Verde, Arg.
Ranitidine (p. 1882·1).
Peptic ulcer; gastric hyperacidity.

Refluxon *Vera, Hung.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Refnot *Refnot, Rus.*
Tumour necrosis factor α-1 (recombinant) (p. 878·1).
Breast cancer.

Refobacin *Merck, Austria; Almirall Hermal, Ger.; Merck Serono, Ger.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Refobacin Bone Cement R *Biomet, Ger.; Biomet, Singaporet†; Merck, Thai.*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methacrylate copolymer (p. 2558·2).
Bone infections; bone cement for orthopaedic surgery.

Refobacin Plus Bone Cement *Biomet, Ger.*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methacrylate copolymer (p. 2558·2).
Bone infections.

Refobacin Revision *Biomet, Ger.*
Gentamicin sulfate (p. 304·2); clindamycin hydrochloride (p. 269·3); methylmethacrylate/methacrylate copolymer (p. 2558·2).
Bone infections.

Refolinon *Pfizer, Gr.; Pharmacia, UK.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Reforce *Farmoz, Port.*
Fluconazole (p. 578·2).
Fungal infections.

Reforgan *Nikkho, Braz.*
Arginine aspartate (p. 2049·1).
Asthenia; fatigue.

Refortan *Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
⊗Pentastarch (p. 1146·1) in sodium chloride.
Hypovolaemia; haemodilution; shock; plasma volume expansion.

Refotax *Farma 1, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Refractyl *Sophia, Mex.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Refrain *Benedetti, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Refrane Bronce *Neo Dermos, Arg.*
Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen; tanning agent.

Refrane Gel *Neo Dermos, Arg.*
SPF 16: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Refrane P *Neo Dermos, Arg.*
SPF 18: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); aloe vera (p. 1693·2).
Sunscreen.

Refrane Plus *Neo Dermos, Arg.*
SPF 33: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); sulisobenzone (p. 1722·1); titanium dioxide (p. 1725·1); aloe vera (p. 1693·2).
Sunscreen.

Refrane Total *Neo Dermos, Arg.*
SPF 50: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); ensulizole (p. 1703·1).
Sunscreen.

Refrat *Strides Arcolab, Singapore.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection; lupus nephritis.

Refresh *Allergan, Austral.; Allergan, Braz.; Allergan, Canad.; Allergan, Fr.; Allergan, Gr.; Allergan, Irl.; Allergan, Israel; Allergan, NZ; Allergan, S.Afr.; Allergan, Singapore; Allergan, Thai.; Abdi, Turk.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes; eye irritation.

Allergan, Hong Kong.
Carmellose sodium (p. 2175·2).
Dry eyes.

Allergan, Mex.
Carbomer (p. 2173·3).
Dry eyes.

Allergan, UK.
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Refresh Celluvisc *Allergan, Canad.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Refresh Classic *Allergan, USA.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Formerly known as Refresh.
Dry eyes.

Refresh Contacts *Allergan, Austral.; Allergan, Canad.; Allergan, Singapore.*
Carmellose sodium (p. 2175·2).
Dry eyes; lubrication and rewetting of contact lenses; eye irritation.

Refresh Dry Eye Therapy *Allergan, USA.*
⊗Glycerol (p. 2517·2); polysorbate 80 (p. 2203·3).
Dry eyes.

Refresh Eye Allergy Relief *Allergan, Canad.*
⊗Antazoline phosphate (p. 615·3); naphazoline hydrochloride (p. 1669·3).

Refresh Gel *Allergan, Arg.; Allergan, Braz.*
Carbomer (p. 2173·3).
Dry eyes.

Refresh Lacri-Lube *Allergan, Canad.; Allergan, USA.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool alcohols (p. 2219·2).
Dry eyes.

Refresh Liquigel *Allergan, Arg.; Allergan, Austral.; Allergan, Canad.; Allergan, Chile; Allergan, Malaysia; Allergan, Mex.; Allergan, S.Afr.; Allergan, Singapore; Abdi, Turk.; Allergan, USA; Allergan, Venez.*
Carmellose sodium (p. 2175·2).
Dry eyes; eye irritation; wetting and lubricating of contact lenses.

Refresh Plus *Allergan, Austral.; Allergan, Canad.; Allergan, China; Allergan, Gr.; Allergan, Malaysia; Allergan, Singapore; Allergan, USA.*
Carmellose sodium (p. 2175·2).
Dry eyes; eye irritation.

Refresh PM *Allergan, USA.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool alcohols (p. 2219·2).
Dry eyes.

Refresh Redness Relief
Note: this name may be used for preparations of different composition.
Allergan, Canad.
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

Allergan, USA.
Phenylephrine hydrochloride (p. 1672·3); polyvinyl alcohol (p. 2204·2).
Eye irritation.

Refresh Tears *Allergan, Arg.; Allergan, Canad.; Allergan, Chile; Allergan, Israel; Allergan, Malaysia; Allergan, Mex.; Allergan, S.Afr.; Allergan, Singapore; Allergan, USA; Allergan, Venez.*
Carmellose sodium (p. 2175·2).
Dry eyes; eye irritation.

Refresh Tears Lubricant *Abdi, Turk.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Refresh Tears Plus *Allergan, Austral.; Allergan, NZ.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Refresh Ultra *Allergan, Canad.*
⊗Boric acid (p. 2459·3); castor oil (p. 2472·1); glycerol (p. 2517·2).
Dry eyes.

Refrianex *Montpellier, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Influenza symptoms.

Refrianex Antigripal *Montpellier, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Refrianex Compuesto *Montpellier, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Reftax *Ranbaxy, S.Afr.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Refulgin *Spyfarma, Spain.†*
Adenosine triphosphate (p. 2430·3); hydroxocobalamin acetate (p. 2107·3); pyritinol hydrochloride (p. 394·3); prosultiamine (p. 2103·1).
Mental function disorders.

Refusal *Daleco, Neth.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Refzil-O *Ranbaxy, India.*
Cefprozil (p. 248·2).
Bacterial infections.

Regadrin B *Berlin-Chemie, Cz.†*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Regain *R&D, USA.*
Nutritional supplement in renal failure.

Regaine *Johnson & Johnson, Austral.; Janssen-Cilag, Austria; McNeil, Belg.†; Johnson & Johnson, Braz.; Pfizer, Chile†; McNeil, Cz.; McNeil, Denm.; McNeil, Fr.†; McNeil, Ger.; Johnson & Johnson, Gr.; Johnson & Johnson, Hong Kong; Johnson & Johnson, Hung.; Pfizer, Indon.†; McNeil Healthcare, Irl.; Pharmacia, Israel; Johnson & Johnson, Ital.; Johnson & Johnson, Malaysia; Johnson & Johnson Consumer, Mex.; Johnson & Johnson, Neth.; Pfizer, Pol.; Johnson & Johnson, Port.; Johnson & Johnson, Rus.; Johnson & Johnson, S.Afr.; Johnson & Johnson, Singapore; Johnson & Johnson, Spain†; Janssen-Cilag, Switz.; Johnson & Johnson, Thai.; McNeil, UK; Johnson & Johnson, Ukr.†*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Regard *Smith & Nephew, S.Afr.†*
⊗Glycerol (p. 2517·2).
Lubrication.

Regasec *Combiphar, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Regasinum antallergicum *Rowa, Ger.*
Apis mellifica (p. 2445·2); aralia racemosa; naja tripudians; acid. formicicum (p. 2507·1).
Homoeopathic preparation.

Regastin *Combiphar, Indon.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Regata *Konimex, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); calamine (p. 1697·2); camphor (p. 2466·2).
Skin irritation.

Regaxidil *Cantabria, Spain.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Régéderm *Synergia, Fr.*
Evening primrose oil (p. 2502·2); fish oil (p. 1460·1); vitamins; minerals.
Skin disorders.

Regenaplex *Regenaplex, Ger.*
A range of homoeopathic preparations.
Homoeopathic preparation.

Regenaplex Haut G *Regenaplex, Ger.*
Arctium lappa (p. 2540·1); arnica montana (p. 2447·2); echinacea angustifolia (p. 2498·1); euphorbia palustris (p. 2501·3); juglans regia (p. 2646·1); levisticum officinale (p. 2545·3); rhus toxicodendron (p. 2603·3); sulfur (p. 1721·1); trigonella foenum graecum (p. 2504·1); viola tricolor (p. 2647·3).
Homoeopathic preparation.

Regenaplex Haut W *Regenaplex, Ger.*
Achillea millefolium (p. 2427·3); acidum nitricum (p. 2572·3); arnica montana (p. 2447·2); artemisia abrotanum; bellis perennis (p. 2454·2); carbo animalis; chamomilla recutita (p. 2474·1); echinacea angustifolia (p. 2498·1); hamamelis virginiana (p. 2523·3); nasturtium officinale.
Homoeopathic preparation.

Regenaplex Nr. 3 *Regena, Switz.*
Aloe (p. 1816·1); angelica archangelica (p. 2443·3); arnica montana (p. 2447·2); atropa belladonna (p. 2453·3); euphrasia (p. 2502·1); gelsemium sempervirens (p. 2511·2); peucedanum ostruthium; ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Regenaplex Nr. 12 *Regena, Switz.*
Acidum arsenicosum (p. 2448·1); aesculus hippocastanum (p. 2431·2); aloe (p. 1816·1); arnica montana (p. 2447·2); cuprum aceticum (p. 2486·2); cuprum metallicum (p. 2057·1); helleborus niger; hypericum perforatum (p. 449·1); natrium tetrachloroauratum (p. 2521·2); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Regenaplex Nr. 79 *Regena, Switz.*
Agrimonia eupatoria (p. 2432·3); ammonium chloratum (p. 1656·1); aurum metallicum (p. 2521·1); chamomilla recutita (p. 2474·1); chelidonium majus (p. 2522·2); hepatica nobilis; lachesis mutus (p. 2538·3); levisticum officinale (p. 2545·3); nasturtium officinale; taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Regenaplex Nr. 25a *Regena, Switz.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); calvatia gigantea; graphites (p. 2522·1); plumbum aceticum (p. 2541·3); semecarpus anacardium (p. 2471·3); strychnos nux-vomica (p. 2573·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Regenaplex Nr 28a *Regena, Switz.*
Acidum arsenicosum (p. 2448·1); acidum hydrochloricum (p. 2528·3); acidum nitricum (p. 2572·3); agave americana (p. 2578·2); angelica archangelica (p. 2443·3); apis mellifica (p. 2445·2); cochlearia officinalis; glechoma hederacea (p. 2523·1); lachesis mutus (p. 2538·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Regenaplex Nr. 31a *Regena, Switz.*
Acidum nitricum (p. 2572·3); aesculus hippocastanum (p. 2431·2); calvatia gigantea; cuprum metallicum (p. 2057·1); hamamelis virginiana (p. 2523·3); pulsatilla pratensis (p. 2600·2); toxicodendron quercifolium (p. 2603·3); veratrum album (p. 2644·3).
Homoeopathic preparation.

Regenaplex Nr 41a *Regena, Switz.*
Acidum arsenicosum (p. 2448·1); aconitum napellus (p. 2428·3); angelica archangelica (p. 2443·3); apisinum dil (p. 2434·3); arnica montana (p. 2447·2); baptisia tinctoria (p. 2647·2); bellis perennis (p. 2454·2); bryonia (p. 2461·3); echinacea (p. 2498·1); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Regenaplex Nr. 49a *Regena, Switz.*
Arctostaphylos uva-ursi (p. 2453·2); arnica montana (p. 2447·2); berberis vulgaris (p. 2502·1); hamamelis virginiana (p. 2523·3); piper cubeba (p. 2489·2); pulsatilla pratensis (p. 2600·2); serenoa repens (p. 2363·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Regenaplex Nr 86a *Regena, Switz.*
Acidum arsenicosum (p. 2448·1); acidum nitricum (p. 2572·3); arctostaphylos uva-ursi (p. 2453·2); arnica montana (p. 2447·2); chondrodendron; lytta vesicatoria (p. 2469·2); pulsatilla pratensis (p. 2600·2); solanum dulcamara (p. 2497·3).
Homoeopathic preparation.

Regenaplex Nr. 80aN *Regena, Switz.*
Agrimonia eupatoria (p. 2432·3); aloe (p. 1816·1); arctium (p. 2540·1); dioscorea villosa (p. 2648·1); genista tinctoria; myrica cerifera; silybum marianum (p. 1561·1); taraxacum officinale (p. 2625·3); veronica virginica.
Homoeopathic preparation.

Regenaplex Nr. 24b *Regena, Switz.*
⊗Acidum arsenicosum (p. 2448·1); argentum nitricum (p. 2615·3); atropa belladonna (p. 2453·3); aurum metallicum (p. 2521·1); capsicum annuum (p. 2469·3); cumarinum (p. 2487·2); cuprum aceticum (p. 2486·2); euspongia officinalis; lachesis mutus (p. 2538·3); lobelia inflata (p. 2323·2).
Homoeopathic preparation.

Regenaplex Nr. 25b *Regena, Switz.*
Achillea millefolium (p. 2427·3); acidum nitricum (p. 2572·3); agrimonia eupatoria (p. 2432·3); aloe (p. 1816·1); apisinum (p. 2434·3); arnica montana (p. 2447·2); calvatia gigantea; strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Regenaplex Nr 28b *Regena, Switz.*
Acidum arsenicosum (p. 2448·1); ammonium carbonicum (p. 1656·1); apisinum (p. 2434·3); baptisia tinctoria (p. 2647·2); lytta vesicatoria (p. 2469·2); natrium chloratum (p. 1795·1); natrium tetraboracicum (p. 2459·2); phytolacca americana (p. 2593·2); ranunculus sceleratus; solanum dulcamara (p. 2497·3).
Homoeopathic preparation.

Regenaplex Nr. 31b *Regena, Switz.*
Acidum benzoicum (p. 1738·2); acidum hydrofluoricum (p. 2529·1); aesculus hippocastanum (p. 2431·2); berberis vulgaris (p. 2502·1); hamamelis virginiana (p. 2523·3); lycopodium clavatum (p. 2547·1); sulfur (p. 1721·1); sulfur iodatum (p. 2624·2).
Homoeopathic preparation.

Regenaplex Nr. 35b *Regena, Switz.*
Acidum arsenicosum (p. 2448·1); agrimonia eupatoria (p. 2432·3); bryonia (p. 2461·3); chamomilla recutita (p. 2474·1); cinchona pubescens (p. 2478·3); lachesis mutus (p. 2538·3); silybum marianum (p. 1561·1); veronica virginica.
Homoeopathic preparation.

Regenaplex Nr 38b *Regena, Switz.*
Aesculus hippocastanum (p. 2431·2); aluminium oxydatum (p. 1690·3); allium sativum (p. 2510·3); atropa belladonna (p. 2453·3); bryonia (p. 2461·3); calcium phosphoricum (p. 1784·2); cephaelis ipecacuanha (p. 1667·2); drosera (p. 2497·2).
Homoeopathic preparation.

Regenaplex Nr. 50b *Regena, Switz.*
Acidum nitricum (p. 2572·3); allium sativum (p. 2510·3); aloe (p. 1816·1); apis mellifica (p. 2445·2); arnica montana (p. 2447·2); bryonia (p. 2461·3); eucalyptus globulus (p. 2501·1); hepar sulfuris (p. 1721·3).
Homoeopathic preparation.

Regenaplex Nr. 59b *Regena, Switz.*
Achillea millefolium (p. 2427·3); acidum nitricum (p. 2572·3); aesculus hippocastanum (p. 2431·2); aloe (p. 1816·1); carbo vegetabilis (p. 1537·3); cinchona pubescens (p. 2478·3); hamamelis virginiana (p. 2523·3); hydrastis canadensis (p. 2528·1); kreosotum (p. 1659·3); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Regenaplex Nr. 71b *Regena, Switz.*
Acidum nitricum (p. 2572·3); aloe (p. 1816·1); aurum chloratum (p. 2521·1); aurum metallicum (p. 2521·1); euphorbia palustris (p. 2501·3); fucus vesiculosus (p. 2612·1); hydrastis canadensis (p. 2528·1); pulsatilla pratensis (p. 2600·2); sulfur (p. 1721·1); verbascum densiflorum (p. 2645·1).
Homoeopathic preparation.

Regenaplex Nr. 88b *Regena, Switz.*
Acidum silicicum (p. 2208·3); argentum nitricum (p. 2615·3); arnica montana (p. 2447·2); aurum metallicum (p. 2521·1); calcium carbonicum hahnemanni (p. 1824·3); magnesium carbonicum (p. 1856·2); stillingia silvatica; symphytum officinale (p. 2484·2).
Homoeopathic preparation.

Regenaplex Nr. 21c *Regena, Switz.*
Acidum lacticum (p. 2539·1); acidum silicicum (p. 2208·3); aconitum napellus (p. 2428·3); calcium fluoratum (p. 2053·1); cimicifuga racemosa (p. 2478·1); colchicum autumnale; helichrysum arenarium; ledum palustre (p. 2550·1); lithium carbonicum (p. 427·3); veratrum album (p. 2644·3).
Homoeopathic preparation.

Regenaplex Nr. 24c *Regena, Switz.*
Acidum silicicum (p. 2208·3); aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); arsenum iodatum (p. 2448·1); aspidosperma quebracho-blanco (p. 2601·2); aurum metallicum (p. 2521·1); graphites (p. 2522·1); kalium iodatum (p. 2336·3); lobaria pulmonaria (p. 2546·1); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

Regenaplex Nr. 25c *Regena, Switz.*
Acidum nitricum (p. 2572·3); aesculus hippocastanum (p. 2431·2); alchemilla vulgaris; causticum hahnemanni (p. 2595·3); ferrum iodatum (p. 2061·3); hamamelis virginiana (p. 2523·3); lachesis mutus (p. 2538·3); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Regenaplex Nr. 31c *Regena, Switz.*
Achillea millefolium (p. 2427·3); aconitum napellus (p. 2428·3); aesculus hippocastanum (p. 2431·2); aloe (p. 1816·1); arnica montana (p. 2447·2); hamamelis virginiana (p. 2523·3); pulsatilla pratensis (p. 2600·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Regenaplex Nr. 51c *Regena, Switz.*
Acidum sulfuricum (p. 2624·2); aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); berberis vulgaris (p. 2502·1); calcium carbonicum hahnemanni (p. 1824·3); calcium fluoratum (p. 2053·1); lithium carbonicum (p. 427·3); lycopodium clavatum (p. 2547·1).
Homoeopathic preparation.

Regenaplex Nr. 21e *Regena, Switz.*
Acidum benzoicum (p. 1738·2); acidum hydrochloricum (p. 2528·3); acidum hydrofluoricum (p. 2529·1); acidum lacticum (p. 2539·1); acidum silicicum (p. 2208·3); berberis vulgaris (p. 2502·1); kalium iodatum (p. 2336·3); petroleum rectificatum (p. 2201·2); plectranthus fruticosus; sanguinaria canadensis (p. 2610·1).
Homoeopathic preparation.

Regenbiol X *Del Sol, Arg.*
Amino acids; vitamins.

Regencel *Latinofarma, Braz.*
Vitamin A acetate (p. 2098·3); amino acids; chloramphenicol (p. 257·1).

Regen-D *Bharat, Thai.*
Recombinant human epidermal growth factor (p. 1894·3).
Diabetic foot ulcers; bedsores; chronic leg ulcers.

Regender *Pharmasac, Port.; Alacan, Spain.*
Polypodium leucotomos.
Skin disorders; psoriasis.

Regenecare *MPM, USA.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Regeneresen *Dyckerhoff, Ger.†*
Ribonucleic acid (p. 2604·1).
Tonic.

Regenesis *Elea, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Regenesis Max *Elea, Arg.*
4 Tablets, alendronate sodium (p. 1171·3); 28 tablets, calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Regenex *Rider, Chile.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Regenia *Floxia, Singapore.*
Emollient.

Regenom *Uniao Quimica, Braz.*
Vitamin A acetate (p. 2098·3); chloramphenicol (p. 257·1); methionine (p. 1558·2).
Infected eye disorders.

Regenon *Temmler, Denm.; Temmler, Ger.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Regental *Tecnofarma, Chile.*
Nimodipine (p. 1455·2).
Alzheimer's disease; cerebrovascular insufficiency; mental function impairment; neurological deficit following subarachnoid haemorrhage.

Regepithel *Alcon, Ger.*
Vitamin A palmitate (p. 2098·3); thiamine hydrochloride (p. 2103·1); calcium pantothenate (p. 2085·2).
Corneal defects.

Regeron Vita *More, Philipp.*
Vitamins; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Regeron Vita with Chlorella *More, Philipp.*
Oral drops: Vitamins; zinc sulfate (p. 2126·2); taurine (p. 2626·2); chlorella (p. 2475·3).
Nutritional supplement.

More, Philipp.
Syrup: Vitamins; zinc sulfate (p. 2126·2); taurine (p. 2626·2); lysine (p. 2079·3); chlorella (p. 2475·3).
Nutritional supplement.

Regeron-C *More, Philipp.*
Vitamins.
Nutritional supplement.

Regeron-E Plus *More, Philipp.*
Vitamins; ferrous sulfate (p. 2062·2); buclizine hydrochloride (p. 618·3).
Appetite stimulant; nutritional supplement.

Regevac B *Binnofarm, Rus.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Regibloc *Intramed, S.Afr.†*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Regimex *WraSer, USA.*
⊗Benzfetamine hydrochloride (p. 2318·1).
Obesity.

Regina Royal Concorde *Regina, UK.*
Royal jelly (p. 2608·1); ginseng (p. 2513·3); damiana aphrodisiaca (p. 2491·3); saw palmetto (p. 2363·3).

Regina Royal Five *Regina, UK.*
Royal jelly (p. 2608·1); bee pollen (p. 2593·3); pure honey (p. 2072·1).

Regina Royal One Hundred *Regina, UK.*
Royal jelly (p. 2608·1).

Reginicid *Themis, Rus.*
Ethionamide (p. 297·3).
Tuberculosis.

Reginon *Kocak, Turk.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).

Regiocaina *Richmond, Arg.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Regioderm *Regiomedica, Neth.*
Acitretin (p. 1690·3).
Psoriasis; keratinisation disorders.

Regioletrozol *Regiomedica, Neth.*
⊗Letrozole (p. 817·1).
Breast cancer.

Regit *Landson, Indon.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia.

Regitina *Novartis, Arg.*
Phentolamine mesilate (p. 1468·3).
Hypertensive crisis.

Regitine *Novartis, Austral.; Novartis, Belg.†; Novartis, China; IFET [ΙΦΕΤ], Gr.; Novartis, Hong Kong†; Novartis, Hung.†; Novartis, Israel; Novartis, Neth.; Novartis, NZ.*
Phentolamine mesilate (p. 1468·3).
Phaeochromocytoma; noradrenaline extravasation.

Régitine *Novartis, Switz.*
Phentolamine mesilate (p. 1468·3).
Phaeochromocytoma; dermal necrosis and sloughing following intravenous administration of noradrenaline.

Regivell *Novell, Indon.; Novell, Thai.*
Bupivacaine hydrochloride (p. 1980·3).
Spinal anaesthesia.

Regla pH *UCB, Gr.; Pierre Fabre, Neth.*
Chewable tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer; antacid.

UCB, Gr.; UCB, Neth.†
Oral suspension: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Antacid; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Regla pH Forte
Note: this name may be used for preparations of different composition.
Pierre Fabre Sante, Belg.
Algeldrate (p. 1817·2); magnesium oxide (p. 1857·3); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastric hyperacidity; peptic ulcer.

Reglan *CFL, India; Ani, USA; Baxter, USA.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastro-oesophageal reflux; diabetic gastroparesis; adjunct in gastrointestinal procedures; gastritis; dyspepsia; postoperative gastric hypotonia.

Reglomar *Brymar, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; motion sickness; Ménière's disease.

Reglus *Landson, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Reglusan *Novag, Mex.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Regnite *Astellas, Jpn.*
Gabapentin enacarbil (p. 524·1).
Restless legs syndrome.

Regolact Plus *Naturmed, Ital.*
Lactic-acid-producing organisms (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Regolpause *Provita, Ital.*
Vitamins; minerals.

Regost *Regiomedica, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Regoxal *Vargas, Venez.*
Bisoxatin acetate (p. 1823·2).
Bowel evacuation; constipation.

Regpara *Kyowa, Hong Kong; Kyowa, Jpn.*
Cinacalcet hydrochloride (p. 1180·1).
Hyperparathyroidism in dialysis patients with chronic renal failure.

Regranex *Janssen-Cilag, Austria†; Janssen-Ortho, Canad.†; Janssen-Cilag, Cz.†; Ethicon, Fr.†; Janssen-Cilag, Ger.†; IFET, Gr.; Janssen-Cilag, Gr.; Janssen-Cilag, Irl.†; Janssen-Cilag, Israel†; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.†; Janssen-Cilag, Port.†; Esteve, Spain†; Janssen-Cilag, Switz.†; Janssen-Cilag, UK†; Smith & Nephew, USA.*
⊗Becaplermin (p. 1695·2).
Diabetic neuropathic ulcers; wounds.

Regresor *Simex, Indon.*
Vitamin C (p. 2110·3); taurine (p. 2626·2).
Dietary supplement.

Regripax *Biofarma, Mex.*
Echinacea (p. 2498·1).
Cold and influenza.

Regro *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Minoxidil (p. 1438·3).
Alopecia androgenetica; alopecia areata.

Regroe *Dermpharma, Philipp.*
Minoxidil (p. 1438·3).
Alopecia.

Regroton *Novartis, Turk.; Rhone-Poulenc Rorer, USA.*
⊗Chlortalidone (p. 1335·2); reserpine (p. 1485·3).
Hypertension.

Regrou *Surya Dermato, Indon.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Regrowth *Medicine Products, Thai.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Regtect *Shinyaku, Jpn.*
Acamprosate calcium (p. 1034·2).
Alcoholism.

Regubil *Riva, Canad.*
Biliary salts (p. 2457·2); dehydrocholic acid (p. 2492·1); deoxycholic acid (p. 2457·2).
Biliary-tract disorders.

Regucal *Baliarda, Arg.*
Calcium pidolate (p. 1784·3).
Calcium deficiency; chronic renal failure.

Regucal D *Baliarda, Arg.*
Calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; hypocalcaemia; osteoporosis.

Regucol *Procter & Gamble, Neth.†*
Ispaghula (p. 1849·1).
Constipation.

Regulacid *Lazar, Arg.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Regulacor-POS *Ursapharm, Ger.†*
Crataegus (p. 2488·1).
Cardiac disorders.

Regulact *Valeant, Mex.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Regulan *Procter & Gamble, Irl.; Procter & Gamble, UK.*
Ispaghula (p. 1849·1).
Constipation.

Regulane *Finadiet, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Regulane AF *Finadiet, Arg.*
Loperamide hydrochloride (p. 1854·2); simeticone (p. 1886·2).
Diarrhoea; flatulence.

Regular Iletin II *Lilly, USA.†*
⊗Insulin injection (porcine) (p. 475·3).
Diabetes mellitus.

Regular Multi-Tar Plus *Valeant, Canad.*
Coal tar (p. 1723·2); cade oil (p. 1723·2); tar (p. 1723·3); pyrithione zinc (p. 1718·1).
Scalp disorders.

Regular Strength Bayer *Sterling Health, USA.*
Aspirin (p. 22·2).
Formerly known as Therapy Bayer.
Pain; fever; inflammation; transient ischaemic attacks; myocardial infarction.

Regular Strength Flu Relief Nightime *Vita Health, Canad.†*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

Regular Strength Lactaid *McNeil Consumer, Canad.*
Tilactase (p. 2631·2).
Lactose intolerance.

Regular Strength Sinus Medication *Vita Health, Canad.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); doxylamine succinate (p. 627·3).

Regular Vita-Vim *Jamieson, Canad.*
Vitamins; minerals.

Regulaten *Juste, Spain.*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Regulaten Plus *Juste, Spain.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Regulator *Floxia, Singapore.*
Zinc gluconate (p. 2126·2); salicylic acid (p. 1719·1); melaleuca oil (p. 2551·1).
Moisturiser for oily skin.

Regulax
Note: this name may be used for preparations of different composition.
Phoenix, Hung.; Krewel Meuselbach, Pol.; Krewel, Rus.; Krewel, Ukr.
Senna (p. 1885·1).
Constipation.

Regulax Picosulfat *Krewel, Ger.*
Sodium picosulfate (p. 1887·2).
Constipation.

Regulax Picosulphate *Krewel, Rus.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Regulax Pikosulfat *Krewel Meuselbach, Cz.*
Sodium picosulfate (p. 1887·2).
Constipation.

Regulim *Atlantic, Thai.†*
Phenolphthalein (p. 1877·3).
Constipation; bowel evacuation.

Regulip *Raffo, Arg.*
Salmon oil (p. 1460·1).
Hyperlipidaemias.

Reguloid *Rugby, USA.*
Psyllium hydrophilic mucilloid (p. 1849·1).
Constipation.

Regulon *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Richter, Pol.; Grunenthal, Port.; Gedeon Richter, Rus.; Gedeon Richter, Spain; Gedeon Richter, Ukr.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Reguloop *Tunggal Idaman, Indon.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Regulose *Novartis Consumer, UK.*
Lactulose (p. 1850·3).
Constipation.

Regulton *Abbott, Belg.; Teofarma, Ger.*
⊗Amezinium metilsulfate (p. 1298·3).
Hypotension.

Regultron *Bajamed, Mex.*
Fluoxetine (p. 417·1).
Depression.

Regumen *Caprifarmindo, Indon.*
Norethisterone (p. 2294·2).
Dysfunctional uterine bleeding; endometriosis; premenstrual syndrome; postponement of menstruation; menorrhagia; dysmenorrhoea.

Regumet *Sydenham, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Regurin *Madaus, Irl.; Speciality European Pharma, UK.*
Trospium chloride (p. 2371·1).
Bladder instability.

Rehalyt *SAD, Denm.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Rehidrat *Eurofarma, Braz.*
Potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Johnson & Johnson, S.Afr.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); glucose (p. 2068·3); sucrose (p. 2096·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Pharmacia, Irl.†
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); glucose (p. 2068·3); sucrose (p. 2096·3); fructose (p. 2068·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Rehmannia Complex *Mediherb, Austral.*
Bupleurum; rehmannia glutinosa root; hemidesmus indicus root; feverfew (p. 676·1).
Tonic.

Rehsal *Laboratorios Chile, Chile.*
Electrolytes (p. 1775·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Rehydralyte *Abbott, Thai.*
Glucose (p. 2068·3); sodium (p. 1795·1); potassium (p. 1793·1); chloride; citrate (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Ross, USA.
Oral rehydration solution (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Rehydrex med glucos *Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Rehydrex med Glucose *Fresenius Kabi, Denm.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Rehydron *Orion, Rus.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Orion, Ukr.
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); anhydrous glucose (p. 2069·1) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Rehydrosol *Teva, Hung.†*
Electrolytes (p. 1775·1); sorbitol (p. 2092·1).
Carbohydrate source; fluid and electrolyte disorders.

Rehyla *Medimetriks, USA.*
Soap substitute.

Reichamox *Medreich, Hong Kong.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Reidramax *Cazi, Braz.*
Glucose (p. 2068·3); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1) (p. 1780·1).
Oral rehydration therapy.

Reidratante *Catarinense, Braz.†*
Glucose (p. 2068·3); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1) (p. 1780·1).
Oral rehydration therapy.

Reinbamate *Chew, Thai.*
Meprobamate (p. 1083·3).

Reinin *Medichem, Philipp.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Reinosan *Singer Natura, Neth.*
Orthosiphon (p. 2536·3).

Reisefit *Hennig, Ger.*
Dimenhydrinate (p. 625·2).
Motion sickness; dizziness; nausea and vomiting.

Reisetabletten *1A, Ger.†; AbZ, Ger.†; Aliud, Ger.†; CT, Ger.†; Ratiopharm, Ger.†*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo; nausea; vomiting.

Rejuva *GSK, Canad.*
SPF 30: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1).
Sunscreen.

Rejuva-A *GSK, Canad.*
Tretinoin (p. 1725·2).
Photodamaged skin.

Rejuvan *UAP, Indon.†*
Vitamin A (p. 2098·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1); ferrous fumarate (p. 2060·3).
Tonic.

RejuvaSkin Anti-Aging Serum *Scar Heal, Singapore.*
Ubidecarenone (p. 2637·1); hyaluronic acid (p. 2526·2); collagen (p. 2483·2).
Skin ageing; sun-induced skin damage.

Rejuvenex *Manix, Philipp.*
Vitamins; minerals; choline bitartrate (p. 2055·2); methionine (p. 1558·2); inositol (p. 2533·2); ginseng (p. 2513·3).
Tonic.

Rejuvon *Eurowest, Philipp.*
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3).
Nutritional supplement.

Reka *Inpac, Thai.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy.

Rekamide *Rekah, Israel.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Rekasitin *Rekah, Israel.†*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3); allantoin (p. 1693·1).
Barrier preparation; burns; nappy rash; skin disorders.

Rekawan *Riemser, Ger.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Rekaxime *CCM, Malaysia.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Rekiv *Rekah, Israel.†*
Magnesium carbonate (p. 1856·2); bismuth subnitrate (p. 1822·1); sodium bicarbonate (p. 1781·1); frangula bark (p. 1843·3); calamus (p. 2464·2).
Gastritis; gastrointestinal hyperacidity; peptic ulcer.

Rekod *Rekah, Israel.*
Codeine phosphate (p. 40·2).
Cough; pain.

Rekont *Madaus, Austria.*
Trospium chloride (p. 2371·1).
Bladder function disorders.

Rekord B12 *Sigma-Tau, Ital.*
Amino acids; vitamin B substances (p. 2102·3).
Tonic.

Rekord Ferro *Sigma-Tau, Ital.*
Iron succinyl-protein complex (p. 2077·3).
Iron deficiency; iron-deficiency anaemia.

Rekostin *Biofarm, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Rektiolax *Marmir, Pol.*
⊗Sodium laurilsulfate (p. 2210·3); sodium citrate (p. 1781·2); sorbitol (p. 2092·1); glycerol (p. 2517·2).
Bowel evacuation; constipation.

Relacon Lax *Cypress, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Relacon-DM *Cypress, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs; nasal congestion.

Relacon-HC *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cough; upper respiratory-tract congestion.

Relactagel *Kora, Ger.; Kora, Irl.; Kora, UK.*
Lactic acid (p. 2539·1).
Bacterial vaginosis; restoration of vaginal pH and flora.

Relacton *Unipharma, Gr.*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1).
Pain; muscle spasm.

Relacum *Pisa, Mex.*
Midazolam (p. 1085·1).
Premedication; general anaesthesia; sedative.

Reladorm *Tarchomin, Rus.*
Diazepam (p. 1063·2); cyclobarbital calcium (p. 1062·3).
Sleep disorders.

Relafen *GSK, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Relaflex *Hertz, Braz.*
Dipyrone (p. 53·3); orphenadrine citrate (p. 909·2); caffeine (p. 1203·3).
Pain; smooth muscle spasm.

Relagesic *International Ethical, USA.*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Relahist-DM *Cypress, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; allergic rhinitis.

Relana *Cederroth, Denm.†; Pharbio, Pol.†; Cederroth, Spain.†*
Valerian (p. 2640·2); melissa (p. 2552·3).
Anxiety; nervous disorders.

Relana Forte *Pharbio, Pol.*
Valerian (p. 2640·2).
Anxiety; insomnia.

Relanium *GSK, Pol.; Medana, Pol.; Polfa Warszawa, Pol.; Warsaw-Polfa, Rus.; Polfa Warsaw, Ukr.*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal syndrome; premedication; skeletal muscle spasm; epilepsy; convulsions; tetanus; eclampsia; delirium tremens.

Relapamil *Orion, Fin.†*
Quinine hydrochloride (p. 665·2); diazepam (p. 1063·2).
Muscle spasm.

Relapax *Cazi, Braz.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm.

Relapaz *Alter, Spain.*
Citalopram hydrobromide (p. 411·1).
Depression; anxiety; obsessive-compulsive disorder.

Relar *Pharmaland, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Muscle pain; tension headache.

Relasin-HCX *Cypress, USA.*
Guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Cough.

Relatene *Mintlab, Chile.*
Ketoprofen (p. 79·1).
Inflammation; pain.

Relatrac *Pisa, Mex.†*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Relavit Fosforo *Lusomedicamenta, Port.*
Glutamine (p. 2070·3); thiamine hydrochloride (p. 2103·1); calcium magnesium fytate (p. 1553·3).
Mental function disorders.

Relax
Note: this name may be used for preparations of different composition.
Marien, Austria.
Ambra grisea (p. 2440·3); aurum metalicum (p. 2521·1); cypripedium calceolus; myristica fragrans (p. 2573·1); scutellaria lateriflora (p. 2617·1); strychnos ignatii (p. 2532·1).
Homoeopathic preparation.

Relax B *Vitalia, UK.*
Valerian (p. 2640·2); lupulus (p. 2546·1); passion flower (p. 2584·1); vitamin B substances (p. 2102·3).

Relax Plus *Lalco, Canad.*
Lupulus (p. 2546·1); tilia (p. 2631·3); origanum (p. 2576·3); paeonia officinalis; passion flower (p. 2584·1).
Nervous disorders; insomnia.

Relaxa *Red Leaf, Canad.*
Macrogol 3350 (p. 2547·3).

Relaxane *Zeller, Switz.*
Butterbur (p. 2463·2); valerian (p. 2640·2); passion flower (p. 2584·1); melissa (p. 2552·3).
Nervous disorders; sleep disorders.

Relaxant *Pharmetics, Canad.*
Lupulus (p. 2546·1); tilia (p. 2631·3); melissa (p. 2552·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Relaxar *Bouty, Ital.*
Ointment: Mephenesin (p. 2025·2); methyl nicotinate (p. 91·3).
Muscular pain.

Relaxa-Tabs *Woods, Austral.†*
Mepyramine maleate (p. 635·1).
Nervous tension; insomnia.

Relaxcol *Cristalfarma, Ital.*
Green clay; fennel (p. 2503·2); star anise (p. 2622·1); caraway (p. 2470·2); fennel oil (p. 2503·3); caraway oil (p. 2470·3); cinnamon oil (p. 2479·3); fruit oligosaccharides (p. 2508·1).
Gastrointestinal disorders with excess gas.

Relaxedan *Bago, Arg.*
Pridinol (p. 2026·1).
Muscle spasm.

RelaxHerb *Schwabe, UK.*
Passion flower (p. 2584·1).
Anxiety.

Relaxic *Chinta, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle pain and spasm.

Relaxil
Note: this name may be used for preparations of different composition.
KVZ, Ukr.
Valerian (p. 2640·2); peppermint (p. 1877·1); melissa (p. 2552·3).
Nervous disorders; sleep disorders; dysmenorrhoea; menopausal symptoms; digestive disorders.

Arrow, Braz.†
Bromazepam (p. 1041·2).
Anxiety.

Relaxil-G *PannonPharma, Hung.*
Guaifenesin (p. 1666·2).
Skeletal muscle spasm and paralysis.

Relaxin *Kyorin, Jpn.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Relaxine *Trenker, Belg.; Trenka, Israel.*
Valerian (p. 2640·2).
Insomnia; nervous disorders; sleep disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Relaxisleep *English Herbal Medicines, UK.*
Valerian (p. 2640·2).
Anxiety; insomnia.

Relaxit
Note: this name may be used for preparations of different composition.
Abigo, Swed.
Sodium bicarbonate (p. 1781·1); potassium acid tartrate (p. 1879·2); calcium silicate (p. 1784·3).
Constipation; faecal incontinence.
Crawford, UK.
⊗Sodium citrate (p. 1781·2); sodium laurilsulfate (p. 2210·3); sorbic acid (p. 1770·2); glycerol (p. 2517·2); sorbitol (p. 2092·1).
Constipation.

Relaxo *UB, Switz.*
Passion flower (p. 2584·1); lupulus (p. 2546·1); valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; sleep disorders.

Relaxol
Note: this name may be used for preparations of different composition.
Biofarma, Turk.
Citalopram hydrobromide (p. 411·1).
Depression.
Bio-Sante, Canad.
Lupulus (p. 2546·1); tilia (p. 2631·3); melissa (p. 2552·3); passion flower (p. 2584·1); valerian (p. 2640·2).
Insomnia; nervous disorders.

Relaxon *Veropharm, Rus.*
Zopiclone (p. 1118·1).
Sleep disturbances.

Relaxophen *Tanta, Canad.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).

Relaxten *Biotenk, Arg.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Relaxyl
Note: this name may be used for preparations of different composition.
Franco-Indian, India.
Ointment: Mephenesin (p. 2025·2); methyl nicotinate (p. 91·3); capsicum oleoresin (p. 2469·3).
Musculoskeletal, joint, and soft-tissue disorders.
Franco-Indian, India.
Slow-release tablets; tablets: Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders.
Franco-Indian, India.
Topical gel: Diclofenac diethylamine (p. 48·3).
Soft-tissue disorders.
Nycomed, Austria.†
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation; constipation.

Relaxyl Plus *Franco-Indian, India.*
Diclofenac sodium (p. 48·3); paracetamol (p. 115·1).
Gout; musculoskeletal and joint disorders.

Relazepam *Pisa, Mex.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; premedication; alcohol withdrawal syndrome; sedative.

Relcer *Glenmark, Rus.; Glenmark, Ukr.†*
Algeldrate (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); liquorice (p. 1853·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer; dyspepsia; meteorism; heartburn.

RelCof CPM *Burel, USA.*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

RelCof DN PE *Burel, USA.*
RelCof PE white tablets, chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3); Relcof CPM blue tablets, chlorphenamine maleate; hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

RelCof DN PSE *Burel, USA.*
⊗RelCof PSE green tablets, chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); pseudoephedrine hydrochloride (p. 1676·1); RelCof CPM blue tablets, chlorphenamine maleate; hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

RelCof PSE *Burel, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Relcofen *Alpharma, UK.*
Ibuprofen (p. 68·2).
Pain; fever.

Re-Leaf *Pascual, Philipp.*
Blumea balsamifera.
Renal calculi; oedema.

Releaf for PMS *Lake, USA.*
Pyridoxine hydrochloride (p. 2105·3) in a base of natural herbs.
Premenstrual syndrome.

Release Ag *Ethicon, Fr.†*
Guluronic acid (p. 2167·2); carmellose (p. 2175·1); silver (p. 2615·1).
Ulcers; wounds.

Relefact *Sanofi-Aventis, Gr.†*
Protirelin (p. 2344·2).
Thyroid function test.

Relefact LH-RH *Sanofi-Aventis, Austria†; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Neth.*
⊗Gonadorelin (p. 2280·2).
Diagnosis of hypothalamic-pituitary-gonadal dysfunction; infertility.

Relefact TRH *Odan, Canad.†; Sanofi-Aventis, Neth.*
Protirelin (p. 2344·2).
Diagnosis of hypothalamic-pituitary-thyroid dysfunction.

Relefrina *Klonal, Arg.†*
⊗Prednisolone (p. 1645·2); phenylephrine (p. 1672·2).
Eye disorders.

Relente *Klonal, Arg.*
Sodium chloride (p. 1795·1).
Dry eye; eye irritation.

Relenza *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; Glaxo Wellcome, USA.*
Zanamivir (p. 1024·1).
Influenza.

Relert *Pfizer, Belg.; Oriform, Denm.; Pfizer, Fin.; Pfizer, Israel; Pfizer, Port.; Pfizer, Spain.*
Eletriptan hydrobromide (p. 673·2).
Migraine.

Reless *ALK Abello, Ger.*
Bee venom extract (p. 2434·3) or wasp venom extract (p. 2434·3).
Allergen immunotherapy.

Relestal *Pediatrica, Philipp.*
Dicycloverine hydrochloride (p. 1834·2).
Colic; gastrointestinal disorders.

Relestat *Allergan, Arg.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Chile; Allergan, Denm.; Allergan, Fin.†; Allergan, Ger.; Allergan, Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Allergan, Neth.; Allergan, Pol.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.†; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK.*
Epinastine hydrochloride (p. 628·3).
Allergic conjunctivitis.

Relexil *Laboratorios Chile, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Relhist *Burel, USA.*
Brompheniramine tannate (p. 618·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Reli Slim *Loock, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).

Reliable Mousse Foaming Antiseptic *Reliable, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Reliagic *O2, China.*
Piroxicam (p. 125·3).
Musculoskeletal and joint pain.

Relicof *Unison, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Cough.

Relide *Fahrenheit, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Relidop *Actavis, Denm.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Relief
Note: this name may be used for preparations of different composition.
Bayer, Rus.; Bayer Consumer, Ukr.
Phenylephrine hydrochloride (p. 1672·3); shark-liver oil (p. 2614·2).
Anorectal disorders.
Iasis, Gr.
Thiocolchicoside (p. 2026·2).
Pain.
Pendopharm, Canad.
Paracetamol (p. 115·1).
Pain; fever.
Allergan, USA.†
Phenylephrine hydrochloride (p. 1672·3).
Minor eye irritation.

Relief Advance *Bayer, Rus.; Bayer Consumer, Ukr.*
Benzocaine (p. 1980·2); shark-liver oil (p. 2614·2).
Anorectal disorders.

Relief ASA *Pendopharm, Canad.*
Aspirin (p. 22·2).

Relief Mouth Ulcer *Thai FD, Thai.*
Quercus infectoria (p. 2508·3); menthol (p. 2553·2); patchouli (p. 2584·2).
Mouth ulcers.

Relief Ultra *Bayer, Rus.; Bayer Consumer, Ukr.*
⊗Hydrocortisone acetate (p. 1640·1); shark-liver oil (p. 2614·2); zinc sulfate (p. 2126·2).
Anorectal disorders.

Relief-Coff *Glenmark, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Reliev *Bayer, Chile.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Reliev 76% *Bayer, Chile.*
Sodium amidotrizoate (p. 1581·3); meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Relieve *Unico, Canad.†*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).

Relievo *Sel-J, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; rheumatoid arthritis; osteoarthritis.

Relievol Allergy Sinus *Tanta, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Relievol PMS *Tanta, Canad.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Relievol Sinus *Tanta, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Relif *Meda, Spain.*
Nabumetone (p. 97·1).
Rheumatoid arthritis; osteoarthritis; peri-articular disorders.

Relifen *Sanwa, Jpn; GSK, S.Afr.†*
Nabumetone (p. 97·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Relifex *Meda, Cz.†; Meda, Denm.; Meda, Fin.; Meda, Ger.; Meda, Gr.; Meda, Hung.; Meda, Irl.; Gamida, Israel†; Meda, Ital.; GSK, Mex.; Meda, Norw.; SmithKline Beecham, Philipp.; GSK, Pol.†; Meda, Swed.; GSK, Thai.†; GSK, Turk.; Meda, UK.*
Nabumetone (p. 97·1).
Gout; inflammation; pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Religan *Nexus, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Religer *Gerard, Irl.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Relimal *Pharmachemie, Philipp.*
⊗Morphine sulfate (p. 92·3).
Pain.

Relipain
Note: this name may be used for preparations of different composition.
Gerolymatos, Gr.
Diclofenac diethylamine (p. 48·3).
Inflammatory disorders.

Relisan *Xixia, S.Afr.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Reliser *Serono, Braz.†*
⊗Leuprorelin acetate (p. 2285·3).
Endometriosis; malignant neoplasms.

Relisorm *EMD, Canad.; Serono, Gr.*
⊗Gonadorelin acetate (p. 2280·3).
Diagnosis of hypothalamic-pituitary-gonadal dysfunction.

Relistor *Wyeth, Arg.; Pfizer, Austral.; TMC, Austria; Wyeth, Belg.; Wyeth, Braz.; Pfizer, Canad.; Wyeth, Chile; TMC, Cz.; Wyeth, Denm.; TMC, Fr.; Pfizer, Ger.; TMC, Gr.; TMC, Hung.; TMC, Irl.; TMC, Ital.; TMC, Neth.; TMC, Norw.; TMC, Pol.; TMC, Port.; TMC, Spain; TMC, Swed.; Medius, Switz.; TMC, UK; Salix, USA.*
Methylnaltrexone bromide (p. 1861·3).
Opioid-induced constipation.

Relitone *Garec, S.Afr.†*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Relium *Tarchomin, Rus.*
Diazepam (p. 1063·2).
Anxiety; alcohol withdrawal syndrome; spasticity; skeletal muscle spasm; status epilepticus; premedication; tetanus.

Reliv
Note: this name may be used for preparations of different composition.
GSK Consumer, Swed.
Paracetamol (p. 115·1).
Pain; fever.
Meprofarm, Indon.†
Thioctic acid (p. 2629·1); curcuminoid (p. 2489·3); vitamin B substances (p. 2102·3); phyllanthus niruri (p. 2590·1).
Liver disorders.

Relivan *Novell, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease; premature labour.

Relive *Zyg, Philipp.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Reliveran
Note: this name may be used for preparations of different composition.
Farmasierra, Spain.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.
Novartis, Arg.
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastro-oesophageal reflux; gastro-intestinal motility disorders; gastrointestinal investigations.

Relivopan *AGA, Neth.*
Nitrous oxide (p. 1908·1); oxygen (p. 1799·3).
Pain.

Relivora Komplex *Sanum-Kehlbeck, Ger.*
Drosera (p. 2497·2); echinacea angustifolia (p. 2498·1); juglans (p. 2463·2).
Homoeopathic preparation.

Relmus *Sanofi-Aventis, Port.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasticity; parkinsonism; neuromuscular pain.

Relokap *Yeni, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Relova *Meda, Switz.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; pain.

Relox *Yarindo, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Reloxyl
Note: this name may be used for preparations of different composition.
Sinclair, Ital.
Benzoyl peroxide (p. 1696·1).
Skin disinfection; acne.

Relpax *Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer,*

Ger.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA.
Eletriptan hydrobromide (p. 673·2).
Migraine.

Relsed *Polfa Warszawa, Pol.*
Diazepam (p. 1063·2).
Convulsions; epilepsy; skeletal muscle spasm; premedication.

Reluri *Cypress, USA.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Relvar Ellipta *GSK, UK.*
⊗Fluticasone furoate (p. 1638·1); vilanterol trifenatate (p. 1239·3).
Asthma; obstructive airways disease.

Relyomycin *Relyo, Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Relyovix *Relyo, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Rem *Chobet, Arg.*
Midazolam (p. 1085·1).
General anaesthesia; premedication; sedative.

Remacam *Mugi, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Remafen *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout.

Remakrim *Medikon, Indon.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); methyl nicotinate (p. 91·3).
Musculoskeletal and joint pain; neuralgia.

Remapro *Mersifarma, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; gout; lower back pain; sciatica.

Remasal *Medikon, Indon.†*
Aluminium aspirin (p. 20·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Rheumatic disorders.

Remasan *Remedia, Austria.*
Arnica montana (p. 2447·2).
Homoeopathic preparation.

Rematof *Bernofarm, Indon.†*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; gout; inflammation; pain.

Remavir *Olainfarm, Ukr.*
Rimantadine hydrochloride (p. 1012·2).
Influenza; tick-borne encephalitis.

Remaxol *Polisan, Rus.*
Succinic acid (p. 2214·3); meglumine (p. 2550·3); inosine (p. 2533·1); methionine (p. 1558·2); nicotinamide (p. 2083·1).
Liver disorders.

Remdue *Biomedica, Ital.*
Flurazepam dihydrochloride (p. 1076·1).
Insomnia.

Remecon *Remexa, Mex.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Remedeine *Napp, UK.*
Paracetamol (p. 115·1); dihydrocodeine tartrate (p. 52·3).
Pain.

Remederm *Widmer, Ger.*
⊗Urea (p. 1727·3); vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2); dexpanthenol (p. 2582·2).
Skin disorders.

Widmer, Philipp.†
⊗Vitamin A (p. 2098·3); vitamin E (p. 2119·1); panthenol (p. 2582·2); urea (p. 1727·3); biostimulines.
Dry skin.

Remedia *Simpex, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Remedin *IQFA, Mex.*
Melatonin (p. 2551·3).
Insomnia.

Remedlor *Remed, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Remedol *Remedica, Malaysia; Remedica, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Remedril *Remed, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Cold symptoms; allergic rhinitis; sinusitis.

Remedy *Medline, USA.*
Benzalkonium chloride (p. 1737·1).

Remedy Calazime *Medline, USA.*
Menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation.

Remeflin *Recordati, Ital.*
Dimefline hydrochloride (p. 2321·2).
Respiratory and circulatory disorders.

Remegel
Note: this name may be used for preparations of different composition.
Medlock, Neth.
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Dyspepsia; heartburn.

SSL, Hung.; SSL, Irl.; SSL, Singapore; SSL, UK.
Calcium carbonate (p. 1824·3).
Dyspepsia; heartburn; gastric hyperacidity.

Remegel Wind Relief *SSL, UK.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Dyspepsia; flatulence; heartburn.

Remena *Remedina, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Remens
Note: this name may be used for preparations of different composition.
Bittner, Austria; Bittner, Rus.; Bittner, Ukr.
Cimicifuga (p. 2478·1); sanguinaria (p. 2610·1); jaborandi; sepia (p. 2613·1); lachesis (p. 2538·3).
Homoeopathic preparation.

Svizera, India.
Progesterone (p. 2300·2).
Progesterone deficiency.

Remergil *MSD, Ger.*
Mirtazapine (p. 436·1).
Depression.

Remergon *Organon, Belg.*
Mirtazapine (p. 436·1).
Depression.

Remeron *Organon, Arg.; MSD, Austral.; Organon, Austria; Schering-Plough, Braz.; Merck, Canad.; MSD, China; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Schering-Plough, Indon.; MSD, Israel; Organon, Ital.; Schering-Plough, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; Schering-Plough, NZ†; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Adcock Ingram, S.Afr.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; Organon, Turk.; Organon, Ukr.; Schering-Plough, Ukr.; Organon, USA; Organon, Venez.*
Mirtazapine (p. 436·1).
Depression.

Remestan *Meda, Ger.*
Temazepam (p. 1109·1).
Sleep disorders.

Remestip *Ferring, Ukr.*
⊗Terlipressin (p. 2626·3).
Gastrointestinal haemorrhage; urogenital haemorrhage; metrorrhagia; haemorrhage during abdominal, pelvic, or cervical surgery.

Remestyp *Zentiva, China; Ferring, Cz.; Ferring, Pol.; Ferring, Rus.*
⊗Terlipressin (p. 2626·3).
Haemorrhage.

Remesulid *Farmak, Ukr.†*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Remethan *Remedica, Hong Kong; Remedica, Malaysia.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Remedica, Singapore; Remedica, Thai.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Remex *Genevrier, Fr.*
Aciclovir (p. 964·1).
Herpes labialis.

Remezine *Alapis, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic disorders.

Remicade *Schering-Plough, Arg.; Janssen-Cilag, Austral.; Centocor, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Janssen, Canad.; Schering-Plough, Chile; Xian-Janssen, China; Centocor, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Centocor, Hung.; Tanabe, Indon.; Janssen, Irl.; Janssen-Cilag, Israel; Schering-Plough, Ital.; Mitsubishi Tanabe, Jpn; Schering-Plough, Malaysia; Schering-Plough, Mex.; Janssen, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Schering-Plough, Philipp.; Centocor, Pol.; Janssen, Port.; Schering-Plough, Rus.; Janssen-Cilag, Singapore; Janssen, Spain; MSD, Swed.; MSD, Switz.; Janssen-Cilag, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; MSD, Ukr.; Centocor, USA; Schering-Plough, Venez.*
Infliximab (p. 74·2).
Ankylosing spondylitis; Crohn's disease; rheumatoid arthritis; psoriatic arthritis; psoriasis; ulcerative colitis; spondyloarthropathies; uveitis.

Remicaine *Adcock Ingram, S.Afr.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; arrhythmias.

Remicalcin + D_3 *Schaper & Brummer, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Remicard *Adcock Ingram, S.Afr.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias.

Remicit *AstraZeneca, Arg.*
⊗Remifentanil hydrochloride (p. 128·1).
Analgesia in anaesthesia.

Remicron *Ranbaxy, Malaysia.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Remicut *Kowa, Jpn.*
Emedastine fumarate (p. 628·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Remid *TAD, Ger.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Remidex *AstraZeneca, Port.†*
⊗Anastrozole (p. 742·1).

Remidon *Deva, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Remifein *Pasteur, Philipp.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

Remifemin *Kwizda, Austria; Schaper & Brummer, China; Midsona, Denm.; Schaper & Brummer, Ger.; Phytotec, Hung.; Merck, Indon.†; Merck, Malaysia; Schaper & Brummer, Norw.; Merck, Philipp.; Schaper & Brummer, Pol.; Schaper & Brummer, Singapore; Schaper & Brummer, Spain; Midsona, Swed.; Schaper & Brummer, Thai.*
Cimicifuga (p. 2478·1).
Menopausal disorders; premenstrual syndrome; menstrual disorders.

Remifemin Plus *Phytotec, Hung.*
St John's wort (p. 449·1); cimicifuga (p. 2478·1).
Menopausal disorders.

Remifemin plus *Kwizda, Austria; Schaper & Brummer, Ger.*
St John's wort (p. 449·1); cimicifuga (p. 2478·1).
Menopausal disorders; menstrual disorders.

Remiflo *Richmond, Arg.*
⊗Remifentanil (p. 128·1).

Remikin *Remedina, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Remilev *Ache, Braz.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Sleep disorders; irritability.

Reminal *Leti, Venez.*
Enalapril maleate (p. 1371·1).
Hypertension.

Reminalet *Leti, Venez.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Reminyl *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Shire, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen, Jpn; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Shire, UK.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Remiprostan uno *Recordati, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Remirta *Actavis, Pol.*
Mirtazapine (p. 436·1).
Depression.

Remisid *Darnitsa, Ukr.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Remisil *BioSaude, Port.*
Piroxicam (p. 125·3).
Peri-articular disorders; arthroses.

Remisol *Degorts, Mex.†*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Remisol-Plus *Degorts, Mex.*
Methocarbamol (p. 2025·3); aspirin (p. 22·2).
Musculoskeletal pain.

Remital *Pharos, Indon.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Remitch *Torii, Jpn.*
Nalfurafine hydrochloride (p. 1714·3).
Pruritus.

Remitex *Bago, Chile.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Remitex D *Bago, Chile.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Remizeral *Raffo, Arg.*
Rivastigmine (p. 394·3).
Alzheimer's disease.

RE-186-MM-1 *CIS, Cz.*
Rhenium-186 (p. 2227·2) colloidal sulfide.
Joint disorders.

Remmax *KVZ, Ukr.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Calcium and magnesium supplement; gastric hyperacidity.

Remnos *DDSA Pharmaceuticals, UK.*
Nitrazepam (p. 1089·1).
Insomnia.

Remodulin *Bago, Arg.; Orphan, Austral.; United Therapeutics, Austria; Therabel, Belg.; Unither, Canad.; Mastercare, Chile; United Therapeutics, Cz.; United Therapeutics, Denm.; United Therapeutics, Fin.; Bioprojet, Fr.; OMT, Ger.; United Therapeutics, Ger.; Ferrer, Gr.; IFET (ΙΦΕΤ), Gr.; United Therapeutics, Israel; Dompe, Ital.; United Therapeutics, Neth.; NordicInfu Care, Norw.; United Therapeutics, Port.; NordicInfu Care, Swed.; OrPha, Switz.; United Therapeutics, USA.*
Treprostinil sodium (p. 1518·1).
Pulmonary hypertension.

Remontal *Qualigen, Spain.†*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage; cognitive impairment in the elderly.

Remood *Gedeon Richter, Cz.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Remopain *Dexa, Indon.; Dexa, Philipp.*
Ketorolac trometamol (p. 80·2).
Pain.

Remora *Nobel, Rus.; Nobel, Turk.*
Roxithromycin (p. 356·2).
Bacterial infections.

Remotil *Azevedos, Port.*
Domperidone (p. 1838·1).
Dyspepsia; nausea; vomiting; aid in gastrointestinal examination.

Remotiv *Flordis, Austral.; Sanova, Austria; Ache, Braz.; Ewopharma, Cz.†; Madaus, Ger.†; Phytotec, Hung.; Zeller, Israel; Abbott, Mex.†; Ewopharma, Pol.†; Zeller, Switz.*
St John's wort (p. 449·1).
Depression; anxiety; stress; sleep disorders; insomnia; mood disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Remotive *Aboca, Ital.*
St John's wort (p. 449·1).
Depression.

Remotrox *Pharmaceutical Enterprises, S.Afr.†*
Dicycloverine hydrochloride (p. 1834·2); dried aluminium hydroxide gel (p. 1817·2); light magnesium oxide (p. 1857·3).
Gastrointestinal disorders.

Remov *Piam, Ital.*
Nimesulide (p. 101·3).
Pain.

Removab *Fresenius Biotech, Austria; Fresenius Biotech, Cz.; Fresenius Biotech, Denm.; Fresenius Biotech, Fr.; Fresenius Biotech, Ger.; Fresenius Biotech, Irl.; Neopharm, Israel; Fresenius Biotech, Neth.; Fresenius Biotech, Norw.; Fresenius Biotech, Pol.; Fresenius Biotech, Port.; Swedish Orphan, Swed.; Fresenius Biotech, UK.*
Catumaxomab (p. 762·2).
Malignant ascites.

Remove *Smith & Nephew, Austral.*
Dipropylene glycol methyl ether.
Adhesive remover.

Removil *Liferpal, Mex.*
⊗Ambroxol (p. 1654·3); salbutamol (p. 1220·2).
Respiratory-tract disorders.

Remoxil *Ulagay, Turk.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Remular-S *International Ethical, USA.*
Chlorzoxazone (p. 2022·2).
Musculoskeletal pain.

Remycin *Remedica, Singapore.*
Doxycycline (p. 288·1).
Bacterial infections.

Remystick *Sella, Ital.*
Camphor (p. 2466·2); ethyl salicylate (p. 56·3); menthol (p. 2553·2); capsaicin (p. 35·1).
Musculoskeletal pain.

Ren *Yung Shin, Hong Kong.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Ren Ao *Si Huan, China.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Ren Gan Tai *Yaoda, China.*
Sodium new houttuyfonate.

Ren Ge Duo Na *Baiyi, China.*
Pazufloxacin mesilate (p. 338·1).

Ren Shu *Lunan, China.*
⊗Salbutamol sulfate (p. 1220·2); ipratropium bromide (p. 1211·3).

Ren Su *Yangtze River, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ren Xin *Suzhong, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ren Yi *Chia Tai, China.*
Pamidronate disodium (p. 1186·3).
Paget's disease of bone' hypercalcaemia of malignancy; bone metastases.

Rena *Pharmaland, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Muscle pain; skeletal muscle spasm.

Rena Vite *Cypress, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement for dialysis patients.

Renabetic *Fahrenheit, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Renabrazin *Fahrenheit, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Renacalcio *Biocontrol, Arg.*
Calcium acetate (p. 1783·1) or calcium carbonate (p. 1824·3).
Calcium supplement; hypocalcaemia; osteoporosis; rickets; osteomalacia; hyperphosphataemia in dialysis patients.

Renacardon *Fahrenheit, Indon.*
Enalapril maleate (p. 1371·1).
Hypertension.

Renacenz *Richmond, Arg.; Pharmavita, Chile.*
Peptide extract (Cerebrolysin) (p. 2444·1).
Dementia; brain disorders; cerebral trauma.

Renacept *Landsteiner, Mex.*
Sirolimus (p. 1966·2).
Renal transplant rejection.

Renacet *Proreo, Switz.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia in renal failure patients on dialysis.

Renacidin
Note: this name may be used for preparations of different composition.
Guardian, USA.
Anhydrous citric acid (p. 2480·3); gluconolactone (p. 2515·2); magnesium carbonate (p. 1856·2).
Renal calculi.

HLB, Arg.
Finasteride (p. 2358·3).
Alopecia androgenetica.

Renacor *Teofarma, Ger.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renadinac *Fahrenheit, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation; gout.

ReNaf *Rivers Edge, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Renafit *Ikapharmindo, Indon.*
Preparation for enteral nutrition.
Renal insufficiency.

Renagas *Fahrenheit, Indon.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Peptic ulcer; gastritis; dyspepsia; nocturnal enuresis; irritable bowel disease; smooth muscle spasm.

Renagel *Genzyme, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Braz.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.†; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Kirin, Hong Kong; Genzyme, Hung.; Genzyme, Irl.; Genzyme, Israel; Genzyme, Ital.; Chugai, Jpn; Genzyme, Neth.; Farmagon, Norw.; Pharmaco, NZ; Genzyme, Pol.; Genzyme, Port.; Genzyme, Rus.; LeBasi, S. Afr.; Genzyme, Spain; Genzyme, Swed.; Genzyme, Switz.; Eczacibasi-Baxter, Turk.; Genzyme, UK; Genzyme, USA.*
Sevelamer hydrochloride (p. 1573·1).
Hyperphosphataemia in chronic renal disease.

Renal Caps *Cypress, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Renal Care *Abbott, Ital.*
Preparation for enteral nutrition in renal failure.

Renalapril *Neo Quimica, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Renalgan *Lekkhim-Kharkov, Rus.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Smooth muscle spasm and pain.

Renalof *Tobbest Busindo, Indon.*
Couch-grass (p. 2487·2).
Renal oxalate calculi.

Renalyte *Fahrenheit, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea; vomiting.

Renamid *Fahrenheit, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Renamil *Kora, UK.*
Preparation for enteral nutrition in renal failure.

RenAmin *Baxter, Canad.; Baxter, USA.†*
Amino acids.
Parenteral nutrition.

Renamoca *Fahrenheit, Indon.†*
Thiamphenicol (p. 376·3).
Bacterial infections.

Renapar *Fahrenheit, Indon.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency.

Renapepsa *Fahrenheit, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Renapril *Meditop, Hung.†*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Renapril Plus *Meditop, Hung.†*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renapro *Kora, UK.*
Protein supplement in dialysis and hypoproteinaemia.

Renapur *Algol, Swed.*
Anhydrous potassium citrate (p. 1780·3); anhydrous sodium citrate (p. 1781·2); anhydrous citric acid (p. 2480·3).
Renal calculi.

Renaquil *Fahrenheit, Indon.*
Lorazepam (p. 1080·3).
Anxiety; premedication.

Renase *Pharmaland, Thai.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hepatic cirrhosis with ascites and oedema; hypertension; oedema.

Renasistin *Fahrenheit, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Renastart *Vitaflo, UK.*
Preparation for enteral nutrition.
Dietary management of renal failure.

Renatabs *Hawthorn, USA.*
Vitamins.
Dietary supplement.

Renatabs with Iron *Hawthorn, USA.*
Yellow tablets, vitamins; red tablets, iron carbonyl (p. 2073·1).
Dietary supplement.

Renatac *Fahrenheit, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Renator *Fahrenheit, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Renatrim *Salvang, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Renatriol *Proreo, Switz.*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; rickets.

Rena-Vite *Cypress, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Renax
Note: this name may be used for preparations of different composition.
Everett, USA.
Vitamins; minerals.
Supplement in renal failure.

Interbat, Indon.
Sericocalyx folium; java tea (p. 2536·3); sonchus arvensis folium; plantain (p. 2592·3).
Renal calculi.

Remedica, Hong Kong.†
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Renaxid *Amuchina, Ital.†*
Peracetic acid (p. 1763·1).
Haemodialysis equipment disinfection.

Renazol *ICN, Pol.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Renazole *Lisapharma, Ital.; Regiomedica, Neth.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Rendapid *Bernofarm, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Rendells *Prisfar, Port.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Rendell, China.
Nonoxinol 9.
Contraceptive.

Rendetil *Biotecnoquimica, Venez.*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Rendializat Sodyum *Biosel, Turk.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); acetic acid (p. 2426·3); sodium bicarbonate (p. 1781·1).
Haemodialysis.

Rendimax *Farmo Quimica, Chile.†*
Vitamins; minerals.
Dietary supplement.

Renedil *Sanofi-Aventis, Belg.; Sanofi-Aventis, Canad.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Reneel *Heel, Canad.†*
Aluminum oxide (p. 1690·3); barberry root (p. 2502·1); cantharides (p. 2469·2); causticum (p. 2595·3); lead acetate (p. 2541·3); nitric acid (p. 2572·3); pareira brava; saw palmetto (p. 2363·3).
Homoeopathic preparation.

Reneel H *Heel, Neth.*
Berberis vulgaris (p. 2502·1); cantharis vesicatoria; equisetum hyemale; populus tremuloides (p. 2450·3); sabal serrulata (p. 2363·3); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Renelix *Pekana, Canad.*
Apis mellifica (p. 2445·2); berberis vulgaris (p. 2502·1); benzoicum acidum (p. 1738·2); coccus cacti (p. 2179·2); colchicum autumnale (p. 607·1); solidago virgaurea (p. 2620·1); nitricum acidum (p. 2572·3); thlaspi bursa pastoris (p. 2614·2).
Homoeopathic preparation.

Reneos *Zentiva, Cz.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Renergie *Lancome, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Renergie Microlift *Lancome, Canad.†*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Renergie Microlift RARE *Lancome, Canad.†*
Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Renese R *Pfizer, Gr.*
⊗Polythiazide (p. 1472·1); reserpine (p. 1485·3).
Hypertension.

Reneuron *Juste, Spain.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Renevil *Pharmanel, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Renew *Christo, Hong Kong.†*
Minoxidil (p. 1438·3).

Renezide *Aspen, S.Afr.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Renfort *Pasteur, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Renicard *Unichem, Rus.; Unichem, S.Afr.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; cardiovascular risk reduction; diabetic nephropathy.

Renicin *Teva, Hung.†; Sandoz, Pol.; Sandoz, Ukr.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Renidac *Tecnoforma, Mex.*
Sulindac (p. 134·2).
Inflammation.

Renidur *MSD, Port.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renilon *Nutricia, Austral.; Nutricia, Denm.; Nutricia, Hong Kong; Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.; Nutricia Clinical, UK.*
Preparation for enteral nutrition.
Renal impairment.

Renipress *Cazi, Braz.*
Enalapril maleate (p. 1371·1).
Hypertension.

Renipril *Farmstandart, Rus.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Renipril HT *Farmstandart, Rus.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renipril Plus *APS, Port.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renistad *Stada, Austria.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left ventricular dysfunction.

Renitec *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, China; MSD, Cz.; MSD, Fin.; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Thai.; MSD, Turk.; MSD, Venez.*
Enalapril maleate (p. 1371·1).
Angina pectoris; heart failure; hypertension; myocardial infarction; left ventricular dysfunction; ischaemic heart disease.

Renitec Comp *MSD, Fin.; MSD, Norw.; MSD, Swed.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renitec Plus *MSD, Austral.; MSD, Austria; MSD, Fin.; MSD, Hung.; MSD, Neth.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Renitecmax *Biopat, Spain.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Reniten *MSD, Switz.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left ventricular dysfunction.

Reniten Plus *MSD, Switz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Rennie *Bayer Consumer, Arg.; Bayer Consumer, Austral.; Bayer, Austria; Bayer, Belg.; Roche, China; Bayer, Cz.; Bayer, Fin.; Bayer Sante, Fr.; Bayer, Ger.; Roche, Gr.; Bayer, Hung.; Bayer Consumer, Israel; Bayer, Ital.; Bayer, Neth.; Bayer, Pol.; Bayer Consumer, Rus.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Turk.; Roche Consumer, UK; Bayer Consumer, Ukr.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Heartburn; gastric pain; pyrosis; dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; flatulence.

Bayer Consumer, Arg.; Bayer, Belg.†; Roche, Belg.†
Oral suspension: Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); sodium alginate (p. 2167·3).
Dyspepsia; gastro-oesophageal reflux; pyrosis.

Rennie Chewable Tablets *Bayer, Irl.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; heartburn.

Rennie Deflatine *Bayer, Irl.; Bayer, Neth.; Bayer, Singapore; Bayer, Switz.; Roche Consumer, UK.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; heartburn; gastric hyperacidity.

Rennie Déflatine *Bayer Sante, Fr.*
Calcium carbonate (p. 1824·3); heavy magnesium carbonate (p. 1856·2); simeticone (p. 1886·2).
Heartburn; meteorism.

Rennie Digestif
Note: this name may be used for preparations of different composition.
Bayer, Austria.
⊗Papain (p. 2582·3); pancreatin (p. 2579·3); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Dyspepsia; flatulence; nausea and vomiting; heartburn; gastric pain.

Bayer, Port.
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastric hyperacidity; dyspepsia.

Rennie Dual Action *Bayer, Irl.*
Alginic acid (p. 2167·2); calcium carbonate (p. 1824·3); heavy magnesium carbonate (p. 1856·2).
Gastro-oesophageal reflux; gastric hyperacidity.

Rennie Duo *Bayer, Cz.†; Bayer, Neth.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); alginic acid (p. 2167·2) or sodium alginate (p. 2167·3).
Gastro-oesophageal reflux; gastric hyperacidity.

Bayer, Turk.; Roche Consumer, UK.†
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); sodium alginate (p. 2167·3).
Dyspepsia; heartburn.

Rennie Gel *Bayer, Switz.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity.

Rennie Ice *Bayer, Switz.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Rennie Peppermint *Bayer, Irl.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastric hyperacidity; heartburn.

Rennie Soft Chews *Roche Consumer, UK.*
Calcium carbonate (p. 1824·3).
Dyspepsia; flatulence; heartburn.

Rennie Spearmint *Bayer, Irl.*
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Gastric hyperacidity; heartburn.

Rennie Sugar Free *Bayer, Irl.*
Calcium carbonate (p. 1824·3); heavy magnesium carbonate (p. 1856·2).
Gastric hyperacidity; heartburn.

Renniechew *Bayer Sante, Fr.†*
Calcium carbonate (p. 1824·3); light magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Rennieliquo *Bayer Sante, Fr.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity.

Reno *Bracco, Canad.†*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Renob Blasen- und Nierentee *Pfleger, Ger.†*
Birch leaf (p. 2457·3); couch-grass rhizome (p. 2487·2); solidago virgaurea (p. 2620·1); ononis (p. 2575·3); liquorice root (p. 1853·2).
Urinary-tract disorders.

Renocal *Bracco, Canad.†*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Renocell *Randril, Philipp.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Renocil *Angelini, Spain.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Renocis *CIS, Fin.; CIS, Fr.; CIS, Irl.; CIS, Port.; Schering, UK.*
Technetium-99m (p. 2228·1) succimer.
Radionuclide imaging of the kidney.

Renodiol *Caprifarmindo, Indon.*
⊗Normethandrone (p. 2297·3); methyloestradiol (p. 2271·1).
Amenorrhoea.

Reno-Dip *Bracco, Canad.†*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Renofundina *Braun, Port.†*
Calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); sodium acetate (p. 1781·1); sodium chloride (p. 1795·1); with or without glucose (p. 2068·3).
Haemodialysis.

Renogen *Biomedis, Philipp.; Great Eastern, Thai.*
⊗Epoetin alfa (p. 1141·1).
Reduction of allogeneic blood transfusion; anaemias; autologous blood transfusion.

Renografin *Squibb Diagnostics, USA.†*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Renolip *Remedina, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Reno-M *Squibb Diagnostics, USA.†*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Renopen *Ativus, Braz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Renopril *Belfar, Braz.*
Enalapril (p. 1371·1).

Renoprotec *Merck, Mex.*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Renorell *Sanorell, Ger.*
Solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Renormax *Schering-Plough, Ital.; Italfarmaco, Spain.†*
Spirapril hydrochloride (p. 1499·3).
Hypertension.

Renosan *Sanbe, Indon.*
Amino acids.
Parenteral nutrition in hepatic encephalopathy.

Renova *Valeant, Canad.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Thai.; Ortho Dermatological, USA.*
Tretinoin (p. 1725·2).
Pigmentation disorders; photoageing of the skin.

Renovate *Forder, Arg.*
Salicylic acid (p. 1719·1).

Renovel *Nevzat, Turk.*
Vinorelbine (p. 885·3).

Renoxacin *Boniscontro & Gazzone, Ital.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Renpress *Novartis, Cz.; Valeant, Spain.†*
Spirapril hydrochloride (p. 1499·3).
Hypertension; heart failure.

Rentamine Pediatric *Major, USA.*
⊗Phenylephrine tannate (p. 1672·2); ephedrine tannate (p. 1663·1); chlorphenamine tannate (p. 620·3); pentoxyverine tannate (p. 1672·1).
Coughs and cold symptoms.

Rentex *Umeda, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Rentibloc *Amdipharm, Ger.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Rentilox *Pharma Line, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Rentop *Montpellier, Arg.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Rentsan *Pharmasan, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rentylin *Amdipharm, Ger.*
Pentoxifylline (p. 1465·3).
Peripheral and ocular vascular disorders.

Renu *Bausch & Lomb, Austral.; Bausch & Lomb, NZ.*
A range of solutions for soft contact lens care.

Bausch & Lomb, Canad.; Bausch & Lomb, USA.
Range of solutions for soft contact lenses.

Renu Enzymatic Cleaner *Bausch & Lomb, USA.†*
⊗Subtilisin A (p. 2624·1).
Cleansing solution for soft contact lenses.

ReNu FizziClean *Bausch & Lomb, S.Afr.†*
Proteolytic enzyme cleaner.
Protein removal for contact lenses.

Renu Multiplus *Bausch & Lomb, UK.*
Solution for cleansing, disinfecting, and removal of protein from contact lenses.

ReNu Multi-Purpose *Bausch & Lomb, S.Afr.*
Cleaning, disinfecting, rinsing, and storage solution for soft contact lenses.

Renu Plus *Bausch & Lomb, Arg.*
Cleansing, wetting, and storage solution for contact lenses.

Bausch & Lomb, Mex.†
Povidone (p. 2204·3).
Lubricating solution for contact lenses.

Renu Plus Gotas *Bausch & Lomb, Arg.*
Povidone (p. 2204·3).
Comfort solution for contact lenses.

Ren-Ur *Lafedar, Arg.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Renuvie *Medichem, Philipp.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; autism.

Renvela *Genzyme, Austria; Genzyme, Belg.; Genzyme, Chile; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Hung.; Genzyme, Irl.; Sanofi-Aventis, Israel; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Port.; Sanofi-Aventis, Singapore; Genzyme, Spain; Genzyme, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Genzyme, UK; Genzyme, USA.*
Sevelamer carbonate (p. 1573·1).
Hyperphosphataemia in chronic renal failure.

Genzyme, Gr.
Sevelamer (p. 1573·1).
Hyperphosphataemia in renal failure.

Renvol *Otto, Indon.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Renxamin *Kalbe, Indon.*
Amino acids.
Parenteral nutrition.

Renxon *Metiska, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Reodar *Darnitsa, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Reodyn *Orion, Fin.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Reoferol *Neves, Port.*
Tocoferil nicotinate (p. 1516·1).
Vitamin E deficiency.

Reoflen *Novis, Gr.*
Triflusal (p. 1519·3).
Thrombosis prophylaxis.

Reoflus *SF, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

ReoHES *Vilan, Rus.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; extracorporeal circulation.

Reolase *Velates, Ital.*
Telmesteine (p. 1678·2).
Respiratory-tract disorders.

Reolin *Hochland, Israel.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus.

Reomax
Note: this name may be used for preparations of different composition.
Marvecs, Ital.
⊗Etacrynic acid (p. 1378·2) or sodium etacrynate (p. 1378·2).
Oedema.

Maxpharma, Ukr.
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Reopemest *Sandoz, Ital.; Sandoz, Neth.†; Sandoz, Pol.*
Meropenem (p. 321·3).
Bacterial infections.

ReoPro *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Centocor, Cz.; Orifarm, Denm.; Janssen-Cilag, Fin.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, India; Lilly, Irl.; Centocor, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Janssen, Neth.; Janssen-Cilag, Norw.; Lilly, NZ; Centocor, Pol.; Centocor, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Janssen, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, UK; Centocor, USA; Lilly, USA.*
Abciximab (p. 1281·1).
Prevention of ischaemic cardiac complications during percutaneous coronary intervention; unstable angina; myocardial infarction.

RéoPro *Lilly, Fr.*
Abciximab (p. 1281·1).
Prevention of ischaemic cardiac complications during angioplasty; unstable angina pectoris.

Reosan *Serral, Mex.*
Meloxicam (p. 86·3).
Inflammation.

Reosil *Cafar, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Reosorbilact *Yuriya-Farm, Rus.; Yuri, Ukr.*
Sorbitol (p. 2092·1); electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Reosvec *Raam, Mex.*
Risedronate (p. 1189·2).
Osteoporosis.

Reotal *Kalbe, Indon.*
Pentoxifylline (p. 1465·3).
Intermittent claudication.

Reotan *Medicus, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Reovex *Baliarda, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Reox *Nobel, Turk.*
Rofecoxib (p. 128·3).
Osteoarthritis; pain.

Reoxyl
Note: this name may be used for preparations of different composition.
Aphth, Gr.
Iron sucrose (p. 2078·1).

Rep Locion Repelente *Aulo Gelio, Arg.*
Citronella oil (p. 2481·1); ruta graviolens (p. 2608·2); quassia (p. 2601·1); eucalyptus citriodora oil.
Pediculosis.

Rep Repelente *Aulo Gelio, Arg.*
Cream; gel; lotion: Citronella oil (p. 2481·1).
Insect repellent.

Aulo Gelio, Arg.
Topical spray: Citronella oil (p. 2481·1); jojoba oil.
Insect repellent.

Repalyte *DHA, Malaysia.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

DHA, Singapore.
Glucose (p. 2068·3); electrolytes (p. 1775·1) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Sanofi-Aventis, Austral.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium acid citrate (p. 1781·1); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Repan *Everett, USA.*
Butalbital (p. 1043·3); caffeine (p. 1203·3); paracetamol (p. 115·1).
Pain.

Reparcillin *New Research, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Reparex *Lafi, Chile.*
Vitamin E (p. 2119·1); selenium (p. 2086·3).
Antoxidant preparation.

Reparil *Madaus, Austria; Nycomed, Braz.; Nycomed, S. Afr.; Madaus, Thai.; Abdi, Turk.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, and soft-tissue disorders; thrombophlebitis; soft-tissue injury; superficial phlebitis; varicose veins; haematomas; vertebral pain syndrome; inflammation.

Madaus, Austria; Madaus, Belg.; Nycomed, Braz.; Nycomed, Braz.; Madaus, Cz.; Madaus, Ger.; Madaus, Hong Kong; Madaus, Pol.; Madaus, Thai.; Madaus, Thai.
Aescin (p. 2431·2).
Pain; inflammation; venous insufficiency; oedema; haematoma; compression spinal cord nerves; soft-tissue injury; haemorrhoids; varicose veins; thrombophlebitis.

Madaus, Belg.; Nycomed, Braz.; Madaus, Hong Kong.
Aescin (p. 2431·2); sodium aescin polysulfate (p. 2431·2); diethylamine salicylate (p. 51·3).
Oedema; inflammation; thrombophlebitis; venous insufficiency; soft-tissue injury; haemorrhoids.

Réparil *Rottapharm, Fr.*
Topical gel: Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Soft-tissue trauma.

Reparil CM *Madaus, Ital.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Soft-tissue injury.

Reparil N *Madaus, Hung.; Madaus, Philipp.; Madaus, Pol.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Soft-tissue injury; joint pain; varicose veins; thrombophlebitis; oedema; haematoma; venous insufficiency; neuralgia.

Réparil N *Zeller Madaus, Switz.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Soft-tissue injury.

Reparilexin *Madaus, Ital.*
Aescin (p. 2431·2).
Venous insufficiency; capillary fragility.

Reparil-Gel N *Madaus, China; Madaus, Cz.; Madaus, Ger.; Rottapharm, Ger.; Madaus, Malaysia; Madaus, Rus.; Madaus, Singapore; Madaus, Ukr.*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Thrombophlebitis; inflammation; vertebral pain syndrome; varicose veins; phlebitis; oedema; soft-tissue injury; musculoskeletal, joint, and peri-articular pain; haematoma.

Repariven *Bayer, Chile.*
Aescin (p. 2431·2); a heparinoid (p. 1401·1); diethylamine salicylate (p. 51·3).
Phlebitis; soft-tissue injury; varices.

Reparon *Egis, Hung.*
Escherichia coli; phenol (p. 1763·3).
Anorectal disorders.

Repasma *Lennon, S.Afr.†*
⊗Amobarbital (p. 1037·2); aminophylline (p. 1201·2); ephedrine hydrochloride (p. 1663·2).
Asthma.

Rep-Cartil *Farmoterapia, Arg.*
Collagen (p. 2483·2); cartilage (p. 2471·3).
Dietary supplement.

Repel Tropical Strength *Skin Shield, NZ.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Repelente Zasu *Zasu, Arg.*
Eucalyptus (p. 2501·1); aloe vera (p. 1693·2).
Insect repellent.

Repelex *Sanitas, Chile.*
Diethyltolumaide (p. 2153·1).
Insect repellent.

Repelselect *Clinova, UK.*
Lavender oil (p. 2541·1); geranium oil (p. 2512·2); clove oil (p. 2481·3); citronella oil (p. 2481·1).
Insect repellent.

Repentil
Note: this name may be used for preparations of different composition.
Nolver, Venez.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Repevax *Sanofi Pasteur, Austria; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Norw.; Sanofi Pasteur, Port.; Sanofi Pasteur, UK.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Repha Orphon *Repha, Ger.*
Java tea (p. 2536·3).
Urinary-tract disorders; gout; rheumatism.

Rephalgin N *Repha, Ger.*
Gelsemium (p. 2511·2); iris versic. (p. 2534·3); sanguinaria (p. 2610·1); spigelia (p. 2621·3).
Homoeopathic preparation.

Rephalysin C *Repha, Ger.†*
Escherichia coli.
Gastrointestinal disorders.

Repha-Os *Repha, Ger.†*
Tormentil root (p. 2633·2); rhatany root (p. 2603·3); myrrh (p. 2566·1); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); clove oil (p. 2481·3); menthol (p. 2553·2).
Mouth and throat disorders.

RepHresh *Lil' Drug Store, Singapore.*
Vaginal gel: Polycarbophil (p. 1879·1).
Vaginal infections.

Rephresh *Sanol, Ger.*
Polycarbophil (p. 1879·1).
Vaginal disorders.

RepHresh Pro-B *Lil Drug Store, USA.*
Lactobacillus reuteri (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).

Řepíkový Čaj; Řepíková Nať *Megafyt-R, Cz.*
Agrimony (p. 2432·3).
Diarrhoea; gastrointestinal inflammation; inflammatory disorders of the skin and mucous membranes; wounds.

Repin B_6 *Biopharm, Rus.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Repinex *Aspire, UK.*
Ropinirole (p. 913·2).
Parkinsonism.

Repisan *Bittner, Austria; Bittner, Rus.*
Calendula (p. 2465·2); arnica (p. 2447·2); hypericum (p. 449·1); ruta (p. 2608·2); symphytum (p. 2484·2).
Homoeopathic preparation.

Repithel *Mundipharma, Ger.*
Carbomer (p. 2173·3); phosphatidyl choline (p. 2588·3); povidone-iodine (p. 1767·1).
Wounds.

Repivate *Cipla-Medpro, S.Afr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Replagal *Shire, Austral.; Shire, Austria; Shire, Belg.; Paladin, Canad.; Shire, Cz.; Shire, Denm.; Shire, Fr.; Shire, Ger.; Shire, Gr.; Shire, Hung.; Shire, Irl.; TKT, Israel; Shire, Ital.; Shire, Neth.; Shire, Norw.; Healthcare Logistics, NZ; Shire, Pol.; Shire, Port.; Shire, Rus.; Shire, Spain; Shire, Swed.; Drac, Switz.; Shire, UK.*
Agalsidase alfa (p. 2437·2).
Fabry disease.

Replavite *WN, Canad.*
Vitamins.

Replena *Abbott, Braz.*
Preparation for enteral nutrition.

Replenate *BPL, UK.*
A factor VIII preparation (p. 1148·1).
Formerly known as BSM.
Haemophilia A.

Replenine *Galenica, Gr.; BPL, Israel; Bio Products, Malaysia; Landsteiner, Mex.†; BPL, Singapore; Abdi, Turk.; BPL, UK.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Replenine-VF *GP, Arg.*
A factor IX preparation (p. 1149·3).
Haemophilia.

Replenin-VF *BPL, Rus.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Replenishing *Sutton, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Replens *Tradiphar, Fr.†; Adcock Ingram, S.Afr.; Anglian, UK.*
Vaginal lubricant.
Vaginal dryness; vaginal irritation.

Teva, Israel.†
Vaginal moisturiser.
Vaginal dryness.

Sanofi-Aventis, Austral.; Wellspring, Canad.; Sanol, Ger.; Mipharm, Ital.; Sanfer, Mex.; Lil' Drug Store, Singapore†; Campus, Swed.; Warner-Lambert, USA.
Polycarbophil (p. 1879·1).
Vaginal dryness; vaginal irritation.

Replesta *Everidis, USA.*
Vitamin D (p. 2112·3).
Dietary supplement.

Replesta NX *Everidis, USA.*
Vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Dietary supplement.

Replete *Clintec, USA.*
Lactose-free, gluten-free preparation for enteral nutrition.

Replicare *Smith & Nephew, Austral.; Smith & Nephew Healthcare, UK.*
Hydrocolloid dressing.
Wounds; ulcers; burns.

Replicare Ultra *Smith & Nephew, Belg.*
A hydrocolloid dressing.
Wounds.

Repliderm *Savant, Arg.*
Terbinafine (p. 593·3).
Fungal skin infections.

Repligen
Note: this name may be used for preparations of different composition.
Panalab, Arg.
Metronidazole (p. 936·1).
Rosacea.

Pharos, Indon.
Gabapentin (p. 523·3).
Neuropathic pain; epilepsy.

Repliva *Ther-Rx, USA.†*
21 Tablets, ferrous glycinate (p. 2061·3); ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); 7 tablets, inert.
Succinic acid (p. 2214·3) is included in the active tablets to increase the absorption and availability of iron.
Iron deficiency.

Repocal
Note: this name may be used for preparations of different composition.
Sigma, Braz.
Calcium amino acid chelate (p. 2048·3).
Calcium supplement.

Repocal D *Legrand, Braz.*
Colecalciferol (p. 2113·1).

Repoflor *Legrand, Braz.*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; restoration of intestinal flora.

Repogen *Libbs, Braz.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Repogen Ciclo *Libbs, Braz.*
14 Tablets, conjugated oestrogens (p. 2260·1); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Repogen Conti *Libbs, Braz.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Repopil *Legrand, Braz.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).

Reposcal D *EMS, Braz.*
Calcium carbonate (p. 1824·3); vitamin D (p. 2112·3).
Calcium and vitamin D supplement.

Reposil *Medipharm, Chile.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia.

Reposium *Unipharma, Gr.*
Temazepam (p. 1109·1).

Reposton *Provit, Mex.†*
Liver extract (p. 2444·1).
Anaemias.

Repotin *Bioclones, S.Afr.*
⊗Epoetin (p. 1141·1).
Anaemias; autologous blood transfusions.

Repozal *Gunsa, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Reprapog *Sandoz, UK.*
Atovaquone (p. 928·2); proguanil hydrochloride (p. 661·3).
Malaria.

Repreve *GSK, Austral.*
Ropinirole (p. 913·2).
Restless legs syndrome.

Reprexain *Hawthorn, USA.*
Hydrocodone tartrate (p. 67·2); ibuprofen (p. 68·2).
Pain.

Repril *Aspen, Braz.*
Captopril (p. 1331·2).

Reprol
Note: this name may be used for preparations of different composition.
Gerolymatos, Gr.
Ketoconazole (p. 585·3).
Fungal skin infections.

Repronex *Ferring, Canad.; Ferring, USA.*
⊗Menotrophin (p. 2284·1).
Female infertility.

Reprostom *Fahrenheit, Indon.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Reproven N *Hanosan, Ger.*
Aesculus hippocastanum (p. 2431·2); calcium fluoratum (p. 2053·1); secale cornutum (p. 2137·1); hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Repso *Teva, Cz.; Teva, Irl.; Teva, Neth.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Reptilase *Solco, China; Troikaa, India.*
Haemocoagulase (p. 1135·1).
Haemorrhage.

Repursan *Biokanol, Ger.†*
Muira-puama; kola (p. 2648·2); vitamins.
Tonic.

Repusan *Genepharm, Gr.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).

REQ49+ *Capellon, USA.*
Vitamin A (p. 2098·3); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1); *d*-alpha tocoferil succinate (p. 2119·2); phytomenadione (p. 2122·2); thiamine hydrochloride (p. 2103·1); riboflavin (p. 2104·3); nicotinic acid (p. 2083·1); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); biotin (p. 2052·2); d-calcium pantothenate (p. 2085·2); calcium carbonate (p. 1824·3); potassium iodide (p. 2336·3); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); sodium selenite (p. 2087·1); copper gluconate (p. 2057·2); manganese gluconate (p. 2081·2); chromium amino acid chelate (p. 2048·3); molybdenum amino acid chelate (p. 2048·3); vanadium citrate; boron amino acid chelate (p. 2048·3); nickel amino acid chelate (p. 2048·3); zeaxanthin (p. 2125·3); lutein (p. 2079·2); lycopene (p. 2546·2).
Dietary supplement.

Requiesan *Klein, Ger.†*
California poppy (p. 2466·1); avena (p. 2451·1).
Sleep disorders.

ReQuip *GSK, Jpn.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Requip *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Beecham, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, USA.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Res Vin *Geymonat, Ital.†*
Vitamins; minerals; rutoside (p. 2505·3); proanthyocyanidins; resveratrol (p. 2603·2).
Nutritional supplement; circulatory disorders.

Resaca *Biotenk, Arg.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Pain; digestive disorders.

Resalut Pro *Berlin-Chemie, Rus.*
Soya bean phospholipids (p. 2092·3).
Liver disorders; hypercholesterolaemia.

Resapin *Soho, Indon.†*
Reserpine (p. 1485·3).
Hypertension.

Resata *Rafarm, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; topical corticosteroid.

Resbron *IAE, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

ResCo *Mediherb, Austral.*
Liquorice (p. 1853·2); verbascum (p. 2645·1); euphorbia (p. 2501·3); grindelia (p. 2522·3); ginger (p. 1844·1); fennel oil (p. 2503·3); elecampane (p. 1662·3).
Respiratory-tract disorders.

Rescon *Capellon, USA.*
Tablets: ⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine hydrochloride (p. 1676·1).
Formerly contained chlorphenamine maleate, hyoscine methonitrate, and phenylephrine hydrochloride.
Upper respiratory-tract disorders.

Rescon-DM *Capellon, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Coughs and cold symptoms.

Rescon-GG *Capellon, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs.

Rescon-Jr *Capellon, USA.*
Phenylephrine hydrochloride (p. 1672·3); dexchlorpheniramine maleate (p. 621·1).
Formerly contained phenylephrine hydrochloride and chlorphenamine maleate.
Upper respiratory-tract disorders.

Rescon-MX *Capellon, USA.*
Phenylephrine hydrochloride (p. 1672·3); dexchlorpheniramine maleate (p. 621·1).
Formerly contained phenylephrine hydrochloride, chlorphenamine maleate, and hyoscine methonitrate.
Upper respiratory-tract disorders.

Rescriptor *ViiV, Austral.; ViiV, Canad.; Pharmacia Upjohn, USA.*
Delavirdine mesilate (p. 972·1).
HIV infection.

RescueFlow *Biophausia, Denm.; Pharmanovia, Fin.; Genopharm, Fr.†; Biophausia, Neth.†; NordMedica, Norw.; Alliance, S.Afr.; NordMedica, Swed.; Dem, Turk.; Vitaline, UK.*
⊗Dextran 70 (p. 1138·3) in sodium chloride.
Plasma volume expansion; hypovolaemic shock.

Rescula *Novartis Ophthalmics, Arg.; Novartis, Braz.; Novartis, Chile†; Novartis, Cz.†; Novartis, Hung.†; Santen, Jpn; Novartis, Mex.; Novartis, Philipp.; Ciba Vision, Rus.; Novartis, Thai.†; Sucampo, USA; Novartis, Venez.*
Unoprostone isopropyl (p. 2013·1).
Ocular hypertension; glaucoma.

Rescuvolin *Teva, Belg.; Medac, China; Medac, Ger.; Chemipharm, Gr.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Neth.; Teva, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Singapore; Pharmachemie, Thai.; Teva, Thai.; Er-Kim, Turk.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia; reduction of high-dose methotrexate toxicity; adjunct to fluorouracil in colorectal cancer; folic acid deficiency.

Resdal *Niche, Irl.†*
Risperidone (p. 1103·2).
Schizophrenia.

Resdil *One Pharma, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Resdone *Pharmacor, Austral.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders.

Resectisol *Braun, Canad.; Eczacibasi-Baxter, Turk.*
⊗Mannitol (p. 1427·3).
Irrigation solution.

Reseptyl-Urea *Wagner, Hung.*
⊗Chloroseptyl; urea (p. 1727·3).
Burns; skin infections; wounds.

Reser *TO-Chemicals, Thai.*
⊗Reserpine (p. 1485·3); hydralazine hydrochloride (p. 1401·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Resfenax *Airela, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Resfenol *Hertz, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Resfeton *Royton, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Resfin *Jofrain, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Resflok *Sanbe, Indon.*
Sparfloxacin (p. 357·3).
Bacterial infections of the respiratory tract.

Resfry *Neo Quimica, Braz.*
Green tablets, paracetamol (p. 115·1); dexchlorpheniramine maleate (p. 621·1); caffeine (p. 1203·3); yellow tablets, ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Resfryneo *Neo Quimica, Braz.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Resibant *Bago, Arg.*
Rimonabant (p. 2606·2).
Obesity.

Resibelacta *Atral, Port.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Resibron *Ikapharmindo, Indon.*
Piracetam (p. 393·3).
Mental function impairment; chronic alcoholism; cerebral trauma.

Resical *Fresenius Medical, Cz.; Fresenius Medical, Port.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Residex P55 *Agropharm, UK.*
Permethrin (p. 2159·3).
Mosquito repellent for nets and clothing.

Resikali *Fresenius Medical, Fr.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia in renal failure.

Resilar *Orion, Fin.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Resimatil *Sanofi Synthelabo, Ger.†*
Primidone (p. 547·1).
Epilepsy.

Resinat *Proel, Gr.*
Codergocrine mesilate (p. 389·2).

Resincalcio *Omedir, Arg.; Rubio, Spain; Rubio, Thai.; TTN, Thai.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Resincolestiramina *Rubio, Singapore; Rubio, Spain; Rubio, Thai.*
Colestyramine (p. 1346·1).
Diarrhoea; hyperlipidaemias; pruritus associated with biliary obstruction; hypercholesterolaemia.

Resinsodio *Rubio, Singapore; Rubio, Spain; Rubio, Thai.†*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Resirentin *Bolar, Cz.; Medico Uno, Hung.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; psychoses.

Resistan mono *IPA, Ger.*
Echinacea purpura (p. 2498·1).
Immunostimulant.

Resistim *Motima, Fr.*
Lavender oil (p. 2541·1); cinnamon oil (p. 2479·3); eucalyptus oil (p. 2501·2); savory oil (p. 2625·1).
Cold symptoms.

Resiston *Vifor, Switz.*
Echinacea purpurea (p. 2498·1); red cherry (p. 2207·2).
Cold symptoms.

Vifor, Switz.
Echinacea purpurea (p. 2498·1); acerola.
Upper respiratory-tract infections.

Reskizof *Pisa, Mex.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders.

Reskuin *Kalbe, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Resma *AstraZeneca, Belg.*
Zafirlukast (p. 1239·3).
Asthma.

Resmavil *Liferpal, Mex.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Resochin *Bayer, Austria; Bayer, Ger.; Bayer, India; Bayer Schering, Indon.; Kern, Spain.*
Chloroquine phosphate (p. 650·1).
Malaria; amoebiasis; lupus erythematosus; rheumatoid arthritis; protozoal infections; connective tissue and collagen disorders.

Resochina *BayHealth, Port.*
Chloroquine phosphate (p. 650·1).
Malaria; rheumatoid arthritis; lupus erythematosus; amoebiasis.

Resodermil *Edol, Port.†*
Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne.

Resoferon *Novartis, Gr.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Resol
Note: this name may be used for preparations of different composition.
Wyeth-Ayerst, USA.
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium citrate (p. 1780·3); citric acid (p. 2480·3); sodium phosphate (p. 1791·2); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Resolor *Shire, Belg.; Movetis, Cz.; Shire, Denm.; Shire, Fr.; Shire, Ger.; Shire, Gr.; Shire, Irl.; Shire, Neth.; Shire, Pol.; Movetis, Port.; Janssen-Cilag, Singapore; Shire, Spain; Opopharma, Switz.; Janssen-Cilag, Thai.; Shire, UK.*
Prucalopride succinate (p. 1880·3).
Chronic constipation in women.

Resolutivo Regium *MG, Spain.†*
Boldo (p. 2458·3); opuntia ficus-indica; equisetum (p. 2500·1); sideritis angustifolia; rosemary (p. 2607·2); cynodon dactylon; arenaria; melissa (p. 2552·3).
Diuresis.

Resolve
Note: this name may be used for preparations of different composition.
Ego, Austral.
Balm: Miconazole nitrate (p. 589·1); bufexamac (p. 30·2).
Fungal skin infections.

Ego, Austral.
Topical solution: Miconazole (p. 588·3) or miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Ego, Malaysia; Ego, Singapore.
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive skin infections; fungal vaginal infections; fungal skin and nail infections.

Reckitt Benckiser, UK.
Paracetamol (p. 115·1); anhydrous citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); potassium bicarbonate (p. 1780·3); sodium carbonate (p. 2617·3); ascorbic acid (p. 2110·3).
Headache; dyspepsia.

Seton, Irl.†
Paracetamol (p. 115·1); citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); potassium bicarbonate (p. 1780·3); sodium carbonate anhydrous (p. 2617·3); ascorbic acid (p. 2110·3).
Headache with gastric upset.

Resolve Extra *Reckitt Benckiser, UK.*
Paracetamol (p. 115·1); sodium bicarbonate (p. 1781·1); caffeine (p. 1203·3).
Dyspepsia; headache.

Resolve Nappy Rash *Ego, Austral.*
Miconazole (p. 588·3); zinc oxide (p. 1729·1).
Nappy rash with fungal infection.

Resolve Plus *Ego, Austral.; Douglas, NZ.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Fungal skin infections with inflammation.

Resolve Thrush *Ego, Austral.*
Miconazole nitrate (p. 589·1).
Vulvovaginal candidiasis.

Resolve Tinea *Ego, Austral.*
Cream: Miconazole nitrate (p. 589·1).
Fungal skin infections.

Ego, Austral.
Topical powder: Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Fungal skin infections.

Resolvebohm *Bohm, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Resolve/GP *Allergan, USA.*
Cleansing solution for hard and gas permeable contact lenses.

Resonium *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Port.; Sanofi-Aventis, Swed.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

Resonium A *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Ger.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi Synthelabo, UK.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Resonium Calcium *Sanofi-Aventis, Canad.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Resorba *Sintez, Rus.*
Zoledronic acid (p. 1192·3).
Bone metastases; osteolysis in multiple myeloma; hypercalcaemia of malignancy.

Résorbane *Spirig, Switz.*
Cineole (p. 2479·1); camphor (p. 2466·2); niaouli oil (p. 2569·1).
Respiratory-tract disorders.

Resorborina *Ern, Spain.*
Mouthwash: ⊗Benzalkonium chloride (p. 1737·1); dexamethasone (p. 1630·3); resorcinol (p. 1718·3); tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.

Resorcal *Andromaco, Chile.*
Racecadotril (p. 1881·3).
Diarrhoea.

Resorpate *Ranbaxy, Pol.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Resostyl *Lavipharm, Gr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Resotran *Janssen, Canad.*
Prucalopride succinate (p. 1880·3).
Chronic constipation in women.

Resotyl *Drugtech, Chile.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Resource *Novartis, Braz.; Nestle, Canad.; Nestle, Cz.; Nestle, Denm.; Nestle, Fin.; Fresenius Kabi, Fr.†; Nestle, Hong Kong; Nestle, Ital.; Novartis Nutrition, Singapore; Nestle, UK; Novartis Nutrition, USA.*
A range of preparations for enteral nutrition.

Resource Benefiber *Nestle, Ital.*
Dietary fibre.

Resource Gelificata *Nestle, Ital.†*
Carrageenan (p. 2176·3); xanthan gum (p. 2220·1); guar gum (p. 475·1).
Dysphagia.

Resource OptiFibre *Nestle, UK.*
Guar gum (p. 475·1).
Formerly known as Resource Benefiber.
Dietary fibre supplement.

Resource Prunogil *Fresenius Kabi, Fr.†*
Prune (p. 1881·1); fig (p. 1843·2).
Constipation.

Resource Rhubagil *Fresenius Kabi, Fr.†*
Rhubarb (p. 1884·2); black currant (p. 2458·1).
Constipation.

Resource ThickenUp *Nestle, Ital.; Novartis, NZ; Nestle, Thai.; Nestle, UK.*
Nutritional supplement for thickening foods.
Dysphagia.

Novartis, Irl.†
Food thickener.
Dysphagia.

Resovist *Bayer, Austria; Bayer, Belg.†; Bayer Schering, Cz.†; Bayer, Ger.†; Schering, Gr.; Bayer, Ital.; Bayer, Neth.†; Bayer Schering, Norw.†; Lusal, Port.†; Bayer, Spain†; Bayer, Swed.†; Bayer, Switz.†*
Ferucarbotran (p. 1584·2).
Contrast agent for magnetic resonance imaging of the liver.

Resoxym *ICN, Pol.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; sinusitis; otitis media.

Respa C&C *Respa, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Respa-DM *Respa, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs; respiratory-tract congestion.

Respahist *Respa, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).

Respahist-II *Respa, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Respair
Note: this name may be used for preparations of different composition.
Berksam, Turk.
Montelukast sodium (p. 1214·3).

Respaire
Note: this name may be used for preparations of different composition.
Laser, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Nasal congestion; cough and cold symptoms.

Respalor *Mead Johnson Nutritionals, USA.*
Lactose-free preparation for enteral nutrition.
Respiratory system disorders.

Respara *Ranbaxy, Rus.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Respa-SA *Respa, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Respa-1st *Respa, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Respatona Chesty Cough & Nasal Congestion *Brauer, Austral.*
Hepar sulf (p. 1721·3); ipecacuanha (p. 1667·2); kali bich. (p. 2476·3); antim. tart. (p. 151·2); phosphorus (p. 2589·2); pulsatilla (p. 2600·2); stannum met. (p. 2632·1); senega officinalis (p. 1677·2).
Homoeopathic preparation.

Respatona Dry Cough & Nasal Congestion *Brauer, Austral.*
Belladonna (p. 2453·3); kali bich. (p. 2476·3); phosphorus (p. 2589·2); aconitum nap. (p. 2428·3); bryonia (p. 2461·3); sanguinaria canadensis (p. 2610·1); hyoscyamus (p. 2530·2); spongia tosta; rumex crisp. (p. 2649·3).
Homoeopathic preparation.

Respatona Head Cold *Brauer, Austral.*
Arsen. alb. (p. 2448·1); hepar sulf. (p. 1721·3); kali bich. (p. 2476·3); pulsatilla (p. 2600·2); aconitum nap. (p. 2428·3); allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); nat. mur. (p. 1795·1); nux vomica (p. 2573·3).
Homoeopathic preparation.

Respatona Nasal Spray Decongestant *Brauer, Austral.*
Hepar sulf. (p. 1721·3); kali bich. (p. 2476·3); pulsatilla (p. 2600·2); lycopodium clavatum (p. 2547·1); silicea (p. 2208·3); sepia (p. 2613·1); kali iod. (p. 2336·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Respatona Sinus Relief *Brauer, Austral.*
Belladonna (p. 2453·3); hepar sulfuris (p. 1721·3); kali bichromicum (p. 2476·3); silicea (p. 2208·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Respatona Sore Throat *Brauer, Austral.*
Lachesis (p. 2538·3); merc. sol. (p. 2555·3); ferrum phos. (p. 2077·1); echinacea ang. (p. 2498·1); bryonia (p. 2461·3); apis mel. (p. 2445·2); ammon. caust. (p. 2441·2); arsen. alb. (p. 2448·1); belladonna (p. 2453·3); aurum met. (p. 2521·1).
Homoeopathic preparation.

Respax *Pfizer, Austral.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Resperal *Cypress, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1); dexchlorpheniramine maleate (p. 621·1).
Cough; upper respiratory-tract disorders.

Resperal-DM *Cypress, USA.†*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; upper respiratory-tract disorders.

Respexil *MSD, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Respibien *Cinfa, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Respibien Antialérgico *Cinfa, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Respibron
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Oxolamine citrate (p. 1671·2) or oxolamine phosphate (p. 1671·2).
Cough.

Bruschettini, Ukr.
Lysate of *Staphylococcus aureus; Streptococcus viridans; Streptococcus pyogenes; Klebsiella pneumoniae; Klebsiella ozaenae; Haemophilus influenzae; Moraxella catarrhalis; Streptococcus pneumoniae.*
Respiratory-tract infections.

Respicil *Senosiain, Mex.*
Procaine benzylpenicillin (p. 344·2); dipyrone (p. 53·3).
Bacterial infections.

Respicur *Altana, Austria; Nycomed, Austria; Nycomed, Ital.*
Theophylline (p. 1229·3).
Obstructive airways disease; asthma; bronchospasm.

Respidon *Torrent, Braz.; Torrent, India.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder.

Respidual *Biogalenic, Venez.*
⊗Ipratropium bromide (p. 1211·3); fenoterol hydrobromide (p. 1208·2).
Obstructive airways disease.

Respifor *Support, Braz.; Nutricia, Cz.; Nutricia, Fin.; Nutricia, Irl.; Nutricia, Ital.*
Preparation for enteral nutrition.
Obstructive airways disease; respiratory disorders.

Respifree *Polifarma Benessere, Ital.*
Sea water (p. 2612·1); sodium hyaluronate (p. 2526·2).
Ear and nasal hygiene.

Respifree Baby *Polifarma Benessere, Ital.*
Sodium chloride (p. 1795·1).
Nasal hygiene.

Respifree Nasale *Polifarma Benessere, Ital.*
Sodium chloride (p. 1795·1); dexpanthenol (p. 2582·2).
Nasal hygiene.

RespiGam *Medimmune, USA.†*
Respiratory syncytial virus immunoglobulins (p. 2415·2).
Passive immunisation.

Respigen *Mylan, NZ.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma.

Respilène *Sanofi-Aventis, Fr.†*
Pholcodine (p. 1675·1).
Cough.

Respimex *Pfizer, Arg.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic conjunctivitis; allergic rhinitis.

Respimox *Wockhardt, India.*
Amoxicillin trihydrate (p. 216·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Respinal *Metz, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Respinol *Innovata, S.Afr.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; rhinitis; sinusitis.

Respinol Compound *Pharmaceutical Enterprises, S. Afr.†*
⊗Pholcodine (p. 1675·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Cough; cold symptoms; rhinitis; sinusitis.

Respinorm *Unipharma, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Respiratory-tract disorders.

Respir *Schering-Plough, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Respiratus *Medley, Braz.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Respiréa *Dietaroma, Fr.†*
Eucalyptus oil (p. 2501·2); siberian fir oil; peppermint oil (p. 1877·1); Scots pine oil (p. 2591·2); turpentine oil (p. 2636·3); balsam fir oil; lavender oil (p. 2541·1).

Respiret *Klonal, Arg.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Respirex
Note: this name may be used for preparations of different composition.
Schering-Plough, Chile.†
Sodium chloride (p. 1795·1).
Nasal cleansing.

Respiro
Note: this name may be used for preparations of different composition.
Deva, Turk.
⊗Fluticasone (p. 1638·1); salmeterol (p. 1224·1).

Respirol *Remedina, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Respiroma *Docta, Spain.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Respisniffers *SA Druggists Self Med, S.Afr.†*
Cineole (p. 2479·1); pine oil (p. 2591·1); chloroxylenol (p. 1748·2); turpentine oil (p. 2636·3); menthol (p. 2553·2).
Nasal congestion; cold symptoms; bronchitis.

Respi-Tann G *Teamm, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Respi-Tann Pd *Teamm, USA.*
⊗Pentoxyverine tannate (p. 1672·1); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Resplen *Chugai, Jpn.*
Eprazinone hydrochloride (p. 1664·3).
Cough.

Respocort *Lavipharm, Gr.; 3M, NZ.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; obstructive airways disease.

Respolin *3M, Chile†; 3M, Hong Kong†; 3M, NZ.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; bronchospasm.

Respontin *Allen & Hanburys, UK.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Resprax *Prodotti, Braz.†*
Green tablets, salicylamide (p. 129·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); yellow tablets, vitamin C (p. 2110·3).
Aluminium hydroxide (p. 1817·2) is included in the green tablets in an attempt to limit adverse effects on the gastrointestinal mucosa.
Cold and influenza symptoms.

Resprim *Alphapharm, Austral.; LCH, Hong Kong†; Teva, Israel; Alphapharm, Malaysia.†*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Resprin
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Venez.
Paracetamol (p. 115·1); pentoxyverine (p. 1672·1); phenylephrine (p. 1672·2); carbinoxamine (p. 619·1).
Cold and influenza symptoms.

Johnson & Johnson, Braz.
Paracetamol (p. 115·1); carbinoxamine maleate (p. 619·1); pentoxyverine citrate (p. 1672·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Rice Steele, Irl.†
Aspirin (p. 22·2).
Pain; fever; inflammation.

Ressital *Biofarma, Turk.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Rest-Aid *Overseas, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Formerly contained doxylamine succinate.
Nausea and vomiting of pregnancy.

Restameth-SR *Adcock Ingram, S.Afr.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Restandol *Organon (Οργανον), Gr.; Organon, Irl.; Organon, UK.*
⊗Testosterone undecylate (p. 2305·2).
Androgen deficiency; male hypogonadism; aplastic anaemia; breast cancer; osteoporosis.

Restas *MSD, Jpn.*
Flutoprazepam (p. 1076·3).
Sleep disorders; depression; nervous disorders.

Restasis *Allergan, Arg.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; IFET (ΙΦΕΤ), Gr.; Allergan, Hong Kong; Allergan, Israel; Allergan, Malaysia; Allergan, Mex.; Allergan, Philipp.; Allergan, Thai.; Abdi, Turk.; Allergan, Ukr.; Allergan, USA; Allergan, Venez.*
Ciclosporin (p. 1945·2).
Dry eyes.

Restaurene *Ivax, Arg.*
Sodium acexamate (p. 2427·3).
Skin lesions.

Restavit *Woods, Austral.*
Doxylamine succinate (p. 627·3).
Insomnia.

Resteclin
Note: this name may be used for preparations of different composition.
Piramal, India.
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Restela *Deva, Turk.*
Risperidone (p. 1103·2).

Restelea *Elea, Arg.*
Risperidone (p. 1103·2).
Schizophrenia.

Resteral *Rayere, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Restex *Roche, Austria; Roche, Ger.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Restless legs syndrome.

Restful *Bros, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Restime *United Laboratories, Philipp.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas.

Restin *Adcock Ingram, S.Afr.†*
Valerian (p. 2640·2); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Restlessness; tension.

Restiva *Raffo, Arg.*
⊗Buprenorphine (p. 30·2).
Pain.

Restofit *Pharmacobel, Belg.*
Calcium carbonate (p. 1824·3); kaolin (p. 1850·1); magnesium hydroxide (p. 1857·2).
Dyspepsia; pyrosis.

Restol *Laboratorios Chile, Chile.*
Domperidone (p. 1838·1).
Aid in gastrointestinal investigation; nausea and vomiting; regurgitation in infants.

Restolax *EuroHealth, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Restopon *Bros, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Restor
Note: this name may be used for preparations of different composition.
Folares, Philipp.
Vitamins; taurine (p. 2626·2); chlorella (p. 2475·3); lysine (p. 2079·3); zinc lactate (p. 2126·2); calcium chloride (p. 1783·1); iron polymaltose (p. 2077·2).
Dietary supplement for children.
Sandoz, Indon.
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Restoralax *Schering-Plough, Canad.*
Macrogol 3350 (p. 2547·3).

Restorativ Glucosamine Muscle and Joint *Holista, Canad.*
Frankincense (p. 2507·3); camphor oil (p. 2466·2); devil's claw (p. 42·3); evening primrose oil (p. 2502·2); glucosamine sulfate (p. 2515·3); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3).
Musculoskeletal and joint pain.

Restore
Note: this name may be used for preparations of different composition.
Brown & Burk, Philipp.; Micro, Singapore.
⊗Mesterolone (p. 2291·1).
Androgen deficiency; male infertility.

Restore CalciCare *Hollister, Canad.*
Calcium sodium alginate (p. 1136·3) (p. 2167·3).
Wounds.

Restore ORS *Ascent, Austral.*
Glucose (p. 2068·3); sodium acid citrate (p. 1781·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Diarrhoea; oral replacement therapy.

Restor-F *Folares, Philipp.*
Vitamins; taurine (p. 2626·2); chlorella (p. 2475·3); ginseng (p. 2513·3); rutoside (p. 2505·3); lecithin (p. 2542·2); iron (p. 2073·1); zinc (p. 2126·1); calcium (p. 1783·1).
Tonic.

Restoril
Note: this name may be used for preparations of different composition.
Sunovion, Canad.; Novartis, USA.
Temazepam (p. 1109·1).
Insomnia.

Restorin *Columbia, Canad.*
Andrographis (p. 2443·2).
Flatulence; colic.

Restorvol *Braun, Fr.*
⊗Etherified starch in sodium chloride (p. 1146·1).

Restovar *MSD, Swed.*
Lynestrenol (p. 2287·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Restrical
Note: this name may be used for preparations of different composition.
Casasco, Arg.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.
DB, Fr.
Liquid paraffin (p. 2191·2).
Constipation.

Restructa H *Heel, Neth.*
Berberis vulgaris (p. 2502·1); bryonia alba; china officinalis (p. 2478·3); colchicum autumnale; rhus toxicodendron (p. 2603·3); sarsaparilla officinalis (p. 2610·3); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Restwel *Adcock Ingram, S.Afr.*
Doxylamine succinate (p. 627·3).
Insomnia.

Restyl *Cipla, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Restyl Forte *Cipla, India.*
Alprazolam (p. 1035·2); sertraline hydrochloride (p. 448·1).
Mixed anxiety depressive states.

Restyl Plus *Cipla, India.*
Alprazolam (p. 1035·2); sertraline hydrochloride (p. 448·1).
Mixed anxiety depressive states.

Restylane *HealthcareLogistics, NZ; Medicis, USA.*
Hyaluronic acid (p. 2526·2).
Lidocaine (p. 1988·1) is included in some injections to reduce the pain of injection.
Facial tissue contour deformities; lip enhancement; facial wrinkles and folds.

Resulax *Meda, Swed.*
Sorbitol (p. 2092·1).
Constipation; bowel evacuation.

Resultz *Nycomed, Canad.*
Isopropyl myristate (p. 2190·3).
Pediculosis.

Resure *Simayla, S.Afr.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Resurmide *IBI, Ital.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage.

Resvelife *Seventy BG, Ital.*
Resveratrol (p. 2603·2); hyaluronic acid (p. 2526·2); enoxolone (p. 54·2); allantoin (p. 1693·1); levomenol (p. 2544·1).
Skin disorders.

Resvelife Sole *Seventy BG, Ital.*
SPF 50+: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); resveratrol (p. 2603·2); enoxolone (p. 54·2); allantoin (p. 1693·1); tocoferil acetate (p. 2119·2).
Sunscreen.

ResveratoX *Bioglan, Austral.*
Fallopia japonica; grape seed (p. 2521·3); vitamins; selenomethionine (p. 2087·1); citrus bioflavonoids (p. 2505·2).
Antoxidant.

Resvica *Dexa, Indon.†*
Grape (p. 2521·3); garlic (p. 2510·3).
Cardiac disorders; hyperlipidaemias.

Resyl *Novartis Consumer, Austria; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis, Swed.†; Novartis Consumer, Switz.*
Guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Resyl DM *Novartis Consumer, Ital.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Resyl mit Codein *Novartis Consumer, Austria.*
Guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Resyl Plus *Novartis Consumer, Switz.*
Guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Cough.

Retabolil *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
⊗Nandrolone decanoate (p. 2293·1).
Anabolic; breast cancer; diabetic retinopathy; muscular dystrophy; osteoporosis; cachexia.
Gedeon Richter, Ukr.
⊗Nandrolone (p. 2293·1).
Anabolic; anaemias.

Retabolin *Cimex, Switz.†*
Vitamin B substances (p. 2102·3).
Neuralgia; neuritis.

Retace *Simayla, S.Afr.*
Ramipril (p. 1483·3).
Diabetic nephropathy; hypertension; heart failure following myocardial infarction; cardiovascular risk reduction.

Retacillin compositum *Mibe, Ger.*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2); benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Retacnyl *Galderma, Arg.; Galderma, Chile; Galderma, Fr.; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Thai.; Galderma, Venez.*
Tretinoin (p. 1725·2).
Acne; photoageing of the skin; keratinisation disorders; stratum corneum formation disorders.

Retacrit *Hospira, Austria; Hospira, Cz.; Hospira, Denm.; Hospira, Fr.; Hospira, Ger.; Hospira, Gr.; Hospira, Hung.; Hospira, Irl.; Hospira, Ital.; Hospira, Neth.; Hospira, Norw.; Hospira, Pol.; Hospira, Port.; Hospira, Spain; Hospira, Swed.; Hospira, UK.*
⊗Epoetin zeta (p. 1141·2).
Anaemias; autologous blood transfusion.

Retafer *Orion, Fin.; Orion, Malaysia.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Retafyllin *Orion, Fin.; Orion, Hung.; Orion, Malaysia; Orion, Thai.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Retager *Ni-The, Gr.*
Dimenhydrinate (p. 625·2).

Retaliate *Redken, Canad.*
Pyrithione zinc (p. 1718·1).

Retamin *Roemmers Osmoph, Venez.*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Re-Tann
Note: this name may be used for preparations of different composition.
Midlothian, USA.
⊗Pentoxyverine tannate (p. 1672·1); pseudoephedrine tannate (p. 1676·1).
Cough.

Retaphyl *Kimia, Indon.*
Theophylline (p. 1229·3).
Asthma.

Ret-A-Pres
Note: this name may be used for preparations of different composition.
Precimex, Mex.
Tretinoin (p. 1725·2).
Acne; actinic keratosis; psoriasis; photodamaged skin; stretch marks; basal cell carcinoma.

Retapres
Note: this name may be used for preparations of different composition.
Biopharm, Rus.
⊗Indapamide (p. 1409·2).
Hypertension.

Retardex *Qualiphar, Belg.; Periproducts, UK.*
Stabilised chlorine dioxide (CloSYS II) (p. 1747·1).
Halitosis; oral hygiene.

Retardillin *Teva, Hung.*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Retarpen
Note: this name may be used for preparations of different composition.
Chemifarma, Spain.
Ampicillin sodium (p. 218·2); ampicillin benzathine (p. 218·2).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Bacterial infections.
Sandoz, Arg.; Sandoz, Austria; Sandoz, Cz.†; Sandoz, Malaysia; Sandoz, Rus.; Sandoz, Singapore; Sandoz, Ukr.
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Retarpen compositum *Sandoz, Austria.*
Benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2); benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Retasol *Retinoids, Rus.*
Isotretinoin (p. 1706·2).
Acne; seborrhoea.

Retavase *Biovail, Canad.; EKR, USA.*
Reteplase (p. 1486·2).
Myocardial infarction.

Retavit *CTS, Israel.*
Tretinoin (p. 1725·2).
Acne.

Retazymon *Medinova (Μεντινοβα), Gr.*
⊗Serrapeptase (p. 2613·3).

Retebem *Gobbi, Arg.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Retef *Spirig, Ger.†*
⊗Hydrocortisone aceponate (p. 1640·1).
Skin disorders.

Retemic *Apsen, Braz.*
Oxybutynin hydrochloride (p. 2361·2).
Urinary incontinence; neurogenic bladder.

Retemicon *Panalab, Arg.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Reten *TO-Chemicals, Thai.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Retens *Chiesi, Spain.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Retensin *Unison, Philipp.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Retep *Fada, Arg.*
⊗Furosemide (p. 1387·1).

Reteven *Nolver, Venez.*
Oxybutynin (p. 2361·2).
Bladder hyperactivity.

Reticne *Cinetic, Arg.*
Tretinoin (p. 1725·2).
Skin disorders.

Reticopen *Landson, Indon.*
Lutein (p. 2079·2); lycopene (p. 2546·2); betacarotene (p. 2051·1); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin B_2 (p. 2104·3).
Cataract; age-related macular degeneration.

Reticor *Pharmacore, Indon.*
Tretinoin (p. 1725·2).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Reticulogen Fortificado *Biomed, Spain.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Reticus *Sinclair, Ital.*
⊗Desonide (p. 1630·1).
Skin disorders.

Retigel-A *Gelpharma, Mex.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

Retimax
Note: this name may be used for preparations of different composition.
Olive Healthcare, Philipp.
Vitamin A palmitate (p. 2098·3).
Vitamin A deficiency.

Alcon Cusi, Spain.†
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Retin-A *Janssen-Cilag, Arg.; Johnson & Johnson, Austral.†; Janssen-Cilag, Austria; Johnson & Johnson, Braz.; Valeant, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.†; Janssen-Cilag, Gr.; Cilag, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel†; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK†; Ortho Dermatological, USA.*
Tretinoin (p. 1725·2).
Acne; photoageing of the skin; keratinisation disorders; wrinkles; hyperpigmentation.

Retinalamin *Geropharm, Rus.; Gerofarm, Ukr.*
Retina extract (bovine) (p. 2444·1).
Retinal disorders.

Retinar *Bunker, Braz.*
Vitamin A acetate (p. 2098·3).

Reti-Nat *Chauvin, Fr.†*
Omega-3 triglycerides (p. 1460·3); lutein (p. 2079·2).
Dietary supplement.

Retinide *Ingens, Arg.*
Isotretinoin (p. 1706·2).
Acne.

Retino *Abdi, Turk.*
Tretinoin (p. 1725·2).
Acne.

Retinofluor *Phebra, Austral.*
Fluorescein sodium (p. 2506·2).
Aid to eye examination.

Retinoic Ointment *Retinoids, Rus.*
Isotretinoin (p. 1706·2).
Acne; seborrhoea.

Retinol Hand Anti-Age Care *Johnson & Johnson, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Retinol-A *Young Again Nutrients, USA.*
Vitamin A palmitate (p. 2098·3).
Minor skin disorders.

Retinova *Janssen-Cilag, Braz.†; Janssen-Cilag, NZ; Janssen-Cilag, Singapore.*
Tretinoin (p. 1725·2).
UV-induced skin disorders.

Retinovit *Exakta, Mex.*
Vitamin A (p. 2098·3); alfa tocopherol (p. 2119·1).
Vitamin deficiency.

INTES, Ital.
Myrtillus (p. 2566·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Circulatory disorders of the eye.

Retinyl *Kleva, Gr.*
Maprotiline hydrochloride (p. 433·3).

Retirides *Ferrer, Spain.*
Tretinoin (p. 1725·2).
Acne; sunlight-induced skin damage.

Retisdin *Isdin, Port.*
Vitamin A betadex; sunscreens.
UV-induced skin damage.

Retisert *Bausch & Lomb, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Uveitis.

Retisol-A *Stiefel, Canad.*
Tretinoin (p. 1725·2).
Acne.

Retiva *Vivax Gynopharm, Venez.*
Vitamin A (p. 2098·3).
Vitamin A deficiency.

Retivit *Sanbe, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1); selenium (p. 2086·3); lutein (p. 2079·2).
Age-related macular degeneration; cataract.

Retivit Plus *Sanbe, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1); selenium (p. 2086·3); lutein (p. 2079·2); lycopene (p. 2546·2); zeaxanthin (p. 2125·3).
Antioxidant; dietary supplement for healthy eye function.

Retodol Compositum *Rimsa, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Pain; smooth muscle spasm.

Retoflam *Ultra, Mex.*
Meloxicam (p. 86·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Retoflam F *Ultra, Mex.*
Meloxicam (p. 86·3); methocarbamol (p. 2025·3).
Musculoskeletal, joint, and periarticular disorders; skeletal muscle spasm.

Retonel *Dexa, Indon.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Retop *Meprofarm, Indon.*
Myrtillus (p. 2566·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin B_2 (p. 2104·3).
Dietary supplement.

Retoxil *Alcon, Arg.; Alcon, Mex.*
Vitamins; minerals.
Dietary supplement; prevention of macular degeneration.

ReTrieve *Dermatech, Austral.; Dermatech, Hong Kong; Valeant, NZ; Dermatech, Singapore.*
Tretinoin (p. 1725·2).
Dry skin disorders; acne; photodamaged skin.

Retroactive *Avon, Canad.†*
SPF 25: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Retroinhi *Dosa, Arg.*
Nelfinavir (p. 1004·1).
HIV infection.

Retrokor *One Pharma, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Retrovir *GSK, Arg.; ViiV, Austral.; GSK, Austria; ViiV, Belg.; GSK, Braz.; ViiV, Canad.; GSK, Chile; GSK, China; ViiV, Cz.; GSK, Denm.; ViiV, Fin.; ViiV, Fr.; ViiV, Ger.; ViiV, Gr.; GSK, Hong Kong; GSK, Hung.†; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; ViiV, Neth.; ViiV, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S. Afr.; GSK, Singapore; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.*
Zidovudine (p. 1024·2).
HIV infection.

Retrovir/3TC Post-HIV Exposure *GSK, S.Afr.*
Capsules, zidovudine (Retrovir) (p. 1024·2); tablets, lamivudine (3TC) (p. 1000·2).
Prophylaxis of HIV infection.

Rettavate *GSK, Gr.*
⊗Clobetasone butyrate (p. 1627·3).
Skin disorders.

Retterspitz Äusserlich *Retterspitz, Ger.*
Rosemary oil (p. 2607·3); citric acid (p. 2480·3); tartaric acid (p. 2626·1); alum (p. 2439·1); thymol (p. 1772·2); arnica (p. 2447·2).
Inflammatory disorders.

Retterspitz Darmreinigungspulver ST *Retterspitz, Ger.*
Magnesium sulfate (p. 1787·3).
Constipation.

Retterspitz Erkältungsöl *Retterspitz, Ger.*
Eucalyptus oil (p. 2501·2).
Cold symptoms; rheumatism.

Retterspitz Heilsalbe ST *Retterspitz, Ger.*
Zinc oxide (p. 1729·1).
Skin disorders.

Retterspitz Innerlich *Retterspitz, Ger.*
Citric acid (p. 2480·3); tartaric acid (p. 2626·1); alum (p. 2439·1); thyme oil (p. 2630·3).
Gastrointestinal disorders.

Retterspitz Muskel- und Nervenöl *Retterspitz, Ger.*
Mint oil (p. 2560·1).
Respiratory-tract congestion; gastrointestinal disorders; musculoskeletal and nerve pain.

Retterspitz Quick Bronchial *Retterspitz, Ger.*
Camphor (p. 2466·2); levomenthol (p. 2553·2); thymol (p. 1772·2).
Cold symptoms.

Retterspitz Quick Muskel *Retterspitz, Ger.*
Rosemary oil (p. 2607·3); noble fir oil; levomenthol (p. 2553·2); thymol (p. 1772·2); arnica (p. 2447·2).
Musculoskeletal and joint disorders.

Return
Note: this name may be used for preparations of different composition.
Euro-Pharma, Ital.
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Rafarm, Gr.
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

RE-U40 *Rivers Edge, USA.†*
⊗Urea (p. 1727·3).
Dry skin.

Reubaxona *Farmaceutica H, Mex.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Reucam *Maver, Mex.*
Piroxicam (p. 125·3).
Inflammation; pain.

Reucid *Otto, Indon.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; hyperuricosuria; renal calculi.

Reucortil *Mayo, Mex.*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Inflammation; pain.

Reudol
Note: this name may be used for preparations of different composition.
Nordin, Mex.
Arnica (p. 2447·2); belladonna (p. 2453·3); bryonia (p. 2461·3).
Musculoskeletal and joint disorders.

Pekana, Neth.
Arnica montana (p. 2447·2); bryonia cretica; colchicum autumnale (p. 607·1); dulcamara (p. 2497·3); gnaphalium polycephalum; guajacum officinale (p. 2523·1); lachnanthes tinctoria; taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Reufin *Sanitas, Chile.*
Glucosamine sulfate (p. 2515·3).
Joint disorders.

Reuflor *Italchimici, Ital.*
Lactobacillus reuteri (p. 2596·3).
Restoration of gastrointestinal flora.

Reugel *Grunenthal, Venez.*
Etofenamate (p. 57·2); pine oil (p. 2591·1); eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Reuginal *Reuffer, Mex.*
Furazolidone (p. 933·3); nifuroxime (p. 590·3).
Vaginal infections.

Reuma-Capsules Dr. Theiss *Naturwaren, Ukr.†*
Martynia fragrans.
Inflammatory and degenerative joint diseases.

Reumacid *Alapis, Gr.*
Indometacin (p. 71·2).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Reumacide *Vitoria, Port.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Reumacor *Herbapol Wrodaw, Pol.*
Salix purpurea (p. 129·2); solidago (p. 2620·1).
Fever; pain.

Reumacort *Teofarma, Ital.*
⊗Hydrocortisone acetate (p. 1640·1); methyl gentisate (p. 91·3).
Muscle and joint pain.

Reumadolor *Bros, Gr.*
Indometacin (p. 71·2).
Inflammatory disorders.

Reumafit *Phytopharm, Ukr.*
Devil's claw root (p. 42·3).
Joint disorders.

Reumaflex *Wassermann, Ital.*
Methotrexate (p. 822·2).

Reumafort *Amnol, Ital.*
Dimethyl sulfone (p. 2493·3); salix (p. 129·2); turmeric (p. 2218·1); boswellia (p. 2507·3); devil's claw root (p. 42·3); minerals.
Joint disorders.

Reuma-Gel *DHU, Ukr.*
Rhus toxicodendron (p. 2603·3); ledum palustre (p. 2550·1); symphytum officinalis (p. 2484·2).
Homoeopathic preparation.

Reumagil *SF, Ital.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Reumaherb *Herbapol Poznan, Pol.*
Echinacea purpurea (p. 2498·1); meadowsweet (p. 2550·2); devil's claw root (p. 42·3).
Degenerative joint disorders.

Reumanisal *Bros, Gr.*
Diacerein (p. 45·3).
Osteoarthritis.

Reumaphyt *Phytofarm Kleka, Pol.*
Devil's claw root (p. 42·3).
Degenerative joint disorders; tendinitis.

Reumaplus *Medichrom, Gr.*
Piroxicam (p. 125·3).

Reuma-Salbe Intensiv Dr. Theiss *Naturwaren, Ukr.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); pine fir-needle oil; eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, and soft-tissue disorders.

Reumastop *Ni-The, Gr.*
Indometacin (p. 71·2).

Reumatik *Theiss Naturwaren, Pol.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); pine oil (p. 2591·1); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Reumil *Keryos, Ital.*
Glucosamine (p. 2515·3); chondroitin sulfate (p. 2476·1); thioctic acid (p. 2629·1); vitamins.
Cartilage disorders.

Reumilase *MDM, Ital.*
Glucosamine (p. 2515·3); galactose (p. 1588·1); glucuronic acid (p. 2517·1); Devil's claw root (p. 42·3); collagen (p. 2483·2); vitamins.
Joint disorders.

Reumilase Plus *MDM, Ital.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); glucuronate sodium; collagen (p. 2483·2); devil's claw root (p. 42·3); vitamins.
Joint disorders.

Reumilase SD *MDM, Ital.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine (p. 2515·3); collagen (p. 2483·2); vitamins.
Joint disorders.

Reumina *Demo, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, and peri-articular disorders.

Reumobonisol *Bonimed, Pol.*
Arnica (p. 2447·2); camphor (p. 2466·2); lavender (p. 2541·1); menthol (p. 2553·2); white mustard (p. 2566·1).
Musculoskeletal and joint disorders; neuralgia.

Reumol *Cabuchi, Arg.*
Camphor (p. 2466·2); menthol (p. 2553·2); salicylic acid (p. 1719·1).

Reumolide *Generis, Port.*
Nimesulide (p. 101·3).
Pain.

Reumon *Bial, Port.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation; neuralgia.

Reumophan Alka *Grisi, Mex.*
Ketoprofen (p. 79·1); chlorzoxazone (p. 2022·2).
Calcium carbonate (p. 1824·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal, joint, and peri-articular disorders; gout.

Reumophan Vit *Grisi, Mex.*
Ketoprofen (p. 79·1); chlorzoxazone (p. 2022·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Musculoskeletal and joint disorders; neuritis; neuropathy; neuralgia; skeletal muscle spasm.

Reumosan *Gezzi, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Reumosan Compuesto *Gezzi, Arg.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate sodium (p. 2515·3).
Joint disorders.

Reumosan Flex *Gezzi, Arg.*
Trolamine (p. 2634·3).
Pain.

Reumosol *Herbapol Pruszkow, Pol.*
Achillea (p. 2427·3); calendula (p. 2465·2); camphor (p. 2466·2); chamomile (p. 2474·1); equisetum (p. 2500·1); menthol (p. 2553·2); pine oil (p. 2591·1); knotgrass (p. 2538·2); salicylamide (p. 129·2); salix (p. 129·2); soapwort (p. 2617·2); myrtillus (p. 2566·2); hay.
Rheumatic disorders.

Reumotec *Viofar, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Reumotherm *Farmanic, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Reumoxib *Arterium, Ukr.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Reumoxicam *Farmak, Ukr.*
Meloxicam (p. 86·3).
Inflammatory and degenerative joint diseases.

Reumoxican *Medinfar, Port.*
Piroxicam (p. 125·3).
Inflammation; pain.

Reumpapai *Cowik, Pol.*
Piper retrofractus; cinnamon bark (p. 2479·2); liquorice (p. 1853·2).
Musculoskeletal and joint disorders; neuralgia.

Reupat *Parggon, Mex.*
Indometacin (p. 71·2); methocarbamol (p. 2025·3).
Rheumatism.

Reuplex *Farmasa, Braz.†*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Reuquinol *Apsen, Braz.*
Hydroxychloroquine sulfate (p. 655·2).
Rheumatoid arthritis; lupus erythematosus; malaria; light-sensitive skin disorders.

Reusan *Reuffer, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Reusin *Stada, Spain.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Reutefene *Age D'or, Singapore.†*
Lactobacillus reuteri protectis (p. 2596·3).
Maintenance of gastrointestinal flora.

Reutenox *Rubio, Spain.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Reuteri *Biogaia, Hong Kong.*
Lactobacillus reuteri (p. 2596·3).
Restoration of normal gastrointestinal flora.

Reutrexato *Apsen, Braz.*
Methotrexate (p. 822·2).
Rheumatoid arthritis.

Reutricam *Liferpal, Mex.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; pain; fever.

Reux *Alvartis, Mex.*
Omeprazole (p. 1867·2).

Reuxen *Tecnifar, Port.*
Naproxen (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; fever; gout.

Revac-Bmcf *Bharat, Thai.*
A hepatitis B vaccine (surface antigen) (p. 2389·3).
Active immunisation.

Reval *Cooper (Κοπερ), Gr.*
Diazepam (p. 1063·2).

Revalan *BioFemme, Philipp.*
Mefenamic acid (p. 85·3).
Fever; pain.

Revaléskin *Stiefel, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Revaleskin
Note: this name may be used for preparations of different composition.
Stiefel, Chile.
Coffee (p. 2648·2).
Skin disorders; antoxidant.

Stiefel, Malaysia.†
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Revaleskin Day *Stiefel, Hong Kong.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); coffeeberry.
Sunscreen; emollient.

Revaleskin Replenishing Eye Therapy *Stiefel, Hong Kong.*
Caffeine (p. 1203·3); coffeeberry.
Emollient.

Revalgin *Shreya, Rus.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Pain; fever.

Revalid *Ewopharma, Cz.; Vifor, Switz.†*
Amino acids; vitamins; aminobenzoic acid (p. 1694·2); millet; wheat germ (p. 2647·1); dried yeast (p. 2125·2); minerals.
Hair and nail disorders.

Ewopharma, Pol.
Methionine (p. 1558·2); cystine (p. 2059·1); vitamins; minerals.
Hair and nail disorders.

Teva, Hung.
Methionine (p. 1558·2); cystine (p. 2059·1); vitamins; aminobenzoic acid (p. 1694·2); millet; wheat germ (p. 2647·1); yeast (p. 2125·2); minerals.
Hair and nail disorders.

Teva, Ukr.
Methionine (p. 1558·2); cystine (p. 2059·1); vitamins; aminomethylbenzoic acid (p. 1132·2); millet; wheat germ (p. 2647·1); yeast (p. 2125·2); copper (p. 2057·1); zinc (p. 2126·1); iron (p. 2073·1).
Hair and nail disorders.

Revalintabs *Chefaro, Neth.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Revapol *AF, Mex.†*
Mebendazole (p. 158·3).
Worm infections.

Revasc *Aventis, Austral.†; Canyon, Austria; Canyon, Cz.; Inresa, Fr.†; Canyon, Ger.; Canyon, Gr.; Canyon, Irl.; Canyon, Neth.; Aventis, NZ†; Canyon, Pol.; Canyon, Port.; Canyon, Spain.*
Desirudin (p. 1351·1).
Postoperative thromboembolism prophylaxis.

Revastin *Neo Quimica, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Revatio *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; IFET (ΙΦΕΤ), Gr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA.*
Sildenafil citrate (p. 2364·1).
Pulmonary hypertension.

Revaxis *Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Port.; Sanofi Pasteur, Switz.; Sanofi Pasteur, UK.*
A diphtheria, tetanus, and poliomyelitis vaccine (p. 2386·2).
Active immunisation.

Reveal *BR Pharmaceuticals, UK.*
Pregnancy test (p. 2596·1).

Revectina *Solvay, Braz.*
Ivermectin (p. 155·1).
Filariasis; strongyloidiasis; onchocerciasis; ascariasis.

Révélatest *Pierre Fabre Sante, Fr.†*
Pregnancy test (p. 2596·1).

Revellex *Schering-Plough, S.Afr.*
Infliximab (p. 74·2).
Ankylosing spondylitis; Crohn's disease; rheumatoid arthritis; psoriatic arthritis; psoriasis; ulcerative colitis.

Revelol *Ipca, India.*
⊗Metoprolol succinate (p. 1434·3).
Angina pectoris; heart failure; hypertension.

Revelplac *Naf, Arg.*
Erythrosine (p. 2184·3).
Plaque disclosing agent.

Revelplac 2001 *Naf, Arg.*
Erythrosine (p. 2184·3); sodium fluoride (p. 2089·2).
Plaque disclosing agent.

Revenil *Sanofi-Aventis, Braz.*
⊗Bufylline (p. 1203·3); doxylamine succinate (p. 627·3); etafedrine hydrochloride (p. 1665·2).
Bronchospastic disorders.

Revenil Dospan *Sanofi-Aventis, Braz.*
⊗Bufylline (p. 1203·3); doxylamine succinate (p. 627·3); etafedrine hydrochloride (p. 1665·2); phenylephrine hydrochloride (p. 1672·3).
Bronchospastic disorders.

Revenil Expectorante *Sanofi-Aventis, Braz.*
⊗Bufylline (p. 1203·3); doxylamine succinate (p. 627·3); etafedrine hydrochloride (p. 1665·2); guaifenesin (p. 1666·2).
Bronchospastic disorders.

Reversa *Dermtek, Canad.*
Glycolic acid (p. 1704·3).
Skin disorders requiring exfoliation.

Reversa UV *Dermtek, Canad.*
SPF 15: Glycolic acid (p. 1704·3); avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Skin disorders.

Reversal *Panalab, Arg.*
Vitamins; minerals; lycopene (p. 2546·2).
Dietary supplement.

Reversol *Organon, USA.†*
Edrophonium chloride (p. 686·1).
Diagnosis of myasthenia gravis; evaluation of emergency treatment of myasthenic crises; reversal of competitive neuromuscular blockade.

Revervir *Richmond, Arg.†*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Rev-Eyes *Bausch & Lomb, USA.†*
Dapiprazole hydrochloride (p. 2006·2).
Reversal of mydriasis.

Revez *Chobet, Arg.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol withdrawal syndrome; opioid withdrawal syndrome.

Revia *BMS, Austral.; Torrex, Austria; Cristalia, Braz.; Apotex, Canad.; Torrex Chiesi, Cz.; Paranova, Fin.; BMS, Fr.; BMS, Hong Kong†; Torrex, Hung.†; BMS, Irl.†; BMS, Mex.†; BMS, Neth.; BMS, Norw.†; BMS, NZ; BMS, Spain; Gervasi, Spain; BMS, Swed.†; BMS, Thai.; Barr, USA.*
Naltrexone hydrochloride (p. 1565·1).
Alcohol withdrawal syndrome; opioid withdrawal syndrome; opioid dependence.

Revi-Atlas *Atlas, Arg.*
Glycolic acid (p. 1704·3); vitamin E (p. 2119·1); hyaluronic acid (p. 2526·2); vitamin F (p. 2509·2).
Skin ageing.

K2 Health & Wellness, Chile.
Glycolic acid (p. 1704·3); hyaluronic acid (p. 2526·2); vitamin E (p. 2119·1); vitamin F (p. 2509·2).
Moisturiser.

Revi-B *YSP, Malaysia.*
Vitamins; minerals.
Dietary supplement.

Revicam *Revifar, Gr.*
⊗Serrapeptase (p. 2613·3).

Revicet *Sager, Hung.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; conjunctivitis; urticaria.

Revici *Kee, India.*
Citric acid (p. 2480·3).
Haemorrhage.

Revici-E *Kee, India.*
Etamsylate (p. 1145·2).
Haemorrhagic disorders.

Revicon *United American, Hong Kong; United American, Malaysia; United American, Singapore; Great Eastern, Thai.†*
Vitamins; minerals; yeast (p. 2125·2); methionine (p. 1558·2).
Dietary supplement.

Revicon Forte (Improved) *United Laboratories, Philipp.*
Vitamins; minerals; methionine (p. 1558·2); lysine (p. 2079·3); inositol (p. 2533·2); yeast (p. 2125·2).
Nutritional supplement.

Revicon Max *United Laboratories, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3); royal jelly (p. 2608·1).
Tonic; nutritional supplement.

ReviDerm *Surya Dermato, Indon.*
Tretinoin (p. 1725·2).
Sun-induced skin damage.

Revigel *Revifar, Gr.*
⊗Alcohol (p. 1733·1); camphor (p. 2466·2); menthol (p. 2553·2); thymol (p. 1772·2); cedar wood oil (p. 2472·3); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); nutmeg oil (p. 2573·2).

Revigonal *Airela, Braz.*
Ginseng (p. 2513·3).

Revil
Note: this name may be used for preparations of different composition.
Nobel, Turk.
Ramipril (p. 1483·3).

Tecnofarma, Chile.
Cyproheptadine hydrochloride (p. 624·1); vitamins.
Reduced appetite.

Revil Plus *Nobel, Turk.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).

Revimine *Uniao Quimica, Braz.†*
Dopamine hydrochloride (p. 1367·2).
Heart failure; hypotension.

Revion *Norma (Νορμα), Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Revionorm *Norma (Νορμα), Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Revirax *Blausiegel, Braz.*
Zidovudine (p. 1024·2).
HIV infection.

Revit *Marbiopharm, Rus.; KVZ, Ukr.*
Vitamins.
Dietary supplement.

RevitaDERM Wound Care *Blaine, USA.*
Silver protein (p. 2616·2).

Revital
Note: this name may be used for preparations of different composition.
Ranbaxy, Malaysia.
Vitamins; minerals; ginseng (p. 2513·3); choline (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2).

Sivaderm, Arg.
Vitamin A (p. 2098·3); glycolic acid (p. 1704·3).
Skin disorders.

Revital Calcium D3 *Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Ukr.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement; calcium and vitamin D deficiency; osteoporosis; osteomalacia; hypocalcaemia; calcium and vitamin D supplement.

Revital Garlic Pearls *Ranbaxy, Ukr.†*
Garlic oil (p. 2510·3).
Hypercholesterolaemia; atherosclerosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Revital Ginseng Plus *Ranbaxy, Rus.†*
Ginseng (p. 2513·3); vitamins; minerals; amino acids.
Tonic.

Revitalift *L'Oreal, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Revitaliv *Ultra, Mex.*
Vitamin B substances (p. 2102·3).

Revitaliv-C *Ultra, Mex.†*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuropathy; neuralgias; vitamin B deficiency.

Revitalizing Q10 Moisturizer *Beiersdorf, Canad.†*
Ensulizole (p. 1703·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Revitalose *Pierre Fabre, Fr.*
Ampoule A, magnesium aspartate (p. 1787·1); L-leucine (p. 2079·1); L-lysine hydrochloride (p. 2079·3); L-phenylalanine (p. 2086·1); L-valine (p. 2098·3); ampoule B, sodium ascorbate (p. 2111·1) or ascorbic acid (p. 2110·3).
Asthenia.

Revitalose C *Pierre Fabre Sante, Belg.*
Amino acids; sodium ascorbate (p. 2111·1).
Tonic.

Robapharm, Switz.
Amino acids; vitamin C (p. 2110·3).
Tonic.

Revitam *Biolab Sanus, Braz.*
Vitamins; with or without minerals.

Revitan *Ranbaxy, Thai.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Revitance *Humana, Philipp.*
Preparation for enteral nutrition in diabetes mellitus.

Revitare E *Gelpharma, Mex.*
Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Revitelle *Menarini, Fin.*
Bilastine (p. 617·3).
Allergic rhinitis; urticaria.

Revitonil
Note: this name may be used for preparations of different composition.
Lichtwer, UK.
Echinacea (p. 2498·1); peppermint (p. 1877·1); clove (p. 2481·2); aniseed (p. 2444·2); liquorice (p. 1853·2); fennel (p. 2503·2); eucalyptus (p. 2501·1).
Cold symptoms.

Pharbio, Norw.; Cederroth, Spain.†
Echinacea (p. 2498·1).
Cold symptoms; immunostimulant.

Revitonus C *Sandoz, Canad.†*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Revitron *Gelpharma, Mex.*
Vitamins; minerals.

Revivan *Zambon, Braz.†; AstraZeneca, Ital.*
Dopamine hydrochloride (p. 1367·2).
Shock; heart failure; hypotension.

Revlimid *Celgene, Austral.; Celgene, Austria; Celgene, Belg.; Celgene, Canad.; Tecnoframa, Chile; Celgene, Cz.; Celgene, Denm.; Celgene, Fr.; Celgene, Ger.; Celgene, Gr.; Celgene, Hong Kong; Celgene, Irl.; Neopharm, Israel; Celgene, Ital.; Celgene, Malaysia; Celgene, Neth.; Celgene, Norw.; Celgene, NZ; Celgene, Philipp.; Celgene, Pol.; Celgene, Port.; Celgene, Rus.; Celgene, Singapore; Celgene, Spain; Celgene, Swed.; Celgene, Switz.; Celgene, Thai.; Celgene, UK; Celgene, USA.*
Lenalidomide (p. 816·1).
Multiple myeloma; myelodysplastic syndromes; mantle cell lymphoma.

Revlon Age Defying *Revlon, Canad.†*
SPF 30: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Revlon Age Defying Dry Skin *Revlon, Canad.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Revlon Colorstay Active *Revlon, Canad.†*
SPF 25: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Revlon Complexion Concealer *Revlon, Canad.†*
Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Revlon Complexion One Step *Revlon, Canad.†*
Titanium dioxide (p. 1725·1).
Sunscreen.

Revlon Lipgloss *Revlon, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Revlon Super Lustrous *Revlon, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Revmelid *Gedeon Richter, Ukr.†*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Oestrogen deficiency; osteoporosis.

Revocon *Sun, India; Capsifar, Port.; Sun, UK.*
Tetrabenazine (p. 2627·3).
Chorea; ballism; tardive dyskinesia; dyskinesias; dystonias; hyperkinetic movement disorders in Huntington's chorea.

Revokarin *Anvi, Rus.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Revolade *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Irl.; GSK, Jpn; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.*
Eltrombopag olamine (p. 1140·1).
Immune thrombocytopenia.

GSK, Israel.
Eltrombopag (p. 1140·1).
Immune thrombocytopenia.

Revolan *Sanbe, Indon.*
Piracetam (p. 393·3).
Mental function impairment; chronic alcoholism; cerebral trauma.

Revonto *US Worldmeds, USA.*
Dantrolene sodium (p. 2023·3).
Malignant hyperthermia.

Revotonine *Hospital Line, Gr.*
Levocarnitine tartrate (p. 2053·2).
Carnitine deficiency.

Revovir *Eisai, Philipp.*
Clevudine.
Chronic hepatitis B.

Revoxin *Frik, Turk.*
Fluvoxamine maleate (p. 425·3).

Revup *Aristo, India.*
Vitamins; minerals.

Rewma-Gel *DHU, Rus.*
Rhus toxicodendron (p. 2603·3); ledum (p. 2550·1); symphytum ad usum externum (p. 2484·2).
Homoeopathic preparation.

Rewodina *AWD, Cz.†; AWD, Ger.†; CT, Ger.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation; pain; soft-tissue disorders.

Dresden, Pol.†
Diclofenac (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Rex *MDM, Ital.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Hypocalcaemia; bone disorders.

Rexacin *Unison, Malaysia; Unison, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Rexacrom *Rex, NZ.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Rexalgan *Dompe, Ital.†*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders.

Rexambro *Boehringer Ingelheim, Neth.*
Ambroxol hydrochloride (p. 1654·3).
Sore throat.

Rexap *Santa, Gr.*
Oxaliplatin (p. 838·1).

Rexapin *Abdi, Turk.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Rexavin *Ifars, Indon.*
Griseofulvin (p. 582·2).
Fungal skin, scalp, and nail infections.

Rexcof *Cipla, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3).
Cough.

Rexcof Plus *Cipla, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2).
Cough.

Rexena *Sanovel, Turk.*
Diacerein (p. 45·3).

Rexer *MSD, Spain.*
Mirtazapine (p. 436·1).
Depression.

Rexetin *Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder; panic disorder; anxiety.

Rexfobys *Renovati, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Rexgenta *Areu, Spain.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Rexicam *Otto, Indon.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Rexichlor *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Skin disinfection.

Rexidol *United American, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Rexil *Metiska, Indon.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Rexilan *Am-Europharma, Philipp.*
Rifampicin (p. 350·3).
Tuberculosis.

Rexilen *Serra Pamies, Spain.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Reximax *Nufarindo, Indon.*
⊗Arginine hydrochloride (p. 2049·1); yohimbe; Siberian ginseng (p. 2614·3); muira-puama; saw palmetto (p. 2363·3); tribulus terrestris (p. 2633·3).
Tonic.

Reximide *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Rexitol *Rekah, Israel.†*
Chloroxylenol (p. 1748·2); terpineol (p. 2627·2).
Disinfection.

Rexivin *Collins, Mex.*
Methocarbamol (p. 2025·3).
Musculoskeletal pain; skeletal muscle spasm.

Rexner *Casasco, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Rexod *Gosnii, Rus.*
Superoxide dismutase (p. 135·2).

Rexodrin *RX, Thai.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm.

Rexofen *Vysali, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Rexophtal N *Bausch & Lomb, Switz.†*
Phenylephrine hydrochloride (p. 1672·3).
Conjunctivitis.

Rexorubia *Lehning, Fr.*
Natrum sulfuricum (p. 1888·1); silicea (p. 2208·3); calcarea carbonica ostrearum (p. 1824·3); calcarea iodata (p. 1658·1); calcarea phosphorica (p. 1784·2); natrum phosphoricum (p. 1791·2); magnesia phosphorica (p. 1787·3); ferrum phosphoricum (p. 2077·1); rubia; juglans regia (p. 2646·1).
Homoeopathic preparation.

Homeocan, Canad.†
Calcium carbonate (p. 1824·3); calcium iodide (p. 1658·1); calcium phosphate tribasic (p. 1784·2); ferrum phosphoricum (p. 2077·1); juglans pulv (p. 2646·1); magnesium phosphate dibasic (p. 1786·3); sodium sulfate (p. 1888·1); rubia tinctorum; silicon dioxide (p. 2208·3); sodium phosphate dibasic (p. 1791·2).
Homoeopathic preparation.

Rexta *Kalbe, Indon.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Rextat *Recordati, Ital.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Reyataz *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, China; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.†; BMS, Irl.; BMS, Israel; BMS, Ital.; BMS, Jpn; BMS, Malaysia; BMS, Mex.; BMS, Neth.; BMS, Norw.; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, UK; BMS, USA.*
Atazanavir sulfate (p. 968·1).
HIV infection.

Reynaven *Loeffler, Mex.*
Cinnarizine (p. 622·1).
Vestibular disorders; nausea and vomiting; motion sickness; mental function impairment; peripheral vascular disorders.

Reyoin *Panalab, Arg.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Reytoil *World Medicine, Ukr.*
Fish oil (p. 1460·3); wheat-germ oil (p. 2647·1).
Dietary supplement.

Rezafil *Filadams, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Rezak *Reddy, S.Afr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder.

Rezamid
Note: this name may be used for preparations of different composition.
Summers, USA.
Resorcinol (p. 1718·3); sulfur (p. 1721·1).
Acne.

Rezerc *Bevo, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Rezidol *Egis, Cz.; Egis, Denm.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Rezin *Raam, Mex.*
⊗Mazindol (p. 2324·1).
Obesity.

Rezira *Cypress, USA.*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Rezoklastin *Sintez, Rus.*
Zoledronic acid (p. 1192·3).
Bone metastases; osteolysis in multiple myeloma; hypercalcaemia of malignancy.

Rezonisate *Valenta, Rus.*
Terizidone (p. 373·1).
Tuberculosis.

Rezonisate Plus *Valenta, Rus.*
Terizidone (p. 373·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Rezosel *Biosel, Turk.*
⊗Mannitol (p. 1427·3).
Bladder irrigation.

Rezplen *Senosiain, Mex.*
Clarithromycin (p. 266·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Rezult *Sun, India.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

ReZyst IM *Zyber, USA.*
Lactobacillus; bifidobacterium (p. 2596·3).

R-Gel *Healthline, USA.†*
Capsaicin (p. 35·1).

R-Gen *Goldline, USA.*
Iodinated glycerol (p. 1667·2).
Coughs.

R-Gene *Kabivitrum, USA.*
Arginine hydrochloride (p. 2049·1).
Test to assess pituitary reserve for growth hormone.

RG-Q *Combiphar, Indon.*
Ubidecarenone (p. 2637·1); *d*-alpha tocopherol (p. 2119·1).
Antoxidant.

Rhamical *Hipolabor, Braz.*
Calcium carbonate (p. 1824·3).

Rhamiglós *Hipolabor, Braz.*
Zinc (p. 2126·1); vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).

Rhea Superscent Oil *Philusa, Philipp.†*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1).
Musculoskeletal, joint, and soft-tissue disorders; pruritus.

RheDQuin *Sanquin, Neth.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhefluin *Zentiva, Cz.; Teva, Switz.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; ascites.

Rhelafen *Lapi, Indon.*
Ibuprofen (p. 68·2).
Fever; pain.

Rhelax *Herbapol Wroclaw, Pol.*
Caraway (p. 2470·2); fennel (p. 2503·2); frangula bark (p. 1843·3); rhubarb (p. 1884·2).
Constipation; obesity; digestive disorders.

Rhemacox *Actavis, Indon.*
Meloxicam (p. 86·3).
Rheumatoid arthritis; osteoarthritis.

Rhemafar *Ifars, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Rhemid *Zwitter, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Rhemofenax *Duopharma, Hong Kong†; CCM, Malaysia.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation.

Rhéobral *Pharma 2000, Fr.†*
Troxerutin (p. 2505·3); vincamine (p. 2645·2).
Mental function impairment in the elderly.

Rhéoflux *Pharma 2000, Fr.*
Troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids.

Rheogluman *Biochimic, Rus.*
⊗Dextran 40 (p. 1138·1); mannitol (p. 1427·3); sodium chloride (p. 1795·1).
Plasma volume expansion; shock; thrombosis prophylaxis; vascular disorders.

Rheohes *Braun, Ger.†*
⊗Pentastarch (p. 1146·1).
Plasma volume expansion.

Rheomacrodex *Meda, Denm.; Meda, Hung.; Pisa, Mex.†; Meda, Norw.; Eczacibasi, Rus.†; Akacia, S.Afr.; Fresenius Kabi, Spain; Meda, Swed.; Eczacibasi-Baxter, Turk.; Pharmacia, USA.*
⊗Dextran 40 (p. 1138·1) in sodium chloride.
Plasma volume expansion; extracorporeal circulation; shock; thromboembolic disorders; cerebral and peripheral vascular disorders; prophylaxis of surgical adhesions; hypovolaemia; organ perfusion.

Rheopolydex *Biosynthesis, Rus.*
⊗Dextran 40 (p. 1138·1) in sodium chloride.
Plasma volume expansion; shock; thrombosis prophylaxis; extracorporeal circulation; vascular eye disorders.

Rheopolyglukin *Biochimic, Rus.*
⊗Dextran 40 (p. 1138·1); with or without glucose (p. 2068·3).
Plasma volume expansion; shock; thrombosis prophylaxis; extracorporeal circulation; vascular eye disorders.

Rheosolon *PannonPharma, Hung.*
⊗Phenylbutazone (p. 125·1); prednisolone (p. 1645·2).
Gout; inflammation; musculoskeletal and joint disorders.

Rheosorbilact *Yuri, Ukr.*
Sorbitol (p. 2092·1); sodium lactate (p. 1781·2); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Detoxification; plasma volume expansion; hypovolaemic shock.

Rheotromb *DeltaSelect, Cz.†; Actavis, Ger.; Actavis, Hung.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Rhesogam *ZLB, Austria.†*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhesogamma *CSL, Arg.; CSL, Spain.†*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhesogamma P *Sanofi Pasteur, Chile†; ZLB, Gr.; CSL, Mex.; Farma-Tek, Turk.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhesonativ *Octapharma, Braz.; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Hung.; Octapharma, Irl.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Pol.; Octapharma, Port.; Octapharma, Rus.; Octapharma, Swed.; Octapharma, Thai.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhesugam *NBI, S.Afr.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhesuman *Faran, Gr.; Berna, Turk.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhetoflam *Caprifarmindo, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and soft-tissue disorders.

Rheubalmin Bad *Hoernecke, Ger.*
Methyl salicylate (p. 92·1); isobornyl acetate (p. 2460·2); camphor (p. 2466·2).
Bath additive; musculoskeletal, joint, and soft-tissue disorders.

Rheubalmin Indo *Hoernecke, Ger.*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rheucostan R *Hanosan, Ger.*
Ruta graveolens (p. 2608·2); berberis vulgaris (p. 2502·1); ledum palustre (p. 2550·1); stellaria media; bryonia (p. 2461·3); colchicum autumnale (p. 607·1); acidum benzoicum (p. 1738·2).
Homoeopathic preparation.

Rheudol *In Vitro, Hung.*
Arnica (p. 2447·2); camphor (p. 2466·2); apis mellifera (p. 2445·2).
Musculoskeletal and joint disorders.

Rheuflam *Standard, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Rheuflex
Note: this name may be used for preparations of different composition.
Medhaus, Philipp.
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders; soft-tissue injury.

Rheugesal *Mucos, Austria.†*
Diethylamine salicylate (p. 51·3); flufenamic acid (p. 65·1); myrtecaine (p. 1993·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rheugesic *Cipla-Medpro, S.Afr.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and soft-tissue disorders; gout; pain.

Rheum *Chinta, Thai.*
Rhubarb (p. 1884·2); sodium bicarbonate (p. 1781·1); vitamin B_1 (p. 2102·3); anise oil (p. 2444·3).

Rheuma
Note: this name may be used for preparations of different composition.
Heel, Austria.
Toxicodendron quercifolium (p. 2603·3); bryonia cretica; causticum (p. 2595·3); arnica montana (p. 2447·2); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Weleda, Austria.
Aconitum napellus (p. 2428·3); arnica (p. 2447·2); betula folium (p. 2457·3); mandragora radix; formica; rosemary oil (p. 2607·3).
Musculoskeletal and joint disorders.

Rheuma Bad
Note: this name may be used for preparations of different composition.
Tetesept, Ger.†
Glycol salicylate (p. 66·2); methyl nicotinate (p. 91·3); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3); camphor (p. 2466·2).
Musculoskeletal disorders.

Rheuma Heilkrauter Tee *Abtswinder, Canad.†*
Betula pendula (p. 2457·3); salix (p. 129·2); urtica (p. 2639·3).

Rheuma- und Schmerzsalbe *Winthrop, Ger.*
Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3).
Musculoskeletal disorders.

Rheumacin *Mylan, NZ.†*
Indometacin (p. 71·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Rheuma-Denk *Universal, Hong Kong.†*
Etofenamate (p. 57·2).

Rheumadoron *Weleda, Fr.*
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); betula alba (p. 2457·3); mandragora radix.
Homoeopathic preparation.

Weleda, Switz.; Weleda, UK.
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); birch (p. 2457·3); mandragora root.
Homoeopathic preparation.

Weleda, UK.
Ointment: Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); betula alba (p. 2457·3); mandragora root; rosemary oil (p. 2607·3).
Homoeopathic preparation.

Weleda, S.Afr.†
Aconitum napellus (p. 2428·3); arnica (p. 2447·2); betula; mandragora.
Homoeopathic preparation.

Rheumafar *Faran, Gr.*
Indometacin (p. 71·2).

Rheumafim *Catafarma, Braz.*
⊗Piroxicam (p. 125·3); dexamethasone (p. 1630·3); cyanocobalamin (p. 2107·2); orphenadrine (p. 909·2).

Rheuma-Gel
Note: this name may be used for preparations of different composition.
Ratiopharm, Ger.†
Etofenamate (p. 57·2).
Musculoskeletal, joint, and soft-tissue disorders.

Rheuma-Heel *Ebi, Switz.*
Toxicodendron quercifolium (p. 2603·3); bryonia cretica; causticum (p. 2595·3); arnica montana (p. 2447·2); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Rheuma-Hek *Strathmann, Ger.*
Urtica (p. 2639·3).
Musculoskeletal and joint disorders.

Rheuma-Hevert *Hevert, Ger.*
Oral drops: Bryonia (p. 2461·3); dulcamara (p. 2497·3); gnaphalium polycephalum; ledum (p. 2550·1); nux vomica (p. 2573·3); spiraea (p. 2550·2); tartarus stib. (p. 151·2).
Homoeopathic preparation.

Hevert, Ger.
Injection: Bryonia (p. 2461·3); dulcamara (p. 2497·3); gnaphalium polycephalum; ledum (p. 2550·1); nux vomica (p. 2573·3); spiraea (p. 2550·2); tartarus stib. (p. 151·2); harpagophytum (p. 42·3).
Homoeopathic preparation.

Hevert, Ger.†
Tablets: Aesculus hippocast. (p. 2431·2); gnaphalium polycephalum; kalmia (p. 2537·2); pulsatilla (p. 2600·2); spirea (p. 2550·2); urtica (p. 2639·3).
Homoeopathic preparation.

Rheuma-Kapseln *Stada, Ger.†*
Urtica (p. 2639·3).
Rheumatic disorders.

Rheumakur *Darya-Varia, Indon.†*
Curcuma oil (p. 2218·1).
Osteoarthritis; rheumatoid arthritis; fat malabsorption.

rheuma-loges *Loges, Ger.*
Berberis (p. 2502·1); ledum (p. 2550·1); thuja (p. 2629·3); rhus tox. (p. 2603·3); colchicum (p. 607·1); formica rufa; lithium carbonicum (p. 427·3).
Homoeopathic preparation.

Rheumamed *Feldhoff, Ger.*
Cayenne pepper (p. 2469·3).
Musculoskeletal and joint disorders.

Rheumanox *Charoen, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Rheuma-Pasc *Pascoe, Ger.*
Injection: Dulcamara (p. 2497·3); ledum (p. 2550·1); rhus toxicodendron (p. 2603·3); bryonia (p. 2461·3); colchicum (p. 607·1); causticum (p. 2595·3); rhododendron; ruta (p. 2608·2); cimicifuga (p. 2478·1).
Homoeopathic preparation.

Pascoe, Ger.
Tablets: Dulcamara (p. 2497·3); ledum (p. 2550·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Pascoe, Ger.
Oral drops: Rhus toxicodendron (p. 2603·3); phytolacca (p. 2593·2); bryonia (p. 2461·3); rhododendron; gnaphalium polycephalum; berberis (p. 2502·1).
Homoeopathic preparation.

Pascoe, Ger.
Oral liquid: Bryonia (p. 2461·3); colchicum (p. 607·1); berberis (p. 2502·1); rhus tox. (p. 2603·3); thuja (p. 2629·3); china (p. 2478·3); dulcamara (p. 2497·3); ledum (p. 2550·1); natrium nitricum (p. 1769·3); ulmus campestris.
Homoeopathic preparation.

Rheumapill *Supra Ferbindo, Indon.†*
Aspirin (p. 22·2).
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2) and magnesium hydroxide (p. 1857·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis.

Rheumaselect *Dreluso, Ger.*
Rhus tox. (p. 2603·3); bryonia (p. 2461·3); nux vomica (p. 2573·3); berberis (p. 2502·1); ledum (p. 2550·1).
Homoeopathic preparation.

Rheuma-Sern *Truw, Ger.*
Devil's claw root (p. 42·3).
Musculoskeletal and joint disorders; dyspepsia.

Rheumatac *Sovereign, UK.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Rheumatex *Wampole, USA.*
Test for rheumatoid factor in serum.

Rheumatic Pain *Cantassium Co., UK.*
Guaiacum resin (p. 2523·1); taraxacum (p. 2625·3); celery (p. 2472·3); menyanthes (p. 2554·2).
Muscle and joint pain.

Rheumatic Pain Relief *Herbal Concepts, UK.*
Menyanthes (p. 2554·2); guaiacum resin (p. 2523·1); capsicum (p. 2469·3); capsicum oleoresin (p. 2469·3); celery oil (p. 2472·3).
Musculoskeletal and joint pain.

Rheumatic Pain Remedy *Potter's, UK.*
Menyanthes (p. 2554·2); lappa root (p. 2540·1); achillea (p. 2427·3); guaiacum resin (p. 2523·1).
Musculoskeletal and joint disorders.

Rheumatica *Nelson, UK.*
Rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Rheumatin *Sandoz, Indon.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2); selenium (p. 2086·3); calcium (p. 1783·1).
Osteoarthritis.

Rheumatin Forte *Sandoz, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); magnesium (p. 1786·3); zinc (p. 2126·1); manganese (p. 2081·2); selenium (p. 2086·3); calcium (p. 1783·1).
Osteoarthritis; dietary supplement for healthy joints.

Rheumaton *Wampole, USA.*
Test for rheumatoid factor in serum or synovial fluid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rheumatrex *Stada, USA.*
Methotrexate (p. 822·2) or methotrexate sodium (p. 822·2).
Psoriasis; rheumatoid arthritis.

Rheumavek *Angelini, Gr.; Faran, Rus.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Rheumeda *Madaus, Ger.*
Bryonia (p. 2461·3); ledum (p. 2550·1); rhus toxicodendron (p. 2603·3); ruta (p. 2608·2); spiraea ulmaria (p. 2550·2).
Homoeopathic preparation.

Rheumesser *Gerot, Austria.*
⊗Kebuzone (p. 78·3); salamidacetic acid (p. 129·2); dexamethasone (p. 1630·3); cyanocobalamin (p. 2107·2).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Rheumetone *Charoon Bhesaj, Thai.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Rheumex *Gebro, Austria.†*
Glycol salicylate (p. 66·2); benzyl nicotinate (p. 29·3); allantoin (p. 1693·1).
Musculoskeletal and joint disorders; sports injuries.

Rheumodoron 1 *Weleda, Ger.*
Aconitum napellus (p. 2428·3); arnica (p. 2447·2); bryonia (p. 2461·3).
Homoeopathic preparation.

Rheumodoron 2 *Weleda, Ger.*
Colchicum (p. 607·1); sabina.
Homoeopathic preparation.

Rheumodoron 102 A *Weleda, Ger.*
Aconitum napellus (p. 2428·3); arnica (p. 2447·2); betula (p. 2457·3); mandragora.
Homoeopathic preparation.

Rheumon *Meda, Austria; Bayer, China; Meda, Cz.†; Meda, Ger.; Meda, Hung.; Bayer Schering, Pol.; Drossapharm, Switz.; Bayer, Turk.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Rheumox *Continental Ethicals, S.Afr.†*
Azapropazone (p. 28·3).
Gout; osteoarthritis; rheumatoid arthritis.

RheuNAC *3-OL, Israel.†*
Acetylcysteine (p. 1652·2).

Rheunervol N *Riemser, Ger.*
Camphor (p. 2466·2).
Musculoskeletal and joint disorders.

Rheu-Tarx 1 *Natiris, Venez.*
Rhubarb (p. 1884·2); taraxacum (p. 2625·3); equisetum (p. 2500·1); senna (p. 1885·1).
Constipation.

Rheutril *T Man, Thai.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Degenerative joint disorders.

Rheutrop *Meda, Austria.*
Acemetacin (p. 16·3).
Musculoskeletal and joint disorders; gout; inflammation; thrombophlebitis; vasculitis.

Rheuvit *Gradiens, Hung.*
Calendula (p. 2465·2); methyl salicylate (p. 92·1); peppermint oil (p. 1877·1).
Musculoskeletal and joint disorders.

Rheuxan *Flamingo, Philipp.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Rhewlin *Beacons, Singapore.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; pain; inflammation.

Rhinaaxia *Agepha, Austria†; Thea, Fr.†; Farmila, Ital.*
Sodium spaglumate (p. 2535·2).
Allergic rhinitis.

Proel, Gr.
Magnesium spaglumate (p. 2535·2); magnesium isospaglumate (p. 2535·2).
Allergic rhinitis.

Rhinadine *Farmaline, Thai.†*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Hypersensitivity reactions; nasal congestion.

Rhinadvil *Pfizer Sante, Fr.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis with headache and fever.

Rhinal
Note: this name may be used for preparations of different composition.
Ahimsa, Arg.; Fada, Arg.
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Zentiva, Cz.†
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion.

Rhinalar *Ivax, Canad.*
⊗Flunisolide (p. 1635·3).
Allergic rhinitis.

Rhinall *Scherer, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Rhinallergy *Boiron, Cz.*
Allium cepa (p. 2575·2); ambrosia artemisiifolia; euphrasia officinalis (p. 2502·1); histamini dihydrochloridum (p. 2525·2); sabadilla (p. 2611·2); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Boiron, Fr.
Allium cepa (p. 2575·2); ambrosia artemisia; euphrasia (p. 2502·1); histaminum muriaticum (p. 2525·2); sabadilla (p. 2611·2); solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Boiron, Switz.
Allium cepa (p. 2575·2); ambrosia artemisiaefolia; euphrasia officinalis (p. 2502·1); histamini dihydrochloridum (p. 2525·2); schoenocaulon officinale (p. 2611·2); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Rhinamex *Chinta, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Rhinamide
Note: this name may be used for preparations of different composition.
Bailly, Fr.
⊗Ephedrine hydrochloride (p. 1663·2); benzoic acid (p. 1738·2).
Congestion of the nose and throat.

Rhinar
Note: this name may be used for preparations of different composition.
TP, Thai.
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion; rhinorrhoea; cold symptoms.

Biological Homeopathic Industries, Canad.†
Calcium sulfide crude (p. 1721·3); euphorbium officinarum; hydrastis canadensis (p. 2528·1); lycopodium clavatum (p. 2547·1); phosphorus (p. 2589·2); potassium dichromate (p. 2476·3); potassium iodide (p. 2336·3); pulsatilla (p. 2600·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Rhinaris *Arbor, USA.*
Sodium chloride (p. 1795·1).

Pendopharm, Canad.
Macrogol (p. 2547·3); propylene glycol (p. 2205·2).
Nasal dryness.

Rhinaris Nozoil *Pendopharm, Canad.*
Sesame oil (p. 2614·1).
Nasal dryness.

Rhinaris Saline *Pendopharm, Canad.*
Sodium chloride (p. 1795·1).
Nasal disorders.

Rhinaris Sinomarin *Pendopharm, Canad.*
Sea water (p. 2612·1).
Nasal hygiene.

Rhinaris Sinus *Pendopharm, Canad.*
Sodium chloride (p. 1795·1).

Rhinaris-CS *Pendopharm, Canad.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Rhinase *Essex, Philipp.†*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Nasal congestion; allergic rhinitis.

Rhinatate *Major, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Upper respiratory-tract symptoms.

Rhinatate-NF *Major, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Rhinathiol *Sanofi-Aventis, Fr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion; otitis; sinusitis.

Sanofi-Aventis, Hung.; Sanofi-Aventis, Port.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Sanofi-Aventis, Hung.
Nasal spray: ⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rhinathiol Antirhinitis *Sanofi-Aventis, Belg.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Rhinitis; sinusitis.

Rhinathiol Cold *Sanofi-Aventis, Hung.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Rhinathiol Promethazine *Sanofi-Aventis, Fr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.†*
Carbocisteine (p. 1658·1); promethazine hydrochloride (p. 638·2).
Cough; respiratory-tract disorders.

Rhinathiol Toux Sèche Pholcodine *Sanofi-Aventis, Fr.†*
Pholcodine (p. 1675·1).
Cough.

Rhinathiol Tusso *Sanofi-Aventis, Hung.*
Prenoxdiazine hydrochloride (p. 1675·3).
Cough.

Rhinatol *Suphong, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Rhinatussol *Sanofi-Aventis, Switz.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Rhinatux *Amido, Fr.†*
Codeine phosphate (p. 40·2); dexchlorpheniramine maleate (p. 621·1).
Cough.

Rhinazin *Polfa Warszawa, Pol.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Rhin-Bac *Hasco-Lek, Pol.*
Camphor (p. 2466·2); mint oil (p. 2560·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); pine oil (p. 2591·1).
Upper respiratory-tract disorders.

Rhinédrine *Cooperation Pharmaceutique, Fr.*
Benzododecinium bromide (p. 1739·2).
Nose and throat infections.

Rhineton *Be-Tabs, S.Afr.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Rhinex
Note: this name may be used for preparations of different composition.
Stada, Thai.
Carbocisteine (p. 1658·1).
Cough associated with increased or viscous mucus.

Rhinigine *Mylan, S.Afr.*
Loratadine (p. 633·2).
Allergic rhinitis.

Rhinil *Aristopharma, Hong Kong; Aristopharma, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; hypersensitivity reactions.

Rhiniramine *DHA, Hong Kong; DHA, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Rhini-San
Note: this name may be used for preparations of different composition.
Takeda, Belg.
Phenylephrine hydrochloride (p. 1672·3); diphenylpyraline hydrochloride (p. 627·2).
Allergic rhinitis.

Rhinisan
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Ger.
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Rhinital *DHU, Rus.*
Luffa operculata (p. 2545·3); galphimia glauca; cardiospermum halicacabum.
Homoeopathic preparation.

DHU, Ukr.
Galphimia glauca; luffa operculata (p. 2545·3); cardiospermum.
Homoeopathic preparation.

Rhinitin *Laves, Switz.*
Diphenhydramine hydrochloride (p. 626·2); caffeine (p. 1203·3).
Cold symptoms; allergic rhinitis.

Rhinitrin *Sigma, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Rhinivict *Dermapharm, Ger.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Rhino Humex *Urgo, Belg.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Rhinobol *Advance, China.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).

Rhinobros *Bros, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Rhinobudesonide *Mylan, Belg.†*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Rhinocap
Note: this name may be used for preparations of different composition.
Grossmann, Hong Kong†; Grossmann, Switz.
Phenylephrine hydrochloride (p. 1672·3); dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Cold symptoms; nasal congestion; sinus congestion; allergic rhinitis.

Inibsa, Spain.†
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2).
Nasal congestion.

Rhinoclenil *Chiesi, Rus.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Rhinoclir
Note: this name may be used for preparations of different composition.
Perrigo, Israel.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Rhinocort
Note: this name may be used for preparations of different composition.
AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Astra, USA; AstraZeneca, Venez.
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.

Teijin, Jpn.
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Rhinocure *Actipharm, Switz.*
Polysorbate 80 (p. 2203·3); sodium chloride (p. 1795·1); chamomile (p. 2474·1); benzethonium chloride (p. 1738·1).
Rhinopharyngeal disorders.

Rhinocure simplex *Actipharm, Switz.*
Polysorbate 80 (p. 2203·3); sodium chloride (p. 1795·1); benzethonium chloride (p. 1738·1).
Rhinopharyngeal disorders.

Rhinodec *Healthprime, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); brompheniramine maleate (p. 618·1).
Nasal congestion; rhinitis.

Rhinodoron *Weleda, Fr.; Weleda, Ger.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); aloe vera (p. 1693·2).
Nasal cleansing; nasal dryness; nasal congestion.

Rhinodose *Pharmanel, Gr.*
Sodium chloride (p. 1795·1).
Dry nasal mucosa.

Rhinofébral *McNeil, Fr.†*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); ascorbic acid (p. 2110·3).
Rhinopharyngeal disorders; cold symptoms.

Rhinofebryl *Melisana, Belg.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Rhinitis with fever and/or headache.

Rhinofed
Note: this name may be used for preparations of different composition.
Dexa, Indon.
⊗Pseudoephedrine (p. 1676·1); terfenadine (p. 640·3).
Rhinitis.

Rhinofluimucil *Zambon, Fr.*
⊗Acetylcysteine (p. 1652·2); tuaminoheptane sulfate (p. 1679·3); benzalkonium chloride (p. 1737·1).
Rhinopharyngeal congestion.

Rhinogan *Beximco, Philipp.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Rhinogen *IBSA, Switz.*
Sodium hyaluronate (p. 2526·2).
Nasal dryness.

Rhinoguttae Argenti diacetylotannici proteinici *Leyh, Ger.†*
Silver protein acetyl tannate (p. 2616·2).
Nasal congestion.

Rhinoguttae pro Infantibus N *Leyh, Ger.†*
Silver protein acetyl tannate (p. 2616·2).
Nasal congestion.

Rhinohist *Seng, Thai.*
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion; allergic rhinitis; rhinorrhoea.

Rhinol *Su-Heung, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Rhinol Plus *Su-Heung, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Obstructive airways disease.

Rhinolast *Meda, Irl.; Meda, Israel; Akacia, S.Afr.; Meda, UK.*
Azelastine hydrochloride (p. 617·1).
Allergic rhinitis.

Rhinolex *Alapis, Gr.*
⊗Ephedrine hydrochloride (p. 1663·2).
Nasal congestion.

Rhinomaxil *Zambon, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Rhinomer *Novartis Consumer, Ger.†; Novartis Consumer, Israel; Novartis Consumer, Switz.; Novartis, Turk.*
Sea water (p. 2612·1).
Nasal congestion; nasal dryness; nasal disorders.

Rhinomer mini *Novartis Consumer, Switz.*
Sea water (p. 2612·1); dexpanthenol (p. 2582·2).
Nasal dryness; nasal congestion.

Rhinon *Sigmapharm, Austria.*
Nasal ointment: ⊗Naphazoline hydrochloride (p. 1669·3); sulfadiazine (p. 361·3).
Rhinitis; sinusitis.
Sigmapharm, Austria.
Nose drops: ⊗Naphazoline hydrochloride (p. 1669·3).
Rhinitis.

Rhinonorm *Ratiopharm, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis media; aid in nasal examination.

Rhinoperd *Agepha, Austria.*
⊗Naphazoline hydrochloride (p. 1669·3).
Rhinitis; sinusitis; aid in rhinoscopy.

Rhinoperd comp *Agepha, Austria.*
⊗Naphazoline hydrochloride (p. 1669·3); diphenhydramine hydrochloride (p. 626·2).
Cold symptoms; rhinitis.

Rhinophenazol *Polfa Warszawa, Pol.*
⊗Antazoline sulfate (p. 616·1); naphazoline nitrate (p. 1669·3).
Allergic rhinitis; nasal congestion.

Rhinopront
Note: this name may be used for preparations of different composition.
Pfizer, Austria†; Olvos, Gr.; Mack, Hong Kong†; Mack, Rus.; Abdi, Turk.
Phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1).
Respiratory-tract congestion; rhinitis; sinusitis; colds; catarrh.
Mack, Hong Kong†; Abdi, Turk.
Oral suspension: syrup: Phenylpropanolamine polistirex (p. 1674·1); carbinoxamine polistirex (p. 619·1).
Respiratory-tract congestion; catarrh; rhinitis; sinusitis.

Rhinopront Kombi *McNeil, Ger.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Rhinopront N *Janssen-Cilag, Switz.†*
Capsules: Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; rhinitis; sinusitis.

Rhinopront Top *Janssen-Cilag, Switz.†*
⊗Tetryzoline hydrochloride (p. 1678·3).
Rhinopharyngeal disorders.

Rhinopront-S *Olvos, Gr.*
Phenylpropanolamine polistirex (p. 1674·1); carbinoxamine polistirex (p. 619·1).
Allergic rhinitis; catarrh.

Rhinorus *Synthesis, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis media; rhinoscopy.

Rhinos *Dexa, Hong Kong.*
⊗Loratadine (p. 633·2); pseudoephedrine (p. 1676·1).
Cold symptoms; allergic rhinitis.
Dexa, Indon.; Dexa, Philipp.†
⊗Loratadine (p. 633·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms.

Rhinos Junior *Dexa, Indon.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Rhinos Neo *Dexa, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Rhinosept *Delta, Braz.†*
⊗Naphazoline hydrochloride (p. 1669·3); diphenhydramine hydrochloride (p. 626·2); neomycin sulfate (p. 330·1).
Nasal congestion.

Rhinoside *Chemica, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Rhinosingulair *MSD, Belg.*
Montelukast sodium (p. 1214·3).
Allergic rhinitis.

Rhinosinutab *Johnson & Johnson Consumer, Belg.*
⊗Pseudoephedrine (p. 1676·1); cetirizine (p. 619·2).
Allergic rhinitis.

Rhinosol *AstraZeneca, Denm.†*
⊗Budesonide (p. 1625·1).
Rhinitis.

Rhinospray *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Ger.; Unilfarma, Port.; Boehringer Ingelheim, Spain.*
⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion; rhinitis; sinusitis; otitis media.

Rhinospray Antialergico *Boehringer Ingelheim, Spain.*
⊗Tramazoline hydrochloride (p. 1679·3); chlorphenamine maleate (p. 620·3).
Nasal congestion.

Rhinospray Atlantik *Boehringer Ingelheim, Ger.†*
Sea water (p. 2612·1).
Nasal disorders.

Rhinospray Eucaliptus *Boehringer Ingelheim, Spain.*
⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Rhinospray met eucalyptus *Boehringer Ingelheim, Neth.*
⊗Tramazoline hydrochloride (p. 1679·3); cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Rhinospray Plus *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.*
⊗Tramazoline hydrochloride (p. 1679·3); cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Rhinosprey *Boehringer Ingelheim, Rus.*
⊗Tramazoline hydrochloride (p. 1679·3).
Rhinitis; sinusitis; otitis media.

Rhino-Stas *Stada, Cz.; Stada, Hung.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis.

Rhinostop
Note: this name may be used for preparations of different composition.
Lekko, Rus.; IBSA, Switz.
⊗Xylometazoline hydrochloride (p. 1680·1).
Otitis media; rhinitis; sinusitis; aid in nasal examination.
Bosnalijek, Ukr.†
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; allergic rhinitis.

Rhino-Sulfuryl *Legras, Fr.*
⊗Sodium thiosulfate (p. 1576·1); ephedrine hydrochloride (p. 1663·2).
Rhinitis; sinusitis.

Rhinosyn *Great Southern, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Rhinosyn-DM *Great Southern, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Rhinosyn-DMX *Great Southern, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Rhinosyn-X *Great Southern, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Rhinotapp *Dynamic, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Nasal congestion; cough.

Rhinotrophyl *Jolly-Jatel, Fr.*
Thenoate monoethanolamine (p. 376·3).
Infections of the nose and throat.

Rhinotussal
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Capsules: Phenylephrine hydrochloride (p. 1672·3); carbinoxamine maleate (p. 619·1); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract congestion.
Abdi, Turk.
Oral liquid: Phenylpropanolamine (p. 1674·1); carbinoxamine maleate (p. 619·1); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract congestion.

Rhino-Vaccin *Rougier, Canad.†*
⊗Camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1); ephedrine hydrochloride (p. 1663·2).
Cold symptoms.

Rhinovent *Boehringer Ingelheim, Switz.*
Ipratropium bromide (p. 1211·3).
Rhinitis.

Rhinovín *Novartis Consumer, Spain.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rhinox *Nycomed, Norw.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Rhinureflex *Reckitt Benckiser, Fr.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; nasal congestion; headache; fever.

Rhin-X *Axapharm, Switz.*
Phenylephrine hydrochloride (p. 1672·3); dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Cold symptoms; nasal congestion; allergic rhinitis.

Rhitecin *Siam Medicare, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria; allergic skin disorders.

Rhodacine *Rhoxalpharma, Canad.†*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout.

Rhodium *Fahrenheit, Indon.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency.

Rhododendron Complexe No 42 *Lehning, Fr.†*
Acidum nitricum (p. 2572·3); aconitum (p. 2428·3); anemone pulsatilla (p. 2600·2); arnica (p. 2447·2); aurum colloidum (p. 2521·1); cuprum aceticum (p. 2486·2); nux vomica (p. 2573·3); rhododendron ferrugineum; sulfur (p. 1721·1); thuya (p. 2629·3).
Homoeopathic preparation.

Rhododendroneel *Heel, Austria.*
Luffa operculata (p. 2545·3); hydrargyrum bijodatum (p. 2555·3); hepar sulfuris (p. 1721·3); argentum nitricum (p. 2615·3); sinusitis-nosode; euphorbium; pulsatilla pratensis (p. 2600·2); mucosa nasalis suis.
Homoeopathic preparation.

Rhodogil *Sanofi-Aventis, Spain.*
Spiramycin (p. 358·3); metronidazole (p. 936·1).
Bacterial infections.

Rhodolith-Gastreu R46 *Reckeweg, Neth.*
Ferrum phosphoricum (p. 2077·1); lithium carbonicum (p. 427·3); natrium sulfuricum (p. 1888·1); nux vomica (p. 2573·3); rhododendron chrysanthum; spiraea ulmaria (p. 2550·2).
Homoeopathic preparation.

RhoGAM *Ortho Diagnostic, Belg.; Ortho, Hong Kong; Ortho, Hung.†; CSL, NZ; Hemat, Turk.; Ortho Diagnostic, USA.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhomuz *Pharos, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Rhonal *Sanofi-Aventis, Spain.†*
Aspirin (p. 22·2).
Pain; musculoskeletal, joint and peri-articular disorders; fever.

Rho-Nitro *Sanofi-Aventis, Canad.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Rhophylac *CSL, Arg.; ZLB, Austria; CSL, Braz.; CSL, Cz.; CSL, Denm.; CSL, Fin.; CSL, Fr.; CSL, Ger.; ZLB, Ger.; CSL, Gr.; CSL, Hung.; CSL, Irl.; CSL, Israel; CSL, Ital.; CSL, Mex.; CSL, Neth.; CSL, Norw.; CSL, Pol.; CSL, Port.; CSL, Spain; CSL, Swed.; CSL, Switz.; Biomeks, Turk.; ZLB, UK; CSL, USA.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation.

Rhotard *Sovereign, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

Rhotral *Sanofi-Aventis, Canad.†*
⊗Acebutolol hydrochloride (p. 1289·2).
Hypertension; angina pectoris.

Rhovane *Sanofi-Aventis, Canad.*
Zopiclone (p. 1118·1).
Insomnia.

Rhu *Lero, Fr.*
Fish oil (p. 1460·1); vitamins; minerals.
Dietary supplement; joint disorders.

Rhuaka *OTC Concepts, UK.*
Cascara (p. 1826·1); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Rhum Creosotado *Arrow, Braz.†*
Creosote (p. 1659·3); sodium hypophosphite (p. 2530·3); calcium hypophosphite (p. 2530·3).
Respiratory-tract congestion.

Rhumacap *Acdhon, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

Rhumadol *Naturactive, Fr.*
Dimethyl sulfone (p. 2493·3); glucosamine sulfate (p. 2515·3); black currant (p. 2458·1).
Joint disorders.

Rhumafen *TO-Chemicals, Thai.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rhumagel *Hoe, Malaysia; Hoe, Singapore.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Rhumagrip *Cooperation Pharmaceutique, Fr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Rhumalgan *Sandoz, UK.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Rhumanol *TO-Chemicals, Thai.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Rhumatab *Acdhon, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

Rhume et Grippe *Confab, Canad.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).

Rhume et de la Grippe *Prodemdis, Canad.†*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Rhume et de la Toux *Prodemdis, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; cough.

Rhumeel *Heel, Neth.*
Rhus toxicodendron (p. 2603·3); bryonia alba; causticum (p. 2595·3); arnica montana (p. 2447·2); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Rhus Med Complex *Dynamit, Austria.*
Arnica (p. 2447·2); bryonia (p. 2461·3); ledum (p. 2550·1); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Rhus Opodeldoc *Knop, Chile.*
Camphor (p. 2466·2); rosemary (p. 2607·2); thyme (p. 2630·2); rhus toxicodendron (p. 2603·3); ammonia (p. 2441·2).
Musculoskeletal, joint, and soft-tissue disorders.

Rhus Toxicodendron Complexe No 80 *Lehning, Fr.*
Rhus toxicodendron (p. 2603·3); mercurius corrosivus (p. 2555·2); nux vomica (p. 2573·3); manganum aceticum; causticum (p. 2595·3); colchicum (p. 607·1); aconitum (p. 2428·3).
Homoeopathic preparation.

Rhus Toxicodendron Composé *Boiron, Fr.*
Rhus toxicodendron (p. 2603·3); urtica urens (p. 2639·3); acide benzoicum (p. 1738·2); acidum formicum (p. 2507·1); berberis vulgaris (p. 2502·1); ranunculus; lithium carbonicum (p. 427·3).
Homoeopathic preparation.

Rhus toxicodendron N Oligoplex *Madaus, Ger.*
Rhus toxicodendron (p. 2603·3); bryonia (p. 2461·3).
Homoeopathic preparation.

Rhus-Plus *Doctor H, Rus.*
Hepar sulfuris (p. 1721·3); lithium carbonicum (p. 427·3); lycopodium clavatum (p. 2547·1); rhus toxicodendron (p. 2603·3); calcium fluoratum (p. 2053·1); colchicum autumnale (p. 607·1).
Homoeopathic preparation.

Rhus-Rheuma-Gel N *DHU, Ger.*
Rhus toxicodendron (p. 2603·3); ledum (p. 2550·1); comfrey (p. 2484·2).
Musculoskeletal and joint disorders.

Rhustoxicorell *Sanorell, Ger.*
Toxicodendron querafolium (p. 2603·3).
Homoeopathic preparation.

Rhynacol *Sunward, Malaysia.†*
Pholcodine (p. 1675·1); triprolidine hydrochloride (p. 642·3).
Cough.

Rhythmiodarone *Farmstandart, Rus.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Rhythmocor
Note: this name may be used for preparations of different composition.
FarKoS, Ukr.
Magnesium gluconate (p. 1787·2); potassium gluconate (p. 1793·2).
Ischaemic heart disease; neurocirculatory dystonia; myocardial infarction; arrhythmias; myocarditis; myocardiopathy; magnesium and potassium deficiency; liver disorders; chronic fatigue syndrome.

Rhythmy *Shionogi, Jpn.*
Rilmazafone hydrochloride (p. 1103·1).
Insomnia; premedication.

RHZ *Overseas, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

RHZ Plus *Overseas, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Ri An *Chia Tai, China.*
Azasetron hydrochloride (p. 1820·2).
Chemotherapy-induced vomiting.

Ri Ao *Sanye, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Ri Jie Ning *Xinhuada, China.*
Povidone-iodine (p. 1767·1).

RiLiDa *Zhonglian, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Riabal *IBI, Ital.; Chiesi, Rus.; Hikma, Ukr.*
Prifinium bromide (p. 1879·3).
Smooth muscle spasm; gastrointestinal investigations.

Rialam *Labesfal, Port.*
Lorazepam (p. 1080·3).
Premedication; status epilepticus.

Riamet *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Cz.†; Novartis, Fr.; Novartis, Ger.; IFET (ΙΦΕΤ), Gr.; Novartis, Gr.; Novartis, Neth.; Novartis, Port.; Novartis, Singapore; Novartis, Swed.; Novartis, Switz.; Novartis, UK.*
Artemether (p. 648·1); lumefantrine (p. 656·3).
Malaria.

RiaSTAP *CSL, Austral.; CSL, Spain; CSL, USA.*
Fibrinogen (p. 1151·3).
Congenital fibrinogen deficiency haemorrhage.

Riastap *CSL, Belg.; CSL, Denm.; CSL, Fin.; CSL, Fr.; CSL, Irl.; CSL, Norw.; CSL, Swed.; CSL, UK.*
Fibrinogen (p. 1151·3).
Congenital fibrinogen deficiency haemorrhage.

Riatul *Baliarda, Arg.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; autism.

Riax *Artesa, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Riaxon *Lyofin, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ribamidil *Biopharma, Rus.*
Ribavirin (p. 1010·2).
Hepatitis C.

Riban *Arlex, Mex.*
Soya bean (p. 2092·3); povidone-iodine (p. 1767·1).
Skin disorders.

RibaPak *Par, USA.†*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Ribapeg *Makiz-Pharma, Rus.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Ribasphere *Biomeks, Turk.; Kadmon, USA.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Ribaspheres *Three Rivers, USA.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Ribastamin
Note: this name may be used for preparations of different composition.
Beta, Arg.
Risedronate sodium (p. 1189·3).
Osteoporosis.

Ribastamin Duo *Beta, Arg.*
4 Tablets, risedronate sodium (p. 1189·3); 24 tablets calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Ribastex *Alter, Port.†*
Ebastine (p. 628·1).
Allergic rhinitis; urticaria.

Ribatab *PRX, USA.†*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Ribatra *Panalab, Arg.*
⊗Clobetasol propionate (p. 1627·1).
Eczema.

Ribav *Biosintetica, Braz.*
Ribavirin (p. 1010·2).
Viral infections.

Ribavin *Lupin, India; BPL, Rus.; Lens, Rus.; Lupin, Rus.*
Ribavirin (p. 1010·2).
Hepatitis C.

Ribavirol *Dosa, Arg.*
Ribavirin (p. 1010·2).

Ribazole *Getz, Philipp.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Riber *Solvang, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Ribex
Note: this name may be used for preparations of different composition.
Quesada, Arg.
Vincamine (p. 2645·2); cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders.
Vianex (Βιανεξ), Gr.
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Ribobandron *Hikma, Neth.*
Ibandronate sodium (p. 1184·2).
Bone metastases; hypercalcaemia of malignancy.

Ribocarbo *Hikma, Ger.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Ribocine *Dexa, Indon.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Ribocler *Monserrat, Arg.*
Clonazepam (p. 519·1).

Ribodocel *Hikma, Ger.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Ribodoxo *Hikma, Ger.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Ribodronat *Hikma, Ger.*
Pamidronate disodium (p. 1186·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Riboepi *Hikma, Ger.*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Ribofentanyl *Hikma, Ger.†*
⊗Fentanyl (p. 60·1).
Pain.

Ribofluor *Hikma, Ger.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Ribofolin *Hikma, Ger.*
Calcium folinate (p. 2066·3).
Adjunct to fluorouracil therapy; methotrexate toxicity; folic acid deficiency.
Ribosepharm, Neth.†
Sodium folinate (p. 2067·1).
Adjunct to fluorouracil therapy; methotrexate toxicity.

Riboirino *Hikma, Ger.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Ribolin *Vianex (Βιανεξ), Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ribomicin *Farmigea, Ital.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Ribomunyl *Germania, Austria.*
Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae.
Respiratory-tract infections.
Pharmafabre (Φαρμαφαμπρ), Gr.; Robapharm, Switz.
Ribosomes of *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* membrane fraction of *Klebsiella pneumoniae.*
Respiratory-tract infections.
Pierre Fabre, Cz.
Ribosomes of *Klebsiella pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* membrane fraction of *Klebsiella pneumoniae.*
Respiratory-tract infections.
Pierre Fabre, Ger.
Ribosomes from *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* proteoglycans from *Klebsiella pneumoniae.*
Respiratory-tract infections.
Pierre Fabre, Hung.
Ribosomal fraction of: *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* membrane fraction of: *Klebsiella pneumoniae.*
Respiratory-tract infections.
Pierre Fabre, Pol.
Ribosomal extract from *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* proteoglycan membrane extract from *KLebsiella pneumoniae.*
Respiratory-tract infections.
Pierre Fabre, Port.
Ribosomal fractions of *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* membrane proteoglycans of *Klebsiella pneumoniae.*
Respiratory-tract infections.
Pierre Fabre, Rus.
Bacterial ribosomes from, *Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae;* proteoglycan extract from *Klebsiella pneumoniae.*
Infections.
Silesia, Chile; PierreFabre, Ukr.
Ribosomal fractions of *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae;* membrane fraction of *Klebsiella pneumoniae.*
Respiratory-tract infections.

Ribomustin *Astellas, Cz.; Mundipharma, Ger.†; IFET (ΙΦΕΤ), Gr.; Mundipharma, Switz.*
Bendamustine hydrochloride (p. 746·2).
Malignant neoplasms.

Ribomustine *Astellas, Rus.; Astellas, Ukr.*
Bendamustine hydrochloride (p. 746·2).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma; multiple myeloma.

Ribon *Therabel, Belg.*
Riboflavin (p. 2104·3).
Vitamin B_2 deficiency; muscle cramps.

Ribone *Trima, Israel.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Ribonosin *October, Rus.*
Inosine (p. 2533·1).
Cardiac disorders; liver disorders; renal protection in isolated kidney surgery.

Riboposid *Hikma, Ger.*
Etoposide (p. 790·2).
Malignant neoplasms.

Riboquin *Dexa, Indon.*
Chloroquine phosphate (p. 650·1).
Malaria.

Ribosetron *Hikma, Ger.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Ribosofol *Hikma, Ger.*
Sodium folinate (p. 2067·1).
Adjunct to fluorouracil therapy; reduction of methotrexate toxicity.

Ribotal *Medicamerc, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Ribotax *Hikma, Ger.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-associated Kaposi's sarcoma.

Ribotrex *Pierre Fabre, Ital.*
Azithromycin (p. 221·2).
Bacterial infections.

Ribotripsin *Grin, Mex.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Soft-tissue inflammation and pain.

Ribovac *Pierre Fabre, Arg.*
Ribosomal fractions of *Klebsiella pneumoniae;* membrane fraction of *Klebsiella pneumoniae.*
Respiratory-tract infections.

Pierre Fabre, Mex.
Ribosomal fractions of *Klebsiella pneumoniae; Streptococcus pneumoniae; Streptococcus pyogenes; Haemophilus influenzae*; membrane fraction of *Klebsiella pneumoniae.*
Respiratory-tract infections.

Ribovact *Mundipharma, Swed.*
Bendamustine hydrochloride (p. 746·2).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma; multiple myeloma.

Ribovir *Plants, Ital.*
Royal jelly (p. 2608·1); echinacea (p. 2498·1); black currant (p. 2458·1).
Nutritional supplement.

Ribovit *Synco, Hong Kong.†*
Riboflavin (p. 2104·3).

Riboxatin *Hikma, Ger.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Riboxin *Arterium, Ukr.*
Inosine (p. 2533·1).
Cardiovascular disorders; liver disorders; radiation-induced leucopenia; glaucoma.

Ribozar *Ebewe, Ger.; Hikma, Ger.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Ribrain *Galenica, Gr.*
Betahistine mesilate (p. 2455·3).
Vertigo; Ménière's disease.

Ribufen *Jofrain, Mex.†*
Ibuprofen (p. 68·2).
Inflammation; pain; rheumatism.

Ribujet *Chiesi, Spain.*
⊗Budesonide (p. 1625·1).
Asthma.

Ribunal *Combiphar, Indon.*
Ibuprofen (p. 68·2).
Fever; musculoskeletal and joint disorders; pain.

Ribuspir *Torrex Chiesi, Cz.†; Chiesi, Gr.; Master Pharma, Neth.†*
⊗Budesonide (p. 1625·1).
Obstructive airways disease; asthma.

RIC Calcio *Dominguez, Arg.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Rical
Note: this name may be used for preparations of different composition.
Iromedica, Switz.
Castor oil (p. 2472·1).
Constipation.

Ricalide *IDI, Ital.*
Flutamide (p. 798·2).
Prostatic cancer.

Ricam *Hovid, Hong Kong.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Hovid, Malaysia; Hovid, Philipp.
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; pruritus; urticaria; allergic skin disorders; cold symptoms; anaphylaxis; allergic rhinitis.

Ricamycin *Asahi, Jpn.*
Rokitamycin (p. 356·1).
Bacterial infections.

Ricap *Savio, Ital.*
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Ricelyt *MM, India.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); rice (p. 1780·1).
Oral rehydration therapy.

Ricerca *Johnson & Johnson, Ital.†*
Vitamins; minerals; amino acids.
Skin, hair, and nail disorders.

Ricfen *Hanmi, China.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Riche Wrinkle Smoothing *Yves Rocher, Canad.*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Richmond Antiseptic Cream *LPC, UK.*
Cetrimide (p. 1742·1).
Burns; skin irritation; wounds.

Richwe *Nangkuang, China.*
Lansoprazole (p. 1851·3).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux.

Ricilaks *Yeni, Turk.*
Castor oil (p. 2472·1).
Bowel evacuation.

Ricilina *Recalcine, Chile.*
Azithromycin hydrochloride (p. 221·2).
Bacterial infections.

Riciment *Sistas, Turk.*
Castor oil (p. 2472·1).
Constipation.

Ricin *Atlantic, Hong Kong; Atlantic, Thai.*
Rifampicin (p. 350·3).
Bacterial infections; bacterial infections including tuberculosis and gonorrhoea.

Ricinus Composé *Boiron, Fr.*
Ricinus communis; citrullus colocynthis; berberis vulgaris (p. 2502·1); hydrastis canadensis (p. 2528·1); lithium carbonicum (p. 427·3); ptelea trifoliata; podophyllum peltatum (p. 1717·1); chamomilla vulgaris (p. 2474·1).
Homoeopathic preparation.

Ricipan *Toprak, Turk.*
Castor oil (p. 2472·1).
Bowel evacuation.

Ricitel *Tecnofarma, Mex.†*
Castor oil (p. 2472·1).
Constipation; bowel evacuation.

Riclasip *Grunenthal, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Riclemed *Medochemie, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Ricoflu *Beacons, Singapore.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Ricola *Cedar Health, UK.*
Menthol (p. 2553·2); peppermint oil (p. 1877·1).
Nasal congestion; sore throat; coughs.

Ricola Herb *Ricola, USA.*
Menthol (p. 2553·2).
Sore throat.

Ricola Herb Throat Drops *Ricola, USA.*
Menthol (p. 2553·2); peppermint (p. 1877·1).
Sore throat.

Riconazol *Bunker, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Ricordo *Adamed, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Ricovir *Mylan, Thai.*
Tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Ricovir-Em *Mylan, Thai.*
Emtricitabine (p. 976·3); tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Rictor *Solfran, Mex.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ricura *Pekana, Neth.*
Capsicum annum (p. 2469·3); cinnabaris (p. 2555·3); echinacea angustifolia (p. 2498·1); kreosotum (p. 1659·3); luffa operculata (p. 2545·3); plantago major (p. 2592·3); sanicula europaea; thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Ricus *Biofarma, Turk.*
Risperidone (p. 1103·2).

Ricyn *Pascual, Philipp.†*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis.

RID *Pfizer, USA.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Ridal *Douglas, NZ; Douglas, Singapore; Giempi, Venez.*
Risperidone (p. 1103·2).
Autism; behaviour disorders; bipolar disorder; psychoses; schizophrenia.

Ridamin *Unison, Malaysia; Unison, Singapore†; Unison, Thai.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Rid-a-Pain *Pfeiffer, USA.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); cineole (p. 2479·1).
Oral lesions.

Rid-a-Pain HP *Pfeiffer, USA.*
Capsaicin (p. 35·1).
Pain.

Ridaq *Aspen, S.Afr.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; diabetes insipidus.

Ridasa *Manuell, Mex.*
Ribonuclease (p. 2604·1); dornase alfa (p. 1662·1).
Viral infections.

Ridate *Rowex, Irl.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Ridaura *Mercury, Austral.; GSK, Austria; Astellas, Belg.; Xediton, Canad.; GSK, China; Goldshield, Denm.; Mercury, Fin.; Vianex (Βιανεξ), Gr.; Goldshield, Hong Kong; Goldshield, Irl.†; Goldshield, Israel; Astellas, Ital.; Goldshield, Norw.†; Boucher & Muir, NZ; Astellas, Port.; Pharmafrica, S.Afr.†; Recordati, Spain†; Abcur, Swed.; Astellas, UK†; SmithKline Beecham, USA.*
Auranofin (p. 27·3).
Rheumatoid arthritis; juvenile arthritis; psoriatic arthritis; Sjögren's syndrome with rheumatoid arthritis.

Ridazin *Taro, Israel.*
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia.

Ridazine *Atlantic, China; Atlantic, Thai.; Hikma, Ukr.†*
Thioridazine hydrochloride (p. 1110·2).
Anxiety; behaviour disorders; schizophrenia; mania; depression; psychoses; senile confusion.

Ridcof *Cipla, India.*
Dextromethorphan (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).
Cough.

Ridefin *Aspen, Arg.*
Finasteride (p. 2358·3).

Ridenol *RID, USA.*
Paracetamol (p. 115·1).

Ridin *Sons, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough; rhinitis; allergic conjunctivitis.

Ridinox *Bell, India.†*
Idoxuridine (p. 985·1).
Herpetic keratitis.

Ridiodent *Ogna, Ital.*
Sodium fluoride (p. 2089·2); cetylpyridinium chloride (p. 1743·1).
Dental caries prophylaxis.

Ridoca *Aenorasis, Neth.*
Temozolomide (p. 865·2).
Malignant glioma.

Ridon *Anpharm (Ανφαρμ), Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Ridoner *ICN, Cz.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders; autism.

Ridonex *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder.

Ri-Donna *Biodelta, Ital.*
Vitamins; selenium (p. 2086·3); betaine (p. 2456·1); soya; rhodiola rosea; dioscorea (p. 2648·1).
Nutritional supplement for menopausal women women.

Rid-O-Pain *New York Chemical, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain.

Ridoron *Gabriel, Gr.*
Risperidone (p. 1103·2).

Ridovet *Iapharm, Gr.*
Levocarnitine (p. 2053·2).

Rid-O-Worm *New York Chemical, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Ridron *Baliarda, Arg.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Ridron Pack *Baliarda, Arg.*
4 Tablets, risedronate sodium (p. 1189·3); 28 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Riduton Ergo *Francia, Ital.*
Carnitine (p. 2053·2); betacarotene (p. 2051·1); glutathione (p. 1555·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Ridutox *SoSe, Ital.*
Glutathione sodium (p. 1555·2).
Drug-induced neuropathy; adjuvant in radiation-induced damage.

Riduvir *Francia, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

RidWind *ICM, Singapore.*
Simeticone (p. 1886·2).
Flatulence; infant colic.

Rieg *Helm, Port.†*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Rielex *Sanval, Braz.*
Dipyrone (p. 53·3); orphenadrine citrate (p. 909·2); caffeine (p. 1203·3).
Skeletal muscle spasm.

Riemid *Egis, Cz.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Rienso *Takeda, Neth.; Takeda, Norw.; Takeda, Switz.; Takeda, UK.*
Ferumoxytol (p. 2063·1).
Iron-deficiency anaemia in renal failure.

RIF
Note: this name may be used for preparations of different composition.
Armoxindo, Indon.
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Rif
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Rifamycin sodium (p. 354·3).
Bacterial infections.

Rifa
Note: this name may be used for preparations of different composition.
Concept, India.
Rifampicin (p. 350·3); isoniazid (p. 311·2). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Grunenthal, Ger.†
Rifampicin (p. 350·3) or rifampicin sodium (p. 350·3).
Tuberculosis.

Rifa E *Concept, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol (p. 296·1).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Rifabiotic *Bernofarm, Indon.†*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Rifacap *Hovid, Hong Kong.†*
Rifampicin (p. 350·3).

Rifacilin *PC India, India.*
Rifampicin (p. 350·3).
Tuberculosis.

Rifacin *Prafa, Indon.†; Healthprime, Philipp.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy; meningitis; biliary-tract infections; respiratory infections.

Rifacin-A *Utopian, Thai.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and leprosy; bacterial meningitis prophylaxis.

Rifacol *Vianex (Βιανεξ), Gr.; Formenti, Ital.*
Rifaximin (p. 355·2).
Gastrointestinal infections; adjuvant in hyperammonaemia; hepatic encephalopathy; bowel sterilisation for gastrointestinal tract surgery.

Rifacomb *Ipca, Rus.*
Isoniazid (p. 311·2); rifampicin (p. 350·3). Pyridoxine (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Bacterial infections including tuberculosis and leprosy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rifacomb Plus *Ipca, Rus.†*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Rifacom-EZ *Indoco, India.*
1 Tablet, rifampicin (p. 350·3); 2 tablets, pyrazinamide (p. 345·2); 1 tablet, ethambutol (p. 296·1); isoniazid (p. 311·2).
Tuberculosis.

Rifadin *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Duncan, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Swed.; Sanofi-Aventis, Thai.; Aventis, Turk.; Aventis, UK; HoechstMarion Roussel, USA; Sanofi-Aventis, Venez.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis; treatment of asymptomatic meningococcal carriers; prophylaxis of meningococcal infection.

Rifadine *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.*
Rifampicin (p. 350·3) or rifampicin sodium (p. 350·3).
Prophylaxis of meningococcal meningitis; bacterial infections including tuberculosis and leprosy.

Rifadom *Dominguez, Arg.*
Rifaximin (p. 355·2).
Gastrointestinal infections; diverticular disease; hepatic encephalopathy.

Rifafour *Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Thai.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol (p. 296·1).
Tuberculosis.

Rifagen
Note: this name may be used for preparations of different composition.
Genepharm, Gr.
Fluconazole (p. 578·2).
Fungal infections.

General Drugs, Thai.
Rifampicin (p. 350·3).
Tuberculosis.

Rifaldin *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile†; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Spain.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Rifalep *Lepetit, Arg.*
Rifampicin (p. 350·3).
Tuberculosis.

Rifam *Siam Bheasach, Thai.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and gonorrhoea.

Rifamate *HoechstMarion Roussel, USA.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Rifamax *Duncan, Philipp.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Rifamazid *Polfa Tarchomin, Pol.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Rifamcin *Pond's, Thai.*
Rifampicin (p. 350·3).
Tuberculosis.

Rifamed *PannonPharma, Hung.*
Rifampicin (p. 350·3).
Brucellosis; leprosy; meningococcal meningitis prophylaxis; tuberculosis.

Rifam-P *PP Lab, Thai.*
Rifampicin (p. 350·3).
Tuberculosis; gonorrhoea.

Rifamp *Neo Quimica, Braz.*
Rifampicin (p. 350·3).
Meningitis prophylaxis; tuberculosis.

Rifampyzid *Pond's, Thai.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Rifamtibi *Sanbe, Indon.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy.

Rifamycin *Biochem, India.*
Rifampicin (p. 350·3).
Tuberculosis.

Rifan *Neo Quimica, Braz.*
Rifamycin sodium (p. 354·3).

Rifanid *Concept, Philipp.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Rifapex *Lupin, Rus.*
Rifapentine (p. 355·1).
Tuberculosis.

Rifaprim *Sanofi-Aventis, Arg.; Sanofi-Aventis, Mex.*
Rifampicin (p. 350·3); trimethoprim (p. 381·2).
Bacterial infections.

Rifaren *Remedica, Singapore.*
Rifampicin (p. 350·3).
Tuberculosis.

Rifasan *EMS, Braz.*
Rifamycin (p. 354·3).

Rifasynt *Medochemie, Hong Kong; Medochemie, Malaysia.*
Rifampicin (p. 350·3).
Tuberculosis.

Rifater *Sanofi-Aventis, Austria; Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.; Grunenthal, Ger.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Lepetit, Ital.; Sanofi-Aventis, Mex.; Duncan, Philipp.; Sanofi-Aventis, Port.; Aventis, S.Afr.†; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, UK; Hoechst Marion Roussel, USA.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Rifateral *Yurtoglu, Turk.*
Rifamycin sodium (p. 354·3).
Bacterial infections.

Rifaxi *LKM, Arg.†*
Ritonavir (p. 1013·1).
HIV infection.

Rifazid *PannonPharma, Hung.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Rifcap *Kocak, Turk.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Riferina *Bajamed, Mex.*
⊗Beclometasone (p. 1621·2).
Corticosteroid.

Rifex *Sanofi-Aventis, Port.†; Atabay, Turk.†*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis.

Rifinah *Sanofi-Aventis, Arg.; Sanofi-Aventis, Fr.; Grunenthal, Ger.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Lepetit, Ital.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Duncan, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, S. Afr.; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi-Aventis, UK.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Riflax *Boniscontro & Gazzone, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Riflux *Polfarmex, Pol.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Rifocin *Aventis, Turk.*
Rifamycin (p. 354·3) or rifamycin sodium (p. 354·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Sanofi-Aventis, Austria; Lepetit, Ital.
Rifamycin sodium (p. 354·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rifocina
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Arg.; Sanofi-Aventis, Port.; Sanofi-Aventis, Venez.
Rifamycin (p. 354·3).
Bacterial infections.

Sanofi-Aventis, Braz.
Rifamycin sodium (p. 354·3).
Staphylococcal infections.

Rifocine *Sanofi-Aventis, Belg.*
Rifamycin sodium (p. 354·3).
Bacterial infections.

Rifocort *Medley, Braz.*
⊗Rifamycin sodium (p. 354·3); prednisolone acetate (p. 1645·2).
Skin disorders.

Rifocus *Gerolymatos, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Rifocyna *Sanofi-Aventis, Mex.*
Rifamycin sodium (p. 354·3).
Impetigo; infected burns and wounds.

Rifoldin *Sanofi-Aventis, Austria.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy; staphylococcal infections; brucellosis; asymptomatic meningococcal carriers; asymptomatic Haemophilus influenzae *carriers.*

Rifoldin mit INH *Sanofi-Aventis, Austria.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Rifonat *Yuri, Ukr.*
Rifamycin sodium (p. 354·3).
Bacterial infections.

Rifun *Nycomed, Ger.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rifzin *Pascual, Philipp.*
Capsule, rifampicin (p. 350·3); tablet, isoniazid (p. 311·2).
Tuberculosis.

Rigat *Vale, Cz.; Vale, Pol.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Rigenin *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders; autism.

Rigenol *Arrow, Ital.*
Mycophenolate mofetil (p. 1961·1).

Rigentex *Bracco, Ital.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Riges *Boniscontro & Gazzone, Ital.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Rigesoft *Gedeon Richter, Hung.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Riget *Biolab, Thai.†*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Rigevidon *2care4, Denm.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Medimpex, Irl.; Gedeon Richter, Malaysia; Richter, Pol.; Gedeon Richter, Rus.; Consilient, UK; Gedeon Richter, Ukr.; Aciprosalud, Venez.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 tablets ferrous fumarate.
Combined oral contraceptive; menstrual disorders.

Gedeon Richter, Philipp.; Gedeon Richter, Thai.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Right Choice AM *Body Wise, Canad.†*
Vitamins; chromium (p. 2125·2).

Right Choice PM *Body Wise, Canad.†*
Vitamins; minerals; methionine (p. 1558·2).

Rigoletten *Marel, Neth.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Rigoran *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Rigotax *Prater, Chile.*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Rigotax-D *Prater, Chile.*
⊗Cetirizine (p. 619·2); pseudoephedrine (p. 1676·1).

Rihest *Otto, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Rikital *Intermed, Gr.*
Flutamide (p. 798·2).
Prostatic cancer.

Rikkosan *Tsumura, Jpn.*
Asiasarum root; cimicifuga rhizome (p. 2478·1); saposhnikovia root; liquorice (p. 1853·2); gentiana scabra.
Traditional Kampo medicine.

Rikkunshito *Tsumura, Jpn.*
Atractylodes lancea rhizome; ginseng (p. 2513·3); pinellia tuber; poria sclerotium; jujube; citrus unshiu peel; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Riklinak *Rivero, Arg.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Riklona *Mersifarma, Indon.*
Clonazepam (p. 519·1).
Epilepsy.

Rikodeine *iNova, Austral.*
Dihydrocodeine tartrate (p. 52·3).
Cough.

Rikospray *Meda, Ital.*
Aldioxa (p. 1692·2); cetylpyridinium chloride (p. 1743·1); terpineol (p. 2627·2); dimeticone (p. 2209·3).
Barrier preparation; skin disinfection.

Rikospray Silicone *Cana, Gr.*
Cetylpyridinium chloride (p. 1743·1); aldioxa (p. 1692·2); dimeticone (p. 2209·3).
Barrier preparation.

Rilace *Sanovel, Rus.; Sanovel, Turk.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Rilace Plus *Sanovel, Rus.; Sanovel, Turk.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Rilamig *Guidotti, Ital.*
Frovatriptan succinate (p. 676·2).
Migraine.

Rilan
Note: this name may be used for preparations of different composition.
Schering-Plough, Venez.
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; influenza symptoms.

UCI, Braz.
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Rilaprost *Guidotti, Ital.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Rilaquin *Microsules, Arg.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Rilasat *Buxton, Arg.*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Rilast *Orifarm, Denm.; Icaro, Spain.*
⊗Formoterol fumarate (p. 1209·2); budesonide (p. 1625·1).
Obstructive airways disease.

Rilastil
Note: this name may be used for preparations of different composition.
Berko, Turk.
Emollient.
Stretch marks.

Rilastil Anti-Oxidante *Dermoteca, Port.*
Fish oil (p. 1460·1); borage oil (p. 2459·2); zinc (p. 2126·1); selenium (p. 2086·3); betacarotene (p. 2051·1); vitamin E (p. 2119·1).
Nutritional supplement; antoxidant.

Rilastil Dermo Solar *Dermoteca, Port.*
Tyrosine (p. 2098·3); borage oil (p. 2459·2); wheat-germ oil (p. 2647·1); betacarotene (p. 2051·1); bearberry (p. 2453·2); vitamin E (p. 2119·1); selenium (p. 2086·3).
Photosensitivity; sun-induced photoageing.

Rilaten *Berlin-Chemie, China; Guidotti, Ital.*
Rociverine (p. 2606·3).
Smooth muscle spasm.

Rilatine *Novartis, Belg.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Narcoleptic syndrome; attention deficit hyperactivity disorder.

Rilax *Marching, Philipp.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Rilaxium *LiveLife, Singapore.*
Lactium.
Stress.

Rilcapton *Medochemie, Rus.; Medochemie, Singapore.*
Captopril (p. 1331·2).
Hypertension; heart failure; left ventricular dysfunction following myocardial infarction; diabetic nephropathy.

Riledron *Sanopharm, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Rileptid *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Philipp.; Egis, Rus.; Egis, Ukr.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders; autism; schizophrenia.

Rilex *Gry, Ger.†*
Tetrazepam (p. 1110·1).
Skeletal muscle tension; skeletal muscle spasticity.

Rilfit-Rheumasalbe *Apomedica, Austria.*
Diethylamine salicylate (p. 51·3); salicylic acid (p. 1719·1); benzyl nicotinate (p. 29·3); camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders; nerve pain.

Rilies *Novum, Neth.*
Ketoprofen (p. 79·1).
Fever; pain.

Rilif *Gerolymatos, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Rillus *Kalbe, Indon.*
Lactobacillus reuteri (p. 2596·3).
Maintenance of gastrointestinal flora; gastrointestinal disorders; immunostimulant.

Rilonacept Regeneron *Regeneron, Neth.†*
Rilonacept (p. 2604·3).
Formerly known as Arcalyst.
Cryopyrin-associated periodic syndromes.

Rilow *Indeco, Arg.*
Alprazolam (p. 1035·2).
Anxiety.

Rilox *Pyridam, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Rilten *Raam, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Rilutek *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Jpn; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, NZ; Aventis, Pol.; Aventis, Port.; Sanofi-Aventis, S. Afr.†; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, Ukr.; Covis, USA; Sanofi-Aventis, Venez.*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Rima *Ranbaxy, Irl.†*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome.

Rimaccin *Chinta, Thai.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and leprosy; bacterial meningitis prophylaxis.

Rimacid *Ranbaxy, UK.†*
Indometacin (p. 71·2).

Rimacillin *Ranbaxy, UK.*
Ampicillin (p. 218·2).
Bacterial infections.

Ranbaxy, Irl.†
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Rimactan *Sandoz, Austria; Sandoz, Denm.; Sandoz, Fr.; Sandoz, Israel; Sandoz, Mex.; Sandoz, Norw.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Switz.; Sandoz, Venez.*
Rifampicin (p. 350·3) or rifampicin sodium (p. 350·3).
Prophylaxis of meningococcal meningitis; bacterial infections including leprosy and tuberculosis.

Rimactane *Sandoz, Hong Kong†; Novartis, India; Sandoz, Indon.; Sandoz, Irl.†; Sandoz, Malaysia; Sandoz, Philipp.; Novartis, Rus.; Sandoz, S.Afr.; Sandoz, Singapore†; Sandoz, Thai.†; Sandoz, UK; Prosam, USA.*
Rifampicin (p. 350·3).
Bacterial infections including leprosy and tuberculosis; meningococcal meningitis prophylaxis.

Rimactazid *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Gr.; Sandoz, Indon.; Sandoz, Irl.; Sandoz, Ital.; Sandoz, Malaysia; Sandoz, Neth.†; Sandoz, Norw.; Sandoz, Philipp.; Novartis, Rus.†; Sandoz, S.Afr.; Sandoz, Singapore; Sandoz, Spain†; Sandoz, Swed.; Sandoz, Switz.; Sandoz, Thai.†; Sandoz, Venez.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Rimactazid + Z *Novartis, India.*
1 Tablet, rifampicin (p. 350·3); isoniazid (p. 311·2); 2 tablets, pyrazinamide (p. 345·2).
Tuberculosis.

Rimadol *Ranbaxy, Irl.†*
Paracetamol (p. 115·1).
Pain; fever.

Rimafen *Ranbaxy, UK.*
Ibuprofen (p. 68·2).

Rimagrip *Rimafar, Spain.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); chlorphenamine maleate (p. 620·3); kola (p. 2648·2).
Cold and influenza symptoms.

Rimanal *Materfarma, Port.*
A heparinoid (p. 1401·1); troxerutin (p. 2505·3).
Soft-tissue disorders; thrombophlebitis; venous insufficiency.

Rimane *Douglas, NZ.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease.

Rimantin *Genexo, Pol.*
Rimantadine hydrochloride (p. 1012·2).
Influenza A.

Rimapam *Ranbaxy, Irl.†; Ranbaxy, UK.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; epilepsy; premedication.

Rimaped *Pediatrica, Philipp.*
Rifampicin (p. 350·3).
Tuberculosis; meningococcal meningitis prophylaxis.

Rimapen
Note: this name may be used for preparations of different composition.
Orion, Fin.
Rifampicin (p. 350·3).
Tuberculosis.

Rimapurinol *Ranbaxy, UK.*
Allopurinol (p. 600·2).

Rimarex *Sun, India.*
Moclobemide (p. 437·2).
Depression; phobias.

Rimastine *Armstrong, Mex.*
Sulpiride (p. 1107·3).
Depression; obsessive-compulsive disorder; vertigo; schizophrenia; nausea and vomiting.

Rimatidine *Ranbaxy, Irl.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity.

Rimatil *Santen, Jpn.*
Bucillamine (p. 2462·1).
Rheumatoid arthritis.

Rimax *Yarindo, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Rimcure *Sandoz, Denm.; Sandoz, Indon.; Sandoz, Irl.†; Sandoz, Ital.; Sandoz, Malaysia; Sandoz, Neth.†; Sandoz, Norw.; Sandoz, Philipp.; Sandoz, S.Afr.; Sandoz, Spain†; Sandoz, Swed.; Sandoz, Venez.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis; mycobacterial infections.

Rimcure 3-FDC *Sandoz, Thai.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Rime *Promed, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Rimecin *Pharmasant, Thai.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis, leprosy, and gonorrhoea.

Rimecor *Makiz-Pharma, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; vascular eye disorders.

Rimecure 3-FDC *Novartis, Rus.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Rimendia *Bayer, Belg.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Bayer, Fr.
Drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3).
Combined oral contraceptive.

Rimevax *GSK, Austral.†; GSK, Mex.†; GSK, NZ; GSK, S.Afr.†; GSK, Spain.†*
A measles vaccine (Schwarz strain) (p. 2398·3).
Active immunisation.

Rimezone *IAE, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Rimifon *Codepharma, Fr.; Roche, Singapore; Labatec, Switz.*
Isoniazid (p. 311·2).
Tuberculosis and other mycobacterial infections.

Riminyl *Janssen-Cilag, Gr.*
Galantamine hydrobromide (p. 391·3).

Rimivat *Andromaco, Chile.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Rimmunos *Biomedica, Ital.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Rimodar *Anglo-French Drugs, India.*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria.

Rimoxallin *Ranbaxy, Irl.†; Ranbaxy, UK.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Rimpazid *Zydus, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Rimpin *Lyka, Rus.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and leprosy.

Rimsalin *Rimsa, Mex.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Rimso *Bioniche, Canad.; Britannia Pharmaceuticals, UK; Research Industries Corp., USA.*
Dimethyl sulfoxide (p. 2182·2).
Interstitial cystitis.

Rimstar *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Irl.; Sandoz, Ital.; Sandoz, Neth.†; Sandoz, Norw.; Sandoz, Philipp.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Switz.; Sandoz, UK.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Mycobacterial infections.

Sandoz, Indon.; Sandoz, S.Afr.; Sandoz, Thai.†
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol (p. 296·1).
Tuberculosis; atypical mycobacterial infections.

Rimstar 4-FDC *Novartis, Rus.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Rimycin *Alphapharm, Austral.; LCH, Hong Kong.†*
Rifampicin (p. 350·3).
Tuberculosis; leprosy; prophylaxis of meningococcal infection.

Rinadex Compuesto *Diba, Mex.*
⊗Dexamethasone sodium phosphate (p. 1631·2); xylometazoline hydrochloride (p. 1680·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Infected skin disorders; otitis externa.

Rinadine *Pharmaland, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Rinafort *Schering-Plough, Malaysia; MSD, Singapore.*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Upper respiratory-tract congestion.

Rinaid *Medipharm, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis.

Rinair *BioSaude, Port.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Rinalgit *ABC, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Rinalix *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
⊗Indapamide (p. 1409·2).
Hypertension.

Rinatec *Boehringer Ingelheim, Irl.; Boehringer Ingelheim, UK.*
Ipratropium bromide (p. 1211·3).
Rhinitis; rhinorrhoea.

Rinavir *GPO, Thai.†*
Ritonavir (p. 1013·1).
HIV infection.

Rinazal *Darnitsa, Ukr.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis media; nasal haemorrhage; adjunct for nasal procedures.

Rinazina *GSK Consumer, Ital.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Rinazoline *Farmak, Ukr.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis; eustachitis; otitis media; adjunct for nasal procedures.

Rince Bouche Antiseptique *Atlas, Canad.*
Cetylpyridinium chloride (p. 1743·1).

Rinder *KRKA, Denm.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Rindex *Teva, Hung.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Rindobion *Yarindo, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Rindofen *Yarindo, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Rindoflox *Yarindo, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Rindomox *Yarindo, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Rindonem *Yarindo, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Rindopump *Yarindo, Indon.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rinelon *Malesci, Ital.; Schering-Plough, Mex.; Essex, Philipp.; MSD, S.Afr.; MSD, Spain†; Schering-Plough, Thai.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis; nasal polyps; sinusitis.

Rinerge *Atral, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Rinex *Aspen Consumer, S.Afr.†*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; allergic rhinitis; Eustachian tube congestion.

Rinexin *Recip, Fin.; Recip, Norw.; Recip, Swed.*
Phenylpropanolamine hydrochloride (p. 1674·1).
Rhinitis; urinary incontinence; nasal congestion.

Ringerfundin *Braun, Cz.; Braun, Denm.; Braun, Fin.; Braun, Norw.; Braun, Swed.; Braun, Switz.*
Electrolytes (p. 1775·1); malic acid (p. 2549·2).
Fluid and electrolyte disorders.

Braun, Hung.
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Ringeruv *Braun, Cz.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Ringworm Ointment *Ascent, Austral.*
Tolnaftate (p. 596·1).
Ringworm.

Rinialer *Bialfar, Port.; Uriach, Spain.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rinicold *Shreya, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Rinicold HotMix *Shreya, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2).
Cold and influenza symptoms.

Rinicold-Broncho *Shreya, Rus.*
Ambroxol hydrochloride (p. 1654·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; cough.

Rinidal *Neo Quimica, Braz.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Rinidin *Berksam, Turk.*
⊗Oxymetazoline hydrochloride (p. 1671·3).

Rinidyl DN *Diba, Mex.†*
⊗Dexamethasone (p. 1630·3); phenylephrine (p. 1672·2); neomycin (p. 329·3).

Rinigran *Legrand, Braz.*
⊗Fenoxazoline (p. 1665·3).

Rinileen *VSM, Neth.†*
Baryta muriatica (p. 2452·3); cinnabaris (p. 2555·3); echinacea angustifolia (p. 2498·1); hydrastis canadensis (p. 2528·1).
Homoeopathic preparation.

Rinilyn *Omega, Spain.†*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Rinisona *Phoenix, Arg.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; obstructive airways disease.

Rinisone *Medley, Braz.*
⊗Prednisolone sodium phosphate (p. 1645·3); ephedrine hydrochloride (p. 1663·2); naphazoline nitrate (p. 1669·3).
Nasal disorders.

Rinitalmit *Gunsa, Turk.†*
⊗Ephedrine hydrochloride (p. 1663·2).
Nasal congestion.

Rinitrin *Svizera, India.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Rinityn *Hovid, Hong Kong; Hovid, Philipp.; Hovid, Singapore.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions; urticaria.

Rinizol *Sandoz, Turk.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rinlaxer *Taisho, Jpn.*
Chlorphenesin carbamate (p. 2022·2).
Skeletal muscle spasm.

Rinnova *Pfizer, Ital.*
Calcium glycerophosphate (p. 1783·3); colecalciferol (p. 2113·1); soya isoflavones (p. 2620·3).
Menopausal disorders.

Rinnovi *Quinnova, USA.†*
⊗Urea (p. 1727·3).
Nail disorders.

Rino Calyptol *SIT, Ital.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Rino Clenil *Chiesi, Ital.; Chiesi, Thai.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Rino Dexa *Sanofi-Aventis, Spain.*
⊗Chlorphenamine maleate (p. 620·3); dexamethasone sodium phosphate (p. 1631·2); muramidase hydrochloride (p. 2565·1); neomycin sulfate (p. 330·1).
Rhinitis; sinusitis; rhinopharyngeal infection.

Rino Ebastel *Almirall, Spain.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ebastine (p. 628·1).
Allergic rhinitis.

Rino Get *Laborest, Ital.*
Dimethyl sulfone (p. 2493·3); silver salts (p. 2615·1); aluminium salts (p. 2439·2).
Nasal cleansing.

Rino-B *Cassara, Arg.; D & M, Chile.*
⊗Budesonide (p. 1625·1).
Pharyngitis; laryngitis; rhinitis; nasal polyps.

Rinobactil *Omega, Spain.*
⊗Ebastine (p. 628·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Rinobanedif *Bago, Chile.*
⊗Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); xylometazoline hydrochloride (p. 1680·1); antazoline phosphate (p. 615·3).
Rhinitis; sinusitis.

Bayer, Spain.
⊗Bacitracin zinc (p. 225·3); phenylephrine hydrochloride (p. 1672·3); neomycin sulfate (p. 330·1); prednisolone (p. 1645·2); cineole (p. 2479·1); niaouli oil (p. 2569·1).
Upper respiratory-tract disorders.

Rinoben *Cazi, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Rinoblanco *M4 Pharma, Spain.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rinocidina *Valeas, Ital.*
⊗Tyrothricin (p. 384·1); naphazoline nitrate (p. 1669·3).
Rhinitis; sinusitis.

Rinoclénil *Chiesi, Fr.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Rinoclenil *Chiesi, Turk.*
⊗Beclometasone dipropionate (p. 1621·2).

Rinocortin *Leontik, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).

Rinocusi Vitaminico *Sanofi-Aventis, Spain.*
Vitamin A acetate (p. 2098·3).
Nasal congestion; nasal irritation.

Rinodan *Medipharm, Chile.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal hygiene; rhinitis.

Rinofilax *Pediapharm, Chile; Recalcine, Chile.*
Desloratadine (p. 625·1).
Allergic rhinitis; urticaria.

Rinofilax AG M *Raffo, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); neomycin sulfate (p. 330·1).
Nasal congestion.

Rinofluimucil *Zambon, Braz.; Zambon, Hong Kong†; Zambon, Hung.; Zambon, Ital.; Zambon, Port.; Zambon, Rus.; Zambon, Switz.; Zambon, Thai.; Zambon, Ukr.*
⊗Acetylcysteine (p. 1652·2); tuaminoheptane sulfate (p. 1679·3).
Rhinitis; sinusitis.

Rinoflumil *Zambon, Spain.*
⊗Acetylcysteine (p. 1652·2); tuaminoheptane sulfate (p. 1679·3).
Rhinitis.

Rinoflux *IMA, Braz.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

Rinofren *Carnot, Mex.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Rhinopharyngitis; hay fever; allergic rhinitis; sinusitis.

Rinofren Pediatrico *Carnot, Mex.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Rinofrenal
Note: this name may be used for preparations of different composition.
Teofarma, Ital.
Sodium cromoglicate (p. 1225·3); chlorphenamine maleate (p. 620·3).
Rhinitis.

Sigma-Tau, Spain.†
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Rinofrenal Plus *Sigma-Tau, Spain.†*
Chlorphenamine maleate (p. 620·3); sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Rinogel *Cassara, Arg.*
⊗Sodium cromoglicate (p. 1225·3); naphazoline hydrochloride (p. 1669·3).
Allergic rhinitis; epistaxis; nasal surgery.

Rinogest *Sanovel, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Rinogest Ekspektoran *Sanovel, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

Rinogutt *Boehringer Ingelheim, Ital.*
Nasal spray 15ml: ⊗Tramazoline hydrochloride (p. 1679·3); cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Boehringer Ingelheim, Ital.
Nasal spray 10ml: ⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Rinogutt Antiallergico Spray *Boehringer Ingelheim, Ital.*
⊗Tramazoline hydrochloride (p. 1679·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Rinogutt Atlantic *Fher, Ital.*
⊗Glycerol (p. 2517·2); copper (p. 2057·1).
Nasal cleansing; nasal dryness.

Rinokid *D & M, Chile.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal hygiene.

Rinolabsa *Labsa, Arg.*
⊗Naphazoline (p. 1669·3); diphenhydramine (p. 626·1).
Nasal congestion.

Rinolan *Berman, Mex.*
Phenylephrine (p. 1672·2).

Rinolar *Saba, Turk.*
Menthol (p. 2553·2); cineole (p. 2479·1); niaouli oil (p. 2569·1); benzoin tincture (p. 2624·3).
Respiratory-tract disorders.

Rinolast *Farma, Venez.*
Fexofenadine hydrochloride (p. 629·1).
Upper respiratory-tract allergies.

Rinolast D *Farma, Venez.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract allergies.

Rino-Lastin *Ache, Braz.*
Azelastine hydrochloride (p. 617·1).
Nasal congestion.

Rinolergan *Grunenthal, Chile.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Cold symptoms; rhinitis; sinusitis.

Rinolet *Leti, Venez.*
⊗Budesonide (p. 1625·1).

Rinoliber *Tecnimede, Port.*
Cetirizine hydrochloride (p. 619·2).

Rinolic *GMP, Indon.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; hyperuricosuria; renal calculi.

Rinomar
Note: this name may be used for preparations of different composition.
Recip, Fin.; Recip, Swed.
Cinnarizine (p. 622·1); phenylpropanolamine hydrochloride (p. 1674·1).
Allergic rhinitis; nasal congestion; vasomotor rhinitis.

Janssen-Cilag, Belg.†
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Rinomax
Note: this name may be used for preparations of different composition.
Hertz, Braz.
⊗Naphazoline (p. 1669·3).

Oftalmi, Venez.
Kanamycin sulfate (p. 314·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis with infection.

Ern, Spain.†
⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine (p. 1676·1).
Nasal congestion.

Rinomex *Recalcine, Chile.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Cold symptoms; otitis media; rhinitis; sinusitis.

Rinomicine *Fardi, Spain.*
Syrup: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).

Fardi, Spain.
Oral sachets: Ascorbic acid (p. 2110·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); salicylamide (p. 129·2).
Influenza and cold symptoms; nasal congestion.

Fardi, Spain.
Tablets: Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); salicylamide (p. 129·2).
Influenza and cold symptoms; nasal congestion.

Rinomicine Activada *Fardi, Spain.†*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); salicylamide (p. 129·2).
Influenza and cold symptoms; nasal congestion.

Rinopaidolo *Deca, Ital.*
Niaouli oil (p. 2569·1); eucalyptus oil (p. 2501·2).
Nasal congestion.

Rinopanteina *DMG, Ital.; Genesis, Turk.*
Dexpanthenol (p. 2582·2); vitamin A (p. 2098·3).
Nasal hygiene; nasal dryness.

Rinoplex
Note: this name may be used for preparations of different composition.
Knop, Chile.
Aralia; allium cepa (p. 2575·2); aurum (p. 2521·1); ammonium carbonicum (p. 1656·1); kalium bichromium (p. 2476·3); sabadilla (p. 2611·2).
Homoeopathic preparation.

Rinoprex *Pinewood, Irl.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease.

Rinorex *Medirex, Port.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rinos-A *Farmasa, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Rinose *Tripharma, Turk.*
⊗Mometasone furoate (p. 1644·1).

Rinosedin *Streuli, Switz.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Cold symptoms; sinus disorders; otitis media; adjunct in rhinoscopy.

Rinosoft S *Hertz, Braz.*
Sodium chloride (p. 1795·1).

Rinosol *Cassara, Arg.; DAST, Gr.; Zekides, Gr.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis; asthma.

Rinosone *Faes, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Nasal polyps; rhinitis.

Rinosoro *Farmasa, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Rinostat *RPG, India.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Formerly contained paracetamol, chlorphenamine maleate, and pseudoephedrine hydrochloride.
Cold symptoms.

Rinoster *Zwitter, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Rinosteryl *Mintlab, Chile.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Rinostil *Deca, Ital.*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2); thymol (p. 1772·2); menthol (p. 2553·2).
Rhinopharyngeal congestion.

Rinot *Arex, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Rinotricina *SIT, Ital.*
Tyrothricin (p. 384·1).
Rhinitis; sinusitis.

Rinotrofina C *Farmila, Ital.*
Beta-glucan (p. 2455·2); lysine (p. 2079·3); zinc (p. 2126·1); sambucus (p. 2609·3); ascorbic acid (p. 2110·3).
Immunostimulant.

Rinovagos *Valeas, Ital.*
Ipratropium bromide (p. 1211·3).
Rhinitis.

Rinoval *Saval, Chile.*
⊗Mometasone furoate (p. 1644·1).
Rhinitis.

Rinovel *Ern, Spain.†*
⊗Naphazoline nitrate (p. 1669·3); neomycin sulfate (p. 330·1); prednisolone (p. 1645·2).
Congestion and infection of the nose and ear.

Rinoven *Medipharm, Chile.*
⊗Pseudoephedrine hydrochloride (p. 1676·1) or pseudoephedrine sulfate (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; upper respiratory-tract congestion.

Rinoven Compuesto *Medipharm, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Bronchitis; cold and influenza symptoms; otitis; rhinitis; sinusitis.

Rinovit *SIT, Ital.*
⊗Ephedrine (p. 1663·1); cineole (p. 2479·1); niaouli oil (p. 2569·1).
Nasal congestion.

Rinovitex *M4 Pharma, Spain.*
Vitamin A acetate (p. 2098·3).
Nasal irritation.

Rinowash *Air Liquide, Ital.*
Sodium chloride (p. 1795·1).
Nasal cleansing.

Rinox VX *Vannier, Arg.*
⊗Oxymetazoline (p. 1671·3).
Nasal congestion.

Rinoxyl *Orion, Cz.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Rinozal *Clonmel, Irl.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Rins-Aqua *Teva, Hung.*
Water for injections (p. 2646·3).

Rinse-Free *Coghlans, Canad.*
Benzalkonium chloride (p. 1737·1).

Rins-Ringer *Teva, Hung.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Rins-Sal *Teva, Hung.*
Sodium chloride (p. 1795·1).

Rinstead *MSD, Irl.; Schering-Plough, UK.*
Mouth gel: Benzocaine (p. 1980·2); chloroxylenol (p. 1748·2).
Mouth pain; mouth ulcers.

MSD, Irl.
Sugar-free pastilles: Cetylpyridinium chloride (p. 1743·1); levomenthol (p. 2553·2).
Mouth and throat irritation.

Schering-Plough, UK.
Sugar-free pastilles: Menthol (p. 2553·2); cetylpyridinium chloride (p. 1743·1).
Mouth ulcers; denture irritation.

Rinsulin NPH *Geropharm, Rus.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Rinsulin R *Geropharm, Rus.*
⊗Soluble insulin injection (human) (p. 475·3).
Diabetes mellitus.

Rint *Farmak, Ukr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; nasal congestion.

Rintacap *T Man, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Rintacin *T Man, Thai.*
Erythromycin estolate (p. 291·2); or erythromycin stearate (p. 291·3).
Bacterial infections.

Rinupret *Bionorica, Ger.*
Sea water (p. 2612·1); aloe vera (p. 1693·2); eucalyptus oil (p. 2501·2).
Nasal disorders.

Rinvox *Yarindo, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Rinxofay *Umeda, Thai.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Rinza *Unique, Rus.; Unique, Ukr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; sinusitis.

Rinza Hotsip *Unique, Ukr.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

Rinza Hotsip with Vitamin C *Unique, Ukr.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Rinza Lorsept *Unique, Rus.; Unique, Ukr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Rinzasip *Unique, Rus.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract disorders.

Rinzasip with Vitamin C *Unique, Rus.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Rio-Bronze *Rogers, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Riodine *Orion, NZ.*
Povidone-iodine (p. 1767·1).
Skin infections; skin and wound disinfection.

Riomet *Ranbaxy, Malaysia; Ranbaxy, USA.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Riomid *Medicus, Gr.*
⊗Furosemide (p. 1387·1).

Rionit *Buxton, Arg.*
Zoledronic acid (p. 1192·3).
Bone metastases; osteoporosis.

Riopan
Note: this name may be used for preparations of different composition.
Nycomed, Arg.; Nycomed, Austria; Takeda, Belg.; Nycomed, Braz.; Nycomed, Fr.; Nycomed, Ger.; Nycomed, Gr.; Nycomed, Ital.; Nycomed, Port.; Takeda, Switz.; Nycomed, Ukr.; Whitehall, USA.†
Magaldrate (p. 1856·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; gastritis; gastrointestinal motility disorders; oesophagitis; heartburn; dyspepsia.

Nycomed, Mex.
Magaldrate (p. 1856·1); dimeticone (p. 1886·2).
Gastrointestinal disorders associated with hyperacidity.

Riopan Plus *Nycomed, Braz.; Whitehall, USA.*
Magaldrate (p. 1856·1); dimeticone (p. 1886·2).
Gastrointestinal disorders; dyspepsia.

Riopone *Akromed, S.Afr.†*
Magaldrate (p. 1856·1).
Gastric hyperacidity.

Riostatin *Adcock Ingram, S.Afr.†*
Tetracycline hydrochloride (p. 373·2); nystatin (p. 590·3); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Bacterial infections.

Riotane *Orion, NZ.†*
Chlorhexidine gluconate (p. 1743·3).
Skin, wound, and instrument disinfection.

Rioven
Note: this name may be used for preparations of different composition.
Novartis, Gr.
Diosmin (p. 2505·2).
Capillary disorders.

Rioworm *Adcock Ingram, S.Afr.*
Mebendazole (p. 158·3).
Worm infections.

Ripavir *Amnol, Ital.*
Astragalus; beta-glucan (p. 2455·2) from *Saccharomyces cerevisiae*; vitamin B substances (p. 2102·3).
Immunostimulant.

Ripax
Note: this name may be used for preparations of different composition.
KRKA, Port.
Perindopril erbumine (p. 1467·1).

KRKA, Port.
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; autism.

Ripedon *Solamed, Hung.*
Risperidone (p. 1103·2).
Schizophrenia; dementia; bipolar disorder; behaviour disorders.

Ripepral *Verisfield, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Ripesil *Ali, Turk.*
Risperidone (p. 1103·2).

Ripetomar *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders; autism.

Ripevil *GSK, Braz.*
Risperidone (p. 1103·2).
Schizophrenia.

Ripexal *Hexal, Denm.*
Risperidone (p. 1103·2).

Ripin *Picco, Thai.*
Rifampicin (p. 350·3).
Bacterial infections including tuberculosis and leprosy; bacterial meningitis prophylaxis.

Ripix *Novartis, Gr.*
⊗Metipranolol (p. 2009·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Ripol
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Sildenafil (p. 2364·1).
Erectile dysfunction.

Yes, Neth.
Propofol (p. 1909·3).
General anaesthesia; sedative.

Riposon *Recordati, Gr.*
Tibezonium iodide (p. 2631·2).
Mouth infections.

Ripox *Biomep, Mex.*
Piroxicam (p. 125·3).

Ripped Max
Note: this name may be used for preparations of different composition.
Empresa de Nutricion, Arg.
Chromium tripicolinate (p. 2056·1).
Dietary supplement.

Gentech, Arg.
Chromium tripicolinate (p. 2056·1); carnitine (p. 2053·2); choline (p. 2055·2); inositol (p. 2533·2); bearberry (p. 2453·2); garcinia cambogia (p. 2510·2).
Slimming aid.

Riprazo *Novartis, Cz.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.*
Aliskiren fumarate (p. 1295·3).
Hypertension.

Novartis, Gr.; Novartis, Port.
Aliskiren (p. 1295·3).
Hypertension.

Riprazo HCT *Novartis, Cz.†; Novartis, Irl.†*
⊗Aliskiren fumarate (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Riprocin *IAE, Philipp.*
Rifampicin (p. 350·3).
Tuberculosis; leprosy; meningococcal meningitis prophylaxis.

Riptam *Asofarma, Mex.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Risarium *Perlier, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Risatarun *Ravensberg, Ger.†*
⊗Deanol aceglumate (p. 2319·1).
Nervous system disorders.

Rischiaril *Piam, Ital.*
Choline (p. 2055·2); thioctic acid (p. 2629·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Mental function impairment.

Risdin *MedChoice, Philipp.*
Risperidone (p. 1103·2).
Psychoses.

Risdonal *Alkaloid, Rus.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behavioural disturbances.

Risedon *Buxton, Arg.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risedro *Aspen, Austral.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risedronel *Legrand, Braz.*
Risedronate sodium (p. 1189·3).

Risedross *Sigma, Braz.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risek *Julphar, Malaysia; Getz, Philipp.; Julphar, UAE.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Riselib *Delegant, Gr.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Riselle *Schering-Plough, Braz.; Organon, Cz.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Risemyl *Mylan, Spain.†*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risenar *Minerva (Μινερβα), Gr.*
Risperidone (p. 1103·2).
Psychoses.

Risendros *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.†*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Riseos *Leiras, Fin.†*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risepro *Valeant, Cz.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Riseratio *Ratiopharm, Denm.; Ratiopharm, Fin.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risfarmal *Brainpharma, Spain.†*
Risperidone (p. 1103·2).
Psychoses; dementia; autism.

Risgal *Starmel, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Risidon *Merck, Port.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Risidral *Pharmanel, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Risina *Tempo Scan Pacific, Indon.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic rhinitis.

Risleptic *Arrow, Braz.*
Risperidone (p. 1103·2).

Risnia *Cipla, India.*
Risperidone (p. 1103·2).
Schizophrenia.

Risocalm *Medifive, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Risocon
Note: this name may be used for preparations of different composition.
Mibe, Ger.
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behavioural disorders; dementia.

Risofos *Cipla, India.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risolid *Actavis, Denm.†; Actavis, Fin.*
Chlordiazepoxide (p. 1044·2).
Anxiety disorders; alcohol withdrawal syndrome; insomnia; muscle spasm; anxiety.

Risonate *Teva, Irl.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Risonato *EMS, Braz.*
Risedronate sodium (p. 1189·3).

Risonel *Abdi, Turk.*
⊗Mometasone furoate (p. 1644·1).

Risontel *Clonmel, Irl.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Risopent *Boehringer Ingelheim, Venez.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Risordan
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Fr.; Wyeth, Gr.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; pulmonary oedema; heart failure; adjunct in coronary angiography.

Risostad *Stada, Denm.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Rispa *Aspen, Austral.*
Risperidone (p. 1103·2).
Behaviour disturbances; schizophrenia.

Rispacor *Accord, S.Afr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders.

Rispadim *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Rispaksole *Grindex, Rus.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Rispal *Pinewood, Irl.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rispalm *Vivax, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Rispatal *Chanelle, Irl.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rispaxol *Grindeks, Ukr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Rispazin *Leiras, Fin.†*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rispe *Ratiopharm, Hung.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Rispedep *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Rispedin *Shine, Philipp.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Rispedolet *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Rispedospes *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Rispefar *Specifar, Gr.; Pharmalogic, Israel.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Rispelen *Elpen (Ελπεν), Gr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rispemar *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders; autism.

Rispemylan *Mylan, Spain.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rispen *Zentiva, Cz.; Gabriel, Gr.; Zentiva, Pol.; Zentiva, Rus.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; psychoses.

Rispenet *Faran, Gr.†*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders.

Rispenon *Tiefenbacher, Neth.†*
Risperidone (p. 1103·2).
Schizophrenia; mania; behaviour disorders.

Rispe-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Risper *Bouzen, Arg.*
Risperidone (p. 1103·2).
Psychoses.

Rispera *Teva, Cz.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Risperanne *Sandoz, Denm.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder.

Risperascol *Alet, Gr.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Risperatio *Ratiopharm, Pol.†*
Risperidone (p. 1103·2).
Schizophrenia.

Risperdal *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Organon, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Johnson & Johnson, India; Alkermes, Indon.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen, Jpn; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Janssen, USA; Janssen-Cilag, Venez.*
Risperidone (p. 1103·2).
Psychoses; mania; behaviour disorders; schizophrenia; bipolar disorder; autism; aggression associated with dementia.

Risperdalconsta *Janssen-Cilag, Fr.*
Risperidone (p. 1103·2).
Schizophrenia.

Risperdaloro *Janssen-Cilag, Fr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Risperdoc *Docpharm, Ger.†*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behavioural disorders; dementia.

Risperger *Gerard, Irl.*
Risperidone (p. 1103·2).
Schizophrenia; mania; behaviour disorders.

Risperid *Roemmers, Venez.*
Risperidone (p. 1103·2).
Psychoses.

Risperidex *Dexcel, Israel.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Risperigamma *Worwag, Cz.†; Worwag, Ger.; Worwag, Hong Kong.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; dementia; psychoses; behaviour disorders.

Risperin *Gador, Arg.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; autism.

Risperinin *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Risperit *Labochem, Cz.†*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder; behaviour disorders.

Risperiwin *Winthrop, Pol.†*
Risperidone (p. 1103·2).
Schizophrenia.

Risperix *Aspen, Braz.*
Risperidone (p. 1103·2).

Risperlet *Janssen-Cilag, S.Afr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders.

Risperom *Integris, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Risperon *Mylan, NZ; Lek-Am, Pol.; Pharma Start, Ukr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; psychoses; autism.

Risperoprol *Proel, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Rispersan *Santa, Gr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Risperstad *Stada, Cz.†*
Risperidone (p. 1103·2).

Rispeva *Teva, Irl.*
Risperidone (p. 1103·2).
Schizophrenia; mania; behaviour disorders.

Rispex *Vannier, Arg.*
Risperidone (p. 1103·2).
Psychoses.

Rispid *Panacea, India.*
Risperidone (p. 1103·2).
Psychoses.

Rispimed *Regiomedica, Cz.†; Regiomedica, Neth.†*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; aggression in dementia.

Rispimedica *Basics, Neth.†*
Risperidone (p. 1103·2).
Schizophrenia.

Rispofren *Biofarm, Pol.†*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Rispogen *Genepharm, Gr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Rispolept *2care4, Denm.; Abacus, Denm.; Europharma, Denm.; Orifarm, Denm.; Orifarm, Norw.; Janssen-Cilag, Pol.; Janssen-Cilag, Rus.*
Risperidone (p. 1103·2).
Psychoses; schizophrenia; behaviour disorders; bipolar disorder; autism; behavioural disorders.

Rispolin *Janssen-Cilag, Austria.†*
Risperidone (p. 1103·2).
Psychoses.

Rispolux *Sandoz, Cz.; Sandoz, Hung.; Sandoz, Mex.; Sandoz, Pol.; Lek, Rus.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder; aggressive behaviour in dementia.

Rispond *Trima, Israel; Brown & Burk, Philipp.; Micro Labs, Ukr.*
Risperidone (p. 1103·2).
Psychoses; schizophrenia; bipolar disorder; behaviour disorders.

Rispone *Rowex, Irl.*
Risperidone (p. 1103·2).
Schizophrenia; mania; behaviour disorders.

Rispons *Actavis, Hung.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Risponz *Zydus, S.Afr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders.

RISS
Note: this name may be used for preparations of different composition.
Patar, Thai.
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Riss
Note: this name may be used for preparations of different composition.
Eurofarma, Braz.
Risperidone (p. 1103·2).
Schizophrenia.

Risset *Pliva, Cz.†; Farmacom, Pol.; Pliva, Rus.; Pliva, Ukr.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; psychoses.

Ristaben *MSD, Cz.; MSD, Irl.; MSD, Neth.; MSD, Pol.; MSD, Port.; MSD, Spain.*
Sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Ristabil *Cristalfarma, Ital.*
Royal jelly (p. 2608·1); pollen (p. 2593·3); Siberian ginseng (p. 2614·3); myrtillus nero; rosa canina; vitamin B substances (p. 2102·3).
Tonic.

Ristart *Biofarma, Turk.*
Rivastigmine hydrogen tartrate (p. 395·1).

Risteon *Yarindo, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1); manganese (p. 2081·2); magnesium glycerophosphate (p. 1787·2).
Joint disorders.

Ristfor *MSD, Cz.; MSD, Irl.; MSD, Neth.; MSD, Pol.; MSD, Port.; Faes, Spain.*
Sitagliptin phosphate (p. 500·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ristidic *Valeant, Cz.; ICN, Neth.; ICN, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia i n parkinsonism.

Risto *Medicine Products, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Ristolzit *Leovan, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Ristotadin *Leovan, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Risumic *Dainippon, Jpn.*
⊗Amezinium metilsulfate (p. 1298·3).
Hypotension.

Ritalin *Novartis, Austral.; Novartis, Austria; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; IFET (ΙΦΕΤ), Gr.; Novartis, Hong Kong; Novartis, Hung.; Phoenix, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Swed.; Novartis, Thai.; Novartis, UK; Novartis, USA; Novartis, Venez.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritalina *Novartis, Arg.; Novartis, Braz.; Novartis, Port.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritaline *Novartis, Fr.; Novartis, Switz.; Novartis, Turk.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritalmex *ICN, Rus.*
Mexiletine (p. 1436·2).
Ventricular arrhythmias.

Valeant, Hung.
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias.

Ritamine *Demo, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Ritechol *Niche, Irl.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Rite-Diet *SHS Nutricia, UK.*
Gluten-free foods for special diets.

Scientific Hospital Supplies, Irl.†
A range of gluten-free and low-protein foods.
Gluten sensitivity; phenylketonuria; renal failure; liver disorders.

Riterid-Z *Ultra, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Rithmik *Arrow, Austral.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Rithrocin *Pharmaspec, Philipp.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Rithroprol *Proel, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Ritin *Eczacibasi, Turk.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Rition *Piam, Ital.*
Glutathione sodium (p. 1555·2).
Cisplatin-type drug-induced neuropathy.

Ritlemi *Helm, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia; post-traumatic stress disorder.

Ritmenal *Sanitas, Chile.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Ritmilan *Biogalenic, Venez.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Ritmocardyl *Sanofi-Aventis, Arg.; Bago, Chile.*
Amiodarone hydrochloride (p. 1300·1).
Angina pectoris; arrhythmias.

Ritmocor *Drugtech, Chile.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Ritmodan *IFET (ΙΦΕΤ), Gr.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Sanofi-Aventis, Ital.
Disopyramide (p. 1363·2) or disopyramide phosphate (p. 1363·3).
Arrhythmias.

Ritmoforine *Sanofi-Aventis, Neth.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Ritmogel *Terapeutico, Ital.*
Royal jelly (p. 2608·1).
Nutritional supplement.

Ritmolol *Cryopharma, Mex.*
⊗Metoprolol tartrate (p. 1434·3).
Heart failure; angina pectoris; myocardial infarction; arrhythmias; hypertension; hyperthyroidism; migraine.

Ritmoneuran *Hertz, Braz.*
Adonis vernalis (p. 2431·1); erythrina mulungu (p. 2564·3); passion flower (p. 2584·1).

Ritmonorm *Abbott, Braz.; Abbott, Rus.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Ritmopuls *Belupo, Cz.†*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Ritmorest *Helm, Cz.; Richter, Pol.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Ritomax-L *Alkem, India.*
Lopinavir (p. 1002·1); ritonavir (p. 1013·1).
HIV infection.

Ritomune *Cipla, India.*
Ritonavir (p. 1013·1).
HIV infection.

Ritopar *Elea, Arg.*
⊗Ritodrine hydrochloride (p. 2145·1).
Premature labour; uterine relaxation.

Ritosin *Biofarma, Turk.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ritovir *Cristalia, Braz.*
Ritonavir (p. 1013·1).
HIV infection.

Ritran *Biosynthesis, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Ritraz *Rivero, Arg.*
Trace elements.
Parenteral nutrition.

Ritro *Germed, Ital.*
Flurithromycin ethyl succinate (p. 300·2).
Bacterial infections.

Ritrocel *Silesia, Chile.†*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritromax *Nabiqasim, Philipp.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Ritromine *Fada, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Rituxan *Roche, Canad.; Chugai, Jpn; Genentech, USA.*
Rituximab (p. 852·1).
Non-Hodgkin's lymphoma; rheumatoid arthritis; chronic lymphocytic leukaemia; Wegener's granulomatosis; microscopic polyangiitis.

Ritvir *AstraZeneca, Arg.; Rontag, Arg.*
Nevirapine (p. 1005·1).
HIV infection.

Rityne *Osoth, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Riuclonaz *Medipharma, Arg.*
Clonazepam (p. 519·1).

Riva *Intermed, Gr.*
Betahistine hydrochloride (p. 2455·3).
Vertigo.

Riva D *Riva, Canad.†*
Colecalciferol (p. 2113·1).

Riva K *Riva, Canad.*
Potassium chloride (p. 1793·2).
Potassium supplement.

Rivacefin *Rivero, Arg.*
Ceftriaxone (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rivacocet *Riva, Canad.*
⊗Paracetamol (p. 115·1); oxycodone hydrochloride (p. 113·1).
Pain.

Rivacor *GL Pharma, Austria.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris.

Rivacor Plus *Lannacher, Austria.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Riva-Fluvox *Riva, Canad.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Rivaller *SymPhar, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia associated with parkinsonism.

Rivalong *Farma-Projekt, Neth.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Rivanase *Riva, Canad.*
⊗Beclometasone dipropionate (p. 1621·2).
Corticosteroid.

Rivanol *Dermapharm, Ger.; Prolab, Pol.; Sifa, Turk.*
Ethacridine lactate (p. 1732·3).
Antiseptic; bacterial infections of skin and mucous membranes; burns; ulcers; wounds; skin disinfection.

Rivanolum *ICN, Pol.*
Ethacridine lactate (p. 1732·3).
Bacterial infections of skin and mucous membranes; burns; wounds.

Rivarlau *Welding, Neth.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Rivasa *Riva, Canad.*
Aspirin (p. 22·2).

Rivasmina *Lafedar, Arg.*
Rivastigmine hydrogen tartrate (p. 395·1).

Rivasol *Riva, Canad.*
Zinc sulfate (p. 2126·2).
Anorectal disorders.

Rivasol HC *Riva, Canad.*
⊗Zinc sulfate (p. 2126·2); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Rivasone *Riva, Canad.*
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders.

Rivastach *Ono, Jpn.*
Rivastigmine (p. 394·3).
Alzheimer's disease.

Rivastinorm *Plus Pharma, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia associated with parkinsonism.

Rivatril *Roche, Fin.*
Clonazepam (p. 519·1).
Epilepsy.

Rivaxel *Frik, Turk.*
Rivastigmine hydrogen tartrate (p. 395·1).

Rivaxon *Biogened, Neth.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Riva-Zide *Riva, Canad.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).

Rivazol *Loeffler, Mex.*
Albendazole (p. 149·1).
Worm infections.

Rivecrum *Rivero, Arg.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Riveka *Unia, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia associated with parkinsonism.

Rivel *Emo-Farm, Pol.*
Ethacridine lactate (p. 1732·3).
Disinfection of skin and mucous membranes; wounds.

Riveparin *Rivero, Arg.; Lapreven, Venez.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders; prevention of clotting in extracorporeal circuits; anticoagulant.

Rivepime *Rivero, Arg.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Rivervan *Rivero, Arg.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Rivescal Tar *Sifarma, Ital.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Seborrhoeic dermatitis.

Rivescal ZPT *Sifarma, Ital.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis.

Rivial *Rivero, Arg.*
Vitamins.
Parenteral nutrition.

Rivilina *Rivero, Arg.*
Aprotinin (p. 1133·2).

Rivitin BC *Lannacher, Austria.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Rivocler *Monserrat, Arg.*
Clonazepam (p. 519·1).

Rivocor *ProMed, Cz.; Rivopharm, Switz.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; hyperkinetic heart syndrome.

Rivodaron *ProMed, Cz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Rivodarone *Rivopharm, Switz.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Rivoleve *Rivopharm, Switz.*
Levetiracetam (p. 531·1).
Epilepsy.

Rivoltan *Krewel, Ger.*
Devil's claw root (p. 42·3).
Degenerative joint disorders.

Rivopam *CCM, Malaysia.*
Clonazepam (p. 519·1).
Epilepsy.

Rivotril *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Cz.; Roche, Denm.; Roche, Fr.; Roche, Ger.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.†; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Venez.*
Clonazepam (p. 519·1).
Epilepsy; status epilepticus; trigeminal neuralgia; panic disorder; anxiety; social phobia; bipolar disorder; depression; restless legs syndrome; vertigo; burning mouth syndrome; obsessive-compulsive disorder; sleep disorders; alcohol withdrawal syndrome; agitation.

Rivuclin *SIFFRA, Ital.*
Vitamins; lactoferrin (p. 2539·3); *Lactobacillus paracasei* (p. 2596·3); myrtillus (p. 2566·2).
Urinary-tract infections.

α-Rix *GSK, Belg.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Rixadone *Alphapharm, Austral.*
Risperidone (p. 1103·2).
Behaviour disturbances; psychoses.

Rixapen *Menarini, Belg.*
Clometocillin potassium (p. 274·3).
Bacterial infections.

Rixil *Bracco, Ital.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Rixivoc *Raam, Mex.*
Ofloxacin (p. 334·3).
Bacterial infections.

Rixofem *ISA, Arg.*
Alendronate (p. 1171·3).
Osteoporosis.

Rixol *Bilim, Turk.*
Risperidone (p. 1103·2).

Rixone *Yarindo, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Rixper *Fako, Turk.*
Risperidone (p. 1103·2).

Rixtal *Biomep, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Rixubis *Baxter, USA.*
A factor IX preparation (p. 1149·3).
Haemophilia B.

Rizaben *Kissei, Jpn.*
Tranilast (p. 1239·1).
Asthma; allergic conjunctivitis; allergic rhinitis; atopic eczema; hypertrophic and keloid scars.

Rizact *Cipla, India.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Rizaldon *Help, Gr.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Rizaliv *Neopharmed, Ital.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Rizalt *MSD, Israel.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Rizan *Meda, Spain.*
Pimecrolimus (p. 1716·1).
Atopic eczema.

Rizat *Baldacci, Port.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Rizatan *MSD, Neth.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Rize *Silesia, Chile; Mitsubishi, Jpn.*
Clotiazepam (p. 1057·2).
Autonomic disorders; sleep disorders; premedication; anxiety; alcohol withdrawal symptoms.

Rizen *Formenti, Ital.*
Clotiazepam (p. 1057·2).
Anxiety disorders; sleep disorders.

Rizetec *Great Eastern, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria.

Rizmsat *Choseido, Jpn.*
Pilsicainide hydrochloride (p. 1470·1).
Arrhythmias.

Rizodal *Guardian, Indon.*
Risperidone (p. 1103·2).
Psychoses.

Rizol *Aspen, Arg.*
Riluzole (p. 2605·1).

Rizonax *Novell, Indon.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Rizosin *Sintez, Rus.*
Sodium chloride (p. 1795·1).
Nasal dryness; nasal hygiene.

Rizumcote *Towa, Jpn.*
Pilsicainide hydrochloride (p. 1470·1).
Arrhythmias.

R-J *Medicine Products, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; delayed gastric emptying; gastro-oesophageal reflux.

Rjativnik *Arterium, Ukr.*
Dexpanthenol (p. 2582·2); chlorhexidine gluconate (p. 1743·3).
Burns; ulcers; wounds; skin disorders; infected skin disorders.

R-Loc *Zydus, S.Afr.; Zydus Cadila, Thai.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; hypersecretory disorders; mastocytosis; gastro-oesophageal reflux; acid aspiration; Zollinger-Ellison syndrome.

Zydus, India.
Ranitidine (p. 1882·1) or ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity; dyspepsia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

RMS
Note: this name may be used for preparations of different composition.
Upsher-Smith, USA.
⊗Morphine sulfate (p. 92·3).
Pain.

RN13 Regeneresen *Dyckerhoff, Ger.†*
Ribonucleic acid (p. 2604·1).
Tonic.

RNA DNA *Natural Life, Arg.*
Ribonucleic acid (p. 2604·1); deoxyribonucleic acid (p. 2492·2); brewer's yeast (p. 2125·2).
Tonic.

Roaccutan *Investi, Arg.; Roche, Austria†; Roche, Fin.; Roche, Gr.; Roche, Hung.; Roche, Ital.; Roche, Mex.; Roche, Norw.†; Roche, Venez.*
Isotretinoin (p. 1706·2).
Acne.

Roaccutane *Roche, Austral.; Roche, Belg.; Roche, Cz.; Roche, Hong Kong; Roche, Irl.; Roche, Israel; Roche, Malaysia; SERP, Mon.; Roche, Neth.; Roche, Philipp.; Roche, Pol.†; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.*
Isotretinoin (p. 1706·2).
Acne.

Roacnetan *Roche, Chile.*
Isotretinoin (p. 1706·2).
Acne.

RoActemra *Roche, Austria; Roche, Belg.; Roche, Cz.; Roche, Denm.; Roche, Fr.; Chugai, Ger.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Irl.; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, Pol.; Roche, Port.; Roche, Spain; Roche, Swed.; Roche, UK.*
Tocilizumab (p. 77·3).
Rheumatoid arthritis; juvenile idiopathic arthritis.

Roacutan *Roche, Braz.; Roche, Spain.†*
Isotretinoin (p. 1706·2).
Acne.

Robafen AC Cough *Major, USA.*
Guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Coughs.

Robafen DAC *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Coughs.

Robafen DM *Major, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Robamox *Combiphar, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Robanul *Richmond, Arg.*
Epirubicin (p. 787·1).
Malignant neoplasms.

RoBathol *Pharmaceutical Specialties, USA.*
Emollient.

Robax Platinum *Pfizer Consumer, Canad.*
Methocarbamol (p. 2025·3); ibuprofen (p. 68·2).
Painful skeletal muscle spasm.

Robaxacet *Pfizer Consumer, Canad.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Musculoskeletal, peri-articular, and soft-tissue pain.

Robaxacet-8 *Pfizer Consumer, Canad.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Musculoskeletal, peri-articular and soft-tissue pain.

Robaxifen *Wyeth Consumer, Mex.; Wyeth Consumer, Venez.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Painful skeletal muscle spasm.

Robaxin *Pfizer Consumer, Canad.; Wyeth, Gr.; Pharmacare, S.Afr.; Faes, Spain; Shire, UK; Westward, USA.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm; musculoskeletal pain.

Robaxisal *Pfizer Consumer, Canad.; Wyeth, Gr.; Wyeth Consumer, Mex.; Pharmacare, S.Afr.†; Wyeth Consumer, Venez.*
Methocarbamol (p. 2025·3); aspirin (p. 22·2).
Musculoskeletal, peri-articular and soft-tissue pain; painful skeletal muscle spasm.

Robaxisal Compuesto *Faes, Spain.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Musculoskeletal pain.

Robaxisal-C *Pfizer Consumer, Canad.*
Methocarbamol (p. 2025·3); aspirin (p. 22·2); codeine phosphate (p. 40·2).
Musculoskeletal, peri-articular and soft-tissue pain.

Robaz *Galderma, Gr.; Galderma, Philipp.; Galderma, Thai.*
Metronidazole (p. 936·1).
Rosacea.

Robencaxil *IQFA, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin (p. 228·1).
Bacterial infections.

Roberfarin *Ferrer, Spain.*
⊗Dequalinium chloride (p. 1749·3); enoxolone (p. 54·2); hydrocortisone acetate (p. 1640·1); oxetacaine (p. 1993·1); tyrothricin (p. 384·1).
Mouth and throat inflammation.

Robervital *Robert, Spain.†*
Oxaceprol (p. 2578·2); tocoferil sodium succinate.
Musculoskeletal and joint disorders; dermatomyositis.

Robiflam *Khandelwal, India.*
Methocarbamol (p. 2025·3); ibuprofen (p. 68·2).
Skeletal muscle spasm; musculoskeletal and joint disorders.

Robilas *Menarini, Ital.*
Bilastine (p. 617·3).

Robimen *Quim-Far, Venez.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Robimycin Robitabs *Robins, USA.*
Erythromycin (p. 291·2).
Bacterial infections.

Robinax *Khandelwal, India.*
Methocarbamol (p. 2025·3).
Skeletal muscle spasm.

Robinaxol *Khandelwal, India.*
Methocarbamol (p. 2025·3); paracetamol (p. 115·1).
Skeletal muscle spasm; musculoskeletal and joint disorders.

Robinia Med Complex *Dynamit, Austria.*
Capsicum (p. 2469·3); hydrastis (p. 2528·1); phosphorus (p. 2589·2); robinia pseudacacia.
Homoeopathic preparation.

Robinson Cough *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2).
Cough.

Robinson Ringworm & Whitespot *Beacons, Singapore.*
Lotion: Methyl salicylate (p. 92·1); salicylic acid (p. 1719·1).

Beacons, Singapore.
Ointment: Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1).

Robinul *Aspen, Austral.; Torrex, Austria; Eumedica, Belg.; Meda, Denm.; Meda, Fin.; Riemser, Ger.; IFET [ΙΦΕΤ], Gr.; Anpharm, Irl.; Meda, Norw.; Healthcare Logistics, NZ; Aspen, S.Afr.; Meda, Swed.; Anpharm, UK; Anpharm, UK†; Shionogi, USA; Westward, USA.*
Glycopyrronium bromide (p. 2519·3).
Hyperhidrosis; premedication; intra-operative management of cardiac vagal reflexes; protection against muscarinic effects of anticholinesterases used to reverse neuromuscular blockade; adjunct in peptic ulcer.

Robinul-Neostigmin *Meda, Denm.; Meda, Fin.; Meda, Norw.; Meda, Swed.*
Neostigmine metilsulfate (p. 687·2). Glycopyrronium bromide (p. 2519·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Robinul-Neostigmine *Eumedica, Belg.; Sintetica, Switz.; Anpharm, UK.†*
Neostigmine metilsulfate (p. 687·2). Glycopyrronium bromide (p. 2519·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Robi's Cough *Beacons, Singapore.*
Ammonium chloride (p. 1656·1); phenylephrine hydrochloride (p. 1672·3); liquorice (p. 1853·2).
Cough.

Robisef *Umedica, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Robisid *Tripharma, Turk.*
Sodium fusidate (p. 302·1).

Robitessin *Wyeth, Venez.*
Guaifenesin (p. 1666·2).
Cough.

Robitessindem *Wyeth, Venez.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin *Pfizer Consumer, Canad.; Neopharm, Israel; Wyeth Consumer, Mex.; Pfizer Consumer, Thai.*
Guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Robitussin AC
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Canad.
Guaifenesin (p. 1666·2); pheniramine maleate (p. 637·2); codeine phosphate (p. 40·2).
Cough.

Robins, USA.
Guaifenesin (p. 1666·2); codeine phosphate (p. 40·2).
Coughs.

Robitussin Adult Lingering Cold Long-Acting Cough *Pfizer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin Adult Peak Cold Nasal Relief *Pfizer, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Robitussin Adult Peak Cold Nighttime Nasal Relief *Pfizer, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Robitussin Antitussicum *Pfizer, Cz.; Wyeth, Hung.; Whitehall, Pol.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin Chest Congestion *Wyeth Consumer, Hong Kong.†*
Guaifenesin (p. 1666·2).
Cough.

Robitussin Chesty Cough *Pfizer Consumer, Austral.; Pfizer Consumer, Irl.; Pfizer Consumer, UK.*
Guaifenesin (p. 1666·2).
Cough.

Robitussin Chesty Cough with Congestion *Pfizer Consumer, UK.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Robitussin Chesty Cough Forte *Pfizer Consumer, Austral.*
Guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Robitussin Chesty Cough & Nasal Congestion PE *Pfizer Consumer, Austral.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; cough.

Robitussin Chesty Cough & Nasal Congestion PS *Pfizer, Austral.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cough.

Robitussin Childrens *Wyeth Consumer, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1).
Formerly known as Robitussin Childrens Cough DM.
Cough.

Robitussin Childrens Cough & Cold *Pfizer Consumer, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Robitussin Children's Cough & Cold *Pfizer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Robitussin Children's Cough & Cold CF *Pfizer Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Robitussin Children's Cough Long-Acting *Pfizer Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin CM *Pfizer Consumer, Singapore.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Robitussin Cold & Cough *Robins, USA.*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Robitussin Cough & Chest Congestion *Pfizer Consumer, Austral.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin Cough & Cold *Pfizer Consumer, Canad.; Wyeth Consumer, USA.*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms; upper respiratory-tract disorders.

Robitussin Cough Drops *Robins, USA.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).

Robitussin CoughGels *Pfizer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin DAC *Robins, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Coughs.

Robitussin DM *Wyeth Consumer, Canad.†; Pfizer Consumer, Hong Kong; Neopharm, Israel; Wyeth Consumer, Mex.; Wyeth Consumer, NZ; Wyeth, Philipp.; Pfizer Consumer, Singapore; Pfizer Consumer, Thai.; Robins, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin DM CoughGels *Pfizer Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin DM-P *Wyeth Consumer, Austral.†; Wyeth Consumer, NZ.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal and sinus congestion; nasal congestion.

Robitussin Dry Cough *Pfizer Consumer, Irl.; Pfizer Consumer, UK.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin Dry Cough Forte *Pfizer Consumer, Austral.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin DX *Pfizer Consumer, Hong Kong; Wyeth Consumer, NZ.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin EX *Wyeth Consumer, Austral.†; Pfizer Consumer, Hong Kong; Wyeth Consumer, NZ; Pfizer Consumer, Singapore.*
Guaifenesin (p. 1666·2).
Cough.

Robitussin Expectorans *Pfizer, Cz.; Wyeth, Hung.; Whitehall, Pol.*
Guaifenesin (p. 1666·2).
Cough.

Robitussin Expectorant
Note: this name may be used for preparations of different composition.
Wyeth, Philipp.
Guaifenesin (p. 1666·2).
Cough.

Robitussin Honey Cold *Whitehall Consumer, NZ†; Pfizer Consumer, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal and sinus congestion.

Robitussin Honey Cough
Note: this name may be used for preparations of different composition.
Pfizer Consumer, Singapore.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Wyeth Consumer, NZ.†
Menthol (p. 2553·2); honey (p. 2072·1).
Cough.

Robitussin Junior *Pfizer, Cz.; Wyeth, Hung.; Wyeth Consumer, Irl.†; Whitehall, Pol.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin Maximum Strength Cough *Wyeth Consumer, Hong Kong.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin Maximum Strength Cough & Cold *Robins, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Robitussin ME *Interphil, Hong Kong; Pfizer Consumer, Hong Kong; Wyeth Consumer, NZ; Pfizer Consumer, Singapore; Pfizer Consumer, Thai.*
Guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion; cough.

Robitussin Medicated Lozenges *Pfizer Consumer, Singapore.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Robitussin Mucus & Chest Congestion *Pfizer Consumer, USA.*
Guaifenesin (p. 1666·2).
Formerly known as Robitussin.
Cough.

Robitussin Night Relief *Robins, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); mepyramine maleate (p. 635·1); paracetamol (p. 115·1).
Coughs and cold symptoms.

Robitussin Ning *Pfizer, China.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; cough.

Robitussin Paediatric Cough *Wyeth Consumer, Hong Kong.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Robitussin PE *Robins, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Robitussin Pediatric *Robins, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Robitussin Pediatric Cough & Cold Formula *Robins, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Robitussin Plus *Pfizer Consumer, Irl.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Robitussin PM Cough & Cold *Wyeth Consumer, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Robitussin PS *Wyeth Consumer, Hong Kong†; Wyeth Consumer, NZ†; Pfizer Consumer, Singapore; Pfizer Consumer, Thai.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Robitussin Severe Congestion *Robins, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Robitussin Total Cough, Cold & Flu *Pfizer Consumer, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold and influenza symptoms.

Robitussin Total Cough, Cold & Flu Nighttime *Wyeth Consumer, Canad.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold and influenza symptoms.

Robitussin Xuan *Pfizer, China.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Robovites Multivitamins *Vita Health, Singapore.*
Oral drops: Vitamins; with or without iron (p. 2073·1).

Vita Health, Singapore.
Chewable tablets: Vitamins; zinc (p. 2126·1).

Vita Health, Singapore.
Syrup: Vitamins; cod-liver oil (p. 2056·3); evening primrose oil (p. 2502·2); echinacea (p. 2498·1); ginkgo biloba (p. 2512·3).

Robumin *Novell, Indon.*
⊗Albumin (p. 1130·2).
Hypoalbuminaemia.

Roburvit *Echo, Ital.*
Royal jelly (p. 2608·1).

ROC Hydra *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

ROC Minesol Actif *Johnson & Johnson, Chile.*
SPF 30: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1); titanium dioxide (p. 1725·1).
Sunscreen.

ROC Minesol Bronze *Johnson & Johnson, Chile.*
SPF 8: Dihydroxyacetone (p. 1700·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); avobenzone (p. 1695·1).
Artificial tanning agent; sunscreen.

ROC Minesol Protect *Johnson & Johnson, Chile.*
SPF 30: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3).
Sunscreen.

Johnson & Johnson, Chile.
SPF 50+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1).
Sunscreen.

Johnson & Johnson, Canad.†
SPF 30; SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

ROC Minesol Protect Ultra High *Johnson & Johnson, Canad.*
SPF 60: Bemotrizinol (p. 1695·3); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

ROC Minesol Protect Very High *Johnson & Johnson, Canad.†*
SPF 30: Bemotrizinol (p. 1695·3); enzacamene (p. 1703·2); bisoctrizole (p. 1697·1); octinoxate (p. 1715·1).
Sunscreen.

ROC Retin-Ol+Day *Johnson & Johnson, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

RoC Sante Soleil *RoC, UK.*
SPF 25: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Formerly known as RoC Total Sunblock.
Sunscreen.

RoC Sunscreen Stick *RoC, UK.*
Dibenzoylmethane (p. 1700·1); a cinnamic ester.
Sunscreen.

Rocainol *CICSA, Mex.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Rocal *ANB, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Rocaltrol *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Fr.; Roche, Ger.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.†; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.†; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Validus, USA; Roche, Venez.*
Calcitriol (p. 2113·1).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets; osteomalacia; vitamin D deficiency; hypocalcaemia; pseudohypoparathyroidism; hypophosphataemia; hyperparathyroidism.

Rocanol *Medichrom, Gr.*
⊗Spironolactone (p. 1499·3).

Rocavit *Vitae, Mex.*
Capsules: Vitamins; minerals.

Vitae, Mex.
Injection: Vitamins.

Vitae, Mex.
Oral drops: Vitamins; lysine (p. 2079·3).
Tonic.

Vitae, Mex.
Oral solution: Vitamins; cyproheptadine (p. 624·1).
Reduced appetite.

Rocef *XL, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Rocefalin *Roche, Spain.†*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocefin *Roche, Braz.; Roche, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Roceftin *Sel-J, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Rocephalin *Roche, Denm.; Roche, Fin.; Roche, Norw.†; Roche, Swed.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in some injections to alleviate the pain of injection.
Bacterial infections.

Rocepherin *Bryntsalov, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Rocephin *Roche, Austral.; Roche, Austria; Roche, Canad.†; Roche, China; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, NZ†; Roche, Philipp.; Roche, Pol.†; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Genentech, USA; Roche, Venez.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocephine *Roche, Belg.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocéphine *Roche, Fr.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocer *Otto, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Roceron *Roche, Norw.*
Interferon alfa-2a (p. 989·2).
Malignant neoplasms; chronic active hepatitis B; chronic hepatitis C.

Rocgel *D&A Pharma, Fr.*
Boehmite.
Gastrointestinal disorders.

Rochagan *Masters, Braz.†*
Benznidazole (p. 929·3).
American trypanosomiasis.

Rociject *Aspen, S.Afr.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Rocilin *Meda, Denm.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Rocin *Pasteur, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rocitro *TNP, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rocki *Bangkok Lab & Cosmetic, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Rockles *Septodont, Fr.*
⊗Dexamethasone acetate (p. 1631·1); phenol (p. 1763·3); guaiacol (p. 1666·1).
Root canal infections.

Roclas *Miklich, Denm.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Rocne *Gabriel, Gr.*
Isotretinoin (p. 1706·2).

Roco *Bayer, Neth.†*
Ibuprofen (p. 68·2).
Pain.

Rocodin *Pharma-Q, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Rocornal *UCB, Ger.; Mochida, Jpn.*
Trapidil (p. 1517·3).
Angina pectoris; ischaemic heart disease.

Rocoz
Note: this name may be used for preparations of different composition.
Alter, Spain.
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Pyridam, Indon.
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Rocta *Southern Cross, Austral.; Southern Cross, Austral.*
Isotretinoin (p. 1706·2).
Acne.

Roctylan *Farmedia, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Roculax *Kalbe, Indon.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Rocuron *Cristalia, Braz.; Zynova, Philipp.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Ro-C-Var *Infinity, Venez.*
Vitamin C (p. 2110·3); rose fruit (p. 2607·1).
Vitamin C supplement.

Rocygen *Rotexmedica, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Rodakin *Kener, Mex.†*
Loratadine (p. 633·2).
Hypersensitivity.

Rodan *Superlife, Mex.*
Evening primrose oil (p. 2502·2); turmeric (p. 2218·1); devil's claw root (p. 42·3); ulmaria (p. 2550·2).
Musculoskeletal and joint disorders.

Rodan & Fields Proactiv *Guthy Renker, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Rodan & Fields Proactiv Antidandruff *Guthy Renker, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Rodan & Fields Proactiv Daily Protection Plus *Guthy Renker, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Rodan & Fields Proactiv Refining Mask *Guthy Renker, Canad.†*
Sulfur (p. 1721·1).

Rodan & Fields Proactiv Renewing Cleanser *Guthy Renker, Canad.*
Benzoyl peroxide (p. 1696·1).

Rodan & Fields Proactiv Repairing *Guthy Renker, Canad.*
Benzoyl peroxide (p. 1696·1).

Rodan & Fields Proactiv Sheer Tint *Guthy Renker, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Rodan & Fields Proactiv Skin Lightening *Guthy Renker, Canad.†*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Rodanol *Lek, Rus.†*
Nabumetone (p. 97·1).

Rodanol S *Sandoz, Pol.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders.

Rodase *Pond's, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; wounds; respiratory-tract congestion.

Rodazid *Pharma Nutria, Philipp.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Roddexil *Roddensers, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Rodenal *Rekah, Israel.*
Trihexyphenidyl hydrochloride (p. 917·3).
Extrapyramidal disorders; parkinsonism.

Rodepan *Pharma Investi, Chile.*
Cyproheptadine hydrochloride (p. 624·1); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); riboflavin sodium phosphate (p. 2104·3); nicotinamide (p. 2083·1); ascorbic acid (p. 2110·3).
Reduced appetite; tonic.

Rodermil *Edol, Port.*
Metronidazole (p. 936·1).
Rosacea.

Rodesa *Specifar, Neth.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rodexa *Schwabe, Neth.†*
Rhodiola rosea.
Fatigue; overwork; nervousness.

Rodinac *Geminis, Arg.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

Rodinac B12 *Geminis, Arg.*
⊗Betamethasone (p. 1623·2); vitamin B_{12} (p. 2107·2); diclofenac potassium (p. 48·3).
Inflammation; neuritis; pain.

Rodinac Biotic *Geminis, Arg.*
Amoxicillin trihydrate (p. 216·2); diclofenac potassium (p. 48·3).
Bacterial infections.

Rodinac Flex *Geminis, Arg.*
Pridinol (p. 2026·1); diclofenac sodium (p. 48·3).
Inflammation; muscle spasm; pain.

Rodinac Gesic *Geminis, Arg.*
Paracetamol (p. 115·1); diclofenac potassium (p. 48·3).
Inflammation; pain.

Rodipal *Quesada, Arg.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; hypertension.

Rodix *Galeno, Venez.*
Tenoxicam (p. 136·2).
Inflammation; musculoskeletal and joint disorders.

Rodogyl *Sanofi-Aventis, Fr.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.*
Spiramycin (p. 358·3); metronidazole (p. 936·1).
Mouth infections.

Rodovit *Allen, Mex.*
Vitamins; with or without minerals.

Rofacin *Corsa, Indon.*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis.

Rofact *Valeant, Canad.*
Rifampicin (p. 350·3).
Tuberculosis.

Rofemax *Fako, Turk.*
Rofecoxib (p. 128·3).
Musculoskeletal and joint disorders.

Rofen *Akdeniz, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Rofenid *Sanofi-Aventis, Belg.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; oedema.

Rofepain *LBS, Thai.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout; inflammation.

Roferon-A *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong†; Roche, Hung.; Piramal, India; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn†; Roche, Malaysia; Roche, Mex.†; Roche, Neth.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, Venez.*
Interferon alfa-2a (p. 989·2).
Malignant neoplasms; viral infections; chronic hepatitis B; chronic hepatitis C; anogenital warts; hepatitis D; essential thrombocythaemia.

Roféron-A *Roche, Fr.; Roche, Switz.*
Interferon alfa-2a (rbe) (p. 989·2).
Malignant neoplasms; chronic hepatitis B and C.

Roferon-A RBV *Roche, NZ.*
Injection, interferon alfa-2a (Roferon-A) (p. 989·2); tablets, ribavirin (Copegus) (p. 1010·2).
Chronic hepatitis C.

Rofex *Piramal, India.*
Cefalexin (p. 234·1).
Bacterial infections.

Rofib *Aristo, India.†*
Rofecoxib (p. 128·3).
Osteoarthritis; pain.

Rofica *Micro Labs, Ukr.†*
Rofecoxib (p. 128·3).
Osteoarthritis; rheumatoid arthritis.

Rofiden *Otto, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; gout.

Rofiz *Wockhardt, India.†*
Rofecoxib (p. 128·3).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Roflazin *Munir, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Rofucal *Probiomed, Mex.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Rofunil *Rotexmedica, Philipp.*
⊗Furosemide (p. 1387·1).
Oedema.

Rofy *Codal Synto, Thai.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Rogaan *Teva, Israel.†*
Dextropropoxyphene hydrochloride (p. 43·3); aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Rogadermis
Note: this name may be used for preparations of different composition.
Lafedar, Arg.
Benzocaine (p. 1980·2); zinc oxide (p. 1729·1); vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).

Rogaine *Janssen-Cilag, Austria; Johnson & Johnson, Canad.; McNeil, Fin.; McNeil, Norw.†; Pfizer, NZ; McNeil, Swed.; Pfizer Consumer, USA.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Rogan *Kocak, Turk.*
Minoxidil (p. 1438·3).

Rogasti *Pacific, Israel.*
Famotidine (p. 1842·1).
Duodenal ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rogastril *Roemmers, Arg.*
Cinitapride acid tartrate (p. 1831·3).
Gastrointestinal motility disorders; gastro-oesophageal reflux.

Rogbaz *Fariberica, Port.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Rogin-E *Bayer, Philipp.*
⊗Ginseng (p. 2513·3); deanol (p. 2319·1); royal jelly (p. 2608·1); lecithin (p. 2542·2); vitamins; minerals; free fatty acids.
Tonic; nutritional supplement.

Rogitine *Paladin, Canad.; Novartis, Singapore; Alliance, UK.†*
Phentolamine mesilate (p. 1468·3).
Phaeochromocytoma; dermal necrosis and sloughing following intravenous administration of noradrenaline.

Roglin *Aristo, India.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Roglin-M *Aristo, India.*
Rosiglitazone maleate (p. 496·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Roglit *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Rosiglitazone potassium (p. 496·3).
Diabetes mellitus.

Rograpon *Vilco, Gr.*
Flurbiprofen (p. 65·2).

Roha-Lax *Tripharma, Turk.*
Sennosides (p. 1885·2).
Constipation.

Rohipnol *Roche, Spain.†*
Flunitrazepam (p. 1073·3).
Insomnia; anxiety; general anaesthesia.

Rohist *Sandoz, S.Afr.*
Loratadine (p. 633·2).
Seasonal allergic rhinitis; urticaria.

Rohto Dry Eye Relief *Laser, UK.*
Hyaluronic acid (p. 2526·2); tamarind polyose (p. 2215·2).
Dry eyes.

Rohto Zi *Mentholatum, UK.*
Camphor (p. 2466·2).
Eye irritation.

Rohydorm *Sigma, Braz.*
Flunitrazepam (p. 1073·3).
Insomnia.

Rohypnol *Invesi, Arg.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Fr.; Roche, Ger.; Roche, Hong Kong; Roche, Irl.; Roche, Mex.; Roche, Pol.†; Roche, Port.†; Roche, Rus.; Roche, S.Afr.; Roche, Switz.; Roche, Thai.†*
Flunitrazepam (p. 1073·3).
Insomnia; premedication; sleep disorders; induction of anaesthesia.

Roical *Shin Poong, Malaysia; Shin Poong, Singapore.*
Calcitriol (p. 2113·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Roiplon *Menarini, Gr.*
Etofenamate (p. 57·2).
Pain; inflammation; musculoskeletal and joint disorders.

Roipnol *Roche, Ital.*
Flunitrazepam (p. 1073·3).
Insomnia.

Rojema *Self-Care Products, UK.*
Royal jelly (p. 2608·1).

Rokacet *Taro, Israel.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Cough; fever; pain.

Rokacet Plus *Taro, Israel.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Cough; fever; pain.

Rokal *Taro, Israel.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Cough; fever; pain.

Rokal Plus *Taro, Israel.†*
Aspirin (p. 22·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Cough; fever; pain.

Rokamol *Taro, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Rokamol Plus Codeine *Taro, Israel.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Cough; fever; pain.

Rokan *Andromaco, Chile.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Rökan *Spitzner, Ger.*
Ginkgo biloba leaf (p. 2512·3).
Mental function disorders; peripheral circulatory disorders.

Rokiprim *Rokitan, Neth.*
Sulfametrole sodium (p. 368·1); trimethoprim (p. 381·2).
Bacterial infections.

Rokital *Formenti, Ital.*
Rokitamycin (p. 356·1).
Bacterial infections.

Roko *Cipla, India.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Roksicap *Caprifarmindo, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Roksimin *Umut, Turk.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roksolit *Eczacibasi, Rus.; Eczacibasi, Turk.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rokumigan *Tsumura, Jpn.*
Rehmannia root; cornus fruit; dioscorea rhizome; alisma rhizome; poria sclerotium; moutan bark.
Traditional Kampo medicine.

Rolab-Amoclav *Sandoz, S.Afr.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Rolab-Anthex *Sandoz, S.Afr.†*
Mebendazole (p. 158·3).
Worm infections.

Rolac *Actavis, Indon.*
Ketorolac trometamol (p. 80·2).
Pain.

Rolac Plus *Wyeth, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; dyspepsia; flatulence.

Rolacsin *Segix, Ital.*
Ketorolac trometamol (p. 80·2).
Pain.

Roladol *Cinay, Turk.*
Mefenamic acid (p. 85·3).

Rolaids *Pfizer Consumer, USA.*
Magnesium hydroxide (p. 1857·2); calcium carbonate (p. 1824·3).
Antacid.

Rolaids Antacid *McNeil Consumer, Canad.†*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Dyspepsia.

Rolaids Extra Strength Softchews *Pfizer Consumer, USA.*
Calcium carbonate (p. 1824·3).
Antacid.

Rolaids Multi-Symptom *McNeil Consumer, Canad.; Pfizer Consumer, USA.*
Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid; flatulence.

Rolaids Plus Gas Relief *Pfizer Consumer, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).

Rolaids Ultra *McNeil Consumer, Canad.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).

Rolak *Mac, Gr.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Rolaket *Elpen (Ελπεν), Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Rolam *Medis, Denm.*
Ramipril (p. 1483·3).
Hypertension; nephropathy; heart failure; myocardial infarction.

Rolan *Nobel, Turk.*
Mefenamic acid (p. 85·3).
Musculoskeletal and joint disorders; pain; menorrhagia.

Rolap *Teva Tuteur, Arg.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Rolaphin *EuroHealth, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Rolar *Pharmaland, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough; cold symptoms; nasal congestion.

Rolast *Phoenix, Arg.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis; bronchospasm.

Rolatuss Expectorant *Huckaby, USA.*
Phenylephrine hydrochloride (p. 1672·3); codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Coughs.

Rolatuss Plain *Major, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Roleca Wacholder *Riemser, Ger.*
Juniper oil (p. 2537·2).
Diuretic.

Rolene *Riva, Canad.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Rolenium *Elpen (Ελπεν), Gr.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Rolesen *Antibioticos, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Roletra *Ozone, Cz.†; Labormed, Hung.; Ranbaxy, Malaysia; Ranbaxy, Mex.†; Ranbaxy, Singapore; Ranbaxy, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Rolexit *Nufarindo, Indon.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rolicyn *Polfa Tarchomin, Pol.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rolicytin *Unipharm, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Rolimycin *Faran, Gr.*
Dibekacin sulfate (p. 286·1).
Bacterial infections.

Rolip *Noreva, Fr.*
alpha-Acetyl mandelic acid (p. 320·3).
Dry lips.

Rolisporin *Vianex (Βιανεξ), Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Roliten *Ranbaxy, Rus.; Ranbaxy, Ukr.*
Tolterodine tartrate (p. 2370·2).
Bladder instability; urinary incontinence.

Rolodiquim *Quimica y Farmacia, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Rolpryna *KRKA, Cz.; KRKA, Irl.; KRKA, Spain.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Rolsical *Sun, India.*
Calcitriol (p. 2113·1).
Osteoporosis; hypocalcaemia; hypoparathyroidism; rickets.

Rolyprexa *Rowex, Irl.*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

Romac *Sandoz, Port.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Romace *Pentafarma, Port.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy; cardiovascular risk reduction.

Romacef *Renata, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Romacox *Ali, Turk.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders; inflammation.

Romaken *Kendrick, Mex.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Romaksen *Ulagay, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Romamed *Medlink, Philipp.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Romapal *Galex, Ital.*
Perindopril (p. 1466·3).

Romarène *Beaufour, Fr.†*
Rosemary (p. 2607·2); taraxacum (p. 2625·3); kinkeliba (p. 2538·2); potassium sodium tartrate (p. 1879·3); sodium citrate (p. 1781·2).
Dyspepsia.

Romarinex *Dissolvurol, Mon.*
Rosemary (p. 2607·2); kinkeliba (p. 2538·2).
Dietary supplement; digestive disorders.

Romarinex Chrome *Dissolvurol, Mon.*
Rosemary (p. 2607·2); milk thistle (p. 1561·1); taraxacum (p. 2625·3); chromium chloride (p. 2055·3).
Dietary supplement; digestive disorders; metabolic disorders.

Romaryd *Ali, Turk.*
Rofecoxib (p. 128·3).

Romasulan *Biofarm, Rus.*
Chamomile (p. 2474·1).
Gastritis, duodenitis, colitis, meteorism; skin disorders; mouth and throat disorders; vaginitis.

Romasulid *Kocak, Turk.*
Nimesulide (p. 101·3).

Romatim *Kurtsan, Turk.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint pain.

Romax *Rowex, Irl.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Romaxin *Prohealth, Philipp.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Romazicon *Roche, USA.*
Flumazenil (p. 1551·3).
Formerly known as Mazicon.
Reversal of benzodiazepine-induced sedation; benzodiazepine overdosage.

Rombay *Apotheke Heiligen Dreifaltigkeit, Austria.*
Talc (p. 1722·2); zinc oxide (p. 1729·1); peru balsam (p. 2587·1).
Skin irritation.

Rombellin *Qualicare, Switz.*
Biotin (p. 2052·2).
Biotin deficiency.

Rombox *GSK, Mex.*
Cefalexin (p. 234·1); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Romed *Medicpharma, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Romenem *LBS, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Romep *Rowex, Irl.*
Omeprazole (p. 1867·2) or omeprazole magnesium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Romeran *Biochimico, Braz.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Romesec *Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Singapore.*
Omeprazole (p. 1867·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Romet *Mitsubishi Tanabe, Jpn.*
Repirinast (p. 1219·2).
Asthma.

Rometor *Ratiopharm, Fin.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Rometran-K *Arlex, Mex.*
Ketorolac (p. 80·2).
Pain.

Romfalak *Rompharm, Rus.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy; hyperammonaemia; salmonella enteritis.

Romicef
Note: this name may be used for preparations of different composition.
Meprofarm, Indon.
Cefpirome (p. 247·2).
Bacterial infections.

Yung Shin, Philipp.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Romicin *Pacific, NZ.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Romidon *Stargen, Gr.*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Romilar
Note: this name may be used for preparations of different composition.
Bayer Consumer, Arg.; Bayer Consumer, Indon.; Bayer Consumer, Mex.; Bayer, Spain; Bayer Consumer, Thai.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Bayer Consumer, Thai.
Syrup: Dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); dexpanthenol (p. 2582·2).
Cough.

Romilar AC *Scot-Tussin, USA.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Coughs.

Romilar Antitussivum *Bayer, Belg.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Romilar Expectorant
Note: this name may be used for preparations of different composition.
Bayer Consumer, Indon.
Dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); panthenol (p. 2582·2).
Cough.

Romilar Mucolyticum *Bayer, Belg.†; Roche, Belg.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with accumulation of mucus.

Rominafort *Rominafort, Arg.*
Betacarotene (p. 2051·1); collagen (p. 2483·2); alpha tocopherol (p. 2119·1).
Dietary supplement.

Rominguer *Fariberica, Port.*
⊗Hydrochlorothiazide (p. 1403·2); losartan potassium (p. 1422·2).
Hypertension.

Romiplate *Kyowa Hakko Kirin, Jpn.*
Romiplostim (p. 1162·2).
Immune thrombocytopenia.

Romir *Diba, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Romisan *Chemo, Neth.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Romiver *Aivax, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Romox-ARL *Ximena Polanco, Chile.*
Rosemary (p. 2607·2); rosa mosqueta (p. 2607·1).

Romulin *Chew, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Romycin *Livzon, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Romyk *Lindopharm, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Romyl *Generics, Hung.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Ronal *Olvos, Gr.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Ronalgin *Dexa, Indon.*
Dipyrone (p. 53·3).
Pain.

Roname *Lacer, Spain.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Ronbetal *Biocad, Rus.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Roncoleukin *Biotech, Rus.*
Interleukin-2 (p. 810·1).
Sepsis; renal cancer.

Rondamine-DM *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); brompheniramine maleate (p. 618·1).
Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, and carbinoxamine maleate.
Coughs and cold symptoms.

Rondec *Abbott, Gr.; Biovail, USA.†*
Oral drops: ⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; allergic and vasomotor rhinitis; nasal congestion.

Biovail, USA.†
Syrup: ⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Rondec-DM
Note: this name may be used for preparations of different composition.
Alliant, USA.†
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms; respiratory symptoms of allergy.

Rondo *ISA, Arg.*
Saccharin (p. 2207·3); cyclamate (p. 2180·2).
Sugar substitute.

Rondo Sweet *ISA, Arg.*
Aspartame (p. 2169·2); acesulfame potassium (p. 2166·2).
Sugar substitute.

Rondover *Farmex, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Ronem *Fahrenheit, Indon.; Norton, Ukr.*
Meropenem (p. 321·3).
Bacterial infections.

Ronemox *Piramal, India.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ronepem *Lyofin, Gr.*
Meropenem (p. 321·3).

Ronex *Pharos, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemorrhage.

Ronexine *Rekah, Israel.*
Levomepromazine maleate (p. 1079·3).
Anxiety; tension; behaviour disorders; psychoses.

Ronfase *Pfizer, Arg.*
Estradiol valerate (p. 2271·2).
Menopausal disorders; osteoporosis; prostatic cancer.

Ronfnyl *Veron, Ger.*
Xanthan gum (p. 2220·1).
Snoring.

Ronfolic *AstraZeneca, Arg.; Rontag, Arg.*
Folic acid (p. 2063·1).
Folic acid deficiency.

Rong Da *Jiu Dian, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Rong Ning *Yangtze River, China.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension; heart failure.

Rongesic *Virgo, Philipp.*
Paracetamol (p. 115·1).
Pain.

Roni *Rowex, Irl.†*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Ronic *Edol, Port.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye disorders.

Ronistina *AstraZeneca, Arg.; Rontag, Arg.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Ronkal *Zentiva, Hung.†*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders.

Ronox *Deltapharm, Hong Kong†; Charoen, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rontafor *Pfizer, Arg.†*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; colorectal cancer; megaloblastic anaemia; reduction of methotrexate toxicity.

Rontagel *Ferring, Arg.; Pfizer, Arg.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Rontilona *Alter, Port.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Rontin *Biolab, Thai.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Rooilavental *Aspen Consumer, S.Afr.*
Nutmeg (p. 2573·1); cinnamon (p. 2479·2); red sanders wood; rosemary oil (p. 2607·3); lavender oil (p. 2541·1).
Dyspepsia; flatulence.

Ropa *Utopian, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Ropaccord *Douglas, NZ.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Ropam *LBS, Thai.*
Diazepam (p. 1063·2).
Anxiety disorders; skeletal muscle spasm.

Ropect *Scherer, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Ropen *LBS, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Ropenem *Sherrington, Philipp.*
Meropenem (p. 321·3).
Bacterial infections.

Ropermide *Medicpharma, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Ropi *Cristalia, Braz.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

Ropiconest *Pisa, Mex.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

Ropidopin *Medico Uno, Hung.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Ropigen *Biohorm, Spain.†*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Ropimed *Medis, Port.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Ropimol *Molteni, Pol.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

Ropin *Mylan, NZ.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism.

Ropinal *Mibe, Ger.*
Ropinirole (p. 913·2).
Restless legs syndrome; parkinsonism.

Ropinict *Sandoz, Denm.*
Ropinirole hydrochloride (p. 913·2).
Restless legs syndrome.

Ropinstad *Stada, Cz.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Ropion *Kaken, Jpn.*
Flurbiprofen axetil (p. 65·2).
Pain.

Ropirade *Clonmel, Irl.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Ropison *Glenmark, Cz.; Glenmark, Neth.*
Ropinirole hydrochloride (p. 913·2).
Parkinsonism; restless legs syndrome.

Ropramin *Iasis, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Propranolol *GPO, Thai.†*
⊗Propranolol (p. 1479·1).
Hypertension; phaeochromocytoma; arrhythmias; migraine; myocardial infarction; angina pectoris; hypertrophic cardiomyopathy; hyperthyroidism; anxiety; tremor.

Ropril *Aegis, Hong Kong.†*
Captopril (p. 1331·2).
Heart failure; hypertension.

Roprima *Miklich, Ital.*
Ropinirole (p. 913·2).

Ropsil *Medipharm, Chile.*
Clonazepam (p. 519·1).
Anxiety; panic disorder; epilepsy.

Roqurum *Jelfa, Pol.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

R.O.R. *Sanofi Pasteur, Fr.†*
A measles, mumps, and rubella vaccine (Edmonston 749D, Jeryl Lynn, and Wistar RA 27/3 strains respectively) (p. 2400·2).
Active immunisation.

Rorendo *KRKA, Cz.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rosa Graf *Natali, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Rosa Mosqueta Sun Protection *Aubrey, Canad.†*
SPF 12: Padimate O (p. 1716·1); titanium dioxide (p. 1725·1).
Sunscreen.

Rosac *GSK, USA.†*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Rosaced *Pierre Fabre Sante, Belg.*
Metronidazole (p. 936·1).
Rosacea.

Rosadan *Medimetriks, USA.*
Metronidazole (p. 936·1).
Rosacea.

Rosaderm *Rivers Edge, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Rosagenus *Leovan, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Rosal
Note: this name may be used for preparations of different composition.
Galenium, Indon.
Salicylic acid (p. 1719·1); resorcinol (p. 1718·3).
Acne.

Mylan, Neth.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Rosalgin *Medicom, Cz.; CSC, Hung.; Angelini, Port.; Angelini, Spain.*
Benzydamine hydrochloride (p. 29·2).
Cervicitis; genital hygiene; vulvovaginal disorders.

Rosaliac
Note: this name may be used for preparations of different composition.
Roche-Posay, Canad.
SPF 15: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1).
Sunscreen.

Roche-Posay, Chile; Roche-Posay, Irl.
Moisturiser.
Diffuses skin redness.

Rosalox *Medimport, Cz.; Drossapharm, Switz.*
Metronidazole (p. 936·1).
Rosacea.

Rosamet *Jadran, Rus.*
Metronidazole (p. 936·1).

Rosanil
Note: this name may be used for preparations of different composition.
Galderma, USA.
Sulfur (p. 1721·1); sulfacetamide sodium (p. 361·1).
Acne.

Loeffler, Mex.
Nitazoxanide (p. 942·2).
Protozoal infections; worm infections.

Rosapinol *Steierl, Ger.†*
Rosemary oil (p. 2607·3).
Rheumatic disorders; circulatory disorders.

Rosart *Actavis, Ukr.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Rosarthron *Steierl, Hung.*
Rosemary oil (p. 2607·3); pumilio pine oil (p. 2591·1).
Musculoskeletal and joint disorders; neuritis.

Rosasol *Stiefel, Canad.*
Metronidazole (p. 936·1); avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Rosacea.

Rosavit C *Biofarma, Mex.*
Ascorbic acid (p. 2110·3); rosa mosqueta.
Respiratory-tract disorders.

Rosazol *Actavis, Fin.; Actavis, Swed.*
Metronidazole (p. 936·1).
Rosacea.

Roscillin *Ranbaxy, India.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Roscilox *Ranbaxy, Hong Kong.†*
Ampicillin trihydrate (p. 218·2); cloxacillin sodium (p. 275·1).
Bacterial infections.

Rose Eye Ruby *Eng An, Hong Kong.†*
Chlorphenamine (p. 620·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Rose Hips C
Note: this name may be used for preparations of different composition.
Kripps, Canad.
Rose hips (p. 2607·1); vitamin C (p. 2110·3).

Rose Skin Care Anti-Aging *Natali, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Rosedex *Roux-Ocefa, Arg.*
Rosuvastatin (p. 1488·2).
Hyperlipidaemias.

Rosel *Wermar, Mex.*
Amantadine hydrochloride (p. 890·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Influenza symptoms.

Roseless *Melora, Port.†*
Metronidazole (p. 936·1).
Rosacea.

Rosemide *Millimed, Thai.†*
⊗Furosemide (p. 1387·1).
Oliguria; oedema; renal failure.

Rosemig *Montrose, Cz.*
Sumatriptan (p. 679·2).
Migraine.

Rosenda *Biofarma, Turk.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Roseti *Rafarm, Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Rosets *Akorn, USA.†*
Rose bengal sodium (p. 2607·1).
Ophthalmic diagnostic agent.

Rosette *Nobel, Turk.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Rosi *Trima, Israel.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Rosic *Pyridam, Indon.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Rosiced *Pierre Fabre Dermatologie, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Ital.; Pierre Fabre, Neth.; Pierre Fabre Dermo-Cosmetique, Port.; Pierre Fabre, UK.*
Metronidazole (p. 936·1).
Rosacea.

Rosicon *Glenmark, India.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Rosicon MF *Glenmark, India.*
Rosiglitazone maleate (p. 496·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Rosiden *Shin Poong, Singapore.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Rosiglit *Lazar, Arg.*
Rosiglitazone maleate (p. 496·3).
Diabetes mellitus.

Rosiglit-Met *Lazar, Arg.*
Rosiglitazone maleate (p. 496·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Rosil *Siam Bheasach, Thai.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmic encephalitis.

Rosilan *Vitoria, Port.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Rosimol *Sandoz, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias.

Rosiniol *Intermed, Gr.*
Flutamide (p. 798·2).

Rosinsuline R *Medsintez, Rus.*
⊗Soluble insulin injection (human) (p. 475·3).
Diabetes mellitus.

Rosinsuline S *Medsintez, Rus.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Rosipin *Medico Uno, Hung.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorders; bipolar disorder.

Rositol *Faran, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Rositaz *Abdi, Turk.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Rosivan *Etex, Chile.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Rosken Skin Repair *Pfizer, NZ.*
⊗Dimeticone (p. 2209·3); glycerol (p. 2517·2).
Barrier cream; bedsores; dry skin.

Pharmacare, Austral.; Pharmacare, Singapore.
Dimeticone (p. 2209·3).
Dry skin; dermatitis; dry or damaged skin.

Rosken Skin Repair High Potency *Pharmacare, Singapore.*
Tocoferil acetate (p. 2119·2); shea butter (p. 2208·2); theobroma oil (p. 2216·1); jojoba oil.
Dry or damaged skin; scars.

Rosken Skin Repair Vitamin E *Pharmacare, Singapore.*
Vitamin E (p. 2119·1).
Dry skin.

Rosone *Riva, Canad.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Rospaz *Rospaw, Arg.*
Alprazolam (p. 1035·2).
Anxiety.

Rossepar *Bio Health Care, Ital.*
Sodium ferric gluconate complex (p. 2089·1).
Iron-deficiency anaemia; iron deficiency.

Rossini *Trima, Israel.†*
Rosiglitazone hydrochloride (p. 496·3).
Diabetes mellitus.

Rossitrol *Sanofi-Aventis, Ital.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rossofolin *Professional Dietetics, Ital.*
Vitamins; minerals.

Rostiran *Vishpha, Ukr.*
Menthol (p. 2553·2); camphor (p. 2466·2); thymol (p. 1772·2); fir oil (p. 2591·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2).
Neuralgia; myalgia; joint pain; respiratory-tract disorders.

Rostrum *Casasco, Arg.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Rostvit *Obolenskoe, Rus.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Rosucard *Zentiva, Cz.; Zentiva, Pol.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Rosucol *Ajanta, Philipp.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Rosucor *Torrent, Braz.*
Rosuvastatin (p. 1488·2).

Rosula *PharmaDerm, USA.†*
⊗Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1); urea (p. 1727·3).
Acne.

Rosula NS *PharmaDerm, USA.†*
⊗Sulfacetamide sodium (p. 361·1); urea (p. 1727·3).
Acne.

Rosulip *Egis, Ukr.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Rosumed *Labomed, Chile.*
Rosuvastatin (p. 1488·2).
Hypercholesterolaemia.

Rosumop *Sandoz, Cz.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Rosustatin *Legrand, Braz.*
Rosuvastatin (p. 1488·2).

Montpellier, Arg.
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias; atherosclerosis.

Rosutech *Bilim, Turk.*
Rosuvastatin (p. 1488·2).

Rosuva *Rowex, Irl.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Rosuvas *Ranbaxy, India.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Rosuvast *Bago, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias; atherosclerosis.

EMS, Braz.
Rosuvastatin (p. 1488·2).

Rosvel
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Sanovel, Turk.
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Rotabiotic *Kendy, Ukr.*
Lactobacillus bulgaris (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3).
Maintenance of normal gastrointestinal flora.

Rotacin *Adelco, Gr.*
Erythromycin ethyl succinate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Rotadin *Anpharm, Pol.†; Egis, Pol.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Rotagermine *Humana, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins.
Restoration of gastrointestinal flora.

Rotamat *Unipharma, Gr.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Rotane *Sanofi-Aventis, India.*
Roxatidine acetate hydrochloride (p. 1884·3).
Peptic ulcer; gastro-oesophageal reflux.

Rotaqor *Sandoz, Malaysia.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Rotarix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.†; GSK, Jpn; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; Litha, S.Afr.; GSK, Singapore; GSK, Spain†; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA; GSK, Venez.*
A rotavirus vaccine (p. 2416·1).
Active immunisation.

RotaTeq *MSD, Arg.; CSL Biotherapies, Austral.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Merck Frosst, Canad.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.†; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Gr.; MSD, Hong Kong; MSD, Hung.; Sanofi Pasteur, Hung.; Sanofi Pasteur, Irl.; MSD, Israel; Sanofi Pasteur, Ital.; MSD, Jpn; MSD, Malaysia; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; MSD, NZ; MSD, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; MSD, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; MSD, Thai.; MSD, Turk.; Merck, USA.*
A live attenuated oral rotavirus vaccine (p. 2416·1).
Active immunisation.

Rotavit Royal *Rottapharm, Ukr.*
Vitamins; minerals; bee pollen (p. 2593·3); ginseng (p. 2513·3); royal jelly (p. 2608·1); soy lecithin (p. 2542·2); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Roter APC *Imgroma, Neth.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Roter Noscapect *Imgroma, Neth.*
Noscapine hydrochloride (p. 1670·3).
Cough.

Roter Paracof *Imgroma, Neth.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Roteroblong Maagtabletten *Imgroma, Neth.*
Bismuth subnitrate (p. 1822·1); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); frangula bark (p. 1843·3).
Peptic ulcer; gastritis; duodenitis; gastric hyperacidity.

Rothacin *Julphar, UAE.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea; gout.

Rothonal *Farmamust, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Rothricin *Siam Bheasach, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rothrin *Iapharm, Gr.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; osteoporosis.

Roth's RKT Tropfen *Infirmarius, Ger.*
⊗Ammonium bromatum (p. 2461·1); arnica montana (p. 2447·2); bellis perennis (p. 2454·2); calcium phosphoricum (p. 1784·2); causticum (p. 2595·3); dactylopius coccus (p. 2179·2); drosera (p. 2497·2); spongia; hepar sulfuris (p. 1721·3); hyoscyamus niger (p. 2530·2); hypericum perforatum (p. 449·1); kalium stibyltartaricum (p. 151·2); lobelia inflata (p. 2323·2); melissa officinalis (p. 2552·3); oenanthe aquatica; primula veris (p. 2596·2); tussilago farfara (p. 1659·2).
Homoeopathic preparation.

Roth's Rotacard *Infirmarius, Ger.*
Arnica montana (p. 2447·2); aurum iodatum (p. 2521·2); camphora (p. 2466·2); chamomilla recutita (p. 2474·1); convallaria majalis (p. 2486·2); crataegus (p. 2488·1); equisetum arvense (p. 2500·1); phosphorus (p. 2589·2); acidum silicicum (p. 2208·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Rotiaz *Richmond, Arg.†*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Rotifar *Duopharma, Hong Kong†; CCM, Malaysia.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Rotilen *Terapeutico, Ital.*
Methacycline hydrochloride (p. 322·3).
Bacterial infections.

Rotocan *Vilar, Rus.*
Calendula (p. 2465·2); chamomile (p. 2474·1); achillea (p. 2427·3).
Mouth disorders.

Rotocin *Rotexmedica, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Rotomide *Rotexmedica, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Rotova *Minerva, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Rotpunkt Apotheke dragées contre les maux de voyage *Parcopharm, Switz.*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Motion sickness.

Rotpunkt Apotheke Mucolytique Sirop *Parcopharm, Switz.†*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion; cough.

Rotpunkt Apotheke nouvelle formule pastilles contre le mal de gorge *Parcopharm, Switz.†*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat pain and inflammation.

Rotpunkt Apotheke pastilles pour les bronches avec codeine *Parcopharm, Switz.*
Codeine phosphate (p. 40·2); tolu balsam (p. 1679·2); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); levomenthol (p. 2553·2); liquorice (p. 1853·2).
Coughs.

Rotrace *Ace, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Rotram *Ranbaxy, Braz.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rotuss *Scherer, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Roug-Mycin *Pharmanik (Φαρμανικ), Gr.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Rouvax *Sanofi Pasteur, Fr.; Pasteur Merieux, Israel†; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Turk.*
A measles vaccine (Schwarz strain) (p. 2398·3).
Active immunisation.

Vianex (Βιανεξ), Gr.
An attenuated measles and mumps vaccine (RIT 4385 and Schwarz strains, respectively) (p. 2400·1).
Active immunisation.

Rovacid *Farmak, Ukr.†*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis.

Rovacor *Ranbaxy, India; Ranbaxy, Rus.; Ranbaxy, Singapore.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; atherosclerosis; hypercholesterolaemia.

Rovadin *Otto, Indon.*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis.

Rovagyl *Medifarma, Turk.*
Spiramycin (p. 358·3).

Rovalcyte *Roche, Fr.; Roche, Port.*
Valganciclovir hydrochloride (p. 1022·1).
Cytomegalovirus infections.

Rovamax *Darvys, Philipp.*
Spiramycin (p. 358·3).
Bacterial infections; protozoal infections.

Rovamicina *Sanofi-Aventis, Braz.; Sanofi-Aventis, Ital.*
Spiramycin (p. 358·3).
Bacterial infections.

Rovamycin *Gerot, Austria; Piramal, India; Sanofi-Aventis, Norw.*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis.

Rovamycine *Sanofi-Aventis, Arg.; Sanofi-Aventis, Belg.; Odan, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Teofarma, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.†; Sanofi-Aventis, Thai.; Eczacibasi, Turk.; Sanofi-Aventis, Ukr.*
Spiramycin (p. 358·3).
Bacterial infections; toxoplasmosis; rheumatic fever prophylaxis; cryptosporidiosis; meningococcal meningitis prophylaxis; amoebic dysentery.

Rovartal *Roemmers, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Rovas *Medis, Ital.*
Atorvastatin (p. 1309·2).

Rovelan *EMS, Braz.*
⊗Furosemide (p. 1387·1).

Rovenal *Leciva, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rovericlin *SJA, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Roveril *Roux-Ocefa, Arg.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Fever; nasal congestion; pain.

Roverton *Ifars, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Rovigon *Bayer, Ital.*
Vitamin A (p. 2098·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Tissue degeneration.

Bayer, Belg.†; Bayer, Chile†; Bayer, Port.†
Vitamin A palmitate (p. 2098·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Vitamin A and E deficiency; dietary supplement.

Piramal, India; Bayer, Philipp.
Vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Vitamin A and E deficiency; disorders of vision.

Rovita *Lejal, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Rovix *Ultramed, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Rovoxid *Pharmanel, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Rowachol *Rowa, Hong Kong; Rowa, Israel; Rowa, Malaysia; Rowa, Thai.; Meadow, UK.*
Menthol (p. 2553·2); menthone (p. 2554·2); pinene (p. 2591·3); borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1).
Gallstones; biliary tract disorders; liver disorders; diabetes mellitus.

Rowa, Philipp.; Zuoz, Venez.
Menthol (p. 2553·2); menthone (p. 2554·2); pinene (p. 2591·3); borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1).
Hepatobiliary disorders; hyperemesis gravidarum; diabetes; dyspepsia.

Nexis, Spain.
Menthol (p. 2553·2); pinenes (p. 2591·3); borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1); emodin; oxidised terpenes.
Hepatobiliary disorders.

Raffo, Chile.
Natural terpenes.
Biliary-tract disorders; liver disorders.

Rosch & Handel, Austria; Rowa, Cz.; Rowa, Ger.; Rowa, Hung.; Rowa, Irl.; Rowa-Wagner, Pol.
Menthol (p. 2553·2); menthone (p. 2554·2); α-pinene (p. 2591·3); β-pinene (p. 2591·3); borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1).
Dyspepsia; hepatobiliary disorders.

Rowadermat *Rosch & Handel, Austria.*
Carbenoxolone sodium (p. 1825·3).
Herpes labialis; aphthous ulcers.

Rowagel *Rowa, Philipp.*
Carbenoxolone sodium (p. 1825·3).
Mouth and face lesions.

Rowalind *Rosch & Handel, Austria.*
Nicotinaldehyde (p. 2569·2); strong ammonia solution (p. 2441·2); ammonium chloride (p. 1656·1); camphor (p. 2466·2); menthol (p. 2553·2); rosemary oil (p. 2607·3); lavender oil (p. 2541·1).
Musculoskeletal, joint, and soft-tissue disorders; neuritis; neuralgia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rowanefrin *Nexis, Spain.*
Anethole (p. 2443·3); borneol (p. 2460·2); camphene (p. 2466·2); rubia tinctorum; oxidised terpenes; pinenes (p. 2591·3); fenchone (p. 2503·1); cineole (p. 2479·1).
Renal calculi; urinary-tract disorders.

Rowarolan *Rowa, Irl.*
Calcium carbonate (p. 1824·3).
Adsorbent in ulcers and sores.

Rowa, Malaysia.
Calcium carbonate (p. 1824·3); silica (p. 2209·1); talc (p. 1722·2).
Minor wounds; ulcers.

Rowasa *Abbott, Fr.; Alaven, USA.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease; ulcerative colitis; proctosigmoiditis; proctitis.

Rowatanal *Rowa, Hong Kong; Rowa, Malaysia; Rowa, Singapore.†*
Bismuth subgallate (p. 1822·1); menthol (p. 2553·2); zinc oxide (p. 1729·1); calcium carbonate (p. 1824·3).
Anorectal disorders; anal irritation; haemorrhoids.

Rowa, Irl.
Bismuth subgallate (p. 1822·1); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Haemorrhoids; anal irritation.

Rowatinex *Eurolab, Arg.; Rosch & Handel, Austria; Rowa, Cz.; Rowa, Ger.; Rowa, Hung.; Rowa, Irl.; Rowa-Wagner, Pol.; Rowa, Rus.*
α-Pinene (p. 2591·3); β-pinene (p. 2591·3); camphene (p. 2466·2); cineole (p. 2479·1); fenchone (p. 2503·1); borneol (p. 2460·2); anethole (p. 2443·3).
Renal calculi; urinary-tract disorders.

Raffo, Chile; Rowa, Hong Kong; Rowa, Israel; Rowa, Malaysia; Rowa, Thai.
Pinene (p. 2591·3); camphene (p. 2466·2); borneol (p. 2460·2); anethole (p. 2443·3); fenchone (p. 2503·1); cineole (p. 2479·1).
Urinary-tract disorders; renal calculi.

Rowa, Philipp.; Zuoz, Venez.
Pinene (p. 2591·3); camphene (p. 2466·2); borneol (p. 2460·2); anethole (p. 2443·3); fenchone (p. 2503·1); cineole (p. 2479·1).
Renal calculi; urinary-tract disorders.

Röwo Rytesthin Rö-Plex (Röwo-318) *Asconex, Ger.*
Myristica fragr. (p. 2573·1); strychnos ignatii (p. 2532·1); valeriana off. (p. 2640·2).
Homoeopathic preparation.

Röwo Vitamin B_{12} *Asconex, Ger.*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Roxacilin *Royton, Braz.*
Oxacillin (p. 336·2).
Bacterial infections.

Roxalia *Boiron, Canad.*
Arnica montana (p. 2447·2); arum triphyllum; belladonna (p. 2453·3); bromium (p. 2461·2); bryonia alba (p. 2461·3); mercurius solubilis (p. 2555·3); pulsatilla (p. 2600·2); phytolacca decandra (p. 2593·2); spongia tosta.
Homoeopathic preparation.

Roxamycin *Inpac, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxane *Lavipharm, Gr.*
Roxatidine acetate hydrochloride (p. 1884·3).
Peptic ulcer.

Roxanne *AFT, NZ.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Roxanol *aai, USA.*
⊗Morphine sulfate (p. 92·3).
Pain.

Roxar *Aspen, Austral.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxazin *Basi, Port.*
Piroxicam (p. 125·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Roxbi *Sandoz, Indon.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Roxcin *Biolab, Malaysia; Biolab, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Roxee *Cipla, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxem *Aristo, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxene *Pliva, Ital.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation.

Roxenil *Caber, Ital.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Roxepar *Labomed, Chile.*
Paroxetine hydrochloride (p. 440·3).
Depression; panic disorder; premenstrual dysphoric disorder; social phobia.

Roxeptin *Ipca, India; Ipca, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxeptin-ME *Ipca, India.*
Roxithromycin (p. 356·2); ambroxol (p. 1654·3).
Respiratory-tract infections associated with viscous mucus.

Roxera *KRKA, Ukr.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Roxetil *Merren, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Roxetin *Cristalia, Braz.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Roxflan *Merck, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Roxi *1A, Ger.†; CT, Ger.†; Riemser, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxibeta *Betapharm, Ger.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxibid *Cadila, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxibron *Viofar, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxicam *Utopian, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Roxicef *Caplin, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Roxicet *Roxane, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Roxicillin *Farmellas, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxicin *Atlantic, Hong Kong; Atlantic, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections of the respiratory tract; bacterial infections; meningococcal meningitis prophylaxis.

Roxicodone *aai, USA.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Roxicur *Velka, Gr.*
Roxithromycin (p. 356·2).

Roxicure *Ajanta, Venez.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxid *Alembic, India; Metz, Philipp.; Alembic, Singapore; Alembic, Ukr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxide *Sandoz, Austral.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxiden *Boniscontro & Gazzone, Ital.*
Piroxicam (p. 125·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal, joint, and peri-articular disorders.

Roxidene *Combiphar, Indon.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Roxidolin *Raam, Mex.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Roxifect *Bangkok Lab & Cosmetic, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxifen
Note: this name may be used for preparations of different composition.
Gulf Drug, S.Afr.; TO-Chemicals, Singapore; TO-Chemicals, Thai.
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

LBS, Philipp.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Roxigamma *Worwag, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxigrün *Grunenthal, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

RoxiHexal *Hexal, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxihexal *Hexal, Rus.; Sandoz, Ukr.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxil *YSS, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxilan *Olan-Kemed, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Roxilid *Darnitsa, Ukr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxilox *Roxane, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Roxime *Steinbach, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Roximed *Medhaus, Philipp.; Burapha, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roximeth *CCM, Malaysia; Duopharma, Singapore.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Roximin *Novis, Gr.; Pharmaland, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roximstad *Pharmacodane, Denm.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roximycin *Alphapharm, Austral.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxin
Note: this name may be used for preparations of different composition.
Aspen, Austral.
Norfloxacin (p. 333·3).
Bacterial infections.

Ulagay, Turk.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Roxina *Cazi, Braz.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxine
Note: this name may be used for preparations of different composition.
Duopharma, Hong Kong†; CCM, Malaysia.
Dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Pharmasant, Thai.
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Motion sickness; nausea and vomiting in pregnancy; radiation sickness.

Roxino *Suphong, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxinox *Deltapharm, Hong Kong†; Charoen Bhaesaj, Malaysia; Charoen, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxinpac *Inpac, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxipan *Panpharma, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; lactation promotion.

Roxi-Puren *Actavis, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxi-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxiratio *Ratiopharm, Pol.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxi-saar *MIP, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxit *Sanofi-Aventis, Ital.*
Roxatidine acetate hydrochloride (p. 1884·3).
Peptic ulcer; gastro-oesophageal reflux.

Roxitaz *Brown & Burk, Philipp.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxitazon *Aivax, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxithro *Millimed, Philipp.; Millimed, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxithro-Lich *Winthrop, Ger.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxithrostad *Stada, Austria.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxithroxyl *Bangkok Lab & Cosmetic, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Roxitin *TP, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxitop *Farmaline, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Roxitran *Neo Quimica, Braz.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxitrol *Grunenthal, Venez.*
Roxithromycin (p. 356·2).
Bacterial infections.

Farmellas, Gr.
Pantoprazole sodium (p. 1875·3).

Roxitrom *Biolab Sanus, Braz.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxitron *ICN, Pol.; Tecnimede, Port.; RX, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxium *M & H, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Roxivinol *Ferakon, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxivista *Cadila, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxl *XL, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxlecon *Pond's, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxo *Trima, Israel.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxodyn *Indeco, Arg.*
Risperidone (p. 1103·2).

Roxoid *Roxall, Ger.*
Allergen extracts of pollen (p. 2593·3), mites (p. 2434·3), fungus, and animal skin (p. 2434·3).
Allergen immunotherapy.

Roxolac *Pierre Fabre, Ital.*
Ciclopirox (p. 575·3).

Roxolan *Nova Argentia, Arg.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; atherosclerosis.

Roxomycin *Silom, Thai.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxon *Karnataka, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Roxorin *Richmond, Arg.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Roxthomed *Medicine Products, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxthrin *TO-Chemicals, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxto *M & H, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxtrocin *Greater Pharma, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Roxulide *Hexal, S.Afr.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxuril *Pharmanel, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxxibid *Cipla-Medpro, S.Afr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxxo *Pharmahof, Thai.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxy *Sriprasit, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxybel *Nobel, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxycam *Greater Pharma, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Roxycan *T Man, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Roxydin *GreatEastern, Thai.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxydral *Proel, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Roxy-Due *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxylor *Shreya, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxym *Asia Pharma, Philipp.†*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Roxyrol *Concept, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Roxyspes *Alet, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Royal E *Cielle, Ital.*
Royal jelly (p. 2608·1); vitamin E (p. 2119·1).
Nutritional supplement.

Royal Life *Bioceuticals, UK.*
Vitamins minerals; amino acids.

Royal-C *ANH, Thai.*
Sodium chloride (p. 1795·1).
Constipation.

Royalin *TO-Chemicals, Thai.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease; cough.

Royen *Omedir, Arg.; Rubio, Spain.*
Calcium acetate (p. 1783·1).
Calcium supplement; hyperphosphataemia.

Royflex
Note: this name may be used for preparations of different composition.
Royton, Braz.
Orphenadrine citrate (p. 909·2); caffeine (p. 1203·3); dipyrone (p. 53·3).

Royken *Kendrick, Mex.*
Phytomenadione (p. 2122·2).
Haemorrhagic disorders.

Royl 6 *Adcock Ingram, S.Afr.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Roytrin *Royton, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Royvac *Waymar, Canad.†*
Magnesium citrate (p. 1857·1).

Royvac Kit *Waymar, Canad.†*
Oral solution, magnesium citrate (p. 1857·1); 3 tablets, bisacodyl (p. 1821·1); 1 suppository, bisacodyl.
Bowel evacuation.

Roza *Orva, Turk.*
Metronidazole (p. 936·1).
Rosacea.

Rozacom *Adamed, Pol.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Rozacrème *Bailleul, Fr.*
Metronidazole (p. 936·1).
Rosacea.

Rozagel *Bailleul, Fr.*
Metronidazole (p. 936·1).
Rosacea.

Rozalin *Adamed, Pol.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Rozek *Galderma, Venez.*
Metronidazole (p. 936·1).
Rosacea.

Rozerem *Takeda, Indon.; Takeda, Jpn; Takeda, Philipp.; Takeda, USA.*
Ramelteon (p. 1103·1).
Insomnia.

Rozex *Galderma, Arg.; Galderma, Austral.; Galderma, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Cz.; Galderma, Denm.; Galderma, Fin.; Galderma, Fr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Israel; Galderma, Ital.; Galderma, Malaysia; Galderma, Neth.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Pol.; Galderma, Rus.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Spain; Galderma, Swed.; Galderma, Switz.; Galderma, UK·*
Metronidazole (p. 936·1).
Rosacea; acne; bacterial vaginosis; wounds; ulcers.

Rozicel *BMS, Ital.†*
Cefprozil (p. 248·2).
Bacterial infections.

Rozidal *Ranbaxy, India; Ranbaxy, Malaysia.*
Risperidone (p. 1103·2).
Psychoses; bipolar disorder.

Rozolam *Farmedia, Gr.*
Ciclopirox olamine (p. 575·3).
Fungal vaginal infections.

Rozon *Ulkar, Turk.†*
Ranitidine hydrochloride (p. 1882·1).

Rozovin *Pharmanik (Φαρμανικ), Gr.*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal and joint disorders.

Roztwor Elkintona Nr 2 *Pliva Krakow, Pol.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Fluid and electrolyte disorders.

Rozucard *Zentiva, Ukr.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

R-Pril *Biochem, India.*
Ramipril (p. 1483·3).
Heart failure; hypertension.

R-Rax *Medicine Products, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; anxiety; premedication.

RT Gen *T Man, Thai.†*
Oral gel: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

T Man, Thai.†
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

R-Tanna *Duramed, USA†*
Suspension: Phenylephrine tannate (p. 1672·2); mepyramine tannate (p. 635·1).
Upper respiratory-tract disorders.

R-Tanna S Pediatric *Prasco, USA.†*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

R-Tannamine *Qualitest, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Upper respiratory-tract symptoms.

R-Tannate *Copley, USA; Schein, USA; Warner Chilcott, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Allergic rhinitis; nasal congestion.

R-Tyflam *Rayere, Mex.†*
Piroxicam (p. 125·3).
Inflammation; pain.

Ru Ning *Conba, China.*
Fluconazole (p. 578·2).
Fungal infections.

Ru Shuang Qi *Kangliyuan, China.*
Azithromycin lactobionate.
Bacterial infections.

Ru Su Mei *Minsheng, China.*
⊗Exemestane (p. 792·2).
Breast cancer.

Rub A-535 Antiphlogistine *Church & Dwight, Canad.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal pain.

Rub A-535 Antiphlogistine Capsaicin *Church & Dwight, Canad.*
Capsaicin (p. 35·1).
Musculoskeletal and joint pain.

Rub A-535 Antiphlogistine Ice *Church & Dwight, Canad.*
Menthol (p. 2553·2).
Musculoskeletal pain.

Rub A-535 Antiphlogistine No Odour *Church & Dwight, Canad.*
Trolamine salicylate (p. 141·2).
Musculoskeletal pain.

Rub A-535 Extra Strength Arthritis *Church & Dwight, Canad.*
Capsaicin (p. 35·1); menthol (p. 2553·2); trolamine salicylate (p. 141·2).

Rub-Arom *Hasco-Lek, Pol.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thymol (p. 1772·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint disorders; neuralgia; cold symptoms.

Rubbex *Vitalab, Canad.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Rubeaten *Faran, Gr.*
An attenuated rubella vaccine (Wistar RA27/3 strain) (p. 2417·1).
Active immunisation.

Rubens *Nevzat, Turk.*
Epirubicin hydrochloride (p. 787·1).

Rubesal *Hamilton, Austral.; Hamilton, Hong Kong.†*
Diethylamine salicylate (p. 51·3); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Rubex
Note: this name may be used for preparations of different composition.
BMS, Braz.
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Rice Steele, Irl.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Rubi *Gador, Arg.*
4 Tablets, estradiol valerate (p. 2271·2); 22 tablets, estradiol valerate; dienogest (p. 2267·2); 2 tablets, inert.
Multiphasic oral contraceptive.

Rubia Complexe No 3 *Lehning, Fr.*
Rubia; berberis vulgaris (p. 2502·1); atropa belladonna (p. 2453·3); terebenthina; pareira brava; acide benzoicum (p. 1738·2).
Homoeopathic preparation.

Rubicalm *Julphar, UAE.*
Diethylamine salicylate (p. 51·3); menthol (p. 2553·2).
Musculoskeletal pain.

Rubide *Lens, Rus.*
Idarubicin hydrochloride (p. 805·2).
Acute leukaemias; breast cancer.

Rubi-Dex *Cazi, Braz.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

Rubidexol *Pisa, Mex.*
⊗Methadone hydrochloride (p. 88·3).
Pain; opioid dependence.

Rubidox
Note: this name may be used for preparations of different composition.
Bergamo, Braz.; Medicus, Gr.; Sandoz, Indon.†; Baxter, Philipp.†
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Rubifen *Neuropharma, Arg.; Rubio, Malaysia; AFT, NZ; Rubio, Port.; Rubio, Singapore; Rubio, Spain.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome; hyperkinetic syndrome; minimal brain dysfunction.

Rubifort *Kinder, Braz.†*
Vitamin A palmitate (p. 2098·3); colecalciferol (p. 2113·1).
Vitamin A and D supplement.

Rubilem *Teva, Mex.*
Daunorubicin hydrochloride (p. 778·3).
Malignant neoplasms.

Rubimar *Arrow, Cz.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Rubimycin *Pharmacare, S.Afr.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Rubina *Eurofarma, Braz.†*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Rubiprol *Proel, Gr.*
Epirubicin hydrochloride (p. 787·1).

Rubira *Sandoz, Denm.; Sandoz, Norw.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Rubiron *Rovafarm, Arg.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; nutritional supplement.

Rubis *Cristalfarma, Ital.*
Cranberry (p. 2488·1); pomegranate (p. 164·1).
Urinary-tract disorders.

Rubisan *DHU, Austria; DHU, Cz.; DHU, Ger.; Peithner, Hung.; VSM, Neth.†*
Mahonia aquifolium (p. 2577·1).
Homoeopathic preparation.

Rubital *Gemi, Pol.*
Althaea (p. 2438·3).
Respiratory-tract inflammation; cough.

Rubital Compositum *Gemi, Pol.*
⊗Althaea (p. 2438·3); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract inflammation; cough.

Rubiten *Rafarm, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Rubjovit *SIFI, Ital.*
Rubidium iodide (p. 2608·2); sodium iodide (p. 2337·1); calcium formate (p. 2507·1);

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

sodium ascorbate (p. 2111·1); thiamine hydrochloride (p. 2103·1).
Cataracts.

Rublex D *Don, Israel.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); salicylic acid (p. 1719·1).
Musculoskeletal and joint pain.

Rublex Massage Cream *Don, Israel.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint pain.

Rubocord *Rafarm, Gr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Ruboderm *Labcatal, Fr.*
Zinc gluconate (p. 2126·2); copper gluconate (p. 2057·2); gluconolactone (p. 2515·2).
Acne; seborrhoea.

Rubophen *Zentiva, Hung.*
Paracetamol (p. 115·1).
Fever; pain.

Ruboril
Note: this name may be used for preparations of different composition.
D & M, Chile.
Enoxolone (p. 54·2); levomenol (p. 2544·1).
Facial flushing; rosacea.

Darier, Mex.
Barrier cream.

Ruboril Al *D & M, Chile.*
Boswellia (p. 2507·3); madecassoside (p. 1698·3); plukenetia volubilis seed oil.
Skin redness; skin irritation.

Rubozinc *Labcatal, Fr.*
Zinc gluconate (p. 2126·2).
Acne; acrodermatitis enteropathica.

Rubramin *BMS, Philipp.†*
Cyanocobalamin (p. 2107·2).
Vitamin B_{12} deficiency.

Rubranova *BMS, Braz.*
Hydroxocobalamin (p. 2107·3).
Vitamin B_{12} deficiency; megaloblastic anaemia.

Rubraplex *Piramal, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1).
Anaemia.

Rubrargil *IQB, Braz.*
Ferric ammonium citrate (p. 2060·1); vitamin B_{12} (p. 2107·2); copper sulfate (p. 2057·2); liver extract (p. 2444·1); gastric mucosa extract (p. 2444·1).
Iron deficiency; iron-deficiency anaemias.

Rubrargil Minerals *IQB, Braz.*
Vitamins; minerals.

Rubriment *Pharmonta, Austria.*
Benzyl nicotinate (p. 29·3); nonivamide (p. 102·3); glycol salicylate (p. 66·2); salicylamide (p. 129·2); camphor (p. 2466·2); turpentine oil (p. 2636·3).
Joint, muscle, and nerve disorders; sport massage; peripheral vascular disorders; frostbite.

Riemser, Ger.†
Bath additive: Benzyl nicotinate (p. 29·3).
Bath additive; peripheral vascular disorders; rheumatism.

Riemser, Ger.†
Ointment: Benzyl nicotinate (p. 29·3); nonivamide (p. 102·3).
Frostbite; inflammation; musculoskeletal and joint disorders; peripheral vascular disorders.

Rubriment-BN *Riemser, Ger.†*
Benzyl nicotinate (p. 29·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; peripheral vascular disorders.

Rubrinal *Vargas, Venez.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1) or thiamine nitrate (p. 2103·2).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Vitamin B deficiency; peripheral neuropathy.

Rubrinex *Vargas, Venez.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Peripheral neuropathy.

Rubrojunior *Piam, Ital.*
Lactoferrin (p. 2539·3); zinc (p. 2126·1); vitamin B substances (p. 2102·3).
Nutritional supplement.

Rubrovital *Piam, Ital.*
Lactoferrin (p. 2539·3); vitamin B substances (p. 2102·3); zinc (p. 2126·1).
Tonic.

Rubrum
Note: this name may be used for preparations of different composition.
Nolver, Venez.
Granisetron (p. 1844·3).
Nausea and vomiting.

Target, Gr.
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Rucaten Forte *Ivax, Arg.*
Acemetacin (p. 16·3); chlorzoxazone (p. 2022·2).
Musculoskeletal, joint, and peri-articular disorders.

Rucaten Prednisolona *Ivax, Arg.*
⊗Acemetacin (p. 16·3); prednisolone (p. 1645·2); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).
Musculoskeletal and joint disorders with neuritis.

Rucef *Lloyd, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Rucela *Verisfield, Gr.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial infections.

Rucin *General Drugs, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ruconest *Pharming, Cz.; Swedish Orphan, Denm.; Swedish Orphan, Fr.; Swedish Orphan, Ger.; Pharming, Irl.; Pharming, Neth.; Swedish Orphan, Norw.; Pharming, Pol.; Pharming, Port.; Swedish Orphan, Swed.; Swedish Orphan, UK.*
Conestat alfa (p. 2485·1).
Hereditary angioedema.

Rudd-U *Frankin, China.*
Oxyphencyclimine hydrochloride (p. 1875·1); simeticone (p. 1886·2); methiosulfonium chloride (p. 2558·1); magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2).
Gastrointestinal disorders.

Rudin *HPP, Hong Kong.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rudistrol *Boiron, Canad.†; Boiron, Neth.†*
Ledum palstre (p. 2550·1); rhododendron ferrugineum; rhus toxicodendron (p. 2603·3); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Boiron, Fr.†
Polyglycolysed glycerides; rhus toxicodendron (p. 2603·3); rhododendron ferrugineum; ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Rudivax *Sanofi Pasteur, Arg.; Sanofi, China; Sanofi Pasteur, Fr.; Aventis Pasteur, Israel; Sanofi Pasteur, Port.†; Sanofi Pasteur, Rus.; Aventis, S.Afr.†*
A rubella vaccine (Wistar RA 27/3M strain) (p. 2417·1).
Active immunisation.

Rudocain *Streuli, Switz.*
Articaine hydrochloride (p. 1980·1).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Rudocyclin *Streuli, Switz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Rudolac *Streuli, Switz.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Rudotel *AWD, Ger.; AWD, Hung.; AWD, Pol.; AWD, Rus.*
Medazepam (p. 1083·2).
Anxiety; migraine; menopausal disorders; alcohol withdrawal syndrome.

Rudoxil *Phoenix, Arg.*
⊗Carvedilol (p. 1333·1) or carvedilol phosphate (p. 1333·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Ruefrien *Nichi-Iko, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Rufebran allergo *Staufen, Ger.†*
Aralia racemosa; atropinum sulfuricum (p. 1310·2); formica rufa; jodum (p. 2336·3); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Rufebran broncho *Staufen, Ger.†*
Cuprum metallicum (p. 2057·1); hepar sulfuris (p. 1721·3); antimonium sulfuratum aurantiacum (p. 2445·1); tartarus stibiatus (p. 151·2); yerba santa (p. 1665·2).
Homoeopathic preparation.

Rufebran gastro *Staufen, Ger.†*
Acidum nitricum (p. 2572·3); argentum nitricum (p. 2615·3); arsenicum album (p. 2448·1); atropinum sulfuricum (p. 1310·2); cadmium sulfuricum (p. 2463·3); kalium bichromicum (p. 2476·3).
Homoeopathic preparation.

Rufebran heparo *Staufen, Ger.†*
Carduus benedictus (p. 2482·2); carduus marianus (p. 1561·1); chelidonium (p. 2522·2); stannum metallicum (p. 2632·1).
Homoeopathic preparation.

Rufebran lympho *Staufen, Ger.†*
Arsenum jodatum (p. 2448·1); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Rufebran neuro *Staufen, Ger.†*
Aconitum (p. 2428·3); formica rufa; magnesium phosphoricum (p. 1787·3).
Homoeopathic preparation.

Rufebran regeno *Staufen, Ger.†*
Acidum phosphoricum (p. 2589·1); kalium phosphoricum (p. 1790·3); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Rufebran rheumo *Staufen, Ger.†*
⊗Acidum formicicum (p. 2507·1); ammonium phosphoricum (p. 2442·1); silicea (p. 2208·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Rufebran thyreo *Staufen, Ger.†*
Ferrum jodatum (p. 2061·3); lycopus virginicus (p. 2462·2).
Homoeopathic preparation.

Ruflex *Sunpab, Philipp.*
Glucosamine hydrochloride (p. 2515·3); manganese (p. 2081·2); gotu kola (p. 1698·3); ginger (p. 1844·1); celery (p. 2472·3).
Joint pain and stiffness.

Sunpab, Singapore.
Glucosamine hydrochloride (p. 2515·3); manganese amino acid chelate (p. 2048·3); centella (p. 1698·3); ginger (p. 1844·1); celery seed (p. 2472·3).
Rheumatoid arthritis.

Rufol *Urgo, Fr.*
Sulfamethizole (p. 365·1).
Cystitis.

Rugantil *Gelfipharma, Ital.†*
Sodium hyaluronate (p. 2526·2).

Rug-Derm *Remexa, Mex.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts.

Rui Di *Sanhome, China.*
Ribavirin (p. 1010·2).
Respiratory syncytial virus infection.

Rui Bai *Qilu, China.*
A granulocyte colony-stimulating factor (human, recombinant).

Rui Bei Ke *Jiangxi, China.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Rui Bo Te *Hanson, China.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Rui Chen *Liang Fu, China.*
Zaleplon (p. 1114·3).
Insomnia.

Rui Da *Ouhua, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Rui Da Xin *Aida, China.*
Gatifloxacin mesilate.
Bacterial infections.

Rui Er Xin *Xinxing, China.*
Pilocarpine nitrate (p. 2010·3).
Dry mouth; dry eye.

Rui Fei *Hengrui, China.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Rui Fu *Lantai, China.*
Loratadine (p. 633·2).
Allergic disorders.

Rui Fu An Kang *HongQi, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Rui Fu Xin *Kairuite, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Rui Gan *QR, China.*
Ornithine aspartate (p. 2085·2).
Liver disorders.

Rui Ge Lin *Rongtai, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Rui Jian *An Te, China.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; gastritis.

Rui Jie *RenFu, China.*
⊗Remifentanil hydrochloride (p. 128·1).
Analgesia in anaesthesia.

Rui Kai Ping *Si Huan Ke Bao, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Rui Kang *Shunfeng, China.*
Ciprofloxacin hydrochloride (p. 261·2).

Rui Ke An *Weigao, China.*
Aceglutamide (p. 2426·2).

Rui Ke Jie *Wei Lun, China.*
Asarone.

Rui Ke Lin *Si Huan Ke Bao, China.*
Ligustrazine hydrochloride.

Rui Ke Sha *Ke Lun, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Rui Li *Sanrui, China.*
Nimesulide (p. 1013).
Pain.

Rui Li Da *Si Huan Ke Bao, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Rui Li Ping *Pingli, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Rui Li Su *Lingkang, China.*
Huperzine A.

Rui Li Tai *Si Huan Ke Bao, China.*
Diclofenac sodium (p. 48·3); lidocaine hydrochloride (p. 1988·2).

Rui Li Xi *Si Huan Ke Bao, China.*
Isosorbide dinitrate (p. 1412·2).
Unstable angina; heart failure.

Rui Lian *Dawnrays, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Rui Lin Li Er *GuoRui, China.*
Matrine.

Rui Ling Ju *Lingkang, China.*
Enoxacin gluconate.
Bacterial infections.

Rui Luo Jian *Lingkang, China.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced sedation; opioid overdose.

Rui Na Ti *Lv Yin, China.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Rui Nuo Mei Xin *Jiangxi, China.*
Micronomicin sulfate (p. 324·2).

Rui Nuo Sai *Huaren, China.*
Tobramycin (p. 380·1).
Bacterial infections.

Rui Nuo Shu *Guangdong, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Rui Pa Ming *KeRui, China.*
Sirolimus (p. 1966·2).
Renal transplant rejection.

Rui Pei En *Guofeng Weiao, China.*
Diclofenac sodium (p. 48·3).

Rui Peng *GuoRui, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Rui Ping *XinShiDai, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Rui Pu Le *Zhongrui Kangzhi, China.*
Nimesulide (p. 101·3).
Pain.

Rui Qi *GuoRui, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Rui Qi Lin *Qian Long, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Rui Qi Tai *Lingkang, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Rui Qin Yuan *Lingkang, China.*
Fructose (p. 2068·2); glucose (p. 2068·3).

Rui Qing *Anlian, China.*
Isoniazid (p. 311·2); pyrazinamide (p. 345·2); rifampicin (p. 350·3).
Tuberculosis.

Rui Ri *Rui Yang, China.*
Sodium alginate diester.

Rui Shan *Ke Lun, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Rui Shen *Minophagen, China.*
Ornidazole (p. 943·1).

Rui Sheng Yi *Sunnyhope, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Rui Shi *Huatuo Tianya, China.*
Matrine.

Rui Shi Kang *Guangdong, China.*
Lysine hydrochloride (p. 2079·3).

Rui Si *Huali Nanhu, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Rui Si Tuo *Tsinghua Yuanxing, China.*
Oxymatrine.

Rui Si Yi *Wanma, China.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Rui Di Su *Sunnyhope, China.*
Azasetron hydrochloride (p. 1820·2).

Rui Tian *Zhonggui, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Rui Ting *Huabang, China.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Rui Tong *Deyuan, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Rui Tong Li *A Hua, China.*
Reteplase (p. 1486·2).
Myocardial infarction; pulmonary embolism.

Rui Xin Le *Tsinghua Yuanxing, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Rui Xin Chao *Lingkang, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Rui Xing Yu *Zhongrui Kangzhi, China.*
Sodium new houttuyfonate.

Rui Xue Xin *Xinpeng, China.*
Granulocyte colony-stimulating factor (human, recombinant).

Rui Yuan *Kangshen, China.*
Clarithromycin lactobionate (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Rui Ze *GuoRui, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Rui Zhi *De Tian, China.*
Nicotinic acid (p. 2083·1).

Rui Zhi Li *Zhongrui Kangzhi, China.*
Nimesulide (p. 101·3).
Pain.

Rui Zhi Qing *Zhongrui Kangzhi, China.*
Nimesulide (p. 101·3).
Pain.

Ruianji *Huajin, China.*
Fructose-1,6-diphosphate (p. 2507·2).
Cerebral ischaemia; myocardial ischaemia.

Ruibei *Tsinghua Yuanxing, China.*
Ranitidine bismuth citrate (p. 1883·3).
Peptic ulcer.

Ruibile *Tsinghua Yuanxing, China.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Ruideming *Merckle, China; Ratiopharm, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ruidi *Sanrui, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Ruifulin *Tsinghua Yuanxing, China.*
Itopride hydrochloride (p. 1850·1).
Dyspepsia.

RuiJie *Livzon, China.*
Oxymatrine.

Ruijiu *Dawnrays, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Ruilibo *HuaLiDa, China.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer.

Ruimai *Dawnrays, China.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Ruipuxin *Likang, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

RuiQi *Hanson, China.*
Mosapride citrate (p. 1865·2).
Gastrointestinal motility disorders.

Ruisutan *Rotam Reddy, China.*
Ramipril (p. 1483·3).
Heart failure; hypertension; myocardial infarction.

Ruitading *Nanxin, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ruitong *Saisheng, China.*
Alprostadil (p. 2352·2).
Myocardial infarction; thrombotic vasculitis; arteriosclerosis obliterans; retinal vein thrombosis.

Rukolok *Ratiopharm, Denm.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; heart failure.

Rukuz *Medimar, Gr.*
Omeprazole (p. 1867·2).

Ru-lets *Rugby, USA.*
Vitamins.

Rulicin *Lifesource, Rus.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rulid *Sanofi-Aventis, Arg.†; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.†; Winthrop, Ger.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Israel; Lepetit, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Switz.†; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, Venez.*
Roxithromycin (p. 356·2).
Bacterial infections; meningococcal meningitis prophylaxis.

Rulide *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi, China; Sanofi-Aventis, Neth.†; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Spain.*
Roxithromycin (p. 356·2).
Bacterial infections.

Rulmenem *Mac, Gr.*
Meropenem (p. 321·3).
Bacterial infections.

Rulofer G *Lomapharm, Ger.†*
Ferrous gluconate (p. 2061·2).
Iron deficiency.

Rulofer N *Lomapharm, Ger.*
Ferrous fumarate (p. 2060·3).
Iron deficiency.

Rulosone *PP Lab, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

RuLox *Rugby, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Hyperacidity.

RuLox Plus *Rugby, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Hyperacidity.

Rulvon *Mac, Gr.*
Vancomycin hydrochloride (p. 384·2).

Rumadene *Chew, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Rumalaya *Himalaya Herbal, Malaysia.*
⊗Indian frankincense (p. 2507·3); guggul (p. 2523·2); galanga; liquorice (p. 1853·2); gokhru (p. 2633·3); tinospora cordifolia.
Joint pain.

Rumalef *Zydus, India.*
Leflunomide (p. 81·3).
Rheumatoid arthritis.

Rumalon *Bryntsalov, Rus.*
Cartilage (p. 2471·3).
Degenerative joint disorders.

Bryntsalov, Ukr.
Glycosaminoglycan peptide complex.
Degenerative joint disorders.

Lafi, Chile.
Cartilage (p. 2471·3); bone-marrow extract (p. 2444·1).
Osteoarthritis.

Rumasian *Asian Pharm, Thai.†*
Ibuprofen (p. 68·2).
Osteoarthritis, rheumatoid arthritis.

Rumasin *Gunsa, Turk.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Rumatifen *Chew, Thai.†*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Rumatifen-Plus *Chew, Thai.†*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain; fever.

Rumatix *Rutland Biodynamics, UK.*
Cimicifuga (p. 2478·1).
Musculoskeletal and joint pain.

Rumaxicam *March, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rumazolidin *Biosel, Turk.†*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Rumisedan *Lanpharm, Arg.*
Piroxicam (p. 125·3); ascorbic acid (p. 2110·3).
Inflammation; pain.

Rumisedan Fuerte *Lanpharm, Arg.*
Piroxicam (p. 125·3); carisoprodol (p. 2021·3); ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3).
Inflammation; pain.

Rumycoz *Valenta, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Run Dan *Run Bang, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Run He Er *Huaxin, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Run Hui *Kangpu, China.*
Levodropropizine (p. 1662·3).
Cough.

Run Jie *Bausch & Lomb, China.*
Vitamin B_6 (p. 2105·3); sodium hyaluronate (p. 2526·2); taurine (p. 2626·2).
Eye irritation; dry eyes.

Run Jing *LuoXin, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Run Ke Long *Huana, China.*
Macrogol 4000 (p. 2547·3).

Run Lai *Yuansen, China.*
Loratadine (p. 633·2).
Allergic disorders.

Run Qi *Qilu, China.*
⊗Dextran 70 (p. 1138·3).

Run Rui *Bausch & Lomb, China.*
Clonidine hydrochloride (p. 1339·1).

Run Tan *Lingrui, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Run Xin Shu *Chaoyang Lingqiao, China.*
Pentoxifylline (p. 1465·3).

Runbao *Bao Long, China.*
⊗Urea (p. 1727·3); vitamin E (p. 2119·1).
Dry skin; keratinisation disorders.

Runbo *Bausch & Lomb, China.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Runde *Rafarm, Gr.*
Tetramethrin (p. 2162·2); piperonyl butoxide (p. 2160·2).
Head, body, and crab lice.

Runjie *Bausch & Lomb, China.*
⊗Naphazoline hydrochloride (p. 1669·3); chlorphenamine maleate (p. 620·3); vitamin B_{12} (p. 2107·2); sodium hyaluronate (p. 2526·2).
Eye irritation.

Runomex *Yeni, Turk.*
Meloxicam (p. 86·3).

Runzheng *Bausch & Lomb, China.*
Tropicamide (p. 2012·2).
Production of cycloplegia and mydriasis.

Ruo Bi Xun *Weigao, China.*
Glyceryl trinitrate (p. 1391·2).
Unstable angina; heart failure; myocardial infarction; control of hypertension in surgery.

Ruo Chang *Weigao, China.*
Diprophylline (p. 1207·3).

Ruo Jing *Weigao, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Ruo Lai *Weigao, China.*
Sodium ferulate.

Ruo Mai *Xudong Haipu, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Ruo Peng *Global, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Ruo Xin Lai *Weigao, China.*
Glyceryl trinitrate (p. 1391·2).
Unstable angina; heart failure; myocardial infarction; control of hypertension in surgery.

Rupafin *Nycomed, Arg.; Madaus, Austria; Biosintetica, Braz.; Recordati, Ger.†; Olvos, Gr.; Uriach, Irl.; Recordati, Ital.; Uriach, Neth.; Uriach, Pol.; Uriach, Spain; Rottapharm, Thai.; Abdi, Turk.; GSK, UK.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

Rupatall *Takeda, Belg.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

Rupedex *Duncan, Arg.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Rupediol *Duncan, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Cold and influenza symptoms; allergic rhinitis; allergic sinusitis; cough.

Rupediz *Duncan, Arg.*
Diazepam (p. 1063·2).
Anxiety.

Rupegen *Duncan, Arg.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Rupek *Duncan, Arg.*
Phytomenadione (p. 2122·2).
Haemorrhage.

Rupemet *Duncan, Arg.*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Rupe-N *Duncan, Arg.*
Hyoscine butylbromide (p. 1845·3).
Muscle spasm.

Rupe-N Compuesto *Duncan, Arg.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Muscle spasm.

Rupesona B *Duncan, Arg.*
⊗Meprednisone (p. 1642·2).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Rupezol *Duncan, Arg.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Rupox *Medipharma, Arg.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Rupton
Note: this name may be used for preparations of different composition.
SMB, Belg.
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Ruscoroid *Sanofi-Aventis, Ital.*
Ruscogenin (p. 2608·3); tetracaine hydrochloride (p. 1996·3).
Anorectal disorders.

Ruscus *Llorens, Spain.*
⊗Cinchocaine hydrochloride (p. 1983·2); prednisolone (p. 1645·2); ruscogenin (p. 2608·3); zinc oxide (p. 1729·1); menthol (p. 2553·2).
Anorectal disorders.

Rusedal *Nycomed, Ger.; Nycomed, Hung.†*
Medazepam (p. 1083·2).
Anxiety disorders.

Ruskorex *Medagro, Pol.*
Ruscogenin (p. 2608·3); tetracaine hydrochloride (p. 1996·3).
Anorectal disorders.

Rusovas *Sigma, Braz.*
Rosuvastatin (p. 1488·2).

Russedyl Plus *Pharmaniaga, Malaysia.*
⊗Pholcodine (p. 1675·1); promethazine hydrochloride (p. 638·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Russisk Rod *Arkopharma, Denm.*
Siberian ginseng (p. 2614·3).
Tonic.

Rustin *Ergha, Irl.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Rustor *Westfield, Philipp.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Rusyde *CP Pharmaceuticals, UK.*
⊗Furosemide (p. 1387·1).
Oedema.

Rutacid *KRKA, Cz.; KRKA, Pol.†; KRKA, Rus.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity; gastritis; duodenitis; peptic ulcer; gastro-oesophageal reflux; heartburn; dyspepsia.

Ruta-Gastreu N R55 *Reckeweg, Ger.*
Arnica (p. 2447·2); calendula (p. 2465·2); hamamelis (p. 2523·3); rhus toxicodendron (p. 2603·3); ruta (p. 2608·2); symphytum (p. 2484·2).
Homoeopathic preparation.

Ruta-Plus *Doctor H, Rus.*
Apis mellifica (p. 2445·2); cinchona pubescens (p. 2478·3); pusatilla pratensis (p. 2600·2); ruta graveolens (p. 2608·2); secale cornutum (p. 2137·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Rutascorbin *Valeant, Hung.*
Rutoside (p. 2505·3); ascorbic acid (p. 2110·3).
Haemorrhage; vascular disorders.

Ruthison *Unison, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ruticalzon *Brady, Austria.†*
Colecalciferol (p. 2113·1); rutoside (p. 2505·3); vitamin C (p. 2110·3); calcium citrate (p. 1783·2).
Capillary haemorrhage; infections.

Rutilina *Bernabo, Arg.*
Troxerutin (p. 2505·3).
Venous insufficiency.

RutinaC *Aflofarm, Pol.†*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Vitamin C supplement.

Rutinice Fortissimo *Menarini, Port.*
Rutoside (p. 2505·3); ascorbic acid (p. 2110·3).
Haemorrhage.

Rutin-Kapsein *Twardy, Ger.*
Rutoside (p. 2505·3).
Venous insufficiency.

Rutinosal C *Labofarm, Pol.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3); salix (p. 129·2).
Fever; pain.

Rutinoscorbin *GSK, Pol.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Vitamin C supplement.

Rutinoscorbin Plus *GSK, Pol.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3); selenium (p. 2086·3); zinc (p. 2126·1).
Dietary supplement.

Rutinoven *RiC, Pol.†*
Troxerutin (p. 2505·3).
Venous insufficiency.

Rutisept extra *Ecolab, Ger.*
Isopropyl alcohol (p. 1758·3); triclosan (p. 1773·2).
Hand disinfection.

Rutiviscal *Aponova, Austria.*
Garlic (p. 2510·3); crataegus (p. 2488·1); mistletoe (p. 2560·2); rutoside (p. 2505·3).
Atherosclerosis.

Rutokal C *Natur Produkt, Pol.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); rutoside (p. 2505·3).
Cold symptoms; capillary fragility; dietary supplement.

Rutosidos *Vannier, Arg.*
Troxerutin (p. 2505·3).

Rutoven *Herbapol Poznan, Pol.†*
Troxerutin (p. 2505·3).
Venous insufficiency.

Rutovit C *Teva, Pol.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3).
Capillary fragility; cold symptoms.

Rutozym *Mucos, Austria.*
⊗Rutoside (p. 2505·3); bromelain (p. 2460·3); trypsin (p. 2635·2).
Pain; inflammation; musculoskeletal and joint disorders; thrombophlebitis.

Rutra *Novagen, S.Afr.*
Risperidone (p. 1103·2).

Rutying *Super Mayoreo Naturista, Mex.*
Ginseng (p. 2513·3).
Tonic.

Ruvamed *Coup, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Ruvetine *Rafarm, Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Ruvominox *Rafarm, Gr.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders; prevention of miosis in ophthalmic surgery.

Rafarm, Hong Kong.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Rux *Saval, Chile.*
Rosuvastatin (p. 1488·2).

Ruxcine *Mugi, Indon.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Ruxicolan *Rafarm, Gr.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Ruxim *Karnataka, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ruxitex *United Drugs, Hong Kong; United Drug, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

RV Paque *ICN, USA.*
Zinc oxide (p. 1729·1); cinoxate (p. 1699·2).
Sunscreen.

ICN, NZ.†
Zinc oxide (p. 1729·1); octinoxate (p. 1715·1).
Sunscreen.

R-Vac *Serum Institute, India.*
A rubella vaccine (Wistar RA 27/3 strain) (p. 2417·1).
Active immunisation.

R-X *Yenisehir, Turk.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal tract radiography.

Rx Support Heartburn & Acid Reflux *Mason, USA.*
Calcium (p. 1783·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin D (p. 2112·3).

Rx Support Heartburn & Acid Reflux Plus Aloe *Mason, USA.*
Calcium (p. 1783·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin D (p. 2112·3); aloe vera (p. 1693·2).

Rybix *Victory, USA.*
Tramadol hydrochloride (p. 139·2).
Pain.

Rycef *Interbat, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Rycin *Medreich, Hong Kong.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Rydene *Astellas, Belg.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension.

Rydex G *Centurion, USA.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Rydian *Guardian, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Rye *Rafarm, Gr.*
Bifonazole (p. 573·3).
Fungal skin infections.

Rylosol *Valeant, Canad.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Rymed *Edwards, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Ryna-12 *Meda, USA.†*
Mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Nasal congestion; rhinitis.

Rynacrom *Sanofi-Aventis, Austral.; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Mex.; Aventis, NZ†; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Eczacibasi, Turk.; Sanofi-Aventis, UK.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Rynacrom Compound *Eczacibasi, Turk.*
⊗Sodium cromoglicate (p. 1225·3); xylometazoline hydrochloride (p. 1680·1).
Allergic rhinitis.

Rynatan *Medpointe, USA.†*
Tablets: Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Rynatuss *Medpointe, USA.†*
⊗Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3); ephedrine tannate (p. 1663·1); phenylephrine tannate (p. 1672·2).
Cough.

Rynesa 12S *Amneal, USA.†*
Mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Rynex PE *Edwards, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Ryneze *Stewart Jackson, USA.*
Chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Rynset *Ali, Turk.*
Cetirizine hydrochloride (p. 619·2).

Ryokankyomishingeninto *Tsumura, Jpn.*
Apricot kernel (p. 2445·3); pinellia tuber; poria sclerotium; schisandra fruit (p. 2611·2); ginger (p. 1844·1); liquorice (p. 1853·2); asiasarum root.
Traditional Kampo medicine.

Ryokeijutsukanto *Tsumura, Jpn.*
Poria sclerotium; cinnamon bark (p. 2479·2); atractylodes lancea rhizome; liquorice (p. 1853·2).
Traditional Kampo medicine.

Ryokyojutsukanto *Tsumura, Jpn.*
Poria sclerotium; ginger (p. 1844·1); atractylodes rhizome; liquorice (p. 1853·2).
Traditional Kampo medicine.

Ryol *Schwarz, Ger.†*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Rysolone *Dedousis, Gr.*
Hexachlorophene (p. 1754·1); resorcinol (p. 1718·3); sulfur (p. 1721·1).

Ryspolit *Polpharma, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Ry-Tann *Midlothian, USA.*
Chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Rytesthin *Asconex, Ger.*
Asa foetida (p. 2449·3); myristica fragrans (p. 2573·1); valeriana officinalis (p. 2640·2); cinnamomum (p. 2479·2); lupulinum; semecarpus anacardium (p. 2471·3); strychnos ignatii (p. 2532·1); kalium bromatum (p. 2461·1).
Homoeopathic preparation.

Rythmex *Teva, Israel.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Rythmical *Trima, Israel.*
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Rythmodan *Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Jpn; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Borg, UK.*
Disopyramide (p. 1363·2) or disopyramide phosphate (p. 1363·3).
Arrhythmias.

IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.
Disopyramide phosphate (p. 1363·3).
Arrhythmias.

Rythmogastryl *Rafarm, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Rythmol *Abbott, Canad.; Abbott, Fr.; Abbott, S.Afr.; GSK, USA.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Rythmorest *Gedeon Richter, Rus.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Rytho-Cap *Medicine Products, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Rythocin *Millimed, Thai.†*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Rytmobeta *Abbott, Ital.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Rytmocard *Abbott, Philipp.†*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Rytmonorm *Abbott, Belg.; Abbott, China; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Pharmalex (Φαρμαλεξ), Gr.†; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.†; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, Venez.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Rytmonorma *Abbott, Austria.*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Rytmopasc *Pascoe, Austria.*
Crataegus (p. 2488·1); cytisus scoparius (p. 2611·3); lilium lancifolium; apocynum; veratrum viride (p. 2644·3); gelsemium (p. 2511·2); nitroglycerinum (p. 1391·2); cheiranthus cheiri.
Homoeopathic preparation.

Pascoe, Ger.
Crataegus (p. 2488·1); spartium scoparium (p. 2611·3); lilium tigrinum; apocynum; veratrum viride (p. 2644·3); gelsemium (p. 2511·2); glonoinum (p. 1391·2); cheiranthus cheiri.
Homoeopathic preparation.

Rytmo-Puren *Actavis, Ger.†*
Propafenone hydrochloride (p. 1477·3).
Arrhythmias.

Ryutanshakanto *Tsumura, Jpn.*
Rehmannia root; angelica acutiloba root (p. 2443·3); akebia stem; skullcap root (p. 2617·1); plantago seed (p. 1849·1); alisma

rhizome; liquorice (p. 1853·2); gardenia fruit; gentiana scabra.
Traditional Kampo medicine.

Ryvel *Novell, Hong Kong†; Novell, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic skin disorders; allergic conjunctivitis.

Ryvina *Rafarm, Gr.*
⊗Pilocarpine hydrochloride (p. 2010·3); dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Rywanol *Hasco-Lek, Pol.†*
Ethacridine lactate (p. 1732·3).
Skin and mucous membrane infections; burns; ulcers; wounds.

Ryzen *UCB, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria; pruritus; allergic conjunctivitis.

Ryzicor *Pharmacore, Indon.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Ryzo *Soho, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Ryzodeg *Novo Nordisk, Neth.*
⊗A mixture of insulin degludec (p. 475·3) 70% and insulin aspart (p. 475·3) 30%.
Diabetes mellitus.

Ryzolt *Purdue, USA.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Rzewex *Herbapol Lodz, Pol.†*
Rhubarb (p. 1884·2).
Constipation.

S-1 *Taiho, China.*
Tegafur (p. 864·2); gimeracil; oteracil potassium.
Gastric cancer.

S-2 *Nephron, USA.*
⊗Racepinefrine hydrochloride (p. 1292·1).
Bronchospasm.

S-26 AR *Pfizer Nutrition, Austral.; Wyeth, Chile; Wyeth, NZ; Wyeth, Venez.*
Infant feed.
Recurrent regurgitation; gastro-oesophageal reflux.

S-26 HA *Wyeth, Hong Kong; Wyeth, Venez.*
Infant feed.
Cows' milk protein allergy; food allergies.

S-26 Lactose-free *Wyeth, Philipp.*
Infant feed.
Lactose intolerance.

S-26 LF *Pfizer Nutrition, Austral.; Wyeth, NZ.*
Infant feed.
Lactose intolerance.

S-26 Mama *Wyeth, Singapore.*
Preparation for enteral nutrition.

S-26 Mom *Wyeth, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Wyeth Nutrition, Thai.
Nutritional supplement in pregnancy and lactation.

S-26 sin Lactosa *Wyeth, Chile; Wyeth, Venez.*
Infant feed.
Lactose intolerance.

S-26 Soy *Pfizer Nutrition, Austral.*
Infant feed.
Lactose intolerance.

SA *Rivers Edge, USA.*
Salicylic acid (p. 1719·1).

Sa Fen *Junan, China.*
Rifaximin (p. 355·2).

Sa Lan Xin *Hayao, China.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Sa Ni Ka *Fuchun, China.*
Aceglutamide (p. 2426·2).

Saaz *Ipca, India.*
Sulfasalazine (p. 1890·1).
Rheumatoid arthritis; ulcerative colitis.

SAB Simplex *Pfizer, Austria; Pfizer, Cz.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Hung.; Pfizer, Rus.; Pfizer, Ukr.*
Simeticone (p. 1886·2).
Meteorism; reduction of intestinal gas before gastrointestinal procedures; detergent poisoning; flatulence; excess gastrointestinal gas.

Saba *Lampugnani, Ital.*
Saw palmetto (p. 2363·3).
Prostatic hyperplasia.

Sabal
Note: this name may be used for preparations of different composition.
Pharmaselect, Austria; Silesia, Chile; Ducray, Fr.; Sandoz, Ger.; Stada, Ger.; PhytoCon, UK.
Saw palmetto (p. 2363·3).
Seborrhoea; benign prostatic hyperplasia.

Pierre Fabre Dermo-Cosmetique, Arg.; Medifarm Ducray, Venez.
Shampoo: Saw palmetto (p. 2363·3); zinc salicylate (p. 1719·1).
Seborrhoea.

Sabal Serrulata Composé *Boiron, Fr.*
Sabal serrulata (p. 2363·3); acide picricum (p. 2634·2); baryta carbonica (p. 2452·2); berberis vulgaris (p. 2502·1); thuya occidentalis (p. 2629·3); anemone pulsatilla (p. 2600·2); conium maculatum (p. 2524·3); thlaspi bursa pastoris (p. 2614·2).
Homoeopathic preparation.

Sabal uno *Apogepha, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sabalaks *Saba, Turk.*
⊗Sorbitol (p. 2092·1); sodium citrate (p. 1781·2); glycerol (p. 2517·2); sodium laurilsulfoacetate.
Constipation.

Sabalasan *Bioforce, Canad.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sabal-Homaccord *Heel, Neth.; Heel, Rus.*
Hepar sulphur (p. 1721·3); sabal serrulata (p. 2363·3).
Homoeopathic preparation.

Sabalia *Boiron, Canad.*
Allium cepa (p. 2575·2); ambrosia artemisiaefolia; euphrasia officinalis (p. 2502·1); histaminum muriaticum (p. 2525·2); sabadilla (p. 2611·2); solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Sabalin *Lichtwer, UK.*
Saw palmetto (p. 2363·3).
Male urinary discomfort.

Saballo *Scherer, Hung.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sabalvit *Ruhrpharm, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sabamin *Bioforce, Swed.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sabax Dianeal *Adcock Ingram Critical Care, S.Afr.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
A range of solutions for peritoneal dialysis.

Sabax Diasol *Adcock Ingram Critical Care, S.Afr.†*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
A range of solutions for haemodialysis.

Sabax Fosenema *Adcock Ingram Critical Care, S.Afr.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Sabax Gentamix *Adcock Ingram Critical Care, S.Afr.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Sabax Haemocarb *Adcock Ingram Critical Care, S. Afr.†*
Electrolytes (p. 1775·1).
Haemodialysis.

Sabax Liquid Bicarbonate *Adcock Ingram Critical Care, S.Afr.†*
Sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1).
Haemodialysis.

Sabax Nebrafen *Adcock Ingram Critical Care, S.Afr.*
⊗Fenoterol hydrobromide (p. 1208·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

SabCaps *Vifor, Switz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sabelin *Argenfarma, Arg.*
Boldo (p. 2458·3); carqueja (p. 2471·2); chamomile (p. 2474·1); melissa (p. 2552·3); peperina.

Sabenyl *Sanofi-Aventis, Gr.*
Mercurobutol (p. 1760·2); sodium laurilsulfate (p. 2210·3).
Antiseptic.

Qualiphar, Belg.†
⊗Chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Hand disinfection.

Sabervel *Glenmark, Neth.; Aspire, UK.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Sabima *Atlantis, Mex.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Sabin *Sanofi Pasteur, Arg.†*
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Sabril *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Lundbeck, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sandoz, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.; Aventis, Turk.; Sanofi-Aventis, UK; Lundbeck, USA.*
Vigabatrin (p. 558·3).
Epilepsy.

Sabrilan *Perrigo, Israel.*
Vigabatrin (p. 558·3).
Epilepsy.

Sabrilex *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Euro Registratie, Neth.†; Sanofi-Aventis, Norw.; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.*
Vigabatrin (p. 558·3).
Epilepsy.

Sabrinin dragées pour les reins et la vessie *Iromedica, Switz.*
Bearberry (p. 2453·2); birch leaf (p. 2457·3); solidago (p. 2620·1).
Urinary-tract disorders.

Sabro *Senosiain, Mex.*
Aloglutamol (p. 1816·2).
Gastrointestinal hyperacidity; gastro-oesophageal reflux; gastritis; peptic ulcer; hiatus hernia.

Sabufarm *Sandoz, Swed.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sabumol *GPO, Thai.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Sabumol Ex *GPO, Thai.*
⊗Salbutamol (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Sac-Bi-Toks *Abbott, Turk.*
Alkyl sulfonate; trolamine (p. 2634·3); malathion (p. 2157·2).
Pediculosis.

Saccharofar *Faran, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sachol żel Stomatologiczny *Jelfa, Pol.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Mouth disorders.

Saciette *Glenmark, Braz.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sacietyl *Finadiet, Arg.†*
⊗Sibutramine (p. 2330·2).
Obesity.

Sacin *Labomed, Chile.†*
⊗Diethylpropion (p. 2321·1).
Obesity.

Sacnel *Teofarma, Ital.*
Colloidal sulfur (p. 1721·1); zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); dithiosalicylic acid (p. 1701·1); hamamelis leaves (p. 2523·3).
Acne; seborrhoeic dermatitis.

Sacodil *Federfarma, Ital.*
Bisacodyl (p. 1821·1).
Constipation.

Sacolène *DB, Fr.*
Methylenated milk proteins.
Diarrhoea.

Sacrum *Alapis, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Sactabs *PSM, NZ.*
Saccharin (p. 2207·3).
Artificial sweetener.

Sactiva *Sandoz, Ital.*
Methotrexate (p. 822·2).

Sadamin *Pliva Krakow, Pol.†*
Xantinol nicotinate (p. 1535·3).
Peripheral vascular disorders; thromboembolic disorders.

Sadeltan F *Hautel, Arg.*
⊗Aloe vera (p. 1693·2); urea (p. 1727·3).
Emollient.

Sades
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Tecnimede, Port.
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Pentafarma, Port.†
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Sadifit *Lektravy, Ukr.*
Blueberry; kidney bean (p. 2587·3); green tea (p. 2648·2); peppermint leaf (p. 1877·1); Jerusalem artichoke tuber; stevia leaf (p. 2214·2).
Diabetes mellitus; digestive disorders.

Sadocin *Farcoral, Mex.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Sadol *Catarinense, Braz.†*
Iron (p. 2073·1); pyridoxine (p. 2105·3); nicotinamide (p. 2083·1); caffeine (p. 1203·3); citric acid (p. 2480·3).
Iron deficiency; iron-deficiency anaemia.

Sadolin *Elpen (Ελπεν), Gr.*
Somatostatin acetate (p. 1930·3).

SAE *Pasteur, Chile.*
Propyphenazone (p. 127·3); adiphenine hydrochloride (p. 2431·1); trasentine.
Smooth muscle spasm.

Saebegin *Chinta, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Saebin F 1-6-12 *Chinta, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Saerogenta-A *Ahn-Gook, Singapore.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders; burns; insect bites.

Saetil *Robapharm, Spain.*
Ibuprofen arginine (p. 68·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Saf Kit *Biochem, India.*
2 Tablets, secnidazole (p. 947·3); 1 tablet azithromycin (p. 221·2); 1 tablet, fluconazole (p. 578·2).
Bacterial and fungal infections.

Safarol *Medichrom, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Saf-Clens *Calgon Vestal, USA.*
Wound cleanser.

Safe Pill *Unicure, Philipp.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Safe Tussin 30 *Kramer, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Safedex *Ebewe, Ital.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Safelo *Siesta, India.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Safemar *Sandoz, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Saferon
Note: this name may be used for preparations of different composition.
Glenmark, Malaysia.
Syrup: Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.
Glenmark, Malaysia.
Tablets: Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron-deficiency anaemia; iron and folic acid deficiency.

SafeStat *Gruppo Medica, Philipp.*
Simvastatin (p. 1489·2); ubidecarenone (p. 2637·1).
Hyperlipidaemias.

Safetec Burn *Safetec, Canad.*
Lidocaine hydrochloride (p. 1988·2).
Burns.

Safetec Sting Relief *Safetec, Canad.*
Lidocaine hydrochloride (p. 1988·2).
Insect stings.

Safetin *Dexa, Indon.†*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Safety T *Volta, Chile.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Safex *Zee, Thai.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Saffid *Safire, Hong Kong.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; primary prevention of ischaemic heart disease.

Safital *Silanes, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

saflineb *Italchimici, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Saflutan *MSD, Austria; MSD, Belg.; MSD, Braz.; MSD-Chibret, Fr.; MSD, Irl.; MSD, Israel; MSD, Neth.; MSD, Spain; MSD, Switz.; MSD, UK.*
Tafluprost (p. 2012·1).
Ocular hypertension; glaucoma.

Safocid *Makiz, Rus.*
Pink tablets, fluconazole (p. 578·2); pink tablets, azithromycin (p. 221·2); white tablets, secnidazole (p. 947·3).
Genito-urinary-tract infections.

Safol *Novell, Indon.*
Propofol (p. 1909·3).
General anaesthesia; sedative.

Saforax *Hong Kong Medical, Hong Kong.†*
Aciclovir (p. 964·1).

Saforelle
Note: this name may be used for preparations of different composition.
IPRAD, Philipp.; BioSaude, Port.; Medifarm, Venez.
Lappa (p. 2540·1).
Soap substitute; vaginal cleanser; skin irritation.
IPRAD, Fr.†
Sodium laurilsulfate (p. 2210·3).
Gynaecological hygiene.

Safoxen *GSK, Arg.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Safralite *Codifra, Fr.*
Saffron (p. 2208·2); griffonia (p. 2522·3); zinc (p. 2126·1); vitamin B_6 (p. 2105·3).
Mood disorders.

Safrosyn S *Pharmaniaga, Malaysia.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Safrux *CPH, Port.†*
Tartaric acid (p. 2626·1); sodium bicarbonate (p. 1781·1); potassium tartrate (p. 1793·3).
Antacid.

Saften *Monserrat, Arg.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Saftra *Norgine, Denm.*
Rifaximin (p. 355·2).
Escherichia coli *associated travellers' diarrhoea.*

Safyr Bleu *Aspen, S.Afr.*
⊗Naphazoline nitrate (p. 1669·3).
Eye irritation.

Safyral *Bayer, USA.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, levomefolate calcium (p. 2053·1).
Combined oral contraceptive.

Sagalon *Surya Dermato, Indon.*
Doxepin hydrochloride (p. 414·2).
Pruritus.

Sagamicin *Kyowa, Jpn†; Kyowa, Singapore.*
Micronomicin sulfate (p. 324·2).
Bacterial infections.

Sagaspray *Diepharmex, Fr.†*
Biclotymol (p. 1740·1).
Mouth disorders; sore throat.

Sage Extract with Vitamin C Dr Theiss *Naturwaren, Ukr.*
Sage (p. 2608·3); sage oil (p. 2609·1); ascorbic acid (p. 2110·3).
Cough and congestion of upper respiratory tract.

Sagenit *Nizpharm, Rus.*
Dipotassium *meso*-3,4-Bis(*p*-sulfophenyl) hexane (p. 2615·1).
Menopausal disorders.

Sagestam *Sanbe, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Saglion *Sieger, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Xerostomia.

Sagras *Mintlab, Chile.*
Orlistat (p. 2577·1).
Obesity.

Sahakarn Mist Stomachic *United Drug, Thai.*
Sodium bicarbonate (p. 1781·1); rhubarb (p. 1884·2); camphor (p. 2466·2); peppermint oil (p. 1877·1).
Gastrointestinal disorders.

Sahakarn Peppermint *United Drug, Thai.*
Peppermint oil (p. 1877·1).
Flatulence; colic; gastrointestinal spasm.

Sahne Krim *Eisai, Indon.*
Moisturiser.

Sai Ai Er *Changchun, China.*
Granulocyte-macrophage colony-stimulating factor (human recombinant).

Sai Ao *Duobao, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Sai Bi Shu *Yabo, China.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sai Bo Er *Saibaoer, China.*
⊗Erythropoietin (p. 1141·1).

Sai Bo Li *Saibaoer, China.*
A low-molecular-weight heparin calcium (p. 1426·1).

Sai Chen *Haixin, China.*
Oxymatrine.

Sai Da Lin *Daxing, China.*
Isosorbide mononitrate (p. 1413·3).

Sai De Long *Wandashan, China.*
Papaverine hydrochloride (p. 2362·3).

Sai Di En *Weixing Bio Product, China.*
Interleukin-2 (human, recombinant) (p. 810·1).

Sai Er *Saisheng, China.*
Defibrase.

Sai Er Gan *Guang Da, China.*
Oxymatrine.

Sai Er Si Ning *Shouhe Jinhai, China.*
Levofloxacin lactate.
Bacterial infections.

Sai Fa Lei *Sangtian, China.*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia.

Sai Feng *Sanofi, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Sai Fu *Saisheng, China.*
Puerarin.

Sai Fu Ding *Huashan, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Sai Fu Mei *United Lab, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Sai Fu Xi *Topsun, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Sai Gao Lu *Kexing, China.*
⊗Growth hormone (human, recombinant) (p. 1919·3).

Sai Ge En *Southwest, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Sai Ge Er *Duoburuifei, China.*
Sodium alginate diester.

Sai Ge Li *Sanwei, China.*
A granulocyte colony-stimulating factor (human, recombinant).

Sai Hong *Duobao, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Sai Jie *Ke Yi, China.*
Ciclopirox olamine (p. 575·3).
Fungal skin infections.

Sai Jin Sha *Tongde, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Sai Ka *Jingfeng, China.*
Telmisartan (p. 1509·3).
Hypertension.

Sai Ke *Xiangyu, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Sai Ke Lu Ding *Duoburuifei, China.*
Fluconazole (p. 578·2).
Fungal infections.

Sai Ke Si *Sunnyhope, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Sai Ke Tong *Yinglian, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Sai Ke Xing *Xinchang, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Sai Lai De *Baike Hengdi, China.*
Balsalazide sodium (p. 1820·2).
Ulcerative colitis.

Sai Lan *Disai, China.*
Homoharringtonine (p. 837·3).

Sai Le Lin *United Lab, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Sai Le Pin *Bosen, China.*
Ropivacaine mesilate.
Local anaesthesia.

Sai Le Xin *United Lab, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Sai Li Ao *Tai Sheng, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Sai Li Mai *Luye, China.*
Smectite (p. 1887·1).

Sai Ling Si *Haixin, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Sai Luo Su *Yingtian, China.*
Lysine hydrochloride (p. 2079·3).

Sai Luo Xi Ping *Huakang, China.*
Heparin sodium (p. 1396·3).

Sai Mei Ao *San Lian, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Sai Mu Si *Livzon, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Sai Ning *Gelalei, China.*
Aspirin (p. 22·2).

Sai Ou Si *Sunnyhope, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Sai Pu *Ao Tuo Kang, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Sai Pu Da *Sunstone, China.*
Nimesulide (p. 101·3).
Pain; fever; inflammation.

Sai Pu Li Er *San Lian, China.*
Aceglutamide (p. 2426·2).

Sai Qi *Dade, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Sai Qi Song *Dadeli, China.*
Oxymatrine.

Sai Rui Chen *Haixin, China.*
Rifamycin sodium (p. 354·3).

Sai Ruo Jin *Kexing, China.*
Interferon alfa-1b (p. 989·2).

Sai Shi Ke *Di Ao, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Sai Ta Le *Wan Long, China.*
Secnidazole (p. 947·3).
Giardiasis; amoebiasis; trichomoniasis.

Sai Tong *Ke Lun, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Sai Tuo *TianJin, China.*
Cytochrome C (p. 2491·2).

Sai Wei *ShiJiaZhuang No 4, China.*
Bromhexine hydrochloride (p. 1656·3).

Sai Xian *Disai, China.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdose; reversal of opioid induced sedation.

Sai Yuan *Jinsai, China.*
Granulocyte-macrophage colony-stimulating factor (human, recombinant).

Saibai *Saisheng, China.*
⊗Fibrinolysin (p. 1382·3).
Thromboembolic disorders; peripheral vascular disorders.

Saibokuto *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; poria sclerotium; skullcap root (p. 2617·1); magnolia bark; jujube; ginseng (p. 2513·3); liquorice (p. 1853·2); perilla herb; ginger (p. 1844·1).
Traditional Kampo medicine.

Saidewei *Hospira, China.*
Cytarabine (p. 774·1).
Leukaemias.

Saifubi *United Lab, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Saifuding *United Lab, China.*
Cefradine (p. 249·1).
Bacterial infections.

Saifulong *United Lab, China.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Saifuning *United Lab, China.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Saikanto *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; skullcap root (p. 2617·1); jujube; ginseng (p. 2513·3); coptis rhizome; liquorice (p. 1853·2); ginger (p. 1844·1); trichosanthes seed.
Traditional Kampo medicine.

Saikeping *Huadong, China.*
Mycophenolate mofetil (p. 1961·1).
Renal transplant rejection.

Saikokaryukotsuboreito *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; cinnamon bark (p. 2479·2); poria sclerotium; skullcap root (p. 2617·1); jujube; ginseng (p. 2513·3); oyster shell; longgu; ginger (p. 1844·1).
Traditional Kampo medicine.

Saikokeishikankyoto *Tsumura, Jpn.*
Bupleurum root; skullcap root (p. 2617·1); trichosanthes root; cinnamon bark (p. 2479·2); oyster shell; ginger (p. 1844·1); liquorice (p. 1853·2).
Traditional Kampo medicine.

Saikokeishito *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; skullcap root (p. 2617·1); liquorice (p. 1853·2); cinnamon bark (p. 2479·2); peony root; jujube; ginseng (p. 2513·3); ginger (p. 1844·1).
Traditional Kampo medicine.

Saikoseikanto *Tsumura, Jpn.*
Bupleurum root; skullcap root (p. 2617·1); phellodendron bark; coptis rhizome; trichosanthes root; liquorice (p. 1853·2); platycodon root; burdock fruit; gardenia fruit; rehmannia root; peony root; cnidium

rhizome; angelica acutiloba root (p. 2443·3); mentha herb; forsythia fruit.
Traditional Kampo medicine.

Sailaile *Baijingyu, China; Jinling, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Sailexi *KeRui, China.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Saimosi *Huadong, China.*
Sirolimus (p. 1966·2).
Renal transplant rejection.

Saintbois
Note: this name may be used for preparations of different composition.
Melisana, Belg.
Ethylmorphine hydrochloride (p. 56·3); sulfogaiacol (p. 1678·1); belladonna (p. 2453·3); tolu balsam (p. 1679·2); aconite (p. 2428·3); senega (p. 1677·2); maidenhair; drosera (p. 2497·2).
Cough.

Saireito *Kracie, Jpn; Tsumura, Jpn.*
Bupleurum root; alisma rhizome; pinellia tuber; skullcap root (p. 2617·1); atractylodes lancea rhizome; jujube; polyporus sclerotium; ginseng (p. 2513·3); poria sclerotium; liquorice (p. 1853·2); cinnamon bark (p. 2479·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Sairong *Saisheng, China.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Saisiping *Huadong, China.*
Ciclosporin (p. 1945·2).
Transplant rejection.

Saitan *WPU, China.*
Telmisartan (p. 1509·3).
Hypertension.

SaiTong *Poly, China.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).

Saizen *Merck Serono, Arg.; Merck Serono, Austral.; Merck, Austria; Merck, Braz.; Serono, Canad.; Merck, Chile; Merck, Cz.; Merck, Fin.; Merck Serono, Fr.; Merck Serono, Ger.; Merck, Gr.; Serono, Gr.; Serono, Hong Kong; Merck Serono, Hung.; Serum Institute, India; Merck, Indon.; Merck Serono, Irl.; Merck Serono, Israel†; Merck Serono, Ital.; Merck Serono, Malaysia; Merck, Mex.; Merck, Norw.; Healthcare Logistics, NZ; Merck, Philipp.; Merck, Port.; Merck Serono, Rus.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure; short children born small for gestational age; cachexia and wasting in AIDS; Prader-Willi syndrome.

Merck Serono, China.
⊗Growth hormone (human, recombinant) (p. 1919·3).
Growth hormone deficiency; Turner' syndrome.

Sakure *Obolenskoe, Rus.*
Lacidipine (p. 1417·3).
Hypertension.

SAL *Novagen, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sal Amargo Purificado *Catarinense, Braz.†*
Magnesium sulfate (p. 1787·3).
Constipation.

Sal de Andrews *GSK, Braz.*
Magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Gastric hyperacidity.

Sal Carolinum Factitium *Ziololek, Pol.*
Sodium sulfate (p. 1888·1); potassium sulfate (p. 1793·2); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1).
Constipation; biliary-tract disorders; obesity.

Sal Dietetica *Reccius, Chile.*
Potassium chloride (p. 1793·2).
Dietary salt substitute.

Sal Ems Artificiale *Galenus, Pol.*
Sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); potassium sulfate (p. 1793·2); sodium sulfate (p. 1888·1); dibasic sodium phosphate (p. 1791·2).
Respiratory-tract disorders.

Sal Ems Factitium *Ziololek, Pol.*
Sodium bicarbonate (p. 1781·1); sodium bromide (p. 2461·1); dibasic sodium phosphate (p. 1791·2); sodium chloride (p. 1795·1); sodium sulfate (p. 1888·1); potassium sulfate (p. 1793·2).
Respiratory-tract disorders.

Sal de Fruta Eno *GSK, Arg.; GSK, Braz.; GSK Consumer, Spain.*
Sodium bicarbonate (p. 1781·1); sodium carbonate (p. 2617·3); citric acid (p. 2480·3).
Gastric hyperacidity.

GSK, Chile.
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Gastrointestinal disorders.

Sal Lite *Rider, Chile.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Dietary salt substitute.

Sal Liviana En Sodio *Reccius, Chile.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Dietary salt substitute.

Sal Vichy Factitium *Ziololek, Pol.*
Sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); dibasic sodium phosphate (p. 1791·2); sodium sulfate (p. 1888·1); potassium bicarbonate (p. 1780·3).
Gastric hyperacidity; gallbladder inflammation; gallstones.

Salac
Note: this name may be used for preparations of different composition.
Andromaco, Arg.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

GenDerm, USA.†
Salicylic acid (p. 1719·1).
Acne.

Sal-Acid *Pedinol, USA.†*
Salicylic acid (p. 1719·1).
Warts.

Salactic Film *Pedinol, USA.*
Salicylic acid (p. 1719·1).
Warts.

Salactol *Dermal Laboratories, Irl.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; verrucas; corns; calluses.

Dermal Laboratories, UK.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); flexible collodion.
Warts; verrucas; corns; calluses.

Salacyn
Note: this name may be used for preparations of different composition.
Ashford, Singapore.
Sodium chloride (p. 1795·1).

Stratus, USA.
Salicylic acid (p. 1719·1).
Hyperkeratotic skin disorders.

Salagen *Novartis, Austria; Novartis, Belg.; Pfizer, Canad.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; MGI, Hong Kong; Novartis Ophthalmics, Hung.; Novartis, Irl.†; MGI, Israel; Novartis, Ital.; Novartis, Neth.; Novartis, Port.; MGI, Singapore; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; American Taiwan, Thai.†; Novartis, Turk.; Novartis, UK; Eisai, USA.*
Pilocarpine hydrochloride (p. 2010·3).
Dry mouth; radiation-induced xerostomia; Sjögren's syndrome.

Salakinase *Fortune Star, Indon.*
Bacillus subtilis natto; *Prunus mume.*
Thrombosis prophylaxis.

Salamflux *Atlantis, Mex.*
⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Salamol *Teva, Denm.; Teva, Hong Kong; Ivax, Irl.; Ivax, Malaysia; Teva, Mex.†; Teva, Neth.; Norton, NZ; Teva, Rus.; Teva, Switz.; Teva, UK.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease; asthma; bronchospasm.

Salamol Steri-Neb *Ivax, Irl.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salamol-Eko *Teva, Ukr.*
⊗Salbutamol (p. 1220·2).
Asthma; obstructive airways disease; bronchospasm.

Salapin *AFT, NZ; Pinewood, UK.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; bronchospasm.

Salarvant *Mylan, Denm.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Salatac *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Calluses; corns; warts; verrucas.

Salavira *Rafarm, Gr.*
⊗Serrapeptase (p. 2613·3).

Salazar *Cadila, India.*
Sulfasalazine (p. 1890·1).
Rheumatoid arthritis.

Salazine *Sriprasit, Thai.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; Crohn's disease; rheumatoid arthritis.

Salazopirina *Jaba Recordati, Port.*
Sulfasalazine (p. 1890·1).
Rheumatoid arthritis; inflammatory bowel disease.

Salazoprin *Cazi, Braz.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease.

Salazopyrin *Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Norw.; Pfizer, NZ; Pfizer, Pol.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Eczacibasi, Turk.; Pfizer, UK; Pfizer, Ukr.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease; rheumatoid arthritis; pyoderma gangrenosum; spondyloarthropathies; idiopathic juvenile arthritis.

Salazopyrina *Pfizer, Spain.*
Sulfasalazine (p. 1890·1).
Crohn's disease; ulcerative colitis.

Salazopyrine *Pfizer, Belg.; Pfizer, Fr.; Pfizer, Neth.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease; rheumatoid arthritis; haemorrhagic colitis.

Salbei *Natur Produkt, Rus.*
Sage (p. 2608·3).
Mouth and throat disorders.

Salbei Curarina *Harras-Curarina, Ger.*
Sage (p. 2608·3).
Mouth and throat inflammation.

Salben *Pulmomed, Rus.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salbetol *FDC, India.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbron *Kalbe, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbron Expectorant *Kalbe, Indon.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Salbroxol *Borshchagovskii, Ukr.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbu *Astellas, Ger.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbuair *Aldo-Union, Singapore; Aldo, Spain.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm; obstructive airways disease.

Salbubronch *Infectopharm, Ger.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbuden *Denver, Arg.*
⊗Salbutamol (p. 1220·2).

Salbuflo *EuroHealthcare, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbuhexal *Hexal, Ger.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbulair *Teva, Ger.; AMPDR, Port.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbulin *Fada, Arg.; Medsan, Turk.; Meda, UK.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; obstructive airways disease.

Salbulis *Proula, Venez.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease; premature labour.

Salbumed *MedGen, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Medifarm, Venez.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salbumed Plus *Lumar, Philipp.*
⊗Salbutamol (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Salbumol *GSK, Fr.; Help, Gr.*
⊗Salbutamol sulfate (p. 1220·2).
Premature labour; asthma.

Salbunova *Lavipharm, Gr.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma.

Salburol *Valmor, Venez.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

SalbuSandoz *Sandoz, Ger.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbusian *Asian Pharm, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutac *Polipharm, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutalan *Quimica y Farmacia, Mex.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutam *Bunker, Braz.; Nobel, Turk.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutamax *Uniao Quimica, Braz.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutamol Expectorant *Pharmaniaga, Malaysia.*
⊗Guaifenesin (p. 1666·2); salbutamol sulfate (p. 1220·2).
Bronchospasm; cough.

Salbutan *GSK, Venez.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutol *Nycomed, Arg.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sandoz, Turk.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutol Beclo *Nycomed, Arg.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease.

Salbutral *Cassara, Arg.; D & M, Chile.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbutral AC *Cassara, Arg.; D & M, Chile.*
⊗Salbutamol sulfate (p. 1220·2); ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Salbutral + Aeromed *Cassara, Arg.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salbutrim *Trima, Israel.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbuven *Pharos, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salbuven Expectorant *Pharos, Indon.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Salbuvent *Nycomed, Denm.; Breathe Pharmaceuticals, Irl.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm; asthma; obstructive airways disease.

Salca *Biotech, Venez.*
⊗Furosemide (p. 1387·1).
Oedema; barbiturate poisoning; hypertension; hepatic cirrhosis with ascites; heart failure.

Sal-Cal
Note: this name may be used for preparations of different composition.
Remedina, Gr.
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Salcal
Note: this name may be used for preparations of different composition.
Saval, Chile.
⊗Fenproporex hydrochloride (p. 2323·1).
Obesity.

Salcat *Pfizer, Port.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Salcatol *Nova, Gr.*
Calcitonin (salmon) (p. 1178·1).

Salcedol *Fardi, Spain.*
Potassium sulfate (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1); tartaric acid (p. 2626·1).
Constipation; digestive disorders.

Salco *Lisapharm, Israel.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Salcoat *Teijin, Jpn.*
⊗Beclometasone dipropionate (p. 1621·2).
Stomatitis.

Salcomed *Bajamed, Mex.*
⊗Salbutamol (p. 1220·2).
Respiratory-tract disorders.

Salda *Millimed, Thai.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Saldanar *Liconsa, Denm.; Liconsa, Irl.; Liconsa, Neth.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Salder S *Medley, Braz.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Acne; pityriasis versicolor; seborrhoea.

Saldeva
Note: this name may be used for preparations of different composition.
Bayer, Spain.
Caffeine (p. 1203·3); dimenhydrinate (p. 625·2); paracetamol (p. 115·1).
Dysmenorrhoea.

Saldiam *Jelfa, Pol.*
Diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Saldol *The Forty-Two, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Saledez *Pharmaceutical Factory of St Petersburg, Rus.*
Salicylic acid (p. 1719·1); chloramphenicol (p. 257·1).
Burns; ulcers; wounds.

Salenga *Zwitter, Gr.*
⊗Fluticasone propionate (p. 1638·1).

Salenol *Pharmahof, Thai.†*
Paracetamol (p. 115·1).
Pain; fever.

Sales Fruta Mag Viviar *Viviar, Spain.†*
Magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Constipation; gastric hyperacidity.

Salese *Nuvora, USA.*
Eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); zinc (p. 2126·1).
Dry mouth.

Saleto *Roberts, USA.*
Paracetamol (p. 115·1); aspirin (p. 22·2); salicylamide (p. 129·2); caffeine (p. 1203·3).
The name Saleto is also used for a preparation containing ibuprofen.
Pain.

Saleto-200 *Roberts, USA.*
Ibuprofen (p. 68·2).
The name Saleto is also used for a preparation containing paracetamol, aspirin, salicylamide, and caffeine.
Rheumatoid arthritis; osteoarthritis; pain; fever.

Salex *Coria, USA.*
Salicylic acid (p. 1719·1).
Skin and scalp disorders.

Salfer *Cofasa, Venez.*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Sal-Fiol *Kripps, Canad.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Salflex *Carnrick, USA.*
Salsalate (p. 130·1).
Musculoskeletal and joint disorders.

Salf-Pas *Salf, Ital.*
Sodium aminosalicylate (p. 215·2).
Tuberculosis.

Salgen *Erlimpex, Indon.*
Gentamicin (p. 304·2).
Skin infections.

Salgen Plus *Erlimpex, Indon.*
⊗Gentamicin (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Salgim *Pulmomed, Rus.*
⊗Salbutamol hemisuccinate (p. 1220·2).
Obstructive airways disease; premature labour.

Salhumin *Sanova, Austria.*
Bath additive: Sodium humate (p. 2618·3); salicylic acid (p. 1719·1).
Rheumatic disorders.

Salhumin Gel *Bastian, Ger.*
Glycol salicylate (p. 66·2).
Soft-tissue injury.

Salhumin Rheuma-Bad *Bastian, Ger.*
Salicylic acid (p. 1719·1); sodium humate (p. 2618·3).
Bath additive; musculoskeletal and joint disorders.

Sali di Salsomaggiore *Scharper, Ital.*
Minerals.
Nose and throat disorders; gynaecological disorders.

Sali-Adalat *Bayer, Ger.*
⊗Nifedipine (p. 1447·2); mefruside (p. 1429·3).
Hypertension.

Sali-Aldopur *Wabosan, Austria.*
⊗Spironolactone (p. 1499·3); bendroflumethiazide (p. 1315·2).
Hyperaldosteronism; hypokalaemia; oedema; hypertension.

Salic *Darrow, Braz.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Keratinisation disorders.

Salicairine *Legras, Fr.*
Loosestrife (p. 2545·2).
Diarrhoea.

SaliCept *Carrington, USA.*
Acemannan (p. 2426·3).
Wounds, injuries, and ulcers of the oral mucosa.

Salicetil *Brasterapica, Braz.*
Aspirin (p. 22·2).

Salicil *Bersan, Ital.*
Salicylic acid (p. 1719·1).
Scalp disorders.

Ducto, Braz.
Aspirin (p. 22·2).
Fever; pain.

Salicin *Greenpharma, Braz.*
Aspirin (p. 22·2).
Fever; pain.

Salicina *Ratiopharm, Ital.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; pain.

Salicort *Cassara, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin and scalp disorders.

Salicortex *Labofarm, Pol.*
Salix purpurea (p. 129·2).
Cold symptoms; rheumatic disorders.

Salicrem *Gezzi, Arg.*
Diethylamine salicylate (p. 51·3); benzocaine (p. 1980·2).
Musculoskeletal and joint disorders.

Salicrem Forte *Gezzi, Arg.*
Diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Salicrem K *Gezzi, Arg.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders.

Salicyd *Polychronus, Gr.*
Salicylic acid (p. 1719·1).
Skin disorders.

Salicylcafeina *Menarini, Port.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Fever; pain.

Salicylol *Profarm, Pol.*
Castor oil (p. 2472·1); salicylic acid (p. 1719·1).
Keratinisation disorders.

Salicyl-Zwavelzalf *Nufarindo, Indon.*
Salicylic acid (p. 1719·1); precipitated sulfur (p. 1721·1).
Skin irritations; scabies.

Sali-Decoderm *Almirall Hermal, Ger.*
⊗Fluprednidene acetate (p. 1637·3); salicylic acid (p. 1719·1).
Skin disorders; scalp disorders (tincture).

Saliderm *Profarm, Pol.*
Salicylic acid (p. 1719·1).
Keratinisation disorders.

Salidex *Braun, Norw.*
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; carbohydrate source.

Salidur *Miralfarma, Spain.*
⊗Furosemide xantinol; triamterene (p. 1518·3).
Oedema; hypertension.

Saliject *Omega, Canad.*
Sodium salicylate (p. 132·2).
Sclerotherapy.

Salikaren *Rekah, Israel.*
Salicylic acid (p. 1719·1).
Keratinisation disorders.

Saliker *Roche-Posay, Braz.*
Salicylic acid (p. 1719·1); piroctone olamine (p. 1716·3); iodopropynyl butyl carbamate (p. 2156·3); capryloyl salicylate; capryloyl glycine (p. 2173·3).
Dandruff; seborrhoeic dermatitis.

Salilax *Orion, Denm.†; Orion, Swed.†*
Magnesium oxide (p. 1857·3).
Bowel evacuation.

Salilex *Medihealth, Mex.*
Salicylic acid (p. 1719·1); dexpanthenol (p. 2582·2); menthol (p. 2553·2); camphor (p. 2466·2).
Acne.

Saliment *Vida, Hong Kong.†*
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Salimidin *LKM, Arg.*
Itraconazole (p. 583·3).
Fungal infections.

Salin *Bayer Schering, Rus.*
Sodium chloride (p. 1795·1).
Nasal hygiene.

SalinaGel *Naveh, Philipp.*
Sodium chloride (p. 1795·1).
Nasal dryness.

Salinagel *Naveh, Israel.*
Sodium chloride (p. 1795·1); hyaluronic acid (p. 2526·2).
Nasal irritation; nasal dryness.

Salinal *Julphar, UAE.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; adjunct in gastroscopy and bowel radiography.

Salinase
Note: this name may be used for preparations of different composition.
Pediapharma, Philipp.
Sodium chloride (p. 1795·1).
Nasal dryness and congestion.

TS, Ital.
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); potassium aspartate (p. 1793·1); sodium bicarbonate (p. 1781·1); magnesium aspartate (p. 1787·1).

Salinex *Sandoz, Canad.; Muro, USA.*
Sodium chloride (p. 1795·1).
Nasal irritation; nasal hygiene.

Salinex Nasal Lubricant *Sandoz, Canad.*
Macrogol (p. 2547·3); propylene glycol (p. 2205·2); sodium chloride (p. 1795·1).
Nasal lubricant.

Salinum *Crawford, UK.*
Polysaccharide-rich linseed extract (p. 2544·2).
Dry mouth.

Salipax *Mepha, Malaysia; Mepha, Pol.†; Mepha, Port.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder; mixed anxiety depressive states; bulimia nervosa.

Salipirin *Geolab, Braz.*
Aspirin (p. 22·2).

Salipra *BMM, Fin.†*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sali-Prent *Bayer, Ger.*
⊗Acebutolol hydrochloride (p. 1289·2); mefruside (p. 1429·3).
Hypertension.

Salipsor *Verisfield, Gr.*
Salicylic acid (p. 1719·1).
Skin disorders.

Salisoap *Galderma, Braz.*
Shampoo: Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Seborrhoeic dermatitis.

Galderma, Braz.
Soap: Salicylic acid (p. 1719·1); sulfur (p. 1721·1); triclosan (p. 1773·2).
Seborrhoeic dermatitis.

Salisol *Rekah, Israel.†*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Keratinisation disorders; skin disinfection.

Salisvit *Cifarma, Braz.*
Aspirin (p. 22·2).
Pain; fever.

Salitanol Estreptomicina *Quimpe, Spain.†*
Albumin tannate (p. 1815·1); dihydrostreptomycin sulfate (p. 286·3); sulfathiazole (p. 368·3).
Gastrointestinal infections.

Salitil *Cifarma, Braz.*
Aspirin (p. 22·2).
Fever; pain.

Saliva Natura *Medac, UK.*
Sorbitol (p. 2092·1); xylitol (p. 2220·3); eriodictyon (p. 1665·2).
Dry mouth.

Saliva natura *Medac, Ger.*
Sorbitol (p. 2092·1); xylitol (p. 2220·3); eriodictyon crassifolium (p. 1665·2).
Dry mouth.

Saliva Orthana *Pharmachemie, Neth.*
Mucin (p. 2186·1); xylitol (p. 2220·3).
Dry mouth.

Salivan *Apsen, Braz.*
Carmellose sodium (p. 2175·2).
Dry mouth.

Salivart *Gebauer, Hong Kong†; Gebauer, USA.*
Carmellose sodium (p. 2175·2); sorbitol (p. 2092·1); electrolytes (p. 1775·1).
Dry mouth.

SalivaSure *Scandinavian Formulas, USA.*
Malic acid (p. 2549·2); citric acid (p. 2480·3); calcium hydrogen phosphate (p. 1783·3); xylitol (p. 2220·3).
Saliva substitute.

Saliveze *Wyvern, UK.*
Electrolytes (p. 1775·1).
Dry mouth.

Salivia *LKM, Arg.*
Ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Inflammation; pain.

Salivix *koGen, UK.*
Malic acid (p. 2549·2); calcium lactate (p. 1784·1); sodium phosphate (p. 1791·2).
Dry mouth.

Salivoral *Novagen, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Xerostomia.

Salix *Scandinavian Natural Health & Beauty, USA.*
Artificial saliva.

Salkera *Onset, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratotic skin disorders.

Salmagne
Note: this name may be used for preparations of different composition.
Fardi, Spain.
⊗Magnesium citrate (p. 1857·1); magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); mannitol (p. 1427·3).
Constipation; digestive disorders.

Remedina, Gr.
⊗Labetalol hydrochloride (p. 1416·2).

Salmaplon *Khandelwal, India.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salmax *CCM, Malaysia.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Salmeflo *Metz, Philipp.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Salment *SJA, Gr.*
⊗Salmeterol xinafoate (p. 1224·1).

Salmetedur *Menarini, Ital.*
⊗Salmeterol xinafoate (p. 1224·1).
Bronchospastic disorders.

Salmeter *Reddy, India.*
⊗Salmeterol (p. 1224·1).
Asthma.

Salmocalcin *Viofar, Gr.; Farmed, Turk.*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; Paget's disease of bone; osteoporosis; osteolysis.

Salmocide *Atlantis, Mex.†*
Furazolidone (p. 933·3).
Gastrointestinal infections.

Salmocin *Mega Lifesciences, Thai.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; osteolytic bone pain; Paget's disease of bone; neurodystrophic disorders.

Salmofar *Adipharm (Αδηφαρμ), Gr.; Lafare, Ital.†*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; osteoporosis; reflex sympathetic dystrophy.

Salmol *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.; Biolab, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm; obstructive airways disease; premature labour.

Salmol Expectorant *Biolab, Thai.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Salmon Oil *Gap, Gr.†*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Hyperlipidaemias.

Salmoten *Adipharm (Αδηφαρμ), Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Salocef *New Research, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Salofalk *Biotoscana, Arg.; Cevallos, Arg.; Orphan, Austral.; Merck, Austria; Aptalis, Canad.; Biotoscana, Chile; Falk, China; Falk, Cz.; Falk, Denm.; Falk, Fin.; Falk, Ger.; Galenica, Gr.; Falk, Hong Kong; Falk, Hung.; Darya-Varia, Indon.; Falk, Indon.; Falk, Irl.; Falk, Malaysia; Farmasa, Mex.; Falk, Neth.; Meda, Norw.; Falk, Philipp.; Falk, Pol.; Falk, Port.; Falk, Rus.; Falk, Singapore; Falk, Spain; Meda, Swed.; Vifor, Switz.; Falk, Thai.; Ali, Turk.; Falk, UK; Falk, Ukr.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease; haemorrhoids.

Sal-Oil-T *Syosset, USA.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Seborrhoea.

Salomethyl *Mitsubishi-Tokyo, Hong Kong.†*
Methyl salicylate (p. 92·1); glycol salicylate (p. 66·2); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); capsaicin (p. 35·1); benzyl nicotinate (p. 29·3).
Musculoskeletal and soft-tissue disorders; neuralgia; insect bites; pruritus; headache.

Salomol *Gerolymatos, Gr.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salonair *Salonpas, UK.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); benzyl nicotinate (p. 29·3); glycol salicylate (p. 66·2).
Muscle and joint pain.

Salongo *Rottapharm, Spain.*
Oxiconazole nitrate (p. 591·3).
Fungal skin and nail infections.

Salonpas *Hisamitsu, USA.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Hisamitsu, Braz.; Andromaco, Chile.
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); glycol salicylate (p. 66·2); thymol (p. 1772·2).
Musculoskeletal and joint pain; neuralgia; musculoskeletal and joint disorders.

Vianex (Βιανεξ), Gr.; Avantgarde, Ital.; Hisamitsu, NZ.
Menthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue pain; inflammation; pain.

Avantgarde, Ital.
Topical spray: Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); benzyl nicotinate (p. 29·3); glycol salicylate (p. 66·2).
Musculoskeletal, joint, and soft-tissue pain.

Hisamitsu, Canad.
Camphor (p. 2466·2); glycol salicylate (p. 66·2); levomenthol (p. 2553·2).

Hisamitsu, Malaysia.
Methyl salicylate (p. 92·1); glycol salicylate (p. 66·2); menthol (p. 2553·2); thymol (p. 1772·2); camphor (p. 2466·2); tocoferil acetate (p. 2119·2).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Salonpas, UK.
Methyl salicylate (p. 92·1); glycol salicylate (p. 66·2).
Musculoskeletal and joint pain.

Salonpas Aqua Patch *Hisamitsu, USA.†*
Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Arthritis Pain Patch *Hisamitsu, USA.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Gel *Veximp, Hung.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Gel Patch Hot *Hisamitsu, USA.*
Capsicum (p. 2469·3); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Gel-Patch
Note: this name may be used for preparations of different composition.
Veximp, Hung.
Menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Hot *Hisamitsu, USA.*
Capsicum (p. 2469·3).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Liniment *Veximp, Hung.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); thymol (p. 1772·2); mint oil (p. 2560·1); capsaicin (p. 35·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Medicated Plaster *DKSH, Hong Kong.†*
Camphor (p. 2466·2); glycol salicylate (p. 66·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); thymol (p. 1772·2).

Salonpas Original *Hisamitsu, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Pain Relief Patch *Hisamitsu, USA.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Patch *DKSH, Hong Kong†; Veximp, Hung.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue pain.

Salonsip Hot Patch *DKSH, Hong Kong.†*
Camphor (p. 2466·2); capsicum (p. 2469·3); glycol salicylate (p. 66·2); menthol (p. 2553·2).

Salonsip Plaster *DKSH, Hong Kong.†*
Camphor (p. 2466·2); glycol salicylate (p. 66·2); menthol (p. 2553·2).

Salopyrine *Adelco, Gr.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease.

Saloril *Cooper (Κοπερ), Gr.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with excess mucus.

Salospir *Unipharma, Gr.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thrombosis prophylaxis.

Salospir C-500 *Unipharma, Gr.*
Aspirin (p. 22·2); vitamin C (p. 2110·3).
Pain; fever.

Salospir Extra *Unipharma, Gr.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Salotannal *Sanofi-Aventis, Pol.†*
Salol (p. 129·3); albumin tannate (p. 1815·1).
Diarrhoea.

Salovit *Medi Service, Ital.*
Yellow tablets: arginine (p. 2049·1); vitamins; ubidecarenone (p. 2637·1); selenium (p. 2086·3); curcuma; green tablets: arginine; carnitine (p. 2053·2); vitamin C (p. 2110·3); zinc (p. 2126·1); spirulina (p. 2622·1).
Tonic for males.

Saloxyl *Herbacos Recordati, Cz.*
Ichthammol (p. 1705·3); salicylic acid (p. 1719·1).
Infected skin disorders.

Salpad *Pharmatrix, Arg.*
Salicylic acid (p. 1719·1).
Acne; keratinisation disorders.

Salpad T *Pharmatrix, Arg.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Dandruff; seborrhoeic dermatitis; psoriasis.

Salpirin *Sun-Farm, Pol.*
Aspirin (p. 22·2).
Pain; fever.

Sal-Plant *Pedinol, USA.*
Salicylic acid (p. 1719·1).
Warts.

Salpraz *Alphapharm, Austral.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Salsep *Libbs, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion; rhinitis.

Salsil *Embil, Turk.*
Salicylic acid (p. 1719·1).
Skin disorders.

Salsitab *Upsher-Smith, USA.*
Salsalate (p. 130·1).
Pain; fever; inflammation.

Salsol
Note: this name may be used for preparations of different composition.
Kee, India.
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Salsol A
Note: this name may be used for preparations of different composition.
Teva, Hung.†
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Salspray *Biogalenic, Venez.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Salsyvase *Meda, Swed.*
Salicylic acid (p. 1719·1).
Skin disorders.

Saltermox *Adcock Ingram, S.Afr.*
Amoxicillin (p. 216·2).
Bacterial infections.

Salterpyn *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Formerly known as Adco-Salterpyn.
Pain with tension.

Salticin *Interbat, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Saltos
Note: this name may be used for preparations of different composition.
Pulmomed, Rus.
⊗Salbutamol hemisuccinate (p. 1220·2).
Obstructive airways disease.

Sal-Tropine *Hope, USA.†*
Atropine sulfate (p. 1310·2).

SaltStable Lo *Humco, USA.*
Isopropyl palmitate (p. 2191·1); lecithin (p. 2542·2).

Salubion *Merck, Chile.*
Vitamins; minerals; rutoside (p. 2505·3).
Tonic.

Salubion Ginseng *Merck, Chile.*
Vitamins; minerals; trace elements; ginseng (p. 2513·3).
Tonic.

Saludex *Salus, Mex.*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Saluket-H1 *Salus, Mex.*
Ketotifen (p. 631·3).
Asthma.

Salumin *Hasco-Lek, Pol.†*
Menthol (p. 2553·2); sage (p. 2608·3); tannic acid (p. 2625·2).
Mouth and throat disorders.

Salures *Pfizer, Swed.*
⊗Bendroflumethiazide (p. 1315·2).
Hypertension; oedema; renal calculi.

Salurin *Julphar, UAE.*
⊗Furosemide (p. 1387·1).
Oedema; forced diuresis.

Saluron *Apothecon, USA.*
⊗Hydroflumethiazide (p. 1406·3).
Oedema; hypertension.

Salus Diuretic *Sal-Bert, Hung.*
Birch leaf (p. 2457·3).
Oedema; renal calculi.

Salus Floragink *Sal-Bert, Hung.*
Ginkgo biloba (p. 2512·3).
Cerebrovascular disorders.

Salus Herz-Schutz *Sal-Bert, Hung.*
Magnesium amino acid chelate (p. 2048·3); tocoferil acetate (p. 2119·2); crataegus (p. 2488·1).
Nervous disorders; cardiovascular disorders.

Salus Mistel-Tropfen *Salushaus, Ger.*
Mistletoe (p. 2560·2).
Atherosclerosis.

Salus Multipretten *Sal-Bert, Hung.*
⊗Caraway (p. 2470·2); fennel (p. 2503·2); aniseed (p. 2444·2); coriander (p. 2486·3); peppermint (p. 1877·1); achillea (p. 2427·3); imperatoria; bromelain (p. 2460·3); aspergillus oryzae; caraway oil (p. 2470·3); fennel oil (p. 2503·3); anise oil (p. 2444·3); peppermint oil (p. 1877·1); coriander oil (p. 2487·1).
Digestive disorders.

Salus Zinnkraut *Salushaus, Ger.*
Equisetum (p. 2500·1).
Oedema.

Salusan *Salus, Canad.†*
Hordeum sativum; bishop's weed; equisetum (p. 2500·1); crataegus (p. 2488·1); lupulus (p. 2546·1); St John's wort (p. 449·1); lemon (p. 2542·3); lemon grass (p. 2543·2); melissa (p. 2552·3); mistletoe (p. 2560·2); sweet orange peel (p. 2576·2); passion flower (p. 2584·1); rosemary (p. 2607·2); bearberry (p. 2453·2); valerian (p. 2640·2); wheat-germ oil (p. 2647·1).

Saluscor Herz-Schutz *Salushaus, Ger.†*
Alpha tocoferil acetate (p. 2119·2); magnesium complex with acid hydrolysate of maize starch; crataegus (p. 2488·1).
Cardiovascular disorders.

Salutaris *Incaico, Arg.*
Ispaghula (p. 1849·1); coriander (p. 2486·3); soluble fibre.
Hypercholesterolaemia; obesity.

Salva vid munsår *Algol, Swed.*
Echinacea purpurea (p. 2498·1).
Cold sores; minor skin wounds.

Salvacam *Salvat, Spain.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Salvacolina *Salvat, Spain.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Salvacoll *Medipharm, Chile.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Salvacolon *Salvat, Spain.*
Bacillus subtilis; vitamins; amino acids.
Restoration of the gastrointestinal flora; gastrointestinal disorders.

Salvacyl *Ipsen, Belg.; Ipsen, Denm.; Ipsen, Fin.; Ipsen, Fr.; Pfleger, Ger.; Ipsen, Neth.; Debio, Switz.; Ipsen, UK.*
⊗Triptorelin embonate (p. 2311·1).
Deviant sexual behaviour in men.

Salvalerg *GSK, Arg.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; rhinitis; urticaria.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Salvapar *Ipsen, Norw.*
⊗Triptorelin embonate (p. 2311·1).
Deviant sexual behaviour in males.

Salvarina *Salvat, Spain.*
Caffeine (p. 1203·3); dimenhydrinate (p. 625·2); ibuprofen (p. 68·2).
Dysmenorrhoea.

Salvarom *Medifarm, Rus.*
Chamomile (p. 2474·1); sage (p. 2608·3).

Salvax *Quinnova, USA.*
Salicylic acid (p. 1719·1).
Hyperkeratosis.

Salvax Duo *Quinnova, USA.*
⊗Topical spray, salicylic acid (p. 1719·1); topical spray, urea (p. 1727·3).
Skin disorders.

Salvaxil *Fada, Arg.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Salvaxil Plus *Fada, Arg.*
Simvastatin (p. 1489·2); ezetimibe (p. 1379·2).
Hyperlipidaemias.

Šalvěj Lékařská List *Leros, Cz.†*
Sage (p. 2608·3).
Mouth disorders; dyspepsia; diarrhoea.

Šalvějová Nať *Megafyt-R, Cz.*
Sage (p. 2608·3).
Gastrointestinal disorders; mouth inflammation; upper respiratory-tract disorders.

Salvelox *EMS, Braz.*
Lidocaine hydrochloride (p. 1988·2); benzethonium chloride (p. 1738·1).

Salvent *Okasa, Thai.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salvesept
Note: this name may be used for preparations of different composition.
Protector, Canad.†
Cetrimonium bromide (p. 1742·3); chlorhexidine gluconate (p. 1743·3).

Salvex *Vamsler, Philipp.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Salvex XP *Vamsler, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Salvi CAL E-G *Baxter, Pol.*
Glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

salviamin G-E *Baxter, Ger.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Salviamin Hepar *Baxter, Pol.†*
Amino acids; electrolytes (p. 1775·1).
Parenteral nutrition in liver disorders.

Salvian *Bio-Health, UK.*
Sage (p. 2608·3).
Menopausal hyperhidrosis.

Salviasept *Herbapol Lublin, Pol.*
Achillea (p. 2427·3); chamomile (p. 2474·1); cineole (p. 2479·1); fennel (p. 2503·2); marjoram oil (p. 2550·1); mint oil (p. 2560·1); peppermint (p. 1877·1); menthol (p. 2553·2); sage (p. 2608·3); sage oil (p. 2609·1); thyme oil (p. 2630·3); thyme (p. 2630·2); clove oil (p. 2481·3).
Mouth and throat disorders; respiratory-tract congestion.

Salviathymol N *Madaus, Ger.; Rottapharm, Ger.*
Sage oil (p. 2609·1); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); fennel oil (p. 2503·3); anise oil (p. 2444·3); menthol (p. 2553·2); thymol (p. 1772·2).
Mouth and throat disorders.

Salviette H *Wyeth Consumer, Ital.*
⊗Hamamelis water (p. 2523·3); glycerol (p. 2517·2).
Anal cleansing; haemorrhoids.

salvilipid *Baxter, Ger.†*
Soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Salvin *Vifitch, Rus.*
Sage (p. 2608·3).
Mouth and throat disorders.

Salvisar *Biochimic, Rus.*
Common viper venom; salicylic acid (p. 1719·1); camphor (p. 2466·2); turpentine oil (p. 2636·3).
Arthralgia; myalgia; neuralgia; sciatica.

Salvit M *Belfar, Braz.*
Vitamins; minerals.

Salvital *Reckitt Benckiser, Austral.*
Magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Dyspepsia; nausea; tonic.

Salvitos *Ronnet, Arg.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Salvituss *FIRMA, Ital.*
Levodropropizine (p. 1662·3).
Cough.

Salvysat *Mayrhofer, Austria†; Ysatfabrik, Ger.*
Sage leaves (p. 2608·3).
Hyperhidrosis; mouth and throat inflammation.

Salzone *Wallace Mfg Chem., UK.*
Paracetamol (p. 115·1).
Pain; fever.

Samarial *Samjin, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Samarin
Note: this name may be used for preparations of different composition.
Berlin Pharm, Thai.
Silymarin (p. 1561·2).
Liver disorders.

Cederroth, Denm.; Cederroth, Swed.
Citric acid (p. 2480·3); potassium sodium tartrate (p. 1879·3); sodium carbonate (p. 2617·3); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).
Heartburn; indigestion.

Cederroth, Hung.
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); sodium carbonate (p. 2617·3); potassium sodium tartrate (p. 1879·3).
Gastric hyperacidity.

Cederroth, Swed.
Chewable tablets: Calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2); magnesium carbonate (p. 1856·2).
Heartburn; indigestion.

Cederroth, Swed.
Effervescent tablets: Citric acid (p. 2480·3); sodium citrate (p. 1781·2); potassium bicarbonate (p. 1780·3); sodium carbonate (p. 2617·3); sodium bicarbonate (p. 1781·1); potassium sodium tartrate (p. 1879·3).
Heartburn; indigestion.

Samaruc
Note: this name may be used for preparations of different composition.
Vitarum, Arg.
Piroxicam (p. 125·3).
Inflammation; pain.

Fabop, Arg.†
Isoxsuprine (p. 2535·2).

Samba *Gedeon Richter, Hung.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Triphasic oral contraceptive.

Sambee *Medicpharma, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).

Sambucus Comp *Weleda, S.Afr.†*
Sambucus nigra (p. 2609·3); berberis; teucrium scorodonia; phosphorus (p. 2589·2).
Homoeopathic preparation.

Sambucus-Plus *Doctor H, Rus.*
⊗Ephedra distachya (p. 1663·1); ambra grisea (p. 2440·3); bryonia cretica (p. 2461·3); drosera (p. 2497·2); lobelia inflata (p. 2323·2); sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Same Plast *Savoma, Ital.*
Emollient.

Samederm *Savoma, Ital.*
Soap substitute.

Samertan *Bago, Chile.†*
Telmisartan (p. 1509·3).
Hypertension.

Same-Seb *Savoma, Ital.*
Colloidal sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Seborrhoea; acne.

Same-Seb Beta *Savoma, Ital.*
Salicylic acid (p. 1719·1); glycolic acid (p. 1704·3).
Acne.

Sametil *Gestafarma, Port.*
Salicylic acid (p. 1719·1); methyl salicylate (p. 92·1).
Seborrhoeic dermatitis; psoriasis.

Sametrix *Savoma, Ital.*
Saw palmetto (p. 2363·3); sitosterol (p. 1471·2); resveratrol (p. 2603·2); zinc gluconate (p. 2126·2).
Dietary supplement.

Sametto *Mega Lifesciences, Thai.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Samezil *KRKA, Cz.†; KRKA, Rus.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Sam-Ginseng Royal *Penta, Hung.*
Vitamins; royal jelly (p. 2608·1); ginseng (p. 2513·3); crataegus (p. 2488·1); mistletoe (p. 2560·2); kola (p. 2648·2).
Tonic.

Samiclar *Ferakon, Gr.*
Glucosamine sulfate (p. 2515·3).

Samilstin *LPB, Ital.*
Octreotide (p. 1924·1).
Endocrinal tumours of the gastrointestinal tract; acromegaly; postoperative complications of pancreatic surgery; pancreatic fistula; diarrhoea associated with immunodeficiency; variceal haemorrhage.

Samin *Weifa, Norw.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Samixon *Hikma, Cz.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Samjizon *Samjin, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Sam-Ko *2M, Thai.*
Zinc oxide (p. 1729·1); methyl salicylate (p. 92·1).

Samkol *Dermapharm, Denm.*
Ketoconazole (p. 585·3).
Seborrhoeic dermatitis; pityriasis.

S-Amlip *Cipla, India.*
S-Amlodipine.
Hypertension.

Sammibi *SAM Nordic, Fin.*
Technetium-99m (p. 2228·1) sestamibi.
Radionuclide imaging.

Sammotsuogonto *Tsumura, Jpn.*
Rehmannia root; skullcap root (p. 2617·1); sophora root.
Traditional Kampo medicine.

Samnir *Siam Bheasach, Thai.*
Cefdinir (p. 238·3).
Bacterial infections.

Samonil *IQFA, Mex.*
Metronidazole (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis.

Samonter *Sanitas, Arg.†*
⊗Mazindol (p. 2324·1).
Obesity.

Samox *Seven Stars, Thai.*
Amoxicillin (p. 216·2).
Bacterial infections.

Samoxil *Olan-Kemed, Thai.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Samoxin *Sriprasit, Thai.*
Amoxicillin (p. 216·2).
Bacterial infections.

Samper *AGIPS, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Samprost *Samson-Med, Rus.*
Bovine prostate extract (p. 2444·1).
Prostatic disorders.

Samsca *Otsuka, Canad.; Otsuka, Cz.; Otsuka, Denm.; Otsuka, Ger.; Otsuka, Irl.; Otsuka, Jpn; Otsuka, Neth.; Otsuka, Norw.; Otsuka, Pol.; Otsuka, Port.; Otsuka, Spain; Otsuka, Swed.; Otsuka, UK; Otsuka, USA.*
⊗Tolvaptan (p. 2632·3).
Hyponatraemia.

Samson *Sanli, Turk.*
Ferric ammonium citrate (p. 2060·1).
Iron deficiency; iron-deficiency anaemia.

Samtirel *GSK, Jpn.*
Atovaquone (p. 928·2).
Pneumocystis pneumonia.

Samyr *Abbott, Ital.; Abbott, Mex.*
Ademetionine sulfate tosilate (p. 2430·1).
Depression; liver disorders.

San Chen *Qilu, China.*
Zopiclone (p. 1118·1).
Insomnia.

San Jiu Jun Bi Sha *Bo Kang, China.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

San Si Teng *Minsheng, China.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

San Le Xi *Kaixi, China.*
Aniracetam (p. 389·1).
Dementia.

San Xiao Ping *Lanling, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

San Yuan Shu Xing *Huitian, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Sanabronch *Sandoz, Switz.*
Ivy (p. 2536·2).
Cough.

Sanadermil *Vifor, Switz.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Sanadorm *Sandoz, Switz.*
Valerian (p. 2640·2).
Nervous disorders; insomnia.

Sanadryl *Sanbe, Indon.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sulfogaiacol (p. 1678·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; respiratory-tract congestion.

Sanadryl DMP *Sanbe, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; respiratory-tract congestion.

Sanafem *Sandoz, Switz.*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Sanaflex *Sandoz, Switz.*
Devil's claw (p. 42·3).
Musculoskeletal and joint disorders.

Sanaflor *Sandoz, Switz.*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea.

Sanaflu *Sanbe, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Influenza symptoms.

Sanaflu Plus *Sanbe, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; cough.

Sanaform *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1).
Surface disinfection.

Sanagás *Ducto, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Sanalepsi N *Bayer, Switz.*
Doxylamine succinate (p. 627·3).
Nervous disorders; hypersensitivity reactions.

Sanaler *Sanitas, Chile.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Sanaler-D *Sanitas, Chile.*
⊗Cetirizine (p. 619·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Sanalgin *Interlogim, Neth.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Sanalgin N *Gebro, Switz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Sanalum *Sandoz, Switz.*
St John's wort (p. 449·1).
Depression; sleep disorders.

Sanamidol *Inkeysa, Spain.†*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Sanapens *Sandoz, Switz.†*
Ginkgo biloba (p. 2512·3).
Mental function impairment; vertigo.

Sanaprav *Daiichi Sankyo, Ital.; Daiichi Sankyo, Port.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Sanasar *Hertz, Braz.*
Benzyl benzoate (p. 2149·1).
Scabies.

Sana-Scrub *Forder, Arg.*
Carica papaya; polyethylene granules.
Skin cleansing.

Sanasepton *Ritsert, Ger.*
Erythromycin (p. 291·2) or erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Sana-Sol *Nycomed, Rus.*
Vitamins.

Sanasol *Eczacibasi, Turk.*
Vitamins.

Sanason *Lek, Cz.†; Lek, Rus.; Lek, Ukr.†*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Sedative; sleep disorders; anxiety.

Sanasthmax *Chiesi, Ger.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; bronchitis.

Sanasthmyl *GSK, Ger.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma; bronchitis; tracheitis.

Sanatison Mono *Taurus, Ger.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders; burns.

Sanatogen *Roche Consumer, UK.*
Vitamins; minerals; nutritional supplements.

Zydus, India.
Dietary supplement.
Tonic.

Roche Consumer, Irl.†
Vitamins; with or without minerals.

Sanaven
Note: this name may be used for preparations of different composition.
Stada, Ger.
Chondroitin sulfate (p. 2476·1).
Superficial vascular disorders.

Sanavir *Hospira, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Sanavitan S *Bottger, Ger.†*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Sanaxeen *Natumin, Malaysia.*
Pollen extract (p. 2593·3).
Urinary-tract disorders.

Sanaxin *Sandoz, Austria.*
Cefalexin (p. 234·1).
Bacterial infections.

Sanazet *Sanbe, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Sanblex *Medipharm, Chile.*
Sulpiride (p. 1107·3).
Depression; behaviour disorders; irritability.

San-B-Plex *Sanbe, Indon.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Nutritional supplement for children and infants.

Sancago *Chinta, Thai.*
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal, joint and soft-tissue disorders; insect bites.

Chinta, Thai.
Tablets: Indometacin (p. 71·2); methocarbamol (p. 2025·3).
Musculoskeletal and joint disorders; gout.

Sancap *Novartis, Gr.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Sancazid *Sandoz, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sancefix *Sandoz, Turk.*
Cefixime (p. 240·3).
Bacterial infections.

Sancoba *Santen, China.*
Vitamin B_{12} (p. 2107·2).
Tired eyes.

Sancom *Hovid, Philipp.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Sancor Biosalud *Sancor, Arg.*
A range of preparations for enteral nutrition.

Sancortmycin *Caprifarmindo, Indon.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone (p. 1640·1).
Skin infections; wounds.

Sancotec *Deltapharm, Hong Kong†; Daehan, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Sanctura *Allergan, Canad.; Allergan, USA; Indevus, USA; Odyssey, USA.*
Trospium chloride (p. 2371·1).
Bladder instability.

Sancuso *ProStrakan, Philipp.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

ProStrakan, UK; ProStrakan, USA.
Granisetron (p. 1844·3).
Nausea and vomiting associated with chemotherapy; nausea and vomiting.

Sanda *Okasa, Thai.; TTN, Thai.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; uveitis; rheumatoid arthritis; nephrotic syndrome; psoriasis.

Sandace *Sandoz, Turk.*
Ramipril (p. 1483·3).

Sandepril *Mersifarma, Indon.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Sanderson's Throat Specific *Sandersons, UK.*
Mixture: Acetic acid (p. 2426·3); quassia (p. 2601·1); squill (p. 1677·3); capsicum (p. 2469·3).
Sore throat; catarrh.

Sandersons, UK.
Pastilles: Honey (p. 2072·1); squill vinegar (p. 1677·3); capsicum (p. 2469·3); tolu (p. 1679·2); menthol (p. 2553·2); cinnamic acid (p. 1748·3); benzoic acid (p. 1738·2); eucalyptus oil (p. 2501·2).
Sore throat; catarrh.

Sandimmun *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, Venez.*
Ciclosporin (p. 1945·2).
Nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis; graft-versus-host disease; atopic eczema; medullary aplasia.

Sandimmune *Novartis, Canad.; Novartis, Neth.; Novartis, USA.*
Ciclosporin (p. 1945·2).
Graft-versus-host disease; transplant rejection.

Sandival *Bouzen, Arg.*
Tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Bouzen, Arg.†
Elixir: Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Sandival Desleible *Bouzen, Arg.*
Benzydamine hydrochloride (p. 29·2).
Inflammation; pain.

Sandocal *Novartis Consumer, Austral.†; Novartis Consumer, Irl.; Sandoz, Port.†; Novartis Consumer, UK.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium deficiency; osteomalacia; osteoporosis; rickets; neonatal tetany; hypocalcaemia; calcium supplement.

Novartis, India; Novartis, Venez.
Calcium carbonate (p. 1824·3).
Calcium supplement; calcium deficiency.

Sandocal with Vit D_3 *Novartis, India.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium supplement; calcium deficiency; osteoporosis.

Sandocal-D *Sandoz, Ger.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Sandocal+D *Novartis Consumer, UK.†*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Sandocef *Sandoz, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Sandoglobulin *CSL, Austral.†; CSL, Austria†; CSL, Canad.†; CSL, Ger.†; CSL, Gr.; CSL, Israel; CSL, NZ; Imed, Pol.; ZLB, UK.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; passive immunisation; Kawasaki disease; immunodeficiency; agammaglobulinaemia; auto-immune disorders; bone marrow transplantation; Guillain-Barré syndrome.

Sandoglobulina *CSL, Arg.; CSL, Braz.; CSL, Ital.; CSL, Mex.; CSL, Port.*
A normal immunoglobulin (p. 2403·3).
Immune thrombocytopenia; immunodeficiency; passive immunisation; hypogammaglobulinaemia; Kawasaki disease; auto-immune disorders; Guillain-Barré syndrome.

Sandoglobuline *CSL, Belg.; CSL, Fr.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; passive immunisation; immune thrombocytopenia; Guillain-Barré syndrome; neuropathies; hypogammaglobulinaemia; Kawasaki disease.

Sando-K *HK Pharma, UK.*
Potassium bicarbonate (p. 1780·3); potassium chloride (p. 1793·2).
Hypokalaemia.

Sandolin *Sanli, Turk.†*
Salol (p. 129·3); mint oil (p. 2560·1); star anise oil (p. 2622·2).
Oral hygiene.

Sandomigran *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Paladin, Canad.; Novartis, Cz.; Novartis, Hong Kong; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, NZ; Novartis, S.Afr.; Laus, Spain; Novartis, Turk.*
Pizotifen malate (p. 678·2).
Migraine; anorexia; cluster headache; vascular headache.

Sandomigrin *Novartis, Denm.; Novartis, Swed.*
Pizotifen malate (p. 678·2).
Migraine; cluster headache.

Sandonorm *Zentiva, Cz.†; Novartis, Gr.; Egis, Hung.; Novartis, Switz.†*
⊗Bopindolol malonate (p. 1326·3).
Angina pectoris; hypertension.

Sandoparin *Sandoz, Austria.*
Certoparin sodium (p. 1334·2).
Thromboembolic disorders.

Sandoparine *Novartis, Switz.*
Certoparin sodium (p. 1334·2).
Thrombosis prophylaxis.

Sandoretic *Novartis, Switz.†*
⊗Bopindolol malonate (p. 1326·3); chlortalidone (p. 1335·2).
Hypertension.

Sandosource *Novartis, Braz.; Novartis, Irl.†; Novartis, UK.*
Preparation for enteral nutrition.

Sandostatin *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Sandoz, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.Novartis, Venez.*
Octreotide (p. 1924·1) or octreotide acetate (p. 1924·1).
Acromegaly; AIDS-associated refractory diarrhoea; prevention of complications following pancreatic surgery; variceal haemorrhage; carcinoid tumours; gastrointestinal neuroendocrine tumours; gastrointestinal fistula.

Sandostatina *Novartis, Ital.; Novartis, Mex.*
Octreotide (p. 1924·1).
Acromegaly; pancreatic fistulae; variceal haemorrhage; gastrointestinal endocrine tumours; refractory diarrhoea associated with HIV infection; prevention of complications following pancreatic surgery.

Novartis, Port.
Octreotide acetate (p. 1924·1).
Acromegaly; gastrointestinal endocrine tumours; AIDS-associated refractory diarrhoea; prevention of complications following pancreatic surgery; variceal haemorrhage; pancreatic and gastrointestinal fistulas.

Sandostatine *Novartis, Belg.*
Octreotide (p. 1924·1).
Acromegaly; gastrointestinal endocrine tumours; external fistulae of the pancreas and small intestine; AIDS-associated refractory diarrhoea; complications following pancreatic surgery; variceal haemorrhage.

Novartis, Fr.; Novartis, Neth.; Novartis, Switz.
Octreotide acetate (p. 1924·1).
Acromegaly; variceal haemorrhage; prevention of complications following pancreatic surgery; gastrointestinal endocrine tumours.

Sandovac *Novartis, Austria.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Sandovask *Sandoz, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Sandoz Ca-D *Sandoz, Belg.; Novartis Consumer, Neth.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; calcium and vitamin D supplement.

Sandoz Calcium *Sandoz, Belg.*
Effervescent tablets; oral powder: Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Osteoporosis; calcium supplement; bone demineralisation; tetany.

Sandoz, Belg.
Injection: Calcium glubionate (p. 1783·2).
Hypocalcaemia; tetany; rickets; potassium poisoning.

Sandoz Calcium + D *Novartis, Mex.*
Effervescent tablets: Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; osteomalacia; hypoparathyroidism; hypocalcaemia.

Novartis, Mex.
Soluble tablets: Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis; osteomalacia; hypoparathyroidism; hypocalcaemia.

Sandoz Calcium/Vitamine D *Novartis Consumer, Neth.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Sandoz K *Sandoz, S.Afr.*
Potassium chloride (p. 1793·2).
Potassium supplement.

Sandoz Schmerzgel *Sandoz, Ger.†*
Diclofenac sodium (p. 48·3).
Joint and soft-tissue injury.

Sandrena *Aspen, Austral.; Schering-Plough, Braz.; Schering-Plough, Chile; Organon, Ital.; Organon, Mex.; Essex, Switz.†; Orion, UK.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Sandrin *Schwabe, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders.

Sanecol *SoSe, Ital.*
Rifaximin (p. 355·2).

Saneloc *Sandoz, Turk.*
⊗Metoprolol succinate (p. 1434·3).

Sanelor *Omega, Belg.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Sanitas, Chile.
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Sanepil *Zentiva, Cz.†*
Phenytoin (p. 538·2); phenobarbital (p. 535·2).
Epilepsy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sanerva *Royal, Chile.*
Alprazolam (p. 1035·2).
Anxiety; panic attacks.

Sanetron *Veltipharm, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Sanexon *Sanbe, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Sanficinate *Sanofi-Aventis, Gr.*
Calcium folinate (p. 2066·3).
Reduction of methotrexate toxicity; folic acid deficiency anaemia.

Sanfloks *Sandoz, Turk.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Sang Ke Ling *Minsheng, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; cough.

Sang Mei *Ya Bang Ai Pu Sen, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori infection.

Sangcya *Lilly, Israel.†*
Ciclosporin (p. 1945·2).
Transplant rejection; uveitis; psoriasis.

Sangen Casa *Marco Viti, Ital.*
Liquid: Benzethonium chloride (p. 1738·1); benzalkonium chloride (p. 1737·1).
Surface disinfection.

Marco Viti, Ital.
Spray: Orthophenylphenol (p. 1762·3); benzalkonium chloride (p. 1737·1).
Surfæ disinfection.

Sangen Sapone Disinfettante *Marco Viti, Ital.*
Triclocarban (p. 1773·2).
Skin disinfection.

Sangenor *Mundipharma, Austria.*
Arginine aspartate (p. 2049·1).
Tonic.

Sangermina *Sandoz, Ital.*
Bacillus subtilis.
Restoration of intestinal flora.

Sangerol *Novartis Consumer, Switz.*
Lidocaine hydrochloride (p. 1988·2); muramidase hydrochloride (p. 2565·1); tyrothricin (p. 384·1).
Mouth and throat disorders.

Sangobion *Merck Consumer, Singapore.*
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); vitamin B_{12} (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Merck, Indon.
Oral drops: Folic acid (p. 2063·1); iron (p. 2073·1).
Iron and folic acid supplement.

Merck, Indon.; Merck, Philipp.
Capsules: Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency.

Merck, Indon.; Merck, Philipp.
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia; iron and vitamin B deficiency.

Merck, Malaysia.
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); minerals.
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Merck, Thai.†
Ferrous gluconate (p. 2061·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); minerals.
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Sangobion ActiFe *Merck, Indon.*
Taurine (p. 2626·2); ferrazone; vitamin B_6 (p. 2105·3); nicotinamide (p. 2083·1); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Tonic.

Sangofer *Sandoz, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); intrinsic factor (p. 2534·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; nutritional supplement.

Sangona *Sandoz, Cz.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Sangona Combi *Sandoz, Cz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sangovitin *Pyridam, Indon.†*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; nutritional supplement.

Sanhelios 333 *Volmix, Hung.*
Garlic (p. 2510·3); mistletoe (p. 2560·2); crataegus (p. 2488·1).
Cardiovascular disorders.

Sanhelios Teufelskralle *Volmix, Hung.*
Devil's claw root (p. 42·3).
Gastrointestinal disorders; liver, bile, and kidney disorders.

Sani Hands AF *Ostrem, Canad.*
Benzalkonium chloride (p. 1737·1).
Hand disinfection.

Sanibiotic *Austral, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Sanicet *Sanus, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Sanicopyrine *Sanico, Belg.*
Paracetamol (p. 115·1).
Pain; fever.

Sanicut *Nordin, Mex.*
Calendula (p. 2465·2); marsh tea (p. 2550·1).
Pruritus; cicatrisation; insect bites.

Sanidecal *Sanitas, Chile.*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis.

Sanidecal-D *Sanitas, Chile.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Saniderm *Quimica y Farmacia, Mex.*
Zinc oxide (p. 1729·1).
Nappy rash; skin disorders; burns.

Sani-Dex *Professional Disposables, Canad.†*
⊗Alcohol (p. 1733·1); chloroxylenol (p. 1748·2).
Hand disinfection.

SaniDrox *Sanitas, Ital.*
Peracetic acid (p. 1763·1).
Instrument disinfection.

Sanifer *Esseti, Ital.†*
Sodium ferric gluconate complex (p. 2089·1).
Anaemias; oligohaemia in infants.

Saniflam *Sanopharm, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Saniflor Collutorio *SoDiFarm, Ital.*
Benzydamine hydrochloride (p. 29·2).
Gingivitis.

Sanifolin *Fargim, Ital.*
Calcium folinate (p. 2066·3).
Folate deficiency; antidote to folic acid antagonists; anaemias; reduction of aminopterin and methotrexate toxicity.

Sanigermin *Sanitas, Chile.*
Triclosan (p. 1773·2).
Hand disinfection; skin infections.

Sanilax *Greenpharma, Braz.*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3); caffeine (p. 1203·3).

Sanilin *Hertz, Braz.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2).

Sanipirina *Bayer, Ital.*
Paracetamol (p. 115·1).
Pain; fever.

Sanipresin *Sanitas, Chile.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; left-ventricular hypertrophy.

Sanipresin-D *Sanitas, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Saniprostol *Sanitas, Chile.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Saniquiet *Sanitalia, Ital.*
Passion flower (p. 2584·1); tilia (p. 2631·3); birch; magnesium (p. 1786·3); lithium; manganese (p. 2081·2).

Sanisop *Pentamedical, Ital.*
Soap substitute.

SaniSteril Deterferri *Sanitas, Ital.*
Benzalkonium chloride (p. 1737·1).
Instrument disinfection.

SaniSteril Sterilferri *Sanitas, Ital.*
Glutaral (p. 1753·2).
Instrument disinfection.

Sani-Supp *G & W, USA.*
⊗Glycerol (p. 2517·2).
Constipation.

Saniter Compuesto *Sanitas, Chile.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Sanitizante *Krolton, Arg.*
⊗Alcohol (p. 1733·1).
Disinfection.

Sanitos *Gifrer Barbezat, Fr.*
Salicylic acid (p. 1719·1).
Corns; calluses; warts.

Sanjin Royal Jelly *Super Mayoreo Naturista, Mex.*
Ginseng (p. 2513·3).
Tonic.

Sanjukei Panax Ginseng *ITBS, Hong Kong.*
Ginseng (p. 2513·3); carotene (p. 2051·1); sunflower oil (p. 2098·1); vitamin E (p. 2119·1).
Dietary supplement.

Sankaijo *Sato, Singapore.*
Aloe (p. 1816·1); rhubarb (p. 1884·2); senna (p. 1885·1).

Sankombi *Sanum-Kehlbeck, Ger.*
Mucor racemosus; aspergillus niger.
Homoeopathic preparation.

Sankorbin *Sanbe, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Sanlin *Sanbe, Indon.*
Tetracycline phosphate (p. 373·2).
Bacterial infections.

Sanmag *Sanbe, Indon.*
Oral suspension: Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Sanbe, Indon.
Tablets: Magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); papaverine hydrochloride (p. 2362·3); chlordiazepoxide hydrochloride (p. 1044·2); vitamin B substances (p. 2102·3).
Gastrointestinal disorders.

Sanmetidin *Sanbe, Indon.*
Cimetidine (p. 1827·1).
Duodenal ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Sanmigran *Novartis, Fr.*
Pizotifen malate (p. 678·2).
Migraine.

Sanmol *Sanbe, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Sanmox *SRS, Philipp.†*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sanmyd-P *Santen, Philipp.*
Tropicamide (p. 2012·2); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis and cycloplegia.

Sano Tuss *Welti, Switz.*
⊗Emetine hydrochloride (p. 932·3); ethylmorphine hydrochloride (p. 56·3); ephedrine hydrochloride (p. 1663·2); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); cherry laurel (p. 2475·2); tolu balsam (p. 1679·2).
Catarrh; cough.

Sano Tuss N *Welti, Switz.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Catarrh; cough.

Sanocef
Note: this name may be used for preparations of different composition.
Sanopharm, Gr.
Cefprozil (p. 248·2).
Bacterial infections.

Sanovel, Turk.
Cefaclor (p. 232·3).
Bacterial infections.

Sanochond *Vitorgan, Ger.*
Extractum lyophilisatum ex column. vertebral. lysat. bovis fetal (p. 2444·1).
Homoeopathic preparation.

Sanoclox *Pharmahof, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Sanoderm *Reccius, Chile.*
Allantoin (p. 1693·1); zinc oxide (p. 1729·1); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Skin disorders.

Sanodin *Ern, Spain.*
Carbenoxolone sodium (p. 1825·3).
Gingivitis; mouth ulcers.

Sanodolin *Sanli, Turk.*
Salol (p. 129·3).

Sanodril *Sandoz, Venez.*
Cefadroxil (p. 233·2).
Bacterial infections.

Sanodryl *Pharmahof, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Sanofen *Pharmahof, Thai.†*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Sanofil *Herbapol Pruszkow, Pol.*
Achillea (p. 2427·3); benzocaine (p. 1980·2); calendula (p. 2465·2); chamomile (p. 2474·1); equisetum (p. 2500·1); menthol (p. 2553·2); oak bark (p. 2574·1); sage (p. 2608·3).
Allergic skin disorders; insect bites.

SANO-Gastril *CGD, Fr.*
Fermented soya bean (p. 2092·3).
Digestive disorders.

Sanogencive *Plan, Switz.*
Rhatany root (p. 2603·3); myrrh (p. 2566·1); horseradish (p. 2526·1); camphor (p. 2466·2).
Oral hygiene; gum disorders.

Sanogyl *Roge-Cavailles, Fr.*
White toothpaste: Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Sanogyl Fluo *Roge-Cavailles, Fr.†*
Sodium monofluorophosphate (p. 2091·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Sanoliv *Indo Sehat, Indon.*
Schisandra (p. 2611·2); vitamin B substances (p. 2102·3).
Liver disorders.

Sanomed *Vitalink, Philipp.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal and joint disorders; pain.

Sanomigran *Novartis, Irl.; Novartis, UK.*
Pizotifen malate (p. 678·2).
Migraine and other vascular headaches.

Sanomox *Pharmahof, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sanopab *Nufarindo, Indon.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Sanopor *Sanus, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Sanor *Biolab, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety.

Sanorex *Novartis, Jpn.*
⊗Mazindol (p. 2324·1).
Obesity.

Sanorflox *Pharmahof, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Sanorin *Ivax, Rus.*
Nasal emulsion drops: ⊗Naphazoline nitrate (p. 1669·3); eucalyptus oil (p. 2501·2).
Nasal congestion.

Teva, Cz.; Ivax, Rus.; Teva, Ukr.
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion; catarrh; otitis media; eye congestion; sinusitis; aid in nasal examination.

Sanorin-Analergin *Teva, Cz.; Ivax, Rus.; Teva, Ukr.*
⊗Naphazoline nitrate (p. 1669·3); antazoline mesilate (p. 615·3).
Eye and nose disorders; allergic rhinitis; conjunctivitis.

Sanorinchik *Ivax, Rus.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Rhinitis; sinusitis.

Sanorine *Sanbe, Indon.; Sanbe, Singapore.*
Hyaluronic acid (p. 2526·2).
Dental plaque prevention; gingivitis; aphthous ulcers.

Sanorvil *Dekaz, Gr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Sanosec *Pharmahof, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

San'oshashinto *Tsumura, Jpn.*
Skullcap root (p. 2617·1); coptis rhizome; rhubarb (p. 1884·2).
Traditional Kampo medicine.

SanoSkin Melladerm Plus *Interbat, Indon.*
Honey (p. 2072·1).
Wounds; ulcers; burns.

Sanostol *Schmidgall, Austria.*
Vitamins.

Sanosvit Calcium *Nycomed, Pol.*
Calcium glubionate (p. 1783·2); calcium lactobionate (p. 1784·2).
Calcium supplement; osteoporosis.

Sanotamid *Sanofi-Aventis, Hung.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Sanotussin *Welti, Switz.*
⊗Ephedrine hydrochloride (p. 1663·2); codeine phosphate (p. 40·2); thyme (p. 2630·2).
Cough.

Sanotyne *Pharmahof, Thai.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Sanovein *Sanus, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; folic acid deficiency.

Sanovit *Nycomed, Mex.*
Cobamamide (p. 2107·2).
Anaemias; tonic.

Sanoxal *Protech, Rus.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Sanoxit *Galderma, Ger.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Sanoyodo *Cinfa, Spain.*
Povidone-iodine (p. 1767·1).
Skin and wound disinfection.

Sanpa *Bilim, Turk.*
Aspartame (p. 2169·2).
Sugar substitute.

Sanpicillin *Sanbe, Indon.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Sanpime *Sel-J, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Sanprid *Sandoz, Turk.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sanprima *Sanbe, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sanprome *SRS, Philipp.†*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Sanpronol *Sanval, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; arrhythmias; hypertension.

Sansacne *Galderma, Mex.; Galderma, Philipp.*
Erythromycin (p. 291·2).
Acne.

San-San *T Man, Thai.*
Albendazole (p. 149·1).
Worm infections.

Sansert *Novartis, Canad.†*
Methysergide maleate (p. 677·1).
Migraine and other vascular headaches.

Sanset *Sanovel, Turk.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Sansoninto *Tsumura, Jpn.*
Jujube seed; poria sclerotium; cnidium rhizome; anemarrhena rhizome; liquorice (p. 1853·2).
Traditional Kampo medicine.

Sansulin *Sanbe, Indon.*
⊗Insulin (human, recombinant) (p. 475·3).
Diabetes mellitus.

Santa Flora S *Madaus, Ger.*
Arnica planta tota (p. 2447·2); grindelia robusta (p. 2522·3); camphora (p. 2466·2); yerba santa (p. 1665·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Santabin *Santa, Gr.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Santacil *Santa, Gr.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Santa-E *Sanbe, Indon.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Santafer *Santa, Turk.*
Iron polymaltose (p. 2077·2).
Iron deficiency.

Santafer Fort *Santa, Turk.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid supplement; iron deficiency.

Santafurin *Santa, Gr.*
Co-trimoxazole (p. 277·3).

Santaherba *Lehning, Fr.*
⊗Yerba santa (p. 1665·2); ipecauanha (p. 1667·2); lobelia inflata (p. 2323·2); adrenalinum (p. 1292·1); belladonna (p. 2453·3); stramonium (p. 2622·3); solidago (p. 2620·1); ephedra (p. 1663·1); galeopsis; sambucus (p. 2609·3); crataegus oxycantha (p. 2488·1).
Homoeopathic preparation.

Santalum Complexe No 30 *Lehning, Fr.†*
Apium petroselinum (p. 2583·3); balsamum capaivae; oleum santali (p. 2610·1); petasites officinal (p. 2463·2); thuya occidentalis (p. 2629·3).
Homoeopathic preparation.

Santalut *Santa, Gr.*
Norethisterone (p. 2294·2).

Santalyt *Medice, Ger.†*
Sodium chloride (p. 1795·1); glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Santamer *Santa, Gr.*
Meropenem (p. 321·3).
Bacterial infections.

Santamex-Expectorant *Medexis, Gr.*
Carbocisteine (p. 1658·1).
Respiratory disorders associated with viscous mucus.

Santamin *Gerolymatos, Gr.*
Codergocrine (p. 389·2).
Peripheral vascular disorders.

Santane A_4 *Iphym, Fr.†*
Meadowsweet flowers (p. 2550·2); black currant leaf (p. 2458·1); salix leaf (p. 129·2); matricaria flowers (p. 2474·1); vervain leaf (p. 2645·1).
Musculoskeletal disorders.

Santane C_6 *Iphym, Fr.†*
Senna leaf (p. 1885·1); mallow flowers (p. 2549·2); boldo leaf (p. 2458·3); peppermint leaf (p. 1877·1); melissa (p. 2552·3); angelica (p. 2443·3); caraway (p. 2470·2); pale rose flowers.
Constipation.

Santane D_5 *Iphym, Fr.†*
Melissa leaf (p. 2552·3); origanum flowers (p. 2576·3); peppermint leaf (p. 1877·1); fennel seed (p. 2503·2); sage (p. 2608·3); matricaria flowers; caraway seed (p. 2470·2); cinnamon bark (p. 2479·2).
Gastrointestinal disorders.

Santane F_{10} *Iphym, Fr.†*
Boldo leaf (p. 2458·3); peppermint leaf (p. 1877·1); rosemary leaf (p. 2607·2); sage (p. 2608·3); caraway seed (p. 2470·2); calendula flower (p. 2465·2); spinacea flower; cinnamon bark (p. 2479·2).
Hepato-biliary insufficiency.

Santane N_9 *Iphym, Fr.*
Tilia flowers (p. 2631·3); crataegus (p. 2488·1); passion flower (p. 2584·1); melissa leaf (p. 2552·3); lupulus (p. 2546·1); pale rose flowers; lavender flowers; bitter-orange (p. 2575·3).
Nervous disorders.

Santane O1 *Iphym, Fr.*
Tea leaves: Black currant leaf (p. 2458·1); meadowsweet flower (p. 2550·2); calluna vulgaris; peppermint leaf (p. 1877·1); rosemary (p. 2607·2); mallow (p. 2549·2); caraway (p. 2470·2).
Adjunct in obesity.

Iphym, Fr.
Tea bags: Black currant leaf (p. 2458·1); java tea (p. 2536·3); green tea (p. 2648·2); ash leaf (p. 2450·1); peppermint leaf (p. 1877·1); thyme (p. 2630·2); mallow (p. 2549·2); caraway (p. 2470·2).
Adjunct in obesity.

Santane R_8 *Iphym, Fr.†*
Black currant leaf (p. 2458·1); calluna vulgaris; meadowsweet flowers (p. 2550·2); peppermint leaf (p. 1877·1); sambucus (p. 2609·3); lavender (p. 2541·1); cinnamon bark (p. 2479·2); rosemary (p. 2607·2).
Kidney disorders.

Santane V_3 *Iphym, Fr.†*
Hamamelis leaf (p. 2523·3); artemisia; melilot (p. 2552·3); ronce; sweet orange peel (p. 2576·2); peppermint leaf (p. 1877·1); bleuet; epinard.
Vascular disorders.

Santanol *Atabay, Turk.†*
Ranitidine hydrochloride (p. 1882·1).

Santapertas *Gerolymatos, Gr.*
⊗Reserpine (p. 1485·3); chlortalidone (p. 1335·2).
Hypertension.

Santasapina *Bioforce, Switz.*
Pine buds.
Upper respiratory-tract disorders.

Santasapina N *Bioforce, Ger.†*
Pine needle.
Catarrh.

Santax S *Asche Chiesi, Ger.†*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea.

Santeson *Santen, Philipp.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Santevini *Novartis, India.*
Vitamin B substances (p. 2102·3); peptone (p. 2086·2); calcium gluconate (p. 1783·3).
Tonic; digestive disorders.

Santiazepam *Santisa, Braz.*
Diazepam (p. 1063·2).

Santibi *Sanbe, Indon.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Santibi Plus *Sanbe, Indon.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Santidor *Santisa, Braz.*
Dipyrone (p. 53·3).

Santis *Sandoz, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Santizor *Pfizer, UK·*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Santo *Sanbe, Indon.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Santocyn *Caprifarmindo, Indon.*
Oxytocin (p. 2143·1).
Labour induction; caesarian section; incomplete abortion; postpartum haemorrhage.

Santoperalgin *Himfarm, Rus.*
Dipyrone (p. 53·3); paracetamol (p. 115·1); codeine (p. 40·2); caffeine (p. 1203·3); phenobarbital (p. 535·2).
Pain; fever.

Santóss *Delta, Braz.*
Carbocisteine (p. 1658·1).

Santotitralgin *Himfarm, Rus.*
Dipyrone (p. 53·3); codeine (p. 40·2); caffeine (p. 1203·3); phenobarbital (p. 535·2).
Pain.

Santoux *Gerolymatos, Gr.*
Camphor (p. 2466·2); menthol (p. 2553·2); thymol (p. 1772·2); turpentine oil (p. 2636·3).

Santrone *Korea United, Hong Kong.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Santropina *Santisa, Braz.*
Atropine sulfate (p. 1310·2).

Santuril *Lipomed, Switz.*
⊗Probenecid (p. 607·3).
Hyperuricaemia.

Santussal *Novartis, Braz.*
Pimethixene (p. 638·1); proxyphylline (p. 1219·2); ammonium chloride (p. 1656·1).
Cough.

Santyl *Healthpoint, Canad.; Knoll, USA.*
⊗Collagenase (p. 2484·1).
Wound debridement; debridement of dermal ulcers and severe burns.

Sanukehl *Sanum-Kehlbeck, Ger.; Ebi, Switz.*
A range of homoeopathic bacterial and fungal extracts.
Homoeopathic preparation.

Sanuvis *Sanum-Kehlbeck, Ger.*
Acidum L(+)lacticum (p. 2539·1).
Homoeopathic preparation.

Sanval *Lek, Hung.; Sandoz, Pol.; Lek, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Sanvaliv *Sanval, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).

Sanvapress *Sanval, Braz.†*
Enalapril maleate (p. 1371·1).
Hypertension.

Sanvisc *Cadila, India.*
Hypromellose (p. 2189·2).

Sanvita Meno *Sanamed, Austria.*
Cimicifuga (p. 2478·1).
Menopausal disorders; premenstrual syndrome.

Sanvita-B *Sanbe, Indon.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Sanvita-B Plus *Sanbe, Indon.*
Vitamins; minerals.
Dietary supplement.

Sanvix *Santa, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Sanyrène *Urgo, Fr.*
Barrier preparation.

Urgo, Ger.
Hyperoxygenated fatty acids of linoleic acid (p. 2509·2).
Leg ulcers.

Sanza *Glenmark, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Synthon, Neth.
Olanzapine benzoate (p. 1089·3).
Schizophrenia; bipolar disorder.

Sanzyme-DS *Uni-Sankyo, India.*
Amylase (p. 2442·1); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); sodium bicarbonate (p. 1781·1).
Dyspepsia; flatulence.

Saocin-D *Pharmex (Φαρμεξ), Gr.*
⊗Dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye or skin disorders.

Sapec *Riemser, Ger.*
Garlic (p. 2510·3).
Hyperlipidaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Saphire *Sanovel, Turk.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Saphris *MSD, Austral.; Schering-Plough, Braz.; Merck, Canad.; MSD, Israel; Lundbeck, Singapore; Organon, USA.*
Asenapine maleate (p. 1040·1).
Bipolar disorder; schizophrenia.

Sapilent *Extractum, Hung.*
Trimipramine (p. 453·1).
Depression.

Sapimol *Arrow, Denm.; Arrow, Swed.*
⊗Ipratropium bromide (p. 1211·3); salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sapoderm *Reckitt Benckiser, Austral.*
Triclosan (p. 1773·2).
Skin cleansing.

Sapona *Konimex, Indon.†*
Benzoic acid (p. 1738·2); peru balsam (p. 2587·1); salicylic acid (p. 1719·1).
Fungal skin infections.

Saponarex *Herbapol Pruszkow, Pol.*
Ribwort plantain (p. 2604·2); soapwort (p. 2617·2); thyme (p. 2630·2).
Cough; respiratory-tract congestion.

Saponaria Composé *Boiron, Fr.*
Saponaria officinal (p. 2617·2); fumaria officinal (p. 2508·2); sarsaparilla (p. 2610·3); hydrocotyle asiatica (p. 1698·3); viola tricolor (p. 2647·3); rhus vernix; lappa major (p. 2540·1); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Sapoven *Hasco-Lek, Pol.*
Aesculus (p. 2431·2).
Superficial phlebitis; haematoma; venous insufficiency.

Sapoven AT *Hasco-Lek, Pol.†*
Aesculus (p. 2431·2); benzocaine (p. 1980·2); troxerutin (p. 2505·3).
Anorectal disorders.

Sapoven T *Hasco-Lek, Pol.*
Aesculus (p. 2431·2); troxerutin (p. 2505·3).
Venous insufficiency; soft-tissue injury; oedema.

Saprame *Probiomed, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Sapresta *Taiho, Jpn.*
Aranidipine (p. 1307·1).
Hypertension.

Sapriken *Kener, Mex.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Saprimix *Cooper (Κοπερ), Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Saquat *Ramini, Ital.†*
Benzalkonium chloride (p. 1737·1).
Disinfection of wounds and burns.

Sara *TNP, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Saracef *Helm, Port.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Sarafem *Warner Chilcott, USA.*
Fluoxetine hydrochloride (p. 417·1).
Premenstrual dysphoric disorder.

Sarai *Steiner, Ger.†*
⊗Agnus castus (p. 2432·2).
Mastalgia; menstrual disorders.

Sarapin *High Chemical, Canad.; High Chemical, USA.*
Sarracenia purpurea (p. 130·2).
Neuromuscular or neuralgic pain.

Saratoga *Blair, USA.*
Zinc oxide (p. 1729·1); boric acid (p. 2459·3); cineole (p. 2479·1); peru balsam (p. 2587·1).
Minor skin irritation.

Saravanta *Daiichi Sankyo, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; cardiovascular risk reduction; diabetic nephropathy; heart failure.

Saravanta D *Daiichi Sankyo, Mex.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sarcitec *Technobio, Mex.*
Ranitidine (p. 1882·1).

Sarcolysin *Gles, Rus.*
Melphalan (p. 819·1).
Malignant neoplasms; polycythaemia vera.

Sarcop *Unipharma, Spain.*
Permethrin (p. 2159·3).
Scabies.

Sarcoton *Medley, Braz.*
Disulfiram (p. 2495·3).
Alcoholism.

Sardip *Darnitsa, Ukr.*
Amlodipine (p. 1304·1); losartan potassium (p. 1422·2).
Hypertension.

Sarf *Julphar, UAE.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Sarfiram *Bergamo, Braz.*
Sulfiram (p. 2161·3).
Scabies.

Sargemag *Meda, Fr.*
Magnesium carbonate (p. 1856·2); magnesium oxide (p. 1857·3).
Magnesium supplement.

Sargenor *Meda, Fr.; Meda, Ital.; Meda, Port.*
Arginine aspartate (p. 2049·1).
Asthenia; tonic.

Sargenor à la Vitamine C *Meda, Fr.*
Arginine aspartate (p. 2049·1); ascorbic acid (p. 2110·3).
Tonic.

Sargenor Plus *Meda, Ital.*
Arginine hydrochloride (p. 2049·1); ascorbic acid (p. 2110·3).
Tonic.

Sargenor Sport *Meda, Ital.†*
Leucine (p. 2079·1); valine (p. 2098·3); isoleucine (p. 2078·2); arginine aspartate (p. 2049·1); vitamin B_6 (p. 2105·3).
Nutritional supplement.

Sargisthene *Meda, Spain.*
Arginine aspartate (p. 2049·1).
Asthenia.

Saribal *Exelixis, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Saridine *Atlantic, Thai.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; rheumatoid arthritis.

Saridon *Bayer Consumer, Arg.; Bayer, Austria; Bayer, Braz.; Roche, Braz.; Bayer, China; Bayer, Cz.; Bayer, Ger.†; Roche, Hong Kong†; Bayer, Hung.; Bayer Consumer, Indon.; Bayer, Ital.; Bayer, Neth.; Bayer, Pol.; Bayer Consumer, Rus.; Bayer, Spain.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever; cold and influenza symptoms.

Bayer, Philipp.
Paracetamol (p. 115·1).
Fever; pain.

Saridon N
Note: this name may be used for preparations of different composition.
Bayer, Port.
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain.

Bayer, Switz.
Ibuprofen sodium (p. 68·2).
Fever; pain.

Sarilen
Note: this name may be used for preparations of different composition.
Ali, Turk.
Losartan potassium (p. 1422·2).
Hypertension.

Sarilen Plus *Ali, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sariu *Kleva, Gr.*
Niflumic acid (p. 101·2).

Sarivanil *EirGen, Cz.*
⊗Exemestane (p. 792·2).
Breast cancer.

Sarixell *Bayer, Neth.*
Ibuprofen sodium (p. 68·2).
Fever; pain.

Sarmed *Mediline, Israel.*
Pramocaine hydrochloride (p. 1993·3).
Pruritus; skin irritation.

Sarmel *Anpharm (Ανφαρμ), Gr.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections.

Sarmine *Specifar, Gr.*
Aspirin (p. 22·2); aluminium hydroxide (p. 1817·2).

Sarna *Stiefel, Austral.†; Stiefel, Malaysia; Stiefel, Philipp.; Stiefel, Singapore; Stiefel, Thai.*
Camphor (p. 2466·2); menthol (p. 2553·2); phenol (p. 1763·3).
Dry skin; pruritus; skin irritation; burns; wounds.

Sarna Anti-Itch *GSK, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Pruritus; sunburn; poison ivy; poison oak.

Sarna HC *Stiefel, Canad.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Sarna Sensitive *GSK, USA.*
Triclosan (p. 1773·2).
Skin cleansing.

Sarna Sensitive Anti-Itch *GSK, USA.*
Pramocaine hydrochloride (p. 1993·3).
Pruritus.

Sarna Ultra *GSK, USA.†*
Pramocaine hydrochloride (p. 1993·3); menthol (p. 2553·2).

Sarna-P *Stiefel, Canad.*
Pramocaine hydrochloride (p. 1993·3); camphor (p. 2466·2); menthol (p. 2553·2).
Skin irritation.

Sarnerico *Belfar, Braz.*
Benzyl benzoate (p. 2149·1).

Sarnilab *Multilab, Braz.†*
Benzyl benzoate (p. 2149·1).
Scabies.

Sarnodex *Bunker, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Sarnol *GSK, Fr.*
Camphor (p. 2466·2); menthol (p. 2553·2); benzyl alcohol (p. 1739·3).
Skin disorders.

Saromet *AstraZeneca, Arg.; Rontag, Arg.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm.

Saronic *Novofarm (Νοβοφαρμ), Gr.*
Salicylic acid (p. 1719·1).

Saronil *Artis, Spain.†*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Saroten *Lundbeck, Austria; Lundbeck, Denm.; Bayer, Ger.; Gerolymatos, Gr.; Lundbeck, Rus.; Lundbeck, S.Afr.†; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Ukr.*
Amitriptyline hydrochloride (p. 401·1).
Depression; pain; sleep disorders; nocturnal enuresis.

Sarotena *Lundbeck, India.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Sarotex *Lundbeck, Neth.; Lundbeck, Norw.*
Amitriptyline hydrochloride (p. 401·1).
Depression; pain; nocturnal enuresis.

Sarovex *Tabuk, Cz.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Sarox *Biomep, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Saroxxo *Pharmahof, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Sartafin Plus *Lyofin, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Sartal *Alter, Port.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular dysfunction; diabetic nephropathy.

Sartaxal *Sandoz, Indon.*
Losartan potassium (p. 1422·2).
Hypertension.

Sarten *Menarini, Cz.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Sarten Plus H *Menarini, Cz.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sarticain *Senese, Ital.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Sartina *Temis, Arg.*
Olanzapine (p. 1089·3).
Schizophrenia.

Sartoc *Aspen, S.Afr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sartol *Stiefel, Spain.†*
Menthol (p. 2553·2); camphor (p. 2466·2).
Insect bites; pruritus; urticaria.

Sartuzin *Help, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Sarval *Baliarda, Arg.*
Valsartan (p. 1521·2).
Heart failure; hypertension; myocardial infarction.

Sarval D *Baliarda, Arg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sarvas *Eczacibasi, Turk.*
Losartan potassium (p. 1422·2).
Hypertension.

Sarvastan *Eczacibasi, Turk.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sarve *Farma-Projekt, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Sarvit a la glucuronamide *Meda, Fr.†*
Glucuronamide (p. 2517·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Tonic.

Sarvit a la lysine *Meda, Fr.†*
Lysine hydrochloride (p. 2079·3); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Tonic.

Sasapir *Erfar, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; acid aspiration; pathological gastric hypersecretion.

Saseem *Pohl, Ger.*
Xylitol (p. 2220·3); dexpanthenol (p. 2582·2); carrageenan (p. 2176·3); sorbic acid (p. 1770·2); electrolytes (p. 1775·1).
Dry mouth.

Sastid *GSK, Arg.; Stiefel, Braz.; Stiefel, Hong Kong; Stiefel, Indon.†; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Philipp.; GSK, S.Afr.; GSK, Singapore; Stiefel, Thai.†; GSK, USA.*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Acne; pityriasis versicolor; seborrhoea; tinea versicolor; skin disorders; fungal skin infections.

Sastid Anti-Fungal *Stiefel, Singapore.*
Clotrimazole (p. 576·2).
Fungal skin and vaginal infections.

Sastid Jabon *Stiefel, Chile.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Acne; pityriasis versicolor; seborrhoea.

Sasulen *Faes, Spain.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Satarmed *Ceamed, Port.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; stroke prophylaxis in left-ventricular hypertrophy.

Sathrocin *Pharmaniaga, Malaysia.*
Erythromycin (p. 291·2).
Bacterial infections.

Satigene *Microsules, Arg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Satil *Biotech, Venez.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Satinique Dandruff Control *Access, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Sativa *Floxia, Singapore.*
A range of emollients and skin cleansers containing avena (p. 2451·1).
Dry skin; pruritus.

Sativex *Bayer, Canad.; GW, Canad.; GW, Cz.; Almirall, Denm.; GW, Fin.; Almirall Hermal, Ger.; Neopharm, Israel; GW, Neth.; Almirall, Norw.; Novartis, NZ; Almirall, Spain; Almirall, Swed.; Bayer Schering, UK.*
Nabiximols (p. 2566·3).
Spasticity and neuropathic pain in multiple sclerosis; advanced cancer pain.

Sativol *Boiron, Fr.†; Boiron, Neth.†*
⊗Avena sativa (p. 2451·1); gentiana lutea (p. 2512·1); acide phosphoricum (p. 2589·1); strychninum phosphoricum (p. 2623·2); guarana (p. 2648·2); aurum muriaticum (p. 2521·1); helonias dioica (p. 2524·3).
Homoeopathic preparation.

Sato Uonome Solution *Sato, Singapore.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Keratinisation disorders.

Satogesic *Sato, Thai.*
Indometacin (p. 71·2).
Musculoskeletal, peri-articular, and soft-tissue pain.

Saton *Saval, Chile.*
⊗Sibutramine (p. 2330·2).
Obesity.

Satoxi *Verum, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Satrogyl *Alkem, India.*
Satranidazole (p. 947·2).
Protozoal infections.

Satrogyl-O *Alkem, India.*
Satranidazole (p. 947·2); ofloxacin (p. 334·3).
Protozoal infections.

Satromax *Ind-Chemie, India.*
Satranidazole (p. 947·2).
Protozoal infections.

Satromax-O *Ind-Chemie, India.*
Satranidazole (p. 947·2); ofloxacin (p. 334·3).
Protozoal infections.

Satural *Polfarmex, Pol.*
Calcium lactate gluconate (p. 1784·2).
Calcium deficiency.

Saturnil *Adelco, Gr.*
Alprazolam (p. 1035·2).
Anxiety disorders; mixed anxiety-depressive states.

Saubasin *Kleva, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Saugella allaitment anti-crevasses *Rottapharm, Fr.*
Mimosa tenuiflora; prunus armeniaca oil (p. 2587·1); calendula (p. 2465·2).
Cracked nipples.

Saugella Antiseptic *Rottapharm, Fr.*
Topical gel: ⊗Thyme (p. 2630·2); sodium hyaluronate (p. 2526·2); glycerol (p. 2517·2).
Vaginal dryness.

Rottapharm, Fr.
Topical liquid: topical mousse: Thyme (p. 2630·2); sage (p. 2608·3); lactic acid (p. 2539·1).
Genital cleansing in women.

Saugella Attiva *Rottapharm, Ital.*
Thyme (p. 2630·2); sage (p. 2608·3).
Personal hygiene.

Saugella Dermolatte *Rottapharm, Ital.*
Chamomile (p. 2474·1); sage (p. 2608·3).
Soap substitute.

Saugella Dermoliquide *Rottapharm, Fr.*
Soap; topical wipes: Sage (p. 2608·3); lactic acid (p. 2539·1).
Skin cleansing.

Rottapharm, Fr.
Vaginal gel: ⊗Loosestrife (p. 2545·2); helichrysum; sodium hyaluronate (p. 2526·2); glycerol (p. 2517·2).
Vaginal dryness.

Saugella Dermoliquido *Rottapharm, Ital.*
Sage (p. 2608·3).
Personal hygiene.

Saugella douceur Poligyn *Rottapharm, Fr.*
Prunus armeniaca oil (p. 2587·1); calendula (p. 2465·2); loosestrife (p. 2545·2); helichrysum; sodium hyaluronate (p. 2526·2).
Vaginal irritation.

Saugella Fitothym *Rottapharm, Ital.*
Thyme (p. 2630·2); wheat extract; sage (p. 2608·3).
Soap substitute.

Saugella Gel *Rottaphann, Ital.*
Vaginal lubricant.

Saugella Girl *Rottapharm, Fr.*
Avena (p. 2451·1); calendula (p. 2465·2); mallow (p. 2549·2).
Urogenital hygiene in girls.

Saugella Homme *Rottapharm, Fr.*
Helichrysum; clove (p. 2481·2); lactic acid (p. 2539·1).
Skin and urogenital cleansing in men.

Saugella HydraSerum *Rottapharm, Fr.*
Sage (p. 2608·3); calendula (p. 2465·2); avena (p. 2451·1).
Skin cleansing.

Saugella Idrocrema *Rottapharm, Ital.*
Vaginal lubricant.

Saugella Intilac *Rottapharm, Ital.*
Lactic acid (p. 2539·1).
Maintenance of vaginal pH.

Saugella Poligyn *Rottapharm, Fr.*
Thyme (p. 2630·2); chamomile (p. 2474·1).
Genital cleansing in women.

Rottapharm, Ital.
Thyme (p. 2630·2); levomenol (p. 2544·1).
Personal hygiene; correction of vaginal pH.

Saugella Salviettine *Rottapharm, Ital.*
Sage (p. 2608·3); lactic acid (p. 2539·1).
Personal hygiene.

Saugella Solido ph 3.5 *Rottapharm, Ital.*
Sage (p. 2608·3).
Soap substitute for oily skin.

Saugella Solido Zolfo *Rottapharm, Ital.*
Sulfur (p. 1721·1).
Soap substitute; acne.

Saugella Uomo *Rottapharm, Ital.*
Helichrysum italicum; clove (p. 2481·2).
Male personal hygiene.

Saurat *Ivax, Arg.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Savacol Mouth and Throat Rinse *Colgate Oral Care, Austral.*
Chlorhexidine gluconate (p. 1743·3).
Mouth ulcers; minor oral infections.

Savarine *AstraZeneca, Fr.; IFET (ΙΦΕΤ), Gr.*
Proguanil hydrochloride (p. 661·3); chloroquine phosphate (p. 650·1).
Malaria.

Savarix *Gemi, Pol.*
Aesculus (p. 2431·2); benzocaine (p. 1980·2); heparin sodium (p. 1396·3).
Soft-tissue injury; venous insufficiency.

Save Face & Body *Arbonne, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Savecal *Ibirn, Ital.†*
Calcium carbonate (p. 1824·3).
Calcium deficiency; calcium supplement.

Savecef *SRS, Philipp.†*
Cefixime (p. 240·3).
Bacterial infections.

Savedar *Pfizer, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Savella *Forest Pharmaceuticals, USA.*
Milnacipran hydrochloride (p. 435·3).
Fibromyalgia.

Savene *TopoTarget, Austria; SpePharm, Cz.; SpePharm, Denm.; Speciality European Pharma, Fr.; SpePharm, Irl.; Adienne, Ital.; SpePharm, Neth.; SpePharm, Norw.; SpePharm, Pol.; Ferrer, Port.; Ferrer, Spain; TopoTarget, Swed.*
Dexrazoxane hydrochloride (p. 1548·1).
Anthracycline extravasation.

Topotarget, Belg.; TopoTarget, Gr.; TopoTarget, UK.
Dexrazoxane (p. 1548·1).
Anthracycline extravasation.

Saveor *Chira, Philipp.*
Simvastatin (p. 1489·2).
Ischaemic heart disease; hypercholesterolaemia.

Saveprost *Salvat, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Saver *Elmor, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Savilen *Sanofi-Aventis, Gr.*
Ciprofibrate (p. 1338·1).
Hyperlipidaemias.

Saving Face *Aubrey, Canad.†*
Padimate O (p. 1716·1).
Sunscreen.

Savior *Abic, Israel; Teva, Israel.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Burn, skin, and wound disinfection.

Saviosol *Otsuka, Jpn.*
⊗Dextran 40 (p. 1138·1).
Plasma volume expansion; circulatory disorders; thrombosis.

Savles *Atlas, Arg.*
Emollient.

K2 Health & Wellness, Chile.
Soap substitute.

Savlex *Drogsan, Turk.*
Chlorhexidine (p. 1743·2); cetrimide (p. 1742·1).
Skin disinfection.

Savlodil *Regent, Canad.†*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Wound disinfection.

Savlon
Note: this name may be used for preparations of different composition.
Novartis Consumer, Irl.; Boots Healthcare, NZ; Pharmedica, S.Afr.
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin, burn, and wound disinfection.

Savlon Antiseptic *Reckitt Benckiser, Austral.*
Cream: Cetrimide (p. 1742·1); chlorhexidine hydrochloride (p. 1743·3).
Skin abrasions; wounds.

Reckitt & Colman, Austral.†
Topical powder: Povidone-iodine (p. 1767·1).
Burns; wounds; skin abrasions; fungal skin infections.

Savlon Antiseptic Cream *Novartis Consumer, UK.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Savlon Antiseptic Liquid *Novartis Consumer, UK.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Savlon Antiseptic Wound Wash *Novartis Consumer, Irl.; Novartis Consumer, UK.*
Chlorhexidine gluconate (p. 1743·3).
Wound disinfection; skin disinfection.

Savlon Dry *Novartis Consumer, Irl.; Novartis Consumer, UK.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Savlosol *Kocak, Turk.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin disinfection; burns.

Savonol *Merkez, Turk.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin disinfection.

Savosan *Vianex (Βιανεξ), Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Savoy Burn Relief *Wing Wai, Hong Kong.†*
Benzocaine (p. 1980·2); chlorhexidine (p. 1743·2).

Savrolin *Oro, Turk.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Skin disinfection.

Savulin *Gedeon Richter, Hung.*
Levofloxacin (p. 315·3).
Bacterial infections.

Saw Palmetto Formula *Quest, Canad.†*
Buchu leaf (p. 2461·3); cayenne (p. 2469·3); corn silk (p. 2487·1); kelp (p. 2612·1); parsley leaf (p. 2583·3); cucurbita seed (p. 2489·2); saw palmetto berry (p. 2363·3).

Sax *Biotech Naturis, Venez.*
Boric acid (p. 2459·3).
Vaginal infections; vaginal hygiene.

Saxacid *Biotech Naturis, Venez.*
Acetic acid (p. 2426·3); sorbic acid (p. 1770·2).
Vaginal infections; vaginal hygiene.

Saxetil *Santa, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Saxib *Target, Gr.*
Mirtazapine (p. 436·1).
Depression.

Saxion *Duncan, Arg.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Saxizon *Teva, Jpn.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Sayana *Pfizer, Austria; Pfizer, Belg.; Pfizer, Cz.; Pfizer, Ger.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Switz.; Pfizer, UK.*
Medroxyprogesterone acetate (p. 2288·1).
Progestogen-only injectable contraceptive.

Sazar *Alkaloid, Rus.*
Lamotrigine (p. 527·2).
Epilepsy.

Sazi *NEGPF, China.*
Stavudine (p. 1015·3).
HIV infection.

Sazo *Wallace, India.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; Crohn's disease; rheumatoid arthritis.

SB Aurico Ear Drops *Universal, S.Afr.†*
Phenol (p. 1763·3).
Earache.

SB Blood Purifying Mixture *Universal, S.Afr.†*
Magnesium sulfate (p. 1787·3); potassium citrate (p. 1780·3); potassium iodide (p. 2336·3); iron and ammonium citrate (p. 2060·1).
Tonic.

SB Cirogin Cough Mixture *Universal, S.Afr.†*
Ipecacuanha (p. 1667·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Respiratory-tract congestion.

SB Diarrhoea Mixture *Universal, S.Afr.†*
Light kaolin (p. 1850·1); calcium carbonate (p. 1824·3); catechu (p. 2472·3).
Diarrhoea.

SB Gripe Water *Universal, S.Afr.†*
Sodium bicarbonate (p. 1781·1).
Infant colic.

SB Laxative Mixture *Universal, S.Afr.†*
Magnesium sulfate (p. 1787·3).
Constipation.

SB Rheumatic Ointment *Universal, S.Afr.†*
Camphor (p. 2466·2); menthol (p. 2553·2); turpentine; eucalyptus oil (p. 2501·2).
Musculoskeletal and joint disorders.

SB Shisalene *Universal, S.Afr.†*
Camphor (p. 2466·2); capsicum oleoresin (p. 2469·3); turpentine; eucalyptus oil (p. 2501·2).
Muscular aches and pains.

SB Strong-Lax *Universal, S.Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

SB Toothache Drops *Universal, S.Afr.†*
Clove oil (p. 2481·3); chloroform (p. 1898·1).
Toothache.

SB Tox Worm *Universal, S.Afr.†*
Piperazine citrate (p. 163·1).
Ascariasis.

SB 3 Triple Action Pills *Universal, S.Afr.†*
Phenolphthalein (p. 1877·3); jalap resin (p. 1850·1); aloin (p. 1816·2); capsicum oleoresin (p. 2469·3).
Constipation.

SB Universal Ointment *Universal, S.Afr.†*
Starch (p. 2095·1); zinc oxide (p. 1729·1); coal tar (p. 1723·2); phenol (p. 1763·3); cod-liver oil (p. 2056·3).
Eczema.

SB Unola Corn Remover *Universal, S.Afr.†*
Salicylic acid (p. 1719·1).
Corns; warts; calluses.

SBOB *TNP, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

SB-Plex *Wescrib, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

SBT *Rafa, Israel.*
⊗Buprenorphine hydrochloride (p. 30·3).
Opioid withdrawal syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Scabenzil *Delta, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Scabiacid *Valetudo, Ital.*
Permethrin (p. 2159·3).
Scabies.

Scabianil *Sofar, Ital.*
Permethrin (p. 2159·3).
Scabies.

Scabicid *Kimia, Indon.*
Lindane (p. 2157·1); usnic acid (p. 2640·2).
Scabies; Gram-positive bacterial skin infections.

Scabicin *Fischer, Israel; Cosmofarma, Port.*
Crotamiton (p. 1699·2).
Scabies; pruritus.

Scabiex *Rekah, Israel.*
Benzyl benzoate (p. 2149·1).
Scabies.

Scabimite *Galenium, Indon.*
Permethrin (p. 2159·3).
Scabies.

Scabin *Abdi, Turk.*
Benzyl benzoate (p. 2149·1).
Scabies; pediculosis.

Scabine *Stadmed, India.*
Lindane (p. 2157·1); cetrimide (p. 1742·1).
Scabies; pediculosis.

Scabioderm *Bajer, Arg.*
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2); benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Scabioid *Legrand, Braz.*
Benzyl benzoate (p. 2149·1).
Scabies.

Scabiosa Complexe No 87 *Lehning, Fr.*
Solanum dulcamara (p. 2497·3); scabiosa; bellis perennis (p. 2454·2); camphora (p. 2466·2); sambucus (p. 2609·3); natrum phosphoricum (p. 1791·2); arsenicum iodatum (p. 2448·1); sulfur (p. 1721·1); hydrastis (p. 2528·1); croton tiglium; viola tricolor (p. 2647·3).
Homoeopathic preparation.

Scabirax *Innoderm, Philipp.†*
Crotamiton (p. 1699·2).
Scabies; pruritus.

Scabisan *Chinoin, Mex.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Scabisan Plus *Chinoin, Mex.*
Permethrin (p. 2159·3).
Scabies.

Scaboma *Glenmark, India.*
Cream: Lindane (p. 2157·1); benzocaine (p. 1980·2).
Scabies; pediculosis.

Glenmark, India; Glenmark, Malaysia.
Lotion: Lindane (p. 2157·1).
Scabies; pediculosis.

Scadan
Note: this name may be used for preparations of different composition.
Medipharm, Chile.
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Miles, USA.
Tetradonium bromide (p. 1742·1); stearyl dimethyl benzyl ammonium chloride.
Seborrhoea.

Scaflam *Mantecorp, Braz.; Lavipharm, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders; fever.

Scaflan *Schering-Plough, Venez.*
Nimesulide (p. 101·3).
Fever; osteoarthritis; rheumatic disorders; pain.

Scalacort DK *Avidas, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Scaldex *Owoc, Pol.*
Bacitracin (p. 225·3); calendula (p. 2465·2); vitamin A (p. 2098·3); propolis (p. 2597·3).
Burns; wounds; skin damage.

Scalid *Uniao Quimica, Braz.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Scalp Relief *Redken, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Scalpe *Glenmark, India.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

Scalpex *Glenmark, Philipp.*
Ketoconazole (p. 585·3); pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

Scalpicin
Note: this name may be used for preparations of different composition.
Combe, Ital.
⊗Hydrocortisone (p. 1640·1); menthol (p. 2553·2).
Skin irritation.

Combe, USA.
Salicylic acid (p. 1719·1); menthol (p. 2553·2).
Formerly contained hydrocortisone, and menthol.

Scalpicin Capilar *Combe, Spain.†*
⊗Hydrocortisone (p. 1640·1).
Scalp disorders.

Scalpin *Specifar, Gr.*
Ketoconazole (p. 585·3).
Fungal scalp infections.

Scan C *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Scanaflam *Tempo Scan Pacific, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Scanalgin *Tempo Scan Pacific, Indon.*
Dipyrone (p. 53·3).
Pain.

Scanarin *Tempo Scan Pacific, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Scanax *Tempo Scan Pacific, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Scancortin *Oriental, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Scandene *Tempo Scan Pacific, Indon.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; sprains.

Scanderma *Tempo Scan Pacific, Indon.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Scanderma Plus *Tempo Scan Pacific, Indon.*
⊗Betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).
Infected skin disorders.

Scandexon *Tempo Scan Pacific, Indon.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Scandicain *AstraZeneca, Austria†; AstraZeneca, Ger.; AstraZeneca, Switz.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Scandicaine *AstraZeneca, Belg.; Septodont, Fr.; Levy, Israel; AstraZeneca, Neth.†*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline (p. 1292·1), adrenaline acid tartrate (p. 1292·2), or noradrenaline acid tartrate (p. 1458·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Scandine *Zambon, Belg.; Zambon, Ital.*
⊗Ibopamine hydrochloride (p. 1407·1).
Heart failure.

Scandinibsa *Inibsa, Port.; Inibsa, Spain.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Scandishake *Aptalis, Canad.; Nutricia, Fin.; Nutricia, Irl.; Nutricia, NZ; Nutricia, Port.; Scientific Hospital Supplies, UK·*
Preparation for enteral nutrition.

Nutricia, Austral.; Nutricia, Ital.
Food for special diets.
Cystic fibrosis.

Scandipharm, Israel.
A range of preparations for enteral nutrition.

Scanditen *Tempo Scan Pacific, Indon.*
Ketotifen fumarate (p. 631·3).
Asthma.

Scandonest *Septodont, Austria; Septodont, Canad.; Septodont, China; Septodont, Cz.†; Septodont, Denm.; Septodont, Fin.; Tsaprazis, Gr.; Septodont, Irl.; Ogna, Ital.; Septodont, Neth.; Septodont, Norw.; Septodont, Port.; Dental Warehouse, S.Afr.; Septodont, Spain; Bigman, Swed.; Wild, Switz.; Septodont, USA.*
Mepivacaine hydrochloride (p. 1992·2). Adrenaline (p. 1292·1), corbadrine hydrochloride (p. 2486·3), noradrenaline (p. 1458·2) or noradrenaline acid tartrate (p. 1458·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Scandrex *Diapit, Gr.*
⊗Hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).

Scanidin *Tempo Scan Pacific, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine (p. 626·1).
Cough.

Scanlin *Quality, Hong Kong.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Scanlux *Sanochemia, Austria; Sanochemia, Cz.; Iasis, Gr.; Sanochemia, Hung.; Sanochemia, Ital.; Sanochemica, Neth.†; Sanochemia, Port.; Iberoinvesa, Spain; Sanochemia, Switz.; Sanochemia, UK.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Scanmecob *Tempo Scan Pacific, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Scanneuron *Tempo Scan Pacific, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Nervous system disorders; vitamin B deficiency; nausea and vomiting of pregnancy; migraine.

Scannotrast *Bracco, Austria.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium for CT scanning.

Scannoxyl *Tempo Scan Pacific, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Scanovir *Tempo Scan Pacific, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Scansepta *Tempo Scan Pacific, Indon.*
Povidone-iodine (p. 1767·1).
Mouth and throat disorders; skin infections; wounds.

Scantaren *Tempo Scan Pacific, Indon.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Scantensin *Tempo Scan Pacific, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Scantipid *Tempo Scan Pacific, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; coronary heart disease.

Scantoma *Tempo Scan Pacific, Indon.*
Bismuth salicylate (p. 1821·3).
Diarrhoea.

Scantropil *Tempo Scan Pacific, Indon.*
Piracetam (p. 393·3).
Mental function impairment; chronic alcoholism; cerebral trauma.

Scar Cream *Clay Park, USA.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Scar Esthetique *Scar Heal, Singapore.*
Palmitoyl tetrapeptide-7; palmitoyl oligopeptide; ascorbyl palmitate (p. 1737·1); vitamin A palmitate (p. 2098·3); pycnogenol (p. 2590·3); glucosamine (p. 2515·3); algae; seaweed (p. 2612·1); onion (p. 2575·2); ubidecarenone (p. 2637·1); arnica (p. 2447·2); dimeticone (p. 2209·3); betacarotene (p. 2051·1); grape seed (p. 2521·3); sodium hyaluronate (p. 2526·2); vitamin E (p. 2119·1).
Scars; burns; keloids.

Scarab *Aristo, India.*
Lindane (p. 2157·1); cetrimide (p. 1742·1).
Pediculosis; scabies.

Scarda *Pharmaland, Thai.*
Piracetam (p. 393·3).
Cerebrovascular disorders; mental function disorders.

Scassh Trouch Lozenge *Watanabe, Hong Kong.*
Dequalinium chloride (p. 1749·3); chlorphenamine maleate (p. 620·3); platycodon root; dipotassium glycyrrhizate (p. 2520·3).
Mouth and throat disorders.

Scat *Cadila, India.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Scaven *Tempo Scan Pacific, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement.

Scelto *Pharos, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Scheribar *Bayer, Arg.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Schericur *Schering, Arg.†; Intendis, Spain.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Scheriderm *Bayer, Arg.; Intendis, Mex.*
⊗Diflucortolone valerate (p. 1634·1); isoconazole nitrate (p. 583·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Scherilan Crema *Intendis, Ital.*
Zinc oxide (p. 1729·1).
Barrier preparation.

Scheriproct
Note: this name may be used for preparations of different composition.
Bayer, Arg.; CSL, Austral.; Intendis, Austria; Bayer, Belg.; Bayer, Chile; Intendis, Fin.; Bayer, Irl.; Intendis, Mex.; Intendis, Norw.; Berlimed, Port.; Bayer Schering, S.Afr.; Bayer, Switz.; Bayer, UK; Schering, Venez.
⊗Prednisolone caproate (p. 1645·3); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders; haemorrhoids; pruritus ani.

Scheriproct N *Bayer, Swed.*
⊗Prednisolone caproate (p. 1645·3); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Intendis, Thai.
⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Scheriproct Neo *Intendis, Gr.; Panagakis, Gr.*
⊗Cinchocaine hydrochloride (p. 1983·2); prednisolone caproate (p. 1645·3).
Haemorrhoids.

Schiwalys Hemofiltration *Baxter, Swed.†*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).

Schizorol *Thebe, S.Afr.*
Risperidone (p. 1103·2).

Schlaf- und Beruhigungsdragees *Aponova, Austria.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Anxiety; insomnia; nervous disorders.

SchlafTabs *Ratiopharm, Ger.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Schlehen Elixir *Weleda, S.Afr.†*
Blackthorn (p. 2458·2).
Tonic.

Schleimhaut-Komplex L Ho-Fu-Complex *Liebermann, Ger.*
Cepa (p. 2575·2); galphimia; kalium bichr (p. 2476·3); luffa (p. 2545·3); natr. chlor. (p. 1795·1); pulsatilla (p. 2600·2); sticta (p. 2546·1); thuja (p. 2629·3).
Homoeopathic preparation.

Schmerz-Dolgit *Dolorgiet, Ger.†*
Ibuprofen (p. 68·2).
Pain; rheumatism; fever.

Schnarchex *Peithner, Austria.*
Cinchona pubescens (p. 2478·3); strychnos nux vomica (p. 2573·3); atropa belladonna (p. 2453·3); pulsatilla pratensis (p. 2600·2); camphora (p. 2466·2).
Homoeopathic preparation.

schnupfen endrine *Chiesi, Ger.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinitis.

Schnupfen Kapseln *Tetesept, Ger.†*
Eucalyptus oil (p. 2501·2).
Respiratory-tract congestion.

Schnupfencreme *Weleda, Ger.*
Aesculinum (p. 2431·2); berberis (p. 2502·1); bryonia (p. 2461·3); echinacea purpurea (p. 2498·1); prunus spinosa (p. 2458·2); hydrargyrum sulfuratum rubrum (p. 2555·3); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Nasal congestion.

Scholl Athlete's Foot *SSL, Irl.; SSL, Singapore; SSL, UK.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Scholl Callous *Titan, Turk.†*
Salicylic acid (p. 1719·1).
Calluses.

Scholl Callus Removal *SSL, UK.*
Salicylic acid (p. 1719·1).
Calluses.

Scholl Callus Remover *Schering-Plough, Canad.*
Salicylic acid (p. 1719·1).
Calluses; corns.

Scholl Corn & Callous Removal *SSL, Irl.*
Salicylic acid (p. 1719·1); camphor (p. 2466·2).
Corns; calluses.

Scholl Corn & Callus Removal Liquid *SSL, UK.*
Salicylic acid (p. 1719·1); camphor (p. 2466·2).
Corns; calluses.

Scholl Corn Removal *SSL, UK.*
Salicylic acid (p. 1719·1).
Corns.

Scholl Corn Remover *Schering-Plough, Canad.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Scholl Corn/Callous Removers *SSL, Israel.*
Salicylic acid (p. 1719·1).
Corns and callouses.

Scholl 2-Drop Corn Remedy *Schering-Plough, Canad.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Scholl Dry Antiperspirant Foot Aerosol Powder *Schering-Plough, Canad.†*
Aluminium chlorohydrate (p. 1694·1).
Foot perspiration; foot odour.

Scholl Seal & Heal *Reckitt Benckiser, UK.*
Salicylic acid (p. 1719·1); camphor (p. 2466·2).
Calluses; corns; verrucas; warts.

Scholl Verucca Removal *Reckitt Benckiser, UK.*
Salicylic acid (p. 1719·1).
Verrucas; warts.

Scholl Warzenfilm *SSL, Switz.†*
Salicylic acid (p. 1719·1).
Warts.

Schoum *Omega, Fr.*
Fumitory (p. 2508·2); ononis (p. 2575·3); Jamaica dogwood (p. 2536·3); sorbitol (p. 2092·1); alverine citrate (p. 1819·1).
Gastrointestinal and kidney disorders.

Schrundensalbe Dermi-cyl *Liebermann, Ger.*
Salicylic acid (p. 1719·1).
Skin disorders.

Schufen *Kenyaku, Hong Kong; Kenyaku, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever; inflammation.

Schweden-Mixtur H *Hanseler, Switz.*
Aloes (p. 1816·1); senna (p. 1885·1); rhubarb (p. 1884·2).
Constipation.

Schwedentrunk Elixier *Infirmarius, Ger.*
Angelica (p. 2443·3); gentian (p. 2512·1); cardamom fruit (p. 2471·1); cinnamon (p. 2479·2); valerian (p. 2640·2).
Digestive-system disorders.

Schwefelbad Dr Klopfer *Protina, Austria; Protina, Ger.†; Protina, Hung.†*
Sulfur (p. 1721·1); sodium thiosulfate (p. 1576·1).
Musculoskeletal and joint disorders; skin disorders; bath additive; rheumatism.

Schwef-Heel *Heel, Neth.*
Sulfur (p. 1721·1).

Schwöneural N *Schworer, Ger.*
Primula veris (p. 2596·2); melilotus officinalis (p. 2552·3); pulsatilla (p. 2600·2); asa foetida (p. 2449·3); cocculus (p. 2483·1); nux vomica (p. 2573·3); rhus toxicodendron (p. 2603·3); iris versicolor (p. 2534·3).
Homoeopathic preparation.

Schwörocard *Schworer, Ger.*
Aurum (p. 2521·1); glonoinum (p. 1391·2); convallaria majalis (p. 2486·2); cactus (p. 2473·2); crataegus (p. 2488·1).
Homoeopathic preparation.

Schwörocor A *Schworer, Ger.*
Chininum arsenicosum (p. 2601·3); selenium (p. 2086·3); panax ginseng (p. 2513·3).
Homoeopathic preparation.

Schwörosin *Schworer, Ger.*
Pulsatilla (p. 2600·2); euphorbium; hydrargyrum biiodatum (p. 2555·3); apisinum (p. 2434·3); hepar sulfuris (p. 1721·3).
Homoeopathic preparation.

Schwörotox *Schworer, Ger.*
Belladonna (p. 2453·3); baptisia (p. 2647·2); bryonia (p. 2461·3); echinacea (p. 2498·1).
Homoeopathic preparation.

Schwörotox A *Schworer, Ger.*
Echinacea angustifolia (p. 2498·1); gelsemium (p. 2511·2); lachesis (p. 2538·3); aconitum (p. 2428·3).
Homoeopathic preparation.

Sciargo *Potter's, UK.*
Shepherd's purse (p. 2614·2); wild carrot (p. 2647·2); clivers (p. 2481·2); bearberry (p. 2453·2); juniper berry oil (p. 2537·2).
Sciatica; lumbago.

Sci-B-Vac *SciGen, Hong Kong; SciGen, Israel.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

SciLin M30 *Bayer, China; SciGen, Hong Kong; SciGen, Philipp.*
⊗A mixture of insulin (human) 30% and isophane insulin (human) 70% (p. 475·3).
Diabetes mellitus.

SciLin N *Bayer, China; SciGen, Hong Kong; SciGen, Philipp.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

SciLin R *Bayer, China; SciGen, Hong Kong; SciGen, Philipp.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

SciLocyte *SciGen, Philipp.*
Filgrastim (p. 1151·3).
Neutropenia; mobilization of peripheral blood progenitor cells.

Scimax *GeneScience, Hong Kong.*
Filgrastim (p. 1151·3).
Neutropenia.

Scintadren *Nycomed Amersham, UK.*
Selenium-75 (p. 2228·1) in the form of 6β-(methyl(^{75}Se)seleno)methyl-19-norcholest-5(10)-en-3β-ol.
Adrenal gland imaging.

Scintimun *CIS, Cz.; CIS, Fr.; CIS, Irl.; CIS, Neth.; CIS, Pol.; CIS, Port.; CIS, Spain.*
Kit for labelling besilesomab with technetium-99m (p. 2228·1).
Scintigraphic imaging for localisation of osteomyelitis.

Sciomir *CT, Ital.*
Thiocolchicoside (p. 2026·2).
Spasticity; parkinsonism; neuromuscular pain.

Scippa *Gedeon Richter, Denm.†; Gedeon Richter, Irl.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; anxiety; social phobia; obsessive-compulsive disorder.

Scipral *AMPDR, Port.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; anxiety; social phobia; obsessive-compulsive disorder.

Sciroppo Berta *Berta, Ital.*
Liquorice (p. 1853·2); sulfogaiacol (p. 1678·1).
Cough; catarrh.

S-Citadep *Cipla, India.*
Escitalopram oxalate (p. 416·2).
Depression.

Scitin *Wermar, Mex.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal motility disorders.

SciTropin *SciGen, Austral.; SciGen, Hong Kong†; SciGen, Philipp.; SciGen, Singapore.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure; Prader-Willi syndrome; short stature in children born small for gestational age.

Sclefic *Actavis, Cz.*
Riluzole (p. 2605·1).
Amyotrophic bilateral sclerosis.

Sclerace *Novartis, India.*
Ramipril (p. 1483·3).
Heart failure; hypertension.

Sclérémo *Bailleul, Fr.*
⊗Chrome alum (p. 2476·2); glycerol (p. 2517·2).
Varicose veins.

Sclerobion *Merck, India.*
Vitamin A (p. 2098·3); vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1).
Vitamin A deficiency; macular degeneration; atherosclerosis; xerosis.

Sclérocalcine *Lehning, Fr.*
Crocus (p. 2208·2); secale cornutum (p. 2137·1); geranium robertianum; senecio (p. 2612·3); silicea (p. 2208·3); crataegus oxycantha (p. 2488·1); sulfur (p. 1721·1); cortex betulae (p. 2457·3).
Homoeopathic preparation.

Sclerodex *Omega, Canad.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); phenethyl alcohol (p. 1763·2).
Sclerotherapy.

Sclerodine *Omega, Canad.*
Iodine (p. 2336·3); sodium iodide (p. 2337·1).
Sclerotherapy.

Sclero-Drainol *Boiron, Fr.†*
Arsenicum iodatum (p. 2448·1); baryta muriatica (p. 2452·3); aconitum ferox (p. 2428·3); glonoinum (p. 1391·2); theridion currassavicum; spigelia marylandica (p. 2621·3); aurum (p. 2521·1); sumbul; naja tripudians.
Homoeopathic preparation.

Sclerofin *Ivax, Arg.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Scleromate *Palisades, USA.*
Sodium morrhuate (p. 2619·2).
Varicose veins.

Scleron *Weleda, Austria; Weleda, Canad.; Weleda, Ger.; Weleda, S.Afr.†*
Plumbum mellitum (p. 2541·3).
Homoeopathic preparation.

Sclerosol *Bryan, USA.*
Sterile talc (p. 1722·2).
Malignant pleural effusion.

Sclerovein *Resinag, Switz.; Resinag, Ukr.*
Lauromacrogol 400 (p. 2194·1).
Variceal sclerosis; varicose veins; telangiectasia; haemorrhoids.

Sclerovis H Plus *Amnol, Ital.*
Borage (p. 2459·1); Iceland moss (p. 2531·2); echinacea (p. 2498·1); melaleuca; peppermint (p. 1877·1); evening primrose (p. 2502·2); prunus dulcis; wheat (p. 2647·1); aloe (p. 1693·2); calendula (p. 2465·2).
Emollient.

Sclerovit *PannonPharma, Hung.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); alpha tocoferil acetate (p. 2119·2).
Dietary supplement.

S-Cloxin *Inpac, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

SCMC *CCM, Malaysia; Beacons, Singapore.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Scoburen *Renaudin, Fr.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal disorders; biliary-tract pain; gynaecological pain.

Scobutrin *Landson, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Scoline *Mayne, Austral.†; GSK, S.Afr.†*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Scolmin *Biolink, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Scopace *Hope, USA.†*
Hyoscine hydrobromide (p. 1845·3).
Parkinsonism.

Scopaject *Mylan, S.Afr.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Scopamin *Otto, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Scopamin Plus *Otto, Indon.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Scopanil *Lafi, Chile.*
Pargeverine (p. 1877·1); metamizole magnesium (p. 53·3).
Smooth muscle spasm and pain.

Scopas *Asian Pharm, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer; gastro-duodenitis; nausea and vomiting.

Scope
Note: this name may be used for preparations of different composition.
Procter & Gamble, USA.
Cetylpyridinium chloride (p. 1743·1).
Minor mouth or throat irritation.

Scopex *Adcock Ingram, S.Afr.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm.

Scopex Co *Adcock Ingram, S.Afr.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm.

Scopinal *Julphar, UAE.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer; aid in gastrointestinal examination.

Scopma *Ifars, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Scopma Plus *Ifars, Indon.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Painful smooth muscle spasm.

Scopoderm *Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
Hyoscine (p. 1845·3).
Motion sickness.

Scopoderm TTS *Novartis Sante, Fr.; Novartis Consumer, Ger.†; IFET (ΙΦΕΤ), Gr.; Novartis, Gr.; Novartis Consumer, Neth.; Enzpharma, NZ; Novartis Nutrition, Singapore; Novartis Consumer, UK.*
Hyoscine (p. 1845·3).
Motion sickness; palliative care in respiratory congestion.

Scopolan *Herbapol Wroclaw, Pol.*
Hyoscine butylbromide (p. 1845·3).
Biliary-tract spasm; peptic ulcer; vomiting; gastrointestinal spasm; spastic constipation; adjunct in radiology.

Scopolan Compositum *Herbapol Wroclaw, Pol.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm; peptic ulcer; pancreatitis; vomiting; adjunct in radiology and endoscopy.

Scorbatate *Seroyal, Canad.†*
Vitamin C (p. 2110·3).

Scorbex *Aspen, S.Afr.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Scorbolamid *Polpharma, Pol.*
Ascorbic acid (p. 2110·3); rutoside (p. 2505·3); salicylamide (p. 129·2).
Cold symptoms; headache; neuralgia.

Scott *GSK Consumer, Venez.*
Vitamin A (p. 2098·3); vitamon D.
Dietary supplement.

Scott Tradicional *GSK Consumer, Venez.*
Cod-liver oil (p. 2056·3).
Vitamin A and D deficiency; vitamin A and D supplement.

Scottopect *Nycomed, Austria.*
Gel: Turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3); menthol (p. 2553·2); camphor (p. 2466·2).
Catarrh; bronchitis.

Nycomed, Austria.
Oral liquid: Thyme (p. 2630·2); wild thyme (p. 2648·1); ribwort plantain (p. 2604·2).
Catarrh; bronchitis.

Scott's Chewyvit C *Sterling, Indon.*
Vitamin C (p. 2110·3).
Dietary supplement.

Scott's Cod Liver *GSK, Thai.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Scott's Cod Liver Oil *Sterling, Indon.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); omega-3 fatty acids (p. 1460·1).
Dietary supplement.

Scott's Emulsion
Note: this name may be used for preparations of different composition.
GSK, Hong Kong.
Cod-liver oil (p. 2056·3).
Dietary supplement.

SmithKline Beecham, USA.
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Sterling, Indon.
Cod-liver oil (p. 2056·3); calcium hypophosphite (p. 2530·3); sodium hypophosphite (p. 2530·3).
Vitamin A and D deficiency.

Scott's Emulsion Orange *GSK, Hong Kong.†*
Cod-liver oil (p. 2056·3); calcium hypophosphite (p. 2530·3).
Dietary supplement.

Scott's Emulsion Original
Note: this name may be used for preparations of different composition.
SmithKline Beecham, Hong Kong.†
Cod-liver oil (p. 2056·3); capelin oil; calcium hypophosphite (p. 2530·3); sodium hypophosphite (p. 2530·3).
Dietary supplement.

Scott's Emulsion Vita *Sterling, Indon.*
Cod-liver oil (p. 2056·3); calcium hypophosphite (p. 2530·3).
Vitamin A and D deficiency.

Sterling, Indon.
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); calcium hypophosphite (p. 2530·3).
Vitamin A and D supplement.

Scott's Hi-Calcium *GSK, Hong Kong.†*
Calcium carbonate (p. 1824·3).
Calcium supplement.

Scot-Tussin Allergy *Scot-Tussin, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Scot-Tussin Diabetes *Scot-Tussin, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Scot-Tussin DM *Scot-Tussin, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Scot-Tussin DM Cough Chasers *Scot-Tussin, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Scot-Tussin Expectorant *Scot-Tussin, USA.*
Guaifenesin (p. 1666·2).
Coughs.

Scot-Tussin Original 5-Action *Scot-Tussin, USA.*
Phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); sodium citrate (p. 1781·2); sodium salicylate (p. 132·2); caffeine citrate (p. 1203·3).
Upper respiratory-tract symptoms.

Scot-Tussin Senior Clear *Scot-Tussin, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

SCR *Pickles, UK.*
Salicylic acid (p. 1719·1).
Cradle cap.

Scribcin *Wescrib, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Scripto-Lyte *Adcock Ingram, S.Afr.*
Potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Scripto-Metic *Adcock Ingram, S.Afr.*
Prochlorperazine maleate (p. 1098·3).
Vestibular disorders; migraine; nausea and vomiting.

Scripto-Pam *Adcock Ingram, S.Afr.*
Diazepam (p. 1063·2).

Scrofularia Composé *Boiron, Fr.*
Scrofularia; mercurius dulcis (p. 2555·3); anemone pulsatilla (p. 2600·2); belladonna (p. 2453·3); phytolacca decandra (p. 2593·2); conium maculatum (p. 2524·3); calcarea iodata (p. 1658·1); solidago virga aurea (p. 2620·1).
Homoeopathic preparation.

Scrub-Atlas *Atlas, Arg.*
Ammonium glycolate (p. 1704·3); polyethylene granules (p. 1690·3).
Exfoliant skin cleanser; acne.

K2 Health & Wellness, Chile.
Glycolic acid (p. 1704·3); polyethylene microspheres (p. 1690·3).
Skin cleansing.

Scullcap & Gentian Tablets *Dorwest, UK.*
Skullcap (p. 2617·1); valerian (p. 2640·2); vervain (p. 2645·1); gentian (p. 2512·1).
Irritability; insomnia; anxiety.

Sculptra *Sanofi-Aventis, NZ; Dermik, USA.*
Polylactic acid.
Facial fat loss in HIV infection.

Sanofi-Aventis, Fr.
Poly L-lactic acid.
Skin irregularities; scars.

SCV 300 *Sigma, Arg.*
dl-alpha tocopherol (p. 2119·1); ginkgo biloba (p. 2512·3).

SDE Tar *Schering-Plough, Ital.*
Coal tar (p. 1723·2).
Scalp disorders.

SDE Zinc *Schering-Plough, Ital.*
Pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis.

SD-Hermal *Almirall Hermal, Ger.*
Clotrimazole (p. 576·2).
Seborrhoeic dermatitis; pityriasis versicolor.

SDN 200 *Sigma, Arg.*
Valerian (p. 2640·2); passion flower (p. 2584·1); valepotriates (p. 2640·2).
Insomnia; nervous disorders; gastrointestinal disorders.

S-Docid *Medicpharma, Thai.*
Indometacin (p. 71·2).
Gout; musculoskeletal and joint disorders; pain.

SE-25 *Marching, Hong Kong.†*
Cinnarizine (p. 622·1); vitamin B_6 (p. 2105·3).

SE BPO *Seton, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

SE SS *Seton, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Sea Clens *Coloplast, Canad.†*
Sodium chloride (p. 1795·1).
Wound cleansing.

Sea Far *Christo, Hong Kong.†*
Meclozine (p. 634·3).

SEA ORS *SEA Pharm, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy; diarrhoea.

Sea Snake Antivenene *Commonwealth Serum, Hong Kong.*
Snake venom antisera from horses treated with Enhydrina schistosa venom (p. 2419·1).
Snake bite.

Sea Snake Antivenom *CSL, Singapore.*
Snake venom antisera from horses treated with Enhydrina schistosa venom (p. 2419·1).
Snake bite.

Sea-Cal *Bioceuticals, UK.*
Calcium carbonate (p. 1824·3).

Seacalcit *Bergamo, Braz.*
Calcitonin (salmon) (p. 1178·1).

Seacor *SPA, Ital.*
Omega-3 triglycerides (p. 1460·3).
Hypertriglyceridaemia; cardiovascular risk reduction.

Seaking *Cipla, India.*
Cod-liver oil (p. 2056·3).

Seaking Plus *Cipla, India.*
Cod-liver oil (p. 2056·3); vitamin E (p. 2119·1).

Seal & Heal *SSL, Hung.; SSL, Pol.*
Salicylic acid (p. 1719·1).
Warts; corns; calluses.

Sealax *Seaford, Canad.†*
Macrogol 3350 (p. 2547·3).

Sea-Legs *SSL, Irl.; Boots Healthcare, NZ; SSL, UK.*
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Seale's Lotion *C & M, USA.*
Sulfur (p. 1721·1); borax (p. 2459·2); zinc oxide (p. 1729·1).
Acne.

Seal-On *Alltracel, Irl.†; Beta Healthcare, UK.*
Calcium oxidised cellulose (p. 1157·3); sodium oxidised cellulose (p. 1157·3).
Capillary haemorrhage.

SeaMist *Schein, USA.*
Sodium chloride (p. 1795·1).
Inflammation and dryness of nasal membranes.

Sea-Omega *Rugby, USA.*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Sea-Sel *Da Vinci, Canad.†*
Minerals.

Seasonale *Paladin, Canad.; Teva, USA.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Seasonique *Paladin, Canad.; Teva, Israel; Duramed, USA.*
84 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, ethinylestradiol.
Combined oral contraceptive.

SeaSorb *Coloplast, Fr.*
Calcium alginate (p. 1136·3); carmellose sodium (p. 2175·2).
Ulcers; wounds.

Coloplast, Arg.†
Calcium alginate (p. 1136·3); sodium alginate (p. 2167·3); carmellose sodium (p. 2175·2).
Exudating wounds.

SeaSorb Soft *Coloplast, Belg.*
Calcium alginate (p. 1136·3).
Wounds.

Coloplast, Ger.; Coloplast, UK.
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Burns; ulcers; wounds; exudating wounds.

SeaSorb-Ag *Coloplast, Ger.*
Calcium alginate (p. 1136·3); carmellose (p. 2175·1); ionic silver (p. 2615·1).
Burns; ulcers; wounds.

Seatone *Peter Black, UK.*
Green-lipped mussel (p. 2522·3).

Seaweed Slimix *English Herbal Medicines, UK.*
Fucus vesiculosus.
Slimming aid.

Seaze *Aspen, Austral.*
Lamotrigine (p. 527·2).
Epilepsy.

Sebamed *Sebapharma, Hong Kong; Bayer, Mex.; Sebapharma, Thai.*
A range of skin cleansers and emollients.

Lofco, Canad.
Liquid paraffin (p. 2191·2); soft paraffin (p. 2211·3).
Nappy rash.

Sebamed Multi Protect Suncream *Sebapharma, Thai.*
SPF 30; SPF 50+: Titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); diethylamino hydroxybenzoyl hexyl benzoate; bemotrizinol (p. 1695·3); iscotrizinol (p. 1706·1); octocrilene (p. 1715·2).
Sunscreen.

Sebamed Suncream 20 *Sebapharma, Thai.*
Octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2).
Sunscreen.

Sebamed Suncream 28 *Sebapharma, Thai.*
Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sebamed Sunlotion 20 *Sebapharma, Thai.†*
SPF 20: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2).
Sunscreen.

Seba-Nil *Healthpoint, USA.*
Skin cleanser.
Acne.

Sebapain *Berman, Mex.*
Ketorolac (p. 80·2).
Pain.

Sebaquin *Summers, USA.*
Diiodohydroxyquinoline (p. 931·1).
Scalp disorders.

Sebasorb *Summers, USA.*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Acne.

Sebaxyl *Mediphar, Venez.*
Salicylic acid (p. 1719·1); boric acid (p. 2459·3); camphor (p. 2466·2).
Acne; seborrhoea.

Sebclair *Sinclair, Fr.*
Emollient.
Seborrhoeic dermatitis.

Sebco *Centrapharm, UK.*
Coal tar (p. 1723·2); precipitated sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Scalp disorders.

Sebcur *Dermtek, Canad.*
Salicylic acid (p. 1719·1).
Seborrhoea of the scalp.

Sebcur-T *Dermtek, Canad.*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Psoriasis of the scalp.

Sebercim *GSK, Ital.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Sebex *Rugby, USA.*
Salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Seborrhoea.

Sebex-T *Rugby, USA.*
Coal tar (p. 1723·2); sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Seborrhoea.

Sebidin *GSK, Pol.; GSK, Ukr.*
Ascorbic acid (p. 2110·3); chlorhexidine hydrochloride (p. 1743·3).
Mouth and throat disorders; mouth disinfection.

GSK, Rus.
Ascorbic acid (p. 2110·3); chlorhexidine (p. 1743·2).
Mouth and throat disorders.

Sebifin *Ranbaxy, Mex.†*
Terbinafine (p. 593·3).

Sebiprox *Stiefel, Denm.; GSK, Fin.†; GSK, Fr.; Stiefel, Ger.; Stiefel, Ital.; Stiefel, Neth.†; Stiefel, Norw.; Stiefel, Port.; Stiefel, Spain; GSK, Swed.; GSK, Switz.*
Ciclopirox olamine (p. 575·3).
Seborrhoeic dermatitis.

Sebirinse *Ego, Austral.; Ego, NZ.*
Dicetyldimonium chloride; dexpanthenol (p. 2582·2); phenethyl alcohol (p. 1763·2).
Dandruff; dry scalp and hair disorders.

Ego, Hong Kong.
Dicetyldimonium chloride; panthenol (p. 2582·2).
Scalp disorders.

Sebitar *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.*
Pine tar (p. 1723·3); coal tar (p. 1723·2); salicylic acid (p. 1719·1); undecylenamide (p. 596·3).
Skin and scalp disorders.

Sebium *Dispolab, Chile.†*
Cream: Moisturiser for greasy skin.

Dispolab, Chile.†
Gel: Skin cleanser.

Sébium *Bioderma, Fr.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1); zinc gluconate (p. 2126·2); enoxolone (p. 54·2); ginkgo biloba (p. 2512·3).
Seborrhoea.

Sebium AKN *Dispolab, Chile†; Bioderma, Venez.*
Zinc gluconate (p. 2126·2); salicylic acid (p. 1719·1); enoxolone (p. 54·2); ginkgo biloba (p. 2512·3); AHA esters.
Acne.

Sebium Gel *Bioderma, Venez.*
Soap substitute.
Acne.

Sebium H2O *Bioderma, Venez.*
Skin cleanser.
Acne.

Dispolab, Chile.†
Zinc gluconate (p. 2126·2); copper sulfate (p. 2057·2).
Acne.

Sebivo *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Cz.; Novartis, Denm.†; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore†; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.*
Telbivudine (p. 1017·2).
Chronic hepatitis B.

Sebizole *Ascent, Austral.; Douglas, NZ; Douglas, Singapore.*
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Sebo *Chew, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Scalp disorders.

Sebo Concept D/A *MLP, Canad.*
Resorcinol (p. 1718·3); salicylic acid (p. 1719·1); sulfur (p. 1721·1).

Sebo Fluid *Widmer, Philipp.†*
Glyceryl stearate; triclosan (p. 1773·2); panthenol (p. 2582·2); cetyl alcohol (p. 2178·2).
Acne; seborrhoea.

Seboclear *Raymos, Arg.*
Minocycline (p. 324·3) or minocycline hydrochloride (p. 325·1).
Bacterial skin infections.

Sebolic *Pharma Investi, Chile.*
A range of skin and scalp preparations containing melaleuca oil (p. 2551·1).
Skin and scalp disorders.

Sebolic Fluido *Pharma Investi, Chile.*
SPF 30: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sebolocion *Szama, Arg.*
Skin cleanser.
Acne; seborrhoea.

Sebolox *Drossapharm, Switz.*
Miconazole nitrate (p. 589·1).
Fungal scalp disorders.

Sebomin *Actavis, UK.*
Minocycline hydrochloride (p. 325·1).
Acne.

Sebon *Akdeniz, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Sébo-Psor *Widmer, Switz.*
⊗Dexamethasone (p. 1630·3); tretinoin (p. 1725·2); urea (p. 1727·3).
Scalp disorders.

Seboreks *Abbott, Turk.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Seboren *Herbapol Pruszkow, Pol.*
Calamus (p. 2464·2); arctium (p. 2540·1); pastinaca sativa; urtica (p. 2639·3).
Seborrhoea; dandruff; alopecia.

Séborhéane *Merck Medication Familiale, Fr.†*
Cream: Glycolic acid (p. 1704·3); piroctone olamine (p. 1716·3); alpha hydroxy acids (p. 1704·3); zinc gluconate (p. 2126·2); levomenol (p. 2544·1); allantoin (p. 1693·1); vitamin A palmitate (p. 2098·3); vitamin E acetate (p. 2119·2).
Seborrhoea; skin irritation.
Merck Medication Familiale, Fr.†
Shampoo: Piroctone olamine (p. 1716·3); alpha hydroxy acids (p. 1704·3); zinc lactate (p. 2126·2).
Dandruff.

Sebosel *Taro, Israel; Taro, Thai.*
Selenium sulfide (p. 1719·3).
Scalp disorders; seborrhoeic dermatitis; dandruff; pityriasis versicolor.

Sebosoap *Szama, Arg.*
Triclosan (p. 1773·2); salicylic acid (p. 1719·1); melaleuca oil (p. 2551·1); allantoin (p. 1693·1).
Exfoliant; seborrhoea.

Sebo-Soufrol *Gebro, Switz.†*
Pyrithione zinc (p. 1718·1); sulfur (p. 1721·1).
Scalp disorders.

Sébosquam *Expanscience, Fr.†*
Ictasol (p. 1706·1); cade oil (p. 1723·2); climbazole (p. 576·2).
Seborrhoeic dermatitis.

Sebozole *Muromsky, Rus.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Seb-Prev Wash *Perrigo, USA.*
Sulfacetamide sodium (p. 361·1).
Bacterial skin infections.

Sebrane
Note: this name may be used for preparations of different composition.
ProStrakan, Neth.; Biomed, Spain.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Sebren *Ivax, UK.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Sebryl *Bioclon, Mex.*
Allantoin (p. 1693·1); clioquinol (p. 273·1); coal tar (p. 1723·2).
Seborrhoeic dermatitis; dandruff.

Sebryl Plus *Bioclon, Mex.*
Allantoin (p. 1693·1); clioquinol (p. 273·1); coal tar (p. 1723·2); triclosan (p. 1773·2).
Seborrhoeic dermatitis; dandruff.

Sebstopp *Exakta, Mex.*
Allantoin (p. 1693·1); coal tar (p. 1723·2); clioquinol (p. 273·1).
Seborrhoea.

Sebulex
Note: this name may be used for preparations of different composition.
Panalab, Arg.
⊗Panthenol (p. 2582·2); salicylic acid (p. 1719·1); triclosan (p. 1773·2); potassium nitrate (p. 1766·2); boric acid (p. 2459·3); capsicum (p. 2469·3).
Seborrhoea.
Westwood-Squibb, Canad.†; Westwood-Squibb, USA.
Sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Itchy scalp; seborrhoeic dermatitis; scalp disorders.

Sebumselen *Llorente, Spain.*
Benzalkonium chloride (p. 1737·1); selenium sulfide (p. 1719·3).
Skin and scalp disorders.

Secabiol *Normon, Spain.*
Carnitine (p. 2053·2).
Carnitine deficiency; cardiac disorders.

Secadine *Mylan, S.Afr.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Secadryckel *Kendrick, Mex.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Secalbum *Nutricia-Bago, Arg.*
Calcium caseinate (p. 2055·2).
Dietary protein supplement.

Secale Med Complex *Dynamit, Austria.*
Arnica (p. 2447·2); barium chloratum (p. 2452·3); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Secale-Gastreu *Reckeweg, Ger.*
Acidum sulfuricum (p. 2624·2); crocus (p. 2208·2); hamamelis (p. 2523·3); secale cornutum (p. 2137·1); aesculus (p. 2431·2); ferrum phosphoricum (p. 2077·1).
Homoeopathic preparation.

Sécalip *Abbott, Fr.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Secalip *Farmasierra, Spain; Solvay, Turk.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Secalosan N *Hanosan, Ger.*
Secale cornutum (p. 2137·1); potentilla anserina; arnica montana (p. 2447·2); aesculus hippocastanum (p. 2431·2); clematis recta; angustura.
Homoeopathic preparation.

Secand *Royal, Chile.*
Sorbitol (p. 2092·1); malic acid (p. 2549·2); electrolytes (p. 1775·1).
Saliva substitute.

Secaris *Pendopharm, Canad.*
Macrogol (p. 2547·3); propylene glycol (p. 2205·2).
Rhinitis.

Secatoxin Forte *Teva, Cz.*
Codergocrine mesilate (p. 389·2).
Dementia; cerebral and peripheral vascular disorders; migraine; hypertension; thrombosis prophylaxis; vestibular disorders.

Secfar *Elofar, Braz.*
Secnidazole (p. 947·3).

Secita *Berksam, Turk.*
Escitalopram oxalate (p. 416·2).

Seclodin *Home, Port.†*
Ibuprofen (p. 68·2).
Fever; pain.

Secloxin *Swiss Health, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Secnal *Teuto, Braz.*
Secnidazole (p. 947·3).

Secnaxidol *EMS, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnics *Delta, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnidal *Sanofi-Aventis, Braz.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Venez.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnidalin *Ducto, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis.

Secnidox *World Medicine, Ukr.*
Secnidazole (p. 947·3).
Trichomoniasis; bacterial vaginosis; amoebiasis; giardiasis.

Secnihexal *Hexal, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnil *Piramal, India.*
Secnidazole (p. 947·3).
Trichomonal vaginitis; bacterial vaginosis; amoebiasis; giardiasis.

Secni-Plus *Farmoquimica, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnitec *Greenpharma, Braz.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnivax *Vivax, Venez.*
Secnidazole (p. 947·3).
Trichomoniasis; amoebiasis; giardiasis.

Secnix *Cifarma, Braz.*
Secnidazole (p. 947·3).

Secnizol *UCI, Braz.*
Secnidazole (p. 947·3).
Bacterial infections; protozoal infections.

Secnol *IPRAD, Fr.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Seco *Sriprasit, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Secokapton *Strallhofer, Austria.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine.

Secol *Odan, Canad.*
Isopropyl myristate (p. 2190·3); wool fat (p. 2219·3); liquid paraffin (p. 2191·2).

Seconal *Flynn, UK; Marathon, USA.*
Secobarbital sodium (p. 1106·3).
Insomnia; sedative.

Secotex *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Secpel *Medinfar, Port.†*
Lactic acid (p. 2539·1); lecithin (p. 2542·2).
Seborrhoeic dermatitis of the scalp.

Secpel Composto *Medinfar, Port.†*
Ichthammol (p. 1705·3); lactic acid (p. 2539·1); lecithin (p. 2542·2).
Psoriasis; scalp disorders.

Secran *Scherer, USA.*
Vitamins.

Secrelux *Sanochemia, Ger.; IFET (ΙΦΕΤ), Gr.*
Secretin hydrochloride (p. 2612·2).
Test of pancreatic function; diagnosis of Zollinger-Ellison syndrome.

Secrepat *Angelini, Spain.*
Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1); aluminium glycinate (p. 1817·2).
Gastric hyperacidity.

Secrepat Forte *Sperko, Ukr.*
Aluminium glycinate (p. 1817·2); aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1).
Digestive disorders.

Secresol *Permamed, Switz.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Secret 28 *Elea, Arg.; Elea, Mex.*
24 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Secretil *Caber, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Secretin *Osoth, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Secril *Baif, Ital.*
Borage oil (p. 2459·2); collagen (p. 2483·2); vitamins; magnesium (p. 1786·3).
Dietary supplement.

Sectil *Brasterapica, Braz.*
Secnidazole (p. 947·3).

Sectral *Sanofi-Aventis, Belg.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Polfa Grodzisk, Pol.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, UK; Reddy, USA.*
⊗Acebutolol hydrochloride (p. 1289·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; hyperthyroidism; obstructive cardiomyopathy.

Sectrazide *Sanofi-Aventis, Belg.; Aventis, Indon.†*
⊗Acebutolol hydrochloride (p. 1289·2); hydrochlorothiazide (p. 1403·2).
Hypertension; angina pectoris; arrhythmias.

Secubar Diu *Sandoz, Spain.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Secuentex-21 *Pfizer, Mex.*
15 Tablets, mestranol (p. 2291·1); 6 tablets, chlormadinone acetate (p. 2257·3); mestranol (p. 2291·1).
Sequential oral contraceptive.

Secufem *Elea, Arg.*
Levonorgestrel (p. 2296·1).
Post-coital oral contraceptive.

Securact *Sandoz, Ital.*
Methotrexate (p. 822·2).

Secural *SecFarm, Pol.*
Nonoxinol 9 (p. 2199·1).
Spermicidal contraceptive.

Securgin *Menarini, Ital.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Securil *Yalacta, Fr.*
Propionibacterium freudenreichii.
Maintenance of gastrointestinal flora.

Securo *Raymos, Arg.*
Ivermectin (p. 155·1).
Onchocerciasis; strongyloidiasis; scabies.

Securon *Abbott, UK.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Seczol
Note: this name may be used for preparations of different composition.
Medley, Braz.
Tioconazole (p. 595·3); tinidazole (p. 949·2).
Fungal vaginal infections.
Valmor, Venez.
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis; vaginal gardnerella infections.

Sedabarb *Be-Tabs, S.Afr.*
Phenobarbital (p. 535·2).

Sedaben *Labima, Belg.*
Lormetazepam (p. 1082·1).
Insomnia.

Sedacalman *Schwarzwalder, Ger.*
Kalium bromat. (p. 2461·1); acid. picrinic. (p. 2634·2); hypericum (p. 449·1); avena sativa (p. 2451·1); valeriana (p. 2640·2); chamomilla (p. 2474·1); lupulus (p. 2546·1).
Homoeopathic preparation.

Sedacid *SMB, Belg.; Anabiosis, Gr.; Pinewood, Irl.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Sédacollyre *Cooperation Pharmaceutique, Fr.*
Cethexonium bromide (p. 1742·1) or cetylpyridinium chloride (p. 1743·1).
Formerly known as Bactyl.
Eye infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Cooperation Pharmaceutique, Fr.†
Oxedrine tartrate (p. 1463·2); berberine hydrochloride (p. 2455·1); benzododecinium bromide (p. 1739·2).
Eye congestion.

Sedacoron *Ebewe, Austria; Ebewe, Cz.; Sandoz, Hong Kong; Ebewe, Hung.†; Ebewe, Rus.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Sedacris *Elea, Arg.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Cough; obstructive airways disease.

Sedacum *Dexa, Indon.*
Midazolam (p. 1085·1).
Sedative; premedication; general anaesthesia.

Sedacur *Schaper & Brummer, Ger.; Phytotec, Hung.; MaxMedica, Swed.*
Valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3).
Anxiety; insomnia; nervous disorders; sleep disorders.

Seda-Do *Grasler, Ger.*
Avena sativa (p. 2451·1); lupulus (p. 2546·1); passiflora incarnata (p. 2584·1); coffea (p. 2648·2).
Homoeopathic preparation.

Sedador *Cristalia, Braz.*
Dipyrone (p. 53·3); promethazine hydrochloride (p. 638·2); adiphenine hydrochloride (p. 2431·1).

Sedafex *Pharmabiotics, Chile.†*
Cefadroxil (p. 233·2).
Bacterial infections.

Sedafiton *Phytopharm, Ukr.*
Valerian (p. 2640·2); leonurus (p. 2564·2); crataegus (p. 2488·1).
Nervous disorders; sleep disorders; cardiac disorders; skin disorders; mental function impairment.

Sedaflora *Abdi, Turk.*
Passion flower (p. 2584·1).
Insomnia; nervous disorders.

Sedagaston *Mylan, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Sedagel
Note: this name may be used for preparations of different composition.
Key, Austral.
Oral gel: Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3); menthol (p. 2553·2).
Painful mouth disorders.
Key, Austral.
Lotion: Cetylpyridinium chloride (p. 1743·1); chlorhexidine acetate (p. 1743·2); lidocaine (p. 1988·1).
Mouth ulcers; toothache; sore gums.

Sédagel *Roche-Posay, Fr.†*
⊗Urea (p. 1727·3).
Skin irritation.

Sedagin *Biocontrolfarm, Ital.*
California poppy (p. 2466·1).

Sedagul *Wild, Switz.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Sedakatt *Kattwiga, Ger.*
Avena sativa (p. 2451·1); coffea (p. 2648·2); passiflora incarnata (p. 2584·1); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Sedakter *Corsa, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Sedalêne *Cristalia, Braz.; Gunther, Braz.*
Dipyrone (p. 53·3); homatropine methylbromide (p. 2007·3); papaverine hydrochloride (p. 2362·3); adiphenine (p. 2430·3) or adiphenine hydrochloride (p. 2431·1).
Smooth muscle spasm.

Sedalex *Teuto, Braz.*
Orphenadrine citrate (p. 909·2); dipyrone (p. 53·3); caffeine (p. 1203·3).
Pain; smooth muscle spasm.

Sedalgina *Teuto, Braz.*
⊗Isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
Pain.

Sedalgin-Neo *Balkanpharma, Rus.*
Paracetamol (p. 115·1); dipyrone (p. 53·3); caffeine (p. 1203·3); phenobarbital (p. 535·2); codeine phosphate (p. 40·2).
Fever; pain.

Sedalia *Boiron, Cz.*
Chamomilla recutita (p. 2474·1); gelsemium (p. 2511·2); hyoscyamus niger (p. 2530·2); kalium bromatum (p. 2461·1); passiflora incarnata (p. 2584·1); datura stramonium (p. 2622·3).
Homoeopathic preparation.

Sedalin
Note: this name may be used for preparations of different composition.
Chi Sheng, Thai.
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Elin, Philipp.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Prodotti, Braz.†
Dipyrone (p. 53·3); papaverine (p. 2362·2); adiphenine (p. 2430·3); homatropine methylbromide (p. 2007·3).

Sedalipid *Steigerwald, Ger.†*
Magnesium-pyridoxal-5′-phosphate-glutamate.
Hyperlipidaemias.

Sedalit *Farmstandart, Rus.*
Lithium carbonate (p. 427·3).
Mania; psychoses; chronic alcoholism; migraine; Ménière's disease.

Sedalito *Merck, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Sedal-M *Sopharma, Rus.; Sopharma, Ukr.*
Paracetamol (p. 115·1); dipyrone (p. 53·3); caffeine (p. 1203·3); phenobarbital (p. 535·2); codeine phosphate (p. 40·2).
Pain; fever.

Sedalmerck *Merck, Mex.*
Tablets: Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; rhinitis; sinusitis.

Merck, Chile†; Merck, Mex.
Effervescent tablets: ⊗Paracetamol (p. 115·1); caffeine (p. 1203·3); pseudoephedrine hydrochloride (p. 1676·1).
Pain; fever; rhinitis; sinusitis; cold and influenza symptoms.

Sedalmerck Flu *Merck, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); brompheniramine maleate (p. 618·1).
Cold and influenza symptoms.

Sedalmine *Abbott, Turk.*
Dipyrone (p. 53·3).
Pain; fever.

Sedalon *Gunsa, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Sédalozia *Iphym, Fr.†*
Crataegus (p. 2488·1); california poppy (p. 2466·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Sedalpan *Teofarma, Ital.*
Methyl nicotinate (p. 91·3); diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, and soft-tissue disorders.

Sedam *Sandoz, Pol.*
Bromazepam (p. 1041·2).
Anxiety disorders.

Sedamed *Cimed, Braz.*
⊗Caffeine (p. 1203·3); dipyrone (p. 53·3); isometheptene (p. 2535·1).

Sedanat *PGN, Arg.†*
Valerian (p. 2640·2); tilia (p. 2631·3); passion flower (p. 2584·1).
Insomnia.

Sedangor *Sintesina, Arg.†*
Dipyridamole (p. 1362·2).

Sedanium-R *Coup, Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Sedans *Ganassini, Ital.*
Amitriptyline hydrochloride (p. 401·1); chlordiazepoxide hydrochloride (p. 1044·2).
Nervous disorders.

Sedante Dia *Serranita, Arg.*
Passion flower (p. 2584·1); valerian (p. 2640·2); tilia (p. 2631·3).
Sedative.

Sedante Noche *Serranita, Arg.*
Passion flower (p. 2584·1).
Insomnia.

Sedantol
Note: this name may be used for preparations of different composition.
Dovalle, Braz.
Valerian (p. 2640·2); melissa (p. 2552·3); passion flower (p. 2584·1).
Sedative.

Recalcine, Chile.
Diazepam (p. 1063·2); chlormezanone (p. 1045·1).
Anxiety; insomnia; skeletal muscle spasm.

Sedanxio *Tilman, Belg.*
Passion flower (p. 2584·1).
Anxiety.

Sedapain
Note: this name may be used for preparations of different composition.
Nichi-Iko, Jpn.
Eptazocine hydrobromide (p. 55·1).
Pain.

Garec, S.Afr.†
Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain with tension.

Sedapap *Merz, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).
Tension headache.

Sedaperidol *Biosel, Turk.*
Haloperidol (p. 1077·1).
Psychoses; agitation; behaviour disorders; anxiety; hiccups; nausea and vomiting.

Sedaphin *Asconex, Ger.†*
Valeriana officinalis (p. 2640·2); lupulinum (p. 2546·1); asa foetida (p. 2449·3); semecarpus anacardium (p. 2471·3); strychnos ignatii (p. 2532·1); kalium bromatum (p. 2461·1); myristica fragrans (p. 2573·1).
Homoeopathic preparation.

Sédaplaie *Zambon, Fr.†*
Dodeclonium bromide (p. 1750·3); amylocaine hydrochloride (p. 1979·3).
Burns; wounds.

Seda-Plantina N *Quiris, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3); passion flower (p. 2584·1).
Nervous disorders; sleep disorders.

Sedaplus *CNP, Ger.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Sedapressin *Biospray, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sedapulpe *Biodica, Fr.†*
Lidocaine hydrochloride (p. 1988·2); creosote (p. 1659·3); phenol (p. 1763·3); eugenol (p. 2501·2).
Dental canal disinfection.

Sédarène *Jolly-Jatel, Fr.†*
Capsules: Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Jolly-Jatel, Fr.†
Suppositories: Paracetamol (p. 115·1).
Pain; fever.

Sedarin *Merck, S.Afr.†*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Sedariston Konzentrat *Steiner, Ger.†*
St John's wort (p. 449·1); valerian root (p. 2640·2).
Anxiety disorders; sleep disorders.

Sedariston plus *Steiner, Ger.†*
Valerian root (p. 2640·2); St John's wort (p. 449·1); melissa leaf (p. 2552·3).
Nervous disorders.

Sedartryl
Note: this name may be used for preparations of different composition.
Prater, Chile.
Zaleplon (p. 1114·3).
Insomnia.

Sedaselect *Dreluso, Ger.*
Avena sativa (p. 2451·1); ignatia (p. 2532·1); valeriana (p. 2640·2); selenium (p. 2086·3); gelsemium (p. 2511·2).
Homoeopathic preparation.

Sedaselect D *Dreluso, Ger.*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Sedasen *Sperko, Ukr.*
Valerian (p. 2640·2); peppermint; melissa (p. 2552·3).
Nervous disorders; insomnia; headache; migraine; dysmenorrhoea; menopausal disorders; functional gastrointestinal disorders; tachycardia; cardialgia; hypertension; pruritus; eczema.

Sedasol eco natura *Sandoz, Switz.†*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders.

Sédaspir *Bride, Fr.*
Codeine phosphate (p. 40·2); caffeine (p. 1203·3); aspirin (p. 22·2).
Pain.

Sedastip *Milte, Ital.*
Fibre; vitamins.
Constipation.

Sedatab *PP Lab, Thai.*
Diphenhydramine hydrochloride (p. 626·2).

Sedatif *Boiron, Austral.†; Boiron, Hung.*
Aconitum napellus (p. 2428·3); atropa belladonna (p. 2453·3); calendula officinalis (p. 2465·2); chelidonium majus (p. 2522·2); abrus precatorius (p. 2426·1); viburnum opulus.
Homoeopathic preparation.

Sédatif PC *Boiron, Cz.; Boiron, Fr.; Boiron, Neth.; Boiron, Port.; Boiron, Switz.*
Aconitum napellus (p. 2428·3); belladonna (p. 2453·3); calendula officinalis (p. 2465·2); chelidonium majus (p. 2522·2); jequirity (p. 2426·1); viburnum opulus.
Homoeopathic preparation.

Sedatif PC *Boiron, Ukr.*
Aconitum napellus (p. 2428·3); belladonna (p. 2453·3); calendula officinalis (p. 2465·2); chelidonium majus (p. 2522·2); abrus precatorius (p. 2426·1); viburnum opulus.
Homoeopathic preparation.

Sédatif Tiber *Poirier, Fr.†*
Crataegus (p. 2488·1); passion flower (p. 2584·1); potassium bromide (p. 2461·1); sodium bromide (p. 2461·1).
Anxiety; insomnia.

Sédatil *Boiron, Canad.*
Abrus precatorius (p. 2426·1); aconitum napellus (p. 2428·3); belladonna (p. 2453·3); calendula officinalis (p. 2465·2); chelidonium majus (p. 2522·2); viburnum opulus.
Homoeopathic preparation.

Sedativae Species No 2 *Zdorovje, Rus.*
Valerian (p. 2640·2); peppermint leaf (p. 1877·1); motherwort (p. 2564·2); liquorice (p. 1853·2); lupulus (p. 2546·1).
Irritability; sleep disorders.

Sedativae Species No 3 *Zdorovje, Rus.*
Valerian (p. 2640·2); red clover (p. 2482·1); oregano (p. 2576·3); motherwort (p. 2564·2); creeping thyme (p. 2648·1).
Sleep disorders.

Sedativa-Injektopas *Pascoe, Ger.*
Avena sativa (p. 2451·1); valeriana (p. 2640·2); tarantula; ignatia (p. 2532·1); veratrum.
Homoeopathic preparation.

Sedatival *Recalcine, Chile.*
Ketazolam (p. 1079·2).
Anxiety; insomnia; skeletal muscle spasm.

Sedatol *EG, Ital.*
Capsules: Passion flower (p. 2584·1); valerian (p. 2640·2); crataegus (p. 2488·1); chamomile (p. 2474·1); piscidia (p. 2536·3).
Insomnia.

EG, Ital.
Syrup: Passion flower (p. 2584·1); chamomile (p. 2474·1); crataegus (p. 2488·1); piscidia (p. 2536·3); melissa (p. 2552·3).
Insomnia.

Sedaton *Actavis, Hung.*
⊗Fentanyl (p. 60·1).
Pain.

Sedatuss DM *Trianon, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).

Sedavit *Arterium, Ukr.*
Valerian (p. 2640·2); crataegus (p. 2488·1); St John's wort (p. 449·1); peppermint leaf (p. 1877·1); lupulus (p. 2546·1); pyridoxine hydrochloride (p. 2105·3); nicotinamide (p. 2083·1).
Nervous disorders; migraine; pruritus; insomnia; tension headache; menopausal disorders.

Sedazin *Lagap, Switz.*
Lorazepam (p. 1080·3).
Anxiety; sleep disorders; premedication.

Sedemol *Melisana, Belg.*
Althaea (p. 2438·3); poppy capsule (p. 1675·3); borax (p. 2459·2); sodium fluoride (p. 2089·2); phenol (p. 1763·3); cloral hydrate (p. 1055·2).
Mouth and throat disorders.

Sedepron *Chinoin, Mex.*
Clonixin lysine (p. 40·1).
Pain.

Sedergine *BMS, Belg.; Uriach Aquilea OTC, Spain.*
Aspirin (p. 22·2).
Fever; pain; musculoskeletal, joint and peri-articular disorders.

Sedergine C *Uriach Aquilea OTC, Spain.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Sedergine Vit-C *Abdi, Turk.*
Aspirin (p. 22·2); vitamin C (p. 2110·3).
Fever; pain.

Sédermyl *Cooperation Pharmaceutique, Fr.*
Isothipendyl hydrochloride (p. 631·2).
Pruritus; insect stings.

Sedesterol *Poen, Arg.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Sedevil *Collins, Mex.†*
Tablets: ⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.
Collins, Mex.†
Syrup: ⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract disorders; hypersensitivity reactions.

Sedi *Putchubun, Thai.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Sediat *Pfleger, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Sediclon *Degorts, Mex.*
Dicycloverine (p. 1834·2).

Sediel *Sumitomo, China; Sumitomo, Jpn.*
Tandospirone citrate (p. 1109·1).
Anxiety; depression; sleep disorders.

Sedigastrol *Ronnet, Arg.*
Omeprazole (p. 1867·2).
Gastric hyperacidity.

Sedilax *Teuto, Braz.*
Carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; smooth muscle spasm.

Sedilit *Sanitas, Chile.*
Diazepam (p. 1063·2); chlormezanone (p. 1045·1).
Anxiety; insomnia; skeletal muscle spasm.

Sedilix
Note: this name may be used for preparations of different composition.
Xepa-Soul Pattinson, Singapore.
⊗Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Sedilix DM *Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); promethazine hydrochloride (p. 638·2).
Cough; nasal congestion; sneezing; rhinorrhoea.

Sedilor *Dolisos, Canad.†*
Coffea cruda (p. 2648·2); ignatia amara (p. 2532·1); passiflora (p. 2584·1); phosphoricum acidum (p. 2589·1).
Homoeopathic preparation.

Sedinal *Melisana, Belg.*
Crataegus (p. 2488·1); ballota; passion flower (p. 2584·1).
Nervous disorders.

Sedinef *Yung Shin, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Sedinol *SA Druggists Self Med, S.Afr.†*
Doxylamine succinate (p. 627·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain and associated tension.

Sedipin *Sel-J, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Sedis *Ipso, Ital.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Sedistress *Tilman, Belg.*
Passion flower (p. 2584·1).
Nervous disorders.

Sedival *Meyer Nature, Venez.*
Valerian (p. 2640·2); melissa (p. 2552·3); passion flower (p. 2584·1).
Insomnia.

Sedocalcio *Deca, Ital.*
Calcium lactate (p. 1784·1); sodium benzoate (p. 1738·2).
Mouth and throat disorders.

Sedofan *Julphar, UAE.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; rhinitis; upper respiratory-tract congestion.

Sedofan II *Julphar, UAE.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinusitis; otitis media.

Sedofan DM *Julphar, UAE.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Sedofan P *Julphar, UAE.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Sedofan T *Julphar, UAE.*
Triprolidine hydrochloride (p. 642·3).
Hypersensitivity reactions.

Sedofantil *Lafi, Chile.*
Calcium bromolactobionate (p. 1044·1).
Hyperactivity in children.

Sedoflame *Neocare, Belg.; IFET (ΙΦΕΤ), Gr.*
Sulfadiazine silver (p. 362·3).
Burns.

Sedogelat *Kwizda, Austria; Penta, Hung.*
Valerian root (p. 2640·2); melissa (p. 2552·3); passion flower (p. 2584·1).
Anxiety disorders; sleep disorders.

Sedol
Note: this name may be used for preparations of different composition.
Cazi, Braz.
⊗Isometheptene hydrochloride (p. 2535·1) or isometheptene mucate (p. 2535·1); dipyrone (p. 53·3); caffeine (p. 1203·3).
OFF, Ital.†
Propyphenazone (p. 127·3); caffeine (p. 1203·3).
Fever; neuralgia; influenza symptoms.

Sedolin *Selen, Turk.†*
Pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1); undecylenamidopropyl betaine.
Scalp disorders.

Sedomix *Leki Natury, Pol.*
Crataegus (p. 2488·1); lupulus (p. 2546·1); St John's wort (p. 449·1); melissa (p. 2552·3); rose fruit (p. 2607·1); valerian (p. 2640·2); avena (p. 2451·1).
Nervous disorders; insomnia.

Sedonat *Soria Natural, Spain.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); valerian (p. 2640·2); bitter-orange oil (p. 2575·3).
Nervous disorders.

Sedonium *Cassella-med, Fin.; Cassella-med, Ger.; Lichtwer, Neth.†; Vifor, Switz.; Lichtwer, UK.*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders; insomnia; agitation.

Se-Donna PB HYOS *Seton, USA.*
Atropine sulfate (p. 1310·2); hyoscyamine sulfate (p. 1848·1); phenobarbital (p. 535·2); hyoscine hydrobromide (p. 1845·3).

Sédopal *Lehning, Fr.*
Crataegus (p. 2488·1); california poppy (p. 2466·1); melilot (p. 2552·3).
Nervous disorders; insomnia.

Sedopan *Norma (Νορμα), Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Sedopect *Andromaco, Chile.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Cold and influenza symptoms; cough.

Sedopram *Sedico, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Sedopretten *Schoning-Berlin, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sedopuer F *SIT, Ital.*
Passion flower (p. 2584·1); valerian (p. 2640·2); crataegus (p. 2488·1); calcium glycerophosphate (p. 1783·3).
Nervous disorders; insomnia.

Sedoran *Raffo, Chile.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder.

Sédorrhoïde *Cooperation Pharmaceutique, Fr.*
Dodeclonium bromide (p. 1750·3); benzocaine (p. 1980·2); esculoside (p. 2431·2); enoxolone (p. 54·2).
Anorectal disorders.

Sédorrhoïde Veinotonique *Cooperation Pharmaceutique, Fr.†*
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility; haemorrhoids.

Sedosolvin *Ipca, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); bromhexine hydrochloride (p. 1656·3).
Cough.

Sedotensil *Sanofi-Aventis, Arg.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Sedotime *Faes, Spain.*
Ketazolam (p. 1079·2).
Anxiety; spasticity.

Sedotusse *Angelini, Port.†*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Sedotussin
Note: this name may be used for preparations of different composition.
UCB, Austria†; UCB, Ger.
Pentoxyverine (p. 1672·1) or pentoxyverine citrate (p. 1672·1).
Cough.
UCB, Hung.†
Pentoxyverine citrate (p. 1672·1).
Cough.

Sedotussin Efeu *UCB, Ger.†*
Ivy (p. 2536·2).
Bronchitis; catarrh.

Sedovanon *Craveri, Arg.*
Clonazepam (p. 519·1).
Epilepsy; anxiety disorders.

Sedovent *Schworer, Ger.†*
Cinnamon (p. 2479·2); dried bitter-orange peel (p. 2575·3); achillea (p. 2427·3); gentian (p. 2512·1).
Gastrointestinal disorders.

Sedoxil *Medibial, Port.*
Mexazolam (p. 1085·1).
Anxiety disorders.

Sedoz *Claris, Philipp.*
Midazolam (p. 1085·1).
Sedative; general anaesthesia; premedication.

Sedral
Note: this name may be used for preparations of different composition.
Synco, Hong Kong.†
⊗Ephedrine (p. 1663·1); phenobarbital (p. 535·2); theophylline (p. 1229·3).

Sedrofen *Interbat, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Sedron *Gedeon Richter, Hung.; Richter, Pol.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Sedural *Rekah, Israel.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain and irritation.

Sedusen *Sanitas, Chile.*
Sulpiride (p. 1107·3).
Anxiety; depression; psychosomatic disorders; neuroses.

Seduxen *Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.†*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety disorders; convulsions; epilepsy; status epilepticus; premedication; skeletal muscle spasm; spasticity; tetanus; delirium tremens; eclampsia.

Sedylin *Vickmans, Hong Kong.†*
⊗Codeine (p. 40·2); ephedrine (p. 1663·1); promethazine (p. 638·2).

Seebri *Novartis, Denm.; Novartis, Israel; Novartis, Jpn; Novartis, Neth.; Novartis, Spain; Novartis, UK.*
Glycopyrronium bromide (p. 2519·3).
Obstructive airways disease.

Seequin *Vivier, Canad.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Sef *Nevzat, Turk.*
Cefalexin (p. 234·1).
Bacterial infections.

Sefadex *Recalcine, Chile.*
Cefadroxil (p. 233·2).
Bacterial infections.

Sefagen *Bilim, Turk.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Sefaktil *Drogsan, Turk.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Sefal
Note: this name may be used for preparations of different composition.
Marvecs, Ital.
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; rickets; osteomalacia; osteoporosis.
Nobel, Turk.
Cinnarizine (p. 622·1).
Vestibular disorders; nausea and vomiting; motion sickness; peripheral vascular disorders.

Sefaller *Sandoz, Hung.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Sefamax *Nobel, Turk.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Sefanem *Meprofarm, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Sefaretic *Unison, Hong Kong; Unison, Thai.†*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; hypokalaemia; heart failure; hepatic cirrhosis with ascites.

Sefasin *LBS, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Sefazol *Nevzat, Turk.*
Cefazolin (p. 237·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Sefbaktam *Bilim, Turk.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Sefdene *Unison, Hong Kong; Unison, Singapore.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; inflammation; pain.

Sefdin *Unichem, India.*
Capsules; syrup: Cefdinir (p. 238·3).
Bacterial infections.

Seferin *General Drugs, Thai.*
Aspirin (p. 22·2).
Pain; inflammation; musculoskeletal and joint disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sefether *Lunan Better, Thai.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Seffur *Tum, Turk.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Sefloc *Unison, Hong Kong†; Unison, Singapore.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; heart failure.

Unison, Thai.
⊗Metoprolol (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Sefmal *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Sefmex *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism; Alzheimer's disease.

Sefmic *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.†*
Mefenamic acid (p. 85·3).
Pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Sefnac *Unison, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; dysmenorrhoea.

Sefnor *Unison, Singapore; Unison, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Sefoksim *Fako, Turk.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Sefotak *Valeant, Cz.; Eczacibasi, Philipp.; Eczacibasi, Turk.; Eczacibasi, Ukr.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Sefoxim *Fako, Turk.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Sefoxiram *Serral, Mex.*
Cefotaxime (p. 244·1).
Bacterial infections.

Sefpime *Shenzhen Zhijun, Thai.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Sefpotec *Nobel, Turk.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Sefsidal *Sanovel, Turk.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Seftem *Shionogi, Jpn.*
Ceftibuten (p. 252·2).
Bacterial infections.

Seftil *Unison, Malaysia; Unison, Thai.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders; inflammation.

Sefulken *Kendrick, Mex.*
Diazoxide (p. 1351·3).
Hypertension.

Sefuroks *Eczacibasi, Turk.*
Cefuroxime (p. 255·2) or cefuroxime axetil (p. 255·2).
Bacterial infections.

Sefuxim *Shenzhen Zhijun, Hong Kong.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Shenzhen Zhijun, Thai.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Segamol *Boehringer Ingelheim, Venez.*
⊗Fenoterol hydrobromide (p. 1208·2).
Threatened abortion; premature labour.

Segan *Polpharma, Pol.; Polpharma, Rus.†; Polpharma, Ukr.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism; Alzheimer's disease.

Seglor *UCB, China; Pharmafar, Ital.; Azevedos, Port.*
Dihydroergotamine mesilate (p. 672·2).
Orthostatic hypotension; migraine and other vascular headaches; vertigo; peripheral vascular disorders.

Séglor *UCB, Fr.*
Dihydroergotamine mesilate (p. 672·2).
Migraine; orthostatic hypotension.

Segol *Sanovel, Turk.*
Codergocrine mesilate (p. 389·2).
Cerebrovascular disorders.

Segurex *Gador, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Seguril *Sanofi-Aventis, Spain.*
⊗Furosemide (p. 1387·1).
Forced diuresis; heart failure; hypertension; nephrotic syndrome; oedema; oliguria; renal failure.

Segurite *Raffo, Arg.*
Levonorgestrel (p. 2296·1).
Post-coital oral contraceptive.

Segusiv *Pisa, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

SeHCAT *GE Healthcare, Belg.†; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Irl.; GE Healthcare, Neth.; GE Healthcare, Spain; GE Healthcare, UK.*
Selenium-75 (p. 2228·1) tauroselcholic acid.
Radionuclide imaging of the biliary-tract, gastrointestinal tract, and enterohepatic circulation.

Sehydrin *Farmsintez, Rus.; Pharmasynthez, Ukr.*
Hydrazine sulfate (p. 2528·2).
Malignant neoplasms.

Seide *Rafarm, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Seidon *Sanovel, Rus.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Seif *Bayer, Philipp.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

Seihaito *Tsumura, Jpn.*
Angelica acutiloba root (p. 2443·3); ophiopogon tuber; poria sclerotium; skullcap root (p. 2617·1); platycodon root; apricot kernel (p. 2445·3); gardenia fruit; mulberry bark; jujube; citrus unshiu peel; asparagus tuber (p. 2450·2); fritillaria bulb; liquorice (p. 1853·2); schisandra fruit (p. 2611·2); ginger (p. 1844·1); bamboo trunk.
Traditional Kampo medicine.

Seijobofuto *Tsumura, Jpn.*
Skullcap root (p. 2617·1); platycodon root; gardenia fruit; cnidium rhizome; glehnia root; angelica dahurica root; forsythia fruit; coptis rhizome; liquorice (p. 1853·2); immature orange; schizonepeta tenuifolia; mentha herb.
Traditional Kampo medicine.

Seis-B *Apsen, Braz.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Seishinrenshiin *Tsumura, Jpn.*
Ophiopogon tuber; poria sclerotium; nelumbo seed; skullcap root (p. 2617·1); plantago seed (p. 1849·1); ginseng (p. 2513·3); astragalus root (p. 2451·1); lycium bark; liquorice (p. 1853·2).
Traditional Kampo medicine.

Seishoekkito *Tsumura, Jpn.*
Atractylodes lancea rhizome; ginseng (p. 2513·3); ophiopogon tuber; astragalus root (p. 2451·1); citrus unshiu peel; angelica acutiloba root (p. 2443·3); phellodendron bark; liquorice (p. 1853·2); schisandra fruit (p. 2611·2).
Traditional Kampo medicine.

Sekamisin *Sanli, Turk.†*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Sekena *Duncan, Arg.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease; anorectal disorders.

Seki *Zambon, Braz.; Zambon, Ital.*
Cloperastine fendizoate (p. 1659·2).
Cough.

Sekin *Almirall, Belg.*
Cloperastine fendizoate (p. 1659·2) or cloperastine hydrochloride (p. 1659·2).
Cough.

Sekisan *Almirall, Mex.*
Cloperastine (p. 1659·1).
Cough.

Almirall, Spain.
Cloperastine fendizoate (p. 1659·2) (p. 1659·2).
Cough.

Sekodin *Akdeniz, Turk.*
Oxolamine citrate (p. 1671·2).
Cough.

Sekolaks *Sanli, Turk.*
Bisacodyl (p. 1821·1).
Constipation.

Sekretovit *Anchor, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Sekretovit Amoxi *Boehringer Ingelheim Promeco, Mex.*
Ambroxol hydrochloride (p. 1654·3); amoxicillin trihydrate (p. 216·2).
Respiratory-tract infections.

Sekretovit Ex *Anchor, Mex.; Boehringer Ingelheim Promeco, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract infections.

Sekrol *Bilim, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Sekucid *Ecolab, Ital.†*
Glutaral (p. 1753·2); isopropyl alcohol (p. 1758·3).
Instrument disinfection.

Sekudrill *Ecolab, Ital.†*
Potassium hydroxide (p. 2595·3); propylene glycol (p. 2205·2).
Instrument disinfection.

Sekumatic *Ecolab, Ital.†*
⊗Glutaral (p. 1753·2); alcohol (p. 1733·1); chloroform (p. 1898·1); acetone (p. 2166·3).
Instrument disinfection.

Sekusept *Ecolab, Ger.; Ecolab, Ital.*
Peracetic acid (p. 1763·1).
Instrument disinfection.

Sekusept Extra N *Ecolab, Ger.*
Benzalkonium chloride (p. 1737·1); glutaral (p. 1753·2).
Instrument disinfection.

Sekusept forte S *Ecolab, Ger.*
Formaldehyde (p. 1752·2); glutaral (p. 1753·2).
Instrument disinfection.

Sekusept Plus *Ecolab, Ger.*
Glucoprotamine (p. 1753·2).
Instrument disinfection.

Sel D *Pharmadeveloppement, Fr.*
Sodium chloride (p. 1795·1); sodium phosphate (p. 1791·2); sodium sulfate (p. 1888·1); sodium iodide (p. 2337·1); sodium bromide (p. 2461·1).
Dietary salt substitute.

Sel d'Ems *Sidroga, Switz.*
Natural sels d'Ems.
Upper respiratory-tract disorders.

Seladin *YSP, Malaysia; Yung Shin, Singapore.*
Naproxen (p. 98·2).
Gout; musculoskeletal and joint disorders.

Selamer *Tymofarm, Pol.†*
Shark-liver oil (p. 2614·2).
Infections.

Selan *GSK, Spain.†*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Selang *Peptogen, Rus.*
Threonyl-lysyl-prolyl-arginyl-prolyl-glycyl-prolyl diacetate.
Anxiety.

Selax *Odan, Canad.*
Docusate sodium (p. 1836·2).
Constipation.

Selaxa *Proel, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Selbex *Eisai, China; Eisai, Jpn; Eisai, Philipp.; Eisai, Thai.*
Teprenone (p. 1893·3).
Gastritis; gastric ulcer; peptic ulcer.

Seldepar *Sandoz, Turk.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selder *Eurolab, Arg.*
Vitamin E (p. 2119·1); lycopene (p. 2546·2); soya isoflavones (p. 2620·3); vitamin C (p. 2110·3); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement.

Seldiyet *Kocak, Turk.*
Potassium chloride (p. 1793·2); ammonium chloride (p. 1656·1); magnesium oxide (p. 1857·3); glutamic acid (p. 2070·2).
Dietary salt substitute.

Seldron *ICM, Singapore.*
Selenium sulfide (p. 1719·3).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Sele200 *Framingham, Arg.*
Selenium (p. 2086·3).
Dietary supplement.

Selebound *Framingham, Arg.*
Selenium (p. 2086·3).
Dietary supplement.

Seleca *Cardinal, Indon.; Pharos, Indon.*
Beta carotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Dietary supplement.

Selecal *Taisho, Jpn.*
⊗Tilisolol hydrochloride (p. 1513·2).
Angina pectoris; hypertension.

Selecom *Fulton, Ital.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Select 1/35 *Pfizer, Canad.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
The 28-day pack also contains 7 inert tablets.
Combined oral contraceptive.

Selecta *Libbs, Braz.*
Conjugated oestrogens (p. 2260·1); medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Selectadoce *Diba, Mex.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin (p. 2107·3).
Anaemias; neuritis.

Selectadril *Arlex, Mex.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; myocardial infarction.

Selectan *Bayer, Arg.*
Norethisterone acetate (p. 2294·3).
Adjunct in hormone replacement therapy.

Selectin *BMS, Ital.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Select-OB + DHA *Everett, USA.*
Chewable tablets, vitamins; iron (p. 2073·1); magnesium (p. 1786·3); zinc (p. 2126·1); capsules, docosahexaenoic acid (p. 1460·1); lauric acid.
Dietary supplement.

Selectofen *Diba, Mex.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain; inflammation.

Selectofur *Diba, Mex.†*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Selectol *Gerot, Austria; Pfizer, Belg.; Sanofi-Aventis, Chile; Leiras, Fin.; Pfizer, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Shinyaku, Jpn; Sanofi-Aventis, Switz.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris; arrhythmias; ischaemic heart disease; hypertrophic obstructive cardiomyopathy; hyperthyroidism; phaeochromocytoma; myocardial infarction.

Selectomycin *Teofarma, Ger.*
Spiramycin (p. 358·3).
Staphylococcal infections; toxoplasmosis.

Selectovit *Diba, Mex.†*
Vitamin B substances (p. 2102·3).

Selectra
Note: this name may be used for preparations of different composition.
Sanovel, Turk.
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Actavis, Rus.
Escitalopram oxalate (p. 416·2).
Depression; panic disorder.

Selectrin *Cifarma, Braz.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Selectrin Balsâmico *Cifarma, Braz.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1).

Selecturon *Gerot, Austria.*
⊗Celiprolol hydrochloride (p. 1334·2); chlortalidone (p. 1335·2).
Hypertension.

Selectus
Note: this name may be used for preparations of different composition.
BA Farma, Port.
Fluoxetine hydrochloride (p. 417·1).
Bulimia nervosa; depression; mixed anxiety depressive disorders; obsessive-compulsive disorder.
Purissimus, Arg.
Dextromethorphan hydrobromide (p. 1660·1); bromhexine hydrochloride (p. 1656·3).
Cough; respiratory-tract congestion.

Selectus FN *Purissimus, Arg.*
Clofedanol hydrochloride (p. 1659·1); bromhexine hydrochloride (p. 1656·3).
Cough.

Seledat *Master Pharma, Ital.*
⊗Selegiline hydrochloride (p. 914·2).
Psychiatric disorders.

Seledie *Italfarmaco, Ital.*
Nadroparin calcium (p. 1443·2).
Venous thrombosis.

Selefit Plus *Galenium, Indon.*
Selenium (p. 2086·3); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc gluconate (p. 2126·2).
Dietary supplement.

Selegel
Note: this name may be used for preparations of different composition.
Medifarm Ducray, Venez.
Selenium sulfide (p. 1719·3).
Scalp disorders.
Pierre Fabre Dermo-Cosmetique, Arg.
Selenium sulfide (p. 1719·3); ictasol (p. 1706·1).
Dandruff.
Silesia, Chile.
Selenium sulfide (p. 1719·3); ichthammol (p. 1705·3).
Scalp disorders.

Sélégel *Ducray, Fr.†*
Selenium sulfide (p. 1719·3); ichthammol (p. 1705·3).
Seborrhoeic dermatitis.

Selegesic *Sel-J, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Selegos *Medochemie, Hong Kong; Medochemie, Rus.†; Medochemie, Singapore.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Seleject *Biosyn, Ger.†*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Selektine *BMS, Neth.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; reduction of cardiovascular risk.

Selemite-B *Blackmores, Austral.†*
Selenomethionine (p. 2087·1).
Selenium deficiency.

Selemix *Provita, Ital.*
Vitamins; minerals; ubidecarenone (p. 2637·1).

Selemycin *Medochemie, Rus.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Selen *Fresenius Kabi, Austria.*
Sodium selenite (p. 2087·1).
Dietary supplement.

Selen Plus *Selenium Pharma, Hung.*
Selenium (p. 2086·3).
Dietary supplement.

Selenarell *Sanorell, Ger.*
Natrium selenosum (p. 2087·1).
Homoeopathic preparation.

Selenase *Biosyn, Austria; Biosyn, Cz.; Biosyn, Ger.; Biosyn, Neth.; Biosyn, Port.; Robapharm, Switz.; Er-Kim, Turk.; Oxford Nutrition, UK.*
Sodium selenite (p. 2087·1).
Dietary supplement; selenium deficiency.

Selenase T *IFET (ΙΦΕΤ), Gr.*
Sodium selenite (p. 2087·1).

Selenaza *Biosyn, Ukr.*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Selene
Note: this name may be used for preparations of different composition.
Biomedica, Ital.
Ademetionine (p. 2429·3); glutamine (p. 2070·3); magnesium (p. 1786·3); vitamin B substances (p. 2102·3); selenium (p. 2086·3).
Mental function impairment.
Eurofarma, Braz.
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Androgenic symptoms in women; polycystic ovary syndrome.
Vivax, Venez.
dl-Alfa tocoferil acetate (p. 2119·2); selenium yeast (p. 2125·2).
Vitamin E deficiency; selenium deficiency.

Selene-Activ *Wassen, UK.*
Selenium (p. 2086·3); broccoli extract; vitamin C (p. 2110·3); vitamin E (p. 2119·1); thioctic acid (p. 2629·1); zinc (p. 2126·1).
Dietary supplement.

Selenica *Kowa, Jpn.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder; migraine.

Selenil *Vita, Venez.*
Selenium sulfide (p. 1719·3); sulfur (p. 1721·1).
Dandruff.

Selenium Bonus *Lifeplan, UK.*
Selenium (p. 2086·3); chromium (p. 2055·3); zinc (p. 2126·1); vitamins.
Antoxidant preparation.

Selenium Complexe No 99 *Lehning, Fr.*
Selenium metallicum (p. 2086·3); aurum muriaticum natronatum (p. 2521·2); chininum sulfuricum (p. 665·2); ferrum phosphoricum (p. 2077·1); natrum carbonicum (p. 2617·3); ginseng (p. 2513·3); kola (p. 2648·2); conium maculatum (p. 2524·3); damiana (p. 2491·3).
Homoeopathic preparation.

Selenium Homaccord *Heel, Canad.†*
Potassium phosphate dibasic (p. 1791·1); selenium (p. 2086·3).
Homoeopathic preparation.

Selenium Med Complex *Dynamit, Austria.*
Acidum phosphoricum (p. 2589·1); conium (p. 2524·3); crataegus (p. 2488·1); ginseng (p. 2513·3); selenium (p. 2086·3).
Homoeopathic preparation.

Selenium + Zinc *Pharma Nord, Fr.†*
Selenium (p. 2086·3); zinc (p. 2126·1); vitamins.

Selenium-ACE *Pharmco, S.Afr.*
Selenium yeast (p. 2125·2); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Merck Medication Familiale, Fr.†
Selenium yeast (p. 2125·2); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Wassen, Ital.†
Selenium (p. 2086·3); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).

Selenix *Novartis Consumer, Port.*
Selenium sulfide (p. 1719·3).
Dandruff; pityriasis versicolor.

Selenk *Strathmann, Ger.*
Urtica (p. 2639·3).
Rheumatic disorders.

Selen-loges *Loges, Ger.*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Seleno Forte *Eagle, Austral.*
Selenomethionine (p. 2087·1).
Selenium supplement.

Selenokehl *Sanum-Kehlbeck, Ger.*
Natrium selenosum (p. 2087·1).
Homoeopathic preparation.

SelenoPrecise *Pharma Nord, Denm.*
Selenium yeast (p. 2125·2).
Selenium deficiency.

Selenor *Fahrvitex, Hung.*
Selenium (p. 2086·3).
Selenium deficiency.

Selenos *Breckenridge, USA.*
Selenium sulfide (p. 1719·3).
Dandruff; seborrhoeic dermatitis.

Selen-Wied *Wiedemann, Ger.*
Natrium selenosum (p. 2087·1).
Homoeopathic preparation.

Sele-Pak *Smith & Nephew SoloPak, USA.†*
Selenious acid (p. 2087·1).
Parenteral nutrition.

Seleparina *Italfarmaco, Ital.*
Nadroparin calcium (p. 1443·2).
Thrombosis prophylaxis.

Selepark *Betapharm, Ger.†*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selepen *APP, Hong Kong; American Pharmaceutical, USA.†*
Selenious acid (p. 2087·1).
Parenteral nutrition.

Pharmaceutical Partners, Canad.†
Selenium (p. 2086·3).
Selenium supplement.

Seler *Pasteur, Chile.†*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Selerin *Cipla, India; Anpharm, Pol.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selerup *Pasteur, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Seles Beta *UCB, Ital.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Selesyn *Biosyn, Hung.; Biosyn, Irl.*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Selevistine *Kleva, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Selexid *Leo, Austria; Leo, Canad.†; Leo, Fin.; Leo, Fr.; Leo, Norw.; CSL, NZ; Leo, Port.; Leo, Swed.*
Pivmecillinam hydrochloride (p. 342·2).
Bacterial infections.

Leo, Denm.; Leo (Λεο), Gr.
Mecillinam (p. 321·1) or pivmecillinam hydrochloride (p. 342·2).
Bacterial infections.

Leo, UK.
Pivmecillinam (p. 342·1) or pivmecillinam hydrochloride (p. 342·2).
Bacterial infections of the urinary tract.

Selezen *Teofarma, Ital.*
Imidazole salicylate (p. 71·2).
Pain; inflammation; fever.

Selezime *Amnol, Ital.*
Octozyme (maltodextrin (p. 2080·3) from fermented rice); fennel oil (p. 2503·3).
Digestive disorders.

Self Defense *Physicians Formula, Canad.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Self Defining *Access, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Self Tanner *California North, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Selfemra *Teva, USA.*
Fluoxetine hydrochloride (p. 417·1).
Premenstrual dysphoric disorder.

Selfide *TO-Chemicals, Thai.*
Selenium sulfide (p. 1719·3).
Seborrhoeic dermatitis; dandruff; pityriasis versicolor.

Selg *Promefarm, Ital.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Selgene *Alphapharm, Austral.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selg-Esse *Promefarm, Ital.*
Macrogol 4000 (p. 2547·3); simeticone (p. 1886·2); electrolytes (p. 1775·1).
Bowel evacuation.

Selgimed *Hennig, Ger.†*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selgin *Intas, India; CTS, Israel; Polfa Pabianice, Pol.†*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selgina *Andromaco, Chile.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Selgine *Teofarma, Fr.*
Sodium chloride (p. 1795·1); sea salt (p. 2612·1).
Mouth disorders.

Selgres *ICN, Pol.*
⊗Selegiline (p. 914·2).
Parkinsonism.

Selimax *Libbs, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Selimax Pulso *Libbs, Braz.*
Azithromycin (p. 221·2).
Acne.

Selincro *Lundbeck, UK.*
Nalmefene hydrochloride (p. 1562·1).
Alcohol dependence.

Selipran *BMS, Switz.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Sellon *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Selenium sulfide (p. 1719·3).
Dandruff; seborrhoeic dermatitis; pityriasis versicolor.

Selm *Kener, Mex.*
Methyldopa (p. 1431·1).
Hypertension.

Selma *Greater Pharma, Thai.*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Selmac *Prosel, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Selmevit *Farmstandart, Rus.*
Vitamins; minerals; rutoside (p. 2505·3); thioctic acid (p. 2629·1); methionine (p. 1558·2).

Selobloc *Lagap, Switz.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Selocomp ZOC *Pfizer, Fin.*
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Selofen *Adamed, Pol.; Adamed, Ukr.*
Zaleplon (p. 1114·3).
Insomnia.

Selokeen *AstraZeneca, Neth.*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; hyperthyroidism.

Seloken *AstraZeneca, Austria; AstraZeneca, Mex.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; migraine; myocardial infarction; heart failure; arrhythmias.
AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Indon.; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Norw.; AstraZeneca, Swed.
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; cardiomyopathy; essential tremor.

Seloken retard Plus *Sanova, Austria.*
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Seloken ZOC *AstraZeneca, Fin.; AstraZeneca, Swed.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; heart failure.

Selokomb *Pfizer, Neth.*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Selomega *Bryssica, Fr.*
Fish oil (p. 1460·1); vitamin E (p. 2119·1); selenium (p. 2086·3).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Selon
Note: this name may be used for preparations of different composition.
Genepharm, Gr.
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

IPA, Ger.
Valerian (p. 2640·2); lupulus (p. 2546·1).
Agitation; sleep disorders.

Selopral *Orion, Fin.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine; hyperthyroidism.

Selopres *AstraZeneca, India.*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

AstraZeneca, Mex.
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Selopress *AstraZeneca, Braz.*
⊗Metoprolol succinate (p. 1434·3) or metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Seloxy *Ferron, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2); vitamin E (p. 2119·1); selenium (p. 2086·3).
Dietary supplement.

Seloxy AA *Ferron, Indon.*
Betacarotene (p. 2051·1); thioctic acid (p. 2629·1); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1); selenium (p. 2086·3).
Antoxidant; dietary supplement for healthy skin.

Selo-Zok *AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Denm.; AstraZeneca, Norw.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; hyperthyroidism; migraine; heart failure.

Selozok *AstraZeneca, Fr.*
⊗Metoprolol succinate (p. 1434·3).
Heart failure.

Selpiran *Diba, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).
Smooth muscle spasm and pain.

Selpiran Compuesto *Diba, Mex.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Selpiran-S *Diba, Mex.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

SelRx *Artesa, USA.*
Selenium sulfide (p. 1719·3).
Scalp disorders.

Sels Calcaires Nutritifs *Weleda, Fr.*
Combination pack: No 1, apatite; cucurbita (p. 2489·2); No 2, conchae (p. 1824·3); quercus cortex (p. 2574·1).
Homoeopathic preparation.

Selso *Luchon, Fr.*
Sodium chloride (p. 1795·1); sulfur (p. 1721·1).
Nasal irrigation; oral hygiene.

Selsun *Church & Dwight, Austral.; Abbott, Austria; Sanofi-Aventis, Belg.; Farmasa, Braz.; Volta, Chile; Chattem, Denm.†; Abbott, Fin.†; Pharmadeveloppement, Fr.; Chattem, Ger.; Abbott, Gr.; Kite, Gr.; Mentholatum, Hong Kong†; Abbott, Indon.; Chattem, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Neth.; Vitaflo, Norw.; Wilson, NZ; Chattem, Pol.; Mentholatum, S.Afr.; Rohto Mentholatum, Singapore; Vitaflo, Swed.; Doetsch, Grether, Switz.; Chattem, Thai.; Fako, Turk.; Sanofi-Aventis, UK; Chattem, USA.*
Selenium sulfide (p. 1719·3).
Dandruff; seborrhoeic dermatitis; scalp disorders; pityriasis versicolor; tinea capitis; tinea versicolor.

Selsun Blu *Bouty, Ital.*
Selenium sulfide (p. 1719·3).
Dandruff.

Selsun Blue *Abbott, Philipp.†*
Selenium sulfide (p. 1719·3).
Dandruff; tinea versicolor; seborrhoeic dermatitis.

Selsun Blue Anti-Dandruff *Sanofi Consumer, Canad.*
Pyrithione zinc (p. 1718·1).
Formerly contained selenium sulfide.
Scalp disorders.

Seltak *Norma (Νορμα), Gr.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Seltifort Gold *Nufarindo, Indon.*
Vitamins; lutein (p. 2079·2); docosahexaenoic acid (p. 1460·1); cod-liver oil (p. 2056·3); amino acids; fructo-oligosaccharides (p. 2508·1).
Dietary supplement.

Seltifort Kids *Nufarindo, Indon.*
Vitamins; docosahexaenoic acid (p. 1460·1); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Seltoc *Apomedica, Austria.†*
Ethenzamide (p. 56·2); diphenhydramine hydrochloride (p. 626·2); quinine hydrochloride (p. 665·2); ascorbic acid (p. 2110·3).
Cold symptoms.

Seltouch *Teikoku Seiyaku, Jpn.*
Felbinac (p. 58·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Seltrans *Stada, Ger.*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Seltroz *Sel-J, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Seltrozol *Sel-J, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Selukos *Meda, Austria; Meda, Fin.; Meda, Ger.†; Meda, Norw.; Meda, Swed.*
Selenium sulfide (p. 1719·3).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis of the scalp; scalp disorders.

Selutrio *Fresenius Medical, Fin.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2) (p. 1778·2).
Formerly known as Gambrosol.
Peritoneal dialysis.

Selva N *Unipharma, Gr.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Selviclor *SF, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Selvigon *Ache, Braz.; Pharmalex (Φαρμαλεξ), Gr.; Transfarma, Indon.; Sanfer, Mex.*
Pipazetate hydrochloride (p. 1675·3).
Cough.

Selvim *Ifars, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Selvigon *Sanofi-Aventis, Ital.*
Pipazetate hydrochloride (p. 1675·3).
Cough.

Selvon-C *Prosel, Philipp.*
Vitamins.
Nutritional supplement.

Selxan *Prosel, Philipp.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Selzef *Prosel, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Selzentry *ViiV, USA.*
Maraviroc (p. 1003·2).
HIV infection.

Semandrol *Teva, Spain.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Semap *Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Denm.†; Alkopharma, Gr.; Janssen-Cilag, Israel†; Janssen-Cilag, Mex.; Alkopharma, Neth.; Janssen-Cilag, Switz.†*
Penfluridol (p. 1094·3).
Psychoses; schizophrenia.

Sema-X *Union Drug, Thai.*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2).
Infected skin disorders.

Semble *Merisant, Arg.*
Saccharin sodium (p. 2208·1); cyclamate; sucrose (p. 2096·3).
Sugar substitute.

Semel *Pharmarte, Ital.*
Magnesium (p. 1786·3); thioctic acid (p. 2629·1); selenomethionine (p. 2087·1); vitamins.
Dietary supplement.

Sementex *Mastelli, Rus.*
Polydeoxyribonucleotide.
Burns; minor wounds; skin ageing; stretch marks.

Semerial *Mediolanum, Ital.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Semerin *Sunward, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); sodium citrate (p. 1781·2).
Cough.

Semeth *Greater Pharma, Thai.*
Simeticone (p. 1886·2).
Flatulence; meteorism; preparation of gastrointestinal tract for radiological examination or gastroscopy.

Semicid *Whitehall, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Semicillin
Note: this name may be used for preparations of different composition.
Pond's, Thai.
Phenoxymethylpenicillin (p. 338·3).

Zentiva, Hung.
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Semid *Ionios (Ιονιος), Gr.*
⊗Furosemide (p. 1387·1).

Semi-Daonil *Aventis, Austral.†; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Port.; Sanofi-Aventis, Switz.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Semi-Diabenol *Greater Pharma, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Semi-Euglucon *Roche, Hong Kong†; Piramal, India; Roche, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Semi-Euglucon N *Sanofi-Aventis, Ger.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Semifluoran F6H6 *Fluoron, Ger.†*
⊗Perfluorohexylhexane (p. 2586·3).
Ophthalmic tamponade.

Semi-Glycigon *Aristo, India.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Seminac *Mahakam Beta, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Semipenil *Magis, Ital.*
Piperacillin sodium (p. 340·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Semor Pain & Fever Relief *Sunward, Singapore.*
Salicylamide (p. 129·2); caffeine (p. 1203·3).
Pain; fever.

Semor Stomach *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).

Sempera *Janssen-Cilag, Ger.*
Itraconazole (p. 583·3).
Fungal infections.

Semprex *GSK, China; GSK, Hong Kong†; GSK, Ital.†; GSK, Malaysia†; ACE, Neth.; GSK, Philipp.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.†; GSK, Switz.†; GSK, Turk.*
Acrivastine (p. 614·3).
Allergic rhinitis; allergic skin disorders; urticaria; eczema; angioedema; allergic conjunctivitis.

Semprex-D *Actient, USA.*
⊗Acrivastine (p. 614·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Semuele *Doctum, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Sen An *Lukang Chenxin, China.*
Matrine.

Sen Ao Xin *Yong He, China.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sen De Ning *Dexin Runsheng, China.*
Tolcapone (p. 916·3).
Parkinsonism.

Sen Ke *Fusen, China.*
Clarithromycin (p. 266·2).
Bacterial infections.

Sen Tai Bao *Changchun, China.*
A tick-borne encephalitis vaccine (p. 2422·1).
Active immunisation.

Sen Ting *San Lian, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Senade *Cipla, India.*
Calcium sennosides (p. 1885·2).
Constipation.

Cipla, Rus.
Senna (p. 1885·1).
Constipation.

Senadex
Note: this name may be used for preparations of different composition.
Biolink, Philipp.
Cefradine (p. 249·1).
Bacterial infections.

Stirol, Ukr.†
Senna (p. 1885·1).
Constipation; bowel evacuation.

Senadexin *Zdorovje, Rus.*
Senna (p. 1885·1).
Constipation.

Senalax
Note: this name may be used for preparations of different composition.
Cipla, India; Hasco-Lek, Pol.
Calcium sennosides (p. 1885·2).
Constipation.

Naturprodukt, Cz.; Pascual, Philipp.
Senna (p. 1885·1).
Constipation.

Senalax K *Hasco-Lek, Pol.*
Frangula bark (p. 1843·3); senna (p. 1885·1).
Constipation.

Senalex *Nabros, Rus.*
Calcium sennoside A (p. 1885·1); calcium sennoside B (p. 1885·1).
Constipation.

Senalina *Omega, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Senan *Ativus, Braz.*
Senna (p. 1885·1).
Constipation.

Sena-Oil *Berko, Turk.*
Liquorice (p. 1853·2); zinc sulfate (p. 2126·2); salicylic acid (p. 1719·1); clove oil (p. 2481·3); peppermint oil (p. 1877·1).
Constipation.

SenAoXin *Yong He, China.*
Sparfloxacin (p. 357·3).

Senaprost *Fuji, Jpn.*
Beraprost sodium (p. 1316·2).
Pulmonary hypertension; occlusive arterial disease.

Sencia *Konsuma, Venez.*
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

Senciderm *Sanofi-Aventis, Gr.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Sendicol *Coronet, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Sendoxan *Baxter, Denm.; Baxter, Fin.; Baxter Oncology, Norw.; Baxter, Swed.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms; auto-immune disorders.

Sendras *Ebewe, Spain.†*
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Sene *Herbarium, Braz.†*
Senna (p. 1885·1).
Constipation.

Senefen *Qualiphar, Belg.†*
Fennel oil (p. 2503·3).
Flatulence; bloating; digestive aid.

Senefol *Labofarm, Pol.*
Senna (p. 1885·1).
Bowel evacuation; constipation.

Senega and Ammonia *McGloin, Austral.*
Ammonium bicarbonate (p. 1655·3); camphor (p. 2466·2); liquorice (p. 1853·2); senega root (p. 1677·2); ammonia solution (p. 2441·2).
Cold symptoms.

Seneuval *Qualiphar, Belg.*
Valerian (p. 2640·2); passion flower (p. 2584·1); crataegus (p. 2488·1).
Nervousness; insomnia.

Senexon
Note: this name may be used for preparations of different composition.
Drugtech, Chile.
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety.
Rugby, USA.
Sennosides (p. 1885·2).
Constipation.

Senexon Plus *Gador, Arg.*
Betacarotene (p. 2051·1); vitamin E (p. 2119·1); vitamin C (p. 2110·3); selenium (p. 2086·3); zinc (p. 2126·1); manganese (p. 2081·2); copper (p. 2057·1).
Antoxidant preparation.

Senflam *Essenpharma, Philipp.†*
Mefenamic acid (p. 85·3).
Pain.

Sengobil *Plusandex, Venez.*
Ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Mental function impairment; erectile dysfunction; circulatory insufficiency; fatigue.

Senidrin *Unipharm, Mex.*
Capsules: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Respiratory-tract disorders.
Unipharm, Mex.
Syrup; tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders.

Seniere *Southern Cross, Austral.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Senilezol *Edwards, USA.*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Senior Multi-One *Swiss Herbal, Canad.†*
Vitamins; minerals.

Senioral *Ern, Spain.*
Clocinizine hydrochloride (p. 623·1); phenylpropanolamine hydrochloride (p. 1674·1).
Upper respiratory-tract congestion.

Seniospray *Rimafar, Spain.†*
⊗Oxymetazoline hydrochloride (p. 1671·3); chlorphenamine maleate (p. 620·3).
Nasal congestion.

Senirex *Algol, Fin.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Seni-Ven *Integris, Gr.*
Gabapentin (p. 523·3).

Senkon Junior Fever *Beacons, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Senkon White Spot *Sunward, Singapore.*
Salicylic acid (p. 1719·1).

Senkyuchachosan *Tsumura, Jpn.*
Cyperus rhizome; cnidium rhizome; notopterygium rhizome; schizonepeta tenuifolia; mentha herb; angelica dahurica root; saposhnikovia root; liquorice (p. 1853·2); tea leaf (p. 2648·2).
Traditional Kampo medicine.

Senlax *Elmor, Venez.*
Sennosides (p. 1885·2).
Constipation.

Senna Plus *Contract Pharmacal, USA.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.

Senna Prompt *Konsyl, USA.*
Sennosides (p. 1885·2); ispaghula (p. 1849·1).
Constipation.

Senna Smooth *Novartis Consumer, USA.*
Sennosides (p. 1885·2).
Constipation.

Senna-Gen *Goldline, USA.*
Senna (p. 1885·1).
Constipation.

Sennalax *Cazi, Braz.; Lennon, S.Afr.†; Abdi, Turk.*
Senna (p. 1885·1).
Constipation.

Senna-S *Alkyma, USA.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.
Tanta, Canad.
Senna (p. 1885·1); docusate sodium (p. 1836·2).
Constipation.

Sennesoft *Herron, Austral.*
Docusate sodium (p. 1836·2); sennosides (p. 1885·2).
Constipation.

Sennetabs *Herron, Austral.*
Sennosides (p. 1885·2).
Constipation.

Sennocol *Meda, Neth.*
Senna (p. 1885·1).
Constipation.

Sennove Lusky *Leros, Cz.*
Senna (p. 1885·1).
Constipation.

Senociclin *Senosiain, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Senokot *Reckitt Benckiser, Belg.; Purdue, Canad.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia; Mundipharma, Norw.†; Mundipharma, Philipp.; Reckitt Benckiser, Singapore; Ali, Turk.; Reckitt Benckiser, UK; Purdue Frederick, USA.*
Senna (p. 1885·1).
Constipation; bowel evacuation.
Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.; Novartis, Mex.; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Thai.; Konsuma, Venez.
Sennosides (p. 1885·2).
Constipation; bowel evacuation.

Sénokot *Meda, Fr.*
Senna (p. 1885·1).
Constipation.

Senokot Direct Relief *Reckitt Benckiser, UK.*
⊗Glycerol (p. 2517·2).
Constipation.

Senokot con Docusato *Konsuma, Venez.*
Sennosides (p. 1885·2); docusate sodium (p. 1836·2).
Constipation.

Senokot Dual Relief *Reckitt Benckiser, UK.*
Senna (p. 1885·1); aloes (p. 1816·1); cascara (p. 1826·1); taraxacum (p. 2625·3); fennel (p. 2503·2).
Constipation; bloating.

Senokot-S *Purdue, Canad.; Purdue Frederick, USA.*
Senna (p. 1885·1); docusate sodium (p. 1836·2).
Constipation.

Senokotxtra *Purdue Frederick, USA.*
Senna (p. 1885·1).
Constipation.

Senol
Note: this name may be used for preparations of different composition.
Bier, Ital.
Cetrimonium bromide (p. 1742·3).
Nipple disinfection.

Senolax *Codilab, Port.*
Sennosides A and B (p. 1885·2).
Constipation.

Senophile
Note: this name may be used for preparations of different composition.
Braun, Belg.
Cholesteryl benzoate (p. 2179·2); zinc oxide (p. 1729·1).
Skin disorders.

Sénophile *Braun, Fr.*
Cholesteryl benzoate (p. 2179·2); zinc oxide (p. 1729·1).
Skin irritation.

Senorm *Sun, Rus.*
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).

Senosan *Cos Farma, Ital.*
Emollient.

Senoside *Quality, Hong Kong.*
Calcium sennosides A and B (p. 1885·1).
Constipation.

Senpicaine *Huons, Philipp.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Senpivac *Harson, Philipp.*
Bupivacaine hydrochloride (p. 1980·3).
Local anaesthesia.

Senro *Biosarto, Spain.†*
Norfloxacin (p. 333·3).
Genito-urinary tract infections.

Sensaid *Dentaid, Chile.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Dental hypersensitivity.

Sensamol *Perrigo, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Sensaton *Temis, Arg.*
Clonazepam (p. 519·1).
Panic disorder; epilepsy.

Sensaval *Lundbeck, Swed.*
Nortriptyline hydrochloride (p. 439·3).
Depression.

Sense Daytime *Usana, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Sense Matte *Biotherm, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Sensedol *Centrum, Spain.*
Capsaicin (p. 35·1).
Neuropathic pain; musculoskeletal pain.

Sensei *Andromaco, Chile.*
Dimeticone (p. 2209·3).
Pediculosis.

Sensibaby *Ducto, Braz.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); zinc (p. 2126·1).
Skin disorders.

Sensibio
Note: this name may be used for preparations of different composition.
Bioderma, Venez.
Emollient or skin cleanser.
Skin disorders.
Dispolab, Chile.†
A range of emollients and soap substitutes.
Skin disorders.
Iasis, Gr.
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Sensibio DS *Bioderma, Venez.*
Piroctone olamine (p. 1716·3); climbazole (p. 576·2); sorbitan undecenoate; enoxolone (p. 54·2).
Seborrhoeic skin disorders.

Sensibit *Liomont, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria.

Sensibit D *Liomont, Mex.*
Loratadine (p. 633·2); paracetamol (p. 115·1).
Formerly contained loratadine and pseudoephedrine sulfate.
Allergic rhinitis; nasal congestion.

Sensibit D-NF *Liomont, Mex.*
Loratadine (p. 633·2); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Respiratory-tract disorders.

Sensibit XP *Liomont, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Cough; respiratory-tract congestion.

SensiBloq *Biomedis, Philipp.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia; pain.

Sensicare *HWS OTC, Austria.*
Euphorbia cyparissias (p. 2501·3); helianthemum canadense; kalium bromatum (p. 2461·1); mahonia aquifolium (p. 2577·1); smilax; thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Sensicutan *Harras-Curarina, Austria; Harras-Curarina, Cz.; Harras-Curarina, Ger.*
Levomenol (p. 2544·1); heparin sodium (p. 1396·3).
Skin disorders.

Sensident
Note: this name may be used for preparations of different composition.
Bernabo, Arg.
⊗Sodium fluoride (p. 2089·2); potassium nitrate (p. 1766·2).
Hypersensitive teeth.

Sensiderm
Note: this name may be used for preparations of different composition.
Koni-Cofarm, Chile.
A range of emollients and skin cleansing preparations.

Sensiderme
Note: this name may be used for preparations of different composition.
Neo Quimica, Braz.
Nitrofurazone (p. 333·1).
Bacterial skin infections.

Sensifil *Nutramedica, Philipp.*
Skin cleanser.

Sensifluid *A-Derma, Fr.*
Avena (p. 2451·1).
Soap substitute.

Sensigard *Copernico, Ital.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sensigel
Note: this name may be used for preparations of different composition.
Rovafarm, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore.
⊗Nicomethanol hydrofluoride (p. 2089·2); potassium nitrate (p. 1766·2).
Hypersensitive teeth; sensitive gums.
Sifarma, Ital.
Allantoin (p. 1693·1); vitamin A (p. 2098·3); vitamin E (p. 2119·1); lactic acid (p. 2539·1); triclosan (p. 1773·2).
Vaginal lubricant.

Sensikol *Nufarindo, Indon.*
Essential phospholipids (p. 2201·2); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Hypercholesterolaemia.

Sensiotin *Steigerwald, Ger.*
Hypericum perf. (p. 449·1); atropinum sulf. (p. 1310·2).
Homoeopathic preparation.

Sensipar *Amgen, Austral.; Amgen, Canad.; IFET (ΙΦΕΤ), Gr.; Amgen, NZ; Amgen, USA.*
Cinacalcet hydrochloride (p. 1180·1).
Hyperparathyroidism in chronic renal disease; hypercalcaemia associated with parathyroid cancer or primary hyperparathyroidism.

Sensipharma *Alpharma, Mex.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Sensiphase *Silesia, Chile.*
A range of skin cleansing and moisturising preparations.

Sensiquell *Sifarma, Ital.*
Milk protein; allantoin (p. 1693·1); lactic acid (p. 2539·1); triclosan (p. 1773·2).
Skin and mucous membrane cleansing.

Sensit *Organon (Οργανον), Gr.*
Fendiline hydrochloride (p. 1381·1).
Angina pectoris.

Sensitex *Kinder, Braz.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Sensitin *Zynova, Philipp.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

2Sensitive *Agys, Singapore.*
⊗Sodium fluoride (p. 2089·2); strontium chloride (p. 2623·1); potassium nitrate (p. 1766·2).
Sensitive teeth; receding gums.

Sensitive Eyes *Bausch & Lomb, Canad.*
Range of solutions for soft contact lenses.
Bausch & Lomb, NZ; Bausch & Lomb, Turk.
A range of solutions for contact lens care.
Bausch & Lomb, USA.
Range of solutions for contact lenses.

Sensitive Eyes Daily Cleaner *Bausch & Lomb, Austral.*
Cleansing solution for soft contact lenses.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sensitive Eyes Protein Removal *Bausch & Lomb, Austral.†*
Proteolytic enzyme.
Cleanser for soft, hard and gas permeable contact lenses.

Sensitive Eyes Saline *Bausch & Lomb, Austral.*
Sodium chloride (p. 1795·1).
Saline solution for soft contact lenses.

Sensitive Skin Facial Astringent *Scott, Canad.†*
Salicylic acid (p. 1719·1).

Sensitivity Protection Crest *Procter & Gamble, USA.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Sensitive teeth.

Sensitram *Libbs, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Sensival *Wallace, India.*
Nortriptyline hydrochloride (p. 439·3).
Bipolar disorder; depression.

Sensivision au plantain *Chauvin, Fr.*
Ribwort plantain (p. 2604·2).
Eye irritation.

Sensocaps *SM, Gr.*
Capsaicin (p. 35·1).
Neuralgia; peripheral neuropathy.

Sensocet *Sensomed, Philipp.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Sensodyne
Note: this name may be used for preparations of different composition.
GSK Consumer, Canad.; GSK Consumer, Venez.
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth; dental caries prophylaxis.
GSK Consumer, Canad.†
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

Sensodyne Antisarro *GSK, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2); tetrapotassium pyrophosphate (p. 2619·3).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Antitartaro *GSK, Braz.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth.

Sensodyne Bicarbonato de Sodio *GSK, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2); sodium bicarbonate (p. 1781·1).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Blanqueador *GSK, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Toothpaste.

Sensodyne C/Bicarbonato de Sodio *GSK, Braz.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth.

Sensodyne Cool *GSK, Arg.; Stafford-Miller, Braz.†*
⊗Sodium fluoride (p. 2089·2); potassium nitrate (p. 1766·2).
Hypersensitive teeth; dental caries prophylaxis.

Sensodyne Cool Gel *Sterling, Indon.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth; dental caries prophylaxis.

Sensodyne Formula Original *GSK, Braz.*
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

Sensodyne Fresh Mint *GSK, Braz.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth.

Sensodyne Gel *Ali, Turk.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth.

Sensodyne Gentle *GSK, Hong Kong.†*
Potassium chloride (p. 1793·2); sodium fluoride (p. 2089·2); triclosan (p. 1773·2).

Sensodyne iso-active *GSK Consumer, USA.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth; dental caries prophylaxis.

Sensodyne med *GSK, Austria.†*
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

Sensodyne Mint *Ali, Turk.*
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

GSK, UK.
Sodium fluoride (p. 2089·2); strontium acetate (p. 2623·1).
Hypersensitive teeth.

Sensodyne Original *GSK, Arg.; GSK, UK.*
Strontium chloride (p. 2623·1).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Proémail Fluorid *GSK, Switz.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Sensodyne ProNamel *GSK Consumer, Canad.*
⊗Sodium fluoride (p. 2089·2) potassium nitrate (p. 1766·2).
Dental caries prophylaxis.

Sensodyne Proschmelz *GSK, Austria; GSK Consumer, Ger.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis; sensitive teeth; hypersensitive teeth.

Sensodyne Protecao Total *GSK, Braz.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth.

Sensodyne Proteccion Total *GSK, Arg.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Rapido Alivio *GSK, Arg.*
Sodium fluoride (p. 2089·2); strontium acetate (p. 2623·1).
Hypersensitive teeth.

Sensodyne-F
Note: this name may be used for preparations of different composition.
Ali, Turk.
Potassium chloride (p. 1793·2); sodium monofluorophosphate (p. 2091·3).
Hypersensitive teeth.

GSK, Arg.; Stafford-Miller, Braz.†; Block, USA.
⊗Potassium nitrate (p. 1766·2); sodium monofluorophosphate (p. 2091·3).
Hypersensitive teeth; dental caries prophylaxis.

GSK Consumer, Canad.
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).
Hypersensitive teeth.

Stafford-Miller, UK.
Potassium chloride (p. 1793·2); sodium fluoride (p. 2089·2); triclosan (p. 1773·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne-SC *Block, USA.*
Strontium chloride (p. 2623·1).
Hypersensitive teeth.

Sensoflox *Sensomed, Philipp.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

SensoGARD *Block, USA.*
Benzocaine (p. 1980·2).
Mouth and throat disorders.

Sensolid *Mac, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Sensonette *Ratiopharm, Hung.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Sensoral *Medifarma, Turk.*
⊗Potassium nitrate (p. 1766·2); sodium fluoride (p. 2089·2).

Sensorcaine *AstraZeneca, Canad.; AstraZeneca, India; AstraZeneca, Philipp.; APP, USA.*
Bupivacaine hydrochloride (p. 1980·3).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Sensu *Bausch & Lomb, Arg.*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Sensur *Glenmark, India.*
Lotion: Peppermint oil (p. 1877·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); sweet birch oil (p. 92·1).
Formerly contained menthol, camphor, menthol oil, eucalyptus oil, clove oil, cinnamon oil, and sweet birch oil.
Osteoarthritis.

Glenmark, India.
Topical oil: Peppermint oil (p. 1877·1); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1).
Formerly contained menthol, camphor, eucalyptus oil, and sweet birch oil.
Sinusitis; rhinitis.

Glenmark, India.
Liniment: Peppermint oil (p. 1877·1); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); clove oil (p. 2481·3); cinnamon oil (p. 2479·3).
Formerly contained menthol, camphor, menthol oil, eucalyptus oil, clove oil, and cinnamon oil.
Low back pain.

Sentapen *Biogalenic, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sentidol *Medipharm, Chile.*
Venlafaxine (p. 454·2) or venlafaxine hydrochloride (p. 454·2).
Anxiety; depression; attention-deficit hyperactivity disorder.

Sentinel Ulcer Mixture *Martyn, S.Afr.†*
⊗Bismuth and ammonium citrate (p. 1821·3); dilute hydrochloric acid (p. 2528·3); pepsin (p. 2586·1); vitamin B_{12} (p. 2107·2).
Peptic ulcer.

Sentionyl *ACME, Philipp.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Senti-Scint *Medi-Radiopharma, Cz.*
Technetium-99m (p. 2228·1) labelled human albumin.
Radionuclide imaging of lymphatic system; diagnosis of breast cancer and melanoma.

Sentor *Gedeon Richter, Ukr.*
Losartan (p. 1422·2).
Hypertension; left ventricular hypertrophy; diabetic nephropathy.

Sentril *Biomedis, Indon.†; Medifarma, Indon.†; Great Eastern, Thai.†*
Dequalinium chloride (p. 1749·3); cetylpyridinium chloride (p. 1743·1); ascorbic acid (p. 2110·3).
Mouth and throat disorders.

Sentual Periodo *Medipharm, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome; dysmenorrhoea.

Sentyl *Sunthi Sepuri, Indon.†*
Secnidazole (p. 947·3).
Amoebiasis; trichomoniasis.

Senzop *Jelfa, Pol.*
Zopiclone (p. 1118·1).
Insomnia.

Senzulin *Siam Bheasach, Thai.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Seotiapim *Sandoz, UK.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; depression.

Sepan *Paranova, Denm.*
Cinnarizine (p. 622·1).
Motion sickness; vestibular disorders.

Sepatren *Sumitomo, Jpn.†*
Cefpiramide sodium (p. 247·2).
Bacterial infections.

Sepazon *Daiichi Sankyo, Jpn.*
Cloxazolam (p. 1057·2).
Anxiety states; premedication; sleep disorders.

Sepcen *Centrum, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Sepexin
Note: this name may be used for preparations of different composition.
Hetero, India.
Cefalexin (p. 234·1).
Bacterial infections.

Sepfadine *TNP, Thai.*
Povidone-iodine (p. 1767·1).
Skin and soft-tissue disinfection; wounds; burns.

Sepia *Wermar, Mex.*
Itraconazole (p. 583·3); secnidazole (p. 947·3).
Vaginal infections.

Sepia comp *Weleda, Ger.*
Conchae (p. 1824·3); ignatia (p. 2532·1); sepia gruneris (p. 2613·1).
Homoeopathic preparation.

Sepia Complexe No 20 *Lehning, Fr.*
Sepia officinalis (p. 2613·1); kalium carbonicum (p. 2595·2); ambra grisea (p. 2440·3); strontium muriaticum (p. 2623·1); calcarea carbonica (p. 1824·3).
Homoeopathic preparation.

Sepia Composé *Boiron, Fr.*
Sepia (p. 2613·1); aloe socotrina (p. 1816·1); arnica montana (p. 2447·2); sanguinaria canadensis (p. 2610·1); collinsonia canadensis (p. 2622·2); paeonia officinal; aesculus hippocastanum (p. 2431·2); hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Sepibest *Best, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; bipolar disorder; alcohol withdrawal syndrome; diabetic neuropathy; diabetes insipidus; polydipsia; polyuria.

Sepioglin *Vaia, Neth.†*
Pioglitazone hydrochloride (p. 493·1).

Sepmax *GSK, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Se-Power *Cantassium Co., UK.*
Selenium yeast (p. 2125·2); myrtillus (p. 2566·2); euphrasia (p. 2502·1); vitamin E (p. 2119·1); zinc gluconate (p. 2126·2); vitamin A (p. 2098·3); riboflavin (p. 2104·3).

Seprafilm *Genzyme, Braz.; Genzyme, Malaysia; Sanofi-Aventis, Singapore; Genzyme, UK; Genzyme, USA.*
Sodium hyaluronate (p. 2526·2); carmellose (p. 2175·1).
Prevention of surgical adhesions.

Sepram *Lundbeck, Fin.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Seproc *Pharmathen, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Sepsilem *Teva, Mex.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Sepso J *Hofmann & Sommer, Ger.*
Povidone-iodine (p. 1767·1).
Burns; infected skin disorders; skin, hand, and mucous membrane disinfection; wounds.

Septacef *Septa, Spain.†*
Cefradine (p. 249·1).
Bacterial infections.

Septacin *Chinoin, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Septacin Amoxi *Chinoin, Mex.*
Ambroxol hydrochloride (p. 1654·3); amoxicillin trihydrate (p. 216·2).
Respiratory-tract infections.

Septacín Ex *Chinoin, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Septacord *Muller Goppingen, Ger.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1); crataegus (p. 2488·1).
Cardiac disorders.

Septacord mono *Muller Goppingen, Ger.†*
Crataegus (p. 2488·1).
Heart failure.

Septadine
Note: this name may be used for preparations of different composition.
Prafa, Indon.; Be-Tabs, S.Afr.
Povidone-iodine (p. 1767·1).
Minor throat infections; skin infections; wound and burn disinfection; mouth infections; skin disinfection; wounds; vaginal infections.
Floris, Israel.
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Septadine Scrub
Note: this name may be used for preparations of different composition.
Floris, Israel.
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Septal *Teva, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Septalan *Chema-Elektromet, Pol.†*
Allantoin (p. 1693·1); acriflavinium chloride (p. 1732·3).
Wounds; ulcers; burns; psoriasis.

Septalone *Teva, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Burns; disinfection in obstetrics; skin and instrument disinfection; wounds.

Septanest *Septodont, Austral.; Septodont, Austria; Septodont, Canad.; Septodont, Denm.; Septodont, Fr.; Tsaprazis, Gr.; Septodont, Israel; Ogna, Ital.; Septodont, Neth.; Ivoclar, NZ; Septodont, Port.; Septodont, Rus.; Septodont, Spain; Wild, Switz.; Septodont, UK.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1), adrenaline acid tartrate (p. 1292·2), or adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septanest S *Septodont, Cz.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septax *Vianex (Βιανεξ), Gr.; Vianex, Israel.*
Ceftazidime (p. 250·2).
Bacterial infections.

Septe FX Skin Formula *Commsept, Canad.†*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Septéal *Pierre Fabre Dermatologie, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection; bacterial skin infections.

Septi-Aid *Pharmaniaga, Malaysia.†*
Povidone-iodine (p. 1767·1).
Skin and wound disinfection.

Septibiotic *Sidus, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Septicide *Bago, Arg.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Septicol
Note: this name may be used for preparations of different composition.
Streuli, Switz.†
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Septicyn *EuroHealth, Philipp.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Septidil *Nuova Farmec, Ital.*
Didecyldimethylammonium chloride (p. 1750·3).
Cleansing and disinfection of wounds and burns; hand disinfection.

Septidine *Osoth, Thai.*
Povidone-iodine (p. 1767·1).
Disinfection of skin, wounds, burns, and umbilicus.

Septidose *Neitum, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Skin and wound disinfection.

Septigyn *Montpellier, Arg.*
Metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); centella (p. 1698·3).
Vulvovaginal infections.

Septil *Azevedos, Port.*
Povidone-iodine (p. 1767·1).
Skin disinfection; wounds; burns; ulcers; skin infections.

Septilin *Himalaya, Singapore.*
Syrup: Commiphora wightii; maharasnadi quath; tinospora cordifolia; rubia cordifolia; Indian gooseberry (p. 2532·2); liquorice (p. 1853·2); piper longum; piper nigrum (p. 2586·1); zingiber officinale; saussurea lappa.
Bacterial infections.

Himalaya, Singapore.
Tablet: Commiphora wightii; shankha bhasma; maharasnadi quath; tinospora cordifolia; rubia cordifolia; Indian gooseberry (p. 2532·2); moringa pterygosperma; liquorice (p. 1853·2).
Bacterial infections.

Himalaya, Ukr.
Balsamodendron; maharasnadi quath; rubia cordifolia; tinospora cordifolia; trikuta (Emblica officinalis fruit; Terminalia chebula fruit (p. 2474·3); Terminalia bellirica fruit (p. 2453·2)); saussurea lappa; Indian gooseberry (p. 2532·2); liquorice (p. 1853·2).
Inflammatory and infectious disorders.

Septiline
Note: this name may be used for preparations of different composition.
Gojo, Canad.
Chloroxylenol (p. 1748·2).
Skin disinfection.

Septilisin
Note: this name may be used for preparations of different composition.
Bago, Arg.
Cefalexin (p. 234·1).
Bacterial infections.

Grin, Mex.
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial eye infections.

Septilisin Duo *Bago, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Septinalis *Unipharma, Gr.*
Mebendazole (p. 158·3).

Septinor *IAE, Philipp.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Septipan *Geofman, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Septisan
Note: this name may be used for preparations of different composition.
Zentiva, Cz.
2-Aminotridecane adipate.
Upper respiratory-tract disorders.

Cederroth, Spain.†
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin, burns, and wounds.

Septisol
Note: this name may be used for preparations of different composition.
Merck Medication Familiale, Fr.†
Salicylic acid (p. 1719·1).
Chronic conjunctivitis.

Septisooth *Aspen, S.Afr.*
Povidone-iodine (p. 1767·1).
Skin infections; wounds; burns; ulcers.

Septivon
Note: this name may be used for preparations of different composition.
Interdelta, Switz.
Triclocarban (p. 1773·2); cetrimonium chloride (p. 1742·3).
Hand disinfection; minor skin lesions.

Omega, Austral.
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Hand disinfection.

Omega, Fr.
Chlorhexidine gluconate (p. 1743·3).
Bacterial skin infections.

Septivoncare *Omega, Fr.*
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Septobore *Cooper (Κοπερ), Gr.*
⊗Naphazoline nitrate (p. 1669·3); boric acid (p. 2459·3).
Eye irritation.

Septocaine *Septodont, Denm.; Septodont, Fin.; Septodont, Norw.; Bigman, Swed.; Deproco, USA.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septocipro *Qualigen, Spain.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial ear infections.

Septocoll *Biomet, Ger.*
Collagen (bovine) (p. 2483·2); gentamicin sulfate (p. 304·2).
Wounds; haemorrhage.

Septoderm Hände *Schumacher, Ger.*
Isopropyl alcohol (p. 1758·3).
Hand disinfection.

Septofervex *BMS, Pol.†*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Septofit *Actavis, Ukr.†*
Sodium usnate.
Mouth and throat disorders; cough.

Septofort *Walmark, Cz.; Walmark, Hung.*
Chlorhexidine gluconate (p. 1743·3).
Mouth and throat disorders.

Septogal *Jadran, Rus.*
Benzalkonium chloride (p. 1737·1); menthol (p. 2553·2); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); thymol (p. 1772·2).
Mouth and throat disorders.

Septol
Note: this name may be used for preparations of different composition.
Teva, Israel.
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Christo, Hong Kong.†
Co-trimoxazole (p. 277·3).

Septol-C *BJ Benjaosoth, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Wounds.

Septolete *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Benzalkonium chloride (p. 1737·1); menthol (p. 2553·2); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); thymol (p. 1772·2).
Mouth and throat disorders.

Septolete Apple *KRKA, Pol.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Septolete Cherry *KRKA, Pol.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Septolete Lemon *KRKA, Pol.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Septolete with lemon/cherry/apple *KRKA, Ukr.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Septolete Neo *KRKA, Rus.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Septolete Plus *KRKA, Pol.; KRKA, Ukr.*
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

KRKA, Rus.
Benzocaine (p. 1980·2); cetylpyridinium bromide (p. 1743·1).
Mouth and throat disorders.

Septolux *ICN, Pol.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Septomixine *Septodont, Cz.; Septodont, Fr.; Wild, Switz.*
⊗Hydrocortisone acetate (p. 1640·1); framycetin sulfate (p. 301·2).
Dental infections; root canal infections.

Septonex *Herbacos, Cz.*
Ointment: Hexachlorophene (p. 1754·1); carbaethopendecinium bromide (p. 1741·3).
Wounds; ulcers; infected skin disorders.

Teva, Cz.
Topical spray: Carbaethopendecinium bromide (p. 1741·3).
Disinfection of surfaces, hands, skin, and mucous membranes; wounds; fungal skin infections.

Septonex Plus *Teva, Cz.*
Trimecaine (p. 1997·3); carbaethopendecinium bromide (p. 1741·3).
Wounds; burns.

Septopal *Biomet, Austral.†; Biomet, Austria; Biomet, Belg.; Merck, Braz.; Heraeus Kulzer, China; Merck, Denm.†; Biomet, Fin.; Biomet, Fr.†; Biomet, Ger.; Biomet, Gr.; Merck, Hong Kong†; Merck, Hung.†; Merck, India†; Biomet, Neth.; Biomet Merck, Norw.; Merck, Philipp.; Merck, Port.; Merck, S.Afr.; Biomet, Singapore; Biomet, Switz.; Merck, Thai.; Biomet Merck, UK.*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methylacrylate copolymer (p. 2558·2).
Bacterial infections of bone and soft tissue.

Septosan
Note: this name may be used for preparations of different composition.
Stiefel, Fr.†; Stiefel, Mex.
Soap: Triclocarban (p. 1773·2); triclosan (p. 1773·2).
Skin cleansing.

Herbapol Lublin, Pol.†
Peppermint leaf (p. 1877·1); sage (p. 2608·3); thyme (p. 2630·2).
Mouth and throat disorders.

Septosol *Cipla, S.Afr.*
Phenol (p. 1763·3).
Sore throat.

Septosples *Specifar (Σπεσιφαρ), Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Septosyl *PannonPharma, Hung.*
Sulfadimidine (p. 363·2).
Bacterial eye infections.

Septozyl *Specifar (Σπεσιφαρ), Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Septra *GSK, Canad.; Monarch, USA.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Septran *GSK, India; GSK, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Septrex *Burapha, Thai.*
Chlorhexidine gluconate (p. 1743·3); cetrimide (p. 1742·1).
Wounds.

Septrin *Aspen, Austral.; GSK, Chile; GSK, Gr.; Sigma, Hong Kong†; GSK, Indon.; GSK, Irl.; Perrigo, Israel; GSK, Mex.; GSK, Philipp.; GSK, Pol.†; Wellcome, Port.; UCB, Spain; Genesis, Turk.; Aspen Medical, UK.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; nocardiosis; toxoplasmosis.

Septus *Merck, Port.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Septyl *Burapha, Thai.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Sepurin *Gross, Braz.*
Methenamine (p. 322·3); methylthioninium chloride (p. 1559·1).
Urinary-tract infections.

Sequacor *Bracco, Ital.*
⊗Bisoprolol fumarate (p. 1325·3).
Heart failure.

Sequals G *Lagos, Arg.*
Rosemary (p. 2607·2); enebro (p. 1723·2); crataegus (p. 2488·1); birch (p. 2457·3).
Scalp disorders.

Sequase *AstraZeneca, Austral.; AstraZeneca, Switz.*
Quetiapine fumarate (p. 1101·1).
Bipolar disorder; schizophrenia.

Sequax *Ivax, Arg.*
Clozapine (p. 1057·3).
Schizophrenia.

Sequidot *Novartis, Cz.†; Novartis, Fin.*
Phase I patch, estradiol (p. 2271·1); phase II patch, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novartis, Ger.; Novartis, Switz.
Phase I, estradiol (p. 2271·1); phase II, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novartis, Norw.; Novartis, Swed.
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Sequidot 2-Phasen *Novartis, Austria.*
Phase I patch, estradiol (p. 2271·1); phase II patch, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Sequilar *Bayer, Austria.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Biphasic oral contraceptive.

Sequilar ED *Schering, Austral.†*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Biphasic oral contraceptive.

Sequinan *Ivax, Arg.*
Risperidone (p. 1103·2).
Psychoses.

Ser Damla *Yenisehir, Turk.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Seraccel *Serum Institute, India.*
⊗Gelatin (p. 1154·1); electrolytes (p. 1775·1).
Shock; plasma volume expansion.

Seracic *IQFA, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Seracin *Pharmaland, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Seractil *Gebro, Austria; Gebro, Cz.†; Galenica, Gr.; Gebro, Hung.; GiEnne, Ital.; Euro Registratie, Neth.; Fisher, Neth.; Biofarm, Pol.; Jaba Recordati, Port.; Gebro, Spain; Gebro, Switz.; Genus, UK.*
Dexibuprofen (p. 43·1).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; fever.

Seractiv *Nordic Drugs, Denm.; Nordic Drugs, Norw.*
Dexibuprofen (p. 43·1).
Pain; inflammation; musculoskeletal and joint disorders.

Seradase *Weida, China.*
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion.

Seradex-LA *Allegis, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Serag-HAES *Serag-Weissner, Cz.†; Serag-Wiessner, Ger.†*
⊗Pentastarch (p. 1146·1) in sodium chloride.
Hypovolaemia; plasma volume expansion; haemodilution.

Seraim *Anglo-French Drugs, India.*
⊗Serrapeptase (p. 2613·3).
Inflammation; breast engorgement; pericoronitis; alveolar abscess.

Seralb-I-125 *CBI, Switz.*
Iodine-125 (p. 2225·2) labelled albumin.
Determination of plasma or blood volume.

Seralin *Eczacibasi, Rus.; Mepha, Switz.; Eczacibasi, Turk.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Seralis *Landsteiner, Mex.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Seralis VIP *Landsteiner, Mex.*
Risedronate sodium (p. 1189·3); colecalciferol (p. 2113·1).
Osteoporosis; Paget's disease of bone.

Seralon *Medochemie, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Seramed *Medifive, Thai.†*
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion.

Seramine *Arlex, Mex.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Ser-Ap-Es *Novartis, Indon.; Novartis, Thai.†*
⊗Reserpine (p. 1485·3); hydralazine hydrochloride (p. 1401·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Serasept *Serag-Wiessner, Ger.*
Polihexanide (p. 1766·1).
Wound disinfection.

Seratil *Christo, Hong Kong.*
Prochlorperazine maleate (p. 1098·3).
Anxiety; nausea and vomiting; psychoses.

Seratio *Ratiopharm, Cz.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Serato-M *Kee, India.*
⊗Serrapeptase (p. 2613·3).
Oedema; inflammation; respiratory-tract congestion.

Seravit *Nutricia, Fr.*
Vitamins; minerals; trace elements.

Scientific Hospital Supplies, Irl.†; Scientific Hospital Supplies, UK.
Vitamins; minerals.
Nutritional supplement.

Serax
Note: this name may be used for preparations of different composition.
Landsteiner, Mex.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Alpharma, USA.†
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.

Seraxol *Serral, Mex.*
⊗Ambroxol (p. 1654·3); clenbuterol (p. 1207·2).
Respiratory-tract congestion.

Seraxol-S *Serral, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Serbendazol *Serral, Mex.*
Albendazole (p. 149·1).
Worm infections.

Serbo *SJA, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Serbol *IQFA, Mex.*
⊗Ambroxol (p. 1654·3); clenbuterol (p. 1207·2).
Respiratory-tract congestion.

Serc *Abbott, Austral.; Abbott, Canad.; Europharma, Denm.; Abbott, Fr.; Abbott, Irl.; Italmex, Mex.; Abbott, NZ; Solvay, Philipp.; Solvay, S.Afr.; Farmasierra, Spain; Abbott, Thai.; Solvay, UK; Zuoz, Venez.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo; vestibular disorders.

Sercim *IQFA, Mex.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Serdas *Inpac, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Serdep *Cipla, Hong Kong; Cipla, India; Cipla-Medpro, S.Afr.; Fako, Turk.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Serdol *Labormed, Rus.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Serdolect *Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ger.; Lundbeck, Gr.; Lundbeck, Hung.; Lundbeck, Irl.; Lundbeck, Israel; Lundbeck, Malaysia; Lundbeck, Neth.; Lundbeck, Norw.; Healthcare Logistics, NZ; Lundbeck, Philipp.; Lundbeck, Pol.; Lundbeck, Port.; Lundbeck, Rus.; Lundbeck, Spain; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Turk.; Lundbeck, UK†; Lundbeck, Ukr.*
Sertindole (p. 1107·1).
Schizophrenia.

Serecid *Douglas, NZ.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; nausea and vomiting; asthma; urticaria; alcohol withdrawal syndrome.

Sérécor *Sanofi-Aventis, Fr.*
Hydroquinidine hydrochloride (p. 1407·1).
Arrhythmias.

Serecur *Panalab, Arg.*
Saw palmetto (p. 2363·3).
Prostatic disorders.

Sered *GSK, Braz.*
Sertraline (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; premenstrual dysphoric disorder.

Seredol *Atlantic, Philipp.*
Haloperidol (p. 1077·1).
Psychoses; Tourette syndrome; neuroses; behaviour disorders in children.

Seredrin *Bioplanta, Norw.†*
Ginkgo biloba (p. 2512·3).
Peripheral vascular disorders.

Sereflo *Cipla-Medpro, S.Afr.*
⊗Fluticasone propionate (p. 1638·1); salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Seregra *Arafarma, Spain.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Sereine *Optikem, Canad.*
Range of solutions for cleaning, wetting, and soaking contact lenses.

Optikem, USA.
Range of solutions for hard contact lenses.

Sérélys *Serelyspharma, Mon.*
Tablets: Pollen (p. 2593·3); pistils; vitamin E (p. 2119·1).
Menopausal disorders; premenstrual symptoms.

Serelyspharma, Mon.
Vaginal gel: Lactic acid (p. 2539·1); lactoserum.
Maintenance of vaginal flora; vaginal dryness; bacterial vaginosis.

Seremaks *Husnu Arsan, Turk.*
Ginkgolides (p. 2513·3).

Seremig *Ifars, Indon.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Serenace *Aspen, Austral.; Pfizer, Hong Kong; RPG, India; Pfizer, Indon.; Ivax, Irl.; Healthcare Logistics, NZ; Pfizer, Philipp.; Pfizer, S.Afr.; Pharmacia, Singapore; Ivax, UK.*
Haloperidol (p. 1077·1).
Psychoses; alcoholism; nausea; vomiting; neuroleptanalgesia; mania; anxiety; tics; hiccups; agitation; bipolar disorder; Tourette's syndrome; premedication; behaviour disorders; aggression.

Serenada *Trima, Israel.*
Sertraline hydrochloride (p. 448·1).
Depression.

Serenal
Note: this name may be used for preparations of different composition.
Daiichi Sankyo, Jpn.
Oxazolam (p. 1093·1).
Anxiety states; premedication; sleep disorders.

Meda, Port.
Oxazepam (p. 1092·2).
Anxiety.

Serenase
Note: this name may be used for preparations of different composition.
Almirall, Belg.
Lorazepam (p. 1080·3).
Anxiety; insomnia; premedication.

Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Lusofarmaco, Ital.
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Psychoses; nausea and vomiting; disturbed behaviour; movement disorders; vomiting; hiccups; alcohol withdrawal syndrome; pain.

Serenata *Torrent, Braz.; Torrent, Philipp.; Torrent, Rus.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serene *VS, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety.

Serengrav *Baldacci, Ital.*
Folic acid (p. 2063·1).
Prevention of neural tube defects during pregnancy.

Serenil *Natufarma, Arg.*
Passion flower (p. 2584·1); valerian (p. 2640·2); tilia (p. 2631·3).
Sedative.

Sérénité *Synergia, Fr.*
Omega-3 marine triglycerides (p. 1460·3); vitamins; minerals.
Nutritional supplement during pregnancy and breast feeding.

Serenus *Biolab Sanus, Braz.*
Passion flower (p. 2584·1); crataegus (p. 2488·1); adonis vernalis (p. 2431·1).
Sedative.

Serepax *Aspen, Austral.; Wyeth, India; Akromed, S.Afr.*
Oxazepam (p. 1092·2).
Anxiety disorders; alcohol withdrawal syndrome; tension; irritability.

Sereprid *Labomed, Chile.*
Tiapride hydrochloride (p. 1111·2).
Alcohol withdrawal syndrome; behaviour disorders; headache; movement disorders.

Sereprile *Sanofi-Aventis, Ital.*
Tiapride hydrochloride (p. 1111·2).
Movement and behaviour disorders; gastrointestinal dyskinesia.

Sereprosta *Reprefar, Port.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sereprostat *Robapharm, Spain.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Seresano *Hexal, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Seresis *Boehringer Ingelheim, Chile.*
Ascorbic acid (p. 2110·3); grape (p. 2521·3); tomato; selenium (p. 2086·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Dietary supplement.

Boehringer Ingelheim Promeco, Mex.
Tomato; grape (p. 2521·3); betacarotene (p. 2051·1); *dl*-alpha tocoferol acetate; ascorbic acid (p. 2110·3); selenium-rich yeast (p. 2125·2).
Antioxidant; skin disorders.

DKSH, Malaysia; Pharmaton, Singapore.†
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); grape seed (p. 2521·3); tomato; selenium yeast (p. 2125·2).
Dietary supplement.

Séresta *Biodim, Fr.*
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.

Seresta *Meda, Belg.; EuroCept, Neth.; Meda, Switz.*
Oxazepam (p. 1092·2).
Anxiety; sleep disorders; alcohol withdrawal syndrome.

Serestill *Chemi, Ital.; Italfarmaco, Rus.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Seretaide *Paranova, Denm.; Glaxo Wellcome, Port.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease; asthma.

Seretide *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; Allen & Hanburys, UK; GSK, Ukr.; GSK, Venez.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease; asthma.

GSK, Philipp.
⊗Salmeterol (p. 1224·1) or salmeterol xinafoate (p. 1224·1); fluticasone (p. 1638·1) or fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Seretover *Iliafarm, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Seretral *Teva, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression.

Seretran *Drugtech, Chile.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Sereupin *Abbott, Ital.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; post-traumatic stress disorder; social phobia.

Serevent *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.†; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia†; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.†; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; Allen & Hanburys, UK; Glaxo Wellcome, USA; GSK, Venez.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease; asthma.

Serex *Nevzat, Turk.*
Quetiapine fumarate (p. 1101·1).

Serez *Adcock Ingram, S.Afr.*
Quetiapine (p. 1101·1).

Serfac *Otto, Indon.*
Citicoline (p. 2480·1).
Head injury; stroke; hemiplegia.

Ser-Fiz *Med-Care, Turk.*
Distilled water (p. 2646·2).
Nasal dryness; nasal congestion.

Serformin *Sandoz, Thai.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sergimax *Surge, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Sergolin *Teva, Ukr.*
Nicergoline (p. 2569·1).
Alzheimer's disease; Raynaud's syndrome.

Sergoline *Siam Bheasach, Thai.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Sériane Stress *Plantes et Medecines, Fr.†*
Hydrolysed milk proteins.
Stress.

Serianon *Fada, Arg.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Serilact *Laborest, Ital.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); *Bifidobacterium breve* (p. 2596·3); zinc (p. 2126·1); inulin (p. 2534·3).
Gastrointestinal disorders.

Serimel *Clonmel, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression.

Serimol *Pharmaniaga, Hong Kong.*
Paracetamol (p. 115·1).
Pain; fever.

Serinflu *Abbott, Spain.†*
An influenza vaccine (p. 2393·3).
Active immunisation.

Serital *Temmler, Ger.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Seritral *Serral, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Serivo *Pasteur, Chile.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder.

Serlain *Pfizer, Belg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Serlan *Rowex, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression.

Serlect *Lundbeck, Mex.*
Sertindole (p. 1107·1).
Psychoses.

Serlife *Ranbaxy, S.Afr.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder.

Serlift *Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Malaysia; Daiichi Sankyo, Mex.; Ranbaxy, Rus.; Ranbaxy, Thai.; Ranbaxy, Ukr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia; obsessive-compulsive disorder; mixed anxiety depressive states.

Serlin *Decomed, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Serlina *AstraZeneca, Arg.; Rontag, Arg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serlinan *Hexal, Denm.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Serline *Giempi, Venez.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serlo *Actavis, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Serlof *Kalbe, Indon.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serlosane *Teva, Hung.†*
Sertraline hydrochloride (p. 448·1).
Depression.

Sermax *Be-Tabs, S.Afr.*
Sertraline (p. 448·1).

Sermetrol *Serral, Mex.*
⊗Metoprolol (p. 1434·3).
Hypertension.

Sermicina *Serral, Mex.*
Amikacin (p. 214·1).
Bacterial infections.

Sermion *Pfizer, Arg.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Sanofi-Aventis, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Ital.; Sanitari, Ital.; Mitsubishi Tanabe, Jpn; Pfizer, Mex.; Pfizer, Philipp.†; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, Spain; Pfizer, Switz.†; Pfizer, Thai.; Deva, Turk.; Pfizer, Ukr.; Pfizer, Venez.*
Nicergoline (p. 2569·1).
Dementia; cerebral infarction; cerebral and peripheral vascular disorders; mental function impairment; vestibular disorders; headache; hypertension; cerebral metabolic disorders; vascular eye disorders.

Sermonil *Pharmaland, Thai.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Sermoxol *Serral, Mex.*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Sernade *Novell, Indon.*
Sertraline hydrochloride (p. 448·1).
Depression.

Sernax *Serra Pamies, Spain.*
Tioconazole (p. 595·3).
Fungal nail infections.

Serobid *Cipla, India.*
⊗Salmeterol xinafoate (p. 1224·1).
Asthma.

Serobif *Serono, Braz.†; Serono, Ital.†*
Interferon beta (p. 996·1).
Viral infections; malignant neoplasms.

Serocalcin *Serono, Braz.†*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Serocel *Verisfield, Gr.*
Citalopram hydrochloride (p. 411·1).

Serocion *Sanwa, Jpn.*
Propagermanium (p. 1009·2).
Hepatitis B.

Serocryptin *Serono, Gr.*
Bromocriptine mesilate (p. 895·3).

Serocytol *Serolab, Switz.*
A range of equine antisera raised against body tissues and organs.

Seroderm *Casel, Turk.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Serofene *Merck Serono, Arg.; Merck Serono, Ital.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Seroflo *Cipla, India.*
⊗Salmeterol (p. 1224·1); fluticasone propionate (p. 1638·1).
Asthma.

Cipla, Thai.
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Seroglubin *Gador, Arg.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

Seroksen *SSK, Turk.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Serolin *Kalbe, Indon.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Serolux *Sandoz, Gr.; Sandoz, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Sandoz, Venez.
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Seromex *Ratiopharm, Fin.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Seromycin *IFET(ΙΦΕΤ), Gr.; Lilly, Hong Kong†; Dura, USA.*
Cycloserine (p. 280·2).
Tuberculosis; urinary-tract infections.

Seronex
Note: this name may be used for preparations of different composition.
Medix, Mex.
Domperidone (p. 1838·1).
Gastrointestinal motility disorders; nausea and vomiting.

Pharmavita, Chile.
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Seronia *Aspen, Austral.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Seronil *Orion, Fin.; Orion, Pol.; Drogsan, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Seronip *UCI, Braz.*
Sertraline hydrochloride (p. 448·1).
Depression.

Serophene *Serono, Austral.; Merck, Braz.; Pharmascience, Canad.; Serono, Canad.; Merck, Chile; Serono, Hong Kong; Merck, Neth.†; Healthcare Logistics, NZ; Merck, Singapore; Merck, Switz.; Merck, Thai.; Serono, Turk.; Serono, USA; Serono, Venez.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; male infertility.

Serophy *Interdelta, Switz.*
Sodium chloride (p. 1795·1).
Nasal disorders.

Seropia *Clonmel, Irl.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Seroplex *Europharma, Denm.; Orifarm, Denm.; Lundbeck, Fr.*
Escitalopram oxalate (p. 416·2).
Depression; social phobia; panic disorder; anxiety; obsessive-compulsive disorder.

Seropram *Lundbeck, Arg.; Lundbeck, Austria; Lundbeck, Cz.; A-Pharma, Denm.; Lundbeck, Fr.; Lundbeck, Gr.; Lundbeck, Hung.; Lundbeck, Ital.; Lundbeck, Mex.; Lundbeck, Spain; Lundbeck, Switz.*
Citalopram hydrobromide (p. 411·1).
Anxiety; depression; obsessive-compulsive disorder; social phobia; panic disorder.

Bayer, Venez.
Citalopram (p. 411·1).
Depression.

Seroquel *Bago, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; Astellas, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; AstraZeneca, USA; AstraZeneca, Venez.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; depression; psychoses; mania.

Seroquin *Cipla, India; Clonmel, Irl.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Seror *Specifar, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Serorex *Scand Pharm, Denm.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic distress disorder.

Serosmine *ITF, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Serostim *Serono, Canad.; Serono, Hong Kong†; Serono, Mex.†; Serono, USA.*
⊗Somatropin (p. 1919·3).
AIDS-related cachexia or weight loss.

Sero-Tet *Green Cross, Malaysia; Green Cross, Philipp.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Serotone *Japan Tobacco, Jpn.*
Azasetron hydrochloride (p. 1820·2).
Nausea and vomiting associated with antineoplastic therapy.

Serotop *Sandoz, Turk.*
Sertraline (p. 448·1).

Serotor *Torrex Chiesi, Hung.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Serotramin *Medix, Mex.*
⊗Sibutramine (p. 2330·2).
Obesity.

Serotulle *SSL, UK.*
Chlorhexidine acetate (p. 1743·2).
Wounds.

Serotyp *Target, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Serox *Micro Labs, Ukr.*
⊗Serrapeptase (p. 2613·3).
Joint, peri-articular, and soft-tissue inflammation; respiratory-tract congestion; inflammatory skin disorders; breast engorgement.

Seroxat *GSK, Austria; GSK, Belg.; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.†; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; Novartis, Turk.; GSK, UK.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder; anxiety; mixed anxiety depressive states; premenstrual dysphoric disorder.

Seroxetabs *Scand Pharm, Denm.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic distress disorder.

Seroxydar *Automedic, Fr.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); aluminium phosphate (p. 1818·3); guar gum (p. 475·1).
Gastrointestinal disorders.

Seroxyl *Arkopharma, Fr.*
Tryptophan (p. 453·2); vitamin B_6 (p. 2105·3).
Tonic.

Serozil *BMS, Turk.*
Cefprozil (p. 248·2).
Bacterial infections.

Sérozinc *Roche-Posay, Fr.*
Sodium chloride (p. 1795·1); zinc sulfate (p. 2126·2).
Skin cleansing.

Serpafar *Angelini, Gr.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility; diagnosis of hormonal disorders.

Serpasil *Biochemie, Indon.*
Reserpine (p. 1485·3).
Hypertension.

Serpax
Note: this name may be used for preparations of different composition.
Medo, Ital.
Oxazepam (p. 1092·2).
Anxiety; depression; alcohol withdrawal syndrome.

Merck, Port.
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serpens *Lisapharma, Ital.*
Saw palmetto (p. 2363·3).
Prostatic hyperplasia.

Serperil *Sanovel, Turk.*
Perindopril (p. 1466·3).

Serperil Plus *Sanovel, Turk.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).

Serphamida *Serral, Mex.*
Quinfamide (p. 947·1).
Amoebiasis.

Serpicam *Serral, Mex.*
Piroxicam (p. 125·3).
Inflammation.

Serracal *Serral, Mex.*
Calcium lactate gluconate (p. 1784·2); calcium carbonate (p. 1824·3).
Calcium deficiency; tetany; osteoporosis; rickets; osteomalacia.

Serradase *Siam Bheasach, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; wounds; respiratory-tract congestion; adjunct in antibiotic therapy; adjunct in cancer chemotherapy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Serragrip *Serra Pamies, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Serralpina *Serral, Mex.*
Hyoscine butylbromide (p. 1845·3).

Serralpina Compuesta *Serral, Mex.*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Serralsina *Serral, Mex.*
Loratadine (p. 633·2).
Hypersensitivity.

Serranasal *Serra Pamies, Spain.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Serranit *Serral, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Serrano *M & H, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema; sinusitis; cystitis; epididymitis; breast engorgement.

Serrao *Masa, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; wounds; respiratory-tract congestion.

Serrapep *Asian Pharm, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; wounds; respiratory-tract congestion.

Serrapress *Pharma Dynamics, S.Afr.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Serrason *Unison, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; wounds; sinusitis; breast engorgement; cystitis; epididymitis; wisdom tooth pericoronitis.

Serratol *Serral, Mex.*
Difenidol (p. 1835·1).
Vertigo; nausea and vomiting.

Serratos *Serra Pamies, Spain.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Serrazyme *Shin Poong, Singapore.*
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion.

Serrin *MacroPhar, Malaysia; Macrophar, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion; wounds; sinusitis; breast engorgement; cystitis; epididymitis; wisdom tooth pericoronitis; alveolar abscess.

Serriten *Serral, Mex.*
Verapamil (p. 1522·1).
Hypertension.

Serta *Unichem, India.*
Sertraline hydrochloride (p. 448·1).
Depression; mixed anxiety depressive states; panic disorder; obsessive-compulsive disorder; post-traumatic stress disorder.

Sertabal *Baldacci, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Sertac *Andromaco, Chile.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Sertacream *Geymonat, Ital.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections.

Sertadepi *Actavis, Hung.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; social phobia; panic disorder; post-traumatic stress disorder.

Sertaderm *Ferrer, Ital.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections.

Sertadie *Geymonat, Ital.*
Sertaconazole nitrate (p. 593·2).
Vaginal candidiasis.

Sertagen *Generics, Hung.; Focus, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder; panic disorder; social phobia.

Sertagyn *Ferrer, Ital.*
Sertaconazole nitrate (p. 593·2).
Vaginal candidiasis.

Sertahexal *Hexal, Pol.†*
Sertraline hydrochloride (p. 448·1).
Depression.

Sertal *Roemmers, Arg.*
Pargeverine (p. 1877·1) or pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm.

Sertal Compuesto *Roemmers, Arg.*
Pargeverine (p. 1877·1) or pargeverine hydrochloride (p. 1877·1); clonixin lysine (p. 40·1).
Smooth muscle spasm.

Sertan *Alkaloida, Hung.*
Primidone (p. 547·1).
Epilepsy.

Sertero *Arrow, Braz.*
Paroxetine hydrochloride (p. 440·3).

Serteva *Med, Turk.*
Sertraline (p. 448·1).

Sertex *Psicofarma, Mex.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Sertidel *Serral, Mex.*
Diltiazem (p. 1359·2).
Hypertension.

Sertidine *Serral, Mex.*
Famotidine (p. 1842·1).
Peptic ulcer.

Chew, Thai.
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; mastocytosis.

Sertikan *Novartis, Ukr.†*
Everolimus (p. 1957·3).
Cardiac or renal transplant rejection.

Sertinal *Bouzen, Arg.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Serti-O *Patar, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Sertivan *Hexal, Cz.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Sertopic *CPH, Port.*
Sertaconazole nitrate (p. 593·2).
Vulvovaginal candidiasis; fungal skin infections.

Sertra *Aspen, Austral.; TAD, Ger.†; Pharmacia, S.Afr.; Medifive, Thai.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; premenstrual dysphoric disorder; mixed anxiety-depressive states; mania; post-traumatic stress disorder.

Sertrabrain *Brainpharma, Spain.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Sertracor *Pharmacor, Austral.*
Sertraline hydrochloride (p. 448·1).
Depression; premenstrual dysphoric disorder.

Sertragen *Streuli, Switz.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Sertra-Isis *Actavis, Ger.†*
Sertraline hydrochloride (p. 448·1).
Depression.

Sertral *Vianex (Βιανέξ), Gr.; Spirig, Switz.†*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Sertraloft *Zdorovje, Ukr.†*
Sertraline hydrochloride (p. 448·1).
Depression.

Sertralon *Krewel, Ger.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; social phobia; post-traumatic stress disorder.

Sertralpharm *Actavis, Port.†*
Sertraline hydrochloride (p. 448·1).
Depression.

Sertramerck *Generics, Spain.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Sertraniche *Niche, Irl.*
Sertraline hydrochloride (p. 448·1).
Depression.

Sertranorm *Plus Pharma, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Sertravis *Actavis, Denm.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Sertrin *Sandoz, Switz.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Sertrix *Hexal, Denm.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Sertrixen *Serral, Mex.*
Naproxen (p. 98·2).
Inflammation; pain.

Sertrom *Serral, Mex.*
Roxithromycin (p. 356·2).
Bacterial infections.

Sertrone *KRKA, Denm.; KRKA, Swed.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Sertwin *Zentiva, Hung.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder.

Sertzol *Simayla, S.Afr.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Serum 15 *Dispolab, Chile.*
Ascorbic acid (p. 2110·3).
Light-induced skin damage.

Serum Fizyolojik *Biofarma, Turk.; Galen, Turk.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Serutan *Menley & James, USA.*
Psyllium seed (p. 1849·1).
Constipation.

Servambutol *Sandoz, Thai.†*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Servamox
Note: this name may be used for preparations of different composition.
Sandoz, Mex.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sandoz, Thai.
Amoxicillin (p. 216·2).
Bacterial infections.

IDI, Ital.†
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Servamox CLV *Sandoz, Mex.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Servamox-F *Sandoz, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Servantax *Vannier, Arg.*
Sertraline (p. 448·1).
Depression.

Servatrin *Aspen, S.Afr.*
⊗Timolol maleate (p. 1513·2); amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Servazolin *Sandoz, Neth.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Servicef
Note: this name may be used for preparations of different composition.
Sandoz, Mex.
Cefalexin (p. 234·1).
Bacterial infections.

Serviclazide *Sandoz, Thai.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Serviclor *Sandoz, Cz.; Sandoz, Mex.; Sandoz, Pol.†*
Cefaclor (p. 232·3).
Bacterial infections.

Servidipine *Novartis, Singapore.†*
Nifedipine (p. 1447·2).
Angina pectoris; Raynaud's syndrome.

Servidoxyne *Sandoz, Thai.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Serviflox *Sandoz, Malaysia; Sandoz, Venez.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Sandoz, Singapore.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Servigenta *Sandoz, Mex.; Sandoz, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Servin *Condrugs, Thai.*
Mianserin hydrochloride (p. 434·2).
Depression.

Serviproxan *Sandoz, Thai.†*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain.

Servira *Kylemore, USA.*
Atropine sulfate (p. 1310·2); hyoscyamine sulfate (p. 1848·1); phenobarbital (p. 535·2); hyoscine hydrobromide (p. 1845·3).
Gastrointestinal disorders.

Serviradine *Sandoz, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Servispor *Sandoz, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Servitrim *Sandoz, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Servitrocin *Sandoz, Thai.†*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Servizol *Sandoz, Mex.†; Sandoz, Philipp.*
Metronidazole (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis; anaerobic bacterial infections.

Sesal *Ophtha, Denm.*
⊗Antazoline hydrochloride (p. 615·3); naphazoline hydrochloride (p. 1669·3).
Allergic conjunctivitis.

Sesame Street *McNeil Consumer, USA.*
Vitamins.

Sesamoil *Gezzi, Arg.*
Bismuth salicylate (p. 1821·3).
Diarrhoea.

Sesaren *Roemmers, Arg.; Roemmers, Chile†; Roemmers, Venez.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social anxiety disorder; anxiety.

Sesden *Tanabe, Indon.; Mitsubishi Tanabe, Jpn; Mitsubishi Tanabe, Singapore.†*
Timepidium bromide (p. 1894·1).
Smooth muscle spasm; premedication for examination of the gastrointestinal or urinary tract; pancreatitis.

Seskadeks *SSK, Turk.*
Sulfogaiacol (p. 1678·1); pentoxyverine citrate (p. 1672·1); diphenhydramine hydrochloride (p. 626·2).
Cough; respiratory-tract congestion.

Seskaljin *SSK, Turk.*
Dipyrone (p. 53·3).
Pain; fever.

Seskamol *SSK, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Seskasid *SSK, Turk.*
Dihydroxyaluminum sodium carbonate (p. 1835·2).
Gastric hyperacidity; peptic ulcer.

Seskasilin *SSK, Turk.*
Ampicillin (p. 218·2).
Bacterial infections.

Seskatidin *SSK, Turk.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Sessoforte *Denk, Hong Kong.†*
⊗Vitamins; methyltestosterone (p. 2291·3); kola (p. 2648·2); damiana (p. 2491·3);

yohimbine (p. 2372·3); strychnos; ephedra (p. 1663·1); testis extract (p. 2304·3).
Tonic.

Sessor *Royal, Chile.*
Eflornithine hydrochloride (p. 932·1).
Facial hirsutism in women.

Sestrine *Beta, Arg.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Setac *Benedetti, Ital.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Setacol *Hamilton, Austral.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm.

Setakaf *Kurtsan, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Setal *Polfarmex, Pol.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic vestibular disorders.

Setaloft *Plus Pharma, Cz.; Plus Pharma, Hung.; Actavis, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Setamol *Hovid, Hong Kong; Hovid, Singapore; Yeni, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Setanol *Vilco, Gr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Setaratio *Ratiopharm, Pol.†*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; anxiety; post-traumatic stress disorder.

Setard *Charoon Bhesaj, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Setarox *Putchubun, Thai.*
Indications not specified 03.13, usual generic list unavailable to check: Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Setatrep *Teva, Mex.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Setegis *Egis, Hung.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Setilin *Olgunsoy, Turk.*
Chlorhexidine (p. 1743·2); cetrimide (p. 1742·1).
Skin disinfection.

Setin *Thebe, S.Afr.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting; aid to gastrointestinal examination.

Siam Bheasach, Thai.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Setinin *Actavis, Denm.; Actavis, Hung.; Actavis, Irl.; Plus Pharma, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Setiral *Toprak, Turk.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Setisin *CCM, Malaysia; Duopharma, Singapore.*
Neostigmine metilsulfate (p. 687·2).
Reversal of competitive neuromuscular blockade; myasthenia gravis; ileus; postoperative urinary retention.

Setlers
Note: this name may be used for preparations of different composition.
Thornton & Ross, UK.
Calcium carbonate (p. 1824·3).
Flatulence; dyspepsia; heartburn; nausea.

Setlers Heartburn & Indigestion Liquid *Stafford-Miller, UK.*
Calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1); sodium alginate (p. 2167·3).
Dyspepsia; heartburn; gastro-oesophageal reflux.

Setmenate *Pharmaniaga, Hong Kong.*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; vertigo.

Setmoxil *Pharmaniaga, Hong Kong.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Setofilm *Norgine, Denm.; Norgine, Fr.; BioAlliance, Irl.; Norgine, Neth.; Norgine, Spain; Norgine, UK.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Setonox *Putchubun, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Seto-o *Putchubun, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Setorilin *Farmochimica, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Setous *Takata, Jpn.*
Zotepine (p. 1119·1).
Schizophrenia.

Setrilan *Essex, Ital.*
Spirapril hydrochloride (p. 1499·3).
Hypertension.

Setriox *SF, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Setrodan *SJA, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Setrof *Hovid, Malaysia.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Setrogen *Mylan, Denm.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Setron
Note: this name may be used for preparations of different composition.
Eczacibasi, Turk.
Granisetron (p. 1844·3).
Nausea and vomiting induced by cytotoxic therapy or radiotherapy; postoperative nausea and vomiting.

Perrigo, Israel.
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting induced by cytotoxic therapy.

Setrona *Ranbaxy, Austral.; Douglas, NZ.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder.

Setronax *DHA, Malaysia; DHA, Singapore.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Setronil *Chemopharma, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression; panic attacks.

Setronon *Teva, Cz.†; Pliva Krakow, Pol.; Pliva, Rus.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Pliva, Ukr.
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Setrovel *Novell, Indon.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting induced by cancer chemotherapy.

Setustop *Johnson & Johnson, Port.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Setux *Sanofi-Aventis, Braz.*
Codeine resinate (p. 40·2); phenyltoloxamine resinate (p. 638·1).
Cough.

Setux Expectorante *Sanofi-Aventis, Braz.*
Codeine resinate (p. 40·2); guaifenesin (p. 1666·2); phenyltoloxamine resinate (p. 638·1).
Cough.

Set-Vit *Gerolymatos, Gr.*
Ascorbic acid (p. 2110·3); calcium fructoheptonate; magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1); lysine (p. 2079·3).

Seudotabs *Parmed, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sevacol *Indeco, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Seven Seas *Abdi, Turk.*
Vitamins.

Merck, Philipp.
Vitamins; minerals.
A range of nutritional supplements.

Merck, Thai.
Vitamins; minerals; with or without fish oils.

Seven Seas, Hong Kong.
A range of tonics, dietary supplements, and multivitamin preparations.

Seven Seas, Singapore.
Vitamins; with or without minerals.

Seven Seas, UK.
Vitamins; minerals; nutritional supplements.

Cana, Gr.
Cod-liver oil (p. 2056·3).

Seven Seas Active Sport *Seven Seas, Irl.†*
Omega 3 nutrients; gamma linolenic acid; vitamin E (p. 2119·1); betacarotene (p. 2051·1); minerals; glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); ginger (p. 1844·1); ginseng (p. 2513·3).
Nutritional supplement.

Seven Seas Cranberry Forte *Seven Seas, Singapore.*
Cranberry (p. 2488·1).
Dietary supplement.

Seven Seas EPO Plus Starflower Oil *Seven Seas, Singapore.*
Evening primrose oil (p. 2502·2); borage oil (p. 2459·2); vitamin E (p. 2119·1).
Dietary supplement.

Seven Seas JointCare *Seven Seas, Singapore.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); fish oil (p. 1460·3).
Degenerative joint disorders.

Seven Seas JointCare High Strength *Seven Seas, Singapore.*
Cod-liver oil (p. 2056·3); fish oil (p. 1460·3); vitamins.
Joint disorders.

Seven Seas JointCare Max *Seven Seas, Singapore.*
Tablets, glucosamine sulfate (p. 2515·3); capsules, fish oil (p. 1460·3); cod-liver oil (p. 2056·3); fish collagen (p. 2483·2); vitamins.
Degenerative joint disorders.

Seven Seas Pulse *Abdi, Turk.*
Cod-liver oil (p. 2056·3).
Ischaemic heart disease; hyperlipidaemias.

Seven Seas Pulse High Strength Triomega *Seven Seas, Singapore.*
Triomega fish oil (p. 1460·1); omega-3 fatty acids (p. 1460·1); vitamin E (p. 2119·1).

Seven Seas Zinc Plus Vitamin C *Seven Seas, Singapore.*
Vitamin C (p. 2110·3); zinc (p. 2126·1).
Dietary supplement.

Sevenal *Valeant, Hung.*
Phenobarbital (p. 535·2).
Epilepsy.

Sevenaletta *Alkaloida, Hung.*
Phenobarbital (p. 535·2).
Epilepsy.

Several *Duncan, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Severin *Chinoin, Mex.*
Nimesulide (p. 101·3).
Pain; fever; inflammation.

Sevikar *MSD, Austral.; Daiichi Sankyo, Austria; Daiichi Sankyo, Belg.; Daiichi Sankyo, Denm.; Daiichi Sankyo, Fin.; Daiichi Sankyo, Fr.; Daiichi Sankyo, Ger.; Pfizer, Gr.; Daiichi Sankyo, Irl.; Daiichi Sankyo, Neth.; Nycomed, Norw.; Daiichi Sankyo, Port.; Daiichi Sankyo, Spain; Daiichi Sankyo, Switz.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Sevikar HCT *Daiichi Sankyo, Ger.; Daiichi Sankyo, Neth.; Daiichi Sankyo, Spain; Daiichi Sankyo, Switz.; Daiichi Sankyo, UK.*
⊗Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sevikar Plus *Daiichi Sankyo, Irl.*
⊗Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sevium *Ni-The, Gr.*
Haloperidol (p. 1077·1).
Psychoses; Huntington's chorea; tics.

Sevlenyl *SJA, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

Sevo *Pharmawealth, Philipp.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Sevocris *Cristalia, Braz.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Sevocristalia *Conifarma, Arg.*
Sevoflurane (p. 1912·3).

Sevofrane *Abbott, China.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Sevorane *Abbott, Arg.; Abbott, Austral.†; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; AbbVie, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; AbbVie, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, Singapore; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, Venez.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Sevorex *CCS, Swed.*
Precipitated sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Scalp disorders.

Sevotam *Ifars, Indon.*
Piracetam (p. 393·3).
Mental function disorders; alcoholism.

Sevredol *Mundipharma, Austral.; Mundipharma, Cz.; Mundipharma, Fr.; Mundipharma, Ger.; Extractum, Hung.; Mundipharma, Hung.; Mundipharma, Irl.; Mundipharma, Neth.†; Douglas, NZ; Norpharma, Pol.; Mundipharma, Port.; Mundipharma, Spain; Mundipharma, Switz.; Napp, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

Sevre-Long *Mundipharma, Switz.*
⊗Morphine sulfate (p. 92·3).
Pain.

Sezolam *Promed, Indon.*
Midazolam (p. 1085·1).
Sedative; premedication; general anaesthesia.

SF Gel *Cypress, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

SF 5000 Plus *Cypress, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

SFC Lotion *Stiefel, USA.†*
Stearyl alcohol (p. 2214·2).
Skin cleanser.

Sfinac *Velka, Gr.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

SG33 *Sigma, Arg.*
Magnesium oxide (p. 1857·3).
Gastro-oesophageal reflux; hypomagnesaemia; constipation.

SG-Glutergen *Terramedic, Philipp.*
Vitamins; cholic acid (p. 2457·2); grain oil; hematoporphyrin hydrochloride; lecithin (p. 2542·2); linseed oil (p. 2544·2); magnesium glutamate (p. 1786·3); potassium chloride (p. 1793·2); ginseng (p. 2513·3); sunflower seed oil; troxerutin (p. 2505·3).
Nutritional supplement.

SGM LLM *Sari Husada, Indon.*
Infant feed.
Low-lactose feed.

Sguardi *Oftagen, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye disinfection.

SGX *Medisys, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

SH3 *Polifarma Benessere, Ital.*
Pyrethrin (p. 2161·1).
Pediculosis.

SH-206 *Assos, Turk.*
Sodium lauril ether sulfate (p. 2210·3); lemon oil (p. 2543·1); acetic acid (p. 2426·3); camphor (p. 2466·2).

Sha Di *Jiasite, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Sha Ba Ke *Open, China.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Sha Bo Te *KeRui, China.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sha Fei *TianJing, China.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Sha Pei Lin *Luya, China.*
A streptococcus A vaccine.

Sha Pu Ai Si *Sha Pu Ai Si, China.*
Bendazac lysine (p. 29·1).

Sha Sai Bo Tong *Huayuan, China.*
Puerarin.

Sha Tai Qi *Nanyang Tianheng, China.*
Telmisartan (p. 1509·3).
Hypertension.

Sha Ting Ning *Weite, China.*
Telmisartan (p. 1509·3).
Hypertension.

Sha Wei Luo *Chengyi, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Sha Yan Long *NEGPF, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Shade
Note: this name may be used for preparations of different composition.
Eveline Charles, Canad.
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Schering-Plough, Chile; Schering-Plough, USA.
SPF 30; SPF 45: Lotion SPF 30; stick SPF 30:
Homosalate (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Schering-Plough, USA.
Gel SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); homosalate (p. 1705·1).
Sunscreen.

Schering-Plough, USA.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Schering-Plough, USA.
SPF 45: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octocrilene (p. 1715·2); octisalate (p. 1715·2).
Sunscreen.

Shade UVAGuard *Schering-Plough, USA.*
Octinoxate (p. 1715·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3).
Sunscreen.

Shajunda *Yangtze River, China.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Shakanzoto *Tsumura, Jpn.*
⊗Rehmannia root; ophiopogon tuber; cinnamon bark (p. 2479·2); jujube; ginseng (p. 2513·3); hemp fruit; ginger (p. 1844·1); liquorice (p. 1853·2); gelatin (p. 1154·1).
Traditional Kampo medicine.

Shaklee DR *Shaklee, Canad.*
Zinc gluconate (p. 2126·2).

Shaklee Lip Protection Stick *Shaklee, Canad.†*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.

Shakti *Progen, Ital.*
Glycolic acid (p. 1704·3).
Skin disorders.

Shakuyakukanzoto *Tsumura, Jpn.*
Liquorice (p. 1853·2); peony root.
Traditional Kampo medicine.

Shalosh B *CTS, Israel.*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1).
Vitamin B supplement; neurological pain; metabolic disorders.

Shampoo Anti Caspa Fortificante *Vichy, Chile.*
Selenium sulfide (p. 1719·3); salicylic acid (p. 1719·1).
Dandruff.

Shampoo Anti-Caspa
Note: this name may be used for preparations of different composition.
Vichy, Chile.
Selenium sulfide (p. 1719·3); salicylic acid (p. 1719·1).
Dandruff.

Shampoo Anticaspa
Note: this name may be used for preparations of different composition.
Beiersdorf, Chile.†
Climbazole (p. 576·2); piroctone (p. 1716·3).
Dandruff.

Shampoo Control *AG Hair, Canad.*
Pyrithione zinc (p. 1718·1).

Shampoo del Tio Nacho *Bustillos, Mex.†*
Norway tar (p. 1723·3); resorcinol (p. 1718·3).
Skin disorders; scalp disorders.

Shampooing Anti-Pelliculaire *Atlas, Canad.; MLP, Canad.; Ultrapac, Canad.*
Pyrithione zinc (p. 1718·1).
Dandruff.

Shampoux *Qualiphar, Belg.†*
Permethrin (p. 2159·3); piperonyl butoxide (p. 2160·2).
Pediculosis.

Shampoux Repel *Qualiphar, Belg.*
(N-Butyl-N-acetyl)-3-ethylaminopropionate (p. 2154·3).
Pediculosis.

Shan An *Xinshitong, China.*
Sodium new houttuyfonate.

Shan Cheng *Yungong, China.*
Ramosetron hydrochloride (p. 1881·3).

Shan De Kang *Conba, China.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Shan Mu Shi *Dexin Runsheng, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Shan Pu Lan *Tianxin, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Shan Qing *Beiyi Union, China.*
Effervescent tablets: Benproperine phosphate (p. 1656·2).

Shanqing, China.
Ointment: Metronidazole (p. 936·1); chlorhexidine acetate (p. 1743·2); clotrimazole (p. 576·2).

Shan Su *Hailing, China; Yangtze River, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Shan Yi Ting *Feihong, China.*
Nimesulide (p. 101·3).
Pain.

Shanferon *Shantha, Philipp.*
Interferon alfa-2b (p. 989·2).
Chronic hepatitis B and C; malignant neoplasms; anogenital warts.

Shang Bang *Ya Bang Sheng Yuan, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Shang Er Ning *Yijian, China.*
Telmisartan (p. 1509·3).
Hypertension.

Shang Qing *Chia Tai, China.*
Levodropropizine.
Cough.

Shang Sheng Gan Di *Shanghai Bio, China.*
A hepatitis B immunoglobulin.
Passive immunisation.

Shang Sheng Lei Tai *Shanghai Bio, China.*
Interferon gamma (human, recombinant) (p. 999·1).
Infections in chronic granulomatous disease; malignant osteopetrosis.

Shang Yan *Xinbai, China.*
Tiapride hydrochloride (p. 1111·2).
Behaviour disorders; dyskinesias.

Shanpoietin *Shantha, Philipp.*
⊗Erythropoetin (p. 1141·1).
Anaemias; autologous blood transfusion.

ShanQing *Quanxin, China.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Shanvac-B *Shantha, India; Shantha, Philipp.; Microgen, Rus.; Shantha, Thai.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Shao Rong *Lukang Chenxin, China.*
Lomerizine hydrochloride (p. 676·3).

Sharko Inside *Sahabat, Indon.*
Shark cartilage (p. 2471·3).
Angiogenesis inhibitor; rheumatism; inflammation.

Sharkoferrol *Alembic, India.*
Ferric ammonium citrate (p. 2060·1); calcium gluconate (p. 1783·3); malt extract (p. 2080·2); vitamins.
Dietary supplement; tonic.

Sharkomalt *Haffkine, India.†*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); malt extract (p. 2080·2).
Vitamin A and D deficiency.

Sharkovit *Haffkine, India.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Vitamin A and D deficiency.

Sharox *Fahrenheit, Indon.*
Cefuroxime (p. 255·2).
Bacterial infections.

Fahrenheit, Philipp.†
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Shave Cream *Mentholatum, Canad.*
Benzoyl peroxide (p. 1696·1).

She Er *Yi Chuang, China.*
Cefixime (p. 240·3).
Bacterial infections.

She Lan *Haishen Tongzhou, China.*
L-Glutamine (p. 2070·3); azulene (p. 2452·1).

She Tai *Haishen Tongzhou, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

She Xin *Haishen Tongzhou, China.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

She Yue *Haishen Tongzhou, China.*
Clindamycin palmitate hydrochloride (p. 269·3).
Bacterial infections.

Sheer Focus *Smashbox, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Sheer Lustre *Balley, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sheer Moisture *Dermalogica, Canad.*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Sheer Protection *Jane & Co, Canad.†*
Octinoxate (p. 1715·1).
Sunscreen.

Sheer Tint Moisture *Dermalogica, Canad.*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Sheer Tint Redness Relief *Dermalogica, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sheik Elite *Schmid, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Shellgel *Cytosol, USA.*
Sodium hyaluronate (p. 2526·2).
Aid in ophthalmic surgery.

Shelly *Abic, Israel.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraception.

Shelly's HC *Health Plus, Canad.†*
Vitamins; zinc (p. 2126·1).

Shelrod-Plus *Medikon, Indon.†*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Musculoskeletal and joint disorders; fever.

Shelrofen *Medikon, Indon.†*
Ibuprofen (p. 68·2).
Pain.

Shemol *Grin, Mex.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Shen Jia *Shyndec, China.*
Cefalexin (p. 234·1).
Bacterial infections.

Shen Jie *Qilu, China.*
Monosialotetrahexosylganglioside sodium (p. 2510·2).

Shen Kai Neng *Hui Pu Sen, China.*
Vitamin B_6 (p. 2105·3).

Shen Luo *Shyndec, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Shen Mai Qi *Jiade, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Shen Ning *Chia Tai, China.*
⊗Mannitol (p. 1427·3).

Shen Shui Qing *Shouhe Jinhai, China.*
⊗Dextran 40 (p. 1138·1).

Shen You *Shyndec, China.*
Cefradine (p. 249·1).
Bacterial infections.

Sheng Di *Changliang, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Sheng Ai *Hayao, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sheng Ao *Hengrui, China.*
Rosiglitazone (p. 496·3).
Diabetes mellitus.

Sheng Ao Ding *Shanghai No 1, China.*
Octreotide acetate (p. 1924·1).
Variceal haemorrhage; acromegaly; endocrine tumours; prevention of complications following pancreatic surgery; HIV-associated diarrhoea.

Sheng Bang Jie *Sibangde, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sheng Chang *Kangya, China.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Sheng Cheng *Haibin, China.*
Topotecan hydrochloride (p. 872·3).
Malignant neoplasms.

Sheng Di Feng *Sanhome, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Sheng Fu Shuang *Sanhome, China.*
Liranaftate (p. 588·1).

Sheng Han *Lukang Chenxin, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Sheng Jin Nuo *Jiu Tai, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Sheng Jun *Hua Lu, China.*
Isoniazid (p. 311·2).
Tuberculosis.

Sheng Mai Fu *Yuhuang, China.*
Aminobutyric acid (p. 2509·2).

Sheng Min *Shengjitang, China.*
Rosiglitazone hydrochloride (p. 496·3).
Diabetes mellitus.

Sheng Neng *Sanhome, China.*
Amino acids; vitamins.
Tonic; dietary protein supplement.

Sheng Nuo De *Sanhome, China.*
Clarithromycin (p. 266·2).
Bacterial infections.

Sheng Nuo *Sanhome, China.*
Ornidazole (p. 943·1).
Amoebiasis; anaerobic bacterial infections.

Sheng Nuo An *Sanhome, China.*
Ornidazole (p. 943·1).
Amoebiasis; anaerobic bacterial infections.

Sheng Nuo Kang *Sanhome, China.*
Ornidazole (p. 943·1).
Bacterial vaginosis; trichomoniasis.

Sheng Nuo Ling *Sanhome, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Sheng Nuo Wei *Sanhome, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Sheng Ping *Shengjitang, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sheng Qi *RenFu, China.*
Deproteinised calf blood extract (p. 2444·1).

Sheng Xi Kai *Topsun, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sheng Di Xin *Sanhome, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Sheng Yi Ge *Sanhome, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Shengda *Juneng, China.*
Dipyridamole (p. 1362·2).
Coronary heart disease.

ShengDi *Xin Ma, China.*
Aceglutamide (p. 2426·2).

Shengfu *Hailing, China; Yangtze River, China.*
Nefopam hydrochloride (p. 100·2).
Pain.

Shenghe *Sanhome, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough.

Shengminqing *Sanhome, China.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

SheNiTing *GSK, China; Meirui, China.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Shenliyu *Taiyang, China.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; gastritis; gastrinoma.

Shensuo *Lukang Chenxin, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Shepard's *Dermik, USA.*
Emollient and moisturiser.

Shepherd *Ke Lun, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Shi Di *Qilu, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Shi De *Tongyong, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Shi Ai Ke *Yujin, China.*
Staphylokinase (recombinant) (p. 1502·3).

Shi Ai Te *Huaxin, China.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Shi Bao Fu *Tianfeng Shibaofu, China.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Shi Dan *Huashidan, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids.

Shi Duo Tai *Hui Pu Sen, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Shi Er Ping *Minsheng, China.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Shi Er Tong *Zhongxin, China.*
⊗Spironolactone (p. 1499·3).
Oedema; ascites; aldosteronism; heart failure; hypertension.

Shi Er Xin *Jinhaifa, China.*
Vitamin B_{12} (p. 2107·2).

Shi Hua Luo *Baicao, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Shi Hui Da *Shihuida, China.*
Levamlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Shi Ji *Meijisi, China.*
Telmisartan (p. 1509·3).
Hypertension.

Shi Ke Yi *Sine, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Shi Li Ke *Baiyunshan, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Shi Lin *A o Li Da Nai De, China.*
Glutamine (p. 2070·3).

Shi Luo Te *Nhwa, China.*
Naproxen (p. 98·2).
Pain; fever; inflammation.

Shi Ni Kang *Shenyang First, China.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Shi Ning *Baiyunshan, China.*
Paracetamol (p. 115·1).
Fever; pain.

Shi Nuo Da *Dadeli, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Shi Nuo Min *Si Bao, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Shi Pu Huan *Hayao, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Shi Pu Li Er *Changchun, China.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Shi Rui Bo *Gencom, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Shi Rui Ke *Gencom, China.*
Cefixime (p. 240·3).
Bacterial infections.

Shi Rui Ping *Gencom, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Shi Tai Le *Jutai, China.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Shi Tai *Zhi Jun, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Shi Tai Shu *Kang Yuan, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Shi Wei *Rongchang, China.*
Famotidine (p. 1842·1); sodium carbonate (p. 2617·3); magnesium hydroxide (p. 1857·2).

Shi Wei Bao *Healthcare Pharma, China.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Shi Xiang *Huangshi Weisheng, China.*
Diclofenac diethylamine (p. 48·3).

Shi Yi *Xincat, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

ShiBo *Hejigong, China.*
Ethyl chloride (p. 1987·1).
Local anaesthesia.

Shichimotsukokato *Tsumura, Jpn.*
Peony root; angelica acutiloba root (p. 2443·3); astragalus root (p. 2451·1); rehmannia root; cnidium rhizome; uncaria hook; phellodendron bark.
Traditional Kampo medicine.

Shida *NCPC, China.*
Verapamil hydrochloride (p. 1522·1).

Shield *GSK, India.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); zinc oxide (p. 1729·1); allantoin (p. 1693·1).
Anorectal disorders.

Shigelat *Gritvak, Rus.*
A shigella vaccine (strain 5063) (p. 2418·2).
Active immunisation.

Shigyakusan *Tsumura, Jpn.*
Bupleurum root; peony root; immature orange; liquorice (p. 1853·2).
Traditional Kampo medicine.

Shii-ta-ker *Holistica, Fr.*
Lentinula edodes.
Immunostimulant.

Shikunshito *Tsumura, Jpn.*
Atractylodes lancea rhizome; ginseng (p. 2513·3); poria sclerotium; liquorice (p. 1853·2); ginger (p. 1844·1); jujube.
Traditional Kampo medicine.

Shilajit *Garuda, Hung.*
Minerals; oligosaccharides; amino acids; phytosterols (p. 1471·2); plant acids; benzoates (p. 1738·2); enzymes; vitamins.
Tonic.

Shilexin *Tianxin, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Shilijing *Southwest, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Shilshul X *CTS, Israel.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Shimbuto *Tsumura, Jpn.*
Poria sclerotium; peony root; atractylodes lancea rhizome; ginger (p. 1844·1); aconite root (p. 2428·3).
Traditional Kampo medicine.

Shiming *Yaoyou, China.*
Calcium folinate (p. 2066·3).
Adjunct to fluorouracil in colorectal cancer; reduction of methotrexate toxicity; megaloblastic anaemia.

Shimotsuto *Tsumura, Jpn.*
Rehmannia root; peony root; cnidium rhizome; angelica acutiloba root (p. 2443·3).
Traditional Kampo medicine.

Shimpito *Tsumura, Jpn.*
⊗Ephedra herb (p. 1663·1); apricot kernel (p. 2445·3); magnolia bark; citrus unshiu peel; liquorice (p. 1853·2); bupleurum root; perilla herb.
Traditional Kampo medicine.

Shinapen *Yung Shin, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Shinasyn *YSP, Malaysia.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Shin-Biofermin S *Takeda, Hong Kong.*
Bifidobacterium bifidum (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Enterococcus faecalis* (p. 2596·3).
Constipation; diarrhoea; meteorism.

Shinbit *Hospira, Jpn.*
Nifekalant hydrochloride (p. 1455·1).
Ventricular arrhythmias.

Shincef *Shin Poong, Philipp.; Shin Poong, Singapore.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Shincort *Yung Shin, Hong Kong; YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore; Yung Shin, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Shine Bio ACE with Selenium *YSP, Malaysia.*
Carotenoids; vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3).
Dietary supplement.

Shine Bio-Cal *Yung Shin, Singapore.*
Lithothamnion calcareum; calcium (p. 1783·1); colecalciferol (p. 2113·1); magnesium (p. 1786·3); iodine (p. 2336·3); boron (p. 2052·3); selenium (p. 2086·3).
Dietary supplement.

Shine Bio-Cal Junior *YSP, Malaysia.*
Calcium (p. 1783·1); colecalciferol (p. 2113·1).
Dietary supplement.

Shine Cutie *YSP, Malaysia.*
Ascorbic acid (p. 2110·3); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Shine Fememino *YSP, Malaysia.*
Soya isoflavones (p. 2620·3); calcium (p. 1783·1); phosphorus (p. 2589·2); colecalciferol (p. 2113·1).
Dietary supplement.

Shine Growell *YSP, Malaysia.*
Ginseng (p. 2513·3); gastrodia; astragalus (p. 2451·1); panax notoginseng; polygala tenuifolia; ocimum gratissimum; houttuynia cordata; hoelen; euryale ferox; atractylodes macrocephala.
Reduced appetite.

Shine Junior Multivitamin *YSP, Malaysia.*
Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Shine Maxtra *YSP, Malaysia.*
Ginseng (p. 2513·3); rhodiola sacra; cordyceps sinensis; cynanchum auriculatum; cinnamomum cassia (p. 2471·3); trigonella foenum (p. 2504·1); pinus koraiensis; hoelen; dioscorea opposita.
Dietary supplement.

Shine Multivitamin Plus *YSP, Malaysia.†*
Vitamins; lysine hydrochloride (p. 2079·3).
Dietary supplement.

Shinfomycin *YSP, Malaysia.†*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Shin'iseihaito *Tsumura, Jpn.*
Gypsum (p. 2173·1); ophiopogon tuber; skullcap root (p. 2617·1); gardenia fruit; anemarrhena rhizome; lilium bulb; magnolia flower; loquat leaf; cimicifuga rhizome (p. 2478·1).
Traditional Kampo medicine.

Shinoxol *YSP, Malaysia; Yung Shin, Singapore.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with viscous mucus.

Shintamet *YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore; YSP, Thai.†*
Cimetidine (p. 1827·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders; acid aspiration; Zollinger-Ellison syndrome; heartburn; pancreatic insufficiency.

Shiomarin *Hailing, China; Shionogi, Jpn.*
Latamoxef sodium (p. 315·2).
Bacterial infections.

Shipeike *Bausch & Lomb, China.*
Sodium hyaluronate (p. 2526·2).

Shiseido Benefiance Daytime *Shiseido, Canad.; Shiseido, Canad.*
Cream SPF 15: Emulsion SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Shiseido Extra Smooth Sun Protection *Shiseido, Canad.*
SPF 34; SPF 38: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Shiseido Pureness Anti-Shine *Shiseido, Canad.†*
Salicylic acid (p. 1719·1).

Shiseido Skincare Day Moisture Protection *Shiseido, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Shiseido Skincare Protective Lip *Shiseido, Canad.*
Octinoxate (p. 1715·1).
Sunscreen.

Shiseido Sun Protection *Shiseido, Canad.*
SPF 35; SPF 36: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Shiseido Sun Protection Eye Cream *Shiseido, Canad.*
SPF 32: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Shiseido Sun Protection Lip Treatment *Shiseido, Canad.†*
SPF 36: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Shiseido Ultra Sun Protection *Shiseido, Canad.*
SPF 50: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Shiseido White Protective Moisturizer *Shiseido, Canad.†*
SPF 35: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Shishitai *Jida, China.*
Somatostatin (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery; gastrointestinal fistulae; diabetic ketoacidosis.

Shiunko *Tsumura, Jpn.*
Sesame oil (p. 2614·1); angelica acutiloba root (p. 2443·3); lithospermum root.
Traditional Kampo medicine.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Shofusan *Tsumura, Jpn.*
Gypsum (p. 2173·1); rehmannia root; angelica acutiloba root (p. 2443·3); lappa fruit (p. 2540·1); atractylodes lancea rhizome; saposhnikovia root; akebia stem; anemarrhena rhizome; liquorice (p. 1853·2); sophora root; schizonepeta tenuifolia; sesame; cicada periostracum.
Traditional Kampo medicine.

Shohangekabukuryoto *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; ginger (p. 1844·1).
Traditional Kampo medicine.

Shokenchuto *Tsumura, Jpn.*
Cinnamon bark (p. 2479·2); peony root; jujube; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Shomakakkonto *Tsumura, Jpn.*
Pueraria root; peony root; cimicifuga rhizome; liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Shorant *Sanofi-Aventis, Mex.*
⊗Insulin glulisine (p. 475·3).
Diabetes mellitus.

Shors Mesan *TO-Chemicals, Thai.†*
Niclosamide (p. 161·2).
Taeniasis.

Shortec *Qdem, UK.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Shosaikoto *Kracie, Jpn; Tsumura, Jpn.*
Bupleurum root; pinellia tuber; skullcap root (p. 2617·1); jujube; ginseng (p. 2513·3); liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Shosaikotokakikyosekko *Tsumura, Jpn.*
Gypsum (p. 2173·1); bupleurum root; pinellia tuber; skullcap root (p. 2617·1); platycodon root; jujube; ginseng (p. 2513·3); liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Shoseiryuto *Tsumura, Jpn.*
⊗Pinellia tuber; liquorice (p. 1853·2); cinnamon bark (p. 2479·2); schisandra fruit; asiasarum root; peony root; ephedra herb (p. 1663·1); ginger (p. 1844·1).
Traditional Kampo medicine.

Shoubishan *Lisheng, China.*
⊗Indapamide (p. 1409·2).
Hypertension.

Shrizine *SM, Philipp.†*
Fluphenazine decanoate (p. 1075·1).
Schizophrenia.

Shu De *Shunfeng, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Shu An *Haibin, China.*
Sultamicillin tosilate (p. 369·1).

Shu An Ling *CSPC, China.*
Pentoxifylline (p. 1465·3).
Cerebrovascular disorders.

Shu An Xin *Asia Pioneer, China.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Shu Bi Lai Te *Huaxin, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Shu Chang *Neptunus, China.*
Levodropropizine (p. 1662·3).
Cough.

Shu Cheng *Duoburuifei, China.*
Nicotinic acid (p. 2083·1).

Shu Er *Gute, China.*
Naftopidil (p. 2361·1).

Shu Er Fen *Jinyang, China.*
Diclofenac sodium (p. 48·3); codeine (p. 40·2).

Shu Er Zhi *XinShiDai, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Shu Fu Lai *Yier, China.*
Zolmitriptan (p. 682·2).
Migraine.

Shu Fu Luo *Kangbao, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Shu Ji *San Lian, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Shu Kang Lin *Jinhui, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Shu Ke Jie *Xudong Haipu, China.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Shu Lan Xin *Shuangding, China.*
Rifampicin (p. 350·3).
Bacterial infections.

Shu Lang *Sanxia, China.*
Lysine hydrochloride (p. 2079·3).

Shu Li Ang *Team, China.*
Ketoprofen (p. 79·1).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; gout; dysmenorrhoea.

Shu Lin *Aiwei, China; Tianya, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Shu Luo Kang *JiChuan, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Shu Luo Ning *Dexin Runsheng, China.*
Telmisartan (p. 1509·3).
Hypertension.

Shu Mai Te *Great Wall, China.*
Nitrendipine (p. 1456·3).
Hypertension.

Shu Mo Ta *Sanjing Aifuxi, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Shu Ning *Tianquan, China.*
Sodium ferulate.

Shu Ou Ting *Wellso, China.*
Tropisetron mesilate.
Chemotherapy-induced nausea and vomiting.

Shu Pu Ren *Jiankun, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Shu Qi *Team, China.*
Doxifluridine (p. 782·3).

Shu Rou *Team, China.*
Matrine.

Shu Rui *Neptunus, China.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Shu Rui Te *NCPC, China.*
Metronidazole (p. 936·1).

Shu Run *ChangSheng Gene, China.*
Interferon alfa-2a (human, recombinant) (p. 989·2).

Shu Sa Lin *Hayao, China.*
Amoxicillin sodium (p. 216·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Shu Si *Suzhou No 1, China.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Shu Tan *Sanhome, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Shu Tan Qing *C&Y, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Shu Tong *Jincheng Haisi, China.*
⊗Bumetanide (p. 1329·1).
Oedema.

Shu Wei *Lanling, China.*
Ranitidine bismuth citrate (p. 1883·3).

Shu Xian Lin *Livzon, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Shu Xu *Funing, China.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety.

Shu Ya *Qilu, China.*
Isosorbide mononitrate (p. 1413·3).

Shu Ya Ke *Yatai, China.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Shu Zhi *Yao Wang, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Shuai An *Shuai Ke, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Shuai Fu *Ang Li Kang, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Shuai Ke Feng *Shuai Ke, China.*
Fluconazole (p. 578·2).
Fungal infections.

Shuai Ke Jia Er *Shuai Ke, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Shuai Ke Tan *Shuai Ke, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Shuai Ning *Shuai Ke, China.*
Aceglutamide (p. 2426·2).

Shuai Qi *Tiancheng, China.*
Deproteinised calf blood extract (p. 2444·1).

Shuai Wei *Lanling, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Shuai Xian *Ang Li Kang, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Shuai Xing *Shuai Ke, China.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids.

Shuai Zhi *Shuai Ke, China.*
Aminomethylbenzoic acid (p. 1132·2).
Haemorrhage.

Shuaijie *Dawnrays, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Shuang Di *Sanyu, China.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; gastritis.

Shuang Bei *BeiLu, China.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Shuang Chang *Yangzhou No 3, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Shuang Chuan *Wanma, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Shuang Da *Jiante, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Shuang Ge Ning *Zhong Bao, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Shuang Hong Ling *Lianshui, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Shuang Ji *Taiyang, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; rhinitis; sinusitis.

Shuang Jia *Suzhou No 1, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Shuang Jiang Ping *Xiuzheng, China.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Shuang Ke *ShiJiaZhuang No 4, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Shuang Li *Huanghai, China.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Shuang Miao *Shouhe Jinhai, China.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity.

Shuang Ning *GuoAo, China.*
Kitasamycin acetate (p. 315·2).

Shuang Ping Le *Haixin, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Shuang Shu Bao *Eastsea, China.*
Bacillus coagulans.

Shuang Te *Huakang, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Shuang Wei *Tiancheng, China.*
Sodium ferulate.

Shuang Wei Du Qing *Duoburuifei, China.*
Fluconazole (p. 578·2).
Fungal infections.

Shuang Ye Hong *Hanyin, China.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; hypoparathyroidism; hypophosphataemia; renal osteodystrophy; rickets; osteomalacia.

Shuang Zuo Tai *Shanqing, China.*
Metronidazole (p. 936·1); chlorhexidine acetate (p. 1743·2); clotrimazole (p. 576·2).

Shuanghedida *Double-Crane, China.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Shuanglang *Yinjian, China.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Shuangyinjie *Changchun, China.*
Interferon alfa-2b (p. 989·2).

Shuangyiping *Fudan Fuhua, China.*
Huperzine A.

Shuanxilin *Haibin, China.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Shubeitinuo *Shin Poong, China.*
Spectinomycin hydrochloride (p. 358·1).
Genito-urinary tract infections.

Shuchibushi N *Tsumura, Jpn.†*
Aconitum carmichaeli root.
Traditional Kampo medicine.

Shudi *Hailing, China.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

ShuEr *Fuzheng, China.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Shuerxin *Likang, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Shuganjieyu Jiaonang *Kanghong, China.*
St John's wort (p. 449·1).
Depression.

Shuheng *Team, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Shui Lin Jia *Tasly, China.*
Silibinin (p. 1561·2).

Shui Qing *Sunstone, China.*
Nifuratel (p. 941·2); nystatin (p. 590·3).

Shukefei *Harvest, China.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Shumeifen *Livzon, China.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Shumeng *Lukang Chenxin, China.*
⊗Metoprolol tartrate (p. 1434·3).
Arrhythmias.

Shun Ling *HaiWang Fuyao, China.*
Ethylenediamine diaceturate.

Shun Qi *Sanyu, China.*
⊗Tranilast (p. 1239·1); salbutamol sulfate (p. 1220·2).

Shun Ru *Run Bang, China.*
Lafutidine (p. 1851·3).
Peptic ulcer; gastritis; acid aspiration.

Shun Song *CSPC, China.*
Acemetacin (p. 16·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain.

Shun Ta Xin *Tianshun, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Shun Xin *Chia Tai, China.*
Matrine.

Shun You *Jianfeng, China.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Shuna *Haisike, China.*
Nalmefene hydrochloride (p. 1562·1).

Shuntan *Haixin, China.*
Aniracetam (p. 389·1).
Memory impairment.

ShuPing LaiShi *RAAS, China.*
Thrombin (p. 1163·2).
Haemorrhage.

Shuqi *Qianjiang, China.*
Troxipide (p. 1894·3).
Peptic ulcer; gastritis.

Shur-Seal *Milex, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

ShuRui *Team, China.*
⊗Toremifene citrate (p. 873·3).
Breast cancer.

Shutabituo *Welman, China.*
Ampicillin (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

ShuTaiQing *Shutaishen, China.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).

Shutaxian *United Lab, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Shuweixin *Team, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Si Ba Te Kang *Baiyunshan, China.*
Matrine.

Si Bei Ge *Nhwa, China.*
Ziprasidone hydrochloride (p. 1115·2).
Schizophrenia.

Si Bi Ke *Huaxin, China.*
Piracetam (p. 393·3).
Mental function impairment.

Si Bi Shen *Huakang, China.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Si Bo Hai *Sangtian, China.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Si Duo Mi *Huili, China.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Si Er Li *Gui Long, China.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Si Fu Sheng *GuoGuang, China.*
Staphylococcus aureus.

Si Fu Si *Wanma, China.*
Ranitidine bismuth citrate (p. 1883·3).

Si Fu Ti *Ke Lun, China.*
Lysine hydrochloride (p. 2079·3).

Si Fu Xin *Jing Wei, China.*
Diclofenac sodium (p. 48·3).

Si Hai Neng *Hailing, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Si Jian *Wei Lun, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Si Jin *Aoyipollen, China.*
Ebastine (p. 628·1).
Allergic rhinitis; urticaria; pruritus; eczema.

Si Jun Yi *Xing'an, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Si Kao Lin *Qilu, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Si Le Ke *Tianping, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Si Ke Lin *Daxing, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Si Ke Te *Wanhui Shuanghe, China.*
Smectite (p. 1887·1).

Si Lai Mei *Yaoyou, China.*
Meloxicam (p. 86·3).
Musculoskeletal and joint disorders.

Si Li An *Beida, China.*
Folic acid (p. 2063·1).
Prevention of neural tube defects in pregnancy.

Si Li Bang *Sine, China.*
Compund codeine phosphate.

Si Li Jia *Qian Long, China.*
Lysine hydrochloride (p. 2079·3).

Si Li Jie *Dawnrays, China.*
Cefixime (p. 240·3).
Bacterial infections.

Si Li Meng *Di Ao, China.*
Acipimox (p. 1290·2).

Si Li Shu *Nhwa, China.*
Risperidone (p. 1103·2).
Schizophrenia.

Si Li Tai *Dawnrays, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Si Lian Kang *Longda Xinke, China.*
Bifidobacteria; lactobacillus; enterococcus; *Bacillus cereus.*

Si Lin *Wuhan, China.*
A measles and mumps vaccine (p. 2400·1).
Active immunisation.

Si Lin Tuo *Tianren, China.*
Calcium acetate (p. 1783·1).
Hyperphosphataemia.

Si Mai Te *Yihe, China.*
Smectite (p. 1887·1).

Si Mei *Haibin, China.*
Zaleplon (p. 1114·3).
Insomnia.

Si Mi An *Zizhu, China.*
Mifepristone (p. 2138·1).
Postcoital oral contraceptive.

Si Mi Kang *Wan Bang, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Si Min Le *Nuo Jin, China.*
Calcium folinate (p. 2066·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia.

Si Na Ge *Longshen Rongfa, China.*
Berberine tannate (p. 2455·1).

Si Di Nuo *Luye, China.*
Elcatonin (p. 1178·1).

Si Nuo Kang Xin *Shengyuan, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Si Nuo Ping *Linuo Kefeng, China.*
Clemastine fumarate (p. 622·3).
Hypersensitivity reactions.

Si Pei Er *Zhen Zhu, China.*
Tolterodine fumarate.
Bladder hyperactivity.

Si Qi Le *Tai Le, China.*
Meleumycin (p. 321·2).

Si Qi Kang *Jiuzhitang Siqi, China.*
A BCG vaccine (p. 2378·1).

Si Qing *Harbin, China.*
Codergocrine mesilate (p. 389·2).

Si Qu Di *Wanma, China.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer.

Si Rui *Huabang, China.*
Nimesulide (p. 101·3).
Pain.

Si Rui Ke *Zihua, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Si Tai *Mayinglong, China.*
Piracetam (p. 393·3).
Mental function impairment.

Si Tai Le *Zhen Zhu, China.*
Telmisartan (p. 1509·3).
Hypertension.

Si Te Chang Jia *Meijisi, China.*
Zaleplon (p. 1114·3).
Insomnia.

Si Te Li *Xinxing, China.*
Calcium citrate (p. 1783·2).

Si Te Li Pu *Wei Kang, China.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Si Te Long *Xianju, China.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism.

Si Te Meng *Jinling, China.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Si Tong Ning *Ansheng Kexing, China.*
Strontium-89 chloride.

Si Tong Tuo Luo *Chengshi, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Si Wei De *Ke Lun, China.*
Sodium alginate diester.

Si Wei Er *Dongbao, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Si Wei Pu *Southwest, China.*
Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).

Si Wei Si *Maidi, China.*
Clebopride malate (p. 1833·1).
Nausea and vomiting.

Si Yi *Wanma, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Si Yi Ke *Yangtian, China.*
Ibudilast (p. 1211·2).

Si Yue *Topfond, China.*
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).

Si Ze *Docan, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Siaara *Heptaforma, Port.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension; cardiovascular risk reduction.

Siadocin *Siam Bheasach, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Siafil *Rider, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Sialexin *Siam Bheasach, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Sialgen *Omega, Canad.†*
Electrolytes (p. 1775·1).

Sialin *Sigmapharm, Austria.*
Carmellose sodium (p. 2175·2); electrolytes (p. 1775·1).
Saliva substitute.

Sialor *Pendopharm, Canad.*
Anethole trithione (p. 2443·3).
Dry mouth.

Siamdopa *Siam Bheasach, Thai.*
Methyldopa (p. 1431·1).
Hypertension.

Siamformet *Siam Bheasach, Thai.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Siamidine *Siam Bheasach, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastric hyperacidity.

Siamik *Siam Bheasach, Thai.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Sia-Mox *Siam Bheasach, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Siampicil *Siam Bheasach, Thai.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Siampraxol *Siam Bheasach, Thai.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Siang Pure Balm *Bertram, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Siang Pure Oil *Bertram, Thai.*
Menthol (p. 2553·2); peppermint oil (p. 1877·1).
Musculoskeletal and joint pain.

Siarizine *Siam Bheasach, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; migraine; motion sickness.

Siaten *Italfarmaco, Spain.*
Zopiclone (p. 1118·1).
Insomnia.

Sibazon *Abbott, Rus.*
Diazepam (p. 1063·2).
Anxiety; insomnia; alcohol withdrawal syndrome; spasticity; status epilepticus; premedication.

Sibectan *Vilar, Rus.*
Birch leaf (p. 2457·3); milk thistle (p. 1561·1); St John's wort (p. 449·1); tanacetum.
Liver and biliary tract disorders.

Sibelium *Janssen-Cilag, Arg.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Pharmascience, Canad.†; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Gr.; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, Venez.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo; vestibular disorders; dizziness; motion sickness; cerebral and peripheral vascular disorders.

Sibélium *Janssen-Cilag, Fr.*
Flunarizine hydrochloride (p. 629·3).
Migraine.

Sibelium Plus *Janssen-Cilag, Arg.*
Flunarizine hydrochloride (p. 629·3); nicergoline (p. 2569·1).
Migraine; vestibular disorders.

Siberian *Rafarm, Gr.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Siberid *Pyridam, Indon.*
Flunarizine (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Sibet
Note: this name may be used for preparations of different composition.
Glenmark, India.
Dexibuprofen (p. 43·1).
Osteoarthritis; dysmenorrhoea; dental pain.
IQFA, Mex.
Metformin (p. 489·1).
Diabetes mellitus.

Sibet-C *IQFA, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Sibicort *Orion, Fin.*
⊗Hydrocortisone (p. 1640·1); chlorhexidine gluconate (p. 1743·3).
Infected skin disorders.

Sibilex *Rimsa, Mex.*
⊗Ambroxol hydrochloride (p. 1654·3); salbutamol sulfate (p. 1220·2); loratadine (p. 633·2).
Respiratory-tract disorders.

Sibital *Mersifarma, Indon.*
Phenobarbital sodium (p. 535·3).
Epilepsy; sedative.

Siblima *Libbs, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Siblix *Beta, Arg.*
Aripiprazole (p. 1038·3).
Schizophrenia; bipolar disorder.

Sibrovita *Permamed, Switz.†*
Eucalyptus oil (p. 2501·2); orange oil (p. 2576·2); lemon oil (p. 2543·1); myrtillus oil.
Bronchitis; sinusitis.

Sibuctil *EMS, Braz.*
⊗Sibutramine (p. 2330·2).
Obesity.

Sibudan *Teva Tuteur, Arg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Sibu-Estirol *Bouzen, Arg.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sibus *Eurofarma, Braz.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sibutin *KVZ, Ukr.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder; nocturnal enuresis.

Sibutral *Abbott, Fr.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sibutran *UCI, Braz.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sibu-Tratobes *Columbia, Arg.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sibutrim *Ultramed, Philipp.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sicadol *Rider, Chile.*
Mefenamic acid (p. 85·3).
Pain.

Sical
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.
Calcitriol (p. 2113·1).
Osteoporosis; hypocalcaemia; osteodystrophy; hypoparathyroidism; rickets.

Sicalan *Loeffler, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Sicaril *Sanofi-Aventis, Gr.*
Malathion (p. 2157·2).
Head and crab lice; scabies.

Sicatem *Richmond, Arg.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Sicazine *Smith & Nephew, Fr.†; Smith & Nephew, Port.*
Sulfadiazine silver (p. 362·3).
Infected burns, wounds, and ulcers.

Siccafluid *Sidus, Arg.; Thea, Fr.; Thea, Gr.; Farmila, Ital.; Thea, Neth.; Thea, Philipp.; Thea, Port.; Thea, Spain; Thea, Switz.; Santa, Turk.; Pfizer, Venez.*
Carbomer (p. 2173·3).
Dry eyes; eye irritation.

Siccafree *Thea, Neth.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Siccagent *Alcon, Belg.*
Povidone (p. 2204·3).
Dry eyes.

Siccalix *Drossapharm, Switz.*
Sea salt (p. 2612·1); dexpanthenol (p. 2582·2).
Nasal dryness.

Siccamed *Thea, Neth.*
Carbomer 974P (p. 2173·3).
Dry eyes.

Siccapos *Ursapharm, Ger.; Ursapharm, Malaysia; Biem, Turk.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Siccaprotect *Croma, Austria; Ursapharm, Cz.; Ursapharm, Ger.; Ursapharm, Switz.; Biem, Turk.*
Dexpanthenol (p. 2582·2); polyvinyl alcohol (p. 2204·2).
Dry eyes; eye irritation.

Sicca-Stulln *Stulln, Ger.*
Hypromellose (p. 2189·2).
Dry eyes.

Siccoral
Note: this name may be used for preparations of different composition.
Drossapharm, Switz.
Sea salt (p. 2612·1).
Mouth and throat disorders.

Siclaxim *Mersifarma, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Siclidon *Sanbe, Indon.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Siclot *Siam Bheasach, Thai.†*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis; maintenance of extracorporeal circulation; unstable angina; intermittent claudication; diabetic retinopathy.

Sicombyl *Takeda, Belg.*
Salicylic acid (p. 1719·1).
Hygiene of the umbilicus in neonates.

Sicopax *Indeco, Arg.†*
Paroxetine (p. 440·3).
Depression.

Sic-Ophtal *Winzer, Ger.*
Hypromellose (p. 2189·2).
Dry eyes.

Sicoplus *Columbia, Arg.*
Idebenone (p. 392·3).
Cerebrovascular disorders.

Sicor *Hexal, Hung.*
Simvastatin (p. 1489·2).
Coronary artery disease; hyperlipidaemias.

Sicorten *Novartis, China; Novartis, Hong Kong; Sandoz, Spain†; Pro Concepta, Switz.†; Novartis, Turk.*
⊗Halometasone (p. 1639·3).
Skin disorders.

Sicorten Plus *Novartis, China; Riemser, Ger.†; Sandoz, Spain†; Pro Concepta, Switz.*
⊗Halometasone (p. 1639·3); triclosan (p. 1773·2).
Infected skin disorders.

Sicotral *Indeco, Arg.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; social phobia; anxiety; panic disorder.

Sicriptin *Serum Institute, India.*
Bromocriptine mesilate (p. 895·3).
Parkinsonism; amenorrhoea; galactorrhoea; female infertility; lactation inhibition; acromegaly.

Sicura3
Note: this name may be used for preparations of different composition.
Esoform, Ital.
Chlorhexidine gluconate (p. 1743·3).
Dental caries prophylaxis; oral hygiene.

Sicura3 Fisionorm *Esoform, Ital.*
Zinc oxide (p. 1729·1).
Nappy rash.

Sicura3 Gel *Esoform, Ital.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Sicura3 Medical *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Skin disinfection.

Sidan *Millimed, Thai.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; rhinitis; cold symptoms.

Sideck Shampoo Antiforfora *Sideck, Ital.*
Piroctone olamine (p. 1716·3); matricaria (p. 2474·1); copper usnate (p. 2640·2); undecenoic acid (p. 596·3).
Seborrhoeic dermatitis.

Sidegra *GPO, Thai.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Sidel *Liferpal, Mex.†*
Nimesulide (p. 101·3).
Pain; rheumatism.

Sidena *Rowex, Irl.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Sidenar *Ivax, Arg.*
Lorazepam (p. 1080·3).
Anxiety; premedication.

Sidenol *Amnol, Ital.*
Tablets: Quercetin (p. 2505·3); polypodium leucotomos; vitamins.
Dietary supplement.

Amnol, Ital.
Topical emulsion: Quercetin (p. 2505·3); aescin (p. 2431·2).
Circulatory disorders.

Sideralce *Lafedar, Arg.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Siderblut *Investi, Arg.*
Controlled-release tablets: Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Investi, Arg.
Oral drops: Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Siderblut Complex *Investi, Arg.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron and folic acid deficiency anaemia.

Siderblut Folic *Investi, Arg.*
Iron polymaltose (p. 2077·2); folic acid (p. 2063·1).
Iron and folic acid deficiency anaemia.

Siderblut Poli *Investi, Arg.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Siderfol *Raptakos, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); copper sulfate (p. 2057·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Sideril *Senosiain, Mex.*
Trazodone (p. 451·1).
Depression.

Sidervim *New Research, Ital.*
Ferrous gluconate (p. 2061·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Sidiadryl *Bernofarm, Indon.†*
Diphenhydramine hydrochloride (p. 626·2).
Allergic disorders.

Sidiadryl Expectorant *Bernofarm, Indon.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Sidina *Welti, Switz.*
Juniper (p. 2537·1).
Digestive disorders.

Sidok *Alkaloid, Cz.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; stroke prophylaxis.

Sidoklop *Actavis, Denm.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Sidomal *Sanitas, Arg.*
Simeticone (p. 1886·2); domperidone (p. 1838·1); alprazolam (p. 1035·2).

Sidomol *GiEnne, Ital.*
Molsidomine (p. 1441·1).
Angina pectoris.

Siduol *Eisai, Thai.*
Alpha tocoferil calcium succinate (p. 2119·1); phytomenadione (p. 2122·2); rutoside (p. 2505·3); muramidase hydrochloride (p. 2565·1); pluronic F-68 (p. 2202·1).
Haemorrhoids.

Siduopu *Xinbao, China.*
Thrombin (p. 1163·2).
Haemorrhage.

Siduro *Meda, Swed.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

Siel *Pliva, Rus.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting.

Siemag *Chew, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); kaolin (p. 1850·1).
Gastric hyperacidity.

Sieral *Farmedia, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; eradication of Helicobacter pylori *in combination with antimicrobials; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.*

Sies *Senosiain, Mex.*
Hidrosmin (p. 2505·2).
Retinal or subconjunctival disorders; oedema.

Siesta-1 *Welti, Switz.*
Anhydrous citric acid (p. 2480·3); tartaric acid (p. 2626·1); magnesium sulfate (p. 1787·3); sodium bicarbonate (p. 1781·1).
Constipation.

Sievert *Farmagen, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sifaas *Sinterapico, Braz.*
Aspirin (p. 22·2).

Sifaclor *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Cefaclor (p. 232·3).
Bacterial infections.

Sifenol *Hiperonline, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Sificetina *SIFI, Ital.*
Chloramphenicol (p. 257·1).
Eye infections.

Sificrom *Ferlito, Ital.*
Sodium cromoglicate (p. 1225·3).
Keratoconjunctivitis; conjunctivitis.

Si-Fixim *Svizera, India.*
Cefixime (p. 240·3).
Bacterial infections.

Siflex *Siam Bheasach, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Sifloks *Eczacibasi, Rus.; Eczacibasi, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Eczacibasi, Ukr.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Siflox *Mersifarma, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Siframin *Fresenius Kabi, Ital.*
Amino acids.
Parenteral nutrition.

Sifrol *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Sifrol/Mirapex *Boehringer Ingelheim, Venez.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism.

Sifulin *Rotam Reddy, China.*
Liranaftate (p. 588·1).
Fungal skin infections.

Sigadoxin *Maver, Chile; Neves, Port.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Sigas *Polipharm, Thai.*
Simeticone (p. 1886·2).
Flatulence.

Sigatricin *Gemardi, Thai.†*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2); benzethonium chloride (p. 1738·1).
Mouth and throat disorders.

Sigestrial *Madaus, Arg.*
Sterocare; sigesbeckia; Matrixyl; shea butter (p. 2208·2); rosa mosqueta oil.
Scars.

Sigilamyl *Actavis, Denm.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Siglaton *Vamsler, Philipp.*
Vitamins; minerals.
Nutritional supplement.

Siglaton Plus *Vamsler, Philipp.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Sigma CE *Sigma, Arg.†*
Vitamin C (p. 2110·3); zinc gluconate (p. 2126·2).
Vitamin C deficiency; zinc supplement.

Sigma Clav *Sigma, Braz.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Sigmacal *Sigma, Arg.*
Calcium citrate (p. 1783·2).
Calcium supplement.

Sigmacalcidol *Sigma, Braz.*
Alfacalcidol (p. 2112·3).
Osteoporosis.

Sigmacalvit *Svizera, India.*
Calcium glubionate (p. 1783·2); cyanocobalamin (p. 2107·2); colecalciferol (p. 2113·1).
Calcium deficiency.

Sigmace Plus *Sigma, Arg.*
Vitamin C (p. 2110·3); zinc gluconate (p. 2126·2).
Vitamin C and zinc supplement.

Sigmachrome *Svizera, India.*
Carbazochrome salicylate (p. 1137·1).
Haemorrhage.

Sigmacip *Sigma, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Sigmacort *Aspen, Austral.; Sigma, Hong Kong.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Sigmaderm *Svizera, India.*
⊗Clotrimazole (p. 576·2); beclometasone dipropionate (p. 1621·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Sigmafem *Sigma, Arg.*
Soya phytoestrogens (p. 2092·3); sage phytoestrogens (p. 2608·3); angelica (p. 2443·3); Siberian ginseng (p. 2614·3); vitamin E (p. 2119·1); magnesium (p. 1786·3).
Menopausal disorders; mastodynia; dysmenorrhoea; osteoporosis; hypercholesterolaemia.

Sigmafem Dermis *Sigma, Arg.*
Vitamins; amino acids.
Dietary supplement.

Sigmafem Free *Sigma, Arg.*
Soya isoflavones (p. 2620·3); sage phytoestrogens (p. 2608·3).
Menopausal disorders.

Sigmaflavon Plus *Sigma, Arg.*
Vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3); magnesium (p. 1786·3); sage (p. 2608·3); soya isoflavones (p. 2620·3).

Sigmaflex *Sigma, Arg.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); calcium carbonate (p. 1824·3); phosphorus (p. 2589·2); magnesium (p. 1786·3).
Joint disorders.

Sigmalac *Sigma, Braz.*
Lactitol (p. 1850·3).
Hepatic encephalopathy; constipation.

Sigman-Haustropfen *Sigmapharm, Austria.*
Peppermint oil (p. 1877·1); caraway oil (p. 2470·3); dexpanthenol (p. 2582·2); chamomile flower (p. 2474·1); condurango bark (p. 2485·3); liquorice root (p. 1853·2); absinthium (p. 2426·1); gentian root (p. 2512·1); bitter orange peel (p. 2575·3).
Gastrointestinal and biliary-tract disorders.

Sigmar Lipo *Sigma, Arg.*
Chromium tripicolinate (p. 2056·1).
Obesity.

Sigmart *Chugai, China; Chugai, Jpn.*
Nicorandil (p. 1446·2).
Angina pectoris; heart failure.

Sigmasedan *Sigma, Arg.*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Insomnia; anxiety; gastrointestinal disorders.

Sigmasol *Sigma, Arg.*
Bixa orellana; betacarotene (p. 2051·1).
Tanning aid.

Sigmasporin *Medipharma, Arg.; Sigma, Braz.; Julphar, UAE.*
Ciclosporin (p. 1945·2).
Transplant rejection; atopic eczema; psoriasis; rheumatoid arthritis; nephrotic syndrome; graft-versus-host disease; uveitis.

Sigmasporon *Helvetia, Cz.*
Ciclosporin (p. 1945·2).
Organ transplant rejection; graft-versus host disease; uveitis; nephrotic syndrome; rheumatoid arthritis; psoriasis; atopic eczema.

Sigmatriol *Germed, Braz.*
Calcitriol (p. 2113·1).
Vitamin D supplement.

Sigmatrofic *Sigma, Arg.*
A range of tissue extracts (p. 2444·1).

Sigmavital *Sigma, Arg.*
Amino acids; vitamins; minerals; lipids.
Tonic.

Sigmax *Sigma, Braz.*
Topiramate (p. 550·3).

Sigmaxin *Aspen, Austral.*
Digoxin (p. 1353·3).
Arrhythmias; heart failure.

Sigmus *Bausch & Lomb, Arg.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Signal *Green Turtle Bay Vitamin Co., USA.*
Omega triglycerides.
Tonic.

Signatry *Gojo, Canad.*
Triclosan (p. 1773·2).
Formerly contained chloroxylenol.

Signelon *Genepharm, Neth.†*
Rivastigmine hydrogen tartrate (p. 395·1).
Dementia.

Signicef *Promed, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Signifor *Novartis, Denm.; Novartis, Fr.; Novartis, Neth.; Novartis, Norw.; Novartis, Switz.; Novartis, UK; Novartis, USA.*
Pasireotide aspartate (p. 1928·1).
Cushing's disease.

Signopam *Tarchomin, Hung.; Polfa Tarchomin, Pol.; Tarchomin, Rus.*
Temazepam (p. 1109·1).
Sleep disorders; premedication; anxiety disorders; depression.

Signum *Amnol, Ital.*
⊗Maritime pine (p. 2590·3); aesculus (p. 2431·2); bromelains (p. 2460·3); vitamin B substances (p. 2102·3).
Respiratory-tract inflammation.

Sigran (C1) *Germed, Braz.*
⊗Sibutramine (p. 2330·2).

Sigrel *QX, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Sigtab-M *Roberts, USA.*
Vitamins; minerals.

Siguent Hycor *Aspen, Austral.*
⊗Hydrocortisone acetate (p. 1640·1).
Inflammatory eye disorders.

Siguon *Leovan, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Siilif *Nycomed, Braz.*
Pinaverium bromide (p. 2590·3).

Sikaitong *Wan Bang, China.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Siklocap *Kocak, Turk.*
Cycloserine (p. 280·2).
Tuberculosis.

Siklomid *Sanovel, Turk.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Siklopleji n *Abdi, Turk.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Siklos *Addmedica, Cz.; Addmedica, Fr.; Nordic, Ger.; Addmedica, Gr.; Addmedica, Irl.; Nordic, Neth.; Addmedica, Pol.; Addmedica, Port.; Rovi, Spain; Nordic, UK.*
Hydroxycarbamide (p. 803·1).
Sickle-cell disease.

SIL-1000, -5000 *DORC, Neth.*
Silicone oil (p. 2209·3).
Ophthalmic tamponade.

Sil Trax Plus *Pascal, Canad.†*
⊗Adrenaline hydrochloride (p. 1292·2); zinc phenolsulfonate (p. 1729·3).

Silabat *Bernofarm, Indon.†*
⊗Guaifenesin (p. 1666·2); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Silace *Tanta, Canad.; Silarx, USA.*
Docusate sodium (p. 1836·2).
Constipation.

Silact *Sofar, Ital.*
Tilactase (p. 2631·2).
Lactose intolerance.

Silacten *Hanseler, Switz.*
Calcium phosphoricum (p. 1784·2); china (cinchona pubescens) (p. 2478·3); galega officinalis; ricinus communis (p. 2472·1); solidago virgaurea (p. 2620·1); urtica (p. 2639·3).
Homoeopathic preparation.

Silada *Sandoz, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Siladex *Konimex, Indon.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Siladryl *Silarx, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Silafed *Silarx, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Silagra *Cipla, India.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Silam *Adamed, Spain.†*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Silamarie *Bio-Health, UK.*
Milk thistle (p. 1561·1).
Dyspepsia.

Silamox *Prafa, Indon.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Silan *Ayrton Saunders, Denm.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Dry skin; skin irritation.

Silanem *Kocak, Turk.*
Cilastatin sodium (p. 260·3); imipenem (p. 309·2).
Bacterial infections.

Silantuss *Kleva, Gr.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).

Silapap *Silarx, USA.*
Paracetamol (p. 115·1).
Pain; fever.

Silapo *Stada, Cz.; CellPharm, Ger.; Stada, Irl.; Stada, Pol.; Stada, Port.*
⊗Epoetin zeta (p. 1141·2).
Anaemias; autologous blood transfusion.

Silardaf *Liconsa, Neth.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Silardex *Glenmark, Cz.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Silarine *Vir, Spain.*
Silymarin (p. 1561·2).
Toxic hepatitis.

Silarsil *World Medicine, Ukr.*
Silymarin (p. 1561·2).
Dietary supplement.

Silarten *Roux-Ocefa, Arg.†*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Silato *Velka, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Silavidon *Leontik, Gr.*
Sulpiride (p. 1107·3).

Silax *Ethica, Indon.*
⊗Furosemide (p. 1387·1).
Pulmonary oedema.

Silaxa
Note: this name may be used for preparations of different composition.
Medico Uno, Cz.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Temis, Arg.
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Silbecor *Biotech, S.Afr.*
Sulfadiazine silver (p. 362·3).
Burns.

Silbephylline *Minerva (Μινερβα), Gr.*
Diprophylline (p. 1207·3).
Asthma; obstructive airways disease.

Silberne *Brady, Austria.†*
Cascara (p. 1826·1); rhubarb (p. 1884·2); ox bile (p. 2457·2).
Constipation.

Silcocks Base *Ovelle, Irl.*
White soft paraffin (p. 2211·3); emulsifying wax (p. 2184·1).
Ointment basis; dry skin disorders; soap substitute.

Sildec-DM *Silarx, USA.*
Syrup: ⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Silarx, USA.
Oral drops: ⊗Carbinoxamine maleate (p. 619·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Sildecross *Pharmacross, Chile.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Sildefil *Pfizer, Arg.†*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Sildegra *Fako, Turk.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Silden *Rowex, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Sildenamed *S Med, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Silder
Note: this name may be used for preparations of different composition.
Eczacibasi, Turk.
Sulfadiazine silver (p. 362·3).

Viofar, Gr.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Silderec
Note: this name may be used for preparations of different composition.
Gedeon Richter, Neth.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Probiomed, Mex.
Risperidone (p. 1103·2).
Schizophrenia.

Sildrem *Sigillata, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Silegon *Teva, Hung.*
Milk thistle (p. 1561·1).
Liver disorders.

Silence
Note: this name may be used for preparations of different composition.
Chefaro, Ger.
⊗Phosphatidyl choline (p. 2588·3); glycerol (p. 2517·2); carrageenan (p. 2176·3).
Snoring.

Omega, Singapore; Interdelta, Switz.
⊗Phosphatidyl choline (p. 2588·3); glycerol (p. 2517·2); carrageenan (p. 2176·3); rose fruit (p. 2607·1).
Snoring.

Yung Shin, Hong Kong.
Lorazepam (p. 1080·3).
Anxiety.

Zambon, Switz.†
Nasal spray: ⊗Phosphatidyl choline (p. 2588·3); glycerol (p. 2517·2); carrageenan (p. 2176·3); potassium carbonate (p. 2595·2); butcher's broom (p. 2463·1); menthol (p. 2553·2); rutoside (p. 2505·3); eucalyptus (p. 2501·1); alcohol (p. 1733·1); sodium chloride (p. 1795·1).
Snoring.

Silencium *Sanofi-Aventis, Braz.*
Syrup: Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); cetylpyridinium chloride (p. 1743·1); sodium citrate (p. 1781·2).
Cough.

Sanofi-Aventis, Braz.
Pastilles: Dextromethorphan (p. 1660·1); benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).
Cough.

Silenil *Biofarm, Pol.*
St John's wort (p. 449·1).
Depression.

Silenor *Somaxon, USA.*
Doxepin (p. 414·2).
Insomnia.

Sileping *Hayao, China.*
Lacidipine (p. 1417·3).
Hypertension.

Silettum *Jaldes, Fr.*
Lithothamnium calcareum; palmaria palmata; hydrolysed sesame protein; vitamin B substances (p. 2102·3).
Hair disorders.

Silex *Darya-Varia, Indon.*
Guaifenesin (p. 1666·2); thyme (p. 2630·2); primula (p. 2596·2); althaea (p. 2438·3); drosera (p. 2497·2); wild thyme (p. 2648·1); eucalyptus oil (p. 2501·2); anise oil (p. 2444·3).
Cough.

Silfedrine *Silarx, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Silfeldrem *Plus Pharma, Cz.; Plus Pharma, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Silfox *Ivax, Arg.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Silfox Flex *Ivax, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint, and peri-articular disorders.

Silgard *MSD, Cz.; MSD, Denm.; MSD, Hung.; MSD, Irl.; MSD, Neth.; MSD, Pol.; MSD, Port.*
A human papillomavirus vaccine (HPV types 6, 11, 16, and 18) (p. 2392·2).
Active immunisation.

Silgel *Nagor, UK.*
Silicone (p. 2209·3).
Hypertrophic and keloid scars.

Silglós *Uniao Quimica, Braz.*
Sulfadiazine silver (p. 362·3).
Skin infections.

Silgonitran *Kleva, Gr.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Silgram *YSS, Philipp.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Silhouette *Gedeon Richter, Ukr.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Silibene *Recordati, Ger.†*
Milk thistle (p. 1561·1).
Liver disorders.

Silibiol *Ineldea, Fr.*
Orthosilicic acid (p. 2208·3); bamboo tabashir; equisetum (p. 2500·1); urtica (p. 2639·3); turmeric (p. 2218·1); salix (p. 129·2); black currant (p. 2458·1); betula alba (p. 2457·3).
Dietary supplement.

Silic *Ego, NZ.*
⊗Dimeticone (p. 2209·3); glycerol (p. 2517·2).
Barrier preparation; bed sores; eczema.

Silic 15 *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.*
Dimeticone 350 (p. 2209·3).
Dry skin; barrier preparation.

Silica Compound *Blackmores, Austral.*
Dibasic sodium phosphate (p. 1791·2); silicon dioxide (p. 2209·1).
Dietary supplement.

Silica-OK *Wassen, UK.*
Silica; selenium (p. 2086·3); vitamins.

Silica-Vite *Bioglan, Austral.†*
Equisetum (p. 2500·1).
Skin disorders; wounds.

Silicea Complexe No 11 *Lehning, Fr.*
Silicea (p. 2208·3); argentum metallicum (p. 2615·1); antimonium crudum (p. 2445·1); arsenicum album (p. 2448·1); calcarea fluorica (p. 2053·1); ferrum phosphoricum (p. 2077·1); magnesia phosphorica (p. 1787·3); mercurius solubilis (p. 2555·3); manganum peroxydatum (p. 2081·2).
Homoeopathic preparation.

Silicin *Greater Pharma, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Silicol *Szama, Arg.*
Barrier preparation.
Dermatitis; nappy rash; skin irritation.

Silics *Biopharma, Ukr.*
Silicon dioxide (p. 2208·3).
Diarrhoea; hepatitis A; hepatitis B.

Silicsan *Rayere, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Silicur *Hexal, Ger.†*
Milk thistle (p. 1561·1).
Liver disorders.

Silidermil *Rottapharm, Spain.*
Ointment: Dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Skin disorders.

Silidral *Spedrog, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Silidral Plus *Spedrog, Arg.*
4 Tablets, alendronate sodium (p. 1171·3); 28 tablets, calcium carbonate (p. 1824·3).
Osteoporosis.

Silidral Uno *Spedrog, Arg.*
Ibandronate sodium (p. 1184·2).
Osteoporosis.

Silidron *GSK, Braz.*
Dimeticone (p. 1886·2).
Flatulence.

Siligaz
Note: this name may be used for preparations of different composition.
Bio-Sante, Canad.; Arkopharma, Fr.
Simeticone (p. 1886·2).
Meteorism.

Prater, Chile.
Domperidone (p. 1838·1).
Dyspepsia; gastroparesis; nausea and vomiting.

Silik *Knop, Chile.*
Aurum metallicum (p. 2521·1); barium carbonicum (p. 2452·2); lycopodium (p. 2546·3); silicea (p. 2208·3).
Homoeopathic preparation.

Silimalon *Nikkho, Braz.*
Methionine (p. 1558·2); silymarin (p. 1561·2).
Liver disorders.

Silimar *Vilar, Rus.*
Milk thistle (p. 1561·1).
Liver disorders.

Silimarin *Germed, Ital.*
Milk thistle (p. 1561·1).
Liver disorders.

Silimarit *Bionorica, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Silimax *Filofarm, Pol.*
Silymarin (p. 1561·2).
Liver disorders.

Sili-Met-San *Therabel, Belg.†*
Dimeticone (p. 1886·2); calcium pantothenate (p. 2085·2).
Trapped gastrointestinal gas; aid to gastrointestinal radiographic examination.

Silina *Husnu Arsan, Turk.*
Ampicillin (p. 218·2).
Bacterial infections.

Silinovéa *Motima, Fr.*
Egg shell; bamboo; ondotella aurita; tyrosine (p. 2098·3); calcium ascorbate (p. 2111·1); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).
Fragile hair and nails; dietary supplement.

Siliprêle *Boiron, Fr.†*
Equisetum (p. 2500·1).
Gastrointestinal and renal disorders.

Silirex *Lampugnani, Ital.*
Silymarin (p. 1561·2).
Liver disorders.

Silisan *Merck, Ital.*
Simeticone (p. 1886·2); calcium pantothenate (p. 2085·2).
Gastrointestinal disorders associated with excess gas; preparation of the stomach for endoscopy and surgery.

Siliumbran *Biotech Naturis, Venez.*
Psyllium (p. 1849·1).
Constipation.

Siliver *Farmasa, Braz.*
Milk thistle (p. 1561·1).
Liver disorders.

Silkies Enriche *Enchantress, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Silkis *Galderma, Belg.†; Galderma, Braz.†; Galderma, Canad.; Galderma, Chile†; Galderma, China; Galderma, Cz.; Galderma, Fin.; Galderma, Fr.; Galderma, Ger.; Galderma, Gr.; Galderma, Hong Kong; Galderma, Hung.†; Galderma, Irl.; Galderma, Ital.; Galderma, Mex.; Galderma, Neth.; Galderma, Norw.; Galderma, Philipp.; Galderma, Pol.†; Galderma, Port.; Galderma, Singapore; Galderma, Spain; Galderma, Switz.; Galderma, UK; Galderma, Venez.*
Calcitriol (p. 2113·1).
Psoriasis.

Silky Smooth *Hovid, Malaysia.*
Glycosaminoglycans; tocotrienol.
Spider veins; varicose veins.

Silmar *Biohealth, Ital.*
Silymarin (p. 1561·2).
Liver disorders.

Silmycetin *Silom, Thai.*
Chloramphenicol (p. 257·1).
Bacterial eye or ear infections.

Sil-Norboral *Silanes, Mex.*
Glibenclamide (p. 472·1); metformin (p. 489·1).
Diabetes mellitus.

Siloam *Medimar, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Silocast *Himreaktivkomplekt, Rus.*
Dimethyl sulfoxide (p. 2182·2); chlormethylsilatrane.
Alopecia areata.

Siloderm *USV, India.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1); calamine (p. 1697·2); cetrimide (p. 1742·1).
Dermatitis; ulcers; burns; insect bites; chapped skin; pruritus; haemorrhoids.

Silodyx *Zambon, Belg.; Recordati, Cz.; Zambon, Fr.; Recordati, Gr.; Recordati, Irl.; Zambon, Neth.; Recordati, Pol.; Recordati, Port.; Almirall, Spain.*
Silodosin (p. 2367·2).
Benign prostatic hyperplasia.

Silogin *Diba, Mex.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Silol *Polon, Pol.†*
Dimeticone (p. 2209·3).
Barrier preparation.

Silomat
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Ger.
Pentoxyverine citrate (p. 1672·1).
Cough.

Boehringer Ingelheim, Gr.
Clobutinol hydrochloride (p. 1658·3).
Cough.

Silomat Compositum *Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Indon.†*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3).
Cough; bronchospasm.

Silomat DMP *Boehringer Ingelheim, Ger.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Silomed *Medicpharma, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Silon *Smith & Nephew, Swed.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Barrier cream; anorectal disorders; dermatitis.

Silopect *Pyridam, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Silopral *Silanes, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration; Zollinger-Ellison syndrome.

Silostar *Menarini, Spain.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Silostar Plus *Menarini, Spain.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Silovir *Eczacibasi, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Silox-50 *Jean-Marie, Hong Kong.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Flatulence; gastritis; heartburn; gastric hyperacidity.

Siloxan *Nycomed, Norw.*
Simeticone (p. 1886·2).
Flatulence; postoperative intestinal gas retention.

Siloxogene *RPG, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); sorbitol (p. 2092·1).
Gastric hyperacidity.

Silphen *Silarx, USA.*
Diphenhydramine hydrochloride (p. 626·2).

Silphen DM *Silarx, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Silphin *Specifar (Σπεσιφαρ), Gr.*
⊗Xylometazoline hydrochloride (p. 1680·1).

Siltussin
Note: this name may be used for preparations of different composition.
Silarx, USA.
Guaifenesin (p. 1666·2).
Coughs.

Silom, Thai.
Guaifenesin (p. 1666·2); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Siltussin DM *Silarx, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Siludrox *Eurofarma, Braz.*
Dimeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal hyperacidity; flatulence.

Silueta Plus *Incaico, Arg.†*
Carnitine (p. 2053·2); fucus (p. 2612·1); garcinia (p. 2510·2); equisetum (p. 2500·1).
Obesity.

Silum *Mersifarma, Indon.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Siluron *Fluoron, Ger.*
Dimeticone (p. 2209·3).
Ophthalmic tamponade.

Silvaden *Eczacibasi, Turk.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers and wounds.

Silvadene *Aventis, Mex.†; Monarch, USA.*
Sulfadiazine silver (p. 362·3).
Infected burns.

Silvadiazin *Toprak, Turk.; Julphar, UAE.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers and wounds.

Silvamed *Kocak, Turk.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers and wounds.

Silvasta *Douglas, NZ.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Silvaysan *Sanum-Kehlbeck, Ger.*
Milk thistle (p. 1561·1).
Liver disorders.

Silvazine *Smith & Nephew, Austral.†; Smith & Nephew, NZ†; Smith & Nephew, Singapore.†*
Sulfadiazine silver (p. 362·3); chlorhexidine gluconate (p. 1743·3).
Prevention of infection in burns, ulcers, and wounds.

Silvederma *Aldo-Union, Hong Kong; Expomedica, Port.; Aldo-Union, Rus.; Aldo, Spain; Medifarm, Venez.*
Sulfadiazine silver (p. 362·3).
Burns; skin ulcers; wounds; bacterial skin infections.

Silver Bullet *D & C Mobility, Canad.*
Bisacodyl (p. 1821·1).
Constipation.

Silvercel *Systagenix, Ital.*
Hydroalginate dressing with silver (p. 2167·2) (p. 2615·1).
Infected wounds.

Silverderm *TO-Chemicals, Thai.*
Sulfadiazine silver (p. 362·3).
Infected burns.

Silverdin *Deva, Turk.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers and wounds.

Silverdres *Deverge, Ital.*
Polyurethane dressing with silver (p. 1718·1) (p. 2615·1).
Wounds; burns.

Silverex *Ranbaxy, India.*
Sulfadiazine silver (p. 362·3); chlorhexidine gluconate (p. 1743·3) or chlorhexidine hydrochloride (p. 1743·3).
Burns; ulcers; wounds; skin infections.

Silverit *SF, Ital.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Silverol *Teva, Israel; Abic-Teva, Thai.*
Sulfadiazine silver (p. 362·3).
Burns; infected skin ulcers; infected wounds.

Silverseal *Alliqua, USA.*
Silver (p. 2615·1).
Wounds.

Silvertone *Resinag, Switz.†*
Sulfadiazine silver (p. 362·3).
Infected burns, wounds, and ulcers.

Silvespray *Casimiro & Moreira, Port.†*
Sulfadiazine silver (p. 362·3).
Burns, ulcers, wounds; skin infections.

Silvex *RX, Hong Kong; Agio, Philipp.; RX, Thai.*
Sulfadiazine silver (p. 362·3).
Burns; skin ulcers; wounds.

Silvia Osteo *Alta Care, Ital.*
Calcium phosphate (p. 1784·2); lithothamnium calcareum; vitamin B substances (p. 2102·3).
Calcium supplement.

Silvin *ICM, Singapore.*
Sulfadiazine silver (p. 362·3); chlorhexidine gluconate (p. 1743·3).
Infected burns, leg ulcers and pressure sores.

SilvrStat *ABL, USA.*
Silver (p. 2615·1).
Wounds.

Silybon *Micro, India.*
Silymarin (p. 1561·2).
Liver disorders.

Silygal *Ivax, Cz.†*
Silymarin (p. 1561·2).
Liver disorders.

Sim *Galmed, Cz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simacor *Berksam, Turk.*
Simvastatin (p. 1489·2).

Simacort *Siam Bheasach, Thai.*
⊗Triamcinolone (p. 1648·3) or triamcinolone acetonide (p. 1649·1).
Musculoskeletal, joint, and peri-articular disorders; skin disorders.

Simacron *Tempo Scan Pacific, Indon.*
Roxithromycin (p. 356·2).
Bacterial infections.

Simagel
Note: this name may be used for preparations of different composition.
Atlantic, Malaysia.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.
Mibe, Ger.; Philopharm, Rus.
Almasilate (p. 1815·3).
Gastrointestinal disorders.

Simaglen *Unison, Hong Kong; Unison, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; systemic mastocytosis.

Simaldoz *Liconsa, Neth.*
Valsartan (p. 1521·2).
Hypertension.

Simar
Note: this name may be used for preparations of different composition.
KRKA, Denm.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simarc-2 *Fahrenheit, Indon.*
Warfarin sodium (p. 1527·1).
Venous thrombosis; coronary occlusion.

Simarlen *Coup, Gr.*
Cinoxacin (p. 261·1).

Simaspen *Ranbaxy, S.Afr.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease.

Simastinteva *Med, Turk.*
Simvastatin (p. 1489·2).

Simator *Arrow, Irl.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simatral *Ethica, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Simbado *Lapi, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simbathree *Hizon, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simbatrix *SF, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simbela *Belupo, Cz.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simbicort *AstraZeneca, Rus.†; AstraZeneca, Ukr.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Obstructive airways disease; asthma.

Simbion *Merck, Chile.*
Vitamins; minerals.
Dietary supplement.

Simbrinza *Alcon, USA.*
⊗Brinzolamide (p. 2005·1); brimonidine tartrate (p. 2004·3).
Glaucoma; ocular hypertension.

Simcard *Cipla, Hong Kong; Cipla, India; Cipla, Malaysia†; Cipla-Medpro, S.Afr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias; atherosclerosis.

Simcef *Erlimpex, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Simchol *Aristo, India; Ikapharmindo, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simciti *Simex, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebrovascular disorders.

Simcomag *Vesco, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Simcomine *TO-Chemicals, Thai.*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Gastrointestinal spasm.

Simcone *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
Simeticone (p. 1886·2).
Flatulence; meteorism; aid in gastrointestinal examination.

Simcor *Abbott, USA.*
Nicotinic acid (p. 2083·1); simvastatin (p. 1489·2).
Hypercholesterolaemia.
Nanxin, China; Medikon, Indon.†
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simcora *Sandoz, Switz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simcovas *Actavis, Irl.; Actavis, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simdax *Abbott, Arg.; Abbott, Austria; Abbott, Braz.; Orion, Cz.; Orion, Fin.; Orion, Gr.; Abbott, Hong Kong†; Orion, Hung.; Orion, Israel; Orion, Ital.; Abbott, Mex.; Orion, Norw.; Abbott, NZ; Abbott, Port.; Orion, Rus.; Orion, Singapore†; Orion, Spain; Abbott, Swed.; Orion, Swed.; Abbott, Turk.; Orion, Ukr.*
Levosimendan (p. 1420·1).
Heart failure.

Simeco *Wyeth, Gr.; Wyeth, India; Wyeth, Philipp.†*
Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).
Antacid; gastric hyperacidity; flatulence; peptic ulcer; hiatus hernia; oesophagitis; aerophagia; heartburn.
Wyeth, Philipp.
Tablets: Simeticone (p. 1886·2); hydrotalcite (p. 1845·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; flatulence.
Sunthi Sepuri, Indon.†; Wyeth Consumer, Thai.†; Wyeth, UK.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastric hyperacidity; gastro-oesophageal reflux.

Simeco Plus *Eurofarma, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastrointestinal hyperacidity; flatulence.

Simecon *Sanitas, Arg.; Chinta, Thai.*
Simeticone (p. 1886·2).
Infant flatulence; gastrointestinal disorders with excess gas; aid to gastrointestinal examination.

Simecon Antiacido *Sanitas, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Flatulence; gastrointestinal hyperacidity.

Simecrin *Crinos, Ital.*
Simeticone (p. 1886·2).
Flatulence.

Simelgat Plus *Munir, Turk.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Simepar *Mepha, Cz.; Mepha, Hong Kong; Mepha, Malaysia; Mepha, Singapore; Mepha, Ukr.*
Silymarin (p. 1561·2); vitamin B substances (p. 2102·3).
Liver disorders; biliary-tract disorders; nutritional supplement.

Simépar *Mepha, Switz.*
Milk thistle (p. 1561·1); vitamin B substances (p. 2102·3).
Liver disorders.

Simestat *Orifarm, Denm.†; Simesa, Ital.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simet *Jelfa, Pol.†*
Simeticone (p. 1886·2).
Excess gastrointestinal gas.

Simetac *Vida, Hong Kong.†*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer.

Simetic *Antonetto, Ital.*
Simeticone (p. 1886·2).
Flatulence.

Simetrid *Nizpharm, Rus.*
⊗Fluocinolone acetonide (p. 1636·1); bismuth subgallate (p. 1822·1); menthol (p. 2553·2); trimecaine (p. 1997·3).
Anorectal disorders.

Simetyl *M & H, Thai.*
Simeticone (p. 1886·2).
Flatulence.

Simex *Hua, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Simgal *Teva, Cz.; Teva, Pol.; Ivax, Rus.; Teva, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Simicol *CTS, Israel; CTS, Rus.*
Simeticone (p. 1886·2).
Flatulence; infant colic; griping pain; meteorism; preparation for gastrointestinal procedures.

Simidon *Actavis, Swed.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Similac Advance Hypoalergenica *Abbott, Venez.*
Infant feed.

Similac Advance LF *Abbott, Indon.*
Infant feed.
Lactose intolerance.
Abbott, Mex.
Lactose-free infant feed.
Lactose intolerance.

Similac Advance libre de lactosa *Abbott, Venez.*
Infant feed.
Lactose intolerance.

Similac Advance Sin Lactosa *Abbott, Chile.*
Infant feed.
Lactose intolerance.

Similac Alimentum *Abbott Nutrition, Singapore; Abbott Nutrition, UK.*
Protein hydrolysate (p. 2086·2) infant feed.
Food allergies; protein sensitivity; lactose intolerance; cows' milk allergy.

Similac Isomil *Abbott, Hong Kong.*
Infant feed.
Formerly known as Isomil.
Lactose intolerance; cows' milk intolerance; galactosaemia.

Similac Lactose Free *Ross, USA.*
Lactose-free infant feed.
Lactose intolerance.

Similac LF *Abbott, Hong Kong†; Abbott, Malaysia; Abbott, Thai.*
Lactose-free infant feed.
Diarrhoea; lactose intolerance; infant colic; flatulence.
Ordesa, Ital.†
Infant feed.
Lactose intolerance.

Similac Mama's Best *Abbott, Indon.*
Nutritional supplement for pregnancy and lactation.

Similac Mum *Abbott Nutrition, Singapore.*
Nutritional supplement for pregnancy and breastfeeding.

Similac PM 60/40 *Ross, USA.*
Low-mineral infant feed.
Hypocalcaemia; renal impairment.

Similac RA *Syrio, Ital.†*
Infant feed.
Hypersensitivity.

Similac Sensitive *Abbott, Canad.*
Lactose-free infant feed.
Formerly known as Similac LF.
Lactose intolerance.

Similac Sensitive for Fussiness & Gas *Abbott, USA.*
Infant feed.
Lactose sensitivity.

Similac Sensitive for Spit-Up *Abbott, USA.*
Infant feed.
Regurgitation.

Similac Soy Isomil *Abbott, USA.*
Infant feed.

Similasan 1 *Ocusoft, USA.*
Artificial tears.

Similase Jr *Integrative, USA.*
Amylase (p. 2442·1); protease; tilactase (p. 2631·2); cellulase (p. 2473·1); lipase (p. 2579·3).
Digestive disorders.

Similibus *Knop, Chile.*
⊗Histaminum (p. 2525·2); aspidosperma (p. 2601·2); blatta orientalis; bryonia dioica (p. 2461·3); carbo vegetabilis (p. 1537·3); eupatorium perfoliatum (p. 2459·1); lobelia inflata (p. 2323·2); natrium sulfuricum (p. 1888·1); radix ipecacuanha (p. 1667·2); sambucus nigra (p. 2609·3); urtica dioica (p. 2639·3).
Homoeopathic preparation.

Simina *Elea, Arg.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Simirex *Sanofi-Aventis, Cz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simlip *Mediwin, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Simlo *Ipca, India; Ipca, Rus.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; hypercholesterolaemia.

Simovil *MSD, Israel.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simoyiam *Siam Bheasach, Thai.*
Flunarizine hydrochloride (p. 629·3).
Migraine; cerebrovascular disorders.

Simp *Esoform, Ital.*
Chlorhexidine gluconate (p. 1743·3); benzalkonium chloride (p. 1737·1).
Skin and wound disinfection.

Simperten *Laboratorios Chile, Chile.*
Losartan potassium (p. 1422·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Simperten-D *Laboratorios Chile, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Simpla *Elea, Arg.*
Zoledronic acid (p. 1192·3).
Osteoporosis; Paget's disease of bone.

Simplacor *Biochemie, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simplaqor *Sandoz, Gr.; Sandoz, Hong Kong; Sandoz, Mex.; Sandoz, Venez.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Simple Essentials Protect *Blistex, Canad.*
Oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Simple HCG *Brassora, Arg.*
Pregnancy test (p. 2596·1).

Simplene *Smith & Nephew, S.Afr.†*
⊗Adrenaline (p. 1292·1).
Open-angle glaucoma.

Simplet *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Simplex *Ophtha, Norw.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Dry eyes; eye irritation.

Simplotan *Pfizer, Austral.*
Tinidazole (p. 949·2).
Protozoal infections; anaerobic bacterial infections.

Simply Botanical Sensations Healing Hands *Germiphene, Canad.*
⊗Urea (p. 1727·3).
Barrier cream; dry skin.

Simply Botanical Sensations Soothing Skin *Germiphene, Canad.*
Triclosan (p. 1773·2).

Simply Cough *McNeil Pharmaceutical, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Simply Sleep *McNeil Consumer, Canad.; McNeil, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders; insomnia.

Simply Stuffy *McNeil Pharmaceutical, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Simponi *Janssen-Cilag, Austral.; Centocor, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Janssen, Canad.; Centocor, Cz.; Janssen-Cilag, Denm.; MSD, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen, Irl.; Janssen-Cilag, Israel; Janssen, Jpn; MSD, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Centocor, Pol.; Janssen, Port.; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, UK; Janssen, USA.*
Golimumab (p. 66·3).
Rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; ulcerative colitis.

Simpottantacinque *Esoform, Ital.*
⊗Benzalkonium chloride (p. 1737·1); chlorhexidine gluconate (p. 1743·3); alcohol (p. 1733·1).
Disinfection of skin, wounds, and burns.

Simpsons *Medico-Biological Laboratories, UK.*
Zinc stearate (p. 2221·2); zinc oxide (p. 1729·1); sublimed sulfur (p. 1721·1); salicylic acid (p. 1719·1).
Skin disorders.

Simratio *Ratiopharm, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simredin *Polfa Kutno, Pol.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simron Plus *SmithKline Beecham, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); iron (p. 2073·1); folic acid (p. 2063·1).

Simrose *Serum Institute, India.*
Evening primrose oil (p. 2502·2).
Eczema; diabetic neuropathy; skin and hair disorders.

Simryl *Simex, Indon.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Simstat *Lupin, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

SimStatin *AFT, NZ.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Simtan *Clonmel, Irl.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simtec *CCM, Hong Kong; CCM, Malaysia; Upha, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Simtin *Eurodrug, Hong Kong; Eurodrug, Malaysia; Eurodrug, Philipp.; Eurodrug, Singapore.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simuc *Cypress, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cough; upper respiratory-tract congestion; otitis media.

Simuc DM *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Simucil *Mersifarma, Indon.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders.

Simucin *Siam Bheasach, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Simulcium G3 *Dermoteca, Port.*
Emollient and moisturiser.
Stretch marks.

Simulect *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Basiliximab (p. 1944·1).
Transplant rejection.

Simultan
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Thioridazine hydrochloride (p. 1110·2).
Childhood behaviour disorders; depression; psychoses.
Lazar, Arg.
Valsartan (p. 1521·2).
Hypertension.

Simultan A *Lazar, Arg.*
Valsartan (p. 1521·2); amlodipine besilate (p. 1304·1).
Hypertension.

Simultan D *Lazar, Arg.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Simusol *Siam Bheasach, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Simva *Sandoz, Cz.†; Hennig, Ger.; TAD, Ger.; Arrow, NZ.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

SimvaAPS *APS, Ger.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvabell *Bellwether, Austral.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvabeta *Betapharm, Ger.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvacard *Zentiva, Cz.; AWD, Ger.†; Zentiva, Pol.; Zentiva, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Simvachol *Medicus, Gr.; Richter, Pol.; Gedeon Richter, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Simvacol *Teva, Hung.; Generis, Port.; Teva, Rus.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; coronary artery disease; hypercholesterolaemia.

Simvacop *Copyfarm, Denm.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simvacor *Kleva, Gr.; Yung Shin, Hong Kong†; Trima, Israel; YSP, Malaysia; Yung Shin, Philipp.; Polfarmex, Pol.; Pharma Dynamics, S.Afr.; Kleva, Singapore; Darnitsa, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias; atherosclerosis.

Simvadoc *Docpharm, Ger.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvador *Discovery, UK.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; secondary prevention of coronary heart disease.

Simvafour *Solvay, Belg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvagamma *Worwag, Ger.; Worwag, Hung.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; coronary artery disease.

Simvagen *Generics, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvahall *Helm, Denm.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvahex *Sandoz, Philipp.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvahexal *Sandoz, Austral.; Hexal, Ger.†; Sandoz, Pol.; Hexal, Rus.; Sandoz, Ukr.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvahot *Helm, Denm.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvaklein *Helm, Denm.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvakol *Nobel, Turk.*
Simvastatin (p. 1489·2).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Simvalark *Ideosmos, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Simvalid *Vivax, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Simvalimit *Grindex, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvalip *Mibe, Ger.; Mibe, Neth.; Genexo, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvanidda *Stada, Denm.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvanox *Verisfield, Gr.*
Simvastatin (p. 1489·2).

Simvaprol *Novendia, Gr.; Proel, Gr.*
Simvastatin (p. 1489·2).

Simvar *Arrow, Austral.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvarcana *Arcana, Austria.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

SimvaRex *Rex, NZ.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Simvas *Micro, Singapore; Masa, Thai.*
Simvastatin (p. 1489·2).
Coronary heart disease; hyperlipidaemias; cardiovascular risk reduction.

Simvasim *Well, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Simvasine *Spirig, Switz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvask *Simex, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Simvass *Rider, Chile.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Simvast *Julphar, UAE.*
Simvastatin sodium (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.
Streuli, Switz.†
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simvastad *Stada, Austria; Stada, Neth.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease; cardiovascular risk reduction.

Simvastaine *Farmaprojects, Neth.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvastamed *Ranbaxy, Belg.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvastat *Hemofarm, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvastec *Permatec, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simvasterol *Med-One, Gr.; Polpharma, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvastil *Medarte, Gr.*
Simvastatin (p. 1489·2).

Simvastin *Geofman, Philipp.; Mepha, Switz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simvastol *Gedeon Richter, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvasyn *GX, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simvatin *GL Pharma, Austria; DAST, Gr.; Pharma International, Ukr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; hypercholesterolaemia; coronary heart disease; cardiovascular risk reduction.

Simvax *Hexal, Cz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis.

Simvaxon *Dexcel, Israel.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvaz *Sel-J, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Simvell *Novell, Hong Kong.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvep *Extractum, Hung.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvoget *Getz, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Simvor *Ranbaxy, Cz.; Ranbaxy, Hong Kong; Ranbaxy, Hung.; Ranbaxy, Malaysia; Ranbaxy, Pol.; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Simvotin *Ranbaxy, India; Ranbaxy, S.Afr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Simzal *Teva, Singapore.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Simzor *Gerard, Irl.; Reddy, S.Afr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sin Colgen Kowa Kaze *Kowa, Jpn.†*
⊗Paracetamol (p. 115·1); tranexamic acid (p. 1164·2); ethenzamide (p. 56·2); chlorphenamine maleate (p. 620·3); tipepidine hibenzate (p. 1679·1); methylephedrine hydrochloride (p. 1669·2).
Cold symptoms.

Sin Q & P Gold *Kowa, Jpn.†*
Vitamins; deer antler velvet; oryzanol (p. 2578·1); oxoamidine; caffeine (p. 1203·3).
Tonic.

Sin Una Cool Liquid *Kowa, Jpn.†*
Diphenhydramine hydrochloride (p. 626·2); lidocaine (p. 1988·1); levomenthol (p. 2553·2); dl-camphor (p. 2466·2).
Skin irritation.

Sinac *Andromaco, Arg.*
Adapalene (p. 1692·1).
Acne.

Sinacid *Rider, Chile.†*
Myrtecaine laurilsulfate (p. 1993·1); galactan sulfate (p. 2508·3); aluminium glycinate (p. 1817·2).
Gastrointestinal disorders.

Si-Nade *GSK, S.Afr.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms; sinusitis; Eustachian tube congestion.

Sinadrin PE *Reese, USA.*
Paracetamol (p. 115·1); dexbrompheniramine (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Sinadrin Plus *Reese, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dexbrompheniramine maleate (p. 618·1).

Sinadryl *Inpac, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Sinaf *Taro, Israel.†*
⊗Oxymetazoline hydrochloride (p. 1671·3); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Sinaflan *Biochimic, Rus.; Nizpharm, Rus.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

SiNaGe *Feima, China.*
Aspirin (p. 22·2); dipyridamole (p. 1362·2).

Sin-A-Gen *Nycomed, Mex.*
Polysaccharide polysulfuric acid ester; nonoxinol (p. 2199·1).
Vaginal contraceptive.

Sinakort-A *Ulagay, Turk.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Sinaler *Cassara, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; laryngitis; sinusitis.

Sinaler B *Cassara, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Allergic rhinitis; allergic skin disorders; laryngitis; sinusitis.

Sinaler D *Cassara, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).

Sinalfa *Amdipharm, Denm.; Amdipharm, Norw.; Amdipharm, Swed.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Sinalgia *Hormona, Mex.*
Fepradinol (p. 64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Sinalgico *Bernabo, Arg.*
Ketorolac (p. 80·2) or ketorolac trometamol (p. 80·2).
Pain.

Sin-Algin *Sanitas, Chile.*
Paracetamol (p. 115·1); chlormezanone (p. 1045·1).
Musculoskeletal and joint disorders; pain.

Sinall Formula *Weleda, Canad.†*
Berberis vulgaris fructus (p. 2502·1); phosphorus (p. 2589·2); sambucus nigra (p. 2609·3); teucrium scorodonia.
Homoeopathic preparation.

Sinamida Accion Caspa *Gezzi, Arg.*
Ketoconazole (p. 585·3).
Dandruff; seborrhoeic dermatitis.

Sinamida Atleta *Gezzi, Arg.*
Bifonazole (p. 573·3).
Fungal skin infections.

Sinamida D *Gezzi, Arg.*
Zinc oxide (p. 1729·1).
Burns; skin abrasions; skin irritation.

Sinamida Econazol *Gezzi, Arg.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Sinamida Gyno *Gezzi, Arg.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Sinamida Pies *Gezzi, Arg.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Sinamida Plus *Gezzi, Arg.*
Bifonazole (p. 573·3).
Fungal skin infections.

Sinamida Terbinafina *Gezzi, Arg.*
Terbinafine (p. 593·3).
Fungal skin infections.

Sinanem *Nucitec, Mex.*
Vitamins; minerals.

Sinapause *Schering-Plough, Chile; Organon, Mex.*
Estriol succinate (p. 2275·1).
Genito-urinary tract disorders associated with oestrogen deficiency.

Sinapdin *Phyto Kemo, Indon.†*
Cyproheptadine hydrochloride (p. 624·1).
Rhinitis; allergic conjunctivitis; angioedema; urticaria.

Sinapis nigra N Oligoplex *Madaus, Ger.*
Sinapis nigra (p. 2566·1); aralia racemosa; cepa (p. 2575·2); sabadilla (p. 2611·2).
Homoeopathic preparation.

Sinapisme Rigollot *SERP, Mon.*
Defatted black mustard paper (p. 2566·1).
Respiratory-tract congestion.

Sinaplin *Rimsa, Mex.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Sinarden *Vitae, Mex.*
Aciclovir (p. 964·1).
Herpes labialis.

Sinarest *Centaur, India.*
Nasal drops: ⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Centaur, India; Ciba, USA.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold symptoms; sinusitis; post nasal drip; nasal congestion; upper respiratory-tract symptoms.

Centaur, India.
Suspension; syrup: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Allergic rhinitis; cold and influenza symptoms; sinusitis; otitis media.

Centaur, India.
Tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold and influenza symptoms; sinusitis; otitis media; tonsillitis.

Sinarest Linctus *Centaur, India.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2).
Cough.

Sinarest Vapocaps *Centaur, India.*
Camphor (p. 2466·2); chlorothymol (p. 1748·2); cineole (p. 2479·1); menthol (p. 2553·2); terpineol (p. 2627·2).
Cold symptoms; sinusitis; rhinitis.

Sinarest-PD *Centaur, India.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; sinusitis.

Sinarex *Frik, Turk.*
Granisetron hydrochloride (p. 1844·3).

Sinarona *Kener, Mex.*
Amiodarone hydrochloride (p. 1300·1).
Angina pectoris; arrhythmias.

Sinarta *Farmak, Ukr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Sinartrol *Pharmanel, Gr.; SPA, Ital.*
Piroxicam cinnamate (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Sinasal *Hevert, Ger.*
Arsenum jod. (p. 2448·1); hepar. sulf. (p. 1721·3); kalium bichrom. (p. 2476·2); mercurius bijod. (p. 2555·3).
Homoeopathic preparation.

Sinasmal *Laboratorios Chile, Chile.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Sinaspril-Paracetamol *Bayer, Neth.*
Paracetamol (p. 115·1).
Pain; fever.

Sinaxial *TRB, Arg.*
Sialogangliosides (porcine).
Peripheral neuropathy; cerebral trauma.

TRB, Braz.
Polysiagoside (p. 2510·2).
Cerebrovascular disorders.

Sinccord *Alpharma, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sincerum *Dallas, Arg.*
Sodium carbonate (p. 2617·3); phenazone (p. 124·1); neomycin sulfate (p. 330·1); cetrimide (p. 1742·1).
Ear disorders.

Sincerum Biotic *Dallas, Arg.*
⊗Neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Infected ear disorders.

Sincerum Biotic L *Dallas, Arg.*
⊗Neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3); polymyxin B sulfate (p. 342·3); lidocaine hydrochloride (p. 1988·2).
Infected ear disorders.

Sincerum Dry *Dallas, Arg.*
⊗Isopropyl alcohol (p. 1758·3); glycerol (p. 2517·2).
Removal of trapped ear water.

Sinchlormine *SSP, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Sinchoni *Chinta, Thai.*
Niclosamide (p. 161·2).
Taeniasis.

Sincimet *SSP, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Sinclonac *SSP, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Sincol *Indeco, Arg.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Sincon *CCS, Swed.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Sincorten-A *RCA, Ital.*
Astaxanthin (p. 2170·1).
Skin irritation.

Sincris *Laboratorios Chile, Chile.*
Olanzapine (p. 1089·3).
Schizophrenia; mania.

Sincrosa *Alpharma, Mex.*
Acarbose (p. 466·2).
Diabetes mellitus.

Sincrover *CT, Ital.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Sincumar *Meda, Ukr.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Sindaxel *Actavis, Hong Kong; Actavis, Indon.; Actavis, Pol.; Makiz-Pharma, Rus.; Sindan, Thai.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Sindel *Liferpal, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Sindo *Nordin, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Sindol *Fada, Arg.*
Ibuprofen (p. 68·2).
Inflammation; pain; fever.

Sindopa *Mylan, NZ.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Sindoxplatin *Actavis, Hong Kong.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Sindrat *Brasterapica, Braz.*
Oral rehydration solution (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Sindronat *Sindan, Pol.*
Clodronate disodium (p. 1180·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Sindroxocin *Actavis, Hong Kong; Makiz, Rus.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Sine-Aid IB *McNeil Consumer, USA.*
⊗Pseudoephedrine (p. 1676·1); ibuprofen (p. 68·2).

Sine-Aid Maximum Strength *McNeil Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinus headache.

Sineamin *Piam, Ital.*
Protein-free and gluten-free food for special diets.

SinEccH *Alpine, Singapore.*
Arnica (p. 2447·2).
Soft-tissue injuries.

Sinecod *Novartis Consumer, Belg.; Novartis, Cz.; Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Neth.; Novartis, Philipp.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.*
Butamirate citrate (p. 1657·3).
Cough.

Sinecod Exp *Novartis, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Sinecod Tosse Fluidificante *Novartis Consumer, Ital.*
Carbocisteine (p. 1658·1).
Cough; catarrh.

Sinecod Tosse Sedativo *Novartis Consumer, Ital.*
Butamirate citrate (p. 1657·3).
Cough.

Sinecosin *Novartis, Cz.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Sinedol
Note: this name may be used for preparations of different composition.
Italmex, Mex.†
Paracetamol (p. 115·1).
Pain; fever.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sinedopa *Duopharma, Hong Kong†; CCM, Malaysia.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Sinefed *SSP, Thai.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Nasal congestion; cold symptoms.

Sineflox *CT, Ital.*
Levofloxacin (p. 315·3).

Sinegastrin
Note: this name may be used for preparations of different composition.
Novag, Mex.†
Cimetidine (p. 1827·1).
Peptic ulcer.

Sinegrip *Farmakopea, Ital.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever; cold and influenza symptoms.

Sinei *Steiner, Ger.†*
Cimicifuga (p. 2478·1).
Menopausal disorders.

Sinekin *Vitarum, Arg.*
Biperiden (p. 895·1).
Parkinsonism.

Sinemet *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.†; MSD, Irl.; Merck, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; Pharmalink, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; BMS, Spain; MSD, Swed.; MSD, Switz.; M & H, Thai.; MSD, Turk.; BMS, UK; MSD, USA; MSD, Venez.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
These ingredients can be described by the British Approved Name Co-careldopa.
Parkinsonism; drug-induced extrapyramidal disorders.

Sine-Off Maximum Strength Allergy/Sinus *SmithKline Beecham, USA.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms.

Sine-Off Maximum Strength No Drowsiness Formula *SmithKline Beecham Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract symptoms.

Sine-Off Sinus/Cold *Hogil, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Sinepin *Marlborough Pharmaceuticals, UK.*
Doxepin hydrochloride (p. 414·2).
Depression.

Sinequan *Pfizer, Austral.; Pfizer, Austria†; Pfizer, Belg.; Erfa, Canad.; Pfizer, Denm.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Irl.†; Pfizer, Mex.; Pfizer, Neth; Pfizer, Norw.; Pfizer, Pol.†; Farmasierra, Spain; Pfizer, Thai.; Pfizer, USA.†*
Doxepin hydrochloride (p. 414·2).
Anxiety; mixed anxiety depressive disorders.

Sinerbe *Plough, Port.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1); guaifenesin (p. 1666·2).
Cough; allergic respiratory-tract disorders.

Sinergen *Biosintetica, Braz.*
Amlodipine besilate (p. 1304·1); enalapril maleate (p. 1371·1).
Hypertension.

Sinergina *Faes, Spain.*
Phenytoin (p. 538·2).
Epilepsy.

Sinergix *Rimsa, Mex.*
Ketorolac trometamol (p. 80·2); tramadol hydrochloride (p. 139·2).
Pain.

Sinerpen *Ranbaxy, Ukr.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Sinertec *MSD, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sinesmin *Best, Mex.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Sinestic *Orifarm, Denm.; Paranova, Denm.; AstraZeneca, Ital.; Euro Registratie, Neth.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Sinesticmite *AstraZeneca, Ital.†*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Asthma.

Sinestron *Medix, Mex.*
Lorazepam (p. 1080·3).
Anxiety; mixed anxiety depressive states.

Sinex
Note: this name may be used for preparations of different composition.
Procter & Gamble, Mex.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Richardson-Vicks, USA.
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Sinex Vicks *Procter & Gamble, Cz.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

SinexSensi *Vicks, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinitis; sinusitis.

Sinexsensi *Procter & Gamble, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Sinezan *Praise, Ital.*
Pyrethrum flower (p. 2161·1); piperonyl butoxide (p. 2160·2); diethyltoluamide (p. 2153·1).
Insect repellent.

Sinfatix *Accord, UK·*
Fluvastatin sodium (p. 1385·1).
Hyperlipidaemias; cardiovascular risk reduction.

Sinfexina *Solara, Mex.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Sinflu *Valma, Chile.*
Paracetamol (p. 115·1).
Pain.

Sinfract *Mavi, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Sinfrontal
Note: this name may be used for preparations of different composition.
Lubapharm, Switz.
Chininum arsenicosum (p. 2601·3); ferrum phosphoricum (p. 2077·1); hydrargyri sulfidum rubrum (cinnabaris) (p. 2555·3); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Muller Goppingen, Ger.
Cinnabaris (p. 2555·3); ferrum phosphoricum (p. 2077·1); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Sinfung *Denver, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Sinfussi *SSP, Thai.*
Terpin hydrate (p. 1678·2); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Singlauc *Bausch & Lomb, Arg.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma; ocular hypertension.

Singlet *SmithKline Beecham Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Singloben *Alpharma, Mex.*
Glipizide (p. 474·1).
Diabetes mellitus.

Singlon *Gedeon Richter, Ukr.*
Montelukast sodium (p. 1214·3).
Asthma.

Singril *Offenbach, Mex.*
Injection: Moroxydine hydrochloride (p. 1004·1); chlorphenamine (p. 620·3); dipyrone (p. 53·3).
Cold and influenza symptoms.

Offenbach, Mex.
Syrup: Moroxydine hydrochloride (p. 1004·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Influenza symptoms.

Singrilen *Offenbach, Mex.*
Moroxydine hydrochloride (p. 1004·1); paracetamol (p. 115·1); phenylephrine (p. 1672·2); chlorphenamine (p. 620·3).
Cold and influenza symptoms.

Singrips *Confar, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Singulair *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; MSD, Ukr.; Merck, USA; MSD, Venez.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis; exercise-induced bronchospasm; obstructive airways disease.

Singulergy *MSD, Port.*
Montelukast sodium (p. 1214·3).
Allergic rhinitis.

Sinhcloran *Vitae, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Sinhidron *Vitae, Mex.*
⊗Chlortalidone (p. 1335·2).

Sinif *Valmor, Venez.*
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Valmor, Venez.
Injection: Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

Sinifev *Abbott, Ital.*
Ibuprofen (p. 68·2).
Fever; pain; juvenile idiopathic arthritis.

Sinket *Calox, Venez.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Sinlip *Gador, Arg.*
Rosuvastatin calcium (p. 1488·2).
Atherosclerosis; hypercholesterolaemia.

Sinlumag *SSP, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); atropine sulfate (p. 1310·2).
Gastric-hyperacidity.

Sinmaline *SSP, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Sinmol *Maxfarma, Spain.†*
Paracetamol (p. 115·1).
Pain; fever.

Sinmoquin *SSP, Thai.*
Chloroquine phosphate (p. 650·1).
Malaria; lupus erythematosus; rheumatoid arthritis; amoebiasis.

Sinobid *Biospray, Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Sinobiotik *Galenium, Indon.†*
⊗Gentamicin sulfate (p. 304·2); fluocinolone acetonide (p. 1636·1).
Infected skin disorders.

Sinoclear *Omega, Austral.*
Sea water (p. 2612·1).
Nasal and sinus congestion.

Sinocort *Sanbe, Indon.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth lesions.

Sinoderm *Galenika, Rus.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Sinofed *Pharmahof, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and flu symptoms.

Sinofuan *Simcere, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Sinogan *Sanofi-Aventis, Chile; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Venez.*
Levomepromazine (p. 1079·3).
Psychoses; anxiety; pain; insomnia; premedication; nausea and vomiting; sedative; neuralgia.

Sanofi-Aventis, Mex.; Sanofi-Aventis, Spain.
Levomepromazine hydrochloride (p. 1079·3) or levomepromazine maleate (p. 1079·3).
Psychoses; anxiety; depression; pain; sleep disorders.

Sinogesic *Pharmahof, Thai.*
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Smooth muscle pain and spasm.

Sinografin *Bracco, Canad.; Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p. 1581·3); meglumine adipiodone (p. 1581·1).
Contrast medium for hysterosalpingography.

Sinoline *SSP, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Sinolip *Apotex, Philipp.†*
Lisinopril (p. 1420·3).
Hypertension; myocardial infarction.

Sinomarin *ITF, Chile; Omega, Fr.†; Gerolymatos, Hong Kong; Gerolymatos, Singapore; OM, Switz.; Genesis, Turk.*
Sea water (p. 2612·1).
Nasal congestion; nasal hygiene; nasal irrigation; nasal cleansing.

Sinomenorm *Plus Pharma, Cz.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Sinomol *Sinochem, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Sinophenin *IFET (ΙΦΕΤ), Gr.*
Promazine hydrochloride (p. 1100·1).
Psychoses.

Sinopil *GSK, India.*
Lacidipine (p. 1417·3).
Hypertension.

Sinopren *Ranbaxy, S.Afr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Sinopril *Eczacibasi, Rus.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Mead Johnson, Gr.
Fosinopril sodium (p. 1386·2).
Hypertension.

Sinopryl *Eczacibasi, Turk.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Sinoral *Biolab, Thai.†*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Sinoretik *Eczacibasi, Turk.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sinorezid *Eczacibasi, Rus.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sinoric *Mersifarma, Indon.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Sinose *Salcura, UK.*
Himalayan rock salt; aloe (p. 1693·2); eucalyptus (p. 2501·1); hippophaes rhamnoides; manuka (p. 2550·1); santalum spicatum; melaleuca oil (p. 2551·1); chamomile (p. 2474·1); mentha arvensis (p. 2560·1); propolis (p. 2597·3); urtica (p. 2639·3).
Rhinitis.

Sinot *Eurofarma, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

Sinotar *Lane, UK·*
Althaea (p. 2438·3); echinacea (p. 2498·1); sambucus (p. 2609·3).
Blocked sinuses; catarrh.

Sinova
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Swed.
Gentian (p. 2512·1); primula veris (p. 2596·2); primula elatior (p. 2596·2); sorrel (p. 2620·3); rumex acetosella; rumex obtusifolius; rumex patientia; yellow dock (p. 2649·3); rumex thyrsiflorus; sambucus (p. 2609·3); vervain (p. 2645·1).
Cold symptoms.

Combiphar, Indon.
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinovial
Note: this name may be used for preparations of different composition.
Genevrier, Fr.; IBSA, Ger.; IBSA, Malaysia; IBSA, Switz.
Sodium hyaluronate (p. 2526·2).
Osteoarthritis; degenerative joint disorders.

Sinovid *Hovid, Malaysia.*
Promethazine hydrochloride (p. 638·2); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; upper respiratory-tract allergies.

Sinoxal *Actavis, Hung.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Sinozol *Best, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Sinozzard *Cryopharma, Mex.*
Prazosin hydrochloride (p. 1473·3).
Hypertension.

Sinpasmon *Sanitas, Chile.*
Pipenzolate bromide (p. 1878·1); phenobarbital (p. 535·2).
Gastrointestinal disorders.

Sinpebac *Grossman, Mex.*
Mupirocin (p. 327·2).
Bacterial skin infections; infected burns, ulcers, and wounds.

Sinpermine *SSP, Thai.*
Piperazine hydrate (p. 163·1).
Worm infections.

Sinper-Tabs *SSP, Thai.*
Niclosamide (p. 161·2).
Taeniasis.

Sinpet *Pharmacos Abug, Mex.†*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Sinphe *Imuna, Cz.*
Food for special diets.
Phenylketonuria.

Sinpor *Neves, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Sinpro N *Worwag, Ger.†*
Paracetamol (p. 115·1).
Pain; fever.

Sinprofen *SSP, Thai.*
Ibuprofen (p. 68·2).
Inflammation; pain; fever.

Sinpyrin *SSP, Thai.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Sinquane *Pfizer, Switz.*
Doxepin hydrochloride (p. 414·2).
Anxiety disorders; depression.

Sinral *Bernofarm, Indon.*
Flunarizine (p. 629·3).
Migraine; vestibular disorders; cerebral and peripheral vascular disorders.

Sinresor *Bioprofarma, Arg.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases.

Sinroncar *Millet-Franklin, Arg.*
Polysorbate 80 (p. 2203·3).
Snoring.

Sinseron *Kyorin, Jpn.*
Indisetron hydrochloride (p. 1848·3).
Nausea and vomiting associated with cancer chemotherapy.

Sinsia *Seoul Pharma, Singapore.†*
⊗Serrapeptase (p. 2613·3).
Inflammation; respiratory-tract congestion.

Sinsufyva *Ultra, Mex.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye and ear disorders.

Sintab *Tripharma, Turk.*
Citalopram hydrobromide (p. 411·1).

Sintalgin *Abbott, Braz.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Sintamel *Santa, Gr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Sintamin *Fresenius Kabi, Ital.*
Amino acids.
Parenteral nutrition.

Sintaser *Serral, Mex.*
⊗Propranolol (p. 1479·1).
Hypertension.

Sintebron *Sintesina, Arg.*
⊗Ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Cough.

Sintecal *Menarini, Hung.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sintegran *Sintesina, Arg.*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Sintemel *Asofarma, Mex.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Sintemicina *Sintesina, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Sintenyl *Sintetica, Switz.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Sintepul *Sintesina, Arg.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Sinterol *Klonal, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Sinterol Compuesto *Klonal, Arg.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hyperlipidaemias.

Sinthecillin *Proel, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Sinthrome *Alliance, UK.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Sintir *Ratiopharm, Cz.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Sintisone *Pfizer, Venez.*
⊗Prednisolone steaglate (p. 1646·1).
Corticosteroid.

Sintocalmy *Ache, Braz.*
Passion flower (p. 2584·1).

Sintocef *Boniscontro & Gazzone, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Sintoclar *Boniscontro & Gazzone, Ital.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; parkinsonism.

Sintoftona *SMB, Chile.*
⊗Chloramphenicol (p. 257·1); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Sintomicetina *Medley, Braz.*
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Sintonal *Europharma, Spain.*
Brotizolam (p. 1042·1).
Insomnia.

Sintonyn *Menarini, Cz.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Sintopen *Magis, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sintopozid *Actavis, Hong Kong; Actavis, Hung.; Sindan, Pol.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Sintopram *Biomedica, Ital.*
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Sintosin *Maver, Chile.*
Ivy (p. 2536·2).

Sintotrat *Bracco, Ital.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Sintozima *Solvay, Braz.†*
⊗Pancreatin (p. 2579·3); metoclopramide hydrochloride (p. 1862·2); bromelains (p. 2460·3); dehydrocholic acid (p. 2492·1); cellulase (p. 2473·1); dimeticone (p. 1886·2).
Digestive disorders.

Sintradon *Synthesis, Rus.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Sintrine *Sandoz, S.Afr.*
Montelukast (p. 1214·3).

Sintrol *Solas, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sintrom *Novartis, Arg.; Novartis, Austria; Novartis, Belg.; Paladin, Canad.; Novartis, Fr.; Novartis, Gr.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Switz.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Sinuberase *Sanofi-Aventis, Mex.†*
Lactic-acid-producing organisms (p. 2596·3).
Restoration of normal intestinal flora; diarrhoea.

Sinuc *Hexal, Ger.†*
Ivy (p. 2536·2).
Bronchitis; catarrh.

Sinuclear *Aspen Consumer, S.Afr.*
Paediatric syrup: ⊗Paracetamol (p. 115·1); triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Aspen Consumer, S.Afr.
Capsules: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Upper respiratory-tract congestion.

Sinucon *Thebe, S.Afr.*
⊗Paracetamol (p. 115·1); ephedrine hydrochloride (p. 1663·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; hay fever; sinus congestion.

Sinueaze *Douglas, Canad.†*
⊗Ephedra (p. 1663·1).

Sinueeze *PlantaPhile, UK.*
Gentian (p. 2512·1); vervain (p. 2645·1); sorrel (p. 2620·3); sambucus (p. 2609·3); primula flower (p. 2596·2).
Nasal congestion; sinusitis.

Sinuend *Thebe, S.Afr.*
⊗Paracetamol (p. 115·1); ephedrine hydrochloride (p. 1663·2); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Sinufed *Trima, Israel.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinus congestion.

Sinufed Timecelles *Roberts, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Nasal congestion; coughs and cold symptoms.

Sinufen *Medicpharma, Thai.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Cold symptoms.

Sinufin *Teva, Mex.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Sinufleur *Bloem Beheer, Neth.*
Ambra grisea (p. 2440·3); arsenicum iodatum (p. 2448·1); hydrastis canadensis (p. 2528·1); luffa operculata (p. 2545·3); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Sinuforte *Invar, Rus.*
Cyclamen europaeum (p. 2490·2).
Sinusitis.

Sinuforton *Winthrop, Ger.†*
Capsules: Anise oil (p. 2444·3); cowslip rhizome (p. 2596·2); thyme (p. 2630·2).
Upper respiratory-tract congestion.

Winthrop, Ger.†
Oral liquid: Cowslip rhizome (p. 2596·2); thyme (p. 2630·2).
Cold symptoms.

Sinugesic *Aspen Consumer, S.Afr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Fever; pain; upper respiratory-tract congestion.

Sinuherb *PlantaPhile, UK.*
Gentian (p. 2512·1); vervain (p. 2645·1); sorrel (p. 2620·3); sambucus (p. 2609·3); primula flower (p. 2596·2).
Nasal congestion; sinusitis.

Sinuhist *Dexo, USA.†*
⊗Brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Sinulen *Mediline, Israel.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Sinumax *Janssen-Cilag, S.Afr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Sinumax Allergy *Janssen-Cilag, S.Afr.*
Levocabastine hydrochloride (p. 632·2).
Allergic rhinitis.

Sinumax Allergy Sinus *Janssen-Cilag, S.Afr.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Allergic rhinitis; cold symptoms.

Sinumax with Codeine *Janssen-Cilag, S.Afr.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cold and influenza symptoms.

Sinumax Cold & Flu *Janssen-Cilag, S.Afr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Cold and influenza symptoms; sinusitis.

Sinumax Cold & Flu Plus Cough *Janssen-Cilag, S. Afr.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Sinumed *Aspen Consumer, S.Afr.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Sinupan *Ion, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Coughs and cold symptoms; nasal congestion.

Sinupas *Pascoe, Ger.*
Luffa operculata (p. 2545·3); antimonium sulfuratum aurantiacum (p. 2445·1); euphorbium; kreosotum (p. 1659·3).
Homoeopathic preparation.

Sinupret *Flordis, Austral.; Bionorica, Austria; Bionorica, Cz.; Bionorica, Ger.; Bionorica, Hong Kong; Bionorica, Hung.; Bionorica, Indon.†; Darya-Varia, Indon.†; Bionorica, Malaysia; Bionorica, Philipp.; Bionorica, Pol.; Bionorica, Rus.; Bionorica, Singapore; Biomed, Switz.; Bionorica, Thai.†; Bionorica, Ukr.*
Gentian root (p. 2512·1); cowslip flower (p. 2596·2); sorrel (p. 2620·3); sambucus flower (p. 2609·3); vervain (p. 2645·1).
Respiratory-tract inflammation; sinusitis; respiratory-tract congestion.

Sinus
Note: this name may be used for preparations of different composition.
Homeocan, Canad.
Allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); hepar sulfuris calcareum (p. 1721·3); hydrastis can. (p. 2528·1); sticta pulmonaria (p. 2546·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Hylands, Canad.
Calcarea carbonica (p. 1824·3); hydrastis canadensis (p. 2528·1); kali bichromicum (p. 2476·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Pasteur, Chile.
Sodium chloride (p. 1795·1).
Nasal congestion.

Sinus Ease *Homeocan, Canad.*
Calcarea carbonica (p. 1824·3); calcarea fluorica (p. 2053·1); manganum sulfuricum (p. 2081·2); belladonna (p. 2453·3); sabadilla (p. 2611·2); hepar sulfuris calcareum (p. 1721·3); hydrastis canadensis (p. 2528·1); kalium sulfuricum (p. 1793·2); silicea (p. 2208·3); thuja occidentalis (p. 2629·3); kalium bichromicum (p. 2476·3); mercurius sulphuratus ruber (p. 2555·3).
Homoeopathic preparation.

Sinus Excedrin *BMS, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sinus Inhalaciones *Reckitt Benckiser, Spain.*
Camphor (p. 2466·2); cineole (p. 2479·1); peppermint oil (p. 1877·1); Scots pine oil

(p. 2591·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Nasal congestion.

Sinus Medication
Note: this name may be used for preparations of different composition.
Vita Health, Canad.
⊗Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).

Sinus Medication Day *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinus disorders.

Sinus Medication Night *Pharmetics, Canad.*
⊗Paracetamol (p. 115·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1).
Sinus disorders.

Sinus Pain & Nasal Congestion Relief *Vita Health, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Sinus Relief *Jamp, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinus disorders.

Sinusaid *Sriprasit, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sinusalia *Boiron, Canad.*
Belladonna (p. 2453·3); sanguinaria canadensis (p. 2610·1); spigelia anthelmia (p. 2621·3).
Homoeopathic preparation.

Sinuselect N *Dreluso, Ger.*
Cinnabaris (p. 2555·3); carbo vegetabilis (p. 1537·3); silicea (p. 2208·3); kalium bichromic. (p. 2476·3); calcium sulfuric. (p. 2173·1); hydrastis (p. 2528·1); thuja (p. 2629·3).
Homoeopathic preparation.

Sinusin *Welti, Switz.*
Acidum silicicum (p. 2208·3); calcium iodatum (p. 1658·1); ferri phosphas (p. 2077·1); hydrargyri sulfidum rubrum (p. 2555·3); hydrastis canadensis (p. 2528·1); kalii dichromas (p. 2476·3).
Homoeopathic preparation.

Sinusitis Hevert *Hevert, Ger.†*
Arsenum jodatum (p. 2448·1); hepar sulfuris (p. 1721·3); kalium bichromicum (p. 2476·3); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Sinusitis Hevert SL *Hevert, Ger.*
Apis (p. 2445·2); baptisia (p. 2647·2); cinnabaris (p. 2555·3); echinacea (p. 2498·1); hepar sulf. (p. 1721·3); kal. bichrom. (p. 2476·3); lachesis (p. 2538·3); luffa (p. 2545·3); mercur. bijod. (p. 2555·3); silicea (p. 2208·3); spongia.
Homoeopathic preparation.

Sinusitis-Weliplex *Weber & Weber, Ger.†*
Hydrargyrum sulf. rubr. (p. 2555·3); kalium bichromicum (p. 2476·3); luffa operculata (p. 2545·3).
Homoeopathic preparation.

Sinuspax *Lehning, Fr.*
Calcarea carbonica (p. 1824·3); calcarea fluorica (p. 2053·1); manganum sulfuricum (p. 2081·2); atropa belladonna (p. 2453·3); sabadilla (p. 2611·2); heparis sulfuris calcareum (p. 1721·3); hydrastis canadensis (p. 2528·1); kalium sulfuricum (p. 1793·2); silicea (p. 2208·3); thuya occidentalis (p. 2629·3); kalium bichromicum (p. 2476·3); cinnabaris (p. 2555·3).
Homoeopathic preparation.

Boiron, Switz.†
Calcii fluoridum (p. 2053·1); hepar sulfuris calcareum (p. 1721·3); hydrargyri sulfidium rubrum (p. 2555·3); hydrastis (p. 2528·1); kali dichromas (p. 2476·3); mangani sulfas (p. 2081·2); sabadilla (p. 2611·2); silicea (p. 2208·3).
Homoeopathic preparation.

Homeocan, Canad.†
Belladonna (p. 2453·3); calcii carbonas (p. 1824·3); calcii fluor (p. 2053·1); heparis sulf calc (p. 1721·3); kali bichromicum (p. 2476·3); mangani sulfas (p. 2081·2); kalium sulfuricum (p. 1793·2); sabadilla (p. 2611·2); silicea (p. 2208·3); thuja (p. 2629·3); cinnabaris (p. 2555·3).
Homoeopathic preparation.

Sinus-Relief *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Sinustat
Note: this name may be used for preparations of different composition.
Goldex, S.Afr.
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Sinustat Flu *Goldex, S.Afr.*
Capsules: Paracetamol (p. 115·1); vitamin C (p. 2110·3); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Goldex, S.Afr.†
Syrup: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Sinustop *Adcock Ingram Self Medication, S.Afr.†*
Tablets: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); phenyltoloxamine citrate (p. 638·1).
Cold and flu symptoms.

Sinustop with Codeine *Adcock Ingram Self Medication, S.Afr.†*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); phenyltoloxamine citrate (p. 638·1); codeine phosphate (p. 40·2).
Cold and flu symptoms.

Sinustop Pro *Murdock, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sinustrat *Zurita, Braz.*
Luffa operculata (p. 2545·3); sodium chloride (p. 1795·1).
Nasal congestion.

Sinustrat Solucao Natural *Zurita, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Sinustrat Vasoconstritor *Zurita, Braz.*
⊗Sodium chloride (p. 1795·1); naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Sinusyx *Syxyl, Ger.*
Arsenum jodatum (p. 2448·1); kalium chloratum (p. 1793·2); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Sinutab *Johnson & Johnson, S.Afr.*
Nasal spray: ⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Elea, Arg.; McNeil, Belg.; McNeil Healthcare, Irl.†
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinusitis; cold and influenza symptoms; allergic rhinitis.

Johnson & Johnson, Braz.
Chlorphenamine maleate (p. 620·3); aspirin (p. 22·2); caffeine (p. 1203·3).
Cold and influenza symptoms.

Johnson & Johnson, Chile; Pfizer Consumer, S.Afr.†
Tablets: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); phenyltoloxamine citrate (p. 638·1).
Otitis; rhinitis; sinusitis; sinus headache; cold and influenza symptoms.

Sinutab II *Johnson & Johnson, Port.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinusitis.

Sinutab Advance *Johnson & Johnson Consumer, Mex.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Upper respiratory-tract disorders.

Sinutab with Codeine
Note: this name may be used for preparations of different composition.
Johnson & Johnson, S.Afr.
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); phenyltoloxamine citrate (p. 638·1); codeine phosphate (p. 40·2).
Sinus congestion and pain; cold and influenza symptoms; hay fever.

McNeil Consumer, Canad.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Nasal congestion; cold symptoms.

Sinutab Extra *Johnson & Johnson Consumer, Mex.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Sinusitis.

Sinutab Extra Strength
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Philipp.
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Sinus headache; nasal congestion; cold and influenza symptoms; sinusitis.

McNeil Consumer, Canad.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Nasal congestion; cold symptoms.

Sinutab Extra Strength Daytime/Nightime *Pfizer Consumer, Canad.†*
⊗Tablets (Daytime), pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); tablets (Nightime), pseudoephedrine hydrochloride; paracetamol; diphenhydramine hydrochloride (p. 626·2).
Sinusitis; rhinitis; cold symptoms.

Sinutab Maximum Strength Sinus Allergy *Warner-Lambert, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Sinutab ND *Johnson & Johnson, S.Afr.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

McNeil Consumer, Canad.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms.

Sinutab ND Extra Strength *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms.

Sinutab Nightime *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; cold symptoms.

Sinutab Non-Drying *McNeil, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cough.

Sinutab NS *Johnson & Johnson, Philipp.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion.

Sinutab NT *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Sinutab PE *Johnson & Johnson, Philipp.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); phenyltoloxamine citrate (p. 638·1).
Sinus headache; nasal congestion; rhinitis; sinusitis.

Sinutab Regular *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Nasal congestion; cold symptoms.

Sinutab Sinus Allergy *Johnson & Johnson, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders.

Sinutab Sinus and Allergy *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Rhinitis; cold symptoms; sinusitis.

Sinutab Sinus Allergy Congestion and Pain *Johnson & Johnson, S.Afr.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1) chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms; rhinitis; sinus pain.

Sinutab Sinus Allergy & Pain Relief *Johnson & Johnson, Austral.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Sinutab Sinus Maximum Strength *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Formerly known as Sinutab Sinus Without Drowsiness Maximum Strength and contained pseudoephedrine hydrochloride and paracetamol.
Upper respiratory-tract symptoms.

Sinutab Sinus Non Drowsy *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; cold symptoms; sinusitis.

Sinutab Sinus & Pain Relief *Johnson & Johnson, Austral.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Sinutab 3-Way *Johnson & Johnson, S.Afr.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sinusitis.

Sinutab Without Drowsiness *Warner-Lambert, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Sinutil *Vincenti, Venez.*
Oral drops: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; teething; post-vaccination symptoms.

Vincenti, Venez.
Syrup: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms; teething; post-vaccination symptoms.

SINUtuss DM *WE, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Coughs.

Sinuvent PE *WE, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Sinvacor *MSD, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sinvalip *Sigma, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinvane *Brasterapica, Braz.†*
Simvastatin (p. 1489·2).

Sinvascor *Baldacci, Braz.*
Simvastatin (p. 1489·2).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction.

Sinvastacor *Hexal, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinvastamed *Cimed, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinvastil *Neo-Farmaceutica, Port.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Sinvaston *Sanval, Braz.*
Simvastatin (p. 1489·2).

Sinvat *EG, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sinvatrox *Legrand, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinvax *Geolab, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinvaz *Biofarma, Venez.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Sinver *Valmor, Venez.*
Cinnarizine (p. 622·1).
Vestibular disorders; cerebral and peripheral vascular disorders.

Sinzac *Taiwan Biotech, Malaysia.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Siochrome *David, India.*
Tablets: Carbazochrome (p. 1137·1); menadione sodium bisulfite (p. 2122·2); vitamin C (p. 2110·3); calcium hydrogen phosphate (p. 1783·3).
Haemorrhagic disorders.

David, India.†
Injection: Carbazochrome (p. 1137·1).
Haemorrhagic disorders.

Siofor *Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Pol.; Menarini, Pol.; Berlin-Chemie, Rus.; Berlin-Chemie, Ukr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Siokof-P *David, India.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); bromhexine hydrochloride (p. 1656·3); menthol (p. 2553·2).
Formerly contained dextromethorphan hydrobromide, pseudoephedrine hydrochloride, bromhexine hydrochloride, ammonium chloride, and menthol.
Cough; nasal congestion; cold and influenza symptoms.

Sioneuron *David, India.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); nicotinamide (p. 2083·1); calcium pantothenate (p. 2085·2) or dexpanthenol (p. 2582·2).
Peripheral neuropathy.

Siopel *Bouwer Bartlett, S.Afr.; Centrapharm, UK.*
Cetrimide (p. 1742·1); dimeticone (p. 2209·3).
Barrier cream; napkin rash.

Sioplex *David, India.*
Capsules: Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency; tonic.

Sioplex Lysine *David, India.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Vitamin B deficiency; tonic.

Sioplex-Z *David, India.*
Vitamins; zinc (p. 2126·1).
Vitamin deficiency; dietary supplement in pregnancy and lactation; tonic.

Sioril *David, India.*
Oxyphenbutazone (p. 114·3).
Ankylosing spondylitis.

Siozam *Verapharm, Rus.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Siozwo *Febena, Ger.*
Nasal solution: Electrolytes (p. 1775·1).
Nasal irrigation.

Febena, Ger.
Nasal gel: ⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Gen, Turk.
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1).
Nasal hygiene.

Febena, Ger.†
Nasal ointment: ⊗Naphazoline hydrochloride (p. 1669·3); peppermint oil (p. 1877·1).
Catarrh; nasal congestion; rhinitis.

Siozwo San *Febena, Ger.*
Dexpanthenol (p. 2582·2); sea salt (p. 2612·1).
Nasal disorders.

Sipam *Siam Bheasach, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; skeletal muscle spasm; neuroses.

Sipar *Duncan, Arg.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Siparox *Loeffler, Mex.*
Bismuth salicylate (p. 1821·3).
Gastrointestinal disorders.

Sipcar *Bernabo, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Sipeiding *Tianxin, China.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Sipental *Siam Bheasach, Thai.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular ear and eye disorders.

Sipentin *Mersifarma, Indon.*
Gabapentin (p. 523·3).
Epilepsy.

Siphene *Serum Institute, India.*
⊗Clomifene citrate (p. 2259·1).
Female infertility.

Sipiel *Alapis, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Sipirac *Chemopharma, Chile.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Sipraktin *Ulagay, Turk.*
Cyproheptadine hydrochloride (p. 624·1).
Hypersensitivity reactions; migraine.

Sipralexa *Lundbeck, Belg.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Siprion *Orion, Fin.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Siprobel *Nobel, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Siprogut *Bilim, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Siprosan *Drogsan, Turk.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Siqualine *BMS, Mex.*
Fluphenazine (p. 1075·1).

Siqualone *BMS, Denm.†; BMS, Fin.; BMS, Swed.*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Siquial *Merck, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Siquil *Sarabhai Piramal, India.*
Triflupromazine hydrochloride (p. 1114·1).
Psychoses.

Sir. Ephedrin *Leiras, Fin.*
⊗Ephedrine hydrochloride (p. 1663·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Siraliden *Medana, Pol.†*
Nitrofurantoin (p. 332·1).
Bacterial infections of the urinary tract.

Siramid *Mersifarma, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Siran *Temmler, Israel.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders associated with viscous mucus.

Siranin *Gedeon Richter, Cz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Sirben *Uniao Quimica, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Sirdalud *Novartis, Arg.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Ital.; Novartis, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Ukr.; Novartis, Venez.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm; spasticity.

Sirec *Ethica, Indon.*
⊗Yohimbine (p. 2372·3); muira-puama; arginine (p. 2049·1); ginseng (p. 2513·3); honey (p. 2072·1); tribulus terrestris (p. 2633·3).
Tonic.

Sirepar *Gedeon Richter, Rus.†; Gedeon Richter, Thai.†*
Liver extract (p. 2444·1).
Liver disorders.

Siridone *Chemopharma, Chile.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Sirio *Chiesi, Ital.*
Melevodopa hydrochloride (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Sirmiogel *Nycomed, Ital.*
Thermal water; hyaluronic acid (p. 2526·2); ursolic acid; galactomannan (p. 2508·3).
Nasal congestion.

Sirоctid *Chemi, Pol.*
Octreotide (p. 1924·1).
Gastrointestinal tumours; acromegaly; complications following pancreatic surgery; variceal haemorrhage.

Sigma-Tau, Fr.
Octreotide acetate (p. 1924·1).
Gastrointestinal endocrine tumours; acromegaly; prevention of complications following pancreatic surgery; variceal haemorrhage.

Siroflex *Farmellas, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Sirop Cocillana Codeine *Atlas, Canad.*
Codeine phosphate (p. 40·2); cocillana (p. 1659·2); euphorbia (p. 2501·3); senega (p. 1677·2); squill (p. 1677·3); wild lettuce (p. 2647·3).

Sirop pectoral *Phytopharma, Switz.*
Thyme (p. 2630·2); primula (p. 2596·2); ivy (p. 2536·2).
Cough.

Sirop pectoral contre la toux S *Hanseler, Switz.*
Codeine phosphate (p. 40·2); drosera (p. 2497·2); hyoscyamus (p. 2530·2); liquorice (p. 1853·2); cowslip (p. 2596·2).
Cough.

Sirop Teyssedre *Bailleul, Fr.†*
Alimemazine tartrate (p. 615·1).
Insomnia; allergic disorders; cough.

Siropar *Adeka, Turk.*
Piperazine hydrate (p. 163·1).
Ascariasis; oxyuriasis.

Siropectan *Streuli, Switz.*
Ribwort plantain (p. 2604·2); sweet chestnut (p. 2625·1); senega (p. 1677·2); tolu balsam (p. 1679·2); primula (p. 2596·2); drosera (p. 2497·2).
Respiratory-tract disorders.

Siros *Janssen-Cilag, Ger.*
Itraconazole (p. 583·3).
Vulvovaginal candidiasis.

Sirotamicin BG *Maigal, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Sirotamicin HC *Maigal, Arg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Siroxyl *Melisana, Belg.; Farmanic, Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with retention of bronchial secretions.

Sirtap *SoSe, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Sirturo *Janssen, USA.*
Bedaquiline fumarate (p. 226·3).
Tuberculosis.

Siruc *Denver, Arg.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Sirupus Pini Compositus *Herbapol Wroclaw, Pol.*
Calcium lactate (p. 1784·1); greater celandine (p. 2522·2); codeine phosphate (p. 40·2); fennel (p. 2503·2); scots pine (p. 2591·1).
Cough and associated respiratory-tract disorders.

Sirupus Tussipini *Hasco-Lek, Pol.*
Calcium lactate (p. 1784·1); greater celandine (p. 2522·2); codeine phosphate (p. 40·2); fennel (p. 2503·2); scots pine (p. 2591·1).
Cough; respiratory-tract congestion.

Sirupus Tussipini D *Hasco-Lek, Pol.*
Calcium lactate (p. 1784·1); greater celandine (p. 2522·2); fennel (p. 2503·2); scots pine (p. 2591·1).
Cough; respiratory-tract congestion.

Siruton *Landsteiner, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Sisare *MSD, Ger.†*
11 Tablets, estradiol valerate (p. 2271·2); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1).
Menopausal disorders.

Sisare 28 *Organon, Ger.†*
White tablets, estradiol valerate (p. 2271·2); blue tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); pink tablets, estradiol valerate.
Menopausal disorders.

Sisare mono *MSD, Ger.†*
Estradiol (p. 2271·1).
Menopausal disorders.

Sisoptin *Themis, India.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Sispres *Ulkar, Turk.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Sistalcin *Merck, Venez.*
Pramiverine hydrochloride (p. 2596·1).
Smooth muscle spasm; aid in duodenography.

Sistalcin Compositum *Merck, Venez.*
Pramiverine (p. 2596·1); dipyrone (p. 53·3).
Smooth muscle spasm and pain.

Sistatin *Austral, Arg.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Sistenol *Dexa, Indon.*
Paracetamol (p. 115·1); acetylcysteine (p. 1652·2).
Fever; pain; respiratory-tract congestion.

Sistopres *Mavi, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Sistral *Ulagay, Turk.†*
Chlorphenoxamine hydrochloride (p. 622·1).
Hypersensitivity reactions; pruritus.

Sita *Schwarz, Ger.†*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sitaleau *Alapis, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Sitandi *SL Pharm, China.*
Naftopidil (p. 2361·1).
Benign prostatic hyperplasia; hypertension.

Sitatinal *Silanes, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sitavig *BioAlliance, USA.*
Aciclovir (p. 964·1).
Herpes labialis.

Sitem *Inpa, Gr.*
Phenothrin (p. 2160·1).
Head, body, and crab lice.

Siterone *Rex, NZ.*
Cyproterone acetate (p. 2261·2).
Androgen-dependent alopecia, acne, hirsutism, and seborrhoea in females; prostatic cancer; hypersexuality in males.

Siticon *Pharmasant, Thai.†*
Simeticone (p. 1886·2).
Excess gastrointestinal gas.

Siticox *Sarabhai Piramal, India.†*
Rifampicin (p. 350·3).
Tuberculosis.

Siticox-INH *Sarabhai Piramal, India.†*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Sitinir *Best, Mex.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sition *Maver, Chile.*
Meloxicam (p. 86·3).

Sitorel *Nevzat, Turk.*
Trimetazidine (p. 1520·1).

Sitosterin *Schwarz, Ger.*
Phytosterol (p. 1471·2).
Benign prostatic hyperplasia.

Sitraks *Sanofi Synthelabo, Turk.*
Levamisole (p. 157·2).
Ascariasis; trichostrongyliasis.

Sitrex PD *Vindex, USA.†*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Sitriol *Alphapharm, Austral.†*
Calcitriol (p. 2113·1).
Osteoporosis; hypocalcaemia.

Sitro *Interbat, Indon.*
Roxithromycin (p. 356·2).
Bacterial infections.

Sitronella *Leontik, Gr.*
Fenofibrate (p. 1381·1).

Sitrox *Biotenk, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Sitzmarks *Dominguez, Arg.*
Radio-opaque markers.
Investigation of gastrointestinal motility.

Konsyl, USA.
Radio-opaque polyvinyl chloride.
Contrast medium for gastrointestinal radiography.

Sival-B *Alapis, Gr.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Sivastin *Sigma-Tau, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sivatin *Rowex, Irl.; Stallion, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sivay Psyllium *Perrigo, Israel.*
Ispaghula (p. 1849·1).
Dietary fibre supplement.

Siverol *Biomedis, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Sivex *Orva, Turk.*
Sulfacetamide sodium (p. 361·1).
Acne.

Sivinar *Anpharm (Ανφαρμ), Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Sivkort *Siu Guan, Malaysia.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Sivylar *Ranbaxy, Thai.†*
Silymarin (p. 1561·2).
Liver disorders; mushroom poisoning; carbon tetrachloride poisoning.

Siweitan *Watson, China.*
Zaleplon (p. 1114·3).
Insomnia.

Six Din *Senosiain, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Sixacina *Rider, Chile.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Sixantone *Takeda, Austria; Takeda, Ger.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer.

Sixime *Siam Bheasach, Thai.*
Cefixime (p. 240·3).
Bacterial infections.

Sixol *Biomep, Mex.*
Colchicine (p. 604·1).
Gout.

Siyafen *Gunsa, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Sizodon *Sun, Rus.*
Risperidone (p. 1103·2).
Psychoses; behaviour disorders; bipolar disorder.

Sizopin *Sun, India.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses associated with parkinsonism.

Sizoril *Meprofarm, Indon.*
Clozapine (p. 1057·3).
Schizophrenia.

SJ Liniment *International Dermatologicals, Canad.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); ammonium hydroxide (p. 2441·2); coal tar (p. 1723·2).

SK Complex *Thompsons, Canad.†*
Apis mellifica (p. 2445·2); rhus toxicodendron (p. 2603·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Skab 2 *Pentamedical, Ital.†*
Benzyl benzoate (p. 2149·1); St John's wort oil (p. 449·1); benzyl alcohol (p. 1739·3); enoxolone (p. 54·2); terpineol (p. 2627·2).
Skin cleanser.

Skabi-Rid *Glenmark, S.Afr.*
Permethrin (p. 2159·3).
Scabies.

Skarflex *Pentamedical, Ital.*
Pelvetia canaliculata (p. 2612·1); tocoferil acetate (p. 2119·2); onion (p. 2575·2).
Prevention of scarring.

Skeeter Stik *Triton, USA.*
Lidocaine (p. 1988·1); phenol (p. 1763·3).
Skin disorders.

Skelan
Note: this name may be used for preparations of different composition.
Amherst, Philipp.
Naproxen sodium (p. 98·2).
Pain; inflammation.

Great Eastern, Thai.†
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Pain.

Skelan IB *Great Eastern, Thai.†*
Ibuprofen (p. 68·2).
Pain; musculoskeletal, joint, and peri-articular disorders; gout.

Skelan Protect *Amherst, Philipp.*
Naproxen sodium (p. 98·2).
Omeprazole (p. 1867·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; inflammation.

Skelaxin *King, USA.*
Metaxalone (p. 2025·2).
Painful musculoskeletal conditions.

Skelid *Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.†; Sanofi-Aventis, Hung.†; Sanofi-Aventis, Neth.†; Sanofi-Aventis, Port.†; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.†; Sanofi-Aventis, UK†; Sanofi Winthrop, USA.*
Tiludronate disodium (p. 1192·2).
Paget's disease of bone.

Skema *Pentamedical, Ital.*
Cream: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Pentamedical, Ital.
Lotion: Octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

Skenan *BMS, Fr.; UPSA, Neth.†; Ethypharm, Port.†; BMS, Spain.†*
⊗Morphine sulfate (p. 92·3).
Pain.

Skiacol *Alcon, Fr.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of cycloplegia and mydriasis.

Skid *Winthrop, Ger.*
Minocycline hydrochloride (p. 325·1).

Skilax *Almirall, Spain.†*
Sodium picosulfate (p. 1887·2).
Constipation.

Skilone *Corsa, Indon.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Skimatix *Valeant, Braz.*
Dimeticone (p. 2209·3).

Skin Activator *Herbalife, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Skin Cap *Volta, Chile; Chemigroup, Fr.*
Pyrithione zinc (p. 1718·1).
Dandruff; seborrhoeic dermatitis.

Skin Care *Dossier, Neth.*
Rhus toxicodendron (p. 2603·3); urtica dioica (p. 2639·3).
Homoeopathic preparation.

Skin Care Nutrients *Lifeplan, UK.*
Vitamins; minerals; bioflavonoids (p. 2505·2); cysteine (p. 2058·3); lecithin (p. 2542·2); choline (p. 2055·2); inositol (p. 2533·2).
Dietary supplement.

Skin Caviar *La Prairie, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Skin Clarifying *Vichy, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Skin Cleansing *Cantassium Co., UK.*
Lappa (p. 2540·1); senna (p. 1885·1); fumitory (p. 2508·2); clivers (p. 2481·2).

Skin Clear *Potter's, Irl.†; Potter's, UK.*
Starch (p. 2095·1); sublimed sulfur (p. 1721·1); zinc oxide (p. 1729·1); melaleuca oil (p. 2551·1).
Skin disorders; eczema; acne.

Potter's, UK.
Tablets: Echinacea root (p. 2498·1).
Skin disorders.

Skin Cure *Young Again Nutrients, USA.*
Pyrithione zinc (p. 1718·1).
Skin disorders.

Skin Des *Promedico, Israel.†*
Isopropyl alcohol (p. 1758·3); 1,3-butanediol (p. 2172·2).
Skin disinfection.

Skin Dry *Darier, Mex.*
Aluminium tetrachlorohydrate (p. 1694·1).
Hyperhidrosis.

Skin Eruptions Mixture *Potter's, UK.*
Iris versicolor (p. 2534·3); lappa root (p. 2540·1); yellow dock (p. 2649·3); sarsaparilla (p. 2610·3); buchu (p. 2461·3); cascara (p. 1826·1).
Skin disorders.

Skin Hair & Nails *Natural Life, Arg.*
Vitamins; minerals; choline (p. 2055·2); inositol (p. 2533·2); bioflavonoids (p. 2505·2); betaine (p. 2456·1); rutoside (p. 2505·3).
Dietary supplement.

Skin ID *Johnson & Johnson, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Skin Nail *Aclae, Fr.*
Quassia (p. 2601·1); denatonium benzoate (p. 2181·1).
Nail disorders.

Skin Perfecting Oil *Johnson & Johnson, UK.*
Soya oil (p. 2092·3); wheat-germ oil (p. 2647·1); sweet almond oil (p. 2437·1); rose hip oil; black currant seed oil (p. 2458·1); vitamin E (p. 2119·1); levomenol (p. 2544·1).
Stretch marks.

Skin Prep *Smith & Nephew, Austral.*
Protective barrier dressing.

Skin Renew *Garnier, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Skin Repair *Pfizer, Hong Kong†; Rosken, Hong Kong.†*
Dimeticone (p. 2209·3).
Cracked and dry skin; dermatitis.

Skin Sec *Darrow, Braz.*
Soap.
Dry skin.

Darrow, Braz.†
Lotion SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Moisturiser; sunscreen.

Skin Shield
Note: this name may be used for preparations of different composition.
Biotech Transfer, Canad.
Triclosan (p. 1773·2).
Skin cleansing.

Del, USA.
Dyclonine hydrochloride (p. 1987·1); benzethonium chloride (p. 1738·1).
Liquid bandage.

Skin Sol 5D *Maigal, Arg.*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Skin Sol T *Maigal, Arg.*
SPF 35: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); octisalate (p. 1715·2).
Sunscreen.

Skin Soln *Srichand, Thai.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).

Skin Support *Blackmores, Austral.*
Echinacea (p. 2498·1); calendula (p. 2465·2); zinc amino acid chelate (p. 2048·3); betacarotene (p. 2051·1).
Acne.

Skinal *Sandoz, Indon.†*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Skinasol *Med-One, Gr.*
Clindamycin phosphate (p. 269·3).

Skin-B *Italfarmacia, Ital.†*
Hyaluronic acid (p. 2526·2).

Skincalm *Aspen, S.Afr.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Valeant, NZ.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Skin-Cap *Catalysis, Arg.; Cheminova, China; Invar, Rus.*
Pyrithione zinc (p. 1718·1).
Skin and scalp disorders; psoriasis; seborrhoeic dermatitis.

Skinceuticals Daily Sun Defense *Skinceuticals, Canad.†*
SPF 20: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Skinceuticals Sport Defense *Skinceuticals, Canad.†*
SPF 45: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Skinceuticals UV Defense *Skinceuticals, Canad.*
SPF 30: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Skinderm A *Maigal, Arg.*
Vitamin A (p. 2098·3).
Skin disorders.

Skinderm CL *Maigal, Arg.*
Collagen (p. 2483·2).
Premature skin ageing; cellulite.

Skinderm R *Maigal, Arg.*
Collagen (p. 2483·2); elastin (p. 2483·2); rosa mosqueta.
Premature skin ageing; dry skin disorders.

Skinderm SIL *Maigal, Arg.*
Silicones (p. 2209·2).
Barrier preparation.

Skindure *March, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Skin-E-Dip *United Bakers, Canad.*
Benzoin (p. 2624·3); zinc oxide (p. 1729·1).

Skinfect *Bangkok Lab & Cosmetic, Thai.*
Gentamicin sulfate (p. 304·2).
Bacterial skin infections.

Skinfect-B *Bangkok Lab & Cosmetic, Thai.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected inflammatory skin disorders.

Skinlogics *Beauticontrol, Canad.*
SPF 20: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Skinman *Ecolab, Irl.*
Denatured alcohol (p. 1760·3).
Hand disinfection.

Skinman Asept *Ecolab, Ger.†*
Propyl alcohol (p. 1768·1).
Hand disinfection.

Skinman clear *Ecolab, Ger.*
Propyl alcohol (p. 1768·1).
Hand disinfection.

Skinman Soft *Ecolab, Ger.*
Isopropyl alcohol (p. 1758·3); benzalkonium chloride (p. 1737·1); undecenoic acid (p. 596·3).
Skin disinfection.

Skinocyclin *Intendis, Ger.†*
Minocycline hydrochloride (p. 325·1).
Acne.

Skinoderm *Perrigo, Israel.*
Azelaic acid (p. 1695·1).
Acne.

Skinola-Fett *Teva, Switz.†*
Bath additive.
Dry skin disorders.

Skinoren *Schering, Austral.†; Intendis, Austria; Bayer, Belg.; Intendis, Cz.; Intendis, Denm.; Intendis, Fin.; Bayer, Fr.; Jenapharm, Ger.; Intendis, Gr.; Intendis, Hong Kong; Intendis, Hung.; Schering, Indon.†; Bayer, Irl.; Intendis, Ital.; Intendis, Malaysia; Intendis, Norw.; CSL, NZ; Schering, Philipp.†; Intendis, Pol.; Berlimed, Port.; Intendis, Rus.; Bayer Schering, S.Afr.; Intendis, Singapore; Intendis, Spain; Bayer, Swed.; Bayer, Switz.; Intendis, Thai.; Schering, Turk.; Bayer, UK; Bayer, Ukr.; Intendis, Ukr.*
Azelaic acid (p. 1695·1).
Acne; rosacea; melasma; skin pigmentation disorders; seborrhoeic dermatitis.

Skinovit *Roi Surya, Indon.†*
Tretinoin (p. 1725·2).
Acne.

Skinox *Tempo Scan Pacific, Indon.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Skin-Prep with Cetramide *Smith & Nephew, Austral.*
Cetrimide (p. 1742·1).
Skin disinfection.

Skinproject *Seventy BG, Ital.*
Resveratrol (p. 2603·2); omega-6 fatty acids (p. 2575·2).

Skin-R *Italfarmacia, Ital.†*
Hyaluronic acid (p. 2526·2).

Skinsept *Ecolab, Austria.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Ecolab, Switz.
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3); benzyl alcohol (p. 1739·3).
Skin disinfection.

Skinsept F *Ecolab, Ger.*
Isopropyl alcohol (p. 1758·3); chlorhexidine gluconate (p. 1743·3); hydrogen peroxide (p. 1755·2).
Skin disinfection.

Skinsept G *Ecolab, Ger.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Skinsept mucosa *Ecolab, Austria†; Ecolab, Ger.*
⊗Alcohol (p. 1733·1); hydrogen peroxide 30% (p. 1755·3); chlorhexidine gluconate (p. 1743·3).
Mucous membrane disinfection.

SkinSolv *Berko, Turk.*
Emollient.
Dry skin disorders.

Skintex
Note: this name may be used for preparations of different composition.
Lloyd, Aimee, UK.
Chloroxylenol (p. 1748·2); camphor (p. 2466·2).
Skin disorders.

Galenium, Indon.†
Zinc undecenoate (p. 596·3); salicylic acid (p. 1719·1); formaldehyde (p. 1752·2); boric acid (p. 2459·3); thymol (p. 1772·2); panthenol (p. 2582·2).
Fungal skin infections.

Skintint *Cover FX, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Skinvisible *Skinvisible, Canad.*
Triclosan (p. 1773·2).
Skin cleanser.

SkinVit *Pharmadass, UK.*
Vitamins; minerals; amino acids.

Skizon *Hexpharm, Indon.†*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Skizon-N *Hexpharm, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Sklice *Sanofi Pasteur, USA.*
Ivermectin (p. 155·1).
Pediculosis.

Skopolin *Tems, Turk.†*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Skopryl Plus H *Alkaloid, Cz.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Skyla *Bayer, USA.*
Levonorgestrel (p. 2296·1).
Progestogen-releasing intra-uterine contraceptive device.

Skylutamide *Stada, Fin.*
Bicalutamide (p. 749·1).
Prostatic cancer.

SL B12 *Dominguez, Arg.*
Cyanocobalamin (p. 2107·2).
Vitamin B12 deficiency.

SL Laxative *Beacons, Singapore.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Slabicap *Synthesis, Rus.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Slabilen *Lens, Rus.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Slap *Temis, Arg.*
Aspartame (p. 2169·2).
Sugar substitute.

Sleep Aid
Note: this name may be used for preparations of different composition.
Rougier, Canad.; Tanta, Canad.; Vita Health, Canad.; Galpharm, UK.
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Perrigo, Israel.
Doxylamine succinate (p. 627·3).
Insomnia.

Sleep Easy *Golden Glow, Austral.*
Piscidia (p. 2536·3); passion flower (p. 2584·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Insomnia.

Sleep & Insomnia Relief *Brauer, Austral.*
Capsicum (p. 2469·3); chamomilla (p. 2474·1); coffea (p. 2648·2); gelsemium (p. 2511·2); humulus (p. 2546·1); hyoscyamus (p. 2530·2); passiflora (p. 2584·1); valeriana (p. 2640·2).
Homoeopathic preparation.

Sleep Naturally *Golden Glow, Austral.*
Passion flower (p. 2584·1); notoginseng (Panatonin).
Insomnia.

Sleep Relax *Natural Factors, Canad.*
Lupulus (p. 2546·1); passion flower (p. 2584·1); skullcap (p. 2617·1); valerian (p. 2640·2).
Sleep disorders.

Sleep Remedy *Brauer, Austral.*
Clematis vitalba; helianthemum nummularium; impatiens glandulifera; ornithogalum umbellatum; prunus cerasifera; aesculus (p. 2431·2).
Bach flower remedy.

Sleep Sound Formula *Blackmores, Austral.*
Valerian (p. 2640·2); melissa (p. 2552·3); magnesium phosphate (p. 1787·3).
Insomnia.

SleepAid
Note: this name may be used for preparations of different composition.
Thompson & Capper, UK.
Valerian (p. 2640·2).
Sleep disorders.

Sleepasil *Organica, Philipp.*
Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); valerian (p. 2640·2); lupulus (p. 2546·1); skullcap (p. 2617·1); chamomile (p. 2474·1); passion flower (p. 2584·1); melatonin (p. 2551·3); jujube.
Insomnia.

Sleepeaze *Galpharm, UK.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

SleepEezy *Natures Aid, UK.*
Valerian (p. 2640·2).
Insomnia.

Sleep-Ettes D *Reese, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sleep-ettes Nighttime Sleep Aid *Reese, USA.*
Diphenhydramine (p. 626·1).
Insomnia.

Sleepex *Sagmel, Rus.*
Peppermint oil (p. 1877·1); cineole (p. 2479·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Snoring; tonsillitis; pharyngitis.

Sleep-Eze D *Medtech, Canad.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sleepeze-PM *Aspen, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sleepium *Arko Diffusion, Switz.*
Coffea arabica (p. 2648·2); cypripedium calceolus var. pubescens; datura stramonium (p. 2622·3); ipomoea purga (p. 1850·1).
Homoeopathic preparation.

Sleepwell *Trianon, Philipp.*
Melatonin (p. 2551·3).
Sleep disorders.

Sleepwell 2-nite *Rugby, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Slenfig *Torrent, Braz.; Torrent, Philipp.; Torrent, Singapore.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Slezovy Kvet *Megafyt-R, Cz.†*
Mallow flower (p. 2549·2).
Upper respiratory-tract inflammation.

Slider *Trima, Israel.*
Sildenafil citrate (p. 2364·1).
Pulmonary hypertension.

Slim 'n Trim *Pharmacon, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Slim-D *Biofarma, Mex.†*
Carnitine (p. 2053·2); garcinia cambogia (p. 2510·2); chromium (p. 2055·3).
Obesity.

Slimia *Torrent, Rus.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Slimmer Plus *Baif, Ital.*
Opuntia ficus-indica; coleus forskohlii; ononis (p. 2575·3); ananas sativus; equisetum (p. 2500·1); betula alba (p. 2457·3); centella (p. 1698·3); Java tea (p. 2536·3); butcher's broom (p. 2463·1); lespedeza capitata piper longum.
Nutritional supplement.

Slimming Aid
Note: this name may be used for preparations of different composition.
Brooke Green, UK; Herb Hands Healing, UK; Swiss Herbal, UK.
Fucus vesiculosus.
Slimming aid.

Winsor, Hong Kong.†
Cider vinegar; kelp (p. 2612·1); lecithin (p. 2542·2); vitamin B_6 (p. 2105·3).

Slimum *Ferrier, Fr.†*
Antimonium crudum (p. 2445·1); calcarea carbonica ostrearum (p. 1824·3); capsicum annuum (p. 2469·3); graphites (p. 2522·1).
Homoeopathic preparation.

Slimwell Herbal Slimming Tablets *Rickard Lanes, UK.*
Fucus vesiculosus; clivers (p. 2481·2).
Slimming aid.

Slipeol *Delpech, Fr.†*
Gelsemium sempervirens (p. 2511·2); avena sativa (p. 2451·1); passiflora incarnata (p. 2584·1); piscidia (p. 2536·3).
Homoeopathic preparation.

Slipirem *Mediolanum, Ital.†*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Slip-iZZZ *Ikapharmindo, Indon.†*
Valerian (p. 2640·2); passion flower (p. 2584·1); calcium (p. 1783·1); magnesium (p. 1786·3).
Sleep disorders.

Slippery Elm Stomach Tablets *Potter's, UK.*
Slippery elm bark (p. 2617·1); cinnamon oil (p. 2479·3); anise oil (p. 2444·3); peppermint oil (p. 1877·1).
Dyspepsia; flatulence.

Slipvell *Nizpharm, Rus.*
Zopiclone (p. 1118·1).
Sleep disorders.

Slit One *ALK Abello, Ger.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Sloan *Chefaro, Ital.†*
Capsicum oleoresin (p. 2469·3); glycol monosalicylate (p. 66·2); white camphor oil (p. 2466·2); pine oil (p. 2591·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); benzyl nicotinate (p. 29·3).
Musculoskeletal, joint, and soft-tissue pain.

Sloan's Heat Rub *Cipla-Medpro, S.Afr.*
Capsicum oleoresin (p. 2469·3); methyl salicylate (p. 92·1); methyl nicotinate (p. 91·3).
Musculoskeletal pain.

Sloan's Liniment *CCM, Indon.†*
Capsicum oleoresin (p. 2469·3); camphor oil (p. 2466·2); pine oil (p. 2591·1); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Zuellig, Hong Kong.†
Camphor (p. 2466·2); capsicum (p. 2469·3); methyl salicylate (p. 92·1); pine oil (p. 2591·1); sassafras oil (p. 2610·3).

Sloan's Liniment Rub *Pfizer Consumer, S.Afr.†*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); capsicum oleoresin (p. 2469·3); turpentine oil (p. 2636·3).
Musculoskeletal pain.

Slocinx *Winthrop, UK.*
Doxazosin (p. 1369·1).

Slodra *KRKA, Denm.†*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Slofedipine *Winthrop, UK.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Slofenac *Sterwin, UK.*
Diclofenac sodium (p. 48·3).

Slo-Indo *Generics, UK.*
Indometacin (p. 71·2).
Pain; inflammation.

Slo-Niacin *Upsher-Smith, USA.*
Nicotinic acid (p. 2083·1).
Nicotinic acid deficiency; pellagra; hyperlipidaemia (adjunct).

Slonnon *Daiichi Sankyo, Jpn.*
Argatroban (p. 1307·2).
Thromboembolic disorders.

Slo-Phyllin *Merck, Irl.†; Merck, UK.*
Theophylline (p. 1229·3).
Asthma; bronchitis; obstructive airways disease.

Slo-Pot *Valeant, Canad.*
Potassium chloride (p. 1793·2).
Potassium supplement.

Slo-Pro *Generics, UK.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; gastrointestinal bleeding; migraine; hypertension; hyperthyroidism; tremor.

Slo-Theo *Ethypharm, Hong Kong.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Slovalgin *Zentiva, Cz.†*
⊗Morphine sulfate (p. 92·3).
Pain.

Slovastan *Sawai, Jpn.†*
Argatroban (p. 1307·2).
Thromboembolic disorders.

Slow Deralin *Teva, Israel.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; hypertension; migraine; tremor; hyperthyroidism.

Slow Fe with Folic Acid *Novartis Consumer, USA.*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Slow-Fe *Novartis Consumer, Canad.; Novartis Consumer, Israel†; Novartis Consumer, USA.*
Dried ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; iron deficiency.

Slow-Fe Folic *Novartis Consumer, Canad.†; Novartis Consumer, Israel.†*
Dried ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency in pregnancy, the puerperium, and lactation.

Slow-K *Novartis, Austral.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Hong Kong; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Neth.; Novartis, NZ†; Novartis, S.Afr.; Novartis, Singapore; Alliance, UK.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium deficiency; potassium supplement.

Slow-Lopresor *Sankyo, Belg.; Novartis, NZ·*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Slow-Mag *Curtis, Pol.; Merck, S.Afr.; Purdue, USA.*
Magnesium chloride (p. 1787·1).
Magnesium deficiency.

Slow-Mag B_6 *Curtis, Pol.*
Magnesium chloride (p. 1787·1); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Slow-Sodium *Novartis, Austral.; HK Pharma, UK.*
Sodium chloride (p. 1795·1).
Hyponatraemia.

Slow-Theo *APT, Hong Kong.*
Theophylline (p. 1229·3).
Bronchospasm.

Slow-Trasicor *Novartis, Switz.†; Amdipharm, UK.*
⊗Oxprenolol hydrochloride (p. 1463·2).
Hypertension; angina pectoris; arrhythmias; anxiety.

Slow-Trasitensine *Novartis, Switz.*
⊗Oxprenolol hydrochloride (p. 1463·2); chlortalidone (p. 1335·2).
Hypertension.

Slozem *Merck, UK.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Slumber *Seven Seas, UK.*
Lupulus (p. 2546·1); piscidia (p. 2536·3); passion flower (p. 2584·1); wild lettuce (p. 2647·3).
Insomnia.

SM *T Man, Thai.*
Minoxidil (p. 1438·3).
Hypertension.

SM-33 *Bayer Consumer, Austral.*
⊗Salicylic acid (p. 1719·1); lidocaine (p. 1988·1); tannic acid (p. 2625·2); menthol (p. 2553·2); thymol (p. 1772·2); glycerol (p. 2517·2); alcohol (p. 1733·1).
Teething pain; oral abrasions.

SM-33 Adult Formula *Bayer Consumer, Austral.*
⊗Lidocaine (p. 1988·1); salicylic acid (p. 1719·1); tannins; alcohol (p. 1733·1).
Mouth ulcers; oral abrasions.

SM Oto *SM, Thai.*
⊗Furaltadone hydrochloride (p. 301·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); fludrocortisone acetate (p. 1634·3); lidocaine hydrochloride (p. 1988·2).
Otitis externa; otitis media.

SMA AR *Wyeth, Mex.*
Infant feed.
Gastro-oesophageal reflux.

SMA High Energy *SMA Nutrition, Irl.*
Infant feed.
Malabsorption; malnutrition; growth failure.

SMA LF *SMA Nutrition, Irl.*
Infant feed.
Lactose intolerance.

SMA Sin Lactosa *Wyeth, Mex.*
Infant feed.
Lactose intolerance.

SMA Staydown *SMA Nutrition, Irl.; SMA Nutrition, UK.*
Infant feed.
Regurgitation; gastro-oesophageal reflux.

SMANCS *Astellas, Jpn.*
Zinostatin stimalamer (p. 887·3).
Hepatic cancer.

Smaril *Coup, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Smaritass *Coup, Gr.*
⊗Serrapeptase (p. 2613·3).

Smarodax *Coup, Gr.*
Sodium cromoglicate (p. 1225·3).

Smart Omega *Delta Medical, Ukr.*
Eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1).
Dietary supplement.

SmartDose *Pro-Med, Austria.†*
Sodium chloride (p. 1795·1).
Diluent for intravenous drugs.

Smartfish *Synco, Hong Kong.†*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Smartmix *Johnson & Johnson, NZ·*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methylacrylate copolymer (p. 2558·2).
Bone cement in orthopaedic surgery.

SmartMix Cemvac GHV *DePuy, Ger.*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methylacrylate copolymer (p. 2558·2).
Bone cement in orthopaedic surgery.

Smartset *Johnson & Johnson, NZ.*
Gentamicin sulfate (p. 304·2); methylmethacrylate/methylacrylate copolymer (p. 2558·2).
Bone cement in orthopaedic surgery.

SmartSet GHV *DePuy, Ger.*
Gentamicin sulfate (p. 304·2); methylmethacrylate methylacrylate copolymer (p. 2558·2).
Bone cement in orthopaedic surgery.

SmartSet HV *DePuy, Ger.*
Methylmethacrylate methylacrylate copolymer (p. 2558·2).
Bone cement in orthopaedic surgery.

Smartshield After Sun *Smartshield, Canad.*
Lidocaine hydrochloride (p. 1988·2).

Smartshield Sunscreen *Smartshield, Canad.†*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); padimate O (p. 1716·1).
Sunscreen.

Smecta *Beaufour-Ipsen, China.*
Montmorillonite.
Gastrointestinal disorders.

Beaufour, Irl.
Dioctahedral smectite (p. 1887·1); aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Diarrhoea.

Ipsen, Cz.; Ipsen, Fr.; Ipsen, Gr.; Beaufour-Ipsen, Hong Kong; Ipsen, Hung.; Beaufour-Ipsen, Malaysia; Beaufour-Ipsen, Pol.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Thai.; Beaufour-Ipsen, Ukr.
Dioctahedral smectite (p. 1887·1).
Diarrhoea; irritable bowel syndrome; gastro-oesophageal reflux in infants; gastrointestinal pain; dyspepsia; abdominal discomfort; peptic ulcer; colitis; inflammatory bowel disease.

Smilitene *Rafarm, Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Sminosan *Rafarm, Gr.*
Terfenadine (p. 640·3).

Smissen *Cinfa, Port.†*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; autism.

SMOFKabiven *Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3), medium-chain triglycerides (p. 2082·2), olive oil (p. 2575·1), and fish oil (p. 1460·3)); with or without electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, Thai.
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3); lipids.
Parenteral nutrition.

SmofKabiven *Fresenius Kabi, Switz.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3), medium-chain triglycerides (p. 2082·2), olive oil (p. 2575·1), and fish oil (p. 1460·3)); electrolytes (p. 1775·1).
Parenteral nutrition.

SMOFlipid *Fresenius Kabi, Austral.; Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK; Fresenius Kabi, Ukr.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2); olive oil (p. 2575·1); fish oil (p. 1460·1).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Turk.
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2); olive oil (p. 2575·1); omega-3 marine triglycerides (p. 1460·3).
Lipid infusion for parenteral nutrition.

Smoke Eze *Brauer, Austral.*
Caladium seguinum; daphne indica; ignatia (p. 2532·1); passiflora (p. 2584·1); tabacum (p. 2632·2).
Homoeopathic preparation.

Smokeless *Inibsa, Spain.†*
⊗Lobeline sulfate (p. 2323·3).
Aid to smoking withdrawal.

Smudal *Rafarm, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

S-Muxine *GPC, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

SMZ-TMP *Apothecon, USA.*
Co-trimoxazole (p. 277·3).

Snake Venom Detection *CSL Biotherapies, Austral.*
Test for detection and identification of snake venom (tiger snake, brown snake, black snake, death adder, taipan) at bite site, in urine and in blood.

Snaplets-FR *Baker Norton, China.*
Paracetamol (p. 115·1).
Fever; pain.

Snell Cell *Wassen, Ital.†*
Kola (p. 2648·2); guarana (p. 2648·2); maté (p. 2648·2); garcinia cambogia (p. 2510·2); coleus; aesculus (p. 2431·2).
Cellulite.

Snell Patch *Gobbi, Arg.*
Hava tonka; ginkgo biloba (p. 2512·3); ivy (p. 2536·2); melilot (p. 2552·3).
Cellulite.

Snell Progress *Gobbi, Arg.*
Hava tonka; ginkgo biloba (p. 2512·3); melilot (p. 2552·3).
Cellulite.

Snella *Investi, Arg.*
Glycine max.
Menopausal disorders.

Snella D + E *Investi, Arg.*
Soya isoflavones (p. 2620·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1).
Menopausal disorders.

Snella Vag *Investi, Arg.*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).
Vaginal lubricant.

Snell'it *Marfarma, Ital.*
Apple vinegar; inulin (p. 2534·3).
Dietary supplement.

Snelvit *Grin, Mex.*
Zeaxanthin (p. 2125·3); lutein (p. 2079·2); minerals; vitamins.
Ocular antoxidant.

Snif *Eurofarma, Braz.; One Pharma, Philipp.*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal dryness.

Sniffle Care *Dossier, Neth.*
Echinacea angustifolia (p. 2498·1); allium cepa (p. 2575·2).
Homoeopathic preparation.

Snizee *Metz, Philipp.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Cold symptoms; allergic rhinitis.

Sno Pro *SHS, Irl.*
Low-protein, low-phenylalanine food for special diets.
Milk substitute; disorders of amino-acid metabolism.

Sno Tears *Chauvin, Irl.†; Bausch & Lomb, UK.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Snoffocin *Seven Stars, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Snooze Fast *BDI, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sno-Pro *Nutricia, Ital.*
Food for special diets.
Renal failure; phenylketonuria.

SHS, UK.
Low protein drink.
Phenylketonuria; low protein diets.

Snor-Away *Munro, UK.*
Almond oil (p. 2437·1); olive oil (p. 2575·1); peppermint oil (p. 1877·1); sesame oil (p. 2614·1); sunflower oil (p. 2098·1); vitamins.
Snoring.

Snore Calm *BSSAA, UK.*
Euphrasia officinalis (p. 2502·1).
Snoring.

Snore Eze *Brauer, Austral.*
Apis mel. (p. 2445·2); histaminum mur. (p. 2525·2); kali bich. (p. 2476·3); lac. can.; lemna min.; nux vom. (p. 2573·3); pulsatilla (p. 2600·2); ratanhia (p. 2603·3); rheum (p. 1884·2); teucrium mar.; zincum met. (p. 2126·1).
Homoeopathic preparation.

Snore No More *Homeocan, Canad.*
Belladonna (p. 2453·3); bryonia alba; colubrina; cuprum metallicum (p. 2057·1); sambucus niger (p. 2609·3).
Homoeopathic preparation.

Snore Stop *Nutravite, Canad.*
Ephedra vulgaris; histaminum hydrochloride (p. 2525·2); hydrastis canadensis (p. 2528·1); kali bichromium (p. 2476·3); teucrium marum.
Homoeopathic preparation.

Snoreeze *Passion for Life, Singapore.*
⊗Glycerol (p. 2517·2); olive oil (p. 2575·1); peppermint oil (p. 1877·1); soya lecithin (p. 2542·2); sunflower oil (p. 2098·1); sweet almond oil (p. 2437·1); sesame oil (p. 2614·1); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3).
Snoring.

Snoreless *Nobel, Turk.*
⊗Almond oil (p. 2437·1); sesame oil (p. 2614·1); glycerol (p. 2517·2); peppermint oil (p. 1877·1); olive oil (p. 2575·1); sunflower oil (p. 2098·1); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Snoring.

Snore-No-More *Anben, Israel.*
Polysaccharides; phosphate (p. 1790·3); sodium chloride (p. 1795·1).
Nasal dryness; snoring.

Snorenz *Enzpharma, NZ.*
Peppermint oil (p. 1877·1); olive oil (p. 2575·1); sunflower oil (p. 2098·1); sesame oil (p. 2614·1); almond oil (p. 2437·1); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3).
Snoring.

Snorestop *Key Sun, Austral.*
Nux vomica (p. 2573·3); belladonna (p. 2453·3); ephedra vulgaris; hydrastis canadensis (p. 2528·1); kali bichromicum (p. 2476·3); teucrium marum; histaminum hydrochloricum (p. 2525·2).
Homoeopathic preparation.

Snovitel *Akrikhin, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Snow Brand *Snow Brand, Hong Kong.*
A range of preparations for enteral nutrition.

Snowfire *Pickles, UK.*
Benzoin (p. 2624·3); citronella (p. 2481·1); thyme oil (p. 2630·3); lemon thyme; clove oil (p. 2481·3); cade oil (p. 1723·2).
Chapped hands; chilblains.

SNP *Quatromed, S.Afr.†*
Sodium nitroprusside (p. 1497·1).
Hypertension; production of controlled hypotension during surgery.

Snufflebabe *Orthodontiki (Ορθοδοντικη), Gr.; Dendron, UK.*
Menthol (p. 2553·2); thyme oil (p. 2630·3); eucalyptus oil (p. 2501·2).
Nasal congestion; common cold.

Snufflebabe Cradle Cap *Ransom, UK.*
Salicylic acid (p. 1719·1).
Cradle cap.

Snup *Stada, Cz.; Stada, Ger.; Stada, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; catarrh; sinusitis; otitis media; rhinoscopy.

Snurdim *TS Reform, Neth.*
Belladonna (p. 2453·3); ephedra vulgaris; histaminum muriaticum (p. 2525·2); hydrastis

canadensis (p. 2528·1); kalium bichromicum (p. 2476·3); nux vomica (p. 2573·3); teucrium marum verum.
Homoeopathic preparation.

Snuzaid *Woods, Austral.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Soaclens *Alcon, Austral.†*
Wetting and storage solution for hard contact lenses (including gas permeable).
Alcon, NZ.†
Wetting, soaking, and storage solution for hard and gas-permeable contact lenses.
Alcon, USA.†
Wetting and soaking solution for hard contact lenses.

Soam *Edol, Port.†*
Emollient.

Soapelle *Darrow, Braz.*
Triclosan (p. 1773·2); aloe vera (p. 1693·2).
Skin disinfection.

Soapex *Galderma, Braz.*
Liquid soap: Triclosan (p. 1773·2).
Skin disinfection.
Galderma, Braz.
Shampoo: Piroctone olamine (p. 1716·3).
Seborrhoeic dermatitis.
Galderma, Braz.
Soap: Triclosan (p. 1773·2); triclocarban (p. 1773·2).
Skin disinfection.

Soapopular *Soapopular, Canad.*
Benzalkonium chloride (p. 1737·1).

Soapy Sudz *Zep, Canad.*
Triclosan (p. 1773·2).

Sobal *Biokraft, Norw.†*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; nervous disorders.

Sobal Forte *Biokraft, Norw.†*
Valerian (p. 2640·2).
Insomnia; nervous disorders.

Sobee Plus *Mead Johnson, Indon.†*
Infant feed.
Milk intolerance.

Sobelin
Note: this name may be used for preparations of different composition.
Pfizer, Ger.
Clindamycin hydrochloride (p. 269·3), clindamycin palmitate hydrochloride (p. 269·3), or clindamycin phosphate (p. 269·3).
Bacterial infections.
TO-Chemicals, Thai.
Flunarizine (p. 629·3).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; migraine; motion sickness.

Sobrein *Biomedica, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

Sobrepin *Farmasa, Braz.; Bayer, Ital.; Tedec Meiji, Spain.*
Sobrerol (p. 1677·2).
Respiratory-tract congestion; respiratory-tract disorders.

Sobrepina *Baldacci, Port.*
Nimodipine (p. 1455·2).
Cerebral vasospasm following subarachnoid haemorrhage; cerebral ischaemia.

Sobril *Pfizer, Norw.; Pfizer, Swed.*
Oxazepam (p. 1092·2).
Anxiety; agitation; insomnia; premedication; alcohol withdrawal syndrome; sleep disorders.

Sobrium *Ranbaxy, Malaysia.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Sobrius *Fada, Arg.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Sobromer *Morishita, Philipp.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Socalm *Ranbaxy, India.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Socef *Soho, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Sochlor *Ocusoft, USA.*
Sodium chloride (p. 1795·1).
Corneal oedema.

Socian *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Port.*
Amisulpride (p. 1036·3).
Psychoses; schizophrenia.

Socid *Soho, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Soclaf *Soho, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Soclonat *Federfarma, Ital.†*
Clodronate disodium (p. 1180·3).
Osteolysis of malignancy; multiple myeloma; hyperparathyroidism; osteoporosis.

Soclor *Soho, Indon.*
Cefaclor (p. 232·3).
Bacterial infections.

Socloxin *Olan-Kemed, Thai.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Socosep *Cetus, Arg.*
Ketoconazole (p. 585·3).
Fungal infections.

SOD Anamix *Nutricia, Fr.*
Food for special diets.
Sulfite oxidase deficiency.
SHS, Irl.
Infant feed.
Sulfite oxidase deficiency.

Soda-Bufer *Yuriya-Farm, Ukr.*
Sodium bicarbonate (p. 1781·1).
Metabolic acidosis; fluid and electrolyte disorders.

Sodalite *Pharmacare, Philipp.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium choride; glucose (p. 2068·3) (p. 1780·1).
Oral rehydration solution; diarrhoea.

Sodamida *Kener, Mex.*
Sulfacetamide (p. 361·1).
Bacterial eye infections.

Sodamint Frx *United Drug, Thai.*
Sodium bicarbonate (p. 1781·1).

Sodampen *Vysali, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Sodecor *Pharmaceutical Factory of St Petersburg, Rus.*
Pimento; elecampane (p. 1662·3); ginger (p. 1844·1); cardamom (p. 2471·1); coriander (p. 2486·3); chinese cassia bark (p. 2471·3); sea buckthorn (p. 2611·3); taraxacum (p. 2625·3); liquorice (p. 1853·2); pine nut.
Tonic.

Sodemethin *Vilco, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Soden *DHA, Hong Kong; DHA, Singapore.*
Naproxen sodium (p. 98·2).
Pain; inflammation; gout; musculoskeletal and joint disorders.

Sodeprol *Iapharm, Gr.*
Omeprazole (p. 1867·2).

Soderm *Dermapharm, Ger.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Soderm Plus *Dermapharm, Ger.*
⊗Betamethasone dipropionate (p. 1623·3); salicylic acid (p. 1719·1).
Skin disorders.

Soderma *Soho, Indon.†*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Sodermix *Swedpharm, Chile.*
Solanum lycopersicum.
Inflammatory skin disorders; pruritus; scars.
Biol, Arg.
Superoxide dismutase (p. 135·2).
Scars; keloids; skin disorders; burns; wounds.
Meprofarm, Indon.
Green tomato; isopropyl myristate (p. 2190·3); propylene glycol (p. 2205·2); dimeticone (p. 2209·3); carbomer (p. 2173·3); sodium laurilsulfate (p. 2210·3).
Scars.

Sodexx Cimetidine *Kwizda, Austria.†*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux.

Sodexx Famotidine *Kwizda, Austria.*
Famotidine (p. 1842·1).
Heartburn.

SodiBic *Arjun, UK.*
Sodium bicarbonate (p. 1781·1).

Sodibic *Aspen, Austral.*
Sodium bicarbonate (p. 1781·1).
Urine alkalinisation.

SodiClor *Arjun, UK.*
Sodium chloride (p. 1795·1).

Sodilen *Motima, Fr.*
Pollen (p. 2593·3).
Antoxidant.

Sodilin *Collins, Mex.†*
Procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Sodime *Soho, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Sodimel *Darier, Mex.*
Superoxide dismutase (p. 135·2); gliadin.
Antoxidant.

Sodiofolin *Medac, Austria†; Medac, Irl.; Medac, Port.; Medac, Spain†; Medac, UK.*
Sodium folinate (p. 2067·1).
Reduction of folic acid antagonist toxicity; adjunct to fluorouracil in colorectal cancer; reduction of methotrexate toxicity.

Sodiopen *Reig Jofre, Spain.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Sodioral con Inulina *CaDiGroup, Ital.*
Oral rehydration solution with inulin (p. 1780·1).
Diarrhoea.

Sodiparin *Baxter Immuno, Arg.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Sodipen *Antibioticos, Mex.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Sodipental *Pisa, Mex.†*
Thiopental sodium (p. 1915·1).
General anaesthesia; convulsions; increased intracranial pressure in neurosurgery.

SodiPhluor *Kylemore, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Sodiphos *Pharmacobel, Belg.*
Dibasic sodium phosphate (p. 1791·2).
Hypophosphataemia.

Sodipryl retard *Sanofi, Switz.*
Naftidrofuryl oxalate (p. 1443·3).
Peripheral and cerebral vascular disease.

Sodium Sulamyd *Sandoz, Canad.; Schering, USA.†*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Sodix *Geolab, Braz.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Sodixen *Rayere, Mex.*
Naproxen sodium (p. 98·2).
Pain; musculoskeletal and joint disorders; fever.

Sodol Compound *Major, USA.*
Aspirin (p. 22·2); carisoprodol (p. 2021·3).
Musculoskeletal pain.

Sodolac *Sofex, Port.*
Etodolac (p. 57·1).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Sodorant *GSK, Arg.*
Deodorant bar: Triclocarban (p. 1773·2).
Hyperhidrosis.
GSK, Arg.
Deodorant roll-on; topical spray: Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.
Stiefel, Arg.
Cream: Guaiazulene (p. 2523·1); aluminium chlorohydrate (p. 1694·1); triclocarban (p. 1773·2).
Hyperhidrosis.

Sodox *Pentamedical, Ital.*
Melon; vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Dietary supplement.

Sodrimax *Pisa, Mex.*
⊗Ciprofloxacin hydrochloride (p. 261·2); benzocaine (p. 1980·2); hydrocortisone (p. 1640·1).
Ear disorders.

Sofarcid *Sofar, Ital.*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Sofargen *Sofar, Ital.*
Sulfadiazine silver (p. 362·3).
Burns; bacterial skin infections; wounds.

Sofasin *Faran, Gr.; Faran, Rus.*
Norfloxacin (p. 333·3).
Bacterial infections.

Sofast *Bausch & Lomb, China.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee; frozen shoulder.

Sofaxin *Soho, Indon.*
Cefalexin (p. 234·1).
Bacterial infections.

Sofden *Soho, Indon.†*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Sofderm *Cipla, India.*
Lotion: Aloe vera (p. 1693·2) vitamin E (p. 2119·1).

Sofelin *Galenus, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Soferax *Fabop, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Soffodex *Dexxon, Israel.†*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Bowel evacuation; constipation.

Soficlor *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Cefaclor (p. 232·3).
Bacterial infections.

Sofidrox *Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Cefadroxil (p. 233·2).
Bacterial infections.

Sofilex *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Cefalexin (p. 234·1).
Bacterial infections.

Sofix *Soho, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Sof-lax
Note: this name may be used for preparations of different composition.
Fleet, USA.
Docusate sodium (p. 1836·2).
Stool softener.

Soflax
Note: this name may be used for preparations of different composition.
Ascent, Austral.
Senna (p. 1885·1); docusate sodium (p. 1836·2).
Constipation.
Cipla-Medpro, S.Afr.
Senna (p. 1885·1).
Constipation.
Julphar, UAE.
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.
Pharmascience, Canad.
Docusate sodium (p. 1836·2).
Constipation.

Soflax C *Pharmascience, Canad.*
Docusate calcium (p. 1836·2).
Constipation.

Soflax EX *Pharmascience, Canad.*
Bisacodyl (p. 1821·1).
Constipation.

Sofloran *Pisa, Mex.†*
Isoflurane (p. 1903·2).
General anaesthesia.

Sofracort *Sanofi-Aventis, Canad.; Sanofi-Aventis, India.*
⊗Framycetin sulfate (p. 301·2); gramicidin (p. 308·3); dexamethasone sodium metasulfobenzoate (p. 1631·1).
Eye disorders; infected eye disorders; otitis externa.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sofradex *Sanofi-Aventis, Denm.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Switz.†; Florizel, UK.*
⊗Dexamethasone sodium metasulfobenzoate (p. 1631·1); framycetin sulfate (p. 301·2); gramicidin (p. 308·3).
Infected eye and ear disorders; otitis externa.

Sanofi-Aventis, Austral.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.
⊗Dexamethasone (p. 1630·3); framycetin sulfate (p. 301·2); gramicidin (p. 308·3).
Infected ear and eye disorders.

Sanofi-Aventis, India.
⊗Dexamethasone acetate (p. 1631·1); framycetin sulfate (p. 301·2).
Infected skin disorders.

Sanofi-Aventis, Ukr.†
⊗Dexamethasone sodium metasulfobenzoate (p. 1631·1); framycetin (p. 301·2); gramicidin S (p. 309·1).
Infected eye disorders; otitis externa.

Sofradex-F *Sanofi-Aventis, India.*
⊗Dexamethasone acetate (p. 1631·1); framycetin sulfate (p. 301·2); clotrimazole (p. 576·2).
Infected skin disorders.

Sofraline *Melisana, Belg.*
⊗Framycetin sulfate (p. 301·2); naphazoline nitrate (p. 1669·3).
Respiratory-tract disorders.

Soframycin
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Austral.†; Erfa, Canad.; Sanofi-Aventis, NZ.†
Ointment: Framycetin sulfate (p. 301·2); gramicidin (p. 308·3).
Bacterial skin infections.

Sanofi-Aventis, Austral.; Erfa, Canad.; Sanofi-Aventis, India; Sanofi-Aventis, Irl.†; Sanofi-Aventis, NZ; Aventis, S. Afr.†; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.†
Framycetin sulfate (p. 301·2).
Bacterial eye and ear infections; burns; skin infections; otitis externa.

Erfa, Canad.
Nasal spray: Framycetin sulfate (p. 301·2); gramicidin (p. 308·3); phenylephrine hydrochloride (p. 1672·3).
Bacterial nasal infections; nasal congestion.

Soframycine *Melisana, Belg.*
Framycetin sulfate (p. 301·2).
Bacterial nose and throat infections.

Sofrasolone *Melisana, Belg.*
⊗Prednisolone acetate (p. 1645·2); framycetin sulfate (p. 301·2); naphazoline nitrate (p. 1669·3).
Allergy or infections of the upper respiratory tract.

Sofra-Tull sine *Sanofi-Aventis, Ger.*
White soft paraffin (p. 2211·3); wool fat (p. 2219·3).
Wounds.

Sofra-Tulle *Sanofi-Aventis, Austral.†; Erfa, Canad.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Aventis, S. Afr.†; Sanofi-Aventis, Thai.; Aventis, UK.†*
Framycetin sulfate (p. 301·2).
Infected wounds, burns or ulcers; medicated dressing; infected skin disorders.

Sof-Sof *CTS, Israel.†*
Phenothrin (p. 2160·1).
Pediculosis.

Soft Care Antibacterial *Johnson Diversey, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Soft Care Antiseptic *Johnson Diversey, Canad.*
Chloroxylenol (p. 1748·2).
Skin cleansing.

Soft Care CHG Antimicrobial *Johnson Diversey, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Skin cleansing.

Soft Care Cross-Contamination Control *Johnson Diversey, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Soft Care Foam Select *Johnson Diversey, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Soft Care Instant Hand Sanitizer *Johnson Diversey, Canad.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Soft Care Nutra-Germ *Johnson Diversey, Canad.*
Triclosan (p. 1773·2).

Soft Care Sanitizing *Johnson Diversey, Canad.*
Chloroxylenol (p. 1748·2).
Hand disinfection.

Soft Corn *SSL, Pol.*
Salicylic acid (p. 1719·1).
Corns; calluses.

Soft Mate *Pilkington Barnes-Hind, USA.*
Range of solutions for soft contact lenses.

Soft Mate Consept *Pilkington Barnes-Hind, USA.*
Hydrogen peroxide (p. 1755·2).
Disinfecting solution for soft contact lenses.

Soft Mate Enzyme Plus Cleaner *Pilkington Barnes-Hind, USA.*
⊗Subtilisin A (p. 2624·1).
Cleansing solution for soft contact lenses.

Soft T Cleanse *Medicom, Canad.†*
Benzalkonium chloride (p. 1737·1).
Skin cleansing.

Soft U Derm *Galenium, Indon.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Softa Man *Braun, Belg.; Braun, Ger.; Braun, Ital.*
⊗Alcohol (p. 1733·1); propyl alcohol (p. 1768·1).
Hand disinfection.

Softab *Alcon, S.Afr.†*
Troclosene sodium (p. 1774·1).
Disinfectant for soft contact lenses.

Sof-Tact *Abbott Diabetes Care, Canad.†*
Test for glucose in blood (p. 2516·3).

Softala-X *Axapharm, Switz.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Softa-Man *Braun, Cz.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Hand disinfection.

Braun, Neth.; Braun, Ukr.†
⊗Alcohol (p. 1733·1); propyl alcohol (p. 1768·1).
Hand disinfection; skin disinfection.

Braun, Switz.†
Isopropyl alcohol (p. 1758·3); propyl alcohol (p. 1768·1).
Hand disinfection.

Softan *Simcere, China.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Softasept *Braun, Port.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Softasept N *Braun, Ger.; Braun, Switz.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3).
Skin disinfection.

Softcain *Esan, Chile.*
Benzocaine (p. 1980·2); triclosan (p. 1773·2); menthol (p. 2553·2); camphor (p. 2466·2).
Allergic skin disorders; insect bites; burns; pruritus.

Softcide EC *Erie, Canad.*
Triclosan (p. 1773·2).

Softcide Handwash *Erie, Canad.*
Chloroxylenol (p. 1748·2).
Hand cleansing.

Soft-Corn *SSL, Irl.†*
Salicylic acid (p. 1719·1).
Corns.

Softene *Melisana, Belg.*
Docusate sodium (p. 1836·2); bisacodyl (p. 1821·1).
Constipation.

Softeron *Aristo, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Formerly contained ferrous fumarate, folic acid, vitamin B12, and vitamin C.
Iron-deficiency anaemia.

Softeron-Z *Aristo, India.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); copper sulfate (p. 2057·2).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Formerly contained ferrous fumarate, folic acid, docusate sodium, and dried yeast.

Softigyn *Arkadia, Ital.*
Lactobacillus plantarum (p. 2596·3).
Vulvovaginal disorders.

Softinelle *Teva, Cz.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Softlips *Mentholatum, Canad.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Softlips French Vanilla *Mentholatum, Canad.†*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Softlips Sweet *Mentholatum, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Softlips Tints *Mentholatum, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Softovak *Lupin, Ukr.*
Ispaghula (p. 1849·1); senna (p. 1885·1); chebulic myrobalan (p. 2474·3); cassia fistula (p. 1826·2); liquorice (p. 1853·2); rosa centifolia; fennel (p. 2503·2); fennel oil (p. 2503·3).
Constipation.

Softram *Grin, Mex.*
⊗Triamcinolone acetonide (p. 1649·1).
Inflammatory eye disorders.

Softramc *Grin, Mex.*
⊗Triamcinolone acetonide (p. 1649·1); ciprofloxacin hydrochloride (p. 261·2).
Infected eye disorders.

Softwear *Ciba Vision, Canad.†*
Sodium chloride (p. 1795·1).
Rinsing and storage solution for soft contact lenses.

Ciba Vision, NZ.†
Rinsing solution for contact lenses.

Sogilen *Pfizer, Spain.*
Cabergoline (p. 899·3).
Parkinsonism.

Sogoon *Steiner, Ger.†*
Devil's claw root (p. 42·3).
Joint disorders.

Sohobal *Soho, Indon.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Sohobion *Soho, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuritis; neuralgia.

Sohoflam *Soho, Indon.†*
Nimesulide (p. 101·3).
Osteoarthritis; peri-articular disorders; pain; inflammation.

Soholin *Soho, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebrovascular disorders; hemiplegia.

Sohopec *Soho, Indon.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Sohotin *Soho, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders.

Soin Autobronzant *Clarins, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Soins Soleil *Somak, Canad.*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Somak, Canad.
SPF 20; SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sojadiol *Sojar, Arg.*
Leciflavone (p. 2620·3).
Menopausal disorders.

Sojar Folico *Sojar, Arg.*
Folic acid (p. 2063·1).
Folic acid supplement.

Sojar Men *Sojar, Arg.*
Soya isoflavones (p. 2620·3).
Dietary supplement.

Sojar Plus-Calcio *Sojar, Arg.*
Soya protein (p. 2092·3); calcium (p. 1783·1); soya isoflavones (p. 2620·3).
Dietary supplement.

Sojar Pro *Sojar, Arg.*
Soya protein (p. 2092·3).
Dietary supplement.

Sojourn *Fahrenheit, Indon.; Medis, Israel; Safeline, S. Afr.; Piramal, Thai.; Adeka, Turk.; Minrad, USA.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Sokeikakketsuto *Tsumura, Jpn.*
Peony root; rehmannia root; cnidium rhizome; atractylodes lancea rhizome; angelica acutiloba root (p. 2443·3); peach kernel; poria sclerotium; clematis root; notopterygium rhizome; achyranthes root; citrus unshiu peel; sinomenium stem; saposhnikovia root; gentiana scabra; liquorice (p. 1853·2); angelica dahurica root; ginger (p. 1844·1).
Traditional Kampo medicine.

Sokol *Biofarma, Turk.*
Liquid paraffin (p. 2191·2).
Constipation.

Sol Bronce Vital *AM, Arg.*
Betacarotene (p. 2051·1); canthaxanthin (p. 2173·2).
Tanning aid.

Solac *Soho, Indon.*
Lactulose (p. 1850·3).
Constipation; hepatic encephalopathy.

Solacid *Dey's, India.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer.

Solacil *Microsules, Arg.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); dipyrone (p. 53·3).
Migraine; headache.

Solacy *Grimberg, Fr.*
Cystine (p. 2059·1); sulfur (p. 1721·1); vitamin A acetate (p. 2098·3); yeast (p. 2125·2).
Upper respiratory-tract disorders.

Solagé *GSK, Canad.*
Mequinol (p. 1711·1); tretinoin (p. 1725·2).
Sun-induced skin hyperpigmentation and damage.

Solage *Aqua, USA.†*
Mequinol (p. 1711·1); tretinoin (p. 1725·2).
Sun-induced skin hyperpigmentation.

Solaire *Lero, Fr.*
Black currant oil (p. 2458·1); fish oil (p. 1460·1); bitter orange (p. 2575·3); vitamins; minerals.
Dietary supplement; tanning aid.

Solamid *Verisfield, Gr.*
Amisulpride (p. 1036·3).
Schizophrenia.

Solamin
Note: this name may be used for preparations of different composition.
Fresenius Kabi, Ital.
Amino acids.
Parenteral nutrition.

Solaneuron *Solas, Indon.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; nervous system disorders; nausea and vomiting in pregnancy; migraine.

Solan-M *Winzer, Ger.†*
Vitamin A palmitate (p. 2098·3).
Eye disorders.

Solans *Soho, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Solantal *Astellas, Jpn.*
Tiaramide hydrochloride (p. 137·3).
Pain; inflammation.

Solaquin
Note: this name may be used for preparations of different composition.
Valeant, Hong Kong†; Valeant, Singapore†; Crawford, UK; Valeant, USA.
Hydroquinone (p. 1705·1) with sunscreens.
Skin hyperpigmentation.

Valeant, Braz.; Valeant, Mex.
Hydroquinone (p. 1705·1); padimate O (p. 1716·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Skin hyperpigmentation.

Solaquin Forte *Valeant, Canad.*
Hydroquinone (p. 1705·1); padimate (p. 1715·3); dioxybenzone (p. 1700·2); oxybenzone (p. 1715·3).
Skin hyperpigmentation.

Valeant, USA.
Cream: Hydroquinone (p. 1705·1); padimate O (p. 1716·1); dioxybenzone (p. 1700·2); oxybenzone (p. 1715·3).
Skin hyperpigmentation.

Investi, Arg.; Valeant, USA.
Topical gel: Hydroquinone (p. 1705·1); padimate O (p. 1716·1); dioxybenzone (p. 1700·2).
Skin hyperpigmentation.

ICN, Malaysia.†
SPF 17: Hydroquinone (p. 1705·1) with sunscreens.
Skin hyperpigmentation.

Solar Defense *Dermalogica, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Solar Screen *Redken, Canad.*
SPF 12: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Solar Sense *CCA, Canad.†*
SPF 45: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Solaraze *CSL Biotherapies, Austral.; Almirall, Austria; Almirall, Denm.; Almirall, Fin.; Almirall, Fr.; Almirall Hermal, Ger.; Almirall, Irl.; Almirall, Ital.; Almirall, Norw.; Almirall, Port.; Almirall, Spain; Meda, Swed.; Almirall, Switz.; Almirall, UK; PharmaDerm, USA.*
Diclofenac sodium (p. 48·3).
Actinic keratoses.

Solarcaine *Mantecorp, Braz.; Balmar, NZ.†*
Benzocaine (p. 1980·2).
Local anaesthesia; skin irritation.

Schering-Plough, Canad.; Schering-Plough, UK; Schering-Plough, USA.
Benzocaine (p. 1980·2); triclosan (p. 1773·2).
Sunburn; skin pain or irritation; minor skin injuries; local anaesthesia.

Vifor, Switz.
Lidocaine (p. 1988·1).
Minor skin lesions and burns.

Balmar, NZ.†
Lotion: Benzocaine (p. 1980·2); camphor (p. 2466·2); menthol (p. 2553·2); triclosan (p. 1773·2).
Sunburn.

Solarcaine Aloe *Balmar, NZ·*
Aloe vera (p. 1693·2); lidocaine (p. 1988·1).
Minor burns; skin irritation; sunburn.

Solarcaine Aloe Extra Burn Relief *Schering-Plough, USA.*
Lidocaine (p. 1988·1); aloe vera (p. 1693·2).
Local anaesthesia.

Solarcaine Aloe Vera Gel *Schering-Plough, Chile.*
Lidocaine hydrochloride (p. 1988·2); aloe vera (p. 1693·2).
Sunburn.

Solarcaine Lidocaine *Schering-Plough, Canad.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Burns; sunburn; wounds.

Solarcaine Spray Aerosol *Schering-Plough, Chile.*
Isopropyl alcohol (p. 1758·3); triclosan (p. 1773·2); benzocaine (p. 1980·2).
Skin irritation.

Solarcaine Stop Itch *Schering-Plough, Canad.†*
⊗Papain (p. 2582·3).
Skin pain and irritation.

Solardril Composto *Bunker, Braz.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2).

Solare *Galenium, Indon.†*
SPF 15; SPF 30: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Sunscreen.

Solaren *Herbapol Pruszkow, Pol.*
Turmeric (p. 2218·1).
Biliary-tract disorders.

Solarisol *Solara, Mex.†*
Fluconazole (p. 578·2).
Fungal infections.

Solasic *Solas, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Solatcit *Actavis, Denm.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Solatran *GSK, S.Afr.†; Doetsch, Grether, Switz.*
Ketazolam (p. 1079·2).
Anxiety disorders; nervous disorders; skeletal muscle spasm.

Solavert *Aspen, Austral.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Solaxin *Eisai, Hong Kong; Eisai, Indon.*
Chlorzoxazone (p. 2022·2).
Painful skeletal muscle spasm.

Solaze *Solvang, Philipp.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Solazin *Leiras, Fin.†*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

SolBar *Person & Covey, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Person & Covey, USA.
SPF 30; SPF 50: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

SolBar Avo *Person & Covey, USA.*
SPF 32: Homosalate (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

Solben *Gap, Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Solblastin *Hospira, Port.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Solbotex *Arlex, Mex.*
⊗Salbutamol (p. 1220·2); ambroxol (p. 1654·3).

Solcer *Solara, Mex.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration.

Solcibrol *Solfran, Mex.*
Ambroxol hydrochloride (p. 1654·3); amoxicillin trihydrate (p. 216·2).
Respiratory-tract infections.

Solciclina *Solfran, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Solclav *Lloyd, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Solclin *Solfran, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Solcode *Reckitt Benckiser, Austral.†*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; fever.

Solcoderm *Dermik, China; Solco, Hong Kong†; Valeant, Rus.; Meda, Switz.; Meda, Ukr.*
Nitric acid (p. 2572·3); acetic acid (p. 2426·3); oxalic acid (p. 2578·2); lactic acid (p. 2539·1); copper nitrate (p. 2057·1).
Warts; verrucas; anogenital warts; naevi; keratoses.

Solco-Derman *Meda, Ger.*
Glacial acetic acid (p. 2426·3); oxalic acid (p. 2578·2); nitric acid (p. 2572·3); lactic acid (p. 2539·1); copper nitrate (p. 2057·1).
Verrucas; warts.

Solcogyn *Meda, Pol.; Meda, Switz.*
Acetic acid (p. 2426·3); nitric acid (p. 2572·3); oxalic acid (p. 2578·2); zinc nitrate (p. 2650·2).
Cervical and uterine disorders; benign cervical lesions.

SolcoKerasal *ICN, Pol.*
⊗Salicylic acid (p. 1719·1); urea (p. 1727·3).
Keratinisation disorders.

Solcoseryl *Adeka, Turk.*
Protein-free blood extract (p. 2444·1); lauromacrogol 400 (p. 2194·1).

Raymos, Arg.; Meda, Austria; Meda, Cz.; Santa, Gr.; Invida, Hong Kong; Pharos, Indon.†; Solco, Indon.†; Taiho, Jpn; Inovail, Malaysia; Invida, Philipp.; Meda, Pol.; Valeant, Rus.; Invida, Singapore; Meda, Switz.; Invida, Thai.; Meda, Ukr.
Protein-free blood extract (p. 2444·1).
Burns; skin ulceration; wounds; corneal disorders; keratitis; irritation due to contact lenses; mouth disorders; radiation-induced skin damage; cerebral and peripheral vascular disorders; frostbite; eye injury.

Solcoseryl akut *Meda, Ger.†*
Protein-free calf blood extract (p. 2444·1); lauromacrogol (p. 2194·1).
Mouth inflammation and pain.

Solcoseryl Dentaire *Meda, Switz.*
Protein-free calf blood extract (p. 2444·1); lauromacrogol 400 (p. 2194·1).
Mouth disorders.

Solcoseryl Dental *Meda, Austria; Valeant, Ger.†; Invida, Hong Kong; Pharos, Indon.†; Solco, Indon.†; Valeant, Malaysia; Invida, Philipp.; Valeant, Rus.; Invida, Singapore; Invida, Thai.; Meda, Ukr.*
Protein-free calf blood extract (p. 2444·1); lauromacrogol 400 (p. 2194·1).
Dental adhesive; mouth and gum disorders.

SolcoTrichovac *Valeant, Rus.; Meda, Switz.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus vaginalis* (p. 2596·3); *Lactobacillus fermentum* (p. 2596·3); *Lactobacillus salivarius* (p. 2596·3).
Vaginal infections; trichomoniasis.

Meda, Ukr.†
Lactobacillus acidophilus (p. 2596·3).
Trichomoniasis; bacterial vaginosis.

Solcovagin *Valeant, Rus.; Meda, Ukr.*
Nitric acid (p. 2572·3); acetic acid (p. 2426·3); oxalic acid (p. 2578·2); zinc nitrate (p. 2650·2).
Vaginal and uterine disorders; cervical disorders.

Soldactone *Continental Pharma, Belg.; Pfizer, Neth.; Pfizer, Switz.*
⊗Potassium canrenoate (p. 1472·2).
Hyperaldosteronism; oedema; liver cirrhosis with ascites and oedema; hypokalaemia.

Solderma *GSK, Ital.*
⊗Clobetasone butyrate (p. 1627·3).

Soldermil *Edol, Port.†*
A range of sunscreens.

Soldesam *Farmacologico Milanese, Ital.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Soldesanil *Diapit, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Soldextam *Solas, Indon.*
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Soldrin *Andromaco, Chile.*
Tiabendazole (p. 166·3).
Worm infections.

Pisa, Mex.
Ear drops: ⊗Hydrocortisone (p. 1640·1); chloramphenicol (p. 257·1); benzocaine (p. 1980·2).
Otitis externa.

Pisa, Mex.
Eye drops: ⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye disorders.

Sole *Vivier, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Solecin *Echo, Ital.†*
⊗Soya lecithin (p. 2542·2); wheat germ (p. 2647·1); gelatin (p. 1154·1); glycerol (p. 2517·2); betacarotene (p. 2051·1).
Nutritional supplement.

Soledum *Cassella-med, Ger.*
Cineole (p. 2479·1).
Bronchitis; sinusitis.

Soledum Balsam *Cassella-med, Ger.*
Cineole (p. 2479·1).
Respiratory-tract disorders.

Soledum Hustensaft *Cassella-med, Ger.*
Thyme (p. 2630·2).
Bronchiitis; catarrh; cough.

Soledum Hustentropfen *Cassella-med, Ger.*
Thyme (p. 2630·2).
Bronchitis; catarrh; cough.

Soleil Expert Sun Care *Lancome, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); octisalate (p. 1715·2).
Sunscreen.

Lancome, Canad.†
SPF 25; SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Soleil Identité *Chanel, Canad.*
Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Soleil Protexion Invisible Touch *Johnson & Johnson, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Soleil Protexion Sun Lip Stick *Johnson & Johnson, Canad.*
SPF 20: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Soleil Protexion Velvet Moisture *Johnson & Johnson, Canad.*
Cream: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Johnson & Johnson, Canad.
Spray SPF 30: Bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1).
Sunscreen.

Johnson & Johnson, Canad.
Spray SPF 60: Bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Soleil Ultra *Lancome, Canad.†*
SPF 40: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Solenil *Fortbenton, Arg.*
SPF 4; SPF 8; SPF 15: Octinoxate (p. 1715·1); benzophenones.
Sunscreen.

Solenil 65 *Fortbenton, Arg.*
Titanium dioxide (p. 1725·1); benzophenone.
Sunscreen.

Solenil Pantalla Fisica *Fortbenton, Arg.*
Octinoxate (p. 1715·1); benzophenone; titanium dioxide (p. 1725·1).
Sunscreen.

Solenil 100 Plus *Fortbenton, Arg.*
Titanium dioxide (p. 1725·1); benzophenone.
Sunscreen.

Solenil Post Solar *Fortbenton, Arg.*
Aloe vera (p. 1693·2); vitamin E (p. 2119·1).

Solenil Post Solar Cool Gel *Fortbenton, Arg.*
Aloe vera (p. 1693·2).

Soleron *Pharma Start, Ukr.*
Amisulpride (p. 1036·3).
Psychoses.

Solesmin *Cipla, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Solesta *Oceana, USA.*
Dextranomer (p. 1699·3); sodium hyaluronate (p. 2526·2).
Faecal incontinence.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Soleton *Cryopharma, Mex.*
Zaltoprofen (p. 142·2).
Inflammation; pain; musculoskeletal, joint, and peri-articular disorders.

Soleve *Dendron, UK.*
Ibuprofen (p. 68·2); isopropyl myristate (p. 2190·3).
Sunburn.

Solevita *Permamed, Switz.*
St John's wort (p. 449·1).
Sleep disorders; agitation; depression.

Solexa *Medinfar, Port.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

Solexin *VS, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Soleye *Premier Research, Neth.†*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Solfa *Takeda, Jpn.*
Amlexanox (p. 1202·2).
Asthma; allergic rhinitis.

Solfac *Bayer, Ital.*
Cyfluthrin (p. 2151·3).
Insecticide.

Solfen
Note: this name may be used for preparations of different composition.
Sunward, Singapore.
Docusate sodium (p. 1836·2).
Constipation.

Solfidin *AstraZeneca, Arg.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Solfoton
Note: this name may be used for preparations of different composition.
Erfar, Gr.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Solfranicol *Solfran, Mex.*
Chloramphenicol (p. 257·1); tetracycline (p. 373·1).
Bacterial infections.

Solfurol *Solfran, Mex.*
Furazolidone (p. 933·3); clioquinol (p. 273·1).
Diarrhoea.

Solganal *Schering, USA.†*
Aurothioglucose (p. 28·2).
Rheumatoid arthritis.

Solgenta *Oftalmi, Venez.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Solgol *Sanofi-Aventis, Spain.*
⊗Nadolol (p. 1442·3).
Angina pectoris; arrhythmias; migraine; hypertension.

Solhidrol *Solara, Mex.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Solia *Prasco, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3); 7 tablets, inert.
Combined oral contraceptive.

Unison, Thai.
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Solian *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi Synthelabo, Turk.; Sanofi Synthelabo, UK; Sanofi-Aventis, Ukr.*
Amisulpride (p. 1036·3).
Psychoses; schizophrenia; depression.

Solibone *Quimica y Farmacia, Mex.†*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis; rickets; osteomalacia; tetany.

Solicam *SMB, Belg.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout; pain.

Solidacur *Rodisma, Ger.*
Solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Solidago Hevert Complex *Hevert, Ger.*
Acidum nitricum (p. 2572·3); apis (p. 2445·2); belladonna (p. 2453·3); cantharis (p. 2469·2); juniperus communis (p. 2537·1); solidago virgaurea (p. 2620·1).
Homoeopathic preparation.

Solidagoren *Klein, Ger.*
Solidago virgaurea (p. 2620·1); potentilla anserina; equisetum (p. 2500·1).
Urinary-tract disorders.

Solidagoren Mono *Klein, Ger.*
Solidago virgaurea (p. 2620·1).
Formerly known as Solidagoren Uro.
Urinary-tract disorders.

Solidagoren mono *Klein, Ger.*
Solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Solidagosan N *Hanosan, Ger.*
Solidago virgaurea (p. 2620·1); urtica urens (p. 2639·3); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Solidon *Adelco, Gr.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; agitation.

Solimar *Teva, Hung.*
Dead Sea salt (p. 2612·1).
Musculoskeletal and joint disorders.

Solimed *Farmedia, Gr.*
Salicylic acid (p. 1719·1).
Skin disorders.

Solin *Saval, Chile.*
Lidocaine hydrochloride (p. 1988·2).
Pain during injection.

Solinase *Astellas, Jpn.†*
Pamiteplase (p. 1464·2).
Myocardial infarction.

Solinfec *Ifars, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Solinitrina *IFET (ΙΦΕΤ), Gr.; Kern, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; induction of hypotension in surgery; myocardial infarction; pulmonary oedema.

Solipred *Solara, Mex.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Soliris *Alexion, Austria; LCA, Belg.; Alexion, Canad.; Alexion, Cz.; Alexion, Denm.; Alexion, Fr.; Alexion, Ger.; Alexion, Irl.; Alexion, Israel; Alexion, Ital.; Alexion, Jpn; Alexion, Neth.; Alexion, Norw.; Alexion, Pol.; Alexion, Port.; Alexion, Spain; Alexion, Swed.; Alexion, Switz.; Alexion, UK; Alexion, USA.*
Eculizumab (p. 2499·1).
Paroxysmal nocturnal haemoglobinuria; atypical haemolytic uraemic syndrome.

Solispasm *Actavis, Fr.*
Phloroglucinol (p. 2588·2).
Smooth muscle spasm.

Solivito N *Fresenius Kabi, Irl.; Fresenius Kabi, UK.*
Vitamins.
Parenteral nutrition.

Soliyod *Munir, Turk.*
Povidone-iodine (p. 1767·1).
Skin and mucous membrane disinfection; wounds; burns; skin infections.

Solkan *Solfran, Mex.*
Kanamycin (p. 314·3).
Bacterial infections.

Sollat *Siegfried, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Sollevare *EMS, Braz.*
Sildenafil (p. 2364·1).

Sollival *Sirval, Ital.*
Emollient.

Solmag *Nutrimed, Switz.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency; arrhythmias.

Proreo, Switz.†
Magnesium aspartate (p. 1787·1).
Magnesium deficiency; magnesium supplement; arrhythmias.

Solmavin *Mavi, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Solmiran *Teijin, Jpn.*
Eicosapentaenoic acid ethyl ester (p. 1460·2).
Occlusive arterial disease; hyperlipidaemias.

Solmirat *Abdi, Turk.*
Butamirate citrate (p. 1657·3).

Solmucaine *IBSA, Switz.*
Acetylcysteine (p. 1652·2); tyrothricin (p. 384·1); lidocaine hydrochloride (p. 1988·2).
Upper respiratory-tract disorders with viscous mucus.

Solmucalm *IBSA, Switz.*
Acetylcysteine (p. 1652·2); chlorphenamine maleate (p. 620·3).
Cough.

Solmucol *IBSA, Cz.; Genevrier, Fr.; IBSA, Hong Kong; IBSA, Hung.; Amsa, Ital.; IBSA, Neth.†; IBSA, Philipp.†; Sonix, Philipp.†; Aspen Consumer, S.Afr.; Genevrier, Singapore; IBSA, Switz.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol overdosage; .

Solmux *Westmont, Hong Kong; Mediforma, Indon.†; UAP, Indon.†; United Laboratories, Philipp.; Westmont, Singapore; Pediatrica, Thai.†; Westmont, Thai.†*
Carbocisteine (p. 1658·1).
Cough associated with excess mucus; otitis media; respiratory-tract congestion; sinusitis.

Solmux-Broncho (Reformulated) *United Laboratories, Philipp.*
⊗Salbutamol (p. 1220·2); carbocisteine (p. 1658·1).
Cough associated with viscous mucus.

Solnasin *Polpharma, Pol.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

Solo *Theralogix, USA.*
Vitamins; minerals; choline (p. 2055·2).
Dietary supplement.

Solo Care Aqua *Ciba Vision, Arg.*
Solution for soft contact lens care.

Solocalm *Bernabo, Arg.*
Piroxicam (p. 125·3) or piroxicam betadex (p. 126·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Solocalm Plus *Bernabo, Arg.*
Tablets: ⊗Piroxicam (p. 125·3); carisoprodol (p. 2021·3); dexamethasone (p. 1630·3); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Musculoskeletal, joint, and peri-articular disorders.

Bernabo, Arg.
Injection: ⊗Piroxicam (p. 125·3); pyridoxine hydrochloride (p. 2105·3); dexamethasone (p. 1630·3); vitamin B_{12} (p. 2107·2).
Musculoskeletal, joint and peri-articular disorders.

Solocalm-B *Bernabo, Arg.*
Piroxicam (p. 125·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Inflammation; neuritis.

Solocalm-Flex *Bernabo, Arg.*
Piroxicam (p. 125·3); carisoprodol (p. 2021·3).
Musculoskeletal and joint disorders.

Solo-care *Novartis, Braz.*
Cleaning solution for contact lenses.

Ciba Vision, Austral.†
Cleansing, rinsing, disinfecting and storing solution for soft contact lenses.

Solo-care Aqua *Ciba Vision, Canad.*
Cleansing, rinsing, disinfecting, and storage solution for soft contact lenses.

Solocare Plus *Ciba Vision, Turk.*
Solution for contact lens care.

Solodiab *Medica Korea, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Solodyn *Medicis, USA.*
Minocycline hydrochloride (p. 325·1).
Acne.

Solof *Farmaceutica H, Mex.*
Diclofenac sodium (p. 48·3).
Inhibition of miosis during cataract surgery; inflammation and pain following eye surgery; prevention of cystoid macular oedema; inflammatory eye disorders.

Sol-O-Flex *Inmunolab, Arg.†*
Povidone (p. 2204·3).
Dry eyes.

Solokinase *Aristo, India.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Solomet *Orion, Fin.*
⊗Methylprednisolone (p. 1642·2), methylprednisolone acetate (p. 1642·3), or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Solomet c bupivacain hydrochlorid *Orion, Fin.*
⊗Methylprednisolone acetate (p. 1642·3); bupivacaine hydrochloride (p. 1980·3).
Musculoskeletal, joint, and peri-articular disorders.

Solomycin *Ipca, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Solon *Taisho, Jpn.*
Sofalcone (p. 1888·2).
Gastritis; peptic ulcer.

Solone
Note: this name may be used for preparations of different composition.
Valeant, Austral.
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Solosa *Sanofi-Aventis, Gr.; Guidotti, Ital.; Sanofi-Aventis, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Solosamet *Sanofi-Aventis, Philipp.*
Glimepiride (p. 473·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Solosin *Sanofi-Aventis, Ger.†; Winthrop, Ger.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

SoloSite *Smith & Nephew, Austral.*
Carmellose sodium (p. 2175·2); allantoin (p. 1693·1).
Wounds.

Solosprin *Cadila, India.*
Isosorbide mononitrate (p. 1413·3); aspirin (p. 22·2).
Angina pectoris; myocardial infarction.

Solotop *Taejoon, Thai.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Solotrate *Zydus Cadila, Thai.*
Isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease; angina pectoris; pulmonary hypertension; myocardial infarction.

Solotrim *Hexal, Austria.†*
Trimethoprim (p. 381·2).
Bacterial infections.

Solotuss *Hawthorn, USA.†*
Pentoxyverine tannate (p. 1672·1).
Cough.

Solovite *Solgar, UK.*
Vitamins; minerals.

Solox *Douglas, NZ.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer.

Solpadeine *GSK Consumer, Cz.†; GSK Consumer, Irl.; GSK Consumer, Pol.; GSK Consumer, Rus.; GSK Consumer, Ukr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain; cold and influenza symptoms; fever.

Solpadeine Cold & Flu *GSK Consumer, Irl.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); pholcodine (p. 1675·1).
Cold and influenza symptoms.

Solpadeine Headache *GSK Consumer, UK.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Solpadeine Max *GSK Consumer, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol.
Fever; pain.

Solpadeine Migraine *GSK, UK.*
Ibuprofen (p. 68·2); codeine (p. 40·2).
Migraine.

Solpadeine Plus *Omega, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Solpadol *Sanofi-Aventis, Irl.; Sanofi-Aventis, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol 30/500.
Pain.

Solpaflex
Note: this name may be used for preparations of different composition.
GSK, Cz.†; GSK Consumer, Hung.†; GSK Consumer, Rus.
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain; fever.

GSK Consumer, UK·
Tablets: Ibuprofen (p. 68·2); codeine phosphate (p. 40·2).
Pain; fever.

Solpa-Flu *GSK Consumer, Irl.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Nasal and sinus congestion; cold and influenza symptoms.

Solpa-Sinus *GSK Consumer, Irl.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion; cold and influenza symptoms.

Solpat *Parggon, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Solpenox *Solas, Indon.*
Amoxicillin (p. 216·2).
Bacterial infections.

Solphride *Solvang, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Solphyllex *Adcock Ingram, S.Afr.*
Theophylline (p. 1229·3); etofylline (p. 1208·2); diphenylpyraline hydrochloride (p. 627·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Solphyllin *Adcock Ingram, S.Afr.*
Theophylline (p. 1229·3); etofylline (p. 1208·2).
Obstructive airways disease.

Solplem *Essenpharma, Philipp.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Solprene *Farmigea, Ital.*
⊗Prednisolone sodium phosphate (p. 1645·3); neomycin sulfate (p. 330·1).
Infected eye disorders.

Solpres *Biotech, Venez.*
Quinapril hydrochloride (p. 1480·2).
Heart failure; hypertension.

Solprin *Reckitt Benckiser, Austral.*
Aspirin (p. 22·2).
Pain; fever; inhibition of platelet aggregation.

Reckitt Benckiser, N.Z.
Calcium aspirin (p. 22·2).
Inflammation; pain.

Solril *XL, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Solsavit *Solfran, Mex.*
Vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).
Neuritis; anaemias.

Soltacina *Solara, Mex.†*
Indometacin (p. 71·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; inflammation; pain.

Soltadol *Solara, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Soltamox *Rosemont, Irl.; Rosemont, Neth.; Rosemont, UK; Oncogenerix, USA.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility.

Soltice *Oakhurst, USA.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Soltin *Oftalmi, Venez.*
⊗Chlorphenamine maleate (p. 620·3); naphazoline hydrochloride (p. 1669·3).
Allergic conjunctivitis.

Soltrictor con Lagrifilm *Allergan, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3); polyvinyl alcohol (p. 2204·2).
Eye irritation.

Soltrim *Almofarma, Spain.*
Sulfamethoxazole lysine (p. 365·2); trimethoprim (p. 381·2).
Bacterial infections; pneumocystis pneumonia.

Bruluart, Mex.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Soltrimox *Richmond, Arg.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Solubacter *Lisapharm, Fr.; Wing Wai, Hong Kong.†*
Triclocarban (p. 1773·2).
Disinfection of skin and mucous membranes.

Solubilax *Alapis, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Solubitrat *Sanova, Austria.†*
Birch leaf (p. 2457·3); solidago virgaurea (p. 2620·1); java tea (p. 2536·3).
Urinary-tract disorders.

Solucal *Jamp, Canad.*
Calcium lactate gluconate (p. 1784·2).

Solucal D *Jamp, Canad.*
Calcium lactate gluconate (p. 1784·2); colecalciferol (p. 2113·1).

Solucaps *Medix, Mex.*
⊗Mazindol (p. 2324·1).
Obesity.

Solucarb BC *Euro-Med, Philipp.*
Sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1).
Haemodialysis.

Solucel
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Venez.
Colloidal infusion.
Plasma volume expansion; extracorporeal circulation.

Stiefel, Spain.
Benzoyl peroxide (p. 1696·1).
Acne.

Solu-Celestan *Aesca, Austria.*
⊗Betamethasone disodium phosphate (p. 1623·3).
Corticosteroid.

Solucer *Fortbenton, Arg.*
Trolamine polypeptide oleate-condensate (p. 2634·3).
Ear wax removal.

Solucetyl *Arrow, Fr.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Soluchrom *Cooperation Pharmaceutique, Fr.†*
Merbromin sodium (p. 1760·1).
Skin, burn and wound disinfection.

Solucid *Euro-Med, Philipp.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders in renal failure.

Solucin *Swiss Parenterals, Philipp.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Solucion Boston Simplus *Bausch & Lomb, Arg.*
Cleaning, lubricating, and disinfecting solution for contact lenses.

Solucion Detergente *Reccius, Chile.*
Sodium lauril ether sulfate (p. 2210·3).

Solución Evacuante *Bohm, Spain.*
Macrogol 4000 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation; constipation.

Solución Fisiológica Respitol *Cinfa, Spain.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Solucion Irrigacion Vesical *Sanderson, Chile.†*
⊗Sorbitol (p. 2092·1); mannitol (p. 1427·3).
Bladder irrigation.

Solucion Oral *Naf, Arg.*
Electrolytes (p. 1775·1); xylitol (p. 2220·3); hypromellose (p. 2189·2).
Dry mouth.

Solucion Schoum *Expanscience, Spain.*
Boldo (p. 2458·3); fumitory (p. 2508·2); hamamelis (p. 2523·3); melissa (p. 2552·3); rhubarb (p. 1884·2); piscidia (p. 2536·3); peppermint oil (p. 1877·1); hydrastis (p. 2528·1).
Hepatobiliary disorders.

Solucis *Pharma-Marketing, Hung.†; Aesculapius, Ital.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Soluclear *Vivax Optipharm, Venez.*
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Inflammatory eye disorders.

Soluclenz *Obagi, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Solu-Cortef *Pfizer, Austral.; Pfizer, Belg.; Uniao Quimica, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Solu-Dacortin *Merck, Austria.*
⊗Prednisolone sodium succinate (p. 1646·1).
Corticosteroid.

Solu-Dacortina *Merck, Port.*
⊗Prednisolone sodium succinate (p. 1646·1).
Corticosteroid.

Soludactone *Pfizer, Fr.*
⊗Potassium canrenoate (p. 1472·2).
Hypokalaemia; hyperaldosteronism; oedema; ascites.

Soludamin *Kleva, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Solu-Decortin H *Merck Serono, Ger.*
⊗Prednisolone sodium succinate (p. 1646·1).
Parenteral corticosteroid.

Soluderme *Schering-Plough, Port.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Soludial *Soludia, Fr.†*
Sodium bicarbonate (p. 1781·1).
Haemodialysis.

Soludor *Lehning, Fr.*
Aurum colloidum (p. 2521·1); natrum muriaticum (p. 1795·1); crataegus oxyacantha (p. 2488·1); valeriana officinalis (p. 2640·2); avena sativa (p. 2451·1); cactus grandifloris (p. 2473·2); camphora (p. 2466·2); ignatia (p. 2532·1); arnica (p. 2447·2); strophantus (p. 1507·2); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Homeocan, Canad.†
Arnica montana (p. 2447·2); cactus grandiflorus (p. 2473·2); camphor (p. 2466·2); oats (p. 2451·1); strophanthus hispidus; valerian (p. 2640·2).
Homoeopathic preparation.

Soludril Antiussivum *Pierre Fabre Sante, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Soludril Expectorans *Pierre Fabre Sante, Belg.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Solufen
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Fr.†; Azevedos, Port.
Ibuprofen (p. 68·2).
Fever; pain.

Solufer *Kocak, Turk.*
Iron polymaltose (p. 2077·2).

Solu-Flur *Germiphene, Canad.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Solufos *Q Pharma, Spain.*
Fosfomycin calcium (p. 300·3).
Bacterial infections.

Solugastril *Pfizer, Austria.*
Aluminium hydroxide (p. 1817·2); calcium carbonate (p. 1824·3).
Gastro-oesophageal reflux; gastritis; duodenitis; dyspepsia; peptic ulcer.

Solugel *GSK, Arg.; Stiefel, Braz.; GSK, Canad.; Stiefel, Chile; Stiefel, Mex.*
Benzoyl peroxide (p. 1696·1).
Acne.

Johnson & Johnson, Austral.
Hydrogel dressing.
Burns; ulcers; wounds.

Solu-Hex *Intra, Venez.*
Hexachlorophene (p. 1754·1).
Disinfection.

Solu-IV CHD Alcool *Solumed, Canad.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).

Solu-IV CHG *Solumed, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Solu-IV CHG Alcohol *Solumed, Canad.†*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).

Solu-Ket *Arriani, Gr.*
Ketoprofen lysine (p. 79·1).
Oral irritation and inflammation.

Solulexin *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Cefalexin (p. 234·1).
Bacterial infections.

Solulip *Pharmanik (Φαρμανικ), Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Solumag *Intermed, Gr.; Geymonat, Ital.*
Magnesium pidolate (p. 1787·3).
Nervous hyperexcitability associated with magnesium deficiency; eclampsia and other obstetric disorders; magnesium deficiency.

Hexal, S.Afr.
Magnesium oxide (p. 1857·3).
Magnesium supplement.

Solumag-D *Chew, Thai.*
Oral suspension: Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2); peppermint oil (p. 1877·1).
Gastric hyperacidity.

Chew, Thai.
Tablets: Aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Solu-Medrol *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Hong Kong; Pfizer, Hung.; Max, India; Pfizer, Indon.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Pfizer, Gr.
⊗Methylprednisolone hydrogen succinate (p. 1642·3) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Solu-Médrol *Pfizer, Fr.*
⊗Methylprednisolone hydrogen succinate (p. 1642·3).
Corticosteroid.

Solu-Medrone *Pfizer, Irl.; Pfizer, UK.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Solumelan *Arafarma, Spain.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Solumerin *Ariston, Arg.*
Benzethonium chloride (p. 1738·1); tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); butimerin.
Burns; mouth disorders; skin infections; ulcers; wounds.

Solumidazol *Diba, Mex.†*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis.

Solu-Moderin *Pfizer, Spain.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Solumol *C & M, USA.*
Vehicle for topical preparations.

Soluna *Elea, Arg.*
Quinestrol (p. 2303·1); etynodiol diacetate (p. 2277·3).
Combined oral contraceptive.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Solunac *Systopic, India.†*
Diclofenac (p. 48·3).
Gout; musculoskeletal and joint disorders.

Solunet 1 *Solumed, Canad.†*
Povidone-iodine (p. 1767·1).

Solunet C *Solumed, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Solunet Mousse *Solumed, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Solunovar Compuesto *Vincenti, Venez.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

Solu-Ped *Huons, Philipp.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Solupen *Winzer, Ger.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Rhinitis; sinusitis.

Solupred
Note: this name may be used for preparations of different composition.
IFET (ΙΦΕΤ), Gr.
⊗Prednisolone (p. 1645·2).
Corticosteroid.
Sanofi-Aventis, Fr.
⊗Prednisolone metasulfobenzoate sodium (p. 1645·3).
Corticosteroid.
Ingens, Arg.†
⊗Prednisolone (p. 1645·2); phenylephrine (p. 1672·2).
Eye disorders.

Solupren *Bergamo, Braz.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Soluprep *Solumed, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Soluprep CHD-Alcohol *Solumed, Canad.*
Chlorhexidine gluconate (p. 1743·3); isopropyl alcohol (p. 1758·3).

Soluprep Povidone Iodee *Solumed, Canad.†*
Povidone-iodine (p. 1767·1).

Soluprick *ALK, Denm.*
Allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.
ALK, Port.
Histamine hydrochloride (p. 2525·2) (p. 2434·3).
Diagnosis of hypersensitivity.

Soluprick Controlevloeistoffen *ALK, Neth.*
Histamine hydrochloride (p. 2525·2) (p. 2434·3).
Diagnosis of hypersensitivity.

Soluprick SQ *ALK, Cz.; ALK, Fin.; ALK, Neth.; ALK, Norw.; ALK, Swed.; ALK, Switz.*
Allergen extracts (p. 2434·3).
Diagnosis of hypersensitivity.
ALK, UK.
Grass pollen allergen extracts (*Phleum pratense*) (p. 2593·3) (p. 2434·3).
Diagnosis of allergy.

Solural *Antibioticos, Mex.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Soluric *Unipharma, Gr.*
Allopurinol (p. 600·2).
Gout; renal calculi; hyperuricaemia associated with cancer chemotherapy.

Solurrinol *Teofarma, Spain.*
Potassium chlorate (p. 2595·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1).
Nasal congestion.

Solus *Lifeplan, UK.*
Vitamins; minerals; nutritional supplments.

Soluseptol *Yuriya-Farm, Ukr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis toxoplasmosis; paracoccidioidomycosis.

Solusin *Genericon, Cz.; Premier Research, Neth.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Solustrep
Note: this name may be used for preparations of different composition.
Bergamo, Braz.
Streptokinase (p. 1503·1).
Thromboembolic disorders.
Caps, S.Afr.
Streptomycin sulfate (p. 359·1).
Tuberculosis.

Solustres *Finadiet, Arg.*
⊗Tetracycline hydrochloride (p. 373·2); papain (p. 2582·3).
Bacterial infections.

Solutan *Galena, Rus.†*
⊗Belladonna (p. 2453·3); dill oil (p. 2493·2); saponin (p. 2207·1); procaine hydrochloride (p. 1994·3); ephedrine hydrochloride (p. 1663·2); sodium iodide (p. 2337·1); tolu balsam (p. 1679·2); bitter almond water.

Solute Physiologique Phenole Lavoisier *Chaix et du Marais, Fr.*
Sodium chloride (p. 1795·1); phenol (p. 1763·3).
Diluent and solvent for allergens.

Soluterb *Mentiterm, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Soluthrombine *Cooper (Κοπερ), Gr.*
Phenindione (p. 1467·3).

Solutina *Alcon, Mex.*
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Conjunctivitis.

Solutio Cordes *Ichthyol, Austria; Ichthyol, Ger.*
Ictasol (p. 1706·1).
Scalp disorders.

Solutio Cordes Dexa N *Ichthyol, Ger.*
⊗Dexamethasone (p. 1630·3).
Scalp disorders.

Solutio Thomas cum Procaino *Ardeapharma, Cz.*
Magnesium chloride (p. 1787·1); potassium chloride (p. 1793·2); procaine hydrochloride (p. 1994·3).
Cardioplegia.

Solution Stago Diluée *Pharmadeveloppement, Fr.*
Boldo (p. 2458·3); chamomile (p. 2474·1); kinkeliba (p. 2538·2); solidago (p. 2620·1).
Digestive disorders.

Solutions AM Ageless Results *Avon, Canad.†*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Solutions AM Complete Balance *Avon, Canad.†*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Solutions AM Maximum Moisture *Avon, Canad.†*
Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Solutions AM Total Radiance *Avon, Canad.*
Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Solutions Winter *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Solutrast *Bracco, Ger.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Solutrat *Sandoz, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones.

Solutricine Maux de Gorge *Sanofi-Aventis, Fr.*
Lozenges: Tetracaine hydrochloride (p. 1996·3).
Mouth and throat disorders.
Sanofi-Aventis, Fr.
Pastilles: Biclotymol (p. 1740·1).
Mouth and throat infections.
Sanofi-Aventis, Fr.†
Throat spray: Tetracaine hydrochloride (p. 1996·3); hexamidine isetionate (p. 1754·3).
Mouth and throat disorders.

Soluvass *Arafarma, Spain.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; heart failure; stroke prevention.

Soluver *Dermtek, Canad.*
Salicylic acid (p. 1719·1).
Verrucas.

Soluver Plus *Dermtek, Canad.*
Salicylic acid (p. 1719·1).
Warts.

Soluvit *Fresenius Kabi, Austria; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Gr.; Fresenius Kabi, Ital.; Fresenius Kabi, Norw.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Spefar, Venez.*
Vitamins.
Parenteral nutrition.

Soluvit N *Fresenius Kabi, Austral.; Fresenius Kabi, Chile; SSPC, China; Fresenius Kabi, Cz.; Baxter, Ger.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Israel; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, NZ; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.*
Vitamins.
Parenteral nutrition.

Soluvit Novum *Fresenius, Belg.*
Vitamins.
Parenteral nutrition.

Soluvite *Pharmics, USA.*
Vitamins; fluoride (p. 2089·2).
Dental caries prophylaxis; dietary supplement.

Solu-Volon A *Dermapharm, Austria.*
⊗Triamcinolone acetonide dipotassium phosphate (p. 1648·3).
Corticosteroid.

Soluwax *Hoe, Malaysia; Hoe, Singapore.*
Docusate sodium (p. 1836·2).
Ear wax removal.

Soluzione Darrow *Diaco, Ital.*
Electrolytes (p. 1775·1).
Infantile diarrhoea.

Soluzione Schoum *Sanofi-Aventis, Ital.*
Fumitory (p. 2508·2); ononis (p. 2575·3); piscidia (p. 2536·3).
Painful spasm of the urinary and biliary tracts.

Soluzyme *Lupin, India.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Inflammation; oedema; viscous mucus and sputum.

Solvamin *Gold Coast, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); brompheniramine maleate (p. 618·1).
Nasal congestion.

Solvanol *Medipharm, Chile.*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3); ammonium chloride (p. 1656·1).
Cough.

Solvaris *Alvartis, Mex.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Solvatan *Helsinn Birex, Irl.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; cardiovascular risk reduction; diabetic nephropathy.

Solvazinc *IFET (ΙΦΕΤ), Gr.; Provalis, Irl.†; koGen, UK.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

SolvEasy *Ego, Austral.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Solvente Indoloro *Apolo, Arg.; Drawer, Arg.; Fada, Arg.; Monserrat, Arg.; Northia, Arg.; Richmond, Arg.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Pain during injection.

Solvertyl *ICN, Pol.*
Ranitidine (p. 1882·1).
Excess gastric acidity; peptic ulcer; acid aspiration.

Solvetan *Europharma, Denm.; GSK, Gr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Solvex
Note: this name may be used for preparations of different composition.
Merz, Ger.
Reboxetine mesilate (p. 447·1).
Depression.
Teva, Israel.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Solvezink *Biophausia, Norw.; Biophausia, Swed.*
Zinc sulfate (p. 2126·2).
Ulcers; acrodermatitis enteropathica; zinc deficiency.

Solvin
Note: this name may be used for preparations of different composition.
Ipca, India.
⊗Bromhexine hydrochloride (p. 1656·3); pseudoephedrine hydrochloride (p. 1676·1).
Formerly contained bromhexine hydrochloride and phenylephrine hydrochloride.
Cold symptoms; cough.
Ipca, Rus.
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders with viscous mucus.

Solvinex *Meprofarm, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Solving *MDM, Ital.*
Nimesulide (p. 101·3).
Pain.

Solvipect *Nycomed, Norw.*
Guaifenesin (p. 1666·2); liquorice (p. 1853·2).
Cough.

Solvipect comp *Nycomed, Norw.*
Guaifenesin (p. 1666·2); liquorice (p. 1853·2); ethylmorphine hydrochloride (p. 56·3).
Cough.

Solvisol *Solfran, Mex.†*
Vitamins.

Solvita Baby *Solas, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3); sodium fluoride (p. 2089·2); docosahexaenoic acid (p. 1460·1); omega-3; omega-6.
Nutritional supplement.

Solvita Plus *Solas, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3); calcium gluconate (p. 1783·3).
Vitamin and calcium supplement.

Solvitral *Solas, Indon.*
Vitamins; minerals; ferrous fumarate (p. 2060·3).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement in pregnancy and lactation.

Solvitron *Solas, Indon.*
Capsules: Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2).
Iron deficiency; anaemias.
Solas, Indon.
Oral syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3); zinc sulfate (p. 2126·2).
Iron deficiency; anaemias.

Solvium *Chefaro, Port.; Omega, Spain.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Solvobil
Note: this name may be used for preparations of different composition.
Silesia, Chile.
Ursodeoxycholic acid (p. 2638·1).
Gallstones.
Farmasa, Braz.
Cynara (p. 2490·3); boldo (p. 2458·3); cascara (p. 1826·1); belladonna (p. 2453·3); peppermint leaf (p. 1877·1); juniper oil (p. 2537·2).
Liver disorders.
Recordati, Ital.†
Sodium cholate (p. 2457·2); nicotinamide (p. 2083·1); boldo (p. 2458·3); cascara (p. 1826·1).
Constipation.

Solvolan *KRKA, Cz.; KRKA, Hung.†*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Solvongrip *Boehringer Ingelheim, Spain.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Solvopret
Note: this name may be used for preparations of different composition.
Bionorica, Austria.†
Gentian (p. 2512·1); primula flower (p. 2596·2); rumex (p. 2620·3); sambucus (p. 2609·3); verbena.
Catarrh.
Bionorica, Thai.†; Pharmalink, Thai.†
Thyme (p. 2630·2); ivy (p. 2536·2).
Bronchitis.

Solvopret TP *Bionorica, Thai.†; Pharmalink, Thai.†*
Thyme (p. 2630·2); primrose root (p. 2596·2).
Bronchitis.

Solvoxine *Solvang, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum bleeding; lactation promotion; missed abortion.

Som Pam *Valeant, Canad.*
Flurazepam dihydrochloride (p. 1076·1).
Sleep disorders.

Soma
Note: this name may be used for preparations of different composition.
Pfizer, Gr.; Wallace, USA.
Carisoprodol (p. 2021·3).
Musculoskeletal disorders.

Somabion *Medicus, Gr.*
Somatostatin acetate (p. 1930·3).
Upper gastrointestinal tract haemorrhage.

Somac
Note: this name may be used for preparations of different composition.
Nycomed, Austral.; Nycomed, Cz.; Nycomed, Fin.; Nycomed, Irl.; Nycomed, Norw.; Mylan, NZ.†
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Belmac, Spain.†
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Somac Control *Nycomed, Neth.; Nycomed, Pol.; Nycomed, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Somacid *Collins, Mex.*
Carisoprodol (p. 2021·3).
Skeletal muscle spasm.

Somac-MA *Altana, Austral.†*
Tablets, pantoprazole sodium (Somac) (p. 1875·3); capsules, amoxicillin trihydrate (Amoxil) (p. 216·2); tablets, metronidazole (Flagyl) (p. 936·1).
Peptic ulcer.

Somadril Compound *Actavis, Indon.*
Carisoprodol (p. 2021·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; musculoskeletal, joint, and soft-tissue disorders.

Somaflam *Wallace, India.*
Carisoprodol (p. 2021·3); ibuprofen (p. 68·2).
Inflammation; pain; skeletal muscle spasm.

Somaflex
Note: this name may be used for preparations of different composition.
Cosmopharm, Gr.
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Somagin *Charoen, Thai.†*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3).
Skeletal muscle spasm.

Somalgen *Bago, Arg.*
Talniflumate (p. 1678·2).
Inflammation.

Somalgesic *Church, Mex.*
Naproxen (p. 98·2); carisoprodol (p. 2021·3).
Musculoskeletal, joint, and peri-articular disorders.

Somalgin *Sigma, Braz.*
Aspirin (p. 22·2).
Aluminium glycinate (p. 1817·2) and magnesium carbonate (p. 1856·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain; thrombosis prophylaxis.

Somalium *Ache, Braz.*
Bromazepam (p. 1041·2).
Anxiety; insomnia.

Somaplus *Cazi, Braz.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Somarexin *Lalco, Canad.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Somargen *Vocate, Gr.*
Somatostatin acetate (p. 1930·3).

Somaritin *Anpharm (Ανφαρμ), Gr.*
Somatostatin (p. 1930·3).

Somasedan *Quesada, Arg.*
Bromazepam (p. 1041·2); clebopride (p. 1833·1); simeticone (p. 1886·2).

Somastin *Angelini, Gr.*
Somatostatin (p. 1930·3).
Upper gastrointestinal tract haemorrhage.

Serum Institute, India.
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; pancreatic, biliary, and intestinal fistulae; postoperative complications following pancreatic surgery; diabetic ketoacidosis.

Somatin *Eumedica, Austria.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery.

Somatoline *Manetti Roberts, Ital.*
Levothyroxine (p. 2339·1); aescin (p. 2431·2).
Adipose states with cellulite.

Somatosan *Dem, Turk.*
Somatostatin acetate (p. 1930·3).
Gastrointestinal haemorrhage.

Somatran *Andromaco, Chile.*
Sumatriptan (p. 679·2).
Migraine.

Somatron *Volchem, Ital.*
L-Arginine (p. 2049·1); L-ornithine (p. 2085·2).
Nutritional supplement.

Somatrop *Biosintetica, Braz.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency.

Somatulina *Ipsen, Port.; Ipsen, Spain.*
Lanreotide acetate (p. 1923·2).
Acromegaly; carcinoid syndrome; neuroendocrine tumours; pituitary adenoma.

Somatuline *Sanofi-Aventis, Arg.; Ipsen, Austral.; Pharma Logistik, Austria; Ipsen, Belg.; EMD, Canad.; Beaufour-Ipsen, China; Ipsen, Cz.; Ipsen, Fin.; Ipsen, Fr.; Ipsen, Ger.; Ipsen, Gr.; Beaufour-Ipsen, Hong Kong; Ipsen, Hung.; Ipsen, Irl.; Medison, Israel; Teijin, Jpn; Ipsen, Neth.; Beaufour-Ipsen, Pol.; Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Swed.; Future Health, Switz.; Gen, Turk.; Ipsen, UK; Ipsen, Ukr.; Tercica, USA.*
Lanreotide acetate (p. 1923·2).
Acromegaly; carcinoid syndrome; neuroendocrine tumours; thyrotrophic adenomas; gastrointestinal fistulae; Grave's ophthalmopathy.

Somavert *Pfizer, Arg.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.†; Pfizer, USA.*
Pegvisomant (p. 1928·2).
Acromegaly.

Somazina *Abbott, Braz.; Andromaco, Chile; Ferrer, Spain; Ferrer, Thai.; Leti, Venez.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; mental function impairment; head injury; stroke; cerebral oedema; dyskinesia; parkinsonism.

Bago, Arg.; Ferrer-Novag, Mex.; CPH, Port.; Ferrer, Ukr.
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders.

Somazinal *Faran, Gr.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Somazine *Patriot, Philipp.*
Citicoline (p. 2480·1).
Cerebral insufficiency.

Somecid *Stallion, Philipp.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Somelin *Daiichi Sankyo, Jpn.*
Haloxazolam (p. 1078·3).
Insomnia.

Someral *Nucitec, Mex.*
Amino acids.
Protein supplement in renal failure.

Somergan *Elmor, Venez.*
Lindane (p. 2157·1).
Pediculosis; scabies.

Somerol *Soho, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Somese *Pfizer, Chile; Pfizer, Malaysia; Pfizer, Venez.*
Triazolam (p. 1112·3).
Insomnia.

Somidal *Alter, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Somidem *Alphapharm, Austral.; CCM, Malaysia.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somin *YSP, Malaysia; Yung Shin, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Sominar *Charoen, Thai.*
Doxylamine succinate (p. 627·3).
Cold symptoms; nasal congestion.

Deltapharm, Hong Kong.†
Doxylamine (p. 627·3).

Sominex
Note: this name may be used for preparations of different composition.
Actavis, UK.
Promethazine hydrochloride (p. 638·2).
Insomnia.

EMS, Braz.
Passion flower (p. 2584·1); crataegus (p. 2488·1); valerian (p. 2640·2).
Sedative.

Prater, Chile.
Valerian (p. 2640·2).
Sleep disorders.

GSK Consumer, Canad.†; SmithKline Beecham Consumer, USA.
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sominex Herbal *Actavis, UK.*
Lupulus (p. 2546·1); valerian (p. 2640·2); passion flower (p. 2584·1).
Insomnia.

Sominex Pain Relief *SmithKline Beecham Consumer, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Insomnia.

Somit *Gador, Arg.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnal *Stada, Austria.*
Zopiclone (p. 1118·1).
Insomnia.

Somnidoron *Weleda, Fr.*
Coffea tosta (p. 2648·2); stramonium (p. 2622·3); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Somnil *Aspen, S.Afr.*
Doxylamine succinate (p. 627·3).
Insomnia.

Tecnofarma, Chile.
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnipax
Note: this name may be used for preparations of different composition.
Ivax, Arg.
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnipron *Sanitas, Chile.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnite *Norgine, UK.†*
Nitrazepam (p. 1089·1).
Insomnia.

Somnium
Note: this name may be used for preparations of different composition.
Vifor, Switz.
Lorazepam (p. 1080·3); diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Somno *Saval, Chile.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnogen *Generics, Hung.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnol
Note: this name may be used for preparations of different composition.
Grindeks, Hung.; Grindex, Rus.
Zopiclone (p. 1118·1).
Insomnia.

Axxess, Canad.†
Flurazepam monohydrochloride (p. 1076·1).
Insomnia.

Somnor *Orion, Fin.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Somnosan *Hormosan, Ger.*
Zopiclone (p. 1118·1).
Sleep disorders.

Somnote *Breckenridge, USA.†*
Cloral hydrate (p. 1055·2).
Sedative; insomnia; alcohol withdrawal syndrome.

Somnoten *Herbapol Lublin, Pol.†*
Lupulus (p. 2546·1); melissa (p. 2552·3); valerian (p. 2640·2).
Anxiety; insomnia.

Somnovit *Teofarma, Spain.*
Loprazolam (p. 1080·2).
Insomnia.

Somnubene *Ratiopharm, Austria.*
Flunitrazepam (p. 1073·3).
Sleep disorders.

Somnwell *Huntley, UK.†*
Cloral betaine (p. 1055·2).
Insomnia.

Somol *Maver, Chile.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Somon *Berko, Turk.*
Omega-3 fatty acids (p. 1460·1).
Hyperlipidaemias; dietary supplement.

Somonal *Juste, Spain.†*
Somatostatin acetate (p. 1930·3).
Variceal haemorrhage; pancreatic fistulae.

Sompraz *Sun, India.*
Esomeprazole (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Somsanit *Kohler, Ger.*
Sodium oxybate (p. 1914·1).
General anaesthesia.

Sonadryl *Allergan, Arg.*
Pilocarpine nitrate (p. 2010·3).
Glaucoma; ocular hypertension.

Sonafine *Stratus, USA.*
Avocado oil (p. 2451·2); paraffins; propylene glycol (p. 2205·2); trolamine (p. 2634·3).

Sonaflam *Multichem, NZ.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; pain; gout.

Sonafrine *Target, Gr.*
Somatostatin (p. 1930·3).
Upper gastrointestinal bleeding.

Sonahist *Rivers Edge, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Sonahist DM *Kylemore, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Sonalent *Aledicine, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Sonap *Sriprasit, Thai.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sonapax *Jelfa, Rus.*
Thioridazine (p. 1110·2).

Jelfa, Ukr.
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia; bipolar disorder; behaviour disorders; abstinence syndromes; agitation; depression; Huntington's disease; tics; severe pruritus.

Sonarin (AD) *Geolab, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Sonarin (INF) *Geolab, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Sonata *Meda, Belg.; Wyeth, Braz.; Meda, Cz.; Meda, Denm.; Meda, Fin.†; Meda, Ger.; Meda, Gr.; Meda, Hung.; Meda, Irl.; Meda, Ital.; Meda, Neth.; Meda, Pol.; Meda, Port.; Meda, Spain†; Meda, Swed.; Meda, Switz.; Meda, UK; King, USA.*
Zaleplon (p. 1114·3).
Insomnia; sleep disorders.

Sonazoid *Daiichi Sankyo, Jpn.*
⊗Perflubutane (p. 1595·1).
Ultrasound contrast medium for detection of liver and breast lesions.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sondalis *Nestle, Fr.; Nestle Clinical, Irl.†*
A range of preparations for enteral nutrition.

Sondate *Teva, UK.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; depression.

Sondex-Of *Sons, Mex.*
⊗Neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Sone *Valeant, Austral.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Sonebon *Sigma, Braz.*
Nitrazepam (p. 1089·1).
Epilepsy; insomnia.

Soneriper *Pharmasant, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm; parkinsonism; obliterative vascular disorders.

Soneryl *Flynn, UK.*
Butobarbital (p. 1044·1).
Insomnia.

Soneto *Rafarm, Gr.*
Simvastatin (p. 1489·2).

Sonexa-C *Aristopharma, Hong Kong.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections with inflammation.

Song Tai Si *Jida, China.*
Reduced glutathione sodium (p. 1555·2).

Songar *Valeas, Ital.*
Triazolam (p. 1112·3).
Insomnia.

Songha *Boehringer Ingelheim, Belg.†*
Valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders; insomnia.

Songha Natt *Boehringer Ingelheim, Norw.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Insomnia.

Songha Night *Pharmaton, Israel; Ginsana, Switz.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sleep disorders; insomnia; nervous disorders.

Sonhare *Boehringer Ingelheim, Braz.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Sedative.

Sonia *Winsunny, China.*
Telmisartan (p. 1509·3).
Hypertension.

Sonias *Takeda, Jpn.*
Pioglitazone hydrochloride (p. 493·1); glimepiride (p. 473·2).
Diabetes mellitus.

Sonicor *GMP, Indon.*
⊗Methylprednisolone (p. 1642·2).
Oral corticosteroid.

Sonidal *Alet, Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Sonidar *Julphar, UAE.*
⊗Budesonide (p. 1625·1).
Asthma.

Sonide *Gufic, India.*
Sodium nitroprusside (p. 1497·1).
Hypertension; mitral regurgitation.

Sonifilan *Kaken, Jpn.*
Sizofiran (p. 857·2).
Radiotherapy enhancement for uterine cervical cancer.

Sonigen *GMP, Indon.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Sonirol *Medis, Neth.†*
Ropinirole hydrochloride (p. 913·2).
Restless legs syndrome.

Sonizin *Gedeon Richter, Rus.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Sonke Abaclamizid *Ranbaxy, S.Afr.*
Lamivudine (p. 1000·2); abacavir (p. 962·3); zidovudine (p. 1024·2).
HIV infection.

Sonke-LamiNevStav *Ranbaxy, S.Afr.*
Lamivudine (p. 1000·2); nevirapine (p. 1005·1); stavudine (p. 1015·3).
HIV infection.

Sonmil *KVZ, Ukr.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Sonnat *Arterium, Ukr.*
Zopiclone (p. 1118·1).
Sleep disorders.

Sonnenbrandspray *Jacoby, Austria.*
Calendula officinalis (p. 2465·2); cantharis; echinacea angustifolia (p. 2498·1); urtica urens (p. 2639·3).
Homoeopathic preparation.

Soñodor *Urgo, Spain.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Sonol *Elanda, Pol.*
Menthol (p. 2553·2); salicylic acid (p. 1719·1); thymol (p. 1772·2).
Herpes labialis.

Sonoprel *Makiz-Pharma, Rus.*
⊗Tablets, indapamide (p. 1409·2); tablets, cilazapril (p. 1336·2).
Hypertension.

Sonoripan *Marjan, Braz.*
Valerian (p. 2640·2).
Sedative.

SonoRx *Bracco, USA.†*
Simeticone coated cellulose (p. 1886·2).
Adjunct in ultrasound imaging.

Sonotabs
Note: this name may be used for preparations of different composition.
Hertz, Braz.†
Valerian (p. 2640·2).

SonoVue *Bracco, Austria; Bracco, Belg.; Bracco, China; Bracco, Cz.; Bracco, Denm.; Bracco, Fin.; Bracco, Fr.; Bracco, Gr.; Bracco, Hung.; Bracco, Irl.; Bracco, Ital.; Bracco, Neth.; Bracco, Norw.; Bracco, Pol.; Bracco, Port.; Bracco, Singapore; Bracco, Spain; Bracco, Swed.; Bracco, Switz.; Bracco, UK·*
Sulfur hexafluoride (p. 1595·3).
Ultrasound contrast medium.

Sonridor *GSK, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Sonridor Caf *GSK, Braz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Sonrisal *GSK, Braz.*
Aspirin (p. 22·2); sodium carbonate anhydrous (p. 2617·3); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Dyspepsia; pain.

Sons *Sons, Mex.*
Difenidol (p. 1835·1).
Nausea and vomiting.

Sons Piral *Sons, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Sons Vit *Sons, Mex.*
Vitamins.

Soolan *Julphar, UAE.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Soolda *Conba, China.*
Flavoxate hydrochloride (p. 2360·1).
Genito-urinary spasm.

Sootha *Nelson, UK·*
Bryonia dioica (p. 2461·3).
Homoeopathic preparation.

Soothaderm *Pharmakon, USA.*
Mepyramine maleate (p. 635·1); benzocaine (p. 1980·2); zinc oxide (p. 1729·1).
Pruritus.

Soothake Toothache Gel *Ransom, UK.*
Clove oil (p. 2481·3).
Toothache.

Soothake Toothache Tincture *Pickles, UK.*
Clove oil (p. 2481·3); lidocaine (p. 1988·1).

Ransom, Irl.
Clove oil (p. 2481·3); lidocaine hydrochloride (p. 1988·2).
Toothache.

Soothe
Note: this name may be used for preparations of different composition.
Alimera, USA.
Polysorbate 80 (p. 2203·3); Restoryl (Drakeol-15 and Drakeol-35).
Dry eyes.

Soothe Aid *Zee, Canad.*
Hexylresorcinol (p. 1755·1).

Soothe & Cool *Medline, USA.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Nappy rash.

Soothe & Cool Protect Moisture Barrier *Medline, USA.*
Barrier preparation.

Soothe Hydration *Bausch & Lomb, USA.*
Povidone (p. 2204·3).
Dry eyes.

Soothe Night Time *Bausch & Lomb, USA.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry eyes.

Soothe XP *Bausch & Lomb, USA.*
Liquid paraffin (p. 2191·2); light liquid paraffin (p. 2191·2); polysorbate 80 (p. 2203·3).
Dry eyes.

Soothelip *Bayer, Irl.; Bayer Consumer, UK.*
Aciclovir (p. 964·1).
Herpes labialis.

Soothe'n Heal *Mentholatum, Austral.†*
⊗Hydrous wool fat (p. 2219·3); glycerol (p. 2517·2); benzyl alcohol (p. 1739·3).
Dry skin.

Soothers Triple Action *Ernest Jackson, UK.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Soothing Cream *Vivier, Canad.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Soothing Eye Wash *Bausch & Lomb, Philipp.*
Boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irritation; eye wash.

Soothing Foot Spray *Kinesys, Canad.*
Chloroxylenol (p. 1748·2); triclosan (p. 1773·2).

Soothing Gel *Energizer, Canad.*
Lidocaine hydrochloride (p. 1988·2).

Soothing Ice Rub *Scott, Canad.†*
Menthol (p. 2553·2).

Soothol *Ayrton, UK.*
Cajuput oil (p. 2464·1); rosemary oil (p. 2607·3); arachis oil (p. 2446·1).
Ear wax removal.

Soov Bite *Ego, Austral.; Ego, NZ.*
Lidocaine hydrochloride (p. 1988·2); cetrimide (p. 1742·1).
Insect bites; stings.

Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.
Lidocaine hydrochloride (p. 1988·2); cetrimide (p. 1742·1); menthol (p. 2553·2).
Insect bites; stings; pruritus.

Soov Burn *Ego, Austral.; Ego, NZ.*
Lidocaine hydrochloride (p. 1988·2); cetrimide (p. 1742·1).
Sunburn; minor burns; minor cuts.

Soov Cream *Ego, Austral.; Ego, Hong Kong; Ego, NZ; Ego, Singapore.*
Lidocaine hydrochloride (p. 1988·2); cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Sunburn; haemorrhoids; minor cuts; abrasions; burns.

Soov Gel *Ego, NZ·*
Lidocaine hydrochloride (p. 1988·2); cetrimide (p. 1742·1).
Insect bites; stings.

Soov It *Ego, Austral.*
⊗Hydrocortisone (p. 1640·1); lidocaine (p. 1988·1).
Anorectal disorders.

Soov Prickly Heat *Ego, Austral.*
Salicylic acid (p. 1719·1); zinc oxide (p. 1729·1); light liquid paraffin (p. 2191·2).
Heat rash.

Ego, Hong Kong.
Salicylic acid (p. 1719·1); zinc oxide (p. 1729·1); liquid paraffin (p. 2191·2).
Heat rash.

Sopain-Plus *Medichrom, Gr.*
⊗Muramidase (p. 2565·1); papain (p. 2582·3); bacitracin (p. 225·3).

Sopa-K *Iasis, Gr.*
Potassium gluconate (p. 1793·2).
Hypokalaemia; potassium depletion.

Sopalamin 3B *Farmanic, Gr.; Iasis, Gr.*
Vitamin B substances (p. 2102·3).

Sopavi *Medis, Ital.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Sopental *Continental Ethicals, S.Afr.†*
Pentobarbital sodium (p. 1095·1).
Insomnia; sedative.

Soperam *Soho, Indon.*
Sulbactam (p. 360·1); cefoperazone (p. 243·1).
Bacterial infections.

Soperil *Diba, Mex.*
Neomycin (p. 329·3); polymyxin B (p. 342·3); gramicidin (p. 308·3).
Bacterial eye infections.

Sophidone *Mundipharma, Fr.*
⊗Hydromorphone hydrochloride (p. 67·3).
Pain.

Sophipren *Volta, Chile; Sophia, Mex.; Elmor, Venez.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Sophivir *Sophia, Mex.*
Aciclovir (p. 964·1).
Herpes simplex keratitis.

Sophixin *Volta, Chile; Sophia, Mex.; Elmor, Venez.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Sophixin DX *Sophia, Mex.*
⊗Ciprofloxacin hydrochloride (p. 261·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Sophtal *Alcon, Fr.*
Eye lotion: Salicylic acid (p. 1719·1); borax (p. 2459·2); rose water.
Eye irritation.

Alcon, Fr.
Eye drops: Salicylic acid (p. 1719·1).
Eye irritation.

Sophtal-POS N *Ursapharm, Cz.; Ursapharm, Ger.*
Salicylic acid (p. 1719·1).
Inflammatory eye disorders; eye irritation.

Sopime *Soho, Indon.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Sopira Citocartin *Heraeus, Austria; Molteni, Denm.; Heraeus, Ger.*
Articaine hydrochloride (p. 1980·1). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Sopirom *Soho, Indon.*
Cefpirome (p. 247·2).
Bacterial infections.

Sopmil *TO-Chemicals, Thai.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Sopodorm *ICN, Pol.*
Midazolam (p. 1085·1).
Premedication; general anaesthesia; sedation in artificially ventilated patients.

Sopolcort N *Jelfa, Rus.†*
⊗Hydrocortisone hydrogen succinate (p. 1640·2).
Corticosteroid.

Sopral *Sopharma, Rus.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Sopralan *Mersifarma, Indon.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Soprano *Sandoz, Turk.*
⊗Bisoprolol fumarate (p. 1325·3).

Soprazon *Kleva, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Soprol *Helsinn Birex, Irl.*
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Soprost *Soho, Indon.†*
Saw palmetto (p. 2363·3); cucurbita (p. 2489·2); zinc picolinate (p. 2126·1).
Benign prostatic hyperplasia.

Soproxen *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, and soft-tissue inflammation; gout; pain; musculoskeletal and joint disorders.

Sopulmin *Scharper, Ital.*
Sobrerol (p. 1677·2).
Respiratory-tract disorders.

Soquette *Barnes Hind, Arg.†*
Polyvinyl alcohol (p. 2204·2); benzalkonium chloride (p. 1737·1).
Wetting and storage solution for contact lenses.

Sor Virginia *Hartmann, Spain.*
Capsicum (p. 2469·3).
Muscle pain.

Soragel *ICM, Singapore.*
Choline salicylate (p. 39·2); cetylpyridinium chloride (p. 1743·1).
Teething; denture irritation; mouth disorders.

Soral *Help, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Soramin *Darrow, Braz.†*
Amino acids.
Parenteral nutrition.

Sorbalgon *Hartmann, Belg.*
Calcium alginate (p. 1136·3).
Wounds.

Sorbalgon Plus *Hartmann, Fr.*
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Ulcers; wounds.

Sorbangil *Recip, Norw.; Recip, Swed.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Sorbeks *Kurtsan, Turk.*
Cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2).
Respiratory-tract disorders.

Sorbenor *Casen Fleet, Spain.*
Arginine aspartate (p. 2049·1).
Tonic.

Sorbex *Pro-Pharma, Ukr.*
Activated charcoal (p. 1537·3).
Poisoning; gastrointestinal disorders; liver disease; hypercholesterolaemia.

Sorbex Baby *Pro-Pharma, Ukr.*
Dioctahedral smectite (p. 1887·1); *Bifobacterium longum infantis* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Diarrhoea; flatulence; maintenance of normal gastrointestinal flora.

Sorbexyl *Aledicine, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

Sorbicet *Bouzen, Arg.*
Cetrimide (p. 1742·1).
Disinfection.

Sorbiclis *SIT, Ital.*
Sorbitol (p. 2092·1); docusate sodium (p. 1836·2).
Constipation.

Sorbidilat *Actavis, Switz.*
Isosorbide dinitrate (p. 1412·2).
Heart failure; angina pectoris; pulmonary oedema.

Sorbidin *Alphapharm, Austral.; ICH, Hong Kong†; Merck, Indon.†; Merck, Thai.†*
Isosorbide dinitrate (p. 1412·2).
Heart failure; ischaemic heart disease; angina pectoris.

Sorbifer *Egis, Cz.; Egis, Hung.; Multicare, Philipp.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron deficiency; iron supplement.

Sorbilact *Yuriya-Farm, Rus.; Yuriya-Farm, Ukr.*
Electrolytes (p. 1775·1); sorbitol (p. 2092·1).
Fluid and electrolyte disorders.

Sorbilax *Pfizer, Austral.*
Sorbitol (p. 2092·1).
Constipation.

Sorbiline *Franco-Indian, India.*
Tricholine citrate (p. 2055·2); sorbitol (p. 2092·1).
Biliary and liver disorders.

Sorbimon *Ratiopharm, Cz.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Sorbinate *Zydus Cadila, Thai.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Sorbisterit *Fresenius Medical, Austria; Fresenius Medical, Belg.; Pentafarma, Chile; Fresenius Medical, Denm.; Fresenius Medical, Fin.; Fresenius Medical, Ger.; Fresenius Medical, Irl.†; Fresenius Medical, Neth.; Fresenius Medical, Spain; Fresenius Medical, Swed.; Fresenius Medical, Switz.; Stanningley, UK.*
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Sorbit *Biochimic, Rus.*
Sorbitol (p. 2092·1).

Sorbitrate *Piramal, India.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Sorbon *Trima, Israel.*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders.

Sorbonit *1A, Pol.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Sorbsan *Unomedical, Austral.; Coffey, Irl.†; Aspen Medical, UK.*
Calcium alginate (p. 1136·3).
Wounds; skin ulcers.

Sorbutuss NR *Teral, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); potassium citrate (p. 1780·3).
Cough.

Sorcal
Note: this name may be used for preparations of different composition.
Wyeth, Braz.
Calcium polystyrene sulfonate (p. 1541·2).
Hyperkalaemia.

Sore Mouth Gel *Boots, Thai.†*
Lidocaine (p. 1988·1); cetylpyridinium chloride (p. 1743·1); menthol (p. 2553·2); cineole (p. 2479·1).
Oral pain.

Sore Throat *Hylands, Canad.*
Baryta carbonica (p. 2452·2); belladonna (p. 2453·3); mercurius iodatus ruber (p. 2555·3); phytolacca (p. 2593·2).
Homoeopathic preparation.

Sore Throat L39 *Homeocan, Canad.†*
Ammonium nitr; dinatrii sulfas (p. 1888·1); kali iodatum (p. 2336·3); kali phosphoricum (p. 1790·3); natrii chloras (p. 1795·1); natrii sulfas (p. 1888·1).
Homoeopathic preparation.

Sore Throat Lozenges *Sutton, Canad.*
Benzocaine (p. 1980·2); menthol (p. 2553·2).
Sore throat.

Soreal *Delpech, Fr.*
Alfalfa (p. 2433·1); solanum dulcamara (p. 2497·3); nux vomica (p. 2573·3); antimonium crudum (p. 2445·1).
Homoeopathic preparation.

Sorebral *Condrugs, Thai.*
Cinnarizine (p. 622·1).
Cerebrovascular disorders; peripheral vascular disorders; vestibular disorders; migraine.

Soredine *Remek, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Sorel Plus *Sandoz, Pol.*
Calcipotriol (p. 1697·2).
Psoriasis.

Sorest *Ranbaxy, India.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Sorestin *Pasteur, Philipp.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Soriacur
Note: this name may be used for preparations of different composition.
Frasca, Arg.
Cade oil (p. 1723·2).
Psoriasis.

Sorial *Fortbenton, Arg.*
Coal tar (p. 1723·2).
Psoriasis.

Soriatane *Actavis, Canad.; Actavis, Fr.; GSK, USA.*
Acitretin (p. 1690·3).
Psoriasis; keratinisation disorders; lichen planus.

Soriclar *Abiogen, Ital.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori *eradication.*

Soridermal *Mintlab, Chile.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Sorilux *Stiefel, USA.*
Calcipotriol (p. 1697·2).
Psoriasis.

Sorine *Ache, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Sorine Adulto *Ache, Braz.*
⊗Sodium chloride (p. 1795·1); naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Sorine Pediatrico *Ache, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Sorini *Asia Pharma, Philipp.†*
Nimesulide (p. 101·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Sorinoheel *Heel, Canad.*
Asclepias vincetoxicum folia; calcarea carbonica (p. 1824·3); calcarea flurica (p. 2053·1); calcarea phosphorica (p. 1784·2); cicuta virosa; natrium muriaticum (p. 1795·1); sulfur (p. 1721·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Soritmik *KVZ, Ukr.*
⊗Sotalol (p. 1498·2).
Arrhythmias.

Sorlex *Genesis, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Sorliv *Ipca, India.*
Sorbitol (p. 2092·1); tricholine citrate (p. 2055·2).
Liver disorders.

Sormodren *Abbott, Austria; Abbott, Ger.; Pharmalex (Φαρμαλεξ), Gr.; Teofarma, Ital.; Abbott, Turk.*
Bornaprine hydrochloride (p. 895·2).
Parkinsonism; hyperhidrosis; drug-induced extrapyramidal disorders.

Sormon *Gerard, Irl.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Sornil *Utopian, Thai.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.

Soroclim *Elofar, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Sorofar *Elofar, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Sorol Citrate *Dismed, S.Afr.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Soroliv *Teuto, Braz.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Soronal *Cimed, Braz.*
Sodium chloride (p. 1795·1); benzalkonium chloride (p. 1737·1).
Nasal congestion.

Soroneo *Neo Quimica, Braz.*
Sodium chloride (p. 1795·1).
Nasal hygiene; nasal congestion.

Soropon *Axxess, Canad.†*
Tyrothricin (p. 384·1); trolamine polypeptide cocoate condensate (p. 2634·3).
Scalp disorders.

Sorot *Ravensberg, Ger.†*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Sorov *Soho, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Sorsis *Fortbenton, Arg.*
Cream: ⊗Coal tar (p. 1723·2); triamcinolone (p. 1648·3).
Seborrhoea; psoriasis.
Fortbenton, Arg.
Shampoo: Salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Dandruff; seborrhoea.

Sorsis Beta *Fortbenton, Arg.*
⊗Salicylic acid (p. 1719·1); betamethasone (p. 1623·2); coal tar (p. 1723·2).
Skin disorders.

Sortal *Biotech, Venez.*
Losartan potassium (p. 1422·2).
Hypertension.

Sortis *Pfizer, Austria; Pfizer, Cz.; Orifarm, Denm.; Pfizer, Ger.; Pfizer, Hung.; Medcor, Neth.†; Pfizer, Pol.; Pfizer, Port.†; Pfizer, Switz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias.

Sorvasta *KRKA, Cz.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia; atherosclerosis.

Sorvilor *Deutsche, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Sosefen *SoSe, Ital.*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis.

Sosefluss *SoSe, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Sosegon *Astellas, Jpn.*
⊗Pentazocine hydrochloride (p. 120·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Sanofi-Aventis, Spain; Sanofi Synthelabo, Thai.
⊗Pentazocine lactate (p. 120·3).
Pain.

Sosenol *Adcock Ingram, S.Afr.*
⊗Pentazocine (p. 120·3).
Pain.

Sosialon *Medicus, Gr.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Sosmin *Santa, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Sostac *Laboratorios Chile, Chile.*
Fluoxetine (p. 417·1).
Depression.

Sostatin *Angelini, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Sostel *Richmond, Arg.*
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; post-traumatic stress disorder; social phobia.

Sostenon *Organon, Mex.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Androgen deficiency; male hypogonadism; osteoporosis.

Sostilar *Pfizer, Belg.*
Cabergoline (p. 899·3).
Hyperprolactinaemia.

Sostril
Note: this name may be used for preparations of different composition.
Vargas, Venez.
Albendazole (p. 149·1).
Worm infections; giardiasis.

GSK, Ger.†
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastrointestinal hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sota *AbZ, Ger.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotabeta *Betapharm, Ger.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotacor *Investi, Arg.; Aspen, Austral.; BMS, Austria; BMS, Braz.; BMS, China; BMS, Fin.; BMS, Hong Kong†; BMS, Irl.; BMS, Jpn; BMS, Malaysia; BMS, Neth.†; BMS, Norw.†; Healthcare Logistics, NZ; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, UK.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias; angina pectoris; hypertension; myocardial infarction.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Volta, Chile.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction.

Sotagamma *Worwag, Ger.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

SotaHexal *Salutas, Singapore.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotahexal *Sandoz, Austral.†; Hexal, Austria; Hexal, Braz.; Hexal, Cz.; Hexal, Ger.†; Sandoz, Hung.; Hexal, NZ†; Sandoz, Pol.; Hexal, Rus.; Sandoz, S.Afr.; Sandoz, Ukr.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias; hypertension; angina pectoris; myocardial infarction; hyperthyroidism.

Sotalex *BMS, Belg.; BMS, Cz.†; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hung.; BMS, Ital.; BMS, Philipp.†; BMS, Rus.; BMS, Switz.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias; myocardial infarction; hypertension; angina pectoris; anxiety; hyperthyroidism; essential tremor.

Sotalin *Ratiopharm, Fin.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotalodoc *Docpharm, Ger.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotamed *S Med, Austria.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotaper *BMS, Mex.*
⊗Sotalol (p. 1498·2).
Arrhythmias; hypertension.

Sotapor *BMS, Spain.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sota-Puren *Actavis, Ger.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotarit *Sandoz, Turk.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sota-saar *MIP, Ger.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotastad *Stada, Austria; Stada, Ger.†*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotatic *Fahrenheit, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Sotazide *BMS, S.Afr.†*
⊗Sotalol hydrochloride (p. 1498·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sotens *Soho, Indon.†*
Noni; garlic (p. 2510·3); nicotinamide (p. 2083·1).
Tonic.

Sotilen *Medochemie, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Sotoger *Gerard, Irl.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Sotomycin *Bros, Gr.*
Clindamycin phosphate (p. 269·3).
Acne.

Sotovastin *Bros, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Sotovon *Bros, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Sotradecol *AngioDynamics, USA.*
Sodium tetradecyl sulfate (p. 2620·1).
Varicose veins.

Sotret *Ranbaxy, Hung.; Ranbaxy, Thai.; Ranbaxy, USA.*
Isotretinoin (p. 1706·2).
Acne.

Sotrexe *Ranbaxy, Mex.*
Isotretinoin (p. 1706·2).
Acne.

Sotrizol *Special Product's Line, Ital.†*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Sotropil *Soho, Indon.*
Piracetam (p. 393·3).
Mental function impairment; cerebral trauma.

Soufrol *Gebro, Switz.*
Mesulphen (p. 1711·3).
Bath additive; musculoskeletal and joint disorders; skin disorders.

Sousibim *Kleva, Gr.*
Zipeprol hydrochloride (p. 1680·3).

Souvenaid *Nutricia Clinical, UK.*
Food for special diets.
Alzheimer's disease.

Sovaldi *Gilead, USA.*
Sofosbuvir (p. 1015·2).
Chronic hepatitis C.

Sove *Ipca, India.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Sovelium *Medicine Products, Thai.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders.

Sovener *Tecnofarma, Mex.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Soventol *Abbott, Austria; Medice, Ger.; Vianex (Βιανεξ), Gr.; Oramon, Neth.; Oramon, Pol.*
Bamipine lactate (p. 617·2).
Allergic disorders; pruritus; insect stings; sunburn; burns; jellyfish stings; frostbite; urticaria; skin irritation.

Soventol HydroCort *Medice, Ger.*
⊗Hydrocortisone (p. 1640·1) or hydrocortisone acetate (p. 1640·1).
Skin disorders.

Soventol HydroSpray *Medice, Ger.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Soviclor *Collins, Mex.*
Aciclovir (p. 964·1).
Herpes simplex infections of the face and lips.

Sovipan *Novis, Gr.*
Aceclofenac (p. 16·2).
Pain; inflammation; rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Sovlan *Yung Shin, Philipp.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Sovriad *Janssen, Jpn.*
Simeprevir (p. 1015·2).
Chronic hepatitis C.

Soxaron *Kener, Mex.*
Neomycin (p. 329·3); polymyxin B (p. 342·3); bacitracin (p. 225·3).
Eye infections.

Soxietas *Soho, Indon.†*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Soxime *Soho, Indon.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Soxsup *Richmond, Arg.†*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Soy 50 *Gross, Braz.*
Soya isoflavones (p. 2620·3).

Soy Power Plus *Bioglan, Austral.†*
Red clover (p. 2482·1); soya bean (p. 2092·3); wild yam (p. 2648·1); calcium hydrogen phosphate (p. 1783·3).
Isoflavone and calcium supplement.

Soya Max *Usana, Hong Kong.†*
Preparation for enteral nutrition.

Soya Meno *Medana, Pol.†*
Soya (p. 2092·3).
Menopausal disorders.

Soyacal *Grifols, Arg.†; Grifols, Cz.†; Grifols, Ger.†; Mitsubishi, Philipp.; Labesfal, Port.; Grifols, Spain.*
Soya oil (p. 2092·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Soyal *FDC, India.*
Food for special diets.
Lactose intolerance; milk intolerance.

Soyalac *Nutricia-Loma Lindar, USA.*
Lactose-free soy protein infant feed.

Soyaloid *Advaita, Mex.*
Soya flour (p. 2092·3); povidone (p. 2204·3).
Bath additive; skin disorders.

Soyaloid Apruri *Advaita, Mex.*
Soya flour (p. 2092·3); pramocaine hydrochloride (p. 1993·3); zinc acetate (p. 2126·1).
Skin disorders.

Soyamil Unico *Milte, Ital.*
Soy-based infant feed.
Cows' milk protein intolerance.

Soyaven *Delicias, Mex.*
Food for special diets.
Lactose and cow's milk intolerance; food allergies.

Soydex *Darier, Mex.*
Soya flour (p. 2092·3); povidone (p. 2204·3).
Bath additive; skin disorders.

Soyfem *Biofarm, Pol.*
Soya (p. 2092·3).
Menopausal disorders.

Soyfemme *Ache, Braz.*
Soya isoflavones (p. 2620·3).
Menopausal disorders.

Soyfit *Janssen-Cilag, Braz.*
Soya (p. 2092·3).

Soymen *Irmed, Ital.*
Soya (p. 2092·3); vitamins.
Menopausal disorders.

Soymen Gel *Irmed, Ital.*
Soya isoflavones (p. 2620·3).
Vaginal dryness.

SoyPlus *Lifeplan, UK.*
Soya isoflavones (p. 2620·3); folic acid (p. 2063·1).
Dietary supplement.

Soyred *Andromaco, Spain.†*
Glycine max; red clover (p. 2482·1).
Menopausal disorders.

Sozinalin *Coup, Gr.*
Vincamine (p. 2645·2).

Sozol *Aspen, Austral.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

SP
Note: this name may be used for preparations of different composition.
SSP, Thai.
Tablets: Aspirin (p. 22·2).
Thrombosis prophylaxis; fever; pain; inflammation.
Suphong, Thai.
Syrup: Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1).
Cough; cold symptoms.

SP 54 *Bene, Hung.; Bene, Malaysia.*
Pentosan polysulfate sodium (p. 1465·1).
Soft-tissue disorders; thromboembolic disorders; thrombosis prophylaxis.

SP gel *Inpac, Thai.*
Methyl salicylate (p. 92·1); eugenol (p. 2501·2); menthol (p. 2553·2).

SP Troches *Meiji, Indon.; Meiji, Malaysia; Meiji, Singapore.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections; mouth and throat disorders.

Spa Complex *Thompsons, Canad.†*
Cicuta virosa; hyoscyamus niger (p. 2530·2); magnesium phosphate dibasic (p. 1786·3).
Homoeopathic preparation.

Spa Sun *Florian, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Spablock *Masa, Thai.†*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm; postoperative pain.

Spabucol
Note: this name may be used for preparations of different composition.
Phoinix Pharm (Φοινιξ Φαρμ), Gr.
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Spacovin *Biopharm, Rus.; MJ Biopharm, Thai.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Spacyl *Proel, Gr.*
Acetylcysteine (p. 1652·2).
Mucolytic.

Spagulax *Almirall, Belg.; Almirall, Fr.*
Ispaghula (p. 1849·1).
Constipation.

Spagulax au Citrate de Potassium *Almirall, Fr.†*
Ispaghula (p. 1849·1); potassium citrate (p. 1780·3).
Constipation.

Spagulax K *Biodiphar, Belg.†*
Ispaghula (p. 1849·1); potassium citrate (p. 1780·3); potassium bicarbonate (p. 1780·3).
Constipation.

Spagulax M *Almirall, Belg.*
Ispaghula (p. 1849·1).
Constipation.

Spagulax Mucilage *Almirall, Fr.*
Ispaghula (p. 1849·1).
Constipation.

Spagulax au Sorbitol *Almirall, Fr.†*
Ispaghula (p. 1849·1); sorbitol (p. 2092·1).
Constipation.

Spagulax Sorbitol *Biodiphar, Belg.†*
Ispaghula (p. 1849·1); sorbitol (p. 2092·1).
Constipation.

Spagymun *Spagyros, Switz.*
Echinacea angustifolia flowers and roots (p. 2498·1); echinacea purpura flowers and roots (p. 2498·1); eupatorium perfoliatum (p. 2459·1).
Immune stimulant.

Spagyrhin *Spagyros, Switz.*
Allium cepa (p. 2575·2); euphrasia officinalis (p. 2502·1); eupatorium cannabinum; sambucus nigra (p. 2609·3).
Homoeopathic preparation.

Spagyrom *Spagyros, Switz.*
Echinacea angustifolia flowers and roots (p. 2498·1); echinacea purpura flowers and roots (p. 2498·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3); juniper oil (p. 2537·2); lavender oil (p. 2541·1); chamomile oil (p. 2474·1); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); savory oil (p. 2625·1); thyme oil (p. 2630·3).
Common cold; mouth and throat disorders.

Spai *INTES, Ital.*
Electrolytes (p. 1775·1).
Ocular irrigation; cleaning solution for contact lens; adjunct in otorhinolaryngeal procedures.

Spalda Sabal *Leo, Cz.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Spalox *Umeda, Thai.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spalt
Note: this name may be used for preparations of different composition.
Santa, Turk.
Paracetamol (p. 115·1); benzyl mandelate (p. 2455·1); caffeine (p. 1203·3).
Fever; pain.

SP-Alusil *Sunward, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).

Spamic *Inpac, Thai.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders; pain.

Spamilan *Egis, Pol.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Spamus *T Man, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm; parkinsonism.

Span C *Freeda, USA.*
Citrus bioflavonoids complex (p. 2505·2); ascorbic acid (p. 2110·3).
Capillary bleeding.

Span Plex *Collins, Mex.†*
Calcium pantothenate (p. 2085·2).
Vitamin supplement.

Spancef *Medikon, Indon.†*
Cefixime (p. 240·3).
Bacterial infections.

SP-Anflam *Sunward, Singapore.*
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; pain; gout.

Spanidin *Kayaku, Cz.; Kayaku, Jpn.*
Gusperimus hydrochloride (p. 1959·3).
Renal transplant rejection.

Spanish Tummy Mixture *Potter's, UK.*
Blackberry root bark; catechu (p. 2472·3).
Diarrhoea.

Span-K *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ.*
Potassium chloride (p. 1793·2).
Potassium deficiency.

Spanomid *Yik Kwan, Hong Kong.†*
Sulpiride (p. 1107·3).

Spanor *Bailleul, Fr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

SP-Anspaz *Sunward, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spara *Sumitomo, China; Dainippon, Jpn.†*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sparax *Utopian, Thai.*
Drotaverine hydrochloride (p. 2497·3).
Postoperative pain; smooth muscle spasm.

Sparbact *Ipca, India; Ipca, Rus.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sparca *Hisun, China.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sparcip *Cipla, India.*
Sparfloxacin (p. 357·3).
Respiratory-tract infections.

Spardac *Zydus, India.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Spardrops *Cipla, India.*
Sparfloxacin (p. 357·3).
Bacterial eye infections.

Sparex *Kanonfarma, Rus.*
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal spasm.

Sparflo *Reddy, Rus.; Reddy, Ukr.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sparine *Wyeth, Gr.; Akromed, S.Afr.†*
Promazine hydrochloride (p. 1100·1).
Psychoses; agitation; anxiety; nausea; vomiting; sedative; premedication; hiccup.

Sparkal *Hexal, Denm.; Hexal, Fin.; Sandoz, Swed.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; liver cirrhosis with ascites.

Sparkles *Lafayette, USA.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); simeticone (p. 1886·2).
Adjunct in endoscopy; flatulence.

Sparkling White Eye Drops *Adcock Ingram, S.Afr.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Allergic eye inflammation.

SP-Arnamin *Sunward, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Allergic conditions.

SP-Arnox *Sunward, Singapore.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1845·3) is included in this preparation to discourage abuse.
Diarrhoea.

Sparos *Pharos, Indon.*
Sparfloxacin (p. 357·3).
Bacterial infections of the respiratory tract.

Sparquin *Aristo, India.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sparta *Pharmasant, Thai.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Spartiol *Klein, Ger.†*
Sarothamnus scoparius (p. 2611·3).
Arrhythmias.

Spartiol Cardio *Klein, Ger.*
Spartium scoparium (p. 2611·3).
Homoeopathic preparation.

Spartocine *UCB, Fin.†*
Ferrous aspartate (p. 2060·3).
Iron deficiency.

Spartofer *UCB, Fin.*
Ferrous glycine sulfate (p. 2061·3).
Iron deficiency; iron-deficiency anaemia.

Sparvista *Cadila, India.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Sparx *Wockhardt, India.*
Sparfloxacin (p. 357·3).
Bacterial infections.

Spascopan *Bangkok Lab & Cosmetic, Thai.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm; peptic ulcer.

Spascopan-510 *Bangkok Lab & Cosmetic, Thai.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).

Spascupreel *Heel, Canad.*
Aconitum napellus (p. 2428·3); agaricus muscarius; belladonna (p. 2453·3); colocynthis (p. 1833·3); cuprum sulphuricum (p. 2057·2); cuprum aceticum (p. 2486·2); gelsemium sempervirens (p. 2511·2); magnesia phosphorica (p. 1786·3); chamomilla (p. 2474·1); passion flower (p. 2584·1); phosphorus (p. 2589·2).
Homoeopathic preparation.

Heel, Ger.
Colocynthis (p. 1833·3); ammonium bromatum (p. 2461·1); atropinum sulfuricum (p. 1310·2); veratrum; magnesium phosphoricum (p. 1787·3); gelsemium (p. 2511·2); agaricus; cuprum sulfuricum (p. 2057·2); aconitum (p. 2428·3); passiflora incarnata (p. 2584·1) matricaria recutita (p. 2474·1).
Homoeopathic preparation.

Peithner, Hung.
Passiflora incarnata (p. 2584·1); amanita muscaria (p. 2565·1); chamomilla recutita (p. 2474·1); cuprum sulfuricum (p. 2057·2); citrullus colocynthis (p. 1833·3); ammonium bromatum (p. 2461·1); atropinum sulfuricum (p. 1310·2); veratrum album (p. 2644·3); magnesium phosphoricum (p. 1787·3); gelsemium sempervirens (p. 2511·2); aconitum napellus (p. 2428·3).
Homoeopathic preparation.

Spascupreel H *Heel, Neth.*
Chamomilla (p. 2474·1); colocynthis (p. 1833·3); cuprum sulphuricum (p. 2057·2); gelsemium sempervirens (p. 2511·2); magnesium phosphoricum (p. 1787·3).
Homoeopathic preparation.

Spascupreel S *Heel, Cz.†*
Citrullus colocynthis; ammonium bromatum (p. 2461·1); atropinum sulfuricum (p. 1310·2); veratrum album (p. 2644·3); magnesium phosphoricum (p. 1787·3); gelsemium sempervirens (p. 2511·2); passiflora incarnata (p. 2584·1); chamomilla recutita (p. 2474·1); cuprum sulfuricum (p. 2057·2); amanita muscaria; aconitum napellus (p. 2428·3).
Homoeopathic preparation.

Spasdic *Medicine Products, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Spasdon *Ad-Drugstel, Philipp.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Spasen *FIRMA, Ital.*
Tablets: Otilonium bromide (p. 2578·2).
Gastrointestinal pain and spasm.

Spasen Somatico *FIRMA, Ital.*
Otilonium bromide (p. 2578·2); diazepam (p. 1063·2).
Gastrointestinal pain and spasm.

Spasflex *Berksam, Turk.*
Mebeverine hydrochloride (p. 1858·3).

Spasfon *Therabel, Belg.; Cephalon, Fr.; Rafarm, Gr.*
Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).
Smooth muscle spasm.

Spasfon-Lyoc *Cephalon, Fr.*
Phloroglucinol (p. 2588·2).
Smooth muscle spasm.

Spasgan *Wockhardt, Rus.; Wockhardt, Ukr.*
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Pain; smooth muscle spasm; joint pain; neuralgia; sciatica; myalgia.

Spasgone *Chew, Thai.*
Paracetamol (p. 115·1); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm with pain.

Spasgone-H *Chew, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spashi *GMP, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spashi Plus *GMP, Indon.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Spasil *Sriprasit, Thai.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Spasium *Bangkok Lab & Cosmetic, Thai.*
Trospium chloride (p. 2371·1).
Bladder instability.

Spaslic *Berlico Mulia, Indon.*
Dipyrone (p. 53·3); papaverine hydrochloride (p. 2362·3); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spasmacine *Kalbe, Indon.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Spasmadol *Stirol, Ukr.†*
Pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3).
Painful smooth muscle spasm.

Spasmag *Grimberg, Canad.†; Grimberg, Fr.*
Magnesium sulfate (p. 1787·3).
Magnesium deficiency; eclampsia; torsades de pointes.

Grimberg, Fr.
Capsules; oral solution: Magnesium sulfate (p. 1787·3); dried yeast (p. 2125·2).
Magnesium deficiency.

Spasmal *Prafa, Indon.*
Dipyrone (p. 53·3); belladonna (p. 2453·3); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Spasmalgan *Apogepha, Ger.†*
Denaverine hydrochloride.
Smooth muscle spasm.

Spasmalgin *Sam-On, Israel.*
Atropine sulfate (p. 1310·2); papaverine hydrochloride (p. 2362·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Smooth muscle spasm.

Spasmalgon *Sopharma, Pol.; Balkanpharma, Rus.; Sopharma, Rus.; Sopharma, Ukr.*
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Pain; fever; musculoskeletal and joint pain; migraine; painful smooth muscle spasm.

Spasmalin *Torrent, Rus.*
Fenpiverinium bromide (p. 2504·1); dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2).
Pain; smooth muscle spasm.

Spasman scop *Recordati, Ger.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spasmed *ProMed, Cz.*
Trospium chloride (p. 2371·1).
Bladder hyperactivity.

Spasmend *Restan, S.Afr.*
Paracetamol (p. 115·1); mephenesin (p. 2025·2).
Skeletal muscle pain and spasm.

Spasmeridan *UCB, Ital.†*
Diazepam (p. 1063·2); hyoscine methobromide (p. 1846·1).
Gastrointestinal pain and spasm.

Spasmex
Note: this name may be used for preparations of different composition.
Biol, Arg.; Rider, Chile; ProMed, Cz.†; Pfleger, Ger.; Pfleger, Israel; Pfleger, Rus.; Pfleger, Thai.; Er-Kim, Turk.
Trospium chloride (p. 2371·1).
Bladder hyperactivity; urinary incontinence; smooth muscle spasms; bladder instability; nocturnal enuresis.

Scharper, Ital.
Injection: Phloroglucinol (p. 2588·2).
Painful spasm of the biliary and urinary tracts.

Scharper, Ital.
Suppositories; tablets: Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).
Painful spasm of the biliary and urinary tracts.

Spasmhalt *Pendopharm, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); methocarbamol (p. 2025·3).

Spasmhalt-ASA *Pendopharm, Canad.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2); methocarbamol (p. 2025·3).

Spasmil-M *Sopharma, Ukr.*
Dipyrone (p. 53·3); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Painful smooth muscle spasm.

Spasminal *Hexpharm, Indon.†*
Dipyrone (p. 53·3); belladonna (p. 2453·3); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Spasminar *Charoen, Thai.*
Dicycloverine hydrochloride (p. 1834·2).
Gastrointestinal spasm.

Spasmine
Note: this name may be used for preparations of different composition.
Jolly-Jatel, Fr.
Valerian (p. 2640·2); crataegus (p. 2488·1).
Nervous disorders; insomnia.

Meda, Belg.
Alverine citrate (p. 1819·1).
Irritable bowel syndrome.

Spasmium
Note: this name may be used for preparations of different composition.
Sanova, Austria.
Caroverine (p. 2471·2) or caroverine hydrochloride (p. 2471·2).
Smooth muscle spasm; tinnitus.

Soho, Indon.
Alverine citrate (p. 1819·1); chlordiazepoxide hydrochloride (p. 1044·2).
Smooth muscle pain and spasm; peptic ulcer.

Spasmo *Pharmahof, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spasmo Claim *Apomedica, Austria.†*
Turmeric (p. 2218·1); benzyl mandelate (p. 2455·1); *p,α*-dimethylbenzyl alcohol (p. 2493·3); peppermint oil (p. 1877·1); caraway oil (p. 2470·3); fennel oil (p. 2503·3); lemon oil (p. 2543·1); camphor (p. 2466·2); thymol (p. 1772·2); guaiazulene (p. 2523·1).
Gastrointestinal disorders.

spasmo gallo sanol N
Note: this name may be used for preparations of different composition.
Sanol, Ger.; UCB, Ger.
Peppermint oil (p. 1877·1).
Gastrointestinal and biliary-tract spasm.

Spasmo-Apotel *Unipharma, Gr.*
Paracetamol (p. 115·1); hyoscine butylbromide (p. 1845·3).
Pain; spasmolytic.

Spasmo-Bomaleb *Hevert, Ger.†*
Carduus marianus (p. 1561·1); chelidonium (p. 2522·2); chionanthus virg.; colocynthis (p. 1833·3); dolichos prur.; leptandra; nux vomica (p. 2573·3); quassia amara (p. 2601·1).
Homoeopathic preparation.

Spasmobru *Brupharmexport, Ukr.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; constipation; postoperative nausea and vomiting; cholecystitis; pancreatitis; peptic ulcer; premedication; organophosphorus poisoning.

Spasmocalm *Cooperation Pharmaceutique, Fr.*
Phloroglucinol (p. 2588·2).
Smooth-muscle spasm.

Spasmo-Canulase *Novartis, Philipp.; Novartis Consumer, S.Afr.†; Novartis Consumer, Switz.*
⊗Metixene hydrochloride (p. 909·2); dimeticone (p. 1886·2); pancreatin (p. 2579·3); cellulase (p. 2473·1); pepsin (p. 2586·1); glutamic acid hydrochloride (p. 2070·3); sodium dehydrocholate (p. 2492·1).
Irritable bowel syndrome; meteorism; dyspepsia; abdominal cramps associated with flatulence.

Spasmocip *Cipla, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Pain.

Spasmocip Plus *Cipla, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1); dicycloverine hydrochloride (p. 1834·2).
Pain; muscle spasm.

Spasmoctyl *Menarini, Arg.; Menarini, Spain.*
Otilonium bromide (p. 2578·2).
Gastrointestinal spasm; irritable bowel syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Spasmoctyl Somatico *Menarini, Arg.*
Otilonium bromide (p. 2578·2); diazepam (p. 1063·2).
Psychosomatic gastrointestinal disorders.

Spasmodex *Crinex, Fr.*
Dihexyverine hydrochloride (p. 1835·2).
Gastrointestinal disorders.

Spasmodil *ABC, Ital.*
Pipethanate ethobromide (p. 1878·2).
Smooth muscle spasm.

Spasmo-Entoxin *Meckel, Ger.*
Citrullis colocynthis; cephaelis ipecacuanha; cinchona pubescens (p. 2478·3).
Homoeopathic preparation.

Spasmofen *Meda, Swed.*
⊗Hyoscine methonitrate (p. 1846·1); papaverine hydrochloride (p. 2362·3); morphine hydrochloride (p. 92·3); noscapine hydrochloride (p. 1670·3); codeine hydrochloride (p. 40·2).
Pain; smooth muscle spasm.

Spasmo-Flexon *Aristo, India.*
Paracetamol (p. 115·1); dicycloverine hydrochloride (p. 1834·2).

Spasmogel *Alliance, S.Afr.*
Dicycloverine hydrochloride (p. 1834·2); light magnesium oxide (p. 1857·3); aluminium hydroxide (p. 1817·2).
Dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Spasmoject F *Syxyl, Ger.*
Colocynthis (p. 1833·3); magnesium phosphoricum (p. 1787·3); potentilla anserina.
Homoeopathic preparation.

Spasmol *Farmstandart, Rus.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Spasmolina *Synteza, Pol.*
Alverine citrate (p. 1819·1).
Smooth muscle spasm.

Spasmolit *Meprofarm, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spasmoliv *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spasmo-Lyt *Madaus, China; Madaus, Denm.; Madaus, Fin.; Megapharm, Israel; Madaus, Thai.; Madaus, Ukr.*
Trospium chloride (p. 2371·1).
Bladder function disorders; bladder instability.

Spasmolyt *Madaus, Austria; Madaus, Ger.; Rottapharm, Ger.; Madaus, Malaysia; Madaus, Singapore.*
Trospium chloride (p. 2371·1).
Smooth muscle spasm; bladder function disorders.

Spasmomen *Menarini, Belg.; Berlin-Chemie, China; Menarini, Cz.; Menarini, Hong Kong; Berlin-Chemie, Hung.; Menarini, Hung.; Dexa, Indon.; Menarini, Indon.; Genmedix, Israel; Menarini, Ital.; Menarini, Port.; Ulagay, Turk.; Berlin-Chemie, Ukr.*
Otilonium bromide (p. 2578·2).
Irritable bowel syndrome; premedication for gastrointestinal procedures; smooth muscle spasm.

Spasmomen Somatico *Menarini, Ital.*
Otilonium bromide (p. 2578·2); diazepam (p. 1063·2).
Gastrointestinal spasm and pain.

Spasmo-Mucosolvan *Boehringer Ingelheim, Ger.*
⊗Clenbuterol hydrochloride (p. 1207·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Spasmonal
Note: this name may be used for preparations of different composition.
Norgine, China; Norgine, Hong Kong†; Norgine, Irl.; Norgine, Singapore; Norgine, Thai.†; Norgine, UK.
Alverine citrate (p. 1819·1).
Smooth muscle spasm; diverticular disease; irritable bowel syndrome; dysmenorrhoea.

Spasmonet *KRKA, Rus.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Spasmonil *Cipla, India.*
Injection: Dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Cipla, India.
Oral drops: Dicycloverine hydrochloride (p. 1834·2); dimeticone (p. 1886·2).
Smooth muscle spasm.

Cipla, India.
Tablets: Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Spasmonil Forte *Cipla, India.*
Mefenamic acid (p. 85·3); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Spasmonil Plus *Cipla, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).
Smooth muscle pain and spasm.

Spasmopan *Zentiva, Cz.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); pitofenone hydrochloride (p. 2592·2); fenpiverinium bromide (p. 2504·1).
Painful smooth muscle spasm.

Spasmo-Panalgine *Atabay, Turk.*
Paracetamol (p. 115·1); allobarbital (p. 1035·2); adiphenine hydrochloride (p. 2431·1).
Fever; pain.

Spasmophen
Note: this name may be used for preparations of different composition.
Polfa Pabianice, Pol.†
Oxyphenonium bromide (p. 1875·1).
Gastrointestinal spasm; peptic ulcer.

Spasmoplex *Orifarm, Denm.†; Madaus, Port.*
Trospium chloride (p. 2371·1).
Urinary incontinence; bladder instability.

Spasmoplus
Note: this name may be used for preparations of different composition.
Novartis, Austria.
Propyphenazone (p. 127·3); drofenine hydrochloride (p. 1839·3); codeine phosphate (p. 40·2).
Painful smooth muscle spasm.

Novartis, Ital.
Propyphenazone (p. 127·3); codeine phosphate (p. 40·2).
Pain.

Spasmopriv
Note: this name may be used for preparations of different composition.
Senosiain, Mex.; Eurodrug, Philipp.; Eurodrug, Singapore; Eurodrug, Thai.†
Fenoverine (p. 2503·3).
Smooth muscle spasm; irritable bowel syndrome.

Sanofi-Aventis, Fr.†
Mebeverine hydrochloride (p. 1858·3).
Gastrointestinal and biliary-tract spasm.

Spasmo-Proxyvon *Wockhardt, India.*
Capsules: Dicycloverine hydrochloride (p. 1834·2); dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Wockhardt, India.
Injection: Dicycloverine (p. 1834·2).
Smooth muscle spasm.

Spasmo-Proxyvon Forte *Wockhardt, India.*
Dicycloverine hydrochloride (p. 1834·2); diclofenac sodium (p. 48·3).
Smooth muscle spasm.

Spasmo-Rhoival TC *Madaus, Ger.†*
Trospium chloride (p. 2371·1).
Bladder function disorders.

Spasmosan
Note: this name may be used for preparations of different composition.
Oriental, Philipp.
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spasmosol *Streuli, Switz.†*
Injection: ⊗Morphine hydrochloride (p. 92·3); codeine hydrochloride (p. 40·2); noscapine hydrochloride (p. 1670·3); atropine sulfate (p. 1310·2); papaverine hydrochloride (p. 2362·3).
Pain.

Spasmosyx F *Syxyl, Ger.*
Chamomilla recutita (p. 2474·1); magnesium phosph. (p. 1787·3).
Homoeopathic preparation.

Spasmotropin *Legrand, Braz.*
Dipyrone (p. 53·3); papaverine hydrochloride (p. 2362·3); homatropine methylbromide (p. 2007·3).
Smooth muscle spasm.

Spasmo-Urgenin *Madaus, Austria; Rottapharm, Spain; Madaus, Thai.*
Trospium chloride (p. 2371·1); echinacea (p. 2498·1); saw palmetto (p. 2363·3).
Prostatic and urinary-tract spasm and pain; prostatic hyperplasia; prostatitis.

Spasmo-Urgenin TC *Madaus, Ger.; Rottapharm, Ger.*
Trospium chloride (p. 2371·1).
Bladder function disorders.

Spasmo-Urgénine Néo *Zeller Madaus, Switz.*
Trospium chloride (p. 2371·1).
Urinary-tract disorders.

Spasrax *Overseas, India.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Peptic ulcer; dyspepsia; gastritis; irritable bowel disorder; colitis.

Spassirex *Sanofi-Aventis, Fr.†*
Phloroglucinol (p. 2588·2).
Smooth muscle pain and spasm.

Spasticol *Farmina, Pol.*
Belladonna (p. 2453·3); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Spasticone *Farmaline, Thai.†*
Dicycloverine hydrochloride (p. 1834·2); simeticone (p. 1886·2).
Gastrointestinal spasm; colic.

Spasuret *Recordati, Ger.†*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Spasuri *Pharmasant, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Spasyt *TAD, Ger.†*
Oxybutynin hydrochloride (p. 2361·2).
Urinary incontinence; bladder instability.

Spatam *Myung In, Singapore.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Spatanil *Farmanic, Gr.*
Cetirizine hydrochloride (p. 619·2).

Spatizalex *Ranbaxy, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Spaxim *Sandoz, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Spaziron *Farmamust, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Spazmol *Deva, Turk.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; premedication for endoscopy.

Spazmol Plus *Deva, Turk.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm and pain.

Spazmotek *Bilim, Turk.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Spazmotek Plus *Bilim, Turk.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle spasm.

Spazmo-Valibrin *Mulda, Turk.*
Diazepam (p. 1063·2); oxyphencyclimine hydrochloride (p. 1875·1).
Alcohol withdrawal syndrome; anxiety disorders; skeletal muscle spasm.

Spazol *Siam Bheasach, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Spazoverin *Shreya, Rus.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

SP-Betasone *Sunward, Singapore.*
⊗Betamethasone (p. 1623·2).
Skin disorders.

SP-Brom *Sunward, Singapore.*
⊗Bromhexine hydrochloride (p. 1656·3); ephedrine hydrochloride (p. 1663·2).
Cough.

SP-Clobesol *Sunward, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

SP-Codin *Sunward, Singapore.*
Codeine phosphate (p. 40·2).

SP-Codrine *Sunward, Singapore.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).

SP-Cordexa *Sunward, Singapore.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

SP-Cortil *Sunward, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

SP-Cosedyl *Sunward, Singapore.*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).

SP-Diafen *Sunward, Singapore.*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2).

SP-Diatab *Sunward, Singapore.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Spec-Ace *Pharmaspec, Philipp.*
Captopril (p. 1331·2).
Hypertension; heart failure following myocardial infarction; diabetic nephropathy.

Spéciafoldine *Sanofi-Aventis OTC, Fr.*
Folic acid (p. 2063·1).
Nutritional deficiency; prevention of neural tube disorders.

Special Formula Bulking Agent *Inno-Vite, Canad.†*
Clove (p. 2481·2); ispaghula (p. 1849·1); taraxacum (p. 2625·3).

Specialflex *Braun, Ital.*
Amino acids; electrolytes (p. 1775·1); glucose (p. 2068·3).
Parenteral nutrition.

Specicef-N *Specifar, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Speci-chol *Pekana, Neth.*
Chionanthus virginica; eichhornia crassipes; hedera helix (p. 2536·2); iberis amara; iris versicolor (p. 2534·3); nux moschata (p. 2573·1); phosphorus (p. 2589·2); glechoma hederacea (p. 2523·1).
Homoeopathic preparation.

Species Cholagogae Planta *Leros, Cz.†*
Elecampane (p. 1662·3); rhubarb (p. 1884·2); agrimony (p. 2432·3); marrubium (p. 1668·3); raspberry leaf (p. 2603·1).
Biliary-tract disorders.

Species Nervinae Planta *Leros, Cz.*
Chamomile (p. 2474·1); St John's wort (p. 449·1); melissa (p. 2552·3); peppermint leaf (p. 1877·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Anxiety; insomnia; neurasthenia.

Species Pectorales Planta *Leros, Cz.*
Verbascum (p. 2645·1); fennel (p. 2503·2); liquorice (p. 1853·2); peppermint leaf (p. 1877·1); plantain (p. 2604·2); althaea (p. 2438·3); coltsfoot leaf (p. 1659·2).
Respiratory-tract disorders.

Species Urologicae Planta *Leros, Cz.*
Birch leaf (p. 2457·3); bearberry (p. 2453·2); ononis (p. 2575·3); parsley root (p. 2583·3); knotgrass (p. 2538·2); sambucus (p. 2609·3); urtica (p. 2639·3); achillea (p. 2427·3).
Urinary-tract inflammation.

Specific Nerve Pain Remedy *Group, S.Afr.†*
⊗Oral liquid, salicylamide (p. 129·2); caffeine (p. 1203·3); alcohol (p. 1733·1); tablets, aspirin (p. 22·2).
Fever; pain.

Specifthir *Specifar, Gr.*
Malathion (p. 2157·2).
Head and crab lice; scabies.

Specilid *Alet, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Specinor *Specifar, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration; Zollinger-Ellison syndrome.

Specisun *Specifar (Σπεσιφαρ), Gr.*
Dimetindene maleate (p. 626·1).

Spec-Pen-V-K *Specpharm, S.Afr.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Spectazole *Ortho Dermatological, USA.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Spectin *Cipla, India.*
Spectinomycin hydrochloride (p. 358·1).
Bacterial infections.

Spectoflux *Globo, Braz.*
Ambroxol (p. 1654·3).

Spectolab *Multilab, Braz.*
Guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Spec-Topistin *Specpharm, S.Afr.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Spectra *Ranbaxy, India.*
Doxepin (p. 414·2).
Depression.

Spectraban *GSK, Arg.*
SPF 18: Dioxybenzone (p. 1700·2); octinoxate (p. 1715·1).
Sunscreen.

GSK, Arg.; Stiefel, Braz.; Stiefel, Mex.
SPF 20: SPF 18: Oxybenzone (p. 1715·3); homosalate (p. 1705·1); octinoxate (p. 1715·1).
Sunscreen.

Stiefel, Braz.
Lotion; stick: Padimate O (p. 1716·1); avobenzone (p. 1695·1).
Sunscreen.

Stiefel, Malaysia; Stiefel, Thai.†
SPF 60: Zinc oxide (p. 1729·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Stiefel, Thai.†
SPF 19: Zinc oxide (p. 1729·1).
Sunscreen.

Spectraban 19 *Stiefel, Philipp.*
Zinc oxide (p. 1729·1).
Sunscreen.

Spectraban 55 *Stiefel, Chile; Stiefel, Mex.*
SPF 55: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); sulisobenzone (p. 1722·1); titanium dioxide (p. 1725·1).
Sunscreen.

Spectraban 60 *Stiefel, Hong Kong; Stiefel, Singapore.*
SPF 60: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Stiefel, Philipp.
Zinc oxide (p. 1729·1); avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Spectraban Sensitive 30 *Stiefel, Hong Kong.*
Bisoctrizole (p. 1697·1); octinoxate (p. 1715·1).
Sunscreen.

Spectraban T *Stiefel, Braz.*
Padimate O (p. 1716·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Spectraban Ultra *Stiefel, Braz.; Stiefel, Chile; Stiefel, Mex.; Stiefel, S.Afr.†; Stiefel, Thai.†; Stiefel, UK.†*
SPF 30: SPF 28+: Avobenzone (p. 1695·1); Padimate O (p. 1716·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Spectraban Ultra 28 *Stiefel, Philipp.†*
Padimate O (p. 1716·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Spectracef *GSK, Gr.; Bayer, Mex.; GSK, Port.; GSK, Spain; Cornerstone, USA.*
Cefditoren pivoxil (p. 239·1).
Bacterial infections.

Spectracil *Alliance, S.Afr.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Spectramox *Thebe, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Spectrapain *Alliance, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Spectrapain Forte *Alliance, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Spectrasone *Thebe, S.Afr.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Spectratet *Schwulst, S.Afr.†*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Spectrem *Armoxindo, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Spectrim *Thebe, S.Afr.; TO-Chemicals, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Spectro Acnecare *GSK Consumer, Canad.*
Benzoyl peroxide (p. 1696·1).
Acne.

Spectro Derm *GSK Consumer, Canad.†*
Skin cleanser and emollient.
Cleansing of abraded and irritated skin.

Spectro Eczemacare *GSK Consumer, Canad.*
⊗Clobetasone butyrate (p. 1627·3).
Eczema.

Spectro Gram *GSK Consumer, Canad.†*
Chlorhexidine gluconate (p. 1743·3).
Disinfection of skin and hands.

Spectro Jel *GSK Consumer, Canad.*
Skin cleanser.

Recsei, USA.
Soap-free skin cleanser.

Spectrocef *Epifarma, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Spectrocycline *Westmont, Indon.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Spectroderm *Meiji, Thai.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Spectroxyl *Sandoz, Switz.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Spectrum
Note: this name may be used for preparations of different composition.
Johnson & Johnson Medical, UK.
⊗Alcohol (p. 1733·1); quaternary ammonium compounds.
Formerly contained alcohol, chlorhexidine gluconate, and quaternary ammonium compounds.
Surface disinfection.

Sigma-Tau, Ital.
Ceftazidime (p. 250·2).
Bacterial infections.

Pharmetics, Canad.†
Vitamins; minerals.

Spedamyl *Help, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Spedifen *Zambon, China; Zambon, Hong Kong; Zambon, Hung.; Zambon, Indon.; Zambon, Malaysia; Zambon, Switz.*
Ibuprofen arginine (p. 68·2).
Pain; fever; soft-tissue injury; musculoskeletal, joint, and peri-articular disorders; inflammation.

Zambon, Thai.
Ibuprofen (p. 68·2).
Pain; fever.

Spédifen *Zambon, Fr.*
Ibuprofen (p. 68·2).
Pain; fever.

Spediol *Med-One, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Speeda *Liaoning Chengda, Philipp.; CDBIO, Thai.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Spegic *Dynamic, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Spektracef *Abdi, Turk.*
Cefditoren pivoxil (p. 239·1).
Bacterial infections.

Spektraforte *Meda, Denm.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Spektramox *Meda, Denm.; Meda, Swed.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Spel *Silesia, Chile.†*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Spelear *Hisamitsu, Jpn.*
Fudosteine (p. 1666·1).
Respiratory-tract congestion.

Speman *Himalaya, Rus.*
⊗Orchis mascula (p. 2576·3); hygrophila auriculata; lactuca serriola; dolichos pruriens; suvarnavang; argyreia speciosa; tribulus terrestris (p. 2633·3); leptadenia reticulata; parmelia perlata.
Benign prostatic hyperplasia; male infertility.

Himalaya, Ukr.
⊗Orchis mascula (p. 2576·3); asteracantha longifolia; lactuca scariola; dolichos pruriens; suvarnavanga; argyreia speciosa; tribulus terrestris (p. 2633·3); leptadenia reticulata; parmelia perlata.
Prostatic hypertrophy; male infertility.

Speman Forte *Himalaya, Rus.*
⊗Orchis mascula (p. 2576·3); hygrophila auriculata; lactuca serriola; itchy velvet bean seed; suvarnavang; argyreia speciosa; tribulus terrestris (p. 2633·3); leptadenia reticulata stalk; parmelia perlata; rauwolfia serpentina (p. 1485·1).
Sexual function disorders in men.

SP-Emoloc *Sunward, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Spenglersan *Meckel, Austria.*
A range of homoeopathic bacterial antigens.
Homoeopathic preparation.

Spenglersan Kolloid *Meckel, Ger.*
A range of homoeopathic preparations containing bacterial antigens.
Homoeopathic preparation.

Sperelax *DAST, Gr.*
Risperidone (p. 1103·2).

Speridan *Actavis, Pol.; Actavis, Rus.*
Risperidone (p. 1103·2).
Schizophrenia and other psychoses.

Speridol *Sandoz, Gr.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Speridone *Tedec Meiji, Israel.*
Risperidone (p. 1103·2).
Schizophrenia; mania; behaviour disorders.

Spermatex *Shreya, Rus.*
Benzalkonium chloride (p. 1737·1).
Contraceptive.

Spersacarpin *OmniVision, Ger.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; reversal of mydriasis.

Spersacarpine *OmniVision, Switz.*
Pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

Spersadex *OmniVision, Ger.; OmniVision, Norw.; Adcock Ingram, S.Afr.; OmniVision, Switz.; Novartis, Turk.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Inflammatory eye and ear disorders.

Spersadex Comp *Thea, Denm.; Novartis, Hong Kong; Novartis, Indon.; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Infected eye disorders.

Spersadex Compositum *Novartis, Cz.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Inflammatory eye infections.

Spersadex Compound *Novartis, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Inflammatory eye disorders.

Spersadex med kloramfenikol *Thea, Norw.*
⊗Dexamethasone sodium phosphate (p. 1631·2); chloramphenicol (p. 257·1).
Inflammatory eye infections.

Spersadexoline *Novartis, Gr.; Novartis, Malaysia†; Adcock Ingram, S.Afr.†; Novartis Ophthalmics, Singapore.*
⊗Chloramphenicol (p. 257·1); dexamethasone sodium phosphate (p. 1631·2); tetryzoline hydrochloride (p. 1678·3).
Inflammatory eye infections.

Novartis, Thai.†
⊗Dexamethasone (p. 1630·3); chloramphenicol (p. 257·1); tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Spersallerg *Novartis, Chile; Novartis, Cz.; Novartis, Ger.†; Thea, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Malaysia; Thea, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Rus.; Restan, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Novartis, Thai.*
⊗Antazoline hydrochloride (p. 615·3); tetryzoline hydrochloride (p. 1678·3).
Allergic conjunctivitis; hay fever.

Spersamide *Adcock Ingram, S.Afr.†*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Spersanicol *Novartis, Indon.†; Adcock Ingram, S.Afr.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Spersapolymyxin *OmniVision, Switz.; Novartis, Thai.†*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Bacterial eye infections.

Spersatear *Adcock Ingram, S.Afr.*
Hypromellose (p. 2189·2).
Dry eyes.

Sperti PH *Wyeth Consumer, Arg.*
Shark-liver oil (p. 2614·2); phenylephrine hydrochloride (p. 1672·3).
Formerly known as Sperti Plus Preparacion H.
Haemorrhoids.

Sperti Praparation H *Pfizer, Austria.*
Rectal ointment; suppositories: Yeast (p. 2125·2); shark-liver oil (p. 2614·2).
Haemorrhoids.

Sperti Preparacao H *Pfizer, Port.*
Yeast (p. 2125·2); shark-liver oil (p. 2614·2).
Anorectal disorders.

Sperti Preparacion H *Wyeth Consumer, Arg.*
Shark-liver oil (p. 2614·2).
Haemorrhoids.

Sperti Preparation H *Pfizer Consumer, Chile; Wyeth, Hung.; Pfizer, Neth.; Whitehall-Robins, Switz.†*
Yeast (p. 2125·2); shark-liver oil (p. 2614·2).
Anorectal disorders; haemorrhoids.

Spesicor *AstraZeneca, Fin.*
⊗Metoprolol succinate (p. 1434·3).
Arrhythmias; myocardial infarction; hypertension; angina pectoris; migraine; heart failure.

Spesimax *Leiras, Fin.*
⊗Metoprolol succinate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; heart failure; migraine.

Spévin *Tradiphar, Fr.†*
Cascara sagrada (p. 1826·1); quassia amara (p. 2601·1).
Constipation.

Spex *Burapha, Thai.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Musculoskeletal and joint pain.

Spexil *Pfizer, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Spezato *Target, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

SPF 15 *Norwood, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

SPF 30 *Norwood, Canad.*
Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

SPF 45 *Norwood, Canad.†*
Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

SPF 50 *Norwood, Canad.*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

100 SPF Cream *Vital Science, Canad.*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

SPF 15 Lotion *L'Oreal, Canad.*
Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

SP-Famic *Sunward, Singapore.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

SP-Febrax *Sunward, Singapore.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).

SP-Fed *Inpac, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

SPF/FPS 30 *Energizer, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

SPF/FPS 50 *Energizer, Canad.*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

SP-Gastril *Sunward, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

SP-Glimed *Sunward, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

SP-Glucomet *Sunward, Singapore.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

SP-Grevin *Sunward, Singapore.*
Griseofulvin (p. 582·2).
Fungal infections of skin, hair, and nails.

Spherulin *ALK, USA.†*
Coccidioidin (p. 2483·1).
Skin test for coccidioidomycosis.

S.P.H.P. *Cantassium Co., UK.*
Prostate gland (p. 2444·1); spinal cord (p. 2444·1); calcium hypophosphite (p. 2530·3); nicotinamide (p. 2083·1); lecithin (p. 2542·2); wheat germ (p. 2647·1); kola (p. 2648·2); vitamin A (p. 2098·3); vitamin D (p. 2112·3).

S-Phylline *SSP, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Spidifen *Zambon, Belg.; Zambon, Ger.; Zambon, Ital.; Zambon, Neth.; Zambon, Port.*
Ibuprofen arginine (p. 68·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Spidox *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Spidufen *Zambon, Braz.*
Ibuprofen arginine (p. 68·2).
Inflammation; pain.

Spifen *Zambon, Fr.*
Ibuprofen (p. 68·2).
Fever; pain.

Spigelon *Heel, Austria; Ebi, Switz.*
Spigelia anthelmia (p. 2621·3); atropa belladonna (p. 2453·3); bryonia cretica; gelsemium sempervirens (p. 2511·2); melilotus officinalis (p. 2552·3); natrium carbonicum (p. 2617·3); acidum silicicum (p. 2208·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Peithner, Hung.
Acidum silicicum (p. 2208·3); atropa belladonna (p. 2453·3); bryonia cretica (p. 2461·3); gelsemium sempervirens (p. 2511·2); melilotus officinalis (p. 2552·3); natrium carbonicum (p. 2618·1); spigelia anthelmia (p. 2621·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Heel, Canad.†
Belladonna (p. 2453·3); bryonia (p. 2461·3); gelsemium sempervirens (p. 2511·2); melilot (p. 2552·3); silicon dioxide (p. 2208·3); sodium carbonate anhydrous (p. 2617·3); spigelia anthelmia (p. 2621·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Spigrow for Boys *Phoenix, Philipp.*
Notoginseng; spirulina (p. 2622·1); atractylodis macrocephalae; lycium; pseudostellariae; carthamus.
Nutritional supplement.

Spigrow for Girls *Phoenix, Philipp.*
Notoginseng; spirulina (p. 2622·1); dong quai (p. 2497·1); rehmannia; paeonia alba; chuanxiong.
Nutritional supplement.

Spilan *Sandoz, Ger.†*
St John's wort (p. 449·1).
Depression; anxiety disorders.

Spinax *Weida, China.*
Baclofen (p. 2014·3).
Skeletal muscle spasm.

Spin-Care *Spineda, Arg.*
Calendula (p. 2465·2).
Nipple care during breastfeeding.

Spinefe *FHC, Port.*
⊗Ephedrine hydrochloride (p. 1663·2).
Hypotension in anaesthesia.

Spinodin *Diba, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Spinoral *Coup, Gr.*
⊗Spironolactone (p. 1499·3).

Spirabiotic *Kimia, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Spiracillin *Help, Gr.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Spiracin *TO-Chemicals, Thai.†*
Spiramycin (p. 358·3).
Bacterial infections.

Spiractin *Alphapharm, Austral.; LCH, Hong Kong†; Aspen, S.Afr.*
⊗Spironolactone (p. 1499·3).
Hypertension; heart failure; oedema; hypokalaemia; hirsutism in women; hyperaldosteronism.

Spiradan *Kalbe, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Spiralgine *Spirig, Switz.*
Mefenamic acid (p. 85·3).
Fever; inflammation; pain.

Spiranter *Interbat, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Spirasin *Sanbe, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Spiraxin *Wassermann, Spain.*
Rifaximin (p. 355·2).
Gastrointestinal infections; hyperammonaemia.

Spirbon *Fresenius Kabi, Austria.†*
⊗Chlorphenoxamine hydrochloride (p. 622·1); ephedrine hydrochloride (p. 1663·2); emetine hydrochloride (p. 932·3).
Respiratory-tract disorders.

Spiresis *Orion, Fin.†*
⊗Spironolactone (p. 1499·3).
Oedema; liver cirrhosis with ascites; hypertension; hyperaldosteronism.

Spirial *SVR, Fr.; SVR, Ital.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

SVR, Fr.
Roll-on deodorant; topical spray: Aluminium chlorohydrate (p. 1694·1); triethyl citrate (p. 2218·1); allantoin (p. 1693·1).
Hyperhidrosis.

Spiricort *Spirig, Switz.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Spiridazide *SIT, Ital.*
⊗Spironolactone (p. 1499·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; renal calculi.

Spirit Salicyl *Floris, Israel; Vitamed, Israel.*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Acne; keratinisation disorders.

Spirit Whitfield *Floris, Israel.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Fungal skin infections.

Spiritus Contra Tussim Drops *Weleda, S.Afr.†*
Angelica (p. 2443·3); clove (p. 2481·2); cinnamon (p. 2479·2); coriander (p. 2486·3); melissa (p. 2552·3); nutmeg (p. 2573·1); lemon oil (p. 2543·1); cherry laurel (p. 2475·2).
Cough.

Spiriva *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Pfizer, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Pfizer, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, USA; Pfizer, USA; Boehringer Ingelheim, Venez.**
Tiotropium bromide (p. 1238·1).
Obstructive airways disease.

Spirix *Nycomed, Denm.; Leiras, Fin.; Nycomed, Norw.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; hyperaldosteronism; liver cirrhosis with ascites; heart failure.

Spiro *CT, Ger.*
⊗Spironolactone (p. 1499·3).
Ascites; hyperaldosteronism; oedema.

Spiro comp *Ratiopharm, Ger.*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Oedema; ascites; hyperaldosteronism; liver cirrhosis; nephrotic syndrome.

Spirobene *Ratiopharm, Austria.*
⊗Spironolactone (p. 1499·3).
Ascites; oedema; hyperaldosteronism; hypertension.

Spirobeta *Betapharm, Ger.*
⊗Spironolactone (p. 1499·3).
Ascites; hyperaldosteronism; oedema.

Spirocort *AstraZeneca, Arg.; AstraZeneca, Denm.; Simesa, Ital.*
⊗Budesonide (p. 1625·1).
Asthma; nasal polyps; rhinitis; bronchitis.

Spiroctan *Biolab Sanus, Braz.; Leurquin, Fr.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; adjuvant in myasthenia; hyperaldosteronism.

Spiroctazine *Leurquin, Fr.*
⊗Spironolactone (p. 1499·3); altizide (p. 1298·2).
Hypertension; oedema.

Spiro-D *Winthrop, Ger.†*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Hyperaldosteronism; oedema; ascites.

Spirodrine *Sevene, Fr.*
Anemone pulsatilla (p. 2600·2); sambucus nigra (p. 2609·3); rumex crispus (p. 2649·3).
Homoeopathic preparation.

Spiroflor *VSM, Neth.*
Cream; gel: Ledum palustre (p. 2550·1); rhus toxicodendron (p. 2603·3); symphytum officinale (p. 2484·2).
Homoeopathic preparation.

VSM, Neth.
Oral drops: Bryonia alba; colocynthis (p. 1833·3); dulcamara (p. 2497·3); gnaphalium polycephalum; phytolacca decandra (p. 2593·2); rhus toxicodendron (p. 2603·3).
Homoeopathic preparation.

Spirofur *Bruno, Ital.*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Oedema; hypertension.

Spirogamma *Worwag, Ger.*
⊗Spironolactone (p. 1499·3).
Ascites; hyperaldosteronism; oedema.

Spirohexal *Hexal, Austria.*
⊗Spironolactone (p. 1499·3).
Ascites; hyperaldosteronism; oedema; hypertension.

Spirokast *Zentiva, Neth.*
Montelukast sodium (p. 1214·3).
Asthma.

Spirol *Serum-Werk Bernburg, Ger.*
⊗Levomenthol (p. 2553·2); peppermint oil (p. 1877·1); alcohol (p. 1733·1).

Spirola *Kalbe, Indon.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; hypokalaemia; aldosteronism.

Spirolacton *Phapros, Indon.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; oedema; hypertension.

Spirolang *SIT, Ital.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; hypertension; cirrhosis with ascites; nephrotic syndrome.

Spirolept *Imaxio, Fr.*
An inactivated leptospirosis vaccine (p. 2397·3).
Active immunisation.

Spirolon *Remedica, Malaysia; Remedica, Singapore.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; heart failure; liver cirrhosis with ascites; hypertension; oedema; hypokalaemia; hirsutism.

Spiromide *RPG, India.*
⊗Furosemide (p. 1387·1); spironolactone (p. 1499·3).
Oedema; hypertension.

Spiromix *Sinclair, Ital.†*
Spiramycin (p. 358·3).
Bacterial infections.

Spiron *Andromaco, Chile.*
Risperidone (p. 1103·2).
Schizophrenia.

Orion, Denm.; Ratiopharm, Hung.
⊗Spironolactone (p. 1499·3).
Ascites; hyperaldosteronism; oedema; hepatic cirrhosis with ascites.

Spironex *PP Lab, Thai.*
⊗Spironolactone (p. 1499·3).
Hypertension; oedema; ascites; primary aldosteronism.

Spirono *Genericon, Austria; Actavis, Ger.†*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; liver cirrhosis with ascites and oedema; hypertension; oedema.

Spirono comp *Genericon, Austria.*
⊗Spironolactone (p. 1499·3); furosemide (p. 1387·1).
Oedema; hyperaldosteronism.

Spironol *Pharmachemie, Israel; Richter, Pol.*
⊗Spironolactone (p. 1499·3).
Hepatic cirrhosis; hypertension; hypokalaemia; oedema; hyperaldosteronism.

Spironone *Dexo, Fr.†*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; hypertension; oedema; adjuvant in myasthenia.

Spironothiazid *Desma, Ger.*
⊗Spironolactone (p. 1499·3); hydrochlorothiazide (p. 1403·2).
Hyperaldosteronism; oedema; ascites; hypertension.

Spiropent *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Teijin, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Philipp.*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease; asthma; bronchitis; emphysema; bronchospasm; stress urinary incontinence.

Spiropitan *Eisai, Jpn.*
Spiperone (p. 1107·3).
Schizophrenia.

Spirosine *Angelini, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Spirotone *Mylan, NZ.*
⊗Spironolactone (p. 1499·3).
Aldosteronism; heart failure; hepatic cirrhosis with ascites; hypertension; hypokalaemia; nephrotic syndrome; oedema; hirsutism.

Spirotop *Topgen, Belg.†*
⊗Spironolactone (p. 1499·3).
Hypertension; heart failure; hyperaldosteronism; cirrhosis with ascites.

Spirumate *Anugerah Pharmindo, Indon.†*
Spirulina (p. 2622·1).
Immunostimulant.

Spiruvita *Campo Esmeralda, Arg.*
Spirulina (p. 2622·1); ascorbic acid (p. 2110·3).
Dietary supplement.

Spitacid *Ecolab, Ger.*
⊗Alcohol (p. 1733·1); isopropyl alcohol (p. 1758·3); benzyl alcohol (p. 1739·3).
Hand disinfection.

Spitaderm
Note: this name may be used for preparations of different composition.
Henkel Hygiene, Gr.
Chlorhexidine gluconate (p. 1743·3).
Paragerm, Indon.†; Ecolab, Ital.†; Ecolab, Neth.†
Isopropyl alcohol (p. 1758·3); chlorhexidine gluconate (p. 1743·3); hydrogen peroxide (p. 1755·2).
Skin disinfection.

Spitomin *Egis, Hung.; Egis, Rus.*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders; depression; sedative.

Spizef
Note: this name may be used for preparations of different composition.
Orchid, Ukr.
Cefuroxime (p. 255·2).
Bacterial infections.
Grunenthal, Austria†; Grunenthal, Ger.†
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

SP-Keto *Inpac, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

SPL *Delmont, USA.*
Two strains of lysed *Staphylococcus aureus* in solution (p. 2420·2).
Staphylococcal infection.

Splash Kids *Energizer, Canad.†*
SPF 45: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Splash Tears *Sophia, Mex.*
Hypromellose (p. 2189·2); chondroitin sulfate sodium (p. 2476·1).
Dry eyes.

Splendil *AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, Jpn.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Splénocarbine *Lesourd, Fr.*
Activated charcoal (p. 1537·3).
Gastrointestinal disorders.

Splentir *Unipharma, Gr.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

SP-Micozol *Sunward, Singapore.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Spm-OK *Marfarma, Ital.*
⊗Magnesium (p. 1786·3); zinc (p. 2126·1); borage oil (p. 2459·2); griffonia simplicifolia (p. 2522·3); agnus castus (p. 2432·2).
Premenstrual syndrome.

SP-Mucoplex *Sunward, Singapore.*
Carbocisteine (p. 1658·1).
Mucolytic.

SP-Nadofen *Sunward, Singapore.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; migraine.

SP-Norvulin *Sunward, Singapore.*
Norethisterone (p. 2294·2).
Menorrhagia; endometriosis; premenstrual syndrome; breast cancer.

Spofaplast *Chemopharma, Cz.†*
Salicylic acid (p. 1719·1).
Corns; calluses.

Spofax *Zentiva, Cz.*
Carmellose calcium (p. 2175·1); bismuth subgallate (p. 1822·1); cinchocaine hydrochloride (p. 1983·2).
Haemorrhoids.

Spolera
Note: this name may be used for preparations of different composition.
OTW, Ger.†
Acmella ciliata.
Soft-tissue injuries.

Spondylon *Riemser, Ger.†*
Capsules: Ketoprofen (p. 79·1).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Spondyvit *Meda, Ger.†*
d-Alpha tocoferil acetate (p. 2119·1).
Vitamin E deficiency.

Spongostan *Ethicon, Ger.; Johnson & Johnson, Ital.*
⊗Gelatin (p. 1154·1).
Haemorrhage.

Spophyllin *Zentiva, Cz.†; Zentiva, Singapore.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Sporacid
Note: this name may be used for preparations of different composition.
Dexa, Hong Kong†; Ferron, Indon.
Itraconazole (p. 583·3).
Fungal infections.

Sporagal *Pharma Start, Ukr.*
Itraconazole (p. 583·3).
Fungal infections.

Sporahexal *Hexal, Austral.†*
Cefalexin (p. 234·1).
Bacterial infections.

Sporal *Janssen-Cilag, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Sporanox *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, SAfr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Johnson & Johnson, Turk.; Janssen-Cilag, UK; Janssen, USA; Janssen-Cilag, Venez.*
Itraconazole (p. 583·3).
Fungal infections.

Sporasec *Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Itraconazole (p. 583·3); secnidazole (p. 947·3).
Vulvovaginal infections.

Sporax *Dexa, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Sporaxyl *Bangkok Lab & Cosmetic, Thai.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Sporcid *Fresenius Kabi, Ger.*
Glutaral (p. 1753·2); formaldehyde (p. 1752·2).
Instrument disinfection.

Sporend *Mugi, Indon.*
Miconazole nitrate (p. 589·1).
Fungal skin and nail infections.

Sporetik *Sanbe, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Sporex
Note: this name may be used for preparations of different composition.
Tempo Scan Pacific, Indon.
Ketoconazole (p. 585·3).
Fungal skin infections.
Toprak, Turk.
Itraconazole (p. 583·3).
Fungal infections.
IMS, Ital.†
Glutaral (p. 1753·2).
Instrument disinfection.

Sporfen *Medinfar, Port.*
Ibuprofen (p. 68·2).
Pain; fever.

Spor-HC *Akorn, Canad.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected ear disorders.

Sporicef *Ranbaxy, Mex.; Ranbaxy, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Sporidex *Nanxin, China; Ranbaxy, Cz.†; Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Philipp.†; Ranbaxy, Singapore; Ranbaxy, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Sporidin *Ranbaxy, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Sporidox Plus *IMS, Ital.†*
Peracetic acid (p. 1763·1).
Instrument disinfection.

Sporiline *MSD-Chibret, Fr.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Sporinex *Medochemie, Thai.†*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis.

Sporizole *Target, Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Sporlab *Biolab, Thai.†*
Itraconazole (p. 583·3).
Fungal infections.

Sporlac *Uni-Sankyo, India.*
Lactobacillus sporogenes (p. 2596·3).
Antibiotic-associated diarrhoea; moniliasis.

Spornar *Charoen, Thai.*
Itraconazole (p. 583·3).
Fungal infections.

Sporobiotic *Medichrom, Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Sporostatin *Mantecorp, Braz.*
Griseofulvin (p. 582·2).
Fungal infections.

Sporoxyl *Bangkok Lab & Cosmetic, Thai.*
Ketoconazole (p. 585·3).
Fungal infections.

Sport 30 *Energizer, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sport 50 *Tanning Research, Canad.†*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sport 30 Continuous Spray *Tanning Research, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sport Gel *Sani-Marc, Canad.†*
Triclosan (p. 1773·2).
Skin cleansing.

Sport Lip Balm *Norwood, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Sport Lotion *Norwood, Canad.*
SPF 50: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Natures Gate, Canad.†
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Sport Performance *Energizer, Canad.*
Lotion SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Energizer, Canad.
SPF 50: SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.
Playtex, Canad.†
Stick, SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

S-Port Reka *Inpac, Thai.*
Anhydrous glucose (p. 2069·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2).

Sporténine *Boiron, Canad.*
Arnica montana (p. 2447·2); sarcolacticum acidum (p. 2539·1); zincum oxydatum (p. 1729·1).
Homoeopathic preparation.

Sportenine *Boiron, Fr.; Boiron, Neth.†*
Arnica montana (p. 2447·2); sarcolacticum acidum (p. 2539·1); zincum oxydatum (p. 1729·1).
Homoeopathic preparation.

Sportflex *Neocare, Belg.*
Indometacin (p. 71·2).

Sportino *Harras-Curarina, Ger.†*
Heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue injury.

Sportino Akut *Harras-Curarina, Ger.†*
Glycol salicylate (p. 66·2); arnica (p. 2447·2).
Musculoskeletal, joint, and soft-tissue disorders.

Sportium *Lyron, Switz.*
Heparin sodium (p. 1396·3); allantoin (p. 1693·1); dexpanthenol (p. 2582·2).
Soft-tissue injuries; venous insufficiency.

Sportium uno *Lyron, Switz.*
Heparin sodium (p. 1396·3).
Varices; soft-tissue injury; scars; superficial thromboses.

Sports Blend *Hunter, Canad.*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sports Ice Bruising Relief *Brauer, Austral.*
Arnica (p. 2447·2).
Soft-tissue injury.

Sports Ice Joint & Muscle *Brauer, Austral.*
Arnica (p. 2447·2); bellis per. (p. 2454·2); ledum (p. 2550·1); apis mel. (p. 2445·2); belladonna (p. 2453·3); bryonia (p. 2461·3); camphora (p. 2466·2); hypericum (p. 449·1); kalmia (p. 2537·2); ranunculus bulb.; rhus tox. (p. 2603·3); ruta grav. (p. 2608·2); strontium carb.; symphytum (p. 2484·2).
Homoeopathic preparation.

SportsAde *Pediapharma, Philipp.*
Electrolytes (p. 1775·1); glucose (p. 2068·3); sucrose (p. 2096·3) (p. 1780·1).
Oral rehydration solution.

Sportscreme *Thompson, USA.*
Trolamine salicylate (p. 141·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Sportscreme Ice *Thompson, USA.*
Menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Sportsmega *Cantassium Co., UK.*
Vitamins; minerals.

Sportupac M *Madaus, Ger.†*
Aesculus (p. 2431·2); aescin (p. 2431·2).
Bruising.

Sportusal *Permamed, Switz.*
Gel: Lauromacrogol 400 (p. 2194·1); dimethyl sulfoxide (p. 2182·2); heparin sodium (p. 1396·3); glycol salicylate (p. 66·2); dexpanthenol (p. 2582·2).
Soft-tissue trauma; superficial thrombophlebitis; varices.
Permamed, Switz.†
Tablets: Mefenamic acid (p. 85·3).
Pain; fever; hypermenorrhoea.

Sportusal assan thermo *Permamed, Switz.*
Flufenamic acid (p. 65·1); glycol salicylate (p. 66·2); benzyl nicotinate (p. 29·3); heparin sodium (p. 1396·3).
Musculoskeletal and joint disorders.

Sportusal cool *Permamed, Switz.*
Levomenthol (p. 2553·2); peppermint (p. 1877·1).
Musculoskeletal, joint, and soft-tissue disorders.

Sportusal Spray sine heparino *Permamed, Switz.*
Lauromacrogol 400 (p. 2194·1); dimethyl sulfoxide (p. 2182·2); glycol salicylate (p. 66·2); dexpanthenol (p. 2582·2); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders.

Spotner *Zurego, UK.*
SPF 50: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); alpha-arbutin; salicylic acid (p. 1719·1); primula veris (p. 2596·2); achillea (p. 2427·3); peppermint leaf (p. 1877·1); mallow (p. 2549·2); alchemilla vulgaris; veronica officinalis; melissa (p. 2552·3).
UV-induced skin hyperpigmentation.

Spotof *CCD, Fr.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Spotoway *Health & Diet Food Co., UK.*
Chlorhexidine (p. 1743·2).
Skin irritation and spots.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Spozol *Delta, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Spralyn *Salus, Mex.*
Sodium cromoglicate (p. 1225·3).
Asthma.

Spray Anti-Séptico *Johnson & Johnson, Braz.*
Lidocaine hydrochloride (p. 1988·2); benzethonium chloride (p. 1738·1).

Spray I Dene *Protector, Canad.†*
Povidone-iodine (p. 1767·1).

Spray Ecran Solaire *Avene, Canad.*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Spray du Marcheur *Laphi, Fr.†*
Irgasan (p. 1773·2); triclocarban (p. 1773·2).
Foot hygiene.

Spray Mint *Kivema, Israel.*
Menthol (p. 2553·2); sorbitol (p. 2092·1).
Nasal dryness.

Spray nasal comp pour adultes *Spirig, Switz.†*
⊗Naphazoline nitrate (p. 1669·3); phenylephrine (p. 1672·2).
Nasal congestion.

Spray nasal neo *Spirig, Switz.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Spray nasal pour enfants *Spirig, Switz.†*
Phenylephrine (p. 1672·2).
Nasal congestion; rhinitis.

Spray Pour Peaux Intolerantes au Soleil *Esthederm, Canad.*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Spray Solaire Sports *Clarins, Canad.*
SPF 15: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Spraydil *SMB, Belg.*
Phenylephrine hydrochloride (p. 1672·3).
Rhinitis.

Spray-on Sunscreen *Kinesys, Canad.*
SPF 30+: Avobenzone (p. 1695·1); meradimate (p. 1711·2); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Kinesys, Canad.
SPF 15: Avobenzone (p. 1695·1); meradimate (p. 1711·2); octinoxate (p. 1715·1).
Sunscreen.

Spray-Pax *Omega, Fr.; Pharmygiene, Rus.; Omega, Ukr.†*
Pyrethrum (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis; pubic pediculosis.

Spray-Tish *Boehringer Ingelheim, Austral.*
⊗Tramazoline hydrochloride (p. 1679·3).
Nasal congestion.

Spray-Tish Menthol *Boehringer Ingelheim, Austral.*
⊗Tramazoline hydrochloride (p. 1679·3); menthol (p. 2553·2); cineole (p. 2479·1); camphor (p. 2466·2).
Nasal congestion.

Sprayzinc *Preval, Canad.*
Pyrithione zinc (p. 1718·1).

Sprayzoin *Geritrex, USA.*
Benzoin compound tincture.
Skin disorders.

Spregal *Olvos, Gr.; Pharmygiene, Neth.; Omega, Rus.; Cipla-Medpro, S.Afr.; Omega, Ukr.*
Esdepallethrine (p. 2154·3); piperonyl butoxide (p. 2160·2).
Scabies.

Wolff, Ger.†
Bioallethrin (p. 2149·2); piperonyl butoxide (p. 2160·2).
Scabies.

Sprégal *Omega, Fr.*
Esdepallethrine (p. 2154·3); piperonyl butoxide (p. 2160·2).
Scabies.

SP-Rhinodyl *Sunward, Singapore.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Spriafil *Schering-Plough, Mex.*
Posaconazole (p. 592·1).
Fungal infections.

Sprilon *Ayrton Saunders, Irl.; Ayrton, UK.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1).
Barrier preparation; eczema; skin fissures; pressure sores; skin ulcers.

Sprimeo *Novartis, Cz.†; Novartis, Irl.†; Novartis, Neth.†; Novartis, Pol.†; Novartis, Port.†*
Aliskiren fumarate (p. 1295·3).
Hypertension.

Novartis, Gr.†
Aliskiren (p. 1295·3).
Hypertension.

Sprimeo HCT *Novartis, Irl.†*
⊗Aliskiren fumarate (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sprintec *Barr, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norgestimate (p. 2295·3); 7 tablets, inert.
Combined oral contraceptive.

Sprix *American Regent, USA.*
Ketorolac trometamol (p. 80·2).
Pain.

S-Pro *LBS, Thai.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; gout.

Sproam *Coloplast, Canad.*
Benzethonium chloride (p. 1738·1).

Sprycel *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.†; BMS, Irl.; BMS, Israel; BMS, Ital.; BMS, Malaysia; BMS, Neth.; BMS, Norw.; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; Byk Gulden, Turk.; BMS, UK; BMS, USA.*
Dasatinib (p. 777·3).
Chronic myeloid leukaemia; acute lymphoblastic leukaemia.

SPS *Carolina, USA.*
Sodium polystyrene sulfonate (p. 1575·2).
Hyperkalaemia.

SP-Sinudyl *Sunward, Singapore.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine hydrochloride (p. 1676·1).

SP-Totifen *Sunward, Singapore.*
Ketotifen fumarate (p. 631·3).
Allergic conditions; asthma.

Sputopur *Teva, Hung.*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with increased or viscous mucus.

SP-Virac *Sunward, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Spyrocon *Interbat, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Squam *Gador, Arg.*
Dental gel: Etidronate disodium (p. 1182·3); sodium fluoride (p. 2089·2); sodium monofluorophosphate (p. 2091·3).
Dental caries prevention.

Gador, Arg.
Toothpaste: Etidronate disodium (p. 1182·3); calcium pyrophosphate; sodium fluoride (p. 2089·2).
Dental caries prevention.

Squamasol *Ichthyol, Austria; Ichthyol, Ger.*
Salicylic acid (p. 1719·1).
Scalp disorders.

Squa-med *Permamed, Switz.*
Pyrithione zinc (p. 1718·1); sodium undecylamide MEA-sulfosuccinate.
Scalp disorders.

Phoenix, Hung.
⊗Pyrithione zinc (p. 1718·1); disodium sulfosuccinated undecenoic acid monoethanolamide (p. 596·3); urea (p. 1727·3).
Scalp disorders.

Squaphane *Biorga, Fr.*
Topical lotion: Malic acid (p. 2549·2); climbazole (p. 576·2); miconazole (p. 588·3); cade oil (p. 1723·2).
Dandruff.

Biorga, Fr.
Cream: Climbazole (p. 576·2); miconazole (p. 588·3); salicylic acid (p. 1719·1); cade oil (p. 1723·2); ichthammol (p. 1705·3).
Scalp disorders; psoriasis.

Squaphane E *Biorga, Fr.*
Climbazole (p. 576·2); miconazole (p. 588·3); cade oil (p. 1723·2); levomenol (p. 2544·1).
Dandruff.

Squaphane P *Biorga, Fr.*
Climbazole (p. 576·2); miconazole (p. 588·3); salicylic acid (p. 1719·1); cade oil (p. 1723·2); melaleuca oil (p. 2551·1).
Dandruff.

Squaphane S *Biorga, Fr.*
Climbazole (p. 576·2); miconazole (p. 588·3); salicylic acid (p. 1719·1); cade oil (p. 1723·2); resorcinol (p. 1718·3).
Scalp disorders.

Squibb-B Complex *BMS, Indon.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Squill and Ammonia *Vidhyasom, Thai.*
Camphorated opium tincture; ammonium bicarbonate (p. 1655·3); squill tincture (p. 1677·3); senega tincture (p. 1677·2).

SRC Expectorant *Edwards, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Coughs.

SRE Sérocytol *Serolab, Switz.†*
An immunoglobulin (equine).
Infections.

Srilane *Merck Serono, Fr.*
Idrocilamide (p. 2025·2).
Soft-tissue disorders.

SRM-Rhotard *Thebe, S.Afr.; Amarin, Singapore.*
⊗Morphine sulfate (p. 92·3).
Pain.

SRO *Rivero, Arg.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration.

Sronyx *Watson, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Combined oral contraceptive.

SSD *Reddy, USA.*
Sulfadiazine silver (p. 362·3).
Burn wound sepsis.

SSKI *Upsher-Smith, USA.*
Potassium iodide (p. 2336·3).
Respiratory-tract disorders.

SSP *Eurolab, Arg.*
Range of dietary supplements.

SSS *Acella, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

SST *Intsel, Fr.†; Medac, UK.*
Sorbitol (p. 2092·1); macrogol (p. 2547·3); malic acid (p. 2549·2); sodium citrate (p. 1781·2).
Dry mouth.

SSZ *Gufic, India.*
Sulfadiazine silver (p. 362·3).
Fungal corneal infections.

ST 37 *Numark, USA.*
Hexylresorcinol (p. 1755·1).
Antiseptic.

St Bonifatius-Tee *Kolassa, Austria.†*
Equisetum (p. 2500·1); citrus aurantium (p. 2575·3); tilia flower (p. 2631·3); boldo leaf (p. 2458·3); juniper wood (p. 2537·1).
Diuretic; biliary-tract disorders.

S-T Forte 2 *Scot-Tussin, USA.*
Chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

St James Balm *Medico-Biological Laboratories, UK.*
⊗Zinc oxide (p. 1729·1); ichthammol (p. 1705·3); salicylic acid (p. 1719·1); urea (p. 1727·3).
Skin disorders.

St Johnswort Compound *Potter's, UK.*
Juniper oil (p. 2537·2); St John's wort (p. 449·1); salix (p. 129·2); cimicifuga (p. 2478·1); skullcap (p. 2617·1).
Sciatica.

St. Joseph Adult Chewable *Schering-Plough, USA.*
Aspirin (p. 22·2).

St Luke's Cold *British Dispensary, Thai.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Rhinitis; nasal congestion; cold symptoms.

St Luke's Cough *British Dispensary, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with viscous mucus.

St Luke's Fever *British Dispensary, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

St Luke's Oil *British Dispensary, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); thyme oil (p. 2630·3).
Muscle pain; soft-tissue injury.

St Luke's Sports Oil *British Dispensary, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Muscle pain; soft-tissue injury.

St Mary's Thistle Plus *Eagle, Austral.†*
Milk thistle (p. 1561·1); myrtillus (p. 2566·2); taraxacum (p. 2625·3).
Liver tonic; peripheral vascular disorders; psoriasis.

Staaldruppels *Aspen Consumer, S.Afr.*
Ferric chloride (p. 2504·2).
Iron-deficiency anaemias; minor haemorrhage.

Stabactam *Fahrenheit, Indon.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Stabicilline *Vifor, Switz.*
Tablets: Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Stabil *TO-Chemicals, Thai.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; psychoses; anxiety; vertigo.

Stabilanol *Pharmathen, Gr.; Trima, Israel.*
Fluconazole (p. 578·2).
Fungal infections.

Stabilised Ceretec *GE Healthcare, Belg.†*
Technetium-99m (p. 2228·1) exametazine.
Cerebral blood flow scintigraphy.

Stabilium *Yalacta, Fr.*
Garum armoricum.
Dietary supplement; stress.

Stabimed *Braun, Ger.*
Cocopropylene-diamine.
Instrument disinfection.

Stabisol *Berlin-Chemie, Rus.*
⊗Hetastarch (p. 1146·1).
Haemodilution; hypovolaemia; shock.

Stabixin *Fahrenheit, Indon.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Stabizol *Berlin-Chemie, Ukr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; hypovolaemic shock; haemodilution.

Stablon *Servier, Arg.; Serdia, India; Servier, Indon.; Servier, Malaysia; Servier, Philipp.†; Servier, Singapore.*
Tianeptine (p. 450·2).
Depression; mixed anxiety depressive states; alcohol withdrawal syndrome.

Servier, Austria; Servier, Braz.; Servier, Fr.; Servier, Mex.; Servier, Port.; Servier, Thai.; Servier, Turk.; Servier, Venez.
Tianeptine sodium (p. 450·2).
Depression; mixed anxiety depressive states; anxiety.

Stacare *Nufarindo, Indon.*
Lycopene (p. 2546·2); selenium (p. 2086·3); zinc (p. 2126·1).
Prostate disorders.

Stacer *Atral, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Stacin *Macrophar, Thai.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Stada K *Stada, Hong Kong.†*
Ketoconazole (p. 585·3).
Dandruff.

Stada Uno *Stada, Singapore; Stada, Thai.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension; ischaemic heart disease.

Stadaglicin *Stada, Hong Kong†; Stada, Malaysia†; Stada, Singapore.†*
Sodium cromoglicate (p. 1225·3).
Conjunctivitis; allergic rhinitis.

Stadalax *Stada, Cz.; Stada, Hung.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Stadamet *Stada, Cz.; Stada, Hung.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Stadanazol *Stada, Denm.*
Fluconazole (p. 578·2).
Fungal infections.

Stadapress *Stada, Cz.*
⊗Quinapril hydrochloride (p. 1480·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Stadaquel *Stada, Cz.; Stada, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; mania.

Stadazar *Stada, Hung.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; left ventricular hypertrophy.

Stadazar HCT *Stada, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Stadelant *Chrispa (Χρισπα), Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Stadenace *Stada, Philipp.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension; left-ventricular dysfunction.

Stadex *Ajanta, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Stadifluven *Stada, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Stadium
Note: this name may be used for preparations of different composition.
Benedetti, Ital.
Cefixime (p. 240·3).
Bacterial infections.
Sanfer, Mex.; Menarini, Neth.
Dexketoprofen trometamol (p. 79·1).
Pain.

Stadol *BMS, Mex.; BMS, Philipp.†; BMS, Rus.; Apothecon, USA.*
Butorphanol tartrate (p. 33·2).
Pain; premedication.

Stadovas *Stada, Hong Kong.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Stafal *Sevapharma, Cz.†*
Antistaphylococcal phages (p. 2420·2).
Staphylococcal infections.

Stafcil *Aurobindo, Philipp.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Stafeks *Drogsan, Turk.*
Sodium fusidate (p. 302·1).

Staficilin N *BMS, Braz.*
Oxacillin sodium (p. 336·2).
Bacterial infections.

Staficort *Mentiterm, Gr.*
⊗Betamethasone valerate (p. 1624·1); fusidic acid (p. 302·1).
Infected skin disorders.

Stafine *Kocak, Turk.*
Sodium fusidate (p. 302·1).
Staphylococcal infections.

Staflex *Magna, USA.*
Phenyltoloxamine citrate (p. 638·1); paracetamol (p. 115·1).
Pain.

Staflocil *Orion, Fin.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Stafloxin *Westmont, Philipp.*
Flucloxacillin magnesium (p. 299·2) or flucloxacillin sodium (p. 299·2).
Bacterial infections.

Staforin *Kalbe, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Stage *Abdi, Turk.*
Rosuvastatin (p. 1488·2).

Stagesic *Magna, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Stagid *MerckSerono, Fr.; Merck, Port.*
Metformin embonate (p. 489·1).
Diabetes mellitus.

Stahist *Huckaby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hyoscyamine sulfate (p. 1848·1); hyoscine hydrobromide (p. 1845·3); atropine sulfate (p. 1310·2).
Upper respiratory-tract symptoms.

Stahist AD *Magna, USA.*
⊗Chlorcyclizine hydrochloride (p. 620·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Stalcare *Epifarma, Ital.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Stalene *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore†; Unison, Thai.*
Fluconazole (p. 578·2).
Fungal infections.

Staleth *Stadmed, India.*
Lithium carbonate (p. 427·3).
Mania; hypomania; bipolar disorder.

Stalev *Novartis, Philipp.*
Levodopa (p. 902·2); carbidopa (p. 900·3); entacapone (p. 901·2).
Parkinsonism.

Stalevo *Novartis, Arg.; Novartis, Austral.; Orion, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Orion, Cz.; Orion, Denm.; Orion, Fin.; Novartis, Fr.; Orion, Ger.; Orion, Gr.; Novartis, Hong Kong; Orion, Hung.; Novartis, Indon.; Orion, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Orion, Norw.; Orion, Pol.; Orion, Port.; Orion, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Orion, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Orion, UK; Orion, Ukr.; Novartis, USA; Novartis, Venez.*
Levodopa (p. 902·2); carbidopa (p. 900·3); entacapone (p. 901·2).
Parkinsonism.

Stalip *Stallion, Philipp.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; hypertension; angina pectoris.

Stallion *Lockerroom, Canad.*
Lidocaine (p. 1988·1).

Staloral *Stallergenes, Cz.; Stallergenes, Ger.; Tracymed, Gr.; Stallergenes, Hung.; Stallergenes, Ital.†; Stallergenes, Pol.*
Allergen extracts (p. 2434·3).
Hyposensitisation; allergen immunotherapy.
Stallergenes, Switz.
Pollen allergen extracts (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

Stamar *LKM, Arg.*
Stavudine (p. 1015·3).
HIV infection.

Stamaril *Sanofi Pasteur, Arg.; Sanofi Pasteur, Austral.†; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Honest Ability, Hong Kong†; Sanofi Pasteur, Hung.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Sanofi-Aventis, NZ; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; Aventis Pasteur, Turk.†; Aventis Pasteur, UK.*
A yellow fever vaccine (17D strain) (p. 2424·3).
Active immunisation.

Stamicis *CIS, Cz.; CIS, Fin.; CIS, Fr.; CIS, Irl.; CIS, Neth.; CIS, Port.; CIS, Spain.*
Technetium-99m (p. 2228·1) sestamibi.
Radionuclide imaging.

Stamidix *IDI, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Stamifen *Pliva, Ital.†*
Ketotifen fumarate (p. 631·3).
Allergic rhinitis.

Stamin *Angelini, Gr.*
Piracetam (p. 393·3).
Mental function disorders.

Stamina *Chi Sheng, Thai.*
Vitamin B substances (p. 2102·3); glucose (p. 2068·3).

Stamino *Tropica Mas, Indon.*
Glutamine (p. 2070·3); echinacea (p. 2498·1); ascorbic acid (p. 2110·3).
Immunostimulant.

Stamlo *Reddy, Philipp.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.
Reddy, S.Afr.
Amlodipine (p. 1304·1).
Reddy, Singapore; Reddy, Ukr.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Stamlo M *Reddy, Rus.*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Stamoist E *Huckaby, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Stamonevrol *Biostam (Βιοσταμ), Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Stamyl *Konsuma, Venez.*
⊗Pancreatin (p. 2579·3); hemicellulase (p. 2473·1); ox bile (p. 2457·2); simeticone (p. 1886·2).
Digestive disorders.

Stanalin *Erlimpex, Indon.*
Mefenamic acid (p. 85·3).
Fever; pain.

Stanback *GSK Consumer, USA.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Formerly contained aspirin, caffeine, and salicylamide.
Pain.

Stancef *Biomedis, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Standacillin *Biochemie, Indon.; Sandoz, Rus.; Sandoz, Singapore.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.
Sandoz, Austria; Sandoz, Hung.; Sandoz, Malaysia.
Ampicillin sodium (p. 218·2).
Bacterial infections.

Standard III *Aguettant, Fr.†*
Electrolytes (p. 1775·1).
Parenteral nutrition.

Standard XXI *Bioquimico, Arg.*
Benzyl alcohol (p. 1739·3); diethyltoluamide (p. 2153·1); ethyl butylacetylaminopropionate (p. 2154·3).
Pediculosis.

Standor *Uniao Quimica, Braz.*
Mefenamic acid (p. 85·3).

Stangesic *GX, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Stangyl *Sanofi-Aventis, Ger.*
Trimipramine maleate (p. 453·1) or trimipramine mesilate (p. 453·1).
Depression; anxiety.

Stanhexidine *Omega, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Stanidine *Apotex, Philipp.†; Pharma 3, Philipp.†*
Pravastatin sodium (p. 1473·1).
Cardiovascular risk reduction; hyperlipidaemias.

Stanlip *Ranbaxy, Thai.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Stannous Agent *Mediam, Neth.*
Kit for the preparation of technetium-99m (p. 2228·1) stannous medronate.
Red blood cell labelling for blood pool scintigraphy.

Stanyn *Tianxin, China.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Stanys *ACME, Philipp.*
Nystatin (p. 590·3).
Oral candidiasis.

Stanza *Hexpharm, Indon.†*
Mefenamic acid (p. 85·3).
Fever; pain.

Stanzil *Idaman, Singapore.*
Metronidazole (p. 936·1).
Protozoal infections; bacterial infections.

Stanztab *Unigen, Thai.*
⊗Stanozolol (p. 2304·2).
Hereditary angioedema.

StaphAseptic *Tec, USA.*
Benzethonium chloride (p. 1738·1); lidocaine hydrochloride (p. 1988·2).

Staphiderm *Trima, Israel.*
Fusidic acid (p. 302·1).
Staphylococcal skin infections.

Staphlex *Alphapharm, Malaysia†; Mylan, NZ.†*
Flucloxacillin sodium (p. 299·2).
Gram-positive bacterial infections.
Pacific, Singapore.†
Flucloxacillin (p. 299·1).
Bacterial infections.

Staphycid *Trenker, Belg.*
Flucloxacillin magnesium (p. 299·2) or flucloxacillin sodium (p. 299·2).
Staphylococcal and streptococcal infections.
Trenker, Thai.†
Flucloxacillin (p. 299·1).
Bacterial infections.

Staphyclox *Norma (Νορμα), Gr.*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Staphylex *Alphapharm, Austral.; Actavis, Ger.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

Staphysagria Complexe No 92 *Lehning, Fr.†*
Staphysagria; anemone pulsatilla (p. 2600·2); arctium lappa (p. 2540·1); arsenicum iodatum (p. 2448·1); artemisia abrotanum; ignatia (p. 2532·1); borax (p. 2459·2); kalium carbonicum (p. 2595·2); sulfur (p. 1721·1); viola tricolor (p. 2647·3).
Homoeopathic preparation.

Stapiride *Sandoz, Denm.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Starasid *Kayaku, Jpn.*
Cytarabine ocfosfate (p. 774·1).
Non-lymphocytic leukaemia; myelodysplastic syndromes.

Starazolin *Polpharma, Pol.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Conjunctivitis.

Starcef
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Cefixime (p. 240·3).
Bacterial infections.
FIRMA, Ital.
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Stardaf *Pharos, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Starezin *Alapis, Gr.; Aledicine, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Starform *Novartis, Braz.; Novartis, Venez.*
Tablets, nateglinide (p. 492·1); tablets, metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Staril *BMS, UK.†*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Starin *Atlantic, Thai.*
Sertraline (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Starket *Zdorovje, Ukr.*
Spiramycin (p. 358·3).
Bacterial infections.

Starlix *Novartis, Arg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Fin.†; Merck, Ger.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain;*

Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.
Nateglinide (p. 492·1).
Diabetes mellitus.

Starmelox *Minerva (Μινερβα), Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

StarMuno *Kalbe, Indon.*
Caplet: Echinacea angustifolia extract (Polinacea) (p. 2498·1); black elderberry (p. 2609·3); zinc picolinate (p. 2126·1); ascorbic acid (p. 2110·3).
Immunostimulant.
Kalbe, Indon.
Syrup: Echinacea angustifolia extract (Polinacea) (p. 2498·1) black elderberry (p. 2110·3); zinc picolinate (p. 2126·1).
Immunostimulant.

Star-Otic *Stellar, USA.*
Glacial acetic acid (p. 2426·3); aluminium acetate (p. 2440·1); boric acid (p. 2459·3).
Ear infection.

Star-Pen *Sandoz, Austria†; Sandoz, Rus.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Starsis *Astellas, Jpn.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Startidine *Inpac, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Startonyl *Tarrex, Austria; Seber, Port.*
Citicoline (p. 2480·1).
Cerebrovascular disorders; head injury.

Starval *Ranbaxy, India.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction.

Starxon *Interbat, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Stas
Note: this name may be used for preparations of different composition.
Faran, Gr.
Itraconazole (p. 583·3).
Fungal infections.

Stasiva *Pharmanel, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Stat-Crit *Wampole, USA.*
Test for haematocrit/haemoglobin measurement.

Statease *Gerard, Irl.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction following angioplasty.

Statex *Paladin, Canad.; Paladin, Singapore.*
⊗Morphine sulfate (p. 92·3).
Pain.

Staticum *Vifor, Spain.*
Glisentide (p. 474·3).
Diabetes mellitus.

Statifil *Mylan, Neth.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Statiflex G *Braun, Switz.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Statinal *Alet, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Statinum *Medichrom, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Stativer *Iapharm, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Stator
Note: this name may be used for preparations of different composition.
Dexa, Indon.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.
Trima, Israel.
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Statosan *Sanus, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Statrol
Note: this name may be used for preparations of different composition.
Alcon, Belg.†; Alkon (Αλκον), Gr.; Alcon, Philipp.†
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Eye infections.

Statstad *KRKA, Denm.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Staurodorm *Madaus, Belg.*
Flurazepam (p. 1076·1).
Insomnia.

Staurodorm Neu *Dolorgiet, Ger.*
Flurazepam (p. 1076·1).
Sleep disorders.

Stavacin *Biol, Arg.*
Staphylococcus aureus.
Staphylococcal infections.

Stavatin *Mylan, Denm.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Staveran *Polpharma, Pol.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; arrhythmias.

Stavid *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Philipp.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia; atherosclerosis.

Stavigile *Libbs, Braz.*
⊗Modafinil (p. 2327·2).

Stavir *Cipla, India; Cipla-Medpro, S.Afr.; GPO, Thai.; Cipla, Venez.*
Stavudine (p. 1015·3).
HIV infection.

Stavit *Nufarindo, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Stavubergen *Paylos, Arg.*
Stavudine (p. 1015·3).
HIV infection.

Stavzor *Noven, USA.*
Valproic acid (p. 553·1).
Bipolar disorder; epilepsy; migraine.

Staxyn *GSK, USA.*
Vardenafil hydrochloride (p. 2372·1).
Erectile dysfunction.

Stay Alert *Apothecary, USA.*
Caffeine (p. 1203·3).
Fatigue.

Staybla *Ono, Jpn.*
Imidafenacin (p. 2360·2).
Bladder hyperactivity.

Stay-Wet 3 *Sherman, USA.†*
Cleansing, wetting, and soaking solution for gas permeable contact lenses.

Stay-Wet 4 *Sherman, USA.†*
Wetting solutions for hard contact lenses.

Stazepine *Polpharma, Hung.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; trigeminal neuralgia.

Stazol *Bernofarm, Indon.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders; stroke prophylaxis.

Stazor *Adipharm, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

STD *Intramed, S.Afr.†*
Sodium tetradecyl sulfate (p. 2620·1).
Varicose veins.

Stecort-NM *Stancare, India.†*
⊗Beclometasone dipropionate (p. 1621·2); neomycin sulfate (p. 330·1); miconazole nitrate (p. 589·1).
Infected skin lesions.

Stédiril *Codepharma, Fr.*
Norgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Stediril *Pfizer, Neth.; Pfizer, Pol.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Stediril 30 *Pfizer, Belg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Stedon *Adelco, Gr.*
Diazepam (p. 1063·2).
Anxiety disorders; sleep disorders; status epilepticus; alcohol withdrawal syndrome; skeletal muscle spasm; tetanus; premedication.

Stedonil *Adelco, Gr.*
Flunitrazepam (p. 1073·3).

Steerometz *Metz, Philipp.†*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Stefaminelle *Sandoz, Fin.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive.

Stefaplex *Opus Materia, Gr.*
⊗Letrozole (p. 817·1).

Stefolant *SJA, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Stei *Sriprasit, Thai.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Steicardin N *Steigerwald, Ger.†*
Crataegus (p. 2488·1); convallaria majalis (p. 2486·2); strophanthus gratus; selenicereus grandiflorus (p. 2473·2).
Homoeopathic preparation.

Steinaclox *Medichrom, Gr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Steiprostat *Steigerwald, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Steirocall *Steierl, Ger.*
Acid. silicicum (p. 2208·3); calcium carbonicum (p. 1824·3); calcium phosphoricum (p. 1784·2); ilex aquifolium; equisetum arvense (p. 2500·1); symphytum (p. 2484·2); alchmeilla vulgaris; acorus calamus (p. 2464·2).
Homoeopathic preparation.

Steirocall S *Steierl, Ger.†*
Ledum palustre (p. 2550·1); pseudognaphalium obtusifolium; ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Steiroderm *Steierl, Ger.*
Graphites (p. 2522·1); petroleum rectificatum (p. 2201·2); sulfur jodatum (p. 2624·2).
Homoeopathic preparation.

Steiroplex *Steierl, Austria; Steierl, Ger.†*
Acidum silicicum (p. 2208·3); calcium carbonicum (p. 1824·3); calcium phosphoricum (p. 1784·2); symphytum (p. 2484·2).
Homoeopathic preparation.

Steitraz *Landsteiner, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Stelabid *Armstrong, Mex.*
Isopropamide iodide (p. 1848·3); trifluoperazine hydrochloride (p. 1113·2).
Gastrointestinal disorders.

Stelapar *Schering-Plough, Arg.*
Trifluoperazine hydrochloride (p. 1113·2); tranylcypromine sulfate (p. 450·3).
Mixed anxiety depressive states.

Stelara *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen, Jpn; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Janssen, USA.*
Ustekinumab (p. 1728·2).
Psoriasis; psoriatic arthritis.

Stelatopia *Interbat, Indon.*
A range of cleansing and moisturising preparations.

Stelax *Aspen, Austral.; Arrow, Hong Kong.*
Baclofen (p. 2014·3).
Multiple sclerosis; skeletal muscle spasm; spasticity.

Stelazine *Schering-Plough, Arg.; Mercury, Austral.; GSK, Braz.; Vianex (Βιανεξ), Gr.; Goldshield, Hong Kong; GSK, Indon.; Pharos, Indon.; Goldshield, Irl.; Armstrong, Mex.; Boucher & Muir, NZ; Pharmafrica, S.Afr.; Goldshield, UK.*
Trifluoperazine hydrochloride (p. 1113·2).
Schizophrenia; behaviour disorders; nausea and vomiting; alcoholism; anxiety; psychoses; agitation; neuroses.

Stelium *Ni-The, Gr.*
Trifluoperazine hydrochloride (p. 1113·2).
Psychoses.

Stella *Actavis, Fin.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Stellanin *Farmpreparat, Rus.*
Diethylbenzimidazolium triiodide.
Burns; ulcers; wounds; tonsillitis; pharyngitis.

Stellatropine *Pharmacobel, Belg.*
Atropine sulfate (p. 1310·2).
Cholinesterase inhibitor intoxication; arrhythmias; premedication.

Stellisan *Hartmann, Switz.*
Octenidine hydrochloride (p. 1762·2).
Disinfection of genital mucous membranes and wounds.

Stellorphine *Pharmacobel, Belg.*
⊗Morphine hydrochloride (p. 92·3).
Pain; premedication; acute pulmonary oedema.

Stelminal *Coup, Gr.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Stelosi *Mersifarma, Indon.*
Trifluoperazine hydrochloride (p. 1113·2).
Psychoses; nervous disorders; nausea and vomiting; bipolar disorder.

Stelpon *Sandoz, Indon.†*
Mefenamic acid (p. 85·3).
Fever; pain; menorrhagia.

Stemeral *Pharmanik (Φαρμανικ), Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Stemetil *Sanofi-Aventis, Austral.; Piramal, India; Teofarma, Ital.; Sanofi-Aventis, Neth.†; Sanofi-Aventis, NZ; Sanofi-Aventis, Singapore.*
Prochlorperazine (p. 1098·2) or prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; migraine; vestibular disorders; vertigo; anxiety; Ménière's disease; psychoses.

Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Norw.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Swed.†; Sanofi-Aventis, Thai.; Sanofi-Aventis, UK.
Prochlorperazine maleate (p. 1098·3).
Psychoses; nausea and vomiting; migraine; vestibular disorders; neuroses; vertigo; alcohol and opioid withdrawal syndromes; anxiety; schizophrenia; mental function disorders; Ménière's disease; paranoid state; adjunct to analgesia; mania.

Stemflova *IS Pharma, Fin.; IS Pharma, Norw.*
⊗Terlipressin acetate (p. 2627·1).
Bleeding oesophageal varices.

Stemgen *Invida, Austral.; CRI, Canad.; Amgen, NZ.*
Ancestim (p. 1132·2).
Mobilisation of autologous peripheral blood progenitor cells.

Stemiz *Cadila, India.*
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Stemokin *Peptos, Rus.*
Isoleucyl-glutamyl-tryptophan sodium.
Furunculosis.

Stemzine *Sanofi-Aventis, Austral.*
Prochlorperazine maleate (p. 1098·3).
Nausea and vomiting; vertigo.

Sten *Atlantis, Mex.*
⊗Prasterone (p. 2299·2); testosterone propionate (p. 2305·2); testosterone cipionate (p. 2305·1).
Androgenic; hypogonadism; erectile dysfunction; breast cancer; loss of libido in females.

Stenac *Synmosa, Thai.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; paracetamol poisoning.

Stendra *Vivus, USA.*
Avanafil (p. 2353·3).
Erectile dysfunction.

Stenirol *Guardian, Indon.*
⊗Methylprednisolone (p. 1642·2).
Oral corticosteroid.

Stenobronchial *Giovanardi, Ital.*
Sulfogaiacol (p. 1678·1); wild thyme (p. 2648·1); tolu balsam (p. 1679·2).
Cough, catarrh.

Stenocrat mono *Schwabe, Ger.*
Crataegus (p. 2488·1).
Heart failure.

Stenox *Atlantis, Mex.*
⊗Fluoxymesterone (p. 2278·1).
Androgenic; erectile dysfunction; hypogonadism.

Steocalcin *Nycomed, Belg.†*
Calcitonin (salmon) (p. 1178·1).
Hypercalcaemia; osteolysis; reflex sympathetic dystrophy; osteoporosis; Paget's disease of bone.

Steocar *Takeda, Belg.*
Calcium carbonate (p. 1824·3).
Calcium deficiency; osteoporosis; calcium supplement.

Steocin *SoSe, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Steofen *Benedetti, Ital.*
Ketoprofen (p. 79·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation.

Steopor *Otto, Indon.*
Calcium phosphate (p. 1784·2); calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1); vitamin C (p. 2110·3); vitamin B_6 (p. 2105·3); vitamin K_1 (p. 2122·2); magnesium (p. 1786·3); copper (p. 2057·1); manganese (p. 2081·2); zinc (p. 2126·1).
Calcium supplement; osteoporosis; tonic.

Steovess *Nycomed, Irl.; Nycomed, Neth.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Steovit D3 *Takeda, Belg.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Step 2
Note: this name may be used for preparations of different composition.
Candioli, Ital.
Extract of *Triticum aestivum* (p. 2647·1).
Aid to removal of lice eggs.

Stephadilat-S *Bros, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; panic disorder.

Stepton *Florin, Hung.*
Alum (p. 2439·1).
Phlebitis; varicose veins.

Ster *Uniao Quimica, Braz.*
⊗Prednisolone acetate (p. 1645·2).

Steradent *Reckitt Benckiser, India.*
Sodium perborate (p. 1770·1).
Denture cleanser.

Sterades *Galderma, Ital.*
⊗Desonide (p. 1630·1).
Skin disorders.

Sterakfin *Jelfa, Hung.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Steramina G *Formevet, Ital.*
Benzalkonium chloride (p. 1737·1).
Disinfection of instruments, surfaces, and skin.

Steranios *Anios, Fr.†*
Glutaral (p. 1753·2).
Instrument disinfection.

Sterapred *Merz, USA.†*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Stercia *Mega Lifesciences, Thai.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Sterdex *Thea, Fr.*
⊗Oxytetracycline (p. 337·1); dexamethasone (p. 1630·3).
Eye disorders.

Sterets *SSL, UK.*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Sterets H *Seton, Israel.*
Isopropyl alcohol (p. 1758·3); chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

SSL, UK.
Isopropyl alcohol (p. 1758·3); chlorhexidine acetate (p. 1743·2).
Skin disinfection.

Sterets Tisept *Medlock Medical, Irl.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin, burn, and wound disinfection.

Sterets Unisept *Medlock Medical, Irl.*
Chlorhexidine gluconate (p. 1743·3).
Skin, burn, and wound disinfection.

Sterex *International Dermatologicals, Canad.†*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Scalp disorders.

Sterex Plus *International Dermatologicals, Canad.†*
⊗Coal tar (p. 1723·2); hydrocortisone (p. 1640·1); salicylic acid (p. 1719·1); sulfur (p. 1721·1).

Sterginox *Novofarm (Νοβοφαρμ), Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Stericef *Ipca, Rus.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Stericlens *Pharmachem, UK.*
Sodium chloride (p. 1795·1).
Wound irrigation.

Stericort *Karnataka, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Steriderm-S *Micro, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Steridine *Cipla-Medpro, S.Afr.*
Povidone-iodine (p. 1767·1).
Mouth and throat infections; burns; skin infections; wounds.

Steridose *Europhta, Mon.*
Borax (p. 2459·2); boric acid (p. 2459·3).
Eye irritation.

Steridrolo *Molteni, Ital.*
Tosylchloramide sodium (p. 1773·1).
Disinfection of wounds, burns, and external genitals.

Sterigel *SSL, UK.*
Hemicellulose (p. 2177·1).
Ulcers; wounds.

Solumed, Canad.
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).

Steril Zeta *Zeta, Ital.*
Cream: Triclosan (p. 1773·2); usnic acid (p. 2640·2); hamamelis (p. 2523·3); cod-liver oil (p. 2056·3).
Disinfection of burns and wounds.

Zeta, Ital.
Topical powder: Triclosan (p. 1773·2); usnic acid (p. 2640·2); zinc oxide (p. 1729·1); zinc stearate (p. 2221·2).
Disinfection of burns and wounds.

Sterilene
Note: this name may be used for preparations of different composition.
Amsa, Ital.
Cetrimonium tosilate (p. 1742·3).
Vaginal disinfection.

Stérilène *Gifrer Barbezat, Fr.*
Cetrimide (p. 1742·1).
Skin and wound disinfection.

SteriLid *Advanced Vision, USA.*
Eyelid cleanser.

Sterilid-V *Vista, Philipp.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Sterilin *Four Ventures, Rus.*
Nonoxinol (p. 2199·1).
Contraceptive.

Sterilium med *Bode, Ger.*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Sterillium *Bode, Austria; Bode, Fin.; Rivadis, Fr.; Bode, Ger.; Pharmachemie, Gr.; PEI, Irl.; Bode, Neth.; Bode, Port.; Berner, Swed.*
Isopropyl alcohol (p. 1758·3); mecetronium etilsulfate (p. 1760·1); propyl alcohol (p. 1768·1).
Skin disinfection.

Sterillium Virugard *Bode, Ger.*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Sterilon *Reckitt Benckiser, Belg.†*
Chlorhexidine gluconate (p. 1743·3) or chlorhexidine hydrochloride (p. 1743·3).
Disinfection of skin and wounds; skin disorders.

Sterimar *Mepro, Chile†; Fumouze, Hong Kong; Ultra, Hung.; Intra Pharma, Irl.†; Fumouze, Israel; Baldacci, Ital.; Fumouze, Malaysia; Church, Mex.; Fumouze, Singapore; GSK, Turk.; Church & Dwight, UK.*
Sea water (p. 2612·1).
Nasal cleansing; nasal dryness; nasal hygiene; nasal congestion.

Stérimar *Fumouze, Fr.*
Sea water (p. 2612·1).
Nasal irrigation.

Sterimar Cu *Baldacci, Ital.*
Sea water (p. 2612·1); copper (p. 2057·1).
Nasal cleansing.

Sterimar Mn *Baldacci, Ital.*
Sea water (p. 2612·1); manganese (p. 2081·2).
Nasal irrigation.

Sterimox *GPC, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Steri-Neb *Ivax, Hong Kong.†*
Ipratropium bromide (p. 1211·3).

Steri-Neb Ipratropium *Ivax, Singapore; Norton Healthcare, Singapore.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Steri-Neb Salamol *Norton, Pol.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Steripaste *Molnlycke, Austral.; Medlock Medical, Irl.; Medlock Medical, UK.*
Zinc oxide (p. 1729·1).
Ulcers.

SteriPet *GE Healthcare, Neth.*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for positron emission tomography.

Steripet *GE Healthcare, Fin.; IBA, Ital.†; GE Healthcare, Port.; GE Healthcare, Spain.†*
Fluorine-18 labelled fludeoxyglucose (p. 2224·1).
Radionuclide for positron emission tomography.

Steripod *Medlock Medical, UK.*
Sodium chloride (p. 1795·1).
Irrigation solution.

Steripod Chlorhexidine Gluconate *SSL, UK.*
Chlorhexidine gluconate (p. 1743·3).
Formerly known as Steripod Pink.
Skin disinfection.

Steri/Sol *Johnson & Johnson, Canad.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Sterisol Fermentmycin *Intramed, S.Afr.†*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Sterisol Peridiasol *Intramed, S.Afr.†*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1) (p. 1778·2).
Peritoneal dialysis.

Steritabs *Sovedis, Fr.*
Troclosene sodium (p. 1774·1).
Disinfection of infant's feeding equipment.

Steri-Tin *Faisal, Philipp.*
Framycetin sulfate (p. 301·2).
Wounds; burns; ulcers.

Steriwipe
Note: this name may be used for preparations of different composition.
Helapet, UK.
Isopropyl alcohol (p. 1758·3).
Surface disinfection.

Sterixin *Sterigen, Canad.*
Chlorhexidine gluconate (p. 1743·3).

Sterizol *Vendiz, Philipp.*
Sulfadiazine silver (p. 362·3).
Burns; leg ulcers.

Sterko *Biovena, Pol.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Sterlane
Note: this name may be used for preparations of different composition.
Pharmadeveloppement, Fr.
Topical solution: Lopobutan (p. 1759·3); dapabutan (p. 1749·2); miristalkonium chloride (p. 1761·3).
Skin infections; skin cleansing.

Sterocort
Note: this name may be used for preparations of different composition.
Phytopharm, Ukr.
⊗Methylprednisolone aceponate (p. 1642·2).
Skin disorders.

Taro, Israel.
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Steroderm
Note: this name may be used for preparations of different composition.
Vendiz, Philipp.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Medikon, Indon.†
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Sterodex *Fischer, Israel.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corneal inflammation; conjunctivitis.

Sterodome *Faran, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Sterofrin *Alcon, Austral.†*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory and allergic eye disorders.

Sterofundin *Braun, Austria; Braun, Belg.; Braun, Hung.*
Electrolytes (p. 1775·1); with or without glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Braun, Ger.; Braun, Hong Kong; Braun, Pol.; Braun, Rus.
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Braun, Ital.
Electrolytes (p. 1775·1); malic acid (p. 2549·2).
Fluid and electrolyte disorders.

Sterofundin BG *Braun, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Sterofundin HEG *Braun, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Sterofundin Iso *Braun, Neth.*
Electrolytes (p. 1775·1); malic acid (p. 2549·2).
Acidosis.

Sterofundin VG *Braun, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Stérogyl *DB, Fr.*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency.

Sterogyl *IFET (ΙΦΕΤ), Gr.*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency.

Spedrog, Arg.
Colecalciferol (p. 2113·1).
Osteoporosis; vitamin D deficiency; hypoparathyroidism; rickets; hypophosphataemia; osteomalacia.

Sterolone *Francia, Ital.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Steromien *Aspen, S.Afr.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Steron *West-Coast, Thai.*
Norethisterone (p. 2294·2).
Menstrual disorders; endometriosis; benign breast disorders; postponement of menstruation.

Steronase Aq *Sanofi-Aventis, Israel.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Steropotassium *Sterop, Belg.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Sterosan *Lachiforma, Ital.*
Benzalkonium chloride (p. 1737·1); orthophenylphenol (p. 1762·3).
Skin, wound, and burn disinfection.

Sterovag *SecFarm, Pol.†*
⊗Chloroxylenol (p. 1748·2); formosulfathiazole (p. 300·2); urea (p. 1727·3).
Vulvovaginal disorders.

Sterozinil *Aesculapius, Ital.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sterylip *Sanopharm, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Ster-Zac *Medlock Medical, UK.†*
Bath additive: Triclosan (p. 1773·2).
Skin disinfection.

Sterzar *Mega Lifesciences, Thai.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Stesolid *Actavis, Austria; Alpharma, Cz.†; Actavis, Denm.; Actavis, Fin.; Actavis, Ger.†; Alapis, Gr.; IFET (ΙΦΕΤ), Gr.; Actavis, Hong Kong; Alpharma, Hung.†; Actavis, Indon.; Actavis, Irl.; CTI, Israel†; Actavis, Neth.; Actavis, Norw.; CSL, NZ; Actavis, Port.; Actavis, Singapore; Faes, Spain; Actavis, Swed.; Actavis, Switz.; Alpharma, UK.*
Diazepam (p. 1063·2).
Premedication; epilepsy; tetanus; febrile convulsions; eclampsia; anxiety; convulsions; neuroses; sleep disorders; skeletal muscle spasm; status epilepticus; agitation; sedative; withdrawal syndromes.

Stevencillin *Alapis, Gr.; Rafarm, Gr.*
Amoxicillin (p. 216·2).
Bacterial infections.

Stevia Dulri *Tanki, Arg.*
Stevia rebaudiana (p. 2214·2).
Sugar substitute.

Sthamizide *Filadams, Philipp.*
Ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Stibenyl *Pharmanel, Gr.*
Ramipril (p. 1483·3).
Hypertension.

Stibenyl HCT *Pharmanel, Gr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Stibium Comp *Weleda, S.Afr.†*
Hamamelis (p. 2523·3); aesculus (p. 2431·2); stibium met (p. 2445·1).
Anorectal disorders.

Stibupatch *Sigma-Tau, Ital.*
Ibuprofen (p. 68·2).

Stick Ecran Total *Vichy, Canad.†*
SPF 25: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Stick Solaire Tres Haute Protection Special Zones Sensibles *Clarins, Canad.†*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Stiefcortil *Stiefel, Arg.; Stiefel, Braz.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Stiefel Acne Gel *GSK, Cz.*
Isotretinoin (p. 1706·2).
Acne.

Stiefotrex *Gabriel, Gr.; GSK, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Stiemazol *Stiefel, S.Afr.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Stiemycin *Stiefel, Arg.; Stiefel, Braz.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Neth.†; Stiefel, NZ; Stiefel, Philipp.; GSK, S.Afr.; Stiefel, Singapore; Stiefel, Thai.; Stiefel, UK.*
Erythromycin (p. 291·2).
Acne.

Stiemycine *Sanova, Austria†; Stiefel, Ger.*
Erythromycin (p. 291·2).
Acne.

Stieprox *GSK, Arg.; Stiefel, Austral.; GSK, Austria; Stiefel, Canad.; GSK, Cz.; Gabriel, Gr.; GSK, Gr.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Malaysia; Stiefel, Norw.†; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Pol.; GSK, Singapore; Stiefel, Thai.*
Ciclopirox olamine (p. 575·3).
Seborrhoeic dermatitis; scalp disorders; dandruff.

Stieproxal *GSK, Arg.*
Ciclopirox olamine (p. 575·3); salicylic acid (p. 1719·1).
Scalp disorders.

Stieva-A *Stiefel, Austral.; GSK, Canad.; Stiefel, Chile; Stiefel, Hong Kong; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Philipp.; GSK, Singapore; Stiefel, Thai.*
Tretinoin (p. 1725·2).
Acne; photoageing of the skin.

Stievamycin *GSK, Arg.; GSK, Canad.; Stiefel, Chile; Stiefel, Mex.*
Tretinoin (p. 1725·2); erythromycin (p. 291·2).
Acne.

Stifarol *Chemica, Gr.*
Calcium dobesilate (p. 2464·3).

Stifimol *KVZ, Ukr.*
Garcinia cambogia (p. 2510·2); chromium picolinate (p. 2056·1); levocarnitine (p. 2053·2); iodine (p. 2336·3); tyrosine (p. 2098·3).
Obesity.

Stigmicarpin *Bros, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Stigmosan *Pharmamagist, Hung.*
Neostigmine metilsulfate (p. 687·2).
Gastrointestinal motility disorders; myasthenia gravis; reversal of competitive neuromuscular blockade; postoperative urinary retention.

Stila *Stila, Canad.†*
SPF 12: Titanium dioxide (p. 1725·1).
Sunscreen.

Stila, Canad.†
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Stilamin *Merck, Braz.; EMD, Canad.†; Merck Serono, China; Vianex (Βιανεξ), Gr.; Serono, Hong Kong; Serum Institute, India; Merck, Indon.; Merck Serono, Ital.; Merck Serono, Malaysia; Omnimed, S.Afr.; Merck, Singapore; Merck, Switz.; Merck, Thai.; Serono, Turk.†; Serono, Venez.*
Somatostatin acetate (p. 1930·3).
Hormone-dependent tumours; variceal haemorrhage; peptic ulcer haemorrhage; prevention of complications following pancreatic surgery; diabetic ketoacidosis; pancreatitis; rheumatoid arthritis; pancreatic, biliary, and intestinal fistulae.

Stilaze *Takeda, Belg.*
Lormetazepam (p. 1082·1).
Insomnia.

Stildem *Aspen, Austral.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Stilene *Omega, Belg.*
Dipropylene glycol salicylate (p. 66·2); capsicum oleoresin (p. 2469·3).
Musculoskeletal, joint, nerve, and soft-tissue pain.

Stileran *Combiphar, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Pain.

Stilex
Note: this name may be used for preparations of different composition.
Vifor, Switz.; Abdi, Turk.
Mepyramine maleate (p. 635·1); lidocaine hydrochloride (p. 1988·2); dexpanthenol (p. 2582·2).
Skin disorders; minor burns.

Farmanic, Gr.; Iasis, Gr.
Butamirate citrate (p. 1657·3).
Cough.

Vifor, Switz.
Cream: Mepyramine maleate (p. 635·1); lidocaine hydrochloride (p. 1988·2); calcium levulinate (p. 1784·2); menthol (p. 2553·2).
Skin disorders; minor burns.

Stilgrip *Hertz, Braz.*
Chlorphenamine (p. 620·3); phenylephrine (p. 1672·2); paracetamol (p. 115·1).
Cold and influenza symptoms.

Stiliden *Meditrina, Gr.; Lifepharma, Ital.; ITF, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Stilizan *Frik, Turk.*
Trifluoperazine hydrochloride (p. 1113·2).
Nausea and vomiting; psychoses; agitation; behaviour disorders; anxiety.

Still *Allergan, Braz.; Allergan, Mex.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders; inhibition of miosis during cataract surgery.

Stilla
Note: this name may be used for preparations of different composition.
Teva, Israel.
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Stilla Decongestionante *Angelini, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Stilla Delicato *Angelini, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye disinfection; eye irritation.

Stilla Unidose *Angelini, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Stillen *Dong-A, Philipp.*
Eupatilin.
Gastric mucosal lesions; gastritis.

Stillergy *Angelini, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3); pheniramine maleate (p. 637·2).
Eye irritation and congestion.

Stilnoct *Sanofi-Aventis, Belg.; Sanofi Synthelabo, Cz.†; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.; Sanofi Synthelabo, UK.*
Zolpidem tartrate (p. 1116·2).
Insomnia; sleep disorders.

Stilnox *Sanofi-Aventis, Austral.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi-Aventis, Venez.*
Zolpidem tartrate (p. 1116·2).
Insomnia; sleep disorders; anxiety.

Stiloz *Glenmark, India.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Stilpane *Aspen, S.Afr.*
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Aspen, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Aspen, S.Afr.†
Capsules: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); meprobamate (p. 1083·3).
Pain and associated tension.

Stilpidem *Quality, Hong Kong.*
Zolpidem (p. 1116·2).
Insomnia.

Stilux *EMS, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Eye disorders.

Stilz *Teva, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Stimate *CSL, USA.*
⊗Desmopressin acetate (p. 2355·1).
Haemophilia A; von Willebrand's disease.

Stimmune *Vertos, Singapore.*
Polysaccharide-K (p. 2594·1).
Dietary supplement.

Stimol *Biocodex, Fr.; Casana, Indon.†; Biocodex, Rus.; Biocodex, Spain; Biocodex, Ukr.*
Citrulline malate (p. 2056·3).
Asthenia; tonic.

Stimovul *Organon, Gr.*
Epimestrol (p. 2270·3).

Stimox *Solas, Indon.*
Echinacea (p. 2498·1); vitamins; bovine colostrum (p. 2380·3); phyllanty.
Immunomodulator.

Stimu-ACTH *Ferring, Fr.*
⊗Corticorelin triflutate (p. 1628·2).
Diagnosis of adrenocortical dysfunction.

Stimu-GH *Ferring, Fr.*
⊗Somatorelin acetate (p. 1930·1).
Diagnosis of hypothalamic-pituitary dysfunction.

Stimulance *Nutricia, Austral.; Eurofarma, Braz.; Nutricia, Fr.†; Nutricia, Ital.; Nutricia, NZ; Nutricia, Port.*
Dietary fibre.
Bowel disorders; constipation; dietary fibre supplement.

Stimulex *Cipan, Port.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency; tonic.

Stimu-LH *Ferring, Fr.†*
⊗Gonadorelin (p. 2280·2).
Diagnosis of hypothalamic-pituitary-gonadal dysfunction.

Stimulit *Fahrenheit, Indon.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Stimulnerv *Columbia, Arg.*
Ginseng (p. 2513·3); glucurolactone (p. 2517·1); phosphorylcolamine (p. 2589·3); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1); vitamin B_{12} (p. 2107·2).
Tonic.

Stimuloton *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Stimunal *Terali, Fr.*
Capsules; syrup: Vitamins; minerals.

Terali, Fr.
Spray: Copper gluconate (p. 2057·2); ascorbic acid (p. 2110·3); pyridoxine hydrochloride (p. 2105·3); calendula (p. 2465·2).
Cleansing of nose, mouth, and throat.

Stimuno *Dexa, Indon.*
Phyllanthus niruri (p. 2590·1).
Immunomodulator.

Stimuplexe *Lehning, Fr.†*
Cobalt gluconate (p. 2482·2); manganese glycerophosphate (p. 2519·2); zinc gluconate (p. 2126·2); copper gluconate (p. 2057·2); lysine hydrochloride (p. 2079·3); phosphoric acid (p. 2589·1).
Asthenia.

Stimu-TSH *Ferring, Fr.†*
Protirelin (p. 2344·2).
Diagnosis of hypothalamic-pituitary-thyroid dysfunction.

Stimycine *Stiefel, Belg.; GSK, Fr.*
Erythromycin (p. 291·2).
Acne.

Sting Stop *Canadian Custom Packaging, Canad.*
Benzalkonium chloride (p. 1737·1).

Sting-Eze *Wisconsin Pharmacal, USA.*
Diphenhydramine hydrochloride (p. 626·2); camphor (p. 2466·2); phenol (p. 1763·3); benzocaine (p. 1980·2); cineole (p. 2479·1).
Pruritus.

Sting-Kill *Randob, USA.*
Benzocaine (p. 1980·2); menthol (p. 2553·2).
Insect bites and stings; minor skin irritation.

Stingose *Johnson & Johnson, Austral.; Hamilton, Hong Kong†; Johnson & Johnson, NZ; Thornton & Ross, UK.*
Aluminium sulfate (p. 2440·2).
Bites and stings.

Stioxyl *GSK, Swed.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Stipatin *Vera, Hung.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; atherosclerosis.

Stiprox *Stiefel, Braz.; Stiefel, Chile; GSK, Fr.; Stiefel, Ital.; Stiefel, Mex.*
Ciclopirox olamine (p. 575·3).
Dandruff; seborrhoeic dermatitis; fungal skin infections; scalp disorders.

Stiproxal *GSK, Fr.*
Ciclopirox olamine (p. 575·3); salicylic acid (p. 1719·1); menthol (p. 2553·2).
Dandruff.

Stisamet *Retinoids, Rus.*
Methyluracil.
Burns; ulcers; wounds.

Stivarga *Bayer, Jpn; Bayer, Switz.; Bayer, UK; Bayer, USA.*
Regorafenib (p. 851·2).
Colorectal cancer; gastrointestinal stromal tumors.

Stivate *Stiefel, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Stixenil *Alter, Ital.*
Bisacodyl (p. 1821·1).
Constipation.

Stobiol *Pharos, Indon.*
Bismuth salicylate (p. 1821·3).
Diarrhoea; dyspepsia.

Stobled *Ethica, Indon.*
Ginseng (p. 2513·3); borneol (p. 2460·2); dioscorea rhizome; geranium herb; herba erodii; rhizoma menispermi.
Haemorrhage.

Stobol *Help, Gr.*
⊗Carteolol hydrochloride (p. 1332·3).

Stocof *Chew, Thai.*
Guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2).
Cough; nasal congestion.

Stocol *Chinta, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); terpin hydrate (p. 1678·2); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Stocrin *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD, Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, Venez.*
Efavirenz (p. 975·1).
HIV infection.

Stodal *Boiron, Canad.*
Pulsatilla (p. 2600·2); antimonium tartaricum (p. 151·2); bryonia dioica (p. 2461·3); coccus cacti (p. 2179·2); ipecacuanha (p. 1667·2); drosera (p. 2497·2).
Homoeopathic preparation.

Boiron, Cz.
Pulsatilla (p. 2600·2); yellow dock (p. 2649·3); bryonia (p. 2461·3); ipecacuanha (p. 1667·2); euspongia officinalis; sticta pulmonaria (p. 2546·1); kalii stibii tartras; myocardium (p. 2444·1); dactylopius coccus (p. 2179·2); drosera (p. 2497·2); tolu balsam (p. 1679·2); senega (p. 1677·2).
Homoeopathic preparation.

Boiron, Fr.
Oral granules: Anemone pulsatilla (p. 2600·2); rumex crispus (p. 2649·3); bryonia dioica (p. 2461·3); ipecacuanha (p. 1667·2); spongia tosta; sticta pulmonaria (p. 2546·1); antimonium tartaricum (p. 151·2); myocarde; coccus cacti (p. 2179·2).
Homoeopathic preparation.

Boiron, Fr.; Boiron, Port.
Anemone pulsatilla (p. 2600·2); rumex crispus (p. 2649·3); bryonia dioica (p. 2461·3); ipecacuanha (p. 1667·2); spongia tosta; sticta pulmonaria (p. 2546·1); antimonium tartaricum (p. 151·2); myocarde; coccus cacti (p. 2179·2); drosera (p. 2497·2); tolu balsam syrup (p. 1679·2); senega syrup (p. 1677·2).
Homoeopathic preparation; cough.

Boiron, Hung.
Pulsatilla vulgaris (p. 2600·2); rumex crispus (p. 2649·3); bryonia dioica (p. 2461·3); ipecacuanha (p. 1667·2); spongia tosta; sticta pulmonaria (p. 2546·1); antimonium tartaricum (p. 151·2); myocardium; coccus cacti (p. 2179·2); drosera (p. 2497·2).
Homoeopathic preparation.

Boiron, Rus.
Pulsatilla (p. 2600·2); rumex crispus (p. 2649·3); bryony (p. 2461·3); ipeca (p. 1667·2); spongia tosta; sticta pulmonaria (p. 2546·1); antimonium tartaricum (p. 151·2); myocarde; coccus cacti (p. 2179·2); drosera (p. 2497·2).
Homoeopathic preparation.

Boiron, Neth.
Antimonium tartaricum (p. 151·2); bryonia alba; coccus cacti (p. 2179·2); drosera rotundifolia (p. 2497·2); ipecacuanha (p. 1667·2); pulsatilla vulgaris (p. 2600·2); rumex crispus (p. 2649·3); spongia tosta; sticta pulmonaria (p. 2546·1).
Homoeopathic preparation.

Boiron, Switz.
Bryonia cretica; cephaelis ipecacuanha; dactylopius coccus (p. 2179·2); drosera (p. 2497·2); euspongia officinalis; kalii stibyli tartras (p. 151·2); lobaria pulmonaria (p. 2546·1); pulsatilla pratensis (p. 2600·2); rumex crispus (p. 2649·3).
Homoeopathic preparation.

Boiron, Ukr.
Anemone pulsatilla (p. 2600·2); rumex crispus (p. 2649·3); bryonia dioica (p. 2461·3); ipecacuanha (p. 1667·2); spongia tosta; sticta pulmonaria (p. 2546·1); antimonium tartaricum (p. 151·2); myocardium (p. 2444·1); coccus cacti (p. 2179·2); drosera (p. 2497·2).
Homoeopathic preparation.

Stodette *Medico Uno, Cz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Stofilan *Takeda, Belg.; Lek, Hong Kong.†*
Codergocrine mesilate (p. 389·2).
Mental function impairment; cerebral and peripheral circulatory disorders; migraine and other vascular headache; hypertension.

Stogar *UCB, Jpn.†*
Lafutidine (p. 1851·3).
Peptic ulcer.

Stoke'Liniment Sahakarn *United Drug, Thai.*
Methyl salicylate (p. 92·1); turpentine oil (p. 2636·3); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Stoko *Stockhausen, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Stoko Hand Sanitizer *Stockhausen, Canad.*
⊗Alcohol (p. 1733·1).
Skin disinfection.

Stolax *Sanbe, Indon.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Stolina *Almirall, Spain.*
Cyproheptadine cyclamate (p. 624·1); amino acids; cyanocobalamin (p. 2107·2).
Anorexia; weight loss; tonic.

Stomaax Plus *Atlas, Canad.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Stomac *Greater Pharma, Thai.*
Oral liquid gel: Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis.

Greater Pharma, Thai.†
Tablets: Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); atropine sulfate (p. 1310·2); peppermint oil (p. 1877·1).
Peptic ulcer; gastric hyperacidity; gastritis.

Stomacain *Combiphar, Indon.*
Aluminium hydroxide-magnesium carbonate-calcium carbonate coprecipitate (p. 1818·2) (p. 1824·3).
Gastric hyperacidity; peptic ulcer; gastritis; dyspepsia.

Stomacer *Sandoz, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Stomach Calm *Brauer, Austral.*
Aloe; carbo veg. (p. 1537·3); chelidonium (p. 2522·2); hydrastis (p. 2528·1); lycopodium (p. 2546·3); nux vomica (p. 2573·3); podophyllum (p. 1717·1).
Homoeopathic preparation.

Stomach Comfort *Natures Sunshine, Canad.*
Alginic acid (p. 2167·2); calcium carbonate (p. 1824·3).
Heartburn.

Stomach Ease *SunOpta, Canad.*
Buchu (p. 2461·3); cascara (p. 1826·1); gentian (p. 2512·1); liquorice (p. 1853·2); juniper (p. 2537·1); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Stomach Mixture *Potter's, UK.*
Bismuth and ammonium citrate (p. 1821·3); taraxacum (p. 2625·3); gentian root (p. 2512·1); compound rhubarb tincture (p. 1884·2).
Dyspepsia.

Stomacid
Note: this name may be used for preparations of different composition.
Orifarm, Swed.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Qualiphar, Belg.
Aluminium oxide (p. 1690·3); magnesium hydroxide (p. 1857·2).
Antacid.

Stomacine
Note: this name may be used for preparations of different composition.
Plan, Switz.
⊗Pepsin (p. 2586·1); condurango (p. 2485·3); cardamom (p. 2471·1); quassia (p. 2601·1).
Digestive disorders; flatulence; meteorism; loss of appetite.

TRB, Arg.
Omeprazole (p. 1867·2).

Stomadon *Soho, Indon.†*
Belladonna (p. 2453·3); peppermint oil (p. 1877·1); aluminium magnesium silicate (p. 2168·2).
Peptic ulcer; gastric hyperacidity.

Stoma-Gastreu S R5 *Reckeweg, Ger.*
Anacardium (p. 2471·3); belladonna (p. 2453·3); carbo vegetabilis (p. 1537·3); chamomilla (p. 2474·1); lycopodium (p. 2546·3).
Homoeopathic preparation.

Stomagel *Darya-Varia, Indon.*
Calcium carbonate (p. 1824·3); magnesium trisilicate (p. 1858·1); silicone emulsion SE-2; bentonite (p. 2170·3).
Peptic ulcer; gastritis; dyspepsia; flatulence; heartburn; gastric hyperacidity.

Stomahesive *BMS, NZ.*
Topical paste; topical powder: ⊗Carmellose sodium (p. 2175·2); gelatin (p. 1154·1); pectin (p. 2200·3).
Stoma care.

Convatec, Austral.
Topical paste: Butyl monoester polymer with ethanol.
Colostomies and ileostomies.

Convatec, Austral.; Convatec, UK.
Wafer: Topical wafer: ⊗Carmellose sodium (p. 2175·2); gelatin (p. 1154·1); pectin (p. 2200·3); polyisobutylene (p. 2202·3).
Colostomies and ileostomies; stoma care.

Stomahésive *Convatec, Fr.†*
Barrier paste.
Fistulae; stoma care.

Stomak-Care *Novartis Consumer, Canad.*
Bismuth salicylate (p. 1821·3).

Stomaran *Leros, Cz.*
Calamus (p. 2464·2); angelica (p. 2443·3); chamomile (p. 2474·1); centaury (p. 2473·2); St John's wort (p. 449·1); agrimony (p. 2432·3); peppermint leaf (p. 1877·1); rubus fruticosus; fennel (p. 2503·2).
Digestive disorders; reduced appetite.

Stomargil *Motima, Fr.*
Myrtillus (p. 2566·2); argile verte (illite); vegetable charcoal (p. 1537·3); cinnamon oil (p. 2479·3); melissa oil (p. 2553·2).
Digestive disorders.

Stomatidin *Bosnalijek, Ukr.*
Hexetidine (p. 1755·1).
Bacterial and fungal infections of the mouth and throat.

Stomatidine *Bosnalijek, Rus.*
Hexetidine (p. 1755·1).
Mouth and throat disorders.

Stomatophit *Phytopharm, Rus.*
Calamus (p. 2464·2); arnica (p. 2447·2); oak bark (p. 2574·1); peppermint leaf (p. 1877·1); chamomile (p. 2474·1); thyme (p. 2630·2); sage (p. 2608·3).
Mouth inflammation.

Stomatophyt *Phytopharm, Ukr.*
Oak bark (p. 2574·1); chamomile (p. 2474·1); sage (p. 2608·3); arnica (p. 2447·2); thyme (p. 2630·2); peppermint (p. 1877·1); calamus (p. 2464·2).
Mouth and gum inflammation.

Stomatophyt A *Phytopharm, Ukr.*
Oak bark (p. 2574·1); chamomile (p. 2474·1); sage (p. 2608·3); arnica (p. 2447·2); thyme (p. 2630·2); peppermint (p. 1877·1); calamus (p. 2464·2); benzocaine (p. 1980·2).
Mouth and gum inflammation.

Stomatosol *Elanda, Pol.*
Arnica (p. 2447·2); oak (p. 2574·1); tormentil (p. 2633·2).
Mouth disorders.

Stomec *Medicine Products, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Stomédine *GSK Sante, Fr.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity.

Stomedine *Osoth, Thai.*
Cimetidine (p. 1827·1).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Stomex *Key, Austral.*
Hyoscine butylbromide (p. 1845·3).
Gastrointestinal spasm.

Stomffler *Loeffler, Mex.*
Metronidazole benzoate (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Stomffler Plus *Loeffler, Mex.*
Metronidazole benzoate (p. 936·1); diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Stomica *Pharos, Indon.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Stompax *Sinnex, Hung.*
Fennel oil (p. 2503·3); caraway oil (p. 2470·3); peppermint oil (p. 1877·1); chamomile oil (p. 2474·1).
Gastrointestinal disorders.

Stomygen *Stomygen, Ital.*
Mouth spray: Cetylpyridinium chloride (p. 1743·1).
Halitosis.

Stomygen, Ital.
Mouthwash: Sodium monofluorophosphate (p. 2091·3); cetylpyridinium chloride (p. 1743·1).
Oral hygiene.

Stona Cold Caplets *Sato, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); guaifenesin (p. 1666·2).

Stona Cold Tablet *Sato, Singapore.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).

Stongel *Cazi, Braz.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Stool Softener *Banner, Canad.; Pharmascience, Canad.; Vita Health, Canad.*
Docusate sodium (p. 1836·2).

Stop *Oral-B, USA.*
Stannous fluoride (p. 2094·3).
Dental caries prophylaxis.

Stop X *Pharos, Indon.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); eugenol (p. 2501·2); benzyl nicotinate (p. 29·3).
Musculoskeletal and joint pain; neuralgia.

Stop Bleed *Gerolymatos, Hong Kong.*
Oxidised cellulose (p. 1157·3).
Haemorrhage.

Stop Cold *Darya-Varia, Indon.; Pharos, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); triprolidine hydrochloride (p. 642·3); guaifenesin (p. 1666·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; fever.

Stop Espinilla Normaderm *Capilares, Spain.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Stop Hemo *Avgerinos, Gr.*
Calcium alginate (p. 1136·3).
Haemostatic.

Stop Hémo *Brothier, Fr.*
Calcium alginate (p. 1136·3).
Wounds; burns; skin disorders.

Stop Itch
Note: this name may be used for preparations of different composition.
Dermatech, Austral.; Balmar, NZ.
⊗Papain (p. 2582·3).
Skin irritation; insect bites; jelly fish stings; minor burns; skin rashes.

Stop Snoring *Essential Health, Singapore.*
Peppermint (p. 1877·1); lemon (p. 2542·3); clove (p. 2481·2); pine silvestris; fennel (p. 2503·2); sage (p. 2608·3); thyme (p. 2630·2); melissa (p. 2552·3); eucalyptus; lavender (p. 2541·1); pistacia lentiscus.
Snoring.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Stopain
Note: this name may be used for preparations of different composition.
Chew, Thai.
Cream: Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); thymol (p. 1772·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal pain.

Chew, Thai.
Topical gel: Menthol (p. 2553·2).
Musculoskeletal pain.

Stopain Cold *Troy, USA.*
Menthol (p. 2553·2).
Musculoskeletal and joint pain.

Stopain Cold Extra Strength *Troy, USA.*
Menthol (p. 2553·2); dimethyl sulfone (p. 2493·3); glucosamine sulfate (p. 2515·3).
Musculoskeletal and joint pain.

Stopaler *LKM, Arg.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Stop-Allerg *Genop, S.Afr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Stopan *Anpharm (Ανφαρμ), Gr.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Stopangin *Ivax, Rus.*
Hexetidine (p. 1755·1); methyl salicylate (p. 92·1); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); neroli oil (p. 2568·3); sassafras oil (p. 2610·3); peppermint oil (p. 1877·1); menthol (p. 2553·2).
Mouth and throat disorders.

Teva, Cz.
Gargle: Hexetidine (p. 1755·1); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); sassafras oil (p. 2610·3); peppermint oil (p. 1877·1); clove oil (p. 2481·3).
Mouth and throat disorders.

Teva, Cz.
Throat spray: Hexetidine (p. 1755·1); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); neroli oil (p. 2568·3); sassafras oil (p. 2610·3); peppermint oil (p. 1877·1).
Mouth and throat disorders.

Teva, Ukr.
Mouthwash: Hexetidine (p. 1755·1) anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); sassafras oil (p. 2610·3); peppermint oil (p. 1877·1); clove oil (p. 2481·3).
Bacterial and fungal infections and inflammation of the mouth and throat.

Teva, Ukr.
Mouth and throat spray: Hexetidine (p. 1755·1) anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); sassafras oil (p. 2610·3); peppermint oil (p. 1877·1); neroli oil (p. 2568·3).
Bacterial and fungal infections and inflammation of the mouth and throat.

Stoparen *Anfarm, Gr.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Stopayne *Adcock Ingram, S.Afr.*
Capsules; tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain; fever.

Adcock Ingram, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

StopBleed *Ransom, UK.*
Micro-dispersed oxidised cellulose (p. 1157·3).
Minor cuts and grazes.

Stopcold *Vedim, Spain.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Stopen *Berman, Mex.*
Di-iodo-kaolin-pectin-sulfa.
Diarrhoea; gastrointestinal infections.

Stoperan *US Pharmacia, Pol.; US Pharmacia, Ukr.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Stopex
Note: this name may be used for preparations of different composition.
Walmark, Cz.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Stopgripan *Ratiopharm, Rus.; Ratiopharm, Ukr.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Stopit *Rafa, Israel.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Stopitch
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Stop-Itch Plus *Dermatech, Singapore.*
⊗Papain (p. 2582·3); hamamelis (p. 2523·3); sodium pidolate (p. 1720·3).
Insect bites; jelly fish stings; rashes; scratches; minor burns; sunburn.

Stoplip *Apotex, Hung.†*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Stop-Mag *Medikon, Indon.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Stopmun *Medikon, Indon.†*
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting.

Stoppot *Parafarm, Pol.*
Methenamine (p. 322·3).
Foot hyperhidrosis.

Stopress *Polpharma, Pol.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Stoptoss *Delta, Braz.†*
Ammonium chloride (p. 1656·1); diphenhydramine hydrochloride (p. 626·2).
Cough.

Stoptussin *Teva, Cz.; Ivax, Rus.; Teva, Ukr.*
Butamirate citrate (p. 1657·3); guaifenesin (p. 1666·2).
Cough.

Stoptussin Fito *Teva, Ukr.*
Wild thyme (p. 2648·1) thyme (p. 2630·2); plantain (p. 2592·3).
Respiratory tract inflammatory disease.

Stoptussin-Fito *Ivax, Rus.*
Plantago (p. 2604·2); thyme (p. 2630·2); wild thyme (p. 2648·1).
Cough.

Stopvom *Cadila, India.*
Domperidone (p. 1838·1).
Nausea and vomiting.

Storilat *Remedica, Singapore.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder.

Storvas *Ranbaxy, Malaysia; Ranbaxy, Pol.; Ranbaxy, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Stoxil *Dermatech, Austral.†*
Idoxuridine (p. 985·1).
Herpes simplex infections of the skin and mucous membranes.

Stozzon *Queisser, Ger.*
Chlorophyllin copper complex sodium (p. 2178·3).
Halitosis.

ST-Pase *Cadila, Philipp.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

STpase *Cadila, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

STP-free *Sanofi-Aventis, Neth.†*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Strabone *Bilim, Turk.*
Calcitonin (salmon) (p. 1178·1).

Stradexa *Eurolab, S.Afr.*
⊗Anastrozole (p. 742·1).

Stradumel *Pharmathen, Gr.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Strain care *Dossier, Neth.*
Rhus toxicodendron (p. 2603·3); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Strains Cream *Nelson, UK.*
Ruta graveolens (p. 2608·2).
Homoeopathic preparation.

Strakir *Genthon, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Strand *Radelkis, Hung.*
⊗Acetic acid (p. 2426·3); sodium acetate (p. 1781·1); glycerol (p. 2517·2).
Ear disorders.

Stranoval *Teofarma, Ital.*
⊗Betamethasone valerate (p. 1624·1); dextran sulfate (p. 2492·2).
Skin disorders.

Strataderm *Stratpharma, Singapore.*
Silicones (p. 2209·2).
Scars.

Stratasin *Landsteiner, Mex.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain; gout.

Strath Gouttes contre la toux *Bio-Strath, Switz.*
Thyme (p. 2630·2); cowslip (p. 2596·2); yeast lysate (p. 2125·2).
Cough.

Strath Gouttes pour le foie et la bile *Bio-Strath, Switz.*
Thistle seed; cynara (p. 2490·3); mint leaf; yeast lysate (p. 2125·2).
Digestive system disorders.

Strath Gouttes pour l'estomac *Bio-Strath, Switz.*
Chamomile (p. 2474·1); liquorice (p. 1853·2); gentian (p. 2512·1); yeast lysate (p. 2125·2).
Digestive-system disorders; loss of appetite.

Strath Gouttes pour les muqueuses *Bio-Strath, Switz.*
Sage (p. 2608·3); chamomile (p. 2474·1); yeast lysate (p. 2125·2).
Mouth and throat inflammation.

Strath Gouttes pour le nerfs et contre l'insomnie *Bio-Strath, Switz.*
Valerian (p. 2640·2); passion flower (p. 2584·1); mint leaf; yeast lysate (p. 2125·2).
Nervous disorders; sleep disorders.

Strath Gouttes pour les reins et la vessie *Bio-Strath, Switz.*
Bearberry (p. 2453·2); taraxacum (p. 2625·3); yeast lysate (p. 2125·2).
Urinary-tract disorders.

Stratofer *Chemi, Ital.*
Iron succinyl-protein complex (p. 2077·3).
Iron-deficiency anaemia.

Strattera *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.†; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Irl.; Lilly, Ital.; Lilly, Jpn; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, Ukr.; Lilly, USA.*
Atomoxetine hydrochloride (p. 2316·3).
Attention-deficit hyperactivity disorder.

Strazal *Alapis, Gr.*
⊗Anastrozole (p. 742·1).

Strefen *Reckitt Benckiser, Denm.; Reckitt Benckiser, Fr.; Reckitt Benckiser, Spain; Crookes Healthcare, UK.*
Flurbiprofen (p. 65·2).
Sore throat.

Stremycil-T *Demo, Gr.*
Co-trimoxazole (p. 277·3).

Strength *Potter's, UK.*
Damiana (p. 2491·3); kola (p. 2648·2); saw palmetto (p. 2363·3).
Tonic.

Strepfen *Reckitt Benckiser, Austral.; Reckitt Benckiser, Austria†; Reckitt Benckiser, Belg.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Gr.; Reckitt Benckiser, Hung.; Reckitt Benckiser, Neth.; Boots Healthcare, NZ; Reckitt Benckiser, Port.; Reckitt Benckiser, Rus.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Switz.*
Flurbiprofen (p. 65·2).
Sore throat.

Strepflam *Reckitt Benckiser, Neth.*
Flurbiprofen (p. 65·2).
Sore throat.

Strepsils *Reckitt Benckiser, Arg.; Reckitt Benckiser, Austral.; Reckitt Benckiser, Belg.; Reckitt Benckiser, Canad.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Denm.; Reckitt Benckiser, Fin.; Reckitt Benckiser, Fr.; Reckitt Benckiser, Gr.; Vianex (Βιανεξ), Gr.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Hung.; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Neth.; Reckitt Benckiser, NZ; Reckitt Benckiser, Philipp.; Reckitt Benckiser, Pol.; Reckitt Benckiser, Port.; Reckitt Benckiser, Rus.; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Spain; Reckitt Benckiser, Swed.; Reckitt Benckiser, Switz.; Abdi, Turk.; Crookes Healthcare, UK; Reckitt Benckiser, Ukr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat; mouth disorders; stomatitis.

Boots, Philipp.
Gargle: Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); chloroxylenol (p. 1748·2).
Sore throat.

Reckitt Benckiser, Austria; Reckitt Benckiser, Braz.
Flurbiprofen (p. 65·2).
Sore throat.

Strepsils Anesthetic Formula *Reckitt Benckiser, Canad.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Strepsils Butter Menthol Capsicum *Reckitt Benckiser, Thai.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Strepsils C *Abdi, Turk.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); vitamin C (p. 2110·3).
Sore throat.

Strepsils Cherry *Reckitt Benckiser, Canad.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Sore throat; nasal congestion.

Strepsils Chesty Cough
Note: this name may be used for preparations of different composition.
Reckitt Benckiser, Malaysia; Reckitt Benckiser, Philipp.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.
Ambroxol hydrochloride (p. 1654·3).
Cough; respiratory-tract congestion.

Strepsils Cool *Reckitt Benckiser, Canad.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2).

Reckitt Benckiser, Irl.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Strepsils Cool Mint *Reckitt Benckiser, Belg.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Sore throat.

Strepsils Cooling Mint *Reckitt Benckiser, Cz.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Strepsils Cough Lozenge *Reckitt Benckiser, Malaysia.†*
Liquorice (p. 1853·2); ocimum sanctum; malabar nut (p. 2549·1); piper longum; ginger (p. 1844·1).
Cough; sore throat.

Strepsils Cough Lozenge (with natural herbs) *Reckitt Benckiser, Singapore.*
Liquorice (p. 1853·2); ocimum sanctum; malabar nut (p. 2549·1); piper longum; ginger (p. 1844·1).
Cough.

Strepsils Cough Relief *Reckitt Benckiser, Austral.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Strepsils Cough Syrup *Reckitt Benckiser, Malaysia†; Reckitt Benckiser, Singapore.†*
Malabar nut (p. 2549·1); ocimum sanctum; liquorice (p. 1853·2); hedychium spicatum; ginger (p. 1844·1); piper longum.
Cough; respiratory-tract congestion; sore throat; cold symptoms.

Strepsils Dry Cough *Reckitt Benckiser, NZ; Reckitt Benckiser, Philipp.; Reckitt Benckiser, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Strepsils Dual Action *Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); lidocaine hydrochloride (p. 1988·2).
Sore throat.

Boots Healthcare, Irl.†
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Sore throat.

Strepsils Echinacea Defence *Boots Healthcare, NZ.†*
Ascorbic acid (p. 2110·3); echinacea (p. 2498·1).
Cold symptoms.

Strepsils Eucalyptus Menthol *Reckitt Benckiser, S. Afr.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Sore throat.

Strepsils Extra *Reckitt & Colman, Austral.†; Reckitt Benckiser, Irl.; Crookes Healthcare, UK.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Reckitt Benckiser, Canad.
Hexylresorcinol (p. 1755·1); levomenthol (p. 2553·2).
Sore throat.

Strepsils Intensiv *Reckitt Benckiser, Ukr.*
Flurbiprofen (p. 65·2).
Sore throat.

Strepsils Intensive *Reckitt Benckiser, Irl.; Reckitt Benckiser, Pol.; Reckitt Benckiser, S.Afr.*
Flurbiprofen (p. 65·2).
Sore throat.

Strepsils Lidocaina *Reckitt Benckiser, Spain.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine (p. 1988·1).
Mouth and throat disorders.

Strepsils Lidocaïne *Reckitt Benckiser, Fr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine hydrochloride (p. 1988·2).
Sore throat; mouth disorders.

Strepsils + Lidocaine *Reckitt Benckiser, Belg.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Mouth disorders; sore throat.

Strepsils Max *Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Strepsils Max Plus *Reckitt Benckiser, Singapore.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); lidocaine hydrochloride (p. 1988·2).
Formerly known as Strepsils Dual Action.
Sore throat.

Strepsils Maxipluzz *Reckitt Benckiser, Thai.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine hydrochloride (p. 1988·2).
Formerly known as Strepsils Plus Anaesthetic.
Sore throat.

Strepsils Menthol *Reckitt Benckiser, Belg.†; Reckitt Benckiser, Fin.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Mouth and throat disorders; nasal congestion; sore throat.

Strepsils Menthol a Eucalyptus *Reckitt Benckiser, Cz.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Strepsils Menthol and Eucalyptus *Reckitt Benckiser, Hung.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Strepsils with Menthol and Eucalyptus *Reckitt Benckiser, Israel.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Strepsils Menthol & Eucalyptus *Reckitt Benckiser, Neth.†*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Strepsils Mentol *Abdi, Turk.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Sore throat.

Strepsils Miel-Citron *Reckitt Benckiser, Fr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Strepsils Numbing *Reckitt Benckiser, Austral.*
Lidocaine hydrochloride (p. 1988·2); dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Strepsils Orange-C *Reckitt Benckiser, S.Afr.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); ascorbic acid (p. 2110·3); menthol (p. 2553·2).
Sore throat.

Strepsils Pain Relief *Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia.†*
Hexylresorcinol (p. 1755·1).
Sore throat.

Strepsils Plus *Reckitt Benckiser, Arg.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Gr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine (p. 1988·1).
Reckitt Benckiser, Austral.†; Reckitt Benckiser, Hung.; Reckitt Benckiser, Israel; Reckitt Benckiser, Rus.; Reckitt Benckiser, S. Afr.; Reckitt Benckiser, Ukr.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine hydrochloride (p. 1988·2).
Sore throat; mouth and throat disorders.

Strepsils Plus Anaesthetic *Boots Healthcare, NZ.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine hydrochloride (p. 1988·2).
Sore throat.

Strepsils +Plus Anaesthetic *Reckitt Benckiser, Irl.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); lidocaine hydrochloride (p. 1988·2) or lidocaine (p. 1988·1).
Sore throat.

Strepsils Plus Vit C *Reckitt Benckiser, Thai.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); vitamin C (p. 2110·3).
Sore throat.

Strepsils Sinaasappel & Vitamine C *Reckitt Benckiser, Neth.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); ascorbic acid (p. 2110·3).
Sore throat.

Strepsils Soothing Honey & Lemon *Reckitt Benckiser, S.Afr.†*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Strepsils Sore Throat Blocked Nose *Reckitt Benckiser, Canad.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); menthol (p. 2553·2).
Sore throat.

Strepsils Sore Throat and Blocked Nose *Reckitt Benckiser, Irl.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); levomenthol (p. 2553·2).
Sore throat; nasal congestion.

Strepsils Sugar Free *Reckitt Benckiser, Thai.†*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2).
Sore throat.

Strepsils Throat *Reckitt Benckiser, Irl.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Strepsils Vit C *Reckitt Benckiser, Belg.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Mouth disorders; sore throat.

Strepsils with Vitamin C *Reckitt Benckiser, Israel; Boots Healthcare, NZ; Reckitt Benckiser, Rus.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); ascorbic acid (p. 2110·3).
Sore throat; mouth and throat disorders.

Crookes Healthcare, UK.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); sodium ascorbate (p. 2111·1).
Sore throat.

Reckitt Benckiser, Switz.
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Sore throat.

Strepsils Vitamin C *Reckitt Benckiser, Cz.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); sodium ascorbate (p. 2111·1).
Sore throat.

Reckitt Benckiser, Hung.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Sore throat.

Reckitt Benckiser, Irl.
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); vitamin C (p. 2110·3).
Sore throat.

Strepsils con Vitamina C *Reckitt Benckiser, Spain.*
Sodium ascorbate (p. 2111·1); ascorbic acid (p. 2110·3); dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Sore throat.

Strepsils Vitamine C *Reckitt Benckiser, Fr.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Sore throat.

Strepsils Zinc Cold Relief *Reckitt & Colman, Austral.†*
Zinc gluconate (p. 2126·2); sodium ascorbate (p. 2111·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Strepsils Zinc Defence *Boots Healthcare, NZ.*
Ascorbic acid (p. 2110·3); zinc gluconate (p. 2126·2).
Cold symptoms.

Strepsilspray *Reckitt Benckiser, Fr.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2); lidocaine (p. 1988·1).
Sore throat; mouth disorders.

Strepsinol *Reckitt Benckiser, Cz.†*
Hexylresorcinol (p. 1755·1).
Mouth and throat disorders.

Streptase *CSL, Arg.; CSL Biotherapies, Austral.†; ZLB, Belg.†; CSL, Braz.; CSL, Canad.†; CSL, China; CSL, Cz.; CSL, Denm.; CSL, Fr.; CSL, Ger.; Hoechst Marion Roussel, Gr.; CSL Biotherapies, Hong Kong; CSL, Hung.; Sanofi-Aventis, India; CSL, Indon.; Dexa, Indon.; Aventis Behring, Israel; CSL, Mex.; CSL, Neth.; CSL, NZ; CSL, Pol.; CSL, Port.; Hoechst Marion Roussel, Rus.; Mirren, S.Afr.; Sanofi-Aventis, Singapore; CSL, Spain†; CSL, Swed.; CSL, Switz.†; Sanofi-Aventis, Thai.; Farma-Tek, Turk.; CSL, UK; CSL, USA; Sanofi-Aventis, Venez.*
Streptokinase (p. 1503·1).
Thromboembolic disorders; myocardial infarction.

Strepto *General Drugs, Thai.*
Streptomycin sulfate (p. 359·1).
Bacterial infections including tuberculosis.

Streptocide *Yaroslavl, Rus.*
Sulfanilamide (p. 368·1).
Bacterial skin infections.

Streptocol-R *Elpen (Ελπεν), Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

Strepto-Fatol *Fatol, Cz.; Riemser, Ger.†*
Streptomycin sulfate (p. 359·1).
Bacterial infections including tuberculosis.

Strepto-Hefa *Riemser, Ger.†*
Streptomycin sulfate (p. 359·1).
Bacterial infections including tuberculosis.

Streptokin *Cristalia, Braz.; Reyon, Philipp.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Streptomagma
Note: this name may be used for preparations of different composition.
Vargas, Venez.
Oral suspension: Attapulgite (p. 1820·1).
Diarrhoea.

Wyeth, Turk.; Vargas, Venez.
Attapulgite (p. 1820·1); pectin (p. 2200·3).
Diarrhoea.

Wyeth Consumer, Ital.
Oral suspension: Aluminium hydroxide (p. 1817·2); heavy kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Streptonase *Blausiegel, Braz.†*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Streptonitol *Darnitsa, Ukr.*
Sulfanilamide (p. 368·1); aminitrozole (p. 926·2).
Skin infections; ulcers; burns.

Streptosil con Neomicina *Boehringer Ingelheim, Ital.*
Neomycin sulfate (p. 330·1); sulfathiazole (p. 368·3).
Bacterial skin infections.

Streptozyme *Wampole, USA.*
Test for streptococcal extracellular antigens in blood, plasma, and serum.

Streptuss *Boots, Philipp.; Reckitt Benckiser, Spain.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Streptuss-AX *Reckitt Benckiser, Thai.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Stresam *Biocodex, Fr.; Adcock Ingram, S.Afr.; Biocodex, Ukr.*
Etifoxine hydrochloride (p. 1073·1).
Anxiety; nervous disorders.

Stresnil *Aristo, India.*
Melatonin (p. 2551·3); alprazolam (p. 1035·2).
Sleep disorders; anxiety disorders.

Stress *Homeocan, Canad.*
Argentum nitricum (p. 2615·3); asa foetida (p. 2449·3); avena sativa (p. 2451·1); ignatia amara (p. 2532·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Twin Laboratories, Canad.†; Wyeth, India.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiency.

Stress 600 *Nion, USA.*
Vitamins; minerals.

Stress B *Future, Canad.*
Vitamin B substances (p. 2102·3).

Stress B Complex *GFR, Canad.; Pharmetics, Canad.*
A range of vitamin and mineral preparations.

Moore, USA.
Vitamins; minerals.

Stress B Formula W C *Gahler, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Stress Formula *Goldline, USA; Major, USA; Nature's Bounty, USA.*
Vitamins; with or without minerals.

Wampole, Canad.
A range of vitamin preparations with or without minerals.
Nutritional supplement.

Jamp, Canad.†
Vitamins; minerals.

Natures Sunshine, Canad.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Stress L72 *Homeocan, Canad.†*
Asa foetida (p. 2449·3); avena sativa (p. 2451·1); cicuta virosa; corydalis for; hyoscyamus (p. 2530·2); oleum gaultheriae (p. 92·1); staphysagria; sumbulus; ignatia (p. 2532·1); valeriana off (p. 2640·2).
Homoeopathic preparation.

Stress Remedy *Brauer, Austral.*
Clematis vitalba; helianthemum nummularium; impatiens glandulifera; ornithogalum umbellatum; prunus cerasifera.
Bach flower remedy.

Stress with Zinc *Natural Life, Arg.*
Vitamins; copper (p. 2057·1); zinc (p. 2126·1).

Stressan *Teuto, Braz.*
Vitamins; minerals.

Stressdoron *Weleda, Fr.*
Avena sativa (p. 2451·1); ignatia amara (p. 2532·1); kalium phosphoricum (p. 1790·3); aurum (p. 2521·1).
Homoeopathic preparation.

Stressen *Medosan, Ital.*
Amino acids; vitamins.
Tonic.

Stressigal *Anfarm, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Stressless
Note: this name may be used for preparations of different composition.
Alapis, Gr.
Fluoxetine hydrochloride (p. 417·1).
Depression.

Diomed, UK.
Lupulus (p. 2546·1); skullcap (p. 2617·1); valerian (p. 2640·2); vervain (p. 2645·1).
Stress.

Stressliv *Cifarma, Braz.*
Vitamins; minerals.

Stresson
Note: this name may be used for preparations of different composition.
Nutricia, China; Nutricia, Turk.†
Preparation for enteral nutrition.

Nutricia, NZ.†
Preparations for enteral nutrition.

Stressout *Progen, Ital.*
Tryptophan (p. 453·2); magnesium (p. 1786·3); melatonin (p. 2551·3); St John's wort (p. 449·1).
Tonic; anxiety; sleep disorders.

Stress-Relax *Bioglan, Austral.†*
St John's wort (p. 449·1).
Anxiety; nervous disorders.

Stresstabs *Wyeth Consumer, Arg.; Wyeth Consumer, Mex.; Pfizer Consumer, Thai.; Lederle, USA.*
Vitamins; with or without minerals.

Pfizer Consumer, Canad.
A range of vitamin preparations with or without minerals.

Pfizer Consumer, Singapore.
Vitamins; minerals.

Whitehall, Braz.
Vitamins; zinc sulfate (p. 2126·2); copper oxide (p. 2057·1).

Wyeth, Philipp.
Vitamins; iron (p. 2073·1).
Nutritional supplement; tonic.

Stresstabs with Zinc *Neopharm, Israel.†*
Vitamins; copper (p. 2057·1); zinc (p. 2126·1).

Stresstein *Sandoz Nutrition, USA.*
Preparation for enteral nutrition.
Stress.

Strevit *Lloyd, Philipp.*
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3); chlorella (p. 2475·3).
Dietary supplement.

Strezam *Biocodex, Rus.*
Etifoxine hydrochloride (p. 1073·1).
Anxiety; depression.

Striacol *Solara, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Striadyne *Genopharm, Fr.*
Adenosine triphosphate, disodium salt (p. 2430·3).
Arrhythmias.

Striafissan *Cana, Gr.*
Benzyl nicotinate (p. 29·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1); vitamin F (p. 2509·2).
Stretch marks prophylaxis.

Strialisin *MDM, Ital.*
Thiocolchicoside (p. 2026·2).
Neuromuscular pain; parkinsonism; spasticity.

Striant *CytoChemia, Ger.†; Ardana, Irl.†; Mipharm, Ital.; Ardana, Neth.†; Ardana, Port.†; Ardana, UK; Actient, USA.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency; male hypogonadism.

Striatal *Tecnifar, Port.*
α-Dihydroergocryptine mesilate (p. 390·2).
Parkinsonism.

Striaton *Abbott, Ger.†*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Striatridin *Opfermann, Ger.†*
Emollient.
Stretch marks.

Stribild *Japan Tobacco, Jpn; Gilead, UK; Gilead, USA.*
Elvitegravir (p. 976·2); cobicistat (p. 2482·3); emtricitabine (p. 976·3); tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Stricef *Biofarma, Venez.*
Cefalexin (p. 234·1).
Bacterial infections.

Stricort *Biofarma, Venez.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Stri-Dex Antibacterial Cleansing *Sterling, USA.*
Triclosan (p. 1773·2).

Stri-Dex Clear *Sterling, USA.*
Salicylic acid (p. 1719·1).

Stri-Dex Face Wash *Sterling Health, USA.*
Triclosan (p. 1773·2).
Skin cleanser.

Stri-Dex Pads *Glenbrook, USA.*
⊗Salicylic acid (p. 1719·1); alcohol (p. 1733·1).
Acne.

Striex *Floxia, Singapore.*
Barrier preparation.
Stretch marks.

Strimol *Natur Produkt, Rus.*
Paracetamol (p. 115·1).
Fever; pain.

Strimox *Biofarma, Venez.*
Amoxicillin (p. 216·2).
Bacterial infections.

DHA, Singapore.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Strinem *Aspen, Mex.*
Meropenem (p. 321·3).
Bacterial infections.

Strix *Ferrosan, Rus.*
Myrtillus (p. 2566·2); betacarotene (p. 2051·1).
Eye disorders.

Strixone *Lapreven, Venez.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Strizole *Solara, Mex.†*
Ketoconazole (p. 585·3).
Fungal infections.

Strobus *Pharmarte, Ital.*
White pine.
Dietary supplement.

Strocain *Eisai, Hong Kong; Eisai, Singapore; Eisai, Thai.*
Oxetacaine (p. 1993·1); polymigel.
Gastrointestinal disorders.

Eisai, Jpn.
Oxetacaine (p. 1993·1).
Gastrointestinal disorders.

Strocain P *Eisai, Indon.*
Polymigel.
Nausea; gastric hyperacidity; abdominal pain; bloating.

Strodival *Meda, Ger.†*
Ouabain (p. 1463·1).
Arrhythmias; heart failure.

Strogen *Strathmann, Ger.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Strogen Uno *Strathmann, Hung.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Strokan *CCM, Malaysia.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Strolin *Tempo Scan Pacific, Indon.*
Citicoline (p. 2480·1).
Cognitive impairment in the elderly.

Stromag *Guardian, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer.

Stromba *IFET (ΙΦΕΤ), Gr.†*
⊗Stanozolol (p. 2304·2).
Anabolic.

Stromectol *MSD, Austral.; MSD-Chibret, Fr.; IFET (ΙΦΕΤ), Gr.; MSD, Jpn; MSD, Neth.; MSD, NZ; MSD, Singapore; Merck, USA.*
Ivermectin (p. 155·1).
Strongyloidiasis; onchocerciasis; scabies; lymphatic filariasis.

Stromic *Strathmann, Ger.†; Strathmann, Hung.*
Solidago (p. 2620·1).
Kidney disorders; urinary-tract disorders.

Stronazon *Alpharma, UK.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Strong Compound Vitamin *Chew, Thai.*
Vitamin B substances (p. 2102·3).

Strong Pot Chloride *Pharmaland, Thai.*
Potassium chloride (p. 1793·2).

Strongos *Veropharm, Rus.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

StrongStart *Savage, USA.*
Vitamins; minerals.

Strongus *Franconpharm, Ger.†*
Garlic (p. 2510·3).
Hyperlipidaemias.

Strontium Composé *Boiron, Fr.*
Strontium metallicum; tantalum metallicum; osmium metallicum; ganglion grand sympathique; cholesterinum (p. 2179·1); chaerophyllum sativum.
Homoeopathic preparation.

Strophanthus comp *Heel, Ger.*
Crataegus (p. 2488·1); selenicereus grandiflorus (p. 2473·2); nitroglycerinum (p. 1391·2); arnica montana (p. 2447·2); kalmia latifolia (p. 2537·2); spigelia anthelmia (p. 2621·3); kalium carbonicum (p. 2595·2); strophanthus gratus.
Homoeopathic preparation.

Strophantus Composé *Boiron, Fr.*
Strophantus hispidus; aurum muriaticum natronatum (p. 2521·2); camphora (p. 2466·2); valeriana officinalis (p. 2640·2); cactus grandiflorus (p. 2473·2); crataegus oxyacantha (p. 2488·1); aether (p. 1900·3).
Homoeopathic preparation.

Strotan *Strathmann, Ger.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders; mastalgia.

StroVac *Strathmann, Ger.*
Escherichia coli; Morganella morganii; Proteus mirabilis; Klebsiella pneumoniae; Enterococcus faecalis (p. 2596·3).
Urinary-tract infections.

Strovite *Everett, USA.*
Vitamins; with or without minerals.

Strox *Dabur, India.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Strubelin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Structoflex *Pierre Fabre, Fr.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

StructoKabiven *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Ger.†; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Irl.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.†; Fresenius Kabi, Port.; Fresenius Kabi, Spain†; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.*
Amino acids; glucose (p. 2068·3); lipids; with or without electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, Fr.
Amino acids; glucose (p. 2068·3); lipid (from soya oil (p. 2092·3)).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, UK.
Amino acids; glucose (p. 2068·3); lipids.
Contains egg phospholipids.
Parenteral nutrition.

Structolipid *Fresenius Kabi, Austria†; Fresenius Kabi, China; SSPC, China; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.†; Fresenius Kabi, Gr.; Fresenius Kabi, Norw.†; Fresenius Kabi, NZ; Fresenius Kabi, Thai.†*
Triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Fin.; Fresenius Kabi, Hung.†; Fresenius Kabi, Irl.†; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Spain†; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, UK.
Soya oil (p. 2092·3); coconut oil or palm oil triglycerides (p. 2082·2).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Ital.
Triglycerides (p. 2092·3) (p. 2082·2).
Contains egg phospholipid.
Lipid infusion for parenteral nutrition.

Structolipide *Fresenius Kabi, Fr.†*
Triglycerides from coconut oil (p. 2082·2) and soya oil (p. 2092·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Structovial *Pierre Fabre, Fr.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Structum *Rovafarm, Arg.; Pierre Fabre, Cz.†; Pierre Fabre, Fr.; Pierre Fabre, Mex.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Robapharm, Switz.; Pierre Fabre, Ukr.*
Chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis; degenerative joint disorders.

Strumazol *Takeda, Belg.; Organon, Neth.; Organon, Philipp.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Strumeel N *Ebi, Switz.*
Calcium jodatum (p. 1658·1); fucus vesiculosus; spongia.
Homoeopathic preparation.

Strumeel T *Biotecnoquimica, Venez.*
Spongia tosta; calcium jodatum (p. 1658·1); fucus vesiculosus (p. 2612·1).
Homoeopathic preparation.

Stryphnasal N *Truw, Ger.*
Bismuth subgallate (p. 1822·1).
Epistaxis.

STS *Concept, Israel.†*
Sodium tetradecyl sulfate (p. 2620·1).
Varices.

Stuart Formula *J&J-Merck, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Stuart One *Everett, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).

Stuart Prenatal *Integrity, USA.*
Vitamins; minerals; folic acid (p. 2063·1); iron (p. 2073·1).
Dietary supplement in pregnancy.

Stuart prenatal + DHA *Xanodyne, USA.*
Tablets, vitamins; minerals; gelcaps, vitamin E (p. 2119·1); fish oil (p. 1460·1).
Dietary supplement.

Stuartnatal 1+1 *Wyeth-Ayerst, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Dietary supplement in pregnancy.

Stuartnatal Plus *Integrity, USA.*
Vitamins; minerals.

Stud *Pound International, UK.*
Lidocaine (p. 1988·1).
Premature ejaculation.

Stud 100 *Key, Austral.; Trupharm, Israel.*
Lidocaine (p. 1988·1).
Premature ejaculation.

Stugerina *Hexal, Braz.*
Cinnarizine (p. 622·1).
Vertigo.

Stugeron *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Gedeon Richter, Cz.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Gedeon Richter, Hung.; Johnson & Johnson, India; Janssen-Cilag, Indon.; McNeil Healthcare, Irl.; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen, Philipp.; Janssen, Port.; Gedeon Richter, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Johnson & Johnson MSD Consumer, UK; Gedeon Richter, Ukr.; Janssen-Cilag, Venez.*
Cinnarizine (p. 622·1).
Motion sickness; vascular headaches; vertigo; vestibular disorders; nausea and vomiting; migraine; cerebral, peripheral and ocular vascular disorders.

Stugesin *Bryntsalov, Rus.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; motion sickness; migraine.

Stugil *Johnson & Johnson, Philipp.*
Cinnarizine (p. 622·1); domperidone maleate (p. 1838·1).
Vestibular disorders; vertigo; motion sickness.

Stugin *Bangkok Lab & Cosmetic, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine; motion sickness.

Stuidruppels *Aspen, S.Afr.*
Valerian (p. 2640·2); cassia oil (p. 2471·3); nutmeg oil (p. 2573·2); rosemary oil (p. 2607·3); spike lavender oil (p. 2621·3); asafetida (p. 2449·3).
Flatulence; colic.

Stulln *Stulln, China; Stulln, China.*
Digitoxin (p. 1353·1); esculoside (p. 2431·2).
Macular degeneration; eye fatigue.

Stunarone *Janssen-Cilag, Israel.*
Cinnarizine (p. 622·1).
Vestibular disorders.

Stuno *Milano, Thai.†*
Cinnarizine (p. 622·1).
Vestibular disorders; cerebral and peripheral vascular disorders; migraine; motion sickness.

Sturon *Medicine Products, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vertigo; migraine; motion sickness.

S-Tussin *Suphong, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Stutgeron *Janssen-Cilag, Austria.†*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

STV *Ivax, Arg.*
Stavudine (p. 1015·3).
HIV infection.

Stye *Del, USA.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry eyes.

Stygapon *Zentiva, Cz.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

stypro *Curasan, Ger.*
⊗Gelatin (p. 1154·1).
Haemostatic.

Styptanon *Organon, Braz.†*
Estriol succinate (p. 2275·1).
Haemorrhage; thrombocytopenia.

Styptin *Zydus, India.*
Norethisterone acetate (p. 2294·3).
Menstrual disorders; mastalgia; endometriosis; postponement of menstruation.

Stypto-Caine *Pedinol, USA.*
Aluminium chloride (p. 1693·3); tetracaine (p. 1996·3); hydroxyquinoline sulfate (p. 2530·1).
Bleeding in minor wounds.

Styptocid *Stadmed, India.*
Injection: Carbazochrome (p. 1137·1).
Haemorrhagic disorders.

Stadmed, India.
Tablets: Carbazochrome (p. 1137·1); menadione sodium bisulfite (p. 2122·2); rutoside (p. 2505·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3); calcium hydrogen phosphate (p. 1783·3).
Haemorrhagic disorders.

Styptocip *Cipla, India.*
Carbazochrome (p. 1137·1); menadione sodium bisulfite (p. 2122·2); ascorbic acid (p. 2110·3); rutoside (p. 2505·3); calcium hydrogen phosphate (p. 1783·3).

Styptysat *Ysatfabrik, Ger.*
Shepherd's purse (p. 2614·2).
Haemorrhagic disorders.

Styralonax *Leontik, Gr.*
⊗Metoprolol tartrate (p. 1434·3).

Su Di *Lianhuan, China.*
Ebastine (p. 628·1).
Hypersensitivity reactions.

Su An *Chang Fu Jie Jing, China.*
Potassium dehydroandrographolide succinate.

Su Bi Lin *Kexing, China.*
⊗Insulin (human) (p. 475·3).
Diabetes mellitus.

Su Bo Te *Lai En, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Su Bu Lin *ShiJiaZhuang No 4, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Su Chang *Yangtze River, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Su Ding *Hua Shen, China.*
Telmisartan (p. 1509·3).
Hypertension.

Su Er Qing *Hayao, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Su Fen Ni *EuroCept, China.*
⊗Sufentanil citrate (p. 132·3).
General anaesthesia.

Su Fu *Yangtze River, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Su Le Juan *Zhaoke, China.*
Haemocoagulase (p. 1135·1).

Su Ka *Hengrui, China.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Su Le Kang *Suzhou No 3, China.*
Vitamin E (p. 2119·1).

Su Ke *GuoGuang, China.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Su Ke Le *Suzhou No 3, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Su Ke Nuo *Wan Bang, China.*
A low-molecular-weight heparin sodium (p. 1426·1).

Su Lai *Qilu, China.*
⊗Exemestane (p. 792·2).
Breast cancer.

Su Li Fei *Jinling, China.*
Ferrous succinate (p. 2062·1).

Su Ling *Kangchen, China.*
Haemocoagulase (from *Agkistrodon acutus*) (p. 1135·1).

Su Luo *Suzhou No 6, China.*
Levofloxacin lactate.
Bacterial infections.

Su Meng *Wan Bang, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Su Mi Lin En *Kexing, China.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Su Na *Suzhong, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Su Ni *Ke Lun, China.*
Ethylenediamine diaceturate.

Su Nuo *Si Huan, China; Wellso, China.*
Naloxone hydrochloride (p. 1562·3).
Opioid overdose; reversal of opioid depression.

Su Qi *Yangtze River, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone; osteoporosis.

Su Shi *Haibin, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Su Shuang *GuoGuang, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Su Shun *Huayu, China.*
⊗Terbutaline sulfate (p. 1228·1).
Bronchospasm.

Su Tai Lin *San Ai, China.*
Potassium dehydroandrographolide succinate.

Su Tai Sheng *Shutaishen, China.*
Nerve growth factor (murine).

Su Ting *Chung-Hwa, China.*
Paracetamol (p. 115·1).
Fever; pain.

Su Xin *Suzhong, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; cardiovascular risk reduction.

Su Ya *Pacific, China.*
⊗Celiprolol hydrochloride (p. 1334·2).
Angina pectoris; hypertension.

Su Yi Ning *Wantong, China.*
Aceglutamide (p. 2426·2).

Su Zhi *Huayu, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Suadian *Intendis, Ital.*
Naftifine hydrochloride (p. 590·1).
Fungal skin and nail infections.

Sual *Del Bel, Arg.*
Bladderwrack (p. 2612·1).
Dietary supplement; slimming aid.

Sualim *Pharma Investi, Chile.*
Soap substitute.

SuAn *Wan Bang, China.*
Meglumine adenosine cyclophosphate.

Suavebaby *Vitapan, Braz.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); zinc (p. 2126·1).

Suavederm *Greenpharma, Braz.*
Zinc (p. 2126·1); calcitriol (p. 2113·1); vitamin A (p. 2098·3); triclosan (p. 1773·2).

Suavene *Remexa, Mex.*
⊗Avena (p. 2451·1); urea (p. 1727·3); calendula (p. 2465·2); chamomile (p. 2474·1).
Skin disorders.

Suavicid *Legrand, Braz.*
⊗Fluocinolone acetonide (p. 1636·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).

Suavigel *D & M, Chile.*
Levomenol (p. 2544·1); enoxolone (p. 54·2).
Emollient.

Suaviler *Lersan, Arg.*
Sodium chloride (p. 1795·1).
Dry eyes.

Suaviplant *Madaus, Spain.†*
Hamamelis (p. 2523·3).
Skin irritation; insect bites; minor burns.

Suavisan N *Medical, Arg.*
Hexylresorcinol (p. 1755·1); neomycin (p. 329·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Suavisol *Barnes Hind, Arg.†*
Cleansing solution for soft contact lenses.

Suaviter *Quidnovi, Ital.*
Aspartame (p. 2169·2).
Sugar substitute.

Suavithiol *Lersan, Arg.†*
⊗Naphazoline hydrochloride (p. 1669·3); chlorphenamine maleate (p. 620·3).
Eye disorders.

Suavuret *MSD, Spain.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Combined oral contraceptive.

Sub Tensin *Altana, Spain.*
Nitrendipine (p. 1456·3).
Hypertension.

Subacillin *Yung Shin, Philipp.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Subalin *Biopharma, Ukr.*
Bacillus subtilis.
Restoration of gastrointestinal flora.

Subamycin *Dey's, India.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Subcuvia *Baxter, Austria; Baxter, Belg.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter BioScience, Ger.; Baxter, Gr.; Baxter, Irl.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.†; Baxter, Pol.; Baxter, Port.; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, Turk.†; Baxter BioScience, UK.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; hypogammaglobulinaemia; immune thrombocytopenia; passive immunisation.

Subelan *Pharmavita, Chile.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Subgam *BPL, UK.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia.

Subitene *Farmakopea, Ital.*
Ibuprofen sodium (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Subitol *Toprak, Turk.*
Oxolamine phosphate (p. 1671·2).
Cough.

Sublimax *Duopharma, Philipp.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Sublimaze *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Irl.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK; Akorn, USA.*
⊗Fentanyl citrate (p. 60·1).
Analgesia in anaesthesia; neuroleptanalgesia; pain; premedication; induction of general anaesthesia; adjunct to general anaesthesia.

Sublime *L'Oreal, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sublinox *Medo, Canad.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Sublivac *Hal, Ger.*
Allergen extracts of pollen (p. 2593·3), house dust mites (p. 2434·3), and skin (p. 2434·3).
Allergen immunotherapy.

Suboligo Zinc *Arkomedika, Fr.†*
Zinc gluconate (p. 2126·2).
Nutritional supplement.

Suboxone *Reckitt Benckiser, Austral.; Schering-Plough, Austria; Reckitt Benckiser, Belg.; Schering-Plough, Canad.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Denm.; Reckitt Benckiser, Fr.; Reckitt Benckiser, Ger.; Reckitt Benckiser, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Reckitt Benckiser, Irl.; Schering-Plough, Ital.; Schering-Plough, Malaysia; Reckitt Benckiser, Neth.; Reckitt Benckiser, Norw.; Reckitt Benckiser, NZ; Schering-Plough, Pol.; Quintiles, Port.; Reckitt Benckiser, Spain; Reckitt Benckiser, Swed.; Schering-Plough, Turk.; Schering-Plough, UK; Reckitt Benckiser, USA.*
⊗Buprenorphine hydrochloride (p. 30·3). Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Opioid withdrawal syndrome.

Subrestine *Bryntsalov, Rus.*
Chloropyramine hydrochloride (p. 620·3).
Hypersensitivity reactions.

Subreum *Nycomed, Austria.*
Immunoactive fraction of *Escherichia coli.*
Chronic polyarthritis.

Nycomed, Ger.†
Escherichia coli antigens.
Chronic polyarthritis.

Subroxine *Substipharm, Fr.†*
Roxithromycin (p. 356·2).
Bacterial infections.

Substitol
Note: this name may be used for preparations of different composition.
Mundipharma, Austria.
⊗Morphine sulfate (p. 92·3).
Substitution therapy in opiate dependence.

Subsyde *Raptakos, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Subsys *Insys, USA.*
⊗Fentanyl (p. 60·1).
Pain.

Sub-Tensin *Altana, Spain.*
Nitrendipine (p. 1456·3).

Subutex *Reckitt Benckiser, Austral.; Aesca, Austria; Schering-Plough, Belg.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Denm.; Reckitt Benckiser, Fin.†; Reckitt Benckiser, Fr.; Reckitt Benckiser, Ger.; Reckitt Benckiser, Gr.; Schering-Plough, Hong Kong†; Schering-Plough, Indon.; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Essex, Ital.; Schering-Plough, Neth.†; Reckitt Benckiser, Norw.; Quintiles, Port.; Schering-Plough, S.Afr.; Reckitt Benckiser, Swed.; Reckitt Benckiser, Switz.; Reckitt Benckiser, UK; Reckitt Benckiser, USA.†*
⊗Buprenorphine hydrochloride (p. 30·3).
Opioid withdrawal syndrome.

Sucari *Jean-Marie, Hong Kong.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Sucaryl *Abbott, Austral.; Abbott, NZ.*
Calcium cyclamate (p. 2180·2) or sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute; sweetening agent.

Merisant, Arg.; Abbott, Fr.
Sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Abbott, Braz.†
Sodium cyclamate (p. 2180·2).
Sugar substitute.

Succedin *Flamingo, Philipp.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Succeev *Sanofi-Aventis, Fr.*
Sodium hyaluronate (p. 2526·2).
Wrinkles; scarring.

Succi *Scott-Cassara, Arg.*
Suxamethonium (p. 2037·1).
Depolarising neuromuscular blocker.

Succicaptal *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Succimer (p. 1576·3).
Mercury and lead poisoning.

Succinolin *Amino, Switz.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Succinyl *Taro, Israel; Sidefarma, Thai.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Succitrat *Ariston, Braz.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Succnil Colin *Uniao Quimica, Braz.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Succus Cineraria Maritima *Walker Pharmacal, USA.†*
Senecio (p. 2612·3); hamamelis (p. 2523·3); boric acid (p. 2459·3).
Homoeopathic preparation.

Sucedal *Pharma Investi, Chile.*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Sucee *Biolab, Malaysia; Biolab, Thai.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, and hirsutism in women; oral contraceptive in women with androgenic symptoms.

Suclear
Note: this name may be used for preparations of different composition.
Braintree, USA.
Oral solution, sodium sulfate (p. 1888·1); potassium sulfate (p. 1793·2); magnesium sulfate (p. 1787·3); powder for oral solution, macrogol 3350 (p. 2547·3); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2).
Bowel evacuation.

HPP, Hong Kong.
Gliclazide (p. 472·3).
Diabetes mellitus.

Sucontral *Harras-Curarina, Ger.†*
Coutarea latiflora (p. 2487·3).
Diabetes mellitus.

Sucrabest *Combustin, Ger.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Sucrafilm *Sigma, Braz.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Sucraid *Orphan Medical, USA.*
Sacrosidase (p. 2608·3).
Sucrase deficiency.

Sucral *Ranbaxy, Thai.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Sucralan *Lannacher, Austria; Lannacher, Cz.†*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux.

Sucralbene *Ratiopharm, Austria.†*
Sucralfate (p. 1889·1).
Gastro-oesophageal reflux; peptic ulcer.

Sucralfin *Sanofi-Aventis, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis.

Sucralmax *Quesada, Arg.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Sucralose *Julphar, UAE.*
Sucralfate (p. 1889·1).
Gastro-oesophageal reflux; peptic ulcer.

Sucramal *Sanofi-Aventis, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis.

Sucramed *S Med, Austria.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux.

Sucranorm *ACME, Philipp.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sucrase *Zydus, India.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Sucrat *Lisapharma, Rus.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; hyperphosphataemia.

Sucrate *Jida, China; Lamda (Λαμδα), Gr.; Lisapharma, Hong Kong; Lisapharma, Ital.; Lisapharma, Thai.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Sucrato *Armstrong, Mex.*
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer; dyspepsia.

Sucrets *Insight, Canad.†*
Dyclonine hydrochloride (p. 1987·1).
Sore throat.

Sucrets Childrens Formula *Insight, USA.*
Dyclonine hydrochloride (p. 1987·1).
Formerly known as Sucrets Childrens Sore Throat.
Sore throat.

Sucrets Complete *Insight, Canad.; Insight, USA.*
Dyclonine hydrochloride (p. 1987·1); menthol (p. 2553·2).
Sore throat.

Sucrets Cough Control *Insight, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Sore throat.

Sucrets Defense Kids Formula *Insight, USA.*
Vitamin C (p. 2110·3); zinc (p. 2126·1); glutathione (p. 1555·2).
Sore throat.

Sucrets DM *Insight, Canad.; Insight, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Sucrets Extra Strength *Insight, Canad.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Sucrets Herbal *Insight, USA.*
Menthol (p. 2553·2); pectin (p. 2200·3).
Sore throat.

Sucrets for Kids *Insight, Canad.*
Dyclonine hydrochloride (p. 1987·1).

Sucrets Maximum Strength Sore Throat *Insight, USA.*
Dyclonine hydrochloride (p. 1987·1); menthol (p. 2553·2).
Sore throat.

Sucrets Original Formula Sore Throat Original Mint *Insight, USA.*
Hexylresorcinol (p. 1755·1).
Sore throat.

Sucrets Original Formula Sore Throat Wild Cherry *Insight, USA.*
Dyclonine hydrochloride (p. 1987·1).
Sore throat.

Sucrets Throat Spray *Insight, USA.*
Dyclonine hydrochloride (p. 1987·1).
Sore throat.

Sucrets Vapor *Insight, Canad.†*
Dyclonine hydrochloride (p. 1987·1).
Sore throat.

Sucrin *Rafa, Israel.*
Sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute.

Sucro *Bioglan, Austral.†*
Vitamins; minerals.

Sucro-Fer *Nephrotech, Gr.*
Iron sucrose (p. 2078·1).

Sucron *Terramedic, Philipp.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Sucroril *Innovex, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Sucroven *Alet, Gr.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Sucrox *Biocontrol, Arg.; Raffo, Chile.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia; iron-deficiency.

Sucryl *Rafarm, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sudafed *Johnson & Johnson, Austral.†; GSK, Fr.; GSK, India; GSK, Indon.†; GSK, Mex.†; McNeil, Pol.; Johnson & Johnson, Port.; GSK, Singapore; GSK, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion; sinusitis; rhinitis.

Sudafed Cold & Cough
Note: this name may be used for preparations of different composition.
McNeil Consumer, Canad.
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cough and cold symptoms.

Warner-Lambert, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); guaifenesin (p. 1666·2).
Coughs and cold symptoms.

Sudafed Cold & Flu *Pfizer Consumer, Canad.†*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Sudafed Day/Nightime Relief *Johnson & Johnson, NZ.†*
⊗Day tablets, pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); night tablets, pseudoephedrine hydrochloride; paracetamol (p. 115·1); triprolidine hydrochloride (p. 642·3).
Cold and influenza symptoms.

Sudafed Decongestant *McNeil Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sudafed Expectorant *GSK, Indon.†; GSK, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; respiratory-tract congestion.

Sudafed Expektoran *GSK, Turk.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract congestion.

Sudafed Head Cold & Sinus *McNeil Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms; sinus pain.

Sudafed 12 Hour Relief *Johnson & Johnson, NZ.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sudafed Inhalant Oil *Pfizer Consumer, UK.*
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); peppermint oil (p. 1877·1).
Nasal congestion.

Sudafed Mucus Relief Day & Night *McNeil, UK.*
Day capsules, paracetamol; phenylephrine hydrochloride (p. 1672·3); night capsules, paracetamol; phenylephrine hydrochloride.
Cold and influenza symptoms.

Sudafed Mucus Relief Triple Action Cold & Flu *McNeil, UK.*
Guaifenesin (p. 1666·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Sudafed Nasal Decongestant *Johnson & Johnson, Austral.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Sudafed Non-Drowsy *McNeil, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sudafed Non-Drowsy Decongestant *McNeil Healthcare, Irl.*
Syrup; tablets: ⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

McNeil Healthcare, Irl.
Nasal spray: ⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Sudafed Non-Drying Sinus *Warner-Lambert, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs and cold symptoms.

Sudafed PE *Johnson & Johnson, Austral.; McNeil Consumer, Canad.; McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; sinus congestion.

Sudafed PE Day & Night *McNeil Consumer, USA.*
Day tablets, phenylephrine hydrochloride (p. 1672·3); night tablets, phenylephrine hydrochloride; diphenhydramine hydrochloride (p. 626·2).
Upper respiratory-tract disorders.

Sudafed PE Multi-Symptom Cold & Cough *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Sudafed PE Multi-Symptom Severe Cold *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Sudafed PE Nasal Decongestant *Johnson & Johnson, NZ.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Sudafed PE Nighttime Cold *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Sudafed PE Nighttime Nasal Decongestant *McNeil, USA.†*
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2).
Upper respiratory-tract disorders.

Sudafed PE Non-Drying Sinus *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Sudafed PE Sinus & Allergy *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Sudafed PE Sinus Allergy & Pain Relief *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Allergic rhinitis; sinusitis; nasal congestion.

Sudafed PE Sinus and Allergy and Pain Relief *Pfizer, NZ.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Hypersensitivity reactions; hay fever; sinus pain; nasal congestion.

Sudafed PE Sinus + Anti-inflammatory Pain Relief *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p. 1672·3) ibuprofen (p. 68·2).
Cold and influenza symptoms; sinusitis.

Sudafed PE Sinus Day & Night *Johnson & Johnson, Austral.*
Day tablets, phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); night tablets, phenylephrine hydrochloride; paracetamol; chlorphenamine maleate (p. 620·3).
Sinusitis.

Sudafed PE Sinus Day and Night Relief *Pfizer, NZ.*
Day tablets, phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); night tablets, phenylephrine hydrochloride; paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Sinus pain.

Sudafed PE Sinus Headache *McNeil, USA.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Sudafed PE Sinus Pain Relief *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Sinusitis; nasal congestion.

Sudafed PE Sinus and Pain Relief *Pfizer, NZ.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Nasal congestion; sinus pain.

Sudafed Plus
Note: this name may be used for preparations of different composition.
Pfizer Consumer, UK.
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis.

Wellcome, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Sudafed Severe Cold *Warner-Lambert, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Coughs and cold symptoms.

Sudafed Sinus *Warner-Lambert, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Nasal congestion.

GSK, S.Afr.†
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract congestion.

Sudafed Sinus Advance *McNeil Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).
Cold symptoms; sinusitis.

Sudafed Sinus & Allergy *Pfizer Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Formerly known as Sudafed Cold & Allergy.

Sudafed Sinus & Anti-inflammatory Pain Relief *Johnson & Johnson, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).

Sudafed Sinus & Cold Non-Drowsy *Warner-Lambert, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Nasal congestion.

Sudafed Sinus Day & Night Relief *Johnson & Johnson, Austral.†*
⊗Day tablets, pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); night tablets, pseudoephedrine hydrochloride; paracetamol (p. 115·1); triprolidine hydrochloride (p. 642·3).

Sudafed Sinus & Nasal Decongestant *Johnson & Johnson, Austral.†; Johnson & Johnson, NZ.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion.

Sudafed Sinus Pain *Johnson & Johnson, S.Afr.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Sudafed Sinus Pain & Allergy Relief *Johnson & Johnson, Austral.†; Johnson & Johnson, NZ.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); triprolidine hydrochloride (p. 642·3).
Sinus disorders; allergic rhinitis; hay fever; nasal congestion; sinus pain.

Sudafed Sinus Pain Relief *Johnson & Johnson, Austral.†; Johnson & Johnson, NZ.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Sinus pain and congestion; nasal congestion.

SudaHist *Larken, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Sudarub *Pfizer Consumer, UK.*
Menthol (p. 2553·2); eucalyptus (p. 2501·1); camphor (p. 2466·2).
Respiratory-tract congestion.

SudaTex G *Larken, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

SudaTex-DM *Larken, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Sudaved *Gap, Gr.*
Ketotifen fumarate (p. 631·3).

Sudevil Vita *Nycomed, Arg.*
Cyproheptadine hydrochloride (p. 624·1); vitamins.
Reduced appetite; tonic.

Sudhinol *Ranbaxy, India.*
Dextropropoxyphene (p. 43·2); paracetamol (p. 115·1).
Pain.

Sudinet *Aurora, Gr.*
Nimesulide (p. 101·3).
Inflammatory disorders.

Sudis *Andromaco, Mex.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Sudocrem *Tosara, Irl.; Forest Laboratories, UK; Forest, Ukr.*
Zinc oxide (p. 1729·1); benzyl benzoate (p. 2149·1); benzyl cinnamate (p. 2454·3); benzyl alcohol (p. 1739·3).
Nappy rash; wounds; skin irritation; bedsores; superficial injury; acne; frostbite; eczema; burns; intertrigo; skin maceration; skin disorders.

Nice Pak, Austral.
Zinc oxide (p. 1729·1).
Skin irritation; eczema; bed sores.

SudoGest Non-Drowsy *Major, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

SudoGest Sinus & Allergy *Major, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Sudomyl *PSM, NZ.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Sudophrine *ANH, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Sudroc *Miklich, Cz.; Miklich, Denm.; Miklich, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Suero Antiofidico Polivalente *Biol, Arg.*
Viper venom antiserum (*Crotalus durissus, Bothrops alternatus, Bothrops neuwiedii*) (p. 2419·1).
Passive immunisation.

Suero Fisiológico *Baxter, Spain; Braun, Spain; Ern, Spain; Fresenius Kabi, Spain.*
Sodium chloride (p. 1795·1).
Diluent for parenteral administration of drugs; fluid and electrolyte disorders.

Suero Fisiologico *Perez Gimenez, Spain.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Suero Glucosado *Baxter, Spain; Ern, Spain.*
Glucose (p. 2068·3).
Carbohydrate source.

Suero Glucosalino *Baxter, Spain; Ern, Spain.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1).
Carbohydrate source; fluid and electrolyte disorders.

Suero Ringer Braun *Braun, Spain.†*
Electrolytes (p. 1775·1).
Fluid and electrolyte depletion.

Sueroral *Casen Fleet, Spain.*
Glucose (p. 2068·3); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); sodium chloride (p. 1795·1) (p. 1780·1).
Oral rehydration therapy; diarrhoea; vomiting.

Sufed *TO-Chemicals, Thai.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms; nasal congestion.

Sufenta *Janssen-Cilag, Arg.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Indon.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Turk.; Akorn, USA.*
⊗Sufentanil citrate (p. 132·3).
Analgesia in anaesthesia; general anaesthesia; pain during surgical procedures; postoperative pain; sedative.

Suffisance *Plumbland, Arg.*
Sulfur (p. 1721·1); salicylic acid (p. 1719·1); resorcinol (p. 1718·3).
Acne.

Suficard *Ivax, Arg.*
⊗Eplerenone (p. 1374·2).
Heart failure following myocardial infarction; hypertension.

Sufigal *Anpharm (Ανφαρμ), Gr.*
Glucosamine sulfate (p. 2515·3).

Sufil *Tora, Spain.*
Mebendazole (p. 158·3).
Worm infections.

Sufisal *Silanes, Mex.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Sufortan *Sanfer, Mex.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; Wilson's disease; heavy-metal poisoning; cystinuria.

Sufrexal *Janssen-Cilag, Mex.*
Ketanserin (p. 1415·3).
Skin ulcers; burns; wounds; cervical ulcers; anal fissures.

Sufrexal P *Janssen-Cilag, Mex.*
Ketanserin (p. 1415·3); benzocaine (p. 1980·2).
Anal fissures.

Sugafen *Idaman, Singapore.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Sugafor *K2 Health & Wellness, Chile.*
Sucralose (p. 2096·2).
Sugar substitute.

Suganril *Piramal, India.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Sugar *Farma 1, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis.

Sugar Balance *Blackmores, Austral.*
Vitamins; minerals.
Dietary supplement.

Sugar Bloc *Cantassium Co., UK.*
Gymnema silvestre; chromium orotate (p. 2578·1).
Diet aid.

Sugarbil *Novag, Spain.†*
Cyclobutyrol sodium (p. 2490·2); magnesium sulfate (p. 1787·3); sorbitol (p. 2092·1).
Hepatobiliary disorders; constipation.

Sugarfree *Cadila, Rus.*
Aspartame (p. 2169·2).
Sugar substitute.

Sugarless C *Cenovis, Austral.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Sugast *SF, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis.

Sugiran *Esteve, Spain.*
Alprostadil alfadex (p. 2352·2).
Peripheral vascular disease.

Sugrarine *Chew, Thai.*
Phenylbutazone (p. 125·1).
Gout; musculoskeletal and joint disorders.

Sugril *Siam Bheasach, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Suguan M *Sanofi-Aventis, Ital.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sui Bin *Baiyunshan, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Sui Yue *BSPC, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Suifac *Sandoz, Mex.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Suiflox *Sandoz, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Suimel *Oriental, Arg.*
Saccharin sodium (p. 2208·1); glucose (p. 2068·3); sodium cyclamate (p. 2180·2).
Sugar substitute.

Suiny *Sanwa, Jpn.*
Anagliptin.
Diabetes mellitus.

Suipen *Sandoz, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Sukafen *Suphong, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Sukar-Sin *Laboratorios Chile, Chile.*
Liquid: Sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute.

Laboratorios Chile, Chile.
Tablets: Saccharin sodium (p. 2208·1).
Sugar substitute.

Sukcee *Indian Drugs, India.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Scurvy; adjunct in wounds and infections.

Sukolin *Orion, Fin.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Sukontrol *Alapis, Gr.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Sukrofer *Kocak, Turk.*
Iron sucrose (p. 2078·1).

Sul 10 *Grin, Mex.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sul BCO *Newcharoen, Thai.*
Sulfadiazine (p. 361·3).
Bacterial infections; toxoplasmosis.

Suladrin *Catarinense, Braz.†*
Sulfadiazine (p. 361·3).
Bacterial infections.

Sulam *Siam Bheasach, Thai.*
Injection: Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Bacterial infections.

Siam Bheasach, Thai.
Tablets: Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Sulamid *Baldacci, Ital.*
Amisulpride (p. 1036·3).
Depression.

Sulamp *Galeno, Venez.*
Sultamicillin (p. 369·1).
Bacterial infections.

Sular *Bayer, Belg.; Bayhealth, Spain; Horizon, USA.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Sularyn *Arlex, Mex.†*
Sulfadiazine (p. 361·3).
Bacterial infections.

Sulazine *Chatfield Laboratories, UK.*
Sulfasalazine (p. 1890·1).
Inflammatory bowel disease; rheumatoid arthritis.

Sulbaccin *Macrophar, Thai.*
Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Bacterial infections.

Sulbacef *Biochem, India; Bernofarm, Indon.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Sulbacillin *Penmix, Philipp.*
Sultamicillin (p. 369·1).
Bacterial infections.

Sulbacilline *Daewoong, Thai.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulbacin *Unichem, Malaysia; Pharmawealth, Philipp.; Krasfarma, Rus.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Unichem, India.
Injection: Sulbactam (p. 360·1); ampicillin (p. 218·2).
Bacterial infections.

Unichem, India; Unichem, Malaysia.
Tablets: Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Sulbacta *Olan-Kemed, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulbaksit *Tum, Turk.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulbamox *Bago, Chile.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); pivsulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Farmasa, Braz.
Amoxicillin trihydrate (p. 216·2); pivsulbactam (p. 360·1).
Bacterial infections.

Sulbamp *Ranbaxy, Malaysia.*
Ampicillin sodium (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sulbenin *Anfarm, Gr.*
Donepezil hydrochloride (p. 390·2).

Sulbuta-N *LBS, Thai.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Sulcain *Shinyaku, Jpn.*
Ethyl *p*-piperidinoacetylaminobenzoate (p. 1987·2).
Gastritis.

Sulcef *Medochemie, Rus.; Siam Bheasach, Thai.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Sulcefazon *Biochimic, Rus.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Bacterial infections.

Sulcid *Ulagay, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ulagay, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Sulcoline *Teva Tuteur, Arg.*
Vinorelbine (p. 885·3).
Breast cancer; non-small cell lung cancer.

Sulcolon *Bernofarm, Indon.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; rheumatoid arthritis; ankylosing spondylitis; seronegative spondylarthritis.

Sulcran *Silesia, Chile.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Sulcrate *Axcan, Canad.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastrointestinal haemorrhage.

Sulderm *Innoderm, Philipp.†*
Sulfur (p. 1721·1).
Acne; scabies; seborrhoeic dermatitis.

Suldisyn *Minerva (Μινερβα), Gr.*
Sulconazole nitrate (p. 593·3).
Fungal skin infections.

Suldox *Actavis, Indon.*
Pyrimethamine (p. 662·3); sulfadoxine (p. 363·3).
Malaria.

Sulen *Medichrom, Gr.*
Sulindac (p. 134·2).

Suleo-C *Seton, Irl.†*
Carbaryl (p. 2150·1).
Pediculosis.

Suleo-M *Seton, Irl.†*
Malathion (p. 2157·2).
Pediculosis.

Sulf-10 *Novartis Ophthalmics, USA.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

Sulfa 10 *Meda, Belg.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulfa Cloran *Grin, Mex.*
Chloramphenicol (p. 257·1); sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulfa Hidro *Grin, Mex.†*
⊗Hydrocortisone acetate (p. 1640·1); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Sulfac *Ocusoft, USA.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulfacet
Note: this name may be used for preparations of different composition.
Oftalmi, Venez.
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulfacet-R *Valeant, Canad.; Dermik, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne; rosacea; seborrhoeic dermatitis; bacterial folliculitis.

Sulfachlor *Genepharm, Gr.*
Chloramphenicol (p. 257·1); sulfacetamide sodium (p. 361·1).

Sulfachloramphenicol *Novartis, Gr.*
Chloramphenicol (p. 257·1); sulfacetamide sodium (p. 361·1).
Eye infections.

Sulfacid *Fischer, Israel.*
Sulfacetamide sodium (p. 361·1).
Eye infections.

SulfaCleanse *PruGen, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Sulfacort *Oftalmi, Venez.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2).
Infected eye disorders.

Sulfacyl *Farmak, Ukr.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulfaderm *Kinder, Braz.†*
Sulfadiazine silver (p. 362·3).

Sulfadiazina de Plata *Denver, Arg.; Richet, Arg.*
Sulfadiazine silver (p. 362·3); vitamin A (p. 2098·3); lidocaine (p. 1988·1).

Sulfadin *Zyg, Philipp.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers, and wounds.

Sulfagrand *Ahimsa, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulfamide *Medical Ophthalmics, USA.*
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Sulfamylon *UDL, USA.*
Mafenide acetate (p. 320·2).
Burns.

Sulfanicole *Cooper (Κοπερ), Gr.*
Chloramphenicol sodium succinate (p. 257·2); sulfacetamide sodium (p. 361·1).
Eye infections.

Sulfanoral T *Sidus, Arg.*
Tyrothricin (p. 384·1); cresol (p. 1749·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Sulfaplat *Lafedar, Arg.*
Sulfadiazine silver (p. 362·3); vitamin A palmitate (p. 2098·3); lidocaine (p. 1988·1).

Sulfaprim *SSK, Turk.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulfargin *Grindeks, Ukr.*
Sulfadiazine silver (p. 362·3).
Burns; ulcers; wounds.

Sulfarhin *Santa, Turk.*
⊗Ephedrine hydrochloride (p. 1663·2); naphazoline hydrochloride (p. 1669·3); menthol (p. 2553·2); cineole (p. 2479·1); antazoline hydrochloride (p. 615·3).
Nasal congestion.

Sulfarinol *Galenus, Pol.*
⊗Naphazoline nitrate (p. 1669·3); sulfathiazole (p. 368·3).
Nasal congestion.

Sulfarlem *Eurogenerics, Belg.; EG, Fr.; Pro Concepta, Switz.; Frik, Turk.*
Anethole trithione (p. 2443·3).
Dry mouth; dry eye; dyspepsia; biliary-tract disorders; liver disorders; constipation; digestive disorders.

Sulfas Ferrosus *Kimia, Indon.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; iron supplement.

Sulfa-Sedemol *Melisana, Belg.*
Sulfanilamide camsilate (p. 368·1); phenol (p. 1763·3); borax (p. 2459·2); althaea (p. 2438·3); poppy capsule (p. 1675·3); sodium fluoride (p. 2089·2); cloral hydrate (p. 1055·2).
Mouth and throat disorders.

Sulfasil *Purna, Belg.*
Sulfadiazine silver (p. 362·3).
Burns.

Sulfast *Vitalink, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sulfato Ferroso Composto *Legrand, Braz.*
Ferrous sulfate (p. 2062·2); thiamine nitrate (p. 2103·2); copper sulfate (p. 2057·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Sulfatral *Lepetit, Arg.*
Sulfadiazine silver (p. 362·3).
Burns; wounds; ulcers.

Sulfatril *Hua, Thai.†*
Sulfadiazine (p. 361·3); sulfadimidine (p. 363·2); sulfamerazine (p. 364·3).
Bacterial infections.

Sulfatrim *Schein, USA.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Sanofi Synthelabo, Turk.†
Trimethoprim (p. 381·2); sulfadiazine (p. 361·3).
Rheumatic fever prophylaxis; toxoplasmosis.

Sulfawal *Novag, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulfayel *Patar, Thai.*
Sulfaguanidine (p. 364·3).
Bacterial infections.

Sulfazine-M *Patar, Thai.*
Sulfadiazine (p. 361·3).
Bacterial infections.

Sulfer Plus *Delta, Braz.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Sulferbel *Belfar, Braz.*
Ferrous sulfate (p. 2062·2).

Sulfergan Composto *Legrand, Braz.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Sulferro *Fontovit, Braz.†*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

Sulferrol *Bunker, Braz.*
Ferrous sulfate (p. 2062·2).
Iron deficiency; iron-deficiency anaemia.

Sulfestrep *Pisa, Mex.*
Streptomycin (p. 359·1).
Bacterial infections.

Sulfex *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulfile *Angelfarma, Port.†*
Arginine tidiacicate (p. 2049·1).
Liver disorders.

Sulfin *American Taiwan, Philipp.; American Taiwan, Thai.*
Sulfinpyrazone (p. 608·3).
Hyperuricaemia; gout; gouty arthritis.

Sulfinav *LKM, Arg.*
Efavirenz (p. 975·1).
HIV infection.

Sulfintestin Neomicina *Normon, Spain.*
Dihydrostreptomycin sulfate (p. 286·3); formosulfathiazole (p. 300·2); neomycin sulfate (p. 330·1).
Gastrointestinal infections.

Sulfitrat *Teuto, Braz.*
Sulfiram (p. 2161·3).

Sulfoam *Doak, USA.*
Sulfur (p. 1721·1).
Formerly contained salicylic acid.
Dandruff; seborrhoea.

Sulfocaine *Biochimic, Rus.*
Sulfocamphoric acid.
Shock.

Sulfocamphocaine *Moschimfarm, Rus.*
Sulfocamphoric acid.
Shock.

Sulfodecortem *Nizhpharm, Rus.*
⊗Hydrocortisone acetate (p. 1640·1); sulfur (p. 1721·1).
Skin and scalp disorders.

Sulfoid Trimetho *Valdecasas, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulfolax *Major, USA.*
Docusate calcium (p. 1836·2).
Constipation.

Sulfometh *Hua, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulfona *IFET (ΙΦΕΤ), Gr.; Zimaia, Port.; Orsade, Spain.†*
Dapsone (p. 281·2).
Leprosy; malaria; pneumocystis pneumonia; dermatitis herpetiformis; polychondritis.

Sulfoprokain *Biosintez, Rus.*
Sulfocamphoric acid.
Shock.

Sulforcin *Healthpoint, USA.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne.

Sulfort *Arlex, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulfoxyl
Note: this name may be used for preparations of different composition.
Stiefel, USA.
Benzoyl peroxide (p. 1696·1); sulfur (p. 1721·1).
Acne.

Sulfur Complexe No 12 *Lehning, Fr.*
Sulfur (p. 1721·1); arsenicum album (p. 2448·1); alumen crudum (p. 2439·1); magnesia sulfurica (p. 1787·3); natrum sulfuricum (p. 1888·1).
Homoeopathic preparation.

Sulfur Med Complex *Dynamit, Austria.*
Bryonia (p. 2461·3); sepia (p. 2613·1); silicea (p. 2208·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Sulfurell *Sanorell, Ger.*
Sulfur (p. 1721·1).
Homoeopathic preparation.

Sulfuryl *Legras, Fr.*
Bath additive; soap: Sulfurated aluminium sodium silicate (p. 1818·3); precipitated sulfur (p. 1721·1).
Skin disorders.

Legras, Fr.†
Chewable tablets; inhalation tablets: Sulfurated aluminium sodium silicate (p. 1818·3).
Respiratory-tract congestion.

Sulgan 99 *Klosterfrau, Austria.*
Ointment; suppositories: Ethyl linoleate (p. 2509·2); ethyl linolenate (p. 1460·1); benzocaine (p. 1980·2); dichlorobenzyl alcohol (p. 1750·2); aluminium chlorohydrate (p. 1694·1); hamamelis (p. 2523·3); camphor (p. 2466·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Anorectal disorders.

Sulgan N *Doetsch, Grether, Switz.*
Ointment; suppositories: Ethyl linoleate (p. 2509·2); ethyl linolenate (p. 1460·1); lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2); dichlorobenzyl alcohol (p. 1750·2); camphor (p. 2466·2); menthol (p. 2553·2); triclosan (p. 1773·2).
Anorectal disorders.

Doetsch, Grether, Switz.
Wipes: Dichlorobenzyl alcohol (p. 1750·2); lidocaine hydrochloride (p. 1988·2); camphor (p. 2466·2); menthol (p. 2553·2).
Anorectal disorders.

Sulgen *Roxall, Ger.*
Allergen extracts of pollen (p. 2593·3), house dust mites (p. 2434·3), fungi, and skin (p. 2434·3).
Allergen immunotherapy.

Sulgin *Biosintez, Rus.; Dalkhimfarm, Rus.*
Sulfaguanidine (p. 364·3).
Gastrointestinal infections.

Sulglic *EMS, Braz.*
Glucosamine (p. 2515·3).

Sulidamor *Damor, Ital.*
Nimesulide (p. 101·3).
Pain.

Sulide *Aurobindo, Ital.*
Nimesulide (p. 101·3).
Pain.

Sulidek *Wermar, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Sulidin *Xeno, Philipp.; Embil, Turk.*
Nimesulide (p. 101·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Sulidol-GB *Nafar, Mex.*
Nimesulide (p. 101·3).
Inflammation; pain; fever.

Sulidor *Caldeira & Metelo, Port.*
Nimesulide (p. 101·3).
Peri-articular disorders.

Sulifur *Teva, Mex.†*
Sulindac (p. 134·2).
Rheumatism; pain.

Sulimed *Decafarma, Port.†*
Nimesulide (p. 101·3).
Pain; osteoarthritis.

Sulin *BioSaude, Port.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Sulindal *Chibret, Spain.†*
Sulindac (p. 134·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Sulingqiong *Changzheng-Xinkai, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Sulix *Rider, Chile.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Sullivan *Medhaus, Philipp.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Sulmasque *C & M, USA.*
Sulfur (p. 1721·1).
Acne.

Sulmetin Papaver *Sanofi-Aventis, Spain.†*
Atropine methobromide (p. 1310·2); magnesium sulfate (p. 1787·3); papaverine hydrochloride (p. 2362·3); propyphenazone (p. 127·3).
Smooth muscle spasm; pain.

Sulmicil *Domesco, Philipp.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Sulmover *Dawnrays, Rus.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Sulmycin *EUSA, Austria; MSD, Ger.*
Gentamicin sulfate (p. 304·2).
Bone and soft tissue infections; bacterial skin infections.

Sulmycin mit Celestan-V *MSD, Ger.*
⊗Gentamicin sulfate (p. 304·2); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Sulmyn *Sons, Mex.†*
Kanamycin (p. 314·3).
Bacterial infections.

Sulned *Pizzard, Mex.*
Neomycin (p. 329·3); polymyxin B (p. 342·3); gramicidin (p. 308·3).
Bacterial eye infections.

Sulnil *Allergan, Braz.*
Chloramphenicol (p. 257·1); sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sulobil *Atlantis, Mex.*
Chenodeoxycholic acid (p. 2475·1).
Cholesterol gallstones.

Sulocten *Microsules, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Sulocten D *Microsules, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Sulodil *Viofar, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Sulonil *Sanval, Braz.*
Nimesulide (p. 101·3).

Suloprost *Sandoz, Arg.*
Estramustine phosphate (p. 790·1).
Prostatic cancer.

Sulorane *Baxter, Israel.*
Desflurane (p. 1898·3).
General anaesthesia.

Sulotil *Lafi, Chile.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Sulpan *Sanofi-Aventis, Braz.*
Sulpiride (p. 1107·3); bromazepam (p. 1041·2).
Depression.

Sulperacef *Abolmed, Rus.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulperason *Pfizer, Rus.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulperasone *Pfizer, Ukr.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Sulperazon *Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia; Pfizer, Pol.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Venez.*
Sulbactam sodium (p. 360·1); cefoperazone sodium (p. 243·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Sulperazone *Pfizer, Philipp.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulpermed *Millimed, Thai.*
Sulbactam (p. 360·1); cefoperazone (p. 243·1).
Bacterial infections.

Sulphargin *Grindex, Rus.*
Sulfadiazine silver (p. 362·3).
Burns; ulcers; wounds.

Sulpho-Lac *Doak, USA.*
Sulfur (p. 1721·1); zinc sulfate (p. 2126·2).
Acne.

Sulphonur *Specpharm, S.Afr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Sulpilan *Labomed, Chile.*
Sulpiride (p. 1107·3).
Depression; psychoses.

Sulpin *Taiwan Biotech, Malaysia.*
Sulpiride (p. 1107·3).
Schizophrenia.

Sülpir *Sanofi Synthelabo, Turk.*
Sulpiride (p. 1107·3).
Schizophrenia.

Sulpirol *Hexal, Cz.*
Sulpiride (p. 1107·3).
Schizophrenia; depression; vestibular disorders.

Sulpisal *Alapis, Gr.*
Amisulpride (p. 1036·3).

Sulpivert *Hennig, Ger.*
Sulpiride (p. 1107·3).
Depression; schizophrenia; vestibular disorders.

Sulpivol *Pharma Investi, Chile.*
Sulpiride (p. 1107·3).
Stimulation of lactation.

Sulpor *Rosemont, UK.*
Sulpiride (p. 1107·3).
Schizophrenia.

Sulprim *Prafa, Indon.†; Berman, Mex.; Asian Pharm, Thai.; Medicpharma, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sulprix *Alphapharm, Austral.*
Amisulpride (p. 1036·3).
Schizophrenia.

Sulquipen *Bohm, Spain.†*
Cefalexin (p. 234·1).
Bacterial infections.

Sulris *Young Il, Singapore.*
Sulpiride (p. 1107·3).
Schizophrenia.

Sulster *Akorn, USA.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Sultacillin *Guangzhou, Philipp.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Sultamat *Atabay, Turk.*
Sultamicillin (p. 369·1).
Bacterial infections.

Sultamilan *Meyer Alian, Venez.*
Sultamicillin (p. 369·1).
Bacterial infections.

Sultanol *GSK, Austria; GSK, Ger.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Sultasid *Toprak, Turk.*
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Toprak, Turk.
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Sultasin *Synthesis, Rus.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Sultax *Ipca, India.*
Cefotaxime sodium (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulterline *TP, Thai.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Sultibac *Biofarma, Turk.; Munir, Turk.*
Oral suspension; tablets: Sultamicillin (p. 369·1).
Bacterial infections.

Biofarma, Turk.; Munir, Turk.
Injection: Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Sulton *Geymonat, Ital.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity; anaemias.

Sultral *Silanes, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Sultrimmix *Bernofarm, Indon.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sultrin *Janssen-Cilag, Gr.; Cilag, Philipp.†; Janssen-Cilag, S.Afr.†; Ortho McNeil, USA.†*
Sulfabenzamide (p. 360·3); sulfacetamide (p. 361·1); sulfathiazole (p. 368·3).
Vaginal infections.

Sultrona *Cryopharma, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Sulvi *Grin, Mex.*
⊗Naphazoline hydrochloride (p. 1669·3); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

SulZee *Larken, USA.†*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Sulzoncef *Sintez, Rus.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Suma-B *Chinoin, Mex.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin (p. 2107·3).
Vitamin B deficiency; neuritis; neuropathy; megaloblastic anaemia.

Sumacal *Sherwood, USA.*
Glucose polymers.
Carbohydrate source.

Sumadan *Medimetriks, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Sumagesic *Medifarma, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Sumagran *Aspen, Austral.; Chanelle, Irl.; Mylan, NZ.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumaklid *Biosintez, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Sumal *Purissimus, Arg.*
⊗Bendroflumethiazide (p. 1315·2); homatropine methylbromide (p. 2007·3); dipyrone (p. 53·3).
Premenstrual syndrome.

Sumalin *Ratiopharm, Neth.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumamecin *Obolenskoe, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Sumamed *Pliva, China; Teva, Cz.; Teva, Hung.; Pliva Krakow, Pol.; Pliva, Rus.; Teva, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Sumamigren *Polpharma, Cz.; Polpharma, Pol.; Polpharma, Rus.*
Sumatriptan succinate (p. 679·2).
Migraine.

Polpharma, Ukr.
Sumatriptan (p. 679·2).
Migraine.

Sumamox *Oxford Laboratories, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Sumamylan *Mylan, Spain.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumapen
Note: this name may be used for preparations of different composition.
United American, Philipp.
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Great Eastern, Thai.†; Westmont, Thai.†
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Sumaprot *Scott-Cassara, Arg.*
Preparation for enteral nutrition.
Dietary supplement.

Sumaprot 90 *Scott-Cassara, Arg.*
Calcium caseinate (p. 2055·2).
Dietary supplement.

Sumaratio *Ratiopharm, Fin.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumario *Medicina, Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Xerostomia.

Sumarix *Ratiopharm, Neth.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumatab *Alphapharm, Austral.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumatran *Fako, Turk.*
Sumatriptan (p. 679·2).
Migraine; cluster headache.

Rowex, Irl.; Sandoz, Singapore.
Sumatriptan succinate (p. 679·2).
Migraine.

Sumatridex *Dexcel, Israel.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumavel *Desitin, Denm.; Zogenix, USA.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

Desitin, Ger.
Sumatriptan (p. 679·2).
Migraine; cluster headache.

Sumax *Libbs, Braz.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumaxin *Medimetriks, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Sumazid *Bryntsalov, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Sumedium *Milano, Thai.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Sumenan *Spedrog, Arg.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Sumetrolim *Egis, Cz.; Egis, Hung.; Egis, Rus.; Egis, Ukr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Sumial *Icaro, Spain.*
⊗Propranolol hydrochloride (p. 1479·1).
Angina pectoris; anxiety; arrhythmias; gastrointestinal haemorrhage; hypertension; hyperthyroidism; migraine; myocardial infarction; obstructive cardiomyopathy; phaeochromocytoma; tremor.

Sumidin *Pharmaland, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema; respiratory-tract congestion.

Sumiferon *Sumitomo, Jpn.*
Interferon alfa (p. 989·2).
Malignant neoplasms; hepatitis B and C; subacute sclerosing panencephalitis; myelopathy.

Sumig *Mareechi, Rus.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

Sumigra *Sandoz, Cz.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sandoz, Pol.
Sumatriptan (p. 679·2).
Migraine.

Sumigran *Aldril, Philipp.*
Sumatriptan succinate (p. 679·2).
Migraine.

Suminat *Sun, India.*
Sumatriptan succinate (p. 679·2).
Migraine.

Sumitran *Reddy, Malaysia; Reddy, Rus.; Reddy, Singapore.*
Sumatriptan succinate (p. 679·2).
Migraine; cluster headache.

Sumitrex *Bajamed, Mex.*
Sumatriptan (p. 679·2).
Migraine.

Summaflox *AGIPS, Ital.*
Levofloxacin (p. 315·3).
Bacterial infections.

Summavac *Cassara, Arg.*
A range of bacterial and fungal allergen extracts (p. 2434·3).
Hypersensitivity reactions.

Summer Glow *Johnson & Johnson, Canad.†*
SPF 20: Avobenzone (p. 1695·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Summer Rain *Zep, Canad.*
Triclosan (p. 1773·2).

Summerberry Skin Cream *Summerberry, Canad.*
White soft paraffin (p. 2211·3).

Summer's Eve *Fleet, Philipp.; De Witt, UK; Fleet, USA.*
A range of feminine hygiene preparations.

Summer's Eve Anti-Itch *Fleet, USA.*
⊗Pramocaine hydrochloride (p. 1993·3); glycerol (p. 2517·2).
Vaginal itching.

Summer's Eve Disposable *Fleet, USA.*
Solution: Vinegar (p. 2426·3).
Vaginal disorders.

Summer's Eve Douche *Fleet, Austral.*
Glacial acetic acid (p. 2426·3).
Vaginal cleanser.

Summer's Eve Feminine *Fleet, Austral.*
Topical powder: Octoxinol 9 (p. 2199·3); starch (p. 2095·1).
Vaginal irritation; intertrigo.

Fleet, Austral.
Towelettes: Octoxinol 9 (p. 2199·3).
Vaginal hygiene.

Fleet, Austral.
Liquid soap: Soap substitute.
Vaginal hygiene.

Summer's Eve Medicated *Fleet, Malaysia; Kozmed, Turk.; Fleet, USA.*
Povidone-iodine (p. 1767·1).
Vaginal disorders.

Summer's Eve Post-Menstrual *Fleet, USA.*
Sodium laurilsulfate (p. 2210·3); monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2); sodium chloride (p. 1795·1); edetic acid (p. 1550·3).
Vaginal disorders.

Summit Gold *Hillestad, Canad.†*
Vitamins; minerals.

Summit Ultra *Pendopharm, Canad.*
Methocarbamol (p. 2025·3); ibuprofen (p. 68·2).

Sumo *Elea, Arg.*
Phenothrin (p. 2160·1).
Pediculosis.

Sumo Full Contact *Elea, Arg.*
Cyclopentaxyloxane (p. 2209·2); dimeticone (p. 2209·3).
Pediculosis.

Sumo Repelente *Elea, Arg.*
Cymbopogon nardus.
Pediculosis.

Sumopen *Cofasa, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sumoxcin *Suphong, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sumoxil *Medichem, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sumycin *Apothecon, USA.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Sun Block *Watkins, Canad.†*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Defense *Kamins, Canad.*
SPF 48: Ensulizole (p. 1703·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.

Keyano, Canad.
SPF 30: Benzophenone; octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sun Defense Sunblock *Norman, Canad.†*
SPF 25: Octinoxate (p. 1715·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Facial *Avalon, Canad.†*
SPF 20: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Fragrance *Avalon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sun Kids *Avalon, Canad.†; Avon, Canad.†*
SPF 30; SPF 32: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); homosalate (p. 1705·1).
Sunscreen.

Sun LEB *Eucerin, Fr.*
SPF 25; SPF 50: Bemotrizinol (p. 1695·3); avobenzone (p. 1695·1); iscotrizinol (p. 1706·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Sun Lip Balm *Avon, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sun Performance *Estee Lauder, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Potion *Tanning Research, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Protection *Vichy, Canad.*
SPF 30; SPF 45: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sun Protection for All Seasons *Hunter, Canad.*
SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Hunter, Canad.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Shade *Aubrey, Canad.†*
SPF 8; SPF 12; SPF 15: Padimate O (p. 1716·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sun Shield *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Johnson & Johnson, Canad.†
SPF 30: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Smart Levres *Lise Watier, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun and Snow Sport *Astley, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Sport *Avalon, Canad.†*
SPF 32: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sun Therapy *CMI, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sun Vue *Sunrex, Fr.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); zinc gluconate (p. 2126·2); vitamins; omega-3 fatty acids (p. 1460·3); omega-6 fatty acids (p. 2509·2); omega-9 fatty acids; selenium (p. 2086·3); green tea (p. 2648·2); myrtillus (p. 2566·2); urtica (p. 2639·3).
Dietary supplement; eye health.

Sunadine *Sunward, Hong Kong.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Sunamine *Sunward, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2).

Sunax *Suphong, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Sunazol *Sunward, Singapore.*
Ketoconazole (p. 585·3).
Fungal infections.

Sunbalance *Vivier, Canad.*
Hydroquinone (p. 1705·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Skin pigmentation disorders.

Sun-Benz *Sun, Canad.*
Benzydamine hydrochloride (p. 29·2).
Sore throat; oropharyngeal mucositis.

Sunblock
Note: this name may be used for preparations of different composition.
Newco, Canad.†
SPF 15: Zinc oxide (p. 1729·1).
Sunscreen.

Sunblock Lotion
Note: this name may be used for preparations of different composition.
Prime Enterprises, Canad.†
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Tanning Research, Canad.†
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Suncodin
Note: this name may be used for preparations of different composition.
Sunward, Malaysia.
Dihydrocodeine tartrate (p. 52·3).
Pain.

Winthrop, S.Afr.
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); phenyltoloxamine citrate (p. 638·1); caffeine (p. 1203·3).
Pain; sinus congestion; cold and influenza symptoms.

Suncures *Avance, Canad.†*
SPF 20: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Sun-Dianox *Sunward, Singapore.*
Diphenoxylate hydrochloride (p. 1835·3). Atropine sulfate (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Sundir *Sons, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Sundown *Johnson & Johnson, Braz.*
SPF 50: Bemotrizinol (p. 1695·3); titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Johnson & Johnson, Braz.; Johnson & Johnson, USA.
SPF 8; SPF 15; SPF 20; SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Johnson & Johnson, Braz.
SPF 30: Bemotrizinol (p. 1695·3); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Sundown Baby *Johnson & Johnson, Braz.*
SPF 30: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Sundown Cabelos *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Sundown Clear Gel *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); homosalate (p. 1705·1); oxybenzone (p. 1715·3).
Sunscreen.

Sundown C/Repelente *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sundown Facial *Johnson & Johnson, Braz.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Sundown Gold *Johnson & Johnson, Braz.*
SPF 6: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Johnson & Johnson, Braz.
SPF 2; SPF 4: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1).
Sunscreen.

Sundown Kids *Johnson & Johnson, Braz.*
SPF 15; SPF 30: Bemotrizinol (p. 1695·3); octinoxate (p. 1715·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sundown Kids Colour *Johnson & Johnson, Braz.*
SPF 30: Bemotrizinol (p. 1695·3); octocrilene (p. 1715·2); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Johnson & Johnson, Braz.
SPF 15: Bemotrizinol (p. 1695·3); octocrilene (p. 1715·2); octinoxate (p. 1715·1).
Sunscreen.

Sundown Labial *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sundown Mousse *Johnson & Johnson, Braz.*
SPF 25: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); bemotrizinol (p. 1695·3).
Sunscreen.

Sundown Pos-Sol *Johnson & Johnson, Braz.*
Moisturiser.

Sundown Sport *Johnson & Johnson, USA.*
SPF 15: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Johnson & Johnson, Braz.
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sundown Spray *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Johnson & Johnson, Braz.
SPF 30: Bemotrizinol (p. 1695·3); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

SuNerven *Lane, UK.*
Motherwort (p. 2564·2); vervain (p. 2645·1); valerian (p. 2640·2); passion flower (p. 2584·1).
Stresses and strains.

Sunflu *Sunward, Singapore.*
Chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3).
Cold symptoms.

Sun-Glizide *Sunward, Hong Kong; Sunward, Malaysia; Sunward, Singapore.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Sunglucon *Sunward, Hong Kong; Sunward, Singapore.*
Glipizide (p. 474·1).
Diabetes mellitus.

Sunicaine *Unipharm, Mex.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Sunicol *Farmanic, Gr.*
Co-trimoxazole (p. 277·3).

Suniderma *Galderma, Spain.*
⊗Hydrocortisone aceponate (p. 1640·1).
Skin disorders.

Suniton *Sunward, Malaysia†; Sunward, Singapore.*
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).
Skeletal muscle pain and spasm; tension headache.

Sunizine *Sunward, Hong Kong; Sunward, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Sunkist *Ciba, USA.*
Ascorbic acid (p. 2110·3).

Sunmax 30 *Stiefel, Braz.*
Oxybenzone (p. 1715·3); homosalate (p. 1705·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2).
Sunscreen.

Sunmax 60 *Stiefel, Braz.*
Avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octil triazone (p. 1715·1); homosalate (p. 1705·1).
Sunscreen.

Sunmax Acqua *Stiefel, Braz.*
Gel SPF 20: Ensulizole (p. 1703·1); sulisobenzone (p. 1722·1).
Sunscreen.

Stiefel, Braz.
Spray SPF 20: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1).
Sunscreen.

Sunmax Autobronzeador *Stiefel, Braz.*
Dihydroxyacetone (p. 1700·1); erythrulose (p. 1703·3).
Artificial suntan.

Sunmax Junior *Stiefel, Braz.*
SPF 35: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sunmide *Sunward, Singapore.*
⊗Furosemide (p. 1387·1).
Hypertension; oedema.

Sunnie *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; glutamine (p. 2070·3); St John's wort (p. 449·1); betaine (p. 2456·1); ginkgo biloba (p. 2512·3).
Tonic.

Sunny Children Cough *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2).
Cough.

Sunny Fever *Beacons, Singapore.*
Paracetamol (p. 115·1).
Pain; fever.

Sunny Laxative *Beacons, Singapore.*
Bisacodyl (p. 1821·1).
Constipation.

Sunny Skin *Beacons, Singapore.*
Methyl salicylate (p. 92·1); salicylic acid (p. 1719·1).

Sun-Off *Mediphar, Venez.*
Ensulizole triethanolamine.
Sunscreen.

Sun-Off Baby *Mediphar, Venez.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Sunolut *Sunward, Malaysia; Sunward, Singapore; Sunward, Thai.*
Norethisterone (p. 2294·2).
Dysfunctional uterine bleeding; endometriosis; menopausal disorders; menstrual disorders; amenorrhoea; postponement of menstruation; mastopathy.

Sunonix *Medipharma, Arg.*
Levomepromazine (p. 1079·3).
Psychoses.

Sunophene *Sunward, Singapore.*
⊗Clomifene citrate (p. 2259·1).
Anovulatory infertility.

Sunpepcin *Sunward, Singapore.*
Famotidine (p. 1842·1).
Peptic ulcer; pathological hypersecretory disorders; gastro-oesophageal reflux.

Sunpla *SK, Kor.*
Eptaplatin (p. 788·1).
Gastric cancer.

Sunpraz *Sun, Rus.*
Pantoprazole sodium (p. 1875·3).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sunprox *Sunward, Malaysia; Sunward, Singapore.*
Naproxen sodium (p. 98·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sunrabin *Asahi, Jpn.*
Enocitabine (p. 786·3).
Leukaemia.

SunRecome *Teguhsindo, Indon.*
Ganoderma lucidum.
Tonic.

Sunright *NSE, Canad.*
SPF 15; SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunright Lip Balm *NSE, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sunrythm *Daiichi Sankyo, Jpn.*
Pilsicainide hydrochloride (p. 1470·1).
Arrhythmias.

Sunscreen *CrocBloc, Canad.*
SPF 50: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

CrocBloc, Canad.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunscreen for Body *Shaklee, Canad.*
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunscreen Continuous Spray
Note: this name may be used for preparations of different composition.
Norwood, Canad.
SPF 30; SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Prime Enterprises, Canad.
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunscreen Cream *Vichy, Canad.*
SPF 60: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sunscreen Gel *Smartshield, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); padimate O (p. 1716·1).
Sunscreen.

Sunscreen Lotion
Note: this name may be used for preparations of different composition.
Norwood, Canad.; Vital Science, Canad.
SPF 30; SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Smartshield, Canad.
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Smartshield, Canad.
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); padimate O (p. 1716·1).
Sunscreen.

Energizer, Canad.†
SPF 32; SPF 52; SPF 15; SPF 30; SPF 45; SPF 70: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunscreen Lotion Ecran *Confab, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Confab, Canad.
SPF 30: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); octinoxate (p. 1715·1); ensulizole (p. 1703·1).
Sunscreen.

Sunscreen Protection *Caty, Canad.*
SPF 15; SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunscreen SPF-30 *Johnson & Johnson, Canad.†*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunscreen Spray
Note: this name may be used for preparations of different composition.
Smartshield, Canad.
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); padimate O (p. 1716·1).
Sunscreen.

Energizer, Canad.†
SPF 30: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Sunsedyl *Sunward, Singapore.*
⊗Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2).

Sunsense *Ego, Austral.; Ego, Hong Kong.†*
Topical gel SPF 30+; Gel SPF 30+: Octinoxate (p. 1715·1); amiloxate (p. 1694·1); oxybenzone (p. 1715·3); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Ego, Austral.
Spray SPF 30+: Enzacamene (p. 1703·2); avobenzone (p. 1695·1); octinoxate (p. 1715·1); octil triazone (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sunsense Aftersun *Ego, Austral.*
Emollient.
Dry skin.

Sunsense Anti Ageing Face *Ego, Austral.*
SPF 30+: Octinoxate (p. 1715·1); bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1); alpha hydroxy acids (p. 1704·3); glycolic acid (p. 1704·3); vitamin E (p. 2119·1); nicotinamide (p. 2083·1).
Moisturiser; sunscreen.

Sunsense Anti-Ageing *Ego, Singapore.*
SPF 50+: Octinoxate (p. 1715·1); bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1).
Sunscreen.

SunSense Anti-Ageing Face *Ego, Malaysia.*
SPF 50: Octinoxate (p. 1715·1); bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1).
Sunscreen.

SunSense Anti-ageing Face Matte *Ego, Hong Kong.*
Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); bemotrizinol (p. 1695·3); glycolic acid (p. 1704·3).
Sunscreen.

Sunsense Bronze Shield *Ego, Austral.*
SPF 30+: Bemotrizinol (p. 1695·3); bisoctrizole (p. 1697·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Sunsense Clear *Ego, Singapore.†*
SPF 35+: Octil triazone (p. 1715·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); oxybenzone (p. 1715·3).
Sunscreen.

Sunsense Clear Mist *Ego, Hong Kong†; Ego, Malaysia.†*
SPF 35+: Avobenzone (p. 1695·1); enzacamene (p. 1703·2); octil triazone (p. 1715·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sunsense Daily Face *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.*
SPF 30+; SPF 50+: Titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); octil triazone (p. 1715·1).
Sunscreen.

SunSense Face Tint *Ego, Singapore.*
SPF 50: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1); octinoxate (p. 1715·1).
Sunscreen.

Sunsense Lip Balm *Ego, Austral.†*
SPF 30+: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); bemotrizinol (p. 1695·3).
Sunscreen.

Sunsense Milk *Ego, Singapore.†*
Octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2).
Sunscreen.

Sunsense Milk Mist *Ego, Hong Kong†; Ego, Malaysia.†*
SPF 30+: Enzacamene (p. 1703·2); avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Sunsense Moisturising Face *Ego, Austral.; Ego, Singapore.*
SPF 30+; SPF 50: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); bemotrizinol (p. 1695·3); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Moisturiser; sunscreen.

Sunsense Self Tanning System Self Tan *Ego, Austral.*
Dihydroxyacetone (p. 1700·1); erythrulose (p. 1703·3).
Tanning aid.

Sunsense Sensitive *Ego, Austral.*
SPF 30+: Titanium dioxide (p. 1725·1).
Sunscreen.

Sunsense Sport *Ego, Austral.*
Topical milk SPF 30+: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); ensulizole (p. 1703·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

Ego, Austral.; Ego, Hong Kong.
Cream SPF 30+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); enzacamene (p. 1703·2).
Sunscreen.

Ego, Malaysia†; Ego, Singapore.†
Gel SPF 30+: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); amiloxate (p. 1694·1).
Sunscreen.

Sunsense Sport Gel
Note: this name may be used for preparations of different composition.
Ego, Malaysia.†
SPF 30+: Amiloxate (p. 1694·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); oxybenzone (p. 1715·3).
Sunscreen.

Sunsense Sun Sensitive *Ego, Hong Kong.*
SPF 60: Titanium dioxide (p. 1725·1).
Sunscreen.

Sunsense Sunsensitive *Ego, Malaysia; Ego, Singapore.*
SPF 50+: Titanium dioxide (p. 1725·1).
Sunscreen.

Sunsense Toddler Milk *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.*
SPF 30+; SPF 50: Titanium dioxide (p. 1725·1); avobenzone (p. 1695·1); octil triazone (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Sunsense Ultra *Ego, Austral.*
SPF 30+: Titanium dioxide (p. 1725·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); bisoctrizole (p. 1697·1).
Sunscreen.

Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.
SPF 50+; SPF 100+: Titanium dioxide (p. 1725·1); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); avobenzone (p. 1695·1); enzacamene (p. 1703·2); ensulizole (p. 1703·1).
Sunscreen.

Crawford, UK.
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Sun-Shades *Melaleuca, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sun/Soleil *Beiersdorf, Canad.*
Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Sunstop *UAS, Philipp.*
SPF 16: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); avobenzone (p. 1695·1).
Sunscreen.

UAS, Philipp.
SPF 30+: Zinc oxide (p. 1729·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Suntacid *Sunward, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); simeticone (p. 1886·2).

Suntotifen *Sunward, Singapore.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic conditions.

Suntrim *Macrophar, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Suntuss *Sunward, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).

Sunvasc *Sunward, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Sunvecon *Sunve, China.*
Fluconazole (p. 578·2).
Fungal infections.

Sunvex *Casasco, Arg.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Sunya *Stragen, Cz.; Stragen, UK.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Sunzepan *Cryopharma, Mex.*
Diazepam (p. 1063·2).
Anxiety; insomnia; premedication; sedative; skeletal muscle spasm.

Suo Le *Huahai, China.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Suo Di *Zhong Bao, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Suo Bang *Double-Crane, China.*
Oxymatrine.

Suo Di Fei *LuoXin, China.*
Guacetisal (p. 1666·1).

Suo Ji *Beisheng Hansheng, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Suo Li An *Bosen, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Suopinchon *Siu Guan, Malaysia.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Supacef *GSK, India.*
Cefuroxime (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Supacid *Pisa, Mex.*
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Supalide *Brown & Burk, Philipp.†*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Supartz *Bioventus, USA.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Super Antioxidant Plus *Lifeplan, UK.*
Vitamins; minerals; fish oil (p. 1460·1); starflower oil (p. 2459·2); garlic oil (p. 2510·3).
Antoxidant preparation.

Super Antioxidante *Natural Life, Arg.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3).
Antoxidant preparation.

Super AO Factors *Future, Canad.*
Betacarotene (p. 2051·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Super AO Formula *Seroyal, Canad.†*
Betacarotene (p. 2051·1); selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Super B *Bullivants, Austral.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Dietary supplement.

Super B1 *Christo, Hong Kong.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 supplement.

Super B2 *Christo, Hong Kong.†*
Riboflavin (p. 2104·3).

Super 3B *Christo, Hong Kong.†*
Cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3); thiamine (p. 2102·3).

Super B6 *Natur-Drogeriet, Denm.*
Pyridoxine hydrochloride (p. 2105·3).
Pyridoxine deficiency.

Christo, Hong Kong.†
Pyridoxine (p. 2105·3).

Super B Complex *Sisu, Canad.*
Vitamin B substances (p. 2102·3).
Nutritional supplement.

Super B-Co *Christo, Hong Kong.†*
Vitamin B substances (p. 2102·3).

Super Beta Prostate *Young Again Products, USA.*
Sitosterol (p. 1471·2); minerals.
Dietary supplement.

Super C *Canadian Sun, Canad.; Natural Factors, Canad.*
Ascorbic acid (p. 2110·3).

Super Cal C *Bioglan, Austral.†*
Calcium ascorbate (p. 2111·1); citrus bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); rutoside (p. 2505·3); rose fruit (p. 2607·1).
Vitamin C supplement.

Super Cal Mag *Seroyal, Canad.*
Minerals; colecalciferol (p. 2113·1).

Super Cal-C Bio *Eagle, Austral.†*
Calcium ascorbate (p. 2111·1); bioflavonoids (p. 2505·2).
Vitamin C deficiency.

Super CC *Health Plus, Canad.†*
Ispaghula (p. 1849·1).
Constipation.

Super City Block *Clinique, Canad.*
SPF 40: Octinoxate (p. 1715·1); octisalate (p. 1715·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Super Colon Cleanse *Aminostar, Hung.*
Ispaghula (p. 1849·1); senna (p. 1885·1).
Constipation.

Super Corega *GSK, Arg.; GSK, Braz.; GSK Consumer, Venez.*
Denture fixative.

Super D Perles *Roberts, USA.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Super E *Christo, Hong Kong.†*
Vitamin E (p. 2119·1).

Super Energex Plus *Sante Naturelle, Canad.†*
Vitamin B substances (p. 2102·3); minerals; kola (p. 2648·2); liver extract (p. 2444·1).

Super Fluid UV Defense *Kiehls, Canad.*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Super 28 Formula *Reese, USA.*
Vitamins; minerals; herbs.

Super GLA *Cantassium Co., UK.*
Gamma linolenic acid (from vegetable oils) (p. 2509·2).

Super Hi Potency *Nion, USA.*
Vitamins; minerals.

Super Ivy Dry *Ivy Corp, USA.*
Zinc acetate (p. 2126·1); benzyl alcohol (p. 1739·3).
Minor skin irritation.

Super LSN *Quantum, Canad.†*
Vitamin C (p. 2110·3).

Super LSN Plus *Quantum, Canad.†*
Echinacea (p. 2498·1).

Super Mega B+C *Quest, UK.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Super Multi *NaturalFactors, Canad.*
Vitamins; minerals.

Super Once A Day *Quest, Canad.†; Quest, UK.*
Vitamins; minerals.

Super One Plus *Alive, Canad.*
Vitamins; minerals.

Super One-A-Day *Foodscience, Canad.†*
Vitamins; minerals.

Super One-a-Day Multi *Golden Glow, Austral.*
Vitamins; minerals; citrus bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); rutoside (p. 2505·3); equisetum (p. 2500·1).
Dietary supplement.

Super Orti-Vite *Seroyal, Canad.*
Vitamins; minerals.

Super Quints *Freeda, USA.*
Vitamin B substances (p. 2102·3).

Super Soluble Duocal *Nutricia, Ital.*
Low-electrolyte, protein-free carbohydrate preparation for special diets.

Super Strength Horseradish Garlic + C *Blackmores, Austral.*
Horseradish (p. 2526·1); garlic (p. 2510·3); ascorbic acid (p. 2110·3); fenugreek (p. 2504·1).
Nasal congestion.

Super Stress Mega B plus Vitamin C *Quest, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Super Sustagen *Mead Johnson, Venez.*
Preparation for enteral nutrition.

Super Tetra *Darya-Varia, Indon.; Pharos, Indon.*
Tetracycline phosphate (p. 373·2).
Bacterial infections.

Super Ultra Mass *Empresa de Nutricion, Arg.*
Preparation for enteral nutrition.
Dietary supplement.

Super Vikaps *Reese, USA.*
Vitamins; minerals.

Super Vita Vim *Jamieson, Hong Kong.*
Vitamins; minerals; choline (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2).

Superace *PharmaSwiss, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Superal *Liferpal, Mex.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Superal Ex *Liferpal, Mex.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1).
Respiratory-tract disorders.

Superal Jarabe *Liferpal, Mex.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract disorders.

Superamin *Vianex (Βιανεξ), Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Superan *Sanofi-Aventis, Braz.*
Alizapride hydrochloride (p. 1815·2).
Nausea and vomiting.

Superanabolon *Spofa, Cz.†*
⊗Nandrolone phenylpropionate (p. 2293·1).
Anabolic; osteoporosis; metastatic breast cancer.

Super-B *EuroHealth, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; lumbago; neuropathy; alcoholism; rheumatic pains; cervical and shoulder-arm syndrome; encephalopathies.

Supercad *Angelini, Gr.; Faran, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Supercarotene C&E *Bioglan, Austral.†*
Betacarotene (p. 2051·1); *d*-alpha tocoferil acid succinate (p. 2119·2); ascorbic acid (p. 2110·3).
Tonic.

Supercent *Philusa, Philipp.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2); cineole (p. 2479·1).
Musculoskeletal and joint disorders; burns; bruises; pruritus.

Supercod *Vivax, Venez.*
Cod-liver oil (p. 2056·3).
Dietary supplement.

Superdophilus *Bioglan, Austral.†; Natren, USA.*
Lactobacillus acidophilus (p. 2596·3).
Dietary supplement; diarrhoea; restoration of gastrointestinal flora.

SuperEPA *Advanced Nutritional Technology, USA.*
Omega-3 marine triglycerides (p. 1460·3).
Dietary supplement.

Superfade
Note: this name may be used for preparations of different composition.
Sunspot, Hong Kong.
Hydroquinone (p. 1705·1); salicylic acid (p. 1719·1).
Skin hyperpigmentation.

Superfade Original *Sunspot, Austral.†*
Hydroquinone (p. 1705·1); salicylic acid (p. 1719·1); padimate O (p. 1716·1).
Skin hyperpigmentation.

Superfade UV Day Shield *Plunkett, Austral.*
SPF 30+: Oxybenzone (p. 1715·3); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Superfade UV Hand Shield *Plunkett, Austral.*
SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Super-Fe *Christo, Hong Kong.†*
Ferrous sulfate (p. 2062·2).

Superheks *Eczacibasi, Turk.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; plaque prevention.

Superhist *Supera, Braz.*
Dexchlorpheniramine maleate (p. 621·1); aspirin (p. 22·2); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Superilop *Panacea, Rus.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Super-O *Biotenk, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Supero *Lifepharma, China; Lifepharma, Ital.; Lifepharma, Rus.*
Cefuroxime sodium (p. 255·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Superol *Chefaro, Neth.†*
Hydroxyquinoline sulfate (p. 2530·1).
Sore throat; burns; wounds.

Super-O-Ligo *Clinique Lafontaine, Canad.*
Minerals.

Superoxylase *Lero, Fr.*
Bioflavonoids (p. 2505·2); vitamin C (p. 2110·3); zinc (p. 2126·1); vitamin E (p. 2119·1); betacarotene (p. 2051·1); carotenoids; manganese (p. 2081·2); selenium (p. 2086·3).
Antoxidant preparation.

Superpep *Hermes, Ger.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea; vertigo; vomiting.

Superplex-T *Major, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Superpyrin *Glenmark, Cz.*
Aloxiprin (p. 20·3).
Fever; pain.

SuperSkin *Medlogic, UK.*
Enbucrilate (p. 2489·3).
Barrier preparation.

Superspor *Zekides, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Super-Tabs *SA Druggists Self Med, S.Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

Supertendin *UCB, Ger.*
⊗Dexamethasone acetate (p. 1631·1); lidocaine hydrochloride (p. 1988·2).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Supertonic *Diafarm, Spain.†*
Amino acids; cyanocobalamin (p. 2107·2).
Tonic.

Supervax *Cassara, Arg.*
A hepatitis B vaccine (p. 2389·3).
Active immunisation.

Superviga *Zdorovje, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Supervit
Note: this name may be used for preparations of different composition.
KVZ, Ukr.
Vitamins; trace elements.
Dietary supplement.

New Pharma, Venez.
Vitamins; minerals.

21-Super-Vita *Minsheng, China.*
Vitamins; minerals.

Supervitaminico *ISA, Arg.†*
Vitamins; magnesium (p. 1786·3); guarana (p. 2648·2).

Supeudol *Sandoz, Canad.*
⊗Oxycodone hydrochloride (p. 113·1).
Pain.

Suphalex *Suphong, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Suphedrine *Suphong, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Suphen *Suphong, Thai.*
Ibuprofen (p. 68·2).
Inflammation; pain; fever.

Suphera *Hawthorn, USA.*
Sulfur (p. 1721·1); sulfacetamide sodium (p. 361·1).
Acne; rosacea; seborrhoeic dermatitis.

Supiroban *Glenmark, S.Afr.*
Mupirocin (p. 327·2).

Supirocin *Glenmark, Braz.; Glenmark, India; Glenmark, Malaysia; Glenmark, Rus.; Glenmark, Singapore.*
Mupirocin (p. 327·2).
Burns; skin infections; wounds.

Supirocin-B *Glenmark, India; Glenmark, Rus.*
⊗Mupirocin (p. 327·2); betamethasone dipropionate (p. 1623·3).
Infected skin disorders.

Suplac *Biolab, Thai.*
Bromocriptine mesilate (p. 895·3).
Female and male infertility; galactorrhoea; amenorrhoea; lactation inhibition.

Suplar *Vedim, Pol.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Suplasyn *Sigma, Braz.; Alveda, Canad.; Nordic, Fr.†; Merckle Recordati, Ger.†; Dipa, Indon.; Premier, Irl.†; Bioniche, Israel; BionicheTeo, Malaysia; Pharmaco, S.Afr.; Bioniche Teoranta, Singapore; Robapharm, Switz.; Bioniche, Thai.; Teva, UK.*
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement following arthrocentesis; osteoarthritis.

Suplecal *Braun, Spain.*
Calcium gluconate (p. 1783·3); calcium saccharate (p. 2172·3).
Calcium deficiency; calcium supplement.

Suplemag B_6 *Polfa Warszawa, Pol.*
Magnesium oxide (p. 1857·3); magnesium aspartate (p. 1787·1); pyridoxine (p. 2105·3).
Magnesium deficiency.

Suplena *Abbott, Arg.; Abbott, Cz.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore.*
Preparation for enteral nutrition in renal failure.

Abbott, Austral.; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Abbott, Mex.†; Abbott, Turk.†; Abbott Nutrition, UK†; Abbott Nutrition, USA.
Preparation for enteral nutrition.
Renal failure; liver disorders.

Abbott, Canad.
Preparation for enteral nutrition in patients with renal disorders.

Suplenex *Siu Guan, Philipp.*
Glucose (p. 2068·3); vitamin B substances (p. 2102·3); dexpanthenol (p. 2582·2); vitamin C (p. 2110·3).
Vitamin deficiency.

Suplentin *Pasteur, Philipp.†*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3) or potassium clavulanate (p. 268·3).
Bacterial infections.

Suplevit *EMS, Braz.*
Tablets: Vitamins; minerals; lysine hydrochloride (p. 2079·3).

EMS, Braz.
Oral liquid: Vitamins.

Riva, Canad.†
Vitamins; minerals.

Supligol NF *Lazar, Arg.*
⊗Prasterone enantate (p. 2299·2); estradiol valerate (p. 2271·2).
Menopausal disorders.

Supofen *Basi, Port.*
Paracetamol (p. 115·1).
Fever; pain.

Supogliz *Perez Gimenez, Spain.†*
⊗Glycerol (p. 2517·2).
Constipation.

Suporin *Umedica, Philipp.*
Cefazolin (p. 237·2).
Bacterial infections.

Supositorios Senosiain *Senosiain, Mex.*
⊗Glycerol (p. 2517·2).
Constipation.

Supotron *Remedina, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Supoviol *Andromaco, Chile.*
Nonoxinol 9 (p. 2199·1).
Vaginal contraceptive.

Supplemin-C *Metro, Philipp.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); lysine (p. 2079·3).
Nutritional supplement.

Suppletive *Dermoteca, Port.*
Moisturiser.
Dry skin.

Supplex *Cedar Health, UK.*
Green-lipped mussel (p. 2522·3).
Joint disorders.

Supplin *Biochemie, Hung.; Sandoz, Hung.; Sandoz, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Support Formula *Quest, Canad.†*
Vitamin B substances; vitamin E; chromium; inositol; ubidecarenone (p. 2637·1).

Supportan *Fresenius Kabi, Chile; SSPC, China; Fresenius Kabi, Cz.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Ital.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.†; Fresenius Kabi, Turk.*
Preparation for enteral nutrition.

Fresenius Kabi, UK.
Preparation for enteral nutrition during chemotherapy.

Suppositoires contre les hemorroides *Weleda, Switz.*
Aesculus (p. 2431·2); hamamelis (p. 2523·3); antimony (p. 2445·1).
Haemorrhoids.

Suppositoria contra haemorrhoides *Pharmachemie, Neth.*
Bismuth subgallate (p. 1822·1); zinc oxide (p. 1729·1).
Haemorrhoids.

Supprelin *Indevus, USA.*
⊗Histrelin acetate (p. 2283·3).
Precocious puberty.

Supra *Valeant, Mex.*
Lidamidine hydrochloride (p. 1853·1).
Gastrointestinal disorders.

Supra Flu *Kimia, Indon.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms; cough.

Suprabion
Note: this name may be used for preparations of different composition.
Berlico Mulia, Indon.
Capsules: Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Berlico Mulia, Indon.
Syrup: Ferrous gluconate (p. 2061·2); vitamin B substances (p. 2102·3).
Anaemias.

Merck, Venez.
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Supracain
Note: this name may be used for preparations of different composition.
Zentiva, Cz.
Articaine hydrochloride (p. 1980·1).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Supracalm *Tecnofarma, Chile.*
Paracetamol (p. 115·1).
Pain; fever.

Supracam *Raffo, Arg.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Supracef *Lusofarmaco, Ital.*
Cefixime (p. 240·3).
Bacterial infections.

Supracefa *Helm, Port.†*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Suprachlor *Meprofarm, Indon.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Supracid
Note: this name may be used for preparations of different composition.
Apotex, Cz.
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Supracof *Loeffler, Mex.*
Benzonatate (p. 1656·2).
Cough.

Supracyclin *Grunenthal, Pol.†*
Doxycycline (p. 288·1).
Bacterial infections.

Supracycline *Grunenthal, Switz.*
Doxycycline (p. 288·1).
Bacterial infections.

Supradex *Dexa, Indon.*
Vitamins; minerals.
Dietary supplement.

Supradol *Liomont, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Supradol-F *Liomont, Mex.*
Ketorolac trometamol (p. 80·2); caffeine (p. 1203·3).
Pain.

Supradyn *Bayer Consumer, Arg.; Bayer, Austria.*
Vitamins; with or without minerals.

Bayer Consumer, Austral.; Bayer, Braz.; Bayer, Chile; Bayer Sante, Fr.; Bayer, Hong Kong†; Bayer, Hung.; Piramal, India; Bayer Consumer, Indon.; Bayer, Israel; Bayer, Ital.; Bayer, Pol.†; Bayer Consumer, Rus.; Bayer, Singapore; Bayer, Switz.; Bayer Consumer, Thai.; Bayer, Turk.; Roche Consumer, UK; Bayer, Ukr.
Vitamins; minerals.
Dietary supplement; tonic.

Bayer Consumer, S.Afr.
Vitamins; minerals; trace elements.

Bayer, China.
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Supradyn Complex Forte *Roche, China.*
Vitamins.

Supradyn Ginseng *Bayer, Chile.*
Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3).
Dietary supplement.

Supradyn Vital 50+ *Bayer, Switz.*
Vitamins; minerals; ginseng (p. 2513·3).

Suprafen *Atabay, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Suprafenid *Meprofarm, Indon.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; gout; pain.

Supraflox *Khandelwal, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Suprafol *Investi, Arg.*
Folic acid (p. 2063·1).
Megaloblastic anaemia; folic acid deficiency; prevention of neural tube defects in pregnancy.

Supragesic
Note: this name may be used for preparations of different composition.
Beta, Arg.
Dextropropoxyphene hydrochloride (p. 43·3) or dextropropoxyphene napsilate (p. 43·3); ibuprofen (p. 68·2) or ibuprofen lysine (p. 68·3).
Pain.

Innovata, S.Afr.
Syrup: Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Pharmaceutical Enterprises, S.Afr.
Capsules: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain.

Supragesic D *Beta, Arg.*
Dextropropoxyphene hydrochloride (p. 43·3); dipyrone (p. 53·3).
Pain.

Suprahyal *Zodiac, Braz.; Tecnofarma, Chile; Asofarma, Mex.; Nolver, Venez.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis; rheumatoid arthritis.

Supralan *Siam Bheasach, Thai.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Supralan-N *Siam Bheasach, Thai.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Supraler *Panalab, Arg.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; allergic skin disorders; pruritus.

Supralip *Solvay, Port.; Abbott, Thai.; Abbott, UK.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Supramol *Sam-On, Israel.*
Paracetamol (p. 115·1).
Fever; pain.

Supramox *Meprofarm, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Sandoz, Switz.†
Amoxicillin (p. 216·2).
Bacterial infections.

Supran *Teva, Israel.†*
Cefixime (p. 240·3).
Bacterial infections.

Supranal *Dexa, Indon.*
Dipyrone (p. 53·3); caffeine (p. 1203·3); thiamine nitrate (p. 2103·2).
Pain.

Suprane *Baxter, Arg.; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Chile; Baxter, China; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Kalbe, Indon.; Baxter, Irl.; Baxter, Ital.; Baxter, Jpn†; Baxter, Malaysia; Baxter, Neth.; Baxter, Norw.; Baxter, NZ; Baxter, Philipp.; Baxter, Pol.; Baxter, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter Anaesthesia, UK; Baxter, USA.*
Desflurane (p. 1898·3).
General anaesthesia.

Supranettes *Alcon, UK.*
Calendula (p. 2465·2); hamamelis (p. 2523·3).
Eyelid cleansing.

Supranettes Naturalag *Alcon, Mex.*
Calendula (p. 2465·2); hamamelis (p. 2523·3).
Skin hygiene.

Supraneuron *Bayer, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; movement disorders; vitamin B deficiency; nausea and vomiting; alcohol withdrawal syndrome.

Supranitrin *Gap, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Supranutrol *Interchemex, Philipp.*
Vitamins; minerals; chlorella growth factor (p. 2475·3); ginseng (p. 2513·3); taurine (p. 2626·2).
Dietary supplement to improve liver function.

Suprapen *GSK, S.Afr.*
Amoxicillin trihydrate (p. 216·2); flucloxacillin sodium (p. 299·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Supraproct-S *Julphar, UAE.*
⊗Betamethasone valerate (p. 1624·1); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders.

Suprarenin *Sanofi-Aventis, Austria; Sanofi-Aventis, Ger.*
⊗Adrenaline hydrochloride (p. 1292·2).
Circulatory collapse; hypersensitivity reactions; shock; adjunct to local anaesthesia; anaphylactic shock.

Suprasec *Janssen-Cilag, Arg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Suprasma *Dexa, Indon.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Suprasorb *Lohmann, Fr.*
Polyurethane foam dressing (p. 1718·1).
Wounds.

Suprasorb A *Lohmann, Belg.; Lohmann, Fr.; Lohmann, Ital.*
Calcium alginate (p. 1136·3).
Wounds.

Suprasorb C *Lohmann, Ital.*
Collagen (p. 2483·2).

Suprasorb F, M, P *Lohmann, Ital.*
Polyurethane dressing (p. 1718·1).

Suprasorb G *Lohmann, Belg.*
A hydrogel dressing.
Wounds.

Suprasorb H *Lohmann, Belg.*
A hydrocolloid dressing.
Wounds.

Suprastin *Egis, Hung.; Egis, Rus.; Egis, Ukr.*
Chloropyramine hydrochloride (p. 620·3).
Hypersensitivity reactions.

Suprastinex *Egis, Rus.*
Levocetirizine hydrochloride (p. 632·3).
Allergic conjunctivitis; allergic rhinitis; urticaria; angioedema; allergic skin disorders.

Supratonin *Grunenthal, Ger.†*
⊗Amezinium metilsulfate (p. 1298·3).
Hypotension.

Supra-Vir *Trima, Israel.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Supraviran *Grunenthal, Ger.†*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Supravis *Vista, Philipp.*
Polymyxin B sulfate (p. 342·3); lidocaine hydrochloride (p. 1988·2).
Bacterial ear infections.

Supravit *Bayer, Turk.*
Vitamins.

Supravital *Liferpal, Mex.*
Royal jelly (p. 2608·1); garlic (p. 2510·3).
Dietary supplement.

Supravit-C *Su-Heung, Philipp.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; nutritional supplement.

Supravite *Nobel, Canad.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Suprax *Sanofi-Aventis, Canad.; Astellas, China; Gedeon Richter, Cz.; Astellas, Ger.†; Gedeon Richter, Hung.; Sanofi-Aventis, Irl.; Wyeth Lederle, Ital.; Richter, Pol.; Gedeon Richter, Rus.; Eczacibasi, Turk.; Sanofi-Aventis, UK; Lupin, USA.*
Cefixime (p. 240·3).
Bacterial infections.

Supraxone *Zhuhai, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Suprazen *Medi-Rx, Philipp.*
Mefenamic acid (p. 85·3).
Pain.

Suprazid *Armoxindo, Indon.*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Suprazole *Teva, S.Afr.*
Metronidazole (p. 936·1).

Suprecur *Sanofi-Aventis, Austria; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Mochida, Jpn; Sanofi-Aventis, Norw.; Sanofi-Aventis, Swed.; Aventis, Turk.; Sanofi-Aventis, UK.*
⊗Buserelin acetate (p. 2256·2).
Endometriosis; ovulation induction; precocious puberty; uterine fibroids.

Suprefact *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.†; Sanofi-Aventis, NZ; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.†; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK.*
⊗Buserelin acetate (p. 2256·2).
Prostatic cancer; ovulation induction; endometriosis; uterine fibroids; precocious puberty; female infertility.

Sanofi-Aventis, Israel.
⊗Buserelin (p. 2256·2) or buserelin acetate (p. 2256·2).
Endometriosis; female infertility; prostatic cancer; uterine fibroids; precocious puberty.

Suprefakt Depo *Sanofi-Aventis, Ukr.†*
⊗Buserelin acetate (p. 2256·2).
Prostatic cancer; reduced testosterone after surgical castration.

Suprekof *Kramer, Philipp.*
Guaifenesin (p. 1666·2).
Cough.

Suprekof DM *Kramer, Philipp.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Suprelip *PharmaSwiss, Cz.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Suprelle *Biolab Sanus, Braz.*
Estradiol (p. 2271·1); norethisterone (p. 2294·2).

Suprema *Biolab Sanus, Braz.*
Norethisterone acetate (p. 2294·3); estradiol (p. 2271·1).
Menopausal disorders.

Supremase *Pentafarma, Port.*
Fluconazole (p. 578·2).
Fungal infections.

Supremin
Note: this name may be used for preparations of different composition.
Pliva Krakow, Pol.
Butamirate citrate (p. 1657·3).
Cough.

St Carlos, Philipp.
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Supremunn *Teva, Mex.*
Ciclosporin (p. 1945·2).
Transplant rejection; rheumatoid arthritis; nephrotic syndrome; atopic eczema; Crohn's disease; uveitis.

Suprenil *Ulagay, Turk.*
⊗Sulfacetamide sodium (p. 361·1); prednisolone acetate (p. 1645·2); phenylephrine hydrochloride (p. 1672·3).
Infected eye disorders.

Suprenza *Akrimax, USA.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Suprep Bowel Prep *Braintree, USA.*
Sodium sulfate (p. 1888·1); potassium sulfate (p. 1793·2); magnesium sulfate (p. 1787·3).
Bowel evacuation.

Supresol *Hospira, Ital.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Parenteral corticosteroid.

Supressin *Pfizer, Austria.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Supresta *Veropharm, Rus.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Suprex *Terramedic, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Suprical D *EMS, Braz.*
Calcium carbonate (p. 1824·3); ergocalciferol (p. 2113·3).

Suprim
Note: this name may be used for preparations of different composition.
Hovid, Hong Kong†; Hovid, Singapore.
Co-trimoxazole (p. 277·3).
Bacterial infections; protozoal infections.

Suprima-Broncho *Shreya, Rus.*
Malabar nut (p. 2549·1); liquorice (p. 1853·2); turmeric (p. 2218·1); ocimum sanctum; ginger (p. 1844·1); solanum xanthocarpum; piper longum; cardamom (p. 2471·1).
Respiratory-tract disorders.

Suprima-Kof *Shreya, Rus.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Suprimal
Note: this name may be used for preparations of different composition.
IPS, Neth.
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Temis, Arg.
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Suprima-Lor *Shreya, Rus.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Suprima-Nos *Shreya, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Suprima-Plus *Shreya, Rus.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); thymol (p. 1772·2); turpentine oil (p. 2636·3).
Catarrh; musculoskeletal and joint disorders.

Suprimox *Ranbaxy, India.*
Amoxicillin (p. 216·2); cloxacillin (p. 274·3) or cloxacillin sodium (p. 275·1).
Bacterial infections.

Suprin
Note: this name may be used for preparations of different composition.
Degorts, Mex.
Dipyrone (p. 53·3).
Pain; fever.

Genepharm, Gr.
Sorbitol (p. 2092·1); adenosine (p. 1291·1); nicotinamide (p. 2083·1); cytochrome C (p. 2491·2).

Supristol *Zydus, India.*
Co-trifamole (p. 277·3).
Bacterial infections.

Suprium
Note: this name may be used for preparations of different composition.
Cazi, Braz.
Vitamins; minerals.

Sanofi-Aventis, Fin.
Sulpiride (p. 1107·3).
Depression; psychoses.

Suprivent *Cadila, India.*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Formerly contained salbutamol sulfate, bromhexine hydrochloride, guaifenesin, and menthol.
Cough.

Suprivent-A *Cadila, India.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2); ambroxol hydrochloride (p. 1654·3).
Formerly contained salbutamol sulfate, guaifenesin, ambroxol, and menthol.
Cough.

Supro *Soprolin, Fr.*
Talc (p. 1722·2); kaolin (p. 1850·1); alum (p. 2439·1); starch (p. 2095·1); boric acid (p. 2459·3); rosa centifolia.
Foot deodorant.

Suprosina *Ultra, Mex.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Suprotide *Fresenius Kabi, Ital.†*
Nutritional supplement.

Suqi *Dihon, China.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Sural *Sanofi-Aventis, Cz.; Extractum, Hung.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Suramine *Suphong, Thai.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Suratin *Suphong, Thai.*
Furazolidone (p. 933·3); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Surbex *Abbott, Gr.*
Vitamin B substances (p. 2102·3).

Abbott, Philipp.; Abbott, USA.
Vitamins.
Vitamin deficiency.

Surbex with C *Abbott, Hong Kong.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiencies.

Surbex T *Abbott, Gr.; Abbott, Hong Kong†; Abbott, Singapore.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Vitamin B and C deficiencies.

Pharma Synth, India.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); liver (p. 2444·1).
Vitamin B and C deficiency; tonic; dietary supplement.

Surbex with Zinc *Abbott, Malaysia.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Nutritional supplement.

Abbott, Singapore.
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Surbex Zinc *Abbott, Hong Kong.†*
Vitamins; zinc (p. 2126·1).
Nutritional supplement.

Surbex-T *Abbott, Indon.; Abbott, Malaysia.†*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C supplement; liver disorders; alcoholism; vitamin supplement.

Surbex-Z *Abbott, Indon.*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Surbex-Zinc *Abbott, Thai.†*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Surbronc *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Fr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Surbu-Gen-T *Goldline, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Sure Step *Johnson & Johnson Medical, Arg.*
Test for glucose in blood (p. 2516·3).

Surecef *Pharmacare, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

SureLac *Caraco, USA.*
Tilactase (p. 2631·2).
Lactose intolerance.

Sure-Lax
Note: this name may be used for preparations of different composition.
Chefaro, UK.
Senna (p. 1885·1).
Constipation.

Sure-Lax (Herbal) *Chefaro, UK.*
Aloes (p. 1816·1); fennel (p. 2503·2); valerian (p. 2640·2); cnicus benedictus (p. 2482·2).
Constipation.

Surélen *Bayer Sante, Fr.†*
Pyridoxine hydrochloride (p. 2105·3); adenosine phosphate (p. 2430·2); potassium aspartate (p. 1793·1); nicotinamide (p. 2083·1); ascorbic acid (p. 2110·3).
Tonic.

Suremine *Taiwan Biotech, Philipp.*
Amino acids.

Surepost *Novo Nordisk, Jpn.*
Repaglinide (p. 495·2).
Diabetes mellitus.

Sureptil *Sanofi-Aventis, Braz.*
Cinnarizine (p. 622·1); heptaminol acefyllinate (p. 1210·3).
Vascular disorders.

Suretin *Allergan, Mex.*
Tazarotene (p. 1724·2).
Psoriasis; acne.

Surfactal *Boehringer Ingelheim, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Neonatal surfactant deficiency; prevention of bronchopulmonary complications following surgery.

Surfactant-BL *Biosurf, Rus.*
Bovine pulmonary surfactant (p. 2599·2).
Respiratory distress syndrome.

Surfactante B *Richet, Arg.*
Bovine pulmonary surfactant (p. 2599·2).

Surfacten *Mitsubishi, Jpn.*
Bovine pulmonary extract (p. 2599·2).
Respiratory distress syndrome.

Surfacur *Biotoscana, Chile.*
Pulmonary surfactant (porcine) (p. 2599·2).
Neonatal respiratory distress syndrome.

Surfak *Chattem, USA.*
Docusate calcium (p. 1836·2).
Constipation.

Surfanios *Anios, Fr.†*
Hydrochlorides of amino acids; didecyldimethylammonium chloride (p. 1750·3).
Surface disinfection.

Surfaxin *Discovery, USA.*
Lucinactant (p. 2599·3).
Neonatal respiratory distress syndrome.

Surfaz *Franco-Indian, India.*
Cream; topical powder; topical solution; vaginal tablets: Clotrimazole (p. 576·2).
Fungal skin and vaginal infections; balanitis.

Franco-Indian, India.
Ear drops: Clotrimazole (p. 576·2); lidocaine (p. 1988·1).
Fungal ear infections.

Surfaz-SN *Franco-Indian, India.*
⊗Clotrimazole (p. 576·2); betamethasone (p. 1623·2); neomycin sulfate (p. 330·1); tolnaftate (p. 596·1).
Formerly contained clotrimazole, betamethasone dipropionate, and neomycin sulfate.
Infected skin disorders.

Surflox *Medreich, Hong Kong.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Surfol *Stiefel, USA.*
Emollient.

Surfolase *Marvecs, Ital.*
Ambroxol acefyllinate (p. 1201·2).
Obstructive airways disease.

Surfont *Ardeypharm, Ger.*
Mebendazole (p. 158·3).
Worm infections.

Surfortan *Alfa Wassermann, Fr.*
Lysine (p. 2079·3); potassium phosphate (p. 1791·1); pyridoxine hydrochloride (p. 2105·3).
Tonic.

Surgam *Sanofi-Aventis, Austral.; Zentiva, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Galenica, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, NZ; Roussel, Pol.; Sanofi-Aventis, Port.; Aventis, S.Afr.†; Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK.*
Tiaprofenic acid (p. 137·1).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Surgamyl *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.†; Scharper, Ital.*
Tiaprofenic acid (p. 137·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Inflammation; musculoskeletal and joint disorders; pain.

Surge *SA Druggists SelfMed, S.Afr.†*
Yellow phenolphthalein (p. 1877·3).
Constipation.

Surgel *Ulmer, USA.*
⊗Carmellose sodium (p. 2175·2); propylene glycol (p. 2205·2); glycerol (p. 2517·2).
Vaginal lubricant.

Surgestone *Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.*
Promegestone (p. 2302·3).
Menstrual disorders; menopausal disorders; mastalgia; fibroids.

Surgi Bac *Ecolab, Canad.†*
Triclosan (p. 1773·2).
Hand disinfection.

Surgical Scrub and Handwash *Vetoquinol, Canad.*
Chloroxylenol (p. 1748·2).
Skin cleansing.

Surgicel *Ethicon, Fr.†; Johnson & Johnson Medical, USA.*
Oxidised regenerated cellulose (p. 1157·3).
Haemorrhage.

Surgicept *Instrumed, Canad.†*
⊗Alcohol (p. 1733·1).
Hand disinfection.

Surgiflo *Johnson & Johnson, Ital.*
⊗Gelatin (p. 1154·1).
Haemostasis.

Surgi-Gel *Orion, NZ.†*
Lubricating gel.

Surgilube *Savage, USA.*
Chlorhexidine gluconate (p. 1743·3).

Suril *Ibirn, Ital.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Sur-Lax *Jean-Marie, Hong Kong.*
Sodium picosulfate (p. 1887·2).
Constipation; stool softener.

Surlid *Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Swed.*
Roxithromycin (p. 356·2).
Bacterial infections.

Surmagal *Demo, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Surmenalit *Faes, Spain.*
Sulbutiamine (p. 2103·1).
Vitamin B1 deficiency.

Surmontil *Aspen, Austral.; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Norw.; Healthcare Logistics, NZ; Patriot, Philipp.; Vitoria, Port.; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.; Aventis, UK; Barr, USA; Duramed, USA.*
Trimipramine maleate (p. 453·1).
Depression; anxiety; insomnia; irritable bowel syndrome; sleep disorders; mixed anxiety depressive states; pain.

Piramal, India; Sanofi-Aventis, Ital.; Sanofi-Aventis, S.Afr.†
Trimipramine (p. 453·1).
Depression; mixed anxiety depressive states; sleep disorders.

Surnox *Sanofi-Aventis, Spain.*
Ofloxacin (p. 334·3) or ofloxacin hydrochloride (p. 334·3).
Bacterial infections.

Surodex *Zizhu, China.*
⊗Dexamethasone (p. 1630·3).
Eye inflammation.

Surong *Yongzheng, China.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Suronit
Note: this name may be used for preparations of different composition.
Degorts, Mex.
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Surpas
Note: this name may be used for preparations of different composition.
Sandoz, Indon.
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Surpass
Note: this name may be used for preparations of different composition.
Wrigley, USA.
Calcium carbonate (p. 1824·3).
Dyspepsia; heartburn.

Surplex *Chi Sheng, Thai.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Intravenous vitamin supplement.

Surquina *Innotech, Fr.*
Quinine hydrochloride (p. 665·2).
Malaria.

Sursum *Abiogen, Ital.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Survanta *Abbott, Arg.; Abbott, Austral.†; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.†; Abbott, Fr.†; Abbott, Ger.†; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Malaysia; Abbott, Mex.; AbbVie, Neth.; Abbott, NZ; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, S. Afr.†; Abbott, Singapore; AbbVie, Spain; AbbVie, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK; Ross, USA; Abbott, Venez.*
Beractant (p. 2599·2).
Neonatal respiratory distress syndrome.

Survector *Servier, Gr.*
Amineptine hydrochloride (p. 400·3).

Survimed *Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Irl.; Fresenius Kabi, Ital.; Fresenius Kabi, Pol.†; Fresenius Kabi, UK.*
Preparation for enteral nutrition.

Survitine *Tradiphar, Fr.†*
Vitamins; minerals.
Nutritional disorders.

Survon-T *Sandoz, Indon.†*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C supplement.

Susano *Halsey, USA.*
Atropine sulfate (p. 1310·2); hyoscine hydrobromide (p. 1845·3); hyoscyamine hydrobromide (p. 1848·1) or hyoscyamine sulfate (p. 1848·1); phenobarbital (p. 535·2).
Gastrointestinal disorders.

Suscard *Forest, Irl.; BioPhausia, Swed.†; Forest Laboratories, UK.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

SuShun *Xinghua, China.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Suspensio Višněvski cum Pice Liquida HBF *Herbacos, Cz.*
Bismuth tribromphenate (p. 1821·3); tar (p. 1723·3); castor oil (p. 2472·1).
Skin disorders.

Suspension Antiacida *Denver, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity; peptic ulcer.

Suspension Antiacida con Simeticona *Denver, Arg.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; gastritis; oesophagitis; flatulence.

Suspiria *Benedetti, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Sustac
Note: this name may be used for preparations of different composition.
KRKA, Hung.; Chemidex, Irl.†; KRKA, Rus.; KRKA, Ukr.†
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; myocardial infarction; acute left ventricular failure.

Pfizer, Arg.
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Sustacal *Novartis, Braz.; Mead Johnson, Indon.; Mead Johnson, Israel.*
Preparation for enteral nutrition.

Mead Johnson Nutritionals, USA.
A range of preparations for enteral nutrition.

Sustagen *BMS, Arg.; Novartis Consumer, Austral.†; Mead Johnson, Braz.; Mead Johnson, Chile; Mead Johnson, Philipp.; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.*
Preparation for enteral nutrition.

Mead Johnson, Indon.; Mead Johnson, NZ.
A range of preparations for enteral nutrition.

Sustain *Support, Braz.*
Preparation for enteral nutrition.

Zee, USA.
Sodium chloride (p. 1795·1); calcium carbonate (p. 1824·3); potassium chloride (p. 1793·2).

Sustained Release C *Blackmores, Austral.*
Ascorbic acid (p. 2110·3); bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); rose fruit (p. 2607·1); rutoside (p. 2505·3).
Vitamin C supplement.

Sustained Release Multi + Antioxidants *Blackmores, Austral.*
Vitamins; minerals.
Dietary supplement.

Sustanon *Organon, Cz.; Organon, Hong Kong; Organon, Ital.; MSD, NZ.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism; masculinisation in gender reassignment of females; osteoporosis in males; androgen deficiency.

Sustanon 100 *Schering-Plough, Austral.†; Organon, India; Organon, Irl.†; Organon, Neth.; Organon, UK.†*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2).
Androgen deficiency; delayed puberty; menorrhagia; female breast cancer; male osteoporosis; male hypogonadism.

Sustanon 250 *Organon, Arg.; MSD, Austral.; Organon, Belg.; Organon, Fin.; Organon, India; Schering-Plough, Indon.; Organon, Irl.†; Organon, Israel; Schering-Plough, Malaysia; Organon, Neth.; Organon, Rus.; Adcock Ingram, S.Afr.; MSD, Singapore; Organon, Turk.; Organon, UK.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism; androgen deficiency; osteoporosis; male infertility; delayed puberty; female breast cancer; supportive therapy for female-to-male transsexuals; male osteoporosis.

Sustemial *Malesci, Ital.*
Ferrous gluconate (p. 2061·2).
Iron deficiency; anaemias.

Sustenan *Organon, Chile.†*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism; osteoporosis.

Sustenan 250 *Schering-Plough, Chile.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism; osteoporosis.

Sustenium *Menarini, Ital.*
Fosfocreatinine disodium (p. 2507·2).
Muscle disorders.

Sustenon 250 *Organon, Port.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism; osteoporosis.

Sustiva *BMS, Canad.; BMS, Cz.; BMS, Fr.; BMS, Ger.; IFET (ΙΦΕΤ), Gr.; BMS, Irl.; BMS, Ital.; MSD, Neth.; BMS, Pol.; BMS, Port.; BMS, Spain; BMS, UK; BMS, USA.*
Efavirenz (p. 975·1).
HIV infection.

Sustonit *Polfa Warszawa, Pol.; Polfa, Rus.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Sustrate *BMS, Braz.*
Propatylnitrate (p. 1478·3).
Angina pectoris.

Sutac *Sriprasit, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

SuTan *Cypress, USA.*
⊗Pseudoephedrine tannate (p. 1676·1); dexchlorpheniramine tannate (p. 620·3).
Allergic rhinitis.

SuTan DM *Cypress, USA.*
⊗Pseudoephedrine tannate (p. 1676·1); dextromethorphan tannate (p. 1660·1); dexchlorpheniramine tannate (p. 620·3).
Cough; cold symptoms; allergic rhinitis.

Sutent *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA.*
Sunitinib malate (p. 859·1).
Gastrointestinal stromal tumours; renal cell carcinoma; pancreatic neuroendocrine tumours.

Suthrocin *Suphong, Thai.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Sutid *Lloyd, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Sutif *Biomed, Spain.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Sutrico *LKM, Arg.*
Finasteride (p. 2358·3).
Alopecia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Sutrico Tar *LKM, Arg.*
Coal tar (p. 1723·2).
Scalp disorders.

Sutril *Ferrer, Spain.*
⊗Torasemide (p. 1516·3).
Oedema; hypertension.

Sutrim *Suphong, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sutriptan *Arrow, Braz.*
Sumatriptan (p. 679·2).

Verisfield, Gr.
Sumatriptan succinate (p. 679·2).
Migraine.

Su-Tuss DM *Cypress, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Su-Tuss HD *Cypress, USA.†*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).

Suvalan *GSK, Austral.; GSK, Irl.*
Sumatriptan succinate (p. 679·2).
Migraine.

Suvardio *Sandoz, Pol.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias.

Suvéal *Densmore, Fr.*
Vitamins; minerals.
A range of dietary supplements.

Suvéveal Intime *Navi, Fr.*
Jojoba; vitamin E (p. 2119·1).
Vaginal cleansing.

Suveelin *Suphong, Thai.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Suvenyl *Chugai, Jpn.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis; periarthritis.

Suvit *Cofasa, Venez.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Suxameton *SAD, Denm.*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Suxidina *Seid, Spain.*
Aspergillus oryzae; dimeticone (p. 1886·2); metoclopramide hydrochloride (p. 1862·2); oxazepam hemisuccinate (p. 1092·2).
Aerophagia; digestive disorders; meteorism.

Suxilep *Mibe, Ger.; Jenapharm, Rus.*
Ethosuximide (p. 521·1).
Epilepsy; absence seizures.

SuXin
Note: this name may be used for preparations of different composition.
Yuekang, China.
Ligustrazine phosphate.

Suxin
Note: this name may be used for preparations of different composition.
Wellso, China.
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Suxinutin *Pfizer, Austria†; Pfizer, Chile†; Pfizer, Swed.*
Ethosuximide (p. 521·1).
Epilepsy; absence seizures.

Suyodil *Continentales, Mex.*
Clioquinol (p. 273·1); kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Suzacrin *Docpharm, Ukr.*
Phospholipid surfactant (p. 2599·2).
Acute lung injury; bronchitis; pulmonary tuberculosis.

SuZhi *Fengan, China.*
Ethylenediamine diaceturate.

Svédkeserű Cream *Naturland, Hung.*
Svedkeseru; camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal pain.

Sveltanet *Ferakon, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Svelty Actifibras *Nestle, Arg.*
Dietary supplement.
Digestive disorders.

Svelty Calcio Plus *Nestle, Arg.*
Dietary supplement.
Calcium supplement.

Svir *Cristalia, Braz.*
Saquinavir (p. 1014·2).
HIV infection.

Sviroxit *Rafarm, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Svitalark *Leovan, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

SVM-Polypac-A *More, Philipp.†*
2 Tablets, ethambutol hydrochloride (p. 296·1); isoniazid (p. 311·2); 1 capsule, rifampicin (p. 350·3); 3 tablets, pyrazinamide (p. 345·2).
Pyridoxine hydrochloride (p. 2105·3) is included in the ethambutol and isoniazid tablets for the prophylaxis of peripheral neuropathy.
Tuberculosis.

SVR 50 *SVR, Fr.*
SPF 50: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

SVR 100 *SVR, Fr.†*
SPF 100: Bisoctrizole (p. 1697·1); a cinnamate derivative (p. 1699·2); a dibenzoylmethane derivative; octil triazone (p. 1715·1); enzacamene (p. 1703·2); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); thermopherol.
Sunscreen.

Svudin *Cristalia, Braz.*
Stavudine (p. 1015·3).
HIV infection.

Swabplus Antiseptic *Swabplus, Canad.†*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Swabplus Insect Bite Relief *Swabplus, Canad.†*
Benzocaine (p. 1980·2).
Insect bites.

Swabplus Mouth Pain Relief *Swabplus, Canad.†*
Benzocaine (p. 1980·2).
Mouth disorders.

Swabplus Teething pain Relief *Swabplus, Canad.†*
Benzocaine (p. 1980·2).
Mouth pain.

Swamlo *Ind-Swift, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Swarm *Pickles, UK.*
Hamamelis (p. 2523·3); dibrompropamidine isetionate (p. 1750·1); calamine (p. 1697·2).
Insect bites and stings.

SW-Dexasone *Sunward, Singapore.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Sweatosan N *Novartis Consumer, Ger.†*
Sage (p. 2608·3).
Hyperhidrosis.

Swecon *YSP, Malaysia.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Swedish Bitters Dr Theiss *Naturwaren, Ukr.†*
Aloes (p. 1816·1); rhubarb (p. 1884·2); myrrh (p. 2566·1); curcuma zedoaria root; gentian (p. 2512·1); carline root; angelica (p. 2443·3); tinnevelly senna (p. 1885·1); camphor (p. 2466·2); tormentil (p. 2633·2); castor (p. 2472·1); bedeguar; calamus (p. 2464·2); nutmeg (p. 2573·1); dictamnus albus root; saffron (p. 2208·2); cimicifuga (p. 2478·1); valerian (p. 2640·2); cinnamon (p. 2479·2); cardamom (p. 2471·1).
Gastrointestinal disorders; reduced appetite; joint and muscle pain; wounds; insect bites.

Sween 24 *Coloplast, Canad.*
Dimeticone (p. 2209·3).

Sween Cream *Coloplast, USA.*
Barrier cream.

Sweet 'n Low *Dietary Foods, UK.*
Acesulfame potassium (p. 2166·2); aspartame (p. 2169·2).
Sugar substitute.

Sweet Sixteen *Abundance, Canad.†*
Vitamins; minerals.

Sweeta C *Combiphar, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Sweetcee *Chew, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Sweety *PGN, Arg.*
Propolis (p. 2597·3).

Swical *Laboratoires Swisse, Canad.*
A range of vitamin and mineral preparations.

Swidro nouvelle formule pastilles contre le mal de gorge *Iromedica, Switz.†*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat pain and inflammation.

Swiff *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Dibasic sodium phosphate (p. 1791·2); monobasic sodium phosphate (p. 1791·1).
Constipation; bowel evacuation.

Swim-Ear *Co-Pharma, UK.*
⊗Isopropyl alcohol (p. 1758·3); glycerol (p. 2517·2).
Removal of trapped ear water.

Swiss Herb Cough Drops *Ricola, Canad.*
Hyssop (p. 2530·3); mallow (p. 2549·2); horehound (p. 1668·3); melissa (p. 2552·3); peppermint (p. 1877·1); menthol (p. 2553·2); sage (p. 2608·3); sambucus (p. 2609·3); wild thyme (p. 2648·1); thyme (p. 2630·2); tilia (p. 2631·3).
Cough; sore throat.

Swiss Kriss *Modern Products, Canad.†*
Senna (p. 1885·1).
Constipation.

Swiss One *Swiss Herbal, Canad.†*
Vitamins; minerals.

Swiss Relief *Temmler, Israel.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Swiss Total One *Swiss Herbal, Canad.†*
Vitamins; minerals.

Swisstec Global Protect *Clarion, Canad.*
SPF 30: Octocrilene (p. 1715·2); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

SX-22 *Sigma, Arg.*
Echinacea purpurea (p. 2498·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1).
Infections.

Syberian *Biofarm, Pol.*
Siberian ginseng (p. 2614·3).
Tonic.

Sybron *Medhaus, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Syclop *Brown & Burk, Philipp.*
Clozapine (p. 1057·3).
Schizophrenia.

Syclopid *Sydenham, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Sycot *Stadmed, India.*
Trifluoperazine hydrochloride (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).
Schizophrenia.

Sycrest *MSD, Belg.; Lundbeck, Cz.; Organon, Denm.; Lundbeck, Fr.; Lundbeck, Ger.; Lundbeck, Neth.; Organon, Norw.; Organon, Pol.; Organon, Port.; Lundbeck, Spain; Lundbeck, Switz.; Lundbeck, UK.*
Asenapine maleate (p. 1040·1).
Bipolar disorder.

Sydenprazole *Okasa, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sydepres *Rotexmedica, Philipp.†*
Fluphenazine decanoate (p. 1075·1).
Psychoses.

Sydnopharm *Sopharma, Rus.; Sopharma, Ukr.*
Molsidomine (p. 1441·1).
Angina pectoris; ischaemic heart disease; heart failure.

Sydolil *Rhein, Mex.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); aspirin (p. 22·2).
Headache including migraine.

Syeda *Sandoz, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1); 7 tablets, inert.
Combined oral contraceptive.

Sygen *TRB, China; Faran, Gr.; Fida-Sinax, Singapore.*
Monosialotetrahexosylganglioside sodium (p. 2510·2).

TRB, Braz.
Monosialoganglioside sodium (p. 2510·2); electrolytes (p. 1775·1).
Cerebrovascular disorders; cNS trauma.

Sykofen *Silom, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; bronchitis; hypersensitivity reactions.

Sykratan *Medis, Ital.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Sylador *Sanofi-Aventis, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Sylatron *Schering, USA.*
Peginterferon alfa-2b (p. 989·2).
Melanoma.

Sylerasamed *Medis, Denm.*
Ramipril (p. 1483·3).
Hypertension; nephropathy; heart failure; myocardial infarction.

Sylfio *Zwitter, Gr.*
Sulfadiazine silver (p. 362·3).
Skin infections; burns; skin ulcers.

Sylgestrel *Actavis, Austria.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Sylicaps *Herbapol Lublin, Pol.†*
Milk thistle (p. 1561·1).
Liver disorders.

Sylicynar *Herbapol Poznan, Pol.*
Cynara (p. 2490·3); silymarin (p. 1561·2).
Liver disorders; atherosclerosis.

Sylifex *Herbapol Poznan, Pol.*
Silymarin (p. 1561·2) phospholipid complex.
Liver disorders.

Sylimarol *Herbapol Pruszkow, Pol.*
Milk thistle (p. 1561·1).
Liver disorders.

Sylimarynal *Herbapol Lublin, Pol.*
Milk thistle (p. 1561·1).
Liver disorders.

Syliverin *Aflofarm, Pol.*
Silymarin (p. 1561·2).
Liver disorders.

Sylivit *Herbapol Poznan, Pol.*
Milk thistle (p. 1561·1); vitamins.
Liver disorders.

Sylk *Sylk, UK.*
Vaginal lubricant.

Syllact *Wallace, USA.*
Ispaghula (p. 1849·1).
Constipation.

Syltrifil *Filadams, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Sylviane *Bayer, Fr.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Bayer Schering, Cz.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Sylvie *SymPhar, Pol.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Symadal M *Chauvin ankerpharm, Ger.*
Dimeticone 200 (p. 2209·3).
Barrier preparation.

Symadin *Alchemy, S.Afr.*
Amantadine (p. 890·3).

Symanastrol *SymPhar, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Symapamid *SymPhar, Pol.*
⊗Indapamide (p. 1409·2).
Hypertension.

Symasteride *SymPhar, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Symax *Capellon, USA.*
Hyoscyamine sulfate (p. 1848·1).
Control of gastrointestinal secretions; cystitis; gastrointestinal spasm; heart block; parkinsonism; renal colic; rhinitis.

Symbenda *Eisai, Singapore.*
Bendamustine hydrochloride (p. 746·2).
Non-Hodgkin's lymphoma; chronic lymphocytic leukaemia.

Symbicord *AstraZeneca, S.Afr.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Asthma.

Symbicort *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗Budesonide (p. 1625·1); formoterol fumarate (p. 1209·2).
Asthma; obstructive airways disease.

Symbioflor 1 *Symbiopharm, Ger.; SymbioPharm, Hung.; Ebi, Switz.*
Cells and autolysate of *Enterococcus faecalis* (p. 2596·3).
Upper respiratory-tract infections; gastrointestinal disorders.

Symbioflor 2 *Symbiopharm, Ger.; SymbioPharm, Hung.; Ebi, Switz.*
Cells and autolysate of *Escherichia coli*.
Gastrointestinal disorders.

Symbioflor E. coli *Symbiopharm, Austria.*
Live cells and autolysate of *Escherichia coli*.
Infections; gastrointestinal disorders.

Symbioflor Enterococcus *Symbiopharm, Austria.*
Live cells and autolysate of *Enterococcus faecalis* (p. 2596·3).
Respiratory-tract disorders.

Symbion *Merck, Indon.†; Merck, Venez.*
Vitamins; minerals.

Symbiotik *Cadila, India.*
Amoxicillin trihydrate (p. 216·2); cloxacillin sodium (p. 275·1); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

Symblasta *SymPhar, Neth.*
Zoledronic acid (p. 1192·3).
Osteoporosis; Paget's disease of bone.

Symblyopia *O2, China.*
Levodopa (p. 902·2).
Amblyopia.

Symbyax *Lilly, Chile; Lilly, Mex.; Lilly, USA.*
Olanzapine (p. 1089·3); fluoxetine hydrochloride (p. 417·1).
Bipolar disorder.

Symelon *SymPhar, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Symepezil *SymPhar, Pol.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Symfaxin *SymPhar, Neth.†; SymPhar, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Symfona
Note: this name may be used for preparations of different composition.
Andromaco, Chile.
Orlistat (p. 2577·1).
Obesity.

Vifor, Switz.
Ginkgo biloba (p. 2512·3).
Mental function impairment; intermittent claudication; vertigo.

Symfonel *Vifor, Switz.*
Ginkgo biloba (p. 2512·3).
Mental function impairment.

Symglic *SymPhar, Pol.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Symicia *Gedeon Richter, Hung.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Symla *SymPhar, Neth.†; SymPhar, Pol.*
Lamotrigine (p. 527·2).
Epilepsy.

Symleptic *SymPhar, Pol.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Symletrol *MD-Pharm, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Symlin *Amylin, USA.*
Pramlintide acetate (p. 494·3).
Diabetes mellitus.

Symlosin *SymPhar, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Symlukast *SymPhar, Pol.*
Montelukast sodium (p. 1214·3).
Asthma.

Symmetrel *Novartis, Austral.; Novartis, Gr.; Novartis, Irl.†; Novartis, Neth.; Novartis, NZ; Novartis, S.Afr.; Novartis, Singapore; Novartis, Switz.; Alliance, UK; Endo, USA.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; herpes zoster; influenza A; drug-induced extrapyramidal disorders.

Symoron *Astellas, Neth.*
⊗Methadone hydrochloride (p. 88·3).
Pain; opioid addiction.

Symoxyl *Piramal, India.*
Amoxicillin (p. 216·2).
Bacterial infections.

Symoxyl-LB *Piramal, India.*
Amoxicillin trihydrate (p. 216·2); *Lactobacillus sporogenes* (p. 2596·3).
Bacterial infections.

SymPak *Dexo, USA.†*
Tablets AM (Sinuvent PE), guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); tablets PM (Omnihist II LA), chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

SymPak II *Dexo, USA.*
⊗Tablets AM (Sinuhist), brompheniramine maleate (p. 618·1); pseudoephedrine hydrochloride (p. 1676·1); tablets PM (Omnihist II LA), chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

SymPak PDX *Dexo, USA.*
Tablets AM (Ah-Chew Ultra), chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1); phenylephrine hydrochloride (p. 1672·3); tablets PM (Dexodryl), chlorphenamine maleate (p. 620·3); hyoscine methonitrate (p. 1846·1).
Upper respiratory-tract disorders.

Sympal *Berlin-Chemie, Ger.*
Dexketoprofen trometamol (p. 79·1).
Pain.

Sympalept *Streuli, Switz.†*
Oxedrine tartrate (p. 1463·2).
Circulatory disorders; hypotension.

Sympathomim *Extractum, Hung.*
Oxedrine tartrate (p. 1463·2).
Hypotension.

Sympathyl *Innotech, Fr.; Innotech, Rus.*
Crataegus (p. 2488·1); california poppy (p. 2466·1); magnesium oxide (p. 1857·3).
Sleep disorders; nervous disorders; anxiety.

Sympatol *Kwizda, Austria†; Boehringer Ingelheim, Ital.†*
Oxedrine tartrate (p. 1463·2).
Hypotension.

Sympavagol *Novartis Sante, Fr.†*
Passion flower (p. 2584·1); crataegus (p. 2488·1).
Nervous disorders; sleep disorders.

Symphocal *Teva, Israel.*
Oxolamine citrate (p. 1671·2).
Cough.

Symphosan
Note: this name may be used for preparations of different composition.
Abbott, Turk.
Arnica (p. 2447·2); hamamelis (p. 2523·3); comfrey (p. 2484·2).
Musculoskeletal, joint, and soft-tissue pain and injury; neuritis.

Bioforce, Switz.†
Comfrey (p. 2484·2).
Soft-tissue injury.

Symphytum Complexe No 48 *Lehning, Fr.†*
Symphytum officinal (p. 2484·2); arnica montana (p. 2447·2); asa foetida (p. 2449·3); aurum metallicum (p. 2521·1); calendula (p. 2465·2); daphne mezereum; echinacea (p. 2498·1); equisetum arvense (p. 2500·1); mercurius corrosivus (p. 2555·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Symphytum Röwo *Asconex, Ger.†*
Symphytum officinale (p. 2484·2); ruta graveolens (p. 2608·2); bellis perennis (p. 2454·2); solanum dulcamara (p. 2497·3); arnica montana (p. 2447·2).
Homoeopathic preparation.

Sympion *SymPhar, Neth.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Sympramol *SymPhar, Pol.*
Opipramol hydrochloride (p. 440·2).
Anxiety disorders.

Symquel *SymPhar, Denm.; SymPhar, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Symtopiram *SymPhar, Neth.†; SymPhar, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Symtrend *SymPhar, Pol.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Synacol CF *Roberts, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Synacort *Syntex, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Synacthen *Defiante, Belg.; Swedish Orphan, Denm.; Sigma-Tau, Ger.; Novartis, Irl.; Novartis, Israel; Defiante, Ital.; Sigma-Tau, Neth.; Novartis, NZ; Defiante, Port.; Novartis, Rus.†; Novartis, Switz.; Alliance, UK.*
⊗Tetracosactide acetate (p. 1648·1).
Diagnosis of adrenocortical insufficiency; adrenocorticotrophic hormone; multiple sclerosis; West's syndrome.

Novartis, Austral.; Defiante, Austria; Novartis, Chile; Swedish Orphan, Swed.; Novartis, Venez.
⊗Tetracosactide (p. 1648·1).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency; multiple sclerosis; infantile spasms; hypsarrhythmia.

Synacthen Depot *Sigma-Tau, Ger.; Novartis, S.Afr.; Novartis, Switz.; Alliance, UK.*
⊗Tetracosactide acetate zinc phosphate complex (p. 1648·1).
Diagnosis of adrenocortical insufficiency; adrenocorticotrophic hormone.

Novartis, Canad.; Novartis, Rus.; Novartis, Turk.
⊗Tetracosactide zinc hydroxide complex (p. 1648·1).
Diagnosis of adrenocortical insufficiency; adrenocorticotrophic hormone.

Synacthene *IFET(ΙΦΕΤ), Gr.*
⊗Tetracosactide (p. 1648·1).
Adrenocorticotrophic hormone; infantile spasm; multiple sclerosis; diagnosis of adrenocortical insufficiency.

Synacthène *Sigma-Tau, Fr.*
⊗Tetracosactide (p. 1648·1).
Diagnosis of adrenocortical insufficiency; adrenocorticotrophic hormone; infantile spasms.

Synaderm *Christo, Hong Kong.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Synaderm-N *Christo, Hong Kong.†*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Synaflan *Phytopharm, Ukr.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Synagis *Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; AbbVie, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Ital.; AbbVie, Jpn; Abbott, Malaysia; Abbott, Mex.; AbbVie, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, Turk.; Abbott, UK; Medimmune, USA; Abbott, Venez.*
Palivizumab (p. 2415·2).
Respiratory syncytial virus infections.

Synalar *Astellas, Belg.†; Valeo, Canad.; Bioglan, Denm.; Jolly-Jatel, Fr.†; Sinclair, Hong Kong; Syntex, Mex.; Bioglan, Norw.; AFT, NZ; Stiefel, Philipp.; Lusomedicamenta, Port.; Glenmark, S.Afr.; Bioglan, Singapore; Astellas, Spain; Bioglan, Swed.; Teofarma, Switz.; Sanofi-Aventis, Thai.†; GP, UK; Medimetriks, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Minerva (Μινερβα), Gr.; Euro Registratie, Neth.
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected ear or eye disorders.

Synalar Bi-Otic *Astellas, Belg.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Inflammatory ear infections.

Synalar C *Syntex, Mex.; Glenmark, S.Afr.; GP, UK.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Synalar med Chinoform *Bioglan, Denm.; Bioglan, Norw.*
⊗Fluocinolone acetonide (p. 1636·1); clioquinol (p. 273·1).
Infected skin disorders.

Synalar N
Note: this name may be used for preparations of different composition.
Sinclair, Hong Kong; Lusomedicamenta, Port.; Glenmark, S. Afr.; Teofarma, Switz.; Sanofi-Aventis, Thai.; GP, UK.
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Syntex, Mex.
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); phenylephrine hydrochloride (p. 1672·3).
Nasal and sinus disorders.

Synalar Nasal *Tora, Spain.*
⊗Phenylephrine hydrochloride (p. 1672·3); fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Nasal congestion and infection.

Synalar Neo *Syntex, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Synalar O *Syntex, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); lidocaine hydrochloride (p. 1988·2).
Otitis externa.

Synalar Oftalmico *Syntex, Mex.†*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Infected eye disorders.

Synalar Otic *Stiefel, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1).
Otitis externa.

Synalar Otico *Tora, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Ear disorders.

Synalar Rectal *Lusomedicamenta, Port.; Astellas, Spain.*
⊗Bismuth subgallate (p. 1822·1); fluocinolone acetonide (p. 1636·1); lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2).
Anorectal disorders.

Synalar Rectal Simple *Astellas, Spain.*
⊗Fluocinolone acetonide (p. 1636·1).
Anorectal disorders.

Synalar Simple *Minerva (Μινερβα), Gr.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Synalgo *Geymonat, Ital.†*
Naproxen aminobutanol (p. 98·2).
Musculoskeletal and joint disorders; sciatica; neuralgia; gout.

Synalgos-DC *Caraco, USA.*
Dihydrocodeine tartrate (p. 52·3); aspirin (p. 22·2); caffeine (p. 1203·3).
Pain.

Synalone *Vickmans, Hong Kong.†*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Synalone-N *Vickmans, Hong Kong.†*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Synalotic *Astellas, Spain.*
⊗Fluocinolone acetonide (p. 1636·1); ciprofloxacin hydrochloride (p. 261·2).
Otitis externa.

Synalten *Ifars, Indon.*
⊗Fluocinolone acetonide (p. 1636·1); gentamicin (p. 304·2).
Infected skin disorders.

Synamox *Idaman, Singapore.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Synap *Adcock Ingram, S.Afr.*
Paracetamol (p. 115·1); dextropropoxyphene napsilate (p. 43·3); diphenhydramine hydrochloride (p. 626·2); caffeine (p. 1203·3).
Pain.

Synapause *Adcock Ingram, S.Afr.*
Estriol (p. 2274·3).
Oestrogen deficiency.

Synapause E *Organon, Ger.†*
Estriol (p. 2274·3).
Menopausal disorders.

Synapause-E$_3$ *Organon, Neth.*
Estriol (p. 2274·3).
Menopausal disorders; adjunct in cervical smear tests; oestrogen deficiency.

Synapsys *Hoch Wertig, Arg.*
Arginine (p. 2049·1); taurine (p. 2626·2); glycine (p. 2071·2).
Dietary supplement.

Synaptiv *Lero, Fr.*
Fish oil (p. 1460·1); vitamins; copper (p. 2057·1); soya phospholipids (p. 2092·3).
Dietary supplement; nervous system disorders.

Synarel *Pfizer, Austral.; Zodiac, Braz.; Pfizer, Canad.; Pfizer, Cz.; 2care4, Denm.; Europharma, Denm.; Orifarm, Denm.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Neth.; Pharmacia, Pol.†; Pharmacia, S.Afr.†; Pfizer, Spain; Ali, Turk.; Pfizer, UK; Pfizer, USA.*
⊗Nafarelin acetate (p. 2292·2).
Endometriosis; ovulation stimulation for in-vitro fertilisation; uterine fibroids; precocious puberty.

Synarela *Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Norw.; Pfizer, Swed.*
⊗Nafarelin acetate (p. 2292·2).
Endometriosis; uterine fibroids; ovarian stimulation for in-vitro fertilisation.

Synarome *Faran, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Synastone *Auden McKenzie, UK.*
⊗Methadone hydrochloride (p. 88·3).
Opioid withdrawal syndrome.

Synavol *Synco, Hong Kong.†*
Dimenhydrinate (p. 625·2).

Synax *Biofarma, Turk.*
Naproxen sodium (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Synazin *Synco, Hong Kong.†*
Perphenazine (p. 1095·3).

Synbetamine *Synco, Hong Kong.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions; inflammatory eye disorders.

Synbio *Kalbe, Indon.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); fructo-oligosaccharides (p. 2508·1).
Digestive disorders.

Synbion *Synco, Hong Kong.†*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

SynBiotics-3 *NutraCea, USA.*
Bifidobacterium longum (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Saccharomyces boulardii* (p. 2596·3).

Synbrozil *Synco, Hong Kong.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Synchlolim *Atlantic, Thai.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Synchloramin *Synco, Hong Kong†; Synco, Singapore.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Synchrobase Duo *General Topics, Ital.*
⊗Lactic acid (p. 2539·1); urea (p. 1727·3).
Dry skin disorders.

Synchrocell *Dermoteca, Port.*
Diosmin (p. 2505·2); aescin (p. 2431·2); acetyl glucosamine (p. 2515·3); glucuronic acid (p. 2517·1).
Cellulite.

General Topics, Ital.
Diosmin (p. 2505·2); acetyl glucosamine (p. 2515·3); glucuronic acid (p. 2517·1).
Cellulite.

Synchro-Levels *Alphrema, Ital.*
Vitamins; amino acids; minerals; fatty acids.

Synchrorose *General Topics, Ital.*
Silymarin (p. 1561·2); dimethyl sulfone (p. 2493·3).
High skin coloration.

Synchrorose Intensivo *Dermoteca, Port.*
Silymarin (p. 1561·2); dimethyl sulfone (p. 2493·3); hyaluronic acid (p. 2526·2); sunscreen.
High skin coloration.

Synchrovit
Note: this name may be used for preparations of different composition.
Dermoteca, Port.
Vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2); acetyl glucosamine (p. 2515·3); glucuronic acid (p. 2517·1); hyaluronic acid (p. 2526·2).
High skin coloration.

General Topics, Ital.
Vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Skin disorders.

Synclar *Cipla, Hong Kong; Cipla, India.*
Clarithromycin (p. 266·2).
Bacterial infections.

Synclovir *Synco, Hong Kong.†*
Aciclovir (p. 964·1).
Herpes simplex infections.

Syncloxil *Jumont, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Synco-CFN *Synco, Hong Kong.†*
⊗Clotrimazole (p. 576·2); fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Syncodrin *Synco, Hong Kong.†*
⊗Pseudoephedrine (p. 1676·1).

Syncofit *Synco, Hong Kong†; Synco, Singapore.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Allergic rhinitis; upper respiratory-tract congestion.

Syncofit Compound *Synco, Hong Kong.†*
⊗Codeine (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).

Syncoforte *Synco, Hong Kong.†*
Vitamin B substances (p. 2102·3).
Vitamin B deficiencies.

Syncol Nocturno *Sanfer, Mex.*
Paracetamol (p. 115·1); diphenhydramine (p. 626·1).

Syncold-P *Synco, Singapore.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).

Synco, Hong Kong.†
⊗Chlorphenamine (p. 620·3); pseudoephedrine (p. 1676·1).

Syncoldtab-M *Synco, Hong Kong.†*
Chlorphenamine (p. 620·3); phenylpropanolamine (p. 1674·1).

Syncomet *Synco, Hong Kong.†*
Cimetidine (p. 1827·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Syncomil *Synco, Hong Kong.†*
Diphenoxylate (p. 1835·3).
Atropine (p. 1310·2) is included in this preparation to discourage abuse.
Diarrhoea.

Syncoquin *Synco, Hong Kong.†*
Chloroquine phosphate (p. 650·1).
Amoebic hepatitis; lupus erythematosus; malaria; rheumatoid arthritis.

Syncort *Synco, Hong Kong.†*
⊗Triamcinolone (p. 1648·3).
Skin disorders.

Syncortyl *Sanofi-Aventis, Fr.*
Desoxycortone acetate (p. 1630·3).
Mineralocorticoid deficiency.

Synco-SMZT *Synco, Hong Kong†; Synco, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Syncro *Fontovit, Braz.†*
Vitamins; minerals; trace elements.

Syncrocor *Ivax, Arg.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Syncumar *Valeant, Hung.; ICN, Pol.; ICN, Rus.*
Acenocoumarol (p. 1290·1).
Thromboembolic disorders.

Syndal *GPC, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Syndi-35 *SymPhar, Pol.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne and hirsutism in women; oral contraceptive in women with androgenic symptoms.

Syndol
Note: this name may be used for preparations of different composition.
SSL, Irl.; Adcock Ingram, S.Afr.; Reckitt Benckiser, UK.
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3); caffeine (p. 1203·3).
Pain and associated tension.

Pharma Investi, Chile.
Ketorolac trometamol (p. 80·2).
Pain.

Husnu Arsan, Turk.†
Naproxen sodium (p. 98·2).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Syndol Period Pain Relief *Boots, UK.*
Naproxen (p. 98·2).
Dysmenorrhoea.

Syndopa *Sun, India; Sun, Rus.; Sun, Thai.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Syndrex *Accord, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Syneclav *Coronet, Indon.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Synédil *Sigma-Tau, Fr.*
Sulpiride (p. 1107·3).
Psychoses; anxiety; behaviour disorders in children.

Synemol *Medicis, USA.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Syneodalin *Synco, Hong Kong†; Synco, Singapore.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Syneolona *Synco, Hong Kong†; Synco, Singapore.*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Syneophylline *Synco, Hong Kong.†*
Diprophylline (p. 1207·3).
Obstructive airways disease.

Syneptine *Sanofi-Aventis, Gr.*
Terfenadine (p. 640·3).

Syner Pro *Natures Sunshine, Canad.†*
A range of vitamin and mineral preparations.

Synera *Ferndale, USA.*
Lidocaine (p. 1988·1); tetracaine (p. 1996·3).
Local anaesthesia.

Synercid *Aspen, Austral.†; Nordic, Fr.†; Monarch, Irl.†; Monarch, Neth.; Healthcare Logistics, NZ; Aventis, Pol.†; Nordic, UK.*
Quinupristin mesilate (p. 347·2); dalfopristin mesilate (p. 347·1).
Bacterial infections.

Sanofi-Aventis, Braz.; Monarch, Cz.†; Monarch, Gr.; Monarch, Hung.†; Monarch, Ital.; Monarch, Port.†; Monarch, USA.
Quinupristin (p. 347·1); dalfopristin (p. 347·1).
Bacterial infections.

Synerga *Laves, Ger.*
Cell-free lysate of *Escherichia coli.*
Allergies.

Synergistic Selenium *Purity Life, Canad.*
Selenium (p. 2086·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Synergon *SERP, Mon.; Biofarma, Turk.*
Progesterone (p. 2300·2); estrone (p. 2275·2).
Amenorrhoea; menopausal disorders.

Synergy B *Bioglan, Austral.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); magnesium (p. 1786·3).

Synergy Defense *Awareness, Canad.*
Amylase (p. 2442·1); protease (p. 2598·1); cellulase (p. 2473·1); lactase (p. 2631·2); sacrosidase (p. 2608·3).
Digestive aid.

Syner-Kinase *IFET (ΙΦΕΤ), Gr.; Syner-Med, UK.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Synermed *Vitalink, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Synermox *Douglas, NZ.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Synerpril *MSD, Denm.†; MSD, Swed.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Synespramid *Ultra, Mex.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastrointestinal motility disorders.

Synesten *Synco, Hong Kong.†*
Clotrimazole (p. 576·2).

Syneudon *Krewel, Ger.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Synfaclor *Synco, Hong Kong.†*
Cefaclor (p. 232·3).
Bacterial infections.

Synfase *Pfizer, Norw.; Pfizer, Swed.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contains 7 inert tablets.
Triphasic oral contraceptive.

Synfenac *Synco, Hong Kong.†*
Diclofenac (p. 48·3).

Synflex *Darya-Varia, Indon.†; Syntex, Indon.† ; Roche, Irl.†; Recordati, Ital.; Roche, Malaysia; Roche, NZ; Roche, S.Afr.; Roche, Singapore; Roche, Thai.; Roche, UK.†*
Naproxen sodium (p. 98·2).
Pain; inflammation; migraine; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Synflorix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Neth.; GSK, Norw.†; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.*
A pneumococcal polysaccharide conjugate vaccine (p. 2410·1).
Active immunisation.

Synfulin *Synco, Singapore.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Synco, Hong Kong.†
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Syngasy *Ultra, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Syngel *Will-Pharma, Belg.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); magnesium hydroxide (p. 1857·2); magnesium trisilicate (p. 1858·1); lidocaine hydrochloride (p. 1988·2).
Gastritis; gastro-oesophageal reflux.

Synglarin *Chibret, Port.†*
Montelukast sodium (p. 1214·3).
Allergic rhinitis.

Syngly *Synmedic, Philipp.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Synhyal *Farmak, Ukr.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Synitidine *Synco, Hong Kong.†*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; oesophagitis; peptic ulcer; Zollinger-Ellison syndrome.

Synium *Synco, Hong Kong.†*
Diazepam (p. 1063·2).

Synizoral *Synco, Hong Kong.†*
Ketoconazole (p. 585·3).
Fungal infections.

Synkapton *Strallhofer, Austria; Strallhofer, Rus.*
Ergotamine tartrate (p. 674·1); dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Migraine and other vascular headaches.

Synkard *Micro, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Synmethasone *Synco, Hong Kong†; Synco, Singapore.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Synmeton *Synmedic, Ukr.*
Nabumetone (p. 97·1).
Musculoskeletal and joint disorders.

Synmex *One Pharma, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Synocrom *Croma, Fr.; Croma, Hong Kong; Italchimici, Ital.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis; knee disorders.

Dee, UK.
Hyaluronic acid (p. 2526·2).
Joint disorders.

Synodium *Synco, Hong Kong.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Synogin *Chinta, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout.

Synol *Lloyd, Philipp.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; uric acid nephropathy.

Synolol *Synco, Singapore.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias; angina pectoris; myocardial infarction; hyperthyroidism; migraine; anxiety; tremor; phaeochromocytoma; hypertrophic cardiomyopathy.

Synco, Hong Kong.†
⊗Propranolol (p. 1479·1).

Synophyt *Isotope Institute, Hung.*
Holmium-166 fytate.
Osteoarthritis of the knee.

Synostep *Ultra, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Synotabs *Croma, Fr.*
Glucosamine sulfate sodium chloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); vitamins; minerals.
Dietary supplement; joint disorders.

Synotec *United Douglas, Philipp.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis.

Synove *Zynova, Philipp.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Synovisol *Baxter, Canad.*
⊗Glycerol (p. 2517·2).

Syn-O-Vits *Osoth, Thai.*
Vitamins; lysine (p. 2079·3).

Synoxicam *Synco, Hong Kong.†*
Piroxicam (p. 125·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Synparyn *Ultra, Mex.*
Albendazole (p. 149·1).
Worm infections.

Synphase *Pharmacia, UK.*
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
Triphasic oral contraceptive.

Synphasec *Pfizer, Ger.*
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
Triphasic oral contraceptive.

Synphasic *Pfizer, Austral.; Pfizer, NZ.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Triphasic oral contraceptive.

Pfizer, Canad.
Ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Synpitan *Deva, Turk.*
Oxytocin (p. 2143·1).
Labour induction; caesarean section; postpartum haemorrhage; incomplete abortion.

Synplex *Synco, Hong Kong.†*
Folic acid (p. 2063·1); vitamins.

Synprofen *Synco, Hong Kong.†*
Ibuprofen (p. 68·2).

Synpurinol *Synco, Hong Kong.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Synrelin *Pfizer, Arg.*
⊗Nafarelin acetate (p. 2292·2).
Endometriosis; female infertility; precocious puberty; uterine fibroids.

Synrelina *Pfizer, Switz.*
⊗Nafarelin acetate (p. 2292·2).
Endometriosis.

Synribo *Teva, USA.*
Omacetaxine mepesuccinate (p. 837·3).
Chronic myeloid leukaemia.

Syntabrax *Synco, Singapore.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable bowel syndrome.

Synco, Hong Kong.†
Chlordiazepoxide (p. 1044·2); clidinium.

Syntalin *Synco, Hong Kong.†*
⊗Salbutamol (p. 1220·2).

Syntam *Synmosa, Malaysia.*
Piracetam (p. 393·3).
Myoclonus.

Syntaris *Docpharma, Belg.†; Roche, Cz.†; Dermapharm, Ger.; Recordati, Ital.; Ivax, Neth.†; Ivax, UK.*
⊗Flunisolide (p. 1635·3).
Allergic rhinitis.

Syntarpen *Polfa Tarchomin, Pol.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Syntemax *Pascual, Philipp.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected ear disorders.

Syntemucol *Synteza, Pol.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Syntermycin *Synco, Singapore.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Synco, Hong Kong.†
Oxytetracycline (p. 337·1).

Syntesor *EuroHealth, Philipp.*
⊗Hydrocortisone sodium succinate (p. 1640·3).
Corticosteroid.

Syntest *Breckenridge, USA.*
⊗Esterified oestrogens (p. 2270·3); methyltestosterone (p. 2291·3).
Menopausal disorders.

Syntestan *Teofarma, Ger.*
⊗Cloprednol (p. 1628·1).
Asthma; polyarthritis.

Synthamin *Baxter, Austral.; Baxter, Ger.; Baxter, Irl.; Baxter, NZ; Baxter, Spain; Baxter, Switz.†; Baxter, UK.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Synthocilin *PC India, India.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Synthol *GSK Sante, Fr.*
Menthol (p. 2553·2); resorcinol (p. 1718·3); salicylic acid (p. 1719·1); veratrol (p. 2644·2).
Soft-tissue trauma; mouth and throat disorders; insect stings.

Synthomanet *Remedina, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Synthomycin *Biosintez, Rus.; Dalkhimfarm, Rus.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Synthomycine *Rekah, Israel; Teva, Israel.*
Chloramphenicol (p. 257·1).
Bacterial eye and skin infections.

Synthroid *Abbott, Arg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, NZ; Abbott, Philipp.; Abbott, S.Afr.; Abbott, USA.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid-stimulating hormone suppression.

Syntocinon *Novartis, Arg.; Novartis, Austral.; Defiante, Austria; Defiante, Belg.; Novartis, Braz.; Novartis, Chile; Swedish Orphan, Denm.; Defiante, Fin.; Sigma-Tau, Fr.; Sigma-Tau, Ger.; Novartis, Hong Kong; Novartis, India; Novartis, Indon.; Novartis, Irl.; Defiante, Ital.; Novartis, Malaysia; Sandoz, Mex.; Sigma-Tau, Neth.; Swedish Orphan, Norw.; Novartis, NZ; Novartis, Philipp.; Defiante, Port.; Novartis, S.Afr.; Novartis, Singapore; Defiante, Spain; Swedish Orphan, Swed.; Novartis, Switz.; Alliance, UK; Novartis, Venez.*
Oxytocin (p. 2143·1).
Postpartum haemorrhage; induction and maintenance of labour; caesarean section; lactation stimulation; third-stage labour induction; incomplete or missed abortion; termination of pregnancy; lochiometra; uterine atony; mastitis.

Syntoclox *Codal Synto, Thai.†*
Cloxacillin sodium (p. 275·1).
Bacterial infections.

Syntocriptine *Codal Synto, Hong Kong.*
Bromocriptine mesilate (p. 895·3).
Lactation inhibition; hyperprolactinaemia; prolactinomas; benign breast disorders; menstrual disorders; acromegaly; parkinsonism.

Syntolexin *Ceutical, Hong Kong.†*
Cefalexin (p. 234·1).
Bacterial infections.

Syntometrine *Novartis, Austral.; Novartis, Hong Kong; Novartis, Irl.; Novartis, Malaysia; Novartis, NZ; Novartis, S.Afr.; Novartis, Singapore; Alliance, UK.*
Ergometrine maleate (p. 2136·2); oxytocin (p. 2143·1).
Postpartum haemorrhage; management of third-stage labour.

Syntomide *Synco, Singapore.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal motility disorders; nausea and vomiting.

Synco, Hong Kong.†
Metoclopramide (p. 1862·2).

Syntonol *Codal Synto, Thai.*
⊗Propranolol hydrochloride (p. 1479·1).
Hypertension; arrhythmias; angina pectoris; phaeochromocytoma; anxiety; tremor.

Syntophyllin *BB, Cz.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Syntopic *Vendiz, Philipp.*
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Syntostigmin *BB, Cz.; Zentiva, Cz.*
Neostigmine bromide (p. 687·2) or neostigmine metilsulfate (p. 687·2).
Decreased gastrointestinal motility; myasthenia gravis; reversal of competitive neuromuscular blockade; urinary retention; glaucoma.

Syntox *Duopharma, Philipp.*
Oxytocin (p. 2143·1).
Postpartum hemorrhage; labour induction; missed abortion.

Synvibra *Synco, Hong Kong.†*
Doxycycline (p. 288·1).
Bacterial infections.

Synvisc *Gobbi, Arg.; Genzyme, Austral.; Novartis, Braz.; Genzyme, Canad.; Novartis, Chile; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Hong Kong; Piramal, India; Genzyme, Jpn; Genzyme, Malaysia; Novartis, Mex.; Healthcare Logistics, NZ; Genzyme, Pol.; Sanofi-Aventis, Singapore; Genzyme, Swed.; Genzyme, Switz.†; Genzyme, Thai.; Wyeth, Turk.; Biomatrix, UK; Genzyme, USA; Novartis, Venez.*
Hylan G-F 20 (p. 2526·2).
Synovial fluid replacement; osteoarthritis; degenerative joint disorders.

Genzyme, Ital.
Hylan A; hylan B (p. 2526·2).
Osteoarthritis.

Genzyme, Israel.
Sodium hyaluronate (p. 2526·2).
Synovial fluid replacement.

Synvodex *Synmedic, Philipp.*
Sulfadiazine silver (p. 362·3).
Infected burns, ulcers, and wounds.

Synvomin *Synco, Hong Kong†; Synco, Singapore.*
Promethazine teoclate (p. 638·2).
Nausea and vomiting.

Synza *Plus Pharma, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Synthon, Neth.; Synthon, Port.
Olanzapine benzoate (p. 1089·3).
Schizophrenia; bipolar disorder.

Syplex *Swiss Health, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2).
Dietary supplement for children.

Syprine *MSD, Singapore; Aton, USA.*
Trientine dihydrochloride (p. 1578·3).
Wilson's disease.

Syprol *Rosemont, UK.*
⊗Propranolol hydrochloride (p. 1479·1).

Syquet *Alphapharm, Austral.*
Quetiapine fumarate (p. 1101·1).
Bipolar disorder; schizophrenia.

Syracol CF *Roberts, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Syrea *Medac, Ger.*
Hydroxycarbamide (p. 803·1).
Chronic myeloid leukaemia; polycythaemia vera; essential thrombocythaemia.

Syrex *Orifarm, Denm.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux.

Syron *Mabo, Spain.*
Ferritin (p. 2060·2).
Iron deficiency; iron-deficiency anaemia.

Syronem *Simpex, Rus.*
Meropenem (p. 321·3).
Bacterial infections.

Syrop Prawoślazowy Złożony *Gemi, Pol.*
⊗Althaea (p. 2438·3); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract infections.

Syrop Sosnowy Złożony *Aflofarm, Pol.*
Calcium lactate (p. 1784·1); greater celandine (p. 2522·2); codeine phosphate (p. 40·2); aniseed (p. 2444·2); scots pine (p. 2591·1).
Cough and associated respiratory-tract disorders.

Herbapol Lublin, Pol.†
Calcium lactate (p. 1784·1); greater celandine (p. 2522·2); codeine phosphate (p. 40·2); fennel (p. 2503·2); scots pine (p. 2591·1).
Cough and associated respiratory-tract disorders.

Syrupred *Brel, Philipp.†*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Syrvite *Barre-National, USA; Major, USA; Moore, USA.*
Vitamins.

Syscan *Torrent, India; Torrent, Philipp.; Torrent, Rus.*
Fluconazole (p. 578·2).
Fungal infections.

Sysco Antimicrobial *Sysco, Canad.†*
Triclosan (p. 1773·2).
Skin cleansing.

Syscor *Bayer, Austria; Bayer, Belg.; AstraZeneca, Braz.; Bayer Schering, Fin.; Bayer, Gr.; Bayer, Ital.; Bayer, NZ; Intendis, Spain; AstraZeneca, Turk.; Forest Laboratories, UK.†*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension; heart failure.

Syspro *Professional Health, Canad.†*
Vitamins; minerals.

Systabon *Merck, Indon.*
Pramiverine hydrochloride (p. 2596·1).
Smooth muscle spasm; post-operative pain.

Systaflam *Systopic, India.*
Diclofenac diethylamine (p. 48·3); menthol (p. 2553·2); mephenesin (p. 2025·2); methyl salicylate (p. 92·1); turpentine oil (p. 2636·3).
Formerly contained chlorzoxazone, diclofenac sodium, and paracetamol.
Musculoskeletal and joint disorders.

Systan UL *Alcon, Israel.*
Macrogol 400 (p. 2547·3); propylene glycol (p. 2205·2).
Dry eyes.

Systane *Alcon, Arg.; Alcon, Austral.; Alcon, Canad.; Alcon, China; Alcon, Hong Kong; Alcon, Indon.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, Philipp.; Alcon, Turk.; Alcon, USA; Alcon, Venez.*
Macrogol 400 (p. 2547·3); propylene glycol (p. 2205·2).
Dry eyes.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Alcon, Chile; Alcon, Fr.; Alcon, Ital.; Alcon, Singapore; Alcon, Thai.
Macrogol 400 (p. 2547·3); propylene glycol (p. 2205·2); guaraprolose (p. 2187·3).
Dry eyes; eye irritation.

Alcon, Ger.; Alcon, Irl.; Alcon, UK.
Guaraprolose (p. 2187·3).
Dry eyes; eye irritation.

Systane Balance *Johnson & Johnson, USA.*
Propylene glycol (p. 2205·2).
Dry eyes.

Systane Nighttime *Alcon, USA.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3); wool fat (p. 2219·3).
Dry eyes.

Systen *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Gr.; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.*
Estradiol (p. 2271·1).
Oestrogen deficiency; osteoporosis; menopausal disorders.

Systen Conti *Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; 2care4, Denm.; Janssen-Cilag, Gr.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders.

Systen Sequi *Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Gr.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.*
4 Patches, estradiol (p. 2271·1); 4 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders.

Systilan *Biomedica, Gr.*
Cisapride (p. 1831·3).
Gastrointestinal motility disorders.

Systral *Meda, Ger.†; Asta, Gr.; Asta Medica, Indon.†; Transfarma, Philipp.; Sidefarma, Port.; Invida, Thai.; Ulagay, Turk.*
Chlorphenoxamine hydrochloride (p. 622·1).
Allergic skin disorders; sunburn; insect bites; skin irritation; pruritus; urticaria; eczema; burns; frostbite; stings.

Systral Hydrocort *Meda, Ger.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Sythro *Desant, Gr.*
Clarithromycin (p. 266·2).

Sytrex *United Drug, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Sytron *Archimedes, UK.*
Sodium feredetate (p. 2088·3).
Iron-deficiency anaemia.

Syu *Anglo-French Drugs, India.*
Nutritional supplement.

Syxyl Heuschnupfen *Syxyl, Ger.*
Adhatoda vasica (p. 2549·1).
Homoeopathic preparation.

Szelén+C *Fahrvitex, Hung.*
Selenium yeast (p. 2125·2); ascorbic acid (p. 2110·3).
Dietary supplement.

Szent Lukács *Zatonyi, Hung.*
Lavender oil (p. 2541·1); calendula oil (p. 2465·2); achillea (p. 2427·3); peppermint oil (p. 1877·1); sage oil (p. 2609·1).
Musculoskeletal and joint pain; skin disorders; headache.

T-1 *Osoth, Thai.†*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

T3
Note: this name may be used for preparations of different composition.
Hoe, Singapore.
Triclosan (p. 1773·2); melaleuca oil (p. 2551·1).
Acne.

Unipharma, Gr.
Liothyronine sodium (p. 2342·3).
Hypothyroidism.

T4 *Montpellier, Arg.; Unipharma, Gr.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroiditis; thyroid cancer.

T3 Acne *Hoe, Malaysia.*
Body wash: Triclosan (p. 1773·2); melaleuca oil (p. 2551·1).
Acne.

Hoe, Malaysia.
Topical solution: Salicylic acid (p. 1719·1); tocoferil acetate (p. 2119·2); aloe vera (p. 1693·2); rosa canina oil.
Acne.

T3 Actin *Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore.*
Tretinoin (p. 1725·2).
Acne.

T3 ADA *Hoe, Malaysia.*
Adapalene (p. 1692·1).
Acne.

T3 Concealer *Hoe, Malaysia.*
Triclosan (p. 1773·2); titanium dioxide (p. 1725·1).
Spots.

T3 Continuous Control Wash *Hoe, Singapore.*
Triclosan (p. 1773·2).
Acne.

T Man Cough Syrup *T Man, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cough; cold symptoms.

T Man Lax *T Man, Thai.*
Bisacodyl (p. 1821·1); docusate sodium (p. 1836·2).
Constipation.

T3 Mycin *Hoe, Hong Kong; Hoe, Malaysia; Hoe, Philipp.*
Clindamycin phosphate (p. 269·3).
Acne.

TA Bäume *Bencard, Ger.*
Allergen extracts of tree pollen (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

TA Gräser *Bencard, Ger.*
Allergen extracts of grass pollen (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

Ta Jiu Shu *Shenyang Medical, China.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

TA Kräuter top *Bencard, Ger.*
Allergen extracts of mixed pollens (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

TA MIX *Bencard, Ger.†*
Allergen extracts of mixed pollens (p. 2593·3) (p. 2434·3).
Allergen immunotherapy.

TA Osoth *Osoth, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tabacum Composé *Boiron, Fr.*
⊗Tabacum (p. 2632·2); cocculus indicus (p. 2483·1); arnica montana (p. 2447·2); petroleum (p. 2587·2); belladonna (p. 2453·3); ipeca (p. 1667·2); ignatia amara (p. 2532·1); coca (p. 1983·3).
Homoeopathic preparation.

Tabacum-Plus *Doctor H, Rus.*
⊗Lobelia inflata (p. 2323·2); magnesium carbonicum (p. 1856·2); nicotiana tabacum (p. 2632·2); passiflora incarnata (p. 2584·1); plantago major (p. 2592·3); sulfur (p. 1721·1).
Homoeopathic preparation.

Tabalon *Teofarma, Ger.†; Sanofi-Aventis, Mex.*
Ibuprofen (p. 68·2).
Fever; gout; pain; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Tabapass *Ferrier, Fr.*
Caladium seguinum; nux vomica (p. 2573·3); tabacum (p. 2632·2).
Homoeopathic preparation.

Tabarell *Sanorell, Ger.*
⊗Nicotiana tabacum (p. 2632·2); lobelia inflata (p. 2323·2); robinia pseudoacacia.
Homoeopathic preparation.

Tabas *Meprofarm, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Tab-A-Vite *Major, USA.*
Vitamins; with or without iron (p. 2073·1).

Tabcin Alergia *Bayer Consumer, Arg.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Tabcin Antigripal *Bayer Consumer, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms.

Tabcin Caliente Descongestivo *Bayer Consumer, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Tabcin Compuesto *Bayer Consumer, Arg.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Tabcin D *Bayer Consumer, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms.

Tabcin Impakt *Bayer, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cold and influenza symptoms.

Tabcin Rapida Accion *Bayer Consumer, Arg.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2).
Cold and influenza symptoms.

Tabcin Trend *Bayer, Pol.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Taberil *Medochemie, Gr.; Pharmacypria, Gr.*
Paroxetine hydrochloride (p. 440·3).
Depression.

Tabex *Sopharma, Bulg.; Sopharma, Pol.; Sopharma, Rus.; Sopharma, Ukr.*
Cytisine (p. 2491·1).
Aid to smoking withdrawal; nicotine dependence.

Tabine *Meizler, Braz.; Korea United, Philipp.*
Cytarabine (p. 774·1).
Malignant neoplasms.

Tabletas Antiacidas *Pasteur, Chile.*
Magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Tabletas Phillips *GSK, Chile.*
Calcium carbonate (p. 1824·3); aluminium hydroxide-sorbitol complex (p. 1817·2) (p. 2092·1); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Tabletas Quimpe *Quimpe, Spain.†*
⊗Atropine methonitrate (p. 1310·2); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); ephedrine hydrochloride (p. 1663·2); phenazone (p. 124·1); propyphenazone (p. 127·3).
Upper respiratory-tract disorders.

Tabletki Przeciw Grypie *Cyntfarm, Pol.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Cold and influenza symptoms.

Tabletki Przeciw Niestrawności *Labofarm, Pol.*
Caraway (p. 2470·2); frangula bark (p. 1843·3); peppermint (p. 1877·1); milk thistle (p. 1561·1); taraxacum (p. 2625·3).
Digestive disorders.

Tabletki Tonizujące *Labofarm, Pol.*
Crataegus (p. 2488·1); motherwort (p. 2564·2); melilot (p. 2552·3).
Cardiac disorders.

Tabletki Uspokajające *Labofarm, Pol.*
Lupulus (p. 2546·1); motherwort (p. 2564·2); melissa (p. 2552·3); valerian (p. 2640·2).
Nervous disorders; insomnia.

Tabloid *Prasco, USA.†*
Tioguanine (p. 871·3).
Acute myeloid leukaemia.

Tabonuco *Vargas, Venez.*
⊗Ipecacuanha (p. 1667·2); ephedrine hydrochloride (p. 1663·2); sodium benzoate (p. 1738·2).
Respiratory-tract congestion.

Taboss *Pharmacross, Chile.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Tabotamp *Ethicon, Ger.; Johnson & Johnson, Ital.*
Oxidised cellulose (p. 1157·3).
Surgical haemorrhage.

Tabphyn *ProStrakan, UK.*
Tamsulosin hydrochloride (p. 2369·1).

Tabrin *Sanofi-Aventis, Gr.*
Ofloxacin (p. 334·3) or ofloxacin hydrochloride (p. 334·3).
Bacterial infections.

Tabritis *Potter's, UK.*
Sambucus (p. 2609·3); achillea (p. 2427·3); prickly ash bark (p. 2650·1); lappa (p. 2540·1); clivers (p. 2481·2); poplar bark (p. 2450·3); bearberry (p. 2453·2); senna (p. 1885·1).
Musculoskeletal and joint disorders.

Tabrol *Aristo, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Tabulan *Biotech, Venez.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Tabulettae Laxantes *ICN, Pol.*
Aloes (p. 1816·1); althaea (p. 2438·3); caraway (p. 2470·2); frangula bark (p. 1843·3).
Constipation; dyspepsia.

Tac *Parnell, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

TAC Esofago *Bracco, Ital.*
Barium sulfate (p. 1583·2).
Contrast medium for computerised tomography of the oesophagus.

Tac Fluor *Grimberg, Arg.*
Fluoride (p. 2089·2); xylitol (p. 2220·3).
Dental caries prophylaxis.

Tacamac *Medicine Products, Thai.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; dyspepsia; heartburn; acid aspiration; Zollinger-Ellison syndrome.

Tacap *Kiron, Irl.; Kiron, Port.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tacardia *Penn, Arg.*
Losartan (p. 1422·2).
Hypertension.

Tacardia D *Penn, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tace
Note: this name may be used for preparations of different composition.
Lafi, Chile.
Levonorgestrel (p. 2296·1).
Post-coital oral contraceptive.

Tacef *Vianex (Βιανεξ), Gr.*
Cefmenoxime hydrochloride (p. 241·2).
Bacterial infections.

Tacex *Probiomed, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tachicaf *Angelini, Ital.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Tachidol *Angelini, Ital.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Tachifludec *Angelini, Ital.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Tachinotte *Angelini, Ital.*
Paracetamol (p. 115·1); promethazine hydrochloride (p. 638·2); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold and influenza symptoms.

Tachipirin *Elmor, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Tachipirina *Angelini, Ital.*
Paracetamol (p. 115·1).
Fever; pain.

Tachmalcor *AWD, Cz.†; AWD, Ger.†*
Detajmium bitartrate (p. 1351·2).
Arrhythmias.

TachoComb *Nycomed, Hong Kong; Nycomed, Rus.; Takeda, Singapore.*
Collagen (p. 2483·2); fibrinogen (p. 1151·3); thrombin (p. 1163·2); aprotinin (p. 1133·2).
Haemorrhage.

Takeda, Ukr.
Collagen (equine) (p. 2483·2); fibrinogen (p. 1151·3); thrombin (p. 1163·2).
Haemorrhage.

Tacholiquin *Bene, Ger.*
Tyloxapol (p. 2218·2).
Respiratory-tract disorders associated with increased or viscous mucus.

TachoSil *Nycomed, Austria; Takeda, Belg.; Nycomed, Braz.; Nycomed, Cz.; Nycomed, Denm.; Nycomed, Fin.; Nycomed, Fr.; Nycomed, Ger.; Nycomed, Gr.; Nycomed, Hung.; Nycomed, Irl.; Nycomed, Israel; Nycomed, Ital.; CSL, Jpn; Nycomed, Neth.; Nycomed, Norw.; Nycomed, Pol.; Nycomed, Port.; Nycomed, Spain; Nycomed, Swed.; Takeda, Switz.; Nycomed, UK; Baxter, USA.*
Fibrinogen (p. 1151·3); thrombin (p. 1163·2); on contact with physiological fluids this forms a fibrin glue (p. 1151·2).
Haemorrhage; wound closure.

Tachystin *Chauvin Ankerpharm, Cz.†; Chauvin ankerpharm, Ger.†; Chauvin Ankerpharm, Hung.†; Chauvin, Rus.†*
Dihydrotachysterol (p. 2113·2).
Hypoparathyroidism; pseudohypoparathyroidism; hypocalcaemia; tetany; osteomalacia.

Tacicul *Denver, Arg.*
Losartan potassium (p. 1422·2).
Hypertension.

Tacidine *Alphapharm, Austral.*
Nizatidine (p. 1866·1).
Gastro-oesophageal reflux; peptic ulcer.

Tacigen *Krugher, Ital.*
Gentamicin sulfate (p. 304·2).
Infected skin disorders.

Tacillin-J *Jodas, Rus.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tacines *Denver, Arg.*
⊗Ciprofloxacin (p. 261·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Tacinol *Polipharm, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tacipram *Ceapharma, Port.; Miklich, Port.†*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Tacirel *Servier, Port.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Taclar *Polfa Tarchomin, Pol.*
Clarithromycin (p. 266·2).
Bacterial infections; peptic ulcer.

Tacli *Egis, Denm.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Taclonex *Roche, Arg.; Leo, USA.*
⊗Calcipotriol (p. 1697·2); betamethasone dipropionate (p. 1623·3).
Psoriasis.

Taclorpil *Spefar, Venez.*
Trifluoperazine hydrochloride (p. 1113·2).
Anxiety; vomiting; psychoses.

Tacna *LKM, Arg.*
Terbinafine (p. 593·3).
Fungal infections.

Tacni *Teva, Cz.; Teva, Fin.; Teva, Irl.; Pharmachemie, Neth.; Teva, Norw.; Teva, Swed.; Teva, UK.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tacosol *YSP, Thai.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Tacpan *Panacea, Ger.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tacraf *Panalab, Arg.†*
Tacrolimus (p. 1968·3).
Atopic eczema.

Tacrocel *Perrigo, Israel.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tacro-cell *CellPharm, Ger.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tacrocin *Intas, Philipp.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tacroinmun *LKM, Arg.*
Tacrolimus (p. 1968·3).
Organ transplant rejection.

Tacron
Note: this name may be used for preparations of different composition.
Farmasierra, Spain.†
Naproxen (p. 98·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Tacro-Tic *Cinetic, Arg.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Tacroz *Glenmark, India.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Tactivin *Biomed, Rus.*
Thymus extract (bovine) (p. 2631·1).
Immunodeficiency.

Tactrim *T Man, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tactrol *Teva, Gr.*
Donepezil hydrochloride (p. 390·2).

tactu-mobil *Feldhoff, Ger.*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint disorders.

Tactuo *Galderma, Canad.; Galderma, Denm.†*
Adapalene (p. 1692·1); benzoyl peroxide (p. 1696·1).
Acne.

Tactuoben *Galderma, Spain.*
Adapalene (p. 1692·1); benzoyl peroxide (p. 1696·1).
Acne.

TAD *Biomedica, Hong Kong.*
Glutathione (p. 1555·2).
Alcohol, drug, or organophosphorus poisoning; liver disorders; radiation injury.

Biomedica, Ital.
Glutathione sodium (p. 1555·2).
Prophylaxis of neuropathy induced by cisplatin analogues.

Tad *Biomedica, China.*
Reduced glutathione (p. 1555·2).
Alcohol poisoning; organophosphorus poisoning; liver disorders; radiation injury.

TAD+ *Seroyal, Canad.*
Vitamins; zinc (p. 2126·1).

Tadacip *Cipla, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

Tadalin *Munir, Turk.*
Sodium cyclamate (p. 2180·2); saccharin sodium (p. 2208·1).
Sugar substitute.

Tadegan *Tarbis, Spain.†*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Tadenan *Abbott, China; Fournier, Cz.†; Abbott, Fr.; Fournier, Gr.; Solvay, Gr.; Solvay, Philipp.; Fournier, Pol.; Solvay, Rus.; Abbott, Switz.; Abbott, Thai.; Retsyfarm, Ukr.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Tadenom *Italmex, Mex.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Tadex *Orion, Fin.; Atafarm, Turk.*
⊗Tamoxifen citrate (p. 860·2).
Anovulatory infertility; breast cancer.

Tadim *Phebra, Austral.; Allertec, Gr.; Cresco, Neth.; Nigaard, Swed.*
Colistimethate sodium (p. 275·3).
Pseudomonal lung infections in cystic fibrosis; Gram-negative bacterial infections.

Tadin *TAD, Ger.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tadinar-C *Arlex, Mex.*
Loratadine (p. 633·2); ambroxol (p. 1654·3).
Respiratory-tract disorders.

Tadixian *Guanghua, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Tadol *Pharmacodane, Denm.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tadolak *Saba, Turk.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis.

Tadroxil *Polfa Tarchomin, Pol.*
Cefadroxil (p. 233·2).
Bacterial infections.

Taeniacide *New York Chemical, Thai.*
Niclosamide (p. 161·2); phenolphthalein (p. 1877·3).
Worm infections.

Tafedim *Tamag, Hung.*
Euphorbia (p. 2501·3).
Gastrointestinal disorders.

Tafen *Lek, Cz.; Sandoz, Pol.; Lek, Rus.; Sandoz, Ukr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps; obstructive airways disease.

Tafenil *Asofarma, Mex.*
Flutamide (p. 798·2).
Prostatic cancer.

Tafil *Pfizer, Denm.; Pharmacia, Ger.; Pfizer, Mex.; Pfizer, Venez.*
Alprazolam (p. 1035·2).
Anxiety; depression; panic disorder; mixed anxiety depressive states.

Tafinlar *GSK, UK; GSK, USA.*
Dabrafenib mesilate (p. 776·1).
Malignant melanoma.

Tafirol *Sidus, Arg.; Asofarma, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Tafirol AC *Asofarma, Mex.*
Paracetamol (p. 115·1); diclofenac potassium (p. 48·3).
Fever; inflammation; pain.

Tafirol Artro *Sidus, Arg.*
Paracetamol (p. 115·1); diclofenac potassium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Tafirol Flex *Asofarma, Mex.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Pain; muscle spasm.

Tafirol Mujer *Sidus, Arg.*
Paracetamol (p. 115·1); hyoscine butylbromide (p. 1845·3).

Tafirol T *Sidus, Arg.*
Paracetamol (p. 115·1).
Pain; fever.

Tafirol T Caliente Plus *Sidus, Arg.*
Paracetamol (p. 115·1); phenylephrine (p. 1672·2); ascorbic acid (p. 2110·3).

Tafloc *Aspen, S.Afr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Taflosin *Menarini, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Taflotan *Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Ger.; Santen, Hong Kong; Santen, Norw.; Santen, Pol.; Santen, Singapore; Santen, Swed.; Santen, Thai.*
Tafluprost (p. 2012·1).
Glaucoma; ocular hypertension.

Tafoxam *Biopharm, Philipp.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Tafril *Polfa Tarchomin, Pol.*
Cefradine (p. 249·1) or cefradine with L-arginine.
Bacterial infections.

Tafrom *Cipla, India.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Tagal *Probiomed, Mex.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tagaliv *Teuto, Braz.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Tagamet *GSK, Austral.; GSK, China; Axcan, Fr.†; Vianex (Βιανεξ), Gr.; GSK, Hong Kong; GSK, Indon.†; GSK, Irl.†; GSK, Israel†; GSK, Ital.; GSK, Malaysia; GSK, Mex.; PCO, Neth.†; GSK, Philipp.; Smith Kline & French, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain†; Chemidex, UK; GSK, UK; GSK, USA.*
Cimetidine (p. 1827·1).
Acid aspiration; dyspepsia; gastrointestinal haemorrhage; gastro-oesophageal reflux; pancreatic insufficiency; peptic ulcer; gastritis; short-bowel syndrome; gastric hypersecretion including Zollinger-Ellison syndrome; gastric hyperacidity.

GSK, Braz.
Cimetidine hydrochloride (p. 1827·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tagapro *Medicine Products, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hyperacidity; Zollinger-Ellison syndrome.

Tagera *Unichem, Rus.*
Secnidazole (p. 947·3).
Protozoal infections.

Tagista *Makiz, Rus.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Tagonib *Microsules, Arg.*
Imatinib (p. 807·3).

Tagonis *GSK, Ger.†*
Paroxetine hydrochloride (p. 440·3).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobia.

Tagraf *Panacea, Philipp.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tagren *KRKA, Cz.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Taguinol *Spyfarma, Spain.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Taharmayim *Concept, Israel.*
Troclosene sodium (p. 1774·1).
Water purification.

Taharsept *Concept, Israel.*
Troclosene sodium (p. 1774·1).
Instrument, surface, and equipment disinfection.

Tahartaf *Concept, Israel.*
Troclosene sodium (p. 1774·1).
Equipment disinfection.

Tahor *Europharma, Denm.†; Pfizer, Fr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Tai Le *Yangtze River, China.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Tai Bai *Chia Tai, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tai Bao *Mao Xiang, China.*
Ibuprofen (p. 68·2).
Pain; inflammation.

Tai Bi *Chung-Hwa, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tai Bi Jie *Yabo, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Tai Bin *Bei Da Gao Ke Hua Tai, China.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Tai Er Sai Ke *Luan, China.*
Hydrotalcite (p. 1845·2).
Dyspepsia.

Tai Er Si *Sine, China.*
Isotretinoin (p. 1706·2).
Acne; pityriasis rubra.

Tai Fang *Topfond, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Tai Fei *Sanjing, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Tai Fu Kang *Double-Crane, China; Hengshan, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Tai Ginseng *Emonta, Switz.†*
Ginseng (p. 2513·3); crataegus (p. 2488·1); vitamins.
Tonic.

Tai Jing *Taihuatang, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Tai Ka *Weiao, China.*
Ammonium glycyrrhizate (p. 2520·3).

Tai Ke *Mao Xiang, China.*
Amantadine hydrochloride (p. 890·3); paracetamol (p. 115·1).

Tai Lai Tai *Xibaishou, China.*
Anti-hepatitis B transfer factor (p. 2633·2).

Tai Li Xing *Zhongsheng Haitian, China.*
Lysine hydrochloride (p. 2079·3).

Tai Lin *Taiji, China.*
Arginine aspirin.

Tai Luo *ZhenYuan, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Tai Luo Ping *Shide, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Tai Mei La *Siwei, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Tai Mei Ding *Hua Yuan Zhong Sheng, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tai Mei Ni Ke *Dongyu, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Tai Ming Ke *Liang Fu, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Tai Ning *Libang, China.*
Fluconazole (p. 578·2).
Fungal infections.

Tai Ruo Tan *Tide, China.*
Octreotide acetate (p. 1924·1).
Variceal haemorrhage; acromegaly; endocrine tumours; prevention of complications following pancreatic surgery; HIV-associated diarrhoea.

Tai Si Neng *Tide, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Tai Di Te *Liuan Huayuan, China.*
Lysine hydrochloride (p. 2079·3).

Tai Tong *Bikang, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Tai Tuo *Jiu Tai, China.*
Tobramycin (p. 380·1).
Bacterial infections.

Tai Wei *Nutricia, China.*
Clemastine fumarate (p. 622·3).
Allergic rhinitis; urticaria; allergic skin disorders.

Tai Wei Luo *Tian Yu, China.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Tai Wei Sheng *Tian Yu, China.*
Troxerutin (p. 2505·3).

Tai Wei Te *Tian Yu, China.*
Diltiazem hydrochloride (p. 1359·2).
Arrhythmias.

Tai Wei Tong *Huali Deze, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Tai Xing *Xinbeijiang, China.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tai Ya Pu Xi *Hua Lu, China.*
Ozagrel sodium (p. 2579·1).

Tai Ze *Pude, China.*
Naproxen sodium (p. 98·2).
Pain.

Tai Zhi Ao *Tian Yu, China.*
Rimantadine hydrochloride (p. 1012·2).

Taididing *Gosun, China.*
Cefradine (p. 249·1).
Bacterial infections.

Taïdo *Cetem, Fr.*
⊗Glycerol (p. 2517·2); honey (p. 2072·1); collagen (p. 2483·2).
Vaginal lubricant.

Taigalor *Nycomed, Ital.*
Lornoxicam (p. 83·2).
Pain; inflammation.

Tailening *Mallinckrodt, China.*
⊗Oxycodone (p. 113·1); paracetamol (p. 115·1).
Pain.

Tailiping *Tailison, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Tailite *Taiyang, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Tailixin *Taiyang, China.*
Cefpiramide sodium (p. 247·2).
Bacterial infections.

Tailuda *Huanghai, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Tailuo *Peiling, China.*
Rosiglitazone sodium.
Diabetes mellitus.

Taimox *Taisheng, Philipp.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Taingel *Cabassi, Ital.*
Royal jelly (p. 2608·1); pollen (p. 2593·3); ginseng (p. 2513·3); Siberian ginseng (p. 2614·3).
Nutritional supplement.

Taiqutabs *GSK, Cz.*
Quetiapine fumarate (p. 1101·1).

Tairal *Rottapharm, Spain.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux.

Tairuining *Neptunus, China.*
Taurine (p. 2626·2).
Fever.

Taisho Kampo *Taisho, Malaysia.*
Anchusan (cinnamon (p. 2479·2); corydalis tuber; oyster shell; fennel (p. 2503·2); amomum seed; liquorice (p. 1853·2); alpiniae officinarum hance); shakuyakukanzouto extract (liquorice (p. 1853·2); peony root).
Stomach ache; dyspepsia; vomiting; flatulence; reduced appetite.

Taixinsheng *Baitai, China.*
Nimotuzumab (p. 836·3).
Malignant neoplasms.

Takadol *Expanscience, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Take Air *CTS, Israel.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Takecef *Sofar, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Takedrol *Vianex (Βιανεξ), Gr.*
Cefotiam hydrochloride (p. 246·1).
Bacterial infections.

Takelin *Mersifarma, Indon.*
Citicoline (p. 2480·1).
Head injury; cerebrovascular disorders.

Takepron *Takeda, China; Takeda, Hong Kong; Takeda, Jpn.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Takesulin *Takeda, Jpn.†*
Cefsulodin sodium (p. 249·3).
Mepivacaine hydrochloride (p. 1992·2) is included in the intramuscular injection to alleviate the pain of injection.
Pseudomonal infections.

Taketiam *Takeda, Fr.*
Cefotiam hexetil hydrochloride (p. 246·1).
Bacterial infections.

Takil *Marjan, Braz.*
Tinidazole (p. 949·2); tioconazole (p. 595·3).
Vaginal infections.

Takilpam *Pisa, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Takipirina *Angelini, Port.; Angelini, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Takipril *Meduna, Ger.*
Prilocaine hydrochloride (p. 1994·1).
Spinal anaesthesia.

Taks *Ceutical, Hong Kong†; Codal Synto, Thai.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Taksen *Kocak, Turk.*
Paclitaxel (p. 839·3).

Taksidem *Berk, Turk.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Takus *Pharmacia, Ger.†*
Ceruletide tris(diethylamine) (p. 2473·3).
Diagnostic agent; postoperative atony; paralytic ileus.

Talacen *Sanofi Winthrop, USA.†*
⊗Pentazocine hydrochloride (p. 120·3); paracetamol (p. 115·1).
Pain.

Talam *Aspen, Austral.; LCH, Hong Kong.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Talasa NF *Andromaco, Arg.*
Butamirate citrate (p. 1657·3).
Cough.

Talate *Baxter, Ital.*
Factor VIII (p. 1148·1).
Factor VIII deficiency; von Willebrand's disease.

Talavir *Sigma-Tau, Ital.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Talcef *Ipca, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Talcid *Bayer, Austria; Bayer, China; Bayer, Cz.; Bayer, Ger.; Bayer, Gr.; Bayer, Hung.; Bayer, Mex.; Bayer, Pol.; Bayer, Port.†; Bayer, Rus.; Bayer, Spain†; Bayer, Turk.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity; antacid; dyspepsia; gastritis; peptic ulcer; gastro-oesophageal reflux.

Talcilina *Ronnet, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Talcom *Salubris, China.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolic disorders.

Talem *LKM, Arg.*
Tacrine (p. 396·1).

Talema *Biotech, Venez.*
Diazepam (p. 1063·2).
Anxiety; aggression; delirium tremens; epilepsy; mania; skeletal muscle spasm; spasticity.

Talerc *Ache, Braz.*
Epinastine hydrochloride (p. 628·3).
Hypersensitivity reactions.

Talerc D *Ache, Braz.; Boehringer Ingelheim, Braz.*
⊗Epinastine hydrochloride (p. 628·3); pseudoephedrine (p. 1676·1).

Talerin *Demo, Gr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Talert *Ginsana, Switz.†*
Ginkgo biloba (p. 2512·3).
Mental function impairment; vertigo.

Taleum *PannonPharma, Hung.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Talflex *Bago, Chile.*
Ketoprofen (p. 79·1).
Gout; inflammation; musculoskeletal, joint peri-articular, and soft-tissue disorders; pain.

Talgan *Anpharm (Ανφαρμ), Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Talgesil *CCM, Malaysia.*
⊗Fentanyl (p. 60·1).
Analgesia during anaesthesia.

Talgo *Ern, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Talgo Codeina *Ern, Spain.*
Paracetamol (p. 115·1); codeine (p. 40·2).
Pain.

Talidat *Cheplapharm, Austria; Bolder, Cz.; Cheplapharm, Ger.*
Hydrotalcite (p. 1845·2).
Heartburn; gastric hyperacidity; dyspepsia.

Talidex *Alan, UK.*
Thalidomide (p. 867·3).

Talifer *Lemery, Thai.; Teva, Thai.*
Desferrioxamine mesilate (p. 1544·1).
Iron overload; aluminium overload.

Talin *Overseal, UK.*
Thaumatin (p. 2216·1).
Sugar substitute.

Talinac *Demo, Gr.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Talion
Note: this name may be used for preparations of different composition.
Tanabe Seiyaku, China; Mitsubishi Tanabe, Jpn.
Bepotastine besilate (p. 617·3).
Allergic rhinitis; urticaria; pruritus.
Herbapol Krakow, Pol.
Taraxacum (p. 2625·3).
Liver and biliary-tract disorders; digestive disorders.

Talirax *Demo, Gr.*
⊗Fluorometholone (p. 1637·2).
Inflammatory eye disorders.

Talisman *Aropharma, Canad.†*
Vitamins; minerals.

Talixane *Galderma, Spain.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Talizer *Advaita, Mex.*
Thalidomide (p. 867·3).
Leprosy; HIV-associated wasting; multiple myeloma.

Talliton *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Rus.; Egis, Ukr.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Talnur *Sandoz, Arg.*
⊗Fentanyl (p. 60·1).
Pain.

Talof *Poen, Arg.*
⊗Loteprednol etabonate (p. 1642·1).
Allergic conjunctivitis; keratoconjunctivitis sicca.

Talofen *Solvay, Ital.*
Promazine hydrochloride (p. 1100·1).
Anxiety; vomiting; psychoses; pain; intractable hiccup.

Talofilina *Novartis, Braz.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Talogen *Mylan, Denm.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety; obsessive-compulsive disorder.

Talohexal *Sandoz, Austral.†*
Citalopram hydrobromide (p. 411·1).
Depression.

Taloken *Kendrick, Mex.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Talol *Saval, Chile.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Talomam *Actavis, Denm.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.

Talopam *Plus Pharma, Hung.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Talopram *Integris, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Talopron *Biomedica, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Taloram *Kleva, Gr.*
Citalopram hydrobromide (p. 411·1).

Talosin *Bennett, Gr.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Aspen, Arg.
Tamsulosin (p. 2369·1).

Talotren *Novartis, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Talowin *Costec, Arg.*
Cream: Aloe vera (p. 1693·2); dexpanthenol (p. 2582·2).
Emollient.
Costec, Arg.
Shampoo: Chloroxylenol (p. 1748·2).
Alopecia; seborrhoea.

Taloxa *Aesca, Austria; MSD, Belg.; MSD-Chibret, Fr.; MSD, Ger.; IFET (ΙΦΕΤ), Gr.; Schering-Plough, Hung.; Schering-Plough, Ital.; MSD, Neth.; Schering-Plough, Norw.; Schering-Plough, Port.; MSD, Swed.; MSD, Switz.*
Felbamate (p. 522·1).
Lennox-Gastaut syndrome; epilepsy.

Talozin *Adeka, Turk.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Talpram *Richmond, Arg.*
Escitalopram (p. 416·2).

Talpramin *Psicofarma, Mex.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis; parasomnias; myoclonus; hyperhidrosis of the hands; pain; urinary incontinence; anxiety.

Talpro *Synthon, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Talquisedan *Atlas, Arg.; K2 Health & Wellness, Chile.*
Tapioca (p. 2095·1); silicone (p. 2209·2); calendula (p. 2465·2); vitamin E (p. 2119·1); talc (p. 1722·2).
Skin irritation; hyperhidrosis; emollient.

Talquistina *Lacer, Spain.†*
Calamine (p. 1697·2).
Insect bites; pruritus.

Talsare *Alter, Port.†*
Valsartan (p. 1521·2).
Myocardial infarction; heart failure; hypertension.

Talso *Sanofi-Aventis, Ger.†; Winthrop, Ger.†*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Talsutin *BMS, Braz.; BMS, Hong Kong†; BMS, Indon.†*
Tetracycline hydrochloride (p. 373·2); amphotericin B (p. 569·2).
Bacterial and fungal infections of the vagina.

Talusin *Abbott, Pol.†*
Proscillaridin (p. 1480·2).
Heart failure.

Taluso *Synthon, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Taluvian
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
Apomorphine hydrochloride (p. 892·3).
Erectile dysfunction.

Talval *Merck, Switz.*
Idrocilamide (p. 2025·2).
Musculoskeletal and joint disorders.

Talvosilen *Bene, Cz.; Bene, Ger.; Bene, Hung.; Bene, Pol.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Talwin *Hospira, Ital.; Abbott, Singapore†; Abbott, USA.*
⊗Pentazocine lactate (p. 120·3).
Pain; premedication.

Hospira, Canad.; Sanofi-Aventis, Canad.
⊗Pentazocine hydrochloride (p. 120·3) or pentazocine lactate (p. 120·3).
Pain; premedication; adjunct to general anaesthesia.

Talwin NX *Sanofi Winthrop, USA.†*
⊗Pentazocine hydrochloride (p. 120·3). Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Talzic *Elmor, Venez.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Tam *Alacan, Spain.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Tamagon *Medochemie, Hong Kong.†*
Terfenadine (p. 640·3).
Hypersensitivity reactions.

Tamagsyn *Synthon, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamalis *Uriach, Cz.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

Tamaril *Marjan, Braz.*
Senna (p. 1885·1); tamarind (p. 1892·2); cassia pulp (p. 1826·2); liquorice (p. 1853·2); coriander (p. 2486·3).
Constipation.

Tamarindus Complexe No 95 *Lehning, Fr.†*
Tamarindus (p. 1892·2); natrum carbonicum (p. 2617·3); nux vomica (p. 2573·3); robinia; solanum tuberosum.
Homoeopathic preparation.

Tamarine *GSK, Chile.*
Senna (p. 1885·1); tamarind (p. 1892·2); prune (p. 1881·1); apple.
Constipation.

Barrenne, Braz.; Wyeth Consumer, Ital.
Tamarind (p. 1892·2); cassia pulp (p. 1826·2); senna (p. 1885·1); coriander (p. 2486·3); liquorice (p. 1853·2).
Constipation.

Barrenne, Braz.; Gerolymatos, Gr.
Tamarind (p. 1892·2); cassia pulp (p. 1826·2); senna (p. 1885·1); coriander (p. 2486·3).
Constipation.

GSKSante, Fr.†
Tamarind (p. 1892·2); senna (p. 1885·1).
Constipation.

Tamarinlax *Fahrvitex, Hung.*
Tamarind (p. 1892·2); fennel (p. 2503·2); sambucus (p. 2609·3); coriander (p. 2486·3); liquorice (p. 1853·2).
Constipation.

Tamate *Alphapharm, Austral.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Tambac *Cadila, India.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Tambocor *iNova, Austral.; Meda, Belg.; Medicis, Canad.; 3M, Chile†; 3M, Cz.; Meda, Denm.; Meda, Fin.; Meda, Ger.; IFET (ΙΦΕΤ), Gr.; iNova, Hong Kong; Meda, Irl.; 3M, Israel; iNova, Malaysia; Graceway, Mex.; Meda, Neth.; Meda, Norw.; iNova, NZ; iNova, Philipp.; iNova, S. Afr.; iNova, Singapore; Meda, Swed.; Meda, Switz.; iNova, Thai.; 3M, UK; Medicis, USA.*
Flecainide acetate (p. 1382·3).
Arrhythmias.

Tambutec *Tecnofarma, Mex.*
Ethambutol (p. 296·1).
Tuberculosis.

Tamcere *Ultra, Mex.*
Paroxetine hydrochloride (p. 440·3).
Depression; anxiety; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Tamcibin *Aurora, Gr.*
Gemcitabine hydrochloride (p. 801·2).

Tamcocin *Pyridam, Indon.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Tamec *Sandoz, Switz.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamechol *Steierl, Ger.*
Acidum silicicum (p. 2208·3); myristica sebifera (p. 2573·1).
Homoeopathic preparation.

Tamex *Serral, Mex.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Hypersensitivity reactions.

Tamexin *Ratiopharm, Fin.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamfrex *Aurobindo, UK.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamgard *Sandoz, Turk.*
Valsartan (p. 1521·2).

Tamicin *Lek, China.*
Cefpiramide sodium (p. 247·2).
Bacterial infections.

Tamicin-G *Alvartis, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Tamictor *Avansor, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamidra *Nobel, Turk.*
Tamsulosin hydrochloride (p. 2369·1).

Tamifen *Medochemie, Rus.†*
⊗Tamoxifen citrate (p. 860·2).

Tamiflu *Investi, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Genentech, USA.*
Oseltamivir phosphate (p. 1006·2).
Influenza.

Tamigen *Solfran, Mex.*
Gentamicin (p. 304·2).
Bacterial infections.

Tamik *Alfa Wassermann, Fr.*
Dihydroergotamine mesilate (p. 672·2).
Migraine; orthostatic hypotension; peripheral venous insufficiency.

Tamin *MSD, Spain.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux.

Taminol
Note: this name may be used for preparations of different composition.
Help, Gr.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Viva, Canad.
Paracetamol (p. 115·1).
Fever; pain.

Tamipro *Jelfa, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamipul *Pro-Pharma, Ukr.*
Paracetamol (p. 115·1); ibuprofen (p. 68·2); caffeine (p. 1203·3).
Pain; fever.

Tamiram *Eurofarma, Braz.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tâmisa *Eurofarma, Braz.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Tamixol *Indeco, Arg.*
Pentoxifylline (p. 1465·3).

Tamizam *Mithra, Belg.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; endometrial cancer.

Tamlic *Epifarma, Ital.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamnexyl *Clonmel, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamnic *Clonmel, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamoa *Biotech, Venez.*
Pyrantel embonate (p. 165·3).
Worm infections.

Tamochir *Pharmeg, Ital.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Tamodex *Biochem, India.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamofen *Sanofi-Aventis, Canad.†; Bayer, China; Bayer Schering, Fin.; Kalbe, Indon.; Rhodia, Israel†; Douglas, NZ†; Bayer Schering, Singapore†; Er-Kim, Turk.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility.

Tamokadin *Kade, Ger.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamol *Sandoz, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Tamol Cold *Sandoz, Turk.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Tamolan *Olan-Kemed, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tamophar *Julphar, UAE.*
⊗Tamoxifen citrate (p. 860·2).
Anovulatory infertility; breast cancer.

Tamoplex *Teva, Belg.; Teva, Cz.; Chemipharm, Gr.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.; Er-Kim, Turk.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamosin *Aspen, Austral.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamox *1A, Ger.†; Gry, Ger.†; Rowex, Irl.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxan *Tecnimede, Port.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxen *Ascent, Austral.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxene *Lisapharma, Ital.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxi *Generics, Israel.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxifencell *Assos, Turk.*
⊗Tamoxifen citrate (p. 860·2).

TamoxiHexal *Sandoz, S.Afr.*
⊗Tamoxifen (p. 860·2).
Breast cancer.

Tamoxin *Euroforma, Braz.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxis *Bioprofarma, Arg.*
⊗Tamoxifen (p. 860·2).
Breast cancer.

Tamoxistad *Stada, Ger.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tamoxsta *Baxter, Philipp.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; endometrial cancer.

Tamper *Gap, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Tampo *TNP, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tamprost *Eczacibasi, Turk.*
Tamsulosin hydrochloride (p. 2369·1).

Tamsact *Actavis, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsec *Walmark, Cz.†; Walmark, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsil *Aspen, Austral.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Tamsin *Arrow, Denm.; Arrow, Fin.; Arrow, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsol *Specifar (Σπεσιφαρ), Gr.; Gedeon Richter, Hung.; Gedeon Richter, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsolet *Alet, Gr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsonic *Cipla, Ukr.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsu *Genericon, Austria; Rowex, Irl.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsu-Anlini *Kiron, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsublock *Pfleger, Ger.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

TamsuCinfa *Kiron, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsuda *Stada, Cz.; Stada, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsudil *Actavis, Hung.; Actavis, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

TamsuGaran *Kiron, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsugen *Generics, Hung.; Generics, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsukon *BMM, Denm.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsul *Aspen, S.Afr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulas *Biokanol, Irl.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

TamsuLek *Sandoz, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulid *Borshchagovskii, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulijn *Elpen (Ελπεν), Gr.; Kiron, Neth.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulin *Rafa, Israel.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulogen *Merck, Denm.†; Mylan, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulo-Isis *Actavis, Ger.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulon *Zodiac, Braz.; Sintez, Rus.; Nolver, Venez.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsulonorm *Plus Pharma, Cz.; Plus Pharma, Hung.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsumedin *Kade, Ger.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsumin *Ratiopharm, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsuna *Sandoz, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsunar *Apogepha, Ger.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsunax *Drossapharm, Switz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsunorm *ICN, Denm.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsunova *Docpharma, Austria.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

TamsuPli *Kiron, Fin.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamsu-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tamurox *Ranbaxy, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tan Fu *Fengyuan Tushan, China.*
Piracetam (p. 393·3).
Mental function impairment.

Tan Jing *Hanjiang, China; Otsuka, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Tan Ke Shu *Zhonggui, China.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Tan Nuo *Xinchang, China.*
Doxifluridine (p. 782·3).
Malignant neoplasms.

Tan Shi *Chia Tai, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Tan Si Ke *Yanan Wanxiang, China.*
Azasetron hydrochloride (p. 1820·2).

Tan Xin Suo *Pingyuan, China.*
Telmisartan (p. 1509·3).
Hypertension.

Tanabid *Portal, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Tanac *Church & Dwight, Canad.; Del, USA.*
Topical liquid: Lipstick: Benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1); tannic acid (p. 2625·2).
Sore lips.
Del, USA.
Topical gel: Allantoin (p. 1693·1); dyclonine hydrochloride (p. 1987·1).
Herpes labialis.
Del, USA.
Topical liquid: Benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1).
Mouth ulcers; sore gums.

Tanac Dual Core *Del, USA.*
Benzocaine (p. 1980·2); tannic acid (p. 2625·2); allantoin (p. 1693·1); benzalkonium chloride (p. 1737·1); padimate O (p. 1716·1).
Oral lesions.

Tanacain *Ipsen, Gr.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Tanacet *Herbal Laboratories, Canad.†; Herbal Laboratories, UK.*
Feverfew (p. 676·1).
Migraine.

Tanaceto *Herbarium, Braz.†*
Feverfew (p. 676·1).
Migraine.

Tanadopa *Mitsubishi Tanabe, Jpn.*
Docarpamine (p. 1367·1).
Circulatory failure.

Tanafed DMX *First Horizon, USA.*
⊗Dextromethorphan tannate (p. 1660·1); dexchlorpheniramine tannate (p. 620·3); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Tanafed DP *First Horizon, USA.*
⊗Pseudoephedrine tannate (p. 1676·1); dexchlorpheniramine tannate (p. 620·3).
Upper respiratory-tract disorders.

Tanagel *Durban, Spain.*
Belladonna (p. 2453·3); gelatin tannate (p. 2625·2); opium (p. 111·3).
Diarrhoea; gastroenteritis; colitis.

Tanagel Polvo *Durban, Spain.*
Gelatin tannate (p. 2625·2).
Diarrhoea.

TanaHist PD *Larken, USA.†*
Chlorphenamine tannate (p. 620·3).

TanaHist-D Pediatric *Larken, USA.*
Chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Tanakan *Phoenix, Arg.; Ipsen, Belg.; Abbott, Braz.; Beaufour-Ipsen, China; Ipsen, Cz.; Ipsen, Fr.; Beaufour-Ipsen, Hong Kong; Ipsen, Hung.†; Beaufour-Ipsen, Malaysia; Beaufour-Ipsen, Pol.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Thai.; Abdi, Turk.; Ipsen, Ukr.; Leti, Venez.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; dizziness; tinnitus; vertigo; mental function impairment; sensorineural disorders; vestibular disorders; venous insufficiency; vascular ear and eye disorders; cerebral ischaemia.

Tanakene *Faes, Spain.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders.

Tanakène *Uhlmann-Eyraud, Switz.†*
Ginkgo biloba (p. 2512·3).
Mental function disorders; cerebral and peripheral vascular disorders.

Tanalone *Labima, Belg.*
Albumin tannate (p. 1815·1); pectin (p. 2200·3).
Diarrhoea.

Tanamof *Amhof, Arg.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Tanap *Ingers, Cz.†*
Trandolapril (p. 1517·2).
Hypertension; left-ventricular dysfunction following myocardial infarction; heart failure.

Tanapas *Elpen (Ελπεν), Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; pathological hypersecretory disorders; acid aspiration.

Tanapress *Tanabe, Indon.*
Imidapril hydrochloride (p. 1409·1).
Hypertension.

Tanatril *Craveri, Arg.; Gerot, Austria; Tanabe Seiyaku, China; Abbott, Cz.; Ipsen, Fr.; Kwizda, Ger.†; Gerolimatos (Γερολυματος), Gr.; Tanabe, Hong Kong; Elder, India; Mitsubishi Tanabe, Jpn; Mitsubishi Tanabe, Malaysia; Jelfa, Pol.; Mitsubishi Tanabe, Singapore; Mitsubishi Tanabe, Thai.; Trinity, UK.*
Imidapril hydrochloride (p. 1409·1).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Tanavat *Microsules, Arg.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Tancofeto *GSK, Ukr.*
Vancomycin (p. 384·2).
Gram-positive bacterial infections.

Tandax *Sandoz, Mex.*
Naproxen sodium (p. 98·2).
Pain; inflammation.

Tandem *US Pharmaceutical, USA.*
Ferrous fumarate (p. 2060·3); polysaccharide-iron complex (p. 2086·2).
Iron deficiency.

Tandem DHA *US Pharmaceutical, USA.*
Vitamins; iron (p. 2073·1); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Tandem F *US Pharmaceutical, USA.*
Iron (p. 2073·1); folic acid (p. 2063·1).

Tandem OB *US Pharmaceutical, USA.*
Vitamins; minerals.

Tandem Plus *US Pharmaceutical, USA.*
Ferrous fumarate (p. 2060·3); polysaccharide iron complex (p. 2086·2); vitamin B substances (p. 2102·3); minerals. Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.

Tandemact *Takeda, Austria; Takeda, Cz.; Takeda, Fr.†; Takeda, Ger.; Takeda, Irl.; Takeda, Ital.; Takeda, Neth.; Takeda, Pol.; Takeda, Port.; Takeda, Spain.*
Pioglitazone hydrochloride (p. 493·1); glimepiride (p. 473·2).
Diabetes mellitus.

Tandene *Bunker, Braz.*
Carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Smooth muscle spasm.

Tanderalgin *Delta, Braz.*
Carisoprodol (p. 2021·3); caffeine (p. 1203·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Tanderon *Pharmaland, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Tanding *NEGPF, China.*
Nitrofurantoin (p. 332·1).
Bacterial infections of the urinary tract.

Tandiur *Raymos, Arg.*
⊗Hydrochlorothiazide (p. 1403·2).

Tandix *Azevedos, Port.*
⊗Indapamide (p. 1409·2).
Hypertension.

Tandpyndruppels *Lennon, S.Afr.†*
Camphor oil (p. 2466·2); opium (p. 111·3); capsicum (p. 2469·3); chloroform spirit; chloroform (p. 1898·1); camphor (p. 2466·2); catechu (p. 2472·3).
Toothache.

Tandriflan *Uniao Quimica, Braz.*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); caffeine (p. 1203·3).

Tandrilax *Ache, Braz.*
Paracetamol (p. 115·1); carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); caffeine (p. 1203·3).
Skeletal muscle spasm.

Tandrotamol *Belfar, Braz.*
Caffeine (p. 1203·3); carisoprodol (p. 2021·3); diclofenac (p. 48·3); paracetamol (p. 115·1).

TanDur D M *Proethic, USA.†*
⊗Dextromethorphan tannate (p. 1660·1); dexchlorpheniramine tannate (p. 620·3); pseudoephedrine tannate (p. 1676·1).
Upper respiratory-tract disorders.

Tanezox *Microsules, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Tanfedin *Roemmers Rowe, Venez.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia.

Tanflex *Combiphar, Indon.; Abdi, Turk.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and inflammation.

Tanflomed *Actavis, Rus.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tang Bei Kang *Conba, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tang Bi Fu *Poly, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tang Feng *Pude, China.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Tang Fu *Beisheng, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Tang Ge *Yi Kang, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tang Ke Jie *Kaicheng, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tang Ke Ning *Jiuming, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tang Li Ke *Aohai, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tang Lin *Hailing, China; Yangtze River, China.*
Epalrestat (p. 470·3).
Diabetic neuropathy.

Tang Ling *Zhi Jun, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Tang Luo *Hayao, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tang Na *Zhong Yi, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Tang Ni Wei *Hua Lu, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Tang Ping *Hui Ren, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tang Ren Xin *Qian Long, China.*
Enoxacin gluconate.
Bacterial infections.

Tang Rui *Deyuan, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Tang Rui Ping *GuoRui, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Tang Tan *Huahai, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tang Xin *San Lian, China.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Tang Yi *Global, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Tanganil *Pierre Fabre, Fr.*
Acetylleucine (p. 2427·2).
Vertigo.

TangNa *Ke Lun, China.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).

Tangshiping *Double-Crane, China.*
Gliquidone (p. 474·3).
Diabetes mellitus.

Tangyn *Choongwae, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Tanidina *Robert, Spain.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Tanilas *Ipsen, Gr.*
Macrogol 4000 (p. 2547·3).
Constipation.

Taninal *Herbapol Wroclaw, Pol.*
Albumin tannate (p. 1815·1).
Diarrhoea; dyspepsia; food poisoning.

Tanipril *Ratiopharm, Denm.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Tanizona *Offenbach, Mex.†*
Naproxen (p. 98·2).
Inflammation.

Tanko-Buskas *Fako, Turk.†*
Hyoscine butylbromide (p. 1845·3); medazepam (p. 1083·2).

Tanlozid *Arrow, Denm.; Arrow, Swed.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tannacomp *Medice, Ger.*
Albumin tannate (p. 1815·1); ethacridine lactate (p. 1732·3).
Diarrhoea.

Tannalbin *Medicopharm, Austria; Medice, Ger.*
Albumin tannate (p. 1815·1).
Diarrhoea.

Tannate Pediatric *Amneal, USA.*
Chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Tannic-12 *Cypress, USA.*
Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3).
Coughs.

Tannidin Plus *GD, Ital.*
Betacarotene (p. 2051·1); selenium (p. 2086·3); vitamin E (p. 2119·1).
Antoxidant.

Tannisol *GD, Ital.*
Betacarotene (p. 2051·1).
Sunscreen.

Tanno-Hermal *Almirall, Ital.*
Barrier preparation.

Almirall, Switz.
Lotion: Talc (p. 1722·2); zinc oxide (p. 1729·1); tannic acid (p. 2625·2).
Skin disorders.

Almirall, Switz.
Cream: Tannic acid (p. 2625·2).
Skin disorders.

Tannolact *Galderma, Ger.*
Condensation product of urea-sodium cresolsulfonic acid.
Skin disorders; hyperhidrosis.

Tannopon *Orion, Fin.†*
Opium (p. 111·3); belladonna (p. 2453·3); bismuth salicylate (p. 1821·3); albumin tannate (p. 1815·1).
Diarrhoea.

Tannosynt
Note: this name may be used for preparations of different composition.
Almirall Hermal, Ger.
Condensation product of urea-sodium cresolsulfonic acid.
Skin disorders; burns; hyperhidrosis.

Almirall, Switz.
Phenol cresol sulfonic acid-formaldehyde condensation product.
Skin disorders; burns.

Hermal, Austria.
2,6-Bis-N′ (2-hydroxy-3-sulfo (5-methyl-) benzyl)-ureidomethyl-phenol(ev. p-cresol) disodium.
Skin disorders.

Tanohalo *Cristalia, Braz.*
Halothane (p. 1902·1).
General anaesthesia.

Tanol *Akdeniz, Turk.*
Calamine (p. 1697·2); zinc oxide (p. 1729·1); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Pruritus.

Tanoral *Parmed, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Upper respiratory-tract symptoms.

Tanser *VP, Spain.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Tansiloprost *Finadiet, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tansinel *ACME, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tansix *Minerva, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Tanssel *Pharmacross, Chile.*
Olanzapine (p. 1089·3).
Psychoses.

Tanston *Pfizer, Chile.*
Mefenamic acid (p. 85·3).
Inflammation; pain.

Tantafed *Tanta, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Tantaphen *Tanta, Canad.†*
Paracetamol (p. 115·1).
Pain; fever.

Tantin *Biolab Sanus, Braz.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).

Tantong *Haixin, China.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Tantrix *Wyeth, Braz.*
Sildenafil (p. 2364·1).

Tantum *CSC, Austria; Medicis, Canad.; Medicom, Cz.; Angelini, Gr.; Angelini, Indon.; Soho, Indon.; Angelini, Ital.; ACRAF, Neth.; Omega, Neth.; Angelini, Pol.; Lepori, Port.; Angelini, Spain; Santa, Turk.; Elmor, Venez.*
Benzydamine hydrochloride (p. 29·2).
Musculoskeletal pain and inflammation; venous insufficiency; gynaecological disorders; phlebitis; peri-articular and soft-tissue disorders; thrombophlebitis; peripheral venous insufficiency; vaginitis; sore throat; mouth and throat pain and inflammation.

Angelini, Spain.†
Throat spray: Benzydamine hydrochloride (p. 29·2); hexamidine di-isetionate (p. 1754·3).
Mouth and throat disorders.

Tantum Activ Gola *Angelini, Ital.*
Flurbiprofen (p. 65·2).
Mouth and throat disorders.

Tantum Lemon *CSC, Hung.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders.

Tantum Orosan *Angelini, Ital.*
Benzydamine hydrochloride (p. 29·2); cetylpyridinium chloride (p. 1743·1).
Mouth and throat inflammation and pain.

Tantum Rosa
Note: this name may be used for preparations of different composition.
CSC, Ger.; Megapharm, Israel; Lepori, Port.
Benzydamine hydrochloride (p. 29·2).
Vulvovaginal disorders.

CSC, Hung.†
Benzydamine hydrochloride (p. 29·2); trimethylacetylammonium toluenesulfonate.
Vulvovaginal disorders.

Tantum Rose *CSC, Rus.; Angelini, Ukr.*
Benzydamine hydrochloride (p. 29·2).
Vulvovaginal disorders.

Tantum Verde *CSC, Ger.; CSC, Hung.; Angelini, Irl.; Angelini, Port.; Angelini, Port.; CSC, Rus.; Angelini, Spain; Angelini, Ukr.; Elmor, Venez.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and inflammation.

Angelini, Port.
Pastilles: Benzydamine hydrochloride (p. 29·2); benzocaine (p. 1980·2).
Mouth and throat pain and inflammation.

Tanvalir *AMPDR, Port.†*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Tanvimil *Raymos, Arg.*
A range of vitamins with or without minerals.

Tanvimil Aminoacidos *Raymos, Arg.*
Amino acids; cyanocobalamin (p. 2107·2).
Tonic.

Tanvimil Gel *Raymos, Arg.*
Soya isoflavones (p. 2620·3); alpha tocoferil acetate (p. 2119·2).
Vaginal disorders; vaginal/rectal lubricant.

Tanvimil Ginseng *Raymos, Arg.*
Vitamins; minerals; ginseng (p. 2513·3).

Tanvimil Isoflavonas *Raymos, Arg.*
Cream: Soya isoflavones (p. 2620·3).
Moisturiser.

Raymos, Arg.
Tablets: Soya isoflavones (p. 2620·3); alpha tocopherol (p. 2119·1); lecithin (p. 2542·2).
Dietary supplement.

Tanvimil Isoflavonas Caclcio D3 *Raymos, Arg.*
Soya isoflavones (p. 2620·3); calcium citrate (p. 1783·2); colecalciferol (p. 2113·1).
Dietary supplement.

Tanwards Combi *General Topics, Ital.*
Betacarotene (p. 2051·1); apple.
Suntanning aid.

Tanyl *Taro, Israel; Intramed, S.Afr.†*
⊗Fentanyl citrate (p. 60·1).
Adjunct to general anaesthesia; pain; premedication.

Tanyz *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tanza *T Man, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; haematoma; respiratory-tract disorders associated with viscous mucous.

Tanzaril *Silom, Thai.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; cardiovascular risk reduction.

Tanzo *Bosch, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tao Te *Hisun, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

TAP *Taejoon, Thai.†*
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1).

Tapain *Daewon, Hong Kong.*
Diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Rheumatoid arthritis; ankylosing spondylitis; gout; renal colic; pain.

Tapazol *Biolab Sanus, Braz.; Rhein, Mex.; Lilly, Venez.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Tapazole *Paladin, Canad.; Teofarma, Ital.; Invida, Philipp.; DKSH, Thai.; King, USA.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Tapclob
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
Clobazam (p. 518·2).
Anxiety; epilepsy.

Tapdin *MedChoice, Philipp.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Tapimycin *Yung Shin, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tapin *Copyfarm, Denm.; Orifarm, Fin.; Orifarm, Norw.; Orifarm, Swed.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Tapocin *CJ, China.*
Teicoplanin (p. 369·3).
Bacterial infections.

Tapocon *Conba, China.*
Puerarin.
Myocardial infarction; angina pectoris; coronary heart disease.

Taponoto *Teofarma, Spain.*
Potassium carbonate (p. 2595·2).
Removal of ear wax.

Taporin *Probiomed, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taprocil *Plus, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Taprodex *Provit, Mex.†*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Tapros *Takeda, Indon.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; endometriosis.

Tapsin Analgesico *Maver, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Tapsin 2 Analgesico *Maver, Chile.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Tapsin Compuesto *Maver, Chile.*
Paracetamol (p. 115·1); noscapine hydrochloride (p. 1670·3); caffeine (p. 1203·3); sodium ascorbate (p. 2111·1).
Cold and influenza symptoms.

Tapsin Compuesto con Clorfenamina *Maver, Chile.*
Paracetamol (p. 115·1); noscapine hydrochloride (p. 1670·3); caffeine (p. 1203·3); sodium ascorbate (p. 2111·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Tapsin Compuesto Dia/Noche Plus *Maver, Chile.*
Day sachet, paracetamol (p. 115·1); noscapine hydrochloride (p. 1670·3); caffeine (p. 1203·3); sodium ascorbate (p. 2111·1); night sachet, paracetamol; noscapine hydrochloride; caffeine; sodium ascorbate; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Tapsin Compuesto DN *Maver, Chile.*
Day capsules, paracetamol (p. 115·1); caffeine (p. 1203·3); noscapine hydrochloride (p. 1670·3); ascorbic acid (p. 2110·3); night capsules, paracetamol; caffeine; noscapine hydrochloride; ascorbic acid; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Tapsin Forte Recubiertos *Maver, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain fever.

Tapsin Infantil *Maver, Chile.*
Paracetamol (p. 115·1).
Fever; pain.

Tapsin Nocturno *Maver, Chile.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).

Tapsin Periodo Menstrual *Maver, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Menstrual disorders.

Tapsin Periodo Premenstrual *Maver, Chile.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1).

Tapsin Puro *Maver, Chile.*
Paracetamol (p. 115·1).
Pain; fever.

Tapsin Puro sin Cafeina *Maver, Chile.†*
Paracetamol (p. 115·1).
Pain; fever.

Tapsin SC *Maver, Chile.*
Paracetamol (p. 115·1).
Fever; pain.

Tapsin Up *Maver, Chile.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Tapsininstaflu Compuesto Plus *Maver, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Tapsininstaflu DN *Maver, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Taquidine *China Chem & Pharma, Philipp.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Tar Isdin Champu *Isdin, Spain.†*
Coal tar (p. 1723·2).
Scalp disorders.

Tar Isdin Plus *Isdin, Spain.†*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Scalp disorders.

Tara *Polipharm, Thai.*
Miconazole nitrate (p. 589·1).
Fungal skin, hair, and nail infections.

Taradyl *Roche, Belg.*
Ketorolac trometamol (p. 80·2).
Pain.

Taranis *Lactalis, Fr.*
A range of foods for special diets.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Taranis LeucinAde *Lactalis, Fr.*
Food for special diets.
Maple syrup urine disease.

Taranis PhenylAde *Lactalis, Fr.*
Food for special diets.
Phenylketonuria.

Taraphilic *Medco, USA.*
Coal tar (p. 1723·2).
Skin disorders.

Tara-Plus *Polipharm, Thai.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Fungal skin and nail infections.

Taraten *Polipharm, Malaysia; Polipharm, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Taraxacum Med Complex *Dynamit, Austria.*
Belladonna (p. 2453·3); carduus marianus (p. 1561·1); chelidonium (p. 2522·2); taraxacum (p. 2625·3).
Homoeopathic preparation.

Taraxan *Sanum-Kehlbeck, Ger.*
Taraxacum officinale (p. 2625·3).
Homoeopathic preparation.

Taraxin *TO-Chemicals, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Allergic skin disorders; pruritus; sedative.

Tarbiglem *Cryopharma, Mex.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Tarcefandol *Polfa Tarchomin, Pol.*
Cefamandole (p. 236·2).
Bacterial infections.

Tarcefoksym *Polfa Tarchomin, Pol.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Tarchomin, Rus.
Cefotaxime (p. 244·1).
Bacterial infections.

Tarceva *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Genentech, USA.*
Erlotinib hydrochloride (p. 788·3).
Non-small cell lung cancer; pancreatic cancer.

Tardan *Odan, Canad.*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Scalp disorders.

Tarden *Abdi, Turk.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Tardipan *Specifar, Neth.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Tardocillin *Infectopharm, Ger.*
Benzathine benzylpenicillin (p. 227·2).
Tolycaine hydrochloride (p. 1997·3) is included in this preparation to alleviate the pain of injection.
Long-term treatment of rheumatic fever; syphilis; neurosyphilis.

Tardyferon *Rovafarm, Arg.; Germania, Austria; Pierre Fabre, Belg.; Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Gedeon Richter, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Robapharm, Switz.; Pierre Fabre, Turk.; Pierre Fabre, Ukr.*
Ferrous sulfate (p. 2062·2); mucoproteose (p. 2564·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Pierre Fabre, Gr.; Pierre Fabre, Israel; Pierre Fabre, Rus.; Pierre Fabre, Spain.
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia; iron deficiency.

Tardyferon B9 *Pierre Fabre, Israel.†*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Pierre Fabre, Fr.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); mucoproteose (p. 2564·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Tardyferon-Fol *Germania, Austria; Pierre Fabre, Cz.; Pierre Fabre, Ger.; Gedeon Richter, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Port.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); mucoproteose (p. 2564·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; iron and folic acid deficiency.

Pierre Fabre, Mex.
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Iron and folic acid deficiency; iron-deficiency anaemia.

Taredon *Medicus, Gr.*
Glucosamine sulfate (p. 2515·3).

Tareg *Novartis, Chile; Orifarm, Denm.; Novartis, Fr.; Novartis, Ital.; Normal, Port.; Novartis, S.Afr.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure; left-ventricular dysfunction.

Tareg-D *Novartis, Chile.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Taremis *Krolton, Arg.*
Metronidazole (p. 936·1).

Tarentula Complexe No 71 *Lehning, Fr.*
⊗Tarentula hispana; hyoscyamus (p. 2530·2); adrenalinum (p. 1292·1); ignatia (p. 2532·1); paeonia officinal; stramonium (p. 2622·3); zincum valerianicum (p. 2641·2); cocculus (p. 2483·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Tarfazolin *Polfa Tarchomin, Pol.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Tarflex *Stiefel, Braz.*
Coal tar (p. 1723·2).
Skin disorders.

Targaxan *Norgine, Fin.; Norgine, UK.*
Rifaximin (p. 355·2).
Hepatic encephalopathy.

Targel
Note: this name may be used for preparations of different composition.
Lagos, Arg.; Odan, Canad.
Coal tar (p. 1723·2).
Scalp disorders; psoriasis.

Targel SA *Odan, Canad.*
Coal tar solution (p. 1723·2); salicylic acid (p. 1719·1).
Psoriasis.

Target *Lisapharma, Hong Kong†; Lisapharma, Ital.; Lisapharma, Malaysia; Lisapharma, Singapore.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Targifor *Sanofi-Aventis, Braz.*
Arginine aspartate (p. 2049·1).
Nutritional supplement.

Targifor C *Sanofi-Aventis, Braz.*
Arginine aspartate (p. 2049·1); ascorbic acid (p. 2110·3).
Nutritional supplement.

Targin *Mundipharma, Austral.; Mundipharma, Austria; Purdue, Canad.; Mundipharma, Cz.; Norpharma, Denm.; Mundipharma, Ger.; Mundipharma, Irl.; Rafa, Israel; Mundipharma, Ital.; Pharmaco, NZ; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Switz.*
⊗Oxycodone hydrochloride (p. 113·1).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to counteract opioid-induced constipation.
Pain.

Targinact *Mundipharma, Belg.; Mundipharma, Fr.; Mundipharma, Neth.; Napp, UK.*
⊗Oxycodone hydrochloride (p. 113·1).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to counteract opioid-induced constipation.
Pain.

Targiniq *Mundipharma, Fin.; Mundipharma, Norw.; Mundipharma, Swed.*
⊗Oxycodone hydrochloride (p. 113·1).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to counteract opioid-induced constipation.
Pain.

Targobone *Biomet, Ger.†*
Collagen (bovine) (p. 2483·2); teicoplanin (p. 369·3).
Bone defects.

Targocid *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Vianex (Βιανεξ), Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis Pasteur, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Jpn; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Aventis, NZ; Aventis, Pol.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, Venez.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Targoplanin *Vianex (Βιανεξ), Gr.*
Teicoplanin (p. 369·3).

Targosid *Lepetit, Ital.; Sanofi-Aventis, Port.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Targretin *Bioprofarma, Arg.; Eisai, Austria; Cephalon, Belg.; Mastercare, Chile; Eisai, Cz.; Eisai, Denm.; Cephalon, Fr.; Cephalon, Ger.; Eisai, Gr.; IFET (ΙΦΕΤ), Gr.; Eisai, Hung.; Cephalon, Irl.; Sigma-Tau, Ital.; Teva, Neth.; Eisai, Norw.; Eisai, Pol.; Eisai, Port.; Eisai, Spain; Teva, Swed.; Cephalon, UK; Eisai, USA.*
Bexarotene (p. 748·3).
Cutaneous T-cell lymphoma.

Targus *Abbott, Braz.*
Flurbiprofen (p. 65·2).
Musculoskeletal and joint disorders; gout; pain.

Taricin *Akrikhin, Rus.*
Ofloxacin (p. 334·3).
Bacterial infections.

Tariferid *Bryntsalov, Rus.*
Ofloxacin (p. 334·3).
Bacterial infections.

Tariflox *Cipla, India; Lapi, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Tariflox Plus *Cipla, India.*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).
Bacterial infections.

Tarim *Trima, Israel.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Tarimyl *Leti, Venez.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Taripel *Mediderm, Chile.*
Clindamycin phosphate (p. 269·3); tretinoin (p. 1725·2).
Acne.

Tarivid *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Daiichi Sankyo, China; Aventis, Cz.†; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Ger.; Daiichi, Hong Kong; Santen, Hong Kong; Gedeon Richter, Hung.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Daiichi, Indon.; Ferron, Indon.; Kalbe, Indon.; Santen, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Daiichi, Jpn; Santen, Jpn; Daiichi Sankyo, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Daiichi Sankyo, Singapore; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Daiichi Sankyo, Thai.; Aventis, Turk.; Aventis, UK.*
Ofloxacin (p. 334·3).
Bacterial infections.

Tarjen *Union Drug, Thai.*
Diclofenac diethylamine (p. 48·3).
Pain; inflammation.

Tarjena *Union Drug, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout.

Tarka *Abbott, Austral.; Abbott, Canad.; Abbott, Cz.; Abbott, Denm.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Ital.; Abbott, Mex.; Abbott, Neth.; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Spain; Abbott, Swed.†; Abbott, Switz.; Abbott, Turk.; Abbott, UK; Abbott, Ukr.; Abbott, USA; Abbott, Venez.*
Verapamil hydrochloride (p. 1522·1); trandolapril (p. 1517·2).
Hypertension.

Tarlene *Medco, USA.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Seborrhoea.

Tarmed *Stiefel, Chile; Stiefel, Ger.; GSK, Gr.; Stiefel, Mex.; Stiefel, Port.; Stiefel, Spain.*
Coal tar (p. 1723·2).
Psoriasis; eczema; seborrhoeic dermatitis; scalp disorders.

Tarnasol *Liconsa, Port.†*
Losartan potassium (p. 1422·2).
Hypertension; stroke prophylaxis; diabetic nephropathy; heart failure.

Tarnex *Medhaus, Philipp.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema.

Tarocidin *Taro, Israel.*
Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3).
Blepharitis; conjunctivitis.

Tarocidin D *Taro, Israel.*
⊗Chloramphenicol (p. 257·1); polymyxin B sulfate (p. 342·3); dexamethasone sodium phosphate (p. 1631·2).
Blepharitis; conjunctivitis.

Taroctyl *Taro, Israel.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychiatric disorders; vomiting.

Tarodent *Taro, Israel.*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Tarodex *Taro, Israel.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Taroflox *Sanofi-Aventis, Cz.*
Ofloxacin (p. 334·3).
Bacterial infections.

Taromentin *Polfa Tarchomin, Pol.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Taron *Biotech, Venez.*
Albendazole (p. 149·1).
Worm infections.

Trigen, USA.
Potassium citrate (p. 1780·3); citric acid (p. 2480·3).

Tarontal *Sanofi-Aventis, Gr.; Bernofarm, Indon.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Tarophed *Taro, Israel.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Aural and nasal congestion.

Taro-Sone *Taro, Canad.*
⊗Betamethasone dipropionate (p. 1623·3).
Skin disorders.

Tarproxen *Polfa Tarchomin, Pol.†*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders.

Tarsime *Polfa Tarchomin, Pol.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Tarsum *Summers, USA.*
Coal tar (p. 1723·2); salicylic acid (p. 1719·1).
Seborrhoea.

Tartar Control Listerine *Pfizer Consumer, UK.*
Zinc chloride (p. 2126·1).
Tooth tartar.

Johnson & Johnson, S.Afr.†
Thymol (p. 1772·2); zinc chloride (p. 2126·1).
Mouth and throat disorders; oral hygiene.

Tartephedreel *Heel, Austria.*
⊗Kalium stibyltartaricum (p. 151·2); atropa belladonna (p. 2453·3); natrium sulfuricum (p. 1888·1); arsenum jodatum (p. 2448·1); aspidosperma quebracho-blanco (p. 2601·2); blatta orientalis; hepatica nobilis; lobelia inflata (p. 2323·2); cephaelis ipecacuanha; ephedra distachya; naphthalinum (p. 2158·2); illicium verum (p. 2622·1); medorrhinum-nosode; stachys officinalis.
Homoeopathic preparation.

Tartriakson *Polfa Tarchomin, Pol.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tartrime *Juste, Spain.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Tarvexol *Sandoz, Arg.; Novartis, Braz.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

Tarzol *Unipharm, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Tasedan *Hormona, Mex.*
Estazolam (p. 1072·2).
Insomnia; premedication.

Tasep *IPS, Spain.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Tasigna *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA.*
Nilotinib hydrochloride (p. 835·2).
Chronic myeloid leukaemia.

Tasker *Doctum, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Tasmacyclin Akne *Gebro, Switz.*
Doxycycline (p. 288·1).
Acne.

Tasmaderm *Gebro, Switz.*
Motretinide (p. 1714·3).
Acne.

Tasmar *Valeant, Arg.†; Meda, Austria; Meda, Belg.; Valeant, Braz.; Roche, Chile; Roche, China; Meda, Cz.; Valeant, Denm.; Meda, Fr.; Meda, Ger.; Meda, Gr.; Valeant, Hung.; Meda, Irl.; Meda, Ital.; Valeant, Mex.; Meda, Neth.; Meda, Norw.; Valeant, NZ; Inovail, Philipp.; Meda, Pol.; Meda, Port.; Roche, Rus.; Pharmaco, S.Afr.†; Meda, Spain; Meda, Swed.; Meda, Switz.; Valeant, UK; Valeant, USA.*
Tolcapone (p. 916·3).
Parkinsonism.

Tasminetta *Sandoz, Fin.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Tasonade *Sanopharm, Gr.*
Citalopram hydrochloride (p. 411·1).
Depression.

Tasovak *Kendrick, Mex.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Taspir *Tatkhimfarm, Rus.*
Aspirin (p. 22·2).
Fever; inflammation; pain; thromboembolism prophylaxis.

Tathion *Choseido, Jpn.*
Reduced glutathione (p. 1555·2).
Corneal injury; liver disorders; skin disorders; vomiting; poisoning; radiation-induced inflammation of oral mucosa.

Tatig *Bioindustria, Ital.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Tatinol *Servier, China.*
Tianeptine sodium (p. 450·2).
Depression.

Tationil *Roche, Ital.*
Glutathione sodium (p. 1555·2).
Prevention of cisplatin-induced neuropathy.

Tatsupilljin *Tatsumi, Jpn.*
Pilsicainide hydrochloride (p. 1470·1).
Arrhythmias.

Tau Kit *Isomed, Spain.*
Carbon-13 labelled urea (p. 2470·3).
Test for gastrointestinal Helicobacter pylori *infection.*

Taucaron *Roemmers, Venez.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Taucor *Sigma-Tau, Spain.*
Lovastatin (p. 1425·2).
Atherosclerosis; hypercholesterolaemia.

Taufon *Infamed, Rus.*
Taurine (p. 2626·2).
Corneal disorders; retinal lesions.

Tauglicolo *Siam Bheasach, Thai.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with increased or viscous mucus.

SIT, Ital.
Bromhexine hydrochloride (p. 1656·3); sulfogaiacol (p. 1678·1).
Respiratory-tract congestion.

Tauliz *Sanofi-Aventis, Ital.*
Tablets: ⊗Piretanide (p. 1470·3).
Oedema; hypertension.

Taural *Roemmers, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; acid aspiration; gastrointestinal haemorrhage; Zollinger-Ellison syndrome.

Tauramin *Grifols, Spain.*
Amino acids.
Parenteral nutrition.

Taurargin *Baldacci, Braz.*
Arginine aspartate (p. 2049·1); taurine aminoesilate; ditetraethylammonium phosphate.
Nutritional supplement.

Tauredon *Nycomed, Cz.; Nycomed, Ger.; IFET (ΙΦΕΤ), Gr.; Nycomed, Neth.; Nycomed, Port.; Takeda, Switz.; Altana, Ukr.†*
Sodium aurothiomalate (p. 130·2).
Rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis; chronic polyarthritis.

Taurex *Medica Pedia, Philipp.*
Taurine (p. 2626·2).
Nutritional supplement.

Tauro *Teofarma, Ital.*
Tauroursodeoxycholic acid (p. 2638·1).
Gallstones.

Taurolin *Chemomedica, Austria; Berlin-Chemie, Ger.; Geistlich, Irl.; DeVriMed, Neth.; Geistlich, Switz.; Saba, Turk.*
Taurolidine (p. 369·2).
Bacterial infections; peritonitis.

Taurolite *Bruschettini, China; Bio-Gen, Turk.*
Tauroursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones.

Taurovit *Bruschettini, Ital.*
Minerals; vitamins; taurine (p. 2626·2).
Nutritional supplement.

Tautax *Lens, Rus.*
Docetaxel (p. 780·3).
Breast cancer; non-small-cell lung cancer; ovarian cancer; head and neck cancer.

Tautoss *Sigma-Tau, Spain.*
Levodropropizine (p. 1662·3).
Cough.

Tau-Tux *Sigma-Tau, Ital.*
Levodropropizine (p. 1662·3).
Cough.

Tauval *Sigma-Tau, Spain.†*
Valerian (p. 2640·2).
Anxiety; insomnia.

Tauxib *Addenda, Ital.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; gout.

Tauxolo *SIT, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Tavacor *Savio, Ital.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Tavag *Germandre, Fr.†*
Sodium phosphate (p. 1791·2); lactose (p. 2078·3).
Maintenance of vaginal pH.

Tavager *Gerard, Irl.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tavagran *Legrand, Braz.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tavaloxx *Cipla-Medpro, S.Afr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tavanic *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Ranbaxy, S.Afr.; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi Pasteur, Turk.; Aventis, UK; Sanofi-Aventis, Venez.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tavanik *Sanofi-Aventis, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tavan-SP 54 *Sanofi-Aventis, S.Afr.*
Pentosan polysulfate sodium (p. 1465·1).
Thromboembolic disorders.

Tavara *Basics, Swed.*
Atorvastatin calcium (p. 1309·2).

Tavegil *2care4, Denm.; Europharma, Denm.; Novartis Consumer, Ger.; Euro Registratie, Neth.; Novartis Consumer, Spain; Novartis Consumer, UK.*
Clemastine fumarate (p. 622·3).
Hypersensitivity reactions; insect bites; pruritus; sunburn.

Tavegyl *Novartis, Cz.†; Novartis, Denm.; Novartis, Indon.; Novartis Consumer, Neth.; Novartis, Philipp.; Novartis Consumer, Rus.; Novartis Consumer, S.Afr.†; Novartis, Swed.; Novartis, Turk.*
Clemastine fumarate (p. 622·3).
Hypersensitivity reactions; anaphylaxis; allergic rhinitis; urticaria; pruritus; eczema; insect stings and bites; allergic skin disorders.

Tavégyl *Novartis Consumer, Port.; Novartis Consumer, Switz.*
Clemastine fumarate (p. 622·3).
Pruritus; hypersensitivity reactions; skin disorders.

Taver *Medochemie, Malaysia; Medochemie, Thai.†*
Carbamazepine (p. 512·2).
Epilepsy; glossopharyngeal neuralgia; trigeminal neuralgia.

Tavetine *CCM, Malaysia.*
Clemastine fumarate (p. 622·3).
Allergic rhinitis.

Tavexyl *Rayere, Mex.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Tavinex *Fada, Arg.; Hexa, Arg.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Tavinex Antigripal *Fada, Arg.; Hexa, Arg.*
Paracetamol (p. 115·1); butetamate citrate (p. 1658·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Tavinex Expectorante *Fada, Arg.; Hexa, Arg.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Tavinex Expectotabs *Fada, Arg.; Hexa, Arg.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with viscous mucus.

Tavipec *Montavit, Austria; Montavit, Thai.*
Spike lavender oil (p. 2621·3).
Respiratory-tract disorders.

Montavit, Ukr.
Lavender oil (p. 2541·1).
Respiratory-tract disorders.

Tavist *Novartis Consumer, Canad.; Novartis, Mex.; Wander, Philipp.; Novartis Consumer, Port.*
Clemastine fumarate (p. 622·3).
Hypersensitivity reactions; pruritus; cold symptoms; urticaria; allergic rhinitis; allergic skin disorders; insect bites and stings.

Tavist Allergy *Novartis, USA.*
Clemastine fumarate (p. 622·3).
Formerly known as Tavist-1.
Allergic rhinitis.

Tavmet *Jaldes, Fr.*
Cinnamon (p. 2479·2); olive leaf (p. 2574·3); aronia melanocarpa; green tea (p. 2648·2); vitamin B substances (p. 2102·3); minerals.
Dietary supplement.

Tavoctame *Hospital Line, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tavolax *Vifor, Switz.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Tavonin *VSM, Belg.; Schwabe, Neth.*
Ginkgo biloba (p. 2512·3).
Peripheral vascular disorders; dementia.

Tavor
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Oxybutynin chloride (p. 2361·2).
Neurogenic bladder.

Gentek, Venez.
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Pfizer, Ger.; Pfizer, Gr.; Wyeth, Gr.; Wyeth Lederle, Ital.
Lorazepam (p. 1080·3).
Anxiety disorders; psychoses; status epilepticus; premedication; sleep disorders; insomnia; epilepsy.

Tecnofarma, Chile.
Fluconazole (p. 578·2).
Fungal infections.

Tavu *Pfizer, Ital.; Pfizer, Port.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Taxacad *Biocad, Rus.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Taxacin *Cipla, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Taxagon *Ivax, Arg.*
Trazodone hydrochloride (p. 451·1).
Depression.

Taxcef *Ranbaxy, Cz.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taxceus *Medac, Ger.; Caduceus, Ital.; Medac, Neth.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Taxecap *Caprifarmindo, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taxef *Phapros, Indon.*
Cefotaxime (p. 244·1).
Bacterial infections.

Taxegram *Sanbe, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taxen *Sandoz, Indon.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Taxenan *Mavi, Mex.†*
Naproxen (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Taxenil *Fabop, Arg.*
Dipyrone (p. 53·3).

Taxfeno *Raffo, Arg.†*
⊗Tamoxifen citrate (p. 860·2).

Taxifur *Teva, Mex.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Taxilan
Note: this name may be used for preparations of different composition.
Bergamo, Braz.
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Lundbeck, Ger.
Perazine dimalonate (p. 1095·2).
Psychoses.

Taxim *Zizhu, China; Taisheng, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taxima *Prodotti, Braz.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taximax *Nufarindo, Indon.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taxime
Note: this name may be used for preparations of different composition.
Hexpharm, Indon.
Cefixime (p. 240·3).
Bacterial infections.

Pharmatex, Ital.
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tax-O-Bid *Orchid, Rus.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Orchid, Ukr.
Cefotaxime (p. 244·1).
Bacterial infections.

Taxobine *Stada, Port.*
Paclitaxel (p. 839·3).

Taxocef
Note: this name may be used for preparations of different composition.
Sel-J, Philipp.
Cefixime (p. 240·3).
Bacterial infections.

Toprak, Turk.
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Taxocris *LKM, Arg.*
Paclitaxel (p. 839·3).
Ovarian cancer.

Taxodiol *Tecnofarma, Chile.*
Paclitaxel (p. 839·3).
Ovarian cancer.

Taxofen *Blausiegel, Braz.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Taxogen *Genepharm, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Taxol *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, China; BMS, Cz.; BMS, Fin.†; BMS, Fr.; BMS, Ger.†; BMS, Gr.; BMS, Hong Kong; BMS, Hung.†; BMS, Indon.†; BMS, Irl.†; BMS, Ital.; BMS, Jpn; BMS, Malaysia; BMS, Neth.; BMS, NZ; BMS, Philipp.†; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.†; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS Oncology, USA.†*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Taxomedac *Medac, Ger.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Taxoprol *Novendia, Gr.*
Paclitaxel (p. 839·3).
Malignant neoplasms.

Taxotere *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Jpn; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Aventis, Pol.; Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, Ukr.; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Taxtam *Orchid, Ukr.*
Cefotaxime (p. 244·1); sulbactam (p. 360·1).
Bacterial infections.

Taxus
Note: this name may be used for preparations of different composition.
Tecnofarma, Chile; Asofarma, Mex.; Nolver, Venez.
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Beta, Arg.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Taxyl *Solfran, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Taycovit *Ivax, Arg.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

Tayderm *Acos, Ital.*
Zinc oxide (p. 1729·1).
Skin disorders.

Tazabax *Ranbaxy, Cz.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazac *Aspen, Austral.*
Nizatidine (p. 1866·1).
Peptic ulcer; gastro-oesophageal reflux.

Tazact *Cipla, India.*
Tazobactam sodium (p. 369·3); piperacillin (p. 340·1).
Bacterial infections.

Tazacylin *Axxon, Pol.*
Tazobactam sodium (p. 369·3); piperacillin sodium (p. 340·1).
Bacterial infections.

Tazalok *Pro-Pharma, Ukr.*
Filipendula (p. 2550·2); curly parsley (p. 2583·3); celery (p. 2472·3); galium (p. 2481·2); linaria vulgaris; calendula (p. 2465·2).
Menstrual disorders; menopausal disorders; fibrocystic breast disorders; endometrial hyperplasia; polycystic ovary syndrome; uterine fibroids.

Tazalux *Sandoz, Neth.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazamel *Clonmel, Irl.†*
Mirtazapine (p. 436·1).
Depression.

Tazamol *Polfa Tarchomin, Pol.†*
Paracetamol (p. 115·1).
Fever; pain.

Tazar *Lupin, Ukr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazcine *Udomphon, Thai.*
⊗Pentazocine (p. 120·3).

Tazen *Eurodrug, Philipp.*
Citalopram hydrobromide (p. 411·1).
Depression; obsessive-compulsive disorder; panic disorder.

Tazepam *Tarchomin, Rus.*
Oxazepam (p. 1092·2).
Anxiety; sleep disorders; premenstrual syndrome; mixed anxiety depressive disorders.

Tazepen *Enorasis, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazicef *Shin Poong, Philipp.; Hospira, USA.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazid *Ranbaxy, Malaysia; Taisheng, Philipp.; Alkem, Thai.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazidan *Syncom, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazidem *Orchid, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazidif *SF, Ital.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Tazidime *Lilly, USA.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazidron *Meditrina, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Taziject *Aspen, S.Afr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazim *Sandoz, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazime *Hanmi, China; Hanmi, Singapore.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tazinet *Domesco, Philipp.†*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; Ménière's disease.

Tazip *Heaton, Cz.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazko *Sanofi-Aventis, Belg.*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Tazmeral *Darier, Mex.*
Tazarotene (p. 1724·2).
Psoriasis; acne; photodamaged skin.

Tazobac *Pfizer, Ger.; Wyeth Lederle, Ital.; Pfizer, Port.; Pfizer, Switz.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tazobak *Swiss Parenterals, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazobax *Aspen, S.Afr.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Tazobion *Medicus, Gr.*
Piperacillin (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazocel *Wyeth, Spain.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazocilina *Biochimico, Braz.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Tazocillin *Vitamed, Israel.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazocilline *Pfizer, Fr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazocin *Pfizer, Austral.; Pfizer, Belg.; Wyeth, Braz.; Pfizer, Canad.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Wyeth, Hung.; Wyeth, Indon.; Pfizer, Irl.; Neopharm, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Wyeth, Philipp.; Pfizer, Pol.; Wyeth, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.†; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tazofast *Ipca, India.*
Tazobactam sodium (p. 369·3); piperacillin (p. 340·1).
Bacterial infections.

Tazolin *Pharmawealth, Philipp.†*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazonam *Wyeth, Arg.; Pfizer, Austria; Wyeth, Chile.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazopen *Biochem, India; Pharmawealth, Philipp.*
Tazobactam sodium (p. 369·3); piperacillin sodium (p. 340·1).
Bacterial infections.

Tazopenil *Magis, Ital.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazoper *Nevzat, Turk.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Tazopet *Sandoz, Cz.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazopip *Aspen, Austral.; Perrigo, Israel.*
Tazobactam sodium (p. 369·3); piperacillin sodium (p. 340·1).
Bacterial infections.

Tazopril *Wyeth, Venez.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazorac *Allergan, Canad.; Pierre Fabre, Cz.†; Allergan, USA.*
Tazarotene (p. 1724·2).
Psoriasis; acne; photo-ageing of the skin.

Tazoratio *Ratiopharm, Cz.; Ratiopharm, Pol.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazorex *Demo, Gr.; Lapidot, Israel.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazotaz *Sherrington, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazpen *Aspen, Mex.; DHA, Singapore; Biofarma, Venez.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tazret *Glenmark, India.*
Tazarotene (p. 1724·2).
Acne; psoriasis.

Tazrobida *GSK, Thai.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Taztia *Andrx, USA.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension.

Tazumara *Bayer Schering, Cz.†*
Fludarabine phosphate (p. 794·1).
Chronic lymphocytic leukaemia.

Tazun *Sun, Mex.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Tazz *ADP, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; neurosensorial ischaemia.

TB Vit 6 *Meprofarm, Indon.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

TB ZET *Meprofarm, Indon.*
Pyrazinamide (p. 345·2).
Tuberculosis.

T-BMP *Seroyal, Canad.*
Thiamine hydrochloride (p. 2103·1); choline tartrate (p. 2055·2).

T-Bon *TO-Chemicals, Thai.*
Calcium carbonate (p. 1824·3).

T-Bren *Korea United, Philipp.*
Triflusal (p. 1519·3).
Thromboembolism prophylaxis.

TBR/X *Ximena Polanco, Chile.*
⊗Flores pectorales (p. 2459·1); tilia cordata (p. 2631·3); plantago major (p. 2592·3); lobelia inflata (p. 2323·2); gelsemium (p. 2511·2).
Homoeopathic preparation.

T-Buffer *Chinta, Thai.*
Tetracycline phosphate (p. 373·2).
Bacterial infections.

TBV *Seroyal, Canad.*
Thiamine (p. 2102·3); nicotinamide (p. 2083·1); magnesium (p. 1786·3).

3TC *GSK, Arg.; ViiV, Austral.; ViiV, Canad.; GSK, Hong Kong; GSK, Indon.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, S.Afr.; ViiV, Switz.*
Lamivudine (p. 1000·2).
HIV infection.

3TC Complex *GSK, Arg.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

3TC/AZT *Elea, Arg.†*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

3TC/Epivir *GSK, Chile.*
Lamivudine (p. 1000·2).
HIV infection.

3TC-HBV *GSK, Indon.*
Lamivudine (p. 1000·2).
Chronic hepatitis B.

TC-Mycin *TC Pharma-Chem, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

TCO *Seroyal, Canad.*
Vitamins; minerals.

TCO-Carbo *Dosa, Arg.*
Carboplatin (p. 759·1).
Malignant neoplasms.

TC-Ointment *TC Pharma-Chem, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

TCP *Chefaro, Irl.; Chefaro, UK.*
Cream: Triclosan (p. 1773·2); chloroxylenol (p. 1748·2); phenol (p. 1763·3); halogenated phenols; sodium salicylate (p. 132·2).
Minor skin disorders; skin disinfection.

Chefaro, Irl.; Chefaro, UK.
Liquid: Phenol (p. 1763·3); halogenated phenols.
Sore throat; minor wounds; mouth ulcers; skin disinfection; sore gums; halitosis; minor skin disorders.

Chefaro, UK.
Lozenges: Hexylresorcinol (p. 1755·1).
Sore throat.

Chefaro, UK.
Ointment: Iodine (p. 2336·3); phenol (p. 1763·3); sodium salicylate (p. 132·2); methyl salicylate (p. 92·1); precipitated sulfur (p. 1721·1); tannic acid (p. 2625·2); camphor (p. 2466·2); salicylic acid (p. 1719·1).
Minor skin disorders; haemorrhoids; pruritus.

Pfizer Consumer, S.Afr.†
Halogenated phenols; phenol (p. 1763·3); sodium salicylate (p. 132·2).
Mouth and throat infections; wounds; insect bites; burns; disinfection.

Td Adsorbed *Sanofi Pasteur, Canad.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

TDA *Beijing Union, Ukr.*
Ftibamzone.
Herpesvirus skin infections; genital warts; fungal skin infections.

TDF AHA Facial Wash for Oily/Acne Prone Skin *EIG, Malaysia.*
Chlorhexidine (p. 1743·2); aloe vera (p. 1693·2); glycolic acid (p. 1704·3).
Acne.

TDF AHA Oily & Acne Solution *EIG, Malaysia.*
Chlorhexidine (p. 1743·2); glycolic acid (p. 1704·3).
Acne.

Td-Impfstoff *Sanofi Pasteur, Ger.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation of older children and adults.

TDL *Patriot, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Td-Polio *Sanofi Pasteur, Canad.; Sanofi-Aventis, S.Afr.†*
An adsorbed diphtheria, tetanus, and inactivated poliomyelitis vaccine (p. 2386·2).
Active immunisation.

Td-pur *Novartis Vaccines, Austria; Novartis Vaccines, Ger.; Novartis, Philipp.; Novartis, Switz.; Novartis Vaccines, Thai.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Td-Rix *GSK, Ger.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation of older children and adults.

Td-Virelon *Chiron Vaccines, Ger.†; Novartis, Switz.†*
A diphtheria, tetanus, and poliomyelitis vaccine (p. 2386·2).
Active immunisation.

Te Di *New Asiatic, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Te Anatoxal *Berna, Hong Kong†; Berna, NZ†; Berna, Philipp.†; Berna, Thai.†; Berna, USA.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Te Bi Ao *Sunshine, China.*
Thrombopoietin (human, recombinant) (p. 1164·1).

Te Er Jing *Tebao, China.*
Granulocyte colony-stimulating factor (human recombinant).

Te Er Kang *Tebao, China.*
Interleukin-2 (human recombinant) (p. 810·1).

Te Er Li *Tebao, China.*
Granulocyte-macrophage colony-stimulating factor (human recombinant).

Te Fen Ta *Minsheng, China.*
Tolfenamic acid (p. 138·3).
Pain.

Te Fu Bi Ke *Pu Kang, China; Topfond, China.*
Levofloxacin mesilate.
Bacterial infections.

Te Laxante *Valma, Chile.†*
Senna (p. 1885·1); rosa mosqueta; boldo (p. 2458·3); baylahuen; spearmint (p. 2621·2).
Constipation.

Te Li Da *Lunan, China.*
Butenafine hydrochloride (p. 574·2).
Fungal skin infections.

Te Li Kang *Saiwei, China.*
Telmisartan (p. 1509·3).
Hypertension.

Te Li Xin *Hui Yin Bi, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Te Lin Na *Jida, China.*
Citalopram hydrobromide (p. 411·1).
Depression.

Te Na Si *Litai, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Te Pu Ning *Direction, China.*
Cefixime (p. 240·3).
Bacterial infections.

Te Su *Haikou, China.*
Paclitaxel (p. 839·3).
Ovarian cancer; breast cancer; non-small cell lung cancer; AIDS-related Kaposi's sarcoma.

Te Su An *Xin Gang Union, China.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Te Su Min *Xin Gang Union, China.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Te Su Ni *Xin Gang Union, China.*
⊗Torasemide (p. 1516·3).
Oedema.

Tea Test *Asofarma, Arg.*
Pregnancy test (p. 2596·1).

Tea Tree & Witch Hazel Cream *Lane, UK.*
Hamamelis (p. 2523·3); eucalyptus oil (p. 2501·2); methyl salicylate (p. 92·1); camphor (p. 2466·2); melaleuca oil (p. 2551·1); zinc oxide (p. 1729·1).
Skin disorders.

Tealep *Raffo, Arg.; Asofarma, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Tealine *Arkopharma, Spain.*
Green tea (p. 2648·2); java tea (p. 2536·3).
Slimming aid.

Téaline *Arkomedika, Fr.†*
Java tea (p. 2536·3); green tea (p. 2648·2).
Slimming aid.

Teamic *Bufa, Indon.*
Mefenamic acid (p. 85·3).
Pain; fever.

Tear drops
Note: this name may be used for preparations of different composition.
Faran, Gr.
Carbomer (p. 2173·3).
Dry eye.

TearGard *Lee, USA.†*
Hyetellose (p. 2188·3).
Artificial tears.

Tear-Gel *Novartis Ophthalmics, Canad.†*
Carbomer 980 (p. 2173·3).
Dry eyes.

Teargel *Adcock Ingram, S.Afr.*
Carbomer (p. 2173·3).
Dry eyes.

Teargen *Goldline, USA.†*
Artificial tear solution.
Dry eyes.

Tearisol
Note: this name may be used for preparations of different composition.
Novartis Ophthalmics, USA.
Hypromellose (p. 2189·2).
Dry eyes.

Tearprol *Proel, Gr.*
⊗Dextran (p. 1138·3); hypromellose (p. 2189·2).

Tears *Sanbe, Indon.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Eye irritation; dry eyes.

Tears Again
Note: this name may be used for preparations of different composition.
Ocusoft, USA.
Eye drops: Carmellose sodium (p. 2175·2).
Dry eyes.

Ocusoft, USA.
Eye drops: Polyvinyl alcohol (p. 2204·2).
Dry eyes.

Ocusoft, USA.
Eye ointment: White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Dry eyes.

Optima, Ger.
Soya lecithin (p. 2542·2); vitamin A palmitate (p. 2098·3); alpha tocopherol (p. 2119·1).
Dry eyes; eye irritation.

Trima, Israel.†
Soya lecithin (p. 2542·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Dry eyes.

Tears Again MC *Ocusoft, USA.*
Hypromellose (p. 2189·2).
Dry eyes.

Tears Humectante *Alcon Cusi, Spain.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Tears Natural
Note: this name may be used for preparations of different composition.
Alcon, Israel.
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Tears Naturale
Note: this name may be used for preparations of different composition.
Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Malaysia; Alcon, Mex.; Eureco, Neth.; Euro Registratie, Neth.; Fisher, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, Ukr.†; Alcon, USA.
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Alcon, Arg.†
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2); glycerol (p. 2517·2).
Dry eyes.

Tears Naturale II *Alcon, China; Alcon, Indon.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Tears Naturale Forte *Alcon, Arg.; Alcon, Canad.; Alcon, China; Alcon, Hong Kong.*
⊗Dextran 70 (p. 1138·3); glycerol (p. 2517·2); hypromellose (p. 2189·2).
Dry eyes; eye irritation.

Tears Naturale PM *Alcon, Canad.*
White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Tears Plus *Allergan, Canad.; Allergan, Neth.†; Allergan, S.Afr.†; Allergan, USA.*
Polyvinyl alcohol (p. 2204·2); povidone (p. 2204·3).
Dry eyes.

Tears Renewed *Akorn, USA.†*
Eye drops: ⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2).
Dry eyes.

Akorn, USA.†
Eye ointment: White soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2).
Dry eyes.

Tears Visine *Johnson & Johnson, Chile.†*
⊗Glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol 400 (p. 2547·3).
Dry eyes; eye irritation.

Teaslim *Arkopharma, Fr.†*
Green tea (p. 2648·2); java tea (p. 2536·3).
Slimming aid.

Téatrois *DB, Fr.*
Tiratricol (p. 2346·3).
Thyroid disorders.

Tebamol *Penta, Hung.*
Melaleuca oil (p. 2551·1).
Skin infections; wounds.

Tebantin *Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Tebegran *Collins, Mex.*
Sumatriptan succinate (p. 679·2).
Migraine.

tebesium *Riemser, Ger.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

tebesium Duo *Riemser, Ger.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

tebesium Trio *Riemser, Ger.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

tebesium-s *Riemser, Ger.*
Isoniazid (p. 311·2).
Tuberculosis.

Tebetane Compuesto *Biomed, Spain.*
Alanine (p. 2048·3); glycine (p. 2071·2); glutamic acid (p. 2070·2); pygeum africanum (p. 2363·2).
Prostatic disorders.

Tebiloba *Belfar, Braz.*
Ginkgo biloba (p. 2512·3).

Tebinisil *Medreich, Hong Kong.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Tebis Plus H *Teva, Cz.†*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tebofortan *Schwabe, Austria; ASI, Hung.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function impairment; vestibular disorders.

Tebofortin *Schwabe, Switz.*
Ginkgo biloba (p. 2512·3).
Mental function impairment; vertigo.

Tebokan *Abdi, Turk.*
Ginkgolides (p. 2513·3).
Dementia; peripheral vascular disorders.

Schwabe, Cz.; Vianex (Βιανεξ), Gr.; Phapros, Indon.; Schwabe, Indon.; Schwabe, Philipp.; Schwabe, Switz.; Leti, Venez.
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; mental function impairment; intermittent claudication.

Tebonin *Austroplant, Austria; Nycomed, Braz.; Schwabe, Ger.; Schwabe, Malaysia; Farmasa, Mex.; Schwabe, Philipp.; Schwabe, Singapore; Schwabe, Thai.*
Ginkgo biloba (p. 2512·3).
Cerebral and peripheral vascular disorders; vertigo; tinnitus; intermittent claudication; vestibular disorders; mental function impairment; dementia.

Teboven *Farmasa, Mex.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Tebovin *T Man, Thai.*
Riboflavin (p. 2104·3).
Riboflavin deficiency; microcytic anaemia.

Te-Br *Provit, Mex.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tebranic *AstraZeneca, Cz.; AstraZeneca, Philipp.; AstraZeneca, Thai.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Tebraxin *Bracco, Ital.†*
Rufloxacin hydrochloride (p. 357·1).
Bacterial infections.

Tebrazid *Kela, Belg.; Valeant, Canad.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Tebruxim *Bruluagsa, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Tecazo *Pentafarma, Port.*
⊗Indapamide (p. 1409·2); perindopril erbumine (p. 1467·1).
Hypertension.

Teceeme *Nutricia-Bago, Arg.*
Medium-chain triglycerides (p. 2082·2).
Nutritional supplement.

Tecelac *Pisa, Mex.†; Biotest, Pol.†*
An antithymocyte immunoglobulin (rabbit) (p. 1939·2).
Cardiac transplant rejection; transplant rejection.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Teceos *CIS, Fin.; CIS, Fr.; CIS, Neth.; CIS, Spain; CBI, Switz.*
Technetium-99m (p. 2228·1) butedronate.
Bone scintigraphy.

Tecepin *Fabop, Arg.*
Clonazepam (p. 519·1).

Tecfazolina *Openfar, Spain.*
Cefazolin sodium (p. 237·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Tecfidera *Biogen, USA.*
Dimethyl fumarate (p. 1704·2).
Multiple sclerosis.

Tecflu *Columbia, Mex.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Techne *Hailing, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Technelite *Lantheus, Israel.†*
Technetium-99m (p. 2228·1) as sodium pertechnetate.
Radionuclide imaging.

TechneScan DMSA *Covidien, Belg.; Mallinckrodt, Cz.; Covidien, Fr.; Mallinckrodt, Irl.; Mallinckrodt, Neth.*
Technetium-99m (p. 2228·1) succimer.
Radionuclide imaging of the kidney.

TechneScan DTPA *Covidien, Belg.; Mallinckrodt, Cz.; Mallinckrodt, Irl.; Mallinckrodt, Neth.; Mallinckrodt, Port.; Mallinckrodt, Spain.*
Technetium-99m (p. 2228·1) calcium trisodium pentetate.
Radionuclide imaging.

TechneScan Has *Mallinckrodt, Cz.†*
Technetium-99m labelled albumin (p. 2228·1).
Blood circulation studies; examination of the heart.

TechneScan HDP *Covidien, Belg.; Mallinckrodt, Cz.; Covidien, Fr.; Mallinckrodt, Irl.; Mallinckrodt, Neth.; Mallinckrodt, Port.; Mallinckrodt, Spain; Mallinckrodt, Switz.; Mallinckrodt, USA.*
Technetium-99m (p. 2228·1) oxidronate disodium.
Bone scintigraphy.

TechneScan HIG *Mallinckrodt, Cz.*
Technetium-99m labelled immunoglobulin G (p. 2228·1).
Localisation of arthritis.

TechneScan LyoMAA *Mallinckrodt, Cz.; Mallinckrodt, Fin.; Covidien, Fr.; Mallinckrodt, Irl.; Mallinckrodt, Neth.; Mallinckrodt, Spain.*
Technetium-99m (p. 2228·1) albumin macroaggregates.
Radionuclide diagnostic agent; lung perfusion studies; vein scintigraphy.

TechneScan MAG3 *BSM, Austria; Mallinckrodt, Cz.; Mallinckrodt, Irl.; Covidien, Ital.; Mallinckrodt, Neth.; Mallinckrodt, Port.; Mallinckrodt, Spain.*
Technetium-99m betiatide (p. 2228·1).
Radionuclide investigation of renal function.

TechneScan MIBI *Mallinckrodt, Irl.*
Technetium-99m (p. 2228·1) sestamibi.
Radionuclide imaging of the heart, breast, and parathyroid gland.

TechneScan PYP *Covidien, Belg.; Mallinckrodt, Cz.; Mallinckrodt, Irl.; Mallinckrodt, Neth.*
Technetium-99m (p. 2228·1) pyrophosphate.
Red blood cell labelling for blood pool scintigraphy; spleen scintigraphy.

TechneScan Sestamibi *Mallinckrodt, Cz.; Mallinckrodt, Fin.; Mallinckrodt, Neth.; Mallinckrodt, Port.*
Technetium-99m sestamibi (p. 2228·1).
Myocardial imaging; parathyroid imaging; diagnosis of breast cancer; diagnosis of myocardial ischaemia; assessment of left ventricular function; thyroid imaging.

Mallinckrodt, Denm.
Copper tetramibi tetrafluoroborate.
For radiolabelling with technetium-99m to produce technetium-99m sestamibi.
Myocardial perfusion scintigraphy; assessment of left ventricular function; breast or parathyroid imaging.

Techxafort *Pharmatechnica, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Tecipul *Mochida, Jpn.*
Setiptiline maleate (p. 449·1).
Depression.

Teclizima *Reuffer, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Teclop *Medana, Cz.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Tecnid *Ativus, Braz.*
Secnidazole (p. 947·3).
Protozoal infections.

Tecnilor *Premium, Port.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tecnocarb *Zodiac, Braz.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Tecnoclor *Tecnofarma, Mex.*
Cefaclor (p. 232·3).
Bacterial infections.

Tecnocris *Zodiac, Braz.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Tecnodron *Tecnofarma, Mex.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Tecnofen *Columbia, Mex.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tecnofer *Baldacci, Ital.*
Iron bisglycinate chelate (p. 2048·3).
Iron supplement.

Tecnoflut *Zodiac, Braz.*
Flutamide (p. 798·2).
Prostatic cancer.

Tecnofox *Bigfarma, Port.*
Levocloperastine fendizoate (p. 1659·1).
Cough.

Tecnolip *Tecnifar, Port.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia; atherosclerosis.

Tecnomax
Note: this name may be used for preparations of different composition.
Raffo, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Zodiac, Braz.
Epirubicin hydrochloride (p. 787·1).
Malignant neoplasms.

Tecnomet *Zodiac, Braz.*
Methotrexate (p. 822·2).
Rheumatoid arthritis; psoriasis.

Tecnomicina *Zodiac, Braz.*
Bleomycin sulfate (p. 749·3).
Malignant neoplasms.

Tecnoplatin *Zodiac, Braz.; Columbia, Mex.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Tecnosal *Tecnifar, Port.*
Triflusal (p. 1519·3).
Thrombosis prophylaxis.

Tecnotax *Zodiac, Braz.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Tecnotecan *Zodiac, Braz.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Tecnovorin *Zodiac, Braz.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemias; adjunct to fluorouracil in colorectal cancer.

Tecnoxima *Tecnofarma, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Tecnu First Aid *Tec, USA.*
Lidocaine hydrochloride (p. 1988·2); benzethonium chloride (p. 1738·1).
Local anaesthesia; antiseptic.

Tecomax *Bunker, Braz.*
Terconazole (p. 595·2).

Teconam *Asian Pharm, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders; gout.

Tecoplax *Sandoz, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Tecphatil *Tecnofarma, Mex.*
Cefalotin sodium (p. 235·1).
Bacterial infections.

Tecprazin *Tecnofarma, Mex.*
Praziquantel (p. 164·1).
Parasitic infections.

Tecradina *Pentafarma, Port.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; acid aspiration.

Tecta *Nycomed, Braz.*
Pantoprazole (p. 1875·3).

Nycomed, Canad.; Nycomed, Mex.
Pantoprazole magnesium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastritis; dyspepsia; acid aspiration.

Tecta Control *Nycomed, Ukr.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux.

Tecxifil *Tecnofarma, Mex.*
Pentoxifylline (p. 1465·3).
Circulatory disorders.

Teczac *Rimsa, Mex.*
Fluoxetine (p. 417·1).
Depression.

Teczem *Hoechst Marion Roussel, USA.*
Enalapril maleate (p. 1371·1); diltiazem malate (p. 1359·2).
Hypertension.

Teczidima *Tecnofarma, Mex.*
Ceftazidime (p. 250·2).
Bacterial infections.

Teczine *Ranbaxy, India.*
Levocetirizine (p. 632·3) or levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Teddy-C *Community Pharmacy, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Tedein *Mekophar, Rus.*
Codeine (p. 40·2); terpin hydrate (p. 1678·2).
Cough.

Tediprima *Estedi, Spain.*
Trimethoprim (p. 381·2).
Genito-urinary infections.

Tedipulmo *Estedi, Spain.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Tedium *T Man, Thai.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Tedivax *GSK, Belg.*
An adsorbed diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Tedol *Edol, Port.*
Ketoconazole (p. 585·3).
Fungal infections.

Tedosin *Help, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Tédralan *SERP, Mon.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Tedrigen *Goldline, USA.*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2); phenobarbital (p. 535·2).
Bronchospasm.

Tee Complex *Thompsons, Canad.†*
Belladonna (p. 2453·3); calcium carbonate (p. 1824·3); chamomile (p. 2474·1); coffee (p. 2648·2).
Homoeopathic preparation.

Teedex *Rice Steele, Irl.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Fever; pain; cold and influenza symptoms.

Teejel *Meda, Belg.; SSL, Irl.†; Rafa, Israel.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3).
Gum and mouth pain; oral lesions; teething.

Teen Derm K *D & M, Chile.*
Glycolic acid (p. 1704·3); gluconolactone (p. 2515·2); salicylic acid (p. 1719·1).
Acne; seborrhoea.

Teen Essentials *Usana, Canad.†*
Vitamins; minerals.

Teen Multi *Blackmores, Austral.*
Omega-3 marine triglycerides (p. 1460·3); vitamins; minerals.
Dietary supplement.

Teen Vitamins *Adams, Canad.†*
Vitamins; minerals.

Teenstick *Arkopharma, Singapore; Arkopharma, UK.*
Clove oil (p. 2481·3); geranium oil (p. 2512·2); palmarosa oil (p. 2579·3); melaleuca oil (p. 2551·1); ylang ylang oil (p. 2649·3); dixeol.
Acne.

Teer-Linola-Fett *Wolff, Ger.*
Coal tar (p. 1723·2).
Skin disorders.

Teeth Tough *Vitamed, Israel.†*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Teetha *Nelson, UK.*
Chamomilla (p. 2474·1).
Formerly known as Teething Granules.
Homoeopathic preparation.

Teething *Hylands, Canad.*
Belladonna (p. 2453·3); calcarea phosphorica (p. 1784·2); chamomilla (p. 2474·1); coffea cruda (p. 2648·2).
Homoeopathic preparation.

Teething Relief *Brauer, Austral.*
Aconitum nap. (p. 2428·3); actaea spicata; belladonna (p. 2453·3); chamomilla (p. 2474·1); colocynthis (p. 1833·3); kreosotum (p. 1659·3); merc. sol. (p. 2555·3); nux vomica (p. 2573·3); silicea (p. 2208·3).
Homoeopathic preparation.

Tefaclor *TO-Chemicals, Thai.*
Cefaclor (p. 232·3).
Bacterial infections.

Tefamin *Recordati, Ital.*
Aminophylline (p. 1201·2).
Asthma; bronchospasm.

Tefavinca *Bohm, Spain.*
Vincamine (p. 2645·2).
Cerebrovascular disorders; cerebral trauma; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Tefazol *Taisheng, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Tefilin *Almirall Hermal, Ger.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tefin
Note: this name may be used for preparations of different composition.
Actavis, Denm.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Brainfarma, Braz.
Butenafine hydrochloride (p. 574·2).

Tefine *Herbacos, Cz.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Teflan *Uniao Quimica, Braz.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Teflaro *Cerexa, USA.*
Ceftaroline fosamil acetate (p. 250·1).
Bacterial infections.

Teflut *Blausiegel, Braz.*
Flutamide (p. 798·2).
Prostatic cancer.

Tefor *Organon, Turk.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Galenika, Ukr.†
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tefudex *Korea United, Philipp.*
Tegafur (p. 864·2); uracil (p. 2637·3).
Malignant neoplasms.

Tegaderm Ag *3M, Canad.*
Nonwoven dressing containing silver sulfate.
Wounds.

Tegaderm Alginate *3M, Belg.; 3M, Fr.*
Calcium alginate (p. 1136·3).
Wounds; ulcers.

3M, Canad.
Calcium alginate (p. 1136·3); sodium alginate (p. 2167·3).
Wounds.

Tegaderm CHG *3M, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Protection of catheter sites.

Tegaderm Foam *3M, Belg.; 3M, Canad.*
A polyurethane dressing (p. 1718·1).
Wounds.

Tegaderm Hydrocolloid *3M, Belg.*
A hydrocolloid dressing.
Wounds.

Tegaderm Hydrogel *3M, Belg.*
A hydrogel dressing.
Wounds.

3M, Canad.
Hydrogel dressing.
Wounds; ulcers.

Tegan *Libbs, Braz.*
Estradiol (p. 2271·1).

Tegarod *Cinetic, Arg.*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome.

Tegasir *Andromaco, Chile.†*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome in females.

Tegasorb *3M, Arg.*
Hydrocolloid dressing.
Burns; ulcers; wounds.

3M, Canad.†
⊗Pectin (p. 2200·3); gelatin (p. 1154·1); and/or carmellose (p. 2175·1).
Wounds.

Tegeline *LFB, Fr.; LFB, Port.; Er-Kim, Turk.*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; hypogammaglobulinaemia; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome; retinochoroiditis; motor neuropathy.

Tegens *Sanofi-Aventis, Ital.; Sanofi-Aventis, Port.*
Myrtillus (p. 2566·2).
Capillary disorders; venous insufficiency.

Tegibs *Torrent, India.*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome in women.

Teglix *Biofarma, Turk.*
Nateglinide (p. 492·1).

Tegod *Cipla, India.*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome in women.

Tegreen *Pharmanex, USA.*
Green tea (p. 2648·2).
Dietary supplement.

Tegrepin *Intas, Philipp.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; bipolar disorder.

Tegretal *Novartis, Chile; Novartis, Ger.*
Carbamazepine (p. 512·2).
Bipolar disorder; epilepsy; neuralgias; diabetic neuropathy; alcohol withdrawal syndrome; multiple sclerosis.

Tegretard *Cristalia, Braz.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; epilepsy; neuralgias.

Tegretol *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Carbamazepine (p. 512·2).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; mania; diabetes insipidus; diabetic neuropathy; neuralgias; psychoses; benzodiazepine withdrawal syndrome; status epilepticus; polyuria; polydipsia.

Tégrétol *Novartis, Fr.; Novartis, Switz.*
Carbamazepine (p. 512·2).
Bipolar disorder; epilepsy; mania; trigeminal neuralgia; glossopharyngeal neuralgia; neuropathic pain; alcohol withdrawal syndrome.

Tegrex *Neo Quimica, Braz.*
Carbamazepine (p. 512·2).
Epilepsy.

Tegrezin *Cazi, Braz.*
Carbamazepine (p. 512·2).
Epilepsy.

Tegrin
Note: this name may be used for preparations of different composition.
Reedco, USA.
Coal tar (p. 1723·2).
Skin disorders.

Tegrin-HC *Block, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Tegrital *Novartis, India.*
Carbamazepine (p. 512·2).
Trigeminal neuralgia; epilepsy; bipolar disorder.

Teguphen *Lupin, India.*
Triprolidine hydrochloride (p. 642·3); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Teico *Cipla, Ukr.*
Teicoplanin (p. 369·3).
Bacterial infections.

Teicomid *Sanofi-Aventis, Ital.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Teicon *Ariston, Braz.†*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Teicoston *Ariston, Braz.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Teicox *Richmond, Arg.*
Teicoplanin (p. 369·3).
Bacterial infections.

Teicozid *Bergamo, Braz.†*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Teikeden *XL, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Teiklonal *Klonal, Arg.*
Teicoplanin (p. 369·3).
Bacterial infections.

Teimurov *Muromsky, Rus.*
Boric acid (p. 2459·3); methenamine (p. 322·3); borax (p. 2459·2); salicylic acid (p. 1719·1); lead acetate (p. 2541·3); talc (p. 1722·2); formaldehyde (p. 1752·2); zinc oxide (p. 1729·1).
Hyperhidrosis; skin chafing.

Teiplan *Uniao Quimica, Braz.*
Teicoplanin (p. 369·3).

Teiroc *Teijin, Jpn.*
Alendronate sodium (p. 1171·3).
Hypercalcaemia of malignancy.

Tejuntivo *Iquinosa, Spain.†*
Oxaceprol (p. 2578·2).
Musculoskeletal, joint, and peri-articular disorders; osteoporosis; soft-tissue injury.

Tekadin *TKS, Braz.*
Ranitidine (p. 1882·1).

Tekaflex *TKS, Braz.*
Diclofenac sodium (p. 48·3).

Tekamen *Nevzat, Turk.*
Irinotecan hydrochloride (p. 812·2).

Tekamlo *Novartis, USA.*
Amlodipine besilate (p. 1304·1); aliskiren (p. 1295·3).
Hypertension.

Tekarin *Med-One, Gr.*
Vidarabine (p. 1023·1).
Herpesvirus infections.

Tekasan *TKS, Braz.*
Ginkgo biloba (p. 2512·3).

Tekasol *Surya Dermato, Indon.*
Centella (p. 1698·3).
Keloid scars; wounds.

Tekazol *Valeant, Hung.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Tekcis *CIS, Fin.; CIS, Neth.; CBI, Switz.*
Technetium-99m (p. 2228·1).
Radionuclide imaging.

Tekfema *Rivero, Arg.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Tekfin *Deva, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Tekmisin *Sanli, Turk.*
Troleandomycin (p. 383·2).
Streptococcal and pneumococcal infections.

Teknazol *Nobel, Rus.*
Itraconazole (p. 583·3).
Fungal infections.

Tekosit *Kocak, Turk.*
Teicoplanin (p. 369·3).

Tekral *Capellon, USA.*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Teksamen *Nevzat, Rus.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders; neuralgia.

Tekturna *Novartis, USA.*
Aliskiren fumarate (p. 1295·3).
Hypertension.

Novartis, Cz.†; Novartis, Port.†
Aliskiren (p. 1295·3).
Hypertension.

Tekturna HCT *Novartis, USA.*
⊗Aliskiren (p. 1295·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Telalgin *Erfar, Gr.*
Dipyrone (p. 53·3).
Fever; pain.

Telament *Adcock Ingram, S.Afr.*
Oral drops: Simeticone (p. 1886·2).
Gripe; infant colic.

Telarix *Help, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Telaroid *Cetus, Arg.†*
Meloxicam (p. 86·3).
Inflammation.

Telavic *Mitsubishi Tanabe, Jpn.*
Telaprevir (p. 1016·3).
Chronic hepatitis C.

Teldrin *SmithKline Beecham Consumer, USA.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Telebrix *Guerbet, Belg.; Guerbet, Hung.†; Guerbet, Israel; Rudefsa, Mex.†; Guerbet, Turk.*
Meglumine ioxitalamate (p. 1594·1) and/or sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Tyco, Canad.; R+N, Gr.
Meglumine ioxitalamate (p. 1594·1); sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Télébrix 12 *Guerbet, Fr.; Guerbet, Switz.*
Sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Telebrix 12 *Guerbet, Neth.; Martins & Fernandes, Port.*
Sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Telebrix 30 *Temis, Arg.; Rider, Chile; Guerbet, Cz.; Neiadas (Νειαδάς), Gr.; Guerbet, Neth.; Martins & Fernandes, Port.; Quifoven, Venez.*
Meglumine ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Télébrix 30 *Guerbet, Fr.; Guerbet, Switz.*
Meglumine ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Telebrix 35 *Rider, Chile; Guerbet, Cz.; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Thai.; Quifoven, Venez.*
Meglumine ioxitalamate (p. 1594·1); sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Télébrix 35 *Guerbet, Fr.; Guerbet, Switz.*
Meglumine ioxitalamate (p. 1594·1); sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Telebrix 38 *Temis, Arg.*
Meglumine ioxitalamate (p. 1594·1); sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Telebrix Coronario *Temis, Arg.*
Meglumine ioxitalamate (p. 1594·1); sodium ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Telebrix Gastro *Guerbet, Belg.; Guerbet, Cz.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Hung.†; Guerbet, Israel; Guerbet, Neth.; Martins & Fernandes, Port.*
Meglumine ioxitalamate (p. 1594·1).
Radiographic contrast medium.

Télébrix Gastro *Guerbet, Fr.; Guerbet, Switz.*
Meglumine ioxitalamate (p. 1594·1).
Contrast medium for gastrointestinal radiography.

Telebrix Hystero *Guerbet, Belg.*
Meglumine ioxitalamate (p. 1594·1); povidone (p. 2204·3).
Contrast medium for hysterosalpingography.

Temis, Arg.; R+N, Gr.; Guerbet, Neth.; Martins & Fernandes, Port.; Quifoven, Venez.
Meglumine ioxitalamate (p. 1594·1).
Contrast medium for hysterosalpingography.

Télébrix Hystéro *Guerbet, Fr.; Guerbet, Switz.*
Meglumine ioxitalamate (p. 1594·1).
Radiographic contrast medium for hysterosalpingography.

Telebrix N 180 and 300 *Guerbet, Ger.*
Meglumine ioxitalamate (p. 1594·1).
Contrast medium for urinary-tract radiography.

Telectol *Obolenskoe, Rus.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; vascular eye disorders; vestibular disorders; menopausal disorders.

Teledol *Casasco, Arg.*
Ketorolac trometamol (p. 80·2).
Pain.

Telergon II *Medicalfarm, Ital.†*
Royal jelly (p. 2608·1).
Nutritional supplement.

Tele-Stulln *Stulln, Ger.†*
⊗Naphazoline hydrochloride (p. 1669·3).
Blepharitis; conjunctivitis.

Televis-Stulln *Stulln, Ger.*
⊗Naphazoline hydrochloride (p. 1669·3).
Allergic conjunctivitis.

Telfast *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Lepetit, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, Ukr.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Telfast D *Sanofi-Aventis, Thai.†*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Telfast Decongestant *Sanofi-Aventis, Austral.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Telfast Plus *Sanofi-Aventis, Indon.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Telfast-D *Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Singapore.*
⊗Fexofenadine hydrochloride (p. 629·1); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion.

Telfastin Allergo *Sanofi-Aventis, Switz.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis.

Telfexo *Polpharma, Pol.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Teliomon *SM, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Tellerge *Aspen, S.Afr.*
Fexofenadine (p. 629·1).
Allergic rhinitis; urticaria.

Telma
Note: this name may be used for preparations of different composition.
Flora, Hung.
Echinacea purpurea (p. 2498·1); urtica (p. 2639·3); melissa (p. 2552·3); mallow (p. 2549·2); St John's wort (p. 449·1); hibiscus (p. 2525·2).
Nervous disorders.

Glenmark, India; Rowex, Irl.; Rowex, Neth.
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Telma-H *Glenmark, India.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Telmitin *Nakornpatana, Thai.*
Niclosamide (p. 161·2).
Cestode infections.

Telmox *Sandoz, Arg.*
Amoxicillin (p. 216·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Telnase *Sanofi-Aventis, Austral.; Sanofi-Aventis, NZ.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Telo *Tedec Meiji, Spain.*
Cefditoren pivoxil (p. 239·1).
Bacterial infections.

Telol *Geolab, Braz.; Medreich, Hong Kong.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Telon 3 Anak *Berlico Mulia, Indon.*
Cajuput oil (p. 2464·1); coconut oil (p. 2179·3); anise oil (p. 2444·3).
Joint and soft-tissue disorders.

Telos *Nycomed, Ger.†*
Lornoxicam (p. 83·2).
Osteoarthritis; rheumatoid arthritis.

Telpres *Piramal, India.*
Telmisartan (p. 1509·3).
Hypertension.

Telpres-H *Piramal, India.*
⊗Telmisartan (p. 1509·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Telset *Medipharm, Chile.*
Tioconazole (p. 595·3).
Fungal and Gram-positive bacterial skin infections.

Telsimox *Ad-Drugstel, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Telsomet *Spefar, Venez.*
Diazepam (p. 1063·2).
Anxiety; epilepsy; skeletal muscle spasm.

Teltonal *Hexal, Ger.†*
Devil's claw root (p. 42·3).
Joint disorders.

Telugren *Royal, Chile.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Telugren Plus *Royal, Chile.*
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1).
Fungal and Gram-positive bacterial skin infections with inflammation.

Telukast *Alet, Gr.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Telumantes *Sigillata, Cz.*
Montelukast sodium (p. 1214·3).
Asthma.

Teluron *Bayer, Jpn.*
Terguride (p. 916·3).
Hyperprolactinaemia; galactorrhoea; suppression of lactation.

Telvarte *Alter, Port.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Telviran *Egis, Hung.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Telvodin *Ivax, Arg.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Telzer *GSK, Mex.*
Fosamprenavir calcium (p. 980·1).
HIV infection.

Telzir *GSK, Arg.; ViiV, Austral.; ViiV, Austria; ViiV, Belg.; GSK, Braz.; ViiV, Canad.; GSK, Chile; ViiV, Cz.; GSK, Denm.; ViiV, Fin.; ViiV, Fr.; ViiV, Ger.; ViiV, Gr.; GSK, Hung.; GSK, Irl.; GSK, Ital.; ViiV, Neth.; GSK, Norw.; GSK, Pol.; ViiV, Port.; GSK, Rus.; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Turk.; GSK, UK.*
Fosamprenavir calcium (p. 980·1).
HIV infection.

Temaccord *Douglas, NZ.*
Temozolomide (p. 865·2).
Glioblastoma multiforme; anaplastic astrocytoma.

Temaco *Nakornpatana, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Temaril
Note: this name may be used for preparations of different composition.
Doctors, Philipp.
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; acid aspiration.

Temaron *KB, Thai.*
Ferrous sulfate (p. 2062·2); copper sulfate (p. 2057·2); vitamin B substances (p. 2102·3).

Temax *Sidus, Arg.*
Amlodipine besilate (p. 1304·1); atorvastatin calcium (p. 1309·2).
Hypertension; angina pectoris; cardiovascular risk reduction; hyperlipidaemias.

Temaze *Alphapharm, Austral.*
Temazepam (p. 1109·1).
Insomnia.

Temazep *CT, Ger.†*
Temazepam (p. 1109·1).
Sleep disorders.

Temerit *Menarini, Fr.*
⊗Nebivolol hydrochloride (p. 1444·2).
Hypertension; heart failure.

Temeritduo *Menarini, Fr.*
⊗Nebivolol hydrochloride (p. 1444·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Témesta *Biodim, Fr.*
Lorazepam (p. 1080·3).
Anxiety; alcohol withdrawal syndrome.

Temesta *Pfizer, Austria; Pfizer, Belg.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Neth.; Pfizer, Swed.; Pfizer, Switz.*
Lorazepam (p. 1080·3).
Premedication; status epilepticus; nausea and vomiting; insomnia; anxiety; mixed anxiety depressive states; alcohol withdrawal syndrome; sleep disorders; sedative.

Temetex *Teofarma, Ital.; Roche, Turk.*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Temgesic *Reckitt Benckiser, Austral.; Aesca, Austria; Schering-Plough, Belg.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Denm.; Reckitt Benckiser, Fin.; Reckitt Benckiser, Ger.; MSD, Hong Kong; Reckitt Benckiser, Irl.; Schering-Plough, Ital.; Schering-Plough, Mex.; Reckitt Benckiser, Neth.; Reckitt Benckiser, Norw.; Reckitt Benckiser, NZ; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Reckitt Benckiser, Swed.; Reckitt Benckiser, Switz.; Reckitt Benckiser, UK.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Mantecorp, Braz.
⊗Buprenorphine (p. 30·2) or buprenorphine hydrochloride (p. 30·3).
Pain.

Temgésic *ReckittBenckiser, Fr.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Temic *Farma 1, Ital.*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Temigran *Teva, Israel.†*
Ergotamine tartrate (p. 674·1); chlorcyclizine (p. 620·2); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Migraine.

Temiral *Sanbe, Indon.*
Aciclovir (p. 964·1).
Herpes simplex keratitis.

Temisartan *Temis, Arg.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy.

Temisartan Diur *Temis, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Temistac *Temis, Arg.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Temnol *Pharmahof, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Temo *Perrigo, Israel.*
Temozolomide (p. 865·2).
Malignant glioma; malignant melanoma.

Temodal *Schering-Plough, Arg.; MSD, Austral.; Schering-Plough, Austria; MSD, Belg.; Schering-Plough, Braz.; Merck, Canad.; Schering-Plough, Chile; MSD, China; Orion, China; Schering-Plough, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Schering-Plough, Gr.; MSD, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; MSD, Irl.; MSD, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Ukr.; Schering-Plough, Venez.*
Temozolomide (p. 865·2).
Malignant glioma; malignant melanoma.

Temodar *Schering-Plough, USA.*
Temozolomide (p. 865·2).
Anaplastic astrocytoma; glioblastoma multiforme.

Temoe Lawak *Singer Natura, Neth.*
Curcuma aromatica; curcuma amara; cascara (p. 1826·1).
Gastrointestinal disorders.

Temola *Dosa, Arg.*
Temozolomide (p. 865·2).

Temomedac *Medac, Cz.; Medac, Denm.; Medac, Ger.; Medac, Gr.; Medac, Irl.; Medac, Neth.; Medac, Pol.; Medac, Port.; Medac, Spain; Medac, Swed.*
Temozolomide (p. 865·2).
Malignant glioma.

Temomid *Jodas, Rus.*
Temozolomide (p. 865·2).
Malignant glioma; malignant melanoma.

Temonas *T Man, Thai.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections; Helicobacter pylori eradication.

Temostad *Stada, Cz.*
Temozolomide (p. 865·2).
Malignant glioma.

Temovate *PharmaDerm, USA.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Temozam *Fresenius Kabi, Philipp.*
Temozolomide (p. 865·2).
Anaplastic astrocytoma.

Temozo-cell *Cell Pharm, Ger.*
Temozolomide (p. 865·2).
Anaplastic astrocytoma; glioblastoma multiforme.

Temp Tab *National Vitamin, USA.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2).
Electrolyte disorders.

Tempain *Blooming Fields, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Tempalgin *Sopharma, Rus.; Sopharma, Ukr.*
Dipyrone (p. 53·3); triacetonamine tosilate (p. 1112·2).
Pain; fever; headache; toothache.

Tempanal *Arterium, Ukr.*
Dipyrone (p. 53·3); triacetonamine tosilate (p. 1112·2).
Pain; fever.

Tempanginol *Balkanpharma, Rus.*
Dipyrone (p. 53·3); triacetonamine tosilate (p. 1112·2).
Fever; pain.

Tempcaire *PediaCare, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Temperal *Allen, Mex.*
Paracetamol (p. 115·1).
Pain; fever.

Temperax *Bago, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression.

Temperol *Monin, Fr.*
Red yeast rice (p. 2603·1).
Disorders of lipid metabolism.

Tempil N *Temmler, Ger.†*
⊗Diphenylpyraline hydrochloride (p. 627·2); metamfepramone hydrochloride (p. 2557·2); aspirin (p. 22·2).
Cold symptoms.

Tempire *Collins, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Templadol *Andromaco, Chile.*
Mefenamic acid (p. 85·3).
Pain.

Temple of Heaven *Unicorn, Canad.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); peppermint oil (p. 1877·1).

Tempo
Note: this name may be used for preparations of different composition.
Thompson, USA.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); calcium carbonate (p. 1824·3).
Hyperacidity.

Akdeniz, Turk.
Paracetamol (p. 115·1).
Fever; pain.

Tempocol *Will-Pharma, Neth.*
Peppermint oil (p. 1877·1).
Gastrointestinal spasm; flatulence.

Tempofin *Collins, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Tempol *CCM, Malaysia.*
Paracetamol (p. 115·1).
Pain; fever.

Tempolax *Hommel, Ger.†*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Tempovate *Tempo Scan Pacific, Indon.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Tempra *Paladin, Canad.; BMS, Gr.; Taisho, Indon.; BMS, Mex.; Taisho, Philipp.; Taisho, Thai.; Mead Johnson Nutritionals, USA; BMS, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

BMS, Mex.
Injection: Propacetamol hydrochloride (p. 127·2).
Pain; fever.

Tempragrip *BMS, Venez.*
Oral granules: Paracetamol (p. 115·1); pheniramine maleate (p. 637·2).
Influenza symptoms.

BMS, Venez.
Tablets: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Tempragrip Dia y Noche *BMS, Venez.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Tempraplus *BMS, Venez.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Temprin *Continentales, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Temrevac-HB *Vaxines, Philipp.*
A hepatitis B vaccine (recombinant) (p. 2389·3).
Active immunisation.

Temserin *Vianex (Βιανεξ), Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Temsofen *Osel, Turk.†*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Temtabs *Aspen, Austral.*
Temazepam (p. 1109·1).
Insomnia.

Temzzard *Pizzard, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Tenace *Combiphar, Indon.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Tenacid *Sigma-Tau, Ital.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Tenadren *Sigma, Braz.*
⊗Propranolol hydrochloride (p. 1479·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tenadrin *Hua, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; nasal congestion.

Tenag *Marjan, Braz.*
⊗Agnus castus (p. 2432·2).

Tenalgin *Vida, Port.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenapril *Dexa, Indon.†*
Ramipril (p. 1483·3).
Hypertension; heart failure.

Tenar PSE *Centrix, USA.†*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Tenaron *Investi, Arg.; Pharma Investi, Chile.*
Meloxicam (p. 86·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Tenaron Flex *Investi, Arg.*
Meloxicam (p. 86·3); pridinol (p. 2026·1).
Musculoskeletal disorders with muscle spasm.

Tenasil *Homeofarm, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Tenaten *Coronet, Indon.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Tenavit *Marjan, Braz.*
Folic acid (p. 2063·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Tenax *Siam Bheasach, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Tenaxum *Servier, Cz.; Egis, Hung.; Servier, Ukr.†*
Rilmenidine phosphate (p. 1487·1).
Hypertension.

Servier, Pol.; Servier, Rus.
Rilmenidine (p. 1487·1).
Hypertension.

Tenazide *Combiphar, Indon.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tenblok *Kimia, Indon.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Ten-Bloka *Aspen, S.Afr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Tenca-1 *Alpharma, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Tencas *Casasco, Arg.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; left-ventricular dysfunction.

Tencas D *Casasco, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tencef *Tedec Meiji, Port.; Tedec Meiji, Spain.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Tencemed *Ceamed, Port.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Tencet *Hauck, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3); caffeine (p. 1203·3).
Formerly known as G-1.
Pain.

Tenchlor *Aspen, S.Afr.; Berk, UK.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Tencilan *Finadiet, Arg.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; delirium tremens; alcohol withdrawal syndrome; panic disorder.

Tencon *International Ethical, USA.*
Paracetamol (p. 115·1); butalbital (p. 1043·3).

Tendan *Biomedica, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety disorders.

Tenderdol *Vifor, Switz.*
Choline salicylate (p. 39·2); cetalkonium chloride (p. 1741·3); levomenol (p. 2544·1).
Mouth disorders.

Tenderwet *Hartmann, Belg.†*
A hydrogel dressing.
Wounds.

Tendigrip *Pietrasanta, Ital.*
Zinc oxide (p. 1729·1).

Tendipina *Arrow, Braz.*
Amlodipine (p. 1304·1).

Tendol *Nepenthes, Fr.*
Diclofenac diethylamine (p. 48·3).
Inflammation.

Tendolon *Elpen (Ελπεν), Gr.; Elpen, Malaysia.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia; algodystrophy.

Tendox *Chefaro, Neth.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Tendrin *Pisa, Mex.†*
⊗Ephedrine (p. 1663·1).

Tendura *Adeka, Turk.*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Teneir *Dosa, Arg.*
Entecavir (p. 977·3).
Hepatitis B.

Tenelia *Mitsubishi, Jpn.*
Teneligliptin hydrobromide (p. 504·1).
Diabetes mellitus.

Teneretic *AstraZeneca, Ger.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Tenervan *Alapis, Gr.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Tenescan *Maver, Mex.*
Clotrimazole (p. 576·2).
Fungal infections.

Tenex *Reddy, USA.*
Guanfacine hydrochloride (p. 1396·1).
Hypertension.

Teneze *PSA, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Tengke *Hezhi, China.*
Nimesulide (p. 101·3).
Pain; inflammation; fever.

Tenglamol *Kener, Mex.*
⊗Timolol (p. 1513·2).
Glaucoma.

Tenibex *Teva, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Tenidon *Mylan, Denm.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Tenif *AstraZeneca, Belg.; AstraZeneca, UK.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Teniken *Kener, Mex.*
Praziquantel (p. 164·1).
Parasitic infections.

Tenitrat *Catarinense, Braz.†*
Devil's claw root (p. 42·3).
Inflammation.

Teniverme *Basi, Port.*
Flubendazole (p. 154·3).
Worm infections.

Ten-K *Summit, USA.*
Potassium chloride (p. 1793·2).
Hypokalaemia; potassium depletion.

Tenkdol *Biotenk, Arg.*
Ketorolac trometamol (p. 80·2).
Pain.

Tenkuoren *Savio, Ital.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Tenliv *Ativus, Braz.*
Feverfew (p. 676·1).
Migraine.

Tenmed *Inpac, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety.

Teno *Ipca, India.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Tenoblock *Leiras, Fin.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; myocardial infarction; migraine.

Tenocam *M & H, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders; gout.

Tenocard
Note: this name may be used for preparations of different composition.
Ipca, Thai.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Klonal, Arg.
Nimodipine (p. 1455·2).

Tenochek *Ipca, India.*
⊗Atenolol (p. 1308·2); amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ipca, Rus.; Ipca, Ukr.
⊗Atenolol (p. 1308·2); amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Tenoclor *Piramal, India.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Tenocor *Merck, Thai.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tenofax *Sandoz, Indon.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Tenofed *Ipca, India.*
⊗Atenolol (p. 1308·2); nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Tenoflam *Julphar, UAE.*
Tenoxicam (p. 136·2).

Tenoftal
Note: this name may be used for preparations of different composition.
Klonal, Arg.
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma.

Teuto, Braz.
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Tenogesic *Chinta, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders.

Tenoksan *Drogsan, Turk.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenoktil *Eczacibasi, Turk.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenol *Sunward, Singapore; Masa, Thai.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Tenoloc *Zentiva, Cz.*
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension; angina pectoris.

Tenolol *Ipca, India; Ipca, Rus.; Ipca, Singapore; Siam Bheasach, Thai.*
⊗Atenolol (p. 1308·2).
Arrhythmias; angina pectoris; myocardial infarction; hypertension; tremor; hypertrophic obstructive cardiomyopathy; phaeochromocytoma; hyperthyroidism; migraine.

Tenolol-AM *Ipca, India.*
⊗Atenolol (p. 1308·2); amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Tenolol-D *Ipca, India.*
⊗Atenolol (p. 1308·2); indapamide (p. 1409·2).
Hypertension.

Tenomax *Boniscontro & Gazzone, Ital.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tenonorm *Biopharm, Rus.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Tenopress *Austell, S.Afr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Tenoprin *Ratiopharm, Fin.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; myocardial infarction.

Tenopt *Aspen, Austral.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Tenor-Bloc *Intas, Philipp.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Ténordate *AstraZeneca, Fr.*
⊗Nifedipine (p. 1447·2); atenolol (p. 1308·2).
Hypertension.

Tenoret *AstraZeneca, Hong Kong; AstraZeneca, Indon.†; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, S. Afr.; AstraZeneca, Singapore†; AstraZeneca, UK.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Tenoretic *AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Cz.; Pfizer, Denm.; AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.†; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore†; AstraZeneca, Spain; AstraZeneca, Switz.; Abdi, Turk.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Tenoric *Ipca, India; Ipca, Rus.; Ipca, Ukr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Tenormin *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Cz.; Pfizer, Denm.; AstraZeneca, Ger.; AstraZeneca, Gr.; Cana, Gr.; AstraZeneca, Hong Kong; Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; Pfizer, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; Pfizer, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; tremor; hypertrophic obstructive cardiomyopathy; phaeochromocytoma; hyperthyroidism; migraine.

Ténormine *AstraZeneca, Fr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction; arrhythmias.

Tenorox *Oxford Laboratories, Rus.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Tenorvas *ACME, Philipp.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; arrhythmias; myocardial infarction; migraine.

Tenostat *Apotex, Philipp.†; Pharma 3, Philipp.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Tenotec *Ache, Braz.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenoten *Materia Medica, Rus.*
Antibodies to brain-specific proteins S-100.
Anxiety disorders.

Tenovate *GSK, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Tenovate G *GSK, India.*
⊗Clobetasol propionate (p. 1627·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Tenovate M *GSK, India.*
⊗Clobetasol propionate (p. 1627·1); miconazole nitrate (p. 589·1).
Infected skin disorders.

Tenovate-N *T Man, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Tenox
Note: this name may be used for preparations of different composition.
Lamda (Λαμδα), Gr.; Deltapharm, Hong Kong†; Charoen, Thai.; Biofarma, Turk.
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

KRKA, Hung.; KRKA, Pol.; KRKA, Rus.
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

KRKA, Ukr.
Amlodipine (p. 1304·1).
Hypertension; angina pectoris.

Orion, Fin.; Orion, Irl.
Temazepam (p. 1109·1).
Insomnia; anxiety; premedication.

Tenoxil *Olan-Kemed, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders.

Tenoxin *Roemmers-Klinos, Venez.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenoxman *T Man, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders.

Tenoxol *Boniscontro & Gazzone, Ital.†*
Neltenexine (p. 1670·2).
Respiratory-tract disorders.

Ten-Quat *Esoform, Ital.*
Benzalkonium chloride (p. 1737·1).
Surface disinfection.

Tenrol *Unique, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tens *Unilfarma, Port.*
Lacidipine (p. 1417·3).
Hypertension.

Tensaar *Kimia, Indon.†*
Losartan potassium (p. 1422·2).
Hypertension.

Tensadiur *Savio, Ital.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tensaid *Generics, UK.*
⊗Indapamide (p. 1409·2).
Hypertension.

Tensaldin *Delta, Braz.*
⊗Caffeine (p. 1203·3); isometheptene hydrochloride (p. 2535·1) or isometheptene mucate (p. 2535·1); dipyrone (p. 53·3).
Migraine.

Tensaliv *Neo Quimica, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension.

Tensamin *Zentiva, Cz.*
Dopamine hydrochloride (p. 1367·2).
Heart failure; shock; hypovolaemia.

Tensamon *Sanitas, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Musculoskeletal disorders.

Tensan *Arcana, Austria.*
Nilvadipine (p. 1455·2).
Hypertension.

Tensanil *Savio, Ital.†*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Tensart
Note: this name may be used for preparations of different composition.
Abdi, Turk.
Candesartan cilexetil (p. 1330·2).

Ativus, Braz.
Passion flower (p. 2584·1).

Egis, Hung.; Egis, Pol.
Valsartan (p. 1521·2).
Myocardial infarction; hypertension; heart failure.

Tensart HCT *Egis, Hung.; Egis, Pol.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tensart Plus *Abdi, Turk.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).

Tensazol *Tecnifar, Port.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure; myocardial infarction; ischaemic heart disease; unstable angina pectoris.

Tensiane *Greenpharma, Braz.†*
Cimicifuga (p. 2478·1).

Tensibloc *Towa, Philipp.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Tensiblock *Epifarma, Ital.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tensicap *Sanbe, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Tensidif *Medifarm, Turk.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Tensidipin *Legrand, Braz.†*
Amlodipine (p. 1304·1).

Tensig *Aspen, Austral.; Treasure Mountain, Hong Kong†; Sigma, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine.

Tensigal *Teva, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Tensigard *Phapros, Indon.*
Celery extract (p. 2472·3); java tea extract (p. 2536·3).
Hypertension.

Tensikey *Pharminicio, Spain.†*
Lisinopril (p. 1420·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tensikey Complex *Pharminicio, Spain.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tensil
Note: this name may be used for preparations of different composition.
Best, Mex.
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy.

Tensilol *LA, Arg.†*
⊗Atenolol (p. 1308·2).
Hypertension.

Tensilon *Valeant, Canad.; Roche, Singapore; Valeant, USA.*
Edrophonium chloride (p. 686·1).
Diagnosis of myasthenia gravis; paroxysmal supraventricular tachycardia; reversal of competitive neuromuscular blockade.

Tensimed *Austral, Arg.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Tensimin *JB Chemicals, India; Pasteur, Philipp.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction.

Tensinop *Sanbe, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure.

Tensinor *Abdi, Turk.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Tensinorm *Medikon, Indon.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

Tensiocap *Giscard, Arg.†*
Pilocarpine (p. 2010·2).

Tensiomax *Bago, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Tensiomin *Egis, Cz.; UCB, Ger.†; Egis, Hong Kong; Egis, Hung.; Egis, Thai.*
Captopril (p. 1331·2).
Hypertension; myocardial infarction; heart failure; diabetic nephropathy.

Tensiomin-Cor *UCB, Ger.†*
Captopril (p. 1331·2).
Heart failure; hypertension.

Tensionorme *Lisapharm, Fr.*
⊗Bendroflumethiazide (p. 1315·2); reserpine (p. 1485·3).
Hypertension.

Tensiopax *Arrow, Braz.*
Citalopram (p. 411·1).

Tensioval *Sanval, Braz.*
Methyldopa (p. 1431·1).
Hypertension.

Tensiphar *Actavis, Indon.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Tensipine *Genus, UK.*
Nifedipine (p. 1447·2).
Hypertension; angina pectoris.

Tensiplex
Note: this name may be used for preparations of different composition.
Kleva, Gr.
⊗Trichlormethiazide (p. 1519·3); reserpine (p. 1485·3).
Hypertension.

Tensisples *Alet, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Tensium
Note: this name may be used for preparations of different composition.
Baliarda, Arg.
Alprazolam (p. 1035·2).
Alcohol withdrawal syndrome; anxiety; mixed anxiety depressive states; panic disorder.

DDSA Pharmaceuticals, UK.
Diazepam (p. 1063·2).
Anxiety; insomnia; alcohol withdrawal syndrome; epilepsy; skeletal muscle spasm; premedication.

Tensium Gastric *Baliarda, Arg.*
Alprazolam (p. 1035·2); domperidone (p. 1838·1); simeticone (p. 1886·2).
Gastrointestinal disorders.

Tensival *Solvay, Port.†*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tensivask *Dexa, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Tensivel-D *Medipharm, Chile.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tenso Stop *Esteve, Spain.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Tenso Stop Plus *Esteve, Spain.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tensobon *Schwarz, Ger.†; Coronet, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Tensobon comp *UCB, Ger.; BMS, Switz.†*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension; heart failure.

Tensocardil *Esteve, Spain.†*
Fosinopril sodium (p. 1386·2).
Heart failure; hypertension.

Tensodeine *Sandoz, Austral.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3).
Pain.

Tensodin *Ativus, Braz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Tensodox *Recalcine, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Tensofar *Pharma Investi, Chile.†*
Nitrendipine (p. 1456·3).
Hypertension.

Tensoflux *Hennig, Ger.*
⊗Bendroflumethiazide (p. 1315·2); amiloride hydrochloride (p. 1299·1).
Oedema; ascites; hypertension; renal calculi.

Tensogard *BMS, Ital.*
Fosinopril sodium (p. 1386·2).
Hypertension; heart failure.

Tensogradal *Kern, Spain.*
Nitrendipine (p. 1456·3).
Hypertension.

Tensoliber *Pentafarma, Port.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure.

Tensoliv *Laboratorios Chile, Chile.*
Chlordiazepoxide (p. 1044·2); clidinium bromide (p. 1833·2).
Irritable colon.

Tensolve *Aspen, S.Afr.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Tensomax *Leti, Venez.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Tensonit *Ivax, Arg.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Tensopin *Leti, Venez.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Tensoprel *Rubio, Spain.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Tensopril
Note: this name may be used for preparations of different composition.
Ivax, Arg.; MSD, Israel.
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction.

Ivax, UK.†
Captopril (p. 1331·2).
Heart failure; hypertension.

Tensopril D *Ivax, Arg.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tensopyn *Mirren, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); doxylamine succinate (p. 627·3); caffeine (p. 1203·3).
Pain and associated tension.

Tensoral *Ultra, Mex.*
⊗Chlortalidone (p. 1335·2).
Hypertension; heart failure; oedema; ascites; renal calculi.

Tensoril *Apotex, Philipp.*
Captopril (p. 1331·2).
Heart failure; hypertension.

Tensostad *Stada, Ger.†*
Captopril (p. 1331·2).
Hypertension; heart failure.

Tensotec *Lavipharm, Gr.; Neo-Farmaceutica, Port.†*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Tensotin *Julphar, UAE.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Tensotrand *Actavis, Pol.*
Trandolapril (p. 1517·2).
Hypertension; left ventricular dysfunction following myocardial infarction.

Tensozide *BMS, Ital.*
⊗Fosinopril sodium (p. 1386·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tenstaten *Bouchara-Recordati, Fr.*
⊗Cicletanine hydrochloride (p. 1336·2).
Hypertension.

Tenston *Adcock Ingram, S.Afr.*
Syrup: Promethazine hydrochloride (p. 638·2); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Adcock Ingram, S.Afr.
Tablets: Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2); meprobamate (p. 1083·3).
Fever; pain.

Adcock Ingram, S.Afr.†
Sustained-release capsules; sustained-release tablets: Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2); meprobamate (p. 1083·3).
Pain; fever.

Tensulan *Marjan, Braz.*
Vitamins.

Tensuril *Cristalia, Braz.*
Diazoxide (p. 1351·3).
Hypertension; hypoglycaemia.

Tentalux *Pharos, Indon.*
Dexpanthenol (p. 2582·2).
Skin irritation; wounds.

Tentepanil *Leovan, Gr.*
Tenoxicam (p. 136·2).
Inflammatory disorders.

Tentex *Himalaya, Rus.*
Abelmoschus moschatus; ashwagandha (p. 2450·2); argyreia speciosa; dolichos pruriens; trivanga bhasma; shilajeet (mineral pitch); saffron (p. 2208·2); nux vomica (p. 2573·3); makardhwaj; orchis mascula

(p. 2576·3); anacyclus pyrethrum; sida cordifolia; bombax ceiba; black pepper (p. 2586·1).
Erectile dysfunction.

Tentex Royal *Himalaya, Singapore.*
⊗Tribulus terrestris (p. 2633·3); hygrophila longifolia; prunus dulcis; blepharis edulis; crocus sativus (p. 2208·2) processed in curculigo orchoides; betel.
Erectile dysfunction.

Tentil *Rafarm, Gr.*
Potassium iodide (p. 2336·3); sodium iodide (p. 2337·1).
Glaucoma.

Tentrini *Nutricia, Denm.†; Nutricia, Ital.; Nutricia Clinical, UK.*
A range of preparations for enteral nutrition.

Nutricia, Fin.†; Nutricia, Irl.
A range of preparations for enteral nutrition in children.

Nutricia, Fr.†; Nutricia, Port.†
Preparation for enteral nutrition.

Tentürdiyot *Drogsan, Turk.; Kocak, Turk.; Oro, Turk.; Radyum, Turk.*
Iodine (p. 2336·3); sodium iodide (p. 2337·1).
Wound disinfection; skin infections.

Tenualax *Bago, Arg.*
Lactulose (p. 1850·3).
Constipation; dyspepsia; gastrointestinal enteropathy; hepatic encephalopathy.

Tenuate *Aventis, Austral.†; Sanofi-Aventis, Canad.†; Watson, USA.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Tenuate Dospan *Aventis, NZ†; Adcock Ingram, S.Afr.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Tenuate Retard *Artegodan, Ger.*
⊗Diethylpropion hydrochloride (p. 2321·1).
Obesity.

Tenutan *PannonPharma, Hung.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Tenutex *Bioglan, Swed.*
Disulfiram (p. 2495·3); benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Tenvasc *Interbial, Port.*
Cilnidipine (p. 1337·1).

Tenvatil *Lafi, Chile.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Tenvic *Spedrog, Arg.*
Iron polymaltose (p. 2077·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Iron and folic acid deficiency.

Tenxil *Unison, Thai.†*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Tenzotran *Actavis, Rus.*
Moxonidine (p. 1442·1).
Hypertension.

Teobag *Eczacibasi-Baxter, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teobid *Farma, Venez.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teodosis *Welt, Arg.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teofilab *Multilab, Braz.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teofylamin *SAD, Denm.*
Aminophylline (p. 1201·2).
Obstructive airways disease.

Teofyllamin *Meda, Swed.*
Aminophylline (p. 1201·2).
Asthma; neonatal apnoea; pulmonary oedema.

Teogrand *Ahimsa, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Teokap *Nobel, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teolixir Compositum *Biogalenica, Spain.†*
⊗Guaifenesin (p. 1666·2); prednisolone (p. 1645·2); theophylline (p. 1229·3).
Obstructive airways disease.

Teolong *Abbott, Braz.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teomuc *Biolab Sanus, Braz.*
Ambroxol theophyllinate (p. 1201·2).
Respiratory-tract disorders.

Teonav *Farmaceutica H, Mex.†*
Risedronate (p. 1189·2).
Osteoporosis.

Teophyl *IQB, Braz.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teoptic *Novartis, Irl.†; Thea, Neth.; Restan, S.Afr.†; Novartis, UK.*
⊗Carteolol hydrochloride (p. 1332·3).
Ocular hypertension; glaucoma.

Teoremac *Sanfer, Mex.*
Glucametacin (p. 66·2).
Fever; pain; inflammation.

Teoremin *Ache, Braz.*
Glucametacin (p. 66·2).
Musculoskeletal, joint, and peri-articular disorders.

Teosal *Dexa, Indon.*
⊗Salbutamol sulfate (p. 1220·2); theophylline (p. 1229·3).
Obstructive airways disease.

Teosel *Biosel, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teosona *Phoenix, Arg.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Teosona Expectorante *Phoenix, Arg.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Teosona Sol *Phoenix, Arg.*
Theophylline (p. 1229·3); theophylline monoethanolamine (p. 1229·3).
Obstructive airways disease.

Teoston *Ariston, Braz.*
Theophylline (p. 1229·3).
Asthma; bronchodilator.

Teotard *KRKA, Rus.*
Theophylline (p. 1229·3).

Téoula *Menarini, Fr.*
Zofenopril calcium (p. 1536·3).
Heart failure; hypertension.

Teovent
Note: this name may be used for preparations of different composition.
Biophausia, Swed.
Choline theophyllinate (p. 1207·1).
Obstructive airways disease.

Tepadina *Adienne, Austria; CSC, Cz.; EuroCept, Denm.; Riemser, Ger.; Adienne, Irl.; EuroCept, Neth.; Adienne, Norw.; Imed, Pol.; Adienne, Port.; Adienne, Spain; Adienne, UK.*
Thiotepa (p. 871·1).
Malignant neoplasms; haematopoietic stem cell transplantation.

Tepanil *Norma (Νορμα), Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Tepavil *Kern, Spain.*
Sulpiride (p. 1107·3).
Anxiety; depression; behaviour disorders.

Tepaxin *Takeda, Indon.*
Cefalexin (p. 234·1).
Bacterial infections.

Tepazepan *Kern, Spain.*
Diazepam (p. 1063·2); pyridoxine (p. 2105·3); sulpiride (p. 1107·3).
Neurosis; psychosomatic disorders; psychoses; anxiety.

Teperin *Extractum, Hung.*
Amitriptyline hydrochloride (p. 401·1).
Depression; neuropathies; migraine.

Tephine *Sandoz, UK.*
⊗Buprenorphine hydrochloride (p. 30·3).
Pain.

Tepilta *Meda, Austria; Meda, Ger.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); oxetacaine (p. 1993·1).
Peptic ulcer; hiatus hernia; gastro-oesophageal reflux; heartburn; gastritis; dyspepsia.

Teplexin *TP, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Tepox Cal *Stada, Spain.*
Calcium pidolate (p. 1784·3).
Calcium deficiency; osteoporosis.

Tepox Cal D *Stada, Spain.*
Calcium pidolate (p. 1784·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Teprix *Sanofi-Aventis, Arg.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Teprix Fem *Sanofi-Aventis, Arg.*
Ibuprofen (p. 68·2); homatropine hydrobromide (p. 2007·3).
Dysmenorrhoea; smooth muscle pain and spasm.

Tepuxin *Direction, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Tequin *BMS, China; BMS, NZ.†*
Gatifloxacin (p. 303·2).
Bacterial infections.

Tequinol *Otto, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Tera *TAD, Ger.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Terablock *Pfleger, Ger.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Terace Zinc *Konsuma, Venez.*
Ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2).
Vitamin C deficiency.

Teradox *Teva, Mex.*
Cefaclor (p. 232·3).
Bacterial infections.

Teradi *GMP, Indon.*
Attapulgite (p. 1820·1).
Diarrhoea.

Teradin *Yeni, Turk.†*
Terfenadine (p. 640·3).
Allergic rhinitis; urticaria.

Teradyl *Hua, Thai.†*
Codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Cough.

Terafin *Fako, Turk.*
Terbinafine (p. 593·3).
Fungal infections of the skin and nails.

Teraflem *Konsuma, Venez.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Terafluss *Rottapharm, Ital.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Tera-Gel *Geritrex, USA.*
Coal tar (p. 1723·2).
Scalp disorders.

Teragran *BMS, Mex.*
Vitamins; minerals.

Teragran JR *BMS, Braz.*
Vitamins.

Teragran M *BMS, Braz.*
Vitamins; minerals.

Teragrip *Konsuma, Venez.; Novapharm, Venez.*
Oral drops; paediatric oral granules; syrup: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Konsuma, Venez.
Capsules; oral granules (adult): Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Cold symptoms.

Teragrip D *Konsuma, Venez.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Teragrip Forte Dia *Konsuma, Venez.*
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1) or pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Teragrip Forte Dia/Forte Noche *Konsuma, Venez.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; chlorphenamine maleate (p. 620·3).
Cold symptoms.

Teragrip Forte Noche *Konsuma, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Teragripem *Konsuma, Venez.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Terak *Akorn, USA.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Teraligen *Valenta, Rus.*
Alimemazine tartrate (p. 615·1).
Anxiety; asthenia; mixed anxiety depressive states; sleep disorders; hypersensitivity reactions.

Téralithe *Sanofi-Aventis, Fr.*
Lithium carbonate (p. 427·3).
Bipolar disorder; psychoses.

Teramic *Andromaco, Chile.*
Itraconazole (p. 583·3).
Fungal infections.

Teramol *Terramedic, Philipp.*
Paracetamol (p. 115·1).
Pain; fever.

Teramoxyl *Terramedic, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Teranar *Apogepha, Ger.; Frik, Turk.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Teranex *Innoderm, Philipp.*
Glycolic acid (p. 1704·3).
Skin cleansing.

Teranfis *Anpharm (Ανφαρμ), Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Teranol *Guardian, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Terap *Sanitas, Chile.*
Midazolam maleate (p. 1085·2).
Insomnia; premedication.

Terapova *Teva, Mex.*
Conjugated oestrogens (p. 2260·1).
Menopausal disorders; osteoporosis.

Teraprost *Malesci, Ital.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Teraquin *Fortbenton, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Terasep *Fada, Arg.*
Cefotaxime (p. 244·1).
Bacterial infections.

Teraside *Krugher, Ital.*
Thiocolchicoside (p. 2026·2).
Spasticity; parkinsonism; neuromuscular pain.

Terasin *YSP, Malaysia; Daewon, Singapore.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Terasma *Medikon, Indon.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terasma Expectorant *Medikon, Indon.†*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Teratos
Note: this name may be used for preparations of different composition.
Konsuma, Venez.
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Recalcine, Chile.
Oxolamine (p. 1671·2).
Respiratory-tract congestion; cough.

Teraumon *Smaller, Spain; Farma-Tek, Turk.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Teravox *Terramedic, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Teraxans *Servier, Fin.; Servier, Irl.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Terazid *Madaus, Ger.†*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Terazoflo *Gry, Ger.†*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Terazol *Janssen-Ortho, Canad.; Janssen-Cilag, S.Afr.†; Ortho McNeil, USA.*
Terconazole (p. 595·2).
Vulvovaginal candidiasis.

Terazosabb *Pharma Logistics, Belg.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Terbac *Syntex, Mex.†*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Terbafin *Kleva, Gr.; Pacific, NZ.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbane *Sandoz, S.Afr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbasil *Actavis, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbasmin *Europharma, Denm.; Orifarm, Denm.; Paranova, Denm.; SinGad, Denm.; Tabs n Caps, Denm.; Euro Registratie, Neth.†; AstraZeneca, Spain; Ern, Spain.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbasmin Expectorante *Ern, Spain.*
⊗Guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbenol *Bernabo, Arg.*
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility.

Terbenol Duo *Bernabo, Arg.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Terbicil *Aspen, S.Afr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbiclear *Glenmark, S.Afr.*
Terbinafine (p. 593·3).

Terbi-Derm *Cinetic, Arg.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections.

Terbiderm *Dermapharm, Austria; Dermapharm, Ger.; Dermapharm, Neth.; Richter, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbifil *Sandoz, Switz.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin, nail, and scalp infections.

Terbifin *Cipla, Hong Kong; Cipla, Indiat; Cipla, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbigalen *Galen, Ger.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

TerbiGen *Generics, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbigen *Generics, Hung.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbigram *Lavipharm, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbihexal *Sandoz, Austral.; Hexal, Cz.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbin *Eczacibasi, Turk.*
Terbinafine (p. 593·3).
Fungal infections of the skin and nails.

Gabriel, Gr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbinac *Hexal, Austria.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbinacol *Arrow, Braz.*
Terbinafine (p. 593·3).

Terbina-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Terbinavita *Stada, Neth.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbinax *Drossapharm, Switz.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin, nail, and vaginal infections.

Terbiner *Mediner, Hung.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbinex *JSJ, USA.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail infections.

Terbinox *Unique, Rus.*
Terbinafine (p. 593·3) or terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terbiox *Rivero, Arg.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Terbiprol *Novendia, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbised *Agio, Rus.*
Terbinafine (p. 593·3).
Fungal skin infections.

Terbisil *Gedeon Richter, Cz.†; Actavis, Denm.; Gedeon Richter, Hung.; Richter, Pol.; Stada, Swed.; Berksam, Turk.; Santa, Turk.; Gedeon Richter, Ukr.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Gedeon Richter, Rus.
Terbinafine (p. 593·3).
Fungal skin and nail infections.

Terbiskin *DAST, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbisol *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbistad *Stada, Cz.; Stada, Denm.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbistada *Stada, Fin.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbix *Altayvitamin, Rus.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbonile *Bilim, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terbron *Biolab, Hong Kong.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbu *Suphong, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbu Expectorant *Suphong, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Terbuken *Kener, Mex.*
⊗Terbutaline sulfate (p. 1228·1).

Terbul *Teofarma, Ger.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbulin *Vitamed, Israel; United American, Philipp.; Charoen, Thai.; Chinta, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease; asthma.

Terbulin Expectorant *Chinta, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Terbuline *Synco, Singapore; Charoen, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Deltapharm, Hong Kongt; Synco, Hong Kong.†
⊗Terbutaline (p. 1228·1).
Obstructive airways disease.

Terbuno *Milano, Thai.†*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbusin *SSP, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbusin Expectorant *SSP, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Terbuta *Christo, Hong Kong.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Terbuta-Expect *Christo, Hong Kong.†*
⊗Guaifenesin (p. 1666·2); terbutaline sulfate (p. 1228·1).

Terbutil *Uniao Quimica, Braz.*
⊗Terbutaline sulfate (p. 1228·1).
Asthma.

Tercef *Balkanpharma, Rus.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Tercette *Gedeon Richter, Denm.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Tercian *Sanofi-Aventis, Fr.*
Cyamemazine (p. 1062·2) or cyamemazine tartrate (p. 1062·2).
Anxiety; psychoses; aggression; depression.

Vitoria, Port.
Cyamemazine tartrate (p. 1062·2).
Anxiety; depression; psychoses; withdrawal syndromes.

Terclovir *Terramedic, Philipp.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Terco-C *Hua, Thai.*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Terco-D *Hua, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Tercodin *Interhim, Rus.*
Codeine phosphate (p. 40·2); sodium bicarbonate (p. 1781·1); terpin hydrate (p. 1678·2).
Cough.

Terconan *EMS, Braz.*
Terconazole (p. 595·2).

Terekol *Panalab, Arg.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin, hair, and nail infections.

Tereonsit *Hautel, Arg.*
Sage (p. 2608·3); trolamine (p. 2634·3).

Terfacef *Sanbe, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Terfamex *Medix, Mex.*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Terfedin *Kleva, Gr.*
Terfenadine (p. 640·3).

Terfex
Note: this name may be used for preparations of different composition.
Mediderm, Chile; Vivax Gynopharm, Venez.
Terbinafine hydrochloride (p. 593·3).
Fungal skin, nail, and hair infections.

Terfimed *ProMed, Cz.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terfin
Note: this name may be used for preparations of different composition.
Elea, Arg.; Pasteur, Chile; Teva, Hung.
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Interbat, Indon.
Terfenadine (p. 640·3).
Allergic rhinitis; allergic skin disorders.

Terfinil *Biomedica, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terfinor *Alet, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Terflurazine *Lennon, S.Afr.†*
Trifluoperazine hydrochloride (p. 1113·2).
Schizophrenia; mania; delirium tremens.

Terfluzine *Valeant, Canad.†*
Trifluoperazine hydrochloride (p. 1113·2).

Tergecef *United American, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Tergecin *Fujisawa, Philipp.†; Medichem, Philipp.†*
Ceftizoxime (p. 253·1).
Bacterial infections.

Tergil *MM, India.†*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Tergil-T *MM, India.†*
⊗Terbutaline sulfate (p. 1228·1); theophylline (p. 1229·3).
Obstructive airways disease.

Tergynan
Note: this name may be used for preparations of different composition.
Bouchara, Rus.; Bouchara-Recordati, Ukr.
⊗Ternidazole (p. 949·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3); prednisolone metasulfobenzoate sodium (p. 1645·3).
Vaginitis.

Bouchara-Recordati, Fr.
Metronidazole (p. 936·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Vaginitis.

Teribone *Asahi, Jpn.*
Teriparatide acetate (p. 1191·2).
Osteoporosis.

Terican *Landsteiner, Mex.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Tericin AT *Ativus, Braz.*
Tetracycline hydrochloride (p. 373·2); amphotericin B (p. 569·2).
Bacterial and fungal vulvovaginal infections.

Teril
Note: this name may be used for preparations of different composition.
Alphapharm, Austral.; Alphapharm, Hong Kong; Merck, Indon.†; Taro, Israel; Mylan, NZ†; Eczacibasi, Turk.; Taro, USA.
Carbamazepine (p. 512·2).
Epilepsy; bipolar disorder; alcohol withdrawal syndrome; neuralgias; diabetes insipidus; diabetic neuropathy; polyuria; polydipsia.

LKM, Arg.
Terazosin (p. 1511·1).
Benign prostatic hyperplasia; hypertension; heart failure; Raynaud's syndrome.

Terimed *Genericon, Denm.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Terimon *Norma (Νορμα), Gr.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Terinateva *Med, Turk.*
Terbinafine hydrochloride (p. 593·3).

Terioxan *Shin Poong, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Teripol *Landsteiner, Mex.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Teriurin *Raam, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Terivalidin *Sanofi-Aventis, S.Afr.*
Terizidone (p. 373·1).
Tuberculosis.

Terix *Teva, Mex.*
Amphotericin B (p. 569·2).
Fungal infections.

Terizidex *Collect, Braz.*
Terizidone (p. 373·1).
Tuberculosis.

Terizin *Seoul Pharma, Singapore.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Terkur *Orva, Turk.*
Aluminium chlorohydrate (p. 1694·1).
Hyperhidrosis.

Terlev *Xeno, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Terline *The Forty-Two, Thai.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease.

Terloc *Ivax, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Laboratorios Chile, Chile.
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Terloc Duo *Ivax, Arg.*
Amlodipine besilate (p. 1304·1); benazepril (p. 1314·3).
Hypertension.

Terloc Max *Ivax, Arg.*
White tablets, amlodipine besilate (p. 1304·1); blue tablets, losartan potassium (p. 1422·2).
Hypertension.

Terlomexin *Effik, Fr.*
Fenticonazole nitrate (p. 578·1).
Candidiasis.

Termacet *Toprak, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Termaldina Codeina *Novartis Consumer, Spain.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Termalfeno *Novartis Consumer, Spain.†*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

Termalgin *Novartis Consumer, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Termalgin Codeina *Novartis, Spain.†*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Termalgine *Novartis, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Termalgine Plus *Novartis, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Termasil *Hasco-Lek, Pol.*
Salix purpurea (p. 129·2); sambucus (p. 2609·3); tilia (p. 2631·3); verbascum (p. 2645·1).
Fever.

Termicef *Nufarindo, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Termicon *Farmstandart, Rus.*
Terbinafine (p. 593·3) or terbinafine hydrochloride (p. 593·3).
Fungal skin, mucous membrane, and nail infections.

Termin C *Terramedic, Philipp.*
Vitamins; iron (p. 2073·1).
Nutritional supplement.

Terminate *Abdi, Turk.*
Olmesartan medoxomil (p. 1459·2).

Terminus *Yeni, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Termisil *Ferron, Indon.*
Terbinafine (p. 593·3).
Fungal skin infections.

Genepharm, Gr.
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Termizol *Teva, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Termo *Beiersdorf, Denm.; Beiersdorf, Swed.*
Cayenne pepper (p. 2469·3).
Musculoskeletal pain.

Termocatil *Gelos, Spain.†*
Paracetamol (p. 115·1).
Pain; fever.

Termofren *Roemmers, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Termogrip *Ronnet, Arg.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); bromhexine hydrochloride (p. 1656·3).
Cold and influenza symptoms.

Termol *Uniao Quimica, Braz.; Ratiopharm, Ital.*
Paracetamol (p. 115·1).
Fever; pain.

Termonal *Sanval, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Termonil *Liferpal, Mex.†*
Dipyrone (p. 53·3).
Fever; pain.

Termo-Niofen *K2 Health & Wellness, Chile.*
Ibuprofen (p. 68·2); paracetamol (p. 115·1).
Fever; pain.

Termopirona *Neo Quimica, Braz.*
Dipyrone (p. 53·3).
Fever; pain.

Termoprins *Cazi, Braz.†*
Dipyrone (p. 53·3).
Fever; pain.

Termopsol *Farmstandart, Rus.*
Thermopsia lanceolata; sodium bicarbonate (p. 1781·1).
Cough.

Termorex *Konimex, Indon.†*
Paracetamol (p. 115·1).
Fever; pain.

Termorex Plus *Konimex, Indon.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Termosan *Salvat, Spain.*
Camphor (p. 2466·2); capsicum oleoresin (p. 2469·3); methyl salicylate (p. 92·1); salicylic acid (p. 1719·1); turpentine oil (p. 2636·3); menthol (p. 2553·2); lavender oil (p. 2541·1); thyme oil (p. 2630·3); eucalyptus oil (p. 2501·2).
Upper respiratory-tract disorders; soft-tissue disorders; muscle pain.

Termox *Solvang, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Termycol *SFD, Port.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Ternadin *Dunar, Spain.*
Terfenadine (p. 640·3).
Hypersensitivity reactions.

Ternaf *Rowex, Irl.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Ternafinol *Dekaz, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Ternel *Medinova (Μεντινοβα), Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Ternelax *Wander, Philipp.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm; spasticity.

Ternelin *Novartis, Jpn.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm; spasticity.

Ternex *Abdi, Turk.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and inflammation; musculoskeletal and joint pain.

Ternolol *Hovid, Hong Kong; Hovid, Singapore.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; migraine.

Ternovag *Novag, Mex.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Terocaps *Medix, Mex.*
Garcinia cambogia (p. 2510·2).
Obesity.

Terocin *Alexso, USA.*
Lidocaine (p. 1988·1); menthol (p. 2553·2).
Formerly contained capsaicin, lidocaine, menthol, and methyl salicylate.

Terodul *Degorts, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Terol
Note: this name may be used for preparations of different composition.
Cipla, India.
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Terolinal *Chrispa (Χρισπα), Gr.*
Lisinopril (p. 1420·3).
Hypertension.

Terolut *Abbott, Fin.*
Dydrogesterone (p. 2270·1).
Menstrual disorders; endometriosis; menopausal disorders.

Teromac *Huons, Philipp.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Teromeg *Mercury, UK.*
Omega-3-acid ethyl esters (p. 1460·2).
Hypertriglyceridaemia; myocardial infarction.

Teromol *Aldo, Spain.*
Theophylline (p. 1229·3).
Obstructive airways disease; heart failure.

Teronac *Sandoz, Gr.; Novartis, Indon.; Novartis, Singapore.†*
⊗Mazindol (p. 2324·1).
Obesity.

Terost *Ativus, Braz.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Terostrant *Chrispa (Χρισπα), Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Teroxina *Bruluagsa, Mex.*
Cefadroxil (p. 233·2).
Bacterial infections.

Terozid *Terramedic, Philipp.*
Isoniazid (p. 311·2).
Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Terpect *Themis Medicare, India.*
Tablets: ⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Themis Medicare, India.
Syrup: ⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough associated with obstructive airways disease.

Terphylate *Overseas, India.*
⊗Terbutaline sulfate (p. 1228·1); bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2); menthol (p. 2553·2).
Cough.

Terphylin *Themis Medicare, India.*
⊗Terbutaline sulfate (p. 1228·1); etofylline (p. 1208·2).
Obstructive airways disease.

Terpichol *Herbapol Wroclaw, Pol.*
Borneol (p. 2460·2); camphene (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2); menthone (p. 2554·2); α-pinene (p. 2591·3); β-pinene (p. 2591·3).
Hepatobiliary disorders.

Terpincod *Farmstandart, Rus.*
Codeine (p. 40·2); sodium bicarbonate (p. 1781·1); terpin hydrate (p. 1678·2).
Cough.

Terpine Gonnon *Merck Medication Familiale, Fr.*
Oral liquid: Terpin (p. 1678·2); tolu balsam (p. 1679·2).
Respiratory-tract disorders.

Terplex *Biomep, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Terpone *Rosa-Phytopharma, Fr.*
Terpin (p. 1678·2); Siberian fir oil; niaouli oil (p. 2569·1); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders.

Terpone Nourrisson *Rosa-Phytopharma, Fr.†*
Siberian fir oil; niaouli oil (p. 2569·1); eucalyptus oil (p. 2501·2).
Respiratory-tract disorders.

Terponil *Vitafarma, Spain.†*
Oxidised terpenes; terpin (p. 1678·2).
Respiratory-tract disorders.

Terposen *Vir, Spain.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Terracol-A *ANH, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Terra-Cortril *Pfizer, S.Afr.†; Farmasierra, Spain.*
Eye/ear drops; eye/ear ointment:
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1); polymyxin B sulfate (p. 342·3).
Eye or ear disorders; eye infections; ear infections.

Pfizer, S.Afr.†; Farmasierra, Spain; Pfizer, USA.
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1).
Infected skin disorders; eye inflammation with bacterial infection.

Pfizer, Arg.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Norw.; Intrapharm, UK.
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone (p. 1640·1).
Infected skin disorders.

Pfizer, Indon.
⊗Oxytetracycline (p. 337·1) or oxytetracycline hydrochloride (p. 337·2); hydrocortisone (p. 1640·1).
Infected skin disorders; infected eye disorders.

Terracortril *Pfizer, Swed.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone (p. 1640·1).
Infected skin disorders; otitis externa.

Terracortril Dexagenta *Mann, Ger.†*
⊗Gentamicin sulfate (p. 304·2); dexamethasone (p. 1630·3) or dexamethasone sodium phosphate (p. 1631·2).
Infected eye disorders.

Terracortril med polymyxin B *Pfizer, Swed.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1); polymyxin B sulfate (p. 342·3).
Otitis externa; infected eye disorders.

Terra-Cortril met polymyxine-B *Pfizer, Neth.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1); polymyxin B sulfate (p. 342·3).
Blepharitis squamosa; inflammatory ear infections.

Terra-Cortril P *Pfizer, Fin.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders; infected ear disorders.

Terra-Cortril Polymyxin B *Pfizer, Norw.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1); polymyxin B sulfate (p. 342·3).
Ear disorders.

Terra-Cortril + Polymyxine B *Pfizer, Belg.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1); polymyxin B sulfate (p. 342·3).
Infected inflammatory ear or eye disorders.

Terrados *Pfizer, Mex.*
Oxytetracycline hydrochloride (p. 337·2).
Acne; rosacea.

Terraferron *Terramedic, Philipp.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; folic acid and vitamin B_{12} deficiency; iron deficiency.

Terraflex *Terraclouds, Singapore.*
Collagen (p. 2483·2).

Terrafor *Claytone, Fr.*
Octalite.
Digestive disorders; slimming aid.

Terrakal *Offenbach, Mex.†*
Tetracycline (p. 373·1).
Bacterial infections.

Terramicina
Note: this name may be used for preparations of different composition.
Pfizer, Braz.; Farmasierra, Spain.
Oxytetracycline hydrochloride (p. 337·2). Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Farmasierra, Spain.
Ointment: Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Skin infections.

Pfizer, Arg.; Pfizer, Mex.; Pfizer, Venez.
Oxytetracycline (p. 337·1). Lidocaine (p. 1988·1) is included in the injection to alleviate the pain of injection.
Bacterial infections.

Pfizer, Mex.
Ointment: Oxytetracycline (p. 337·1); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Terramicina c/Polimixina *Pfizer, Braz.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial skin infections; bacterial eye infections.

Terramicina con Polimixina B *Pfizer, Venez.*
Oxytetracycline (p. 337·1); polymyxin B (p. 342·3).
Bacterial eye and skin infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Terramycin
Note: this name may be used for preparations of different composition.
Pfizer, Gr.; Pfizer, India.
Oxytetracycline hydrochloride (p. 337·2). Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection
Bacterial infections.

Pfizer, Indon.
Oxytetracycline (p. 337·1) or oxytetracycline hydrochloride (p. 337·2).
Bacterial infections; bacterial eye infections.

Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, S.Afr.†; Pfizer, Turk.
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial infections.

Pfizer, Israel†; Pfizer, Singapore.
Oxytetracycline (p. 337·1); polymyxin B sulfate (p. 342·3).
Bacterial infections of the eye or skin.

Pfizer, Thai.
Eye ointment; ointment: Oxytetracycline (p. 337·1) or oxytetracycline hydrochloride (p. 337·2); polymyxin B (p. 342·3) or polymyxin B sulfate (p. 342·3).
Eye infections; infected skin disorders.

Terramycin N *Mann, Ger.†*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Terramycin Plus *Pfizer, Philipp.*
Polymyxin B sulfate (p. 342·3); bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1).
Skin infections.

Terramycin Poly *Pfizer, Indon.†*
Eye ointment: Oxytetracycline (p. 337·1); polymyxin B (p. 342·3).
Eye infections.

Pfizer, Indon.†
Ointment: Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Skin infections.

Terramycin with Polymyxin *Pfizer, Gr.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Skin infections; eye infections.

Terramycin Polymyxin B *Pfizer, Denm.; Pfizer, Norw.; NordMedica, Swed.†*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial skin and eye infections.

Terramycin with Polymyxin B *Pfizer, Hong Kong; Pfizer, USA.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial eye and skin infections; bacterial eye infections.

Terramycin SF *Pfizer, India.*
Oxytetracycline hydrochloride (p. 337·2); vitamin B substances (p. 2102·3).
Bacterial infections.

Terramycin w Polymyxin Otic *Pfizer, Gr.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3); benzocaine (p. 1980·2).

Terramycine + Polymyxine B *Pfizer, Belg.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial infections.

Terranas *MSD, Jpn.*
Lomerizine hydrochloride (p. 676·3).
Migraine.

Terraxin *Sophia, Mex.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).
Bacterial eye infections.

Terrell *Minrad, China; Fahrenheit, Indon.; Piramal, USA.*
Isoflurane (p. 1903·2).
General anaesthesia.

Terricil *Edol, Port.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial eye infections.

Terrilytin *St Petersburg Institute of Vaccines & Sera, Rus.*
Protease from *Aspergillus terricola*.
Burns; ulcers.

Tersaseptic *Doak, USA.*
Soap substitute.

Stiefel, Canad.
Triclosan (p. 1773·2).
Skin cleanser; skin disorders.

Tersa-Tar *Stiefel, Canad.*
Coal tar (p. 1723·2).
Psoriasis; seborrhoea.

Tersif *Baliarda, Arg.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Tersigan *Boehringer Ingelheim, Jpn.*
Oxitropium bromide (p. 1218·1).
Obstructive airways disease.

Tertensif *Servier, Cz.; 2care4, Denm.†; Servier, Fin.; Servier, Pol.; Danval, Spain.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Tertensif Bi-Kombi *Anpharm, Pol.*
⊗Indapamide (p. 1409·2); perindopril arginine (p. 1466·3).
Hypertension.

Tertensif Kombi *Servier, Pol.*
⊗Indapamide (p. 1409·2); perindopril arginine (p. 1466·3).
Hypertension.

Tertensif kombi *Europharma, Denm.*
⊗Perindopril arginine (p. 1466·3); indapamide (p. 1409·2).
Hypertension.

Tertroxin *Aspen, Austral.; Goldshield, Irl.†; GSK, NZ†; Aspen, S.Afr.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism; diagnostic testing of hyperthyroidism; thyrotoxicosis; myxoedema coma.

Tervalon
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Zentiva, Hung.
Losartan potassium (p. 1422·2).
Heart failure; hypertension.

Tervalon HCT *Zentiva, Hung.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Terveson *Doctum, Gr.*
Lovastatin (p. 1425·2).
Hypercholesterolaemia.

Terysol *SM, Venez.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; hypercalcaemia; oliguria.

Terzine *Seven Stars, Thai.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders.

Terzolin *McNeil, Ger.; Janssen-Cilag, Switz.*
Ketoconazole (p. 585·3).
Scalp disorders; seborrhoeic dermatitis; pityriasis versicolor.

Tesacof *Novartis, Mex.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Tesalin Allergy *Zeller, Switz.†*
Butterbur (p. 2463·2).
Allergic rhinitis.

Tesalin N *Zeller, Switz.*
Butterbur (p. 2463·2).
Hayfever.

Tesalitos *Novartis, Mex.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Cold symptoms; cough.

Tesalon *Novartis, Mex.*
Benzonatate (p. 1656·2).
Cough.

Tesalon Tenalif *Novartis, Mex.*
Ambroxol (p. 1654·3); oxeladin (p. 1671·2).
Cough.

Tesavel *MSD, Cz.; MSD, Irl.; Addenda, Ital.; MSD, Neth.; MSD, Pol.; MSD, Port.; MSD, Spain.*
Sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Tesero Voyage *Iromedica, Switz.*
Dimenhydrinate (p. 625·2); caffeine (p. 1203·3).
Motion sickness.

Tesical *Sintesina, Arg.*
Mebendazole (p. 158·3).
Worm infections.

Tesin *1A, Pol.†*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Teslascan *GE Healthcare, Austriat; GE Healthcare, Belg.†; GE Healthcare, Canad.; GE Healthcare, Cz.†; GE Healthcare, Fr.†; GE Healthcare, Ger.†; Amersham, Gr.†; GE Healthcare, Hung.†; GE Healthcare, Irl.†; GE Healthcare, Ital.†; GE Healthcare, Neth.†; Amersham, Norw.†; GE Healthcare, NZ; GE Healthcare, Pol.†; GE Healthcare, Port.†; Nycomed, Rus.; GE Healthcare, Spain†; GE Healthcare, Swed.†; GE Healthcare, Switz.†; Opakim, Turk.; Nycomed Amersham, UK†; GE Healthcare, USA.†*
Mangafodipir trisodium (p. 1594·1).
Contrast medium for magnetic resonance imaging of the liver and pancreas.

Tesofan Ex *Teva, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion; cough.

Tesofan-J *Teva, Mex.†*
Diphenhydramine (p. 626·1); dextromethorphan (p. 1660·1).
Cough; cold symptoms.

Tesol *Vianex (Βιανεξ), Gr.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Tesopen *Collins, Mex.†*
Benzonatate (p. 1656·2).
Cough.

Tesoprel *UCB, Ger.†*
Bromperidol lactate (p. 1041·3).
Schizophrenia.

Tess
Note: this name may be used for preparations of different composition.
Troikaa, India.
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions and inflammation.

Uniao Quimica, Braz.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Tess 35
Note: this name may be used for preparations of different composition.
Biotenk, Arg.
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Tessalon *Pfizer, USA.*
Benzonatate (p. 1656·2).
Cough.

Tessamag con Codeina *Vargas, Venez.*
Ipecacuanha (p. 1667·2); codeine phosphate (p. 40·2).
Cough.

Tessifol *Zimaia, Port.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tessiron *Gedeon Richter, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Tessyron *Gedeon Richter, Cz.; Richter, Pol.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Test Pack Plus *Abbott, UK.*
Pregnancy test (p. 2596·1).

Testanon 25 *Organon, India.†*
⊗Testosterone propionate (p. 2305·2).
Androgen deficiency; osteoporosis.

Testanon 50 *Organon, India.†*
⊗Testosterone phenylpropionate (p. 2305·2).
Androgen deficiency; osteoporosis.

Test-Comp *Unigen, Thai.*
⊗Testosterone propionate (p. 2305·2); testosterone phenylpropionate (p. 2305·2); testosterone isocaproate (p. 2305·2); testosterone decanoate (p. 2305·1).
Male hypogonadism.

Testerell *Sanorell, Ger.*
Turnera diffusa (p. 2491·3).
Homoeopathic preparation.

Testex *Ariston, Arg.*
⊗Testosterone (p. 2305·1).

Desma, Spain.
⊗Testosterone cipionate (p. 2305·1) or testosterone propionate (p. 2305·2).
Male hypogonadism and androgen deficiency; female breast cancer; endometriosis; menopausal disorders; osteoporosis; aplastic anaemia; lactation inhibition.

Testim *Ferring, Belg.; Paladin, Canad.; Ferring, Denm.; Ferring, Fin.; Ferring, Ger.; Ferring, Gr.; Ferring, Irl.; Ipsen, Ital.; Ferring, Neth.; Ferring, Norw.; Ferring, Port.; Ferring, Spain; Ferring, Swed.; Ferring, UK; Auxilium, USA.*
⊗Testosterone (p. 2305·1).
Male hypogonadism.

Testisan *Mintlab, Chile.*
Phthalylsulfathiazole (p. 339·3); nifuroxazide (p. 331·3).

Testitein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Testocaps *Schering-Plough, Belg.; Schering-Plough, Chile.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism; osteoporosis.

Testo-Enant *Geymonat, Ital.*
⊗Testosterone enantate (p. 2305·1).
Anabolic; hypogonadism; osteoporosis.

Testogel *Bayer, Austral.; Besins, Austria; Besins, Denm.; Besins, Fin.; Bayer, Ger.; Besins, Gr.; Bayer, Irl.; Besins, Ital.; Besins, Neth.; Besins, Norw.; Besins, Port.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Schering, Turk.; Schering, UK.*
⊗Testosterone (p. 2305·1).
Male hypogonadism.

Testolic *TP, Thai.*
⊗Testosterone propionate (p. 2305·2).
Male hypogonadism; delayed puberty; breast cancer; postpartum breast engorgement.

Testomax *Perrigo, Israel.*
⊗Testosterone (p. 2305·1).
Hypogonadism.

Teston *Remek, Gr.*
⊗Methyltestosterone (p. 2291·3).

Testopatch *Pierre Fabre, Cz.†; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Ital.; Pierre Fabre, Port.; Pierre Fabre, Spain.*
⊗Testosterone (p. 2305·1).
Male hypogonadism; testosterone deficiency.

Testopel *Slate, USA.*
⊗Testosterone (p. 2305·1).
Androgen deficiency; delayed puberty.

Testoprim-D *Tocogino, Mex.*
⊗Testosterone (p. 2305·1).
Androgenic.

Testosterone Implants *Organon, UK.*
⊗Testosterone (p. 2305·1).
Male hypogonadism.

Testosteronum Prolongatum *Jelfa, Pol.*
⊗Testosterone enantate (p. 2305·1).
Male hypogonadism; breast cancer; endometrial cancer.

Testotop *Galen, Ger.*
⊗Testosterone (p. 2305·1).
Hypogonadism; testosterone deficiency.

Testoviron *Bayer, Gr.*
⊗Testosterone enantate (p. 2305·1).
Androgen deficiency; male hypogonadism; aplastic anaemia; breast cancer.

Bayer, Ital.
⊗Testosterone enantate (p. 2305·1); testosterone propionate (p. 2305·2).
Anabolic; hypogonadism; osteoporosis.

Testoviron Depot *Bayer, Hong Kong; Bayer, Israel; Bayer, Port.; Bayer, Switz.; Bayer, Thai.*
⊗Testosterone enantate (p. 2305·1).
Breast cancer; delayed puberty; male hypogonadism and androgen deficiency; aplastic anaemia; erectile dysfunction; male infertility.

Zydus, India.
⊗Testosterone propionate (p. 2305·2); testosterone enantate (p. 2305·1).
Breast cancer; male hypogonadism; androgen deficiency; aplastic anaemia.

Testoviron Depot 100 *Bayer, Arg.*
⊗Testosterone enantate (p. 2305·1); testosterone propionate (p. 2305·2).
Breast cancer; male hypogonadism.

Testoviron Depot 250 *Bayer, Arg.; Paranova, Denm.†; Jenapharm, Ger.*
⊗Testosterone enantate (p. 2305·1).
Breast cancer; male hypogonadism; delayed puberty in boys.

Testovis *SIT, Ital.*
⊗Testosterone propionate (p. 2305·2).
Anabolic; hypogonadism; osteoporosis.

Testovital *Gynopharm, Chile.*
⊗Testosterone (p. 2305·1).
Testosterone deficiency.

Testpack hCG-Urine *Abbott, Irl.†*
Pregnancy test (p. 2596·1).

TestPack Plus hCG-Urine *Abbott, USA.*
Pregnancy test (p. 2596·1).

Testred *Valeant, USA.*
Capsules: ⊗Methyltestosterone (p. 2291·3).
Androgen replacement therapy; breast cancer.

Tesuxin *Xin Gang Union, China.*
Lomerizine hydrochloride (p. 676·3).

Teta Extra *Fresenius Kabi, Ger.†*
Didecyldimethylammonium chloride (p. 1750·3); polihexanide (p. 1766·1).
Surface disinfection.

Tetabulin *Baxter, Arg.; Baxter, Austria; Baxter, Cz.; Baxter, Irl.; Baxter, Ital.; Baxter, Pol.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetabuline *Baxter, Belg.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetagam *CSL, Austria; CSL, Ger.; CSL Biotherapies, Hong Kong; CSL, Port.; NBI, S.Afr.; CSL, Switz.; CSL, Thai.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetagam P *CSL, Indon.; Dexa, Indon.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetagamma P *CSL, Spain.†*
An tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetagam-P *CSL, Gr.; Zydus, India; CSL, Philipp.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tétagrip *Sanofi Pasteur, Fr.†*
A tetanus and influenza vaccine (p. 2421·3).
Active immunisation.

Tetalin *Pharmasant, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tetamyn *Bioclon, Mex.†*
A tetanus vaccine (p. 2421·1).
Active immunisation.

Tetanea *Sanofi Pasteur, Philipp.; Sanofi Pasteur, Turk.*
A tetanus immunoglobulin (equine) (p. 2420·3).
Passive immunisation.

Tetanobulin *Baxter, Ger.†*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetanogamma *CSL, Braz.; CSL, Mex.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetanol *Elea, Arg.; Novartis, Arg.; Novartis Vaccines, Austria; Novartis Vaccines, Cz.; Novartis Vaccines, Ger.; Gerolymatos, Gr.; Novartis Vaccines, Hung.; Sanofi-Aventis, Mex.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetanol pur *Novartis, Switz.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetanosson *Remek, Gr.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetanox *Shanghai Serum, Philipp.*
A tetanus antitoxin (p. 2420·2).
Passive immunisation.

Tetanus Gamma *Kedrion, Thai.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetanus-Gamma *Kedrion, Ital.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

TetaQuin *Sanquin, Neth.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetaquintetatus *Centurion, Turk.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Teta-S *Fresenius Kabi, Ger.†*
Didecylmethylalkoxiammonium propionate; cocospropylenediamineguanidinium diacetate; polihexanide (p. 1766·1).
Surface disinfection.

Tetatox *InterVax, Hong Kong.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetavax *Sanofi Pasteur, Arg.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Norw.; Sanofi Pasteur, Philipp.; Sanofi Pasteur, S. Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetesept *Merz, Pol.†*
Ascorbic acid (p. 2110·3); cetylpyridinium chloride (p. 1743·1); dequalinium chloride (p. 1749·3).
Mouth and throat disorders.

Tetesept Erkältungs *Tetesept, Ger.*
Capsules: Thyme (p. 2630·2).
Respiratory-tract disorders.

Tetesept Erkältungs Bad *Tetesept, Ger.*
Eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); thyme oil (p. 2630·3); pine needle oil (p. 2591·1); camphor (p. 2466·2).
Bath additive; cold symptoms.

Tetesept Hals-activ *Tetesept, Ger.*
Iceland moss (p. 2531·2).
Mouth and throat disorders.

Tetesept Husten Saft *Tetesept, Ger.*
Ribwort plantain (p. 2604·2).
Respiratory-tract congestion.

Tetesept Husten Tropfen *Tetesept, Ger.*
Ribwort plantain (p. 2604·2).
Cold symptoms; mouth and throat inflammation.

Tetesept Rheuma Badekonzentrat *Tetesept, Ger.*
Eucalyptus oil (p. 2501·2); pine needle oil (p. 2591·1); levomenthol (p. 2553·2).
Rheumatic disorders.

Tetig *Human BioPlazma, Hung.*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Tetinox *Target, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Tetinox *Silanes, Mex.*
A tetanus vaccine (p. 2421·1).
Active immunisation.

Tetliv *Finlay, Philipp.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetlong *Sobet, Ukr.*
Disulfiram (p. 2495·3).
Alcoholism; opioid dependence.

Tetmodis *Orpha-Devel, Cz.; Orpha-Devel, Denm.; AOP Orphan, Fin.; Desitin, Ger.; Orpha-Devel, Irl.; Orpha-Devel, Neth.; Campus, Swed.; Beacon, UK.*
Tetrabenazine (p. 2627·3).
Hyperkinetic movement disorders.

Tetmosol *AstraZeneca, Braz.; Piramal, India; AstraZeneca, S.Afr.*
Sulfiram (p. 2161·3).
Scabies.

Tetox *Sinochem, Philipp.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetra *Atlantis, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Sanbe, Indon.†; Nevzat, Turk.
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetra Central *Pharmasant, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetra Frx *United Drug, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetra HCl *PP Lab, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetrabact *Cipla, India.*
Tetracycline (p. 373·1).
Bacterial infections.

Tetraben *Cazi, Braz.*
Tetracycline (p. 373·1).
Bacterial skin infections.

Tetrabik *Osaka University, Jpn.*
An adsorbed diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Tetrac *Zwitter, Gr.*
Tetracycline hydrochloride (p. 373·2).
Acne.

Tetracap *Hovid, Singapore.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetracaps *Brasterapica, Braz.†*
Tetracycline (p. 373·1).
Bacterial infections.

Tetracem *Crown, S.Afr.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial infections.

Tetracilil *Greenpharma, Braz.*
Tetracycline (p. 373·1).
Bacterial infections.

Tetracina *Bunker, Braz.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetraclin *Teuto, Braz.; Synco, Hong Kong.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetracoq *Vianex (Βιανεξ), Gr.; Pasteur Merieux, Israel†; Aventis Pasteur, Philipp.†; Sanofi Pasteur, Turk.*
An adsorbed diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Tetract-HIB *Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.†; Sanofi Pasteur, Indon.; Sanofi Pasteur, Israel†; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Singapore†; Sanofi Pasteur, Thai.†; Sanofi Pasteur, Turk.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Tetraderm *Teuto, Braz.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); tolnaftate (p. 596·1); clioquinol (p. 273·1).
Infected skin disorders.

Tetradin *Caldeira & Metelo, Port.*
Disulfiram (p. 2495·3).
Chronic alcoholism; nickel dermatitis.

Tetradox
Note: this name may be used for preparations of different composition.
Fako, Turk.
Doxycycline (p. 288·1).
Bacterial infections; oral herpes simplex infections; malaria.

Ranbaxy, Singapore; Ranbaxy, Thai.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Richmond, Arg.
Paracetamol (p. 115·1).
Fever; pain.

Tetrafilm *ANH, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetragel *Multilab, Braz.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetra-Gelomyrtol *Pohl, Austria†; Pohl, Ger.*
Oxytetracycline hydrochloride (p. 337·2); myrtol (p. 2566·3).
Bronchitis; sinusitis.

Tetragynon *Bayer, Port.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Postcoital oral contraceptive.

TetraHES *Promed, Indon.*
⊗An etherified starch (p. 1146·1).
Hypovolaemia; shock; haemodilution.

TetraHes *Claris, Thai.*
⊗An etherified starch (p. 1146·1).
Hypovolaemia.

Tetrakain *Bausch & Lomb, Swed.*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Tetralet *Fako, Turk.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetralgin
Note: this name may be used for preparations of different composition.
Craveri, Arg.
Ergotamine (p. 674·1); caffeine (p. 1203·3); chlorphenamine (p. 620·3); dipyrone (p. 53·3); metoclopramide (p. 1862·2).
Migraine.

Vilar, Rus.; Vilar, Ukr.
Codeine (p. 40·2); caffeine (p. 1203·3); dipyrone (p. 53·3); phenobarbital (p. 535·2).
Pain; fever.

Tetralgin APC *Craveri, Arg.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Tetralgin Novo *Craveri, Arg.*
Ergotamine (p. 674·1); caffeine (p. 1203·3); chlorphenamine (p. 620·3); dipyrone (p. 53·3); domperidone (p. 1838·1).
Migraine.

Tetralim *Atlantic, Thai.*
Tetracycline phosphate complex (p. 373·2).
Bacterial infections.

Tetralin *Alvartis, Mex.*
Amikacin (p. 214·1).
Bacterial infections.

Tetralisal *Galderma, Mex.*
Lymecycline (p. 320·1).
Acne.

Tetralysal *Galderma, Arg.; Galderma, Belg.; Galderma, Braz.; Galderma, Chile; Galderma, Denm.; Galderma, Fin.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Ital.; Galderma, Norw.; Healthcare Logistics, NZ; Galderma, Philipp.; Galderma, S.Afr.; Galderma, Swed.; Galderma, Switz.; Galderma, UK; Galderma, Venez.*
Lymecycline (p. 320·1).
Bacterial infections; acne.

Galderma, Pol.
Lymecycline hydrochloride.
Acne; rosacea.

Tétralysal *Galderma, Fr.*
Lymecycline (p. 320·1).
Bacterial infections.

Tetra-Mag *Cypress, USA.†*
Magnesium salicylate (p. 85·2); phenyltoloxamine citrate (p. 638·1).

Tetraman *T Man, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetramil *Wassermann, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3); pheniramine maleate (p. 637·2).
Eye irritation and congestion; conjunctivitis.

Tetramin *Adeka, Turk.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetran *Wagner, Hung.*
Oxytetracycline hydrochloride (p. 337·2).
Bacterial skin infections.

Tetrana *Atlantic, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetran-Hydrocortison *Wagner, Hung.*
⊗Oxytetracycline hydrochloride (p. 337·2); hydrocortisone acetate (p. 1640·1).
Infected skin disorders.

Tetrano *Milano, Thai.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetrapar *Parggon, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Tetraphos *Medicpharma, Thai.*
Tetracycline hydrochloride phosphate buffer (p. 373·2).
Bacterial infections.

Tetrapres *Precimex, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Tetrapulmo *Medley, Braz.†*
Capsules; syrup: Sodium camsilate (p. 2617·3); chlorphenamine maleate (p. 620·3); dipyrone (p. 53·3); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cold and influenza symptoms.

Medley, Braz.†
Injection: Dipyrone (p. 53·3); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); cineole (p. 2479·1); niaouli oil (p. 2569·1); sodium camsilate (p. 2617·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Cold and influenza symptoms.

Tetraratio *Ratiopharm, Pol.†*
Tetrazepam (p. 1110·1).
Painful skeletal muscle spasm.

Tetrarco *Armoxindo, Indon.*
Tetracycline hydrochloride (p. 373·2).
Skin infections.

Tetra-saar *MIP, Ger.†*
Tetrazepam (p. 1110·1).
Skeletal muscle tension and spasticity.

Tetrasin *SSP, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetraspan *Braun, Austria; Braun, Cz.; Braun, Fin.; Bioser (Βιοσερ), Gr.; Braun, Hung.; Braun, Neth.; Braun, Pol.; Braun, Port.; Braun, Rus.; Braun, Swed.; Braun, Switz.*
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion; shock; hypovolaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Braun, Belg.; Braun, Denm.; Braun, Ger.; Braun, Hong Kong; Braun, Ital.; Braun, Norw.; Braun, UK.†
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; shock.

Braun, Thai.
⊗An etherified starch (p. 1146·1); electrolytes.
Plasma volume expansion; shock.

Tetravac *Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Fin.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Norw.; Sanofi Pasteur, Port.; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Tétravac *Sanofi Pasteur, Fr.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Tetravisc *IFET (ΙΦΕΤ), Gr.*
Tetracaine hydrochloride (p. 1996·3).

Tetraxil *Delta, Braz.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tetraxim *Sanofi Pasteur, Arg.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Philipp.; Sanofi-Aventis, S.Afr.†; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Tetrazep *CT, Ger.†*
Tetrazepam (p. 1110·1).
Skeletal muscle tension and spasticity.

Tetrazic *Ariston, Arg.*
Mirtazapine (p. 436·1).
Depression.

Tetra-Zil *Arlex, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Tetrazol *Grin, Mex.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Tetrex *BMS, Braz.; Bristol, USA.*
Tetracycline phosphate complex (p. 373·2).
Bacterial infections.

BMS, Austral.†; Hormona, Mex.; BMS, S.Afr.†
Tetracycline hydrochloride (p. 373·2).
Bacterial infections; adjunct in intestinal amoebiasis.

Tetrex-F *BMS, S.Afr.†*
Tetracycline hydrochloride (p. 373·2); nystatin (p. 590·3).
Bacterial infections; candidiasis.

Tetrilin *CNP, Ger.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion.

Tetrim *IQFA, Mex.*
Tetracycline (p. 373·1).
Bacterial infections.

Tetrin *Interbat, Indon.*
Tetracycline phosphate (p. 373·2).
Bacterial infections.

Tetris *Sandoz, Indon.*
⊗Tribulus terrestris (p. 2633·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Tonic.

Tetrisal *MIP, Ger.*
Sodium chloride (p. 1795·1).
Dry nose; nasal congestion.

Tetrix *Coria, USA.*
Barrier cream.
Eczema of the hands.

Tetroid *Ache, Braz.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Tetryvil *Hasco-Lek, Pol.†*
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion; rhinitis; sinusitis.

Tet-Tox *CSL, Austral.†; CSL, NZ.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tetuman *Faran, Gr.; Berna, Turk.†*
A tetanus immunoglobulin (p. 2420·3).
Passive immunisation.

Teturam *Farmstandart, Rus.; Borshchagovskii, Ukr.*
Disulfiram (p. 2495·3).
Chronic alcoholism.

Tet-vac *Shanghai IBP, Philipp.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Teufelskralle *1A, Ger.; Ratiopharm, Ger.; Stada, Ger.*
Devil's claw root (p. 42·3).
Joint disorders.

Teufin *Unifa, Port.†*
Amlodipine besilate (p. 1304·1).

Teufron *Teuto, Braz.*
Alprazolam (p. 1035·2).

Teuloft *Teuto, Braz.*
Sertraline hydrochloride (p. 448·1).

Teutoformin *Teuto, Braz.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Teutomicin *Teuto, Braz.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3).

Teutovit-E *Teuto, Braz.*
Tocoferil acetate (p. 2119·2).

Teutrin *Teuto, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Tevableo *Teva, Braz.*
Bleomycin (p. 749·3).

Tevabone
Note: this name may be used for preparations of different composition.
AWD, Ger.; Teva, Ital.
Alendronate sodium (p. 1171·3).
Osteoporosis.

Teva, Rus.
Tablets, alendronate sodium (p. 1171·3); capsules, alfacalcidol (p. 2112·3).
Osteoporosis.

Tevacaine *Negrin, Gr.*
Mepivacaine hydrochloride (p. 1992·2).
Local anaesthesia.

Tevacarbo *Teva, Braz.*
Carboplatin (p. 759·1).

Tevacept *Teva, Mex.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Tevacomb *Teva, Rus.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Tevacutan *Teva, Israel.*
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Tevacycline *Teva, Israel.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Tevaderm *Teva, Israel.*
⊗Isoconazole nitrate (p. 583·2); diflucortolone valerate (p. 1634·1).
Infected skin disorders.

Tevadocel *Teva, Neth.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer; prostatic cancer; gastric adenocarcinoma; head and neck cancer.

Tevaetopo *Teva, Braz.*
Etoposide (p. 790·2).

Tevafolin *Teva, Braz.*
Folinic acid (p. 2066·3).

TevaGrastim *Teva, Switz.; Teva, Ukr.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Tevagrastim *Aspen, Austral.; Teva, Belg.; Teva, Braz.; Teva, Cz.; Teva, Fr.; Teva, Gr.†; Teva, Hung.; Teva, Irl.; Teva, Israel; Pharmachemie, Neth.; Teva, Norw.; Teva, Pol.; Teva, Port.; Teva, Rus.; Teva, Swed.; Teva, UK.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Teval Plus H *Teva, Cz.†*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tevalet *Teva, Spain.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; menstrual disorders.

Tevalfa *Teva, Israel.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; hypoparathyroidism; hyperparathyroidism; hypocalcaemia; rickets; osteomalacia; osteoporosis.

Tevalgiespray *Teva, Fr.†*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Tevalos *Teva, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy; cardiovascular risk reduction; heart failure.

Tevamesna *Teva, Braz.*
Mesna (p. 1557·2).

Tevametho *Teva, Braz.*
Methotrexate (p. 822·2).

Tevanate *Gry, Ger.†; Teva, Gr.; Teva, Irl.; Teva, Israel; Teva, Philipp.; Teva, Rus.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Tevanel *Ingers, Cz.*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Tevaoxali *Teva, Braz.*
Oxaliplatin (p. 838·1).

Tevapacli *Teva, Braz.*
Paclitaxel (p. 839·3).

Tevapirin *Teva, Israel.*
Aspirin (p. 22·2).
Thrombosis prophylaxis.

Tevaquel *Teva, Irl.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania.

Tevaryl *Teva, Irl.†*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; coronary artery disease.

Tevavaltan comp *Teva, Denm.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tevavinor *Teva, Braz.*
Vinorelbine (p. 885·3).

Tevax
Note: this name may be used for preparations of different composition.
Teva, Irl.
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Teveten *Abbott, Austral.; Solvay, Austria; Solvay, Belg.; Abbott, Canad.; Abbott, China; Abbott, Cz.; Abbott, Denm.†; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Indon.; Abbott, Irl.; Abbott, Neth.; Abbott, Norw.; Healthcare Logistics, NZ; Solvay, Philipp.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.†; Solvay, Turk.; Abbott, UK; Solvay, Ukr.; Abbott, USA.*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Teveten Comp *Abbott, Denm.; Abbott, Fin.; Abbott, Norw.; Abbott, Swed.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Teveten HCT *Abbott, USA.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Teveten Plus *Abbott, Austral.; Solvay, Austria; Solvay, Belg.; Abbott, Canad.; Abbott, Ger.; Abbott, Gr.; Solvay, Hong Kong; Abbott, Irl.; Abbott, Neth.; Solvay, Philipp.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Abbott, Switz.; Solvay, Turk.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Teveten Plus H *Solvay, Cz.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tevetens *Abbott, Spain.*
Eprosartan mesilate (p. 1376·2).
Hypertension.

Tevetens Plus *Abbott, Spain.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tevetenz *Orifarm, Denm.†; Solvay, Ital.; Italmex, Mex.*
Eprosartan mesilate (p. 1376·2).
Hypertension; myocardial infarction; heart failure; diabetic nephropathy.

Tevetenz Dox *Italmex, Mex.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tevoril *Novendia, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Tevotev *Teva, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tevox *Actavis, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Tevozol *Teva, Mex.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tev-Tropin *Gate, USA.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency.

Teweisi *Donghai, China.*
Isotretinoin (p. 1706·2).
Acne; pityriasis rubra pilaris.

Texa *Pharma Dynamics, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; pruritus.

Texacand *Helm, Cz.; Helm, Neth.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Texacand HCT *Helm, Neth.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Texacandozid *Helm, Cz.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Texacort *Mission Pharmacal, USA.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Texamen *Nevzat, Ukr.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Texate *Columbia, Mex.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Texis *Atlantis, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Texodil *Grunenthal, Fr.*
Cefotiam hexetil hydrochloride (p. 246·1).
Bacterial infections of the respiratory-tract.

Texot *Filaxis, Arg.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Texoven *Tecnofarma, Mex.*
Benzonatate (p. 1656·2).
Cough.

Texpami *Pharmatex, Ital.†*
Pamidronate disodium (p. 1186·3).
Osteolysis or malignancy; multiple myeloma; hypercalcaemia of malignancy.

Texx *Krewel, Ger.*
St John's wort (p. 449·1).
Anxiety; depression.

Texzine *GX, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Texzor *Farmogene, Port.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Teys's *Ivax, Arg.*
⊗Calcium carbonate (p. 1824·3); potassium nitrate (p. 1766·2).
Hypersensitive teeth.

Teysuno *Taiho, Cz.; Nordic Drugs, Denm.; Nordic, Irl.; Nordic, Neth.; Nordic Drugs, Norw.; Nordic, Swed.; Nordic, UK.*
Tegafur (p. 864·2); gimeracil; oteracil potassium.
Gastric cancer.

Tezacef *Shin Poong, China.*
Ceftezole sodium (p. 252·2).
Bacterial infections.

Tezastin *Epifarma, Ital.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Tezeo *Zentiva, Cz.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Tezoteva *Med, Turk.*
Terazosin hydrochloride (p. 1511·1).

Tezulina *Microsules, Arg.*
Temozolomide (p. 865·2).

TFE *Seroyal, Canad.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

T-Five *TS Pharma, Thai.*
Dipotassium clorazepate (p. 1056·3).

TFT *Bausch & Lomb, S.Afr.*
Trifluridine (p. 1020·3).
Herpes simplex keratitis.

TFT Ophtiole *Tramedico, Neth.†*
Trifluridine (p. 1020·3).
Viral eye infections.

TFT-Thilo *Liba, Turk.*
Trifluridine (p. 1020·3).
Herpes simplex eye infections.

TFX *Finepharm, Pol.*
Thymostimulin (p. 2631·1).
Immunomodulator.

TG PSE/BRM/DM *TG United, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

T/Gel
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Israel†; Johnson & Johnson, UK.
Coal tar (Neutar) (p. 1723·2).
Scalp disorders.

T/Gel Daily Control *Johnson & Johnson, Canad.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

T/Gel Therapeutic *Johnson & Johnson, Canad.*
Coal tar (p. 1723·2).
Scalp disorders.

T-Gesic *Williams, USA.*
Paracetamol (p. 115·1); hydrocodone tartrate (p. 67·2).
Pain.

TGI *Krolton, Arg.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

TGQ DM/PEH/CPM *TG United, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TGQ PEH/BRM/DM *Trigen, USA.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

TGQ PSE/BRM/DM *TG United, USA.*
⊗Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

TGQ 30PSE/150GFN/15DM *TG United, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

THA *Woods, Austral.†*
Tacrine hydrochloride (p. 396·1).
Reversal of competitive neuromuscular blockade; postoperative respiratory stimulant.

Thacapzol *Recip, Swed.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Thaden *Aspen, S.Afr.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Thainocort *TP, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Thaïs *Besins, Fr.*
Estradiol (p. 2271·1).
Menopausal disorders.

Thalamag *IPRAD, Fr.*
Magnesium oxide (p. 1857·3); sea water (p. 2612·1).
Magnesium supplement.

Thalamag fer B_9 *IPRAD, Fr.*
Magnesium oxide (p. 1857·3); sea water (p. 2612·1); ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).
Tonic.

Thalamonal *Janssen-Cilag, Gr.*
⊗Droperidol (p. 1072·1); fentanyl citrate (p. 60·1).

Thalanex *Pharmamag, Canad.†*
Sodium chloride (p. 1795·1).

Thalaris *Pharmamag, Canad.†*
Sodium chloride (p. 1795·1).
Oral hygiene.

Thalatex *Chew, Thai.*
Phthalylsulfathiazole (p. 339·3).
Diarrhoea.

Thaled *Fujimoto, Jpn.*
Thalidomide (p. 867·3).
Multiple myeloma; erythema nodosum leprosum.

Thalitone *Monarch, USA.*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema.

Thalix *Dabur, India; Fresenius Kabi, Philipp.*
Thalidomide (p. 867·3).
Erythema nodosum leprosum; multiple myeloma.

Thalizide *Ipca, India.*
⊗Chlortalidone (p. 1335·2).
Hypertension.

Thalomid *Celgene, Austral.; Celgene, Canad.; Douglas, NZ; Celgene, USA.*
Thalidomide (p. 867·3).
Multiple myeloma; erythema nodosum leprosum.

Tham *Abbott, Austral.†; Hospira, Canad.; Kohler, Ger.; IFET (ΙΦΕΤ), Gr.; Hospira, Singapore.*
⊗Trometamol (p. 2635·1).
Metabolic acidosis.

Thamesol *Diaco, Ital.*
⊗Trometamol (p. 2635·1).
Metabolic acidosis.

Thank God *Panacea, India.*
Euphorbia prostata (p. 2501·3).
Haemorrhoids.

Thateron *Alapis, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

The Blue One *Bioglan, Austral.†*
⊗Avena (p. 2451·1); tribulus terrestris (p. 2633·3); damiana (p. 2491·3); capsicum (p. 2469·3); california poppy (p. 2466·1); zinc amino acid chelate (p. 2048·3); rutoside (p. 2505·3).
Tonic for males.

Thé Chambard-Tee *Brady, Austria.*
Senna leaf (p. 1885·1); althaea leaf (p. 2438·3); peppermint leaf (p. 1877·1); melissa leaf (p. 2552·3); hyssop (p. 2530·3); anthyllidis flower; calendula (p. 2465·2); cyanae flower.
Constipation.

Thé d'avoine verte Vollmers *Dunner, Switz.†*
Avena (p. 2451·1); urtica (p. 2639·3); St John's wort (p. 449·1); alchemilla alpina.
Nervous disorders.

The Ginseng King *Medicalfarm, Ital.†*
Fish milk; fish brain extract; cod-liver extract; myrtillus (p. 2566·2); acacia honey (p. 2072·1); fructose (p. 2068·2); ginseng (p. 2513·3).
Nutritional supplement.

The Guard Seichojo *Kowa, Jpn.*
Bacillus natto; lactic-acid-producing organisms (p. 2596·3); dimeticone (p. 1886·2); swertia; cinnamon bark (p. 2479·2); fennel (p. 2503·2); methiosulfonium chloride (p. 2558·1); magnesium carbonate (p. 1856·2); calcium carbonate (p. 1824·3).
Flatulence; carminative.

The Magic Bullet *D & C Mobility, Canad.*
Bisacodyl (p. 1821·1).

The Neutral Solution *Niagara, Canad.†*
Monobasic potassium phosphate (p. 1790·3); monobasic sodium phosphate (p. 1791·1).

The Original Hollywood Celebrity *HBS, Canad.*
Vitamins; potassium (p. 1793·1).

Thé Salvat *Leros, Cz.*
Boldo (p. 2458·3); marrubium (p. 1668·3); agrimony (p. 2432·3); taraxacum (p. 2625·3); frangula bark (p. 1843·3); chamomile (p. 2474·1); peppermint leaf (p. 1877·1).
Liver and biliary-tract disorders.

The Secret Ointment *Golden Pride, Canad.†; Rawleigh, Canad.†*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Thea Bona *Urtekram, Denm.*
Senna (p. 1885·1).
Constipation.

Theanorf *Farmila, Ital.*
Norfloxacin (p. 333·3).
Bacterial eye infections.

Thecort *Guardian, Indon.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Théinol *Bailly, Fr.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Thelban *Biolab, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Thelin *Pfizer, Austral.†; Pfizer, Austria†; Pfizer, Belg.†; Pfizer, Canad.†; Encysive, Cz.†; Encysive, Denm.†; Encysive, Fr.†; Encysive, Ger.†; Pfizer, Ger.†; Encysive, Gr.†; Pfizer, Irl.†; Encysive, Ital.†; Encysive, Neth.†; Encysive, Port.†; Pfizer, Spain†; Pfizer, Swed.†; Encysive, UK.†*
Sitaxentan sodium (p. 1496·2).
Pulmonary hypertension.

Thelmox *Remedica, Malaysia.*
Mebendazole (p. 158·3).
Worm infections.

Themibutol *Themis Medicare, India.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Thenil *Interbat, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Theo *CT, Ger.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theo-24 *UCB, USA.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theo PA *GSK, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Theo-Asthalin *Cipla, India.*
⊗Salbutamol sulfate (p. 1220·2); theophylline (p. 1229·3).
Obstructive airways disease.

Theobid *Cipla, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Theobric *AstraZeneca, India.*
⊗Terbutaline sulfate (p. 1228·1); theophylline (p. 1229·3).
Obstructive airways disease.

Theobron *Interbat, Indon.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theo-Bros *Bros, Gr.*
Theophylline (p. 1229·3).
Asthma; obstructive airways disease; neonatal apnoea and bradycardia.

Theocap *ANH, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theochodil *GMP, Indon.*
⊗Ephedrine hydrochloride (p. 1663·2); theophylline (p. 1229·3).
Asthma; bronchitis.

Theochron *Forest Pharmaceuticals, USA.*
Theophylline (p. 1229·3).
Asthma; reversible bronchospasm in chronic bronchitis and emphysema.

Theoday *Cipla, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Theodrine *Rugby, USA.*
⊗Theophylline (p. 1229·3); ephedrine hydrochloride (p. 1663·2); phenobarbital (p. 535·2).
Bronchospasm.

Theo-Dur *Biophausia, Denm.; Lavipharm, Gr.; Recordati, Ital.; Biophausia, Norw.; AstraZeneca, Philipp.†; Vegal, Spain; Biophausia, Swed.; Schering-Plough, Turk.†*
Theophylline (p. 1229·3).
Obstructive airways disease; asthma; neonatal apnoea and bradycardia; paroxysmal dyspnoea; heart failure.

Theodur *Mitsubishi Tanabe, Jpn.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theofil *Oriental, Philipp.*
Aminophylline (p. 1201·2).
Obstructive airways disease; neonatal apnoea.

Theofol *Leiras, Fin.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theofol Comp *Leiras, Fin.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).
Obstructive airways disease.

Theogel *KG, Ital.*
Royal jelly (p. 2608·1).

Theolair *Meda, Belg.; Medicis, Canad.; Meda, Ital.; Meda, Neth.; Meda, Spain.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Théolair *Meda, Switz.†*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theolin *Beacons, Singapore; T Man, Thai.*
Theophylline (p. 1229·3).
Asthma; obstructive airways disease.

Theolong *Eisai, Jpn.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theomax DF *Barre-National, USA; Schein, USA.*
⊗Theophylline (p. 1229·3); ephedrine sulfate (p. 1663·2); hydroxyzine hydrochloride (p. 630·3).
Bronchospasm.

Theopec *Farmapek, Rus.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theoped *Cipla, India.*
Theophylline (p. 1229·3).
Bronchospasm.

Theophar *Julphar, UAE.*
Theophylline (p. 1229·3) or theophylline sodium glycinate (p. 1229·3).
Obstructive airways disease.

Theophedrinum-N *Moschimfarm, Rus.*
⊗Belladonna (p. 2453·3); caffeine (p. 1203·3); paracetamol (p. 115·1); theophylline (p. 1229·3); phenobarbital (p. 535·2); cytisine (p. 2491·1); ephedrine hydrochloride (p. 1663·2).
Obstructive airways disease.

Theophen *Aspen, S.Afr.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theophen Comp *Aspen Consumer, S.Afr.*
Theophylline (p. 1229·3); etofylline (p. 1208·2); diphenylpyraline hydrochloride (p. 627·2); ammonium chloride (p. 1656·1).
Cough.

Theophtard *Teva, Hung.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theophylline Expectorant *Pharmaniaga, Malaysia.*
Guaifenesin (p. 1666·2); theophylline (p. 1229·3).
Obstructive airways disease.

Theoplus *Pierre Fabre, Cz.; Pierre Fabre, Pol.†; Nycomed, S.Afr.; Pierre Fabre, Spain.†*
Theophylline (p. 1229·3).
Obstructive airways disease; paroxysmal dyspnoea; heart failure.

Pierre Fabre, Gr.
Theophylline hydrate (p. 1229·3).
Asthma; obstructive airways disease; neonatal apnoea and bradycardia.

Theori *Meditab, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theospirex *Gebro, Austria; Novartis, Hung.; Biofarm, Pol.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Théostat *Pierre Fabre, Fr.*
Theophylline hydrate (p. 1229·3).
Asthma; obstructive airways disease.

Theotard *CTS, Israel; KRKA, Ukr.*
Theophylline (p. 1229·3).
Bronchospasm; obstructive airways disease; nocturnal paroxysmal apnoea.

Theotex *Terapeutico, Ital.*
Metalkonium chloride (p. 1760·2).
Skin disinfection; personal hygiene.

Theotrim *Trima, Hong Kong†; Trima, Israel; Trima, Thai.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theovent *GSK, Pol.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Theovix *Bros, Gr.*
Erdosteine (p. 1665·1).
Mucolytic.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Thephidron *Combiphar, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders.

Théprubicine *Sanofi-Aventis, Fr.†*
Pirarubicin (p. 847·1).
Breast cancer.

Ther *Laboratorios Chile, Chile.†*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome.

Thera Hematinic *Major, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

Thera M Plus *Major, USA.*
Vitamins; minerals.
Dietary supplement.

Thera Natal *Theralogix, USA.*
Vitamins; trace elements.

Therabex *Combiphar, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3).
Vitamin B and C supplement.

Therabloc *Therapharma, Philipp.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; myocardial infarction.

TheraCal D *Theralogix, USA.*
Vitamin D (p. 2112·3); vitamin K (p. 2122·1); calcium (p. 1783·1); magnesium (p. 1786·3); strontium; boron (p. 2052·3).

Theracap *GE Healthcare, Belg.†; GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Israel; GE Healthcare, Neth.; GE Healthcare, Port.; GE Healthcare, Spain; GE Healthcare, Switz.; GE Healthcare, UK.*
Iodine-131 (p. 2225·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

TheraCIM *Innogene, Indon.; Innogene, Thai.*
Nimotuzumab (p. 836·3).
Malignant glioma; head and neck cancer.

Theracim *Innogene, Philipp.*
Nimotuzumab (p. 836·3).
Malignant glioma.

Theraclox *Great Eastern, Thai.†; Therapharma, Thai.†*
Cloxacillin (p. 274·3).
Bacterial infections.

Theracne *Theraskin, Braz.*
Triclosan (p. 1773·2).
Acne.

Theracof Plus *Reese, USA.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2).

Theracort *Theraskin, Braz.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Theracough *Novartis, Swed.*
Guaifenesin (p. 1666·2).
Cough.

TheraCys *Sanofi Pasteur, USA.*
A BCG vaccine (p. 2378·1).
Bladder cancer.

Thera-D *Theralogix, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

TheraDerm
Note: this name may be used for preparations of different composition.
Major, USA.
Emollient.
Dry skin.

Theradol *Therabel, Neth.*
Tramadol hydrochloride (p. 139·2).
Pain.

Theraflex *Sagmel, Rus.; Bayer Consumer, Ukr.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis; osteochondrosis.

Theraflex Advance *Sagmel, Rus.; Bayer Consumer, Ukr.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1); ibuprofen (p. 68·2).
Osteoarthritis; osteochondrosis.

Theraflex M *Sagmel, Rus.; Bayer Consumer, Ukr.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); camphor (p. 2466·2); peppermint oil (p. 1877·1).
Osteoarthritis; osteochondrosis; degenerative joint disorders.

TheraFlu
Note: this name may be used for preparations of different composition.
Novartis, Mex.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Novartis, Turk.
Paediatric syrup: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Novartis, Turk.
Powder for oral solution: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Novartis, Turk.
Tablets: Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Respiratory-tract congestion.

Theraflu
Note: this name may be used for preparations of different composition.
Novartis Consumer, Rus.; Novartis Consumer, Ukr.
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; symptoms of influenza and other viral respiratory disease.

TheraFlu 24 *Novartis, Mex.*
⊗Pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Allergic rhinitis.

TheraFlu Alergia *Novartis Consumer, Arg.†*
Diphenhydramine hydrochloride (p. 626·2).
Allergic rhinitis; cold symptoms; allergic skin disorders.

Theraflu Bro *Novartis Consumer, Rus.*
Rosemary oil (p. 2607·3); eucalyptus oil (p. 2501·2); Peru balsam (p. 2587·1); camphor (p. 2466·2).
Respiratory-tract disorders.

Theraflu Caplets Nighttime Severe Cold *Novartis Consumer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TheraFlu CM *Novartis, Mex.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

TheraFlu CN *Novartis, Mex.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

TheraFlu Cold & Cough *Novartis Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TheraFlu Cold & Flu
Note: this name may be used for preparations of different composition.
Novartis Consumer, Canad.
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Novartis Consumer, S.Afr.†
⊗Pseudoephedrine hydrochloride (p. 1676·1) chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

TheraFlu Colds & Flu *Novartis Consumer, Israel.†*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Theraflu Cough *Novartis, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

TheraFlu Cough & Colds *Novartis Consumer, Israel.†*
Dextromethorphan hydrobromide (p. 1660·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cough; nasal congestion.

TheraFlu Daytime Severe Cold *Novartis Consumer, USA.†*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

Theraflu Daytime Severe Cold & Cough *Novartis Consumer, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TheraFlu Ex *Novartis, Mex.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Theraflu Extra *Novartis Consumer, Ukr.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

TheraFlu ExtraGRIP *Novartis Consumer, Pol.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); pheniramine maleate (p. 637·2).
Cold and influenza symptoms.

Theraflu Extratab *Novartis Consumer, Rus.; Novartis Consumer, Ukr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract disorders; cold and influenza symptoms.

TheraFlu Flu & Chest Congestion Non-Drowsy *Novartis Consumer, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Formerly known as TheraFlu Maximum Strength Flu & Congestion Non-Drowsy.
Upper respiratory-tract disorders.

Thera Flu Flu and Cold *Patheon, Rus.; Novartis, Ukr.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Symptoms of influenza and other viral respiratory disease.

Novartis, USA.
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and flu symptoms.

TheraFlu Flu, Cold & Cough *Novartis, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

TheraFlu Forte *Novartis, Turk.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Theraflu KV *Novartis Consumer, Rus.*
Guaifenesin (p. 1666·2).
Respiratory-tract disorders with viscous mucus.

Theraflu LAR *Novartis Consumer, Ukr.†*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Theraflu Lar *Novartis Consumer, Rus.*
Benzoxonium chloride (p. 1739·2); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

TheraFlu N 12 *Novartis, Mex.*
⊗Pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Allergic rhinitis.

Theraflu Nighttime Severe Cough & Cold *Novartis Consumer, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TheraFlu Ninos VP *Novartis, Mex.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Cold symptoms.

TheraFlu Non-Drowsy Severe Cold *Novartis Consumer, USA.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Formerly known as TheraFlu Non-Drowsy Formula Maximum Strength.
Coughs and cold symptoms.

Thera Flu Severe Cold *Novartis Consumer, USA.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Formerly known as TheraFlu Maximum Strength NightTime Formula Flu, Cold & Cough.
Coughs and cold symptoms.

Theraflu Severe Cold & Cough Daytime/ Nighttime *Novartis, USA.*
Daytime, paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); nighttime, paracetamol; diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride.
Cough; cold symptoms.

Theraflu SNS *Novartis Consumer, Ukr.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

TheraFlu TD *Novartis, Mex.*
⊗Paracetamol (p. 115·1); pseudoephedrine sulfate (p. 1676·1); loratadine (p. 633·2).
Allergic rhinitis.

TheraFlu Tenalif *Novartis, Mex.*
Oxeladin citrate (p. 1671·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with increased or viscous mucus.

Theraflu Thinstrips Daytime Cough & Cold *Novartis Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Theraflu Thinstrips Nighttime Cold & Cough *Novartis, USA.†*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TheraFlu Vapor Stick *Novartis, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Upper respiratory-tract congestion; musculoskeletal pain.

Theraflu Warming Relief Daytime Multi-Symptom Cold *Novartis, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold symptoms.

Theraflu Warming Relief Flu & Sore Throat *Novartis, USA.*
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Theraflu Zatoki *Novartis Consumer, Pol.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Thera-Flur *Colgate Oral, USA.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Theragen *Harmony, Singapore; Reese, USA.†*
Capsaicin (p. 35·1).

Theragenerix *Goldline, USA.*
Vitamins.

Theragenerix-H *Goldline, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

Thera-gesic *Mission Pharmacal, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Theragran *Mead Johnson Nutritionals, USA.*
Vitamins.

Taisho, Indon.
Vitamins; minerals.

Theragran AntiOxidant *BMS, USA.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); minerals.

Theragran Junior *BMS, China.*
Vitamins.
Dietary supplement.

Theragran M *Sarabhai Piramal, India.*
Vitamins; minerals.

Theragran-M *BMS, China.*
Vitamins; trace elements.
Dietary supplement.

BMS, S.Afr.†; BMS, Thai.
Vitamins; minerals.

Theralen *Sanofi-Aventis, Swed.*
Alimemazine tartrate (p. 615·1).
Anxiety; premedication; hypersensitivity reactions; alcoholism; vomiting; behaviour disorders; sleep disorders.

Théralène *Erempharma, Fr.*
Alimemazine tartrate (p. 615·1).
Hypersensitivity reactions; insomnia; cough; pruritus; premedication.

Theralene *Sanofi-Aventis, Belg.*
Alimemazine tartrate (p. 615·1).
Hypersensitivity reactions.

Theralexin *UAP, Indon.†*
Cefalexin (p. 234·1).
Bacterial infections.

Thera-M *Prime Enterprises, USA.*
Vitamins; minerals.

Theramatic *Unipharma, Gr.*
Chenodeoxycholic acid (p. 2475·1).

Theranal *Bayer, Neth.*
Bismuth subnitrate (p. 1822·1); zinc oxide (p. 1729·1); lidocaine (p. 1988·1).
Haemorrhoids.

TheraNatal Complete *Theralogix, USA.*
Tablets, vitamins; trace elements; capsules, vitamins; docosahexaenoic acid (p. 1460·1).

Theranex *Medifarma, Indon.†; UAP, Indon.†*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage.

TheraPatch Cold Sore *Lectec, USA.*
Lidocaine (p. 1988·1); camphor (p. 2466·2).
Herpes labialis.

Therapelcin *Rafarm, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; pathological gastric hypersecretory disorders; acid aspiration.

Therapeutic Aquaderm *Pendopharm, Canad.*
SPF 15: Octisalate (p. 1715·2); avobenzone (p. 1695·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Therapeutic Bath *Goldline, USA.*
Emollient and moisturiser.

Therapeutic Mineral Ice *Novartis, USA.*
Menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Theraplex AF *Robert, Canad.*
Vitamin A (p. 2098·3).

Theraplex B *Therapeutic Foods, Canad.†*
Vitamin B substances (p. 2102·3).

Theraplex F *Therapeutic Foods, Canad.†*
Potassium iodide (p. 2336·3).

Thera-Plus *Hi-Tech, USA.*
Vitamins.

Therapsor *Theraskin, Braz.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Therapy Ice *Major, USA.*
Menthol (p. 2553·2).

Therarubicin *Meiji, Jpn.*
Pirarubicin hydrochloride (p. 847·1).
Malignant neoplasms.

TheraSeal *Coria, USA.*
Barrier cream.

Therasil *Sel-J, Philipp.; Rezlov, Rus.*
Amylmetacresol (p. 1736·3); dichlorobenzyl alcohol (p. 1750·2).
Mouth and throat disorders.

Therasona *Theraskin, Braz.*
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

Therasonid *AG Therapy, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Thera-Tabs M *Geri-Care, USA.*
Vitamins; minerals.
Dietary supplement.

Theratar *Theraskin, Braz.*
Coal tar (p. 1723·2).
Skin disorders.

TheraTears *Contact Lens Centre, Austral.; Advanced Vision, Canad.; Kivema, Israel; Advanced Vision, USA.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Theravask *Darya-Varia, Indon.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Theravee *Vangard, USA.*
Vitamins.

Theravee Hematinic *Vangard, USA.*
Iron (p. 2073·1); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

Theravim *Nature's Bounty, USA.*
Vitamins; minerals.

Theravit *Sagmel, Rus.*
Vitamins; minerals.

Theravit Antistress *Bayer Consumer, Ukr.*
Vitamins; minerals; ginkgo biloba (p. 2512·3); ginseng (p. 2513·3).
Tonic; mineral and vitamin supplement.

Theravit Tonic *Bayer, Rus.; Bayer Consumer, Ukr.†*
Vitamins; minerals; ginseng (p. 2513·3); schisandra (p. 2611·2).
Tonic; mineral and vitamin supplement.

Theravite *Goldline, USA.*
Vitamins.

Therems *Rugby, USA.*
Vitamins; with or without minerals and trace elements.

Therevac Plus *Jones, USA.*
⊗Docusate sodium (p. 1836·2); glycerol (p. 2517·2); benzocaine (p. 1980·2); soft soap (p. 2212·3).
Constipation.

Therevac SB *Jones, USA.*
⊗Docusate sodium (p. 1836·2); glycerol (p. 2517·2); soft soap (p. 2212·3).
Constipation.

Thermal FIX UV *Vichy, Canad.†*
SPF 20: Avobenzone (p. 1695·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2).
Sunscreen.

ThermalGesic *Rhema, Singapore.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Thermazene *Ascend, USA.*
Sulfadiazine silver (p. 362·3).
Infected burns.

Thermo Bürger *Ysatfabrik, Ger.*
Capsicum (p. 2469·3).
Musculoskeletal and joint disorders.

Thermo Gomenol *Gomenol, Fr.*
Niaouli oil (p. 2569·1); grapefruit oil; eucalyptus oil (p. 2501·2); sweet birch oil (p. 92·1); orange oil (p. 2576·2).
Skeletal muscle pain.

Thermocream *Sterop, Belg.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); capsicum oleoresin (p. 2469·3).
Musculoskeletal disorders.

Thermo-Doline *Tripharma, Turk.*
Etofenamate (p. 57·2); benzyl nicotinate (p. 29·3).
Musculoskeletal, joint, peri-articular, and soft-tissue pain.

Thermoflex *Santa, Turk.*
Etofenamate (p. 57·2); benzyl nicotinate (p. 29·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Thermo-Gel *Confab, Canad.*
Camphor (p. 2466·2); menthol (p. 2553·2); benzocaine (p. 1980·2); thymol (p. 1772·2).
Musculoskeletal pain.

Thermogene *Montefarmaco, Ital.*
Ointment (water-soluble): Capsicum oleoresin (p. 2469·3).
Musculoskeletal and joint pain.

Thermo-Rheumon *Meda, Austria; Bayer, Pol.; Bayer, Turk.*
Benzyl nicotinate (p. 29·3); etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Thermo-Roiplon *Menarini, Gr.*
Etofenamate (p. 57·2); benzyl nicotinate (p. 29·3).
Musculoskeletal and joint disorders.

Thermo-Rub
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Methyl salicylate (p. 92·1).
Rheumatism; muscular pain.

Thermorub
Note: this name may be used for preparations of different composition.
Pharmaniaga, Malaysia.†
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Musculoskeletal pain.

Thermove *Frik, Turk.*
Etofenamate (p. 57·2); benzyl nicotinate (p. 29·3).

Thervan *Alter, Spain.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Thevier *Aspen, Ger.; GSK, Ger.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Thex Forte *Lee, USA.*
Vitamin B (p. 2102·3); vitamin C (p. 2110·3).

Thiaben *UCI, Braz.*
Tiabendazole (p. 166·3).
Nematode infections.

Thiabena *UCI, Braz.*
Tiabendazole (p. 166·3); neomycin sulfate (p. 330·1).
Skin infections.

Thiabene *Ratiopharm, Cz.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Thiabose *UCI, Braz.†*
Tiabendazole (p. 166·3).

Thiacomin *Medichrom, Gr.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Thialgin *Zentiva, Cz.†*
Tiaprofenic acid (p. 137·1).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Thiambiotic *Prafa, Indon.†*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thiamcin *General Drugs, Thai.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thiamet *Ethica, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thiamfilex *Molex Ayus, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thiamiject *Omega, Canad.*
Thiamine hydrochloride (p. 2103·1).

Thiamika *Ikapharmindo, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thiam-P *PP Lab, Thai.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thiamycin *Interbat, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thianax *Cazi, Braz.*
Tiabendazole (p. 166·3).
Worm infections.

Thiaton *Abbott, Jpn.*
Tiquizium bromide (p. 1894·1).
Smooth muscle spasm and hypermotility.

Thiavit *Julphar, UAE.*
Thiamine hydrochloride (p. 2103·1).
Vitamin B_1 deficiency.

Thicazol *Ethica, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Thick & Easy *Fresenius Kabi, Fr.; Hormel, Hong Kong; Fresenius Kabi, Irl.; Hormel, Israel; Hormel, Singapore.*
Food thickener.
Dysphagia.

Thickhead *Principle Healthcare, UK.*
Vitamins; minerals; activated charcoal (p. 1537·3).
Dietary supplement.

Thidim *Kalbe, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Thidomin *Inpac, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Thilo Tears *Alcon, Belg.*
Carbomer (p. 2173·3).
Dry eyes.

Thiloadren *Alcon, Austria.†*
⊗Dipivefrine hydrochloride (p. 2495·1); pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Thilocof *Pharmex (Φαρμεξ), Gr.*
Azidamfenicol (p. 221·1).
Eye infections.

Thilocombin
Note: this name may be used for preparations of different composition.
Alkon (Αλκον), Gr.
⊗Dipivefrine hydrochloride (p. 2495·1); pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Thilodexine *Pharmex (Φαρμεξ), Gr.*
⊗Dexamethasone sodium metasulfobenzoate (p. 1631·1).
Inflammatory eye disorders; skin disorders.

Thilodexine-N *Alcon, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); gramicidin (p. 308·3).

Thilodigon *Alcon, Ger.†; Alcon, Gr.*
⊗Guanethidine monosulfate (p. 1395·2); dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Thilodrin *Alcon, Gr.*
⊗Dipivefrine hydrochloride (p. 2495·1).
Glaucoma.

Thilogel *Alcon, Gr.*
Carbomer (p. 2173·3).
Dry eyes.

Thilol *Farmex, Gr.*
Trifluridine (p. 1020·3).
Herpes simplex infections in the eye.

Thilomaxine *Liba, Turk.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Thilo-micine *Farmex, Gr.*
Tobramycin (p. 380·1).
Eye infections.

Thilomicine Dex *Farmex, Gr.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Thilomide *Farmex, Gr.; Liba, Turk.*
Lodoxamide trometamol (p. 2545·1).
Allergic conjunctivitis.

Thilonium *Alkon (Αλκον), Gr.*
⊗Befunolol hydrochloride (p. 2004·2).
Glaucoma.

Thilorbin *Alcon, Ger.*
Oxybuprocaine hydrochloride (p. 1993·2); fluorescein sodium (p. 2506·2).
Ophthalmic procedures.

Thilo-Tears *Alcon, Ger.; Alcon, Neth.; Liba, Turk.*
Carbomer (p. 2173·3).
Dry eyes.

Thilotim *Pharmex (Φαρμεξ), Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Thimelon *Ethica, Indon.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Thinber Fiber Complex *Dapha, Philipp.†*
⊗Fruit fibre; glucomannan (p. 2515·2); gelatin (p. 1154·1); oat fibre; red clover (p. 2482·1); apple vinegar; chromium yeast (p. 2125·2); magnesium stearate (p. 2195·3).
Dietary fibre supplement.

Thincal *Kocak, Turk.*
Orlistat (p. 2577·1).

Thinz *Aspen, S.Afr.*
⊗Cathine hydrochloride (p. 2318·2).
Obesity.

Thiobitum *Riemser, Ger.*
Ichthammol (p. 1705·3).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Thiocase *Almirall, Spain.†*
Thiomucase (p. 2629·3).
Cellulitis; obesity; soft-tissue disorders; haemorrhoids; premenstrual syndrome.

Thiocilline *Abdi, Turk.*
Bacitracin (p. 225·3); neomycin sulfate (p. 330·1).
Bacterial eye and skin infections.

Thiocodin
Note: this name may be used for preparations of different composition.
Unia, Pol.
Codeine phosphate (p. 40·2); sulfogaiacol (p. 1678·1).
Cough.
Bros, Gr.†
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Thioctacid *Meda, Austria; Merck, Braz.; Meda, Cz.; Meda, Ger.; Meda, Hung.; Bayer, Mex.; Viatris, Rus.; Meda, Ukr.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.
Sidefarma, Port.
Trometamol thioctate (p. 2629·1).
Diabetic neuropathy.

Thiodantol *Rekah, Israel.*
Isothipendyl hydrochloride (p. 631·2).
Skin irritation; pruritus; insect stings; sunburn.

Thiodazine *Sun, Rus.*
Thioridazine hydrochloride (p. 1110·2).
Psychoses; depression; anxiety disorders; behaviour disorders; alcohol withdrawal syndrome; vomiting.

Thioderon *Shionogi, Jpn.*
⊗Mepitiostane (p. 2290·3).
Renal anaemia in dialysis patients; breast cancer.

Thiogamma *Worwag, Cz.; Worwag, Hong Kong; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.; Worwag, Ukr.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy; toxic liver disorders.
Worwag, Ger.
Meglumine thioctate (p. 2629·1) or thioctic acid (p. 2629·1).
Diabetic neuropathy.

Thiola *IFET (ΙΦΕΤ), Gr.; Coop. Farm., Ital.; Mission Pharmacal, USA.*
Tiopronin (p. 1578·1).
Liver disorders; prevention of cystine renal calculi.

Thiolepta *Kanonfarma, Rus.*
Thioctic acid (p. 2629·1).
Neuropathies.

Thiolipon *Biosintez, Rus.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Thiomed *Medifive, Thai.*
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia; mania; anxiety.

Thiomersalate *SA Druggists, S.Afr.†*
Thiomersal (p. 1771·3).
Skin disinfection; skin infections; wounds.

Thiomucase *Farmasa, Braz.*
⊗Mucopolysaccharidase (p. 2629·3); amylase (p. 2442·1); chymotrypsin (p. 2477·3).
Oedema.

Thionembutal *Abbott, Braz.*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Thiopectol *Gifrer Barbezat, Fr.*
Codeine (p. 40·2); eucalyptus (p. 2501·1); terpin (p. 1678·2); tolu balsam (p. 1679·2).
Cough.

Thiopen *Unique, Thai.*
Thiopental sodium (p. 1915·1).
General anaesthesia; convulsions.

Thiopentax *Cristalia, Braz.*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Thiophenicol *Sanofi-Aventis, Fr.; Sanofi Synthelabo, Turk.†*
Thiamphenicol (p. 376·3) or thiamphenicol glycinate hydrochloride (p. 377·1).
Bacterial infections.

Thioplex *AVI, Gr.; Adienne, Ital.; Amgen, USA.*
Thiotepa (p. 871·1).
Malignant neoplasms.

Thioprine *Alphapharm, Austral.; Pacific, NZ.†*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Thioril *Torrent, India.*
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia.

Torrent, Rus.
Thioridazine (p. 1110·2).
Psychoses; depression; anxiety.

Thiosia *Asian Pharm, Thai.*
Thioridazine hydrochloride (p. 1110·2).
Anxiety; depression.

Thiosol *Coop. Farm., Ital.†*
Tiopronin (p. 1578·1).
Respiratory-tract congestion.

Thiospa *Eczacibasi, Turk.*
Thiocolchicoside (p. 2026·2).

Thiospot
Note: this name may be used for preparations of different composition.
Dermoteca, Port.
Thioctic acid (p. 2629·1); ethyl linoleate (p. 2509·2); octadecenedioic acid; salicylic acid (p. 1719·1).
Hyperpigmentation disorders.
Q-Med, Ital.
Thioctic acid (p. 2629·1); lactic acid (p. 2539·1).
Hyperpigmentation disorders.

Thiovalone *Pfizer, Fr.*
⊗Tixocortol pivalate (p. 1648·3); chlorhexidine gluconate (p. 1743·3).
Inflammation of the mouth and throat.

Thiozine *Shine, Philipp.*
Thioridazine hydrochloride (p. 1110·2).
Schizophrenia.

Thiprasolan *Lepetit, Arg.*
Alprazolam (p. 1035·2).
Anxiety; depression.

Thiramil *Farmedia, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Thiroyd *Greater Pharma, Thai.*
Thyroid (p. 2345·3).
Hypothyroidism.

Thisilyn *Schwabe, UK.*
Milk thistle (p. 1561·1).
Dyspepsia.

Thislacol *Metiska, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Thixit *Douglas, NZ.†*
Tiotixene hydrochloride (p. 1112·1).
Psychoses.

Thlascose *Delpech, Fr.†*
Hamamelis (p. 2523·3); hydrastis (p. 2528·1); lachesis (p. 2538·3); solidago (p. 2620·1).
Homoeopathic preparation.

Thoho *T Man, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Thomapyrin *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Turk.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Thomapyrin Brausetabletten *Boehringer Ingelheim, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain.

Thomapyrin Medium *Boehringer Ingelheim, Ger.†*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Thomapyrin mit Vitamin C *Boehringer Ingelheim, Austria.*
Aspirin (p. 22·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Thomasin *Apogepha, Ger.*
⊗Etilefrine hydrochloride (p. 1379·1).
Hypotension.

Thombran *Boehringer Ingelheim, Ger.†*
Trazodone hydrochloride (p. 451·1).
Depression.

Thoraxx *Alapis, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Thorazine *GSK, Philipp.*
Chlorpromazine hydrochloride (p. 1045·2).
Behavioural disorders in children; intractable hiccup; nausea and vomiting; porphyria; premedication; psychoses.

Thoreus *Montrose, Hung.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Those Moments *IFA, Mex.*
Test to identify premenopause or menopause.

THR *Seroyal, Canad.†*
Vitamin E (p. 2119·1); magnesium (p. 1786·3); potassium (p. 1793·1).

Threchop *Collins, Mex.†*
Diiodohydroxyquinoline (p. 931·1); furazolidone (p. 933·3); homatropine (p. 2007·3).
Amoebic dysentery.

Three-B *VS, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Threolone *Teva, Israel.*
⊗Prednisolone (p. 1645·2); chloramphenicol (p. 257·1).
Infected skin disorders.

Threptin *Rafarm, Gr.*
Pirenzepine hydrochloride (p. 1878·2).

Threptin Micromix *Raptakos, India.*
Nutritional supplement.

Thriamox *Antor, Gr.*
Clarithromycin (p. 266·2).

Thriazol *Alpharma, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Thrififin *Zekides, Gr.*
Nitrendipine (p. 1456·3).

Thriolan *Antor, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Thrionipen *Antor, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Thriostaxil *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Thriusedon *DAST, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Thrive *Novartis Consumer, Canad.*
Nicotine policrilex (p. 2569·3).
Aid to smoking withdrawal.
Novartis, USA.
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Throat Discs *SmithKline Beecham, USA.*
Capsicum (p. 2469·3); peppermint oil (p. 1877·1); liquid paraffin (p. 2191·2).
Sore throat.

Throat Lozenges
Note: this name may be used for preparations of different composition.
Novopharm, Canad.
Cetylpyridinium chloride (p. 1743·1).
Novopharm, Canad.
Benzocaine (p. 1980·2); cetylpyridinium chloride (p. 1743·1).

Throat-Clear *Bioglan, Austral.*
Eucalyptus oil (p. 2501·2); fennel oil (p. 2503·3); peppermint oil (p. 1877·1); thyme oil (p. 2630·3); nigella sativa oil; vitamin C (p. 2110·3); echinacea (p. 2498·1); primula root (p. 2596·2); zinc gluconate (p. 2126·2).
Upper respiratory-tract disorders.

Throaties Anti-Bacterial Pastilles *Ernest Jackson, UK.*
Amylmetacresol (p. 1736·3).
Sore throat.

Throaties Pastilles *Ernest Jackson, UK.*
Blackcurrant flavour: Honey (p. 2072·1); menthol (p. 2553·2).
Coughs; sore throat.
Ernest Jackson, UK.
Original flavour: Benzoin tincture (p. 2624·3); menthol (p. 2553·2).
Coughs; sore throat.

Throatsil *Millimed, Thai.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3).
Mouth and throat disorders.

Throatsil Dex *Millimed, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Throatsil Plus *Millimed, Thai.*
Dichlorobenzyl alcohol (p. 1750·2); amylmetacresol (p. 1736·3); lidocaine hydrochloride (p. 1988·2).
Sore throat.

Throatsil-CBS *Millimed, Thai.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Thrody *Greater Pharma, Thai.*
Neomycin sulfate (p. 330·1); bacitracin zinc (p. 225·3); amylocaine hydrochloride (p. 1979·3).
Mouth and throat disorders.

Throimper *Farmedia, Gr.*
Clopidogrel (p. 1342·3).

Thrombace Neo *Drossapharm, Switz.†*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Thrombareduct *Sandoz, Ger.†*
Heparin sodium (p. 1396·3).
Soft-tissue disorders; soft-tissue injury.

Thrombate *Bayer, Canad.; Talecris, Canad.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Thrombate III *Talecris, USA.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Thrombescina *Lacer, Spain.*
Aesculus (p. 2431·2).
Venous insufficiency.

Thrombhibin *Immuno, Austria.†*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Thrombi-Gel *King, USA.*
Thrombin (p. 1163·2).
Haemorrhage.

Thrombinar *Jones, USA.*
Thrombin (p. 1163·2).
Minor haemorrhage.

Thrombi-Pad *King, USA.*
Thrombin (p. 1163·2).
Haemorrhage.

Thrombixil *Omrix, Israel.*
Calcium chloride (p. 1783·1); thrombin (p. 1163·2).
Haemorrhage.

Thrombo AS *Merck, Chile.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Thrombo ASA *Lannacher, Fin.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Thrombo Aspilets *Medifarma, Indon.; UAP, Indon.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Thrombo ASS *Lannacher, Austria; Lannacher, Rus.*
Aspirin (p. 22·2).
Migraine; thromboembolism prophylaxis.

Thrombocid *Bene, Cz.; Bene, Ger.; Neo-Farmaceutica, Port.*
Pentosan polysulfate sodium (p. 1465·1); pumilio pine oil (p. 2591·1); rosemary oil (p. 2607·3); melissa oil (p. 2553·2).
Thrombophlebitis; vascular disorders; soft-tissue injury; venous insufficiency.
Sigmapharm, Austria; Bene, Ger.; Neo-Farmaceutica, Port.
Pentosan polysulfate sodium (p. 1465·1); guaiazulene (p. 2523·1); thymol (p. 1772·2).
Vascular disorders; soft-tissue injury; superficial vascular disorders; burns; insect bites.
Lacer, Spain; Bene, Ukr.
Pentosan polysulfate sodium (p. 1465·1).
Phlebitis; venous insufficiency; soft-tissue injuries; scars; haematoma; varicose veins.
Bene-Chemie, Hong Kong.
Pentosan polysulfate sodium (p. 1465·1); guaiazulene (p. 2523·1).
Haemorrhoids; insect stings; sunburn; superficial phlebitis; venous insufficiency.

Thrombodine *Lannacher, Austria.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Thromboflux *Biosano, Chile; Xeno, Philipp.; Bharat, Rus.; Bharat, Thai.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Thromboparin *Angelini, Gr.*
Parnaparin (p. 1464·2).
Thrombosis prophylaxis.

Thrombophob *Nordmark, Austria; Nordix, Ger.; Nordmark, Ger.; Zydus, India; Nordmark, Indon.; Tunggal Idaman, Indon.*
Topical gel: Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders; phlebitis; varices; venous insufficiency.

Nordmark, Austria; Zydus, India; Nordmark, Indon.; Tunggal Idaman, Indon.
Injection; ointment: Heparin sodium (p. 1396·3); benzyl nicotinate (p. 29·3).
Superficial vascular disorders; soft-tissue injury; phlebitis; varices; venous insufficiency.

Winthrop, S.Afr.†
Topical gel: Heparin (p. 1396·3).
Superficial vascular disorders; soft-tissue injuries.

Thrombophob-S *Nordmark, Austria.*
Heparin sodium (p. 1396·3).
Superficial vascular disorders; soft-tissue injury.

Thromboreductin *Orpha-Devel, Austria; Orpha-Devel, Cz.; Hospira, Hong Kong; Orpha-Devel, Hung.; AOP Orphan, Indon.; Combiphar, Indon.; AOP, Malaysia; Key Oncologics, S.Afr.; OrPha, Switz.; Hospira, Thai.; Dem, Turk.*
Anagrelide hydrochloride (p. 2442·2).
Thrombocythaemia.

Thrombostad *Stada, Austria.*
Aspirin (p. 22·2).
Thrombotic disorders; migraine.

Thrombostat *Pfizer, NZ†; Parke, Davis, Singapore; Parke, Davis, USA.*
Thrombin (p. 1163·2).
Haemorrhage.

Thrombotrol-VF *CSL Biotherapies, Austral.; CSL, NZ.*
Antithrombin III (p. 1132·3).
Antithrombin III deficiency.

Thromyn *Zynova, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Throsyn *Aspen, S.Afr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Throzimax *Medilat, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Thuja Med Complex *Dynamit, Austria.*
Arnica (p. 2447·2); ledum (p. 2550·1); thuja (p. 2629·3).
Homoeopathic preparation.

Thuja N Oligoplex *Madaus, Ger.†*
Thuja (p. 2629·3); clematis; kalium jodatum (p. 2336·3).
Homoeopathic preparation.

Thuja WA Oligoplex *Madaus, Ger.*
Thuja (p. 2629·3); clematis; kalium jodatum (p. 2336·3); phosphorus (p. 2589·2); platinum chloratum (p. 2593·1).
Homoeopathic preparation.

Thujaderm *Knop, Chile.*
Thuja (p. 2629·3).
Warts.

Thujarell *Sanorell, Ger.*
Thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Thuroclens *Woodward, Canad.*
Benzalkonium chloride (p. 1737·1).

Thuya Complexe No 37 *Lehning, Fr.*
Thuya occidentalis (p. 2629·3); solanum dulcamara (p. 2497·3); mercurius corrosivus (p. 2555·2); phytolacca (p. 2593·2); arsenicum iodatum (p. 2448·1); anemone pulsatilla (p. 2600·2); phosphorus (p. 2589·2); acidum nitricum (p. 2572·3); kalium bichromicum (p. 2476·3).
Homoeopathic preparation.

Thuyalite *Holland Pharma, Neth.*
Hepar sulphur (p. 1721·3); sulphur (p. 1721·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Thwart *Alliance, Irl.*
Salicylic acid (p. 1719·1).
Verrucas.

Thybon *Henning, Ger.; Sanofi-Aventis, Ger.*
Liothyronine hydrochloride (p. 2342·3).
Hypothyroidism.

Thycapzol *Sandoz, Denm.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Thymalin *Samson-Med, Rus.*
Thymus (bovine) (p. 2631·1).
Immunodeficiency disorders.

Thymanax *Servier, Cz.; Servier, Irl.; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, Spain.*
Agomelatine (p. 400·2).
Depression.

Thymazen *Polfa Warszawa, Pol.†*
⊗Tymazoline hydrochloride (p. 1679·3).
Nasal congestion; sinusitis.

Thymazide *AZT, Rus.*
Zidovudine (p. 1024·2).
HIV infection.

Thymazole *CCM, Malaysia.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Thymcal *Nufarindo, Indon.*
⊗Paracetamol (p. 115·1); ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3); calcium gluconate (p. 1783·3); ammonium chloride (p. 1656·1); thyme (p. 2630·2); ammonium bromide (p. 2461·1); sassafras oil (p. 2610·3).
Cough.

Thymi Syrup *Vitamed, Israel.*
Thyme (p. 2630·2).
Cough.

Thymian Erkältungs-Bad *Li-il, Ger.*
Thyme oil (p. 2630·3).
Bath additive; respiratory-tract disorders; skin disorders.

Thymipin N *Novartis Consumer, Ger.†*
Oral drops; syrup: Thyme (p. 2630·2).
Bronchitis; catarrh; cough.

Thymiverlan *Verla, Ger.*
Thyme (p. 2630·2).
Respiratory-tract disorders.

Thymodepressin *Peptos, Rus.*
Thymodepressin.
Auto-immune disorders; neutropenia; transplant rejection.

Thymogam *Biosano, Chile; Xeno, Philipp.*
An antithymocyte immunoglobulin (horse) (p. 1939·2).
Aplastic anaemia; transplant rejection.

Thymoglobulin *Genzyme, Canad.; Genzyme, Ger.; Genzyme, Hung.; Genzyme, Irl.; Genzyme, Rus.*
An antithymocyte immunoglobulin (rabbit) (p. 1939·2).
Transplant rejection; graft-versus-host disease; aplastic anaemia.

Thymoglobuline *Genzyme, Austria; Genzyme, Belg.; Genzyme, Braz.; Genzyme, China; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Gr.; IFET (ΙΦΕΤ), Gr.; Genzyme, Hong Kong; Sanofi-Aventis, India; Genzyme, Israel; Genzyme, Ital.; Genzyme, Jpn; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Norw.; Sanofi Pasteur, Philipp.; Genzyme, Pol.; Genzyme, S.Afr.†; Sanofi-Aventis, Singapore; Genzyme, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Genzyme, Turk.; Genzyme, UK; Genzyme, Ukr.†*
An antithymocyte immunoglobulin (rabbit) (p. 1939·2).
Transplant rejection; aplastic anaemia; graft-versus-host disease; immunosuppressive therapy.

Thymoject *Biosyn, Ger.†; Loges, Ger.†*
Bovine thymus extract (p. 2631·1).
Immunological disorders.

Thymomel *Teva, Cz.*
Thyme (p. 2630·2); wild thyme (p. 2648·1); plantain (p. 2604·2).
Respiratory-tract congestion.

Thymontil *Ni-The, Gr.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Thymophysin *CytoChemia, Ger.†*
Thymus extract (p. 2631·1).
Immunotherapy.

Thymorell *Sanorell, Ger.*
Glandulae thymi bovis (p. 2631·1).
Homoeopathic preparation.

Thymoseptine *Tilman, Belg.*
Thyme (p. 2630·2); wild thyme (p. 2648·1); ammonium acetate (p. 1655·3).
Respiratory-tract disorders; sore throat.

Thymunes *Eagle, Austral.†*
Thymus (p. 2631·1).

Thymusin N *Streuli, Switz.†*
Thyme (p. 2630·2).
Cough.

Thym-Uvocal *Strathmann, Ger.†*
Calf thymus extract (p. 2631·1).
Immunotherapy.

Thyodyn *Nutri-Dyn, Canad.*
Kelp (p. 2612·1).
Iodine supplement; thyroid disorders.

Thyprotect *Henning, Ger.†; Sanofi Synthelabo, Ger.†*
Potassium iodide (p. 2336·3).
Blockade of thyroid uptake of radioiodine.

Thyradin-S *Teikoku, Jpn.*
Levothyroxine sodium (p. 2339·1).
Goitre; hypothyroidism.

Thyrax *Organon, Belg.; Schering-Plough, Indon.; Organon, Neth.; Organon, Philipp.; Organon, Port.; Organon, Venez.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; euthyroid goitre; thyroid cancer; diagnostic suppression of thyroid activity.

Thyrazol *Transfarma, Philipp.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Thyreocomb *Berlin-Chemie, Rus.*
Levothyroxine sodium (p. 2339·1); liothyronine (p. 2342·3); potassium iodide (p. 2336·3).
Hypothyroidism; goitre.

Thyreogutt mono *Schwabe, Ger.*
Lycopus europaeus (p. 2462·2).
Mild hyperthyroidism; mastalgia.

Thyreo-Injektopas *Pascoe, Ger.*
Lycopus virginicus (p. 2462·2); ferrum jodatum (p. 2061·3); avena sativa (p. 2451·1); lupulus (p. 2546·1).
Homoeopathic preparation.

thyreo-loges *Loges, Ger.*
Lycopus europaeus (p. 2462·2).
Hyperthyroidism.

thyreo-loges comp *Loges, Ger.*
Lycopus europ. (p. 2462·2); badiaga.
Homoeopathic preparation.

Thyreo-Pasc *Pascoe, Ger.*
Lycopus virg. (p. 2462·2); spongia; fucus vesic. (p. 2612·1).
Homoeopathic preparation.

Thyreotom *Berlin-Chemie, Cz.*
Liothyronine (p. 2342·3); levothyroxine (p. 2339·1).
Hypothyroidism.

Berlin-Chemie, Rus.
Liothyronine (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism; goitre.

Thyrex *Sandoz, Austria.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Thyro-4 *Angelini, Gr.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Thyro-Block *Wallace, USA.*
Potassium iodide (p. 2336·3).
Blockade of thyroid uptake of radioiodine.

Thyrogen *Genzyme, Austria; Sanofi-Aventis, Belg.; Genzyme, Canad.; Genzyme, Chile; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Hung.; Genzyme, Irl.; Genzyme, Israel; Genzyme, Ital.; Sato, Jpn; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Genzyme, Singapore; Genzyme, Spain; Genzyme, Swed.; Sanofi-Aventis, Switz.; Genzyme, Thai.; Sanofi-Aventis, Thai.; Genzyme, Turk.; Genzyme, UK; Genzyme, USA.*
Thyrotropin alfa (p. 2346·1).
Ablation of thyroid remnant tissue; detection of thyroid remnants and thyroid cancer following thyroidectomy; measurement of serum thyroglobulin in thyroid cancer.

Thyrohex *Hexal, Philipp.†*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Thyrohormone *Ni-The, Gr.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Thyroid Complex *Mediherb, Austral.*
Fucus vesiculosus; ashwagandha (p. 2450·2); bacopa (p. 2452·1).
Thyroid disorders.

Thyroid-S *Sriprasit, Thai.*
Thyroid extract (p. 2345·3).
Hypothyroidism.

Thyrolar *Forest Pharmaceuticals, USA.*
Liothyronine sodium (p. 2342·3); levothyroxine sodium (p. 2339·1).
Hypothyroidism; tSH suppression; evaluation of thyroid function.

Thyroliberin *Merck, Ger.†*
Protirelin (p. 2344·2).
Assessment of pituitary and thyroid function.

Thyromazol *Abdi, Turk.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Thyronajod *Henning, Ger.; Sanofi-Aventis, Ger.*
Levothyroxine sodium (p. 2339·1); potassium iodide (p. 2336·3).
Hypothyroidism.

ThyroSafe *Recip, USA.*
Potassium iodide (p. 2336·3).
Blockade of thyroid uptake of radioiodine.

Thyrosan *Sun-Farm, Pol.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

ThyroShield *Fleming, USA.*
Potassium iodide (p. 2336·3).
Blockade of thyroid uptake of radioiodine.

Thyrosit *Sriprasit, Singapore; Sriprasit, Thai.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Thyrostat *Ni-The, Gr.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Thyrotardin *Henning, Ger.†; Sanofi-Aventis, Ger.†*
Liothyronine hydrochloride (p. 2342·3).
Hypothyroidism.

Thyrozol *Merck, Chile; Merck Serono, China; Merck, Cz.; Merck Serono, Fr.; Merck Serono, Ger.; Merck, Indon.; Merck, Pol.; Nycomed, Rus.; Merck, Singapore; Merck, Ukr.*
Thiamazole (p. 2345·2).
Hyperthyroidism; goitre; thyrotoxic crisis.

ThySat *Hameln, UK.*
Potassium iodide (p. 2336·3).
Blockade of thyroid uptake of radioiodine.

Tl Baby Natural *Fischer, USA.*
SPF 16: Titanium dioxide (p. 1725·1).
Sunscreen.

Ti Bi *Huayu, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3).
Tuberculosis.

Ti Bo Ding *Di Ao Jiu Hong, China.*
Thymopentin (p. 2631·1).

Tl Lite *Fischer, USA.*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ti Ma Er *NCPC, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tl Screen *Pedinol, USA.*
SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Pedinol, USA.†
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Tl Screen Natural *Pedinol, USA.*
SPF 16: Titanium dioxide (p. 1725·1).
Sunscreen.

Tl Screen Sports *Pedinol, USA.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); avobenzone (p. 1695·1).
Sunscreen.

Tl Screen Sunless *Pedinol, USA.*
SPF 17; SPF 23: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Ti Ta Ding *Bosen, China.*
Gamma-aminobutyric acid (p. 2509·2).

Ti Yu *Dinuo, China.*
Telmisartan (p. 1509·3).
Hypertension.

Tia Puppy *Nordin, Mex.*
Hamamelis (p. 2523·3).
Varices.

Tiabet *Tunggal Idaman, Indon.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Tiabexol *Offenbach, Mex.†*
Cyanocobalamin (p. 2107·2); thiamine (p. 2102·3).
Vitamin supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Tiabiose *UCI, Braz.*
Tiabendazole (p. 166·3).
Nematode infections.

Tiacob *Hexal, Neth.†*
Tiapride hydrochloride (p. 1111·2).
Neuroleptic-induced tardive dyskinesia.

Tiaden
Note: this name may be used for preparations of different composition.
Gap, Gr.
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure.

Tiadilon *Crinex, Fr.*
Arginine tidiacicate (p. 2049·1).
Liver disorders.

Tiadipona *Abbott, Spain.*
Bentazepam (p. 1041·1).
Anxiety disorders.

Tiadol *Bunker, Braz.*
Tiabendazole (p. 166·3).

Tiadyl *Abbott, Arg.*
Candesartan cilexetil (p. 1330·2).
Hypertension.

Tiadyl Plus *Abbott, Arg.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tiager *GL Pharma, Hung.*
Tiapride hydrochloride (p. 1111·2).
Dyskinesias; alcohol withdrawal syndrome.

Tiaglib *Tunggal Idaman, Indon.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Tialin *Roemmers, Venez.*
Sertraline hydrochloride (p. 448·1).
Depression.

Tialipol *Lafedar, Arg.†*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Tialorid *Polpharma, Pol.*
⊗Amiloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Tial-Z *Performa, Ital.*
Levomenol (p. 2544·1); allantoin (p. 1693·1).
Skin irritation.

Tiamidexal *Silanes, Mex.*
⊗1 Ampoule, cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1); 1 ampoule, dexamethasone sodium phosphate (p. 1631·2).
Gout; musculoskeletal, joint, and peri-articular disorders; neuritis.

Tiamidon *Medipharma, Arg.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Tiamin *Neo Quimica, Braz.*
Vitamin B substances (p. 2102·3).

Tiaminal B_{12} *Silanes, Mex.*
Cyanocobalamin (p. 2107·2); thiamine hydrochloride (p. 2103·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Vitamin B deficiencies; neuritis; neuralgia.

Tiaminal B_{12} Trivalente *Silanes, Mex.*
Cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiencies; neuritis; neuralgia; pernicious anaemia.

Tiamol
Note: this name may be used for preparations of different composition.
Ashford, Singapore.
⊗Timolol maleate (p. 1513·2).
Glaucoma.
Taro, Canad.
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Tiamon Mono *Temmler, Ger.*
Dihydrocodeine tartrate (p. 52·3).
Cough.

Tian An Xin *San Lian, China.*
Adenosine cyclophosphate (p. 2430·2).

Tian Cao *Ruibang, China.*
Kitasamycin acetate (p. 315·2).

Tian Cun *Tian Fu, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Tian Di Da *Kanghai, China.*
Amifostine (p. 1539·2).
Reduction of neutropenia due to cytotoxic therapy; reduction of cisplatin-induced renal toxicity; radiotherapy-associated xerostomia.

Tian En Fu *Weike, China.*
Tumour necrosis factor (human recombinant) (p. 878·1).

Tian Er Xin *Sine, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; coronary heart disease; hypertension.

Tian Fen *Shenlong, China.*
Matrine.

Tian Fu Chu *San Lian, China.*
Propyl gallate (p. 1736·1).

Tian Fu Xin *Hailing, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Tian He Heng *Tianhedi Sainuo, China.*
Telmisartan (p. 1509·3).
Hypertension.

Tian Jia Mei *Dandong, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Tian Jia Yuan *Beiqi, China.*
Magnesium sulfate (p. 1787·3).

Tian Jian *Qinghai, China.*
Ligustrazine hydrochloride.

Tian Jun Di *Rui Yang, China.*
Enoxacin gluconate.
Bacterial infections.

Tian Jun Li *Linuo Kefeng, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Tian Kai *Tian Da, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Tian Ke *Maxim, China.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Tian Li *Haini, China.*
Glucose (p. 2068·3); electrolytes (p. 1775·1).

Tian Li Ning *Tianli, China.*
Metronidazole (p. 936·1).

Tian Mai *Changlian Laifu, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Tian Nuo Xin *Dongbao, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Tian Qi *Junan, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Tian Qian *Yangzhou No 3, China.*
Ibuprofen (p. 68·2).
Pain; fever.

Tian Quan Tai Ning *Tianquan, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Tian Quan Xi Ning *Tianquan, China.*
Diprophylline (p. 1207·3).
Obstructive airways disease.

Tian Rui *Yangtze River, China.*
Imiquimod (p. 985·2).
Anogenital warts; solar keratosis; basal cell carcinoma.

Tian Shu *Tiantaishan, China.*
Zolmitriptan (p. 682·2).
Migraine.

Tian Shu Qing *San Lian, China.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment.

Tian Shu Xin *Hui Ren, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Tian Tai *Chung-Hwa, China.*
Moclobemide (p. 437·2).
Depression; social phobia.

Tian Di Xin *Kanghai, China.*
Lentinan (p. 2543·2).

Tian Xin *Yangzhou No 3, China.*
Gatifloxacin mesilate.
Bacterial infections.

Tian Xin Li Bo *Xinxin, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Tian Xin Li Do *Xinxin, China.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Tian Xin Shuang *Xinxin, China.*
Nicotinic acid (p. 2083·1).

Tian Xing *Zhongsheng Haitian, China.*
Aceglutamide (p. 2426·2).

Tian Xuan Qing *KunMing, China.*
Gastrodin.

Tian Yi *Wuhan Wujing, China.*
Glutathione (p. 1555·2).

Tian Yi An *Chang An, China.*
Lysine hydrochloride (p. 2079·3).

Tian Yi Shu *Duoburuifei, China.*
Etamsylate (p. 1145·2).
Haemorrhage.

Tian Zan *Chia Tai, China.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Tianak *Wermar, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; gastrointestinal haemorrhage.

Tiance *Chia Tai, China.*
Biapenem (p. 231·1).

TianCheng Nuo Er *Tiancheng, China.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Tiancheng Xi Er *Tiancheng, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Tianke *NCPC, China.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; lupus; nephrotic syndrome.

Tianli Runzhu *Sinphar Tian-Li, China.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Tianlong Taike *Tianlong, China.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Tianruite *Zhengda Haier, China.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Tiantong *Chia Tai, China.*
Balofloxacin (p. 226·3).

TianYi *Topfond, China.*
Telmisartan (p. 1509·3).
Hypertension.

Tiaplex *Delta, Braz.*
Tiabendazole (p. 166·3).
Worm infections.

Tiapra *Zentiva, Cz.*
Tiapride hydrochloride (p. 1111·2).
Dementia; alcohol withdrawal syndrome; movement disorders; Huntington's chorea.

Tiapralan *GL Pharma, Cz.*
Tiapride hydrochloride (p. 1111·2).
Dyskinesias; movement disorders.

Tiapridal *Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.*
Tiapride hydrochloride (p. 1111·2).
Choreic movements; psychiatric disorders; tardive dyskinesia; behaviour disorders; alcohol withdrawal syndrome; pain; Tourette's syndrome; agitation; aggression; anxiety; drug-induced extrapyramidal disorders; dementia; neuropathic pain.

Tiapridex *Sanofi-Aventis, Ger.†*
Tiapride hydrochloride (p. 1111·2).
Drug-induced extrapyramidal disorders; chorea.

Tiaprizal *Sanofi-Aventis, Spain.*
Tiapride hydrochloride (p. 1111·2).
Behaviour disorders; Huntington's chorea.

Tiaquin *Generics, Denm.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; mania; bipolar disorder.

Tiarix *Casasco, Arg.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety; social phobia.

Tiartan *Solvay, Ital.*
⊗Eprosartan mesilate (p. 1376·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tiaryt *Fahrenheit, Indon.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias.

Tiasar *Bioavenir, Israel; Pentafarma, Port.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; diabetic nephropathy; cardiovascular risk reduction.

Tiatral 100 SR *Novartis, Switz.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Tiavase *Hexal, Denm.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tiavit *Nutrilab, Arg.*
Thiamine (p. 2102·3).
Insect repellent.

Tiazac
Note: this name may be used for preparations of different composition.
Biovail, Canad.; Forest Pharmaceuticals, USA.
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.
Drugtech, Chile.
Pioglitazone (p. 493·1).
Diabetes mellitus.

Tiazam *Vocate, Gr.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Tiazet *Ratiopharm, Neth.*
Tiapride hydrochloride (p. 1111·2).
Neuroleptic-induced tardive dyskinesia.

Tiazidol *Carbel, Mex.†*
⊗Metoprolol (p. 1434·3).

Tiazinol *Cipan, Port.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tiba *Pharmaland, Thai.†*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Tibaldix *ICN, Neth.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia.

Tiberal *Lamepro, Belg.; Roche, NZ; Roche, Rus.; OrPha, Switz.; Roche, Ukr.†*
Ornidazole (p. 943·1).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections; protozoal infections.

Tibéral *SERB, Fr.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Tibial *Neo Quimica, Braz.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Tibifor *Lisapharma, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Tibigon *Hexpharm, Indon.†*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Tibinide *Meda, Swed.*
Isoniazid (p. 311·2).
Tuberculosis.

Tibirim INH *Ranbaxy, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Tibitab *TO-Chemicals, Thai.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Tibitol *Mersifarma, Indon.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.
PC India, India.
Ethambutol (p. 296·1).
Tuberculosis.

Tiboclim *Panalab, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Tibofem *Organon, Arg.; Cipla, India.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Tibolvivax *Organon, Cz.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Tibomax *Zydus, India.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Tibozole *Tibotec, Belg.*
Miconazole nitrate (p. 589·1).
Oral candidiasis.

Tiburon *Merck Medication Familiale, Fr.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ticalma *Kelemata, Ital.*
Valerian root (p. 2640·2).
Nervous disorders; insomnia.

Ticar *GSK, USA.†*
Ticarcillin sodium (p. 378·2).
Bacterial infections.

Ticarcin *Shanxi, Philipp.*
Ticarcillin sodium (p. 378·2); clavulanic acid (p. 268·3).
Bacterial infections.

Ticard *Sanbe, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis.

Ticarpen *GSK, Fr.*
Ticarcillin sodium (p. 378·2).
Bacterial infections.

Ticavent *Caber, Ital.*
⊗Fluticasone propionate (p. 1638·1).
Rhinitis.

Tice *Organon, USA.*
A BCG vaccine (p. 2378·1).
Bladder cancer; active immunisation.

Ticinan *Formenti, Ital.†*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Ticinil Calcio *Boehringer Ingelheim, Venez.*
Phenylbutazone calcium (p. 125·1).
Gout; musculoskeletal and joint disorders; neuritis; neuralgia.

Tickly Cough & Sore Throat Relief *Herbal Concepts, UK.*
Hyssop (p. 2530·3); senega (p. 1677·2); liquorice (p. 1853·2).
Coughs and cold symptoms; sore throat.

Ticlapsor *Abiogen, Ital.*
Tacalcitol (p. 1722·1).
Psoriasis.

Ticlid *Sanofi-Aventis, Arg.; Roche, Austral.†; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile†; Sanofi, China; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Malaysia; Syntex, Mex.†; Sanofi-Aventis, Norw.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.†; Sanofi-Aventis, Thai.; Sanofi Synthelabo, Turk.; Roche, USA; Sanofi-Aventis, Venez.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis; thromboembolic disorders; thromboembolism prophylaxis; intermittent claudication; maintenance of extracorporeal circulation; cerebrovascular and cardiovascular disorders; peripheral vascular disease; .

Ticlo *Vedim, Pol.; Schwarz, Rus.; Greater Pharma, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Peripheral vascular disease; thromboembolic disorders; thromboembolism prophylaxis.

Ticlobal *Baldacci, Braz.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Ticlobest *Aristo, India.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Ticlocard *Kocak, Turk.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Ticlodin *TO-Chemicals, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis following coronary stent implantation.

Ticlodix *Vitoria, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Ticlodone *Alapis, Gr.; Sigma-Tau, Ital.; Almirall, Spain.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders; thromboembolism prophylaxis.

Ticlogal *Teva, Hung.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Ticlon *Interbat, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis.

Ticlop *Zydus, India.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Ticlopat *BioSaude, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Intermittent claudication; maintenance of extracorporeal circulation; stroke prophylaxis; thromboembolism prophylaxis.

Ticlophar *Actavis, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Ticlopid *Cipla, India.*
Ticlopidine hydrochloride (p. 1512·1).

Ticlopine *Sunward, Malaysia†; Umeda, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Maintenance of extracorporeal circulation; thromboembolism prophylaxis.

Ticocin *Cipla, India.*
Teicoplanin (p. 369·3).
Gram-positive bacterial infections.

Ticofarma
Note: this name may be used for preparations of different composition.
Pentafarma, Port.
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; obsessive-compulsive disorder.
Tecnimede, Port.
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.
Pentafarma, Port.†
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Ticolcin *Tecnofarma, Mex.*
Colchicine (p. 604·1).
Gout; hepatic cirrhosis; familial Mediterranean fever; amyloidosis; Behçet's syndrome.

Ticomag *Solas, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; peptic ulcer; oesophagitis; flatulence.

Ticon *Hauck, USA.*
Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Ticopar *Julphar, UAE.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis; thrombosis prophylaxis in coronary stent implantation.

TicoVac *Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Irl.; Baxter, Ital.; Baxter, Norw.; Baxter, UK.*
A tick-borne encephalitis vaccine (p. 2422·1).
Separate preparations are available for adults and for infants and children.
Active immunisation.

Ticuring *Lapi, Indon.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Tidact *Yung Shin, Hong Kong†; YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.*
Clindamycin hydrochloride (p. 269·3) or clindamycin phosphate (p. 269·3).
Bacterial infections.

Tidar *Sriprasit, Thai.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle pain and spasm; spasticity.

Tideca *Sanovel, Turk.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Tidigesic *Sun, India.*
⊗Buprenorphine (p. 30·2).
Pain.

Tidomel *Volta, Chile.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome.

Tidomet *Torrent, Philipp.; Torrent, Rus.; Torrent, Singapore; Torrent, Thai.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Tie Long *Xinshitong, China.*
Vitamins.

Tie Xin *Feihong, China.*
Ferrous lactate (p. 2062·1).

Tielle *Johnson & Johnson Consumer, Belg.; Ethicon, Fr.†*
A polyurethane dressing (p. 1718·1).
Wounds; ulcers.
Johnson & Johnson Medical, Arg.; Systagenix, Ital.; Johnson & Johnson Medical, UK.
Foamed hydrogel.
Burns; wounds.

Tienam *MSD, Belg.; MSD, Braz.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S. Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, Ukr.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tienor *Farmaka, Ital.*
Clotiazepam (p. 1057·2).
Anxiety; insomnia.

Tiepem *Biochimico, Braz.*
Imipenem (p. 309·2); cilastatin (p. 260·3).

Tierlite *Bros, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Tifaxin *Stada, Cz.; Tiefenbacher, Neth.†; Genus, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Tifforly *CBC, Hong Kong.*
Adapalene (p. 1692·1).
Acne.

Tiffy *TNP, Thai.*
Syrup: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.
TNP, Thai.
Tablets: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.
Medochemie, Hong Kong.†
Paracetamol (p. 115·1).
Fever; pain.

Tiffy Dey *TNP, Thai.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; upper respiratory-tract congestion.

Tiffy Fu *TNP, Thai.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Tiffy Kiddi *TNP, Thai.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Tifinidat *Tiefenbacher, Neth.†*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder.

Tifisterid *Actavis, Fin.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Tifival *Tiefenbacher, Neth.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Tiflodipina *TAD, Port.†*
Amlodipine maleate (p. 1304·1).
Hypertension; angina pectoris.

Tiflox *Norton, Ukr.†*
Ofloxacin (p. 334·3); ornidazole (p. 943·1).
Bacterial infections; protozoal infections.

Tifol *KRKA, Ukr.*
Folic acid (p. 2063·1).
Prenatal and pregnancy supplement.

Tifripex *Neuraxpharm, Denm.†*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Tigacil *Pfizer, Rus.*
Tigecycline (p. 379·2).

Tigal *Sanovel, Turk.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections of the skin and nails.

Tigalin *Erlimpex, Indon.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Impetigo; wounds; burns.

Tigan *JHP, USA.*
Capsules; injection: Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Tigason *Chugai, Jpn.*
Etretinate (p. 1703·3).
Keratinisation disorders; psoriasis; oral lichen planus.

Tigel Coaltar *Royal, Chile.*
Coal tar (p. 1723·2).
Scalp disorders.

Tiger Balm *Chattem, USA.*
Menthol (p. 2553·2); camphor (p. 2466·2); cajuput oil (p. 2464·1); clove oil (p. 2481·3); mint oil (p. 2560·1).
Olvos, Gr.; SSL, UK.
Camphor (p. 2466·2); cajuput oil (p. 2464·1); clove oil (p. 2481·3); menthol (p. 2553·2).
Musculoskeletal pain.

Tiger Balm Arthritis Rub *Haw Par, Canad.*
Camphor (p. 2466·2); clove oil (p. 2481·3); dementholised mint oil (p. 2560·1); menthol (p. 2553·2); cajuput oil (p. 2464·1).
Musculoskeletal pain.

Tiger Balm Liniment *Haw Par, Canad.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, and soft-tissue pain.

Tiger Balm Oil *Key, Austral.*
Cajuput oil (p. 2464·1); camphor (p. 2466·2); clove oil (p. 2481·3); dementholised mint oil (p. 2560·1); menthol (p. 2553·2).
Musculoskeletal aches and pains.

Tiger Balm Patch Warm *Haw Par, Canad.*
Camphor (p. 2466·2); capsaicin (p. 35·1); dementholised mint oil (p. 2560·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal pain.

Tiger Balm Red *Ceuta, Irl.*
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); clove oil (p. 2481·3); dementholised mint oil (p. 2560·1); cinnamon oil (p. 2479·3).
Musculoskeletal pain.
Haw Par, Canad.
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); peppermint oil (p. 1877·1).
Musculoskeletal and joint pain.
Haw Par, Israel.
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); dementholised mint oil (p. 2560·1); clove oil (p. 2481·3).
Key, Austral.
Cajuput oil (p. 2464·1); camphor (p. 2466·2); cassia oil (p. 2471·3); clove oil (p. 2481·3); dementholised mint oil (p. 2560·1); menthol (p. 2553·2).
Musculoskeletal aches and pains.
Naturprodukt, Hung.
Camphor (p. 2466·2); levomenthol (p. 2553·2); cajuput oil (p. 2464·1); mint oil (p. 2560·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3).
Musculoskeletal and joint pain; soft-tissue injury; insect bites; cold symptoms.

Tiger Balm rot N *Klosterfrau, Ger.*
Camphor (p. 2466·2); levomenthol (p. 2553·2); cajuput oil (p. 2464·1); peppermint oil (p. 1877·1).
Musculoskeletal pain.

Tiger Balm Ultra *Haw Par, Canad.*
Camphor (p. 2466·2); cajuput oil (p. 2464·1); cinnamon oil (p. 2479·3); clove oil (p. 2481·3); peppermint oil (p. 1877·1); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Tiger Balm weiss *Klosterfrau, Ger.*
Camphor (p. 2466·2); levomenthol (p. 2553·2); clove oil (p. 2481·3); cajuput oil (p. 2464·1); peppermint oil (p. 1877·1).
Cold symptoms; musculoskeletal and soft-tissue pain.

Tiger Balm White *Key, Austral.; Ceuta, Irl.; Haw Par, Israel.*
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); clove oil (p. 2481·3); dementholised mint oil (p. 2560·1).
Musculoskeletal pain; nasal congestion.
Haw Par, Canad.
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); clove oil (p. 2481·3); peppermint oil (p. 1877·1).
Musculoskeletal and joint pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Naturprodukt, Hung.
Camphor (p. 2466·2); levomenthol (p. 2553·2); cajuput oil (p. 2464·1); mint oil (p. 2560·1); clove oil (p. 2481·3).
Musculoskeletal and joint pain; soft-tissue injury; insect bites; cold symptoms.

Tiger Balsam Rot *Klosterfrau, Austria.*
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); peppermint oil (p. 1877·1); clove oil (p. 2481·3); cinnamon oil (p. 2479·3).
Muscle pain.

Tiger Balsam Weiss *Klosterfrau, Austria.*
Camphor (p. 2466·2); menthol (p. 2553·2); cajuput oil (p. 2464·1); clove oil (p. 2481·3).
Musculoskeletal pain.

Tiger Snake *Commonwealth Serum, Hong Kong.*
A tiger snake venom antisera (p. 2419·1).
Snake bite.

Tighum *Gervasi, Spain.†*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Tigina *Interpharma, Chile.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Tigre de Chine *Equilibre Sinovital, Fr.*
Dementholised mint oil (p. 2560·1); camphor (p. 2466·2); ginseng (p. 2513·3); methyl salicylate (p. 92·1); jasmine flower; comfrey (p. 2484·2); myrrh (p. 2566·1); frankincense (p. 2507·3); carthamus tinctorius; drynaria fortunei rhizome; angelica (p. 2443·3); arnica (p. 2447·2); capsicum (p. 2469·3); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); cajuput oil (p. 2464·1); cymbopogon nardus oil; cinnamon oil (p. 2479·3); clove oil (p. 2481·3); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Tigreat *Menarini, Fin.†; Menarini, Fr.*
Frovatriptan succinate (p. 676·2).
Migraine.

Tigridol *Phytomedica, Fr.*
Camphor (p. 2466·2); menthol (p. 2553·2); clove oil (p. 2481·3); eucalyptus oil (p. 2501·2); peppermint oil (p. 1877·1); cinnamon oil (p. 2479·3).
Musculoskeletal and joint disorders; insect bites.

Tikacillin *Meda, Swed.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Tikl *Monserrat, Arg.*
Ketoconazole (p. 585·3).
Scalp disorders.

Tikleen *Ipca, India; Ipca, Rus.†*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis.

Tiklid *Sanofi-Aventis, Austria; Sanofi-Aventis, Ital.; Sanofi-Aventis, Spain.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Tiklyd *Sanofi-Aventis, Ger.; Sanofi-Aventis, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Tikosyn *Pfizer, USA.*
Dofetilide (p. 1367·1).
Arrhythmias.

Tikpid *Duopharma, Philipp.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis.

Tilac *Bilim, Turk.*
Etodolac (p. 57·1).

TilactaMed *Strathmann, Ger.*
Tilactase (p. 2631·2).
Lactose intolerance.

Tilad *Sanofi-Aventis, Spain.*
Nedocromil sodium (p. 1216·2).
Asthma.

Tilade *Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Aventis, NZ; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Eczacibasi, Turk.†; Sanofi-Aventis, UK.*
Nedocromil sodium (p. 1216·2).
Asthma; obstructive airways disease; allergic rhinitis; allergic conjunctivitis.

Tilalgin *Grunenthal, Neth.†; Grunenthal, Port.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Tilarco *Coronet, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Tilarin *Sanofi-Aventis, Austria†; Sanofi-Aventis, Ital.*
Nedocromil sodium (p. 1216·2).
Allergic rhinitis.

Tilatil *Roche, Braz.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders.

Tilavist *Sanofi-Aventis, Austria; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Port.; Teofarma, Spain; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.†*
Nedocromil sodium (p. 1216·2).
Allergic conjunctivitis; allergic eye disorders.

Tilazem *Elea, Arg.; Pfizer, Chile; Pfizer, Mex.; Pfizer, S. Afr.; Pfizer, Venez.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; reduction of ciclosporin nephrotoxicity following renal transplant.

Tilcin *Atral, Port.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Tilcitin *Europharma, Denm.; Meda, Gr.; Roche, Gr.*
Tenoxicam (p. 136·2).
Musculoskeletal and joint disorders; inflammation; pain; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Tilcotil *Meda, Belg.; Roche, Chile; Meda, Denm.; Roche, Fin.†; Meda, Fr.; Roche, Hong Kong†; Teva, Hung.; Roche, Indon.; Meda, Ital.; Chugai, Jpn†; Roche, Malaysia; Roche, Mex.†; Valeant, NZ; Roche, Philipp.†; Meda, Port.; Roche, S.Afr.†; Meda, Switz.; Roche, Thai.†; Roche, Turk.*
Tenoxicam (p. 136·2).
Gout; pain; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; dysmenorrhoea.

Tildiem *Sanofi-Aventis, Belg.; Chemopharma, Chile; 2care4, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Switz.†; Ulkar, Turk.†; Sanofi-Aventis, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension; arrhythmias; myocardial ischaemia.

Tildomet *Greenpharma, Braz.†*
Methyldopa (p. 1431·1).
Hypertension.

Tilekin *Kinder, Braz.†*
Paracetamol (p. 115·1).
Pain; fever.

Tilene *Francia, Ital.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Tilexim *Caber, Ital.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Tilferan *Vocate, Gr.*
Etidronate disodium (p. 1182·3).
Paget's disease of bone; osteoporosis.

Tilflam *Dexa, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Tili Comp *1A, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilia Fe *Watson, USA.*
21 Tablets, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
Triphasic oral contraceptive.

Tilicomp *Betapharm, Ger.*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilidin *Ratiopharm, Ger.*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilidin comp *Aliud, Ger.†; Axcount, Ger.†; CT, Ger.†; Hexal, Ger.†; Stada, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilidin N *Sandoz, Ger.†; Winthrop, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilidin plus *Ratiopharm, Ger.*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilidin-saar *MIP, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilidon *Interbat, Indon.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Tilios *Microsules, Arg.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Tili-Puren *Actavis, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tiliros *Labofarm, Pol.*
Ascorbic acid (p. 2110·3); rose flower (p. 2607·1); tilia (p. 2631·3).
Cough; sore throat.

Tilium *Janssen-Cilag, Venez.*
Domperidone (p. 1838·1).
Gastrointestinal motility disorders; gastro-oesophageal reflux; nausea and vomiting.

Tiliv *Ativus, Braz.†*
Black currant (p. 2458·1).

Tiliv L *Ativus, Braz.*
Borage oil (p. 2459·2).

Tilker *Sanofi-Aventis, Denm.†; Sanofi-Aventis, Port.†; Sanofi-Aventis, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Tilko *Kocak, Turk.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Till *Amnol, Ital.*
Triclosan (p. 1773·2); alkylamidobetaine.
Personal hygiene.

Tilmat *Douglas, NZ.*
⊗Timolol maleate (p. 1513·2).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Tilmetin *Mavi, Mex.*
Phloroglucinol (p. 2588·2); trimethylphloroglucinol (p. 2588·2).

Tilnalox *CT, Ger.†*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tilnoxcam *TO-Chemicals, Thai.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Tilodene *Alphapharm, Austral.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Tilodol *Sandoz, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tilodrin *Meyer, Venez.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tiloetca Combi *Tillomed, UK.*
Etidronate disodium (p. 1182·3); calcium carbonate (p. 1824·3).
Osteoporosis.

Tilofyl *Tillomed, UK.*
⊗Fentanyl (p. 60·1).
Pain.

Tiloket *Tillomed, UK.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea.

Tilomix *Nufarindo, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); noscapine (p. 1670·3); chlorphenamine maleate (p. 620·3).
Cough or pain due to allergy.

Tilonax *Cifarma, Braz.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Tilopin *Unison, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Thrombosis prophylaxis; peripheral vascular disease; diabetic retinopathy.

Tiloptic *MSD, Israel.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Tiloryth *Tillomed, UK.*
Erythromycin (p. 291·2).
Bacterial infections.

Tiloxican *Hexal, Braz.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tilsan *Otto, Indon.*
Maprotiline hydrochloride (p. 433·3).
Depression.

Tilstigmin *Tablets, India.*
Neostigmine bromide (p. 687·2) or neostigmine metilsulfate (p. 687·2).
Myasthenia gravis.

Tiltis *Apotex, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Tilugen *Neo Quimica, Braz.*
Cloperastine fendizoate (p. 1659·2).

Tilur *Drossapharm, Switz.*
Acemetacin (p. 16·3).
Musculoskeletal, joint, and peri-articular disorders; superficial thrombophlebitis.

TIM *Seroyal, Canad.†*
Vitamins; zinc (p. 2126·1).

Timab
Note: this name may be used for preparations of different composition.
LKM, Arg.
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia; gastrointestinal stromal tumours.

Timabak *Agepha, Austria†; Thea, Belg.; Allergan, Braz.; Pfizer, Chile†; Thea, Fr.; Pharmex (Φαρμεξ), Gr.; Thea, Hong Kong; Thea, Philipp.; Thea, Port.; Pfizer, Singapore; Thea, Spain; Santa, Turk.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timacar *MSD, Denm.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Timacor *Gerda, Fr.*
⊗Timolol maleate (p. 1513·2).
Hypertension; angina pectoris; myocardial infarction.

Timact *Fahrenheit, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Timadren *Hemofarm, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Tim-Ak *Akorn, Canad.*
⊗Timolol maleate (p. 1513·2).
Raised intra-ocular pressure.

Tim-Alcon *Alcon, Gr.*
⊗Timolol maleate (p. 1513·2).

Timarol *Laboratorios Chile, Chile.*
Tramadol hydrochloride (p. 139·2).
Pain.

Timarol-Par *Laboratorios Chile, Chile.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Timasen *Ache, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Timazol *Sriprasit, Malaysia; Sriprasit, Thai.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Time Action B Complex with C *Hall, Canad.†*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Time Rel Mult Vit and Min *Lee-Adams, Canad.†*
Vitamins; minerals.

Time Rel Vit C *Lee-Adams, Canad.†*
Vitamin C (p. 2110·3).

Time Repair *Shaklee, Canad.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Time Zone *Estee Lauder, Canad.*
SPF 15 for dry skin: Avobenzone (p. 1695·1); octisalate (p. 1715·2).
Sunscreen.

Estee Lauder, Canad.
SPF 15 for normal skin; SPF 15 lotion: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Time-Cee *Danlex, Philipp.*
Syrup: Ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3); chlorella growth factor (p. 2475·3).
Vitamin C deficiency.

Danlex, Philipp.
Tablets: Ascorbic acid (p. 2110·3); calcium phosphate dibasic (p. 1783·3).
Vitamin C deficiency.

Timecef *Sanofi-Aventis, Austria†; Lepetit, Ital.; Aventis, NZ.†*
Cefodizime sodium (p. 242·2).
Lidocaine hydrochloride (p. 1988·2) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

Timed *Bausch & Lomb, Arg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timed Action Balanced B *Hall, Canad.†*
Vitamin B substances (p. 2102·3).

Timed D *Bausch & Lomb, Arg.*
⊗Timolol maleate (p. 1513·2); dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Timed Release B Complex *GFR, Canad.†*
Vitamin B substances (p. 2102·3).

Timed Release B Complex with Vitamin C *GFR, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Timed Release Ultra Mega *General Nutrition, Canad.*
A range of vitamin and mineral preparations.

Timeless *Norman, Canad.*
SPF 20: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Timentin *GSK, Austral.; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, China; GSK, Cz.†; GSK, Gr.; GSK, Hong Kong; GSK, India†; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, Turk.; GSK, UK; GSK, Ukr.; SmithKline Beecham, USA.*
Ticarcillin sodium (p. 378·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Timet *Universal, Hong Kong.†*
Cimetidine (p. 1827·1).

Timewise Day Soultion Sunscreen *Kay, Canad.*
SPF 35: Octisalate (p. 1715·2); oxybenzone (p. 1715·3); avobenzone (p. 1695·1); homosalate (p. 1705·1); octocrilene (p. 1715·2).
Sunscreen.

Timewise Sunscreen *Kay, Canad.†*
SPF 25: Homosalate (p. 1705·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Timezol *Penn, Arg.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Timi *Sriprasit, Thai.*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Fungal skin and nail infections with inflammation.

Timicon *MSD, Ital.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Ocular hypertension; glaucoma.

Timipen *Interbat, Indon.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Bacterial infections.

Timisol *Sandoz, Switz.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timivudin *Landsteiner, Mex.†*
Zidovudine (p. 1024·2).
HIV infection.

Timizol *Sel-J, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Timlatan *Jelfa, Irl.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timobrim *Atlas, Arg.*
⊗Brimonidine tartrate (p. 2004·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timo-COMOD *Croma, Austria†; Ursapharm, Cz.; Horus, Fr.; Ursapharm, Ger.; Ursapharm, Malaysia; Ursapharm, Neth.; Ursapharm, Pol.†; Ursapharm, Singapore; Ursapharm, Switz.; Biem, Turk.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timod *Visufarma, Ital.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Timodine *Alliance, Irl.; Reckitt Benckiser, UK.*
⊗Nystatin (p. 590·3); hydrocortisone (p. 1640·1).
Infected skin disorders.

Timodose *Pharmanel, Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Timodrop *Biolab, Thai.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

TimoEDO *Mann, Ger.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timoferol *Elerte, Fr.*
Ferrous sulfate (p. 2062·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Timofluid *Thea, Irl.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timoftal *Agepha, Austria; Sanovel, Turk.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timoftol *Frosst, Spain.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timogel *Thea, Austria; 2care4, Denm.; Thea, Ital.; Thea, Neth.; Thea, Port.; Thea, Spain; Thea, Switz.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timoglau *Edol, Port.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension.

Timoglau Plus *Edol, Port.†*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Timoglobulina *Genzyme, Arg.; Genzyme, Chile; Genzyme, Port.; Genzyme, Spain.*
An antithymocyte immunoglobulin (p. 1939·2).
Aplastic anaemia; graft-versus-host disease; transplant rejection.

Timohexal *Hexal, Austria; Hexal, Cz.; Hexal, Ger.†; Hexal, Pol.†; Hexal, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timo-Komod *Ursapharm, Rus.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timolabak *Farmila, Ital.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timolast *Alcon, Malaysia; Alcon, Thai.†*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timolen *Davi, Port.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timoler *Lersan, Arg.†*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension.

Timolide *Merck, USA.†*
⊗Timolol maleate (p. 1513·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Timolo *Bell, India.†*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timolpres *Vannier, Arg.*
⊗Timolol (p. 1513·2).
Glaucoma.

Timolux *Tubilux, Ital.; AFT, NZ.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timomann *Mann, Ger.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timoneo *Neo Quimica, Braz.*
⊗Timolol maleate (p. 1513·2).

Timonil *Desitin, Cz.; Europharma, Denm.; Desitin, Ger.; Desitin, Hung.; Desitin, Israel; Desitin, Pol.; Desitin, Switz.*
Carbamazepine (p. 512·2).
Epilepsy; diabetic neuropathy; alcohol withdrawal syndrome; bipolar disorder; neuralgias; multiple sclerosis; mania; diabetes insipidus.

Timonor *Aventis, Gr.*
⊗Piretanide (p. 1470·3).

Timo-optal *Olan-Kemed, Thai.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timop *Laboratorios Chile, Chile.†*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Tim-Ophtal *Agepha, Austria; Winzer, Ger.; Sanbe, Indon.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timo-POS *Ursapharm, Belg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Timoptic *MSD, Arg.; MSD, Austria; Merck Frosst, Canad.; MSD, Pol.; MSD, Switz.; MSD, Turk.; Valeant, USA.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timoptol *MSD, Austral.; MSD, Belg.; MSD, Braz.; MSD, China; MSD, Cz.; Europharma, Denm.; MSD-Chibret, Fr.; MSD, Hong Kong; MSD, Irl.; MSD, Ital.; Santen, Jpn; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, NZ; MSD, Philipp.; Chibret, Port.; MSD, S.Afr.; MSD, Singapore; MSD, Thai.; MSD, UK; MSD, Venez.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Timoptolgel *MSD, Belg.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timoptol-XE *MSD, Chile.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timosan *Santen, Denm.; Santen, Fin.; Santen, Norw.; Santen, Swed.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timosil *Silom, Thai.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timosol *Bilim, Turk.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timosopt *MSD, Denm.†; MSD, Port.†*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma.

Timo-Stulln *Stulln, Ger.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timotein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Timotem *Bilim, Turk.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension.

Timo-Vision *OmniVision, Ger.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Timox *Desitin, Ger.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Timozzard *Pizzard, Mex.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Timpacil *Diba, Mex.†*
⊗Neomycin (p. 329·3); dexamethasone (p. 1630·3).
Infected ear disorders.

Timpilo *MSD, Austral.†; Vianex (Βιανεξ), Gr.; MSD, Hong Kong†; MSD, Israel†; MSD, NZ.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma; ocular hypertension.

Timuss-Kit *Ximena Polanco, Chile.*
Honey (p. 2072·1); thyme (p. 2630·2); propolis (p. 2597·3).

Timuss-Kit (sin azucar) *Ximena Polanco, Chile.*
Thyme (p. 2630·2); propolis (p. 2597·3).

Tina-A *2M, Thai.*
Tretinoin (p. 1725·2).
Acne; skin hyperpigmentation.

Tinacef *Richmond, Arg.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tinactin *Schering-Plough, Canad.; Schering-Plough, Philipp.; Assos, Turk.; Schering-Plough, USA.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tinaderm *MSD, Austral.; Schering-Plough, Chile†; Schering-Plough, Gr.; Fulford, India; MSD, Irl.; Schering-Plough, Mex.; Schering-Plough, S.Afr.; Schering-Plough, UK; Schering-Plough, Venez.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tinaderm Extra *Schering-Plough, Austral.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Tinaderme *Plough, Port.*
Tolnaftate (p. 596·1).
Fungal skin and nail infections.

Tinaderm-M *Schering-Plough, Irl.†; Schering-Plough, UK.†*
Tolnaftate (p. 596·1); nystatin (p. 590·3).
Fungal skin and nail infections.

Tinalox *Sandoz, Belg.*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Tinasil *Alphapharm, Austral.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections of the skin and nails.

Tinasin *Giempi, Venez.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; ischaemic heart disease; cerebral ischaemia.

Tinasol *Fischer, Israel.†*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tinatox *Riemser, Ger.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tinax *Eurofarma, Braz.*
⊗Epoetin (p. 1141·1).
Anaemias.

Tinaxina *ISA, Arg.*
Oxybutynin (p. 2361·2).
Bladder hyperactivity.

Tinazol
Note: this name may be used for preparations of different composition.
Hovid, Singapore.
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Hovid, Hong Kong.†
Miconazole (p. 588·3).

Tinazole *General Drugs, Thai.*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis.

TinBen *Ferndale, USA.*
Barrier preparation.

TinCoBen *Ferndale, USA.*
Barrier preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Tincture Sahakarn *United Drug, Thai.*
Iodine (p. 2336·3); potassium iodide (p. 2336·3).
Skin disinfection.

Tindamax *Presutti, USA.*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis; trichomoniasis.

Tinder *Sanofi-Aventis, Gr.*
Cimetidine (p. 1827·1).

Tindol *Ranbaxy, Malaysia.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Tindortec *Tecnofarma, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tineafax
Note: this name may be used for preparations of different composition.
Ascent, Austral.
Tolnaftate (p. 596·1).
Tinea pedis.

Tinéafine *Spirig, Switz.*
Terbinafine hydrochloride (p. 593·3).
Fungal, skin, scalp, and nail infections.

Tineal *Reddy, Hung.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Tinelle *Silesia, Chile.*
21 Tablets, dienogest (p. 2267·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Tineril *Gedeon Richter, Denm.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Tineuron *Lapi, Indon.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Tinexa *Aspen, Austral.*
Cabergoline (p. 899·3).
Hyperprolactinaemia; inhibition of lactation.

Ting *Insight, USA.*
Powder spray: Miconazole nitrate (p. 589·1).
Fungal skin infections.

Insight, USA.
Cream; topical spray: Tolnaftate (p. 596·1).
Fungal skin infections.

Tiniasil *Loeffler, Mex.*
Ketoconazole (p. 585·3).
Vulvovaginal candidiasis.

Tiniazol *Liferpal, Mex.*
Ketoconazole (p. 585·3).
Fungal skin, nail, and vaginal infections.

Tiniba *Zydus, India; Cadila, Rus.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections; trichomoniasis; amoebiasis; giardiasis.

Tinidafyl *Jagsonpal, India.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Tinidafyl Plus *Jagsonpal, India.*
Tinidazole (p. 949·2); diloxanide furoate (p. 931·2); dimeticone (p. 2209·3).
Amoebiasis.

Tinidazol Compuesto *Laboratorios Chile, Chile.*
Tinidazole (p. 949·2); miconazole (p. 588·3).
Vaginal candidiasis; trichomoniasis.

Tinifas *Cipla, India.*
Tinidazole (p. 949·2).

Tinijing *Chung-Hwa, China.*
Tinidazole (p. 949·2).
Bacterial infections; protozoal infections.

Tinin *Geolab, Braz.*
Tioconazole (p. 595·3); tinidazole (p. 949·2).

Tinkair *Italchimici, Cz.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; nasal polyps.

T-Inmun *Biomedical, Chile; Mediderm, Chile.*
Tacrolimus (p. 1968·3).
Atopic eczema; transplant rejection.

Tinnic *Nicholas, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Tinnitin *Sanova, Austria.*
Caroverine hydrochloride (p. 2471·2).
Smooth muscle spasm; tinnitus.

Tinoin *Okasa, Thai.*
Isotretinoin (p. 1706·2).
Acne.

Tinok AF *Rekah, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Tinoprost *Verisfield, Gr.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Tinoral *Uniao Quimica, Braz.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Tinox *Gynopharm, Chile; Vivax Gynopharm, Venez.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Tinoxal *Loeffler, Mex.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tinset *Janssen-Cilag, Arg.; Janssen-Cilag, Austria†; Janssen-Cilag, Chile†; Janssen-Cilag, Fr.†; Janssen-Cilag, Gr.; Janssen-Cilag, Indon.; Formenti, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Thai.*
Oxatomide (p. 636·3).
Hypersensitivity reactions; allergic skin disorders; allergic rhinitis; allergic conjunctivitis; pruritus; durticaria.

Tinsole *Erfar, Gr.*
Povidone-iodine (p. 1767·1).

Tinted Lip Balm *Kay, Canad.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3); zinc oxide (p. 1729·1).
Sunscreen.

Tinted Lip Conditioner *MAC, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Tintus *Orion, Fin.*
Guaifenesin (p. 1666·2).
Cough.

Tinver *Pilkington Barnes-Hind, USA.*
Sodium thiosulfate (p. 1576·1); salicylic acid (p. 1719·1); isopropyl alcohol (p. 1758·3).
Pityriasis versicolor.

Tinvista *Cadila, India.*
Tinidazole (p. 949·2).
Protozoal infections.

Tinvista-CF *Cadila, India.*
Tinidazole (p. 949·2); ciprofloxacin (p. 261·1).
Bacterial infections; protozoal infections.

Tinvista-NF *Cadila, India.*
Tinidazole (p. 949·2); norfloxacin (p. 333·3).
Bacterial infections; protozoal infections.

Tiobarbital *Braun, Spain.*
Thiopental sodium (p. 1915·1).
General anaesthesia; epilepsy.

Tiobec *Laborest, Ital.*
Thioctic acid (p. 2629·1); vitamins.
Nutritional supplement; neuropathies.

Tiobec Crema *Laborest, Ital.*
Thioctic acid (p. 2629·1).
Premature skin ageing.

Tiocalmina *Polifarma Benessere, Ital.*
Sulfogaiacol (p. 1678·1); dropropizine (p. 1662·2).
Cough.

Tiocan *Toprak, Turk.*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Tiocell *Sanovel, Turk.*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Tiocetam *Arterium, Ukr.*
Piracetam (p. 393·3); thiotriazoline (p. 2629·3).
Cerebrovascular disorders; encephalopathy; alcohol withdrawal syndrome.

Tiochax *Plusandex, Venez.*
Thiocolchicoside (p. 2026·2).
Muscle spasm.

Tioconax *Delta, Braz.*
Tioconazole (p. 595·3).
Fungal infections.

Tiocosol *OFF, Ital.†*
Sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Catarrh; cough.

Tioctan
Note: this name may be used for preparations of different composition.
Purissimus, Arg.; Rothpharma, Austria.
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Tioctic *Temis, Arg.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Tiodaron *Arterium, Ukr.*
Amiodarone hydrochloride (p. 1300·1); thiotriazoline (p. 2629·3).
Arrhythmias.

Tioderma
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Tioconazole (p. 595·3).
Fungal skin infections.

Tiodin *TO-Chemicals, Singapore.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis.

Tiodrix *Merck Serono, Arg.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Tiof *Saval, Chile.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Tiof Plus *Saval, Chile.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Tiofen *Sanovel, Turk.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Tiofeniclin *Sanofi Synthelabo, Mex.†*
Thiamphenicol (p. 376·3).
Bacterial infections.

Tiofort *Amnol, Ital.*
Thioctic acid (p. 2629·1); linoleic acid (p. 2509·2); asparagine (p. 2050·3); vitamins; minerals.
Nutritional supplement.

Tioguaialina *Montefarmaco, Ital.*
Sulfogaiacol (p. 1678·1).
Cough; catarrh.

Tiola *Pyridam, Indon.*
Thioctic acid (p. 2629·1); biotin (p. 2052·2); chromium (p. 2055·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Tiomicol *Panalab, Arg.*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Tionamid *Kocak, Turk.*
Protionamide (p. 345·1).
Tuberculosis.

Tionazen *Cazi, Braz.*
Tioconazole (p. 595·3).
Fungal infections.

Tioner *Gebro, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tioneurol *Richmond, Arg.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Tiopex *Spectrum, UK.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Tiopram *Biofarma, Turk.†*
Escitalopram (p. 416·2).

Tiorelax *Santa, Turk.*
Thiocolchicoside (p. 2026·2).
Skeletal muscle spasm.

Tiorfan *Bago, Braz.; Bioprojet, Fr.; Abbott, Ger.†; Ferrer, Port.; Ferrer, Spain.*
Racecadotril (p. 1881·3).
Diarrhoea.

Tiorfanor *Bioprojet, Fr.*
Racecadotril (p. 1881·3).
Diarrhoea.

Tiorfast *Bioprojet, Fr.*
Racecadotril (p. 1881·3).
Diarrhoea.

Tiorfix *Takeda, Belg.; Abbott, Ital.*
Racecadotril (p. 1881·3).
Diarrhoea.

Tiorilene *Merck, Ital.†*
Thiocolchicoside (p. 2026·2).
Neuromuscular pain; parkinsonism; spasticity.

Tiosalis *Teva Tuteur, Arg.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Tioside *Caber, Ital.*
Thiocolchicoside (p. 2026·2).
Neuromuscular pain; parkinsonism; spasticity.

Tiotau *Damor, Ital.*
Taurosteine.
Respiratory-tract congestion.

Tiotil *Nevada, Swed.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Tiotrax *EMS, Braz.*
Tinidazole (p. 949·2); tioconazole (p. 595·3).

Tiova *Cipla, India.*
Tiotropium bromide (p. 1238·1).
Obstructive airways disease.

Tioxad *Fahrenheit, Indon.*
Pentoxifylline (p. 1465·3).
Intermittent claudication.

Tip *Farmalider, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tipac *Mintlab, Chile.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Tiparol *BMM, Swed.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tiperin *Sanitas, Chile.*
Amitriptyline (p. 401·1); chlordiazepoxide (p. 1044·2).
Depression associated with anxiety.

Tipidin *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Ticlopidine hydrochloride (p. 1512·1).
Stroke prophylaxis.

Tipidine *Seven Stars, Thai.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis; diabetic retinopathy; intermittent claudication; unstable angina pectoris.

Tipkin *TP, Thai.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Tiplac
Note: this name may be used for preparations of different composition.
Roemmers, Venez.
Haloperidol (p. 1077·1) or haloperidol decanoate (p. 1077·2).
Psychoses; behaviour disorders; Tourette syndrome.

Tipo II *Gerolymatos, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Tipodex *Ern, Spain.†*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux.

Tipol *Carysfort, Irl.*
Paracetamol (p. 115·1).
Pain; fever.

Tipotaf *Vitamed, Israel.*
Sodium chloride (p. 1795·1).
Nasal congestion.

Tiptipot Ferripel + D *CTS, Israel.*
Colecalciferol (p. 2113·1); iron polymaltose (p. 2077·2).
Iron-deficiency anaemia; vitamin D supplement.

Tiptipot Ibutaf *CTS, Israel.*
Ibuprofen (p. 68·2).
Pain; fever.

Tipuric *Clonmel, Irl.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Tirabicin *Kleva, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Tiracetin *Stada, Denm.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Tiracrin *Geymonat, Ital.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Tiradine *British Dispensary, Thai.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders.

Tiran *Teva, Israel.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract disorders with viscous mucus.

Tirbas *Alter, Spain.*
Levetiracetam (p. 531·1).
Epilepsy.

Tirdicef *Bernofarm, Indon.*
Cefotaxime (p. 244·1).
Bacterial infections.

Tirgon *McNeil, Ger.*
Tablets: Bisacodyl (p. 1821·1).
Constipation.

Tiritek Allergy *Cipla Chanelle, Irl.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Tiriz *Lapi, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Tirizin *GL Pharma, Austria.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Tirizine *Bright Future, Hong Kong.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Tirlor *Sandoz, Gr.; Sandoz, Malaysia; Sandoz, Singapore†; Sandoz, Thai.; Sandoz, Venez.*
Loratadine (p. 633·2).
Hypersensitivity reactions; allergic rhinitis; allergic skin disorders; urticaria; hay fever; asthma (adjunct).

Tirmaclo *Mersifarma, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Tirocal *Cryopharma, Mex.*
Calcitriol (p. 2113·1).
Hypocalcaemia; hypoparathyroidism; renal osteodystrophy; osteoporosis; rickets.

Tirocular *Angelini, Ital.; Angelini, Port.*
Acetylcysteine (p. 1652·2).
Dry eyes; corneal disorders.

Tirodril *Estedi, Spain.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Tirogen *Genzyme, Ukr.*
Thyrotropin alfa (p. 2346·1).
Detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients.

Tiroide Amsa *Amsa, Ital.*
Levothyroxine sodium (p. 2339·1); liothyronine sodium (p. 2342·3).
Hypothyroidism.

Tiroide Vister *Teofarma, Ital.*
Thyroglobulin (p. 2345·3).
Hypothyroidism.

Tiroidin *Neo Quimica, Braz.*
Levothyroxine sodium (p. 2339·1).

Tiroidine *Sanofi-Aventis, Mex.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Tiroler Steinöl *Tiroler, Austria.*
Yellow soft paraffin (p. 2212·1); yellow beeswax (p. 2170·2); hydrous wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Skin disorders.

Tiromel *Abdi, Turk.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism.

Tiropa *Rotta, Port.*
Ticlopidine hydrochloride (p. 1512·1).

Tirosint *Amsa, Ital.; IBSA, Neth.; IBSA, Switz.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroid cancer.

Tirotax *Sandoz, Hung.; Sandoz, Mex.; Sandoz, Neth.; Sandoz, Pol.†; Hikma, Rus.; Sandoz, Venez.*
Cefotaxime sodium (p. 244·1).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tirotein *Teingro, Arg.*
Amino acids.
Dietary supplement.

Tirovarina *Biol, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders.

Tirovel *Duncan, Arg.*
Piroxicam (p. 125·3).
Inflammation; pain.

Tirs *Almus, Ital.*
Benzalkonium chloride (p. 1737·1); hypromellose (p. 2189·2).
Eye disinfection; dry eyes.

Tirselon *Zekides, Gr.*
Tobramycin sulfate (p. 380·2).
Bacterial eye infections.

Tisacef *Metiska, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Tisacid *Alkaloida, Hung.; ICN, Rus.*
Hydrotalcite (p. 1845·2).
Gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer; gastric hyperacidity.

Tisalud *Veropharm, Rus.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm; spasticity.

Tisamid *Orion, Fin.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Tisana Kelemata *Kelemata, Ital.*
Granules; tablets: Senna (p. 1885·1).
Constipation.

Kelemata, Ital.
Tea; teabags: Senna (p. 1885·1); couch-grass (p. 2487·2); guaiacum (p. 2523·1); hyssop (p. 2530·3); parietaria; peppermint leaf (p. 1877·1); sarsaparilla (p. 2610·3); aniseed (p. 2444·2); melissa (p. 2552·3).
Constipation.

Tisane antirhumatismale *Sidroga, Switz.*
Spearmint (p. 2621·2); passion flower (p. 2584·1); salix (p. 129·2).
Rheumatism.

Tisane calmante pour les enfants *Sidroga, Switz.*
Valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3); orange flowers (p. 2575·3); passion flower (p. 2584·1).
Nervous excitement; sleep disorders.

Tisane contre les refroidissements *Sidroga, Switz.*
Rose fruit (p. 2607·1); sambucus (p. 2609·3); chamomile (p. 2474·1); tilia (p. 2631·3); wild thyme (p. 2648·1).
Cold symptoms.

Tisane contre le toux irritative *Sidroga, Switz.*
Mallow (p. 2549·2).
Cough.

Tisane D'Ars *Dietetique et Sante, Fr.†*
Centaury (p. 2473·2); sage (p. 2608·3); couch-grass (p. 2487·2); althaea (p. 2438·3); senna (p. 1885·1); aloes (p. 1816·1); rhapontic rhubarb (p. 1884·2); anhydrous sodium sulfate (p. 1888·1).
Constipation.

Tisane Diurétique *Sidroga, Switz.*
Birch leaf (p. 2457·3); bean pods; urtica (p. 2639·3); equisetum (p. 2500·1).
Urinary-tract disorders.

Tisane des Familles *Merck Medication Familiale, Fr.†*
Senna (p. 1885·1).
Constipation.

Tisane favorisant l'allaitement *Sidroga, Switz.*
Aniseed (p. 2444·2); fennel (p. 2503·2); caraway (p. 2470·2); melissa (p. 2552·3).
Lactation stimulant.

Tisane Franklin *Densmore, Fr.†*
Senna (p. 1885·1).
Constipation.

Tisane Garfield *Densmore, Fr.†*
Senna (p. 1885·1); boldo (p. 2458·3).
Constipation.

Tisane hépatique et biliaire *Sidroga, Switz.*
Cynara (p. 2490·3); boldo (p. 2458·3); taraxacum (p. 2625·3); milk thistle (p. 1561·1); peppermint leaf (p. 1877·1); achillea (p. 2427·3).
Digestive system disorders.

Tisane Hépatique de Hoerdt *Iderne, Fr.†*
Absinthium (p. 2426·1); achillea (p. 2427·3); agrimony (p. 2432·3); boldo (p. 2458·3); centaury (p. 2473·2); couch-grass (p. 2487·2); menyanthes (p. 2554·2); sage (p. 2608·3).
Liver and biliary-tract disorders.

Tisane laxative *Sidroga, Switz.*
Fennel (p. 2503·2); senna (p. 1885·1); star anise (p. 2622·1); liquorice (p. 1853·2).
Constipation.

Tisane pectorale et antitussive *Sidroga, Switz.*
Sage (p. 2608·3); althaea (p. 2438·3); fennel (p. 2503·2); iceland moss (p. 2531·2); red-poppy petal (p. 2207·3); plantain (p. 2592·3); star anise (p. 2622·1); liquorice (p. 1853·2); thyme (p. 2630·2).
Cough; respiratory-tract congestion.

Tisane pectorale pour les enfants *Sidroga, Switz.*
Althaea (p. 2438·3); cowslip flower (p. 2596·2); plantain (p. 2592·3); liquorice (p. 1853·2); thyme (p. 2630·2).
Cold symptoms.

Tisane pour le coeur et la circulation *Sidroga, Switz.*
Birch leaf (p. 2457·3); motherwort (p. 2564·2); spearmint (p. 2621·2); melissa (p. 2552·3); crataegus (p. 2488·1).
Cardiac and circulatory disorders.

Tisane pour l'estomac *Sidroga, Switz.*
Calamus (p. 2464·2); chamomile (p. 2474·1); spearmint (p. 2621·2); melissa (p. 2552·3); achillea (p. 2427·3); centaury (p. 2473·2).
Digestive-system disorders.

Tisane pour nourissons et enfants *Sidroga, Switz.*
Fennel (p. 2503·2); chamomile (p. 2474·1); tilia (p. 2631·3); melissa (p. 2552·3); peppermint leaf (p. 1877·1); vervain (p. 2645·1).
Flatulence.

Tisane pour les problemes de prostate *Sidroga, Switz.*
Urtica (p. 2639·3); peppermint leaf (p. 1877·1); ginger (p. 1844·1); clove (p. 2481·2); cinnamon (p. 2479·2).
Prostate disorders.

Tisane pour les reins et la vessie *Sidroga, Switz.*
Bearberry (p. 2453·2); birch leaf (p. 2457·3); Java tea (p. 2536·3); lovage root (p. 2545·3); peppermint leaf (p. 1877·1); juniper (p. 2537·1).
Urinary-tract disorders.

Tisane pour le sommeil et les nerfs *Sidroga, Switz.*
Valerian (p. 2640·2); lupulus (p. 2546·1); spearmint (p. 2621·2); melissa (p. 2552·3); orange flower (p. 2575·3).
Nervous excitation; sleep disorders.

Tisane Provençale no 1 *Tisane Provencale, Fr.*
Senna (p. 1885·1); althaea (p. 2438·3).
Constipation.

Tisane Provencale no 1 *Uhlmann-Eyraud, Switz.*
Senna (p. 1885·1); althaea (p. 2438·3).
Constipation.

Tisane Provençale no 2 *Tisane Provencale, Fr.†*
Equisetum (p. 2500·1); ash (p. 2450·1); erica cinerea flower; meadowsweet (p. 2550·2); fucus (p. 2612·1).
Constipation.

Tisane Provençale no 3 *Tisane Provencale, Fr.†*
Red vine (p. 2521·3); shepherd's purse (p. 2614·2); hamamelis (p. 2523·3).
Venous insufficiency; haemorrhoids.

Tisane Provençale no 4 *Tisane Provencale, Fr.†*
Crataegus (p. 2488·1); tilia (p. 2631·3); passion flower (p. 2584·1); vervain (p. 2645·1); mint (p. 2621·2).
Nervous disorders; insomnia.

Tisane Provençale no 5 *Tisane Provencale, Fr.†*
Aniseed (p. 2444·2); coriander (p. 2486·3); achillea (p. 2427·3); thyme (p. 2630·2).
Digestive disorders.

Tisane Provençale no 6 *Tisane Provencale, Fr.†*
Black currant (p. 2458·1); ash (p. 2450·1); meadowsweet (p. 2550·2).
Joint pain.

Tisane Saint-Urbain *Iderne, Fr.†*
Senna (p. 1885·1); althaea (p. 2438·3); mallow (p. 2549·2).
Constipation.

Tisane de Santé *Lehning, Fr.†*
Ash (p. 2450·1); peppermint leaf (p. 1877·1); couch-grass (p. 2487·2); meadowsweet (p. 2550·2); fumitory (p. 2508·2); solidago (p. 2620·1).
Renal and digestive disorders.

Tisasen *ICN, Rus.*
Senna (p. 1885·1).
Constipation.

Valeant, Hung.
Sennosides A and B (p. 1885·2).
Bowel evacuation; constipation.

Tisept *Seton, Israel; SSL, Singapore; Medlock Medical, UK.*
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Skin, burn, and wound disinfection.

Tisercin *Egis, Cz.; Egis, Hung.*
Levomepromazine maleate (p. 1079·3).
Psychoses.

Egis, Pol.; Egis, Rus.; Egis, Ukr.
Levomepromazine (p. 1079·3).
Psychoses; epilepsy; mixed anxiety depressive states; pain; general anaesthesia; anxiety disorders; obsessive-compulsive disorder; insomnia; agitation; bipolar disorder; depression; neuroses; pruritus.

Tisit *Pfeiffer, USA.*
Pyrethrins (p. 2161·1); piperonyl butoxide (p. 2160·2).
Pediculosis.

Tismafam *Metiska, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Tismalin *Metiska, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Tismamisin *Metiska, Indon.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Tismazol *Metiska, Indon.*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Tisobrif *Chiesi, Spain.†*
Isoniazid (p. 311·2); rifampicin (p. 350·3). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Tisogen *Bioproforma, Arg.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; small-cell lung cancer.

Tisolon *Nufarindo, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Tison
Note: this name may be used for preparations of different composition.
Landson, Indon.
⊗Methylprednisolone (p. 1642·2).
Oral corticosteroid.

Veropharm, Rus.
Thioridazine (p. 1110·2).
Agitation; alcohol withdrawal syndrome; behaviour disorders; bipolar disorder; depression; pruritus; psychoses; tics.

Tispol Ibu-DD *McNeil, Ger.*
Ibuprofen lysine (p. 68·3).
Fever; pain.

Tisseel *Baxter, Austria; Baxter, Cz.; Baxter, Fin.; Baxter, Gr.; Baxter, Thai.; Baxter, USA.*
Component 1, fibrinogen (p. 1151·3); aprotinin (p. 1133·2); component 2, thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Baxter, Canad.; Baxter, Hong Kong; Immuno, Israel†; Baxter, UK.
1 Vial, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); 1 vial, aprotinin (p. 1133·2); 2 vials, thrombin (p. 1163·2); 1 vial, calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Wounds; haemorrhage; dural sealing.

Baxter, Irl.
1 Vial, clottable protein; factor XIII (p. 1150·3); 1 vial, aprotinin (p. 1133·2); 2 vials, thrombin (bovine) (p. 1163·2); 1 vial, calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Wounds.

Baxter, Neth.; Baxter, Norw.; Baxter, Switz.
Component 1, fibrinogen (p. 1151·3); factor XIII (p. 1150·3); aprotinin (p. 1133·2); component 2, thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Adcock Ingram Critical Care, S.Afr.†
Clottable protein (fibrinogen) (p. 1163·2).
Haemostatic; wounds.

Tisseel Duo *Baxter, Austral.†; Baxter, NZ.*
1 Syringe, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); aprotinin (p. 1133·2); 1 syringe, thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemostasis during surgery; adjunct in colostomy closure.

Tisseel Duo Quick *Baxter, Denm.*
1 Vial, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); aprotinin (p. 1133·2); factor XIII

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 1150·3); plasminogen (p. 1471·3); 1 vial, thrombin (p. 1163·2); calcium chloride (p. 1783·1); On mixing this forms a fibrin glue (p. 1151·2).
Wounds; haemorrhage.

Baxter, Fin.
⊗1 Vial, plasma protein (p. 1159·2); fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); aprotinin (p. 1133·2); 1 vial, thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Baxter, Swed.
⊗1 Vial, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); aprotinin (p. 1133·2); albumin (p. 1130·2); 1 vial, thrombin (p. 1163·2); plasma protein (p. 1159·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Tisseel VH *Eczacibasi-Baxter, Turk.*
Fibrinogen (p. 1151·3); aprotinin (p. 1133·2); thrombin (p. 1163·2); calcium chloride (p. 1783·1).
Haemorrhage.

Tissucol *Baxter, Austria†; Baxter, Cz.; Baxter, Fr.; Baxter, Switz.†*
1 Vial, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); aprotinin (p. 1133·2); 1 vial, thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Baxter Immuno, Arg.
Fibrinogen (p. 1151·3); factor XIII (p. 1150·3); aprotinin (p. 1133·2); thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).

Baxter, Ital.
⊗Plasma protein fraction (p. 1159·2); aprotinin (p. 1133·2); thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Baxter, Neth.
1 Vial, aprotinin (p. 1133·2); 2 vials, calcium chloride (p. 1783·1); thrombin (p. 1163·2); 1 vial, fibrinogen (p. 1151·3); factor XIII (p. 1150·3); fibronectin (p. 2504·2); 1 vial, calcium chloride; on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Tissucol Duo *Baxter, Belg.; Baxter, Spain.*
1 Syringe, aprotinin (p. 1133·2); factor XIII (p. 1150·3); fibrinogen (p. 1151·3); fibronectin (p. 2504·2); plasminogen (p. 1471·3); 1 syringe, calcium chloride (p. 1783·1); thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Baxter, Neth.
1 Vial, aprotinin (p. 1133·2); fibrinogen (p. 1151·3); factor XIII (p. 1150·3); fibronectin (p. 2504·2); 1 vial, calcium chloride (p. 1783·1); thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Baxter, Port.†
1 Vial, aprotinin (p. 1133·2); factor XIII (p. 1150·3); fibrinogen (p. 1151·3); 1 vial, calcium chloride (p. 1783·1); thrombin (p. 1163·2); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage.

Tissucol Duo Quick *Baxter, Austria.†*
1 Vial, fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); aprotinin (p. 1133·2); 1 vial, thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Wounds.

Tissucol Duo S *Baxter, Ger.; Baxter, Switz.†*
⊗1 ampoule: plasma protein fraction (p. 1159·2); fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); aprotinin (p. 1133·2); 1 ampoule: thrombin (p. 1163·2); calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Wounds; haemorrhage.

Tissucol Kit *Baxter, Belg.; Baxter, Rus.*
1 vial, factor XIII (p. 1150·3); fibrinogen (p. 1151·3); fibronectin (p. 2504·2); plasminogen (p. 1471·3); 1 vial, aprotinin (p. 1133·2); 2 vials, thrombin (p. 1163·2); 1 vial, calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Haemorrhage; wounds.

Tissucol-Kit *Baxter, Ger.; Baxter, Hung.*
⊗1 Ampoule: plasma protein fraction (p. 1159·2); fibrinogen (p. 1151·3); fibronectin (p. 2504·2); factor XIII (p. 1150·3); plasminogen (p. 1471·3); 1 ampoule: aprotinin (p. 1133·2); 2 ampoules: thrombin (p. 1163·2); 1 ampoule: calcium chloride (p. 1783·1); on mixing this forms a fibrin glue (p. 1151·2).
Wounds; haemorrhage.

TissuCone *Baxter, Ger.*
Collagen (p. 2483·2).
Haemorrhage.

TissuFleece *Baxter, Ger.*
Collagen (p. 2483·2).
Haemorrhage.

TissuFoil *Baxter, Ger.*
Collagen (p. 2483·2).
Haemorrhage.

Tissulest *Liferpal, Mex.*
Pravastatin sodium (p. 1473·1).
Atherosclerosis; hypercholesterolaemia; cardiovascular risk reduction; cerebrovascular risk reduction.

Tisuderma *Cinfa, Spain.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Skin infections with inflammation.

Tis-U-Sol *Baxter, Canad.; Baxter, USA.*
Electrolytes (p. 1775·1).
Irrigation solution.

Titan
Note: this name may be used for preparations of different composition.
Hexpharm, Indon.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Barnes Hind, Arg.†; Pilkington Barnes-Hind, USA.†
Cleansing solution for hard contact lenses.

Titania Sunblock *Aubrey, Canad.†*
SPF 25: Padimate O (p. 1716·1); titanium dioxide (p. 1725·1).
Sunscreen.

Titanoral *Johnson & Johnson, Fr.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids; capillary fragility.

Titanorein *McNeil, Spain.*
Carrageenan (p. 2176·3); titanium dioxide (p. 1725·1); lidocaine (p. 1988·1).
Haemorrhoids.

Titanoréïne *Johnson & Johnson, Fr.*
Carrageenan (p. 2176·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Titanoreine *Xian-Janssen, China.*
Cream: Carrageenan (p. 2176·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); lidocaine (p. 1988·1).
Anorectal disorders.

Xian-Janssen, China.
Suppositories: Carrageenan (p. 2176·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Titanoréïne Lidocaïne *Johnson & Johnson, Fr.*
Carrageenan (p. 2176·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1); lidocaine (p. 1988·1).
Anorectal disorders.

Titanox *Demo, Gr.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions.

Titenil *Geolab, Braz.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Titho-Gel *Galenica, Gr.*
Progesterone (p. 2300·2).

Titralac *3M, Austral.; Medа, Gr.; 3M, Hong Kong†; 3M, NZ; 3M, S.Afr.†*
Calcium carbonate (p. 1824·3); glycine (p. 2071·2).
Heartburn; dyspepsia; gastric hyperacidity; calcium supplement; peptic ulcer; gastritis.

Nycomed, Norw.; Zuoz, Venez.
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; peptic ulcer; heartburn; dyspepsia.

Titralac Extra Strength *3M, USA.*
Calcium carbonate (p. 1824·3).
Hyperacidity.

Titralac Plus *3M, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).
Hyperacidity.

Titralgan *Berlin-Chemie, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Ti-Tre *Teofarma, Ital.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism.

Titretta Schmerz *Berlin-Chemie, Ger.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Titretta Zäpfchen *Berlin-Chemie, Ger.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Titus *Help, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Tivagil *PP Lab, Thai.*
Tinidazole (p. 949·2).
Protozoal infections; bacterial infections; Helicobacter pylori eradication.

Tivarun *Raform, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Tivicay *ViiV, USA.*
Dolutegravir sodium (p. 974·3).
HIV infection.

Tivilac *Fahrenheit, Indon.*
Vitamins; minerals.
Nutritional supplement for pregnant and lactating women.

Tivirlon *Coup, Gr.*
Lisinopril (p. 1420·3).
Hypertension.

Tivision *Bell, India.†*
Lidocaine hydrochloride (p. 1988·2).
Eye-strain.

Tivitis *Llorens, Spain.†*
⊗Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); tetryzoline hydrochloride (p. 1678·3).
Bacterial eye infections.

Tivomit *Berlico Mulia, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Tivoral *Galenika, Ukr.†*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism; thyroiditis; thyroid cancer.

Tivortin *Yuri, Ukr.*
Arginine aspartate (p. 2049·1) or arginine hydrochloride (p. 2049·1).
Cerebral and peripheral vascular disorders; hypercholesterolaemia; hepatitis; hypoxic conditions; asthenia; metabolic alkalosis; thymus gland disorders; foetal developmental delay; pre-eclampsia.

Tixobar *Justesa Imagen, Arg.*
Barium sulfate (p. 1583·2).
Gastrointestinal radiography.

Tixycolds *Novartis Consumer, UK.†*
⊗Diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Tixycolds Cold and Allergy *Novartis Consumer, UK.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinitis; sinusitis.

Tixylix *Novartis Consumer, UK.*
⊗Glycerol (p. 2517·2).
Cough.

Piramal, India; Aventis, NZ.
Promethazine hydrochloride (p. 638·2); pholcodine citrate (p. 1675·1).
Cough.

Aspen Consumer, S.Afr.†
Promethazine hydrochloride (p. 638·2); pholcodine (p. 1675·1).
Cough and cold symptoms.

Tixylix Chest Rub *Aventis, NZ.*
Cineole (p. 2479·1); pine oil (p. 2591·1); rosemary oil (p. 2607·3); thyme oil (p. 2630·3); terpineol (p. 2627·2).
Nasal congestion.

Tixylix Chesty Cough *Novartis Consumer, Irl.; Novartis Consumer, UK.*
Guaifenesin (p. 1666·2).
Cough.

Tixylix Cough & Cold *Novartis Consumer, UK.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); pholcodine (p. 1675·1).
Cough and cold symptoms.

Tixylix Daytime *Aspen, Austral.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract congestion.

Tixylix Dry Cough *Novartis Consumer, UK.†*
Pholcodine (p. 1675·1).
Cough.

Tixylix Flu *Aspen Consumer, S.Afr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Tixylix Night *Aspen, Austral.†*
Promethazine hydrochloride (p. 638·2); pholcodine (p. 1675·1).
Cough.

Tixylix Night-Time *Novartis Consumer, UK.†*
Promethazine hydrochloride (p. 638·2); pholcodine (p. 1675·1).
Coughs.

Tixyplus *Novartis Consumer, UK.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms.

Tizabri *Nycomed, Ukr.*
Natalizumab (p. 2567·2).
Multiple sclerosis.

Tizacom *Combiphar, Indon.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm; spasticity.

Tizaflex *Actavis, Irl.*
Tizanidine hydrochloride (p. 2026·2).
Spasticity.

Tizalud *KVZ, Ukr.*
Tizanidine (p. 2026·2).
Skeletal muscle spasm.

Tizan *Sun, Thai.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm; spasticity.

Tizanidal *Driburg, Arg.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm.

TizaniTeva *Teva, Pol.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasticity.

Tizanor *Orion, Pol.*
Tizanidine (p. 2026·2).

Tizime *Lupin, Rus.*
Ceftazidime (p. 250·2).
Bacterial infections.

Tizina *Helm, Port.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Tizine *Hua, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Tizorol *Sanofi-Aventis, Mex.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Tizos *Dexa, Indon.*
Ceftizoxime (p. 253·1).
Bacterial infections.

TKC *Royal, Chile.*
Ketoconazole (p. 585·3).
Scalp disorders.

T-Kl *Seroyal, Canad.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3).

TL *Trigen, USA.*
⊗Urea (p. 1727·3).
Dry skin disorders.

TL Icon *Trigen, USA.*
Iron (p. 2073·1); folic acid (p. 2063·1); intrinsic factor (p. 2534·2); vitamin B_{12} (p. 2107·2).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

TL-Assure *Trigen, USA.†*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1).
Dietary supplement.

TL-Assure ONE *Trigen, USA.†*
Vitamins; trace elements; docosahexaenoic acid (p. 1460·1).

TLC Vita *Remed, Philipp.*
Vitamins; minerals; chlorella growth factor (p. 2475·3); taurine (p. 2626·2); lysine (p. 2079·3).
Dietary supplement.

TLC Vita-OB *Scheele, Philipp.*
Vitamins; ferrous fumarate (p. 2060·3).
Iron and vitamin deficiency; iron-deficiency anaemia.

TL-DEX DM *Trigen, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

TL-Hist CM *Trigen, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).

TL-Hist DM *Trigen, USA.*
Brompheniramine maleate (p. 618·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

TLI *Seroyal, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); copper (p. 2057·1); iron (p. 2073·1).

TLM *Seroyal, Canad.*
Vitamin C (p. 2110·3); minerals.

T-long *AWD, Ger.†*
Tramadol hydrochloride (p. 139·2).
Pain.

T-LU *Seroyal, Canad.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Tlusic *Coronet, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

TM Bet *T Man, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

TM Cough Syrup *T Man, Thai.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

TM Dazole *T Man, Thai.*
Tinidazole (p. 949·2).
Bacterial infections; giardiasis; trichomoniasis; Helicobacter pylori eradication; amoebiasis.

TM Dryl *T Man, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

TM Fen *T Man, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

TM Gin *T Man, Thai.†*
Paracetamol (p. 115·1).
Fever; pain.

TM Mycin *T Man, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

T-MA *Seroyal, Canad.*
Vitamin A (p. 2098·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

Tmide *Cadila, India.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

T-Minic *Novartis, India.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract congestion; cold symptoms.

T-Minic Plus *Novartis, India.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract congestion; cold symptoms.

TMP *Mylan, NZ.*
Trimethoprim (p. 381·2).
Bacterial infections of the urinary tract.

TMS *TAD, Ger.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

T3Mycin *Hoe, Singapore.*
Clindamycin phosphate (p. 269·3).
Acne.

TNKase *Roche, Canad.; Genentech, USA.*
Tenecteplase (p. 1510·2).
Myocardial infarction.

T-Nol *Volta, Chile.*
Mefenamic acid (p. 85·3).
Pain.

TO Balm *TO-Chemicals, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain.

TO Cillin *TO-Chemicals, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

TO Corte *TO-Chemicals, Thai.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

TO Gel *TO-Chemicals, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; heartburn; peptic ulcer.

TO Nil *TO-Chemicals, Singapore; TO-Chemicals, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

TO Vir *TO-Chemicals, Thai.*
Zidovudine (p. 1024·2).
HIV infection.

Toa *Wyeth Consumer, Mex.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; nasal congestion.

Tobacin *Aristo, India.*
Tobramycin (p. 380·1).
Bacterial infections.

Tobacoff *Colfarm, Pol.*
Anise oil (p. 2444·3); peppermint oil (p. 1877·1); guarana (p. 2648·2); tormentil (p. 2633·2).
Aid to smoking withdrawal.

Tobazon *Bell, India.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobazon DM *Bell, India.†*
⊗Tobramycin sulfate (p. 380·2); dexamethasone sodium phosphate (p. 1631·2).
Inflammation and infection following cataract surgery.

Tobe *Laboratorios Chile, Chile.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Tobedoce *Jofrain, Mex.†*
Vitamin B substances (p. 2102·3).

Tobel *Nobel, Turk.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobi *Teva Tuteur, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Dompe, Ital.; Novartis, Jpn; Novartis, Neth.; Novartis, Norw.; Novartis, Port.; Novartis, Rus.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, USA.*
Tobramycin (p. 380·1).
Pseudomonal lung infections in cystic fibrosis.

Novartis, Canad.; Novartis, Pol.; Novartis, S.Afr.
Tobramycin sulfate (p. 380·2).
Pseudomonal lung infections in cystic fibrosis.

Tobitil *Ranbaxy, India.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and soft-tissue disorders.

Tobra Gobens *Normon, Spain.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobrabact *Doliage, Fr.; Tubilux, Ital.; Medicom, Neth.; Bausch & Lomb, Spain.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrabiotic *Denver, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrabiotic D *Denver, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections with inflammation.

Tobra-cell *Cell Pharm, Ger.†*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobracin *Latinofarma, Braz.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobracin D *Latinofarma, Braz.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Tobracort *Tetrafarm, Arg.†; Uniao Quimica, Braz.; Antibioticos, Mex.; Vivax Optipharm, Venez.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections with inflammation.

Tobracular *Legrand, Braz.*
Tobramycin (p. 380·1).

Tobra-Day *Phebra, Austral.; AFT, NZ.*
Tobramycin sulfate (p. 380·2).
Bacterial lung infections in cystic fibrosis.

TobraDex *Alcon, China.*
⊗Dexamethasone (p. 1630·3); tobramycin (p. 380·1).
Infected eye disorders.

Tobradex *Alcon, Arg.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Gervasi, Spain; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, Ukr.; Alcon, USA; Alcon, Venez.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders; ear disorders.

Tobradiclo *Pharmadorf, Arg.†*
Tobramycin (p. 380·1); diclofenac sodium (p. 48·3).
Eye inflammation and infection following cataract surgery.

Tobradosa *Dosa, Arg.*
Tobramycin (p. 380·1).

Tobrafen *Zwitter, Gr.; Alcon, Switz.*
Diclofenac sodium (p. 48·3); tobramycin (p. 380·1).
Postoperative eye inflammation; inflammatory eye disorders with infection.

Tobraftal *Teuto, Braz.*
Tobramycin (p. 380·1).

Tobragan *Allergan, Arg.; Allergan, Braz.; Allergan, Chile.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobragan D *Allergan, Arg.; Allergan, Chile; Allergan, Venez.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Tobra-Gobens *Normon, Port.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobral *Lafedar, Arg.; Alcon, Ital.*
Tobramycin (p. 380·1).
Bacterial infections of the eye and external ear.

Tobralep *Lepetit, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobralep DX *Lepetit, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Tobraler *Lersan, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobraler DX *Lersan, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).

Tobralox *EMS, Braz.*
Tobramycin (p. 380·1).

Tobramaxin *Alcon, Ger.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobramina *Lilly, Braz.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobranax *Vivax Optipharm, Venez.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobraneg *Elder, India.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobranet *Tetrafarm, Arg.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobranom *Genom, Braz.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrased *Bilim, Turk.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrasix *Infectopharm, Austria.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobrasol *Ocusoft, USA; Oftalmi, Venez.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrasone
Note: this name may be used for preparations of different composition.
Alcon, Fin.; Alcon, Norw.; Alcon, Swed.
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders; reduction of inflammation and infection following cataract surgery.

Cadila, Rus.
⊗Tobramycin sulfate (p. 380·2); dexamethasone sodium phosphate (p. 1631·2).
Infected inflammatory eye disorders.

Tobrastill *Bruschettini, Ital.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobratlas *Atlas, Arg.*
Diclofenac sodium (p. 48·3); tobramycin (p. 380·1).
Eye inflammation and infection following cataract surgery.

Tobratlas Dexa *Atlas, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Tobra-V *Vista, Philipp.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobravisc *Alcon, Belg.; Alcon, Irl.†; Alcon, UK.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrex *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, Ukr.; Alcon, USA; Alcon, Venez.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrexan *Alcon, Pol.; Alcon, Port.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobridavi *Davi, Port.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrimed *World Medicine, Ukr.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrin
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.
Tobramycin (p. 380·1).
Bacterial eye infections.

Solfran, Mex.
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

Tobrin-D *Laboratorios Chile, Chile.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections with inflammation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Tobrineb *Master, Port.; Chiesi, Spain.*
Tobramycin (p. 380·1).
Pseudomonal lung infections in cystic fibrosis.

Tobrinex *Mecom, Turk.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobropt *Rompharm, Rus.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobrosopt *Polfa Warszawa, Pol.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobryne *Fahrenheit, Indon.†*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tobsin *Ulagay, Turk.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Tobumide *Sunward, Singapore.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Tobutol *General Drugs, Thai.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Tocalfa *Marvecs, Ital.*
dl-Alpha tocoferil acetate (p. 2119·2); vitamin A (p. 2098·3).
Vitamin A and E deficiency.

Tocalm *Prater, Chile.*
Ambroxol (p. 1654·3).
Respiratory-tract congestion.

To-Care *Rekah, Israel.*
⊗Codeine phosphate (p. 40·2); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Tocarlol *TO-Chemicals, Thai.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Tocas *Boehringer Ingelheim, Turk.*
Tamsulosin hydrochloride (p. 2369·1).

Tocasol *Mediderm, Chile.*
Imiquimod (p. 985·2).
Anogenital warts.

Toccata *Kyowa, Jpn.†*
Oxazolam (p. 1093·1).
Anxiety states; premedication; sleep disorders.

Tocef *Bernofarm, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Tocid *TO-Chemicals, Thai.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); simeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2).
Gastric hyperacidity.

Tocinox *Geofman, Philipp.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; incomplete abortion.

Tocitrap *LKM, Arg.*
Temozolomide (p. 865·2).
Malignant glioblastoma.

Toclase *UCB, Fin.†; UCB, Philipp.; UCB, Thai.†*
Pentoxyverine citrate (p. 1672·1).
Cough.

UCB, Hong Kong†; UCB, Turk.
Pentoxyverine hydrochloride (p. 1672·2).
Cough.

Toclase Expectorant *UCB, Fin.†*
Pentoxyverine citrate (p. 1672·1); terpin hydrate (p. 1678·2).
Cough.

Toclase Toux Sèche *Pierre Fabre, Fr.*
Pentoxyverine citrate (p. 1672·1).
Cough.

Tocline *AstraZeneca, Arg.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Toco *Pharma 2000, Fr.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Tocobion *Medikon, Indon.†*
Thiamine disulfide (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Reduced appetite; digestive disorders; nervous system disorders; neurasthenia; nausea and vomiting of pregnancy.

Tocoderm *Tocogino, Mex.*
Tretinoin (p. 1725·2).
Hyperkeratosis.

Tocodyl Expectotant *TO-Chemicals, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; cold symptoms.

Toco-E *CCM, Malaysia.*
d-Tocotrienols (p. 2119·1).
Nutritional supplement.

Tocofeno *Ferring, Arg.*
⊗Clomifene citrate (p. 2259·1).
Female infertility.

Tocolion *Sciencex, Fr.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Toconal *Cryopharma, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Tocopa *Arkopharma, Fr.*
Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Tocopherine *Soho, Indon.†*
Vitamin E (p. 2119·1).
Vitamin E deficiency; fatigue; muscular dystrophy; recurrent miscarriage.

Tocorectal *Spedrog, Arg.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Tocorell *Sanorell, Ger.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Tocovenos *Fresenius Kabi, Austria.†*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Tocovid *Hovid, Hong Kong.*
Vitamin E (p. 2119·1); squalene (p. 2213·3); phytosterol complex; phyto-carotenoid complex.
Vitamin E supplement.

Hovid, Singapore.
Vitamin E (p. 2119·1); squalene (p. 2213·3); phytosterol complex; phyto-carotenoid complex.
Vitamin E supplement.

Hovid, Malaysia.†
Mixed tocotrienols (p. 2119·1).
Dietary supplement.

Tocovid Emulsion Plus *Hovid, Malaysia.*
Evening primrose oil (p. 2502·2); carotenoids; omega-3 marine triglycerides (p. 1460·3); mixed tocotrienols.
Dietary supplement.

Tocovid Suprabio *Hovid, Malaysia; Hovid, Philipp.*
Vitamin E substances (p. 2119·1); squalene (p. 2213·3); phytosterol complex; phytocarotenoid complex.
Dietary supplement.

Tocovid Suprabio with DHA *Hovid, Malaysia.*
Vitamin E substances (p. 2119·1); squalene (p. 2213·3); phytosterol complex; phytocarotenoid complex; docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Dietary supplement.

Tocril *Gedeon Richter, Cz.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Toctino *Basilea, Austria; Actelion, Canad.; Basilea, Denm.; Basilea, Fin.; Basilea, Fr.; Basilea, Ger.; Neopharm, Israel; Stiefel, Neth.; Stiefel, Norw.; GSK, Switz.; Basilea, UK.*
Alitretinoin (p. 738·2).
Eczema of the hands.

Toczol *Tocogino, Mex.*
Clotrimazole (p. 576·2).
Fungal skin and mucous membrane infections.

Todacin *TO-Chemicals, Thai.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Todalgil *Angelini, Spain.*
Ibuprofen (p. 68·2).
Fever; pain.

Today *Mayer, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Today Ovulation Test *Omega, Irl.†*
Fertility test (p. 2596·1).

Todenac *Oftalmi, Venez.*
Tobramycin sulfate (p. 380·2); diclofenac sodium (p. 48·3).
Infected eye disorders.

Todex *Oftalmi, Venez.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Todexona *SMB, Chile.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Bacterial eye infections with inflammation.

Todolac *Norpharma, Denm.*
Etodolac (p. 57·1).
Gout; inflammation; musculoskeletal and joint disorders.

Toepedo *Dendron, UK.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1).
Fungal skin infections.

Toetal Fresh *Medimetriks, USA.*
⊗Urea (p. 1727·3); camphor (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2).

Tofago *TO-Chemicals, Thai.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3).
Migraine and other vascular headache.

Tofen
Note: this name may be used for preparations of different composition.
Beximco, Singapore.
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Utopian, Thai.
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal and joint disorders.

Tofexo *TO-Chemicals, Thai.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Toff MD *Panacea, India.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold symptoms; sinus congestion; cough.

Toff Plus *Panacea, Rus.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; allergic rhinitis.

Tofib *Techsphere, Arg.*
Tobramycin (p. 380·1).
Bacterial infections.

Tofiel *Ohara, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Tofilsin *Shiono, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Tofis *Sawai, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Toflam *Lafedar, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Toflam Plus *Lafedar, Arg.*
⊗Tobramycin (p. 380·1); betamethasone (p. 1623·2); tetryzoline (p. 1678·3).
Eye disorders.

Toflamixina *Novartis Ophthalmics, Arg.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Toflamixina Plus *Novartis Ophthalmics, Arg.†*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Toflex *TO-Chemicals, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Tofranil *Novartis, Arg.; Novartis, Austral.; Pharma Logistics, Belg.; Novartis, Canad.†; CSP, Fr.; Dolorgiet, Ger.; Novartis, Indon.; Novartis, Irl.†; Novartis, Israel; Amdipharm, Ital.; AFT, NZ; Novartis, Philipp.; Amdipharm, Port.; Novartis, S.Afr.; Amdipharm, Spain; Novartis, Switz.; Novartis, Turk.; Novartis, Venez.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis; panic disorder; chronic pain syndromes; night terrors; anxiety disorders; sleep disorders.

Novartis, Braz.; Novartis, Mex.; Mallinckrodt, USA.
Imipramine embonate (p. 426·2) or imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis; panic attacks; pain; parasomnias.

Tofupill *CV Directo, Mex.*
Linseed (p. 2544·2); DT56a (p. 2620·3).
Dietary supplement; menopausal disorders; osteoporosis.

Togal
Note: this name may be used for preparations of different composition.
Togal, Neth.†
Aspirin (p. 22·2).
Fever; pain.

Togal ASS *Togal, Ger.; Ars Vitae, Switz.*
Aspirin (p. 22·2).
Pain; fever; inflammation.

Togal Classic *Togal, Ger.†*
Aspirin (p. 22·2); lithium citrate (p. 427·3); quinine dihydrochloride (p. 665·1).
Pain; inflammation; fever.

Togal Classic Duo *Togal, Ger.*
Aspirin (p. 22·2); paracetamol (p. 115·1).
Pain.

Togal Kopfschmerzbrause + Vitamin C *Togal, Ger.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Pain.

Togal Mono *Sanova, Austria.†*
Aspirin (p. 22·2).
Fever; pain.

Togesic
Note: this name may be used for preparations of different composition.
Sel-J, Philipp.
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Utopian, Thai.
Paracetamol (p. 115·1); orphenadrine citrate (p. 909·2).
Skeletal muscle pain and spasm.

Togilin *Beacons, Singapore.*
Docusate sodium (p. 1836·2); magnesium lactate (p. 1787·2).

Togine *Utopian, Thai.*
Codergocrine mesilate (p. 389·2).
Cerebral and peripheral vascular disorders.

Togran *Andromaco, Chile.*
Omeprazole (p. 1867·2).

Togrel *Ivax, Arg.*
Levomepromazine maleate (p. 1079·3).
Anxiety; psychoses.

Togrisol *Solfran, Mex.*
Aspirin (p. 22·2); caffeine (p. 1203·3).
Cold symptoms.

Toh Skin *ICM, Singapore.*
Salicylic acid (p. 1719·1).
Keratinisation disorders; acne.

Toilax *Orion, Denm.; Orion, Fin.; Orion, Irl.; Orion, Norw.; Orion, Swed.*
Bisacodyl (p. 1821·1).
Constipation; bowel evacuation.

Tointex *GSK, Pol.†*
Allantoin (p. 1693·1); heparin sodium (p. 1396·3).
Hyperkeratosis; keloids.

Tokakujokito *Tsumura, Jpn.*
Peach kernel; cinnamon bark (p. 2479·2); rhubarb (p. 1884·2); liquorice (p. 1853·2); mirabilitum.
Traditional Kampo medicine.

Token *Intendis, Ital.*
⊗Calcipotriol (p. 1697·2); betamethasone dipropionate (p. 1623·3).
Psoriasis.

Tokiinshi *Tsumura, Jpn.*
⊗Angelica acutiloba root (p. 2443·3); rehmannia root; tribulus fruit (p. 2633·3); peony root; cnidium rhizome; saposhnikovia root; polygonum root; astragalus root (p. 2451·1); schizonepeta tenuifolia; liquorice (p. 1853·2).
Traditional Kampo medicine.

Tokikenchuto *Tsumura, Jpn.*
Peony root; cinnamon bark (p. 2479·2); jujube; angelica acutiloba root (p. 2443·3); liquorice (p. 1853·2); ginger (p. 1844·1).
Traditional Kampo medicine.

Tokishakuyakusan *Tsumura, Jpn.*
Peony root; atractylodes lancea rhizome; alisma rhizome; poria sclerotium; cnidium rhizome; angelica acutiloba root (p. 2443·3).
Traditional Kampo medicine.

Tokishigyakukagoshuyushokyoto *Tsumura, Jpn.*
Jujube; cinnamon bark (p. 2479·2); peony root; angelica acutiloba root (p. 2443·3); akebia stem; liquorice (p. 1853·2); evodia fruit; asiasarum root; ginger (p. 1844·1).
Traditional Kampo medicine.

Tokito *Tsumura, Jpn.*
Angelica acutiloba root (p. 2443·3); pinellia tuber; cinnamon bark (p. 2479·2); magnolia bark; peony root; ginseng (p. 2513·3); astragalus root (p. 2451·1); ginger (p. 1844·1); zanthoxylum fruit (p. 2650·1); liquorice (p. 1853·2).
Traditional Kampo medicine.

Tokolirio *Tocogino, Mex.*
Zinc (p. 2126·1); boric acid (p. 2459·3).
Eye disorders.

Tokovit A + E *Hasco-Lek, Pol.*
Vitamin A palmitate (p. 2098·3); *d*-alpha tocopherol (p. 2119·1).
Vitamin A and E deficiency.

Tokovit E *Hasco-Lek, Pol.*
Tocopherol (p. 2119·1).
Atherosclerosis; ischaemic heart disease; vitamin E deficiency.

Tol *Leti, Ger.†; Novartis, Ger.†*
Allergen extracts (p. 2434·3).
Hyposensitisation.

Tol 12 *Saval, Chile.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis; reduced appetite; tonic.

Tol 12 Plus *Saval, Chile.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Vitamin B deficiency.

Tol Total *Saval, Chile.*
Vitamins; with or without minerals.
Dietary supplement.

Tolan *Solfran, Mex.†*
Methyl salicylate (p. 92·1).
Peri-articular and soft-tissue injury.

Tolargin *GSK, Pol.†*
Atropine methonitrate (p. 1310·2); dipyrone (p. 53·3); papaverine hydrochloride (p. 2362·3).
Smooth muscle spasm.

Tolbanasin *Taisho, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Tolbin
Note: this name may be used for preparations of different composition.
Elea, Arg.
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Unison, Malaysia; Unison, Singapore; Unison, Thai.
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Unison, Thai.
Expectorant: ⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease; cough.

Tolbin Expectorant *Unison, Malaysia.*
⊗Terbutaline sulfate (p. 1228·1); guaifenesin (p. 1666·2).
Obstructive airways disease; cough.

Tolchicine *TO-Chemicals, Thai.*
Colchicine (p. 604·1).
Gout.

Tolcrem *Solfran, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Toldex *Bial, Port.*
Aspirin (p. 22·2).
Pain; fever; thromboembolic disorders.

Toldin *Biofarma, Turk.*
Tolterodine (p. 2370·2).

Tolectin *Janssen-Cilag, Gr.; Janssen-Cilag, S.Afr.†; Santa, Turk.; Ortho McNeil, USA.*
Tolmetin sodium (p. 139·1).
Musculoskeletal, joint, and peri-articular disorders.

Janssen-Cilag, Mex.
Tolmetin (p. 139·1) or tolmetin sodium (p. 139·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; pain.

Toledomin *Asahi, Jpn.*
Milnacipran hydrochloride (p. 435·3).
Depression.

Tolep *Novartis, Ital.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Tolerade *PMP, Austral.*
Imipramine hydrochloride (p. 426·2).
Depression; nocturnal enuresis.

Tolerancia Extrema *Pierre Fabre Dermo-Cosmetique, Arg.†*
Emollient; skin cleanser.
Skin irritation.

Tolerane
Note: this name may be used for preparations of different composition.
Alcon, Arg.
Flurbiprofen (p. 65·2).
Inflammatory eye disorders; prevention of intra-operative miosis.

Bago, Chile.†
Disulfiram (p. 2495·3).
Alcoholism.

Tolerdilan *Nucleus, Cz.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Tolerex *Nestle, Canad.*
Preparation for enteral nutrition.

Procter & Gamble, USA.
Lactose-free preparation for enteral nutrition.

Tolériane *Roche-Posay, Arg.*
Emollient.
Skin irritation.

Roche-Posay, Braz.
A range of emollient preparations.

Toleriane *Roche-Posay, Chile.*
A range of moisturisers and skin cleansers.

Roche-Posay, Irl.
Emollient.
Dry skin.

Tolesper *Specifar, Neth.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Tolestan *Roemmers, Arg.*
Cloxazolam (p. 1057·2).
Anxiety; muscle spasm.

Tolevas *Nobel, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Tolexine *D & M, Chile; Bailleul, Fr.*
Doxycycline (p. 288·1).
Bacterial infections; rosacea; acne.

Tolfamic *Medinova (Μεντινοβα), Gr.*
Tolfenamic acid (p. 138·3).
Pain; inflammation; musculoskeletal and joint disorders.

Tolflex *Lagap, Switz.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle spasm.

Tolfrinic *Ascher, USA.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Tolgin *Saval, Chile.†*
Vitamins; minerals; ginseng (p. 2513·3).
Asthenia; tonic.

Tolid *Dolorgiet, Ger.*
Lorazepam (p. 1080·3).
Anxiety; premedication; sleep disorders.

Toliken *Pharmex (Φαρμεξ), Gr.*
Clindamycin phosphate (p. 269·3).
Acne.

Toliman *Scharper, Ital.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders.

Tolimed *Medifive, Thai.*
Mianserin hydrochloride (p. 434·2).
Depression.

Tolindol *Therabel, Belg.*
Proglumetacin maleate (p. 127·1).
Musculoskeletal, joint, and peri-articular disorders.

Tolip *Utopian, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Toliscrin *Dosa, Arg.*
Colistin (p. 275·3).
Bacterial infections.

Tollwutglobulin *Sanofi Pasteur, Ger.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Tollwut-Impfstoff (HDC) *Sanofi Pasteur, Ger.*
A rabies vaccine (human diploid cell) (p. 2413·2).
Active immunisation.

Tolma *Pasteur, Philipp.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tolmex *Flupal, Venez.*
Bromhexine hydrochloride (p. 1656·3); pentoxyverine citrate (p. 1672·1).
Cough.

Tolmicen *Pharmacia, NZ†; Pharmacia Upjohn, Rus.*
Tolciclate (p. 596·1).
Fungal skin infections.

Tolmicil *Pfizer, Gr.*
Tolciclate (p. 596·1).
Fungal skin infections.

Tolmide *Beacons, Singapore.*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Tolmin *Sandoz, Denm.*
Mianserin hydrochloride (p. 434·2).
Depression.

Tolnaderm *Sterfil, India†; Hoe, Malaysia; Hoe, Philipp.; Hoe, Singapore.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tolnaftan *Roemmers Osmoph, Venez.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tolnexa *KRKA, Neth.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer; prostatic cancer; gastric adenocarcinoma; head and neck cancer.

Tolol *Suphong, Thai.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; migraine.

Tolopelon *Daiichi Sankyo, Jpn.*
Timiperone (p. 1111·3).
Schizophrenia.

Toloran *Rayere, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Toloxim *Merck, Port.*
Mebendazole (p. 158·3).
Worm infections.

Toloxin
Note: this name may be used for preparations of different composition.
Pendopharm, Canad.; TO-Chemicals, Thai.
Digoxin (p. 1353·3).
Heart failure; arrhythmias.

Tolpa *Micro, Singapore.*
⊗Serrapeptase (p. 2613·3).
Inflammation; oedema.

Tolperil *Zdorovje, Ukr.*
Tolperisone hydrochloride (p. 2027·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Skeletal muscle spasm; spasticity.

Tolperis *ICN, Pol.*
Tolperisone hydrochloride (p. 2027·3).
Skeletal muscle pain and spasm; intermittent claudication.

Tolrest *Biosintetica, Braz.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; social phobia; premenstrual dysphoric disorder; panic disorder; post-traumatic stress.

Tolsom *Amway, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Toltem *Temis, Arg.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Toltex *Kocak, Turk.*
Tolterodine tartrate (p. 2370·2).

Toluidinblau *Kohler, Cz.; Kohler, Ger.*
Tolonium chloride (p. 2632·3).
Methaemoglobinaemia.

Tolura *KRKA, Cz.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Tolu-Sed DM *Scherer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Tolvin *Organon, Ger.†*
Mianserin hydrochloride (p. 434·2).
Depression.

Tolvon *MSD, Austral.; Organon, Austria; Schering-Plough, Braz.; MSD, China; Organon, Denm.†; Organon, Fin.; Organon, Gr.; Organon, Hong Kong†; Organon, Hung.; Organon, Irl.†; Organon, Mex.; Organon, Neth.; Organon, Norw.; MSD, NZ; Organon, Port.; MSD, Swed.†; MSD, Switz.; MSD, Thai.; Organon, Turk.*
Mianserin hydrochloride (p. 434·2).
Depression; sleep disorders; mixed anxiety depressive states.

Tolydol *Ipca, India.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Tolzep *Tolmann, Philipp.†*
Cefradine (p. 249·1).
Bacterial infections.

Tomaag *Yarindo, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Tomaflex *Boehringer Ingelheim, Cz.†*
Ibuprofen (p. 68·2).
Pain; fever.

Tomag *Temis, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity.

Tomanil *Nycomed, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis; oedema.

Tomanil Flex *Nycomed, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Tomapyrin *Boehringer Ingelheim, Cz.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; inflammation; pain.

Tomat *Apsen, Braz.*
Lycopene (Lyc-O-Mato) (p. 2546·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1).
Lycopene and vitamin supplement.

Tomcin *General Drugs, Thai.*
Erythromycin estolate (p. 291·2) or erythromycin stearate (p. 291·3).
Bacterial infections.

Tomevit *Spyfarma, Spain.†*
Adenosine triphosphate (p. 2430·3); arginine aspartate (p. 2049·1); glutathione (p. 1555·2); hydroxocobalamin acetate (p. 2107·3); lysine hydrochloride (p. 2079·3); pyritinol hydrochloride (p. 394·3).
Tonic.

Tomid *Gufic, India.*
Metoclopramide hydrochloride (p. 1862·2).
Motion sickness; vomiting.

Tomiko *Wermar, Mex.*
Ketoconazole (p. 585·3).
Fungal infections.

Tomil *Delicias, Mex.*
Preparation for enteral nutrition.

Tomiporan *Taisho, Jpn.*
Cefbuperazone sodium (p. 238·2).
Bacterial infections.

Tomiron *Toyama, China; Taisho, Jpn.*
Cefteram pivoxil (p. 252·1).
Bacterial infections.

Tomit *Interbat, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastro-oesophageal reflux; nausea and vomiting.

Tomix *Pentafarma, Port.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Tomocat *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Tomohexol *Farmak, Ukr.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Tomoray 76C *Variforma, Arg.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Tomovist *Farmak, Ukr.*
Meglumine gadopentetate (p. 1586·1).
Contrast agent for magnetic resonance imaging.

Tomudex *AstraZeneca, Arg.; Hospira, Austral.; AstraZeneca, Austria; Hospira, Belg.; AstraZeneca, Braz.; Hospira, Canad.; Hospira, Cz.; Hospira, Fr.; Hospira, Hung.; Hospira, Irl.; Hospira, Ital.; AstraZeneca, Mex.; Hospira, Norw.; AstraZeneca, Philipp.†; Hospira, Port.; AstraZeneca, Rus.; Hospira, Singapore; AstraZeneca, Spain; Hospira, Switz.; AstraZeneca, Turk.; AstraZeneca, UK.*
Raltitrexed (p. 850·3).
Colorectal cancer; malignant pleural mesothelioma.

Tomycin *Orion, Fin.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Ton 1 Complex *Thompsons, Canad.†*
Calcium phosphate tribasic (p. 1784·2); ferrum phosphoricum (p. 2077·1); magnesium phosphate dibasic (p. 1786·3); potassium phosphate dibasic (p. 1791·1).
Homoeopathic preparation.

Ton 2 Complex *Thompsons, Canad.†*
Cinchona officinalis (p. 2478·3); gold (p. 2521·1); oats (p. 2451·1); phosphoric acid (p. 2589·1).
Homoeopathic preparation.

Ton Was *Chiesi, Spain.*
Vitamin B substances (p. 2102·3); ginseng (p. 2513·3).
Tonic.

Ton-A *Mergers Drugfil, Philipp.*
Vitamins; minerals with calcium (oyster shell) (p. 1783·1).
Calcium deficiency; nutritional supplement.

Tonacal D3 *Formenti, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Tonactil *Arkopharma, Fr.†*
Kola (p. 2648·2); ginseng (p. 2513·3).
Asthenia.

Tonadron *Medix, Mex.†*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Tonaf *Seng, Thai.*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tonal *Beta, Arg.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain.

Tonalgen *Andromaco, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Musculoskeletal pain.

Tonalin *Knop, Chile.*
Essential fatty acids.
Dietary supplement.

Tonamil *Ecobi, Ital.*
Thonzylamine hydrochloride (p. 642·1).
Allergic skin disorders; insect bites; pruritus.

Tonar *Sandoz, Indon.; Sandoz, Thai.*
Amino acids.
Chronic renal insufficiency.

Tonaril *Laboratorios Chile, Chile.*
Trihexyphenidyl (p. 917·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Tonaton *Sankyo, Braz.*
⊗Yohimbine (p. 2372·3); fevillea trilobata; labiadas; ephedrine hydrochloride (p. 1663·2); atropine methonitrate (p. 1310·2).
Erectile dysfunction.

Tonavir *Richmond, Arg.*
Stavudine (p. 1015·3).
HIV infection.

Tonavital *Lafi, Chile.*
Amino acids; vitamins; minerals.
Tonic.

Tonbac *Conba, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Toncils *Vitabalans, Fin.*
Chlorhexidine hydrochloride (p. 1743·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Tondex *Hormona, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Tondinel *Pfluger, Ger.*
Acidum phosphoricum (p. 2589·1); avena sativa (p. 2451·1); kalium phosphoricum (p. 1790·3); lycopodium clavatum (p. 2546·3); panax ginseng (p. 2513·3); selenium (p. 2086·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Tondinel H *Pfluger, Ger.*
Acidum phosphoricum (p. 2589·1); aurum metallicum (p. 2521·1); avena sativa (p. 2451·1); passiflora incarnata (p. 2584·1); selenium amorphum (p. 2086·3); ambra grisea (p. 2440·3); humulus lupulus (p. 2546·1); valeriana officinalis (p. 2640·2).
Homoeopathic preparation.

Tone *Vitalco, Fr.*
Buckwheat (p. 2462·1); myrtillus (p. 2566·2); lupulus (p. 2546·1); galanga; nicotinamide (p. 2083·1); minerals.
Dietary supplement; hearing disorders.

Tonekin *Assistance, Arg.*
Chromium tripicolinate (p. 2056·1).
Slimming aid.

Tonergon *Farmedia, Gr.*
Dihydroergocristine mesilate (p. 390·1).
Peripheral vascular disorders.

Tong Di *Jincheng Haisi, China.*
Ligustrazine phosphate.

Tong An Qi *Xingtong, China.*
Zaleplon (p. 1114·3).
Insomnia.

Tong An Xin *Haier No 3, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Tong Ao *Hengrui, China.*
Calcium folinate (p. 2066·3).
Methotrexate toxicity; megaloblastic anaemia.

Tong Bei De *Zhengda Haier, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Tong Bo *Fuchun, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Tong Da Rui *Ruige, China.*
Tiopronin (p. 1578·1).

Tong Du Ding *Tongyao, China.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Tong Er Qi *Lingrui, China.*
Felbinac (p. 58·3).

Tong Fen *Baotou, China.*
Ketotifen (p. 631·3).

Tong Ke *Baoguang, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Tong Li Tuo *Shenyang First, China.*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Tong Ming *Fuchun, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Tong Nuo Xin *Dadongfang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Tong Qi *Qilu, China.*
Pazufloxacin mesilate (p. 338·1).

Tong Shu *Haixin, China.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).

Tong Shu Tong *Langyi, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Tong Tai Qi Li *Yi Kang, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Tong Tan Kang *Yi Kang, China.*
Piracetam (p. 393·3).
Mental function impairment.

Tong Ting *Shenlong, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tong Xin Di *Guoda, China.*
Oxymatrine.

Tong Xin *Minophagen, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Tong Zhou *Chang An, China.*
Diammonium glycyrrhizate (p. 2520·3).

Tonginal *Bittner, Rus.; Bittner, Ukr.*
Camphora (p. 2466·2); tabacum (p. 2632·2); veratrum album (p. 2644·3); glonoinum (p. 1391·2); acidum hydrocyanicum (p. 2156·2).
Homoeopathic preparation.

Toni Com *Vitalab, Canad.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Tonibral
Note: this name may be used for preparations of different composition.
Gador, Arg.
Memantine hydrochloride (p. 393·1).
Alzheimer's disease.

Tonic Yeast *Seven Seas, UK.*
Yeast (p. 2125·2); vitamin B substances (p. 2102·3).
Formerly known as Phillips P.T.Y. Yeast Tablets.

Tonicalcium *Bouchara-Recordati, Fr.*
DL-Lysine ascorbate (p. 2110·3); calcium ascorbate (p. 2111·1).
Asthenia.

Tonice *Confar, Port.*
Oral liquid: ⊗Deanol pidolate (p. 2319·1); magnesium aminobenzoate; ascorbic acid (p. 2110·3).
Tonic.

Confar, Port.
Syrup: ⊗Deanol pidolate (p. 2319·1); calcium gluceptate (p. 1783·2); lysine hydrochloride (p. 2079·3).
Tonic.

Tonico Calmante Fisiologico *Roche-Posay, Chile.*
Emollient.
Dry skin.

Tonico Juventus *Juventus, Spain.*
Cyproheptadine hydrochloride (p. 624·1); cobamamide (p. 2107·2).
Tonic.

Tonico Pasteur *Pasteur, Chile.*
Vitamins; minerals.
Tonic.

Tonicum B12 *SIT, Ital.*
Amino acids; vitamin B_{12} (p. 2107·2).

Tonid *Milano, Thai.†*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Tonight *CTS, Israel.*
Doxylamine succinate (p. 627·3).
Insomnia.

Tonigin *CCD, Fr.†*
Ginseng (p. 2513·3).
Tonic.

Tonikum Bayer *Bayer Consumer, Indon.*
Vitamin B_1 (p. 2103·1); Vitamin B_2 (p. 2104·3) vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); nicotinamide (p. 2083·1); vitamin C (p. 2110·3); calcium (p. 1783·1); manganese (p. 2081·2); zinc (p. 2126·1).
Nutritional supplement.

Tonikum Bode *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); liver extract (p. 2444·1); sodium glycerophosphate (p. 2519·2); manganese sulfate (p. 2081·2); caffeine (p. 1203·3); potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Tonic.

Tonilax *Merck Medication Familiale, Fr.*
Frangula bark (p. 1843·3); aloes (p. 1816·1).
Constipation.

Tonimax *Soria Natural, Spain.*
Siberian ginseng (p. 2614·3); rosemary oil (p. 2607·3); savory oil (p. 2625·1).
Fatigue.

Tonimer
Note: this name may be used for preparations of different composition.
Berko, Turk.
Sea water (p. 2612·1).
Nasal congestion.

Tonimine *Herbes Universelles, Canad.†*
Potassium hypophosphite (p. 2530·3); sodium hypophosphite (p. 2530·3); calcium hypophosphite (p. 2530·3).

Tonimol *Herbes Universelles, Canad.†*
Vitamins.

Tonin Cough *Sato, Singapore.*
Guaifenesin (p. 1666·2); noscapine hydrochloride (p. 1670·3).
Cough.

Tonipan *Actavis, Norw.†*
Vitamin B substances (p. 2102·3); manganese (p. 2081·2).
Vitamin B deficiency.

Tonique D liquide *Vifor, Switz.†*
Vitamins; minerals; ginseng (p. 2513·3); kola (p. 2648·2); caffeine citrate (p. 1203·3).
Tonic.

Tonique Végétal *Lehning, Fr.*
Podophyllum peltatum (p. 1717·1); avena sativa (p. 2451·1); cola (p. 2648·2); artemisia; rheum rhaponticum (p. 1884·2); frangula (p. 1843·3); cinchona (p. 2478·3); nux vomica (p. 2573·3); cinnamomum (p. 2479·2); arsenicum album (p. 2448·1); gentiana lutea (p. 2512·1).
Homoeopathic preparation.

Tonirem *Elvipe, Gr.*
Temazepam (p. 1109·1).

Tonizep *TO-Chemicals, Thai.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Tonizin *Betapharm, Ger.†*
St John's wort (p. 449·1).
Depression.

Tonlit *Salvat, Spain.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Tono *Milano, Thai.†*
Tolnaftate (p. 596·1).
Fungal skin infections.

Tonobexol *Novartis Ophthalmics, Arg.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma.

Tonocalcin *Medicom, Cz.; Angelini, Gr.; Demo, Gr.; Faran, Gr.; Alfa Wassermann, Indon.; Tempo Scan Pacific, Indon.; Alfa Wassermann, Pol.; Alfa Wassermann, Thai.; Santa, Turk.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; hypercalcaemia; osteoporosis; reflex sympathetic dystrophy.

Tonocaltin *Biara, Port.; Wassermann, Spain.†*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis; hypercalcaemia; osteolysis of malignancy.

Tonocardin *Teva, Rus.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Tonoferon *East India Pharma, India.*
Oral drops: Colloidal iron hydroxide (p. 2073·1); lysine hydrochloride (p. 2079·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Iron-deficiency anaemias.

East India Pharma, India.
Paediatric syrup; syrup: Colloidal iron hydroxide (p. 2073·1); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2).
Iron-deficiency anaemias.

Tonoferrin *Ulagay, Turk.*
Ferric ammonium citrate (p. 2060·1).
Iron deficiency; iron-deficiency anaemia.

Tonoflex *Sanitas, Chile.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Skeletal muscle spasm and pain.

Tonofolin *Teofarma, Ital.*
Calcium folinate (p. 2066·3).
Megaloblastic anaemias.

Tonogen *ABC, Ital.*
Haematoporphyrin hydrochloride (p. 2523·3); cyanocobalamin (p. 2107·2).
Tonic.

Gedeon Richter, Hung.
⊗Adrenaline (p. 1292·1).
Anaphylaxis; asthma; circulatory collapse; glaucoma; haemorrhage; nasal disorders.

Tonoglutal *Wild, Switz.*
Glutamic acid (p. 2070·2); sodium hydroxybenzylphosphinate; ascorbic acid (p. 2110·3); magnesium glycerophosphate (p. 1787·2); thiamine nitrate (p. 2103·2).
Tonic.

Tonojug *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Tonopan
Note: this name may be used for preparations of different composition.
Novartis, Austria; Novartis, Braz.; Sandoz, Mex.; Mizar, Spain.
Caffeine (p. 1203·3); dihydroergotamine mesilate (p. 672·2); propyphenazone (p. 127·3).
Migraine and other vascular headaches; facial neuralgia.

Novartis Consumer, Switz.
Diclofenac potassium (p. 48·3).
Pain; fever.

Tonopaque *Mallinckrodt, USA.†*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Tonopron Fuerte Con Vit. B12 *Sanitas, Chile.*
Vitamin B substances (p. 2102·3); liver extract (p. 2444·1).
Tonic.

Tonopron Ginseng *Sanitas, Chile.*
⊗Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); deanol tartrate (p. 2319·1).
Tonic.

Tonopron Jarabe *Sanitas, Chile.*
Vitamins; inositol (p. 2533·2).
Tonic.

Tonopron Plus *Sanitas, Chile.*
Vitamins; minerals; fish oil (p. 1460·1).

Tonorma *Darnitsa, Ukr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2); nifedipine (p. 1447·2).
Hypertension.

Tonoten *Dollder, Venez.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Tonotensil *Laboratorios Chile, Chile.*
Lisinopril (p. 1420·3).
Heart failure; hypertension.

Tonotensil D *Laboratorios Chile, Chile.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tonotil-N *Vianex [Βιανεξ], Gr.*
Glutamine (p. 2070·3); arginine hydrochloride (p. 2049·1); hydroxocobalamin (p. 2107·3); phosphothreonine (p. 2589·3); phosphoserine; arginine (p. 2049·1).
Tonic.

Tonovit
Note: this name may be used for preparations of different composition.
Remek, Gr.
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Tonovital Antioxidante *Bago, Arg.*
Tocopherol acetate (p. 2119·2); vitamin C (p. 2110·3); betacarotene (p. 2051·1); zinc (p. 2126·1); selenium (p. 2086·3).
Antoxidant preparation.

Tonovital E *Bago, Arg.†*
Tocopherol acetate (p. 2119·2).

Tonovital Plus Antioxidante *Bago, Arg.*
Tocopherol acetate (p. 2119·2); vitamin C (p. 2110·3); betacarotene (p. 2051·1); zinc (p. 2126·1); copper (p. 2057·1); selenium yeast (p. 2125·2); manganese (p. 2081·2).
Antoxidant preparation.

Tonox *Utopian, Thai.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Tonpular *Wockhardt, Irl.; Wockhardt, Pol.; Wockhardt, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression; panic disorder; anxiety; social phobia.

Tonsan akut *Bittner, Austria.*
Eucalyptus (p. 2501·1); belladonna (p. 2453·3); bryonia (p. 2461·3); phosphorus (p. 2589·2); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Tonsan chronisch *Bittner, Austria.*
Thymus vulgaris (p. 2630·2); tartarus emeticus (p. 151·2); ipecacuanha (p. 1667·2); balsamum peruvianum (p. 2587·1); ammonium carbonicum (p. 1656·1).
Homoeopathic preparation.

Tonsan-Akut *Bittner, Rus.*
Eucalyptus (p. 2501·1); belladonna (p. 2453·3); bryonia (p. 2461·3); phosphorus (p. 2589·2); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Tonsil *Gap, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Tonsilgon N *Bionorica, Rus.; Bionorica, Ukr.†*
Althaea (p. 2438·3); chamomile (p. 2474·1); equisetum (p. 2500·1); English walnut (p. 2646·1); achillea (p. 2427·3); oak bark (p. 2574·1); taraxacum (p. 2625·3).
Upper respiratory-tract disorders.

Tonsiline *Oakhurst, USA.*
⊗Tolu balsam (p. 1679·2); iron chloride; magnesium carbonate (p. 1856·2); glycerol (p. 2517·2); alcohol (p. 1733·1).
Mouth and throat disorders.

Tonsillol *Ratiopharm, Austria.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

Tonsillopas *Pascoe, Austria; Pascoe, Ger.*
Baptisia tinctoria (p. 2647·2); hydrargyrum bicyanatum (p. 2555·3); ammonium bromatum (p. 2461·1); kalium bichromicum (p. 2476·3); kalium chloratum (p. 1793·2); apisinum (p. 2434·3).
Homoeopathic preparation.

Tonsillosyx *Syxyl, Ger.*
Acidum silicicum (p. 2208·3); aconitum napellus (p. 2428·3); hydrargyrum cyanatum (p. 2555·3).
Homoeopathic preparation.

Tonsilon *Charoon Bhesaj, Thai.*
Tyrothricin (p. 384·1); benzethonium chloride (p. 1738·1); benzocaine (p. 1980·2).
Mouth, nose, and throat infections.

Tonsilotren *DHU, Rus.; DHU, Ukr.*
Atropinum sulfuricum (p. 1310·2); hepar sulfuris (p. 1721·3); kalium bichromicum (p. 2476·3); silicea (p. 2208·3); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Tonsiotreen *VSM, Neth.*
Belladonna (p. 2453·3); hepar sulfuri (p. 1721·3); silicea (p. 2208·3); mercurius iodatus ruber (p. 2555·3).
Homoeopathic preparation.

Tonsiotren *DHU, Austria.*
Atropinum sulfuricum (p. 1310·2); hepar sulfuris (p. 1721·3); kalium bichromicum (p. 2476·3); silicea (p. 2208·3); mercurius bijodatus (p. 2555·3).
Homoeopathic preparation.

Tonsiotren H *DHU, Ger.*
Atropinum sulf. (p. 1310·2); hepar sulf. (p. 1721·3); kalium bichrom. (p. 2476·3); silicea (p. 2208·3); merc. bijodat. (p. 2555·3).
Homoeopathic preparation.

Tonsipret *Bionorica, Ger.; Bionorica, Rus.; Bionorica, Ukr.*
Capsicum annuum (p. 2469·3); guaiacum (p. 2523·1); phytolacca americana (p. 2593·2).
Homoeopathic preparation.

Tonum *Biotech, Venez.†*
Domperidone (p. 1838·1).
Gastro-oesophageal reflux; delayed gastric emptying.

Tonval *Saval, Chile.†*
Vitamins; calcium gluconate (p. 1783·3); lysine (p. 2079·3).
Tonic.

Toothache Gel *Roberts, USA.*
Benzocaine (p. 1980·2); clove oil (p. 2481·3).
Toothache.

Top 1 *Gerolymatos, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Top C *Lane, UK.*
Rose fruit (p. 2607·1); acerola; ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Top Calcium *Benedetti, Ital.†*
Calcium carbonate (p. 1824·3).
Calcium depletion; calcium supplement.

Top dent fluor *Meda, Swed.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Topaal *Pierre Fabre Sante, Fr.; Pierre Fabre, Irl.*
Aluminium hydroxide (p. 1817·2); light magnesium carbonate (p. 1856·2); alginic acid (p. 2167·2); silicon dioxide (p. 2208·3).
Gastro-oesophageal reflux; hiatus hernia.

Topaben *Pharmathen, Denm.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topaben-N *British Dispensary, Thai.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Skin disorders.

Topace *Fawns & McAllan, Austral.†*
Captopril (p. 1331·2).
Hypertension.

Topacéta *Streuli, Switz.†*
Aluminium acetotartrate (p. 2440·1); chamomile (p. 2474·1); arnica (p. 2447·2).
Skin disorders; soft-tissue injury.

Topactin *Nealab, Canad.†*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Topafis *Cipla, Cz.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topal *Pierre Fabre, UK.*
Aluminium hydroxide (p. 1817·2); light magnesium carbonate (p. 1856·2); alginic acid (p. 2167·2).
Gastro-oesophageal reflux; gastritis; gastric hyperacidity.

Topalepsin *Akrikhin, Rus.*
Topiramate (p. 550·3).
Epilepsy.

Topalex *Sanofi-Aventis, S.Afr.*
Topiramate (p. 550·3).

Topalgic *Sanofi-Aventis, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Topalgon *Lavipharm, Gr.*
Diclofenac diethylamine (p. 48·3).
Inflammatory disorders.

Topalkan *Pierre Fabre, Fr.†*
Alginic acid (p. 2167·2); aluminium hydroxide (p. 1817·2); silicon dioxide (p. 2208·3); magnesium carbonate (p. 1856·2).
Gastro-oesophageal reflux.

Topamac *Janssen-Cilag, Arg.; Janssen-Cilag, Gr.; Johnson & Johnson, India.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topamate *Cipla, India.*
Topiramate (p. 550·3).
Epilepsy.

Topamax *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Xian-Janssen, China; Janssen-Cilag, Cz.; SinGad, Denm.†; Janssen-Cilag, Ger.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Janssen, USA; Janssen-Cilag, Venez.*
Topiramate (p. 550·3).
Epilepsy; migraine; bipolar disorder; neuropathic pain; cluster headache.

Topamine *Burapha, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms.

Toparal *Novag, Mex.*
Methyldopa (p. 1431·1).
Hypertension.

Topazolam *Apotex, Belg.†*
Alprazolam (p. 1035·2).
Anxiety.

Top-Cat *Varifarma, Arg.*
Barium sulfate (p. 1583·2).
Contrast medium for computerised tomography.

Topcillin *Kalbe, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Topcoid *Uniao Quimica, Braz.*
A heparinoid (p. 1401·1).

Topcort
Note: this name may be used for preparations of different composition.
Cipla, Hong Kong; Cipla, India.
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Sanbe, Indon.
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Top-Dal *Randall, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ostomy management.

Topepil *Alapis, Gr.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topepsil *Egis, Hung.; Egis, Neth.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Toperit *LKM, Arg.*
Erythromycin (p. 291·2).
Acne.

Topex
Note: this name may be used for preparations of different composition.
Pierre Fabre, Fr.
Benzocaine (p. 1980·2).

Topfans *OP, Ital.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Topféna *Zydus, Fr.†*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Topgesic *Kimia, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Topharmin *Main Life, Hong Kong.†*
Amantadine (p. 890·3).

Topher-E *Scherer, Hong Kong.†*
α-Tocopherol (p. 2119·1).
Vitamin E supplement.

Topialyse *SVR, Fr.*
Capsules: Borage oil (p. 2459·2); vitamin E (p. 2119·1).
Skin disorders.

SVR, Ital.
Gamolenic acid (p. 2509·2); borage oil (p. 2459·2).
Nutritional supplement.

Topialyse Sensitive *SVR, Fr.*
Bath oil: Borage oil (p. 2459·2); camelina oil.
Dry skin disorders.

SVR, Fr.
Cream: Borage oil (p. 2459·2); camelina oil; liquorice derivative (p. 1853·2); lappa (p. 2540·1).
Dry skin disorders.

SVR, Fr.
Soap substitute: Borage oil (p. 2459·2); camelina oil; lappa (p. 2540·1).
Skin cleansing.

Topibrain *Brainpharma, Spain.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topic *Syntex, USA.*
Benzyl alcohol (p. 1739·3); camphor (p. 2466·2); menthol (p. 2553·2).
Pruritus.

Topicaine
Note: this name may be used for preparations of different composition.
Biomed, NZ.
Tetracaine hydrochloride (p. 1996·3); lidocaine hydrochloride (p. 1988·2). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

ESBA, USA.
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Topical *Tecnimede, Port.*
Bifonazole (p. 573·3).
Fungal infections.

Topicasone *Franco-Indian, India.*
⊗Betamethasone benzoate (p. 1623·3).
Skin disorders.

Topicasone with Neomycin *Franco-Indian, India.*
⊗Betamethasone benzoate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Topicide *Konimex, Indon.†*
Lindane (p. 2157·1); hexachlorophene (p. 1754·1); salicylic acid (p. 1719·1).
Scabies.

Topicil *Douglas, Malaysia; Douglas, NZ; Douglas, Singapore.*
Clindamycin phosphate (p. 269·3).
Acne.

Topicort *Valeant, Canad.; Taro, USA.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Topicorte *Sanofi-Aventis, Neth.; Sanofi-Aventis, Thai.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Topicrem
Note: this name may be used for preparations of different composition.
Nigy, Fr.†; Nigy, Singapore.
⊗Urea (p. 1727·3); glycerol (p. 2517·2).
Dry skin disorders.

Topicrem Traitement PV *Nigy, Fr.†*
Piroctone olamine (p. 1716·3).
Fungal skin infections.

Topictal *Raffo, Arg.; Tecnofarma, Chile.*
Topiramate (p. 550·3).
Epilepsy.

Topicycline *Shire, Irl.†; Amdipharm, UK.†*
Tetracycline hydrochloride (p. 373·2).
Acne.

Topida *T Man, Thai.*
Niclosamide (p. 161·2).
Taeniasis.

Topiderm
Note: this name may be used for preparations of different composition.
Olvos, Gr.
Flutrimazole (p. 582·1).
Fungal skin infections.

Topidexa *Kinder, Braz.†*
⊗Dexamethasone acetate (p. 1631·1).
Skin disorders.

Topidil *TO-Chemicals, Thai.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Topiegis *Egis, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topifar *Biofarm, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topifort *Franco-Indian, India.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Topiframn *Sanofi-Aventis, Thai.*
⊗Desoximetasone (p. 1630·2); framycetin sulfate (p. 301·2); gramicidin (p. 308·3).
Infected skin disorders.

Topigel *Clarben, Port.*
Benzocaine (p. 1980·2).
Local anaesthesia.

Topigen *Vendiz, Philipp.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Biogened, Pol.
Topiramate (p. 550·3).
Epilepsy.

Topiglós *Kinder, Braz.†*
Cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Barrier preparation.

TopiLek *Sandoz, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topilepsin *Zdorovje, Ukr.*
Topiramate (p. 550·3).
Epilepsy.

Topilept *Egis, Cz.; Egis, Neth.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topilex *Gerot, Austria; GL Pharma, Cz.; GL Pharma, Hung.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topilone *Chew, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Topiloric *Fuji, Jpn.*
Topiroxostat.
Hyperuricaemia; gout.

Topimark *Glenmark, Cz.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topimatil *Jelfa, Denm.†; Jelfa, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topimax *Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Norw.; Janssen-Cilag, Swed.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topimerck *Generics, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topimylan *Mylan, Spain.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topina *Kyowa, Jpn.*
Topiramate (p. 550·3).
Epilepsy.

Topionic *Esteve, Spain.*
Povidone-iodine (p. 1767·1).
Skin, burn, and wound disinfection.

Topiragamma *Worwag, Ger.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topiragen *Upsher-Smith, USA.*
Topiramate (p. 550·3).
Epilepsy.

Topiragis *Tiefenbacher, Cz.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topirama *Arrow, Irl.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topiramed *Mibe, Ger.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topiratore *Stada, Denm.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topiref *Specifar (Σπεσιφαρ), Gr.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topirex *Indeco, Arg.†*
Topiramate (p. 550·3).
Epilepsy.

Topiromax *Veropharm, Rus.; Pharma Start, Ukr.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topisalen
Note: this name may be used for preparations of different composition.
Trima, Israel.
⊗Flumetasone pivalate (p. 1635·2); salicylic acid (p. 1719·1).
Skin disorders.

Topisel *Galenium, Indon.†*
Selenium sulfide (p. 1719·3).
Fungal skin and scalp disorders.

Topisolon *Sanofi-Aventis, Ger.; Abbott, Switz.†*
Fatty ointment; ointment: ⊗Desoximetasone (p. 1630·2).
Skin disorders; burns.

Topison *Libbs, Braz.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Topi-Spray
Note: this name may be used for preparations of different composition.
Bial, Port.†
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Topispray
Note: this name may be used for preparations of different composition.
Clarben, Spain.
Benzocaine (p. 1980·2).
Local anaesthesia.

Topistad *Stada, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topistin *AFT, NZ.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Elpen (Ελπεν), Gr.
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Elpen, Singapore.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Topit *Rowex, Irl.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topitex *Apotex, Neth.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topitrim *Trima, Israel.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topivate *Pharma-Q, S.Afr.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Topix *Solas, Indon.†*
Salicylic acid (p. 1719·1); undecenoic acid (p. 596·3); benzoic acid (p. 1738·2).
Fungal akin infections.

Topixidil *Flupal, Venez.*
Minoxidil (p. 1438·3).
Alopecia.

Topizide *TO-Chemicals, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Topizol *Douglas, Austral.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Top-K *Ultra, Mex.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Topkin *Biomet, Ger.†*
Lactid caprolactone copolymer.
Wounds.

Topla *Omnimed, S.Afr.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Toplanina *Meizler, Braz.*
Teicoplanin (p. 369·3).

Toplep *Ranbaxy, S.Afr.*
Topiramate (p. 550·3).
Epilepsy.

Toplexil
Note: this name may be used for preparations of different composition.
Melisana, Belg.
Oxomemazine (p. 637·1); guaifenesin (p. 1666·2); sodium benzoate (p. 1738·2); paracetamol (p. 115·1).
Cough.

Sanofi-Aventis, Braz.
Oxomemazine hydrochloride (p. 637·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1); sodium benzoate (p. 1738·2).
Cough.

Sanofi-Aventis, Fr.; Sanofi-Aventis, Neth.
Oxomemazine (p. 637·1).
Cough.

Sanofi-Aventis, Gr.
Oxomemazine (p. 637·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).

Sanofi-Aventis, Indon.
Oxomemazine (p. 637·1); guaifenesin (p. 1666·2).
Cough in allergic disorders.

Toplexil N *Sanofi-Aventis, Switz.*
Oxomemazine (p. 637·1).
Cough.

Topliv *Hypermarcas, Braz.*
⊗Mometasone furoate (p. 1644·1).

Top-Mag *H2 Pharma, Fr.†*
Magnesium pidolate (p. 1787·3).
Magnesium deficiency.

Top-Nitro *Schering-Plough, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Topo *Huons, Thai.*
Etoposide (p. 790·2).
Malignant neoplasms.

Topogyne *Exelgyn, UK.*
Misoprostol (p. 2140·3).
Termination of pregnancy.

Topokebir *Aspen, Arg.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer.

Toporan *Meizler, Braz.*
Topotecan hydrochloride (p. 872·3).

Toposar *Sicor, USA.*
Etoposide (p. 790·2).
Testicular cancer; small-cell lung cancer.

Toposin *Pharmachemie, Neth.*
Etoposide (p. 790·2).
Malignant neoplasms.

Topotecin *Daiichi Sankyo, Jpn.*
Irinotecan hydrochloride (p. 812·2).
Malignant neoplasms.

Topotel *Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; small-cell lung cancer.

Topoxy *Sriprasit, Thai.*
⊗Desoximetasone (p. 1630·2).
Skin disorders.

Topper *Chinta, Thai.*
Vitamins; minerals.

Topral *Alkaloid, Rus.*
Sultopride hydrochloride (p. 1108·3).
Psychoses; behaviour disorders; mania.

Topramine *Condrugs, Thai.*
Imipramine (p. 426·2).
Depression; nocturnal enuresis.

Topramoxin *Toprak, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Topras *Gracia, Indon.*
Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Influenza symptoms.

Topraz *Reddy, S.Afr.*
Montelukast (p. 1214·3).

Toprazole *Tabuk, Malaysia.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Toprec *Sanofi-Aventis, Fr.*
Ketoprofen (p. 79·1).
Pain; fever.

Toprel *Drugtech, Chile.*
Topiramate (p. 550·3).
Epilepsy.

Topresid *Biomedis, Philipp.*
Etoposide (p. 790·2).
Malignant neoplasms.

Toprifar *Nafar, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; diabetic nephropathy; myocardial infarction.

Toprilem *Teva, Mex.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Toprim *TNP, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Toprol *AstraZeneca, Austral.; AstraZeneca, USA.*
⊗Metoprolol succinate (p. 1434·3).
Heart failure; hypertension; angina pectoris.

Topron *Chinoin, Mex.*
Nifuroxazide (p. 331·3).
Gastro-enteritis.

Topsaver *Pliva, Rus.*
Topiramate (p. 550·3).
Epilepsy.

Topsiton *Triomed, S.Afr.†*
Vitamins; anhydrous caffeine (p. 1203·3); calcium gluconate (p. 1783·3); calcium citrate (p. 1783·2).
Tonic.

Topster *Sofar, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Inflammatory bowel disease.

Topsy *Galenium, Indon.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Topsym *Teofarma, Ger.; Teofarma, Switz.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Topsym polyvalent
Note: this name may be used for preparations of different composition.
Teofarma, Switz.
⊗Fluocinonide (p. 1636·3); gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3).
Infected skin disorders.

Topsyn *Medicis, Canad.†; Teofarma, Ital.; Syntex, Mex.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Topsyn-Y *Syntex, Mex.*
⊗Fluocinonide (p. 1636·3); clioquinol (p. 273·1).
Infected skin disorders.

Toptear *Poen, Chile; Roemmers Poen, Venez.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; eye irritation.

Toptil *Sandoz, Braz.*
Topiramate (p. 550·3).

Toptrix *Merck, Port.†*
Topiramate (p. 550·3).
Epilepsy; migraine.

Topzole *Nycomed, S.Afr.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

T-Ora *2M, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth ulcers.

Toracard *AWD, Ger.†*
⊗Torasemide (p. 1516·3).
Heart failure; oedema.

Toracin *Sam Chun Dang, Hong Kong.†*
Tobramycin (p. 380·1).
Bacterial eye infections.

Toradiur *Meda, Ital.*
⊗Torasemide sodium (p. 1516·3).
Oedema; ascites; heart failure; renal failure.

Tora-Dol *Innova, Ital.; Roche, S.Afr.; Roche, Switz.*
Ketorolac trometamol (p. 80·2).
Pain; renal colic.

Toradol *Roche, Austral.; Roche, Braz.; Roche, Canad.; Roche, Denm.; Roche, Fin.; IFET (ΙΦΕΤ), Gr.; Roche, Hong Kong; Roche, Indon.; Roche, Malaysia; Roche, Norw.; Roche, Philipp.; Roche, Port.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, UK.*
Ketorolac trometamol (p. 80·2).
Pain; renal colic.

Toragamma *Worwag, Ger.†*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; heart failure; renal failure.

Toragesic *Sigma, Braz.*
Ketorolac trometamol (p. 80·2).
Pain.

ToraHexal *Sandoz, S.Afr.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Toral
Note: this name may be used for preparations of different composition.
Synergen, Philipp.
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Teva, Mex.
Ketorolac trometamol (p. 80·2).
Pain.

Toramat *Pharmathen, Gr.; Glenmark, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Toramide *Spirig, Switz.†*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; ascites.

Toramine *Otto, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Toranex *Alternavida, Mex.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer.

Toras *Pharos, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Torasem *Mepha, Switz.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; ascites.

Toraseptol *Warner Chilcott, Spain.†*
Azithromycin (p. 221·2).
Bacterial infections.

Torasic *Kalbe, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Torasid *Gry, Ger.†*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; heart failure.

Torasis *Sandoz, Switz.†*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; renal failure; nephrotic syndrome.

Torastin *Caber, Ital.*
Atorvastatin (p. 1309·2).

Toraxan *Schering-Plough, Arg.*
Loratadine (p. 633·2); ambroxol hydrochloride (p. 1654·3).
Allergic respiratory-tract disorders with excess mucous.

Torbetol
Note: this name may be used for preparations of different composition.
Torbet Laboratories, UK.
Cetrimide (p. 1742·1); chlorhexidine gluconate (p. 1743·3).
Acne.

Torbet, Irl.†
Cetrimide (p. 1742·1); benzalkonium chloride (p. 1737·1); hexachlorophene (p. 1754·1).
Acne.

Toreal *Lekko, Rus.*
Topiramate (p. 550·3).
Epilepsy.

Torecan *Egis, Hung.; KRKA, Rus.*
Thiethylperazine (p. 641·3).
Nausea and vomiting; vestibular disorders.

KRKA, Cz.; KRKA, Pol.
Thiethylperazine malate (p. 641·3).
Vestibular disorders; nausea and vomiting; cerebrovascular atherosclerosis.

Novartis, Chile; Novartis, Ital.; Novartis, Mex.; Novartis, Spain; Novartis, Swed.†
Thiethylperazine maleate (p. 642·1).
Nausea and vomiting; motion sickness; vestibular disorders; vertigo.

Torécan *Novartis, Switz.*
Thiethylperazine maleate (p. 642·1).
Nausea; vomiting; vertigo; motion sickness.

Torella *SVUS, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Torem *Roche, Arg.; Berlin-Chemie, Ger.; Meda, Swed.; Meda, Switz.; Roche, UK.*
⊗Torasemide (p. 1516·3) or torasemide sodium (p. 1516·3).
Heart failure; hypertension; oedema; renal failure.

Toremol *Niadas, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Torendo *KRKA, Hung.; HCS, Neth.†; KRKA, Pol.; KRKA, Rus.*
Risperidone (p. 1103·2).
Schizophrenia; psychoses; behavioural disorders; bipolar disorder; mania; aggression associated with dementia.

Torental *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.†*
Pentoxifylline (p. 1465·3).
Intermittent claudication; vascular disorders; mental function impairment in the elderly.

Torgyn *Raffo, Arg.*
Clindamycin (p. 269·3).
Vaginal bacterial infections.

Torgyn Duo *Raffo, Arg.*
Clindamycin (p. 269·3); ketoconazole (p. 585·3).
Vaginal infections.

Toribix *Target, Gr.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting associated with cancer chemotherapy; nausea and vomiting associated with radiotherapy.

Torid *Trima, Israel.*
Atorvastatin magnesium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Toridon *Torrent, Philipp.*
Domperidone (p. 1838·1).
Vomiting; nausea; dyspepsia.

Toridran-N *Streger, Mex.*
Bromhexine (p. 1656·3).
Respiratory-tract congestion.

Torimibe *Baliarda, Arg.*
Atorvastatin calcium (p. 1309·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Torin *Veropharm, Rus.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Torio *Unison, Thai.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Torisel *Wyeth, Arg.; Pfizer, Austral.; Wyeth, Austria; Pfizer, Belg.; Wyeth, Braz.; Pfizer, Canad.; Wyeth, Chile; Wyeth, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Wyeth, Hung.; Wyeth, Irl.; Wyeth Lederle, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Rus.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK; Wyeth, USA.*
Temsirolimus (p. 866·2).
Mantle cell lymphoma; renal-cell carcinoma.

Torivas *Baliarda, Arg.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Torivas AT *Baliarda, Arg.*
Tablets, atorvastatin calcium (p. 1309·2); gastro-resistant tablets, aspirin (p. 22·2).
Cardiovascular risk reduction.

Torixal *Phytopharm, Ukr.*
⊗Torasemide (p. 1516·3).
Oedema; hypertension.

Torkol *Sandoz, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Torlasporin *Torlan, Spain.†*
Cefalexin (p. 234·1).
Bacterial infections.

Torlós *Torrent, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Torlós H *Torrent, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tormentan *Leros, Cz.*
Myrtillus (p. 2566·2); tormentil (p. 2633·2); burnet (p. 2462·3); chamomile (p. 2474·1); sage (p. 2608·3); peppermint leaf (p. 1877·1); liquorice (p. 1853·2).
Diarrhoea; dyspepsia; meteorism.

Tormentasan *Bioforce, Switz.†*
Tormentil (p. 2633·2).
Diarrhoea; mouth and throat inflammation.

Tormentile Forte *Farmina, Pol.*
Borax (p. 2459·2); ichthammol (p. 1705·3); tormentil (p. 2633·2); zinc oxide (p. 1729·1).
Wounds; burns; skin disorders.

Tormentiol *GSK, Pol.*
Borax (p. 2459·2); ichthammol (p. 1705·3); tormentil (p. 2633·2); zinc oxide (p. 1729·1).
Wounds.

Tornalate *Dura, USA.†*
⊗Bitolterol mesilate (p. 1203·2).
Asthma; bronchospasm.

Tornetis *Lek, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Tornix *Steierl, Ger.*
Crataegus (p. 2488·1); valerian (p. 2640·2); passion flower (p. 2584·1); rutoside (p. 2505·3).
Cardiac disorders.

Torocef *Torrent, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Torrent, Rus.
Ceftriaxone (p. 253·3).
Bacterial infections.

Torolac *Micro, India.*
Ketorolac trometamol (p. 80·2).
Pain; allergic conjunctivitis.

Torpain *Ikapharmindo, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Torpas *Sanofi-Aventis, Venez.*
Tiaprofenic acid (p. 137·1).
Inflammation; pain.

Torrem *Meda, Belg.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Torsid *Farmak, Ukr.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Torsilax *Neo Quimica, Braz.*
Caffeine (p. 1203·3); carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1).

Torson *Torrent, Rus.*
Zopiclone (p. 1118·1).
Sleep disorders.

Torva *Liferpal, Mex.*
Ambroxol (p. 1654·3); dextromethorphan (p. 1660·1).
Cough.

Torvacard *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Torvacol *Clonmel, Irl.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Torval *Torrent, Braz.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Torvalipin *Actavis, Hung.; Actavis, Pol.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; hypercholesterolaemia.

Torvaplus *Iasis, Gr.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Torvast *Orifarm, Denm.; Paranova, Denm.; Pfizer, Ital.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Torvastin *Biomedica, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Torvaxal *Sandoz, Turk.*
Atorvastatin (p. 1309·2).

Torvazin *Egis, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Torvic *Arlex, Mex.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Toryl *Remek, Gr.*
⊗Ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Torylet *Remek, Gr.*
⊗Ephedrine hydrochloride (p. 1663·2); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); ipecacuanha (p. 1667·2).

Torymycin *Chinta, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

T-OS *Seroyal, Canad.*
Calcium (p. 1783·1); molybdenum (p. 2082·3); phosphorus (p. 2589·2); vitamin D (p. 2112·3).

Tos Mai *Gayoso, Spain.*
Dextromethorphan hydrobromide (p. 1660·1); benzocaine (p. 1980·2); guaiacol (p. 1666·1); sodium benzoate (p. 1738·2).
Cough.

Tosambrex *Sertex, Arg.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Tosan *TO-Chemicals, Thai.*
Losartan potassium (p. 1422·2).
Hypertension.

Tosano *Jean-Marie, Hong Kong.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Toscacalm *Genepharm, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Toscacort *Genepharm, Gr.*
⊗Fluorometholone (p. 1637·2).
Eye disorders.

Toscalmin *Benitol, Arg.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Toscamycin-R *Genepharm, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Toscapen *Genepharm, Gr.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Toscof *Cipla, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline sulfate (p. 1228·1); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Tosdrope *Schering-Plough, Port.*
⊗Dexchlorpheniramine maleate (p. 621·1); pseudoephedrine sulfate (p. 1676·1); guaifenesin (p. 1666·2).
Cough.

Tosedrin Compuesto *Lafedar, Arg.†*
Noscapine (p. 1670·3); guaifenesin (p. 1666·2).
Cough.

Tosedrin Jarabe *Lafedar, Arg.*
Ambroxol hydrochloride (p. 1654·3).
Bronchial catarrh.

Tosedrin NF *Lafedar, Arg.*
Gramicidin (p. 308·3); neomycin (p. 329·3); benzocaine (p. 1980·2).
Mouth and throat disorders.

Toseína *Italfarmaco, Port.*
Codeine phosphate (p. 40·2).
Cough.

Toseina *Italfarmaco, Spain.*
Codeine phosphate (p. 40·2).
Cough.

Tosicalcin *Pharmanel, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia.

Tosidrin *Fardi, Spain.*
Dihydrocodeine tartrate (p. 52·3).
Cough.

Tosifan *Precimex, Mex.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tos-Mai *Sperko, Ukr.*
Dextromethorphan hydrobromide (p. 1660·1); benzocaine (p. 1980·2); sodium benzoate (p. 1738·2); sulfogaiacol (p. 1678·1).
Cough.

T-Osmin *T Man, Thai.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Chronic venous insufficiency; haemorrhoids.

Tossamine *Novartis Consumer, Switz.*
Codeine phosphate (p. 40·2); noscapine (p. 1670·3).
Cough.

Tossamine plus *Novartis Consumer, Switz.*
⊗White capsules (daytime), codeine phosphate (p. 40·2); noscapine (p. 1670·3); *dl*-methylephedrine hydrochloride (p. 1669·2); blue capsules (nighttime), codeine phosphate; noscapine (p. 1670·3); diphenhydramine hydrochloride (p. 626·2).
Cough.

Tossa-X *Axapharm, Switz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tosse *Novartis, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Mucolytic.

Tossec *Klonal, Arg.*
Butamirate (p. 1657·3).
Cough.

Tossemed *Iodosan, Ital.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Tosseque *Medinfar, Port.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Tossex *Piramal, India.*
Codeine phosphate (p. 40·2); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2); sodium citrate (p. 1781·2).
Cough.

Tossex-S *Sarabhai Piramal, India.†*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Cough.

Tossilerg *Bunker, Braz.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Tossoral *Recordati, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tostop *Savant, Arg.*
Bromhexine (p. 1656·3) or bromhexine hydrochloride (p. 1656·3).
Cough.

Tostran *ProStrakan, Cz.†; ProStrakan, Denm.; ProStrakan, Fin.; ProStrakan, Ger.; ProStrakan, Gr.; ProStrakan, Hung.; ProStrakan, Irl.; ProStrakan, Neth.; ProStrakan, Norw.; Ferring, Pol.; ProStrakan, Port.; Cederberg, Switz.; ProStrakan, UK.*
⊗Testosterone (p. 2305·1).
Male hypogonadism; testosterone deficiency.

Tostrex *ProStrakan, Ital.; ProStrakan, Swed.*
⊗Testosterone (p. 2305·1).
Male hypogonadism.

Tosuben *Pisa, Mex.*
Etoposide (p. 790·2).

Tosuman *Faran, Gr.; Berna, Turk.*
A pertussis immunoglobulin (p. 2408·2).
Passive immunisation.

Totacef *BMS, Rus.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Totagesic *Ashford, Philipp.*
Mefenamic acid (p. 85·3).
Pain; fever.

Total *Allergan, USA.†*
Cleansing, soaking and wetting solution for hard contact lenses.

Total BRN Formula *Inno-Vite, Canad.†*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); *d*-alpha tocoferil acid succinate (p. 2119·2).

Total C *Roche, Hong Kong.†*
Hesperidin (p. 2505·2); rutoside (p. 2505·3); ascorbic acid (p. 2110·3).

Total Care *AMO, Austral.*
Cleansing, disinfecting, wetting, and storage solution for hard and gas permeable contact lenses.

Total Cold and Flu *Trillium, Canad.; Vita Health, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Total Eclipse *Triangle, USA.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3); lisadimate (p. 1710·3).
Sunscreen.

Total Eclipse Moisturizing *Triangle, USA.*
SPF 15: Padimate O (p. 1716·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Total Formula *Vitaline, USA.*
Vitamins; minerals.

Total Magnesiano *Temis, Arg.*
Effervescent tablets: Magnesium carbonate (p. 1856·2); magnesium fluoride (p. 2080·2); magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3).
Magnesium deficiency.

Temis, Arg.
Granules: Magnesium chloride (p. 1778·2); magnesium fluoride (p. 2080·2); magnesium iodide (p. 1786·3); magnesium carbonate (p. 1856·2); magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3).
Magnesium deficiency.

Temis, Arg.
Tablets: Magnesium citrate (p. 1857·1).
Magnesium deficiency.

Temis, Arg.
Effervescent powder: Magnesium chloride (p. 1778·2); magnesium fluoride (p. 2080·2); magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3).
Magnesium deficiency.

Total Magnesiano Antioxidante *Temis, Arg.*
Magnesium lactate (p. 1787·2); alpha-tocoferil acetate (p. 2119·2).
Magnesium and vitamin E deficiency.

Total Magnesiano B6 *Temis, Arg.*
Magnesium citrate (p. 1857·1); pyridoxine (p. 2105·3).
Magnesium and vitamin B_6 deficiency.

Total Magnesiano E *Temis, Arg.*
Oral powder: magnesium chloride; magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3); magnesium carbonate (p. 1856·2); ginseng (p. 2513·3); caffeine (p. 1203·3); tablets: vitamin E (p. 2119·1).
Tonic.

Total Magnesiano Energizante *Temis, Arg.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium sulfate (p. 1787·3).
Dietary supplement.

Total Magnesiano Fem *Temis, Arg.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2); magnesium sulfate (p. 1787·3).
Dietary supplement.

Total Magnesiano con Ginseng *Temis, Arg.*
Magnesium chloride (p. 1787·1); magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3); magnesium carbonate (p. 1786·3); ginseng (p. 2513·3); caffeine (p. 1203·3).
Tonic.

Total Magnesiano Limon *Temis, Arg.*
Magnesium chloride (p. 1787·1); magnesium fluoride (p. 2080·2); magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3).
Magnesium deficiency; renal calculi.

Total Magnesiano NF *Temis, Arg.*
Magnesium oxide (p. 1857·3); vitamin E acetate (p. 2119·2).
Magnesium and vitamin E supplement.

Total Magnesiano Sport *Temis, Arg.*
Magnesium chloride (p. 1778·2); magnesium sulfate (p. 1787·3); magnesium carbonate (p. 1856·2); magnesium fluoride (p. 2080·2); magnesium phosphate (p. 1787·3); ginseng (p. 2513·3); arginine aspartate (p. 2049·1); citrulline (p. 2056·3); vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); zinc sulfate (p. 2126·2); cobalt sulfate (p. 2482·2).
Dietary supplement.

Total Magnesiano Stress *Temis, Arg.*
Magnesium pidolate (p. 1787·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Magnesium deficiency; renal calculi.

Total Magnesiano con Vitamina C *Temis, Arg.*
Vitamin C (p. 2110·3); magnesium carbonate or magnesium chloride; magnesium fluoride (p. 2080·2); magnesium sulfate (p. 1787·3); magnesium phosphate (p. 1787·3).
Tonic.

Total Magnesiano con Vitaminas y Minerales *Temis, Arg.*
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Total NRG Lift *Inno-Vite, Canad.†*
Vitamins; minerals.

Total One Daily *Pro-Shop, Canad.†*
Vitamins; minerals.

Total Solucion *AMO, Arg.†; Visiontec, Arg.†*
Polyvinyl alcohol (p. 2204·2).
Cleansing, wetting, and soaking solution for hard and gas permeable contact lenses.

Total Vitamins *Natural Life, Arg.*
Vitamins; minerals.

TotalCare
Note: this name may be used for preparations of different composition.
Aus Biomed, Austral.†
Lactoferrin (p. 2539·3); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2); minerals; vitamins.
Immunomodulator; tonic; restoration of gastrointestinal flora.

Totalday *Natures Blend, USA.*
Minerals; vitamins; citrus bioflavonoids (p. 2505·2); inositol (p. 2533·2); rutoside (p. 2505·3).

Totalflora *Roux-Ocefa, Arg.*
Lactobacillus acidophilus (p. 2596·3); *Lactobacillus bifidus* (p. 2596·3); *Bacillus subtilis*; yeast (p. 2125·2); bacteriophages.
Restoration of gastrointestinal flora.

Totalip *Guidotti, Ital.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction.

Totalos Plus *Rovafarm, Arg.*
Collagen (p. 2483·2); proteoglycans; amino acids; hydroxyapatite (p. 2529·3).
Mineral supplement; osteogenesis imperfecta; osteomalacia; osteoporosis.

Totalprost *Teva, Hung.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Totalsolona *Paylos, Arg.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Totalvit *Somapharm, Canad.†*
Vitamins; minerals.

Totam *Hikma, Port.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Totamine *Baxter, Fr.*
Amino acids; electrolytes (p. 1775·1); vitamins.
Parenteral nutrition.

Totamol
Note: this name may be used for preparations of different composition.
TO-Chemicals, Thai.
Paracetamol (p. 115·1).
Fever; pain.

LCH, Hong Kong.†
⊗Atenolol (p. 1308·2).

Totaretic *CP Pharmaceuticals, UK.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Totasedan *Recalcine, Chile.†*
Bromazepam (p. 1041·2).
Anxiety.

Totect *TopoTarget, USA.*
Dexrazoxane (p. 1548·1).
Reduction of doxorubicin cardiotoxicity.

Totelle *Wyeth, Braz.*
Estradiol (p. 2271·1); trimegestone (p. 2310·3).
Menopausal disorders; osteoporosis.

Totelle Ciclico *Wyeth, Arg.*
Pink tablets, estradiol (p. 2271·1); red tablets, estradiol; trimegestone (p. 2310·3).
Menopausal disorders.

Wyeth, Chile.
Pale pink tablets, estradiol (p. 2271·1); pink tablets, estradiol; trimegestone (p. 2310·3).
Osteoporosis; menopausal disorders.

Wyeth, Venez.
14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; trimegestone (p. 2310·3).
Menopausal disorders.

Totelle Ciclo *Wyeth, Braz.*
14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; trimegestone (p. 2310·3).
Menopausal disorders; osteoporosis.

Totelle Continuo *Wyeth, Arg.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Venez.*
Estradiol (p. 2271·1); trimegestone (p. 2310·3).
Menopausal disorders; osteoporosis.

Totelle Secuencial *Wyeth, Mex.*
14 Tablets, estradiol (p. 2271·1); 14 tablets, estradiol; trimegestone (p. 2310·3).
Menopausal disorders; osteoporosis.

Totephan *Expanscience, Fr.†*
Cream: ⊗Glycerol (p. 2517·2); cholesterol (p. 2179·1); oleic acid (p. 2200·1); urea (p. 1727·3).
Nail disorders.

Expanscience, Fr.†
Oral powder: Plant proteins; vitamins; minerals.
Hair and nail tonic.

Tot'Hema *Confar, Port.*
Ferrous gluconate (p. 2061·2); manganese gluconate (p. 2081·2); copper gluconate (p. 2057·2); cobalt glutamate; cyanocobalamin (p. 2107·2).
Anaemia.

Innotech, Fr.; Innotech, Rus.; Innotech, Ukr.
Ferrous gluconate (p. 2061·2); manganese gluconate (p. 2081·2); copper gluconate (p. 2057·2).
Iron deficiency; iron-deficiency anaemia.

Totifen
Note: this name may be used for preparations of different composition.
Elpen (Ελπεν), Gr.
Ketoprofen (p. 79·1).
Inflammatory disorders.

Tottizim *SoSe, Ital.*
Ceftazidime (p. 250·2).
Gram-negative bacterial infections.

Totilac *Kalbe, Indon.; Innogene, Malaysia; Delex, Philipp.*
Sodium lactate (p. 1781·2); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1).
Fluid and electrolyte disorders; resuscitation in post cardiac surgery.

Totocortin *Winzer, Ger.†*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Eye disorders.

Totonik *Pharmaceutical Enterprises, S.Afr.*
Vitamins.
Tonic.

Toularynx *Qualiphar, Belg.*
Codeine phosphate (p. 40·2); euphorbia (p. 2501·3).
Cough.

Toularynx Thym *Qualiphar, Belg.*
Thyme (p. 2630·2).
Cough.

Touristil *Johnson & Johnson Consumer, Belg.*
Cinnarizine (p. 622·1); domperidone maleate (p. 1838·1).
Motion sickness; nausea; vomiting; dyspepsia; vertigo; sleep disorders.

Touro A & H *Dartmouth, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Allergic rhinitis; nasal congestion.

Touro Allergy *Dartmouth, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Rhinitis; upper respiratory-tract congestion.

Touro CC *Dartmouth, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs; nasal congestion.

Touro DM *Dartmouth, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Touro LA *Dartmouth, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs and cold symptoms.

Touxium Antitussivum *SMB, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Toux-San *Takeda, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Toux-San Codeine *Takeda, Belg.*
Codeine phosphate (p. 40·2).
Cough.

Tovalt *Biovail, USA.†*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Tovanira *Crinos, Ital.*
Atorvastatin (p. 1309·2).

Tovanor *Novartis, Neth.*
Glycopyrronium bromide (p. 2519·3).
Obstructive airways disease.

Tovene *Stada, Ger.†*
Diosmin (p. 2505·2).
Venous insufficiency.

Toverine *TO-Chemicals, Thai.*
Drotaverine hydrochloride (p. 2497·3).
Smooth muscle spasm.

Toviaz *Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA.*
Fesoterodine fumarate (p. 2358·1).
Bladder hyperactivity; urinary incontinence; bladder instability.

Tovita *Osteofit, Hung.*
Vitamins; minerals.
A range of dietary supplements.

Towazuren *Towa, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Toxam *Austral, Arg.*
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1).
Cough.

Toxambay *Austral, Arg.*
Bromhexine hydrochloride (p. 1656·3); clofedanol hydrochloride (p. 1659·1).
Cough.

Toxex *Pekana, Canad.*
Bryonia alba (p. 2461·3); clematis erecta; echinacea angustifolia (p. 2498·1); galium aparine (p. 2481·2); glechoma hederacea (p. 2523·1); hydrastis canadensis (p. 2528·1); ledum palustre (p. 2550·1); argentum nitricum (p. 2615·3).
Homoeopathic preparation.

Pekana, Hung.
Argentum nitricum (p. 2615·3); clematis recta; echinacea angustifolia (p. 2498·1); galium aparine (p. 2481·2); glechoma hederacea (p. 2523·1); hydrastis canadensis (p. 2528·1); magnesium fluoratum (p. 2080·2); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Pekana, Neth.
Argentum nitricum (p. 2615·3); clematis erecta; echinacea angustifolia (p. 2498·1); galium aparine (p. 2481·2); glechoma hederacea (p. 2523·1); hydrastis canadensis (p. 2528·1); pulsatilla pratensis (p. 2600·2); calcarea fluorica (p. 2053·1).
Homoeopathic preparation.

Toxicarb *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Activated charcoal (p. 1537·3).
Poisoning.

Toxicol *Eagle, Austral.*
Amino acids; vitamin B substances (p. 2102·3); minerals; taraxacum (p. 2625·3); angelica (p. 2443·3); chelidonium majus (p. 2522·2); gentian (p. 2512·1); lycopodium clavatum (p. 2547·1); inositol; lecithin; taurine; urea.
Liver disorders; tonic.

Toxigen *Serum Institute, Philipp.*
A tetanus antitoxin (p. 2420·2).
Passive immunisation.

toxi-loges *Jacoby, Austria; Loges, Ger.*
Oral drops: Echinacea (p. 2498·1); eupatorium perfoliatum (p. 2459·1); baptisia tinctoria (p. 2647·2); cinchona succirubra (p. 2478·3); bryonia cretica (p. 2461·3); aconitum napellus (p. 2428·3); cephaelis ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Loges, Ger.
Tablets: Eupatorium perfol. (p. 2459·1); baptisia (p. 2647·2); aconitum (p. 2428·3); ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Loges, Ger.
Injection: Echinacea angustifolia (p. 2498·1); apis mellifica (p. 2445·2); ferrum phosphoricum (p. 2077·1); lachesis (p. 2538·3); baptisia (p. 2647·2); hepar sulfuris (p. 1721·3).
Homoeopathic preparation.

Loges, Ger.†
Oral liquid: Echinacea purpurea (p. 2498·1).
Respiratory- and urinary-tract infections.

Toxipen *Unison, Philipp.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Toxiselect *Dreluso, Ger.*
Echinacea purpurea (p. 2498·1); lachesis (p. 2538·3); sulfur (p. 1721·1); bryonia (p. 2461·3); apis mellifica (p. 2445·2).
Homoeopathic preparation.

Toxogonin *Merck, Austria†; Merck, Chile; Merck, Cz.; Merck Serono, Ger.; Merck, Neth.; Merck, S.Afr.*
Obidoxime chloride (p. 1566·3).
Organophosphorus poisoning.

Toxogonine *Merck, Switz.*
Obidoxime chloride (p. 1566·3).
Organophosphorus poisoning.

Toxol *Antibioticos, Mex.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Toynox *Johnson & Johnson, China.*
Liquorice (p. 1853·2).
Sore throat.

Tozam *Torrent, Philipp.*
Losartan potassium (p. 1422·2); amlodipine besilate (p. 1304·1).
Hypertension.

Tozide *Utopian, Thai.*
Glipizide (p. 474·1).
Diabetes mellitus.

Tozolden *Denver, Arg.*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; angina pectoris; myocardial infarction.

T+P *Sambrook, Gr.*
⊗Timolol maleate (p. 1513·2); pilocarpine (p. 2010·2).
Glaucoma.

TPH *Baxter, Ital.*
Amino acids.
Parenteral nutrition for neonates and infants.

Tpiao *Shenyang Sunshine, Philipp.*
Recombinant human thrombopoietin (p. 1164·1).
Thrombocytopenia.

TPN *Hospira, Canad.*
Electrolytes (p. 1775·1).

TP-Ophtal *Winzer, Ger.*
⊗Pilocarpine hydrochloride (p. 2010·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

TR *T Man, Thai.*
Thyroid (p. 2345·3).

TR-01 *Sigma, Arg.*
Vitamins.

Tr Iodine Sahakarn *United Drug, Thai.*
Iodine (p. 2336·3); potassium iodide (p. 2336·3).
Skin disinfection.

Trabar *Mepha, Israel†; Acino, Switz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trabecan *Teva, Hung.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Trabilin *Mepha, Braz.†; Mepha, Malaysia.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trabiran *AMPDR, Port.†*
Irbesartan (p. 1411·1).
Hypertension.

Trablene *Ranbaxy, Mex.†*
Adapalene (p. 1692·1).
Acne.

Trablok *Teva, Mex.†*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Trac *Duopharma, Philipp.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Tracaine *Duopharma, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tracefusin *Pisa, Mex.*
Trace elements.
Parenteral nutrition.

Tracel *Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Trace elements.
Parenteral nutrition.

Tracelyte *Sanderson, Chile.*
Trace elements.
Parenteral nutrition.

Tracetin *Otto, Indon.*
Neomycin sulfate (p. 330·1); bacitracin (p. 225·3).
Skin infections.

Trachilid *Engelhard, Ger.; Engelhard, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Sore throat.

Trachisan
Note: this name may be used for preparations of different composition.
Engelhard, Cz.; Engelhard, Neth.
Lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders; sore throat.

Engelhard, Singapore.
Lozenges: Chlorhexidine gluconate (p. 1743·3); lidocaine (p. 1988·1); tyrothricin (p. 384·1).
Mouth and throat disorders.

Farmasyn, Gr.; Engelhard, Ukr.
Chlorhexidine gluconate (p. 1743·3); lidocaine hydrochloride (p. 1988·2); tyrothricin (p. 384·1).
Mouth and throat disorders.

Trachisan Halsschmerztabletten *Engelhard, Ger.†*
Lidocaine hydrochloride (p. 1988·2).
Sore throat.

Trachitol *Kempharm, Neth.*
Lidocaine hydrochloride (p. 1988·2); alum (p. 2439·1); propyl hydroxybenzoate (p. 1757·2).
Sore throat.

Trachon *Bernofarm, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Tracidol *YSP, Malaysia.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tracilarin *Norma (Νορμα), Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Tracine *Medicine Products, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tracitrans *Fresenius Kabi, Fr.*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

Tracitrans Infant *Paesel, Ger.*
Trace elements.
Parenteral nutrition.

Tracitrans Plus *Fresenius Kabi, Chile; Fresenius Kabi, Ger.; Fresenius Kabi, Mex.*
Electrolytes (p. 1775·1); trace elements.
Parenteral nutrition.

Tracleer *Biotoscana, Arg.; Actelion, Austral.; Actelion, Austria; Actelion, Belg.; Actelion, Braz.; Actelion, Canad.; Actelion, China; Actelion, Cz.; Actelion, Denm.; Actelion, Fin.; Actelion, Fr.; Actelion, Ger.; Actelion, Gr.; Actelion, Hong Kong; Actelion, Hung.; Actelion, Irl.; Neopharm, Israel; Actelion, Ital.; Actelion, Malaysia; Actelion, Neth.; Actelion, Norw.; Healthcare Logistics, NZ; Actelion, Pol.; Actelion, Port.; Actelion, Rus.; Actelion, Singapore; Actelion, Spain; Actelion, Swed.; Actelion, Switz.; Actelion, Thai.; Actelion, Turk.; Actelion, UK; Actelion, USA.*
Bosentan (p. 1327·1).
Pulmonary hypertension; systemic sclerosis.

Tracne *Interbat, Indon.*
Tretinoin (p. 1725·2).
Acne.

Traconal *Ache, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Tracor *Pharmacore, Indon.*
Itraconazole (p. 583·3).
Fungal infections.

Tracozon *Ariston, Braz.†*
Itraconazole (p. 583·3).
Fungal infections.

Tracrium *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Fr.; GSK, Ger.†; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.†; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; Hospira, USA.†*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Tractocile *Ferring, Arg.; Ferring, Austria; Ferring, Belg.; Ferring, Chile†; Ferring, China; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Irl.; Ferring, Ital.; Ferring, Malaysia; Ferring, Mex.; Ferring, Neth.; Ferring, Norw.; Pharmaco, NZ; Ferring, Pol.; Ferring, Port.; Ferring, S.Afr.; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, Thai.; Ferring, Turk.; Ferring, UK; Ferring, Ukr.*
Atosiban acetate (p. 2132·2).
Premature labour.

Tractoclin *Quesada, Arg.*
Macrogol 3350 (p. 2547·3); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); sodium sulfate (p. 1888·1).
Bowel evacuation.

Tractoduo *Quesada, Arg.*
Bisacodyl (p. 1821·1).
Bowel evacuation.

Tractolax *Quesada, Arg.*
Macrogol 3350 (p. 1775·1).
Constipation.

Tractoven *Amnol, Ital.*
Capsules: Centella (p. 1698·3); melilot (p. 2552·3); rutoside (p. 2505·3); vitamin E (p. 2119·1).
Nutritional supplement.

Tracur *Cristalia, Braz.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Tracurix *Richmond, Arg.*
Atracurium (p. 2030·1).
Competitive neuromuscular blocker.

Tracuron *Scott-Cassara, Arg.*
Atracurium (p. 2030·1).
Competitive neuromuscular blocker.

Tracutil *Braun, Arg.; Braun, Austria; Braun, Cz.*
Minerals; trace elements.
Parenteral nutrition.

Braun, Belg.; Braun, Chile; Braun, Fr.; Braun, Ger.; Braun, Hung.; Braun, Pol.; Braun, Port.; Braun, Turk.; Braun, UK.
Trace elements.
Parenteral nutrition.

Braun, Switz.
Minerals.
Parenteral nutrition.

Tracyclin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Tetracycline hydrochloride (p. 373·2).
Acne.

Tradea *Psicofarma, Mex.*
⊗Methylphenidate hydrochloride (p. 2326·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Tradef *Vulm, Cz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradelia *Wolff, Ger.*
Estradiol (p. 2271·1).
Menopausal disorders.

Traderma *Advaita, Mex.*
Tacrolimus (p. 1968·3).
Atopic eczema.

Tradil *Nordic, Swed.; Nobel, Turk.*
Dexibuprofen (p. 43·1).
Inflammation; pain; osteoarthritis.

Tradimed *PlantaPhile, UK.*
Ginger (p. 1844·1).
Digestive disorders; motion sickness.

Tradimed Vapour & Muscle Rub *PlantaPhile, UK.*
Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); rosemary oil (p. 2607·3).
Nasal congestion; musculoskeletal pain and stiffness.

Traditional Herbal Laxative *Douglas, Canad.†*
Aloes (p. 1816·1); cascara (p. 1826·1); liquorice (p. 1853·2); senna (p. 1885·1); taraxacum (p. 2625·3).
Constipation.

Traditional Laxative *Desilets, Canad.*
Aloes (p. 1816·1); cascara (p. 1826·1).
Constipation.

Tradiver *Aurora, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Tradjenta *Boehringer Ingelheim, USA.*
Linagliptin (p. 488·1).
Diabetes mellitus.

Tradol *Medicus, Gr.; Rowex, Irl.; Grunenthal, Mex.; Rusan, Rus.; Shin Poong, Singapore.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradolan *Lannacher, Austria; GL Pharma, Denm.; Nordic Drugs, Fin.; Nordic, Swed.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradolgesic *Bangkok Lab & Cosmetic, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradomal *Harson, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradonal *Aspen, Austral.; Meda, Belg.; Meda, Ital.; Meda, Neth.; Transfarma, Philipp.; Meda, Spain; Meda, Switz.; Meda, Thai.†; Pharmalink, Thai.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradorec *Paladin, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradosik *Sanbe, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tradox *Andromaco, Chile.*
Lamotrigine (p. 527·2).
Epilepsy.

Tradyl *Interbat, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Traflan *Bayer, Venez.*
Etofenamate (p. 57·2).
Inflammation; pain.

Traflash *Meda, Ital.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trafloxal *Tramedico, Belg.; Bausch & Lomb, Neth.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

Trafuril *Faran, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Tragesik *Kalbe, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trajenta *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Neth.; Lilly, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Lilly, Spain; Boehringer Ingelheim, UK; Lilly, UK.*
Linagliptin (p. 488·1).
Diabetes mellitus.

Trakor *Savio, Ital.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Tral
Note: this name may be used for preparations of different composition.
Duopharma, Philipp.
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Tralen *Pfizer, Braz.; Pfizer, Venez.*
Tioconazole (p. 595·3).
Fungal skin and nail infections.

Tralgi *IPI, Indon.*
Mebhydrolin napadisilate (p. 634·2).
Allergic disorders.

Tralgit *Zentiva, Cz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trali *AstraZeneca, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation; bowel evacuation.

Tralic *Andromaco, Mex.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tralin *BioSaude, Port.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Tralinan *Hexal, Denm.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Tralinser *Interpharma, Chile.†*
Sertraline (p. 448·1).
Depression.

Tralisen *Epifarma, Ital.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Tralix *Hexal, Denm.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Tralodie *GiEnne, Ital.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tram *TNP, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Trama *Kade, Ger.†; Rafa, Israel.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramabene *Ratiopharm, Austria; Ratiopharm, Cz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramabeta *Betapharm, Ger.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramacet *Janssen-Cilag, Arg.; Janssen-Ortho, Canad.; Janssen-Cilag, Mex.; Euro Registratie, Neth.; Janssen-Cilag, S.Afr.; Grunenthal, UK.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain; fever.

Tramacip *Cipla, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramacip Plus *Cipla, India.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Tramactil Uno *Gebro, Switz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramada *Charoen Bhaesaj, Malaysia; Charoen, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramaden *Neo Quimica, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramadex *Dexcel, Israel.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramadil *Union Drug, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramadin *Ratiopharm, Fin.; Utopian, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramadoc *Docpharm, Ger.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramadolor *Hexal, Austria; Sandoz, China; Hexal, Ger.†; Sandoz, Hung.; Sandoz, Turk.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramadon *Cristalia, Braz.; Utopian, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramagetic *Nycomed, Fin.†; Mundipharma, Neth.; Mundipharma, Norw.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramagit *Krewel Meuselbach, Cz.†; Krewel, Ger.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramahexal *Sandoz, Austral.; Sandoz, Pol.; Sandoz, S. Afr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramajuna *Disphar, Neth.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramake *Galen, Irl.; koGen, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trama-Klosidol *Bago, Arg.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramaklosidol *Bago, Rus.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trama-Klosidol Plus *Bago, Arg.†*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Tramal *Nycomed, Arg.; CSL, Austral.; Grunenthal, Austria; Pfizer, Braz.; Grunenthal, Chile; Grunenthal, China; Grunenthal, Cz.; Leciva, Cz.; Orion, Fin.; Grunenthal, Ger.; Vianex (Βιανεξ), Gr.; Grunenthal, Hong Kong†; Grunenthal, Indon.; Pharos, Indon.; Grunenthal, Israel; Shinyaku, Jpn; Grunenthal, Neth.; CSL, NZ; Mundipharma, Philipp.; Grunenthal, Pol.; Grunenthal, Port.; Grunenthal, Rus.; Janssen-Cilag, S.Afr.; Grunenthal, Singapore; Grunenthal, Switz.; Sanofi-Aventis, Thai.; Grunenthal, Venez.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramal Plus *Nycomed, Arg.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Tramalgic *Nycomed, Hung.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramalgin *Stirol, Ukr.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramalin *EG, Ital.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramaliv *Teuto, Braz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramamed *Hexal, Ital.; Medifive, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramanovag *Gobbi, Arg.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramapine *Pinewood, Irl.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramaspen *Aspen, S.Afr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramastad *Stada, Austria.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramax *Pond's, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramazac *Zydus, India; Zydus, S.Afr.; Zydus Cadila, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramazela *Disphar, Neth.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Trambo *Actavis, Fin.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramcet *Janssen, Jpn.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Tramcod *Polfa Warszawa, Pol.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramcontin *Mundipharma, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramed *Bajamed, Mex.*
Tramadol (p. 139·2).
Pain.

Tramedo *Alphapharm, Austral.; Pacific, NZ.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramelene *Ethypharm, Neth.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramentel *Mavi, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Tramex *Antigen, Irl.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramgesic *Adcock Ingram, S.Afr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramic *TO-Chemicals, Thai.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders.

Tramid *Euro-Med, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramil *Pfizer Consumer, Irl.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Traminer *Ativus, Braz.†*
Valerian (p. 2640·2).
Anxiety.

Tramisal *Ipsen, Fr.*
Ginkgo biloba (p. 2512·3).
Mental function impairment in the elderly; peripheral vascular disorders.

Tramium *SMB, Belg.; 2care4, Denm.; SMB, Fin.; SMB, Singapore.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramkor *Samjin, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramo *Jean-Marie, Hong Kong.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramoda *LBS, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramolin *Bryntsalov, Rus.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramox *Avex, Malaysia.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramquel *Meda, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramsilone *Greater Pharma, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Mouth disorders; skin disorders.

Tramsone *Hoe, Malaysia; Hoe, Singapore.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tramulief *Sovereign, UK.*
Tramadol (p. 139·2).
Pain.

Tramundal *Mundipharma, Austria.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramundin *Mundipharma, Cz.; Mundipharma, Ger.; Mundipharma, Malaysia; Mundipharma, Philipp.; Norpharma, Pol.; Mundipharma, Switz.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tramus *Dexa, Indon.*
Atracurium besilate (p. 2030·1).
Competitive neuromuscular blocker.

Tramy *Neves, Port.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Tran *Vitamex, Pol.*
Cod-liver oil (p. 2056·3).
Vitamin A, D, and E deficiency.

Tranadon-S *Acdhon, Thai.*
Dipotassium clorazepate (p. 1056·3).

Tranalpha *Alphapharm, Austral.*
Trandolapril (p. 1517·2).
Hypertension; left ventricular dysfunction following myocardial infarction.

Tranarest *Zydus, India.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; menorrhagia.

Tranavan *Polipharm, Thai.*
Lorazepam (p. 1080·3).
Anxiety.

Tranax *Cipla, India.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Tran cap *TP, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia; mixed anxiety depressive states; dystonias.

Tranclocin *Proel, Gr.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Tranclor *Siam Bheasach, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; mixed anxiety depressive states; dystonias.

Trancolon *Astellas, Jpn.*
Mepenzolate bromide (p. 1859·1).
Irritable bowel syndrome.

Trancolon P *Astellas, Jpn.*
Mepenzolate bromide (p. 1859·1); phenobarbital (p. 535·2).
Irritable bowel syndrome.

Trancolong *Kade, Ger.*
Flupirtine maleate (p. 65·2).
Pain.

Trancon *Condrugs, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; mixed anxiety depressive states; dystonias.

Trancopal Dolo *Kade, Ger.*
Flupirtine maleate (p. 65·2).
Pain.

Trandate *Aspen, Austral.; GSK, Austria; GSK, Belg.; Paladin, Canad.; GSK, Chile; Cenexi, Cz.; GSK, Denm.; Genopharm, Fr.; GSK, Gr.; IFET (ΙΦΕΤ), Gr.; Sigma, Hong Kong†; UCB, Irl.; Perrigo, Israel; Teofarma, Ital.; GSK, Malaysia; Aspen, Neth.; Aspen, Norw.; Healthcare Logistics, NZ; Aspen, S.Afr.; GSK, Singapore; Kern, Spain; GSK, Swed.; Pro Concepta, Switz.; Invida, Thai.; Focus, UK; Prometheus, USA.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension; angina pectoris; controlled hypotension.

Trandiur *Teofarma, Ital.*
⊗Labetalol hydrochloride (p. 1416·2); chlortalidone (p. 1335·2).
Hypertension.

TrandoGen *Generics, Pol.*
Trandolapril (p. 1517·2).
Hypertension; myocardial infarction.

Trandrozine *Asian Pharm, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus.

Trane *Omega, Arg.*
Chlorpropamide (p. 470·1).
Diabetes mellitus.

Tranec *Gracia, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; inflammation; haemorrhage.

Tranex *Malesci, Ital.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Tranexal *Rivero, Arg.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Tranexam *Mir, Rus.; Stada, Ukr.*
Tranexamic acid (p. 1164·2).
Fibrinolytic haemorrhage; hereditary angioedema; hypersensitivity reactions; oropharyngeal inflammation.

Tranexid *Dexa, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; haemophilia.

Tranfib *Cipla, India.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Tranfib MF *Cipla, India.*
Tranexamic acid (p. 1164·2); mefenamic acid (p. 85·3).
Menorrhagia.

Trangina *Alpharma, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Trangorex *Sanofi-Aventis, Spain; Sanofi-Aventis, Venez.*
Amiodarone hydrochloride (p. 1300·1).
Arrhythmias; heart failure.

Tranic *Pharmafrica, S.Afr.*
Tranexamic acid (p. 1164·2).

Tranizolo *EG, Ital.*
Itraconazole (p. 583·3).
Fungal infections.

Tranject *Mylan, S.Afr.*
Diazepam (p. 1063·2).
Premedication; alcohol withdrawal syndrome; status epilepticus; febrile convulsions; skeletal muscle spasm; anxiety disorders.

Trankil *Rotexmedica, Philipp.*
Diazepam (p. 1063·2).
Anxiety; delirium tremens; epilepsy; skeletal muscle spasm; tetanus.

Trankilium *Ni-The, Gr.*
Lorazepam (p. 1080·3).
Anxiety disorders; insomnia; status epilepticus.

Trankimazin *Pfizer, Spain.*
Alprazolam (p. 1035·2).
Anxiety disorders.

Trankitec *Tecnofarma, Mex.*
Magnesium valproate (p. 553·1).
Epilepsy; bipolar disorder; migraine.

Tranko-Buskas *Fako, Turk.*
Medazepam (p. 1083·2); hyoscine butylbromide (p. 1845·3).
Anxiety; smooth muscle spasm.

Trankvezipam *Dalkhimfarm, Rus.*
Phenazepam (p. 1096·3).
Anxiety; psychoses; insomnia; withdrawal syndromes; epilepsy; skeletal muscle spasm; movement disorders; premedication.

Tranmed *Medicpharma, Thai.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Tranolan *Olan-Kemed, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; epilepsy; alcohol withdrawal syndrome; skeletal muscle spasm; premedication.

Tranon *Recip, Swed.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema.

Tranoxy *Biolink, Philipp.*
Oxytocin (p. 2143·1).
Lactation induction; labour induction; missed abortion; postpartum haemorrhage.

Tranpate *T Man, Thai.†*
Dipotassium clorazepate (p. 1056·3).
Anxiety; epilepsy; alcohol withdrawal syndrome.

Tranpon *LSP, Thai.*
Dipotassium clorazepate (p. 1056·3).

Tran-Q *Guardian, Indon.†*
Buspirone (p. 1042·1).
Anxiety.

Tranqipam *Aspen, S.Afr.*
Lorazepam (p. 1080·3).
Anxiety; sedative; premedication; alcohol withdrawal syndrome.

Tranquigor *Lavigor, Spain.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Nervous disorders; insomnia.

Tranquil *Pharmadass, UK.*
Magnolia; valerian (p. 2640·2); St John's wort (p. 449·1).
Formerly contained crataegus, tilia flower, viburnum, and hawthorn oil.

Tranquil Night *Blackmores, Austral.*
Lavender (p. 2541·1); lupulus (p. 2546·1); passion flower (p. 2584·1); avena (p. 2451·1).
Anxiety.

Tranquilimag *Automedic, Fr.†*
Magnesium sulfate (p. 1787·3); yeast from saccharomyces cerevisiae (p. 2125·2).
Magnesium deficiency.

Tranquinal *Bago, Arg.; Bago, Braz.*
Alprazolam (p. 1035·2).
Anxiety; insomnia.

Tranquinal Soma *Bago, Arg.*
Alprazolam (p. 1035·2); sulpiride (p. 1107·3).
Psychosomatic disorders.

Tranquirit *Sanofi-Aventis, Ital.*
Diazepam (p. 1063·2).
Anxiety; psychoses; insomnia; epilepsy.

Tranquital *Novartis Sante, Fr.*
Valerian (p. 2640·2); crataegus (p. 2488·1).
Nervous disorders; insomnia.

Tranquo
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Belg.
Oxazepam (p. 1092·2).
Anxiety disorders.

Transacalm *Pharmadeveloppement, Fr.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

TransAct *Reckitt Benckiser, S.Afr.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, and soft-tissue disorders.

Transact Lat *Amdipharm, Ital.; Amdipharm, Port.*
Flurbiprofen (p. 65·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Transamin *Nikkho, Braz.; Daiichi Sankyo, China; Nikolakopoulos (Νικολακοπουλος), Gr.; Daiichi, Hong Kong; Daiichi, Indon.; Otto, Indon.; Daiichi, Jpn; Daiichi Sankyo, Malaysia; Daiichi Sankyo, Thai.*
Tranexamic acid (p. 1164·2).
Fibrinolysis; hereditary angioedema; inflammation; hyperfibrinolytic haemorrhage.

Transamine *Fako, Turk.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders.

Transantor *Antor, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Transbronchin *Meda, Ger.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Transbroncho *Kalbe, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with excess or viscous mucus.

Transcalcium *Verisfield, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Transcop *Recordati, Ital.*
Hyoscine (p. 1845·3).
Motion sickness.

TransCyte *Smith & Nephew, UK; Smith & Nephew, USA.*
Bioengineered human skin equivalent (p. 1720·2).
Burns.

Transderm Scop *Novartis Consumer, USA.*
Hyoscine (p. 1845·3).
Motion sickness.

Transderma B *Szama, Arg.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Transderma H *Szama, Arg.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Transdermal-NTG *Warner Chilcott, USA.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Transderm-Nitro *Novartis, Canad.; Novartis, Philipp.; Novartis, USA.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; phlebitis.

Transderm-V *Novartis, Canad.*
Hyoscine (p. 1845·3).
Motion sickness.

Transene *Sanofi-Aventis, Ital.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia; nervous disorders.

Transic *TP, Thai.*
Tranexamic acid (p. 1164·2).
Haemorrhage.

Transiderm TTS *Euro Registratie, Neth.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; prophylaxis of phlebitis and extravasation.

Transiderm-Nitro *Novartis, Austral.; Novartis, Fin.; Novartis, Irl.; Novartis, Neth.; Novartis, Norw.; Novartis, Swed.; Novartis, UK.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; prophylaxis of phlebitis and extravasation.

Transifine *Lero, Fr.*
Fructo-oligosaccharides (p. 2508·1); pectin (p. 2200·3); tamarind (p. 1892·2); prune (p. 1881·1).

Transilan *Innotech, Ukr.*
Ispaghula (p. 1849·1).
Constipation.

Transilane *Innotech, Fr.*
Ispaghula (p. 1849·1).
Constipation.

Innotech, Hong Kong.†
Psyllium hemicellulose (p. 1849·1).
Constipation.

Transilax *Mayoly-Spindler, Mex.*
Lactulose (p. 1850·3); liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Constipation.

Transimune *Troikaa, India.*
Azathioprine (p. 1940·3).
Organ transplantation; auto-immune disorders.

Transipeg *Bayer Consumer, Arg.; Bayer, Belg.; Bayer Sante, Fr.; Bayer, Irl.†; Bayer, Neth.; Bayer Consumer, Rus.; Mundipharma, Switz.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Constipation.

Bayer, Port.†; Roche, Turk.†
Macrogol 3350 (p. 2547·3).
Constipation.

Transipen *Demo, Gr.*
⊗Indapamide (p. 1409·2).
Hypertension.

Transitol
Note: this name may be used for preparations of different composition.
Aptalis, Fr.
White soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2).
Constipation.

Therabel, Belg.; GiEnne, Ital.
Lactulose (p. 1850·3); liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Constipation.

Transityl *SMB, Belg.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Translipo-Triple *Centaur, India.*
⊗Beclometasone dipropionate (p. 1621·2); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Transmer *Tradiphar, Fr.†*
⊗Promethazine hydrochloride (p. 638·2); ephedrine hydrochloride (p. 1663·2).
Motion sickness.

Transmetil *Abbott, China; Abbott, Cz.; Therabel, Ital.*
Ademetionine butanedisulfonate (p. 2429·3).
Liver disorders.

Transmin *Vargas, Venez.*
Menthol (p. 2553·2); cineole (p. 2479·1); camphor (p. 2466·2).

Transmuco *Kalbe, Indon.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders with excess or viscous mucus.

Transorbin *Bayer, Gr.*
Macrogol 3350 (p. 2547·3).
Laxative.

Trans-Plantar *Bradley, Canad.†*
Salicylic acid (p. 1719·1).
Plantar warts.

Transpon *LSP, Thai.*
Dipotassium clorazepate (p. 1056·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Transpulmin
Note: this name may be used for preparations of different composition.
Ache, Braz.
Syrup: Guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Ache, Braz.
Suppositories: Camphor (p. 2466·2); guaiacol (p. 1666·1); cineole (p. 2479·1); menthol (p. 2553·2).
Respiratory-tract congestion.

Transfarma, Indon.
Pipazetate (p. 1675·2); isothipendyl hydrochloride (p. 631·2); liquorice extract (p. 1853·2); guaifenesin (p. 1666·2).
Cough.

Meda, Cz.†
Eucalyptus oil (p. 2501·2); pumilio pine oil (p. 2591·1).
Cold symptoms.

Transpulmin Balsam
Note: this name may be used for preparations of different composition.
Transfarma, Indon.
Eucalyptus oil (p. 2501·2); menthol (p. 2553·2); camphor (p. 2466·2); sage oil (p. 2609·1); chamomile (p. 2474·1).
Cough; influenza symptoms.

Meda, Ger.†
Cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2).
Cold symptoms.

Transfarma, Philipp.†
Camphor (p. 2466·2); chamomile (p. 2474·1); cineole (p. 2479·1); menthol (p. 2553·2); sage oil (p. 2609·1).
Cough; cold and influenza symptoms; respiratory congestion.

Transpulmin Balsamo *Ache, Braz.*
Camphor (p. 2466·2); guaiacol (p. 1666·1); cineole (p. 2479·1); menthol (p. 2553·2).
Respiratory-tract congestion.

Transpulmin BB Balsam *Transfarma, Indon.*
Chamomile (p. 2474·1); cineole (p. 2479·1).
Headache; backache; influenza symptoms.

Transpulmin G *Transfarma, Philipp.*
Guaifenesin (p. 1666·2).
Cough.

Transpulmin Kinderbalsam S *Meda, Ger.†*
Eucalyptus oil (p. 2501·2); pine needle oil (p. 2591·1).
Cold symptoms.

Transpulmin N *Meda, Switz.*
Camphor (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2).
Respiratory-tract congestion.

Transpulmina *Meda, Port.*
Adult ointment; adult and paediatric suppositories: Camphor (p. 2466·2); cineole (p. 2479·1); menthol (p. 2553·2).
Respiratory-tract disorders.

Meda, Port.
Paediatric ointment: Camphor (p. 2466·2); cineole (p. 2479·1).
Respiratory-tract disorders.

Transpulmina Gola *Bayer, Ital.*
Dequalinium chloride (p. 1749·3); menthol (p. 2553·2); cineole (p. 2479·1).
Mouth and throat infections.

Transpulmina Tosse *Bayer, Ital.†*
Pastilles: Guaifenesin (p. 1666·2); menthol (p. 2553·2); cineole (p. 2479·1); camphor (p. 2466·2).
Cough; catarrh.

Bayer, Ital.†
Syrup: Guaifenesin (p. 1666·2); menthol (p. 2553·2); cineole (p. 2479·1).
Cough; catarrh.

Transtec *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Denm.; AWD, Ger.; Grunenthal, Ger.; Grunenthal, Hung.; Mundipharma, Irl.; Formenti, Ital.; Grunenthal, Mex.; Grunenthal, Neth.; Grunenthal, Pol.; Grunenthal, Port.; Grunenthal, Rus.; Grunenthal, Spain; Grunenthal, Switz.; Napp, UK.*
⊗Buprenorphine (p. 30·2).
Pain.

Transulose *Aptalis, Fr.; Chemineau, Ital.; Pharmasearch, Neth.*
Lactulose (p. 1850·3); liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).
Constipation.

Transuloza *Mayoly-Spindler, Ukr.*
Lactulose (p. 1850·3); white soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2).
Constipation.

Transvane *Omega, Belg.*
Thurfyl salicylate (p. 137·1); hexyl nicotinate (p. 67·1); ethyl nicotinate (p. 56·3); benzocaine (p. 1980·2).
Musculoskeletal, joint, and soft-tissue disorders.

Transvasin *Thornton & Ross, Irl.†*
Ethyl nicotinate (p. 56·3); hexyl nicotinate (p. 67·1); thurfyl salicylate (p. 137·1).
Rheumatic and muscular pain; strains; sprains.

Transvasin Heat Rub *Thornton & Ross, UK.*
Ethyl nicotinate (p. 56·3); hexyl nicotinate (p. 67·1); thurfyl salicylate (p. 137·1).
Musculoskeletal and joint pain; sprains; strains.

Transvasin Heat Spray *Thornton & Ross, UK.*
Glycol salicylate (p. 66·2); diethylamine salicylate (p. 51·3); methyl nicotinate (p. 91·3).
Musculoskeletal and joint pain.

Transvercid *Ducray, Fr.; Pierre Fabre Dermo-Cosmetique, Port.*
Salicylic acid (p. 1719·1).
Warts.

Trans-Ver-Sal *Bradley, Canad.†; Mediline, Israel; Difa, Ital.; Darier, Mex.; Genop, S.Afr.†*
Salicylic acid (p. 1719·1).
Warts; verrucas; calluses.

Trans-Ver-Sal AdultPatch *Doak, USA.*
Salicylic acid (p. 1719·1).
Verrucas.

Trans-Ver-Sal PediaPatch *Doak, USA.*
Salicylic acid (p. 1719·1).
Formerly known as PediaPatch.
Warts.

Trans-Ver-Sal PlantarPatch *Doak, USA.*
Salicylic acid (p. 1719·1).
Formerly known as Trans-Plantar.
Warts.

Transvital *Lafi, Chile.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Transzone *Par, USA.*
Melatonin (p. 2551·3).

Trant *Maver, Chile.*
Trazodone hydrochloride (p. 451·1).
Depression.

Trantalol
Note: this name may be used for preparations of different composition.
CCM, Malaysia; Duopharma, Singapore.
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Pinewood, Irl.
⊗Atenolol (p. 1308·2).
Arrhythmias; myocardial infarction; angina pectoris; hypertension.

Tranvit *Gal, Pol.†*
Cod-liver oil (p. 2056·3); colecalciferol (p. 2113·1); vitamin A (p. 2098·3).
Vitamin A and D deficiency.

Tranxa *Bernofarm, Indon.*
Tranexamic acid (p. 1164·2).
Fibrinolysis.

Tranxal *CTS, Israel.*
Dipotassium clorazepate (p. 1056·3).
Alcohol withdrawal syndrome; anxiety; seizures.

Tranxamax *Vesco, Thai.*
Tranexamic acid (p. 1164·2).

Tranxen *Sanofi-Aventis, Venez.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndromes; premedication.

Tranxene *Sanofi-Aventis, Belg.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Lundbeck, USA.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; seizures; neuroses; mixed anxiety depressive states; psychoses; premedication; insomnia; disturbed behaviour; sleep disorders; epilepsy; alcohol and drug withdrawal syndromes; agitation; tetany; delirium tremens.

Tranxène *Sanofi-Aventis, Fr.*
Dipotassium clorazepate (p. 1056·3).
Anxiety disorders; agitation; alcohol withdrawal syndrome; premedication; tetany.

Tranxic *Bangkok Lab & Cosmetic, Thai.*
Tranexamic acid (p. 1164·2).
Haemorrhage; hereditary angioedema.

Tranxilene *Sanofi-Aventis, Braz.; Sanofi Synthelabo, Turk.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; alcohol withdrawal syndrome; epilepsy.

Tranxilium *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austria; Rider, Chile; Sanofi-Aventis, Ger.; Euro Registratie, Neth.†; Sanofi-Aventis, Spain; Sanofi-Aventis, Switz.*
Dipotassium clorazepate (p. 1056·3).
Alcohol withdrawal syndrome; anxiety; convulsions; premedication; sleep disorders; delirium tremens; agitation; insomnia.

Tranxilium Digest *Sanofi-Aventis, Arg.*
Dipotassium clorazepate (p. 1056·3); sulpiride (p. 1107·3).
Anxiety; peptic ulcer; digestive disorders.

Tranxilium N *Sanofi Synthelabo, Ger.†*
Nordazepam (p. 1089·3).
Anxiety; sleep disorders.

Tranzelm *Helm, Port.†*
Trazodone hydrochloride (p. 451·1).
Depression.

Tranzep *Pandrugs, Thai.*
Dipotassium clorazepate (p. 1056·3).

Tranzicalm *Vocate, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Trapamafin *Acino, Port.*
⊗Buprenorphine (p. 30·2).

Trapamaphin *Acino, Cz.*
⊗Buprenorphine (p. 30·2).
Pain.

Trapanal *Nycomed, Ger.*
Thiopental sodium (p. 1915·1).
General anaesthesia.

Traparac *Nordic, Cz.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Trapax *Wyeth, Arg.*
Lorazepam (p. 1080·3).
Anxiety; premedication; alcohol withdrawal syndrome; delirium tremens.

Trasédal *Elerte, Fr.†*
Tramadol hydrochloride (p. 139·2).
Pain.

Trasic *Kopran, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trasicor *Novartis, Canad.†; Novartis, Fr.†; Novartis, Ger.†; Novartis, Gr.; Sandoz, Neth.†; Novartis, Spain†; Novartis, Switz.†; Novartis, Turk.†; Amdipharm, UK.*
⊗Oxprenolol hydrochloride (p. 1463·2).
Angina pectoris; hypertension; arrhythmias; hyperthyroidism; phaeochromocytoma; myocardial infarction; obstructive cardiomyopathy; anxiety.

Trasidrex *Goldshield, UK.†*
⊗Oxprenolol hydrochloride (p. 1463·2); cyclopenthiazide (p. 1347·2).
These ingredients can be described by the British Approved Name Co-prenozide.
Hypertension.

Trasik *Fahrenheit, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trasitensin *Novartis, Gr.; Teofarma, Ital.; Novartis, Spain.*
⊗Oxprenolol hydrochloride (p. 1463·2); chlortalidone (p. 1335·2).
Hypertension.

Trasitensine *Novartis, Fr.†*
⊗Oxprenolol hydrochloride (p. 1463·2); chlortalidone (p. 1335·2).
Hypertension.

Trasolette *PharmaSwiss, Cz.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Trast *SK, China.*
Piroxicam (p. 125·3).
Pain.

Trastal *Servier, China.*
Piribedil (p. 911·1).
Mental function impairment; peripheral vascular disorders; parkinsonism.

Trastocir *Ivax, Arg.*
Cilostazol (p. 1337·1).
Peripheral vascular disorders.

Trastocir Duo *Ivax, Arg.*
Cilostazol (p. 1337·1); aspirin (p. 22·2).
Occlusive peripheral vascular disease.

Trastoner *Ivax, Arg.*
Piribedil (p. 911·1).
Cognitive impairment in the elderly; parkinsonism; ischaemic eye disorders; arterial occlusive disorders.

Trasylol *Bayer, Belg.†; Bayer, Braz.†; Bayer, Canad.; Bayer, Denm.; Bayer, Indon.†; Bayer, Philipp.; Bayer, Pol.; Bayer Schering, S.Afr.; Bayer, Singapore; Bayer, Switz.; Bayer, Turk.; Bayer, Ukr.†; Bayer, Venez.*
Aprotinin (p. 1133·2).
Reduction of blood loss in coronary bypass surgery; hyperfibrinolytic haemorrhage.

Tratacne *Raymos, Arg.*
Tretinoin (p. 1725·2); erythromycin (p. 291·2).
Acne.

Tratina *LKM, Arg.†*
Estramustine (p. 790·1).

Tratinal *Serral, Mex.*
Pravastatin (p. 1473·1).
Hypercholesterolaemia.

Tratobes *Columbia, Arg.*
⊗Diethylpropion hydrochloride (p. 2321·1); fenproporex hydrochloride (p. 2323·1); diazepam (p. 1063·2).
Obesity.

Tratomax *Lafedar, Arg.*
Pessaries: ⊗Metronidazole (p. 936·1); nystatin (p. 590·3); dexamethasone (p. 1630·3); lidocaine (p. 1988·1); neomycin sulfate (p. 330·1).
Vulvovaginal infections.

Lafedar, Arg.
Tablets: Metronidazole (p. 936·1); nystatin (p. 590·3).
Fungal infections; trichomoniasis.

Tratul *Gerot, Austria.*
Diclofenac (p. 48·3) or diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; inflammation; pain; fever; biliary and renal colic.

Tratzol *Cazi, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Traulen *OP, Ital.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular pain and inflammation.

Trauma SL *Hevert, Ger.*
Arnica (p. 2447·2); rhus tox. (p. 2603·3).
Homoeopathic preparation.

Traumac *Catarinense, Braz.†*
Benzocaine (p. 1980·2); camphor (p. 2466·2); lavender (p. 2541·1); turpentine oil (p. 2636·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint disorders.

TraumaCal *Mead Johnson Nutritionals, USA.†*
Lactose-free preparation for enteral nutrition.
Stress.

Novartis Nutrition, Canad.†
Gluten-free preparation for enteral nutrition.

Traumacel P *Synapse, Irl.†*
Calcium oxidised cellulose (p. 1157·3).
Capillary bleeding.

Trauma-cyl *Liebermann, Ger.†*
Chamomile oil (p. 2474·1); sage oil (p. 2609·1); arnica (p. 2447·2); aesculus (p. 2431·2); hamamelis (p. 2523·3).
Vascular disorders; soft-tissue injury.

Trauma-Dolgit *Dolorgiet, Ger.*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; sports injuries.

Traumagel *Sanval, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint disorders.

Traumakatt *Kattwiga, Ger.*
Arnica montana (p. 2447·2); bryonia (p. 2461·3); toxicodendron quercifolium (p. 2603·3).
Homoeopathic preparation.

Traumalgyl *Pharmadeveloppement, Fr.†*
Mephenesin (p. 2025·2); diethylamine salicylate (p. 51·3); lidocaine (p. 1988·1).
Muscular pain.

Traumalix *Drossapharm, Switz.*
Etofenamate (p. 57·2).
Peri-articular and soft-tissue disorders.

TraumAmine *Eczacibasi-Baxter, Turk.*
Amino acids.
Parenteral nutrition.

Traumanase *Cassella-med, Ger.; Sanofi-Aventis, Switz.*
⊗Bromelains (p. 2460·3).
Inflammation with oedema.

Traumaplant *HWS OTC, Austria; Prater, Chile; Harras-Curarina, Cz.; Cassella-med, Ger.; Harras-Curarina, Ger.; Trima, Israel; Zeller, Switz.; Cofasa, Venez.*
Comfrey (p. 2484·2).
Sports injuries; wounds; musculoskeletal, joint, and soft-tissue disorders.

Traumasal *Mucos, Austria.*
Diethylamine salicylate (p. 51·3); flufenamic acid (p. 65·1); myrtecaine (p. 1993·1).
Soft-tissue injury; sprains; lumbago.

Trauma-Salbe kühlend *Kwizda, Austria.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Trauma-Salbe wärmend *Kwizda, Austria.*
Methyl salicylate (p. 92·1); capsicum (p. 2469·3); turpentine oil (p. 2636·3).
Musculoskeletal, joint, and soft-tissue disorders.

Traumasept *Wolff, Ger.*
Povidone-iodine (p. 1767·1).
Vaginal infections.

Traumasik *Medikon, Indon.†*
Tramadol (p. 139·2).
Pain.

Traumasive *Hexal, Ger.†*
Hydrocolloid dressing.
Burns; wounds.

Traumatil *Tilman, Belg.*
Aescin (p. 2431·2).
Soft-tissue disorders; vascular disorders.

Traumaven *Amnol, Ital.*
Thioctic acid (p. 2629·1); diosmin (p. 2505·2); grape (p. 2521·3); melilot (p. 2552·3); vitamins; zinc (p. 2126·1).
Circulatory disorders.

Traumazol *Chinoin, Mex.*
Ethyl chloride (p. 1987·1).
Local anaesthesia; muscle cramps; soft-tissue disorders.

Traumazym *Mucos, Austria.*
⊗Rutoside (p. 2505·3); bromelains (p. 2460·3); trypsin (p. 2635·2).
Pain; inflammation; thrombophlebitis; musculoskeletal and joint disorders.

Traumed
Note: this name may be used for preparations of different composition.
Medicpharma, Thai.
Tramadol hydrochloride (p. 139·2).
Pain.

Traumeel *Ebi, Switz.; Biotecnoquimica, Venez.*
Calendula (p. 2465·2); hamamelis (p. 2523·3); chamomile (p. 2474·1); echinacea (p. 2498·1); bellis perennis (p. 2454·2); achillea (p. 2427·3); belladonna (p. 2453·3); aconite (p. 2428·3); arnica (p. 2447·2); symphytum officinalis (p. 2484·2); hypericum perforatum (p. 449·1); hepar sulfuris (p. 1721·3); mercurius (p. 2555·3).
Homoeopathic preparation.

Heel, Austria.
Mercurius solubilis (p. 2555·3); hepar sulfuris (p. 1721·3); symphytum officinale (p. 2484·2); chamomilla recutita (p. 2474·1); achillea millefolium (p. 2427·3); calendula officinalis (p. 2465·2); atropa belladonna (p. 2453·3); aconitum napellus (p. 2428·3); bellis perennis (p. 2454·2); hypericum perforatum (p. 449·1); echinacea augustifolia (p. 2498·1); echinacea purpurea (p. 2498·1); hamamelis virginiana (p. 2523·3); arnica montana (p. 2447·2).
Homoeopathic preparation.

Peithner, Hung.
Hypericum perforatum (p. 449·1); echinacea purpurea (p. 2498·1); echinacea angustifolia (p. 2498·1); bellis perennis (p. 2454·2); calendula officinalis (p. 2465·2); hamamelis virginiana (p. 2523·3); achillea millefolium (p. 2427·3); arnica montana (p. 2447·2); chamomilla recutita (p. 2474·1); symphytum officinale (p. 2484·2); aconitum napellus (p. 2428·3); mercurius solubilis (p. 2555·3); hepar sulfuris calcareum (p. 1721·3); atropa belladonna (p. 2453·3).
Homoeopathic preparation.

Heel, Canad.; Heel, USA.
Millefolium (p. 2427·3); aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); belladonna (p. 2453·3); bellis perennis (p. 2454·2); hepar sulphuris calcareum (p. 1721·3); calendula officinalis (p. 2465·2); symphytum officinale (p. 2484·2); echinacea angustifolia (p. 2498·1); echinacea purpurea (p. 2498·1); chamomilla (p. 2474·1); hamamelis virginiana (p. 2523·3); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Heel, Cz.
Arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); hamamelis virginiana (p. 2523·3); achillea millefolium (p. 2427·3); atropa belladonna (p. 2453·3); aconitum napellus (p. 2428·3); mercurius solubilis hahnemanni (p. 2555·3); calcii sulfidum (p. 1721·3); chamomilla recutita (p. 2474·1); symphytum officinalis (p. 2484·2); bellis perennis (p. 2454·2); echinacea angustifolia (p. 2498·1); echinacea purpurea (p. 2498·1); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Traumeel H *Heel, Neth.*
Arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); millefolium (p. 2427·3); mercurius solubilis (p. 2555·3); chamomilla (p. 2474·1); symphytum officinale (p. 2484·2); bellis perennis (p. 2454·2); hypericum perforatum (p. 449·1).
Homoeopathic preparation.

Traumeel S *Heel, Ger.; Heel, S.Afr.*
Arnica (p. 2447·2); calendula (p. 2465·2); chamomilla (p. 2474·1); symphytum (p. 2484·2); millefolium (p. 2427·3); belladonna (p. 2453·3); aconitum (p. 2428·3); bellis perennis (p. 2454·2); hypericum (p. 449·1); echinacea ang. (p. 2498·1); echinacea purp. (p. 2498·1); hamamelis (p. 2523·3); mercurius solub. (p. 2555·3); hepar sulfuris (p. 1721·3).
Homoeopathic preparation.

Heel, Neth.; Heel, Ukr.
Aconitum napellus (p. 2428·3); arnica montana (p. 2447·2); belladonna (p. 2453·3); bellis perennis (p. 2454·2); calendula officinalis (p. 2465·2); chamomilla (p. 2474·1); echinacea angustifolia (p. 2498·1); echinacea purpurea; hamamelis virginiana (p. 2523·3); hepar sulphur (p. 1721·3); hypericum perforatum (p. 449·1); mercurius solubilis (p. 2555·3); millefolium (p. 2427·3); symphytum officinale (p. 2484·2).
Homoeopathic preparation.

Heel, Rus.
Arnica montana (p. 2447·2); calendulae officinalis (p. 2465·2); hamamelis virginiana (p. 2523·3); achillea millefolium (p. 2427·3); atropa belladonna (p. 2453·3); aconitum napellus (p. 2428·3); mercurius solubilis (p. 2555·3); hepar sulfuris (p. 1721·3); chamomilla recutita (p. 2474·1); symphytum officinale (p. 2484·2); bellis perennis (p. 2454·2); echinacea pupurea (p. 2498·1); hypericum (p. 449·1).
Homoeopathic preparation.

Traumicid *Sanofi Pasteur, Chile.†*
Clonixin lysine (p. 40·1).
Inflammation; pain.

Traumon *Meda, Austria; Bayer, Cz.; Meda, Ger.†; Bayer, Pol.; Bial, Port.†*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Traumox *Medpro, S.Afr.†*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; gout; dysmenorrhoea.

Traumselamin *Biosel, Turk.†*
Amino acids.
Parenteral nutrition.

Trausan *Vitoria, Port.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders.

Travacalm *Key, Austral.*
Dimenhydrinate (p. 625·2); hyoscine hydrobromide (p. 1845·3); caffeine (p. 1203·3).
Motion sickness.

Travacalm HO *Key, Austral.*
Hyoscine hydrobromide (p. 1845·3).
Motion sickness.

Travacalm Natural *Key, Austral.*
Ginger (p. 1844·1).
Motion sickness.

Travahex *Baxter, Fin.*
Chlorhexidine acetate (p. 1743·2).
Skin, wound, and mucous membrane disinfection.

Travamed *Germed, Braz.*
Travoprost (p. 2012·1).

Travamin *Rekah, Israel.*
Dimenhydrinate (p. 625·2).
Motion sickness; radiation sickness.

Travasept *Baxter, Israel; Baxter, UK.†*
Cetrimide (p. 1742·1); chlorhexidine acetate (p. 1743·2).
Disinfection of burns and wounds; skin disinfection.

Travasol *Baxter, Canad.*
Amino acids; carbohydrate; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Baxter Immuno, Arg.†; Baxter, USA.
Amino acids; with or without carbohydrates and electrolytes (p. 1775·1).
Parenteral nutrition.

Baxter, Israel; Baxter, Neth.
Amino acids.
Parenteral nutrition.

Travasorb *Clintec, USA.*
A range of preparations for enteral nutrition.

Travatan *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, China; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, Ukr.; Alcon, USA; Alcon, Venez.*
Travoprost (p. 2012·1).
Glaucoma; ocular hypertension.

Travazol *Bilim, Turk.*
⊗Isoconazole nitrate (p. 583·2); diflucortolone valerate (p. 1634·1).
Infected skin disorders.

Traveget *Cafar, Venez.*
Belladonna (p. 2453·3); ergotamine tartrate (p. 674·1); phenobarbital (p. 535·2).

Travel Sickness *Cantassium Co., UK.*
Ginger (p. 1844·1).

Homeocan, Canad.
Cocculus indicus (p. 2483·1); vinca minor; valeriana off. (p. 2640·2); pulsatilla (p. 2600·2); nitroglycerin (p. 1391·2); plumbum aceticum (p. 2541·3); argentum nitricum (p. 2615·3); artemisia vulgaris.
Homoeopathic preparation.

Travel Tabs *Tanta, Canad.; Vita Health, Canad.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Travel Well *M4, Spain.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Travelan *Immuron, Austral.*
Bovine colostrum (p. 2380·3).
Travellers' diarrhoea.

Travelbac *Healthcare Innovations, UK.*
Bacterial extracts; vitamin B substances (p. 2102·3); yeast (p. 2125·2).
Dietary supplement for travellers.

Traveleeze *Ernest Jackson, UK.*
Meclozine hydrochloride (p. 634·3).
Motion sickness.

Travelex *Peithner, Austria.*
Anamirta cocculus (p. 2483·1); cephaelis ipecacuanha; nicotiana tabacum (p. 2632·2); okoubaka aubrevillei; petroleum rectificatum (p. 2201·2).
Homoeopathic preparation.

Travel-Gum *Meda, Austria; Meda, Cz.*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo.

Travelgum *Vianex (Βιανεξ), Gr.; Meda, Ital.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting.

Travelin *VSM, Neth.*
Cocculus indicus (p. 2483·1); ipecacuanha (p. 1667·2); nux vomica (p. 2573·3); petroleum (p. 2587·2); tabacum (p. 2632·2).
Homoeopathic preparation.

Travella *Nelson, UK.*
Apomorph (p. 892·3); staphisagria; cocculus (p. 2483·1); theridion; petroleum (p. 2587·2); tabacum (p. 2632·2); nux vomica (p. 2573·3).
Homoeopathic preparation.

Travellers Relief *Brauer, Austral.*
Nux vomica (p. 2573·3); tabacum (p. 2632·2); apomorphinum muriaticum (p. 892·3); cocculus (p. 2483·1); petroleum (p. 2587·2); sepia (p. 2613·1).
Homoeopathic preparation.

Travello *McNeil, Swed.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Travelmin *Roux-Ocefa, Arg.*
Betahistine hydrochloride (p. 2455·3).
Vertigo; Ménière's disease.

Travelon *Sinnex, Hung.*
Ginger (p. 1844·1); melissa (p. 2552·3); tormentil (p. 2633·2).
Nausea; vomiting; motion sickness.

Travert *Baxter, USA.*
Invert sugar (p. 2072·3); electrolytes (p. 1775·1).
Fluid and electrolyte disorders; carbohydrate source.

Travex *Meda, Port.*
Tramadol hydrochloride (p. 139·2).
Pain.

Travex One *Meda, Ger.*
Tramadol hydrochloride (p. 139·2).
Pain.

Traviata *Andromaco, Chile.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic attacks; social phobia.

Travictol *Actavis, Pol.*
Tramadol hydrochloride (p. 139·2).
Pain.

Travid *Suphong, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Travilan *Anfarm, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Travisco *Chiesi, Braz.; Master Pharma, Ital.*
Trapidil (p. 1517·3).
Ischaemic heart disease; prevention of restenosis following angioplasty; thromboembolism prophylaxis.

Travisil *Plethico, Ukr.*
Malabar nut (p. 2549·1); piper longum; black pepper (p. 2586·1); ginger (p. 1844·1); liquorice (p. 1853·2); Indian gooseberry (p. 2532·2); curcuma longa; black catechu (p. 2457·3); fennel (p. 2503·2); ocimum sanctum; terminalia chebula (p. 2474·3); terminalia bellirica (p. 2453·2); alpinia galanga; abrus precatorius (p. 2426·1); menthol (p. 2553·2).
Cough.

Rezlov, Rus.
Malabar nut (p. 2549·1); piper longum; black pepper (p. 2586·1); ginger (p. 1844·1); liquorice (p. 1853·2); Indian gooseberry (p. 2532·2); turmeric (p. 2218·1); catechu (p. 2472·3); fennel (p. 2503·2); basil (p. 2453·1); chebulic myrobalan (p. 2474·3); beleric myrobalan (p. 2453·2); alpinia officinarum; abrus (p. 2426·1); menthol (p. 2553·2).
Respiratory-tract disorders.

Travocort *Intendis, Austria; Bayer, Belg.; Intendis, Ger.; Intendis, Gr.; Intendis, Hong Kong; Transfarma, Indon.; Bayer, Irl.; Intendis, Ital.; Intendis, Malaysia; Intendis, Philipp.; Intendis, Pol.; Bayer, Port.; Intendis, Rus.; Bayer Schering, S.Afr.; Intendis, Singapore; Bayer, Switz.; Intendis, Thai.; Schering, Turk.; Bayer, Ukr.; Intendis, Ukr.*
⊗Isoconazole nitrate (p. 583·2); diflucortolone valerate (p. 1634·1).
Skin disorders with fungal infection.

Travogen *Intendis, Austria; Bayer, Belg.; Bayer, Gr.; Intendis, Hong Kong; Intendis, Ital.; Intendis, Malaysia; Intendis, Philipp.; Intendis, Pol.; Intendis, Rus.; Intendis, Singapore; Bayer, Switz.; Intendis, Thai.; Schering, Turk.; Bayer, Ukr.; Intendis, Ukr.*
Isoconazole nitrate (p. 583·2).
Bacterial vaginosis; erythrasma; fungal infections of the skin, vulva, and vagina.

Travogyn
Note: this name may be used for preparations of different composition.
Ativus, Braz.
Tioconazole (p. 595·3); tinidazole (p. 949·2).
Vaginal infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Trawell *Meda, Switz.*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; Ménière's disease.

Trax *Arlex, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Traxam *Goldshield, Irl.; Goldshield, UK.*
Felbinac (p. 58·3).
Soft-tissue injury; musculoskeletal, joint, and peri-articular disorders.

Traxelan *Merck, Mex.*
Clotrimazole (p. 576·2).
Fungal vaginal infections.

Traxetrine *Flamingo, Philipp.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Traxonol *Geolab, Braz.*
Itraconazole (p. 583·3).
Fungal infections.

Tray-Te *Gray, Arg.†*
Tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Trazec *Novartis, Cz.†*
Nateglinide (p. 492·1).
Diabetes mellitus.

Trazel *Behrens, Venez.*
Trace elements.
Parenteral nutrition.

Trazenta *Boehringer Ingelheim, Jpn.*
Linagliptin (p. 488·1).
Diabetes mellitus.

Trazep *Fahrenheit, Indon.*
Diazepam (p. 1063·2).
Convulsions; premedication.

Trazer *Boniscontro & Gazzone, Ital.*
Itraconazole (p. 583·3).
Fungal infections.

Trazidex *Sophia, Mex.; Elmor, Venez.*
⊗Tobramycin sulfate (p. 380·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Volta, Chile.
⊗Tobramycin (p. 380·1) or tobramycin sulfate (p. 380·2); dexamethasone (p. 1630·3).
Infected eye disorders.

Trazil *Sophia, Mex.*
Tobramycin sulfate (p. 380·2).
Bacterial eye infections.

Volta, Chile.
Tobramycin (p. 380·1).
Bacterial eye infections.

Trazinac *Sophia, Mex.; Elmor, Venez.*
Diclofenac sodium (p. 48·3); tobramycin sulfate (p. 380·2).
Infected eye disorders; bacterial eye infections; adjunct to eye surgery.

Trazo *Medifive, Thai.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety.

Trazodil *Trima, Israel.*
Trazodone hydrochloride (p. 451·1).
Depression.

Trazograf *Juste, Spain.†*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Trazograph *Unique, Rus.; Unique, Ukr.†*
Meglumine amidotrizoate (p. 1581·3) with or without sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Trazolan *Continental Pharma, Belg.; Pfizer, Neth.*
Trazodone hydrochloride (p. 451·1).
Depression.

Trazone *Tecnifar, Port.*
Trazodone hydrochloride (p. 451·1).
Depression.

Trazorel *Valeant, Canad.*
Trazodone hydrochloride (p. 451·1).
Depression.

Trazoteva *Teva Tuteur, Arg.*
Docetaxel (p. 780·3).
Breast cancer; non-small cell lung cancer.

Trazyl *Angelini, Ital.†*
⊗Ibopamine hydrochloride (p. 1407·1).
Production of mydriasis; diagnosis of glaucoma; postoperative ocular hypotension.

TRCS ERIG *Thai Red Cross, Thai.*
A rabies immunoglobulin (equine) (p. 2413·1).
Passive immunisation.

TRD-Contin *Modi-Mundipharma, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Treagan *Trigen, USA.*
Phenazone (p. 124·1); benzocaine (p. 1980·2).
Otitis media; ear wax removal.

Treakisym *Eisai, Jpn.*
Bendamustine hydrochloride (p. 746·2).
Non-Hodgkin's lymphoma; mantle cell lymphoma.

Treanda *Lundbeck, Canad.; IFET (ΙΦΕΤ), Gr.; Cephalon, Hong Kong; Teva, USA.*
Bendamustine hydrochloride (p. 746·2).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma.

Trebanol *Collins, Mex.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; myocardial infarction.

Trebon-N *Unipharma, Gr.*
Acetylcysteine (p. 1652·2).
Respiratory disorders associated with viscous mucus.

Trecator *IFET (ΙΦΕΤ), Gr.; Wyeth-Ayerst, USA.*
Ethionamide (p. 297·3).
Tuberculosis.

Trecifan *Vocate, Gr.*
Isotretinoin (p. 1706·2).
Acne.

Trecloran *Collins, Mex.†*
Chloramphenicol (p. 257·1); tetracycline (p. 373·1).
Bacterial infections.

Treda *Sanfer, Mex.*
Neomycin sulfate (p. 330·1); pectin (p. 2200·3); kaolin (p. 1850·1).
Gastro-enteritis.

Tredalat *Bayer, Ger.*
⊗Nifedipine (p. 1447·2); acebutolol hydrochloride (p. 1289·2).
Hypertension; angina pectoris.

Tredaptive *MSD, Austria†; MSD, Belg.†; MSD, Cz.†; MSD, Denm.†; MSD-Chibret, Fr.†; MSD, Ger.†; MSD, Gr.†; MSD, Hong Kong†; MSD, Irl.†; MSD, Israel†; MSD, Neth.†; MSD, Norw.†; MSD, NZ†; MSD, Philipp.†; MSD, Pol.†; MSD, Port.†; MSD, Singapore†; MSD, Spain†; MSD, Swed.†; MSD, Switz.†; MSD, UK.†*
Nicotinic acid (p. 2083·1); laropiprant (p. 2540·3).
Hyperlipidaemias; hypercholesterolaemia.

Tredemine *IFET (ΙΦΕΤ), Gr.*
Niclosamide (p. 161·2).
Tapeworm infections.

Trédémine *Sanofi-Aventis, Fr.*
Niclosamide (p. 161·2).
Taeniasis.

Tredol
Note: this name may be used for preparations of different composition.
Aegis, Hong Kong.
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Tre-en-en *GNLD, Austral.*
Rice bran oil; soya oil (p. 2092·3); wheat-germ oil (p. 2647·1).
Dietary supplement.

tregor *Stegropharm, Ger.*
Amantadine sulfate (p. 890·3).
Parkinsonism.

Trekpleister Anti-Worm *Marel, Neth.*
Mebendazole (p. 158·3).
Worm infections.

Trekpleister APC *Marel, Neth.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Trekpleister Diarreeremmer *Marel, Neth.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Trekpleister Hoesttabletten *Marel, Neth.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Trekpleister Laxeertabletten *Marel, Neth.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Trekzalf *Remark, Neth.*
Ichthammol (p. 1705·3).
Pustules.

Trelibec *Mintlab, Chile.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trellium Plus *Breckenridge, USA.†*
Phenazopyridine hydrochloride (p. 124·3); hyoscyamine hydrobromide (p. 1848·1); butalbital (p. 1043·3).

Trelstar *Paladin, Canad.; Watson, USA.*
⊗Triptorelin embonate (p. 2311·1).
Prostatic cancer; endometriosis.

Tremac *Sanovel, Turk.*
Azithromycin (p. 221·2).
Bacterial infections.

Tremak *Sanovel, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Tremaril *Novartis, Hung.; LPB, Ital.*
Metixene hydrochloride (p. 909·2).
Parkinsonism; senile tremor.

Tremarit *AWD, Ger.†*
Metixene hydrochloride (p. 909·2).
Parkinsonism and other hyperkinetic disorders.

Tremax *Sandoz, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Tremblex *Janssen-Cilag, Neth.†*
Dexetimide hydrochloride (p. 901·1).
Drug-induced extrapyramidal disorders.

Tremecox *Rimsa, Mex.*
Gabapentin (p. 523·3); meloxicam (p. 86·3).
Neuropathic pain; neuralgia.

Tremenza *Sanbe, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Influenza symptoms.

Tremepen *Rimsa, Mex.*
Gabapentin (p. 523·3); tramadol (p. 139·2).
Neuropathic pain.

Tremesal *Grunenthal, Venez.*
Doxycycline (p. 288·1).
Bacterial infections.

Tremexal *Cosmopharm, Gr.*
Flutamide (p. 798·2).
Prostatic cancer.

Treminel *Ivax, Arg.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Tremital *Tanic, Gr.*
Simvastatin (p. 1489·2).

Tremonorm *Teva, Rus.*
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.

Tremytoine *Omega, Canad.*
Phenytoin sodium (p. 538·2).

Tren *YSP, Malaysia.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders; hereditary angioedema.

Trenantone *Takeda, Austria; Takeda, Ger.*
⊗Leuprorelin acetate (p. 2285·3).
Prostatic cancer; breast cancer; endometriosis; uterine fibroids.

Trenat *Interbat, Indon.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Trenaxin *Yung Shin, Philipp.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders.

Trencir *Pisa, Mex.*
Carbamazepine (p. 512·2).

Trenelone *Schering-Plough, Port.*
Dexchlorpheniramine maleate (p. 621·1).
Hypersensitivity reactions.

Trenfyl *Pharos, Indon.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Trenlin *CCM, Hong Kong; CCM, Malaysia; Upha, Singapore.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Trenpe *Pisa, Mex.*
Haloperidol (p. 1077·1).

Trenpental *Bryntsalov, Rus.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular ear and eye disorders.

Trentadil *UCB, Fr.*
Bamifylline hydrochloride (p. 1203·2).
Asthma; obstructive airways disease.

Trentafilina *Sigma, Braz.*
Pentoxifylline (p. 1465·3).

Trental *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi-Aventis, Chile; Nycomed, Cz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Ger.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.†; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.†; Sanofi-Aventis, Singapore; Sanofi-Aventis, Switz.†; Aventis, Thai.; Sanofi-Aventis, Thai.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, Ukr.; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Pentoxifylline (p. 1465·3).
Intermittent claudication; cerebral and peripheral vascular disorders; angioneurotic disorders; stroke; circulatory disorders of the eye or ear; otosclerosis.

Trentilin *Santa, Turk.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Trentin *Ikapharmindo, Indon.*
Tretinoin (p. 1725·2).
Acne.

Trentofil *UCI, Braz.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Trentox *Ferron, Indon.*
Pentoxifylline (p. 1465·3).
Intermittent claudication.

Trenxy *Danpac, Indon.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Treo
Note: this name may be used for preparations of different composition.
Biopharm, USA.
SPF 8; SPF 15; SPF 30: Octocrilene (p. 1715·2); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); citronella oil (p. 2481·1).
Sunscreen.

Meda, Denm.; Meda, Fin.; McNeil, Swed.
Aspirin (p. 22·2); caffeine (p. 1203·3).
Pain; fever.

Treo comp *McNeil, Swed.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain.

Treomycin *Chew, Thai.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Trepal *Okasa, Thai.; TTN, Thai.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Trepar *Korea United, Philipp.*
Dactinomycin (p. 776·3).
Malignant neoplasms.

Treparasen *Norma (Νορμα), Gr.*
⊗Pindolol (p. 1470·1).

Treparin *Omikron, Ital.*
Sulodexide (p. 1507·3).
Chronic venous ulcer.

Trepetan *Alpharma, Mex.*
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Trepidan *Max Farma, Ital.*
Prazepam (p. 1098·2).
Anxiety.

Trepiline *Aspen, S.Afr.*
Amitriptyline hydrochloride (p. 401·1).
Mixed anxiety depressive states.

Trepina *Alpharma, Mex.†*
Carbamazepine (p. 512·2).
Epilepsy; neuralgia; diabetic neuropathy; diabetes insipidus; bipolar disorder; alcohol withdrawal syndrome.

Trepol *Teva, Mex.†*
Dipyridamole (p. 1362·2).
Cardiovascular disorders.

Trerief *Dainippon, Jpn.*
Zonisamide (p. 560·2).
Parkinsonism.

Tres *Sandoz, Philipp.*
1 Tablet, rifampicin (p. 350·3); isoniazid (p. 311·2) (Rimactazid); 1 tablet, ethambutol (p. 296·1).
Tuberculosis.

Tres Orix Forte *Almirall, Hong Kong.†*
Cyproheptadine orotate (p. 624·1); amino acids; vitamins.
Anorexia; constitutional thinness; growth retardation.

Tresaride *ISA, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Tres-Be *Cafar, Venez.*
Capsules: Cobamamide (p. 2107·2); benfotiamine (p. 2102·3); pyridoxal phosphate (p. 2105·3).
Neuritis.

Cafar, Venez.
Injection: Cobamamide (p. 2107·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neuritis.

Tresiba *Novo Nordisk, Denm.; Novo Nordisk, Jpn; Novo Nordisk, Neth.; Novo Nordisk, Switz.; Novo Nordisk, UK.*
⊗Insulin degludec (p. 475·3).
Diabetes mellitus.

Tresite F *Temis, Arg.*
⊗Liothyronine (p. 2342·3); flumetasone pivalate (p. 1635·2).
Skin disorders; keloids.

Tresivac *Serum Institute, India.*
A live attenuated measles, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

Tresleen *Pfizer, Austria.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobia.

Tresos B *Eagle, Austral.*
Vitamins; amino acids; minerals.
Dietary supplement.

Tresos B PluSe *Eagle, Austral.*
⊗Vitamins; amino acids; minerals; bromelains (p. 2460·3); citrus bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); rutoside (p. 2505·3); papain (p. 2582·3); thioctic acid (p. 2629·1); rose fruit (p. 2607·1).
Dietary supplement.

Tressliv *Mabra, Braz.*
Vitamins; minerals.

Tretin
Note: this name may be used for preparations of different composition.
Assos, Turk.
Tretinoin (p. 1725·2).
Acne; keratinisation disorders.

Geralymatos, Gr.
Isotretinoin (p. 1706·2).
Acne.

Trétinac *Spirig, Switz.*
Isotretinoin (p. 1706·2).
Acne.

Tretinak *Medicine & Business, Hung.†*
Isotretinoin (p. 1706·2).
Acne.

Tretinax *Roemmers Rowe, Venez.*
Tretinoin (p. 1725·2).
Acne.

Tretinex *Medana, Pol.*
Isotretinoin (p. 1706·2).
Acne.

Tretinoderm *Defuen, Arg.*
Tretinoin (p. 1725·2).
Acne; photodamaged skin; keratinisation disorders.

Tretinon *YSP, Malaysia.*
Tretinoin (p. 1725·2).
Acne.

Tretin-X
Note: this name may be used for preparations of different composition.
Onset, USA.
Tretinoin (p. 1725·2).
Acne.

Tretiosan *Hexal, Denm.*
Isotretinoin (p. 1706·2).
Acne.

Treupel Dolo Ibuprofen *Meda, Switz.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Treupel Dolo Paracetamol *Meda, Switz.*
Paracetamol (p. 115·1).
Fever; pain.

Treupel Grippe *Meda, Switz.*
Aspirin (p. 22·2); paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Treuphadol *Treupha, Switz.†*
Paracetamol (p. 115·1).
Pain; fever.

Treuphadol Plus *Treupha, Switz.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Trevadyn *MSD, Cz.†; MSD, Irl.†; MSD, Neth.†; MSD, Pol.†; MSD, Port.†*
Nicotinic acid (p. 2083·1); laropiprant (p. 2540·3).
Hyperlipidaemias.

Trevilor *Pfizer, Ger.*
Venlafaxine hydrochloride (p. 454·2).
Anxiety; depression; social phobia; panic disorder.

Trevina *Orion, Denm.*
70 Tablets, estradiol valerate (p. 2271·2); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); 7 tablets, inert.
Menopausal disorders.

Trev-Iron *Metro, Philipp.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3).
Anaemias; dietary supplement.

Trev-Iron Plus *Metro, Philipp.*
Ferrous fumarate (p. 2060·3); vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Anaemias; dietary supplement.

Trevis *Medicopharm, Austria; Unilab, Hung.†; Meda, Swed.*
Lactobacillus acidophilus (p. 2596·3); *Bifidobacterium animalis* (p. 2596·3); *Lactobacillus bulgaricus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Diarrhoea.

Trevix *Roux-Ocefa, Arg.*
Colecalciferol (p. 2113·1).
Osteoporosis.

Trex *Saval, Chile.*
Azithromycin (p. 221·2).
Bacterial infections.

Trexacont *Legrand, Braz.*
Tranexamic acid (p. 1164·2).

Trexall *Barr, USA.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Trexam *Richmond, Arg.*
Pemetrexed (p. 844·3).
Malignant neoplasms.

Trexan
Note: this name may be used for preparations of different composition.
Atafarm, Turk.
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

BMS, Singapore; Du Pont, USA.
Naltrexone hydrochloride (p. 1565·1).
Opioid dependence.

Orion, Cz.; Orion, Fin.; Orion, Hung.; Orion, Pol.
Methotrexate (p. 822·2).
Rheumatoid arthritis; psoriasis; psoriatic arthritis; malignant neoplasms; transplant rejection; graft-versus-host disease.

Trexapin *Taro, Israel.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Trexbrom *Capellon, USA.*
Pentoxyverine citrate (p. 1672·1); phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Symptoms associated with upper-respiratory tract disorders; cough.

Trexen *Asofarma, Mex.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginitis.

Trexen Duo *Asofarma, Mex.*
Clindamycin phosphate (p. 269·3); ketoconazole (p. 585·3).
Vaginal infections.

Trexil *Medic+Aid, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Treximet *GSK, USA.*
Naproxen sodium (p. 98·2); sumatriptan succinate (p. 679·2).
Migraine.

Trexina *Vitarum, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Trexofin *CJ, Singapore.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Trexol *Atlantis, Mex.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trexyl *Ranbaxy, India.*
Terfenadine (p. 640·3).
Allergic rhinitis; urticaria.

Trezalka v Nalevovych Sacchich *Leros, Cz.†*
St John's wort (p. 449·1).
Depression; nervous disorders.

Třezalková Nať *Megafyt-R, Cz.*
St John's wort (p. 449·1).
Depression; anxiety.

Třezalkový Čaj *Megafyt-R, Cz.*
St John's wort (p. 449·1).
Depression; anxiety.

Trezam *Glenmark, India.*
Aztreonam (p. 224·1).
Bacterial infections.

Trezix *WraSer, USA.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); dihydrocodeine tartrate (p. 52·3).
Pain.

Trezor
Note: this name may be used for preparations of different composition.
Alapis, Gr.
⊗Letrozole (p. 817·1).

TRH *Ferring, Arg.; Ferring, Ger.; IFET (ΙΦΕΤ), Gr.; Ferring, Israel; Ferring, Singapore; Er-Kim, Turk.*
Protirelin (p. 2344·2).
Assessment of hypothalamic-pituitary-thyroid function.

TRH Prem *Novartis Consumer, Spain.†*
Protirelin (p. 2344·2).
Evaluation of thyroid function.

Trhelea *Elea, Arg.*
Protirelin (p. 2344·2).
Diagnosis of hypothalamic-pituitary-thyroid dysfunction.

Tri Act *Bernofarm, Indon.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); dimeticone (p. 1886·2).
Peptic ulcer; gastric hyperacidity; gastritis.

Tri Hachemina *Medea, Spain.†*
Inositol (p. 2533·2); calcium pantothenate (p. 2085·2); aminobenzoic acid (p. 1694·2) or sodium aminobenzoate (p. 2617·2).
Skin disorders; infertility.

Triacana *Sidus, Arg.*
Tiratricol (p. 2346·3).
Thyroid disorders; obesity.

Triacef *Unison, Thai.†*
Ceftriaxone (p. 253·3).
Bacterial infections.

Triacéfan *Gerda, Fr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Triacel *Sanofi Pasteur, Arg.*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Triacet *Lemmon, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triacomb *Technilab, Hong Kong†; Technilab, Pol.*
⊗Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Triacor *Sanofi-Aventis, Arg.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Mex.*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Triacort *Akrikhin, Rus.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triacutan *Arterium, Ukr.*
⊗Betamethasone (p. 1623·2); gentamicin sulfate (p. 304·2); clotrimazole (p. 576·2).
Infected skin disorders.

Triacyl *Ashford, Singapore.*
Tropicamide (p. 2012·2).
Production of mydriasis or cycloplegia.

Triad *Forest Pharmaceuticals, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Tension headache.

Triadene *Bayer, UK.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Triphasic oral contraceptive.

Triaderm
Note: this name may be used for preparations of different composition.
Taro, Canad.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Ivax, Cz.†
⊗Triamcinolone acetonide (p. 1649·1); chloroxine (p. 260·1).
Infected skin disorders.

Triadex *Interbat, Indon.*
Diphenhydramine hydrochloride (p. 626·2); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); phenylpropanolamine hydrochloride (p. 1674·1).
Cough; cold symptoms.

Triafem *Medimpex, Denm.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triafemi *Effik, Fr.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive in women with acne.

Triagynon *Bayer, Spain.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triaken *Kendrick, Mex.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Triaklim *Gedeon Richter, Hung.*
18 Tablets, estradiol (p. 2271·1); 10 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Gedeon Richter, Rus.
12 Tablets, estradiol (p. 2271·1); 10 tablets, estradiol; norethisterone acetate (p. 2294·3); 6 tablets, estradiol.
Menopausal disorders; osteoporosis.

Trial AG *Zee, USA.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Antacid; flatulence.

Trial Antacid *Zee, Canad.†; Zee, USA.*
Calcium carbonate (p. 1824·3).
Antacid.

Trial Combi *Beta, Arg.*
2 Patches, estradiol (p. 2271·1); 2 patches, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Trial Gel *Beta, Arg.*
Estradiol (p. 2271·1).
Oestrogen deficiency.

Trial Gest *Beta, Arg.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Trial SAT *Beta, Arg.*
Estradiol (p. 2271·1).
Menopausal disorders.

Trialam *Alphapharm, Thai.*
Triazolam (p. 1112·3).
Insomnia.

Trialgex *Hertz, Braz.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2); menthol (p. 2553·2).

Trialix *Sanofi-Aventis, Irl.; Sanofi-Aventis, Switz.*
⊗Ramipril (p. 1483·3); piretanide (p. 1470·3).
Hypertension.

Trialmin *Menarini, Spain.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; cardiovascular risk reduction.

Trialona *GSK, Spain.*
⊗Fluticasone propionate (p. 1638·1).
Obstructive airways disease.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Trialone *Janssen-Cilag, S.Afr.†*
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Trialyn *Trianon, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Triam *Winthrop, Ger.; Denk, Hong Kong.†*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Triam Tiazida R *Normal, Port.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Triam-A *Hyrex, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Triama *Union Drug, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triambutol *Doctors, Philipp.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Triamcinal *Polychronus, Gr.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Triamcinolon *Teva, Cz.*
Lotion: ⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Teva, Cz.
Tincture: ⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1); carbaethopendecinium bromide (p. 1741·3).
Skin disorders.

Triamcinolon E *Zentiva, Cz.*
⊗Triamcinolone acetonide (p. 1649·1); chloroxine (p. 260·1).
Skin disorders.

Triamcinolon S *Zentiva, Cz.*
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Skin disorders.

Triamciterap
Note: this name may be used for preparations of different composition.
Frasca, Arg.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Medica, Arg.
Emollient.

Triam-Co *Norton, Rus.†*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Hypertension.

Triamco *Ivax, UK.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
These ingredients can be described by the British Approved Name Co-triamterzide.
Oedema; hypertension.

Triamcort *Helvepharm, Switz.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Interbat, Indon.
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

TriamCreme *Winthrop, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triamecon *Bright Future, Hong Kong.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections with inflammation.

Triamgalen *Galen, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triamhexal *Hexal, Ger.†*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Triamid *Beta, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Triaminic *Novartis Consumer, Ital.*
Powder for oral solution: ⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Triaminic Allergy Congestion *Novartis Consumer, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Triaminic Allergy Sinus & Headache *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Triaminic AM Non-Drowsy Cough & Decongestant *Novartis Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Triaminic Batuk & Pilek *Novartis, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

Triaminic Chest Congestion *Novartis, Singapore.*
⊗Guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Triaminic Chest & Nasal Congestion *Novartis Consumer, Canad.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Nasal congestion; cough.

Novartis, USA.
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Triaminic Children's Allergy *Novartis Consumer, USA.†*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Triaminic Cold & Allergy *Novartis Consumer, Canad.; Novartis, Singapore; Novartis, USA.†*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Nasal and sinus congestion; cold and allergy symptoms.

Triaminic Cold & Cough *Novartis Consumer, Canad.; Novartis Consumer, Israel; Novartis, Singapore; Novartis, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold symptoms.

Triaminic Cold Cough & Fever *Novartis Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; cough.

Triaminic Cold, Cough & Fever *Novartis, Singapore.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms; cough.

Novartis Consumer, Israel.†
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Triaminic Cold & Cough Thin Strips *Novartis, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Triaminic Cold and Nighttime Cough *Novartis Consumer, Canad.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Triaminic Cold & Sore Throat *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Triaminic Cough *Novartis Consumer, Canad.*
Lozenges: Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Novartis Consumer, Israel†; Novartis, Singapore; Novartis, USA.
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; upper respiratory-tract congestion.

Triaminic Cough & Cold *Novartis Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Triaminic Cough & Congestion *Novartis Consumer, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; nasal congestion.

Triaminic Cough & Fever *Novartis Consumer, Canad.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Triaminic Cough with Mucous *Novartis Consumer, Israel.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; upper respiratory-tract congestion.

Triaminic Cough & Runny Nose *Novartis, USA.*
Chewable tablets: Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Novartis Consumer, USA.†
Oral strips: Diphenhydramine hydrochloride (p. 626·2).
Cough.

Triaminic Cough & Sore Throat *Novartis Consumer, Canad.; Novartis Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough and cold symptoms.

Novartis Consumer, Canad.
Oral Liquid; tablets (chewable): Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).

Triaminic Daytime Cough & Cold *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Triaminic DM *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Triaminic Expectorant & Pilek *Novartis, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Triaminic Fever & Cough *Novartis Consumer, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Triaminic Flu *Novartis Consumer, Ital.*
Paracetamol (p. 115·1); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Triaminic Flu, Cough & Fever *Novartis Consumer, USA.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Coughs and cold symptoms.

Triaminic Infant Decongestant Plus Cough *Novartis Consumer, USA.*
Dextromethorphan (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Triaminic Infant Thin Strips Decongestant *Novartis Consumer, USA.†*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Triaminic Infant's Fever Reducer/ Pain Reliever *Novartis, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Triaminic Long Acting Cough *Novartis Consumer, Canad.; Novartis Consumer, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Triaminic Night Time Cold & Cough *Novartis Consumer, USA.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Triaminic Nighttime Cough & Cold *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p. 1672·3); diphenhydramine hydrochloride (p. 626·2).

Triaminic Pilek *Novartis, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Triaminic Softchews *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract disorders.

Triaminic Sore Throat Spray *Novartis Consumer, USA.*
Phenol (p. 1763·3).
Sore throat.

Triaminic Thin Strips Cold *Novartis Consumer, USA.*
Phenylephrine hydrochloride (p. 1672·3).
Nasal congestion.

Triaminic Thin Strips Cough & Congestion *Novartis Consumer, Canad.†*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).

Triaminic Thin Strips Nasal Congestion *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p. 1672·3).

Triaminic Thin Strips Nighttime Cough & Runny Nose *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p. 626·2).

Triaminic Throat Pain & Cough *Novartis, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1) dextromethorphan hydrobromide (p. 1660·1).
Coughs; sore throat.

Triaminic Vapor Patch *Novartis Consumer, USA.*
Camphor (p. 2466·2); menthol (p. 2553·2).

Triaminic-D *Novartis, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Triamizide *Mylan, NZ.†*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Hypertension; oedema.

Triamnone *Sunward, Singapore.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triamonide *Forest Pharmaceuticals, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Triampoen *Poen, Arg.*
⊗Triamcinolone (p. 1648·3).
Eye disorders.

Triampur Compositum *AWD, Ger.; Teva, Rus.; Teva, Ukr.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure.

TriamSalbe *Winthrop, Ger.†*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Triamsicort *Diba, Mex.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Triamtel *Valenta, Rus.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Hypertension; oedema.

Triamteren comp *Genericon, Austria; Ratiopharm, Ger.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; heart failure.

Triamteren HCT *Aliud, Ger.†; Betapharm, Ger.†; Sandoz, Ger.†*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; oedema.

Triamteren tri-comp *Sandoz, Ger.†*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2); propranolol hydrochloride (p. 1479·1).
Hypertension.

Triamteril *Deva, Turk.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Triamvirgi *Fisiopharma, Ital.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Trian *Demo, Gr.*
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Trianal
Note: this name may be used for preparations of different composition.
Trianon, Canad.
Aspirin (p. 22·2); caffeine (p. 1203·3); butalbital (p. 1043·3).
Pain; sedative.
Will-Pharma, Belg.; Will-Pharma, Neth.
⊗Triamcinolone acetonide (p. 1649·1); lidocaine hydrochloride (p. 1988·2).
Haemorrhoids; anal eczema and pruritus; pruritus ani.

Trianal C *Trianon, Canad.*
Aspirin (p. 22·2); caffeine (p. 1203·3); butalbital (p. 1043·3); codeine phosphate (p. 40·2).
Pain; sedative.

Triancil *Apsen, Braz.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Trianex *Upsher-Smith, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Trianol
Note: this name may be used for preparations of different composition.
Lek, Rus.; Lek, Ukr.†
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.
Pharma Nutria, Philipp.
Allopurinol (p. 600·2).
Hyperuricaemia.

Triaphin *MDI, S.Afr.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Triapin *Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Aventis, UK.*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Triapten *Riemser, Ger.*
Foscarnet sodium (p. 981·1).
Herpes simplex infections of the skin and mucous membranes.

Triarese *Hexal, Ger.†*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Triaspar *Beta, Arg.*
Cabergoline (p. 899·3).
Parkinsonism.

Triasporin *Italfarmaco, Ital.*
Itraconazole (p. 583·3).
Fungal infections.

Triastad HCT *Stada, Austria.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension; heart failure.

Triastonal *Schwarz, Ger.†*
Sitosterol (p. 1471·2).
Benign prostatic hyperplasia.

Triasyn *Sanofi-Aventis, Austral.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Triatec
Note: this name may be used for preparations of different composition.
Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Norw.; Sanofi-Aventis, Port.; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.
Ramipril (p. 1483·3).
Heart failure; hypertension; myocardial infarction; nephropathy; cardiovascular risk reduction.

Triatec-8
Note: this name may be used for preparations of different composition.
Trianon, Canad.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine citrate (p. 1203·3).
Pain; fever; cough.

Triatec-30
Note: this name may be used for preparations of different composition.
Trianon, Canad.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever; cough.

Triatec Comp *Sanofi-Aventis, Denm.†; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Triatec Composto *Sanofi-Aventis, Port.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Triatec D *Sanofi-Aventis, Braz.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Triatec HCT *Sanofi-Aventis, Ital.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Triatec Plus *Sanofi-Aventis, Gr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Triateckit *Sanofi-Aventis, Fr.†*
Ramipril (p. 1483·3).
Cardiovascular risk reduction.

Triativ *Ativus, Braz.*
St John's wort (p. 449·1).
Depression; agitation; sleep disorders.

Triatop *Janssen-Cilag, Arg.; Xian-Janssen, China; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.*
Ketoconazole (p. 585·3).
Dandruff; scalp disorders.

Triatus *Kocak, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Triaval *Orion, Switz.†*
70 Tablets, estradiol valerate (p. 2271·2); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Triaver *Biosel, Turk.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Tri-A-Vite F *Major, USA.*
Vitamins; fluoride (p. 2089·2).

Triax *Taro, Israel†; Sel-J, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Triaxin *Eurofarma, Braz.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Triaxiphin *Be-Tabs, S.Afr.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Triaxis *Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Triaxis Polio *Sanofi Pasteur, Neth.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Triaxon *Teuto, Braz.; Multicare, Philipp.; Kocak, Turk.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Triaxone *Aurobindo, Rus.; Hanmi, Singapore; Julphar, UAE.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Triaxton *Ariston, Braz.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Triaz *Medicis, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Triazine *Aspen, S.Afr.*
Cyclizine hydrochloride (p. 623·2).
Motion sickness; Ménière's disease.

Triazol *Biolab Sanus, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Tribakin *Farcoral, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Triban
Note: this name may be used for preparations of different composition.
Solfran, Mex.†
Vitamin B_{12} (p. 2107·2); vitamin B_1 (p. 2103·1).
Anaemias; neuritis.

Tribe 12 *Exakta, Mex.*
Vitamin B substances (p. 2102·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Anaemias; neuritis.

Tribedoce *Bruluart, Mex.*
Hydroxocobalamin (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neuritis; neuralgia.

Tribedoce Compuesto *Bruluart, Mex.*
1 Ampoule, diclofenac sodium (p. 48·3); 1 ampoule, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia.

Tribeksol *Deva, Turk.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Tribemed *Medicpharma, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Tribemin *Sam-On, Israel.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgias; vitamin B supplement; metabolic disorders.

Tribemine *Utopian, Thai.*
Vitamin B_1 (p. 2103·1) vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Tribena *Vitae, Mex.*
Vitamins.
Anaemias; neuritis.

Tribesian *Asian Pharm, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; migraine; neuritis; anaemias.

Tribesona *ITF, Chile.*
⊗Clotrimazole (p. 576·2); dexamethasone acetate (p. 1631·1).
Infected skin disorders.

Tribestan *Teguhsindo, Indon.; Sopharma, Rus.; Sopharma, Singapore; Sopharma, Ukr.*
⊗Tribulus terrestris (p. 2633·3).
Atherosclerosis; hypercholesterolaemia; male impotence; male infertility; menopausal disorders; female infertility; dyslipoproteinaemia.

Tribevit *Elvipe, Gr.*
Vitamin B substances (p. 2102·3).

Tribiocort *Biosintex, Arg.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); miconazole nitrate (p. 589·1).
Infected skin disorders.

Tribion *Universal, Hong Kong.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B supplement.

Tribiot *Grin, Mex.*
Neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); bacitracin (p. 225·3).
Bacterial eye infections.

Tribiotic *Kato, Pol.*
Bacitracin zinc (p. 225·3); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Wounds.

Tri-Biozene *Reese, USA.*
Bacitracin (p. 225·3); polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); pramocaine hydrochloride (p. 1993·3).

Triblix *Lepetit, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Tribonat *Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
⊗Trometamol (p. 2635·1); electrolytes (p. 1775·1).
Metabolic and respiratory acidosis; buffer.

Tribost *Ethica, Indon.*
Echinacea (p. 2498·1); phyllanthus niruri (p. 2590·1); black elderberry.
Immunostimulant; cold symptoms.

Tribudat *Santa, Turk.; Amoun, Ukr.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal motility disorders; gastrointestinal disorders.

Tri-Buffered ASA *Zee, Canad.†*
Aspirin (p. 22·2).
Calcium carbonate (p. 1824·3), magnesium carbonate (p. 1856·2), and magnesium oxide (p. 1857·3) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Tribulus & Epimedium Compound *Phytomedicine, Austral.*
⊗Tribulus terrestris (p. 2633·3); epimedium; Siberian ginseng (p. 2614·3); damiana (p. 2491·3); *d*-alpha tocoferil acid succinate (p. 2119·2); zinc sulfate (p. 2126·2).
Tonic for men.

Tributina *Lafedar, Arg.†*
Trimebutine maleate (p. 2634·1).
Gastrointestinal motility disorders.

Tribux *Biofarm, Pol.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Tri-B-Vit *Acdhon, Thai.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

TriBvit *Meda, Belg.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Vitamin deficiency.

Tricaine-MPS *RPG, India.*
Oxetacaine (p. 1993·1); simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Oesophagitis; gastritis; peptic ulcer; heartburn.

Trical-D *Knop, Chile.*
Calcium carbonate (p. 1824·3); calcium phosphate (p. 1784·2); calcium gluconate (p. 1783·3); colecalciferol (p. 2113·1).
Dietary supplement.
Svizera, India.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium deficiency.

Tricalma
Note: this name may be used for preparations of different composition.
Generis, Port.
Ibuprofen (p. 68·2).
Fever; pain.
Sanofi-Aventis, Chile.
Alprazolam (p. 1035·2).
Anxiety; panic attacks; mixed anxiety depressive states.

Trican *Pfizer, Israel.*
Fluconazole (p. 578·2).
Fungal infections.

Tricandil *SPA, Ital.; Prospa, Port.*
Mepartricin (p. 588·1).
Fungal vulvovaginitis.

Tricangine *Ache, Braz.*
Mepartricin (p. 588·1); tetracycline (p. 373·1).
Bacterial and fungal vulvovaginal infections.

Tricard *KVZ, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; chorioretinal ischaemia.

Tricardia *Meditec, Israel; Sam-On, Israel.*
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Elevated homocysteine levels.

TriCare Prenatal Compleat *Medecor, USA.*
Tablets, vitamins; minerals; capsules, omega-3 fatty acids (p. 1460·1).
Dietary supplement.

Tricavita *Frankin, Hong Kong.†*
Cyproheptadine (p. 624·1); lysine (p. 2079·3); vitamins.

Tricban *Greenpharma, Braz.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Tricef
Note: this name may be used for preparations of different composition.
Merck, Austria; Merck, Chile; Bialport, Port.
Cefixime (p. 240·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vianex (Βιανεξ), Gr.
Cefprozil (p. 248·2).
Bacterial infections.

Tricefi *Roemmers-Klinos, Venez.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Tricefin *Dexa, Indon.; Dexa, Singapore.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tricen *Abbott, Spain.†*
Verapamil hydrochloride (p. 1522·1); trandolapril (p. 1517·2).
Hypertension.

Tricephin *Atlantic, Thai.†*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tricept *Cuprocept, S.Afr.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Tricerol *Pharmacia, Braz.*
Etofibrate (p. 1379·2).
Hyperlipidaemias.

Tricexone *Caplin, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Trichazole *Aspen, S.Afr.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Trichek *Zydus Cadila, Philipp.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Trichex *GL Pharma, Austria.*
Metronidazole (p. 936·1).
Trichomoniasis; Gardnerella vaginalis *infections.*

Tri-Chlor *Gordon, USA.*
Trichloroacetic acid (p. 1727·2).
Warts.

Trichlorol *Lysoform, Ger.*
Tosylchloramide sodium (p. 1773·1).
Surface disinfection.

Trichobiol *Therasophia, Fr.*
Amino acids; minerals; vitamins; herbs.
Skin, hair, and nail disorders.

Trichobrol *Bryntsalov, Rus.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Trichodazol *Sanbe, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Trichogin *Farmanic, Gr.*
Tinidazole (p. 949·2).

Trichol *Galenium, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Trichomar *Brymar, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Trichonas *Pharmasant, Thai.*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis; anaerobic bacterial infections.

Tricho-PIN *North Star, Rus.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Trichopol *Polpharma, Rus.; Polpharma, Ukr.*
Metronidazole (p. 936·1).
Protozoal infections; trichomoniasis; giardiasis; amoebiasis; anaerobic bacterial infections; eradication of Helicobacter pylori.

Trichostatic *Pharos, Indon.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Trichotine *Schwarz, USA.*
Powder: Sodium laurilsulfate (p. 2210·3); sodium perborate (p. 1770·1); sodium chloride (p. 1795·1).
Vaginal disorders.

Trichovagil *Ni-The, Gr.*
Metronidazole (p. 936·1).
Vaginal infections.

Trichozole *Mylan, NZ.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Tricia *Gedeon Richter, Cz.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Tri-Ciclomex *Gynopharm, Chile.†*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triciclor *Wyeth, Spain.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triciderm *Ni-The, Gr.*
Tyrothricin (p. 384·1).
Skin infections.

Tricifa
Note: this name may be used for preparations of different composition.
Richet, Arg.
⊗Gentamicin (p. 304·2); miconazole (p. 588·3); betamethasone valerate (p. 1624·1).
Infected skin disorders.

TriCilest *Janssen-Cilag, Austria; Janssen-Cilag, Fr.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive; triphasic oral contraceptive in women with acne.

Janssen-Cilag, S.Afr.; Janssen-Cilag, Thai.
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive; acne.

Tricin
Note: this name may be used for preparations of different composition.
Agio, Philipp.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tricivir *GSK, Arg.; GSK, Chile.*
Abacavir sulfate (p. 963·1); lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Tricker *Meprofarm, Indon.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Tricloderm *APT, Hong Kong.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Triclofem *Tunggal Idaman, Indon.†*
Medroxyprogesterone acetate (p. 2288·1).
Injectable contraceptive.

Triclonam *CTS, Israel.*
Triclofos sodium (p. 1113·2).
Insomnia; sedative; premedication.

Tricloryl *GSK, India.*
Triclofos sodium (p. 1113·2).
Insomnia; sedative.

Triclose *Finderm, Ital.*
Azanidazole (p. 929·3).
Vaginal trichomoniasis.

Tricocet *Legrand, Braz.*
Nystatin (p. 590·3).
Candidiasis.

Tricocilin B *EMS, Braz.*
Tetracycline (p. 373·1); amphotericin B (p. 569·2).
Vaginal infections.

Tricodazole *Proel, Gr.*
Metronidazole (p. 936·1).
Rosacea.

Tricodein *Valeant, Austria.†*
Codeine phosphate (p. 40·2).
Cough.

Tricodene Cough & Cold *Pfeiffer, USA.*
Mepyramine maleate (p. 635·1); codeine phosphate (p. 40·2).
Coughs and cold symptoms.

Tricodene Sugar Free *Pfeiffer, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Tricoderm F *Farmachimici, Ital.*
Salicylic acid (p. 1719·1); piroctone olamine (p. 1716·3); ichthammol (p. 1705·3).
Scalp disorders.

Tricodex *Ecofarm, Ital.*
Amino acids; vitamins; minerals.
Hair and nail disorders.

Tricofarma *Investi, Arg.*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Tricofin *Raymos, Arg.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Tricogyn *Pharmaland, Thai.*
Tinidazole (p. 949·2).
Amoebiasis; giardiasis.

Tricolam *Farmasierra, Spain.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Tricolocion *Investi, Arg.*
Minoxidil (p. 1438·3).
Alopecia.

Tricolpex *Bunker, Braz.*
⊗Metronidazole (p. 936·1); nystatin (p. 590·3); urea (p. 1727·3).
Vulvovaginal infections.

Tricomax
Note: this name may be used for preparations of different composition.
Cassara, Arg.
Copper gluconate (p. 2057·2); zinc gluconate (p. 2126·2); selenium yeast (p. 2125·2); liver extract (p. 2444·1); cystine (p. 2059·1); methionine (p. 1558·2).
Dietary supplement.

Cazi, Braz.
⊗Metronidazole (p. 936·1); nystatin (p. 590·3); muramidase hydrochloride (p. 2565·1); urea (p. 1727·3); benzalkonium chloride (p. 1737·1).
Vaginal infections.

Tricomax 2 *Cassara, Arg.*
Amino acids; minerals.
Dietary supplement.

Tricomed
Note: this name may be used for preparations of different composition.
Hua, Thai.
Metronidazole (p. 936·1).
Trichomoniasis; vaginitis.

Myrex Ethica, Philipp.
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tricomycin *Terramedic, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Triconal *Investi, Arg.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); calcium pantothenate (p. 2085·2); methionine (p. 1558·2); arginine (p. 2049·1); pyridoxine hydrochloride (p. 2105·3); lecithin (p. 2542·2).
Dietary supplement.

Triconazole *Quality, Hong Kong.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections with inflammation.

Triconex *Multicare, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Tricoplus
Note: this name may be used for preparations of different composition.
ITF, Chile.
Finasteride (p. 2358·3).
Alopecia androgenetica.

Raymos, Arg.
Minoxidil (p. 1438·3).
Alopecia.

Tricor
Note: this name may be used for preparations of different composition.
Teijin, Jpn; Abbott, Rus.; Fournier, Ukr.†; AbbVie, USA.
Fenofibrate (micronized) (p. 1381·1).
Hyperlipidaemias.

Sanofi-Aventis, Chile.
Adenosine (p. 1291·1).
Arrhythmias; diagnosis of arrhythmias.

Tricorex *Provita, Ital.*
Amino acids; vitamins; minerals.
Nutritional supplement.

Tricort *Cadila, India.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Neo-Derm, Philipp.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tricortin *Fidia, Ital.*
Phosphatides (p. 2542·2); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Peripheral and central nervous system disorders.

Tricortone *Aspen, Austral.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tricosal
Note: this name may be used for preparations of different composition.
Biomedica, Gr.
Terfenadine (p. 640·3).

Tricostéril Coripel *Polive, Fr.†*
Salicylic acid (p. 1719·1).
Warts.

Tricovivax *Medinfar, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Tricowas B *Chiesi, Spain.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Tricox *Themis Medicare, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Tricoxane *ITF, Chile.*
Minoxidil (p. 1438·3).
Alopecia androgenetica; alopecia areata.

Tricoxen *IDI, Ital.*
Ubidecarenone acetate (p. 2637·1).

Tricoxidil *Johnson & Johnson, Ital.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Tricozole *Pharmasant, Thai.*
⊗Econazole nitrate (p. 577·3); triamcinolone acetonide (p. 1649·1).
Fungal skin infections with inflammation.

Tricozone *Hua, Thai.*
Tinidazole (p. 949·2).
Trichomoniasis; amoebiasis; giardiasis.

Tricur *Andromaco, Arg.*
⊗Ketoconazole (p. 585·3); hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Tricuval *Norma (Νορμα), Gr.*
⊗Trypsin (p. 2635·2); chymotrypsin (p. 2477·3).

Tri-Cyclen *Janssen, Canad.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
The 28-day packs also contain 7 inert tablets.
Triphasic oral contraceptive; acne.

Tricylamil *Norma (Νορμα), Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

Tridanil-H *Ultra, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Tridecon *Medi-Rx, Philipp.*
Chlorphenamine maleate (p. 620·3); phenylpropanolamine hydrochloride (p. 1674·1).
Nasal congestion.

Tridel *Choongwae, Philipp.*
Metronidazole (p. 936·1).
Protozoal infections.

Tridelta *Ceccarelli, Ital.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Trident *Adams, Canad.*
Xylitol (p. 2220·3).
Dental caries prophylaxis.

Triderm
Note: this name may be used for preparations of different composition.
Del-Ray, USA.
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Medley, Braz.
⊗Fluocinolone acetonide (p. 1636·1); hydroquinone (p. 1705·1); tretinoin (p. 1725·2).
Skin hyperpigmentation.

MSD, Hong Kong; Schering-Plough, Israel; Schering-Plough, Mex.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Rus.; MSD, Singapore; MSD, Switz.; Schering-Plough, Ukr.; Schering-Plough, Venez.
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Triderm 5 *ICIM, Ital.*
Barrier preparation.

Triderm Crema *ICIM, Ital.*
Zinc oxide (p. 1729·1).

Triderm Zeta *ICIM, Ital.*
Zinc oxide (p. 1729·1).
Skin disorders.

Tridermal *Panalab, Arg.*
⊗Ketoconazole (p. 585·3); hydrocortisone acetate (p. 1640·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Triderm-C *Schering-Plough, Malaysia.*
⊗Betamethasone dipropionate (p. 1623·3); clotrimazole (p. 576·2).
Fungal skin infections.

Tridesilon *Perrigo, Canad.*
⊗Desonide (p. 1630·1).
Skin disorders.

Tridésonit *Sinclair, Fr.*
⊗Desonide (p. 1630·1).
Skin disorders.

Tridestan N *Gador, Arg.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Tridestra *Orion, UK.*
70 Tablets, estradiol valerate (p. 2271·2); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Tridetarmon *Roemmers Rowe, Venez.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2); clioquinol (p. 273·1).
Infected skin disorders.

Tridette *Gador, Arg.*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Tridewel *Bright Future, Hong Kong.†*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2); gentamicin (p. 304·2).
Infected skin disorders.

Tridex *Sanbe, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Tridez *Sandoz, Indon.†*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Tridiavir *Serra Pamies, Spain.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Tridigestivo Soubeiran *Chobet, Arg.*
⊗Pancreatin (p. 2579·3); takadiastase (p. 2442·1); pepsin (p. 2586·1).
Digestive disorders.

Tridil *Cristalia, Braz.; Sanofi Synthelabo, S.Afr.†*
Glyceryl trinitrate (p. 1391·2).
Control of blood pressure during surgery; heart failure; ischaemic heart disease.

Tridin *Madaus, Ger.; Rottapharm, Ger.*
Sodium monofluorophosphate (p. 2091·3); calcium gluconate (p. 1783·3); calcium citrate (p. 1783·2).
Osteoporosis.

Rottapharm, Cz.; Rotta, Hong Kong; Rottapharm, Hung.; Rottapharm, Ital.
Glutamine monofluorophosphate (p. 2091·3); calcium gluconate (p. 1783·3); calcium citrate (p. 1783·2).
Osteoporosis; calcium deficiency.

Tridin Forte *Opfermann, Ger.†*
Sodium monofluorophosphate (p. 2091·3); calcium carbonate (p. 1824·3).
Osteoporosis.

Triditol-G *Loyal Advance, Hong Kong.*
⊗Triamcinolone acetonide (p. 1649·1); gentamicin sulfate (p. 304·2); diphenhydramine hydrochloride (p. 626·2); tolnaftate (p. 596·1).
Inflamed bacterial and fungal skin infections.

Tridomose *Aventis, S.Afr.†*
⊗Gestrinone (p. 2280·2).
Endometriosis.

Triductan *Pharma Start, Ukr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vestibular disorders; chorioretinal ischaemia.

Tridural *Paladin, Canad.; Kironfarma, Port.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tridyl *Condrugs, Thai.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism; drug-induced extrapyramidal disorders.

Triella *Janssen-Cilag, Fr.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triene *Wassermann, Ital.*
Polyenacid (p. 2509·2).
Wounds; burns; skin irritation; barrier preparation.

Trienter *Farmedia, Gr.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

Trienyl *Lek, Pol.†*
Fish oil (p. 1460·3).
Hyperlipidaemias; atherosclerosis; cerebrovascular disorders; cardiovascular disorders.

Triesence *Alcon, Norw.; Alcon, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Visualisation during vitrectomy; inflammatory eye disorders.

Tri-Estarylla *Sandoz, USA.*
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic combined oral contraceptive.

Triette *Aliud, Ger.†*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triexidyl *Cristalia, Braz.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

Trifacilina *Bago, Arg.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Trifalac *Medicus, Gr.*
Dibasic sodium phosphate (p. 1791·2); phosphoric acid (p. 2589·1).
Constipation.

Trifamox *Bago, Arg.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Bago, Braz.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); pivsulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Trifamox Bronquial *Bago, Arg.*
Amoxicillin trihydrate (p. 216·2); brovanexine hydrochloride (p. 1657·3).
Bacterial infections of the respiratory tract.

Trifamox Bronquial Duo *Bago, Arg.*
Amoxicillin trihydrate (p. 216·2); ambroxol hydrochloride (p. 1654·3).
Respiratory-tract infections.

Trifamox Duo *Bago, Arg.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Trifamox IBL *Bago, Arg.; Armstrong, Mex.; Bago, Rus.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); pivsulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Bago, China.
Amoxicillin (p. 216·2) or amoxicillin sodium (p. 216·2); pivsulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Trifamox IBL Duo *Bago, Arg.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2); sulbactam (p. 360·1) or pivsulbactam (p. 360·1).
Bacterial infections.

Trifas
Note: this name may be used for preparations of different composition.
Berlin-Chemie, Pol.; Menarini, Pol.; Berlin-Chemie, Ukr.
⊗Torasemide (p. 1516·3).
Oedema; hypertension; heart failure.

Trifatrim *Acdhon, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trifed *Interbat, Indon.; Nakornpatana, Thai.; Hikma, Ukr.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms; sinusitis; allergic rhinitis; hay fever; nasal congestion; upper respiratory-tract disorders.

Trifed-C Cough *Geneva, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); triprolidine hydrochloride (p. 642·3).
Coughs and cold symptoms.

Trifed-Expectorant *Hikma, Ukr.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders with cough.

Trifedrin
Note: this name may be used for preparations of different composition.
Farmoquimica, Braz.
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3); sulfogaiacol (p. 1678·1).
Cough.

Otto, Indon.
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Cold symptoms; sinusitis.

Trifedrin Plus *Otto, Indon.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3); paracetamol (p. 115·1).
Cold symptoms.

Trifeme *Pfizer, Austral.; Pfizer, NZ.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, inert.
Triphasic oral contraceptive.

Tri-Femoden *Bayer Schering, Fin.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trifen
Note: this name may be used for preparations of different composition.
Aroma, Turk.
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Be-Tabs, S.Afr.
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Hertz, Braz.
Paracetamol (p. 115·1).
Fever; pain.

Trifene *Medinfar, Port.*
Ibuprofen (p. 68·2).
Pain; fever.

Triferexx *Axxess, Canad.*
Polysaccharide-iron complex (p. 2086·2).
Iron deficiency.

Trifibra Mix *Sanofi-Aventis, Braz.*
Bran (p. 1823·3).
Dietary supplement; constipation.

Triflexor *Combiphar, Indon.*
Glucosamine (p. 2515·3); chondroitin (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis.

Triflucan *Pfizer, Arg.; Pfizer, Fr.; Pfizer, Israel; Pfizer, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Trifluid *Otsuka, Indon.; Otsuka, Jpn.*
Glucose (p. 2068·3); fructose (p. 2068·2); xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Triflumann *Mann, Ger.*
Trifluridine (p. 1020·3).
Herpesvirus keratitis.

Triflumed *Medifive, Thai.*
Trifluoperazine (p. 1113·2).
Anxiety; psychoses; nausea and vomiting.

Triflux *Scharper, Ital.*
Triflusal (p. 1519·3).
Thromboembolic disorders.

Triforam *Foramen, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Triforte *Rafarm, Gr.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Trifosfaneurina *Angelini, Port.*
Cocarboxylase chloride (p. 2102·3).
Neuromuscular disorders; neuritis; neuralgia.

Trifuncan *Micro, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Trigamma *Moschimfarm, Rus.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuritis; neuralgia; neuropathy.

Trigan *Cadila, Rus.*
Dicycloverine hydrochloride (p. 1834·2).
Smooth muscle spasm.

Trigan-D *Cadila, India; Cadila, Rus.*
Tablets: Dicycloverine hydrochloride (p. 1834·2); paracetamol (p. 115·1).
Smooth muscle spasm; pain.

Tri-Gel *Vida, Hong Kong.†*
⊗Triamcinolone acetonide (p. 1649·1); lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Oral lesions.

Trigen *Rimsa, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Trigesico *BMS, Chile.†*
Paracetamol (p. 115·1); aspirin (p. 22·2); caffeine (p. 1203·3).
Cold symptoms; pain.

Trigestrel *Famy, Malaysia; Famy, Thai.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trigilab *Interpharma, Chile.*
Lamotrigine (p. 527·2).
Epilepsy.

Triginet *KRKA, Cz.†; KRKA, Pol.†; KRKA, Rus.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Trigliceril CM *Support, Braz.*
Preparation for enteral nutrition.

Triglide *Shionogi, USA.*
Fenofibrate (p. 1381·1).
Hypercholesterolaemia.

Triglistab *Arkopharma, Fr.*
Omega-3 marine triglycerides (p. 1460·3).
Hyperlipidaemias.

Triglobe *AstraZeneca, Braz.; AstraZeneca, Philipp.†*
Sulfadiazine (p. 361·3); trimethoprim (p. 381·2).
Bacterial infections.

Triglyx *Ingers, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Trigoa *Pfizer, Ger.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trigofen DM *Trigen, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Trigogine *Atlantic, China; Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
Codergocrine mesilate (p. 389·2).
Cerebral and peripheral vascular disorders; mental function impairment.

Trigolax *Coup, Gr.*
Potassium sodium tartrate (p. 1879·3).
Laxative.

Trigon Depot *BMS, Spain.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Trigopax *ACM, Fr.*
Tapioca starch (p. 2095·1); sunflower oil (p. 2098·1); zinc oxide (p. 1729·1); ciclopirox olamine (p. 575·3).
Skin irritation.

Trigrim *Polpharma, Rus.; Polpharma, Ukr.*
⊗Torasemide (p. 1516·3).
Oedema; hypertension.

Trigrip *Stada, Cz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Tri-Gynera *Bayer, Port.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Trigynera *Bayer, Gr.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Triphasic oral contraceptive.

Trigynon *Bayer, Austria†; Bayer, Belg.; Bayer, Neth.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trigynovin *Bayer, Spain.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

TriHEMIC *Lederle, USA.*
Ferrous fumarate (p. 2060·3); vitamin B_{12} substances (p. 2107·2); intrinsic factor concentrate (p. 2534·2); folic acid (p. 2063·1); vitamin E (p. 2119·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of ferrous fumarate; docusate sodium (p. 1836·2) is included to reduce the constipating effects of ferrous fumarate.
Anaemias.

Wyeth, Philipp.
Ferrous fumarate (p. 2060·3); vitamin B_{12} (p. 2107·2); intrinsic factor concentrate (p. 2534·2); folic acid (p. 2063·1); vitamin E (p. 2119·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of ferrous fumarate. Docusate sodium (p. 1836·2) is included to reduce the constipating effects of ferrous fumarate.
Anaemias.

Triherpine *Novartis, Gr.; Medivis, Ital.†; Novartis, Thai.†*
Trifluridine (p. 1020·3).
Herpes simplex infections of the eye.

Trihexid *Trident, Singapore.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; gingivitis.

Trihexy *Richard, Fr.; Geneva, USA.*
Trihexyphenidyl hydrochloride (p. 917·3).
Parkinsonism.

TriHIBit *Sanofi Pasteur, USA.†*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Trihistalex *Kela, Belg.*
Diphenhydramine hydrochloride (p. 626·2); cinchocaine hydrochloride (p. 1983·2); nicotinamide (p. 2083·1).
Pain; cutaneous hypersensitivity reactions.

Triiodothyronine Injection *Goldshield, UK.*
Liothyronine sodium (p. 2342·3).
Myxoedema coma.

Trijec *Landson, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tri-K *Century, USA.*
Potassium acetate (p. 1793·1); potassium bicarbonate (p. 1780·3); potassium citrate (p. 1780·3).
Hypokalaemia; potassium depletion.

Trikacide *Pharmascience, Canad.†*
Metronidazole (p. 936·1).
Bacterial infections; protozoal infections.

Trikal *IBN, Ital.†*
Calcitriol (p. 2113·1).
Renal osteodystrophy; hypoparathyroidism; pseudohypoparathyroidism; rickets; osteoporosis.

Trikatu *Code, Fr.*
Ginger (p. 1844·1); black pepper (p. 2586·1); piper longum.
Dietary supplement; digestive disorders.

Tri-Kort *Keene, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Trikozol *Orion, Fin.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; antibiotic-associated colitis; Crohn's disease; eradication of Helicobacter pylori *in peptic ulcer; protozoal infections.*

Trikvilar *Bayer Schering, Fin.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trilac
Note: this name may be used for preparations of different composition.
Allergon, Pol.
Bifidobacterium bifidum (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3).
Restoration of gastrointestinal flora; constipation.

Novell, Indon.
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Trilafon *Schering-Plough, Indon.; Schering-Plough, Ital.; Schering-Plough, Norw.; Schering-Plough, Philipp.†; Schering-Plough, Pol.; MSD, Swed.; MSD, Switz.*
Perphenazine (p. 1095·3) or perphenazine decanoate (p. 1096·1).
Psychoses; nausea; vomiting; alcohol or opioid withdrawal syndromes; anxiety; premedication; pain; pruritus; depression; intractable hiccups.

Schering-Plough, Denm.
Perphenazine decanoate (p. 1096·1).
Psychoses; hiccups; nausea; vomiting.

Trilagavit *Farmanic, Gr.; Lagap, Switz.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Peripheral neuropathies.

Trilam *Gerard, Irl.†*
Triazolam (p. 1112·3).
Insomnia.

Trilax
Note: this name may be used for preparations of different composition.
Coup, Gr.
Potassium sodium tartrate (p. 1879·3).

Hexal, Braz.
Carisoprodol (p. 2021·3); diclofenac sodium (p. 48·3); paracetamol (p. 115·1); caffeine (p. 1203·3).

Trilaxis *Filaxis, Arg.*
Abacavir sulfate (p. 963·1); lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Tri-Legest *Barr, USA.*
21 Tablets, norethisterone acetate (p. 2294·3); ethinylestradiol (p. 2275·3); 7 tablets, ferrous fumarate (p. 2060·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trileptal *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.†; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Oxcarbazepine (p. 533·2).
Epilepsy; trigeminal neuralgia; neuropathic pain; bipolar disorder.

Trileptin *Novartis, Israel.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Trilifan *Schering-Plough, Fr.†*
Perphenazine enantate (p. 1096·1).
Psychoses.

Tri-Linyah *NorthStar, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norgestimate (p. 2295·3); 7 tablets, inert.
Triphasic oral contraceptive.

Trilip *Elea, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Trilipid *Sydenham, Philipp.*
Phytosterol complex esters (p. 1471·2); docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Hyperlipidaemias.

Trilipix *Abbott, USA.*
Choline fenofibrate (p. 1381·2).
Hyperlipidaemias.

Triliver *Northia, Arg.*
⊗Betamethasone (p. 1623·2); gentamicin (p. 304·2); miconazole (p. 588·3).
Infected skin disorders.

Triloc *AstraZeneca, Austria.†*
⊗Metoprolol tartrate (p. 1434·3); hydrochlorothiazide (p. 1403·2); hydralazine hydrochloride (p. 1401·2).
Hypertension.

Trilog *Hauck, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Trilogan *Medhel, Gr.*
Co-trimoxazole (p. 277·3).

Trilombrin *Farmasierra, Spain.*
Pyrantel embonate (p. 165·3).
Worm infections.

Trilosil *Silom, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Tri-Lo-Sprintec *Barr, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norgestimate (p. 2295·3); 7 tablets, inert.
Triphasic oral contraceptive.

Triloxane *Vickmans, Hong Kong.†*
Magnesium hydroxide (p. 1857·2) or magnesium trisilicate (p. 1858·1); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Tri-Luma *Galderma, Arg.; Galderma, Braz.; Galderma, Chile; Galderma, Hong Kong; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Galderma, Thai.; Galderma, Venez.*
⊗Hydroquinone (p. 1705·1); tretinoin (p. 1725·2); fluocinolone acetonide (p. 1636·1).
Facial melasma; skin hyperpigmentation.

Galderma, USA.
⊗Hydroquinone (p. 1705·1); tretinoin (p. 1725·2); fluocinolone (p. 1636·1).
Facial melasma.

TriLyte *Alaven, USA.*
Macrogol 3350 (p. 2547·3); electrolytes (p. 1775·1).
Bowel evacuation.

Trim
Note: this name may be used for preparations of different composition.
Saval, Chile.
Trimebutine maleate (p. 2634·1).
Gastrointestinal disorders.

M & H, Thai.
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Trima *Jin Yang, Malaysia.†*
Trimebutine maleate (p. 2634·1).
Gastritis; irritable bowel syndrome.

Tri-Mactex *Gynopharm, Chile.†*
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trimada *Code, Fr.*
Linoleic acid (p. 2509·2); gymnema silvestre; fenugreek seed (p. 2504·1).
Promotion of fat metabolism.

Trimadan *Dankos, Indon.†*
Clotrimazole (p. 576·2).
Fungal skin infections.

Trimagen *Trigen, USA.†*
Iron (p. 2073·1); vitamin B_{12} (p. 2107·2); dessicated stomach extract (p. 2444·1). Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Trimate-E *Kimia, Indon.*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); hydroxocobalamin (p. 2107·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Tonic; neuralgia; neuritis; musculoskeletal pain; anaemia.

Trimaxazole *Beacons, Singapore.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Trimaze *Aspen, S.Afr.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Trimazen *Multilab, Braz.*
Clotrimazole (p. 576·2).

Trimazimyl *Mylan, Fin.*
Mirtazapine (p. 436·1).
Depression.

Trimazol *Vannier, Arg.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Trimeba *Bajamed, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Trimecor *Corsalud, Venez.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Trimedal *Novartis, Braz.*
Dimetindene maleate (p. 626·1); rutoside (p. 2505·3); paracetamol (p. 115·1); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Trimedal D&F *Novartis, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Trimedal Tosse *Novartis, Braz.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Trimedat *Valenta, Rus.*
Trimebutine maleate (p. 2634·1).
Gastrointestinal motility disorders.

Trimedil
Note: this name may be used for preparations of different composition.
Novartis Consumer, Austria.
Paracetamol (p. 115·1).
Pain; fever.

Trimedil compositum *Novartis Consumer, Austria.†*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dimetindene maleate (p. 626·1); ascorbic acid (p. 2110·3); oxerutins (p. 2505·3).
Cold symptoms.

Trimedil plus C *Novartis Consumer, Austria.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever; cold symptoms.

Trimedin *Kleva, Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Trimedor *Biomedica, Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Trimegtante *Cinetic, Arg.*
⊗Fluocinolone (p. 1636·1); tretinoin (p. 1725·2); hydroquinone (p. 1705·1).
Melasma.

Trimektal *Vertex, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vascular eye disorders; vestibular disorders.

Trimelot *Alapis, Gr.*
Oxaprozin (p. 112·3).
Inflammatory disorders.

Trimephar *Am-Europharma, Philipp.*
Co-trimoxazole (p. 277·3).
Urinary-tract infections.

Trimepharma *Ratiopharm, Port.†*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Trimepol *Ingens, Arg.†*
Trimethoprim (p. 381·2); polymyxin B (p. 342·3).
Bacterial eye infections.

Trimepol D *Ingens, Arg.†*
⊗Trimethoprim (p. 381·2); polymyxin B (p. 342·3); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections.

Trimepranol *Glenmark, Cz.*
⊗Metipranolol (p. 2009·2).
Arrhythmias; myocardial infarction; angina pectoris; hypertension; tremor; hypertrophic obstructive cardiomyopathy.

Tri-Merci *Organon, Rus.; Organon, Ukr.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Trimerel *Domesco, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo; tinnitus; circulatory eye disorders.

Trimesan *Sun-Farm, Pol.*
Trimethoprim (p. 381·2).
Bacterial infections; pneumocystis pneumonia.

Trimet *Torrent, Rus.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vascular eye disorders; vestibular disorders.

Trimetabol *Uriach, Spain.*
Cyproheptadine acefyllinate (p. 624·1); amino acids; vitamins.
Anorexia; weight loss; tonic.

Uriach, Ukr.
Cyproheptadine acefyllinate (p. 624·1); lysine hydrochloride (p. 2079·3); dl-carnitine hydrochloride (p. 2053·2); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Reduced appetite.

Arrow, Braz.†
Cyproheptadine acefyllinate (p. 624·1); lysine hydrochloride (p. 2079·3); carnitine hydrochloride (p. 2053·2); vitamin B substances (p. 2102·3).
Tonic; reduced appetite.

Trimetaratio *Ratiopharm, Pol.*
Trimetazidine hydrochloride (p. 1520·1).
Ischaemic heart disease; ischaemic eye disorders; ischaemic vestibular disorders.

Trimetazide *Pabianice, Rus.*
Trimetazidine (p. 1520·1).
Angina pectoris; vascular eye disorders; vestibular disorders.

Trimetazole *Gruppo Medica, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimethop *Charoon Bhesaj, Thai.*
Trimethoprim (p. 381·2).
Bacterial infections.

Trimethox *Caps, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimetin *Vitabalans, Fin.*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Trimetin Duplo *Vitabalans, Fin.†*
Sulfadiazine (p. 361·3); trimethoprim (p. 381·2).
Respiratory-tract and urinary-tract infections.

Trimetoger *Streger, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimeton *Schering-Plough, Ital.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions; motion sickness; vomiting.

Trimetox *Rimsa, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimetrin *Vickmans, Hong Kong.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimetrox *Richmond, Arg.†*
⊗Tamoxifen citrate (p. 860·2).

Trimetyl-HIDA *Rez, Cz.*
Technetium-99m mefenin (p. 2228·1).
Radionuclide imaging of the biliary tract and liver.

Trimevert *Med-One, Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Trimex *Ratiopharm, Fin.†*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Trimexazol *Sanofi-Aventis, Braz.; Valeant, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Trimexazole *CCM, Malaysia; Pharmasant, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimexine *Valeant, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Trimexol *Trima, Israel.*
Pramipexole hydrochloride (p. 911·2).
Parkinsonism; restless legs syndrome.

Trimexole *Rayere, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Trimexole Compositum *Rayere, Mex.*
Co-trimoxazole (p. 277·3); guaifenesin (p. 1666·2).
Respiratory-tract infections.

Trimezol *Mugi, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trim-Fit *Quest, Canad.†*
Bitter orange (p. 2575·3); enzyme blend; camelia sinensis (p. 2648·2); kelp (p. 2612·1); thioctic acid (p. 2629·1); St John's wort (p. 449·1); tonalin.

Tri-Micon
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
⊗Betamethasone valerate (p. 1624·1); miconazole nitrate (p. 589·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Trimicon
Note: this name may be used for preparations of different composition.
Unison, Thai.
⊗Miconazole nitrate (p. 589·1); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Trimicro *Microsules, Arg.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Trimigren *Nizhpharm, Rus.*
Sumatriptan succinate (p. 679·2).
Migraine.

Trimikos *HealthCare, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Trimin *Pharmmalaysia, Singapore.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Trimine *Sandoz, Switz.†*
Trimipramine maleate (p. 453·1).
Depression; pain.

Triminetta *Sandoz, Denm.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Triphasic oral contraceptive.

Trimineurin *Hexal, Ger.†*
Trimipramine maleate (p. 453·1) or trimipramine mesilate (p. 453·1).
Depression; sleep disorders.

Triminex *Konimex, Indon.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tri-Minulet *Pfizer, Belg.; Pfizer, Cz.; Pfizer, Fr.; Wyeth, Gr.; Pfizer, Irl.; Wyeth Lederle, Ital.; Wyeth, Pol.†; Pfizer, Port.; Wyeth, Spain.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Akromed, S.Afr.†
21 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 7 tablets, placebo.
Triphasic oral contraceptive.

Trimiron *MSD, Swed.†*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Trimistin *Darnitsa, Ukr.*
⊗Triamcinolone acetonide (p. 1649·1); miramistin (p. 1761·2).
Skin disorders.

Trimitrix *Morishita, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tri-Mix
Note: this name may be used for preparations of different composition.
Wedgewood, USA.
Papaverine (p. 2362·2); alprostadil (p. 2352·2); phentolamine (p. 1468·3).
Erectile dysfunction.

Trimline *Lane, Pol.*
Xanthogenic fibre; vitamins; trace elements.
Obesity.

Trimocom *Jumont, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimoks *Atabay, Turk.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Trimol *Julphar, UAE.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis; nocardiosis.

Trimol-A *Julphar, UAE.*
Trimethoprim (p. 381·2).
Bacterial infections; pneumocystis pneumonia.

Trimolep *Psicofarma, Mex.*
Lamotrigine (p. 527·2).
Epilepsy; bipolar disorder.

Trimonase *Finderm, Ital.*
Tinidazole (p. 949·2).
Trichomoniasis; giardiasis; amoebiasis.

Trimonil *Desitin, Denm.; Desitin, Norw.; Desitin, Swed.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; alcohol withdrawal syndrome; diabetes insipidus; benzodiazepine withdrawal syndrome; diabetic neuropathy; mania; bipolar disorder.

Trimonit *Sanofi-Aventis, Pol.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Trimopan *Orion, Denm.; Orion, Fin.; Berk, UK.*
Trimethoprim (p. 381·2).
Urinary-tract and respiratory-tract infections.

Trimoptin *Athlone, Irl.*
Trimethoprim (p. 381·2).
Bacterial infections.

Trimo-San *Cooper, USA.*
⊗Hydroxyquinoline sulfate (p. 2530·1); boric acid (p. 2459·3); borax (p. 2459·2); sodium laurilsulfate (p. 2210·3); glycerol (p. 2517·2).
Vaginal deodoriser.

Trimosin *SSK, Turk.*
Amoxicillin (p. 216·2).
Bacterial infections.

Trimovate *GSK, UK.*
Cream: ⊗Clobetasone butyrate (p. 1627·3); oxytetracycline calcium (p. 337·1); nystatin (p. 590·3).
Skin disorders with bacterial or fungal infection.

Trimovax *Sanofi Pasteur, Arg.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Sanofi Pasteur, Philipp.; Litha, S.Afr.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
A measles, mumps, and rubella (Schwarz, Urabe, and Wistar strains respectively) vaccine (p. 2400·2).
Active immunisation.

Trimox
Note: this name may be used for preparations of different composition.
Apothecon, USA.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Delta, Braz.
Amoxicillin (p. 216·2).
Bacterial infections.

Trimoxal *Elmor, Venez.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Trimoxazole *Sandoz, Austral.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimoxis *Genesis, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimoxsul *Interbat, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimpex *Roche, USA.*
Trimethoprim (p. 381·2).
Urinary-tract infections.

Trim-S *Dynamic, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trimstat
Note: this name may be used for preparations of different composition.
Fada, Arg.
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Trimulex *Medi-Rx, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Trimycin *BioFemme, Philipp.*
Bacitracin (p. 225·3); neomycin (p. 329·3); polymyxin B sulfate (p. 342·3).
Bacterial skin infections.

Trimycin-H *BioFemme, Philipp.*
⊗Bacitracin (p. 225·3); hydrocortisone (p. 1640·1); neomycin (p. 329·3); polymyxin B sulfate (p. 342·3).
Skin infections.

Trimzol *Randall, Mex.; Schwulst, S.Afr.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Trinagesic *Adcock Ingram, S.Afr.*
Meprobamate (p. 1083·3); paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain and associated tension.

Trinalin
Note: this name may be used for preparations of different composition.
Norma (Νορμα), Gr.
Levocarnitine (p. 2053·2).
Myocardial ischaemia; carnitine deficiency.

Trinalion *Neo-Farmaceutica, Port.*
Nimodipine (p. 1455·2).
Cerebral vasospasm following subarachnoid haemorrhage; cerebral ischaemia.

Trinate *Cypress, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Trinazole *Sunward, Singapore.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Trinell *Beres, Ukr.†*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Pain; fever.

Trinell Pro *Beres, Hung.*
Paracetamol (p. 115·1); propyphenazone (p. 127·3); caffeine (p. 1203·3).
Fever; pain.

Trinergic *Unichem, India.*
Capsules: Vitamins; ginseng (p. 2513·3); zinc (p. 2126·1).
Tonic.

Trinergot *Atlantis, Mex.*
Caffeine (p. 1203·3); ergotamine tartrate (p. 674·1).
Migraine and other vascular headaches.

TriNessa *Watson, USA.*
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Trinestril *Sanofi-Aventis, Braz.*
⊗Estradiol hexahydrobenzoate (p. 2271·2); testosterone hexahydrobenzoate (p. 2305·1); hydroxyprogesterone enantate (p. 2285·1).
Menopausal disorders.

Trineurin *Orion, Fin.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Trineurovita *Maver, Mex.*
Hydroxocobalamin acetate (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Vitamin B deficiency; neuritis; neuralgias; neuropathy.

Trineurovita Compuesto *Maver, Mex.*
⊗1 Ampoule, hydroxocobalamin acetate (p. 2107·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); 1 ampoule, dexamethasone sodium phosphate (p. 1631·2); lidocaine hydrochloride (p. 1988·2).
Neuritis; neuralgias; inflammation.

Trinevrina B6 *Guidotti, Ital.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Neuritis; neuralgias; toxicosis; radiation sickness.

Trinicalm *Torrent, India.*
Trifluoperazine (p. 1113·2).
Anxiety; mixed anxiety depressive states; schizophrenia; senile agitation.

Trinicalm Forte *Torrent, India.*
Chlorpromazine hydrochloride (p. 1045·2); trifluoperazine hydrochloride (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).
Schizophrenia.

Trinicalm Plus *Torrent, India.*
Trifluoperazine hydrochloride (p. 1113·2); trihexyphenidyl hydrochloride (p. 917·3).
Schizophrenia.

Trinidex *Diaco, Ital.*
Glucose (p. 2068·3); vitamins; sodium chloride (p. 1795·1).
Fluid and electrolyte disorders; carbohydrate source.

Trinigyn *Grunenthal, Mex.*
Tinidazole (p. 949·2).
Protozoal infections; anaerobic bacterial infections.

Trinipatch *Solvay, Belg.; Paladin, Canad.; Lavipharm, Fr.; Pfizer, Gr.; Lavipharm, Neth.; Procter & Gamble, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Triniplas *Novartis, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Trinispray *Sanofi-Aventis, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectori's.

Triniton *Apogepha, Ger.†*
⊗Dihydralazine sulfate (p. 1358·3); hydrochlorothiazide (p. 1403·2); reserpine (p. 1485·3).
Hypertension.

Trinitrina *Pharmafar, Ital.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; myocardial infarction; pulmonary oedema; hypertension.

Trinitrine *Sanofi, Switz.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; pulmonary oedema; heart failure.

Trinitrine Cafein Dubois *Santa, Gr.*
Glyceryl trinitrate (p. 1391·2); caffeine hydrate (p. 1203·3).

Trinitrine Simple Laleuf *Santa, Gr.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Trinitrolong *TsSKB-Progress, Rus.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Trinitron *Quesada, Arg.*
Glyceryl trinitrate (p. 1391·2); caffeine (p. 1203·3).
Angina pectoris.

Trinitrosan *Merck Serono, Ger.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; controlled hypotension; myocardial infarction; heart failure; hypertensive crisis.

Trinizol M *UCI, Braz.*
Tinidazole (p. 949·2); miconazole nitrate (p. 589·1).
Vulvovaginal infections.

Trinodazol *Geolab, Braz.*
Tablets; vaginal gel: Metronidazole (p. 936·1).

Geolab, Braz.
Vaginal cream: Metronidazole (p. 936·1); nystatin (p. 590·3).

Trinodazol Nistatina *Geolab, Braz.*
Metronidazole (p. 936·1); nystatin (p. 590·3).

Trinolon *Kimia, Indon.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Trinolone *Nida, Singapore.*
⊗Triamcinolone acetonide (p. 1649·1).
Oral lesions.

Trinoman *T Man, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Trinordiol
Note: this name may be used for preparations of different composition.
Boizot, Spain.
Delapril hydrochloride (p. 1350·2).
Hypertension.

Wyeth, Arg.; Eurim, Austria; Pfizer, Belg.; Wyeth, Braz.; Wyeth, Chile; Wyeth Lederle, Cz.†; Wyeth, Denm.†; Pfizer, Fr.; Wyeth, Gr.; Wyeth, Hung.†; Pfizer, Irl.; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Wyeth, Philipp.; Wyeth, Pol.; Pfizer, Port.; Wyeth, Singapore†; Wyeth, Venez.
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive; menstrual disorders.

Sunthi Sepuri, Indon.†; Wyeth, Indon.†; Pfizer, Swed.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Tri-Norinyl *Searle, USA.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inerttablets.
Triphasic oral contraceptive.

TRI-Normin *Teofarma, Ger.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2); hydralazine hydrochloride (p. 1401·2).
Hypertension.

Trinotecan *Filaxis, Arg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Trinovin *Novogen, Austral.; Ikapharmindo, Indon.*
Red clover (p. 2482·1).
Prostate disorders.

Trinovum *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.†; Janssen-Cilag, Ger.; Janssen-Cilag, Neth.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Janssen-Cilag, S.Afr.
21 Tablets, norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Janssen-Cilag, Pol.†
Ethinylestradiol (p. 2275·3); norethisterone acetate (p. 2294·3).
Triphasic oral contraceptive.

Trinsicon *UCB, USA.†*
Ferrous fumarate (p. 2060·3); vitamin B_{12} substances (p. 2107·2); intrinsic factor (liver-stomach preparation) (p. 2534·2); folic acid (p. 2063·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Trintek *Goldshield, UK.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Trio *Deva, Turk.*
Tablets, clarithromycin (p. 266·2); capsules, lansoprazole (p. 1851·3); tablets, amoxicillin trihydrate (p. 216·2).
Helicobacter pylori-associated peptic ulcer.

Trio D *Noreva, Fr.*
Liquorice (p. 1853·2).
Hyperpigmentation disorders.

Trio S *Noreva, Fr.*
SPF 50: Ensulizole (p. 1703·1); octocrilene (p. 1715·2); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Trio Val *Saval, Chile.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Trio Val Dia y Noche *Saval, Chile.*
⊗Night tablets, paracetamol (p. 115·1); pseudoephedrine (p. 1676·1); chlorphenamine (p. 620·3); day tablets, paracetamol; pseudoephedrine.
Cold and influenza symptoms.

TrioBe *Recip, Denm.; Recip, Fin.; Recip, Norw.; Recip, Swed.*
Folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Vitamin B and folic acid deficiency.

Triocaps *Vifor, Switz.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Triocetin *OFF, Ital.†*
Troleandomycin (p. 383·2).
Bacterial infections.

Triodanin *Norma (Νορμα), Gr.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Trioden *Schering, Austral.†*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Triodena *Bayer, Austria; Bayer Schering, Hung.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triodene *Bayer, Belg.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Bayer Schering, S.Afr.
21 Tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Triofan Allergie *Vifor, Switz.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Triofan Rhume *Vifor, Switz.*
⊗Xylometazoline hydrochloride (p. 1680·1); carbocisteine (p. 1658·1).
Upper respiratory-tract disorders.

Triofed *Pharmasant, Thai.; Barre-National, USA.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Triofix *Medichem, Philipp.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Triofusin *Kalbe, Indon.*
Carbohydrates.
Parenteral nutrition.

Triofusin E *Kalbe, Indon.*
Carbohydrates; electrolytes (p. 1775·1); vitamins.
Parenteral nutrition.

Triolan *Landsteiner, Mex.†*
Calcitriol (p. 2113·1).

Triolip *Sofar, Ital.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement.

Triomar *Pharmagic, Ital.*
Omega-3 marine triglycerides (p. 1460·3).
Hyperlipidaemias; joint disorders; skin disorders.

Swiss Caps, Israel.
Omega-3 triglycerides (p. 1460·1); omega-9 triglycerides.
Dietary supplement; hyperlipidaemias.

Triombrast *Farmak, Rus.*
Sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Tri-Omega Extra EPA *Trima, Israel.*
Omega-3 triglycerides (p. 1460·1).
Dietary supplement; hyperlipidaemias.

Tri-Omega Super *Trima, Israel.*
Omega-3 triglycerides (p. 1460·1); omega-9 triglycerides.
Dietary supplement; hyperlipidaemias.

Triomel *Baxter, Irl.*
Amino acids; lipid (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); glucose (p. 2068·3); with or without electrolytes (p. 1775·1).
Contains egg phosphatide.
Parenteral nutrition.

Triomer *Vifor, Switz.*
Sterile sea water (p. 2612·1).
Nasal disorders.

Triomin *Xixia, S.Afr.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Triomin-E *Bufa, Indon.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).
Vitamin supplement; nausea and vomiting; neuritis; radiation sickness.

Triomune *Cipla, India; Cipla-Medpro, S.Afr.; Cipla, Venez.*
Lamivudine (p. 1000·2); stavudine (p. 1015·3); nevirapine (p. 1005·1).
HIV infection.

Trionetta *Bayer, Swed.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Triopan *Korea United, Philipp.*
Tiropramide hydrochloride (p. 2632·2).
Smooth muscle spasm.

Trioplex *Aspen, S.Afr.*
Vitamins; minerals.

Trioptec *Dergam, Fr.*
Vitamins; minerals; evening primrose oil (p. 2502·2); fish oil (p. 1460·1); squalene (p. 2213·3); lutein (p. 2079·2); hesperidin (p. 2505·2); anthocyanosides; zeaxanthin (p. 2125·3).
Aid in preventing ocular degeneration.

Triostat *JHP, USA.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism; evaluation of thyroid function.

Triostee *Tropica Mas, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3).
Osteoarthritis.

Triosules *Microsules, Arg.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Triotann *Prasco, USA.†*
Phenylephrine tannate (p. 1672·2); mepyramine tannate (p. 635·1); chlorphenamine tannate (p. 620·3).
Allergic rhinitis; nasal congestion.

Triovit *KRKA, Rus.; KRKA, Ukr.*
Betacarotene (p. 2051·1); tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); selenium (p. 2086·3).
Vitamin and selenium supplement.

Triovit Kardio *KRKA, Rus.*
Pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).

Triox *Solara, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Triox NF *Andromaco, Chile.*
Naproxen sodium (p. 98·2).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Trioxal *Polpharma, Pol.; Polpharma, Ukr.†*
Itraconazole (p. 583·3).
Fungal infections.

Trioxazin *Extractum, Hung.†*
Trimetozine (p. 1114·2).
Alcohol withdrawal syndrome; anxiety disorders; neuropathies; premenstrual syndrome.

TriOxin *Vertical, USA.*
⊗Benzocaine (p. 1980·2); chloroxylenol (p. 1748·2); hydrocortisone acetate (p. 1640·1).
Ear disorders.

Trioxina *Uniao Quimica, Braz.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Triozine *Pharmasant, Thai.*
Trifluoperazine hydrochloride (p. 1113·2).
Anxiety; psychoses; nausea and vomiting.

Tripac-Cyano *Adcock Ingram, S.Afr.*
4 Vials, sodium thiosulfate (p. 1576·1); 2 vials, sodium nitrite (p. 1574·3); 6 vials, amyl nitrite (p. 1540·2).
Cyanide poisoning.

Tripacel *Sanofi Pasteur, Austral.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Hong Kong†; Sanofi Pasteur, Indon.; Sanofi Pasteur, Israel; CSL, NZ†; Sanofi-Aventis, NZ†; Aventis Pasteur, Philipp.†; Sanofi Pasteur, Pol.; Sanofi Pasteur, Singapore†; Sanofi Pasteur, Thai.†; Sanofi Pasteur, Turk.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Tripanzym *Sanbe, Indon.*
⊗Pancreatin (p. 2579·3); simeticone (p. 1886·2).
Meteorism; flatulence; pancreatic insufficiency; aid in abdominal radiography.

Triparen *Otsuka, Indon.*
Carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Otsuka, Jpn.
Fructose (p. 2068·2); glucose (p. 2068·3); xylitol (p. 2220·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Triparsean *Pantofarma, Spain.†*
Piketoprofen hydrochloride (p. 125·3).
Peri-articular and soft-tissue disorders.

Tri-Pase *Acella, USA.*
Pancreatic enzymes (p. 2579·3).
Pancreatic insufficiency.

Tripavac *Vaxines, Philipp.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Tripe P *Universal, Hong Kong.*
Promethazine hydrochloride (p. 638·2); pholcodine (p. 1675·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cough and cold symptoms.

Tripedia *Sanofi Pasteur, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation of infants and young children.

Tripel *Corsa, Indon.*
Tripelennamine hydrochloride (p. 642·3).
Allergic skin disorders; pruritus; insect bites; sunburn.

Tripenem *Dexa, Indon.*
Meropenem (p. 321·3).
Bacterial infections.

Triperidol *Johnson & Johnson, India.*
Trifluperidol (p. 1114·1) or trifluperidol hydrochloride (p. 1114·1).
Psychoses.

Triphala *Code, Fr.*
Emblica officinalis (p. 2532·2); terminalia bellerica (p. 2453·2); terminalia chebulia (p. 2474·3).
Gastrointestinal motility disorders.

Tri-Phasic White Day Milk *Nu Skin, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Triphasil *Pfizer, Austral.; Aspen, S.Afr.*
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive; menstrual disorders; acne.

Pfizer, NZ; Wyeth-Ayerst, USA.†
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Triphenaze *Norma (Νορμα), Gr.*
Perphenazine (p. 1095·3); amitriptyline hydrochloride (p. 401·1).

Triphidus *Motima, Fr.*
Lactobacillus acidophilus (p. 2596·3); bifidobacterium; *Lactobacillus bulgaricus* (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3).
Maintenance of gastrointestinal flora.

Triphimox *Lloyd, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Triphosphates *Boiron, Fr.*
Calcarea phosphorica (p. 1784·2); kalium phosphoricum (p. 1790·3); natrum phosphoricum (p. 1791·2).
Homoeopathic preparation.

Triphtazine *Dalkhimfarm, Rus.; Moscow Endocrine, Rus.; Zdorovje, Rus.*
Trifluoperazine (p. 1113·2) or trifluoperazine hydrochloride (p. 1113·2).
Psychoses; agitation; anxiety; nausea and vomiting.

Tripid *Teguhsindo, Indon.*
Turmeric (p. 2218·1); ginseng (p. 2513·3); essential phospholipids (p. 2201·2); vitamin E (p. 2119·1).
Liver disorders.

Tripirol *Tecnofarma, Mex.*
Piroxicam (p. 125·3).
Inflammation.

Triple Antibiotic Ointment *Jamp, Canad.; Melaleuca, Canad.; Pharmetics, Canad.; Taro, Canad.*
Bacitracin zinc (p. 225·3); gramicidin (p. 308·3); polymyxin B sulfate (p. 342·3).

Triple Antigen *GSK, India; Serum Institute, India; CSL, NZ.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Triple B *Maccabi Care, Israel.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Triple Blend Echinacea *Swiss Herbal, Canad.†*
Echinacea angustifolia (p. 2498·1); echinacea purpurea (p. 2498·1); echinacea pallida (p. 2498·1).

Triple Care Cleanser *Smith & Nephew, Austral.*
Emollient and skin cleanser.
Skin disorders associated with incontinence.

Triple Care Cream *Smith & Nephew, Austral.*
White soft paraffin (p. 2211·3); zinc oxide (p. 1729·1); aloe vera (p. 1693·2); allantoin (p. 1693·1).
Barrier preparation.

Triple Cream *Summers, USA.*
Emollient.

Triple Paste *Summers, USA.*
Zinc oxide (p. 1729·1).
Nappy rash.

Triple Paste AF *Summers, USA.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Triple Protect *Johnson & Johnson, Canad.*
SPF 20: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Triple Sulphas *Chew, Thai.*
Sulfadiazine (p. 361·3); sulfadimidine (p. 363·2); sulfamerazine (p. 364·3).
Bacterial infections.

Triple-B *Hua, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Tri-Plen *Sanofi-Aventis, S.Afr.*
Ramipril (p. 1483·3); felodipine (p. 1380·3).
Hypertension.

Triplex
Note: this name may be used for preparations of different composition.
LKM, Arg.
⊗Miconazole nitrate (p. 589·1); betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Sriprasit, Thai.†
Trifluoperazine hydrochloride (p. 1113·2).
Psychoses; anxiety; nausea and vomiting.

Triplex AD *Breckenridge, USA.†*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Triplovit *Intermed, Gr.*
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).

Tripo *Hua, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; cold symptoms; hay fever; upper respiratory-tract congestion.

Tripohist D *Breckenridge, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract disorders.

Tripondil *Alphrema, Ital.*
Day tablets, levocarnitine tartrate (p. 2053·2); fennel (p. 2503·2); faseolamina; chromium polynicotinatehromium; calcium phosphate (p. 1784·2); pyridoxine hydrochloride (p. 2105·3); night tablets, pineapple; selenium-rich yeast (p. 2086·3); bioflavonoids (p. 2505·2); equisetum (p. 2500·1).
Obesity.

Triposed *Halsey, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).
Upper respiratory-tract symptoms.

Tripote *Dexa, Indon.†*
Damiana (p. 2491·3); Siberian ginseng (p. 2614·3); muira-puama.
Tonic; infertility.

Tripoten *Dexa, Pol.*
Siberian ginseng (p. 2614·3); muira-puama; damiana (p. 2491·3).
Erectile dysfunction.

Tripress *Mylan, NZ.†*
Trimipramine maleate (p. 453·1).
Depression.

Tri-Previfem *Qualitest, USA.*
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Tripride *Micro Labs, Ukr.*
Glimepiride (p. 473·2); pioglitazone (p. 493·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tripril *CCM, Malaysia.*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction.

Triprim *Aspen, Austral.; Ratiopharm, Austria; Ratiopharm, Cz.*
Trimethoprim (p. 381·2).
Bacterial infections.

Pharmaland, Thai.†
Co-trimoxazole (p. 277·3).
Bacterial infections.

Triprodrine *Asian Pharm, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; cold symptoms; hay fever; respiratory-tract congestion.

Tri-Profen *3M, Austral.†*
Ibuprofen (p. 68·2).
Pain; inflammation; musculoskeletal and joint disorders; fever.

Tripsol *Cazi, Braz.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Tripsor *Orion, Fin.†*
Trioxysalen (p. 1727·2).
Psoriasis; lichen obtusus; lichen planus.

Tripsyline *Polipharm, Thai.*
Amitriptyline (p. 401·1).
Depression; neuropathic pain; migraine.

Tripta *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Triptafen *AMCo, UK.*
Amitriptyline hydrochloride (p. 401·1); perphenazine (p. 1095·3).
Mixed anxiety depressive states.

Triptagic *Tempo Scan Pacific, Indon.*
Sumatriptan succinate (p. 679·2).
Migraine.

Triptagram *Plus Pharma, Hung.; Actavis, Pol.*
Sumatriptan succinate (p. 679·2).
Migraine.

Triptam *Aspen, S.Afr.*
Sumatriptan (p. 679·2).
Migraine.

Triptilin *Ulagay, Turk.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Triptizol *SIT, Ital.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Triptofem *Karmed, Neth.*
⊗Triptorelin acetate (p. 2310·3).
Controlled ovarian stimulation.

Tript-OH *Sigma-Tau, Cz.; Sigma-Tau, Ital.; Sigma-Tau, Switz.†*
Oxitriptan (p. 440·3).
Depression; sleep disorders; myoclonus; migraine.

Triptone *Del, USA.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Triptosig *Sigillata, Neth.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Triptyl *Orion, Fin.*
Amitriptyline hydrochloride (p. 401·1).
Depression; insomnia; pain; migraine; tension headache.

Triptyline *Medifive, Thai.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Tripur *Galeno, Venez.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tripvac *Biological E, India.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Tripzol *Medicine Products, Thai.*
Amitriptyline hydrochloride (p. 401·1).

Triquilar *Bayer, Arg.; Schering, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer, Denm.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.†; Zydus, India; Bayer, Mex.; Bayer Schering, Pol.; Bayer, Port.†; Bayer Schering, Rus.; Schering, Turk.†; Bayer, Ukr.; Schering, Venez.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Bayer, Austral.; Bayer Schering, Indon.; Bayer, NZ; Bayer, Thai.
21 Tablets, levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Triquisic *Grunenthal, Austria; Grunenthal, Port.*
⊗Buprenorphine (p. 30·2).
Pain.

Tri-Regol *Gedeon Richter, Cz.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.; Aciprosalud, Venez.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 tablets ferrous fumarate.
Triphasic oral contraceptive.

Triregol *2care4, Denm.; Sandoz, Swed.; Consilient, UK.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Triphasic oral contraceptive.

Triresid K *Pliva, Rus.†*
⊗Reserpine (p. 1485·3); dihydralazine sulfate (p. 1358·3); hydrochlorothiazide (p. 1403·2); potassium chloride (p. 1793·2).

Tris *Braun, Ger.*
⊗Trometamol (p. 2635·1).
Metabolic acidosis.

Trisedyl *Biomedia, Singapore.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3).

Trisekvens *Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Norw.; Novo Nordisk, Swed.†*
18 Tablets, estradiol (p. 2271·1); 10 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Trisel *Klonal, Arg.*
Vitamin B_{12} (p. 2107·2); pyridoxine (p. 2105·3); thiamine (p. 2102·3).

Trisenox *Cephalon, Austria; Cephalon, Belg.; Zodiac, Braz.; Cephalon, Cz.; Cephalon, Fr.; Cephalon, Ger.; Cephalon, Gr.; IFET (ΙΦΕΤ), Gr.; Cephalon, Irl.; CP, Israel; Cephalon, Ital.; Shinyaku, Jpn; Teva, Neth.; Cephalon, Pol.; Cephalon, Port.; Teva, Spain; Cephalon, UK; Cephalon, USA.*
Arsenic trioxide (p. 2448·1).
Acute promyelocytic leukaemia.

Triseptil
Note: this name may be used for preparations of different composition.
Degorts, Mex.
Tinidazole (p. 949·2).
Amoebiasis; trichomoniasis; giardiasis.

Gedis, Ital.†
Chlorhexidine gluconate (p. 1743·3).
Hand disinfection.

Trisequens *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Silesia, Chile; Novo Nordisk, China; Novo Nordisk, Cz.; Paranova, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Gr.; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, NZ; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Isdin, Spain; Novo Nordisk, Switz.; Novo Nordisk, Turk.; Novo Nordisk, UK.*
18 Tablets, estradiol (p. 2271·1); 10 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency; hormone replacement therapy.

Novo Nordisk, Ger.
16 Tablets, estradiol (p. 2271·1); 12 tablets, estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Novo Nordisk, Hong Kong; Novo Nordisk, Singapore.
18 Tablets, estradiol (p. 2271·1); 10 tablets estradiol; norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Novo Nordisk, Israel.
Blue tablets, estradiol (p. 2271·1); white tablets, estradiol; norethisterone acetate (p. 2294·3); red tablets, estradiol.
Menopausal disorders; osteoporosis.

Trisiston *Jenapharm, Ger.; Jenapharm, Pol.; Jenapharm, Rus.*
Ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1).
Triphasic oral contraceptive.

Trisodine *Chinta, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold and influenza symptoms.

Trisofort *Westmont, Hong Kong†; Westmont, Philipp.†*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy; vitamins B_1 and vitamin B_{12} are also included.
Tuberculosis.

Trisolvenol *Pharmathen, Gr.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; gastritis; pathological hypersecretory disorders; acid aspiration.

Trisolvetan *Pharmathen, Gr.*
Mebeverine hydrochloride (p. 1858·3).

Trisomatol *UCI, Braz.*
Amitriptyline hydrochloride (p. 401·1).

Trisoralen *Pharmex (Φαρμεξ), Gr.*
Trioxysalen (p. 1727·2).

Trisorb *Alcon, Braz.*
⊗Dextran 70 (p. 1138·3); hypromellose (p. 2189·2); glycerol (p. 2517·2).
Dry eyes; eye irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Trispec *Vista, Philipp.*
Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Bacterial eye infections.

Trispec PSE *Deliz, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Trisporal *Janssen-Cilag, Neth.; Janssen-Cilag, S.Afr.*
Itraconazole (p. 583·3).
Fungal infections.

Tri-Sprintec *Barr, USA.*
21 Tablets, norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Trissil
Note: this name may be used for preparations of different composition.
Brunifarma, Ital.
Levofloxacin (p. 315·3).
Bacterial infections.

Tristan *Medikon, Indon.†*
⊗Tribulus terrestris (p. 2633·3); damiana (p. 2491·3); ginseng (p. 2513·3).
Tonic.

Tri-Statin II *Rugby, USA.*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Skin disorders.

Tristin *Gedeon Richter, Ukr.†*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Triphasic oral contraceptive.

Trisul *LCH, Hong Kong†; Mylan, NZ.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Trisulfa
Note: this name may be used for preparations of different composition.
Berlico Mulia, Indon.
Sulfadiazine (p. 361·3); sulfadimidine (p. 363·2); sulfamerazine (p. 364·3).
Bacterial infections.

Jaapharm, Canad.
Co-trimoxazole (p. 277·3).

Trisulfa Co-P *PP Lab, Thai.*
Sulfadiazine (p. 361·3); sulfadimidine (p. 363·2); sulfamerazine (p. 364·3); potassium citrate (p. 1780·3).
Bacterial infections.

Trisulfapyrimidines *ANH, Thai.*
Sulfadiazine (p. 361·3); sulfamerazine (p. 364·3); sulfadimidine (p. 363·2).
Bacterial infections.

Trisulfose *Wyeth, India.*
Co-trimoxazole (p. 277·3).
Bacterial infections; toxoplasmosis; pneumocystis pneumonia.

Tritab
Note: this name may be used for preparations of different composition.
Sidus, Arg.
Azithromycin (p. 221·2).
Bacterial infections.

United American, Philipp.
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Tritace *Sanofi-Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Aventis, NZ†; Sanofi-Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Thai.; Aventis, UK.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction; diabetic nephropathy; heart failure following myocardial infarction; stroke prophylaxis.

Tritace Comb *Sanofi-Aventis, Pol.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tritace Comp *Sanofi-Aventis, Israel.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tritace Plus *Sanofi-Aventis, Ukr.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tritace-HCT *Sanofi-Aventis, Arg.; Sanofi-Aventis, Hung.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Trital DM *Breckenridge, USA.†*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).

Tritan *Eon, USA.*
Chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Allergic rhinitis; nasal congestion.

Tri-Tannate *Rugby, USA.*
Phenylephrine tannate (p. 1672·2); chlorphenamine tannate (p. 620·3); mepyramine tannate (p. 635·1).
Upper respiratory-tract symptoms.

Tri-Tannate Plus Pediatric *Rugby, USA.*
⊗Phenylephrine tannate (p. 1672·2); ephedrine tannate (p. 1663·1); chlorphenamine tannate (p. 620·3); pentoxyverine tannate (p. 1672·1).
Coughs and cold symptoms.

Tritanrix HB *GSK, India; GSK, Indon.†; GSK, Irl.; GSK, Malaysia; GSK, Mex.; GSK, Philipp.; Litha, S.Afr.; GSK, Spain†; GSK, Thai.; GSK, Turk.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Tritanrix HB + HIB *GSK, NZ.†*
Tritanrix-HB, a diphtheria, tetanus, pertussis, and hepatitis B vaccine; Hiberix, a haemophilus influenzae conjugate vaccine (p. 2384·3).
Active immunisation.

Tritanrix HB + Hiberix *GSK, Mex.*
A diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenzae vaccine (p. 2384·3).
Active immunisation.

Tritanrix HB-HIB *GSK, Arg.*
A diphtheria, tetanus, pertussis, haemophilus influenzae, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Tritanrix HepB *GSK, Cz.; GSK, Port.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Tritanrix-HepB *GSK, Neth.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Tritar *Aspen, S.Afr.*
Tar (p. 1723·3); coal tar (p. 1723·2); cade oil (p. 1723·2).
Seborrhoeic dermatitis.

Tritazide *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Thai.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Tritenk *Biotenk, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Tritet *Akromed, S.Afr.†*
Tetracycline hydrochloride (p. 373·2); chlortetracycline hydrochloride (p. 260·2); demeclocycline hydrochloride (p. 285·2).
Bacterial infections.

Tri-Thiazid *Stada, Ger.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Heart failure; hypertension; oedema.

Triticum *Angelini, Port.*
Trazodone hydrochloride (p. 451·1).
Depression.

Tritopam *Klonal, Arg.*
Bromazepam (p. 1041·2).
Anxiety.

Trittico *CSC, Austria; Angelini, Gr.; Angelini, Hong Kong; CSC, Hung.; Aziende, Israel†; Angelini, Ital.; Angelini, Pol.; CSC, Rus.; Angelini, Singapore; Vifor, Switz.; Angelini, Ukr.; Elmor, Venez.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety; premedication; neuroleptanalgesia; pain; erectile dysfunction; insomnia; mixed anxiety depressive states; benzodiazepine withdrawal.

Laboratorios Chile, Chile.
Trazodone (p. 451·1) or trazodone hydrochloride (p. 451·1).
Alcohol withdrawal syndrome; anxiety; depression; schizophrenia.

Trittico AC *Medicom, Cz.*
Trazodone hydrochloride (p. 451·1).
Depression; anxiety; insomnia; sexual dysfunction.

TriTuss *Everett, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Trituss-A *Everett, USA.*
Carbinoxamine maleate (p. 619·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Trium *Santen, Ger.*
Sodium hyaluronate (p. 2526·2); ginkgo biloba (p. 2512·3).
Eye disorders.

Triv *Boyle, USA.*
Hydroxyquinoline sulfate (p. 2530·1); alkyl aryl sulfonate; edetic acid (p. 1550·3); sodium sulfate (p. 1888·1).
Vaginal disorders.

Tri-V Plus *Sagmel, Rus.†*
Betacarotene (p. 2051·1); alpha-tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); zinc oxide (p. 1729·1); sodium selenate (p. 2087·1); copper oxide (p. 2057·1).

Trivagel N *Marjan, Braz.*
⊗Dexamethasone phosphate (p. 1631·1); neomycin sulfate (p. 330·1); nystatin (p. 590·3); tyrothricin (p. 384·1).
Vulvovaginal disorders.

Trivalumen *Borshchagovskii, Ukr.*
Valerian (p. 2640·2); peppermint leaf (p. 1877·1); menyanthes (p. 2554·2); lupulus (p. 2546·1).
Insomnia; neurocirculatory dystonia with tachycardia, cardialgia and hypertension; reduced appetite.

Trivam *Hana, Indon.; Pharos, Indon.*
Propofol (p. 1909·3).
General anaesthesia; sedation of ventilated patients in intensive care.

Trivanex *Pharmasant, Thai.*
Griseofulvin (p. 582·2).
Fungal infections.

Trivaris *Allergan, USA.*
⊗Triamcinolone acetonide (p. 1649·1).
Inflammatory eye disorders.

Trivastal *Servier, Arg.; Servier, Braz.; Servier, Fr.; Servier, Gr.; Serdia, India; Servier, Malaysia; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Thai.; Servier, Turk.; Servier, Venez.*
Piribedil (p. 911·1).
Parkinsonism; vascular eye disorders; vestibular disorders; mental function impairment; ischaemic eye disease; cerebral and peripheral vascular disorders.

Trivastan *Stroder, Ital.*
Piribedil (p. 911·1).
Vascular disorders; mental function impairment.

Trivax-AD *Chiron Vaccines, UK.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation of infants and young children.

Trive-1000 *Baxter, Gr.*
Amino acids; lipids (from soya oil (p. 2092·3)).
Parenteral nutrition.

Trivedon *Cipla, Hong Kong; Cipla, India.*
Trimetazidine hydrochloride (p. 1520·1).
Ischaemic heart disease; angina pectoris.

Triveen-PRx RNF *Trigen, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Triveen-Ten *Trigen, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1); ubidecarenone (p. 2637·1); lycopene (p. 2546·2).
Dietary supplement.

Trivico *Charoen, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Trividuran *Genepharm, Gr.*
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).

Tri-Vi-Flor *Zylera, USA.*
Vitamins; fluoride (p. 2089·2).
Dietary supplement; dental caries prophylaxis.

Tri-Vi-Floro *Deston, USA.*
Fluoride (p. 2089·2); vitamins.
Dietary supplement.

Tri-Vi-Fluor *BMS, Arg.*
Sodium fluoride (p. 2089·2); vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3).
Dental caries prophylaxis; vitamin supplement.

Tri-Vi-Flúor *Mead Johnson, Braz.*
Vitamins; fluoride (p. 2089·2).
Dental caries prophylaxis; dietary supplement.

Trivimine *Alapis, Gr.; Cooper (Κοπερ), Gr.*
Vitamin B substances (p. 2102·3).

Trivin *Norton, Ukr.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Trivina *Orion, Swed.*
70 White tablets, estradiol valerate (p. 2271·2); 14 blue tablets estradiol valerate; medroxyprogesterone acetate (p. 2288·1); 7 yellow tablets, inert.
Menopausal disorders; osteoporosis.

Aspen, S.Afr.†
White tablets, estradiol valerate (p. 2271·2); blue tablets, estradiol valerate; medroxyprogesterone acetate (p. 2288·1); yellow tablets, inert.
Menopausal disorders; osteoporosis.

Triviraten *Scott-Cassara, Arg.; Berna, NZ†; Berna, Philipp.†; Berna, Turk.*
A measles, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

Tri-Vi-Sol *BMS, Arg.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3).

Mead Johnson, Braz.; BMS, Mex.†; Mead Johnson Nutritionals, USA.
Vitamins.

Mead Johnson, Chile; Mead Johnson, Venez.
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Vitamin supplement.

Tri-Vi-Sol with Iron *Mead Johnson Nutritionals, USA.†*
Vitamins; iron (p. 2073·1).

Tri-Vita *Major, USA.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin C (p. 2110·3).
Dietary supplement.

Tri-Vitamin *Rugby, USA.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Trivitamin *Maccabi Care, Israel.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1).
Elevated homocysteine levels.

Trivitamin Fluoride Drops *Schein, USA.*
Vitamins; fluoride (p. 2089·2).

Trivitamins *Pharmetics, Canad.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Trivitana DM *Merck, Chile.†*
Vitamin A (p. 2098·3); vitamin B_6 (p. 2105·3); vitamin E (p. 2119·1).
Dietary supplement.

Trivitana Q10 *Merck, Chile.*
Vitamin A (p. 2098·3); vitamin B (p. 2102·3); vitamin E (p. 2119·1); ubidecarenone (p. 2637·1).
Dietary supplement.

Trivit-B *TP, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; vitamin B deficiency.

Trivivac *Sevapharma, Cz.*
A measles, mumps, and rubella vaccine (Schwarz, Jeryl Lynn, and Wistar RA 27/3 strains, respectively) (p. 2400·2).
Active immunisation.

Trivon *Great Eastern, Thai.†; Therapharma, Thai.†*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Tonic.

Trivora *Watson, USA.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trivorin *Teva, Mex.; Teva, Rus.*
Ribavirin (p. 1010·2).
Viral infections; chronic hepatitis C.

Trivudin *Richmond, Arg.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2); abacavir (p. 962·3).
HIV infection.

Trixate *AstraZeneca, Arg.*
Methotrexate (p. 822·2).
Rheumatoid arthritis; psoriasis; gestational trophoblastic disorders.

Trixazole *MDI, S.Afr.*
Co-trimoxazole (p. 277·3).

Trixéra *Avene, Fr.*
Emollients.
Dry skin disorders.

Trixera *Silesia, Chile; Medifarm, Venez.*
Emollient.
Dry skin disorders.

Trixicam *Vitarum, Arg.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Trixilan *Chrispa (Χρισπα), Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Trixilem *Laboratorios Chile, Chile; Teva, Mex.; Teva, Thai.*
Methotrexate (p. 822·2).
Malignant neoplasms; rheumatoid arthritis; mycosis fungoides.

Trixim *Ferron, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Trixin *Pliva, Cz.*
Mycophenolate mofetil (p. 1961·1).
Transplant rejection.

Trixne *Pharmatrix, Arg.*
Erythromycin (p. 291·2).
Acne.

Trixon *Phapros, Indon.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Trixone *LBS, Malaysia; LBS, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Trixophin *Shenzhen, Philipp.; Shenzhen Zhijun, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Trixotene *Sandoz, Braz.*
Docetaxel (p. 780·3).

Trixviral *Kilab, Arg.*
Aciclovir (p. 964·1).

Trixzol *Westmont, Indon.†; Great Eastern, Thai.†; Westmont, Thai.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Triyosom *Justesa Imagen, Arg.*
Meglumine amidotrizoate (p. 1581·3); and/or sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Triyotex *Medix, Mex.*
Liothyronine sodium (p. 2342·3).
Hypothyroidism.

Triz *Indoco, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders.

Trizac *Unichem, S.Afr.†*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Trizadol *Addenda, Ital.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Trizedon *Servier, Indon.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Tri-zel *Rochester, USA.*
Nicotinamide (p. 2083·1); vitamin B_6 (p. 2105·3); folic acid (p. 2063·1); copper (p. 2057·1); zinc (p. 2126·1); azelaic acid (p. 1695·1).

Trizidine *Pharmasant, Thai.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo; tinnitus.

Trizina *Francia, Ital.†*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Trizine *DHA, Malaysia; Phoenix, Philipp.; DHA, Singapore.*
Sulfadiazine (p. 361·3); trimethoprim (p. 381·2).
Bacterial infections.

Trizinet *Teva, Mex.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Trizipin *Microkhim, Ukr.*
Meldonium (p. 1429·3).
Ischaemic heart disease; cerebrovascular disorders; retinal haemorrhage; alcohol withdrawal syndrome.

Trizivar *GSK, S.Afr.*
Abacavir sulfate (p. 963·1); lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Trizivir *ViiV, Austral.; ViiV, Austria; ViiV, Belg.; ViiV, Canad.; GSK, China; GSK, Cz.; GSK, Denm.; ViiV, Fin.; ViiV, Fr.; ViiV, Ger.; GSK, Gr.; GSK, Hong Kong; ViiV, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Mex.; ViiV, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Singapore; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Turk.; GSK, UK; ViiV, USA; GSK, Venez.*
Abacavir sulfate (p. 963·1); lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Trizol
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Fluconazole (p. 578·2).
Fungal infections.
Royal, Chile.
Lamotrigine (p. 527·2).
Epilepsy.

Trizole *Mediforma, Indon.; CCM, Malaysia; Pediatrica, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Trizolin *Remedica, Malaysia; Remedica, Singapore.*
Norfloxacin (p. 333·3).
Bacterial infections.

Trizon *Samjin, Singapore.*
Ceftriaxone (p. 253·3).
Bacterial infections.

Trobalt *GSK, Belg.; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Irl.; GSK, Israel; GSK, Neth.; GSK, Norw.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Retigabine (p. 547·3).
Epilepsy.

Trobicin *Pharmacia, Austral.†; Pfizer, Belg.; Pfizer, China; Pfizer, Gr.; Pfizer, Hong Kong; Pharmacia, India; Pfizer, Mex.; Pfizer, Rus.; Pharmacia, S.Afr.†; Pfizer, Singapore; Pfizer, Thai.*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea; genito-urinary-tract infections; chancroid.

Trobicine *Pfizer, Fr.*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea.

Troc *Melisana, Belg.*
Aspirin (p. 22·2); caffeine hydrate (p. 1203·3); paracetamol (p. 115·1).
Pain; fever.

Troca Cationi *Laborest, Ital.*
Magnesium (p. 1786·3); potassium (p. 1793·1); zinc (p. 2126·1).
Mineral deficiencies; stress; viral infections.

Troca Donna *Laborest, Ital.*
Vitamins; minerals.

Troca Flu *Laborest, Ital.*
Zinc (p. 2126·1); magnesium (p. 1786·3); potassium (p. 1793·1); vitamin C (p. 2110·3); vitamin A (p. 2098·3).
Viral infections; candidiasis.

Troca Flu Spray Nasale *Laborest, Ital.*
Sodium chloride (p. 1795·1); sulfur (p. 1721·1).
Nasal cleansing.

Troca Maternum *Laborest, Ital.*
Vitamins; minerals.
Nutritional supplement in pregnancy and breast feeding.

Troca Vit *Laborest, Ital.*
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3); myrtillus (p. 2566·2).
Dietary supplement.

Trocacin *Nakornpatana, Thai.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Trocaine *Roberts, USA.*
Benzocaine (p. 1980·2).
Obesity; sore throat.

Trocal
Note: this name may be used for preparations of different composition.
Nova Argentia, Arg.
Prasugrel hydrochloride (p. 1472·3).
Thromboembolism prophylaxis during percutaneous coronary intervention.
Roberts, USA.†
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Trochain *Adcock Ingram, S.Afr.*
Cetrimide (p. 1742·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Trociletas *Streger, Mex.*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat infections.

Trociletas B *Streger, Mex.*
Cetylpyridinium (p. 1743·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Trodeb *Tropica Mas, Indon.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Trodex
Note: this name may be used for preparations of different composition.
Aristo, Philipp.
Roxithromycin (p. 356·2).
Bacterial infections.
Tropica Mas, Indon.
⊗Dexamethasone (p. 1630·3); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Trodorol *Andromaco, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Troezel *Duncan, Arg.*
Losartan potassium (p. 1422·2).
Hypertension.

Trofalgon *Farmasierra, Spain.*
Cyanocobalamin (p. 2107·2); muramidase hydrochloride (p. 2565·1).
Anorexia; weight loss; tonic.

Trofen *TP, Thai.*
Ibuprofen (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

Trofentyl *Troikaa, India; Troikaa, Philipp.*
⊗Fentanyl citrate (p. 60·1).
Analgesia in anaesthesia; adjunct in general anaesthesia; neuroleptanalgesia; pain.

Troferit *Chinoin, Mex.*
Dropropizine (p. 1662·2).
Cough.

Trofesil *Solfran, Mex.†*
Vitamins.

Trofinan *Biol, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Trofinerv *Bausch & Lomb, Ital.*
Omega-3 marine triglycerides (p. 1460·3); vitamins.
Nutritional supplement.

Trofinerv Antiox *Bausch & Lomb, Ital.*
Omega-3 triglycerides (p. 1460·3); gamolenic acid (p. 2509·2); vitamins; minerals.
Nutritional supplement.

Troflam *Tropica Mas, Indon.*
Diclofenac potassium (p. 48·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; pain.

Trofo 5 *Uniderm, Ital.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3); hyaluronic acid (p. 2526·2); chamomile oil (p. 2474·1).
Skin disorders.

Trofocard *Unipharma, Gr.*
Magnesium aspartate (p. 1787·1); magnesium chloride (p. 1787·1).
Hypomagnesaemia.

Trofocell *SoSe, Ital.†*
Vitamins.

Trofodermin *Pfizer, Braz.; SIT, Ital.*
⊗Clostebol acetate (p. 2260·1); neomycin sulfate (p. 330·1).
Skin infections; wounds; burns; ulcers; cervical and vaginal injury; skin trauma.
Pfizer, Chile.†
⊗Clostebol (p. 2260·1).
Skin disorders.

Trofodermin Neomicina *Pfizer, Chile.†*
⊗Clostebol acetate (p. 2260·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Trofogin *Wassermann, Ital.*
Estriol (p. 2274·3).
Menopausal disorders; oestrogen deficiency; cervicitis.

Trofomed *Trofomed, Ital.*
Royal jelly (p. 2608·1).

Troforex Pepsico *Reig Jofre, Spain.†*
⊗Cyproheptadine hydrochloride (p. 624·1); amino acids; hydroxocobalamin (p. 2107·3); pepsin (p. 2586·1).
Anorexia; weight-loss; tonic.

Trofselamin *Biosel, Turk.†*
Amino acids.
Parenteral nutrition.

Trogiar *Tropica Mas, Indon.*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis; giardiasis; Bacteroides fragilis infections.

Trogine *Ranbaxy, Pol.*
Lamotrigine (p. 527·2).
Epilepsy.

Trogran *Glenmark, Cz.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.
Glenmark, Pol.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Trogyl *Otto, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Trojan *Church & Dwight, Canad.†*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

Trok *Eurofarma, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3).
Fungal skin infections.

Troken *Bago, Arg.; Montpellier, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Cardiovascular risk reduction; thrombosis prophylaxis.

Trokendi *Supernus, USA.*
Topiramate (p. 550·3).
Epilepsy.

Trok-N *Eurofarma, Braz.*
⊗Ketoconazole (p. 585·3); betamethasone dipropionate (p. 1623·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Trolab *Almirall, Neth.*
A range of allergen extract (p. 2434·3).
Diagnosis of allergic contact dermatitis.

Trolac *Bernofarm, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Trolar *Proel, Gr.*
Methocarbamol (p. 2025·3).

Trolic *Gulf Drug, S.Afr.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

Trolip *Dexa, Indon.; Dexa, Philipp.; Dexa, Singapore.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Trolise *Bouchara-Recordati, Fr.*
Pitavastatin (p. 1471·1).
Hypercholesterolaemia.

Trolit *Silesia, Chile.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Menstrual disorders; triphasic oral contraceptive.

Trolovol *D&A Pharma, Fr.; Dexo, Port.*
Penicillamine (p. 1567·1).
Rheumatoid arthritis; Wilson's disease.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Tromadil *Biolab, Thai.†*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Tromagesic *Themis Medicare, India.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders.

Tromalyt *Neo-Farmaceutica, Port.; Rottapharm, Spain.*
Aspirin (p. 22·2).
Thrombosis prophylaxis; stroke prophylaxis.

Tromax *Aristo, India.*
Diclofenac (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain.

Trombenal *Bago, Arg.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Trombex
Note: this name may be used for preparations of different composition.
Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Trombix *Standard, Philipp.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Trombless *Nizpharm, Rus.*
Heparin sodium (p. 1396·3).
Soft-tissue disorders; superficial vascular disorders.

Trombocil *Imperial, Philipp.*
Cilostazol (p. 1337·1).
Chronic arterial occlusion; stroke prophylaxis.

Trombofob *Abbott, Braz.*
Ointment: Heparin sodium (p. 1396·3); benzyl nicotinate (p. 29·3).
Soft-tissue injury; superficial vascular disorders.
Abbott, Braz.
Topical gel: Heparin sodium (p. 1396·3).
Superficial vascular disorders.

Tromboject *Omega, Canad.*
Sodium tetradecyl sulfate (p. 2620·1).
Varicose veins.

Trombolisin *Proge, Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Tromboliz *Kocak, Turk.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Trombonet *Farmak, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Myocardial infarction; thromboembolism prophylaxis; atherosclerosis; unstable angina.

Trombonot *Penn, Arg.*
Cilostazol (p. 1337·1).

Tromboparin *BioSaude, Port.*
Parnaparin sodium (p. 1464·2).
Gerolimatos (Γερολυματος), Gr.; Elmor, Venez.
Parnaparin (p. 1464·2).
Thromboembolic disorders.

Trombopat *Pentafarma, Port.*
Ticlopidine hydrochloride (p. 1512·1).
Stoke prophylaxis; thrombosis prophylaxis; extracorporeal circulation.

Trombopol *Polpharma, Rus.*
Aspirin (p. 22·2).
Thromboembolism prophylaxis.

Trombosentin *Kocak, Turk.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Trombosol *Orion, Fin.*
Heparin sodium (p. 1396·3); benzyl nicotinate (p. 29·3).
Soft-tissue injury; superficial vascular disorders.

Trombovar *Kreussler, Fr.; Bouty, Ital.†; Innothera, Neth.; Promedica, Rus.†; Promedica, Singapore.†*
Sodium tetradecyl sulfate (p. 2620·1).
Superficial varices; varicose veins; oesophageal varices; cysts.

Trombovasim *SCPB, Rus.*
Bacillus subtilis protease.
Chronic venous insufficiency.

Trombyl *Pfizer, Swed.*
Aspirin (p. 22·2).
Myocardial infarction; angina pectoris; prevention of cerebrovascular ischaemia.

Tromcardin *Trommsdorff, Cz.†; Trommsdorff, Ger.†; Trommsdorf, Hung.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Arrhythmias; heart failure; myocardial infarction; angina pectoris; potassium and magnesium deficiency.

Tromcor *Integrated Pharmaceutical, Philipp.*
Aspirin (p. 22·2).
Thromboembolic disorders.

Tromderm *Silesia, Chile.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections; seborrhoeic dermatitis.

Tromedal *Farcoral, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Tromiatlas *Atlas, Arg.*
Azithromycin (p. 221·2).
Bacterial eye infections.

Tromicina *Offenbach, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Tromine *Pharmaniaga, Hong Kong.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Tromix *Ariston, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Tromizir *Belfar, Braz.*
Azithromycin (p. 221·2).

Tromlipon *Trommsdorff, Ger.*
Thioctic acid (p. 2629·1).
Diabetic neuropathy.

Trommcardin *Jacoby, Austria.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Potassium and magnesium deficiency; digitalis intoxication; heart failure; arrhythmias; myocardial infarction.

Tromphyllin *Trommsdorff, Ger.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Tromypen *Vocate, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections.

Troncel *Roux-Ocefa, Arg.*
Strontium ranelate (p. 1190·3).
Osteoporosis.

Trondamet *Pharmathen, Gr.*
Ondansetron hydrochloride (p. 1872·1).

Troneo *TNP, Thai.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat infections.

Tronex *Tocogino, Mex.*
Ampicillin (p. 218·2).
Bacterial infections.

Tronheim *Nichi-Iko, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

Tronolane *Lee, USA.*
Cream: Pramocaine hydrochloride (p. 1993·3); zinc oxide (p. 1729·1).
Haemorrhoids.
Monticello, USA.
Suppositories: Phenylephrine hydrochloride (p. 1672·3).
Formerly contained zinc oxide.
Haemorrhoids.

Tronotene *Teofarma, Ital.*
Pramocaine hydrochloride (p. 1993·3).
Haemorrhoids.

Tronothane *Lisapharm, Fr.; Abbott, USA.*
Pramocaine hydrochloride (p. 1993·3).
Local anaesthesia; anal pain and pruritus.

Tronoxal *Baxter, Spain.*
Ifosfamide (p. 806·1).
Malignant neoplasms.

Tronsalan *Medipharm, Chile.*
Trazodone hydrochloride (p. 451·1).
Depression; bulimia; diabetic neuropathy; migraine; alcohol withdrawal syndrome.

Tropamid *Bilim, Turk.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Tropargal *Sanofi-Aventis, Spain.*
Diazepam (p. 1063·2); nortriptyline hydrochloride (p. 439·3).
Depression with anxiety or agitation.

Troparinum *Extractum, Hung.*
Papaverine hydrochloride (p. 2362·3); phenobarbital (p. 535·2); homatropine methylbromide (p. 2007·3).
Gastrointestinal disorders; asthma.

Tropex *Rowa, Hong Kong; Rowa, Irl.*
Phenazone (p. 124·1).
Inflammatory ear disorders; ear wax removal; otitis media.
Rowa, Singapore.
⊗Phenazone (p. 124·1); glycerol (p. 2517·2).
Inflammatory ear disorders; ear wax removal.

Tropfen bei Verletzungen *Jacoby, Austria.*
Arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); hypericum perforatum (p. 449·1); ruta graveolens (p. 2608·2).
Homoeopathic preparation.

TrophAmine *Eczacibasi-Baxter, Turk.*
Amino acids.
Parenteral nutrition.

Trophamine *Pisa, Mex.; McGaw, Singapore; Braun, Spain; McGaw, USA; Victus, Venez.*
Amino acids.
Parenteral nutrition.

Tropharma *Alpharma, Mex.*
Erythromycin stearate (p. 291·3).
Bacterial infections.

Trophicard *Kohler, Ger.; Kohler-Pharma, Ger.*
Potassium aspartate (p. 1793·1); magnesium aspartate (p. 1787·1).
Magnesium or potassium deficiency; cardiac disorders.

Trophicrème *Sanofi-Aventis, Fr.*
Estriol (p. 2274·3).
Postmenopausal vulvovaginal disorders.

Trophigil *Besins, Fr.*
Lactobacillus casei var *rhamnosus* (p. 2596·3); estriol (p. 2274·3); progesterone (p. 2300·2).
Atrophic vaginitis; pre- and postoperative gynaecological care.

Trophirès *Sanofi-Aventis, Fr.*
Suppositories: Eucalyptus oil (p. 2501·2); thenoate sodium (p. 376·3).
Respiratory-tract disorders.
Sanofi-Aventis, Fr.†
Syrup: Pholcodine (p. 1675·1); thenoate sodium (p. 376·3); eucalyptus oil (p. 2501·2).
Cough.

Trophirès Composé *Sanofi-Aventis, Fr.*
Paracetamol (p. 115·1); eucalyptus oil (p. 2501·2); thenoate sodium (p. 376·3).
Respiratory-tract disorders; fever.

Trophoseptine *Theramex, Port.*
Promestriene (p. 2302·3); chlorquinaldol (p. 260·1).
Vaginal infections.

Trophox *Raptakos, India.*
High-protein dietary supplement.

Tropicacyl *Akorn, Canad.; Akorn, USA.*
Tropicamide (p. 2012·2).
Induction of mydriasis and cycloplegia.

Tropical Blend Dark Tanning *Schering-Plough, USA.*
Lotion SPF 4: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, USA.
Oil SPF 4: Padimate O (p. 1716·1); oxybenzone (p. 1715·3).
Sunscreen.
Schering-Plough, USA.
SPF 2: Homosalate (p. 1705·1).
Sunscreen.

Tropical Blend Dry Oil *Schering-Plough, USA.*
SPF 2: Homosalate (p. 1705·1).
Sunscreen.
Schering-Plough, USA.
SPF 4: Homosalate (p. 1705·1); oxybenzone (p. 1715·3).
Sunscreen.

Tropical Blend Tan Magnifier *Schering-Plough, USA.*
SPF 2; SPF 4: Trolamine salicylate (p. 141·2).
Sunscreen.

Tropical Gold Dark Tanning *Goldline, USA.*
SPF 2: Octinoxate (p. 1715·1); padimate O (p. 1716·1).
Sunscreen.
Goldline, USA.
SPF 4: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Tropical Gold Sunblock *Goldline, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.
Goldline, USA.
SPF 30: Octinoxate (p. 1715·1); octisalate (p. 1715·2); homosalate (p. 1705·1); oxybenzone (p. 1715·3).
Sunscreen.

Tropical Gold Sunscreen *Goldline, USA.*
SPF 8: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Tropical Vanilla *Eminence, Canad.*
SPF 32: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Tropicee *Multicare, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Tropicee Plus *Multicare, Philipp.*
Ascorbic acid (p. 2110·3); taurine (p. 2626·2); lysine hydrochloride (p. 2079·3).
Vitamin C deficiency; nutritional supplement.

Tropicil Top *Edol, Port.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Tropico
Note: this name may be used for preparations of different composition.
Bell, India.†
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Tropico Plus *Bell, India.†*
Phenylephrine hydrochloride (p. 1672·3); tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Tropicol *Thea, Belg.*
Tropicamide (p. 2012·2).
Production of mydriasis.

Tropicur *Investi, Arg.*
Mefloquine hydrochloride (p. 657·1).
Malaria.

Tropidene *Tropica Mas, Indon.*
Piroxicam (p. 1253).
Musculoskeletal and joint disorders; gout; pain.

Tropidrol *Tropica Mas, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Tropidryl Plus *Tropica Mas, Indon.*
Diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Tropifer *Tropica Mas, Indon.*
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2) vitamin E (p. 2119·1).
Iron supplement; iron-deficiency anaemia.

Tropilex *Prafa, Indon.*
Piracetam (p. 393·3).
Mental function impairment; chronic alcoholism; cerebral trauma; behavioural disorders in children; enuresis.

Tropimil *Farmigea, Ital.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Tropinal *Sigma, Braz.*
Dipyrone (p. 53·3); homatropine methylbromide (p. 2007·3); hyoscine butylbromide (p. 1845·3); hyoscyamine hydrobromide (p. 1848·1).
Smooth muscle spasm.

Tropindol *Lens, Rus.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Tropineuron *Tropica Mas, Indon.*
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia.

Tropinom *Uniao Quimica, Braz.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Tropioftal F *Denver, Arg.*
Tropicamide (p. 2012·2); phenylephrine hydrochloride (p. 1672·3).
Production of cycloplegia and mydriasis.

Tropistan *Tropica Mas, Indon.*
Mefenamic acid (p. 85·3).
Pain.

Tropium *DDSA Pharmaceuticals, UK.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome.

Tropivag *Finadiet, Arg.*
Lactobacillus rhamnosus (p. 2596·3).
Restoration of vaginal flora.

Tropivag Plus *Finadiet, Arg.*
Lactobacillus rhamnosus (p. 2596·3); progesterone (p. 2300·2); estriol (p. 2274·3).
Vaginal disorders.

Tropixal *Demo, Gr.*
Tropicamide (p. 2012·2).
Production of mydriasis.

Tropix-HC *Alpharma, Mex.†*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction.

Tropocer *Megat, Venez.*
Nimodipine (p. 1455·2).
Stroke; cerebrovascular insufficiency; neurological deficit following subarachnoid haemorrhage; dementia; vertigo.

Tropofin *Coup, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Tropyn *Zafiro, Mex.*
Atropine sulfate (p. 1310·2).
Premedication; gastrointestinal disorders; organophosphorus pesticide poisoning.

Trorix *Baxter, Chile.†*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Trosderm *Omega, Spain.*
Tioconazole (p. 595·3).
Fungal skin infections.

Trosec *Sunovion, Canad.*
Trospium chloride (p. 2371·1).
Bladder instability.

Trosic *General Drugs, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trosid *Pfizer, Spain.*
Tioconazole (p. 595·3).
Fungal nail infections.

Trospi *Medac, Ger.*
Trospium chloride (p. 2371·1).
Bladder instability.

Trosycort *Pfizer, Fin.*
⊗Tioconazole (p. 595·3); hydrocortisone acetate (p. 1640·1).
Inflammatory fungal skin infections with secondary bacterial infection.

Trosyd *Pfizer, Arg.; Pfizer, Austria; Pfizer, Fin.; Teofarma, Fr.; Johnson & Johnson, Hong Kong; Pfizer, Indon.; Giuliani, Ital.; Pfizer, Malaysia; Johnson & Johnson, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Janssen-Cilag, Switz.†; Pfizer, Thai.*
Tioconazole (p. 595·3).
Fungal and Gram-positive bacterial infections of the skin, nails, and vagina.

Trosyl *Pfizer, Irl.; Pfizer, UK.*
Tioconazole (p. 595·3).
Fungal and bacterial infections of the nails.

Trovensis *Sanbe, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Troviakol *Tropica Mas, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Trovost *Ophtalkener, Mex.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Troxac *Eurolab, Arg.*
Saw palmetto (p. 2363·3); urtica (p. 2639·3); zinc (p. 2126·1).
Dietary supplement; prostate disorders.

Troxegel *Arterium, Ukr.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Troxeratio *Ratiopharm, Pol.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Troxescorbin *Synteza, Pol.*
Troxerutin (p. 2505·3); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; vascular disorders.

Troxevazin *Balkanpharma, Rus.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Troxeven *Craveri, Arg.*
Troxerutin (p. 2505·3); aescin (p. 2431·2).
Chronic venous insufficiency; haemorrhoids.

Kreussler, Ger.
Troxerutin (p. 2505·3).
Venous disorders.

Troxidol *Relonchem, Irl.*
Tramadol hydrochloride (p. 139·2).
Pain.

Troxolid *Flamingo, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

Troxxil *Laboratorios Chile, Chile.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; protozoal infections.

Trozara *Actavis, Cz.*
⊗Letrozole (p. 817·1).
Breast cancer.

Trozel *Medicamenta, Cz.; Glenmark, Pol.*
⊗Letrozole (p. 817·1).
Breast cancer.

Trozet *Dabur, India; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.*
⊗Letrozole (p. 817·1).
Breast cancer.

Trozin *Tempo Scan Pacific, Indon.; Mercury, Philipp.*
Azithromycin (p. 221·2).
Bacterial infections.

Trozocina *Sigma-Tau, Ital.*
Azithromycin (p. 221·2).
Bacterial infections.

Trozolet *Tecnofarma, Chile; Nolver, Venez.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Trozolite *Raffo, Arg.*
⊗Anastrozole (p. 742·1).
Malignant neoplasms.

Trozyman *IQB, Braz.†*
Azithromycin (p. 221·2).
Bacterial infections.

Tru *Elea, Arg.*
Pyrvinium embonate (p. 166·1).
Oxyuriasis.

Pasteur, Chile.
Sulfathiazole sodium (p. 368·3); lidocaine hydrochloride (p. 1988·2).
Otitis.

Tru Bronz *Hamilton, Austral.*
Dihydroxyacetone (p. 1700·1).
Tanning aid.

Tru Compuesto *Elea, Arg.*
Mebendazole (p. 158·3); tinidazole (p. 949·2).
Worm infections.

Tru M *Elea, Arg.*
Mebendazole (p. 158·3).
Worm infections.

Truasinol *Medipharm, Chile.*
Mefenamic acid (p. 85·3).
Pain.

Trubloc *Pasteur, Philipp.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Tructum *Nolver, Venez.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Trudexa *Abbott, Gr.*
Adalimumab (p. 17·2).

True Finish *Fashion Fair, Canad.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

True Test *Bipharma, Belg.†; Spexell, Canad.; Mekos, Denm.; Stallergenes, Fr.; Mekos, Israel; Bipharma, Neth.; CSL, NZ; NZ Medical & Scientific, NZ; Stallergenes, Switz.; Glaxo Wellcome, USA.*
A range of allergen-impregnated patches (p. 2434·3).
Diagnosis of allergic contact dermatitis.

Truetest *Mekos, Port.*
A range of allergen-impregnated patches (p. 2434·3).
Diagnosis of allergic contact dermatitis.

Trufree *Cantassium Co., UK.*
Tablets: Vitamins; minerals.

Nutricia Dietary, UK.
Gluten-free, wheat-free flours and foods for special diets.
Gluten sensitivity.

Trumepen *Deutsche, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Trumsal *Centrum, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Trunal *Ferron, Indon.; Heumann, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Trund *Glenmark, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Truoxin *Helsinn Birex, Irl.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Trusil *Intermed, Gr.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Trusopt *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, NZ; MSD, Philipp.; MSD, Pol.; Chibret, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; Neurogard, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
⊗Dorzolamide hydrochloride (p. 2006·3).
Glaucoma; ocular hypertension.

Trust Pill *Pond's, Philipp.*
21 Tablets, ethinylestradiol (p. 2275·3); levonorgestrel (p. 2296·1); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive; menstrual disorders.

Truvada *Gador, Arg.; Gilead, Austral.; Gilead, Austria; Gilead, Belg.; Gilead, Canad.; Pharma Investi, Chile; Gilead, Cz.; Gilead, Denm.; Gilead, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hong Kong; Gilead, Irl.; Gilead, Israel; Gilead, Ital.; Stendhal, Mex.; Gilead, Neth.; Gilead, Norw.; Gilead, NZ; Gilead, Pol.; Gilead, Port.; Aspen, S.Afr.; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; Gilead, Thai.; Gilead, UK; Gilead, USA.*
Emtricitabine (p. 976·3); tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Truvalin *Winthrop, S.Afr.*
Quetiapine (p. 1101·1).

Truvaz *Kalbe, Indon.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Truvent *Cipla, Rus.*
Troventol.
Obstructive airways disease.

Truvit *Solas, Indon.*
Vitamins; calcium gluconate (p. 1783·3); docosahexaenoic acid (p. 1460·1); lysine hydrochloride (p. 2079·3); bovine colostrum (p. 2380·3).
Nutritional supplement.

Truw Gold *Truw, Ger.*
Adonis vernalis (p. 2431·1); selenicereus grandiflorus (p. 2473·2); strophanthus gratus; urginea maritima (p. 1677·3).
Homoeopathic preparation.

Truxa
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Azithromycin (p. 221·2).
Bacterial infections.

Truxal *Lundbeck, Austria; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Rus.; Lundbeck, Swed.; Lundbeck, Switz.*
Chlorprothixene hydrochloride (p. 1054·1).
Anxiety disorders; sleep disorders; neuroses; vomiting; pain; alcohol and drug withdrawal syndromes; psychoses; agitation; behaviour disorders; mania; depression.

Lundbeck, Ger.; Lundbeck, Gr.; Lundbeck, Ukr.
Chlorprothixene (p. 1053·3) or chlorprothixene hydrochloride (p. 1054·1).
Psychoses; alcohol and drug withdrawal syndromes; depression; epilepsy; pain; behaviour disorders in children and the elderly.

Lundbeck, Hung.
Chlorprothixene acetate (p. 1053·3) or chlorprothixene hydrochloride (p. 1054·1).
Alcohol withdrawal syndrome; anxiety disorders; epilepsy; behaviour disorders in the elderly; psychoses; opioid withdrawal syndrome.

Truxaletten *Lundbeck, Switz.†*
Chlorprothixene hydrochloride (p. 1054·1).
Psychoses; mania; anxiety disorders; alcohol and drug withdrawal syndromes; depression; behaviour disorders in children; pain.

Try *Bayer Sante, Fr.*
Vaginal lubricant.

Trycam *Douglas, Thai.*
Triazolam (p. 1112·3).
Insomnia.

Trycet *Auriga, USA†; Tryon, USA.†*
Dextropropoxyphene napsilate (p. 43·3); paracetamol (p. 115·1).
Pain.

Trymo *Raptakos, India.*
Colloidal bismuth subnitrate (p. 1822·1) or tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer; dyspepsia.

Trypsan *Grifols, Arg.; Grifols, Chile.*
Alpha$_1$-proteinase inhibitor (p. 2438·1).
Alpha$_1$ antitrypsin deficiency.

Trypsidan *Norton, Ukr.†*
Centella (p. 1698·3); bacopa (p. 2452·1); ashwagandha (p. 2450·2); convolvulus pluricaulis; nardostachys jatamansi; valerian (p. 2640·2); embelia ribes (p. 154·2); prunus amygdalus; calamus (p. 2464·2); terminalia chebula (p. 2474·3); Indian gooseberry (p. 2532·2); tinospora cordifolia; celastrus pannculata; oroxylum indicum; mucuna prurita; cardamom (p. 2471·1); arjuna (p. 2447·2); fennel (p. 2503·2); pueria tuberosa; orchis mascula (p. 2576·3); ginger (p. 1844·1); terminalia bellerica (p. 2453·2); nutmeg (p. 2573·1); clove (p. 2481·2).
Nervous disorders; sleep disorders; menopausal disorders; premenstrual syndrome; psychosomatic disorders.

Trypsone *Grifols, Cz.; Grifols, Spain.*
Alpha$_1$-proteinase inhibitor (p. 2438·1).
Congenital alpha$_1$ antitrypsin deficiency.

Tryptal *Unipharm, Israel.†*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Tryptalgin *Craveri, Arg.*
Amitriptyline (p. 401·1).
Depression; pain.

Tryptan *Valeant, Canad.*
Tryptophan (p. 453·2).
Adjunct in treatment of depression and bipolar disorder.

Tryptanol *MSD, Arg.; MSD, Austral.†; MSD, Braz.; MSD, Malaysia†; MSD, Mex.; MSD, S.Afr.; M & H, Thai.; MSD, Venez.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Tryptizol *MSD, Austria†; MSD, Neth.; MSD, Port.; Frosst, Spain; MSD, Swed.; MSD, Switz.†*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis; neuropathic pain.

Tryptomer *Wockhardt, India.*
Amitriptyline hydrochloride (p. 401·1).
Depression; nocturnal enuresis.

Tryptozen 5-HTP *Erjean, Fr.*
Preparation for enteral nutrition.

Tryzan *Alphapharm, Austral.*
Ramipril (p. 1483·3).
Hypertension; heart failure; cardiovascular risk reduction; nephropathy.

TS-1 *Taiho, Jpn.*
Tegafur (p. 864·2); gimeracil; oteracil potassium.
Malignant neoplasms.

T-Samag *Vargas, Venez.*
Thyme (p. 2630·2); sweet chestnut (p. 2625·1).
Cough.

TS-Bac *Ultra, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Tsoncel *Chrispa (Χρισπα), Gr.*
⊗Serrapeptase (p. 2613·3).

TS-One *Taiho, Singapore; Taiho, Thai.*
Tegafur (p. 864·2); gimeracil; oteracil potassium.
Gastric cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

T-Stat *BMS, Mex.*
Erythromycin (p. 291·2).
Acne.

Tsudosan *Tsumura, Jpn.*
Immature orange; rhubarb (p. 1884·2); angelica acutiloba root (p. 2443·3); liquorice (p. 1853·2); safflower; magnolia bark; sappan wood; citrus unshiu peel; akebia stem; mirabilitum.
Traditional Kampo medicine.

Tsurubel *Tsuruhara, Jpn.*
Tofisopam (p. 1112·2).
Autonomic dystonia; menopausal disorders.

TT 380 *CCD, Fr.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

TT Vaccine *Bio Farma, Malaysia; Bio Farma, Thai.*
An adsorbed tetanus vaccine (p. 2421·1).
Active immunisation.

Tu Er *Jinhui, China.*
Aceglutamide (p. 2426·2).

Tu Ting *Double-Crane, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Tu Tu *Double-Crane, China.*
Gamma-aminobutyric acid (p. 2509·2).

Tuaplex *Cetus, Arg.*
Pyridoxine (p. 2105·3); phosphoserine; glutamine (p. 2070·3).
Tonic.

Tuba *Kurtsan, Turk.*
Salicylic acid (p. 1719·1); acetic acid (p. 2426·3).
Calluses.

Tubarine
Note: this name may be used for preparations of different composition.
Spedrog, Arg.
Troxerutin (p. 2505·3); aescin (p. 2431·2).
Venous insufficiency; haemorrhoids.

Tubavit *Valenta, Rus.*
Rifampicin (p. 350·3); isoniazid (p. 311·2). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Bacterial infections including tuberculosis and leprosy.

Tuberbut *LKM, Arg.; Kampar, Chile.*
Tobramycin (p. 380·1).
Pseudomonal lung infections in cystic fibrosis; bacterial infections.

Tubernax *Sandoz, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Tubersol *Sanofi Pasteur, Canad.; Sanofi Pasteur, Israel; Sanofi-Aventis, NZ; Sanofi Pasteur, USA.*
Tuberculin purified protein derivative (p. 2635·3).
Diagnosis of tuberculosis.

Tubertest *Sanofi Pasteur, Fr.*
Tuberculin (p. 2635·3).
Test for tuberculin sensitivity.

Tubilux *Transdermal, UK.*
Sodium chloride (p. 1795·1).
Nasal dryness; nasal hygiene.

Tubilysin *Orion, Fin.*
Isoniazid (p. 311·2).
Tuberculosis.

Tucare *Rekah, Israel.*
⊗Codeine phosphate (p. 40·2); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2); ephedrine hydrochloride (p. 1663·2).
Cough.

Tucks *Pfizer Consumer, USA.*
Suppositories: Benzyl alcohol (p. 1739·3); soybean oil (p. 2092·3); tocoferil acetate (p. 2119·2).
Formerly known as Anusol.
Anorectal disorders.

Pfizer Consumer, USA.
Ointment: Pramocaine hydrochloride (p. 1993·3); zinc oxide (p. 1729·1).
Formerly known as Anusol-HC and contained hydrocortisone acetate.
Anorectal disorders; skin disorders.

Pfizer Consumer, Canad.†; Warner-Lambert, USA.
⊗Hamamelis (p. 2523·3); glycerol (p. 2517·2).
Perianal cleansing; haemorrhoids; vaginal cleansing.

Tuclase *UCB, Gr.; Pierre Fabre, Neth.†*
Pentoxyverine citrate (p. 1672·1).
Cough.

UCB, Ital.†
Pentoxyverine hydrochloride (p. 1672·2).
Cough.

Tudcabil *Bruschettini, Ital.†*
Tauroursodeoxycholic acid (p. 2638·1).
Biliary disorders.

Tuderm-N *Meprofarm, Indon.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Tudiab *Meprofarm, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Tudor *Alapis, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Tudorza *Forest Laboratories, USA.*
Aclidinium bromide (p. 1201·1).
Obstructive airways disease.

Tuen *Tian Da, China.*
Ibuprofen (p. 68·2).
Fever; pain.

Tueor *Sofar, Ital.*
Barrier cream.

Tufam *Unison, Thai.†*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Tugesal *Meprofarm, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Tuinal *Flynn, UK; Lilly, USA.*
Secobarbital sodium (p. 1106·3); amobarbital sodium (p. 1037·3).
Insomnia; sedative.

Tukol *Atlantis, Mex.†*
Guaifenesin (p. 1666·2).
Cough.

Tukol-D *Genomma, Mex.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tulerin *Specifar, Neth.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Tulgrasum Antibiotico *SIT, Spain.*
Bacitracin zinc (p. 225·3) neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Burns; skin disorders; skin ulcers; wounds.

Tulgrasum Cicatrizante *SIT, Spain.*
Glycine (p. 2071·2); benzyl benzoate (p. 2149·1); benzalkonium chloride (p. 1737·1); amino acids.
Burns; skin disorders; skin ulcers; wounds.

Tulip
Note: this name may be used for preparations of different composition.
Lek, Cz.; Sandoz, Pol.; Lek, Rus.; Sandoz, Ukr.
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Wermar, Mex.†
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Tulipe-R *Coup, Gr.*
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Tulipt *Sinensix, Thai.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Tulita *Gedeon Richter, Hung.*
Estradiol (p. 2271·1); norethisterone acetate (p. 2294·3).
Menopausal disorders; osteoporosis.

Tulle Gras *Abbott, Fr.*
White soft paraffin (p. 2211·3).
Burns; ulcers; wounds.

Tulosin *Egis, Rus.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Tulotract *Ardeypharm, Ger.†*
Lactulose (p. 1850·3).
Hepatic encephalopathy; constipation.

Tulox *Mintlab, Chile.*
Oxolamine citrate (p. 1671·2) or oxolamine phosphate (p. 1671·2).
Cough.

Tulzol *Teva, Cz.; Teva, Irl.†; Teva, Pol.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Tuma *Robugen, Ger.*
Ivy (p. 2536·2).
Respiratory-tract disorders.

Tumarol *Robugen, Ger.*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2); menthol (p. 2553·2).
Cold symptoms.

Tumarol Kinderbalsam *Robugen, Ger.*
Eucalyptus oil (p. 2501·2); Scots pine oil (p. 2591·2).
Cold symptoms.

Tumarol-N *Robugen, Ger.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Cold symptoms.

Tumax *Sriprasit, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).
Peptic ulcer; gastrointestinal disorders; smooth muscle spasm.

Tumdi *Sriprasit, Thai.†*
Paracetamol (p. 115·1).
Pain; fever.

Tumetil *Boehringer Ingelheim, Venez.*
Mexiletine hydrochloride (p. 1436·2).
Arrhythmias.

Tummy Ease *Cadila, India.†*
Ferula asafetida (p. 2449·3); trachyspermum ammi; gardenia gummifera; ginger (p. 1844·1); black pepper (p. 2586·1).
Stomach disorders.

Tumoglin *Pfluger, Ger.†*
Juglans regia (p. 2646·1).
Homoeopathic preparation.

Tums *GSK Consumer, Canad.; GSK, Israel; GSK, Mex.; GSK, Philipp.; GSK Consumer, Port.; Group, S.Afr.†; GSK Consumer, UK; GSK, USA; GSK Consumer, Venez.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity; calcium supplement; dyspepsia; heartburn; flatulence; nausea; calcium deficiency.

GSK Consumer, Cz.†; GSK, Gr.
Calcium carbonate (p. 1824·3); magnesium carbonate (p. 1856·2).
Antacid; gastric hyperacidity; dyspepsia; peptic ulcer.

Tums Dual Action *GSK, USA.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).
Heartburn.

Tums Plus *SmithKline Beecham, USA.*
Calcium carbonate (p. 1824·3); simeticone (p. 1886·2).

Tundra *Lamsa, Arg.*
Naproxen (p. 98·2).
Fever; inflammation; pain.

Tuneluz *Baldacci, Port.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Tunelzin *Lavipharm, Gr.*
Paracetamol (p. 115·1).
Pain; fever.

Tunik *Baliarda, Arg.*
Ademetionine sulfate tosilate (p. 2430·1). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Osteoarthritis; depression; liver disorders.

Tunik B12 *Baliarda, Arg.*
Ademetionine sulfate tosilate (p. 2430·1); vitamin B_{12} (p. 2107·2). Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Osteoarthritis; liver disorders; depression.

Tunitol-BX *Streger, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Tunxin *IQFA, Mex.*
⊗Salbutamol (p. 1220·2).

Tuo Di *Jincheng Haisi, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Tuo Bi Lai *Beiqi, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Tuo Er *Bikai, China.*
⊗Carvedilol (p. 1333·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Tuo Fu Ning *Jinsha, China.*
Zolmitriptan (p. 682·2).
Migraine.

Tuo Jia *Yang Jiang, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Tuo Li Shi Ning *Minsheng, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Tuo Neng *Haixin, China.*
Azithromycin lactobionate.
Bacterial infections.

Tuo Ping *Tian Da, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Tuo Pu You *Rui Yang, China.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Tuo Qi *Yang Jiang, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Tuo Shu *Huitian, China.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

Tuo Su *Ke Lun, China.*
Ornidazole (p. 943·1).
Bacterial infections; protozoal infections.

Tuo Tai *Qing Hua Zi Guang Gu Han, China.*
Gamma-aminobutyric acid (p. 2509·2).

Tuo Xi *Wanle, China.*
Hydroxycamptothecin.

Tuo Xi Er Kang *Southwest, China.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; heart failure.

Tuo Xin *Tong Yong Tong Meng, China.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Tuo Xing *Harbin, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Tuoan *Tian Da, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Influenza symptoms.

TuoQi *Jinfeng, China.*
Azithromycin hydrochloride (p. 221·2).
Bacterial infections.

Tuosai *Suzhong Haixin, China.*
⊗Torasemide (p. 1516·3).
Oedema; hypertension.

Tuosomin *BayerSchering, Thai.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; endometrial cancer; anovulatory infertility.

Tupast *Kleva, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Tupper-E *Chinta, Thai.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; vitamin E supplement.

Turbaund *Meditrina, Gr.*
Tolfenamic acid (p. 138·3).
Pain; inflammation; musculoskeletal and joint disorders.

Turbinal *Valeas, Ital.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Turbogesic *Laboratorios Chile, Chile.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Turbonatal *Medipharm, Chile.*
Vitamins; minerals.
Dietary supplement.

Turbovit *Medipharm, Chile.*
Vitamins; with or without minerals.
Tonic.

Turexan Capilla *Turimed, Switz.†*
⊗Cetrimonium bromide (p. 1742·3); urea (p. 1727·3); dexpanthenol (p. 2582·2).
Scalp disorders.

Turexan Creme *Turimed, Switz.†*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Skin disorders; barrier cream.

Turexan Douche *Turimed, Switz.†*
Undecenoic acid (p. 596·3).
Skin disorders; soap substitute.

Turfa *Worwag, Ger.*
⊗Triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Oedema; hypertension.

Turgent Colageno *GSK, Arg.*
⊗Collagen (p. 2483·2); octinoxate (p. 1715·1); urea (p. 1727·3).
Dry skin disorders.

Turgent Emulsion *GSK, Arg.*
⊗Octinoxate (p. 1715·1); urea (p. 1727·3).
Dry skin.

Turifam *Reuffer, Mex.*
Rifampicin (p. 350·3).
Bacterial infections.

Turimonit *Mibe, Ger.†*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Turimycin *Mibe, Ger.†*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Turinal *Gedeon Richter, Hong Kong†; Gedeon Richter, Philipp.; Gedeon Richter, Rus.†; Gedeon Richter, Ukr.†*
Allylestrenol (p. 2255·2).
Threatened or recurrent miscarriage; premature labour.

Turisan *Turimed, Switz.†*
Cetrimonium bromide (p. 1742·3).
Skin disinfection; acne.

Turixin *GSK, Ger.*
Mupirocin calcium (p. 327·2).
Nasal carriage of staphylococci.

Turm *Biores, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Turmerik *Knop, Chile.*
Turmeric (p. 2218·1).
Musculoskeletal and joint disorders; liver disorders.

Turoptin *Bausch & Lomb, Ital.; Novartis, Turk.*
⊗Metipranolol (p. 2009·2).
Ocular hypertension; glaucoma.

Turox *MSD, Fin.†; Vianex (Βιανεξ), Gr.; MSD, Port.; MSD, Swed.*
Etoricoxib (p. 57·3).
Osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; gout.

Turpan *Corsa, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Turresis *Sanofi-Aventis, Port.*
Ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Turulington Tincture *Lennon, S.Afr.†*
Benzoin (p. 2624·3); storax (p. 2622·3); tolu balsam (p. 1679·2); aloes (p. 1816·1).
Cough; bronchitis; minor wounds.

Turusol *Yuri, Ukr.*
⊗Sorbitol (p. 2092·1); mannitol (p. 1427·3).
Irrigation solution.

Tusabron *Bago, Chile.†*
⊗Clobutinol hydrochloride (p. 1658·3); orciprenaline sulfate (p. 1217·3); ammonium chloride (p. 1656·1).
Cough.

Tusacdon *Acdhon, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tusamol *Atabay, Turk.*
Butamirate citrate (p. 1657·3).

Tusana-D *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Tusant *Lupin, India.*
Terfenadine (p. 640·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tusapres *Sandoz, Indon.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2).
Cough; bronchospasm; respiratory-tract disorders with excess mucus.

Tusben *TS, Ital.*
Dimemorfan phosphate (p. 1661·3).
Cough.

Tuscalman
Note: this name may be used for preparations of different composition.
DMS, Austria; Desma, Switz.
Oral drops; suppositories: Noscapine hydrochloride (p. 1670·3); guaifenesin (p. 1666·2).
Respiratory-tract disorders; cough; catarrh; bronchitis; sore throat; laryngitis.

Desma, Switz.
Syrup: Noscapine hydrochloride (p. 1670·3); guaifenesin (p. 1666·2); althaea (p. 2438·3).
Respiratory-tract disorders.

DMS, Austria.
Syrup: Noscapine hydrochloride (p. 1670·3); guaifenesin (p. 1666·2); althaea (p. 2438·3); sambucus (p. 2609·3).
Cough; catarrh; bronchitis; sore throat; laryngitis.

SIT, Spain.
Suppositories; syrup: Noscapine hydrochloride (p. 1670·3).
Cough.

Tusco *Hua, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tuscolgen *Great Eastern, Thai.†; Westmont, Thai.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough.

Tusdec-DM *Cypress, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Upper respiratory-tract disorders.

Tusdec-HC *Cypress, USA.†*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3).
Coughs.

Tusebron *Hakay, Turk.*
Oxolamine phosphate (p. 1671·2).

Tusedex *Medhaus, Philipp.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; allergic rhinitis.

Tusedon *Zekides, Gr.*
Dihydroergotamine mesilate (p. 672·2).

Tuselin Descongestivo *Korhispana, Spain.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; nasal congestion.

Tuseptil *Munir, Turk.*
Guaifenesin (p. 1666·2); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).
Respiratory-tract congestion.

Tuseran
Note: this name may be used for preparations of different composition.
Medichem, Hong Kong.
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); paracetamol (p. 115·1).
Cough and cold symptoms.

Mediframa, Indon.†
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Cough; cold symptoms.

Tuseran Forte *United Laboratories, Philipp.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Tuseran Forte (Reformulated) formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, and paracetamol.
Cough; cold symptoms.

Mediframa, Indon.†
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cough; cold symptoms.

Tuseran Pedia DMP *Mediframa, Indon.; UAP, Indon.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough; rhinitis; nasal congestion.

Tuseran (Reformulated) *Medichem, Philipp.†*
Dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); guaifenesin (p. 1666·2).
Cough.

Tusibron
Note: this name may be used for preparations of different composition.
Kener, Mex.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Kenwood, USA.
Guaifenesin (p. 1666·2).
Coughs.

Tusibron-DM *Kenwood, USA.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Tusical *Andromaco, Mex.†*
Benzonatate (p. 1656·2).
Cough.

Tusifon *Munir, Turk.*
Terpin hydrate (p. 1678·2); chlorphenamine maleate (p. 620·3); noscapine (p. 1670·3).
Cough.

Tusigen *Bago, Chile.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough.

Liomont, Mex.
Zipeprol hydrochloride (p. 1680·3).
Cough.

Tusilan *Landson, Indon.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tusilen *Allen, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough; respiratory-tract congestion.

Tusilen Pediatrico *Allen, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Cough; fever.

Tusilin *Mecom, Turk.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Tusitato *Teva, Mex.*
Benzonatate (p. 1656·2).
Cough.

Tusminal *Medipharm, Chile.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tusnel C *Llorens, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Tusnel-DM *Llorens, USA.*
⊗Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Tusnel-HC *Llorens, USA.†*
Hydrocodone tartrate (p. 67·2); brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Tusno *Milano, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3).
Cough.

Tusol
Note: this name may be used for preparations of different composition.
Mecom, Turk.
Ambroxol hydrochloride (p. 1654·3).

Tusorama *Quimifar, Spain.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tuspel *Indoco, India.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough.

Tuspel Plus *Indoco, India.*
⊗Bromhexine hydrochloride (p. 1656·3); terbutaline (p. 1228·1); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Tuspress *Indoco, India.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); menthol (p. 2553·2).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, chlorphenamine maleate, and menthol.
Cough.

Tusquit *Xixia, S.Afr.†*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough.

Tussa *Silom, Thai.†*
Guaifenesin (p. 1666·2).
Cough.

Tussafed-EX *Everett, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs; respiratory-tract congestion.

Tussafed-HCG *Everett, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Coughs; cold symptoms; allergic rhinitis.

Tussafin Expectorant *Rugby, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Coughs.

Tussafug *Robugen, Ger.*
Benproperine phosphate (p. 1656·2).
Cough.

Tussal Antitussicum *Biofarm, Pol.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussal Expectorans *Biofarm, Pol.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Tussall *Everett, USA.*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); dexbrompheniramine maleate (p. 618·1).
Coughs; nasal congestion.

Tussalpront *Janssen-Cilag, Switz.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussamag *Montavit, Austria.*
Ointment: Spike lavender oil (p. 2621·3); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); camphor (p. 2466·2).
Catarrh; cough; bronchitis.

Montavit, Austria.
Oral liquid: Thyme (p. 2630·2); sweet chestnut (p. 2625·1).
Catarrh; cough; bronchitis.

Ratiopharm, Rus.
Thyme (p. 2630·2).
Cough.

Teofarma, Ital.
Wild thyme (p. 2648·1); sweet chestnut leaves (p. 2625·1).
Respiratory-tract congestion.

Tussamag Balsam *CT, Rus.†*
Pine oil (p. 2591·1); eucalyptus oil (p. 2501·2).

Tussamag Complex *Teofarma, Ital.*
Wild thyme (p. 2648·1); dropropizine (p. 1662·2).
Cough.

Tussamag Fieber- und Schmerztabletten *CT, Ger.†*
Ibuprofen (p. 68·2).
Fever; pain.

Tussamag Hustenlösung *CT, Ger.†*
Thyme (p. 2630·2).
Bronchitis; catarrh.

Tussamag Hustensaft N *CT, Ger.†*
Thyme (p. 2630·2).
Bronchitis; catarrh.

Tussamag NAC *CT, Ger.†*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Tussamag Nasenspray *CT, Ger.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Tussamag Nasenspray Pur *CT, Ger.†*
Sodium chloride (p. 1795·1).
Nasal congestion; nasal cleansing.

Tussamag Zink *CT, Ger.†*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Tussanil DH *Misemer, USA.*
Syrup: Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Coughs and cold symptoms.

Tussanil N *Vifor, Switz.*
Noscapine hydrochloride (p. 1670·3).
Cough.

Tussanil Plain *Misemer, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Tussantiol *Medisa, Switz.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with increased mucus.

Tussanyl
Note: this name may be used for preparations of different composition.
ANH, Thai.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussar-2 *Rhone-Poulenc Rorer, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Tussar DM *Rhone-Poulenc Rorer, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Tussar SF *Rhone-Poulenc Rorer, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Coughs.

Tussastopp *Ratiopharm, Austria.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussavit *Montavit, Ukr.*
— *see* TussavitThyme (p. 2630·2); ribwort plantain (p. 2604·2).
Respiratory-tract disorders with cough.

Tussdra *Pharmacross, Chile.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Tussefar *Angelini, Gr.; Faran, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Tusselin *Angelini, Gr.*
Erdosteine (p. 1665·1).
Mucolytic.

Tussend *Monarch, USA.*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Coughs.

TussEx *Herbamed, Switz.*
Drosera (p. 2497·2); hepar sulfuris (p. 1721·3); bryonia (p. 2461·3); eucalyptus (p. 2501·1); echinacea purpurea (p. 2498·1); ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Tussi-12 *Meda, USA.*
Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Cough.

Tussi-12 D *Meda, USA.*
Pentoxyverine tannate (p. 1672·1); mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Cough.

Tussia *Tripharma, Turk.*
Butamirate citrate (p. 1657·3).

Tussibron *Sella, Ital.*
Oxolamine citrate (p. 1671·2).
Cough.

TussiCaps *ECR, USA.*
Chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2).
Upper respiratory-tract disorders.

Tussicare DG *ST, Thai.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussicom *Sanofi-Aventis, Pol.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion; cystic fibrosis.

Tussicon *The Forty-Two, Thai.*
Syrup: Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

The Forty-Two, Thai.
Tablets: Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cough.

Doctors, Philipp.
Diphenhydramine hydrochloride (p. 626·2).

Tussi-12D S *Wallace, USA.*
Pentoxyverine tannate (p. 1672·1); mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Tussidane *Elerte, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussidermil N *Li-il, Ger.*
Eucalyptus oil (p. 2501·2).
Catarrh; musculoskeletal and joint disorders.

Tussidex *Hasco-Lek, Pol.; Xepa-Soul Pattinson, Singapore.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussidex Forte *Xepa-Soul Pattinson, Malaysia.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussidon DG *Acdhon, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Tussidoron *Weleda, Fr.*
Thyme (p. 2630·2); drosera (p. 2497·2).
Cough.

TussiDrill *Pierre Fabre, Pol.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussidrill *Pierre Fabre, Cz.; Pierre Fabre, Spain.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussidyl
Note: this name may be used for preparations of different composition.
VS, Thai.
Codeine phosphate (p. 40·2); promethazine (p. 638·2).

Tussiflex D *Abbott, Braz.*
Dropropizine (p. 1662·2).
Cough.

Tussiflorin Hom *Pascoe, Ger.*
Ipecacuanha (p. 1667·2); hyoscyamus (p. 2530·2); drosera (p. 2497·2).
Homoeopathic preparation.

Tussiflorin Thymian *Pascoe, Ger.*
Thyme (p. 2630·2).
Respiratory-tract congestion; bronchitis.

Tussifren *Intermed, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).

Tussigon
Note: this name may be used for preparations of different composition.
King, USA.
Hydrocodone tartrate (p. 67·2); homatropine methylbromide (p. 2007·3).
Cough.

Novell, Indon.
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine (p. 1676·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Tussilen *Teva, Cz.†*
⊗Drosera (p. 2497·2); thyme oil (p. 2630·3); gypsophila saponin (p. 2610·2); ephedrine hydrochloride (p. 1663·2).
Respiratory-tract inflammation.

Tussilene
Note: this name may be used for preparations of different composition.
Azevedos, Port.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussilène *Zydus, Fr.†*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders.

Tussilinct *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Tussiliv *Delta, Braz.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Tussils *Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussimont *Pharmonta, Austria.*
Oral liquid: Senega (p. 1677·2); thyme (p. 2630·2); bitter-orange (p. 2575·3).
Cough.

Tussin
Note: this name may be used for preparations of different composition.
Weifa, Norw.; Sagmel, Rus.
Guaifenesin (p. 1666·2).
Cough.

Teva, Cz.
Butamirate citrate (p. 1657·3).
Cough.

Tussin DM *Perrigo, Israel.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Tussin Plus *Sagmel, Rus.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussinol *Johnson & Johnson, Austral.†*
Pholcodine (p. 1675·1).
Cough.

Tussinol Expectorant *Johnson & Johnson, Austral.†*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough.

Tussionex *Sanofi-Aventis, Canad.*
Hydrocodone resin complex (p. 67·2); phenyltoloxamine resin complex (p. 638·1).
Cough.

Tussionex Pennkinetic *UCB, USA.*
Hydrocodone polistirex (p. 67·2); chlorphenamine polistirex (p. 620·3).
Coughs and cold symptoms.

Tussi-Organidin DM NR *Victory, USA.†*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Tussi-Organidin NR *Victory, USA.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Coughs.

Tussipax *Bailleul, Fr.*
Oral solution; tablets: Ethylmorphine hydrochloride (p. 56·3); codeine (p. 40·2).
Cough.

Bailleul, Fr.
Syrup: Ethylmorphine hydrochloride (p. 56·3); codeine (p. 40·2); tolu balsam (p. 1679·2); pectoral concentrate.
Cough.

Tussipect
Note: this name may be used for preparations of different composition.
Herbapol Poznan, Pol.
Syrup: ⊗Ephedrine hydrochloride (p. 1663·2); thyme (p. 2630·2); saponin.
Cough and associated respiratory-tract disorders.

Herbapol Poznan, Pol.
Tablets: ⊗Ephedrine hydrochloride (p. 1663·2); liquorice (p. 1853·2); saponin.
Cough and associated respiratory-tract disorders.

Qualiphar, Belg.†; Qualiphar, Neth.
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussi-Pres *Kramer, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Tussirex *Scot-Tussin, USA.*
Codeine phosphate (p. 40·2); pheniramine maleate (p. 637·2); phenylephrine hydrochloride (p. 1672·3); sodium citrate (p. 1781·2); sodium salicylate (p. 132·2); caffeine citrate (p. 1203·3); menthol (p. 2553·2).
Cough.

Tussisana *Muller Goppingen, Ger.*
Drosera (p. 2497·2); ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Tussisédal *Elerte, Fr.*
Noscapine (p. 1670·3); promethazine (p. 638·2); polysorbate 85 (Tween 85).
Cough.

Tussistin *DHU, Ger.*
Aconitum (p. 2428·3); ipecacuanha (p. 1667·2); bryonia (p. 2461·3); eucalyptus (p. 2501·1).
Homoeopathic preparation.

VSM, Neth.
Antimonium sulfuratum auratum (p. 2445·1); bryonia alba or bryonia cretica; drosera rotundifolia (p. 2497·2); eucalyptus globulus (p. 2501·1); ipecacuanha (p. 1667·2).
Homoeopathic preparation.

Tussistin S *DHU, Ger.*
Bryonia (p. 2461·3); ipecacuanha (p. 1667·2); drosera (p. 2497·2); eucalyptus (p. 2501·1); antimonium sulf. aurant. (p. 2445·1).
Homoeopathic preparation.

Tussitot *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p. 626·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Tussizone *Mallinckrodt, USA.†*
Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Tuss-LA *Hyrex, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Tusso DMR *Everett, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Tusso Rhinathiol *Sanofi-Aventis, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tusso-C *Everett, USA.†*
Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2).
Cough.

Tussodan DM *Odan, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Tusso-DF *Everett, USA.*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Coughs.

Tussodryl *ANH, Thai.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity reactions.

Tussodryl Expectorant *ANH, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

Tusso-HC *Everett, USA.†*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Tussol
Note: this name may be used for preparations of different composition.
Amnol, Ital.
Myrtillus (p. 2566·2); thyme (p. 2630·2); tilia (p. 2631·3); liquorice (p. 1853·2).
Respiratory-tract disorders.

Tussolvina *Marvecs, Ital.*
Nepinalone hydrochloride (p. 1670·2).
Cough.

Tussophedrine NF *Trima, Israel.*
⊗Ephedrine hydrochloride (p. 1663·2); dextromethorphan hydrobromide (p. 1660·1); sulfogaiacol (p. 1678·1); sodium benzoate (p. 1738·2).
Cough.

Tussopront *Pierre Fabre, Hung.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tussoret *Maxmedic, Ger.*
Codeine phosphate (p. 40·2).
Cough.

Tussosedan *Teva, Israel.†*
⊗Pheniramine maleate (p. 637·2); ephedrine hydrochloride (p. 1663·2); codeine phosphate (p. 40·2); ammonium chloride (p. 1656·1).
Cough.

Tusso-ZMR *Everett, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Tusso-ZR *Everett, USA.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cough.

Tusspac *Inpac, Thai.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); terpin hydrate (p. 1678·2).
Cough.

Tussplex *Breckenridge, USA.*
Hydrocodone tartrate (p. 67·2); mepyramine maleate (p. 635·1); phenylephrine hydrochloride (p. 1672·3).
Cough; cold symptoms.

Tuss-Tan *Econolab, USA.*
⊗Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3); ephedrine tannate (p. 1663·1).
Upper respiratory-tract symptoms.

Tusstat *Century, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Coughs.

Tussycalm *Sanofi-Aventis, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tustan 12S *Amneal, USA.*
Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3).
Upper respiratory-tract disorders.

Tusulin *Mecom, Turk.*
Ambroxol hydrochloride (p. 1654·3).

Tutofusin *Baxter, Ger.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders; peritoneal irrigation.

Tutofusin BG *Baxter, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Tutofusin G5 *Baxter, Ger.†*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Tutofusin H G5 *Baxter, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Tutofusin LC *Kalbe, Indon.*
Amino acids; electrolytes (p. 1775·1); sorbitol (p. 2092·1); vitamins.
Liver disorders.

Tutofusin OP *Baxter, Ger.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Tutofusin OP G *Baxter, Ger.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Tutofusin OpS *Kalbe, Indon.*
Electrolytes (p. 1775·1); sorbitol (p. 2092·1).
Fluid and electrolyte disorders; carbohydrate source.

Tuttozem N *Strathmann, Ger.*
⊗Dexamethasone (p. 1630·3).
Skin disorders.

Tuulix *Verman, Fin.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Tuxedon *Valeant, Cz.; Valeant, Hung.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Tuxi *Leiras, Fin.†*
Pholcodine (p. 1675·1).
Cough.

Tuxium *SMB, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Tuzalos *Sanbe, Indon.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylpropanolamine hydrochloride (p. 1674·1); chlorphenamine maleate (p. 620·3).
Pain; fever; cough; nasal congestion.

Tuzanil *Bohm, Spain.*
Pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

TuZen *Ferring, Canad.*
Lactobacillus plantarum (p. 2596·3).
Flatulence in irritable bowel syndrome.

Tuzzil *IQFA, Mex.*
Benzonatate (p. 1656·2).
Cough.

TV Gin *T Man, Thai.*
Mefenamic acid (p. 85·3).
Pain; inflammation.

TV Lone *T Man, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

TV Mox *T Man, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

T-Vac *Serum Institute, Philipp.*
A tetanus toxoid (p. 2421·1).
Active immunisation.

T-Vites *Freeda, USA.*
Vitamins; minerals.

Twelve Resin-K *Key, USA.*
Vitamin B_{12} (p. 2107·2).

Twice *Angelini, Ital.*
⊗Morphine sulfate (p. 92·3).
Pain.

Twice-A-Day *Major, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Twilite *Pfeiffer, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Twina *T Man, Thai.*
⊗Clotrimazole (p. 576·2); betamethasone valerate (p. 1624·1).
Inflammatory skin disorders.

Twinject *Paladin, Canad.; Shionogi, Cz.; Shionogi, Port.*
⊗Adrenaline (p. 1292·1).
Anaphylaxis.

Twinkle Calamine *Pharmaniaga, Malaysia.†*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).
Dermatitis.

Twinline *Otsuka, Jpn.*
Preparation for enteral nutrition.

Twinrix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; Litha, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA; GSK, Venez.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p. 2391·3).
Separate preparations are available for infants and children and for adults.
Active immunisation.

TwinVisc *Zeiss Meditec, Ger.*
Sodium hyaluronate (p. 2526·2).
Aid in eye surgery.

Two Cal HN *Abbott, Austral.*
High calorie, high nitrogen preparation for enteral nutrition.

Abbott, Irl.
High-protein preparation for enteral nutrition.

Abbott, NZ.
Preparation for enteral nutrition.

Abbott, Mex.†
High-nitrogen preparation for enteral nutrition.

TwoCal HN *Abbott, Hong Kong; Abbott Nutrition, UK.*
Preparation for enteral nutrition.

Ross, USA.
High calorie, high nitrogen lactose-free preparation for enteral nutrition.

Two-Septol *Cyntfarm, Pol.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Twynsta *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Thai.*
Telmisartan (p. 1509·3); amlodipine besilate (p. 1304·1).
Hypertension.

Tyarena *Mepha, Switz.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Tyason *Combiphar, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Tyavax *Sanofi Pasteur, Fr.*
An inactivated hepatitis A and typhoid (Vi capsular polysaccharide) vaccine (p. 2392·1).
Active immunisation.

Tybikin *M & H, Thai.*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Tybost *Gilead, UK.*
Cobicistat (p. 2482·3).
HIV infection.

Tycod *Rafarm, Gr.*
Theophylline (p. 1229·3); guaifenesin (p. 1666·2).

Tycoytycoy *Bouzen, Arg.*
Povidone-iodine (p. 1767·1).
Disinfection.

Tycveolum *Europe Biofarm, Rus.*
Cucurbita oil (p. 2489·2).
Liver and biliary-tract disorders; gastritis; colitis; haemorrhoids; atherosclerosis; benign prostatic hyperplasia; skin disorders; burns; cervical disorders; periodontal disease.

Tydadex *Lennon, S.Afr.†*
Tolbutamide (p. 504·2).
Diabetes mellitus.

Tydamine *Aspen, S.Afr.*
Trimipramine maleate (p. 453·1).
Depression; nocturnal enuresis; obsessive-compulsive disorder.

Tyflen *Brasterapica, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Tygacil *Wyeth, Arg.; Pfizer, Austral.; Wyeth Lederle, Austria; Pfizer, Belg.; Wyeth, Braz.; Pfizer, Canad.; Wyeth, Chile; Pfizer, China; Wyeth, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; IFET (ΙΦΕΤ), Gr.; Pfizer, Gr.; Pfizer, Hong Kong; Wyeth, Hung.; Wyeth, Indon.; Pfizer, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Pfizer, Jpn; Wyeth, Malaysia; Wyeth, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Singapore; Wyeth, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Wyeth, Turk.; Pfizer, UK; Pfizer, Ukr.; Wyeth, USA; Wyeth, Venez.*
Tigecycline (p. 379·2).
Community-acquired pneumonia; intra-abdominal bacterial infections; bacterial skin and soft-tissue infections.

Tyglan *Pekana, Canad.†*
Calcium fluoride (p. 2053·1); conium maculatum (p. 2524·3); cytisus scoparius (p. 2611·3); goose grass (p. 2481·2); hawthorn (p. 2488·1); ivy (p. 2536·2); lophophytum leandri; magnesium carbonate (p. 1856·2).
Homoeopathic preparation.

Tyhofen *Pharmahof, Thai.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Tykerb *GSK, Austral.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Hong Kong; GSK, Indon.; GSK, Israel; GSK, Jpn; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Philipp.; GSK, Singapore; GSK, Thai.; GSK, Turk.; GSK, USA.*
Lapatinib tosilate (p. 815·1).
Breast cancer.

Tyklid *Torrent, India.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Tylalgin *Geolab, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Tylalgin Caf *Geolab, Braz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).

Tylecetamol *Sandoz, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Tylenol *Johnson & Johnson, Braz.; McNeil Consumer, Canad.; Johnson & Johnson, China; Johnson & Johnson, Gr.; Johnson & Johnson Consumer, Mex.; Johnson & Johnson, Neth.; Johnson & Johnson, Philipp.; Johnson & Johnson, Port.; Johnson & Johnson, S.Afr.; Johnson & Johnson, Singapore; Johnson & Johnson, Spain†; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Johnson & Johnson, Thai.; McNeil Consumer, USA; Johnson & Johnson, Venez.*
Paracetamol (p. 115·1).
Pain; fever.

Tylenol Allergy *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Allergic rhinitis.

Tylenol Allergy Complete Multi-Symptom *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Formerly known as Tylenol Allergy Sinus Maximum Strength.
Upper respiratory-tract symptoms.

Tylenol Allergy Complete NightTime *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Formerly known as Tylenol Allergy Sinus NightTime Maximum Strength.

Tylenol Allergy Multi-Symptom *McNeil Consumer, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Tylenol Allergy Sinus *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Sinus pain and congestion; allergy symptoms.

Tylenol Allergy Sinus Day & Night *McNeil, USA.*
⊗Day capsules, pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); night capsules, pseudoephedrine hydrochloride; diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Tylenol Allergy Sinus Nighttime *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergy symptoms; sinus pain and congestion.

Tylenol Arthritis Pain *McNeil Consumer, Canad.; Janssen-Cilag, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Tylenol Back Pain *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); methocarbamol (p. 2025·3).

Tylenol Chest Congestion Daytime *McNeil Consumer, USA.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2).
Upper respiratory-tract disorders.

Tylenol Children's Cold *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Tylenol Childrens Cold & Cough Nighttime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough.

Tylenol Children's Cold Plus Cough *McNeil Consumer, USA.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Tylenol Childrens Cough & Runny Nose *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold symptoms; cough.

Tylenol Childrens Plus Cold Nighttime *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold symptoms.

Tylenol Childrens Plus Flu *McNeil Consumer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Tylenol Childrens Plus Multi-Symptom Cold *McNeil Consumer, USA.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Tylenol with Codeine *Janssen, Canad.; McNeil Consumer, Canad.; Janssen-Cilag, Thai.; Janssen, USA.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Tylenol with Codeine No 4 *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Tylenol with Codeine No 2 or Tylenol with Codeine No 3 *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain; fever.

Tylenol Cold *Janssen-Cilag, Thai.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms.

Johnson & Johnson, China.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms; cough.

Tylenol Cold Complete Formula *McNeil Consumer, USA.*
⊗Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Coughs and cold symptoms.

Tylenol Cold Daytime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Formerly contained paracetamol, pseudoephedrine hydrochloride, and dextromethorphan hydrobromide.
Cold symptoms; cough.

Tylenol Cold DM *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms.

Tylenol Cold & Flu
Note: this name may be used for preparations of different composition.
Janssen-Cilag, S.Afr.†
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; allergic rhinitis.

Tylenol Cold and Flu Daytime *McNeil Consumer, Canad.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Tylenol Cold and Flu Nighttime *McNeil Consumer, Canad.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Tylenol Cold Infant's *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; allergy symptoms.

Tylenol Cold Nighttime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Formerly contained paracetamol, chlorphenamine maleate, pseudoephedrine hydrochloride, and dextromethorphan hydrobromide.
Cold symptoms.

Tylenol Cold Non-Drowsy *McNeil Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Tylenol Cold Rapid Release *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Tylenol Cold Severe Congestion *McNeil Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs and cold symptoms.

Tylenol Cold & Sinus Daytime *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Tylenol Cold & Sinus Nighttime *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).

Tylenol Complete Cold Cough & Flu *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).

Tylenol Cough *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; sore throat; pain; fever.

Tylenol DC *Johnson & Johnson, Braz.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Tylenol Flu Daytime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1).
Formerly contained paracetamol, pseudoephedrine hydrochloride, and dextromethorphan hydrobromide.
Influenza symptoms; cough.

Tylenol Flu Maximum Strength *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Tylenol Flu Maximum Strength Non-Drowsy *McNeil Consumer, USA.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Tylenol Flu NightTime
Note: this name may be used for preparations of different composition.
McNeil Consumer, USA.
⊗Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Tylenol Flu Nighttime
Note: this name may be used for preparations of different composition.
McNeil Consumer, Canad.
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Influenza symptoms; cough.

Tylenol Flu Nighttime Gelcap *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); diphenhydramine hydrochloride (p. 626·2).
Influenza symptoms.

Tylenol Infants Drops Plus Cold *McNeil Consumer, USA.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Pain; fever; congestion.

Tylenol Menstrual *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1); mepyramine maleate (p. 635·1).
Premenstrual syndrome.

Tylenol Muscle Aches & Body Pain *McNeil Consumer, Canad.*
Paracetamol (p. 115·1).
Pain; fever.

Tylenol Night Pain *Janssen-Cilag, S.Afr.†*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia with pain.

Tylenol No 1 *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain.

Tylenol Plus Cold & Cough Infants *McNeil, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Formerly known as Tylenol Infants Cold Decongestant & Fever Reducer Plus Cough.
Cough; cold symptoms.

Tylenol PM *Johnson & Johnson, China; Johnson & Johnson, S.Afr.†*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia with pain.

Tylenol PM Extra Strength *McNeil Consumer, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Insomnia.

Tylenol Severe Allergy *McNeil Consumer, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity symptoms.

Tylenol Sinus
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Braz.
⊗Paracetamol (p. 115·1); pseudoephedrine (p. 1676·1).

Johnson & Johnson Consumer, Mex.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Rhinitis; rhinopharyngitis; respiratory-tract congestion.

McNeil Consumer, Canad.
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinusitis; cold symptoms.

Tylenol Sinus Children's *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion; sinusitis.

Tylenol Sinus Congestion & Pain Nighttime Caplets *McNeil Consumer, USA.*
Phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Tylenol Sinus Congestion & Pain Severe Daytime Caplets *McNeil Consumer, USA.*
Phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Tylenol Sinus Daytime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Sinusitis.

Tylenol Sinus (Daytime Relief) *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinusitis; cold symptoms.

Tylenol Sinus Nighttime *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Sinusitis.

Tylenol Sinus (Nighttime Relief) *McNeil Consumer, Canad.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3).
Sinusitis; cold symptoms.

Tylenol Sinus Non-Drowsy *McNeil Consumer, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Upper respiratory-tract symptoms.

Tylenol Sinus Pain and Congestion Daytime *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).
Sinusitis; cold symptoms.

Tylenol Sinus Pain and Congestion Nighttime *McNeil Consumer, Canad.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Sinusitis.

Tylenol Sore Throat Daytime *McNeil Consumer, USA.*
Paracetamol (p. 115·1).
Sore throat.

Tylenol Sore Throat Nighttime *McNeil Consumer, USA.*
Diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1).
Sore throat.

Tylenol Ultra Relief *McNeil Consumer, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Tylephen *IQB, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Tyler Prenatal *Integrative, USA.*
Vitamins; minerals; citrus bioflavonoids (p. 2505·2); choline (p. 2055·2); betaine hydrochloride (p. 2456·1); inositol (p. 2533·2); glutamic acid (p. 2070·2); hesperidin (p. 2505·2); rutoside (p. 2505·3).
Dietary supplement.

Tylex
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Braz.; Schwarz, Irl.; UCB, UK.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol 30/500.
Pain.

Janssen-Cilag, Mex.; Janssen-Cilag, Venez.
Paracetamol (p. 115·1).
Pain; fever.

Tylex CD *Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Fever; pain.

Tylex Flu *Janssen-Cilag, Mex.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Tylidol *Teuto, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Tylofen Hot *Nobel, Ukr.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Tylol *Nobel, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Tylol Cold *Nobel, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Tylol Hot *Nobel, Turk.; Nobel, Ukr.†*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion; cold and influenza symptoms.

Tylol Plus *Nobel, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Fever; pain.

Tylonic *Metiska, Indon.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Tylox *Ortho McNeil, USA.*
⊗Oxycodone hydrochloride (p. 113·1); paracetamol (p. 115·1).
Pain.

Tymedon *Ace, Philipp.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; colostomy or ileostomy management.

Tymol *Pharmaland, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Tymsal *Herbapol Krakow, Pol.*
Sage (p. 2608·3); thyme (p. 2630·2).
Upper respiratory-tract disorders.

Tyneo *Neo Quimica, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Tynostan *Gruppo Medica, Philipp.*
Mefenamic acid (p. 85·3).
Fever; musculoskeletal and joint disorders; pain.

Tyoflex *Abdi, Turk.*
Thiocolchicoside (p. 2026·2).

Ty-oxone *Geofman, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Typanol *Pharmahof, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Typbar *Bharat, Thai.*
A typhoid vaccine (Vi capsular polysaccharide) (p. 2422·2).
Active immunisation.

Typherix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong†; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; Smith Kline & French, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, UK.*
A typhoid vaccine (Vi capsular polysaccharide) (p. 2422·2).
Active immunisation.

Typhiclor *Vysali, Philipp.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Typhim *Aventis Pasteur, Turk.†*
A typhoid vaccine (Vi capsular polysaccharide) (p. 2422·2).
Active immunisation.

Typhim Vi *Sanofi Pasteur, Arg.; Sanofi Pasteur, Austral.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, China; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Cadila, India; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Aventis Pasteur, UK; Sanofi Pasteur, USA.*
A typhoid vaccine (Vi capsular polysaccharide) (p. 2422·2).
Active immunisation.

Typhoral *Sanofi-Aventis, India.*
An oral typhoid vaccine (attenuated Ty21a Berna strain) (p. 2422·2).
Active immunisation.

Typhoral L *Novartis Vaccines, Ger.*
A live oral typhoid vaccine (p. 2422·2).
Active immunisation.

Typh-Vax *CSL, NZ.*
An oral typhoid vaccine (attenuated Ty21a Berna strain) (p. 2422·2).
Active immunisation.

Typofen *Kleva, Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

TYR *Nutricia, Ital.*
Food for special diets.
Tyrosinaemia.

TYR Anamix *Nutricia, Austral.*
Food for special diets.
Formerly known as Xphen, Tyr Analog.
Tyrosinaemia.

SHS, Irl.
Infant feed.
Tyrosinaemia.

Tyr Anamix *Nutricia, Fr.*
Food for special diets.
Tyrosinaemia.

TYR 1and 2 *Nutricia-Bago, Arg.*
Food for special diets.
Metabolic disorders.

TYR Express *Vitaflo, UK.*
Food for special diets.
Tyrosinaemia.

Tyran *Pyridam, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Tyrazol *Orion, Fin.*
Carbimazole (p. 2334·3).
Hyperthyroidism.

Tyrenol *Remedina, Gr.*
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Tyrex *Ross, USA.*
Phenylalanine- and tyrosine-free preparation for enteral nutrition.
Tyrosinaemia types I, II, and III.

Tyrex Dermose *Coup, Gr.*
Tyrothricin (p. 384·1).

Tyricine *Christo, Hong Kong.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Bacterial mouth and throat infections.

Tyricten *Novagen, S.Afr.*
Tenofovir disoproxil fumarate (p. 1018·1); emtricitabine (p. 976·3).

Tyrocaine *Synco, Hong Kong†; Synco, Singapore.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders; mouth and throat infections.

Tyrodone *Major, USA.*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).

Tyro-Drops *Nycomed, Belg.†*
Tyrothricin (p. 384·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

TyroMILBE *Bencard, Ger.*
House-dust mite allergen extracts (p. 2434·3).
Allergen immunotherapy.

Tyroqualine *Spirig, Switz.*
Tyrothricin (p. 384·1); dequalinium chloride (p. 1749·3); lidocaine hydrochloride (p. 1988·2).
Mouth and throat disorders.

Tyros *Mead Johnson, Fr.*
Food for special diets.
Tyrosinaemia; alkaptonuria.

Tyrosin TU *Bencard, Ger.*
Mixed allergen extracts (p. 2434·3).
Allergen immunotherapy.

Tyrosum *Summers, USA.*
Skin cleanser.

Tyrosur *Engelhard, Ger.; Engelhard, Hung.*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1).
Infected wounds; infected skin disorders.

Engelhard, Ger.; Engelhard, Ukr.
Tyrothricin (p. 384·1).
Infected wounds and burns; infected skin disorders.

Tyrothricin *Streuli, Switz.†*
Tyrothricin (p. 384·1); ethacridine lactate (p. 1732·3); lidocaine hydrochloride (p. 1988·2); menthol (p. 2553·2); mint oil (p. 2560·1).
Mouth and throat disorders.

Tyrothricin Co *Jean-Marie, Hong Kong.*
Tyrothricin (p. 384·1); codeine phosphate (p. 40·2); benzocaine (p. 1980·2).
Sore throat.

Tyrothricin comp *Sigmapharm, Austria.*
Lozenges: Tyrothricin (p. 384·1); neomycin sulfate (p. 330·1); benzalkonium chloride (p. 1737·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Tyrothricine + Gramicidine *Vifor, Switz.†*
Tyrothricin (p. 384·1); gramicidin (p. 308·3); tetracaine hydrochloride (p. 1996·3); benzethonium chloride (p. 1738·1).
Mouth and throat disorders.

Tyrozets *McNeil Healthcare, Irl.; Johnson & Johnson MSD Consumer, UK.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2).
Mouth and throat disorders.

Tysabri *Biogen, Austral.; Elan, Austria; Biogen, Belg.; Biogen, Braz.; Biogen, Canad.; Elan, Cz.; Elan, Denm.; Biogen, Fr.; Biogen, Ger.; Elan, Gr.; Elan, Hung.; Biogen, Irl.; Biogen, Israel; Biogen Dompe, Ital.; Biogen Idec, Neth.; Elan, Norw.; Biogen, NZ; Elan, Pol.; Biogen, Port.; Biogen, Spain; Biogen, Swed.; Biogen, Switz.; Biogen, UK; Biogen, USA.*
Natalizumab (p. 2567·2).
Multiple sclerosis; Crohn's disease.

Tystatin *TO-Chemicals, Thai.*
Nystatin (p. 590·3).
Intestinal and oral candidiasis.

Tytin *Wockhardt, India.*
Tyrothricin (p. 384·1); benzocaine (p. 1980·2); phenazone (p. 124·1); hexylresorcinol (p. 1755·1).
Ear infections; inflammatory ear disorders; otorrhoea.

Tyvaso *Rafa, Israel.*
Treprostinil sodium (p. 1518·1).
Pulmonary hypertension.

United Therapeutics, USA.
Treprostinil (p. 1518·1).
Pulmonary hypertension.

Tyvera *Auden McKenzie, UK.*
Thiamine hydrochloride (p. 2103·1).
Thiamine deficiency.

Tyverb *GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK; GSK, Ukr.*
Lapatinib tosilate (p. 815·1).
Breast cancer.

Tyzeka *Novartis, USA.*
Telbivudine (p. 1017·2).
Chronic hepatitis B.

Tyzine *Pfizer, Hung.†; Pfizer, Rus.; McNeil, Ukr.; Kenwood, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion; rhinitis; pharyngitis; sinusitis.

Tyzine Xylo *Johnson & Johnson, Rus.; McNeil, Ukr.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinitis; sinusitis; otitis media.

T-ZA *Siam Bheasach, Thai.†*
Zidovudine (p. 1024·2).
HIV infection.

Tzarevet X *CTS, Israel.*
Calcium carbonate (p. 1824·3).
Calcium supplement; antacid.

TZM *TO-Chemicals, Thai.†*
Pyrazinamide (p. 345·2).
Tuberculosis.

U10 *2M, Thai.*
⊗Urea (p. 1727·3).
Dry skin.

U20 *2M, Thai.*
⊗Urea (p. 1727·3).
Dry skin.

U Lactin *Cosmofarma, Port.†*
⊗Urea (p. 1727·3); alpha hydroxy acids (p. 1704·3).
Dry skin disorders.

UAA *Econo Med, USA.*
Methenamine (p. 322·3); salol (p. 129·3); atropine sulfate (p. 1310·2); hyoscyamine sulfate (p. 1848·1); benzoic acid (p. 1738·2); methylthioninium chloride (p. 1559·1).
Urinary-tract infections.

UAD-Otic *UAD, USA.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Bacterial ear infections.

U-Amox *United Drug, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Ubenzima *Pentafarma, Port.*
Ubidecarenone (p. 2637·1).
Heart failure; prevention of cardiotoxicity associated with anthracyclines.

Ubicoenzyme *Heel, Canad.*
Beta vulgaris; cerium oxalicum (p. 1826·2); acidum citricum (p. 2480·3); hydrastis canadensis (p. 2528·1); alpha lipoicum acidum (p. 2629·1); nadidum (p. 2567·1); calcium carbonicum (p. 1824·3); selenium (p. 2086·3); silicea (p. 2208·3); succinicum acidum (p. 2214·3); sulfur (p. 1721·1); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Ubicor
Note: this name may be used for preparations of different composition.
Magis, Ital.
Ubidecarenone (p. 2637·1).
Coenzyme Q10 deficiency.

Ubidenone *Esseti, Ital.†*
Ubidecarenone (p. 2637·1).
Coenzyme Q10 deficiency; cardiac disorders.

Ubidex *OFF, Ital.†*
Ubidecarenone (p. 2637·1).
Coenzyme Q10 deficiency; cardiac disorders.

Ubimaior *Chiesi, Ital.*
Ubidecarenone (p. 2637·1).
Coenzyme Q10 deficiency.

Ubi-Q *Eisai, Indon.; Fourtts, Singapore.*
Ubidecarenone (p. 2637·1).
Antoxidant; nutritional supplement.

Ubistesin *Espe, Austria; 3M Espe, Cz.; 3M, Denm.; 3M, Fin.; 3M, Ger.; 3M Espe, Gr.; 3M Espe, Hong Kong; 3M, Hung.; 3M, Israel; 3M Espe, Ital.; 3M, Neth.; 3M, NZ; 3M, Port.; 3M, Rus.; iNova, Singapore; 3M, Spain; 3M, Swed.; 3M, Switz.*
Articaine hydrochloride (p. 1980·1).
Adrenaline (p. 1292·1) or adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ubistesin Adrénalinée *3M, Fr.*
Articaine hydrochloride (p. 1980·1).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ubit *Otsuka, Fr.†; Otsuka, Port.*
Carbon-13 urea (p. 2470·3).
Diagnosis of Helicobacter pylori infection.

Ubiten *Labomed, Chile.*
Levocarnitine (p. 2053·2); ubidecarenone (p. 2637·1); magnesium (p. 1786·3); vitamin C (p. 2110·3); aspartic acid (p. 2050·3).
Dietary supplement.

Ubizol *Alter, Port.*
⊗Fluticasone propionate (p. 1638·1).
Skin disorders.

Ubretid *Nycomed, Cz.; Takeda, Ger.; IFET (ΙΦΕΤ), Gr.; Nycomed, Gr.; Nycomed, Hong Kong; Takeda, Neth.; Nycomed, Pol.; Nycomed, Rus.; Takeda, Singapore; Takeda, Switz.; Sanofi, UK.†*
Distigmine bromide (p. 685·3).
Myasthenia gravis; urinary incontinence; urinary retention; postoperative ileus; postoperative bladder atony; postoperative gastrointestinal atony; neurogenic bladder; atonic constipation.

UBTest *Otsuka, Neth.†*
Carbon-13 (p. 2470·3) labelled urea.
Diagnosis of Helicobacter pylori *infection.*

Ubtest *Otsuka, Spain.*
Carbon-13-labelled urea (p. 2470·3).
Test for Helicobacter pylori *infection.*

Ucalm *Natures Aid, UK.*
St John's wort (p. 449·1).
Low mood; anxiety.

UCD *Support, Braz.; Nutricia, Ital.*
Food for special diets.
Hyperammonaemia; argininosuccinic aciduria; citrullinaemia; hyperargininaemia; ornithinaemia; urea cycle disorders.

UCD 1 and 2 *Nutricia-Bago, Arg.*
Food for special diets.
Metabolic disorders.

Ucecal *UCB, Austria; UCB, Gr.; UCB, Turk.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis; Paget's disease of bone; hypercalcaemia of malignancy; hypercalcaemia.

Ucemine PP *Pierre Fabre Sante, Belg.*
Nicotinamide (p. 2083·1).
Nicotinamide deficiency.

Ucephan *Ucyclyd, USA.†*
Sodium benzoate (p. 1738·2); sodium phenylacetate (p. 2619·2).
Hyperammonaemia.

Ucerax *UCB, Irl.; UCB, UK.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; agitation; premedication; pruritus.

Uceris *Santarus, USA.*
⊗Budesonide (p. 1625·1).
Ulcerative colitis.

Ucetal *Serral, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

UCG-Slide *Wampole, USA.*
Pregnancy test (p. 2596·1).

Ucholine *M & H, Thai.*
Bethanechol chloride (p. 2456·2).
Urinary retention; neurogenic bladder.

U-Closone *Hoe, Malaysia; Hoe, Thai.*
⊗Clobetasone butyrate (p. 1627·3).
Skin disorders.

U-Cort
Note: this name may be used for preparations of different composition.
Taro, USA.
⊗Hydrocortisone acetate (p. 1640·1).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ucort
Note: this name may be used for preparations of different composition.
YSP, Malaysia; Yung Shin, Singapore.
⊗Urea (p. 1727·3); hydrocortisone acetate (p. 1640·1).
Skin disorders.

Udamin *Poly, USA.*
Vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin E substances (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1); folic acid (p. 2063·1); lycopene complex (p. 2546·2).
Dietary supplement.

Udamin SP *Poly, USA.*
Vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3); vitamin E substances (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1); folic acid (p. 2063·1); lycopene complex (p. 2546·2); saw palmetto (p. 2363·3).
Dietary supplement.

UDC *Hexal, Ger.†*
Ursodeoxycholic acid (p. 2638·1).
Biliary disorders; dyspepsia; cholesterol gallstones.

UDCA *Ferring, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Liver and biliary-tract disorders; gallstones.

Udderly Smooth *Redex, USA.*
Emollient.

Udesogel *Angelini, Gr.*
⊗Budesonide (p. 1625·1).
Skin disorders.

Udesospray *Angelini, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

U-Diclox *Utopian, Thai.*
Dicloxacillin sodium (p. 286·1).
Staphylococcal infections.

Udihep *Win-Medicare, Thai.†*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders; dyspepsia; hepatitis.

Udiliv *Solvay, India.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; cholestatic liver disease.

Udima *Dermapharm, Austria; Dermapharm, Ger.*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Udocaine *Umeda, Thai.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias; local anaesthesia.

Udolac *Norma (Νορμα), Gr.*
Sulindac (p. 134·2).

Udolin *Rafarm, Gr.*
Sisomicin sulfate (p. 357·2).
Bacterial infections.

Udopa *Dipa, Indon.*
Dopamine hydrochloride (p. 1367·2).
Heart failure; hypotension; shock.

Udopar-250 *Pond's, Thai.*
Levodopa (p. 902·2); benserazide (p. 894·1).

Udoxan *CCM, Malaysia.*
Oxytocin (p. 2143·1).
Postpartum atony; postpartum hemorrhage; labour induction.

Udrik *Abbott, Ger.*
Trandolapril (p. 1517·2).
Hypertension; heart failure following myocardial infarction.

Udzapen *Terramedic, Philipp.†*
Ketoprofen (p. 79·1).
Osteoarthritis; rheumatoid arthritis; pain.

U-Enema *Unison, Thai.*
Sodium chloride (p. 1795·1).
Constipation; bowel evacuation.

Ufarene *Proel, Gr.*
Sucralfate (p. 1889·1).

Ufarin *Bayer, Chile.*
Isoconazole nitrate (p. 583·2).
Fungal skin infections; fungal and Gram-positive bacterial vaginal infections.

Ufexil *Demo, Gr.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Demo, Israel; Multichem, NZ.
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Uflahex *Hexal, Philipp.†; Salutas, Philipp.†*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Ufocard *Proel, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Ufocollyre *Proel, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Ufonitren *Novendia, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ufor *Valdecasas, Mex.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastric hyperacidity.

Ufoxillin *Proel, Gr.*
Cefaclor (p. 232·3).
Bacterial infections.

UFT *Merck, Arg.; Merck, Austria; Merck, Belg.; BMS, Braz.; Merck, Cz.†; Orifarm, Denm.; Merck Serono, Fr.; Merck Serono, Ger.; Merck, Gr.; Merck Serono, Hong Kong†; Merck, Hung.†; Merck Serono, Irl.†; Merck Serono, Israel; Merck Serono, Ital.; Taiho, Jpn; Merck Serono, Malaysia; Merck, Mex.; Merck, Neth.; Merck, Norw.†; Merck, Philipp.; Merck, Pol.; Merck, Port.; Nycomed, Rus.; Merck, S.Afr.; Taiho, Singapore; Merck, Spain†; Merck, Swed.†; Merck, Thai.†; Merck, Turk.*
Tegafur (p. 864·2); uracil (p. 2637·3).
Malignant neoplasms.

Uftoral *Merck, Denm.†; Merck Serono, UK.†*
Tegafur (p. 864·2); uracil (p. 2637·3).
Colorectal cancer.

UFUR *American Taiwan, Thai.*
Tegafur (p. 864·2); uracil (p. 2637·3).
Breast cancer; gastric cancer; colorectal cancer.

U-Gesic Balm *Utopian, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2); peppermint oil (p. 1877·1); turpentine oil (p. 2636·3).
Musculoskeletal and joint pain.

Ugetin *Demo, Gr.*
Pilocarpine nitrate (p. 2010·3).

Ugotrex *Alapis, Gr.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Ugurol *Rottapharm, Ital.*
Tranexamic acid (p. 1164·2).
Haemorrhagic disorders.

UGX *Healthcomm, Canad.†*
Vitamins; minerals.

Ukase Dermo *Farmagal, Arg.*
Sulfur (p. 1721·1); resorcinol (p. 1718·3); zinc oxide (p. 1729·1); vitamin A palmitate (p. 2098·3).
Acne; seborrhoea.

Ukase Lulitis *Farmagal, Arg.*
Soya oil (p. 2092·3); collagen (p. 2483·2); vitamin E acetate (p. 2119·2); marine algae; ivy (p. 2536·2); vitamin A palmitate (p. 2098·3); vitamin D (p. 2112·3).

Ukel *Gray, Arg.†*
Midazolam maleate (p. 1085·2).

Ukidan *Serono, Fr.; Serono, Gr.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

UL 250 *Merck, Port.*
Saccharomyces boulardii (p. 2596·3).
Restoration of normal gastrointestinal flora.

U-Lactin *Fischer, Israel; Allerderm, Singapore.†*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).
Dry, hyperkeratotic skin disorders.

U-Lactin Foot Cream *Fischer, Israel.*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Dry skin disorders of the foot.

Ulax-C *Ultra, Mex.*
⊗Salbutamol sulfate (p. 1220·2); ambroxol hydrochloride (p. 1654·3).
Obstructive airways disease.

Ulax-F *Ultra, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Ulcacin *Utopian, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Ulcaid
Note: this name may be used for preparations of different composition.
Ranbaxy, Austral.; Ranbaxy, S.Afr.†
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity; heartburn.

Ulcar *Sanofi-Aventis, Fr.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Ulceclar *Amnol, Ital.*
Cream: Thioctic acid (p. 2629·1); unsaturated fatty acids; β-bisabolol; zinc oxide (p. 1729·1).
Amnol, Ital.
Dressing: Hyaluronic acid (p. 2526·2); echinacea (p. 2498·1).
Wound healing.

Ulcedin
Note: this name may be used for preparations of different composition.
AGIPS, Ital.
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulcedine *Sanofi-Aventis, Braz.; UAP, Indon.†; Great Eastern, Thai.†; Westmont, Thai.†*
Cimetidine (p. 1827·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; systemic mastocytosis.

Ulcedrug *EuroHealth, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer; acid aspiration.

Ulcefam *Unison, Philipp.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcefate *Siam Bheasach, Thai.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; mucositis.

Ulcefor *Elofar, Braz.†*
Omeprazole (p. 1867·2).
Peptic ulcer.

Ulcegel *TO-Chemicals, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; heartburn.

Ulcelac *Bago, Arg.*
Famotidine (p. 1842·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Bago, Chile.†
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcemed *Medica Korea, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcemet *TO-Chemicals, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulcemex *Lafi, Chile.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux.

Ulcened *Euroned, Gr.*
Pantoprazole sodium (p. 1875·3).

Ulcenol *Elmor, Venez.*
Famotidine (p. 1842·1).
Gastritis; oesophagitis; peptic ulcer; Zollinger-Ellison syndrome.

Ulcenon *Legrand, Braz.; Unison, Philipp.†*
Cimetidine (p. 1827·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastritis.

Ulcepac *Myung In, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ulcepraz *Invida, Philipp.*
Pantoprazole (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer.

Ulcerac *Delta, Braz.†*
Cimetidine (p. 1827·1).
Peptic ulcer.

Ulceragon *Torrent, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulceral
Note: this name may be used for preparations of different composition.
Tedec Meiji, Spain.
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Vamsler, Philipp.†
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulceran
Note: this name may be used for preparations of different composition.
Medochemie, Malaysia; Medochemie, Rus.†; Medochemie, Singapore; Medochemie, Thai.
Famotidine (p. 1842·1).
Gastrointestinal haemorrhage; peptic ulcer; pathological hypersecretory disorders; Zollinger-Ellison syndrome.

Sandoz, Indon.
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux.

Teva, Hung.
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulceranin *Otto, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcerase *Smith & Nephew, Port.*
⊗Collagenase (p. 2484·1).
Burns; ulcers; wounds.

Ulcerease *Med-Derm, USA.*
Liquefied phenol (p. 1763·3).
Mouth and throat pain.

Ulcerfen *Finadiet, Arg.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulcergo *ACME, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Ulcerid *Lapi, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; Zollinger-Ellison syndrome; endocrine adenoma.

Ulceridina *Kinder, Braz.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ulcerin *Quality, Hong Kong.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome; short bowel syndrome.

Ulcerix *Oboi, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcerlmin *Chugai, Jpn.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Ulcermate *Jaba Recordati, Port.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; variceal haemorrhage.

Ulcermin *Jaba Recordati, Port.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage.

Ulcerocin *Cimed, Braz.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Ulceron *Anpharm (Ανφαρμ), Gr.*
Pantoprazole sodium (p. 1875·3).

Ulcertec *Tecnimede, Port.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

DHA, Malaysia†; DHA, Singapore.†
Sucralfate (p. 1889·1).
Peptic ulcer.

Ulcesep *Centrum, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Ulcestop
Note: this name may be used for preparations of different composition.
Diffucap, Braz.
Lansoprazole (p. 1851·3).

Ulcetab *Lennon, S.Afr.†*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Ulcetal *Colfarm, Pol.*
Hydrotalcite (p. 1845·2).
Peptic ulcer; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Ulcetrax *Salvat, Spain.*
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastric hyperacidity; gastro-oesophageal reflux.

Ulcevit *Bruluart, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Ulcex *Guidotti, Ital.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastritis or duodenitis associated with acid hypersecretion.

Ulcezol *SF, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Ulci-Cure *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer; acid aspiration.

Ulcid
Note: this name may be used for preparations of different composition.
Astellas, Irl.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Sandoz, Indon.
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; flatulence; dyspepsia; heartburn.

TO-Chemicals, Thai.†
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).
Gastric hyperacidity.

Ulcidine
Note: this name may be used for preparations of different composition.
Valeant, Canad.
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Spirig, Switz.†
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; dyspepsia.

Ulcim *Quatromed, S.Afr.†*
Cimetidine hydrochloride (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage.

Ulcimax *Cipla, India.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulcimer *Labesfal, Port.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Ulcimet *Farmasa, Braz.; Polipharm, Thai.*
Cimetidine (p. 1827·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcin
Note: this name may be used for preparations of different composition.
Biolab, Philipp.
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcinax *Neo Quimica, Braz.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Ulcine *Pharmahof, Thai.†*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Ulcinil *Farmoz, Port.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Ulciram *Vargas, Venez.*
Sucralfate (p. 1889·1).
Gastro-oesophageal reflux; peptic ulcer.

Ulcitrat *Bunker, Braz.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Ulcizole *Volta, Chile.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulco *TO-Chemicals, Thai.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Ulco-cyl L Ho-Len-Complex *Liebermann, Ger.*
Acidum nitricum (p. 2572·3); belladonna (p. 2453·3); carbo animalis; hydrastis (p. 2528·1); kreosotum (p. 1659·3); thuja (p. 2629·3).
Homoeopathic preparation.

Ulcoderma *Abbott, Mex.†*
⊗Collagenase (p. 2484·1); chloramphenicol (p. 257·1).
Skin ulcers; burns; wounds.

Ulcodin *Alkaloid, Rus.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration.

Ulcogant *Merck, Austria; Merck, Belg.†; Merck, Cz.; Merck Serono, Ger.; Merck, Hung.; Merck, Neth.; Merck, Switz.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastrointestinal haemorrhage.

Ulcogastrin *Zekides, Gr.*
Nizatidine (p. 1866·1).
Peptic ulcer.

Ulcogranil *Medichrom, Gr.*
Cimetidine (p. 1827·1).

Ulcoid *Valdecasas, Mex.*
Diphenhydramine hydrochloride (p. 626·2).
Hypersensitivity; sleep disorders.

Ulcomet
Note: this name may be used for preparations of different composition.
Medochemie, Hong Kong.
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration; gastric hypersecretion; gastrointestinal haemorrhage; adjunct in pancreatic insufficiency.

Pharmathen, Gr.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; acid aspiration; pathological gastric hypersecretion.

Ulcometin *Ratiopharm, Austria.†*
Cimetidine (p. 1827·1) or cimetidine hydrochloride (p. 1827·1).
Gastrointestinal haemorrhage; acid aspiration; hypersensitivity reactions; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulcon *Farma, Venez.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer; gastro-oesophageal reflux.

Ulcoreks *Bilim, Turk.*
Pantoprazole (p. 1875·3).

Ulcoren *Medley, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcosan *Teva, Cz.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Ulcosin *Ivax, Hung.†*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcostad *Stada, Austria.*
Cimetidine (p. 1827·1) or cimetidine hydrochloride (p. 1827·1).
Gastrointestinal haemorrhage; acid aspiration; hypersensitivity reactions; peptic ulcer; gastro-oesophageal reflux disease; Zollinger-Ellison syndrome.

Ulcotenal *Nycomed, Spain.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflex; Zollinger-Ellison syndrome.

Ulcotenk *Biotenk, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcourona *Neuropharma, Arg.*
Idebenone (p. 392·3).
Cerebrovascular disorders.

Ulc-Out *Raffo, Chile.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcozol *Bago, Arg.; Mibe, Ger.; Bago, Rus.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; heartburn.

Ulcrafate *Polipharm, Thai.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; gastritis.

Ulcrast *Boniscontro & Gazzone, Ital.*
Sucralfate (p. 1889·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulcratex *Recalcine, Chile.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer.

Ulcrux *Prater, Chile.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Ulcumaag *Pyridam, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis.

Ulcumet *Soho, Indon.*
Cimetidine (p. 1827·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastritis; duodenitis; gastrointestinal haemorrhage; gastro-oesophageal reflux.

Ulcuran *Fako, Turk.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; dyspepsia; gastritis; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Ulcusan
Note: this name may be used for preparations of different composition.
Kwizda, Austria.
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; stress-related ulcer; gastrointestinal haemorrhage; acid aspiration.

Pyridam, Indon.†
Cimetidine (p. 1827·1).
Peptic ulcer; pathological hypersecretory disorders.

Ulcusar *Umut, Turk.*
Famotidine (p. 1842·1).

Ulcyte *Alphapharm, Austral.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Uldapril *Collins, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Uldoral *Bago, Arg.*
Pantoprazole (p. 1875·3).
Peptic ulcer.

Ulesfia *Sciele, USA.*
Benzyl alcohol (p. 1739·3).
Pediculosis.

Ulfam *Soho, Indon.†*
Famotidine (p. 1842·1).
Peptic ulcer; pathological hypersecretory disorders.

Ulfamet *TO-Chemicals, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulfamid *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity; hiatus hernia.

Ulfaprim *Hexpharm, Indon.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ulfaret *Vianex (Βιανεξ), Gr.*
Cefsulodin sodium (p. 249·3).
Bacterial infections.

Ul-Flam *Ultra, Mex.*
Nimesulide (p. 101·3).
Fever; inflammation; pain.

Ulflex *Utopian, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Ulgafen *Jelfa, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Ulgamax *Jelfa, Pol.†*
Calcium carbonate (p. 1824·3); dimeticone (p. 1886·2); magnesium carbonate (p. 1856·2).
Gastric hyperacidity.

Ulgastran *Richter, Pol.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Ulgastrin
Note: this name may be used for preparations of different composition.
Biomep, Mex.
Ranitidine (p. 1882·1).
Peptic ulcer.

Diedenhofen, Thai.
Liquorice (p. 1853·2); bismuth subnitrate (p. 1822·1); aluminium sodium silicate (p. 1818·3); anhydrous sodium sulfate (p. 1888·1).
Peptic ulcer; gastritis; heartburn.

Ulgel *Dabur, India.*
Magaldrate (p. 1856·1); simeticone (p. 1886·2).
Gastric hyperacidity; gastritis; peptic ulcer; flatulence.

Liferpal, Mex.
Aluminium (p. 2439·2); magnesium (p. 1786·3); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

Ulgix *Hasco-Lek, Pol.*
Simeticone (p. 1886·2).
Excess gastrointestinal gas; aid in gastrointestinal investigation.

Ulgut *Shionogi, Jpn.*
Benexate hydrochloride betadex (p. 1821·1).
Peptic ulcer; gastritis.

Ulis *SF, Ital.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

U-Lite *Winwa, Malaysia.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); sodium citrate (p. 1781·2); tartaric acid (p. 2626·1).
Urinary tract infections; renal calculi.

Ulkodin *Precimex, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; Zollinger-Ellison syndrome.

Ulmarin *Precimex, Mex.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Ulmely *Ultra, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; bulimia nervosa; premenstrual dysphoric disorder.

Ulmicy *Ultra, Mex.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Ulmo *Pyridam, Indon.*
Famotidine (p. 1842·1).
Duodenal ulcer; pathological hypersecretory disorders.

Ulmodhyl *Sons, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; acid aspiration; gastrointestinal haemorrhage.

Ulnor *Sandoz, Ger.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulone *Graceway, Canad.*
Clofedanol hydrochloride (p. 1659·1).
Cough.

Uloric *Takeda, Canad.; Takeda, Jpn†; Takeda, USA.*
Febuxostat (p. 607·1).
Gout; hyperuricaemia.

Ulpafie *Ultra, Mex.*
Paracetamol (p. 115·1).
Fever; pain.

Ulpafie Compuesto *Ultra, Mex.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Allergic rhinitis; sinusitis; hay fever.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ulpafie-N *Ultra, Mex.*
Paracetamol (p. 115·1); naproxen (p. 98·2).
Fever; pain.

Ulpax *Hormona, Mex.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulpracid *Polipharm, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Ulpraz *Coronet, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulprazole *Polipharm, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulprix *Glenmark, Cz.; Actavis, Denm.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulran *Pasteur, Philipp.; KRKA, Rus.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration; dyspepsia.

Ulsafate *Combiphar, Indon.*
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Ulsal *Gebro, Austria.*
Ranitidine hydrochloride (p. 1882·1).
Stress-related ulcer; gastrointestinal haemorrhage; acid aspiration; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulsamet *Burapha, Thai.*
Cimetidine (p. 1827·1).
Peptic ulcer; acid aspiration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; heartburn; pancreatic insufficiency.

Ulsanic *Chugai, Hong Kong; Teva, Israel; Aspen Consumer, S.Afr.; Chugai, Thai.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Ulsanol *Nova Argentia, Arg.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulsaven *Collins, Mex.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; hyperchlorhydria.

Ulsek *Standard, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulsen *Senosiain, Mex.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; gastritis; peptic ulcer; Zollinger-Ellison syndrome.

Ulserral *Serral, Mex.*
Cimetidine (p. 1827·1).
Peptic ulcer.

Ulsicral *Ikapharmindo, Indon.; Ultra, Mex.*
Sucralfate (p. 1889·1).
Duodenal ulcer; peptic ulcer; gastritis.

Ulsidex *Dexa, Indon.*
Sucralfate (p. 1889·1).
Peptic ulcer.

Ulsikur *Hexpharm, Indon.*
Cimetidine (p. 1827·1).
Peptic ulcer; pathological hypersecretory disorders.

Ultac *Cipla, India.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; hypersecretory disorders; acid aspiration.

Ultacit *Sanofi-Aventis, Neth.*
Hydrotalcite (p. 1845·2).
Gastric hyperacidity.

Ultak *Cipla-Medpro, S.Afr.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ultane *Abbott, China; Abbott, S.Afr.; AbbVie, USA.*
Sevoflurane (p. 1912·3).
General anaesthesia.

Ultera *Actavis, Ukr.†*
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ulticadex *Rafarm, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Ulticer *Medreich, Hong Kong.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Ultidin
Note: this name may be used for preparations of different composition.
Gelcaps, Mex.
Famotidine (p. 1842·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Geolab, Braz.
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Ultiflox *Volta, Chile.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Ultilac N *Bittermedizin, Ger.*
Almasilate (p. 1815·3); calcium carbonate (p. 1824·3); skimmed milk powder.
Gastrointestinal disorders.

Ultilap *Ultra, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Ultilox *Coronet, Indon.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; gastro-oesophageal reflux; gastritis; flatulence.

Ultima *Sydenham, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3).

Ultimag *Mirren, S.Afr.*
Magnesium chloride (p. 1787·1); zinc oxide (p. 1729·1).
Magnesium and zinc supplement.

Ulti-mate *Orchid, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Ultimate *Ultimate, Turk.*
⊗Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); bromelain (p. 2460·3); Indian frankincense (p. 2507·3); manganese (p. 2081·2).

Ultimate OB DHA *Trigen, USA.*
Tablets, vitamins; trace elements; capsules, docosahexaenoic acid (p. 1460·1); vitamin E (p. 2119·1).

Ultimax *Hovid, Philipp.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Musculoskeletal pain.

Ultiva *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; AbbVie, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Bioniche, USA; GSK, Venez.*
⊗Remifentanil hydrochloride (p. 128·1).
Analgesia in anaesthesia; analgesia and sedation in mechanically ventilated patients; postoperative pain.

Ultizol *Vitae, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ultop *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastritis; dyspepsia.

Ultra A O *Douglas, Canad.*
Vitamins; minerals.

Ultra Adsorb *Lainco, Spain.*
Activated charcoal (p. 1537·3).
Diarrhoea; meteorism; flatulence.

Ultra Allergy Defense *Golden Glow, Austral.*
Horseradish (p. 2526·1); fenugreek (p. 2504·1); althaea (p. 2438·3); garlic (p. 2510·3); ascorbic acid (p. 2110·3).
Allergic disorders.

Ultra Balance *Douglas, Canad.*
A range of vitamin and mineral preparations.

Ultra Calm *Golden Glow, Austral.*
Ashwagandha (p. 2450·2); bacopa (p. 2452·1); Indian gooseberry (p. 2532·2); ocimum sanctum.
Anxiety; insomnia.

Ultra Calming *Johnson & Johnson, Canad.*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Ultra Chloraseptic *Prestige, UK.*
Gargle: Phenol (p. 1763·3).
Sore throat.

Prestige, UK.
Throat spray: Benzocaine (p. 1980·2).
Sore throat.

Ultra Clearasil *Boots, Philipp.†*
Benzoyl peroxide (p. 1696·1).
Acne.

Ultra Color Rich Cool Bliss *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Ultra Color Rich Mega Impact *Avon, Canad.†*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Ultra COQ10 *Twin Laboratories, Canad.†*
Ubidecarenone (p. 2637·1).

Ultra Corega *GSK, Arg.; GSK, Braz.†; Stafford-Miller, Braz.†; GSK Consumer, Venez.*
Denture fixative.

Ultra Correction *Chanel, Canad.*
SPF 10: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

Ultra Defense Spray *Energizer, Canad.*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Energizer, Canad.
SPF 60: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Defense Sunscreen Lotion *Energizer, Canad.*
SPF 15: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Energizer, Canad.
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Defense Sunscreen Stick *Energizer, Canad.†*
SPF 50: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Disc *Douglas, Canad.†*
Vitamins; minerals.

Ultra Facial Moisturizer *Kiehls, Canad.*
SPF 15: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Facial Tinted Moisturizer *Kiehls, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Ultra Headache Relief *Vita Health, Canad.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Ultra Heartburn Relief *Galpharm, UK.*
Famotidine (p. 1842·1).
Dyspepsia; heartburn.

Ultra Inflavogen *Healthcomm, Canad.†*
Vitamins; minerals.

Ultra Maintain Non-Dairy *Healthcomm, Canad.†*
Vitamins; minerals.

Ultra Mide *Ivax, USA.*
⊗Urea (p. 1727·3).
Dry skin; hyperkeratosis.

Ultra Mist Banana Boat Kids *Playtex, Canad.†*
SPF 50: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Ultra Mist Banana Boat Sports *Playtex, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Mist Banana Boat Ultra Clear *Playtex, Canad.†*
SPF 30: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Multi *Natural Factors, Canad.*
Vitamins; minerals.

Ultra One-A-Day *Da Vinci, Canad.†*
Vitamins; minerals.

Ultra Protection Sunscreen *Kiehls, Canad.*
SPF 25: Ensulizole (p. 1703·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Vichy, Canad.
SPF 60: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Ultra Quercitin *Jamieson, Canad.†*
Urtica (p. 2639·3); perilla fruit; quercetin (p. 2505·3).

Ultra Sheer *Johnson & Johnson, Canad.*
SPF 55; SPF 100; SPF 110: Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Sport *Norwood, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Norwood, Canad.†
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultra Strength D *Mason Natural, USA.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Ultra Strength Gas Relief *Banner, Canad.; Vita Health, Canad.*
Simeticone (p. 1886·2).
Flatulence.

Ultra Strength Ovol *Church & Dwight, Canad.*
Simeticone (p. 1886·2).
Flatulence.

Ultra Strength Pain Relieving Rub *G & W, Canad.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1).
Musculoskeletal and joint pain.

Ultra Strength Phazyme *GSK Consumer, Canad.*
Simeticone (p. 1886·2).
Flatulence.

Ultra Stress *Nutriforma, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Ultra Tears *Alcon, USA.†*
Hypromellose (p. 2189·2).
Dry eyes.

Ultra TechneKow *Mallinckrodt, Neth.*
Technetium-99m (p. 2228·1).
Diagnostic radionuclide scintigraphy.

Ultra Technekow *Mallinckrodt, Spain.*
Technetium-99m (p. 2228·1).
Diagnostic radionuclide scintigraphy.

Ultra TechneKow FM *Covidien, Belg.; Mallinckrodt, Irl.; Mallinckrodt, Port.*
Technetium-99m (p. 2228·1) as sodium pertechnetate.
Diagnostic radionuclide scintigraphy.

Ultra Technekow FM *BSM, Austria; Mallinckrodt, Cz.*
Technetium-99m as sodium pertechnetate (p. 2228·1).
Diagnostic radionuclide scintigraphy.

Ultra Vita Time *Nature's Bounty, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).

Ultra Vite Forte *GFR, Canad.†*
Vitamins; minerals.

Ultra-Adsorb *Lainco, Rus.*
Activated charcoal (p. 1537·3).
Dyspepsia; flatulence; poisoning; diarrhoea.

Ultrabalance *Healthcomm, Canad.†*
Vitamins; minerals.

Ultrabalance-Herbulk *Healthcomm, Canad.†*
Plantago seed (p. 2592·3).

Ultrabarit *Nutriforma, Turk.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Ultrabase *Bayer, UK.*
Emollient.
Pharmaceutical diluent; dry skin.

Ultrabeta *Vitoria, Port.*
⊗Salmeterol xinafoate (p. 1224·1).
Obstructive airways disease.

Ultrabiotic
Note: this name may be used for preparations of different composition.
Bago, Chile.
Mupirocin (p. 327·2).
Bacterial skin infections; infected burns and wounds.

Montpellier, Arg.
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ultrabiotic Duo *Montpellier, Arg.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Ultrabiotique *Nutrisante, Fr.*
Lactococcus lactis (p. 2596·3); *Lactobacillus casei* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3).
Restoration of gastrointestinal flora.

ULTRAbrom *WE, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); brompheniramine maleate (p. 618·1).
Upper respiratory-tract symptoms.

Ultrac *Tecnofarma, Chile.*
⊗Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); deanol tartrate (p. 2319·1).
Dietary supplement; tonic.

Ultrac E *Tecnofarma, Chile.*
⊗Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); deanol tartrate (p. 2319·1).
Dietary supplement; tonic.

Ultrac Q10 *Tecnofarma, Chile.*
Vitamins; minerals; ginseng (p. 2513·3); rutoside (p. 2505·3); ubidecarenone (p. 2637·1).
Dietary supplement.

Ultracain *Sanofi-Aventis, Ger.; Sanofi-Aventis, Rus.; Normon, Spain; Aventis, Turk.*
Articaine hydrochloride (p. 1980·1). Adrenaline hydrochloride (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain Dental *Sanofi-Aventis, Austria.*
Articaine hydrochloride (p. 1980·1). Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain D-S *Sanofi-Aventis, Ger.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Ukr.*
Articaine hydrochloride (p. 1980·1). Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain D-Suprarenin *Sanofi-Aventis, Fin.*
Articaine hydrochloride (p. 1980·1). Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain Suprarenin *Sanofi-Aventis, Ger.*
Articaine hydrochloride (p. 1980·1). Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracaine D-S *Hansamed, Canad.; Sanofi-Aventis, Switz.*
Articaine hydrochloride (p. 1980·1). Adrenaline (p. 1292·1) or adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracal
Note: this name may be used for preparations of different composition.
Baliarda, Arg.
Saw palmetto (p. 2363·3); pygeum africanum (p. 2363·2).
Benign prostatic hyperplasia.

Mead Johnson, NZ†; Mead Johnson Nutritionals, USA.
Lactose-free preparation for enteral nutrition.

Nestle, Hong Kong; Mead Johnson, Philipp.
Preparation for enteral nutrition.

Ultracalcium *Temis, Arg.*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis.

Ultracalcium D3 *Temis, Arg.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Ultracarbon *Merck, Ger.; Galenica, Gr.; Merck, Malaysia; Merck Consumer, Singapore; Merck, Thai.*
Activated charcoal (p. 1537·3).
Flatulence; diarrhoea; acute poisoning; drug overdosage.

UltraCare
Note: this name may be used for preparations of different composition.
AMO, Canad.†; Allergan, USA.
Disinfecting solution, hydrogen peroxide 3% (p. 1755·2); neutralising tablets, catalase (p. 2472·2).
Contact lens care.

Ultradent, Israel.
Benzocaine (p. 1980·2).
Local anaesthesia.

Ultracare
Note: this name may be used for preparations of different composition.
Ultradent, Canad.; Optident, UK.
Benzocaine (p. 1980·2).
Local anaesthesia.

Ultracef
Note: this name may be used for preparations of different composition.
BMS, Gr.; BMS, Irl.†
Cefadroxil (p. 233·2).
Bacterial infections.

Ultracet *Janssen-Cilag, Braz.; Xian-Janssen, China; Janssen, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Malaysia; Janssen-Cilag, Singapore; Janssen-Cilag, Thai.; Ortho McNeil, USA; Janssen-Cilag, Venez.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Ultracillin *Caps, S.Afr.†*
Benzathine benzylpenicillin (p. 227·2); benzylpenicillin sodium (p. 228·2); procaine benzylpenicillin (p. 344·2).
Bacterial infections.

Ultracin *Cal, USA.*
Capsaicin (p. 35·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Ultraclear *Healthcomm, Canad.†; Ultrabalance, Canad.†*
Vitamins; minerals.

Ultracod *Zentiva, Cz.; Zentiva, Pol.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain.

Ultracortenol *Novartis, Arg.; Agepha, Austria; Agepha, Ger.; Novartis, Hong Kong†; Novartis, Hung.†; Novartis, Israel†; Agepha, Norw.*
⊗Prednisolone acetate (p. 1645·2) or prednisolone pivalate (p. 1645·3).
Inflammatory eye disorders.

Novartis, Belg.†; Novartis, Cz.; Agepha, Denm.; Novartis, Fin.; Agepha, Neth.; Agepha, Swed.; Novartis, Switz.
⊗Prednisolone pivalate (p. 1645·3).
Inflammatory eye disorders.

Ultracortin *Collins, Mex.†*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Inflammation.

Ultracur S *Bayer, Arg.*
⊗Fluocortolone (p. 1637·1); fluocortolone caproate (p. 1637·1).
Skin disorders.

Ultraderm
Note: this name may be used for preparations of different composition.
Ecobi, Ital.
⊗Fluocinolone acetonide (p. 1636·1).
Skin disorders.

Ultrafastin *Medana, Pol.; Polpharma, Ukr.*
Ketoprofen lysine (p. 79·1).
Musculoskeletal joint, and peri-articular pain.

Ultrafen *Beximco, Singapore.*
Diclofenac (p. 48·3).
Gout; musculoskeletal and joint disorders; pain.

Dincsa, Turk.
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Ultrafer *Farmoquimica, Braz.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Ultraflox *Bal, Thai.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ultraflu *Germed, Ital.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Ultra-Fluid Body Milk *Biotherm, Canad.*
SPF 15; SPF 30: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ultra-Fluid Protection *Vichy, Canad.†*
SPF 20: Avobenzone (p. 1695·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ultra-Fluid Sun Protection *Vichy, Canad.*
SPF 30: Avobenzone (p. 1695·1); drometrizole trisiloxane (p. 1702·1); octocrilene (p. 1715·2); ecamsule (p. 1702·1); titanium dioxide (p. 1725·1).
Sunscreen.

Ultra-Freeda *Freeda, USA.*
Vitamins; minerals.

Ultragesic *Medic+Aid, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Ultragin *Wyeth, India.*
Syrup; tablets: Paracetamol (p. 115·1).
Fever; pain.

Ultragrip *Mugi, Indon.*
Syrup: Paracetamol (p. 115·1); phenylpropanolamine maleate (p. 1674·1); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms; cough.

Mugi, Indon.†
Caplets: Paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1); dexchlorpheniramine maleate (p. 621·1); dextromethorphan hydrobromide (p. 1660·1).
Colds; fever; influenza; cough; allergic symptoms.

Ultra-K *Melisana, Belg.*
Potassium gluconate (p. 1793·2).
Potassium depletion.

Ultralan *Intendis, Austria; Intendis, Israel; Intendis, Ital.; Schering, Turk.*
⊗Fluocortolone pivalate (p. 1637·1); fluocortolone caproate (p. 1637·1).
Skin disorders.

Chiesi, Ger.; Bayer, Turk.
Tablets: ⊗Fluocortolone (p. 1637·1).
Skin disorders; corticosteroid.

Galagen, USA.
Lactose-free, gluten-free preparation for enteral nutrition.

Intendis, Austria; Bayer, Fr.†; Intendis, Hong Kong; Intendis, Ital.; Schering, Philipp.†
⊗Fluocortolone (p. 1637·1); fluocortolone caproate (p. 1637·1).
Skin disorders.

Ultralan Crinale *Schering, Turk.*
⊗Fluocortolone pivalate (p. 1637·1); salicylic acid (p. 1719·1).
Skin disorders.

Ultralan M *Intendis, Spain.*
⊗Fluocortolone (p. 1637·1).
Skin disorders.

Ultralanum *Bayer, Gr.*
⊗Fluocortolone caproate (p. 1637·1); fluocortolone pivalate (p. 1637·1).
Skin disorders.

Ultralanum Plain *Meadow, UK.*
⊗Fluocortolone (p. 1637·1) or fluocortolone pivalate (p. 1637·1); fluocortolone caproate (p. 1637·1).
Skin disorders.

Ultra-Lax *Natural Factors, Canad.†*
Cascara (p. 1826·1); liquorice (p. 1853·2); rhubarb (p. 1884·2); senna (p. 1885·1).
Constipation.

Ultra lente *Novo Nordisk, USA.*
⊗Insulin zinc suspension (bovine) (p. 475·3).
Diabetes mellitus.

Ultra-Levura *Biocodex, Spain; Zambon, Spain.*
Saccharomyces boulardii (p. 2596·3).
Restoration of the gastrointestinal flora.

Ultra-Levure *Biocodex, Fr.; Petsiavas (Πετσιαβας), Gr.; Biomed, Switz.†*
Saccharomyces boulardii (p. 2596·3).
Diarrhoea; restoration of gastrointestinal flora.

Ultra-Lift Anti-Wrinkle *Garnier, Canad.†*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Ultra-Lift Glow Anti-Wrinkle *Garnier, Canad.†*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Ultralytic 2 *Ivax, USA.*
⊗Urea (p. 1727·3); ammonium lactate (p. 1694·3).
Dry skin.

Ultram *Janssen, Canad.; Janssen, USA.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ultramex *Adeka, Turk.*
Tramadol hydrochloride (p. 139·2).
Pain.

Ultra-Mg *Melisana, Belg.; Farmanic, Gr.*
Magnesium gluconate (p. 1787·2).
Magnesium deficiency; neuromuscular hyperexcitability.

Ultramicina
Note: this name may be used for preparations of different composition.
Ariston, Arg.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Q Pharma, Spain.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ultramicina Plus *Salvat, Spain.*
⊗Ciprofloxacin (p. 261·1); fluocinolone acetonide (p. 1636·1).
Otitis externa.

Ultramidol *Sanofi-Aventis, Port.*
Bromazepam (p. 1041·2).
Anxiety.

Ultramist Banana Boat Dark Tanning *Playtex, Canad.†*
SPF 4: Octinoxate (p. 1715·1); octisalate (p. 1715·2).
Sunscreen.

Ultramol *Sterwin, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Fever; pain.

Ultramop *Canderm, Canad.†*
Methoxsalen (p. 1711·3).
Psoriasis; vitiligo.

Ultramox *Royton, Braz.*
Amoxicillin (p. 216·2).
Bacterial infections.

United American, Philipp.
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2); sulbactam (p. 360·1) or sulbactam sodium (p. 360·1).
Bacterial infections.

Ultran *Randall, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux; gastrointestinal haemorrhage; acid aspiration; gastric hypersecretion.

Ultra-Natal *Ethex, USA.*
Vitamins; minerals; carbonyl iron (p. 2073·1).
Nutritional supplement in pregnancy and postnatal period.

Ultraneural *Raffo, Arg.*
Gabapentin (p. 523·3).
Epilepsy.

Ultrapen *UAP, Indon.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Ultraproct
Note: this name may be used for preparations of different composition.
Bayer, Arg.; Schering, Austral.†; Bayer, Belg.; Bayer, Chile; Bayer, Fr.; Bayer, Irl.; Intendis, Ital.; Intendis, Mex.; CSL, NZ; Intendis, Philipp.; Intendis, Rus.; Schering, Turk.; Meadow, UK; Bayer, Ukr.; Intendis, Ukr.
⊗Fluocortolone pivalate (p. 1637·1); fluocortolone caproate (p. 1637·1); cinchocaine hydrochloride (p. 1983·2).
Anorectal disorders; haemorrhoids; proctitis; anal eczema; pruritus ani.

Bayer, Port.
⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Intendis, Braz.; Schering, Indon.†
⊗Fluocortolone pivalate (p. 1637·1); fluocortolone caproate (p. 1637·1); cinchocaine hydrochloride (p. 1983·2); clemizole undecylate (p. 623·1).
Anorectal disorders.

Ultraproct N *Intendis, Hong Kong; Transfarma, Indon.*
⊗Fluocortolone pivalate (p. 1637·1); lidocaine hydrochloride (p. 1988·2).
Anorectal disorders.

Ultraquin
Note: this name may be used for preparations of different composition.
Panalab, Arg.
Levofloxacin (p. 315·3).
Bacterial infections.

Ultraquin Hydroquinone with Sunscreens *Canderm, Canad.*
Hydroquinone (p. 1705·1); homosalate (p. 1705·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Skin hyperpigmentation.

Ultraquin Plain *Canderm, Canad.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Ultra-R *E-Z-EM, Canad.†*
Barium sulfate (p. 1583·2).
Contrast medium for radiography of the small bowel.

Ultrase *Scandipharm, Arg.; Aptalis, Canad.; Axcan, USA.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic enzyme deficiency.

Ultraselem *Vita Api, Fr.*
Selenium (p. 2086·3); resveratrol (p. 2603·2); olive leaf (p. 2574·3); superoxide dismutase (p. 135·2); vitamin E (p. 2119·1); spirulina (p. 2622·1).
Dietary supplement; tonic.

Ultrasept *Thebe, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Ultraskin *Albephar, Venez.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Ultrasol-F *Fresenius Kabi, Ger.*
Formaldehyde (p. 1752·2); glyoxal (p. 1754·1); glutaral (p. 1753·2); benzalkonium chloride (p. 1737·1).
Surface disinfection.

UltraTag *Mallinckrodt, Neth.*
Technetium-99m (p. 2228·1) stannous chloride.
Red blood cell labelling.

UltraTag RBC *Mallinckrodt, Cz.*
Technetium-99m labelled stannous chloride (p. 2228·1).
Red blood cell labelling.

Ultratard *Novo Nordisk, Gr.; Novo Nordisk, NZ.*
⊗Insulin zinc suspension (human) (p. 475·3).
Diabetes mellitus.

Ultratard HM *Novo Nordisk, Hong Kong†; Novo Nordisk, Pol.†; Novo Nordisk, Singapore.*
⊗Insulin zinc suspension (crystalline) (human, monocomponent) (p. 475·3).
Diabetes mellitus.

UltratechneKow *Mallinckrodt, Switz.*
Technetium-99m (p. 2228·1).
Radionuclide scanning.

Ultrathon *3M, UK.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Ultratransit *Nutrisante, Fr.*
Senna (p. 1885·1); tamarind (p. 1892·2).
Constipation.

Ultravac *Microgen, Rus.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Ultravate *Valeant, Canad.; Ranbaxy, USA.*
⊗Ulobetasol propionate (p. 1650·3).
Skin disorders.

Ultra-Vinca *Tecnimede, Port.*
Vinpocetine (p. 2645·3).
Cerebral and peripheral vascular disorders.

Ultraviral *Raffo, Arg.†*
Lamivudine (p. 1000·2).
HIV infection.

Ultraviral Duo *Raffo, Arg.†*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Ultravisin *Farmigea, Ital.*
Myrtillus (p. 2566·2); *dl*-alpha tocoferil acetate (p. 2119·2).
Vascular retinopathy; vision disorders.

Ultravist *Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer, China; Bayer Schering, Cz.; Bayer Schering, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Schering, Turk.; Bayer, UK; Bayer, USA.*
Iopromide (p. 1591·3).
Radiographic contrast medium.

Ultra-Vit Plus *Total Health Antiaging Research, Canad.†*
Vitamins; selenium yeast (p. 2125·2).

Ultravita *Caprifarmindo, Indon.*
Vitamins; minerals.
Dietary supplement.

Ultravit-TL *Boie, Philipp.*
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2).
Dietary supplement for children.

Ultraxime *Pediatrica, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Ultrazac *Zydus, India.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Ultrazyme *AMO, Arg.; AMO, Austral.; AMO, Canad.†; Allergan, NZ; Allergan, USA.*
⊗Subtilisin A (p. 2624·1).
Cleanser for soft contact lenses; protein removal for soft contact lenses.

Ultreon *Pfizer, Ger.; Pfizer, S.Afr.*
Azithromycin (p. 221·2).
Bacterial infections.

Ultrepyl *Ultra, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; diabetic neuropathy.

Ultresa *Aptalis, USA.*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Ultrex
Note: this name may be used for preparations of different composition.
Beta, Arg.
Esomeprazole (p. 1841·1).
Carrington, USA.
Acemannan (p. 2426·3).
Wounds.

Ultrimin *Mintlab, Chile.*
Ergotamine tartrate (p. 674·1); dipyrone (p. 53·3); chlorphenamine maleate (p. 620·3); caffeine (p. 1203·3).
Migraine.

Ultromep *Ultra, Mex.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Ultrox *Nabel, Turk.*
Rosuvastatin calcium (p. 1488·2).

Ulventroten *Herbapol Lublin, Pol.†*
Chamomile (p. 2474·1); melissa (p. 2552·3); linseed (p. 2544·2).
Peptic ulcer; irritable bowel syndrome; constipation.

Ulzec *Triomed, S.Afr.†*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulzol *Pliva, Hung.†; Dabur, India; Ethica, Indon.; Pliva Krakow, Pol.†; Pliva, Rus.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Umafen *Umeda, Thai.†*
Ibuprofen (p. 68·2).
Musculoskeletal and joint disorders; pain; fever.

Umamett *Umeda, Thai.†*
Cimetidine (p. 1827·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Uman-Big *Kedrion, Ital.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Uman-Complex DI *Kedrion, Ital.; Kedrion, Rus.*
A factor IX preparation (p. 1149·3).
Deficiency of factors II, IX or X; haemorrhagic disorders.

Uman-Serum *Kedrion, Ital.*
⊗Plasma protein fraction (p. 1159·2).
Shock; hypoproteinaemia.

Umaren *Egis, Hung.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Umasam *Szama, Arg.*
Undecenoic acid monoethanolamide (p. 596·3).
Fungal skin infections; seborrhoea.

Umatrope *Lilly, Fr.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure.

Umbrella *Medihealth, Mex.*
Zinc oxide (p. 1729·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); enzacamene (p. 1703·2).
Sunscreen.

Roemmers Medihe, Venez.
A range of sunscreen preparations.

Umbrella Plus *Medihealth, Mex.*
SPF 30+: Octinoxate (p. 1715·1); bisoctrizole (p. 1697·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Sunscreen.

Umca *Abdi, Turk.*
Pelargonium sidoides (p. 2585·2).
Respiratory-tract infections.

Umckaloabo *Iso, Ger.; Farmasa, Mex.; Schwabe, Switz.*
Pelargonium sidoides (p. 2585·2).
Respiratory-tract infections; bronchitis.

Umckalor *Schwabe, Rus.; DHU, Ukr.*
Pelargonium sidoides (p. 2585·2).
Infectious and inflammatory diseases of upper respiratory tract.

Umckan *Farmoquimica, Braz.*
Pelargonium sidoides (p. 2585·2).
Respiratory-tract infections.

Umecortil *Pisa, Mex.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infection.

Umecta *Innocutis, USA.*
⊗Urea (p. 1727·3).
Nail and skin disorders.

Umeda Para-J *Umeda, Thai.*
Paracetamol (p. 115·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Pain; fever.

Umine *Douglas, Singapore.†*
⊗Phentermine hydrochloride (p. 2329·2).
Obesity.

Umkan *Schwabe, Neth.*
Pelargonium sidoides (p. 2585·2).
Common cold.

Umma *Biotenk, Arg.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Umoder *Rafarm, Gr.*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias.

Umolit *Rafarm, Gr.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Umprel *Meda, Austria.*
Bromocriptine mesilate (p. 895·3).
Parkinsonism.

Umuline NPH *Lilly, Fr.*
⊗Isophane insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Umuline Profil 30 *Lilly, Fr.*
⊗A mixture of neutral insulin injection (human, prb) 30% and isophane insulin injection (human, prb) 70% respectively (p. 475·3).
Diabetes mellitus.

Umuline Rapide *Lilly, Fr.*
⊗Neutral insulin injection (human, prb) (p. 475·3).
Diabetes mellitus.

Una A *Kowa, Jpn.*
⊗Dexamethasone acetate (p. 1631·1); diphenhydramine hydrochloride (p. 626·2); crotamiton (p. 1699·2); cinchocaine hydrochloride (p. 1983·2).
Pruritus.

Una A Gel *Kowa, Jpn.†*
⊗Dexamethasone acetate (p. 1631·1); crotamiton (p. 1699·2); cinchocaine hydrochloride (p. 1983·2).

Una Repellent *Kowa, Jpn.†*
Diethyltoluamide (p. 2153·1); N-(2-ethylhexyl)-bicyclo(2,2,1)-hepta-5-en-2,3-dicarboxyimide.
Insect repellent.

Unacefin *Foko, Turk.*
Ceftriaxone (p. 253·3).
Lidocaine (p. 1988·1) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Unacid *Pfizer, Ger.*
Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Bacterial infections.

Unacid PD *Pfizer, Ger.*
Sultamicillin (p. 369·1) or sultamicillin tosilate (p. 369·1).
Bacterial infections.

Unacim *Pfizer, Fr.*
Injection: Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Unagen *Medifarma, Indon.; UAP, Indon.*
Dipyrone (p. 53·3).
Pain.

Unakalm *Tecnifar, Port.*
Ketazolam (p. 1079·2).
Anxiety.

Un-Alfa *Leo, Fr.*
Alfacalcidol (p. 2112·3).
Renal osteodystrophy; rickets; hypoparathyroidism; hypocalcaemia.

Unalium *Guardian, Indon.*
Flunarizine (p. 629·3).
Vestibular disorders; cerebral and peripheral vascular disorders; migraine.

Unalmes *Andromaco, Chile.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Combined injectable contraceptive.

Unamine *Unison, Thai.†*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; hypersensitivity reactions; pruritus.

Unamol *Senosiain, Mex.*
Cisapride (p. 1831·3).
Gastro-oesophageal reflux; gastroparesis; dyspepsia; constipation; gastrointestinal motility disorders.

Unaril *Unison, Thai.†*
Enalapril (p. 1371·1).
Heart failure; hypertension.

Unasal *Senosiain, Mex.*
Terbinafine hydrochloride (p. 593·3).
Fungal infections of the skin, nails, and scalp.

Unasan *Sel-J, Philipp.*
Ampicillin (p. 218·2); sulbactam (p. 360·1).
Bacterial infections.

UN-Aspirin *Zee, USA.*
Paracetamol (p. 115·1).
Fever; pain.

Unasyn *Pfizer, Austria; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, Rus.†; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Ukr.†; Pfizer, USA; Pfizer, Venez.*
Injection: Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Lidocaine hydrochloride (p. 1988·2) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

Pfizer, Austria; Pfizer, Braz.; Pfizer, Philipp.
Oral suspension; tablets: Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Pfizer, China; Polfa Tarchomin, Pol.
Injection: Sulbactam (p. 360·1); ampicillin (p. 218·2).
Bacterial infections.

Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Pol.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, Venez.
Oral suspension; tablets: Sultamicillin (p. 369·1) or sultamicillin tosilate (p. 369·1).
Bacterial infections.

Unasyna *Pfizer, Arg.; Pfizer, Mex.*
Tablets: Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Pfizer, Chile.
Sultamicillin (p. 369·1).
Bacterial infections.

Pfizer, Arg.†; Pfizer, Mex.
Injection: Sulbactam sodium (p. 360·1); ampicillin sodium (p. 218·2).
Bacterial infections.

Unasyn-S *Pfizer, Jpn.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Unat *Roche, China; Meda, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, S.Afr.†; Roche, Thai.†*
⊗Torasemide (p. 1516·3).
Hypertension; oedema; renal insufficiency; heart failure; cirrhosis with ascites; nephrotic syndrome.

Unathène *Streuli, Switz.†*
Dexpanthenol (p. 2582·2); mint oil (p. 2560·1); camphor oil (p. 2466·2).
Nasal disorders.

Unava *Investi, Arg.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Uncadol *Knop, Chile.*
Uncaria tomentosa.
Inflammation; musculoskeletal, joint, and periarticular disorders.

Uncough *Yung Shin, Hong Kong.*
Cloperastine (p. 1659·1).
Cough.

Undecyl *Kimia, Indon.; Rekah, Israel.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Undelenic *Gordon, USA.*
Undecenoic acid (p. 596·3).
Fungal skin infections.

Underan *Saval, Chile.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Underberg *Underberg, Canad.†*
Gentian (p. 2512·1).

Undestor *Organon, Arg.; Organon, Cz.; Organon, Pol.; MSD, Swed.*
⊗Testosterone undecylate (p. 2305·2).
Male hypogonadism; male infertility; osteoporosis in men; female to male gender reassignment.

Undetab *KVZ, Ukr.*
Vitamins; rutoside (p. 2505·3).
Dietary supplement.

Undevit *Uralbiopharm, Rus.; KVZ, Ukr.*
Vitamins; rutoside (p. 2505·3).
Asthenia; dietary supplement.

Undex
Note: this name may be used for preparations of different composition.
Farmanic, Gr.
Zinc undecenoate (p. 596·3); undecenoic acid (p. 596·3).

Melisana, Switz.
Ointment: ⊗Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); tolnaftate (p. 596·1); urea (p. 1727·3); calcium lactate (p. 1784·1).
Tinea pedis.

Melisana, Switz.†
Topical liquid: Triclosan (p. 1773·2); undecenoic acid diethanolamide (p. 596·3); benzethonium chloride (p. 1738·1); dexpanthenol (p. 2582·2).
Tinea pedis.

Undex au clotrimazole *Melisana, Switz.*
Ointment: Clotrimazole (p. 576·2).
Fungal foot infections.

Undofen *GSK, Pol.*
Cetylpyridinium chloride (p. 1743·1); undecenoic acid (p. 596·3).
Fungal and bacterial skin infections.

Undofen Max *GSK, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Undo-Pate *Sandoz, Turk.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); benzocaine (p. 1980·2).
Fungal skin and nail infections.

Undorlan *Landsteiner, Mex.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Undo-Talk *Sandoz, Turk.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3); boric acid (p. 2459·3); salicylic acid (p. 1719·1).
Fungal skin infections.

Unebril *Onedose, Spain.*
Paracetamol (p. 115·1).
Fever; pain.

Unexym mono *Repha, Ger.*
⊗Pancreatin (p. 2579·3).
Pancreatic disorders.

Ung Vernleigh *Adcock Ingram, S.Afr.*
Sulfanilamide (p. 368·1); merbromin (p. 1760·1); peru balsam (p. 2587·1); cod-liver oil (p. 2056·3).
Infected wounds; burns; ulcers.

Ungapiven *Phytopharm, Rus.*
Bee venom (p. 2434·3).
Musculoskeletal and joint disorders; neuralgia.

Ungava *Aerokure, Canad.*
Diethyltoluamide (p. 2153·1).
Insect repellent.

Ungel *GSK, Arg.*
Triclocarban (p. 1773·2).
Dandruff.

Unguentacid *Mucos, Ger.†*
Linoleic acid triglyceride (p. 2509·2); vitamin A palmitate (p. 2098·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Skin disorders.

Unguentine *Mentholatum, USA.*
Ointment: Phenol (p. 1763·3); zinc oxide (p. 1729·1); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3).
Pain in minor burns.

Unguentine Maximum Strength *Lee, USA.*
Benzocaine (p. 1980·2); resorcinol (p. 1718·3).

Unguentine Plus *Mentholatum, USA.*
Lidocaine hydrochloride (p. 1988·2); chloroxylenol (p. 1748·2); phenol (p. 1763·3).
Skin disorders.

Ungüento del Bebe *Nordin, Mex.*
Zinc (p. 2126·1).
Skin disorders.

Unguento Callicida Naion *Puerto Galiano, Spain.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Callosities.

Ungüento Cruz *Tocogino, Mex.*
Sulfathiazole (p. 368·3); zinc (p. 2126·1).

Unguento Dermico Antibiotico
Note: this name may be used for preparations of different composition.
Laboratorios Chile, Chile.†
Neomycin (p. 329·3); bacitracin (p. 225·3).
Bacterial skin infections.

Unguento Leon *Beiersdorf, Chile.†*
Methyl salicylate (p. 92·1); camphor (p. 2466·2).
Musculoskeletal and joint disorders.

Ungüento de la Madre *Nordin, Mex.*
Vitamins; allantoin (p. 1693·1); zinc (p. 2126·1).
Skin disorders.

Unguento Morry *Teofarma, Spain.*
Salicylic acid (p. 1719·1).
Calluses.

Ungüento Picrato de Butesin *Abbott, Braz.*
Butyl aminobenzoate picrate (p. 1982·3).
Skin disorders.

Ungüento Sulfatiazol Rojtier *Nordin, Mex.*
Sulfathiazole (p. 368·3); zinc (p. 2126·1).
Skin infections.

Unguentolan *Gebro, Switz.*
Cod-liver oil (p. 2056·3); vitamin A acetate (p. 2098·3).
Superficial wounds; burns.

Heyl, Ger.
Cod-liver oil (p. 2056·3).
Wounds.

Unguentum contra haemorrhoides PCH *Pharmachemie, Neth.†*
Lidocaine hydrochloride (p. 1988·2).
Haemorrhoids.

Unguentum lymphaticum *PGM, Ger.†*
Hemlock (p. 2524·3); colchicum (p. 607·1); digitalis (p. 1352·3); podophyllum (p. 1717·1); hyoscyamus (p. 2530·2); calendula (p. 2465·2).
Lymphatic disorders.

Unguentum M *Boots Healthcare, Irl.†; Crookes Healthcare, UK.*
Emollient.
Nappy rash; dry skin; barrier cream; pharmaceutical vehicle.

Unguentum Undecylenicum *Chema-Elektromet, Pol.*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Ungvita *Bayer Consumer, Austral.; Roche, NZ.*
Ointment: Vitamin A palmitate (p. 2098·3).
Skin trauma; chafed skin; cracked heels; cracked nipples; dry skin; minor burns.

Uni Amox *Uniao Quimica, Braz.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Uni Aztrenam *Uniao Quimica, Braz.*
Aztreonam (p. 224·1).

Uni Bromazepax *Uniao Quimica, Braz.*
Bromazepam (p. 1041·2).
Anxiety.

Uni Carbamaz *Uniao Quimica, Braz.*
Carbamazepine (p. 512·2).
Epilepsy; neuritis.

Uni Clonazepax *Uniao Quimica, Braz.*
Clonazepam (p. 519·1).
Anxiety; epilepsy.

Uni Dexa *Uniao Quimica, Braz.*
⊗Dexamethasone acetate (p. 1631·1) or dexamethasone phosphate (p. 1631·1).
Corticosteroid.

Uni Diamicron *Servier, Belg.; Orifarm, Denm.; Servier, Spain.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Uni Diazepax *Uniao Quimica, Braz.*
Diazepam (p. 1063·2).
Anxiety.

Uni Doxiciclin *Uniao Quimica, Braz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Uni Fenicol *Genom, Braz.†*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Uni Haloper *Uniao Quimica, Braz.*
Haloperidol (p. 1077·1).
Psychoses.

Uni Hioscin *Uniao Quimica, Braz.*
Hyoscine butylbromide (p. 1845·3).
Muscle spasm.

Uni Imiprax *Uniao Quimica, Braz.*
Imipramine hydrochloride (p. 426·2).
Depression; pain; nocturnal enuresis.

Uni Masdil *Esteve, Spain.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Uni Norflox *Uniao Quimica, Braz.*
Norfloxacin (p. 333·3).

Uni Propralol *Uniao Quimica, Braz.*
⊗Propranolol hydrochloride (p. 1479·1).
Arrhythmias; hypertension.

Uni Timolol *Unimed, Cz.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Uni Vir *Uniao Quimica, Braz.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Uni-Ace *URL, USA.*
Paracetamol (p. 115·1).

Uni-Acetil *Universal, Hong Kong.†*
Aspirin (p. 22·2).

Uniakum *Gache, Venez.*
Oral drops: Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Gache, Venez.
Tablets: Paracetamol (p. 115·1); caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Uni-Ampicin *Universal, Hong Kong.†*
Ampicillin (p. 218·2).
Bacterial infections.

Unianf *Uniao Quimica, Braz.*
Amphotericin B (p. 569·2).

Uni-Bana *Universal, Hong Kong.†*
Camphor (p. 2466·2); eucalyptus (p. 2501·1); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Unibar *Therapex, Canad.†*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Unibaryt-R *IFET (ΙΦΕΤ), Gr.*
Barium sulfate (p. 1583·2).
Radiographic contrast medium.

Unibase *Gallipot, USA.*
Vehicle for topical preparations.

Unibasis *Pampa, Pol.*
⊗White soft paraffin (p. 2211·3); liquid paraffin (p. 2191·2); glycerol (p. 2517·2).
Skin disorders.

Unibenestan *Sanofi-Aventis, Spain.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Uni-Betamine *Universal, Hong Kong.†*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine (p. 620·3).

Unibios Simple *Fabra, Arg.*
Dipyrone (p. 53·3).
Fever; inflammation; pain.

Uni-Breth *Universal, Hong Kong.†*
⊗Terbutaline (p. 1228·1).

Uni-Breth Expectorant *Universal, Hong Kong.†*
⊗Guaifenesin (p. 1666·2); terbutaline (p. 1228·1).

Unibron *Unipharm, Mex.*
⊗Salbutamol (p. 1220·2).
Asthma.

Uni-Butamol *Universal, Hong Kong.†*
⊗Salbutamol (p. 1220·2).

Uni-Butamol Expectorant *Universal, Hong Kong.†*
⊗Salbutamol (p. 1220·2); guaifenesin (p. 1666·2).

Unicaine
Note: this name may be used for preparations of different composition.
Thea, Belg.
Oxybuprocaine hydrochloride (p. 1993·2).
Local anaesthesia.

Unipharm, Mex.
Lidocaine hydrochloride (p. 1988·2). Adrenaline acid tartrate (p. 1292·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Unicalm *Raffo, Arg.*
Ketorolac (p. 80·2).
Inflammation; pain.

Uni-Calmin *Universal, Hong Kong.†*
Calamine (p. 1697·2); zinc oxide (p. 1729·1).

Unicap *Upjohn, USA.*
Vitamins.

Pharmacia, Braz.†
Vitamins; minerals.

Unison, Thai.†
Paracetamol (p. 115·1).
Pain; fever.

Unicap M *Pfizer, Philipp.†*
Vitamins; minerals.
Nutritional supplement.

Unicap T *Eczacibasi, Turk.*
Vitamins; minerals.

Unicarbazan *Unichem, India.*
Diethylcarbamazine citrate (p. 153·1); chlorphenamine maleate (p. 620·3).
Tropical eosinophilia; filariasis.

Unicat *Bracco, Denm.*
Barium sulfate (p. 1583·2).
Contrast medium for gastrointestinal radiography.

Unicet *Bal, Thai.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders.

Unicexal *Italchimici, Ital.*
Ciprofloxacin hydrochloride (p. 261·2).
Ear infections.

Uni-Check *Exxe, Ital.†*
Test for glucose in blood (p. 2516·3).

Unichol *Merck, Austria.†*
Hymecromone (p. 2530·2).
Biliary-tract disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Unicide *Unison, Thai.†*
Niclosamide (p. 161·2).
Cestode infections.

Uni-Cidine *Universal, Hong Kong.†*
Famotidine (p. 1842·1).

Unicil 3/1 *Unipharm, Mex.*
Procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Unicil 6:3:3 *Unipharm, Mex.*
Benzathine benzylpenicillin (p. 227·2); procaine benzylpenicillin (p. 344·2); benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Unicil L-A *Unipharm, Mex.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Unicil Mega *Unipharm, Mex.*
Benzylpenicillin sodium (p. 228·2).
Bacterial infections.

Unicilin
Note: this name may be used for preparations of different composition.
Mustafa, Philipp.
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Uniclar *Schering-Plough, Arg.; Schering-Plough, Chile; Schering-Plough, Mex.*
⊗Mometasone furoate (p. 1644·1).
Allergic rhinitis; nasal polyps; sinusitis.

Uniclonax *Unison, Philipp.†*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Uniclophen *Unimed, Cz.; Unimed, Rus.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders; ocular pain; prevention of postoperative cystoid macular oedema; intraoperative miosis inhibition.

Uniclor *Solfran, Mex.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Uni-Colex *Universal, Hong Kong.*
Guaifenesin (p. 1666·2).
Cough.

Unicomplex *Rugby, USA.*
Vitamins; minerals.

Unicontin *Modi-Mundipharma, India; Meda, Port.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Uni-Cophedene *Universal, Hong Kong.†*
Ammonium chloride (p. 1656·1); ipecacuanha (p. 1667·2).

Unicordium *Schering-Plough, Fr.†*
Bepridil hydrochloride (p. 1316·2).
Angina pectoris.

Uni-Cort *Universal, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Uni-Cort-N *Universal, Hong Kong.†*
⊗Hydrocortisone (p. 1640·1); neomycin (p. 329·3).
Infected skin disorders.

Unicough Chesty *Pinewood, Irl.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Uni-Cycolac *Universal, Hong Kong.†*
Dicycloverine (p. 1834·2).
Diarrhoea.

Uni-Cycolac-SM *Universal, Hong Kong.†*
Dicycloverine (p. 1834·2); dimeticone (p. 1886·2).

Uni-Dac *Universal, Hong Kong.†*
Vitamins.

Unidasa *Roux-Ocefa, Arg.*
Hyaluronidase (p. 2527·2).

Unidazol *Zuoz, Venez.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Uni-Derm
Note: this name may be used for preparations of different composition.
Smith & Nephew, Austral.
Moisturiser.

Uniderm
Note: this name may be used for preparations of different composition.
Akrikhin, Rus.
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Unipharm, Mex.
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Schering-Plough, Swed.†
⊗Hydrocortisone (p. 1640·1).
Eczema; anogenital pruritus.

Uni-Dermo *Universal, Hong Kong.†*
⊗Clobetasol (p. 1627·1).
Skin disorders.

Unidermo *Uniderm, Ital.*
Lactic acid (p. 2539·1); collagen (p. 2483·2).
Skin cleansing.

Uni-Dexmine *Universal, Hong Kong.†*
Dexchlorpheniramine (p. 620·3).

Uni-DM *Universal, Hong Kong.†*
Dextromethorphan (p. 1660·1).

Uni-Dox
Note: this name may be used for preparations of different composition.
Unipharm, Mex.
Diclofenac sodium (p. 48·3); thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; neuropathy.

Unidox
Note: this name may be used for preparations of different composition.
Astellas, Neth.; Astellas, Pol.; Astellas, Rus.; Astellas, Ukr.
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Unidrin D *Unipharm, Mex.*
⊗Pseudoephedrine (p. 1676·1); chlorphenamine (p. 620·3).
Influenza symptoms.

Unidrox *ACRAF, Austria; ACRAF, Cz.; Angelini, Hung.; Angelini, Ital.; Angelini, Port.*
Prulifloxacin (p. 345·1).
Bacterial infections.

Unidryl CD *Union, Singapore.*
Ammonium chloride (p. 1656·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2).

Uni-Dur *Schering-Plough, Gr.*
Theophylline (p. 1229·3).

Uni-Dyphine *Universal, Hong Kong.†*
Diprophylline (p. 1207·3).

Unienzyme *Unichem, India.*
Oral liquid: ⊗Amylase (p. 2442·1); papain (p. 2582·3).
Dyspepsia; flatulence.

Unichem, India.
Tablets: ⊗Amylase (p. 2442·1); activated charcoal (p. 1537·3); pepsin (p. 2586·1).
Formerly contained amylase, papain, simeticone, nicotinamide, and activated charcoal.
Flatulence; dyspepsia; gastritis.

Unienzyme c MPS *Transatlantic, Rus.*
⊗Amylase (p. 2442·1); papain (p. 2582·3); simeticone (p. 1886·2); activated charcoal (p. 1537·3); nicotinamide (p. 2083·1).
Pancreatic insufficiency; flatulence; nausea.

Unif *Tek, Thai.†*
⊗Triamcinolone acetonide (p. 1649·1).
Skin and scalp disorders.

Uni-Febrin *Universal, Hong Kong.*
Paracetamol (p. 115·1).
Fever; pain.

Unifed *Altaire, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Uni-Fedra *Universal, Hong Kong.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).

Uni-Fedra Compound *Universal, Hong Kong.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); codeine phosphate (p. 40·2).
Cough; nasal congestion.

Uni-Fedra DM *Universal, Hong Kong.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Unifedrine *Uniao Quimica, Braz.*
⊗Ephedrine sulfate (p. 1663·2).

Uni-Fenamic *Universal, Hong Kong.†*
Mefenamic acid (p. 85·3).

Unifenitoin *Uniao Quimica, Braz.*
Phenytoin (p. 538·2) or phenytoin sodium (p. 538·2).
Epilepsy.

Uni-Feno *Universal, Hong Kong.†*
Phenobarbital (p. 535·2).

Unifenobarb *Uniao Quimica, Braz.*
Phenobarbital (p. 535·2).
Epilepsy.

Unifental *Uniao Quimica, Braz.*
⊗Fentanyl citrate (p. 60·1).
Pain.

Unifepim *Uniao Quimica, Braz.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Unifer *Grossman, Mex.*
Iron carbonyl (p. 2073·1).
Iron-deficiency anaemia; iron deficiency.

Rider, Chile.
Ferrous gluceptate (p. 2061·2).
Iron deficiency; iron-deficiency anaemia.

Uniferfol *Grossman, Mex.*
Iron carbonyl (p. 2073·1); folic acid (p. 2063·1).
Iron-deficiency anaemia; folic acid deficiency.

Uniferon *Getz, Philipp.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; hepatitis B; hepatitis C.

Unifiber *Niche, USA.*
Powdered cellulose (p. 2177·2).
Constipation.

Unifibre *Niche, Singapore.*
Dietary fibre.
Constipation; dietary fibre supplement.

Unifilin *Uniao Quimica, Braz.*
Aminophylline (p. 1201·2).
Asthma.

Uniflex
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Orphenadrine citrate (p. 909·2); paracetamol (p. 115·1).

Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Uniflex-N *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗Betamethasone valerate (p. 1624·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Uniflox
Note: this name may be used for preparations of different composition.
Bayer, Fr.; Huons, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Raffo, Arg.
Levofloxacin (p. 315·3).
Bacterial infections.

Unimed, Rus.
Ofloxacin (p. 334·3).
Bacterial eye and ear infections.

Uniflu Colds and Flu *Beacons, Singapore.*
Caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Uniflu with Gregovite C *Alliance, UK.*
Uniflu tablets, phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1); Gregovite C tablets, ascorbic acid (p. 2110·3).
Cold and influenza symptoms; nasal congestion.

Uniflu Plus with Vitamin C *Uniphar, Irl.*
Uniflu Plus tablets, paracetamol (p. 115·1); codeine phosphate (p. 40·2); diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3); caffeine (p. 1203·3); Vitamin C tablets, ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Uniflu with Vitamin C *Uniphar, Irl.*
Uniflu tablets, caffeine (p. 1203·3); diphenhydramine hydrochloride (p. 626·2); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3); Vitamin C tablets, ascorbic acid (p. 2110·3).
Cold and influenza symptoms.

Unifluid *Thea, Fr.*
Povidone (p. 2204·3).
Dry eyes.

Uni-Fluocin *Universal, Hong Kong.†*
⊗Fluocinolone (p. 1636·1).
Skin disorders.

Uni-Folic *Universal, Hong Kong.†*
Folic acid (p. 2063·1).

Unifungicid *Unia, Pol.†*
Chlormidazole hydrochloride (p. 575·3).
Fungal and bacterial skin and nail infections.

Unifungin *Intermed, Gr.*
Econazole nitrate (p. 577·3).
Fungal skin infections.

Unifyl *Mundipharma, Austria; Mundipharma, Switz.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Unigamma *Unipharm, Rus.*
Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuropathy; neuralgia; neuritis.

Unigan *Unison, Hong Kong; Unison, Philipp.; Unison, Thai.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Unigo *Unison, Hong Kong; Unison, Thai.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections; amoebiasis; trichomoniasis; vaginosis.

Uni-Gold hCG *Kora, Irl.†*
Pregnancy test (p. 2596·1).

Unigrip *Uniao Quimica, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Unigyn
Note: this name may be used for preparations of different composition.
Sigma, Braz.
Secnidazole (p. 947·3).
Protozoal infections.

Uniderm, Ital.
Lactic acid (p. 2539·1).
Vaginal douche; personal hygiene.

Unihepa *CCM, Malaysia.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Uni-Heptadine *Universal, Hong Kong.†*
Cyproheptadine (p. 624·1).

Uni-Hexine *Universal, Hong Kong.†*
Bromhexine (p. 1656·3).

Unihexol *Unique, Rus.*
Iohexol (p. 1590·1).
Radiographic contrast medium.

Unihist *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Cold symptoms; allergic rhinitis; asthma; hay fever.

Uni-Hydrin *Universal, Hong Kong.†*
Dimenhydrinate (p. 625·2).

Unihype *Samjin, Philipp.*
Captopril (p. 1331·2).
Hypertension.

Uni-Injekt *Kohler-Pharma, Ger.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Unijab *Rotexmedica, Singapore.*
Algestone acetophenide (p. 2255·2); estradiol benzoate butyrate (p. 2271·1).
Combined injectable contraceptive.

Uni-Kaotin *Universal, Hong Kong.*
Kaolin (p. 1850·1); pectin (p. 2200·3).
Diarrhoea.

Unike *Kohler, Ger.*
Sodium hyaluronate (p. 2526·2).
Joint disorders.

Uniket *Lacer, Spain.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Uni-Kinase *Unichem, India.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Uniklar *Nevzat, Turk.*
Clarithromycin (p. 266·2).
Bacterial infections.

Unikpef *Unique, Rus.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Unil *Umeda, Thai.†*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Unilan *Laquifa, Port.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Unilarm *Europhta, Mon.*
Sodium chloride (p. 1795·1).
Dry eye.

Unilat *Unimed, Cz.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Unilax
Note: this name may be used for preparations of different composition.
Beacons, Singapore.
Bisacodyl (p. 1821·1).
Constipation.

Uniloc *Nycomed, Denm.; Nycomed, Norw.*
⊗Atenolol (p. 1308·2).
Hypertension; arrhythmias; myocardial infarction; angina pectoris; migraine; hyperthyroidism.

Unilux *Sanochemia, Ger.*
Iopamidol (p. 1590·3).
Radiographic contrast medium.

Uni-Ma *Unison, Thai.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Unima *Unison, Hong Kong; Unison, Malaysia.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel evacuation.

Uni-Magel *Universal, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).

Uni-Magel-SM *Universal, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); dimeticone (p. 1886·2); magnesium trisilicate (p. 1858·1).

Unimax *AstraZeneca, Fin.; AstraZeneca, Ger.; AZ, Port.†; AstraZeneca, Switz.†*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Unimazole *Unipharma, Gr.*
Thiamazole (p. 2345·2).
Hyperthyroidism.

Unimedrol *Uniao Quimica, Braz.*
⊗Methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Uni-Menadol *Universal, Hong Kong.†*
Acetomenaphthone (p. 2122·1).

Unimet *Pasteur, Chile.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Uni-Methicone *Universal, Hong Kong.†*
Dimeticone (p. 2209·3).

Uni-Mizole *Universal, Hong Kong.†*
Miconazole (p. 588·3).
Fungal skin infections.

Uni-Mizole-HC *Universal, Hong Kong.†*
⊗Miconazole (p. 588·3); hydrocortisone (p. 1640·1).
Infected skin disorders.

Unimol *Unison, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Uni-Motil *Universal, Hong Kong.†*
Loperamide (p. 1854·2).
Diarrhoea.

Unimox *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Uninapro *Farmakopea, Ital.*
Naproxen sodium (p. 98·2).
Pain; fever.

Uni-Neoderm *Universal, Hong Kong.†*
Neomycin (p. 329·3).

Unipak *Unique, Ukr.*
Iohexol (p. 1590·1).
Contrast medium for radiography and computerised tomography.

Uni-Pamol *Universal, Hong Kong.†*
Paracetamol (p. 115·1).
Fever; pain.

Uni-Panolol *Universal, Hong Kong.†*
⊗Propranolol (p. 1479·1).

Uni-Paptase *Universal, Hong Kong.†*
⊗Amylase (p. 2442·1); pepsin (p. 2586·1).

Uni-Per *Yuhan, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Unipexil *Gifrer Barbezat, Fr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Uni-Phen *Universal, Hong Kong.*
Ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); diphenhydramine hydrochloride (p. 626·2); menthol (p. 2553·2).
Cough; nasal congestion.

Uni-Pholco *Universal, Hong Kong.*
Pholcodine (p. 1675·1).
Cough.

Uniphyl *Purdue, Canad.; Adcock Ingram, S.Afr.; Purdue Frederick, USA.†*
Theophylline (p. 1229·3).
Obstructive airways disease; bronchospasm.

Uniphyllin *Mundipharma, Ger.; Unipharma, Gr.*
Theophylline (p. 1229·3).
Obstructive airways disease; asthma; neonatal apnoea and bradycardia.

Uniphyllin Continus *Mundipharma, Irl.; Napp, UK.*
Theophylline (p. 1229·3).
Heart failure; obstructive airways disease; bronchospasm; asthma.

Uni-Plex
Note: this name may be used for preparations of different composition.
Universal, Hong Kong.
Vitamin B substances (p. 2102·3).
Vitamin B supplement.

Uniplex
Note: this name may be used for preparations of different composition.
Aristopharma, Hong Kong.
Vitamin B substances (p. 2102·3).
Vitamin B supplement.

Cimed, Braz.
Amino acids; vitamins; minerals.

Unipharma, Gr.
Aciclovir (p. 964·1).
Herpes simplex infections.

Uniplus *Angelini, Ital.*
Suppositories: Oxolamine citrate (p. 1671·2); propyphenazone (p. 127·3).
Otorhinolaryngeal inflammation; tracheobronchitis; oral inflammation; influenza symptoms.

Uniprazol *Uniao Quimica, Braz.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Unipred *Osoth, Thai.*
⊗Prednisolone (p. 1645·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Unipres *KRKA, Cz.; KRKA, Hung.*
Nitrendipine (p. 1456·3).
Hypertension.

Unipril *AstraZeneca, Ital.*
Ramipril (p. 1483·3).
Hypertension; heart failure; renal insufficiency.

Uniprildiur *AstraZeneca, Ital.*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Uniprofen *Uniao Quimica, Braz.*
Ibuprofen (p. 68·2).
Inflammation; pain.

Uni-Proxamol *Universal, Hong Kong.†*
Paracetamol (p. 115·1); dextropropoxyphene (p. 43·2).
Pain.

Uni-Prozine *Universal, Hong Kong.†*
Promethazine (p. 638·2).

Uni-Quaderm *Universal, Hong Kong.†*
⊗Clobetasol (p. 1627·1); clotrimazole (p. 576·2); neomycin (p. 329·3); nystatin (p. 590·3).
Infected skin disorders.

Unique PH *Alcon, Braz.*
Cleansing and wetting solution for hard contact lenses.

Unique Plus *Eurofarma, Braz.*
Sodium monofluorophosphate (p. 2091·3).
Dental caries prophylaxis.

Uniquin *Sandoz, Austria†; Rottapharm, Ital.; Medinfar, Port.†; GSK, S.Afr.†*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Uni-Ramine *Universal, Hong Kong.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Uni-Ramine CE *Universal, Hong Kong.*
⊗Codeine phosphate (p. 40·2); ephedrine hydrochloride (p. 1663·2); ammonium chloride (p. 1656·1); chlorphenamine maleate (p. 620·3).
Cough.

Uni-Ramine Expectorant *Universal, Hong Kong.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough.

Uni-Rantac *Universal, Hong Kong.†*
Ranitidine (p. 1882·1).

Uniranz *Yungjin, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Uni-Rax-HC *Universal, Hong Kong.†*
⊗Crotamiton (p. 1699·2); hydrocortisone (p. 1640·1).

Unirelaxed *Alpharma, Mex.†*
Naproxen (p. 98·2).
Fever; inflammation; pain.

Uniren *Unison, Hong Kong.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Unison, Malaysia; Unison, Singapore; Unison, Thai.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Uniretic *GSK, Philipp.; Adeka, Turk.; Schwarz, USA.*
⊗Moexipril hydrochloride (p. 1440·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Uniroid-HC *Chemidex, UK.*
⊗Cinchocaine hydrochloride (p. 1983·2); hydrocortisone (p. 1640·1).
Anorectal disorders.

Unisedil *Laquifa, Port.*
Diazepam (p. 1063·2).
Anxiety disorders; skeletal muscle spasm.

Unisef *Nevzat, Turk.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Uniselen *Kohler-Pharma, Ger.†*
Sodium selenite (p. 2087·1).
Selenium deficiency.

Unisens *Universal, Port.*
Itraconazole (p. 583·3).
Fungal infections.

Unisept
Note: this name may be used for preparations of different composition.
Medlock Medical, UK.
Chlorhexidine gluconate (p. 1743·3).
Skin disinfection.

Unipharma, Gr.
Urea hydrogen peroxide (p. 1774·2).

Unisia *Takeda, Jpn.*
Candesartan cilexetil (p. 1330·2); amlodipine besilate (p. 1304·1).
Hypertension.

Unisol *Alcon, USA.*
Rinsing and storage solutions for soft contact lenses.

Uni-Solve *Smith & Nephew, Austral.*
Dipropylene glycol methyl ether; isopropyl alcohol (p. 1758·3); isoparaffin.
Medical adhesive remover.

Unisom
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Philipp.; Pfizer, Turk.
Doxylamine succinate (p. 627·3).
Insomnia.

Petrus, Austral.; Paladin, Canad.; Pfizer, Hong Kong†; Pharmaco, NZ.
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Unisom-2 *Paladin, Canad.*
Doxylamine succinate (p. 627·3).
Insomnia.

Unisom with Pain Relief *Pfizer Consumer, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia; pain.

Unisom PM Pain SleepCaps *Chattem, USA.*
Paracetamol (p. 115·1); diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Unisom SleepMelts *Chattem, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Unisom SleepTabs *Pfizer Consumer, USA.*
Doxylamine succinate (p. 627·3).
Insomnia.

Unison Enema *Unison, Hong Kong; Unison, Thai.*
Sodium chloride (p. 1795·1).
Constipation; bowel evacuation.

Unison Ointment *Unison, Thai.*
Chloramphenicol (p. 257·1).
Bacterial skin infections.

Unispas *Unique, Ukr.*
Paracetamol (p. 115·1); drotaverine hydrochloride (p. 2497·3); codeine phosphate (p. 40·2).
Pain.

Unispaz *Unique, Rus.*
Paracetamol (p. 115·1); drotaverine hydrochloride (p. 2497·3); codeine phosphate (p. 40·2).
Pain; smooth muscle spasm.

Unispaz N *Unique, Rus.*
Paracetamol (p. 115·1); drotaverine hydrochloride (p. 2497·3).
Pain; smooth muscle spasm.

Unispera *Belupo, Cz.†*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; autism.

Unistep hCG *Orion, USA.*
Pregnancy test (p. 2596·1).

Uni-Sufed *Universal, Hong Kong.†*
⊗Pseudoephedrine (p. 1676·1).

Uni-Sulfaprim *Universal, Hong Kong.†*
Co-trimoxazole (p. 277·3).

Unitaxel *Korea United, Philipp.*
Paclitaxel (p. 839·3).
Breast cancer; ovarian cancer.

United American Tiki Tiki Plus *United Laboratories, Philipp.*
Vitamins.
Nutritional supplement.

United American Tiki Tiki Star *United Laboratories, Philipp.*
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3).
Nutritional supplement.

United Home Burn Ointment *Amherst, Philipp.*
Benzocaine (p. 1980·2); eucalyptus oil (p. 2501·2); boric acid (p. 2459·3).
Burns; itching.

United Home Calactate *United Laboratories, Philipp.*
Calcium lactate (p. 1784·1).
Calcium supplement; osteoporosis.

United Home Fersulfate Iron *United Laboratories, Philipp.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

United Home Glydolax *Amherst, Philipp.*
⊗Glycerol (p. 2517·2).
Constipation.

United Home Whitfield's Ointment *Amherst, Philipp.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Tinea infections; ringworm.

Unitens *AstraZeneca, Gr.*
Felodipine (p. 1380·3); ramipril (p. 1483·3).
Hypertension.

Unitest *Igefarma, Braz.*
Pregnancy test (p. 2596·1).

Uni-Theodal *Universal, Hong Kong.†*
⊗Ephedrine (p. 1663·1); phenobarbital (p. 535·2); theophylline (p. 1229·3).

Unithroid *Stevens, USA.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Unitidazin *Uniao Quimica, Braz.*
Thioridazine hydrochloride (p. 1110·2).

Unitin *Unipharm, Mex.*
Ranitidine (p. 1882·1).
Peptic ulcer.

Unitone *D & M, Chile; Darier, Mex.*
SPF 30: Betacarotene (p. 2051·1); avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Skin pigmentation disorders; skin hyperpigmentation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Unitone 4 *D & M, Chile.*
SPF 20: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

D & M, Chile.
Hydroquinone (p. 1705·1); kojic acid (p. 1710·2); glycolic acid (p. 1704·3).
Skin pigmentation disorders.

Unitrac *Kalbe, Indon.; Dankos, Malaysia; Dankos, Singapore.*
Itraconazole (p. 583·3).
Fungal infections.

Unitral *Unison, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Unitrama *Angelini, Ital.*
Tramadol hydrochloride (p. 139·2).
Pain.

Unitramarim *Angelini, Ital.*
Tramadol hydrochloride (p. 139·2).
Pain.

Uni-Tranxene *Sanofi-Aventis, Belg.*
Dipotassium clorazepate (p. 1056·3).
Anxiety; mixed anxiety depressive states.

Unitrim
Note: this name may be used for preparations of different composition.
Intermed, Gr.
Metronidazole (p. 936·1).
Rosacea.

Unitron PEG *Merck, Canad.†*
Peginterferon alfa-2b (p. 989·2).
Chronic hepatitis C.

Unitropic *Unimed, Cz.*
Tropicamide (p. 2012·2).
Production of mydriasis and cycloplegia.

Unituss *Unison, Thai.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2); menthol (p. 2553·2).
Cough; nasal congestion.

Unituss HC *URL, USA.*
Hydrocodone tartrate (p. 67·2); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Uni-tussin DM *URL, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

UniVaccin *Pohl, Ger.†; UniVaccin, Ger.†*
Inactivated bacterial preparation.
Immunotherapy.

Unival *Lafi, Chile.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Senosiain, Mex.
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

Univasc *GSK, Philipp.; Adeka, Turk.; Schwarz, USA.*
Moexipril hydrochloride (p. 1440·3).
Hypertension.

Uni-Vasin *Universal, Hong Kong.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); phenylpropanolamine hydrochloride (p. 1674·1).
Upper respiratory-tract disorders.

Univate *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Univent *Rex, NZ.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Univer *Cephalon, UK.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris.

Universal Anti-Aging Daily Moisturizing Cream *Bath & Body Works, Canad.†*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Universal Brand Enema *Unicorn, Canad.†*
⊗Glycerol (p. 2517·2).

Universal Earache Drops *Universal, S.Afr.†*
Phenazone (p. 124·1); procaine hydrochloride (p. 1994·3); potassium hydroxyquinoline sulfate (p. 2530·1).
Ear disorders.

Universal Eye Drops *Universal, S.Afr.†*
Phenylephrine hydrochloride (p. 1672·3); boric acid (p. 2459·3).
Eye irritation; eye inflammation.

Universal Nasal Drops *Universal, S.Afr.†*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline nitrate (p. 1669·3).
Sinusitis; allergic rhinitis.

Universal Throat Lollies *Universal, S.Afr.†*
Cetylpyridinium chloride (p. 1743·1).
Mouth and throat infections.

Uni-Vico *Universal, Hong Kong.*
Vitamins.

Univit
Note: this name may be used for preparations of different composition.
Farmakopea, Ital.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

KVZ, Ukr.
Vitamins; calcium (p. 1783·1); phosphorus (p. 2589·2).
Nutritional supplement.

Univitan K1 *Xing Tai, Hong Kong.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency.

Univoxy *Tropica Mas, Indon.*
Thioctic acid (p. 2629·1); chromium (p. 2055·3); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3).
Dietary supplement.

Uniwarfin *Unichem, India.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

UniXan *Norpharma, Denm.*
Theophylline (p. 1229·3).
Obstructive airways disease.

Unixime *FIRMA, Ital.*
Cefixime (p. 240·3).
Bacterial infections.

Unixone *Unimex, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Unizef *Samjin, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; conjunctivitis; urticaria.

Unizen *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
⊗Serrapeptase (p. 2613·3).
Inflammation; wounds; respiratory-tract congestion; adjunct in antibacterial therapy; sinusitis; breast engorgement; cystitis; epididymitis; wisdom tooth pericoronitis; alveolar abscess.

Unizink *Kohler, Ger.*
Zinc aspartate (p. 2126·1).
Zinc deficiency.

Unizitro *Tecnimede, Port.*
Azithromycin (p. 221·2).
Bacterial infections.

Unizol *Farmoquimica, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Uni-Zolate *Universal, Hong Kong.†*
Pipenzolate bromide (p. 1878·1).

Unizox *One Pharma, Philipp.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Unizuric *Quimica y Farmacia, Mex.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Uni-Zyme *Universal, Hong Kong.†*
Muramidase (p. 2565·1).

Unizyme *Ciba Vision, Canad.†; Novartis, Turk.*
⊗Subtilisin A (p. 2624·1).
Protein removal from contact lenses.

Unkeito *Tsumura, Jpn.*
⊗Ophiopogon tuber; pinellia tuber; angelica acutiloba root (p. 2443·3); liquorice (p. 1853·2); cinnamon bark (p. 2479·2); peony root; cnidium rhizome; ginseng (p. 2513·3); moutan bark; evodia fruit; ginger (p. 1844·1); gelatin (p. 1154·1).
Traditional Kampo medicine.

Uno *Ratiopharm, Cz.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders.

Uno Ciclo *Glenmark, Braz.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive.

Unocef *CCM, Malaysia.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Unodex *PP Lab, Thai.*
Iron dextran (p. 2075·3).
Iron-deficiency anaemia.

Unodol *Onedose, Spain.*
Ibuprofen (p. 68·2).
Fever; pain.

unofem *Hexal, Ger.†*
Levonorgestrel (p. 2296·1).
Post-coital oral contraceptive.

Unolin *PP Lab, Thai.*
Lincomycin hydrochloride (p. 317·1).
Anaerobic bacterial infections.

Unoplex *Offenbach, Mex.†*
Vitamins.

Unoprost
Note: this name may be used for preparations of different composition.
Apsen, Braz.
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia.

Guidotti, Ital.
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Unorox *Centaur, India.*
Roxithromycin (p. 356·2).
Bacterial infections.

Uno-Vit *Wiedemann, Ger.†*
dl-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Unoximed *Tai Yu, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Unplaque *Angelini, Gr.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis.

Unprozy *Condrugs, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Unseiin *Tsumura, Jpn.*
Rehmannia root; peony root; cnidium rhizome; angelica acutiloba root (p. 2443·3); skullcap root (p. 2617·1); phellodendron bark; coptis rhizome; gardenia fruit.
Traditional Kampo medicine.

Unstress *Heremco, Gr.*
Citalopram hydrochloride (p. 411·1).

Untano *Rafarm, Gr.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Unthecol *Bernofarm, Indon.†*
Dipyrone (p. 53·3); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Unwind Herbal Nytol *GSK Consumer, UK.*
Valerian (p. 2640·2); lupulus (p. 2546·1); wild lettuce (p. 2647·3).
Insomnia; stress.

UO *YSP, Malaysia; Yung Shin, Singapore; YSP, Thai.*
⊗Urea (p. 1727·3).
Dry skin disorders; ichthyosis; hyperkeratotic skin disorders.

Uonin *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections; meningitis prophylaxis.

U-Oscine *Umeda, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Uospan *Utopian, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Upanil *Leontik, Gr.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

U-Pasta *Kowa, Jpn.*
Sucrose (p. 2096·3); povidone-iodine (p. 1767·1).
Skin ulcers.

Upbutol *Unique, Rus.†*
Ethambutol hydrochloride (p. 296·1).

UP C *Metagenics, Canad.†*
Vitamin C (p. 2110·3).

UpCal D *Global Health, USA.*
Oral powder: Calcium (p. 1783·1); colecalciferol (p. 2113·1).

Global Health, USA.
Chewable tablets: Calcium citrate (p. 1783·2); magnesium (p. 1786·3); colecalciferol (p. 2113·1).
Dietary supplement.

Upderm *Genepharm, Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial skin and vaginal infections.

Upfen *UPSA Conseil, Fr.*
Ibuprofen (p. 68·2).
Pain; fever.

Upha B6 *CCM, Malaysia.*
Pyridoxine (p. 2105·3).
Vitamin B6 deficiency; isoniazid neuropathy; idiopathic sideroblastic anaemia; nausea and vomiting in pregnancy; radiation sickness.

Upha C *CCM, Malaysia.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Upha Dextrophan *CCM, Malaysia.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Upha e-Lyte *CCM, Malaysia.*
Sodium chloride (p. 1795·1); sodium citrate (p. 1781·2); potassium chloride (p. 1793·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration; diarrhoea; vomiting.

Upha Lozenges *CCM, Malaysia.*
Dequalinium chloride (p. 1749·3); tyrothricin (p. 384·1).
Mouth and throat infections.

Uphadyl Forte *CCM, Malaysia.*
Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1).
Cough; allergic respiratory-tract disorders.

Uphageron *CCM, Malaysia.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; migraine; nausea; vertigo.

Uphalexin *CCM, Malaysia; Upha, Singapore.*
Cefalexin (p. 234·1).
Bacterial infections.

Uphalyte *CCM, Malaysia; Upha, Singapore.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); sodium bicarbonate (p. 1781·1); potassium chloride (p. 1793·2) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Uphamol *CCM, Malaysia; Upha, Singapore.*
Paracetamol (p. 115·1).
Fever; pain.

Uphamol Flu *CCM, Malaysia.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Influenza symptoms.

Uphamol Plus Codeine *CCM, Malaysia.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
Pain; fever.

Uphastatin *CCM, Malaysia.*
Nystatin (p. 590·3).
Candidiasis.

Uphavit *CCM, Malaysia.*
Vitamins.
Dietary supplement.

Uphavit Plus *CCM, Malaysia.*
Vitamins; minerals.
Dietary supplement.

Uphaxicam *CCM, Malaysia.*
Piroxicam (p. 125·3).
Gout; musculoskeletal and joint disorders.

Uphold Plus *Johnson Diversey, Canad.*
Chloroxylenol (p. 1748·2); triclosan (p. 1773·2).

U-Pid *Patar, Thai.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Upixon *Bayer Consumer, Indon.*
Pyrantel embonate (p. 165·3).
Formerly contained piperazine.
Worm infections.

Uplores *Sanbe, Indon.; Sanbe, Singapore.*
Roxithromycin (p. 356·2).
Bacterial infections.

Upmotev *Teva, Mex.*
Risperidone (p. 1103·2).
Schizophrenia.

Upodine *Umeda, Thai.*
Povidone-iodine (p. 1767·1).
Disinfection of skin, wounds, and burns.

Upostelle *Consilient, UK.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Upperzin *Randril, Philipp.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Upren *Casel, Turk.*
Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Uprima *Abbott, Braz.; Abbott, Thai.*
Apomorphine hydrochloride (p. 892·3).
Erectile dysfunction.

Upro *Douglas, Canad.*
Vitamins; zinc (p. 2126·1).

Uprox *Farma-Projekt, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

U-Proxyn *Unison, Thai.†*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout.

Upsa C *BMS, Belg.; UPSA, China.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Upsala *Omega, Arg.*
Soya isoflavones (p. 2620·3); vitamin E (p. 2119·1).
Menopausal disorders.

Upsalgin-N *BMS, Gr.*
Aspirin (p. 22·2).
Pain; fever; inflammation.

Upsarin *BMS, Pol.; BMS, Rus.*
Aspirin (p. 22·2).
Fever; pain; thrombosis prophylaxis.

Upsarin C *BMS, Cz.; BMS, Pol.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Fever; pain.

Upsarin with Vitamin C *BMS, Rus.*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Pain; fever.

Upsaton *BMS, Gr.*
Magnesium aspartate (p. 1787·1); potassium aspartate (p. 1793·1); calcium fructoheptonate; lysine (p. 2079·3); vitamin B_6 (p. 2105·3); vitamin C (p. 2110·3).
Tonic.

Upsavit Vitamin C *BMS, Rus.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).

Uptran *Upson, Thai.*
Dipotassium clorazepate (p. 1056·3).

Upzene *Medicpharma, Thai.*
Dipotassium clorazepate (p. 1056·3).

UR 03 *Lafedar, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Liver and biliary-tract disorders; gallstones.

Uracet *Umeda, Thai.†*
Paracetamol (p. 115·1).
Pain; fever.

Uracid
Note: this name may be used for preparations of different composition.
Wesley, USA.
Methionine (p. 1558·2).
Odour, dermatitis, and ulceration in incontinent adults.

Uraciflor *Medicus, Gr.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Uracil *Pharmasant, Thai.*
Propylthiouracil (p. 2343·3).
Hyperthyroidism.

Uractone *SPA, Ital.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; hepatic cirrhosis; hypertension; nephrotic syndrome.

Uractonum *Medochemie, Singapore.*
⊗Spironolactone (p. 1499·3).
Hypertension; heart failure; liver cirrhosis with oedema; hyperaldosteronism; nephrotic syndrome.

Uracyst *Stellar, Canad.*
Chondroitin sulfate sodium (p. 2476·1).
Replacement of glycosaminoglycan layer in the bladder.

Uracyst Test Kit *Stellar, Canad.†*
Chondroitin sulfate sodium (p. 2476·1); potassium chloride (p. 1793·2).
Test for and treatment of bladder-wall glycosaminoglycan deficiency.

Urader Lactato *Medihealth, Mex.*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).
Dry skin disorders.

Uragem *Youliang, China.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Ural *Aspen, Austral.; Abbott, Malaysia; Abbott, NZ; Sigma, Philipp.*
Sodium bicarbonate (p. 1781·1); anhydrous sodium citrate (p. 1781·2); anhydrous citric acid (p. 2480·3); tartaric acid (p. 2626·1).
Dysuria; gout; urinary-tract infections; adjunct in antibacterial therapy; dyspepsia; urinary alkalinisation.

Uralit-U *Madaus, Rus.*
Potassium sodium hydrogen citrate (p. 1780·3).
Renal calculi; urinary alkalinisation.

Uralos *Casasco, Arg.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Uralyt Urato *Rottapharm, Spain.*
Citric acid (p. 2480·3); potassium citrate (p. 1780·3).
Renal calculi; renal tubular acidosis; hypocitraturia.

Uralyt-U *Madaus, Austria; Madaus, Belg.; Madaus, China; Madaus, Cz.; Madaus, Ger.; Rottapharm, Ger.; Madaus, Israel; Rottapharm, Ital.; Neo-Farmaceutica, Port.; Nycomed, S.Afr.; Madaus, Thai.; Madaus, Ukr.*
Potassium sodium hydrogen citrate (p. 1780·3).
Renal calculi; urinary alkalinisation; cystinuria; porphyria cutanea tarda.

Uramaxin *Medimetriks, USA.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders; nail disorders.

Uramilon *Biomedica, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Uramol *Stiefel, Chile; Stiefel, Mex.*
⊗Urea (p. 1727·3).
Dry skin.

Uramox *Taro, Israel.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; oedema; acute mountain sickness.

Urandil *Zentiva, Pol.†*
⊗Chlortalidone (p. 1335·2).
Hypertension; oedema.

Uranium Composé *Boiron, Fr.†*
Uranium nitricum; manganum (p. 2081·2); syzygium jambolanum; cineraria maritima; juglans regia (p. 2646·1); pancreine.
Homoeopathic preparation.

Uraplex *Madaus, Austria; Madaus, Cz.; 2care4, Denm.; Rottapharm, Gr.; Rottapharm, Ital.†; Rottapharm, Spain.*
Trospium chloride (p. 2371·1).
Bladder instability; urinary incontinence; bladder hyperactivity.

Urarthone *Lehning, Fr.*
Colchicum (p. 607·1); bryonia alba; solanum dulcamara (p. 2497·3); viscum album (p. 2560·2); kalium iodatum (p. 2336·3); aurum muriaticum natronatum (p. 2521·2); aqua silicata; sulfur (p. 1721·1); rubia; natrum salicylicum (p. 132·2); betula (p. 2457·3); mercurius corrosivus (p. 2555·2); aqua destillata (p. 2646·2); spiritus vini.
Homoeopathic preparation.

Homeocan, Canad.†
Betula pendula (p. 2457·3); bryonia alba; colchicum autumnale; dulcamara (p. 2497·3); kali iodatum (p. 2336·3); natrum salicylicum (p. 132·2); rubia tinctorium; silicata marina; sulfur (p. 1721·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Urasal *Axxess, Canad.†*
Methenamine (p. 322·3).
Urinary-tract infections.

Urasix *HB, Braz.*
⊗Furosemide (p. 1387·1).

Uratina *Prieto, Arg.*
Nitrofurantoin (p. 332·1).
Bacterial infections of the urinary tract.

Urazide *ANH, Thai.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema; diabetes insipidus.

Urazol *Tecnofarma, Chile.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability.

Urbal *Merck, Spain.*
Sucralfate (p. 1889·1).
Peptic ulcer; gastrointestinal haemorrhage.

Urbanil *Sanofi-Aventis, Braz.*
Clobazam (p. 518·2).
Anxiety; epilepsy.

Urbanol *Sanofi-Aventis, S.Afr.*
Clobazam (p. 518·2).
Anxiety; premedication; alcohol withdrawal syndrome.

Urbanyl *Sanofi-Aventis, Fr.; Sanofi-Aventis, Switz.*
Clobazam (p. 518·2).
Anxiety; alcohol withdrawal syndrome; epilepsy.

Urbason *Sanofi-Aventis, Austria; Sanofi-Aventis, Ger.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Spain; Sanofi-Aventis, Turk.*
⊗Methylprednisolone (p. 1642·2) or methylprednisolone sodium succinate (p. 1642·3).
Corticosteroid.

Urcyston Planta *Leros, Cz.*
Chamomile (p. 2474·1); sambucus (p. 2609·3); bearberry (p. 2453·2); equisetum (p. 2500·1); myrtillus (p. 2566·2); solidago (p. 2620·1); thyme (p. 2630·2).
Urinary-tract disorders.

Urdafalk *Darya-Varia, Indon.; Falk, Indon.*
Ursodeoxycholic acid (p. 2638·1).
Liver disorders; cholesterol gallstones.

Urdahex *Kalbe, Indon.*
Ursodeoxycholic acid (p. 2638·1).
Hepatitis; gallstones.

Urdes *Errekappa, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary disorders.

Urdox *Wockhardt, UK.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; primary biliary cirrhosis.

Urdoxa *Farmproekt, Rus.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; primary biliary cirrhosis; hepatitis; biliary dyspepsia.

Ureacin *Pedinol, USA.*
⊗Urea (p. 1727·3).
Dry skin; hyperkeratosis.

Ureacort *Orva, Turk.*
⊗Hydrocortisone acetate (p. 1640·1); urea (p. 1727·3).
Skin disorders.

Ureaderm Lactato *Medihealth, Mex.; Roemmers Medihe, Venez.*
⊗Urea (p. 1727·3); sodium lactate (p. 1781·2).
Dry skin disorders; hyperkeratosis.

Ureadin *Isdin, Arg.; Isdin, Braz.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders; dry skin disorders.

Isdin, Port.
⊗Urea (p. 1727·3); glycolic acid (p. 1704·3); salicylic acid (p. 1719·1).
Hyperkeratotic skin disorders.

Ureadin 5, 10, 20, 30, and 40 *Isdin, Port.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders; dry skin.

Ureadin 10 and 20 *Isdin, Chile.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders.

Ureadin 30
Note: this name may be used for preparations of different composition.
Isdin, Chile.
⊗Urea (p. 1727·3); dimeticone (p. 2209·3); arginine (p. 2049·1); lactic acid (p. 2539·1); allantoin (p. 1693·1).
Dry skin; hyperkeratotic skin disorders.

Ureadin Facial *Isdin, Arg.*
SPF 10: ⊗Urea (p. 1727·3); borage oil (p. 2459·2); ceramide 3 (p. 1699·1); glycerol (p. 2517·2); vitamin E acetate (p. 2119·2); lactic acid (p. 2539·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1).
Face cream containing sunscreens.

Isdin, Chile.
⊗Urea (p. 1727·3); borage oil (p. 2459·2); ceramide (p. 1699·1); sunscreens.
Dry skin.

Isdin, Port.
SPF 10: ⊗Urea (p. 1727·3); glycerol (p. 2517·2); borage oil (p. 2459·2); sunscreens.
Dry skin.

Ureadin Facial Antiarrugas *Isdin, Chile.*
SPF 10: ⊗Urea (p. 1727·3); ubidecarenone (p. 2637·1); dexpanthenol (p. 2582·2); ceramide (p. 1699·1); vitamin E (p. 2119·1); borage oil (p. 2459·2).
Photoaging of the skin.

Ureadin Forte *Isdin, Chile; Isdin, Port.*
⊗Urea (p. 1727·3); glycolic acid (p. 1704·3); nicotinamide (p. 2083·1); salicylic acid (p. 1719·1).
Hyperkeratotic skin disorders; dry skin disorders.

Ureadin Manos *Isdin, Port.*
⊗Urea (p. 1727·3); glycerol (p. 2517·2); lactic acid (p. 2539·1).
Dry skin.

Ureadin Pediatrics *Isdin, Chile.*
⊗Urea (p. 1727·3); gamolenic acid (p. 2509·2).
Skin disorders.

Ureadin 10 Plus *Isdin, Port.*
⊗Urea (p. 1727·3); dexpanthenol (p. 2582·2).
Dry skin disorders.

Ureadin Rx DB *Isdin, Chile.*
⊗Urea (p. 1727·3); Ureadyl; glycerol (p. 2517·2); lauromacrogol 400 (p. 2194·1); rosa mosqueta oil; centella triterpenes (p. 1698·3); allantoin (p. 1693·1); panthenol (p. 2582·2); arginine (p. 2049·1); bioecolia; dextran sulfate (p. 2492·2); vitamin E acetate (p. 2119·2); carnosita; aloe vera (p. 1693·2).
Dry skin; hyperkeratotic foot disorders.

Ureadin Rx PS *Isdin, Chile.*
⊗Urea (p. 1727·3); Ureadyl; salicylic acid (p. 1719·1); lauromacrogol 400 (p. 2194·1); allantoin (p. 1693·1); sorbitol (p. 2092·1); nicotinamide (p. 2083·1).
Psoriasis.

Ureadin Rx RD *Isdin, Chile.*
⊗Urea (p. 1727·3); Ureadyl; panthenol (p. 2582·2); hyaluronic acid (p. 2526·2); glycerol (p. 2517·2); lauromacrogol 400 (p. 2194·1); allantoin (p. 1693·1); panthenol (p. 2582·2); arginine (p. 2049·1); vitamin E (p. 2119·1); aloe vera (p. 1693·2); nicotinamide (p. 2083·1).
Dry skin; skin irritation.

Urealac *Hi-Tech, USA.†*
⊗Urea (p. 1727·3).
Dry skin disorders.

Urealeti *Bago, Chile.*
⊗Urea (p. 1727·3); panthenol (p. 2582·2); ceramide (p. 1699·1).

Ureaphil *Abbott, USA.†*
⊗Urea (p. 1727·3).
Cerebral oedema; raised intra-ocular pressure.

Ureaplasma-Immun *Biopharma, Ukr.*
Ureaplasma urealyticum immunoglobulin.
Passive immunisation.

Ureativ *Glenmark, Braz.*
⊗Urea (p. 1727·3).

Urecare *Orion, Austral.†; Orion, Hong Kong; Pfizer Consumer, Singapore.†*
⊗Urea (p. 1727·3).
Dry skin disorders; eczema.

Urecholine *MSD, Thai.; Barr, USA; Duramed, USA.*
Bethanechol chloride (p. 2456·2).
Urinary retention; neurogenic bladder; postoperative abdominal distension; congenital megacolon.

Urecortin *Proel, Gr.*
⊗Dexamethasone sodium phosphate (p. 1631·2); urea (p. 1727·3).
Skin disorders.

Urecrem *Ethicus, Arg.*
⊗Urea (p. 1727·3); lactic acid (p. 2539·1).
Dry skin disorders.

Urecrem Hidro *Ethicus, Arg.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Urederm *Valeant, Austral.; Chartwell, Canad.†; Hamilton, Hong Kong†; Roi Surya, Indon.†; Orva, Turk.*
⊗Urea (p. 1727·3).
Dry skin disorders; skin irritation; hyperkeratotic skin disorders.

Uree *Boiron, Canad.†; Riva, Canad.†*
⊗Urea (p. 1727·3).

Uregyt *Egis, Rus.; Egis, Ukr.*
⊗Etacrynic acid (p. 1378·2).
Oedema; hypertension.

PannonPharma, Hung.
⊗Sodium etacrynate (p. 1378·2).
Oedema.

Urelief Plus *Cypress, USA.*
Phenazopyridine hydrochloride (p. 124·3); hyoscyamine hydrobromide (p. 1848·1); secbutabarbital sodium (p. 1106·2).
Lower urinary-tract disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Urelium Neu *Kwizda, Austria.*
Ammi visnaga fruit (p. 2441·2); solidago virgaurea (p. 2620·1); taraxacum (p. 2625·3); aescin (p. 2431·2).
Renal calculi.

Urelle *Pharmelle, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract infections.

Urem *Kade, Ger.*
Ibuprofen (p. 68·2).
Pain; fever.

Uremide *Alphapharm, Austral.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension.

Uremol *GSK, Arg.; Stiefel, Canad.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Uremol-HC *Stiefel, Canad.*
⊗Hydrocortisone acetate (p. 1640·1); urea (p. 1727·3).
Skin disorders.

Uren *Laboratorios Chile, Chile.*
⊗Hydrochlorothiazide (p. 1403·2); triamterene (p. 1518·3).
Hypertension; oedema.

Ureotop *Dermapharm, Ger.*
⊗Urea (p. 1727·3).
Skin disorders.

Ureotop + VAS *Dermapharm, Ger.*
⊗Urea (p. 1727·3); tretinoin (p. 1725·2).
Keratinisation disorders.

Urepel *Uniao Quimica, Braz.*
⊗Urea (p. 1727·3).

Urequin *Craveri, Arg.*
Oxybutynin (p. 2361·2).
Bladder instability.

Uresan *Menarini, Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Uresix *Caprifarmindo, Indon.*
⊗Furosemide (p. 1387·1).
Oedema; ascites; hypertension.

Ureson *Vickmans, Hong Kong.†*
⊗Urea (p. 1727·3).

Uretic *Mylan, S.Afr.†*
⊗Furosemide (p. 1387·1).
Oedema.

Uretren Comp *Orion, Fin.*
⊗Triamterene (p. 1518·3); trichlormethiazide (p. 1519·3).
Hypertension; oedema.

Uretron *Marin, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract infections.

Urever *Biosel, Turk.*
⊗Furosemide (p. 1387·1).

Urex
Note: this name may be used for preparations of different composition.
Aspen, Austral.; Fawns & McAllan, Hong Kong; Healthcare Logistics, NZ; Biosel, Turk.
⊗Furosemide (p. 1387·1).
Oedema; hypertension; oliguria.

Vatring, USA.
Methenamine hippurate (p. 323·1).
Urinary-tract infections.

Urezol *Mavi, Mex.*
Phenazopyridine (p. 124·3).
Urinary-tract disorders.

Urfadyn PL *Zambon, Belg.*
Nifurtoinol (p. 331·3).
Urinary-tract infections.

Urfamycin *Zambon, Hong Kong; Zambon, Indon.; Zambon, Thai.; Bilim, Turk.†*
Thiamphenicol (p. 376·3) or thiamphenicol glycinate hydrochloride (p. 377·1).
Bacterial infections.

Urfamycine *Zambon, Belg.*
Thiamphenicol (p. 376·3) or thiamphenicol glycinate hydrochloride (p. 377·1).
Bacterial infections.

Urfekol *Medikon, Indon.†*
Thiamphenicol (p. 376·3).
Bacterial infections.

Urfetem *Ulagay, Turk.*
Thiamphenicol glycinate hydrochloride (p. 377·1).

Urgendol *Win-Medicare, India.*
Tramadol hydrochloride (p. 139·2).
Pain.

Urgenin *Madaus, Austria; Madaus, Belg.; Madaus, Hong Kong†; Madaus, Israel.†*
Echinacea purpurea (p. 2498·1); saw palmetto (p. 2363·3).
Prostatic and urinary-tract disorders.

Rottapharm, Spain.†
Echinacea angustifolia (p. 2498·1); saw palmetto (p. 2363·3); esculoside (p. 2431·2).
Prostatic and urinary-tract disorders.

Urgenin Cucurbitae oleum *Madaus, Ger.*
Cucurbita seed oil (p. 2489·2).
Urinary-tract disorders.

Urginol *Panalab, Arg.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Urgis *Cetus, Arg.†*
Ranitidine (p. 1882·1).
Peptic ulcer.

Urgo *Urgo, Cz.†*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Urgo Cicatrices *Urgo, Fr.*
⊗Hyaluronic acid (p. 2526·2); glycerol (p. 2517·2); allantoin (p. 1693·1); BioEcolia; sunscreens.
Skin lesions.

Urgo Cor *Urgo, Pol.†*
Salicylic acid (p. 1719·1).
Corns; calluses.

Urgo Hydrogel *Urgo, Ger.*
Guar gum (p. 475·1).
Wounds; ulcers.

Urgo sterile *Urgo, Ger.*
Sodium chloride (p. 1795·1).
Wounds.

Urgocall *Urgo, Spain.†*
Salicylic acid (p. 1719·1).
Corns; calluses.

UrgoCell Adhesive *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

Urgocell Ag *Urgo, Fr.*
Silver (p. 2615·1).
Wounds.

UrgoCell Contact *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

UrgoCell Heel Contact *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

Urgocell Lite *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

UrgoCell Non Adhesive *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

UrgoCell Silver *Urgo, Ger.*
Carmellose sodium (p. 2175·2); silver salt (p. 2615·1).
Wounds; burns.

UrgoCell Start *Urgo, Ger.*
Carmellose sodium (p. 2175·2); nano-oligosaccharide factor.
Wounds.

Urgoclean Kompresse *Urgo, Ger.*
Carmellose (p. 2175·1); ammonium polyacrylate.
Wounds.

Urgoclean Tamponade *Urgo, Ger.*
Ammonium polyacrylate.
Wounds.

Urgocor *Urgo, Cz.; Urgo, Fr.†; Urgo, Ger.†; Crefar, Port.*
Salicylic acid (p. 1719·1).
Calluses; corns.

Urgocor Coricide *Urgo, Rus.*
Salicylic acid (p. 1719·1).
Skin disorders.

Urgomed *Urgo, Belg.*
A hydrocolloid dressing.
Wounds.

Urgo, Fr.
Carmellose (p. 2175·1).
Wounds; burns.

Urgosan *Urgo, Ger.*
Zinc (p. 2126·1); iron (p. 2073·1); cocamidopropyl betaine; polihexanide (p. 1766·1); disodium edetate (p. 1550·3).
Wounds.

Urgosorb *Urgo, Belg.; Urgo, Ger.*
Calcium alginate (p. 1136·3).
Wounds.

Urgo, Fr.
Calcium alginate (p. 1136·3); carmellose (p. 2175·1).
Ulcers; wounds.

Urgosorb Silver *Urgo, Ger.*
Calcium alginate (p. 1136·3); silver (p. 2615·1).
Wounds.

UrgoSTART *Urgo, Ger.*
Carmellose sodium (p. 2175·2); nano-oligosaccharide factor.
Wounds.

Urgotul *Urgo, Fr.*
Carmellose (p. 2175·1).
Burns; ulcers; wounds.

Urgotül *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Burns; wounds.

Urgotül comfort *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

Urgotül Duo *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

Urgotül Lite Border *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

Urgotul S.Ag *Urgo, Fr.*
Carmellose (p. 2175·1); sulfadiazine silver (p. 362·3).
Burns.

Urgotül S.Ag *Urgo, Ger.*
Sulfadiazine silver (p. 362·3); carmellose sodium (p. 2175·2).
Burns.

Urgotül Silver *Urgo, Ger.*
Carmellose sodium (p. 2175·2); silver (p. 2615·1).
Wounds.

Urgotül Soft *Urgo, Ger.*
Carmellose sodium (p. 2175·2).
Wounds.

Uriadec *Sanwa, Jpn.*
Topiroxostat.
Hyperuricaemia; gout.

Uriage *D & M, Chile.*
Range of skin cleansers, moisturisers, and emollients.
Dry skin.

Saninter, Port.
A range of emollients, moisturisers, and soap substitutes.

Uriage Bariederm *D & M, Chile.*
Barrier preparation.

Uriage Bruma Autobronceante *D & M, Chile.*
Dihydroxyacetone (p. 1700·1).
Artificial suntan.

Uriage Crema Color *D & M, Chile.*
SPF 50: Titanium dioxide (p. 1725·1); bisoctrizole (p. 1697·1); octocrilene (p. 1715·2); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Sunscreen.

Uriage Crema Extra *D & M, Chile.*
SPF 50+: Bisoctrizole (p. 1697·1); octocrilene (p. 1715·2); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Sunscreen.

Uriage Crema Extrema *D & M, Chile.*
SPF 90: Titanium dioxide (p. 1725·1); aluminium hydroxide (p. 1817·2); octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Uriage Cu-Zn *D & M, Chile.*
Copper pidolate (p. 1720·3); zinc pidolate (p. 1720·3); zinc oxide (p. 1729·1).
Skin disorders.

Uriage Desodorante Tri-Actif *D & M, Chile.*
Aluminium chlorohydrate (p. 1694·1); ethylhexylglycerin (p. 1752·1); triethyl citrate (p. 2218·1).
Hyperhidrosis.

Uriage Extreme *Saninter, Port.†*
Cinnamate (p. 1699·2); titanium dioxide (p. 1725·1).
Sunscreen.

Uriage Protector Solar *D & M, Chile.†*
SPF 60: Bisoctrizole (p. 1697·1); octinoxate (p. 1715·1); avobenzone (p. 1695·1); octil triazone (p. 1715·1).
Sunscreen.

Uri-Alk *Medchem, S.Afr.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); anhydrous citric acid (p. 2480·3).
Urinary alkalinisation.

Uriben *Rosemont, UK.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Uribenz *RAN, Ger.†*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Uribeta *Probiomed, Mex.*
Interferon beta-1b (p. 996·1).
Multiple sclerosis.

Urica *Sandoz, Indon.*
Allopurinol (p. 600·2).
Gout; renal calculi; hyperuricaemia; hyperuricosuria.

Uricad *GreatEastern, Thai.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Uricalm *Cipla, Singapore.*
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); anhydrous citric acid (p. 2480·3); sodium citrate (p. 1781·2).
Urinary alkalinisation.

Uricine *Millimed, Thai.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; peptic ulcer; gastro-duodenitis; postoperative nausea and vomiting.

Uriclin *Astellas, Neth.†; Astellas, Port.*
Solifenacin succinate (p. 2367·3).
Bladder hyperactivity.

Uricnol *Kimia, Indon.*
Allopurinol (p. 600·2).
Gout; uric acid and calcium oxalate renal stones.

Uricon *Nycomed, S.Afr.*
Trospium chloride (p. 2371·1).
Bladder instability.

Uriconorm *Streuli, Switz.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Uricont *Rider, Chile.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder; urinary incontinence.

Uricrim *Mediphar, Venez.*
⊗Urea (p. 1727·3).
Hyperkeratosis; eczema.

Uridactone *Faran, Gr.*
⊗Spironolactone (p. 1499·3).
Oedema; liver cirrhosis; malignant ascites; nephrotic syndrome; heart failure; primary hyperaldosteronism.

Uridon *Panalab, Arg.*
Cranberry (p. 2488·1); ascorbic acid (p. 2110·3).
Dietary supplement; lower urinary-tract infections.

Uridoz *Therabel, Fr.*
Fosfomycin trometamol (p. 300·3).
Cystitis.

Uridril *Ni-The, Gr.*
Nalidixic acid (p. 328·3).

Uriduct *TAD, Ger.†*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia.

Urief *Kissei, Jpn.*
Silodosin (p. 2367·2).
Benign prostatic hyperplasia.

Uriflex C *SSL, UK.*
Chlorhexidine gluconate (p. 1743·3).
Urinary catheter care.

Uriflex G *Coloplast, UK.*
Citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1); light magnesium oxide (p. 1857·3); disodium edetate (p. 1550·3).
Urinary catheter care.

Uriflex R *Coloplast, UK.*
Citric acid (p. 2480·3); light magnesium carbonate (p. 1856·2); gluconolactone (p. 2515·2); disodium edetate (p. 1550·3).
Urinary catheter care.

Uriflex S *Coloplast, UK.*
Sodium chloride (p. 1795·1).
Urinary catheter care.

Uriflex W *Coloplast, UK.*
Sterile pyrogen free water (p. 2646·3).
Urinary catheter care.

Uriflorin *Mosfarma, Rus.*
Bearberry (p. 2453·2).
Urinary-tract inflammation.

Uriflow *Ying Yuan, Philipp.*
Bethanechol chloride (p. 2456·2).
Urinary retention.

Uriform *LRN, Fr.*
Cranberry (p. 2488·1).
Cystitis.

Urifron *Probiomed, Mex.*
Interferon alfa-2b (p. 989·2).
Malignant neoplasms; hepatitis B; hepatitis C.

Urigon *Demo, Gr.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Urihexal *Sandoz, S.Afr.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder; nocturnal enuresis.

Urikal *Rafa, Israel.*
Sodium citrate (p. 1781·2); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); sodium carbonate (p. 2617·3).
Urinary-tract infections.

Ürikoliz *Sandoz, Turk.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Urikrat Novum *Pharmacia Upjohn, Gr.*
Emepronium carrageenate (p. 2358·1).

Urilzid *Interhealthcare, Philipp.*
⊗Hydrochlorothiazide (p. 1403·2).
Hypertension; oedema.

Urimar-T *Marnel, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract infections.

Urimax
Note: this name may be used for preparations of different composition.
Bros, Gr.
Ofloxacin (p. 334·3).
Bacterial infections.

Cipla, India.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Xanodyne, USA.
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Lower urinary-tract disorders.

Urimax F *Cipla, India.*
Tamsulosin hydrochloride (p. 2369·1); finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Urinefrol *Lanpharm, Arg.*
Sarsaparilla (p. 2610·3); liquorice (p. 1853·2).

Urineg *Armoxindo, Indon.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Urinex *Kern, Switz.*
Birch leaf (p. 2457·3); buchu (p. 2461·3); java tea (p. 2536·3); bearberry (p. 2453·2); haricot bean; equisetum (p. 2500·1); solidago virgaurea (p. 2620·1); meadowsweet (p. 2550·2); calamus (p. 2464·2); calendula (p. 2465·2).
Urinary-tract disorders.

Urinol *JRalph, Philipp.; Lennon, S.Afr.†*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Urinorm *Torii, Jpn; ProStrakan, Spain.*
Benzbromarone (p. 603·3).
Hyperuricaemia; gout.

Urinox *Charoen Bhaesaj, Malaysia; Charoen, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Urinter *Interbat, Indon.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Urion *Zambon, Fr.; Sanofi-Aventis, Ger.†*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Uripax *YSP, Malaysia.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Uripiser *Serral, Mex.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Uriprim *Bial, Port.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Urirex-K *Aspen, S.Afr.*
⊗Hydrochlorothiazide (p. 1403·2); potassium chloride (p. 1793·2).
Oedema; hypertension.

Urisan *Tedec Meiji, Spain.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Urisec *Odan, Canad.*
⊗Urea (p. 1727·3).
Dry skin conditions.

Urisedon *Unipharma, Gr.*
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Urisept NF *Schering-Plough, Arg.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Uriseptic *SDA, USA.*
Methenamine (p. 322·3); salol (p. 129·3); methylthioninium chloride (p. 1559·1); benzoic acid (p. 1738·2); atropine sulfate (p. 1310·2); hyoscyamine sulfate (p. 1848·1).
Urinary-tract infections.

Uriseptin *Mulda, Turk.*
Nitrofurantoin (p. 332·1); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Urisoda *Cipla, India; Cipla, Malaysia.*
Sodium bicarbonate (p. 1781·1); tartaric acid (p. 2626·1); anhydrous citric acid (p. 2480·3); sodium citrate (p. 1781·2).
Urinary alkalinisation.

Urisol *Stadmed, India.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Urisold *Demo, Gr.*
Norfloxacin (p. 333·3).

Urispadol *Abigo, Denm.*
Flavoxate hydrochloride (p. 2360·1).
Neurogenic bladder.

Urispas *Takeda, Belg.; Paladin, Canad.; Negma, Fr.; Recordati, Hong Kong; Bushnell, India; Recordati, Irl.; Recordati, Malaysia; Takeda, Neth.; Jaba Recordati, Port.; Adcock Ingram, S.Afr.; Recordati, Singapore; Robapharm, Switz.; Recordati, Thai.; Shire, UK; SmithKline Beecham, USA.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract spasm; urinary-tract disorders.

Ürispas *Fako, Turk.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Uristix *Bayer, Austral.†; Siemens, Canad.†; Bayer Diagnostics, Irl.†; Bayer Diagnostics, UK; Siemens, USA.*
Test for glucose and protein in urine.

Uristix 4 *Siemens, USA.*
Test for glucose, protein, nitrite, and leucocytes in urine.

Uritact *Cypress, USA.*
Hyoscyamine sulfate (p. 1848·1); methenamine (p. 322·3); salol (p. 129·3); atropine sulfate (p. 1310·2); methylthioninium chloride (p. 1559·1); benzoic acid (p. 1738·2).
Lower urinary-tract disorders.

Uritent *Rottapharm, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).

Uritest *Siemens, Fr.†*
Test for glucose, protein, nitrite, and leucocytes in urine.

Uritest 2 *Siemens, Fr.†*
Test for leucocytes and nitrites in urine.

Uritest 10 *Urit, UK.*
Test for bilirubin, glucose, ketones, leucocytes, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen in urine.

Uritest 11A *Urit, UK.*
Test for ascorbic acid, bilirubin, glucose, ketones, leucocytes, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen in urine.

Uritest 11G *Urit, UK.*
Test for ascorbic acid, bilirubin, glucose, ketones, leucocytes, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen in urine.

Uritest 13G *Urit, UK.*
Test for nitrite, pH, glucose, protein, occult blood, ketones, urobilinogen, specific gravity, leucocytes, bilirubin, creatinine, calcium, and microalbumin in urine.

Uritest 10U *Urit, UK.*
Test for bilirubin, glucose, ketones, leucocytes, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen in urine.

Uritest 4V *Urit, UK.*
Test for glucose, ketones, occult blood, and protein in urine.

Uritest 5V *Urit, UK.*
Test for glucose, ketones, occult blood, pH, and protein in urine.

Uritest 1VG *Urit, UK.*
Test for glucose in urine.

Uritest 2VGK *Urit, UK.*
Test for glucose in urine.

Uritest 1VK *Urit, UK.*
Test for ketones in urine.

Uritest 1VP *Urit, UK.*
Test for protein in urine.

Uritest 2VPG *Urit, UK.*
Test for glucose, ketones, protein, and specific gravity in urine.

Uritest 3VPGp *Urit, UK.*
Test for pH and protein in urine.

Uritest 4VPGpSP *Urit, UK.*
Test for glucose, ketones, pH, protein, and specific gravity in urine.

Uritos *Kyorin, Jpn.*
Imidafenacin (p. 2360·2).
Bladder hyperactivity.

Uritracin *BioFemme, Philipp.; Great Eastern, Thai.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Uritrat *Libbs, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Urivesc *Madaus, Austria; 2care4, Denm.; Madaus, Ger.; Rottapharm, Ger.; Rottapharm, Gr.; Madaus, Ital.; Madaus, Port.; Madaus, Spain; Madaus, Thai.*
Trospium chloride (p. 2371·1).
Bladder hyperactivity.

Urixin *Abbott, Indon.; Abbott, Philipp.†*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Urizine *Unison, Hong Kong; Unison, Thai.†*
Cinnarizine (p. 622·1).
Vestibular disorders; motion sickness; cerebral and peripheral vascular disorders; migraine.

Urizone *Adcock Ingram, S.Afr.*
Fosfomycin trometamol (p. 300·3).
Urinary-tract Escherichia coli *infections.*

Uro Albin *Homviora, Ger.*
Solidago virgaurea (p. 2620·1); colchicum autumnale (p. 607·1); nasturtium aquaticum.
Homoeopathic preparation.

Uro Angiografin *Bayer, Spain.†*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Uro Blue *McNeil, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract infections.

Uroalquine *Rider, Chile.*
Sodium citrate (p. 1781·2); potassium citrate (p. 1780·3); anhydrous citric acid (p. 2480·3).
Acidosis; gout; renal calculi.

Urobacid *Sandoz, Gr.; Sandoz, Malaysia; Sandoz, Philipp.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Urobilin *Frankin, Hong Kong.†*
Nitrofurantoin (p. 332·1); phenazopyridine (p. 124·3).

Urobiotic-250 *Pfizer, USA.*
Oxytetracycline hydrochloride (p. 337·2); sulfamethizole (p. 365·1); phenazopyridine hydrochloride (p. 124·3).
Genito-urinary infections.

Uroc *Lampugnani, Ital.†*
Cinoxacin (p. 261·1).
Urinary-tract infections.

Urocalm *Sevene, Fr.*
Uva ursi (p. 2453·2); equisetum hiemale (p. 2500·1); urtica urens (p. 2639·3).
Homoeopathic preparation.

Urocalun *Shinyaku, China; Shinyaku, Hong Kong†; Shinyaku, Jpn; Shinyaku, Singapore.*
Quercus salicina (p. 2574·1).
Renal calculi.

Urocarb *Mayne, Austral.*
Bethanechol chloride (p. 2456·2).
Urinary retention; neurogenic bladder.

Urocard *Stada, Austria.*
Terazosin hydrochloride (p. 1511·1).
Hypertension; benign prostatic hyperplasia.

Urocare *Drogsan, Turk.*
Fosfomycin trometamol (p. 300·3).

Uro-Cephoral *Merck Serono, Ger.*
Cefixime (p. 240·3).
Bacterial infections.

Urochinasi *IFET (ΙΦΕΤ), Gr.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Urochol *Zhytomyr, Ukr.†*
Wild carrot (p. 2647·2); orthosiphon (p. 2536·3); knotgrass (p. 2538·2); corn silk (p. 2487·1); sambucus (p. 2609·3); equisetum (p. 2500·1); lupulus (p. 2546·1); birch buds (p. 2457·3); St John's wort (p. 449·1); peppermint leaf (p. 1877·1).
Renal calculi; biliary-tract disorders.

Urocholesan *Vifiteh, Rus.*
Oregano (p. 2576·3); castor oil (p. 2472·1); wild carrot (p. 2647·2); peppermint oil (p. 1877·1); fir oil (p. 2591·1); lupulus (p. 2546·1).
Urinary-tract disorders; biliary-tract disorders.

Urocinox *Biohealth, Ital.*
Cinoxacin (p. 261·1).
Urinary-tract infections.

UroCiproxin *Bayer, Turk.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Urocit *Pro Farma, Switz.*
Potassium citrate (p. 1780·3).
Renal calculi.

Urocit-K *Orphan, Austral.; Mission Pharmacal, Canad.; Mission Pharmacal, Hong Kong; Mission Pharmacal, Malaysia; Mission Pharmacal, Singapore; Aymed, Turk.; Mission Pharmacal, USA.*
Potassium citrate (p. 1780·3).
Hyperchloraemic acidosis; renal calculi; urinary alkalinising agent.

Uroclar *Eurodrug, Philipp.*
Rufloxacin hydrochloride (p. 357·1).
Urinary-tract infections.

Uroclasio NF *Italmex, Mex.*
Potassium citrate (p. 1780·3); citric acid (p. 2480·3).
Renal calculi; urinary alkalinisation.

Uro-Control *Delta Medical, Ukr.*
Cranberry (p. 2488·1); echinacea pupurea (p. 2498·1); buchu (p. 2461·3); juniper (p. 2537·1); bearberry (p. 2453·2); ascorbic acid (p. 2110·3).
Urinary-tract infections.

Urocran *Kapharma, Ukr.*
Cranberry (p. 2488·1); blueberry; bearberry (p. 2453·2); corn silk (p. 2487·1); parsley (p. 2583·3).
Urinary-tract disorders.

Uroctal *Almirall, Hong Kong†; Almirall, Spain.†*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Uroctrim *Legrand, Braz.*
Co-trimoxazole (p. 277·3); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Urocystil *Tilman, Belg.*
Bearberry (p. 2453·2).
Urinary-tract disorders.

Urodantina *Boehringer Ingelheim, Arg.*
Nitrofurantoin (p. 332·1).
Bacterial infections of the urinary tract.

Urodene *OFF, Ital.†*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Urodial *Bago, Chile.*
Flavoxate hydrochloride (p. 2360·1).
Genito-urinary-tract disorders.

Urodie *Sigmar, Ital.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Urodin *Streuli, Switz.†*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Urodixin *Santa, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Urodren *Sevene, Fr.*
Solidago virga aurea (p. 2620·1); thlaspi bursa pastoris (p. 2614·2); spiraea ulmaria (p. 2550·2).
Homoeopathic preparation.

Urodulox *Eurolab, Arg.*
Aceclofenac (p. 16·2).
Inflammation; pain.

Urofin *Mertens, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Uroflo *Amdipharm, Austria.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Uroflow *Zentiva, Cz.; Zentiva, Pol.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Uroflox
Note: this name may be used for preparations of different composition.
Armstrong, Mex.; Eurodrug, Thai.
Rufloxacin hydrochloride (p. 357·1).
Bacterial infections.

Bialfar, Port.
Norfloxacin (p. 333·3).
Bacterial infections.

Urofort *Leki Natury, Pol.*
Bearberry (p. 2453·2); solidago (p. 2620·1); urtica (p. 2639·3).
Urinary-tract disorders.

Urofos *Panalab, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Urofosfabol *Abolmed, Rus.*
Fosfomycin sodium (p. 300·3).
Bacterial infections.

Urofossat *Dreluso, Ger.*
Sabal serrulat (p. 2363·3); cantharis (p. 2469·2); tritic. repens (p. 2487·2).
Homoeopathic preparation.

Urofrin *Ameda, Ukr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Urofuran *Eurolab, Arg.*
Nitrofurantoin (macrocrystalline) (p. 332·1).
Bacterial infections of the urinary tract.

Urogem *Prodotti, Braz.†*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Urogesic *Atlantic, Singapore; Edwards, USA.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract disorders; irritation of the lower urinary tract.

Urogesic Blue *Edwards, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract infections.

Urogetix *Transfarma, Indon.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

Urogin *Sinnex, Hung.*
Bearberry (p. 2453·2); achillea (p. 2427·3); agrimony (p. 2432·3); urtica (p. 2639·3); equisetum (p. 2500·1); birch (p. 2457·3).
Urinary-tract disorders.

Urogliss *Montavit, Neth.†*
Chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Catheterisation.

Urogliss-S *Montavit, Neth.*
Chlorhexidine hydrochloride (p. 1743·3).
Catheterisation.

Urogotan A *Silesia, Chile.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Urografin *Bayer, Austral.; Bayer Schering, Denm.; Bayer, Gr.; Zydus, India; Bayer, Irl.; Bayer, Neth.; Bayer, NZ; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Swed.†*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Bayer, Turk.
Sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Urografin 150 *Bayer, UK.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Urografina *Bayer, Arg.; Bayer, Braz.; Bayer, Port.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Urografine *Bayer, Belg.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Urogutt
Note: this name may be used for preparations of different composition.
Farmasa, Mex.; Schwabe, Thai.
Saw palmetto (p. 2363·3).
Benign prostatic hyperplasia.

Schwabe, Austria.
Saw palmetto (p. 2363·3); urtica (p. 2639·3).
Benign prostatic hyperplasia.

Uroherb *Sinnex, Hung.*
Urtica (p. 2639·3); sage (p. 2608·3); bearberry (p. 2453·2); cucurbita (p. 2489·2); birch (p. 2457·3); salix (p. 129·2); achillea (p. 2427·3).
Prostatic disorders.

Uro-Hytrin *Abbott, Belg.†*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Urokam *Kamelia, Rus.*
Birch leaf (p. 2457·3); cranberry (p. 2488·1); bearberry (p. 2453·2).
Urinary-tract disorders.

Urokatt *Kattwiga, Ger.*
Serenoa repens (p. 2363·3); populus tremuloides (p. 2450·3).
Homoeopathic preparation.

Urokit *Casasco, Arg.*
Potassium citrate (p. 1780·3).
Renal calculi.

Uroknop *Knop, Chile.*
Lithium carbonicum; colchicum (p. 607·1); methenamine (p. 322·3); tartaric acid (p. 2626·1).
Gout; hyperuricaemia.

Uro-KP-Neutral *Star, USA.*
Minerals.
Phosphorus supplement.

Urol
Note: this name may be used for preparations of different composition.
Apogepha, Ger.
Solidago virgaurea (p. 2620·1).
Urinary-tract disorders.

Urol methin *Apogepha, Ger.*
Methionine (p. 1558·2).
Urinary acidification in antibiotic therapy.

Urol pros *Apogepha, Ger.*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Urolene Blue *Star, USA.†*
Methylthioninium chloride (p. 1559·1).
Cyanide poisoning; drug-induced methaemoglobinaemia; cystitis: urethritis.

Urolesan *Arterium, Rus.*
Marjoram (p. 2550·1); castor oil (p. 2472·1); wild carrot (p. 2647·2); peppermint oil (p. 1877·1); fir oil (p. 2591·1); lupulus (p. 2546·1).
Urinary-tract disorders; biliary-tract disorders.

Arterium, Ukr.
Pine oil (p. 2591·1); peppermint oil (p. 1877·1); castor oil (p. 2472·1); wild carrot (p. 2647·2); lupulus (p. 2546·1); origanum vulgare (p. 2576·3).
Renal calculi; cholelithiasis; cholecystitis; biliary tract dyskinesia.

Urolin *Polfa Grodzisk, Pol.†*
Pipemidic acid (p. 339·3).
Bacterial infections of the urinary tract.

Uroline *Mithra, Neth.*
Tolterodine tartrate (p. 2370·2).
Bladder hyperactivity.

Uro-Linfol *Omega, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract.

uro-loges *Loges, Ger.*
Ol. terebinthinae (p. 2636·3); berberis (p. 2502·1); solidago virgaurea (p. 2620·1); sarsaparilla (p. 2610·3).
Homoeopathic preparation.

Urologic G *Hospira, Canad.*
Citric acid (p. 2480·3); magnesium oxide (p. 1857·3); sodium carbonate anhydrous (p. 2617·3).

Urologická Čajová Směs *Megafyt-R, Cz.*
Birch leaf (p. 2457·3); bearberry (p. 2453·2); peppermint leaf (p. 1877·1); ononis (p. 2575·3); parsley (p. 2583·3); herniaria (p. 2525·1).
Urinary-tract disorders.

Urologin *Delta, Braz.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract disorders.

Urolosin *Boehringer Ingelheim, Spain.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Urolux Retro *Sanochemia, Ger.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for urinary-tract radiography.

Uro-Mag *Blaine, USA.*
Magnesium oxide (p. 1857·3).
Magnesium deficiency; hyperacidity.

Uromax
Note: this name may be used for preparations of different composition.
Cipla-Medpro, S.Afr.; Drogsan, Turk.
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Purdue, Canad.
Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity.

Uromed *Cimed, Braz.*
Bearberry (p. 2453·2).

Uromes *Sanfer, Mex.*
Mesna (p. 1557·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Uro-Micinovo *Bago, Chile.*
Co-trimoxazole (p. 277·3); phenazopyridine (p. 124·3).
Urinary-tract infections.

Uromil *IPRAD, Fr.*
Bearberry (p. 2453·2); green tea (p. 2648·2).
Dietary supplement; urinary-tract disorders.

Uromiro *Zambas, Gr.*
Meglumine iodamide (p. 1588·3).
Radiographic contrast medium.

Uromiron *Schering, Venez.*
Meglumine iodamide (p. 1588·3).
Radiographic contrast medium.

Uromisin *Kocak, Turk.*
Fosfomycin (p. 300·3).

Uromitexan *Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Chile; Baxter, China; Baxter Oncology, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter Oncology, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Zydus, India; Transfarma, Indon.; Baxter, Irl.; Baxter, Ital.; Shionogi, Jpn; Baxter, Neth.; Baxter Oncology, Norw.; Baxter, NZ; Baxter, Philipp.†; Baxter Oncology, Pol.; Baxter, Port.; Baxter, Rus.; Sanofi-Aventis, S.Afr.; Baxter Oncology, Singapore; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
Mesna (p. 1557·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Uromix
Note: this name may be used for preparations of different composition.
Agropharm, Pol.†
Betula; orthosiphon aristatus (p. 2536·3); solidago (p. 2620·1).
Urinary-tract disorders; rheumatism; gout; skin disorders.

Uromont *Montavit, Austria.*
⊗Dexamethasone (p. 1630·3); chlorhexidine hydrochloride (p. 1743·3); lidocaine hydrochloride (p. 1988·2).
Stricture prevention following transurethral procedures.

Uromunal *Leti, Venez.*
Escherichia coli.
Immunostimulant.

Uromykol *Maxmedic, Ger.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Uron *Aksu, Turk.*
Methenamine anhydromethylenecitrate (p. 322·3).
Urinary-tract infections.

Uronalin *Vitae, Mex.*
Nalidixic acid (p. 328·3).
Urinary-tract infections.

Uronase *Mochida, Jpn.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Uro-Nebacetin N *Nycomed, Ger.†*
Neomycin sulfate (p. 330·1).
Urinary-tract infections.

Uronefrex *Ferrer, Spain.*
Acetohydroxamic acid (p. 2427·1).
Renal calculi due to bacterial urease.

Uronephron *Farmak, Ukr.*
Onion (p. 2575·2); wheat grass root; birch leaf (p. 2457·3); fenugreek (p. 2504·1); parsley (p. 2583·3); solidago (p. 2620·1); equisetum (p. 2500·1); knotgrass (p. 2538·2); lovage root (p. 2545·3).
Urinary-tract disorders.

Uronid *Euro Registratie, Neth.†; Recordati, Spain.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders; bladder instability.

Uronovag
Note: this name may be used for preparations of different composition.
Gobbi, Arg.
Norfloxacin (p. 333·3).
Bacterial infections.

Novag, Mex.
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Uropac *EMS, Braz.*
Sulfamethoxypyridazine (p. 367·2); nitrofurantoin (p. 332·1); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Üropan *Kocak, Turk.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder instability; nocturnal enuresis.

Urophyton *Zeppenfeldt, Ger.*
Couch-grass (p. 2487·2).
Urinary-tract disorders.

Urophytum *Arkopharma, Fr.†*
Buchu (p. 2461·3); bearberry (p. 2453·2).
Urinary-tract disorders.

Uropielon *Legrand, Braz.*
Ampicillin (p. 218·2); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Uropimid *CT, Ital.; CT, Rus.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Uropimide *Rider, Chile.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Uropipedil *Viamedica, Spain.†*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Uropipemid *Carnot, Mex.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Uropol
Note: this name may be used for preparations of different composition.
Medac, Ger.
Chondroitin sulfate sodium (p. 2476·1).
Interstitial cystitis.

IMA, Braz.†
Co-trimoxazole (p. 277·3).
Urinary-tract infections.

Uro-POS *Croma, Austria†; Ursapharm, Ger.†*
Urtica (p. 2639·3).
Micturition disorders in males; benign prostatic hyperplasia.

Uropres *Farmak, Ukr.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus test of renal concentrating capacity.

Uroprost *Hasco-Lek, Pol.*
Arnica (p. 2447·2); shepherd's purse (p. 2614·2); St John's wort (p. 449·1); solidago (p. 2620·1); valerian (p. 2640·2); rapeseed.
Benign prostatic hyperplasia.

Altfarm, Rus.
Prostate extract (bovine) (p. 2444·1).
Prostate disorders.

Uroprost-Q *Ariston, Arg.*
Tamsulosin (p. 2369·1).

Uroprot *Laboratorios Chile, Chile; Teva, Mex.; Teva, Thai.*
Mesna (p. 1557·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Uropurat *Kwizda, Austria.†*
Bearberry (p. 2453·2); herniaria (p. 2525·1); equisetum (p. 2500·1); ononis (p. 2575·3).
Urinary-tract disorders.

Uropyrine *Pharmacobel, Belg.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract disorders.

Uroquidan *UCB, Spain.†*
Urokinase (p. 1520·3).
Thromboembolic disorders; intra-ocular haemorrhage.

Urorec *Recordati, Cz.; Bouchara-Recordati, Fr.; Recordati, Ger.; Recordati, Gr.; Recordati, Irl.; Recordati, Neth.; Recordati, Pol.; Recordati, Port.; Bouchara, Rus.; Recordati, Spain; Recordati, Ukr.*
Silodosin (p. 2367·2).
Benign prostatic hyperplasia.

Urorenal *Cheplapharm, Ger.†*
Birch leaf (p. 2457·3).
Urinary-tract disorders.

Urosal *Vis, Pol.*
Methenamine (p. 322·3); salol (p. 129·3).
Urinary-tract disorders; biliary-tract disorders; gastrointestinal disorders.

Urosamine *Unipharma, Gr.*
Methionine (p. 1558·2).

Urosan
Note: this name may be used for preparations of different composition.
AGIPS, Ital.
Pipemidic acid (p. 339·3).
Urinary-tract infections.
Herbapol Lublin, Pol.†
Birch leaf (p. 2457·3); equisetum (p. 2500·1); cowberry (p. 2487·3); chicory (p. 2475·2).
Urinary-tract disorders.

Urosedac *Eurolab, Arg.*
Cranberry (p. 2488·1); vitamin C (p. 2110·3).
Dietary supplement; urinary-tract disorders.

Urosedac Probiotic *Eurolab, Arg.*
Cranberry (p. 2488·1); lactobacillus (p. 2596·3); vitamin C (p. 2110·3).
Dietary supplement; urinary-tract disorders.

Uroselect *Dreluso, Ger.*
Cantharis (p. 2469·2); sarsaparilla (p. 2610·3); scilla (p. 1677·3).
Homoeopathic preparation.

Urosept *Herbapol Poznan, Pol.*
Birch (p. 2457·3); chamomile (p. 2474·1); petroselinum sativum; phaseolus vulgaris (p. 2587·3); cranberry (p. 2488·1); potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Urinary-tract disorders.

Uroseptal *Bago, Arg.; Bago, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Uroseptic *Arafarma, Spain.*
Fosfomycin trometamol (p. 300·3).
Urinary-tract infections.

Urosin
Note: this name may be used for preparations of different composition.
Roche, Austria.
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.
Yeni, Turk.
Ofloxacin (p. 334·3).
Bacterial infections.
YSP, Malaysia; Yung Shin, Singapore.
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension; migraine.

Urosiphon *Pierre Fabre, Fr.*
Java tea (p. 2536·3).
Diuretic; slimming aid.

Urospes-N *Specifar, Gr.*
Norfloxacin (p. 333·3).
Bacterial infections.

Urostad *Stada, Cz.; Stada, Hung.; Steigerwald, Pol.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Urostix *Bayer, India.†*
Test for glucose and protein in urine.

Uro-Tablinen *Winthrop, Ger.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Uro-Tainer *Braun, Belg.*
Chlorhexidine acetate (p. 1743·2).
Urinary-bladder lavage; urinary catheter care.

Uro-Tainer M *Braun, UK.*
Sodium chloride (p. 1795·1).
Vehicle for intravesical administration of drugs.

Uro-Tainer Solution R *Braun, UK.*
Citric acid (p. 2480·3); gluconolactone (p. 2515·2); light magnesium carbonate (p. 1856·2).
Urinary catheter care.

Uro-Tainer Suby G *Braun, UK.*
Citric acid (p. 2480·3); light magnesium oxide (p. 1857·3); sodium bicarbonate (p. 1781·1).
Urinary catheter care.

Uro-Tam *Valeant, Hung.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Urotam *Valeant, Cz.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Uro-Tarivid *Sanofi-Aventis, Ger.; Aventis, Israel.†*
Ofloxacin (p. 334·3).
Bacterial infections.

Urotem *Temis, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections of the urinary tract.

Urotem Dol *Temis, Arg.*
10 Tablets, norfloxacin (p. 333·3); 10 tablets, phenazopyridine (p. 124·3).
Bacterial infections of the urinary tract.

Urotisan *Lehning, Fr.†*
Birch leaf (p. 2457·3); black currant leaf (p. 2458·1); maize (p. 2487·1); ash (p. 2450·1); juniper (p. 2537·1); couch-grass (p. 2487·2).
Diuretic.

Urotol *Zentiva, Rus.; Zentiva, Ukr.*
Tolterodine tartrate (p. 2370·2).
Bladder instability; bladder hyperactivity.

Uroton *Biovena, Pol.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder.

Urotone *Samarth, India.*
Bethanechol chloride (p. 2456·2).
Neurogenic bladder; urinary retention.

Urotonin *VHB, India.*
Bethanechol chloride (p. 2456·2).
Urinary retention; neurogenic bladder.

Urototal *Fortbenton, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Urotractin *Eurodrug, Hong Kong; Sanbe, Indon.; Zambeletti, Indon.; Teofarma, Ital.; Eurodrug, Malaysia; Eurodrug, Rus.; Eurodrug, Singapore; Eurodrug, Thai.*
Pipemidic acid (p. 339·3).
Genito-urinary-tract infections.

Urotricef *Merck, Chile.*
Cefixime (p. 240·3).
Bacterial infections.

Urotrim *Medana, Pol.*
Trimethoprim (p. 381·2).
Bacterial infections of the urinary tract.

Urotrobel *Belfar, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Urotrol *Almirall, Spain.*
Tolterodine tartrate (p. 2370·2).
Bladder instability.

Urotruw N *Truw, Ger.*
Serenoa repens (p. 2363·3); pulsatilla pratensis (p. 2600·2); smilax (p. 2610·3); delphinium staphisagria; populus tremuloides (p. 2450·3).
Homoeopathic preparation.

Uro-Vaxom *Eurolab, Arg.; OM, Austria; Abbott, Belg.; Apsen, Braz.; Andromaco, Chile; Grunenthal, Mex.; OM, Philipp.; OM, Pol.; OM, Rus.; OM, Switz.; Abdi, Turk.; Astellas, Ukr.*
Escherichia coli.
Urinary-tract infections.
Gap, Gr.
Lyophilised *Escherichia coli.*
Lower urinary-tract infections.
OM, Cz.
Lysate of *Escherichia coli.*
Urinary-tract infections.
OM, Port.
Lyophilised extract of *Escherichia coli.*
Urinary-tract infections.
Vifor, Ger.
Lysed immuno-active fraction of *Escherichia coli.*
Urinary-tract infections.

Urovec *Collins, Mex.†*
Phenazopyridine (p. 124·3); sulfafurazole (p. 364·1); tetracycline (p. 373·1).
Urinary-tract infections.

Urovideo *Santa, Turk.*
Amidotrizoic acid (p. 1581·2).
Radiographic contrast medium.

Urovisona *Bayer, Arg.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Contrast medium for urography.

Urovist-Angiografin *Bayer, Turk.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Urovit *Uniao Quimica, Braz.*
Phenazopyridine hydrochloride (p. 124·3).

Uroxacin
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Norfloxacin (p. 333·3).
Bacterial infections of the genito-urinary tract.

Uroxal
Note: this name may be used for preparations of different composition.
Fournier, Cz.; Fournier, Hung.
Oxybutynin hydrochloride (p. 2361·2).
Urinary incontinence; bladder instability; nocturnal enuresis; urge incontinence.
Sandoz, Indon.
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Uroxate *General Drugs, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

UroXatral *Sanofi-Aventis, Arg.; Sanofi-Aventis, Chile; Sanofi-Aventis, Ger.†; Covis, USA.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Uroxazol-N *Bunker, Braz.*
Norfloxacin (p. 333·3).
Bacterial infections.

Uroxin
Note: this name may be used for preparations of different composition.
Julphar, UAE.
Norfloxacin (p. 333·3).
Bacterial infections.
Unison, Hong Kong; Unison, Singapore.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.
Unison, Thai.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Uroxina *Farmalab, Braz.*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Urozide *Valeant, Canad.*
⊗Hydrochlorothiazide (p. 1403·2).

Urpem *Zwitter, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

URSA *Daewoong, Thai.*
Ursodeoxycholic acid (p. 2638·1).
Liver disorders; biliary-tract disorders.

Ursacol *Zambon, Braz.; Zambon, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Ursa-Fenol *Farmex, Gr.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Ursa-Fin *Farmex, Gr.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye inflammation.

Ursical Formula *Herbasante, Canad.†*
Calcium carbonate (p. 1824·3); calcium phosphate tribasic (p. 1784·2); calcium silicate (p. 1784·3); sodium phosphate dibasic (p. 1791·2); urtica dioica (p. 2639·3).
Homoeopathic preparation.

Ursidesox *Duncan, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; biliary-tract disorders.

Ursilon *IBI, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Ursinol *Steierl, Ger.*
Chimaphila umbellata; populus tremuloides (p. 2450·3); serenoa repens (p. 2363·3).
Homoeopathic preparation.

Ursinus Inlay-Tabs *Novartis, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); aspirin (p. 22·2).
Upper respiratory-tract symptoms.

Urso *Aspen, Austral.; Aptalis, Canad.; Mitsubishi Tanabe, Hong Kong; Mitsubishi Tanabe, Jpn; Aptalis, USA.*
Ursodeoxycholic acid (p. 2638·1).
Cholestatic liver disorders; hypercholesterolaemia; anorexia; dyspepsia; cholesterol gallstones; biliary-tract disorders.

Ursobil *ABC, Ital.*
Ursodeoxycholic acid (p. 2638·1) or sodium sulfate ursodeoxycholate.
Biliary-tract disorders.

Ursobilane *Estedi, Spain.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; biliary cirrhosis.

Ursocam *Polfarmex, Pol.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; hepatobiliary cirrhosis.

Ursochol *Zambon, Belg.; Zambon, Cz.; Zambon, Ger.; Zambon, Indon.; Zambon, Neth.; Zambon, Spain; Zambon, Switz.; Darnitsa, Ukr.*
Ursodeoxycholic acid (p. 2638·1).
Cholestatic liver disorders; hepatitis; biliary-tract disorders; cystic fibrosis; cholesterol gallstones; dyspepsia.

Ursodamor *Damor, Ital.†*
Sodium succinate ursodeoxycholate (p. 2638·1).
Biliary-tract disorders.

Ursodex *Sun, Rus.*
Ursodeoxycholic acid (p. 2638·1).
Primary biliary cirrhosis; biliary reflux; cholesterol gallstones.

Ursofalk *Biotoscana, Arg.; Orphan, Austral.; Merck, Austria; Falk, Belg.; Biotoscana, Chile; Falk, China; Falk, Cz.; Falk, Ger.; Galenica, Gr.; Falk, Hong Kong; Falk, Hung.; Falk, Irl.; Falk, Israel; Falk, Malaysia; Farmasa, Mex.; Falk, Neth.; Falk, Norw.; Healthcare Logistics, NZ; Falk, Philipp.; Falk, Pol.; Falk, Port.; Falk, Rus.; Falk, Singapore; Meda, Swed.; Vifor, Switz.; Falk, Thai.; Ali, Turk.; Falk, UK; Falk, Ukr.*
Ursodeoxycholic acid (p. 2638·1).
Biliary tract disorders; cholesterol gallstones; dyspepsia; gastritis; gastric reflux; sclerosing cholangitis; cholestatic liver disease.

Ursoflor *SoSe, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Ursogal *Galen, UK.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones.

Ursolic *Guardian, Indon.*
Ursodeoxycholic acid (p. 2638·1).
Hepatitis; cholesterol gallstones.

Ursolin *Berlin Pharm, Thai.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders; liver disorders; dyspepsia.

Ursolisin *Magis, Ital.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders.

Ursolit *CTS, Israel.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; liver disorders.

Ursoliv *Avva, Rus.*
Ursodeoxycholic acid (p. 2638·1).
Primary biliary cirrhosis; biliary reflux; cholesterol gallstones.

Ursolvan *Sanofi-Aventis, Fr.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; cholestasis.

Ursomax *Larco, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Biliary-tract disorders; cholesterol gallstones.

Ursopol *ICN, Pol.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; hepatobiliary cirrhosis.

Ursorom *Rompharm, Rus.*
Ursodeoxycholic acid (p. 2638·1).
Liver and biliary-tract disorders.

Ursosan *ProMed, Cz.; Mitsubishi-Tokyo, Hong Kong†; ProMed, Rus.; Evolan, Swed.; ProMed, Ukr.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones; liver and biliary-tract disorders; cystic fibrosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Ursotan *Sanofi-Aventis, S.Afr.*
Ursodeoxycholic acid (p. 2638·1).
Cholesterol gallstones.

Urtica Complexe No 82 *Lehning, Fr.†*
⊗Urtica urens (p. 2639·3); ledum palustre (p. 2550·1); kalium nitricum (p. 1766·2); acide benzoicum (p. 1738·2); kalium iodatum (p. 2336·3); aconitum (p. 2428·3); atropa belladonna (p. 2453·3); thuya (p. 2629·3); mercurius corrosivus (p. 2555·2); arsenicum album (p. 2448·1).
Homoeopathic preparation.

Urticalcin *Bioforce, Canad.; Bioforce, Switz.*
Urtica dioica (p. 2639·3); silicea (p. 2208·3); calcarea carbonica (p. 1824·3); calcarea phosphorica (p. 1784·2); natrum phosphoricum (p. 1791·2).
Homoeopathic preparation.

Urtica-Plus
Note: this name may be used for preparations of different composition.
Doctor H, Rus.
Apis mellifera (p. 2445·2); calendula officinalis (p. 2465·2); graphites (p. 2522·1); sulfur (p. 1721·1); urtica urens (p. 2639·3); calcium carbonicum (p. 1824·3).
Homoeopathic preparation.

Urticef *Pediatrica, Indon.; Prafa, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Urtigen *Sons, Mex.†*
Astemizole (p. 616·1).
Hypersensitivity.

Urtikalma *Fecofar, Arg.*
Calamine (p. 1697·2); diphenhydramine hydrochloride (p. 626·2).
Pruritus.

Urtilar *Promed, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Urtimed *Pfleger, Ger.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

Urtisin *Pisa, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Urtivac *Darrow, Braz.*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Urtivit *Ruhrpharm, Ger.†*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Urtix *Labofarm, Pol.*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Urtizon complex *TS Reform, Neth.*
Apis mellifica (p. 2445·2); calcarea carbonica ostrearum (p. 1824·3); glandula suprarenalis suis (p. 2444·1); histaminum muriaticum (p. 2525·2); ledum palustre (p. 2550·1); mezereum; natrium muraticum (p. 1795·1); sulfur (p. 1721·1); urtica urens (p. 2639·3).
Homoeopathic preparation.

Urtotre *SarPharm, Ital.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Uryl *Portal, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).

Urzac *Quesada, Arg.*
Ursodeoxycholic acid (p. 2638·1).
Gallstones; liver and biliary-tract disorders.

Usaltron *Maver, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Usamema *Icon, Philipp.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; uterine bleeding.

Usana AO Pro *Usana, Mex.*
Vitamins.

Usana Min *Usana, Mex.*
Minerals.

Usanatal *Icon, Philipp.*
Vitamins; minerals; ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Nutritional supplement for pregnancy and lactation.

Usanimals *Usana, Canad.; Usana, Mex.*
Vitamins; minerals.

Usana, Singapore.†
Vitamins; minerals; phytonutrients.

Usana, Hong Kong.†
Vitamins; minerals; hesperidin (p. 2505·2).

Usenta *Raffo, Arg.†; Tecnofarma, Chile.*
Bosentan (p. 1327·1).
Pulmonary hypertension.

Uslin *United Lab, China.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Usneabasan *Sanum-Kehlbeck, Ger.*
Usnea barbata e thallo siccato (p. 2640·2).
Homoeopathic preparation.

Usniderm *Proel, Gr.*
⊗Neomycin sulfate (p. 330·1); dexamethasone sodium phosphate (p. 1631·2).

Usno *Biomedica, Gr.*
Diltiazem hydrochloride (p. 1359·2).

Usocalm *Utopian, Thai.*
Tolperisone hydrochloride (p. 2027·3).
Spasticity; skeletal muscle spasm.

Usovan *Utopian, Thai.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

U-Spa *Sriprasit, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Uspokoi *Materia Medica, Rus.*
Cimicifuga (p. 2478·1); strychnos ignatii (p. 2532·1); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Ustell *BioComp, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract disorders.

Ustilakehl *Sanum-Kehlbeck, Ger.*
Ustilago zeae e sporibus.
Homoeopathic preparation.

Ustiosan *Kelemata, Ital.*
Procaine hydrochloride (p. 1994·3); lidocaine hydrochloride (p. 1988·2); hydroxyquinoline sulfate (p. 2530·1).
Minor wounds and burns; skin irritation.

Usualix *Elea, Arg.*
⊗Ephedrine hydrochloride (p. 1663·2); phenazone (p. 124·1).
Allergic conjunctivitis; eye irritation.

UT 380 *CCD, Fr.; Amnol, Ital.*
Copper-wound plastic (p. 2057·1).
Intra-uterine contraceptive device.

Utabon *Uriach, Singapore†; Uriach Aquilea OTC, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Utabon Complex *Uriach Aquilea OTC, Spain.*
⊗Oxymetazoline hydrochloride (p. 1671·3); chlorphenamine maleate (p. 620·3).
Allergic rhinitis.

Utac
Note: this name may be used for preparations of different composition.
Breckenridge, USA.
Methenamine mandelate (p. 323·1); monobasic sodium phosphate (p. 1791·1).
Urinary-tract infections.

Millimed, Thai.†
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Utahzone *Daewon, Hong Kong.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Utalk *Kurtsan, Turk.†*
Undecenoic acid (p. 596·3); zinc undecenoate (p. 596·3).
Fungal skin infections.

Utefos *Mylan, Spain.*
Tegafur (p. 864·2).
Malignant neoplasms.

Utel *Farmex, Gr.*
Loratadine (p. 633·2).
Allergic disorders.

Uteplex *Biodim, Fr.*
Trisodium uridine triphosphate (p. 2638·1).
Musculoskeletal disorders.

Utergin *Svizera, India; Ikapharmindo, Indon.*
Methylergometrine maleate (p. 2137·3).
Postpartum atony; postpartum haemorrhage; uterine subinvolution; puerperal sepsis; uterine bleeding.

Uterine
Note: this name may be used for preparations of different composition.
LBS, Philipp.
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage; uterine subinvolution.

Omega, Arg.
Isoxsuprine hydrochloride (p. 2535·2).
Premature labour; threatened miscarriage; uterine tetany.

Uterjin *Biofarma, Turk.*
Methylergometrine maleate (p. 2137·3).
Postpartum haemorrhage.

Uterone *Jagsonpal, India.*
Progesterone (p. 2300·2).
Dysfunctional uterine bleeding; premenstrual syndrome; puerperal depression; assisted conception; recurrent miscarriage.

Utibid *Lupin, Rus.*
Norfloxacin (p. 333·3).
Bacterial infections.

Utiblack *Rafarm, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Mouth disorders.

Uticap *Cypress, USA.*
Methenamine (p. 322·3); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); hyoscyamine sulfate (p. 1848·1).
Urinary-tract disorders.

Uticin *Pharmacare, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Uticina *SoSe, Ital.*
Norfloxacin (p. 333·3).
Bacterial urinary-tract infections.

Uticox *Yer, Spain.†*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Utidol *Diba, Mex.*
Dipyrone (p. 53·3).
Pain; fever.

Utiflox *Blue Sky, Philipp.*
Norfloxacin (p. 333·3).
Bacterial infections.

Utifloxa *Watson, S.Afr.*
Norfloxacin (p. 333·3).

Utilin H *Sanum-Kehlbeck, Ger.*
Bacillus subtilis.
Homoeopathic preparation.

Utilin S *Sanum-Kehlbeck, Ger.†*
Mycobacterium phlei.
Immunotherapy.

Utiminx *Madaus, Austria; Rottapharm, Gr.*
Ciprofloxacin hydrochloride (p. 261·2).
Urinary-tract infections in women.

Utin *Cipla-Medpro, S.Afr.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Utinor *Neopharmed, Ital.; Unison, Philipp.; MSD, UK.*
Norfloxacin (p. 333·3).
Bacterial infections.

Utira *Hawthorn, USA.*
Hyoscyamine sulfate (p. 1848·1); methylthioninium chloride (p. 1559·1); monobasic sodium phosphate (p. 1791·1); methenamine (p. 322·3); salol (p. 129·3).
Urinary-tract pain and irritation.

Utisept *ST, Thai.†*
Trimethoprim (p. 381·2).
Urinary-tract infections.

utk *TAD, Ger.*
Urtica (p. 2639·3).
Benign prostatic hyperplasia.

Utmos *Berlin Pharm, Thai.*
Pioglitazone (p. 493·1).
Diabetes mellitus.

Uto Lincomycin *Utopian, Thai.*
Lincomycin hydrochloride (p. 317·1).
Gram-positive bacterial infections.

Uto Vitavit *Utopian, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Dietary supplement.

Utocillin *Utopian, Thai.*
Ampicillin (p. 218·2).
Bacterial infections.

Utofin *Utopian, Thai.*
Ceftriaxone sodium (p. 253·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Utoin *Umeda, Thai.*
Phenytoin sodium (p. 538·2).
Epilepsy; arrhythmias; seizures following neurosurgery; status epilepticus.

Utolid *Utopian, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Utomycin *Utopian, Thai.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Utopic *Artesa, USA.*
⊗Urea (p. 1727·3).
Hyperkeratotic skin disorders.

Utoral *Korea United, Philipp.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Utorax *Utopian, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2); clidinium bromide (p. 1833·2).

Utosamide *Utopian, Thai.*
Niclosamide (p. 161·2).
Taeniasis.

Utovlan *Pharmacia, UK.*
Norethisterone (p. 2294·2).
Menstrual disorders; breast cancer; endometriosis.

Utrex *Sandoz, Indon.†*
Pipemidic acid (p. 339·3).
Urinary-tract infections.

Utrogest *Besins, Ger.; Kade, Ger.*
Progesterone (p. 2300·2).
Menopausal disorders.

Utrogestan *Ferring, Arg.; Meda, Austria; Besins, Belg.; Farmoquimica, Braz.; Besins, China; Besins, Cz.; Besins, Fr.; Angelini, Gr.; Faran, Gr.; Besins, Hong Kong; Besins, Hung.; Besins, Irl.; Besins International, Israel; Besins, Malaysia; CORNE, Mex.; Besins, Neth.; Pharmaco, NZ; Jaba Recordati, Port.; Besins, Rus.; Medi Challenge, S.Afr.; Besins, Singapore; Seid, Spain; Vifor, Switz.; Besins, Thai.; Marlborough Pharmaceuticals, UK; Besins, Ukr.; Biopas, Venez.*
Progesterone (p. 2300·2).
Menstrual disorders; benign breast disorders; menopausal disorders; female infertility; premature labour; endometriosis; dysfunctional uterine bleeding; amenorrhoea; mastalgia; threatened or recurrent miscarriage; progesterone deficiency; uterine fibroids; premenstrual syndrome; mastopathy.

Utrona-C *Cypress, USA.*
Hyoscyamine sulfate (p. 1848·1); monobasic sodium phosphate (p. 1791·1); salol (p. 129·3); methylthioninium chloride (p. 1559·1); methenamine (p. 322·3).
Urinary-tract disorders.

UV Essentiel *Chanel, Canad.*
Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

UV Protectant *Norwood, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

UV Protective *Kiehl's, USA.*
Avobenzone (p. 1695·1); ecamsule (p. 1702·1); octocrilene (p. 1715·2).
Sunscreen.

UV Triplegard *Valeant, Austral.*
SPF 30+; SPF 15: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

UV Triplegard Face *Valeant, Austral.*
SPF 30+: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

UV Triplegard Kids *Valeant, Austral.*
SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); zinc oxide (p. 1729·1).
Sunscreen.

UV Triplegard Natural *Valeant, Austral.*
SPF 30+: Zinc oxide (p. 1729·1).
Sunscreen.

UV Triplegard Sensitive *Valeant, Austral.*
SPF 30+: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

UV Triplegard Sports *Valeant, Austral.*
SPF 30+: Octinoxate (p. 1715·1); enzacamene (p. 1703·2); avobenzone (p. 1695·1); octocrilene (p. 1715·2).
Sunscreen.

UV Triplegard SunStick *Valeant, Austral.*
SPF 30+: Octocrilene (p. 1715·2); oxybenzone (p. 1715·3); octinoxate (p. 1715·1); avobenzone (p. 1695·1).
Sunscreen.

UV Triplegard Sunstick & Lip Balm *Boots Healthcare, Austral.†*
SPF 30+: Octinoxate (p. 1715·1); octocrilene (p. 1715·2); zinc oxide (p. 1729·1).
Sunscreen.

Uva Ursi Complexe No 9 *Lehning, Fr.*
Uva ursi (p. 2453·2); anemone pulsatilla (p. 2600·2); euphrasia (p. 2502·1); helleborus; atropa belladonna (p. 2453·3); argentum colloidal (p. 2616·2); aconitum (p. 2428·3); coccus cacti (p. 2179·2).
Homoeopathic preparation.

Uvacin *Lichtwer, UK.*
Taraxacum (p. 2625·3); bearberry (p. 2453·2).
Female bladder discomfort.

Uvadex *Johnson & Johnson, Cz.; Therakos, Fr.; Therakos, Ger.; IFET (ΙΦΕΤ), Gr.; Therakos, Gr.; Johnson & Johnson, Neth.; Johnson & Johnson, Port.; Janssen-Cilag, Switz.†; Therakos, USA.*
Methoxsalen (p. 1711·3).
Cutaneous T-cell lymphoma.

Uvagen *Medifarm, Venez.*
Resveratrol (p. 2603·2); vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3); ubidecarenone (p. 2637·1); yeast (p. 2125·2).
Antoxidant.

Uvalysat *Ysatfabrik, Ger.*
Bearberry leaf (p. 2453·2).
Urinary-tract infections.

Uvamin *Mepha, Israel.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Uvamine retard *Mepha, Switz.*
Nitrofurantoin (p. 332·1).
Urinary-tract infections.

Uvanox *Knop, Chile.*
Grape (p. 2521·3).
Lymphoedema; sight disorders; venous insufficiency.

Uvasal *GSK, Arg.*
Sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3); sodium carbonate (p. 2617·3).
Dyspepsia.

Uvasal Doble Accion *GSK, Arg.*
Sodium bicarbonate (p. 1781·1); paracetamol (p. 115·1).

Uvasal Tums *GSK, Arg.*
Calcium carbonate (p. 1824·3).
Gastric hyperacidity.

Uvédose *Crinex, Fr.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Uvega *Hormona, Mex.*
Lidocaine hydrochloride (p. 1988·2).
Otitis externa.

Uveil PS *Medihealth, Mex.; Roemmers Medihe, Venez.*
Titanium dioxide (p. 1725·1).
Sunscreen.

Uversan *Medana, Pol.*
Bearberry (p. 2453·2).
Urinary-tract infections; disturbances of gastrointestinal flora.

Uvestérol ADEC *Crinex, Fr.*
Vitamins.

Uvestérol D *Crinex, Fr.*
Ergocalciferol (p. 2113·3).
Vitamin D deficiency.

Uvicol *Alcon, Fr.†*
Actinoquinol (p. 2429·3); oxedrine hydrochloride (p. 1463·2).
Eye congestion.

Uvimag B_6 *Zambon, Fr.*
Magnesium glycerophosphate (p. 1787·2); pyridoxine hydrochloride (p. 2105·3).
Vitamin and mineral supplementation.

Uvirgan mono *Abbott, Ger.†*
Cucurbita (p. 2489·2).
Urinary-tract disorders.

Uvistat *LPC, UK.*
SPF 50: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octocrilene (p. 1715·2); bisoctrizole (p. 1697·1); amiloxate (p. 1694·1).
Sunscreen.

LPC, UK.
SPF 20; SPF 30: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octocrilene (p. 1715·2); bisoctrizole (p. 1697·1).
Sunscreen.

Uvistat Eye Drops *LPC, UK.*
Hypromellose (p. 2189·2); dexpanthenol (p. 2582·2).
Dry eyes.

Uvistat Lipscreen *LPC, UK.*
SPF 50: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1); octocrilene (p. 1715·2); bemotrizinol (p. 1695·3).
Sunscreen.

Boehringer Ingelheim, Irl.†
SPF 25; SPF 30: Avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Uvistat Lotion *Boehringer Ingelheim, Irl.†*
SPF 15; SPF 20; SPF 30; SPF 50: Octinoxate (p. 1715·1); avobenzone (p. 1695·1); titanium dioxide (p. 1725·1).
Sunscreen.

Uvless *Theraskin, Braz.*
Panthenol (p. 2582·2); avobenzone (p. 1695·1); oxybenzone (p. 1715·3); enzacamene (p. 1703·2); octinoxate (p. 1715·1); padimate (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

UV-Luar *Luar, Arg.†*
Hydroxymethylquinoline.
Sunscreen.

Uvox *Salvay, India.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Uvu *Chemica, Gr.*
Codergocrine mesilate (p. 389·2).

UV-X-Ribo-Dextran *Concept, Israel.*
Riboflavin (p. 2104·3) in dextran.
Corneal cross-linking in keratoconus.

Uwobletten Arteriosklerose-Complex *Hevert, Ger.†*
Arnica (p. 2447·2); arsenum jodat. (p. 2448·1); crataegus (p. 2488·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Uxalun *Sandoz, Arg.; Novartis, Braz.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Uxen *Sanofi-Aventis, Arg.*
Amitriptyline hydrochloride (p. 401·1).
Depression.

Uxicolin *Pisa, Mex.†*
Suxamethonium chloride (p. 2037·1).
Depolarising neuromuscular blocker.

Uzara
Note: this name may be used for preparations of different composition.
Hemopharm, Ger.; Stada, Rus.
Xysmalobium undulatum.
Diarrhoea.

Stada, Hung.; Stada, Ukr.
Xysmalobium undulatum root.
Diarrhoea.

Uze Active *Biosintex, Arg.*
Quassia (p. 2601·1); acetic acid (p. 2426·3).
Pediculosis.

Uzel *Taiho, Jpn.*
Calcium folinate (p. 2066·3).

Uzix *Rafarm, Gr.*
Amikacin sulfate (p. 214·2).
Bacterial infections.

Uzone-T *Utopian, Thai.*
Phenazopyridine hydrochloride (p. 124·3).
Urinary-tract pain.

3V *Julphar, UAE.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Neuritis; neuralgia; neuropathy; dietary supplement.

V 1-6-12 *Osoth, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

V cap *Patar, Thai.*
Simeticone (p. 1886·2).
Flatulence.

V Day 1612 *PP Lab, Thai.*
Prosultiamine (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

V Day Lozenges *PP Lab, Thai.*
Dequalinium chloride (p. 1749·3).
Mouth and throat infections.

V Day Milk *PP Lab, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

V Day Prazide *PP Lab, Thai.*
Praziquantel (p. 164·1).
Worm infections.

V Day Pyrin *PP Lab, Thai.*
Dipyrone (p. 53·3).
Fever; pain.

V Day Vit *PP Lab, Thai.*
Thiamine propyl disulfide (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

V Day Zepam *PP Lab, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia.

V Nolone *TC Pharma-Chem, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Vabadin *Menarini, Cz.; Farmaprojects, Neth.†; Menarini, Swed.; Menarini, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Vaben *Rafa, Israel.*
Oxazepam (p. 1092·2).
Anxiety.

Vabicin *Atlantic, Thai.†*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea.

Vabon *Biolab, Thai.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disorders; hereditary angioedema; gynaecomastia; menorrhagia; precocious puberty.

Vac Antigripal *Leti, Spain†; Sanofi Pasteur, Spain.†*
Inactivated polyvalent influenza vaccines (whole virion or split virion) (p. 2393·3).
Active immunisation.

Vac Polio Sabin *GSK, Spain.†*
An oral poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Vac Poliomielitica *Berna, Spain.†*
A poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Vacanyl *Atlantic, Thai.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Vacciflu *Abbott, Neth.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Vaccin Antipoliomyelitique/Merieux *Vianex (Βιαγνεξ), Gr.*
An oral poliomyelitis vaccine (Sabin) (p. 2411·1).
Active immunisation.

Vaccin Meningococcique *Vianex (Βιαγνεξ), Gr.*
A meningococcal vaccine (groups A and C, or A, C, Y, and W135) (p. 2401·3).
Active immunisation.

Vaccin Rubeole *Vianex (Βιαγνεξ), Gr.*
A rubella vaccine (p. 2417·1).
Active immunisation.

Vacer *Sandoz, Mex.*
Nimodipine (p. 1455·2).
Mental function impairment; vertigo; ischaemic neurological deficit following subarachnoid haemorrhage.

Vacidox *Gynopharm, Chile.*
Estriol (p. 2274·3).
Menopausal vulvovaginal disorders.

Vacillin *Atlantic, Thai.†*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Vacina Acel Ads Contra Dif, Tet, Coq e Polio Inat Comb C/Vac Conj Contra Hib *Sanofi Pasteur, Braz.†*
An adsorbed diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Vacina Acel Ads Contra Dif, Tet e Coq *Sanofi Pasteur, Braz.*
An adsorbed diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Vacina Acel Ads Contra Dif, Tet e Coq Pol *Sanofi Pasteur, Braz.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Vacina Ads Cont Dift, Tet, Coq Acel Polio *Sanofi Pasteur, Braz.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Vacina Adsorvida Contra Dif, Tet, Coq Acel, Polio Inat Hepat B (Rec) e Hib Conj *Sanofi Pasteur, Braz.†*
A diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae vaccine (p. 2385·1).
Active immunisation.

Vacina Anti-Rabica Humana *Sanofi Pasteur, Braz.†*
A rabies vaccine (p. 2413·2).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel *GSK, Braz.*
A diphtheria, tetanus and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel e HIB *GSK, Braz.*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel Hepat.B r-DNA, Polio Inat e HIB *GSK, Braz.*
A diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·1).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel, Polio Inat e HIB *GSK, Braz.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Vacina Comb. Contra Dif.-Tet.-Pert.Acel e Hepat.B *GSK, Braz.*
A diphtheria, tetanus, acellular pertussis, and hepatitis B (recombinant) vaccine (p. 2384·3).
Active immunisation.

Vacina Comb. Contra Dift.-Tet.-Coq.Acel *GSK, Braz.*
A diphtheria, tetanus, and acellular pertussis vaccine (p. 2383·3).
Active immunisation.

Vacina Comb. Contra Hepatite A e B *GSK, Braz.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p. 2391·3).
Active immunisation.

Vacina Comb. Contra Sarampo, Caxumba e Rubeola *GSK, Braz.*
A measles, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

Vacina Conj Contra Haemophilus Influenzae Tipo B *GSK, Braz.*
A haemophilus influenzae vaccine (tetanus toxoid conjugate) (p. 2387·2).
Active immunisation.

Vacina Conj Com Proteina Tetanica HIB *Sanofi Pasteur, Braz.*
A haemophilus influenzae vaccine (tetanus protein conjugate) (p. 2387·2).
Active immunisation.

Vacina Contra A Varicela (Virus Atenuado) *MSD, Braz.*
A varicella-zoster (Oka/Merck) vaccine (p. 2423·3).
Active immunisation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vacina Contra Gripe *Abbott, Braz.; GSK, Braz.; Sanofi Pasteur, Braz.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Vacina Contra Hepatite A *GSK, Braz.; MSD, Braz.; Sanofi Pasteur, Braz.*
An inactivated hepatitis A vaccine (p. 2388·3).
Active immunisation.

Vacina Contra Hepatite B *GSK, Braz.; MSD, Braz.; Sanofi Pasteur, Braz.*
A recombinant hepatitis B vaccine (p. 2389·3).
Active immunisation.

Vacina Contra Sarampo, Caxumba e Rubeola *Sanofi Pasteur, Braz.*
A measle, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

Vacina Contra Varicela *GSK, Braz.; Sanofi Pasteur, Braz.*
A varicella-zoster (Oka strain) vaccine (p. 2423·3).
Active immunisation.

Vacina Meningococica A+C *Sanofi Pasteur, Braz.*
A meningococcal vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Vacina Meningococica Conjugada Grupo C *Baxter, Braz.; Blausiegel, Braz.; Wyeth, Braz.*
A meningococcal C conjugate vaccine (tetanus toxoid conjugate) (p. 2401·3).
Active immunisation.

Vacina Oral Contra Colera *Sanofi Pasteur, Braz.*
An inactivated oral cholera vaccine (p. 2381·1).
Active immunisation.

Vacina Pneumococica Conjugada 7-Valente *Wyeth, Braz.*
A pneumococcal conjugate vaccine (7-valent, diphtheria CRM_{197} protein conjugate) (p. 2410·1).
Active immunisation.

Vacina Pneumococica Polivalente *MSD, Braz.; Sanofi Pasteur, Braz.*
A pneumococcal vaccine (23-valent) (p. 2410·1).
Active immunisation.

Vacina de Virus Inativado Contra Gripe *GSK, Braz.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Vacina de Virus Vivos de Sarampo, Caxumba e Rubeola *MSD, Braz.*
Measles, mumps, and rubella vaccine (p. 2400·2).
Active immunisation.

Vacinolone *Atlantic, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Vacirex *Obolenskoe, Rus.*
Valaciclovir hydrochloride (p. 1021·1).
Varicella zoster infection; cytomegalovirus infection.

Vaclo *Dexa, Indon.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Vaclovir *Alphapharm, Austral.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Vaclox *Atlantic, Thai.†*
Cloxacillin (p. 274·3).
Bacterial infections.

Vacolax *Atlantic, Thai.†*
Bisacodyl (p. 1821·1).
Constipation.

Vacontil *Medochemie, Malaysia; Medochemie, Singapore.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Vacopan *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; nausea and vomiting; peptic ulcer; gastroduodenitis; postoperative nausea and vomiting.

Vacper *Medipharm, Chile.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Vacrax *Samchully, Malaysia; Samchully, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vacromil *Gynopharm, Chile.†*
⊗Goserelin acetate (p. 2282·3).

Vacsol *Solara, Mex.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vactiv *Pharos, Indon.*
⊗Procaterol hydrochloride (p. 1219·1).
Obstructive airways disease.

Vactyph *Zydus, India.*
A typhoid vaccine (Vi capsular polysaccharide) (p. 2422·2).
Active immunisation of adults and children.

Vacudol *Xixia, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); promethazine hydrochloride (p. 638·2).
Pain; fever.

Vacudol Forte *Xixia, S.Afr.†*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3); meprobamate (p. 1083·3).
Pain and associated tension.

Vacu-Mix Plus with CMW gentamicin *Johnson & Johnson, NZ.*
Polymethylmethacrylate (p. 2558·2); gentamicin sulfate (p. 304·2).
Bone cement for orthopaedic surgery.

Vacuna Adsorbida Pentavalente *Sanofi Pasteur, Venez.*
A diphtheria, tetanus, pertussus, poliomyelitis, and haemophilus influenzae vaccine (p. 2385·3).
Active immunisation.

Vacuna Adsorbida Tetravalente *Sanofi Pasteur, Venez.*
A diphtheria, tetanus, pertussus, and poliomyelitis vaccine (p. 2385·2).
Active immunisation.

Vacuna Antigripal *Sanofi Pasteur, Spain.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Vacuna Antipiogena *Biol, Arg.*
A vaccine containing micro-organisms responsible for respiratory-tract and skin infections.
Active immunisation.

Vacuna Antirrabica *Sanofi Pasteur, Spain.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Vacuna Conjugada Hexavalente (Hexaca) *Sanofi Pasteur, Venez.*
A diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p. 2385·1).
Active immunisation.

Vacuna Doble *Biol, Arg.*
A diphtheria and tetanus vaccine (p. 2383·1).
Active immunisation.

Vacuna Haptenica *Puebla, Arg.*
Polysaccharides from *Pseudomonas aeruginosa*; proteins from *Klebsiella pneumoniae*.
Immunotherapy.

Vacuna Liofilizadas Broncopulmonar *Casasco, Arg.*
A vaccine prepared from micro-organisms responsible for respiratory-tract infections.
Active immunisation.

Vacuna Liofilizadas Piodermitis *Casasco, Arg.*
A vaccine prepared from micro-organisms responsible for skin infections.
Active immunisation.

Vacuna Oral *Casasco, Arg.*
Oral drops: Streptococcus pneumoniae; Moraxella catarrhalis; Haemophilus influenzae; respiratory streptococci; *Klebsiella pneumoniae*; respiratory micrococci; vitamin A palmitate (p. 2098·3).
Immunostimulant.

Casasco, Arg.
Tablets: Streptococcus pneumoniae; respiratory micrococci; *Haemophilus influenzae; Klebsiella pneumoniae; Moraxella catarrhalis*; vitamin A acetate (p. 2098·3).
Immunostimulant.

Vacuna Purificada *Sanofi Pasteur, Venez.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Vacuna Tetravalente *Sanofi Pasteur, Venez.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p. 2384·2).
Active immunisation.

Vacuna Triple *Biol, Arg.*
A diphtheria, tetanus, and pertussis vaccine (p. 2383·3).
Active immunisation.

Vacuna Triple MSD *Sanofi Pasteur, Spain.†*
A measles, mumps, and rubella vaccine (attenuated Enders, Jeryl Lynn, and Wistar RA 27/3 strains respectively) (p. 2400·2).
Active immunisation.

Vacunace *Casasco, Arg.*
Lyophilised microorganisms; vitamin C (p. 2110·3).
Respiratory-tract disorders; otitis; pharyngitis.

Vacuobil *Ivax, Arg.*
Methylenedioxycinnamic acid (p. 2558·1).
Liver and biliary-tract disorders.

Vacuobil Plus *Ivax, Arg.*
Methylenedioxycinnamic acid (p. 2558·1); metoclopramide hydrochloride (p. 1862·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Vadarex *Bell, UK.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); sweet birch oil (p. 92·1); cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2).
Musculoskeletal pain.

Vadazol *Ikapharmindo, Indon.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Vadel *Ivax, Arg.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Vademin-Z *Hauck, USA; Roberts, USA.*
Vitamins; minerals.

Vaden *Help, Gr.*
Acetylcysteine (p. 1652·2).
Mucolytic.

Vadeplatin *Opus Materia, Gr.*
Carboplatin (p. 759·1).

Vadilex *Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.*
Ifenprodil tartrate (p. 1408·1).
Intermittent claudication.

Vadinar *Serral, Mex.*
Dipyridamole (p. 1362·2).
Thromboembolic disorders.

Vadiral *Mediderm, Chile.*
Valaciclovir (p. 1021·1).
Viral infections.

Vaditon *Euro Registratie, Neth.†; Visfarm, Spain.*
Fluvastatin sodium (p. 1385·1).
Hyperlipidaemias; cardiovascular risk reduction; hypercholesterolaemia; prevention of cardiac complications in patients undergoing angioplasty.

Vadosilan *BMS, Mex.*
Isoxsuprine (p. 2535·2).
Premature labour; peripheral and cerebral vascular disorders.

Vaff *Shin Poong, Philipp.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Vafluson *Kleva, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Vag Oral *IQB, Braz.†*
Allergen extracts (p. 2434·3).
Allergen immunotherapy.

Vagaka *Atlantic, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Vagantin *Riemser, Ger.*
Methanthelinium bromide (p. 1861·3).
Gastrointestinal disorders.

Vagantyl *Sidus, Arg.*
Mosapride citrate (p. 1865·2).
Dyspepsia; gastritis; gastro-oesophageal reflux.

Vagarsol *Aspen, S.Afr.*
Diiodohydroxyquinoline (p. 931·1); cetylpyridinium chloride (p. 1743·1); aminoacridine hydrochloride (p. 1732·3); boric acid (p. 2459·3).
Vaginal infections.

Vagi Biotic *Cimed, Braz.*
⊗Nystatin (p. 590·3); metronidazole (p. 936·1); benzalkonium chloride (p. 1737·1); urea (p. 1727·3).
Vulvovaginal infections.

Vagi C *Marjan, Braz.*
Ascorbic acid (p. 2110·3).
Vaginal disorders.

Vagi-C *Taurus, Ger.; Isse, Turk.*
Ascorbic acid (p. 2110·3).
Vaginal disorders.

VagiCare *Key, Austral.*
Ascorbic acid (p. 2110·3).
Regulation of vaginal pH.

Vagicillin *Schur, Ger.†*
Neomycin sulfate (p. 330·1).
Vaginal infections.

Vagicin
Note: this name may be used for preparations of different composition.
Charoen, Thai.
Diiodohydroxyquinoline (p. 931·1); nystatin (p. 590·3); chloramphenicol (p. 257·1).
Vaginal infections.

Zdorovje, Ukr.
Clindamycin phosphate (p. 269·3).
Bacterial vaginosis.

VagiClear Duo *Key, Austral.*
Capsule, fluconazole (p. 578·2); cream, clotrimazole (p. 576·2).
Vaginal candidiasis.

Vagiclin *Mediapharm, Gr.*
Clindamycin phosphate (p. 269·3).
Bacterial vaginal infections.

Vagicural *Raymos, Arg.*
⊗Hydrocortisone (p. 1640·1); neomycin sulfate (p. 330·1); nitrofurazone (p. 333·1); vitamin A (p. 2098·3); thymol (p. 1772·2); tyrothricin (p. 384·1); benzethonium chloride (p. 1738·1).
Vaginal infections.

Vagicural Plus *Raymos, Arg.*
Centella (p. 1698·3); metronidazole (p. 936·1); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Vaginal infections.

Vagifem *Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Canad.; Silesia, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, NZ; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Isdin, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.†; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, USA.*
Estradiol (p. 2271·1).
Atrophic vaginitis; vulvovaginal disorders.

Vagiflor *Chiesi, Ger.*
Lactobacillus acidophilus (p. 2596·3).
Vaginitis; disorders of the vaginal flora.

Vagi-Gard Medicated Cream *Lake, USA.*
Benzocaine (p. 1980·2); benzalkonium chloride (p. 1737·1).
Vaginal irritation.

Vagi-Gard Personal Lubricating Gel *Lake, USA.*
Vaginal lubricant.

Vagi-Hex *Drossapharm, Ger.; Drossapharm, Philipp.; Drossapharm, Switz.; Assos, Turk.*
Hexetidine (p. 1755·1).
Vaginitis.

Vagiklin
Note: this name may be used for preparations of different composition.
Euro Lifecare, Ukr.
Clindamycin (p. 269·3); clotrimazole (p. 576·2).
Bacterial vaginosis.

Kinder, Braz.†
Tetracycline hydrochloride (p. 373·2); amphotericin B (p. 569·2).

Vagil *PP Lab, Thai.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Vagilan *Union Drug, Thai.*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Vagilen
Note: this name may be used for preparations of different composition.
Biol, Arg.
⊗Metronidazole (p. 936·1); nystatin (p. 590·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3); lidocaine (p. 1988·1).
Vulvovaginal disorders.

Wassermann, Ital.
Metronidazole (p. 936·1).
Trichomoniasis.

Vagimax *Prodotti, Braz.†*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vulvovaginal infections.

Vagi-Metro *Drossapharm, Ger.*
Metronidazole (p. 936·1).
Trichomoniasis; bacterial vaginitis.

Vagimid *Apogepha, Ger.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Vagimycin *BMS, Philipp.†*
Amphotericin B (p. 569·2); tetracycline (p. 373·1).
Vaginitis.

Vaginol *Dermofarma, Ital.*
Hyaluronic acid (p. 2526·2); 18 beta glycyrrhetic acid (p. 54·2); lactic acid (p. 2539·1); calcium lactate (p. 1784·1); centella (p. 1698·3); calendula (p. 2465·2); arnica (p. 2447·2); melaleuca oil (p. 2551·1).
Vulvovaginal disorders.

Vaginorm C *Polichem, Ukr.*
Ascorbic acid (p. 2110·3).
Bacterial vaginal infections; restoration of vaginal flora.

Vaginorm-C *Solvay, Rus.*
Ascorbic acid (p. 2110·3).
Vaginitis; restoration of vaginal microflora.

Vagin-X *Associated National Brokerage, Canad.*
Tripelennamine hydrochloride (p. 642·3).

Vaginyl *DDSA Pharmaceuticals, UK.*
Metronidazole (p. 936·1).

Vagisan
Note: this name may be used for preparations of different composition.
Jadran, Ukr.
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3).
Restoration of vaginal flora.

Sidus, Arg.
Dihydrostreptomycin sulfate (p. 286·3); tyrothricin (p. 384·1); nitrofurazone (p. 333·1).
Vaginal infections.

Wolff, Ger.
Lactic acid (p. 2539·1); sodium lactate (p. 1781·2).
Vaginitis; vaginal dryness.

Vagisan Bakterien *Wolff, Ger.*
Lactobacillus gasseri (p. 2596·3); *Lactobacillus rhamnosus* (p. 2596·3).
Restoration of vaginal flora.

Vagisan Compuesto *Sidus, Arg.*
Dihydrostreptomycin sulfate (p. 286·3); tyrothricin (p. 384·1); nitrofurazone (p. 333·1); clotrimazole (p. 576·2).
Vaginal infections.

Vagisil
Note: this name may be used for preparations of different composition.
Combe, Canad.; Combe, USA.
Benzocaine (p. 1980·2); resorcinol (p. 1718·3).
External vaginal irritation; skin disorders.

Combe, Ital.
Lidocaine (p. 1988·1); chlorothymol (p. 1748·2).
Anal and vulvar pruritus.

Combe, UK.
Lidocaine (p. 1988·1).
Vaginal pruritus.

Combe, USA.
Topical powder: Aloes (p. 1816·1); liquid paraffin (p. 2191·2); benzethonium chloride (p. 1738·1).
Vaginal disorders.

Combe, USA.
Topical wipes: Pramocaine hydrochloride (p. 1993·3).

Vagistat-1 *Novartis, USA.*
Tioconazole (p. 595·3).
Vulvovaginal candidiasis.

Vagistat-3 *Novartis, USA.*
Miconazole nitrate (p. 589·1).
Fungal vaginal infections.

Vagistatina *Belfar, Braz.*
Nystatin (p. 590·3).

Vagistin *Combiphar, Indon.*
Metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginal infections.

Vagi-Sulfa *Janssen-Cilag, Braz.*
⊗Sulfathiazole (p. 368·3); sulfacetamide (p. 361·1); sulfabenzamide (p. 360·3); urea (p. 1727·3).
Vaginal infections.

VagiTest *Key, Austral.*
Vaginal pH testing kit.

Vagitrene *Euroforma, Braz.*
Wheat germ (p. 2647·1).
Vulvovaginal disorders.

Vagitrin-N *Bunker, Braz.*
⊗Dexamethasone phosphate (p. 1631·1); nystatin (p. 590·3); neomycin sulfate (p. 330·1); tyrothricin (p. 384·1); sodium propionate (p. 593·1); boric acid (p. 2459·3).
Vulvovaginal infections.

Vagitrol-V *Bayer Consumer, Mex.*
⊗Fluocinolone acetonide (p. 1636·1); metronidazole (p. 936·1); nystatin (p. 590·3).
Vaginitis; vulvitis; cervicitis.

Vagizol
Note: this name may be used for preparations of different composition.
Gelnova, Philipp.
Clotrimazole (p. 576·2).
Vaginal candidiasis.

Kimia, Indon.
Metronidazole (p. 936·1).
Urethral and vaginal trichomoniasis; giardiasis; amoebiasis.

Vagizole *Union Drug, Thai.*
Clotrimazole (p. 576·2).
Vulvovaginal candidiasis.

Vagmycin *BMS, S.Afr.†*
Tetracycline (p. 373·1); amphotericin B (p. 569·2).
Vaginal infections.

Vagodyss *Braun, Switz.*
Lactic acid (p. 2539·1).
Vaginal infections and irritation.

Vagopax *Jaba Recordati, Port.*
Pargeverine (p. 1877·1).
Smooth muscle spasm.

Vagosinol *Pharmathen, Gr.*
⊗Atenolol (p. 1308·2); chlortalidone (p. 1335·2).
Hypertension.

Vagostabil *Cristalfarma, Ital.*
Crataegus (p. 2488·1); melissa (p. 2552·3); magnesium (p. 1786·3).
Anxiety disorders.

Vagostabil Junior *Cristalfarma, Ital.*
Passion flower (p. 2584·1); california poppy (p. 2466·1); melissa (p. 2552·3).
Agitation; hyperactivity.

Vagostabyl *Biocodex, Fr.*
Crataegus (p. 2488·1); calcium lactate (p. 1784·1); melissa (p. 2552·3); magnesium thiosulfate (p. 1576·1).
Nervous disorders; insomnia.

Vagostal *Gynea, Spain.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; gastric hyperacidity; Zollinger-Ellison syndrome.

Vagostesyl *Gross, Braz.*
Atropine sulfate (p. 1310·2); papaverine hydrochloride (p. 2362·3); phenobarbital (p. 535·2); leptolobium elegans; passion flower (p. 2584·1).
Smooth muscle spasm.

Vagothyl *Polfa, Cz.†; Pabianice, Hung.; Polfa Pabianice, Pol.; Pabianice, Rus.*
Policresulen (p. 1160·2).
Vaginal disorders; ulcers; burns; inflammatory skin disorders; urinary-tract infections; haemorrhage; gynaecological disorders; wounds; vulvovaginal disorders; urological disorders; capillary bleeding; mouth and throat disorders.

Vagotrosin *Pharmathen, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Vagran
Note: this name may be used for preparations of different composition.
Dollder, Venez.
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Finadiet, Arg.
Loratadine (p. 633·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Vagran D *Finadiet, Arg.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis.

Vagrecor *Liconsa, Neth.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Vagyl *Atlantic, Thai.†*
Metronidazole (p. 936·1).
Trichomoniasis; amoebiasis; giardiasis.

Vakocil *Swiss Parenterals, Philipp.†*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections.

Valacor
Note: this name may be used for preparations of different composition.
Pasteur, Chile.
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Ranbaxy, Austral.
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valacor D *Pasteur, Chile.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valamin *Sanbe, Indon.*
Amino acids; sorbitol (p. 2092·1).
Parenteral nutrition.

Valaplex *Laboratorios Chile, Chile.*
Valsartan (p. 1521·2).
Hypertension.

Valaplex-D *Laboratorios Chile, Chile.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valaric *Liconsa, Cz.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valatan *Silom, Thai.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Valavir *Orion, Fin.; Alter, Port.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Farmak, Ukr.
Valaciclovir (p. 1021·1).
Herpesvirus infections.

Valax
Note: this name may be used for preparations of different composition.
Saval, Chile.
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

TMN Impex, Thai.; Utopian, Thai.
Diazepam (p. 1063·2).

Valaxam *Saval, Chile.*
Valsartan (p. 1521·2); amlodipine besilate (p. 1304·1).
Hypertension.

Valaxona *Actavis, Denm.†*
Diazepam (p. 1063·2).
Anxiety; spasticity; alcohol withdrawal syndrome.

Valbacomp *Crinos, Ital.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).

Valbet *Delta, Braz.; Lupin, India; Biolab, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders; infected scalp disorders.

Lupin, India.
Cream: ⊗Betamethasone valerate (p. 1624·1) or betamethasone dipropionate (p. 1623·3); miconazole nitrate (p. 589·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Valbet-N *Biolab, Thai.*
⊗Betamethasone (p. 1623·2); neomycin (p. 329·3).
Infected skin disorders.

Valbil *CPH, Port.†*
Febuprol (p. 2502·3).
Biliary-tract dyskinesia; dyspepsia.

Valcap *Terapeutico, Ital.*
Bioflavonoids (p. 2505·2); green tea (p. 2648·2); lecithin (p. 2542·2); propolis (p. 2597·3); chilli (p. 2469·3); inulin (p. 2534·3); garlic (p. 2510·3); selenium amino-acid chelate (p. 2086·3).
Genito-urinary disorders.

Valcas *Casasco, Arg.*
Valproate semisodium (p. 553·2).
Epilepsy; mania; migraine.

Valcatil *Panalab, Arg.*
⊗Methionine (p. 1558·2); cystine (p. 2059·1); gelatin (p. 1154·1).
Hair and nail disorders.

Valcatil Max *Panalab, Arg.*
Biotin (p. 2052·2); cystine (p. 2059·1); methionine (p. 1558·2); pyridoxine (p. 2105·3); calcium pantothenate (p. 2085·2); zinc (p. 2126·1).
Dietary supplement; hair, nail, and skin disorders.

Valcatil Plus *Panalab, Arg.*
⊗Biotin (p. 2052·2); cystine (p. 2059·1); methionine (p. 1558·2); gelatin (p. 1154·1); pyridoxine hydrochloride (p. 2105·3); calcium pantothenate (p. 2085·2); zinc (p. 2126·1).
Hair and nail disorders; dietary supplement.

Valcatuna *Liconsa, Neth.*
Valsartan (p. 1521·2).
Hypertension.

Valchlor *Ceptaris, USA.*
Chlormethine hydrochloride (p. 765·1).
Mycosis fungoides.

Valcivir *Cipla, India.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valclan *Wandel, Mex.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Valcontin *Modi-Mundipharma, India.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Valcote *Abbott, Arg.*
Valproic acid (p. 553·1) or valproate semisodium (p. 553·2).
Bipolar disorder; epilepsy; migraine.

Abbott, Chile.
Sodium valproate (p. 553·1) or valproate semisodium (p. 553·2).
Bipolar disorder; epilepsy; migraine.

Abbott, Venez.
Valproate semisodium (p. 553·2).
Epilepsy; mania; migraine.

Valcox *Unichem, India.*
Parecoxib sodium (p. 119·3).
Postoperative pain.

Valcumin *Jiangsu Sihuan, Philipp.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia.

Valcyte *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, USA.*
Valganciclovir hydrochloride (p. 1022·1).
Cytomegalovirus infections.

Valda
Note: this name may be used for preparations of different composition.
GSK Sante, Fr.†
Menthol (p. 2553·2); cineole (p. 2479·1); thymol (p. 1772·2); terpineol (p. 2627·2); guaiacol (p. 1666·1).
Throat irritation.

Sterling, Indon.†
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); guaifenesin (p. 1666·2).
Cough; cold symptoms.

Valda Propoli *Valda, Ital.*
Pastilles: Propolis (p. 2597·3); menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Valda, Ital.†
Throat spray: Propolis (p. 2597·3); peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); cinnamon oil (p. 2479·3); coriander oil (p. 2487·1); rosemary oil (p. 2607·3).
Throat disorders.

Valda Respiraverde *Valda, Ital.†*
Levomenthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Sore throat.

Valda Rhume *GSK Sante, Fr.†*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); ascorbic acid (p. 2110·3).
Cold symptoms.

Valda Timo e Limone *Valda, Ital.*
Lemon oil (p. 2543·1); eucalyptus oil (p. 2501·2); thyme oil (p. 2630·3); menthol (p. 2553·2).
Sore throat.

Valda Toux Sèche *GSK Sante, Fr.†*
Pholcodine (p. 1675·1).
Cough.

Valdefer *Valdecasas, Mex.*
Ferrous sulfate (p. 2062·2).
Iron-deficiency anaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Valderma *Ransom, UK.*
Cream: Potassium hydroxyquinoline sulfate (p. 2530·1); chlorocresol (p. 1748·1).
Acne.

Roche Consumer, UK.
Soap: Triclocarban (p. 1773·2).
Acne.

Valdiff *Ipca, India.*
Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Valdimex *Mersifarma, Indon.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; premedication; sedative.

Valdispert *Vemedia, Neth.; Solvay, Port.; Solvay, Rus.; Vemedia, Spain; Solvay, Switz.†*
Valerian (p. 2640·2).
Nervous disorders; sleep disorders; insomnia.

Valdispert Complex *Vemedia, Spain.*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Insomnia; nervous disorders.

Valditas *Solvay, Port.†*
Valerian (p. 2640·2).

Valdixx *Cipla, India.*
Injection: Parecoxib sodium (p. 119·3).
Pain.

Cipla, India.
Tablets: Valdecoxib (p. 141·3).
Pain.

Valdone *Cadila, India.*
Tablets: Valdecoxib (p. 141·3).
Osteoarthritis; rheumatoid arthritis; dysmenorrhoea.

Valdone-P *Cadila, India.*
Parecoxib (p. 119·3).
Pain.

Valdorm
Note: this name may be used for preparations of different composition.
Barrenne, Braz.
Valerian (p. 2640·2).
Anxiety; insomnia.

Valeas, Ital.
Flurazepam monohydrochloride (p. 1076·1).
Insomnia.

Valdoxan *Servier, Arg.; Servier, Austral.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, China; Servier, Cz.; Servier, Denm.; Servier, Fr.; Servier, Ger.; Servier, Gr.; Servier, Hong Kong; Servier, Hung.; Servier, Irl.; Servier, Malaysia; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, Rus.; Servier, Singapore; Servier, Spain; Servier, Swed.; Servier, Switz.; Servier, Thai.; Servier, Turk.; Servier, UK.*
Agomelatine (p. 400·2).
Depression.

Valdren *Lannacher, Cz.†*
Mirtazapine (p. 436·1).
Depression.

Valdres *Pharos, Indon.*
Diphenhydramine (p. 626·1).
Allergic disorders; insomnia.

Valdrian *Bio-Health, Irl.; Bio-Health, UK.*
Valerian (p. 2640·2).
Anxiety; insomnia.

Valeans *Valeas, Ital.*
Alprazolam (p. 1035·2).
Anxiety.

Valecid *Medifarma, Ital.†*
Cefonicid sodium (p. 242·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Valeclor *Francia, Ital.*
Cefaclor (p. 232·3).
Bacterial infections.

Valederm *Stiefel, Arg.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Valedol *Cielle, Ital.*
Indian frankincense (p. 2507·3); devil's claw root (p. 42·3).
Musculoskeletal and joint pain.

Valemia *Sanbe, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Valemidin *Euromed, Rus.*
Crataegus (p. 2488·1); valerian (p. 2640·2); diphenhydramine (p. 626·1); peppermint leaf (p. 1877·1); motherwort (p. 2564·2).
Anxiety; dystonias.

Valemine *Vamsler, Philipp.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Valenium *Kenyaku, Thai.*
Diazepam (p. 1063·2).
Anxiety.

Valerbet *Polipharm, Thai.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Valerecen *Abigo, Swed.*
Valerian (p. 2640·2).
Sedative.

Valergen *Hyrex, USA.*
Estradiol valerate (p. 2271·2).
Menopausal vasomotor symptoms; vulval and vaginal atrophy; female hypogonadism; female castration; primary ovarian failure; prostatic cancer; prevention of breast engorgement.

Valerial *Zambon, Belg.*
Valerian (p. 2640·2).
Sleep disorders; nervous disorders.

Valerian Complex *Mediherb, Austral.*
Valerian (p. 2640·2); passion flower (p. 2584·1); ziziphus spinosa.
Nervous disorders; insomnia.

Valerian Passiflora and Hops *Lifeplan, UK.*
Vitamins; minerals; kava kava; passion flower (p. 2584·1); motherwort (p. 2564·2); wild lettuce (p. 2647·3); scullcap (p. 2617·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Herbal supplement.

Valeriana *Garden House, Arg.*
Valerian (p. 2640·2); thiamine (p. 2102·3).

Valeriana Beruhigungsdragees *Hevert, Ger.*
Valerian (p. 2640·2); melissa (p. 2552·3); passion flower (p. 2584·1).
Nervous disorders; sleep disorders.

Valeriana Compuesta *Lafarmen, Arg.*
Passion flower (p. 2584·1); valerian (p. 2640·2); melissa (p. 2552·3); tilia (p. 2631·3); vitamin B_1 (p. 2102·3); copper sulfate (p. 2057·2).
Nervous disorders; sleep disorders.

Valeriana Diates *Provefarma, Arg.†*
Valerian (p. 2640·2); thiamine (p. 2102·3).
Herbal supplement.

Valeriana Leo *Angelini, Spain.*
Valerian (p. 2640·2); passion flower (p. 2584·1); crataegus (p. 2488·1).
Nervous disorders; insomnia.

Valeriana Oligoplex *Madaus, Arg.*
Melissa (p. 2552·3); valerian (p. 2640·2); avena (p. 2451·1).
Sedative.

Valeriana Orto *Normon, Spain.†*
Valerian (p. 2640·2).
Insomnia; nervous disorders.

Valeriana Relax Diates *Provefarma, Arg.†*
Valerian (p. 2640·2); melissa (p. 2552·3); calcium pantothenate (p. 2085·2).
Herbal supplement.

Valerianaheel *Heel, Austria.*
Valeriana officinalis (p. 2640·2); humulus lupulus (p. 2546·1); crataegus (p. 2488·1); hypericum perforatum (p. 449·1); melissa officinalis (p. 2552·3); chamomilla recutita (p. 2474·1); avena sativa (p. 2451·1); acidum picrinicum (p. 2634·2); kalium bromatum (p. 2461·1); ammonium bromatum (p. 2461·1); natrium bromatum (p. 2461·1).
Homoeopathic preparation.

Valerianaheel Comp *Heel, Canad.†*
German chamomile (p. 2474·1); hops (p. 2546·1); hypericum perforatum (p. 449·1); melissa officinalis (p. 2552·3); oats (p. 2451·1); picric acid (p. 2634·2); squill (p. 1677·3); valerian (p. 2640·2).
Homoeopathic preparation.

Valeriana-Plus *Doctor H, Rus.*
Bromum (p. 2461·2); leonurus cardiaca (p. 2564·2); ambra grisea (p. 2440·3); hyoscyamus niger (p. 2530·2); passiflora incarnata (p. 2584·1); strychnos ignatii (p. 2532·1); valeriana officinalis (p. 2640·2); zincum valerianicum (p. 2641·2); crataegus laevigata (p. 2488·1).
Homoeopathic preparation.

Valeriane *Nikkho, Braz.*
Valerian (p. 2640·2).
Sleep disorders; nervous disorders.

Valeric *Atlantic, China; Atlantic, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Valerimed *Cimed, Braz.*
Valerian (p. 2640·2).
Sleep disorders; nervous disorders.

Valerin *Fontovit, Braz.†; Aflofarm, Pol.*
Valerian (p. 2640·2).
Nervous disorders; insomnia; anxiety.

Valerina *Cederroth, Swed.*
Valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3).
Sleep disorders.

Valerina Day Time *Lichtwer, UK.*
Valerian (p. 2640·2); melissa (p. 2552·3).
Stress; strain.

Valerina Forte *Cederroth, Denm.; Pharbio, Norw.*
Valerian (p. 2640·2).
Anxiety; sleep disorders; insomnia; nervous disorders.

Valerina Natt *Pharbio, Norw.*
Valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3).
Insomnia.

Valerina Night-Time *Cederroth, UK.*
Valerian (p. 2640·2); lupulus (p. 2546·1); melissa (p. 2552·3).
Insomnia.

Valerix *Ativus, Braz.*
Valerian (p. 2640·2).
Anxiety; sleep disturbances.

Valeron *Konimex, Indon.†*
⊗Diflucortolone valerate (p. 1634·1).
Skin disorders.

Valetol *Herbacos Recordati, Cz.*
Propyphenazone (p. 127·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Valeton *Rekah, Israel.*
Valerian (p. 2640·2).
Nervous disorders.

Valette *Bayer, Austral.; Bayer, Austria; Jenapharm, Ger.; Berlifarma, Port.*
Dienogest (p. 2267·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive; androgen-dependent acne in females.

Valexime *SF, Ital.*
Ceftriaxone sodium (p. 253·3).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Valezen *Teuto, Braz.*
Valerian (p. 2640·2).
Anxiety.

Valfam *Valdecasas, Mex.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea; ileostomy management.

Valfiran *Sanval, Braz.*
Sulfiram (p. 2161·3).
Pediculosis; scabies.

Valflex *Sanval, Braz.*
Cefalexin (p. 234·1).
Bacterial infections.

ValHelen *KRKA, Denm.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valherpes *GSK, Spain.†*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valian-x *Mega Lifesciences, Thai.*
Valerian (p. 2640·2).
Sleep disorders.

Validol
Note: this name may be used for preparations of different composition.
Farmak, Pol.; Farmagen, Rus.; Farmak, Ukr.
Menthyl isovalerate (p. 2554·1).
Angina pectoris; neurosis; motion sickness; nitrate-induced headache; neurovegetative disorders; migraine; gastrointestinal spasm.

Hakay, Turk.
Hydroxyzine hydrochloride (p. 630·3).
Pruritus; anxiety.

Validroc *SoSe, Ital.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valiflox *Baliarda, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Valifol *Valdecasas, Mex.*
Isoniazid (p. 311·2).
Tuberculosis.

Valinir *Serral, Mex.*
Valaciclovir (p. 1021·1).
Herpesvirus infections.

Valinor
Note: this name may be used for preparations of different composition.
Prater, Chile.
Losartan (p. 1422·2).

Baxter, Fr.†
Amino acids.
Parenteral nutrition.

Valiquid *Roche, Ger.*
Diazepam (p. 1063·2).
Anxiety disorders; skeletal muscle spasm; premedication; sleep disorders.

Valirem *Genepharm, Gr.*
Sulpiride (p. 1107·3).
Psychoses.

Valisanbe *Sanbe, Indon.*
Diazepam (p. 1063·2).
Neuroses; psychosomatic disorders; muscular disorders; alcohol withdrawal syndrome; status epilepticus; premedication; sedative.

Valisone *Valeo, Canad.; Schering, USA.*
⊗Betamethasone valerate (p. 1624·1).
Skin disorders; scalp disorders.

Valisone-G *Valeo, Canad.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Valium *Investi, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Fr.; Roche, Ger.; Piramal, India; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Norw.; Roche, Philipp.; Roche, Port.; Roche, S.Afr.; Roche, Spain; Roche, Switz.; Roche, Thai.†; Roche, USA.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety; convulsions; epilepsy; premedication; sedative; skeletal muscle spasm; insomnia; spasticity; panic attacks; status epilepticus; tetanus; eclampsia; sleep disorders; febrile convulsions; general anaesthesia; psychiatric disorders; agitation; delirium tremens; cerebral spasticity; autonomic disorders.

Valixa *Roche, Arg.; Roche, Venez.*
Valganciclovir (p. 1022·1).
Cytomegalovirus infection.

Roche, Chile; Roche, Neth.
Valganciclovir hydrochloride (p. 1022·1).
Cytomegalovirus infections.

Vallclara *Leon, Neth.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Vallergan *Sanofi-Aventis, Austral.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Norw.; Sanofi-Aventis, NZ; Sanofi-Aventis, S.Afr.; Castlemead, UK.*
Alimemazine tartrate (p. 615·1).
Urticaria; pruritus; adjunct in anaesthesia; sedative; premedication; sleep disorders.

Vallup *Herbapol Lodz, Pol.†*
Lupulus (p. 2546·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Valmane *Abbott, Braz.*
Valerian (p. 2640·2).
Anxiety disorders.

Pharmaselect, Austria; Abbott, Gr.
Valepotriates (p. 2640·2).
Nervous disorders; anxiety disorders.

Valmax *Cipla, Ukr.*
Valaciclovir (p. 1021·1).
Herpesvirus infections.

Valmed *Helm, Cz.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valmetrol-3 *Valdecasas, Mex.*
Colecalciferol (p. 2113·1).
Formerly contained calcitriol and colecalciferol.
Hypocalcaemia; osteoporosis; hyperparathyroidism; hypoparathyroidism; rickets; osteomalacia.

Valmicin *Sanval, Braz.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Valmidex *Valeant, Hung.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Valmocel *IAE, Philipp.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Valmox *IAE, Philipp.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Valnar *Ivax, Arg.*
Valproate semisodium (p. 553·2).
Bipolar disorder; epilepsy; migraine.

Valni *Winthrop, UK.*
Nifedipine (p. 1447·2).

Valnir *Aspen, Austral.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valnoc *Drugtech, Chile.*
Eszopiclone (p. 1072·3).
Insomnia.

Valobion *Remedica, Malaysia.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; vitamin B supplement.

Valocordin *Krewel, Rus.*
Phenobarbital (p. 535·2).
Insomnia; nervous disorders.

Valocordin-Diazepam *Krewel, Ger.*
Diazepam (p. 1063·2).
Anxiety disorders; sleep disorders.

Valocordin-Doxylamin *Krewel, Ger.*
Doxylamine succinate (p. 627·3).
Sleep disorders.

Valocormid *Phytopharm, Rus.; Yaroslavl, Rus.*
Belladonna (p. 2453·3); valerian (p. 2640·2); convallaria (p. 2486·2); menthol (p. 2553·2); sodium bromide (p. 2461·1).
Cardiovascular disorders.

Valofyt Neo *Leros, Cz.†*
Valerian (p. 2640·2); crataegus (p. 2488·1); lupulus (p. 2546·1); lavender (p. 2541·1); melissa (p. 2552·3); avena (p. 2451·1); salix (p. 129·2); angelica (p. 2443·3); peppermint leaf (p. 1877·1).
Nervous disorders; insomnia.

Valoid *AFT, NZ; Amdipharm, UK.*
Cyclizine lactate (p. 623·2).
Nausea; vestibular disorders; vomiting; acid aspiration.

Amdipharm, Irl.; GSK, S.Afr.
Cyclizine hydrochloride (p. 623·2) or cyclizine lactate (p. 623·2).
Nausea; vomiting; vestibular disorders; motion sickness.

Valonorm *Zenith, UK.*
Atropine sulfate (p. 1310·2); peppermint oil (p. 1877·1); magnesium carbonate (p. 1856·2); magnesium trisilicate (p. 1858·1); calcium carbonate (p. 1824·3); sodium bicarbonate (p. 1781·1); aluminium hydroxide (p. 1817·2).
Dyspepsia; gastrointestinal spasm.

Valontan *Recordati, Ital.*
Dimenhydrinate (p. 625·2).
Motion sickness.

Valopin *Julphar, UAE.*
Sodium valproate (p. 553·1).
Epilepsy.

Valopon *Biomedica, Gr.*
Piroxicam (p. 125·3).
Inflammatory disorders.

Valopride *Pharmafar, Ital.*
Bromopride (p. 1824·2).
Gastrointestinal disorders.

Valoran *Medochemie, Hong Kong.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Valorel *Royal, Chile.*
Etofenamate (p. 57·2).
Peri-articular and soft-tissue disorders.

Valoron *Pfizer, S.Afr.; Pfizer, Switz.*
Tilidine hydrochloride (p. 137·3).
Pain.

Valoron N *Godecke, Ger.; Parke, Davis, Ger.; Pfizer, Ger.*
Tilidine hydrochloride (p. 137·3) or tilidine phosphate (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

Valoserdin *Mosfarma, Rus.*
Origanum oil (p. 2576·3); peppermint oil (p. 1877·1); phenobarbital (p. 535·2); ethyl alpha-bromoisovalerate (p. 1073·1).
Anxiety; cardiovascular disorders; insomnia; colic.

Valosin *Svizera, India.*
Valethamate bromide (p. 1895·2).
Labour induction; colic.

Valosine *Standard Chem & Pharm, Thai.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Valotix *Rowex, Irl.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valour *Qwatro, Canad.*
Triclosan (p. 1773·2).
Hand cleansing.

Valoxin
Note: this name may be used for preparations of different composition.
Plus, Gr.
Meloxicam (p. 86·3).
Inflammatory disorders.

Sanval, Braz.
Digoxin (p. 1353·3).
Arrhythmias; heart failure.

Valpakine *Sanofi-Aventis, Braz.*
Sodium valproate (p. 553·1).
Bipolar disorder; epilepsy.

Valpam *Aspen, Austral.; Arrow, Hong Kong.*
Diazepam (p. 1063·2).
Alcohol withdrawal syndrome; anxiety disorders; skeletal muscle spasm; spasticity.

Valpar *Valdecasas, Mex.*
Metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis.

Valparin *Sanofi-Aventis, India; Torrent, Singapore; Torrent, Thai.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Valparin XR *Torrent, Philipp.; Torrent, Rus.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Valparina *Valdecasas, Mex.†*
Pyridoxine (p. 2105·3).
Vitamin deficiency.

Valpax *Drugtech, Chile.*
Clonazepam (p. 519·1).
Epilepsy; panic disorder.

Valpeda *Ransom, UK.*
Halquinol (p. 309·1).
Skin infections.

Valperal *Valeant, Cz.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Valpex *Ivax, Arg.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Valpiform *General Dietary, UK.*
A range of gluten-free foods.

Valpin *Recalcine, Chile.*
Octatropine methylbromide (p. 1866·2); phenobarbital (p. 535·2).
Colic; vomiting in infants.

Valpinax *Crinos, Ital.*
Octatropine methylbromide (p. 1866·2); diazepam (p. 1063·2).
Gastrointestinal spasm.

Valporal *Teva, Israel.*
Valproic acid (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy.

Valprastin *IQFA, Mex.*
Pravastatin (p. 1473·1).

Valprease *Aspen, Austral.*
Sodium valproate (p. 553·1).
Epilepsy; bipolar disorder.

Valprene *Teuto, Braz.*
Sodium valproate (p. 553·1).
Epilepsy.

Valpression *Menarini, Ital.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valpro *Alphapharm, Austral.; Aliud, Ger.†; TAD, Ger.†; Alphapharm, Hong Kong.*
Sodium valproate (p. 553·1).
Epilepsy; mania.

Valpro Beta *Betapharm, Ger.*
Sodium valproate (p. 553·1).
Epilepsy.

Valpro Beta chrono *Betapharm, Ger.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Valpro chrono *TAD, Ger.†*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Valprocom Chrono *Pharma Start, Ukr.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy; bipolar disorder.

ValproLek *Sandoz, Pol.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Valpron *Farma, Venez.*
Valproic acid (p. 553·1) or sodium valproate (p. 553·1).
Epilepsy.

Valpro-Ratiopharm Chrono *Ratiopharm, Pol.*
Sodium valproate (p. 553·1); valproic acid (p. 553·1).
Epilepsy.

Valrate *Ipca, India.*
Sodium valproate (p. 553·1).
Epilepsy.

ValRelax
Note: this name may be used for preparations of different composition.
Herb Hands Healing, UK.
Valerian (p. 2640·2).
Anxiety; insomnia.

Valrelax *Esteve, Spain.†*
Passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; insomnia.

Valrem *Meditab, Thai.*
Sodium valproate (p. 553·1).
Epilepsy.

Vals *Esteve, Spain.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valsabio *Tiefenbacher, Neth.†*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Valsacell HCT *Medcell, Neth.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsacombi *KRKA, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsacor *Legrand, Braz.; KRKA, Cz.; TAD, Ger.; KRKA, Hung.; KRKA, Ital.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Valsacor comp *TAD, Ger.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsacor H *KRKA, Rus.; KRKA, Ukr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsacor HD *KRKA, Rus.; KRKA, Ukr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsaforce *Promo-Med, Rus.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Valsanorm *Plus Pharma, Cz.; Plus Pharma, Neth.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valsaratio Plus H *Ratiopharm, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsargamma *Worwag, Cz.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valsarstad *Stada, Fin.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valsarstad Comp *Stada, Fin.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsartamib *Mibe, Neth.†*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Valsartamyl *Mylan, Denm.†*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valsartan comp *Betapharm, Ger.; Ratiopharm, Ger.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsartan HCT *Sandoz, Hung.; Teva, Hung.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsartan plus HCT *Hennig, Ger.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsartan/HCT *Aliud, Ger.; Stada, Ger.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsavil *Pharmacodane, Denm.; Centrafarm, Neth.†*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valsavil HCT *Pharmacodane, Denm.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsedan *Cederroth, Spain.†*
Valerian (p. 2640·2).
Nervous disorders; insomnia.

Valsera *Polifarma, Ital.*
Flunitrazepam (p. 1073·3).
Insomnia.

Valsol Plus *Liconsa, Irl.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valsotens *Aramis, Hung.; Actavis, Irl.†; Actavis, Pol.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Valsotens HCT *Aramis, Hung.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valstar *Anthra, Israel†; Endo, USA.*
Valrubicin (p. 878·3).
Bladder cancer.

Valsweet *Valma, Chile.†*
Aspartame (p. 2169·2).
Sugar substitute.

Valtan *Clonmel, Irl.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valtan comp *Clonmel, Irl.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valtap *Zentiva, Pol.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Valtap HCT *Zentiva, Pol.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valtaxin *Paladin, Canad.*
Valrubicin (p. 878·3).
Bladder cancer.

Valtec *Cipla, India.*
Sodium valproate (p. 553·1).

Valtension comp *Teva, Denm.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valto *Nufarindo, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; inflammation.

Valtran *Pfizer, Belg.*
Tilidine hydrochloride (p. 137·3).
Naloxone hydrochloride (p. 1562·3) is included in this preparation to discourage abuse.
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Valtrax *Valeas, Ital.*
Diazepam (p. 1063·2); isopropamide iodide (p. 1848·3).
Gastrointestinal spasm.

Valtrex *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; Glaxo Wellcome, USA; GSK, Venez.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valtrian *Medley, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Valtrian HCT *Medley, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Valtropin *BioPartners, Cz.†; BioPartners, Irl.†; BioPartners, Pol.†; BioPartners, Port.†*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency; Turner' syndrome; growth disorders in renal failure.

Valtroplex *IAE, Philipp.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Valtrovir *Arterium, Ukr.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valublock *Valuge, Arg.*
SPF 35: Bisoctrizole (p. 1697·1); octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Valublock V *Valuge, Arg.*
SPF 29: Bisoctrizole (p. 1697·1); octinoxate (p. 1715·1).
Sunscreen.

Valuca Flex *Vannier, Arg.*
Diclofenac (p. 48·3); pridinol (p. 2026·1).

Valuca Plus *Vannier, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Inflammation; pain.

Valucne PB *Valuge, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Valuherb *Herbapol Poznan, Pol.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Insomnia; nervous disorders.

Valupass *Knop, Chile.*
Valerian (p. 2640·2); lupulus (p. 2546·1); passiflora coerulea.
Depression; insomnia; nervous disorders.

Valus *Glenmark, India.*
Valdecoxib (p. 141·3).
Rheumatoid arthritis; osteoarthritis; dysmenorrhoea.

Valusal *Grindeks, Ukr.*
Ketoprofen (p. 79·1).
Soft-tissue inflammation.

Valused *Hasco-Lek, Pol.*
Lupulus (p. 2546·1); passion flower (p. 2584·1); valerian (p. 2640·2).
Nervous disorders; insomnia; vegetative neurosis.

Valus-P *Glenmark, India.*
Parecoxib sodium (p. 119·3).
Pain.

Valvala *Novartis, Austral.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Val-Vanco *Valeo, Canad.†*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Valved *GMP, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; upper respiratory-tract disorders.

Valved DM *GMP, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; upper respiratory-tract disorders.

Valverde Apaisement *Sidroga, Switz.*
Passion flower (p. 2584·1).
Nervous disorders.

Valverde Boutons de fievre creme *Sidroga, Switz.*
Melissa (p. 2552·3).
Herpes labialis.

Valverde buco-pharynge *Sidroga, Switz.*
Sage (p. 2608·3).
Mouth and throat disorders.

Valverde Coeur *Sidroga, Switz.*
Tablets: Crataegus leaves and fruit (p. 2488·1); passion flower (p. 2584·1); lupulus (p. 2546·1); valerian (p. 2640·2).
Cardiac disorders.

Valverde Constipation dragées *Sidroga, Switz.*
Fig (p. 1843·2); senna (p. 1885·1); butterbur root (p. 2463·2).
Constipation.

Valverde Constipation sirop *Sidroga, Switz.*
Fig (p. 1843·2); senna (p. 1885·1).
Constipation.

Valverde Detente dragées *Sidroga, Switz.*
Butterbur root (p. 2463·2); passion flower (p. 2584·1); valerian (p. 2640·2); melissa (p. 2552·3).
Nervous disorders.

Valverde Prostate capsules *Sidroga, Switz.*
Urtica (p. 2639·3).
Prostate disorders.

Valverde Sommeil *Sidroga, Switz.*
Tablets: Lupulus (p. 2546·1); valerian (p. 2640·2).
Sleep disorders.

Valvexin *EuroHealth, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Valvir *Soho, Indon.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Valvulan *Armstrong, Mex.*
Digoxin (p. 1353·3).
Supraventricular arrhythmias; heart failure.

Valz *Actavis, Rus.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Valz H *Actavis, Rus.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valzap *Zentiva, Cz.; Zentiva, Ukr.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Valzap Combi *Zentiva, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valzap Plus *Zentiva, Ukr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Valzek *Celon, Pol.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Valzepam *LBS, Philipp.*
Diazepam (p. 1063·2).
Anxiety; epilepsy; tetanus; premedication.

Valzimox *IAE, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Vamac *Pharmex (Φαρμεξ), Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Vamadrid *Liconsa, Irl.; Liconsa, Neth.*
Valsartan (p. 1521·2).
Myocardial infarction; heart failure; hypertension.

Vamazole *Nakornpatana, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Vamcee *Vamsler, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vamcloxil *Vamsler, Philipp.*
Cloxacillin (p. 274·3).
Bacterial infections.

Va-Mengoc-BC *Caif, Arg.; Alvartis, Mex.*
A meningococcal vaccine (p. 2401·3).
Active immunisation.

Vamgesic *Vamsler, Philipp.†*
Mefenamic acid (p. 85·3).
Fever; pain.

Vamin *Fresenius Kabi, Austral.; SSPC, China; Fresenius Kabi, Cz.†; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Swed.; Fresenius Kabi, UK.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Fresenius Kabi, Denm.; Fresenius Kabi, Israel; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Spain; Fresenius Kabi, Turk.†
Amino acids.
Parenteral nutrition.

Vamin con Glucosa *Fresenius Kabi, Spain.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Vamin Glucose *Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong†; Fresenius Kabi, Indon.; Pharmacia Upjohn, Israel†; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, S.Afr.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Pharmatel, Austral.†; Fresenius Kabi, Irl.†; Fresenius Kabi, Port.; Fresenius Kabi, UK.
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Vamin Glukos *Fresenius Kabi, Denm.†*
Amino acids; carbohydrate; electrolytes (p. 1775·1).
Parenteral nutrition.

Fresenius Kabi, Fin.†; Fresenius Kabi, Norw.†; Fresenius Kabi, Swed.†
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Vamin Glukoz *Fresenius Kabi, Turk.†*
Amino acids; glucose (p. 2068·3).
Parenteral nutrition.

Vamin mit Glukose *Fresenius Kabi, Austria.*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Vamin N/I *Fresenius Kabi, Fin.†*
Amino acids.
Parenteral nutrition.

Vamina Glucose *Fresenius Kabi, Switz.†*
Amino acids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Vamine Glucose *Fresenius Kabi, Fr.†*
Amino acids; glucose (p. 2068·3); electrolytes (p. 1775·1).
Parenteral nutrition.

Vamin-Glu+Intralipid *Fresenius Kabi, Gr.†*
Amino acids; lipids; carbohydrates; electrolytes (p. 1775·1).
Parenteral nutrition.

Vaminolac *Fresenius Kabi, Denm.*
Amino-acid infusion.
Parenteral nutrition.

Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.
Amino acids.
Parenteral nutrition.

Vaminolact *Fresenius Kabi, Fr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, NZ.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.†; Fresenius Kabi, Thai.; Fresenius Kabi, UK.*
Amino acids.
Parenteral nutrition.

Vaminoven *Fresenius Kabi, Irl.†; Fresenius Kabi, Port.*
Amino acids; with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Vamistol *Demo, Gr.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vamlo *Ranbaxy, Malaysia.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Vamogyl *Vamsler, Philipp.†*
Metronidazole (p. 936·1).
Amoebiasis; trichomoniasis.

Vamosef *Vamsler, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Vamox *Terramedic, Philipp.*
Amoxicillin trihydrate (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Vamsoxid *Vamsler, Philipp.†*
Isoniazid (p. 311·2).
Vitamin B_6 (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Vamstat *Vamsler, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; ischaemic heart disease.

Vamysin *Teva, Belg.*
Vancomycin (p. 384·2).
Antibiotic-associated colitis; Gram-positive bacterial infections.

Vanacof-8 *GM, USA.*
Clofedanol hydrochloride (p. 1659·1); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Vanacof APE *GM, USA.*
Clofedanol hydrochloride (p. 1659·1); thonzylamine hydrochloride (p. 642·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Vanacof DM *GM, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Vanacof DX *GM, USA.*
⊗Clofedanol hydrochloride (p. 1659·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

Vanacof GPE *GM, USA.*
Clofedanol hydrochloride (p. 1659·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Vanadyl *Best, Mex.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Vanafen *Atlantic, Thai.*
Chloramphenicol (p. 257·1).
Bacterial eye or ear infections.

Vanahist PD *GM, USA.*
Triprolidine hydrochloride (p. 642·3).
Hypersensitivity reactions.

Vanamide *Dermik, USA.*
⊗Urea (p. 1727·3).
Dry skin.

Vanatex *Polpharma, Cz.; Polpharma, Pol.*
Valsartan (p. 1521·2).
Hypertension; myocardial infarction; heart failure.

Vanatex HCT *Polpharma, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vanator *Vannier, Arg.*
Atorvastatin (p. 1309·2).
Hypercholesteroladmia.

Vanaurus *Pisa, Mex.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections; antibiotic-associated colitis due to Clostridium difficile.

Vancel *Darrow, Braz.*
Carboplatin (p. 759·1).
Malignant neoplasms.

Vancep *Fahrenheit, Indon.*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections.

Vancin *Yoo Young, Philipp.*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections.

Vancin-S *Siam Bheasach, Thai.*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections.

Vanclomin *Teuto, Braz.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vanco *CellPharm, Ger.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancoabbott *Abbott, Braz.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancocin *Aspen; Austral.; Astro, Austria; GSK, Belg.; Iroko, Canad.; Lilly, China; Lilly, Cz.; Farma Plus, Denm.; Lilly, Hong Kong†; Hungaro-Gen, Hung.; Lilly, India; Flynn, Irl.; Sandoz, Mex.; EuroCept, Neth.; GSK, Philipp.; Lilly, Pol.†; Lilly, Rus.; Sandoz, S.Afr.; Pharmacodane, Swed.; Teva, Switz.; Abbott, Turk.; Lilly, UK; ViroPharma, USA.*
Vancomycin hydrochloride (p. 384·2).
Antibiotic-associated colitis; bacterial infections.

Vancocina *Lilly, Braz.; Lilly, Ital.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancogen *Alkem, Thai.; Alkem, Ukr.†*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancogram *Biochem, India.*
Vancomycin (p. 384·2).
Bacterial infections.

Vancoled *Lederle, USA.†*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancolon *Julphar, UAE.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancomabol *Abolmed, Rus.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancomax *Klonal, Arg.*
Vancomycin (p. 384·2).

Vancomet *Korea United, Philipp.*
Vancomycin hydrochloride (p. 384·2).
Gram-positive bacterial infections.

Vanconal *Axellia, China.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vanco-ratiopharm *Ratiopharm, Ger.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancorin *CJ, China; Hemat, Turk.*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections; antibiotic-associated colitis; bacterial infections.

Vancorus *Sintez, Rus.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vanco-saar *MIP, Ger.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancosan *MIP, Fin.; Sanofi-Aventis, Gr.*
Vancomycin hydrochloride (p. 384·2).
Gram-positive bacterial infections; antibiotic-associated colitis.

Vancoson *Ariston, Braz.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancotek *Kocak, Turk.*
Vancomycin hydrochloride (p. 384·2).

Vancotenk *Biotenk, Arg.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vanco-Teva *Teva, Israel.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancotex *Pharmatex, Ital.; Pharmatex, Malaysia; Polpharma, Pol.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancotrat *Uniao Quimica, Braz.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vancox *Teva, Mex.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vandazole *Upsher-Smith, USA.*
Metronidazole (p. 936·1).
Vaginal infections.

Vanderbumin *Teva, Mex.†*
⊗Albumin (p. 1130·2).
Shock; hypovolaemia.

Vandifen *Crisdy-Na, Philipp.†*
Mefenamic acid (p. 85·3).
Pain.

Vandix *Wandel, Mex.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Vandol *Schering-Plough, Philipp.; Schering-Plough, Venez.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Skin disorders.

Vandral *Wyeth, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Vanesin *Leovan, Gr.*
Carbocisteine (p. 1658·1); sobrerol (p. 1677·2).
Mucolytic.

Vanesten *Atlantic, Thai.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Vanestrin-V *Loeffler, Mex.*
Metronidazole (p. 936·1).
Vaginal infections.

Vaneular *Medichem, Philipp.*
Vitamin B substances (p. 2102·3).
Neuropathy; neuralgia; vitamin B deficiency.

Vanex Expectorant *Abana, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2); hydrocodone tartrate (p. 67·2).
Coughs.

Vanex-HD *Tiber, USA.*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders; cough; cold symptoms.

Vanicream *Pharmaceutical Specialties, USA.*
SPF 35: Octinoxate (p. 1715·1); zinc oxide (p. 1729·1).
Sunscreen.

Pharmaceutical Specialties, USA.
Vehicle for topical preparations; moisturiser.

Pharmaceutical Specialties, USA.
Lip protectant SPF 30: Titanium dioxide (p. 1725·1).
Sunscreen.

Pharmaceutical Specialties, USA.
Cream SPF 30: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.

Vanid *Unison, Thai.*
Flunarizine (p. 629·3).
Cerebral and peripheral vascular disorders; migraine; vertigo.

Vanilone *Tradiphar, Fr.*
Cyclovalone (p. 2490·2).
Dyspepsia.

Vaniqa *LKM, Arg.; CSL Biotherapies, Austral.; Almirall, Austria; Almirall, Belg.; Triton, Canad.; Silesia, Chile; Almirall, Cz.; Almirall, Denm.; Almirall, Fr.; Almirall Hermal, Ger.; Shire, Irl.; Shire, Israel; Almirall, Ital.; Almirall, Neth.; Almirall, Norw.; Shire, Pol.; Almirall, Port.; Almirall, Spain; Almirall, Swed.; Almirall, Switz.; Almirall, UK; SkinMedica, USA.*
Eflornithine hydrochloride (p. 932·1).
Facial hirsutism in women.

Vanish *Silesia, Chile.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Vanlid *Cipla, India.*
Vancomycin hydrochloride (p. 384·2).
Staphylococcal infections.

Vanmoxol *Wandel, Mex.†*
Amoxicillin (p. 216·2); ambroxol (p. 1654·3).
Respiratory-tract infections.

Vanmycetin *FDC, India.*
Chloramphenicol (p. 257·1).
Corneal ulcer; trachoma; bacterial eye infections.

Vannair *AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, NZ; AstraZeneca, Switz.*
⊗Formoterol fumarate (p. 1209·2); budesonide (p. 1625·1).
Asthma.

Vanocin *Stratus, USA.*
Sulfacetamide sodium (p. 361·1).
Acne; rosacea; seborrhoeic dermatitis.

Vanogel *Faran, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Vanorid *Landsteiner, Mex.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Vanos *Medicis, USA.*
⊗Fluocinonide (p. 1636·3).
Skin disorders.

Vanosyn *Samjin, Philipp.*
Vancomycin hydrochloride (p. 384·2).
Gram-positive bacterial infections.

Vanoxide-HC *Summers, USA.*
⊗Benzoyl peroxide (p. 1696·1); hydrocortisone (p. 1640·1).
Acne; seborrhoea.

Vanquin *Recip, Denm.; Recip, Norw.; Recip, Swed.*
Pyrvinium embonate (p. 166·1).
Enterobiasis.

Vanquish *Glenbrook, USA.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).
Aluminium hydroxide (p. 1817·2) and magnesium hydroxide (p. 1857·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Vanra *Novagen, S.Afr.*
Stavudine (p. 1015·3).

Vansame *Valuge, Arg.*
⊗Vitamin A (p. 2098·3); alpha tocopherol (p. 2119·1); urea (p. 1727·3).
Dry skin disorders.

Vansame G *Valuge, Arg.*
Glycolic acid (p. 1704·3).
Dry skin disorders.

Vansame GS *Valuge, Arg.*
Glycolic acid (p. 1704·3); salicylic acid (p. 1719·1).
Acne.

Vansame Plus *Valuge, Arg.*
Glycolic acid (p. 1704·3); vitamin A (p. 2098·3); salicylic acid (p. 1719·1).
Dry skin disorders.

Vantal *Grossman, Mex.*
Benzydamine hydrochloride (p. 29·2).
Peri-articular disorders; soft-tissue disorders; mouth and throat inflammation; vulvovaginitis.

Vantas *Teva Tuteur, Arg.; Paladin, Canad.; Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Ger.; Orion, Irl.; Indevus, Malaysia†; Orion, Norw.; Orion, Pol.; Indevus, Singapore; Orion, Spain; Orion, Swed.; Orion, Switz.; BioPro, Thai.†; Orion, UK; Orion, Ukr.; Endo, USA.*
⊗Histrelin acetate (p. 2283·3).
Prostatic cancer.

Vantasse *Eumedica, Belg.; Orion, Neth.*
⊗Histrelin acetate (p. 2283·3).
Prostatic cancer.

Vantavo *MSD, Cz.; MSD, Irl.; MSD, Neth.; MSD, Port.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).
Osteoporosis.

Vantelin *Kowa, Jpn.*
Indometacin (p. 71·2); levomenthol (p. 2553·2).

Vantelinkowa *Kowa, China.*
Indometacin (p. 71·2); menthol (p. 2553·2).

Vantex *Fashion Fair, Canad.*
Hydroquinone (p. 1705·1).
Skin pigmentation disorders.

Vantil *Neckerman, Braz.*
Ibuprofen (p. 68·2).

Vantin
Note: this name may be used for preparations of different composition.
Best, Mex.
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; inflammation; pain.

Pharmacia Upjohn, USA.
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Christo, Hong Kong.†
⊗Salbutamol (p. 1220·2).

Vantiz *Cardinal, Indon.; Pharos, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); copper (p. 2057·1); selenium (p. 2086·3); zinc (p. 2126·1).
Antioxidant; dietary supplement.

Vantoxyl *Bruluart, Mex.*
Pentoxifylline (p. 1465·3).
Cerebral, ocular, and peripheral vascular disorders.

Vantux *Royal, Chile.*
Methionine (p. 1558·2); cystine (p. 2059·1); zinc chelate.
Dietary supplement.

Vantux Plus *Royal, Chile.*
Methionine (p. 1558·2); cystine (p. 2059·1); zinc chelate; biotin (p. 2052·2).
Dietary supplement.

Vaopin N *Riemser, Ger.†*
Camphor (p. 2466·2).
Pruritus; insect stings.

Vap *Rougier, Canad.*
Chlorhexidine gluconate (p. 1743·3).
Skin cleansing.

Vapesin *Boehringer Ingelheim, Venez.*
Feprazone (p. 64·3).
Inflammation.

Vapoflu *Lafi, Chile.*
⊗Clobutinol (p. 1658·3); orciprenaline (p. 1217·3); ammonium chloride (p. 1656·1).
Cough.

Vapolatum Inhalador *Maver, Chile.*
Camphor (p. 2466·2); methyl salicylate (p. 92·1); menthol (p. 2553·2).
Nasal congestion.

Vapolatum Unguento *Maver, Chile.*
Methyl salicylate (p. 92·1); camphor (p. 2466·2).
Musculoskeletal pain; respiratory-tract congestion.

Vapores Pyt *Fardi, Spain.†*
Peru balsam (p. 2587·1); cypress (p. 2491·1); eucalyptus (p. 2501·1); niaouli oil (p. 2569·1); diplotaxis tenuifolia; abies pectinata; Scots pine oil (p. 2591·2); beech.
Upper respiratory-tract congestion.

Vaporil *Gestafarma, Port.*
Eucalyptus oil (p. 2501·2); benzoin (p. 2624·3); thyme oil (p. 2630·3).
Nasal congestion.

Vaporisateur Nasal Decongestionnant *Confab, Canad.*
⊗Xylometazoline hydrochloride (p. 1680·1).

Vaporizing Colds Rub *Lander, Canad.†; Scott, Canad.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).

Vaporizing Ointment *Prodemdis, Canad.†*
Camphor (p. 2466·2); cedar; eucalyptus oil (p. 2501·2); menthol (p. 2553·2); nutmeg oil (p. 2573·2); thymol (p. 1772·2); turpentine.

Vaposyrup *Procter & Gamble, Gr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vapour Rub
Note: this name may be used for preparations of different composition.
Numark, UK.
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2); menthol (p. 2553·2).

Vaprasil *Loeffler, Mex.*
Pravastatin (p. 1473·1).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction; cerebrovascular risk reduction.

Vapresan *Temis, Arg.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Vapresan Diur *Temis, Arg.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vapril *Phapros, Indon.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Vaprisol *Astellas, USA.*
⊗Conivaptan hydrochloride (p. 2486·1).
Hyponatraemia.

VAQTA *MSD, Arg.; CSL Biotherapies, Austral.; Merck Frosst, Canad.; MSD, China; MSD, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.†; Sanofi Pasteur, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; Sanofi Pasteur, Irl.; MSD, Israel; Sanofi Pasteur, Ital.; MSD, Mex.; Sanofi Pasteur, Neth.; MSD, NZ; MSD, Pol.; Sanofi Pasteur, Port.; MSD, Rus.; MSD, Singapore; Sanofi Pasteur, Spain; MSD, Thai.; MSD, Turk.; Sanofi Pasteur, UK; Merck, USA.*
An inactivated hepatitis A vaccine (p. 2388·3).
Separate preparations are available for children and adolescents and for adults.
Active immunisation.

Varaxil *Merck, Mex.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Vardolin *Help, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Varedet *Fada, Arg.*
Vancomycin (p. 384·2).
Staphylococcal infections.

Varemoid *Novartis, Philipp.*
Oxerutins (p. 2505·3).
Haemorrhoids.

Varexan *Novartis, Hung.†*
Valsartan (p. 1521·2).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Varexan HCT *Novartis, Hung.†*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Varfine *Teofarma, Port.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Varginko *Infinity, Venez.*
Ginkgo biloba (p. 2512·3).
Tonic.

Variargil *Logogen, Spain.*
Alimemazine tartrate (p. 615·1).
Hypersensitivity reactions.

Varibar *Bracco, USA.*
Barium sulfate (p. 1583·2).
Gastrointestinal radiography.

Varibona *PSI, Neth.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Varicela Biken *Sanofi Pasteur, Arg.*
A live attenuated varicella-zoster vaccine (OKA strain) (p. 2423·3).
Active immunisation.

Varicellon *CSL, Ger.*
A varicella-zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Varicex *Lohmann, Ital.*
Zinc oxide (p. 1729·1).
Medicated dressing.

Varicid *Lacer, Spain.†*
Aesculus (p. 2431·2).
Venous insufficiency; skin disorders; diarrhoea.

Vari-Cocodamol *LeBasi, S.Afr.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).

Varicofem *Argenfarma, Arg.*
⊗Hesperidin (p. 2505·2); ginkgo biloba (p. 2512·3); vitamin B_{15} (p. 2582·1); butcher's broom (p. 2463·1); bromelains (p. 2460·3).

Varicose Ointment *Potter's, UK.*
Cade oil (p. 1723·2); hamamelis (p. 2523·3); zinc oxide (p. 1729·1).
Skin irritation due to varicosity.

Varicoss *Cifarma, Braz.*
Coumarin (p. 2487·2); troxerutin (p. 2505·3).
Vascular disorders.

Varicura *Futerman, Arg.*
Centella (p. 1698·3); melilot (p. 2552·3); hamamelis (p. 2523·3); bearberry (p. 2453·2); butcher's broom (p. 2463·1); lemon (p. 2542·3).
Venous insufficiency.

Varicyl *Integral Health, Mex.*
⊗Aesculus (p. 2431·2); cinnamon (p. 2479·2); camphor (p. 2466·2); centella (p. 1698·3); menthol (p. 2553·2); alcohol (p. 1733·1); glycerol (p. 2517·2).
Circulatory disorders; inflammation.

Varicylum N *Liebermann, Ger.*
Aesculus (p. 2431·2); arnica mont. (p. 2447·2); calc. fluor. (p. 2053·1); hamamelis (p. 2523·3); pulsat. prat. (p. 2600·2); rutinum (p. 2505·3).
Homoeopathic preparation.

Varicylum-S *Liebermann, Ger.†*
Chamomile oil (p. 2474·1); sage oil (p. 2609·1); arnica (p. 2447·2); aesculus (p. 2431·2); hamamelis (p. 2523·3).
Vascular disorders; soft-tissue injury; haemorrhoids.

Varidasa *Wyeth, Mex.; Cantabria, Spain.*
Streptokinase (p. 1503·1); streptodornase (p. 2623·1).
Inflammation; tissue damage; local removal of blood clots; oedema.

Varidase *Riemser, Austria; Meda, Fin.†; Riemser, Ger.; Meda, Norw.†*
Streptokinase (p. 1503·1); streptodornase (p. 2623·1).
Wounds; ulcers; inflammation; oedema; bruising; haematoma; local removal of blood clots, fibrin, and purulent matter.

Variderm *Profarm, Pol.*
Benzocaine (p. 1980·2); menthol (p. 2553·2); zinc oxide (p. 1729·1).
Skin irritation; pruritus; burns.

Varidoid *General Drugs, Thai.*
A heparinoid (p. 1401·1).
Phlebitis; thrombosis; varicose veins; haematoma; oedema; scars; sunburn.

Varidoxo *Varifarma, Arg.*
Doxorubicin (p. 782·3).
Malignant neoplasms.

Varidronico *Varifarma, Arg.*
Zoledronic acid (p. 1192·3).

Varigestrol *Varifarma, Arg.*
Megestrol (p. 2289·2).

Varihes *Eczacibasi-Baxter, Turk.*
⊗Hetastarch (p. 1146·1).
Hypovolaemia.

Varikopax *Florin, Hung.*
Alum (p. 2439·1).
Phlebitis; varicose veins.

Varilise *Ativus, Braz.*
Aesculus (p. 2431·2).
Haemorrhoids; varices.

Varilrix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; Litha, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, Venez.*
A live attenuated varicella-zoster vaccine (OKA strain) (p. 2423·3).
Active immunisation.

Varimer *Varifarma, Arg.*
Mercaptopurine (p. 820·3).
Malignant neoplasms.

Varimesna *Varifarma, Arg.*
Mesna (p. 1557·2).

Varimine *Atral, Port.*
Vitamins; minerals.

Varinar *Landsteiner, Mex.*
Ribavirin (p. 1010·2).
Viral infections.

Varipan *Specpharm, S.Afr.*
Paracetamol (p. 115·1).
Fever; pain.

Variplant *Knop, Chile.*
Aesculus hippocastanum (p. 2431·2); carduus marianus (p. 1561·1); hamamelis (p. 2523·3).
Homoeopathic preparation.

Variplex *Knop, Chile.*
Castano de India (p. 2431·2); bursa pastoris (p. 2614·2); millefolium (p. 2427·3); hamamelis (p. 2523·3).
Homoeopathic preparation.

Varipox *Zydus, India.†*
A live attenuated varicella-zoster vaccine (OKA strain) (p. 2423·3).
Active immunisation.

Variquel *Hospira, Belg.; IS Pharmaceutical, Denm.; Hospira, Spain; Hospira, Swed.; IS Pharma, UK.*
⊗Terlipressin acetate (p. 2627·1).
Variceal haemorrhage.

VariQuin *Sanquin, Neth.*
A varicella zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Varirix *Allen, Gr.*
A live attenuated varicella-zoster vaccine (Oka strain) (p. 2423·3).
Active immunisation.

Varirtan *AMPDR, Port.†*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Varisedan *Wierhom, Arg.*
Rutoside (p. 2505·3); garlic (p. 2510·3).
Venous insufficiency; haemorrhoids.

Varisedan Gel *Wierhom, Arg.*
Ivy (p. 2536·2); bladderwrack (p. 2612·1); camphor (p. 2466·2); menthol (p. 2553·2).
Venous insufficiency.

Varison
Note: this name may be used for preparations of different composition.
Schwabe, Port.
Aesculus (p. 2431·2).
Venous insufficiency.

Varitect *Biogam, Arg.; Biotest, Austria; Biotest, Ger.; IFET (ΙΦΕΤ), Gr.; Biotest, Hong Kong†; Intra Pharma, Irl.†; Biotest, Israel; Biotest, Ital.; Biotest, Pol.†; Boehringer Ingelheim, Port.†; Biotest, Singapore†; Biotest, Switz.; Biotest, Thai.†; Kansuk, Turk.*
A varicella-zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Varithena *Biocompatibles, USA.*
Lauromacrogol 400 (p. 2194·1).
Varicose veins.

Variton *Hormona, Mex.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Varivax *CSL Biotherapies, Austral.; Sanofi Pasteur, Austria; Merck Frosst, Canad.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; MSD, Mex.; MSD, NZ; Sanofi Pasteur, Port.; Sanofi Pasteur, Spain; Sanofi Pasteur, Switz.; Aventis Pasteur, UK; Merck, USA.*
A live attenuated varicella-zoster vaccine (OKA/Merck strain) (p. 2423·3).
Active immunisation.

Varivenot *Bros, Gr.*
Astemizole (p. 616·1).
Allergic rhinitis; urticaria.

VariZIG *Cangene, Canad.*
A varicella-zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Varizig *Cangene, USA.*
A varicella-zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Varizil *Droxter, Braz.*
Melilot (p. 2552·3).

Varlex *Arlex, Mex.*
Pravastatin (p. 1473·1).
Hyperlipidaemias.

Varmec *Kleva, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Varnoline *MSD-Chibret, Fr.*
Desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Varoc *Pyridam, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Varom *Lyofin, Gr.*
Citalopram hydrobromide (p. 411·1).

Varsil *BioSaude, Port.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular dysfunction; diabetic nephropathy.

Varson *Pantofarma, Spain.*
Nicergoline (p. 2569·1).
Vascular disorders.

Vartalan *Drugtech, Chile.*
Valsartan (p. 1521·2).
Hypertension.

Vartalan AM *Drugtech, Chile.*
Amlodipine besilate (p. 1304·1); valsartan (p. 1521·2).
Hypertension.

Vartalan D *Drugtech, Chile.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vartalon
Note: this name may be used for preparations of different composition.
Asofarma, Mex.; Nolver, Venez.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Vartalon Complemento *Sandoz, Arg.*
Glucosamine sulfate (p. 2515·3). Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.
Osteoarthritis; joint disorders.

Vartalon Compositum *Asofarma, Mex.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Osteoarthritis; degenerative joint disorders.

Vartalon Duo *Sandoz, Arg.*
Chondroitin sulfate sodium (p. 2476·1); glucosamine sulfate (p. 2515·3).
Joint disorders.

Vartalon Duo K *Sandoz, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3); chondroitin sulfate sodium (p. 2476·1).
Joint disorders.

Vartalon K *Sandoz, Arg.*
Glucosamine sulfate potassium chloride (p. 2515·3).
Joint disorders.

Vartelon *Christo, Hong Kong.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Vartelon-B *Christo, Hong Kong.*
Diclofenac sodium (p. 48·3); vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Musculoskeletal and joint disorders; pain; inflammation.

Vartrual *Merck, Port.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

V-AS
Note: this name may be used for preparations of different composition.
Medicine Products, Thai.†
Aspirin (p. 22·2).
Rheumatoid arthritis; osteoarthritis; pain; fever.

Vas
Note: this name may be used for preparations of different composition.
Geymonat, Ital.†
Suleparoid (p. 1507·2).
Thrombosis prophylaxis.

Vasactife *Ferring, Port.*
Ginkgo biloba (p. 2512·3).
Vascular disorders.

Vasa-Gastreu N R63 *Reckeweg, Ger.*
Cuprum acet. (p. 2486·2); secale corn. (p. 2137·1); tabacum (p. 2632·2).
Homoeopathic preparation.

Vasagrin *Pentafarma, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Vasalat *Apotex, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Vasalen *Millimed, Thai.†*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation; renal colic; biliary colic.

Vasalgin *Extractum, Hung.†*
Proxibarbal (p. 1100·2).
Headache; migraine; Raynaud's syndrome.

Vasanter *Alter, Port.†*
Valsartan (p. 1521·2).
Myocardial infarction; heart failure; hypertension.

Vasaprostan *Schwarz, Rus.*
Alprostadil alfadex (p. 2352·2).
Arterial occlusion.

Vasar *Actavis, Ukr.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Vasar H *Actavis, Ukr.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasaten
Note: this name may be used for preparations of different composition.
Leti, Venez.
Valsartan (p. 1521·2).
Hypertension.

Vasaten HCT *Leti, Venez.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasativ *Eurofarma, Braz.*
Cilostazol (p. 1337·1).
Cerebral and peripheral vascular disorders.

Vascace *Roche, Irl.; Roche, Israel†; Roche, Philipp.; Roche, UK.†*
Cilazapril (p. 1336·2).
Heart failure; hypertension.

Vascace Plus *Roche, Israel†; Roche, Philipp.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vascal
Note: this name may be used for preparations of different composition.
UCB, Ger.
Isradipine (p. 1414·2).
Hypertension.
Viatris, Austria.†
Carbasalate calcium (p. 36·2).
Thromboembolism prophylaxis.

Vascalpha *Alpharma, UK.*
Felodipine (p. 1380·3).
Hypertension.

Vascardin *Nicholas, Indon.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; myocardial infarction; heart failure.

Vascase *Roche, Braz.; Roche, Gr.; Roche, Neth.; Pfizer, Port.*
Cilazapril (p. 1336·2).
Hypertension; heart failure.

Vascase Plus *Roche, Braz.; Roche, Gr.; Pfizer, Port.*
⊗Cilazapril (p. 1336·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vascepa *Amarin, USA.*
Eicosapentaenoic acid ethyl ester (p. 1460·2).
Hypertriglyceridaemia.

Vascer *Uniao Quimica, Braz.*
Pentoxifylline (p. 1465·3).

Vasclin *Libbs, Braz.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).
Angina pectoris; myocardial infarction; heart failure.

Vasclor *Verisfield, Gr.*
Progesterone (p. 2300·2).
Female infertility.

Vascocitrol *H2 Pharma, Fr.†*
Citroflavonoids (p. 2505·2); ascorbic acid (p. 2110·3); light magnesium carbonate (p. 1856·2).
Venous insufficiency.

Vascodin *Help, Gr.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Vascodran *Sevene, Fr.*
Carduus marianus (p. 1561·1); anemone pulsatilla (p. 2600·2); berberis vulgaris (p. 2502·1).
Homoeopathic preparation.

Vascoflor *Sevene, Fr.*
Hamamelis virginiana (p. 2523·3); carduus marianus (p. 1561·1); aesculus hippocastanum (p. 2431·2).
Homoeopathic preparation.

Vascoman *Takeda, Ital.*
Manidipine hydrochloride (p. 1427·2).
Hypertension.

Vascon *Fahrenheit, Indon.*
⊗Noradrenaline acid tartrate (p. 1458·2).
Hypotension; cardiac arrest.

Vascor
Note: this name may be used for preparations of different composition.
CCM, Malaysia; Upha, Singapore; Biolab, Thai.
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction; hypercholesterolaemia; atherosclerosis.
Therapharma, Philipp.
Imidapril hydrochloride (p. 1409·1).
Hypertension.

Vascoray *Tyco, Canad.†*
Meglumine iotalamate (p. 1592·2); sodium iotalamate (p. 1592·2).
Radiographic contrast medium.

Vascord
Note: this name may be used for preparations of different composition.
Menarini, Switz.
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Vascoride *Therapharma, Philipp.*
⊗Imidapril hydrochloride (p. 1409·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vascorim *Vida, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Vascoten *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.†*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Vasculat *Boehringer Ingelheim, Braz.*
Bamethan sulfate (p. 1314·1).
Peripheral vascular disorders.

Vasculflow *Rimsa, Mex.*
Calcium dobesilate (p. 2464·3); diosmin (p. 2505·2); hesperidin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Vasculin *Biolab, Thai.†*
Codergocrine mesilate (p. 389·2).
Mental function disorders.

Vasculocis *CIS, Fin.; CIS, Fr.*
Technetium-99m (p. 2228·1) albumin.
Radionuclide blood imaging.

Vascuprax *Ikapharmindo, Indon.*
Naftidrofuryl oxalate (p. 1443·3).
Cerebral and peripheral vascular disorders.

Vasdalat *Hexpharm, Indon.; Kalbe, Singapore.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Vasdecom *Raam, Mex.*
Orlistat (p. 2577·1).
Obesity.

Vasdilat *Marvecs, Ital.*
Isosorbide mononitrate (p. 1413·3).
Ischaemic heart disease.

Vaselatum *Stiefel, Spain.*
Liquid paraffin (p. 2191·2); benzalkonium chloride (p. 1737·1); triclosan (p. 1773·2).
Eczema.

Vaselec *Nabiqasim, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Vaselina *Belfar, Braz.*
White soft paraffin (p. 2211·3).

Vaselina Boricada *Orravan, Spain.†*
Boric acid (p. 2459·3); white soft paraffin (p. 2211·3).
Skin disorders; urethral or rectal lubricant.

Vaselina Emulsionada *Laboratorios Chile, Chile.*
Liquid paraffin (p. 2191·2); agar (p. 2167·2); tragacanth (p. 2217·1); acacia (p. 2166·1); methylcellulose (p. 2197·3).
Constipation.

Vaseline *Tyco, Canad.; Unilever, Canad.; Lever, UK.*
White soft paraffin (p. 2211·3).
Minor skin disorders; barrier preparation.

Vaseline Borique *Ni-The, Gr.*
White soft paraffin (p. 2211·3); boric acid (p. 2459·3).

Vaseline Gomenolée *Gomenol, Fr.*
Niaouli oil (p. 2569·1); white soft paraffin (p. 2211·3).
Nasal disorders.

Vaseline Intensive Care *Chesebrough-Pond's, USA.*
SPF 25: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.
Chesebrough-Pond's, USA.
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.
Chesebrough-Pond's, USA.
SPF4; SPF 8; SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Vaseline Intensive Care Active Sport *Chesebrough-Pond's, USA.*
SPF 8; SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Vaseline Intensive Care Baby *Chesebrough-Pond's, USA.*
SPF 15: Titanium dioxide (p. 1725·1); zinc oxide (p. 1729·1).
Sunscreen.
Chesebrough-Pond's, USA.
SPF 30+: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Vaseline Intensive Care Blockout *Chesebrough-Pond's, USA.*
SPF 40: Padimate (p. 1715·3); octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2); titanium dioxide (p. 1725·1).
Sunscreen.

Vaseline Intensive Care No Burn No Bite *Chesebrough-Pond's, USA.*
SPF 8; SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Vaseline Oxyde Zinc *Ni-The, Gr.*
White soft paraffin (p. 2211·3); zinc oxide (p. 1729·1).

Vaseline Pure *Ni-The, Gr.*
White soft paraffin (p. 2211·3).

Vaselitulle *Abbott, Fr.*
White soft paraffin (p. 2211·3).
Burns; ulcers; wounds.

Vaselpin *Faran, Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Vaseretic *Merck Frosst, Canad.; Valeant, USA.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasexten
Note: this name may be used for preparations of different composition.
Solvay, Belg.; Astellas, Cz.; Astellas, Gr.; Italfarmaco, Ital.; Astellas, Neth.; Astellas, Port.†
Barnidipine hydrochloride (p. 1314·1).
Hypertension.
Bernabo, Arg.
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Vasexten-D *Bernabo, Arg.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasfilm *Braun, Spain.*
White soft paraffin (p. 2211·3).
Skin disorders; urethral or rectal lubricant.

Vasgard *Nufarindo, Indon.*
Amlodipine (p. 1304·1).
Angina pectoris; hypertension.

Vasian *Asian Pharm, Thai.*
Codergocrine mesilate (p. 389·2).
Mental function disorders.

Vasican *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Vasifil *Germed, Braz.*
Sildenafil (p. 2364·1).

Vasilip *KRKA, Cz.; KRKA, Denm.; KRKA, Hong Kong; Egis, Hung.; KRKA, Pol.; KRKA, Rus.; KRKA, Singapore; KRKA, Ukr.*
Simvastatin (p. 1489·2).
Cardiovascular risk reduction; hypercholesterolaemia; hyperlipidaemias.

Vasilium *BioSaude, Port.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Vaslip *Biolab Sanus, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Vasmulax *Integrated Pharmaceutical, Philipp.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Vasobion *Merck, Mex.*
Pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Vitamin deficiency.

Vasobrain *Errekappa, Ital.*
Phospholipids (p. 2201·2); vitamin E (p. 2119·1); ginkgo biloba (p. 2512·3).
Mental function disorders.

Vasobrain Plus *Errekappa, Ital.*
Papaya; thioctic acid (p. 2629·1); ginkgo biloba (p. 2512·3); vitamins.
Mental function impairment; tonic.

Vasobral *Chiesi, China; Chiesi, Fr.; Chiesi, Hong Kong; Chiesi, Rus.*
Dihydroergocryptine mesilate (p. 390·2); caffeine (p. 1203·3).
Cerebral and peripheral vascular disorders; Raynaud's syndrome; mental function impairment; migraine; vestibular disorders; retinopathy.

Vasocard *Fako, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Vasocardin *Nycomed, Cz.; Zentiva, Cz.; Zentiva, Rus.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; myocardial infarction; arrhythmias; hyperthyroidism; migraine.

Vasocardol *Sanofi-Aventis, Austral.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Vasocedine *Qualiphar, Belg.*
⊗Naphazoline nitrate (p. 1669·3).
Nasal congestion.

Vasocedine Pseudoephedrine *Qualiphar, Belg.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis.

Vasocidin *Novartis, USA.*
⊗Prednisolone sodium phosphate (p. 1645·3); sulfacetamide sodium (p. 361·1).
Eye inflammation with bacterial infection.

Vasocine *Novartis Ophthalmics, USA.*
⊗Prednisolone acetate (p. 1645·2); sulfacetamide sodium (p. 361·1).
Infected eye disorders.

Vasoclear *Vista, Philipp.*
⊗Naphazoline hydrochloride (p. 1669·3).
Eye irritation.

VasoClear A *Novartis Ophthalmics, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.

Vasocon-A *Novartis Ophthalmics, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); antazoline phosphate (p. 615·3).
Eye irritation.

Vasoconstrictor Pensa *Pensa, Spain.*
⊗Naphazoline hydrochloride (p. 1669·3).
Nasal congestion.

Vasodexa *Llorens, Spain.*
⊗Dexamethasone phosphate (p. 1631·1); tetryzoline hydrochloride (p. 1678·3).
Inflammatory eye disorders.

Vasodil *Nycomed, Mex.*
Ginkgo biloba (p. 2512·3).
Cerebral, ocular, and peripheral vascular disorders.

Vasodilan *Apothecon, USA.*
Isoxsuprine hydrochloride (p. 2535·2).
Cerebrovascular disorders; peripheral vascular disorders.

Vasodin *Teofarma, Ital.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension; angina pectoris; heart failure.

Vasodip *Dexcel, Israel.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Vasodip Combo *Dexcel, Israel.*
Lercanidipine hydrochloride (p. 1419·3); enalapril maleate (p. 1371·1).
Hypertension.

Vasodipin *Merck, Port.*
⊗Indapamide (p. 1409·2).
Hypertension.

Vasodipina *Neo Quimica, Braz.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Vaso-E-Bion *Rodisma, Ger.†*
Troxerutin (p. 2505·3); *dl*-alpha tocoferil acetate (p. 2119·2).
Vascular disorders.

Vasofen *Tubilux, Ital.*
Chloramphenicol sodium hemisuccinate (p. 257·2); phenylephrine (p. 1672·2); mepyramine maleate (p. 635·1).
Eye disorders.

Vasofrinic *Trianon, Canad.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory congestion.

Vasofrinic DH *Trianon, Canad.*
⊗Chlorphenamine maleate (p. 620·3); hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1).

Vasofrinic Plus *Trianon, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough; respiratory congestion.

Vasofyl *Teva, Mex.*
Pentoxifylline (p. 1465·3).
Cerebral, ocular, and peripheral vascular disorders.

Vasogard *Biosintetica, Braz.*
Cilostazol (p. 1337·1).
Cerebral and peripheral vascular disorders.

Vasogen *Hind Wing, Hong Kong†; Forest, Irl.†; Forest Laboratories, UK.*
Dimeticone (p. 2209·3); zinc oxide (p. 1729·1); calamine (p. 1697·2).
Nappy rash; barrier cream.

Vasojet *Uniao Quimica, Braz.*
Lisinopril (p. 1420·3).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vasoket *UCB, Ukr.*
Diosmin (p. 2505·2).
Venous insufficiency; capillary fragility.

VasoKINOX *Air Liquide, Belg.; Air Liquide, Spain.*
Nitric oxide (p. 1457·1).
Pulmonary hypertension.

Vasokor *Medikon, Indon.*
Dipyridamole (p. 1362·2).
Angina pectoris; myocardial infarction; thromboembolic disorders.

Vasolan
Note: this name may be used for preparations of different composition.
Eisai, Jpn.
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; myocardial infarction; ischaemic heart disease.

Vasolapril *Deva, Turk.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Vasolator *Sanwa, Jpn.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure; hypertension in surgery.

Vasolex *Stratus, USA.*
⊗Peru balsam (p. 2587·1); castor oil (p. 2472·1); trypsin (p. 2635·2).
Burns; ulcers; wounds.

Vasolexin *Korea United, Philipp.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris.

Vasolipid *Braun, Denm.; Braun, Fin.; Braun, Norw.; Braun, Swed.*
Soya oil (p. 2092·3); medium-chain triglycerides (p. 2082·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Vasomed *Chemopharma, Chile.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Vasomil *Aspen, S.Afr.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias.

Vasomotal *Royal, Chile; Abbott, Ger.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Vason
Note: this name may be used for preparations of different composition.
Millimed, Thai.†
Diazepam (p. 1063·2).
Anxiety; insomnia; alcohol withdrawal syndrome; premedication; epilepsy; skeletal muscle spasm.
Sandoz, Indon.†
⊗Betamethasone valerate (p. 1624·1).
Skin disorders.

Vasonase *Astellas, Spain.*
Nicardipine hydrochloride (p. 1445·2).
Cerebrovascular disorders; hypertension; angina pectoris.

Vasonit *Lannacher, Austria; Lannacher, Cz.; Lannacher, Rus.*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders; vascular eye and ear disorders.

Vasonorm
Note: this name may be used for preparations of different composition.
Kocak, Turk.
Amlodipine besilate (p. 1304·1).

Vasopid *YSS, Philipp.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolic disorders.

Vasoplan *Nevzat, Turk.*
Pentoxifylline (p. 1465·3).
Vascular disorders.

Vasoplant *Leti, Venez.*
Aesculus (p. 2431·2).

Vasoplus *CPH, Port.†*
Amlodipine besilate (p. 1304·1).

Vasopos N *Ursapharm, Cz.; Ursapharm, Ger.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Vasopren *Sopharma, Rus.†*
Enalapril (p. 1371·1).
Hypertension; heart failure.

Vasopress *Gedeon Richter, Philipp.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Vasopril
Note: this name may be used for preparations of different composition.
Indeco, Arg.; Biolab Sanus, Braz.
Enalapril maleate (p. 1371·1).
Hypertension.

Vasopril Plus *Biolab Sanus, Braz.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasoprost *Esteve, Port.*
Alprostadil alfadex (p. 2352·2).
Peripheral vascular disease.

Vasopt *Bausch & Lomb, Ital.*
Ginkgo biloba (p. 2512·3); vitamin E acetate (p. 2119·2); minerals.
Vascular disorders of the eye.

Vasorel *Servier, China.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo.

Vasoretic *MSD, Ital.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasorinil *DMG, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Nasal congestion.

Vasosan *Felgentrager, Cz.; Felgentrager, Ger.; Felgentrager, Pol.*
Colestyramine (p. 1346·1).
Hypercholesterolaemia; cholestasis-associated pruritus; diarrhoea; hyperlipidaemias; chologenic diarrhoea.

Vasoserc *Mecom, Rus.; Abdi, Turk.; Mecom, Turk.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.
Abdi, Ukr.
Betahistine (p. 2455·3).
Ménière's disease; vestibular disturbances.

Vasostad *Stada, Philipp.*
Captopril (p. 1331·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Vasostat *Zdorovje, Ukr.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Vasosterone Oto *Angelini, Ital.†*
⊗Flumetasone pivalate (p. 1635·2); gentamicin sulfate (p. 304·2).
Otitis externa.

Vasosulf *Ciba Vision, USA.†*
Sulfacetamide sodium (p. 361·1); phenylephrine hydrochloride (p. 1672·3).
Eye infections.

Vasosuprina *Lusofarmaco, Ital.*
Isoxsuprine hydrochloride (p. 2535·2).
Premature labour; threatened miscarriage.

Vasotec *Merck Frosst, Canad.; Biovail, USA.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Vasotenal *Roemmers, Arg.; Pharma Investi, Chile†; Roemmers, Venez.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Vasotenal EZ *Roemmers, Arg.*
Simvastatin (p. 1489·2); ezetimibe (p. 1379·2).
Hypercholesterolaemia.

Vasotenz *Actavis, Rus.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Vasotenz H *Actavis, Rus.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vasotin *Metiska, Indon.*
Dipyridamole (p. 1362·2).
Angina pectoris; thrombosis prophylaxis.

Vasoton
Note: this name may be used for preparations of different composition.
Ariston, Braz.
Verapamil hydrochloride (p. 1522·1).
Hypertension; arrhythmias.

Vasotonal *Amnol, Ital.*
Aescin (p. 2431·2); caffeine (p. 1203·3); ruscus; centella (p. 1698·3); arnica (p. 2447·2); hedera; capsicum (p. 2469·3); ginkgo biloba (p. 2512·3); menthol (p. 2553·2).
Skin disorders.

Vasotop *Cipla, India.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Vasotrate *Torrent, Philipp.; Torrent, Singapore.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Vasovist *Bayer, Belg.†; Bayer, Canad.; Schering, Denm.†; Bayer, Fr.†; TMC, Hung.; Bayer, Ital.†; Bayer Schering, Pol.; Bayer, Switz.†; Bayer, Turk.*
Gadofosveset trisodium (p. 1585·3).
Contrast medium for magnetic resonance imaging.

Vasovitol *Lannacher, Austria.†*
Vitamin A palmitate (p. 2098·3); alpha tocoferil acetate (p. 2119·2).
Vitamin A and E deficiency.

Vasoxen *Ulagay, Turk.*
⊗Nebivolol (p. 1444·2).
Hypertension.

Vaspit *Intendis, Ital.; Intendis, Spain.*
⊗Fluocortin butyl (p. 1637·1).
Skin disorders; burns; insect stings.

Vasprim *Millimed, Philipp.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Vasran *Ranbaxy, UK.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Vassapro *Vamsler, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; neurosensorial ischaemia.

Vassor *Gerolymatos, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Vastaflux *Landsteiner, Mex.†*
Fluvastatin (p. 1385·1).

Vastamox *Danlex, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Vastan *ICN, Pol.; Meyer Alian, Venez.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Vastarel *Servier, Arg.; Servier, Austria†; Servier, Braz.; Grunenthal, Chile; Servier, Denm.; Servier, Fr.; Servier, Gr.; Servier, Hong Kong; Servier, Irl.; Stroder, Ital.; Servier, Malaysia; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Thai.; Servier, Turk.; Servier, Venez.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; ischaemic heart disease; vascular eye disorders; vertigo; tinnitus; Ménière's disease; vestibular disorders; chorioretinal ischaemia; peripheral vascular disorders.

Vastat
Note: this name may be used for preparations of different composition.
Lewison, Philipp.
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.
Esteve, Spain.†
Mirtazapine (p. 436·1).
Depression.

Vastatifix *Tiefenbacher, Neth.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias; cardiovascular risk reduction.

Vastatil *Mabra, Braz.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Vastatin *Vocate, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Vastazor *Vocate, Gr.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Vastec *Pentafarma, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Vastecel *Medix, Mex.*
Aspirin (p. 22·2).

Vasten *Sanofi-Aventis, Fr.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Vastensium *Salvat, Spain.†*
Nitrendipine (p. 1456·3).
Hypertension.

Vaster *Nicholas, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Vastgen *Genetic, Ital.*
Simvastatin (p. 1489·2).

Vastichol *Pharmaspec, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Vasticor *Segix, Ital.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Vastigmex *Bolar, Cz.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Vastigo *Dexa, Indon.*
Betahistine mesilate (p. 2455·3).
Vertigo; Ménière's disease.

Vastil *Pharmanel, Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Vastilan *Aldril, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; ischaemic heart disease.

Vastin *Novartis, Austral.*
Fluvastatin sodium (p. 1385·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Vastina *Penn, Arg.*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Vastinol *TO-Chemicals, Thai.*
Trimetazidine hydrochloride (p. 1520·1).
Ischaemic heart disease.

Vastionin *Farmaceutica H, Mex.*
Isotretinoin (p. 1706·2).
Acne.

Vaston *Medis, Cz.†*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Vastor *Farmalter, Port.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Vastoran *Ranbaxy, Mex.*
Pravastatin (p. 1473·1).
Ranbaxy, Austral.†
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia.

Vastripine *Aledicine, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Vastus *Sandoz, Arg.*
Albendazole (p. 149·1).
Worm infections.
Tecnofarma, Chile.
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Vasvita *Armoxindo, Indon.*
Vitamin B substances (p. 2102·3).
Neuritis; anaemia.

Vataceph *Seven Stars, Thai.†*
Cefalexin (p. 234·1).
Bacterial infections.

Vatacil *Elin, Philipp.*
Ampicillin sodium (p. 218·2).
Bacterial infections.

Vatan *Rowex, Irl.; APS, Port.†*
Valsartan (p. 1521·2).
Myocardial infarction; heart failure; hypertension.

Vatanal *Farmo Quimica, Chile.*
Cod-liver oil (p. 2056·3); a macrogol lauril ether (p. 2193·3); chlorocarvacrol (p. 1747·3).
Anorectal disorders.

Vatarax *Vickmans, Hong Kong.†*
Hydroxyzine (p. 630·3).

Va-t'en *Melisana, Switz.*
Aspirin (p. 22·2) or salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Calluses.

Vatoud *IWA, Cz.; Germed, Ital.; Focus Farma, Neth.; Alter, Spain.*
Clopidogrel besilate (p. 1342·3).
Thromboembolism prophylaxis; acute coronary syndrome.

Vatran *Valeas, Ital.*
Diazepam (p. 1063·2).
Anxiety; epilepsy; psychosomatic disorders; skeletal muscle spasm; premedication; eclampsia.

Vatrem *Kener, Mex.*
Piroxicam (p. 125·3).

Vaxcel Ceftazidime *Kotra, Malaysia.*
Ceftazidime (p. 250·2).
Bacterial infections.

Vaxcel Ceftriaxone *Kotra, Malaysia.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Vaxcel Cefuroxime *Kotra, Malaysia.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Vaxem Hib *Novartis Vaccines, Ital.; Novartis Vaccines, Philipp.; Novartis Vaccines, Thai.*
A Haemophilus influenzae conjugate vaccine (p. 2387·2).
Active immunisation.

Vaxigrip *Sanofi Pasteur, Arg.; Sanofi Pasteur, Austral.; Sanofi Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, China; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Indon.; Sanofi Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Turk.*
An inactivated influenza vaccine (p. 2393·3).
Active immunisation.

Vaxim HIB *Aventis, India.†*
A haemophilus influenzae conjugate vaccine (p. 2387·2).
Active immunisation.

Vaxitiol *Bouty, Ital.*
Lactobacillus sporogenes (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Streptococcus thermophilus* (p. 2596·3); *Bifidobacterium bifidum* (p. 2596·3); vitamins; minerals.
Maintenance of normal gastrointestinal flora.

Vaxman *Tolmann, Philipp.†*
Amoxicillin (p. 216·2).
Bacterial infections.

Vaxol *Naturfarm, Ukr.*
Olive oil (p. 2575·1).
Ear wax removal.

Vaxolem *Teva, Mex.†*
Pentoxifylline (p. 1465·3).

Vaxosin *Norton, Pol.†*
Doxazosin mesilate (p. 1369·1).
Hypertension.

Vazamide *Torrent, Philipp.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Vazaprostan *UCB, Ukr.*
Alprostadil (p. 2352·2).
Arterial occlusion.

Vazigam *NBI, S.Afr.*
A varicella-zoster immunoglobulin (p. 2423·2).
Passive immunisation.

Vazim *Sandoz, Indon.†*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Vazkor *Deva, Turk.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris; Raynaud's syndrome.

Vazobid PD *WraSer, USA.*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).

VaZol-D *WraSer, USA.†*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1).
Upper respiratory-tract disorders.

Vazonat *Olainfarm, Ukr.*
Meldonium (p. 1429·3).
Cardiovascular and cerebrovascular disorders; tonic; alcoholism.

Vazopro *Farmak, Ukr.*
Meldonium (p. 1429·3).
Ischaemic heart disease; cerebrovascular disorders; tonic; alcoholism.

Vazortan-H *Medley, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vazosin *Biotenk, Arg.*
Doxazosin (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Vazotab *WraSer, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Vazotan *Gentex, USA.*
Phenylephrine hydrochloride (p. 1672·3); brompheniramine maleate (p. 618·1); pentoxyverine citrate (p. 1672·1).
Upper respiratory-tract disorders.

Vazotuss HC *WraSer, USA.†*
Hydrocodone tannate (p. 67·2); brompheniramine tannate (p. 618·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Vazy *Sigma, Braz.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Vazz *Foramen, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

V-Bloc *Kalbe, Indon.*
⊗Carvedilol (p. 1333·1).
Heart failure; hypertension.

V-C *Millimed, Thai.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

V-Calcium *VS, Thai.*
Calcium carbonate (p. 1824·3).

VCF *Apothecus, Canad.†; Apothecus, Hong Kong; Apothecus, USA.*
Nonoxinol 9 (p. 2199·1).
Contraceptive.

V-Cof *Macoven, USA.*
Brompheniramine maleate (p. 618·1); pentoxyverine citrate (p. 1672·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

V-Crima *Vitamed, Israel.*
Povidone (p. 2204·3); hyetellose (p. 2188·3).
Dry eyes.

VCS *Boryung, Thai.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

V-Dalgin *Vitamed, Israel.*
Dipyrone (p. 53·3).
Pain; fever.

V-D-Bone *Verisfield, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

V-Dec-M *Seatrace, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Ve *Tecnifar, Port.*
Vitamin E (p. 2119·1).
Vitamin E supplement.

Vebac *Fahrenheit, Indon.*
Aztreonam (p. 224·1).
Gram-negative bacterial infections.

Vebemin *TNP, Thai.*
Vitamin B substances (p. 2102·3).
Dietary supplement.

Vecasten *Marjan, Braz.*
Melilot (p. 2552·3).
Venous insufficiency.

Vecetam *Richmond, Arg.*
Levetiracetam (p. 531·1).
Epilepsy.

Veclam *Malesci, Ital.*
Clarithromycin (p. 266·2).
Bacterial infections.

Vecredil *Jagsonpal, India.*
Ethacridine lactate (p. 1732·3).
Termination of pregnancy.

Vecta *Norton, Ukr.†*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Vectarion *Servier, Braz.; Servier, Fr.†; Servier, Irl.†; Servier, Port.†; Servier, Spain.†*
Almitrine dimesilate (p. 2315·3).
Respiratory insufficiency; hypoxic chronic obstructive airways disease.

Vectavir *Novartis Consumer, Austral.; Novartis Consumer, Belg.; Novartis, Braz.†; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; GSK, Gr.; Novartis Consumer, Irl.; Novartis Consumer, Ital.; Novartis Consumer, Neth.†; Novartis, Norw.; Novartis, Singapore; Novartis Consumer, Spain†; Novartis, Swed.; Novartis, Turk.; Novartis Consumer, UK.*
Penciclovir (p. 1008·2).
Herpes labialis.

Vectibix *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Mantecorp, Braz.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fr.; Amgen, Ger.; Amgen, Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Israel; Amgen, Ital.; Takeda, Jpn; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Rus.; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Amgen, UK; Amgen, USA.*
Panitumumab (p. 843·1).
Colorectal cancer.

Vectical *Galderma, USA.*
Calcitriol (p. 2113·1).
Psoriasis.

Vectocilina *Panalab, Arg.*
Azithromycin (p. 221·2).
Bacterial infections.

Vector *Trima, Israel.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Vector Plus *Trima, Israel.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vectoryl *Aspen, S.Afr.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Vectoryl Plus *Aspen, S.Afr.*
⊗Perindopril erbumine (p. 1467·1); indapamide (p. 1409·2).
Hypertension.

Vectra-P *Cipla, India.*
Valdecoxib (p. 141·3); paracetamol (p. 115·1).
Pain.

Vectrine *Pharma 2000, Fr.; Dexa, Indon.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Vectrum Calcium *Akrikhin, Rus.*
Colecalciferol (p. 2113·1); phytomenadione (p. 2122·2); ascorbic acid (p. 2110·3); pyridoxine hydrochloride (p. 2105·3); calcium carbonate (p. 1824·3).
Calcium and vitamin deficiency; osteoporosis.

Vecural *Richmond, Arg.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Vecure *Aspen, Austral.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Vecurol *Demo, Gr.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Vecuron *Scott-Cassara, Arg.; Cristalia, Braz.; Zynova, Philipp.; Pharmakin Korea, Venez.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Vedafil *Mylan, NZ.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vediblok *Arrow, S.Afr.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure.

Védica *Apsen, Braz.*
Boswellia serrata (p. 2507·3).

Vedicardol *Sintez, Rus.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Vedilan-T *Pharmathen, Gr.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Vedilol *Spirit, Austral.*
⊗Carvedilol (p. 1333·1).
Heart failure.

Vedium *Medikon, Indon.†*
Hesperidin (p. 2505·2); diosmin (p. 2505·2).
Venous insufficiency; phlebitis; haemorrhoids.

Vedivril *Ipca, Port.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Vedixal *Rowex, Irl.; Sandoz, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Vedrin *Polifarma, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Vedrop *Orphan, Cz.; Orphan, Denm.; Orphan, Fr.; Orphan, Ger.; Orphan, Irl.; Orphan, Ital.; Orphan, Neth.; Orphan Europe, Norw.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Orphan Europe, Swed.; Orphan, UK.*
Tocofersolan (p. 2119·1).
Vitamin E deficiency.

Veedol *VS, Thai.*
Nimesulide (p. 101·3).
Pain; osteoarthritis; peri-articular disorders.

Veelanz's Cough Syrup *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2).

Veelanz's Ointment *Beacons, Singapore.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1); sulfur (p. 1721·1); titanium dioxide (p. 1725·1).

Veemycin *Osoth, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Veenac *Medicine Products, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; gout; pain; inflammation.

Veen-D *Kowa, Jpn.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders.

Veen-F *Kowa, Jpn.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Veetids *Apothecon, USA.†*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Vefarol *Vamsler, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Vefed *PP Lab, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; cold symptoms.

Vefren *Baliarda, Arg.*
Tablets: Ibuprofen (p. 68·2).
Fever; inflammation; pain.

Vefren Flex *Baliarda, Arg.*
Ibuprofen (p. 68·2); chlorzoxazone (p. 2022·2).
Musculoskeletal spasm.

Vefron *Opus Materia, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Vega *Ono, Jpn.*
Ozagrel hydrochloride (p. 2579·1).
Asthma.

Vegabon *Kocak, Turk.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Vegabon Plus D *Kocak, Turk.*
Alendronate sodium (p. 1171·3); colecalciferol (p. 2113·1).

Vegal *Jofrain, Mex.†*
Dipyrone (p. 53·3).
Pain.

Veganin
Note: this name may be used for preparations of different composition.
Chefaro, UK.
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Formerly contained aspirin, paracetamol, and codeine phosphate.
Pain; fever.
Johnson & Johnson, Austral.†
Aspirin (p. 22·2); codeine phosphate (p. 40·2).
Pain; fever.

Veganin Plus *Chefaro, Irl.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2); caffeine (p. 1203·3).
Pain; cold and influenza symptoms.

Veganix *Bioethic, Fr.*
Sodium hyaluronate (p. 2526·2); centella (p. 1698·3); mallow (p. 2549·2); chamomile (p. 2474·1); niaouli oil (p. 2569·1); vitamin E acetate (p. 2119·2).
Vaginal dryness; vaginal irritation.

Vegantalgin H *GSK, Pol.*
Paracetamol (p. 115·1); hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm; gastrointestinal procedures.

Vegarex *Hexal, Austria.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Vege Swiss One *Swiss Herbal, Canad.†*
Vitamins; minerals.

Vegenat *Alchemy, UK.*
Preparation for enteral nutrition.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vegestabil *Investi, Arg.*
Sulpiride (p. 1107·3); dipotassium clorazepate (p. 1056·3).
Psychosomatic disorders.

Vegestabil Digest *Investi, Arg.*
Domperidone (p. 1838·1); bromazepam (p. 1041·2); simeticone (p. 1886·2).

Vegetable Cough Remover *Potter's, UK.*
⊗Capsicum (p. 2469·3); cimicifuga (p. 2478·1); ipecacuanha (p. 1667·2); lobelia (p. 2323·2); pleurisy root (p. 2593·2); skullcap (p. 2617·1); skunk cabbage (p. 2617·1); valerian (p. 2640·2); elecampane (p. 1662·3); marrubium (p. 1668·3); hyssop (p. 2530·3); anise oil (p. 2444·3); liquorice (p. 1853·2).
Coughs.

Vegetal Tonic *Homeocan, Canad.*
Artemisia vulgaris; avena sativa (p. 2451·1); china (p. 2478·3); cinnamomum (p. 2479·2); gentiana (p. 2512·1); podophyllum (p. 1717·1); rhamnus frangula (p. 1843·3); rheum rhapontica (p. 1884·2); vinum dulce.
Homoeopathic preparation.

Vegetallumina *Pietrasanta, Ital.*
Camphor (p. 2466·2); aluminium subacetate (p. 2440·1); methyl salicylate (p. 92·1); thyme oil (p. 2630·3).
Soft-tissue and peri-articular disorders.

Vegetarian Protein Supplement *GNLD, Austral.†*
Nutritional supplement.

Vegetex *Lane, UK.*
Celery (p. 2472·3); menyanthes (p. 2554·2); cimicifuga (p. 2478·1).
Muscular pain.

Végétosérum *Aerocid, Fr.*
Adult syrup: Ethylmorphine hydrochloride (p. 56·3); grindelia (p. 2522·3).
Cough.
H2 Pharma, Fr.†
Paediatric syrup: Ethylmorphine hydrochloride (p. 56·3); orange flowers (p. 2575·3).
Cough.

Vegevit B_{12} *Lane, Pol.*
Cyanocobalamin (p. 2107·2); brewer's yeast (p. 2125·2).
Vitamin B deficiency.

Vegie Digestaid *Eagle, Austral.*
⊗Amylase (p. 2442·1); protease; lipase (p. 2579·3); tilactase (p. 2631·2); cellulase (p. 2473·1); bromelains (p. 2460·3); papain (p. 2582·3); taraxacum (p. 2625·3); ginger (p. 1844·1).
Digestive disorders.

Veil *Blake, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Vein Relief *Golden Glow, Austral.*
Grape seed (p. 2521·3); aesculus (p. 2431·2); hesperidin (p. 2505·2).
Circulatory disorders; varicose veins.

Veinamitol *Negma, Belg.; Negma, Fr.*
Troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids.

Veino Gomenol *Gomenol, Fr.*
Niaouli oil (p. 2569·1); rosemary oil (p. 2607·3); cypress oil (p. 2491·1); copaiba; sweet birch oil (p. 92·1); juniper oil (p. 2537·2).
Venous insufficiency.

Veinobiase *Abbott, Fr.*
Black currant (p. 2458·1); butcher's broom (p. 2463·1); ascorbic acid (p. 2110·3).
Venous insufficiency; haemorrhoids.

Veino-Drainol *Boiron, Fr.†*
Hamamelis virginiana (p. 2523·3); viburnum prunifolium (p. 2458·1); acide fluoricum (p. 2529·1); anemone pulsatilla (p. 2600·2); graphites (p. 2522·1); silicea (p. 2208·3); arnica montana (p. 2447·2); calcarea carbonica (p. 1824·3); carbo ligni officinal (p. 1537·3); lachesis (p. 2538·3).
Homoeopathic preparation.

Veinofytol *Tilman, Belg.*
Aesculus (p. 2431·2).
Capillary disorders; venous insufficiency.

Veinophytum *Arkopharma, Fr.†*
Aesculus (p. 2431·2); red vine (p. 2521·3).
Capillary disorders; haemorrhoids; venous insufficiency.

Veinopress A3 and A4 *Innothera, Fr.*
Zinc oxide (p. 1729·1).
Care after variceal surgery; ulcers; post-sclerotherapy care; lymphoedema; venous insufficiency.

Veinosium *Ferrier, Fr.†*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); hamamelis virginiana (p. 2523·3); nux vomica (p. 2573·3).
Homoeopathic preparation.

Veinostase *Tradiphar, Fr.*
Aesculus (p. 2431·2); hamamelis (p. 2523·3); cypress (p. 2491·1); ascorbic acid (p. 2110·3).
Venous insufficiency; capillary fragility; haemorrhoids.

Veinotonyl *Merck-Lipha, Fr.*
Aesculus (p. 2431·2); metesculetol sodium (p. 2557·3).
Peripheral vascular disorders.

Vejicur *Medac, Spain.*
A BCG vaccine (p. 2378·1).
Bladder cancer.

Vekfanol *Angelini, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Vekfazolin *Angelini, Gr.; Faran, Gr.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Velafax *Farmacom, Pol.; Teva, Rus.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Velamox *Mediolanum, Ital.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.
Sigma, Braz.
Amoxicillin (p. 216·2).
Bacterial infections.

Velaril *Roemmers-Klinos, Venez.*
Clonidine hydrochloride (p. 1339·1).
Hypertension.

Velasor *Vocate, Gr.*
Tenoxicam (p. 136·2).
Inflammatory disorders.

Velaspir *Teva, Pol.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Velastina *Polfa Pabianice, Pol.*
Rivastigmine hydrogen tartrate (p. 395·1).
Alzheimer's disease; dementia in parkinsonism.

Velatuss *Rayere, Mex.*
Levodropropizine (p. 1662·3).
Cough.

Velax *Daquimed, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder.

Velaxatin *Sigillata, Denm.†*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Velaxin *Egis, Cz.; Egis, Hong Kong; Egis, Hung.; Egis, Pol.; Egis, Rus.; Egis, Ukr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Velban *ABL, Braz.; Lilly, USA.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Velbastine *Korea United, Hong Kong; Korea United, Philipp.; Korea United, Singapore.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Velbe *Aspen, Austral.†; Stada, Austria; Pharmacodane, Denm.; Pharmacodane, Fin.; IFET (ΙΦΕΤ), Gr.; Lilly, Gr.; Crinos, Ital.; Pharmacodane, Norw.; Stada, Swed.; Teva, Switz.; Genus, UK.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms; Letterer-Siwe disease.

Velbé *EG, Fr.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Velbin *Actavis, Rus.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer; prostatic cancer.

Velcade *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Ben Venue, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Millenium, USA; Janssen-Cilag, Venez.*
Bortezomib (p. 752·1).
Multiple myeloma; mantle cell lymphoma.

Velcox *Novell, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Veldom *Viofar, Gr.*
Clindamycin phosphate (p. 269·3).
Vaginal infections.

Veldrol *Collins, Mex.*
Tramadol hydrochloride (p. 139·2).
Pain.

Velept *Proton, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Veletri *Actelion, Switz.; Actelion, UK; Actelion, USA.*
Epoprostenol sodium (p. 1375·1).
Pulmonary hypertension.

Velexina *Klonal, Arg.*
Cefalexin (p. 234·1).
Bacterial infections.

Velexor *Actavis, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Véliten *Zambon, Fr.*
Vitamins; rutoside (p. 2505·3).
Vascular disorders.

Velivet *Barr, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Triphasic oral contraceptive.

Velkacalcin *Velka, Gr.*
Calcitonin (salmon) (p. 1178·1).
Osteoporosis.

Velkacet *Velka, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Velkaderm *Velka, Gr.*
Clindamycin phosphate (p. 269·3).
Vaginal infections.

Velkalov *Velka, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Velkastatin *Velka, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Vellena *Actavis, Denm.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Vellodrying *Remedina, Gr.*
Etofenamate (p. 57·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Vellutan *Abiogen, Ital.*
Tacalcitol (p. 1722·1).
Psoriasis.

Velmetia *MSD, Austria; MSD, Cz.; Pierre Fabre, Fr.; Berlin-Chemie, Ger.; MSD, Hung.; MSD, Irl.; Gentili, Ital.; MSD, Neth.; MSD, Pol.; MSD, Port.; MSD, Spain; Menarini, Switz.*
Sitagliptin phosphate (p. 500·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Velocef *BMS, Spain.†*
Cefradine (p. 249·1).
Bacterial infections.

Velodan *Qualigen, Spain.†*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Velodine *Soho, Indon.*
Cefradine (p. 249·1).
Bacterial infections.

Velodrom *Ethica, Indon.*
Cefradine (p. 249·1).
Bacterial infections.

Velodyne *Dexa, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Velorin
Note: this name may be used for preparations of different composition.
Fako, Turk.
Mirtazapine (p. 436·1).
Remedica, Hong Kong; Remedica, Malaysia; Remedica, Philipp.; Remedica, Singapore; Remedica, Thai.
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Velorium *Vivax, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Velosalic *Schering-Plough, Chile.†*
⊗Mometasone furoate (p. 1644·1); salicylic acid (p. 1719·1).
Hyperkeratotic skin disorders; psoriasis.

Velosef *BMS, Belg.†; BMS, China; BMS, Gr.; BMS, Hong Kong†; BMS, Indon.†; BMS, Irl.†; BMS, UK.†*
Cefradine (p. 249·1).
Bacterial infections.

Velostin *Solas, Indon.*
Portulaca; chamomile (p. 2474·1); aloe vera (p. 1693·2); vitamin E (p. 2119·1).
Vaginal disorders.

Velosulin *Novo Nordisk, Cz.†; Novo Nordisk, Gr.; Novo Nordisk, Jpn†; Novo Nordisk, Neth.†; Novo Nordisk, Port.†*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Velosulin HM *Novo Nordisk, NZ.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Velosulin MC *Novo Nordisk, NZ.*
⊗Neutral insulin injection (porcine, monocomponent) (p. 475·3).
Diabetes mellitus.

Veloxin *Pharm-D, Malaysia.*
Meclozine hydrochloride (p. 634·3); pyridoxine hydrochloride (p. 2105·3).
Vestibular disorders.

Velphoro *Fresenius Medical, USA.*
Sucroferric oxyhydroxide (p. 1577·2).
Hyperphosphataemia.

Velpine *Medochemie, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Velpro *Alpharma, Mex.*
Benzonatate (p. 1656·2).
Cough.

Velsay *Sons, Mex.*
Naproxen (p. 98·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Velsay-S Compuesto *Sons, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Veltadim *Novell, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Veltamir *Richmond, Arg.*
Oseltamivir (p. 1006·2).
Influenza.

Veltex *Adcock Ingram, S.Afr.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders; gout.

Veltifer *Rafarm, Gr.; Eczacibasi, Turk.*
Iron polymaltose (p. 2077·2).
Iron deficiency.

Veltion *Alapis, Gr.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Velvachol *Valeant, USA.*
Vehicle for topical preparations.

Velzina *Mezina, Norw.†*
St John's wort (p. 449·1).
Anxiety; depression.

Vematina *Cryopharma, Mex.*
Magnesium valproate (p. 553·1).
Epilepsy; bipolar disorder; migraine.

Vemed *Utopian, Thai.*
Lorazepam (p. 1080·3).

Vemizol *CCM, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Vemol *PP Lab, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Venaclar *Forte Pharma, Fr.*
Diosmin (p. 2505·2).
Haemorrhoids; vascular disorders.

Venacol
Note: this name may be used for preparations of different composition.
Mugi, Indon.
Thiamphenicol (p. 376·3).
Bacterial infections.

Llorens, Spain.†
Aescin (p. 2431·2); esculoside (p. 2431·2); heparin sodium (p. 1396·3); ruscogenin (p. 2608·3).
Peripheral vascular disorders; oedema.

Venacorn *Filofarm, Pol.*
Dihydroergocristine mesilate (p. 390·1); esculoside (p. 2431·2); rutoside (p. 2505·3).
Cerebral and peripheral vascular disorders; migraine; venous insufficiency.

Venactive
Note: this name may be used for preparations of different composition.
Les 3 Chenes, Ital.
Centella (p. 1698·3); aesculus (p. 2431·2); hamamelis (p. 2523·3).
Tired legs.

Venadoron *Weleda, Switz.*
Lemon (p. 2542·3); arnica (p. 2447·2); lappa (p. 2540·1); iris (p. 2534·3); blackthorn (p. 2458·2); hamamelis (p. 2523·3); silicic acid (p. 2088·3); lemon oil (p. 2543·1); copper sulfate (p. 2057·2).
Venous insufficiency.

Venafleur *Bloem Beheer, Neth.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); hamamelis virginiana (p. 2523·3); calcarea carbonica (p. 1824·3).
Homoeopathic preparation.

Venaflon *Teuto, Braz.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency.

Venaforce *Vogel, Fin.†; Bioforce, Irl.; Bioforce, UK.*
Aesculus (p. 2431·2).
Venous insufficiency.

Venafort *Teuto, Braz.*
Aesculus (p. 2431·2).
Venous insufficiency; oedema.

Venalax *Jumont, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Venalax XPT *Jumont, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease.

Venalitan *Meda, Ger.†*
Ointment: Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Venalot *Schaper & Brummer, Ger.*
Soft capsules: Aesculus (p. 2431·2).
Venous insufficiency.

Nycomed, Braz.; Schaper & Brummer, Ger.†; Nycomed, Mex.
Coumarin (p. 2487·2); troxerutin (p. 2505·3).
Venous insufficiency; oedema; haemorrhoids.

Venalot H *Nycomed, Braz.*
Coumarin (p. 2487·2); heparin (p. 1396·3).
Peripheral vascular disorders; soft-tissue injury.

Venalta *Alta Care, Ital.*
Aesculus (p. 2431·2); arnica (p. 2447·2); grape (p. 2521·3); ginkgo biloba (p. 2512·3); hamamelis (p. 2523·3); cypress oil (p. 2491·1); lemon oil (p. 2543·1); sage oil (p. 2609·1); mint oil (p. 2560·1); lavender oil (p. 2541·1).

Alta Care, Ital.
Red vine (p. 2521·3); vitamin E (p. 2119·1); vitamin C (p. 2110·3).
Circulatory disorders.

Venapasta *Mitsubishi Tanabe, Jpn.*
Diphenhydramine laurilsulfate (p. 626·1).
Urticaria; eczema; pruritus; insect bites.

Venaphyt N *Lyron, Switz.*
Aesculus (p. 2431·2); calendula (p. 2465·2); achillea (p. 2427·3).
Venous insufficiency.

Venapulse *Pharmacare, S.Afr.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris.

Venaron *Teguhsindo, Indon.*
Oxerutins (p. 2505·3).
Varices; haemorrhoids.

Venart *Casasco, Arg.*
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Venous insufficiency; haemorrhoids.

Venart Crema *Casasco, Arg.*
Butcher's broom (p. 2463·1); melilot (p. 2552·3).
Venous insufficiency.

Venartel *Andromaco, Chile.*
Citrus bioflavonoids (p. 2505·2); diosmin (p. 2505·2).
Haemorrhoids; venous insufficiency.

Venarus *Obolenskoe, Rus.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Venastat *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Hung.; Armstrong, Mex.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Swed.*
Aesculus (p. 2431·2).
Venous insufficiency.

Venatren *Pharmathen, Gr.*
Phenothrin (p. 2160·1).

Venavit N *UB, Switz.*
Aesculus (p. 2431·2).
Venous insufficiency.

Venaxen *Heremco, Gr.*
Donepezil hydrochloride (p. 390·2).

Venaxibene *Ratiopharm, Austria.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venaxol *Scientific Pharma, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venaxx *Goldshield, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venbig *Kedrion, Austria; Kedrion, Denm.; Kedrion, Gr.; Kedrion, Ital.; Kedrion, Port.; Kedrion, Swed.; Kedrion, Thai.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Vencano *Genepharm, Gr.*
Vincamine (p. 2645·2).

Vendal *Lannacher, Austria; GL Pharma, Cz.; Polfa Warszawa, Pol.†; Liba, Turk.*
⊗Morphine hydrochloride (p. 92·3).
Pain.

Vendazol *Zuoz, Venez.*
Albendazole (p. 149·1).
Worm infections.

Vendep *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venderol *Beacons, Singapore.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Ven-Detrex *Therabel, Belg.*
Diosmin (p. 2505·2).
Peripheral vascular disorders.

Vendios *Bilim, Turk.*
Diosmin (p. 2505·2).

Vendrex *IQB, Braz.*
Diclofenac sodium (p. 48·3).

Venefon *Pharmathen, Gr.*
Imipramine hydrochloride (p. 426·2).

Venelex *Stratus, USA.*
Peru balsam (p. 2587·1); castor oil (p. 2472·1); white soft paraffin (p. 2211·3).
Emollient.

Venen *Naturprodukt, Hung.*
Aesculus (p. 2431·2); calendula (p. 2465·2).
Phlebitis; varicose veins.

Venen Theiss *Naturwaren, Ukr.*
Aesculus (p. 2431·2); calendula (p. 2465·2).
Varices; phlebitis; oedema; venous insufficiency.

Venen-Komplex Ho-Fu-Complex *Liebermann, Ger.*
Aesculus (p. 2431·2); arnica (p. 2447·2); calcium fluoratum (p. 2053·1); hamamelis (p. 2523·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Venen-Tabletten *Stada, Ger.*
Aesculus (p. 2431·2).
Venous insufficiency.

Venentabs *Ratiopharm, Ger.*
Aesculus (p. 2431·2).
Venous insufficiency.

Venen-Tropfen N *Bioforce, Ger.†*
Aesculus (p. 2431·2).
Venous insufficiency.

Venergy *Maxi Herbs, Hong Kong.*
Eurycoma longifolia.
Health supplement for men.

Venescin *Herbapol Wroclaw, Pol.*
Aesculus (p. 2431·2); esculoside (p. 2431·2); rutoside (p. 2505·3).
Venous insufficiency; haemorrhoids.

Venesden *Raam, Mex.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; cardiovascular risk reduction; diabetic nephropathy.

Venex
Note: this name may be used for preparations of different composition.
Clonmel, Irl.
Venlafaxine hydrochloride (p. 454·2).
Depression.

Decomed, Port.
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Venfalex *Medochemie, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Ven-Fax *Rafarm, Gr.*
Venlafaxine hydrochloride (p. 454·2).

Venfecto *Eczacibasi, Turk.*
Venlafaxine hydrochloride (p. 454·2).

Venforin *Sigma, Braz.*
Venlafaxine (p. 454·2).
Depression; panic disorder; obsessive-compulsive disorder.

Veniba *Bilim, Turk.*
Venlafaxine hydrochloride (p. 454·2).

Venicol *Vickmans, Hong Kong.†*
Chloramphenicol (p. 257·1).

Venidium *Ivax, Arg.*
Butcher's broom (p. 2463·1); hesperidin methyl chalcone (p. 2505·2); ascorbic acid (p. 2110·3).
Venous insufficiency; haemorrhoids.

Venilon *Teijin, Jpn.†*
A normal immunoglobulin (p. 2403·3).
Infections.

Venimicetin *Doctors, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial infections.

Venimmun *Centeon, Pol.*
A normal immunoglobulin (p. 2403·3).
Immunodeficiency; passive immunisation; immune thrombocytopenia; Kawasaki disease; Guillain-Barré syndrome; auto-immune disorders.

Venimmun N *CSL, Cz.†*
A normal immunoglobulin (p. 2403·3).
Passive immunisation; immune thrombocytopenia.

Venimmuna *ZLB, Braz.†*
A normal immunoglobulin (p. 2403·3).
Passive immunisation.

Vénirène *Sanofi-Aventis, Fr.*
Diosmin (p. 2505·2).
Capillary disorders; haemorrhoids; venous insufficiency.

Veniron *Viofar, Gr.*
Iron sucrose (p. 2078·1).

Venisse *Bago, Arg.*
Yellow tablets, gestodene (p. 2279·3); ethinylestradiol (p. 2275·3); red tablets, inert.
Combined oral contraceptive.

Venital *Kedrion, Ital.*
A normal immunoglobulin (p. 2403·3).

Venitan *Lek, Cz.; Lek, Pol.; Sandoz, Ukr.*
Aesculus (p. 2431·2).
Venous insufficiency; soft-tissue injury; oedema; haematoma; neuralgia.

Lek, Rus.
Aescin (p. 2431·2).
Venous insufficiency; soft-tissue disorders.

Venitan Forte *Lek, Rus.; Sandoz, Ukr.*
Aescin (p. 2431·2); heparin sodium (p. 1396·3).
Venous insufficiency; varicose veins; soft-tissue injury; superficial thrombophlebitis; scars.

Venitrin *Meda, Ital.*
Glyceryl trinitrate (p. 1391·2).
Myocardial infarction; left-ventricular failure; hypertensive crises; angina pectoris.

Venium
Note: this name may be used for preparations of different composition.
LBS, Thai.
Aluminium hydroxide gel (p. 1817·2); os sepiae (p. 2613·1); liquorice (p. 1853·2); peppermint oil (p. 1877·1).
Gastric ulcers.

Venixaf *Teva, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venla *Ranbaxy, Austral.; Trima, Israel.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlabacher *Genericon, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlabrain *Brainpharma, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlaburg *GL Pharma, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Venlacross *Pharmacross, Chile.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venladem *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Venladima *Pharmathen, Denm.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venladoz *Sandoz, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlafab *Lannacher, Austria; Lannacher, Cz.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Venlafex *Niche, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlagamma *Worwag, Cz.†; Worwag, Ger.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlakato *Pharmathen, Denm.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlalic *Dallas Burston Ashbourne, Irl.; Dallas Burston Ashbourne, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlamed *Sigillata, Denm.†*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlamyl *Jenson, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlamylan *Mylan, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; panic disorder; anxiety.

Venlanofi *Winthrop, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Venlapete *Pharmathen, Denm.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlapine *Qualigen, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlapol *Pharmathen, Denm.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlaraf *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlaran *Ranbaxy, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlasan *Mibe, Ger.; Gerolymatos, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlasand *Sandoz, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlathen *Pharmathen, Denm.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlatif *Acis, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Venlatio *Tiefenbacher, Neth.†*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Venlax *Drossapharm, Switz.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Saval, Chile.
Venlafaxine (p. 454·2) or venlafaxine hydrochloride (p. 454·2).
Anxiety; depression.

Venlaxgen *Generics, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlaxin *Eurofarma, Braz.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlaxor *Grindex, Rus.; Grindeks, Ukr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety.

Venlectine *ICN, Pol.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlexor *Ascent, Austral.; Mibe, Neth.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia; anxiety; panic disorder.

Venlifax *Baliarda, Arg.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Venlift *Torrent, Braz.; Ranbaxy, Irl.†; Torrent, Philipp.*
Venlafaxine hydrochloride (p. 454·2).
Depression; obsessive-compulsive disorder; anxiety.

Venlix *Ratiopharm, Norw.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlofex *Gerard, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venlor *Cipla, India; Cipla-Medpro, S.Afr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Vennaxa *Ratiopharm, Belg.†*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Veno V *Decafarma, Port.*
Diosmin (p. 2505·2).
Vascular disorders; oedema.

Veno SL *Ursapharm, Ger.*
Troxerutin (p. 2505·3).
Vascular disorders.

Venobene *Ratiopharm, Austria.*
Heparin sodium (p. 1396·3); dexpanthenol (p. 2582·2).
Superficial vascular disorders; anorectal disorders; soft-tissue injury.

veno-biomo *Biomo, Ger.†*
Aesculus (p. 2431·2).
Venous insufficiency.

Venocur Triplex *Abbott, Braz.*
Rutoside (p. 2505·3); aesculus (p. 2431·2); miroton.
Venous insufficiency.

Venodin
Note: this name may be used for preparations of different composition.
Amnol, Ital.
Diosmin (p. 2505·2); hesperidin (p. 2505·2); melilot (p. 2552·3); vitamins.
Circulatory disorders.

Venodiol *World Medicine, Ukr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2); ascorbic acid (p. 2110·3).
Venous insufficiency.

Venodril *Marien, Austria.*
Aesculus hippocastanum (p. 2431·2); hamamelis virginiana (p. 2523·3); melilotus officinalis (p. 2552·3); silybum marianum (p. 1561·1).
Homoeopathic preparation.

Venofer *Biosintex, Arg.; Aspen, Austral.; Vifor, Austria; Vifor, Belg.; Genpharm, Canad.; Mastercare, Chile; Vifor, China; Vifor, Cz.; Vifor, Denm.; Vifor, Fin.; Vifor, Fr.; Vifor, Ger.; Vifor, Gr.; Vifor, Hong Kong; Vifor, Hung.; Combiphar, Indon.; Vifor, Indon.; Vifor, Irl.; Vifor, Israel; Geymonat, Ital.; Vifor, Malaysia; Vifor, Neth.; Vifor, Norw.; Healthcare Logistics, NZ; Vifor, Philipp.; Vifor, Pol.; Ferraz, Lynce, Port.; Vifor, Rus.; Nycomed, S.Afr.; Vifor, Singapore; Vifor, Spain; Renapharma, Swed.; Vifor International, Switz.; Vifor, Thai.; Abdi, Turk.; Syner-Med, UK; American Regent, USA; Zuoz, Venez.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia; iron deficiency; dialysis-induced anaemia.

Venoferrum *Nycomed, Mex.*
Iron sucrose (p. 2078·1).
Iron-deficiency anaemia.

Venoforton *Leki Natury, Pol.*
Aesculus (p. 2431·2); arnica (p. 2447·2); crataegus (p. 2488·1); ginkgo biloba (p. 2512·3); mistletoe (p. 2560·2).
Cerebral and peripheral vascular disorders; atherosclerosis.

Venoful *Garden House, Arg.; Rominafort, Arg.*
Centella (p. 1698·3); ginkgo biloba (p. 2512·3); hamamelis (p. 2523·3); aesculus (p. 2431·2).
Haemorrhoids; oedema; varices; cerebrovascular disorders.

Venofundin *Braun, Arg.; Braun, Austria; Braun, China; Braun, Denm.; Braun, Fin.; Braun, Ger.; Vioser, Gr.; Braun, Irl.†; Braun, Neth.; Braun, Norw.; Braun, NZ; Braun, Port.; Braun, S.Afr.; Braun, Swed.; Braun, Switz.; Braun, UK†; Braun, Ukr.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; shock; haemodilution; hypovolaemia.

Venofusin Bicarbonato *Fresenius Kabi, Spain.*
Sodium bicarbonate (p. 1781·1).

Veno-Gel *Ouiheng, Thai.†*
Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Varicose veins; thrombophlebitis.

Venoglobulin *Alpha, Israel; Mitsubishi Tanabe, Jpn; Grifols, Singapore.*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; agammaglobulinaemia; immunodeficiency; Kawasaki disease; passive immunisation.

Venogyl *Teva, Israel.†*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Venohepanol *Borshchagovskii, Ukr.*
Troxerutin (p. 2505·3); heparin sodium (p. 1396·3); dexpanthenol (p. 2582·2).
Superficial vascular disorders; haemorrhoids; soft-tissue injury; scars; inflammation.

Venohes *Braun, Belg.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; shock.

Veno-Injektopas *Pascoe, Ger.*
Calcium fluoratum (p. 2053·1); hamamelis (p. 2523·3); aesculus (p. 2431·2).
Homoeopathic preparation.

Venokatt *Kattwiga, Ger.*
Hamamelis virginiana (p. 2523·3); aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); achillea millefolium (p. 2427·3); ruta graveoleus (p. 2608·2).
Homoeopathic preparation.

Venolan *Richter, Pol.; Gedeon Richter, Ukr.†*
Troxerutin (p. 2505·3).
Venous insufficiency; phlebitis; superficial vascular disorders; oedema; haemorrhoids.

Venolen *Pharma Line, Ital.*
Troxerutin (p. 2505·3).
Venous insufficiency; capillary fragility.

Venolep *Angelini, Spain.*
Hidrosmin (p. 2505·2).
Venous insufficiency.

Venolife *Akrikhin, Rus.*
Troxerutin (p. 2505·3); dexpanthenol (p. 2582·2); heparin sodium (p. 1396·3).
Soft-tissue injury; venous insufficiency.

Venolise *Ativus, Braz.*
Melilot (p. 2552·3).

veno-loges N *Loges, Ger.*
Aesculus (p. 2431·2); arnica (p. 2447·2); melilotus off. (p. 2552·3); lachesis (p. 2538·3); carduus marianus (p. 1561·1).
Homoeopathic preparation.

Venolone *Chemica, Gr.*
⊗Metoprolol tartrate (p. 1434·3).

Venolyte *Fresenius Kabi, Pol.*
Sodium acetate (p. 1781·1); sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Dehydration; hypovolaemia; metabolic acidosis.

Venomenhal *Hal, Ger.; Hal, Hung.; Haarlems Allergenen, Pol.*
Allergen extract from insects (p. 2434·3).
Diagnosis and desensitisation of wasp and bee stings; allergen immunotherapy.

Venomil *Hollister-Stier, Canad.; Bencard, Ger.; Miles, USA.†*
Allergen extract of bee venom (p. 2434·3) or wasp venom (p. 2434·3).
Allergen immunotherapy.

Venoparil *Neo-Farmaceutica, Port.*
Topical gel: Aescin (p. 2431·2); diethylamine salicylate (p. 51·3).
Musculoskeletal, joint, and soft-tissue injury; thrombophlebitis; varices.

Venoplant *Aesculapius, Ital.*
Cream: Aescin (p. 2431·2); centella (p. 1698·3); heparin (p. 1396·3).
Circulatory disorders.

Aesculapius, Ital.
Tablets: Diosmin (p. 2505·2); troxerutin (p. 2505·3); melilot (p. 2552·3); centella (p. 1698·3).
Circulatory disorders.

Aesculapius, Ital.
Topical spray: Arnica (p. 2447·2); aescin (p. 2431·2); melilot (p. 2552·3); boswellia; rutoside (p. 2505·3); centella (p. 1698·3).
Soft-tissue injury.

VSM, Belg.; Schwabe, Ger.; Schwabe, Pol.; Schwabe, Rus.; Schwabe, Ukr.
Aesculus (p. 2431·2).
Venous insufficiency.

Venopressin *TKS, Braz.*
Methyldopa (p. 1431·1).

Venopyronum *Abbott, Ger.†*
Delayed-release tablets: Aesculus (p. 2431·2).
Venous insufficiency.

Venorell *Sanorell, Ger.*
Hamamelis virginiana (p. 2523·3).
Homoeopathic preparation.

Venorix *Medinfar, Port.*
Dermatan sulfate sodium (p. 1350·3).

Venorugel *Novartis Consumer, Spain.*
Troxerutin (p. 2505·3).
Venous insufficiency; haematoma.

Venorutin retard Rosskastanie *Novartis Consumer, Ger.†*
Aesculus (p. 2431·2).
Venous insufficiency.

Venoruton *Novartis, Braz.; Novartis, Philipp.; Novartis, Thai.*
Troxerutin (p. 2505·3).
Chronic venous insufficiency; haemorrhoids; oedema; venous ulcers; diabetic retinopathy.

Novartis Consumer, Arg.; Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis Consumer, Ger.†; Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Ital.; Novartis Consumer, Neth.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, Spain; Novartis Consumer, Switz.; Novartis, Turk.
Oxerutins (p. 2505·3).
Inflammation; haemorrhoids; oedema; chronic venous insufficiency; soft-tissue injury; diabetic retinopathy; vascular reactions following radiotherapy.

Novartis Consumer, Israel.
Monoxerutin (p. 2505·2).
Chronic venous insufficiency; varicose veins.

Novartis Consumer, Rus.
Rutoside (p. 2505·3).
Venous insufficiency; haemorrhoids.

Venoruton Emulgel *Novartis Consumer, Ger.†*
Heparin sodium (p. 1396·3).
Soft-tissue injury; superficial vascular disorders.

Venoruton Heparin *Novartis Consumer, Austria.*
Heparin sodium (p. 1396·3).
Superficial venous disorders; soft-tissue injury.

Venos *Soho, Indon.*
Butcher's broom (p. 2463·1); centella (p. 1698·3).
Varicose veins; haemorrhoids.

Venos Cough Mixture *GSK Consumer, UK.*
Glucose (p. 2068·3); treacle (p. 2096·3).
Coughs.

Venos Expectorant *GSK Consumer, Irl.*
Guaifenesin (p. 1666·2); liquid glucose (p. 2068·3); treacle (p. 2096·3).
Cough.

GSK Consumer, UK.
Guaifenesin (p. 1666·2); glucose (p. 2069·1); treacle (p. 2096·3).
Coughs.

Venos Honey & Lemon
Note: this name may be used for preparations of different composition.
GSK Consumer, Irl.
Ammonium chloride (p. 1656·1); ipecacuanha (p. 1667·2); liquid glucose (p. 2068·3); honey (p. 2072·1); lemon juice.
Cough.

GSK Consumer, UK.
Purified honey (p. 2072·1); glucose (p. 2068·3).
Coughs; sore throat.

Venos for Kids *GSK Consumer, UK.*
Guaifenesin (p. 1666·2).
Coughs.

Venosan
Note: this name may be used for preparations of different composition.
Bosnalijek, Ukr.
Phospholipids (p. 2201·2); aescin (p. 2431·2); heparin sodium (p. 1396·3).
Venous insufficiency; oedema; phlebitis; haematoma.

Venoselect N *Dreluso, Ger.*
Aesculus (p. 2431·2); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Venoserin *Labomed, Chile.*
Butcher's broom (p. 2463·1).
Venous insufficiency.

Venosin *Astellas, Austria.*
Capsules: Aesculus (p. 2431·2).
Chronic venous insufficiency; superficial vascular disorders; oedema.

Venosman *Pharmanel, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Vascular disorders.

Venosmil *Sidus, Arg.; Kalbe, Indon.; Vitoria, Port.; Faes, Spain; Farmasoft, Ukr.*
Hidrosmin (p. 2505·2).
Peripheral vascular disorders; venous insufficiency; haemorrhoids; capillary disorders; inflammatory skin disorders; vascular eye disorders.

Venosmin
Note: this name may be used for preparations of different composition.
Phytopharm, Ukr.
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Venosmine *Geymonat, Hong Kong; Geymonat, Ital.*
Diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids; peripheral vascular disorders.

Venostabil *Cosmopharm, Gr.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).

Venostasin *Ariston, Arg.; Astellas, Austria; Astellas, Ger.; Klinge, Ger.; Takeda, Switz.*
Aesculus (p. 2431·2).
Venous insufficiency; soft-tissue injury; inflammation.

Klinge, Ger.
Topical gel: Aescin (p. 2431·2).
Vascular disorders; soft-tissue injury.

Ariston, Arg.
Tablets: Aescin (p. 2431·2); vitamin B_1 (p. 2102·3).
Venous insufficiency.

Ariston, Arg.
Topical gel: Aescin (p. 2431·2); heparin sodium (p. 1396·3); glycol salicylate (p. 66·2).
Soft-tissue injury; venous insufficiency.

Venotac *Ativus, Braz.*
Aesculus (p. 2431·2).

Venoton *Dermofarma, Ital.*
Bioflavonoids (p. 2505·2); melilot (p. 2552·3); docosahexaenoic acid (p. 1460·1); aesculus (p. 2431·2); vitamins.
Nutritional supplement.

Venotonin *Phytofarm Kleka, Pol.*
Aesculus (p. 2431·2).
Venous insufficiency; haemorrhoids; soft-tissue oedema.

Venotop *Novartis, Austria.†*
Dihydroergotamine tartrate (p. 672·2); troxerutin (p. 2505·3).
Chronic venous insufficiency.

Venotrex *Abdi, Turk.*
Aesculus (p. 2431·2).

Pliva Krakow, Pol.
Troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids.

Venotrix *Alternova, Fin.*
Iron sucrose (p. 2078·1).
Iron deficiency.

Venotrulan Trox *Truw, Ger.†*
Troxerutin (p. 2505·3).
Venous insufficiency.

Venovaz *Mabra, Braz.*
Diosmin (p. 2505·2); hesperidin (p. 2505·2).
Venous insufficiency.

Venoxil *Mavi, Mex.*
Cinnarizine (p. 622·1).

Venożel *Emo-Farm, Pol.*
Diclofenac sodium (p. 48·3); aescin (p. 2431·2); tribenoside (p. 2633·3).
Oedema; rheumatoid arthritis; tendinitis.

Vensa *Bittner, Austria; Bittner, Rus.*
Aesculus (p. 2431·2); carduus (p. 1561·1); hamamelis (p. 2523·3); lachesis (p. 2538·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Vensaxa *Gondane-Vitality, Hung.*
Urtica (p. 2639·3); thea folium (p. 2648·2); taraxacum (p. 2625·3); equisetum (p. 2500·1); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Tonic.

Vensir *Morningside, Irl.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Ventadepress *Sandoz, Hung.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia.

Ventamol *Norton Waterford, Irl.; Hovid, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm; obstructive airways disease.

Hovid, Hong Kong.†
⊗Salbutamol (p. 1220·2).

Ventar *GX, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventar EXP *GX, Philipp.*
⊗Guaifenesin (p. 1666·2); salbutamol (p. 1220·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Ventarone *Umeda, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout; pain; inflammation.

Ventavis *Bayer, Arg.; Bayer, Austral.; Bayer Schering, Austria; Bayer, Belg.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer Schering, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer Schering, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Italfarmaco, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, NZ; Bayer Schering, Pol.; Bayer Schering, Port.; Bayer Schering, Rus.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Actelion, USA.*
Iloprost trometamol (p. 1408·2).
Pulmonary hypertension.

Venter
Note: this name may be used for preparations of different composition.
KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; Akrikhin, Rus.; KRKA, Ukr.
Sucralfate (p. 1889·1).
Peptic ulcer; gastro-oesophageal reflux; hyperphosphataemia; gastritis.

Vent-3, Arg.
Paracetamol (p. 115·1); salicylamide (p. 129·2); ascorbic acid (p. 2110·3); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Venterol *Greater Pharma, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventero-Nova *Qixing, Ukr.*
Sepia esculenta bone; fritillaria hupehensis; melia toosendan; coptis chinensis; apricot (p. 2445·3); corydalis yanhusuo; diospyros kaki; evodia rutaecarpa; aquilaria sinensis.
Gastritis; peptic ulcer.

Ventexxair *Schwarz, Fr.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Venteze
Note: this name may be used for preparations of different composition.
Aspen, S.Afr.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Biolab, Philipp.
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract disorders.

Venticil *Sandoz, Arg.*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Venticoll *GE Healthcare, Denm.*
⊗Albumin colloidal particles (p. 1130·2).
For radiolabelling with technetium-99m.
Radioimaging of the lungs.

GE Healthcare, Belg.†; GE Healthcare, Fin.
Technetium-99m (p. 2228·1) albumin colloid.
Radionuclide imaging of the respiratory tract.

Venticort *Oftalmi, Venez.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Asthma.

Ventide *GSK, Arg.; GSK, Chile; GSK, Hong Kong†; GSK, Indon.†; GSK, Mex.; GSK, Turk.; GSK, Venez.*
⊗Salbutamol (p. 1220·2); beclometasone dipropionate (p. 1621·2).
Obstructive airways disease; asthma.

Ventilan
Note: this name may be used for preparations of different composition.
Glaxo Wellcome, Port.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour.

Ventilastin *Meda, Cz.; Meda, Fin.; Meda, Fr.; Meda, Ger.; Meda, Spain†; Meda, Swed.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventimol *Tetrafarm, Arg.*
⊗Salbutamol (p. 1220·2).

Ventisol *Teva, Mex.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity.

Ventmax *Chiesi, Ital.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Trinity, UK.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventnaze *Aspen, S.Afr.*
⊗Beclometasone dipropionate (p. 1621·2).
Rhinitis.

Ventoaldo *Aldo, Spain.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Vento-Broncho *San Marino, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Vento-Broncho G *San Marino, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Cough.

Ventodisk *GSK, Turk.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

GSK, Pol.†
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Ventodisks *GSK, Hong Kong.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventoflu *Biomedica, Ital.*
⊗Flunisolide (p. 1635·3).
Asthma; bronchitis; rhinitis.

Ventofor *Bilim, Turk.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Ventofor-Combi *Bilim, Turk.*
⊗Formoterol fumarate (p. 1209·2); budesonide (p. 1625·1).

Ventolair *Ivax, Ger.*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Ventolase *Juste, Spain.†*
⊗Clenbuterol hydrochloride (p. 1207·2).
Obstructive airways disease.

Ventoliber *Tecnimede, Port.*
⊗Ambroxol hydrochloride (p. 1654·3); clenbuterol hydrochloride (p. 1207·2).
Respiratory-tract disorders.

Ventolin *GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Neth.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, S. Afr.; Allen & Hanburys, UK; Glaxo Wellcome, USA.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Bronchospasm; obstructive airways disease; premature labour; status asthmaticus.

GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Canad.; GSK, China; GSK, Cz.; 2care4, Denm.; GSK, Hong Kong; GSK, Indon.; GSK, Malaysia; GSK, Mex.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, Ukr.
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour; status asthmaticus; bronchospasm.

Ventolin Expectorant *GSK, Hong Kong†; GSK, Indon.; GSK, Malaysia†; GSK, Thai.†*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease associated with increased or viscous mucus.

GSK, Philipp.
⊗Salbutamol (p. 1220·2); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Ventoline *GSK, Denm.; GSK, Fr.; GSK, Norw.; GSK, Swed.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease; premature labour.

GSK, Fin.
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventomol *APT, Hong Kong.†*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventoplus *Phoenix, Arg.*
⊗Levosalbutamol hydrochloride (p. 1213·3).
Obstructive airways disease.

Ventor *Rafarm, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

Ventorlin Exp *GSK, India.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Obstructive airways disease with excess mucus.

Vent-o-sal *Bilim, Turk.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Ventosal *Essenpharma, Philipp.†*
⊗Salbutamol (p. 1220·2).
Obstructive airways disease.

Ventracid N *Repha, Ger.†*
⊗Sodium bicarbonate (p. 1781·1); pancreatin (p. 2579·3); curcuma (p. 2218·1).
Gastrointestinal disorders.

Ventricon N *Syxyl, Ger.†*
Bismuth subnitrate (p. 1822·1); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3).
Gastrointestinal disorders.

Ventrigutt M *Hanosan, Ger.*
Artemisia absinthium (p. 2426·1); china (p. 2478·3); lycopodium clavatum (p. 2547·1); atropa belladonna (p. 2453·3); semecarpus anacardium (p. 2471·3); strychnos nux-vomica (p. 2573·3).
Homoeopathic preparation.

ventri-loges N *Loges, Ger.†*
Absinthium (p. 2426·1); calamus (p. 2464·2); gentian (p. 2512·1).
Appetite loss; dyspepsia.

Ventu *Landsteiner, Mex.*
Orlistat (p. 2577·1).
Obesity.

Venucreme *Permamed, Switz.*
Heparin sodium (p. 1396·3); glycol salicylate (p. 66·2); dimethyl sulfoxide (p. 2182·2); lauromacrogol 400 (p. 2194·1); dexpanthenol (p. 2582·2).
Soft-tissue disorders; phlebitis; venous insufficiency.

Venugel *Permamed, Switz.*
Heparin sodium (p. 1396·3); glycol salicylate (p. 66·2); dimethyl sulfoxide (p. 2182·2); lauromacrogol 400 (p. 2194·1); dexpanthenol (p. 2582·2).
Soft-tissue disorders; phlebitis; venous insufficiency.

Venusmin *Bushnell, India.*
Diosmin (p. 2505·2).
Haemorrhoids; varicose veins; menorrhagia; metrorrhagia; bleeding during intra-uterine device use.

Venutabs *Permamed, Switz.*
Troxerutin (p. 2505·3).
Venous insufficiency; haemorrhoids.

Venvanse *Shire, Braz.*
⊗Lisdexamfetamine mesilate (p. 2323·2).
Attention-deficit hyperactivity disorder.

Venxin *Decomed, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; mixed anxiety depressive states; panic disorder; anxiety; social phobia.

Venxor *Hovid, Hong Kong; Hovid, Malaysia.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Venzadril *More, Philipp.*
⊗Salbutamol sulfate (p. 1220·2); guaifenesin (p. 1666·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Vepacel *Baxter, Neth.*
An influenza vaccine (H51N strain) (p. 2393·3).
Pandemic influenza prophylaxis.

Vepan *Indoco, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Vepesid *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, China; BMS, Cz.†; BMS, Denm.; BMS, Fin.; BMS, Ger.; BMS, Gr.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong†; BMS, Hung.†; BMS, Irl.; BMS, Ital.; BMS, Mex.; BMS, Neth.; BMS, Norw.; BMS, NZ; BMS, Philipp.†; BMS, Pol.; BMS, Port.†; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.†; BMS, Turk.; BMS, UK; BMS Oncology, USA.*
Etoposide (p. 790·2).
Malignant neoplasms.

Vépéside *Genopharm, Fr.†*
Etoposide (p. 790·2).
Malignant neoplasms.

Vepicombin *Nycomed, Denm.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Vepiltax *Tecnofarma, Mex.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Vera *AbZ, Ger.; CT, Ger.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Vera Plus *Giscard, Arg.*
Aloe vera (p. 1693·2); hyaluronic acid (p. 2526·2); vitamin E (p. 2119·1).
Skin disorders.

Verabeta *Betapharm, Ger.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veracaps *Aspen, Austral.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris.

Veracapt *Ebewe, Austria.*
Verapamil hydrochloride (p. 1522·1); captopril (p. 1331·2).
Hypertension.

Veracef *BMS, Mex.; BMS, Venez.*
Cefradine (p. 249·1).
Bacterial infections.

Veracer *Medic, Ital.*
Heparin sodium (p. 1396·3).
Thromboembolic disorders.

Veracol *Demo, Gr.; Multichem, NZ.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Veracolate
Note: this name may be used for preparations of different composition.
Elea, Arg.†; Pfizer, Thai.†
Bile salts (p. 2457·2); cascara (p. 1826·1); phenolphthalein (p. 1877·3); capsicum oleoresin (p. 2469·3).
Constipation; biliary-tract disorders; intestinal motility disorders.

Veracold *TP, Thai.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Veracor *Cofasa, Venez.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; heart failure; hypertension.

Veracur *Typharm, UK.*
Formaldehyde (p. 1752·2).
Warts; verrucas.

Veracuril *Fada, Arg.*
Oxytocin (p. 2143·1).
Labour induction.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Veragamma *Worwag, Ger.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Veragel *United American, Hong Kong; United American, Singapore; Great Eastern, Thai.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2); dimeticone (p. 1886·2); dicycloverine hydrochloride (p. 1834·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; gastritis; heartburn; gastrointestinal motility disorders; pylorospasm; duodenitis; dyspepsia; flatulence; epigastric pain.

UAP, Indon.†
Aluminium hydroxide-magnesium carbonate co-dried gel (p. 1818·2).
Gastrointestinal disorders.

Verahexal *Hexal, Austral.†; Hexal, Cz.; Hexal, Ger.†; Sandoz, S.Afr.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Verakard *Nycomed, Norw.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; arrhythmias.

Veraken *Kener, Mex.*
Verapamil (p. 1522·1).

Veral
Note: this name may be used for preparations of different composition.
Zentiva, Pol.
Diclofenac (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Herbacos Recordati, Cz.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; inflammation; gout; pain.

Investi, Arg.
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veraldid *Chobet, Arg.*
Troxerutin (p. 2505·3); magnesium ascorbate (p. 1787·1).
Varices.

Vera-Lich *Winthrop, Ger.†*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Veraligral *Sanofi Synthelabo, Mex.†*
Veralipride (p. 1114·2).
Menopausal disorders.

Veralipral *Finadiet, Arg.*
Veralipride (p. 1114·2).
Menopausal disorders.

Veralipral T *Finadiet, Arg.*
Veralipride (p. 1114·2); bromazepam (p. 1041·2).
Menopausal disorders.

Veraljin *Radyum, Turk.*
Dipyrone (p. 53·3).
Fever; pain.

Veraloc *Orion, Denm.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; hypertension; angina pectoris; myocardial infarction.

Veralox *Demo, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Veralpres *Volta, Chile.*
Valsartan (p. 1521·2).
Hypertension; left-ventricular dysfunction; heart failure.

Veralpres D *Volta, Chile.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Veramex *Sanofi-Aventis, Ger.†; Winthrop, Ger.†*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veramil *Ducto, Braz.; Orion, Irl.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; arrhythmias; angina pectoris.

Themis Medicare, India.
Verapamil (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Veramina *Roux-Ocefa, Arg.*
Fosfomycin calcium (p. 300·3).
Bacterial infections.

Veramon
Note: this name may be used for preparations of different composition.
Sofar, Ital.
Propyphenazone (p. 127·3); paracetamol (p. 115·1).
Pain; fever.

Veramyst *GSK, USA.*
⊗Fluticasone furoate (p. 1638·1).
Allergic rhinitis.

Verana *Ratiopharm, Ger.*
Chlormadinone acetate (p. 2257·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Veranil *Royal, Chile.*
Emollient.

Veranorm *Actavis, Ger.†*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Veranzol *Collins, Mex.†*
Albendazole (p. 149·1).
Worm infections.

Verap *Rowex, Irl.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension.

Verapabene *Ratiopharm, Austria.*
Verapamil hydrochloride (p. 1522·1).
Heart failure; arrhythmias; hypertension; hypertrophic obstructive cardiomyopathy; angina pectoris.

Verapal *Lafedar, Arg.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias.

Verapam *Streuli, Switz.†*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; myocardial infarction; cardiomyopathy; hypertension; coronary spasm.

Verapime *Demo, Gr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Verapin *Berlin Pharm, Thai.†*
Verapamil hydrochloride (p. 1522·1).
Hypertension; heart failure; angina pectoris; arrhythmias.

Veraplex *Teva Tuteur, Arg.; Teva, Belg.; Combiphar, Indon.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Teva, Rus.; Pharmachemie, Thai.; Teva, Thai.*
Medroxyprogesterone acetate (p. 2288·1).
Malignant neoplasms.

Verapress *Greenpharma, Braz.†; Dexcel, Israel; Dexcel, UK.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension.

Veraptin *Boniscontro & Gazzone, Ital.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; myocardial infarction; arrhythmias; hypertension.

Verasal *TAD, Ger.†*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veraskin *Pharma 2000, Fr.†*
Aloe vera (p. 1693·2).
Skin disorders; superficial burns and wounds.

Veraspir *Alter, Port.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Obstructive airways disease.

Veratard *Borshchagovskii, Ukr.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; supraventricular tachycardia.

Veraten *Elea, Arg.*
⊗Carvedilol (p. 1333·1) or carvedilol phosphate (p. 1333·1).
Hypertension; heart failure.

Veratide *Basics, Ger.†*
⊗Verapamil hydrochloride (p. 1522·1); triamterene (p. 1518·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vératran *CSP, Fr.*
Clotiazepam (p. 1057·2).
Anxiety; alcohol withdrawal syndrome.

Veratropan Composto *IQB, Braz.†*
Hyoscine (p. 1845·3); dipyrone (p. 53·3).
Muscle spasm; pain.

Veratrum Med Complex *Dynamit, Austria.*
Acidum phosphoricum (p. 2589·1); veratrum album (p. 2644·3); vipera berus; viscum album (p. 2560·2).
Homoeopathic preparation.

Veraval *Sanval, Braz.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Veravorin *Opus Materia, Gr.; Rafarm, Gr.*
Calcium folinate (p. 2066·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Verax *Tosi, Hong Kong†; Federfarma, Ital.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat disorders; vulvovaginal disorders.

Veraxatin *Opus Materia, Gr.*
Oxaliplatin (p. 838·1).

Verazinc *Forest Pharmaceuticals, USA.*
Zinc sulfate (p. 2126·2).
Dietary supplement.

Verbinaf *Pliva, Cz.†; Farmacom, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Verbital *Faran, Gr.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Verbodon *Veltipharm, Gr.*
Diacerein (p. 45·3).

Verboril
Note: this name may be used for preparations of different composition.
Chemedica, Austria; Angelini, Gr.
Diacerein (p. 45·3).
Osteoarthritis.

TRB, Arg.
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Verbram *Antibioticos, Mex.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Vercef *Ranbaxy, Cz.; Ranbaxy, Hong Kong; Ranbaxy, Hung.†; Ranbaxy, Malaysia; Ranbaxy, Pol.; Ranbaxy, Rus.†; Ranbaxy, S.Afr.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Cefaclor (p. 232·3).
Bacterial infections.

Vercite *IFET (ΙΦΕΤ), Gr.; Abbott, Ital.*
Pipobroman (p. 847·1).
Polycythaemia vera; chronic myeloid leukaemia.

Vercithin *Bernofarm, Indon.*
Lecithin (p. 2542·2); vitamin E (p. 2119·1); vitamin B substances (p. 2102·3).
Dietary supplement.

Verclav *Kapl, Thai.*
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Vercol *Viofar, Gr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Vercure *Tempo Scan Pacific, Indon.*
Betahistine mesilate (p. 2455·3).
Vertigo; Ménière's disease.

Vercyte *Abbott, Fr.*
Pipobroman (p. 847·1).
Polycythaemia vera.

Verdal
Note: this name may be used for preparations of different composition.
Olvos, Gr.
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Fungal skin infections with inflammation.

Verdauungstropfen Gastrofunkten *Robugen, Ger.†*
Caraway oil (p. 2470·3); bay-laurel oil; clove oil (p. 2481·3); fennel oil (p. 2503·3); anise oil (p. 2444·3); eucalyptus oil (p. 2501·2); cinnamon oil (p. 2479·3); camphor (p. 2466·2); levomenthol (p. 2553·2).
Digestive disorders.

Verdeso *Stiefel, Canad.; GSK, USA.*
⊗Desonide (p. 1630·1).
Skin disorders.

Verdeval *Novartis Consumer, Spain.†*
Valerian (p. 2640·2).
Nervous disorders; insomnia.

Verdilac *Cryopharma, Mex.*
Verapamil (p. 1522·1).
Arrhythmias; angina pectoris.

Verdiz *Teva, Philipp.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Verecolene CM
Note: this name may be used for preparations of different composition.
GSK Consumer, Ital.
Bisacodyl (p. 1821·1).
Constipation.

Veregen *Solvay, Austria; Abbott, Ger.; Will-Pharma, Neth.; Bial, Spain; Abbott, Switz.*
Camellia sinensis (p. 2648·2).
Anogenital warts.

Abic, Israel; Bradley, USA.
Sinecatechins (p. 1720·2).
Anogenital warts.

Verel *Astellas, Ital.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); copper acetate (p. 2486·2).
Warts; verrucas; hard skin.

Verelait *Bouty, Ital.*
Lactulose (p. 1850·3).
Constipation.

Verelan *Elan, Canad.; OEP, Philipp.; Schwarz, USA.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Verfid *Continentales, Mex.†*
Piperazine (p. 163·1).
Amoebiasis; worm infections.

Vergentan *Sanofi-Aventis, Ger.*
Alizapride hydrochloride (p. 1815·2).
Nausea and vomiting; radiation sickness.

Vergéturine *Bailleul, Fr.†*
Emollients; vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Skin disorders.

Vergo *Mylan, NZ.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Verhist *US Pharmacia, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Vericaps *Ovelle, Irl.†*
Salicylic acid (p. 1719·1).
Warts.

Vericin *Giempi, Venez.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Vericordin *Lazar, Arg.*
⊗Atenolol (p. 1308·2).
Angina pectoris; hypertension.

Vericordin Compuesto *Lazar, Arg.*
⊗Atenolol (p. 1308·2); hydrochlorothiazide (p. 1403·2); amiloride hydrochloride (p. 1299·1).
Hypertension.

Vericort *Viofar, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; topical corticosteroid.

Veriderm Medrol *Pfizer, Gr.*
⊗Methylprednisolone acetate (p. 1642·3).
Skin disorders.

Veriderm-Neo Medrol *Pfizer, Gr.*
⊗Methylprednisolone acetate (p. 1642·3); neomycin sulfate (p. 330·1).
Infected skin disorders.

Verilax
Note: this name may be used for preparations of different composition.
Airela, Braz.
Cascara (p. 1826·1).

Bernabo, Arg.
Sodium picosulfate (p. 1887·2).
Constipation.

Verile *Medikon, Indon.*
Salicylic acid (p. 1719·1); boric acid (p. 2459·3); resorcinol (p. 1718·3); allantoin (p. 1693·1); triclosan (p. 1773·2).
Acne.

Veripred *Hawthorn, USA.*
⊗Prednisolone sodium phosphate (p. 1645·3).
Corticosteroid.

Verisan
Note: this name may be used for preparations of different composition.
CT, Ital.
Citalopram hydrochloride (p. 411·1).
Depression; anxiety disorders.

Verisan Triplex *Abbott, Mex.*
Aesculus (p. 2431·2); rutoside (p. 2505·3); Miroton (adonis vernalis (p. 2431·1); convallaria (p. 2486·2); oleander (p. 2574·3); squill (p. 1677·3)).
Venous insufficiency; haemorrhoids.

Veriscal D *Faes, Spain.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency; osteoporosis.

Verisop *Generics, Irl.*
Verapamil hydrochloride (p. 1522·1).
Supraventricular tachycardia; angina pectoris; hypertension.

Verispasmin *Recordati, Gr.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Verist *Synmedic, Philipp.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Veristin *Viofar, Gr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Veritrat *Pharmex (Φαρμεξ), Gr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Verladyn *Verla, Ger.*
Dihydroergotamine mesilate (p. 672·2).
Hypotension; migraine and related vascular headaches.

Verla-Lipon *Verla, Ger.†*
Thioctic acid (p. 2629·1).
Diabetic polyneuropathy.

Verlost *Rafarm, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Vermalon *Vargas, Venez.*
Mebendazole (p. 158·3).
Worm infections.

Vermanol *Verma, Gr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); with or without potassium chloride (p. 1793·2).
Haemofiltration.

Vermanol VD *Verma, Gr.†*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); calcium chloride (p. 1783·1); magnesium chloride (p. 1787·1); sodium lactate (p. 1781·2); with or without glucose (p. 2068·3).
Haemodialysis; haemofiltration; haemodiafiltration.

Vermazol *Ulagay, Turk.*
Mebendazole (p. 158·3).
Worm infections.

Vermectil *Mabra, Braz.*
Ivermectin (p. 155·1).
Onchocerciasis; strongyloidiasis; filariasis; scabies; pediculosis.

Vermectin *Atlantic, Thai.*
Ivermectin (p. 155·1).
Strongyloidiasis.

Vermedis *Baldacci, Port.*
Topiramate (p. 550·3).
Epilepsy.

Vermex *Hua, Thai.†*
Piperazine citrate (p. 163·1).
Enterobiasis; ascariasis.

Vermi *Quimpe, Spain.*
Piperazine adipate (p. 163·1).
Worm infections.

Vermiben *Cifarma, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Vermiclase *Cifarma, Braz.*
Albendazole (p. 149·1).
Worm infections.

Vermicol *Degorts, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Vermidil *Diba, Mex.†*
Mebendazole (p. 158·3).
Worm infections.

Vermidon *Sandoz, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Vermidon Cold *Sandoz, Turk.*
⊗Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Respiratory-tract congestion.

Vermidon Hot *Sandoz, Turk.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).

Vermidon-K *Sandoz, Turk.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine (p. 40·2).
Fever; pain.

Vermifuge *Sorin-Maxim, Fr.*
Piperazine hydrate (p. 163·1).
Intestinal nematode infections.

Vermin
Note: this name may be used for preparations of different composition.
Streger, Mex.
Piperazine (p. 163·1).
Worm infections.

Ratiopharm, Fin.†
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; hypertension; myocardial infarction; arrhythmias.

Vermin Plus *Streger, Mex.*
Albendazole (p. 149·1).
Intestinal nematode infections.

Vermin-Dazol *Streger, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Vermine *Pharmasant, Thai.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Vermis *Utopian, Thai.*
Aciclovir (p. 964·1).
Herpes simplex infections.

Vermisen *Novag, Mex.*
Albendazole (p. 149·1).
Worm infections.

Vermisol *Khandelwal, India.*
Levamisole (p. 157·2).
Worm infections.

Vermital *Elofar, Braz.*
Albendazole (p. 149·1).
Worm infections.

Vermixide *Polipharm, Thai.*
Albendazole (p. 149·1).
Worm infections.

Vermizole *Lafedar, Arg.*
Albendazole (p. 149·1).
Worm infections.

Vermoil *Farmo Quimica, Chile.*
Albendazole (p. 149·1).
Worm infections.

Vermol
Note: this name may be used for preparations of different composition.
Mecom, Turk.
Paracetamol (p. 115·1); caffeine (p. 1203·3).

Vermoplex *Cimed, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Vermoral *Legrand, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Vermox *Janssen-Cilag, Austral.; Johnson & Johnson Consumer, Belg.; Janssen-Ortho, Canad.; Xian-Janssen, China; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Gedeon Richter, Hung.; Janssen-Cilag, Indon.; McNeil Healthcare, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Johnson & Johnson, Neth.; McNeil, Norw.; Janssen-Cilag, NZ; Richter, Pol.; Gedeon Richter, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Gedeon Richter, Ukr.; Janssen, USA.*
Mebendazole (p. 158·3).
Worm infections.

Vermox-Plus *Janssen-Cilag, Mex.*
Mebendazole (p. 158·3); quinfamide (p. 947·1).
Worm infections.

Vernarin *Nakornpatana, Thai.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; vestibular disorders; migraine; motion sickness.

Verneg *Verisfield, Gr.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Vernies *Parke, Davis, Spain.*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris.

Vernleigh Baby Cream *Adcock Ingram, S.Afr.*
Zinc oxide (p. 1729·1).
Skin disorders.

Vernoral *Pharmanel, Gr.*
⊗Budesonide (p. 1625·1).
Obstructive airways disease.

Verocod *Viofar, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Verodex *Opus Materia, Gr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Verogalid *Teva, Cz.; Ivax, Rus.; Teva, Ukr.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris; arrhythmias.

Veroklast *Lens, Rus.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases.

Verolax *Angelini, Ital.; Angelini, Port.; Angelini, Spain.*
⊗Glycerol (p. 2517·2).
Constipation.

Verolin *Demo, Gr.*
⊗Serrapeptase (p. 2613·3).
Inflammatory disorders.

Verolinex *Demo, Gr.*
Vincamine (p. 2645·2).

Veromil *Bryntsalov, Rus.†*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic obstructive cardiomyopathy; pulmonary hypertension.

Verona
Note: this name may be used for preparations of different composition.
Herbion, Rus.
⊗Tribulus terrestris (p. 2633·3); withania (p. 2450·2); dolichos pruriens; argyreia speciosa.
Sexual functional disorders in men.

Herbion, Ukr.
⊗Tribulus terrestris (p. 2633·3); ashwagandha (p. 2450·2); mucunae pruriens; argyreia speciosa.
Sexual functional disorders in men.

Solas, Indon.
Javanese turmeric (p. 2636·2); milk thistle (p. 1561·1); lecithin (p. 2542·2).
Liver disorders.

Vero-Narcap *Veropharm, Rus.*
Aprotinin (p. 1133·2).
Opioid withdrawal syndrome.

VeroPol *Statens Serum Institute, Cz.; Statens Serum Institut, Fin.; Scandinavian Biopharma, Swed.*
An inactivated poliomyelitis vaccine (p. 2411·1).
Active immunisation.

Veroprazol *Sant Gall, Arg.*
Omeprazole (p. 1867·2).

Veroptin *Sandoz, Turk.*
Verapamil hydrochloride (p. 1522·1).
Arrhythmias; angina pectoris; hypertension.

Veroptinstada *Stada, Austria; Stada, Ger.†*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic cardiomyopathy; myocardial infarction.

Verorab *Sanofi Pasteur, Arg.; Sanofi Pasteur, Chile; Sanofi Pasteur, China; Sanofi Pasteur, Cz.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Sanofi Pasteur, Israel; Sanofi Pasteur, Malaysia; Sanofi-Aventis, NZ; Sanofi Pasteur, Philipp.; Sanofi Pasteur, Pol.; Litha, S.Afr.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Venez.*
An inactivated rabies vaccine (Wistar PM/WI38 1503-3M strain) (p. 2413·2).
Active immunisation.

Veroscan *Tempo Scan Pacific, Indon.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Verospilactone *Obolenskoe, Rus.*
⊗Spironolactone (p. 1499·3).
Oedema; ascites; hypertension; hyperaldosteronism; hypokalaemia.

Verospiron *Gedeon Richter, Cz.; Hormosan, Ger.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Ukr.*
⊗Spironolactone (p. 1499·3).
Oedema; hyperaldosteronism; hypertension; hypokalaemia; nephrotic syndrome; hepatic cirrhosis with ascites.

Verotekan *Lens, Rus.*
Topotecan hydrochloride (p. 872·3).
Ovarian cancer; non-small cell lung cancer.

Verotina *Libbs, Braz.*
Fluoxetine hydrochloride (p. 417·1).
Obsessive-compulsive disorder; depression; panic disorder; bulimia nervosa; premenstrual dysphoric disorder.

Veroven *Angelini, Port.*
Hidrosmin (p. 2505·2).
Chronic venous insufficiency.

Verox *Medicine Products, Thai.*
Piroxicam (p. 125·3).
Pain; gout; musculoskeletal and joint disorders.

Veroxil
Note: this name may be used for preparations of different composition.
Anfarm, Gr.
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Baldacci, Ital.
⊗Indapamide (p. 1409·2).
Hypertension.

Verpamil *Orion, Fin.; Jacobson, Hong Kong†; Orion, Malaysia; Mylan, NZ; Orion, Singapore.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Verpir *Kleva, Gr.*
Aciclovir (p. 964·1).
Labial and genital herpes simplex infections.

Verpirol *Proula, Venez.*
Piperazine (p. 163·1).
Ascariasis; oxyuriasis.

Verra-med *Phoenix, Hung.; Permamed, Switz.*
Tretinoin (p. 1725·2); salicylic acid (p. 1719·1); dimethyl sulfoxide (p. 2182·2).
Warts.

Verruca Hermal *Olvos, Gr.*
Salicylic acid (p. 1719·1); fluorouracil (p. 795·2).
Verrucas.

Verruca Removal *SSL, Cz.†*
Salicylic acid (p. 1719·1).
Verrucas.

Verrucare *Medinfar, Port.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); fluorouracil (p. 795·2).
Warts.

Verrucid *Galen, Ger.*
Salicylic acid (p. 1719·1).
Calluses; corns; warts.

Verruclean *LDA, Arg.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Verrufilm
Note: this name may be used for preparations of different composition.
D & M, Chile; Bailleul, Fr.; BUDP, Hong Kong.
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Medinfar, Port.
Salicylic acid (p. 1719·1).
Warts.

Verrugard *Atlas, Arg.*
Salicylic acid (p. 1719·1); tretinoin (p. 1725·2); dimethyl sulfoxide (p. 2182·2).
Warts.

Verrugon *Ransom, Irl.; Ransom, UK.*
Salicylic acid (p. 1719·1).
Verrucas.

Verrulia *Boiron, Fr.*
Antimonium crudum (p. 2445·1); nitricum acidum (p. 2572·3); thuya occidentalis (p. 2629·3).
Homoeopathic preparation.

Verrulyse-Méthionine *Sinclair, Fr.*
Magnesium oxide (p. 1857·3); methionine (p. 1558·2); calcium glycerophosphate (p. 1783·3); ferric glycerophosphate (p. 2519·2); manganese glycerophosphate (p. 2519·2).
Warts.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Verrumal *Hermal, Austria; Almirall Hermal, Cz.; Hermal, Ger.; iNova, Hong Kong; Almirall, Hung.; Hermal, Israel; Almirall, Malaysia; Almirall, Singapore; Almirall, Switz.; iNova, Thai.*
Fluorouracil (p. 795·2); salicylic acid (p. 1719·1); dimethyl sulfoxide (p. 2182·2).
Warts.

Almirall, Pol.; Almirall, Port.
Fluorouracil (p. 795·2); salicylic acid (p. 1719·1).
Warts; verrucas; actinic keratoses.

Verrupan *Pharmadeveloppement, Fr.*
Thuja (p. 2629·3); salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts.

Verrupatch *Vinas, Spain.*
Salicylic acid (p. 1719·1).
Warts.

Verruplan *Vinas, Spain.*
Salicylic acid (p. 1719·1).
Warts.

Verrupor *Sella, Ital.*
Trichloroacetic acid (p. 1727·2).
Verrucas; warts; hard skin.

Verrutol *Orva, Turk.*
Salicylic acid (p. 1719·1); fluorouracil (p. 795·2).
Warts.

Verrutopic *Andromaco, Arg.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Hyperkeratosis; warts.

Verrutopic AS *Andromaco, Arg.*
Salicylic acid (p. 1719·1).
Warts.

Verrutrix *Pharmatrix, Arg.*
Salicylic acid (p. 1719·1).
Warts.

Verrux *Theraskin, Braz.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts.

Versa *Humco, USA.*
A range of pharmaceutical bases.

Versacaps *Seatrace, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Versacloz *Jazz, USA.*
Clozapine (p. 1057·3).
Schizophrenia.

Versal *Pro Medica, Swed.†*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Versalba *Angelini, Gr.*
Bendazac (p. 29·1).
Inflammatory skin conditions.

Versamiv *Novag, Mex.*
Diiodohydroxyquinoline (p. 931·1).
Amoebiasis.

Versant *Imperial, Philipp.*
Felodipine (p. 1380·3).
Hypertension.

Versatic *Duncan, Arg.*
Cefadroxil (p. 233·2).
Bacterial infections.

Versatil
Note: this name may be used for preparations of different composition.
Intermed, Gr.
⊗Celiprolol hydrochloride (p. 1334·2).
Hypertension.

Versatis *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Denm.; Grunenthal, Fr.; Grunenthal, Ger.; IFET (ΙΦΕΤ), Gr.; Grunenthal, Irl.; Grunenthal, Norw.; Grunenthal, Rus.; Grunenthal, Spain; Grunenthal, Swed.; Grunenthal, UK; Grunenthal, Ukr.*
Lidocaine (p. 1988·1).
Postherpetic neuralgia; neuropathic pain; local anaesthesia; myositis.

Versed *Roche, Fr.*
Midazolam (p. 1085·1).
Sedative.

Versef *Ranbaxy, Philipp.†*
Cefaclor (p. 232·3).
Bacterial infections.

Versel *Valeo, Canad.*
Selenium sulfide (p. 1719·3).
Fungal skin infections.

Versiclear *Hope, USA.*
Sodium thiosulfate (p. 1576·1); salicylic acid (p. 1719·1).
Fungal infections.

Versid *Mulda, Turk.*
Mebendazole (p. 158·3).
Worm infections.

Versigen *Chew, Thai.*
Gentamicin (p. 304·2).
Bacterial skin infections.

Versilon *Mersifarma, Indon.*
Betahistine mesilate (p. 2455·3).
Vertigo; tinnitus; Ménière's disease.

Versiva *Convatec, Ital.*
Foamed hydrogel.
Wounds.

Versol
Note: this name may be used for preparations of different composition.
Aguettant, UK.
Sodium chloride (p. 1795·1) for irrigation.

Versterkdruppels *Aspen Consumer, S.Afr.*
Cinchona bark (p. 2478·3); gentian (p. 2512·1); dried bitter-orange peel (p. 2575·3); quassia (p. 2601·1).
Tonic.

Versus *Angelini, Ital.*
Bendazac (p. 29·1).
Skin disorders.

Vert *InnoGen, Philipp.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vertigo.

Vertab *Trinity, UK.*
Verapamil hydrochloride (p. 1522·1).
Hypertension; angina pectoris.

Verteblan *Demo, Gr.*
Dihydroergotamine mesilate (p. 672·2).
Migraine.

Vertegra *Integra, Philipp.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vestibular disorders.

Vertex
Note: this name may be used for preparations of different composition.
Meprofarm, Indon.
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Vertibetis *Jelfa, Cz.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Vertigen *Biogened, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Vertigeron *Greenpharma, Braz.*
Cinnarizine (p. 622·1).
Vestibular disorders.

Vertigil *Cipla, India.*
Cinnarizine (p. 622·1); domperidone (p. 1838·1).
Motion sickness.

Vertiginkgo *Pharmaval, Ital.*
Ginkgo biloba (p. 2512·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); manganese (p. 2081·2).
Nutritional supplement.

Vertigium *Neo Quimica, Braz.*
Flunarizine hydrochloride (p. 629·3).

Vertigmine *Lafedar, Arg.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo.

Vertigo Hevert SL *Hevert, Ger.*
Cocculus (p. 2483·1); conium (p. 2524·3); tabacum (p. 2632·2).
Homoeopathic preparation.

Vertigoheel *Heel, Austria; Heel, Cz.; Heel, Ger.; Peithner, Hung.; Heel, S.Afr.; Ebi, Switz.; Heel, USA.*
Conium maculatum (p. 2524·3); ambra grisea (p. 2440·3); petroleum (p. 2587·2); anamirta cocculus (p. 2483·1).
Homoeopathic preparation.

Heel, Neth.
Cocculus indicus (p. 2483·1); conium maculatum (p. 2524·3); petroleum (p. 2587·2).
Homoeopathic preparation.

Vertigo-Hevert *Hevert, Ger.*
Oral drops: Cocculus (p. 2483·1); glonoinum (p. 1391·2).
Homoeopathic preparation.

Hevert, Ger.
Injection: Cocculus (p. 2483·1); conium (p. 2524·3); nux vomica (p. 2573·3); secale cornutum (p. 2137·1).
Homoeopathic preparation.

Vertigo-Meresa *Dolorgiet, Ger.*
Sulpiride (p. 1107·3).
Ménière's disease.

Vertigon
Note: this name may be used for preparations of different composition.
Gerard, Irl.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Manx, UK.
Promethazine teoclate (p. 638·2).
Vertigo.

Nida, Singapore.
Cinnarizine (p. 622·1).
Vertigo; nausea and vomiting; motion sickness; migraine; tinnitus.

vertigo-neogama *Hormosan, Ger.*
Sulpiride (p. 1107·3).
Vestibular disorders.

Vertigopas *Pascoe, Austria; Pascoe, Ger.*
Cocculus (p. 2483·1); conium (p. 2524·3); ambra (p. 2440·3); oenanthe crocata; petroleum rectificatum (p. 2201·2).
Homoeopathic preparation.

Vertigo-Vomex *Astellas, Ger.; Klinge, Ger.*
Dimenhydrinate (p. 625·2).
Vertigo; vestibular disorders.

Galenica, Gr.
Dimenhydrinate (p. 625·2); nicotinic acid (p. 2083·1); vitamin B_6 (p. 2105·3).
Nausea; vertigo.

Vertilate *Crisdy-Na, Philipp.*
Betahistine mesilate (p. 2455·3).
Ménière's disease; vertigo.

Vertilium *Macrophar, Thai.*
Flunarizine (p. 629·3).
Migraine; vestibular disorders.

Vertin
Note: this name may be used for preparations of different composition.
Solvay, India.
Betahistine hydrochloride (p. 2455·3).
Ménière's syndrome; vertigo.

Vertipam *Orion, Fin.†*
Diazepam (p. 1063·2); cyclizine hydrochloride (p. 623·2); nicotinic acid (p. 2083·1).
Vestibular disorders.

Vertiron *Cipla, India.*
Cinnarizine (p. 622·1).

Vertirosan *Sigmapharm, Austria; IFET (ΙΦΕΤ), Gr.*
Dimenhydrinate (p. 625·2).
Vestibular disorders; nausea and vomiting; migraine; motion sickness.

Vertirosan Vitamin B_6 *Sigmapharm, Austria.*
Dimenhydrinate (p. 625·2); pyridoxine hydrochloride (p. 2105·3).
Vestibular disorders; nausea and vomiting; migraine; motion sickness.

Vertisal *Silanes, Mex.*
Metronidazole (p. 936·1) or metronidazole benzoate (p. 936·1).
Amoebiasis; giardiasis; trichomoniasis; anaerobic bacterial infections.

Vertisan *Hennig, Cz.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Vertiserc *Solvay, Ital.; Frik, Turk.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders.

Vertisin *Littman, Philipp.*
Cinnarizine (p. 622·1).
Vestibular disorders; motion sickness; cerebral and peripheral vascular disorders.

Vertivom *GMP, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Gastrointestinal disorders.

Vertix *Ache, Braz.*
Flunarizine hydrochloride (p. 629·3).
Vertigo.

Farma-Projekt, Pol.
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Vertizin *Pfluger, Ger.*
Ambra grisea (p. 2440·3); phosphorus (p. 2589·2); schoenocaulon officinale (p. 2611·2); toxicodendron quercifolium (p. 2603·3); viscum album (p. 2560·2).
Homoeopathic preparation.

Vertizine *Bernofarm, Indon.*
Cinnarizine (p. 622·1).
Cerebral and peripheral vascular disorders; motion sickness.

Vertizine D *Ache, Braz.*
Dihydroergocristine mesilate (p. 390·1); flunarizine hydrochloride (p. 629·3).
Vertigo.

Vertizole *Rayere, Mex.*
Mebendazole (p. 158·3).
Worm infections.

Vertuss *Madaus, Ital.*
Ivy (p. 2536·2).
Cough.

Verucid
Note: this name may be used for preparations of different composition.
Galderma, Denm.; Galderma, Norw.
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; hard skin.

Veruderm B *Legrand, Braz.*
⊗Fusidic acid (p. 302·1); betamethasone (p. 1623·2).

Verufil *Stiefel, Spain.*
Lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Verunec *Savoma, Ital.*
⊗Salicylic acid (p. 1719·1); lactic acid (p. 2539·1); urea (p. 1727·3).
Verrucas; warts; hard skin.

Verus
Note: this name may be used for preparations of different composition.
Unipharma, Gr.
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Verutex *Roche, Braz.*
Fusidic acid (p. 302·1).
Bacterial skin infections.

Verutex B *Roche, Braz.*
⊗Fusidic acid (p. 302·1); betamethasone valerate (p. 1624·1).
Infected skin disorders.

Verutil *Novartis, Venez.*
Troxerutin (p. 2505·3).
Haemorrhoids; varices; phlebitis.

Verzachtende Hoestsiroop met tijm *SAN, Neth.*
Aniseed (p. 2444·2); althaea (p. 2438·3); liquorice (p. 1853·2); thyme (p. 2630·2).
Cough.

Verzat *Randril, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Verzatec *Farbio, Port.*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Verzol *Delta, Braz.*
Mebendazole (p. 158·3).
Worm infections.

Verzum *Elofar, Braz.*
Cinnarizine (p. 622·1).
Vertigo.

Vesagex *Co-Pharma, Irl.; Co-Pharma, UK.*
Cetrimide (p. 1742·1).
Burns; skin disorders; minor wounds; nappy rash.

Vesagex Heelbalm *Co-Pharma, UK.*
⊗Allantoin (p. 1693·1); peppermint oil (p. 1877·1); urea (p. 1727·3); moisturisers.
Dry, cracked skin on the heels and soles of the feet.

Vesalion *Nova Argentia, Arg.*
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Vesalion B12 *Nova Argentia, Arg.*
⊗Diclofenac potassium (p. 48·3); betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Neuralgias.

Vesalion Flex *Nova Argentia, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Inflammation; muscle spasm; pain.

Vesalion Gesic *Nova Argentia, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Peri-articular disorders; pain.

Vesanoid *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Intrapharm, UK; Roche, Ukr.; Roche, USA†; Roche, Venez.*
Tretinoin (p. 1725·2).
Acute promyelocytic leukaemia.

Vesanoïd *Roche, Fr.*
Tretinoin (p. 1725·2).
Acute promyelocytic leukaemia.

Vesconac *Vesco, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation; pain; musculoskeletal, joint, and peri-articular disorders; gout.

Vescopam *Vesco, Thai.*
Diazepam (p. 1063·2).
Premedication; seizures; anxiety; skeletal muscle spasm; alcohol withdrawal syndrome; epilepsy.

Vescopolamine *Vesco, Thai.*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Vesdil *AstraZeneca, Ger.†*
Ramipril (p. 1483·3).
Hypertension; heart failure; myocardial infarction; nephropathy; cardiovascular risk reduction.

Vesdil plus *AstraZeneca, Ger.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vesema *Pharmex (Φαρμεξ), Gr.*
Citalopram hydrobromide (p. 411·1).
Depression.

Vesevedo *Naturland, Hung.*
Chelidonium majus (p. 2522·2); solidago (p. 2620·1); urtica (p. 2639·3); equisetum (p. 2500·1); agrimony (p. 2432·3).
Kidney disorders.

Vesicade *Astellas, Braz.*
Solifenacin succinate (p. 2367·3).
Urinary incontinence.

Vesicare *Eurolab, Arg.; CSL Biotherapies, Austral.; Astellas, Austria; Astellas, Belg.; Astellas, Braz.; Astellas, Canad.; Astellas, China; Astellas, Cz.; Astellas, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Gr.; Astellas, Hong Kong; Astellas, Hung.; Astellas, Indon.; Astellas, Israel; Astellas, Jpn; GSK, Malaysia; Liomont, Mex.; Astellas, Neth.; Astellas, Norw.; CSL, NZ; Astellas, Philipp.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, S.Afr.; GSK, Singapore; Astellas, Spain; Astellas, Swed.; Astellas, Switz.; Astellas, Thai.; Astellas, UK; Astellas, Ukr.; Astellas, USA.*
Solifenacin succinate (p. 2367·3).
Bladder instability; bladder hyperactivity.

Vesiherb *Cesra, Ger.*
Cucurbita (p. 2489·2).
Prostatic disorders.

Vesiker *Astellas, Ital.*
Solifenacin succinate (p. 2367·3).
Bladder instability disorders.

Vesikur *Astellas, Ger.*
Solifenacin succinate (p. 2367·3).
Urinary incontinence.

Vesilac *Yung Shin, Philipp.*
Bisacodyl (p. 1821·1).
Bowel evacuation; constipation.

Vesimycin *Naprod, Thai.*
Mitomycin (p. 830·3).

Vesitirim *Astellas, Irl.*
Solifenacin succinate (p. 2367·3).
Bladder instability.

Vesix *Leiras, Fin.*
⊗Furosemide (p. 1387·1).
Oedema; hypertension; renal failure.

Vesmotidine *Vesco, Thai.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Vesnidan *Medipharm, Chile.*
Hesperidin (p. 2505·2); diosmin (p. 2505·2).
Venous insufficiency; haemorrhoids.

Vesnon *Vesco, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Vesoflox *VS, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Vesoph *Vesco, Thai.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1).
Infected eye and ear disorders.

Vespa Complexe No 46 *Lehning, Fr.†*
⊗Vespa; valeriana officinalis (p. 2640·2); atropa belladonna (p. 2453·3); adonis vernalis (p. 2431·1); spongia; adrenalinum (p. 1292·1); lycopus virginicus (p. 2462·2); arsenicum iodatum (p. 2448·1); kalium carbonicum (p. 2595·2).
Homoeopathic preparation.

Vesparax
Note: this name may be used for preparations of different composition.
Lazar, Arg.
Quetiapine fumarate (p. 1101·1).
Bipolar disorder; schizophrenia.

Vesperidone *Vesco, Thai.*
Domperidone (p. 1838·1).
Nausea and vomiting; delayed gastric emptying.

Vesperum *Ifars, Indon.*
Domperidone (p. 1838·1) or domperidone maleate (p. 1838·1).
Dyspepsia; nausea and vomiting.

Vesprocin *Vesco, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Vesprolid-HCl *Vesco, Thai.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Rhinitis; cold symptoms; upper respiratory-tract congestion.

Vessatis *Grunenthal, Port.*
Lidocaine (p. 1988·1).
Postherpetic neuralgia.

Vessel
Note: this name may be used for preparations of different composition.
Wassermann, Ital.; BioSaude, Port.; Abbott, Thai.
Sulodexide (p. 1507·3).
Thromboembolic disorders; diabetic retinopathy; diabetic neuropathy; diabetic nephropathy; thrombosis prophylaxis; venous ulcer.

Vessel Due *Elmor, Venez.*
Sulodexide (p. 1507·3).
Thromboembolic disorders; diabetic nephropathy; diabetic peripheral arterial disease.

Vessel Due F *Alfa Wassermann, China; Alfa Wassermann, Cz.; Alfa Wassermann, Hung.; Wassermann, Malaysia; Wassermann, Philipp.; Alfa Wassermann, Pol.; Alfa Wassermann, Rus.*
Sulodexide (p. 1507·3).
Thrombosis prophylaxis; thrombosis; angiopathies.

Vesselvite *Bajamar, USA.*
Folic acid (p. 2063·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin E (p. 2119·1).

Vestam *Pharmasant, Thai.*
Ketoprofen (p. 79·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Vestan *Vesco, Thai.*
Mefenamic acid (p. 85·3).
Musculoskeletal and joint disorders; pain.

Vestar *Therapharma, Philipp.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; neurosensorial ischaemia.

Vestax *Vargas, Venez.*
Paracetamol (p. 115·1).
Fever; pain.

Vesthromycin *Vesco, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Vestibo *Actavis, Pol.; Actavis, Rus.; Fako, Turk.; Actavis, Ukr.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease; vestibular disorders.

Vestinorm *Farmak, Ukr.*
Betahistine hydrochloride (p. 2455·3).
Vestibular disorders; Ménière's disease.

Vestura *Watson, USA.*
24 Tablets, ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1); 4 tablets, inert.
Combined oral contraceptive.

Vesxacin *Vesco, Thai.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Vesyca *YSP, Malaysia; Yung Shin, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Vetamol
Note: this name may be used for preparations of different composition.
Vesco, Thai.
Paracetamol (p. 115·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Fever; pain.

Viofar, Gr.
Norfloxacin (p. 333·3).
Urinary-tract infections.

Vetansil *IQB, Braz.†*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm.

Vetevel *Belmac, Spain.†*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Vethisel *Rafarm, Gr.*
Cefradine (p. 249·1).
Bacterial infections.

Vethoine *Kela, Belg.*
Phenytoin (p. 538·2); phenobarbital (p. 535·2); cascara (p. 1826·1).
Epilepsy.

Vetic *Sato, Singapore.*
Enoxolone (p. 54·2); undecenoic acid (p. 596·3); with or without zinc undecenoate (p. 596·3).

Vetilax *Teva, Port.†*
Ispaghula (p. 1849·1).
Constipation.

Vetio *Ivax, Arg.*
Mitomycin (p. 830·3).
Malignant neoplasms.

Vetiprost *Ivax, Arg.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Vetira *Adamed, Neth.*
Levetiracetam (p. 531·1).
Epilepsy.

Vetland *IFA, Mex.*
Imiquimod (p. 985·2).
Genital warts.

Vetoben *Community Pharmacy, Thai.*
Albendazole (p. 149·1).
Worm infections.

Vetren *Nycomed, Austria; Madaus, Ger.; Rottapharm, Ger.*
Heparin sodium (p. 1396·3).
Soft-tissue injury; venous insufficiency; superficial vascular disorders.

Vetria *Biofarma, Turk.*
Levetiracetam (p. 531·1).

Veuen *Eriochem, Arg.*
⊗Letrozole (p. 817·1).

Vexa *Laboratorios Chile, Chile.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Vexamet *Vamsler, Philipp.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Vexazone *Alphapharm, Austral.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Vexell *Gross, Braz.*
Isosorbide mononitrate (p. 1413·3).

Vexicam *Armedica, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Vexol *Alcon, Austria; Alcon, Braz.; Alcon, Canad.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Irl.; Alcon, Ital.; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, NZ; Alcon, Port.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Turk.; Alcon, UK; Alcon, USA.*
⊗Rimexolone (p. 1647·3).
Inflammatory eye disorders; allergic conjunctivitis; uveitis; postoperative eye inflammation.

Vexolon *Alcon, Belg.*
⊗Rimexolone (p. 1647·3).
Inflammatory eye disorders.

Vexor *Cadila, India.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Vexotil *Biomep, Mex.*
Enalapril (p. 1371·1).
Hypertension.

Vexurat *Medinova (Μεντινοβα), Gr.*
Famotidine (p. 1842·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Vezepra *Kowa, Neth.*
Pitavastatin calcium (p. 1471·1).
Hyperlipidaemias.

Vezuran *Medico Uno, Hung.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Vfend *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Roerig, USA.*
Voriconazole (p. 597·1).
Fungal infections.

VG Med *T Man, Thai.*
Nystatin (p. 590·3); diiodohydroxyquinoline (p. 931·1); benzalkonium chloride (p. 1737·1).
Vaginal infections.

Vhellox *Flamingo, Philipp.*
Amoxicillin sodium (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Vi Rid-Ready *Geritrex, USA.*
Octyldecyldimethylammonium chloride (p. 1762·2); dioctyldimethylammonium chloride (p. 1750·3); didecyldimethylammonium chloride (p. 1750·3); benzalkonium chloride (p. 1737·1).
Disinfectant.

Via-Avenir *Bioavenir, Israel.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Viabom *CPH, Port.*
Dimenhydrinate (p. 625·2).
Motion sickness; vertigo.

Viaclav *Kalbe, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Viactiv *McNeil Consumer, Canad.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement.

Viactiv Calcium *McNeil Nutritionals, USA.†*
Calcium (p. 1783·1); vitamin D (p. 2112·3); vitamin K (p. 2122·1).
Dietary supplement.

Viactiv Multi-Vitamin *McNeil Nutritionals, USA.*
Vitamins; minerals.
Dietary supplement.

Viaderm-KC *Taro, Canad.; AFT, NZ.*
⊗Gramicidin (p. 308·3); neomycin sulfate (p. 330·1); nystatin (p. 590·3); triamcinolone acetonide (p. 1649·1).
Infected skin disorders.

Viadil *Pharma Investi, Chile.*
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm; nausea and vomiting.

Viadil Compuesto *Pharma Investi, Chile.*
Pargeverine hydrochloride (p. 1877·1); metamizole magnesium (p. 53·3).
Smooth muscle spasm and pain.

Viadoxin *Pyridam, Indon.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Viaflex *Mega Lifesciences, Thai.*
Glucosamine sulfate sodium chloride (p. 2515·3).
Degenerative joint disorders.

Viaflex Hartmann Ringer Lactada *Baxter, Spain.†*
Calcium chloride (p. 1783·1); potassium chloride (p. 1793·2); sodium chloride (p. 1795·1); sodium lactate (p. 1781·2).
Fluid and electrolyte disorders.

Viagra *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer,*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Viajesan *Calox, Venez.*
Dimenhydrinate (p. 625·2).
Nausea; vertigo.

Vial *Farmak, Ukr.*
⊗Tetryzoline (p. 1678·3).
Eye irritation; conjunctival congestion; allergic conjunctivitis.

Vialbone *Frankin, Hong Kong.†*
Glucosamine (p. 2515·3).

Vialebex *LFB, Fr.; Er-Kim, Turk.*
⊗Albumin (p. 1130·2).
Hyperbilirubinaemia; plasma volume expansion.

Vialerg *Orifarm, Denm.*
Cetirizine hydrochloride (p. 619·2).
Urticaria; allergic rhinoconjunctivitis.

Vialyn *Nicholas, Indon.*
Vitamins; calcium gluconate (p. 1783·3); zinc sulfate (p. 2126·2); lysine hydrochloride (p. 2079·3).
Dietary supplement.

Viamal Trauma *Polifarma Benessere, Ital.*
Diethylamine salicylate (p. 51·3); heparin sodium (p. 1396·3); menthol (p. 2553·2).
Soft-tissue disorders.

Viani *Allen, Austria; GSK, Belg.†; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Irl.*
⊗Salmeterol xinafoate (p. 1224·1); fluticasone propionate (p. 1638·1).
Asthma; obstructive airways disease.

Viapres *Crinos, Ital.*
Lacidipine (p. 1417·3).
Hypertension.

Viarex *Schering-Plough, Israel.†*
⊗Beclometasone dipropionate (p. 1621·2).
Asthma.

Viartril
Note: this name may be used for preparations of different composition.
Angelini, Gr.
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Viartril Flex *Spedrog, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders; muscle spasm.

Viartril NF *Spedrog, Arg.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Viartril S *Rottapharm, China; Rottapharm, Hong Kong; Rottapharm, Irl.; Rotta, Malaysia; Rotta, Philipp.; Delta, Port.; Rottapharm, Singapore; Rottapharm, Thai.; Rottapharm, Thai.*
Glucosamine sulfate (p. 2515·3).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Osteoarthritis; degenerative joint disorders; joint and cartilage disorders; musculoskeletal and joint disorders.

Meyer Alian, Venez.
Glucosamine (p. 2515·3).
Osteoarthritis.

Viasan-LF *Lekfarm, Rus.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Viasek *Leti, Venez.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Viasil *SM, Venez.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

ViaSpan *BMS, Belg.; BMS, Fin.; BMS, Irl.; BMS, Neth.; BMS, Norw.; BMS, Port.; BMS, Swed.*
Solution for flushing and cold storage of donor organs.

BMS, Switz.
Solution for preservation of donor organs.

Viaspan *BMS, Arg.; BMS, Chile; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; Boots, Hong Kong†; Du Pont, Hong Kong†; BMS, Ital.; BMS, Spain.*
Solution for flushing and cold storage of donor organs.

Viastrol *Vianex (Βιανεξ), Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

ViATIM *Sanofi Pasteur, Austria; Sanofi Pasteur, Ger.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Port.; Sanofi Pasteur, UK.*
An inactivated hepatitis A and typhoid (Vi capsular polysaccharide) vaccine (p. 2392·1).
Active immunisation.

Viatol *Axcan, Fr.*
Glucose (p. 2068·3); sodium chloride (p. 1795·1); potassium citrate (p. 1780·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Viatop AM *Ativus, Braz.*
Arginine (p. 2049·1); menthol (p. 2553·2).

Viatopin *GSK, Hung.†*
Topotecan hydrochloride (p. 872·3).
Small-cell lung cancer; ovarian cancer.

Viatromb *Cyathus, Austria; Cyathus, Cz.*
Heparin sodium (p. 1396·3).
Superficial venous disorders; soft-tissue injuries; muscle and peri-articular disorders; thrombophlebitis; phlebitis; varices; oedema; ulcus cruris.

Viavox *Sankyo, Venez.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Viaxal *Menarini, Gr.*
Dexketoprofen trometamol (p. 79·1).
Inflammatory disorders.

Viaxol *Maver, Mex.*
Ambroxol (p. 1654·3).
Respiratory-tract disorders.

Viazem *Genus, UK.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Vi-Balsabron *Lafedar, Arg.*
Noscapine hydrochloride (p. 1670·3); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough.

Vibativ *Astellas, Irl.†; Theravance, USA.*
Telavancin hydrochloride (p. 371·1).
Gram-positive bacterial skin and skin structure infections; methicillin-resistant Staphylococcal aureus pneumonia.

Vibazine *Pfizer, India.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Vibe *Rica, Hung.*
Uncaria tomentosa.
Musculoskeletal disorders.

Vibeden *Sandoz, Denm.*
Hydroxocobalamin (p. 2107·3).
Pernicious anaemia; vitamin B_{12} deficiency.

Vibee *Biolab, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Biolab, Singapore.
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Viberol Tirotricina *Teofarma, Spain.*
Formaldehyde (p. 1752·2); tyrothricin (p. 384·1).
Mouth and throat inflammation; oral hygiene.

Vibion *Jean-Marie, Hong Kong.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgias; neuritis; neuropathies; vitamin B deficiency.

Vibomil *Teva, Pol.*
Vitamins.

Viboral *The Forty-Two, Thai.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Dietary supplement.

Vibovit *Polfa Kutno, Pol.†*
Vitamins; with or without minerals.

Vibrabiotic *IFET (ΙΦΕΤ), Gr.*
Doxycycline hyclate (p. 288·2).

Vibracina *Invicta, Spain.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Vibradox *Sandoz, Denm.*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Vibradoxin *Hexal, Braz.*
Doxycycline (p. 288·1).

Vibragel *Novartis Consumer, Arg.*
Dimetindene maleate (p. 626·1); phenylephrine (p. 1672·2).
Nasal congestion; otitis media.

Vibral *Abbott, Braz.*
Dropropizine (p. 1662·2).
Cough.

Vibramicina *Pfizer, Arg.; Pfizer, Braz.; Pfizer, Chile.*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Pfizer, Port.
Doxycycline carrageenate (p. 288·1).
Bacterial infections; malaria; amoebiasis.

Pfizer, Mex.
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Vibramicina C *Pfizer, Venez.*
Doxycycline (p. 288·1).
Bacterial infections.

Vibramox *Pyridam, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Vibramycin *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.†; Pfizer, Philipp.; Pfizer, S.Afr.†; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria; amoebiasis; leptospirosis.

Pfizer, Austria; Pfizer, Gr.; KRKA, Rus.†; Pfizer, UK; Pfizer, USA.
Doxycycline (p. 288·1).
Bacterial infections.

NordMedica, Swed.†
Doxycycline carrageenate (p. 288·1) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Pfizer, Israel.†
Doxycycline calcium chelate (p. 288·2) or doxycycline hyclate (p. 288·2).
Bacterial infections.

Vibramycine *Pfizer, Switz.*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Vibramycine N *Sinclair, Fr.*
Doxycycline (p. 288·1).
Bacterial infections; rosacea.

Vibranat *Pyridam, Indon.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Vibranord *NordMedica, Norw.; NordMedica, Swed.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Vibratab *Pfizer, Belg.*
Doxycycline (p. 288·1).
Bacterial infections; malaria.

Vibra-Tabs *Pfizer, Austral.; Pfizer, Canad.; Pfizer, USA.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Vibraveineuse *SERB, Fr.; Pfizer, Switz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Vibravenos *IFET (ΙΦΕΤ), Gr.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Vibravenös *Pfizer, Austria.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Vibravenosa *IFET (ΙΦΕΤ), Gr.; Pfizer, Spain.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Vibrazin *Delta, Braz.*
Dropropizine (p. 1662·2).
Cough.

Vibrocil
Note: this name may be used for preparations of different composition.
Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Cz.; Novartis Consumer, Hung.; Novartis Consumer, Israel; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, Switz.; Novartis Consumer, Ukr.
Dimetindene maleate (p. 626·1); phenylephrine (p. 1672·2).
Rhinitis; sinusitis; otitis media; nasal congestion; cold and influenza symptoms; rhinorrhoea.

Novartis Consumer, S.Afr.
Dimetindene maleate (p. 626·1); phenylephrine (p. 1672·2); neomycin sulfate (p. 330·1).
Nasal infections; rhinitis; sinusitis; cold symptoms.

VibrocilFen *Novartis Consumer, Port.*
Phenylephrine (p. 1672·2).
Nasal congestion.

Vibrocil-S *Novartis, Gr.; Novartis Consumer, S.Afr.*
Dimetindene maleate (p. 626·1); phenylephrine (p. 1672·2).
Nasal and sinus congestion; rhinitis.

Vibrumin *GeneralDrugs, Thai.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Vibtil *Therabel, Belg.; SERP, Mon.*
Tilia (p. 2631·3).
Digestive and renal disorders.

Viburcol *Heel, Canad.; Heel, Cz.; Peithner, Hung.; Heel, S.Afr.*
Belladonna (p. 2453·3); dulcamara (p. 2497·3); chamomilla (p. 2474·1); calcarea carbonica (p. 1824·3); plantago major (p. 2592·3); pulsatilla (p. 2600·2).
Homoeopathic preparation.

Viburcol H *Heel, Neth.*
Belladonna (p. 2453·3); calcarea carbonica ostrearum (p. 1824·3); chamomilla (p. 2474·1); plantago major (p. 2592·3); pulsatilla pratensis (p. 2600·2).
Homoeopathic preparation.

Viburcol N *Ebi, Switz.*
Atropa belladonna (p. 2453·3); calcium carbonicum (p. 1824·3); chamomilla recutita (p. 2474·1); plantago major (p. 2592·3); pulsatilla pratensis (p. 2600·2); solanum dulcamara (p. 2497·3).
Homoeopathic preparation.

Heel, Ger.
Chamomilla (p. 2474·1); belladonna (p. 2453·3); plantago major (p. 2592·3); pulsatilla (p. 2600·2); calcium carbonic. (p. 1824·3).
Homoeopathic preparation.

Vibuzol *Sandoz, Arg.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Vica Natal Plus *Armoxindo, Indon.*
Vitamins; minerals.
Dietary supplement.

Vicair *Dalkhimfarm, Rus.; Farmstandart, Rus.; Valenta, Rus.; Arterium, Ukr.*
Bismuth subnitrate (p. 1822·1); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); frangula bark (p. 1843·3); calamus (p. 2464·2).
Gastritis; dyspepsia; peptic ulcer; gastric hyperacidity.

Vical *Molex Ayus, Indon.*
Vitamins; calcium gluconate (p. 1783·3); calcium hypophosphite (p. 2530·3); sodium hypophosphite (p. 2530·3); calcium glycerophosphate (p. 1783·3).
Vitamin supplement; calcium supplement.

Vicalin *Arterium, Ukr.*
Bismuth subnitrate (p. 1822·1); magnesium carbonate (p. 1856·2); calamus (p. 2464·2); sodium bicarbonate (p. 1781·1); frangula bark (p. 1843·3); khellin (p. 2538·1); rutoside (p. 2505·3).
Gastritis; dyspepsia; gastro-oesophageal reflux.

Farmstandart, Rus.
Calamus (p. 2464·2); bismuth subnitrate (p. 1822·1); khellin (p. 2538·1); buckthorn (p. 1824·2); magnesium carbonate (p. 1856·2); sodium bicarbonate (p. 1781·1); rutoside (p. 2505·3).
Peptic ulcer; gastric hyperacidity.

Vicalvit *Polfa Kutno, Pol.†*
Calcium carbonate (p. 1824·3).
Calcium supplement; osteoporosis.

Vicalvit D *Teva, Pol.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

Vica-Natal *Armoxindo, Indon.*
Vitamins; trace elements; calcium carbonate (p. 1824·3); iron (p. 2073·1).
Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Nutritional supplement; tonic.

Vi-Caps *Grossmann, Hong Kong.†*
Vitamins; minerals.

Vicard *Amdipharm, Austria.*
Terazosin hydrochloride (p. 1511·1).
Hypertension.

Vicardol *Penn, Arg.*
⊗Carvedilol (p. 1333·1).
Hypertension.

Viccillin *Meiji, Indon.; Meiji, Thai.†*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Viccillin-S *Meiji, Thai.†*
Ampicillin (p. 218·2); cloxacillin (p. 274·3).
Bacterial infections.

Viccillin-SX *Meiji, Indon.*
Sultamicillin (p. 369·1).
Bacterial infections.

Vi-Cê *Novartis, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Vicebrol *Biofarm, Cz.; Biofarm, Pol.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Vi-Cee *Doctors, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vicee *Prafa, Indon.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency; vitamin C supplement.

Vicef
Note: this name may be used for preparations of different composition.
Abolmed, Rus.
Ceftazidime (p. 250·2).
Bacterial infections.

Help, Gr.
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Vicefar *Biofarm, Pol.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vicefeno *Fabra, Arg.*
Dextropropoxyphene hydrochloride (p. 43·3) or dextropropoxyphene napsilate (p. 43·3); dipyrone (p. 53·3).
Pain.

Vicemycetin *Poly, China.*
Thiamphenicol (p. 376·3).
Genitourinary-tract infections.

Vicenrik *Fada, Arg.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

ViCetamol *Gebro, Hung.†*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Fever; pain.

Viceten *Bernofarm, Indon.†*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin A, C, and E deficiency.

Viceten-Z *Bernofarm, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc oxide (p. 1729·1); sodium selenite (p. 2087·1).
Dietary supplement.

Vichy Dercos Shampooing Antipelliculaire *Vichy, Fr.*
Selenium sulfide (p. 1719·3).
Dandruff.

Vici *Monico, Ital.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vick 44 *Procter & Gamble, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Vick 44 Exp *Procter & Gamble, Arg.; Procter & Gamble, Mex.*
Guaifenesin (p. 1666·2).
Cough.

Vick Inalador *Procter & Gamble, Braz.*
Camphor (p. 2466·2); menthol (p. 2553·2); methyl salicylate (p. 92·1); Siberian fir oil.
Nasal congestion.

Vick Pastilhas *Procter & Gamble, Braz.†*
Cineole (p. 2479·1); menthol (p. 2553·2); camphor (p. 2466·2); tolu balsam (p. 1679·2).

Vick Pyrena *Procter & Gamble, Braz.*
Paracetamol (p. 115·1); vitamin C (p. 2110·3).
Cold and influenza symptoms.

Vick Vaporub
Note: this name may be used for preparations of different composition.
Procter & Gamble, Braz.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar leaf oil (p. 2629·3); turpentine oil (p. 2636·3); thymol (p. 1772·2).
Nasal congestion.

Procter & Gamble, Mex.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Cold symptoms.

Vick Vaporub Inhalador *Procter & Gamble, Mex.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion; cold symptoms.

Vick Vaporub NF *Procter & Gamble, Arg.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Nasal congestion.

Vick Vitapyrena *Procter & Gamble, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Vick Vitapyrena Forte *Procter & Gamble, Arg.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Vick Xarope *Procter & Gamble, Braz.*
Guaifenesin (p. 1666·2).
Cough.

Vickamicron *Vickmans, Hong Kong.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Vick-Clarcid *Vickmans, Hong Kong.*
Clarithromycin (p. 266·2).
Bacterial infections.

Vickclor *Vickmans, Hong Kong.*
Cefaclor (p. 232·3).
Bacterial infections.

Vick-Flucan *Vickmans, Hong Kong.*
Fluconazole (p. 578·2).
Fungal infections.

Vick-Hexidine *Vickmans, Hong Kong.†*
Chlorhexidine (p. 1743·2).

Vickmiel *Procter & Gamble, Arg.*
Guaifenesin (p. 1666·2).
Cough.

Vickmodine *Vickmans, Hong Kong.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Vicknox *Vickmans, Hong Kong.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Vickolax *Vickmans, Hong Kong.†*
Chlorphenamine (p. 620·3); codeine (p. 40·2); papaverine (p. 2362·2).

Vicks *Famar, Gr.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine (p. 1676·1).

Vicks Acta Plus *Procter & Gamble, S.Afr.†*
Pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2); sodium citrate (p. 1781·2); chloroform (p. 1898·1); cetylpyridinium chloride (p. 1743·1).
Cough.

Vicks Acta Plus Expectorant *Procter & Gamble, S. Afr.†*
Guaifenesin (p. 1666·2).
Cough.

Vicks Action *Procter & Gamble, Irl.†*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms; sore throat.

Vicks Active Complete *Procter & Gamble, Pol.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms; cough.

Vicks Baby Balsam *Procter & Gamble, Austral.; Procter & Gamble, NZ.*
Eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); rosemary oil (p. 2607·3); aloe vera (p. 1693·2).
Nasal congestion.

Vicks Chest Congestion Relief *Procter & Gamble, Canad.*
Guaifenesin (p. 1666·2).

Vicks Children's NyQuil Allergy/Head Cold *Richardson-Vicks, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Upper respiratory-tract symptoms.

Vicks Children's Nyquil Cold & Cough *Procter & Gamble, Canad.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).

Vicks Children's NyQuil Cold & Cough Relief *Procter & Gamble, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Coughs and cold symptoms.

Vicks Cough Drops *Procter & Gamble, USA.*
Menthol (p. 2553·2).
Sore throat.

Vicks Cough Lozenges with Honey *Procter & Gamble (H&B Care), UK.*
Dextromethorphan (p. 1660·1).
Cough.

Vicks 44 Cough Relief *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Vicks Cough Syrup
Note: this name may be used for preparations of different composition.
Procter & Gamble, Austral.†
Pentoxyverine citrate (p. 1672·1); menthol (p. 2553·2).
Cough.

Procter & Gamble, S.Afr.†
Sodium citrate (p. 1781·2); citric acid (p. 2480·3); cetylpyridinium chloride (p. 1743·1).
Cough.

Vicks Cough Syrup for Chesty Cough *Procter & Gamble, Austral.*
Guaifenesin (p. 1666·2).
Cough.

Vicks Cough Syrup for Chesty Coughs *Procter & Gamble (H&B Care), UK.*
Guaifenesin (p. 1666·2).
Cough.

Vicks Cough Syrup with Honey for Dry Coughs *Procter & Gamble (H&B Care), UK.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Cough Syrup with Honey for Dry & Irritating Coughs *Procter & Gamble (H&B Care), UK.*
Levomenthol (p. 2553·2).
Cough.

Vicks Custom Care Body Aches *Procter & Gamble, Canad.*
Paracetamol (p. 115·1).
Fever; pain.

Vicks Custom Care Chest Congestion/Cough *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Vicks Custom Care Cough & Cold PM *Procter & Gamble, Canad.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1).
Cold symptoms; cough.

Vicks Custom Care Dry Cough *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Custom Care Nasal Congestion/Cough *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Cough; nasal congestion.

Vicks Daymed *Procter & Gamble (H&B Care), UK.*
Capsules: Paracetamol (p. 115·1); caffeine (p. 1203·3); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Procter & Gamble (H&B Care), UK.
Hot drink powder: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Vicks DayQuil Cold & Flu Multi-symptom Relief *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).

Vicks DayQuil Cough *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks DayQuil Mucus Control *Procter & Gamble, Canad.*
Guaifenesin (p. 1666·2).

Vicks Dayquil Mucus Control *Procter & Gamble, USA.*
Guaifenesin (p. 1666·2).
Cough.

Vicks DayQuil Mucus Control DM *Procter & Gamble, Canad.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks DayQuil Multi-Symptom Cold/Flu Relief *Procter & Gamble, USA.*
Phenylephrine hydrochloride (p. 1672·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, and paracetamol.
Coughs.

Vicks DayQuil Sinex *Procter & Gamble, USA.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Vicks DayQuil Sinus *Procter & Gamble, Canad.*
Phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Sinusitis; nasal congestion.

Vicks DayQuil Sinus & Pain Relief *Procter & Gamble, Canad.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); ibuprofen (p. 68·2).

Vicks DayQuil Sinus Pressure & Pain Relief *Procter & Gamble, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).

Vicks Decongestant *Procter & Gamble, S.Afr.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinorrhoea; sinusitis.

Vicks 44E *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Vicks Expectorant *Procter & Gamble, Fr.*
Guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Vicks Febbre e Dolore *Procter & Gamble, Ital.*
Ibuprofen sodium (p. 68·2).
Fever; pain.

Vicks Flu-Action *Procter & Gamble, Ital.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).
Cold and influenza symptoms.

Vicks Formula 44
Note: this name may be used for preparations of different composition.
Procter & Gamble, NZ.
Dextromethorphan hydrobromide (p. 1660·1); menthol (p. 2553·2).
Cough.

Procter & Gamble, Canad.†
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Formula 44 Chesty Cough *Procter & Gamble, Austral.†*
Guaifenesin (p. 1666·2).
Cough.

Vicks Formula 44 Custom Care Dry Cough *Procter & Gamble, USA.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Formula 44D Cough & Head Congestion Relief *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Coughs and cold symptoms.

Vicks Formula 44 Dry Cough *Procter & Gamble, Austral.†*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Formula 44E *Procter & Gamble, Canad.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Vicks Formula 44M *Procter & Gamble, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).
Cough and cold symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vicks Formula 44M Cough, Cold, & Flu Relief *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1).

Vicks Formule 44 Calmine *Procter & Gamble, Switz.†*
Dextromethorphan (p. 1660·1) or dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Hoestsiroop *Procter & Gamble, Neth.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Hoesttabletten *Procter & Gamble, Neth.*
Dextromethorphan (p. 1660·1).
Cough.

Vicks Inalador *Procter & Gamble, Port.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Vicks Inalante *Procter & Gamble, Ital.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); pine oil (p. 2591·1).
Nasal congestion.

Vicks Inhalador *Procter & Gamble, Spain.†*
Camphor (p. 2466·2); menthol (p. 2553·2).
Nasal congestion.

Vicks Inhaler
Note: this name may be used for preparations of different composition.
Procter & Gamble, Austral.; Procter & Gamble, NZ.
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); pumilio pine oil (p. 2591·1).
Nasal congestion.

Procter & Gamble, Canad.; Procter & Gamble, Gr.
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Procter & Gamble (H&B Care), UK.
Menthol (p. 2553·2); camphor (p. 2466·2); siberian fir oil.
Nasal congestion.

Procter & Gamble, Irl.
Menthol (p. 2553·2); camphor (p. 2466·2); pine needle oil.
Nasal congestion.

Procter & Gamble, Fr.
Camphor (p. 2466·2); menthol (p. 2553·2); Siberian fir oil; methyl salicylate (p. 92·1).
Nasal congestion.

Vicks Inhaler N *Procter & Gamble, Switz.*
Menthol (p. 2553·2); camphor (p. 2466·2); methyl salicylate (p. 92·1); pine needle oil.
Nasal congestion.

Vicks MediNait
Note: this name may be used for preparations of different composition.
Eczacibasi, Turk.
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Respiratory-tract congestion.

Vicks Medinait *Procter & Gamble, Ital.*
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Procter & Gamble, Switz.
⊗Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); ephedrine sulfate (p. 1663·2); paracetamol (p. 115·1).
Cold and influenza symptoms.

Vicks Medinite *Procter & Gamble (H&B Care), UK.*
⊗Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold symptoms.

Procter & Gamble, S.Afr.†
⊗Paracetamol (p. 115·1); ephedrine sulfate (p. 1663·2); doxylamine succinate (p. 627·3); dextromethorphan hydrobromide (p. 1660·1).
Cold and influenza symptoms.

Vicks Menthol Cough Drops *Procter & Gamble, USA.*
Menthol (p. 2553·2); thymol (p. 1772·2); eucalyptus oil (p. 2501·2); camphor (p. 2466·2); tolu balsam (p. 1679·2).
Sore throat.

Vicks Nature Fusion Cough *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Nature Fusion Cough & Chest Congestion *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Vicks 44 Non-Drowsy Cold & Cough LiquiCaps *Procter & Gamble, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).

Vicks Nyquil Cold & Flu *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); doxylamine succinate (p. 627·3).

Vicks NyQuil Cough *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cough.

Vicks NyQuil LiquiCaps *Richardson-Vicks, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); doxylamine succinate (p. 627·3).
Coughs and cold symptoms.

Vicks NyQuil Multi-Symptom Cold Flu Relief *Procter & Gamble, USA.*
Doxylamine succinate (p. 627·3); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold symptoms.

Vicks NyQuil Sinex *Procter & Gamble, USA.*
Phenylephrine hydrochloride (p. 1672·3); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Upper respiratory-tract disorders.

Vicks Nyquil Sinus *Procter & Gamble, Canad.*
Phenylephrine hydrochloride (p. 1672·3); doxylamine succinate (p. 627·3); paracetamol (p. 115·1).
Sinusitis; nasal congestion.

Vicks Original Cough Syrup Chesty *Procter & Gamble, Irl.*
Guaifenesin (p. 1666·2); cetylpyridinium chloride (p. 1743·1); sodium citrate (p. 1781·2).
Cough; upper respiratory-tract irritation.

Vicks Paracetamol *Procter & Gamble, Neth.*
Paracetamol (p. 115·1).
Pain; fever.

Vicks Pastihas *Procter & Gamble, Port.*
Dextromethorphan (p. 1660·1).
Cough.

Vicks Pastil *Eczacibasi, Turk.†*
Vitamin C (p. 2110·3).
Sore throat.

Vicks Pectoral *Procter & Gamble, Fr.*
Pentoxyverine citrate (p. 1672·1).
Cough.

Vicks Pediatric Formula 44 *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Pediatric Formula 44D *Procter & Gamble, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough and cold symptoms.

Vicks Pediatric Formula 44E *Procter & Gamble, Canad.; Richardson-Vicks, USA.†*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Vicks Pediatric Formula 44M *Procter & Gamble, Canad.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cold symptoms.

Vicks Pediatric Formula 44M Cough & Cold Relief *Procter & Gamble, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).
Coughs and cold symptoms.

Vicks Sinex
Note: this name may be used for preparations of different composition.
Procter & Gamble, Austral.; Procter & Gamble, Belg.; Procter & Gamble, Canad.; Procter & Gamble, Fin.; Procter & Gamble, Irl.; Procter & Gamble, Neth.; Procter & Gamble, Swed.; Procter & Gamble (H&B Care), UK.
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; rhinitis; rhinopharyngitis.

Procter & Gamble (H&B Care), UK.
Capsules: Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Cold and influenza symptoms.

Procter & Gamble, Ital.; Procter & Gamble, NZ†; Procter & Gamble, Switz.
⊗Oxymetazoline hydrochloride (p. 1671·3); menthol (p. 2553·2); camphor (p. 2466·2); cineole (p. 2479·1).
Cold symptoms; nasal congestion.

Vicks Sinex 12-Hour *Procter & Gamble, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Formerly known as Sinex Long Acting.
Nasal congestion.

Vicks Sirop Expectorant *Procter & Gamble, Switz.*
Guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Vicks Spray *Procter & Gamble, Spain.†*
⊗Oxymetazoline hydrochloride (p. 1671·3); menthol (p. 2553·2).
Nasal congestion.

Vicks SymptoMed *Procter & Gamble, Cz.*
Paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms.

Vicks SymptoMed Complete *Procter & Gamble, Cz.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms; cough.

Vicks Throat Drops *Procter & Gamble, NZ.*
Menthol (p. 2553·2).

Vicks Tosse Fluidificante *Procter & Gamble, Ital.*
Guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Vicks Tosse Pastiglie *Procter & Gamble, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Tosse Sedativo *Procter & Gamble, Ital.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Toux Sèche *Procter & Gamble, Fr.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Procter & Gamble, Switz.
Dextromethorphan (p. 1660·1) or dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks TriActin Complete *Procter & Gamble, Cz.*
Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Influenza symptoms; cough.

Vicks Vapo Expectorant *Eczacibasi, Turk.*
Guaifenesin (p. 1666·2).
Cough.

Vicks Vapo Steam *Kaz, Canad.†*
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); lavender oil (p. 2541·1); menthol (p. 2553·2); methyl salicylate (p. 92·1); peppermint oil (p. 1877·1).

Vicks VapoDrops *Procter & Gamble, Canad.*
Menthol (p. 2553·2).
Throat irritation.

Vicks Vapodrops *Procter & Gamble, NZ.*
Menthol (p. 2553·2).

Vicks Vapodrops Blue Peppermints *Procter & Gamble, Austral.†*
Menthol (p. 2553·2); peppermint oil (p. 1877·1).
Throat irritation.

Vicks Vapodrops Butter and Menthol *Procter & Gamble, Austral.†*
Menthol (p. 2553·2).
Nasal congestion; sore throat.

Vicks Vapodrops Original *Procter & Gamble, Austral.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).
Nasal congestion; sore throat.

Vicks VapoDry *Eczacibasi, Turk.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Vicks Vapomist *Procter & Gamble, S.Afr.†*
Sodium chloride (p. 1795·1).
Nasal congestion.

Vicks Vapor Inhaler *Procter & Gamble, USA.*
⊗Levmetamfetamine (p. 1668·3).
Nasal congestion.

Vicks VapoRub
Note: this name may be used for preparations of different composition.
Procter & Gamble, Canad.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2).
Cold symptoms.

Vicks Vaporub
Note: this name may be used for preparations of different composition.
Procter & Gamble, Austral.; Procter & Gamble, Belg.; Procter & Gamble, Fr.; Procter & Gamble, S.Afr.†; Eczacibasi, Turk.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); nutmeg oil (p. 2573·2); cedar leaf oil (p. 2629·3); thymol (p. 1772·2); turpentine oil (p. 2636·3).
Cold symptoms; muscle pain; rhinitis; rhinopharyngitis; sinusitis; catarrh; nasal congestion.

Procter & Gamble, Fin.; Procter & Gamble, Gr.; Procter & Gamble, Neth.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); thymol (p. 1772·2).
Cold and influenza symptoms.

Procter & Gamble, Irl.; Procter & Gamble, Ital.; Procter & Gamble, Port.; Procter & Gamble (H&B Care), UK.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Nasal congestion; respiratory-tract congestion; sore throat; cough.

Procter & Gamble, NZ; Procter & Gamble, Swed.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); nutmeg oil (p. 2573·2); cedar wood oil (p. 2472·3); thymol (p. 1772·2).
Nasal congestion; cold and influenza symptoms.

Procter & Gamble, USA.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); cedar leaf oil (p. 2629·3); nutmeg oil (p. 2573·2); turpentine oil (p. 2636·3).

Vicks, Spain.
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine; thymol (p. 1772·2).
Upper-respiratory-tract disorders.

Vicks Vaporub N *Procter & Gamble, Switz.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); nutmeg oil (p. 2573·2); cedar leaf oil (p. 2629·3); thymol (p. 1772·2).
Upper respiratory-tract disorders.

Vicks Vapospray *Procter & Gamble, Gr.; Procter & Gamble, Port.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Vicks VapoSyrup
Note: this name may be used for preparations of different composition.
Eczacibasi, Turk.
Guaifenesin (p. 1666·2).
Respiratory-tract congestion.

Vicks Vaposyrup Antitussif *Procter & Gamble, Belg.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Vaposyrup for Chesty Coughs *Procter & Gamble (H&B Care), UK.*
Guaifenesin (p. 1666·2).
Coughs.

Vicks Vaposyrup for Dry Coughs *Procter & Gamble (H&B Care), UK.*
Dextromethorphan hydrobromide (p. 1660·1).
Coughs.

Vicks Vaposyrup Expectorant *Procter & Gamble, Belg.*
Guaifenesin (p. 1666·2).
Cough.

Vicks Vaposyrup for Tickly Coughs *Procter & Gamble (H&B Care), UK.*
Menthol (p. 2553·2).
Coughs.

Vicks Vapour Inhaler *Procter & Gamble, Canad.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Nasal congestion.

Vicks Victors Dual Action Cough Drops *Richardson-Vicks, USA.*
Menthol (p. 2553·2); eucalyptus oil (p. 2501·2).

Vicks Vitamin C Orange *Procter & Gamble, Canad.*
Ascorbic acid (p. 2110·3).

Vicks Xarope Antitussico *Procter & Gamble, Port.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Vicks Xarope Expectorante *Procter & Gamble, Port.*
Guaifenesin (p. 1666·2).
Cough.

Vicktaline *Vickmans, Hong Kong.†*
⊗Terbutaline (p. 1228·1).

Vick-Tec *Vickmans, Hong Kong.†*
Cetirizine (p. 619·2).

Vick-Thiaden *Vickmans, Hong Kong.*
Dosulepin hydrochloride (p. 414·1).
Depression.

Vicktilin *Vickmans, Hong Kong.†*
Domperidone (p. 1838·1).

Vicktilium *Vickmans, Hong Kong.†*
Domperidone (p. 1838·1).

Vick-Zocostatin *Vickmans, Hong Kong.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Vick-Zyrt *Vickmans, Hong Kong.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Viclofen *Sandoz, Austral.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Viclofenac *Vickmans, Hong Kong.†*
Diclofenac (p. 48·3).

Viclor *Richet, Arg.*
Paracetamol (p. 115·1).
Fever; pain.

Viclor Grip *Richet, Arg.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3); levophenylephrine hydrochloride (p. 1672·2).
Cold and influenza symptoms.

Viclоran *Cryopharma, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viclovir *Precimex, Mex.*
Aciclovir sodium (p. 964·1).
Herpesvirus infections.

Vicloxa *United Drug, Thai.*
Cloxacillin sodium (p. 275·1).
Staphylococcal infections.

Vicmafen *Offenbach, Mex.†*
Diclofenac diethylamine (p. 48·3).
Inflammation.

Vicodin *AbbVie, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Vicodin Tuss *Abbott, USA.*
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Coughs.

Vicodrine *Vickmans, Hong Kong.†*
⊗Pseudoephedrine (p. 1676·1).

Vicog *Marjan, Braz.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders.

Vicombil *Bial, Port.*
Vitamins.

Vicomin A C *Omega, Spain.*
Ascorbic acid (p. 2110·3); vitamin A palmitate (p. 2098·3).
Deficiency of vitamins A and C.

Vicon *UCB, USA.†*
Vitamins; with or without minerals.

Vicoprofen *Abbott, USA.*
Hydrocodone tartrate (p. 67·2); ibuprofen (p. 68·2).
Pain.

Vicotrum *Graha, Indon.*
Bovine colostrum (p. 2380·3); vitamins.
Dietary supplement.

Vicrom *Aventis, NZ.*
Sodium cromoglicate (p. 1225·3).
Asthma.

Vicromil *Recalcine, Chile.†*
⊗Goserelin (p. 2282·3).

Victan *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Mex.; Sanofi-Aventis, Port.; Sanofi Synthelabo, Thai.†*
Ethyl loflazepate (p. 1073·1).
Psychosomatic disorders; sleep disorders; alcohol withdrawal syndrome; anxiety; panic disorder; social phobia; obsessive-compulsive disorder.

Victoza *Novo Nordisk, Arg.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Canad.; Novo Nordisk, China; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Ger; Novo Nordisk, Gr.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Jpn; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, UK; Novo Nordisk, Ukr.; Novo Nordisk, USA.*
Liraglutide (p. 488·2).
Diabetes mellitus.

Victrelis *MSD, Austral.; MSD, Belg.; MSD, Denm.; MSD-Chibret, Fr.; MSD, Ger.; MSD, Irl.; MSD, Israel; MSD, Neth.; MSD, Norw.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, UK; Merck, USA.*
Boceprevir (p. 969·1).
Chronic hepatitis C.

Victrix *Farmasa, Braz.*
Omeprazole (p. 1867·2) or omeprazole sodium (p. 1867·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Vi-D3 *Berko, Turk.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Vida Cough *Vida, Hong Kong.†*
Chlorphenamine maleate (p. 620·3); bromhexine hydrochloride (p. 1656·3); pentoxyverine citrate (p. 1672·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms; cough.

Vida Famodine *Vida, Hong Kong.†*
Famotidine (p. 1842·1).
Peptic ulcer; gastrointestinal haemorrhage; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Vida Flatugel *Vida, Hong Kong.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastrointestinal disorders.

Vida Neurotab *Vida, Hong Kong.†*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuralgia; neuritis; muscle and joint pain.

Vida Salirub *Vida, Hong Kong.†*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eucalyptus oil (p. 2501·2); cajuput oil (p. 2464·1).
Muscle pain; soft-tissue disorders; insect bites; pruritus.

Vida-Butaline *Vida, Hong Kong.†*
⊗Terbutaline sulfate (p. 1228·1).
Asthma; chronic bronchitis.

Vidaclofen-Plus *Vida, Hong Kong.†*
Diclofenac sodium (p. 48·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Musculoskeletal, joint, and soft-tissue disorders; neuritis; neuralgias.

Vidaclovir *Vida, Hong Kong.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vidadrine *Vida, Hong Kong.†*
⊗Pseudoephedrine (p. 1676·1).
Allergic rhinitis; nasal congestion.

Vi-Dailin *Abbott, Port.*
Vitamins.

Vidalat *Vida, Hong Kong.†*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Vidalidine *Vida, Hong Kong.†*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; cold and influenza symptoms.

Vidamil *Alpharma, Mex.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1).
Skin disorders; respiratory-tract infections.

Vidan *Vianex (Βιανεξ), Gr.*
Mefenamic acid (p. 85·3).
Pain; inflammation; musculoskeletal and joint disorders.

Vidaperamide *Vida, Hong Kong.†*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Vidapirocam *Vida, Hong Kong.†*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders.

Vidapril *Angelfarma, Port.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Vidaspan *Vida, Hong Kong.†*
Hyoscine butylbromide (p. 1845·3).
Smooth muscle spasm.

Vidastat *Therapharma, Hong Kong; Darya-Varia, Indon.; Therapharma, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease; hyperlipidaemias; cardiovascular risk reduction; atherosclerosis.

Vidatapp *Vida, Hong Kong.†*
Brompheniramine maleate (p. 618·1) phenylephrine hydrochloride (p. 1672·3) phenylpropanolamine hydrochloride (p. 1674·1).
Cold and influenza symptoms.

Vidatapp Forte *Vida, Hong Kong.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3); bromhexine hydrochloride (p. 1656·3); paracetamol (p. 115·1).
Cold and influenza symptoms; rhinitis.

Vidatifen *Vida, Hong Kong.†*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Vidatril *Vida, Hong Kong.†*
Glucosamine sulfate (p. 2515·3).
Rheumatic disorders.

Vi-Daylin *Abbott, Malaysia.*
Vitamins; with or without minerals and choline (p. 2055·2), inositol (p. 2533·2), or lysine (p. 2079·3).

Adcock Ingram Consumer, S.Afr.
Vitamins; with or without minerals.

Fako, Turk.; Ross, USA.
Vitamins.

Abbott, NZ.†
Vitamins; minerals.

Abbott, Canad.†
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).

Vidaylin *Pharmacia, India; Abbott, Philipp.*
Vitamins; minerals.
Nutritional supplement.

Abbott, Singapore.
Vitamins; with or without minerals.

Vidaylin L *Abbott, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3); choline (p. 2055·2); inositol (p. 2533·2).
Nutritional supplement; tonic.

Vi-Daylin with Lysine *Abbott, Hong Kong.*
Vitamins; lysine (p. 2079·3).

Vidaylin MiniBear *Abbott, Singapore.*
Protein; carbohydrate; vitamin C (p. 2110·3); spinach; tomato; carrot; beetroot; cynara (p. 2490·3).

Vi-Daylin plus Iron *Abbott, Israelt; Adcock Ingram Consumer, S.Afr.*
Vitamins; iron (p. 2073·1).

Vi-Daylin/F *Ross, USA.*
Vitamins; fluoride (p. 2089·2).

Vidaza *Celgene, Austral.; Celgene, Austria; Celgene, Belg.; United Medical, Braz.; Celgene, Canad.; Celgene, Cz.; Celgene, Denm.; Celgene, Fr.; Celgene, Ger.; Celgene, Gr.; IFET (ΙΦΕΤ), Gr.; Celgene, Hong Kong; Celgene, Irl.; Neopharm, Israel; Celgene, Ital.; Shinyaku, Jpn; Celgene, Malaysia; Celgene, Neth.; Celgene, Norw.; Celgene, NZ; Pharmion, Philipp.; Celgene, Pol.; Celgene, Port.; Key Oncologics, S.Afr.; Celgene, Singapore; Celgene, Spain; Celgene, Swed.; Celgene, Switz.; Celgene, Thai.; Er-Kim, Turk.; Celgene, UK; Celgene, USA.*
Azacitidine (p. 745·2).
Myelodysplastic syndromes; acute myeloid leukaemia; chronic myeloid leukaemia.

Vid-COMOD *Ursapharm, Rus.*
Povidone (p. 2204·3).
Dry eyes.

Vi-De$_3$ *Wabosan, Austria; Wild, Switz.*
Colecalciferol (p. 2113·1).
Rickets; osteomalacia; vitamin D_3 supplement.

Vi-Dea-C *Degorts, Mex.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); ascorbic acid (p. 2110·3).

Videcalcio *Venifer, Gr.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Calcium and vitamin D deficiency.

Videne *Adams, Hong Kong; Ecolab, Irl.; Ecolab, Thai.; Adams, UK.*
Povidone-iodine (p. 1767·1).
Wounds; burns; hand and skin disinfection.

Video-Light *Wealth, Ital.*
Benzalkonium chloride (p. 1737·1).
Eye disinfection.

Vidermina *Ganassini, Ital.*
Copper usnate (p. 2640·2).
Vaginal disinfection.

Videstim *Retinoids, Rus.*
Vitamin A palmitate (p. 2098·3).
Skin disorders.

Videx *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, China; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.†; BMS, Irl.; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, Neth.; BMS, Norw.; BMS, NZ; BMS, Pol.†; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS, USA; BMS, Venez.*
Didanosine (p. 972·3).
HIV infection.

Vidilac *Kite (Κιτε), Gr.*
Hypromellose (p. 2189·2).
Dry eyes.

Vidintal *Tunggal Idaman, Indon.†*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Vidisep *Kimia, Indon.*
Povidone-iodine (p. 1767·1).
Wounds; burns.

Vidisept *Mann, Ger.; Mann, Pol.*
Povidone (p. 2204·3).
Dry eyes.

Vidisept N *Bausch & Lomb, Philipp.; Mann, Singapore.†*
Povidone (p. 2204·3).
Dry eyes; eye irritation.

Vidisic *Agepha, Austria; Bausch & Lomb, Belg.; Bausch & Lomb, Braz.; Mann, China; Mann, Cz.; Mann, Ger.; Mann, Hung.; Pharma-Global, Irl.; Bausch & Lomb, Neth.; Bausch & Lomb, Philipp.; Mann, Pol.; Angelini, Port.; Bausch & Lomb, Rus.; Bausch & Lomb, Singapore; Mann, Singapore; Bausch & Lomb, Thai.; Bausch & Lomb, Ukr.*
Carbomer (p. 2173·3).
Dry eyes.

Vidisic PVP *Bausch & Lomb, Neth.*
Povidone (p. 2204·3).
Dry eyes.

Vidokcine *Abolmed, Rus.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Vidora *Leurquin, Fr.*
Indoramin hydrochloride (p. 1410·2).
Migraine.

Vidoran *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamins; minerals.
Dietary supplement.

Vidoran Emulsion Rasa *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamins; cod-liver oil (p. 2056·3); turmeric (p. 2218·1); calcium hypophosphite (p. 2530·3).
Dietary supplement; tonic.

Vidoran Imun Up *Bode, Indon.; Tempo Scan Pacific, Indon.*
Echinacea (p. 2498·1); vitamin C (p. 2110·3).
Immunostimulant.

Vidoran Plus *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamins; lysine hydrochloride (p. 2079·3); turmeric (p. 2218·1).
Dietary supplement; tonic.

Vidoran Smart *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamins; taurine (p. 2626·2).
Dietary supplement.

Vidoran Smart Plus *Bode, Indon.; Tempo Scan Pacific, Indon.*
Oral syrup: Vitamins; docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Dietary supplement for children.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Bode, Indon.; Tempo Scan Pacific, Indon.
Tablets: Vitamins; taurine (p. 2626·2); docosahexaenoic acid (p. 1460·1).
Dietary supplement for children.

Vidotin *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.*
Perindopril erbumine (p. 1467·1).
Hypertension; heart failure; cardiovascular risk reduction.

Vidovir *Vida, Port.†*
Aciclovir (p. 964·1).

Vidox *Veinfar, Arg.*
Mupirocin (p. 327·2).
Bacterial skin infections.

Vidyn *Sigma, Braz.*
Vitamins; minerals.

Vieby *Wermar, Mex.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

VienOks *Toprak, Turk.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

ViePax *Dexcel, Singapore.†*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Viepax *Dexcel, Israel.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia.

Viessia *Teva, Mex.; Lemery, Thai.; Teva, Thai.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Vieta *Bunker, Braz.*
dl-Alpha tocoferil acetate (p. 2119·2).

View *Fischer, Israel.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Viewgam *Bacon, Arg.; Landsteiner, Mex.†*
Meglumine gadopentetate (p. 1586·1).
Contrast medium for magnetic resonance imaging.

Viewgel *Taiho, Jpn.*
Hydrogel wound dressing.

Vifaderm *Vianex (Βιανεξ), Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Vifas *Siam Bheasach, Thai.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Vifazolin *Vianex (Βιανεξ), Gr.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Vifenac *Pan-Ject, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Vifor, Switz.
Diclofenac epolamine (p. 48·3) or diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Vi-Fer *Deva, Turk.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B substances (p. 2102·3). Vitamin C (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Viferon *Feron, Rus.; Feron, Ukr.*
Interferon alpha-2b (recombinant) (p. 989·2).
Infectious and inflammatory diseases.

Vi-Ferrin *Elofar, Braz.*
Iron chelate (p. 2073·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).
Iron deficiency; iron-deficiency anaemias.

Viferron *Kalbe, Indon.*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).
Vitamin and mineral deficiencies.

Viflox *Tropica Mas, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Vifloxina *Vitae, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Viforcit *Nikolakopoulos, Gr.*
Ascorbic acid (p. 2110·3).

Vifortol *Elea, Arg.*
Vitamins; minerals; ginseng (p. 2513·3).
Dietary supplement.

Vifortol Prenatal *Elea, Arg.*
Vitamins; ferrous sulfate (p. 2062·2); calcium carbonate (p. 1824·3).
Nutritional supplement in pregnancy and lactation.

ViG *Key, Austral.*
Tablets: Guarana (p. 2648·2); ginseng (p. 2513·3); ginkgo biloba (p. 2512·3).
Tonic.

Vigadexa *Alcon, Arg.*
⊗Moxifloxacin hydrochloride (p. 326·3); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections with inflammation.

Alcon, Thai.
⊗Moxifloxacin hydrochloride (p. 326·3); dexamethasone phosphate (p. 1631·1).
Bacterial eye infections; eye inflammation and infection following surgery.

Vigam *GP, Arg.; BPL, Israel; Bio Products, Malaysia; Landsteiner, Mex.; BPL, Singapore; BPL, Thai.; Sodhan, Turk.; BPL, UK.*
A normal immunoglobulin (p. 2403·3).
Immune thrombocytopenia; immunodeficiency; Kawasaki disease; hypogammaglobulinaemia; agammaglobulinaemia; Guillain-Barré syndrome; bone marrow transplantation; Wiskott-Aldrich syndrome; passive immunisation.

Vigamed *Cimed, Braz.*
Phentolamine mesilate (p. 1468·3).
Erectile dysfunction.

Vigamox *Alcon, Arg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Indon.; Alcon, Irl.†; Alcon, Israel; Alcon, Malaysia; Alcon, Neth.; Alcon, NZ; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, USA; Alcon, Venez.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections; eye sterilisation in ocular surgery.

Vigamoxi *Alcon, Mex.*
Moxifloxacin hydrochloride (p. 326·3).
Bacterial eye infections.

Vigantol *Merck, Cz.; Merck Serono, Ger.; Merck, Hung.; Merck, Pol.; Merck, Port.; Nycomed, Rus.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency; rickets; osteomalacia; hypoparathyroidism; osteoporosis; spasmophilia; osteopathy; hypocalcaemia; tetanus; pseudohypoparathyroidism.

Vigantoletten *Merck Serono, Ger.; Merck, Pol.*
Colecalciferol (p. 2113·1).
Rickets; osteomalacia; osteoporosis; vitamin D deficiency.

Vigarol *Vickmans, Hong Kong.†*
Liquid paraffin (p. 2191·2).
Constipation.

Vigasil *Loeffler, Mex.*
Miconazole nitrate (p. 589·1).
Fungal vulvovaginal infections.

Vi-Gel *Diamond, Philipp.*
Indometacin (p. 71·2).
Inflammation; pain.

Vigencial *Estedi, Spain.*
Methylrosanilinium chloride (p. 1761·1).
Skin infections.

Vigicer *Beta, Arg.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Vigil *Torrex Chiesi, Cz.; Teva, Ger.; Torrex Chiesi, Hung.; Torrex Chiesi, Pol.†*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome.

Vigilia *Grands Espaces, Fr.†*
Tilia (p. 2631·3); vervain (p. 2645·1).
Nervous disorders.

Vigitem *Home, Port.†*
Lidocaine hydrochloride (p. 1988·2); zinc oxide (p. 1729·1).
Haemorrhoids.

Vigocid *YSS, Philipp.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Vigofortal *Pasteur, Chile.†*
⊗Strychnine sulfate (p. 2623·2); sodium phosphate (p. 1791·2); potassium phosphate (p. 1791·1); phosphoric acid (p. 2589·1).
Asthenia; tonic.

Vigogel *Bioetrusca, Ital.*
Royal jelly (p. 2608·1); liver extract (p. 2444·1); dried yeast (p. 2125·2).

Vigomar Forte *Marlop, USA.*
Vitamins; minerals.

Vi-Gor *Marching, Hong Kong.†*
Vitamins.

Vigor
Note: this name may be used for preparations of different composition.
Herbamed, Switz.
Siberian ginseng (p. 2614·3).
Tonic.

US Pharmacia, Pol.†
Vitamins; minerals.

Vigor Plus
Note: this name may be used for preparations of different composition.
Ariston, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vigor-ACE *United American, Philipp.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1); lecithin (p. 2542·2).
Nutritional supplement.

Vigor-Ace *United American, Singapore.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3); zinc (p. 2126·1); lecithin (p. 2542·2).
Tonic.

Vigoran
Note: this name may be used for preparations of different composition.
Konsuma, Venez.
Ginseng (p. 2513·3); vitamins; minerals.
Tonic.

Vigorex *Volta, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vigortol *Rugby, USA.†*
Vitamin B substances (p. 2102·3); minerals.

Vigorup *Heremco, Gr.*
Levocarnitine (p. 2053·2).

Vigorvit *Vamsler, Philipp.*
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3); chlorella growth factor (p. 2475·3).
Nutritional supplement.

Vigrande *Zentiva, Cz.; Zentiva, Pol.; Eczacibasi, Turk.; Sanofi-Aventis, Ukr.; Zentiva, Ukr.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vigranon B *Wallace Mfg Chem., UK.*
Vitamin B substances (p. 2102·3).

Vigrasol *Giempi, Venez.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Vigueur *Marching, Hong Kong.†*
Cyproheptadine (p. 624·1); vitamins.

Viibryd *Trovis, USA.*
Vilazodone hydrochloride (p. 457·2).
Depression.

Vikatron *Ariston, Braz.*
Phytomenadione (p. 2122·2).

Vikela *Sanova, Austria; Perryment, Neth.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Viken *Kendrick, Mex.†*
Cefotaxime sodium (p. 244·1). Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Viketo *Invent, Port.†*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Viking *Rafarm, Gr.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Vikonon *Neo Laboratories, UK.*
Calcium glycerophosphate (p. 1783·3); calciferol (p. 2113·3); thiamine hydrochloride (p. 2103·1); α-tocoferil acid succinate (p. 2119·3).
Vitamin supplement.

Vikool *UnitedDrug, Thai.*
Paracetamol (p. 115·1).
Fever; pain.

Vikrol *Mavi, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Vilacril *Leovan, Gr.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Viladil *Berlin Pharm, Thai.†*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Viladol Plus *Loeffler, Mex.*
Hyoscine butylbromide (p. 1845·3); paracetamol (p. 115·1).
Smooth muscle pain and spasm.

Viladol-Met *Loeffler, Mex.†*
Hyoscine butylbromide (p. 1845·3); dipyrone (p. 53·3).

Vilan *Lannacher, Austria; Lannacher, Denm.; Synmedic, Switz.*
Nicomorphine hydrochloride (p. 101·1).
Pain; smooth muscle spasm; premedication.

Vilapon *Metiska, Indon.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; gastro-oesophageal reflux.

Vilarib *ICN, Neth.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Vilbitan *Stada, Port.†*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vilcolut *Vilco, Gr.*
Norethisterone (p. 2294·2).
Menstrual disorders; hormone replacement therapy; oral contraceptive; endometriosis; hirsutism; malignant neoplasms; female infertility.

Vilconir *Stada, Neth.†*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Vilerm *Siam Bheasach, Thai.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Vilgendra *Actavis, Neth.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Viliron *Otto, Indon.*
Vitamin B substances (p. 2102·3); liver extract (p. 2444·1); iron (p. 2073·1); copper (p. 2057·1).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron. Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Tonic.

Vilne *Dosa, Arg.*
Vinorelbine (p. 885·3).
Malignant neoplasms.

ViloFane-Dp *Seton, USA.*
Levomefolate.

Vilona *Valeant, Mex.*
Ribavirin (p. 1010·2).
Viral infections.

Vilonit *Kleva, Gr.*
Diclofenac sodium (p. 48·3) or diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; eye inflammation.

Vilox *Behrens, Venez.*
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Antioxidant for eye health.

Vilpin *Teva, Pol.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Viltar *Dallas, Arg.*
Loperamide (p. 1854·2).
Diarrhoea.

Vilvom *Medimar, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Vi-Magna *Wyeth, India.*
Vitamins.

Vimax
Note: this name may be used for preparations of different composition.
Roemmers, Arg.; Roemmers, Chile; Sandoz, Indon.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vimetrol *Vamsler, Philipp.†*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Vimifor Multivitamin with Beta-Carotene *NBTY, Ukr.†*
Betacarotene (p. 2051·1); pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2); biotin (p. 2052·2); pantothenic acid (p. 2085·2); calcium phosphate (p. 1784·2); calcium carbonate (p. 1824·3); ferrous fumarate (p. 2060·3); potassium iodide (p. 2336·3); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); sodium selenate (p. 2087·1); copper oxide (p. 2057·1); manganese sulfate (p. 2081·2); chromium trichloride (p. 2055·3); sodium molybdate (p. 2082·3); potassium chloride (p. 1793·2).
Vitamin and mineral supplement.

Vimin *Berko, Turk.*
Vitamins; minerals.

Viminate *Barre-National, USA.*
Vitamins; minerals.

Vi-Mineral *Deva, Turk.*
Vitamins; minerals.

Vimineral *Offenbach, Mex.†*
Vitamins; minerals.

Viminfort *Solfran, Mex.*
Vitamins; minerals.

Vimoli *Vitamed, Israel.†*
Paracetamol (p. 115·1).
Fever; pain.

Vimonzil *Yung Shin, Philipp.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Vimotadine *Casasco, Arg.*
Codergocrine (p. 389·2).
Cerebrovascular disorders; mental function impairment.

Vimovo *AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK; AstraZeneca, USA.*
Naproxen (p. 98·2).
Esomeprazole (p. 1841·1) or esomeprazole magnesium (p. 1841·1) is included in this preparation to reduce the risk of NSAID-associated gastric ulcer.
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Vimpat *HLB, Arg.; UCB, Austral.; UCB, Austria; UCB, Belg.; UCB, Canad.; UCB, Cz.; UCB, Denm.; UCB, Fr.; UCB, Ger.; UCB, Gr.; UCB, Irl.; UCB, Israel; UCB, Neth.; UCB, Norw.; CSL, NZ; UCB, Pol.; UCB, Port.; UCB, Rus.; UCB, Spain; UCB, Swed.; UCB, Switz.; UCB, UK; UCB, Ukr.; UCB, USA.*
Lacosamide (p. 526·3).
Epilepsy.

Vimultisa *Fabra, Arg.*
Diclofenac potassium (p. 48·3).
Inflammation.

Vimultisa Flex *Fabra, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).

Vin *Patar, Thai.*
Simeticone (p. 1886·2).
Flatulence.

Vinafluor *Nicholas, Indon.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Vinalac *Novogen, UK.*
Lactobacillus rhamnosus (p. 2596·3); vitamins; minerals.
Dietary supplement in pregnancy and breast feeding.

Vinarine *LKM, Arg.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Vinatal *Triomed, S.Afr.†; British Dispensary, Thai.*
Vitamins; minerals.

Vinate DHA *Breckenridge, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1).

Vinate GT *Breckenridge, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.

Vinate IC *Breckenridge, USA.*
Vitamins; minerals.
Dietary supplement.

Vinatin *Meizler, Braz.*
Vinblastine sulfate (p. 881·3).

Vinblasin *Teva, Belg.†*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Vincacen *Medizin, Spain.†*
Vincamine hydrochloride (p. 2645·2).
Cerebrovascular disorders; cerebral trauma; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Vincaminor *Synthelabo Lavipharm, Gr.*
Vincamine (p. 2645·2).

Vincapan *Sanofi-Aventis, Mex.*
Vincamine (p. 2645·2).
Cerebrovascular disorders.

Vincarutine *SERP, Mon.*
Vincamine (p. 2645·2); rutoside (p. 2505·3).
Mental function impairment in the elderly.

Vincasar PFS *Sicor, USA.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vincatera *Tuteur, Rus.*
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small cell lung cancer.

Vinca-Treis *Ecobi, Ital.*
Vincamine (p. 2645·2).
Cerebrovascular disorders.

Vinceel H *Heel, Neth.*
Apis mellifica (p. 2445·2); belladonna (p. 2453·3); calendula officinalis (p. 2465·2); echinacea purpurea (p. 2498·1); phytolacca decandra (p. 2593·2); plantago major (p. 2592·3); salvia officinalis (p. 2608·3); vincetoxicum officinale.
Homoeopathic preparation.

Vinces *Ivax, Arg.†*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vincetin *Farmstandart, Rus.†*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; vascular eye disorders; vestibular disorders.

Vincidal *Rayere, Mex.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Vincigrip *Salvat, Spain.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1); paracetamol (p. 115·1).
Cold and influenza symptoms; pain; fever.

Vinciseptil Otico *Salvat, Spain.*
⊗Benzydamine hydrochloride (p. 29·2); fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3); tetracaine hydrochloride (p. 1996·3).
Ear disorders.

Vincitos *Salvat, Spain.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1).
Cough; cold symptoms.

Vincizina *Pfizer, Braz.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vincosedan *Nupel, Spain.*
Diazepam (p. 1063·2).
Contains pyridoxine.
Anxiety; convulsions; skeletal muscle spasm; spasticity; alcohol withdrawal syndrome.

Vincrisin *Teva, Belg.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vincrisul *Stada, Spain.†*
Vincristine sulfate (p. 882·3).
Immune thrombocytopenia; malignant neoplasms.

Vindacin *Best, Mex.*
Sulindac (p. 134·2).
Gout; musculoskeletal and joint disorders; inflammation; pain.

Vinecort *Genepharm, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis; skin disorders.

Vinelbin *Fresenius Kabi, Rus.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer; prostatic cancer.

Vinelbine *Dabur, India.*
Vinorelbine (p. 885·3).
Non-small-cell lung cancer; breast cancer.

Fresenius Kabi, Thai.†
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small cell lung cancer.

Vinera *Ativus, Braz.*
Grape (p. 2521·3).
Capillary disorders.

Vinerton *Pyridam, Indon.*
Vitamins; minerals.
Dietary supplement.

Vineuron *Vamsler, Philipp.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuralgia; neuropathy; vitamin B deficiency.

Vingional *Fabra, Arg.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer.

Vingraf *Emcure, Philipp.*
Tacrolimus (p. 1968·3).
Transplant rejection.

Vinicard *Lehning, Fr.†*
Camphora (p. 2466·2); nux vomica (p. 2573·3); ignatia (p. 2532·1); veratrum album (p. 2644·3); ammonium chloricum (p. 1656·1); digitalis purpurea (p. 1352·3); aurum muriaticum natronatum (p. 2521·2); cactus grandiflorus (p. 2473·2); cascarilla.
Homoeopathic preparation.

Vinilex *Alternavida, Mex.*
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small cell lung cancer.

Vinitus *Rafarm, Gr.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma.

Vinkebir *Aspen, Arg.*
Vinorelbine (p. 885·3).

Vinkhum *Frasca, Arg.*
Vincamine (p. 2645·2).
Cerebrovascular disorders; vestibular disorders.

Vinko *Kocak, Turk.*
Vinblastine (p. 881·3).

Vino Nordin Vitaminado *Nordin, Mex.*
Vitamin B substances (p. 2102·3).

Vinocard Q10 *Marjan, Braz.*
Ubidecarenone (p. 2637·1).
Co-enzyme Q10 deficiency.

Vinorel *Capsifar, Port.; Pharmaplan, S.Afr.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer.

Eriochem, Arg.
Vinorelbine (p. 885·3).
Malignant neoplasms.

Vinorgen *Bioprofarma, Arg.*
Vinorelbine tartrate (p. 885·3).
Breast cancer; non-small cell lung cancer.

Vinotel *Fresenius Kabi, Philipp.*
Vinorelbine tartrate (p. 885·3).
Malignant neoplasms.

Vinoxin *Pharma Start, Ukr.*
Vincamine (p. 2645·2).
Cerebrovascular disorders.

Vinpocen *Pharmasant, Thai.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; vascular eye disorders.

Vinpo-E *Hexpharm, Indon.*
Vitamin E (p. 2119·1).
Vitamin E deficiency; antoxidant.

Vinpotin *MJ Biopharm, Thai.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; circulatory disorders of the eye and ear.

Vinpoton *Richter, Pol.; Grodzisk, Rus.†*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; vascular ear and eye disorders; vestibular disorders.

Vinpotropile *Kanonfarma, Rus.*
Vinpocetine (p. 2645·3); piracetam (p. 393·3).
Cerebrovascular disorders; parkinsonism; mental function disorders; asthenia; vestibular disorders; migraine; motion sickness.

Vinracine *Korea United, Hong Kong; Korean United, Malaysia†; Korea United, Singapore.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vinsef *EuroHealth, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Vinsen *Chew, Thai.*
Naproxen (p. 98·2).
Musculoskeletal and joint disorders; gout; dysmenorrhoea.

Vinsilar *Chew, Thai.*
Sulfadoxine (p. 363·3); pyrimethamine (p. 662·3).
Malaria.

Vinsulgen *Serum Institute, Philipp.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vintec *Columbia, Mex.*
Vincristine sulfate (p. 882·3).
Malignant neoplasms.

Vintecan *Aurora, Gr.*
Irinotecan hydrochloride (p. 812·2).

Vintène *Baxter, Fr.*
Amino acids.
Parenteral nutrition.

Vintix *Roemmers, Venez.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Vinylin *Himreactive, Rus.*
Polyvinox.
Ulcers; burns; wounds.

Vinzam *Almirall, Spain.*
Azithromycin (p. 221·2).
Bacterial infections.

Vio C *Biopharm, Thai.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Viobrest *Biogen, Gr.*
⊗Letrozole (p. 817·1).
Breast cancer.

Viocort *Aspen, S.Afr.*
⊗Hydrocortisone acetate (p. 1640·1); diiodohydroxyquinoline (p. 931·1).
Skin disorders.

Viodor *Aspen, S.Afr.†*
Diiodohydroxyquinoline (p. 931·1); benzocaine (p. 1980·2).
Skin infections with pruritus.

Viofer *Viofar, Gr.*
Ferrous gluconate (p. 2061·2).

Vioform-Hydrocortisone *Paladin, Canad.; Novartis Consumer, Irl.†; Novartis Consumer, UK.†*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Infected skin disorders; infected insect bites; anogenital intertrigo; skin disorders.

Viofórmio-Hidrocortisona *Novartis, Braz.*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Skin disorders.

Vioformo *Novartis, Mex.*
Clioquinol (p. 273·1).
Skin infections.

Vioformo-Cort *Novartis, Mex.*
⊗Clioquinol (p. 273·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

Viogen-C *Goldline, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); minerals.

Viohydrocort *Combiphar, Indon.*
⊗Hydrocortisone acetate (p. 1640·1); clioquinol (p. 273·1); camphor (p. 2466·2).
Skin disorders; skin infections.

Viojen *Gunsa, Turk.*
Methylrosanilinium chloride (p. 1761·1).
Wound disinfection.

Viokace *Aptalis, USA.*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Viokase *Aptalis, Canad.; Axcan, USA.†*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Pharmacare, S.Afr.†
⊗Pancreatin (p. 2579·3).
Pancreatic insufficiency.

Viola *Melisana, Switz.*
Viola tricolor (p. 2647·3); zinc oxide (p. 1729·1); almond oil (p. 2437·1).
Skin disorders.

Violaforce *Bioforce, Switz.*
Viola.
Acne.

Violin *TO-Chemicals, Thai.*
⊗Salbutamol (p. 1220·2).
Bronchospasm.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Viometil *Mediderm, Chile.*
Emollient.

Vionate *Mylan, Denm.; Mylan, Fin.†*
Risedronate sodium (p. 1189·3).
Osteoporosis.

Vionell *Combe, Ger.*
Vaginal lubricant.
Vaginal dryness and pain.

Vioneurin-6 *Galenica, Gr.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Vionin *IPI, Indon.*
Folic acid (p. 2063·1); biotin (p. 2052·2); nicotinamide (p. 2083·1); vitamin E (p. 2119·1); methionine (p. 1558·2); choline (p. 2055·2).
Nutritional supplement.

Vionin NF *Tempo Scan Pacific, Indon.*
Silymarin (p. 1561·2); methionine (p. 1558·2); essential phospholipids (p. 2201·2); zinc (p. 2126·1); vitamin B_1 (p. 2103·1).
Liver disorders.

Viopexa *Ultra, Mex.*
Losartan potassium (p. 1422·2).
Hypertension; left-ventricular hypertrophy; diabetic nephropathy; heart failure.

Vioplex-T *DAST, Gr.*
Neomycin (p. 329·3); bacitracin (p. 225·3).
Bacterial infections.

Viopor *Otto, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1).
Osteoarthritis; dietary supplement for healthy joints.

Viopor-M *Otto, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1).
Osteoarthritis; dietary supplement for healthy joints.

Viopor-M Forte *Otto, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); vitamin C (p. 2110·3); manganese (p. 2081·2); magnesium (p. 1786·3); selenium (p. 2086·3); zinc (p. 2126·1).
Osteoarthritis; joint disorders.

Vioquin *Gracia, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Vioref *Biofarma, Turk.*
Rofecoxib (p. 128·3).
Osteoarthritis; pain.

Viorele *Glenmark, USA.*
21 Tablets, desogestrel (p. 2266·3); ethinylestradiol (p. 2275·3); 5 tablets, ethinylestradiol; 2 tablets, inert.
Biphasic oral contraceptive.

Vioridon *Viofar, Gr.*
Baclofen (p. 2014·3).
Spasticity.

Viosept *Jelfa, Pol.†; Jelfa, Ukr.†*
Clioquinol (p. 273·1); domiphen bromide (p. 1751·1); tripelennamine hydrochloride (p. 642·3).
Skin infections.

Viosex *Galeno, Venez.*
Sildenafil (p. 2364·1).
Erectile dysfunction.

Vioson *Unison, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Viostin Com *Pharos, Indon.*
Glucosamine sulfate (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); manganese (p. 2081·2); selenium (p. 2086·3).
Osteoarthritis.

Viostin Com DS *Pharos, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); manganese (p. 2081·2).
Osteoarthritis.

Viostin S *Pharos, Indon.*
Chondroitin sulfate (p. 2476·1).
Osteoarthritis.

Viostin-X *Pharos, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); dimethyl sulfone (p. 2493·3); manganese (p. 2081·2).
Osteoarthritis.

Viotisone *Unison, Hong Kong; Unison, Thai.*
Ofloxacin (p. 334·3).
Bacterial infections.

Viotrum Multivitamin Plus *Biopharm, Thai.*
Amino acids; vitamins; minerals.
Dietary supplement.

Vioxy *Fahrenheit, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3); manganese (p. 2081·2); copper (p. 2057·1).
Dietary supplement.

Vioxy-fm *Fahrenheit, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); selenium (p. 2086·3); manganese (p. 2081·2); copper (p. 2057·1); folic acid (p. 2063·1).
Dietary supplement.

Vipdomet *Takeda, UK.*
Alogliptin benzoate (p. 467·2); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Vipefime *Pan-Ject, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Viper *Pascual, Philipp.†*
2 Tablets, pyrazinamide (p. 345·2); 1 capsule, rifampicin (p. 350·3); 1 tablet, isoniazid (p. 311·2); 1 tablet, ethambutol (p. 296·1); 1 tablet, vitamins; minerals (Vitalivin-E).
Tuberculosis.

Viper B 12 *Chinta, Thai.*
Vitamin B substances (p. 2102·3); calcium gluconate (p. 1783·3).
Dietary supplement.

Viper Bee *Chinta, Thai.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Viperfav *Sanofi Pasteur, Fr.*
European viper venom antiserum (p. 2419·1).
European viper bite.

Vipidia *Takeda, UK.*
Alogliptin benzoate (p. 467·2).
Diabetes mellitus.

Vipime *Kalbe, Indon.*
Cefepime (p. 239·2).
Bacterial infections.

Vipirina Ginsex Corazon *Benitol, Arg.*
Aspirin (p. 22·2).
Fever; inflammation; thrombosis prophylaxis.

Viplan *Medipharm, Chile.*
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm; nausea and vomiting.

Viplan Compuesto *Medipharm, Chile.*
Pargeverine hydrochloride (p. 1877·1); metamizole magnesium (p. 53·3).
Smooth muscle spasm; pain.

Viplena *Recalcine, Chile.*
Orlistat (p. 2577·1).
Obesity.

Viplex *Riva, Canad.†*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Vi-Plex K *Biosel, Turk.*
Menadione sodium bisulfite (p. 2122·2).

Viplura Forte *IQFA, Mex.*
Vitamins; minerals.

Viplus *Parggon, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Fever; pain.

Vipocem *Alter, Port.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; vascular disorders of the eye and ear.

Vipodo *Novag, Mex.*
Podophyllum (p. 1717·1).
Keratolytic.

Vipooll *Alvartis, Mex.*
Camphor (p. 2466·2); menthol (p. 2553·2); eucalyptus (p. 2501·1).
Cold and influenza symptoms.

Vipral *Ivax, Arg.*
Sulpiride (p. 1107·3).
Dyspepsia; peptic ulcer; colitis; irritable colon; psychosomatic disorders; psychoses.

Vipram *Novell, Indon.*
Spiramycin (p. 358·3).
Bacterial infections.

Vipratox *Teva, Ukr.*
Vipera ammodytes toxin; salicylic acid (p. 1719·1); camphor (p. 2466·2); fir oil (p. 2591·1).
Muscle, nerve, and joint pain.

Vipratox nova *Serum-Werk Bernburg, Ger.*
Vipera ammodytes toxin; camphor (p. 2466·2).
Musculoskeletal, joint, and soft-tissue disorders.

Viprazo *Pan-Ject, Philipp.*
Omeprazole sodium (p. 1867·2).
Peptic ulcer; dyspepsia; gastro-oesophageal reflux; acid aspiration; Zollinger-Ellison syndrome.

Vipres *Ferrer, Spain.*
Enalapril maleate (p. 1371·1); nitrendipine (p. 1456·3).
Hypertension.

Viprocin *Inpac, Thai.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Vipro-G *Simex, Indon.*
Sachet: Epigallocatechin gallate (p. 1720·2); taurine (p. 2626·2); vitamin C (p. 2110·3).
Antoxidant.

Simex, Indon.
Tablet: Epigallocatechin gallate (p. 1720·2); taurine (p. 2626·2); vitamin C (p. 2110·3); zinc picolinate (p. 2126·1).
Antoxidant.

Viprolox *Aegis, Hong Kong.†*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Viprosal B *Grindeks, Ukr.*
Viper venom; camphor (p. 2466·2); turpentine oil (p. 2636·3); salicylic acid (p. 1719·1).
Musculoskeletal and joint pain.

Grindex, Rus.
Common viper venom; salicylic acid (p. 1719·1); camphor (p. 2466·2); turpentine oil (p. 2636·3).
Musculoskeletal and joint disorders; neuralgia.

Tallin, Pol.
Viper toxin; salicylic acid (p. 1719·1); menthol (p. 2553·2); siberian fir oil.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Viproxil *Andromaco, Chile.*
Pargeverine hydrochloride (p. 1877·1).
Smooth muscle spasm; nausea and vomiting.

Viproxil Compuesto *Andromaco, Chile.*
Pargeverine hydrochloride (p. 1877·1); metamizole magnesium (p. 53·3).
Smooth muscle spasm; pain.

Vipsogal *Harley Street Supplies, UK.*
⊗Betamethasone dipropionate (p. 1623·3); fluocinonide (p. 1636·3); gentamicin sulfate (p. 304·2); salicylic acid (p. 1719·1); panthenol (p. 2582·2).
Skin disorders.

Viqmigil *IQFA, Mex.*
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3).

Viraban
Note: this name may be used for preparations of different composition.
AFT, NZ.
Aciclovir (p. 964·1).
Herpes labialis.

Viracept *Roche, Austral.†; Roche, Austria†; Roche, Belg.†; Roche, Braz.; Pfizer, Canad.; Roche, Chile†; Roche, China; Roche, Cz.†; Roche, Fr.†; Roche, Ger.†; Roche, Gr.†; Roche, Hong Kong; Roche, Hung.†; Roche, Irl.†; Roche, Israel†; Roche, Ital.†; Japan Tobacco, Jpn; Roche, Malaysia; Roche, Mex.†; Roche, Neth.†; Roche, NZ†; Roche, Philipp.†; Roche, Pol.†; Roche, Port.†; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain†; Roche, Switz.†; Roche, Thai.†; Roche, UK†; Roche, Ukr.†; Pfizer, USA; Roche, Venez.*
Nelfinavir mesilate (p. 1004·1).
HIV infection.

Viractin *Medibrands, Canad.*
Tetracaine hydrochloride (p. 1996·3).

Virafer *Teofarma, Ital.*
Vitamins; minerals.
Iron-deficiency anaemia.

Viraferon *Schering-Plough, Cz.†; Schering-Plough, Port.†*
Interferon alfa-2b (p. 989·2).
Chronic hepatitis B; chronic hepatitis C.

ViraferonPeg *Schering-Plough, Cz.; MSD-Chibret, Fr.; Schering-Plough, Irl.; MSD, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.; MSD, UK.*
Peginterferon alfa-2b (p. 989·2).
Chronic hepatitis C.

Viragil *Steierl, Ger.*
⊗Acidum picrinicum (p. 2634·2); vitex agnus-castus (p. 2432·2).
Homoeopathic preparation.

Viraguard Antiseptic Hand Spray *Veridien, Canad.*
Isopropyl alcohol (p. 1758·3).
Hand disinfection.

Viraguard Antiseptic Hand Wipes *Veridien, Canad.*
Isopropyl alcohol (p. 1758·3).
Hand disinfection.

Virainhi *Dosa, Arg.*
Nevirapine (p. 1005·1).
HIV infection.

Virakam *LKM, Arg.*
Tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.

Viralief *Clonmel, Irl.*
Aciclovir (p. 964·1).
Herpes labialis.

Viralis *GMP, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viralkey *Pharminicio, Spain.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3); paracetamol (p. 115·1).
Cold and influenza symptoms.

Viramid *Valeant, Braz.*
Ribavirin (p. 1010·2).
Viral infections.

Viramixal *Panalab, Arg.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Viramune *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, China; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.†; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Ukr.; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
Nevirapine (p. 1005·1).
HIV infection.

Viranet *LKM, Arg.*
Valaciclovir (p. 1021·1).

Virasal *Elorac, USA.*
Salicylic acid (p. 1719·1).

Virasolve *Hamilton, Austral.; Pfizer, NZ.*
Idoxuridine (p. 985·1); lidocaine hydrochloride (p. 1988·2); benzalkonium chloride (p. 1737·1).
Herpes labialis.

Virasoothe *Thornton & Ross, UK.*
Osmo 4 gel.
Pruritus associated with chicken pox.

Virasorb *Thornton & Ross, UK.*
Aciclovir (p. 964·1).
Herpes labialis.

Viratop *Apotex, Belg.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viravan *Pediamed, USA.*
Phenylephrine tannate (p. 1672·2); mepyramine tannate (p. 635·1).

Viravan-DM *Pediamed, USA.*
Dextromethorphan tannate (p. 1660·1); mepyramine tannate (p. 635·1); phenylephrine tannate (p. 1672·2).
Upper respiratory-tract disorders.

Viravan-P *Tiber, USA.†*
⊗Pseudoephedrine hydrochloride (p. 1676·1); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Viravan-PDM *Tiber, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); pseudoephedrine hydrochloride (p. 1676·1); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Viraxy *General Drugs, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virazide *Valeant, Austral.†; Armoxindo, Indon.; Grossman, Mex.*
Ribavirin (p. 1010·2).
Respiratory syncytial virus infection; influenza.

Virazole *Meda, Belg.; UCI, Braz.; Valeant, Canad.; Meda, Ger.; IFET (ΙΦΕΤ), Gr.; Meda, Gr.; Invida, Hong Kong; Valeant, Ital.; Meda, Neth.; Meda, Rus.; Invida, Singapore; Meda, Spain; Meda, Swed.; ICN, UK; ICN, USA.*
Ribavirin (p. 1010·2).
Influenza; haemorrhagic fever with renal syndrome; respiratory syncytial virus infection.

Vircella *Galenium, Indon.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vircovir *Corsa, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virdam *Pyridam, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virdec *Virtus, USA.*
Chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Virdec DM *Virtus, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Virdex *Fulton, Ital.*
Ergotamine tartrate (p. 674·1); caffeine (p. 1203·3); aminophenazone (p. 21·1).
Migraine; headache; vertigo.

Virdos *UCB, Neth.†*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Viread *Gador, Arg.; Gilead, Austral.; Gilead, Austria; Gilead, Belg.; Gilead, Canad.; Pharma Investi, Chile; Pharmacare, China; Gilead, Cz.; Gilead, Denm.; Gilead, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hong Kong; Gilead, Hung.; Gilead, Irl.; Gilead, Israel; Gilead, Ital.; Stendhal, Mex.; Gilead, Neth.; Gilead, Norw.; Gilead, NZ; Gilead, Pol.; Gilead, Port.; Aspen, S.Afr.; Gilead, Singapore; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; Gilead, Thai.; Gilead, UK; Gilead, USA.*
Tenofovir disoproxil fumarate (p. 1018·1).
HIV infection; chronic hepatitis B.

Viregyt *Egis, Hung.*
Amantadine hydrochloride (p. 890·3).
Influenza; parkinsonism.

Viregyt K *Egis, Pol.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza A.

Viregyt-K *Egis, Cz.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza.

Viremax *Medimar, Gr.*
Glucosamine sulfate (p. 2515·3).

Viremix *Ranbaxy, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virerpin *Kleva, Gr.*
Vidarabine (p. 1023·1).
Herpesvirus infections.

Virest *Hovid, Hong Kong; Hovid, Philipp.; Hovid, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virestat *Liferpal, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vireth *Ethica, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virexen *Will-Pharma, Neth.†; Vinas, Spain.*
Idoxuridine (p. 985·1) in dimethyl sulfoxide.
Herpesvirus infections of skin and mucous membranes.

Virfen *Specifar, Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Virgan *Sidus, Arg.; Thea, Belg.; Thea, Cz.; Thea, Fr.; Thea, Ger.; Thea, Gr.; Silroc, Hong Kong†; Thea, Hung.; Farmila, Ital.; Thea, Philipp.; Thea, Pol.; Thea, Port.; Thea, Spain; Spectrum, UK.*
Ganciclovir (p. 982·3).
Herpesvirus eye infections.

Virgangel *Pisa, Mex.*
Aciclovir (p. 964·1).
Herpesvirus eye infections.

Virgogel *Virgo, Philipp.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Peptic ulcer; gastric hyperacidity.

Virgomine *Virgo, Philipp.†*
Chlorphenamine maleate (p. 620·3).
Allergic and inflammatory skin disorders.

Virgovit *Virgo, Philipp.*
Vitamins.
Nutritional supplement.

Virherpes *Esteve, Spain.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viridal *UCB, Ger.; UCB, Irl.; Schwarz, Ital.†; UCB, UK.*
Alprostadil alfadex (p. 2352·2).
Erectile dysfunction.

Viridil *Roemmers Rowe, Venez.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Viridin *Davi, Port.†*
Trifluridine (p. 1020·3).
Viral eye infections.

Virigen
Note: this name may be used for preparations of different composition.
Organon, Turk.
⊗Testosterone undecylate (p. 2305·2).
Androgen deficiency.
Actavis, Denm.†
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction.

Virilis-Gastreu S R41 *Reckeweg, Ger.*
⊗Acid. phosphoricum (p. 2589·1); agnus castus (p. 2432·2); damiana (p. 2491·3).
Homoeopathic preparation.

Virilit *Bayer, Ger.†*
Cyproterone acetate (p. 2261·2).
Sexual deviation in men; prostatic cancer; androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Virilon
Note: this name may be used for preparations of different composition.
Star, USA.
Capsules: ⊗Methyltestosterone (p. 2291·3).
Androgen replacement therapy; prepubertal cryptorchidism; male hypogonadism; breast cancer; postpartum breast engorgement.
Temis, Arg.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Virineo *Hypermarcas, Braz.*
Sildenafil (p. 2364·1).

Viripotens *Microsules, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Virkon *Antec Dupont, Singapore.*
Peroxygen compounds (p. 1763·1).
Surface disinfection.

Virless *YSP, Malaysia; Yung Shin, Singapore; YSP, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virlix *Sanofi-Aventis, Fr.; GSK, Mex.; GSK, Philipp.; Pliva Krakow, Pol.; Vedim, Port.†; Lacer, Spain; Bilim, Turk.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; allergic rhinitis; urticaria; allergic conjunctivitis.

Virlix Plus *Lacer, Spain.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Virlix-D *GSK, Mex.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; nasal congestion; eye irritation.

Virman Plus *Corypharma, Ital.*
Vitamin E (p. 2119·1); nicotinic acid (p. 2083·1); zinc (p. 2126·1).
Nutritional supplement.

Virmen *Menarini, Spain.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virobex-P *Microbex, Canad.*
Chloroxylenol (p. 1748·2).

Virobin
Note: this name may be used for preparations of different composition.
Lafi, Chile.
Oseltamivir phosphate (p. 1006·2).
Influenza.

Virobron *Temis, Arg.*
Nimesulide (p. 101·3).
Inflammation.

Virobron B12 NF *Temis, Arg.*
⊗Betamethasone (p. 1623·2) or betamethasone sodium phosphate (p. 1623·3); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3); diclofenac potassium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Virobron Gel *Temis, Arg.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint and soft-tissue disorders.

Virobron NF *Temis, Arg.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Viroclear *Christo, Hong Kong.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viroclon *Medicus, Gr.*
Zidovudine (p. 1024·2).
HIV infection.

Virofik *Sinensix, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viroflu *Crucell, UK.*
An influenza vaccine (surface antigen) (p. 2393·3).
Active immunisation.

Virogel *Jadran, Ukr.*
Interferon alfa-2b (p. 989·2).
Herpesvirus infections.

Virogerm *Zedchem, S.Afr.†*
Glutaral (p. 1753·2).
Instrument disinfection.

Virogon *Silom, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virohep-A *Novartis, Arg.*
A hepatitis A vaccine (p. 2388·3).
Active immunisation.

Virolan *Olan-Kemed, Thai.†*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Virolex *KRKA, Cz.†; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.; KRKA, Ukr.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

ViroMed
Note: this name may be used for preparations of different composition.
S Med, Austria.
Aciclovir (p. 964·1).
Herpesvirus infections.

Viromed
Note: this name may be used for preparations of different composition.
Medicine Products, Thai.
Aciclovir (p. 964·1).
Herpesvirus infections.

Viromidin *IFET (ΙΦΕΤ), Gr.*
Trifluridine (p. 1020·3).

Vi-Ron *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); liquorice (p. 1853·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).

Viron
Note: this name may be used for preparations of different composition.
Sanovel, Turk.
Ribavirin (p. 1010·2).
Chronic hepatitis C.
Yarindo, Indon.
Dipyrone (p. 53·3); vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuralgia; neuritis.

Viron Wart Lotion *Odan, Canad.*
Glacial acetic acid (p. 2426·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Verrucae; warts.

Vironida *Laboratorios Chile, Chile.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vironil *Burapha, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viropect *DHU, Ger.*
Ipecacuanha (p. 1667·2); drosera (p. 2497·2); cuprum aceticum (p. 2486·2).
Homoeopathic preparation.

Viropel *Pelpharma, Austria.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Virophta *Horus, Fr.*
Trifluridine (p. 1020·3).
Viral infections of the eye.

Viropon *Novagen, S.Afr.*
Nevirapine (p. 1005·1).

Viroptic *Valeant, Canad.; Glaxo Wellcome, USA; Monarch, USA.*
Trifluridine (p. 1020·3).
Herpes simplex keratitis and keratoconjunctivitis.

Virormone *Nordic, UK.*
⊗Testosterone (p. 2305·1) or testosterone propionate (p. 2305·2).
Male hypogonadism; delayed puberty; cryptorchidism; breast cancer.

Virorrever *Richmond, Arg.*
Efavirenz (p. 975·1).
HIV infection.

Virosil *Saba, Turk.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virosol *Phoenix, Arg.*
Amantadine hydrochloride (p. 890·3).
Parkinsonism; influenza; drug-induced extrapyramidal disorders.

Virostatic *Cassara, Arg.*
Aciclovir (p. 964·1).
Herpes labialis.

Virostav *Ranbaxy, Malaysia.*
Stavudine (p. 1015·3).
HIV infection.

Virosupril *Raymos, Arg.*
Imiquimod (p. 985·2).
Actinic keratoses; superficial basal cell carcinoma; anogenital warts.

Virotek Intim *Pro-Pharma, Ukr.*
Benzalkonium chloride (p. 1737·1).
Sexually transmitted infections; urethral infections.

Virovir *Opus, UK.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Viroxil *Quimica y Farmacia, Mex.*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Viro-Z *Ranbaxy, Rus.*
Zidovudine (p. 1024·2).
HIV infection.

Virpes *Bernofarm, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virtaz *Fahrenheit, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virt-Bal DHA *Virtus, USA.*
Tablets, vitamins; minerals; capsules, omega-3 fatty acids (p. 1460·1).
Dietary supplement.

Virtec *Sel-J, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Virtex *Medica Korea, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Virti-Sulf *Virtus, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Virt-PN *Virtus, USA.*
Vitamins; minerals.

Virt-PN DHA *Virtus, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Virt-PNV-DHA *Virtus, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Virtrium *Aspen, S.Afr.*
Lamivudine (p. 1000·2); stavudine (p. 1015·3); nevirapine (p. 1005·1).

Virt-Select *Virtus, USA.*
Vitamins; iron (p. 2073·1); calcium (p. 1783·1); docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Virt-Vite *Virtus, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).
Dietary supplement.

Virt-Vite Forte *Virtus, USA.*
Vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); folate (p. 2063·1).
Dietary supplement.

Virt-Vite Plus *Virtus, USA.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Dietary supplement.

Virucalm *Zambon, Fr.; Zambon, Switz.*
Aciclovir (p. 964·1).
Herpes labialis.

Virucid
Note: this name may be used for preparations of different composition.
Aegis, Hong Kong; Aegis, Malaysia.
Aciclovir (p. 964·1).
Herpesvirus infections.

Viruderm *Cinfa, Spain.*
Aciclovir (p. 964·1).
Herpes simplex infection.

Virudermin *Robugen, Ger.; Iromedica, Switz.*
Zinc sulfate (p. 2126·2).
Herpes labialis.

Virules *Kimia, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Virulex
Note: this name may be used for preparations of different composition.
Pose, Thai.†
Hand gel; hand rub: Triclosan (p. 1773·2).
Skin disinfection.

Pose, Thai.†
Powder for solution: Monopersulfate compound; sodium chloride (p. 1795·1); sulphamic acid.
Instrument disinfection.

Virulex Forte *Pascual, Hong Kong.*
Moroxydine hydrochloride (p. 1004·1); paracetamol (p. 115·1); atropine methonitrate (p. 1310·2); hyoscine methonitrate (p. 1846·1).
Viral infections.

Virulizin *Mayne, Mex.*
Ox bile extract (p. 2457·2).
Malignant melanoma.

Viru-Merz *Merz, Cz.; Merz, Hong Kong; Merz, Hung.; Combiphar, Indon.; Merz, Indon.; Merz, Israel; Merz, Malaysia; Merz, Philipp.†; Merz, Pol.; Medinfar, Port.; Merz, Singapore.*
Tromantadine hydrochloride (p. 1021·1).
Herpesvirus infections of the skin and mucous membranes.

ViruMerz *Merz, China.*
Tromantadine.
Herpesvirus infections of skin and mucous membranes.

Viru-Merz Serol *Merz, Austria; Merz, Ger.; Sarantis, Gr.; Merz, Rus.; Merz, Switz.†*
Tromantadine hydrochloride (p. 1021·1).
Herpes simplex infections of the skin and mucous membranes.

Virunguent *Almirall Hermal, Ger.†; Hermal, Singapore; Reckitt Benckiser, Switz.†*
Idoxuridine (p. 985·1) in dimethyl sulfoxide.
Herpes simplex infections of the skin and mucous membranes; herpes labialis.

Viru-POS *Ursapharm, Pol.*
Aciclovir (p. 964·1).
Herpesvirus eye infections.

Virupos *Ursapharm, Ger.; Biem, Turk.*
Aciclovir (p. 964·1).
Herpes simplex eye infections.

Virusept *Merz, Ger.†*
⊗Propyl alcohol (p. 1768·1); alcohol (p. 1733·1).
Hand disinfection.

Viru-Serol *Merz, Mex.; Lacer, Spain.†*
Tromantadine hydrochloride (p. 1021·1).
Herpesvirus infections of the skin and mucous membranes.

Virusteril *Biospray, Gr.*
Aciclovir (p. 964·1).
Labial and genital herpes simplex infections.

Viruxan *Sigma-Tau, Ital.*
Inosine pranobex (p. 988·3).
Immunodeficiency; viral infections.

Virval *GSK, Spain.†*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Virzin *Dermapharm, Ger.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Visabelle *Bayer, Israel.*
Dienogest (p. 2267·2).
Endometriosis.

Visacor *AstraZeneca, Austral.; Orifarm, Denm.; AstraZeneca, Port.; AstraZeneca, Swed.†*
Rosuvastatin calcium (p. 1488·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Visadron *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Alcon, Ger.; Boehringer Ingelheim, Neth.; Unilfarma, Port.; Boehringer Ingelheim, Spain.*
Phenylephrine hydrochloride (p. 1672·3).
Conjunctivitis; eye irritation; conjunctival irritation.

Visag *Poen, Arg.*
Azithromycin (p. 221·2).
Bacterial eye infections.

Visaline *Bausch & Lomb, Switz.†*
⊗Buphenine hydrochloride (p. 2462·3); betacarotene (p. 2051·1); alpha tocopherol (p. 2119·1); ascorbic acid (p. 2110·3).
Eye disorders.

Visalmin *Bunker, Braz.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Visancort *Sanbe, Indon.*
⊗Hydrocortisone (p. 1640·1); clioquinol (p. 273·1); camphor (p. 2466·2).
Skin disorders; skin infections.

Visanne *Bayer, Austral.; Bayer, Austria; Bayer, Canad.; Bayer Schering, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Ger.; Bayer Schering, Hung.; Bayer, Neth.; Bayer, Norw.; Berlex, Port.; Bayer, Singapore; Bayer, Swed.; Bayer, Switz.*
Dienogest (p. 2267·2).
Endometriosis.

Visannette *Bayer, Gr.; Bayer, Spain.*
Dienogest (p. 2267·2).
Endometriosis.

Visazul *Neo Quimica, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc phenolsulfonate (p. 1729·3); berberine sulfate (p. 2455·1).

Viscaplus *Sifarma, Ital.*
Marine cartilage; amino acids; minerals; antoxidants.
Nutritional supplement; alopecia.

Viscard *Norma (Νορμα), Gr.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Visceel *Heel, Canad.†*
Goose grass (p. 2481·2); mistletoe (p. 2560·2).
Homoeopathic preparation.

Viscéralgine *MSD-Chibret, Fr.*
Tiemonium metilsulfate (p. 1893·3).
Smooth muscle spasm.

Visceralgine *Schering-Plough, Indon.*
Tiemonium metilsulfate (p. 1893·3).
Smooth muscle spasm.

Visclair *Sinclair, Irl.†; Sinclair, UK.*
Mecysteine hydrochloride (p. 1669·1).
Bronchitis; respiratory-tract disorders with excessive or viscous mucus.

Visclear *McNeil, Fin.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visco *Aristo, India.*
Alginic acid (p. 2167·2) or sodium alginate (p. 2167·3); magnesium hydroxide (p. 1857·2); aluminium hydroxide (p. 1817·2); simeticone (p. 1886·2).
Gastric hyperacidity; heartburn; gastro-oesophageal reflux; dyspepsia; excess gastrointestinal gas.

Viscoat *Alcon, Arg.†; Alcon, Austral.†; Alcon, Fr.†; Alcon, Ger.; Alcon, Gr.; Alcon, Ital.; Alcon, Malaysia.†; Alcon, NZ; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore†; Alcon, Thai.; Nobel, Turk.; Alcon, USA.*
Chondroitin sulfate sodium (p. 2476·1); sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Viscoblast *DMG, Ital.*
Carboxymethyl beta-glucan (p. 2455·2); n-hydroxymethylglycinate.

Viscoblast Mono *DMG, Ital.*
Carboxymethyl beta-glucan (p. 2455·2).

Viscodec *Ashford, Philipp.*
Carbocisteine (p. 1658·1).
Cough.

Viscoderm *Bago, Arg.*
Sodium hyaluronate (p. 2526·2).
Skin ageing.

Viscofresh *Allergan, Spain.*
Carmellose sodium (p. 2175·2).
Dry eyes.

Viscol *Liba, Turk.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

Viscolex *Pinewood, Irl.*
Carbocisteine (p. 1658·1).
Respiratory-tract disorders with excessive or viscous mucus.

Viscomucil *ABC, Ital.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Viscopaste *Smith & Nephew, Austral.; Smith & Nephew, Irl.*
Zinc oxide (p. 1729·1).
Medicated bandage; leg ulcers; varicose eczema; dermatitis.

Viscopaste PB7 *Smith & Nephew, Canad.; Smith & Nephew, Ital.; Smith & Nephew, S.Afr.†; Smith & Nephew, UK.*
Zinc oxide (p. 1729·1).
Medicated bandage.

Visc-Ophtal *Winzer, Ger.*
Carbomer (p. 2173·3).
Dry eyes.

Viscoseal *Chemedica, Ger.; Chemedica, Malaysia; Chemedica, Switz.; Chemedica, UK.*
Sodium hyaluronate (p. 2526·2).
Adjunct in arthroscopy; synovial fluid replacement in arthroscopy or joint lavage.

Viscotears *Novartis, Arg.; Novartis, Austral.; Novartis, Braz.; Novartis, Chile; Alcon, Denm.; Alcon, Fin.; Novartis, Hong Kong†; Novartis, Israel; Novartis, Mex.; Thea, Norw.; Novartis, NZ; Alcon Cusi, Spain; Novartis Ophthalmics, Swed.; Alcon, Switz.; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
Carbomer (p. 2173·3).
Dry eyes; eye irritation.

Viscoteína *Faes, Spain.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Viscoter *Thea, Gr.*
Carbomer (p. 2173·3).
Dry eyes.

Viscotirs *Novartis, Ital.*
Carbomer (p. 2173·3).
Dry eyes.

Viscotraan *Adcock Ingram, S.Afr.*
Hypromellose (p. 2189·2).
Dry eyes.

Visco-Vision *OmniVision, Ger.*
Carbomer 980 (p. 2173·3).
Dry eyes.

Viscozyme *Roche, Chile.*
Dornase alfa (p. 1662·1).
Cystic fibrosis.

Viscum album H *Pfluger, Ger.†*
Aconitum napellus (p. 2428·3); anamirta cocculus (p. 2483·1); veratrum album (p. 2644·3); kalium phosphoricum (p. 1790·3); rauwolfia serpentina (p. 1485·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Viscum Album HM *Pfluger, Ger.†*
Anamirta cocculus (p. 2483·1); viscum album (p. 2560·2).
Homoeopathic preparation.

Viscum-Entoxin N *Meckel, Ger.*
Nitroglycerinum (p. 1391·2); viscum album (p. 2560·2).
Homoeopathic preparation.

Viscure *Kalofolias, Gr.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis.

Viscysat *Ysatfabrik, Ger.†*
Mistletoe (p. 2560·2).
Circulatory disorders.

Visderm *Wyeth, Thai.*
⊗Amcinonide (p. 1621·1).
Skin disorders.

Visderm H *Darier, Mex.*
⊗Amcinonide (p. 1621·1).
Inflammatory skin disorders.

Visebad *Otto, Indon.*
Vitamins.
Nutritional supplement.

Visentiel *Synergia, Fr.*
Vitamins; minerals.
Dietary supplement.

Visertral *Serral, Mex.*
Cetirizine (p. 619·2).

Visial *Cadila, India.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Visible Lift *L'Oreal, Canad.†*
SPF 17: Octinoxate (p. 1715·1).
Sunscreen.

Visible Results *L'Oreal, Canad.†*
SPF 15: Octinoxate (p. 1715·1); titanium dioxide (p. 1725·1).
Sunscreen.

Vi-Siblin *Meda, Denm.; Pfizer, Fin.; Meda, Norw.; Meda, Swed.*
Ispaghula (p. 1849·1).
Constipation; irritable bowel syndrome.

Visicol *Salix, USA.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Bowel evacuation.

Visidic *Laboratorios Chile, Chile.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes; eye irritation.

Visine *McNeil, Belg.; Johnson & Johnson, Chile; McNeil, Cz.; Johnson & Johnson, Gr.; Johnson & Johnson, Hung.; Pfizer, India†; Pfizer, Indon.; Janssen-Cilag, Israel; Pfizer, Malaysia†; Johnson & Johnson, NZ; Johnson & Johnson, Philipp.; McNeil, Pol.; Johnson & Johnson, Port.; Johnson & Johnson, Rus.; Johnson & Johnson, S.Afr.; Janssen-Cilag, Switz.; Pfizer, Thai.†; Pfizer, Turk.; McNeil, Ukr.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation; eye congestion.

Visine AC *Pfizer, Hong Kong†; Janssen-Cilag, Israel.*
⊗Tetryzoline hydrochloride (p. 1678·3); zinc sulfate (p. 2126·2).
Eye irritation.

Visine AD *Pfizer Consumer, Mex.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye irritation.

Visine Advance Allergy *Johnson & Johnson, Canad.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).

Visine Advance Triple Action *Johnson & Johnson, Canad.*
⊗Tetryzoline hydrochloride (p. 1678·3); macrogol 400 (p. 2547·3); dextran 70 (p. 1138·3); povidone (p. 2204·3).

Visine Advance True Tears *Johnson & Johnson, Canad.*
Hypromellose (p. 2189·2).
Dry eyes.

Visine Advanced Relief
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Austral.; Johnson & Johnson, NZ.
⊗Tetryzoline hydrochloride (p. 1678·3); dextran 70 (p. 1138·3); macrogol 400 (p. 2547·3); povidone (p. 2204·3).
Dry eyes; eye irritation.

Pfizer, Philipp.†
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visine All Day Eye Itch Relief *Johnson & Johnson, USA.*
Ketotifen (p. 631·3).
Allergic conjunctivitis.

Visine Allergy
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Austral.; Johnson & Johnson, NZ.
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye irritation; allergic conjunctivitis.

Johnson & Johnson, Canad.
⊗Tetryzoline hydrochloride (p. 1678·3); zinc sulfate (p. 2126·2).
Eye irritation.

Visine Clear *Johnson & Johnson, Austral.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visine Contact Lens *Johnson & Johnson, Canad.*
Hypromellose (p. 2189·2).
Eye irritation during contact lens wear.

Visine for Contacts *Pfizer, Hong Kong.†*
⊗Hypromellose (p. 2189·2); glycerol (p. 2517·2).
Eye irritation during contact lens wear.

Visine Cool
Note: this name may be used for preparations of different composition.
Johnson & Johnson, Canad.
⊗Tetryzoline hydrochloride (p. 1678·3); macrogol 400 (p. 2547·3).
Eye irritation.
Pfizer, Philipp.†
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visine D *Pfizer, Arg.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye irritation.

Visine Dry Eyes *Johnson & Johnson, Ital.†*
Povidone (p. 2204·3); carbomer 974P (p. 2173·3); medium-chain triglycerides (p. 2082·2).
Dry eyes.

Visine Extra *Johnson & Johnson Consumer, Mex.*
⊗Tetryzoline hydrochloride (p. 1678·3); macrogol 400 (p. 2547·3); povidone (p. 2204·3); dextran 70 (p. 1138·3).
Eye irritation.
Pfizer, Indon.
⊗Tetryzoline hydrochloride (p. 1678·3); macrogol (p. 2547·3).
Eye irritation; dry eyes.

Visine Intensiv *McNeil, Ger.*
Tamarind seed polysaccharide (p. 2215·2).
Dry eyes.

Visine Intensive *Johnson & Johnson, Ital.†*
Tamarind seed polysaccharide (p. 2215·2).
Dry eyes.

Visine Lagrimas *Pfizer, Arg.*
⊗Glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol 400 (p. 2547·3).
Dry eyes.

Visine LR *Pfizer, Indon.; Pfizer Consumer, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye irritation.

Visine Maximum Redness Relief *Johnson & Johnson, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3); glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol (p. 2547·3).
Eye irritation.

Visine Moisturizing *Pfizer, Hong Kong.†*
⊗Tetryzoline hydrochloride (p. 1678·3); macrogol 400 (p. 2547·3).
Eye irritation; dry eyes.

Visine Müde *McNeil, Ger.*
Tamarind seed polysaccharide (p. 2215·2).
Eye irritation.

Visine Original *Johnson & Johnson, Canad.; Pfizer, Hong Kong†; Pfizer Consumer, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visine Plus *Pfizer, Arg.*
⊗Dextran 70 (p. 1138·3); macrogol 400 (p. 2547·3); povidone (p. 2204·3); tetryzoline hydrochloride (p. 1678·3).
Dry eyes; eye irritation.

Visine Professional *Johnson & Johnson, Austral.†*
Eye drops: Tamarind seed polysaccharide (p. 2215·2).
Dry eyes; eye irritation.
Johnson & Johnson, Austral.†
Liquid gel drops: Povidone (p. 2204·3); carbomer (p. 2173·3); medium-chain triglycerides (p. 2082·2).
Dry eyes.

Visine Pure Tears *Pfizer Consumer, USA.*
⊗Glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol 400 (p. 2547·3).
Dry eyes.

Visine Refresh *Johnson & Johnson, Philipp.*
⊗Macrogol 400 (p. 2547·3); glycerol (p. 2517·2); hypromellose (p. 2189·2).
Eye irritation; dry eyes.

Visine Tears *Johnson & Johnson, USA.*
⊗Glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol 400 (p. 2547·3).
Dry eyes.

Visine Tired Eye Relief *Johnson & Johnson, USA.*
⊗Glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol (p. 2547·3).
Eye irritation.

Visine Tired Eyes *Johnson & Johnson, Austral.†; Johnson & Johnson, Ital.†*
Tamarind seed polysaccharide (p. 2215·2).
Dry eyes; eye irritation.

Visine Totality Multi-Symptom Relief *Johnson & Johnson, USA.*
⊗Tetryzoline hydrochloride (p. 1678·3); glycerol (p. 2517·2); hypromellose (p. 2189·2); macrogol (p. 2547·3); zinc sulfate (p. 2126·2).
Eye irritation.

Visine Trockene Augen *McNeil, Ger.*
Povidone (p. 2204·3); carbomer 974P (p. 2173·3); medium-chain triglycerides (p. 2082·2).
Dry eyes.

Visine Visiclear *McNeil, Denm.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye congestion; allergic conjunctivitis; eye irritation.

Visine Workplace *Johnson & Johnson, Canad.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Eye irritation.

Visine Yxin *McNeil, Ger.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye disorders.

Visine zur Nacht *McNeil Consumer, Ger.*
Povidone (p. 2204·3); carbomer 974P (p. 2173·3).
Dry eyes.

Visine-A *Pfizer Consumer, USA.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye disorders.

Visiodose *Cooperation Pharmaceutique, Fr.*
Chlorhexidine gluconate (p. 1743·3); phenylephrine hydrochloride (p. 1672·3).
Conjunctivitis.

Visiol *Chemedica, Ger.; Chemedica, Malaysia; Chemedica, Switz.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Visio-Max *Wassen, UK.*
Selenium (p. 2086·3); vitamins; bilberry (p. 2566·2).

Vision Care Enzymatic Cleaner *Alcon, USA.†*
⊗Pancreatin (p. 2579·3).
Cleansing solution for soft contact lenses.

Vision Tabs *Knop, Chile.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamins; minerals.
Age-related macular degeneration; cataract.

Visionace *Vitabiotics, UK.*
Vitamins; minerals; nutrients.
Eye disorders.

Visional Gotas *Maver, Chile.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye congestion.

VisionBlue *DORC, Neth.; Dutch Ophthalmic, USA.*
Trypan blue (p. 2635·2).
Ophthalmic stain.

Visionex *Beacons, Singapore.*
Capsules: Lutein (p. 2079·2); vitamin A (p. 2098·3).
Dietary supplement for healthy eyes.
Usana, Canad.
Myrtillus (p. 2566·2); lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamin C (p. 2110·3).
Dietary supplement.
Usana, Hong Kong.†
Ascorbic acid (p. 2110·3); zinc citrate (p. 2126·2); zinc ascorbate (p. 2110·3); lutein (as marigold extract) (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement for healthy eyes.
Usana, Malaysia.†
Lutein (p. 2079·2); zinc (p. 2126·1); vitamin C (p. 2110·3).
Usana, Singapore.†
Tablets: Vitamin C (p. 2110·3); zinc (p. 2126·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); myrtillus (p. 2566·2).
Dietary supplement.

Vision-Eze *Bioglan, Austral.†*
Myrtillus (p. 2566·2); ginkgo biloba (p. 2512·3).
Eye fatigue; poor night vision; peripheral circulatory disorders.

Visionom *Uniao Quimica, Braz.*
Hamamelis (p. 2523·3); chamomile (p. 2474·1).
Eye disorders.

Visioprev *Doliage, Fr.*
Omega-3 fatty acids (p. 1460·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); vitamins.
Dietary supplement; eye health.

Visipaque *HLB, Arg.; GE Healthcare, Austral.; GE Healthcare, Austria; GE Healthcare, Belg.; GE Healthcare, Canad.; General Electric, Chile; GE Healthcare, China; GE Healthcare, Cz.; GE Healthcare, Denm.; GE Healthcare, Fin.; GE Healthcare, Fr.; GE Healthcare, Ger.; Amersham, Gr.; GE Healthcare, Gr.; GE Healthcare, Hung.; GE Healthcare, Irl.; GE Healthcare, Israel; GE Healthcare, Ital.; GE Healthcare, Neth.; GE Healthcare, Norw.; GE Healthcare, NZ; Satis, Port.; GE Healthcare, Rus.; GE Healthcare, Spain; GE Healthcare, Swed.; GE Healthcare, Switz.; Opakim, Turk.; GE Healthcare, UK; Nycomed, Ukr.; Amersham, USA.*
Iodixanol (p. 1589·2).
Radiographic contrast medium.

Visiplex *Bunker, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2); boric acid (p. 2459·3); borax (p. 2459·2).
Ocular congestion.

Visivit *Soho, Indon.*
Myrtillus (p. 2566·2); vitamin A (p. 2098·3).
Supplement for healthy eyes.

Viskaldix *Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Fr.; Novartis, Ger.†; Novartis, Gr.; Egis, Hung.; Novartis, Irl.†; Novartis, Malaysia; Euro Registratie, Neth.†; Novartis, Philipp.; Egis, Rus.; Novartis, Switz.; Amdipharm, UK.*
⊗Pindolol (p. 1470·1); clopamide (p. 1342·3).
Hypertension.

Viskazide *Novartis, Canad.*
⊗Pindolol (p. 1470·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Viskeen *Novartis, Neth.*
⊗Pindolol (p. 1470·1).
Angina pectoris; arrhythmias; hypertension.

Visken *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.†; Novartis, Gr.; Novartis, Hong Kong; Egis, Hung.; Novartis, India; Novartis, Irl.†; Teofarma, Ital.; Novartis, Mex.; Novartis, Philipp.; Novartis, Pol.; Egis, Rus.; Novartis, Swed.; Novartis, Turk.; Amdipharm, UK; Novartis, USA.*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris; arrhythmias; hyperthyroidism; hypertrophic obstructive cardiomyopathy; phaeochromocytoma; myocardial infarction; ischaemic heart disease.

Viskén *Novartis, Denm.*
⊗Pindolol (p. 1470·1).
Hypertension; angina pectoris; arrhythmias; myocardial infarction.

Viskène *Novartis, Switz.*
⊗Pindolol (p. 1470·1).
Hypertension; cardiac disorders.

Viskoferm *Nordic, Swed.*
Acetylcysteine (p. 1652·2).
Bronchitis.

Viskøse øjendråber *Ophtha, Denm.*
Hypromellose (p. 2189·2).
Dry eyes.

Vislin *Alcon, Braz.*
⊗Tetryzoline hydrochloride (p. 1678·3); methylthioninium chloride (p. 1559·1).
Ocular congestion.

Vislube *Chemedica, Ger.; Chemedica, Malaysia†; TRB, Singapore†; Chemedica, Switz.; Chemedica, Thai.*
Sodium hyaluronate (p. 2526·2).
Contact lens lubricant; dry eyes; eye irritation.

Vislus *Northia, Arg.*
⊗Nitrofurazone (p. 333·1); ephedrine (p. 1663·1); phenazone (p. 124·1); diphenhydramine (p. 626·1).
Eye disorders.

Vismed *Chemedica, Ger.; Chemedica, Hong Kong; Medivis, Ital.; Chemedica, Malaysia; TRB, Singapore; Chemedica, Switz.; Chemedica, UK.*
Sodium hyaluronate (p. 2526·2).
Dry eyes; lubrication for contact lens; eye irritation.

Vis-nol *Farmak, Ukr.*
Tripotassium dicitratobismuthate (p. 1822·2).
Peptic ulcer; gastritis; dyspepsia; Helicobacter pylori *eradication.*

Visodin *Farmasa, Braz.*
⊗Tetryzoline hydrochloride (p. 1678·3); methylthioninium chloride (p. 1559·1).
Ocular congestion.

Visofid *Fidia, Ital.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-associated acne, alopecia, and hirsutism in females.

Visol *Duopharma, Philipp.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visolin *Darya-Varia, Indon.†*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Visolon *Igefarma, Braz.*
⊗Naphazoline hydrochloride (p. 1669·3); benzalkonium chloride (p. 1737·1); zinc sulfate (p. 2126·2); berberine sulfate (p. 2455·1).
Ocular congestion.

Visolvit *GSK, Pol.†*
Vitamins.

Visonest *Allergan, Braz.*
Proxymetacaine hydrochloride (p. 1995·3).
Local anaesthesia.

Visopt *Treasure Mountain, Hong Kong.†*
Phenylephrine (p. 1672·2).

Visoptic *Geolab, Braz.*
⊗Betaxolol (p. 1322·3).

Visotone *British Dispensary, Thai.*
Eye drops: Phenylephrine hydrochloride (p. 1672·3); boric acid (p. 2459·3); borax (p. 2459·2); sodium chloride (p. 1795·1).
Eye irritation.
British Dispensary, Thai.
Eye lotion: Boric acid (p. 2459·3); borax (p. 2459·2); salicylic acid (p. 1719·1); zinc sulfate (p. 2126·2).
Eye irritation.

Visozyme *Vickmans, Hong Kong.†*
Muramidase (p. 2565·1).

Vispam *Utopian, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; epilepsy; alcohol withdrawal syndrome; skeletal muscle spasm; premedication.

Vispring *Johnson & Johnson, Gr.; Johnson & Johnson, Spain.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Conjunctival congestion; eye irritation.

Visquo *Sigma-Tau, Ital.*
Ibuprofen (p. 68·2).

Vistabel *Allergan, Belg.; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Allergan, Gr.; Allergan, Hung.; Allergan, Irl.; Allergan, Neth.; Allergan, Norw.; Allergan, Pol.; Allergan, Port.; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, UK.*
Botulinum A toxin (p. 2017·1).
Facial wrinkles; glabellar lines.

Vistabex *Allergan, Ital.*
Botulinum A toxin (p. 2017·1).
Facial wrinkles.

Vistachlor *Vista, Philipp.*
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Vistacom *Vista, Philipp.*
⊗Polymyxin B sulfate (p. 342·3); neomycin sulfate (p. 330·1); dexamethasone (p. 1630·3).
Bacterial eye infections with inflammation.

Vistadex *Ronnet, Arg.*
⊗Dexamethasone sodium phosphate (p. 1631·2); naphazoline hydrochloride (p. 1669·3); tobramycin (p. 380·1).
Conjunctivitis.

Vistadrox *Cadila, India.*
Cefadroxil (p. 233·2).
Bacterial infections.

Vistaflox *Vista, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Vistafrin *Allergan, Spain.†*
Phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vistagan *Allergan, Austria; Allergan, Cz.; Allergan, Ger.; Allergan, Gr.; Allergan, Hung.; Allergan, Ital.; Allergan, Switz.; Allergan, Venez.*
⊗Levobunolol hydrochloride (p. 2008·3).
Ocular hypertension; glaucoma.

Vistalens *Vista, Philipp.*
Potassium iodide (p. 2336·3); sodium iodide (p. 2337·1).
Dry eye; lens opacities.

Vistallerg *Vista, Philipp.*
⊗Pheniramine maleate (p. 637·2); naphazoline hydrochloride (p. 1669·3).
Allergic eye disorders.

Vista-Methasone
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
⊗Betamethasone sodium phosphate (p. 1623·3).
Inflammatory disorders of the ear, eye, or nose.

Vistamethasone
Note: this name may be used for preparations of different composition.
LCH, Hong Kong.†
⊗Betamethasone (p. 1623·2); neomycin (p. 329·3).

Vista-Methasone N
Note: this name may be used for preparations of different composition.
Martindale Pharmaceuticals, UK.
⊗Betamethasone sodium phosphate (p. 1623·3); neomycin sulfate (p. 330·1).
Inflammatory disorders of the ear, eye, or nose with bacterial infection.

Vistamycin *Meiji, Jpn.*
Ribostamycin sulfate (p. 348·2).
Bacterial infections.

Vistapred *Vista, Philipp.*
⊗Prednisolone acetate (p. 1645·2).
Inflammatory eye disorders.

Vistaril *Pfizer, Turk.; Pfizer, USA.*
Hydroxyzine embonate (p. 630·3).
Anxiety; premedication; sedative; urticaria; nausea and vomiting; pruritus.

Vistasulf *Vista, Philipp.*
Sulfacetamide sodium (p. 361·1).
Bacterial eye infections.

Vistatears *Vista, Philipp.*
Hypromellose (p. 2189·2).
Dry eyes.

Vista-Tone *LCH, Hong Kong.†*
⊗Naphazoline (p. 1669·3); antazoline (p. 615·3).

VisThesia *Zeiss Meditec, Ger.*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Vistide *Gilead, Austral.; Gilead, Austria; Gilead, Belg.; Gilead, Cz.; Gilead, Denm.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; IFET (ΙΦΕΤ), Gr.; Gilead, Irl.; Gilead, Ital.; Gilead, Neth.; Pfizer, Pol.; Gilead, Port.; Gilead, Spain; Gilead, Swed.; Gilead, Switz.; Gilead, UK; Gilead, USA.*
Cidofovir (p. 970·1).
Cytomegalovirus retinitis; HIV infection.

Vistil *Santen, Ger.; Tubilux, Ital.*
Polyvinyl alcohol (p. 2204·2).
Dry eyes; eye irritation.

Visto *GMP, Indon.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Vistoxyn *Allergan, Ger.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Conjunctival disorders.

Vistra *Darvys, Philipp.*
Tramadol hydrochloride (p. 139·2).
Pain.

Vistrum *Pharos, Indon.*
Bovine colostrum (p. 2380·3); fructo-oligosaccharides (p. 2508·1); zinc (p. 2126·1).
Nutritional supplement.

Visu Q10 *Visufarma, Ital.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1); lutein (p. 2079·2).
Antoxidant.

Visual *Sandoz, Braz.*
⊗Zinc sulfate (p. 2126·2); naphazoline hydrochloride (p. 1669·3).
Ocular congestion.

Visual-Eyes *Optopics, USA.†*
Electrolytes (p. 1775·1).
Eye irrigation.

Visubiotic *Medichrom, Gr.*
Doxycycline hyclate (p. 288·2).

Visublefarite *Visufarma, Ital.*
⊗Betamethasone (p. 1623·2); sulfacetamide sodium (p. 361·1); tetryzoline phosphate (p. 1678·3).
Blepharitis.

Visubril *Allergan, Arg.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye inflammation; eye irritation.

Visuclar *Elea, Arg.*
⊗Naphazoline hydrochloride (p. 1669·3); pheniramine maleate (p. 637·2).
Eye disorders.

Visucloben *Visufarma, Ital.*
⊗Clobetasone butyrate (p. 1627·3).
Eye disorders.

Visucloben Antibiotico *Visufarma, Ital.*
⊗Clobetasone butyrate (p. 1627·3); bekanamycin sulfate (p. 227·1).
Infected eye disorders.

Visucloben Decongestionante *Visufarma, Ital.*
⊗Clobetasone butyrate (p. 1627·3); tetryzoline hydrochloride (p. 1678·3).
Eye congestion, irritation, and inflammation.

Visudine *Novartis, Gr.*
Verteporfin (p. 880·2).
Neovascular (wet) age-related macular degeneration; choroidal neovascularisation.

Visudyne *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile†; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Hong Kong; Parkedale, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S. Afr.; Novartis Ophthalmics, Singapore; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis Ophthalmics, UK; Novartis Ophthalmics, USA; Novartis, Venez.*
Verteporfin (p. 880·2).
Neovascular (wet) age-related macular degeneration; subfoveal choroidal neovascularisation.

Visuglican *Visufarma, Ital.*
Sodium cromoglicate (p. 1225·3); chlorphenamine maleate (p. 620·3).
Allergic conjunctivitis.

Visu-len *DermoDuemila, Ital.*
Lutein (p. 2079·2); selenium (p. 2086·3); zinc (p. 2126·1); grape (p. 2521·3); thioctic acid (p. 2629·1).
Nutritional supplement.

Visumetazone *Visufarma, Ital.*
⊗Dexamethasone (p. 1630·3).
Inflammatory eye disorders.

Visumetazone Antibiotico *Visufarma, Ital.*
⊗Bekanamycin sulfate (p. 227·1); tetryzoline hydrochloride (p. 1678·3); betamethasone (p. 1623·2).
Eye infections associated with inflammation and congestion.

Visumetazone Antistaminico *Visufarma, Ital.*
⊗Dexamethasone (p. 1630·3); chlorphenamine maleate (p. 620·3).
Allergic eye disorders.

Visumetazone Decongestionante *Visufarma, Ital.*
⊗Dexamethasone (p. 1630·3); tetryzoline hydrochloride (p. 1678·3).
Conjunctivitis.

Visumidriatic *Visufarma, Ital.*
Tropicamide (p. 2012·2).
Production of mydriasis.

Visumidriatic Fenilefrina *Visufarma, Ital.*
Tropicamide (p. 2012·2); phenylephrine hydrochloride (p. 1672·3).
Production of mydriasis.

VisuQ10 *Visufarma, Ital.*
Ubidecarenone (p. 2637·1); vitamin E (p. 2119·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Eye disorders.

Visurex *Aristopharma, Hong Kong.*
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2).
Conjunctivitis.

Visustrin *Pietrasanta, Ital.*
⊗Tetryzoline hydrochloride (p. 1678·3); methylthioninium chloride (p. 1559·1).
Eye congestion and irritation; conjunctival oedema.

Visu-ton *Biodelta, Ital.*
Lutein (p. 2079·2); myrtillus (p. 2566·2); grape (p. 2521·3); vitamin A (p. 2098·3); vitamin B_6 (p. 2105·3).
Nutritional supplement.

Visymplex Plus *Eadriex, Philipp.*
Vitamins; with or without lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Vi-Syneral *Sanofi Pasteur, Chile†; Grossman, Mex.*
Vitamins; minerals.
Dietary supplement.

USV, India.
Vitamins.
Vitamin deficiency.

Vi-Syneral GE *Beta, Arg.*
Tablets, vitamins; tablets, minerals.
Dietary supplement.

Vi-Syneral IMV *Beta, Arg.*
Vitamins.
Parenteral nutrition.

Vit C Frx *United Drug, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vit C-Mile *Osoth, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vita *Poen, Arg.*
Vitamin A acetate (p. 2098·3); vitamin E (p. 2119·1); vitamin P (p. 2505·2).
Vitamin supplement.

Vita 1000 *Sigma, Arg.*
Lapachos.
Tonic.

Vita Anti-Ox *Uniao Quimica, Braz.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); minerals.

Vita 3B *Riva, Canad.*
Vitamin B substances (p. 2102·3).

Vita Bambin *Le Naturiste, Canad.*
Vitamins.

Vita Bee *Rugby, USA.*
Vitamins.

Vita Brains *Vita Green, Hong Kong.†*
Vitamin B substances (p. 2102·3).

Vita Buerlecithin *Nycomed, Pol.*
Lecithin (p. 2542·2); vitamins.
Tonic.

Takeda, Switz.
Vitamin B (p. 2102·3); lecithin (p. 2542·2).
Tonic.

Vita C *CCM, Malaysia.*
Vitamin C (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Vita 3B+C *Riva, Canad.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).

Vita Calmag Zn *Vita Health, Singapore.*
Calcium (p. 1783·1); magnesium (p. 1786·3); zinc (p. 2126·1).
Calcium deficiency; osteoporosis.

Vita Care C-Long *Jemo, Denm.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vita Care Q_{10} *Jemo-Pharm, Pol.*
Ubidecarenone (p. 2637·1).
Cardiovascular disorders; periodontitis; tonic.

Vita Co-Enzyme Q10 *Vita Health, Singapore.*
Ubidecarenone (p. 2637·1).
Heart failure; hypertension; angina pectoris; arrhythmias; cardiomyopathy.

Vita Coldycin Echinacea Plus *Great Liaison, Hong Kong.†*
Echinacea (p. 2498·1); eucalyptus (p. 2501·1); melaleuca oil (p. 2551·1); peppermint oil (p. 1877·1); propolis (p. 2597·3); slippery elm (p. 2617·1).

Vita C-R15 *Reckeweg, Cz.†*
Acidum phosphoricum (p. 2589·1); anamirta cocculus (p. 2483·1); chamaelirium luteum (p. 2524·3); sepia officinalis (p. 2613·1); strychnos ignatii (p. 2532·1); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Vita C-R15 forte *Reckeweg, Cz.†*
Acidum phosphoricum (p. 2589·1); anamirta cocculus (p. 2483·1); chamaelirium luteum (p. 2524·3); panax ginseng (p. 2513·3); strychnos ignatii (p. 2532·1); sepia officinalis (p. 2613·1); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Vita CT Prenatal *Jaymac, USA.*
Vitamins; minerals.
Dietary supplement.

Vita D *Austral, Arg.*
Ergocalcigerol (p. 2113·3).
Hypocalcaemia; hypophosphataemia; osteodystrophy; rickets.

Vita Ferin C *Geistlich, Switz.†*
Vitamins; minerals.

Vita Fizz C *Hexa, Arg.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vita Grip *Sinterapico, Braz.†*
Ascorbic acid (p. 2110·3); caffeine (p. 1203·3); salicylamide (p. 129·2); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Vita Jam *Garuda, Hung.*
Indian gooseberry (p. 2532·2).
Tonic.

Vita Jr *Uniao Quimica, Braz.*
Vitamins.

Vita K *Uniao Quimica, Braz.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding.

Vita K Plus *Dicofarm, Ital.*
Phytomenadione (p. 2122·2).
Vitamin K supplement.

Vita Kids *Douglas, Canad.*
Vitamins; minerals.

Vita Lift *L'Oreal, Canad.*
SPF 15: Ensulizole (p. 1703·1); octinoxate (p. 1715·1).
Sunscreen.

Vita Menal *Alacan, Spain.*
Cyproheptadine hydrochloride (p. 624·1); amino acids; cyanocobalamin (p. 2107·2); phosphorylcolamine (p. 2589·3).
Tonic.

Vita Multicap *Sriprasit, Thai.*
Vitamins; minerals; choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2).

Vita Natal *Vita Health, Singapore.*
Capsules: Vitamins; minerals; folic acid (p. 2063·1).
Dietary supplement in pregnancy.

Vita Health, Singapore.
Cream: Evening primrose oil (p. 2502·2); jojoba oil.
Dry skin; massage therapy during and after pregnancy.

Vita OB *Vonnace, Philipp.*
Vitamins; minerals.
Supplement for pregnant and lactating women.

Vita 1000 Plus *Sigma, Arg.*
Lapachos; ginkgo biloba (p. 2512·3); camellia thea.
Tonic.

Vita Senior *Uniao Quimica, Braz.*
Vitamins; minerals; ginseng (p. 2513·3).

Vita SL *Dynamic, Philipp.*
Vitamins; hematoporphyrin hydrochloride; magnesium carbonate (p. 1856·2); orotic acid (p. 2578·1); lysine hydrochloride (p. 2079·3); lecithin (p. 2542·2); ginseng (p. 2513·3); royal jelly (p. 2608·1).
Nutritional supplement.

Vita SL with lecithin *Dynamic, Philipp.†*
Vitamins; calcium lactate (p. 1784·1); lysine hydrochloride (p. 2079·3); lecithin (p. 2542·2).
Nutritional supplement.

Vita SL Plus *Dynamic, Philipp.*
Vitamins; zinc (p. 2126·1); lysine (p. 2079·3); taurine (p. 2626·2); chlorella growth factor (p. 2475·3).
Nutritional supplement.

Vita Stress *Vita Green, Hong Kong.†*
Choline (p. 2055·2); inositol (p. 2533·2); vitamin B substances (p. 2102·3).

Vita-Ace *Ace, Philipp.*
Vitamins.

Vita-B *Vesco, Thai.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency.

Vita-B6 *Vitabalans, Fin.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Vitabact *Thea, Fr.; Novartis, Rus.*
Picloxydine hydrochloride (p. 1766·1).
Bacterial eye infections.

Vitabe *Andromaco, Chile.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Vitabee-1-10 *SSP, Thai.*
Thiamine hydrochloride (p. 2103·1).

Vitabee-2-25 *SSP, Thai.*
Riboflavin (p. 2104·3).

3-Vitabee *Chew, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency.

Vitabeks *SSK, Turk.*
Vitamin B substances (p. 2102·3).

Vita-Bel *Offenbach, Mex.†*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3); iron (p. 2073·1).
Appetite loss.

Vitaben *SSK, Turk.*
Thiamine (p. 2102·3); pyridoxine (p. 2105·3).
Vitamin B_1 and vitamin B_6 deficiency; neuritis; neuropathy.

Vitaber A E *Llorens, Spain.*
Di-isopropylammonium dichloroacetate (p. 1359·1); vitamin A acetate (p. 2098·3); tocoferil acetate (p. 2119·2).
Deficiency of vitamins A and E; skin disorders; eye disorders; recurrent miscarriage; infertility.

Vitabex A *Universal, Hong Kong.†*
Choline (p. 2055·2); vitamin B substances (p. 2102·3).

Vitabin *Stada, Neth.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin infections.

Vitabiol *Ulagay, Turk.*
Vitamins.

Vitabiol C *Ulagay, Turk.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Vitabiol C-Fort *Ulagay, Turk.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3).
Leave the -Fort to distinguish from earlier entry for Vitabiol C.

Vitabion
Note: this name may be used for preparations of different composition.
GMP, Indon.
Ferrous gluconate (p. 2061·2); manganese sulfate (p. 2081·2); copper sulfate (p. 2057·2); vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1). Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; dietary supplement.

Unison, Hong Kong; Unison, Malaysia.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; pernicious anaemia; vitamin B supplement.

Unison, Thai.
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neuritis; neuropathy; neurological disorders.

Cipla, India.†
Vitamins.

Vitabite *Vitaflo, Irl.†*
Food for special diet.
Disorders requiring protein restriction.

Vita-Bo *Marching, Hong Kong.†*
Vitamins.

Vita-Bo Calcium *Marching, Hong Kong.†*
Calcium gluconate (p. 1783·3); lysine (p. 2079·3); vitamins.

Vita-Bo Multivitamins *Marching, Hong Kong.†*
Lysine (p. 2079·3); vitamins.

Vita-Bob *Scot-Tussin, USA.*
Vitamins.

Vitabo-Cal *Marching, Hong Kong.†*
Calcium gluconate (p. 1783·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Vita-C *Freeda, USA.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; scurvy.

Vitac *Sanofi-Aventis, Chile.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Vita-C Derms's *LDA, Arg.*
Ascorbic acid (p. 2110·3); hyaluronic acid (p. 2526·2).
Dry skin; skin ageing.

Vita-Cal *Pharmasant, Thai.*
Ferrous fumarate (p. 2060·3); calcium dihydrogen phosphate (p. 1783·3); ascorbic acid (p. 2110·3); folic acid (p. 2063·1); vitamin B_2 (p. 2104·3).
Vitamin and mineral deficiencies.

Columbia, S.Afr.†
Calcium (p. 1783·1); vitamins.
Calcium and vitamin supplement.

Vitacal
Note: this name may be used for preparations of different composition.
Bago, Arg.
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Dietary supplement.

Pro Farma, Switz.
Calcium phosphate (p. 1784·2); colecalciferol (p. 2113·1).
Calcium and vitamin D supplement; osteoporosis.

Vita Health, Singapore.
Tablets: Calcium (p. 1783·1).
Calcium deficiency; osteoporosis.

Vita Health, Singapore.
Effervescent tablets: Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; osteoporosis.

Vitacal + D *Vita Health, Singapore.*
Calcium (p. 1783·1); vitamin D (p. 2112·3).
Calcium deficiency; osteoporosis.

Vita-Calcea *Ratiopharm, Belg.†*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).
Osteoporosis.

Vitacalcin *Zentiva, Cz.*
Calcium carbonate (p. 1824·3).
Osteoporosis; osteomalacia; calcium deficiency.

Vitacal-D *Otto, Indon.*
Calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); colecalciferol (p. 2113·1).
Nutritional supplement.

Vitacap *Mega Lifesciences, Philipp.; Neopharm, Thai.*
Vitamins; minerals.
Dietary supplement.

VitaCarn *Kendall McGaw, USA.*
Carnitine (p. 2053·2).
Carnitine deficiency.

Vita-C-Cal *Vita Green, Hong Kong.†*
Calcium (p. 1783·1); ascorbic acid (p. 2110·3).

Vitace
Note: this name may be used for preparations of different composition.
Prisfar, Port.
Echinacea purpurea (p. 2498·1); vitamin C (p. 2110·3); zinc (p. 2126·1).
Tonic.

Vitacee *Charoen, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vitacelsia Plus *Prisfar, Port.*
Vitamins; minerals.

Vitacen C *Amavita, Switz.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vitacharm *Veropharm, Rus.*
Vitamins.

Vita-Chel *Douglas, Canad.†*
Vitamins; minerals.

Vitachol *Landson, Indon.*
Lecithin (p. 2542·2); vitamins; ferrous fumarate (p. 2060·3); copper (p. 2057·1); iodine (p. 2336·3).
Nutritional supplement for pregnancy and lactation.

Vitacic *Europhta, Mon.*
Adenosine (p. 1291·1); thymidine (p. 2631·1); cytidine (p. 2491·1); uridine (p. 2637·3); disodium guanylate (p. 2495·2).
Corneal damage.

Wing Wai, Hong Kong.†
Adenosine (p. 1291·1); cytidine (p. 2491·1); guanosine (p. 2523·2); thymidine (p. 2631·1); uridine (p. 2637·3).

Vitacid *Theraskin, Braz.; Surya Dermato, Indon.*
Tretinoin (p. 1725·2).
Acne; photoageing; light-induced skin damage.

Vitacid Acne *Theraskin, Braz.*
Clindamycin (p. 269·3); tretinoin (p. 1725·2).
Acne.

Vitacid Plus *Theraskin, Braz.*
⊗Tretinoin (p. 1725·2); hydroquinone (p. 1705·1); fluocinolone acetonide (p. 1636·1).
Skin hyperpigmentation.

Vitacillin *Casel, Turk.*
Oxytetracycline hydrochloride (p. 337·2); polymyxin B sulfate (p. 342·3).

Vitacimin *Takeda, Indon.; Takeda, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement; skin pigmentation disorders; circulatory disorders.

Vitacimin Sweetlet *Takeda, Hong Kong.†*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Vitacin *Geolab, Braz.*
Ascorbic acid (p. 2110·3).

Vitacip *Cipla, India.*
Vitamins; ginseng (p. 2513·3).

VitaCirc-B *Macoven, USA.*
Mecobalamin (p. 2108·1); calcium methylfolate (p. 2053·1); pyridoxal phosphate (p. 2105·3).

Vitacon *Polfa Warszawa, Pol.*
Phytomenadione (p. 2122·2).
Coagulation disorders.

Vitacor *UB, Switz.*
Crataegus (p. 2488·1).
Cardiac disorders.

Vitacore *Coronet, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamin A, C, and E deficiencies.

Vitacortil *Fada, Arg.*
⊗Betamethasone dipropionate (p. 1623·3); gentamicin sulfate (p. 304·2); clotrimazole (p. 576·2).
Infected skin disorders.

Vitacortil B *Fada, Arg.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

VitaCris *Cris Flower, Ital.*
Vitamins.
Nutritional supplement.

Vitacuivre *Monin, Fr.*
Ascorbic acid (p. 2110·3); copper gluconate (p. 2057·2); shiitake.
Dietary supplement.

Vitacur *Lapi, Indon.*
Curcuminoid; betacarotene (p. 2051·1); vitamin B substances (p. 2102·3); vitamin D (p. 2112·3); calcium pidolate (p. 1784·3); fructo-oligosaccharides (p. 2508·1).
Reduced appetite; vitamin supplement.

Vitacymin *Universal, Hong Kong.†*
Choline (p. 2055·2); vitamin B substances (p. 2102·3).

Vitacymin Syrup with Lysine *Universal, Hong Kong.†*
Lysine (p. 2079·3); vitamin B substances (p. 2102·3).

Vita-D3 *Forum, UK.*
Colecalciferol (p. 2113·1).
Vitamin D supplement.

Vitadece *Klonal, Arg.*
Ascorbic acid (p. 2110·3); vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Vitamin supplement.

Vita-Dermacide *Sinclair, Fr.*
Nicotinamide (p. 2083·1); glutamic acid (p. 2070·2); tryptophan (p. 453·2).
Irritative dermatitis.

Vitaderme *Cristalia, Braz.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); vitamin E (p. 2119·1); allantoin (p. 1693·1).
Barrier preparation.

Vitadesan *Sanval, Braz.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).

Vitadol-C *Karicare, NZ.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Vitamin supplement.

Vitadoron *Weleda, Swed.*
Fragaria vesca; grape (p. 2521·3).
Constipation; eczema.

Vitadrop *Kalbe, Indon.*
Hyaluronic acid (p. 2526·2); vitamin B_{12} (p. 2107·2).
Eye irritation; dry eyes.

Tubilux, Malaysia.
Sodium hyaluronate (p. 2526·2); vitamin B_{12} (p. 2107·2).
Eye irritation; dry eyes.

Vitadye *Dermatech, Austral.†*
Dihydroxyacetone (p. 1700·1).
Vitiligo.

Vitadyn *Bilim, Turk.†*
Vitamins; minerals.

Vitadyn C *Oftalmi, Venez.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vita-E *Ache, Braz.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Cambridge Healthcare, UK.
d-Alpha tocopherol (p. 2119·1) or *d*-alpha tocoferil acetate (p. 2119·1).

Vitae *Vivax, Venez.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

VitaEPA *Vita Health, Singapore.*
Docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).
Hyperlipidaemias.

VitaEPA Plus *Vita Health, Singapore.*
Eicosapentaenoic acid (p. 1460·2); evening primrose oil (p. 2502·2).
Hyperlipidaemias; circulatory disorders; inflammation.

Vitafardi C B12 *Fardi, Spain.†*
Ascorbic acid (p. 2110·3); hydroxocobalamin (p. 2107·3).
Deficiency of vitamins B_{12} and C.

Vitafer
Note: this name may be used for preparations of different composition.
EMS, Braz.
Ferrous sulfate (p. 2062·2).

Vitaferol *Otto, Indon.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Vitaferro *Hexal, Ger.†*
Ferrous gluconate (p. 2061·2).
Iron deficiency; iron-deficiency anaemia.

Vitafissan N *Uhlmann-Eyraud, Switz.*
Caseine hydrolysate (Labiline) (p. 2055·2); vitamin A (p. 2098·3); vitamin E (p. 2119·1); linoleic acid (p. 2509·2); linolenic acid (p. 1460·2).
Skin disorders.

Vitafluid *Mann, Ger.*
Vitamin A palmitate (p. 2098·3).
Eye disorders.

Vitaflur *Maver, Chile.*
Sodium fluoride (p. 2089·2).

Vitafol *Cipla, India.*
Folic acid (p. 2063·1).
Folic acid supplement; prevention of neural tube defects in pregnancy; megaloblastic anaemia.

Everett, USA.
Tablets: Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); calcium carbonate (p. 1824·3); vitamins.
Iron-deficiency anaemias.

Hi-Tech, USA.
Syrup: Ferric pyrophosphate (p. 2060·2); folic acid (p. 2063·1); vitamin B substances (p. 2102·3).
Iron-deficiency anaemia.

Vitafol-OB *Everett, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.

Vitafol-One *Everett, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement.

Vitafol-Plus *Propharma, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1); lauric acid.
Dietary supplement.

Vitafol-PN *Everett, USA.*
Vitamins; minerals.

Vitafol-Ultra *Everett, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vitaforce *Pharma-Natura, S.Afr.†*
Vitamins; minerals.

Vitaforce Acerola C *Pharma-Natura, S.Afr.†*
Acerola; rosehip; green pepper; blackcurrant (p. 2458·1); ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1); rutoside (p. 2505·3); citrus bioflavonoids (p. 2505·2); hesperidin (p. 2505·2); tissue salts (Combin J).
Dietary supplement; vitamin C deficiency.

Vitaforce C *Pharma-Natura, S.Afr.†*
Ascorbic acid (p. 2110·3).
Dietary supplement; vitamin C deficiency.

Vitaforce E *Pharma-Natura, S.Afr.†*
Vitamin E (p. 2119·1).
Dietary supplement; vitamin E deficiency.

Vitaforce Massif-C *Pharma-Natura, S.Afr.†*
Ascorbic acid (p. 2110·3).
Dietary supplement; vitamin C deficiency.

Vitaforce Nutri-B *Pharma-Natura, S.Afr.†*
Vitamin B substances (p. 2102·3); potassium phosphate (p. 1791·1); lecithin (p. 2542·2); yeast (p. 2125·2).
Dietary supplement.

Vitaftor *Tekhnolog, Ukr.†*
Vitamin A acetate (p. 2098·3) or vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); ascorbic acid (p. 2110·3); sodium fluoride (p. 2089·2).
Dental caries; periodontitis; osteoporosis; bone injury.

Vitafusal *Serum-Werk Bernburg, Ger.*
⊗An etherified starch (p. 1146·1); electrolytes (p. 1775·1).
Plasma volume expansion; shock.

Vitagama Fluor *Almirall, Spain.†*
Sodium fluoride (p. 2089·2); vitamins.
Vitamin and fluoride deficiencies.

Vitagamma *Bryntsalov, Rus.*
Pyridoxine hydrochloride (p. 2105·3); thiamine hydrochloride (p. 2103·1); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neuritis, neuralgia; neuropathy.

Vita-Gard *GNLD, Austral.*
Vitamins; zinc oxide (p. 1729·1); citrus bioflavonoids (p. 2505·2).
Antoxidant; dietary supplement.

Golden Neo-Life, Canad.
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1).

Vitagel *Mann, Ger.*
Vitamin A palmitate (p. 2098·3).
Eye disorders.

Vita-Gem C *Gemi, Pol.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vitagen *Cadila, India.*
Vitamin B substances (p. 2102·3).

Interhealthcare, Philipp.
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuritis; anaemias.

Vitagen Advance *Midlothian, USA.*
Vitamin B_{12} (p. 2107·2); dessicated stomach (p. 2444·1); iron (p. 2073·1).
Succinic acid (p. 2214·3) and vitamin C (p. 2110·3) are included in this preparation to increase the absorption and availability of iron.

Vitagenol *Sanofi-Aventis, Chile.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); selenium (p. 2086·3).
Dietary supplement.

Vitagenol Plus *Boehringer Ingelheim, Arg.*
Ginseng (p. 2513·3); minerals; vitamins; trace elements.
Tonic.

Vita-Gerin *Chemomedica, Austria.*
⊗Deanol orotate (p. 2319·1); vitamins; minerals; adenosine (p. 1291·1); choline bitartrate (p. 2055·2).
Tonic.

Geistlich, Switz.
⊗Deanol orotate (p. 2319·1); vitamins; minerals; rutoside (p. 2505·3); choline bitartrate (p. 2055·2).
Tonic.

Vita-Gerin N *Cassella-med, Ger.*
⊗Deanol orotate (p. 2319·1); magnesium orotate (p. 1786·3); vitamins; minerals; choline bitartrate (p. 2055·2).
Tonic.

Vitaginseng *Korean Ginseng, Philipp.*
Vitamins; minerals; ginseng (p. 2513·3); aloe; lecithin (p. 2542·2).
Dietary supplement.

Vita-Grin *Grin, Mex.†*
Vitamins; minerals.

Vitagrow *Mahakam Beta, Indon.*
Curcuminoid (p. 2489·3); calcium citrate (p. 1783·2); vitamins; fructo-oligosaccharides (p. 2508·1).
Appetite stimulant; dietary supplement.

Vitaguarin *Hepart, Switz.*
Guar gum (p. 475·1).
Obesity.

Vitaherpavac *Vitafarma, Rus.*
An inactivated herpes simplex vaccine (p. 2392·2).
Active immunisation.

VitaHES *Serum-Werk Bernburg, Ger.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; shock.

Vitahes *Adcock Ingram Critical Care, S.Afr.*
⊗An etherified starch (p. 1146·1) in sodium chloride.

Vita-Hexin *Streuli, Switz.*
Chlorhexidine gluconate (p. 1743·3); vitamin A palmitate (p. 2098·3); cod-liver oil (p. 2056·3); zinc oxide (p. 1729·1).
Skin lesions.

Vita-Iodurol *Novartis, Rus.; Novartis, Ukr.†*
Adenosine (p. 1291·1); magnesium chloride (p. 1787·1); calcium chloride (p. 1783·1); nicotinic acid (p. 2083·1).
Cataract.

Vitakap *Mega Lifesciences, Ukr.*
Vitamins; minerals.
Dietary supplement.

Vitakay *Doctors, Philipp.*
Menadione sodium bisulfite (p. 2122·2).

Vita-Kid *Solgar, UK.*
Vitamins; folic acid (p. 2063·1).

Solgar, USA.
Vitamins.

Vitakid *Pharmaland, Thai.*
Vitamins; lysine hydrochloride (p. 2079·3).
Tonic.

Vitakids *Vitalink, Philipp.*
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3); chlorella growth factor (p. 2475·3).
Nutritional supplement.

Vital
Note: this name may be used for preparations of different composition.
Yu Sheng, Singapore.
Glucosamine sulfate (p. 2515·3).
Joint and cartilage disorders.

Vital B *Teingro, Arg.*
Vitamin B substances (p. 2102·3).
Vitamin supplement.

Vital BE *Media Power, Canad.†*
Vitamins; minerals.

Vital Ear Oil *Medikon, Indon.*
Thymol (p. 1772·2); menthol (p. 2553·2); camphor (p. 2466·2).
Otitis.

Vital Eyes
Note: this name may be used for preparations of different composition.
Novartis Consumer, UK.
Lavender (p. 2541·1); orange flower (p. 2575·3); hamamelis (p. 2523·3); euphrasia (p. 2502·1).
Eye irritation.

Vital High Nitrogen *Abbott, Hong Kong.*
Preparation for enteral nutrition.

Ross, USA.
A preparation for enteral nutrition.

Vital HN *Abbott, Austral.; Abbott, Canad.; Abbott, NZ.*
Preparation for enteral nutrition.

Vital Sun Protection *Kiehls, Canad.*
SPF 30: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kiehls, Canad.
SPF 40: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Kiehls, Canad.†
SPF 15: Avobenzone (p. 1695·1); octisalate (p. 1715·2); octocrilene (p. 1715·2).
Sunscreen.

Vitala *Bernofarm, Indon.*
Thioctic acid (p. 2629·1); vitamin B_{12} (p. 2107·2); chromium tripicolinate (p. 2056·1).
Dietary supplement.

Vitalac BL *Sari Husada, Indon.*
Infant feed.
Lactose intolerance.

Vitalaif *Medix, Mex.*
Vitamins; minerals; ginseng (p. 2513·3).

Vita-Lea *Shaklee, Canad.*
Vitamins; minerals.
Dietary supplement.

Vitalee *MedChem, USA.*
Vitamins.
Dietary supplement.

Vitalene *Kalbe, Indon.*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Vitamins A, C, and E deficiency.

Vitalets *Freeda, USA.*
Vitamins; minerals; iron (p. 2073·1).

Vitalex *Molex Ayus, Indon.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Vitalfort Antioxidante *Biokosma, Arg.*
Vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); tomato; camelia sinensis (p. 2648·2); lapacho.
Dietary supplement.

Vitalic *Katra, Singapore.*
Cyanocobalamin (p. 2107·2); pyridoxine (p. 2105·3); thiamine (p. 2102·3).

Deltapharm, Hong Kong.†
Vitamin B_1 (p. 2103·1); vitamin B_{12} (p. 2107·2); vitamin B_6 (p. 2105·3).

Vitalil K *Linfar, Arg.*
A range of dietary supplements.

Vitalin
Note: this name may be used for preparations of different composition.
Beres, Hung.
Vitamins; minerals; trace elements.

Vitaline Selenium *Integrative, USA.*
Calcium (p. 1783·1); selenium (p. 2086·3).

Vitalipid *Fresenius, Belg.; Fresenius Kabi, Fin.; Baxter, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Norw.; Fresenius Kabi, NZ; Fresenius Kabi, Port.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Thai.*
Vitamin A (p. 2098·3); vitamin D_2 (p. 2113·3); vitamin E (p. 2119·1); vitamin K_1 (p. 2122·2).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, Austria.
Vitamin A (p. 2098·3); vitamin D (p. 2112·3); vitamin E (p. 2119·1); vitamin K (p. 2122·1).
Contains egg lipid.
Parenteral nutrition.

Fresenius Kabi, Denm.; Fresenius Kabi, Ital.
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); vitamin E (p. 2119·1); phytomenadione (p. 2122·2).
Parenteral nutrition.

Vitalipid N *Fresenius Kabi, Austral.; Fresenius Kabi, Chile; Fresenius Kabi, Hong Kong; Fresenius Kabi, Israel; Fresenius Kabi, Malaysia†; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.*
Vitamin A (p. 2098·3); vitamin D_2 (p. 2113·3); vitamin E (p. 2119·1); vitamin K_1 (p. 2122·2).
Contains egg lecithin.
Parenteral nutrition.

Fresenius Kabi, Cz.
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); alpha tocopherol (p. 2119·1); phytomenadione (p. 2122·2).
Parenteral nutrition.

SSPC, China; Fresenius Kabi, Indon.
Vitamin A (p. 2098·3); ergocalciferol (p. 2113·3); vitamin E (p. 2119·1); phytomenadione (p. 2122·2).
Parenteral nutrition.

Vitalipide *Fresenius Kabi, Fr.*
Vitamin A (p. 2098·3); vitamin D_2 (p. 2113·3); vitamin E (p. 2119·1); K_1 (p. 2122·2).
Parenteral nutrition.

Vitalitan *Ducto, Braz.†*
Vitamins; minerals.

Vitalium
Note: this name may be used for preparations of different composition.
Cifarma, Braz.
Vitamins; minerals.

Angelini, Spain.†
St John's wort (p. 449·1).
Tonic; sleep disorders.

Vitalivin-E Reformulated *Pascual, Philipp.†*
Vitamins; minerals; lysine hydrochloride (p. 2079·3).
Nutritional supplement.

Vitalix *Roemmers, Arg.*
Iron polymaltose (p. 2077·2).
Iron deficiency; iron-deficiency anaemia.

Vitalix Complex *Roemmers, Arg.*
Iron polymaltose (p. 2077·2); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Anaemias.

Vitalize *Scot-Tussin, USA.*
Ferric pyrophosphate (p. 2060·2); vitamin B substances (p. 2102·3); L-lysine (p. 2079·3).
Iron-deficiency anaemias.

Vitalmin Nutraenergy *Recalcine, Chile.*
Preparation for enteral nutrition.

Vitalmix Complex *Montefarmaco, Ital.*
Myrtillus (p. 2566·2); guarana (p. 2648·2); ginseng (p. 2513·3); ubidecarenone (p. 2637·1); bioflavonoids (p. 2505·2); vitamins.
Nutritional supplement.

Vitalmix Fast *Montefarmaco, Ital.*
Creatine (p. 2488·3); vitamins; ginseng (p. 2513·3); guarana (p. 2648·2).

VitalmixFos *Montefarmaco, Ital.*
Phosphorylserine; Siberian ginseng (p. 2614·3); arginine aspartate (p. 2049·1); ginkgo biloba (p. 2512·3); ubidecarenone (p. 2637·1); vitamins.
Nutritional supplement.

Vitalmix Junior *Montefarmaco, Ital.*
Vitamin B_{12} (p. 2107·2); folic acid (p. 2063·1); lactoferrin (p. 2539·3); oligopin; amino acids; phosphorylserine.
Nutritional supplement.

Vitalogink *Mylan, Fr.*
Ginkgo biloba (p. 2512·3).
Mental function impairment; peripheral vascular disorders; vertigo.

Vitalong C TRC *Bernofarm, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Vitalorange *GSK, Mex.†*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).
Nutritional supplement.

Vitalpen *Labomed, Chile.*
Flucloxacillin (p. 299·1).
Gram-positive bacterial infections.

Vitalsea *Oleosea, Fr.*
Krill oil.
Dietary supplement.

Vitalsex *Biokosma, Arg.*
Siberian ginseng (p. 2614·3); guarana (p. 2648·2); damiana (p. 2491·3); pfaffia paniculata; vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3).
Dietary supplement.

Vitalumiere *Chanel, Canad.*
SPF 15: Octinoxate (p. 1715·1).
Sunscreen.

Vitalux *Medivis, Ital.*
Betacarotene (p. 2051·1); vitamins; minerals; soya lecithin (p. 2542·2); beeswax (p. 2170·2); wheat-germ oil (p. 2647·1).
Nutritional supplement.

Novartis, Canad.
A range of vitamin and mineral preparations.

Novartis, Chile; Novartis, Fr.†; Novartis, Hong Kong; Novartis, Mex.; Novartis, Philipp.; Novartis, Turk.
Vitamins; minerals.
Antioxidant preparation; nutritional supplement; eye disorders.

Novartis, Indon.
Vitamins; minerals; lecithin (p. 2542·2).
Dietary supplement for healthy eyes.

Novartis, Venez.
Vitamins; zinc gluconate (p. 2126·2); manganese gluconate (p. 2081·2); selenium yeast (p. 2125·2).
Nutritional supplement.

Vitalux Plus *Alcon, Fr.*
Vitamins; minerals; fish oil (p. 1460·1); lutein (p. 2079·2).
Dietary supplement; eye health.

Novartis Ophthalmics, Arg.; Novartis, Indon.; Novartis, Israel; Novartis, Malaysia; Novartis, Mex.; Alcon, Singapore; Novartis, Thai.; Novartis, Venez.
Vitamins; minerals; lutein (p. 2079·2).
Dietary supplement; cataract-related macular degeneration.

Medivis, Ital.
⊗Vitamins; lecithin (p. 2542·2); lutein (p. 2079·2); gelatin (p. 1154·1); monoglycerides; iron oxides.
Nutritional supplement.

Novartis, UK.
Lutein (p. 2079·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1); copper (p. 2057·1); nicotinamide (p. 2083·1).

Vitalyn *Fontovit, Braz.†*
Vitamins; minerals.

Vita-M *Patar, Thai.*
Vitamins.

Vitam *KVZ, Ukr.†*
Vitamins; minerals.
Dietary supplement.

Vitam Doce *Frasca, Arg.*
Cyanocobalamin (p. 2107·2).
Neuritis.

Vitamag *Aspen Consumer, S.Afr.*
Vitamin B substances (p. 2102·3); magnesium (p. 1786·3); zinc (p. 2126·1).
Vitamin and mineral supplement.

Vitamalt *Faran, Gr.*
Vitamins.

Vitamam 1 *Novell, Indon.*
Vitamins; minerals; ginger (p. 1844·1); fructo-oligosaccharides (p. 2508·1).
Nutritional supplement in pregnancy.

Vitamam 2 *Novell, Indon.*
Capsules, vitamins; minerals; fructo-oligosaccharides (p. 2508·1); capsules, ferrous fumarate (p. 2060·3).
Nutritional supplement in pregnancy.

Vitamam 3 *Novell, Indon.*
Capsules, vitamins; minerals; fructo-oligosaccharides (p. 2508·1); capsules, ferrous fumarate (p. 2060·3).
Nutritional supplement in pregnancy.

Vitamax
Note: this name may be used for preparations of different composition.
GSK, Rus.†
⊗Vitamins; minerals; royal jelly (p. 2608·1); ginseng (p. 2513·3); wheat-germ oil (p. 2647·1); soya phosphatides; safflower oil (p. 2086·3); L-arginine; L-lysine; orotic acid (p. 2578·1); deanol tartrate (p. 2319·1); pollen.
Tonic.

VitaMed MD Iron 21/7 *TherapeuticsMD, USA.*
21 Tablets, iron (p. 2073·1); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); folic acid (p. 2063·1); succinic acid (p. 2214·3); threonic acid; 7 tablets, folic acid; succinic acid.
Dietary supplement.

Vitamedin *Sankyo, Hong Kong.†*
Vitamin B substances (p. 2102·3).
Anaemias; neuritis; rheumatic disorders; sciatica.

VitaMedMD One Rx *TherapeuticsMD, USA.*
Vitamins; iron (p. 2073·1); zinc (p. 2126·1); docosahexaenoic acid (p. 1460·1).
Dietary supplement.

VitaMedMD Plus Rx *TherapeuticsMD, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1).
Dietary supplement.

VitaMedMD RediChew Rx *TherapeuticsMD, USA.*
Vitamin B substances (p. 2102·3); colecalciferol (p. 2113·1).
Dietary supplement.

Vitamen *Beta, Ital.*
Protein; vitamins.

Vita-Merfen *Novartis Consumer, Switz.; Novartis, Turk.*
Chlorhexidine gluconate (p. 1743·3); benzoxonium chloride (p. 1739·2); vitamin A palmitate (p. 2098·3).
Minor wounds and burns.

Vita-Merfen NF *Novartis Consumer, Israel.*
Chlorhexidine gluconate (p. 1743·3); benzoxonium chloride (p. 1739·2); vitamin A (p. 2098·3).
Burns; wounds.

Vitamet *Pan-Ject, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Vitamex C *Konimex, Indon.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Vitamfenicolo *Tubilux, Ital.*
Chloramphenicol (p. 257·1) or chloramphenicol sodium succinate (p. 257·2).
Bacterial eye infections.

Vitamicê *Greenpharma, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Vitamicin *Vitapan, Braz.†*
Gentamicin (p. 304·2).
Bacterial infections.

Vitamidyne A and D *Fischer, Israel.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).
Vitamin A and D deficiency.

Vitamin A Acid *Dermik, Hong Kong.†*
Tretinoin (p. 1725·2).
Acne.

Vitamin B Complex *DHA, Singapore.*
Vitamin B substances (p. 2102·3); ergocalciferol (p. 2113·3).
Vitamin deficiency; dietary supplement.

Vitamin B duo *Mibe, Ger.*
Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3).
Neurological system disorders.

Vitamin B Forte *DHA, Malaysia.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Polyneuritis; neuralgia; diabetic neuropathy.

Vitamin C-500 *Yung Shin, Singapore.*
Vitamin C (p. 2110·3); calcium pantothenate (p. 2085·2).
Dietary supplement.

Vitamin C - Threshold Controlled *GNLD, Austral.*
Ascorbic acid (p. 2110·3); citrus sinensis (p. 2576·2); citrus bioflavonoids (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2).
Dietary supplement.

Vitamin C YSP *YSP, Malaysia.*
Ascorbic acid (p. 2110·3); calcium pantothenate (p. 2085·2); sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Vitamin Cee *T Man, Thai.*
Vitamin C (p. 2110·3).

Vitamin E Complex *GNLD, Austral.*
d-Alpha tocopherol (p. 2119·1); wheat-germ oil (p. 2647·1); soya lecithin (p. 2542·2).
Dietary supplement.

Vitamin E.F.C. *YSP, Malaysia.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Vitamin for the Hair *Natural Life, Arg.*
Soya protein; vitamin B substances (p. 2102·3); minerals.

Vitamina A Composta *Labesfal, Port.*
Vitamin A (p. 2098·3); vitamin D (p. 2112·3).

Vitamina C Plus *ISA, Arg.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); betacarotene (p. 2051·1).
Dietary supplement.

Vitamina C-Complex *Natural Life, Arg.*
Rose fruit (p. 2607·1); citrus bioflavonoids (p. 2505·2); rutoside (p. 2505·3); hesperidin (p. 2505·2) complex; red cherry (p. 2207·2).
Vitamin C supplement.

Vitamina F99 Topica *Vitafarma, Spain.†*
Peru balsam (p. 2587·1); vitamin F (p. 2509·2).
Skin disorders.

Vitaminac Retard *Confar, Port.*
Vitamin C (p. 2110·3).

Vitaminal *Proula, Venez.*
Vitamin B substances (p. 2102·3).
Vitamin B supplement; neuropathies.

Vitaminoftalmina *Davi, Port.*
Vitamin A palmitate (p. 2098·3).
Eye disorders.

Vitaminol *Bio-Sante, Canad.*
Vitamins; minerals.

Vitaminorum *Sigma, Austral.*
Vitamins; minerals.

Vitamins Only *Solgar, UK.*
Vitamins.

Vitamix *Knop, Chile.*
Vitamins; ginseng (p. 2513·3).

Vitamixin *Nutrigen, UK.*
Vitamins; minerals.
Dietary supplement.

Vitamon *Cipla, India.*
Ferric ammonium citrate (p. 2060·1); folic acid (p. 2063·1); cyanocobalamin (p. 2107·2).

Vitamon K *Omega, Belg.*
Phytomenadione (p. 2122·2).
Vitamin K deficiency bleeding.

Vitamoren *IAE, Philipp.*
Vitamins; calcium (p. 1783·1).
Nutritional supplement.

Vitamult *CTI, Israel.*
Vitamins.
Dietary supplement.

VitaMulti *Otto, Indon.*
Vitamins; minerals.
Nutritional supplement in pregnancy and lactation.

Vitamuruine *Medgenix, Belg.*
Vitamin A acetate (p. 2098·3).
Burns; skin disorders; wounds.

Vitamycetin *Wyeth, India.*
Chloramphenicol (p. 257·1) or chloramphenicol palmitate (p. 257·1).
Bacterial infections.

Vit-A-N
Note: this name may be used for preparations of different composition.
Farmigea, Ital.
Vitamin A acetate (p. 2098·3).
Corneal lesions.

Vitana *Vifor International, Switz.*
Vitamins; minerals; trace elements.

Vitana-EZ *Kenyaku, Thai.*
Vitamins; minerals; iron (p. 2073·1); dehydrocholic acid (p. 2492·1).
Tonic.

Vitanam *Anapo, Rus.*
Yeast extract (p. 2125·2).
Vitamin B deficiency; tonic.

Vita-Nat *Laboratorios Chile, Chile.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1); ascorbic acid (p. 2110·3).
Vitamin A, D, and E supplement.

Vitaneed *Sherwood, USA.*
Lactose-free preparation for enteral nutrition.

Vitaneral *Natufarma, Arg.*
Vitamins; minerals.
Dietary supplement.

Vitanerv *Unison, Philipp.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Vitamin B deficiency; neuritis; neuralgia; neuropathy.

Vitaneurin *Takeda, Jpn.*
Fursultiamine hydrochloride (p. 2102·3); pyridoxal phosphate (p. 2105·3); hydroxocobalamin acetate (p. 2107·3).

Vitaneuron
Note: this name may be used for preparations of different composition.
Tunggal Idaman, Indon.†
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Nutritional supplement.

Vitango *Schwabe, Austria; Schwabe, Neth.; Schwabe, Spain; Pharma Hus, Swed.; Schwabe, Switz.*
Rhodiola rosea.
Tonic; stress; fatigue.

Vitanidia *Lusoterapia, Port.†*
Sulbutiamine (p. 2103·1).

Vitano *Schwabe, UK.*
Rhodiola rosea.
Stress.

Vitanoin *Panalab, Arg.*
Ascorbic acid (p. 2110·3); tocopherol acetate (p. 2119·2).
Skin ageing.

Vitanol *Stiefel, Spain.†*
Tretinoin (p. 1725·2).
Acne; photodamaged skin.

Vitanol-A *Stiefel, Braz.*
Tretinoin (p. 1725·2).
Acne.

Vitanorm *Nizpharm, Rus.*
Cucurbita seed oil (p. 2489·2).
Gastrointestinal disorders; liver and biliary-tract disorders; atherosclerosis; prostatitis; benign prostatic hyperplasia; cervical erosion; worm infections.

Vitanox
Note: this name may be used for preparations of different composition.
GMP, Indon.
Betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin E (p. 2119·1); vitamin B_2 (p. 2104·3); selenium (p. 2086·3); zinc gluconate (p. 2126·2); copper (p. 2057·1); lutein (p. 2079·2).
Dietary supplement for healthy eyes.

Mediherb, Austral.
Vitis vinifera (p. 2521·3); green tea (p. 2648·2); turmeric (p. 2218·1); rosemary (p. 2607·2).
Circulatory disorders.

Vitanumonyl C *Sanofi Synthelabo, Mex.†*
Ascorbic acid (p. 2110·3); chlorphenamine (p. 620·3); paracetamol (p. 115·1).

Vitap *GMP, Indon.*
Adenosine triphosphate (p. 2430·3); vitamin B_6 (p. 2105·3).
Fatigue; skeletal muscle atrophy.

Vita-Ped *Stiefel, Braz.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); colecalciferol (p. 2113·1).

Vitaplex *Bernofarm, Indon.*
Vitamins; docosahexaenoic acid (p. 1460·1); bovine colostrum (p. 2380·3).
Nutritional supplement.

Healthprime, Philipp.
Vitamins; taurine (p. 2626·2); lysine (p. 2079·3); zinc (p. 2126·1).
Nutritional supplement.

Sigmapharm, Austria.
Vitamins.

Viva, Canad.
Vitamins; minerals.

Vitaplex mineral *McNeil, Swed.†*
Vitamins; minerals.

Vita-Plus
Note: this name may be used for preparations of different composition.
Scot-Tussin, USA.
Vitamins; minerals.

VitaPlus
Note: this name may be used for preparations of different composition.
Sari Husada, Indon.
Preparation for enteral nutrition.

Vitaplus B Plus *Adcock Ingram Consumer, S.Afr.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); calcium (p. 1783·1).
Vitamin and calcium supplement.

Vitaplus C Plus *Adcock Ingram Consumer, S.Afr.*
Ascorbic acid (p. 2110·3); calcium (p. 1783·1).
Vitamin C and calcium supplement.

Vita-Plus E *Scot-Tussin, USA.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Vita-PMS *Cyclin, USA.*
Vitamins; minerals.

VitA-POS *Scope, UK.*
Vitamin A palmitate (p. 2098·3); white soft paraffin (p. 2211·3); light liquid paraffin (p. 2191·2); liquid paraffin (p. 2191·2); wool fat (p. 2219·3).
Dry eyes.

Vita-POS *Ursapharm, Rus.; Pharma Medica, Switz.*
Vitamin A palmitate (p. 2098·3).
Dry eyes; eye disorders.

Ursapharm, Ger.
Vitamin A palmitate (p. 2098·3); liquid paraffin (p. 2191·2); light liquid paraffin

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2191·2); wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Eye disorders.

Ursapharm, Israel.
Vitamin A (p. 2098·3); light liquid paraffin (p. 2191·2); wool fat (p. 2219·3); white soft paraffin (p. 2211·3).
Dry eyes; eye irritation.

Vitapro A *Professional Health, Canad.*
Vitamin A palmitate (p. 2098·3).

Vita-Procee *Lloyd, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vitaprost *Nizpharm, Rus.; Nizhfarm, Ukr.*
Prostate gland extract (bovine) (p. 2444·1).
Prostatitis; benign prostatic hyperplasia.

Vitaquick *Vitaflo, Irl.*
Thickening agent.
Dysphagia.

Vitaquin *Surya Dermato, Indon.*
Hydroquinone (p. 1705·1).
Skin hyperpigmentation.

Vitaral *Kenyaku, Thai.*
Vitamins; minerals; rutoside (p. 2505·3); dehydrocholic acid (p. 2492·1); liver concentrate (p. 2444·1).
Vitamin and mineral deficiency.

Jelfa, Pol.†
Vitamins; minerals.

Vitareds *Gallivit, Fr.†*
Vitamins; minerals; with or without lutein (p. 2079·2).

Vitarex *Pasadena, USA.*
Vitamins; minerals; iron (p. 2073·1).

Vitarnin *Grossmann, Hong Kong.†*
Vitamins; minerals.

Vitaroxima *Pan-Ject, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Vitarubin *Streuli, Switz.*
Cyanocobalamin (p. 2107·2) or hydroxocobalamin acetate (p. 2107·3).
Vitamin B_{12} deficiency; anaemias; neurological disorders.

Vitarutine *Europhta, Mon.*
Rutoside sodium sulfate (p. 2505·2); nicotinamide (p. 2083·1).
Capillary fragility in the eye.

Vitasavoury *Vitaflo, UK.*
High energy sip feed.

Vitascor *ICN, Hung.†*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Vitascorbol *Cooperation Pharmaceutique, Fr.*
Ascorbic acid (p. 2110·3) with or without sodium ascorbate (p. 2111·1).
Vitamin C deficiency; asthenia.

Vitaseptol *Europhta, Mon.†*
Thiomersal (p. 1771·3).
Ocular antiseptic.

Vitaseve *Rider, Chile.*
Calcium ascorbate (p. 2111·1).
Vitamin C supplement.

Vitasilin *Casel, Turk.†*
Tetracycline hydrochloride (p. 373·2).
Bacterial skin infections.

Vitaslim *Soho, Indon.*
Poliglusam (p. 2593·2); garcinia cambogia (p. 2510·2); levocarnitine fumarate (p. 2053·2); chromium picolinate (p. 2056·1); vitamin C (p. 2110·3).
Obesity.

VitaSohn *Antonetto, Ital.*
Vitamins; minerals.

Vitasol F *Austral, Arg.*
Vitamin A palmitate (p. 2098·3); ascorbic acid (p. 2110·3); ergocalciferol (p. 2113·3); sodium fluoride (p. 2089·2).
Dental caries prophylaxis; dietary supplement.

Vitaspectrum *Veropharm, Rus.*
Vitamins; minerals.

Vitasprint B12 *Pfizer Consumer, Switz.*
Cyanocobalamin (p. 2107·2); L-phosphoserine (p. 2589·1); glutamine (p. 2070·3).
Tonic.

Vitasprint Complex *Whitehall-Robins, Switz.†*
Dexfosfoserine (p. 2589·1); arginine hydrochloride (p. 2049·1); L-phosphothreonine (p. 2589·3); glutamine (p. 2070·3); hydroxocobalamin (p. 2107·3).
Tonic.

Vita-Squares *GNLD, Austral.*
Vitamins; minerals.

Vitastat *Medicamenta, Cz.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction.

Vita-Thion
Note: this name may be used for preparations of different composition.
Adcock Ingram, S.Afr.
Vitamins; glutathione (p. 1555·2); sodium adenosine triphosphate; calcium fytate.
Tonic.

Vitathion
Note: this name may be used for preparations of different composition.
Servier, Fr.
Ascorbic acid (p. 2110·3); thiamine hydrochloride (p. 2103·1); calcium magnesium fytate (p. 1553·3).
Asthenia.

Vitathion-ATP *Servier, Canad.†*
Ascorbic acid (p. 2110·3); adenosine triphosphate (p. 2430·3); calcium inositohexaphosphate; glutathione (p. 1555·2); magnesium inositohexaphosphate; thiamine (p. 2102·3).
Stress conditions.

Vitaton *Allen, Mex.*
Vitamin B substances (p. 2102·3).

Vita Health, Singapore.
Vitamins; minerals; bee pollen (p. 2593·3); cysteine (p. 2058·3); ginseng (p. 2513·3); kelp (p. 2612·1); lecithin (p. 2542·2); lysine (p. 2079·3); royal jelly (p. 2608·1); yeast (p. 2125·2).

Vitaton Gold *Vita Health, Singapore.*
Vitamins; minerals; cysteine (p. 2058·3); lysine hydrochloride (p. 2079·3); ginkgo biloba (p. 2512·3); ginseng (p. 2513·3); lycopene (p. 2546·2).

Vitatona *Brauer, Austral.†*
Angelica (p. 2443·3); ascorbic acid (p. 2110·3); kola nitida (p. 2648·2); vitamin B substances (p. 2102·3); alfalfa (p. 2433·1); ginseng (p. 2513·3); urtica (p. 2639·3); aurum muriaticum (p. 2521·1); calcarea phosphorica; ferrum metallicum (p. 2073·1); ferrum phosphoricum (p. 2077·1); hypericum perforatum (p. 449·1); kali phosphoricum (p. 1790·3); magnesia phosphorica; phosphoricum acidum (p. 2589·1).
Tonic.

Vitatona Energy *Brauer, Austral.†*
Arsen. alb (p. 2448·1); carbo veg. (p. 1537·3); phosphoricum acidum (p. 2589·1); picricum acidum (p. 2634·2); china (p. 2478·3); muriaticum acidum (p. 2528·3); nat. mur. (p. 1795·1); veratrum album (p. 2644·3).
Homoeopathic preparation.

Vitatonin *Ipex, Swed.†*
⊗Vitamins; caffeine (p. 1203·3); vin. vermuth.; alcohol (p. 1733·1).
Tonic.

Vitatonus *Bunker, Braz.*
Thiamine nitrate (p. 2103·2); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).

Vitatonus Dexa *Bunker, Braz.*
⊗Vitamin B substances (p. 2102·3); dexamethasone (p. 1630·3) or dexamethasone phosphate (p. 1631·1).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.

Vitatrans *Medice, Ger.†*
Ethylenediamine thioctate (p. 2629·1).
Diabetic polyneuropathy.

Vitatress *Veropharm, Rus.*
Vitamins; minerals.

Vitatron *Errelife, Ital.*
Amino acids; vitamins; minerals.
Nutritional supplement.

Vitaum *Geolab, Braz.*
Vitamin B_1 (p. 2102·3).

Vitaveran Fólico *Hormona, Mex.*
Vitamins; minerals.

Vita-Vision
Note: this name may be used for preparations of different composition.
Teguhsindo, Indon.
Myrtillus (p. 2566·2); lutein (p. 2079·2); vitamin A (p. 2098·3).
Dietary supplement for eye disorders.

Vitavision
Note: this name may be used for preparations of different composition.
Oftalmi, Venez.
Vitamins; minerals; lutein (p. 2079·2); zeaxanthin (p. 2125·3).
Dietary supplement for eye disorders.

Vitavital *Multilab, Braz.*
Vitamins; minerals; amino acids.

Vitavitin *Sriprasit, Thai.†*
Vitamin B substances (p. 2102·3).
Neuritis; vitamin B deficiency.

Vitavox *Escaned, Spain.†*
⊗Camphor (p. 2466·2); cineole (p. 2479·1); chlorophyll (p. 2178·3); ephedrine hydrochloride (p. 1663·2); niaouli oil (p. 2569·1); menthol (p. 2553·2); sulfanilamide sodium mesilate (p. 368·1); peppermint (p. 1877·1).
Mouth and throat disorders.

Vitawund *Novartis Consumer, Austria.*
Ointment: Chlorhexidine gluconate (p. 1743·3); halibut-liver oil (p. 2071·3).
Wounds; burns.

Vitax
Note: this name may be used for preparations of different composition.
Frik, Turk.
Paclitaxel (p. 839·3).

Vitax Derm *Ativus, Braz.*
Vitamins; minerals.

Vitaxicam *Ferrer, Singaporet; Robert, Spain.†*
Piroxicam (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

Vitaxon *Farmak, Ukr.*
Tablets: Benfotiamine (p. 2102·3); pyridoxine hydrochloride (p. 2105·3).
Neurological disorders.

Farmak, Ukr.
Injection: Thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Neurological disorders.

Vitaxon C *Airela, Braz.*
Ascorbic acid (p. 2110·3).

Vitayde C *Saval, Chile.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin D (p. 2112·3).
Dietary supplement.

Vitazell E *Kohler-Pharma, Ger.*
d-Alpha tocopherol (p. 2119·1).
Vitamin E deficiency.

Vitazet *Interbat, Indon.*
Vitamins; calcium carbonate (p. 1824·3); zinc sulfate (p. 2126·2).
Vitamin and mineral deficiencies.

Vitazinc
Note: this name may be used for preparations of different composition.
Medlink, Philipp.
Vitamins; lysine (p. 2079·3); taurine (p. 2626·2); zinc (p. 2126·1).
Nutritional supplement.

Vitazink
Note: this name may be used for preparations of different composition.
Strathmann, Ger.
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Vitazol *Rochester, USA.†*
Metronidazole (p. 936·1).
Rosacea.

Vitazym *Kalbe, Indon.*
Amylase (p. 2442·1); protease (p. 2598·1); lipase (p. 2579·3); docosahexaenoic acid (p. 1460·1); dimeticone (p. 1886·2); vitamin B substances (p. 2102·3).
Digestive disorders; liver and bile disorders; tonic.

Vitazyme *East India Pharma, India.*
Capsules: Amylase (p. 2442·1); *Lactobacillus sporogenes* (p. 2596·3).
Dyspepsia; reduced appetite.

East India Pharma, India.
Oral drops; oral liquid: Amylase (p. 2442·1); cinnamon oil (p. 2479·3); caraway oil (p. 2470·3); cardamom oil (p. 2471·1).
Dyspepsia; reduced appetite.

Vite *Douglas, Canad.†*
Vitamins; minerals.

Vitec *Pharmaceutical Specialties, USA.*
dl-Alpha tocoferil acetate (p. 2119·2).
Skin disorders.

Vitef *Teofarma, Ital.*
Polyenacid (p. 2509·2).
Skin disorders.

Vit-E-Far *Farcoral, Mex.*
Alpha tocopherol (p. 2119·1).

Viteksir *Yeni, Turk.*
Vitamin B substances (p. 2102·3).
Vitamin B deficiency.

Vitekta *Gilead, UK.*
Elvitegravir (p. 976·2).
HIV infection.

Vitelle Nesentials *Fielding, USA.*
Vitamins; minerals.

Vitelle Nestabs *Fielding, USA.*
Vitamins; minerals; iron (p. 2073·1); folic acid (p. 2063·1).
Prenatal supplement.

Vitelsix *Unison, Thai.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; loss of appetite.

Vit-E-Nat *Infinity, Venez.*
d-Alpha tocoferil acetate (p. 2119·1).
Antoxidant.

Vitenon *Ativus, Braz.*
⊗Agnus castus (p. 2432·2).
Menopausal disorders.

Viteparin *Teofarma, Ital.*
Heparin sodium (p. 1396·3); tocoferil acetate (p. 2119·2).
Inflammatory eye disorders.

Viteral
Note: this name may be used for preparations of different composition.
Be-Tabs, S.Afr.
Vitamins; minerals.

Vivax, Venez.
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Vitercal C *Mabra, Braz.*
Ascorbic acid (p. 2110·3); calcium carbonate (p. 1824·3).
Calcium and vitamin C supplement.

Vitergan Master *Marjan, Braz.*
Ginseng (p. 2513·3); vitamins; minerals.

Vitergan Pré-Natal *Marjan, Braz.*
Vitamins; minerals.

Vitergan Zinco *Marjan, Braz.*
Vitamins; minerals.

Vitergyl C *Cifarma, Braz.*
Ascorbic acid (p. 2110·3).
Vitamin C supplement.

Viterkids *Marjan, Braz.*
Calcium (p. 1783·1); vitamin D; vitamin C (p. 2110·3).

Viternum *Labomed, Chile; Senosiain, Mex.; OM, Port.; Desma, Spain.*
Cyproheptadine pyridoxal phosphate (p. 624·1).
Anorexia; urticaria; allergic rhinitis; reduced appetite; tonic.

Viternum Vitaminado *Labomed, Chile.*
Cyproheptadine pyridoxal phosphate (p. 624·1); vitamins.
Reduced appetite; tonic.

Viterra M *Pfizer, Thai.†*
Vitamins; minerals.

Vitestable *Alcor, Spain.*
Royal jelly (p. 2608·1); ginseng (p. 2513·3); tocopherol (p. 2119·1).
Tonic.

Vit-E-Var *Infinity, Venez.*
dl-Alpha tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Vitex *Herbarium, Braz.*
⊗Agnus castus (p. 2432·2).
Menstrual disorders.

Vitexid *Svizera, India.*
Spirulina (p. 2622·1); vitamin B substances (p. 2102·3); vitamin E (p. 2119·1).
Vitamin B and E deficiency.

Viticalm *Atlas, Arg.; Mediderm, Chile.*
Grape (p. 2521·3).
Dry skin.

ViTicolor *Crawford, UK.*
Dihydrocyacetone (p. 1700·1); erythrulose (p. 1703·3).
Vitiligo.

Viticolor *ACM, Fr.*
Dihydroxyacetone (p. 1700·1); erythrulose (p. 1703·3); brilliant blue FCF (p. 2171·3); tartrazine (p. 2215·2); CI 14700 (Scarlet GN).
Skin depigmentation disorders.

Vitile *Actavis, Irl.; Actavis, UK.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Vitinelin *Antor, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Vitintra *Fresenius Kabi, Neth.*
Vitamin A (p. 2098·3); vitamin D_2 (p. 2113·3); vitamin E (p. 2119·1); vitamin K_1 (p. 2122·2).
Parenteral nutrition.

Vition *Meditop, Hung.*
Zinc aspartate (p. 2126·1); magnesium aspartate (p. 1787·1); monobasic potassium phosphate (p. 1790·3); dibasic potassium phosphate (p. 1791·1).
Arrhythmias; mineral supplement.

Vitiron *Mepha, Singapore.*
Vitamins; minerals; methionine (p. 1558·2).
Vitamin and mineral supplement.

Mepha, Switz.
Vitamins; minerals; choline bitartrate (p. 2055·2); inositol (p. 2533·2); methionine (p. 1558·2).

Mepha, Ukr.
Vitamins; minerals; inositol (p. 2533·2); choline bitartrate (p. 2055·2); DL-methionine.
Dietary supplement.

Mepha, Hong Kong.†
Vitamins; minerals.

Vitis Encias Colutorio *Dentaid, Chile.*
Metesculetol sodium (p. 2557·3); dexpanthenol (p. 2582·2); cetylpyridinium chloride (p. 1743·1); zinc lactate (p. 2126·2).
Oral hygiene.

Vitis Encias Pasta *Dentaid, Chile.*
Metesculetol sodium (p. 2557·3); dexpanthenol (p. 2582·2); cetylpyridinium chloride (p. 1743·1); zinc lactate (p. 2126·2); sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Vitis Orthodontic Colutorio *Dentaid, Chile.*
Cetylpyridinium chloride (p. 1743·1); sodium fluoride (p. 2089·2).
Dental hygiene; dental caries prophylaxis.

Vitis Orthodontic Pasta *Dentaid, Chile.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Vitis Pasta *Dentaid, Chile.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Vitisival *Valmor, Venez.*
Vitamin B substances (p. 2102·3); lysine hydrochloride (p. 2079·3).
Vitamin B deficiency; tonic.

ViTiX *ACM, Fr.*
Cucurbita (p. 2489·2).
Skin depigmentation disorders.

Vitix *Valeant, Arg.*
Cucumis melo.
Skin depigmentation disorders.

Vitizin *Ativus, Braz.*
Vitamins; minerals.

Vitizin Beta *Ativus, Braz.*
Betacarotene (p. 2051·1).

Vitizin E *Ativus, Braz.*
Tocoferil acetate (p. 2119·2).

Vitlipid N *Fresenius Kabi, Irl.*
Vitamin A (p. 2098·3); vitamin D_2 (p. 2113·3); vitamin E (p. 2119·1); vitamin K_1 (p. 2122·2).
Parenteral nutrition.

Fresenius Kabi, UK.
Vitamin A (p. 2098·3); vitamin D_2 (p. 2113·3); vitamin E (p. 2119·1); vitamin K_1 (p. 2122·2).
Parenteral nutrition.

Vitnatal *SM, Venez.*
Vitamins; folic acid (p. 2063·1); ferrous fumarate (p. 2060·3).
Nutritional supplement for pregnancy and breast feeding.

Vitner-Z *Molex Ayus, Indon.*
Vitamins; zinc (p. 2126·1).
Vitamin and zinc deficiencies.

Vitneurin *GSK, India.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2); dexpanthenol (p. 2582·2).
Neuropathies.

Vitobel *Vianex (Βιανεξ), Gr.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Vitocalcit *SJA, Gr.*
Alfacalcidol (p. 2112·3).
Vitamin D deficiency.

Vitokan *Fitapharm, Ukr.*
Inonotus obliquus; sandy immortelle; horse sorrel; St John's wort (p. 449·1); centaury (p. 2473·2); calendula (p. 2465·2); viburnum; liquorice (p. 1853·2); knotgrass (p. 2538·2); equisetum (p. 2500·1); echinacea purpurea (p. 2498·1); garlic (p. 2510·3); crataegus (p. 2488·1); wild rose cinnamon fruit; strawberry timber leaves; sage (p. 2608·3); periwinkle; burdock (p. 2540·1); peony root; black currant leaf (p. 2458·1); calamus (p. 2464·2).
Menstrual and menopausal disorders.

Vitol *Orion, Fin.†*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3).
Vitamins A and D deficiency.

Vitole E *Medana, Pol.†*
d-Alpha tocopherol (p. 2119·1).
Atherosclerosis; ischaemic heart disease.

Vitolide *Pharmout, Port.†*
Nimesulide (p. 101·3).
Osteoarthritis; pain.

Vitomil AF *Mersifarma, Indon.*
Vitamins; minerals.
Dietary supplement in pregnancy and lactation.

Vitomin *Cipla, India.†*
Vitamins.

Vitonal *SM, Venez.*
Vitamin B substances (p. 2102·3).
Vitamin B supplement; vitamin B deficiency.

Tempo Scan Pacific, Indon.
Vitamin B substances (p. 2102·3); ferrous fumarate (p. 2060·3); copper (p. 2057·1); manganese (p. 2081·2).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Vitonic *Cypress, USA.*
Vitamin B substances (p. 2102·3); minerals.
Dietary supplement.

Vitônico *Legrand, Braz.*
Ferrous sulfate (p. 2062·2); phosphoric acid (p. 2589·1); aloes (p. 1816·1); myrrh (p. 2566·1); nutmeg (p. 2573·1); clove (p. 2481·2).
Iron-deficiency anaemias; tonic.

Vitop
Note: this name may be used for preparations of different composition.
Fahrenheit, Indon.
Myrtillus (p. 2566·2); betacarotene (p. 2051·1); vitamin C (p. 2110·3); vitamin B_2 (p. 2104·3).
Dietary supplement for healthy eyes; antioxidant.

Olan-Kemed, Thai.
Vitamins; minerals; choline bitartrate (p. 2055·2); rutoside (p. 2505·3); methionine (p. 1558·2); inositol (p. 2533·2).

Vitoport *Christo, Hong Kong.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Vitopril *Stada, Ukr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Vitorange *Unipharma, Gr.*
Vitamin C (p. 2110·3).

Vitorange + Calcium *Unipharma, Gr.*
Vitamins; calcium (p. 1783·1).

Vitosal
Note: this name may be used for preparations of different composition.
Demo, Gr.
Vitamins.

Vitotal *Tecnofarma, Chile.†*
Ascorbic acid (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); magnesium (p. 1786·3).
Dietary supplement.

Vitox *Nu Skin, Canad.†*
Vitamins; minerals.

Vitpso *Orva, Turk.*
Methoxsalen (p. 1711·3).
Vitiligo; psoriasis; eczema.

Vitrace *Columbia, S.Afr.†*
Vitamins; minerals.
Tonic.

Vitral
Note: this name may be used for preparations of different composition.
Darya-Varia, Indon.; Pharos, Indon.
Vitamins; minerals.
Nutritional supplement.

Pan-Ject, Philipp.
Tramadol hydrochloride (p. 139·2).
Pain.

Vitrase *Bausch & Lomb, USA.*
Hyaluronidase (p. 2527·2).
Adjuvant to increase the absorption and dispersion of injected drugs; hypodermoclysis; adjunct in subcutaneous urography.

Vitrasert *Bausch & Lomb, Austral.; Bausch & Lomb, USA.†*
Ganciclovir (p. 982·3).
Cytomegalovirus retinitis.

Vitrax *Allergan, Fr.†*
Sodium hyaluronate (p. 2526·2).
Adjunct in eye surgery.

Vitrecor *Densmore, Fr.*
White tea (p. 2648·2); lutein (p. 2079·2); sodium hyaluronate (p. 2526·2); pyridoxine hydrochloride (p. 2105·3).
Dietary supplement; eye health.

Vitreoclar *SIFI, Ital.*
Red vine (p. 2521·3); minerals; vitamin E (p. 2119·1); amino acids.
Nutritional supplement; connective tissue disorders.

Vitreoclar Crono *SIFI, Ital.*
Glucosamine (p. 2515·3); vitamin E (p. 2119·1); collagen (p. 2483·2).
Nutritional supplement.

Vitreolent *Novartis, Gr.; Novartis, Hong Kong†; Novartis, Philipp.; Pharm Supply, Pol.; Novartis Ophthalmics, Singapore; OmniVision, Switz.*
Potassium iodide (p. 2336·3); sodium iodide (p. 2337·1).
Glaucoma; lens opacities; cataract; clouding and haemorrhage of the vitreous humour.

Vitreolux *Novartis, Ital.*
Vitamins; bioflavonoids (p. 2505·2); betacarotene (p. 2051·1); glucosamine (p. 2515·3); zinc (p. 2126·1); methionine (p. 1558·2); myrtillus (p. 2566·2); yeast (p. 2125·2).
Nutritional supplement.

Vitreosan *DMG, Ital.*
Potassium bicarbonate (p. 1780·3); magnesium oxide (p. 1857·3); vitamin C (p. 2110·3).
Nutritional supplement.

Vitrexon *Vargas, Venez.*
Ascorbic acid (p. 2110·3).

Vitrimix *Fresenius Kabi, Fr.†; Fresenius Kabi, Indon.†; Fresenius Kabi, Port.; Fresenius Kabi, Turk.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)).
Contains egg phospholipids.
Parenteral nutrition.

Fresenius Kabi, Thai.†
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg phospholipids.
Parenteral nutrition.

Vitrimix KV *Fresenius Kabi, Hong Kong†; Fresenius Kabi, Irl.†; Fresenius Kabi, Neth.†*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)).
Contains egg phospholipids.
Parenteral nutrition.

Vitrisert *Bausch & Lomb, Austral.*
Ganciclovir (p. 982·3).
Cytomegalovirus retinitis.

Vitro-Mega *Solas, Indon.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1); omega-3.
Nutritional supplement.

Vitromix *Fresenius Kabi, Austria.*
Amino acids; glucose (p. 2068·3); lipids (from soya oil (p. 2092·3)); electrolytes (p. 1775·1).
Contains egg lecithin.
Parenteral nutrition.

Vitron *Pharmaland, Thai.*
Vitamin B_1 (p. 2102·3); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Neurological disorders; neuropathy; toxaemia of pregnancy; anorexia; neurasthenia.

Vitron-C *Insight, USA.*
Ferrous fumarate (p. 2060·3).
Ascorbic acid (p. 2110·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Vitrosups *Llorens, Spain.†*
⊗Glycerol (p. 2517·2).
Constipation.

Vitrum *Unipharm, Pol.; Unipharm, Rus.; Unipharm, Ukr.*
Vitamins; minerals.
Dietary supplement.

Vitrum Beauty *Unipharm, Ukr.*
⊗Vitamins; minerals; aminobenzoic acid (p. 1694·2); cysteine (p. 2058·3); methionine (p. 1558·2); papain (p. 2582·3); betaine (p. 2456·1); rutoside (p. 2505·3); inositol (p. 2533·2); choline (p. 2055·2); citrus bioflavonoids (p. 2505·2); equisetum (p. 2500·1).
Dietary supplement.

Vitrum Beauty Elite *Unipharm, Ukr.*
⊗Vitamins; minerals; aminobenzoic acid (p. 1694·2); papain (p. 2582·3); betaine (p. 2456·1); rutoside (p. 2505·3); inositol (p. 2533·2); choline (p. 2055·2); arginine (p. 2049·1); cysteine (p. 2058·3); lysine (p. 2079·3); methionine (p. 1558·2); aloe vera (p. 1693·2); citrus bioflavonoids (p. 2505·2); green tea (p. 2648·2); olive leaf (p. 2574·3); grape seed (p. 2521·3); kelp (p. 2612·1); peppermint (p. 1877·1); ginger (p. 1844·1); urtica (p. 2639·3); aniseed (p. 2444·2); turmeric (p. 2218·1); equisetum (p. 2500·1); lavender (p. 2541·1); cinnamon (p. 2479·2); rosemary (p. 2607·2).

Vitrum Beauty Q10 *Unipharm, Ukr.†*
Ubidecarenone (p. 2637·1); *dl*-alpha tocoferil acetate (p. 2119·2); grape seed (p. 2521·3); citrus bioflavonoids (p. 2505·2).

Vitrum Calcium 600 + D400 *Unipharm, Ukr.*
Colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Calcium and vitamin D deficiency; osteoporosis.

Vitrum Calcium with Vitamin D3 *Unipharm, Ukr.*
Colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3).
Calcium and vitamin D deficiency; osteoporosis.

Vitrum Cardio *Unipharm, Ukr.*
Vitamins; selenium (p. 2086·3); zinc (p. 2126·1); cod-liver oil (p. 2056·3); sitosterol (p. 1471·2); oat bran; plantain seed; soya bean lecithin; chromium from beer yeast (p. 2125·2).

Vitrum Cardio Omega-3 *Unipharm, Ukr.*
Ethyl ether omega-3 polyunsaturated fatty acids: eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); other fatty acids: *d*-alpha tocopherol (p. 2119·1).
Atherosclerosis; ischaemic heart disease; hypertension; myocardial infarction.

Vitrum Century *Unipharm, Ukr.*
Vitamins; minerals.
Dietary supplement.

Vitrum Energy *Unipharm, Ukr.*
Vitamins; minerals; ginseng (p. 2513·3).
Dietary supplement; tonic.

Vitrum Folicum *Unipharm, Ukr.*
Folic acid (p. 2063·1).
Megaloblastic anaemias; prevention of neural tube defects in pregnancy.

Vitrum Foreyes *Unipharm, Ukr.*
Betacarotene (p. 2051·1); lutein (p. 2079·2); zeaxanthin (p. 2125·3); *dl*-alpha tocoferil acetate (p. 2119·2); ascorbic acid (p. 2110·3); copper sulfate (p. 2057·2); zinc oxide (p. 1729·1).
Eye disorders.

Vitrum Foreyes Forte *Unipharm, Ukr.*
Lutein (p. 2079·2); zeaxanthin (p. 2125·3); myrtillus (p. 2566·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); zinc (p. 2126·1); riboflavin (p. 2104·3); selenium (p. 2086·3); rutoside (p. 2505·3).
Eye disorders.

Vitrum Memory *Unipharm, Ukr.*
Ginkgo biloba (p. 2512·3); zinc (p. 2126·1); thiamine nitrate (p. 2103·2); riboflavin

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

(p. 2104·3); pyridoxine hydrochloride (p. 2105·3); ascorbic acid (p. 2110·3).
Cerebrovascular and mental function disorders.

Vitrum Osteomag *Unipharm, Ukr.*
Colecalciferol (p. 2113·1); calcium carbonate (p. 1824·3); magnesium oxide (p. 1857·3); zinc oxide (p. 1729·1); manganese sulfate (p. 2081·2); copper oxide (p. 2057·1); borax (p. 2459·2).
Calcium and vitamin D deficiency; osteoporosis; nutritional supplement.

Vitrum Prenatal *Unipharm, Ukr.*
Vitamins; calcium carbonate (p. 1824·3); ferrous fumarate (p. 2060·3); zinc oxide (p. 1729·1).

Vitrum Prenatal Forte *Unipharm, Ukr.*
Vitamins; minerals.

Vitussin
Note: this name may be used for preparations of different composition.
Vitamed, Israel.
Guaifenesin (p. 1666·2).
Cough.

Cypress, USA.†
Hydrocodone tartrate (p. 67·2); guaifenesin (p. 1666·2).
Cough.

Vituz *Hawthorn, USA.*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3).
Cold symptoms; cough.

Vi-Uril *Bago, Chile.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Vius *SM, Gr.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Viusid *SM, Venez.*
Vitamins; zinc sulfate (p. 2126·2); glycyrrhizic acid (p. 2520·2); honey (p. 2072·1); malic acid (p. 2549·2); arginine (p. 2049·1).
Nutritional supplement in immunodeficiency.

Tobbest Busindo, Indon.
Glycyrrhizic acid (p. 2520·2); malic acid (p. 2549·2); glucosamine (p. 2515·3); zinc sulfate (p. 2126·2); arginine (p. 2049·1); glycine (p. 2071·2); ascorbic acid (p. 2110·3); vitamin B substances (p. 2102·3).
Supplement in viral infections.

Viva *Viva, Canad.†*
A range of vitamin and mineral preparations.

Vivabec *Lexon, UK.*
⊗Beclometasone dipropionate (p. 1621·2).
Hypersensitivity reactions.

Vivacaine *Septodont, Canad.*
Bupivacaine hydrochloride (p. 1980·3). Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Vivace
Note: this name may be used for preparations of different composition.
Actavis, Indon.; Actavis, Pol.
Ramipril (p. 1483·3).
Hypertension; myocardial infarction; heart failure; cardiovascular risk reduction; non-diabetic nephropathy.

Torrex Chiesi, Austria†; Chiesi, Ger.; Chiesi, Gr.; Chiesi, Spain.
Delapril hydrochloride (p. 1350·2); manidipine hydrochloride (p. 1427·2).
Hypertension.

Vivacor
Note: this name may be used for preparations of different composition.
Anpharm, Pol.; Egis, Pol.
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

AstraZeneca, Braz.; Biolab Sanus, Braz.
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Lexon, UK.
⊗Bisoprolol fumarate (p. 1325·3).
Angina pectoris; hypertension.

Vivactil *Barr, USA; Duramed, USA.*
Protriptyline hydrochloride (p. 446·3).
Depression.

Vivacton *Remedina, Gr.*
Vitamin B substances (p. 2102·3); lysine (p. 2079·3).

Vivadone *Lexon, UK.*
Domperidone maleate (p. 1838·1).
Dyspepsia.

Viva-Drops *Vision, USA.*
Polysorbate 80 (p. 2203·3).
Formerly known as Vit-A-drops.
Dry eyes.

Vivafeks *Fako, Turk.*
Fexofenadine hydrochloride (p. 629·1).

Vivag *Pharma-Vinci, Denm.; Ferrosan, Swed.*
Lactobacillus acidophilus (p. 2596·3).
Restoration of vaginal flora.

Vivaglobin *CSL, Austria; CSL, Belg.; CSL, Canad.; CSL, Cz.†; CSL, Denm.; CSL, Fin.†; CSL, Fr.; CSL, Ger.†; CSL, Gr.; CSL, Hung.; CSL, Ital.; CSL, Neth.†; CSL, Pol.; CSL, Port.; CSL, Spain†; CSL, Swed.†; CSL, Switz.; ZLB, UK†; CSL, USA.†*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immunodeficiency; immune thrombocytopenia; passive immunisation; primary immunodeficiency.

Vival *Actavis, Norw.*
Diazepam (p. 1063·2).
Anxiety; sleep disorders; skeletal muscle spasm.

Vivalcid *Aivax, Gr.*
Calcium folinate (p. 2066·3).
Folate deficiency; antidote to folic acid antagonists.

Vivalessence *Motima, Fr.*
A range of preparations containing essential oils and plant extracts.
Tonic.

Vivamin *Medicine Products, Thai.*
Vitamins.

Vivanza *Bayer, Austria; Medley, Braz.†; Bayer Schering, Cz.; Bayer, Gr.; Bayer Schering, Irl.; Bayer, Neth.; Bayer, Pol.; Bayer Schering, Port.; Bayer, Spain; Berlis, Switz.*
Vardenafil hydrochloride (p. 2372·1).
Erectile dysfunction.

Vivarin *Meda, USA.*
Caffeine (p. 1203·3).
Fatigue.

Vivastin *QX, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Vivatec *MSD, Norw.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Vivatec Comp *MSD, Norw.†*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vivax *Osoth, Thai.†*
Aciclovir (p. 964·1).
Herpes simplex infections of the skin and mucous membranes.

Vivaxim *Sanofi Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Malaysia; Sanofi-Aventis, NZ.*
A typhoid (Vi capsular polysaccharide) and inactivated hepatitis A vaccine (p. 2392·1).
Active immunisation.

Vive Men *L'Oreal, Canad.†*
Pyrithione zinc (p. 1718·1).
Dandruff.

Vivelisi *Atlantis, Mex.*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Vivelle
Note: this name may be used for preparations of different composition.
Janssen-Cilag, Austria.
Norgestimate (p. 2295·3); ethinylestradiol (p. 2275·3).
Acne; triphasic oral contraceptive.

Novartis, Belg.; Novartis, USA.
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Vivelle Dot *Novartis, Denm.*
Estradiol (p. 2271·1).
Menopausal disorders.

Vivelledot *Novartis, Fr.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Vivelon *Xeno, Philipp.*
Clopidogrel (p. 1342·3).
Thromboembolism prophylaxis.

Vivène *Theratech, Fr.†*
Aesculus (p. 2431·2); troxerutin (p. 2505·3).
Peripheral vascular disorders; haemorrhoids.

Viveo *Orion, Ger.†*
Tolperisone hydrochloride (p. 2027·3).
Spasticity.

Viverdal *Uniao Quimica, Braz.*
Risperidone (p. 1103·2).
Psychoses.

Viviant *Pfizer, Jpn.*
⊗Bazedoxifene acetate (p. 2256·1).
Osteoporosis.

Vivicrom *Nucare, UK.†*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis.

Vivides *Gedeon Richter, Irl.*
Ethinylestradiol (p. 2275·3); desogestrel (p. 2266·3).
Combined oral contraceptive.

Vividrin *Riel, Austria; Mann, Ger.; Kite (Kite), Gr.; Bausch & Lomb, Irl.; Tramedico, Neth.†; Bausch & Lomb, Philipp.; Mann, Pol.; Bausch & Lomb, S.Afr.; Bausch & Lomb, Singapore; Mann, Singapore; Gebro, Switz.†; Bausch & Lomb, Thai.; Abbott, Turk.; Bausch & Lomb, UK.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis; keratoconjunctivitis.

Vividrin akut Azelastin *Mann, Ger.*
Azelastine hydrochloride (p. 617·1).
Allergic conjunctivitis; allergic rhinitis.

Vivimed
Note: this name may be used for preparations of different composition.
Bausch & Lomb, Austria.
Propyphenazone (p. 127·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Vivimed mit Coffein *Mann, Ger.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Vivimed N *Mann, Ger.*
Paracetamol (p. 115·1).
Pain; fever.

Vivimex *Royal, Chile.*
Memantine (p. 393·1).
Mental function impairment.

Vivin C
Note: this name may be used for preparations of different composition.
Menarini, Ital.
Aspirin (p. 22·2); ascorbic acid (p. 2110·3).
Cold and influenza symptoms; pain; fever.

Alter, Port.†
Ascorbic acid (p. 2110·3).
Cold and influenza symptoms; tonic.

Vivinox
Note: this name may be used for preparations of different composition.
Kite (Kite), Gr.
Valerian (p. 2640·2); lupulus (p. 2546·1); passion flower (p. 2584·1).
Nervous disorders; sleep disorders.

Vivinox Day *Mann, Ger.*
Melissa (p. 2552·3); valerian (p. 2640·2); passion flower (p. 2584·1).
Nervous disorders; sleep disorders.

Vivinox Sleep *Mann, Ger.*
Diphenhydramine hydrochloride (p. 626·2).
Sleep disorders.

Vivioptal *Novum, Mex.*
Vitamins; minerals; lysine (p. 2079·3).

Pharma-Global, Irl.†; Pharma-Global, UK.
Vitamins; minerals.

Vivir *Unison, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vivitar *Armstrong, Mex.*
⊗Spironolactone (p. 1499·3).
Heart failure; hypertension; myocardial infarction; metabolic syndrome; oedema; hyperaldosteronism; Bartter's syndrome; premenstrual syndrome; hirsutism associated with polycystic ovary syndrome.

Vivitrol *Alkermes, USA.*
Naltrexone hydrochloride (p. 1565·1).
Withdrawal syndromes.

Johnson & Johnson, Rus.
Naltrexone (p. 1565·1).
Alcohol withdrawal syndrome; opioid withdrawal syndrome.

Vivokar *Labormed, Cz.†*
Ramipril (p. 1483·3).
Hypertension; cardiovascular risk reduction; heart failure; diabetic nephropathy.

Vivol *Axxess, Canad.†*
Diazepam (p. 1063·2).
Anxiety; sedative.

Vivonex *Nestle, Canad.; Nestle, China.*
Preparation for enteral nutrition.

Nestle, Hong Kong.
Preparations for enteral nutrition.

Novartis Consumer, Braz.
A range of preparations for enteral nutrition.

Procter & Gamble, USA.
Lactose-free preparation for enteral nutrition.

Vivorax *Cadila, Rus.; Cadila, Singapore.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vivotif *Scott-Cassara, Arg.; CSL Biotherapies, Austral.; Berna, Austria; Janssen-Cilag, Belg.; Crucell, Canad.; Biosano, Chile; Berna, Denm.; Crucell, Fin.; Faran, Gr.; Crucell, Hong Kong; Berna, Indon.; Berna, Ital.; Berna, Malaysia; Crucell, Neth.; Crucell, Norw.; CSL, NZ; Berna, Philipp.; Berna, Singapore; Crucell, Spain; Crucell, Swed.; Crucell, Switz.; Berna, Thai.†; Masta, UK; Berna, USA.*
A live oral typhoid vaccine (p. 2422·2).
Active immunisation.

Vivradoxil *Alpharma, Mex.*
Doxycycline (p. 288·1).
Bacterial infections.

Vixalerg *Cassara, Arg.*
⊗Chlorphenamine maleate (p. 620·3); dexamethasone (p. 1630·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria; angioedema.

Vixcef *Bago, Arg.*
Cefixime (p. 240·3).
Bacterial infections.

Vixiderm E *Investi, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Vixidone *Valeant, Arg.*
⊗Dexamethasone (p. 1630·3); chlorphenamine maleate (p. 620·3).

Vixidone L *Valeant, Arg.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Vixidone LB *Valeant, Arg.*
⊗Loratadine (p. 633·2); betamethasone (p. 1623·2).
Allergic rhinitis; urticaria; angioedema; anaphylaxis.

Vixmicina *Uniao Quimica, Braz.*
Chloramphenicol sodium succinate (p. 257·2).
Bacterial infections.

Vixorfit *Gezzi, Arg.*
⊗Glycerol (p. 2517·2).
Eye irritation.

Viza *Royal, Chile.*
Aripiprazole (p. 1038·3).
Schizophrenia.

Vi-Zac *UCB, USA.*
Vitamins; minerals.

Vizamyl *GE Healthcare, USA.*
Fluorine-18 flutemetamol (p. 2224·1).
Radioactive diagnostic agent for investigation of cognitive impairment.

Vizarsin *KRKA, Cz.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Spain; Consilient, UK.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vizcarra *Green Cross, Philipp.*
A normal immunoglobulin (p. 2403·3).
Agammaglobulinaemia; hypogammaglobulinaemia; passive immunisation.

Vizendo *GSK, Pol.*
Montelukast sodium (p. 1214·3).
Asthma; allergic rhinitis.

Vizerul *Montpellier, Arg.; Dollder, Venez.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration.

Vizibex *Mugi, Indon.*
Vitamins; zinc (p. 2126·1).
Dietary supplement.

Vizivit *KVZ, Ukr.*
Bilberry (p. 2566·2); sodium selenite (p. 2087·1).
Dietary supplement for healthy eyes.

Vizo *Farmaline, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vizole *MM, India.†*
Levamisole (p. 157·2) or levamisole hydrochloride (p. 157·2).
Worm infections.

Vizomet *Xepa-Soul Pattinson, Malaysia.*
⊗Mometasone furoate (p. 1644·1).
Inflammatory and pruritic skin disorders.

Vizoptik *Rompharm, Rus.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation; allergic conjunctivitis.

Vizylac *Unichem, India.*
Lactobacillus sporogenes (p. 2596·3); vitamin B substances (p. 2102·3).
Imbalance of intestinal flora.

Vlanodrin *Cosmopharm, Gr.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Vlenolys *Intermed, Gr.*
Acetylcysteine (p. 1652·2).
Paracetamol poisoning.

VM-2000 *Solgar, UK.*
Vitamins; minerals.

V-Natal *Virtus, USA.*
Vitamins; minerals.

V-Natal DHA *Virtus, USA.*
Tablets, vitamins; minerals; capsules, docosahexaenoic acid (p. 1460·1); eicosapentaenoic acid (p. 1460·2).

Vnikon *NEGPF, China.*
Fosfomycin calcium (p. 300·3).
Bacterial infections.

V-Nolone *Vesco, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Joint disorders; keloids; lupus erythematosus.

VNS 45 *Sigma, Arg.*
Vitamin E (p. 2119·1); hamamelis (p. 2523·3); aesculus (p. 2431·2); centella (p. 1698·3); ginkgo biloba (p. 2512·3); arginine (p. 2049·1); quercetin (p. 2505·3); tannins; triterpene acids; asiaticoside (p. 1698·3); rutoside (p. 2505·3); aescin (p. 2431·2).
Venous insufficiency; atherosclerosis; erectile dysfunction; haemorrhoids; mental function impairment.

Voalla *Maruho, Jpn.*
⊗Dexamethasone valerate (p. 1630·3).
Skin disorders.

Vobaderm *Hermal, Austria; Almirall Hermal, Ger.*
⊗Fluprednidene acetate (p. 1637·3); miconazole nitrate (p. 589·1).
Infected skin disorders.

Vobamyk *Almirall Hermal, Ger.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin infections.

Vobilon *Adipharm, Ukr.*
Ginkgo biloba (p. 2512·3).
Cerebrovascular disorders.

Vocado *Berlin-Chemie, Ger.*
Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1).
Hypertension.

Vocado HCT *Berlin-Chemie, Ger.*
⊗Olmesartan medoxomil (p. 1459·2); amlodipine besilate (p. 1304·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Vocadys *Cooperation Pharmaceutique, Fr.*
Enoxolone (p. 54·2); lidocaine hydrochloride (p. 1988·2); erysimum (p. 2524·2).
Sore throat.

Vocalzone *Kestrel, UK.*
Menthol (p. 2553·2); peppermint oil (p. 1877·1); myrrh (p. 2566·1); liquorice (p. 1853·2).
Throat irritation.

Vocara *Bittner, Austria; Bittner, Rus.; Bittner, Ukr.*
Salvia (p. 2608·3); belladonna (p. 2453·3); phytolacca (p. 2593·2); lachesis (p. 2538·3); mercurius solubilis (p. 2555·3).
Homoeopathic preparation.

Vocarxil *Quality, Hong Kong.*
Glucosamine sulfate (p. 2515·3).
Rheumatic disorders.

Vocefa *Gracia, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Vociflon *Pharmathen, Gr.*
Valaciclovir hydrochloride (p. 1021·1).

Vodefen *Mercury, Philipp.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; gout.

Vodelan *Rayere, Mex.*
Ciprofloxacin hydrochloride (p. 261·2); phenazopyridine hydrochloride (p. 124·3).
Urinary-tract infections.

Vodelax *Sanovel, Turk.*
Citalopram hydrobromide (p. 411·1).

Vodol *Uniao Quimica, Braz.*
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Vofen *Lamda (Λαμδα), Gr.*
Ketoprofen (p. 79·1).
Sucralfate (p. 1889·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Voflan *Pharmathen, Denm.†*
Levofloxacin (p. 315·3).
Bacterial infections.

Voflaxin *Teva, Mex.*
Levofloxacin (p. 315·3).
Bacterial infections.

Voflox *Aspen, Arg.; EON, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Vogalene *Aventis, Gr.*
Metopimazine (p. 1865·1).

Vogalène *Cephalon, Fr.*
Metopimazine (p. 1865·1).
Nausea and vomiting.

Vogalib *Cephalon, Fr.*
Metopimazine (p. 1865·1).
Nausea and vomiting.

Vogast *Fako, Turk.*
Lansoprazole (p. 1851·3).
Peptic ulcer.

Vogracen *Ultra, Mex.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Voir *Grammenidis, Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Vokam *YSP, Malaysia.*
Diclofenac potassium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; migraine; gout.

Voker *YSP, Malaysia.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Volamin *Volchem, Ital.*
Amino acids.
Fatigue; liver disorders.

Volcano *Gentech, Arg.*
Amino acids.
Tonic.

Volcidol *Pharmasant, Thai.*
Tramadol hydrochloride (p. 139·2).
Pain.

Volcolon *Meda, Neth.*
Ispaghula (p. 1849·1).
Constipation.

Voldiamer B6 *Tunggal Idaman, Indon.*
Parathiazine teoclate (p. 637·1); pyridoxine hydrochloride (p. 2105·3).
Nausea; vomiting; motion sickness.

Voldilex *Solas, Indon.*
Cimicifuga (p. 2478·1); vitamin E (p. 2119·1).
Menopausal symptoms.

Voleca *Dexa, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Volecam *Biochimic, Rus.*
⊗An etherified starch (p. 1146·1).
Hypovolaemia; shock; haemodilution.

Voleflok *Kocak, Turk.*
Levofloxacin (p. 315·3).
Bacterial infections.

Volemcor *Medpolimer, Rus.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; haemodilution.

Volequin *Dexa, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Volfen *Pharmahof, Thai.†*
Diclofenac sodium (p. 48·3).
Inflammation; pain.

Volfenac *Collins, Mex.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

General Drugs, Thai.
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Volfenaks *Ulagay, Turk.*
Diclofenac sodium (p. 48·3).
Gout; musculoskeletal and joint disorders.

Volfenn *Jean-Marie, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; renal and biliary colic.

Volflanil *Pharlab, Braz.*
Diclofenac sodium (p. 48·3).

Volforte *Omicron, Arg.*
Diclofenac (p. 48·3) or diclofenac diethylamine (p. 48·3).
Inflammation.

Volibris *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Ambrisentan (p. 1298·2).
Pulmonary hypertension.

Volina *Gedeon Richter, Hung.; Gedeon Richter, Neth.*
Ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive.

Volinol *Pyridam, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Vollmers präparierter grüner N *Salushaus, Ger.*
Avena (p. 2451·1); urtica (p. 2639·3); alchemilla.
Urinary-tract disorders.

Volmatik *Mugi, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; gout.

Volmax *GSK, Denm.†; GSK, Hong Kong†; GSK, Indon.†; Glaxo Allen, Ital.†; GSK, Malaysia; GSK, Mex.†; GSK, NZ; Sekunjalo, S.Afr.; GSK, Singapore; GSK, Turk.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Volnac *TO-Chemicals, Thai.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; fever.

Volnostin *Sandoz, Cz.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Volog *BMS, Turk.*
⊗Halcinonide (p. 1639·3).
Skin disorders.

Volon *Dermapharm, Austria; Dermapharm, Ger.*
⊗Triamcinolone (p. 1648·3).
Corticosteroid.

Volon A *Dermapharm, Austria; Dermapharm, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Corticosteroid.

Volon A antibiotikahaltig *Dermapharm, Austria.†*
⊗Triamcinolone acetonide (p. 1649·1); neomycin sulfate (p. 330·1); gramicidin (p. 308·3).
Skin disorders.

Volon A Tinktur *Dermapharm, Austria.*
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Skin disorders; otitis externa.

Volon A Tinktur N *Dermapharm, Ger.*
⊗Triamcinolone acetonide (p. 1649·1); salicylic acid (p. 1719·1).
Skin disorders; otitis externa.

Volon A-Schüttelmix *Dermapharm, Ger.*
⊗Triamcinolone acetonide (p. 1649·1); zinc oxide (p. 1729·1).
Skin disorders.

Volonimat *Dermapharm, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Volonimat N *Dermapharm, Ger.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Volonimat Plus N *Dermapharm, Ger.†*
⊗Triamcinolone acetonide (p. 1649·1); nystatin (p. 590·3).
Eczema with secondary yeast infection.

Volonten *Viofar, Gr.*
Nimesulide (p. 101·3).
Pain; inflammation; musculoskeletal disorders.

VoLox *Interbat, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Volpan *Husnu Arsan, Turk.*
Paracetamol (p. 115·1).
Fever; pain.

Volplex *Maelor, UK.*
⊗Succinylated gelatin (p. 1154·1) in sodium chloride.
Blood volume expansion.

Volraman *LPC, UK.*
Diclofenac sodium (p. 48·3).
Musculoskeletal disorders; gout; pain; inflammation.

Volsaid *Trinity, UK.*
Diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal, joint, and peri-articular disorders.

Volta *Seng, Thai.; T Man, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; eye disorders.

Vol-Tab *Trigen, USA.*
Vitamins; minerals.

Voltadex *Dexa, Indon.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Voltadol *Novartis Consumer, Austria; Novartis Consumer, Port.; Novartis Consumer, Spain.*
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Novartis Consumer, Ital.
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular pain and inflammation.

Voltadvance *Novartis Consumer, Ital.*
Diclofenac sodium (p. 48·3).
Pain; fever.

Voltadyn *Novartis, Cz.†*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Voltaflam *Biofarma, Turk.*
Diclofenac sodium (p. 48·3).

Voltaflan *Bunker, Braz.*
Diclofenac sodium (p. 48·3).
Lidocaine hydrochloride (p. 1988·2) is included in the injection to alleviate the pain of injection.

Voltaflex
Note: this name may be used for preparations of different composition.
EMS, Braz.
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Novartis Consumer, Belg.†; Novartis Sante, Fr.; Novartis Consumer, Ger.†; Novartis, Gr.; Novartis Consumer, Hong Kong; Novartis Consumer, Switz.†
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis; joint disorders.

Voltaflex Glucosamine *Novartis Consumer, Neth.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

Voltak *Medirex, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Voltamicin *Novartis, Austria†; Novartis, China; OmniVision, Switz.*
Diclofenac sodium (p. 48·3); gentamicin sulfate (p. 304·2).
Eye inflammation with bacterial infection.

Voltanac *Pharmasant, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Voltapatch *Novartis Consumer, Belg.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Voltaren *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.; Novartis Consumer, Ukr.; Endo, USA; Novartis, USA; Novartis, Venez.*
Diclofenac (p. 48·3), diclofenac colestyramine, diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; rheumatoid arthritis; osteoarthritis; fever; gout; eye inflammation and pain; intra-operative miosis inhibition; renal and biliary colic; cystoid macular oedema.

Novartis, Neth.
Diclofenac potassium (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; pain; inflammation; gout; renal and biliary colic.

Voltaren Colirio *Novartis, Arg.*
Diclofenac sodium (p. 48·3).
Eye inflammation.

Voltaren Colírio *Novartis, Braz.*
Diclofenac sodium (p. 48·3).
Inflammatory eye disorders.

Voltaren Dolo *Novartis, Switz.*
Diclofenac diethylamine (p. 48·3) or diclofenac potassium (p. 48·3).
Fever; inflammation; pain.

Voltaren Emulgel *Novartis Consumer, Neth.; Novartis Consumer, Switz.*
Diclofenac diethylamine (p. 48·3).
Joint pain; musculoskeletal, joint, peri-articular and soft-tissue disorders.

Voltaren Flex *Novartis, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Voltaren Forte *Novartis, Arg.; Novartis, Mex.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Pain.

Voltaren Migra *Novartis, Arg.†*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Voltaren Ophta *Novartis, Hung.; Novartis, Switz.; Novartis, Turk.*
Diclofenac sodium (p. 48·3).
Ocular pain and inflammation; cystoid macular oedema; prevention of miosis during eye surgery; allergic conjunctivitis.

Voltaren Ophtha *Novartis, Austral.; Novartis, Canad.; Novartis, Ger.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Israel; Thea, Norw.; Novartis, NZ; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis Ophthalmics, Swed.*
Diclofenac sodium (p. 48·3).
Cystoid macular oedema; inhibition of miosis during cataract surgery; ocular pain and inflammation.

Voltaren Plus *Novartis, Ger.*
Diclofenac sodium (p. 48·3); codeine phosphate (p. 40·2).
Pain.

Voltaren T *Novartis, Swed.*
Diclofenac potassium (p. 48·3).
Pain.

VoltarenActigo *Novartis Sante, Fr.*
Diclofenac diethylamine (p. 48·3).
Joint and soft-tissue disorders.

Voltarendolo *Novartis Sante, Fr.*
Diclofenac potassium (p. 48·3).
Fever; pain.

Voltarène *Novartis, Fr.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; dysmenorrhoea; renal colic; oedema.

Novartis, Switz.
Diclofenac (p. 48·3), diclofenac potassium (p. 48·3), diclofenac resinate (p. 48·3), or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation; gout.

Voltarènophta *Thea, Fr.*
Diclofenac sodium (p. 48·3).
Inhibition of intraoperative miosis; inflammation following eye surgery; eye pain.

Voltarol *Novartis, Irl.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout.

Novartis, Norw.
Diclofenac potassium (p. 48·3).
Pain; fever.

Novartis, UK.
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3), diclofenac epolamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; gout; pain; inflammation.

Voltarol Ophtha *Novartis, Irl.; Spectrum, UK.*
Diclofenac sodium (p. 48·3).
Inhibition of peri-operative miosis; prevention of cystoid macular oedema; inflammation and pain following eye surgery; allergic conjunctivitis.

Voltatrauma *Novartis Consumer, Ital.*
Oxerutin (p. 2505·3); sodium calcium methylgalactopolysulfate.
Minor trauma.

Volten *Oftalmi, Venez.*
Diclofenac sodium (p. 48·3).
Eye inflammation; intra-operative miosis inhibition; cystoid macular oedema; uveitis.

Voltenac *Sanofi-Aventis, Pol.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Volterenplast *Novartis Sante, Fr.*
Diclofenac sodium (p. 48·3).
Joint and soft-tissue disorders.

Voltex *United Drug, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain.

Voltex Kool *United Drug, Thai.*
Diclofenac diethylamine (p. 48·3).
Inflammation; pain.

Voltfast *Novartis, Austral.; Novartis, Irl.; Novartis, Ital.; Novartis, NZ; Novartis, Singapore; Novartis, Switz.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Volton *Bright Future, Hong Kong.†*
Diclofenac (p. 48·3).

Voltrix *Bunker, Braz.*
Diclofenac diethylamine (p. 48·3), diclofenac potassium (p. 48·3), or diclofenac resinate (p. 48·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Volulyte *Fresenius Kabi, Austria; Fresenius Kabi, Canad.; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Irl.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Thai.; Fresenius Kabi, UK.†*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion.

Fresenius Kabi, Ital.
⊗An etherified starch (p. 1146·1); electrolytes.
Plasma volume expansion.

Volunta *Medley, Braz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Volutol *Teva, Mex.*
Carbamazepine (p. 512·2).
Epilepsy; neuralgias; diabetic neuropathy.

Voluven *Fresenius Kabi, Arg.; Fresenius Kabi, Austral.; Fresenius Kabi, Austria; Fresenius Kabi, Canad.; Fresenius Kabi, Chile; Fresenius Kabi, China; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Irl.; Fresenius Kabi, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, NZ; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK†; Fresenius Kabi, Ukr.; Hospira, USA.*
⊗An etherified starch (p. 1146·1).
Plasma volume expansion; hypovolaemia; haemodilution; extracorporeal circulation.

Volverac *TP, Thai.*
Diclofenac sodium (p. 48·3).
Inflammation following cataract surgery; prevention or reduction of intraoperative miosis; postoperative cystoid macular oedema.

Vomacur *Hexal, Ger.†*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; vertigo; motion sickness.

Vomaine *Gland, Philipp.*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting.

Vomceran *Kalbe, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Vomecho *Nicholas, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Vomed *Cmed, Thai.; Utopian, Thai.*
Diazepam (p. 1063·2).

Vomen *Medicine Products, Thai.*
Dimenhydrinate (p. 625·2).
Motion sickness; Ménière's disease.

Vomerin *Soho, Indon.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting.

Vomesea *The Forty-Two, Thai.*
Metoclopramide hydrochloride (p. 1862·2).
Gastric stasis; nausea and vomiting; gastro-oesophageal reflux.

Vomet *Ulagay, Turk.*
Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Vometa *Dexa, Indon.; Dexa, Philipp.*
Domperidone (p. 1838·1).
Gastrointestinal disorders; dyspepsia; nausea and vomiting.

Vometil *Cipla, India.*
Prochlorperazine maleate (p. 1098·3).

Vometraz *Dexa, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Vometron *Mahakam Beta, Indon.*
Ondansetron (p. 1872·1).
Nausea and vomiting.

Pertiwi Agung, Philipp.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Vomex A *Astellas, Ger.; Klinge, Ger.; IFET (ΙΦΕΤ), Gr.; Olvos, Gr.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo; motion sickness.

Vomidex *Dexa, Indon.†*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Vomidon *Be-Tabs, S.Afr.*
Domperidone (p. 1838·1).
Delayed gastric emptying; nausea and vomiting.

Vomidone *Pharos, Indon.*
Domperidone maleate (p. 1838·1).
Nausea and vomiting; dyspepsia.

Vomidrine *Azevedos, Port.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea; vomiting; vertigo.

Vomifene *Adcock Ingram, S.Afr.*
Buclizine hydrochloride (p. 618·3); pyridoxine (p. 2105·3).
Nausea and vomiting; motion sickness.

Vomil *Solas, Indon.*
Ginger (p. 1844·1); folic acid (p. 2063·1); vitamin B_6 (p. 2105·3).
Nausea and vomiting.

Vomilat *Kalbe, Indon.*
Pyridoxine hydrochloride (p. 2105·3); folic acid (p. 2063·1).
Vitamin B_6 and folic acid supplement in pregnancy.

Vomina *Hexpharm, Indon.*
Domperidone (p. 1838·1).
Dyspepsia; nausea and vomiting.

Vominate *Cipla, India.*
Doxylamine succinate (p. 627·3); pyridoxine hydrochloride (p. 2105·3).
Nausea and vomiting of pregnancy.

Vominorm *Cipla, India.*
Metoclopramide (p. 1862·2).
Nausea and vomiting.

Vomiof *Stadmed, India.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by cytotoxics and radiotherapy.

Vomipram *Corsa, Indon.*
Metoclopramide (p. 1862·2).
Gastrointestinal disorders.

Vomisin *Rayere, Mex.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Vomistop
Note: this name may be used for preparations of different composition.
Cipla, India; Gracia, Indon.
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Pfluger, Ger.
Aethusa cynapium; apomorphinum hydrochloricum (p. 892·3); cucurbita pepo (p. 2489·2); gossypium herbaceum; kalium stibyltartaricum (p. 151·2); symphoricarpus albus e fructibus.
Homoeopathic preparation.

Vomitas *Kalbe, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Vomitin *Akdeniz, Turk.*
Trimethobenzamide hydrochloride (p. 642·2).
Nausea and vomiting.

Vomitoran *Norma (Νορμα), Gr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Vomitran *Asfarma, Ukr.*
Granisetron (p. 1844·3).
Nausea and vomiting induced by cytotoxics.

Vomitrol *Pharos, Indon.*
Metoclopramide (p. 1862·2).
Delayed gastric emptying; gastrointestinal procedures.

Vomitusheel *Heel, Austria; Ebi, Switz.*
Caphaelis ipecacuanha; aethusa cynapium; strychnos nux vomica (p. 2573·3); apomorphinum hydrochloricum (p. 892·3); colchicum autumnale; strychnos ignatii (p. 2532·1).
Homoeopathic preparation.

Vomiz *Zydus, S.Afr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Vonau *Biolab Sanus, Braz.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Vonax *Delta, Braz.*
Levofloxacin (p. 315·3).
Bacterial infections.

Voncon *Lilly, Gr.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vondem *Demo, Gr.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Vonodiol *Teva, Irl.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraception.

Vontrol *GSK, Chile; Sanfer, Mex.*
Difenidol hydrochloride (p. 1835·1).
Nausea and vomiting; vestibular disorders; vertigo.

Vonum *Gerot, Austria.*
Indometacin (p. 71·2); lauromacrogol 400 (p. 2194·1).
Musculoskeletal, joint, and soft-tissue disorders.

Vonum Cutan *Winthrop, Cz.*
Indometacin (p. 71·2).
Musculoskeletal, joint, and soft-tissue disorders; inflammation.

Vopac *Athlon, USA.*
Codeine phosphate (p. 40·2); paracetamol (p. 115·1).
Pain.

Vopar *Unison, Thai.*
Levodopa (p. 902·2); benserazide hydrochloride (p. 894·1).
Parkinsonism.

Vopecidex *PharmaSwiss, Neth.*
Capecitabine (p. 757·3).
Colorectal cancer; gastric cancer; breast cancer.

V-Optic *Vitamed, Israel.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Voraclor *New Research, Ital.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Voractiv *Sandoz, UK.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Vorafon *VS, Thai.*
Paracetamol (p. 115·1); chlorzoxazone (p. 2022·2).
Skeletal muscle spasm.

Voragas *VS, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity.

Vorange *DHA, Hong Kong; DHA, Singapore.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Voranin *Ind-Swift, India.*
Progesterone (p. 2300·2).
Dysfunctional uterine bleeding; amenorrhoea; recurrent miscarriage.

Vorapam *VS, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; epilepsy; alcohol withdrawal syndrome; skeletal muscle spasm; premedication.

Voratadine *Vida, Hong Kong.†*
Loratadine (p. 633·2).
Allergic rhinitis; skin disorders.

Voraxaze *BTG, USA.*
Glucarpidase (p. 1555·1).
Methotrexate toxicity.

Vorcum *Pfizer, Venez.*
Voriconazole (p. 597·1).
Fungal infections.

Voredanin *Labormed, Cz.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Vo-Remi *Offenbach, Mex.*
Meclozine (p. 634·3); pyridoxine (p. 2105·3).
Nausea and vomiting.

Voren *Medikon, Indon.; YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore; YSP, Thai.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; fever.

Yung Shin, China.
Diclofenac diethylamine (p. 48·3).
Musculoskeletal, joint, and soft-tissue pain.

Voren Plus *YSP, Malaysia; Yung Shin, Singapore.*
Diclofenac sodium (p. 48·3); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

VoriNa *Teva, Belg.; Teva, Cz.; Hospira, Ger.; Teva, Hung.†; Teva, Irl.; Pharmachemie, Neth.; Pharmachemie, Philipp.; Teva, Port.†*
Sodium folinate (p. 2067·1).
Adjunct to fluorouracil in colorectal cancer; reduction of methotrexate toxicity; reduction of folic-acid antagonist toxicity.

Vormil *Mili, Ukr.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Voromin *Viofar, Gr.*
Terfenadine (p. 640·3).

Voroste *Combiphar, Indon.*
Alendronate sodium (p. 1171·3).
Osteoporosis; Paget's disease of bone.

Vorst *Bernabo, Arg.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Vorta *Glenmark, Pol.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder.

Vorth-P *Glenmark, India.*
Parecoxib sodium (p. 119·3).
Pain.

Vosedon *Sanbe, Indon.*
Domperidone (p. 1838·1).
Gastrointestinal disorders.

Vosene Kids 3 in 1 *Lornamead, UK.*
Melaleuca oil (p. 2551·1).
Pediculosis.

VoSoL *Wilson, NZ.*
Propylene glycol diacetate (p. 2206·2); acetic acid (p. 2426·3); benzethonium chloride (p. 1738·1).
Otitis externa.

VoSoL HC *ECR, USA.*
⊗Acetic acid (p. 2426·3); benzethonium chloride (p. 1738·1); hydrocortisone (p. 1640·1).
Otitis externa.

VoSpire *Dava, USA.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Vosrym *Farmaceutica H, Mex.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Vossecal *Landson, Indon.*
Hydroxyapatite (p. 2529·3); colecalciferol (p. 2113·1); vitamin C (p. 2110·3); magnesium (p. 1786·3); zinc (p. 2126·1).

Vostem *Sanbe, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); vitamin C (p. 2110·3); minerals.
Joint disorders.

Vosteon *Meprofarm, Indon.*
Glucosamine hydrochloride (p. 2515·3); chondroitin sulfate (p. 2476·1); ipriflavone (p. 1185·3); calcium citrate (p. 1783·2).
Osteoarthritis.

Votag *Ativus, Braz.*
Marine polyunsaturated fatty acids (p. 1460·3).
Dietary supplement.

Votag O6 *Ativus, Braz.*
Fish oil (p. 1460·3); borage oil (p. 2459·2); soya oil (p. 2092·3).
Dietary supplement.

Votalen *Marching, Hong Kong.†*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis.

Votamed *Medifive, Thai.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Votan *Taiwan Biotech, Philipp.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Votaxil *Cafar, Venez.*
Diclofenac sodium (p. 48·3).
Inflammation; musculoskeletal and joint disorders; pain.

Votazine *CCM, Malaysia; Duopharma, Singapore.*
Promethazine teoclate (p. 638·2).
Motion sickness; nausea and vomiting.

Votmine *CCM, Malaysia; Duopharma, Singapore.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; motion sickness; vertigo; Ménière's disease.

Votrace *Verisfield, Gr.*
Calcitriol (p. 2113·1).
Psoriasis.

Votrient *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Irl.; GSK, Israel; GSK, Jpn; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Ukr.; GSK, USA.*
Pazopanib hydrochloride (p. 843·3).
Renal cell carcinoma; soft-tissue sarcoma.

Votripax *Pisa, Mex.*
Ampoule 1, thiamine hydrochloride (p. 2103·1); pyridoxine hydrochloride (p. 2105·3); cyanocobalamin (p. 2107·2); ampoule 2, diclofenac sodium (p. 48·3).
Musculoskeletal, joint, and peri-articular pain; neuralgias; neuritis; neuropathy.

Votubia *Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Irl.; Novartis, Neth.; Novartis, Norw.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, UK.*
Everolimus (p. 1957·3).
Giant cell astrocytoma; renal angiomyolipoma.

Votum *Berlin-Chemie, Ger.; Menarini, Switz.*
Olmesartan medoxomil (p. 1459·2).
Hypertension.

Votum Plus *Berlin-Chemie, Ger.; Menarini, Switz.*
⊗Olmesartan medoxomil (p. 1459·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Voveran *Novartis, India.*
Diclofenac (p. 48·3), diclofenac diethylamine (p. 48·3), or diclofenac sodium (p. 48·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; prevention of miosis in cataract surgery; eye inflammation and pain; allergic conjunctivitis.

Vowlo *Horii, Jpn.*
Sodium gualenate (p. 1887·1).
Mouth and throat disorders.

Voxafen *Sandoz, Gr.*
Venlafaxine hydrochloride (p. 454·2).

Voxam *Sandoz, Austral.*
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Voxamine
Note: this name may be used for preparations of different composition.
Armstrong, Mex.
Difenidol hydrochloride (p. 1835·1).
Nausea and vomiting; vertigo.

Brown & Burk, Philipp.
Fluvoxamine maleate (p. 425·3).
Depression; obsessive-compulsive disorder.

Voxate *Masa, Thai.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

Voxfor *Escaned, Spain.†*
⊗Dextromethorphan hydrobromide (p. 1660·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).
Cold symptoms.

Voxin
Note: this name may be used for preparations of different composition.
Gracia, Indon.
Levofloxacin (p. 315·3).
Bacterial infections.

Vianex (Βιανεξ), Gr.
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Voxoll *Aldril, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Voxpax *Lehning, Fr.*
Arum triphyllum; pimpinella anisum (p. 2444·2); carbo vegetabilis (p. 1537·3); calcium polysulfidum (p. 1721·3); manganum peroxydatum (p. 2081·2); olibanum (p. 2507·3); arsenicum album (p. 2448·1); sisymbrium officinale (p. 2524·2).
Homoeopathic preparation.

Homeocan, Canad.†
Arum triphyllum; olibanum (p. 2507·3); pimpinella anisum (p. 2444·2).
Homoeopathic preparation.

Voxra *GSK, Fin.; GSK, Swed.*
Bupropion hydrochloride (p. 408·2).
Depression.

Voxsuprine *Major, USA.*
Isoxsuprine hydrochloride (p. 2535·2).
Cerebrovascular and peripheral vascular disorders.

Voxyl *Naturactive, Fr.†*
Erysimum (p. 2524·2).
Mouth and throat disorders.

Voxytane *Pharm-D, Malaysia.*
Oxybutynin hydrochloride (p. 2361·2).
Neurogenic bladder.

Voydol *Raam, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Voydol-C *Raam, Mex.*
Ketorolac trometamol (p. 80·2); tramadol hydrochloride (p. 139·2).
Pain.

VP-CH-PNV *Virtus, USA.*
Vitamins; calcium (p. 1783·1); iron (p. 2073·1); docosahexaenoic acid (p. 1460·1). Docusate sodium (p. 1836·2) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

V-Pen *Orion, Fin.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

VP-Gen *Bioprofarma, Arg.*
Etoposide (p. 790·2).
Malignant neoplasms.

VP-GGR-B6 *Virtus, USA.*
Folic acid (p. 2063·1); calcium (p. 1783·1); vitamin B_6 (p. 2105·3); ginger (p. 1844·1).
Dietary supplement.

VP-Heme One *Virtus, USA.*
Vitamins; minerals; docosahexaenoic acid (p. 1460·1).
Dietary supplement.

V-piryna *Natur Produkt, Pol.†*
Aspirin (p. 22·2); ascorbic acid (p. 2110·3); caffeine (p. 1203·3).
Cold and influenza symptoms.

VPRIV *Shire, Denm.; Shire, Fr.; Shire, Ger.; Shire, Irl.; Medison, Israel; Shire, Neth.; Shire, Norw.; Shire, Pol.; Shire, Port.; Shire, Swed.; Shire, UK; Shire, USA.*
Velaglucerase alfa (p. 2433·2).
Gaucher disease.

Vpriv *Shire, Spain.*
Velaglucerase alfa (p. 2433·2).
Gaucher disease.

VP-Syrup *Procter & Gamble, Gr.*
Guaifenesin (p. 1666·2).
Cough.

VP-Tec *Columbia, Mex.*
Etoposide (p. 790·2).
Testicular cancer; small cell lung cancer.

VP-Zel *Virtus, USA.*
Vitamin B_3 (p. 2083·1); vitamin B_6 (p. 2105·3); folate (p. 2063·1); copper (p. 2057·1); zinc (p. 2126·1); azelaic acid (p. 1695·1).
Dietary supplement.

VQ *Molex Ayus, Indon.; Daewoong, Thai.†*
Ubidecarenone (p. 2637·1).
Dietary supplement; heart failure.

V-Rab *Shanghai Serum, Philipp.*
A rabies vaccine (p. 2413·2).
Active immunisation.

Vrachor *Kleva, Gr.*
⊗Oxprenolol hydrochloride (p. 1463·2).

V-Ral *Vitamed, Israel.*
Aciclovir (p. 964·1).
Herpes labialis.

Vratizolin *Jelfa, Pol.; Jelfa, Ukr.*
Denotivir (p. 972·3).
Herpesvirus infections of skin and mucous membranes; bacterial skin infections; herpes labialis.

Vrbovkova Nat *Megafyt-R, Cz.†*
Epilobium.
Benign prostatic hyperplasia; gastrointestinal disorders.

Vredian *Permatec, Arg.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Vreya *Heaton, Cz.; Stragen, Denm.; Stragen, Fin.*
Ethinylestradiol (p. 2275·3); cyproterone acetate (p. 2261·2).
Combined oral contraceptive in women with androgenic symptoms; androgen-induced acne, alopecia, hirsutism, and seborrhoea in women.

V-Rox *VS, Thai.*
Roxithromycin (p. 356·2).
Bacterial infections.

Vroxil *Promed, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

VS *VS, Thai.*
Chlorphenamine maleate (p. 620·3); ammonium chloride (p. 1656·1); sodium citrate (p. 1781·2).
Cough; cold symptoms.

VSL 3 *CD Investments, Ital.*
Lactic-acid-producing bacteria (p. 2596·3).

Hyphens, Singapore; Ferring, UK; Sigma-Tau, USA.
Streptococcus thermophilus (p. 2596·3); *Bifidobacterium breve* (p. 2596·3); *Bifidobacterium longum* (p. 2596·3); *Bifidobacterium infantis* (p. 2596·3); *Lactobacillus acidophilus* (p. 2596·3); *Lactobacillus plantarum* (p. 2596·3); *Lactobacillus paracasei* (p. 2596·3); *Lactobacillus delbrueckii* (p. 2596·3).
Dietary supplement; maintenance of gastrointestinal flora; ulcerative colitis; irritable bowel syndrome.

V-Tabur *Vitamed, Israel.*
⊗Alcohol (p. 1733·1); chlorhexidine gluconate (p. 1743·3).
Skin and umbilical cord disinfection.

V-Talgin *Vitamed, Israel.†*
Dipyrone (p. 53·3).
Fever; pain.

V-Tears *Vitamed, Israel.*
Hyetellose (p. 2188·3).
Dry eyes.

V-Therlen *Patar, Thai.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Inflammation; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Vuclodir *Richmond, Arg.*
Lamivudine (p. 1000·2).
HIV infection.

Vudirax *Blausiegel, Braz.*
Lamivudine (p. 1000·2).
HIV infection.

Vulamox *Ethica, Indon.*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Vulbefer *Coup, Gr.*
Buspirone hydrochloride (p. 1042·1).

Vulbegal *Coup, Gr.*
Flunitrazepam (p. 1073·3).
Insomnia.

Vulcase *Teofarma, Fr.*
Aloes (p. 1816·1).
Constipation.

Vulcasid *Atlantis, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Vulmizolin *Biotika, Cz.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Vulnagen *Neo Quimica, Braz.*
Tinidazole (p. 949·2); tioconazole (p. 595·3).

Vulnizol *Gelpharma, Mex.*
Nitrofurazone (p. 333·1).
Vaginal infections.

Vulnopur *Deverge, Ital.*
Decylglucoside; sodium chloride (p. 1795·1); aloe vera (p. 1693·2); silver chloride (p. 2615·1).
Cleansing of skin and mucous membranes; burns; wounds.

Vulnostimulin *Dermapharm, Ger.*
Wheat germ (p. 2647·1).
Wounds; burns.

Vulnusan *Sopharma, Rus.*
Pomeranian lakes extract.
Pyogenic wounds; abscess; ulcers.

Vulpuran *Rosch & Handel, Austria.*
Lead plaster-mass (p. 2541·3); chamomile oil (p. 2474·1); St John's wort oil (p. 449·1); cod-liver oil (p. 2056·3); elemi; colophony (p. 2484·2); emplastrum minii; turpentine oil (p. 2636·3); peru balsam (p. 2587·1); oxycholesterin.
Wounds; ulcers; furuncles.

Vultin *Unison, Thai.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Vuminix *Sun, Mex.*
Fluvoxamine maleate (p. 425·3).
Depression.

Vumon *BMS, Arg.; BMS, Austral.; BMS, Austria†; BMS, Braz.; BMS, Canad.; BMS, Chile†; BMS, China; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong†; BMS, Mex.; BMS, Neth.; BMS, NZ; BMS, Pol.; BMS, Port.†; BMS, S.Afr.†; BMS, Spain†; BMS Oncology, USA.*
Teniposide (p. 867·1).
Malignant neoplasms.

Vunot *Medipharma, Arg.*
Sertraline (p. 448·1).
Depression.

Vunsu *Costec, Arg.*
Padimate O (p. 1716·1).
Sunscreen.

Vurdon *Help, Gr.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Pain; inflammation; musculoskeletal and joint disorders.

Vurtas *Landsteiner, Mex.*
Abacavir sulfate (p. 963·1).
HIV infection.

Vuscobras *Vargas, Venez.*
Hyoscine butylbromide (p. 1845·3); oxazepam (p. 1092·2).
Smooth muscle spasm.

Vusion *GSK, USA.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Nappy rash.

Vuyator *Sandoz, Cz.*
Fluvastatin sodium (p. 1385·1).

Vykmin *Valeant, Hong Kong.†*
Vitamins; minerals.

Vyling Anti-Cough Menthol *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); guaifenesin (p. 1666·2).

Vyling Gastric *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); liquorice (p. 1853·2); magnesium trisilicate (p. 1858·1); sodium bicarbonate (p. 1781·1).

Vyling Vyfunsil *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); sodium bicarbonate (p. 1781·1).

Vyloma *Medicis, Canad.*
Imiquimod (p. 985·2).
Anogenital warts.

Vyndaqel *Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Irl.; Pfizer, Neth.; Pfizer, Swed.; Pfizer, UK.*
Tafamidis meglumine (p. 2625·2).
Amyloidosis.

Vyrohexal *Hexal, S.Afr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Vytinal *Legrand, Braz.*
Vitamins; amino acids; minerals.

Vytone *Artesa, USA.*
⊗Hydrocortisone (p. 1640·1); diiodohydroxyquinoline (p. 931·1).

Vytorin *MSD, Arg.; MSD, Austral.; MSD, Braz.; MSD, Chile; MSD, China; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Ital.; MSD, Malaysia; Schering-Plough, Malaysia; MSD, Mex.; MSD, NZ; Schering-Plough, Philipp.; MSD, Port.; MSD, Singapore; Schering-Plough, Singapore; MSD, Spain; MSD, Thai.; Merck, USA; Schering-Plough, USA; MSD, Venez.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia; hyperlipidaemias.

Vytral *Alpharma, Mex.*
Vitamins; minerals.

Vyvanse *Shire, Canad.; Shire, USA.*
⊗Lisdexamfetamine mesilate (p. 2323·2).
Attention deficit hyperactivity disorder.

V-Z Vax *Green Cross, Philipp.*
A live, attenuated varicella-zoster vaccine (p. 2423·3).
Active immunisation.

V-Zoline *Vitamed, Israel.*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Wadil *Biomep, Mex.*
Metformin (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Wail Treatment *Frankin, Hong Kong.†*
Benzyl benzoate (p. 2149·1).
Head lice.

Wake Ups *Adrem, Canad.*
Caffeine (p. 1203·3).
Fatigue.

Wala Baume nasal *Wala, Switz.*
European barberry (p. 2502·1); blackthorn (p. 2458·2); Peru balsam (p. 2587·1); cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2); silicic acid (p. 2088·3).
Nasal inflammation.

Wala Baume nasal doux *Wala, Switz.*
European barberry (p. 2502·1); blackthorn (p. 2458·2); peru balsam (p. 2587·1); silicic acid (p. 2088·3).
Nasal disorders.

Wala Baume pectoral au plantain *Wala, Switz.*
Venice turpentine; camphor (p. 2466·2); eucalyptus oil (p. 2501·2) thyme oil (p. 2630·3); ribwort plantain (p. 2604·2); drosera (p. 2497·2); butterbur (p. 2463·2).
Cough.

Wala Echinacea *Wala, Switz.*
Echinacea (p. 2498·1); calendula (p. 2465·2); sage (p. 2608·3); eucalyptus globulus (p. 2501·1); argentum nitricum (p. 2615·3); tonsillae palatinae bovis (p. 2444·1); gingiva bovis (p. 2444·1).
Mouth and throat disorders.

Wala Elixir amer *Wala, Switz.*
Gentian (p. 2512·1); absinthium (p. 2426·1); ginger (p. 1844·1); calamus (p. 2464·2); black pepper (p. 2586·1).
Digestive disorders.

Wala Pulmonium suc contre la toux *Wala, Switz.*
Ribwort plantain (p. 2604·2); Norway spruce; butterbur (p. 2463·2).
Cough.

Walacort *Wallace, India.*
⊗Betamethasone (p. 1623·2).
Corticosteroid.

Walagesic *Wallace, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Walamycin *Wallace, India.*
Colistin sulfate (p. 275·3).
Bacterial diarrhoea.

Walaphage *Wallace, India.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Walavin *Wallace, India.*
Griseofulvin (p. 582·2).
Fungal infections of the skin, hair, and nails.

Waldheim Abführdragees forte *Sanochemia, Austria.†*
Aloes (p. 1816·1); phenolphthalein (p. 1877·3); hard soap (p. 2212·3).
Constipation; bowel evacuation.

Waldheim Rheuma-Creme *Sanochemia, Austria.†*
Salicylamide (p. 129·2).
Musculoskeletal, joint, and soft-tissue disorders.

Walesolone *MBD, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Walix *Silesia, Chile; Fidia, Ital.*
Oxaprozin (p. 112·3).
Musculoskeletal, joint, and peri-articular disorders; musculoskeletal and joint disorders; gout.

Walyte *Wallace, India.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Oral rehydration therapy.

Wamag *Hasco-Lek, Pol.*
Calcium glubionate (p. 1783·2); calcium lactobionate (p. 1784·2); magnesium lactate (p. 1787·2).
Calcium and magnesium supplement.

Wampole Vitamin Syrup *Jamieson, Canad.*
Vitamin B substances (p. 2102·3); iron (p. 2073·1).

Wan Bang Lin *Wan Bang, China.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Wan Bang Lin N *Wan Bang, China.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Wan Bang Lin R *Wan Bang, China.*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Wan Fu *Wu Zhou Tong, China.*
Meglumine adenosine cyclophosphate.

Wan Fu Luo *Wan Xing, China.*
Interferon alfa-2a (p. 989·2).
Chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Wan Fu Yin *Wan Xing, China.*
Interferon alfa-2b (p. 989·2).

Wan Ji *RenFu, China.*
Kitasamycin acetate.

Wan Min Xin *Huali Nanhu, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Wan Pu Ding *Biochem, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Wan Qi *RenFu, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Wan Shi Ning *Sunstone, China.*
Pidotimod (p. 2590·2).
Immunostimulant.

Wan Shi Qi *Tongyong, China.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Wan Su Lin *Wan Bang, China.*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Wan Su Min *Wan Bang, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Wan Su Ping *Wan Bang, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Wan Su Qi *Wan Bang, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Wan Su Xin *Wan Bang, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Wan Ting *San Lian, China.*
Amino acids; polypeptides; nucleotides.

Wan Wei *Wanma, China.*
Azasetron hydrochloride (p. 1820·2).
Chemotherapy-induced vomiting.

Wan Xin Neng *Kangnuo, China.*
Aceglutamide (p. 2426·2).

Wan Yan Ting *Rui Yang, China.*
Diclofenac sodium (p. 48·3); lidocaine hydrochloride (p. 1988·2).

Wan Yi *RenFu, China.*
Oxcarbazepine (p. 533·2).
Epilepsy.

Wan Yu Ping *Hacon, China.*
Amino acids.
Parenteral nutrition.

Wan Yuan *Si Huan, China.*
Thymalfasin (p. 2630·1).
Chronic hepatitis B and C.

Wan Yue *RenFu, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Wanfuluo *Yong He, China.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Wang You *Sunstone, China.*
Citalopram hydrobromide (p. 411·1).
Depression; bipolar disorder; panic disorder.

Wanmycin *DHA, Hong Kong; DHA, Singapore.†*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Wanse *Yu Sheng, Singapore.*
Ferrous fumarate (p. 2060·3); cyanocobalamin (p. 2107·2); folic acid (p. 2063·1).
Anaemias.

Wantong Artiplas *Wantong, Rus.*
Aconite (p. 2428·3); borneol (p. 2460·2); allspice; diphenhydramine hydrochloride (p. 626·2); angelica daurian (p. 2443·3); Chinese cinnamon (p. 2479·2); Sichuan lovage (p. 2545·3); methyl salicylate (p. 92·1); menthol (p. 2553·2); safflower (p. 2086·3); achyranthes bidentata; corydalis.
Osteoarthritis.

War Complex *Thompsons, Canad.†*
Antimony trisulfide (p. 2445·1); causticum (p. 2595·3); nitric acid (p. 2572·3); thuja occidentalis (p. 2629·3).
Homoeopathic preparation.

Waran *Paranova, Denm.; Nycomed, Swed.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Warca *Pharmasant, Thai.*
Mebendazole (p. 158·3).
Worm infections.

Warf *Cipla, India.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Warfant *Antigen, Irl.*
Warfarin sodium clathrate (p. 1527·1).
Thromboembolic disorders.

Warfarex *Grindex, Rus.*
Warfarin sodium clathrate (p. 1527·1).
Thromboembolic disorders.

Warfin *Orion, Pol.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

WariActiv *Ritter, Hong Kong.*
Ethyl chloride (p. 1987·1).
Local anaesthesia.

Warik *Ajanta, Philipp.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Wari-Procomil *Ritter, Hong Kong.†*
⊗Yohimbine hydrochloride (p. 2372·3); methyltestosterone (p. 2291·3); testis extract (p. 2304·3); kola (p. 2648·2); lecithin (p. 2542·2); muira-puama.
Impotence.

Wariviron *Ritter, Hong Kong.†*
Aciclovir (p. 964·1).
Herpes simplex infections.

Warix *Drossapharm, Switz.*
Podophyllotoxin (p. 1717·1).
Anogenital warts.

Warlin *Teva, Jpn.*
Warfarin potassium (p. 1526·3).
Thromboembolic disorders.

Wart Remover *Glades, USA; Rugby, USA; Stiefel, USA.*
Salicylic acid (p. 1719·1).

Wartec *Stiefel, Austral.; Stiefel, Belg.; Stiefel, Braz.; Stiefel, Canad.; Stiefel, China; GSK, Cz.; Stiefel, Denm.; GSK, Fin.; Stiefel, Ger.; Gabriel, Gr.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, Ital.; Stiefel, Mex.; Stiefel, Neth.; Stiefel, Norw.; Stiefel, NZ; Stiefel, Pol.; Stiefel, Rus.; GSK, S.Afr.; GSK, Singapore; Stiefel, Spain; GSK, Swed.; GSK, Ukr.*
Podophyllotoxin (p. 1717·1).
Anogenital warts; warts.

Wartex *Ransom, Irl.; Ransom, UK.*
Salicylic acid (p. 1719·1).
Warts.

Warticon *Stiefel, Irl.; Stiefel, UK.*
Podophyllotoxin (p. 1717·1).
Genital warts.

Wartner *Chefaro, Ger.; Omega, Irl.; Naveh, Israel†; PSM, NZ; Omega, Singapore; Interdelta, Switz.; Passion for Life, UK.*
Dimethyl ether (p. 1798·3); propane (p. 1802·3).
Warts; verrucas.

Wartner Kids *Chefaro, Ger.†*
Difluoroethane (p. 1799·1).
Warts.

Wartner Stift *Chefaro, Ger.*
Trichloroacetic acid (p. 1727·2).
Warts.

Wart-Off *Pfizer, Philipp.†; Pfizer, USA.*
Salicylic acid (p. 1719·1).
Warts; corns; calluses.

Waruzol
Note: this name may be used for preparations of different composition.
Intermedica, Switz.
Acetic acid (p. 2426·3); lactic acid (p. 2539·1); salicylic acid (p. 1719·1).
Warts.

Pharmanik (Φαρμανικ), Gr.
Astemizole (p. 616·1).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Warz-ab Extor *Uhlmann-Eyraud, Switz.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Warts; corns; calluses.

Warzenmittel *Sanova, Austria.†*
Monochloroacetic acid (p. 1714·3).
Warts.

Warzin *Rosch & Handel, Austria.*
Lactic acid (p. 2539·1).
Warts.

Wash E45 *Crookes Healthcare, UK.*
Soap substitute.
Dry skin.

Wasiprobil *Carbel, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Wasotonal *Euronational, Ital.†*
Aescin (p. 2431·2); caffeine (p. 1203·3); rusco (p. 2463·1); centella (p. 1698·3); arnica (p. 2447·2); ivy (p. 2536·2); capsicum (p. 2469·3); menthol (p. 2553·2).
Skin disorders.

Wasp-Eze *SSL, Irl.; SSL, UK.*
Topical spray: Mepyramine maleate (p. 635·1); benzocaine (p. 1980·2).
Insect bites; stings.

Water Babies *Schering-Plough, USA.*
SPF 15: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3).
Sunscreen.

Schering-Plough, USA.
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); homosalate (p. 1705·1); octisalate (p. 1715·2).
Sunscreen.

Schering-Plough, USA.
SPF 45: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octocrilene (p. 1715·2); octisalate (p. 1715·2).
Sunscreen.

Water Babies Little Licks *Schering-Plough, USA.*
SPF 30: Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); octisalate (p. 1715·2).
Sunscreen.

Water Joe *Water Concepts, Canad.†*
Caffeine (p. 1203·3).

Water Naturtabs *Larkhall Laboratories, UK.*
Bladderwrack (p. 2612·1); lappa (p. 2540·1); ground ivy (p. 2523·1); clivers (p. 2481·2).

Water Soluble E *Bioglan, Austral.†*
d-Alpha tocopherol (p. 2119·1).
Vitamin E supplement.

Waterblock *Dermalogica, Canad.*
SPF 30: Homosalate (p. 1705·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Waterguard Kids *Johnson & Johnson, Canad.*
Avobenzone (p. 1695·1); homosalate (p. 1705·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Water-Jel *Zee, Canad.*
Lidocaine hydrochloride (p. 1988·2).
Burns.

Water-Resistant Sunscreen *Arbonne, Canad.*
SPF 30: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); octocrilene (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Watershed *Potter's, UK.*
Oral mixture: Wild carrot (p. 2647·2); pellitory; buchu (p. 2461·3); juniper (p. 2537·1); clivers (p. 2481·2).
Water retention.

Potter's, UK.
Tablets: Buchu (p. 2461·3); bearberry (p. 2453·2).
Water retention.

Waterwhite *H2O Plus, Canad.†*
SPF 15: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Watkins Aloe Vera Botanical Lip Balm *Watkins, Canad.*
Meradimate (p. 1711·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Watkins Cough Medicine *Watkins, Canad.†*
Camphor (p. 2466·2); white pine.
Cough.

Watkins Harvest *Watkins, Canad.†*
Betacarotene (p. 2051·1); vitamin C (p. 2110·3).

Watkins Liniment *Watkins, Canad.†*
Camphor (p. 2466·2).

Watkins Medicated Ointment *Watkins, Canad.*
Camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Watkins Settelz *Watkins, Canad.†*
Bismuth salicylate (p. 1821·3); pectin (p. 2200·3); salol (p. 129·3).

Watkins SHN Formula *Watkins, Canad.†*
Vitamins; minerals.

Watkin's Super Multi *Watkins, Canad.†*
Vitamins; minerals.

Watkins Vision *Watkins, Canad.†*
Vitamins; selenium (p. 2086·3); zinc (p. 2126·1).

Watkins White Cream Liniment *Watkins, Canad.†*
Camphor (p. 2466·2); turpentine.

Waucosin *Proel, Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Waucoton *Farmanic, Gr.*
⊗Propranolol hydrochloride (p. 1479·1).

Wave *Ratiopharm, Austria.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Waxolve *Bell, India.†*
Paradichlorobenzene (p. 2583·2); benzocaine (p. 1980·2); chlorobutanol (p. 1747·2); turpentine oil (p. 2636·3).
Ear wax removal.

Waxsol *Norgine, Austral.; Norgine, Hong Kong†; Alpharma, Indon.†; Meda, Irl.; Norgine, NZ; Norgine, S. Afr.; Norgine, Singapore; Norgine, Thai.; Norgine, UK.*
Docusate sodium (p. 1836·2).
Ear wax removal.

4-Way Fast Acting *Novartis, USA.*
⊗Phenylephrine hydrochloride (p. 1672·3); naphazoline hydrochloride (p. 1669·3); mepyramine maleate (p. 635·1).
Nasal congestion.

4-Way Long Lasting *Bristol-Myers Products, USA.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

4-Way Menthol *Novartis Consumer, USA.*
Phenylephrine hydrochloride (p. 1672·3); menthol (p. 2553·2).
Nasal congestion.

4-Way Moisturizing Relief *Novartis Consumer, USA.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

WCS Dusting Powder *Weleda, UK.*
Arnica montana (p. 2447·2); calendula (p. 2465·2); echinacea angustifolia (p. 2498·1); silica; stibium met. praep. (p. 2445·1).
Homoeopathic preparation.

Webcol *Covidien, Canad.*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Wecesin *Weleda, Ger.; Weleda, S.Afr.†*
Arnica montana (p. 2447·2); calendula officinalis (p. 2465·2); echinacea purpurea (p. 2498·1); quarz; stibium metallicum (p. 2445·1).
Homoeopathic preparation; burns; ulcers; wounds; skin disorders.

Weleda, Switz.
Arnica (p. 2447·2); calendula (p. 2465·2); echinacea (p. 2498·1); quartz; antimony (p. 2445·1).
Skin abrasions; cicatrisation.

Wechseltee St Severin *Smetana, Austria.*
Passion flower (p. 2584·1); valerian (p. 2640·2); lupulus (p. 2546·1); St John's wort (p. 449·1); melissa (p. 2552·3); crataegus (p. 2488·1); mistletoe (p. 2560·2).
Menopausal disorders; nervousness; anxiety disorders; sleep disorders.

Wee Care *Centurion, USA.*
Iron carbonyl (p. 2073·1).
Iron deficiency.

Weewa ORS *Millimed, Thai.*
Sodium chloride (p. 1795·1); potassium chloride (p. 1793·2); sodium citrate (p. 1781·2); glucose (p. 2068·3) (p. 1780·1).
Diarrhoea; oral rehydration therapy.

Wei Di Le *Duoburuifei, China.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Wei Di *Yangtze River, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Wei Ai *General Pharmaceutical, China.*
Tretinoin (p. 1725·2).
Acne.

Wei Ai Ao *SL Pharm, China.*
Matrine.

Wei An *Weifang, China.*
Cyclic adenosine phosphate (p. 2430·2).

Wei An Ke Xin *Yadong, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Wei Bao *Tangshi, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Wei Bei Xian *Ke Lun, China.*
Fructose (p. 2068·2).

Wei Bi Lai *Yixin, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Wei Bo *San Lian, China.*
Dihydroergocornine mesilate.

Wei Chang *Neptunus, China.*
Ibudilast (p. 1211·2).
Asthma.

Wei Chun *Shenlong, China.*
Tiopronin (p. 1578·1).

Wei Ding *Bei Do Gao Ke Hua Tai, China.*
Gamma-aminobutyric acid (p. 2509·2).

Wei Ding Xi *Southwest, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Wei Er *Jingzhong Weier, China.*
Zinc citrate (p. 2126·2).

Wei Er Gu *Chengyi, China.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis; rheumatoid arthritis.

Wei Er Tan *San Lian, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Wei Er Tang *Juneng, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Wei Er Xin *Qiaoguang, China.*
Tocoferil nicotinate (p. 1516·1).
Hyperlipidaemias; atherosclerosis.

Wei Er Ya *Shenghuaxi, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Wei Fei *Tangshi, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Wei Fu De *Global, China.*
Aspartic acid (p. 2050·3); magnesium (p. 1786·3); potassium (p. 1793·1).

Wei Fu Duo *Pude, China.*
Levofloxacin mesilate.
Bacterial infections.

Wei Fu Lai *Longli, China.*
Cisapride (p. 1831·3).
Reduced gastrointestinal motility; dyspepsia; gastro-oesophageal reflux.

Wei Fu Xin *Huabang, China.*
Rifampicin (p. 350·3).
Bacterial infections.

Wei He *Lishizhen, China.*
Calcium carbonate (p. 1824·3); dimeticone (p. 1886·2).

Wei Heng
Note: this name may be used for preparations of different composition.
De Tian, China.
Diammonium glycyrrhizate (p. 2520·3).

Yandi, China.
Clebopride malate (p. 1833·1).

Wei Jian Xin *Kangnuo, China.*
Polypeptides; xanthine.

Wei Jing *Star, China.*
Amoxicillin (p. 216·2); dicloxacillin sodium (p. 286·1).
Bacterial infections.

Wei Ka *Liansheng, China.*
Aminomethylbenzoic acid (p. 1132·2).
Haemorrhage.

Wei Kang *Tianquan, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Wei Kang Li *Saite, China.*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; pain.

Wei La Ke *Chengyi, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Wei Ke *Hengrui, China.*
Etoposide (p. 790·2).
Malignant neoplasms.

Wei Ke An *Mei Luo, China.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Wei Ke Da *NCPC, China.*
Vitamin B_{12} (p. 2107·2).
Tired eyes.

Wei Ke Hen *Jiangxi, China.*
Fluconazole (p. 578·2).
Fungal infections.

Wei Ke Lai *Hanson, China.*
Ambroxol hydrochloride (p. 1654·3).

Wei Ke Rui Da *Defeier, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Wei Ke Xin *Yerui, China.*
Zinc acexamate (p. 2427·3).

Wei Kuai *Weiao, China.*
⊗Paracetamol (p. 115·1); loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).

Wei Kun *Haishen Liansheng, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Wei Li *Hacon, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Wei Li Ang *Lingkang, China.*
Phenylephrine hydrochloride (p. 1672·3).
Hypotension; supraventricular tachycardia.

Wei Li Ke *Sine, China.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Wei Li Ming *Dari, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Wei Li Ning *Zhebei, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Wei Li Qing *Qingfeng, China.*
Azithromycin lactobionate.
Bacterial infections.

Wei Li Si Da *Tian Fu, China.*
Ligustrazine phosphate.

Wei Li Tian *Kang Le, China.*
Calcium gluconate (p. 1783·3).

Wei Li Xian *Cuccess, China.*
Pazufloxacin mesilate (p. 338·1).

Wei Lin *Qi Li, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Wei Lu De *Jianfeng, China.*
Azithromycin sulfate.
Bacterial infections.

Wei Lun *Bausch & Lomb, China.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Wei Mai Xin *Shenghe, China.*
Tocoferil nicotinate (p. 1516·1).

Wei Man *Deyuantang, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Wei Mei *Beiqi, China.*
Sodium glutamate (p. 2198·2).

Wei Mei Le *Biochem, China.*
Sodium glucuronate (p. 2517·1).

Wei Di Mei *Huasen, China.*
Hydrotalcite (p. 1845·2).
Dyspepsia.

Wei Mei Jia *Pude, China.*
Levofloxacin mesilate.
Bacterial infections.

Wei Mei Sheng *Meien, China.*
Iodine-131 (p. 2225·3) tumour necrosis therapy monoclonal antibody.

Wei Di Min *Zhebei, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Wei Neng *Zhebei, China.*
Glibenclamide (p. 472·1); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Wei Ni An *New Hualian, China.*
Nilestriol.
Menopausal disorders.

Wei Ning Jia *TaiYuan, China.*
Pefloxacin mesilate (p. 338·1).
Bacterial infections.

Wei Le Nuo *Duoburuifei, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Wei Nuo *Fenghuang, China.*
Zidovudine (p. 1024·2).
HIV infection.

Wei Nuo Ding *Guangdong, China.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Wei Nuo Ping *Taihuatang, China.*
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).

Wei Ou Lu *Wei Kang, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Wei Peng *Global, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Wei Ping *Zhong Bao, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Wei Pu *President Pharmagenesis, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Wei Pu Fen *Weiao, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Wei Pu Xin *Xianqiang, China.*
Enoxacin gluconate.
Bacterial infections.

Wei Qi *Lianshui, China.*
Tiapride hydrochloride (p. 1111·2).

Wei Qi Da *C&Y, China.*
Amoxicillin sodium (p. 216·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Wei Qi Ting *Pude, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Wei Ru *Zhangjiagang, China.*
Ganciclovir sodium (p. 982·3).
Cytomegalovirus infection.

Wei Le Rui *Duoburuifei, China.*
Levocarnitine (p. 2053·2).

Wei Rui *Yangtze River, China.*
Cefetamet pivoxil hydrochloride (p. 240·2).
Bacterial infections.

Wei Rui Ke *Jinchan, China.*
Ribavirin (p. 1010·2).
Chronic hepatitis C.

Wei Rui Te *Hengrui, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Wei Sai Lai *Welman, China.*
Lysine hydrochloride (p. 2079·3).

Wei Sai Rui An *Zhongke Yuan, China.*
A hepatitis A vaccine (p. 2388·3).
Active immunisation.

Wei Sai Rui Ji *Zhongke Yuan, China.*
A hepatitis A vaccine (p. 2388·3).
Active immunisation.

Wei Sai Xin *Welman, China.*
Fosfructose trisodium (p. 2507·2).

Wei Sai Yin *Welman, China.*
Ropivacaine mesilate.
Local anaesthesia.

Wei Shan *Topfond, China.*
Risedronate sodium (p. 1189·3).
Osteoporosis; Paget's disease of bone.

Wei Shuang *Liansheng, China.*
Aspartic acid (p. 2050·3); magnesium (p. 1786·3); potassium (p. 1793·1).

Wei Le Si *Sunho, China.*
Nevirapine (p. 1005·1).
HIV infection.

Wei Si Ning *Si Huan Ke Bao, China.*
Polypeptides; hypoxanthine.

Wei Suan Su *San Lian, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Wei Ta Ting *Jing Xin, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual syndrome.

Wei Tai *Guanglian, China.*
Hydrotalcite (p. 1845·2).
Dyspepsia.

Wei Tai Kang *Luofu Taikang, China.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1); methiosulfonium chloride (p. 2558·1); amylase (p. 2442·1); liquorice (p. 1853·2); tetrahydropalmatine; bletilla striata; bile (p. 2457·2); menthol (p. 2553·2).
Gastric hyperacidity; gastritis.

Wei Te *Lunan, China; XinShiDai, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Wei Ti Yin *Kechuang, China.*
Calcium ascorbate (p. 2111·1).

Wei Tian *Liansheng, China.*
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Wei Xin
Note: this name may be used for preparations of different composition.
Chang Fu Jie Jing, China.
Aciclovir (p. 964·1).
Herpesvirus infections.
Tianquan, China.
Famotidine (p. 1842·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Wei Xin Hong *Pude, China.*
⊗Bumetanide (p. 1329·1).
Oedema.

Wei Xin Kai *Shengtai, China.*
Amino acids; polypeptides; nucleotides.

Wei Xin Ping *San Lian, China.*
Isosorbide dinitrate (p. 1412·2).

Wei Di Ya *Weimin, China.*
Colloidal bismuth pectin (p. 1821·3).

Wei Yi *Liansheng, China.*
Sodium alginate (p. 2167·3).

Wei Yi Shu *Ke Lun, China.*
Ramosetron hydrochloride (p. 1881·3).

Wei Yi Xing *San Lian, China.*
Glycyrrhizin (p. 2520·2); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Wei You *Bai Ao, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Wei Yu Qing *Zhongshi, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Wei Yuan *Kai Bao, China; Xinyi, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Wei Ze *Hanson, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Wei Zhi Wei *Changchun, China.*
A varicella-zoster vaccine (p. 2423·3).
Active immunisation.

Wei Zong *Bikang, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Weibaisi *NCPC, China.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Weibaoding *Hospira, China.*
Vinblastine sulfate (p. 881·3).
Malignant neoplasms.

Weicon *Utopian, Thai.*
Oxyphencyclimine hydrochloride (p. 1875·1).
Peptic ulcer.

Weidi *Livzon, China.*
Sucralfate (p. 1889·1).
Peptic ulcer.

WeiDing *Pude, China.*
Diammonium glycyrrhizate (p. 2520·3).

Weifa-Calcium *Weifa, Thai.†*
Calcium carbonate (p. 1824·3).
Osteoporosis; calcium supplement.

Weifapenin *Weifa, Norw.*
Phenoxymethylpenicillin potassium (p. 338·3).
Bacterial infections.

Weigeluo *Sunve, China.*
Rosiglitazone hydrochloride (p. 496·3).
Diabetes mellitus.

Weight Control *Homeocan, Canad.*
Fucus vesiculus (p. 2612·1); kali iodatum (p. 2336·3); rhamnus frangula (p. 1843·3); thyoidinum (p. 2345·3).
Homoeopathic preparation.

Weight Loss Aid *Herbal Concepts, UK.*
Taraxacum (p. 2625·3); bladderwrack (p. 2612·1); boldo (p. 2458·3).
Slimming aid.

Weight Loss Kit *Dolisos, Canad.†*
Fucus vesculus (p. 2612·1); hieracium pilosella; zinc (p. 2126·1); cobalt (p. 2482·2); nickel.
Homoeopathic preparation.

Weight Maximum *Lafarmen, Arg.*
Nutritional supplement.
Aid to gaining weight.

Weight-Less *Blackmores, Austral.*
Amorphaphallus rivieri (LuraLean).
Slimming aid.

Weihong *CSPC, China.*
Azithromycin (p. 221·2).
Bacterial infections.

WeiJia
Note: this name may be used for preparations of different composition.
Guang Da, China.
Potassium glutamate.
Liansheng, China.
Aciclovir (p. 964·1).
Herpesvirus infections.

Weijiangzhi *Sunve, China.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Weijiexin *Sunve, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

WeiKa *Longkema, China.*
A BCG vaccine (p. 2378·1).

Weikang DiKe *Weigao, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Weikangda *XinShiDai, China.*
Tegafur (p. 864·2); gimeracil; oteracil potassium.
Gastric cancer.

Weike *Hisun, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Weilexing *Harvest, China.*
Ribavirin (p. 1010·2).
Viral infections.

Weiliufen *Sunve, China.*
Sulfasalazine (p. 1890·1).
Ulcerative colitis; rheumatoid arthritis.

WeiMei *Changlian Laifu, China.*
Ethylenediamine diaceturate.

WeiMeiJia *Pudu, China.*
Inosine (p. 2533·1).

Weimerquin *Biokanol, Ger.†*
Chloroquine phosphate (p. 650·1).
Malaria.

WeiPing
Note: this name may be used for preparations of different composition.
Lunan, China.
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.
Southwest, China.
Famotidine (p. 1842·1); calcium carbonate (p. 1824·3); magnesium hydroxide (p. 1857·2).

Weiruile *Tiantan, China.*
A varicella-zoster vaccine (p. 2423·3).
Active immunisation.

Weisanlian *Livzon, China.*
Bismuth subcitrate; clarithromycin (p. 266·2); tinidazole (p. 949·2).
Helicobacter pylori eradication.

Weiscal *Valdecasas, Mex.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Weisen-U *Shigaken, China.*
Compund methiosulfonium chloride.
Shigaken, Singapore.
Methiosulfonium chloride (p. 2558·1); biodiastase (p. 2442·1); aluminium hydroxide (p. 1817·2).
Gastric hyperacidity; heartburn; dyspepsia; flatulence.

Weishaxin *Sunve, China.*
Levofloxacin lactate.
Bacterial infections.

Weishike *BSPC, China.*
Tocoferil nicotinate (p. 1516·1).

Weisi *Yangtze River, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Weisida *Double-Crane, China.*
Lafutidine (p. 1851·3).
Peptic ulcer; gastritis; acid aspiration.

WeiTai *Disha, China.*
Itopride hydrochloride (p. 1850·1).
Nausea and vomiting; reduced gastrointestinal motility.

WeiTian *Langyi, China.*
Pidotimod (p. 2590·2).
Immunostimulant.

WeiTong *Shule, China.*
Ligustrazine hydrochloride.

WeiXin *Caoxian, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

WeiYi
Note: this name may be used for preparations of different composition.
NEGPF, China.
Sucralfate (p. 1889·1).
Gastritis; peptic ulcer.

San Jin, China.
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Welchol *Daiichi Sankyo, USA.*
Colesevelam hydrochloride (p. 1345·1).
Hypercholesterolaemia.

Welcome Matte *Dermalogica, Canad.*
SPF 15: Octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Wel-Coplex *Universal, Hong Kong.†*
Noscapine (p. 1670·3); phenylephrine (p. 1672·2); promethazine (p. 638·2).

Weleda Avena Valeriana *Weleda, Neth.*
Avena sativa (p. 2451·1); humulus lupulus (p. 2546·1); passiflora incarnata (p. 2584·1); valeriana officinalis (p. 2640·2); coffea tosta (p. 2648·2).
Homoeopathic preparation.

Weleda Bronchialbalsam *Weleda, Ger.*
Eucalyptus oil (p. 2501·2); fennel oil (p. 2503·3); pine needle oil (p. 2591·1); peppermint oil (p. 1877·1); rosemary oil (p. 2607·3); sage oil (p. 2609·1); juniper berry oil (p. 2537·2).
Respiratory tract disorders.

Weleda Fieber- und Zahnungszäpfchen *Weleda, Ger.*
Belladonna (p. 2453·3); chamomilla (p. 2474·1); echinacea angustifolia (p. 2498·1); echinacea purpurea (p. 2498·1); papaver somniferum; argentum metallicum (p. 2615·1).
Homoeopathic preparation.

Weleda Hamorrhoidalzapfchen *Weleda, Ger.*
Hamamelis (p. 2523·3); aesculus (p. 2431·2); stibium metall..
Anorectal disorders.

Weleda Hauttonikum *Weleda, Ger.†*
Arnica (p. 2447·2); blackthorn (p. 2458·2); iris (p. 2534·3); lappa (p. 2540·1); lemon (p. 2542·3); hamamelis (p. 2523·3).
Venous insufficiency.

Weleda Heilsalbe *Weleda, Ger.*
Calendula officinalis (p. 2465·2); mercurialis perennis; balsamum peruvianum (p. 2587·1); resina laricis; stibium metallicum (p. 2445·1).
Homoeopathic preparation.

Weleda Heuschnupfenspray *Weleda, Ger.*
Citric acid (p. 2480·3); cydonia.
Allergic respiratory-tract disorders.

Weleda Hustenelixier *Weleda, Ger.*
Althaea (p. 2438·3); solanum dulcamara (p. 2497·3); marrubium vulgare (p. 1668·3); aniseed (p. 2444·2); wild thyme (p. 2648·1); thyme (p. 2630·2); drosera (p. 2497·2); malt (p. 2080·2); ipecacuanha (p. 1667·2); pulsatilla vulgaris (p. 2600·2).
Respiratory-tract disorders.

Weleda Nasenöl *Weleda, Ger.*
Calendula (p. 2465·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); hydragyrum sulfuratum rubrum (p. 2555·3); chamomile (p. 2474·1); peppermint oil (p. 1877·1); thyme oil (p. 2630·3).
Nasal congestion.

Weleda Sleedoorn *Weleda, Neth.†*
Prunus spinosa (p. 2458·2).
Homoeopathic preparation.

Weleda-Rheumasalbe M *Weleda, Ger.†*
Basil (p. 2453·1); camphor (p. 2466·2); fluorit; castanospermum oil; venice turpentine; sea water (p. 2612·1); murmeltierfett; rosemary oil (p. 2607·3).
Frostbite; gout; musculoskeletal, joint, and soft-tissue disorders.

Wellbutrin *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK, Braz.; Valeant, Canad.; GSK, Chile; GSK, Cz.; 2care4, Denm.; Orifarm, Denm.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, USA; Valeant, USA; GSK, Venez.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal; depression; seasonal affective disorder.

Wellconal *Aspen, S.Afr.*
Dipipanone hydrochloride (p. 53·2); cyclizine hydrochloride (p. 623·2).
Pain.

Welldorm *Marlborough Pharmaceuticals, UK.*
Cloral betaine (p. 1055·2) or cloral hydrate (p. 1055·2).
Insomnia.

Wellferon *GSK, Rus.†*
Interferon alfa-n1 (p. 989·2).
Leukaemias; chronic hepatitis B; hepatitis C; renal cell carcinoma; genital warts; laryngeal papillomatosis.

Wellman *Vitabiotics, Hong Kong; Vitabiotics, Rus.*
Vitamins; minerals; ginseng (p. 2513·3); bioflavonoids (p. 2505·2); garlic (p. 2510·3); amino acids.

Vitabiotics, UK.
Vitamins; minerals.

Vitabiotics, Ukr.
Vitamins; trace elements; carotenoids (p. 2176·2); ginseng (p. 2513·3); garlic (p. 2510·3); citrus bioflavonoids (p. 2505·2).
Dietary supplement.

Vitabiotics, Hong Kong.†
Oral liquid: Vitamins; minerals; ginseng (p. 2513·3); green tea (p. 2648·2); cynara (p. 2490·3).

Wellnara *Jenapharm, Ger.*
Estradiol (p. 2271·1); levonorgestrel (p. 2296·1).
Menopausal disorders.

Wellvone *GSK, Austral.; GSK, Belg.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Ital.; GSK, Neth.; Wellcome, Port.; Aspen, S.Afr.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Atovaquone (p. 928·2).
Pneumocystis pneumonia.

Wellwoman *Potter's, UK.*
Tablets: Achillea (p. 2427·3); motherwort (p. 2564·2); tilia (p. 2631·3); skullcap (p. 2617·1); valerian (p. 2640·2).
Menopausal disorders.

Vitabiotics, Ukr.
Borage oil (p. 2459·2); evening primrose oil (p. 2502·2); vitamins; trace elements; carotenoids; citrus bioflavonoids (p. 2505·2).
Dietary supplement.

Welsan Dual Shower Oil *Weluga, Hong Kong.*
Gamolenic acid (p. 2509·2).
Dry skin; eczema.

Welsan Lipocream *Weluga, Hong Kong.*
Gamolenic acid (p. 2509·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1).
Barrier preparation; dry skin disorders; corticosteroid cream diluent.

Welticilina *Welt, Arg.†*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Welt-Sulfazol *Welt, Arg.*
Sulfathiazole (p. 368·3).
Burns; skin infections; wounds.

Welusil *Beacons, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium trisilicate (p. 1858·1).

Wemid *Bernabo, Arg.*
Erythromycin (p. 291·2) or erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Wen Fei *Tasly, China.*
Eszopiclone (p. 1072·3).

Wen Qing *Lunan, China.*
Fluconazole (p. 578·2).
Fungal infections.

Wenflox *Raffo, Arg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Wenglitong *NCPC, China.*
Coix seed; fritillaria; chuan mu tong.
Urinary-tract disorders.

Wepox *Wockhardt, India; Wockhardt, Philipp.; Wockhardt, Ukr.†*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Wermy *Wermar, Mex.*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Wesfem *Farmanic, Gr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

West Antiseptic Soap *West Penetone, Canad.*
Triclosan (p. 1773·2).

Westcarbox *Lloyd, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Westcort *BMS, Braz.†; Westwood-Squibb, Canad.†; BMS, Mex.; Ranbaxy, USA.*
⊗Hydrocortisone valerate (p. 1640·3).
Skin disorders.

Westfimox *Lloyd, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Westhroid *RLC, USA.*
Thyroid (p. 2345·3).

Wesulc *Farmanic, Gr.*
Magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2).

Wet *Fidia, Ital.*
Electrolytes (p. 1775·1).
Nasal irrigation.

Wet Gel *Agis, Israel.*
Hyaluronic acid benzyl ester (Hydeal-D).
Nasal dryness.

Wet Mini Spray *Agis, Israel.*
Hyaluronic acid benzyl ester (Hydeal-D).
Nasal hygiene; nasal dryness.

Wet Stuff *Universal, Hong Kong.*
⊗Glycerol (p. 2517·2).
Vaginal and rectal lubricant.

Wet-COMOD *Ursapharm, Ger.; Visufarma, Ital.*
Povidone (p. 2204·3).
Dry eyes.

Wetirin *Ferring, Spain.*
⊗Desmopressin acetate (p. 2355·1).
Diabetes insipidus; nocturnal enuresis.

Wetol *Beta, Arg.*
Pilocarpine hydrochloride (p. 2010·3).
Radiotherapy-induced xerostomia; Sjögren's syndrome.

White & Black *Bayer, China.*
⊗Daytime tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); nighttime tablets, paracetamol; pseudoephedrine hydrochloride; dextromethorphan hydrobromide; diphenhydramine hydrochloride (p. 626·2).
Cold and influenza symptoms; cough.

White Cloverine *Medtech, USA.*
Barrier preparation.

White Spot *ICM, Singapore.*
Salicylic acid (p. 1719·1).
Acne; hyperkeratotic skin disorders.

White-C *Shandong Kexing, Philipp.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Whitfield's Antifungal *Ovelle, Irl.*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2).
Fungal skin infections.

Whitfields (Benzoic Acid Compound) Ointment *Biotech, Austral.*
Benzoic acid (p. 1738·2); salicylic acid (p. 1719·1).
Fungal skin infections.

Wiacid *Landson, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders; gastro-oesophageal reflux.

Wiaflox *Landson, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Wiamox *Landson, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Wiatrim *Landson, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Wibi *Valeant, USA.*
Moisturiser.

Wibical *GP, Spain.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Wibotin HM *Pfluger, Ger.*
Aesculus hippocastanum (p. 2431·2); arnica montana (p. 2447·2); silybum marianum (p. 1561·1); hamamelis virginiana (p. 2523·3); lachesis mutus (p. 2538·3).
Homoeopathic preparation.

Wicaran *Widmer, Fin.*
⊗Tretinoin (p. 1725·2); dexpanthenol (p. 2582·2); urea (p. 1727·3).
Keratinisation disorders.

Wicarba *Widmer, Fin.*
⊗Vitamin A palmitate (p. 2098·3); dexpanthenol (p. 2582·2); urea (p. 1727·3).
Skin disorders.

Wick Daymed Erkältungs *Wick, Ger.*
Capsules: Dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); phenylpropanolamine hydrochloride (p. 1674·1).
Cold symptoms.

Wick, Ger.†
Powder for oral liquid: Paracetamol (p. 115·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3); ascorbic acid (p. 2110·3).
Cold symptoms.

Wick Erkaltungs-Saft fur die Nacht *Procter & Gamble, Austria.†*
⊗Doxylamine succinate (p. 627·3); ephedrine sulfate (p. 1663·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold symptoms.

Wick Erkältungssirup für die Nacht *Procter & Gamble, Austria.*
⊗Doxylamine succinate (p. 627·3); ephedrine sulfate (p. 1663·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1); anethole (p. 2443·3).
Cough and cold symptoms.

Wick Erste Abwehr *Wick, Ger.*
Viscous nasal gel.
Cold prophylaxis.

Wick Formel 44 Husten-Pastillen *Procter & Gamble, Austria.*
Dextromethorphan (p. 1660·1).
Cough.

Wick Formel 44 Hustenstiller *Procter & Gamble, Austria.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Wick Husten-Löser *Wick, Ger.*
Guaifenesin (p. 1666·2).
Cough and associated respiratory-tract disorders.

Wick Hustenlöser *Wick, Ger.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Wick Husten-Pastillen gegen Reizhusten mit Honig *Wick, Ger.*
Dextromethorphan (p. 1660·1).
Cough; catarrh.

Wick Hustensaft *Procter & Gamble, Austria.†*
Dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3); sodium citrate (p. 1781·2).
Cough.

Wick Husten-Sirup gegen Reizhusten mit Honig *Wick, Ger.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Wick Inhalierstift N *Wick, Ger.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Wick Medinait für die Nacht *Wick, Ger.*
⊗Doxylamine succinate (p. 627·3); ephedrine sulfate (p. 1663·2); dextromethorphan hydrobromide (p. 1660·1); paracetamol (p. 115·1).
Cold and influenza symptoms.

Wick Medinait mit Honig und Kamillenaroma *Wick, Ger.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cold and influenza symptoms.

Wick Sinex *Wick, Ger.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Catarrh; nasal congestion.

Wick SinexAloe *Procter & Gamble, Austria.*
⊗Oxymetazoline hydrochloride (p. 1671·3); aloe (p. 1693·2); menthol (p. 2553·2); cineole (p. 2479·1).
Cold symptoms.

Wick Sulagil *Wick, Ger.*
Lidocaine hydrochloride (p. 1988·2); dequalinium chloride (p. 1749·3); cetylpyridinium chloride (p. 1743·1).
Mouth and throat disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Wick Vaporub *Procter & Gamble, Austria.*
Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); cedar wood oil (p. 2472·3); turpentine oil (p. 2636·3); thymol (p. 1772·2).
Cough and cold symptoms; catarrh.

Procter & Gamble, Pol.
Camphor (p. 2466·2); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); thymol (p. 1772·2); turpentine oil (p. 2636·3); nutmeg oil (p. 2573·2); cedar oil.
Respiratory-tract disorders.

Wick, Ger.
Ointment: Menthol (p. 2553·2); camphor (p. 2466·2); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3).
Cough; catarrh; cold symptoms.

Wick-Inhalierstift *Procter & Gamble, Austria.*
Menthol (p. 2553·2); camphor (p. 2466·2).
Nasal congestion.

Wicnelact *Widmer, Fin.*
Triclosan (p. 1773·2); zinc sulfate (p. 2126·2); lactic acid (p. 2539·1); magnesium sulfate (p. 1787·3); salicylic acid (p. 1719·1).
Acne; seborrhoea.

Wida *Widatra Bhakti, Indon.*
Glucose (p. 2068·3).
Fluid replacement; carbohydrate source.

Wida D NS *Widatra Bhakti, Indon.*
Sodium chloride (p. 1795·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Wida DaD *Widatra Bhakti, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Wida NS *Widatra Bhakti, Indon.*
Sodium chloride (p. 1795·1).
Fluid and electrolyte disorders.

Wida NSI *Widatra Bhakti, Indon.*
Sodium chloride (p. 1795·1).
Irrigation solution for surgical procedures.

Wida RD *Widatra Bhakti, Indon.*
Electrolytes (p. 1775·1); glucose (p. 2068·3).
Fluid and electrolyte disorders; carbohydrate source.

Wida RL *Widatra Bhakti, Indon.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

Wida RS *Widatra Bhakti, Indon.*
Electrolytes (p. 1775·1).
Fluid and electrolyte disorders.

WIDAHES *Widatra Bhakti, Indon.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Plasma volume expansion; haemodilution.

Widecillin *Meiji, Indon.*
Amoxicillin (p. 216·2) or amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Widrox *Landson, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Wiedimmun *Wiedemann, Ger.*
Injection: Echinacea angustifolia (p. 2498·1); lachesis mutus (p. 2538·3); eupatorium perfoliatum (p. 2459·1); gelsemium (p. 2511·2); aconitum (p. 2428·3).
Homoeopathic preparation.

Wiedimmun N *Wiedemann, Ger.†*
Echinacea (p. 2498·1); eupatorium perfoliatum (p. 2459·1); aconitum napellus (p. 2428·3); atropa belladonna (p. 2453·3).
Homoeopathic preparation.

Wiewohl *Diethelm, Switz.†*
Peppermint oil (p. 1877·1); eucalyptus oil (p. 2501·2); juniper oil (p. 2537·2); sage oil (p. 2609·1).
Musculoskeletal and joint disorders; pain; insect bites; cough catarrh.

Wilate *Varifarma, Arg.; Octapharma, Austria; Octapharma, Belg.; Octapharma, Canad.; Octapharma, Cz.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Irl.; Octapharma, Israel; Octapharma, Neth.; Octapharma, Norw.; Octapharma, NZ; Octapharma, Port.; Octapharma, Rus.; Octapharma, Spain; Octapharma, Swed.; Octapharma, Switz.; Octapharma, UK; Octapharma, USA.*
A factor VIII preparation (p. 1148·1).
Von Willebrand's disease; haemophilia A; haemorrhagic disorders.

Wild Yam Complex *Mediherb, Austral.*
Wild yam (p. 2648·1); asparagus (p. 2450·2); St John's wort (p. 449·1); sage (p. 2608·3); cimicifuga (p. 2478·1); ginseng (p. 2513·3).
Tonic; menopausal symptoms.

Wildkräuteröl spezial N *Johanser, Ger.*
Peppermint oil (p. 1877·1).
Respiratory-tract disorders; skeletal muscle and nerve pain; gastrointestinal disorders.

Wilfactin *CAF-DCF, Belg.; LFB, Fin.; LFB, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; LFB, Neth.*
von Willebrand factor (p. 1165·3).
Von Willebrand's disease; haemorrhagic disorders.

Wilkinson *Mega, Turk.†*
Coal tar (p. 1723·2); sulfur (p. 1721·1); savon noir; calcium carbonate (p. 1824·3).
Psoriasis; eczema.

Will-Anal *Will-Pharma, Neth.*
⊗Lidocaine hydrochloride (p. 1988·2); triamcinolone acetonide (p. 1649·1).
Anorectal disorders.

Willfact *LFB, Cz.; LFB, Denm.; LFB, Ger.; LFB, Norw.; Opopharma, Switz.*
von Willebrand factor (p. 1165·3).
Von Willebrand's disease.

Willgo *Panacea, India.*
Nimesulide (p. 101·3).
Osteoarthritis; rheumatoid arthritis; pain.

Williams Cough *Beacons, Singapore.*
⊗Ammonium chloride (p. 1656·1); ephedrine hydrochloride (p. 1663·2); ipecacuanha (p. 1667·2).

Willlong *Will-Pharma, Belg.†*
Glyceryl trinitrate (p. 1391·2).
Angina pectoris; heart failure.

Willydina *Tocogino, Mex.*
Dextromethorphan (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Wilnativ *Octapharma, Denm.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Wilom *Hizon, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Wilopres *Hizon, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Wilopres Plus *Hizon, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Wilovex *Hizon, Philipp.*
Levofloxacin (p. 315·3).
Bacterial infections.

Wilpan Antigripal *Bernabo, Arg.*
Phenylephrine hydrochloride (p. 1672·3); vitamin C (p. 2110·3); pentoxyverine citrate (p. 1672·1); paracetamol (p. 115·1).
Influenza symptoms.

Wilprafen *Astellas, Rus.; Astellas, Ukr.*
Josamycin (p. 314·2) or josamycin propionate (p. 314·2).
Bacterial infections.

Wilsim *Hizon, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Wilstart *LFB, Fr.*
Von Willebrand factor (p. 1165·3).
Von Willebrand's disease.

Wilvit *Sons, Mex.*
Vitamins; minerals; ginseng (p. 2513·3).

Wilzin *Orphan, Austria; Orphan, Belg.; Orphan, Cz.; Orphan Europe, Denm.; Orphan, Fr.†; Orphan, Ger.; IFET (ΙΦΕΤ), Gr.; Orphan, Irl.; Orphan, Ital.; Orphan, Neth.; Orphan Europe, Norw.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Orphan Europe, Swed.; Orphan, UK.*
Zinc acetate (p. 2126·1).
Wilson's disease.

Winaflox *Dynamic, Philipp.†*
Norfloxacin (p. 333·3).
Bacterial infections.

Winasorb *Recalcine, Chile; Rudefsa, Mex.†*
Paracetamol (p. 115·1).
Fever; pain.

Winasorb Flex *Recalcine, Chile.*
Chlorzoxazone (p. 2022·2); paracetamol (p. 115·1).
Skeletal muscle spasm and pain.

Winasorb Flu DN *Recalcine, Chile.*
⊗Day tablets, paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Winasorb UP *Recalcine, Chile.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Winatin *Ifars, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Winch *SoSe, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Winclar *Savio, Ital.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Wincocef *XL, Philipp.*
Cefadroxil (p. 233·2).
Bacterial infections.

Wind & Dyspepsia Relief *Herbal Concepts, UK.*
Ginger (p. 1844·1); hydrastis (p. 2528·1); myrrh (p. 2566·1); rhubarb (p. 1884·2); valerian (p. 2640·2); taraxacum (p. 2625·3).
Dyspepsia; flatulence.

Windar *Gador, Arg.*
Clarithromycin (p. 266·2).
Bacterial infections.

Wind-Eze *GSK Consumer, UK.*
Simeticone (p. 1886·2).
Formerly known as Setlers Wind-Eze.
Flatulence.

Windol *Dermapharm, Ger.†*
Bufexamac (p. 30·2).
Inflammatory skin disorders.

Windoxa *Sanofi-Aventis, Cz.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Winfex *Winthrop, UK.*
Venlafaxine hydrochloride (p. 454·2).
Depression.

Wingel *Sanofi Synthelabo, Mex.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); dimeticone (p. 1886·2).
Gastric hyperacidity; flatulence.

40 Winks *Roberts, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Winlomylon *Adcock Ingram, S.Afr.†*
Nalidixic acid (p. 328·3).
Gram-negative bacterial urinary-tract infections.

Winning Hands Hand Cleanser *Betco, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Winning Hands Hand Sanitizer *Betco, Canad.*
Benzethonium chloride (p. 1738·1).
Hand disinfection.

Winnipeg *SF, Ital.*
Bacampicillin hydrochloride (p. 225·2).
Bacterial infections.

Winofit *Wockhardt, India.*
Vitamin E (p. 2119·1); vitamin C (p. 2110·3); vitamin A (p. 2098·3); eicosapentaenoic acid (p. 1460·2); docosahexaenoic acid (p. 1460·1); zinc sulfate (p. 2126·2); manganese (p. 2081·2); chromium tripicolinate (p. 2056·1); selenium dioxide (p. 2087·1).
Tonic.

Winol *Raffo, Arg.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Winopam *Liwinner, Thai.*
Diazepam (p. 1063·2).

Winpain *Brunel, S.Afr.*
Paracetamol (p. 115·1).
Pain; fever.

Winpar *Alpharma, Mex.*
Cinnarizine (p. 622·1).
Vestibular disorders; nausea and vomiting; cerebral and peripheral vascular disorders.

Winpred *Valeant, Canad.*
⊗Prednisone (p. 1647·2).
Corticosteroid.

WinRho *Cangene, Austral.; Baxter, Belg.†; Cangene, Canad.; Cangene, Gr.; Cangene, Hong Kong; Cangene, Israel; Baxter, Ital.†; Cangene, Neth.†; Baxter, NZ; Cangene, Philipp.; Cangene, Port.†; Cangene, Singapore†; Tibbi, Turk.; Baxter, UK†; Baxter, USA.*
An anti-D immunoglobulin (p. 2377·1).
Prevention of rhesus sensitisation; immune thrombocytopenia.

Winstrol *Desma, Spain.*
⊗Stanozolol (p. 2304·2).
Anabolic; anaemia in renal failure; osteoporosis; breast cancer.

Wintanyl *Winthrop, Cz.†*
⊗Fentanyl (p. 60·1).
Pain.

Winter AP *Merck, Braz.*
⊗Dexbrompheniramine maleate (p. 618·1); pseudoephedrine sulfate (p. 1676·1).
Respiratory-tract congestion.

Wintermin *Shionogi, Jpn.*
Chlorpromazine hydrochloride (p. 1045·2) or chlorpromazine phenolphthalinate (p. 1045·2).
Schizophrenia; mania; depression; anxiety; nausea and vomiting; hiccups; tetanic spasms; premedication; induction of hypothermia; pain.

Wintogeno *Actavis, Indon.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).
Musculoskeletal pain; soft-tissue injury.

Wintogeno Extra *Actavis, Indon.*
Methyl salicylate (p. 92·1); levomenthol (p. 2553·2).
Musculoskeletal pain; soft-tissue injury.

Wintomylon *Sanofi-Aventis, Braz.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong†; Sanofi Synthelabo, Mex.†*
Nalidixic acid (p. 328·3).
Urinary-tract infections; Gram-negative bacterial intestinal infections.

Winton *Sanofi-Aventis, Spain.†*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Dyspepsia; gastric hyperacidity.

Wintus *Sandoz, Turk.*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3); chlorphenamine maleate (p. 620·3).
Respiratory-tract congestion.

Wirbelsaule- und Gelenkstropfen Nr 2 *Doskar, Austria.†*
Symphytum (p. 2484·2); ruta graveolens (p. 2608·2); aesculus hippocastanum (p. 2431·2); hypericum perforatum (p. 449·1); toxicodendron quercifolium (p. 2603·3).
Homoeopathic preparation.

Wiserdex *Advaita, Mex.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

Wisperdon *Proton, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Wispra *Pfizer, Cz.*
Sumatriptan succinate (p. 679·2).
Migraine.

Witagin *Labofarm, Pol.*
Vitamins; trace elements; ginseng (p. 2513·3).
Tonic.

Witch Doctor *De Witt, UK.*
Hamamelis (p. 2523·3).
Skin disorders.

Witch Sunsore *De Witt, UK.*
Hamamelis (p. 2523·3).
Sunburn.

Witdulsies *Aspen Consumer, S.Afr.*
Ethyl nitrite (p. 2500·3).
Cold symptoms; fever; asthma; vertigo.

With 6 SPF Sunscreen Self Tanning Essential Bronze Milk *Coty, Canad.*
SPF 6: Avobenzone (p. 1695·1); octinoxate (p. 1715·1).
Sunscreen.

With 6 SPF Sunscreen Self Tanning Ultra Natural Bronze Care *Coty, Canad.*
SPF 6: Avobenzone (p. 1695·1); octinoxate (p. 1715·1); octocrilene (p. 1715·2).
Sunscreen.

Withania Complex *Mediherb, Austral.*
Skullcap (p. 2617·1); liquorice (p. 1853·2); ashwagandha (p. 2450·2); ginseng (p. 2513·3).
Tonic.

Withania Compound *Phytomedicine, Austral.*
Ashwagandha (p. 2450·2); astragalus (p. 2451·1); Siberian ginseng (p. 2614·3).
Anxiety.

Witromin *Pisa, Mex.†*
Erythromycin (p. 291·2).
Bacterial infections.

Witte Kruis *Vemedia, Neth.*
Paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain; fever.

Witty *Gezzi, Arg.*
Permethrin (p. 2159·3).
Pediculosis.

Wizol *Landson, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

WND *Mead Johnson, Fr.*
Food for special diets.
Urea cycle disorders.

Wo Er De *Shouhe Jinhai, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Wo Ka *Lianshui, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Wo Ping *Limin, China.*
Cyclic adenosine phosphate (p. 2430·2).

Wo Sen Gan Tai *Yangling Huasheng, China.*
Oxymatrine.

Wo Ting *San Lian, China.*
Homoharringtonine (p. 837·3).

Wobe-Mugos *Mucos, Austria.*
⊗Pancreatic proteolytic enzymes (p. 2444·1); calf thymus (p. 2631·1); pisum sativum; lens esculenta; papain (p. 2582·3).
Adjunct to treatment of malignant neoplasms.

Romsa, Mex.
⊗Papain (p. 2582·3); trypsin (p. 2635·2); chymotrypsin (p. 2477·3).
Inflammatory and degenerative disorders; varicella-zoster infections.

Wobe-Mugos E *Mucos, Rus.; Mucos, Ukr.†*
⊗Chymotrypsin (p. 2477·3); trypsin (p. 2635·2); papain (p. 2582·3).
Reduction of adverse effects of radiation and chemotherapy; herpesvirus infections; adjunct to treatment of malignant neoplasms and viral infections.

Wobenzym *Mucos, Austria; Mucos, Cz.; Romsa, Mex.; Mucos, Rus.; Mucos, Ukr.*
⊗Pancreatin (p. 2579·3); papain (p. 2582·3); bromelains (p. 2460·3); trypsin (p. 2635·2); lipase (p. 2579·3); amylase (p. 2442·1); chymotrypsin (p. 2477·3); rutoside (p. 2505·3).
Inflammation; oedema; musculoskeletal, joint, and soft-tissue disorders.

Mucos, Canad.
⊗Bromelain (p. 2460·3); chymotrypsin (p. 2477·3); pancreatin (p. 2579·3); papain (p. 2582·3); rutoside (p. 2505·3); trypsin (p. 2635·2).

Wobenzym mono *Mucos, Ger.†*
⊗Bromelains (p. 2460·3).
Inflammation.

Wobenzym N *Mucos, Venez.*
⊗Pancreatin (p. 2579·3); trypsin (p. 2635·2); chymotrypsin (p. 2477·3); bromelains (p. 2460·3); papain (p. 2582·3); rutoside (p. 2505·3).
Inflammation.

Mucos, Ger.†
Tablets: ⊗Pancreatin (p. 2579·3); bromelains (p. 2460·3); papain (p. 2582·3); rutoside (p. 2505·3).
Inflammation; thrombophlebitis.

Wobenzym plus *Mucos, Ger.*
⊗Bromelains (p. 2460·3); trypsin (p. 2635·2); rutoside (p. 2505·3).
Thrombophlebitis; arthritis.

Wokadine *Wockhardt, India; Wockhardt, Rus.†; Wockhardt, Ukr.*
Povidone-iodine (p. 1767·1).
Skin infections; disinfection of hands, skin and mucous membranes; burns; wounds; mouth and throat disorders; vaginal infections; mouth and throat infections.

Wokex-2 *Wockhardt, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2). Pyridoxine hydrochloride (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Wokex-3 *Wockhardt, India.*
1 Tablet, rifampicin (p. 350·3); isoniazid (p. 311·2); 1 tablet, ethambutol (p. 296·1). Pyridoxine (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Wokex-4 *Wockhardt, India.*
1 Tablet, rifampicin (p. 350·3); isoniazid (p. 311·2); 2 tablets, pyrazinamide (p. 345·2); 1 or 2 tablets, ethambutol (p. 296·1). Pyridoxine (p. 2105·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Wolff Basis *Wolff, Cz.†*
Emollient.
Skin disorders; pharmaceutical diluent.

Woman's Laxative *Guardian, Canad.*
Bisacodyl (p. 1821·1).
Constipation.

Women's 45+ *Natural Factors, Canad.†*
Vitamins; minerals.

Womens Bio Balance *Blackmores, Austral.*
Lactobacillus rhamnosus (p. 2596·3); *Lactobacillus reuteri* (p. 2596·3).
Maintenance of vaginal flora.

Women's D-Stress *Blackmores, Austral.*
Vitamins; minerals; ashwagandha (p. 2450·2).
Anxiety; tonic.

Women's Formula *Natures Sunshine, Canad.*
Cimicifuga (p. 2478·1).
Menopausal disorders; menstrual disorders.

Womens Multi *Bioglan, Austral.*
Vitamins; minerals; Siberian ginseng (p. 2614·3); camellia sinensis; lycopene (p. 2546·2); thioctic acid (p. 2629·1); citrus bioflavonoids (p. 2505·2).
Dietary supplement.

Womens One-a-Day Multi *Golden Glow, Austral.*
Vitamins; minerals; citrus bioflavonoids (p. 2505·2); lysine hydrochloride (p. 2079·3); evening primrose oil (p. 2502·2).
Dietary supplement for women's health.

Womens Tylenol Multi-Symptom Menstrual Relief *McNeil Consumer, USA.*
Paracetamol (p. 115·1); pamabrom (p. 1464·1).

Women's Vitality Multi *Blackmores, Austral.*
Vitamins; minerals; milk thistle (p. 1561·1); Siberian ginseng (p. 2614·3).
Tonic.

Womosol *Costec, Arg.*
Padimate O (p. 1716·1).
Sunscreen.

Woncare *Hovid, Philipp.*
Sodium fusidate (p. 302·1).
Bacterial skin infections.

Wonder Ice *Pedinol, USA.*
Menthol (p. 2553·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Wonder Oil *Citron Remedies, Canad.*
Clove oil (p. 2481·3); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Wondergel *Lake, USA.*
Vaginal lubricant.

Wonderkroonessens *Aspen Consumer, S.Afr.*
Rhubarb (p. 1884·2); gentian (p. 2512·1); valerian (p. 2640·2); ginger (p. 1844·1); elecampane (p. 1662·3); aloes (p. 1816·1); camphor (p. 2466·2); potassium carbonate (p. 2595·2).
Constipation; dyspepsia; flatulence.

Wondra *Richardson-Vicks, USA.*
Emollient and moisturiser.

Wontizem *Daewon, Hong Kong.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Woods' Peppermint Antitussive *Kalbe, Indon.*
Dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2).
Cough with allergy.

Wood's Peppermint Cough Syrup *Kalbe, Singapore.*
Guaifenesin (p. 1666·2).
Cough.

Woods' Peppermint Expectorant *Kalbe, Indon.*
Bromhexine hydrochloride (p. 1656·3); guaifenesin (p. 1666·2).
Cough; bronchitis; emphysema.

Woodward's Baby Chest Rub *SSL, Singapore.*
Turpentine oil (p. 2636·3); eucalyptus oil (p. 2501·2); menthol (p. 2553·2).
Nasal congestion; nasal catarrh.

Woodward's Diaper Rash *Pharmacare, Canad.*
Zinc oxide (p. 1729·1).
Nappy rash.

Woodwards Gripe Water
Note: this name may be used for preparations of different composition.
Pharmacare, Canad.; LRC, Israel; SSL, Thai.†; SSL, UK.
Terpeneless dill seed oil (p. 2493·2); sodium bicarbonate (p. 1781·1).
Infant colic and flatulence.

Seton, Pol.
Fennel oil (p. 2503·3); sodium bicarbonate (p. 1781·1).
Infant colic.

Woodward's Gripe Water
Note: this name may be used for preparations of different composition.
SSL, Hung.
Sodium bicarbonate (p. 1781·1); terpeneless dill seed oil (p. 2493·2).
Infant colic.

Woodwards Inhalant *Aspen Consumer, S.Afr.*
Cineole (p. 2479·1); chloroxylenol (p. 1748·2); pine oil (p. 2591·1); turpentine oil (p. 2636·3); menthol (p. 2553·2).
Respiratory-tract disorders.

Woodwards Teething Gel *SSL, UK.*
Lidocaine hydrochloride (p. 1988·2); cetylpyridinium chloride (p. 1743·1).
Teething pain; mouth ulcers; denture irritation.

Wörishofener *Volmix, Hung.*
Crataegus (p. 2488·1); valerian (p. 2640·2); melissa (p. 2552·3); solidago (p. 2620·1).
Nervous disorders.

Wormadole *Be-Tabs, S.Afr.*
Albendazole (p. 149·1).
Worm infections; giardiasis.

Wormex
Note: this name may be used for preparations of different composition.
Ace, Philipp.
Mebendazole (p. 158·3).
Worm infections.

Wormgo *Aspen Consumer, S.Afr.*
Mebendazole (p. 158·3).
Worm infections.

Wormicide *Greater Pharma, Thai.*
Praziquantel (p. 164·1).
Trematode infections.

Wormin *Cadila, India; Cadila, Rus.*
Mebendazole (p. 158·3).
Worm infections.

Wormob *T Man, Thai.†*
Mebendazole (p. 158·3).
Worm infections.

Wormstop *Be-Tabs, S.Afr.*
Mebendazole (p. 158·3).
Worm infections.

Wormwood Complex *Mediherb, Austral.*
Stemona sessilifolia root; black walnut (p. 2646·1); absinthium (p. 2426·1); clove oil (p. 2481·3).
Gastrointestinal disorders.

Wosulin 30/70 *Pentafarma, Chile†; Wockhardt, Philipp.; Wockhardt, Ukr.†*
⊗A mixture of insulin injection (human) 30% and isophane insulin (human) 70% (p. 475·3).
Diabetes mellitus.

Wosulin 30/70 and 50/50 *Wockhardt, India.*
⊗Mixtures of neutral insulin injection (human, highly purified) 30% and 50% and isophane insulin injection (human, highly purified) 70% and 50% respectively (p. 475·3).
Diabetes mellitus.

Wosulin N *Wockhardt, India.*
⊗Isophane insulin injection (human) (p. 475·3).
Diabetes mellitus.

Wosulin R *Wockhardt, India.*
⊗Insulin injection (human, highly purified) (p. 475·3).
Diabetes mellitus.

Wosulin-N *Pentafarma, Chile†; Wockhardt, Philipp.; Wockhardt, Ukr.†*
⊗Isophane insulin (human) (p. 475·3).
Diabetes mellitus.

Wosulin-R *Pentafarma, Chile†; Wockhardt, Philipp.; Wockhardt, Ukr.†*
⊗Insulin injection (human) (p. 475·3).
Diabetes mellitus.

Wotinex *Wockhardt, India.*
Tinidazole (p. 949·2); diloxanide furoate (p. 931·2).
Amoebiasis.

Wound Cleanser *Geritrex, USA.*
Chlorophyllin copper complex (p. 2178·3); vitamin E (p. 2119·1); zinc (p. 2126·1).

W-Tal *Costec, Arg.*
Soap substitute.

W-Tropfen *Hofmann & Sommer, Ger.*
Salicylic acid (p. 1719·1); lactic acid (p. 2539·1).
Calluses; corns.

Wu Hen *Treeful, China.*
Lappaconitine hydrobromide (p. 1418·1).

Wu Du Li *Tianhedi Sainuo, China.*
⊗Amiloride hydrochloride (p. 1299·1); hydrochlorothiazide (p. 1403·2).

Wu Mei *Yung Shin, China.*
Miconazole nitrate (p. 589·1).

Wu Sheng Wang Ning *Wuhan Institute, China.*
A rabies vaccine (Vero cell) (p. 2413·2).
Active immunisation.

Wu Ti Lin Si *Jinxing Jiankang, China.*
A BCG vaccine (p. 2378·1).

Wu Yan *Zhonghui, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Wunderbalsam *Wunderpharm, Arg.*
Juniper (p. 2537·1); angelica (p. 2443·3); alkanna tinctoria; peppermint (p. 1877·1); boldo (p. 2458·3); cynara (p. 2490·3); star anise (p. 2622·1); aniseed (p. 2444·2); cedron; peperina; poleo (p. 2599·1); rhubarb (p. 1884·2); coriander (p. 2486·3); colombo (p. 2466·1).
Appetite stimulant.

Wundesin *Novartis Consumer, Austria.*
Povidone-iodine (p. 1767·1).
Wounds.

Wurzeltod *Elixan Aromatica, Switz.*
Salicylic acid (p. 1719·1).
Corns; callouses; verrucas.

Wuxin *General Sanyang, China.*
Furbicillin sodium.
Bacterial infections.

Wyanoids Relief Factor *Wyeth-Ayerst, USA.*
Live yeast cell derivative (p. 2125·2); shark-liver oil (p. 2614·2).
Haemorrhoids.

Wycakon-G *Seiko Eiyo, China.*
Gefarnate (p. 1844·1).
Peptic ulcer; gastritis; colitis; stomach cramp.

Wycillin
Note: this name may be used for preparations of different composition.
Euroforma, Braz.
Procaine benzylpenicillin (p. 344·2); benzylpenicillin potassium (p. 228·2).
Bacterial infections.

Wycort *Wyeth, India.*
⊗Hydrocortisone acetate (p. 1640·1).
Corticosteroid.

Wycort with Neomycin *Wyeth, India.*
⊗Hydrocortisone acetate (p. 1640·1); neomycin sulfate (p. 330·1).
Burns; wounds; skin ulcers; infected skin disorders; anal or vulval pruritus.

Wydora *Riemser, Ger.†; Wyeth, Gr.*
Indoramin hydrochloride (p. 1410·2).
Hypertension.

Wydox *YSS, Philipp.*
Oxacillin sodium (p. 336·2).
Staphylococcal infections.

Wygesic *Wyeth, India.*
Dextropropoxyphene hydrochloride (p. 43·3); paracetamol (p. 115·1).
Pain.

Wylaxine *Omega, Belg.*
Bisoxatin acetate (p. 1823·2).
Constipation; bowel evacuation.

Wymesone *Wyeth, India.*
⊗Dexamethasone (p. 1630·3).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Wymzya Fe *Lupin, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Wysolone *Wyeth, India.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Wysoy *SMA Nutrition, Irl.*
Infant feed.
Cows' milk intolerance.

Wyeth, UK.
Lactose-free food for special diets.
Cows' milk or lactose intolerance; galactosaemia; galactokinase deficiency.

Wystamm *Bouchara-Recordati, Fr.*
Rupatadine fumarate (p. 640·1).
Allergic rhinitis; urticaria.

Wytens *Meda, Fr.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Wytensin *Wyeth-Ayerst, USA.†*
Guanabenz acetate (p. 1395·1).
Hypertension.

X-2 *Investigaciones Filosoficas y Cientificas, Mex.*
Cocarboxylase (p. 2103·1).
Thiamine deficiency.

Xacin *Pharmasant, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Xadevil *Minerva (Μινερβα), Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Xadorek *Minerva (Μινερβα), Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Xados *Menarini, Cz.*
Bilastine (p. 617·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Xadosin *Macrophar, Thai.*
Doxazosin mesilate (p. 1369·1).
Hypertension; benign prostatic hyperplasia.

Xafenor *Solvay, Gr.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Xaflo *Richmond, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Xafon *Nycomed, China.*
Lornoxicam (p. 83·2).
Pain; inflammation.

Xagrid *Shire, Belg.; Shire, Cz.; Shire, Denm.; Shire, Fin.; Shire, Fr.; Shire, Ger.; IFET (ΙΦΕΤ), Gr.; Shire, Gr.; Shire, Irl.; Shire, Ital.; Shire, Neth.; Shire, Norw.; Shire, Pol.; Shire, Port.; Shire, Spain; Swedish Orphan, Swed.; Opopharma, Switz.; Shire, UK.*
Anagrelide hydrochloride (p. 2442·2).
Essential thrombocythaemia.

Xal *Pharmadeveloppement, Fr.*
Potassium chloride (p. 1793·2); ammonium chloride (p. 1656·1); magnesium chloride (p. 1787·1); glutamic acid (p. 2070·2).
Dietary salt substitute.

Xalacom *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Europharma, Denm.†; Orifarm, Denm.†; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.†; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pfizer, Venez.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Xalam *New Life, Thai.*
Alprazolam (p. 1035·2).

Xalaprost *Cooper (Κοπερ), Gr.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Xalatan *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ†; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Ukr.; Pharmacia Upjohn, USA; Pfizer, Venez.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Xalavista *Sandoz, Spain.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Xalazin *Astellas, Hung.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Xalazina *HLB, Arg.*
Mesalazine (p. 1859·2).
Inflammatory bowel disease.

Xalcom *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Xaleec *Sandoz, Cz.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Xaleec Combi *Sandoz, Cz.*
⊗Candesartan cilexetil (p. 1330·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Xaliplat *Richmond, Arg.*
Oxaliplatin (p. 838·1).
Malignant neoplasms.

Xalkori *Pfizer, Canad.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Israel; Pfizer, Jpn; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Switz.; Pfizer, UK; Pfizer, USA.*
Crizotinib (p. 770·2).
Non-small cell lung cancer.

Xaloptic *Polpharma, Cz.; Polpharma, Pol.*
Latanoprost (p. 2008·1).
Ocular hypertension; glaucoma.

Xaloptic Combi *Polpharma, Irl.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Xalos *Medano, Switz.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Xaluprine *Nova, Denm.; Nova, Neth.; Nova, Norw.; Nova, UK.*
Mercaptopurine (p. 820·3).
Leukaemias.

Xalyn-Or *Atlantis, Mex.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Xamamina *Bracco, Ital.; Sanovel, Turk.*
Dimenhydrinate (p. 625·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Xamiol *Leo, Austria; Leo, Belg.; Leo, Canad.; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Gr.; Leo, Hong Kong; Leo, Irl.; Leo, Israel; Formenti, Ital.; Leo, Neth.; Leo, Norw.; Leo, Philipp.; Leo, Pol.; Leo, Port.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Switz.; Leo, Thai.; Leo, UK.†*
⊗Calcipotriol (p. 1697·2); betamethasone dipropionate (p. 1623·3).
Psoriasis.

Xanacine *Medicine Products, Thai.*
Alprazolam (p. 1035·2).
Anxiety.

Xanaes *Klonal, Arg.*
Azelastine hydrochloride (p. 617·1).
Eye disorders.

Xanaflu *Abbott, Neth.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Xanagis *Perrigo, Israel.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states; panic disorders.

Xanalife *Target, Gr.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis.

Xanalin *Silom, Thai.*
Neomycin sulfate (p. 330·1); polymyxin B (p. 342·3); gramicidin (p. 308·3).
Bacterial eye infections.

Xanator *Sieger, Gr.*
Atorvastatin (p. 1309·2).
Hyperlipidaemias.

Xanax *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, NZ; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Eczacibasi, Turk.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder; alcohol withdrawal syndrome; mixed anxiety-depressive states; depression; sleep disorders.

Xanazole *Virgo, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Xanbon *Kissei, Jpn.*
Ozagrel sodium (p. 2579·1).
Cerebral vasospasm; cerebral thrombosis.

Xanda *Teguhsindo, Indon.*
Curcuma; fructo-oligosaccharides (p. 2508·1); lysine (p. 2079·3); taurine (p. 2626·2); inositol (p. 2533·2).
Reduced appetite.

Xandase *Charoon Bhesaj, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Xanef *MSD, Ger.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Xanidil *Zentiva, Cz.†*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Xanidine *Berlin Pharm, Singapore.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia; acid aspiration.

Berlin Pharm, Thai.
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Xanline *Rafarm, Gr.*
Ampicillin (p. 218·2) or ampicillin sodium (p. 218·2).
Bacterial infections.

Xanol
Note: this name may be used for preparations of different composition.
Pharmasant, Thai.
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Phoenix, Arg.
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Xanomel *Clonmel, Irl.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastric hyperacidity.

Xanor *Pfizer, Austria; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Swed.*
Alprazolam (p. 1035·2).
Panic disorder; anxiety; mixed anxiety depressive states.

Xanternet *SIFI, Ital.*
Hyaluronic acid (p. 2526·2); xanthan gum (p. 2220·1); netilmicin (p. 331·1).
Eye abrasion.

Xantervit *SIFI, Ital.*
Xanthopterin (p. 2649·1); vitamins.
Ocular trauma and lesions.

Xantervit Antibiotico *SIFI, Ital.*
Xanthopterin (p. 2649·1); chloramphenicol (p. 257·1); vitamins.
Ocular trauma and lesions.

Xantervit Eparina *SIFI, Ital.*
Xanthopterin (p. 2649·1); heparin sodium (p. 1396·3); vitamins.
Ocular burns.

Xanthium *SMB, Fr.; SMB, Thai.; Medsan, Turk.*
Theophylline (p. 1229·3).
Obstructive airways disease; asthma.

SMB, Belg.; SMB, Singapore.
Theophylline hydrate (p. 1229·3).
Obstructive airways disease.

Xantinon B12 *Nycomed, Braz.*
Methionine (p. 1558·2); vitamin B substances (p. 2102·3); choline chloride (p. 2055·2); liver extract (p. 2444·1); with or without manganese (p. 2081·2) and gastric mucosa extract (p. 2444·1).
Liver disorders.

Xantinon Complex *Nycomed, Braz.*
Acetylmethionine (p. 1558·2); inositol (p. 2533·2); choline citrate (p. 2055·2); betaine hydrochloride (p. 2456·1); cyanocobalamin (p. 2107·2); pyridoxine hydrochloride (p. 2105·3).
Liver disorders.

Xantromid *Richmond, Arg.*
Methotrexate (p. 822·2).
Malignant neoplasms.

Xantrosin *Teva, Belg.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Xanturenasi *Teofarma, Ital.*
Pyridoxine hydrochloride (p. 2105·3).
Vitamin B_6 deficiency.

Xanturic *Pyridam, Indon.*
Allopurinol (p. 600·2).
Gout; hyperuricosuria.

Xanurace *Ace, Philipp.*
Allopurinol (p. 600·2).
Hyperuricaemia.

Xanvit *Soho, Indon.*
Curcuminoid; vitamin B substances (p. 2102·3).
Tonic.

Xao Pil *Ingens, Arg.†*
Pilocarpine (p. 2010·2).
Glaucoma; production of miosis.

Xao T *Ingens, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Xapnev *Merck, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; panic disorder; social phobia.

Xapritx *Alter, Port.†*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Xapro *Jenapharm, Ger.*
Estriol (p. 2274·3).
Vulvovaginal disorders.

Xarator *Pfizer, Ital.*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Xarb *Piramal, India.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Xarb-H *Piramal, India.*
⊗Irbesartan (p. 1411·1); hydrochlorothiazide (p. 1403·2).
Hypertension.

Xarelto *Bayer, Arg.; Bayer, Austral.; Bayer Schering, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer Schering, Cz.; Bayer Schering, Denm.; Bayer, Fr.; Bayer, Ger.; Bayer Schering, Gr.; Bayer, Hong Kong; Bayer Schering, Hung.; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer, Jpn; Bayer Schering, Malaysia; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer, Pol.; Bayer Schering, Port.; Bayer, Rus.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, UK; Bayer, Ukr.; Janssen, USA.*
Rivaroxaban (p. 1487·2).
Thrombosis prophylaxis following hip or knee replacement surgery; thromboembolic disorders; stroke and systemic embolism prophylaxis in atrial fibrillation; thromboembolism prophylaxis in acute coronary syndrome.

Xaritic *SJA, Gr.*
Levocarnitine tartrate (p. 2053·2).

Xarope 44E *Procter & Gamble, Braz.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cough.

Xarope de Macas Reinetas *Gestafarma, Port.*
⊗Senna (p. 1885·1); mannitol (p. 1427·3); apple pulp.
Constipation.

Xarope Neo *Neo Quimica, Braz.*
Potassium iodide (p. 2336·3).
Cough.

Xarope Vick Mel *Procter & Gamble, Braz.*
Guaifenesin (p. 1666·2).

Xartan *Farma Iberica, Philipp.; Adamed, Pol.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure; stroke prophylaxis in left-ventricular hypertrophy; diabetic nephropathy.

Xasmun *Stada, Spain.*
Norfloxacin (p. 333·3).
Urinary-tract infections.

Xatger *Gerard, Irl.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Xatinate *Bryntsalov, Rus.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders; hyperlipidaemias.

Xatral *Sanofi-Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Canad.; Sanofi, China; Sanofi-Aventis, Cz.; Sanofi-Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Norw.†; Sanofi-Aventis, Philipp.; Sanofi-Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Swed.; Sanofi-Aventis, Switz.; Sanofi-Aventis, Thai.; Sanofi Synthelabo, Turk.; Sanofi Synthelabo, UK; Sanofi-Aventis, Venez.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Xavetta *Hameln, Neth.*
Irinotecan hydrochloride (p. 812·2).
Colorectal cancer.

Xavin
Note: this name may be used for preparations of different composition.
Teva, Ital.
⊗Budesonide (p. 1625·1).
Asthma; croup.
Extractum, Hung.†
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Xavitor *Tabuk, Pol.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Xazal *UCB, Spain.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Xazexy *Brown & Burk, Philipp.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

X-Cam *Meprofarm, Indon.*
Meloxicam (p. 86·3).
Osteoarthritis; rheumatoid arthritis.

Xclair *Sinclair, Israel.*
Levomenol (p. 2544·1); enoxolone (p. 54·2); sodium hyaluronate (p. 2526·2); grape (p. 2521·3); telmesteine (p. 1678·2); piroctone olamine (p. 1716·3); allantoin (p. 1693·1).
Radiation dermatitis.
Sinclair, UK.
Levomenol (p. 2544·1); enoxolone (p. 54·2); hyaluronic acid (p. 2526·2); vitis vinifera (p. 2521·3); telmesteine (p. 1678·2).
Radiation dermatitis.

Xebramol *Medicine Products, Thai.*
Paracetamol (p. 115·1).
Pain; fever.

Xebyl *Basi, Port.*
Chenodeoxycholic acid (p. 2475·1).
Gallstones.

Xedec *Cypress, USA.†*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Xedenol *Baliarda, Arg.*
Diclofenac diethylamine (p. 48·3) or diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Xedenol B12 *Baliarda, Arg.*
⊗Diclofenac sodium (p. 48·3); betamethasone (p. 1623·2) or betamethasone phosphate (p. 1623·2); cyanocobalamin (p. 2107·2) or hydroxocobalamin (p. 2107·3).
Peri-articular disorders.

Xedenol Flex *Baliarda, Arg.*
Diclofenac sodium (p. 48·3); pridinol mesilate (p. 2026·1).
Musculoskeletal and joint disorders.

Xedenol Gesic *Baliarda, Arg.*
Diclofenac potassium (p. 48·3); paracetamol (p. 115·1).
Peri-articular disorders; pain.

Xedocine *Stada, Rus.*
Doxycycline (p. 288·1).
Bacterial infections.

Xedron *Aspen, Arg.†*
Zoledronic acid (p. 1192·3).

Xeed 2 *Panacea, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Xeed 4 *Panacea, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1); pyrazinamide (p. 345·2).
Tuberculosis.

Xeed 3E *Panacea, India.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); ethambutol hydrochloride (p. 296·1).
Tuberculosis.

Xeface *Ace, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Xefo *Nycomed, Arg.; Nycomed, Austria; Biolab Sanus, Braz.; Nycomed, Cz.; Nycomed, Denm.; Nycomed, Gr.; Nycomed, Hung.; Nycomed, Irl.; Nycomed, Israel; Nycomed, Neth.†; Nycomed, Pol.; Nycomed, S.Afr.; Nycomed, Swed.; Takeda, Switz.; Abdi, Turk.*
Lornoxicam (p. 83·2).
Musculoskeletal, joint, and peri-articular disorders; pain; rheumatoid arthritis; osteoarthritis; sciatica; inflammation.

Xefocam *Nycomed, Rus.; Nycomed, Ukr.*
Lornoxicam (p. 83·2).
Pain; rheumatoid arthritis; osteoarthritis; musculoskeletal and joint disorders.

Xelacef *Actavis, Pol.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Xelent *Westmont, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Xelevia *MSD, Cz.; Pierre Fabre, Fr.; Berlin-Chemie, Ger.; MSD, Gr.; MSD, Hung.; MSD, Irl.; Gentili, Ital.; MSD, Neth.; MSD, Pol.; MSD, Port.; MSD, Spain; Menarini, Switz.*
Sitagliptin phosphate (p. 500·1).
Diabetes mellitus.

Xeljanz *Pfizer, Jpn; Pfizer, USA.*
Tofacitinib citrate (p. 138·1).
Rheumatoid arthritis.

Xeloda *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Genentech, USA; Roche, Venez.*
Capecitabine (p. 757·3).
Breast cancer; colorectal cancer; gastric cancer; oesophageal cancer; stomach cancer.

Xelor *Tedec Meiji, Spain.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Xeltic *Unison, Hong Kong; Unison, Thai.*
Glibenclamide (p. 472·1).
Diabetes mellitus.

Xemestan *Avansor, Fin.*
⊗Exemestane (p. 792·2).
Breast cancer.

Xemos *Recalcine, Chile.*
⊗Salmeterol (p. 1224·1).
Asthma.

Xenaderm *Healthpoint, USA.*
⊗Trypsin (p. 2635·2); Peru balsam (p. 2587·1); castor oil (p. 2472·1).

Xénalon *Mepha, Switz.*
⊗Spironolactone (p. 1499·3).
Hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Xenar *Wassermann, Ital.*
Naproxen (p. 98·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Xenazina *Chiesi, Ital.*
Tetrabenazine (p. 2627·3).
Huntington's chorea; dyskinesias.

Xenazine *EUSA, Fr.; IFET (ΙΦΕΤ), Gr.; Megapharm, Israel; ICN, Neth.; AFT, NZ; Medilink, Swed.; Proreo, Switz.; Lundbeck, UK; Lundbeck, USA.*
Tetrabenazine (p. 2627·3).
Movement disorders; Huntington's chorea; ballism.

Xenbilox *Sigma-Tau, Ger.*
Chenodeoxycholic acid (p. 2475·1).
Cholesterol gallstones.

Xendin *Salus, Mex.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Xenetic *Temis, Arg.†*
Iobitridol (p. 1588·2).
Radiographic contrast medium.

Xenetix *Temis, Arg.; Guerbet, Austria; Guerbet, Belg.; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Hung.; Guerbet, Irl.; Guerbet, Israel; Guerbet, Ital.; Guerbet, Neth.; Guerbet, Norw.; Martins & Fernandes, Port.; Guerbet, Rus.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.; Guerbet, Thai.; Guerbet, Turk.; Quifoven, Venez.*
Iobitridol (p. 1588·2).
Radiographic contrast medium; contrast medium for computerised tomography.

Xenical *Invesi, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, China; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Farmagon, Norw.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Ukr.; Roche, USA; Roche, Venez.*
Orlistat (p. 2577·1).
Obesity.

Xenid *Ranbaxy, Fr.*
Diclofenac epolamine (p. 48·3).
Musculoskeletal, joint, and peri-articular disorders.

Xenifar *Ifars, Indon.*
Naproxen sodium (p. 98·2).
Pain; rheumatoid arthritis; ankylosing spondylitis; osteoarthritis; gout.

Xeniplus *Elea, Arg.†*
Orlistat (p. 2577·1).
Obesity.

Xenius *Mac, Gr.*
Paclitaxel (p. 839·3).

Xenna *US Pharmacia, Pol.*
Senna (p. 1885·1).
Bowel evacuation; constipation.

Xenobid *Rallis, India; Shreya, India.*
Naproxen (p. 98·2) or naproxen sodium (p. 98·2).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Xenoflox *Xeno, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Xenoprom *Novell, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Xenorac's *Farmaceutica H, Mex.*
Naproxen sodium (p. 98·2); paracetamol (p. 115·1).
Pain; fever.

Xenovate *Aspen, S.Afr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Xentafid *Fidia, Ital.*
Benzydamine hyaluronate (p. 29·2).
Mouth and throat disorders.

Xentic *Farma-Projekt, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Xeomeen *Merz, Mex.*
Botulinum A toxin (p. 2017·1).
Blepharospasm; spasmodic torticollis.

Xeomin *Phoenix, Arg.; Merz, Austria; Biolab Sanus, Braz.; Merz, Canad.; Desitin, Denm.; Merz, Fin.; Merz, Fr.; Merz, Ger.; Merz, Ital.; Desitin, Norw.; Merz, Pol.; Merz, Port.; Merz, Rus.; Merz, Spain; Orion, Swed.; Merz, UK; Merz, USA.*
Botulinum A toxin (p. 2017·1).
It is also described as containing incobotulinumtoxinA.
Blepharospasm; spasmodic torticollis; upper limb spasticity following stroke; glabellar lines.

Xepabet *Metiska, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Xepabion *Metiska, Indon.*
Vitamins; minerals.
Dietary supplement.

Xepacaine *Gland, Philipp.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xepacillin *Metiska, Indon.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Xepacycline *Xepa-Soul Pattinson, Singapore.*
Tetracycline hydrochloride (p. 373·2).
Bacterial infections.

Xepadergin *Metiska, Indon.*
Codergocrine mesilate (p. 389·2).
Mental function impairment in the elderly.

Xepagan *Tack Fung, Hong Kong; Xepa-Soul Pattinson, Singapore.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; sedative.

Xepalat *Metiska, Indon.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Xepalium *Metiska, Indon.*
Flunarizine (p. 629·3).
Migraine; dizziness; peripheral vascular disorders.

Xepalodin *Metiska, Indon.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Xepamet *Metiska, Indon.; Xepa-Soul Pattinson, Singapore.*
Cimetidine (p. 1827·1).
Peptic ulcer; pathological hypersecretory disorders; gastrointestinal haemorrhage; gastro-oesophageal reflux; adjunct in pancreatic insufficiency; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Xepamol *Metiska, Indon.*
Paracetamol (p. 115·1).
Fever; pain.

Xepaneuron *Metiska, Indon.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; nervous system disorders; morning sickness; tonic.

Xepanicol *Metiska, Indon.*
Chloramphenicol palmitate (p. 257·1).
Bacterial infections.
Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.
Chloramphenicol (p. 257·1).
Bacterial eye infections.

Xepaprim *Metiska, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Xepare *Metiska, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Xepasone *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Singapore.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Xepathritis *Metiska, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders; inflammation.

Xepavit *Metiska, Indon.*
Vitamins; zinc (p. 2126·1).
Vitamin and zinc deficiencies.

Xepazym *Metiska, Indon.*
Lipase (p. 2579·3); amylase (p. 2442·1); protease (p. 2598·1); dimeticone (p. 1886·2).
Flatulence; aerophagia; pancreatic insufficiency.

Xepin *Typharm, Irl.†; Cambridge Healthcare, UK.*
Doxepin hydrochloride (p. 414·2).
Pruritus.

Xeplion *Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen, UK.*
Paliperidone palmitate (p. 1093·1).
Schizophrenia.

Xepol *Xepol, Swed.†*
A normal immunoglobulin (p. 2403·3).
Hypogammaglobulinaemia; immune thrombocytopenia; immunodeficiency.

Xerac AC *Dispolab, Chile; Person & Covey, USA.*
Aluminium chloride (p. 1693·3).
Hyperhidrosis.

Xeracil *Xeragen, S.Afr.†*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Xeradin *Metiska, Indon.*
Ranitidine (p. 1882·1).
Peptic ulcer; pathological hypersecretory disorders.

Xeragel *Dispolab, Arg.*
Silicones (p. 2209·2).
Scars.
Dispolab, Chile.
Silica (p. 2208·3); dimeticone (p. 2209·3).
Barrier ointment; wounds.

Xeramel *Pharma-Q, S.Afr.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Xérand *Roche-Posay, Fr.*
Emollient.
Dry skin; skin irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Xerand *Roche-Posay, Irl.†*
Emollient.
Dry skin; skin irritation.

Xeraspor *Qestmed, S.Afr.†*
Clotrimazole (p. 576·2).
Fungal skin infections; vulvovaginal candidiasis.

Xerazole *Q-Med, S.Afr.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Xerclear *Medivir, Cz.; Medivir, Denm.; Medivir, Swed.*
⊗Aciclovir (p. 964·1); hydrocortisone (p. 1640·1).
Herpes labialis.

Xeredien *Valeas, Ital.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia nervosa.

Xerendip *Pisa, Mex.*
⊗Somatropin (p. 1919·3).
Growth hormone deficiency.

Xerese *Valeant, USA.*
⊗Aciclovir (p. 964·1); hydrocortisone (p. 1640·1).
Herpes labialis.

Xerfelan *Landsteiner, Mex.*
Interferon beta-1a (p. 996·1).
Multiple sclerosis.

Xergic *Alphapharm, Austral.; Mylan, NZ.*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Xérial *SVR, Fr.*
A range of emollients.
Dry skin and scalp disorders; hyperkeratotic skin disorders.

Xerial *SVR, Ital.*
⊗Urea (p. 1727·3); allantoin (p. 1693·1); emollients.
Dry skin.

Xerid *Plurisystem, Ital.*
Emollient.
Dry skin; skin irritation.

Xeristar *Lilly, Cz.; Lilly, Denm.; Lilly, Gr.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Lilly, Neth.; Boehringer Ingelheim, Pol.; Lilly, Port.; Lilly, Spain.*
Duloxetine hydrochloride (p. 415·1).
Depression; anxiety; diabetic peripheral neuropathic pain.

Xerobase *Cassara, Arg.*
⊗Urea (p. 1727·3).
Dry skin disorders.

Xerocarp *Vianex (Βιανεξ), Gr.*
Pilocarpine hydrochloride (p. 2010·3).
Xerostomia.

Xerodent *Actavis, Fin.; Actavis, Norw.; Actavis, Swed.*
Sodium fluoride (p. 2089·2); malic acid (p. 2549·2).
Dental caries prophylaxis; dry mouth.

Xeroderm *Roche-Posay, Arg.*
Emollient.
Dry skin disorders.

Xeroform *Tyco, Canad.*
Bismuth tribromphenate (p. 1821·3).

Xerolube *Colgate-Palmolive, Canad.†*
Sodium fluoride (p. 2089·2).

Xeroquel *AstraZeneca, Fr.*
Quetiapine fumarate (p. 1101·1).
Schizophrenia; bipolar disorder; depression.

Xerotic *Neo Dermos, Arg.*
Moisturiser.

Xerotil *Boniscontro & Gazzone, Ital.*
⊗Midodrine hydrochloride (p. 1437·3).
Hypotension.

Xerotin *Speciality European Pharma, Ger.; SpePharm, UK.*
Sorbitol (p. 2092·1); carmellose (p. 2175·1); electrolytes (p. 1775·1).
Dry mouth.

Xerumenex *Meda, Belg.*
Trolamine polypeptide oleate-condensate (p. 2634·3).
Removal of impacted ear wax; cleansing of external ear before otoscopy.

Xet *Zydus, India.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; anxiety disorders; post-traumatic stress disorder; social phobia; mixed anxiety depressive states.

Zydus, S.Afr.
Paroxetine (p. 440·3).
Depression; obsessive-compulsive disorder; social phobia; panic disorder.

Xetam-Opta *Pascual, Philipp.*
⊗Gentamicin sulfate (p. 304·2); dexamethasone sodium phosphate (p. 1631·2).
Bacterial eye infections with inflammation.

Xetanor *Plus Pharma, Hung.; Glenmark, Pol.; Fako, Turk.*
Paroxetine hydrochloride (p. 440·3).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder; anxiety.

Xeter *Gedeon Richter, Hung.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias; cardiovascular risk reduction.

Xetin
Note: this name may be used for preparations of different composition.
T Man, Thai.
Fluoxetine (p. 417·1).
Depression; mixed anxiety-depressive states; obsessive-compulsive disorder.

Teva, Spain.
Paroxetine hydrochloride (p. 440·3).
Anxiety; depression; obsessive-compulsive disorder; social phobia; panic disorder.

Xetiran *Biovena, Pol.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; bulimia.

Xetroran *Ranbaxy, Mex.*
Paroxetine hydrochloride (p. 440·3).
Depression; anxiety; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Xeviram *KSK, Denm.†*
⊗Ramipril (p. 1483·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Xevolac *Novell, Indon.*
Ketorolac trometamol (p. 80·2).
Postoperative pain.

Xeztron *Talmann, Philipp.†*
Cefaclor (p. 232·3).
Bacterial infections.

X-Flam *Combiphar, Indon.*
Diclofenac potassium (p. 48·3).
Inflammation; pain.

Xgeva *Amgen, Austral.; Amgen, Belg.; Amgen, Canad.; Amgen, Denm.; Amgen, Fr.; Amgen, Ger.; Amgen, Irl.; GSK, Israel; Amgen, Neth.; Amgen, Norw.; Amgen, Spain; Amgen, Swed.; Amgen, UK; Amgen, USA.*
Denosumab (p. 1182·1).
Prevention of skeletal events associated with bone metastases from solid tumours; osteoporosis; giant cell tumour of bone.

XGLY Analog *Nutricia, Ital.*
Food for special diets.
Hyperglycinaemia.

SHS, Irl.
Infant feed.
Nonketotic hyperglycinaemia.

X-Graf *Lafedar, Arg.*
Meglumine amidotrizoate (p. 1581·3).
Radiographic contrast medium.

X-Graf C *Lafedar, Arg.*
Meglumine amidotrizoate (p. 1581·3); sodium amidotrizoate (p. 1581·3).
Radiographic contrast medium.

Xi Le *Tai Sheng, China.*
Cilnidipine (p. 1337·1).
Hypertension.

Xi Ai Ke *Minsheng, China.*
Vindesine sulfate (p. 884·2).
Malignant neoplasms.

Xi An Lin *Changzhou, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Xi Bei Ta *Di Ao Jiu Hong, China.*
⊗Salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Xi Bi Kang *Bosen, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Xi Bo Fen *Huading Xiandai, China.*
Hematoporphyrin.

Xi Bo Te Xin *Shenwei, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Xi Chang *Hexin, China.*
Cefmetazole sodium (p. 241·3).
Bacterial infections.

Xi Cun *Wanle, China.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Xi Dian Ning *Xidian, China.*
Matrine.

Xi Er Da *Huanghai, China.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Xi Er Ke *Zhonglian, China.*
⊗Guaifenesin (p. 1666·2); methylephedrine hydrochloride (p. 1669·2); chlorphenamine maleate (p. 620·3).

Xi Er Sheng *New Asiatic, China.*
Selenium sulfide (p. 1719·3).
Acne.

Xi Fu Lin *Jinhui, China.*
Theophylline (p. 1229·3).
Bronchospasm.

Xi Fu Ni *Central, China.*
Cefdinir (p. 238·3).
Bacterial infections.

Xi Gai Ke *Qinghai, China.*
Dihydrocodeine tartrate (p. 52·3).
Pain.

Xi Jie *Sanye, China.*
Rifaximin (p. 355·2).

Xi Jing *Jimin Kexin Shanhe, China.*
Aldioxa (p. 1692·2).

Xi Jun Ning *Baiyunshan, China.*
Candesartan cilexetil (p. 1330·2).
Hypertension; heart failure.

Xi Di Ke *Everlife, China.*
Uroacitides (hippuric acid; phenylacetylglutamine; hydroxyphenylacetic acid; hydroxy indole acetic acid; polypeptide).

Xi Ke Qi *Qinghai, China.*
Platycodon grandiflorus; codeine phosphate (p. 40·2).

Xi Lai Mei *Jinghua, China.*
Carbidopa (p. 900·3); levodopa (p. 902·2).
Parkinsonism.

Xi Li *Yangtze River, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Xi Li Shu *Xili, China.*
Phenobarbital (p. 535·2); nitrazepam (p. 1089·1); chlorphenamine (p. 620·3).

Xi Li Te *Yunmen, China.*
Aceclofenac (p. 16·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Xi Li Xi Meng *Huaren, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Xi Lin *Yafeng, China.*
Amoxicillin (p. 216·2); pivsulbactam (p. 360·1).
Bacterial infections.

Xi Lu Xin *Jinshi, China.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Xi Luo *Huasen, China.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Xi Luo An *Lai Mei, China.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Xi Luo Ning *Jindian, China.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Xi Mai Shu *Jiang Shi, China.*
Meglumine adenosine cyclophosphate.

Xi Mei *C & O, China.*
Azithromycin hydrochloride (p. 221·2).
Community-acquired pneumonia; pelvic inflammatory disease.

Xi Mei Na *Luye, China.*
Sodium glycididazole.
Radiosensitisation in radiotherapy for malignant neoplasms.

Xi Mei Xin *Jiu Tai, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Xi Meng *Meiyou, China.*
Cefaclor (p. 232·3); bromhexine (p. 1656·3).

Xi Mo Bi *Hiteck Bio, China.*
Enoxacin gluconate.
Bacterial infections.

Xi Mu Sheng *Bei Da Gao Ke Hua Tai, China.*
Alginic sodium diester.

Xi Neng *Yi Hua, China.*
Cefprozil (p. 248·2).
Bacterial infections.

Xi Ni Di *Haixia, China.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

Xi Ning *Changjiang, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Xi Nuo *Hui Pu Sen, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Xi Pu Ke Ding *Baite Qiaoguang, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Xi Pu Ning *Baite Qiaoguang, China.*
Tinidazole (p. 949·2).
Protozoal infections; anaerobic bacterial infections.

Xi Qi Ting *Zhonggui, China.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Xi Qing *Pacific, China.*
Coated aldehyde oxystarch.

Xi Rui *Rui Nian Qian Jin, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Xi Rui Li *Rotam Reddy, China.*
Lomerizine hydrochloride (p. 676·3).
Migraine.

Xi Ruo Fei *Jiang Shi, China.*
Ossotide.

Xi Sai *Qilu, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Xi Shi Ning *Sunstone, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Xi Shu *Southwest, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Xi Shu Tong *Huanqiu, China.*
Pentoxifylline (p. 1465·3).

Xi Si Ning *Rui Feng, China.*
⊗Procaterol hydrochloride (p. 1219·1).

Xi Si Nuo *An Shi, China.*
Doxofylline (p. 1208·1).

Xi Si Qi *Qinghai, China.*
Aspirin (p. 22·2); codeine phosphate (p. 40·2).

Xi Song *Jin Lan, China.*
Lappaconitine hydrobromide (p. 1418·1).

Xi Suo *Lishizhen, China.*
Hydroxycamptothecin.

Xi Tai Meng *Banzhou, China.*
Naproxen (p. 98·2); codeine phosphate (p. 40·2).

Xi Te Rui *Kangli, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Xi Tong Jing *Huajin, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual syndrome.

Xi Wa Ding *Chung-Hwa, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Xi Wei *Yibin, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Xi Wei Er *Ling Tai, China.*
Selenium yeast (p. 2125·2).

Xi Le Xin *Lukang Chenxin, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Xi Xin *Suzhong, China.*
Bismuth subsalicylate (p. 1821·3).

Xi Xin Sheng *Lifeshine, China.*
Diammonium glycyrrhizate (p. 2520·3).

Xi You Luo *Central, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Xi Zhi Da *Ruibang, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Xiaflex *Auxilium, USA.*
⊗Collagenase (p. 2484·1).
Dupuytren's contracture.

Xialine *Olea, Turk.*
Xanthan gum (p. 2220·1); sodium fluoride (p. 2089·2).
Dry mouth; radiation-induced xerostomia.

Xian Bi Ta *ZhongNuo, China.*
Cefoperazone sodium (p. 243·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Xian Chen *Lukang Chenxin, China.*
Potassium sodium dehydroandrographolide succinate.

Xian Da An *Hanmi, China.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Xian Ding *Guang Da, China.*
Arginine hydrochloride (p. 2049·1).

Xian Feng Mei Nuo *Asia Pioneer, China; Shanghai Pharma, China.*
Cefminox sodium (p. 242·1).
Bacterial infections.

Xian Jia *Beiqi, China.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Xian Jing *Beiqi, China.*
Arginine hydrochloride (p. 2049·1).

Xian Ke Nuo *Dawnrays, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Xian Ke Xin *Bao Long, China.*
⊗Ketoconazole (p. 585·3); clobetasol propionate (p. 1627·1); neomycin sulfate (p. 330·1).
Fungal skin infections.

Xian Kui Sha *Bai Li, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Xian Li *Xianju, China.*
Nicardipine (p. 1445·2).
Hypertension.

Xian Li Kang *FuXing, China.*
Potassium sodium dehydroandrographolide succinate.
Viral infections of the upper-respiratory-tract.

Xian Li Ke *Lai Mei, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Xian Li Xiao *Xianju, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Xian Lin *Xianju, China.*
Vecuronium bromide (p. 2040·2).
Competitive neuromuscular blocker.

Xian Lin Na *Mei Luo, China.*
Famciclovir (p. 979·1).
Herpesvirus infections.

Xian Luo Ke *Kaiyuan, China.*
Dextromethorphan hydrobromide (p. 1660·1).
Cough.

Xian Ning *Hui Ren, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Xian Qiang *Welman, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Xianbi *Hailing, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Xianbixian *Dawnrays, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Xianding *Dawnrays, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Xianfengjiu *Xincat, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Xiang Di *Lunan, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Xiang Yang *Jintaiyang, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Xianjie *Dawnrays, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Xiankai *Dawnrays, China.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Xiankang *Dawnrays, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Xianleke *Dawnrays, China.*
Nimesulide (p. 101·3).
Pain; fever; inflammation.

Xianlisu *Baiyunshan, China.*
Cefathiamidine.
Bacterial infections.

Xianpu *Dawnrays, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Xianqin *Dawnrays, China.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Xianqing *Lukang Chenxin, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Xianshu *Dawnrays, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Xianyi *Dawnrays, China.*
Cefradine (p. 249·1).
Bacterial infections.

Xiao Bai *Bayer, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).
Cough; cold and influenza symptoms.

Xiao Le Dun *Man Xiu Lei Dun, China.*
Taurine (p. 2626·2).

Xiao Ran *Bohua, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; protozoal infections.

Xiao Shan Ping *Bosen, China.*
Cyclic adenosine phosphate (p. 2430·2).

Xiao Tong Da *San Lian, China.*
Potassium sodium dehydroandrographolide succinate.

XiaoDing *Lianhuan, China.*
Felodipine (p. 1380·3).
Angina pectoris; hypertension.

Xiaojun *Daxin, China.*
Kitasamycin acetate (p. 315·2).
Gram-positive bacterial infections.

Xiaoke *Shenyang First, China.*
Co-trimoxazole (p. 277·3); pentoxyverine citrate (p. 1672·1); bromhexine hydrochloride (p. 1656·3).
Respiratory-tract infections.

Xiaoli *Yangtian, China.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections; trichomoniasis.

Xiaomei *Shyndec, China.*
Dextromethorphan (p. 1660·1).
Cough; sore throat.

Xiapex *Auxilium, Austria; Auxilium, Belg.; Auxilium, Cz.; Auxilium, Denm.; Auxilium, Fin.; Auxilium, Fr.; Auxilium, Ger.; Auxilium, Gr.; Auxilium, Hung.; Auxilium, Irl.; Auxilium, Ital.; Auxilium, Neth.; Auxilium, Norw.; Auxilium, Pol.; Auxilium, Port.; Auxilium, Spain; Auxilium, Swed.; Pfizer, Switz.; Auxilium, UK.*
⊗Collagenase (p. 2484·1).
Dupuytren's contracture.

Xibac *Sandoz, Turk.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Xiboge *Xincat, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Xibol *Reig Jofre, Spain.*
Diclofenac sodium (p. 48·3).
Peri-articular and soft-tissue disorders.

Xibradex *Vannier, Arg.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Xibrax *Vannier, Arg.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Xibrom *Ista, USA.†*
Bromfenac sodium (p. 30·1).
Postoperative eye pain and inflammation.

Xicalom *Solas, Indon.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Xicam *Pharmasant, Thai.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Xicanil *Gramon, Arg.*
Benzoyl peroxide (p. 1696·1).
Acne.

Xicanil Control *Gramon, Arg.†*
Irgasan (p. 1773·2); sulfur (p. 1721·1); resorcinol (p. 1718·3).
Acne.

Xicanil Control Dermo *Gramon, Arg.*
Triclosan (p. 1773·2).
Acne.

Xicanil Control NF *Gramon, Arg.*
Triclosan (p. 1773·2); sodium laurilsulfate (p. 2210·3).
Acne.

Xicanil Control NF Crema *Gramon, Arg.*
Triclosan (p. 1773·2); salicylic acid (p. 1719·1).
Acne.

Xicanil Control NF Locion *Gramon, Arg.*
Triclosan (p. 1773·2); aloe vera (p. 1693·2).
Acne.

Xicard *Getz, Philipp.*
⊗Carvedilol (p. 1333·1).
Hypertension; angina pectoris; heart failure.

Xicil *BB, Ital.*
Glucosamine sulfate (p. 2515·3).

Rottapharm, Spain.
Glucosamine sulfate sodium chloride (p. 2515·3).
Osteoarthritis of the knee.

Xiclav *GL Pharma, Austria.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Xiclovir *Lazar, Arg.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Xidan EDO *Mann, Ger.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Xiderm *Plurisystem, Ital.*
Emollient.

Xidilin *Shenyang First, China.*
Amoxicillin sodium (p. 216·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Xie Da Li *Wantang, China.*
Calcium carbonate (p. 1824·3).

Xie Ke *Changzhou Siyao, China.*
Valsartan (p. 1521·2).
Hypertension.

Xie Kun *Beijing Union, China.*
Estradiol valerate (p. 2271·2).

Xie Mei Da *Beijing Union, China.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Xie Yi Li *Lunan, China.*
Riluzole (p. 2605·1).
Amyotrophic lateral sclerosis.

Xiemed *Medifive, Thai.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Xiety *Lapi, Indon.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Xifaxan *Norgine, Denm.; Norgine, Ger.; Norgine, Neth.; Alfa Wassermann, Pol.; BioSaude, Port.; Salix, USA.*
Rifaximin (p. 355·2).
Gastrointestinal infections; hepatic encephalopathy.

Xifaxanta *Norgine, UK.*
Rifaximin (p. 355·2).
Travellers' diarrhoea.

Xifen *New Hualian, China; Naprod, Philipp.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Xifulai *Guanghua, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Xifushen *Alfa Wassermann, China.*
Rifaximin (p. 355·2).
Gastrointestinal infections; hyperammonaemia.

Xigenast *Valeas, Ital.*
Montelukast sodium (p. 1214·3).
Asthma.

Xigris *Lilly, Arg.†; Lilly, Austral.†; Lilly, Austria†; Lilly, Belg.†; Lilly, Braz.†; Lilly, Canad.†; Lilly, Chile†; Lilly, Cz.†; Lilly, Denm.†; Lilly, Fin.†; Lilly, Fr.†; Lilly, Ger.†; Lilly, Gr.; Lilly, Hong Kong†; Lilly, Hung.†; Lilly, India†; Lilly, Irl.†; Lilly, Israel†; Lilly, Ital.†; Lilly, Malaysia†; Lilly, Mex.†; Lilly, Neth.†; Lilly, Norw.†; Lilly, NZ†; Lilly, Pol.†; Lilly, Port.†; Lilly, Rus.†; Lilly, S.Afr.†; Lilly, Singapore†; Lilly, Spain†; Lilly, Swed.†; Lilly, Switz.†; Lilly, Turk.†; Lilly, UK†; Lilly, USA†; Lilly, Venez.†*
Drotrecogin alfa (activated) (p. 1161·1).
Sepsis.

XiJing *C & O, China.*
Lomerizine hydrochloride (p. 676·3).
Migraine.

Xikewei *Dawnrays, China.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; pruritus.

Xikexin *Dawnrays, China.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Xilanic
Note: this name may be used for preparations of different composition.
Bosch, Philipp.
Amoxicillin sodium (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Investi, Arg.†
Paroxetine hydrochloride (p. 440·3).
Depression; panic disorder; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; anxiety.

Xilatril *Darier, Mex.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Xilen *Lens, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; otitis media.

Xiliarx *Novartis, Cz.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Port.; Novartis, Spain.*
Vildagliptin (p. 504·3).
Diabetes mellitus.

Xilide *Gramon, Arg.*
Denture fixative.

Xilocler *Monserrat, Arg.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Xilodase *Apsen, Braz.*
Neomycin sulfate (p. 330·1); lidocaine (p. 1988·1); hyaluronidase (p. 2527·2).
Infected skin disorders; anorectal disorders.

Xilo-Mynol *Curaden, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xilon *Mahakam Beta, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Xilonibsa *Inibsa, Port.*
Injection; topical spray: Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) or noradrenaline (p. 1458·2) is included in the injection as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Inibsa, Spain.
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in the injection as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xilopar
Note: this name may be used for preparations of different composition.
Cephalon, Austria; Cephalon, Ger.; Cephalon, Ital.; Cephalon, Port.
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Filaxis, Arg.
Ribavirin (p. 1010·2).
Hepatitis C.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Xilox *Guidotti, Hung.*
Nimesulide (p. 101·3).
Pain.

Xiltrop *Tropica Mas, Indon.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Xim *Ipca, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ximaken *Kendrick, Mex.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Ximede *Combiphar, Indon.*
Nimesulide (p. 101·3).
Pain; inflammation.

Ximeprim *PP Lab, Thai.*
Sulfadimethoxine (p. 363·2); trimethoprim (p. 381·2).
Bacterial infections.

Ximex Cylowam *Konimex, Indon.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Ximex Konigen *Konimex, Indon.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Ximex Opticom *Konimex, Indon.*
⊗Timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Ximex Optixitrol *Konimex, Indon.*
⊗Dexamethasone sodium phosphate (p. 1631·2); neomycin sulfate (p. 330·1); polymyxin B sulfate (p. 342·3).
Infected eye disorders.

Ximin *Watson, China.*
Olanzapine (p. 1089·3).
Schizophrenia.

Ximino *Ranbaxy, USA.*
Minocycline hydrochloride (p. 325·1).
Acne.

Ximovan *Sanofi-Aventis, Ger.*
Zopiclone (p. 1118·1).
Insomnia.

Ximun *Transfarma, Indon.*
Echinacea (p. 2498·1); zinc picolinate (p. 2126·1); curcuminoid (p. 2489·3).
Immunostimulant.

Ximvast *Xeno, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; ischaemic heart disease.

Ximve *Farma-Projekt, Pol.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Xin Di *Jishi, China.*
⊗Bumetanide (p. 1329·1).
Oedema.

Xin Ai De *Luan, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Xin An Lin *CSPC, China.*
Ampicillin sodium (p. 218·2); sulbactam sodium (p. 360·1).
Bacterial infections.

Xin Ao Le *Tongyong, China; Xinzhongzheng, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Xin Ao Xin *Yi Ao, China.*
Piracetam (p. 393·3).
Mental function impairment.

Xin Bai Chang *Xinzhongzheng, China.*
Sodium alginate (p. 2167·3).

Xin Bai Ke *Mei Luo, China.*
Azelastine hydrochloride (p. 617·1).

Xin Bei *Qilu, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Xin Chang Fu *Xinzhongzheng, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Xin Da Kang *Salubris, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Xin Da Su *Yangtze River, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Xin Da Yue *Salubris, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Xin Dong *Meng Xin, China.*
Aspirin (p. 22·2).
Fever; pain; inflammation; thromboembolism prophylaxis.

Xin Le Dun *Man Xiu Lei Dun, China.*
⊗Panthenol (p. 2582·2); potassium aspartate (p. 1793·1); vitamin B_6 (p. 2105·3); dipotassium glycyrrhizate (p. 2520·3); naphazoline hydrochloride (p. 1669·3); chlorphenamine maleate (p. 620·3); neostigmine metilsulfate (p. 687·2).

Xin Er Luo *Bosen, China.*
Diammonium glycyrrhizate (p. 2520·3).

Xin Fei *Dongfeng, China.*
⊗Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); diphenhydramine hydrochloride (p. 626·2); pseudoephedrine hydrochloride (p. 1676·1).

Xin Di Fen *Xinan, China.*
Ibuprofen (p. 68·2).
Pain; inflammation; fever.

Xin Feng *Lukang Chenxin, China.*
Inosine (p. 2533·1).

Xin Fu Da *SL Pharm, China.*
Stavudine (p. 1015·3).
HIV infection.

Xin Fu Neng *Yige, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Xin Fu Ning *Huaxin, China.*
Interferon alfa-2b (human recombinant) (p. 989·2).

Xin Fu Su *Baiyunshan, China.*
Cefixime (p. 240·3).
Bacterial infections.

Xin Fu Tai *Tiancheng, China.*
Thymalfasin (p. 2630·1).
Chronic hepatitis B; chronic hepatitis C.

Xin Gan Ning *Sine, China.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Xin Ge *Xinjiang, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Xin Ge Er Tai *Duoburuifei, China.*
Polypeptides; hypoxanthine.

Xin Gui Shu *Zhonggui, China.*
Sodium ferulate.

Xin Hai Neng *Zhengda Fenghai, China.*
Carbohydrate; electrolytes (p. 1775·1).

Xin He Ping *Yao Wang, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Xin Hong Kang *Wanhe, China.*
Erythromycin (p. 291·2).
Bacterial infections.

Xin Hua Nuo *Huaxin, China.*
Interferon alfa-2b (human recombinant) (p. 989·2).

Xin Huo Su *Rhodiola, China.*
Brain natriuretic peptide (human recombinant).
Heart failure.

Xin Ji Er *SL Pharm, China.*
Interleukin-2 (human recombinant) (p. 810·1).

Xin Jia Ji *Shi Xin, China.*
Ethylenediamine diaceturate.

Xin Jian Ju *Lingkang, China.*
Potassium chloride (p. 1793·2).
Hypokalaemia.

Xin Jie *Zhongsheng Haitian, China.*
Sodium ferulate.

Xin Jie Ming *Lunan, China.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial eye infections.

Xin Junbizhi *Welman, China.*
Ceftriaxone sodium (p. 253·3); sulbactam sodium (p. 360·1).
Bacterial infections.

Xin Kang *Lunan, China; XinShiDai, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Xin Kang Si Da *Huanqiu, China.*
Aspirin (p. 22·2); paracetamol (p. 115·1); caffeine (p. 1203·3).

Xin Ke Duo Na *Baiqiuen, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Xin Ke Fei *Yangtze River, China.*
Nadifloxacin (p. 328·1).
Follicultitis; impetigo.

Xin Ke Lai *Zitonggong, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Xin Ke Nuo *Sanye, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Xin Kun Chang *Lingkang, China.*
Glutamine (p. 2070·3).

Xin Lai *Double-Crane, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Xin Li De *ZhenYuan, China.*
Metadoxine (p. 2105·3).
Alcoholic liver disorders.

Xin Li Ke *Tianlong, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Xin Li Sheng *Si Huan, China.*
Granulocyte colony-stimulating factor (human recombinant).

Xin Li Tai *San Lian, China.*
Sodium new houttuyfonate.

Xin Li Wei *Aibujia, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Xin Li Xin *Salubris, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Xin Long
Note: this name may be used for preparations of different composition.
Winguide Huangpu, China.
⊗Glycerol (p. 2517·2).
Constipation.
Winguide Huangpu, China.
Ofloxacin (p. 334·3).
Bacterial eye infections.

Xin Long Ning *Ke Lun, China.*
Adenosine triphosphate disodium (p. 2430·3).

Xin Lu *Lukang Chenxin, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias; ischaemic heart disease.

Xin De Lu Sheng *Si Huan, China.*
Interleukin-2 (human, recombinant) (p. 810·1).

Xin Lu Xin *Jinshi, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Xin Luo *Kang Ji Er, China.*
Matrine.

Xin Luo Er *Huaxin, China.*
Interleukin-2 (human recombinant) (p. 810·1).

Xin Luo Ping *Linuo Kefeng, China.*
⊗Esmolol hydrochloride (p. 1377·3).
Arrhythmias; hypertension in anaesthesia.

Xin Luo Shu *Bai Li, China.*
Emtricitabine (p. 976·3).
HIV infection.

Xin Luo Wei *Xiuzheng, China.*
Thymus protein (p. 2631·1).

Xin Mai Lin *Lisite, China.*
Glutamine (p. 2070·3).

Xin Mei Ge *CP Guojian, China.*
Interleukin-11 (human recombinant).
Malignant neoplasms.

Xin Mei Jia *Pude, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Xin Mei Luo *Mei Luo, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Xin Ming Ting *Salubris, China.*
Desloratadine (p. 625·1).
Hypersensitivity reactions.

Xin Na Xing *Lijian, China.*
Silver nitrate (p. 2615·3).

Xin Naolilong *Livzon, China.*
Cinnarizine (p. 622·1); vitamin E (p. 2119·1); vitamin B_6 (p. 2105·3).
Cerebrovascular disorders.

Xin Neng *Fuchun, China.*
Levocarnitine (p. 2053·2).

Xin Di Ning *Wushi, China.*
Matrine.

Xin Nuo Jin *Suzhong Haixin, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Xin Nuo Kang *Yi Kang, China.*
Ligustrazine hydrochloride.

Xin Nuo Shu *Kangnuo, China.*
Gamma-aminobutyric acid (p. 2509·2).

Xin Ou Rui *Jiang Shi, China.*
Deproteinised calf blood extract (p. 2444·1).

Xin Pa Er Ke *Sine, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1); chlorphenamine maleate (p. 620·3).

Xin Ping *Kang Ji Er, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Xin Pu Ao *Si Huan, China.*
Naloxone hydrochloride (p. 1562·3).
Opioid dependence; reversal of opioid-induced sedation; opioid overdose.

Xin Pu Fen *Tianlong, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Xin Pu Feng *Duoburuifei, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Xin Pu Lu Tong *Tianlong, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Xin Pu Rui *Tianlong, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Xin Qi *Longgui, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Xin Qi Bang *Lingkang, China.*
Arginine hydrochloride (p. 2049·1).

Xin Qi Si *Wu Zhou Tong, China.*
Chondroitin sulfate (p. 2476·1).

Xin Qian Ping *Shangwei, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Xin Qing Yu *Lianshui, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Xin Qu *Zitonggong, China.*
Rizatriptan benzoate (p. 678·3).
Migraine.

Xin Ran *Shyndec, China.*
Nifedipine (p. 1447·2).
Angina pectoris; hypertension.

Xin Rui *Yuanqu, China.*
Telmisartan (p. 1509·3).
Hypertension.

Xin Run *LuoXin, China.*
Asarone.

Xin Run Luo *Lingkang, China.*
⊗Dextran 40 (p. 1138·1).
Plasma volume expansion; thromboembolic disorders.

Xin Sai Si Ping *Huadong, China.*
Ciclosporin (p. 1945·2).
Transplant rejection; graft-versus-host disease; lupus; nephrotic syndrome.

Xin De Sheng *Double-Crane, China.*
Ambroxol hydrochloride (p. 1654·3).

Xin Shu
Note: this name may be used for preparations of different composition.
Linuo Kefeng, China.
Isosorbide dinitrate (p. 1412·2).
Angina pectoris.
Yangtze River, China.
Puerarin.

Xin Shu Li Da *Hua Lu, China.*
Nicardipine hydrochloride (p. 1445·2).
Hypertension.

Xin Shu Shi Ning *Wushi, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Xin Shuang *Kang Yuan, China.*
Secnidazole (p. 947·3).
Protozoal infections.

Xin Shun Er *SL Pharm, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Xin Si Da *Sanjing Qianhe Wangkui, China.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Xin Tai *Linuo Kefeng, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Xin Tai Luo Qi *United Lab, China.*
⊗Codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1); triprolidine hydrochloride (p. 642·3); sulfogaiacol (p. 1678·1).
Cold symptoms; cough.

Xin Tang Ping *Yuanqu, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Xin Te *Kangliyuan, China.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment.

Xin Tong *Guoda, China.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

HaiWang Fuyao, China.
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Xin Wei *Simcere, China.*
Ibuprofen (p. 68·2).
Pain; fever.

Xin Wei An *Sine, China.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; pathological gastric hypersecretory disorders; peptic ulcer.

Xin Wei Ning *Grand, China.*
Tirofiban hydrochloride (p. 1515·1).

Xin Wei Xi *Shengbaotang, China.*
Sodium ascorbate (p. 2111·1).
Vitamin C supplement.

Xin Wei Zhi *Kangnaier, China.*
Deproteinised calf blood extract (p. 2444·1).

Xin Xi Ping *Chaoyang Lingqiao, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Xin Xin *Jinshan, China.*
Naftifine hydrochloride (p. 590·1).
Fungal skin infections.

Xin Xue Ping *Wan Lian, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Xin Yi *Tian Fu, China.*
Adenosine (p. 1291·1).

Xin Yi Er *SL Pharm, China.*
Telmisartan (p. 1509·3).
Hypertension.

Xin Yi Gan *Xing Qun, China.*
Malotilate (p. 2549·3).

Xin Yi Kang *Guo Jing, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Xin Yi Sheng *Sine, China.*
Ipriflavone (p. 1185·3).
Osteoporosis.

Xin You Zhi *Shyndec, China.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease.

Xin Yu Sen *Lingkang, China.*
⊗Labetalol hydrochloride (p. 1416·2).
Hypertension.

Xin Yuan Da *Lingkang, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Xin Yue *Jin Lan, China.*
Sodium ferulate.

Xin Zhi Ming *White Swan, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Xinamin *Mavi, Mex.*
Vitamin B substances (p. 2102·3).

Xinamod *Proge, Ital.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

XinBei *Bohua, China.*
Indobufen (p. 1410·1).
Thromboembolic disorders.

Xincatlor *Xincat, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Xindabao *Xincat, China.*
Cefalexin (p. 234·1); trimethoprim (p. 381·2).
Bacterial infections.

Xindabeining *Xincat, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Xindadelei *Xincat, China.*
Cefradine (p. 249·1).
Bacterial infections.

Xindaxin *Xincat, China.*
Cefixime (p. 240·3).
Bacterial infections.

Xinder *D & M, Chile.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Xindite *Huajin, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Xinebrom *Virgo, Philipp.*
Bromhexine hydrochloride (p. 1656·3).
Respiratory-tract congestion.

XiNeng *Jimin Kexin Shanhe, China.*
Etimicin sulfate (p. 298·2).

Xinfading *Sine, China.*
Famotidine (p. 1842·1).
Gastro-oesophageal reflux; peptic ulcer.

Xinflex *Terramedic, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Xinfu *Qi Li, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

Xinfunuo *SL Pharm, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Xinfuxin *Tianxin, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Xing An Yi *Sunho, China.*
Octreotide acetate (p. 1924·1).
Variceal bleeding; acromegaly; endocrine tumours; prevention of complications following pancreatic surgery; HIV-associated diarrhoea.

Xing Bao *Hairong, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Xing Bi De *Fengan, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Xing Lu *Lukang Medicine, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Xing Le Ning *Xing'an, China.*
Paracetamol (p. 115·1).
Fever; pain.

Xing Rui Ke *XingYin, China.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Xing Rui Ling *XingYin, China.*
Zinc gluconate (p. 2126·2).
Common cold.

Xing Suo Ning *Sunho, China.*
Rifamycin sodium (p. 354·3).

Xing Te *Xincat, China.*
Sparfloxacin lactate.
Bronchitis; community-acquired pneumonia.

Xing Le Xin *Chang An, China.*
Gastrodin.

Xing Ya *Lingkang, China.*
Fructose (p. 2068·2).

Xing You Da *Chang An, China.*
Sodium demethylcantharidate.

Xing You Fu *Chang An, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid deficit.

Xing You Shan *Chang An, China.*
Aminophylline (p. 1201·2).
Bronchospasm.

Xing Yuan Jia *Sunho, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Xingfuxin *FuXing, China.*
Lomefloxacin (p. 319·2).
Bacterial infections.

Xinhong *Sine, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Xinjielin *Ankexinxing, China.*
Lysine hydrochloride (p. 2079·3).

XinKang *Wushi, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Xinkuaixin *Tianxin, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Xinle *Livzon, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

Xinlituo *Sine, China.*
Ofloxacin (p. 334·3).
Bacterial eye infections.

XinLiWei *Salubris, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Xinlizuo *Sine, China.*
Fluconazole (p. 578·2).
Fungal infections.

Xinluona *Kanghong, China.*
Mosapride citrate (p. 1865·2).
Gastrointestinal disorders.

XinLuoPing *Jinghao, China.*
Amlodipine mesilate (p. 1304·1).
Angina pectoris; hypertension.

Xinplex *Craveri, Arg.*
Orlistat (p. 2577·1).
Obesity.

Xinqing *Nhwa, China.*
Naloxone hydrochloride (p. 1562·3).
Reversal of opioid-induced depression; opioid overdose; alcohol poisoning.

Xinruipuxin *Likang, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

XinShu
Note: this name may be used for preparations of different composition.
Sine, China.
Glyceryl trinitrate (p. 1391·2).
Heart failure; myocardial infarction.

Xinshu
Note: this name may be used for preparations of different composition.
Keyuan, China; Qingan, China.
Amlodipine maleate (p. 1304·1).
Angina pectoris; hypertension.

Xinsol *Solara, Mex.†*
Pentoxifylline (p. 1465·3).
Cerebral and peripheral vascular disorders.

Xinta *Simcere, China.*
Levamlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Xintai *Sine, China.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Xintailin *Gosun, China.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Xintemie *Welman, China.*
Piperacillin sodium (p. 340·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Xintianxin *Tianxin, China.*
Ceftazidime (p. 250·2).
Bacterial infections.

Xintilan *Landsteiner, Mex.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Xinweiling *Sine, China.*
Ribavirin (p. 1010·2).
Viral infections of the respiratory tract.

Xinya Quling *New Asiatic, China; Shanghai Pharma, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder.

Xinze *Ruinian Baisite, China.*
Topotecan hydrochloride (p. 872·3).
Malignant neoplasms.

Xinzhijun *Welman, China.*
Cefotaxime sodium (p. 244·1); sulbactam sodium (p. 360·1).
Bacterial infections.

X-Iop *Verisfield, Gr.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Xipa *TAD, Ger.*
⊗Xipamide (p. 1536·1).
Hypertension; oedema.

Xipagamma *Worwag, Ger.; Worwag, Ukr.*
⊗Xipamide (p. 1536·1).
Hypertension; oedema.

Xipa-Isis *Actavis, Ger.†*
⊗Xipamide (p. 1536·1).
Hypertension; oedema.

Xipamid *Zydus, India.*
⊗Xipamide (p. 1536·1).
Oedema.

Xipen *Best, Mex.*
Pentoxifylline (p. 1465·3).
Cerebral, ocular, and peripheral vascular disorders.

Xipocol *SoSe, Ital.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Xipofuxing *Changzheng-Xinkai, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Xippatin *Tabuk, Cz.†*
Atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Xipral *Silanes, Mex.*
Pravastatin sodium (p. 1473·1).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Xiprine *Maver, Chile.*
Glipizide (p. 474·1).
Diabetes mellitus.

Xipro *Terramedic, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Xipuxing *Baite Qiaoguang, China.*
Ciprofloxacin lactate (p. 261·2).
Bacterial infections.

XiraHist DM *Hawthorn, USA.*
Dextromethorphan hydrobromide (p. 1660·1); carbinoxamine maleate (p. 619·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

XiraTuss *Hawthorn, USA.*
Pentoxyverine tannate (p. 1672·1); chlorphenamine tannate (p. 620·3); phenylephrine tannate (p. 1672·2).
Cough; nasal congestion.

Xirui *Yangtze River, China.*
Cefonicid sodium (p. 242·3).
Bacterial infections.

Xishumai *Antai, China.*
Amlexanox (p. 1202·2).

Xishumin *Zizhu, China.*
Daytime tablets, chlorphenamine maleate (p. 620·3); vitamin B_1 (p. 2102·3); nighttime tablets, chlorphenamine maleate; paracetamol (p. 115·1).
Allergic rhinitis.

Xismox *Genus, UK.*
Isosorbide mononitrate (p. 1413·3).

Xithrom *Aldril, Philipp.*
Roxithromycin (p. 356·2).
Bacterial infections.

xitix *McNeil, Ger.*
Ascorbic acid (p. 2110·3); sodium ascorbate (p. 2111·1).
Vitamin C deficiency.

Xitocin *Cryopharma, Mex.*
Oxytocin (p. 2143·1).
Labour induction; postpartum haemorrhage; uterine atony.

Xitong *Pacific, China.*
Feprazone (p. 64·3).
Pain.

Xitrin *Chemiphar, Thai.*
Potassium citrate (p. 1780·3); sodium citrate (p. 1781·2).
Urinary alkalinisation; metabolic acidosis.

Xitrocin *Polfa Pabianice, Pol.; Pabianice, Ukr.*
Roxithromycin (p. 356·2).
Bacterial infections.

Xiu Fu *Beisheng, China.*
Sodium glucuronate (p. 2517·1).

Xiweining *Huajin, China.*
Cimetidine (p. 1827·1).
Peptic ulcer; gastro-oesophageal reflux; gastrinoma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Xiyin *New Hualian, China.*
Mifepristone (p. 2138·1).
Termination of pregnancy.

XLEU Analog *Nutricia, Fr.; SHS, UK.*
Food for special diets.
Isovaleric acidaemia.
SHS, Irl.
Infant feed.
Isovaleric acidaemia.

XLEU Faladon *SHS, Irl.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Isovaleric acidaemia.

XLEU Maxamaid *SHS, Irl.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Isovaleric acidaemia.

XLEU Maxamum *Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.*
Food for special diets.
Isovaleric acidaemia.

XLS *Cinetic, Arg.*
Poliglusam (p. 2593·2); succinic acid (p. 2214·3); inulin (p. 2534·3); calcium ascorbate (p. 2111·1); zinc citrate (p. 2126·2).
Dietary supplement.

XLS-Medical *Omega, UK.*
Fibre complex derived from prickly pear cactus leaf.
Aid in weight management.

XLYS Analog *Nutricia, Fr.; SHS, UK.*
Food for special diets.
Hyperlysinaemia.
SHS, Irl.
Infant feed.
Hyperlysinaemia.

XLYS Hyperlidon *Nutricia, Ital.*
Food for special diets.
Hyperlysinaemia.

XLYS Low TRY Analog *SHS, Irl.*
Infant feed.
Glutaric aciduria type I.

XLYS Low Try Analog *Nutricia, Fr.*
Food for special diets.
Glutaric aciduria.

XLYS Low TRY Maxamaid *SHS, Irl.; SHS, UK.*
Food for special diets.
Glutaric aciduria.

XLYS, Low Try Maxamaid *Nutricia, Ital.*
Food for special diets.
Glutaric aciduria.

XLYS Low TRY Maxamum *SHS, Irl.*
Food for special diets.
Glutaric aciduria type I.

XLYS, Low Try Maxamum *Nutricia, Ital.*
Food for special diets.
Glutaric aciduria.

XLYS Maxamaid *Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Hyperlysinaemia.

XLYS TRY Glutaridon *SHS, UK.*
Food for special diets.
Glutaric aciduria.

XLYS, TRY Glutaridon *Nutricia, Ital.*
Food for special diets.
Glutaric aciduria.

X-M *Yenisehir, Turk.*
Calcium sennosides (p. 1885·1).
Bowel evacuation; constipation.

Xmet *Glenmark, India; Glenmark, Malaysia; Glenmark, Philipp.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

XMET Analog *Nutricia, Fr.; SHS, Irl.; SHS, UK.*
Food for special diets.
Homocystinuria; hypermethioninaemia.

XMET, Cys Analog *Nutricia, Fr.*
Food for special diets.
Sulfite oxidase deficiency.

XMET Homidon *SHS, Irl.; SHS, UK.*
Food for special diets.
Homocystinuria; hypermethioninaemia.

XMET Maxamaid *Nutricia, Austral.; Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Homocystinuria; hypermethioninaemia.

XMET Maxamum *Nutricia, Austral.; Support, Braz.; Nutricia, Fr.; SHS, Irl.; Nutricia, Ital.; Nutricia, NZ; SHS Nutrition, NZ; SHS, UK.*
Food for special diets.
Homocystinuria; hypermethioninaemia.

XMTVI Analog *Support, Braz.; Nutricia, Fr.; SHS, Israel; SHS, UK.*
Infant feed.
Methylmalonic acidaemia; propionic acidaemia.

XMTVI Asadon *Nutricia, Austral.†; SHS, UK.*
Food for special diets.
Methylmalonic acidaemia; propionic acidaemia.

XMTVI Maxamaid *Nutricia, Austral.; Support, Braz.; Nutricia, Fr.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Methylmalonic acidaemia; propionic acidaemia.

XMTVI Maxamum *Nutricia, Austral.; Nutricia, Fr.; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Methylmalonic acidaemia; propionic acidaemia.

XMTVIL Maxamaid *Nutricia, Fr.*
Food for special diets.
Methylmalonic or propionic acidaemia.

Xodol *Shionogi, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Xofemina *Farmaceutica H, Mex.*
Medroxyprogesterone acetate (p. 2288·1); estradiol cipionate (p. 2271·1).
Injectable contraceptive.

Xofigo *Bayer, UK; Bayer, USA.*
Radium-223 (p. 2227·2) chloride.
Bone metastases in castration-resistant prostatic cancer.

Xogel *Septodont, Fr.*
Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Mouth disorders.

Xolaam *Ranbaxy, Fr.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

Xolair *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Genentech, USA; Novartis, Venez.*
Omalizumab (p. 1216·3).
Asthma.

Xolegel *GSK, USA.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Xolegel CorePak *GSK, USA.*
⊗Xolegel, ketoconazole (p. 585·3); Xebcort, hydrocortisone (p. 1640·1).
Seborrhoeic dermatitis.

Xolegel Duo *GSK, USA.*
Topical gel, ketoconazole (p. 585·3); shampoo, pyrithione zinc (p. 1718·1).
Seborrhoeic dermatitis.

Xolido *Enovachem, USA.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xolin *Ratiopharm, Norw.†*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis.

Xolof *Saval, Chile.*
Tobramycin (p. 380·1).
Bacterial eye infections.

Xolof D *Saval, Chile.*
⊗Tobramycin (p. 380·1); dexamethasone (p. 1630·3).
Infected eye disorders.

Xolox *WraSer, USA.*
⊗Paracetamol (p. 115·1); oxycodone hydrochloride (p. 113·1).
Pain.

Xoltiva *Anabiosis, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Xolvax *Vivax, Venez.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Xomolix *Torrex Chiesi, Austria; Torrex Chiesi, Cz.; ProStrakan, Ger.; ProStrakan, Gr.; Torrex Chiesi, Hung.; ProStrakan, Irl.; ProStrakan, Port.; ProStrakan, Spain; ProStrakan, UK.*
Droperidol (p. 1072·1).
Nausea and vomiting.

Xonatil *Precimex, Mex.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Xon-Ce *Kalbe, Indon.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Xonef *Promed, Rus.*
⊗Betaxolol hydrochloride (p. 1322·3).
Glaucoma; ocular hypertension.

Xopenex *Sepracor, USA.*
⊗Levosalbutamol hydrochloride (p. 1213·3) or levosalbutamol tartrate (p. 1214·1).
Obstructive airways disease.

Xorim *Sandoz, Hung.; Sandoz, Pol.†; Sandoz, Rus.; Sandoz, Venez.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Xorimax *Sandoz, Cz.; Sandoz, Hong Kong; Sandoz, Hung.; Sandoz, Malaysia; Sandoz, Philipp.; Sandoz, Pol.; Sandoz, Singapore.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Xorin *Pyridam, Indon.*
Roxithromycin (p. 356·2).
Bacterial infections.

Xorovir *Kwizda, Pol.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Xorox *Agepha, Austria; Kite (Kite), Gr.; Filiz, Turk.*
Aciclovir (p. 964·1).
Herpes simplex eye infections; herpesvirus infections.

Xorucin *Actavis, Cz.*
Doxorubicin hydrochloride (p. 783·1).
Malignant neoplasms.

Xorufec *Antibioticos, Mex.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Xoten *MedChem, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2).

Xoten-C *MedChem, USA.*
Capsicum (p. 2469·3); menthol (p. 2553·2); methyl salicylate (p. 92·1).

Xotepic *Farmacom, Pol.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Xotilon *Pyridam, Indon.*
Tenoxicam (p. 136·2).
Musculoskeletal, joint, and peri-articular disorders.

Xozal *UCB, Gr.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

XP Analog *Support, Braz.†; Scientific Hospital Supplies, Irl.; SHS, Israel; Nutricia, Ital.; Scientific Hospital Supplies, NZ; SHS Nutrition, NZ; SHS, UK.*
Food for special diets.
Phenylketonuria.

XP Analog LCP *Nutricia, Fr.; SHS, Irl.; SHS, Pol.*
Food for special diets.
Phenylketonuria.

XP Maxamaid *Nutricia, Austral.; Nutricia, Fr.; SHS, Irl.; SHS, Israel; Nutricia, Ital.; SHS, UK.*
Food for special diets.
Phenylketonuria.

XP Maxamum *Nutricia, Austral.; Nutricia, Fr.; SHS, Irl.; SHS, Israel; Nutricia, Ital.; SHS, Pol.; SHS, UK.*
Food for special diets.
Phenylketonuria.

X-Pain *ST, Thai.*
Methyl salicylate (p. 92·1); eugenol (p. 2501·2); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue disorders.

Xpand *Claris, Philipp.*
⊗An etherified starch (p. 1146·1) in sodium chloride.
Shock; haemodilution; plasma volume expansion.

Xpe Expectorante *EMS, Braz.*
⊗Guaifenesin (p. 1666·2); etafedrine hydrochloride (p. 1665·2); bufylline (p. 1203·3); doxylamine succinate (p. 627·3).

Xpect *Hawthorn, USA.*
Guaifenesin (p. 1666·2).
Coughs.

Xpect-AT *Hawthorn, USA.*
Guaifenesin (p. 1666·2); pentoxyverine citrate (p. 1672·1).
Coughs; respiratory-tract congestion.

Xpect-PE *Hawthorn, USA.*
Guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract congestion.

Xphen Tyr Analog *SHS, Israel.*
Food for special diets.
Phenylketonuria; tyrosinaemia.

XPHEN, Tyr Analog *Nutricia, Fr.*
Food for special diets.
Tyrosinaemia.

XPhen, Tyr Analog *SHS, UK.*
Food for special diets.
Tyrosinaemia.

XPHEN Tyr Maxamaid *Nutricia, Fr.*
Food for special diets.
Tyrosinaemia.

XPhen Tyr Maxamaid *SHS, UK.*
Phenylalanine- and tyrosine-free food for special diets.
Tyrosinaemia.

XPhen, Tyr Maxamaid *Nutricia, Austral.*
Food for special diets.
Tyrosinaemia.

XPHEN TYR Maxamum *SHS, UK.*
Food for special diets.
Tyrosinaemia.

XPHEN Tyr, Maxamum *Nutricia, Fr.*
Food for special diets.
Tyrosinaemia.

XPhen, Tyr Maxamum *Nutricia, Austral.*
Food for special diets.
Tyrosinaemia.

XPHEN TYR Tyrosidon *SHS, UK.*
Food for special diets.
Tyrosinaemia.

X-Praep *Meda, Neth.*
Sennosides (p. 1885·2).
Bowel evacuation; constipation.

X-Prep *Meda, Fr.; Lavipharm, Gr.; Extractum, Hung.; Mundipharma, Hung.; Norpharma, Pol.†; Adcock Ingram, S.Afr.; Meda, Spain.*
Sennosides A and B (p. 1885·2).
Bowel evacuation; constipation.
Mundipharma, Austria; Meda, Ital.; Ferring, Mex.; Mundipharma, Norw.†; Meda, Port.; Mundipharma, Switz.; Gray, USA.†
Senna (p. 1885·1).
Bowel evacuation; constipation.

X-Prep Bowel Evacuant Kit-1 *Gray, USA.†*
Combination pack: 2 tablets, standardised senna concentrate (p. 1885·1); docusate sodium (p. 1836·2) (Senokot-S); oral liquid, senna (X-Prep); 1 suppository, bisacodyl (Rectolax) (p. 1821·1).
Bowel evacuation.

Xpri *Zambon, Denm.*
Ibuprofen arginine (p. 68·2).
Pain; fever; musculoskeletal and joint disorders.

XPT Analog *Support, Braz.*
Tyrosine and phenylalanine-free food for special diets.
Tyrosinaemia.

XPT Maxamaid *Support, Braz.*
Tyrosine and phenylalanine-free food for special diets.
Tyrosinaemia.

XPT Tyrosidon *Scientific Hospital Supplies, UK.*
Tyrosine- and phenylalanine-free amino acids.
Tyrosinaemia.

XPTM Analog *SHS, UK.*
Food for special diets.
Tyrosinaemia.

XPTM Tyrosidon *Scientific Hospital Supplies, UK.*
Phenylalanine-, tyrosine-, and methionine-free amino acids.
Tyrosinaemia.
Nutricia, Austral.†; SHS, UK.
Food for special diets.
Tyrosinaemia.

X-Seb *Pharmascience, Canad.; Baker Cummins, USA.*
Salicylic acid (p. 1719·1).
Seborrhoea; scalp disorders.

X-Seb Plus *Pharmascience, Canad.; Baker Cummins, USA.*
Pyrithione zinc (p. 1718·1); salicylic acid (p. 1719·1).
Scalp disorders.

X-Seb T *Pharmascience, Canad.; Baker Cummins, USA.*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Seborrhoea; scalp disorders.

X-Seb T Plus *Ivax, USA.*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2).
Formerly contained salicylic acid, coal tar, and menthol.
Scalp disorders.

Pharmascience, Canad.
Salicylic acid (p. 1719·1); coal tar (p. 1723·2); menthol (p. 2553·2).
Scalp disorders.

Xsert *Cadila, India.*
Sertraline hydrochloride (p. 448·1).
Depression.

Xspas *Elin, Philipp.; Neon, Philipp.*
Hyoscine butylbromide (p. 1845·3).
Peptic ulcer; smooth muscle spasm.

XSP-Bena *Xepa-Soul Pattinson, Singapore.*
Diphenhydramine hydrochloride (p. 626·2); sodium citrate (p. 1781·2); ammonium chloride (p. 1656·1).
Cough; nasal and bronchial congestion.

XT Luis *Novum, Neth.*
Dimeticone (p. 2209·3).
Pediculosis.

X'tac *CCM, Malaysia.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; reduction of gastric acid secretion; Zollinger-Ellison syndrome.

Xtandi *Astellas, UK; Astellas, USA.*
Enzalutamide (p. 786·3).
Prostatic cancer.

X-Tar *Dormer, Canad.†*
Salicylic acid (p. 1719·1); coal tar (p. 1723·2); menthol (p. 2553·2).
Scalp disorders.

X-Tardine *Pharmasant, Thai.*
Povidone-iodine (p. 1767·1).
Skin disinfection.

Xtenda *Orchid, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Xtendrol *Atlantis, Mex.*
⊗Oxandrolone (p. 2298·2).
Anabolic; osteoporosis; Turner' syndrome.

Xtor *Ipca, India.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

Xtrair *Behrens, Venez.*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2).

X-Trant *Natco, India.*
Estramustine phosphate (p. 790·1).
Prostatic cancer.

Xtreme Fuel *Teingro, Arg.*
Amino acids; protein.
Dietary supplement.

Xu Hong *Di Ao, China.*
Theophylline (p. 1229·3); ketotifen fumarate (p. 631·3).

Xu Jian *Star, China.*
Ethylenediamine diaceturate.

Xu Luo *Nanshaolin, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Xu Luo Ling *Hailing, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Xu Yuan *Pingyuan, China.*
Pazufloxacin mesilate (p. 338·1).

Xuan Bo *Jiangxi, China.*
Pazufloxacin mesilate (p. 338·1).

Xuan Ning *O u Yi, China.*
Levamlodipine maleate.
Angina pectoris; hypertension.

999 Xuanling *SanJiu, China.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Xubil *Unison, Thai.*
Monobasic sodium phosphate (p. 1791·1); dibasic sodium phosphate (p. 1791·2).
Constipation; bowel excavation.

Xuclamin *Sons, Mex.*
Clarithromycin (p. 266·2).
Bacterial infections.

Xue An *Changyuan, China.*
⊗Succinylated gelatin (p. 1154·1).

Xue Da Sheng *Haoyao, China.*
⊗Epoetin (p. 1141·1).

Xue Fei *Dongfeng, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Xue Na Rui *Zhiyuan, China.*
Meglumine adenosine cyclophosphate.

Xue Qing *Daxin, China.*
Lovastatin (p. 1425·2).
Hyperlipidaemias.

Xue Rui *Bausch & Lomb, China.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Xue Ting *Open, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Xue Yi Ting *Weifang, China.*
Carbazochrome sodium sulfonate (p. 1137·1).
Haemorrhage.

Xue Ying Ping *Kangrui, China.*
Telmisartan (p. 1509·3).
Hypertension.

Xuezhikang *WPU, China.*
Monascus.
Hyperlipidaemias; atherosclerosis.

Xumadol *ITF, Chile; Italfarmaco, Port.; Italfarmaco, Spain.*
Paracetamol (p. 115·1).
Pain; fever.

Xun Di *Tongyong, China.*
Etamsylate (p. 1145·2).
Haemorrhage.

Xun Ao *Kang Yuan, China.*
Prulifloxacin (p. 345·1).

Xun Bo *Jinhua, China.*
Aceglutamide (p. 2426·2).

Xuric *Craveri, Arg.*
Colchicine (p. 604·1).
Gout.

Xuric-A *Craveri, Arg.*
Colchicine (p. 604·1); allopurinol (p. 600·2).
Gout.

Xusal *UCB, Ger.*
Levocetirizine hydrochloride (p. 632·3).
Hypersensitivity reactions.

Xuzal *GSK, Chile; UCB, Mex.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Xybatron *Sydenham, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Xycalm *Ipca, India.*
Alprazolam (p. 1035·2).
Anxiety.

Xycam *Aspen, S.Afr.*
Piroxicam (p. 125·3).
Musculoskeletal and joint disorders; gout.

Xyclomed *Korea United, Philipp.*
Cyclophosphamide (p. 771·1).
Malignant neoplasms.

Xydep *Pfizer, Austral.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; premenstrual dysphoric disorder.

Xydifon *Moschimfarm, Rus.*
Etidronic acid (p. 1182·3).
Renal calculi; hyperparathyroidism; osteoporosis; heavy metal poisoning.

Xyladur *Premier Research, Neth.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Xylanaest *Gebro, Austria.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylanal *Epsilon Health, Gr.*
Amikacin sulfate (p. 214·2).

Xylat *Yuriya-Farm, Ukr.*
Xylitol (p. 2220·3); sodium acetate (p. 1781·1); sodium chloride (p. 1795·1); calcium chloride (p. 1783·1); potassium chloride (p. 1793·2); magnesium chloride (p. 1787·1).
Detoxification; fluid and electrolyte disorders; carbohydrate source.

Xylésine *Amino, Switz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xylestesin
Note: this name may be used for preparations of different composition.
Cristalia, Braz.
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) or noradrenaline acid tartrate (p. 1458·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Faratzi, Gr.
Lidocaine hydrochloride (p. 1988·2).
Noradrenaline hydrochloride (p. 1458·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-A *3M Espe, Gr.; 3M, Hong Kong; 3M, NZ; 3M, Singapore.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline hydrochloride (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-S Special *Faratzi, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline hydrochloride (p. 1292·2) and noradrenaline hydrochloride (p. 1458·2) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylia *Sandoz, Austria.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-associated acne and hirsutism in women.

Xylid *Pharmaniaga, Malaysia.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Xyliette *Sandoz, Austria.*
Levonorgestrel (p. 2296·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

XyliMelts *OraHealth, USA.*
Xylitol (p. 2220·3).
Dry mouth.

Xylisol *Cassara, Arg.*
Sodium chloride (p. 1795·1).
Sinusitis; nasal hygiene.

Xylit *Braun, Ger.†; DeltaSelect, Ger.†*
Xylitol (p. 2220·3).
Carbohydrate source; fluid disorders.

Xylocain *AstraZeneca, Austria; AstraZeneca, Denm.; AstraZeneca, Fin.; Dentsply, Fin.; AstraZeneca, Ger.; Dentsply, Ger.; AstraZeneca, Norw.; Dentsply, Norw.; AstraZeneca, Swed.; Dentsply, Swed.; AstraZeneca, Switz.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; arrhythmias; pain; endoscopy.

AstraZeneca, Turk.
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xylocain (Kardiologie) *AstraZeneca, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias.

Xylocaina *AstraZeneca, Arg.; AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, Ital.; Dentsply, Ital.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or noradrenaline (p. 1458·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

AstraZeneca, Port.; Inibsa, Spain.†
Ointment; topical gel: Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xylocaína *AstraZeneca, Mex.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylocaine *AstraZeneca, Austral.; Dentsply, Austral.; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Gr.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hong Kong; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Neth.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Thai.; AstraZeneca, UK; APP, USA.*
Lidocaine (p. 1988·1) or lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; endoscopy; catheterisation; pain; arrhythmias; instrument insertion.

AstraZeneca, Belg.; AstraZeneca, NZ; Dentsply, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, UK; Dentsply, UK.
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylocaïne *AstraZeneca, Fr.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) or naphazoline nitrate (p. 1669·3) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylocaine Jelly with Chlorhexidine *AstraZeneca, Austral.†*
Lidocaine hydrochloride (p. 1988·2); chlorhexidine gluconate (p. 1743·3).
Local anaesthesia; endoscopy; catheterisation.

Xylocaine Special Adhesive *AstraZeneca, Austral.*
Lidocaine (p. 1988·1).
Topical anaesthesia in dentistry.

Xylocaine Visqueuse *AstraZeneca, Belg.*
Lidocaine hydrochloride (p. 1988·2).
Painful oral and oesophageal conditions; adjunct in radiology and endoscopy.

Xylocard *AstraZeneca, Austral.; AstraZeneca, Austria†; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Fr.; AstraZeneca, India; AstraZeneca, NZ; AstraZeneca, Philipp.†; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Switz.†*
Lidocaine hydrochloride (p. 1988·2).
Arrhythmias; status epilepticus.

Xylocitin *Mibe, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylocitin cor *Mibe, Ger.*
Lidocaine hydrochloride (p. 1988·2).
Ventricular arrhythmias.

Xylo-COMOD *Croma, Austria; GenTop, Cz.; Ursapharm, Ger.†; Ursapharm, Neth.†; Biem, Turk.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinitis; sinusitis.

Xylocontact *Pierre Rolland, Fr.*
Lidocaine (p. 1988·1).
Mouth disorders.

Xylocream *Verisfield, Gr.*
Lidocaine (p. 1988·1); prilocaine (p. 1994·1).
Local anaesthesia.

Xylodent *Rekah, Israel.†*
Chlorhexidine gluconate (p. 1743·3).
Mouth disorders.

Xyloderm *AstraZeneca, Mex.*
⊗Lidocaine hydrochloride (p. 1988·2); hydrocortisone acetate (p. 1640·1); clotrimazole (p. 576·2); neomycin sulfate (p. 330·1).
Infected skin disorders.

Xylogel *Pediapharma, Philipp.*
Xylitol (p. 2220·3).
Teething pain; gum, mouth and lip sores; dental caries prophylaxis.

Polfa Warszawa, Pol.
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis; otitis media.

Xylohexal *Sandoz, Ukr.†*
⊗Xylometazoline (p. 1680·1).
Rhinitis; sinusitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Xylol *Demo, Gr.*
Lidocaine (p. 1988·1).
Local anaesthesia.

Xylolin *Julphar, UAE.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal and sinus congestion.

Xyloma *Jean-Marie, Hong Kong.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; otitis media.

Xylo-Mepha *Mepha, Switz.; Teva, Ukr.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; otitis media; aid in rhinoscopy.

Xylonest *AstraZeneca, Ger.; Dentsply, Ger.; AstraZeneca, Switz.*
Prilocaine hydrochloride (p. 1994·1).
Adrenaline acid tartrate (p. 1292·2) or felypressin (p. 2502·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xyloneural *Gebro, Austria; Strathmann, Ger.; Gebro, Switz.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia; headache; migraine; vertigo; tinnitus.

Xylonor *Septodont, Fr.; Ogna, Ital.*
Injection: Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) or noradrenaline acid tartrate (p. 1458·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septodont, Canad.; Ogna, Ital.
Topical spray: Topical gel: Lidocaine (p. 1988·1); cetrimonium bromide (p. 1742·3).
Local anaesthesia.

Septodont, Austria; Septodont, Canad.; Septodont, Fr.; Septodont, Irl.; Septodont, Israel; Wild, Switz.
Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Local anaesthesia.

Septodont, Spain.
Lidocaine hydrochloride (p. 1988·2); cetrimonium bromide (p. 1742·3).
Local anaesthesia.

Xylonor Especial *Septodont, Spain.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) and noradrenaline acid tartrate (p. 1458·2) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylonor Noradrenaline *Tsaprazis, Gr.; Septodont, Israel.*
Lidocaine hydrochloride (p. 1988·2).
Noradrenaline (p. 1458·2) or noradrenaline acid tartrate (p. 1458·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylonor 2% Sin Vasoconst *Prats, Spain.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xyloplyin *Dentsply, Denm.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this injection as a vasoconstrictor to diminish absorption and localise the effects of the local anaesthetic.
Local anaesthesia.

Xyloplyina *Dentsply, Ital.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylo-POS *Ursapharm, Ger.†; Ursapharm, Israel; Ursapharm, Neth.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Xyloproct *AstraZeneca, Austral.; Astra, Gr.; AstraZeneca, Irl.†; AstraZeneca, NZ; AstraZeneca, Swed.; AstraZeneca, UK.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); aluminium acetate (p. 2440·1); zinc oxide (p. 1729·1).
Anorectal disorders; pruritus vulvae.

AstraZeneca, Braz.; AstraZeneca, Malaysia; AstraZeneca, Norw.†
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); aluminium subacetate (p. 2440·1); zinc oxide (p. 1729·1).
Anorectal disorders.

AstraZeneca, Hong Kong.
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Xyloproct Plus *AstraZeneca, Mex.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1); aluminium subacetate (p. 2440·1); zinc oxide (p. 1729·1).
Anorectal disorders.

Xyloprocto *AstraZeneca, Arg.*
⊗Lidocaine (p. 1988·1); hydrocortisone acetate (p. 1640·1).
Anorectal disorders.

Xyloprocto Toallas *AstraZeneca, Arg.*
Aloe vera (p. 1693·2); hamamelis (p. 2523·3); mallow (p. 2549·2).
Personal hygiene.

Xylorane *Ranbaxy, Mex.†*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Xylorin *Orion, Cz.; GSK, Pol.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; sinusitis.

Xylorinse *Pediapharma, Philipp.*
Xylitol (p. 2220·3); sodium fluoride (p. 2089·2); cetylpyridinium chloride (p. 1743·1).
Oral hygiene; dental caries prophylaxis.

Xylorolland *Pierre Rolland, Fr.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline acid tartrate (p. 1292·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylotox *Adcock Ingram, S.Afr.*
Lidocaine hydrochloride (p. 1988·2).
Adrenaline (p. 1292·1) or noradrenaline (p. 1458·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylovit *Vitamed, Israel.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Xylozan *Demo, Gr.*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Xylozolin *Pharmachemie, Neth.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion.

Xymel *Clonmel, Irl.; Kellpharm, Irl.*
Tramadol hydrochloride (p. 139·2).
Pain.

Xymelin *Nycomed, Rus.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; otitis media; sinusitis.

Xymelin Extra *Nycomed, Rus.; Nycomed, Ukr.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Rhinitis; sinusitis.

Xyntha *Pfizer, Austral.; Pfizer, Canad.; Wyeth, Israel; Pfizer, NZ.*
Moroctocog alfa (p. 1148·2).
Haemophilia A.

Wyeth, USA.
A factor VIII preparation (recombinant) (p. 1148·1).
Haemophilia A.

Xypen *Medhaus, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Xyprody *Roddensers, Philipp.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Xyralid *Auriga, USA.*
⊗Lidocaine hydrochloride (p. 1988·2); hydrocortisone acetate (p. 1640·1).
Skin disorders.

Xyrem *UCB, Austria; UCB, Belg.; Valeant, Canad.; UCB, Cz.; UCB, Denm.; UCB, Fr.; UCB, Ger.; UCB, Irl.; UCB, Ital.; UCB, Neth.; UCB, Norw.; UCB, Pol.; UCB, Port.; UCB, Spain; UCB, Swed.; UCB, Switz.; UCB, UK; Jazz, USA.*
Sodium oxybate (p. 1914·1).
Cataplexy in narcoleptic syndrome.

Xyrocin *VS, Thai.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Xysvol *Raam, Mex.*
Felodipine (p. 1380·3).
Hypertension; angina pectoris.

Xyvion *MSD, Austral.*
⊗Tibolone (p. 2309·2).
Menopausal disorders; osteoporosis.

Xyzal *UCB, Austral.; UCB, China; UCB, Cz.; UCB, Denm.; UCB, Fin.; GSK, Hong Kong; UCB, Hung.; UCB, Indon.; UCB, Irl.; UCB, Ital.; GSK, Jpn; GSK, Malaysia; UCB, Neth.; UCB, Norw.; GSK, Philipp.; Vedim, Pol.; UCB, Port.; UCB, Rus.; AHN, S.Afr.; GSK, Singapore; UCB, Switz.; GSK, Thai.; UCB, Turk.; UCB, UK; UCB, Ukr.; Sanofi-Aventis, USA.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria; pruritus; allergic conjunctivitis.

Xyzall *UCB, Austria; UCB, Belg.; UCB, Fr.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Xyzine *TNP, Thai.*
Hydroxyzine hydrochloride (p. 630·3).
Anxiety; pruritus; sedative.

8 Y *Galenica, Gr.*
A factor VIII preparation (p. 1148·1).
Haemorrhagic disorders.

Ya Bang *Jinchang, China.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Ya Bang Li Er *Shengyuan, China.*
Sisomicin.
Bacterial infections.

Ya Bao Xin *Ya Bao, China.*
Malotilate (p. 2549·3).

Ya Bing *Lukang Chenxin, China.*
Diclofenac sodium (p. 48·3); lidocaine hydrochloride (p. 1988·2).

Ya Fu Xin *Tiancheng, China.*
Calcium folinate (p. 2066·3).
Methotrexate toxicity; megaloblastic anaemia.

Ya Jian Chang *Lingkang, China.*
Levofloxacin mesilate.
Bacterial infections.

Ya Jie *Yu Heng, China.*
Ornidazole (p. 943·1).

Ya Kang *Xi Cheng, China.*
Metronidazole (p. 936·1).

Ya Ke *Changzhou Siyao, China.*
⊗Ibuprofen (p. 68·2); pseudoephedrine hydrochloride (p. 1676·1).

Ya Kun Yu *Lingkang, China.*
Disodium clodronate (p. 1180·3).
Bone metastases; hypercalcaemia of malignancy.

Ya Li Di *Fu He Hua Xing, China.*
Urapidil (p. 1520·2).
Hypertension.

Ya Li *Huahai, China.*
⊗Azosemide (p. 1314·1).

Ya Li Ding *Ya Bang A i Pu Sen, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Ya Li Xi *Yatai, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Ya Liang *Sunnyhope, China.*
Cetylpyridinium chloride (p. 1743·1).

Ya Ni Ding *Renhu, China.*
Moxonidine hydrochloride.
Hypertension.

Ya Ning *Kai Bao, China.*
Captopril (p. 1331·2).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

Ya Nuo *Dikang, China.*
Chlorhexidine gluconate (p. 1743·3).
Gingivitis; oral hygiene.

Ya Ping *Kang Yuan, China.*
Telmisartan (p. 1509·3).
Hypertension.

Ya Pu Yi *Lingkang, China.*
Di-isopropylammonium dichloroacetate (p. 1359·1).

Ya Qing Ning *Lingkang, China.*
Xylitol (p. 2220·3).

Ya Rong *Kang Yuan, China.*
⊗Indapamide (p. 1409·2).
Hypertension; oedema.

Ya Rui *Yatai, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ya Run Ji *Lingkang, China.*
Nicergoline (p. 2569·1).
Cerebral and peripheral vascular disorders.

Ya Sen *Lukang Chenxin, China.*
Oxymatrine.

Ya Shi Da *BSPC, China.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ya Shu *Jincheng Haisi, China.*
Lysine hydrochloride (p. 2079·3).

Ya Si Ke Ping *DHY, China.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Ya Tan *Shihuida, China.*
Telmisartan (p. 1509·3).
Hypertension.

Ya Xu *Grand, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Ya Yi Jia *Ya Bang Ai Pu Sen, China.*
Lomerizine hydrochloride (p. 676·3).

Ya Zheng *Qilu, China.*
Moclobemide (p. 437·2).
Depression; social phobia.

Ya Zheng Li *Yabang, China.*
Pazufloxacin mesilate (p. 338·1).

Ya Zhou Kang *Suzhou No 3, China.*
Metronidazole (p. 936·1); ibuprofen (p. 68·2).
Gingivitis; periodontitis; gum abscess.

Yabao Like *Ya Bao, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Yacesal *Smaller, Spain.†*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Yacriton *Flupal, Venez.*
Vitamin B substances (p. 2102·3); inositol (p. 2533·2).

Yadegal Compuesto *Rayere, Mex.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); chlorphenamine maleate (p. 620·3).
Cough; respiratory-tract congestion.

Yadid *Gezzi, Arg.*
Urea hydrogen peroxide (p. 1774·2).
Ear wax removal.

Yadim *Yarindo, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Yadine *Bayer Schering, Cz.; Bayer Schering, Hung.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Yael *Dexxon, Israel.*
Ethinylestradiol (p. 2275·3); gestodene (p. 2279·3).
Combined oral contraceptive.

Yafix *Yarindo, Indon.*
Cefixime (p. 240·3).
Bacterial infections.

Yal *Jacoby, Austria; Trommsdorff, Cz.; Trommsdorff, Ger.; Gebro, Switz.; Adeka, Turk.*
Docusate sodium (p. 1836·2); sorbitol (p. 2092·1).
Bowel evacuation; constipation.

Yalipent *CT, Ital.†*
Gabapentin (p. 523·3).
Epilepsy; neuropathic pain.

Yalone *Yarindo, Indon.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

Yalta Corn Salve *Technikon, S.Afr.†*
Salicylic acid (p. 1719·1).
Corns; callouses.

Yam *Florin, Hung.*
Dead Sea salt (p. 2612·1); zinc sulfate (p. 2126·2); potassium bromide (p. 2461·1).
Psoriasis.

Yamasiv *AAA, Denm.*
Ramipril (p. 1483·3).
Hypertension.

Yamoxiclav *Astellas, Fin.†*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Yan Le *Conba, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Yan Di *Hayao, China.*
Roxithromycin (p. 356·2).
Bacterial infections.

Yan De *Yanjing, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Yan Bi Er *Ao Dong, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Yan Er *Sine, China.*
Theophylline sodium glycinate (p. 1229·3).
Asthma.

Yan Hua *Huayu, China.*
Lactic acid bacteria (p. 2596·3).

Yan Hua Xing *Sine, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Yan Jin *Meng Xin, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Yan Ke Xian *Shenyang First, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Yan Li *Johnson & Johnson, China.*
Oral rehydration solution (p. 1780·1).

Yan Li Da *Fang Sheng, China.*
Fleroxacin (p. 298·3).
Bacterial infections.

Yan Li Fei *Yi Kang, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Yan Lie Shu *Zhendong Jinjing, China.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Yan Ling *Xianqiang, China.*
Cefixime (p. 240·3).
Bacterial infections.

Yan Lun Xin *Ao Dong, China.*
Matrine.

Yan Luo Qi *Ao Dong, China.*
Inosine (p. 2533·1).

Yan Di Nuo *Sine, China.*
Alfacalcidol (p. 2112·3).
Hypocalcaemia; hypoparathyroidism; hypophosphataemia; renal osteodystrophy; rickets; osteomalacia.

Yan Nuo Xin *Sine, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Yan Pa Rui *Ao Dong, China.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Yan Quan *Pu Kang, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Yan Sha *Xibaishou, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Yan Yi *White Swan, China.*
Cefixime (p. 240·3).
Bacterial infections.

Yan Zhi *Kang Le, China.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Yanal *Benitol, Arg.*
⊗Atropine (p. 1310·2); adrenaline (p. 1292·1).
Asthma.

Yanchang *Zizhu, China.*
⊗Gestrinone (p. 2280·2).
Endometriosis.

YanDi *Zhendong Jinjing, China.*
Tropisetron hydrochloride (p. 1894·1).
Nausea and vomiting.

Yang Da Ning *Huaxin, China.*
Ofloxacin (p. 334·3).
Bacterial infections.

Yangyi *NCPC, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Yanlei *Yangtze River, China.*
Pazufloxacin mesilate (p. 338·1).
Bacterial infections.

Yanthi Baby & Bath Powder *Minorock Mandiri, Indon.†*
Zinc oxide (p. 1729·1); magnesium carbonate (p. 1856·2); talc (p. 1722·2).
Nappy rash; skin irritation.

Yanthi Baby Oil *Minorock Mandiri, Indon.†*
Wool fat (p. 2219·3); nipagin; coconut oil (p. 2179·3); liquid paraffin (p. 2191·2).
Emollient.

Yantil *Grunenthal, Cz.; Grunenthal, Irl.; Grunenthal, Neth.*
Tapentadol hydrochloride (p. 136·1).
Pain.

Yanuvia *MSD, Ukr.*
Sitagliptin (p. 500·1).
Diabetes mellitus.

YaoKe *Jiahui, China.*
Moxonidine hydrochloride.
Hypertension.

Yapamicin *Novag, Mex.†*
Ampicillin (p. 218·2).
Bacterial infections.

Yapircam *Newcharoen, Thai.*
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); menthol (p. 2553·2); eugenol (p. 2501·2).
Musculoskeletal and joint pain.

Yara *Pharmacypria, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Yardel *Delegant, Gr.*
Sodium hyaluronate (p. 2526·2).
Osteoarthritis of the knee.

Yariba *Dendron, UK.*
Kola (p. 2648·2).
Fatigue.

Yaricef *Yarindo, Indon.*
Cefadroxil (p. 233·2).
Bacterial infections.

Yaridon *Yarindo, Indon.*
Domperidone (p. 1838·1).
Nausea and vomiting; dyspepsia.

Yariflam *Yarindo, Indon.*
Diclofenac potassium (p. 48·3).
Rheumatoid arthritis; ankylosing spondylitis; osteoarthritis.

Yarina *Bayer, Ital.; Bayer Schering, Rus.; Bayer, Ukr.*
Ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1).
Combined oral contraceptive; androgen-associated acne and seborrhoea in women.

Yarisma *Yarindo, Indon.*
⊗Terbutaline sulfate (p. 1228·1).
Obstructive airways disease.

Yariven *Yarindo, Indon.*
Ibuprofen (p. 68·2).
Fever; pain.

Yarocen *Egis, Hung.*
Mirtazapine (p. 436·1).
Depression.

Yarox *Yarindo, Indon.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Yasmin *Bayer, Arg.; Bayer, Austral.; Bayer, NZ; Bayer Schering, S.Afr.*
21 Tablets, drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3); 7 tablets, inert.
Combined oral contraceptive.

Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, China; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, Neth.; Bayer Schering, Norw.; Bayer, Philipp.; Bayer Schering, Pol.; Bayer, Port.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Bayer, UK; Bayer, USA; Schering, Venez.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
>Combined oral contraceptive; acne in women who require oral contraception.

Yasminelle *Bayer, Arg.; Bayer, Austria; Bayer, Belg.; Bayer Schering, Cz.; Bayer Schering, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer Schering, Hung.; Bayer, Irl.; Bayer, Israel†; Bayer, Ital.; Bayer, Neth.; Bayer Schering, Norw.; Bayer Schering, Pol.; Berlex, Port.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.*
Drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3).
28-day packs also contain 7 inert tablets.
Combined oral contraceptive.

Bayer, Denm.
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Yasnal *KRKA, Cz.; KRKA, Fin.; KRKA, Pol.; KRKA, Rus.; KRKA, Spain.*
Donepezil hydrochloride (p. 390·2).
Alzheimer's disease.

Yasnoro *KRKA, Ital.*
Donepezil hydrochloride (p. 390·2).

Yasta *Bayer, Chile.*
Aspirin (p. 22·2); sodium bicarbonate (p. 1781·1); citric acid (p. 2480·3).
Dyspepsia; pain.

Bayer Consumer, Arg.
Sodium bicarbonate (p. 1781·1); sodium carbonate (p. 2617·3); caffeine (p. 1203·3); tartaric acid (p. 2626·1); sodium citrate (p. 1781·2).
Dyspepsia; gastric hyperacidity.

Yatrox *Qualigen, Spain.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Yavon *Yarindo, Indon.*
Bromhexine hydrochloride (p. 1656·3).
Cough.

Yaweiyi *Shutaishen, China.*
Telmisartan (p. 1509·3).
Hypertension.

Yaxinbituo *New Asiatic, China; Shanghai Pharma, China.*
Levofloxacin lactate.
Bacterial infections.

Yaxing *New Asiatic, China; Shanghai Pharma, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

YAZ *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer, Chile; Bayer Schering, Cz.; Bayer, Denm.; Bayer Schering, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer Schering, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer Schering, Malaysia.; Bayer, Neth.; Bayer, Norw.; Bayer, NZ; Bayer, Philipp.; Bayer Schering, Pol.; Berlex, Port.; Bayer Schering, Rus.; Bayer Schering, S.Afr.; Bayer, Spain; Bayer, Swed.; Bayer, Thai.; Bayer, UK.*
24 Tablets, drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3); 4 tablets, inert.
Combined oral contraceptive; premenstrual dysphoric disorder; acne; premenstrual syndrome.

Bayer, Braz.; Bayer, Israel; Bayer, Singapore; Bayer, Switz.; Bayer, USA.
Drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3).
Combined oral contraceptive; premenstrual syndrome; premenstrual dysphoric disorder; acne.

Yazon *Yarindo, Indon.*
Cefoperazone (p. 243·1).
Bacterial infections.

Yazz *Bayer, Turk.*
24 Tablets; drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3); 4 tablets, inert.

Ybecor *Alapis, Gr.*
⊗Fluticasone propionate (p. 1638·1).
Allergic rhinitis; skin disorders.

Ybersigax *Galex, Neth.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Yderm *Liferpal, Mex.*
⊗Clioquinol (p. 273·1); fluocinolone (p. 1636·1).
Infected skin disorders.

Ydroquinidine *Alapis, Gr.*
Hydroquinidine hydrochloride (p. 1407·1).
Arrhythmias.

Ye & To *Landson, Indon.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); guaifenesin (p. 1666·2).
Cold and influenza symptoms.

Ye Li Ning *Taihe, China.*
Boanmycin hydrochloride.

Ye Ning *Zhong Bao, China.*
Oxymatrine.

Ye Xin *Double-Crane, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Yeast Vite *Thornton & Ross, UK.*
Caffeine (p. 1203·3); vitamin B substances (p. 2102·3); dried yeast (p. 2125·2).
Tonic.

Yeastafort *Kimia, Indon.*
Brewer's yeast (p. 2125·2); vitamin B_1 (p. 2103·1); vitamin B_2 (p. 2104·3); nicotinamide (p. 2083·1).
Acne; vitamin B deficiency.

Yeastazol *Zyg, Philipp.*
Clotrimazole (p. 576·2).
Fungal skin infections.

Yeast-Gard *Lake, USA.†*
Pulsatilla (p. 2600·2); Candida parapsilosis; Candida albicans.
Homoeopathic preparation.

Yeast-Gard Medicated *Lake, USA.*
Povidone-iodine (p. 1767·1).
Vaginal irritation.

Yectafer *AstraZeneca, Arg.*
Iron dextran (p. 2075·3).
Iron deficiency.

Yectafer Complex *AstraZeneca, Arg.*
Iron dextran (p. 2075·3); folic acid (p. 2063·1); hydroxocobalamin (p. 2107·3).
Iron deficiency.

Yectames *Grossman, Mex.*
Algestone acetophenide (p. 2255·2); estradiol enantate (p. 2271·2).
Injectable contraceptive.

Yectamicina *Grossman, Mex.*
Gentamicin sulfate (p. 304·2).
Bacterial infections.

Yectamid *Collins, Mex.†*
Amikacin sulfate (p. 214·2).
Gram-negative bacterial infections.

Yectaspirin *Northia, Arg.†*
Lysine aspirin (p. 84·3).

Yectolin *Grossman, Mex.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Yedoc *Novartis, Gr.*
Gentamicin sulfate (p. 304·2).
Bacterial eye infections.

Yelets *Freeda, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemia.

Yellon *Zentiva, Cz.†*
β-Aescin (p. 2431·2).
Venous insufficiency; inflammation; oedema.

Yellow Dock Combination *Seroyal, Canad.†*
Echinacea purpurea (p. 2498·1); figwort; goose grass (p. 2481·2); sarsaparilla (p. 2610·3); taraxacum officinale (p. 2625·3); trifolium pratense (p. 2482·1); yellow dock (p. 2649·3).
Homoeopathic preparation.

Yellow Siang Pure Balm *Bertram, Thai.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); camphor (p. 2466·2).
Musculoskeletal and joint pain.

Yellox *Bausch & Lomb, Denm.; Chauvin, Fr.; Mann, Ger.; Bausch & Lomb, Irl.; Bausch & Lomb, Neth.; Croma, Norw.; Bausch & Lomb, Spain; Bausch & Lomb, Swed.; Bausch & Lomb, UK.*
Bromfenac sodium (p. 30·1).
Eye inflammation following cataract surgery.

Yeluoshu *Yaoyou, China.*
Reboxetine (p. 447·1).
Depression.

Yemifer-HE *Ultra, Mex.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1).
Iron-deficiency anaemia; folate deficiency.

Yendol *Faes, Spain.*
Caffeine (p. 1203·3); chlorphenamine maleate (p. 620·3); paracetamol (p. 115·1); salicylamide (p. 129·2).
Cough; cold and influenza symptoms.

Yenizin *Yeni, Turk.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Yentreve *Lilly, Austria; Lilly, Belg.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Boehringer Ingelheim, Ger.; Lilly, Ger.; Lilly, Gr.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Boehringer Ingelheim Promeco, Mex.; Lilly, Neth.; Lilly, Pol.; Lilly, Port.; Lilly, Swed.; Lilly, UK.*
Duloxetine hydrochloride (p. 415·1).
Stress urinary incontinence in women.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Yepotin *Teva, Mex.†*
⊗Epoetin alfa (p. 1141·1).
Anaemias; autologous blood transfusion.

Yerba Diet *ISA, Arg.*
Vitamin B_6 (p. 2105·3); magnesium (p. 1786·3); mate (p. 2648·2); bladderwrack (p. 2612·1); green tea (p. 2648·2); passion flower (p. 2584·1).
Dietary supplement.

Yerba Santa *Roemmers Osmoph, Venez.*
Sodium benzoate (p. 1738·2); polygala (p. 1677·2); pentoxyverine citrate (p. 1672·1); eriodictyon (p. 1665·2); tolu balsam (p. 1679·2).
Cough; respiratory-tract disorders.

Yerbalaxa *Iphym, Fr.*
Frangula bark (p. 1843·3); senna (p. 1885·1); mallow (p. 2549·2).
Constipation.

Yervoy *BMS, Austral.; BMS, Belg.; BMS, Canad.; BMS, Denm.; BMS, Fr.; BMS, Ger.; BMS, Irl.; BMS, Israel; BMS, Neth.; BMS, Norw.; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, UK; BMS, USA.*
Ipilimumab (p. 812·1).
Malignant melanoma.

Yesan *Rafarm, Gr.*
⊗Timolol maleate (p. 1513·2).
Glaucoma.

Yestamin *Peter Black, UK.*
Vitamin B substances (p. 2102·3); ascorbic acid (p. 2110·3); iron (p. 2073·1).

YF-Vax *Sanofi Pasteur, Canad.; Sanofi Pasteur, USA.*
A yellow fever vaccine (17D strain) (p. 2424·3).
Active immunisation.

Ygielle *Frezyderm, Gr.*
Clindamycin phosphate (p. 269·3).
Vaginal infections.

Yi Du *Changxing, China.*
Phenazopyridine hydrochloride (p. 124·3).
Pain in cystitis, prostatitis, and urethritis.

Yi Di *Sanhome, China.*
Oxymatrine.

Yi Di An *Pacific, China.*
Doxifluridine (p. 782·3).

Yi An Fen *San Lian, China.*
Gamma-aminobutyric acid (p. 2509·2).

Yi An Lin *RenFu, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Yi An Nuo *Sanjiu Yimin, China.*
Piracetam (p. 393·3).
Mental function impairment.

Yi Bang *Ya Bang Sheng Yuan, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Yi Bei *Di Ao Jiu Hong, China.*
⊗Erythropoietin (human recombinant) (p. 1141·1).

Yi Bi Fu *Hisun, China.*
Rifampicin (p. 350·3); isoniazid (p. 311·2); pyrazinamide (p. 345·2).
Tuberculosis.

Yi Bo Te *Ke Lun, China.*
Sodium ferulate.

Yi Chuang *Jianglibao, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Yi Da *Hanfang, China.*
Cefadroxil (p. 233·2).
Bacterial infections.

Yi Da Li *Hisun, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Yi Da Sheng *Boda, China.*
Edaravone (p. 1370·2).
Stroke.

Yi Da Tong *Poly, China.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Yi Dan *Hua Lu, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Yi Ding *Jiu Xu, China.*
Neostigmine metilsulfate (p. 687·2).
Reversal of neuromuscular blockers; postoperative urinary retention; ileus; diagnosis of myasthenia gravis.

Yi Ding Lai *Tong Yang Tong Meng, China.*
Gastrodin.

Yi Er *Yatai, China.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Yi Er Ning *Nuo De, China.*
Methylbenactyzium bromide (p. 1861·3).

Yi Er Song *Fudan Fuhua, China.*
Diclofenac sodium (p. 48·3).
Pain; inflammation.

Yi Fang *Bright Future, China.*
Valsartan (p. 1521·2).
Hypertension; heart failure; myocardial infarction.

Yi Fei *Hengrui, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Yi Fen *SL Pharm, China.*
Etodolac (p. 57·1).
Osteoarthritis; rheumatoid arthritis; pain.

Yi Fen Ning *Yabo, China.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Yi Feng *Xinan, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Yi Fu *Tianmu Beidou, China.*
Epidermal growth factor (mouse).

Yi Fu Lin *Qilu, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Yi Fu Ping *Stada, China.*
Liranaftate (p. 588·1).

Yi Fu Qing *Sanmenxia Sinoway, China; Wan Te, China.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Yi Fu Yun *Sanmenxia Sinoway, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Yi Fu Zheng *Li Neng Kang Tai, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Yi Gan Lin *Daxing, China.*
Matrine.

Yi Ge *Zhong Bao, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Yi Ge Ding *Jiangxi, China.*
Irsogladine maleate (p. 1848·3).

Yi Gu Tai *Shengtai, China.*
Melon extract.

Yi Han Ning *Yimin, China.*
Dimenhydrinate (p. 625·2).
Nausea and vomiting; vertigo.

Yi Heng *Yi Hua, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Yi Hong *Dayuan, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Yi Hu Wei Mei Su Chong Ji *Jintai, China.*
Erythromycin ethyl succinate (p. 291·2).
Bacterial infections.

Yi Huan *Yangtze River, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Yi Ji Xin *Sanjiu Yimin, China.*
Ligustrazine phosphate.

Yi Jia Lin *Yaoyou, China.*
Trace elements.

Yi Jie *Shenlong, China.*
Sodium new houttuyfonate.

Yi Jie Ka *Runduo Mintong, China.*
Levobupivacaine hydrochloride (p. 1987·3).
Local anaesthesia.

Yi Jing *Yi Hua, China.*
Oxybutynin hydrochloride (p. 2361·2).
Bladder hyperactivity.

Yi Jiu Bo *Sanjiu Yimin, China.*
Cisplatin (p. 766·1).
Malignant neoplasms.

Yi Jun *Double-Crane, China.*
Piperacillin sodium (p. 340·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Yi Jun Ding *Southwest, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Yi Kai *Qianhong, China.*
Kininogenase (pancreatic).

Yi Kang Ning *Tianping, China.*
Irbesartan (p. 1411·1).
Hypertension.

Yi Ke *Anlian, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Yi Ke Fu *Wei Kang, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Yi Ke Lin *Suzhou No 1, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Yi Ke Long *Huana, China.*
Docusate sodium (p. 1836·2).
Constipation.

Yi Ke Tie *Taitai, China.*
⊗Dexamethasone acetate (p. 1631·1).
Mouth ulcers.

Yi Ke Xian *Shihuida, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Yi Ke Xin *Dayinhaiyang, China.*
Vitamin A (p. 2098·3); vitamin D.
Vitamin A and D deficiency.

Yi Ke Xing *Yunzhong, China.*
Sodium ferulate.

Yi Ke Ya *Yaoyou, China.*
Foscarnet sodium (p. 981·1).

Yi Ke Ya Xin *Kangerwei, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Yi Lai *Fenghuang, China.*
Norfloxacin lactate.
Bacterial infections.

Yi Lai Ning *Rui Yang, China.*
Matrine.

Yi Li *Si Huan, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

Yi Li An *Livzon, China.*
Ilaprazole (p. 1848·2).

Yi Li Kang *ShiJiaZhuang No 4, China.*
Fluconazole (p. 578·2).
Fungal infections.

Yi Li Miao *Gerui, China.*
Paracetamol (p. 115·1).
Fever; pain.

Yi Li Ping *Deyer, China.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Yi Li Tong *Di Ao Jiu Hong, China.*
Staphylokinase (p. 1502·3).

Yi Li Xi *Wanma, China.*
Rosiglitazone hydrochloride (p. 496·3).
Diabetes mellitus.

Yi Li Xin
Note: this name may be used for preparations of different composition.
Huajin, China.
Dirithromycin (p. 287·1).
Bacterial infections.

Suzhong Haixin, China.
Loratadine (p. 633·2).
Hypersensitivity reactions.

Yi Li Zhi *Gerui, China.*
Megestrol acetate (p. 2289·2).
Breast cancer; endometrial cancer; AIDS- or cancer-induced cachexia.

Yi Lin
Note: this name may be used for preparations of different composition.
Jiuyang, China.
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Yangtze River, China.
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Yi Ling Shu *Lunan, China.*
Aniracetam (p. 389·1).
Memory impairment.

Yi Lu *Shenlong, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial infections.

Yi Lu Mei *Southwest, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Yi Lun Ding *Jiu Tai, China.*
Ethylenediamine diacetate.

Yi Luo Ping *Wan Bang, China.*
Sodium demethylcantharidate.

Yi Luo Qing *Sanjiu Yimin, China.*
Citicoline sodium (p. 2480·2).
Cerebrovascular disorders; brain injury; parkinsonism.

Yi Ma Xin *Xianju, China.*
Progesterone (p. 2300·2).
Menopausal disorders; amenorrhoea; dysfunctional uterine bleeding.

Yi Mai Ge *Baike Hengdi, China.*
⊗Torasemide (p. 1516·3).
Hypertension; oedema.

Yi Mai Ou *Dongbao, China.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Yi Mai Qing *Hayao, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; coronary heart disease.

Yi Mai Xi *Minsheng, China.*
Magnesium potassium aspartate.

Yi Mei
Note: this name may be used for preparations of different composition.
Dong Fang, China.
Mezlocillin sodium (p. 324·1).
Bacterial infections.

Yi Ao, China.
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Yi Mei Li *Jianglibao, China.*
Nimesulide (p. 101·3).
Pain.

Yi Mei Ning *Keyuan, China.*
Isoflurane (p. 1903·2).
General anaesthesia.

Yi Mei Tai *Dadeli, China.*
Aprotinin (p. 1133·2).
Blood loss in open-heart surgery.

Yi Mei Xin *Hengrui, China.*
Cefoperazone sodium (p. 243·1).
Bacterial infections.

Yi Meng *Jianglibao, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Yi Ming *Sanjiu Yimin, China.*
Aceglutamide (p. 2426·2).

Yi Na Lin *Changzhou, China.*
Enalapril maleate (p. 1371·1).
Heart failure; hypertension.

Yi Neng Sen *Qingfeng, China.*
Enoxacin gluconate.
Bacterial infections.

Yi Ning Shi *Pude, China.*
Lysine hydrochloride (p. 2079·3).

Yi Nuo *Wellso, China.*
Huperzine A.

Yi Nuo Da *ShiJiaZhuang No 4, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Yi Nuo Ni Kang *HongQi, China.*
Ethambutol hydrochloride (p. 296·1); pyrazinamide (p. 345·2); rifampicin (p. 350·3); isoniazid (p. 311·2).
Tuberculosis.

Yi Nuo Shu *TianJing, China.*
Ambroxol hydrochloride (p. 1654·3).

Yi Nuo Tai *ShiJiaZhuang No 4, China.*
Gatifloxacin lactate.
Bacterial infections.

Yi Nuo Wei *ShiJiaZhuang No 4, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Yi Nuo Xin *Jialing, China.*
Spiramycin (p. 358·3).
Protozoal infections.

Yi Nuo Xing *ShiJiaZhuang No 4, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Yi Ou Qing *Qilu, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Yi Pei *Double-Crane, China.*
Aceglutamide (p. 2426·2).

Yi Pin *Pu Kang, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Yi Ping *Shenglang, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Yi Pu Bi Shan *Si Huan, China.*
Octreotide acetate (p. 1924·1).
Variceal bleeding; acromegaly; endocrine tumours; prevention of complications following pancreatic surgery; AIDS-associated diarrhoea.

Yi Pu Ding *Kexing, China.*
⊗Erythropoietin (human recombinant) (p. 1141·1).

Yi Pu Li *KHB, China.*
⊗Erythropoietin (human recombinant) (p. 1141·1).

Yi Pu Ning *Tiantaishan, China.*
Octreotide acetate (p. 1924·1).
Variceal bleeding; acromegaly; endocrine neoplasms; prevention of complications following pancreatic surgery; AIDS-associated diarrhoea.

Yi Qi Di *Bei Te, China.*
Prulifloxacin (p. 345·1).

Yi Qi *Shenlong, China.*
Tinidazole (p. 949·2).
Bacterial vaginosis.

Yi Qi Fu *Bei Te, China.*
Fluconazole (p. 578·2).
Fungal infections.

Yi Qi Kang *Bei Te, China.*
Itraconazole (p. 583·3).
Fungal infections.

Yi Qi Xian *Yu Heng, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Yi Di Qing *Hanyin, China.*
Paracetamol (p. 115·1).
Fever; pain.

Yi Qing *Jiangxi, China.*
Etimicin sulfate (p. 298·2).

Yi Qiong *Hua Lu, China.*
Azasetron hydrochloride (p. 1820·2).

Yi Qu Shan *Tianlong, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Yi Ren *Gerui, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Yi Rong Xin *Guo Jing, China.*
Inosine (p. 2533·1).

Yi Ru Te *Tian Yu, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Yi Rui *Dayinhaiyang, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Yi Sa Lin *Hayao, China.*
Amoxicillin sodium (p. 216·2).
Bacterial infections.

Yi Sha Ning *Jinsha, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Yi Shang *Xinhua, China.*
Paracetamol (p. 115·1).
Fever; pain.

Yi Shen *Liang Fu, China.*
Liranaftate (p. 588·1).

Yi Shen Bao *NCPC, China.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Yi Sheng *Kawin, China.*
Interferon alfa-2b (human recombinant) (p. 989·2).
Hepatitis B; hepatitis C; malignant neoplasms; herpes zoster infection; anogenital warts; viral pneumonia.

Yi Sheng Bao Er *Weiwu Guangming, China.*
A rabies immunoglobulin (p. 2413·1).
Passive immunisation.

Yi Shou *Fang Ming, China.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment.

Yi Shu *Nhwa, China.*
Buspirone hydrochloride (p. 1042·1).
Anxiety.

Yi Shu Chang *Yishu, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Yi Shu Da *Hua Lu, China.*
Isosorbide dinitrate (p. 1412·2).
Angina pectoris; heart failure.

Yi Shu Ning *Sanjiu Yimin, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Yi Shu Sheng *Yishu, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Yi Shu Song *Dadeli, China.*
Oxymatrine.

Yi Shu Tong *Zhong Hua, China.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Yi Shuang *Dezhong, China.*
⊗Enalapril maleate (p. 1371·1); hydrochlorothiazide (p. 1403·2).

Yi Shuang Bi *Yiheng, China.*
Ranitidine (p. 1882·1); bismuth citrate potassium (p. 1822·1).

Yi Si Tan *Tong Yang Tong Meng, China.*
⊗Exemestane (p. 792·2).
Breast cancer.

Yi Song *De Zhou, China.*
Azithromycin fumarate.
Bacterial infections.

Yi Su *Yangtze River, China.*
Enalapril maleate (p. 1371·1).
Hypertension; heart failure.

Yi Su Ge *Gupeng, China.*
Potassium dehydroandrographolide succinate.

Yi Su Lin *Daxing, China.*
Azasetron hydrochloride (p. 1820·2).

Yi Su Xin *Minsheng, China.*
Povidone-iodine (p. 1767·1).
Oral hygiene.

Yi Suo *Rui Yang, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

Yi Suo Jie *Hisun, China.*
Glucosamine sulfate (p. 2515·3).
Osteoarthritis; rheumatism.

Yi Suo Ming *Hisun, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual syndrome.

Yi Tai *Wuhan, China.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p. 2384·3).
Active immunisation.

Yi Tai Da *Harbin, China.*
Arsenic trioxide (p. 2448·1).

Yi Tai Li *Maidihai, China.*
Estradiol benzoate (p. 2271·1).

Yi Tai Na *Nhwa, China.*
Citalopram hydrobromide (p. 411·1).
Depression.

Yi Tai Qing *Rundu Mintong, China.*
Irbesartan (p. 1411·1).
Hypertension; diabetic nephropathy.

Yi Tan *Hayao, China.*
Piperacillin sodium (p. 340·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Yi Tan Ning *Kanghong, China.*
Eszopiclone (p. 1072·3).
Insomnia.

Yi Te Le *Xingao, China.*
Estriol (p. 2274·3).
Atrophic vaginitis.

Yi Te An *Pu Luo Kang Yu, China.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Yi Ti Bi *Huayu, China.*
Isoniazid (p. 311·2); rifampicin (p. 350·3); pyrazinamide (p. 345·2).
Tuberculosis.

Yi Ti Xin *Hayao, China.*
Ceftezole sodium (p. 252·2).
Bacterial infections.

Yi Tian *Rundu Mintong, China.*
Itopride hydrochloride (p. 1850·1).
Vomiting; gastrointestinal motility disorders.

Yi Ting *San Lian, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Yi Tong *Handu, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Yi Wei *Sanye, China.*
Methionine (p. 1558·2); vitamin B_1 (p. 2102·3).

Yi Wei Kang *Yi Ao, China.*
Mecobalamin (p. 2108·1).
Megaloblastic anaemia; peripheral neuropathy.

Yi Wei Shi *Renrenkang, China.*
Acetylcysteine (p. 1652·2).
Respiratory-tract congestion.

Yi Wei Tuo *Meirui, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Yi Wei Xian *Xianju, China.*
Estradiol valerate (p. 2271·2); norethisterone (p. 2294·2).

Yi Xi Qing *Gaoxin, China.*
⊗Theophylline (p. 1229·3); salbutamol (p. 1220·2).
Obstructive airways disease.

Yi Xin *Ankehengyi, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Minsheng, China.
Cetylpyridinium chloride (p. 1743·1).

Runkang, China.
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Yi Xin Jian *Wanhui Shuanghe, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Yi Xin Jing *Sanjiu Yimin, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Yi Xing *Di Ao Jiu Hong, China.*
Interleukin-11 (human recombinant).

Yi Ya Ping *Yichun, China.*
Telmisartan (p. 1509·3).
Hypertension.

Yi Ya Xuan *Hong Yi, China.*
Nimesulide (p. 101·3).
Pain.

Yi Yang *SanJiu JiShi, China.*
Asarone.

Yi Yi *Pu Sheng, China.*
Enoxacin gluconate.
Bacterial infections.

Yi You *Chenji, China.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Yi You Li An *Dongfang Xiehe, China.*
Nateglinide (p. 492·1).
Diabetes mellitus.

Yi You Li Ning *Dongfang Xiehe, China.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Yi You Ning *Yabang, China.*
Nadifloxacin (p. 328·1).

Yi You Rui Kang *Dongfang Xiehe, China.*
Docetaxel (p. 780·3).
Malignant neoplasms.

Yi You Rui Xin *Dongfang Xiehe, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Yi Yu *Gerui, China.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Yi Yuan Sheng *Xidian, China.*
Ferrous sulfate (p. 2062·2); folic acid (p. 2063·1).

Yi Zhen Kang *Pude, China.*
Ranitidine hydrochloride (p. 1882·1).
Pathological gastric hypersecretory disorders; peptic ulcer; acid aspiration.

Yi Zhen Shi *Sanjiu Yimin, China.*
Fluconazole (p. 578·2).
Fungal infections.

Yi Zhi *Zaozhuang, China.*
Ethylenediamine diaceturate.

Yi Zhi Te *Rotam Reddy, China.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Yibang *Yabang, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Yibao *Wan Bang, China.*
⊗Erythropoietin (p. 1141·1).
Anaemia in renal failure.

YiBei *Huanuowei, China.*
Epidermal growth factor (human recombinant).

Yibida *Xingsha, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Yifangtong *Kawin, China; Qinwutian, China.*
Nabumetone (p. 97·1).
Osteoarthritis; rheumatoid arthritis.

Yifen *Tai Sheng, China.*
Flucloxacillin sodium (p. 299·2).
Bacterial infections.

YiFu
Note: this name may be used for preparations of different composition.
Huanuowei, China.
Epidermal growth factor (human recombinant).

Yifu
Note: this name may be used for preparations of different composition.
Kangnuo, China.
Lysine hydrochloride (p. 2079·3).

YiFuQing *Yung Shin, China.*
⊗Econazole nitrate (p. 577·3); triamcinolone (p. 1648·3).

YiHeng
Note: this name may be used for preparations of different composition.
Dayinhaiyang, China.
Epalrestat (p. 470·3).

Yiheng
Note: this name may be used for preparations of different composition.
Hayao, China.
Quinapril hydrochloride (p. 1480·2).
Hypertension; heart failure.

Yijikang *Xinbeijiang, China.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy.

YiKangNing *Baima, China.*
Anti-hepatitis B transfer factor (p. 2633·2).

Yiketing *Sine, China.*
Norethisterone (p. 2294·2); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Yilaifen *Qilu, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

YiLi *Xinan, China.*
Doxofylline (p. 1208·1).
Obstructive airways disease.

YiLin
Note: this name may be used for preparations of different composition.
ChangSheng Gene, China.
Interferon alfa-2a (human recombinant) (p. 989·2).

Yilin
Note: this name may be used for preparations of different composition.
Chia Tai, China.
Etidronate disodium (p. 1182·3).
Osteoporosis.

Yilishu *Dawnrays, China.*
Ranitidine hydrochloride (p. 1882·1); bismuth subcitrate potassium (p. 1822·1).
Peptic ulcer.

Yiluoze *Wan Bang, China.*
Pemetrexed disodium (p. 844·3).
Non-small cell lung cancer; malignant pleural mesothelioma.

YiMei *Qianhong, China.*
⊗Trypsin (p. 2635·2); pepsin (p. 2586·1); diastase (p. 2442·1); pancrelipase (p. 2580·1).

Yin Fu *Ge Dian Ren Fu, China.*
Incadronate disodium (p. 1185·3).

Yin Jia *Haixin, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Yin Ke Luo *Neptunus, China.*
Ginkgo biloba (p. 2512·3).
Angina pectoris; cerebral infarction.

Yin Li Da *XinShiDai, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone; osteoporosis.

Yin Pei Kang *Jin Si Li, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Yin Rui Qing *Guang Da, China.*
Enoxacin gluconate.
Bacterial infections.

Yin Shu *Kangya, China.*
Sultamicillin tosilate (p. 369·1).

Yin Si Da *Qilu, China.*
Indobufen (p. 1410·1).
Thrombotic disorders.

Yin Tai *Dikang, China.*
Boric acid (p. 2459·3).

Yin Te Kang *Jin Si Li, China.*
Interleukin-2 (human recombinant) (p. 810·1).

Yinchi *Beacons, Singapore.*
Anhydrous caffeine (p. 1203·3); paracetamol (p. 115·1); phenylephrine hydrochloride (p. 1672·3).

Ying Fan Shu *Treeful, China.*
Glucose (p. 2068·3); fructose (p. 2068·2).

Ying Fu Ning *Lanzhou Bio, China.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Ying Jia *Hongsheng, China.*
Gatifloxacin hydrochloride.
Bacterial infections.

Ying Lan *Qilu, China.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Ying Luo En *Kaiyuan, China.*
Pyritinol hydrochloride (p. 394·3).
Cerebrovascular disorders; mental function impairment.

Ying Qu *Qing Yu Tang, China.*
Cimetidine (p. 1827·1).

Ying Si Tiao *Healthcare Pharma, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder.

Ying Di Te *Youcare, China.*
Citicoline sodium (p. 2480·2); inosine (p. 2533·1).

Ying Te Fu Lu *Neptunus, China.*
An influenza vaccine (p. 2393·3).
Active immunisation.

Ying Te Kang Xin *Neptunus, China.*
Aldesleukin (p. 810·1).

Ying Tong *Runkang, China.*
Gastrodin.

Ying Yuan *Double-Crane, China.*
⊗An etherified starch (p. 1146·1).

Yingkangli *Sine, China.*
Colecalciferol (p. 2113·1).
Rickets.

Yingtaiqing *Simcere, China.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Yingxin MeiShu *Nanfang Yingxin, China.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Yinlishu *Baiyunshan, China.*
Cefprozil (p. 248·2).
Bacterial infections.

YiNuo *Ankehengyi, China.*
Benorilate (p. 29·1).
Pain.

YiPing *Lunan, China.*
Acipimox (p. 1290·2).
Hyperlipidaemias.

YiQing
Note: this name may be used for preparations of different composition.
Biochem, China.
Matrine.
Poly, China.
Aceglutamide (p. 2426·2).

Yira *Bayer, Neth.†; Bayer, Spain.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Yirala *Bayer, Austria.*
Drospirenone (p. 2269·1); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

Yirui *Jing Xin, China.*
Cisapride (p. 1831·3).
Reduced gastrointestinal motility; dyspepsia; gastro-oesophageal reflux.

Yisadin *Spefar, Venez.*
Erythromycin estolate (p. 291·2).
Bacterial infections.

Yisafer *Spefar, Venez.*
Ferrous gluconate (p. 2061·2).
Iron-deficiency anaemia.

Yisaipu *CP Guojian, China.*
Etanercept (p. 55·1).
Rheumatoid arthritis; ankylosing spondylitis; psoriasis.

YiShu *Shenlong, China.*
Pentoxifylline (p. 1465·3).
Peripheral vascular disorders.

YiShuang *Ou Yi, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1); dextromethorphan hydrobromide (p. 1660·1).

Yisu *Qilu, China.*
Buflomedil hydrochloride (p. 1328·3).
Cerebral and peripheral vascular disorders.

Yisuoman *Hisun, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure; myocardial infarction.

YiTai *Chia Tai, China.*
Zoledronic acid (p. 1192·3).
Osteolytic bone metastases.

YiTeAn *Hisun, China.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

YiTing *San Lian, China.*
Piracetam (p. 393·3).
Mental function impairment.

YiTong *Chia Tai, China.*
Gatifloxacin mesilate.
Bacterial infections.

Yitongxin *Donghai, China.*
Vitamin A (p. 2098·3); colecalciferol (p. 2113·1).
Vitamin A and D deficiency.

Yixide *Xincat, China.*
Ampicillin (p. 218·2).
Bacterial infections.

YiXin
Note: this name may be used for preparations of different composition.
Pude, China.
Arginine hydrochloride (p. 2049·1).
Qi Du, China.
Aceglutamide (p. 2426·2).
Zhongtai, China.
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Yixin
Note: this name may be used for preparations of different composition.
Winsunny, China.
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Yixinke *NCPC, China.*
Sirolimus (p. 1966·2).
Renal transplant rejection.

Yixinxue *Lisheng, China.*
Aspirin (p. 22·2).
Pain; fever; inflammation; thromboembolism prophylaxis.

Ylestrom *Bros, Gr.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Ylox *Fortbenton, Arg.*
Minoxidil (p. 1438·3).
Alopecia.

Y-Lut *Fahrenheit, Indon.*
Lutein (p. 2079·2).
Dietary supplement for healthy eye function.

Ymea
Note: this name may be used for preparations of different composition.
Chefaro, UK.
Soya (p. 2092·3); lupulus (p. 2546·1); cucurbita (p. 2489·2).
Menopausal disorders.

Yochimbin Spiegel *Solvay, Ukr.†*
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction; male climacteric.

Yocon *Glenwood, Austria; Palisades, Canad.†; Laboratorios Chile, Chile; Glenwood, Ger.; Glenwood, USA.*
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction.

Yocoral *Infarama, Belg.; Cevidra, Fr.*
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction.

Yodacua *Manuell, Mex.†*
Povidone-iodine (p. 1767·1).
Water purification.

Yodafar *Bial, Spain.*
Potassium iodide (p. 2336·3).
Iodine deficiency.

Yodine *Manuell, Mex.*
Povidone-iodine (p. 1767·1).
Infected burns, ulcers, or wounds; mouth and throat infections; seborrhoeic dermatitis; skin, mucous membrane, and instrument disinfection; skin infections; vaginal infections.

Yodiquer *Valomed, Spain.*
Potassium iodide (p. 2336·3).
Iodine deficiency.

Yodocefol *Italfarmaco, Spain.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); potassium iodide (p. 2336·3).
Iodine deficiency; folic acid and vitamin B_{12} deficiency; prevention of neural tube defects in pregnancy.

Yodofol *World Medicine, Ukr.*
Potassium iodide (p. 2336·3); folic acid (p. 2063·1).
Dietary supplement.

Yodolactina *Manuell, Mex.*
Iodocasein (p. 2336·3).
Tuberculosis; obstructive airways disease; immunostimulant; sclerosis; obesity; rheumatoid disorders; goitre.

Yodolin *Fada, Arg.*
Sodium picosulfate (p. 1887·2).
Constipation.

Yodoxin *Glenwood, USA.*
Diiodohydroxyquinoline (p. 931·1).
Intestinal amoebiasis.

Yodozona *Offenbach, Mex.*
Furazolidone (p. 933·3); clioquinol (p. 273·1); pectin (p. 2200·3); kaolin (p. 1850·1); homatropine methylbromide (p. 2007·3).
Diarrhoea.

Yodsaben *Nufarindo, Indon.†*
Salicylic acid (p. 1719·1); benzoic acid (p. 1738·2); iodine (p. 2336·3).
Fungal skin infections.

Yoduk *Recordati, Spain.*
Potassium iodide (p. 2336·3).
Iodine deficiency.

Yoduk Complex *Recordati, Spain.*
Cyanocobalamin (p. 2107·2); folic acid (p. 2063·1); potassium iodide (p. 2336·3).
Iodine deficiency; folic acid and vitamin B_{12} deficiency; prevention of neural tube defects in pregnancy.

Yofolvit *Italfarmaco, Spain.*
Folic acid (p. 2063·1); vitamin B_{12} (p. 2107·2); potassium iodide (p. 2336·3).
Dietary supplement in pregnancy.

Yohimbex-Garmonia *Borshchagovskii, Ukr.*
Yohimbine (p. 2372·3); ginseng (p. 2513·3); ascorbic acid (p. 2110·3); sodium selenite (p. 2087·1); zinc oxide (p. 1729·1).
Erectile dysfunction; loss of libido.

Yokel *Bros, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Yokuininto *Tsumura, Jpn.*
⊗Coix seed; atractylodes lancea rhizome; angelica acutiloba root (p. 2443·3); ephedra herb (p. 1663·1); cinnamon bark (p. 2479·2); peony root; liquorice (p. 1853·2).
Traditional Kampo medicine.

Yokukansan *Tsumura, Jpn.*
Atractylodes lancea rhizome; poria sclerotium; cnidium rhizome; uncaria hook; angelica acutiloba root (p. 2443·3); bupleurum root; liquorice (p. 1853·2).
Traditional Kampo medicine.

Yokukansankachimpihange *Tsumura, Jpn.*
Pinellia tuber; atractylodes lancea rhizome; poria sclerotium; cnidium rhizome; uncaria hook; citrus unshiu peel; angelica acutiloba root (p. 2443·3); bupleurum root; liquorice (p. 1853·2).
Traditional Kampo medicine.

Yolecol *Nycomed, Arg.*
Mesalazine (p. 1859·2).
Ulcerative colitis; anorectal disorders; proctitis.

Yomax
Note: this name may be used for preparations of different composition.
Apsen, Braz.
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction; orthostatic hypotension.
Actor, S.Afr.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Yomesan *Bayer, Belg.; Bayer, Ger.; IFET (ΙΦΕΤ), Gr.†; Bayer, Israel†; Bayer, Ital.; Bayer, Neth.; Bayer Schering, S. Afr.; Bayer, Swed.; Bayer, Thai.; Bayer, Turk.; IDIS, UK; Medisource, UK.*
Niclosamide (p. 161·2).
Cestode infections; taeniasis; diphyllobothriasis; hymenolepiasis.

Yomogi *Emonta, Austria; Ardeypharm, Ger.*
Saccharomyces cerevisiae (p. 2125·2).
Diarrhoea; acne.

Yonal *Arex, Venez.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).
Cough.

Yondelis *Janssen-Cilag, Arg.; Pharma Mar, Austria; Pharma Mar, Belg.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Pharma Mar, Cz.; Pharma Mar, Denm.; Pharma Mar, Fr.; Pharma Mar, Ger.; Pharma Mar, Gr.; Pharma Mar, Hung.; Pharma Mar, Irl.; Janssen-Cilag, Israel; Pharma Mar, Ital.; Pharma Mar, Neth.; Pharma Mar, Norw.; Pharma Mar, Pol.; Pharma Mar, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, Singapore; Pharma Mar, Spain; Swedish Orphan, Swed.; Pharma Mar, Switz.; Janssen-Cilag, Thai.; Pharma Mar, UK.*
Trabectedin (p. 874·3).
Soft-tissue sarcoma; ovarian cancer.

Yong Bang *Biochem, China.*
Diammonium glycyrrhizate (p. 2520·3).

Yong Qi *Shenlong, China.*
Azithromycin hydrochloride (p. 221·2).
Bacterial infections.

Yong Rui Neng *Jinfeng, China.*
Inosine (p. 2533·1).

Yong Xi *Yung Shin, China.*
Doxycycline hyclate (p. 288·2).
Bacterial infections.

Yong Xin *Yangtze River, China.*
Matrine.

Yonka *Andromaco, Chile.*
Potassium gluconate (p. 1793·2).
Hypokalaemia.

Yontal *Duncan, Arg.*
⊗Salbutamol (p. 1220·2).
Asthma.

Yosenob *Nufarindo, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

You Bi Da *Henghe, China.*
Flavoxate hydrochloride (p. 2360·1).
Urinary-tract disorders.

You Bu Ding *Xinlibang, China.*
⊗Bumetanide (p. 1329·1).
Oedema.

You Er Jian *Tian Yuan, China.*
Haemorrhagic fever with renal syndrome vaccine (p. 2388·2).
Active immunisation.

You Fu Lin *Rui Yang, China.*
Gastrodin.

You Jia *Topfond, China.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias.

You Jin *Tian Yao, China.*
⊗Methylprednisolone (p. 1642·2).
Corticosteroid.

You Jing An *Zhaoke, China.*
Interferon alfa-2b (human recombinant) (p. 989·2).

You Ka Dan *Renhe, China.*
Paracetamol (p. 115·1); amantadine hydrochloride (p. 890·3).

You Kang *Qing Hua Zi Guang Gu Han, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

You Ke Nuo *Baiyunshan, China.*
Cefaclor (p. 232·3).
Bacterial infections.

You Ke Xin *Renhe, China.*
Secnidazole (p. 947·3).
Amoebiasis; giardiasis; trichomoniasis.

You Ke Yi *Qing Hua Zi Guang, China.*
⊗Exemestane (p. 792·2).
Breast cancer.

You Lin Jia *Shengda, China.*
Amoxicillin (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

You Lun *Sanhome, China.*
Ornidazole (p. 943·1).
Anaerobic bacterial infections; amoebiasis.

You Ma Lin *C & O, China.*
Domperidone maleate (p. 1838·1).
Gastrointestinal disorders.

You Ni *Qing Hua Zi Guang, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

You Ni Le *Tong Yang Tong Meng, China.*
Calcium citrate malate (p. 1783·1).

You Ni An *Huatuo Tianya, China.*
Fluconazole (p. 578·2).
Fungal infections.

You Ni Da *Tong Yang Tong Meng, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

You Ni Ding *Tong Yang Tong Meng, China.*
Cimetidine (p. 1827·1).

You Ni Fen *Tong Yang Tong Meng, China.*
Granulocyte-macrophage colony-stimulating factor (human recombinant).

You Ni Kai *Tong Yang Tong Meng, China.*
Sodium glucuronate (p. 2517·1).

You Ni Ke *Tong Yang Tong Meng, China.*
Azithromycin (p. 221·2).
Bacterial infections.

You Ni Ling *Tong Yang Tong Meng, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

You Ni Long *Tong Yang Tong Meng, China.*
Interferon alfa-2b (human recombinant) (p. 989·2).

You Ni Ming *Tong Yang Tong Meng, China.*
Lysine hydrochloride (p. 2079·3).

You Ni Ping *Tong Yang Tong Meng, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

You Ni Qing *Tong Yang Tong Meng, China.*
Meglumine adenosine cyclophosphate.

You Ni Sheng *Tong Yang Tong Meng, China.*
Aceglutamide (p. 2426·2).

You Ni Shu *Tong Yang Tong Meng, China.*
A low molecular-weight heparin calcium.

You Ni Xin *Tong Yang Tong Meng, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

You Ni Xue *Tong Yong Tong Meng, China.*
Ferrous lactate (p. 2062·1).

You Ni Yi *Tong Yang Tong Meng, China.*
Ligustrazine phosphate.

You Ni Ze *Tong Yong Tong Meng, China.*
Ethylenediamine diaceturate.

You De Ning *Ou Yi, China.*
Nisoldipine (p. 1456·2).
Angina pectoris; hypertension.

You Nuo *Kangpu, China.*
Benzbromarone (p. 603·3).
Hyperuricaemia.

You Nuo An *Sanhome, China.*
Levornidazole.
Anaerobic bacterial infections.

You Nuo Ping *SanJiu, China.*
⊗Dexamethasone acetate (p. 1631·1).

You Peng *Huanqiu, China.*
Antofloxacin hydrochloride.

You Pu Luo Kang *Meida Kanghua, China.*
Levofloxacin hydrochloride.
Bacterial infections.

You Ruo *TianAn, China.*
Puerarin.

You Sai Le *Sainuo, China.*
Macrogol 4000 (p. 2547·3).

You Si Luo *Bikai, China.*
Cantharidin (p. 2469·2).

You Su *Yangtze River, China.*
Glimepiride (p. 473·2).
Diabetes mellitus.

You Suo Jin *Otsuka, China.*
Levofloxacin hydrochloride.
Bacterial infections.

You Tuo Xin *Huawei, China.*
Podophyllotoxin (p. 1717·1).
Anogenital warts.

You Xian *Kangpu, China.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

You Xin *Lunan, China.*
Citicoline sodium (p. 2480·2).
Brain injury; disturbances of consciousness.

You Yi Xin *Kangnuo, China.*
Lappaconitine hydrobromide (p. 1418·1).

Youbaifen *Condition, China.*
Dexketoprofen trometamol (p. 79·1).
Pain; inflammation.

Youbiqing *United Lab, China.*
Imiquimod (p. 985·2).
Anogenital warts.

Youdaling *Sine, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Youfei *Yimin, China.*
Oxazepam (p. 1092·2).
Anxiety; alcohol withdrawal syndrome.

Youheding *YSY, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Youkai *Xinbao, China.*
Urokinase (p. 1520·3).
Thromboembolic disorders.

Youke *Watson, China.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Youlexin *Chung-Hwa, China.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Youlifu *Changzhou Siyao, China.*
Crotamiton (p. 1699·2).
Scabies.

Youmin *Jida, China.*
Edaravone (p. 1370·2).
Neurological disorders following stroke.

Youngflex Massage 168 *Youngflex, Canad.*
Menthol (p. 2553·2); cajuput oil (p. 2464·1); eucalyptus oil (p. 2501·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

YouNiDi *Tong Yong Tong Meng, China.*
Ammonium glycyrrhizate (p. 2520·3); cysteine hydrochloride (p. 2058·3); glycine (p. 2071·2).

Your Choice *Amcon, USA.†*
Saline rinsing and storage solutions for soft contact lenses (p. 1795·1).

Youshu *Simcere, China.*
Sumatriptan succinate (p. 679·2).
Migraine.

Youthful Look *Faces, Canad.*
Octinoxate (p. 1715·1); oxybenzone (p. 1715·3); titanium dioxide (p. 1725·1).
Sunscreen.

Youtong *Watson, China.*
Leflunomide (p. 81·3).
Rheumatoid arthritis; psoriatic arthritis.

YouXin *Huahai, China.*
Indinavir sulfate (p. 986·1).
HIV infection.

Youzhouer *TianJin, China.*
⊗Hydrocortisone butyrate (p. 1640·1).
Skin disorders.

Youzuren S *Yoshindo, Jpn.*
Sodium gualenate (p. 1887·1); glutamine (p. 2070·3).
Peptic ulcer; gastritis.

Yovis *Sigma-Tau, Ital.*
Streptococcus salivarius subsp. thermophilus; *Bifidobacterium breve (p. 2596·3); Bifidobacterium infantis (p. 2596·3); Bifidobacterium longum (p. 2596·3); Lactobacillus acidophilus (p. 2596·3); Lactobacillus plantarum (p. 2596·3); Lactobacillus casei (p. 2596·3); Lactobacillus delbrueckii subsp. bulgaricus (p. 2596·3); Enterococcus faecium (p. 2596·3).*
Disturbance of gastrointestinal flora.

Yovita *Pharma Italia, Ital.*
Lactic-acid-producing organisms (p. 2596·3); vitamins.
Nutritional supplement; disturbances of the intestinal flora.

Yperod *Alapis, Gr.*
⊗Mometasone furoate (p. 1644·1).
Skin disorders.

Ypsila *KRKA, Hung.*
Ziprasidone bisulfate (p. 1115·2).
Schizophrenia; bipolar disorder.

Ypsiloheel *Heel, Cz.*
Asa foetida (p. 2449·3); strychnos ignatii (p. 2532·1); paris quadrifolia; thuja occidentalis (p. 2629·3); pulsatilla pratensis (p. 2600·2); lachesis mutus (p. 2538·3); moschus (p. 2198·2); glyceroli trinitras (p. 1391·2).
Homoeopathic preparation.

Ypsiloheel N *Heel, Ger.*
Asa foetida (p. 2449·3); ignatia (p. 2532·1); paris quadrifolia; thuja (p. 2629·3); pulsatilla (p. 2600·2); lachesis (p. 2538·3); glonoinum (p. 1391·2).
Homoeopathic preparation.

Yranicid Arsenical *Zizine, Fr.*
⊗Ephedrine hydrochloride (p. 1663·2); lidocaine (p. 1988·1); arsenic trioxide (p. 2448·1).
Dental disorders.

Yranicid sans Arsenic *Zizine, Fr.*
Lidocaine (p. 1988·1); paraformaldehyde (p. 1763·1).
Dental disorders.

Yranol Eugenole *Zizine, Fr.*
Lidocaine hydrochloride (p. 1988·2); creosote (p. 1659·3); phenol (p. 1763·3); eugenol (p. 2501·2).
Root canal infections.

Yris *Kwizda, Austria.*
Gestodene (p. 2279·3); ethinylestradiol (p. 2275·3).
Combined oral contraceptive.

YSE *Monin, Fr.†*
Zinc gluconate (p. 2126·2); kola (p. 2648·2).
Asthenia.

YSE Glutamique *Monin, Fr.†*
Zinc gluconate (p. 2126·2); glutamic acid (p. 2070·2).
Asthenia.

Ysol 206 *Rabi & Solabo, Fr.†*
Acetic acid (p. 2426·3); camphor (p. 2466·2); Java citronella oil (p. 2481·1); sodium laurilsulfate (p. 2210·3).
Pediculosis.

Ysomega *Pierre Fabre, Fr.*
Omega-3 marine triglycerides (p. 1460·3).
Hypertriglyceridaemia.

Ystheal *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.*
Retinaldehyde (p. 1719·1).
Photodamaged skin; pigmentation disorders; dry skin.

Ytracis *CIS, Cz.; CIS, Fr.; CIS, Hung.; CIS, Irl.; Bayer, Israel; CIS, Ital.; Cyclotron, Neth.; CIS, Pol.; CIS, Port.; CIS, Spain; CBI, Switz.; Schering, UK.*
Yttrium-90 (p. 2230·1).
Radiolabelling.

Yttriga *Eckert & Ziegler, Cz.; Eckert & Ziegler, Irl.; Eckert & Ziegler, Neth.; Eckert, Pol.; QSA, Port.; Nucliber, Spain.*
Yttrium-90 (p. 2230·1).
Radiolabelling.

Yu An Li Ke *Yuan, China.*
⊗Paracetamol (p. 115·1); pseudoephedrine hydrochloride (p. 1676·1).

Yu An Li Qing *Yuan, China.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Yu Chang *Jinchuang, China.*
Naftopidil (p. 2361·1).

Yu Chuan Tong *Feiying, China.*
Ticlopidine hydrochloride (p. 1512·1).
Thromboembolism prophylaxis.

Yu Da *Jiu Dian, China.*
Dirithromycin (p. 287·1).
Bacterial infections.

Yu Er *Huayu, China.*
Aluminium phosphate (p. 1818·3).
Peptic ulcer; gastritis; gastro-oesophageal reflux.

Yu Gan Ning *Tian Yuan, China.*
An influenza vaccine (split virion) (p. 2393·3).
Active immunisation.

Yu Ge *Yu Heng, China.*
Alprostadil (p. 2352·2).
Erectile dysfunction.

Yu Hai Xiang *Jinhaifa, China.*
Compound vitamin B_{12} (p. 2107·2).

Yu Hui Luo *Qi Du, China.*
Gamma-aminobutyric acid (p. 2509·2).

Yu Jie *Yu Heng, China.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Yu Jun Tai *Aiwei, China.*
Gatifloxacin mesilate.
Bacterial infections.

Yu Jun Xian *Pu Luo Kang Yu, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Yu Ka *Wei Kang, China.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).

Yu Kuai *Yu Heng, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Yu Lang *Jinchuang, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder; panic disorder; social phobia; premenstrual syndrome.

Yu Li *Yu Heng, China.*
Levocarnitine (p. 2053·2).

Yu Li Sen *Tian Yu, China.*
Ammonium glycyrrhetate; cysteine hydrochloride (p. 2058·3); ammonium glycyrrhizate (p. 2520·3).

Yu Li Xing *Lek, China.*
Levofloxacin hydrochloride or levofloxacin mesilate.
Bacterial infections.

Yu Lu An *Zhebei, China.*
Diammonium glycyrrhizate (p. 2520·3).

Yu Luo Shu *Kaiyuan, China.*
Diclofenac sodium (p. 48·3); lidocaine hydrochloride (p. 1988·2).

Yu Luo Tong *Kaiyuan, China.*
Nicardipine hydrochloride (p. 1445·2).
Angina pectoris; hypertension.

Yu Luo Xin *Luling, China.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorders; panic disorder; post-traumatic stress disorder; social phobia; premenstrual syndrome.

Yu Nao Ning *Tian Yuan, China.*
A meningococcal polysaccharide vaccine (groups A, C, W135, and Y) (p. 2401·3).
Active immunisation.

Yu Nao Ning A+C *Tian Yuan, China.*
A meningococcal polysaccharide vaccine (groups A and C) (p. 2401·3).
Active immunisation.

Yu Le Ning *Chung-Hwa, China.*
Telmisartan (p. 1509·3).
Hypertension.

Yu Ning *Yangtze River, China.*
Tinidazole (p. 949·2).
Anaerobic bacterial infections.

Yu Di Ning *Yaoyou, China.*
Aspartic acid (p. 2050·3); potassium (p. 1793·1); magnesium (p. 1786·3).

Yu Qi *Limin, China.*
Azithromycin lactobionate.
Bacterial infections.

Yu Shu *Yu Heng, China.*
Cefixime (p. 240·3).
Bacterial infections.

Yu Tian Qing *Rundu Mintong, China.*
Rabeprazole sodium (p. 1881·1).
Gastro-oesophageal reflux; pathological gastric hypersecretory disorders; peptic ulcer.

Yu Ting *Zizhu, China.*
Levonorgestrel (p. 2296·1).
Postcoital oral contraceptive.

Yu Tong *Nanfang Yingxin, China.*
Tramadol hydrochloride (p. 139·2).
Pain.

Yu Wu Tai *Shuang Cheng, China.*
Diclofenac sodium (p. 48·3); lidocaine hydrochloride (p. 1988·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Yu You Ding *Huayu, China.*
Urapidil (p. 1520·2).
Hypertension; heart failure.

Yuan Ce Su *YuanCe, China.*
Interferon alfa-2b (human recombinant) (p. 989·2).

Yuan Ce Xin *YuanCe, China.*
Interleukin-2 (125Ala) (p. 810·1).

Yuan Fu *Binhu Shuanghe, China.*
Nifedipine (p. 1447·2).

Yuan Gan *Li Jie Xun, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Yuan Qi *Zhuoyikangna, China.*
⊗Sotalol hydrochloride (p. 1498·2).
Arrhythmias.

Yuan Sheng Li Wei *Kaikai Yuansheng, China.*
Trimebutine maleate (p. 2634·1).
Irritable bowel syndrome; gastritis.

Yuan Shou *Yuanshou, China.*
Bacillus cereus.

Yuan Shun *Huanghai, China.*
⊗Paracetamol (p. 115·1); caffeine (p. 1203·3); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).

Yuan Tan *HuaXia, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Yuan Ting *San Lian, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Yuan Tuo *Ba Da, China; Luye, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Yuan Zhi *HuaXia, China.*
Benidipine hydrochloride (p. 1316·1).
Angina pectoris; hypertension.

YuanJie *Luye, China.*
Meglumine adenosine cyclophosphate.

YuanQi *Li Jie Xun, China.*
Naproxen sodium (p. 98·2).
Pain.

Yuanrui *Yangtze River, China.*
Cefprozil (p. 248·2).
Bacterial infections.

Yucca Complexe No 110 *Lehning, Fr.*
Yucca (p. 2649·3); carduus marianus (p. 1561·1); chelidonium (p. 2522·2); taraxacum (p. 2625·3); lycopodium (p. 2546·3); nux vomica (p. 2573·3); artemesia absinthium (p. 2426·1); aloe (p. 1816·1).
Homoeopathic preparation.

Yucomy *YSP, Malaysia; Yung Shin, Singapore.*
Ketoconazole (p. 585·3).
Fungal infections.

Yucro *Renovati, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Yudinef *Yuhan, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Yue Bao *Xinghu, China.*
Adefovir dipivoxil (p. 967·1).
Chronic hepatitis B.

Yue Bo *Sanhome, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Yue Da Ning *Youcare, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Yue Kang Xian *Kexing, China.*
Interleukin-2 (human recombinant) (p. 810·1).

Yue Ke *ZhongTian, China.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Yue Min Xing *Dongle, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Yue Nan Shan *Pacific, China.*
⊗Indapamide (p. 1409·2).
Hypertension; heart failure.

Yue Ting *Wan Te, China.*
Bupropion hydrochloride (p. 408·2).
Depression; aid to smoking withdrawal.

Yueketing *Zizhu, China.*
Levonorgestrel (p. 2296·1); quinestrol (p. 2303·1).
Combined oral contraceptive.

Yuelai *Xinzheng, China.*
Glipizide (p. 474·1).
Diabetes mellitus.

Yugofin *Medichrom, Gr.*
⊗Clobetasol propionate (p. 1627·1).
Skin disorders.

Yugorex *Medichrom, Gr.*
Mebeverine hydrochloride (p. 1858·3).

Yugovasin *Medichrom, Gr.*
Dihydroergotamine mesilate (p. 672·2).

Yugoxil *Elin, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Yun Di En *Longjin, China.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Yun Ke Di *Yunzhong, China.*
Levofloxacin lactate.
Bacterial infections.

Yun Ke Shu *Yunzhong, China.*
Aceglutamide (p. 2426·2).

Yun Sheng *Huakang, China.*
Oxymatrine.

Yun Tai *Lukang Medicine, China.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Yunir *Eurodrug, Mex.*
Pinazepam (p. 1097·3).
Insomnia; anxiety; skeletal muscle spasm; epilepsy; alcohol withdrawal syndrome; premedication.

Yuredol *Grossman, Mex.*
Cyclobenzaprine hydrochloride (p. 2023·1); clonixin lysine (p. 40·1).
Skeletal muscle spasm and pain.

Yurelax *Meda, Spain.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Skeletal muscle spasm.

Yusin *Maigal, Arg.*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion; eye irritation.

Yusin Tears I *Maigal, Arg.*
Sodium chloride (p. 1795·1).
Dry eyes.

Yusin Tears II *Maigal, Arg.*
Sodium chloride (p. 1795·1); hyaluronic acid (p. 2526·2).
Dry eyes.

Yutopar *Galenica, Gr.; Solvay, India; Solvay, Indon.; Durbin, UK.†*
⊗Ritodrine hydrochloride (p. 2145·1).
Premature labour; fetal distress.

Yuyo *Incaico, Arg.*
Senna (p. 1885·1); chamomile (p. 2474·1); sambucus (p. 2609·3).
Constipation; digestive disorders.

Yvano *Rafarm, Gr.*
⊗Timolol maleate (p. 1513·2); pilocarpine hydrochloride (p. 2010·3).
Glaucoma.

Yvidually *Bayer, Neth.*
Drospirenone (p. 2269·1); ethinylestradiol betadex clathrate (p. 2275·3).
Combined oral contraceptive.

3Z *Jaba Recordati, Port.*
Azithromycin (p. 221·2).
Bacterial infections.

Z Frin *Grin, Mex.*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).
Eye disorders.

Zaarpress *Sigma, Braz.*
Losartan potassium (p. 1422·2).
Hypertension.

Zaarpress HCT *Sigma, Braz.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Zaart *Cipla, Hong Kong; Cipla, India.*
Losartan potassium (p. 1422·2).
Hypertension.

Zaart-H *Cipla, India.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zabak *Thea, Cz.; Thea, Port.; Thea, Switz.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Zabart *Vir, Port.†; Vir, Spain.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zabel *Alphapharm, Austral.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Zaby *Alapis, Gr.; Rafarm, Gr.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Zabysept *Rafarm, Gr.*
⊗Naphazoline nitrate (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.

Zabytrex *Rafarm, Gr.*
Cefalexin (p. 234·1).
Bacterial infections.

ZAC *Ikapharmindo, Indon.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Zacalen *Farmazak, Gr.*
Venlafaxine hydrochloride (p. 454·2).
Depression; anxiety; social phobia; panic disorder.

Zacare Kit *Hawthorn, USA.*
Cleansing lotion, benzoyl peroxide (p. 1696·1) (Zaclir); topical gel, sodium hyaluronate (p. 2526·2) (Hylira).
Acne.

Zacef *Borshchagovskii, Ukr.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zacetin *Medica Korea, Singapore.*
Alprazolam (p. 1035·2).
Anxiety; mixed anxiety depressive states.

Zacidate *Medico Uno, Neth.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy.

Zacin *Lavipharm, Gr.; Cephalon, Irl.; Cephalon, UK.*
Capsaicin (p. 35·1).
Osteoarthritis; musculoskeletal and joint pain.

Zaclir *Hawthorn, USA.*
Benzoyl peroxide (p. 1696·1).
Acne.

Zacnan *Merck Serono, Fr.†*
Minocycline hydrochloride (p. 325·1).
Bacterial infections.

Zacne *Bial, Port.†*
Benzoyl peroxide (p. 1696·1); miconazole nitrate (p. 589·1).
Acne.

Zacofalk *Falk, Ukr.*
Calcium butyrate; inulin (p. 2534·3).
Dietary supplement.

Zacosteo *Farmazak, Gr.*
Glucosamine hydrochloride (p. 2515·3).
Osteoarthritis of the knee.

ZacPac *Abbott, Ger.; Nycomed, Ger.*
Tablets, pantoprazole sodium (p. 1875·3); tablets, amoxicillin trihydrate (p. 216·2); tablets, clarithromycin (p. 266·2).
Peptic ulcer.

Zactin *Alphapharm, Austral.; Alphapharm, China; Merck, Indon.†; Alphapharm, Singapore.*
Fluoxetine hydrochloride (p. 417·1).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder; bulimia nervosa; premenstrual syndrome; panic disorder.

Zactos *Lilly, Mex.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Zadaxin *Oriental, Arg.; SciClone, China; SciClone, Hong Kong; SciClone, Indon.; Tempo Scan Pacific, Indon.; SciClone, Ital.; SciClone, Malaysia; Columbia, Mex.; Getz, Philipp.; SciClone, Rus.; SciClone, Singapore; SciClone, Thai.*
Thymalfasin (p. 2630·1).
Immunomodulator; chronic hepatitis B; chronic hepatitis C; adjuvant in influenza and hepatitis B vaccination; adjuvant in chemotherapy-induced immunosuppression.

Zadec *Novartis, Philipp.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic disorders.

Zad-G *Gufic, India.*
Zinc sulfate (p. 2126·2); sulfadiazine sodium (p. 361·3).
Bacterial skin infections.

Zadim *Karnataka, Philipp.; Samarth, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zadine
Note: this name may be used for preparations of different composition.
UCI, Braz.
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Schering-Plough, Austral.†
Azatadine maleate (p. 616·3).
Hypersensitivity reactions; vasomotor rhinitis.

Zadino *Milano, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Zaditen *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Defiante, Belg.; Novartis, Braz.; Teva, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Thea, Fin.; Novartis, Fr.; Sigma-Tau, Ger.; Thea, Ger.; Defiante, Gr.; Thea, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Defiante, Ital.; Alcon, Jpn; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Sigma-Tau, Neth.; Thea, Neth.; Thea, Norw.; Novartis, NZ; Novartis, Philipp.; Sandoz, Philipp.; Novartis, Port.; Novartis, Rus.; Adcock Ingram, S.Afr.; Novartis, S.Afr.; Alcon, Singapore; Novartis, Singapore; Thea, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; Alcon, Thai.; Novartis, Turk.; Spectrum, UK; Swedish Orphan, UK; Novartis, Ukr.; Novartis, Venez.*
Ketotifen fumarate (p. 631·3).
Asthma; allergic conjunctivitis; allergic rhinitis; allergic skin disorders; eczema; pruritus; urticaria; bronchitis; hypersensitivity reactions; allergic rhinoconjunctivitis.

Novartis, Pol.
Ketotifen (p. 631·3) or ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Zaditor *Aurium, Canad.; Novartis, USA.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Zadivonal *Rayere, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zadolina *Salus, Mex.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zadorin *Mepha, Switz.*
Doxycycline hyclate (p. 288·2).
Bacterial infections; malaria.

Zaf *Alpharma, Mex.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Zafen *Zambon, Neth.*
Ibuprofen arginine (p. 68·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Zambon, Port.
Ibuprofen (p. 68·2).

Zafibral *Medochemie, Singapore.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Zafidol *Zafiro, Mex.*
Ketorolac trometamol (p. 80·2).
Pain.

Zafil *Sandoz, Hong Kong.†*
Fexofenadine hydrochloride (p. 629·1).
Allergic rhinitis; urticaria.

Zafimida *Zafiro, Mex.*
⊗Furosemide (p. 1387·1).
Oedema; forced diuresis; hypertension.

Zafin *Saval, Chile.*
Paracetamol (p. 115·1); tramadol hydrochloride (p. 139·2).
Pain.

Zafira *2care4, Denm.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne and hirsutism in women.

Zafiron *Adamed, Pol.; Adamed, Ukr.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease.

Zafirst *Chiesi, Ital.*
Zafirlukast (p. 1239·3).
Asthma.

Zafitral *Rafarm, Gr.*
Risperidone (p. 1103·2).
Psychoses.

Zagapsol *Aspen, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zagorine *Rafarm, Gr.; Santa, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zagyl *Xixia, S.Afr.†*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Zahnkügelchen *Jacoby, Austria.*
Calcium carbonicum (p. 1824·3); calcium fluoratum (p. 2053·1); calcium phosphoricum (p. 1784·2); chamomilla (p. 2474·1); ferrum phosphoricum (p. 2077·1); podophyllum peltatum (p. 1717·1).
Homoeopathic preparation.

Zahnungstropfen Escatitona *Madaus, Ger.*
Apis mellifica (p. 2445·2); chamomilla (p. 2474·1); cuprum (p. 2057·1); mercurius solub. (p. 2555·3); gelsemium (p. 2511·2).
Homoeopathic preparation.

Zahron *Adamed, Cz.; Adamed, Pol.*
Rosuvastatin calcium (p. 1488·2).
Hypercholesterolaemia.

Zai An Lie *Rongtai, China.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Zai Chang *Simcere, China.*
Naftopidil (p. 2361·1).
Benign prostatic hyperplasia.

Zai Li Ke *Simcere, China.*
Arbidol.

Zai Lin *Simcere, China.*
Amoxicillin (p. 216·2).
Bacterial infections.

Zai Sheng *Huayu, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; hypertension; myocardial infarction.

Zai Shun *Jurong, China.*
Guaifenesin (p. 1666·2); dextromethorphan hydrobromide (p. 1660·1).

Zai Wo *Jinling, China.*
Cefixime (p. 240·3).
Bacterial infections.

Zaijia *Cuccess, China.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris; heart failure.

Zaikang *Simcere, China.*
Ibuprofen (p. 68·2); zinc gluconate (p. 2126·2); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Zaike *Simcere, China.*
Cefaclor (p. 232·3).
Bacterial infections.

Zaiqi *Simcere, China.*
Azithromycin (p. 221·2).
Bacterial infections.

ZaiXing *Huayang, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Zakofin *Farmazak, Gr.*
Terbinafine hydrochloride (p. 593·3).
Fungal nail and skin infections.

Zakondronate *Farmazak, Gr.†*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Zalain *Temis, Arg.; Pharmacia, Braz.†; Andromaco, Chile; Ferrer, China; Ferrer, Hong Kong; Egis, Hung.; Metro, Philipp.; Egis, Rus.; Ferrer, Singapore; Robert, Singapore; Ferrer, Spain; Ferrer, Thai.; Adeka, Turk.; Egis, Ukr.; Leti, Venez.*
Sertaconazole nitrate (p. 593·2).
Fungal and Gram-positive bacterial vaginal infections; fungal skin and nail infections.

Zalaïn *Trommsdorff, Ger.*
Sertaconazole nitrate (p. 593·2).
Fungal skin infections.

Zalanzo *Temapharm, Pol.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zalarlos comp *Actavis, Cz.; Actavis, Denm.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zalasta *KRKA, Cz.; KRKA, Denm.; KRKA, Ger.; TAD, Ger.; KRKA, Gr.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.; KRKA, Rus.; KRKA, Spain; KRKA, Swed.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder; mania.

Zalbu *Innova, Thai.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma; bronchospasm.

Zaldaks *Ilacsan, Turk.*
Paracetamol (p. 115·1).
Pain; fever.

Zaldiar *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Fr.; Grunenthal, Ger.; Grunenthal, Gr.; Grunenthal, Hung.; Pharos, Indon.; Tec-O-Pharm, Israel; Grunenthal, Mex.; Grunenthal, Neth.; Grunenthal, Pol.; Grunenthal, Port.; Grunenthal, Rus.; Grunenthal, Spain; Grunenthal, Switz.; Abdi, Turk.; Grunenthal, Ukr.; Grunenthal, Venez.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Zaledor *Medipharm, Chile.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zaledor-P *Medipharm, Chile.*
Tramadol hydrochloride (p. 139·2); paracetamol (p. 115·1).
Pain.

Zalep *Cipla, India.*
Zaleplon (p. 1114·3).
Insomnia.

Zalepin *Iasis, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zalerg *Thea, Denm.; Thea, Fr.*
Ketotifen fumarate (p. 631·3).
Allergic conjunctivitis.

Zalipan *Demo, Gr.*
Piracetam (p. 393·3).

Zalit *Regiomedica, Neth.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy.

Zallyre *Europhta, Mon.†*
Sodium cromoglicate (p. 1225·3).
Allergic eye disorders.

Zalor *Alkem, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Zaloxy *Pharmachem, S.Afr.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Zalpen *YSS, Philipp.*
Benzathine benzylpenicillin (p. 227·2).
Bacterial infections.

Zalsterim *Welding, Neth.*
Zolmitriptan (p. 682·2).
Migraine.

Zaltrap *Sanofi-Aventis, Neth.; Sanofi-Aventis, Switz.; Sanofi, UK; Regeneron, USA.*
Ziv-aflibercept (p. 736·2).
Colorectal cancer.

Žaludeční Čajová Směs *Megafyt-R, Cz.*
Absinthium (p. 2426·1); achillea (p. 2427·3); peppermint leaf (p. 1877·1); lovage root (p. 2545·3); St John's wort (p. 449·1); liquorice (p. 1853·2); fennel (p. 2503·2).
Digestive disorders.

Zalulin *Alkem, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zalux *Laboratorios Chile, Chile.*
⊗Modafinil (p. 2327·2).
Narcoleptic syndrome; idiopathic hypersomnia.

Zalvor *GSK, Belg.; GSK, Turk.*
Permethrin (p. 2159·3).
Pediculosis; scabies.

Zalvos *Demo, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2) or ciprofloxacin lactate (p. 261·2).
Bacterial infections.

Zam *Medicine Products, Thai.*
Diazepam (p. 1063·2).

Zamacort *Aventis, Mex.†*
⊗Triamcinolone acetonide (p. 1649·1).
Asthma.

Zamadol *Bergamo, Braz.; Meda, Irl.†; Meda, Swed.†; Meda, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zamalin *Rafarm, Gr.*
Cefprozil (p. 248·2).
Bacterial infections.

Zamanon *Sanofi-Aventis, S.Afr.*
Dolasetron mesilate (p. 1837·2).
Nausea and vomiting.

Zamboprim *Vamsler, Philipp.†*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Zam-Buk *Roche, S.Afr.*
Eucalyptus oil (p. 2501·2); camphor (p. 2466·2); thyme oil (p. 2630·3); sassafras oil (p. 2610·3).
Wounds; burns; pruritus; chapped hands; insect bites; muscular pain.

Zameg *Helm, Port.†*
Trazodone hydrochloride (p. 451·1).
Depression.

Zamel *Novell, Indon.*
Vitamins; minerals; choline (p. 2055·2); inositol (p. 2533·2); lysine (p. 2079·3); glutamine (p. 2070·3).
Dietary supplement for children.

Zamene *Menarini, Spain.*
⊗Deflazacort (p. 1629·3).
Corticosteroid.

Zamenit *Unipharma, Gr.*
Calcium folinate (p. 2066·3).
Folic acid deficiency; antidote to folic acid antagonists.

Zametrixal *Ferakon, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Zamicet *Hawthorn, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Zamil *Mylan, Denm.*
Olanzapine (p. 1089·3).
Schizophrenia; mania; bipolar disorder.

Zamol *Helm, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zamotil *Mylan, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zamudol *Meda, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zamur *Mepha, Pol.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zanacodar *PharmaSwiss, Cz.; Liconsa, Irl.; Liconsa, Neth.*
Telmisartan (p. 1509·3).
Hypertension; cardiovascular risk reduction.

Zanaflex *Paladin, Canad.; Cephalon, Irl.; Cephalon, UK; Acorda, USA.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasticity.

Zanamet *TO-Chemicals, Thai.*
Ranitidine (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Zandid *Kocak, Turk.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zandil *Therapharma, Philipp.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Zandixin *Lukang Chenxin, China.*
Cefodizime sodium (p. 242·2).
Bacterial infections.

Zanedip *Orifarm, Denm.†; Recordati, Ital.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zaneril *Meda, Ger.; Recordati, Gr.; Pharmaplan, S.Afr.*
Lercanidipine hydrochloride (p. 1419·3); enalapril maleate (p. 1371·1).
Hypertension.

Zan-Extra *Abbott, Austral.*
Lercanidipine hydrochloride (p. 1419·3); enalapril maleate (p. 1371·1).
Hypertension.

Zanextra *Bouchara-Recordati, Fr.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanfel *Zanfel, USA.*
Polyethylene granules (p. 1690·3) in a surfactant base.
Urushiol-induced contact dermatitis.

Zanic *Niche, Denm.*
Tizanidine hydrochloride (p. 2026·2).
Spasticity.

Zanicombo *Zambon, Belg.; Recordati, Cz.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanicor *Delta, Port.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanidex *Dexcel, Israel.†*
Ranitidine hydrochloride (p. 1882·1).
Gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer.

Zanidip *Abbott, Austral.; Kwizda, Austria; Zambon, Belg.; Medley, Braz.; Andromaco, Chile†; Recordati, China; Meda, Denm.; Leiras, Fin.; Bouchara-Recordati, Fr.; Galenica, Gr.; Recordati, Hong Kong; Kwizda, Hung.; Solvay, Indon.; Recordati, Irl.; Recordati, Malaysia; Sanfer, Mex.; Meda, Norw.; Abbott, NZ; Solvay, Philipp.; Jaba Recordati, Port.; Pharmaplan, S.Afr.; Recordati, Spain; Meda, Swed.; Robapharm, Switz.; Abbott, Thai.; Recordati, UK; Recordati, Ukr.; Elmor, Venez.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanipram *Vocate, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression.

Zanipress *Recordati, Denm.; Recordati, Fin.; Recordati, Ger.; Meda, Norw.; Jaba Recordati, Port.; Recordati, Spain; Robapharm, Switz.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanipril *Recordati, Austria.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanisor *Diba, Mex.*
Isosorbide dinitrate (p. 1412·2).

Zanitek *Recordati, Port.*
Enalapril maleate (p. 1371·1); lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zanlan *Sandoz, Fin.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Zanlytab *AAA, Denm.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux.

Zanoc *Delta, Braz.*
Ketoconazole (p. 585·3).
Fungal infections; seborrhoeic dermatitis.

Zanocin *Nanxin, China; Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Mex.†; Ranbaxy, Rus.; Ranbaxy, S.Afr.; Ranbaxy, Ukr.*
Ofloxacin (p. 334·3).
Bacterial infections.

Zanopro *Clonmel, Irl.*
Latanoprost (p. 2008·1).
Glaucoma; ocular hypertension.

Zanopro Plus *Clonmel, Irl.*
⊗Latanoprost (p. 2008·1); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Zanosar *Pfizer, Canad.; CSP, Fr.; IFET (ΙΦΕΤ), Gr.; Pfizer, Israel†; Pfizer, Switz.†; Gensia, USA.*
Streptozocin (p. 858·3).
Malignant neoplasms.

Zanovic *Virgo, Philipp.*
Mefenamic acid (p. 85·3).
Musculoskeletal and joint disorders; pain.

Zanoxina *Decomed, Port.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; anxiety; post-traumatic stress disorder.

Zanprex *Shine, Philipp.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zanprol *Omega, UK.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux.

Zantac *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; McNeil Consumer, Canad.; GSK, Chile; GSK, China; GSK, Cz.†; GSK, Denm.; GSK, Fin.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; Boehringer Ingelheim, USA; GSK, USA; GSK, Venez.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; gastrointestinal haemorrhage; acid aspiration;

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

dyspepsia; gastric hyperacidity; gastric hypersecretion including Zollinger-Ellison syndrome; gastritis; duodenitis; heartburn; pancreatitis.

GSK, Arg.
Ranitidine (p. 1882·1) or ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Zantadin *Soho, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; hypertrophic gastritis; duodenitis.

Zantic *GSK Consumer, Ger.; GSK, Switz.*
Ranitidine hydrochloride (p. 1882·1).
Gastric hyperacidity; heartburn; peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; dyspepsia; acid aspiration.

Zantidon *Siam Bheasach, Thai.*
Ranitidine (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zantifar *Ifars, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Zantin *Bryntsalov, Rus.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration.

Zantipres *FIRMA, Ital.*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

Zantipride *FIRMA, Ital.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zantol *Duopharma, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Gastro-oesophageal reflux; peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Zantron *Pyridam, Indon.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zanzipik *Alckamed, Ital.*
Insect repellent.

Zao Er Kang *Zaozhuang, China.*
Sodium ferulate.

Zaolin *Farmazak, Gr.*
Vinorelbine tartrate (p. 885·3).
Non-small cell lung cancer; breast cancer; prostatic cancer.

ZAP
Note: this name may be used for preparations of different composition.
Germiphene, Canad.
Benzocaine (p. 1980·2); tetracaine hydrochloride (p. 1996·3).
Local anaesthesia.

Zap
Note: this name may be used for preparations of different composition.
Pendopharm, Canad.
Star anise oil (p. 2622·2).
Pediculosis.

Zapain *Goldshield, UK.*
Paracetamol (p. 115·1); codeine phosphate (p. 40·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain.

ZapAn *Icon, Philipp.†*
Mefenamic acid (p. 85·3).
Pain.

Zapatabs *Medis, Denm.†*
Mirtazapine (p. 436·1).
Depression.

Zapedia *Pascual, Philipp.†*
Pyrazinamide (p. 345·2).
Tuberculosis.

Zapex
Note: this name may be used for preparations of different composition.
Sun, Mex.
Mirtazapine (p. 436·1).
Depression.

Zapil *Daquimed, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Zapilux *Sandoz, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zapine *Taiwan Biotech, Malaysia.*
Clozapine (p. 1057·3).
Schizophrenia.

Zapinex *Andromaco, Chile.*
Olanzapine (p. 1089·3).
Psychoses.

Zap-It *Melaleuca, Canad.†*
Salicylic acid (p. 1719·1).
Skin disorders.

Zaplon *Torrent, India.*
Zaleplon (p. 1114·3).
Insomnia.

Zaponex *Ivax, UK.*
Clozapine (p. 1057·3).
Schizophrenia; psychoses in parkinsonism.

Zappa *Trima, Israel.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zappelin N *Iso, Ger.*
Chamomilla (p. 2474·1); kalium phosphoricum (p. 1790·3); staphisagria; valeriana (p. 2640·2).
Homoeopathic preparation.

Zaprace *Ranbaxy, China.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Zaprace-D *Nanxin, China.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zapril *Mylan, NZ.*
Cilazapril (p. 1336·2).
Heart failure; hypertension.

Zaprilis *Actavis, Fr.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria.

Zaprine *Sandoz, S.Afr.*
Azathioprine (p. 1940·3).
Transplant rejection; auto-immune disorders.

Zapris *Alter, Spain.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zaprol *Poliformа, Ital.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zaprym *Krewel, Denm.†*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zapto *Aspen, S.Afr.*
Captopril (p. 1331·2).
Hypertension; heart failure.

Zapto Co *Aspen, S.Afr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zaptrol *Mugi, Indon.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

ZapTron *Ratiopharm, Cz.†*
Galantamine hydrobromide (p. 391·3).
Alzheimer's disease.

Zarah *Watson, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); drospirenone (p. 2269·1); 7 tablets, inert.
Combined oral contraceptive.

Zaranta *Richter, Pol.*
Rosuvastatin calcium (p. 1488·2).
Hyperlipidaemias.

Zarator *Phoenix, Arg.; Wyeth, Braz.; Pfizer, Chile; Pfizer, Denm.; Win Medica, Gr.; Pfizer, Port.; Parke, Davis, Spain.*
Atorvastatin calcium (p. 1309·2).
Hyperlipidaemias; cardiovascular risk reduction; hypercholesterolaemia.

Zarcad *Frezyderm, Gr.*
Benzoyl peroxide (p. 1696·1); erythromycin (p. 291·2).
Acne.

Zarcop *Mintlab, Chile.*
Doxylamine succinate (p. 627·3).
Insomnia.

Zardil *Unison, Thai.†*
Ranitidine (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Zarelis *Italfarmaco, Ital.; Italfarmaco, Spain.*
Venlafaxine hydrochloride (p. 454·2).
Depression; social phobia.

Zarelix *Italfarmaco, Port.*
Venlafaxine hydrochloride (p. 454·2).
Depression; panic disorder.

Zargus *Biosintetica, Braz.*
Risperidone (p. 1103·2).
Psychoses.

Zaricort *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Fungal skin infections with inflammation.

Zaridex *Dexcel, Israel.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux.

Zarin *Tack Fung, Hong Kong†; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Miconazole nitrate (p. 589·1).
Fungal infections of the skin, nails, and mucous membranes.

2Zaris *Zydus Cadila, Philipp.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zariviz *Sanofi-Aventis, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Zarmol *Demo, Gr.*
Bicalutamide (p. 749·1).
Prostatic cancer.

Zarnat *Corbridge, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension.

Zarocs *Pharmazam, Spain.†*
Roxatidine acetate hydrochloride (p. 1884·3).
Gastro-oesophageal reflux; peptic ulcer.

Zarom *Pyridam, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Zarondan *Pfizer, Denm.*
Ethosuximide (p. 521·1).
Absence seizures.

Zarontin *Elea, Arg.; Pfizer, Austral.; Pfizer, Belg.; Erfa, Canad.; Pfizer, Fr.; IFET (ΙΦΕΤ), Gr.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, NZ; Pfizer, S.Afr.; Pfizer, UK; Parke, Davis, USA.*
Ethosuximide (p. 521·1).
Absence seizures; myoclonic seizures; epilepsy.

Zarosen *Cetylite, Canad.†*
Strontium chloride (p. 2623·1).

Zaroxolyn *Sanofi-Aventis, Canad.; UCB, Hong Kong; UCB, Israel; Teofarma, Ital.; UCB, USA.*
⊗Metolazone (p. 1434·1).
Oedema; hypertension.

Zarquin *Farmasintez, Rus.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Zartan
Note: this name may be used for preparations of different composition.
Pharma Dynamics, S.Afr.
Losartan (p. 1422·2).
Hypertension.

Zartan Co *Pharma Dynamics, S.Afr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zarten *Integrated Pharmaceutical, Philipp.*
Losartan potassium (p. 1422·2).
Hypertension; diabetic nephropathy.

Zarv *Ativus, Braz.*
Aesculus (p. 2431·2).
Haemorrhoids.

Zarzio *Sandoz, Austria; Sandoz, Belg.; Sandoz, Cz.; Sandoz, Denm.; Sandoz, Fr.; Sandoz, Gr.; Sandoz, Hung.; Sandoz, Irl.; Sandoz, Neth.; Sandoz, Norw.; Sandoz, Pol.; Sandoz, Port.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Switz.; Sandoz, UK.*
Filgrastim (p. 1151·3).
Neutropenia; mobilisation of peripheral blood progenitor cells.

Zaso *Cadila, India.*
Zaleplon (p. 1114·3).
Insomnia.

Zasten *Novartis, Spain.*
Ketotifen (p. 631·3).
Asthma; allergic rhinitis.

Zasterid *Richter, Pol.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Zatin *Wermar, Mex.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Zatium *Merck Serono, Arg.; Merck, Chile.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Zatrol *Andromaco, Chile.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zauris *Crinos, Ital.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Zavedos *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Carlo Erba, Turk.; Deva, Turk.; Pfizer, UK; Actavis, Ukr.; Pfizer, Venez.*
Idarubicin hydrochloride (p. 805·2).
Malignant neoplasms.

Zavesca *Actelion, Austral.; Actelion, Austria; Actelion, Belg.; Actelion, Braz.; Actelion, Canad.; Actelion, Cz.; Actelion, Denm.; Actelion, Fin.; Actelion, Fr.; Actelion, Ger.; Actelion, Gr.; Actelion, Hung.; Actelion, Irl.; Oxford Glycosciences, Israel; Actelion, Ital.; Actelion, Neth.; Actelion, Norw.; Healthcare Logistics, NZ; Actelion, Pol.; Actelion, Port.; Actelion, Spain; Actelion, Swed.; Actelion, Switz.; Actelion, UK; Actelion, USA.*
Miglustat (p. 2559·3).
Gaucher disease; Niemann-Pick disease type C.

Zaveska *Actelion, Rus.*
Miglustat (p. 2559·3).
Gaucher disease; Niemann-Pick disease type C.

Zaxan *Intermed, Gr.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).

Zaxinat *Columbia, Mex.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zaxine *Madaus, Spain.†*
Rifaximin (p. 355·2).
Gastrointestinal infections.

Zaxter *Alkem, Thai.*
Meropenem (p. 321·3).
Bacterial infections.

Zayasel *Salvat, Spain.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Zazole *PharmaDerm, USA.†*
Terconazole (p. 595·2).
Fungal vaginal infections.

Z-Bec
Note: this name may be used for preparations of different composition.
Gap, Gr.
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Pfizer Consumer, Thai.
Vitamins; zinc (p. 2126·1).

Robins, USA.
Vitamins; minerals.

Z-Bec Plus *Gap, Gr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Z-Clindacin *Panalab, Arg.*
Clindamycin (p. 269·3); zinc (p. 2126·1).
Acne.

Z-Cof *Zyber, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Coughs.

Z-Cof I *Pernix, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Z-Cof 8DM *Zyber, USA.*
⊗Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Z-Cof HC *Zyber, USA.*
Hydrocodone tartrate (p. 67·2); chlorphenamine maleate (p. 620·3); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Z-Crim *Alpharma, Mex.†*
Zinc (p. 2126·1).
Skin disorders.

Zcure *Natrapharm, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Z-Dex *Trigen, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Cough.

Z-Dex 12D *Trigen, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Z-Dorm *Sandoz, S.Afr.*
Zopiclone (p. 1118·1).
Insomnia.

Zdrój *Sulphur Zdroj, Pol.*
Sulfur (p. 1721·1); sodium chloride (p. 1795·1); bromide; iodide; borate.
Scalp disorders.

Ze Bei *ChangJiang, China.*
Inosine (p. 2533·1).

Ze Er Sheng *HeBei, China.*
Pemirolast potassium (p. 1218·2).
Asthma; allergic rhinitis.

Ze Fei *Hanson, China.*
Gemcitabine hydrochloride (p. 801·2).
Malignant neoplasms.

Ze Kang *Qing Hua Zi Guang Gu Han, China.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Ze Li *Bright Future, China.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ze Lun *Jiu Xu, China.*
Doxapram hydrochloride (p. 2321·2).
Respiratory depression; respiratory failure.

Ze Ming *White Swan, China.*
Matrine.

Ze Ning *Hairong, China.*
Levothyroxine sodium (p. 2339·1).
Hypothyroidism.

Ze Qi *Hicin, China.*
Azithromycin (p. 221·2).
Bacterial infections.

Ze Rong *Lukang Chenxin, China.*
Ropivacaine mesilate.
Local anaesthesia.

Ze Tong *Hicin, China.*
⊗Torasemide (p. 1516·3).
Oedema.

Ze Wei Er *Winsunny, China.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris; vertigo; tinnitus.

Zeadema *Farmila, Ital.*
Vitamins; minerals; zeaxanthin (p. 2125·3); red vine (p. 2521·3).
Antoxidant nutritional supplement.

Zeadema Crono *Farmila, Ital.*
Vitamins; minerals; zeaxanthin (p. 2125·3); calendula (p. 2465·2); grape (p. 2521·3); lycopene (p. 2546·2).
Nutritional supplement.

Zealor *Flamingo, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

ZeaSorb *GSK, Arg.; Stiefel, Austral.†; Stiefel, Canad.; Stiefel, Irl.; Stiefel, Thai.†; Stiefel, UK.*
Aldioxa (p. 1692·2); chloroxylenol (p. 1748·2); cellulose (p. 2177·1).
Hyperhidrosis; skin disorders; intertrigo; bromhidrosis; prophylaxis of fungal skin infections; skin irritation; napkin rash; tinea pedis; prickly heat.

Stiefel, Fr.
Aldioxa (p. 1692·2); cellulose (p. 2177·1); magnesium silicate (p. 2195·3).
Hyperhidrosis.

Stiefel, Indon.; Stiefel, Philipp.; Stiefel, S.Afr.†; Stiefel, Singapore.
Aldioxa (p. 1692·2); chloroxylenol (p. 1748·2).
Hyperhidrosis; nappy rash; fungal skin infections; intertrigo; bromhidrosis; tinea pedis.

ZeaSorb AF
Note: this name may be used for preparations of different composition.
Stiefel, Chile†; GSK, USA.†
Miconazole nitrate (p. 589·1).
Fungal skin infections.

Stiefel, Canad.†
Tolnaftate (p. 596·1).
Fungal skin infections.

Zeatax *Gondane-Vitality, Hung.*
Corn silk (p. 2487·1); urtica (p. 2639·3); taraxacum (p. 2625·3); viola tricolor (p. 2647·3); caesalpinia spinosa.
Aid in weight reduction.

Zeben *Siam Bheasach, Thai.*
Albendazole (p. 149·1).
Worm infections.

Zebet *Hovid, Philipp.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Zebeta *Teva, USA.*
⊗Bisoprolol fumarate (p. 1325·3).
Hypertension.

Zebinix *Bial, Austria; Bial, Cz.; Bial, Denm.; Eisai, Fr.; Eisai, Ger.; Bial, Gr.; Eisai, Irl.; Eisai, Neth.; Eisai, Norw.; Bial, Pol.; Bial, Port.; Bial, Spain; Eisai, Swed.; Eisai, UK.*
Eslicarbazepine acetate (p. 520·3).
Epilepsy.

Zebinor *Rafarm, Gr.*
Bendazac lysine (p. 29·1).

Zebrak *Royal, Chile.*
Citalopram (p. 411·1).
Depression.

Zebu *Pond's, Thai.†*
⊗Salbutamol (p. 1220·2).
Bronchospasm.

Zebutal *Victory, USA.*
Butalbital (p. 1043·3); paracetamol (p. 115·1); caffeine (p. 1203·3).
Pain.

Zecid *Zee, Thai.†*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; dyspepsia; Zollinger-Ellison syndrome.

Zecidec *Decomed, Port.†*
Escitalopram oxalate (p. 416·2).

Zeclar *Orion, Fin.; Abbott, Fr.; Abbott, Gr.; Abbott, Port.†*
Clarithromycin (p. 266·2).
Bacterial infections.

Zeclaren *Abbott, Gr.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Zeclicid *Verisfield, Gr.*
Citalopram hydrobromide (p. 411·1) or citalopram hydrochloride (p. 411·1).
Depression; panic disorder.

Zeclor *Medica Korea, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Zecovir *Guidotti, Ital.*
Brivudine (p. 970·1).
Herpes zoster infections.

Zecuity *NuPathe, USA.*
Sumatriptan (p. 679·2).
Migraine.

Zeda *Verisfield, Gr.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Zedace *Alphapharm, Austral.*
Captopril (p. 1331·2).
Hypertension; myocardial infarction; heart failure; diabetic nephropathy.

Zedbac *Aspire, UK.*
Azithromycin (p. 221·2).
Community-acquired pneumonia; pelvic inflammatory disease.

Zedchem PVP-I *Cipla-Medpro, S.Afr.*
Povidone-iodine (p. 1767·1).
Burns; ulcers; wounds; skin infections; disinfection of skin and mucous membranes.

Zedd *Aspen, Austral.*
Azithromycin (p. 221·2).
Bacterial infections.

Zedex *Wockhardt, India; Wockhardt, Rus.†; Wockhardt, Ukr.*
Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough; respiratory-tract disorders associated with viscous mucus.

Zedex-P *Wockhardt, India.*
⊗Bromhexine hydrochloride (p. 1656·3); dextromethorphan hydrobromide (p. 1660·1); ammonium chloride (p. 1656·1); menthol (p. 2553·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough; respiratory-tract disorders associated with viscous mucus.

Zedim *Great Eastern, Thai.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zeditapp *Medhaus, Philipp.*
Phenylpropanolamine hydrochloride (p. 1674·1); brompheniramine maleate (p. 618·1).
Cough; nasal congestion.

Zedprex *Adeka, Turk.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder.

Zedroxyn *Orchid, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Zee *Patar, Thai.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency.

Zeecof *Cipla, India.*
Diphenhydramine (p. 626·1); guaifenesin (p. 1666·2); bromhexine (p. 1656·3); ammonium chloride (p. 1656·1); menthol (p. 2553·2).
Cough.

Zeefra *Bouchara-Recordati, Fr.†; Bouchara-Recordati, Hong Kong.†*
Cefradine (p. 249·1).
Bacterial infections.

Zeel *Heel, S.Afr.*
Injection: Cartilago suis (p. 2471·3); funiculus umbilicalis suis (p. 2444·1); embryo suis (p. 2444·1); placenta suis (p. 2444·1); rhus toxicodendron (p. 2603·3); arnica (p. 2447·2); dulcamara (p. 2497·3); symphytum (p. 2484·2); sanguinaria (p. 2610·1); sulfur (p. 1721·1); nadid; coenzyme A (p. 2483·2); thioctic acid (p. 2629·1); natrium oxalaceticum (p. 2578·3).
Musculoskeletal and joint disorders.

Heel, S.Afr.
Ointment; tablets: Cartilago suis (p. 2471·3); funiculus umbilicalis suis (p. 2444·1); embryo suis (p. 2444·1); placenta suis (p. 2444·1); rhus toxicodendron (p. 2603·3); flor arnicae; dulcamara (p. 2497·3); symphytum (p. 2484·2); sanguinaria (p. 2610·1); sulfur (p. 1721·1); acidum silicicum colloidale (p. 2208·3); nadid; coenzyme A (p. 2483·2); thioctic acid (p. 2629·1); natrium oxalaceticum (p. 2578·3).
Musculoskeletal and joint disorders.

Peithner, Hung.
Cartilago suis (p. 2471·3); funiculus umbilicalis suis (p. 2444·1); embryo suis (p. 2444·1); placenta suis (p. 2444·1); toxicodendron quercifolium e summitatibus (p. 2603·3); arnica montana (p. 2447·2); solanum dulcamara (p. 2497·3); symphytum officinale (p. 2484·2); sanguinaria canadensis (p. 2610·1); sulfur (p. 1721·1); nadidum (p. 2567·1); coenzym A (p. 2483·2); acidum alpha-liponicum (p. 2629·1); natrium diethyloxalaceticum (p. 2578·3); acidum silicicum (p. 2208·3).
Homoeopathic preparation.

Zeel Comp *Heel, Canad.*
Arnica montana (p. 2447·2); dulcamara (p. 2497·3); rhus toxicodendron (p. 2603·3); sanguinaria canadensis (p. 2610·1); sulphur (p. 1721·1).
Homoeopathic preparation.

Zeel comp *Heel, Ger.*
Toxicodendron quercifolium e summ. rec. (p. 2603·3); arnica montana (p. 2447·2); solanum dulcamara (p. 2497·3); sanguinaria canadensis (p. 2610·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Zeel comp N *Heel, Neth.*
Arnica montana (p. 2447·2); dulcamara (p. 2497·3); rhus toxicodendron (p. 2603·3); sanguinaria canadensis (p. 2610·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Zeel Compositum *Heel, Cz.*
Rhus toxicodendron (p. 2603·3); arnica montana (p. 2447·2); solanum dulcamara (p. 2497·3); sanguinaria canadensis (p. 2610·1); sulfur (p. 1721·1).
Homoeopathic preparation.

Zeel Salbe *Heel, Cz.†*
Cartilago suis (p. 2471·3); funiculus umbilicalis suis (p. 2444·1); embryo suis (p. 2444·1); placenta suis (p. 2444·1); rhus toxicodendron (p. 2603·3); arnica montana (p. 2447·2); solanum dulcamara (p. 2497·3); symphytum officinale (p. 2484·2); sanguinaria canadensis (p. 2610·1); sulfur (p. 1721·1); nadidum (p. 2567·1); coenzymum A (p. 2483·2); acidum thiocticum (p. 2629·1); ethyloxalacetatum natricum (p. 2578·3); silicii dioxidum (p. 2208·3).
Homoeopathic preparation.

Zeel T *Heel, Rus.*
Cartilago suis (p. 2471·3); funiculus umbilicalis suis (p. 2444·1); embryo totalis bovis (p. 2444·1); placenta suis (p. 2444·1); solanum dulcamara (p. 2497·3); symphytum officinale (p. 2484·2); nadidum (p. 2567·1); coenzym A (p. 2483·2); sanguinaria canadensis (p. 2610·1); natrium diethyloxalaceticum (p. 2578·3); acidum DL-alpha liponicum (p. 2629·1); toxicodendron quercifolium (p. 2603·3); arnica montana (p. 2447·2); sulfur (p. 1721·1).
Homoeopathic preparation.

Zeelinax *Hexal, Denm.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Zeemide *Brimpharm, S.Afr.*
Azithromycin (p. 221·2).

Zeenix *Betapharm, Denm.†*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Zeeplus *Pediatrica, Philipp.*
Ascorbic acid (p. 2110·3); zinc sulfate (p. 2126·2).
Vitamin C deficiency; zinc deficiency.

Zee-Seltzer *Zee, USA.*
Aspirin (p. 22·2); citric acid (p. 2480·3); sodium bicarbonate (p. 1781·1).

Zeet
Note: this name may be used for preparations of different composition.
Alembic, India.
Syrup: Diphenhydramine hydrochloride (p. 626·2); ammonium chloride (p. 1656·1); guaifenesin (p. 1666·2); bromhexine hydrochloride (p. 1656·3); menthol (p. 2553·2).
Cough.

Alembic, India.
Tablets: Bromhexine hydrochloride (p. 1656·3); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Idaman, Singapore.
Mefenamic acid (p. 85·3).
Pain; inflammation.

Zeet Linctus *Alembic, India.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylpropanolamine hydrochloride (p. 1674·1).
Cough.

Zefa *M & H, Thai.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zefadin *Pharmawealth, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Zefan *Drogsan, Turk.*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Zefaxone *M & H, Thai.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zefcid *Triveni, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zefecort *Vocate, Gr.*
⊗Budesonide (p. 1625·1).

Zefei *Jiangsu Hansen, Philipp.*
Gemcitabine hydrochloride (p. 801·2).
Pancreatic cancer; non-small cell lung cancer.

Zefen *Suzhou No 4, China.*
Ibuprofen (p. 68·2).
Musculoskeletal, joint, and soft-tissue disorders; pain; fever.

Zeferom *Pharmawealth, Philipp.*
Cefpirome sulfate (p. 247·2).
Bacterial infections.

Zeffix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK.*
Lamivudine (p. 1000·2).
Chronic hepatitis B; HIV infection.

Zefidim *Kalbe, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zefin
Note: this name may be used for preparations of different composition.
Novagen, S.Afr.
Tenofovir disoproxil fumarate (p. 1018·1).
HIV infection.
Millimed, Thai.†
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Zefipime *Vocate, Gr.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Zefiran *Sandoz, Turk.*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Zefirolum *Kocak, Turk.*
Benzalkonium chloride (p. 1737·1).
Skin and mucous membrane disinfection.

Zefnart *Torii, Jpn.*
Liranaftate (p. 588·1).
Fungal skin infections.

Zefocent *Samjin, Philipp.*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Zefol *Akdeniz, Turk.*
Benzalkonium chloride (p. 1737·1).
Skin and mucous membrane disinfection.

Zefomen *Nevzat, Turk.*
Lamivudine (p. 1000·2).

Zefort *Merkez, Turk.†*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Zefral *United American, Philipp.*
Cefixime (p. 240·3).
Bacterial infections.

Zefroxe *Adcock Ingram, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zefsolin *Oro, Turk.*
Benzalkonium chloride (p. 1737·1).
Disinfection of clothing, mucous membranes, skin, and surgical instruments.

Zefsur *Medchem, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Zeftam *M & H, Thai.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zeftera *Janssen-Ortho, Canad.†; Janssen-Cilag, Rus.*
Ceftobiprole medocaril sodium (p. 253·2).
Bacterial skin and skin structure infections.

Zeftrix *Kalbe, Indon.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Zefur *InnoGen, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Zefurime *Aspen, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zefuxim *Pharmawealth, Philipp.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zefxon *Biolab, Philipp.; Biolab, Singapore; Biolab, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration.

Zegacid *Ajanta, Philipp.*
Omeprazole (p. 1867·2); sodium bicarbonate (p. 1781·1).
Peptic ulcer; gastro-oesophageal reflux.

Zegase *Kalbe, Indon.*
Vitamins; minerals.
Vitamin and mineral supplement.

Zegavit *Kalbe, Indon.*
Vitamins; calcium (p. 1783·1); zinc (p. 2126·1).
Vitamin and mineral supplement.

Zegen *United American, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Zegerid *Santarus, USA.*
Omeprazole (p. 1867·2); sodium bicarbonate (p. 1781·1).
Gastro-oesophageal reflux; peptic ulcer.

Zeglidia *Plus Pharma, Denm.; Plus Pharma, Hung.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Zeglydia *Plus Pharma, Cz.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Zegren *Lapi, Indon.*
Diclofenac sodium (p. 48·3).
Musculoskeletal and joint disorders.

Zehu-Ze *Teva, Israel.†*
Permethrin (p. 2159·3).
Pediculosis.

Zeid *Senosiain, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Zeklen *MSD, Ital.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).

Zela *Unison, Thai.*
Albendazole (p. 149·1).
Worm infections.

Zeladrol *Medico Uno, Hung.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zelaika *Intendis, Spain.†*
Azelaic acid (p. 1695·1).
Acne.

Zelapar *Valeant, Arg.; Cephalon, UK; Cardinal Health, USA.*
⊗Selegiline hydrochloride (p. 914·2).
Parkinsonism.

Zelavel *Novell, Indon.*
Ofloxacin (p. 334·3).
Bacterial infections.

Zelboraf *Roche, Austral.; Roche, Belg.; Roche, Canad.; Roche, Denm.; Roche, Fr.; Roche, Israel; Roche, Neth.; Roche, Norw.; Roche, Swed.; Roche, Switz.; Roche, UK; Roche, USA.*
Vemurafenib (p. 879·3).
Malignant melanoma.

Zeldilon *Zeler, Port.*
Minoxidil (p. 1438·3).
Alopecia androgenetica.

Zeldox *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Hong Kong; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Norw.; Pfizer, NZ; Pfizer, Philipp.†; Pfizer, Port.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, Ukr.*
Ziprasidone hydrochloride (p. 1115·2) or ziprasidone mesilate (p. 1115·2).
Schizophrenia; bipolar disorder; psychoses; mania.
Pfizer, Hung.; Pfizer, Pol.
Ziprasidone (p. 1115·2) or ziprasidone mesilate (p. 1115·2).
Schizophrenia; bipolar disorder.

Zelefion *Blau, Pol.*
Terbinafine hydrochloride (p. 593·3).
Fungal skin and nail infections.

Zeleft *Deva, Turk.*
Sertraline hydrochloride (p. 448·1).

Zelenin *Phytopharm, Rus.; Yaroslavl, Rus.*
Belladonna (p. 2453·3); valerian (p. 2640·2); convallaria (p. 2486·2); menthol (p. 2553·2).
Cardiovascular disorders; anxiety; heart failure.

Zeleven *Alapis, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Zelface *Ferron, Indon.*
Azelaic acid (p. 1695·1).
Acne.

Zelfin *Randall, Mex.*
Albendazole (p. 149·1).
Worm infections.

Zelian *Rafarm, Gr.†*
Buflomedil hydrochloride (p. 1328·3).
Peripheral vascular disorders.

Zelicrema *Biomedica, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Zeliderm *Vinas, Spain.*
Azelaic acid (p. 1695·1).
Acne.

Zeliris *Caprifarmindo, Indon.*
Azelaic acid (p. 1695·1).
Acne.

Zelis *Prospa, Ital.†*
Piroxicam cinnamate (p. 125·3).
Musculoskeletal and joint disorders.

Zelitrex *GSK, Austral.; GSK, Belg.; GSK, Denm.; GSK, Fr.; GSK, Ital.; GSK, Neth.; Aspen, S.Afr.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Zelium
Note: this name may be used for preparations of different composition.
Abbott, Port.†; Eczacibasi, Turk.
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.
Masa, Thai.
Flunarizine (p. 629·3).
Cerebrovascular disorders; migraine.

Zelivire *Ranbaxy, S.Afr.*
Valaciclovir hydrochloride (p. 1021·1).
Herpesvirus infections.

Zelix *Ativus, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Zelixa *Biofarm, Pol.†*
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.

Zellaforte *Novum, Mex.*
Vitamins; minerals.

Zeller Sommeil *Zeller, Switz.*
Valerian (p. 2640·2); lupulus (p. 2546·1).
Sleep disorders.

Zelleta *Morningside, UK.*
Desogestrel (p. 2266·3).
Progestogen-only oral contraceptive.

Zellox-II *Hoe, Malaysia; Hoe, Singapore.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn.

Zellulean with Escin *Bioglan, Austral.†*
Aesculus (p. 2431·2); ginkgo biloba (p. 2512·3); vitis vinifera (p. 2521·3); bladderwrack (p. 2612·1); bioflavonoids (p. 2505·2); lecithin (p. 2542·2); pectin (p. 2200·3); tyrosine (p. 2098·3); evening primrose oil (p. 2502·2); omega-3 marine triglycerides (p. 1460·3); yellow sweet clover (p. 2552·3).
Aid to skin tissue repair; obesity.

Zelmac *Novartis, Arg.; Novartis, Braz.; Novartis, Chile†; Novartis, China; Novartis, Hong Kong†; Novartis, Indon.†; Novartis, Mex.; Novartis, NZ; Novartis, Rus.; Novartis, Singapore; Novartis, Thai.†; Novartis, Turk.; Novartis, Venez.*
Tegaserod maleate (p. 1893·1).
Chronic constipation; irritable bowel syndrome.

Zelmar *Biomedica, Gr.*
Loratadine (p. 633·2).
Allergic rhinitis; pruritus.

Zelnorm *Novartis, Philipp.†; Novartis, S.Afr.†*
Tegaserod maleate (p. 1893·1).
Irritable bowel syndrome; chronic constipation.

Zeloram *Epifarma, Ital.*
Lorazepam (p. 1080·3).
Anxiety; insomnia.

Zelotrin *PharOS, Cz.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zeloxim *Bilim, Turk.*
Meloxicam (p. 86·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Zeltac *Sel-J, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; acid aspiration.

Zelvartan *Galex, Pol.*
Valsartan (p. 1521·2).
Hypertension; heart failure.

Zelvartancombo *Galex, Cz.*
⊗Valsartan (p. 1521·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zem *Faran, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Hypertension; angina pectoris.

Zema
Note: this name may be used for preparations of different composition.
Macoven, USA.
⊗Dexamethasone (p. 1630·3).
Corticosteroid.
Union Drug, Thai.
Cream: Clotrimazole (p. 576·2).
Fungal skin infections.
Union Drug, Thai.
Lotion: Phenol (p. 1763·3); resorcinol (p. 1718·3); salicylic acid (p. 1719·1).
Infected skin disorders.

Zema B *Union Drug, Thai.†*
⊗Betamethasone (p. 1623·2); clotrimazole (p. 576·2).
Infected skin disorders.

Zemaira *CSL, USA.*
$Alpha_1$-proteinase inhibitor (p. 2438·1).
$Alpha_1$-proteinase inhibitor deficiency.

Zemalex *Italfarmaco, Port.*
Piketoprofen hydrochloride (p. 125·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; phlebitis.

Zeman *Mega Lifesciences, Philipp.*
Magnesium (p. 1786·3); zinc (p. 2126·1); levocarnitine (p. 2053·2); selenium (p. 2086·3); vitamin B substances (p. 2102·3).
Dietary supplement.
Mega We Care, Singapore.
Magnesium (p. 1786·3); zinc (p. 2126·1); vitamin B_6 (p. 2105·3).
Dietary supplement.

Zemaros *Verisfield, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Zemax *Cipla-Medpro, S.Afr.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Zemidral *Med-One, Gr.*
Ketoconazole (p. 585·3).
Fungal infections.

Zemon *Neolab, UK.*
Isosorbide mononitrate (p. 1413·3).
Angina pectoris.

Zemplar *Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Braz.; Abbott, Canad.†; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; AbbVie, Fin.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; AbbVie, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, Singapore; AbbVie, Spain; Abbott, Swed.; AbbVie, Switz.; Abbott, Turk.; Abbott, UK; AbbVie, USA; Abbott, Venez.*
Paricalcitol (p. 2113·3).
Hyperparathyroidism.

Zemtard *Galen, UK.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Zemtrial *IAE, Philipp.†*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Zemuron *Merck, Canad.; Organon, USA.*
Rocuronium bromide (p. 2036·1).
Competitive neuromuscular blocker.

Zemyc *Pharos, Indon.*
Fluconazole (p. 578·2).
Fungal infections.

Zenalb *GP, Arg.; Galenica, Gr.; Ikapharmindo, Indon.; BPL, Israel; Bio Products, Malaysia; BPL, Philipp.; BPL, Rus.; BPL, Singapore; BPL, Thai.; Sodhan, Turk.; BPL, UK.*
⊗Albumin (p. 1130·2).
Burns; hypoalbuminaemia; plasma volume expansion; hypovolaemia; shock.

Zenalia *Boiron, Fr.*
Gelsemium sempervirens (p. 2511·2); ignatia amara (p. 2532·1); kalium phosphoricum (p. 1790·3).
Homoeopathic preparation.

Zenapax *Roche, Arg.; Roche, Austral.†; Roche, Austria†; Roche, Belg.; Roche, Braz.; Roche, Canad.†; Roche, Chile; Roche, China; Roche, Cz.†; Roche, Denm.†; Roche, Fin.†; Roche, Fr.†; Roche, Ger.†; Roche, Gr.; Roche, Hong Kong†; Roche, Hung.; Roche, Irl.†; Roche, Israel†; Roche, Ital.†; Roche, Mex.; Roche, Neth.†; Roche, NZ†; Roche, Philipp.; Roche, Pol.†; Roche, Rus.; Roche, S.Afr.†; Roche, Singapore; Roche, Spain†; Roche, Swed.†; Roche, Switz.†; Roche, Thai.†; Roche, Turk.; Roche, UK†; Roche, USA†; Roche, Venez.*
Daclizumab (p. 1957·1).
Renal transplant rejection.

Zenaro *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Ukr.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria.

Zenatane *Reddy, USA.*
Isotretinoin (p. 1706·2).
Acne.

Zenavan *Bial, Spain.*
Etofenamate (p. 57·2).
Peri-articular disorders; pain.

Zenaxin *Maver, Mex.*
Albendazole (p. 149·1).
Worm infections.

Zenbrest *Zentiva, Cz.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zen Care *Hoe, Malaysia.*
⊗Glycerol (p. 2517·2).
Soap substitute.

Zencef *Lapreven, Venez.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zenchent *Watson, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, inert.
Combined oral contraceptive.

Zenchent Fe *Watson, USA.*
21 Tablets, ethinylestradiol (p. 2275·3); norethisterone (p. 2294·2); 7 tablets, ferrous fumarate (p. 2060·3).
Combined oral contraceptive.

Zencia *Stratus, USA.*
Sulfacetamide sodium (p. 361·1); sulfur (p. 1721·1).
Acne.

Zencocin *Zenith, Indon.*
Lincomycin (p. 317·1).
Gram-positive bacterial infections.

Zenda *TNP, Thai.*
Niclosamide (p. 161·2); phenolphthalein (p. 1877·3).
Worm infections.

Zendal *Eipico, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Zendhin *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; dyspepsia.

Zendiab *Zenith, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Zendol *Serum Institute, India.*
⊗Danazol (p. 2263·2).
Endometriosis; benign breast disease.

Zendor *Sanovel, Turk.*
Escitalopram (p. 416·2).

Zenemia *Verisfield, Gr.*
Calcium folinate (p. 2066·3).
Folic acid deficiency; antidote to folic acid antagonists.

Zenfektol *Olgunsoy, Turk.†*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Zengac *Fisiopharma, Ital.*
Vancomycin hydrochloride (p. 384·2).
Bacterial infections.

Zengxiao Lianhuangpian *Double-Crane, China.*
Sulfamethoxazole (p. 365·2); sulfadiazine (p. 361·3); trimethoprim (p. 381·2).
Bacterial infections.

Zenhale *Merck, Canad.*
⊗Mometasone furoate (p. 1644·1); formoterol fumarate (p. 1209·2).
Asthma.

Zeniac *Noreva, Fr.*
Lotion: Mandelic acid (p. 320·3); salicylic acid (p. 1719·1); ammonium lactate (p. 1694·3).
Acne.

Noreva, Fr.
Roll-on: Mandelic acid (p. 320·3); salicylic acid (p. 1719·1); sulfur (p. 1721·1).
Acne.

Noreva, Fr.
Topical gel: Lappa-biotin-zinc complex (p. 2540·1) (p. 2052·2) (p. 2126·1).
Skin cleansing.

Zeniac LP *Noreva, Fr.*
Mandelic acid (p. 320·3); salicylic acid (p. 1719·1); ammonium lactate (p. 1694·3); lappa-biotin-zinc complex (p. 2540·1) (p. 2052·2) (p. 2126·1).
Acne.

Zeniac LP Fort *Noreva, Fr.*
Mandelic acid (p. 320·3); tartaric acid (p. 2626·1); salicylic acid (p. 1719·1); ammonium lactate (p. 1694·3).
Acne.

Zenibroz *Zenith, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias.

Zenic *Temis, Arg.*
Levofloxacin (p. 315·3).
Bacterial infections.

Zenieva *Rivers Edge, USA.*
Emollient.

Zeniflox *Zenith, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Zenilev *Zenith, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Zenith *Amherst, Philipp.*
Azithromycin (p. 221·2).
Bacterial infections.

Zenkain *Gunsa, Turk.†*
⊗Tetryzoline hydrochloride (p. 1678·3).
Eye irritation.

Zenmex *CCM, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Zenmolin *DHA, Hong Kong; DHA, Singapore.*
⊗Salbutamol sulfate (p. 1220·2).
Bronchospasm.

Zenol *Vianex (Βιανεξ), Gr.*
Paracetamol (p. 115·1).
Fever; pain.

Zenolen *ACME, Philipp.†*
⊗Atenolol (p. 1308·2).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; migraine.

Zenopar *Remedina, Gr.*
Cisapride (p. 1831·3).
Gastroparesis; gastro-oesophageal reflux.

Zenostig *Labormed, Cz.; Labormed, Hung.; Labormed, Neth.; Labormed, Pol.*
Betahistine hydrochloride (p. 2455·3).
Ménière's disease.

Zenoxim *Indchemie, Philipp.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zenoxone *Biorex, UK.*
⊗Hydrocortisone (p. 1640·1).
Skin disorders.

Zenpep *Aptalis, USA.*
⊗Pancrelipase (p. 2580·1).
Pancreatic insufficiency.

Zenpro *Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; Helicobacter pylori eradication.

Zenriz *Pyridam, Indon.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria.

Zensil *Silom, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis.

Zensoderm *Zenith, Indon.*
⊗Betamethasone valerate (p. 1624·1); gentamicin sulfate (p. 304·2).
Infected skin disorders.

Zentan *Ilsan, Turk.†*
Benzalkonium chloride (p. 1737·1).
Skin disinfection.

Zentavion *Warner Chilcott, Spain.†*
Azithromycin (p. 221·2).
Bacterial infections.

Zentel *GSK, Austral.; GSK, Braz.; GSK, Chile; GSK, China; GSK, Cz.†; GSK, Fr.; Vianex (Βιανεξ), Gr.; GSK, India; GSK, Ital.; GSK Consumer, Malaysia; GSK, Mex.; GSK, Philipp.; GSK, Pol.; GSK Consumer, Port.; GSK, S. Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Ukr.; GSK, Venez.*
Albendazole (p. 149·1).
Worm infections; giardiasis; ascariasis; enterobiasis; echinococcosis.

Zenti *Zenith, Indon.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; pathological hypersecretory disorders.

Zentius *Roemmers, Arg.; Roemmers, Chile.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Zentius D *Farmed, Turk.*
Calcium carbonate (p. 1824·3); colecalciferol (p. 2113·1).

Zentox *Hugel, Thai.*
Botulinum A toxin (p. 2017·1).
Blepharospasm.

Zentozide *Bangkok Lab & Cosmetic, Thai.*
Praziquantel (p. 164·1).
Worm infections.

Zentra *Zenith, Indon.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).
Cold symptoms; nasal congestion; sinusitis.

Zentraferin *Ariston, Arg.*
Iron (as microspheres) (p. 2073·1); folic acid (p. 2063·1).
Anaemias; menorrhagia.

Zentralin *Pasteur, Chile.*
Flunarizine hydrochloride (p. 629·3).
Cerebral and peripheral vascular disorders; vestibular disorders; sleep disorders.

Zentramin Bastian N *Bastian, Ger.†*
Electrolytes (p. 1775·1).
Hypersensitivity disorders; psychosomatic disorders; tetanus.

ZentroOlimel *Baxter, Austria.*
Glucose (p. 2068·3); amino acids; lipid (from olive oil (p. 2575·1) and soya oil (p. 2092·3)); with or without electrolytes (p. 1775·1).
Parenteral nutrition.

Zentropil *Sandoz, Ger.†*
Phenytoin (p. 538·2).
Epilepsy; trigeminal neuralgia.

Zenvas *AstraZeneca, Arg.*
Escitalopram (p. 416·2).
Depression.

Zenzedi *Arbor, USA.*
⊗Dexamfetamine sulfate (p. 2319·1).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Zenzera *Bangkok Lab & Cosmetic, Thai.*
Albendazole (p. 149·1).
Worm infections.

Zeoklamin *Ferakon, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Zep *Zep, Canad.*
Triclosan (p. 1773·2).
Skin cleansing.

Zep E-3 *Zep, Canad.†*
Isopropyl alcohol (p. 1758·3).
Skin disinfection.

Zep Foam San *Zep, Canad.*
Benzethonium chloride (p. 1738·1).

Zep Instant Hand Sanitizer *Zep, Canad.*
Isopropyl alcohol (p. 1758·3).
Hand disinfection.

Zepac *Ist. Chim. Inter., Ital.*
Heparin calcium (p. 1396·3).
Thromboembolic disorders.

Zepam *Modern Manu, Thai.; S Co Pharma, Thai.*
Diazepam (p. 1063·2).

Zepan *Jofrain, Mex.†*
Diazepam (p. 1063·2).
Anxiety.

Zepax *Yoo Young, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Zepaxid *Udomphon, Thai.*
Diazepam (p. 1063·2).
Anxiety; insomnia; epilepsy; alcohol withdrawal syndrome; skeletal muscle spasm; premedication.

Zepaz *Royal, Chile.*
Escitalopram (p. 416·2).
Depression; panic disorder.

Zepdril *Aldril, Philipp.*
Cefradine (p. 249·1).
Bacterial infections.

Zepelin
Note: this name may be used for preparations of different composition.
Boehringer Ingelheim, Ital.
Feprazone (p. 64·3).
Pain; inflammation.

Wakamoto, Jpn.
Acitazanolast (p. 2428·3).
Allergic conjunctivitis.

Zephanal *Zenith, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zepharyl *Medi-Rx, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Zephiran *Sanofi Winthrop, USA.*
Benzalkonium chloride (p. 1737·1).
Skin, mucous membrane, and wound disinfection; eye, bladder, urethra, and body cavity irrigation; vaginal douching.

Zepholin
Note: this name may be used for preparations of different composition.
Astellas, Irl.
Theophylline (p. 1229·3).
Bronchospasm.

Genepharm, Gr.
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Zephrex *Sanofi Synthelabo, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1); guaifenesin (p. 1666·2).
Coughs.

Zephrex-D *Westport, USA.*
⊗Pseudoephedrine hydrochloride (p. 1676·1).
Nasal congestion.

Zepid *Unison, Malaysia.*
Drotaverine hydrochloride (p. 2497·3).
Gastrointestinal spasm.

Zepiken *Kener, Mex.*
Carbamazepine (p. 512·2).

Zepilen *AFT, NZ.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zepim *PharmAsia, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Zepime *Pharmawealth, Philipp.*
Cefepime hydrochloride (p. 239·2).
Bacterial infections.

Zeplex *M & H, Thai.*
Cefalexin (p. 234·1).
Bacterial infections.

Zeporin *Dynamic, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Zepose *Cipla, India.*
Diazepam (p. 1063·2).

Zepotex *Nestor, Philipp.; Yoo Young, Philipp.*
Cefalexin sodium (p. 234·1).
Bacterial infections.

Zepotin *Pharmawealth, Philipp.*
Cefoxitin sodium (p. 246·2).
Bacterial infections.

Zepoxide *TP, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; insomnia; skeletal muscle spasm; premedication.

Zepoxin *Chew, Thai.*
Chlordiazepoxide hydrochloride (p. 1044·2).
Anxiety; alcohol withdrawal syndrome; insomnia; muscle spasms; premedication.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zeppeliton *Plus Pharma, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zepral *Ikapharmindo, Indon.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zeprazol *Zenith, Indon.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zeprid *Nobel, Turk.*
Sulpiride (p. 1107·3).
Schizophrenia.

Zepril *Richmond, Arg.*
Abacavir (p. 962·3).
HIV infection.

Zeprola *Umut, Turk.*
Olanzapine (p. 1089·3).

Zeprosil *Xixia, S.Afr.†*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction.

Zeptag *Bosch, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zeptol *Sun, Rus.; Sun, Thai.*
Carbamazepine (p. 512·2).
Epilepsy; trigeminal neuralgia; bipolar disorder; glossopharyngeal neuralgia.

Zeptrigen *Westmont, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zera *Tecnimede, Port.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Zeramil *Elpen (Ελπεν), Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zerdin *Genesis, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; acid aspiration.

Zerelin *Biomedica, Gr.*
Meloxicam (p. 86·3).
Inflammatory disorders.

Zerella *Theramex, Ital.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis.

Zerene *Meda, Cz.; Meda, Irl.; Biofutura, Ital.†; Wyeth, Neth.†; Meda, Pol.; Meda, Port.*
Zaleplon (p. 1114·3).
Insomnia.

Zerfun *IDI, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Zeridame *Actavis, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zerinetta *Boehringer Ingelheim, Ital.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Zerinoflu *Boehringer Ingelheim, Ital.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3); sodium ascorbate (p. 2111·1).
Cold and influenza symptoms.

Zerinol *Boehringer Ingelheim, Ital.*
Paracetamol (p. 115·1); chlorphenamine maleate (p. 620·3).
Cold and influenza symptoms.

Zerinol Gola *Boehringer Ingelheim, Ital.*
Ambroxol hydrochloride (p. 1654·3).

Zerit *Merck Serono, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Canad.; BMS, Chile; BMS, China; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.†; BMS, Irl.; BMS, Ital.; BMS, Jpn; BMS, Mex.; BMS, Neth.; BMS, Norw.†; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.†; BMS, Turk.; BMS, UK; BMS, USA; BMS, Venez.*
Stavudine (p. 1015·3).
HIV infection.

Zeritavir *BMS, Braz.†*
Stavudine (p. 1015·3).
HIV infection.

Zerlex *Sel-J, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Zerlin *Pharos, Indon.*
Sertraline (p. 448·1).
Depression.

Zerlon *Hemofarm, Rus.*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Zermed *Medicine Products, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Zeroac *Mavi, Ital.*
Azelaic acid (p. 1695·1); phosphatidyl choline (p. 2588·3).
Acne.

Zerobase *Thornton & Ross, UK.*
Liquid paraffin (p. 2191·2).
Diluent for topical steroids; dry skin; emollient.

Zerocid *Sun, Rus.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zerocream *Thornton & Ross, UK.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).

Zerodiar *Proel, Gr.*
Tobramycin sulfate (p. 380·2).
Bacterial infections.

Zerodol *Ipca, India; Ipca, Ukr.*
Aceclofenac (p. 16·2).
Inflammation; pain; rheumatoid arthritis; osteoarthritis; ankylosing spondylitis.

Zerodol-MR *Ipca, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1); tizanidine hydrochloride (p. 2026·2).
Muscle pain, inflammation, and spasm.

Zerodol-P *Ipca, India.*
Aceclofenac (p. 16·2); paracetamol (p. 115·1).
Fever; inflammation; pain.

Zeroflog *Valeas, Ital.*
Diclofenac (p. 48·3).
Mouth and throat disorders.

Zeroform *Konimex, Indon.*
Loperamide hydrochloride (p. 1854·2).
Diarrhoea.

Zeroguent *Thornton & Ross, UK.*
Liquid paraffin (p. 2191·2); white soft paraffin (p. 2211·3).

Zeroid *NeoPharm, Singapore.*
A range of skin cleansers and moisturisers.
Dry skin; skin irritation.

Zerolatum *Thornton & Ross, UK.*
Liquid paraffin (p. 2191·2).
Bath additive.

Zerone *Umedica, Philipp.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Zeroneum *Thornton & Ross, UK.*
Soya oil (p. 2092·3).
Bath additive.

Zero-P *Deva, Turk.*
Flurbiprofen (p. 65·2).

Zeropain *Konimex, Indon.*
Menthol (p. 2553·2); methyl salicylate (p. 92·1); eugenol (p. 2501·2); benzyl nicotinate (p. 29·3).
Musculoskeletal, joint, peri-articular, and soft-tissue pain; neuralgia.

Zerosorin SN *Schuck, Ger.†*
Anamirta cocculus (p. 2483·1); conium maculatum (p. 2524·3); gelsemium sempervirens (p. 2511·2); zincum metallicum (p. 2126·1).
Homoeopathic preparation.

Zerospasm *Proel, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Zerozole *Thornton & Ross, UK.†*
Macrogol (p. 2547·3); soya oil (p. 2092·3).
Bath additive.

Zerpex *Menarini, Belg.*
Brivudine (p. 970·1).
Herpes zoster infections.

Zerpyco *Atlantis, Mex.*
Pinaverium bromide (p. 2590·3).
Gastrointestinal spasm; gastrointestinal motility disorders.

Zerrsox *Pharmatechnica, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Zerru B-Plex *Pharmatechnica, Philipp.*
Vitamin B_1 (p. 2103·1); vitamin B_6 (p. 2105·3); vitamin B_{12} (p. 2107·2).
Vitamin B deficiency; neuritis.

Zerrucee *Pharmatechnica, Philipp.*
Ascorbic acid (p. 2110·3).
Vitamin C deficiency; vitamin C supplement.

Zertalin *Collins, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Zertin *GSK, Philipp.*
Erdosteine (p. 1665·1).
Respiratory-tract congestion.

Zertine *Bangkok Lab & Cosmetic, Hong Kong; Farmaline, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic skin disorders.

Zesger *Gerard, Irl.*
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Zesger Plus *Gerard, Irl.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ze-Spas *Kee, India.*
Dicycloverine hydrochloride (p. 1834·2); mefenamic acid (p. 85·3).
Smooth muscle spasm.

Zespira *Bilim, Turk.*
Montelukast sodium (p. 1214·3).
Asthma.

Zestagesic *Ad-Drugstel, Philipp.*
Paracetamol (p. 115·1).
Fever; pain.

Zestam *Kalbe, Indon.*
⊗Betamethasone (p. 1623·2); dexchlorpheniramine maleate (p. 621·1).
Allergic disorders.

Zestan
Note: this name may be used for preparations of different composition.
Ad-Drugstel, Philipp.
Mefenamic acid (p. 85·3).
Pain.

Clonmel, Irl.
Lisinopril (p. 1420·3).
Heart failure; hypertension; myocardial infarction; diabetic nephropathy.

Zestat *Abdi, Turk.*
Mirtazapine (p. 436·1).

Zestoretic *AstraZeneca, Arg.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Spain; AstraZeneca, Swed.†; AstraZeneca, Switz.; Abdi, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zestozide *Mylan, S.Afr.*
⊗Lisinopril (p. 1420·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zestril *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, China; AstraZeneca, Fr.; AstraZeneca, Gr.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; Abdi, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
Lisinopril (p. 1420·3).
Hypertension; heart failure; myocardial infarction; diabetic nephropathy; diabetic retinopathy.

Zeta N *Chefaro, Ital.†*
Usnic acid (p. 2640·2).
Vaginal disinfection.

Zetacet *Stiefel, USA.†*
Sulfur (p. 1721·1); sulfacetamide sodium (p. 361·1).
Acne.

Zetagal *Elpen (Ελπεν), Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zetalax *Zeta, Ital.*
⊗Glycerol (p. 2517·2).
Constipation.

Zetalerg *UCI, Braz.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Zetamac *Pfizer, Cz.*
Azithromycin (p. 221·2).
Bacterial infections.

Zetamaks *Pfizer, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections of the respiratory tract.

Zetamax *Pfizer, Pol.; Pfizer, Rus.; Pfizer, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zetamicin *Menarini, Ital.*
Netilmicin sulfate (p. 331·1).
Bacterial infections.

Zetapron *Unipharma, Gr.*
Butamirate citrate (p. 1657·3).
Cough.

Zetar *Dermik, Hong Kong†; Dermik, USA.*
Coal tar (p. 1723·2).
Scalp disorders.

Zetarina *Zafiro, Mex.*
Dopamine hydrochloride (p. 1367·2).
Hypotension; shock; extracorporeal circulation.

Zetavit *Zeta, Ital.*
Vitamins; minerals.

Zetavudin *Richmond, Arg.*
Zidovudine (p. 1024·2); lamivudine (p. 1000·2).
HIV infection.

Zetaxim *Wockhardt, India.†*
Cefotaxime sodium (p. 244·1).
Bacterial infections.

Zetecine *Suphong, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Zethrinal *Biomedica, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Zetia *Schering-Plough, Arg.; Schering-Plough, Braz.; Schering-Plough, Ital.; Merck, USA; Schering-Plough, USA; Schering-Plough, Venez.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia.

Zetifen *Cadila, Rus.†*
Ketotifen fumarate (p. 631·3).

Zetilox *Minerva (Μινερβα), Gr.*
Itraconazole (p. 583·3).
Fungal infections.

Zetion *Nevzat, Turk.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Zetir *Abbott, Braz.; Umedica, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; allergic rhinitis; urticaria; allergic conjunctivitis.

Zetitec *UCI, Braz.*
Ketotifen fumarate (p. 631·3).
Hypersensitivity reactions.

Zetitor *Glenmark, India.*
Ezetimibe (p. 1379·2); atorvastatin calcium (p. 1309·2).
Hypercholesterolaemia.

Zetix *Recalcine, Chile.*
Zopiclone (p. 1118·1).
Insomnia.

Zeto *Trima, Israel.*
Azithromycin (p. 221·2).
Bacterial infections.

Zetofen *TO-Chemicals, Thai.*
Ketotifen (p. 631·3).
Asthma; hypersensitivity reactions.

Zetong *C & O, China.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Zetonium *Elpen (Ελπεν), Gr.*
⊗Oxprenolol hydrochloride (p. 1463·2).

Zetonna *Sunovion, USA.*
⊗Ciclesonide (p. 1626·3).
Allergic rhinitis.

Zetop *Arrow, NZ; Thebe, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic skin disorders; pruritus.

Zetran
Note: this name may be used for preparations of different composition.
Masa, Thai.†
Dipotassium clorazepate (p. 1056·3).
Anxiety; insomnia.

Zetrinal *Tripharma, Rus.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Zetrix *ADP, Philipp.; Charoen, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Zetron
Note: this name may be used for preparations of different composition.
Biolab, Thai.
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.
Libbs, Braz.
Bupropion hydrochloride (p. 408·2).
Depression; aid to smoking withdrawal.
Vocate, Gr.
Ondansetron (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Zetrotax *Richmond, Arg.*
Zidovudine (p. 1024·2).
HIV infection.

Zetrynal *Abdi, Ukr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Zetsim *Schering-Plough, Braz.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia.

Zetsyl *Aurobindo, Rus.*
Ampicillin sodium (p. 218·2) or ampicillin trihydrate (p. 218·2).
Bacterial infections.

Zeufor *Pharos, Indon.*
Citicoline (p. 2480·1).
Head injury; stroke; hemiplegia.

Zevalin *Schering, Austria; Bayer, Belg.; Bayer, Canad.; Bayer Schering, Cz.; Spectrum, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Hong Kong; Bayer Schering, Hung.; Schering, Irl.; Bayer, Israel; Bayer, Ital.; Spectrum, Neth.; Bayer Schering, Norw.; Bayer, NZ†; Bayer Schering, Pol.; Bayer Schering, Port.; Bayer Schering, S.Afr.†; Spectrum, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Schering, Turk.; Bayer, UK; Spectrum, USA.*
Ibritumomab tiuxetan (p. 804·3).
For radiolabelling with indium-111 or yttrium-90.
Non-Hodgkin's lymphoma; follicular lymphoma.

Zevamab *Bayer, Arg.*
Ibritumomab tiuxetan (p. 804·3).
For radiolabelling with yttrium-90.
Non-Hodgkin's lymphoma.

Zevesin *Zentiva, Cz.*
Solifenacin succinate (p. 2367·3).
Bladder instability.

Zevibex *Armoxindo, Indon.*
Vitamins; zinc (p. 2126·1).
Vitamin and zinc supplement.

Zevin *Biolab, Hong Kong†; Biolab, Malaysia; Biolab, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections of the skin and mucous membranes.

Zevit *GSK, India.*
Vitamins; zinc (p. 2126·1).
Tonic.

Zevit C *Tempo Scan Pacific, Indon.*
Vitamin C (p. 2110·3).
Vitamin C deficiency.

Zevit Grow *Tempo Scan Pacific, Indon.*
Caplets: Vitamins; calcium (p. 1783·1); copper (p. 2057·1); zinc (p. 2126·1).
Dietary supplement.
Tempo Scan Pacific, Indon.
Sachets: Vitamins; inositol (p. 2533·2); calcium (p. 1783·1); zinc (p. 2126·1).
Dietary supplement.

Zeviton *Pyridam, Indon.*
Vitamins; zinc (p. 2126·1).
Vitamin and zinc supplement.

Zexanta *Brown & Burk, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Zexat *Dabur, Rus.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Zexate *Fresenius Kabi, Philipp.; Biogalenic, Venez.*
Methotrexate (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.
Fresenius Kabi, Thai.†
Methotrexate sodium (p. 822·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Zezac *Suphong, Thai.*
Fluoxetine hydrochloride (p. 417·1).
Depression; bulimia nervosa; obsessive-compulsive disorder; premenstrual dysphoric disorder; panic disorder.

Z-Fin *Ultra, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

ZFlex *Huckaby, USA.*
Paracetamol (p. 115·1); phenyltoloxamine citrate (p. 638·1).
Pain.

Z-Fluor *Novartis Consumer, Belg.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis.

Z-G *Patar, Thai.*
Zinc gluconate (p. 2126·2).
Dietary supplement.

Z-gen *Goldline, USA.*
Vitamins; minerals.

Zgesic *Capellon, USA.*
Paracetamol (p. 115·1); phenyltoloxamine citrate (p. 638·1).
Pain; fever.

Zha Wei *GuoRui, China.*
Clindamycin phosphate (p. 269·3).
Bacterial infections.

Zhao Min Xin *Qingfeng, China.*
Mecobalamin (p. 2108·1).
Peripheral neuropathy.

Zhao Wei *Lanling, China.*
Metformin hydrochloride (p. 489·1); glibenclamide (p. 472·1).
Diabetes mellitus.

Zhaohuile *Zhaohui, China.*
⊗Triamcinolone acetonide (p. 1649·1); econazole nitrate (p. 577·3).
Fungal skin infections; mixed bacterial and fungal skin infections.

Zhe Peng *Xinbai, China.*
Gatifloxacin (p. 303·2).
Bacterial infections.

Zhedon *Berksam, Turk.*
Donepezil hydrochloride (p. 390·2).

Zhen De *Zhenshiming, China.*
⊗Triamcinolone acetonide (p. 1649·1).
Allergic rhinitis.

Zhen Da *Aosaikang, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone; osteoporosis.

Zhen Ke *Mingshen, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Zhen Li Xin *Double-Crane, China.*
Diammonium glycyrrhizate (p. 2520·3).

Zhen Liang *Lukang Chenxin, China.*
Cefetamet (p. 240·2).
Bacterial infections.

Zhen Tong *Hujiang, China.*
Lysine hydrochloride (p. 2079·3).

Zhen Tong Yan *Xing'an, China.*
Loxoprofen sodium (p. 83·3).
Musculoskeletal and joint disorders.

Zhen Xi *Chang Fu Jie Jing, China.*
Piracetam (p. 393·3).
Mental function impairment.

Zhen Xin *Kangnaier, China.*
Lomefloxacin aspartate.
Bacterial infections.

Zheng Chang Sheng *Shenyang First, China.*
Bacillus licheniformis.
Restoration of gastrointestinal flora.

Zheng Da Su Ke *Qingjiang, China.*
Cefaclor (p. 232·3); bromhexine hydrochloride (p. 1656·3).

Zheng Shu *Yizhou, China.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia; hypertension.

Zheng Ting *Langyi, China.*
Lornoxicam (p. 83·2).
Musculoskeletal and joint disorders.

Zheng Tong Gao *United Lab, China.*
Methyl salicylate (p. 92·1); eucalyptus oil (p. 2501·2); turpentine oil (p. 2636·3); menthol (p. 2553·2).
Musculoskeletal, joint, and soft-tissue injury.

Zheng Tuo *Fengyuan, China.*
⊗Betamethasone sodium phosphate (p. 1623·3).
Corticosteroid.

Zheng Zhi *Yangzhou No 3, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Zhengda Jiepu *Bausch & Lomb, China.*
Aciclovir (p. 964·1).
Herpes simplex keratitis.

Zhengmeiting *Jean-Marie, China.*
Clotrimazole (p. 576·2).
Vaginal candidiasis.

ZhengQing *Hengkang, China.*
Potassium chloride (p. 1793·2); sodium bicarbonate (p. 1781·1); sodium chloride (p. 1795·1); sodium sulfate (p. 1888·1); macrogol 4000 (p. 2547·3).

Zhengrui *Bausch & Lomb, China.*
Anethole trithione (p. 2443·3).
Sjögren's syndrome; radiotherapy-induced xerostomia.

ZhengShu *Chia Tai, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

ZhengYuan *Topfond, China.*
Didanosine (p. 972·3).
HIV infection.

ZhenKe *Zhenshiming, China.*
Clarithromycin (p. 266·2).
Bacterial infections; Helicobacter pylori eradication.

Zhenrui *Bausch & Lomb, China.*
Pilocarpine nitrate (p. 2010·3).
Glaucoma; production of miosis.

ZhenXin *Luya, China.*
Lenampicillin hydrochloride (p. 315·3).

Zhi Ai *Yangtze River, China.*
Doxifluridine (p. 782·3).

Zhi Fu Bao *NCPC, China.*
Clindamycin phosphate (p. 269·3).
Acne.

Zhi Gan Bao *NCPC, China.*
Diammonium glycyrrhizate (p. 2520·3).

Zhi Li *Shuguang, China.*
Phentolamine mesilate (p. 1468·3).

Zhi Mai Xin *Yatai, China.*
Lysine hydrochloride (p. 2079·3).

Zhi Min *Xinzhongzheng, China.*
Loratadine (p. 633·2).
Hypersensitivity reactions.

Zhi Qing *Conba, China.*
Diclofenac potassium (p. 48·3).
Pain; inflammation.

Zhi Tai *Yizhou, China.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Zhi Teng *Pu Sheng, China.*
Lappaconitine hydrobromide (p. 1418·1).

Zhi Wei Bao *NCPC, China.*
Vitamin A palmitate (p. 2098·3); ergocalciferol (p. 2113·3); vitamin E (p. 2119·1); phytomenadione (p. 2122·2).

Zhi Xin *Fengyuan, China.*
Cilnidipine (p. 1337·1).
Hypertension.

Zhi Xin Feng *Changzhou, China.*
Telmisartan (p. 1509·3).
Hypertension.

Zhile *Qilu, China.*
Probucol (p. 1475·2).
Atherosclerosis; hyperlipidaemias.

ZhiLi *Rui Yang, China.*
Troxerutin (p. 2505·3).
Venous insufficiency.

Zhiruo *Chia Tai, China.*
Palonosetron hydrochloride (p. 1875·1).
Nausea and vomiting.

Zhong Bao Luo Tai *Zhong Bao, China.*
Lomefloxacin hydrochloride (p. 319·2).

Zhong Chang *Chia Tai, China.*
Fudosteine (p. 1666·1).

Zhong Jia Tai *Zhongjia, China.*
Ganciclovir (p. 982·3).
Cytomegalovirus infection.

Zhong Sheng Rui Xing *Tailong, China.*
Isosorbide dinitrate (p. 1412·2).
Heart failure; unstable angina.

Zhong Sheng Yan Kang *Tailong, China.*
Potassium dehydroandrographolide succinate.

Zhong Shi De *Zhonglian, China.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Zhong Wei *Topfond, China.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Zhong Xin Tai *New Asiatic, China.*
L-Alanyl-L-glutamine (p. 2070·2).
Parenteral nutrition.

Zhong Yi Mei Song *Guang Da, China.*
⊗Dexamethasone sodium phosphate (p. 1631·2).
Corticosteroid.

Zhongxin *Chushin, China.*
Allantoin (p. 1693·1); vitamin B; vitamin E (p. 2119·1); taurine (p. 2626·2).

Zhou Bang *Jingyou, China.*
Ozagrel sodium (p. 2579·1).

Zhu Li *Yinhu, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zhu Long *Huada, China.*
⊗Bambuterol hydrochloride (p. 1203·1).
Obstructive airways disease.

Zhu Lu *Yao Wang, China.*
Inosine (p. 2533·1).

Zhu Ning *Shuangke, China.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Zhu Zhong Xin *Wansheng, China.*
Gamma-aminobutyric acid (p. 2509·2).

Zhuang Qi *Lianshui, China.*
⊗Loratadine (p. 633·2); pseudoephedrine sulfate (p. 1676·1).
Allergic rhinitis; cold symptoms.

Zhuang Tong *Lianshui, China.*
Arbidol hydrochloride.

Zhuang Yuan *Lianshui, China.*
Levofloxacin lactate.
Bacterial infections.

Zhuo Fang *Ao Dong, China.*
Diammonium glycyrrhizate (p. 2520·3).

Zhuo Fei *TianJing, China.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Zhuo Fu *Qilu, China.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder.

Zhuo Ka *Wei Lun, China.*
Levocarnitine (p. 2053·2).

Zhuo Lai *Xidian, China.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; Paget's disease of bone; osteoporosis.

Zhuo Li *Shuang Cheng, China.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections.

Zhuo Ning *Shuang Cheng, China.*
Lappaconitine hydrobromide (p. 1418·1).

Zhuo Qing *Lukang Chenxin, China.*
Spectinomycin hydrochloride (p. 358·1).
Gonorrhoea.

Zhuo Tan *Qilu, China.*
Ropivacaine hydrochloride (p. 1996·1).
Local anaesthesia.

Zhuo Tong *Gaozhuo, China.*
⊗Ampicillin (p. 218·2); probenecid (p. 607·3).
Bacterial infections.

Zhuo Xun *Changlian Laifu, China.*
Etamsylate (p. 1145·2).
Haemorrhage.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zhuo Yi *Xiuzheng, China.*
⊗Carvedilol (p. 1333·1).
Hypertension; heart failure; angina pectoris; left ventricular dysfunction following myocardial infarction.

Zhuo Yue *Baijingyu, China.*
Lomefloxacin hydrochloride (p. 319·2).
Bacterial eye infections.

Zhuobisha *Pude, China.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Zhuolixin *C & O, China.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Zi Jun *Southwest, China.*
Rifaximin (p. 355·2).

Zi Lin *Hexin, China.*
Aspirin (p. 22·2); isosorbide mononitrate (p. 1413·3).

Zi Luo Su *Bosen, China.*
Levofloxacin mesilate.
Bacterial infections.

Zi Mo *HeBei, China.*
Azulene (p. 2452·1); glutamine (p. 2070·3).

Zi Wei *Shenhua, China.*
L-Alanyl-L-glutamine (p. 2070·2).
Parenteral nutrition.

Zi Yun *Ge Dian Ren Fu, China.*
Mifepristone (p. 2138·1); anordrin.

Ziac *Merck Serono, Arg.; Merck, Chile; Merck, Philipp.; Teva, USA; Merck, Venez.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ziacaine *Zizine, Fr.*
Compress; mouth spray; topical solution: Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Local anaesthesia.

Zizine, Fr.
Injection: Lidocaine hydrochloride (p. 1988·2). Adrenaline acid tartrate (p. 1292·2) or noradrenaline acid tartrate (p. 1458·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ziagel *Zizine, Fr.*
Lidocaine (p. 1988·1); cetrimide (p. 1742·1).
Local anaesthesia.

Ziagen *ViiV, Austral.; ViiV, Austria; ViiV, Belg.; ViiV, Canad.; GSK, Chile; GSK, China; GSK, Cz.; GSK, Denm.; ViiV, Fin.; ViiV, Fr.; ViiV, Ger.; ViiV, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; ViiV, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; ViiV, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; ViiV, Spain; GSK, Swed.; ViiV, Switz.; GSK, Turk.; GSK, UK; ViiV, USA.*
Abacavir sulfate (p. 963·1).
HIV infection.

GSK, Venez.
Abacavir (p. 962·3) or abacavir sulfate (p. 963·1).
HIV infection.

Ziagenavir *GSK, Arg.; GSK, Braz.; GSK, Mex.; GSK, Thai.*
Abacavir sulfate (p. 963·1).
HIV infection.

Ziak *Merck, S.Afr.*
⊗Bisoprolol fumarate (p. 1325·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Ziamid *Vysali, Philipp.*
Ceftazidime (p. 250·2).
Bacterial infections.

Ziana *Medicis, USA.*
Clindamycin phosphate (p. 269·3); tretinoin (p. 1725·2).
Acne.

Ziapro *Aspen, S.Afr.*
⊗Bisoprolol fumarate (p. 1325·3).

Ziatir *Richmond, Arg.*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia.

Ziaxel *Abbott, Gr.; Abbott, Neth.; Abbott, NZ†; Abbott, Port.*
Verapamil hydrochloride (p. 1522·1); trandolapril (p. 1517·2).
Hypertension.

Zibac *Fahrenheit, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zibelant *Chrispa (Χρισπα), Gr.*
Tenoxicam (p. 136·2).
Pain; inflammation; rheumatoid arthritis; spondyloarthropathies; osteoarthritis; gout.

Zibil *Sandoz, Mex.*
⊗Salbutamol (p. 1220·2) or salbutamol sulfate (p. 1220·2).
Obstructive airways disease.

Zibor *Menarini, Cz.; Berlin-Chemie, Hung.; Helsinn Birex, Irl.; Archimedes, UK†; Berlin-Chemie, Ukr.*
Bemiparin sodium (p. 1314·2).
Thromboembolic disorders; thromboembolism prophylaxis.

Zibramax *Guardian, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Zibren *Sigma-Tau, Ital.*
Acetylcarnitine or acetylcarnitine hydrochloride (p. 2053·2).
Cerebrovascular disorders; peripheral neuropathy.

Zibrine *Merck, Belg.*
St John's wort (p. 449·1).
Depression.

Zicam Congestion Relief *Zicam, Canad.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).
Nasal congestion.

Zicam Multi-Symptom Cold & Flu Daytime *Zicam, Canad.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2).
Cold and influenza symptoms.

Zicam Multi-Symptom Cold & Flu Nighttime *Zicam, Canad.†*
Paracetamol (p. 115·1); dextromethorphan hydrobromide (p. 1660·1); doxylamine succinate (p. 627·3).
Cold and influenza symptoms.

Zicam Sinus Relief *Zicam, Canad.†*
⊗Oxymetazoline hydrochloride (p. 1671·3).

Zicet *Jin Yang, Hong Kong†; Jin Yang, Malaysia.†*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria; rhinitis.

Zicho *Nicholas, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Ziclin *Knoll, S.Afr.†*
Gliclazide (p. 472·3).
Diabetes mellitus.

Ziclob *Farmo Quimica, Chile.*
Cyclobenzaprine hydrochloride (p. 2023·1).
Musculoskeletal spasm.

Zicomplex *Ipca, India.*
Vitamin B substances (p. 2102·3); vitamin C (p. 2110·3); zinc sulfate (p. 2126·2).
Dietary supplement; tonic.

Ziconal *Pharmaniaga, Hong Kong.†*
Ketoconazole (p. 585·3).
Fungal infections.

Zicoten *ITF, Gr.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zicron *Bristol, UK.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Zidalev *Ifars, Indon.*
Levofloxacin (p. 315·3).
Bacterial infections.

Zidaxim *Flamingo, Philipp.*
Ranitidine hydrochloride (p. 1882·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; acid aspiration; Zollinger-Ellison syndrome.

Zidepril *Minerva (Μινερβα), Gr.*
⊗Captopril (p. 1331·2); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zideron *Norma (Νορμα), Gr.*
Dextropropoxyphene hydrochloride (p. 43·3).
Pain.

Zidiar *Tempo Scan Pacific, Indon.*
Zinc sulfate (p. 2126·2).
Dietary supplement in diarrhoea.

Zidic-C *Arlex, Mex.†*
Zidovudine (p. 1024·2).
HIV infection.

Zidicef *Precimex, Mex.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Zidifec *Sanbe, Indon.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zidim *Tum, Turk.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zidima *Fabop, Arg.†*
Ceftazidime (p. 250·2).
Bacterial infections.

Zidimax *Laboris, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Zidimox *Farmoz, Port.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zidin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Zidofen *Genepharm, Gr.*
Ketotifen fumarate (p. 631·3).
Allergic eye disorders.

Zido-H *Hetero, Rus.*
Zidovudine (p. 1024·2).
HIV infection.

Zidolam *Euroforma, Braz.*
Lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Zidomuv *LKM, Arg.*
Abacavir sulfate (p. 963·1); lamivudine (p. 1000·2); zidovudine (p. 1024·2).
HIV infection.

Zidonil *Rafarm, Gr.*
Fluconazole (p. 578·2).
Fungal infections.

Zidoril *Unifa, Port.†*
Finasteride (p. 2358·3).
Benign prostatic hyperplasia.

Zidoval *iNova, Austral.; Meda, Denm.; Meda, Fin.; 3M, Israel; Meda, Ital.; Meda, Norw.; Meda, Spain; Meda, Swed.; 3M, UK.*
Metronidazole (p. 936·1).
Bacterial vaginosis.

Zidovimm *Anfarm, Gr.*
Aciclovir (p. 964·1).
Labial and genital herpes simplex infections.

Zidovir *Cristalia, Braz.; Cipla, India; Cipla, Venez.*
Zidovudine (p. 1024·2).
HIV infection.

Zidovirine *Veropharm, Rus.*
Zidovudine (p. 1024·2).
HIV infection.

Zidoxer *Labormed, Cz.; Labormed, Pol.*
Topiramate (p. 550·3).
Epilepsy; migraine.

Zidrevir *Kleva, Gr.*
Zidovudine (p. 1024·2).
HIV infection.

Zidrid *Doctors, Philipp.*
Isoniazid (p. 311·2).
Tuberculosis.

Zidrol *Demo, Gr.*
Codergocrine mesilate (p. 389·2).

Zidrolin *Demo, Gr.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Ziegella *Peterer, Switz.†*
Juniper oil (p. 2537·2); ethyl nicotinate (p. 56·3); rosemary oil (p. 2607·3); sage oil (p. 2609·1); St John's wort oil (p. 449·1); lavender oil (p. 2541·1); pine-needle oil (p. 2591·1); calendula oil (p. 2465·2).
Musculoskeletal and joint disorders; neuritis.

Zienam *MSD, Arg.; MSD, Austria; MSD, Ger.; MSD, Venez.*
Imipenem (p. 309·2); cilastatin sodium (p. 260·3).
Lidocaine hydrochloride (p. 1988·2) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Zient *Schering-Plough, Chile; MSD, Cz.†; Schering-Plough, Mex.; Schering-Plough, Venez.*
Ezetimibe (p. 1379·2).
Hypercholesterolaemia; sitosterolaemia; hyperlipidaemias; atherosclerosis.

ZI-Factor *Veropharm, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Zifam *Polfa Warszawa, Pol.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; cardiovascular risk reduction.

Zifartel *Continentales, Mex.†*
Praziquantel (p. 164·1).
Cysticercosis.

Zifin *Fahrenheit, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Zigabal *Tecnimede, Port.*
Oxcarbazepine (p. 533·2).
Epilepsy; trigeminal neuralgia.

Zigacap *Bangkok Lab & Cosmetic, Thai.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ziga-Gel *Bangkok Lab & Cosmetic, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).
Gastric hyperacidity; peptic ulcer; flatulence; abdominal distension.

Zigatab *Bangkok Lab & Cosmetic, Thai.*
Aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2); simeticone (p. 1886·2).

Zigmadone *Virgo, Philipp.*
Povidone-iodine (p. 1767·1).
Wounds; skin and mucous membrane disinfection.

Ziguli *Falqui, Ital.*
A range of vitamin preparations.

Zikaral *Sanovel, Turk.*
Tenoxicam (p. 136·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Ziken *Kendrick, Mex.†*
Mesna (p. 1557·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Ziks *Nnodum, USA.*
Methyl salicylate (p. 92·1); menthol (p. 2553·2); capsaicin (p. 35·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Zil *Piramal, India.*
Ornidazole (p. 943·1).
Trichomoniasis; anaerobic bacterial infections; amoebiasis; giardiasis.

Zilaben *Cristalia, Braz.*
Benzyl benzoate (p. 2149·1).
Pediculosis; scabies.

Zilactin
Note: this name may be used for preparations of different composition.
Blairex, USA.
Benzyl alcohol (p. 1739·3).
Herpes labialis.

Zila, Philipp.
⊗Tannic acid (p. 2625·2); alcohol (p. 1733·1).
Canker sores; fever blisters; cold sores.

Zilactin-B Medicated *Zila, USA.*
Benzocaine (p. 1980·2).
Canker sores.

Zilactin-L
Note: this name may be used for preparations of different composition.
Blairex, USA.
Benzyl alcohol (p. 1739·3).
Formerly contained lidocaine.
Herpes labialis.

Ziladent
Note: this name may be used for preparations of different composition.
Zila, Philipp.
⊗Alcohol (p. 1733·1); lidocaine (p. 1988·1).
Mouth pain.

Zilarex *Sandoz, Austral.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Zilast *Ipca, India.*
Cilostazol (p. 1337·1).
Intermittent claudication.

Zilavir *GPO, Thai.*
Zidovudine (p. 1024·2); lamivudine (p. 1000·2).
HIV infection.

Zilden *Genepharm, Gr.*
Diltiazem hydrochloride (p. 1359·2).
Angina pectoris; hypertension.

Pascual, Philipp.
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Zildox *Naprod, Philipp.*
Oxaliplatin (p. 838·1).
Colorectal cancer.

Ziledon *Sandoz, Braz.*
Donepezil hydrochloride (p. 390·2).

Zileze *Chiesi, Irl.*
Zopiclone (p. 1118·1).
Insomnia.

Zilfic *Mintlab, Chile.*
Sildenafil citrate (p. 2364·1).
Erectile dysfunction.

Zilion *Cadila, India.*
Zidovudine (p. 1024·2).
HIV infection.

Zilip *LPB, Ital.*
Penciclovir (p. 1008·2).
Herpes labialis.

Zilisten *Demo, Gr.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zilium *Kela, Belg.*
Domperidone maleate (p. 1838·1).
Delayed gastric emptying; nausea and vomiting.

Zillt *KRKA, Rus.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Zilola *Gedeon Richter, Ukr.*
Levocetirizine (p. 632·3).
Allergic rhinitis; urticaria.

Zilongjin *Longshunrong, Philipp.*
Astragalus; angelica (p. 2443·3).
Nutritional supplement.

Zilop *Nicholas, Indon.*
Gemfibrozil (p. 1390·3).
Hyperlipidaemias; coronary heart disease.

Zilopur *Apsen, Braz.†*
Allopurinol (p. 600·2).
Gout.

Zilovis *Intermed, Gr.*
⊗Celiprolol hydrochloride (p. 1334·2).

Zilrin *Raam, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Zilt *KRKA, Ukr.*
Clopidogrel bisulfate (p. 1342·3).
Atherosclerosis.

Zilutra *Zentiva, Cz.*
Trimetazidine hydrochloride (p. 1520·1).
Angina pectoris.

Zimadoce *Rubio, Spain.†*
Cobamamide (p. 2107·2).
Tonic.

Zimaks *Bilim, Turk.*
Cefixime (p. 240·3).
Bacterial infections.

Zimalgin *Shreya, India.*
Paracetamol (p. 115·1); caffeine (p. 1203·3); codeine phosphate (p. 40·2).
Pain.

Zimanel *Proge, Ital.*
Cefotaxime sodium (p. 244·1).
Lidocaine hydrochloride (p. 1988·2) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Zimaquin *Gynopharm, Chile.*
⊗Clomifene citrate (p. 2259·1).
Female and male infertility; menstrual disorders.

Zimbacol *Link, UK.*
Bezafibrate (p. 1323·2).
Hyperlipidaemias.

Zimcor *Sydenham, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Zimerol
Note: this name may be used for preparations of different composition.
Cetus, Arg.
Orotic acid (p. 2578·1); dehydrocholic acid (p. 2492·1); deoxycholic acid (p. 2457·2); homatropine (p. 2007·3).
Liver disorders.

Zimerz *Ildong, Philipp.*
Memantine hydrochloride (p. 393·1).
Dementia in parkinsonism; Alzheimer's disease.

Zimetek *Biotenk, Arg.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia.

Zimeton
Note: this name may be used for preparations of different composition.
Sons, Mex.
⊗Pancreatin (p. 2579·3); bile salts (p. 2457·2); simeticone (p. 1886·2).
Digestive disorders.

Zimicina *Hexal, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Zimmex *Silom, Thai.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease.

Zimocel *SIT, Ital.*
Dried yeast (p. 2125·2).

Zimoclone *Generics, Irl.*
Zopiclone (p. 1118·1).
Insomnia.

Zimor *Rubio, Malaysia; Rubio, Singapore; Rubio, Spain.*
Omeprazole (p. 1867·2).
Peptic ulcer; Zollinger-Ellison syndrome; gastro-oesophageal reflux.

Zimotris *Italmex, Mex.*
⊗Amylase (p. 2442·1); lipase (p. 2579·3); pepsin (p. 2586·1); chymotrypsin (p. 2477·3); trypsin (p. 2635·2).
Digestive disorders; pancreatic insufficiency.

Zimovane *Meda, Irl.; Sanofi, UK.*
Zopiclone (p. 1118·1).
Insomnia.

Zimox
Note: this name may be used for preparations of different composition.
Angelini, Gr.
Levodopa (p. 902·2); carbidopa (p. 900·3).
Parkinsonism.
Pfizer, Ital.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Zimpax *Vera, Hung.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zim's Max Freeze *Perfecta, USA.*
Ilex flower; arnica (p. 2447·2); vitamin E (p. 2119·1); aloe vera (p. 1693·2); melaleuca oil (p. 2551·1); camphor (p. 2466·2); menthol (p. 2553·2).
Musculoskeletal and joint pain.

Zimstat *Alphapharm, Austral.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Zimulti *Sanofi-Aventis, Cz.†; Sanofi-Aventis, Neth.†; Sanofi-Aventis, Port.†; Sanofi-Aventis, Rus.*
Rimonabant (p. 2606·2).
Obesity.

Zimuvite *Pediapharma, Philipp.*
Ascorbic acid (p. 2110·3); betacarotene (p. 2051·1); *dl*-alpha tocoferil acetate (p. 2119·2); zinc gluconate (p. 2126·2).
Immune stimulant; tonic.

Zimva *GPO, Thai.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Zimvacor *Prohealth, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; ischaemic heart disease.

Zimycan *Neopharm, Israel†; Barrier Therapeutics, Neth.†; Barrier Therapeutics, Port.†*
Miconazole nitrate (p. 589·1).
Candidal nappy rash; fungal skin infections.

Zinace *Ace, Philipp.*
Cefalexin (p. 234·1).
Bacterial infections.

Zinacef *GSK, Belg.; GSK, Braz.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.†; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; GSK, Ukr.; Covis, USA; GSK, Venez.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

GSK, China; GSK, Philipp.
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Zinaderm *Rougier, Canad.*
Zinc oxide (p. 1729·1).
Skin disorders.

Zinadiur *Errekappa, Ital.*
⊗Benazepril hydrochloride (p. 1314·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zinadol *GSK, Gr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zinadril *Errekappa, Ital.*
Benazepril hydrochloride (p. 1314·3).
Hypertension; heart failure.

Zinaf
Note: this name may be used for preparations of different composition.
2 World Lab, Philipp.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zinalow *Indeco, Arg.*
Topiramate (p. 550·3).
Epilepsy.

Zinamide *CSL, Austral.†; MSD, NZ†; Genus, UK.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Zinaplex *Pediatrica, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Zinaprim *Tolmann, Philipp.*
Pyrazinamide (p. 345·2).
Tuberculosis.

Zinasen *Atral, Port.*
Flunarizine hydrochloride (p. 629·3).
Migraine; vertigo.

Zinat *GSK, Switz.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zinaxin *Ferrosan, Rus.; Ferrosan, Ukr.*
Ginger (p. 1844·1); alpinia galanga.
Osteoarthritis.

Vita Healthcare, UK.
Ginger (p. 1844·1).
Musculoskeletal and joint disorders.

Zinaxin Plus *Eurovita, Thai.†*
Ginger (p. 1844·1); alpinia galanga.
Osteoarthritis.

Zinbee *Pediapharma, Philipp.*
Zinc gluconate (p. 2126·2).
Nutritional supplement; zinc deficiency.

Zinc for Acne *Natural Life, Arg.*
Zinc gluconate (p. 2126·2); vitamin C (p. 2110·3); vitamin B_6 (p. 2105·3); vitamin A (p. 2098·3); vitamin E (p. 2119·1).

Zinc Antioxidante + Guarana *Tecnonat, Arg.*
Zinc gluconate (p. 2126·2); vitamin C (p. 2110·3); vitamin E (p. 2119·1); betacarotene (p. 2051·1); guarana (p. 2648·2).
Dietary supplement.

Zinc Cream White *Faulding Consumer, Austral.*
SPF 30+: Zinc oxide (p. 1729·1); octinoxate (p. 1715·1); enzacamene (p. 1703·2).
Sunscreen; skin irritation; skin abrasions.

Zinc Lotion *Vitamed, Israel.*
Zinc oxide (p. 1729·1).
Skin irritation.

Zinc Ofteno *Sophia, Mex.*
Zinc sulfate (p. 2126·2); phenylephrine hydrochloride (p. 1672·3).
Eye irritation.

Zinc Pharmacore *Pharmacore, Indon.*
Copper gluconate (p. 2057·2); zinc gluconate (p. 2126·2); zinc picolinate (p. 2126·1).
Dietary supplement for healthy skin and hair; wounds.

Zinc Plus *Cenovis, Austral.*
Zinc amino acid chelate (p. 2048·3); manganese amino acid chelate (p. 2048·3); pyridoxine hydrochloride (p. 2105·3).
Dietary supplement.

Swiss Herbal, Canad.†
Zinc gluconate (p. 2126·2); zinc proteinate; vitamin C (p. 2110·3).

Zinc Tab *T Man, Thai.*
Zinc gluconate (p. 2126·2).

Zinc Zap *Nutrimmune, Canad.*
Pyrithione zinc (p. 1718·1).

Zinc Zenith *Eagle, Austral.*
Zinc amino acid chelate (p. 2048·3); ascorbic acid (p. 2110·3); pyridoxine hydrochloride (p. 2105·3); minerals.
Zinc supplement.

Zincaband *SSL, Austral.; Medlock Medical, UK.*
Zinc oxide (p. 1729·1).
Medicated bandage; eczema; leg ulcers.

Zinc-ACE *Wassen, UK.*
Zinc (p. 2126·1); vitamins.

Zinca-Pak *Smith & Nephew SoloPak, USA.†*
Zinc sulfate (p. 2126·2).
Additive for intravenous total parenteral nutrition solutions.

Zincaps *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ; ST, Thai.*
Zinc sulfate (p. 2126·2).
Zinc supplement.

Zincare *Kalbe, Indon.*
Zinc sulfate (p. 2126·2).
Diarrhoea in children.

Zincas *Farmapol, Pol.*
Zinc hydroaspartate (p. 2126·1).
Skin disorders; wounds; depression; nervous disorders; aggression; schizophrenia; erectile dysfunction; growth disorders in children; immunological disorders.

Zincate *ST, Thai.; Paddock, USA.*
Zinc sulfate (p. 2126·2).
Dietary supplement.

Zincation *Isdin, Spain.†*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Zincation Plus *Isdin, Spain.*
Pyrithione zinc (p. 1718·1); coal tar (p. 1723·2).
Scalp disorders.

Zincfrin *Alcon, Austral.†; Alcon, Belg.†; Alcon, Canad.†; Alcon, Denm.†; Alcon, Gr.; Alcon, Mex.; Alcon, NZ†; Alcon, Swed.†; Alcon, USA.†*
Phenylephrine hydrochloride (p. 1672·3); zinc sulfate (p. 2126·2).
Eye irritation; conjunctivitis; eye congestion.

Zincfrin-A *Alcon, Canad.†; Alcon, Gr.; Alcon, Mex.; Alcon, S.Afr.†*
⊗Antazoline phosphate (p. 615·3); naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Allergic conjunctivitis.

Zinc-Imizol *Farmigea, Ital.*
⊗Zinc sulfate (p. 2126·2); naphazoline nitrate (p. 1669·3).
Conjunctivitis, alone or associated with blepharitis.

Zinco *Berko, Turk.*
Zinc sulfate (p. 2126·2).
Zinc deficiency; zinc supplement.

Zinco Acqua *Sella, Ital.*
Zinc oxide (p. 1729·1).
Skin disorders.

Zinco C *Berko, Turk.*
Zinc sulfate (p. 2126·2); vitamin C (p. 2110·3).
Zinc deficiency; zinc supplement.

Zinco Sulpha *Bell, India.†*
Sulfacetamide sodium (p. 361·1); zinc sulfate (p. 2126·2).
Eye infections.

Zincobest *Drogsan, Turk.*
Zinc sulfate (p. 2126·2).

Zincod *Vitamed, Israel.*
Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3); kaolin (p. 1850·1).
Nappy rash; skin irritation.

Zincoderm *Taro, Canad.†; Bersan, Ital.*
Zinc oxide (p. 1729·1).
Skin disorders.

Zincoderma *Confar, Port.*
Zinc oxide (p. 1729·1).
Cicatrisation.

Zincofax *Pendopharm, Canad.*
Zinc oxide (p. 1729·1).
Nappy rash.

Zincol *Sam-On, Israel.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zincolok *Allergan, Braz.*
⊗Zinc sulfate (p. 2126·2); naphazoline hydrochloride (p. 1669·3).
Ocular congestion.

Zincomed *Focus, UK.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zincometil *Farmila, Ital.*
Benzalkonium chloride (p. 1737·1); zinc sulfate (p. 2126·2).
Eye disinfection.

Zincon *Lederle, USA.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zincopan *Gunther, Braz.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zincopto *Armoxindo, Indon.*
⊗Naphazoline hydrochloride (p. 1669·3); zinc sulfate (p. 2126·2).
Eye irritation.

Zincoral *Mavi, Ital.*
Zinc (p. 2126·1); copper (p. 2057·1).

Zincosol *Bioceuticals, UK.*
Zinc sulfate (p. 2126·2).

Zincotape *Lohmann, Ital.*
Zinc oxide (p. 1729·1).
Medicated dressing.

Zincover *Atlas, Turk.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zincovit *Labomed, Chile.*
Vitamin A (p. 2098·3); vitamin C (p. 2110·3); vitamin E (p. 2119·1); zinc (p. 2126·1).
Dietary supplement.

Theraskin, Braz.
Vitamins; copper (p. 2057·1); zinc (p. 2126·1).

Zincoxid *Framingham, Arg.*
Zinc oxide (p. 1729·1).
Dietary supplement.

Zinc-Oxyde Plus *First Aid Research, USA.*
Zinc oxide (p. 1729·1); menthol (p. 2553·2).
Skin disorders.

Zincpro *Combiphar, Indon.*
Zinc sulfate (p. 2126·2).
Dietary supplement in diarrhoea.

ZinCream *Medinova, Switz.*
Zinc oxide (p. 1729·1).
Wounds; nappy rash.

Zinc-S Plus *DNR, Arg.*
Pyrithione zinc (p. 1718·1); undecylenamide (p. 596·3); sulfurated amino acids; collagen (p. 2483·2).
Scalp disorders.

Zincstic *Ideal Health, UK.*
Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Zinctab *Pharmasant, Thai.*
Zinc (p. 2126·1).
Zinc supplement.

Zincteral *Polfa, Cz.†; Teva, Pol.; Teva, Rus.; Teva, Ukr.*
Zinc sulfate (p. 2126·2).
Zinc supplement; zinc deficiency; skin and nail disorders.

Zincum Cyanidum Complexe No 101 *Lehning, Fr.†*
Zincum cyanidum; amanita muscaria; arnica montana (p. 2447·2); avena sativa (p. 2451·1); cuprum aceticum (p. 2486·2); stramonium (p. 2622·3); gelsemium (p. 2511·2); hyoscyamus (p. 2530·2); hypericum (p. 449·1); kalium iodatum (p. 2336·3).
Homoeopathic preparation.

Zincum Hevert N *Hevert, Ger.*
Cimicifuga (p. 2478·1); hyoscyamus (p. 2530·2); ignatia (p. 2532·1); platinum metallicum (p. 2593·1); phosphorus (p. 2589·2); zincum met. (p. 2126·1).
Homoeopathic preparation.

Zincum valerianicum comp *Hevert, Ger.*
Cimicifuga (p. 2478·1); cocculus (p. 2483·1); cypripedium pubescens; ignatia (p. 2532·1); passiflora incarnata (p. 2584·1); platinum metallicum (p. 2593·1); valeriana (p. 2640·2); zincum val. (p. 2641·2).
Homoeopathic preparation.

Zincum valerianicum-Hevert N *Hevert, Ger.†*
Oral drops: Cimicifuga (p. 2478·1); cocculus (p. 2483·1); cypripedium pubescens; ignatia (p. 2532·1); lilium tigrinum; passiflora incarnata (p. 2584·1); platinum (p. 2593·1); valeriana (p. 2640·2); zincum valerianicum (p. 2641·2).
Homoeopathic preparation.

Zincuprin *Sun-Farm, Pol.†*
Copper hydroaspartate; zinc hydroaspartate (p. 2126·1).
Copper and zinc deficiency.

Zincvit *Kenwood, USA.*
Vitamins; minerals.

Zindaclin *Ascent, Austral.; Crawford, Cz.†; ProStrakan, Hong Kong; Crawford, Irl.; Taro, Israel; Difa, Ital.; Wolff, Malaysia; Crawford, Pol.; Astellas, Port.; Cantabria, Spain; Crawford, UK.*
Clindamycin phosphate (p. 269·3).
Acne.

Pharma Logistics, Belg.; Strakan, Singapore.
Clindamycin (p. 269·3).
Acne.

Zindacline *DB, Fr.*
Clindamycin phosphate (p. 269·3).
Acne.

Zindal *Prosel, Philipp.*
Clindamycin hydrochloride (p. 269·3).
Bacterial infections; protozoal infections.

Zindel *SoSe, Ital.*
Azithromycin (p. 221·2).

Zinecard *Pfizer, Canad.; IFET (ΙΦΕΤ), Gr.*
Dexrazoxane (p. 1548·1).
Prevention of doxorubicin cardiotoxicity.

Pharmacia Upjohn, USA.
Dexrazoxane hydrochloride (p. 1548·1).
Prevention of doxorubicin cardiotoxicity.

Zineli *Rafarm, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic conjunctivitis; allergic rhinitis.

Zineryt *Eurolab, Arg.; Astellas, Belg.; Astellas, Cz.; Almirall Hermal, Ger.; Astellas, Hung.; Astellas, Irl.; Astellas, Ital.; Astellas, Neth.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, S.Afr.; Yamanouchi, Spain; Astellas, UK; Astellas, Ukr.*
Erythromycin (p. 291·2); zinc acetate (p. 2126·1).
Acne.

Zinetac *GSK, India.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal hyperacidity; dyspepsia.

Zinetrin *Stiefel, Braz.†*
Cetirizine (p. 619·2).
Hypersensitivity reactions.

Zinex *Verheilen, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Zinfect *Verisfield, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zinforo *AstraZeneca, Denm.; AstraZeneca, Norw.; AstraZeneca, UK.*
Ceftaroline fosamil acetate (p. 250·1).
Bacterial infections.

AstraZeneca, Neth.
Ceftaroline fosamil.
Skin and soft-tissue infections; community-acquired pneumonia.

Zingibir *Labofarm, Pol.*
Ginger (p. 1844·1).
Motion sickness.

Zingo *Anesivo, USA.†*
Lidocaine hydrochloride (p. 1988·2).
Local anaesthesia.

Zinit *Livzon, China.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; pruritus.

Zink AL *Aliud, Ger.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zink beta *Betapharm, Ger.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zink Hexal *Hexal, Ger.†*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zink Verla *Verla, Ger.; Biomed, Switz.*
Zinc gluconate (p. 2126·2).
Zinc deficiency.

Zinkamin *Falk, Ger.*
Bis(L-histadinato) zinc (p. 2048·3).
Zinc deficiency.

Zinkaspart *Twardy, Ger.*
Zinc aspartate (p. 2126·1).
Zinc deficiency.

Zinkbrause *Verla, Ger.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zink-D Longoral *Drossapharm, Ger.*
Zinc gluconate (p. 2126·2).
Zinc deficiency.

Zinke *Key Sun, Austral.*
SPF 30+: Zinc oxide (p. 1729·1).
Sunscreen.

Zinke White *Key Sun, Austral.*
SPF 30+: Zinc oxide (p. 1729·1); titanium dioxide (p. 1725·1).
Sunscreen.

Zink-Injekt N *Worwag, Ger.*
Zinc gluconate (p. 2126·2).
Zinc deficiency.

Zinkit *Worwag, Ger.; Worwag, Ukr.*
Zinc sulfate (p. 2126·2).
Zinc deficiency; zinc supplement.

Zinkokehl *Sanum-Kehlbeck, Ger.*
Zincum gluconicum (p. 2126·2).
Homoeopathic preparation.

Zinkolie *Remark, Neth.*
Zinc oxide (p. 1729·1).
Skin disorders.

Zinkorell *Sanorell, Ger.*
Injection: Zincum gluconicum (p. 2126·2).
Homoeopathic preparation.

Zinkorot *Worwag, Ger.*
Zinc orotate (p. 2126·1).
Zinc deficiency.

Zinkorotat-POS *Urspharm, Cz.†*
Zinc orotate (p. 2126·1).
Zinc deficiency.

Zinkotase *Biosyn, Ger.*
Zinc aspartate (p. 2126·1).
Zinc deficiency.

Zink-Ratiopharm *Ratiopharm, Ger.*
Zinc sulfate (p. 2126·2).
Zinc deficiency.

Zinksalbe
Note: this name may be used for preparations of different composition.
CT, Ger.
⊗Zinc oxide (p. 1729·1); cod-liver oil (p. 2056·3); glycerol (p. 2517·2).
Wounds.

Zinksalbe Lichtenstein *Winthrop, Ger.*
Zinc oxide (p. 1729·1).
Skin disorders.

Zink-Sandoz *Sandoz, Ger.†*
Zinc gluconate (p. 2126·2) or zinc sulfate (p. 2126·2).
Zinc deficiency.

Zinkzalf *Remark, Neth.*
Zinc oxide (p. 1729·1).
Skin disorders.

Zinmet *Oboi, Philipp.*
Promethazine hydrochloride (p. 638·2).
Hypersensitivity reactions; nausea and vomiting; vestibular disorders; premedication.

Zinnat *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Etex, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.†; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, NZ; Duncan, Philipp.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.†; GSK, Thai.; GSK, UK; GSK, Ukr.; GSK, Venez.*
Cefuroxime axetil (p. 255·2).
Lidocaine hydrochloride (p. 1988·2) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

GSK, Turk.
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zinnia *Bernabo, Arg.*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; contraception in patients with androgenic symptoms.

Zinnober D6 *Weleda, S.Afr.†*
Cinnabarit (p. 2555·3).
Homoeopathic preparation.

Zino *Reckitt Benckiser, Gr.*
Salicylic acid (p. 1719·1).
Calluses.

Zinocep *Glaxo Allen, Ital.*
Cefuroxime sodium (p. 255·3).
Bacterial infections.

Zinone *Ethica, Indon.*
Vitamins; zinc sulfate (p. 2126·2).
Vitamin and zinc deficiencies.

Zinopin *Pynogin, UK.*
Pycnogenol (p. 2590·3); ginger (p. 1844·1).
Deep-vein thrombosis prophylaxis for travellers; motion sickness.

Zinopril *Teuto, Braz.*
Lisinopril (p. 1420·3).
Hypertension.

Zinor *Patar, Thai.*
Norfloxacin (p. 333·3).
Bacterial infections.

Zinothin *Naprod, Thai.*
Azathioprine (p. 1940·3).

Zinotic *Arbor, USA.†*
Chloroxylenol (p. 1748·2); pramocaine hydrochloride (p. 1993·3); zinc acetate (p. 2126·1).
Otitis externa; ear wax removal.

Zinovat *Unipharma, Gr.*
Fluoxetine hydrochloride (p. 417·1).
Depression.

Zinoxid *Universal, Hong Kong.†*
Zinc oxide (p. 1729·1).

Zinoxime *Montrose, Cz.†; Actor, S.Afr.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zinoxx *Tabuk, Pol.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zinsomine *Christo, Hong Kong.*
Diphenhydramine hydrochloride (p. 626·2); cetrimide (p. 1742·1); zinc oxide (p. 1729·1).
Dermatitis; pruritus.

Zintion *Drogsan, Turk.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Zintona *Grunwalder, Austria; Grunwalder, Ger.*
Ginger (p. 1844·1).
Motion sickness; dizziness; nausea; vomiting.

Zintrepid *Schering-Plough, Chile; Schering-Plough, Mex.; Schering-Plough, Venez.*
Ezetimibe (p. 1379·2); simvastatin (p. 1489·2).
Hypercholesterolaemia.

Zinulin *Sarabhai Piramal, India.*
⊗Insulin zinc injection (porcine) (30% amorphous, 70% crystalline) (p. 475·3).
Diabetes mellitus.

Zinvalon *Vifel, Gr.*
Codergocrine mesilate (p. 389·2).

Zinvel *Mega Lifesciences, Thai.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases; osteolysis of malignancy.

Zinvit *Blackmores, Austral.*
Zinc sulfate (p. 2126·2); magnesium sulfate (p. 1787·3); vitamin B substances (p. 2102·3).
Zinc deficiency.

Zinvit C *Blackmores, Austral.†*
Zinc sulfate (p. 2126·2); magnesium sulfate (p. 1787·3); ascorbic acid (p. 2110·3).
Skin disorders; wounds; herpes labialis; mouth ulcers.

Zinvit G *Blackmores, Austral.†*
Zinc sulfate (p. 2126·2); magnesium sulfate (p. 1787·3); vitamin B substances (p. 2102·3).
Zinc deficiency; skin disorders.

Zinvital *Adeka, Turk.*
Zinc sulfate (p. 2126·2).

Zinx Chlor-D *Auriga, USA.*
⊗Chlorphenamine maleate (p. 620·3); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Ziohex *Sandoz, Philipp.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zionel *Vitalink, Philipp.*
⊗Metoprolol tartrate (p. 1434·3).
Hypertension; angina pectoris; arrhythmias; myocardial infarction; heart failure.

Zioptan *Merck, USA.*
Tafluprost (p. 2012·1).
Glaucoma; ocular hypertension.

Ziox *Stratus, USA.†*
⊗Papain (p. 2582·3); urea (p. 1727·3); chlorophyllin copper complex (p. 2178·3).

Zip-A-Dol *Labialfarma, Port.*
Ibuprofen (p. 68·2).
Fever; pain.

Zipantol *Decomed, Port.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zipantola *Teva, Rus.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ziperid *Valeant, Hung.; ICN, Pol.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders.

Zipos *Alter, Port.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zipra *Columbia, Mex.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Zipragen *Biogened, Pol.*
Ziprasidone (p. 1115·2).
Bipolar disorder; schizophrenia.

Ziprax *Ciplo, India.*
Cefixime (p. 240·3).
Bacterial infections.

Ziproc *Torrent, Philipp.*
Clozapine (p. 1057·3).
Schizophrenia.

Ziprocap *Interhealthcare, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Ziprodec *Decomed, Port.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Ziprol *Baldacci, Braz.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer.

Zipsi *Actavis, Cz.*
Ziprasidone hydrochloride (p. 1115·2).
Schizophrenia; bipolar disorder.

Zipsor *Depomed, USA.*
Diclofenac potassium (p. 48·3).
Pain.

Zipsydon *Sun, India.*
Ziprasidone (p. 1115·2).
Schizophrenia.

Ziptek *UCB, Gr.†*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity disorders.

Zipwell *Actavis, Pol.*
Ziprasidone (p. 1115·2).
Schizophrenia; bipolar disorder.

Zipzoc *Smith & Nephew, Austral.; Smith & Nephew, Canad.; Smith & Nephew, Denm.; Smith & Nephew, Fin.; Smith & Nephew, Irl.; Smith & Nephew, Neth.†; Smith & Nephew, Port.; Smith & Nephew Healthcare, UK.*
Zinc oxide (p. 1729·1).
Venous insufficiency; leg ulcers.

Zipzoc Salvstrumpa *Smith & Nephew, Swed.*
Zinc oxide (p. 1729·1).
Vascular disorders; skin ulcers.

Ziradryl *Parke, Davis, USA.*
Diphenhydramine hydrochloride (p. 626·2); zinc oxide (p. 1729·1); camphor (p. 2466·2).
Pruritus.

Ziravir *Marvecs, Ital.†*
Famciclovir (p. 979·1).
Herpesvirus infections.

Zircam *Orchid, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Zircol *Alphapharm, Austral.*
Lercanidipine hydrochloride (p. 1419·3).
Hypertension.

Zirconia *Wermar, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Ziremex *Demo, Gr.*
Nimodipine (p. 1455·2).
Neurological deficit following subarachnoid haemorrhage.

Ziremilon *Demo, Gr.*
⊗Nandrolone decanoate (p. 2293·1).

Zirenol *Demo, Gr.*
Cefatrizine propylene glycol (p. 237·2).
Bacterial infections.

Zirgan *Bausch & Lomb, USA.*
Ganciclovir (p. 982·3).
Herpetic keratitis.

Zirofalen *Chrispa (Χρισπα), Gr.*
Sulindac sodium (p. 134·2).

Zirotan *Santa, Gr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Zirpine *Pinewood, Irl.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; pruritus.

Zirtec *UCB, Ital.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; conjunctivitis; urticaria.

Zirtek *UCB, Irl.; UCB, UK.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; pruritus; allergic conjunctivitis.

Zirtek Plus *UCB, Irl.*
⊗Cetirizine hydrochloride (p. 619·2); pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Zirtene *Gerard, Irl.*
Cetirizine hydrochloride (p. 619·2).
Rhinitis; urticaria; pruritus.

Zirvit *Ativus, Braz.*
Vitamins; minerals.

Zirvit Beta *Ativus, Braz.*
Betacarotene (p. 2051·1).
Vitamin A deficiency; photosensitivity.

Zirvit E *Ativus, Braz.*
Tocoferil acetate (p. 2119·2).
Vitamin E deficiency.

Ziserfin *Demo, Gr.*
⊗Propranolol hydrochloride (p. 1479·1).

Zismirt *Gerard, Irl.*
Mirtazapine (p. 436·1).
Depression.

Zispin *Organon, Irl.; Organon, UK.*
Mirtazapine (p. 436·1).
Depression.

Zistic *Bernofarm, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Zita *LPC, UK.*
Cimetidine (p. 1827·1).
Gastrointestinal disorders associated with hyperacidity.

Zitanid *Novell, Indon.*
Tizanidine hydrochloride (p. 2026·2).
Skeletal muscle spasm.

Zitazonium *Egis, Cz.†; Egis, Hong Kong; Egis, Hung.; Egis, Malaysia; Egis, Philipp.; Egis, Rus.; Egis, Thai.*
⊗Tamoxifen citrate (p. 860·2).
Breast cancer; anovulatory infertility; endometrial cancer; prostatic cancer; melanoma; mastalgia.

Zitep *Andromaco, Mex.†*
Sulfadiazine silver (p. 362·3).
Burns; wounds.

Zithran *Ranbaxy, Mex.†*
Azithromycin (p. 221·2).
Bacterial infections.

Zithranol-RR *Elorac, USA.*
Dithranol (p. 1701·2).
Psoriasis.

Zithrobest *Lyofin, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithrocin *Biochem, India; Unique, Rus.; Unique, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithro-Due *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithrogen *Mylan, S.Afr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithrolex *October Pharma, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithromac *Pfizer, Jpn.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithromax *Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pfizer, Chile; Pfizer, China; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Pfizer, USA.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithrome *Hailing, China.*
Azithromycin lactobionate.
Bacterial infections.

Zithroned *Euroned, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithropan *Vocate, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithroplus *Balu, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithrotel *Anpharm (Ανφαρμ), Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zithroxyn *Help, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitolex *Decomed, Port.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; social phobia.

Zitotox *Rafarm, Gr.*
Malathion (p. 2157·2).

Zitoxil
Note: this name may be used for preparations of different composition.
Elmor, Venez.
Minoxidil (p. 1438·3).
Alopecia.

Zitrax *Genepharm, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrazol *Novell, Indon.†*
Itraconazole (p. 583·3).
Fungal infections.

Zitriasol *Aspen, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Zitril *Cazi, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrina *Decomed, Port.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrobiotic *Epifarma, Ital.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrocin *Pfizer, Austral.; Teva, Cz.; Teva, Hung.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitroflam *Rimsa, Mex.*
Azithromycin (p. 221·2); nimesulide (p. 101·3).
Bacterial infections.

Zitroken *Kendrick, Mex.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrolid *Valenta, Rus.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitromax *Pfizer, Arg.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Denm.; Pfizer, Ital.; Pfizer, Spain; Pfizer, Turk.; Pfizer, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitromil *GSK, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitronensäurezyklus-Heel *Heel, Ger.*
Magnesium phosphoricum (p. 1787·3); manganum phosphoricum; natrium pyruvicum (p. 2619·3); natrium oxalaceticum (p. 2578·3); acidum citricum (p. 2480·3); acidum cis-aconiticum; barium oxalicum succinicum (p. 2452·2); acidum α-ketoglutaricum (p. 2579·1); acidum succinicum (p. 2214·3); acidum fumaricum (p. 1704·2); acidum DL-malicum (p. 2549·2).
Homoeopathic preparation.

Zitroneo *Neo Quimica, Braz.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrotek *Pfizer, Turk.*
Azithromycin (p. 221·2).
Bacterial infections.

Zitrozina *Neves, Port.*
Azithromycin (p. 221·2).
Bacterial infections.

Zittec *Vesco, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis; insect bites.

Zitumex *Rafarm, Gr.*
Piroxicam (p. 125·3).
Pain; inflammation; musculoskeletal and joint disorders; gout.

Zival *Valmor, Venez.*
Azithromycin (p. 221·2).
Bacterial infections.

Zivas *Pascual, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; ischaemic heart disease.

Zivatar *Intermed, Gr.*
Simeticone (p. 1886·2); aluminium hydroxide (p. 1817·2); magnesium hydroxide (p. 1857·2).
Gastrointestinal disorders.

Ziverone *Rayere, Mex.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zivon *IPI, Indon.*
Vitamins; copper (p. 2057·1); zinc (p. 2126·1).
Vitamin and mineral deficiencies.

Ziz *Chatfield Laboratories, UK.*
Promethazine hydrochloride (p. 638·2).
Insomnia.

Zizolid *Biofarma, Turk.*
Linezolid (p. 317·3).

Zlatobýlová Naťˇ *Megafyt-R, Cz.†*
Solidago (p. 2620·1).
Urinary-tract disorders.

Zleep *Wockhardt, India.*
Zolpidem (p. 1116·2).
Insomnia.

Žlučníková Čajová Směs *Megafyt-R, Cz.*
Agrimony (p. 2432·3); marrubium (p. 1668·3); rhubarb (p. 1884·2); peppermint leaf (p. 1877·1).
Biliary-tract disorders.

Zmax
Note: this name may be used for preparations of different composition.
Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Israel; Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, USA.
Azithromycin (p. 221·2).
Bacterial infections.

ZN Shampoo *Stiefel, Braz.*
Pyrithione zinc (p. 1718·1).
Seborrhoea.

Zn-A-C *Bioglan, Austral.†*
Ascorbic acid (p. 2110·3); vitamin A (p. 2098·3); zinc amino acid chelate (p. 2048·3); calcium pantothenate (p. 2085·2); rutoside (p. 2505·3).
Vitamin and mineral supplement.

Zn-Diar *Hexpharm, Indon.*
Zinc sulfate (p. 2126·2).
Diarrhoea in children.

ZNP *Stiefel, Canad.†; Stiefel, Chile†; Stiefel, Fr.†; Stiefel, Ital.; Stiefel, Mex.; GSK, USA.*
Pyrithione zinc (p. 1718·1).
Scalp disorders; seborrhoeic dermatitis; dandruff; pityriasis versicolor; skin infections.

Znupril *Velka, Gr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus.

Zoafalet-H *Continentales, Mex.*
Ibuprofen (p. 68·2).
Pain; fever; inflammation.

Zobacide *Garec, S.Afr.†*
Metronidazole (p. 936·1).
Protozoal infections; anaerobic bacterial infections.

Zobactam *Vocate, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Zoben *Pharmaniaga, Malaysia.*
Albendazole (p. 149·1).
Worm infections.

Zobid *SM, Philipp.*
Diclofenac sodium (p. 48·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Zobone *Pharmaplan, S.Afr.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; Paget's disease of bone; osteoporosis.

Zobrixol *Natrapharm, Philipp.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory-tract congestion.

Zocardis *Berlin-Chemie, Rus.; Menarini, Rus.; Berlin-Chemie, Ukr.†*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zocardis Plus *Berlin-Chemie, Ukr.†*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zocef *Ranbaxy, Malaysia; Alkem, Thai.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zocet *Agio, Philipp.*
Levocetirizine (p. 632·3).
Allergic rhinitis; urticaria.

Zocid *Decomed, Port.*
Clarithromycin (p. 266·2).
Bacterial infections.

Zocital *Genedec, Port.†*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder; social phobia; anxiety.

Zodix *Verisfield, Gr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Zocor *MSD, Arg.; MSD, Austral.; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, China; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; Neopharmed, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; hyperlipidaemias; coronary heart disease; atherosclerosis; ischaemic heart disease; stroke; cerebrovascular risk reduction.

Zocord *MSD, Austria; MSD, Swed.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; coronary heart disease; cardiovascular risk reduction.

Zocovin *TO-Chemicals, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zodac *Ascent, Austral.; Zentiva, Cz.; Zentiva, Rus.; Sanofi-Aventis, Ukr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria; allergic conjunctivitis; pruritus.

Zodalin *Elpen (Ελπεν), Gr.*
Codergocrine mesilate (p. 389·2).
Peripheral vascular disorders.

Zodatron *Proton, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Zodeac *Econo Med, USA.*
Ferrous fumarate (p. 2060·3); folic acid (p. 2063·1); vitamins; minerals.
Iron-deficiency anaemias.

ZoDen DM *Trigen, USA.*
Chlorphenamine maleate (p. 620·3); dextromethorphan hydrobromide (p. 1660·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

ZoDen PD *Trigen, USA.*
Diphenhydramine hydrochloride (p. 626·2); phenylephrine hydrochloride (p. 1672·3).

Zoderm
Note: this name may be used for preparations of different composition.
Confab, Canad.
Capsaicin (p. 35·1).
Musculoskeletal and joint pain.
Doak, USA.
⊗Benzoyl peroxide (p. 1696·1); urea (p. 1727·3).
Acne.
GSK, India.
Oxiconazole nitrate (p. 591·3); benzoic acid (p. 1738·2).
Fungal skin infections.

Zodin *Trommsdorff, Ger.; Ferrer, Gr.; Ferrer, Port.*
Omega-3-acid ethyl esters (p. 1460·2).
Hyperlipidaemias; myocardial infarction.

Zodol *Saval, Chile.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zodonrel *Condrugs, Thai.*
Trazodone hydrochloride (p. 451·1).
Depression; insomnia.

Zodorm *Trima, Israel; Unipharm, Israel.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zodryl AC *codaDOSE, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Zodryl DAC *codaDOSE, USA.†*
⊗Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Zodryl DEC *codaDOSE, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Upper respiratory-tract disorders.

Zoely *MSD, Austral.; MSD, Denm.; Merck Serono, Irl.; Theramex, Mon.; MSD, Neth.; MSD, Norw.; Teva, Spain; MSD, Swed.; MSD, Switz.; MSD, UK.*
24 Tablets, nomegestrol acetate (p. 2294·1); estradiol (p. 2271·1); 4 tablets, inert.
Combined oral contraceptive.

Zofadep *Biopharm, Philipp.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zofen
Note: this name may be used for preparations of different composition.
Pharmaland, Thai.
Pizotifen (p. 678·2).
Anorexia; reduced appetite.
Tack Fung, Hong Kong; Xepa-Soul Pattinson, Singapore.
Ibuprofen (p. 68·2).
Rheumatoid arthritis; osteoarthritis.

Zofenil *Menarini, Austria; Menarini, Fin.; Menarini, Fr.; Menarini, Irl.; Menarini, Port.; Menarini, Switz.†*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

Zofenil Comp *Menarini, Denm.; Menarini, Fin.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zofenil Diu *Menarini, Spain.†*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zofenil Plus *Menarini, Austria; Menarini, Irl.; Menarini, Port.; Menarini, Switz.†*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zofenilduo *Menarini, Fr.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zofepril *Menarini, Gr.*
Zofenopril calcium (p. 1536·3).
Hypertension.

Zofepril Plus *Menarini, Gr.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zofer *Pharmaplan, S.Afr.; Adeka, Turk.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zofex *Claris, Philipp.*
Ofloxacin (p. 334·3).
Bacterial infections.

Zoff *Smith & Nephew, Austral.*
Dipropylene glycol methyl ether.
Adhesive plaster remover.
Smith & Nephew Healthcare, UK.
Trichloroethane (p. 2217·3).
Adhesive plaster removal.

Zofil *Menarini, Neth.*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

Zofil HCTZ *Menarini, Neth.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zoflox *Nevzat, Rus.*
Ofloxacin (p. 334·3).
Bacterial infections.

Zoflut *Cipla, India.*
⊗Fluticasone propionate (p. 1638·1).
Inflammatory skin disorders.

Zoflux *Libbs, Braz.*
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Zofora *Pharmy, Fr.*
Piroxicam (p. 125·3).
Musculoskeletal, joint, and peri-articular disorders.

Zofran *GSK, Arg.; GSK, Belg.; GSK, Hong Kong; GSK, Indon.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; Glaxo Wellcome, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Turk.; GSK, USA; GSK, Venez.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.
GSK, Austral.; GSK, Austria; GSK, Braz.; GSK, Canad.; GSK, China; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; GSK, Ukr.
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zofredal *Kalbe, Indon.*
Risperidone (p. 1103·2).
Psychoses.

Zofron *GSK, Gr.*
Ondansetron hydrochloride (p. 1872·1).
Chemotherapy or radiotherapy-induced nausea and vomiting.

Zohydro *Zogenix, USA.*
Hydrocodone tartrate (p. 67·2).
Pain.

Zoiral *Aegis, Hong Kong.†*
Clomipramine hydrochloride (p. 412·1).
Depression; obsessive-compulsive disorder; panic disorder.

Zoiron *Multicare, Philipp.*
Ferrous fumarate (p. 2060·3); vitamins.
Nutritional supplement; iron deficiency.

Zok-Zid *Pfizer, Belg.; Pfizer, Denm.*
⊗Metoprolol succinate (p. 1434·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zol *Jinling, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections.

Zolacap *Caprifarmindo, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zolacin *Acino, Switz.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; bone metastases.

Zolacort *GMP, Indon.*
⊗Miconazole nitrate (p. 589·1); hydrocortisone (p. 1640·1).
Infected skin disorders.

ZolaCos CP *AstraZeneca, Austral.; AstraZeneca, NZ.*
⊗Tablets, bicalutamide (Cosudex) (p. 749·1); implant, goserelin acetate (Zoladex) (p. 2282·3).
Prostatic cancer.

Zoladex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Teva, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Ukr.; Zeneca, USA; AstraZeneca, Venez.*
⊗Goserelin acetate (p. 2282·3).
Breast cancer; endometriosis; female infertility; prostatic cancer; uterine fibroids; presurgical endometrial thinning; controlled ovarian stimulation.
AstraZeneca, Philipp.
⊗Goserelin (p. 2282·3) or goserelin acetate (p. 2282·3).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids; endometrial thinning.

Zolafren *CSC, Cz.; Adamed, Pol.; Adamed, Port.†; Adamed, Spain.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder; mania.

Zolagel *GMP, Indon.*
Miconazole nitrate (p. 589·1).
Infected skin and nail disorders.

Zolagel Diaper *GMP, Indon.*
Miconazole nitrate (p. 589·1); zinc oxide (p. 1729·1).
Nappy rash.

Zolam *Stadmed, India; Medicpharma, Thai.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder; mixed anxiety depressive states.

Zolamid *Mayne, Port.*
Midazolam hydrochloride (p. 1085·1).

Zolamox *Cazi, Braz.*
⊗Acetazolamide (p. 2001·1).
Glaucoma.

Zolandil *Delegant, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zolanix *Stiefel, Braz.†*
Fluconazole (p. 578·2).
Fungal infections.

Zolapack *AstraZeneca, Arg.*
⊗Tablets, bicalutamide (Casodex) (p. 749·1); injection, goserelin acetate (Zoladex) (p. 2282·3).
Prostatic cancer.

Zolargene *Pentafarma, Port.*
Loratadine (p. 633·2).

Zolastin *Gracia, Indon.*
Alprazolam (p. 1035·2).
Anxiety.

Zolastrol *Biogened, Pol.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zolaten *Sigma, NZ.*
Aciclovir (p. 964·1).
Herpes labialis.

Zolax *Sanovel, Turk.*
Fluconazole (p. 578·2).
Fungal infections.

Zolaxa *Polpharma, Pol.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zolben *Novartis, Chile; Welti, Switz.*
Paracetamol (p. 115·1).
Fever; pain.
Sanofi-Aventis, Braz.
Albendazole (p. 149·1).
Worm infections.

Zolben C *Welti, Switz.*
Paracetamol (p. 115·1); ascorbic acid (p. 2110·3).
Pain; fever.

Zoldac *Zydus, Braz.*
Alprazolam (p. 1035·2).

Zoldem *Lannacher, Austria; Hexal, Ger.†; Anglo-French Drugs, India; Gerard, Irl.; Medichem, Philipp.*
Zolpidem tartrate (p. 1116·2).
Insomnia; sleep disorders.

Zoldicam *Rayere, Mex.*
Fluconazole (p. 578·2).
Fungal infections.

Zoldorm *Sandoz, Switz.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zoldria *Cipla, India; Cipla, Venez.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; metastatic bone disease.

Zole *Ranbaxy, India.*
Miconazole nitrate (p. 589·1).
Fungal and Gram-positive bacterial skin and vaginal infections.

Zoledreenos *Mithra, Neth.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy.

Zoledrin *Deva, Turk.*
Zoledronic acid (p. 1192·3).

Zole-F *Ranbaxy, India.*
⊗Miconazole nitrate (p. 589·1); fluocinolone acetonide (p. 1636·1).
Fungal and Gram-positive bacterial skin infections.

Zolelcon *Farmedia, Gr.*
Omeprazole (p. 1867·2).

Zolenat *Nevzat, Turk.*
Zoledronic acid (p. 1192·3).

Zolenia *Pharmathen, Neth.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy.

Zolennic *Siam Bheasach, Thai.*
Zoledronic acid (p. 1192·3).
Bone metastases; osteolysis of malignancy; hypercalcaemia of malignancy.

Zolepant *Pinewood, Irl.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; pathological hypersecretory disorders.

Zoleprim *PP Lab, Thai.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Zoleptil *Actavis, Cz.; Italfarmaco, Port.; Eczacibasi, Turk.; Movianto, UK.†*
Zotepine (p. 1119·1).
Schizophrenia.

Zolerix *Biocad, Rus.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Zoleta *Ranbaxy, India.†*
Imatinib mesilate (p. 807·3).
Chronic myeloid leukaemia; gastrointestinal stromal cancer.

Zoletad *TAD, Gr.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zolev *Euro Lifecare, Ukr.*
Levofloxacin (p. 315·3).
Bacterial infections.

Zolex *Regiomedica, Neth.*
Esomeprazole magnesium (p. 1841·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zolfin *Ipca, Rus.*
Cefazolin (p. 237·2).
Bacterial infections.

Zolicef
Note: this name may be used for preparations of different composition.
Harbin, Philipp.
Cefradine (p. 249·1).
Bacterial infections.
Millimed, Thai.†
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zolico *Versalya, Spain.*
Folic acid (p. 2063·1).
Prevention of neural tube defects.

Zolid
Note: this name may be used for preparations of different composition.
Getz, Philipp.
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.
Novagen, S.Afr.
Sertraline (p. 448·1).

Zoliden *Unipharma, Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Zolief *Genthon, Hong Kong.*
Zopiclone (p. 1118·1).
Insomnia.

Zolim *Sanofi-Aventis, Ger.*
Mizolastine (p. 636·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zolimed *Unison, Thai.†*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zolin
Note: this name may be used for preparations of different composition.
Aurobindo, Rus.
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zolina
Note: this name may be used for preparations of different composition.
Llorens, Spain.
⊗Boric acid (p. 2459·3); naphazoline hydrochloride (p. 1669·3).
Eye irritation.
Megat, Venez.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Zoline *Pyridam, Indon.*
Mebhydrolin napadisilate (p. 634·2).
Allergic disorders.

Zolinox *Ranbaxy, Rus.*
Zopiclone (p. 1118·1).
Sleep disorders.

Zolinza *MSD, Arg.; Merck Frosst, Canad.; IFET (ΙΦΕΤ), Gr.; MSD, Jpn; Merck, USA.*
Vorinostat (p. 887·2).
Cutaneous T-cell lymphoma.

Zoliparin *Mann, Ger.†*
Aciclovir (p. 964·1).
Herpes simplex eye infections.

Zolistam *Sanofi-Aventis, Ital.; Sanofi-Aventis, Port.†*
Mizolastine (p. 636·1).
Allergic rhinitis; allergic conjunctivitis; urticaria; allergic rhinoconjunctivitis.

Zolistan *Ferrer, Spain.*
Mizolastine (p. 636·1).
Allergic rhinitis; urticaria.

Zolitrat *Medicamerc, Gr.; Rafarm, Gr.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zolival *Virgo, Philipp.; Reig Jofre, Spain.*
Cefazolin sodium (p. 237·3).
Bacterial infections.

Zolken *Kener, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Zolkir *Pharmacenter, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zolldenol *Novis, Gr.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Zollocid *Landson, Indon.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zolmach *Rafarm, Gr.*
Omeprazole (p. 1867·2).

Zolmed *Medhaus, Philipp.*
Co-trimoxazole (p. 277·3).
Bacterial infections; pneumocystis pneumonia.

Zolmep *Kopran, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; dyspepsia.

Zolmia *Fahrenheit, Indon.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolmic
Note: this name may be used for preparations of different composition.
Delta, Braz.
Fluconazole (p. 578·2).
Fungal infections.
Medinova (Μεντινοβα), Gr.
Norfloxacin (p. 333·3).
Bacterial infections.

Zolmicol *Geolab, Braz.*
Ketoconazole (p. 585·3).
Fungal skin infections.

Zolmid *Laboratorios Chile, Chile.*
Midazolam (p. 1085·1).
Premedication; general anaesthesia; sedative.

Zolmide *Vista, Philipp.*
⊗Acetazolamide (p. 2001·1).
Glaucoma; epilepsy; high-altitude disorders.

Zolmigren *Farmak, Ukr.*
Zolmitriptan (p. 682·2).
Migraine.

Zolmiles *Actavis, Cz.; Actavis, Denm.; Actavis, Irl.†; Actavis, Pol.*
Zolmitriptan (p. 682·2).
Migraine.

Zolmistad *Stada, Fin.*
Zolmitriptan (p. 682·2).
Migraine.

Zolnid *Alkem, Philipp.*
Metronidazole (p. 936·1).
Anaerobic bacterial infections; protozoal infections.

Zolnod *Rowex, Irl.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolnor *Menarini, Port.*
Amlodipine besilate (p. 1304·1); olmesartan medoxomil (p. 1459·2).
Hypertension.

Zolnoxs *Aspen, S.Afr.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zoloatlas *Atlas, Arg.*
Olopatadine (p. 636·2).

Zoloder *SF, Ital.*
Fluconazole (p. 578·2).
Fungal infections.

Zolodin *MedChoice, Philipp.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; post-traumatic stress disorder; obsessive-compulsive disorder; social phobia; anxiety.

Zolodorm *Richmond, Arg.*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Zoloft *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, China; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia; premenstrual dysphoric disorder; mixed anxiety depressive states.
Pfizer, Norw.
Sertraline (p. 448·1) or sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; social phobia; post-traumatic stress disorder.

Zolom *Aspen, Arg.*
Temozolomide (p. 865·2).

Zolomaks *Grindex, Rus.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder; sleep disorders.

Zolon *Taiwan Biotech, Malaysia.*
Zopiclone (p. 1118·1).
Insomnia.

Zoloral *Ikapharmindo, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Zoloser *Verisfield, Gr.*
Amisulpride (p. 1036·3).
Schizophrenia.

Zolotrin *Specifar, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression.

Zolpeptid *Mavi, Mex.*
Pantoprazole (p. 1875·3).

Zolpibell *Bellwether, Austral.†*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpic *Polpharma, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpid *Brown & Burk, Philipp.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpidex *Giempi, Venez.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

ZolpiGen *Generics, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpihexal *Sandoz, S.Afr.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpi-Lich *Winthrop, Ger.†*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Zolpimerck *Generics, Cz.†*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpimist *ECR, USA.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpinox *SVUS, Cz.; Krewel, Ger.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolpi-Q *Juta, Ger.†; Q-Pharm, Ger.†*
Zolpidem tartrate (p. 1116·2).
Sleep disorders.

Zolpitop *Apotex, Belg.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolplat *Monte Verde, Arg.*
Cilostazol (p. 1337·1).

Zolpra *Ranbaxy, Mex.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; Zollinger-Ellison syndrome; peptic ulcer.

Zolsana *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zolstan *Reddy, Malaysia.*
Fluconazole (p. 578·2).
Fungal infections.

Zolstro *Accord, Mex.*
⊗Letrozole (p. 817·1).
Breast cancer.

Zolt *Orion, Fin.*
Lansoprazole (p. 1851·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zoltar *Alfa Biotech, Ital.*
Parnaparin sodium (p. 1464·2).

Zoltax *Ultramed, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Zoltec *Pfizer, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Zoltem *Nobel, Turk.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by cytotoxic therapy or radiotherapy; postoperative nausea and vomiting.
Nobel, Ukr.
Ondansetron (p. 1872·1).
Nausea and vomiting.

Zoltenk *Biotenk, Arg.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zolterol *CCM, Hong Kong; CCM, Malaysia; Upha, Singapore.*
Diclofenac sodium (p. 48·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; inflammation; dysmenorrhoea.

Zoltralina *Sigma, Braz.*
Sertraline hydrochloride (p. 448·1).

Zoltren *Teuto, Braz.*
Fluconazole (p. 578·2).
Fungal infections.

Zoltrim *Sandoz, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Zoltum
Note: this name may be used for preparations of different composition.
Asofarma, Mex.
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux.
AstraZeneca, Fr.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zolufen *Nafar, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zolvastin *Medlink, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Zolvera *Rosemont, UK.*
Verapamil hydrochloride (p. 1522·1).
Angina pectoris; arrhythmias; hypertension.

Zolvit *ECR, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Zolzyn *Lannacher, Neth.*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zom *Dynamit, Austria.*
Arnica (p. 2447·2); echinacea (p. 2498·1); mercurius solubilis (p. 2555·3); silicea (p. 2208·3).
Homoeopathic preparation.

Zomacton *Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Irl.; Ferring, Ital.; Ferring, Neth.; Ferring, Norw.; Ferring, Port.; Ferring, Spain; Ferring, Swed.; Er-Kim, Turk.; Ferring, UK.*
⊗Somatropin (p. 1919·3).
Turner's syndrome; growth hormone deficiency; Prader-Willi syndrome; growth disorders in renal failure.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zomarist
Note: this name may be used for preparations of different composition.
Montpellier, Arg.
Vildagliptin (p. 504·3).
Diabetes mellitus.

Novartis, Cz.; Novartis, Gr.; Novartis, Irl.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Spain.
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Zomarist Met *Montpellier, Arg.*
Vildagliptin (p. 504·3); metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Zomax *Hikma, Ukr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zomebon *Kocak, Turk.*
Zoledronic acid (p. 1192·3).

Zomedron *Cipla-Medpro, S.Afr.*
Zoledronic acid (p. 1192·3).

Zomel *Clonmel, Irl.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zomep *Twilight Litaka, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; dyspepsia; peptic ulcer.

Zomepral *Laboratorios Chile, Chile.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zomera *Novartis, Israel.*
Zoledronic acid (p. 1192·3).
Hypercalcaemia of malignancy; multiple myeloma; bone metastases.

Zometa *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, China; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, NZ; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Ukr.; Novartis, USA; Novartis, Venez.*
Zoledronic acid (p. 1192·3).
Bone metastases; hypercalcaemia of malignancy; osteolysis of malignancy; osteoarthritis.

Zometic *Chemopharma, Chile.*
Zopiclone (p. 1118·1).
Insomnia.

Zomevek *Novartis, S.Afr.*
Valsartan (p. 1521·2).

Zomexil *Novartis, Pol.*
⊗Formoterol fumarate (p. 1209·2).
Obstructive airways disease; bronchospasm.

Zomig *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, China; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin; AstraZeneca, Fr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; Gervasi, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Impax, USA; AstraZeneca, Venez.*
Zolmitriptan (p. 682·2).
Migraine.

Zomigon *AstraZeneca, Arg.; AstraZeneca, Gr.*
Zolmitriptan (p. 682·2).
Migraine.

Zomigoro *AstraZeneca, Fr.*
Zolmitriptan (p. 682·2).
Migraine.

Zomiren *KRKA, Pol.*
Alprazolam (p. 1035·2).
Anxiety disorders.

Zomni *Jean-Marie, Hong Kong.*
Zopiclone (p. 1118·1).
Insomnia.

Zomorph *Archimedes, Spain; Archimedes, UK.*
⊗Morphine sulfate (p. 92·3).
Pain.

Zomrac *Umedica, Philipp.*
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Zomsol *Solara, Mex.†*
Midazolam (p. 1085·1).

Zon *Antula, Fin.†; Antula, Norw.†; Antula, Swed.†*
Ketoprofen (p. 79·1).
Musculoskeletal and joint disorders; sports injuries; soft-tissue pain; pain.

Zonadin *Pliva-Lachema, Cz.†*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zonadine *Pliva, Rus.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zonaker *Grin, Mex.*
Sodium hyaluronate (p. 2526·2).
Dry eyes.

Zonal
Note: this name may be used for preparations of different composition.
Kalbe, Indon.
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Zonalon *Medicis, Canad.; Medicis, USA.*
Doxepin hydrochloride (p. 414·2).
Pruritus.

Zonapin *Elogis, Gr.*
Olanzapine (p. 1089·3).

Zonapir *Alter, Port.†*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zonatian *LKM, Arg.*
Isotretinoin (p. 1706·2).
Acne.

Zonatuss *Vertical, USA.*
Benzonatate (p. 1656·2).
Cough.

Zonavir *Menarini, Belg.*
Brivudine (p. 970·1).
Herpes zoster infections.

Zonbactam *Great Eastern, Thai.*
Cefoperazone (p. 243·1); sulbactam (p. 360·1).
Bacterial infections.

Zondar *Pharma 2000, Fr.*
Diacerein (p. 45·3).
Osteoarthritis of the hip and knee.

Zondra *Liomont, Mex.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Zone-A *UAD, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine (p. 1993·3).

Zonef *Unison, Thai.†*
Cefuroxime (p. 255·2).
Bacterial infections.

Zonegran *Eisai, Austria; Eisai, Cz.; Eisai, Denm.; Eisai, Fr.; Eisai, Ger.; Eisai, Gr.; Eisai, Hung.; Eisai, Indon.; Eisai, Irl.; Eisai, Ital.; Eisai, Malaysia; Eisai, Neth.; Eisai, Norw.; Dainippon, Philipp.; Eisai, Pol.; Eisai, Port.; Eisai, Spain; Eisai, Swed.; Eisai, Switz.; Eisai, Thai.; Eisai, UK; Eisai, USA.*
Zonisamide (p. 560·2).
Epilepsy; partial seizures.

Zonema *T Man, Thai.*
Indometacin (p. 71·2).
Musculoskeletal and joint disorders; gout; pain.

Zonesis *Novartis, Cz.†*
Terbinafine (p. 593·3).

Zonite *Menley & James, USA.*
Benzalkonium chloride (p. 1737·1); edetic acid (p. 1550·3); sodium acetate (p. 1781·1); propylene glycol (p. 2205·2); menthol (p. 2553·2); thymol (p. 1772·2).
Vaginal disorders.

Zonix *Mintlab, Chile.*
Zopiclone (p. 1118·1).
Insomnia.

Zonnic *Niconovum, Denm.; Niconovum, Swed.*
Nicotine (p. 2569·3).
Aid to smoking withdrawal.

Zonoct *Pharmacodane, Denm.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zontron *Ulagay, Turk.*
Ondansetron hydrochloride (p. 1872·1).

Zoodermina Crema *Bajer, Arg.*
Vitamin A palmitate (p. 2098·3); spermaceti (p. 2178·2); beeswax (p. 2170·2).
Emollient.

Zoom *Fabop, Arg.*
⊗Salbutamol sulfate (p. 1220·2).
Asthma.

Zoom Protective Lip Cream *Discus Dental, Canad.*
Meradimate (p. 1711·2); octinoxate (p. 1715·1); octisalate (p. 1715·2); oxybenzone (p. 1715·3).
Sunscreen.

Zop *Hexal, Ger.†*
Zopiclone (p. 1118·1).
Sleep disorders.

Zopam *Pharmasant, Thai.*
Diazepam (p. 1063·2).
Anxiety; skeletal muscle spasm; insomnia; neuroses.

Zopax *Cipla-Medpro, S.Afr.*
Alprazolam (p. 1035·2).
Anxiety disorders; mixed anxiety depressive states; panic disorder.

Zopax Plus *Cipla, India.*
⊗Alprazolam (p. 1035·2); propranolol hydrochloride (p. 1479·1).

Zopercin *Orchid, Ukr.*
Piperacillin (p. 340·1); tazobactam (p. 369·3).
Bacterial infections.

Zophix *Eczacibasi, Turk.*
Olanzapine (p. 1089·3).

Zophralen *Demo, Gr.; Dem, Turk.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting induced by chemotherapy.

Zophren *GSK, Fr.*
Ondansetron (p. 1872·1) or ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zopicalma *VP, Spain.*
Zopiclone (p. 1118·1).
Insomnia.

Zopicon *Intas, India.*
Zopiclone (p. 1118·1).
Insomnia.

Zopide *Decomed, Port.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Zopigen *Generics, Hung.; Mylan, S.Afr.*
Zopiclone (p. 1118·1).
Insomnia.

Zopim *Taiwan Biotech, Malaysia.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zopinon *Laboratorios Chile, Chile.*
Eszopiclone (p. 1072·3).
Insomnia.

Zopinox *Orion, Fin.*
Zopiclone (p. 1118·1).
Sleep disorders.

Zopi-Puren *Actavis, Ger.†*
Zopiclone (p. 1118·1).
Sleep disorders.

Zopiratio *Ratiopharm, Pol.*
Zopiclone (p. 1118·1).
Sleep disorders.

Zopirol *Elea, Arg.*
⊗Timolol maleate (p. 1513·2).
Ocular hypertension; glaucoma.

Zopirol DM *Elea, Arg.*
⊗Dorzolamide hydrochloride (p. 2006·3); timolol maleate (p. 1513·2).
Glaucoma; ocular hypertension.

Zopitan *Clonmel, Irl.*
Zopiclone (p. 1118·1).
Insomnia.

Zopitin *Vitabalans, Cz.; Vitabalans, Fin.*
Zopiclone (p. 1118·1).
Insomnia.

Zopivane *Cipla-Medpro, S.Afr.*
Zopiclone (p. 1118·1).
Insomnia.

Zopix *Sigma, Braz.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zopral *Alphapharm, Austral.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; gastritis; dyspepsia.

Zopranol *Menarini, Belg.; Guidotti, Gr.; Guidotti, Ital.; Menarini, Neth.; Menarini, Port.*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

Zopranol Diu *Guidotti, Spain.†*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zopranol HCTZ *Menarini, Neth.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zopranol Plus *Menarini, Belg.; Guidotti, Gr.; Menarini, Port.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zoprazide *Guidotti, Ital.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zoprol *Taprak, Turk.*
Lansoprazole (p. 1851·3).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zoprost *Sandoz, Gr.*
Alfuzosin hydrochloride (p. 2351·3).

Zoprotec *UFSA, Turk.*
Zofenopril calcium (p. 1536·3).
Hypertension; myocardial infarction.

Zoprotec Plus *UFSA, Turk.*
⊗Zofenopril calcium (p. 1536·3); hydrochlorothiazide (p. 1403·2).
Hypertension.

Zopya *Norpharm, Cz.; KRKA, Irl.; Norpharm, Neth.†; Norpharm, Pol.; Norpharm, Port.*
Clopidogrel hydrochloride (p. 1342·3).
Thromboembolism prophylaxis.

Zora *General Drugs, Thai.*
Lorazepam (p. 1080·3).
Anxiety.

Zorac *Ascent, Austral.; Allergan, Austria†; Pierre Fabre Sante, Belg.; Pierre Fabre Dermatologie, Fr.; Pierre Fabre, Gr.; Allergan, Irl.†; Pierre Fabre, Israel†; Pierre Fabre, Ital.; Pierre Fabre, Pol.; Pierre Fabre, Spain; Pierre Fabre, Switz.†; Allergan, UK.*
Tazarotene (p. 1724·2).
Psoriasis; acne.

Zoracilin *Suan, Gr.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Zorak *Allergan, S.Afr.*
Tazarotene (p. 1724·2).
Psoriasis.

Zoral
Note: this name may be used for preparations of different composition.
Andromaco, Mex.
Omeprazole (p. 1867·2).
Peptic ulcer; gastro-oesophageal reflux; gastritis; Zollinger-Ellison syndrome.

DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.
Aciclovir (p. 964·1).
Herpesvirus infections.

Zoralin *Medikon, Indon.*
Ketoconazole (p. 585·3).
Fungal infections.

Zoralix *Hoe, Malaysia.*
Promethazine (p. 638·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting; sedative.

Zoralone *Hoe, Malaysia.*
⊗Prednisolone (p. 1645·2).
Corticosteroid.

Zoramine *Hoe, Malaysia.*
Chlorphenamine maleate (p. 620·3).
Hypersensitivity reactions.

Zoran *Reddy, Rus.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; gastrointestinal haemorrhage; acid aspiration.

Zoranate *Hoe, Malaysia.*
Dimenhydrinate (p. 625·2).
Nausea; vomiting; motion sickness.

Zoratio *Ratiopharm, Pol.*
Zolpidem tartrate (p. 1116·2).
Insomnia.

Zoratral *Medochemie, Gr.*
Alfuzosin hydrochloride (p. 2351·3).
Benign prostatic hyperplasia.

Zorax *Sunward, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zoraxin *Duopharma, Hong Kong†; CCM, Malaysia; Duopharma, Singapore.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zorbtive *Serono, USA.*
⊗Somatropin (p. 1919·3).
Short bowel syndrome.

Zorcaine *Carestream, Canad.*
Articaine hydrochloride (p. 1980·1).
Adrenaline acid tartrate (p. 1292·2) is included in this preparation as a vasoconstrictor to diminish absorption and to localise the effect of the local anaesthetic.
Local anaesthesia.

Zorced *Collins, Mex.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction; cerebrovascular risk reduction.

Zorclone *Synthon, Irl.*
Zopiclone (p. 1118·1).
Insomnia.

Zordyl *Julphar, UAE.*
Chlorhexidine gluconate (p. 1743·3).
Oral hygiene; mouth infections.

Zoref *Glaxo Allen, Ital.; Glaxo Wellcome, Port.*
Cefuroxime axetil (p. 255·2).
Bacterial infections.

Zorel
Note: this name may be used for preparations of different composition.
Utopian, Thai.
Trazodone hydrochloride (p. 451·1).
Depression.

Ferron, Indon.†
Aciclovir (p. 964·1).
Herpes simplex skin and mucous membrane infections.

Zorem *Pfizer, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zoretanin *Fako, Turk.*
Isotretinoin (p. 1706·2).

Zorex *Valenta, Rus.; Valenta, Ukr.*
Dimercaprol (p. 1549·3); calcium pantothenate (p. 2085·2).
Chronic alcoholism; heavy metal poisoning; cardiac glycoside poisoning; alcoholic intoxication; alcoholic abstinence syndrome.

Zoric *VS, Thai.*
Colchicine (p. 604·1).
Gout.

Zoridal *Decomed, Port.*
Risperidone (p. 1103·2).
Schizophrenia; bipolar disorder; behaviour disorders; autism.

Zorituss *Gold & Silver Bell, Thai.*
Codeine phosphate (p. 40·2).

Zorix *Decomed, Port.*
Moclobemide (p. 437·2).
Depression; social phobia.

Zorkenil *Intermed, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Zoroflog *SM, Gr.*
Galantamine hydrobromide (p. 391·3).
Alzheimer's dementia.

Zoroxin *MSD, Austria; MSD, Belg.*
Norfloxacin (p. 333·3).
Bacterial infections.

Zorpex *Ranbaxy, China.*
Zidovudine (p. 1024·2).
HIV infection.

ZORprin *Par, USA.*
Aspirin (p. 22·2).
Rheumatoid arthritis; osteoarthritis; pain; fever.

Zorstat *Pliva, Rus.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Zortal *AVI, Gr.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; obsessive-compulsive disorder; social phobia; post-traumatic stress disorder.

Zortress *Novartis, USA.*
Everolimus (p. 1957·3).
Transplant rejection.

Zortrix *Ativus, Braz.*
Salix (p. 129·2).
Fever; inflammation; pain.

Zorvolex *Iroko, USA.*
Diclofenac (p. 48·3).
Pain.

Zosec *Shijiazhuang, Philipp.*
Omeprazole (p. 1867·2).
Acid aspiration; gastro-oesophageal reflux; dyspepsia; peptic ulcer; Zollinger-Ellison syndrome.

Zosert *Pharmaplan, S.Afr.*
Sertraline (p. 448·1).

Zosta *USV, Ukr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia.

Zostatin *Shou Chan, Philipp.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction.

Zostavax *CSL Biotherapies, Austral.; Sanofi Pasteur, Austria; Merck Frosst, Canad.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Ger.†; Sanofi Pasteur, Irl.; MSD, Israel; Sanofi Pasteur, Neth.; MSD, NZ; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Switz.; Sanofi Pasteur, UK; Merck, USA.*
A live varicella-zoster vaccine (Oka/Merck strain) (p. 2423·3).
Active immunisation.

Zostevir *Berlin-Chemie, Cz.; Guidotti, Gr.*
Brivudine (p. 970·1).
Herpes zoster infections.

Zostex *Guidotti, Austria; Berlin-Chemie, China; Berlin-Chemie, Ger.; Menarini, Port.; UFSA, Turk.*
Brivudine (p. 970·1).
Herpes zoster infection.

Zostin *Vickmans, Hong Kong.†*
Aciclovir (p. 964·1).

Zostinol *Vickmans, Hong Kong.†*
Aciclovir (p. 964·1).

Zostrix *Link, Austral.; Medicis, Canad.; Rafa, Israel; AFT, NZ; Health Care Products, USA.*
Capsaicin (p. 35·1).
Osteoarthritis; diabetic neuropathy; postherpetic neuralgia; rheumatoid arthritis; post-surgical pain.

Zostrix Hot & Cold Therapy System *Health Care Products, USA.*
Hot therapy cream, capsaicin (p. 35·1); cold therapy cream, menthol (p. 2553·2).

Zostydol *Menarini, Arg.*
Brivudine (p. 970·1).
Herpes zoster infections.

Zosul *Cipla, India.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Zosyn *Wyeth, India; Taiho, Jpn; Lederle, USA.*
Piperacillin sodium (p. 340·1); tazobactam sodium (p. 369·3).
Bacterial infections.

Zotac *Neo Quimica, Braz.*
Diclofenac colestyramine (p. 48·3).

Zotaline *M & H, Thai.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Zotam *Meprofarm, Indon.*
Cefoperazone sodium (p. 243·1); sulbactam sodium (p. 360·1).
Bacterial infections.

Zotanixin *Sanfer, Mex.*
Nitazoxanide (p. 942·2).
Protozoal infections; worm infections.

Zotax *Hovid, Hong Kong.*
Azithromycin (p. 221·2).
Bacterial infections.

Zotefox *Verisfield, Gr.*
⊗Losartan potassium (p. 1422·2); hydrochlorothiazide (p. 1403·2).

Zoteon *Novartis, Chile.*
Tobramycin (p. 380·1).
Pseudomonal lung infections in cystic fibrosis.

Zoter
Note: this name may be used for preparations of different composition.
Gap, Gr.
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Interbat, Indon.
Aciclovir (p. 964·1).
Herpesvirus infections.

Zoteran *Interbat, Philipp.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zotex *Vertical, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Zotex-C *Vertical, USA.*
Codeine phosphate (p. 40·2); phenylephrine hydrochloride (p. 1672·3); mepyramine maleate (p. 635·1).
Upper respiratory-tract disorders.

Zotex-D *Vertical, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Formerly contained pentoxyverine citrate, pseudoephedrine hydrochloride, and mepyramine maleate.
Upper respiratory-tract disorders.

Zotex-EX *Vertical, USA.*
Dextromethorphan hydrobromide (p. 1660·1); guaifenesin (p. 1666·2); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Zotex-PE *Vertical, USA.†*
Brompheniramine maleate (p. 618·1); phenylephrine hydrochloride (p. 1672·3).
Upper respiratory-tract disorders.

Zotinar *Atral, Port.*
⊗Desonide (p. 1630·1).
Skin disorders.

Zotinar-N *Atral, Port.*
⊗Desonide (p. 1630·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Zoto-HC *Horizon, USA.*
⊗Chloroxylenol (p. 1748·2); pramocaine hydrochloride (p. 1993·3); hydrocortisone (p. 1640·1).
Formerly known as Xotic.
Ear disorders.

Zoton *Pfizer, Austral.; Pfizer, Irl.; Neopharm, Israel; Wyeth Lederle, Ital.; Wyeth, UK.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; gastritis; dyspepsia; Zollinger-Ellison syndrome.

Zotral *Brown & Burk, Philipp.; Polpharma, Pol.; Polpharma, Pol.*
Sertraline hydrochloride (p. 448·1).
Depression; panic disorder; post-traumatic stress disorder; obsessive-compulsive disorder.

Zotran *Pfizer, Chile.*
Alprazolam (p. 1035·2).
Anxiety; panic attacks.

Zotril *Andromaco, Mex.*
Itraconazole (p. 583·3).
Fungal infections.

Zotrilax *Ranbaxy, Ital.†*
Triazolam (p. 1112·3).
Insomnia.

Zotrim *Natures Remedies, UK.*
Maté (p. 2648·2); guarana (p. 2648·2); damiana (p. 2491·3).
Slimming aid.

Zotrix *Alternova, Austria†; Alternova, Denm.†; Alternova, Swed.†*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zotrole *Pinewood, Irl.*
Lansoprazole (p. 1851·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zov800 *Wellcome, Port.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zovast *Darya-Varia, Indon.; Cipla, Philipp.*
Simvastatin (p. 1489·2).
Hyperlipidaemias; hypercholesterolaemia; cardiovascular risk reduction.

Zovatin *Eczacibasi, Rus.; Eczacibasi, Turk.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; cardiovascular risk reduction; atherosclerosis.

Zovia *Watson, USA.*
Ethinylestradiol (p. 2275·3); etynodiol diacetate (p. 2277·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Zovicrem *GSK Consumer, Spain.*
Aciclovir (p. 964·1).
Herpes labialis.

Zovilam *Mylan, Thai.*
Zidovudine (p. 1024·2); lamivudine (p. 1000·2).
HIV infection.

Zovir *GSK, Denm.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zovirax *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK Consumer, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, China; GSK, Cz.; Europharma, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; Aspen, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK Consumer, Ukr.; Valeant, USA; GSK, Venez.*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections.

Zoxadon *Pharma Dynamics, S.Afr.*
Risperidone (p. 1103·2).
Schizophrenia; behaviour disorder.

Zoxan
Note: this name may be used for preparations of different composition.
FDC, India.
Ciprofloxacin (p. 261·1).
Bacterial infections.

Pfizer, Fr.
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia.

Zoxapar *Eczacibasi, Turk.*
Paroxetine (p. 440·3).

Zoxil
Note: this name may be used for preparations of different composition.
Mylan, S.Afr.
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Gap, Gr.
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zoxim *Shanxi, Philipp.*
Ceftizoxime sodium (p. 253·1).
Bacterial infections.

Zoxinat *Aflofarm, Pol.*
Ketoconazole (p. 585·3).
Fungal skin and scalp infections.

Zoxipan *Medley, Braz.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder; obsessive-compulsive disorder.

Zoxon *Medreich, Hong Kong.*
Ceftriaxone sodium (p. 253·3).
Bacterial infections.

Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.; Zentiva, Ukr.
Doxazosin mesilate (p. 1369·1).
Benign prostatic hyperplasia; hypertension.

Zoxx *Casasco, Arg.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder.

ZP Dermil *Edol, Port.*
Pyrithione zinc (p. 1718·1).
Scalp disorders.

Z-Pak *Pfizer, Canad.*
Azithromycin (p. 221·2).
Bacterial infections.

Z-Plus *Dormer, Canad.*
Pyrithione zinc (p. 1718·1); menthol (p. 2553·2).
Dandruff; seborrhoeic dermatitis.

ZSC *Aspen, Austral.*
Zinc oxide (p. 1729·1); starch (p. 2095·1); chlorphenesin (p. 575·3); talc (p. 1722·2).
Skin irritation; nappy rash; hyperhidrosis.

Z-Tus AC *Magna, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Z-Tuss AC *Magna, USA.*
Chlorphenamine maleate (p. 620·3); codeine phosphate (p. 40·2).
Upper respiratory-tract disorders.

Z-Tuss E *Magna, USA.*
⊗Codeine phosphate (p. 40·2); guaifenesin (p. 1666·2); pseudoephedrine hydrochloride (p. 1676·1).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zuacta *Sanofi-Aventis, Canad.*
Zucapsaicin (p. 35·1).

Zuantrip *GP, Spain.*
Tamsulosin hydrochloride (p. 2369·1).
Benign prostatic hyperplasia.

Zubes *Ernest Jackson, UK.*
Menthol (p. 2553·2); anise oil (p. 2444·3).

Zubes Blackcurrant *Ernest Jackson, UK.*
Citric acid (p. 2480·3); menthol (p. 2553·2); anise oil (p. 2444·3).

Zubes Honey & Lemon *Ernest Jackson, UK.*
Honey (p. 2072·1); citric acid (p. 2480·3); menthol (p. 2553·2).

Zubsolv *Orexo, USA.*
⊗Buprenorphine hydrochloride (p. 30·3); naloxone hydrochloride (p. 1562·3).
Opioid dependence.

Zuccarin Mûrier *Vitalco, Fr.*
Mulberry.
Blood sugar control.

Zuckli *Berlin-Chemie, Rus.†*
Saccharin sodium (p. 2208·1); sodium cyclamate (p. 2180·2).
Sugar substitute.

Zucoflaxin *Zuiko, Philipp.†*
Cefalexin (p. 234·1).
Bacterial infections.

Zudan *Team, China.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zudem *Aldril, Philipp.*
Cefpodoxime proxetil (p. 248·1).
Bacterial infections.

Zudenina *Pharma Invesi, Chile.*
Adapalene (p. 1692·1).
Acne.

Zufalm *Ratiopharm, Cz.*
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Zufen *Team, China.*
Baclofen (p. 2014·3).
Skeletal muscle spasm; spasticity.

Zuflax *Richmond, Arg.*
Isoflurane (p. 1903·2).
General anaesthesia.

Zuglimet *Sanofi-Aventis, Ital.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Zui Xing *Nuo Jin, China.*
Vinpocetine (p. 2645·3).
Cerebrovascular disorders; dementia.

Zuidex *Q-Med, UK.*
Dextranomer (p. 1699·3); hyaluronic acid (p. 2526·2).
Female stress urinary incontinence.

Zukedib *Loeffler, Mex.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Zulbex *KRKA, Cz.*
Rabeprazole sodium (p. 1881·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zulboral *Farmedia, Gr.*
Sodium cromoglicate (p. 1225·3).
Allergic rhinitis.

Zuledin *Demo, Gr.*
Chlorpromazine hydrochloride (p. 1045·2).
Psychoses; agitation.

Zuleptan *Bago, Chile.*
Mirtazapine (p. 436·1).
Anxiety; depression; insomnia.

Zuletel *Microsules, Arg.*
Efavirenz (p. 975·1).
HIV infection.

Zulex *Almirall, Spain.†*
Acamprosate calcium (p. 1034·2).
Alcoholism.

Zulexen *Demo, Gr.*
Nitrendipine (p. 1456·3).
Hypertension.

Zulgar *Medical Pharmaquality, Gr.*
Alendronate sodium (p. 1171·3).
Osteoporosis.

Zulida *Team, China.*
Sulindac (p. 134·2).
Musculoskeletal, joint, and peri-articular disorders; pain; inflammation.

Zulmedx *Bajamed, Mex.*
Omeprazole (p. 1867·2).
Peptic ulcer.

Zulsol *Solara, Mex.†*
Sulindac (p. 134·2).
Musculoskeletal, joint, and peri-articular disorders; gout.

Zultrop *Tropica Mas, Indon.*
Co-trimoxazole (p. 277·3).
Bacterial infections.

Zumablok *Sandoz, Indon.*
⊗Atenolol (p. 1308·2).
Angina pectoris; arrhythmias; hypertension.

Zumaderm-N *Sandoz, Indon.†*
⊗Fluocinolone acetonide (p. 1636·1); neomycin sulfate (p. 330·1).
Infected skin disorders.

Zumadiac *Sandoz, Indon.*
Gliclazide (p. 472·3).
Diabetes mellitus.

Zumafen *Sandoz, Indon.†*
Amoxicillin (p. 216·2); clavulanic acid (p. 268·3).
Bacterial infections.

Zumafib *Sandoz, Indon.*
Fenofibrate (p. 1381·1).
Hyperlipidaemias.

Zumaflox *Sandoz, Indon.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Zumalgic *Erempharma, Fr.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zumalin *Sandoz, Indon.*
Lincomycin hydrochloride (p. 317·1).
Bacterial infections.

Zumamet *Sandoz, Indon.*
Metformin hydrochloride (p. 489·1).
Diabetes mellitus.

Zumaran *Sandoz, Indon.†*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Zumasid *Sandoz, Indon.†*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zumatab *Sandoz, Indon.*
Thiamphenicol (p. 376·3).
Bacterial infections.

Zumatic *Sandoz, Indon.*
Clindamycin (p. 269·3).
Bacterial infections.

Zumatram *Sandoz, Indon.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zumatrol *Sandoz, Indon.†*
Metoclopramide hydrochloride (p. 1862·2).
Nausea and vomiting; dyspepsia; anorexia.

Zumazol *Sandoz, Indon.†*
Ketoconazole (p. 585·3).
Fungal skin infections.

Zumba
Note: this name may be used for preparations of different composition.
Crefar, Port.
Yohimbine hydrochloride (p. 2372·3).
Erectile dysfunction.
Novum, Mex.
Vitamins; minerals; damiana (p. 2491·3); guarana (p. 2648·2); arginine (p. 2049·1).

Zumenon *Abbott, Austral.; Solvay, Belg.; Abbott, Fin.; Abbott, Neth.; Abbott, Port.; Solvay, Switz.†; Solvay, UK.*
Estradiol (p. 2271·1).
Menopausal disorders; osteoporosis; oestrogen deficiency.

Zumilin *Farmedia, Gr.*
Azelaic acid (p. 1695·1).
Acne.

Zumo *Meda, Swed.†*
Sumatriptan succinate (p. 679·2).
Migraine.

Zumorin *Sons, Mex.*
Ampicillin trihydrate (p. 218·2).
Bacterial infections.

Zunamyn *Randril, Philipp.*
Sultamicillin tosilate (p. 369·1).
Bacterial infections.

Zundic *Raffo, Arg.*
Amlodipine besilate (p. 1304·1).
Angina pectoris; hypertension.

Zunun *Sun, Mex.*
Citicoline (p. 2480·1).

Zuo Ding *Qing Hua Zi Guang Gu Han, China.*
Fluorouracil (p. 795·2).
Malignant neoplasms.

Zuo Fu Kang *United Lab, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Zuo Fu Ke *Double-Crane, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Zuo He *Chang Fu Jie Jing, China.*
Inosine (p. 2533·1).

Zuo Kang *Ziguanggu Hannanyue, China.*
Levofloxacin lactate.
Bacterial infections.

Zuo Ke *Yangtze River, China.*
Levofloxacin hydrochloride.
Bacterial infections.

Zuo Ning *Yada, China.*
Eperisone hydrochloride (p. 2025·1).
Skeletal muscle spasm.

Zuo Nuo *Chang Fu Jie Jing, China.*
Xantinol nicotinate (p. 1535·3).
Cerebral and peripheral vascular disorders.

Zuo Pai Xin *FuDong, China.*
Levodropropizine (p. 1662·3).
Cough.

Zuo Tan *LuoXin, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Zuobenneng *NEGPF, China.*
Methacycline hydrochloride (p. 322·3).
Bacterial infections.

Zuolexin *Xin Gang Union, China.*
Reboxetine (p. 447·1).
Depression.

Zuorui *SSPC, China.*
Zoledronic acid (p. 1192·3).
Osteolytic bone metastases.

Zuplenz *Par, USA.*
Ondansetron hydrochloride (p. 1872·1).
Nausea and vomiting.

Zuplyn *Arrow, Braz.*
Paracetamol (p. 115·1).
Fever; pain.

Zurcal *Nycomed, Austria; Novartis, Braz.; Royal, Chile; Nycomed, Mex.; Nycomed, Port.; Takeda, Switz.*
Pantoprazole sodium (p. 1875·3).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome; gastritis.

Zurcale *Takeda, Belg.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Zurcamed *Takeda, Belg.*
Pantoprazole (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux.

Zurcazol *Nycomed, Gr.*
Pantoprazole sodium (p. 1875·3).
Peptic ulcer; gastro-oesophageal reflux.

Zürcher Bahnhof Apotheke pastilles contre le mal de gorge *Iromedica, Switz.†*
Tyrothricin (p. 384·1); cetylpyridinium chloride (p. 1743·1); lidocaine hydrochloride (p. 1988·2).
Mouth and throat pain and inflammation.

Zure oordruppels met hydrocortison *TioFarma, Neth.*
⊗Hydrocortisone (p. 1640·1).
Otitis externa.

Zure oordruppels met triamcinolonacetonide *TioFarma, Neth.*
⊗Triamcinolone acetonide (p. 1649·1).
Otitis externa.

Zurenix *Flamingo, Philipp.*
Cefuroxime axetil (p. 255·2) or cefuroxime sodium (p. 255·3).
Bacterial infections.

Zurfix *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastric hypersecretion including Zollinger-Ellison syndrome; conditions where gastric acid reduction is beneficial.

Zuria *Italfarmaco, Spain.*
Paroxetine hydrochloride (p. 440·3).
Depression; obsessive-compulsive disorder; anxiety; social phobia; post-traumatic stress disorder; panic disorder.

Zurim *Atral, Port.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout.

Zurinel *Prater, Chile.†*
Atorvastatin (p. 1309·2).
Hypercholesterolaemia.

Zurocid *Aurora, Gr.; Stargen, Gr.*
Simvastatin (p. 1489·2).
Hyperlipidaemias.

Zutectra *Biotest, Austria; Reg, Cz.; Biotest, Fr.; Biotest, Ger.; Biotest, Irl.; Fidia, Ital.; Biotest, Pol.; Biotest, Port.; Biotest, Spain; Anthrop, Swed.; Biotest, Switz.; Biotest, UK.*
A hepatitis B immunoglobulin (p. 2389·1).
Passive immunisation.

Zutra *Gerolymatos, Gr.*
Glimepiride (p. 473·2).
Diabetes mellitus.

Zutripro *Hawthorn, USA.*
⊗Hydrocodone tartrate (p. 67·2); pseudoephedrine hydrochloride (p. 1676·1); chlorphenamine maleate (p. 620·3).
Cough; nasal congestion.

Zuvair *Reddy, India.*
Zafirlukast (p. 1239·3).
Asthma.

Zuxin *Team, China.*
Granisetron hydrochloride (p. 1844·3).
Nausea and vomiting.

Z-Vita *Pediapharma, Philipp.*
Lysine hydrochloride (p. 2079·3); vitamin B substances (p. 2102·3); zinc gluconate (p. 2126·2).
Nutritional supplement.

Z-Xin *Biomep, Mex.*
Ciprofloxacin (p. 261·1).
Bacterial infections.

Z-Xtra *Magna, USA.*
Mepyramine maleate (p. 635·1); benzocaine (p. 1980·2); zinc oxide (p. 1729·1).
Skin disorders.

Zyatrol *Smith Kline & French, Port.†*
Ropinirole hydrochloride (p. 913·2).

Zyban *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Valeant, Canad.; GSK, Cz.†; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, NZ; GSK, Pol.; Glaxo Wellcome, Port.; GSK, S.Afr.; GSK, Singapore†; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Zycalcit *Zydus, India.*
Calcitonin (salmon) (p. 1178·1).
Paget's disease of bone; osteoporosis; hypercalcaemia of malignancy; metastatic bone pain.

Zycel *Zydus, India.*
Celecoxib (p. 36·3).
Osteoarthritis; rheumatoid arthritis.

Zycin *Cadila, India; Interbat, Indon.*
Azithromycin (p. 221·2).
Bacterial infections.

Zycitapran *Zydus, Braz.*
Citalopram (p. 411·1).

Zyclara *Medicis, Canad.; Meda, UK; Medicis, USA.*
Imiquimod (p. 985·2).
Actinic keratosis.

Zyclir *Arrow, Austral.†*
Aciclovir (p. 964·1) or aciclovir sodium (p. 964·1).
Herpesvirus infections; HIV infection.

Zyclorax *Mugi, Indon.*
Aciclovir (p. 964·1).
Herpesvirus infections.

ZyComb *Nycomed, Swed.†*
⊗Ipratropium bromide (p. 1211·3); xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinorrhoea.

Zycomb *Nycomed, Norw.; Nycomed, Ukr.†*
⊗Ipratropium bromide (p. 1211·3); xylometazoline hydrochloride (p. 1680·1).
Nasal congestion; rhinorrhoea; rhinitis; sinusitis.

Zydalis *Zydus, India.*
Tadalafil (p. 2368·1).
Erectile dysfunction.

Zydan *SM, Venez.*
Benzydamine (p. 29·2).
Mouth and throat inflammation.

Zydarin *Zydus Cadila, Thai.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Zydena *Dong-A, Malaysia; Dong-A, Philipp.; Valenta, Rus.*
Udenafil (p. 2371·3).
Erectile dysfunction.

Zyderm *Collagen, Austral.†; Allergan, NZ.*
Collagen (bovine) (p. 2483·2).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Skin contour defects.

Zydinol *More, Philipp.†*
Paracetamol (p. 115·1).
Fever; pain.

Zydol *Aspen, Austral.; Grunenthal, Irl.; Grunenthal, Port.; Grunenthal, UK.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zydone *Endo, USA.*
Hydrocodone tartrate (p. 67·2); paracetamol (p. 115·1).
Pain.

Zydowin *Zydus, India.*
Zidovudine (p. 1024·2).
HIV infection.

Zyfarin *Zydus Cadila, Philipp.*
Warfarin sodium (p. 1527·1).
Thromboembolic disorders.

Zyflo *Cornerstone, USA.*
Zileuton (p. 1240·3).
Asthma.

Zyflox
Note: this name may be used for preparations of different composition.
Promed, Indon.
Ofloxacin (p. 334·3).
Bacterial infections.

Zydus, Philipp.
Ciprofloxacin hydrochloride (p. 261·2).
Bacterial infections.

Zyfloxin *Zydus, Braz.*
Fluoxetine (p. 417·1).

Zygium *Solara, Mex.†*
Calcitriol (p. 2113·1).
Osteoporosis; renal osteodystrophy; hypoparathyroidism; pseudohypoparathyroidism; rickets.

Zykast *Ajanta, Philipp.*
Levocetirizine hydrochloride (p. 632·3) montelukast sodium (p. 1214·3).
Allergic rhinitis.

Zykinase *Cadila, India.*
Streptokinase (p. 1503·1).
Thromboembolic disorders.

Zykolat-EDO *Mann, Ger.*
Cyclopentolate hydrochloride (p. 2005·3).
Production of mydriasis and cycloplegia.

Zylagren *KRKA, Cz.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis.

Zylap *Aspen, Austral.*
Olanzapine (p. 1089·3).
Psychoses; bipolar disorder.

Zylapour *Iasis, Gr.*
Allopurinol (p. 600·2).
Gout; renal calculi; hyperuricaemia associated with cancer chemotherapy.

Zylet *Bausch & Lomb, Arg.; Bausch & Lomb, Braz.; Teva, Israel; Bausch & Lomb, Singapore; Bausch & Lomb, Thai.; Bausch & Lomb, USA.*
⊗Loteprednol etabonate (p. 1642·1); tobramycin (p. 380·1).
Infected eye disorders.

Zyleth *Bausch & Lomb, Mex.*
⊗Loteprednol etabonate (p. 1642·1); tobramycin (p. 380·1).
Infected eye disorders.

Zylfina *APS, Port.†*
Finasteride (p. 2358·3).
Alopecia androgenetica.

Zylic *Suphong, Thai.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia.

Zylin *Zydus, S.Afr.*
Sertraline hydrochloride (p. 448·1).
Depression; obsessive-compulsive disorder; panic disorder.

Zylinox *Zydus, Braz.*
Zolpidem (p. 1116·2).

Zylium *Farmasa, Braz.*
Ranitidine hydrochloride (p. 1882·1).
Acid aspiration; gastrointestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zyllergy *Dexcel, Israel.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Zyllt *KRKA, Cz.; KRKA, Irl.; KRKA, Neth.; KRKA, Pol.; KRKA, Port.; KRKA, Rus.; KRKA, Spain.*
Clopidogrel bisulfate (p. 1342·3).
Thromboembolism prophylaxis; atherosclerosis.

Zylohist *GX, Philipp.*
Loratadine (p. 633·2).
Allergic rhinitis; urticaria; allergic conjunctivitis.

Zyloprim *Aspen, Austral.; AA, Canad.; GSK, Mex.; GSK, Philipp.; Aspen, S.Afr.; Prometheus, USA.*
Allopurinol (p. 600·2).
Gout; hyperuricaemia; renal calculi.

Zyloram *Ranbaxy, Cz.; Ranbaxy, Hung.*
Citalopram hydrobromide (p. 411·1).
Depression; panic disorder.

Zyloric *Aspen, Austria; SMB, Belg.; GSK, Braz.; GSK, Chile; Aspen, Fin.; HAC, Fr.; Mibe, Ger.; GSK, Gr.; Sigma, Hong Kong†; GSK, India; GSK, Indon.; GSK, Irl.; Teofarma, Ital.; Aspen, Malaysia; Aspen, Neth.; Orion, Norw.; Aspen, Pol.; Vitoria, Port.; Aspen, Singapore; Faes, Spain; Orion, Swed.; Pro Concepta, Switz.; Aspen, Thai.; GSK, UK; GSK, Venez.*
Allopurinol (p. 600·2).
Hyperuricaemia; gout; renal calculi.

Zylotin *Virgo, Philipp.*
Carbocisteine (p. 1658·1).
Cough.

Zylovir *Nanxin, China.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zylpen *Aspen, Braz.*
Meropenem (p. 321·3).

Zymacap *Roberts, USA.*
Vitamins.

Zymacter *Remedina, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Zymad *Novartis Sante, Fr.*
Colecalciferol (p. 2113·1).
Vitamin D deficiency.

Zymaduo *Novartis Sante, Fr.; Novartis, Turk.*
Sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1).
Dental caries prophylaxis; rickets.

Zymafluor *Novartis Consumer, Austria; Novartis, Cz.; Novartis Sante, Fr.; Novartis Consumer, Ger.†; Novartis Consumer, Hung.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Neth.; Novartis Consumer, Pol.†; Novartis Consumer, Port.; Novartis Consumer, S.Afr.; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.*
Sodium fluoride (p. 2089·2).
Dental caries prophylaxis; fluoride supplement.

Zymafluor D *Novartis Consumer, Ger.†*
Sodium fluoride (p. 2089·2); colecalciferol (p. 2113·1).
Rickets; dental caries prophylaxis.

Zymanta *Asofarma, Mex.*
Clonazepam (p. 519·1).
Anxiety; epilepsy.

Zymar *Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Israel; Allergan, Malaysia; Allergan, Mex.; Allergan, Philipp.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Thai.; Abdi, Turk.; Allergan, USA.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Zymaran *Allergan, Arg.*
Gatifloxacin (p. 303·2).
Bacterial eye infections.

Zymaxid *Allergan, Israel; Allergan, USA.*
Gatifloxacin (p. 303·2).
Bacterial conjunctivitis.

Zyme *Blooming Fields, Philipp.*
Vitamin E (p. 2119·1).
Vitamin E deficiency.

Zymechol *Blooming Fields, Philipp.*
Omega-3 fish oil (p. 1460·3).
Hyperlipidaemias.

Zymed *Millimed, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Zymelin *Nycomed, Denm.; Nycomed, Norw.*
⊗Xylometazoline hydrochloride (p. 1680·1).
Rhinitis; sinusitis; otitis.

Zymelin Plus *Nycomed, Denm.*
⊗Xylometazoline hydrochloride (p. 1680·1); ipratropium bromide (p. 1211·3).
Rhinitis.

Zymelytic *Blooming Fields, Philipp.*
Carbocisteine (p. 1658·1).
Respiratory-tract congestion.

Zymine *Vindex, USA.†*
Triprolidine hydrochloride (p. 642·3) or triprolidine tannate (p. 642·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Zymine HC *Vindex, USA.†*
⊗Hydrocodone tartrate (p. 67·2); triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).

Zymine-D *Vindex, USA.*
⊗Triprolidine hydrochloride (p. 642·3); pseudoephedrine hydrochloride (p. 1676·1).

Zymocomb *Chrispa (Χρισπα), Gr.*
Sulpiride (p. 1107·3).

Zymolav *Hikma, Neth.*
Amoxicillin trihydrate (p. 216·2); potassium clavulanate (p. 268·3).
Bacterial infections.

Zymoplex
Note: this name may be used for preparations of different composition.
Genepharm, Gr.
⊗Tamoxifen citrate (p. 860·2).
Breast cancer.

Zambon, Fr.†
Amylase, cellulase, and protease from *Aspergillus*; lipase from *Rhizopus*; dimeticone (p. 1886·2).
Dyspepsia.

Zymoptic *Cooper (Κοπερ), Gr.*
⊗Carteolol hydrochloride (p. 1332·3).
Glaucoma.

Zymoxyl *Blooming Fields, Philipp.*
Amoxicillin trihydrate (p. 216·2).
Bacterial infections.

Zynapse *Ferrer, Philipp.; Hizon, Philipp.*
Citicoline (p. 2480·1).
Cerebrovascular disorders.

Zynaraam *Raam, Mex.*
Zidovudine (p. 1024·2).
HIV infection.

Zyncet *Unichem, Rus.; Unichem, S.Afr.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria; allergic skin disorders.

Zyneva *Medicus, Gr.*
Mitoxantrone hydrochloride (p. 833·1).
Malignant neoplasms.

Zynicor *Zydus, India.*
Nicorandil (p. 1446·2).
Angina pectoris.

Zynilmed *Medis, Denm.†*
Olanzapine (p. 1089·3).
Schizophrenia; mania; bipolar disorder.

Zyno *Bangkok Lab & Cosmetic, Thai.*
⊗Triamcinolone acetonide (p. 1649·1).
Skin disorders.

Zynol *Micro, Singapore.*
Ranitidine hydrochloride (p. 1882·1).
Peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome; acid aspiration; dyspepsia.

Zynolex *Walnut, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Zynor
Note: this name may be used for preparations of different composition.
Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia.
Amlodipine besilate (p. 1304·1).
Hypertension; angina pectoris.

Ivax, Irl.†
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; pruritus; urticaria.

Zynotril *Meiji, Thai.*
Glucosamine sulfate (p. 2515·3).
Degenerative joint disorders.

Zynox *Intramed, S.Afr.†*
Naloxone hydrochloride (p. 1562·3).
Opioid overdosage; reversal of opioid depression.

Zyntabac *GSK, Neth.; GSK, Port.†; GSK, Spain.*
Bupropion hydrochloride (p. 408·2).
Aid to smoking withdrawal.

Zynzol *GL Pharma, Cz.; Gerot, Hung.†*
⊗Anastrozole (p. 742·1).
Breast cancer.

Zyolaif *Medimar, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Zyom *Zydus, Philipp.*
Omeprazole (p. 1867·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zyomet *Goldshield, UK.*
Metronidazole (p. 936·1).
Rosacea.

Zyon *Minerva (Μινερβα), Gr.*
Pravastatin sodium (p. 1473·1).
Hyperlipidaemias.

Zyoston *Medimar, Gr.*
Calcitonin (salmon) (p. 1178·1).

Zyoxipina *Zydus, Braz.*
Oxcarbazepine (p. 533·2).

Zypadhera *Lilly, Austria; Lilly, Belg.; Lilly, Cz.; Lilly, Denm.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hung.; Lilly, Irl.; Lilly, Israel; Lilly, Neth.; Lilly, Norw.; Lilly, Pol.; Lilly, Port.; Lilly, Spain; Lilly, Swed.; Lilly, UK.*
Olanzapine embonate (p. 1090·1).
Schizophrenia.

Zyparox *Zydus, Braz.*
Paroxetine hydrochloride (p. 440·3).

Zypefar *Specifar, Gr.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zypi *Zydus Cadila, Philipp.*
Pioglitazone hydrochloride (p. 493·1).
Diabetes mellitus.

Zypina *Dermapharm, Neth.†*
Cyproterone acetate (p. 2261·2); ethinylestradiol (p. 2275·3).
Androgen-dependent acne, hirsutism, or seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Zypine *Alphapharm, Austral.*
Olanzapine (p. 1089·3).
Schizophrenia; bipolar disorder.

Zyplast *Collagen, Austral.†; Allergan, NZ.*
Collagen (bovine) (p. 2483·2).
Lidocaine (p. 1988·1) is included in this preparation to alleviate the pain of injection.
Skin contour defects.

Zyplo *Bago, Braz.; Armstrong, Mex.*
Levodropropizine (p. 1662·3).
Cough.

Zypol *Mergers Drugfil, Philipp.*
Vitamins.
Dietary supplement.

ZyPram *Vertical, USA.*
⊗Hydrocortisone acetate (p. 1640·1); pramocaine hydrochloride (p. 1993·3).
Anorectal disorders.

Zypraz *Kalbe, Indon.*
Alprazolam (p. 1035·2).
Anxiety; panic disorder.

Zypred *Allergan, Braz.*
⊗Gatifloxacin (p. 303·2); prednisolone (p. 1645·2).

Zyprexa *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, China; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Jpn; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, NZ; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, Ukr.; Lilly, USA; Lilly, Venez.*
Olanzapine (p. 1089·3).
Bipolar disorder; psychoses; schizophrenia; mania; dementia; depression; agitation.

Zypsila *KRKA, Cz.*
Ziprasidone bisulfate (p. 1115·2).
Schizophrenia; bipolar disorder.

KRKA, Pol.
Ziprasidone (p. 1115·2).
Schizophrenia; bipolar disorder.

Zypsilan *KRKA, Spain.*
Ziprasidone bisulfate (p. 1115·2).
Schizophrenia; bipolar disorder.

Zyquin *Zydus, India.*
Gatifloxacin (p. 303·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p. viii)

Zyrac *Osoth, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; insect bites.

Zyral *Sinopharm, Thai.*
Cetirizine (p. 619·2).

Zyramycin *Leovan, Gr.*
Azithromycin (p. 221·2).
Bacterial infections.

Zyrantol *Leovan, Gr.*
Ambroxol hydrochloride (p. 1654·3).
Respiratory disorders associated with viscous mucus.

Zyrazine *British Dispensary, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis; insect bites.

Zyrcef *Basic, Philipp.*
Cefaclor (p. 232·3).
Bacterial infections.

Zyrcon *Condrugs, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders.

Zyrex *Masa, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic skin disorders; allergic conjunctivitis.

Zyril *Utopian, Thai.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions.

Zyrlergic *Macrophar, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; allergic skin disorders; insect bites.

Zyrlex *UCB, Swed.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; pruritus; urticaria.

Zyrolen *Demo, Gr.*
Ipratropium bromide (p. 1211·3).
Obstructive airways disease.

Zyrona *Orifarm, Denm.; Orifarm, Norw.; Orifarm, Swed.*
Cyproterone acetate (p. 2261·2);
ethinylestradiol (p. 2275·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea.

Zyrrigin *Unison, Philipp.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; urticaria.

Zyrtec *GSK, Arg.; Johnson & Johnson, Austral.; UCB, Austria; UCB, Belg.; GSK, Braz.; GSK, Chile; UCB, China; UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; GSK, Hong Kong; UCB, Hung.; UCB, India; UCB, Jpn; GSK, Malaysia; UCB, Mex.; UCB, Neth.; UCB, Norw.; Pharmabroker, NZ; GSK, Philipp.; Vedim, Pol.; UCB, Port.; UCB, Rus.; AHN, S.Afr.; GSK, Singapore; UCB, Spain; UCB, Switz.; GSK, Thai.; UCB, Turk.; UCB, Ukr.; McNeil Consumer, USA; Pfizer, Venez.*
Cetirizine hydrochloride (p. 619·2).
Hypersensitivity reactions; allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria; insect bites; eczema.

Zyrtec D *UCB, Pol.*
⊗Cetirizine hydrochloride (p. 619·2);
pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis.

Zyrtec Decongestant *Pharmabroker, NZ.†*
⊗Cetirizine hydrochloride (p. 619·2);
pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; cold symptoms.

Zyrtec Itchy Eye Drops *McNeil, USA.*
Ketotifen (p. 631·3).
Allergic conjunctivitis.

Zyrtec-D *Rontag, Arg.; GSK, Braz.; GSK, Hong Kong; UCB, Hung.; GSK, Malaysia; UCB, Mex.†; GSK, Singapore; GSK, Thai.†; Pfizer, USA; Pfizer, Venez.*
⊗Cetirizine hydrochloride (p. 619·2);
pseudoephedrine hydrochloride (p. 1676·1).
Allergic rhinitis; allergic conjunctivitis; nasal congestion; rhinitis.

ZyrtecSet *UCB, Fr.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; allergic conjunctivitis; urticaria.

Zysacar *Cadila, Rus.*
Losartan potassium (p. 1422·2).
Hypertension; heart failure.

Zysertin *Zydus, Braz.*
Sertraline hydrochloride (p. 448·1).

Zysim *Zydus, S.Afr.*
Simvastatin (p. 1489·2).
Hypercholesterolaemia; atherosclerosis; cardiovascular risk reduction.

Zystol *Veltipharm, Gr.*
Clopidogrel (p. 1342·3).

Zytaz *Zydus, India.*
Ceftazidime (p. 250·2).
Bacterial infections.

Zytee *Raptakos, India.*
Oral gel: Choline salicylate (p. 39·2).
Aphthous ulcers; denture irritation; teething pain.

Zytiga *Janssen-Cilag, Belg.; Janssen, Canad.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen, UK; Centocor, USA.*
Abiraterone acetate (p. 735·1).
Prostatic cancer.

Zytizine *Asian Pharm, Thai.*
Cetirizine hydrochloride (p. 619·2).
Allergic rhinitis; pruritus; urticaria.

Zytofen *Medicine Products, Thai.*
Ketotifen fumarate (p. 631·3).
Asthma; hypersensitivity reactions.

Zytomil *Pharma Dynamics, S.Afr.*
Escitalopram oxalate (p. 416·2).
Depression; panic disorder.

Zytram *Purdue, Canad.; Pharmaco, NZ; Napp, Port.†; Zambon, Spain.*
Tramadol hydrochloride (p. 139·2).
Pain.

Zytrim
Note: this name may be used for preparations of different composition.
Imperial, Philipp.†
⊗Sibutramine hydrochloride (p. 2330·2).
Obesity.
Recordati, Ger.†
Azathioprine (p. 1940·3).
Organ transplant rejection; auto-immune disorders.

Zytrin *Stadmed, India.*
Terazosin hydrochloride (p. 1511·1).
Benign prostatic hyperplasia.

Zytual *Panagiotis, Gr.*
⊗Budesonide (p. 1625·1).
Allergic rhinitis.

Zyvalprex *Zydus, Braz.*
Valproate semisodium (p. 553·2).
Epilepsy; migraine.

Zyvir *Novartis, Port.†*
Famciclovir (p. 979·1).
Herpesvirus infections.

Zyvirpac *Inpac, Thai.*
Aciclovir (p. 964·1).
Herpesvirus infections.

Zyvox *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Chile; Pfizer, China; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK; Pfizer, Ukr.; Pfizer, USA; Pfizer, Venez.*
Linezolid (p. 317·3).
Bacterial infections.

Zyvoxam *Pfizer, Canad.; Pfizer, Mex.*
Linezolid (p. 317·3).
Gram-positive bacterial infections.

Zyvoxid *Pfizer, Austria; Pfizer, Belg.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pharmacia, Israel; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.*
Linezolid (p. 317·3).
Bacterial infections.

Zyx *Antula, Denm.; Meda, Fin.; Antula, Swed.*
Benzydamine hydrochloride (p. 29·2).
Mouth and throat pain and irritation.
Biofarm, Pol.
Levocetirizine hydrochloride (p. 632·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zyxem *Chiesi, Braz.; GSK, Mex.*
Levocetirizine hydrochloride (p. 632·3).
Allergic rhinitis; urticaria; allergic conjunctivitis; allergic skin disorders.

Zyzapin *Biofarma, Turk.*
Olanzapine (p. 1089·3).

ZzzQuil *Procter & Gamble, USA.*
Diphenhydramine hydrochloride (p. 626·2).
Insomnia.

Directory of Manufacturers

In Martindale, the names of manufacturers and distributors are abbreviated. These and their full names are given alphabetically in this directory together with contact details if available.

10B International, Malaysia. 10B International (M) Sdn Bhd, 19th Fl Plaza VADS, 1 Jln Tun Mohd Fuad, Taman Tun Dr Ismail, 60000 Kuala Lumpur, Malaysia.
url: www.10binternational.com

10B International, Singapore. See *Apex, Singapore.*

139673 Canada, Canad. 139673 Canada Inc., 1190 Lemay St, Acton Vale, Quebec, J0H 1A0, Canada.

1A, Austria. 1A Pharma GmbH, Sandleitengasse 15, A-1160 Vienna, Austria.

1A, Cz. See *1A, Ger.*

1A, Denm. 1A Farma A/S, Herstedøstervej 27-29, 2620 Albertslund, Denmark.
url: www.1a-farma.com

1A, Ger. 1 A Pharma GmbH, Keltenring 1 + 3, 82041 Oberhaching, Germony.
url: www.1apharma.de

1A, Hung. 1A Pharma, Pf 66, 1301 Budapest, Hungary.
url: www.1apharma.hu

1A, Pol. See *Hexal, Pol.*

1x2, Ital. 1x2 Pharma Srl, Via Concordia 5, 20094 Corsico (MI), Italy.

2 World Lab, Philipp. See *2 World Traders, Philipp.*

2 World Traders, Philipp. 2 World Traders, Unit 1 Makro Sucat, East Service Rd, South Super Highway, Muntinlupa City, Philippines.
url: www.2worldtraders.net

21st Century, USA. 21st Century HealthCare Inc., 2119 Silson St, Tempe, AZ 85282, USA.
url: www.21stcenturyvitamins.com

2care4, Denm. 2care4 ApS, Tømrervej 10, Saedding Øst, 6710 Esbjerg V, Denmark.

2K, Denm. See *Pliva, UK.*

2M, Thai. 2M (Med-Maker) Co Ltd, 222 Soi Ramkhamhaeng 199, Ramkhamhaeng Rd, Minburi, Bangkok 10510, Thailand.

3a, India. 3a Pharmaceuticals, 304 Sai Kirti, Appt. No.1, Punit Nagar, Old Padra Road, Vadodara 390 015, India.

3DDD, Belg. 3DDD NV, Diestersteenweg 349, 3510 Kermt, Belgium.

3M, Arg. 3M Argentina S.A.C.I.F.I.A., Los Arboles 842, 1686 Hurlingham, Buenos Aires, Argentina.
url: www.3m.com

3M, Austral. 3M Pharmaceuticals P/L, P.O. Box 101, Pennant Hills, NSW 2120, Australia.
url: www.3m.com

3M, Austria. See *3M, UK.*

3M, Belg. 3M Pharma SA/NV, Hermeslaan 7, 1831 Diegem, Belgium.The Marketing Manager
url: www.mmm.com

3M, Canad. 3M Pharmaceuticals, P.O.Box 5757, London, Ontario, N6A 4T1, Canada.
url: www.3m.com

3M, Chile. 3M Chile SA, Santa Isabel 1001, Santiago, Chile.

3M, China. 3M China Ltd, Mando Center Building 38-41 Floor, 8 Xingyi Rd, Shanghai 200336, China.
url: www.3m.com

3M, Cz. See *3M, UK.*

3M, Denm. 3M ESPE, Fabriksparken 15, 2600 Glostrup, Denmark.
url: www.3mespe.dk

3M, Fin. Suomen 3M Oy/3M Pharma, Lars Sonckin kaari 6, PL 90, 02601 Espoo, Finland.
url: www.3m.com

3M, Fr. Laboratoires 3M Santé, Bd de l'Oise, 95029 Cergy-Pontoise cdx, France.
url: www.3m.com

3M, Ger. See *Meda, Ger.*

3M, Gr. 3M Hellas Ltd., Kifisias 20, 151 25 Marousi, Greece.
url: www.3m.com

3M, Hong Kong. 3M Hong Kong Ltd, 5/F Victoria Ctr, 15 Watson Rd, North Point, Hong Kong.
url: www.3m.com

3M, Hung. 3M Hungária Kft, Váci út 178, 1138 Budapest, Hungary.

3M, Irl. 3M Ireland Ltd, The Iveagh Building, The Park, Carrickmines, Dublin 18, Ireland.
url: www.3M.ie

3M, Israel. 3M Israel Ltd, 91 Medinat Haehudim St, P.O. Box 2042, Herzliya 46120, Israel.
url: www.3m.com

3M, Ital. 3M Italia S.p.A., Via Norberto Bobb, 20096 Pioltello (MI), Italy.
url: solutions.3mitalia.it

3M, Malaysia. 3M Malaysia Sdn Bhd, Bangunan 3M, 6 Persiaran Tropicana, 47410 Petaling Jaya, Selangor, Malaysia.
url: www.3m.com

3M, Mex. 3M Mexico S.A. de C.V., Av. Santa Fe No. 55, 01210 Mexico D.F., Mexico.
url: www.3m.com.mx

3M, Neth. 3M Pharma Nederland BV, Industrieweg 23, 2382 NW Zoeterwoude, Netherlands.
url: www.3m.com

3M, NZ. 3M Pharmaceuticals, C.P.O. Box 2201, Auckland, New Zealand.
url: www.3m.com

3M, Philipp. 3M Pharmaceuticals, 18/F PCI Bank Tower II, Makati Ave, Makati City, Philippines.

3M, Pol. 3M Poland Sp. zo.o., al. Katowicko 117, Kajetany, 05-830 Nadarzyn, Poland.
url: www.3m.pl

3M, Port. See *Agostinho, Port.*

3M, Rus. 3M, ul. Krilatskaya Dom 17, Building 3, Business Park Krilatsky Hills, 121614 Moscow, Russia.
url: solutions.3mrussia.ru

3M, S.Afr. 3M SA (Pty) Ltd, Private Bag X926, Rivonia 2128, South Africa.
url: www.3m.com

3M, Singapore. See *Zuellig, Singapore.*

3M, Spain. 3M España, Juan Ignacio Luca de Tena 19-25, 28027 Madrid, Spain.
url: www.3m.com

3M, Swed. 3M Svenska AB, 191 89 Sollentuna, Sweden.
url: www.3m.se

3M, Switz. 3M (Schweiz) AG, Eggstrasse 93, 8803 Rüschlikon, Switzerland.
url: www.3m.com

3M, Thai. See *Diethelm, Thai.*
url: www.3m.com

3M, UK. 3M Health Care Ltd, Derby Rd, Loughborough, Leicestershire, LE11 5SF, UK.
url: www.3M.co.uk

3M, USA. 3M Pharmaceuticals, 3M Center, St Paul, MN 55133-1000, USA.
url: www.3m.com

3M Espe, Austria. See *3M Espe, Ger.*

3M Espe, Belg. See *3M, Belg.*

3M Espe, Cz. See *3M Espe, Ger.*

3M Espe, Ger. 3M ESPE AG, ESPE Platz, 82229 Seefeld, Germany.
url: www.3mespe.de

3M Espe, Gr. See *3M Espe, Ger.*

3M Espe, Hong Kong. See *3M, Hong Kong.*

3M Espe, Irl. See *3M, Irl.*

3M Espe, Ital. See *3M, Ital.*

3M Espe, Switz. See *3M, Switz.*

3M Espe, USA. 3M Espe Dental Products, Building 275-2SE-03, 3M Center, St Paul, MN 55144, USA.
url: www.solutions.3m.com

3-OL, Israel. 3-OL Ltd, P.O. Box 3906, Petach Tikva, Israel.

7 Oaks, USA. 7 Oaks Pharmaceutical Corp., 161 Harry Stanley Drive, Easley, SC 29640, USA.
url: www.7oaksphama.com

A&Z, China. See *Baiyoung, China.*

A.S., Ger. See *Teva, Ger.*

A.S., UK. A.S. Pharma Ltd, P.O. Box 181, Polegate, East Sussex, BN26 6WD, UK.
url: www.aspharma.co.uk

A Hua, China. A Hua Biological Pharmaceutical Co. Ltd, Shandong, China.

A La Bin Du Tong Ling, China. A La Bin Du Tong Ling Pharmaceutical Co Ltd, China.

A Max Biocare, Hong Kong. See *International Medical, Hong Kong.*

AA, Canad. AA Pharma Inc., Unit 1, 1165 Creditstone Rd, Vaughan, Ontario, L4K 4N7, Canada.

AAA, Denm. See *AAA, Ger.*

AAA, Fr. Advanced Accelerator Applications, 126 Rocade Sud, 62660 Beuvry, France.
url: www.adacap.com

AAA, Ger. AAA-Pharma GmbH, Leibknechstr. 33, 70565 Stuttgart, Germany.

AAA, Spain. Advanced Accelerator Applications, Josep Anselm Clavé 100, 08950 Esplugues de Llobregat, Spain.
url: www.adacap.com

Aacifar, Port. Aacifar Produtos Químicos e Farmacêuticos Lda, Av. José Malhoa 16-B 2, 1070-159 Lisbon, Portugal.

Aaciphar, Belg. See *Organon, Belg.*

AAH, UK. AAH Pharmaceuticals Ltd, Sapphire Court, Walsgrave Triangle Park, Coventry, Warwickshire, CV2 2TX, UK.
url: www.aah-hospitalservice.co.uk

aai, USA. aai Pharma Inc., 2320 Scientific Park Drive, Wilmington, NC 28405, USA.
url: www.aaipharma.com

Aamorb, India. Aamorb Pharmaceuticals Pvt Ltd, UG-47-48 Bansi Trade Centre, 581/5, M.G. Road, Indore (M.P.) 452001, India.
url: www.aamorb.com

aar, Ger. aar pharma GmbH & Co. KG, Alleestr. 11, 42853 Remscheid, Germany.
url: www.aar.de

Aareen, Indio. Plot No. D/9/2/B, Diamond Park, G.I.D.C, Narada, Amnedabod 382 325, Indio.

Aaron, India. Aaran Pharmaceuticals Pvt Ltd, Industry House, Mahakali Road, Andheri (E), MUMBAI 93, India.

Aarpik, India. Aarpik Pharmaceuticals Pvt Ltd, A-81 Corporate House, S.G.Raad, Bodakdev, Ahmedabad 380 054, India.

AB, Ital. AB Analitica S.r.l., Via Svizzera 16, 35127 Padova, Italy.
url: www.abanalitica.it

Abacus, Denm. Abacus Medicine ApS, Vesterbragade 149, 1620 Copenhagen 5, Denmark.

Abalon, Spain. Abalon Pharma SL, C/ Capitán Haya 19 A, 28020 Madrid, Spain.

Abamed, Spain. Abamed Pharma SL, Pasaje Can Politic 17, 08907 Hospitalet de Llobregat, Barcelona, Spain.

Abana, USA. See *King, USA.*

Abatron, UK. Abatron Ltd, Chapel St, Potton, Sandy, Bedfordshire, SG19 2PT, UK.

Abba, Ukr. Abba Ukraine Ltd, Yaroslav Val 13/2B, Kiev, 01034, Ukraine.
url: www.avva-rus.ru

Abbey, UK. Abbey Pharmaceuticals Ltd, 13 Islet Park Drive, Maidenhead, Berkshire, SL6 8LF, UK.

Abbott, Arg. Abbott Laboratories Argentina S.A., Ing. Butty 240, Piso 13, 1001 Capital, Buenos Aires, Argentina.
url: www.abbott.com

Abbott, Austral. Abbott Australasia P/L, P.O. Box 101, Cronulla, NSW 2230, Australia.
url: www.abbottlabs.com.au

Abbott, Austria. Abbott GmbH, Perfektastrasse 86, A-1230 Vienna, Austria.
url: www.abbott.com

Abbott, Belg. Abbott SA, Parc Scientific, Rue du Bosquet 2, 1348 Louvain-la-Neuve, Belgium.
url: www.abbott.com

Abbott, Braz. Abbott Laboratórios do Brasil Ltda, Rua Michigan 735, 4566905 São Paulo, SP, Brazil.
url: www.abbottbrasil.com.br

Abbott, Canad. Abbott Laboratories Ltd, P.O. Box 6150, Station Centre-Ville, Montreal, Quebec, H3C 3K6, Canada.
url: www.abbott.ca

Abbott, Chile. Abbott Laboratories de Chile Ltda, El Salto 5380, Huechuraba, Santiago, Chile.

Abbott, China. Abbott Laboratories Ltd, Ciro's Plaza 32, Nanjing West Rd 388, Shanghai, 200003, China.
url: www.abbott.com.cn

Abbott, Cz. Abbott Laboratories sro, Šafaříkova 17, 120 00 Prague 2, Czech Republic.
url: www.abbott.com

Abbott, Denm. Abbott Laboratories A/S, Emdrupvej 28 C, 2100 Copenhagen Ø, Denmark.
url: www.abbott.dk

Abbott, Fin. Abbott Oy, Pihatörmä 1 A, 02240 Espoo, Finland.
url: www.abbott.fi

Abbott, Fr. Abbott-France, 10 rue d'Arcueil, Silic 233, 94528 Rungis cdx, France.
url: www.abbott.fr

Abbott, Ger. Abbott GmbH & Co. KG, Max-Planck-Ring 2, 65205 Wiesbaden, Germany.
url: www.abbott.de

Abbott, Gr. Abbott (Hellas) S.A., 512 Vouliagmenis Ave, 174 56 Alimos, Greece.
url: www.abbott.com

Abbott, Hong Kong. Abbott Laboratories Ltd, 20/F AIA Tower, 183 Electric Rd, North Point, Hong Kong.
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Abbott, Hung. Abbott Laboratories (Magyarország) Kft, Teve u 1/a-c, 1139 Budapest, Hungary.

Abbott, India. Abbott India Ltd, 3-4 Corporate Park, Sion Trombay Rd, Mumbai 400022, India.
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Abbott, Indon. PT Abbott Indonesia, Wisma Pondok Indah 2, Suite 1000, Jl. Sultan Iskandar Muda Kav.V-TA, Pondok Indah, Jakarta 12310, Indonesia.
url: www.abbott.co.id

Abbott, Irl. Abbott Laboratories, Ireland Ltd, 4051 Kingswood Drive, Citywest Business Campus, Dublin 24, Ireland.
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Abbott, Israel. Abbott Laboratories S.A., Atidim Science Park, Bldg 4, P.O. Box 58099, Tel Aviv 61580, Israel.
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Abbott, Ital. Abbott S.r.l., Via Pontina Km 52, 04010 Campoverde (LT), Italy.
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Abbott, Jpn. Abbott Japan Co Ltd, 2-53 Shiromi 2-chome, Chuo-ku, Osaka, Japan.

Abbott, Malaysia. Abbott Laboratories (M) Sdn Bdh, 22 Jln Pemaju U1/15, Seksyen U1, Hicom-Glenmarie Industrial Park, 40150 Shah Alam, Selangor, Malaysia.
url: www.abbott.com.my

Abbott, Mex. Abbott Laboratories de Mexico S.A. de C.V., Av. Coyoacan 1622, Benito Juarez del Valle, 03100 Mexico D.F., Mexico.
url: www.abbott.com

Abbott, Neth. Abbott BV, Wegalaan 9, 2132 WT Hoofddorp, Netherlands.
url: www.abbott.com

Abbott, Norw. Abbott Norge AS, Nesoyv.4, Postboks 123, 1361 Billingstad, Norway.
url: www.abbott.no

Abbott, NZ. Abbott Laboratories (NZ) Ltd, P.O. Box 35-128, Naenae, Lower Hutt, New Zealand.
url: www.abbott.com

Abbott, Philipp. Abbott Labs (Phils) Inc., 102 EDSA, Cor Modison Ave, Mandaluyong City, Philippines.

Abbott, Pol. Abbott Laboratories Poland Sp. zo.o., ul. Domaniewska 41, 02-672 Warsaw, Poland.
url: www.abbott.pl

Abbott, Port. Abbott Laboratórios, Lda, Rua Cidade de Córdova, 1, Alfragide, 2720 Amadora, Portugal.
url: www.abbott.com

Abbott, Rus. Abbott Laboratories SA, 9 Dimitrovsky per., 103031 Moscow, Russia.
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Abbott, S.Afr. Abbott South Africa (Pty) Ltd, P.O. Box 7208, Weltevredenpark, Johannesburg 1715, South Africa.
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Abbott, Singapore. Abbott Laboratories (S) Pte Ltd, 1 Maritime Square, 12-01 Harbour Front Centre, S 099253, Singapore.
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Abbott, Swed. Abbott Scandinavia AB, Box 509, 169 29 Solna, Sweden.
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Abbott, Switz. Abbott AG, Neuhofstrasse 23, Postfach, 6341 Baar, Switzerland.
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Abbott, Thai. Abbott Laboratories Ltd, 2/4 Nai Lert Tower, 5th and 9th Floor, Wireless Rd, Lumpini, Pathumwan, Bangkok 10330, Thailand.
url: www.abbott.co.th

Abbott, Turk. Abbott Laboratuarları Ltd. Şti., Ekinciler Caddesi, Hedef Plaza K:6, Kavacyk/Beykoz, Istanbul, 81640, Turkey.
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Abbott, UK. Abbott Laboratories Ltd, Abbott House, Norden Rd, Maidenhead, Berkshire, SL6 4XE, UK.
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Abbott, Ukr. Abbott Products, ul. Vyshgorodska 63, 04114 Kiev, Ukraine.

Abbott, USA. Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064-3500, USA.
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Abbott, Venez. Abbott Laboratories C.A., Aptdo Postal No. 1412, Caracas 1010, Venezuela.
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Abbott Cientifica, Spain. See *Abbott, Spain.*

Abbott Diabetes Care, Austral. See *Abbott, Austral.*

Abbott Diabetes Care, Canad. See *Abbott Diabetes Care, USA.*

Abbott Diabetes Care, Fr. Abbott Diabetes Care (Lob), 12 rue de la Couture, B.P. 20235, 94528 Rungis cdx, France.

Abbott Diabetes Care, UK. See *Abbott, UK.*

Abbott Diabetes Care, USA. Abbott Diabetes Care Inc., 1360 South Loop Rd, Alameda, CA 94502, USA.

Abbott Diagnostics, Ital. Abbott S.p.A. Divisione Diagnostici, Via Mar della Cina 262, 00144 Rome, Italy.
url: www.abbott.com

Abbott Medisense, Fr. See *Abbott, Fr.*

Abbott Nutrition, Singapore. See *Abbott, Singapore.*

Abbott Nutrition, UK. See *Abbott, UK.*

Abbott Nutrition, USA. Abbott Nutrition, 625 Cleveland Ave, Columbus, OH 4325-1724, USA.
url: www.abbottnutrition.com

AbbVie, Belg. AbbVie SA, Avenue Einstein 14, 1300 Wavre, Belgium.

AbbVie, Canad. AbbVie Corp., 8401 Trans-Canada Highway, Saint-Laurent, Quebec, H4S 1Z1, Canada.

AbbVie, Fin. See *Abbott, Fin.*

AbbVie, Ger. AbbVie Deutschland GmbH & Co. KG, Max-Planck-Ring 2a, 65205 Wiesbaden, Germany.
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AbbVie, Jpn. See *Abbott, Jpn.*

AbbVie, Neth. See *Abbott, Neth.*

AbbVie, Spain. AbbVie Farmacéutica SLU, Avda de Burgos 91, 28050 Madrid, Spain.

AbbVie, Switz. See *Abbott, Switz.*

AbbVie, UK. AbbVie Ltd, Abbott House, Vanwall Business Park, Vanwall Rd, Maidenhead, Berkshire, SL6 4XE, UK.
url: www.abbvie.co.uk

AbbVie, USA. AbbVie Inc., 1 North Waukegan Rd, North Chicago, IL 6006, USA.
url: www.abbvie.com

ABC, Canad. See *ABC, USA.*

ABC, Fr. ABC Pharmacare SAS, Normandial, 2 av du Pays-de-Caen, 14460 Colombelles, France.

ABC, Ital. ABC Farmaceutici S.p.A., C.so Vittorio Emanuele II 72, 10121 Turin, Italy.
url: www.abcfarmaceutici.it

ABC, Port. See *Pierre Fabre, Port.*

ABC, Ukr. See *Megakom, Ukr.*

ABC, USA. ABC Compounding Co Inc., 6970 Jonesboro Rd, Morrow, Georgia, 30260-2980, USA.

AB-Consult, Austria. AB-Consult Handels-GmbH, Eichenstrasse 32, A-1120 Vienna, Austria.

Abcur, Fin. See *Abcur, Swed.*

Abcur, Swed. Abcur AB, Campus Gräsvik 5, 371 75 Karlskrona, Sweden.

Abdi, Rus. Abdi Ibrahim Pharmaceutical, Barklayo St 6, str 26, 121086 Moscow, Russia.
url: www.abdiibrahim.com

Abdi, Turk. Abdi İbrahim Ilaç San. ve Tic. A.Ş., Kore Şehitleri Cad. No: 19, Zincirlikuyu, İstanbul, Turkey.
url: www.abdiibrahim.com

Abdi, Ukr. See *Trifarma, Ukr.*

Abd Ibrahim, Indon. See *Combiphar, Indon.*

Abdi-Med, Switz. Abdi-med, Bahnhofstrasse 9, 9630 Wattwil, Switzerland.

Abello, Spain. See *MSD, Spain.*

Abello Linde, Spain. Abelló Linde S.A., Ctra. Alcala, Daganzo Km 3.8, Pol. Ind. Banuelos, 28006 Madrid, Spain.
url: www.abellolinde.es

Abfar, Turk. See *Fako, Turk.*

Abic, Cz. See *Teva, Cz.*

Abic, Hong Kong. See *International Medical, Hong Kong.*

Abic, Israel. See *Teva, Israel.*

Abic, Neth. See *Multipharma, Neth.*

Abic, Thai. See *RX, Thai.*

Abic-Teva, Singapore. See *Green Cross, Singapore.*

Abic-Teva, Thai. See *RX, Thai.*

Abigo, Denm. Abigo Pharma A/S, Stengårdsvej 25, 4340 Tølløse, Denmark.
url: www.dhc.dk

Abigo, Fin. See *Abigo, Swed.*

Abigo, Norw. See *Abigo, Swed.*

Abigo, Swed. Abigo Medical AB, 436 32 Askim, Sweden.
url: www.abigo.com

Abiogen, Hong Kong. See *Four Star, Hong Kong* and *Sino-Asia, Hong Kong.*

Abiogen, Ital. Abiogen Pharma S.p.A., Via Meucci 36, 56121 Ospedaletto (PI), Italy.
url: www.abiogen.it

ABJ, Canad. ABJ Custom Packaging, 1379 Colborne Street East, Brantford, Ontario, N3T 5M1, Canada.

ABL, Braz. Antibioticos do Brasil Ltda, Rod. Gal. Milton T de Souza SP 332 Km 1, 13150000 Cosmopolis, São Paulo, Brazil.

ABL, USA. ABL Medical LLC, 705 E 50 S, American Fork, UT 84003, USA.
url: www.silvrstat.com

Able, USA. Able Laboratories Inc., 6 Hollywood Court, South Plainfield, NJ 07080, USA.
url: www.ablelabs.com

Abnoba, Ger. Abnoba GmbH, Hohenzollernstr. 16, 75177 Pforzheim, Germany.
url: www.abnoba.de

Aboca, Ital. Aboca SpA, Localita Aboca 20, 52037 San Sepoicro (AR), Italy.

Abolmed, Rus. Abolmed, Lesnaya ul 57 str 4, 127055 Moscow, Russia.

Abraxis, Austral. See *Specialised Therapeutics, Austral.*

Abraxis, Cz. See *Abraxis, UK.*

Abraxis, Ger. See *Celgene, Ger.*

Abraxis, Irl. See *Abraxis, UK.*

Abraxis, Pol. See *Abraxis, UK.*

Abraxis, Port. See *Abraxis, UK.*

Abraxis, Spain. See *Abraxis, UK.*

Abraxis, UK. Abraxis BioScience Ltd, Rosanne House, Parkway, Welwyn Garden City, Hertfordshire, AL8 6HG, UK.

Abtei, Austria. See *Abtei, Ger.*

Abtei, Ger. Abtei Pharma Vertriebs GmbH, Abtei 1, 37696 Marienmünster, Germany.

Abtswinder, Canad. See *Abtswinder, Ger.*

Abtswinder, Ger. Abtswinder Naturheilmittel GmbH & Co KG, Gewürzstrasse 1-3, 97355 Abtswind, Germany.
url: www.abtswinder.de

Abundance, Canad. Abundance Marketing Inc., 301 Highway 8, Stoney Creek, Ontario, L8G 1E5, Canada.
url: www.abundance.com

AbZ, Denm. See *AbZ, Ger.*

AbZ, Ger. AbZ-Pharma GmbH, Dr. Georg-Spohn-Str. 7, 89143 Blaubeuren, Germany.
url: www.abz-pharma.de

AC Helcor, Hung. AC Helcor-Hungary Kft, Madarász Viktor u 27 VIII em. 50, 1131 Budapesy, Hungary.

ac Pharma, Hong Kong. See *Weston, Hong Kong.*

Acambis, USA. Acambis, 38 Sidney St, Cambridge, MA 02139, USA.
url: www.acambis.com

acaSan, Austria. acaSan Pharma GmbH, Rauchfangkehrergasse 7/17, A-1150 Vienna, Austria.

Accentia, USA. Accentia Biopharmaceuticals, 324 South Hyde Park Ave, Suite 350, Tampa, FL 33606, USA.
url: www.accentia.net

Accera, USA. Accera Inc., Interlocken Advanced Technology Park, 380 Interlocken Cres., Suite 780, Broomfield, CO 80021, USA.
url: www.accerapharma.com

Access, Canad. See *Access, USA.*

Access, USA. Access Pharmaceuticals Inc., 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107, USA.
url: www.accesspharma.com

Accord, Braz. Accord Farmaceutica Ltda, Av. Guido Caloi 1985, Cond River Side, 5802140 Sao Paulo, Brazil.

Accord, Irl. See *Accord, UK.*

Accord, Mex. Accord Farma SA de CV, Calle 2 Mz. 6 LT 11, 50200 Pque Ind. Toluca, Mexico.

Accord, S.Afr. Accord Healthcare Pty Ltd, Ground Floor Building 5, Tuscany Office Park, 6 Coombe Place, Rivonia 2129, Johannesburg, South Africa.
url: www.accord-healthcare.com

Accord, UK. Accord Healthcare Ltd, Sage House, 319 Pinner Rd, North Harrow, Middlesex, HA1 4HF, UK.

Accredo, USA. Accredo Health Group Inc., 1640 Century Center Parkway, Memphis, TN 38134, USA.
url: www.accredo.com

Accudial, Canad. See *Accudial, USA.*

Accudial, USA. Accudial Pharmaceutical Inc., 202 11300 US Highway One, Palm Beach Gardens, Florida 33408, USA.

Accure, India. Accure Labs, A-44 Sector 63, Noida 201301, Uttar Pradesh, India.
url: accurelabs.com

Accure, Rus. See *Accure, India.*

Accurex, Canad. Accurex Health Care Manufacturing Inc., 20 Sage Court, Brantford, Ontario, N3R 7T4, Canada.

Acdhon, Thai. Acdhon Co Ltd, 136/51 Soi Latphrao, 110 Latphrao Rd, Wangthonglang, Bangkok 10310, Thailand.

ACE, Fin. See *ACE, Neth.*

ACE, Neth. ACE Pharmaceuticals BV, Schepenveld 41, 3891 ZK Zeewolde, Netherlands.
url: www.ace-pharm.nl

Ace, Philipp. Ace Pharmaceuticals Inc., 101 Don Vicente St, Don Antonio Heights, Commonwealth Ave, Quezon City, Philippines.

Acekinetic, India. Acekinetic Healthcare Ltd, SCF-266 1st Floor, Motor Market, Mamimajra, Chandigarh 160 047, India.

Acella, USA. Acella Pharmaceuticals LLC, 9005 Westside Drive, Alpharetta, GA 30009, USA.
url: www.acellapharma.com

Acemed, Hung. See *PannonPharma, Hung.*

Acertus, Malaysia. See *United Italian, Malaysia.*

Acertus, Singapore. See *United Italian, Singapore.*

Ache, Braz. Ache Laboratórios Farmacêuticos S.A., Rodovia Presidente Dutra Km 222.2, 07034-904 Guarulhos, São Paulo, Brazil.
url: www.ache.com.br

Acino, Cz. See *Acino, Ger.*

Acino, Ger. Acino AG, Am Windfeld 35, 83714 Miesbach, Germany.

Acino, Neth. See *Acino, Ger.*

Acino, Port. See *Acino, Ger.*

Acino, Switz. Acino Pharma AG, Birsweg 2, 4253 Liesberg, Switzerland.
url: www.acino-pharma.com

Acino, USA. Acino Products LLC, 681 Main St, Belleville, NJ 07109, USA.
url: www.acinoproducts.com

Aciprosalud, Venez. Importadora Aciprosalud C.A., Av. Libertador, c/Calle Alameda, Edif. Folgana, Piso 9 Of.9-A El Rosal, Caracas, Venezuela.

Acis, Ger. acis Arzneimittel GmbH, Lil-Dagover-Ring 7, 82031 Grüwald, Germony.
url: www.acis.de

Acis, Neth. See *Acis, Ger.*

Aclae, Fr. Aclae Santé, 64 rue Anatole-France, 92300 Levallois-Perret, France.

ACM, Fr. Laboratoires ACM, 17 rue de Neuilly, Impasse Passoir, 92110 Clichy-la-Garenne, France.

ACM, Neth. ACM Ooms Allergie BV, Comeniuslaan 65, 3706 XC Zeist, Netherlands.

Acme, India. Acme Pharmaceuticals, 203 Parshwa Towers, Opp. Rajpth Club, Bodakdev, Ahmedabad 380 015, India.

ACME, Philipp. See *Lantaka, Philipp.*

Acme, USA. Acme United Corp., 1931 Black Rock Turnpike, Fairfield, CT 06432, USA.
url: www.acmeunited.com

ACO, Swed. ACO AB, 183 25 Täby, Sweden.
url: www.pharmacia.se

ACO Hud, Denm. See *ACO Hud, Swed.*

ACO Hud, Fin. ACO Pharma Oy, Pihatörmä 1A, 02240 Espoo, Finland.

ACO Hud, Norw. See *ACO Hud, Swed.*

ACO Hud, Swed. ACO Hud AB, 194 26 Upplands Väsby, Sweden.
url: www.aconordic.com

ACOM, Ital. ACOM Spa, Località Cavallino, 62010 Montecasaro Scal (MC), Italy.
url: www.acompet.it

Acorda, USA. Acorda Therapeutics, 15 Skyline Drive, Hawthorn, NY 10532, USA.

Acorus, Irl. See *Acorus, UK.*

Acorus, Spain. See *Sinclair, UK.*

Acorus, UK. Acorus Therapeutics Ltd, High Crane Lodge, Hamsterley, County Durham, DL13 3QS, UK.
url: www.acorus-therapeutics.com

Acos, Ital. Acos Industria Chimico Farmaceutica S.r.l., Via Giuseppe Lusina 20, 00171 Rome (RM)

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ACP, UK. ACP Solutions Ltd, 35 Whitecroft, Nailsworth, Glaucestershire, GL6 0NS, UK.

ACRAF, Austria. See *Angelini, Ital.*

ACRAF, Belg. See *Angelini, Ital.*

ACRAF, Cz. See *Angelini, Ital.*

ACRAF, Fin. See *Angelini, Ital.*

ACRAF, Hung. See *Angelini, Ital.*

ACRAF, Ital. See *Angelini, Ital.*

ACRAF, Neth. See *Angelini, Ital.*

ACRAF, Port. See *Angelini, Ital.*

ACS Dobfar, Ital. ACS Dobfar S.p.A., Viale Addetta 6/8/10, 20067 Tribiano (MI), Italy.

ACS Dobfar, Switz. ACS Dobfar Info SA, Casai, 7749 Campascio, Switzerland.

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Actavis, Austria. Actavis GmbH, Münchner Bundesstrasse 142, 5020 Salzburg, Austria.
url: www.actavis.at

Actavis, Belg. Actavis Belgium, P.O.Box 61, 3500 Hasselt, Belgium.
url: www.actavis.be

Actavis, Canad. See *Actavis, USA.*

Actavis, China. Actavis (Foshan) Pharmaceuticals Co. Ltd, Room 3009 South Tower, World Trade Center, 371-375 Huan Shi Dong Rd, Guangzhou 510095, China.
url: www.actavis.com

Actavis, Cz. See *Avalanche, Cz.*

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url: www.actavis.fi

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url: www.actavis.com

Actavis, Ger. Actavis Deutschland GmbH & Co KG, Elisabeth-Selbert-Str. 1, 40764 Langenfeld, Germany.
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Actavis, Gr. See *Actavis, UK.*

Actavis, Hong Kong. See *Primal, Hong Kong* and *Unipharm, Hong Kong.*

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url: www.actavis.hu

Actavis, Indon. Actavis, Jl. Raya Bogor Km 28, Jakarta Timur 13710, Indonesia.
url: www.actavis.co.id

Actavis, Irl. Actavis Ireland, Euro House, Euro Business Park, Little Industrial Estate, Cork, Ireland.
url: www.actavis.com

Actavis, Ital. Actavis Italy, Viale Pasteur 10, 20014 Nerviano (MI), Italy.
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Actavis, Malaysia. See *Apex, Malaysia.*

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Actavis, Pol. Actavis Polska Sp. z.o.o., ul. Odrowąża 15, 03-310 Warsaw, Poland.
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Actavis, Rus. Actavis, Suschevsky Val St, Building 18 floor 13, 127018 Moscow, Russia.
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Actavis, Singapore. See *Delfi, Singapore.*

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Actavis, Swed. Actavis AB, Drottninggatan 11, 252 21 Helsingborg, Sweden.
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Actavis, Switz. Actavis Switzerland AG, Wehntalerstrasse 190, 8105 Regensdorf-Zürich, Switzerland.
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Actavis, Thai. See *RX, Thai.*

Actavis, UK. Actavis UK Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK.
url: www.actavis.co.uk

Actavis, Ukr, Bulv. Shevchenko, 33, Section BS-3, Kiev, 01032, Ukraine.
url: www.actavis.com.ua

Actavis, USA. Actavis Pharma, Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054, USA.
url: www.actavis.com

Actelion, Austral. Actelion Pharmaceuticals Australia Pty Ltd, P.O. Box 372, Frenchs Forest, NSW 1640, Australia.
url: www.actelion.com

Actelion, Austria. See *Actelion, UK.*

Actelion, Belg. Actelion Pharmaceuticals Belgium NV, Bedrijvenlaan 1, 2800 Mechelen, Belgium.
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Actelion, Braz. Actelion Pharmaceuticals do Brasil Ltda, Praia de Botafogo 501 1 andar, 22250040 Rio de Janeiro Torre Corcovad, Rio de Janeiro, Brazil.

Actelion, Canad. Actelion Pharmaceuticals Canada Inc., 2525 Daniel-Johnson Blvd, Suite 205, Laval, Quebec, H7T 1S9, Canada.
url: www.actelion.com

Actelion, China. Actelion Pharmaceutical Co. Ltd, 1601-2 Cross Tower, 318 Fuzhou Road, Shanghai, 200001, China.

Actelion, Cz. Actelion Pharmaceuticals Ltd, Belgicka 115/40, 1200 00 Prague 2, Czech Republic.
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Actelion, Denm. See *Actelion, Swed.*

Actelion, Fin. See *Actelion, Swed.*

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Actelion, Ger. Actelion Pharmaceuticals Deutschland GmbH, Basler Strasse 65, D-79100 Freiburg, Germany.
url: www.actelion.de

Actelion, Gr. Actelion Pharmaceuticals Hellas SA, 7 Paleologou St, Chalandri, 152 32 Athens, Greece.
url: www.actelion.com

Actelion, Hong Kong. See *Pharmalink, Hong Kong* and *Zuellig, Hong Kong.*

Actelion, Hung. See *Actelion, UK.*

Actelion, Irl. See *Allphar, Irl.*

Actelion, Ital. Actelion Pharmaceuticals Italia Srl, Via Trebazio 4, 20145 Milan (MI), Italy.
url: www.actelion.com

Actelion, Jpn. Actelion Pharmaceuticals Japan Ltd, Ebisu Prime Square Tower, 1-1-39 Hiroo shibuya-ku, Tokyo 150-0012, Japan.
url: www.actelion.co.jp

Actelion, Malaysia. See *Zuellig, Malaysia.*

Actelion, Neth. See *Actelion, UK.*

Actelion, Norw. See *Swedish Orphan, Norw.*

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url: www.actelion.com

Actelion, Port. Actelion Pharmaceuticals Portugal Lda, Praça Marquês de Pambal 15 - 8, 1250-163 Lisbon, Portugal.
url: www.actelion.com

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Actelion, Singapore. See *Zuellig, Singapore.*

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url: www.actelion.com

Actelion, Thai. See *Zuellig, Thai.*

Actelion, Turk. Actelion İlaç Tic. Ltd Sti, Kurucesme Cad. No 3, Kurucesme, Istanbul 34345, Turkey.
url: www.actelion.com

Actelion, UK. Actelion Pharmaceuticals UK Ltd, BSI Building, 13th Floor, 389 Chiswick High Rd, Chiswick, London, W4 4AL, UK.
url: www.actelion.com

Actelion, USA. Actelion Pharmaceuticals US Inc., 5000 Shoreline Court, Suite 200, South San Francisco, CA 94080, USA.
url: www.actelion.com

Acteon, China. Acteon, 433 Jingping Rd, Jhonghe, Taiwan, Taipei, 23563, China.
url: www.acteongroup.com.tw

Acteon, Fr. Acteon Group, 17 ave Gustave Eiffel, B.P. 30216, 33708 Merignac cdx, France.
url: www.acteongroup.com

Acteon, Rus. Acteon, Valdajski proezd 16, Bldg 1 office 243, 125445 Moscow, Russia.
url: www.acteongroup.com

Actient, USA. Actient Pharmaceuticals, 150 S Saunders Rd, Suite 120, Lake Forest, IL 60045, USA.
url: www.actientpharma.com

Actimex, Ital. Actimex Srl, Area Science Park Basovizza, SS 14 Km 163.15, 34012 Trieste (TS), Italy.
url: www.actimex.it

Actipharm, Switz. Actipharm SA, 42 rue Prevost-Martin, 1211 Geneva 9, Switzerland.

Activa Sport, Ital. Activa Sport Srl, Via Taurianova 54, 00178 Rome (RM), Italy.
url: www.farmaenergy.it

Active, India. Active Healthcare, 211 Blue Diamond Complex, Fatehgunj, Vadodara 390 002, India.

Activo, S.Afr. Activo Health, P.O. Box 11911, Zwartkop 0051, South Africa.
url: www.activo.co.za

Acto, India. Acto Pharmaceutical Laboratories, 11-12-23 Road No 1, Income Tax Colony, Sri Rama Krishna Puram, Saroorangar, Hyderabod 500 035, India.

Actor, S.Afr. Actor Pharma, P.O. Box 7408, Halfway House 1685, South Africa.
url: www.actorpharmo.co.za

Acuition, India. Acuition Pharmaceuticals, Kha 920/1/26 2nd Floor, Near Kodigehalli Bus Stans, Sahakoranagar Post, Bangalore 560 092, India.

Acupharm, S.Afr. Acupharm (Pty) Ltd, 43 Richards Drive, Halfway House 1685, South Africa.

Adamed, Cz. See *Adamed, Pol.*

Adamed, Denm. See *Adamed, Pol.*

Adamed, Hung. See *Adamed, Pol.*

Adamed, Neth. See *Adamed, Pol.*

Adamed, Pol. Adamed Sp. zo.o., Pieńków 149, 05-152 Czosnów k/Warsaw, Poland.
url: www.adamed.com.pl

Adamed, Port. See *Adamed, Pol.*

Adamed, Spain. Adamed Laboratorios SLU, c/Golondrina 26, 28023 Aravaca, Madrid, Spain.

Adamed, Ukr. Adamed Cp zoo, Saksaganskogo St 52A, 01033 Kiev, Ukraine.

Adams, Canad. See *Pfizer Consumer, Canad.*

Adams, Hong Kong. See *ICH, Hong Kong.*

Adams, Thai. See *Pharmaland, Thai.*

Adams, UK. Adams Healthcare Ltd, Lotherton Way, Garforth, Leeds, South Yorkshire, LS25 2JY, UK.
url: www.adams-healthcare.co.uk

Adams, USA. Adams Laboratories Inc., 14801 Sovereign Rd, Fort Worth, TX 76155-2645, USA.
url: www.adamslabs.com

Adams Confectionery, UK. See *Ernest Jackson, UK.*

Adaptogen, Rus. Adaptogen, 47/5 Piskarevsky prospect, 195067 St Petersburg, Russia.
url: www.adaptogen.ru

Adco, S.Afr. Adco Drug Co (Pty) Ltd, 491 Sydney Rd, Durban 4000, South Africa.

Adcock Ingram, S.Afr. Adcock Ingram Pharmaceuticals Ltd, Adcock Ingram Park, 17 Harrison Ave, Bryanston 2021, South Africa.
url: www.adcock.co.za

Adcock Ingram, UK. See *Novartis, UK.*

Adcock Ingram Consumer, S.Afr. See *Adcock Ingram, S.Afr.*

Adcock Ingram Critical Care, S.Afr. Adcock Ingram Critical Care, P.O. Box 6888, Johannesburg 2000, Sauth Africa.
url: www.adcock.co.za

Adcock Ingram Generics, S.Afr. See *Adcock Ingram, S.Afr.*

Adcock Ingram Self Medication, S.Afr. See *Adcock Ingram, S.Afr.*

Addenda, Ital. Addenda Pharma Srl, Viale Shakespeare 47, 00144 Rome (RM), Italy.

Addicare, Ger. See *Hexal, Ger.*

Addmedica, Cz. See *Addmedica, Fr.*

Addmedica, Fr. Addmedica, 101 rue Saint-Lazare, 75009 Paris, France.
url: www.addmedica.com

Addmedica, Gr. See *Addmedica, Fr.*

Addmedica, Irl. See *Addmedica, Fr.*

Addmedica, Pol. See *Addmedica, Fr.*

Addmedica, Port. See *Addmedica, Fr.*

Ad-Drugstel, Philipp. Ad-Drugstel Pharmaceutical Lab., Unit A, 2/F Ad-Drugstel Building, 75 Tandang Sora Ave, Quezon City, Philippines.

Adeka, Turk. Adeka İlaç ve Kimyasal Ürünler San. ve Tic. A. Ş., General Cahit Aybar Sok., Akademiler sitesi E Blok. No. 5, Zincirlikuyu, İstanbul, 80600, Turkey.
url: www.adeka.com.tr

Adelco, Gr. Adelco Chromataurgia Athinon, E. Colocotroni's Bros. S.A., 37 Pireos Str., 183 46 Moschato, Greece.
url: www.adelco.gr

A-Derma, Fr. Laboratoires Dermatalogiques A-Derma, 45 place Abel-Gance, 92100 Boulogne, France.
url: www.aderma.com

Adienne, Austria. See *Adienne, Ital.*

Adienne, Irl. See *Adienne, Ital.*

Adienne, Ital. Adienne Srl, Via Broseta 64/B, 24100 Bergamo (BG), Italy.
url: www.adienne.com

Adienne, Neth. See *Adienne, Ital.*

Adienne, Norw. See *EuroCept, Neth.*

Adienne, Port. See *Adienne, Ital.*

Adienne, Spain. Adienne Spain SL, Passeig del Canal 5, 08980 Sant Feliu de Ilobregat, Barcelona, Spain.

Adienne, UK. See *Adienne, Ital.*

Adilna, Turk. Adilna, Turkey.

Adipharm, Gr. ADiPharm Ltd., 54 Marni St, 104 37 Athens, Greece.
url: www.adipharm.gr

Adipharm, Rus. Adipharm, Mosfilmovskaya st. dom. 52 office 52, 119590 Moscow, Russia.

Adipharm, Ukr. See *Rotapharm, Ukr.*

Adipharm (Αδηφαρμ), Gr. See *Adipharm, Gr.*

Adivar, Ital. See *Angelini, Ital.*

Adler, Austria. Adler-Apotheke, Wahringer Strasse 149, A-1180 Vienna, Austria.

Adley, India. Adley Formulation, SCO 915, 2nd Floor, NAC, Manimazra, Chandigarh, India.
url: www.adleylab.com

Admac, India. Admac Pharma Ltd, SCO 84 1st floor, Sector 5, Panchkula 134 112, India.

Admeda, Cz. See *Admeda, Ger.*

Admeda, Ger. Admeda Arzneimittel GmbH, Trift 4, 23863 Nienwohld, Germany.
url: www.admeda.de

Admeda, Hung. See *Admeda, Ger.*

Admeda, Port. See *Admeda, Ger.*

ADOH, Neth. ADOH Pharma Services, Postbus 38121, 6503 AC Nijmegen, Netherlands.

Adolphs, USA. Adolphs, 75 Merritt Blvd, Trumbull, CT 06611, USA.

Adore, Philipp. See *Ambica, Philipp.*

ADP, Hong Kong. See *Australian Medic-Care, Hong Kong.*

ADP, Philipp. ADP Pharma, 9/F ETON Cyberpod Centris, EDSA cor Quezon Ave, Quezon City, Philippines.

Adrem, Canad. Adrem Ltd, 2000 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.

Adria, Canad. See *Pfizer, Canad.*

Adria, USA. See *Pfizer, USA.*

Adroit, India. Adroit Healthcare Pvt Ltd, 11 Jaldhoro Complex, Surdhara Circle, Memnagar, Ahmedabad 380 052, India.

Adroka, Switz. Adroka AG, Postfach, 4123 Allschwil, Switzerland.
url: www.adroka.ch

Advacare, Austral. Advacare, Biologic Health Solutions Pty Ltd, P.O. Box 2586, Fortitude Valley BC, QLD 4006, Australia.
url: www.advacare.com.au

Advaita, Mex. Advaita Pharmaceuticals, Adolfo Prieto 1427, 3100 Del Valle, Mexico DF, Mexico.

Advance, Canad. Advance Chemicals Ltd, 2023 Kingsway Ave, Port Coquitlam, British Columbia, V3C 1S9, Canada.

Advance, China. See *Advance, Hong Kong.*

Advance, Hong Kong. Advance Pharmaceutical Co. Ltd, Hong Kong.
url: www.apc.com.hk

Advance, Malaysia. Advance Pharma Sdn Bhd, 13 Ground Floor Jln Bp 7/13, 47100 Puchong, Selangor, Malaysia.

Advance, Singapore. See *Wellchem, Singapore.*

Advance, Thai. See *Olic, Thai.*

Advance, USA. Advance, 2201-F 5th Avenue, Ronkonkoma, NY 11779, USA.

Advance Diagnostic, Irl. Advance Diagnostic Products Ltd, Church Rd, Greystones, Co. Wicklow, Ireland.

Advanced, Singapore. Advanced Medi Mart Pte Ltd, 53 Kim Keat Rd, 05-02C Mun Hean Building, S 328823, Singapore.

Advanced Biotechnologies, Israel. See *Rafa, Israel.*

Advanced Care, USA. Advanced Care Products, 199 Grandview Rd, Skillman, NJ 08558-9418, USA.
url: www.jnj.com

Advanced Generic, USA. Advanced Generic, P.O.Box 669384, Miami, FL 33166, USA.
url: www.advancedgeneric.com

Advanced Magnetics, Israel. See *Dexxon, Israel.*

Advanced Medical Enterprises, USA. Advanced Medical Enterprises, 4755 E 91st St, Tulsa, OK 74137, USA.
url: www.ameinc.org

Advanced Medical Optics, Austral. See *AMO, Austral.*

Advanced Medical Optics, NZ. Advanced Medical Optics, 3-5 Westfield Place, Mt Wellington, Auckland, New Zealand.
url: www.amo-inc.com

Advanced Medical Optics, UK. See *Allergan, UK.*

Advanced Nutritional Technology, USA. Advanced Nutritional Technology Inc., P.O. Box 2130, 6988 Sierra Court, Dublin, CA 94568-2641, USA.
url: www.antlab.com

Advanced Polymer, USA. See *AP, USA.*

Advanced Remedies, Philipp. See *Pharma-Surrey, Philipp.*

Advanced Remedies, Thai. See *Kaspa, Thai.*

Advanced Sterilization Products, USA. Advanced Sterilization Products, a Johnson & Johnson Company, 33 Technalogy Drive, Irvine, CA 92618-9824, USA.
url: www.sterrad.com

Advanced Vision, Canad. See *Advanced Vision, USA.*

Advanced Vision, USA. Advanced Vision Research, 12 Alfred St., Suite 200, Woburn, MA 01801, USA.
url: www.theratears.com

Advantage, Canad. Advantage Ckn, Unit 4, Esna Park Drive, Markham, Ontario, L3R 3B1, Canada.

Advent, Cz. Advent International sro, Na Poříčí 1079/3a, 110 00 Prague 1, Czech Republic.
url: www.adventinternational.com

Adventure Life Science, India. Adventure Life Science, India.

Advertising Unlimited, Canad. See *Advertising Unlimited, USA.*

Advertising Unlimited, USA. Advertising Unlimited Inc. (AUI), 5151 Moundview Drive, Red Wing, Minnesota, 55066, USA.

Advfarma, Braz. See *Tayuyna, Braz.*

Advik, India. Advik Laboratories Ltd, 106-07 Allied House, 1 LSC, Madangir, New Delhi 110 062, India.
url: www.advikindia.com

Advil, Austral. Advil P/L, P.O. Box 4082, Doncaster Heights, VIC 3109, Australia.

Aegerion, UK. Aegerion Pharmaceuticals Ltd, Lakeside House, 1 Furzeground Way, Stockley Park East, Uxbridge, Middlesex, UB11 1BD, UK.
url: www.aegerion.com

Aegerion, USA. Aegerion Pharmaceuticals, Inc., 101 Main Street, Suite 1850, Cambridge, Massachusetts, MA 02142, USA.
url: www.aegerion.com

Aegis, Hang Kong. See *Universal, Hong Kong.*

Aegis, Malaysia. See *Apex, Malaysia* and *Zyfas, Malaysia.*

Aegis, Singapore. See *Zyfas, Singapore.*

Aelslife, Fr. Aelslife, 138 rue Francis Garnier, 58000 Nevers, France.
url: www.aelslife.com

Aenorasis, Gr. Aenorasis SA, Trapezountos 17 & A Papondreou St, Melissia, 151 27 Athens, Greece.
url: www.aenorasis.gr

Aenorasis, Neth. See *Aenorasis, Gr.*

Aero, USA. Aero Pharmaceuticals, 3848 FAU Bvld, Suite 100, Boca Raton, FL 33431, USA.
url: www.aeropharmaceuticals.com

Aerocare, Thai. AeroCare Co Ltd, 126/18 Thaisri Bldg 5 Fl, Krungthanburi Rd, Khlongsan, Bangkok 10600, Thailand.

Aeroceuticals, USA. See *Graham-Field, USA.*

Aerocid, Fr. Laboratoires Aérocid, 248 bis, rue Gabriel-Peri, 94230 Cachan, France.

Aerokure, Canad. Aerokure International Inc., 330 Racine St, St-Elie d'Orford, Quebec, J0B 2S0, Canada.

Aesca, Austria. Aesca GmbH, Badener Strasse 23, A-2514 Traiskirchen, Austria.

Aesculapius, Ital. Aesculapius Farmaceutici S.r.l., Via Cozzaglio 24, 25125 Brescia (BS), Italy.

Aesthetic Plus, Singapore. See *Wellchem, Singapore.*

Aetna Felt, Canad. See *Aetna Felt, USA.*

Aetna Felt, USA. Aetna Felt Corp., 2401 West Emaus Ave, Allentown, Pennsylvania, 18103, USA.

AF, Mex. A.F. Laboratorios, Aplicaciones Farmaceuticas S.A. de C.V., Heriberto Frias No. 1035, Benito Juarez del Valle, 03100 Mexico D.F., Mexico.

Afamia, Hung. Afamia Trade Kft, Vahot u 1, 1119 Budapest, Hungary.

Afaxys, USA. Afaxys Pharmaceuticals, P.O.Box 20639, Charleston, SC 29413, USA.
url: www.afaxys.com

Afexa, Canad. Afexa Life Sciences, 9604 20th Ave, Edmonton, Alberta, T6N 1G1, Canada.
url: www.afexa.com

Affy, India. Affy Pharma Pvt Ltd, 510-513 Davika Tower, Chander Nagar, Sahibabad, Ghaziabad 110 032, India.

Affymax, USA. Affymax Inc., 4001 Miranda Ave, Palo Alto, CA 94304, USA.
url: www.affymax.com

AFI, Norw. See *Nycomed, Norw.*

Aflofarm, Pol. Aflofarm Farmacja Polska, ul. Partyzancka 133/151, 95-200 Pabianice, Poland.
url: www.aflofarm.com.pl

AFOM, Ital. AFOM Medical S.p.A., Via Amundsen 6, 20148 Milan (MI), Italy.

Afrox, S.Afr. Afrox, Africa Oxygen Ltd, 8 Van Dyk Rd, Industrial Sites, Benoni 1501, South Africa.
url: www.afrox.com

AFT, Austral. Aft Pharmaceutical, 49-51 Eton St, Sutherland, NSW 2232, Australia.

AFT, NZ. AFT Pharmaceuticals Ltd, 9 Anzac St (level 2), Takapuna, Auckland, New Zealand.
url: www.aftpharm.com

AG Hair, Canad. AG Hair Cosmetics, 3765 William St, Burnaby, British Columbia, V5C 3H8, Canada.

AG Therapy, Gr. A.G. Therapy, Koritsas 13, 145 61 Kifisia, Greece.

AGA, Cz. See *AGA, Swed.*

AGA, Denm. See *AGA, Swed.*

AGA, Fin. See *AGA, Swed.*

AGA, Gr. AGA, Greece.

AGA, Neth. See *AGA, Swed.*

AGA, Norw. See *Linde Gas, Norw.*

AGA, Pol. See *Linde Gaz, Pol.*

AGA, Spain. See *Abello Linde, Spain.*

AGA, Swed. AGA AB, 181 81 Lidingö, Sweden.
url: www.linde-healthcare.com

Age D'or, Singapore. Age D'or Healthcare Pte Ltd, 51 Ayer Rajah Crescent, 07-01/02, S 139948, Singapore.
url: www.agedorgroup.com

Agen, Spain. Agen Genericos Farmaceuticos, Av Conde de Guadalhorce 43, 33400 Aviles, Spain.

Agenus, Rus. See *Agenus, USA.*

Agenus, USA. Agenus Inc., 3 Forbes Rd, Lexington, MA 02421-7305, USA.
url: www.agenusbio.com

Agepha, Austria. Agepha GmbH, Packerstrasse 164, A-8561 Sädingen, Austria.
url: www.agepha.com

Agepha, Denm. See *Agepha, Austria.*

Agepha, Ger. See *Agepha, Austria.*

Agepha, Neth. See *Agepha, Austria.*

Agepha, Norw. See *Agepha, Austria.*

Agepha, Swed. See *Agepha, Austria.*

Agepha, UK. Agepha Pharmaceuticals Ltd, 9 High St, Woburn Sands, Buckinghamshire, MK17 8RF, UK.
url: www.agepha.com

AGEPS, Fr. AGEPS, Agence Générale des Equipements et Produits de Santé, Établissement Pharmaceutique des Hôpitaux de Paris, 7 rue du Fer-à-Moulin, B.P. 09, 75221 Paris cdx 5, France.
url: www.ap-hop-paris.fr

Agfa, Ger. Agfa HealthCare Imaging Agents GmbH, Am Coloneum 4, 50829 Cologne, Germany.
url: www.agfa.com

Agfa, Neth. Agfa Healthcare, Polakweg 10-11, 2288 GG Rijswijk, Netherlands.
url: www.agfahealthcare.com

Agio, India. Agio Pharmaceuticals Ltd, A-38 Nandjyot Industrial Estate, Kurla Andheri Road, Safedpool, Mumbai 400 072, India.
url: www.agio-pharma.com

Agio, Philipp. See *Ambica, Philipp.*

Agio, Rus. Agio Pharmaceuticals Ltd, Nagornii Proezd 12V, 117105 Moscow, Russia.
url: www.agio-pharma.com

AGIPS, Ital. AGIPS Farmaceutici S.r.l., Via Amendola Giovanni 4, 16035 Rapallo (GE), Italy.

Agis, Israel. See *Perrigo, Israel.*

Aglowmed, India. Aglowmed Limited, 702-A Poonam Chambers, Worli, Mumbai 400 018, India.
url: www.aglowmed.com

Agostinho, Port. António Pacheco Agostinho, SA, Rua Rodrigues Sampaio 15, 1169-012 Lisbon, Portugal.

Agouron, Canad. See *Pfizer, Canad.*

Agouron, USA. See *Pfizer, USA.*

AGP, Denm. See *AGP, Swed.*

AGP, Swed. A Generic Pharmaceutical AB, Kalendegatan 25, 211 35 Malmø, Sweden.

Agpharm, Switz. Agpharm AG, Postfach, 4123 Allschwil 1, Switzerland.

Agrichem, Hung. Agrichem Kft, Kárpát u 50 111/9, 1133 Budapest, Hungary.

Agri-Pharma, Hung. Agri-Pharma Kft, Kórösi J u. 15, 1117 Budapest, Hungary.

Agrophorm, Pol. Agropharm SA, ul. Starościańska 33, 95-080 Tuszyn, Poland.
url: www.agropharm.com.pl

Agropharm, UK. Agropharm Ltd, Buckingham House, Church Rd, Penn, High Wycombe, Buckinghamshire, HP10 8LN, UK.
url: www.agropharm.co.uk

Agrophytopharm, Rus. Agrophytopharm, Russia.

Aguettant, Fr. Laboratoires Aguettant, 1 rue Alexander-Fleming, 69007 Lyon, France.
url: www.aguettant.com

Aguettant, UK. Aguettant Ltd., Bishops House, Bishops Road, Claverham, Somerset, BS49 4NF, UK.
url: www.aguettant.co.uk

Agys, Singapore. See *Pan-Malayan, Singapore.*

Ahimsa, Arg. Lab. Ahimsa S.A., Lima 369 Piso 11 Of. F, 1073 Buenos Aires, Argentina.

Ahlcon, Philipp. See *IE Medica, Philipp.*

AHN, S.Afr. AHN Pharma Pty Ltd, P.O. Box 31036, Braamfontein 2017, South Africa.

Ahn-Gook, Philipp. See *Medhaus, Philipp.*

Ahn-Gook, Singapore. See *Uni, Singapore.*

AHP, Belg. See *Wyeth, Belg.*

AHP, Neth. See *Wyeth, Neth.*

AHP, Switz. AHP (Schweiz) AG, Grafenauweg 10, 6301 Zug, Switzerland.

Ahua Bio, China. See *Dongeejiao, China.*

Ai Sheng, China. Ai Sheng Pharma Co. Ltd, Zhejiang, China.

Aibujia, China. Aibujia Pharmaceutical Co. Ltd, Beijing, China.

Aida, China. Aida Pharmaceuticals, 31 Jiang Rd, Riverside District Qianjiang New City, Hangzhou 310016, China.

Aiden, USA. Aiden Industries LLC, 2412 Calle San Miguel, Encinitas, CA 92024, USA.
url: www.miaderm.com

Aike, China. Aike Pharmaceutical Co Ltd, 283 Nanhai Ave, Haikou City 570216, Hainan, China.
url: www.aikepharm.com

AIM, Fr. AIM (Actions Innovations Médicales), Mogoro-Plouagat, 22170 Châtelaudren, France.

Aima, Ital. See *Kedrion, Ital.*

Aimeijin, China. Aimeijin Pharmaceutical Co. Ltd, Suzhou, China.

Aimil, India. Aimil Pharmaceuticals Ltd, 2994/4 Street No.17, Ranjeet Nagar, New Delhi 110 008, India.
url: www.aimilpharmaceuticals.com

Ain Medicare, Malaysia. Ain Medicare Sdn Bhd, Jln 6/44, Kawasan Perindustrian, Pengkalan Chepa 2, 16100 Kota Bharu, Kelantan, Malaysia.
url: www.ainmedicare.com.my

Air Liquide, Belg. Air Liquide Medical SA/NV, Parc d'affaires Zénobe Gramme, Quai des Vennes 8, 4020 Liège, Belgium.
url: www.airliquide.com

Air Liquide, Canad. Air Liquide Canada Inc., 1700 1250 René-Lévesque Ouest, Montreal, Quebec, H3B 5E6, Canada.

Air Liquide, Denm. See *Air Liquide, Fr.*

Air Liquide, Fr. Air Liquide Santé, 75 Quai d'Orsay, 75321 Paris cdx, France.
url: www.airliquide.com

Air Liquide, Ger. Air Liquide Medical GmbH, Hans-Günther-Sohl Strasse 5, 40235 Düsseldorf, Germany.
url: www.airliquide.de

Air Liquide, Ital. Air Liquide Italia Siege, Via Capecelatro 69, 20148 Milan, Italy.
url: www.airliquide.it

Air Liquide, Neth. See *Air Liquide, Ger.*

Air Liquide, Port. See *Air Liquide, Fr.*

Air Liquide, Spain. Air Liquide Espana SA, Pasei de Castellana 35, 28046 Madrid, Spain.
url: www.es.airliquide.com

Air Products, Belg. Air Products SAS, Chaussée de Wavre 1789, 1160 Brussels, Belgium.
url: www.airproducts.be

Air Products, Cz. Air Products spal sro, Ustecka 30, 405 30 Decin, Czech Republic.

Air Products, Fr. Air Products SAS, 78 rue Championnet, 75881 Paris Cedex 18, France.
url: www.airproducts.fr

Air Products, Neth. Air Products Nederland BV, Kanaalweg 15, 3526 KL Utrecht, Netherlands.

Airela, Braz. Airela Ind. Farmaceutica Ltds Epp, Rua Luiz Spiandorelli, Neto 60 Sala 907, 13271570 Valinhos, Sao Paulo, Brazil.

Airflow, NZ. Airflow Products, P.O. Box 1485, Wellington, New Zealand.
url: www.air-flow.co.nz

Aivax, Gr. Aivax Ltd, Filellinon 26, 54645 Thessaloniki, Greece.

Aiwei, China. Aiwei Pharmaceutical Co. Ltd, Weihai, China.

Ajanta, India. Ajanta Pharma Ltd, 98 Ajanta House, Charkop, Kandiviti (West), Mumbai 400 067, India.
url: www.ajantapharma.com

Ajanta, Philipp. See *Metro, Philipp.*

Ajanta, Rus. See *Ajanta, India.*

Ajanta, Venez. See *PG, Venez.*

Ajantha, Malaysia. See *Ronbaxy, Malaysia.*

AJC, Fr. Laboratoires AJC, Usine de Fantaury, 16120 Chateauneuf, France.

AJC, Rus. See *LDP, Rus.*

Ajinomoto, Jpn. Ajinomoto Pharma Co. Ltd, 2-7-2 Yaesu, Chuo-ku, Tokyo 104-0028, Japan.

Ajinomoto, Philipp. See *Morishita, Philipp.*

Ajinomoto, Thai. See *Far East, Thai* and *Zuellig, Thai.*

Akacia, S.Afr. Akacia Healthcare, 4 Brewery St, Isando, Gauteng 1600, South Africa.
url: akaciahealthcare.com

Akdeniz, Turk. Akdeniz İlaç San. ve Tic. A.Ş., Abidnpaşa Cad. 28, Sok No. 3, Adana, Turkey.

Akesiss, India. Akesiss Pharma Pvt Ltd, 243 Ground Floor, Bosappa Layout, Hennur, Kalyan Nagar Post, Bangalore 560 043, India.
url: www.akesissindia.com

Akita, UK. See *Manx, UK.*

Akorn, Canad. Akorn Pharmaceuticals Canada a Division of Innova Medical Ophthalmics Inc., 1430 Birchmount Rd, Toronto, Ontario, M1P 2E8, Canada.

Akorn, Israel. See *Tradis-Gat, Israel.*

Akorn, USA. Akorn, Inc., 2500 Millbrook Drive, Buffalo Grove, IL 60089, USA.
url: www.akorn.com

AkPharma, USA. AkPharma Inc., P.O. Box 111, Pleasantville, NJ 08232, USA.
url: www.akpharma.com

Akrikhin, Rus. Akrikhin OAO, Moskovskaya obl., Kirova ul. 29, 142450 Staraya Kupavna, Russia.
url: www.akrihin.ru

Akrikhin, Ukr. See *Akrikhin, Rus.*

Akrimax, USA. Akrimax Pharmaceuticals, 11 Commerce Dr, 1st Floor, Suite 100, Cranford, NJ 07016, USA.
url: www.akrimax.com

Akromed, S.Afr. See *Wyeth, S.Afr.*

Aksigen, India. Aksigen Hospital Care, 81/A Mittal Chambers, Nariman Point, Mumboi, 400 021, India.

Aksu, Turk. Aksu Farma Tibbi Ürünler San. ve Tic. A.Ş., Rıfkı Tongsir Cad. No. 58, Ideallepe-Küçükyalı, İstanbul, Turkey.

Akti-M, Rus. NPMP Akti-M OOO, 3-ya Rybinskaya ul. 18, Of. 419, 107113 Moscow, Russia.

Aktipol, Rus. See *Akti-M, Rus.*

Akums, India. Akums Drugs & Pharmaceuticals Ltd, 304 Mohan Place, L.S.C Block Sarawati Vihar, New Delhi 110 034, India.
url: www.akums.in

Akums, Philipp. See *Ambica, Philipp* and *Suhitas, Philipp.*

Akvion, Rus. Akvion Pharmaceutical Co, 3 Yamskogo polya ul. 28, 125040 Moscow, Russia.
url: www.akvion.ru

Akyma, USA. Akyma Pharmaceuticals LLC, 701 Columbia Ave, Glasgow, KY 42141, USA.
url: www.akyma.com

Akzo, Braz. Akzo Nobel Ltda, Al. Vicente Pinzon 144 cj23, 04547-130 São Paulo, SP, Brazil.
url: www.akzonobel.com

Akzo Organon, Braz. See *Akzo, Braz.*

Alacan, Spain. See *ASAC, Spain.*

Alan, UK. Alan Pharmaceuticals, Highgate Business Centre, 33 Greenwood Place, London, NW5 1LB, UK.
url: www.alanpharmaceuticals.com

Alapis, Denm. See *Alapis, Gr.*

Alapis, Gr. Alapis Abee, Emperor Nicholas 2, 176 71 Athens, Greece.

Alapis, Irl. See *Alapis, Gr.*

Alarsin, India. Alarsin Pharmaceuticals, Alarsin House, A/32 Street No.3, M.I.D.C. Andheri (East), Mumbai 400 093, India.
url: www.alarsin.com

Alaven, USA. Alaven Pharmaceuticals LLC, 2260 Northwest Parkway, Marietta, GA 30067, USA.
url: www.alavenpharm.com

Alba, Ukr. Alba, Shevchenko 100, Boryspil, Kiev, 08300, Ukraine.
url: www.alba.kiev.ua

Alba, USA. See *Bart, USA.*

Alba Thyment, Pol. Alba Thyment Sp. zo.o., ul. J Kossaka 21, 60-760 Poznań, Poland.
url: www.albathyment.com.pl

Albephar, Venez. Lab. Albephar, Av Alameda, Qta Gabor, Lomas San Rafael La Florida, 1050 Caracas, Venezuela.

Albert, Canad. See *Sanofi, Canad.*

Albert, S.Afr. See *Sanofi-Aventis, S.Afr.*

Albert-Roussel, Austria. See *Sanofi-Aventis, Austria.*

Albert-Roussel, Ger. See *Sanofi-Aventis, Ger.*

Alboran, Spain. Alborán Farma SL, Polígono Sector 20 C Carbón, Parque Empresarial Jarquil, Edificio 1 Oficina 29, 04009 Almería, Spain.

Alcala, Spain. Alcala Farma, Ctra M-300 Km 29.920, Alcalá de Henares, 28802 Madrid, Spain.
url: www.alcala-farma.es

Alcare, Canad. Alcare 1, 1627-178 Street, Edmonton, Alberta, T5S 1N6, Canada.

Alcare, Singapore. Alcare Pharmaceuticals Pte, 12A Jalan Ampas, 03-03, S 329516, Singapore.
url: www.alcare.sg

Alcavis, Canad. See *Alcavis, USA.*

Alcavis, USA. Alcavis HDC LLC, 8322 Helgerman Court, Gaithersburg, Maryland, 20877, USA.

Alchem, India. Alchem Phytoceuticals, 201 Empire Plaza, MG Road, Sultanpur, New Delhi 110 030, India.
url: alchemphytoceuticals.com

Alchemed, Canad. Alchemed Canada, 808-15 Park Hill Court, Brampton, Ontario, L6V 1P6, Canada.

Alchemia, Cz. See *Alchemia, UK.*

Alchemia, Denm. See *Alchemia, UK.*

Alchemia, Ital. See *Alchemia, UK.*

Alchemia, UK. Alchemia Ltd, 86 Jermyn St, 5th Floor, London, SW1 6AW, UK.

Alchemy, S.Afr. Alchemy Pharmaceuticals CC, 21 Dadoo Ave., Mackenzieville, Nigel 1490, South Africa.

Alchemy, UK. Alchemy, Alchemy House, 38 East St, Andover, Hampshire, SP10 1ES, UK.

Alcina, Switz. Alcina AG, Bahnhofstrasse 160, 4132 Muttenz/BL, Switzerland.
url: www.alcina.de

Alckamed, Ital. Alcka-Med S.r.l., Piazzale Principessa Clotilde 8, 20121 Milano (MI), Italy.

Alclin, S.Afr. Alclin (Pty) Ltd, P.O. Box 1119, Harrismith 9880, South Africa.

Alcon, Arg. Alcon Laboratorios Argentina S.A., Estados Unidos 5335, 1667 Tortuguitas, Buenos Aires, Argentina.
url: www.alconlabs.com

Alcon, Austral. Alcon Laboratories (Australia) P/L, Private Bag 19, Frenchs Forest, NSW 1640, Australia.
url: www.alconlabs.com

Alcon, Austria. Alcon Ophthalmika GmbH, Mariahilferstrasse 121b, A-1060 Vienna, Austria.
url: www.alconlabs.com

Alcon, Belg. Alcon-Couvreur SA/NV, Rijksweg 14, 2870 Puurs, Belgium.
url: www.alconlabs.com

Alcon, Braz. Alcon Laboratórios do Brasil Ltda, Avenida Nações Unidas 12.495 3 andar, 4578902 Brooklin Novo, São Paulo, Brazil.
url: www.alconlabs.com

Alcon, Canad. Alcon Canada Inc., 2665 Meadowpine Blvd, Mississauga, Ontario, L5N 8C7, Canada.
url: www.alcon.ca

Alcon, Chile. Laboratorios Alcon Chile Ltda, Av. Los Leones 1459, Providencia, Santiago, Chile.

Alcon, China. Alcon (China) Ophthalmology Products Co Ltd, New Henderson Building 12th Floor, 3 Maizidian Rd, Chaoyang District, Beijing 100016, China.
url: www.alcon.com.cn

Alcon, Cz. Alcon Pharmaceuticals Ltd, Sokolovská 28/77, 180 00 Prague 8, Czech Republic.

Alcon, Denm. Alcon Danmark A/S, Rødovre Parkvej 25, 2610 Rødovre, Denmark.
url: www.alconlabs.com

Alcon, Fin. Alcon Finland Oy, PL 13, 01641 Vantaa, Finland.
url: www.alconlabs.com

Alcon, Fr. Laboratoires Alcon, 4 rue Henri-Ste-Claire-Deville, 92563 Rueil-Malmaison, France.
url: www.alconlabs.com

Alcon, Ger. Alcon Pharma GmbH, Blankreutestr. 1, 79108 Freiburg, Germany.
url: www.alconlabs.com/de

Alcon, Gr. Alcon Laboratories Hellas S.A., 18 Kifissias Ave, 151 25 Marousi, Greece.
url: www.alconlabs.com

Alcon, Hong Kong. Alcon Hong Kong Ltd, Suites 1201-2, 625 King's Rd, North Point, Hong Kong.
url: www.alconlabs.com

Alcon, Hung. Alcon Hungaria Kft, Irinyi József u 4-20, 1117 Budapest, Hungary.

Alcon, India. Alcon Laboratories Pvt Ltd, Unit 502, Tower D, 5th Floor, RMZ Infinity, Benniganahalli, Old Madras Road, Bangalore 560 016, India.
url: www.alcon.com

Alcon, Indon. Alcon Pharmaceuticals Ltd, Plaza Permata 10th Floor, Jalan M. H. Thamrin No.57, Jakarta 10350, Indonesia.
url: www.alcon.com

Alcon, Irl. See *Allphar, Irl.*

Alcon, Israel. See *Luxembourg, Israel.*

Alcon, Ital. Alcon Italia S.p.A., Viale Giulio Richard 1/B, 20143 Milan (MI), Italy.
url: www.alconlabs.com

Alcon, Jpn. Alcon Japan Ltd, Koraku Kokusai Building, 1-5-3, Koraku, Bunkyo-Ku, Tokyo 112-0004, Japan.
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Alcon, Malaysia. Alcon Laboratories (Malaysia) Sdn Bhd, 1001A & 1001D, 9th Floor, Block C Kompleks Kelana Centre Point, No 3 Jalan SS 7/19, Kelana Jaya, 47301 Petaling Jaya, Selangor, Malaysia.
url: www.alconlabs.com

Alcon, Mex. Alcon Laboratorios, S.A. de C.V., Adolfo Prieto 1644, Benito Juarez del Valle, 03100 Mexico D.F., Mexico.
url: www.alconlabs.com

Alcon, Neth. Alcon Nederland BV, Avelingen-West 5, 4202 MS Gorinchem, Netherlands.
url: www.alconlabs.com

Alcon, Norw. Alcon Norge AS, Eyvind Lychesv 10, Postboks 22, 1300 Sandvika, Norway.
url: www.alconlabs.com

Alcon, NZ. Alcon Laboratories Ltd, P.O. Box 14-562, Panmure, Auckland, New Zealand.
url: www.alconlabs.com

Alcon, Philipp. Alcon Lab (Phils) Inc., 3/F LGI Building, Ortigas Ave, Green Hills, San Juan, Metro Manila, Philippines.

Alcon, Pol. Alcon Polska Sp. zo.o., ul. Żelazna 28/30, 00-832 Warsaw, Poland.
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Alcon, Port. Alcon Portugal, Lda, Rua Castilho, 201-1, 1070-051 Lisbon, Portugal.
url: www.alconlabs.com

Alcon, Rus. Alcon Moscow, Nikoloyamskaya 54, 109004 Moscow, Russia.
url: www.alconlans.com

Alcon, S.Afr. Alcon Laboratories (South Africa) (Pty) Ltd, 261 Surrey Ave, Randburg, South Africa.
url: www.alconlabs.com

Alcon, Singapore. Alcon Pte Ltd, 159 Sin Ming Rd, 06-05 Amtech Building, S 575625, Singapore.
url: www.alconlabs.com

Alcon, Spain. See *Alcon Cusi, Spain.*

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url: www.alconlabs.com

Alcon, Switz. Alcon Pharmaceuticals Ltd, Bosch 69, Postfach 62, 6331 Hunenberg, Switzerland.
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Alcon, Thai. Alcon Laboratories (Thailand) Ltd, 191 Silom Rd, 18 Fl, Silom Complex Building, Bangkok 10500, Thailand.
url: www.alconlabs.com

Alcon, Turk. Alcon Laboratuarlari Tic. A.Ş., Cumhuriyet Cad. No: 10, Beykoz, İstanbul, 81640, Turkey.
url: www.alconlabs.com

Alcon, UK. Alcon UK Ltd, Park View, Riverside Way, Watchmoor Park, Camberley, Surrey, GU15 3YL, UK.
url: www.uk.alcon.com

Alcon, Ukr. Alcon Pharmaceuticals, 13, Pimonenko Street, Building 4A, Office 31, Kiev, 04050, Ukraine.
url: www.alcon.com

Alcon, USA. Alcon Laboratories Inc., 6201 South Freeway, Fort Worth, TX 76134, USA.
url: www.alconlabs.com

Alcon, Venez. Alcon Pharmaceutical C.A., Av. Diego Cisneros, Edificio Siemens, Torre Sur, Mezzanina, Los Ruices, Caracas 1070, Venezuela.
url: www.alconlabs.com

Alcon Cusi, Malaysia. See *Alcon, Malaysia* and *Summit, Malaysia.*

Alcon Cusi, Singapore. See *Alcon, Singapore.*

Alcon Cusi, Spain. Alcon Cusi, Camil Fabra 58, El Masnou, 08320 El Masnou Barcelona, Spain.
url: www.alconlabs.com

Alcon PR, USA. See *Alcon, USA.*

Alcon-Thilo, Ger. See *Alcon, Ger.*

Alcor, Spain. Alcor, P Del Prado 14 1 C, 28014 Madrid, Spain.

Alcure, India. Alcure Pharmaceuticals Laboratories (India), 42 Vidhya Vihar, Kasturba Nagar, Ratlam, India.

Alcusal, Austral. Alcusal Inc. P/L, 12 Mahogany Drive, New Lambton, NSW 2302, Australia.

Alde Medi Impex, India. Alde Medi Impex Ltd, K-33 Udyog Nagar, Industrial Area, Rohtak Road, Delhi, India.

Aldo, Spain. Aldo Union, Baronesa de Malda 73, Esplugas de Llobregat, 08950 Barcelona, Spain.
url: www.aldo-union.com

Aldo-Union, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Aldo-Union, Philipp. See *Cathay, Philipp.*

Aldo-Union, Rus. See *Invar, Rus.*

Aldo-Union, Singapore. See *Green Cross, Singapore.*

Aldo-Union, Thai. See *Greater Pharma, Thai.*

Aldril, Philipp. Aldril Pharmaceuticals, Suite 402-403, Cedar Exec Bldg II, 26 Timog Ave, Cor Scout Tobias St, Quezon City, Philippines.

Aledicine, Gr. Aledicine, Menandrou 58, 104 32 Athens, Greece.

Alembic, India. Alembic Ltd, Alembic Rd, Vadodara 390 003, India.
url: www.alembic-india.com

Alembic, Rus. Alembic Ltd, Donskaya St 18/7, str. 1, Of. 3, 119049 Moscow, Russia.

Alembic, Singapore. See *Zyfas, Singapore.*

Alembic, UK. Alembic Products Ltd, River Lane, Saltney, Chester, Cheshire, CH4 8RQ, UK.
url: www.alembicproducts.co.uk

Alembic, Ukr. Alembic Ltd, Koshitsa Street, 9B, Office 8, Kiev, 02068, Ukraine.

Alenfarma, Port. Alenfarma Especialidades Farmacêuticas Lda, R. Dr. António Loureiro Borges 3, Arquiporque Miraflores, 1495-131 Algés, Portugal.

Aleph, Ital. See *Pharmatre, Ital.*

Alergomed, Braz. See *Daudt, Braz.*

Alet, Gr. Alet Pharmaceuticals SA, 26 Aidinou Str. Haidari, 12461 Athens, Greece.

Alet, Neth. See *Alet, Gr.*

Aletheia, USA. Aletheia, 644 Church Rd, Unit 10, Madison, MS 39110, USA.

Alex Pharm, Ukr. Alex Pharm, Ukraine.
url: www.alexpharm.com

Alexandria, Rus. Alexandria Company for Pharmaceuticals & Chemical Industries, Russia.
url: alexcopharma.com

Alexion, Austria. See *Alexion, Fr.*

Alexion, Belg. Alexion Pharma Belgium, Ave Louise 65, 1050 Brussels, Belgium.
url: www.alexionpharma.com

Alexion, Canad. Alexion Pharmaceuticals, Toronto, Canada.
url: www.alxn.com

Alexion, Cz. See *Alexion, Fr.*

Alexion, Denm. See *Alexion, Fr.*

Alexion, Fr. Alexion Europe SAS, 25 Boulevard de l'Amiral Bruix, 75016 Paris, France.
url: www.alxn.com

Alexion, Ger. Alexion Pharma Germany GmbH, Landsberger Str. 155, 80687 München, Germany.
url: www.alxn.com

Alexion, Irl. See *Alexion, UK.*

Alexion, Israel. See *Alexion, Switz.*

Alexion, Ital. Alexion Pharma Italy Srl, Largo Corsia dei Servi 3, 20122 Milan (MI), Italy.

Alexion, Jpn. Alexion Pharma Godo Kaisha, 12th Floor Ebisu Prime Square Tower, 1-1-39 Hiro-o, Shibuya-ku, Tokyo, 150-0012, Japan.
url: www.alxn.com

Alexion, Neth. See *Alexion, Belg.*

Alexion, Norw. See *Alexion, Belg.*

Alexion, Pol. See *Alexion, Fr.*

Alexion, Port. See *Alexion, Spain.*

Alexion, Spain. Alexion Pharma Spain SL, World Trade Center, Moll de Barcelona s/n, Edificio sur 2 planta, 08039 Barcelona, Spain.
url: www.alxn.com

Alexion, Swed. See *Alexion, Fr.*

Alexion, Switz. Alexion Pharma International Sarl, av. du Tribunal-Fédéral 34, 1005 Lausanne, Switzerland.
url: www.alexionpharm.com

Alexion, UK. Alexion UK, 14 Horizon Business Village, 1 Brooklands Rd, Weybridge, Surrey, KT13 0TJ, UK.
url: www.alxn.com

Alexion, USA. Alexion Pharmaceuticals Inc, 352 Knotter Drive, Cheshire, CT 06410, USA.
url: www.alexionpharm.com

Alexso, USA. Alexso Inc., 215 N Moorpark Rd, Ste 1, Thousand Oaks, CA 91360, USA.
url: terocin.com

Alexza, USA. Alexza Pharmaceuticals Inc., 2091 Stierlin Court, Mountain View, CA 94043, USA.
url: www.alexza.com

Alfa Biotech, Cz. See *Medicom, Cz.*

Alfa Biotech, Ital. Alfa Biotech S.r.l., Via Ragazzi del 99 n.5, 40133 Bologna (BO), Italy.

Alfa Farmaceutici, Ital. See *Wassermann, Ital.*

Alfa Intes, Ital. Industrio Terapeutica Splendore - S.r.l., Via F.lli Bandiera 26, 80026 Casoria (NA), Italy.
url: www.alfaintes.it

Alfa Medis, Gr. Alfa Medisyst, 115 26 Athens, Greece.

Alfa Wassermann, China. Alfa Wassermann (China), Oriental Ginza office 20, F/G, 48 Dongzhimen Wai St, Dongcheng District, Beijing 100027, China.

Alfa Wassermann, Cz. See *Medicom, Cz.*

Alfa Wassermann, Fr. Alfa Wassermann Pharma, 67 rue Anatole-France, 92300 Levallais-Perret, France.

Alfa Wassermann, Gr. See *Demo, Gr.*

Alfa Wassermann, Hung. See *CSC, Hung.*

Alfa Wassermann, Indon. See *Tempo Scan Pacific, Indon.*

Alfa Wassermann, Pol. Alfa Wassermann Polska Sp. zo.o., ul. Grójecka 186 m 317, 02-390 Warsaw, Poland.
url: www.alfawassermann.pl

Alfa Wassermann, Rus. See *CSC, Rus.*

Alfa Wassermann, Thai. See *Charoen, Thai.*

Alfarm, Rus. Alfarm, ul Kostyakova D 6/5, 125422 Moscow, Russia.

Alfarma, Spain. See *Daiichi Sankyo, Spain.*

Alfatreid, Rus. Alfatreid Kosmetiks, 1 Volkovskii Proezd D 4 Kor 1, 125171 Moscow, Russia.

Alfpol, Pol. Alfpol SC Hurtownia Farmaceutyczno, ul. Sklodowskiej-Curie 91, 42-700 Lubliniec, Poland.

Alfresa, Jpn. Alfresa Pharma Corporation, 2-2-9 Koku-machi, Chuo-ku, Osaka, 540-8575, Japan.
url: www.alfresa-pharma.co.jp

Algol, Fin. Algol Pharma Oy, Karapellontie 6, PL 13, 02611 Espoo, Finland.
url: www.algolpharma.com

Algol, Norw. Algol Pharma AS, Smuget 1, 1383 Asker, Norway.
url: www.algolpharma.no

Algol, Swed. Algol Pharma AB, Hammarby Fabriksväg 23, 120 33 Stockholm, Sweden.
url: www.algolpharma.com

Ali, Turk. Ali Raif İlaç Sanayii Ltd. Şti., Haseyad II., Kısım No.228, İkitelli, İstanbul, Turkey.
url: www.aliraif.com.tr

Alico Impex, Philipp. Alico Impex International Corp., 201 AS Building, Don Antonio Heights, Diliman, Philippines.

Alicon, India. Alicon Pharmaceuticals Pvt Ltd, 323 Diamond Ind Estate, Ketkipada Road, Dahisar (E), Mumbai 400 068, India.
url: www.aliconpharma.com

Align, USA. Align Pharmaceuticals, 5625 Dillard Drive, Suite 201, Cary, NC 27511, USA.

aligna, Ger. aligna AG, Bernhard-wicki-Strasse 5, 80636 München, Germany.
url: www.aligna.de

Alimera, UK. Alimera Sciences Ltd, Centaur House, Ancells Business Park, Fleet, Hampshire, GU51 2UL, UK.
url: www.alimerasciences.com

Alimera, USA. Alimera Sciences, 6120 Windward Parkway, Suite 290, Alpharetta, GA 30005, USA.

Alinter, UK. Alinter Ltd, New Abbey Court, 51-53 Stert St, Abingdon, Oxfordshire, OX14 3HB, UK.
url: www.alinter.co.uk

Aliud, Cz. Aliud Pharma Cz sro, Papovová 1/948, 143 00 Prague 4, Czech Republic.
url: www.aliud.cz

Aliud, Ger. Aliud Pharma GmbH, Gottlieb-Daimler-Str. 19, 89150 Laichingen, Germany.
url: www.aliud.de

Aliud, Hung. See *Medicine & Business, Hung.*

Alive, Canad. Alive Vitamins, 228 2680 Shell Rd, Richmond, British Columbia, V6X 4C9, Canada.

ALK, Austria. Alk-Abello Allergie-Service GmbH, Backermuhlweg 59, A-4030 Linz, Austria.
url: www.alk-abello.at

ALK, Belg. See *ALK, Neth.*

ALK, Canad. See *ALK, USA.*

ALK, China. See *ALK, Fin.*

ALK, Cz. See *ALK, Denm.*

ALK, Denm. ALK-Abellö Danmark, Fruebjergvej 3, boks 80, 2100 Copenhagen Ø, Denmark.
url: www.alk-abello-nordic.com

ALK, Fin. ALK-Abellö A/S, Liluodontie 17 B, 2. krs, 00980 Helsinki, Finland.
url: www.alk-abello.fi

ALK, Fr. ALK Abello, 55270 Varennes en Argonne Cedex, France.
url: www.alk-abello.com

ALK, Gr. See *ALK, Denm.*

ALK, Hung. See *Spiromed, Hung.*

ALK, Irl. See *ALK, UK.*

ALK, Ital. Alk-Abellò S.p.A., Via Ramazzotti 12, 20020 Lainate (MI), Italy.
url: www.allergia.it

ALK, Neth. ALK-Abellò BV, Edisonbaan 30, 3439 MN Nieuwegein, Netherlands.
url: www.alk-abello.com

ALK, Norw. ALK Norge, Spireav. 6, Postboks 218 Okern, 0580 Oslo, Norway.
url: www.alk-abello.no

ALK, NZ. See *CSL, NZ.*

ALK, Pol. Alk-Abello A/S, ul. Duchnicka 3, 01-796 Warsaw, Poland.
url: www.alk-abello.pl

ALK, Port. See *ALK, Denm.*

ALK, Spain. Alk Abello, Miguel Fleta 19, 28037 Madrid, Spain.
url: www.alk-abello.com

ALK, Swed. ALK Sverige AB, Smörhålevägen 3, 434 42 Kungsbacka, Sweden.
url: www.alk.se

ALK, Switz. ALK-Abellò AG, Industriestrasse 30, 8604 Volketswil, Switzerland.

ALK, UK. ALK-Abellò (UK), 2 Tealgate, Hungerford, Berkshire, RG17 0YT, UK.
url: www.alk-abello.com

ALK, USA. ALK-Abellò Inc., 1700 Royston Lane, Round Rock, TX 78664, USA.
url: www.alk-abello.com

ALK Abello, Ger. Alk-Abellò Arzneimittel GmbH, Feldstr. 170, 22880 Wedel, Germany.
url: www.alk-abello.de

Alkaloid, Cz. See *ProMed, Cz.*

Alkaloid, Rus. See *Satex, Rus.*

Alkaloid, Ukr. See *Delta Medical, Ukr.*

Alkaloida, Hung. Alkaloida Vegyészeti Gyár Zrt, Kabay J út 29, H-4440 Tiszavasvári, Hungary.

Alkaloida, Thai. See *Medline, Thai.*

Alkapharm, Singapore. See *Wellchem, Singapore.*

Alkem, India. Alkem Laboratories Ltd, Devashish, Alkem House, Senapati Bapat Marg, Lower Parel, Mumbai 400 013, India.
url: www.alkemlabs.com

Alkem, Philipp. See *Pharmasan, Philipp.*

Alkem, Rus. See *Alkem, India.*

Alkem, Thai. See *Kaspa, Thai.*

Alkem, Ukr. Alkem Lab., ul Dragomanova 17, Office A, Kiev, Ukraine.
url: www.alkemlabs.com

Alkermes, Indon. See *Janssen-Cilag, Indon.*

Alkermes, Irl. Alkermes, Connaught House, 1 Burlington Rd, Dublin 4, Ireland.
url: www.alkermes.com

Alkermes, Neth. See *Alkermes, Irl.*

Alkermes, USA. Alkermes Inc., 88 Sidney St, Cambridge, MA 02139, USA.
url: www.alkermes.com

Alkon (Αλκον), Gr. See *Alcon, Gr.*

Alkopharma, Gr. See *Alkopharma, Switz.*

Alkopharma, Neth. See *Alkopharma, Switz.*

Alkopharma, Norw. See *Alkopharma, Switz.*

Alkopharma, Swed. See *Alkopharma, Switz.*

Alkopharma, Switz. Alkopharma SA, Rue des Finettes 55, 1920 Martigny, Switzerland.

Alkoy, Rus. Alkoy Ltd, Dosflota pr-D 2 str.1, 125364 Moscow, Russia.

Alk-Scherax, Ger. See *ALK Abello, Ger.*

Allan, USA. Allan Pharmaceutical, 21 Radcliffe Dr., Southampton, PA 18966, USA.

Allard, Fr. See *BMS, Fr.*

Allcock, Norw. See *Nycomed, Norw.*

Allcura, Ger. allcura Naturheilmittel GmbH, Reichenäcker 7, 97877 Wertheim, Germany.
url: www.allcura.de

Allegis, USA. Allegis Pharmaceuticals, 276 Nissan Parkway, B-2, Canton, MS 39056, USA.
url: www.allegispharma.com

AlleMan, Ger. AlleMan Pharma GmbH, Benzstr. 5, 72793 Pfullingen, Germany.

Allen, Austria. See *GSK, Austria.*

Allen, Gr. See *GSK, Gr.*

Allen, Mex. Allen Laboratorios, S.A. de C.V., Av. Instituto Politécnico Nacional No. 4728, Gustavo A Madero, Tlacamaca, 07380 Mexico D.F, Mexico.

Allen, Spain. See *GSK, Spain.*

Allen & Hanburys, Austral. See *GSK, Austral.*

Allen & Hanburys, Irl. See *GSK, Irl.*

Allen & Hanburys, SAfr. See *GSK, S.Afr.*

Allen & Hanburys, UK. See *GSK, UK.*

Allen & Hanburys, USA. See *GSK, USA.*

Allendale, Canad. See *Allendale, USA.*

Allendale, USA. Allendale Pharmaceuticals Inc., 73 Franklin Turnpike, Allendale, NJ 07401, USA.
url: www.allendalepharm.com

Allenge, India. Allenge India, S.C.O-96 1st Floor, Sector 5, Panchkula, India.
url: www.allengeindia.com

Allens, UK. Allens & Co. (Anglesey) Ltd, Freshwinds, Pentraeth, Isle of Anglesey, Gwynedd, LL75 8YF, UK.
url: www.allenshealthcare.co.uk

Allerderm, Singapore. See *Green Cross, Singapore.*

Allergan, Arg. Allergan-Loa S.A.I.C. y F., Av. del Libertador 498, Piso 20 Sect. Sur, 1001 Buenos Aires, Argentina.
url: www.allergan.com

Allergan, Austral. Allergan Australia P/L, 77 Ridge St, Gordon, NSW 2072, Australia.
url: www.allergan.com

Allergan, Austria. Pharm-Allergan GmbH, Wienerbergstrasse 11 Twin Tower, A-1100 Vienna, Austria.
url: www.allergan.com

Allergan, Belg. Allergan SA, Meir 44 A, 2000 Antwerp, Belgium.
url: www.allergan.com

Allergan, Braz. Allergan Produtos Farmacêuticos Ltda, Av. Cardoso de Melo 1955 13 andar, 4548005 São Paulo, Brazil.

Allergan, Canad. Allergan Inc., 110 Cochrane Dr., Markham, Ontario, L3R 9S1, Canada.
url: www.allergan.com

Allergan, Chile. Laboratorios Allergan Ltda, Vitacura 2736, Piso 15, Las Condes, Santiago, Chile.

Allergan, China. Allergan, Suites 5605-07 Phase 1, Plaza 66, 1266 West Nanjing Road, Shanghai 200040, China.
url: www.allergan.com

Allergan, Cz. See *Eco-Med-Poll, Cz.*

Allergan, Denm. See *Allergan, Swed.*

Allergan, Fin. Allergan Norden AB, Rajatarpantie 41 C, 01640 Vantaa, Finland.
url: www.allergan.com

Allergan, Fr. Allergan France, Font de l'Orme, av Dr Maurice-Donat, B.P. 442, 06254 Mougins, France.
url: www.allergan.fr

Allergan, Ger. Pharm-Allergan GmbH, Pforzheimer Str.160, 76275 Ettlingen, Germany.
url: www.allergan.de

Allergan, Gr. Allergan, Greece.

Allergan, Hong Kong. Allergan Asia Ltd, Unit 3012 30/F Metroplaza Tower 1, 223 Hing Fong Rd, Kwai Fong, N.T., Hong Kong.
url: www.allergan.com

Allergan, Hung. See *Inthera, Hung.*

Allergan, India. Allergan India Pvt Ltd, 1st Floor, North Wing, Silver Jubilee Block, Unity Building Complex, Mission Road, Bangalore 560 027, India.
url: www.agnindia.com

Allergan, Indon. See *Allergan, Singapore.*

Allergan, Irl. Allergan Pharmaceuticals Ireland Ltd, Castlebar Rd, Westport, Co. Mayo, Ireland.
url: www.allergan.com

Allergan, Israel. See *Tradis-Gat, Israel.*

Allergan, Ital. Allergan S.p.A., Via S Quasimodo 134/138, 00100 Rome (RM), Italy.
url: www.allergan.com

Allergan, Malaysia. See *DKSH, Malaysia.*

Allergan, Mex. Allergan, S.A. de C.V., Mier y Pesado 126, Col Del Valle, 03100 Mexico D.F., Mexico.
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Allergan, Norw. See *Allergan, Swed.*

Allergan, NZ. Allergan Pharmaceuticals, P.O. Box 1873, Auckland 1, New Zealand.
url: www.allergan.com

Allergan, Philipp. See *Zuellig, Philipp.*

Allergan, Pol. See *Ewopharma, Pol.*

Allergan, Port. Allergan S.A., Av. Do Forte 3 - Edif. Suécia IV, 1 Piso, 2795-504 Carnaxide, Portugal.
url: www.allergan.com

Allergan, Rus. See *Family Health, Rus.*

Allergan, S.Afr. Allergan Pharmaceuticals (Pty) Ltd, P.O. Box 3911, Halfway House 1685, South Africa.
url: www.allergan.com

Allergan, Singapore. Allergan Singapore PTE Ltd, 20 Pasir Panjang Rd, 09-25 Mapletree Business City, Singapore 117 439, Singapore.
url: www.allergan.com

Allergan, Spain. Allergan S.A.U., Edificio La Encina, Plaza de la Encina 10-11, 28760 Madrid, Spain.
url: www.allergan.com

Allergan, Swed. Allergan Norden AB, Business Campus, 194 81 Upplands Väsby, Sweden.
url: www.allergan.se

Allergan, Switz. Allergan AG, Feldmoosstrasse 6, 8853 Lachen, Switzerland.
url: www.allergan.com

Allergan, Thai. See *Maxim, Thai.*

Allergan, UK. Allergan Ltd, 1st Floor Marlow International, The Parkway, Marlow, Buckinghamshire, SL7 1YL, UK.
url: www.allergan.com

Allergan, Ukr. See *Ewopharma, Ukr.*

Allergan, USA. Allergan Pharmaceuticals Inc., 2525 Dupont Dr., P.O. Box 19534, Irvine, CA 92623-9534, USA.
url: www.allergan.com

Allergan, Venez. Laboratorios Allergan, Hans Neumann, Ed. Corimon, Pso.3, Merck S.A., Cortijos de Lourdes, Caracas, Venezuela.
url: www.allergan.com

Allergan Herbert, USA. See *Allergan, USA.*

Allergan-Frumtost, Braz. See *Allergan, Braz.*

Allergo, Turk. Allergo İlaç Saglik Ürünleri Diş Tic. Ltd, Millet Cd Hamdibey iş Merkezi 150, Kat 3 Büro 19 Şehremini, Çapa, Istanbul, Turkey.

Allergomed, Switz. Allergomed AG, Erlenstrasse 29, Postfach 117, 4106 Therwil, Switzerland.

Allergon, Pol. See *Krotex, Pol.*

Allergopharma, China. See *Merck Serono, China.*

Allergopharma, Ger. Allergopharma Joachim Ganzer KG, Hermann-Körner-Str. 52, 21465 Reinbek, Germany.
url: www.allergopharma.de

Allergopharma, Ital. Allergopharma Spa, Via Stephenson 94, 20157 Milan, Italy.
url: www.allergopharma.com

Allergopharma, Neth. Allergopharma BV, Kwikstaartlaan 26, 3704 GS Zeist, Netherlands.

Allergopharma, Pol. Allergopharma Nexter Sp. z.o.o., ul. Jordana 7B, 40-056 Katowice, Poland.
url: www.nexter.pl

Allergopharma, Switz. See *Allergomed, Switz.*

Allergy Therapeutics, Canad. See *Western Allergy, Canad.*

Allergy Therapeutics, Cz. Allergy Therapeutics sro, Na Výtoni 12, 128 00 Prague 2, Czech Republic.
url: www.allergytherapeutics.com

Allergy Therapeutics, Neth. Allergy Therapeutics Netherlands BV, Maanlander 10, 3824 MP Amersfoort, Netherlands.

Allergy Therapeutics, Pol. See *Pliva Krakow, Pol.*

Allergy Therapeutics, UK. Allergy Therapeutics Ltd, Dominion Way, Worthing, West Sussex, BN14 8SA, UK.
url: www.allergytherapeutics.com

AllergyCare, Switz. AllergyCare Pharmaceutical GmbH, Dorfstrasse 147, 8802 Kilchberg, Switzerland.
url: www.allergycare.ch

Allertec, Gr. Allertec Hellas A.E., 18 Faethonos Str., 55 132 Kalamaria, Greece.
url: www.allertec.gr

Alliance, Fin. See *Alliance, UK.*

Alliance, Irl. See *United Drug, Irl.*

Alliance, Neth. See *Alliance, UK.*

Alliance, Port. Alliance Healthcare SA, Rua Eng Ferreira Dias 772, 4149-014 Porto, Portugal.

Alliance, S.Afr. Alliance Pharmaceuticals Ltd, P.O. Box 261269, Excom 2023, South Africa.
url: www.alliancepharmaceuticals.co.za

Alliance, Thai. Alliance Pharma Co. Ltd, 20 Fl Olympia Thai Tower, 444 Ratchadapisek Rd, Somsennok, Bangkok, 10310, Thailand.

Alliance, UK. Alliance Pharmaceuticals Ltd, Avonbridge House, Bath Rd, Chippenham, Wiltshire, SN15 2BB, UK.
url: www.alliancepharma.co.uk

Alliance, USA. Alliance Pharmaceuticals, 4660 La Jolla Village Drive, Suite 825, San Diego, CA 92122, USA.
url: www.oltp.com

Alliant, USA. Alliant Pharmaceuticals Inc, 312 Maxwell Rd, Suite 400, Alpharetta, GA 30004, USA.
url: www.alliantpharma.com

Allied, S.Afr. Allied Pharmaceuticals Ltd, P.O. Box 5237, Rivonia 2128, South Africa.

Allied, USA. Allied Pharmacy, 801 Stadium Drive, Suite 111, Arlington, TX 76111, USA.

Allied Drug, S.Afr. Allied Drug Co (Pty) Ltd, 27 Hannah Rd, Congella, Durban 4001, South Africa.

Alliqua, USA. Alliqua Biomedical, 2150 Cabot Blvd West, Langhorne, PA 19047, USA.
url: alliqua.com

Allmi-Care, UK. Allmi-Care Ltd, U20 Lenton Business Centre, Lenton Boulevard, Nottingham, Nottinghamshire, NG7 2BY, UK.
url: www.quool.co.uk

Alloga, Ital. Alloga Italia S.r.l., Via Moggia 75/A, 16033 Lavagna (GE), Italy.
url: www.alloga-europe.com

Allos, USA. Allos Therapeutics Inc., 11080 CirclePoint Rd, Suite 200, Westminster, Colorado, 80020, USA.
url: www.allos.com

Allphamed, Cz. See *Hexanel, Cz.*

Allphar, Irl. Allphar Services Ltd, Belgard Rd, Tallaght, Dublin 24, Ireland.
url: www.allphar.ie

Alltracel, Hong Kong. See *Mekim, Hong Kong.*

Alltracel, Irl. Alltracel Pharma Ltd, Alltracel House, Church Place, Sallynoggin, Co. Dublin, Ireland.
url: www.alltracel.com

Almatica, USA. Almatica Pharma Inc., 10 Bloomfield Ave, Pine Brook, NJ 07058, USA.
url: www.almatica.com

Almet, India. Almet Corporation Ltd, 332 Adhyaru Industrial Estate, Sun Mill Compound, Lower Parel, Mumbai 400 013, India.

Almirall, Austria. See *Almirall Hermal, Ger.*

Almirall, Belg. Almirall Prodesfarma, Medialaan 32 B 4, 1800 Vilvoorde, Belgium.
url: www.almirallprodesfarma.com

Almirall, Chile. See *Grunenthal, Chile.*

Almirall, China. See *Nycomed, China.*

Almirall, Cz. See *Almirall, Spain.*

Almirall, Denm. Almirall ApS, Strandvejen 102B, 2900 Hellerup, Denmark.
url: www.almirall.com

Almirall, Fin. See *Almirall, Spain.*

Almirall, Fr. Almirall SAS (Lab), 1 bd Victor, 75015 Paris, France.
url: www.almirall.com

Almirall, Ger. See *Almirall Hermal, Ger.*

Almirall, Gr. See *Almirall, Spain.*

Almirall, Hong Kong. See *Sincerity, Hong Kong.*

Almirall, Hung. See *Almirall, Spain.*

Almirall, Irl. See *Almirall, UK.*

Almirall, Ital. Almirall S.p.A., Via Messina, 38 Torre C, 20154 Milan (MI), Italy.
url: www.almirall.com

Almirall, Malaysia. See *Zuellig, Malaysia.*

Almirall, Mex. Almirall S.A. de C.V., Avenida Alborada 124, piso 13, Colonia Parques del Pedregal, 14010 Mexico D.F., Mexico.
url: www.almirallprodesfarma.com

Almirall, Neth. Almirall, Netherlands.

Almirall, Norw. See *Nycomed, Norw.*

Almirall, Pol. Almirall Spzoo, ul. Pileckiego 63, 02-781 Warsaw, Poland.

Almirall, Port. Almirall Lda, Rua João Chagas 53A, 2 Escritório 201, 1495-072 Alges, Portugal.
url: www.almirallprodesfarma.com

Almirall, Rus. See *Nycomed, Rus.*

Almirall, Singapore. See *Zyfas, Singapore.*

Almirall, Spain. Almirall S.A., Rda General Mitre 151, 08022 Barcelona, Spain.
url: www.almirall.es

Almirall, Swed. See *Almirall, Denm.*

Almirall, Switz. Almirall AG, Dorfstrasse 38, 6340 Baar, Switzerland.

Almirall, UK. Almirall Ltd, 4 The Square, Stockley Park, Uxbridge, Middlesex, UB11 1ET, UK.
url: www.almirall.com

Almirall Hermal, Cz. See *Almirall Hermal, Ger.*

Almirall Hermal, Ger. Almirall Hermal GmbH, Scholtzstr. 3, 21465 Reinbek, Germany.
url: www.almirall.de

Almofarma, Spain. See *Almirall, Spain.*

Almus, Ital. Almus Srl, Via Moggia 75/A, 16033 Lavagna (GE), Italy.

Almus, Port. Almus Lda, Rua Engenheiro Ferreira Dias 772, 4149-014 Porto, Portugal.

Alna, India. Alna Biotech, SCF 320 2nd Floor, Motor Market, Maninajra, Chandigarh, India.

Alodial, Port. Alodial Farmacêutica Lda, Estrada Marco do Grilo, Zemouto, 2830 Coina, Portugal.

Aloe Care, Canad. See *Aloe Care, USA.*

Aloe Care, USA. Aloe Care International, Suite H, 9700 West 76th St, Eden Prairie, Minnesota, 55344, USA.

Aloette, Canad. See *Aloette, USA.*

Aloette, USA. Aloette Cosmetics Inc., 200 3715 Northside Parkway NW Building 200, Atlanta, Georgia, 30327, USA.

Alonga, Spain. See *Sanofi-Aventis, Spain.*

Alpen, Ukr. Alpen Pharma AG, 30-A Lisna str., Pushcha-Vodytsya, 04075 Kiev, Ukraine.
url: www.alpenpharma.ua

Alpes Chemie, Chile. Alpes Chemie SA, Av. Pedro de Valdivia 1307, Providencia, Santiago, Chile.

Alpex, Cz. See *Alpex, UK.*

Alpex, Switz. Alpex Pharma SA, via Cantonale, 6805 Mezzovico, Switzerland.
url: www.alpex.com

Alpex, UK. Alpex Pharma (UK) Ltd, Yew Tree Lodge, Southill, Biggleswade, Bedfordshire, SG18 9LP, UK.

Alpha, Hong Kong. See *Keller, Hong Kong.*

Alpha, Israel. See *Medogar, Israel.*

Alpha, NZ. Alpha Pharmaceuticals Ltd, P.O. Box 705, Palmerston North, New Zealand.

Alpha Aromatic, India. Alpha Aromatic Pvt Ltd, Banglow No.6, Kariappa Road, Cantt., Varanasi 221 002, India.

Alpha Therapeutic, Ital. Alpha Therapeutic Italia S.p.A., C.so di Porta Vittoria 9, 20122 Milan (MI), Italy.

Alpha Therapeutic, Singapore. Alpha Therapeutic Asia Pte Ltd, 1 Maritime Square, 10-33A World Trade Centre, S 099253, Singapore.
url: www.alphather.com

Alpha Therapeutic, UK. See *Grifols, UK.*

Alpha Therapeutic, USA. See *Grifols, USA.*

Alphapharm, Austral. Alphapharm P/L, P.O. Box 36, Camperdown, NSW 1450, Australia.
url: www.alphapharm.com.au

Alphapharm, China. See *Alphapharm, Austral.*

Alphapharm, Hong Kong. See *ICH, Hong Kong.*

Alphapharm, Malaysia. See *Summit, Malaysia and Zuellig, Malaysia.*

Alphapharm, Philipp. See *Merck, Philipp.*

Alphapharm, Singapore. See *Zuellig, Singapore.*

Alphapharm, Thai. See *JDH Borneo, Thai.*

Alphapole, Fr. Alphapole (Lab), 73 rue Pierre Audry, 69009 Lyon, France.
url: www.alphapole.com

Alpharma, Cz. See *Alpharma, Norw.*

Alpharma, Denm. See *Actavis, Denm.*

Alpharma, Fin. Alpharma Oy, Sinimäentie 10 B, 02630 Espoo, Finland.
url: www.alpharma.fi

Alpharma, Fr. Alpharma France, 40 rue Lecuyer, 93300 Aubervilliers, France.
url: www.alpharma.fr

Alpharma, Hong Kong. See *Primal, Hong Kong.*

Alpharma, Hung. Alpharma Gyógyszervegyeszeti Kft, Szállás u 3, 1107 Budapest, Hungary.

Alpharma, Indon. Alpharma PT, Jl Majapahit 101, Semarang 50249, Indonesia.

Alpharma, Irl. See *Actavis, UK.*

Alpharma, Malaysia. See *Apex, Malaysia.*

Alpharma, Mex. Laboratorios Alpharma, S.A. de C.V., Renato Leduc 363, Toriello Guerra, 14050 Mexico D.F., Mexico.
url: www.alpharma.com

Alpharma, Neth. Alpharma BV, Baarnsche Dijk 1, 3741 LN Baarn, Netherlands.

Alpharma, Norw. Alpharma AS, Harbitzalleen 3, Postboks 158 Skøyen, 0212 Oslo, Norway.
url: www.alpharma.no

Alpharma, Port. Alpharma ApS, Rua Virgílio Correia 11A, 1600-219 Lisbon, Portugal.
url: www.alpharma.pt

Alpharma, Singapore. See *Pharmed, Singapore and Sime Darby, Singapore.*

Alpharma, Swed. Alpharma AB, Nordenflychtsvägen 74, 112 89 Stockholm, Sweden.
url: www.alpharma.se

Alpharma, Switz. See *Medinova, Switz.*

Alpharma, UK. See *Actavis, UK.*

Alpharma, USA. Alpharma USPD Inc, 7205 Windsor Blvd, Baltimore, MD 21244, USA.
url: www.alpharmauspd.com

Alpharma-Isis, Ger. See *Actavis, Ger.*

Alphrema, Ital. Alphrema S.r.l., Via Caduti della Liberazione 48, 21047 Saronno (VA), Italy.
url: www.alphrema.it

Alpic, India. Alpic Biotech Ltd, 414 4th Floor, Satyam Mall, Nr. Satellite, Ahmedabad 380 015, India.
url: www.alpicbiotech.com

Alpinamed, Switz. Alpinamed AG, Pharmazeutische Produkte, 9306 Freidorf, Switzerland.

Alpine, Singapore. Alpine, Singapore.

Alpro, Spain. See *Almirall, Spain.*

Alps, S.Afr. See *Aspen, S.Afr.*

Alra, USA. Alra Laboratories Inc., 3850 Clearview Court, Gurnee, IL 60031, USA.

Alta Care, Ital. Alta Care Laboratoires, Piazza di Spagna 6, 00187 Rome (RM), Italy.
url: www.altacare.com

Altacomp, Canad. Altacomp Enterprises Inc., 10440 Wapiti Drive SE, Calgary, Alberta, T2J 1J4, Canada.

Altacor, UK. Altacor Ltd, StJohn's Innovation Centre, Cowley Rd, Cambridge, Cambridgeshire, CB4 0WS, UK.
url: www.altacor-pharma.com

Altair, India. Altair Pharmaceuticals Pvt Ltd, 79/38 AK Swamy Nagar 4th St, Kilpauk, Chennai, Tamil Nadu, India.

Altair, Rus. See *Altair, India.*

Altaire, USA. Altaire Pharmaceuticals Inc., P.O. Box 849, 311 West Lane, Aquebogue, NY 11931, USA.
url: www.otcdruggist.com

Altana, Austral. Altana Pharma Pty Ltd, Level 2, 71 Epping Rd, North Ryde, NSW 2113, Australia.
url: www.altana.com

Altana, Austria. Altana Pharma GmbH, Ketzergasse 2000, A-1235 Vienna, Austria.

Altana, Belg. Altana Pharma SA/NV, Lambroekstraat 5 C, 1831 Diegem, Belgium.
url: www.altanapharma.be

Altana, Braz. Altana Pharma Ltda, Rua do Estilo Barroco 721, Santo Amaro, 04709-011 São Paulo, SP, Brazil.
url: www.altana.com

Altana, China. See *Nycomed, Ger.*

Altana, Cz. See *Nycomed, Ger.*

Altana, Denm. See *Nycomed, Denm.*

Altana, Fr. ALTANA Pharma S.A.S., 389 rue du Pressoir, 77350 le Mee-sur-Seine, France.
url: www.altana.com

Altana, Ger. See *Nycomed, Ger.*

Altana, Gr. See *Nycomed, Gr.*

Altana, Hong Kong. Altana Pharma (HK), 608, 6/F, Devon House, Taikoo Place, Quarry Bay, Hong Kong.
url: www.altanapharma.com

Altana, Hung. Altana Pharma AG Képviselet, Hermina út 17, 1146 Budapest, Hungary.

Altana, Indon. See *Darya-Varia, Indon* and *Pharos, Indon.*

Altana, Irl. Altana Ltd, Unit 2051 Castle Drive, Citywest Business Campus, Dublin 24, Ireland.

Altana, Ital. Altana Pharma SpA, Via Libero Temolo 4, 20126 Milan, Italy.

Altana, Mex. Altana Pharma S.A. de C.V., Av Primero de Mayo No. 130, Col. San Andres Atoto, 53519 Naucalpan d e Juarez., Mexico.
url: www.altana.com

Altana, Norw. See *Pfizer, Norw.*

Altana, Pol. Altana Pharma Sp. z.o.o., al. Jerozolimskie 146 A, 02-305 Warsaw, Poland.
url: www.altanapharma.com

Altana, Port. Produtas Farmacêuticas Altana Pharma Lda, Quinta da Fonte, Edifício Gil Eanes, Porto Salvo, 2770-192 Paco d'Arcos, Portugal.

Altana, S.Afr. Altana Madaus Pty Ltd, 1st Floor, Uplands 12, The Woodlands, ZA-2080 Woodmead, Sandton, South Africa.
url: www.altana.com

Altana, Singapore. See *DKSH, Singapore.*

Altana, Spain. Altana Pharma, Francisca Delgado 1, Parque Empresarial, Arryo de la Vega – Alcobendas, 28108 Madrid, Spain.
url: www.altanapharma.es

Altana, Switz. Altana Pharma Ltd, Bachstrasse 10, 8280 Kreuzlingen, Switzerland.

Altana, Thai. See *Zuellig, Thai.*

Altana, UK. See *Nycomed, UK.*

Altana, Ukr. See *Delta Medical, Ukr.*

Altana, USA. Altana Inc., 60 Baylis Rd, P.O. Box 2006, Melville, NY 11747, USA.
url: www.altanainc.com

Altana Consumer, Ger. See *Nycomed, Ger.*

Altana Madaus, SAfr. See *Altana, S.Afr.*

AltaSelect, Ital. AltaSelect, Via XXIV Maggio 62/A, 37057 San Giovanni Lupatota (VR), Italy.
url: www.altaselect.it

Altayvitamin, Rus. Altayvitamin JSC, ul Zavodskaya 69, Biysk uk, 659325 Altaiskii Krai, Russia.
url: www.altayvitamin.ru

Alter, Ital. Laboratori Alter s.r.l., Via Egadi 7, 20144 Milan (MI), Italy.
url: www.laboratorialter.it

Alter, Port. Alter, SA, Estrada Marco do Grilo, Zemouto, 2830 Coina, Portugal.

Alter, Spain. Alter, Mateo Inurria 30, 28036 Madrid, Spain.
url: www.alter.es

Alter, Ukr. Alter EGO, Vyborgskaya St 70A, 03067 Kiev, Ukraine.

Alterna, Canad. See *Alterna, USA.*

Alterna, USA. Alterna LLC, Suite 1409, 89 Headquarters Plaza, Norristown, New Jersey, 07960, USA.

Alternavida, Mex. See *Savi, Mex.*

Alternova, Austria. Alternova Arzneimittel GmbH, Wagramerstrasse 4 OG Top 7, A-1220 Vienna, Austria.

Alternova, Denm. Alternova A/S, Lodshusvej 11, 4230 Skælskør, Denmark.
url: www.alternova.dk

Alternova, Fin. Oy Alternova AV, Valkjarventie 1, 02130 Espoo, Finland.
url: www.alternova.fi

Alternova, Swed. Alternova AB, Vallgatan 11, 170 67 Solna, Sweden.

Altfarm, Rus. Altfarm, Damodedovskii r-n D Sudakovo, 142073 Moscow, Russia.
url: www.altfarm.ru

Althin, Swed. See *Baxter, Swed.*

Altimed, Canad. See *Ratiopharm, Canad.*

Altius, Arg. Altius Farmaceutica SA, Vuelta de Obligado 2680, Piso 7 B, Buenos Aires, Argentina.

Alva, Canad. See *Alva, USA.*

Alva, USA. Alva-Amco Pharmacal Inc., 7711 North Meremac Ave, Niles, IL 60714-3423, USA.
url: www.alva-amco.com

Alvartis, Mex. Alvartis Pharma SA de CV, Av. Taxqueña 1498, 4200 Coyoacán Campestre Churubusco, Mexico DF, Mexico.

Alvear, Arg. Laboratorio Alvear, Av. Rivadavia 14644, Piso 1 A, 1704 Ramos Mejia, Buenos Aires, Argentina.

Alveda, Canad. Alveda Pharmaceuticals Inc., 801 40 Holly St, Toronto, Ontario, M4S 3C3, Canada.

Alvia (Αλβια), Gr. ALVIA AE, 18o chlm. L. Athinon-Marathonos, 153 44 Pallini, Greece.

Alvogen, Neth. See *Alvogen, UK.*

Alvogen, UK. Alvogen UK Ltd, The Coach House, 19 Macaulay Rd, London, SW4 0QP, UK.
url: www.alvogen.com

Alza, Canad. See *Janssen-Ortho, Canad.*

Alza, China. See *XianJanssen, China.*

Alza, Denm. See *AstraZeneca, Denm.*

Alza, Irl. See *Cambridge, UK.*

Alza, Israel. See *Alza, USA.*

Alza, Singapore. See *Mayne, Singapore.*

Alza, Switz. See *Biomed, Switz.*

Alza, USA. Alza Corp., 1900 Charleston Ave, Mountain View, CA 94039-7210, USA.
url: www.alza.com

AM, Arg. Laboratorio A.M. Farma Activ, Italia 743, 2000 Rosario, Santa Fe, Argentina.

AMAG, USA. AMAG Pharmaceuticals Inc., 100 Hayden Avenue, Lexington, MA 02421, USA.
url: www.amagpharma.com

Amakris, Canad. Amakris Products Inc., 99 Squire Drive, Richmond Hill, Ontario, L4S 1C7, Canada.

Amarin, Singapore. See *Kyowa, Singapore.*

Amarin, USA. See *Valeant, USA.*

Amatus, Port. See *Gestafarma, Port.*

Amavita, Switz. Amavita Health Care AG, Industriestrasse 2, 4704 Niederbipp, Switzerland.

Ambalal Sarabhai, Thai. See *Pacific, Thai.*

Ambe Medical, UK. Ambe Medical Group, Unit c6 Upper Floor, Chaucer Business Park, Watery Lane, Kemsing, Kent, TN15 6PL, UK.
url: www.ambemedical.com

AMBI, USA. See *Nutrition 21, USA.*

Ambica, Philipp. Ambica International Trading Corp., 9 Amsterdam Ext., Merville Park Subd, Parañaque City, Philippines.

Ambix, USA. Ambix Laboratories Inc., 210 Orchard St, Rutherford, NJ 07073, USA.

AMCo, UK. Amdipharm Mercury Co. Ltd, 12-16 Addiscombe Rd, Croydon, Surrey, CR0 0XT, UK.
url: www.amcolimited.com

Amcon, USA. Amcon Laboratories, 40 North Rock Hill Rd, St Louis, MO 63119, USA.
url: www.amcon-labs.com

Amcron, Thai. Amcron Enterprise Co. Ltd, 2711 Pattanakarn Rd, Suan Luang, Bangkok 10250, Thailand.

Amdipharm, Austria. See *Amdipharm, Irl.*

Amdipharm, Cz. See *Amdipharm, Irl.*

Amdipharm, Denm. See *Amdipharm, UK.*

Amdipharm, Fin. See *Amdipharm, UK.*

Amdipharm, Fr. See *Amdipharm, UK.*

Amdipharm, Ger. See *Amdipharm, Irl.*

Amdipharm, Gr. See *Amdipharm, Irl.*

Amdipharm, Hong Kong. See *Invida, Hong Kong.*

Amdipharm, Hung. See *Amdipharm International, UK.*

Amdipharm, Irl. Amdipharm Ltd, Temple Chambers, 3 Burlington Rd, Dublin 4, Ireland.
url: www.amdipharm.com

Amdipharm, Ital. See *Amdipharm International, UK.*

Amdipharm, Neth. See *Amdipharm, UK.*

Amdipharm, Norw. See *Amdipharm, UK.*

Amdiphann, Pol. See *Amdipharm, Irl.*

Amdipharm, Port. See *Amdipharm, Irl.*

Amdipharm, Singapore. See *Zuellig, Singapore.*

Amdipharm, Spain. See *Amdipharm, Irl.*

Amdipharm, Swed. See *Amdipharm, UK.*

Amdipharm, Thai. See *Zuellig, Thai.*

Amdipharm, UK. Amdipharm Plc, Savereign House, Miles Gray Rd, Basildon, Essex, SS14 3FR, UK.
url: www.amdipharm.com

Amdipharm International, UK. Amdipharm International Ltd, 1st Floor Mielles House, North Tower 29/31 Esplanade, La Rue des Mielles, St Helier, Jersey, JE2 3QD, UK.
url: www.amdipharm.com

Amdipharma, Hong Kong. See *DKSH, Hong Kong.*

Ameda, Port. See *Ameda, UK.*

Ameda, UK. Ameda Egnell Ltd, Belvedere Trading Estate, Taunton, Somerset, TA1 1BH, UK.
url: www.ameda.demon.co.uk

Ameda, Ukr. See *Ekostatus, Ukr.*

Amedis, Hong Kong. Amedis Co Ltd, Unit 5, 8/F Austin Twr, 22-26 Austin Ave, Tsim Sha Tsui, Hong Kong.

Amedius, Philipp. See *PharmAsia, Philipp.*

Amedra, USA. Amedra Pharmaceuticals LLC, 215 Wood Ave, Middlesex, NJ, USA.
url: www.amedrapharma.com

Amenite, Arg. Laboratorio Amenite, Caracas 4721, 1419 Buenos Aires, Argentina.

Americal, USA. See *Akorn, USA.*

American Biocare, India. American Biocare, Maa Sharda Niwas, 266 Napier Town, Near Bhawartal Garden, Jabalpur 482 001, India.
url: www.americanbiocare.in

American Dermal, USA. See *Sanofi-Aventis, USA.*

American Health, Hong Kong. See *Jebsen, Hong Kong.*

American Home Products, USA. See *Wyeth Consumer, USA.*

American Institutional, Hong Kong. See *IDS, Hong Kong.*

American Institutional, Singapore. See *JDH, Singapore.*

American Lecithin, USA. American Lecithin Co., 115 Hurley Rd, Unit 2B, Oxford, CT 06478, USA.

American Pharmaceutical, USA. American Pharmaceutical Partners Inc., 10866 Wiltshire Blvd, Suite 1270, Los Angeles, CA 90024, USA.
url: www.appdrugs.com

American Red Crass, USA. American Red Cross, 1616 Ft Myer Drive 17th Floor, Arlington, VA 22209-3100, USA.
url: www.redcross.org

American Regent, USA. See *Luitpold, USA.*

American Remedies, India. American Remedies Ltd, 124 Lattice Bridge Rd, Adyar, Chennai, 600 020, India.

American Remedies, Malaysia. See *Antah, Malaysia.*

American Taiwan, Philipp. American Taiwan Biopharma Phils Inc., Unit 2703 C East Tower, PSE Building, Ortigas Center, Pasig City 1605, Metro Manila, Philippines.

American Taiwan, Thai. American Taiwan Biopharm Co Ltd, Unit 1806, 18 Fl, The Millennia Bldg, 62 Langsuan Rd, Lumpini, Prathumwan, Bangkok 10330, Thailand.

American Urologicals, USA. American Urologicals Inc., 10031 Pines Blvd, Suite 216, Pembroke Pines, FL 33024, USA.

Ameriderm, USA. AmeriDerm, 126 Pennsylvania Ave, Paterson, NJ 07503, USA.
url: www.ameriderm.com

Amerifit, Canad. See *Amerifit, USA.*

Amerifit, USA. Amerifit Pharma Inc., 11 State St, Woburn, MA 01801, USA.
url: www.amerifit.com

AmerisourceBergen, USA. AmerisourceBergen Corp., 1300 Morris Drive, Suite 100, Chesterbrook, PA 19087, USA.
url: www.amerisourcebergen.com

Amersham, Arg. See *Nycomed, Arg.*

Amersham, Austral. Amersham Health Pty Ltd, Unit 4, 2 Eden Park Drive, North Ryde, NSW 2113, Australia.
url: www.amershamhealth.com

Amersham, Austria. Amersham Health Handels GmbH, Lembockgasse 49, A-1230 Vienna, Austria.
url: www.amershamhealth.at

Amersham, Belg. See *GE Healthcare, Belg.*

Amersham, Canad. Amersham Health Inc., 1166 South Service Rd West, Oakville, Ontario, L6L 5T7, Canada.
url: www.amershamhealth-ca.com

Amersham, Denm. See *GE Healthcare, Denm.*

Amersham, Fin. Oy Amersham Health AB, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.amershamhealth.com

Amersham, Fr. Amersham Health SA, 140 av Jean-Lolive, 93500 Pantin, France.
url: www.amershamhealth.com

Amersham, Ger. See *GE Healthcare, Ger.*

Amersham, Gr. Amersham Health AE, 139 Plapouta & Lamias Str., 141 21 N Heraklion, Greece.
url: www.amershamhealth.com

Amersham, Hung. Amersham Health (CEE) Handels GmbH Magyarországi Közvetlen Kereskedelmi Képviselete, Konkoly-Thege Miklós út 29-33, 1121 Budapest, Hungary.

Amersham, Norw. Amersham Health AS, Nycov. 2, Postbaks 4220 Nydalen, 0401 Oslo, Norway.
url: www.amershamhealth.no

Amersham, NZ. Amersham Health Ltd, P.O. Box 101-241, North Shore Mail Centre, Auckland, New Zealand.
url: www.amershamhealth.com

Amersham, Spain. Amersham Health, Randa de Poniente, 12, Tres Cantos, 28760 Madrid, Spain.
url: www.amershamhealth.es

Amersham, Swed. Amersham Health AB, Box 602, 16926 Solna, Sweden.
url: www.amershamhealth.com

Amersham, UK. Amersham Health, The Grove Centre, White Lion Rd, Amersham, Buckinghamshire, HP7 9LL, UK.
url: www.amershamhealth.co.uk

Amersham, USA. See *Amersham Biosciences, USA.*

Amersham Biosciences, USA. Amersham Biosciences Corp., 800 Centennial Avenue, P.O. Box 1327, Piscataway, NJ 08855-1327, USA.
url: www.amersham.com

Amersham Buchler, Ger. See *GE Healthcare, Ger.*

Amersham International, UK. See *Amersham, UK.*

Amerx, USA. Amerx Health Care Corp., 1150 Cleveland St, Suite 410, Clearwater, FL 33755, USA.

Ames, Fr. See *Bayer Diagnostics, Fr.*

Ames, Irl. See *Bayer, Irl.*

Ames, Israel. See *Perrigo, Israel.*

Ames, S.Afr. See *Bayer, S.Afr.*

Ames, UK. See *Bayer, UK.*

Am-Europharma, Philipp. Am-Europharma Corp., Km 16, West Service Rd, South Superhighway, Parañaque City, Philippines.
url: www.am-europharma.com

Amgen, Austral. Amgen Australia P/L, P.O. Box 410, North Ryde, NSW 1670, Australia.
url: www.amgen.com

Amgen, Austria. Amgen GmbH, Prinz Eugen-Strasse 8-10, A-1040 Vienna, Austria.
url: www.amgen.at

Amgen, Belg. Amgen SA, Ave Ariane 5, 1200 Brussels, Belgium.
url: www.amgen.be

Amgen, Canad. Amgen Canada Inc., 6755 Mississauga Rd, Suite 400, Mississauga, Ontario, L5N 7Y2, Canada.
url: www.amgen.com

Amgen, Cz. Amgen sro, Klimentska 46, 110 02 Praha 1, Czech Republic.
url: www.amgen.com

Amgen, Denm. Amgen AB, Strandvejen 70, 2900 Hellerup, Denmark.
url: www.amgen.dk

Amgen, Fin. Amgen AB, PL 75, 02201 Espoo, Finland.
url: www.amgen.com

Amgen, Fr. Amgen, 192 av Charles-de-Gaulle, 92200 Neuilly-sur-Seine, France.
url: www.amgen.fr

Amgen, Ger. Amgen GmbH, Hanauer Str. 1, 80992 Munich, Germany.
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Amgen, Gr. See *Genesis, Gr.*

Amgen, Hong Kong. See *IDS, Hong Kong.*

Amgen, Hung. See *Amgen, Neth.*

Amgen, Irl. See *United Drug, Irl.*

Amgen, Israel. See *Megapharm, Israel.*

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Amgen, Neth. Amgen Europe BV, Minervum 7061, 4817 ZG Breda, Netherlands.
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Amgen, Norw. Amgen, Kronprinsensg 1, 0251 Oslo, Norway.
url: www.amgen.com

Amgen, NZ. Amgen New Zealand, a branch of Amgen Australia Pty Ltd, P.O. Box 9-104, Newmarket, Auckland, New Zealand.
url: www.amgen.com

Amgen, Pol. Amgen Sp. zo.o., al. Jana Pawła II 25, 00-854 Warsaw, Poland.
url: www.amgen.com

Amgen, Port. Amgen Biofarmaceutica, Lda, Tagus Park, Edifício Eastécnica, 2780-920 Porto Salvo, Portugal.
url: www.amgen.com

Amgen, Rus. See *Amgen, Neth.*

Amgen, Singapore. See *Steward Cross, Singapore.*

Amgen, Spain. Amgen S.A., Moll de Barcelona s/n, World Trade Centre, 08039 Barcelona, Spain.
url: www.amgen.es

Amgen, Swed. Amgen AB, Box 34107, 100 26 Stockholm, Sweden.
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Amgen, Switz. Amgen Switzerland AG, Alpenquai 30, 6002 Lucerne, Switzerland.

Amgen, UK. Amgen Ltd, 240 Cambridge Science Park, Milton Rd, Cambridge, Cambridgeshire, CB4 4WD, UK.
url: www.amgen.com

Amgen, USA. Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA.
url: www.amgen.com

Amgros, Denm. Amgras I/S, Dampfærgevej 22 (postboks 2593), 2100 Copenhagen Ø, Denmark.

Amherst, Philipp. See *United American, Philipp* and *Westmont, Philipp.*

Amhof, Arg. Lab. Amhof Maurino S.A., Nogoya 4811/15, 1407 Buenos Aires, Argentina.

Amide, Hong Kong. See *Pan-Well, Hong Kong.*

Amide, USA. Amide Pharmaceuticals Inc., 101 East Main Street, Little Falls, NJ 07424, USA.

Amideep, India. Amideep Pharmaceuticals, C/804 Shakamba Tower, Opp. Sterling Hospital, Gurukul Road, Ahmedabad 380 052, India.

Amido, Fr. Laboratoires Amido, 37 av Gabriel-Peri, 92500 Rueil-Malmaison, France.

Amino, Switz. Amino AG, Althofstrasse 12, 5432 Neuenhof, Switzerland.

Aminostar, Hung. See *Walmark, Hung.*

Amirose, UK. Amirose International, 249 Cranbrook Rd, Ilford, Essex, UK.

Amis, Hung. See *Axellus, Pol.*

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AMN Life Science, Thai. See *Kaspa, Thai.*

Amneal, USA. Amneal Pharmaceuticals LLC, 85 Adams Ave, Hauppauge, NY 11788, USA.
url: www.amneal.com

Amnol, Ital. Amnol Chimica Biologica S.r.l., Corso della Vittoria 12/B, 28100 Novara (NO), Italy.
url: www.amnol.eu

AMO, Arg. See *Visiontec, Arg.*

AMO, Austral. Advanced Medical Optics, Level 1, 77 Ridge St, Gordon, NSW 2072, Australia.
url: www.amo-inc.com

AMO, Canad. AMO Canada Co., Unit 2, 80 Whitehall Drive, Markham, Ontario, L3R 0P3, Canada.

AMO, Israel. See *Abbott, Israel.*

AMO, Malaysia. See *DKSH, Malaysia* and *Zuellig, Malaysia.*

AMO, Singapore. See *JDH, Singapore.*

AMO, UK. AMO (UK) Ltd, Jupiter House, Mercury Park, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0HH, UK.

AMO, USA. Abbott Medical Optics, 1700 East St Andrew Place, Santa Ana, CA 92705-4933, USA.
url: www.amo-inc.com

Amol, Canad. See *Amol, Ger.*

Amol, Ger. Amol Pharma GmbH, Mühlen Kamp 29/31, Hamburg 22303, Germany.

Amomed, Austria. Amomed Pharma GmbH, Nikolsdorfergasse 1/15, 1050 Vienna, Austria.

Amoun, Ukr. Amoun, Ukraine.

AMPDR, Port. AMPDR Consultadoria Lda, Av. Bombeiros Voluntarios 146, 2765-201 Estoril, Portugal.

Amphastar, Canad. See *Amphastar, USA.*

Amphastar, USA. Amphastar Pharmaceuticals Inc., 11570 6th St, Rancho Cucamonga, CA 91730, USA.
url: www.amphastar.com

Amrad, Austral. See *MSD, Austral.*

Amred, UK. Amred Healthcare Ltd, 11 Sixpence Close, Coventry, CV4 8HL, UK.
url: www.amredhealthcare.com

Amrit, India. Amrit Remedies Pvt Ltd, SCO 162-164 Indian Airlines Towers, Top Floor, Sector-34A, Chandigarh 160 036, India.
url: www.amritremedies.com

Amrutanjan, India. Amrutanjan Health Care Limited, 103 Luz Church Road, Mylapore, Chennai 600 004, India.
url: www.amrutanjan.com

Amsa, Ital. Amsa S.r.l., Passeggiata di Ripetta 22, 00186 Rome (RM), Italy.

Amsco, USA. See *Steris, USA.*

Amson, Philipp. See *Sahar, Philipp.*

Amternes, Denm. Amternes Laegemiddelregistreringskontor I/S, Amtsrädsforeningen, Dampfaergevej 22 (postboks 2593), 2100 Copenhagen O, Denmark.

Amuchina, Ital. Amuchina S.p.A., Via Pontasso 13, 16015 Casella (GE), Italy.

Amway, Arg. Amway Argentina Inc., Av. Cabildo 86 2 piso, 1426 Buenos Aires, Argentina.

Amway, Canad. Amway Corp., 375 Exeter Rd, London, Ontario, N5Y 5V6, Canada.
url: www.amway.com

Amylin, Philipp. See *Zuellig, Philipp.*

Amylin, USA. Amylin Pharmaceuticals, Inc., 9360 Towne Centre Drive, Ste. 110, San Diego, CA 92121, USA.

An Jie, China. An Jie Pharmaceutical Biotechnology Co. Ltd, Weihai, China.
An Shi, China. An Shi Pharmaceutical Co. Ltd, Zhongshan, China.
An Te, China. An Te Bio Pharm, Shan Xian, China.
Anabiosis, Gr. Anabiosis Hellas, Al. Panagouli 50, 142 31 N. Ionia, Greece.
Ananta, Ukr. Ananta Medicare, ul. Iskrinskaya 37, Karkov, 61001, Ukraine.
url: www.anantamedicare.com
Anapo, Rus. Anapo-2000, Derbenevskaya 22, 115114 Moscow, Russia.
Anaquest, USA. See *Baxter, USA.*
Anasco, Fin. Anasco Oy, PL 480, 00181 Helsinki, Finland.
Anasco, Ger. See *Klosterfrau, Ger.*
ANB, Malaysia. See *Sime Darby, Malaysia.*
ANB, Singapore. See *Pharma 2000, Singapore.*
ANB, Thai. ANB Laboratories Co. Ltd, 39/1 Ram-Intra Rd, Kanayao, Bangkok 10230, Thailand.
url: www.anblab.com
Anben, Israel. See *Kivema, Israel.*
Anben, Malaysia. See *Antah, Malaysia.*
Anbex, Israel. See *Anbex, USA.*
Anbex, USA. Anbex Inc., 110 Royal Musselburgh, Williamsburg, VA 23188, USA.
url: www.anbex.com
Anchor, Mex. Anchor Farma SA de CV, Calle 28 2625, 44940 Guadalajara Zona Industrial, Jalisco, Mexico.
Andersen, Norw. Jan F. Andersen A/S, Postboks 1132 Flattum, 3501 Honefoss, Norway.
url: www.jfa-as.no
Andre, India. Andre Laboratories Pvt Ltd, 495/7 & 8 GIDC, Makarpura, Vadodara 390 101, India.
Andre, Norw. See *Andre, Swed.*
Andre, Swed. André Pharma AB, Postboks 63, 182 11 Danderyd, Sweden.
url: www.andrepharma.se
Andreabal, Switz. Andreabal AG, Rudolfstrasse 2, 4054 Basle, Switzerland.
url: www.andreabal.ch
Andreu, Spain. See *Roche, Spain.*
Andromaco, Arg. Laboratorios Andrómaco S.A.I.C.I., Ingeniero Huergo 1145, 1107 Buenos Aires, Argentina.
url: www.andromaco.com.ar
Andromaco, Braz. See *Andromaco, Arg.*
Andromaco, Chile. Laboratorios Andromaco SA, Av. Quilin 5273, Penalolen, Santiago, Chile.
Andromaco, Cz. See *Grunenthal, Spain.*
Andromaco, Mex. Industria Farmacéutica Andrómaco, S.A. de C.V., Andrómaco No. 104, Col. Ampliación Granada, Deleg. Miguel Hidalgo, 11520 Mexico D.F., Mexico.
url: www.andromaco.com.mx
Andromaco, Rus. See *Grunenthal, Rus.*
Andromaco, Spain. See *Grunenthal, Spain.*
Andrx, USA. Andrx Pharmaceuticals Inc., 4001 SW 47th Ave, Fort Lauderdale, FL 33314, USA.
url: www.andrx.com
Anesiva, USA. Anesiva Inc., 650 Gareway Blvd, South San Francisco, CA 94080, USA.
url: www.anesiva.com
Anfarm, Gr. See *Anpharm (Ανφαρμ), Gr.*
Anfarm, Hong Kong. See *Sincerity, Hong Kong.*
Anfarm, Rus. See *Medochemie, Rus.*
Anfarm, Thai. See *JDH Borneo, Thai.*
Ang Li Kang, China. Ang Li Kang Pharmaceutical Co. Ltd, Zhejiang, China.
Angelfarma, Port. Angelfarma Lda, Rua João Chagas 53, Piso 3, 1495-764 Cruz Quebrada - Dafundo, Portugal.
Angelini, Gr. See *Angelini, Ital.*
Angelini, Hong Kong. See *IDS, Hong Kong.*
Angelini, Hung. See *Angelini, Ital.*
Angelini, Indon. See *Soho, Indon.*
Angelini, Irl. See *Angelini, Ital.*
Angelini, Israel. See *Rafa, Israel.*
Angelini, Ital. Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F S.p.A., Viale Amelia 70, 00181 Rome (RM), Italy.
url: www.angelini.it
Angelini, Philipp. See *Croma, Philipp.*
Angelini, Pol. See *Medagro, Pol.*
Angelini, Port. Angelini, Rua João Chagas 53, Piso 3, 1495-072 Alges, Portugal.
Angelini, Rus. See *CSC, Rus.*
Angelini, Singapore. See *Indrugco, Singapore.*
Angelini, Spain. Angelini Farmaceutica SA, Carrer d'Osi 7, 08034 Barcelona, Spain.
url: www.angelini.es
Angelini, Ukr. See *Dileo, Ukr.*
Angenerico, Ital. Angenerico S.p.A., Via Nocera Umbra 75, 00181 Rome (RM), Italy.
url: www.angelini.it
Angenerico, Spain. Lab. Angenerico SL, C/ Osi 7-9, 08034 Barcelona, Spain.
AngioDynamics, USA. AngioDynamics, 603 Queensbury Ave, Queensbury, NY12904, USA.
url: www.angiodynamics.com
Anglian, UK. Anglian Pharma Plc, P.O. Box 161, Hitchin, Hertfordshire, SG47WE, UK.
url: www.anglianpharma.com
Anglo-French Drugs, India. Anglo-French Drugs & Industries Ltd (Ankare), 41, 3rd Cross, 5th Block, Rajajinagar, Bangalore 560 010, India.
url: www.afdil.com
Anglo-French Laboratories, Canad. Anglo-French Laboratories, Canada.
Angtai, China. Angtai Pharmaceutical Co. Ltd, East Industrial Area, Jiujiang 332300, Wuning, Jiangxi, China.
url: www.angtai.com
ANH, Thai. ANH Products Ltd, 105 Soi Samprasong 3, New Petchaburi Rd, Ratchatheveee, Bangkok 10400, Thailand.
Ani, USA. Ani Pharmaceuticals, Gulfport, MS 39501, USA.
Anifer, Austria. See *Hofmann, Austria.*
Anika, Canad. See *Anika, USA.*
Anika, Israel. See *Rafa, Israel.*
Anika, Singapore. See *Wellchem, Singapore.*
Anika, USA. Anika Therapeutics Inc., 236 West Cummings Park, Woburn, MA 01801, USA.
Anios, Fr. Laboratoires Anios, Pavé du Moulin, 59260 Lille-Hellemmes, France.
url: www.anios.com
AnJieLun, China. AnJieLun Pharmaceutical Co. Ltd, New technology Industrial Park, Beichen Science & Technology Industrial Park, Tianjin 300402, China.
Ankang, China. Ankang Beiyida Pharmaceutical Co. Ltd., 2 Yixing East Rd, Ankang, Shaanxi, China.
Anke, China. Anke Biotechnology Co. Ltd, 669 Changjiang Rd, West Hefei, Anhui, 230088, China.
url: www.ankebio.com
Ankehengyi, China. Ankehengyi Pharmaceutical Co. Ltd., Xincheng, Economic & Technological Development Zone, Tongling, Anhui, 244000, China.
url: www.akhy.com
Ankerpharm, Cz. See *Chauvin Ankerpharm, Cz.*
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Ankexinxing, China. Ankexinxing Pharmaceutical Co. Ltd, Anhui, China.
Ankom, India. Ankom Laboratories, 201 Tejpal Apartments, Boriwali, Mumbai 400 092, India.
Anlian, China. Anlian Pharmaceutical Co. Ltd., 1-2 Jiangdi Road, Wuxue, Huanggang, Hubei, 435400, China.
url: www.alyy.net.cn
Anmarate, S.Afr. Anmaraté (Pty) Ltd, P.O. Box 9350, George, Western Cape, South Africa.
url: www.anmarate.co.za
Anotaciones, Spain. Anotaciones Farmaceuticas SL, Edificio Forum, Carretera de Rubi a Sant Cugat km 1, No 40-50 6 planta 7 puerta, 08174 Sant Cugat del Valles Barcelona, Spain.
url: www.anotafarm.com
Anpharm, Hung. See *Egis, Hung.*
Anpharm, Irl. Anpharm Ltd, Roscrea, Co. Tipperary, Ireland.
Anpharm, Pol. Anpharm Przedsiębiorstwo Farmaceutyczne, ul. Annopol 6 B, 03-236 Warsaw, Poland.
url: www.anpharm.com.pl
Anpharm, Rus. See *Servier, Rus.*
Anpharm, UK. See *Antigen, UK.*
Anpharm (Ανφαρμ), Gr. ANFARM ELLAS AE, Perikleous 27, 152 32 Chalandri, Greece.
Anphar-Rolland, Fr. See *Merck-Lipha, Fr.*
Ansell, Canad. Ansell Canada Inc., 105 Lauder St, Cowansville, Quebec, J2K 2K8, Canada.
url: www.ansell.com
Ansell, Fr. Ansell SA, 2 bd du Moulin-àvent, B.P. 78395, 95805 Cergy-Pontoise cdx, France.
url: www.anselleurope.com
Ansell, NZ. See *Ebos, NZ.*
Ansheng Kexing, China. Ansheng Kexing Pharmaceutical Co. Ltd., 1885 North Sichuan Road, Hongkou, Shanghai, 200081, China.
url: ke-xing.com
Anstar, Rus. Anstar AG, ul. Oruanskaya D.5 4th floor, Office 401G, 119590 Moscow, Russia.
url: anstar.ch
Antah, Malaysia. Antah Pharma Sdb Bhd, 3 Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.ahcg.com.my
Antai, China. Antai Pharmaceutical Co. Ltd, 19 Lanyan Ave, Shandong, China.
Antares, USA. Antares Pharma Inc., 250 Phillips Blvd, Suite 290, Ewing, USA.
url: www.antarespharma.com
Antec, Singapore. See *Pharmacon, Singapore.*
Antec Dupont, Singapore. See *Pharmacon, Singapore.*
Anthiea, India. Anthiea Labs Pvt Ltd, A-13 Hari Niwas, Virar West, Mumbai 401 303, India.
Anthra, Israel. See *Rafa, Israel.*
Anthrop, Swed. Anthrop Pharmaceuticals AB, Frösundaviks allé 15, 169 70 Solna, Sweden.
url: www.anthroppharma.se
Anthus, India. Anthus Pharmaceuticals Pvt Ltd, 190A Pettukola Towers, P. H. Road, Kilpauk, Chennai 600 010, India.
url: www.anthus.in
Antibiotic, Hung. See *Agrichem, Hung.*
Antibiotici, Gr. Antibiotici, 18 Hilm Leoforo Marathon, 153 00 Pallini Attikis, Greece.
Antibioticos, China. See *ABL, Braz.*
Antibioticos, Mex. Antibióticos de Mexico S.A. de C.V., Las Flores 56, 4380 Coyoacán la Candelaria, Mexico D.F., Mexico.
Antibioticos, Spain. Antibioticos Farma, Ctra M-134 Km 1.5, Alcalá de Henares, 28903 Madrid, Spain.
Antigen, Hong Kong. See *Universal, Hong Kong.*
Antigen, Irl. Antigen Pharmaceuticals Ltd, Monarch Industrial Estate, Belgrade Rd, Tallaght, Dublin 24, Ireland.
url: www.antigenpharma.com
Antigen, Israel. See *Pharmateam, Israel.*
Antigen, NZ. See *Baxter, NZ.*
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Antigen, UK. Antigen Pharmaceuticals Ltd, 82 Waterloo Rd, Southport, Merseyside, PR8 4QW, UK.
url: www.antigenpharma.com
Antipiol, Ital. Laboratorio di Chimica Medica dell' Antipiol S.n.c., Via Chaberton 15, 10156 Turin (TO), Italy.
url: www.antipiol.it
Antistress, Switz. Antistress AG, Gesellschaft fur Gesundheitsschutz, Fluhstrasse 30, 8640 Rapperswil, Switzerland.
url: www.antistress.ch
Antiviral, Rus. Antiviral ZAO, Prof. Popova ul. 15/17, 197376 Saint Petersburg, Russia.
url: www.an-vi.ru
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Antonetto, Ital. Marco Antonetto S.p.A., Via Arsenale 29, 10121 Turin (TO), Italy.
url: www.marcoantonetto.it
Antonetto, Switz. See *Corifel, Switz.*
Antor, Gr. ANTOR, Omirou 4, 151 26 Marousi, Greece.
Antrivex, Ital. Antrivex srl, Via Parmense 12, 47900 Rimini (RN), Italy.
Antula, Denm. See *Antula, Swed.*
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Antula, Norw. See *Antula, Swed.*
Antula, Swed. Antula Healthcare AB, Östermalmsgatan 19, 114 26 Stockholm, Sweden.
url: www.antula.se
Anugerah Pharmindo, Indon. Anugerah Pharmindo Lestari (APL) PT, Jl Pulolentut Kav II E/4, Kawasan Industri Pulogadung, 13920 Jakarta, Indonesia.
url: www.aplcare.com
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url: www.an-vi.ru
Anvik, India. Anvik Biotech, Anvik House, 12 Shivaji Colony, Sonepat 131 001, India.
url: www.anvikbiotech.com
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Ao Dong Yan Bian, China. Ao Dong Yan Bian Pharmaceutical Co. Ltd, Liaoning, China.
Ao Hong, China. Ao Hong Pharmaceuticals Co. Ltd, Jinzhou, China.
Ao Hua, China. Ao Hua Pharmaceutical Co. Ltd, China.
Ao Li Da Nai De, China. Ao Li Da Nai De Pharmaceutical Co Ltd, Heilongjiang, China.
Ao Tuo Kang, China. Ao Tuo Kang Pharmaceutical Group, Ting Yip, Wucheng, Jinhua 321053, Zhejiang, China.
url: www.zjatk.com
Aoda, China. Aoda Pharmaceutical Co. Ltd, LuNan New & High-Tech Zone, YingKou, LiaoNing, 115001, China.
url: www.aoda.com.cn
Aodong Baoyi, China. Aodong Baoyi Pharmaceutical Co. Ltd, Jilin, China.
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Aoer, China. Aoer Pharmaceutical Co. Ltd, Shanxi, China.
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Aolin, China. Aolin Pharmaceutical Co. Ltd, Guilin, China.
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AOP Orphan, Austria. AOP Orphan Pharmaceuticals AG, Wilhelminenstrasse 91/IIf, 1160 Vienna, Austria.
url: www.aoporphan.at
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AOP Orphan, UK. AOP Orphan Pharmaceuticals AG, Lakeside House, 1 Furzeground Way, Stockley Park, Uxbridge, Middlesex, UB11 1BD, UK.
url: www.aoporphan.com
Aosaikang, China. Aosaikang Pharmaceutical Co. Ltd, 699 Kejian Rd, Jiangning Science Park, Nanjing 210012, China.
url: eng.ask-pharm.com
Aoya, China. Aoya Biotechnology Co. Ltd, Hangzhou, China.
Aoyipollen, China. Aoyipollen Pharmaceutical Co. Ltd, 5 Paul Ling Rd, Hangzhou 310022, China.
url: www.aoyipollen.com
AP, USA. AP Pharma, 123 Saginaw Drive, Redwood City, CA 94063, USA.
url: www.appharma.com
AP Oranienburg, Hung. See *Altana, Hung.*
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APC, UK. APC Pharmaceuticals & Chemicals (Europe) Ltd, 9th Floor CP House, 97-107 Uxbridge Rd, Ealing, London, W5 5TL, UK.
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Apex, India. Apex Laboratories Ltd, III Floor, SIDCO Garment Complex, Guindy, Chennai 600 032, India.
url: www.apexlab.com
Apex, Indon. Apex Pharma Indonesia PT, Menara Batavia 12th Floor, Jl KH Mas Mansyur Kav 126, 10220 Jakarta, Indonesia.
Apex, Malaysia. Apex Pharmacy (Marketing) Sdn Bhd, 2 Jln SS13/5, 47500 Subang Jaya, Selangor, Malaysia.
Apex, NZ. Apex Health & Nutrition, P.O. Box 97588, South Aukland Mail Centre, Aukland, New Zealand.
url: www.apexrepel.com
Apex, Singapore. Apex Pharma Marketing Pte Ltd, 12 Jarper Rd 06-00, Sulisam Bldg, S 369677, Singapore.
url: www.apexpharmacy.com.sg
A-Pharma, Denm. A-Pharma ApS, Usserød Kongevej 32, 2970 Hørsholm, Denmark.
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API, NZ. API Consumer Brands, 14-16 Norman Spencer Drive, Manukau City, Auckland 2241, New Zealand.
Apipol, Pol. Apipol-Farma Przedsiębiorstwo Pszczelarsko-Farmaceutyczne, ul. H Cegielskiego 2, 32-400 Myślenice, Poland.
url: www.apipol.com.pl
Apivita, Gr. Apivita SA, 3 Koletti St, 144 52 Metamorfosi Attikis, Greece.
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Aplicaciones Farmacodinamicas, Spain. Laboratorio de Aplicaciones Farmacodinámicas SA, Grassot 16, 08025 Barcelona, Spain.
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url: www.aplicare.com
Apo, USA. Apo-Pharma Inc., 9605 Med Center Drive 390, Rockville, MD 20850, USA.
Apocare, Ger. Apocare Pharma GmbH, Hauptstr. 198, 33647 Bielefeld, Germany.
url: www.apocarepharma.de
Apocare, Neth. See *Apocare, Ger.*
Apofri, Swed. Apofri AB, Box 120, 182 12 Danderyd, Sweden.
Apogepha, Cz. See *Medex, Cz.*
Apogepha, Ger. Apogepha Arzneimittel GmbH, Kyffhäuserstr. 27, 01309 Dresden, Germany.
url: www.apogepha.de
Apogepha, Hong Kong. See *DKSH, Hong Kong.*
Apogepha, Philipp. See *Metro, Philipp.*
Apogepha, Port. See *Apogepha, Ger.*
Apogepha, Singapore. See *Pharmaforte, Singapore.*
Apogepha, Thai. See *Zuellig, Thai.*
Apollo, Canad. Apollo Health & Beauty Care, 20 Graniteridge Rd, Concord, Ontario, L4K 5M8, Canada.
Apolo, Arg. Lab. Apolo S.A., Alem 2967, Santa Fe, Argentina.
Apomedica, Austria. Apomedica GmbH, Roseggerkai 3, A-8011 Graz, Austria.
Aponova, Austria. Aponova Pharma Handels GmbH, Niederhart 100, A-6253 Hart, Austria.
Apostolou, Gr. Eugenia Nicholas Apostolou, Pericles 23, Mati Attikis, Greece.
Apotex, Arg. Apotex SA, Blas Parera 4233/37, (1636) Olivos, Buenos Aires, Argentina.
Apotex, Austral. Apotex Pty Ltd, 66 Waterloo Rd, North Ryde, NSW 2113, Australia.
Apotex, Austria. See *Apotex, Neth.*
Apotex, Belg. SA Apotex NV, Avenue E Demunterlaan 5 bte/bus 8, 1090 Brussels, Belgium.
url: www.apotex.com/be
Apotex, Canad. Apotex Inc., 150 Signet Dr., Weston, Ontario, M9L 1T9, Canada.
url: www.apotex.ca
Apotex, China. Apotex Pharmaceutical Co. Ltd, 3 Jian Guo Men Wai Ave, Beijing 100020, China.
url: www.apotex.com
Apotex, Cz. Apotex ČR sro, Salvátorská 10, 110 00 Prague 1, Czech Republic.
url: www.apotex.cz
Apotex, Denm. See *Orphan, Denm.*
Apotex, Fin. See *Apotex, UK.*
Apotex, Ger. See *Swedish Orphan, Ger.*
Apotex, Gr. See *Help, Gr.*
Apotex, Hong Kong. See *Hind Wing, Hong Kong.*
Apotex, Hung. See *Keri, Hung.*
Apotex, India. Apotex Lifesciences, SCF 30 2nd Floor, Manimajra, Shimla, India.
Apotex, Irl. See *Apotex, UK.*
Apotex, Malaysia. See *Pharmaforte, Malaysia.*
Apotex, Mex. See *Protein, Mex.*
Apotex, Neth. Apotex Europe BV, Darwinweg 20, 2333 CR Leiden, Netherlands.
Apotex, Norw. See *Swedish Orphan, Norw.*
Apotex, NZ. Apotex NZ Ltd, Private Bag 102-995, North Shore Mail Centre, Auckland, New Zealand.
url: www.apotexnz.co.nz
Apotex, Philipp. See *One Pharma, Philipp.*
Apotex, Pol. Apotex Inc., Oddział w Warszawie, ul. Homera 46, 04-624 Warsaw, Poland.
Apotex, Port. See *Apotex, UK.*
Apotex, Rus. See *Sun Ventures, Rus.*
Apotex, S.Afr. Apotex S.A. (Pty) Ltd, C/o Watt and Fleming Streets, Meadowdale Ext. 1, South Africa.
Apotex, Singapore. See *Pharmaforte, Singapore.*
Apotex, Spain. Apotex España SL, C/ Calendula 93, Miniparc III, Edificio G 2a Planta, 28109 El Soto de la Moraleja, Alcobendas, Madrid, Spain.
Apotex, Thai. See *Berlin Pharm, Thai* and *Biogenetech, Thai.*
Apotex, UK. Apotex UK Ltd, 6 Ridgeway Court, Leighton Buzzard, Bedfordshire, LU7 4SF, UK.
url: www.apotex.com
Apotex, USA. Apotex Corp., 50 Lakeview Parkway, Suite 127, Vernon Hills, IL 60061, USA.
url: www.apotexcorp.com
Apotheca, Singapore. Apotheca Marketing Pte Ltd, 63 Hillview Ave, 09-12 Lam Soon Industrial Building, S 669569, Singapore.
url: www.apotheca.com.sg
Apotheca Pacis, Pol. Apotheca Pacis SC, ul. Broniewskiego 23, 44-217 Rybnik-Nowiny, Poland.
Apothecary, USA. Apothecary Products Inc., 11750 12th Ave S, Burnsville, MN 55337, USA.
Apothecon, Neth. Apothecon BV, Nijverheidsweg 3, 3771 ME Barneveld, Netherlands.
Apothecon, USA. See *BMS, USA.*
Apothecus, Canad. See *Apothecus, USA.*
Apothecus, Hong Kong. See *Hind Wing, Hong Kong.*
Apothecus, USA. Apothecus Inc., 20 Audrey Ave, Oyster Bay, NY 11771, USA.
Apotheke Gnadenmutter, Austria. Apotheke zur Gnadenmutter, Hauptplatz 4, A-8630 Mariazell, Austria.
Apotheke Heiligen Dreifaltigkeit, Austria. Apotheke zur Heiligen Dreifaltigkeit, Kirchengasse 5, A-2460 Bruck a. d. Leitha, Austria.

Apotheke Heiligen Rupertus, Austria. Apotheke zum Heiligen Rupertus, Maxglaner Hauptstrasse 13, A-5020 Salzburg, Austria.

Apotheke Roten Krebs, Austria. Apotheke zum Roten Krebs, Lichtensteg 4, A-1011 Vienna, Austria.

APP, Hong Kong. See *LCH, Hong Kong.*

APP, Thai. See *Berli Jucker, Thai.*

APP, USA. APP Pharmaceuticals, 1501 East Woodfield Rd, Suite 300 East, Schaumburg, IL 60173-5837, USA.
url: www.apppharmm.com

APPI, Hong Kong. See *Pharmalink, Hong Kong.*

Approved Drug, USA. See *Health for Life, USA.*

Approved Prescription Services, UK. See *Teva, UK.*

APS, Cz. See *ProStrakan, Ger.*

APS, Ger. See *ProStrakan, Ger.*

APS, Port. Farma-APS Produtos Farmacêuticos SA, Rua João de Deus 19, Venda Nova, 2700-487 Amadora, Portugal.
url: www.farma-aps.com

Apsen, Braz. Apsen Farmacêutica SA, Rua La Paz 37/67, 04755-020 São Paolo, SP, Brazil.
url: www.apsen.com.br

APT, Hong Kong. APT Pharma Ltd, 3/F, 4/F & 6B Tai Fung Industrial Bldg, 61 Hung To Rd, Kwun Tong, Kowloon, Hong Kong.

Aptalis, Canad. See *Axcan, Canad.*

Aptalis, Fr. Aptalis, La Prévôté, Route de Bû, 78550 Houdan, France.
url: www.aptalispharma.com

Aptalis, Ger. See *Aptalis, Fr.*

Aptalis, Neth. See *Aptalis, Fr.*

Aptalis, USA. Aptalis Pharma, 22 Inverness Center Parkway, Birmingham, AL 35242, USA.
url: www.aptalispharma.com

Aqua, USA. Aqua Pharmaceuticals LLC, 158 West Gay St, Suite 310, West Chester, PA 19355, USA.
url: www.aquapharm.com

Aqualife, India. Aqualife Pharmaceuticals, TC 6/1211-6, 1st Floor Hariprabha Towers, Kanjirampara P.O., Thiruvananthapuram, 600 030, India.

Aquamarine, UK. Aquamarine Products Ltd, Unit 2b, Eppingdene, Ivy Chimneys, Epping, Essex, CM16 4EL, UK.

Aquila, S.Afr. Aquila Healthcare, 37 Milner Rd, Woodstock, Western Cape, South Africa.

Aquilea, Spain. Laboratorios Diviser-Aquilea S.L., Pont Reixat 5, Saint Just Desvern, 08960 Barcelona, Spain.
url: www.aquilea.com

AR Scientific, USA. AR Scientific Inc., 1100 Orthodox St, Philadelphia, PA 19124, USA.

Arab, Malaysia. See *Antah, Malaysia.*

Arabis, Spain. Arabis, Gran Vis de les Corts Catalanes 774, 08013 Barcelona, Spain.

Araforma, Spain. Araforma Group, C/Fray Gabriel de San Antonio, Marchamalo, 19180 Guadalajara, Spain.

Aramis, Hung. Aramis Pharma Ltd, Mester u. 28 B III/5, 1095 Budapest, Hungary.
url: www.aramispharma.hu

Arbonne, Canad. See *Arbonne, USA.*

Arbonne, USA. Arbonne International LLC, 9400 Jeronimo Rd, Irvine, CA 92618, USA.

Arbor, USA. Arbor Pharmaceuticals Inc., 4505 Falls of Neuse Rd, Suite 420, Raleigh, NC 27609, USA.
url: www.arborpharma.com

Arbro, India. Arbro Pharmaceuticals Ltd, 6/14 Kirti Nagar, Industrial Area, New Delhi 110 015, India.
url: www.arbropharmaindia.com

Arcana, Austria. Arcana Arzneimittel GmbH, Zimbagasse 5, A-1147 Vienna, Austria.

Archifar, Thai. See *TP, Thai.*

Archimedes, Cz. See *Archimedes, UK.*

Archimedes, Fr. Archimedes Pharma France SARL, 10-12 rue du Sergent Bobillot, 92400 Courbevoie, France.
url: www.archimedespharma.com

Archimedes, Ger. Archimedes Pharma GmbH, Janderstr. 2, 68199 Mannheim, Germany.
url: www.archimedespharma.com

Archimedes, Irl. Archimedes Pharma, Pharmapark, Chapelizod, Dublin 20, Ireland.
url: www.archimedespharma.com

Archimedes, Neth. See *Archimedes, UK.*

Archimedes, Port. See *Archimedes, UK.*

Archimedes, Spain. Archimedes Pharma Ibérica SL, Avenida de Monte Alina 1-A, 28223 Pozuelo de Alarcón, Madrid, Spain.
url: www.archimedespharma.com

Archimedes, UK. Archimedes Pharma UK Ltd, 250 South Oak Way, Green Park, Reading, Berkshire, RG2 6UG, UK.
url: www.archimedespharma.com

Archimedes, USA. Archimedes Pharma US Inc., One Crossroads Drive, Bedminster, NJ 07921, USA.
url: www.archimedespharma.com

Arco, Norw. See *Inpharma, Norw.*

Arco, USA. Arco Pharmaceuticals Inc., 105 Orville Dr., Bohemia, NY 11716, USA.

Arcola, USA. Arcola Laboratories, P.O. Box 1200, Collegeville, PA 19426, USA.

Arcolab, Philipp. See *Metz, Philipp.*

Arcon, Norw. Arcon Norway AS, Frolandsv 6A, 4847 Arendal, Norway.
url: www.arcon-norway.no

Ardana, Denm. See *Pharmacuro, Denm.*

Ardana, Fin. See *Ardana, UK.*

Ardana, Irl. Ardana Ltd, MODE Medical, 10 Sandyford Hall Walk, Dublin 18, Ireland.
url: www.ardana.co.uk

Ardana, Neth. See *Ardana, UK.*

Ardana, Port. See *Ardana, UK.*

Ardana, UK. Ardana Bioscience Ltd, 58 Queen St, Edinburgh, EH2 3NS, UK.
url: www.ardana.co.uk

Ardeapharma, Cz. Ardeapharma as, Třeboňská 229, 373 63 Ševětin, Czech Republic.
url: www.ardeapharma.cz

Arden, Canad. Elizabeth Arden (Canada) Ltd, 505 Apple Creek Blvd, Unit 2, Markham, Ontario, L3R 5B1, Canada.
url: corporate.elizabetharden.com

Ardern, Irl. See *Ardern, UK.*

Ardern, UK. Ardern Healthcare Ltd, Pipers Brook Farm, Eastham, Tenbury Wells, Worcestershire, WR15 8NP, UK.
url: www.ardernhealthcare.com

Ardeypharm, Austria. See *Ardeypharm, Ger.*

Ardeypharm, Cz. See *Ardeypharm, Ger.*

Ardeypharm, Ger. Ardeypharm GmbH, Loerfeldstr. 20, 58313 Herdecke, Germany.
url: www.ardeypharm.de

Ardeypharm, Hung. See *Ardeypharm, Ger.*

Ardeypharm, Switz. See *Medipharm, Switz.*

Ardeypharm, Ukr. See *Farmasoft, Ukr.*

Ardez, Cz. Ardez Pharma sro, Praha, Czech Republic.

Ares, Mex. See *Psicofarma, Mex.*

Ares, Pol. Ares Trading SA, Oddział w Polsce, al. Jana Pawła II 34/10, 00-141 Warsaw, Poland.

Arese, Braz. See *Ativus, Braz.*

Ares-Serono, Austria. See *Serono, Austria.*

Ares-Serono, Cz. See *Serono, Cz.*

Arete, Gr. See *Ariti, Gr.*

Areu, Spain. Areu, Ctra Madrid Valencia, Km 23.5, Arganda del Rey, 28500 Madrid, Spain.

Arex, Venez. Arex Technology, Calle del Arenal Edif. Biotech, Urb. La Trinidad, Caracas, Venezuela.

Argenfarma, Arg. Lab. Argenfarma S.R.L., Llavallol 2649, 1417 Buenos Aires, Argentina.

Arges, Arg. See *Cassara, Arg.*

Argil, India. Argil Life Sciences, B-207, 1st Floor Sector 19, Noida, 201 301, India.

Argon, India. See *Argil, India.*

Ariad, UK. Ariad Pharma Ltd, Brooklands Business Park, Wellington Way, Weybridge, UK.
url: www.ariad.com

Ariad, USA. Ariad Pharmaceuticals Inc., 26 Lansdowne St, Cambridge, MT 02139-4234, USA.
url: www.ariad.com

Arika, India. Arika Healthcare, 310 W-Mall, Manglam Place, Sector-3, Rohini, Delhi 110 085, India.
url: www.arikahealthcare.com

Aringa, Ukr. Aringa, Ukraine.

Aristegui, Spain. See *Ifidesa Aristegui, Spain.*

Aristo, Ger. Aristo Pharma GmbH, Wallenroder Str. 8-10, 13435 Berlin, Germany.
url: www.aristo-pharma.de

Aristo, India. Aristo Pharmaceuticals Ltd, 23-A Shah Industrial Estate, Veera Desai Road, Andheri (W), Mumbai 400 053, India.
url: www.aristopharma.org

Aristo, Philipp. See *Pasteur, Philipp.*

Aristo, Spain. Aristo Pharma Iberia SL, Solana 26, 28850 Torrejon de Ardoz, Madrid, Spain.

Ariston, Arg. Química Ariston S.A.C.I.F., O'Connor 550/5, 1707 V. Sarmiento, Buenos Aires, Argentina.

Ariston, Braz. Ariston Industrias Químicas e Farm. Ltda, Rua Adherbal Stresser 84, 05566-000 São Paulo, SP, Brazil.

Aristopharma, Hong Kong. See *Sincerity, Hong Kong.*

Aristopharma, Singapore. See *Indrugco, Singapore.*

Aristos, USA. The Aristos Group, P.O. Box 684715, Austin, TX 78768, USA.
url: www.aristos.com

Ariti, Gr. ARITI AE, 246 Tatoiou Ave, 136 71 Acharnes, Greece.
url: www.ariti.gr

Arjun, UK. Arjun Products Ltd, Wellington Way, Brooklands Business Park, Weybridge, Surrey, KT13 0TT, UK.
url: www.specialproducts.biz

Ark, China. Ark Pharmaceutical Co Ltd, Room 609, High-tech Three-way CP Building, Xi'an 710075, China.
url: www.arkmed.com

Ark, UK. Ark Therapeutics Ltd, 79 New Cavendish St, London, W1W 6XB, UK.
url: www.arktherapeutics.com

Arkadia, Ital. Arkadia Pharma Srl, Via Soresina 11, 20144 Milano (MI), Italy.

Arko, Ger. See *Arkopharma, Fr.*

Arko Diffusion, Switz. Arko Diffusion SA, 5 d Route des Jeunes, 1211 Geneva 26, Switzerland.

Arkochim, Spain. Arkochim España, Meneses 2, 28045 Madrid, Spain.
url: www.arkochim.es

Arkofarm, Ital. Arkofarm S.r.l., Via Maneira 17/C - Frazione Bevera, 18039 Ventimiglia (IM), Italy.
url: www.arkopharma-italia.com

Arkomedika, Fr. See *Arkapharma, Fr.*

Arkopharma, Austria. See *Arkopharma, Fr.*

Arkopharma, Belg. Arkopharma, Edisonlaan 13, 1300 Wavre, Belgium.
url: www.arkopharma.be

Arkopharma, Denm. See *Arkopharma, Fr.*

Arkopharma, Fr. Laboratoires Arkopharma, B.P. 28, 06511 Carros cdx, France.
url: www.arkopharma.com

Arkopharma, Hong Kong. See *Primal, Hong Kong.*

Arkopharma, Israel. See *Guri, Israel.*

Arkopharma, Neth. See *Arkopharma, Fr.*

Arkopharma, Port. See *Arkopharma, Fr.*

Arkopharma, Singapore. See *Indrugco, Singapore.*

Arkopharma, Spain. Arkopharma SA, C/Amaltea 9, 2a planta, 28045 Madrid, Spain.

Arkopharma, Switz. See *Naturpharma, Switz.*

Arkopharma, UK. Arkopharma UK Ltd, 6 Redlands Centre, Redlands, Coulsden, Surrey, CR5 2HT, UK.
url: www.arkopharma.com

Arla, Fin. Oy Arla Foods AB, PL 91, 00401 Helsinki, Finland.

Arlak, India. Arlak Biotech, 1st Floor SCO 11, Puri Market Near 22 No, Fatak Patiala, Punjab 147 001, India.

Arlex, Mex. Arlex de México, S.A.deC.V., Puerto Acapulco No.35, Col. Piloto, Deleg. Alvaro Obregon, 01290 Mexico D.F., Mexico.

Arlor, Fr. Lab Arlor, 92-94 avenue Jean-Baptiste-Lebas, 59051 Roubaix cdx 1, France.
url: www.alpharegul.com

Arma, Turk. Arma İlac San.ve Tic. Ltd, Turkey.

Armavir, Rus. See *Pharmasoft, Rus.*

Armedica, Gr. Armedica AE, Ag. Marcellis 17, 118 55 Athens, Greece.

Armedica, Rus. See *Gedeon Richter, Rus.*

Armkel, Switz. See *Doetsch, Grether, Switz.*

Armour, Ger. See *CSL, Ger.*

Armour, India. Armour Remedies India Ltd, 56-C Udham Singh Nagar, Civil Lines, Ludhiana 141 001, Punjab, India.

Armour, Israel. See *Sanofi-Aventis, Israel.*

Armour, UK. See *ZLB, UK.*

Armour, USA. See *CSL, USA.*

Armoxindo, Indon. Armoxindo Farma PT, Jl Arjuna No 28, Tanjung Duren, Jakarta Barat 11470, Indonesia.

Armstrong, Arg. Lab. Armstrong S.A.C.I.F., Joaquin V. Gonzalez 653, 1407 Buenos Aires, Argentina.

Armstrong, Mex. Armstrong Laboratorios de Mexico S.A. de C.V., Periférico Sur No. 6677-1er Piso, Col. Ejidos de Tepepan, Deleg. Xochimilco, 16018 Mexico D.F., Mexico.
url: www.lab-armstrong.com.mx

Aroli-Aromes, Fr. Aroli-Aromes Ligeriens Jean d'Aveze, 2 rue Georget, 37000 Tours, France.

Aroma, Turk. Aroma İlaç Sanayi Ltd. Şti., Abdi İpekçi Cad., Özel İdare İş Merakezi K:2 No. 201, Bayrampaşa, İstanbul, Turkey.

Aroma Femi, Israel. Aroma Femi, P.O. Box 8418, Moshav Magshimim, 56910, Israel.

Aromapharm, Irl. Aromapharm Ireland Ltd, Regus House, Harcourt Rd, Dublin 2, Ireland.

Aron, Fr. See *Merck-Lipha, Fr.*

Aronex, India. Aronex Life Sciences Pvt Ltd, 217 Platinum Plaza, Near Judges Bunglows, Bodakdev, Ahmedabad 380 054, India.

Aropharma, Canad. Aropharma Inc., 4569 Bismark Crescent, Mississauga, Ontario, L5R 1K1, Canada.

Arovet, Switz. Arovet AG, Binderstrasse 49, 8702 Zollikon-Station, Switzerland.

Arriani, Gr. Arriani Pharmaceuticals SA, 85 Lavriou Ave, 190 02 Peania, Athens, Greece.

Arrow, Austral. Arrow Pharmaceuticals Ltd, P.O. Box 397, Surry Hills, NSW 2010, Australia.
url: www.arrowpharma.com

Arrow, Braz. Arrow Farmacêutica SA, Rua Barão de Petrópolis 311, 20251061 Rio de Janeiro, Rio de Janeiro, Brazil.

Arrow, Canad. Arrow OTC Inc., 6500 Kitimat Rd, Mississauga, Ontario, L5N 2B8, Canada.

Arrow, Cz. See *Arrow, UK.*

Arrow, Denm. Arrow Pharma ApS, Sankt Peders Straede 2, 1, 4000 Roskilde, Denmark.
url: www.watson.com

Arrow, Fin. See *Arrow, UK.*

Arrow, Fr. Arrow, France.

Arrow, Hong Kong. See *LCH, Hong Kong.*

Arrow, Hung. See *Arrow, UK.*

Arrow, Irl. See *Selamine, Irl.*

Arrow, Ital. See *Arrow, Denm.*

Arrow, Neth. See *Arrow, UK.*

Arrow, Norw. Arrow Generics, Idrettsv. 11, 1401 Ski, Norway.

Arrow, NZ. Arrow Pharmaceuticals (NZ) Ltd, 33a Normanby Rd, Mt Eden, Auckland, New Zealand.

Arrow, Pol. Arrow Poland, al. Jana Pawla II 23, 00-854 Warsaw, Poland.

Arrow, S.Afr. Arrow Pharma South Africa Pty Ltd, 1 Stirrup Lane, Woodmead Office Park, Van Reenans Ave, Woodmead 2052, Gauteng, South Africa.
url: www.arrowgenerics.com

Arrow, Swed. Arrow Läkemedel AB, Nybrogatan 59, 114 40 Stockholm, Sweden.

Arrow, UK. Arrow Generics Ltd, Unit 2 Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK.

Arrowblue, Port. Arrowblue Produtos Farmacêuticos SA, Av. D João II, Torre Fernão de Magalhães 10 Esq., Sonta Maria dos Olivais, 1998-025 Lisbon, Portugal.

Arrowin, India. Arrowin Pharmaceuticals, P No 9/503 Kanchan Tower, Section-25, Nerul, Navi Mumboi 400 076, India.

Ars, Ital. See *San Carlo, Itol.*

Ars Vitae, Switz. Ars Vitae AG, Dellenbodenweg 8, 4452 Itingen, Switzerland.
url: www.arsvitae.ch

Arsalud, Spain. See *Sanofi-Aventis, Spain.*

Arsmedendi, Gr. Arsmedendi, Valaoritou 7, 152 32 Chalandri, Greece.

Artecef, Neth. Artecef BV, Schepenveld 41, 3890 BB Zeewolde, Netherlands.
url: www.artecef.nl

Artegodan, Ger. Artegodan GmbH, Wendlandstrasse 1, 29439 Lüchow, Germany.

Arterium, Rus. See *Arterium, Ukr.*

Arterium, Ukr. Arterium Corporation, Saksaganskogo Street, 139, Kiev, 01032, Ukraine.
url: www.arterium.ua

Artesa, USA. Artesa Labs LLC, 137585 Research Blvd, Suite 125, Austin, TX 78750, USA.
url: artesalabs.com

Artesan, Cz. See *Artesan, Ger.*

Artesan, Ger. Artesan Pharma GmbH & Co. KG, Wendlandstr. 1, 29439 Lüchow, Germany.
url: www.ortesan.de

Artesan, Switz. See *Lubapharm Arlesheim, Switz.*

Artex, NZ. Artex Ltd, P.O. Box 249, Waipukurau, New Zealand.

Arti, Pol. See *Blau, Pol.*

Artis, Spain. See *Novartis, Spain.*

Artropharm, Norw. See *Algol, Norw.*

Artu, Neth. Artu Biologicals Europe BV, Vijzelweg 11, 8243 PM Lelystad, Netherlands.

Artur, Ukr. Artur-K FC Ltd, ul V Chaika 4, 08130 Kiev, Ukraine.
url: www.arturk.com.ua

Arun, UK. Arun Pharmaceuticals Ltd, Unit 37, Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.

Arunabh, India. Arunabh Pharma, RZ Dabri Extension East, Opp. Gopal Mandir, Near Janak puri, New Delhi, India.

Arvincare, India. Arvincare Healthcare, 315 Phase 2 Industrial Area, Panchkula, Haryana 134 119, India.
url: www.indiamart.com

AS, India. AS Pharmaceutical, 20 (Old 47) Dasan Rd, Teynampet, Chennai, 600 018, India.
url: www.aspharma.org

ASAC, Spain. A.S.A.C. Pharma, Sagitario 14, 03006 Alicante, Spain.
url: www.asac.net

Asahi, China. Asahi Kasei Pharma Corp., NCI Building, Room 1407A, 12 Jian Guo Men Wai Ave, Beijing, 100022, China.

Asahi, Jpn. Asahi Kasei Pharma, 1-105 Kanda Jinbocho, Chiyoda-ku, Tokyo 101-8101, Japan.
url: www.asahi-kasei.co.jp

Ascend, USA. Ascend Therapeutics Inc., 607 Herndon Pkwy, Suite 210, Herndon, VA 20170, USA.
url: www.ascendtherapeutics.com

Ascende Medz, Philipp. Ascende Medz Phils Inc., Suite 2207 Antel Global Corporate Ctr, Julia Vargas Ave, Ortigas Ctr, Pasig City, Philippines.

Ascent, Austral. Ascent Pharmaceuticals, 151-153 Clarendon St, South Melbourne, Victoria 3205, Australia.
url: www.ascentpharma.com.au

Ascent, USA. Ascent Pediatrics Inc., 187 Ballardvale St, Suite B125, Wilmington, MA 01887, USA.
url: www.ascentpediatrics.com

Asche, Ger. See *Chiesi, Ger.*

Asche Chiesi, Ger. See *Chiesi, Ger.*

Ascher, USA. B.F. Ascher & Co., 15501 W 109th St, Lenexa, KS 66219, USA.

Asclepius, India. Asclepius Remedies, LG-1 Pankaj Central Market, Local Shopping Centre Ip Extn, Patparganj, New Delhi 110 092, India.

Asconex, Ger. Asconex Arzneimittelvertriebs GmbH, Kapellenstr. 18, 65606 Villmar, Germany.
url: www.asconex.de

ASD Pharma, Fr. Laboratoires ASD Pharma, 13 rue Saint-Honoré, 78000 Versailles, France.

Asepta, Mon. Laboratoires Asepta, 17 bd Prince-Héréditaire-Albert, MC 98000, Monaco.
url: www.asepta.com

Aset, Turk. See *Sanovel, Turk.*

Asetris, Switz. Asetris SA, Via Nassa/Piazza Maraini, 6901 Lugano, Switzerland.
url: www.pillola.com

Asfarma, Ukr. Asfarma International Pharmamarketing, Timoshenko 21, Kiev, 04210, Ukraine.
url: www.asfarma.com

Ashaninka, Hung. Ashaninka Kft, Fehér Ló u. 10, 1112 Budapest, Hungary.

Ashbourne, UK. See *Sinclair, UK.*

Ashford, Philipp. See *Celsus, Philipp.*

Ashford, Singapore. See *FP, Singapore.*

ASI, Hung. ASI Budapest Kft, Üllői u 91/b I/7, 1091 Budapest, Hungary.

ASI, Israel. ASI Pharma Ltd, 50 Bazel St, Herzliya Pituach, Israel.

Asia Pacific, Hong Kong. See *Pharmalink, Hong Kong.*

Asia Pacific, Philipp. PL Asia Pacific (Phils) Inc., 26/F AXA Life Bldg, Ayala Ave Ext, Makati City, Philippines.

Asia Pharma, Malaysia. See *Summit, Malaysia.*

Asia Pharma, Philipp. See *Corbridge, Philipp.*

Asia Pioneer, China. Asia Pioneer, 1146 West Yan'an Rd, 200052 Shanghai, China.
url: www.asiapioneer.com.cn

Asian Pharm, Thai. Asian Pharmaceutical Ltd Part, 9/4 Soi Wathanawong, Rajprarob Rd, Rajthavee, Bangkok 10400, Thailand.

Asian TJD, Thai. Asian TJD Enterprise Ltd, 90 Soi Ladprao 91 (Kesorn), Ladprao Rd, Wangthonglang Dist, Bangkok 10310, Thailand.

Asian Union, Thai. Asian Union Laboratories Co Ltd, 203 Suksawad Rd, Pakklongbangpakod, Phra Samut Chedi, SamutPrakan 10290, Thailand.

Asiapharm, Malaysia. See *Apex, Malaysia.*

Asiapharm, Singapore. See *Steward Cross, Singapore.*

Aska, Jpn. ASKA Pharmaceutical Co. Ltd, 5-1 Shibaura 2-chome, Minato-ku, Tokyo 108-8532, Japan.
url: www.aska-pharma.co.jp

Askit, UK. Askit Laboratories Ltd, 47 Deerdykes View, Westfield, Cumbernauld, Glasgow, G68 9HN, UK.

ASL, Canad. ASL International Enr., 1495 rue Evergreen, St-Bruno, Quebec, J3V 4C6, Canada.

Asmeco, Thai. See *Zuellig, Thai.*

Asmopul, Arg. Lab. Asmopul S.A., Independencia 4030, 1226 Buenos Aires, Argentina.

Asofarma, Arg. Lab. Asofarma S.A., Av. Cabildo 159, 1426 Buenos Aires, Argentina.

Asofarma, Mex. Asofarma de Mexico S.A. de C.V., Calz. Mexico-Xochimilco No. 43, Col. San Lorenzo Huipulco, Deleg. Tlalpan, 14370 Mexico D.F., Mexico.
url: www.asofarma.com.mx

Aspar, Irl. See *Aspar, UK.*

Aspar, UK. Aspar Pharmaceuticals Ltd, 29-30 Capitol Way, Capitol Way Industrial Estate, Colindale, London, NW9 0EQ, UK.

Aspen, Arg. Lab. Aspen S.A., Remedios 3439/43, 1407 Buenos Aires, Argentina.

Aspen, Austral. Aspen Pharmacare Australia P/L, Suite 3, 34-36 Chandos St, St Leonards, NSW 2065, Australia.
url: www.aspenpharma.com.au

Aspen, Austria. See *Aspen, Ger.*

Aspen, Braz. Aspen Pharma Industria Farmaceutica Ltda, Av. das Américas 3.500, Bl. 3 Tor 2000, 22640102 Rio de Janeiro, Brazil.

Aspen, Cz. See *GSK, Cz.*

Aspen, Fin. See *Aspen, Ger.*

Aspen, Ger. Aspen Europe GmbH, Industriestr. 32-36, 23843 Bad Oldesloe, Germany.
url: www.aspenpharma.com

Aspen, Hong Kong. Aspen Asia Co Ltd, Room 23, 23/4 One Island East, 18 Westlands Rd, Quarry Bay, Hong Kong.
url: www.aspenpharma.com

Aspen, Hung. See *Aspen, Ger.*

Aspen, Irl. Aspen Pharma Trading Ltd, 12/13 Exchange Place, Dublin 1, Ireland.

Aspen, Malaysia. See *Averroes, Malaysia.*

Aspen, Mex. Aspen Laboratorios SA de CV, Monte Elbruz 124-4, 11590 Miguel Hidalgo Palmitas Polanco, Mexico.

Aspen, Neth. See *Aspen, Ger.*

Aspen, Norw. See *Orion, Norw* and *Vitaflo, Norw.*

Aspen, NZ. See *Healthcare Logistics, NZ.*

Aspen, Pol. See *GSK, Pol* and *PharmaSwiss, Pol.*

Aspen, Port. See *Aspen, Ger.*

Aspen, S.Afr. Aspen Pharmacare, Aspen Park, 98 Armstrong Ave, La Lucia Ridge, Durban 4019, South Africa.
url: www.aspenpharma.com

Aspen, Singapore. See *Zuellig, Singapore.*

Aspen, Spain. See *Aspen, Irl.*

Aspen, Thai. See *Diethelm, Thai.*

Aspen Consumer, S.Afr. See *Aspen, S.Afr.*

Aspen Medical, UK. Aspen Medical Europe Ltd, Thornhill Rd, North Moons Moat, Redditch, Worcestershire, B98 9NL, UK.

Aspid, Mex. Aspid, S.A. de C.V., Belgica No. 518, Col. Portales, 03300 Mexico D.F., Mexico.
url: www.fibroquel.com

Aspire, Irl. See *Aspire, UK.*

Aspire, UK. Aspire Pharma Ltd, Antrobus House Business Centre, 18 College St, Petersfield, GU31 4AD, UK.
url: www.aspirepharma.co.uk

Aspro-Nicholas, Austria. See *Roche, Austria.*

Assistance, Arg. Assistance S.R.L., Av. Cordoba 950 Piso 13 A, 1954 Buenos Aires, Argentina.

Associated Hospital Supply, UK. Associated Hospital Supply, Sherwood Rd, Aston Fields, Bromsgrove, Worcestershire, B60 3DR, UK.

Associated Medical, Hong Kong. Associated Medical Supplies Co. Ltd, Rm 1201, Fo Tan Industrial Ctr, 26 Au Pui Wan St, Fo Tan, N.T., Hong Kong.

Associated National Brokerage, Canad. Associated National Brokerage Inc., 120 Harry Walker Parkway N, Newmarket, Ontario, L3Y 7B2, Canada.
url: www.anbcanada.com

Assos, Turk. Assos İlaç San ve. Tic. Ltd. Şti., Acibadem Cad., Erdem Sok. No. 2/12, Axibadem, Istanbul, Turkey.

Assper, Mex. Assper Basser SA de CV, Temistocles 23 Desp. 5, 11560 Polanco, Mexico DF, Mexico.

Asta, Denm. See *Viatris, Swed.*

Asta, Gr. See *Baxter, Gr.*

Asta Medica, Arg. See *Kampel Martian, Arg.*

Asta Medica, Austria. See *Viatris, Austria.*

Asta Medica, Belg. See *Viatris, Belg.*

Asta Medica, Canad. See *Baxter, Canad.*

Asta Medica, Cz. Asta Medica sro, Čistovicka 11/249, 163 00 Prague 6, Czech Republic.
url: www.astamedica.cz

Asta Medica, Denm. See *Viatris, Swed* and *AstraZeneca, Denm.*

Asta Medica, Fin. See *Viatris, Swed.*

Asta Medica, Fr. See *Viatris, Fr.*

Asta Medica, Ger. See *Baxter Oncology, Ger* and *Viatris, Ger.*

Asta Medica, Hong Kong. See *Unico, Hong Kong.*

Asta Medica, Hung. See *Baxter, Hung* and *Pliva, Hung.*

Asta Medica, Indon. Asta Medica, Indonesia.

Asta Medica, Irl. See *Meda, UK.*

Asta Medica, Israel. See *Megapharm, Israel.*

Asta Medica, Ital. See *Meda, Ital.*

Asta Medica, Malaysia. See *JDH, Malaysia* and *Zuellig, Malaysia.*

Asta Medica, Neth. See *Viatris, Neth.*

Asta Medica, Norw. See *Viatris, Swed.*

Asta Medica, NZ. See *NZ Medical & Scientific, NZ.*

Asta Medica, Port. See *Viatris, Port.*

Asta Medica, Rus. See *Pliva, Rus.*

Asta Medica, Singapore. See *JDH, Singapore.*

Asta Medica, Spain. See *Viatris, Spain.*

Asta Medica, Swed. See *Viatris, Swed.*

Asta Medica, Switz. See *Viatris, Switz.*

Asta Medica, Thai. See *Zuellig, Thai.*

Asta Medica, UK. See *Meda, UK.*

Asta Medica, USA. See *Muro, USA.*

Asta Oncologia, Braz. Asta Medica Oncologia Ltda, Rua Eng. Franisco Pitta Brito 779, 4753080 São Paulo, Brazil.

Astellas, Austria. Astellas Pharma GmbH, Linzerstrasse 221/E0.2, A-1140 Vienna, Austria.

Astellas, Belg. Astellas Pharma Belux, Square Marie Curie 50/1, Building 5, 1070 Brussels, Belgium.
url: www.astellas-europe.co.uk

Astellas, Braz. Astellas Farma Brasil Imp. e Distr. de Med. Ltda, Av. Das Nações Unidas, 14171 Torre B-Sal, 4794000 São Paulo, Brazil.

Astellas, Canad. Astellas Pharma Canad Inc., 1000 625 Cochrane Drive, Markham, Ontario, L3R 9R9, Canada.

Astellas, China. Astellas Pharma China Inc., SK Building Room 1901-1904, 6 Jian Guo Men Wai Ave, Chaoyang District, Beijing 100022, China.

Astellas, Cz. Astellas Pharma sro, Sokolovská 100/94, 18600 Praja 8, Czech Republic.

Astellas, Denm. Astellas Pharma a/s, Naverland 4, 2600 Glastrup, Denmark.
url: www.astellas-europe.co.uk

Astellas, Fin. See *Algol, Fin.*

Astellas, Fr. Astellas Pharma, 114 rue Victor-Hugo, 92300 Levallois-Perret, France.
url: www.astellas-europe.co.uk

Astellas, Ger. Astellas Pharma GmbH, Georg-Brauchle-Ring 64-66, 80992 Munich, Germany.
url: www.astellas.com/de

Astellas, Gr. Astellas Pharma A.B., 10th Klm National Rd, Metamorfosi, 144 51 Lamia, Greece.
url: www.astellas-europe.co.uk

Astellas, Hong Kong. Astellas Pharma Hong Kong Co Ltd, Suite 708-09, 7/F Prudential Twr, The Gateway, Harbour City, Kowloon, Hong Kong.

Astellas, Hung. Astellas Pharma Kft, Kelenhegyi út 43, 1118 Budapest, Hungary.
url: www.astellas-europe.co.uk

Astellas, Indon. Astellas Pharma Indonesia PT, Kyoei Prince Bldg 11/F, Jl Jend Sudirmman Kav 3, Jakarta 10220, Indonesia.

Astellas, Irl. Astellas Pharma Co., Ltd (Ireland), 25 The Courtyard, Kilcarberry Business Park, Clondalkin, Dublin 22, Ireland.
url: www.astellas-europe.co.uk

Astellas, Israel. See *Medison, Israel.*

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url: www.astellas-europe.co.uk

Astellas, Jpn. Astellas Pharma Inc., 17-1 Hasune 3-chome, Tokyo, Japan.

Astellas, Neth. Astellas Pharma BV, Elisabethhof 19, 2353 EW Leiderdorp, Netherlands.

Astellas, Norw. Astellas Pharma, Solbrav 47, 1383 Asker, Norway.
url: www.astellas-europe.co.uk

Astellas, Philipp. See *Zuellig, Philipp.*

Astellas, Pol. Astellas Pharma Sp. zo.o., ul. Poleczki 21, 02-822 Warsaw, Poland.

Astellas, Port. Astellas Farma Lda, Edifício Cinema, Rua José Fontana 1, 1 Andar, 2770-101 Paco de Arcos, Portugal.

Astellas, Rus. Astellas Pharma Europe BV, Marksistskaya St 16, Business Centre Mosalarko Plaza 1, et. 3, 109147 Moscow, Russia.

Astellas, S.Afr. Astellas Pharma (Pty), Gillooly View Office Park, Block A, First Floor, 5 Osborne Lane. Bedfordview, Johannesburg, South Africa.
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Astellas, Spain. Astellas Pharma, Centro Empresarial La Finca, Paseo. del Club Deportivo, n: 1, Bloque 14, 2 planta, 28223 Pozuelo de Alarcsn (Madrid), Spain.
url: www.astellas-europe.co.uk

Astellas, Swed. Astellas Pharma AB, Haraldsgatan 5, 431 14 Goteborg, Sweden.

Astellos, Switz. Astellas Pharma AG, Route de Moncor 10, 1752 Villars-sur-Gläne, Switzerland.

Astellas, Thai. Astellas Pharma (Thailand) Co Ltd, 10 Fl, Wave Place, 55 Wireless Rd, Lumpini, Patumwan, Bangkok 10330, Thailand.

Astellas, UK. Astellas Pharma Ltd, Lovett House, Lovett Rd, Staines, Middlesex, TW18 3AZ, UK.
url: www.astellas-europe.co.uk

Astellas, Ukr. Astellas Pharma Europe B.V., Glubochitskaya Street, 4, Kiev, 04050, Ukraine.

Astellas, USA. Astellas Pharma US Inc., 3 Parkway North, Deerfield, IL 60015, USA.
url: www.astellas.com

Astier, Fr. See *Beaufour, Fr.*

Astley, Canad. David Astley & Co Inc., 30154 Township Rd 250, Calgary, Alberta, T3Z 1L5, Canada.

Astra, Austral. See *AstraZeneca, Austral.*

Astra, Austria. See *AstraZeneca, Austria.*

Astra, Belg. See *AstraZeneca, Belg.*

Astra, Braz. See *AstraZeneca, Braz.*

Astra, Canad. See *AstraZeneca, Canad.*

Astra, Denm. See *AstraZeneca, Denm.*

Astra, Fr. See *AstraZeneca, Fr.*

Astra, Ger. See *AstraZeneca, Ger.*

Astra, Gr. See *AstraZeneca, Gr.*

Astra, Hong Kong. See *AstraZeneca, Hong Kong.*

Astra, Irl. See *AstraZeneca, Irl.*

Astra, Israel. See *Teva, Israel.*

Astra, Ital. See *AstraZeneca, Ital.*

Astra, Jpn. See *AstraZeneca, Jpn.*

Astra, Mex. See *AstraZeneca, Mex.*

Astra, Neth. See *AstraZeneca, Neth.*

Astra, Norw. See *AstraZeneca, Norw.*

Astra, Port. See *AstraZeneca, Port.*

Astra, S.Afr. See *AstraZeneca, S.Afr.*

Astra, Spain. See *AstraZeneca, Spain.*

Astra, Swed. See *AstraZeneca, Swed.*

Astra, Switz. See *AstraZeneca, Switz.*

Astra, UK. See *AstraZeneca, UK.*

Astra, USA. See *AstraZeneca, USA.*

Astra Merck, USA. See *AstraZeneca, USA.*

Astra Tech, Norw. Astra Tech AS, Luhrtoppen 2, Postboks 160, 1471 Lørenskog, Norway.
url: www.astratech.no

Astrofarm, Ukr. Astrofarm, Vyshneve, Kiev, Ukraine.

Astrapin, Ger. See *Hameln, Ger.*

Astrapin, Malaysia. See *Propharm, Malaysia.*

Astrapin, Philipp. See *PharmAsia, Philipp.*

AstraZeneca, Arg. AstraZeneca Argentina S.A., Argerich 536, 1706 Haedo, Buenos Aires, Argentina.
url: www.astrazeneca.com

AstraZeneca, Austral. Astrazeneca P/L, P.O. Box 131, North Ryde, NSW 1670, Australia.
url: www.astrazeneca.com.au

AstraZeneca, Austria. AstraZeneca Österreich GmbH, Schwarzenbergplatz 7, A-1037 Vienna, Austria.
url: www.astrazeneca.com

AstraZeneca, Belg. AstraZeneca Pharmaceuticals SA, Rue Egide Van Ophem 110, 1180 Brussels, Belgium.
url: www.astrazeneca.be

AstraZeneca, Braz. AstraZeneca do Brasil Ltda, Rod Raposo Tavares km 26.9, 06714-025 Cotia Moinho Velho, SP, Brazil.
url: www.astrazeneca.com.br

AstraZeneca, Canad. AstraZeneca Canada Inc., 1004 Middlegate Rd, Mississauga, Ontario, L4Y 1M4, Canada.
url: www.astrazeneca.ca

AstraZeneca, Chile. AstraZeneca de Chile Ltda, Francisco de Paula Taforo 1081, Nunoa, Santiago, Chile.

AstraZeneca, China. AstraZeneca Trading Co Ltd, 43/F CITIC Square, 1168 Nan Jing Xi Road, Shanghai 200041, China.
url: www.astrazeneca.com

AstraZeneca, Cz. AstraZeneca Czech Republic sro, IBC Building, Pobřežní 3, 186 00 Prague 8, Czech Republic.
url: www.astrazeneca.cz

AstraZeneca, Denm. AstraZeneca A/S, Roskildevej 22, 2620 Albertslund, Denmark.
url: www.astrazeneca.dk

AstraZeneca, Fin. AstraZeneca Oy, Luomanportti 3, 02200 Espoo, Finland.
url: www.astrazeneca.fi

AstraZeneca, Fr. AstraZeneca, 1 place Renault, 92844 Rueil-Malmaison cdx, France.
url: www.astrazeneca.fr

AstraZeneca, Ger. AstraZeneca GmbH, Tinsdaler Weg 183, 22880 Wedel, Germany.
url: www.astrazeneca.de

AstraZeneca, Gr. ASTRA-ZENECA, P.O. Box 62042, 152 01 K. Halandri, Greece.
url: www.astrazeneca.com

Astra-Zeneca, Gr. See *AstraZeneca, Gr.*

AstraZeneca, Hong Kong. AstraZeneca Hong Kong Ltd, 2301 Cosco Tower, Grand Millenium Plaza, 183 Queen's Rd Central, Hong Kong.
url: www.astrazeneca.com

AstraZeneca, Hung. AstraZeneca Kft, Park u 3, 2045 Törökbálint, Hungary.

AstraZeneca, India. AstraZeneca Pharma India Ltd, Bellary Road, Hebbal, Bangalore 560 024, India.
url: www.astrazenecaindia.com

AstraZeneca, Indon. AstraZeneca, Perkantoran Hijau Arkadia, Tower C 11th Fl., Jl TB Simatupang Kav 88, Jakarta 12520, DKI Jaya, Indonesia.

AstraZeneca, Irl. AstraZeneca, College Park House, 20 Nassau St, Dublin 2, Ireland.
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AstraZeneca, Israel. See *Teva, Israel.*

AstraZeneca, Ital. AstraZeneca S.p.A., Via F. Sforza - Palazzo Volta, 20080 Basiglio (MI), Italy.
url: www.astrazeneca.it

AstraZeneca, Jpn. AstraZeneca K.K., 1-1-88 Oyodonaka, Kita-ku, Osaka 531-0076, Japan.
url: www.astrazeneca.co.jp

AstraZeneca, Malaysia. AstraZeneca Malaysia Sdn Bhd, 17 Jln Sri Semantan Satu, Damansara Heights, 50490 Kuala Lumpur, Malaysia.
url: www.astrazeneca.com

AstraZeneca, Mex. AstraZeneca S.A. de C.V., Super Avenida Lomas Verdes No. 67, 53120 Naucalpan de Juarez, Mexico.
url: www.astrazeneca.com

AstraZeneca, Neth. AstraZeneca Pharmaceutica BV, Postbus 599, 2700 AN Zoetermeer, Netherlands.
url: www.astrazeneca.nl

AstraZeneca, Norw. AstraZeneca AS, Hoffsv 70 B, Postboks 200 Vinderen, 0319 Oslo, Norway.
url: www.astrazeneca.no

AstraZeneca, NZ. AstraZeneca Ltd, P.O. Box 1301, Auckland, New Zealand.
url: www.astrazeneca.com

AstraZeneca, Philipp. AstraZeneca Pharmaceuticals (Phils) Inc., Km 14, South Superhighway, Parañaque City, Philippines.

AstraZeneca, Pol. AstraZeneca Pharma Poland Sp. zo.o., ul. Postepu 18, 02-676 Warsaw, Poland.
url: www.astrazeneca.pl

AstraZeneca, Port. AstraZeneca - Produtos Farmacêuticos, Lda, Rua Humberto Madeira 7, Valejas, 2745-663 Barcarena, Portugal.
url: www.astrazeneca.com

AstraZeneca, Rus. AstraZeneca Russia, Timura Frunze ul. 11, Str. 2-5, 1190211 Moscow, Russia.
url: www.astrazeneca.ru

AstraZeneca, S.Afr. AstraZeneca Pharmaceuticals, Private Bag X30, Sunninghill 2157, South Africa.
url: www.astrazeneca.com

AstraZeneca, Singapore. AstraZeneca Singapore Pte Ltd, 6 Temasek Boulevard, 06-01 Suntec Tower Four, S 038986, Singapore.
url: www.astrazeneca.com

AstraZeneca, Spain. AstraZeneca Farmaceutica Spain, Parque Norte Ed Roble, C/Serrano Galvache 56, 28033 Madrid, Spain.
url: www.astrazeneca.es

AstraZeneca, Swed. AstraZeneca Sverige AB, Storgatan 42, 151 85 Södertälje, Sweden.
url: www.astrazeneca.se

AstraZeneca, Switz. AstraZeneca AG, Grafenau 10, 6301 Zug, Switzerland.
url: www.astrazeneca.ch

AstraZeneca, Thai. AstraZeneca (Thailand) Ltd, 20 Fl, Phairojkijja Building, 400 Bangna-Trad Km 4, Bangkok 10260, Thailand.
url: www.astrazeneca.co.th

AstraZeneca, Turk. AstraZeneca İlaç San. ve. Tic. Ltd. Şti., Yapi Kredi Plaze B Blok Kat: 4, Levent, İstanbul, 34330, Turkey.
url: www.astrazeneca.com.tr

AstraZeneca, UK. AstraZeneca UK Ltd, Horizon Place, 600 Capability Green, Luton, Bedfordshire, LU1 3LU, UK.
url: www.astrazeneca.co.uk

AstraZeneca, Ukr. AstraZeneca, Frunze Street, 1-3, Block C, office 32, Kiev, 04080,, Ukraine.
url: www.astrazeneca.com

AstraZeneca, USA. AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA.
url: www.astrazeneca-us.com

AstraZeneca, Venez. AstraZeneca Venezuela S.A., Avenida Principal de la Castellana, c/calle José Angel Lamas Torre, La Castellana, Caracas 1062, Venezuela.
url: www.astrazeneca.com.ve

Astro, Austria. Astro Pharma GmbH, Allerheiligenplatz 4, A-1200 Vienna, Austria.

Asubio, Jpn. Asubio Pharma Co. Ltd, 3F Orix Akasaka 2-chome Building 9-11, Akasaka 2-chome, Minato-ku, Tokyo 107-8541, Japan.
url: www.asubio.co.jp

Atabay, Turk. Atabay İlaç Fobrikasi San. ve. Tic. Ltd. Şti., Acibendem, Köftüncü Sok. No. 1, Kadiköy, Istanbul, Turkey.
url: www.atabay.com

Atafarm, Turk. See *Atabay, Turk.*

Atenea, Spain. See *AstraZeneca, Spain.*

Athena, Ital. Athena Pharma Italia Srl, Viale Città d'Europa 681, 00144 Rome, Italy.

Athena Neurosciences, UK. See *Elan, UK.*

Athena Neurosciences, USA. See *Elan, USA.*

Athenstaedt, Cz. See *Athenstaedt, Ger.*

Athenstaedt, Ger. athenstaedt GmbH & Co. KG, Bahnhofstr. 11, 82515 Wolfratshausen, Germany.
url: www.athenstaedt.de

Athenstaedt, Switz. Athenstaedt AG, Rigistrasse 6, 6440 Brunnen, Switzerland.

Athenstaedt & Redeker, Hong Kong. See *Mekim, Hong Kong.*

Athlon, USA. Athlon Pharmaceuticals Inc., P.O. Box 3181, Ridgeland, MS 39158, USA.

Athlone, Hong Kong. See *Universal, Hong Kong.*

Athlone, Irl. Athlone Laboratories, Ballymurray, Roscommon, Ireland.
url: www.athlone-laboratories.com

Atid, Ger. See *Dexcel, Ger.*

Atis, Turk. Atis Gida Turizm Inşaat Kosmetik Ilaç, Mahmut Yesari Cd N: 14 Koşuyolu, Kadiköy, Istanbul, Turkey.

Ativus, Braz. Ativus Farmacêutica Ltda, Rua Fonte Mecio 2050, 13270000 Valinhos, São Paulo, Brazil.
url: www.ativus.com.br

Atlanta, Thai. Atlanta Medicare Co. Ltd, 99/28-30 Ramindra 19, Anusawaree, Bangkean, Bangkok, 10220, Thailand.
url: www.atlantamedicare.co.th

Atlantic, China. Atlantic Laboratories Inc. Ltd, Lonquan Building, Haikou, China.

Atlantic, Hong Kong. Atlantic Laboratories Ltd, Block A, 18/F, Wing Wah Industrial Bldg, 677 King's Rd, North Point, Hong Kong.

Atlantic, Malaysia. Atlantic Laboratories (M) Sdn Bhd, 14 & 16 Jln Angklung 33/20, Shah Alam Technology Park, Seksyen 33, 40400 Shah Alam, Selangor, Malaysia.

Atlantic, Philipp. See *Pharmawealth, Philipp.*

Atlantic, Port. Atlantic Pharma Produções SA, Rua da Tapada Grande 2, Abrunheira, 2710-089 Sintra, Portugal.

Atlantic, Singapore. Atlantic Pharmaceutical (S) Pte Ltd, 152 Paya Lebar Rd, 04-03 Citipoint Industrial Complex, S 409020, Singapore.

Atlantic, Thai. Atlantic Pharmaceutical Co. Ltd, 2038 Sukhumvit Rd, Bangkok 10250, Thailand.
url: www.atlanticlab.com

Atlantis, Mex. Atlantis, S.A. de C.V., Tiburcio Montiel No. 16, M Hidalgo SM Chapultepec, 11850 Mexico D.F., Mexico.

Atlas, Arg. Atlas Farmaceutica, JV Gonzalez 2456, 1417 Buenos Aires, Argentina.

Atlas, Canad. Laboratoire Atlas, 900 Blvd des Sciences, Suite 200, St-Leonard, Quebec, H1H 1H1, Canada.

Atlas, Turk. Atlas İlaç, Yukari Dudullu Mah. Akinci Sok. No 17 Y Dudullu, Umraniye, Istanbul, Turkey.
url: www.atlasilac.com.tr

Atley, USA. Atley Pharmaceuticals Inc., 10511 Old Ridge Rd, Ashland, VA 23005, USA.
url: www.atley.com

Atmos, Ger. See *GSK, Ger.*

Atoma, Swed. AB Atoma, Mellangården 1, 194 51 Upplands Väsby, Sweden.
url: www.atoma.se

Atoms, Canad. Atoms FD Inc., 3485 Ashby, Ville Saint-Laurent, Quebec, H4R 2K3, Canada.

Aton, Canad. See *Aton, USA.*

Aton, Thai. See *Zuellig, Thai.*

Aton, USA. Aton Pharma Inc., 700 Rt 202/206 North, Bridgewater, NJ 08807, USA.
url: www.atonrx.com

ATOZ, India. ATOZ Pharmaceuticals, 2/896 Zota House, Hiramodi St, Sagrampura, Surat 395 002, India.

Atral, Port. Atral Cipan, Apartado 60, 2601-962 Castanheira do Ribatejo, Portugal.
url: www.atralcipan.com

Atral, Rus. See *Atral, Port.*

Atral-Vida, Port. See *Atral, Port.*

Atrix, Denm. See *Meda, Denm.*

Atrix, Ger. Atrix Laboratories GmbH, Hessenring 119-121, 61348 Bad Homburg, Germany.

Atrix, Neth. See *Atrix, Ger.*

Atrix, Port. See *Atrix, Ger.*

Au Naturel, Canad. See *Au Naturel, USA.*

Au Naturel, USA. Au Naturel Inc., 2B 1500 Kearns Blvd, Park City, Utah, 84060, USA.

Aubrey, Canad. See *Aubrey, USA.*

Aubrey, USA. Aubrey Organics Inc., 4419 North Manhattan Ave, Tampa, FL 33614-7650, USA.

Auden McKenzie, Neth. See *Auden McKenzie, UK.*

Auden McKenzie, UK. Auden McKenzie (Pharma Div.) Ltd, McKenzie House, Bury St, Ruislip, Middlesex, HA4 7TL, UK.

Aulo Gelio, Arg. Aulo Gelio Argentina S.R.L., A. R. Bufano 1265, 1416 Buenos Aires, Argentina.

Aura, Cz. Aura Medical s r o, K Verneráku 4, 148 00 Praha 4, Czech Republic.

Aurantis, Braz. See *Biochimico, Braz.*

Aurel, India. Aurel Biolife, 24/1 Phase 2, Industrial Area, Chandigarh, India.

Auriga, Hong Kong. See *Primal, Hong Kong.*

Auriga, USA. Auriga Pharmaceuticals, 5555 Triangle Parkway, Norcross, GA 30092, USA.

Aurium, Canad. Aurium Pharma Inc., 102 7577 Keele St, Concord, Ontario, L4K 4X3, Canada.

Aurobindo, India. Aurobindo Pharma Ltd, Plot No.2, Maitrivihar Complex, Ameerpet, Hyderabad 500 038, India.
url: www.aurobindo.com

Aurobindo, Ital. Aurobindo Pharma (Italia) Srl, Via Pergolesi 15, 20124 Milan, Italy.
url: www.aurobindo.com

Aurobindo, Philipp. See *Pharmawealth, Philipp.*

Aurobindo, Rus. Aurobindo Pharma Ltd, LLC Yura Trade, Mikhalkovskaya Ulitsa Dom 63B Kor 1, 125438 Moscow, Russia.
url: www.aurobindo.com

Aurobindo, S.Afr. Aurobindo Pharma Pty Ltd, Woodhill Office Park, Building 1, 53 Phillip Engelbrecht Ave, Meyersdal Ext 12, Johannesburg 1448, South Africa.
url: www.aurobindo.com

Aurobindo, UK. Aurobindo Pharma, Odyssey Business Park, Ares Block, West End Rd, South Ruislip, Middlesex, HA4 6QD, UK.

Aurochem, India. Aurochem Labs, Unit 333 3rd Floor, Gundecha Industrial Estate, Kandivali (E), Mumbai 400 101, India.

Aurora, Austral. Aurora Pharmaceuticals Ltd, Level 1, 16 Byfield St, North Ryde, NSW 2113, Australia.
url: www.aurorapharm.com

Aurora, Gr. Aurora Pharmaceuticals Ltd, 105 Marathonos Ave, 153 44 Gerakas, Greece.

Aurum, India. Aurum Labs Pvt Ltd, 144 Narayanian, Exchange Rd, Rehari, 180 005, India.

Aurum, UK. See *Martindale Pharmaceuticals, UK.*

Aus Biomed, Austral. Aus Biomed, Level 39 Citigroup, 2 Park St, Sydney, NSW 2000, Australia.
url: www.ausbiomed.com.au

Aus Biopharm, Austral. See *Max Biocare, Austral.*

Auspi, India. Auspi Medicaments, B-2/H-6 Aggarwal Tower, Netaji Subhash Place, Pitampura, New Delhi 110 034, India.

Aust Ind, India. Aust Industrial Lab, SCF 104, Sector 11, Panchkula, Chandigarh 134 109, India.

Austell, S.Afr. Austell Laboratories Pty Ltd, 30 Marlborough Rd, Springfield, Gauteng 2190, South Africa.
url: www.austell.co.za

Austral, Arg. Lab Austral SA, Av. Olascoaga 951, 8300 Neuquén, Argentina.

Australasian Medical, Austral. Australasian Medical and Scientific Ltd, Unit 16, Artarmon Central, 54 Dickson Ave, Artarmon, NSW 2064, Australia.

Australian Bodycare, UK. Australian Bodycare Ltd, Danegate, Eridge Green, Tunbridge Wells, Kent, TN3 9JA, UK.
url: www.australianbodycare.co.uk

Australian Medic-Care, Hong Kong. Australian Medic-Care Co. Ltd, Suite 2810, Metroplaza Tower 2, 223 Hing Fong Rd, Kwai Fong, Kwai Chung, Hong Kong.

Austroplant, Austria. Austroplant-Arzneimittel GmbH, Richard-Strauss-Strasse 13, A-1232 Vienna, Austria.

Austroplant, Cz. See *Schwabe, Cz.*

Automedic, Fr. Automedic (Lab), 19 rue Poliveau, 75005 Paris, France.

Auvex, Fr. Laboratoires Auvex, 20 rue des Bouleaux, 63100 Clermont-Ferrand, France.

Auxilium, Austria. See *Auxilium, UK.*

Auxilium, Belg. See *Auxilium, UK.*

Auxilium, Cz. See *Auxilium, UK.*

Auxilium, Denm. See *Auxilium, UK.*

Auxilium, Fin. See *Auxilium, UK.*

Auxilium, Fr. See *Auxilium, UK.*

Auxilium, Ger. See *Auxilium, UK.*

Auxilium, Gr. See *Auxilium, UK.*

Auxilium, Hung. See *Auxilium, UK.*

Auxilium, Irl. See *Auxilium, UK.*

Auxilium, Ital. See *Auxilium, UK.*

Auxilium, Neth. See *Auxilium, UK.*

Auxilium, Norw. See *Auxilium, UK.*

Auxilium, Pol. See *Auxilium, UK.*

Auxilium, Port. See *Auxilium, UK.*

Auxilium, Spain. See *Auxilium, UK.*

Auxilium, Swed. See *Auxilium, UK.*

Auxilium, UK. Auxilium UK Ltd, Orchard Lea, Winkfield Lane, Windsor, Berkshire, SL4 4RU, UK.
url: xiapex.eu

Auxilium, USA. Auxilium Pharmaceuticals Inc., 640 Lee Rd, Chesterbrook, PA 19087, USA.
url: www.auxilium.com

Avalanche, Cz. Pharma Avalanche sro, Na Žvahově 25, 152 00 Prague 5, Czech Republic.

Avalanche, India. Avalanche Pharmaceuticals, 40 Laxmanpuri, Indira Nagar, Faizabad Road, Lucknow 226 016, India.
url: www.avalanchepharma.com

Avalon, Canad. See *Avalon, USA.*

Avalon, USA. Avalon Natural Products, 1105 Industrial Ave, Petaluma, CA 94952, USA.

Avance, Canad. See *Avance, USA.*

Avance, USA. Avance Inc., 21-21 Broadway, Fair Lawn, NJ 07410, USA.

Avanir, USA. Avanir Pharmaceuticals, 101 Enterprise, Suite 300, Aliso Viejo, CA 92656, USA.
url: www.avanir.com

Avansor, Fin. Avansor Pharma Oy, Teknikantie 14, 02150 Espoo, Finland.
url: www.avansorpharma.fi

Avant, Ukr. Avant Ltd, Blvd Ivan Lepse 4, 03680 Kiev, Ukraine.

Avantgarde, Ital. Avantgarde Gruppo Sigma-Tau S.p.A., Via Treviso 4, 00040 Pomezia (Rome), Italy.

Aveda, Canad. See *Aveda, USA.*

Aveda, USA. Aveda Corp., 4000 Pheasant Ridge Drive, Minneapolis, Minnesota, 55449, USA.

Avefarm, Cz. Avefarm sro, Praha, Czech Republic.

Aveflor, Pol. See *Salus, Pol.*

Avene, Canad. See *Avene, Fr.*

Avene, Fr. Avène, Laboratoires Dermatologiques, 45 place Abel-Gance, 92100 Boulogne, France.

Aventis, Arg. See *Sanofi-Aventis, Arg.*

Aventis, Austral. See *Sanofi-Aventis, Austral.*

Aventis, Austria. See *Sanofi-Aventis, Austria.*

Aventis, Belg. See *Sanofi-Aventis, Belg.*

Aventis, Braz. Aventis Pharma Ltda, Avenida Marginal do Rio Pinheiros 5200, 05693-000 São Paulo, SP, Brazil.
url: www.aventispharma.com.br

Aventis, Canad. See *Sanofi, Canad.*

Aventis, Chile. Laboratorio Aventis Pharma SA, Hernando de Aguirre 268, Providencia, Santiago, Chile.

Aventis, Cz. See *Sanofi-Aventis, Cz.*

Aventis, Denm. See *Sanofi-Aventis, Denm.*

Aventis, Fin. See *Sanofi-Aventis, Fin.*

Aventis, Fr. See *Sanofi-Aventis, Fr.*

Aventis, Ger. See *Sanofi-Aventis, Ger.*

Aventis, Gr. See *Sanofi-Aventis, Gr.*

Aventis, Hong Kong. Aventis Pharma Ltd, 24/F DCH Commercial Ctr, 25 Westlands Rd, Quarry Bay, Hong Kong.
url: www.aventis.com

Aventis, Hung. See *Sanofi-Aventis, Hung.*

Aventis, India. See *Sanofi-Aventis, India.*

Aventis, Indon. See *Sanofi-Aventis, Indon.*

Aventis, Irl. See *Sanofi-Aventis, Irl.*

Aventis, Israel. See *Sanofi-Aventis, Israel.*

Aventis, Ital. See *Sanofi-Aventis, Ital.*

Aventis, Jpn. Aventis Pharma Ltd, Tokyo Opera City Tower, 20-2 Nishishinjuku 3-chome, Shinjuku-ku, Tokyo 163-1488, Japan.
url: www.aventispharma.jp

Aventis, Malaysia. See *Sanofi-Aventis, Malaysia.*

Aventis, Mex. See *Sanofi-Aventis, Mex.*

Aventis, Neth. See *Sanofi-Aventis, Neth.*

Aventis, Norw. See *Sanofi-Aventis, Norw.*

Aventis, NZ. See *Sanofi-Aventis, NZ.*

Aventis, Pol. See *Sanofi-Aventis, Pol.*

Aventis, Port. See *Sanofi-Aventis, Port.*

Aventis, Rus. See *Sanofi-Aventis, Rus.*

Aventis, S.Afr. See *Sanofi-Aventis, S.Afr.*

Aventis, Singapore. See *Sanofi-Aventis, Singapore.*

Aventis, Spain. See *Sanofi-Aventis, Spain.*

Aventis, Swed. See *Sanofi-Aventis, Swed.*

Aventis, Switz. See *Sanofi-Aventis, Switz.*

Aventis, Thai. See *Sanofi-Aventis, Thai.*

Aventis, Turk. See *Sanofi-Aventis, Turk.*

Aventis, UK. See *Sanofi, UK.*

Aventis, USA. See *Sanofi-Aventis, USA.*

Aventis, Venez. See *Sanofi-Aventis, Venez.*

Aventis Behring, Arg. See *Sanofi-Aventis, Arg.*

Aventis Behring, Austria. See *Sanofi-Aventis, Austria.*

Aventis Behring, Belg. See *ZLB, Belg.*

Aventis Behring, Cz. See *CSL, Ger.*

Aventis Behring, Denm. See *Aventis Behring, Swed.*

Aventis Behring, Fin. See *Aventis Behring, Swed.*

Aventis Behring, Fr. Aventis Behring SA, 46 quai de la Rapee, 75012 Paris, France.
url: www.aventisbehring.com

Aventis Behring, Ger. See *CSL, Ger.*

Aventis Behring, Hong Kong. Aventis Behring Asia Pacific Ltd, Unit 1208-1208, 12/F K Wah Ctr, 191 Java Rd, North Point, Hong Kong.

Aventis Behring, Hung. See *Plazmed, Hung.*

Aventis Behring, Irl. See *Sanofi-Aventis, Irl.*

Aventis Behring, Israel. See *Medibrands, Israel.*

Aventis Behring, Ital. See *Sanofi-Aventis, Ital.*

Aventis Behring, Mex. Aventis Behring S.A. de C.V., Calz. de Tlalpan No. 4255, Bosques de Tetlameya, 04730 Mexico D.F., Mexico.
url: www.aventisbehring.com

Aventis Behring, Neth. See *CSL, Ger.*

Aventis Behring, Norw. See *Aventis Behring, Swed.*

Aventis Behring, Pol. See *Sanofi-Aventis, Pol.*

Aventis Behring, Spain. See *ZLB, Spain.*

Aventis Behring, Swed. Aventis Behring AB, Berga Backe 2, 182 17 Danderyd, Sweden.
url: www.aventisbehring.se

Aventis Behring, Switz. Aventis Behring AG, Herostrasse 7, 8048 Zurich, Switzerland.
url: www.aventisbehring.com

Aventis Behring, UK. See *ZLB, UK.*

Aventis Behring, USA. See *CSL, USA.*

Aventis Centeon, Braz. See *Aventis, Braz.*

Aventis Pasteur, Arg. See *Sanofi-Aventis, Arg.*

Aventis Pasteur, Austral. Aventis Pasteur P/L, P.O. Box 7025, Baulkham Hills Business Centre, NSW 2153, Australia.
url: www.aventispasteur.com

Aventis Pasteur, Austria. See *Sanofi Pasteur, Austria.*

Aventis Pasteur, Belg. See *Sanofi Pasteur, Belg.*

Aventis Pasteur, Braz. Aventis Pasteur Ltda, Rua do Rocio 351 10 degrees andar, 04552-905 São Paulo, SP, Brazil.
url: www.aventispasteur.com.br

Aventis Pasteur, Canad. Aventis Pasteur Ltd, Connaught Campus, 1755 Steeles Ave. W, Toronto, Ontario, M2R 3T4, Canada.
url: www.aventispasteur.com

Aventis Pasteur, Chile. See *Aventis, Chile.*

Aventis Pasteur, Cz. Aventis Pasteur GmbH os, Havelská 14, 110 00 Prague 1, Czech Republic.

Aventis Pasteur, Denm. See *Sanofi Pasteur, Denm.*

Aventis Pasteur, Fin. See *Sanofi Pasteur, Denm.*

Aventis Pasteur, Fr. See *Sanofi Pasteur, Fr.*

Aventis Pasteur, Ger. See *Sanofi Pasteur, Ger.*

Aventis Pasteur, Hong Kong. See *Aventis, Hong Kong.*

Aventis Pasteur, India. Aventis Pasteur India Ltd, Chaitanya 1 Charnan Farm Villa, Bundh Road, Gadaipur, New Delhi 110 030, India.

Aventis Pasteur, Irl. See *Sanofi Pasteur, Irl.*

Aventis Pasteur, Israel. See *Sanofi-Aventis, Israel.*

Aventis Pasteur, Ital. See *Sanofi Pasteur, Ital.*

Aventis Pasteur, Malaysia. See *Sanofi-Aventis, Malaysia.*

Aventis Pasteur, Mex. See *Sanofi-Aventis, Mex.*

Aventis Pasteur, Neth. See *Sanofi Pasteur, Neth.*

Aventis Pasteur, Norw. See *Sanofi Pasteur, Norw.*

Aventis Pasteur, Philipp. Aventis Pasteur, 4/F & 5/F Gammon House Bldg, 110 Rada St, Legaspi Vill, Makati City, Philippines.

Aventis Pasteur, Pol. Aventis Pasteur, Sanofi Pasteur Sp. zo.o., ul. Grzybowska 80/82, 00-884 Warsaw, Poland.

Aventis Pasteur, Port. See *UCB, Port.*

Aventis Pasteur, Singapore. See *Zuellig, Singapore.*

Aventis Pasteur, Spain. See *Sanofi Pasteur, Spain.*

Aventis Pasteur, Thai. See *Sanofi Pasteur, Thai.*

Aventis Pasteur, Turk. See *Sanofi-Aventis, Turk.*

Aventis Pasteur, UK. See *Sanofi Pasteur, UK.*

Aventis Pasteur, USA. See *Sanofi Pasteur, USA.*

Averroes, Malaysia. Averroes Pharmaceuticals Sdn Bhd, 11E Level 5, Block 1, Worldwide Business Ctr, Jln 13/50 Section 13, 40000 Shah Alam, Selangor, Malaysia.

Aveva, Canad. See *Aveva, USA.*

Aveva, USA. Aveva Drug Delivery Systems Inc., 3250 Commerce Parkway, Miramar, Florida, 33025, USA.

Avex, Malaysia. See *Apex, Malaysia.*

Avgerinos, Gr. AVGERINOS ChR., Greece.

AVI, Gr. A.V.I. Pharma International SA Greece, Andreas Papandreou St, 151 24 Maroussi, Greece.

Avid, USA. See *Lilly, USA.*

Avidas, USA. Avidas Pharmaceuticals LLC, 196 W Ashland St, Doylestown, PA 18901, USA.
url: www.avidaspharma.com

Avinash, India. Avinash Health Products Pvt Ltd, No.1, 31st Cross Street, M.G.Road, Besant Nagar, Chennai 600 090, India.
url: www.avinashhealth.com

Avion, USA. Avion Pharmaceuticals, 8505 Dunwoody Place, Atlanta, GA 30350, USA.
url: www.avionrx.com

Avmor, Canad. Avmor Ltd, 950 Michelin, Laval, Quebec, H7L 5C1, Canada.

Avocet, USA. Avocet Polymer Technologies Inc., 4047 West 40th St, Chicago, IL 60632, USA.
url: www.avocetcorp.com

Avon, Canad. Avon Canada Inc., 5500 Trans Canada Hwy, Pointe-Claire, Quebec, H9R 1B6, Canada.

Avva, Rus. Avva Rus Corp., 30 Krylatskie Holmy St, 121614 Moscow, Russia.
url: www.avva-rus.ru

Awareness, Canad. Awareness Corp., 210-9087B-198th Street, Langley, British Columbia, V1M 3B1, Canada.

AWD, China. See *AWD, Ger.*

AWD, Cz. See *AWD, Ger.*

AWD, Fin. See *AWD, Ger.*

AWD, Ger. AWD.pharma GmbH & Co. KG, Wasastr. 50, 01445 Radebeul, Germany.
url: www.awd-pharma.com

AWD, Hung. See *AWD, Ger.*

AWD, Neth. See *AWD, Ger.*

AWD, Pol. See *Pliva Krakow, Pol.*

AWD, Rus. See *Pliva, Rus.*

Axapharm, Switz. Axapharm AG, Zugerstrasse 8a, 6340 Baar, Switzerland.
url: www.axapharm.ch

Axcan, Canad. Axcan Pharma Inc., 597 Laurier Blvd, Mont St-Hilaire, Quebec, J3H 6C4, Canada.

Axcan, China. See *Beijing Union, China.*

Axcan, Cz. See *Axcan, Neth.*

Axcan, Fin. See *Axcan, Neth.*

Axcan, Fr. Axcan Pharma SA, Route de Bu, B.P. 41, 78550 Houdan, France.
url: www.axcan.com

Axcan, Ger. See *Axcan, Fr.*

Axcan, Hong Kong. See *Silroc, Hong Kong.*

Axcan, Hung. Axcan, Hungary.

Axcan, Irl. See *Axcan, UK.*

Axcan, Israel. See *Megapharm, Israel.*

Axcan, Neth. Axcan Pharma International BV, Engelenkampstraat 72, 6131 JJ Sittard, Netherlands.

Axcan, Pol. See *Czet, Pol.*

Axcan, Port. See *Axcan, Neth.*

Axcan, Singapore. See *Summit, Singapore.*

Axcan, Thai. See *Diethelm, Thai.*

Axcan, UK. Axcan Pharma UK, Unit 4 Goldalming Business Centre, Woolsack Way, Godalming, Surrey, GU7 1XW, UK.
url: www.axcan.com

Axcan, USA. Axcan Scandipharm, 22 Inverness Center Pkwy, Suite 310, Birmingham, AL 35242, USA.
url: www.axcanscandipharm.com

Axcount, Ger. axcount Generika AG, Max-Planck-Str. 36b, 61381 Friedrichsdorf, Germany.
url: www.axcount.de

Axelia, Indon. Axelia Healthcare, a division of Pro-Health International PT, Perkantoran Fantasi Blok W/29, Tanam Palem Lestari, Jl Kamal Raya Outer Ring Rd, Cengkareng, Jakarta 11730, DKI Jaya, Indonesia.

Axellia, China. Axellia Pharmaceuticals APS, China.

Axellus, Pol. Axellus Sp. zo.o., ul. Poleczki 17, 02-515 Warsaw, Poland.
url: axellus.pl

Axellus, Swed. Axellus AB, Box 1336, 171 26 Solna, Sweden.
url: www.axellus.se

axios, Ger. axios Pharma GmbH, Haupstr. 198, 33647 Bielefeld, Germany.
url: www.axios-pharma.de

Axmed, Fr. Axmed-Donjoy, 8 allee du Canal, 64600 Anglet, France.

Axofarma, Spain. See *Lundbeck, Spain.*

Axon, Chile. Lab. Axon-Pharma Farmaceutica Ltda, Av. Condell 376, Providencia, Santiago, Chile.

Axxess, Canad. Axxess Pharma Inc., Unit 105, 20 Valleywood Drive, Markham, Ontario, L3R 6G1, Canada.

Axxon, Neth. See *Axxon, Pol.*

Axxon, Pol. Axxon Sp.zo.o, ul. Pulawska 314, 02-819 Warsaw, Poland.

Ayerst, Austral. See *Wyeth, Austral.*

Ayerst, Belg. See *Wyeth, Belg.*

Ayerst, Israel. See *Dexxon, Israel* and *Neopharm, Israel.*

Ayerst, Ital. See *Wyeth Lederle, Ital.*

Ayerst, USA. See *Whitehall-Robins, USA* and *Wyeth, USA.*

Aymed, Turk. Aymed, Guvenlik Cad 15/2, 06450 A Ayranci, Ankara, Turkey.
url: www.aymed.com

Ayrton, Denm. See *Pharmasol, UK.*

Ayrton, Neth. See *Ayrton, UK.*

Ayrton, UK. Ayrton Saunders Ltd, Ayrton House, Commerce Way, Parliament Business Park, Liverpool, Merseyside, L8 7BA, UK.
url: www.ayrtons.com

Ayrton Saunders, Denm. See *Smith & Nephew, Denm.*

Ayrton Saunders, Irl. See *Ayrton, UK.*

AyurCore, Singapore. See *MD, Singapore.*

A-Z, Philipp. A-Z Market Enterprise Developers Inc., Philippines.

AZ, Port. AZ Farma Produtos Farmacêuticos Lda, Rua Humberto Madeira 7, Valejas, 2745-663 Barcarena, Portugal.

Aza, Austral. See *Lilly, Austral.*

Azerfarm, Rus. Azerfarm, Russia.

Azevedos, Port. Laboratórios Azevedos, SA, Estrada Nacional 117-2, 2614-503 Amadora, Portugal.

Aziende, Israel. Aziende, Israel.

Azine, India. Azine Healthcare Pvt Ltd, 49/2A Hirabhai Market, Diwan Ballubhai Road, Ahmedabad 380 022, India.
url: www.azinehealthcare.com

AZT, Rus. AZT Pharma KB Ltd

Aztex, Canad. Aztex Enterprises Ltd, 925 Century Dr, Burlington, Ontario, L7L 5J8, Canada.

Azuchemie, Ger. See *Sandoz, Ger.*

Azupharma, Cz. See *Sandoz, Ger.*

Azupharma, Ger. See *Sandoz, Ger.*

Azupharma, Hong Kong. See *Jebsen, Hong Kong.*

Azur, Irl. Azur Pharma Ltd, 45 Fitzwilliam Square, Dublin 2, Ireland.
url: www.azurpharma.com

Azur, Neth. See *Azur, Irl.*

Azur, USA. Azur Pharma Inc., 102 Pickering Way, Suite 200, Exton, PA 19341, USA.
url: www.azurpharma.com

B&S, Irl. See *B&S, UK.*

B&S, UK. B&S Healthcare, Unit 4, Bradfield Rd, Ruislip, Middlesex, HA4 0NU, UK.

Ba Da, China. Ba Da Pharmaceutical Co Ltd, Shantou City, Guangdong, China.

BA Farma, Port. Laboratorio B.A. Farma, Lda, R. Professor Sousa da Câmara 207/211, 1070-803 Lisbon, Portugal.

Bach, UK. Bach Flower Remedies Ltd, 1D Gilray, Diss, Norfolk, IP22 4EU, UK.
url: www.bach-flowers.co.uk

Bacon, Arg. Lab. Bacon, Uruguay 136, 1603 Villa Martelli, Buenos Aires, Argentina.

Bactolac, India. Bactolac Formulations Pvt Ltd, 2-73/2 Chaitanyapuri, Hyderabad 500 060, India.

Bad Heilbrunner, Ger. Bad Heilbrunner Naturheilmittel GmbH & Co.KG, Am Krebsenbach 5-7, 83670 Bad Heilbrunn, Germany.
url: www.bad-heilbrunner.de

Bafeng, China. Bafeng Pharmaceutical Co. Ltd, Hubei, China.

BAG, Cz. See *BAG, Ger.*

BAG, Ger. BAG-Biologische Analisensystem GmbH, Amtsgerichtsstr. 1-5, 35423 Lich, Germany.
url: www.bag-germany.com

BAG, Rus. See *BAG, Ger.*

Bago, Arg. Laboratorios Bagó S.A., Bernardo de Irigoyen 248, 1072 Buenos Aires, Argentina.
url: www.bago.com.ar

Bago, Braz. Laboratorios Bagó Ltda, Rua Cônego Felipe 365, 22713-010 Rio de Janeiro, Brazil.

Bago, Chile. Laboratorios Bagó SA, Av. Vicuna Mackenna 1835, Santiago, Chile.

Bago, China. See *Nanxin, China.*

Bago, Rus. Bago, 26-ti Bakinskikh Komissarov St 9, Of 22-23, 119571 Moscow, Russia.
url: www.bago.ru

Bago, Singapore. See *Zyfas, Singapore.*

Bai Ao, China. Bai Ao Pharmaceutical Co. Ltd, Beijing, China.

Bai Ke, China. Bai Ke Pharmaceutical Co. Ltd, Hubei, China.

Bai Li, China. Bai Li Pharmaceuticals Co. Ltd, Sichuan, China.

Bai Ling, China. See *J&K, China.*

Bai Yang, China. Bai Yang Pharmaceutical Co. Ltd, Qingdao, China.

Baicao, China. Baicao Pharmaceutical Co. Ltd, Hunan, China.

Baif, Ital. Baif International Products, New York S.n.c., Via XX Setembre 20/68, 16121 Genoa (GE), Italy.
url: www.baifinternational.it

Baijingyu, China. Baijingyu Pharmaceutical Co. Ltd, 8/F Golden Eagle Hanzhong Garden, 1 Hanzhongmen Street, Nanjing, 210029, China.
url: www.baijingyu.com

Baike Hengdi, China. Baike Hengdi Pharmaceutical Co. Ltd, Hubei, China.

Baili Tianhua, China. Baili Tianhua Pharmaceutical Co. Ltd, Dalian, China.

Bailleul, Fr. Laboratoires Bailleul Biorga, 8 rue Laugier, 75017 Paris, France.
url: www.bailleul-biorga.com

Bailleul, Hong Kong. See *CNW, Hong Kong* and *Chun Cheong, Hong Kong.*

Bailly, Fr. Laboratoires Bailly SPEAB, 60 rue Pierre-Charron, 75008 Paris, France.

Bailly-Creat, Fr. Laboratoires Bailly-Creat, Chemin de Nuisement, ZI des 150 Arpents, 28509 Vernouillet cdx, France.
url: www.bailly-creat.com

Bailu, China. Bailu Pharmaceutical Co. Ltd., 17 Ocean Tower, Fengcheng Road, Xion, Shaanxi, 710018, China.
url: www.bizy.cn

Baima, China. Baima Pharmaceutical Co. Ltd, 43-1 DaGuan Rd, Kunming, Sanjiu, China.

Bainian Kangxin, China. Henan 100 Kangxin Pharmaceutical Co. Ltd., 666 Gaoxin Avenue, Donghu High-tech Zone, Wuhan, Hubei, China.
url: www.100kangxin.com

Baiqiuen, China. Baiqiuen Medical University Pharmaceutical Co. Ltd, China.

Baitai, China. Baitai Biopharmaceutical Co. Ltd, China.

Baite Qiaoguang, China. Baite Qiaoguang Pharmaceutical Co. Ltd, Guangzhou, China.

Baiyi, China. Baiyi Pharmaceutical Co. Ltd, 2 Qingfeng Road, Teixi, Wulanhaote, Inner Mongolia, 137400, China.

Baiyoung, China. Baiyoung Medical Science & Technology Co. Ltd, Guorui Building Room 1106, 16 Chongwenmenwoi St, Beijing, Qingdao, China.
url: www.baiyyy.com.cn

Baiyunshan, China. Guangzhou Baiyunshan Pharmaceutical Co. Ltd, Yunxiang Rd 88, Baiyun District, Guangzhou City 510515, China.
url: www.gzbys.com

Bajamar, USA. Bajamar Chemical Co. Inc., 9609 Dielman Rock Island, St Louis, MO 63132, USA.
url: www.vesselvite.com

Bajamed, Mex. Laboratorios Bajamed SA de CV, Av Esteban Cantu 2, 22180 Tijuana el Rubi Sur, Mexico.

Bajer, Arg. Laboritorios Felipe Bajer S.A.I.C., Alfredo R. Bufano 1265, 1416 Buenos Aires, Argentina.
url: www.bajer.com.ar

Baker, USA. See *Mallinckrodt-Baker, USA.*

Baker Cummins, Canad. See *Janssen-Ortho, Canad.*

Baker Cummins, USA. See *Ivax, USA.*

Baker Norton, China. Kunming Baker Norton Pharmaceutical Co Ltd, Oriental Zhongxin Building Room 707, 699 Nanjing West Rd, Wujiang 31, Shanghai 200041, China.
url: www.kbn.net.cn

Baker Norton, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Baker Norton, Irl. See *Ivax, Irl.*

Baker Norton, Singapore. See *Green Cross, Singapore.*

Baker Norton, USA. See *Ivax, USA.*

Bai, India. Bal Pharma Ltd, 5th Floor Laxmi Narayan Complex, 10/1 Palace Road, Bangalore 560 052, India.
url: www.balpharma.com

Bal, Thai. See *Cosma, Thai.*

Balan, USA. See *Ivax, USA.*

Baldacci, Braz. Laboratórios Baldacci S.A., Rua Pedro de Toledo 520, 04039-001 São Paula, SP, Brazil.

Baldacci, Ital. Laboratori Baldacci S.p.A., Via S. Michele degli Scalzi 73, 56124 Pisa, Italy.
url: www.baldacci.it

Baldacci, Port. Baldacci Portugol SA, Rua Candido de Figueiredo 84-B, 1549-005 Lisbon, Portugal.
url: www.baldacci.pt

Baldacci, Rus. See *CSC, Rus.*

Baliarda, Arg. Lab. Baliarda S.A., Alberti 1283, 1247 Buenos Aires, Argentina.
url: www.baliarda.com.ar

Balkanpharma, Rus. Balkanpharma Holding Co., Kuskovskaya ul. 20, Of. 709, Moscow, Russia.
url: www.balkanpharmo.ru

Ballay, USA. Ballay Pharmaceuticals Inc., 200 Stillwater, P.O. Box 1356, Wimberley, TX 78676, USA.

Balley, Canad. Balley Direct, PO Box 91994, Stn W Vancouver, British Columbia, V7V 3P2, Canada.
url: www.muradcanada.com

Balmar, NZ. Balmar, P.O. Box 41-014, St Lukes, Auckland, New Zealand.
url: www.balmar.co.nz

Balneopharm, Ger. See *Hanosan, Ger.*

Baltian, Fin. Baltian Sairaalapalvelu Oy, Valimotie 13 A, 00380 Helsinki, Finland.

Balu, Gr. Balu, 30o klm. Athinon - Lavriou, 190 03 Markopoulo, Greece.

Bama, Spain. Bama Geve, Avda Diagonal 490, 08006 Barcelona, Spain.
url: www.bamageve.es

Bamford, NZ. W.M. Bamford & Co. Ltd, Private Bag 31-346, Lower Hutt, Wellington, New Zealand.
url: www.bamford.co.nz

Banana Boat, Canad. The Banana Boat Company, 6363 Northam Drive, Mississauga, Ontario, L4V 1N5, Canada.

Bang Yu, China. Bang Yu Pharmaceutical Co Ltd, Kunming, China.

Bangkok Drug, Thai. Bangkok Drug Co. Ltd, 874 Soi, 23 Rama 6 Rd, Rajthevee, Bangkok 10400, Thailand.

Bangkok Lab & Cosmetic, Hong Kong. See *T-Boma, Hong Kong.*

Bangkok Lab & Cosmetic, Thai. See *Bangkok Drug, Thai.*

Bangmin, China. Bangmin Pharmaceutical Co. Ltd, 33 Bangmin Rd, Jianghai, Jiangmen, Guangdong, 529080, China.
url: www.bangmin.com.cn

Banner, Canad. Banner Pharmacaps (Canada) Ltd, 5807 47th Avenue, Olds, Alberta, T4H 1S7, Canada.

Banner, Hong Kong. See *Well Favoured, Hong Kong.*

Banner, Malaysia. See *IDS, Malaysia.*

Banner, Rus. See *Boots, Rus.*

Banner, USA. Banner Pharmacaps, 4125 Premier Drive, High Point, NC 27265, USA.
url: www.banpharm.com

Banner Pharmacaps, Malaysia. See *JDH, Malaysia.*

Bano, Austria. Mag. J. Bano chem. pharmazeutische Präparate, A-6580 St Anton/Arlberg 485, Austria.

Banyu, Hong Kong. See *Hing Ah, Hong Kong.*

Banyu, Jpn. Banyu Pharmaceutical Co. Ltd, Kitanomaru Square, 1-13-12 Kudan Kita, Chiyoda-ku, Tokyo 102-8667, Japan.

Banyu, Thai. See *Asian TJD, Thai.*

Banzhou, China. Banzhou Pharmaceutical Co. Ltd, Guangxi, China.

Bao Ling Fu Jin, China. Bao Ling Fu Jin Bio Tech, China.

Bao Long, China. Bao Long Pharmaceutical Co. Ltd, 358 Tianchen Rd, Qingpu Industrial Zone, Shanghai 201702, China.
url: www.shblyy.com

Baoguang, Chino. Baoguang Pharmaceutical Co. Ltd, 8 Wangjiang Rd, Luzhong, Sichuan, 646000, China.

Baotou, China. Baotou TCM Pharmaceutical Co. Ltd, China.

Barcino, Spain. Barcino, Tuset 1, 08006 Barcelona, Spain.

Bard, Cz. See *Bard, UK.*

Bard, Hong Kong. See *US Summit, Hong Kong.*

Bard, Thai. Bard, Thailand.

Bard, UK. Bard Ltd, Forest House, Brighton Rd, Crawley, West Sussex, RH11 9BP, UK.
url: www.crbard.com

Baren-Apotheke, Switz. Bären-Apatheke AG, Kalkbreitestrosse 131, 8003 Zurich, Switzerland.

Barnatron, Spain. Barnatron, Avd Josep Anselm Clave 100, 08950 Esplugues de Llobregat, Barcelona, Spain.

Barnes Hind, Arg. See *Maurino, Arg.*

Barnes Hind, NZ. See *Allergan, NZ.*

Barnes-Hind, Austral. See *Pilkington Barnes-Hind, Austral.*

Barnes-Hind, Switz. See *Dispersa, Switz.*

Baroda, India. Baroda Pharma Pvt Ltd, 1 R.C. Patel Industrial Estate, Post Box No. 2518, Akota Road, Baroda 390 020, India.

Baroli, USA. Baroli LLC, 4718 SW 74th Ave, Miami, FL 33155, USA.

Barr, Canad. See *Barr, USA.*

Barr, USA. Barr Laboratories Inc., 2 Quaker Rd, Pomona, NY 01970, USA.
url: www.barrlabs.com

Barre-National, USA. See *Alpharma, USA.*

Barrenne, Braz. Barrenne Indústria Farmacêutica Ltda, Rua Antunes Maciel 86, São Cristovao, 20940-010 Rio de Janeira, RJ, Brazil.
url: www.barrene.com.br

Barrier Therapeutics, Belg. Barrier Therapeutics NV, Cipalstraat 3, 2440 Geel, Belgium.

Barrier Therapeutics, Fin. See *Bitelab, Fin.*

Barrier Therapeutics, Neth. See *Barrier Therapeutics, Belg.*

Barrier Therapeutics, Port. See *Barrier Therapeutics, Belg.*

Bart, USA. A.J. Bart Inc., Gurabo Industrial Park, P.O. Box 1360, Guraba, PR 00658, Puerto Rico.

Basel, Turk. Basel Ilaç Sanayi ve Ticoret A.Ş., General Ali Riza Gürcan Cod., Merter İş Merkezi No. 291/B, Tozkorporan Merter, İstanbul, 34010, Turkey.
url: www.baselilac.com.tr

Basel, USA. See *Novartis, USA.*

BASF, Braz. See *Knoll, Braz.*

Basi, Port. Laboratorios Basi, R.do do Padrão 98, 3000-312 Coimbra, Portugal.

Basic, Canad. Basic Packaging Industries Inc., 5591 McAdam Rd, Mississauga, Ontario, L4Z 1N4, Canada.

Basic, Philipp. Basic Pharmaceutical Corp., BPC Bldg, 38 Barasoain St, Little Baguio, San Juan, Metro Manila, Philippines.

Basics, Fin. See *Basics, Ger.*

Basics, Ger. Basics GmbH, Hemmelrather Weg 201, 51377 Leverkusen, Germany.
url: www.basics.de

Basics, Neth. See *Basics, Ger.*

Basics, Swed. See *Basics, Ger.*

Basilea, Austria. See *Basilea, Ger.*

Basilea, Denm. Basilea Pharmaceuticals A/S, Blokken 15 st. tv., 3460 Birkerød, Denmark.
url: www.basilea.com

Basilea, Fin. See *Basilea, Denm.*

Basilea, Fr. Basilea Pharma SAS, 121 rue d'Aguesseau, 92100 Boulogne-Billancourt, France.
url: www.basilea.com

Basilea, Ger. Basilea Pharmaceutica Deutschland GmbH, Kistlerhofstr. 75, 81379 München, Germany.
url: www.basilea.com

Basilea, Neth. See *Basilea, Switz.*

Basilea, Switz. Basilea Pharmaxeutica Ltd, Grenzacherstrasse 487, 4005 Basel, Switzerland.
url: www.basilea.com

Basilea, UK. Basilea Pharmaceuticals Ltd, 14/16 Frederick Sanger Rd, The Surrey Research Park, Guildford, Surrey, GU2 7YD, UK.
url: www.basilea.com

Basotherm, Ger. See *Galderma, Ger.*

Basotherm, Switz. See *Boehringer Ingelheim, Switz.*

Bastian, Ger. Bastian-Werk GmbH, August-Exter-Str. 4, 81245 Munich, Germany.
url: www.bastian-werk.de

Bastian, Switz. See *Globopharm, Switz.*

Bath & Body Works, Canad. Bath & Body Works (Canada) Corp., 1608 Blvd St-Regis, Dorval, Quebec, H9P 1H6, Canada.

Batteur, Ital. Groupe Batteur Italia Srl, Via Roncati 6, 40134 Bologna (BO), Italy.
url: www.groupebatteur.fr

Batteur, Malaysia. See *Germax, Malaysia.*

Bausch & Lomb, Arg. Lab. Bausch & Lomb Argentina S.R.L., Av. Montevideo 160, 1019 Buenos Aires, Argentina.
url: www.bausch.com

Bausch & Lomb, Austral. Bausch & Lomb (Australia) P/L, Level 4, 113 Wicks Rd, North Ryde, NSW 2113, Australia.
url: www.bausch.com

Bausch & Lomb, Austria. See *Bausch & Lomb, Ger.*

Bausch & Lomb, Belg. Bausch & Lomb, Regent Building, Uitbreidingsstraat 46, 2600 Antwerp, Belgium.
url: www.bausch.com

Bausch & Lomb, Braz. Bausch & Lomb (BL) Indústria Otica Ltda, Rua Dona Alzira 139, 91110010 Porto Alegre, Rio Grande da Sul, Brazil.
url: www.bausch.com.br

Bausch & Lomb, Canad. Bausch & Lomb Canada Inc., 3762 Fourteenth Ave, 2nd Floor, Markham, Ontario, L3R 0G7, Canada.
url: www.bousch.com

Bausch & Lomb, China. Bausch & Lomb-Freda Pharmaceutical Co. Ltd, Shando 264, Jinan City 250014, China.

Bausch & Lomb, Denm. See *Bausch & Lomb, UK.*

Bausch & Lomb, Fin. See *Bausch & Lomb, UK.*

Bausch & Lomb, Fr. See *Chauvin, Fr.*

Bausch & Lomb, Ger. Bausch & Lomb GmbH, Brunsbüttler Damm 165-173, 13581 Berlin, Germany.

Bausch & Lomb, Hong Kong. Bausch & Lomb (Hong Kong) Ltd, 26/F City Plaza 1, Taikoo Shing, Hong Kong.

Bausch & Lomb, Irl. See *Bausch & Lomb, UK.*

Bausch & Lomb, Ital. Bausch & Lomb IOM S.p.A., Via Pasubio 34, 20050 Macherio (MI), Italy.
url: www.bausch.it

Bausch & Lomb, Malaysia. See *Apex, Malaysia.*

Bausch & Lomb, Mex. Laboratorio Bausch & Lomb Mexico SA de CV, Av. Santa Fe 505 Piso 6, 5349 Cuajimalpa Cruz Manca Santo Fe, Mexico DF, Mexico.

Bausch & Lomb, Neth. Bausch & Lomb BV, Koolhovenlaan 110, 1119 NH Schiphol-Rijk, Netherlands.
url: www.bausch.co.uk

Bausch & Lomb, NZ. Bausch & Lomb New Zealand Ltd, P.O. Box 24-138, Royal Oak, Auckland, New Zealand.
url: www.bousch.com

Bausch & Lomb, Philipp. See *Croma, Philipp.*

Bausch & Lomb, Pol. Bausch & Lomb Polska Sp. zo.o., ul. Zwiqzkowa 20, 04-522 Warsaw, Poland.
url: www.bausch.com.pl

Bausch & Lomb, Port. Bousch & Lomb SA, Av. do Forte 3, Edificio Suécia IV, Piso 0 Esq., 2795-504 Carnaxide, Portugal.

Bausch & Lomb, Rus. Bousch & Lomb, 1st Floor, 1-2 bld., 6 Shtuzovaya emb., 113114 Moscow, Russia.
url: www.bausch.com

Bausch & Lomb, S.Afr. Bausch & Lomb (SA) (Pty) Ltd, P.O. Box 5435, Rivonia 2128, South Africa.
url: www.bausch.com

Bausch & Lomb, Singapore. See *DKSH, Singapore.*

Bausch & Lomb, Spain. Bausch & Lomb Espana S.A., Avda Valdeparra 4, Alcobendas, 28109 Madrid, Spain.
url: www.bausch.com

Bausch & Lomb, Swed. Bausch & Lomb Nordic AB, Box 15070, 104 65 Stockholm, Sweden.
url: www.bausch.com

Bausch & Lomb, Switz. Bausch & Lomb Swiss AG, Sumpfstrasse 3, 6312 Steinhausen, Switzerland.

Bausch & Lomb, Thai. See *Zuellig, Thai.*

Bausch & Lomb, Turk. Bausch & Lomb Sağlik ve Optik Ürünleri Tic A.Ş., Sasmaz Plaza No:4 Kat 12, Daire 24 Kozyatagi, İstanbul, Turkey.
url: www.bausch.com

Bausch & Lomb, UK. Bausch & Lomb UK Ltd, 106-114 London Rd, Kingston-upon-Thames, Surrey, KT2 6TN, UK.
url: www.bousch.co.uk

Bausch & Lomb, Ukr. See *Chauvin Ankerpharm, Ukr.*

Bausch & Lomb, USA. Bausch & Lomb Pharmaceuticals, 8500 Hidden River Parkway, Tampa, FL 33637, USA.
url: www.bausch.com

Baxter, Arg. See *Baxter Immuno, Arg.*

Baxter, Austral. Baxter Healthcare P/L, P.O. Box 88, Toongabbie, NSW 2146, Australia.
url: www.baxterhealthcare.com.au

Baxter, Austria. Baxter AG, Industriestrasse 67, A-1221 Vienna, Austria.
url: www.baxter.at

Baxter, Belg. Baxter SA, Bvld de la Plaine 5, 1050 Brussels, Belgium.
url: www.baxter.be

Baxter, Braz. Baxter Hospitalar Ltda, Rua Eng. Francisco Pitta Brito 779, 04753-080 São Paulo Santo Amara, SP, Brazil.
url: www.baxter.com.br

Baxter, Canad. Baxter Corporation, 4 Robert Speck Pkwy, Suite 700, Mississauga, Ontorio, L4Z 3YA, Canada.
url: www.baxter.ca

Baxter, Chile. Labaratorio Baxter/Asta Medica, General Salvo 68, Providencia, Santiago, Chile.

Baxter, Chino. Baxter, Century Business Plaza 12th Floor, 989 Changle Rd, Shanghai, China.
url: www.baxter.com

Baxter, Cz. Baxter Czech sro, Opletalová 55/57, 110 00 Prague 1, Czech Republic.
url: www.baxter.cz

Baxter, Denm. Baxter A/S, Gydevang 43, 3450 Allerød, Denmark.
url: www.baxter.com

Baxter, Fin. Baxter Oy, Pakkalankuja 6, PL 46, 01511 Vantaa, Finland.
url: www.baxter.fi

Baxter, Fr. Baxter SA, 6 av Louis-Pasteur, B.P. 56, 78311 Maurepas cdx, France.
url: www.baxter.com

Baxter, Ger. Baxter Deutschland GmbH, Edisonstr. 4, 85716 Unterschleissheim, Germany.
url: www.baxter.de

Baxter, Gr. Baxter Hellas EPE, Ethnarhou Makariou 34, 163 41 Ilioupolis, Greece.
url: www.baxter.com

Baxter, Hong Kong. Baxter Healthcare Ltd, Rm 2006, MassMutual Tower, 38 Gloucester Rd, Wanchai, Hong Kong.
url: www.baxter.com

Baxter, Hung. Baxter Hungary Kft, Buday László utca 12, 1024 Budapest, Hungary.

Baxter, India. Baxter (India) Pvt Ltd, 2nd Floor Tower-C Building no.8, DLF Cyber City, DLF Phase-II, Gurgaon 122002, India.
url: www.baxter.in

Baxter, Indon. See *Darya-Varia, Indon.*

Baxter, Irl. Baxter Healthcare Ltd, 7 Deansgrange Industrial Estate, Blackrock, Dublin, Ireland.
url: www.baxter.com

Baxter, Israel. See *Teva, Israel.*

Baxter, Ital. Baxter S.p.A., Viale Tiziano 25, 00196 Rome (RM), Italy.
url: www.baxter.com

Baxter, Jpn. Baxter Ltd, 4 Banchi, 6 Bancho, Chiyoda-ku, Tokyo 102-8468, Japan.

Baxter, Malaysia. See *United Italian, Malaysia.*

Baxter, Neth. Baxter BV, Kobaltweg 49, 3542 CE Utrecht, Netherlands.
url: www.baxter.nl

Baxter, Norw. Baxter AS, Gjerdrumsv. 11, Postboks 70 Grefsen, 0409 Oslo, Norway.
url: www.baxter.no

Baxter, NZ. Baxter Healthcare Ltd, 33 Vestey Drive, Mt Wellington, Auckland, New Zealand.
url: www.baxter.co.nz

Baxter, Philipp. Baxter Healthcare Phils Inc., 19/F Wynsum Corp.Plaza, Emerald Ave, Pasig City, Philippines.

Baxter, Pol. Baxter Poland Sp. zo.o., ul. Kruczkowskiego 8, 00-380 Warsaw, Poland.
url: www.oncology.pl

Baxter, Port. Baxter, Lda, Urbanização Industrial Cabra Figa, Estrada Nacional 249/4, Lote 3, Cabra Figa, 2735 Rio de Mouro, Portugal.
url: www.tissuesealing.com

Baxter, Rus. See *Serono, Rus.*

Baxter, Singapore. See *United Italian, Singapore.*

Baxter, Spain. Baxter, Parque Empresarial San Fernando, Edificio Londres, 28830 Madrid, Spain.
url: www.baxter.es

Baxter, Swed. Baxter Medical AB, Box 63, 164 94 Kista, Sweden.
url: www.baxter.se

Baxter, Switz. Baxter AG, Muellerenstrasse 3, 8604 Volketswil., Switzerland.
url: www.baxter.ch

Baxter, Thai. Baxter Healthcare (Thailand) Co. Ltd, 10 Fl, Tanapoom Tower, 1550 New Petchburi Rd, Makasan, Rajthevi, Bangkok 10310, Thailand.
url: www.baxter.com

Baxter, Turk. See *Eczacibasi-Baxter, Turk.*

Baxter, UK. See *Baxter BioScience, UK.*

Baxter, USA. Baxter Healthcare, One Baxter Parkway, Deerfield, IL 60015, USA.
url: www.baxter.com

Baxter, Venez. Baxter de Venezuela C.A., Calle 9 Edif, Siete, Urb. La Urbina, Caracas, Venezuela.
url: www.baxter.com

Baxter Anaesthesia, UK. See *BaxterBioScience, UK.*

Baxter BioScience, Ger. See *Baxter, Ger.*

Baxter BioScience, Norw. See *Baxter, Norw.*

Baxter BioScience, Turk. See *Eczacibasi-Baxter, Turk.*

Baxter BioScience, UK. Baxter BioScience, Wallingford Rd, Compton, Newbury, Berkshire, RG20 7QW, UK.
url: www.baxterhealthcare.co.uk

Baxter Healthcare, Switz. See *Opopharma, Switz.*

Baxter Immuno, Arg. Baxter Immuno S.A., Entre Rios 1632, 1636 Olivos, Buenos Aires, Argentina.
url: www.baxter.com

Baxter Nutrition, USA. See *Baxter, USA.*

Baxter Oncology, Cz. See *Baxter, Cz.*

Baxter Oncology, Fr. See *Baxter, Fr.*

Baxter Oncology, Ger. Baxter Oncology GmbH, Kantstr. 2, 33790 Halle (Westfalen), Germany.
url: www.baxter-oncology.com

Baxter Oncology, Israel. See *Teva, Israel.*

Baxter Oncology, Malaysia. See *Zuellig, Malaysia.*

Baxter Oncology, Norw. See *Baxter, Norw.*

Baxter Oncology, Pol. See *Baxter, Pol.*

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Baxter Oncology, Singapore. See *Zuellig, Singapore.*

Baxter Oncology, UK. See *Baxter BioScience, UK.*

Baxter Renal, Norw. See *Baxter, Norw.*

Baxter-Hyland, Ger. See *Baxter, Ger.*

Baxter-Hyland, Hong Kong. See *Baxter, Hong Kong.*

Baxter-Hyland, USA. See *Baxter, USA.*

Baycare, Ital. See *Bayer, Ital.*

Bayer, Arg. Bayer Argentina S.A., Ricardo Gutierrez 3652, 1605 Munro, Buenos Aires, Argentina.
url: www.bayer.com.ar

Bayer, Austral. Bayer Australia Ltd (Pharmaceutical Business Group), P.O. Box 903, Pymble, NSW 2073, Australia.
url: www.bayer.com

Bayer, Austria. Bayer Austria GmbH, Herbststrasse 6-10, A-1160 Vienna, Austria.
url: www.bayer.at

Bayer, Belg. Bayer SA/NV, Louizalaan 143, 1050 Brussels, Belgium.
url: www.bayer.be

Bayer, Braz. Bayer S.A., Rua Domingos Jorge 1100, 04779900 São Paulo, SP, Brazil.
url: www.bayer.com/br

Bayer, Canad. Bayer Inc., 77 Belfield Rd, Toronto, Ontario, M9W 1G6, Canada.
url: www.bayer.ca

Bayer, Chile. Bayer SA, Carlos Fernandez 260, San Joaquin, Santiago, Chile.

Bayer, China. Bayer China Ltd, 33 Huayuan Shiqiao Rd, Shanghai 200120, China.
url: www.bayer.com.cn

Bayer, Cz. Bayer sro, Litvínovská 609/3, 190 21 Prague 9, Czech Republic.
url: www.bayer-cz.cz

Bayer, Denm. Bayer A/S, Nørgaardsvej 32, 2800 Lyngby, Denmark.
url: www.bayer.dk

Bayer, Fin. Bayer Oy, Suomalaistentie 7, PL 13, 02270 Espoo, Finland.
url: www.bayer.fi

Bayer, Fr. Bayer SAS, 13 rue Jean Jaurès, 92815 Puteaux Cedex, France.
url: www.bayer.fr

Bayer, Ger. Bayer Vital GmbH, 51368 Leverkusen, Germany.
url: www.bayervital.de

Bayer, Gr. Bayer Hellas AG, Sorou 18-20, 151 25 Maroussi-Athens, Greece.
url: www.bayer.gr

Bayer, Hong Kong. Bayer Healthcare Ltd, 20/F Gee Chang Hong Ctr, 65 Wong Chuk Hang Rd, Hong Kong.
url: www.bayerchina.com.hk

Bayer, Hung. Bayer Hungária Kft, Pálya utca 4-6, 1012 Budapest, Hungary.

Bayer, India. Bayer Pharmaceuticals Pvt Ltd, 1st Floor, Bayer Corporate Office, Kolshet Rd, Thane 400 607, India.
url: www.bayergroupindia.com

Bayer, Indon. Bayer Indonesia, Mid Plaza 1, 14/F, Jl Jend Sudirman Kav 10-11, Jakarta 10220, DKI Jaya, Indonesia.

Bayer, Irl. Bayer Ltd, The Atrium, Blackthorn Rd, Dublin 18, Ireland.
url: www.boyer.ie

Bayer, Israel. Bayer Israel Ltd, 36 Hacharash St, Hod Hasharon 45240, Israel.
url: www.bayer.com

Bayer, Ital. Bayer S.p.A., Viale Certosa 130, 20156 Milan (MI), Italy.
url: www.bayer.it

Bayer, Jpn. Bayer Yakuhin Ltd, 3-5-36 Miyahara, Yodogawa-ku, Osaka 532-8577, Japan.
url: www.boyer.co.jp

Bayer, Malaysia. Bayer Healthcare, Bayer Schering Pharma, T1-14 Jaya 33, 3 Jln Semangat, Seksyen 13, 46200 Petaling Jaya, Selangor, Malaysia.
url: www.bayer.com.my

Bayer, Mex. Bayer de Mexico S.A. de C.V., Division Farmaceutica, Blvd.M. de Cervantes Saavedra 259, Col. Ampl. Granada, 11520 Mexico D.F., Mexico.
url: www.bayer.com

Bayer, Neth. Bayer BV, Energieweg 1, 3641 RT Mijdrecht, Netherlands.
url: www.bayer.com

Bayer, Norw. Bayer AS, Drammensv. 147 B, Postboks 14, 0212 Oslo, Norway.
url: www.bayer.no

Bayer, NZ. Bayer New Zealand Ltd, P.O. Box 2825, Auckland, New Zealand.
url: www.bayer.co.nz

Bayer, Philipp. Bayer Philippines Inc., Cecilia Araneta-Yulo Ave, Canlubang Industrial Estate, Canlubang, Calamba, Laguna, Philippines.

Bayer, Pol. Bayer Polska Sp. zo.o., al. Jerozolimskie 158, 02-326 Warsaw, Poland.
url: www.bayer.com.pl

Bayer, Port. Bayer Portugal, SA, Apartado 666, 2795 Carnaxide, Portugal.
url: www.bayer.com

Bayer, Rus. Bayer A/O Russia, 3 Rybinskaya ul d 18 str 2, 107113 Moscow, Russia.
url: www.bayer.com

Bayer, S.Afr. Bayer (Pty) Ltd, 27 Wrench Rd, Isando 1600, South Africa.
url: www.bayer.co.za

Bayer, Singapore. Bayer (South East Asia) Pte Ltd, Pharmaceutical & OTC Division, 9 Benoi Sector, S 629844, Singapore.
url: www.bayer.com

Bayer, Spain. See *Bayer Schering, Spain.*

Bayer, Swed. Bayer AB, Box 5237, 402 24 Göteborg, Sweden.
url: www.bayer.se

Bayer, Switz. Bayer (Schweiz) AG, Pharma, Postfach, Grubenstrasse 6, 8045 Zurich, Switzerland.
url: www.bayer.ch

Bayer, Thai. Bayer Thai Co. Ltd, 28/19 Chaengwattana Rd, Pakkred. Nontthaburi 11120, P.O. Box 106 Laksi Post Office, Bangkok 10210, Thailand.
url: www.bayer.co.th

Bayer, Turk. Bayer Tük Kimya San. Ltd. Sti., Çakmak Mah., Balkan Cad. No:53, Ümraniye, Istanbul, 34770, Turkey.
url: www.bayer.com.tr

Bayer, UK. Bayer plc, Bayer Schering Pharma, Bayer House, Strawberry Hill, Newbury, Berkshire, RG13 1JA, UK.
url: www.bayer.co.uk

Bayer, Ukr. Bayer Ltd, Upper Val St 4B, 04050 Kiev, Ukraine.
url: www.bayer.ua

Bayer, USA. Bayer HealthCare Pharmaceuticals, 400 Morgan Lane, West Haven, CT 06516-4175, USA.
url: www.bayerus.com

Bayer, Venez. Bayer de Venezuela C.A., Av. Tamanaco - Torre Bayer, Urb. El Rosal, Caracas, Venezuela.
url: www.bayer.com

Bayer Allergy, USA. See *Bayer, USA.*

Bayer Biological, Hong Kong. See *ICH, Hong Kong.*

Bayer Consumer, Arg. See *Bayer, Arg.*

Bayer Consumer, Austral. See *Bayer, Austral.*

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Bayer Consumer, Thai. See *Bayer, Thai.*

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Bayer Consumer, Ukr. See *Bayer, Ukr.*

Bayer Consumer, USA. Bayer Consumer Care Division, 36 Columbia Rd, P.O. Box 1910, Morristown, NJ 07962-1910, USA.
url: www.bayerus.com
url: www.consumercare.bayer.com

Bayer Diabetes, UK. See *Bayer, UK.*

Bayer Diabetes Care, Arg. See *Bayer, Arg.*

Bayer Diabetes Care, Fr. See *Bayer Sante, Fr.*

Bayer Diabetes Care, Mex. See *Bayer, Mex.*

Bayer Diagnostici, Ital. See *Bayer, Ital.*

Bayer Diagnostics, Austral. See *Bayer, Austral.*

Bayer Diagnostics, Fr. Bayer Diagnostics, Tour Horizon, 52 quai de Dion Bouton, 92807 Puteaux cdx, France.
url: www.bayerdiag.com

Bayer Diagnostics, Irl. See *Bayer, Irl.*

Bayer Diagnostics, Mex. Bayer de Mexico S.A. de C.V., Division Diagnosticos, Av. Coyoacan 1553, Col del Valle, 03100 Mexico D.F., Mexico.
url: www.bayerdiag.com

Bayer Diagnostics, UK. See *Bayer, UK.*

Bayer Healthcare, Switz. See *Medinova, Switz.*

Bayer Sante, China. See *Bayer, China.*

Bayer Sante, Fr. Bayer Santé Familiale, 33 rue de l'Industrie, 74240 Gaillard, France.
url: www.bayerhealthcare.fr

Bayer Schering, Austral. See *Bayer, Austral.*

Bayer Schering, Austria. See *Bayer, Austria.*

Bayer Schering, China. See *Bayer, China.*

Bayer Schering, Cz. See *Bayer, Cz.*

Bayer Schering, Denm. See *Bayer, Denm.*

Bayer Schering, Fin. Bayer Schering Pharma Oy, Pansiontie 47, 20210 Turku, Finland.

Bayer Schering, Fr. See *Bayer, Fr.*

Bayer Schering, Gr. See *Bayer, Gr.*

Bayer Schering, Hung. Bayer Schering Pharma Magyarország, Hungary.
url: www.schering.hu

Bayer Schering, Indon. See *Bayer, Indon.*

Bayer Schering, Irl. See *Bayer, Irl.*

Bayer Schering, Malaysia. See *Bayer, Malaysia.*

Bayer Schering, Neth. See *Bayer, Neth.*

Bayer Schering, Norw. See *Bayer, Norw.*

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Bayer Schering, S.Afr. See *Bayer, S.Afr.*

Bayer Schering, Singapore. See *Zuellig, Singapore.*

Bayer Schering, Spain. Bayer Schering Pharma Medical SL, Avd Baix Llobregat 3-5, 08970 Sant Joan Despi, Barcelona, Spain.
url: www.bayersalud.com

Bayer Schering, Thai. See *Bayer, Thai.*

Bayer Schering, UK. See *Bayer, UK.*

BayHealth, Port. BayHealth Comercialização de Produtos Farmacêuticos Unipessoal Lda, Rua da Quinta do Pinheiro 5, 2794-003 Carnaxide, Portugal.

Bayhealth, Spain. See *Bayer Schering, Spain.*

Baypharm, Austral. See *Bayer, Austral.*

Bayropharm, Ger. See *Bayer, Ger.*

Bayropharm, Ital. See *Bayer, Ital.*

Bayropharm, Spain. See *Bayer Schering, Spain.*

Baysalud, Spain. Baysalud SL, Av. Baix Llobregat 3-5, 08970 Saint Joan Despi, Barcelona, Spain.

Bayvit, Spain. See *Stada, Spain.*

Baywood, Canad. See *Baywood, USA.*

Baywood, USA. Baywood International Inc., A201 9380 E Bahia, Scottsdale, AZ 85260, USA.

BB, Cz. BB Pharma as, Kovriginova 1416/6, 147 00 Praha 4, Czech Republic.

BB, Ital. BB Farma Srl, Viale Europa 160, 21017 Samarate (VA), Italy.

BBCA, China. Anhui BBCA Pharmaceutical Co., Ltd., 16 Weisi Road, Baohe Industrial Park, HeFei, AnHui, 230051, China.
url: www.bbcayy.com

BBI, UK. BBI Healthcare, Unit A Kestrel Way, Garngoch Industrial Estate, Gorseinon, Swansea, SA4 9WN, UK.

BB-NCIPD, Philipp. See *Global, Philipp.*

BC Lutz, Switz. BCLutz Company Ltd, Pharmaceutical Products Switzerland, Dachslerenstrasse 11, P.O. Box, 8702 Zollikon, Switzerland.

BCL, Switz. See *BC Lutz, Switz.*

BCM, UK. BCM Ltd, Dio First 114, Nottingham, Nottinghamshire, NG90 2PR, UK.

BCP, Philipp. BCP Dermatological Corp., Dela Paz Bldg, 1570 Dapitan St, Sampaloc, Manila, Philippines.

BCS, Fr. See *CSP, Fr.*

BD, Mex. See *Becton Dickinson, Mex.*

BDF, Mex. See *Beiersdorf, Mex.*

BDH, India. BDH Industries Ltd, Nair Baug, Akurli Rd, Kandivli (East), Mumbai 400 101, India.
url: www.bhdind.com

BDI, USA. BDI Pharmaceuticals, Inc., 9700 North Michigan Rd, Carmel, IN 46220, USA.
url: www.bdi-marketing.com

Beach, USA. Beach Pharmaceuticals, 201 Delaware St, Greenville, SC 29605, USA.

Beaco, Hung. Beaco Bt, Retek u 32, 1024 Budapest, Hungary.

Beacon, Irl. See *Beocon, UK.*

Beacon, UK. Beacon Pharmaceuticals Ltd, 85 High St, Tunbridge Wells, Kent, TN1 1YG, UK.
url: www.beaconpharma.co.uk

Beacons, Hong Kong. See *Mekim, Hong Kong* and *Unipharm, Hong Kong.*

Beacons, Singapore. Beacons Pharmaceuticals Pte Ltd, 21 Chin Bee Ave, S 619942, Singapore.
url: www.beacons.com.sg

Beaubour Nutrition, Fr. Beaubour Nutrition, ZI La Conterie, B.P. 38, 37800 Sainte-Maure-de-Touraine, France.
url: www.beaubour.com

Beaufour, Cz. See *Beaufour, Fr.*

Beaufour, Fr. Beaufour Ipsen Pharma, 24 rue Erlanger, 75781 Paris cdx 16, France.
url: www.beaufour-ipsen.com

Beaufour, Irl. See *Beaufour, Fr.*

Beaufour, Switz. See *Uhlmann-Eyroud, Switz.*

Beaufour-Ipsen, China. Beaufour Ipsen (Tianjin) Pharmaceutical Co. Ltd., 18 Kaihua Road, Tianjin Huayan Hi-Tech Industry Park, Fukang Road, Nankoi District, Tianjin, 300384, China.
url: www.ipsen.com

Beaufour-Ipsen, Cz. Beaufour Ipsen International, Středni 57/7, 162 00 Prague 6, Czech Republic.

Beaufour-Ipsen, Hong Kong. See *IDS, Hong Kong.*

Beaufour-Ipsen, Hung. See *Ipsen, Hung.*

Beaufour-Ipsen, Israel. See *Medison, Israel.*

Beaufour-Ipsen, Malaysia. See *Antah, Malaysia.*

Beaufour-Ipsen, Pol. See *Ipsen, Pol.*

Beaufour-Ipsen, Rus. Beaufour Ipsen International SNC, Mosenka Park Tower, Taganskaya ul. 19, 109004 Moscow, Russia.
url: www.ipsen.com

Beaufour-Ipsen, Singapore. See *Sime Darby, Singapore.*

Beaufour-Ipsen, Switz. See *Uhlmann-Eyraud, Switz.*

Beaufour-Ipsen, Thai. See *Pacific, Thai.*

Beaufour-Ipsen, Ukr. Beaufour Ipsen International, Pushkinskaya Street, 36, Kiev, 01004, Ukraine.

Beaumont, Canad. See *Beaumont, USA.*

Beaumont, USA. Beaumont Bio-Med Inc., 23 1st Ave NE, Waukon, Iowa, 52172, USA.

Beauticontrol, Canad. See *Beauticontrol, USA.*

Beauticontrol, USA. Beauticontrol Inc., 4717 Plano Parkway, Carrollton, TX 75010, USA.

Beckman, Canad. See *Beckman, USA.*

Beckman, USA. Beckman Coulter Inc, 4300 North Harbour Bvld, P.O. Box 3100, Fullerton, CA 92834-3100, USA.
url: www.beckmancoulter.com

Beckmann, Ger. Dr Beckmann Pharma GmbH, Alte Traubinger Str. 17, 82340 Garatshausen, Germany.
url: www.drbeckmann.de

Becton Dickinson, Mex. Becton Dickinson de Mexico S.A. de C.V., Monte Pelvoux No. 111, Col. Lomas de Chapultepec, 11000 Mexico D.F., Mexico.
url: www.bd.com

Becton Dickinson, USA. Becton Dickinson & Co., 1 Becton Drive, Franklin Lakes, NJ 07417, USA.
url: www.bd.com

Bedford, USA. Bedford Laboratories, a Boehringer Ingelheim Company, 300 Northfield Rd, Bedford, OH 44146, USA.
url: www.bedfordlabs.com

Beecham, Belg. See *GSK, Belg.*

Beecham, Canad. See *GSK, Canad.*

Beecham, Fr. See *GSK, Fr.*

Beecham, Ger. See *GSK, Ger.*

Beecham, Irl. See *GSK, Irl.*

Beecham, Ital. See *GSK, Ital.*

Beecham, Neth. See *GSK, Neth.*

Beecham, Port. See *GSK, Port.*

Beecham, Spain. See *GSK, Spain.*

Beecham Research, UK. See *GSK, UK.*

Beethoven, Ger. Beethoven-Pharma Dr Wiemann GmbH, Steinthalstr. 1, 90455 Nurnberg, Germany.

Behrens, Venez. Laboratorio Behrens C.A., Industrio Farmacéutico Nacional, calle Real de Chopellín, Edif. Behrens, Caracas, Venezuela.
url: www.labbehrens.com

Behring, Israel. See *Medibrands, Israel.*

Behring, Ital. See *Sanofi-Aventis, Ital.*

Behring, Neth. See *Sanofi-Aventis, Neth.*

Behring, Norw. See *Aventis, Norw* and *Aventis Behring, Swed.*

Behring, Spain. See *ZLB, Spain.*

Behringwerke, Ger. See *CSL, Ger.*

Behringwerke, Hung. See *Plazmed, Hung.*

Behringwerke, Israel. See *Chemipharm, Israel.*

Bei Da Gao Ke Hua Tai, China. Bei Da Gao Ke Hua Tai Pharmaceutical Co Ltd, Shandong, China.

Bei Shi, China. Bei Shi Pharmaceutical Co. Ltd, Guangzhou, China.

Bei Te, China. Brilliant Pharmaceutical Co. Ltd, 15 Gao Peng Ave, Hi-Tech Industrial Development Zone, Changdu 610041, China.
url: www.btyy.com

Beida, China. Beida Pharmaceutical Co. Ltd, 4 Wan Shing St, Beijing Economic & Technological Development Zone, Beijing, 100176, China.

Beidefu, China. Beidefu Pharmaceutical Co. Ltd, Longshan, Cixi, Ningbo, Zhejiang, 315311, China.
url: www.cnbeidefu.com

Beiersdorf, Arg. Beiersdorf S.A., Triunvirato 2902, 1427 Buenos Aires, Argentina.
url: www.beiersdorf.com

Beiersdorf, Austria. Beiersdorf GmbH, Laxenburger Strasse 151, A-1101 Vienna, Austria.
url: www.beiersdorf.com

Beiersdorf, Belg. Beiersdorf NV SA, Industrielaan 30, B-1070 Brussels, Belgium.
url: www.beiersdorf.be

Beiersdorf, Canad. See *Smith & Nephew, Canad.*

Beiersdorf, Chile. Beiersdorf SA, Lo Espejo 501, Maipu, Santiago, Chile.

Beiersdorf, Denm. Beiersdorf A/S, Sydhavnsgade 16, 2 sal, 2450 Copenhagen SV, Denmark.
url: www.beiersdorf.dk

Beiersdorf, Fin. Beiersdorf Oy, Hovirinnantie, 20780 Kaarina, Finland.

Beiersdorf, Ger. Beiersdorf AG, Unnastr. 48, 20245 Hamburg, Germany.
url: www.beiersdorf.de

Beiersdorf, Gr. Beiersdorf, Ag. Nektariou 2, 153 44 Yerakas, Greece.

Beiersdorf, Hung. Beiersdorf Kft, Tartsay Vilmos u 3, 1126 Budapest, Hungary.

Beiersdorf, Irl. Beiersdorf Ireland Ltd, First Floor, Block 8, St John's Court, Santry, Dublin 9, Ireland.
url: www.beiersdorf.ie

Beiersdorf, Malaysia. See *Delfi, Malaysia.*

Beiersdorf, Mex. Beiersdorf Mexico S.A. de C.V., Poniente 116 No. 509, Col. Industrial Vallejo, 02300 Mexico D.F., Mexico.

Beiersdorf, Port. Beiersdorf Portuguesa, Lda, Rua Soeiro Pereira Gomes 59, 2746-952 Queluz, Portugal.
url: www.beiersdorf.com

Beiersdorf, Spain. Beiersdorf, Ctra Mataro-Granollers Km 5.4, Argentona, 08310 Barcelona, Spain.
url: www.beiersdorf.com

Beiersdorf, Swed. Beiersdorf Aktiebolag, Gullbergs Strandgata 4, 41104 Gothenburg, Sweden.
url: www.beiersdorf.se

Beiersdorf, Switz. Beiersdorf AG, Aliothstrasse 40, 4142 Münchenstein, Switzerland.
url: www.beiersdorf.com

Beiersdorf, Thai. Beiersdorf (Thailand) Co. Ltd, 12 Fl, Sathorn Thani Building 1, 90/30-33 North Sathorn Rd, Silom, Bangrak, Bangkok 10500, Thailand.
url: www.beiersdorf.com

Beiersdorf, UK. Beiersdorf UK Ltd, 2010 Solihull Parkway, Birmingham Business Park, Birmingham, B37 7YS, UK.
url: www.beiersdorf.com

Beiersdorf, USA. Beiersdorf Inc., Wilton Corporate Center, 187 Danbury Road, Wilton, CT 06897, USA.
url: www.beiersdorf.com

Beiersdorf, Venez. Beiersdorf S.A., Avenida Francisco de Miranda, Edificio Parque Cristal, Torre Este, piso 14 oficina 14A, Los Palos Grandes, Caracas, Venezuela.
url: www.beiersdorf.com

Beiersdorf-Lilly, Ger. See *Beiersdorf, Ger.*

Beifang, China. Beifang Pharmaceutical Co. Ltd, Shenyang, Liaoning, China.

Beige, S.Afr. See *Brunel, S.Afr.*

Beijing Four Rings, Philipp. See *Global Pharmatrade, Philipp.*

Beijing Kawin, Philipp. See *Pharma-Surrey, Philipp* and *Sahar, Philipp.*

Beijing Union, China. Beijing Union Pharmaceuticals, Metalworking Hongyang Tower A 6/F, 26 South Riverside Rd, Guang An Men, Beijing 100055, China.
url: www.unionpharm.net

Beijing Union, Ukr. See *Ekostatus, Ukr.*

BeiLu, China. BeiLu Pharmaceutical Co., Ltd, 7F Block A, Maples International Center, 32 XiZhiMen N. St., Haidian District, Beijing, 100082, China.
url: www.beilu.com.cn

Beiqi, China. Beiqi Pharmaceutical Co. Ltd, Liaoning, China.

Beisheng, China. Beisheng Pharmaceutical Co. Ltd, Guangxi, China.

Beisheng Hansheng, China. Beisheng Hansheng Pharmaceutical Co. Ltd, Zhejiang, China.

Beiyi Union, China. Beiyi Union Pharmaceutical Co. Ltd, 8 Hongda Road, Economic & Technological Development Zone, Beijing, 100176, China.

Beiyuan, China. Beiyuan Pharmaceutical Co. Ltd, 34 Fuxing West Rd, Xuhui District, Shanghai, 200031, China.

Beldenta, Switz. Beldenta-Anstalt, Birkenweg 6, FL-9490 Vaduz, Switzerland.

Belfar, Braz. Belfar Indústria Farmacêutica Ltda, Rua Alair Marques Rodrigues 516, 031560-220 Belo Horizonte, MG, Brazil.
url: www.belfar.com.br

Belkozin, Rus. Belkozin Ltd, 4 8th Verkhniy Pereulok, Promzona Parnas, St Petersburg, Russia.

Bell, India. Bell Pharma Pvt. Ltd, 119/7 Taikalwadi Road, Mahim, Mumbai 400 016, India.

Bell, UK. Bell, Sons & Co. (Druggists), P.O. Box 62, Tanhouse Lane, Widnes, Cheshire, WA8 0SA, UK.
url: www.bells-healthcare.com

Bell Kenz, Philipp. Bell Kenz Pharma Inc., R-II Bldg, 136 Malakas St, Diliman, Quezon City, Philippines.

Bellis, Hung. See *Phoenix, Hung.*

Bellon, Belg. See *GSK, Belg.*

Bellon, Fr. See *Sanofi-Aventis, Fr.*

Bellpharma, Irl. Bellpharma Ltd, First Floor, 69 St Patricks Rd, Dalkey, Co. Dublin, Ireland.

Bellwether, Austral. Bellwether, Australia.

Belmac, Spain. Belmac, C/Teide No 4, Planta Baja, Parque Empresarial La Marina, San Sebastian de los Reyes, 28700 Madrid, Spain.
url: www.belmac.com

Belmed, Rus. Belmed Preparat, ul. Partizanskaya d. 6 kv. 71, Altayskiy kray g Belokuriha, Russia.

Belmed, Ukr. Belmedpreparaty
url: www.belmedpreparaty.com

Belphar, Belg. See *Continental Pharma, Belg.*

Belpharma, Belg. See *Bournonville, Belg.*

Belupo, Cz. See *Podravka, Cz.*

Belupo, Pol. See *Nepentes, Pol.*

Belupo, Rus. Belupo, Lomonosovskii 38, kv 71-72, 119330 Moscow, Russia.
url: www.belupo-dd.ru

Belvedere, Canad. Belvedere International Inc., 5675 Keaton Cres., Mississauga, Ontario, L5R 3G3, Canada.

Bemed, Thai. Bemed Pharmaceuticals LP, 254 Suksawad Rd, Ratburana, Bangkok, 10140, Thailand.

Ben Venue, China. See *Three Rivers, USA.*

Ben Venue, Rus. See *AstraZeneca, Rus.*

Benarth, Canad. Produits Pharmaceutiques Benarth, 118 rue St-Odilon, Beauce Nord, Quebec, G0S 3A0, Canada.

Bencard, Belg. See *GSK, Belg.*

Bencard, Canad. See *Western Allergy, Canad.*

Bencard, Ger. Bencard Allergie GmbH, Messerschmittstr. 4, 80992 Munich, Germany.
url: www.bencard.de

Bencard, Irl. See *GSK, Irl.*

Bencard, Neth. See *GSK, Neth.*

Bencard, S.Afr. See *GSK, S.Afr.*

Bencard, UK. See *GSK, UK.*

Bendalis, Ger. Bendalis GmbH, Keltenring 17, 82041 Oberhaching, Germany.

Bene, China. See *Bene, Ger.*

Bene, Cz. See *Bene, Ger.*

Bene, Ger. bene-Arzneimittel GmbH, Herterichstr. 1, 81479 Munich, Germany.
url: www.bene-arzneimittel.de

Bene, Hung. See *Keri, Hung.*

Bene, Malaysia. See *Mederis, Malaysia.*

Bene, Pol. See *Miralex, Pol.*

Bene, Switz. See *Max Ritter, Switz.*

Bene, Ukr. See *Alpen, Ukr.*

Bene-Chemie, Hong Kong. See *Universal, Hong Kong.*

Benecor, Philipp. See *Diethelm, Philipp.*

Benedetti, Ital. Benedetti S.p.A., Vicolo Dè Bacchettoni 1, 51100 Pistoia (PT), Italy.

Benefoot, UK. Benefoot UK Ltd, Branson Court, Branson St, Manchester, M40 7FP, UK.

Benesis, Jpn. Benesis Corp. Ltd, 2-6-18 Kitahama, Chuo-ku, Osaka 541-8505, Japan.

Bengue, Irl. See *Roche, Irl.*

Bengue, UK. See *Solvay, UK.*

Benguerel, Chile. See *Andromaco, Chile.*

Benitol, Arg. Laboratorios Benitol S.A.C.I., Felipe Vallese 3340/44, 1407 Buenos Aires, Argentina.
url: www.laboratoriosbenitol.com

Benmoon, India. Benmoon Pharma Research Pvt Ltd, 403 Jeet Complex, Nr Jain Temple Lane, CG Road, Ahmedabad 380 009, India.
url: www.benmoonpharma.com

Bennet, India. Bennet Pharmaceuticals Ltd, 608 'B' Wing Manubhai Tower, Sayajigung, Gujarat, Baroda 390 005, India.
url: www.bennetpharmaceuticals.com

Bennett, Gr. Bennett Farmakevtiki AE, K Korela 15 & Parnithos, 145 64 N Kifisia, Greece.

Bennett, UK. Bennett Natural Products, Enterprise House, Richmond Hill, Wigan, Lancashire, WN5 8AA, UK.
url: www.healthremedies.co.uk

Bennetts, S.Afr. Bennetts, P.O. Box 76076, Wendywood 2144, South Africa.
url: www.colic.co.za

Bensons Bottom, USA. Bensons Bottom, P.O. Box 5342, North Muskegon, MI 49445, USA.
url: www.bensonsbottompaint.com

Bentfield, Canad. See *Benfield, Neth.*

Bentfield, Neth. Bentfield Europe BV, Hillgom, 2180 AG, Netherlands.

Bentley, Cz. See *Bentley, Irl.*

Bentley, Irl. Bentley Pharmaceuticals Ireland Ltd, 25/28 North Wall Quay, Dublin 1, Ireland.

Benzon, Neth. See *Lundbeck, Neth.*

Benzon, Swed. See *Nycomed, Swed.*

Benzon, UK. See *Amersham, UK.*

Berenguer Infale, Spain. See *Almirall, Spain.*

Beres, Hung. Béres Gyógyszergyár Rt, Szépvölgyi u 135, 1037 Budapest, Hungary.

Beres, Rus. Beres Pharmaceuticals Co. Ltd, Krasnaya Presnya ul. 1-7, Moscow, Russia.

Beres, Ukr. Béres Pharmaceuticals Co. Ltd., Streletskaya Street, 16, Kiev, 01034, Ukraine.
url: www.beres.hu

Bergamo, Braz. Lab. Quím. Farmacêutico Bergamo Ltda, Rua Rafael de Marco 43, 06765-000 Taboao da Serra, SP, Brazil.

Bergamon, Ital. See *Chefaro, Ital.*

Bergen Brunswig, USA. See *AmerisourceBergen, USA.*

Berk, Cz. See *Glynn, Cz.*

Berk, Irl. See *Blackhall, Irl.*

Berk, Turk. Berk İlaç İthalat ve Pazarlama A.Şti., Abc Yolu, Abc Plaza, Istinye, İstanbul, 80860, Turkey.
url: www.berkilac.com

Berk, UK. See *Teva, UK.*

Berk Farma, Turk. See *Dem, Turk.*

Berko, Turk. Berko İlaç ve Kimya San Ltd. Şti., Yeni Çamlıca Mah. Baraj Yolu, Cad. Özgür Sok. No:16, Y. Dudullu-Ümraniye, İstanbul, Turkey.
url: www.berko.com.tr

Berksam, Turk. Berksam İlaç Ticaret AS, PK 226 Sirkeci, Istanbul, Turkey.

Berlex, NZ. See *Schering, NZ.*

Berlex, Port. Berlex Especialidades Farmacêuticas Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.

Berlex, USA. See *Bayer, USA.*

Berli Jucker, Thai. Berli Jucker Public Co Ltd, 99 Soi Rubia, Sukhumvit 42 Rd, Phrakanong, Klongtoey, Bangkok 10110, Thailand.
url: www.bjc.co.th

Berlico Mulia, Indon. Berlico Mulia Farma, Jl Juwangen Kalasan Km 10.6, Tromol Pos No 8, Yogyakarta 55571, DI Yogyakarta, Indonesia.

Berlifarma, Port. Berlifarma Especialidades Farmacêuticas Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.

Berlimed, Braz. See *Schering, Braz.*

Berlimed, Israel. See *Berlimed, Port.*

Berlimed, Port. Berlimed Especialidades Farmacêuticas Lda, Estrada Nacional 249, Km 15, 2725-397 Mem-Martins, Portugal.

Berlin, Hong Kong. See *Ebewe, Hong Kong.*

Berlin Pharm, Rus. Berlin-Pharma ZAO Moscow, ul. Kashirskoe 22-3, Str. 3, 115201 Moscow, Russia.
url: www.berlin-chemie.ru

Berlin Pharm, Singapore. See *Polymedic, Singapore.*

Berlin Pharm, Thai. Berlin Pharmaceutical Industry Co. Ltd, 359 New Rd, Bangkok 10100, Thailand.
url: www.berlinpharm.com

Berlin-Chemie, China. Berlin-Chemie, 19 Jianguomenwai St, R00m 801B International Building, Beijing 100004, China.

Berlin-Chemie, Cz. Berlin-Chemie Menarini Group, Komarková 27, 148 00 Prague 4, Czech Republic.

Berlin-Chemie, Denm. Berlin Chemie ApS, Sdr. Jernbanevej 4C 2, 3400 Hillerød, Denmark.

Berlin-Chemie, Fin. See *Berlin-Chemie, Ger.*

Berlin-Chemie, Ger. Berlin-Chemie AG, Glienicker Weg 125, 12489 Berlin, Germany.
url: www.berlin-chemie.de

Berlin-Chemie, Hung. Berlin-Chemie Képviselet, Váci út 113, 1138 Budapest, Hungary.

Berlin-Chemie, Pol. Berlin-Chemie/Menarini Polska Sp. zo.o., ul. Cybernetyki 7, 02-677 Warsaw, Poland.
url: www.berlin-chemie.pl

Berlin-Chemie, Rus. See *Berlin Pharm, Rus.*

Berlin-Chemie, Ukr. Berlin-Chemie Menarini, Bereznyakovskaya Street, 29, 7th floor, Kiev, 02098, Ukraine.
url: www.berlin-chemie.ua

Berlipharm, Fr. See *Schering, Fr.*

Berlipharm, Irl. See *Clissmann, Irl.*

Berlipharm, Neth. Berlipharm BV, Van Houten Industriepark 1, 1381 MZ Weesp, Netherlands.

Berlis, Switz. Berlis AG 704 Blegistrasse 3, 6341 Baar, Switzerland.

Berman, Mex. Berman Laboratorios S.A. de C.V., Laboratoristas No. 46, Col. Iztapalapa Sifon, 09400 Mexico D.F., Mexico.

Berna, Austria. See *Berna, Ital.*

Berna, Belg. See *Docpharma, Belg.*

Berna, Canad. See *Berna, USA.*

Berna, China. See *Crucell, China.*

Berna, Cz. See *Berna, Switz.*

Berna, Denm. See *SBL, Swed.*

Berna, Fin. See *SBL, Swed.*

Berna, Hong Kong. See *Keller, Hong Kong.*

Berna, Indon. Berna Biotech Korea Corp., 501A Graha Bumiputra, Jl Asia Afrika No 141-149, Bandung 40112, Indonesia.
url: www.bernabiotech.co.kr

Berna, Irl. See *Crucell, UK.*

Berna, Israel. See *Crucell, Neth.*

Berna, Ital. Berna Biotech Italia S.r.l., Via Zambeletti 25, 20021 Baranzate (MI), Italy.
url: www.bernabiotech.it

Berna, Malaysia. See *DKSH, Malaysia.*

Berna, Neth. See *Berna, Ital.*

Berna, Norw. See *SBL, Norw.*

Berna, NZ. See *Pharmabroker, NZ.*

Berna, Philipp. See *Diethelm, Philipp* and *Vizcarra, Philipp.*

Berna, Pol. See *Biomed Krakow, Pol.*

Berna, Port. See *Vieira, Port.*

Berna, Rus. See *Crucell, Neth.*

Berna, Singapore. See *DKSH, Singapore.*

Berna, Spain. Berna Biotech España, Ctra de Irun Km 20.9, 28700 San Sebastian de los Reyes, Madrid, Spain.
url: www.bernabiotech.es

Berna, Switz. Berna Biotech AG, Rehhagstrasse 79, 3018 Berne, Switzerland.

Berna, Thai. See *Diethelm, Thai.*

Berna, Turk. C/o Yeni Şark Ecza Deposu A.Ş., Balmumcu, Barbaros Bulvarı, Hoşsohbet Sok. 2, Beşiktaş, İstanbul, Turkey.
url: www.bernabiotech.com

Berna, Ukr. See *Crucell, Neth.*

Berna, USA. Berna Products Corp., 4216 Ponce de Leon Blvd, Coral Gables, FL 33146, USA.
url: www.bernaproducts.com

Berna, Venez. See *Farma, Venez.*

Bernabo, Arg. Laboratorios Bernabo SA, Terrada 2346, 1416 Buenos Aires, Argentina.

Berner, Swed. Bröderna Berner Hab, Box 50132, 202 11 Malmö, Sweden.
url: fiberweb01.berner.fi

Bernofarm, Indon. Bernofarm PT, Kompleks Harmoni Plaza, Blok J No 3-4, Jl Suryopranoto, Jakarta Pusat 10130, DKI Jaya, Indonesia.

Berren, Fin. Berren Oy, Pohjoinen Hesperiankatu 13 B 15, 00260 Helsinki, Finland.

Bersan, Ital. Bersan Cosmetica Ipoallergenica S.r.l., Via delle Pervinche 10, 00171 Rome (RM), Italy.
url: www.bersan.it

Berta, Ital. Berta S.r.l., Via Andrea Doria 7, 20124 Milan (MI), Italy.

Bertek, USA. Bertek Pharmaceuticals Inc, 781 Chestnut Ridge Rd, Morgantown, WV 26505, USA.
url: www.bertek.com

Bertram, Thai. Bertram Chemical (1982) Co Ltd, 71 Soi Chantima 5, Ladprao 80, Wangtonglang, Bangkok 10310, Thailand.
url: www.bertram1982.com

Bescansa, Spain. Bescansa, Pl. Inds. Tambre-via Pasteur 8, Santiago de Compostela, 15890 La Coruna, Spain.

Besins, Austria. See *Besins, Fr.*

Besins, Belg. Besins Distribution Belgium, rue Villain XIIII 53-55, 1000 Brussels, Belgium.
url: www.besins.be

Besins, China. See *Besins, Fr.*

Besins, Cz. See *Besins, Fr.*

Besins, Denm. See *Bayer, Denm.*

Besins, Fin. See *Besins, Fr.*

Besins, Fr. Laboratoires Besins International, 13 rue Perier, 92120 Montrouge, France.

Besins, Ger. See *Kade, Ger.*

Besins, Gr. See *Besins, Fr.*

Besins, Hong Kong. See *Bi Asian Pacific, Hong Kong.*

Besins, Hung. Besins, Hungary.

Besins, Irl. See *Besins, Belg.*

Besins, Israel. See *CTS, Israel.*

Besins, Ital. See *Bayer, Ital.*

Besins, Malaysia. See *Wellchem, Malaysia.*

Besins, Neth. See *Besins, Fr.*

Besins, Norw. See *Schering, Swed.*

Besins, Pol. See *Solvay, Pol.*

Besins, Port. See *Besins, Fr.*

Besins, Rus. Besins Healthcare Russia, Bolshoy Tishinskiy, Pereulok 38 2nd floor, Moscow 123557, Russia.

Besins, Singapore. See *Pharmed, Singapore.*

Besins, Thai. See *Berli Jucker, Thai.*

Besins, UK. See *Besins, Fr.*

Besins, Ukr. See *Besins, Rus.*

Besins International, Israel. See *CTS, Israel.*

Besins-Iscovesco, Fr. See *Besins, Fr.*

Besins-Iscovesco, Hong Kong. See *Bi Asian Pacific, Hong Kong* and *JDH, Hong Kong.*

Besins-Iscovesco, Israel. See *CTS, Israel.*

Besins-Iscovesco, Malaysia. See *Wellchem, Malaysia.*

Besins-Iscovesco, Switz. See *Golaz, Switz.*

Besins-Iscovesco, Thai. See *International Pharmaceuticals, Thai.*

Besius, Hung. See *Pliva, Hung.*

Best, Mex. Laboratorios Best S.A. de C.V., Municipio Libre No. 199, Col. Benito Juarez Portales, 03300 Mexico D.F., Mexico.

Best Medical, Belg. Best Medical Belgium SA, Zoning Industriel, 6220 Fleurus, Belgium.

Best Medical, Neth. See *Best Medical, Belg.*

Bestochem, India. Bestochem Formulations (India) Ltd, 2 Mohakampur Industrial Complex, Phase I, Delhi Road, Meerut 250 002, India.
url: www.bestochem.com

Beta, Arg. Laboratorios Beta S.A., Av. San Juan 2266, 1232 Buenos Aires, Argentina.
url: www.betalab.com.ar

Beta, China. Beta Pharmaceutical Co. Ltd, Beigong Software Park Building 29, Economic Development Zone, Sheng North St, Beijing, 100176, China.
url: www.betapharma.com.cn

Beta, Ital. Laboratorio Biologico Chemioterapico Beta S.r.l., Via IV Novembre 171/173, 25080 Prevalle (BS), Italy.

Beta, S.Afr. Beta Pharmaceuticals CC, 17 Seaway Ave, Kine Bay, Port Elizabeth 6011, South Africa.

Beta, Spain. See *AstraZeneca, Spain.*

Beta, USA. Beta Dermaceuticals, P.O. Box 691106, San Antonio, TX 78269-1106, USA.
url: www.beta-derm.com

Beta Healthcare, UK. Beta Healthcare, Standard House, Prospect Place, Lenton, Nottingham, Nottinghamshire, NG7 1RX, UK.

Be-Tabs, S.Afr. Be-Tabs Pharmaceuticals (Pty) Ltd, P.O. Box 43486, Industria 2042, South Africa.
url: www.be-tabs.co.za

Betamadrileno, Spain. Betamadrileño, Area Empresarial Andalucia, Sector 4 Parcela 28, Getafe, 28906 madrid, Spain.

Betapharm, Denm. See *Betapharm, Ger.*

Betapharm, Fin. See *Betapharm, Ger.*

Betapharm, Ger. betapharm Arzneimittel GmbH, Kobelweg 95, 86156 Augsburg, Germany.
url: www.betapharm.de

Betapharm, Neth. See *Betapharm, Ger.*

Betco, Canad. See *Betco, USA.*

Betco, USA. Betco Corp., 1001 Brown Ave, Toledo, OH 43607, USA.

Beutlich, USA. Beutlich Pharmaceuticals, 1541 Shields Drive, Waukegan, IL 60085, USA.
url: www.beutlich.com

Bevo, Gr. Bevo, 104 38 Athens, Greece.

Bewell, India. Bewell Labs Pvt Ltd, Rabindra Nagar, P.O. Laskarpur, Kolkata 700 153, India.

Bexal, Spain. Bexal Farmaceutica, C/ Osa Mayor n: 4, Edificio Osa Mayor, Oficina B, Aravaca, 28023 Madrid, Spain.
url: www.bexal.es

Beximco, Philipp. See *Interlink, Philipp.*

Beximco, Singapore. See *Advanced, Singapore.*

Bharat, India. Bharat Serum & Vaccines Ltd, Hoechst House 16th Floor, Nariman Point, Mumbai 400 021, India.
url: www.bharatserums.com

Bharat, Philipp. See *Pharmawealth, Philipp.*

Bharat, Rus. See *Bharat, India.*

Bharat, Thai. See *Biogenetech, Thai.*

BHR, UK. BHR Pharmaceuticals Ltd, 41 Centenary Business Centre, Hammond Close, Attleborough Fields, Nuneaton, Warkwickshire, CV11 6RY, UK.
url: www.bhr.co.uk

BI, Gr. See *Boehringer Ingelheim, Gr.*

Bi Asian Pacific, Hong Kong. Bi Asian Pacific Ltd, Flat B, 22/F, Tak Lee Commercial Building, 113-117 Wan Chai Rd, Wanchai, Hong Kong.

Biagini, Cz. See *Kedrion, Ital.*

Biagini, Ital. See *Kedrion, Ital.*

Bial, Austria. See *Bial, Port.*

Bial, Cz. See *Bial, Port.*

Bial, Denm. See *Cephalon, Denm.*

Bial, Gr. See *Bial, Port.*

Bial, Irl. See *Bial, Port.*

Bial, Neth. See *Bial, Port.*

Bial, Pol. See *Bial, Port.*

Bial, Port. Laboratorios Bial (Portela & Co., SA), Av da Siderurgia Nacional, Apartado 19, 4745-457 São Mamede do Coronado, Portugal.
url: www.bial.com

Bial, Spain. Bial-Industrial Farmaceutica, Alameda de Urquijo 27, Bilbao, 48008 Vizcaya, Spain.
url: www.bial.es

Bial-Aristegui, Spain. See *Bial, Spain.*

Bialfar, Port. See *Bial, Port.*

Bialport, Port. See *Bial, Port.*

Biara, Port. Biara Produtos Farmacêuticos Lda, Rua Ramalho Ortigão 45 A, 1070-228 Lisbon, Portugal.

Bichsel, Switz. Laboratorium Dr G Bichsel AG, Bahnhofstrasse 5a, 3800 Interlaken, Switzerland.

Bicther, Spain. See *Inkeysa, Spain.*

Bieffe, Cz. See *Bieffe, Ital.*

Bieffe, Ital. Bieffe Medital S.p.A., Via Nuova Provinciale, 23034 Grosotto (SO), Italy.

Bieffe, Spain. See *Baxter, Spain.*

Biem, Turk. Biem İlaç, 57 Sokak No:19/1, Emek, İstanbul, Turkey.
url: www.biemilac.com.tr

Bier, Ital. Bier Farmaceutici di A. di Finizio S.a.s., Via Cupa Capodichino 19, 80144 Naples (NA), Italy.
url: www.bierfarmaceutici.it

Biex, Irl. See *Helsinn Birex, Irl.*

Bifarma, Ital. Bifarma Fitoterapici di Bignardi Sergio, Via Pallia 5, 20139 Milan, Italy.

Bifodan, Denm. Bifodan A/S, Bogbinderivej 6, 3390 Hundested, Denmark.
url: www.bifodan.com

Bifodan, Pol. See *Krotex, Pol.*

Bifodan, Swed. See *Bifodan, Denm.*

Bigfarma, Port. Bigfarma, Av. Principal 79, Pinhal dos Frades, 2840-166 Seixal, Portugal.

Bigman, Swed. Bigman AB, Järnvägsgatan 5, 172 75 Sundbyberg, Sweden.
url: www.bigmandental.se

Bikai, China. Bikai Pharmaceutical Co. Ltd, Hainan, China.

Bikang, China. Bikang Pharmaceutical Co. Ltd, Shaanxi, China.

Biken, Canad. See *Osaka University, Jpn.*

Bilim, Thai. See *JDH Borneo, Thai.*

Bilim, Turk. Bilim İlaç San. ve Tic A.Ş., Ayazaga Koyu Yolu No:6, Maslak, İstanbul, 34398, Turkey.
url: www.bilimpharma.com

Bilim, Ukr. See *Delta Medical, Ukr.*

Billev, Denm. Billev Pharma Aps, Elmegardsvej 1A, 3630 Jaegerspris, Denmark.
url: www.billevpharma.dk

Billev, Fin. See *Billev, Denm.*

Billev, Pol. See *Merck, Pol.*

Binesa, Spain. See *Pfizer, Spain.*

Binhu Shuanghe, China. Binhu Shuanghe Pharmaceutical Co. Ltd, Chengnan Industrial Zone, Tongxin, Rongcheng, Jianli Jingzhou, Hubei, 433300, China.

Binnofarm, Rus. See *Moschimfarm, Rus.*

Bintang Toedjoe, Indon. Bintang Toedjoe PT, Jl Jend A Yani 2, Pulo Mas, 13210 Jakarta, Indonesia.

Bio Farma, Malaysia. See *Propharm, Malaysia.*

Bio Farma, Thai. See *Biogenetech, Thai.*

Bio Health Care, Ital. Bio Health Care Srl, Via Marco Polo 69/4, 30019 Chioggia (VE), Italy.

Bio Macro, Braz. Bio Macro Laboratório Farmaceutico Ltda, Av. do Café 277, 4311900 Sao Paulo, Brazil.

Bio Minerals, Philipp. See *Zuellig, Philipp.*

Bio Portugal, Port. Bioportugal Quimico Farmacêutica Lda, Alameda Fernão Lopes 19 E, Miraflores, 1495-135 Algés, Portugal.

Bio Products, Malaysia. See *Germax, Malaysia.*

Bio Sidus, Thai. See *Berli Jucker, Thai.*

BioAlliance, Cz. See *BioAlliance, Fr.*

BioAlliance, Denm. See *BioAlliance, Fr.*

BioAlliance, Fin. See *BioAlliance, Fr.*

BioAlliance, Fr. BioAlliance Pharma AS, Boulevard du Général Martial Valin 49, 75015 Paris, France.
url: www.bioalliancepharma.com

BioAlliance, Ger. See *BioAlliance, Fr.*

BioAlliance, Irl. See *BioAlliance, Fr.*

BioAlliance, Neth. See *BioAlliance, Fr.*

BioAlliance, Pol. See *BioAlliance, Fr.*

BioAlliance, USA. See *BioAlliance, Fr.*

Bioavenir, Israel. Bioavenir Ltd, 13 Kehilat Saloniki St, 69513 Tel Aviv Yafo, Israel.

Biobasal, Cz. See *Biobasal, Switz.*

Biobasal, Switz. Biobasal AG, Eulerstrasse 55, 4003 Basle, Switzerland.

Biobasit, Canad. Biobasit Distribution, 1053 Châteauneuf, St-Jérôme, Quebec, J5L 1H7, Canada.

Biobras, Braz. See *Novo Nordisk, Braz.*

Biocad, Rus. Biocad, selo Petrovo-Dalbiee, Kranogorskii raion, 143422 Moscow, Russia.
url: www.biocad.ru

BioCalth, UK. BioCalth International (UK) Ltd., Airdale Business Centre, Millennium Road, Skipton, North Yorkshire, BD23 2TZ, UK.
url: www.biocalth.co.uk

Biocel, Turk. Biocel, Turkey.

Biocell, Singapore. See *MD, Singapore.*

Bioceutica, Arg. Biocéutica SA, Blas Parera 4233/37, 1636 Olivos, Buenos Aires, Argentina.

Bioceuticals, UK. Bioceuticals Ltd, 26 Zennor Rd, London, SW12 0PS, UK.
url: www.bioceuticals.co.uk

Biochefa, Pol. Biochefa Farnaceutyczny Zakład Naukowo-Produkcyjny, ul. Kasztanowa 3, 41-205 Sosnowiec, Poland.
url: www.biochefa.pl

Biochem, Canad. See *Shire Biologics, Canad.*

Biochem, China. Biochem Pharmaceutical Factory, Plant C1, Yuanlin Rd, Zhuhai City 519015, China.

Biochem, Gr. Biochem Diagnostics S.A., 6 Zisimopoulou Str. & Sygrou Ave, 175 64 P. Faliro, Greece.
url: www.biochem.gr

Biochem, India. Biochem Pharmaceutical Industries Ltd, Aidun Building, John Crasto Lane, Mumbai 400 002, India.
url: www.biochemgroup.com

Bio-Chemical, Canad. See *Ratiopharm, Canad.*

Biochemie, China. See *Sandoz, China.*

Biochemie, Cz. Biochemie Austria, Ulice 1. pluku 17, 186 00 Prague 8, Czech Republic.
url: www.biochemie-generics.cz

Biochemie, Denm. See *Orphan, Denm.*

Biochemie, Fin. See *Novartis, Fin.*

Biochemie, Hong Kong. See *Unipharm, Hong Kong.*

Biochemie, Hung. See *Novartis, Hung.*

Biochemie, Indon. See *Anugerah Pharmindo, Indon.*

Biochemie, Israel. See *Novartis, Israel.*

Biochemie, Norw. See *Novartis, Norw.*

Biochemie, NZ. See *CSL, NZ.*

Biochemie, Rus. See *Novartis, Rus.*

Biochemie, Singapore. See *FP, Singapore.*

Biochemie, Swed. See *Novartis, Swed.*

Biochemie, Thai. See *Novartis, Thai.*

Biochemie, Venez. See *Novartis, Venez.*

Biochemix, India. Biochemix Health Care Pvt Ltd, 7F DAV Market Yamuna Nagar, 135 001, India.

Biochimic, Rus. Biochimic Ltd, Vasenko ul 15a, 430030 Saransk, Russia.
url: www.biohim.moris.ru

Biochimici, Ital. Biochimici PSN S.p.A., Via Viadagola 30, 40050 Quarto Inferiore (BO), Italy.
url: www.biochimici.it

Biochimico, Braz. Instituto Biochimico Ltda, Rod. Presidente Dutra km 310, 27580-000 Rio de Janeiro, RJ, Brazil.

Biocide, S.Afr. Biocide Ltd, P.O. Box 33, 236 Sir Lowry Rd, Woodstock 7915, South Africa.

Biocin, India. Biocin Genetics & Pharma, 414 Satyam Mall, Near Satellite Tower, Ahmedabad, India.

Biocine, Ital. See *Novartis Vaccines, Ital.*

Bioclon, Mex. Laboratorios Bioclon S.A. de C.V., Calz. de Tlalpan 4687, Coyoacan Toriello Guerra, 14050 Mexico D.F., Mexico.
url: www.bioclon.com.mx

Bioclones, S.Afr. Bioclones (Pty) Ltd, P.O. Box 784351, Sandton 2146, South Africa.
url: www.bioclones.co.za

Biocodex, Belg. See *Biocodex, Fr.*

Biocodex, China. See *CMS, China.*

Biocodex, Cz. See *Biocodex, Fr.*

Biocodex, Denm. See *Biolac, Swed.*

Biocodex, Fin. See *Algol, Fin.*

Biocodex, Fr. Laboratoires Biocodex, 7 ave Gallieni, 94257 Gentilly Cdx, France.
url: vdocx.biocodex.com

Biocodex, Hong Kong. See *Primal, Hong Kong.*

Biocodex, Hung. See *Biocodex, Fr.*

Biocodex, Irl. See *Biocodex, Fr.*

Biocodex, Neth. See *Biocodex, Fr.*

Biocodex, Pol. See *Perffarma, Pol.*

Biocodex, Port. See *Biocodex, Fr.*

Biocodex, Rus. See *Pharmaregie, Rus.*

Biocodex, Spain. See *Biocodex, Fr.*

Biocodex, Switz. See *Biomed, Switz.*

Biocodex, Thai. See *Diethelm, Thai.*

Biocodex, Ukr. See *Brupharmexport, Ukr.*

Biocodex, USA. Biocodex, 300 North Mill St, Cresswell, OR 97426, USA.

Bio-Collagen, Malaysia. See *Averroes, Malaysia.*

BioComp, USA. BioComp, 10999 IH 10 West, Suite 1000, San Antonio, TX 78230, USA.
url: biocomppharma.com

Biocompatibles, USA. Biocompatibles Inc., 115 Hurley Rd, Building 3F, Oxford, CT 06478, USA.
url: www.btgplc.com

Biocon, India. Biocon Ltd, 20th KM Hosur Road, Electronics City, Bangalore 560 100, India.
url: www.biocon.com

Biocon, Thai. See *Berlin Pharm, Thai.*

Bioconcepts, UK. Bioconcepts Ltd, P.O. Box 15, Havant, Hampshire, PO9 1RQ, UK.
url: www.bioconcepts.co.uk

Biocontrol, Arg. Biocontrol S.A., Fraga 1504, 1427 Buenos Aires, Argentina.

Biocontrolfarm, Ital. Biocontrolfarm s.n.c., Via dell'Epomeo 72, 80126 Naples, Italy.

Biocraft, USA. See *Teva, USA.*

Biocrom, Arg. Lab. Biocrom Esp. Med. S.A., Luis Viale 965, 1416 Buenos Aires, Argentina.

Biocur, Ger. See *Hexal, Ger.*

Biodeal, India. Biodeal Laboratories Pvt Ltd, 508 GIDC Estate, Wadhwan City 363 035, Gujarat, India.
url: www.savaglobal.com

Biodeal, Rus. See *Biodeal, India.*

Biodeal, Thai. See *ST, Thai.*

Biodelta, Ital. Biodelta Sas del Dott. Pantaleone Di Lauro, Via Grottole 80, 81020 Castel Morrone (CE), Italy.

Bioderma, Fr. Bioderma, 75 cours Albert-Thomas, 69447 Lyon cdx 03, France.
url: www.bioderma.com

Bioderma, Ital. Bioderma Italia S.r.l., Piazzale Luigi Cadorna 10, 20123 Milan (MI), Italy.
url: www.bioderma.it

Bioderma, Venez. Laboratorios Bioderma (Dermabel S.A.), Calle los Manguitos, Torre Mega III, Piso 3, Of. 3D Urb. Las Palmas, Caracas, Venezuela.

Biodiagnostics, Austral. See *National Diagnostic, Austral.*

Bio-Diat, Cz. See *Bio-Diat, Ger.*

Bio-Diat, Ger. Bio-Diät-Berlin GmbH, Selerweg 43-45, 12169 Berlin, Germany.
url: www.bio-diaet-berlin.de

Bio-Diat, Israel. See *Bio-Diat, Ger.*

Bio-Diat, Norw. See *Bio-Diat, Ger.*

Biodica, Austral. Biodica Pty Ltd, 14 Cliffbrook Cres, Emu Plains, NSW 2750, Australia.

Biodica, Fr. Laboratoires Biodica, 1 rue Raymond Aron, 92160 Antony cdx, France.

Biodim, Fr. Biodim, 17 rue de l'Ancienne Mairie, 92100 Boulogne-Billiancourt, France.

Biodiphar, Belg. Biodiphar SA, Rue des Trois Arbres 16a, 1180 Brussels, Belgium.
url: www.biodiphar.be

Bio-Dis, Canad. Bio-Dis 9185-5908 Quebec Inc., 2675 Blvd Ford, Chateauguay, Quebec, J6J 4Z2, Canada.

Bio-Drug, India. Bio-Drug Laboratories Pvt Ltd, 348 Maharaja Nanda Kumar Rd (N), Kolkata 700 035, India.

Bioenvision, Austria. See *Genzyme, UK.*

Bioenvision, Cz. See *Genzyme, UK.*

Bioenvision, Neth. See *Genzyme, UK.*

Bioenvision, Port. See *Genzyme, UK.*

Bioenvision, Spain. See *Genzyme, UK.*

Bioenvision, UK. See *Genzyme, UK.*

Bioethic, Fr. Laboratoires Bioethic, 51 bd de Courcelles, 75008 Paris, France.

Bioethical, Ital. Bioethical S.r.l., Piazza Mazzini 2, 41100 Modena (MO), Italy.

Bioetrusca, Ital. Bioetrusca di cesare Pini, Via Lorenzo il Magnifico 69, 50129 Firenze, Italy.

Bioextra, Hung. Bioextra Kft, Bibor u 10, 1149 Budapest, Hungary.

Biofarm, Cz. See *Biofarm, Pol.*

Biofarm, Fin. See *Biofarm, Pol.*

Biofarm, Neth. See *Biofarm, Pol.*

Biofarm, Pol. Biofarm Sp. zo.o., ul. Wałbrzyska 13, 60-198 Poznań, Poland.
url: www.biofarm.pl

Biofarm, Rus. See *Marvel, Rus.*

Biofarma, Mex. Biofarma Natural CMD SA de CV, Industria Hulera 97 Fracc. Indust., 45130 Zapopan Norte Zapopan, Jalisco, Mexico.

Biofarma, Turk. Biofarma İlaç San. Ltd. Şti., Samandira Baldesi, Veysel Karani Mah. No:48, Kartal, İstanbul, 81470, Turkey.
url: www.biofarma.com.tr

Biofarma, Venez. Laboratorio Biofarma C.A., Av. Rio Caura Torre Humboldt Piso 11, Oficina 1107, Prados del Este, Caracas 1080, Venezuela.

Biofarmkombinat, Rus. Biofarmkombinat "Roskarfarm", ul. Sedina D.70, 350000 G Krasnodar, Russia.

BioFemme, Philipp. BioFemme Inc. (Unilab Womens Healthcare), 2/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Philippines.

Biofilm, USA. Biofilm Inc., 3225 Executive Ridge 1707 Vista, CA 92081, USA.
url: www.astroglide.com

Bio-Fizik, Turk. Bio-Fizik Medical, Meşrutiyet Cad. No: 29/23, Kizilay, Ankara, Turkey.

Biofarce, Canad. Bioforce Canada Inc., 1111 Gorham, Unit 9, Newmarket, Ontario, L3Y 7V1, Canada.
url: www.bioforce.ca

Bioforce, Denm. Bioforce Danmark AS, Håndvaerkervej 17 B, 8643 Ans, Denmark.

Bioforce, Ger. Bioforce GmbH, Brühlstr. 15, 78465 Constance, Germany.
url: www.bioforce.de

Bioforce, Irl. See *Bioforce, UK.*

Bioforce, Norw. See *Bioforce, Swed.*

Bioforce, Swed. Svenska Bioforce AB, Box 147, 221 00 Lund, Sweden.
url: www.bioforce.se

Bioforce, Switz. Bioforce AG, Postfach 76, 9325 Roggwil/TG, Switzerland.
url: www.bioforce.ch

Bioforce, UK. Bioforce UK Ltd, 2 Brewster Place, Irvine, Ayrshire, KA11 5DD, UK.
url: www.bioforce.co.uk

BioForm, USA. BioForm Medical Inc., 4133 Courtney Rd, Suite 10, Franksville, WI 53126, USA.
url: www.bioform.com

Biofrontera, Denm. See *Desitin, Denm.*

Biofrontera, Norw. See *Desitin, Norw.*

Biofutura, Ital. See *Sigma-Tau, Ital.*

Biogaia, Hong Kong. See *Health Enterprise, Hong Kong.*

BioGaia, Ukr. See *Delta Medical, Ukr.*

Biogal, Cz. See *Biogal-Teva, Hung.*

Biogal, Hong Kong. See *International Medical, Hong Kong.*

Biogal, Hung. See *Biogal-Teva, Hung.*

Biogal, Israel. See *Teva, Israel.*

Biogal, Pol. See *Salus, Pol.*

Biogal, Rus. See *Teva, Rus.*

Biogalenic, Venez. Laboratorios Biogalenic C.A., Calle Bernardo Smilak, Edif. Jayor, Piso 1, San Martin, Caracas, Venezuela.
url: www.biogalenic.com

Biogalenica, Spain. Biogalenica, Ramon Trias Fargas 7-11 Ed, Marina Village, 08005 Barcelona, Spain.

Biogal-Teva, Hung. Biogal-Teva Pharma Rt, Róbert Károly krt 66, 1134 Budapest, Hungary.

Biogam, Arg. Biogam Argentina S.A., Av. Jujuy 1152, 1229 Buenos Aires, Argentina.
url: www.biogam-argentina.com

Biogam, Switz. See *Kart, Switz* and *Serolab, Switz.*

Biogaran, Fr. Biogaran, 15 bd Charles-de-Gaulle, 92707 Colombes cdx, France.

Biogaran, S.Afr. See *Servier, S.Afr.*

Biogel, Arg. See *Valles de Aloe, Arg.*

Biogen, Austral. Biogen P/L, Suite 2601, Level 26, 100 Miller St, North Sydney, NSW 2060, Australia.
url: www.biogen.com

Biogen, Austria. See *Biogen, Fr.*

Biogen, Belg. Biogen Idec Belgium NV/SA, Regus Parc Atrium, 11000 Brussels, Belgium.
url: www.biogen.be

Biogen, Braz. Biogen Idec Brasil Produtos Farmaceuticos Ltda, Av. Juscelino Kubitscheck 1400 Cj 61, 4543000 São Paulo, Brazil.

Biogen, Canad. Biogen Idec Canada Inc., 3 Robert Speck Pkwy, Suite 300, Mississauga, Ontario, L4Z 2G5, Canada.
url: www.biogen.com

Biogen, Cz. See *Biogen Idec, Neth.*

Biogen, Denm. Biogen Idec A/S, Ørestads Boulevard 67, 2300 Copenhagen S, Denmark.
url: www.biogenidec.dk

Biogen, Fin. Biogen Idec Finland Oy, Äyritie 12, 01510 Vantaa, Finland.
url: www.biogen.com

Biogen, Fr. Biogen Idec France SAS, Le Capitole, 55 av. des Champs-Pierreux, 92012 Nanterre cdx, France.
url: www.biogenidec.fr

Biogen, Ger. Biogen Idec GmbH, Carl-Zeiss-Ring 6, 85737 Ismaning, Germany.
url: www.biogenidec.de

Biogen, Gr. See *Biogen, UK.*

Biogen, Hung. Biogen, Hungary.

Biogen, Irl. Biogen Idec Ltd, United Drug House, Magna Drive, Magna Business Park, Citywest Rd, Dublin 2, Ireland.

Biogen, Israel. See *Medison, Israel.*

Biogen, Neth. See *Biogen Idec, Neth.*

Biogen, Norw. Biogen Idec Norway AS, Karenslyst alle 8b, 0278 Oslo, Norway.
url: www.biogen.com

Biogen, NZ. Biogen Idec NZ Ltd, 54 Carbine Rd, Mt Wellington, New Zealand.

Biogen, Pol. See *Richter, Pol.*

Biogen, Port. Biogen Idec Portugal Sociedade Farmacêutica Unipessoal Lda, Av. Duque d'Avila 185, Floor 8, 1050-082 Lisbon, Portugal.
url: www.biogenidec.com

Biogen, Rus. See *Gedeon Richter, Rus.*

Biogen, Spain. Biogen Idec Iberica S.L., Paseo de la Castellana 41,3rd floor, 28046 Madrid, Spain.
url: www.biogenidec.com

Biogen, Swed. BiogenIdec Sweden AB, Kanalvägen 1 A, plan 2, 194 61 Upplands Väsby, Sweden.
url: www.biogen.com

Biogen, Switz. Biogen-Dompé AG, Bundesplatz 9, 6300 Zug, Switzerland.
url: www.biogen.ch

Bio-Gen, Turk. Bio-Gen İlaç San. Ltd. Şti., Bosna Hersek Cad. No:32/2, Emek, Ankara, 06510, Turkey.
url: www.bio-gen.net

Biogen, UK. Biogen Idec Ltd, Thames House, Foundation Park, Maidenhead, Berkshire, SL6 3UD, UK.
url: www.biogen.com

Biogen, USA. Biogen Idec, 14 Cambridge Center, Cambridge, MA 02142, USA.
url: www.biogenidec.com

Biogen Dompe, Ital. See *Dompe, Ital.*

Biogen Dompe, Switz. Dompé-Biogen AG, Landis + Gry-Strasse 3, 6300 Zug, Switzerland.
url: www.biogen.ch

Biogen Idec, Neth. Biogen Idec International BV, Prins Mauritslaan 13-19, 1171 LP Badhoevedorp, Netherlands.
url: www.biogenidec.nl

Biogened, Neth. See *Polon, Pol.*

Biogened, Pol. See *Polon, Pol.*

Biogenetech, Thai. Biogenetech Co. Ltd, 18 Soi Udomsuk 37, Sukhumvit 103 Rd, Bangjak, Prakanong, Bangkok 10260, Thailand.

Bioglan, Austral. Bioglan Ltd, 8/10 Yalgar Rd, Yalgar Business Park, Kirrawee, NSW 2232, Australia.
url: www.bioglan.com.au

Bioglan, Austria. See *Derma, UK.*

Bioglan, Denm. See *Bioglan, Swed.*

Bioglan, Fin. See *Bioglan, Swed.*

Bioglan, Ger. See *Riemser, Ger.*

Bioglan, Hong Kong. See *Keller, Hong Kong.*

Bioglan, Hung. See *Ventiv, Hung.*

Bioglan, Irl. See *Derma, UK.*

Bioglan, Israel. See *Gamida, Israel.*

Bioglan, Malaysia. See *United Italian, Malaysia.*

Bioglan, Norw. See *Bioglan, Swed.*

Bioglan, Singapore. See *Biomed, Singapore* and *Pharmed, Singapore.*

Bioglan, Swed. Bioglan Pharma AB, Box 50577, 202 15 Malmö, Sweden.
url: www.maxmedica.com

Bioglan, Thai. See *Hua, Thai.*

Bioglan, UK. See *Derma, UK.*

Bioglan, USA. See *Bradley, USA.*

Bio-Health, Irl. See *Bio-Health, UK.*

Biohealth, Ital. Biohealth Italia S.r.l., Lungo Po Antonelli 45, 10153 Turin (TO), Italy.
url: www.biohealth-italia.it

Bio-Health, UK. Bio-Health Ltd, Culpeper Close, Medway City Estate, Rochester, Kent, ME2 4HU, UK.
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url: www.biokplus.com

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url: www.biokanol.de

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Biokem, Turk. Biokem İlaç Sanayi ve Ticaret AS, Eski Edirne Asfalti N:564 GO Paşa, Sultançiftligi, Istanbul, Turkey.
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url: www.bio-kem.com
Biokirch, Ger. Biokirch GmbH, Bei den Kämpan 11, 21220 Seevetal, Germany.
url: www.biokirch-gmbh.de
Biokosma, Arg. Laboratorio Natural Biokosma SC, Ruta 1 Km 4, (5881) Merlo, San Luis, Argentina.
Biokosma, Fr. Lab Biokosma France, 2 rue des Lilas, 39004 Lons-le-Saunier cdx, France.
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Biokraft, Swed. Biokraft Pharma AB, Box 1010, Helsingborg, Sweden.
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url: www.biomarinpharm.com
BioMarin, USA. BioMarin Pharmaceutical Inc., 105 Digital Drive Novato, CA 94949, USA.
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url: www.biomaxbiotechnics.com
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Biomed, Canad. Biomed International Products Corp., 102 3738 North Fraser Way, Burnaby, British Columbia, V5J 5G7, Canada.
Biomed, Ital. Biomed Pharma Srl, Via Colla 6/3, 17014 Cairo Montenotte (SV), Italy.
Biomed, NZ. Biomed Ltd, 52 Carrington Rd, Pt Chevalier, Auckland, New Zealand.
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Biomedica, India. Biomedica Life Science, SF1 Vijay apartment, 16 School Street, Radha Nagar, Chennai 600 944, India.
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Biomet, Austral. Biomet Australia Ltd, 4/6-8 Byfield St, North Ryde, NSW 2113, Australia.
url: www.biomet.com
Biomet, Austria. Biomet Austria GmbH, Breitwies 1, A-5303 Thalgau, Austria.
Biomet, Belg. Biomet Belgium BVBA, Fotografielann 5, 2610 Wilrijk, Belgium.
url: www.biomet.be
Biomet, Denm. Biomet Danmark ApS, Hattingvej 7, 8700 Horsens, Denmark.
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Bionax, Singapore. Bionax Singapore Pte Ltd, 99 Bukit Timah Rd, Alfa Centre 03-06, S 229835, Singapore.
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Bioniche, Canad. Bioniche Pharma, 275 Labrosse Ave, Pointe-Claire, Quebec, H9R 1A3, Canada.
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Bioniche, USA. Bioniche Pharma USA LLC, 272 East Deerpath Rd, Suite 304, Lake Forest, IL 60045, USA.
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Bionutre, Arg. Laboratorio Bionutre SRL, Lavalle 1145, 2000 Rosario, Santa Fe, Argentina.
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Biopha, Fr. Laboratoires Dermopharmaceutiques Biopha, 15 rue Ampere, 91748 Massy cdx, France.
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url: www.biopharm.co.th
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Bioquimed, Mex. Laboratorio Médico Biológico SA de CV, Reforma 9, 4400 Coyoacán Atlántida, Mexico.
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Biosciences Pharmakon, India. Biosciences Pharmakon, 810 Siddharth, R.C. Dutt Road, Vadodara 390 007, India.
url: www.biosciencespharmakon.com
Bioscrip, USA. BioScrip, 10900 Red Circle Drive, Minnetonka, MN 55343, USA.
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Biosearch, Spain. Biosearch SA, Camino de Purchil 66, 18004 Granada, Spain.
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url: www.biosintetica.com.br
Biosintex, Arg. Laboratorio Biosintex-Ofar SA, Salom 657, 1277 Buenos Aires, Argentina.

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url: www.biotech.co.za

Biotech, Singapore. See *Goldplus, Singapore.*

Bio-Tech, USA. Bio-Tech Pharmacal, P.O. Box 1992, Fayetteville, AR 72702, USA.
url: www.bio-tech-pharm.com

Biotech, Venez. Laboratorios Biotech C.A., Calle del Arenal Edif. Biotech, Urb. La Trinidad, Caracas, Venezuela.
url: www.biotech.com.ve

Biotech Naturis, Venez. See *Biotech, Venez.*

Biotech Transfer, Canad. Biotech Transfer Consulting Inc., 60 165 Chandos Drive, Kitchener, Ontario, N2A 4A2, Canada.

Biotechnologia, Gr. Biotechnologia Ltd, Thebes 3, 173 43 Agios Dimitrios, Greece.

Biotechnology, Israel. Biotechnology General Israel Ltd, Kiryat Weisman, Rehovot 76326, Israel.

Biotechnology, Singapore. See *SciGen, Singapore.*

Bio-Technology, USA. Bio-Technology General Corp., 1 Tower Center, East Brunswick, NJ 08816, USA.

Biotecnoquimica, Venez. Laboratorio Biotecnoquímica, Calle 10 con 5 Edif. Wafpirema, Piso 1, La Urbina, Caracas, Venezuela.
url: www.biotecnoquimica.com

Biotehnos, Rus. See *Rompharm, Rus.*

Biotehnos, Ukr. See *Artur, Ukr.*

Biotek, NZ. See *In Vitro, NZ.*

Biotek, Turk. Biotek İlaçlari, Akkavak Sok. No:6, Nişantaşi, İstanbul, Turkey.

Biotekhna, Rus. See *Sicor, Rus.*

Biotene, Austral. See *Advil, Austral.*

Biotenk, Arg. Laboratorio Farmaceutico Biotenk S.A., Zuvirma 5747, 1439 Buenos Aires, Argentina.
url: www.biotenk.com

Biotest, Austria. Biotest Pharmazeutika GmbH, Einsiedlergasse 58, Postfach 8, A-1053 Vienna, Austria.
url: www.biotest.at

Biotest, Cz. See *Reg, Cz.*

Biotest, Fin. See *Leo, Fin.*

Biotest, Fr. Biotest France, 375 rue Morane Saulnier, ZI Centre BP 405, 78534 Buc Cedex, France.
url: www.biotest.fr

Biotest, Ger. Biotest Pharma GmbH, Landsteinerstr. 3-5, 63303 Dreieich, Germany.
url: www.biotest.de

Biotest, Gr. Biotest, Kyprion Agoniston 25, 151 26 Marousi, Greece.

Biotest, Hong Kong. See *Chong Lap, Hong Kong.*

Biotest, Hung. Biotest Hungária Kft, Beregszasz út 55/b, 1118 Budapest, Hungary.

Biotest, Irl. See *Biotest, UK.*

Biotest, Israel. See *Margalit, Israel.*

Biotest, Ital. Biotest Italia S.r.l., Via L. da Vinci 43, 20090 Trezzano Sul Naviglio (MI), Italy.
url: www.biotest.de

Biotest, Malaysia. See *Lazuli, Malaysia.*

Biotest, Neth. See *Biotest, Ger.*

Biotest, Pol. See *Nobipharm, Pol.*

Biotest, Port. See *Boehringer Ingelheim, Port.*

Biotest, Rus. Biotest, ul. Vavilova 5 korpus 3 office 403, 119334 Moscow, Russia.
url: www.biotest.de

Biotest, S.Afr. See *IEPSA, S.Afr.*

Biotest, Singapore. See *Summit, Singapore.*

Biotest, Spain. Biotest Medical SLU, Beethoven 15, 4a Planta, 08021 Barcelona, Spain.

Biotest, Switz. Biotest (Schweiz) AG, Schutzenstrasse 17, 5102 Rupperswil, Switzerland.
url: www.biotest.ch

Biotest, Thai. See *Charoen, Thai.*

Biotest, Turk. See *Kansuk, Turk.*

Biotest, UK. Biotest (UK) Ltd, 28 Monkspath Business Park, Highlands Rd, Shirley, Solihull, West Midlands, B90 4NZ, UK.
url: www.biotestuk.com

Biotest, USA. Biotest Pharmaceuticals Corp., 5800 Park of Commerce Blvd NW, Boca Raton, FL 33487, USA.
url: www.biotestpharma.com

Biothera, Belg. See *AstraZeneca, Belg.*

Bio-Therabel, Belg. See *Therabel, Belg.*

Biotherapie, Fr. See *Expanscience, Fr.*

Biotherax, Ger. See *Boehringer Ingelheim, Ger.*

Biotherm, Canad. Biotherm Canada, 2115 Crescent St, Montreal, Quebec, H3G 2C1, Canada.

Biotika, Cz. Biotika Bohemia sro, Kovrigínová 1416/6, 147 00 Prague 4, Czech Republic.

Biotiki, Rus. Biotiki Ltd, Luganskaya St 9, Moscow, Russia.

Biotime, Canad. See *Abbott, Canad.*

Biotis, Israel. Biotis Ltd, 22 Hamelacha St, P.O. Box 11372, Rosh Ha'Ayin 48091, Israel.
url: www.biotis.co.il

Bioton, Pol. Bioton Sp. zo.o., ul. Starościńska 5, 02-516 Warsaw, Poland.
url: www.bioton.pl

Bioton, Rus. Bioton Wostok, ul. Liwenskaja d.1, Pos. Kulikowskij, Orel 302516, Russia.
url: www.bioton.pl

Bioton, Ukr. See *Artur, Ukr.*

Biotoscana, Arg. Biotoscana Argentina, Ortiz de Ocampo 3302 Módulo III 5, (1425) Buenos Aires, Argentina.

Biotoscana, Chile. Biotoscana Farma SA, Carmen Covarrubias 271, Nuñoa, Santiago, Chile.

Biotrading, Ital. Biotrading di Maurizio Mannone, Via Francesco Struppa 4, 91025 Marsala (TP), Italy.

Biotrends, Gr. BIOTRENDS, Vor Ipeirou 65, 146 71 N. Erythraia, Greece.

Biotrol, Fr. See *Braun Medical OPM, Fr.*

Biovac, S.Afr. Biovac SA CC, P.O. Box 14374, Wadeville 1422, South Africa.
url: www.biovac.co.za

Biovail, Canad. Biovail Pharmaceuticals, 7150 Mississauga Rd, Mississauga, Ontario, L5N 8M5, Canada.
url: www.biovail.com

Biovail, Denm. See *Gea, Denm.*

Biovail, USA. Biovail Technologies Ltd, 700 Route 202/206 North, Bridgewater, NJ 08807, USA.
url: www.biovail.com

Biovalys, Thai. Biovalys Co. Ltd, 19 BioNet-Asia Bldg 3 Fl Udomsuk 37, 103 Sukhumvit Rd, Bangjak Prakanong, Bangkok, 10260, Thailand.

Bio-Ved, Singapore. See *MD, Singapore.*

Biovena, Pol. See *Actavis, Pol* and *Bioton, Pol.*

Bioventus, USA. Bioventus LLC, 4721 Emperor Blve, Suite 100, Durham, NC 27703, USA.
url: www.bioventusglobal.com

Biovita, Ukr. Biovita Laboratories, Ukraine.

Biovital, Austral. Biovital Pty Ltd, 24/10 Yalgar Road, Kirrawee, NSW 2232, Australia.

Biovitrum, Austria. See *Biovitrum, Swed.*

Biovitrum, Cz. See *Biovitrum, Swed.*

Biovitrum, Denm. Biovitrum AB, Naesseslottet, Dronninggårds Allé 136, 2840 Holte, Denmark.
url: www.biovitrum.com

Biovitrum, Fin. See *Biovitrum, Swed.*

Biovitrum, Fr. See *Swedish Orphan, Swed.*

Biovitrum, Gr. See *Genesis, Gr.*

Biovitrum, Irl. See *Biovitrum, Swed.*

Biovitrum, Ital. See *Swedish Orphan, Ital.*

Biovitrum, Neth. See *Biovitrum, Swed.*

Biovitrum, Norw. Biovitrum AB, CJ Hambros plass 2 C, 0164 Oslo, Norway.

Biovitrum, Port. See *Biovitrum, Swed.*

Biovitrum, Spain. See *Swedish Orphan, Spain.*

Biovitrum, Swed. Biovitrum AB, Plasma Products, 112 76 Stockholm, Sweden.
url: www.biovitrum.com

Biovitrum, UK. See *Biovitrum, Swed.*

Biovitrum, USA. See *Swedish Orphan, Swed.*

Bioway, China. Bioway Biotech Pharmaceutical Co. Ltd, Xiamen, China.

Bipharma, Belg. See *Bipharma, Neth.*

Bipharma, Hong Kong. See *US Summit, Hong Kong.*

Bipharma, Neth. Bipharma BV, Kwikzilverstraat 21, 1320 AA Almere, Netherlands.
url: www.bipharma.com

Birchwood, USA. Birchwood Laboratories Inc., 7900 Fuller Rd, Eden Prairie, MN 53344-2195, USA.
url: www.birchlabs.com

Bird, USA. Bird Products Corp., 1100 Bird Center Drive, Palm Springs, CA 92262, USA.
url: www.viasyscriticalcare.com

Birger Ledin, Swed. Birger Ledin AB, Norra Vägen 12, 542 33 Mariestad, Sweden.
url: www.ledins.se

Birochem, Hung. Birochem Kft, Csanády u. 25/A, 1132 Budapest, Hungary.

Biropharma, Hung. Biropharma, IV kärzet 6, 6413 Kunfeherto, Hungary.
url: www.biropharma.hu

Birz, India. Birz Pharmaceuticals, 122, Windsor Plaza, R.C. Dutt Road, Alkapuri, Vadodara, India.

Biscova, Ger. Biscova-Arzneimittel, Fuhrenkamp 7, 29559 Wrestedt/Stederdorf, Germany.

Bissendorf, Neth. See *Byk, Neth.*

Bitelab, Fin. Bitelab Oy, Paloheinäntie 62 b A, 00670 Helsinki, Finland.
url: www.bitelab.fi

Bittermedizin, Ger. Bittermedizin Arzneimittel Vertriebs-GmbH, Taku-Fort-Str. 20, 81827 Munich, Germany.
url: www.bittermedizin.de

Bittner, Austria. Richard Bittner GmbH, A-9344 Weitensfeld 183, Austria.

Bittner, Hung. See *Omega, Belg.*

Bittner, Pol. Bittner Pharma International Sp. zo.o., ul. Dąbrowskiego 247/249, 92-232 Łódź, Poland.
url: www.bittner.pl

Bittner, Rus. See *Herbs Trading, Rus.*

Bittner, Ukr. See *Bittner, Austria.*

BJ Benjaosoth, Thai. BJ Benjaosoth Ltd, 225 Soi Na Vachirapayaban Samsen Rd, Dusit, Bangkok 10300, Thailand.

BL, Braz. See *Bausch & Lomb, Braz.*

BL, India. BL Pharma Limited, Plot No. 29 & 30, Sainagar, Ganesh Nagar Colony, Nagole, Hyderabad 500 068, India.

Blackhall, Irl. Blackhall Pharmaceutical Distributors Ltd, Saucertown, Swords, Dublin, Ireland.
url: www.united-drug.ie

Blackhawk, Canad. Blackhawk Indian Remedy Co., 2639 Thompson Drive, Kamloops, British Colombia, V2C 4L5, Canada.

Blackmores, Austral. Blackmores Ltd, P.O. Box 258, Balgowlah, NSW 2093, Australia.
url: www.blackmores.com.au

Blackmores, Thai. Blackmores Ltd, 20B Mahanakorn Gypsum Building, 539/2 Sriayuddhaya Rd, Ratchathewi, Bangkok 10400, Thailand.

Blackmores, UK. Blackmores UK, 37 Rotasckild Rd, Chiswick, London, W4 5HT, UK.

Blackwell, UK. Blackwell Supplies Ltd, Medcare House, Centurion Close, Gillingham Business Park, Gillingham, Kent, ME8 0SB, UK.

Blaine, USA. Blaine Pharmaceuticals Co. Inc., 1717 Dixie Highway, Suite 700, Fort Wright, KY 41011, USA.
url: www.blainepharma.com

Blair, USA. See *Purdue Frederick, USA.*

Blairex, Canad. See *Blairex, USA.*

Blairex, USA. Blairex Labs Inc., 1600 Brain Drive, P.O. Box 2127, Columbus, IN 47202-2127, USA.
url: www.blairex.com

Blake, UK. Thomas Blake & Co., The Byre House, Fearby, Nr Masham, North Yorkshire, HG4 4NF, UK.
url: www.veilcover.com

Blansett, USA. Blansett Pharmacal Co., Inc., P.O. Box 638, North Little Rock, AR 72115, USA.
url: www.blansett.com

Blau, Pol. Blau Farma Sp. zo.o., ul. Jutrzenki 94, 02-230 Warsaw, Poland.
url: www.blaufarma.pl

Blausiegel, Braz. Blausiegel Indústria e Comércio Ltda, Rodovia Raposo Tavares km 30.5 no.2833, 06705-030 Cotia Barro Branco, SP, Brazil.
url: www.blausiegel.com.br

Bledina, Fr. Bledina SA, B.P. 432, 69654 Villefranche-sur-Saône cdx, France.
url: www.bledina.com

Blend-a-med, Ger. See *Procter & Gamble, Ger.*

Bles, Canad. Bles Chemicals Inc., 8-60 Pacific Court, London, Ontario, N5V 3K4, Canada.

BLH, Thai. BLH Trading Co. Ltd, 7/1 Wireless Rd, Bangkok 10330, Thailand.

Blis, NZ. Blis Technologies, P.O. Box 1229, Level 4, 31 Waring Taylor St, Wellington, New Zealand.
url: www.blis.co.nz

Bliss, India. Bliss Chemicals & Pharma India Ltd, Unit No 29-A Udit Mittal Indl., Premises Co-op. Soc. Ltd, Kurla Road, Andheri (East), Mumbai 400 059, India.

Bliss, S.Afr. Bliss Pharmaceuticals, P.O. Box 604, Ridgeway 2099, South Africa.
url: www.blisspharma.co.za

BlissMed, Singapore. BlissMed Pte Ltd, 362 Upper Paya Lebar Rd, 02-16 Da Jin Factory Bldg, S 534963, Singapore.

Blistex, Canad. Blistex Ltd, 5915 Airport Rd, Suite 908, Mississauga, Ontario, L4V 1T1, Canada.

Blistex, Hong Kong. See *Mekim, Hong Kong.*

Blistex, Israel. See *Medibrands, Israel.*

Blistex, USA. Blistex Inc., 1800 Swift Drive, Oak Brook, IL 60523, USA.
url: www.blistex.com

Block, Austria. See *GSK, Austria.*

Block, Canad. See *GSK Consumer, Canad.*

Block, Ger. See *GSK Consumer, Ger.*

Block, USA. See *GSK Consumer, USA.*

Bloem Beheer, Neth. Bloem Beheer BV, Papierbaan 50a, 9672 BH Winschoten, Netherlands.

Blooming Fields, Philipp. Blooming Fields Phils, Inc., 6/F Textron Bldg, 168 Luna Mencias St, San Juan, Metro Manila, Philippines.

Blossoms, India. Blossoms Biologicals, A-12 1st Floor Hari Singh Market, Kotla, Mayur Vihar, New Delhi 110 091, India.

Blubell, India. Blubell Pharma, 10 Eight Maria, Behind Gurudwara, Sanepat, Haryana 131 001, India.

Blubit, Pol. Blubit Sp. zo.o., ul. Wolska 84/86, 01-141 Warsaw, Poland.
url: www.blubit.com.pl

Blue Bio, Cz. See *Blue Bio, Irl.*

Blue Bio, Denm. See *Pharmazan, Denm.*

Blue Bio, Gr. See *Blue Bio, Irl.*

Blue Bio, Irl. Blue Bio Pharmaceuticals Ltd, 5th Floor Beaux Lane House, Mercer St Lower, Dublin 2, Ireland.
url: www.bluebiopharma.com

Blue Bio, Neth. See *Blue Bio, Irl.*

Blue Bio, Port. See *Blue Bio, Irl.*

Blue Bio, UK. See *Blue Bio, Irl.*

Blue Cross, India. Blue Cross Laboratories Ltd, Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel West, Mumbai 400 013, India.
url: www.bluecrosslabs.com

Blue Cross, Ital. Blue Cross S.r.l., SS 156 Km 50, 04010 Borgo S Michele (LT), Italy.

Blue Ocean, UK. Blue Ocean Sales Brokers, Cams Hall Estate, Fareham, Hampshire, PO16 8UU, UK.

Blue Sky, Philipp. Blue Sky Trading Co. Inc., Blue Sky Building, 416 Dasmariñas St, Binondo, Manila, Philippines.

Bluefish, Cz. See *Bluefish, Swed.*

Bluefish, Irl. See *Pinewood, Irl.*

Bluefish, Swed. Bluefish Pharmaceuticals AB, Stockholm, Sweden.

Bluepharma, Port. Bluepharma Genéricos Comércio de Medicamentos SA, S Martinho do Bispo, 3045-016 Coimbra, Portugal.

Blumont, Fin. See *Blumont, UK.*

Blumont, UK. Blumont Pharma Ltd, Suite 205, Springfield House, Caunt Rd, Grantham, Lincolnshire, NG31 7FZ, UK.
url: www.blumontpharma.com

BMM, Denm. See *Biophausia, Denm.*

BMM, Fin. See *BMM, Swed.*

BMM, Swed. BMM Specialty Pharma AB, Blaiseholmsgatan 2, 111 48 Stockholm, Sweden.
url: www.bmmpharma.se

BMPC, China. See *Mundipharma, China.*

BMS, Arg. Bristol-Myers Squibb Argentina S.A., Monroe 801, 1428 Buenos Aires, Argentina.
url: www.bms.com

BMS, Austral. Bristol-Myers Squibb, Division of Bristol-Myers Australia P/L, P.O. Box 39, Noble Park, VIC 3174, Australia.
url: www.bmsa.com.au

BMS, Austria. Bristol-Myers Squibb GmbH, Columbusgasse 4, A-1100 Vienna, Austria.
url: www.b-ms.at

BMS, Belg. Bristol-Myers Squibb Belgium SA, Parc de l'Alliance, Avenue de Finlande, 8, 1420 Braine-l'Alleud, Belgium.
url: www.bms.be

BMS, Braz. Bristol-Myers Squibb Farmacêutica Ltda, Rua Carlos Gomes 924, 04743-903 São Paulo, SP, Brazil.
url: www.bristol.com.br

BMS, Canad. Bristol-Myers Squibb Canada Inc., 2365 Cote-de-Liesse Rd, Montreal, Quebec, H4N 2M7, Canada. The Medical Director
url: www.bms.com

BMS, Chile. Bristol-Myers Squibb, Av. Pte. Balmaceda 2174, Santiago, Chile.

BMS, China. Bristol-Myers Squibb (China), 15-17 Floor Wheelock Square, 1717 Nanjing Rd West, Jing'an District, Shanghai 200040, China.
url: www.bms.com.cn

BMS, Cz. Bristol-Myers Squibb sro, Lazarská 6, 120 00 Prague 2, Czech Republic.
url: www.b-ms.cz

BMS, Denm. Bristol-Myers Squibb, Lyngby Hovedgade 98, 2800 Lyngby, Denmark.
url: www.bmsdanmark.dk

BMS, Fin. Oy Bristol-Myers Squibb (Finland) AB, Metsänneidonkuja 8, 02130 Espoo, Finland.
url: www.bmsfinland.com

BMS, Fr. Bristol-Myers Squibb, 3 rue Joseph-Monier, 92506 Rueill-Malmaison cdx, France.
url: www.bms.com

BMS, Ger. Bristol-Myers Squibb GmbH & Co. KGaA, Arnulfstr. 29, 80636 Munich, Germany.
url: www.b-ms.de

BMS, Gr. Bristol-Myers Squibb, 102 Tatoiou Ave, 146 71 N. Erythrea, Greece.
url: www.bms.gr
url: www.bms.com

BMS, Hong Kong. Bristol-Myers Squibb (Hong Kong) Ltd, Unit 3001-2, 30/F, New York Life Tower, Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.
url: www.bms.com

BMS, Hung. Bristol-Myers Squibb Gyógyszerkereskedelmi Kft, Szabadság tér 7, 1054 Budapest, Hungary.

BMS, India. Bristol Myers Squibb India, 7th Floor Peninsula Towers A, Peninsula Corporate Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, India.
url: www.bmsi.co.in

BMS, Indon. Bristol-Myers Squibb, Tamara Ctr Bldg, 10th Fl, Jl Jend Sudirman Kav 24, 12920 Jakarta, DKI Jaya, Indonesia.

BMS, Irl. Bristol-Myers Squibb Pharmaceuticals, Watery Lane, Swords, Co. Dublin, Ireland.
url: www.bmsireland.ie

BMS, Israel. Bristol-Myers Squibb Ltd, P.O. Box 3311, Petach Tikva, Israel.
url: www.bms.com

BMS, Ital. Bristol-Myers Squibb S.r.l., Via Virgillio Maroso 50, 00142 Roma (RM), Italy.
url: www.bms.it

BMS, Jpn. See *Bristol, Jpn.*

BMS, Malaysia. Bristol-Myers Squibb (Malaysia) Sdn Bhd, 16th Floor, Menara Lien Hoe, 8 Persiaran Tropicana, 47410 Petaling Jaya, Selangor, Malaysia.
url: www.bms.com

BMS, Mex. Bristol-Myers Squibb de Mexico S. de R.L. de C.V., Av. Revolución No. 1267, Col. Tlacopac, Deleg. A. Obregón, 01040 Mexico D.F., Mexico.
url: www.bms.com.mx

BMS, Neth. Bristol-Myers Squibb, Vijzelmolenlaan 9, 3447 GX Woerden, Netherlands.
url: www.bms.com

BMS, Norw. Bristol-Myers Squibb Norway Ltd, Veritasv. 26, Postboks 464, 1323 Hovik, Norway.
url: www.bms.no

BMS, NZ. Bristol-Myers Squibb, P.O. Box 62663, Central Park, Aukland, New Zealand.
url: www.bms.com

BMS, Philipp. Bristol-Myers Squibb (Phil) Inc., 2309 Don Chino Roces Ave, Makati City, Philippines.

BMS, Pol. Bristol-Myers Squibb Polska Sp. zo.o., al. Armii Ludowej 26, 00-609 Warsaw, Poland.
url: www.b-ms.pl

BMS, Port. Bristol-Myers Squibb Farmacêutica Portuguesa, Lda, Edifício Fernão de Magalhães, Quinta da Fonte, 2780-730 Paço de Arcos, Portugal.
url: www.bms.com

BMS, Rus. Bristol-Myers Squibb, Trekhprudny per 9, korp 1b, 103001 Moscow, Russia.
url: www.bms.com

BMS, S.Afr. Bristol-Myers Squibb (Pty) Ltd, P.O. Box 1408, Bedfordview, 2008 Johannesburg, South Africa.
url: www.bms.com

BMS, Singapore. Bristol-Myers Squibb (S) Pte Ltd, 66 East Coast Rd, 05-00, S 428778, Singapore.
url: www.bms.com

BMS, Spain. Bristol Myers Squibb España, Campus Empresarial Jose Ma Churruca, Almansa 101, 28040 Madrid, Spain.
url: www.bms.es

BMS, Swed. Bristol-Myers Squibb AB, Box 15200, 167 15 Bromma, Sweden.
url: www.bms.se

BMS, Switz. Bristol-Myers Squibb AG, Neuhofstrasse 6, 6340 Baar, Switzerland.
url: www.bms.ch

BMS, Thai. Bristol-Myers Squibb (Thailand) Ltd, Bristol-Myers Squibb Building, 10/10-11 Srinakarin Rd, Bangplee, Samutprakarn 10540, Thailand.
url: www.bms.com

BMS, Turk. Bristol-Myers Squibb İlaçlari Ltd. Şti., Buyukdere Cad. Meydan Sok, Plaza Spring Giz. K:8, Maslak, İstanbul, 80670, Turkey.
url: www.bms.com

BMS, UK. Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge Business Park, Sanderson Rd, Uxbridge, Middlesex, UB8 1DH, UK.
url: www.bms.com

BMS, Ukr. See *BMS, Rus.*

BMS, USA. Bristol-Myers Squibb, P.O. Box 4500, Princeton, NJ 08543-4500, USA.
url: www.bms.com

BMS, Venez. Bristol-Myers Squibb de Venezuela S.A., Calle Bernardette-Edif. Bristol-Myers Squibb, Los Cortijos de Lourdes, Aptd. Postal 61173, Caracas 1060-A, Venezuela.
url: www.bms.com.ve

BMS Oncology, USA. See *BMS, USA.*

BMW, India. BMW Pharmaco India Pvt. Ltd., Jurgyan House, 2-3 Badi Omti, Jabalpur 482 002, India.
url: www.bmwpharmaco.com

Bo Er Tai Li, China. Bo Er Tai Li Pharmaceutical Co. Ltd, Yinchuan, Ningxia, China.

Bo Jian, China. Henan Bo Jian Pharmaceutical Co., Ltd., Western Industrial Zone, Xiancheng, Henan, 466200, China.

Bo Kang, China. Bo Kang, China.

BOC, Irl. BOC Gases Ireland Ltd, Bluebell Industrial Estate, Bluebell, Dublin 12, Ireland.

BOC, UK. BOC Gases, The Priestley Centre, 10 Priestley Rd, Surrey Research Park, Surrey, GU2 7XY, UK.
url: www.boc.com

Boca, USA. Boca Pharmacal Inc., 6601 Lyons Rd, Coconut Creek, FL 33073, USA.
url: www.bocamedicalproducts.com

BocaGreenMD, USA. BocaGreenMD, 951 Broken Sound Parkway, Suite 300, Boca Raton, FL 33487, USA.
url: www.bocagreenmd.com

Bock, USA. See *Sanofi-Aventis, USA.*

Boda, China. See *Simcere, China.*

Bode, Austria. See *Bode, Ger.*

Bode, Fin. See *Bode, Ger.*

Bode, Ger. Bode Chemie GmbH & Co. KG, Melanchthonstr. 27, 22525 Hamburg, Germany.
url: www.bode-chemie.de

Bode, Indon. See *Tempo Scan Pacific, Indon.*

Bode, Neth. See *Bode, Ger.*

Bode, Port. See *Bode, Ger.*

Bodene, S.Afr. See *Fresenius Kabi, S.Afr.*

Body Shop, Canad. The Body Shop Canada Ltd, Unit 144, 16 Famous Ave, Woodbridge, Ontario, L4L 9M3, Canada.

Body Spring, Ital. See *Angelini, Ital.*

Body Wise, Canad. See *Body Wise, USA.*

Body Wise, USA. Body Wise International LLC, Suite 101, 17101 Armstrong Ave, Irvine, CA 92414, USA.

BodyForm, Hung. BodyForm Kft, Rét köz 5, 2071 Páy, Hungary.

Boehringer de Angeli, Braz. See *Boehringer Ingelheim, Braz.*

Boehringer Ingelheim, Arg. Boehringer Ingelheim S.A., Av. del Libertador 7208, 1429 Buenos Aires, Argentina.
url: www.bai.boehringer-ingelheim.com

Boehringer Ingelheim, Austral. Boehringer Ingelheim P/L, P.O. Box 1969, Macquarie Centre, North Ryde, NSW 2113, Australia.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Austria. Boehringer Ingelheim Austria GmbH, Dr Boehringer-Gasse 5-11, A-1121 Vienna, Austria.
url: www.boehringer-ingelheim.at

Boehringer Ingelheim, Belg. Boehringer Ingelheim SA/NV, Ave Ariane 16, 1200 Brussels, Belgium.
url: www.boehringer-ingelheim.be

Boehringer Ingelheim, Braz. Boehringer Ingelheim do Brasil Quím. e Farm. Ltda, Av. Maria Coelho Aguair 215, Bl. F. 3 degrees andar, 05805-000 São Paulo, SP, Brazil.
url: www.boehringer-ingelheim.com.br

Boehringer Ingelheim, Canad. Boehringer Ingelheim (Canada) Ltd, 5180 South Service Rd, Burlington, Ontario, L7L 5H4, Canada.Regulatory Affairs Director
url: www.boehringer-ingelheim.ca

Boehringer Ingelheim, Chile. Boehringer Ingelheim, Carlos Fernandez 260, San Joaquin, Santiago, Chile.

Boehringer Ingelheim, China. Boehringer Ingelheim International Trading Co Ltd, 29/F Park Place, 1601 Nanjing Road (West), Shanghai 200040, China.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Cz. Boehringer Ingelheim sro, Lublaňská 21, 120 00 Prague 2, Czech Republic.
url: www.boehringer-ingelheim.cz

Boehringer Ingelheim, Denm. Boehringer Ingelheim Danmark A/S, Strødamvej 52, 2100 Copenhagen Ø, Denmark.
url: www.boehringer-ingelheim.dk

Boehringer Ingelheim, Fin. Boehringer Ingelheim Finland Ky, Tammasaarenkatu 5, 00180 Helsinki, Finland.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Fr. Boehringer Ingelheim France, 37-9 rue Boissière, 75116 Paris, France.
url: www.boehringer-ingelheim.fr

Boehringer Ingelheim, Ger. Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Str. 173, 55218 Ingelheim, Germany.
url: www.medworld.de

Boehringer Ingelheim, Gr. Boehringer Ingelheim Ellas A.E., 2 Ellinikou Str., 167 77 Elliniko, Greece.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Hong Kong. Boehringer Ingelheim (Hong Kong) Ltd, Suite 1504-7, Great Eagle Ctr, 23 Harbour Rd, Wanchai, Hong Kong.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Hung. Boehringer Ingelheim Pharma Magyarországi Kereskedelmi Képviselet, Dobsinai u 19, 1024 Budapest, Hungary.

Boehringer Ingelheim, Indon. Boehringer Ingelheim Indonesia PT, Sampoerna Strategic Square, North Tower Level 6, Jl. Jendral Sudirman Kav. 45-46, Jakarta 12930, Indonesia.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Irl. Boehringer Ingelheim Ltd, Corrig Court, Corrig Road, Sandyford Business Estate, Dublin 18, Ireland.
url: www.boehringer-ingelheim.ie

Boehringer Ingelheim, Israel. See *Teva, Israel.*

Boehringer Ingelheim, Ital. Boehringer Ingelheim Italia S.p.A., Via Lorenzini 8, 20139 Milan (MI), Italy.
url: www.boehringer-ingelheim.it

Boehringer Ingelheim, Jpn. Nippon Boehringer Ingelheim Co. Ltd, 3-10-1 Yato, Kawanishi-shi, Hyogo 666-0193, Japan.
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Boehringer Ingelheim, Malaysia. Boehringer Ingelheim, Division Diethelm Malaysia Sdn Bhd, P.O. Box 3031, 47620 Subang Jaya, Selangor, Malaysia.
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Boehringer Ingelheim, Mex. Boehringer Ingelheim Promeco, S.A. de C.V., Calle del Maiz No. 49, Col. Xaltocan, Deleg. Xochimilco, 16090 Mexico D.F., Mexico.
url: www.boehringer-ingelheim.com.mx

Boehringer Ingelheim, Neth. Boehringer Ingelheim BV, Berenkoog 28, 1822 BJ Alkmaar, Netherlands.
url: www.boehringer-ingelheim.nl

Boehringer Ingelheim, Norw. Boehringer Ingelheim Norway KS, Drengsrudbekken 25, Postboks 405, 1371 Asker, Norway.
url: www.boehringer-ingelheim.no

Boehringer Ingelheim, NZ. Boehringer Ingelheim (NZ) Ltd, 47 Druces Rd, Wiri, Manukau City, Auckland, New Zealand.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Philipp. Boehringer Ingelheim (Phils) Inc., 23/F Citibank Tower, 8741 Paseo de Roxas, Salcedo Vil, Makati City, Philippines.

Boehringer Ingelheim, Pol. Boehringer Ingelheim Marketing Sp. zo.o., ul. Domaniewska 41, 02-672 Warsaw, Poland.
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Boehringer Ingelheim, Port. Boehringer Ingelheim, Lda, Av. António Augusto de Aguiar 104, 1069-029 Lisbon, Portugal.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Rus. Boehringer Ingelheim Pharma GmbH, Moscow Office, Donskaya ul. 39/9, Str. 1, 119049 Moscow, Russia.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, S.Afr. Boehringer Ingelheim (Pty) Ltd, Private Bag X3032, Randburg 2125, South Africa.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Singapore. See *DKSH, Singapore.*

Boehringer Ingelheim, Spain. Boehringer Ingelheim, Prat d ela Riba S/N, Sector Turo de Can Matas, Sant Cugat del Vales, 08190 Barcelona, Spain.
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Boehringer Ingelheim, Swed. Boehringer Ingelheim AB, Box 47608, 117 94 Stockholm, Sweden.
url: www.boehringer-ingelheim.se

Boehringer Ingelheim, Switz. Boehringer Ingelheim (Schweiz) GmbH, Dufourstrasse 54, 4002 Basle, Switzerland.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Thai. Boehringer Ingelheim (Thai) Ltd, 12 Fl, Charn Issara Tower II, 2922/207-208 New Petchburi Rd, Bangkapi, Huay Kwang, Bangkok 10310, Thailand.
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Boehringer Ingelheim, Turk. Boehringer Ingelheim İlaç Tic. A.Ş., Eski Buyukdere Caddesi, USO Center, No: 61 Kat 13,14, Maslak, İstanbul, 80670, Turkey.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, UK. Boehringer Ingelheim Ltd, Ellesfield Ave, Bracknell, Berkshire, RG12 4YS, UK.
url: www.boehringer-ingelheim.co.uk

Boehringer Ingelheim, Ukr. Boehringer Ingelheim Pharma Ges mbH, Yurkovskaya Street, 28, Kiev, 04080, Ukraine.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, USA. Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Rd, P.O. Box 368, Ridgefield, CT 06877-0368, USA.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim, Venez. Boehringer Ingelheim C.A., Av. La Estancia, Torre B, piso 3, Centro Banaven (Cubo negro), Apartado Postal 64745, Caracas, Venezuela.
url: www.boehringer-ingelheim.com

Boehringer Ingelheim Consumer, Canad. See *Boehringer Ingelheim, Canad.*

Boehringer Ingelheim Consumer, USA. See *Boehringer Ingelheim, USA.*

Boehringer Ingelheim Promeco, Mex. See *Boehringer Ingelheim, Mex.*

Boehringer Ingelheim Self Medication, Canad. See *Boehringer Ingelheim, Canad.*

Boehringer Ingelheim Self Medication, Irl. See *Allphar, Irl.*

Boehringer Ingelheim Self Medication, UK. See *Boehringer Ingelheim, UK.*

Boehringer Mannheim, Austral. See *Roche Diagnostics, Austral.*

Boehringer Mannheim, Austria. See *Roche, Austria.*

Boehringer Mannheim, Belg. See *Roche, Belg.*

Boehringer Mannheim, Canad. See *Roche, Canad.*

Boehringer Mannheim, Fr. See *Roche Diagnostics, Fr.*

Boehringer Mannheim, Ger. See *Roche, Ger.*

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Boehringer Mannheim, Israel. See *Teva, Israel.*

Boehringer Mannheim, Ital. See *Roche, Ital.*

Boehringer Mannheim, Jpn. See *Roche, Jpn.*

Boehringer Mannheim, Neth. See *Roche, Neth.*

Boehringer Mannheim, Norw. See *Roche, Norw.*

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Boehringer Mannheim, Spain. See *Roche, Spain.*

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Boehringer Mannheim, Switz. See *Roche, Switz.*

Boehringer Mannheim, UK. See *Roche Diagnostics, UK.*

Boehringer Mannheim, USA. See *Roche, USA.*

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Boehringer Mannheim Diagnostics, UK. See *Roche Diagnostics, UK.*

Boehringer Mannheim Diagnostics, USA. See *Roche, USA.*

Boehringer Mannheim Roche, Spain. See *Roche, Spain.*

Bohai, China. Bohai Pharmaceutical Co. Ltd., 110 Houju Road, High-Tech Development Zone, Tangshan, Hebei, 063020, China.

Bohm, Spain. Bohm, Molina Seca 23 Plg. Cobo Calleja, Fuenlabrada, 28947 Madrid, Spain.
url: www.lab-bohm.com

Bohua, China. Bohua Pharmaceutical Co. Ltd, Xi'an, China.

Bohusovicka Mlekarna, Cz. Bohušovická mlékárna as, Brňany 125, 411 54 Bohušovice nad Ohří, Czech Republic.

BOI, Spain. See *Merck, Spain.*

Boie, Philipp. Boie Inc., 520 Alabang-Zapote Rd, Almanza 1, Las Piñas City, Philippines.
url: www.boie.com.ph

Boileau & Boyd, Irl. See *Allphar, Irl.*

Boiron, Austral. See *Boiron, Fr.*

Boiron, Canad. Boiron Canada Inc., 816 Guimond St, Longueil, Quebec, J4G 1T5, Canada.
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Boiron, Cz. Boiron CZ sro, Vlková 40, 130 00 Prague 3, Czech Republic.

Boiron, Fr. Boiron, 20 rue de la Liberation, 69110 Sainte-Foy-les-Lyon, France.The Managing Director
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Boiron, Hung. Boiron Hungaria Kft, Ady Endre ut 8, 1024 Budapest, Hungary.
url: www.boiron.hu

Boiron, Ital. Laboratoires Boiron S.r.l., Via Cassanese 100, 20090 Segrate (MI), Italy.
url: www.boiron.it

Boiron, Neth. See *Boiron, Fr.*

Boiron, Port. See *Prisfar, Port.*

Boiron, Rus. Boiron Ltd, Orlikov per 2, 107078 Moscow, Russia.
url: www.boiron.ru

Boiron, Switz. See *Serolab, Switz.*

Boiron, Ukr. See *Boiron, Fr.*

Boizot, Spain. Boizot, Spain.

Boke, China. Boke Pharmaceutical Co. Ltd, Guangxi, China.

Bolan, USA. See *Allied, USA.*

Bolar, Cz. See *Bolar, Hung.*

Bolar, Hung. Bolar Bt, Borbolya u 3, 1020 Budapest, Hungary.

Bolder, Cz. See *Bolder, Ger.*

Bolder, Ger. Bolder Arzneimittel GmbH & Co. KG, Koblenzer Str. 65, 50968 Cologne, Germany.
url: www.bolder.de

Bolder, Hong Kong. See *Mekim, Hong Kong.*

Bombay Tablet, India. Bombay Tablet Mfg. Co. Pvt Ltd, Off. 304, S. Gandhi Marg, Mumbai 400 002, India.
url: www.bombaytablet.com

Bonafarma, Port. See *Jaba, Port.*

Bonapace, Thai. Bonapace, Thailand.

Bonimed, Pol. Bonimed Laboratorium Medycyny Naturalnej, ul. Stawowa 23, 34-300 Żywiec, Poland.
url: www.bonimed.ig.pl

Boniscontro & Gazzone, Ital. Laboratorio Prodotti Farmaceutici Boniscontro & Gazzone S.r.l., Via Pavia 6, 20136 Milan (MI), Italy.

Bonnington, Austral. See *GSK, Austral.*

Boots, Austral. See *Boots Healthcare, Austral.*

Boots, Belg. See *Boots Healthcare, Belg.*

Boots, Denm. See *Novartis, Denm.*

Boots, Fin. See *Novartis, Fin.*

Boots, Fr. See *Abbott, Fr.*

Boots, Ger. See *Abbott, Ger.*

Boots, Hong Kong. See *Keller, Hong Kong.*

Boots, Israel. See *Teva, Israel.*

Boots, Ital. See *Abbott, Ital* and *Boots Healthcare, Ital.*

Boots, Neth. See *Boots Healthcare, Neth.*

Boots, Philipp. The Boots Company (Phils) Inc., 22/F Equitable Bank Tower, 8751 Paseo de Roxas, Makati City, Philippines.

Boots, Pol. Boots Healthcare, ul. Chłodna 51, 00-867 Warsaw, Poland.

Boots, Rus. Boots Healthcare (CIS) Ltd, Tverskaya ul. 16/2, et. 7, Moscow, Russia.

Boots, Singapore. The Boots Company (Far East) Pte Ltd, 180-B Bencoolen St, 09-03 The Bencoolen, S 189648, Singapore.

Boots, Spain. See *Boots Healthcare, Spain.*

Boots, Switz. See *Doetsch, Grether, Switz.*

Boots, Thai. See *Olic, Thai.*

Boots, UK. Boots the Chemists, Thane Rd, D90 East FO8, Nottingham, NG90 1BS, UK.
url: www.boots.com

Boots, USA. See *Abbott, USA.*

Boots Healthcare, Austral. Boots Healthcare Australia P/L, Locked Bag 2067, North Ryde, NSW 1670, Australia.
url: www.skinexpert.net

Boots Healthcare, Austria. See *Reckitt Benckiser, Ger.*

Boots Healthcare, Belg. Boots Healthcare NV/SA, Koningin Astridlaan 164, 1780 Wemmel, Belgium.
url: www.bootshealthcare.be

Boots Healthcare, Canad. Boots Healthcare USA Inc., 1680 Tech Ave, Mississauga, Ontario, L4W 5S9, Canada.

Boots Healthcare, Cz. Boots Healthcare CEE Ltd, Sokolovská 84-86, 180 00 Prague 8, Czech Republic.
url: www.skinexpert.net

Boots Healthcare, Fr. Laboratoires Boots Healthcare, 35 rue Baudin, 92300 Lavallois-Perret, France.
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Boots Healthcare, Ger. See *Reckitt Benckiser, Ger.*

Boots Healthcare, Irl. Boots Healthcare Ltd, Parkview House, Beech Hill Office Campus, Clonskeagh, Dublin 4, Ireland.
url: www.skinexpert.net

Boots Healthcare, Ital. Boots Healthcare S.p.A., Via Tarantelli 13/15, 22076 Mozzate (CO), Italy.
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Boots Healthcare, Malaysia. Boots Trading (Malaysia) Sdn Bhd, Level 4, Wisma Samudra, 1 Jln Kontraktor U1/14, Hicom-Glenmarie Industrial Park, 40150 Shah Alam, Selangor, Malaysia.
url: www.skinexpert.net

Boots Healthcare, Neth. Boots Healthcare BV, Gooimeer 6-26, 1411 DD Naarden, Netherlands.
url: www.skinexpert.net

Boots Healthcare, NZ. Boots Healthcare New Zealand Ltd, P.O. Box 27-341, Wellington 1, New Zealand.
url: www.skinexpert.net

Boots Healthcare, Port. Boots Healthcare Portugal, Lda, Av. Duque d'Ávila, 185, 1050-082 Lisbon, Portugal.
url: www.skinexpert.net

Boots Healthcare, S.Afr. Boots Healthcare (SA) (Pty) Ltd, 20 Zulberg Close, Building A, Entrance 2, Johannesburg 2198, South Africa.
url: www.skinexpert.net

Boots Healthcare, Spain. Boots Healthcare, Doctor Zamenhof 36 Dup 2, 28027 Madrid, Spain.
url: www.bootshealthcare.es

Boots Healthcare, Switz. Boots Healthcare (Switzerland) AG, Hermal, Untermuli 11, 6300 Zug, Switzerland.
url: www.skinexpert.net

Boots Piramal, India. See *Piramal, India.*

Boots-Flint, USA. See *Abbott, USA.*

Borg, UK. Borg Medicare Ltd, P.O. Box 99, Hitchin, Hertfordshire, SG5 2GF, UK.

Borisov, Belarus. Borisov Pharmaceuticals Plant, 64/27 Chapayeva St, Borisov 222120, Belarus.

Borisov, Rus. See *Borisov, Belarus.*

Borshchagovskii, Ukr. Borshchagovskii HFZ, Mira St 17, 03134 Kiev, Ukraine.

Boryung, China. Boryung Pharmaceutical Co. Ltd, China.

Boryung, Thai. See *Masu, Thai.*

Bosch, Philipp. See *Clinbaxy, Philipp.*

Bosen, China. Bosen Bio Pharmaceutical Co Ltd, China.

Bosnalek, Rus. See *Bosnalijek, Rus.*

Bosnalijek, Rus. Bosnalijek Pharmaceuticals, ul. Dimitria Ulianova 16, korp. 2, kv. 321, 117292 Moscow, Russia.
url: www.bosnalijek.com

Bosnalijek, Ukr. Bosnalijek, Raisa Okipnaya Street 4, Office 81, Kiev, 02002, Ukraine.
url: www.bosnalijek.ba

Boston Healthcare, UK. Boston Healthcare, Unit 6 Navigtion Court, Calder Park, Wakefield, West Yorkshire, WF2 7BJ, UK.

Botanica, NZ. Botanica, New Zealand Pharmacology Ltd, P.O. Box 32128, Christchurch, New Zealand.
url: www.botanica.co.nz

Botanicals International, Hong Kong. See *Great Eastern, Hong Kong.*

Bottger, Ger. Böttger GmbH, Albrechtstr. 22-26, 12167 Berlin, Germany.

Bottu, Fr. See *Sanofi-Aventis, Fr.*

Bouchara, Fr. See *Bouchara-Recordati, Fr.*

Bouchara, Port. See *Neo-Farmaceutica, Port.*

Bouchara, Rus. See *FIC, Rus.*

Bouchara, Singapore. See *Pharmacon, Singapore.*

Bouchara, Switz. See *Interdelta, Switz.*

Bouchara-Recordati, Fr. Laboratoires Bouchara-Recordati, 68 rue Marjolin, 92302 Levallois-Perret, France.

Bouchara-Recordati, Hong Kong. See *Rich Plan, Hong Kong.*

Bouchara-Recordati, Singapore. See *Pharmacon, Singapore.*

Bouchara-Recordati, Ukr. See *Recordati, Ukr.*

Boucher & Muir, Austral. Boucher & Muir P/L, P.O. Box 333, North Sydney, NSW 2059, Australia.
url: www.bnmgroup.com

Boucher & Muir, NZ. Boucher & Muir New Zealand, Level 14 Forsythe Barr Tower, 55-56 Shortland St, Auckland, New Zealand.

Bouhon, Ger. Apotheker Walter Bouhon GmbH, Walter-Bouhan-Str. 4, 90427 Nurnberg, Germany.
url: www.frei-hautpflege.de

Bournonville, Belg. Bournonville Eumedica SA/NV, W. Churchill Av. 67, 1180 Brussels, Belgium.
url: www.belpharma.com

Bournonville, Neth. Bournonville Pharma BV, Nassaulaan 13, 2514 JS Den Haag, Netherlands.
url: www.belpharma.com

Bouty, Ital. Bouty S.p.A., V.le Casiraghi 471, 20099 Sesto San Giovanni (MI), Italy.
url: www.bouty.it

Bouwer Bartlett, S.Afr. 512 The Granger, 40 Beach Rd, Granger Bay, Cape Town, South Africa.
url: www.bouwerbartlett.co.za

Bouzen, Arg. Bouzen S.A.C, I.F.A.F., Calle 36 No. 165/67, 1900 La Plata, Buenos Aires, Argentina.
url: www.bouzensa.com.ar

Bowman, USA. Bowman Pharmaceuticals Inc., 119 Schroyer Ave SW, Canton, OH 44702, USA.

Boya, China. Boya Biopharmaceutical Co. Ltd, 161 Gandong Rd, Fuzhou, Jiangxi, 344000, China.

Boyle, USA. Boyle & Co. Pharmaceuticals, 1613 Chelsea Rd, San Marino, CA 91108, USA.

Bozhou, China. Bozhou Pharmaeutical Co. Ltd., 4th Floor Training Building Compound, 99 Xian Lie Zhong Road, Guangzhou, Guangdong, 510310, China.
url: www.gdbozhou.com

BPC, Switz. See *Globopharm, Switz.*

BPC, UK. The Bolton Pharmaceutical 100 Ltd (BPC 100 Ltd), 2 Chapel Drive, Ambrosden, Oxfordshire, OX25 2RS, UK.

B-Phar, Philipp. B-Phar Inc., 137 Matatag St, Central District, Quezon City 1100, Manila, Philippines.

BPL, Hong Kong. See *IDS, Hong Kong.*

BPL, India. BPL Pharmaceuticals Pvt Ltd, 380/82 Sankersett Rd, J.Sankersett Smriti, Chira Bazar, Mumbai 400 002, India.

BPL, Israel. See *Kamada, Israel.*

BPL, Philipp. See *Britton, Philipp.*

BPL, Rus. Bio Products Laboratory, Kuskovskaya ul 20A of. 709, 111141 Moscow, Russia.
url: www.lifefactor.ru

BPL, Singapore. See *JDH, Singapore.*

BPL, Thai. See *Berli Jucker, Thai.*

BPL, UK. Bio Products Laboratory, Dagger Lane, Elstree, Hertfordshire, WD6 3BX, UK.
url: www.bpl.co.uk

BPL, USA. BPL Inc., 8601 Six Forks Rd, Suite 400, Raleigh, NC 27615, USA.

BPL-Meizler, Braz. See *Meizler, Braz.*

BPRL, Singapore. See *Zyfas, Singapore.*

BR Pharmaceuticals, UK. BR Pharmaceuticals Ltd, Clayton Wood Close, West Park Ring Rd, Leeds, West Yorkshire, LS16 6QE, UK.
url: www.brpharmaceuticals.co.uk

Bracco, Austral. See *Regional Health, Austral.*

Bracco, Austria. See *Bracco, Ital.*

Bracco, Belg. See *Bracco, Neth.*

Bracco, Canad. Bracco Diagnostics Inc, Suite 103, Unit 11, 2600 Skymark Avenue, Mississauga, Ontario, L4W 5B2, Canada.
url: www.bracco.com

Bracco, China. Brocco Sine Pharmaceutical Co. Ltd, Room 610-612 Gangtai Plaza, 700 Yan An East Rd, Hunogpu, Shanghai 200001, China.
url: www.braccosine.com

Bracco, Cz. See *Bracco, Ital.*

Bracco, Denm. See *Initios, Denm.*

Bracco, Fin. See *Bracco, Ital.*

Bracco, Fr. Bracco Imaging France, 7 place Copernic, Courcouronnes, 91 023 Évry cdx, France.

Bracco, Ger. Bracco Imaging Deutschland GmbH, Max-Stromeyer-Str. 116, 78467 Konstanz, Germany.
url: www.bracco.com

Bracco, Gr. See *Bracco, Ital.*

Bracco, Hung. See *Ewopharma, Hung.*

Bracco, Irl. See *Bracco, UK.*

Bracco, Israel. See *Dexxon, Israel.*

Bracco, Ital. Bracco S.p.A., Via E. Folli 50, 20134 Milan (MI), Italy.
url: www.bracco.com

Bracco, Neth. Bracco International BV, Strawinskylaan 3051, 1077 ZX Amsterdam, Netherlands.

Bracco, Norw. See *Astra Tech, Norw.*

Bracco, Pol. See *Bracco, Neth.*

Bracco, Port. See *Dario Correia, Port.*

Bracco, Rus. See *Bracco, Ital.*

Bracco, Singapore. See *Lf, Singapore.*

Bracco, Spain. See *Bracco, Ital.*

Bracco, Swed. Bracco Imaginf Scandinavia AB, Salsmästaregatan 32, 422 46 Hisings Backa, Sweden.
url: www.braccoimaging.se

Bracco, Switz. Bracco Suisse SA, C.P. 1764, 6850 Mendrisio, Switzerland.

Bracco, UK. Bracco UK Ltd, Bracco House, Mercury Park, Wycombe Lane, Woaburn Green, High Wycombe, Buckinghamshire, HP10 0HH, UK.
url: www.bracco.com

Bracco, USA. Bracco Diagnostics, 107 College Road East, Princeton, NJ 08540, USA.
url: www.bracco.com

Bracey, UK. Bracey's Pharmaceuticals, 209 Menlove Ave, Liverpool, Merseyside, L18 3EF, UK.
url: www.odaban.com

Bradford Chemists Alliance, UK. See *Unichem, UK.*

Bradley, Canad. Bradley Pharmaceuticals Inc., 1031 Meyerside Drive, Unit 12, Mississauga, Ontario, L5T 2H5, Canada.

Bradley, Israel. See *Medison, Israel.*

Bradley, Singapore. See *Pan-Malayan, Singapore.*

Bradley, USA. Bradley Pharmaceuticals, 383 Route 46 West, Fairfield, NJ 07004-2402, USA.
url: www.bradpharm.com

Brady, Austria. Brady C. KG, Hörlgasse 5, 1090 Wien, Austria.
url: www.brady.co.at

Bragg, UK. J L Bragg (Ipswich) Ltd, 34 Boss Hall Rd, Ipswich, Suffolk, IP1 5BN, UK.
url: www.charcoal.uk.com

Brainfarma, Braz. Brainfarma Ind. Quim. e Farmaceutica Ltda, Estrada dos Bandeirantes 3191 Parte I, 22775111 Rio de Janeiro, Brazil.

Brainpharma, Spain. Brainpharma SL, Avda Diagonal 549, 08029 Barcelona, Spain.

Braintree, Canad. See *Source, Canad.*

Braintree, USA. Braintree Laboratories Inc., 60 Columbian St West, P.O. Box 850929, Braintree, MA 02185-0929, USA.
url: www.braintreelabs.com

Brainware, S.Afr. Brainware Compu (Pty) Ltd, 476 Kings Highway, Lynnwood, Pretoria, South Africa.

Brands Worldwide, Austral. Brands Worldwide, 205 Victoria St, Beaconsfield, NSW 2015, Australia.
url: www.brandsworldwide.com.au

Brandt, Switz. See *Uhlmann-Eyraud, Switz.*

Brassora, Arg. Brassora SA, Estados Unidos 609, 1101 Capital, Argentina.

Brasterapica, Braz. Brasterapica Indústria Farmacêutica Ltda, Rua Bela Cintra 299 7 andar, 01415-002 São Paulo, SP, Brazil.
url: www.brasterapica.com.br

Bratch, Canad. Bratch Laboratories, 1397 Milburough Line, R R 3, Cambellville, Ontario, L0P 1B0, Canada.

Brauer, Austral. Brauer Natural Medicine P/L, P.O. Box 234, Tanunda, SA 5352, Australia.
url: www.brauer.com.au

Braun, Arg. B. Braun Medical S.A., J. E. Uriburu 663 Pso. 7, 1027 Buenos Aires, Argentina.
url: www.bbraun.com

Braun, Austral. B Braun Australia P/L, Norwest Business Park, 17 Lexington Drive, Bella Vista, NSW 2153, Australia.
url: www.bbraun.com.au

Braun, Austria. Braun Austria GmbH, In den Langackern 5, A-2344 Maria Enzersdorf, Austria.
url: www.bbraun.com

Braun, Belg. B. Braun Medical NV/SA, Woluwelaan 140 B, 1831 Diegem, Belgium.
url: www.bbraun.be

Braun, Canad. See *Broun, USA.*

Braun, Chile. B Braun Medical SA, Calle Nueva 5319, Conchalf, Sontiago, Chile.

Braun, China. B Braun Medical Co. Ltd, Shun Yuan Enterprise Development Building 21, 398 Jiangsu Rd, Shanghai 200050, China.

Braun, Cz. B Braun Medical sro, Cigánková 1861, 148 00 Prague 11, Czech Republic.
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Braun, Denm. B Braun Medical A/S, Solbjergvej 5, 3., 2000 Frederiksberg, Denmark.
url: www.bbraun.dk

Braun, Fin. B. Braun Medical Oy, Huopalahdentie 24, 00350 Helsinki, Finland.
url: www.bbraun.com

Braun, Fr. B Braun Medical SA, 204 av du Mal-Juin, B.P. 331, 92107 Boulogne cdx, France.
url: www.bbraun.fr

Braun, Ger. B. Braun Melsungen AG, Carl-Braun-Str. 1, 34212 Melsungen, Germany.
url: www.bbraun.de

Braun, Gr. See *Braun, Ger.*

Braun, Hong Kong. B Braun Medical (HK) Ltd, 13-14/F Henan Bldg, 90 Jaffe Rd, Wanchai, Hong Kong.
url: www.bbraun.com.hk

Braun, Hung. B Braun Medical Kft, Felhévizi u 3-5, 1023 Budapest, Hungary.

Braun, India. B. Braun Medical (India) Private Ltd, Unit No.1, 5th Floor East Quadrant, The IL&FS Financial Centre, Bandra-Kurla Complex, Bandra (East), Mumbai 400 051, India.
url: www.bbraun.co.in

Braun, Indon. See *Buminusantara, Indon.*

Braun, Irl. B. Braun Medical Ltd, 3 Naas Rd Industrial Park, Dublin 12, Ireland.
url: www.bbraun.ie

Braun, Israel. See *Teva, Israel.*

Braun, Ital. B. Braun Milano S.p.A., Via V. da Seregno 14, 20161 Milan (MI), Italy.
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Braun, Neth. See *Braun, Ger.*

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Braun, NZ. B Braun New Zealand Pty Ltd, 54 Carbine Rd, Mt Wellington, Auckland, New Zealand.

Braun, Philipp. B Braun Medical Supplies Inc., 2/F JMT Corporate Cond., ADB Ave, Ortigas Ctr, Pasig City

Braun, Pol. B. Braun, Aesculap Chifa Sp. z.o.o., ul. Tysiąclecia 14, 64-300 Nowy Tomyśl, Poland.
url: www.chifa.pl

Braun, Port. B. Braun Medical, Lda, Estrada Consiglieri Pedroso 80, Queluz Park, Queluz de Baixo, 2745-533 Barcarena, Portugal.
url: www.bbraun.com

Braun, Rus. See *Merz, Rus.*

Braun, S.Afr. B Braun (Pty) Ltd, P.O. Box 1787, Randburg 2125, South Africa.
url: www.bbraun.co.za

Braun, Singapore. B Braun Singapore Pte Ltd, 460 Alexandra Rd, 34-03 PSA Building, S 119963, Singapore.
url: www.bbraun.com.sg

Braun, Spain. Braun Medical, Ctra Tarrasa 121, Rubi, 08191 Barcelona, Spain.
url: www.bbraun.com

Braun, Swed. B. Braun Medical AB, Box 110, 182 12 Danderyd, Sweden.
url: www.bbraun.com

Braun, Switz. B. Braun Medical AG, Hospital Care, Postfach, 6020 Emmenbrucke, Switzerland.
url: www.bbraun.ch

Braun, Thai. B Braun (Thailand) Ltd, 12 Fl, Q-House Ploenchit Building, 598 Ploenchit Rd, Lumpini Pathumwan, Bangkok 10330, Thailand.
url: www.bbraun.co.th

Braun, Turk. B Braun İlaç Tiscaret Şti., Universite Mahallesi, Civan Sokak, No: 15/2, Avcilar, Istanbul, 34850, Turkey.
url: www.bbraun.com

Braun, UK. B. Braun Medical Ltd, Thorncliffe Park Industrial Estate, Chapeltown, Sheffield, South Yorkshire, S35 2PW, UK.
url: www.bbraun.co.uk

Braun, Ukr. See *Artur, Ukr.*

Braun, USA. B. Braun Medical, 1601 Wallace Drive, Suite 150, Carrollton, TX 75006, USA.
url: www.bbraunusa.com

Braun Biotrol, Fr. See *Braun Medical OPM, Fr.*

Braun Biotrol, UK. See *Braun, UK.*

Braun McGaw, Hong Kong. See *ICH, Hong Kong.*

Braun Medical OPM, Fr. B Braun Medical SAS, Division OPM, 69 rue de la Grange-aux-Belles, 75010 Paris, France.
url: www.bbraun.com

Braun Melsungen, Ital. See *Braun, Ital.*

Braun Omnimed, S.Afr. See *Braun, S.Afr.*

Brawn, India. Brawn Laboratories Ltd, 4/4B Asaf Ali Road, II Floor Delhi Stock Exchange Building, New Delhi 110 002, India.
url: www.brawnlabs.com

Bray, UK. Bray Health & Leisure (Solport Ltd), 1 Regal Way, Faringdon, Oxfordshire, SN7 7BX, UK.
url: www.bray.co.uk

Breath Asure, USA. See *Health Assure, USA.*

Breathe Pharmaceuticals, Irl. Breathe Pharmaceuticals Ltd, Unit 20A Beckett Way, Park West Business Park, Dublin 12, Ireland.

Breckenridge, USA. Breckenridge Pharmaceutical Inc, 1141 South Rogers Circle, Suite 3, Boca Raton, FL 33487, USA.
url: www.breckenridgepharma.com

Bregenzer, Austria. Herbert Bregenzer, Am Damm 20, A-6820 Frastanz, Austria.

Brel, Philipp. Brel Pharmaceutical Inc., Suite 709, National Life Insurance Building, 6762 Ayala Ave, Makati City, Philippines.

Brenner-Efeka, Ger. See *Pfizer, Ger.*

Brenntag, Denm. Brenntag Disinfection, Gl Strandv. 16, 2990 Niva, Denmark.
url: www.brenntag-nordic.com

Brenntag, Norw. See *Brenntag, Denm.*

Bride, Cz. See *Bride, Fr.*

Bride, Fr. Laboratoires Bride, 263 c av de Laon, 51100 Reims, France.

Bride, Hung. See *PDP, Hung.*

Bridoux, Fr. Laboratoires Bridoux, 6 rue Salengro, 62160 Bully-les-Mines, France.

Bright Future, China. Bright Future Pharmaceuticals Factory, Room 1904-05, 300 North Zhongshan Rd, Putuo District, Shanghai, China.
url: www.brightfuture.com.hk

Bright Future, Hong Kong. Bright Future Pharmaceutical Laboratories Ltd, BF Pharmaceutical Ctr, 8 Wang Fu St, Yuen Long Industrial Estate, Yuen Long, N.T., Hong Kong.

Brighton, USA. Brighton Pharmaceuticals, 201 Shannon Oaks Circle 200, Cary, NC 27511, USA.

Brill, Spain. Brill Pharma SL, Mandri 66, Escalera A, despacho 2, 08022 Barcelona, Spain.

Brimms, Canad. See *Shield, USA.*

Brimms, Israel. See *Trima, Israel.*

Brimms, USA. See *BMS, USA.*

Brimpharm, S.Afr. Brimpharm SA (Pty) Ltd, Suite 2 F, Nautica, Waterclub Beach Rd, Cape Town, Western Cape 8005, South Africa.

Brioschi, Canad. See *Unico, Canad.*

Bripharm, Irl. See *Astellas, Irl.*

Briskon, India. Briskon Laboratories, Bansal Bhavan, 1st Floor 5 Mikipura, Near Mohan Talies, Ujjain 456 006, India.

Bristol, Austral. See *BMS, Austral.*

Bristol, Canad. See *BMS, Canad.*

Bristol, Fr. See *BMS, Fr.*

Bristol, Ger. See *BMS, Ger.*

Bristol, Ital. See *BMS, Ital.*

Bristol, Jpn. Bristol Pharmaceuticals K.K., 6-5-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 163-1328, Japan.

Bristol, Neth. See *BMS, Neth.*

Bristol, UK. Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Rd, Berkhamsted, Hertfordshire, HP4 1EG, UK.
url: www.bristol-labs.co.uk

Bristol, USA. See *BMS, USA.*

Bristol-Myers, Austral. See *BMS, Austral.*

Bristol-Myers, Spain. See *BMS, Spain.*

Bristol-Myers Products, USA. See *BMS, USA.*

Britannia Health, UK. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, Denm. See *Nordicinfu Care, Denm.*

Britannia Pharmaceuticals, Fin. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, Irl. See *Clonmel, Irl.*

Britannia Pharmaceuticals, Neth. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, Norw. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, Port. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, Spain. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, UK. Britannia Pharmaceuticals Ltd, Park View House, 65 London Rd, Newbury, Berkshire, RG14 1JN, UK.
url: www.britannia-pharm.co.uk

Britannia Pharmaceuticals, USA. See *Britannia Pharmaceuticals, UK.*

BritCair, UK. See *BMS, UK.*

BritHealth, UK. See *Cintas, UK.*

Britisfarma, Spain. See *GSK, Spain.*

British Biologicals, India. British Biologicals, No. 30, 10th Main Ashoka Pillar Road, Jayanagar, II Block, Bangalore 560 011, India.
url: www.britishbiologicals.com

British Cod Liver Oils, Hong Kong. See *Keller, Hong Kong.*

British Dispensary, Thai. British Dispensary, 272 Moo 1 Soi Pattanasuk, Teparak Rd, Samutprakarn 10270, Thailand.

British Pharmaceuticals, Austral. See *Organon, Austral.*

Britton, Philipp. Britton Distributions Inc., Unit 17B Strata Bldg, 9 F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Brocades, Ital. See *Astellas, Ital.*

Brocades, Singapore. See *Indrugco, Singapore.*

Brocades, UK. See *Astellas, UK.*

Brooke Green, UK. Brooke Green Ltd, Woodfield House, Moreton Valence, Gloucestershire, GL2 7NB, UK.

Brookstone, USA. Brookstone Pharmaceuticals LLC, 9005 Westside Parkway, Alpharetta, GA 30004, USA.
url: www.brookstonepharma.com

Bros, Gr. Bros E.P.E., Avgis & Galinis 15, 145 64 Nea Kifissia, Greece.

Brostel, Canad. Brostel Inc., 1688 50E Ave, Lachine, Quebec, H8T 2V5, Canada.

Brothier, Fr. Laboratoires Brothier, 41 rue de Neuilly, 92000 Nanterre, France.Bruno Gerady, Regulatory Affairs
url: www.brothier.com

Brothier, Switz. See *Uhlmann-Eyraud, Switz.*

Brovar, S.Afr. Brovar S & P (Pty) Ltd, South Africa.

Brown & Burk, India. Brown & Burk Pharmaceuticals Ltd, 303, A Wing, Queen's Corner Apartments, Bangalore 560 001, India.

Brown & Burk, Malaysia. See *Zyfas, Malaysia.*

Brown & Burk, Philipp. Brown & Burk Phils Inc., 3/F RCI Bldg, 105 Rada St, Legaspi Village, 1229 Makati City, Philippines.

Brown & Burk, Rus. See *Brown & Burk, India.*

Braxa, Ital. See *Cabon, Ital.*

Bruluagsa, Mex. Bruluagsa SA de CV, Calle 18, Lote 10, Manzana 23 2 sec. Pqu, 50450 Atlacomulco, Estado de Mexico, Mexico.

Bruluart, Mex. Importadora y Manufacturera Bruluart SA, Geranias 9, 54940 Tultitlan San Fco. Chilpan, Estado de Mexico, Mexico.

Brunel, S.Afr. Brunel Laboratories (Pty) Ltd, P.O. Box 23103, Innesdale 0031, South Africa.

Brunet, Fr. See *Martin-Johnson & Johnson, Fr.*

Brunifarma, Ital. Brunifarma Research srl, Via Maestra la Barbera n 12/A, 90017 Santa Flavia (PA), Italy.
url: www.brunifarma.com

Bruno, Ital. Bruno Farmaceutici S.p.A., Via delle Ande 15, 00100 Rome (RM), Italy.

Brupharmexport, Ukr. Brupharmexport, Byelorussian Street, 34, Office 28, Kiev, 04119, Ukraine.

Bruschettini, China. See *Trendful, Hong Kong.*

Bruschettini, Hong Kong. See *Jebsen, Hong Kong.*

Bruschettini, Ital. Bruschettini S.r.l., Via Isonzo 6, 16147 Genoa (GE), Italy.
url: www.bruschettini.com

Bruschettini, Malaysia. See *DKSH, Malaysia.*

Bruschettini, Neth. See *Bruschettini, Ital.*

Bruschettini, Pol. See *Pharm Supply, Pol.*

Bruschettini, Switz. See *Galenica, Switz.*

Bruschettini, Ukr. See *Mili, Ukr.*

Brussels, India. Brussels Laboratories Pvt Ltd, 317 Abhishree Complex, Opp.Star India Bazar, Satellite Road, Ahmedabad 380 015, India.
url: www.brusselslaboratories.com

Bryan, USA. Bryan Corp., 4 Plympton St., Woburn, MA 01801, USA.
url: www.bryancorporation.com

Brymar, Philipp. Brymar Pharmaceuticals, Rm 409 Integrated Professionals Offices Bldg, 14 Quezon Ave, Quezon City, Philippines.

Bryntsalov, Rus. Bryntsalov-A zao, 1 Nagatinskaya ul, Moscow 113105, Russia.

Bryntsalov, Ukr. Bryntsalov, Ukraine.

Bryssica, Fr. Laboratoires Bryssica, 5 rue de Turbigo, 75001 Paris, France.

bsa, Fr. bsa (Lab), BP 432, 69654 Villefranche-sur-Saône cdx, France.

BSIA, Gr. See *Typharm, UK.*

BSIA, UK. See *Typharm, UK.*

BSM, Austria. BSM Diagnostica GesmbH, Alser Strasse 25, A-1080 Vienna, Austria.

BSN, Austral. BSN Medical, 211 Wellington Rd, Clayton, Vic 3168, Australia.
url: www.bsnmedical.com

BSN, Fr. See *Smith & Nephew, Fr.*

BSN, Ital. BSN Medical S.r.l., Viale Colleoni 17, 20041 Agrate Brianza (MI), Italy.

BSN, USA. BSN Medical Inc., 5825 Varnegie Blvd, Charlotte, NC 28209, USA.
url: www.bsnmedical.com

BSPC, China. Beijing Second Pharmaceutical Co Ltd (BSPC), 21st Floor, Building 2 Jinhai Wealth Commercial Center, Baiziwan Xili 402a, Chaoyang District, Beijing 100124, China.
url: www.saike.com.cn

BSSAA, UK. British Snoring & Sleep Apnoea Assaciation Ltd, 2nd Floor Suite, 52 Albert Rd North, Reigate, Surrey, RH2 9EL, UK.
url: www.britishsnoring.co.uk

BTA, USA. See *Biovail, USA.*

BTG, USA. See *Bio-Technology, USA.*

BTG, USA. BTG international Inc., Five Tower Bridge, Suite 800, 300 Barr Harbor Drive, West Conshohocken, PA 19428, USA.
url: www.btgplc.com

Bu Chang, China. Bu Chang Pharmaceutical Co. Ltd, Xianyang, China.

Bucaneve, Ital. Bucaneve Medicinali S.r.l., Via Sercognani 15, 20156 Milan (MI), Italy.

Bucheli, Switz. Bucheli AG, Bahnhofstrasse 27, 9100 Herisau AR, Switzerland.
url: www.bucheliag.ch

Buckley, Canad. W.K. Buckley Ltd, 5230 Orbitar Drive, Mississauga, Ontario, L4W 5G7, Canada.
url: www.buckleys.com

Budapharma, Hung. Budapharma Kft, Kevélyhegyi u 15/a, 1028 Budapest, Hungary.

BUDP, Hong Kong. See *CNW, Hong Kong.*

Bufa, Indon. Bufa Aneka PT, Jl Tambak, Aji V No 4, Semarang 50185, Jawa Tengah, Indonesia.

Bulgarian Rose, Rus. Bulgarian Rose Sevtapolis, Russia.
url: www.bulgarian-rose-sevtopolis.com

Bull, Malaysia. See *Schmidt, Malaysia.*

Bull, Singapore. See *Mayne, Singapore.*

Bullivants, Austral. Bullivants, Campus Pharmacy, St. Lucia, QLD 4067, Australia.
url: www.campuspharmacy.com.au

Buminusantara, Indon. Buminusantara bestari Perkasa, Rukan Blok B No 21, Groha Cempaka Mas, Jl Ietjen Suprapto Sumur Batu, 10640 Jakarta, Indonesia.

Bunker, Braz. Bunker Indústria Farmacêutica Ltda, Rua Anibal dos Anjos Carvalho 212, 04810-050 São Paulo, SP, Brazil.

Burapha, Thai. Burapha Dispensary Co Ltd, 19/19 Soi Ngamwongwan 6, Ngamwongwan Rd, Bangkhen Muang, Nonthaburi 1100, Thailand.

Burel, USA. Burel Pharmaceuticals, 464 Church Rd, Suite 100, Madison, MS 39110, USA
url: www.burelpharmaceuticals.com

Burgeon, India. Burgeon Pharmaceuticals Pvt Ltd, 19 South Raja Street, Alandur, Chennai 600 016, India.
url: www.burgeon.in

Burnet, Fr. See *Clement-Thekan, Fr.*

Burnishine, Canad. See *Burnishine, USA.*

Burnishine, USA. Burnishine products, Division of Weiman Products LLC, 755 Tri State Parkway, Gurnee, IL 60031, USA.

Burnshield, Israel. Burnshield, Israel.

Bushnell, India. Walter Bushnell Ltd, Apeejay Chambers, Wallace Street, Mumbai 400 001, India.

Bustillos, Mex. Laboratorios Bustillos, S.A. de C.V., Manuel Dublan No. 40, Col. Tacubaya, Deleg. Miguel Hidalgo, 11800 Mexico D.F., Mexico.

Butler, Ger. See *Sunstar, Ger.*

Buxton, Arg. Laboratorios Buxton SA, Santos Dumont 4671, 1427 Buenos Aires, Argentina.

Byk, Austria. Byk Österreich Pharma GmbH, Ketzergasse 200, A-1235 Vienna, Austria.

Byk, Belg. See *Altana, Belg.*

Byk, Braz. See *Altana, Braz.*

Byk, Fr. See *Altana, Fr.*

Byk, Neth. Byk Nederland BV, Weerenweg 29, 1161 AG Zwanenburg, Netherlands.

Byk, Port. See *Altana, Port.*

Byk, Switz. See *Altana, Switz.*

Byk Elmu, Spain. See *Altana, Spain.*

Byk Gulden, Denm. See *Nycomed, Denm.*

Byk Gulden, Ger. See *Nycomed, Ger.*

Byk Gulden, Hong Kong. See *Altana, Hong Kong.*

Byk Gulden, Mex. See *Altana, Mex.*

Byk Gulden, Norw. See *Pfizer, Norw.*

Byk Gulden, S.Afr. See *Altana, S.Afr.*

Byk Gulden, Singapore. See *Pacific Biosciences, Singapore.*

Byk Gulden, Thai. See *Zuellig, Thai.*

Byk Gulden, Turk. See *Nycomed, Ger.*

Byk Leo, Spain. See *Altana, Spain.*

Byk Madaus, S.Afr. See *Altana, S.Afr.*

Byk Roland, Switz. See *Altana, Switz.*

Byk Tosse, Ger. See *Nycomed, Ger.*

Bykomed, Port. See *Altana, Port.*

BYS, Philipp. See *Health Vision, Philipp* and *Lantaka, Philipp.*

C&V, Arg. C&V Int. Servicios Comerciales, Av. Del Libertador 5190 Piso 1, 1426 Buenos Aires, Argentina.

C&Y, China. C&Y Pharmaceutical Co. Ltd, Shanxi, China.

C & G, Ital. C & G Formaceutici Srl, Via Benedetto Croce 26, 00142 Roma (RM), Italy.

C & L, Hong Kong. C & L Pharmaceutical Ltd, Unit A-C, 19/F Flourish Food Manufactory Ctr, 18 Tai Lee St, Yuen Long, N.T., Hong Kong.
url: www.candl.com.hk

C & M, USA. See *Genesis, USA.*

C & O, China. C & O Pharmaceutical Co Ltd, 800 Road 2, Luhe District, Nanjing 211500, Jiangsu, China.
url: www.changao.com

Caan, Philipp. Caan Pharmaceuticals, G/F 2053 Building, Edison St, San Isidro, Makati, Philippines.

Cabassi, Ital. Cabassi & Giuriati S.p.A., Via Uruguay 20/22, 35129 Padova (PD), Italy.
url: www.cabassi-giuriati.it

Caber, Ital. Farmaceutici Caber S.p.A., Viale Citta d'Europa 681, 00144 Rome (RM), Italy.

Cablon, Neth. Cablon medical BV, Klepelhoek 11, 3833 GZ Leusden, Netherlands.

Cabon, Ital. Cabon-Denit S.p.A., Via T. Cremona 10, 20092 Cinisello Balsamo (MI), Italy.

Cabuchi, Arg. Lab. Cabuchi S.A., Tucuman esq. San Juan, 5220 Jesus Marma, Cordoba, Argentina.

Cachet, India. Cachet Pharmaceuticals Pvt Ltd, 415 Shah Nahar Ind. Estate, Dr. E. Moses Road, Worli Naka, Mumbai 400 018, India.
url: www.cachetindia.com

CAD PET, Spain. Centro Andaluz de Diagnostico Pet, Rd Capuchinos 11, 41009 Seville, Spain.

Cadence, USA. Cadence Pharmaceuticals Inc., 12481 High Bluff Drive, Suite 200, San Diego, CA 92130, USA.
url: www.cadencepharm.com

CaDiGroup, Ital. Ca.Di.Group S.r.l., Via Pieve Tesino 75, 00124 Rome (RM), Italy.
url: www.cadigroup.it

Cadila, India. Cadila Pharmaceuticals Ltd, Cadila Corporate Campus, Sarkhej-Dholka Rd, Bhat, Ahmedabad 382 210, India.
url: www.cadilapharma.com

Cadila, Malaysia. See *Zyfas, Malaysia.*

Cadila, Philipp. See *Brel, Philipp.*

Cadila, Rus. Cadilla Healthcare Ltd, Gubkina ul. 14, Of. 39, 117312 Moscow, Russia.
url: www.cadilapharma.com

Cadila, Singapore. See *Uni, Singapore.*

Cadila, Thai. See *Pharmaland, Thai.*

Cadillac, Canad. Produits Cadillac (1984) Ltd, 1160 Taillon, Quebec City, Quebec, G1N 4M1, Canada.

Caduceus, Ital. See *Caduceus, UK.*

Caduceus, UK. Caduceus Pharma Ltd, 6th Floor, 94 Wigmore St, London, W1U 3RF, UK.

Cady, Ital. Cady Paris by Caselli Alda, Via dei Maceri 11, 40139 Bologna (BO), Italy.

Caesaro, Austria. Caesaro Med GmbH, Raidenstrasse 46, A-4060 Leonding, Austria.

Cafar, Venez. CAFAR (Compania Anonima Farmaceutica), Avenida M. Perez Pisanti, Sector Industrial Los 3 puentes, Urb. El Tambor Los Teques, Caracas, Venezuela.
url: www.cafar.com.ve

CAF-DCF, Belg. CAF-DCF CV, De Tyraslaan 109, 1120 Brussels, Belgium.
url: www.caf-dcf.redcross.be

CAG, Fr. C.A.G. Pharma, 8 rue de la Source, 92310 Sèvres, France.
url: www.cagpharma.com

Cagdas, Turk. Çağdaş Eczacılar Labatatuvarı San. ve Tic. A.Ş., 1649 Sok. No:15, Bayraklı, İzmir, Turkey.
url: www.cagdasecza.com.tr

Cahill May Roberts, Irl. See *Movionto, Irl.*

Caif, Arg. Campaña Argentina de Invest. Farmaceuticas SA, Solvs 1702, 1134 Buenos Aires, Argentina.

Cal, USA. Cal Pharma, USA.
url: www.calpharma.com

Calao Resfar, Ital. Calao S.r.l. Resfar Division, Via G.B Grassi 15, 20157 Milan (MI), Italy.
url: www.calao.it

Caldeira & Marques, Port. Caldeira & Marques, Lda, Rua 25 de Abril, Lote 32-B, Brandoa, 2650-061 Amadora, Portugal.

Caldeira & Metelo, Port. Caldeira & Metelo, Lda, Rua 25 de Abril, Lote 26, loja, Brandoa, 2650-061 Amadora, Portugal.

Caldern, India. Caldern Pharmaceuticals Ltd, 229 Block B, Lake Town, Kolkata 700 089, India.

Calea, Canad. Calea Ltd, 2785 Skymark Ave, Unit 2, Mississauga, Ontario, L4W 4Y3, Canada.
url: www.calea.com

Caleb, Hong Kong. See *Health Alliance, Hong Kong.*

Calgon Vestal, USA. See *Steris, USA.*

California Department of Health, USA. California Department of Health, 850 Marina Bay Parkway, Room E-361, Richmond, CA 94804, USA.

California North, Canad. See *California North, USA.*

California North, USA. California North, Sausalito, CA 94966-2820, USA.

California Scientific, Arg. California Scientific Argentina SA, Belgrano 3380, Mar del Plata, (B7600GKZ), Pcia. de Buenos Aires, Argentina.

Calmante Vitaminado, Spain. Calmante Vitaminado, Glorieta Perez Gimenez 1, Pol Ind de Chinales, 14080 Cordoba, Spain.

Calmic, Irl. See *GSK, Irl.*

Calmic, UK. See *GSK, UK.*

Calmic, USA. See *GSK, USA.*

Calmoseptine, Canad. See *Calmoseptine, USA.*

Calmoseptine, Philipp. See *Metro, Philipp.*

Calmoseptine, USA. Calmoseptine Inc., 16602 Burke Lane, Huntington Beach, CA 92647, USA.
url: www.calmoseptine.com

Calox, Venez. Laboratorios Calox C.A., Av. Don Diego Cisneras Edificio Calox, Los Ruices, Apartado 62483, Caracas 1071, Venezuela.
url: www.calox.com

Cal-White, USA. Cal-White Mineral Co., P.O. Box 7890, Klamath Falls, OR 97602, USA.

Cambridge, Irl. Cambridge Laboratories (Ireland) Ltd, Alexandra House, The Sweepstakes, Ballsbridge, Dublin 4, Ireland.
url: www.camb-labs.com

Cambridge, Neth. See *Cambridge, Irl.*

Cambridge, UK. Cambridge Laboratories, Deltic House, Kingfisher Way, Silverlink Business Park, Wallsend, Tyne & Wear, NE28 9NX, UK.
url: www.camb-labs.com

Cambridge Healthcare, UK. See *Typharm, UK.*

Cambridge Neuroscience, USA. See *Baxter, USA.*

Cambridge Nutraceuticals, USA. See *Baxter, USA.*

Cambridge Theranostics, UK. Cambridge Theranostics, The Babraham Research Campus, Babraham, Cambridge, Cambridgeshire, CB22 3AT, UK.

Camden, Singapore. See *Advanced, Singapore.*

Camox, S.Afr. Camox Pharmaceuticals Pty Ltd, Entrance No 2, Sanlem Arena, 10 Cradock Ave, Rosebank 2132, South Africa.

Campo Esmeralda, Arg. Campo Esmeralda SRL, Urquiza 1047, (2451) San Jorge, Santa Fe, Argentina.

Campro, Ger. Campro Scientific GmbH, P.O. Box 36 02 65, 2 Hof-EG, 10972 Berlin, Germany.
url: www.campro.eu

Campro, Neth. See *Compro, Ger.*

Campus, Swed. Campus Pharma AB, Svärdvägen 13, 182 33 Danderyd, Sweden.
url: www.campuspharma.se

Cana, Gr. Cana S.A., 446 Irakliou Ave, 141 22 Iraklio Attikis, Greece.
url: www.cana.gr

Canadian, China. See *Rosso, China.*

Canadian Custom Packaging, Canad. Canadian Custom Packaging Co., 333 Rimrock Rd, Toronto, Ontario, M3J 3J9, Canada.

Canadian Sun, Canad. Canadian Sun Health Products, Vancouver, British Columbia, Canada.
url: www.canadiansun.com

Can-Am Care, USA. Can Am Care Corp., 3780 Mansell Rd, Suite T-50, Alpharetta, GA 30022, USA.
url: www.canamcare.com

Cancernova, Ger. Cancernova GmbH onkologische Arzneimittel, Hirtenweg 2-4, 79276 Reute, Germany.
url: www.cancernova.de

Cancernova, Neth. See *Cancernova, Ger.*

Canderm, Canad. Canderm Pharma, 5353 Thimens Blvd, Saint-Laurent, Quebec, H4R 2H4, Canada.

Candioli, Gr. See *Candioli, Ital.*

Candioli, Ital. Istituta Candiali Profitattico & Farmaceutico S.p.A., Via Manzoni 2, 10092 Beinasco (TO), Italy.
url: www.cadioli.it

Candor, India. Candor Biotech Ltd, SCO 66, Sector 32-C, Chandigarh 160 032, India.
url: www.candorbiotechltd.com

Cangene, Austral. See *Cangene, Canad.*

Cangene, Canad. Cangene Corporation, 155 Innovation Drive, Winnipeg, Manitoba, R3T 5Y3, Canada.
url: www.cangene.com

Cangene, Gr. Cangene, Greece.

Cangene, Hong Kong. See *Hind Wing, Hong Kong.*

Cangene, Israel. See *Luxembourg, Israel.*

Cangene, Neth. See *Cangene, UK.*

Cangene, Philipp. See *GenAsia, Philipp.*

Cangene, Port. See *Cangene, UK.*

Cangene, Singapore. See *Pharmaforte, Singapore.*

Cangene, UK. Cangene Europe Ltd, Parkshot House, 5 Kew Rd, Richmond, Surrey, TW9 2PR, UK.

Cangene, USA. See *Cangene, Canad.*

Cankat, Turk. Cankat İlaç Ltd. Şti., Erciyes İşyerleri Sitesi 4. Cad. No:16, Macunköy, Ankara, 06370, Turkey.
url: www.cankat.com.tr

Can-Med, Canad. Can-Med Pharma Inc., Toronto, Ontario, Canada.
url: canmedpharma.com

Canonne, Braz. Laboratório Canonne Ltda, Avenida Canal do Anil 1263, 22765-430 Rio de Janeiro, RJ, Brazil.

Cansin, Turk. Cansın İlaç Ltd. Şti., Süleyman Sırrı Sakak No:16/5, Yenişehir, Ankara, Turkey.
url: www.cansinmed.com

Cantabria, Indon. See *Combiphar, Indon.*

Cantabria, Neth. See *Contabria, Spain.*

Cantabria, Spain. Industrial Farmaceutica Cantobria SA, Ctra. Cazoña-Adarzo, 39011 Santander, Spain.

Cantassium Co., UK. The Cantassium Company, Larkhill Farm, Putney, UK.

Canyon, Austria. See *Canyon, UK.*

Canyon, Cz. See *Canyon, UK.*

Canyon, Ger. Canyon Pharmaceuticals GmbH, Unter Gereuth 10, 79353 Bahlingen, Germany.
url: canyonpharma.com

Canyon, Gr. See *Canyon, Switz.*

Canyon, Irl. See *Canyon, UK.*

Canyon, Neth. See *Canyon, UK.*

Canyon, Pol. See *Canyon, UK.*

Canyon, Port. See *Canyon, UK.*

Canyon, Spain. See *Canyon, UK.*

Canyon, Switz. Canyon Pharmaceuticals AG, Hirschgasslein 11, 4051 Basel, Switzerland.
url: www.canyonpharma.com

Canyon, UK. Canyon Pharmaceuticals Ltd, 20-22 Bedford Row, London, WC1R 4JS, UK.

Caoxian, China. Caoxian Pharmaceutical Co. Ltd, Yanbian, China.

Capellon, USA. Capellon Pharmaceuticals Inc., 7509 Flagstone St, Fort Worth, TX 76118, USA.
url: www.capellon.com

Capilares, Spain. Productos Capilares, Lopez Bravo 78, Plg. Ind. Villalonquejar, 09080 Burgos, Spain.

Capital, USA. Capital, USA.

Caplet, India. Caplet India, 207 Lake Town, Block A, Kolkata 700 089, India.
url: www.capletindia.com

Caplin, Philipp. See *Caplin Point, India.*

Caplin Point, India. Caplin Point Laboratories Ltd, 3 Lakshmanan St, T Nagar, Chennai-600 017, Tamil Nadu, India.
url: www.caplinpoint.net

Capo Sole, Ital. Capo Sole S.r.l., Via Edison 60, 20019 Settimo Milanese (MI), Italy.

Caprifarmindo, Indon. Caprifarmindo Laboratories, Jl Purnawarman No 47, Bandung 40116, Indonesia.
url: www.caprifarmindo.com

Caps, S.Afr. Caps Pharmaceuticals (SA) (Pty) Ltd, P.O. Box 2801, Johannesburg 2000, South Africa.

Capsifar, Port. Capsifar - Comércio de Produtos Químico-Farmacêuticos Lda, Rua de Santa Rita, Lote 3, Loja Esq., 2765-281 São João do Estoril, Cascais, Portugal.

Capsule, Singapore. Capsule Pharma Pte Ltd, 54 Serangoon North Ave 4, 06-01 Cyberhub North, S 555854, Singapore.
url: www.capsulepharma.com

Captab, India. Captab Biotech, SCO 322, 1st Floor, Sector 38D, Chandigarh 160 038, India.

Caraco, USA. Caraco Pharmaceutical Labs, 1150 Elijah McCoy Drive, Detroit, MI 48202, USA.
url: www.caraco.com

Carbagas, Switz. Carbagas, Hofgut, 3073 Gümligen, Switzerland.

Carbel, Mex. Grupo Carbel S.A. de C.V., Temistocles 96, Polanco Chapultepec, 11550 Mexico D.F., Mexico.

Carburos Metalicos, Spain. SE Carburos Metalicos SA, C/ Aragon 300, 08009 Barcelona, Spain.

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Cardinal, Hong Kong. See *Star, Hong Kong.*

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Cardinal Health, USA. Cardinal Health Inc., 7000 Cardinal Place, Dublin, OH 43017, USA.
url: www.cardinal-health.com

Cardinova, Hung. See *Cardinova, Swed.*

Cardinova, Swed. Cardinova AB, Ullforsgatan 15, 752 28 Uppsala, Sweden.
url: www.cardinova.com

Care, Austral. Care Pharmaceuticals Pty Ltd, Bondi Junction, NSW 2022, Australia.
url: www.carepharmaceuticals.com.au

Care, Singapore. See *Steward Cross, Singapore.*

Care, UK. See *AstraZeneca, UK.*

CareFusion, Fin. CareFusion Finland, Äyritie 8 B, 01511 Vantaa, Finland.

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CareFusion, Neth. See *CareFusion, UK.*

CareFusion, Swed. CareFusion Sweden AB, Box 452, 191 24 Sollentuna, Sweden.
url: www.carefusion.com

CareFusion, UK. CareFusion, Reigate Place, 43 London Rd, Reigate, Surrey, RH2 9PW, UK.
url: www.chloraprep.co.uk

Carelife, China. Carelife Pharmaceutical Co. Ltd, Chongqing, China.

Carestream, Canad. Carestream Health Canada Co, 200 6 Monogram Place, Toronto, Ontario, M9R 0A1, Canada.

Caribbean Breeze, Canad. See *Caribbean Breeze, USA.*

Caribbean Breeze, USA. Caribbean Breeze International Inc., 81501 Commercial Park Drive, Yulee, FL 32097-4090, Canada.

Carinopharm, Austria. See *Carinopharm, Ger.*

Carinopharm, Ger. Carinopharm GmbH, Rochusstr. 175-177, 53123 Bonn, Germany.
url: www.carinopharm.de

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Carlo Erba, Turk. See *Deva, Turk.*

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Carlo Erba Reogents, Ital. Carlo Erba Reagenti srl, Viale Luraghi snc, 20020 Arese (MI), Italy.
url: www.carloerbareagents.com

Carlson, USA. J.R. Carlson Laboratories Inc., 15 College Drive, Arlington Heights, IL 60004-1985, USA.
url: www.carlsonlabs.com

Corma, Canad. See *Carma, USA.*

Carma, USA. Carma Laboratories Inc., 5801 W Airways Ave, Franklin, Wisconsin, 53132-9111, USA.
Carme, USA. See *Senetek, USA.*
Carnation, USA. See *Nestle, USA.*
Carnot, Mex. Carnot Laboratorios, Productos Cientificos, S.A. de C.V., Nicolas San Juan No.1046, Col del Valle, 03100 Mexico D.F., Mexico.
Carnrick, USA. See *Elan, USA.*
Carolina, USA. Carolina Medical Products Co., P.O. Box 147, Farmville, NC 27828, USA.
url: www.carolinamedical.com
Carrare, Fr. Laboratoires Carrare, 1 rue Frederic-Bastiat, 75008 Paris, France.
url: www.laboratoires-carrare.com
Carrington, USA. Carrington Labs, 2001 Walnut Hill Lane, Irving, TX 75038, USA.
url: www.carringtonlabs.com
Carringtons, Singapore. See *ICM, Singapore.*
Carter, Austral. Carter Products (Australia) P/L, 1/108 Old Pittwater Road, Brookvale, NSW 2100, Australia.
Carter, NZ. See *Wilson, NZ.*
Carter, UK. Carter Products Ltd, Wear Bay Rd, Folkestone, Kent, CT19 6PG, UK.
url: www.carterproducts.co.uk
Carter Horner, Canad. Carter Horner Inc., 6600 Kitimat Rd, Mississauga, Ontario, L5N 1L9, Canada.
Carter Horner, Hong Kong. See *US Summit, Hong Kong.*
Carter Horner, Philipp. See *Zenaust, Philipp.*
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Carter-Wallace, Switz. See *Doetsch, Grether, Switz.*
Carter-Wallace, UK. See *Carter, UK.*
Carter-Wallace, USA. See *Medpointe, USA.*
Carwin, USA. Carwin Associates Inc., Cropwell, AL 35054, USA.
url: www.carwinassoc.com
Carysfort, Irl. Carysfort Healthcare Ltd, 93 Carysfort Park, Blackrock, Co. Dublin, Ireland.
Casa Grando, Braz. See *Granado, Braz.*
Casana, Indon. Casana, Indonesia.
Casasco, Arg. Lab. Casasco S.A.I.C., Carabobo 22, 1406 Buenos Aires, Argentina.
url: www.casasco.com
Casca, India. Casca Remedies Pvt Ltd, Kuldip Nagar, Ambala Cantt, Haryana 133 004, India.
url: www.cascaremedies.tradeindia.com
Cascan, Ger. See *GSK, Ger.*
Casel, Turk. Casel İlaç San. ve Tic. Ltd. Şti., Nadide Sk. No:5, Merter, Istanbul, Turkey.
url: www.casel.com
Casen Fisons, Spain. See *Casen Fleet, Spain.*
Casen Fleet, Austria. See *Casen Fleet, Spain.*
Casen Fleet, Denm. See *Casen Fleet, Spain.*
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Casen Fleet, Ital. See *Casen Fleet, Spain.*
Casen Fleet, Norw. See *Ferring, Norw.*
Casen Fleet, Port. See *Casen Fleet, Spain.*
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Casen Fleet, UK. Casen Fleet Laboratories, High Common Lane, Tickhill, Doncaster, Yorkshire, DN11 9HE, UK.
Casen Fleet, Ukr. See *Pharm Union, Ukr.*
Casil, India. Casil Health Products Ltd, 708 Sarkhej Dholka Road, Bhat, Ahmedabad 382 210, India.
Casimiro & Moreira, Port. Casimiro & Moreira Lda, Rua das Água Férreas 50 A/P 3.5, 4440 Valongo, Portugal.
Cassara, Arg. Lab. Pablo Cassara S.R.L., Carhue 1096, 1408 Buenos Aires, Argentina.
Cassella-med, Cz. See *Cassella-med, Ger.*
Cassella-med, Fin. See *Cassella-med, Ger.*
Cassella-med, Ger. Cassella-med GmbH & Co. KG, Gereonsmühlengasse 1, 50670 Cologne, Germany.
Cassella-med, Ital. See *Sanofi-Aventis, Ital.*
Cassella-med, UK. See *Cassella-med, Ger.*
Cassella-Riedel, Ger. See *Sanofi-Aventis, Ger.*
Cassenne, Fr. See *Sanofi-Aventis, Fr.*
Castalia, Gr. Castalia Laboratoires Dermatologiques, Greece, Agia Marinas, Paiania Attica, Greece.
Castlemead, UK. See *Sanofi, UK.*
Catafarma, Braz. Catafarma Industria Farmaceutica Ltda, Rua Luiz Peicher de Carvalho 100, 88705240 Tubarão Aeroporto, Santa Catarina, Brazil.
Catalent, Austral. Catalent Pharm, Braeside, Melbourne, Australia.
url: www.catalent.com
Catalent, China. Catalent, Section C Building 10, 353 North Riying Road, Waigaoqiao Free Trade Zone, Shanghai, China.
url: www.catalent.com
Catalent, Philipp. See *Philusa, Philipp.*
Catalysis, Arg. Catalysis Argentina S.A., Av. Raul S. Ortiz 1277, 1414 Buenos Aires, Argentina.
Catarinense, Braz. Laboratório Catarinense S.A., Rua Doutor João Colin 1053, 89204-001 Joinville, SC, Brazil.
url: www.labcat.com.br
Cathay, Philipp. The Cathay Drug Co. Inc., 2/F Vernida I Cond, 120 Amorsolo St, Legaspi Vill, Makati City, Philippines.
Cavalheiro, Port. See *Confar, Port.*
Cavico, Malaysia. See *DKSH, Malaysia.*
Cazi, Braz. Cazi Química Farmacêutica Indústria e Comércio Ltda, Rua Antônio Lopes 17, 06600-000 Jandira, SP, Brazil.

CBC, Hong Kong. See *Zenfields, Hong Kong.*
CBI, Switz. CBI Medical Products Vertriebs GmbH, Picardiestrasse 3, 5040 Schönftland, Switzerland.
url: www.cbimedical.ch
CCA, Canad. See *CCA, USA.*
CCA, USA. CCA Industries Inc., East Rutherford, NJ 07073, USA.
url: www.ccaindustries.com
CCD, Fr. Laboratoires CCD, 60 rue Pierre-Charron, 75008 Paris, France.
url: www.ccd-lab.com
CCM, Hong Kong. See *Zuellig, Hong Kong.*
CCM, Indon. CCM Indonesia PT, Plaza DM 8th Floor, Suite 805, Jl Jend Sudirman Kav 25, Jakarta 12920, Indonesia.
url: www.ccmchemicals.com
CCM, Malaysia. CCM Duopharma Bio Tech Behad, Lot 2599, Jln Seruling 59, Kawasan 3, Taman Klang Jaya, 41200 Klang, Selangor, Malaysia.
CCM, Singapore. CCM Pharmaceuticals (S) Pte Ltd, 25 International Business Park, 02-68 Ferman Ctr, S 609916, Singapore.
url: www.ccmpharmaceuticals.com
CCM, Thai. See *Cosma, Thai.*
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CCPC, Hong Kong. See *Kai Yuen, Hong Kong.*
CCPC, Philipp. See *Britton, Philipp.*
CCS, Norw. See *CCS, Swed.*
CCS, Swed. CCS Clean Chemical Sweden AB, Tunavägen 277 B, 781 73 Borlänge, Sweden.
url: www.ccs-se.com
CD Investments, Ital. CD Investments, Italy.
CD Medical, UK. CD Medical Ltd, Wigan Rd, Westhoughton, Bolton, BL5 2AL, UK.
CDBIO, Thai. See *Biovalys, Thai.*
CDL, UK. CDL London Ltd, Unit 1, Fitzroy Business Park, Sandy Lane, Sidcup, Kent, DA14 5NL, UK.
C-Dragon, China. C-Dragon Pharmaceutical Co. Ltd, 351 Guangling Quad, Shanghai 200083, China.
url: www.c-dragon.com.cn
Ceamed, Port. CeaMed Serviço e Consultadoria Farmacêutica Lda, Av. Arriaga, Edifício Marina Club, 5 Andar Apartamento 506, 9000-533 Funchal, Portugal.
Ceapharma, Port. Ceapharma Consultadoria Farmacêutica Lda, Largo do Avião Lusitânia 1, 2780-203 Oeiras, Portugal.
Cebert, USA. Cebert Pharmaceuticals Inc., 1200 Corporate Drive, Suite 370, Birmingham, Alabama 35242, USA.
url: www.cebert.com
Ceccarelli, Ital. Ceccarelli Farmaceutici S.r.l., Via G. Caponsacchi 31, 50126 Florence, Italy.
Cedar Health, UK. Cedar Health Ltd, Pepper Rd, Bramhall Moor Lane, Hazel Grove, Stockport, Cheshire, SK7 5BW, UK.
url: www.cedarhealth.co.uk
Cederberg, Switz. Cederberg GmbH, Neuhofweg 4, 4102 Basel/Binningen, Switzerland.
url: www.cederberg.ch
Cederroth, Denm. Cederroth A/S, Vassingerødvej 7, 3540 Lynge, Denmark.
Cederroth, Hung. See *Cederroth, Swed.*
Cederroth, Norw. Cederroth A/S, Postboks 23, 3164 Revetal, Norway.
url: www.cederroth.com
Cederroth, Spain. Cederroth, C/Jose Bardasano Baos 9, Edificio Gorbea 3, 28016 Madrid, Spain.
url: www.cederroth.com
Cederroth, Swed. Cederroth AB, Kanalvägen 10A, 194 27 Upplands Väsby, Sweden.
url: www.cederroth.com
Cederroth, UK. See *Cederroth, Swed.*
Cedoan, Thai. See *Pacific, Thai.*
Cefak, Austria. See *Cefak, Ger.*
Cefak, Cz. See *Cefak, Ger.*
Cefak, Ger. Cefak KG, Ostbahnhofstr. 15, 87437 Kempten, Germany.
url: www.cefak.com
Cefak, Hung. See *Vicis, Hung.*
Cefak, Malaysia. See *Summit, Malaysia.*
Cefak, Swed. See *Cefak, Ger.*
Cefak, Ukr. See *Megakom, Ukr.*
Celgene, Austral. Celgene Pty Ltd, Level 7, 607 St Kilda Rd, Melbourne, Vic 3004, Australia.
Celgene, Austria. See *Celgene, UK.*
Celgene, Belg. Celgene BVBA, Parc de l'Alliance, Blvd de France 9, 1420 Braine-l'Alleud, Belgium.
url: www.celgene.eu
Celgene, Canad. Celgene, 301 231 Oak Park Blvd, Oakville, Ontario, L6H 7S8, Canada.
Celgene, Cz. See *Celgene, UK.*
Celgene, Denm. Celgene ApS, Kristianiagade 8, 3, 2100 Copenhagen Ø, Denmark.
url: www.celgene.com
Celgene, Fr. Celgene, 6/8 Blvd Haussmann, 75009 Paris, France.
url: www.celgene.com
Celgene, Ger. Celgene GmbH, Joseph-Wild-Str. 20, 81829 München, Germany.
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Celgene, Gr. See *Celgene, UK.*
Celgene, Hong Kong. Celgene Ltd, 45/F The Lee Gardens, 33 Hysan Ave, Causeway Bay, Hong Kong.
url: www.celgene.com
Celgene, Hung. See *Celgene, Switz.*
Celgene, Irl. See *Celgene, UK.*
Celgene, Ital. Celgene srl, Corso Garibaldi 86, 20121 Milan, Italy.
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Celgene, Malaysia. See *Zuellig, Malaysia.*
Celgene, Neth. See *Celgene, UK.*

Celgene, Norw. Celgene AS, Nydalsv. 33, Postboks 4814 Nydalen, 0484 Oslo, Norway.
url: www.celgene.com
Celgene, NZ. Celgene Pty Ltd, Quigg Partners, Level 7, 28 Brandon St, Wellington, New Zealand.
Celgene, Philipp. See *Invida, Philipp* and *Zuellig, Philipp.*
Celgene, Pol. Celgene Sp z o o, ul. Królowej Marysienki 4A, 02-954 Warsaw, Poland.
url: www.celgene.com
Celgene, Port. Celgene Portugal, Lagoas Park, Edificio 11-1, 2740-270 Porto Salvo, Portugal.
url: www.celgene.eu
Celgene, Rus. Celgene, Krasnopresnenskaya nab 18, Blok C 4, 123317 Moscow, Russia.
Celgene, Singapore. See *Zuellig, Singapore.*
Celgene, Spain. See *Celgene, UK.*
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url: www.celgene.com
Celgene, Switz. Celgene GmbH, Bändliweg 20, 8048 Zürich, Switzerland.
url: www.celgene.com
Celgene, Thai. See *Invida, Thai.*
Celgene, UK. Celgene Ltd, Morgan House, Madeira Walk, Windsor, Berkshire, SL4 1EP, UK.
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Celgene, USA. Celgene Corp., 7 Powder Horn Drive, Warren, NJ 07059, USA.
url: www.celgene.com
Celina, Arg. Lab. Celina, Charrua 3124, 1437 Buenos Aires, Argentina.
Cell Pathways, USA. See *OSI, USA.*
Cell Pharm, Denm. See *Pharmacodane, Denm.*
Cell Pharm, Fin. See *Cell Pharm, Ger.*
Cell Pharm, Ger. cell pharm GmbH, Theodor-Heuss-Str. 52, 61118 Bad Vilbel, Germany.
url: www.cellpharm.com
Cell Pharm, Irl. See *Cell Pharm, Ger.*
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Cell Therapeutics, Austria. See *Cell Therapeutics, UK.*
Cell Therapeutics, Neth. See *Cell Therapeutics, UK.*
Cell Therapeutics, Spain. See *Cell Therapeutics, UK.*
Cell Therapeutics, UK. Cell Therapeutics (UK) Ltd, 100 Pall Mall, London, SW1Y 5HP, UK.
url: www.celltherapeutics.com
Cellegy, Singapore. See *Steward Cross, Singapore.*
CellEra, USA. CellEra LLC, 1045 Reed Rd, Unit C, Monroe (Cincinnati), OH 45050, USA.
url: celleralle.com
Cellex-C, Canad. Cellex-C International Inc., 9 New St, Toronto, Ontario, M5R 1P7, Canada.
Celltech, Austria. See *UCB, UK.*
Celltech, Belg. See *UCB, Belg.*
Celltech, Denm. See *UCB, Denm.*
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Celltech, Fr. Laboratoires Celltech Pharma, 6 pl Boulnois, 75017 Paris, France.
url: www.celltechgroup.com
Celltech, Ger. See *UCB, Ger.*
Celltech, Hong Kong. See *International Medical, Hong Kong.*
Celltech, Irl. See *United Drug, Irl.*
Celltech, Israel. See *Margalit, Israel.*
Celltech, Neth. See *UCB, UK.*
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Celltech, Singapore. See *Ziwell, Singapore.*
Celltech, Spain. Celltech Pharma, Montalban 5, 2 Izda, 28014 Madrid, Spain.
url: www.celltechgroup.com
Celltech, Swed. See *UCB, Denm.*
Celltech, Switz. See *Lifebiotech, Switz.*
Celltech, UK. See *UCB, UK.*
Celltech, USA. Celltech Pharmaceuticals Co., 755 Jefferson Rd, Rochester, NY 14623, USA.
url: www.celltechgroup.com
CellTran, UK. CellTran Ltd, The Innovation Centre, 217 Portobello, Sheffield, S1 4DP, UK.
url: www.celltran.co.uk
Celon, India. Celon Laboratories Ltd, Plot No. 16 Achutha Co-op-Housing Society, Road No. 10, Banjara Hills, Hyderabad 500 034, India.
url: www.celonlabs.com
Celon, Pol. Celon Pharma Sp. zo.o., ul. Ogrodowa 2 a, 05-092 Łomianki Kiełpin, Poland.
url: www.celonpharma.com
Celso, Arg. Celso, Av. Pueyrredón 1109, C.A.B.A., Argentina.
Celsus, Philipp. Celsus Pharmaceuticals Phils, Inc., 115 Scout Rallos St, Cor 11th Jamboree St, Quezon City, Philippines.
Celudrop, Arg. See *Lagos, Arg.*
Cem, Turk. Cem Farma İlaç Ltd. Şti., Sağlık 1 Sok. No: 36/7, Yenişehir, Ankara, Turkey.
url: www.cemfarma.com.tr
Cenexi, Cz. See *Cenexi, Fr.*
Cenexi, Fr. Cenexi, 52 rue Marcel et Jacques Gaucher, 94120 Fontenay sous bois, France.
url: www.cenexi.fr
Ceninter, Spain. Ceninter, Juan Ignacio Luca de Tena 8, 28027 Madrid, Spain.
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Centaur, India. Centaur Pharmoceuticals Pvt Ltd, Opposite Grand Hyatt, Vakala, Santacruz East, Mumboi 400 155, India.
url: www.centaurpharma.com
Centeon, Austria. See *CSL, Ger.*
Centeon, Braz. See *Aventis, Braz.*

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Centeon, Denm. See *Aventis Behring, Swed.*
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Centeon, Hong Kong. See *Primal, Hong Kong.*
Centeon, Irl. See *ZLB, UK.*
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Centeon, Ital. See *Sanofi-Aventis, Ital.*
Centeon, Mex. See *Aventis Behring, Mex.*
Centeon, Norw. See *Aventis, Norw* and *Aventis Behring, Swed.*
Centeon, Pol. Centeon Pharma GmbH Oddział w Warszawie, al. Jerozolimskie 183, 02-486 Warsaw, Poland.
Centeon, Spain. See *ZLB, Spain.*
Centeon, Swed. See *Aventis Behring, Swed.*
Centeon, Switz. See *Aventis Behring, Switz.*
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Centeon, USA. See *CSL, USA.*
Center, Israel. See *Rekah, Israel.*
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Centocor, Neth. Centocor Europe BV, Einsteinweg 101, 2333 CB Leiden, Netherlands.
url: www.centocor.com
Centocor, Norw. See *Lilly, Norw.*
Centocor, Pol. See *Lilly, Pol.*
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Centocor, USA. Centocor, Inc., 200 Great Valley Parkway, Malvern, PA 19355, USA.
url: www.centocor.com
Centrafarm, Neth. Centrafarm BV, Nieuwe Donk 9, 4879 AC Etten-Leur, Netherlands.
Central, China. Central Pharmaceutical Co. Ltd, 1 Fujin Rd, Beichen District, Tianjin 300400, China.
url: www.centralpharma.com
Central, Irl. See *Moyne, Irl.*
Central, Thai. Central Poly Trading Co. Ltd, 100/261 Moo 3, Saima Muang, Nonthaburi 11000, Thailand.
Central Clinical, Pol. See *SecFarm, Pol.*
Central European Pharmaceutical, Rus. Central European Pharmaceutical Company JSC, Russia.
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Centrix, USA. Centrix Pharmaceutical Inc., 31 Inverness Center Parkway, Suite 270, Birmingham, AL 35242, USA.
url: www.cenrx.com
Centroframa, Ital. Centrifarma Srl, Via del Corno 12, 40069 Zola Predosa (BO), Italy.
Centroframa, Port. Centroframa Indústria e Comércio de Produtos Farmacêuticos Unipessoal Lda, R. da Quinta do Pinheiro 5, 2794-003 Carnaxide, Portugal.
Centrum, Spain. See *ASAC, Spain.*
Centurion, Turk. Centurion Pharma İlaç Tic. Ltd. Şti., Hoşsohbet Sok. Seyyare İş, Merkezi No: 2/1, Balmumcu, İstanbul, Turkey.
url: www.centurion.com.tr
Centurion, USA. Centurion Labs LLC, 4700 Caldwell Mill Rd, Birmingham, AL 35234, USA.
url: www.centurionlabs.com
Century, Canad. See *Century, USA.*
Century, USA. Century Pharmaceuticals Inc., 10377 Hague Rd, Indianapolis, IN 46256-3399, USA.
url: www.centurypharmaceuticals.com
CEP, China. CEP Pharmaceutical Co. Ltd., 1299 Changchun Economic and Technological Development Zone, Changchun, Jilin, 130033, China.
url: www.ccepcd.com
Cephalon, Austria. See *Cephalon, Ger* and *Cephalon, UK.*
Cephalon, Belg. See *Cephalon, Fr.*
Cephalon, Cz. See *Cephalon, Fr.*
Cephalon, Denm. Cephalon Pharma ApS, Sluseholmen 2-4, 2450 Copenhagen SV, Denmark.
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Cephalon, Fin. See *Cephalon, UK.*
Cephalon, Fr. Cephalon France, 20 rue Charles-Martigny, 94700 Maisons-Alfort, France.
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Cephalon, Ger. Cephalon GmbH, Fraunhoferstr. 9a, 82152 Martinsried, Germany.
url: www.cephalon.de
Cephalon, Gr. See *Cephalon, Fr.*
Cephalon, Hong Kong. Cephalon Inc., 45/F The Lee Gardens, 33 Hysan Ave, Causeway Bay, Hong Kong.
Cephalon, Hung. See *Cephalon, Fr.*
Cephalon, Irl. Cephalon Pharma Ireland Ltd, Unit 43, Block F2, Northwood Court, Northwood Business Campus, Santry, Dublin 9, Ireland.
url: www.cephalon-europe.com
Cephalon, Israel. See *Medison, Israel.*

Cephalon, Ital. Cephalon Sr.l., Piazza Marconi 25, 00144 Roma (RM), Italy.
url: www.cephalon.com

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Cephalon, Norw. See *Swedish Orphan, Norw.*

Cephalon, Pol. Cephalon Sp z o.o., ul. Nowogrodzka 68, 02-014 Warsaw, Poland.
url: www.cephalon.com

Cephalon, Port. See *Cephalon, Fr.*

Cephalon, Spain. Cephalon Pharma SLU, Avda Alcalide Barnils 70, 08174 Sant Cugat del Valles, Barcelona, Spain.
url: www.cephalon.com

Cephalon, Swed. See *Cephalon, Denm.*

Cephalon, Switz. See *Globopharm, Switz.*

Cephalon, UK. Cephalon UK Ltd, Abel Smith House, Gunnels Wood Rd, Stevenage, Hertfordshire, SG1 2BT, UK.
url: www.cephalon.com

Cephalon, USA. Cephalon Inc., 41 Moores Rd, Frazer, PA 19355, USA.
url: www.cephalon.com

Ceptaris, USA. Ceptaris Therapeutics Inc., Malvern, PA 19355, USA.

Cera, USA. Cera Products Inc., Suite 220, 55 Mathews Drive, Hilton Head Island, SC 29926, USA.
url: www.ceraproductsinc.com

Cerebos, Hong Kong. See *IDS, Hong Kong.*

Cerenex, USA. See *GSK, USA.*

Cerexa, USA. Cerexa Inc., 2100 Franklin St, Suite 900, Oakland, CA 94612, USA.
url: www.cerexa.com

Cernelle, Swed. AB Cernelle, Höganäsvägen 365, 262 94 Ängelholm, Sweden.
url: www.cernelle.se

Cesra, Cz. See *Cesra, Ger.*

Cesra, Ger. Cesra Arzneimittel GmbH & Co. KG, Braunmattstr. 20, 76532 Baden-Baden, Germany.
url: www.cesra.de

Cesra, Pol. See *Solpharm, Pol.*

Cesra, Ukr. See *Alpen, Ukr.*

Cetem, Fr. Laboratoires Cetem, 18 rue E. & H.-Rousselle, 75013 Paris, France.

Cetin, Turk. Cetin, Turkey.

Cetus, Arg. Lab. Cetus S.R.L, Querandmes 4275, 1183 Buenos Aires, Argentina.

Cetylite, Canad. See *Cetylite, USA.*

Cetylite, USA. Cetylite Industries Inc., 9051 River Rd, Pennsauken, NJ 08110, USA.
url: www.cetylite.com

Ceuta, Irl. See *Ceuta, UK.*

Ceuta, UK. Ceuta Healthcare Ltd, Hill House, 41 Richmond Hill, Bournemouth, Dorset, BH2 6HS, UK.
url: www.ceuta-healthcare.co.uk

Ceutical, Hong Kong. Ceutical Trading Co. Ltd, Rm 24, 12/F, Goldfield Industrial Ctr, 1 Sui Wo Rd, Fo Tan, Shatin, N.T., Hong Kong.

Cevallos, Arg. Lab. Cevallos Salud S.R.L., Zapiola 2836/40, 1428 Buenos Aires, Argentina.

Cevidra, Fr. Laboratoire Cevidra, Le Castillan, 1 rue de la Belette, 91410 Dourdan, France.
url: www.cevidra.com

CFL, India. See *Cosme, India.*

CGD, Fr. CGD (Cie Générale de Diététique), 97 rue du Général-Moulin, 14050 Caen cdx, France.

CGF, Canad. CGF Pharmatec, 3516 Griffith, Montreal, Quebec, H4T 1A7, Canada.

Chaix et du Marais, Fr. Ste des Laboratoires Chaix et du Marais, 7 rue Labie, 75017 Paris, France.
url: www.lavoisier.com

Chalermchai, Thai. Chalermchai, Thailand.

Chance, Pol. Chance Spółka Jawna Zakład Produkcji Farmaceutycznej, Pieńków 11, 05-152 Czosnów, Poland.
url: www.chance.pl

Chandra Bhagat, India. Chandra Bhagat Pharma Pvt Ltd, 323-F Bhagat Bhuvan, Dr. B. Ambedkar Road, Matunga (E), Mumbai 400 019, India.
url: www.cbcpharma.com

Chanel, Canad. Chanel Inc., 55 Blvd Marie-Victorin, Candiac, Quebec, J5R 1B6, Canada.

Chanelle, Cz. See *Chanelle, Irl.*

Chanelle, Fin. See *Chanelle, Irl.*

Chanelle, Irl. Chanelle Medical Ltd, Loghrea, Co. Galway, Ireland.

Chanelle, Neth. See *Chanelle, Irl.*

Chang An, China. Hainan Chang'An International Pharmaceutical Co. Ltd, National Hi-Tech Industrial Development Zone A-6, Xiuying District, Haikou, Hainan, 570314, China.
url: www.caip.cn

Chang Fu Jie Jing, China. Chang Fu Jie Jing Pharmaceutical Co. Ltd, Shandong, China.

Changchun, China. Changchun Institute of Biological Products (CCIBP), 137 Xi'an Rd, Ivyuan, Changchun, Jilin, 130062, China.
url: www.ccibp.com

Changjiang, China. Jiangsu Changjiang Pharmaceutical Co. Ltd, 28 Hongqi Road, Sheyang, Yancheng, Jiangsu, 224300, China.
url: www.zgcjyy.com

Changlian Laifu, China. Changlian Laifu Pharmaceutical Co. Ltd, Wuhan Medicine Industry Park, Miaoshan, Jiangxia, Wuhan, Hubei, China.
url: www.whbalance.com

Changlong, China. Huinan Changlong Bio-Pharmaceutical Co. Ltd, Huinan, Jilin, China.
url: www.jlchanglong.com

ChangSheng Gene, China. Changchun Changsheng Gene Pharmaceutical Co., Ltd., No. 666 Huoju Road, High & New Zone, Changchun, Jilin, China.

Changxing, China. Changxing Pharmaceutical Co. Ltd, China.

Changyi, China. Changyi Pharmaceutical Co. Ltd, Northern Industrial District, Enping, Jiangmen, Guangdong, 529400, China.

Changyuan, China. Changyuan Pharmaceutical Co. Ltd., 1009 Zhanjiang Road, Changyuan Economic and Technological Development Zone, Changchun, Jilin, 592200, China.

Changzheng, China. Changzheng Pharmaceutical Co Ltd, Leshan, China.

Changzheng-Xinkai, China. Changzheng-Xinkai Pharmaceutical Co Ltd, 2 Soochow South Rd, Suzhou City 215167, Jiangsu, China.
url: www.fuxing.com.cn

Changzhou, China. Changzhou Pharmaceutical Factory, 518 Laodong East Rd, Changzhou, Jiangsu, 213018, China.
url: www.czzyc.com

Changzhou Siyao, China. Changzhou Siyao Pharmaceutical Co. Ltd, Meron Dam, Changzhou 213004, Jiangsu, China.
url: www.czsiyao-pharm.com

Chaoyang Lingqiao, China. Chaoyang Lingqiao Pharmaceutical Co. Ltd, China.

Charak, India. Charak Pharma Pvt Ltd, Evergreen Industrial Estate 2nd Floor, Shakti Mills Lane, Dr.E. Moses Road, Mumbai 400 011, India.
url: www.charak.com

Charlieu, Fr. See *Nigy, Fr.*

Charoen, Thai. S Charoen Bhaesaj Trading Co. Ltd, 713-715-717 Mahachai Rd, Bangkok 10200, Thailand.

Charoen Bhaesaj, Malaysia. See *Propharm, Malaysia.*

Charoon Bhesaj, Thai. Charoon Bhesaj Ltd, 776/2-4 Ratchadapisek Rd, Daokanong, Thonburi, Bangkok 10600, Thailand.
url: www.crb.co.th

Charton, Canad. See *Ratiopharm, Canad.*

Chartwell, Canad. Chartwell Industries (Canada) Ltd, 106 3060 Norland Ave, Burnaby, British Columnbia, V5B 3A6, Canada.

Charwell, Israel. See *Pfizer, Israel.*

Charwell, Singapore. See *JDH, Singapore.*

Charwell Pharmaceuticals, UK. See *Pfizer, UK.*

Chase, USA. See *Banner, USA.*

Chase Sun, China. Chase Sun Pharmaceutical Co. Ltd, Tianjin, China.

Chatfield Laboratories, UK. Chatfield Laboratories, Kramer Mews, London, SW5 9JL, UK.

Chattem, Canad. Chattem (Canada) Inc., 2220 Argentia Rd, Mississauga, Ontario, L5N 2K7, Canada.

Chattem, Denm. See *Vitaflo, Denm.*

Chattem, Ger. See *Chattem, UK.*

Chattem, Hong Kong. See *Mentholatum, Hong Kong.*

Chattem, Irl. Chattem Global Consumer Products Ltd, The Mary Rosse Centre, Holland Rd, National Technology Park, Limerick, Ireland.

Chattem, Neth. See *Chattem, UK.*

Chattem, Pol. See *Nepentes, Pol.*

Chattem, Singapore. See *Green Cross, Singapore.*

Chattem, Thai. See *Rohto-Mentholatum, Thai.*

Chattem, UK. Chattem UK Ltd, Guerry House, Ringway Centre, Edison Rd, Basingstoke, Hampshire, RG21 2YH, UK.

Chattem, USA. Chattem Consumer Products, 1715 West 38th St, Chattanooga, TN 37409, USA.
url: www.chattem.com

Chauvin, Austria. See *Chauvin, UK.*

Chauvin, Belg. See *Bausch & Lomb, Belg.*

Chauvin, Canad. See *Chauvin, UK.*

Chauvin, Cz. See *Chauvin Ankerpharm, Cz.*

Chauvin, Fr. Laboratoires Chauvin Bausch & Lomb, 416 rue Samuel-Morse, B.P. 1174, 34009 Montpellier cdx 1, France.
url: www.bausch.com

Chauvin, Hong Kong. See *Rich Plan, Hong Kong.*

Chauvin, Hung. See *Chauvin Ankerpharm, Hung.*

Chauvin, Irl. See *Fulcrum, Irl.*

Chauvin, Israel. See *Rekah, Israel.*

Chauvin, Malaysia. See *Apex, Malaysia.*

Chauvin, Neth. See *Bausch & Lomb, Belg.*

Chauvin, Norw. See *Novartis, Norw.*

Chauvin, Pol. See *Bausch & Lomb, Pol.*

Chauvin, Rus. See *Bausch & Lomb, Rus.*

Chauvin, Singapore. See *Pan-Malayan, Singapore.*

Chauvin, Spain. See *Chauvin, Fr.*

Chauvin, Thai. See *Neopharm, Thai.*

Chauvin, UK. Chauvin Pharmaceuticals Ltd, 106 London Rd, Kingston-Upon-Thames, Surrey, KT2 6TN, UK.

Chauvin Ankerpharm, Cz. Chauvin Ankerpharm GmbH, Radlická 61, 150 00 Prague 5, Czech Republic.

Chauvin ankerpharm, Ger. Chauvin ankerpharm GmbH, Brunsbütteler Damm 165-173, 13581 Berlin, Germany.

Chauvin Ankerpharm, Hung. Chauvin ankerpharm Képviselet, Ferenc krt 27, 1094 Budapest, Hungary.

Chauvin Ankerpharm, Pol. See *Bausch & Lomb, Pol.*

Chauvin Ankerpharm, Ukr. Chauvin Ankerpharm, GmbH, Ukraine

Chauvin Novopharma, Switz. See *Bausch & Lomb, Switz.*

Cheer Sails, China. Cheer Sails Medical, Room L 4/F Suotaike Building, 5 Bagua 4th Rd, Futian, Shenzhen 518029, China.
url: www.csmhk.com

Chefaro, Belg. See *Bausch & Lomb, Belg.*

Chefaro, Cz. See *Chefaro, Neth.*

Chefaro, Fin. See *Tamro, Fin.*

Chefaro, Fr. See *Roche Nicholas, Fr.*

Chefaro, Ger. Deutsche Chefaro Pharma GmbH, Im Wirrigen 25, 45731 Waltrop, Germany.
url: www.deutsche-chefaro.de

Chefaro, Irl. Chefaro Ireland Ltd, Farnham Drive, Finglas, Dublin 11, Ireland.

Chefaro, Israel. See *Neopharm, Israel.*

Chefaro, Ital. Chefaro Pharma Italia S.r.l., Viale Castello della Magliana 18, 00148 Rome (RM), Italy.
url: www.chefaro.it

Chefaro, Neth. Chefaro Nederland BV, Keileweg 8, 3029 BS Rotterdam, Netherlands.
url: www.chefaro.com

Chefaro, Port. Chefaro Portuguesa Distribuição de Produtos Farmacêuticos Unipessoal Lda, Av. Tomaz Ribeiro 43, Edificio Neopark, Bloco 1-4 A, 2795-574 Carnaxide, Portugal.

Chefaro, Spain. Chefaro Española, Pza Xavier Cugat 2, San Cugat Del Valles, 08174 Barcelona, Spain.

Chefaro, UK. Chefaro UK Ltd, 1 Tower Close, St Peters Industrial Park, Huntingdon, Cambridgeshire, PE29 7DH, UK.
url: www.chefaro.com

Cheil, Singapore. See *Zyfas, Singapore.*

Cheil Jedang, Philipp. See *Pharmawealth, Philipp.*

Chelsea, USA. See *Watson, USA.*

Chema-Elektromet, Pol. Chema-Elektromet Spółdzielnia Pracy, ul. Przemysłowa 9, 35-105 Rzeszów, Poland.
url: www.chema.rzeszow.pl

Chemech, India. Chemech Laboratories Ltd, Chemech House, No. 5 10th Sector, 65th Street, K.K. Nagar (W), Chennai 600 078, India.
url: www.chemechlab.com

Chemedica, Austria. TRB Chemedica (Austria) AG, Porzellangasse 56/11/4, A-1091 Vienna, Austria.

Chemedica, Fr. Chemedica, B.P. 51, 74500 St-Gingolph, France.

Chemedica, Ger. TRB Chemedica AG, Richard-Reitzner-Allee 1, 85540 Haar/Munich, Germany.
url: www.trbchemedica.de

Chemedica, Hong Kong. TRB Chemedica Hong Kong Ltd, Rm 2104, 21/F CC Wu Building, 302-8 Hennessy Rd, Wanchai, Hong Kong.
url: www.trbchemedica.com

Chemedica, Malaysia. TRB Chemedica Malaysia Sdn Bhd, Lot 3A-01 & 02 Level 3A Cheras Plaza, 11 Jln Manis 1, Taman Segar Cheras, 56100 Kuala Lumpur, Wilayah Persekutuan
url: www.trbchemedica.com

Chemedica, Rus. See *Chemedica, Switz.*

Chemedica, Singapore. See *Pharmaforte, Singapore.*

Chemedica, Switz. TRB Chemedica SA, Chemin St Marc 3, Case Postale 240, 1896 Vouvry, Switzerland.
url: www.trbchemedica.com

Chemedica, Thai. TRB Chemedica (Thailand) Ltd, No 66, Q House Asoke Bldg, 14 Fl, Sukhumvit 21 Rd, North Klongtoey Subdistrict, Wattana District, Bangkok 10110, Thailand.

Chemedica, UK. TRB Chemedica UK Ltd, 14 Brindley Court, Lymedale Business Park, Newcastle-under-Lyme, Staffordshire, ST5B 9QA, UK.

Chemi, Ital. Chemi SpA, Via dei Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy.
url: www.chemi.com

Chemi, Pol. See *Chemi, Ital.*

Chemia, Mex. See *Probiomed, Mex.*

Chemica, Gr. Chemica AE, 21 Km Athens-Layriou, 19400 Koropi, Greece.

Chemical, Fr. Chemical Farma, 131 av du Général-de-Gaulle, 92200 Neuilly-sur-Seine, France.

Chemical Research, Pol. Chemical Research, ul. Grunwaldzka 102, 80-244 Gdańsk, Poland.

Chemical Specialties, Canad. Chemical Specialties Manufacturing Corp., 200 Confederation Parkway, Concord, Ontario, L4K 4T8, Canada.

Chemical Works Argon, Hung. See *Polcommerce, Hung.*

Chemidex, Irl. See *Allphar, Irl.*

Chemidex, UK. Chemidex Pharma Ltd, Chemidex House, Egham Business Village, Crabtree Rd, Egham, Surrey, TW20 8RB, UK.
url: www.chemidex.co.uk

Chemifarma, Spain. Chemifarma SA, Sierra de Guadarrama 11, Polígono Industrial II, San Fernando de Henares, Madrid 28850, Spain.

Chemigroup, Fr. Chemigroup, 57 bd de la République, 78406 Chatou, France.

Chemil, Ital. See *Vedim, Ital.*

Chemineau, Fr. Laboratoires Chemineau, 93 rte de Monnaie, 37210 Vouvray, France.
url: www.chemineau.com

Chemineau, Ital. See *Chemineau, Fr.*

Cheminova, China. See *Extrawell, China.*

Chemipal, Israel. Chemipal, P.O. Box 8111, Netanya 42293, Israel.
url: www.chemipal.co.il

Chemiphar, China. See *Chemiphar, Jpn.*

Chemiphar, Jpn. Nippon Chemiphar Co. Ltd, 2-2-3 Iwamoto-cho, Chiyoda-ku, Tokyo 101-8678, Japan.

Chemiphar, Thai. See *Ouiheng, Thai.*

Chemipharm, Gr. Chemipharm SG Ntetsaves & Co EE, Kapodistriou 42, 104 32 Athens, Greece.

Chemipharm, Israel. Chemipharm Ltd, Brodetzky 43, Tel Aviv 61170, Israel.

Chemipharma, Gr. Iasis Chemipharma A.E., Agiou Konstantinou 40, 151 242 Maroussi, Greece.

Chemists Own, Austral. Chemists Own Pty Ltd, P.O. Box 105, Ingleburn, NSW 1890, Australia.
url: www.chemistsown.com.au

Chemo, Cz. See *Chemo, Spain.*

Chemo, Neth. See *Chemo, Spain.*

Chemo, Spain. Chemo Iberica SA, Gran Via Carlos III 98, 7a, 08028 Barcelona, Spain.
url: www.chemogroup.com

Chemo-Drugs, India. Chemo-Drugs, A-54 GT Karnal Rd, Industrial Complex, 110 033, India.

Chemomedica, Austria. Chemomedica Medizintechnik und Arzneimittel GmbH, Wipplingerstrasse 19, A-1013 Vienna, Austria.

Chemopharma, Chile. See *Sanitas, Chile.*

Chemopharma, Cz. Chemopharma as, Ústí nad Labem, Czech Republic.

Chemosan, Austria. See *Liebermann, Ger.*

Chemotrade, Cz. Chemotrade sro, Mala Štěpánská 15, 120 00 Prague 2, Czech Republic.

ChemVet, Denm. ChemVet dk A/S, AC Illumsvej 6, 8600 Silkeborg, Denmark.
url: www.chemvet.dk

Chen Pai, China. Chen Pai Pharm, China.

Chengdu Institute, China. Chengdu Institue of Biological Products, 379 Jinhua Road 3rd Section, Jinjiang, Chengdu, Sichuan, 610023, China.
url: www.cdibp.com

Chengdu Institute, Thai. See *Biogenetech, Thai.*

Chengshi, China. Chengshi Pharmaceutical Co. Ltd, Anhui, China.

Chengyi, China. Chengyi Pharmaceutical Co. Ltd, Zhejiang, China.

Chenji, China. Chenji Pharmaceutical Co. Ltd, Shaanxi, China.

Chenlong, China. Chenlong Pharmaceutical Co. Ltd., Longquan, China.

Chephasaar, Ger. See *MIP, Ger* and *Rosen, Ger.*

Chephasaar, Pol. See *MIP, Pol.*

Cheplapharm, Austria. See *Cheplapharm, Ger.*

Cheplapharm, Ger. Cheplapharm Arzneimittel GmbH, Bahnhofstr 1a, 17498 Mesekenhagen, Germany.
url: www.cheplapharm.de

Cheplapharm, Swed. See *Cheplapharm, Ger.*

Cherish, Canad. Cherish Nutrition Canada, 28 Woodward Ave, Thornhill, Ontario, Canada.
url: cherishnutrition.yolasite.com

Chesebrough-Pond's, USA. See *Unilever, USA.*

Chester, Canad. See *Ratiopharm, Canad.*

Chew, Thai. Chew Brothers & Co. Ltd Part, 1561/3 Petchburi Rd, New Extension, Makason, Bangkok 10310, Thailand.

Chi Sheng, China. Chi Sheng Chemical Corp., 3 Shijian Road, Hsinchu Industrial Park, Hukou, Hsinchu, Taiwan, 30352, China.
url: www.cscp.com.tw

Chi Sheng, Thai. See *Charoen, Thai.*

Chia Tai, China. Chia Tai Tianqing Pharmaceutical Co Ltd, 8 North Julong Rd, Xinpu Lianyungang 222006, Jiangsu, China.
url: www.cttq.com

Chibret, Denm. See *MSD, Denm.*

Chibret, Ger. See *MSD, Ger.*

Chibret, Neth. See *MSD, Neth.*

Chibret, Port. See *MSD, Port*

Chibret, Spain. See *MSD, Spain.*

Chief Medical Supplies, Canad. Chief Medical Supplies Ltd, 411-19 St SE, Calgary, Alberta, T2E 6J7, Canada.

Chiesi, Belg. See *Chiesi, Ital.*

Chiesi, Braz. Chiesi Farmaceutica Ltda, Rua Alexandre Dumas 1658, 14717004 Sao Paulo, Brazil.

Chiesi, China. Chiesi Pharmaceutical Co. China, 12F Careri Building, 432 West Huai Rd, Shanghai, China.
url: www.chiesigroup.com

Chiesi, Cz. See *Medicom, Cz.*

Chiesi, Denm. See *Teva, Denm.*

Chiesi, Fr. Chiesi SA, Imm. le Doublon, bat B, 11 av. Dubonnet, 92400 Courbevoie, France.
url: www.chiesigroup.com

Chiesi, Ger. Chiesi GmbH, Gasstr. 6, 22761 Hamburg, Germany.

Chiesi, Gr. Chiesi Hellas S.A., 1 Pentelis Ave, 152 35 Vrilissia, Greece.
url: www.chiesigroup.com

Chiesi, Hong Kong. See *CNW, Hong Kong.*

Chiesi, Hung. See *Torrex, Hung.*

Chiesi, Irl. See *Chiesi, UK.*

Chiesi, Israel. See *Chiesi, Ital.*

Chiesi, Ital. Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122 Parma (PR), Italy.
url: www.chiesigroup.com

Chiesi, Malaysia. See *Germax, Malaysia.*

Chiesi, Neth. See *Multipharma, Neth.*

Chiesi, Norw. See *Andre, Swed.*

Chiesi, Philipp. See *Metro, Philipp.*

Chiesi, Pol. See *Torrex Chiesi, Pol.*

Chiesi, Port. See *Chiesi, Ital.*

Chiesi, Rus. See *Pharmaregie, Rus.*

Chiesi, Singapore. See *JDH, Singapore.*

Chiesi, Spain. Chiesi España, Berlin 38-48, 7 planta, 08029 Barcelona, Spain.
url: www.chiesigroup.com

Chiesi, Swed. See *Chiesi, Ital.*

Chiesi, Thai. See *Pacific, Thai.*

Chiesi, Turk. Chiesi İlaç Ticaret AS, Beybi Giz Plaza Ayazaga Mh Meydan Sk N:28 K:27, Maslak, Istanbul, Turkey.

Chiesi, UK. Chiesi Ltd, Cheadle Royal Business Park, Highfield, Cheadle, SK8 3GY, UK.
url: www.chiesi.uk.com

Chilton, USA. Chilton Labs Inc., 299B Fairfield Ave, Fairfield, NJ 07004, USA.

Chimicor, Fr. See *Chimicor, Ital.*

Chimicor, Ital. Chimicor S.r.l., Via Veneto 54, 36061 Bassano Del Grappa (VI), Italy.
url: www.chimicor.it

Chimin, China. Chimin Pharmaceutical Co. Ltd, 888 Beiyuao Road, Huangyuan, Zhejiang, China.
url: www.chimin.cn

Chin Teng, China. Ching Teng Pharmaceutical Co. Ltd., 9 Gongjiu Road, Youshih Industrial Area, Dajia, Taichung, Taiwan, China.
url: www.chteng.com.tw

China Chem & Pharma, Malaysia. See *Antah, Malaysia.*

China Chem & Pharma, Philipp. See *Britton, Philipp* and *Endure, Philipp.*

China Chem & Pharma, Singapore. See *MD, Singapore.*

China Chem & Pharma, Thai. See *Charoen, Thai.*

Chinoin, China. See *Sanofi, China.*

Chinoin, Cz. See *Sanofi-Aventis, Cz.*

Chinoin, Hung. Chinoin Pharmaceutical and Chemical Works Ltd, P.O. Box 110, 1325 Budapest, Hungary.

Chinoin, Mex. Chinoin, Productos Farmaceuticos, S.A. de C.V., Lago Tanganica No. 18, Col. Granada, Deleg. Miguel Hidalgo, 11520 Mexico D.F., Mexico.

Chinoin, Pol. See *Sanofi-Aventis, Pol.*

Chinoin, Rus. See *Sanofi-Aventis, Rus.*

Chinoin, Ukr. See *Sanofi-Aventis, Ukr.*

Chinosolfabrik, Ger. See *Dermapharm, Ger.*

Chinta, Thai. See *Square, Thai.*

Chira, Philipp. Chira Pharmaceuticals Inc., 3/F RBC Corp. Ctr, Don Jesus Blvd, Alabang Hills, Muntinlupa City, Philippines.

Chiral, Philipp. Chiral Pharma Corp., 2291 Don Chino Roces Ext, Makati City, Philippines.

ChiRhoClin, USA. ChiRhoClin Inc., 4000 Blackburn Lane, Suite 270, Burtonsville, MD 20866, USA.
url: www.chirhoclin.com

Chiron, Austria. See *Chiron, Neth.*

Chiron, Belg. See *Chiron, Neth.*

Chiron, Canad. Chiron Canada Ltd, 3300 Côte-Vertu Bvld, Suite 403, St. Laurent, Quebec, H4R 2B7, Canada.
url: www.chiron.com

Chiron, Cz. See *Medicom, Cz.*

Chiron, Denm. See *Orphan, Denm.*

Chiron, Fr. Chiron France, 10 rue Chevreul, 92150 Suresnes, France.
url: www.chiron.com

Chiron, Ger. See *Novartis Behring, Ger.*

Chiron, Hong Kong. See *Honbase, Hong Kong.*

Chiron, Hung. See *Chiron Behring, Hung.*

Chiron, Irl. See *Allphar, Irl* and *United Drug, Irl.*

Chiron, Israel. See *Concept, Israel.*

Chiron, Ital. See *Novartis Vaccines, Ital.*

Chiron, Neth. Chiron BV, Paasheuvelweg 30, 1105 BJ Amsterdam Zuidoost, Netherlands.
url: www.chiron.com

Chiron, Norw. See *Swedish Orphan, Norw.*

Chiron, NZ. See *Baxter, NZ.*

Chiron, Pol. See *Medagro, Pol.*

Chiron, Singapore. See *Pacific Biosciences, Singapore* and *Sime Darby, Singapore.*

Chiron, Swed. See *Novartis Vaccines, Ital.*

Chiron, Thai. See *Biogenetech, Thai.*

Chiron, Turk. See *Novartis, Turk.*

Chiron, UK. See *Novartis, UK.*

Chiron, USA. Chiron Therapeutics, 4560 Horton St, Emeryville, CA 94608-2916, USA.
url: www.chiron.com

Chiron Behring, Austria. See *Novartis Behring, Ger.*

Chiron Behring, Fin. See *Novartis Behring, Ger.*

Chiron Behring, Ger. See *Novartis Behring, Ger.*

Chiron Behring, Hung. Chiron Behring GmbH & Co, Pf 732/21, 1388 Budapest 62, Hungary.

Chiron Behring, Israel. See *Medibrands, Israel.*

Chiron Behring, Malaysia. See *Novartis Behring, Ger.*

Chiron Behring, Norw. See *Novartis Behring, Ger.*

Chiron Behring, Pol. See *Imed, Pol.*

Chiron Panacea, India. See *Panacea, India.*

Chiron Vaccin, Fr. See *Chiron, Fr.*

Chiron Vaccines, Ger. See *Novartis Behring, Ger.*

Chiron Vaccines, Hong Kong. See *IDS, Hong Kong.*

Chiron Vaccines, Irl. See *Allphar, Irl.*

Chiron Vaccines, Ital. See *Novartis Vaccines, Ital.*

Chiron Vaccines, Neth. See *Novartis Vaccines, UK.*

Chiron Vaccines, Philipp. See *Marketlink, Philipp.*

Chiron Vaccines, Thai. See *Biogenetech, Thai.*

Chiron Vaccines, UK. See *Novartis Vaccines, UK.*

Chiron Vision, USA. See *Bausch & Lomb, USA.*

Chitin, Hong Kong. See *Trinity, Hong Kong.*

Choay, Fr. See *Sanofi-Aventis, Fr.*

Choay, Israel. See *Promedico, Israel.*

Choay, Port. See *Sanofi-Aventis, Port.*

Chobet, Arg. Soubeiran Chobet S.R.L., Ibera 5055, 1431 Buenos Aires, Argentina.

Choisy, Canad. Laboratoires Choisy Ltee, 390 Blvd St-Laurent Est, Louiseville, Quebec, J5V 2L7, Canada.

Chong Kun Dang, Singapore. See *Zyfas, Singapore.*

Chong Kun Dang, Thai. See *Charoen, Thai.*

Chong Lap, Hong Kong. Chong Lap (HK) Co. Ltd, Unit 715-6, Lippo Sun Plaza, 28 Canton Rd, Tsim Sha Tsui, Kowloon, Hong Kong.

Choongwae, China. See *Choongwae, Kor.*

Choongwae, Hong Kong. See *Vantone, Hong Kong.*

Choongwae, Kor. Choongwae Pharma Corp., Sindehbahng-1 Dong, Dongjahk-Gu, Seoul 156-010, Korea.
url: www.choongwae.com

Choongwae, Philipp. See *Endure, Philipp.*

Choongwae, Singapore. See *Kyowa, Singapore.*

Choongwae, Thai. See *Siam Pharm, Thai.*

Chosei, Jpn. Chosei Pharmaceutical Industries Ltd, 2-6-1-chome, Chuo-ku, Osaka, Utiawazi, Japan.

Choseido, Jpn. Choseido Pharmaceutical Co Ltd, Fuchuu 92, Tokushima-shi, Tokushima-ken, Shikoku, 779-3122, Japan.
url: www.choseido.com

CHR Hansen, Singapore. See *MD, Singapore.*

Chrisopoulos, Gr. Chrisopoulos Peter, Papadiamantopoulou 188, 145 68 Goudi, Greece.

Chrispa Alpha, Hong Kong. See *CNW, Hong Kong.*

Christiaens, Belg. See *Nycomed, Belg.*

Christo, Hong Kong. Christo Pharmaceuticals Ltd, Blk A-D, 14/F, Stage 2, Superluck Industrial Ctr, 57 Sha Tsui Rd, Tsuen Wan, N.T., Hong Kong.

Chronimed, USA. See *Bioscrip, USA.*

Chugai, China. Chugai Pharmaceutical Co. Ltd., 2101-2102 Beijing Development Building, 5 East Third Ring Road, Chaoyang, Beijing, 100004, China.

Chugai, Denm. See *Sanofi-Aventis, Denm.*

Chugai, Fr. Laboratoires Chugai Pharma France, Immeuble Lafayette, La Défense 5, 2 place des Vosges, Paris-LA Défense cdx, France.
url: www.chugai.fr

Chugai, Ger. Chugai Pharma Marketing Ltd, Lyoner Str. 15, 60528 Frankfurt/Main, Germany.
url: www.chugaipharma.de

Chugai, Hong Kong. See *Fandasy, Hong Kong* and *Tai Tong, Hong Kong.*

Chugai, Irl. See *Chugai, UK.*

Chugai, Jpn. Chugai Pharmaceutical Co. Ltd, 2-1-9 Kyobashi, Chuo-ku, Tokyo 104-8301, Japan.
url: www.chugai-pharm.co.jp

Chugai, Norw. See *Sanofi-Aventis, Norw.*

Chugai, Pol. See *Sanofi-Aventis, Pol.*

Chugai, Thai. See *Siam Pharm, Thai.*

Chugai, UK. Chugai Pharma UK, Mulliner House, Flanders Rd, Turnham Green, London, W4 1NN, UK.
url: www.chugai.co.uk

Chugai-Aventis, Norw. See *Sanofi-Aventis, Norw.*

Chun Cheong, Hong Kong. Firma Chun Cheong Lda, Rua dos Pescadores, 354-408 Edificio Industrial, Nam Fung Fase 2 11/F (E), Macau.

Chunggei, Philipp. See *International Apex, Philipp.*

Chung-Hwa, China. Chun-Hwa Chemical & Pharmaceutical Industrial Co. Ltd, 100 Golden Hill Rd, Suzhou 215011, China.

Church, Mex. Church & Dwight SRL de CV, Calz. de las Armas 110, 54080 Fracc. las Armas, Estado de Mexico, Mexico.

Church & Dwight, Austral. Church & Dwight Australia Pty Ltd, Unit 1, 108 Old Pittwater Rd, Brookvale, NSW 2100, Australia.

Church & Dwight, Canad. Church & Dwight Canada Corp., 635 Secretariat Court, Mississauga, Ontario, L5S 0A5

Church & Dwight, Hong Kong. See *US Summit, Hong Kong.*

Church & Dwight, Thai. See *US Summit, Thai.*

Church & Dwight, UK. Church & Dwight UK Ltd, Wear Bay Rd, Folkestone, Kent, CT19 6PG, UK.

Church & Dwight, USA. Church & Dwight Co Inc., 469 North Harrison St, Princeton, NJ 08543-5297, USA.
url: www.churchdwight.com

Chushin, China. Chushin Pharmaceutical Co. Ltd, China.

CHX, Canad. CHX Technologies Inc., 105 4800 Dundas Street West, Toronto, Ontario, M9A 1B1, Canada.

CHX, Irl. CHX Technologies Europe Ltd, Guiness Enterprise Centre, Taylor's Lane, Dublin 8, Ireland.

Ci & Di, Ital. Ci & Di S.r.l., Via Merlo 1, 20122 Milan, Italy.

Ciba, Canad. See *Novartis, Canad.*

Ciba, Ger. See *Novartis, Ger.*

Ciba, Gr. See *Novartis, Gr.*

Ciba, Ital. See *Novartis, Ital.*

Ciba, Neth. See *Novartis, Neth.*

Ciba, Norw. See *Novartis, Norw.*

Ciba, Port. See *Novartis, Port.*

Ciba, Switz. See *Novartis, Switz* and *Novartis Consumer, Switz.*

Ciba, UK. See *Novartis, UK.*

Ciba, USA. See *Novartis, USA.*

Ciba Consumer, UK. See *Novartis, UK.*

Ciba Consumer, USA. See *Novartis, USA.*

Ciba Vision, Arg. See *Novartis, Arg.*

Ciba Vision, Austral. Ciba Vision Australia P/L, Private Bag 100, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153, Australia.
url: www.cibavision.com.au

Ciba Vision, Austria. See *Novartis, Austria.*

Ciba Vision, Braz. See *Novartis, Braz.*

Ciba Vision, Canad. See *Novartis, Canad.*

Ciba Vision, Cz. See *Novartis, Cz.*

Ciba Vision, Denm. See *Novartis, Denm.*

Ciba Vision, Fin. See *Novartis, Fin.*

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Ciba Vision, Ger. See *Novartis, Ger.*

Ciba Vision, Hong Kong. See *Novartis, Hong Kong.*

Ciba Vision, Irl. See *United Drug, Irl.*

Ciba Vision, Israel. See *Promedico, Israel.*

Ciba Vision, Mex. See *Novartis, Mex.*

Ciba Vision, Norw. See *Novartis, Norw.*

Ciba Vision, NZ. See *Novartis, NZ.*

Ciba Vision, Port. See *Novartis, Port.*

Ciba Vision, Rus. See *Novartis Ophthalmics, Rus.*

Ciba Vision, Singapore. See *Novartis, Singapore.*

Ciba Vision, Spain. See *Novartis Consumer, Spain.*

Ciba Vision, Swed. See *Novartis, Swed.*

Ciba Vision, Switz. See *Novartis, Switz.*

Ciba Vision, Thai. See *Zuellig, Thai.*

Ciba Vision, Turk. See *Novartis, Turk.*

Ciba Vision, UK. See *Novartis, UK.*

Ciba Vision, USA. See *Novartis Ophthalmics, USA.*

Ciba-Geigy, Austral. See *Novartis, Austral.*

Ciba-Geigy, Austria. See *Novartis, Austria.*

Ciba-Geigy, Belg. See *Novartis, Belg.*

Ciba-Geigy, Fr. See *Novartis, Fr.*

Ciba-Geigy, Mex. See *Novartis, Mex.*

Ciba-Geigy, Port. See *Novartis, Port.*

Ciba-Geigy, S.Afr. See *Novartis, S.Afr.*

Ciba-Geigy, Spain. See *Novartis, Spain.*

Ciba-Geigy, Swed. See *Novartis, Swed.*

Ciba-Geigy, Switz. See *Novartis, Switz* and *Novartis Consumer, Switz.*

Ciba-Geigy, USA. See *Novartis, USA.*

Cibageneva, USA. See *Geneva, USA* and *Novartis, USA.*

CIC, Spain. See *Schering, Spain.*

Ciclum, Port. Ciclum Farma Unipessoal Lda, R Alfredo da Silva 16, 2610-016 Amadora, Portugal.

Ciclum, Spain. Ciclum Farma, Doctor Zamenhof 38, 28027 Madrid, Spain.

CICSA, Mex. Compañia Internacional de Comercio SA de CV, Monzón 184, 9860 Iztapalapa Cerro de la Estrella, Mexico.

Ciech, Rus. Ciech AO, Kutuzovski Prospekt 7/14, Korp. 5, kv. 11-12, 121248 Moscow, Russia.
url: www.ciech.ru

Cielle, Ital. Farma Cielle S.r.l., Via Michele Amari 15, 90139 Palermo, Italy.
url: www.farmacielle.com

Cifarma, Braz. Cifarma Cientifica Farmacêutica Ltda, Av. das Industrias 3651, 33040-130 Belo Horizonte, MG, Brazil.
url: www.cifarma.com.br

Cilag, Austral. See *Janssen-Cilag, Austral.*

Cilag, Belg. See *Janssen-Cilag, Belg.*

Cilag, Cz. See *Janssen-Cilag, Cz.*

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Cilag, Hong Kong. See *Janssen, Hong Kong* and *Keller, Hong Kong.*

Cilag, Ital. See *Janssen-Cilag, Ital.*

Cilag, Neth. See *Janssen-Cilag, Neth.*

Cilag, Philipp. See *Zuellig, Philipp.*

Cilag, Rus. See *Janssen-Cilag, Rus.*

Cilag, Spain. See *Janssen, Spain.*

Cilag, Swed. See *Janssen-Cilag, Swed.*

Cilag, UK. See *Janssen, UK.*

Cimed, Braz. Cimed Indústria de Medicamentos Ltda, Rua Engenheiro Prudente 119, 01550-000 São Paulo Vila Monumento, SP, Brazil.
url: www.cimed.ind.br

Cimex, Cz. See *Swisspharma, Cz.*

Cimex, Hong Kong. See *ICH, Hong Kong.*

Cimex, Israel. See *Taro, Israel.*

Cimex, Singapore. See *Pharma 2000, Singapore.*

Cimex, Switz. Cimex AG Pharmazeutika, Birsweg 2, 4253 Liesberg, Switzerland.

Cinay, Turk. Çinay Kimya San ve Tic AS, Turkey.

Cinerea, India. Cinerea Biotech, SCF-271 1st Floor, M. Market, Manimajra, Chandigarh, India.

Cinetic, Arg. Cinetic Laboratories Argentina S.A., Av. Triunvirato 2734/6, 1427 Buenos Aires, Argentina.

Cinfa, Port. Cinfa Portugal Lda, Av. Tomas Ribeiro 43, Bloco 1-4 B, Edificio Neopark, 2790-221 Carnaxide, Portugal.

Cinfa, Spain. Cinfa, Olaz-Chipi 10, Poligono Areta, Huarte-Pamplona, 31620 Navarra, Spain.
url: www.cinfa.com

Cintas, UK. Cintas Pharma, a division of BritHealth Limited, Business & Technology Centre, Bessemer Drive, Stevenage, Hertfordshire, SG1 2DX, UK.
url: www.pharmalicensing.com

Cintex, USA. Cintex Services LLC, 9330 LBJ Freeway, Suite 900, Dallas, TX 75243, USA.

Cipan, Port. Cipan, Companhia Industrial Produtora de Antibioticos SA, Vala do Carregado, Apartado 60, 2600-733 Castanheira do Ribatejo, Portugal.
url: www.cipan.pt

Cipher, Canad. Cipher Pharmaceuticals Inc., 5650 Tomken Rd, Unit 16, Mississauga, Ontario, L4W 4P1, Canada.
url: www.cipherpharma.com

Cipla, Austral. Cipla GenPharm Australia Pty Ltd, Kaybank Plaza, 33 Scarborough St, Southport, Qld 4215, Australia.

Cipla, Cz. See *CZ, Cz.*

Cipla, Hong Kong. See *Lifetech, Hong Kong.*

Cipla, India. Cipla Ltd, Mumbai Central, Mumbai 400 008, India.
url: www.cipla.com

Cipla, Israel. See *Margalit, Israel.*

Cipla, Malaysia. See *Antah, Malaysia.*

Cipla, Neth. See *Cipla, UK.*

Cipla, Philipp. See *Pharmawealth, Philipp.*

Cipla, Rus. See *Teva, Rus.*

Cipla, S.Afr. See *Cipla-Medpro, S.Afr.*

Cipla, Singapore. See *Goldplus, Singapore.*

Cipla, Thai. See *Neopharm, Thai.*

Cipla, UK. Cipla (EU) Ltd, Hillbrow House, Hillbrow Rd, Esher, Surrey, KT10 9NW, UK.

Cipla, Ukr. Cipla, ul. Vadima Hetman 27, 5th Floor Office 50, 03056 Kiev, Ukraine.
url: www.kgplabs.com

Cipla, Venez. See *PG, Venez.*

Cipla Chanelle, Denm. See *Cipla Chanelle, Irl.*

Cipla Chanelle, Irl. Cipla Chanelle Ltd, Loghrea, Co. Galway, Ireland.

Cipla-Medpro, S.Afr. Cipla-Medpro (Pty) Ltd, Rosen Heights, Rosen Park, Bellville 7530, South Africa.
url: www.ciplamedpro.co.za

Circa, USA. See *Watson, USA.*

Circle, USA. Circle Pharmaceuticals Inc., 6788 Hawthorn Park Drive, Indianapolis, IN 46220, USA.

CIS, Austria. See *CIS, Fr.*

CIS, Cz. See *CIS, Fr.*

CIS, Fin. See *CIS, Fr.*

CIS, Fr. CIS bio International, B.P. 32, 91192 Gif-sur-Yvette cdx, France.
url: www.cisbiointernational.fr

CIS, Gr. See *CIS, Fr.*

CIS, Hung. See *CIS, Fr.*

CIS, Irl. See *CIS, Fr.*

CIS, Ital. Cis Bio SpA, C.so Italia 13, 20100 Milan (MI), Italy.

CIS, Neth. See *CIS, Fr.*

CIS, Pol. See *CIS, Fr.*

CIS, Port. See *CIS, Fr.*

CIS, Spain. See *CIS, Fr.*

CIS, UK. See *CIS, Fr.*

Citadel, India. Citadel Fine Pharma Pvt Ltd, 265 TTK Rd, Chennai 600 018, India.

Citomed, Rus. Citomed ZAO, Muchnojj per. 2, 191023 Saint Petersburg, Russia.

Citopharma, Braz. Citopharma, Casula & Vasconselos Ind. Farm. e Com. Ltda, Rua Caetano Pirri 520, Milionarios, 30620070 Belo Horizonte, Minas Gerais, Brazil.

Citrage, Fr. Citrage, ZA Europarc CITEC, 1 allée des Rochers, 94045 Créteil, France.

Citron Remedies, Canad. Citron Remedies Ltd, 502 200 Tuxedo Ave, Winnipeg, Manitoba, R3P 0R3, Canada.

CJ, China. Cheil Jedang (CJ) Corp., China.

CJ, Philipp. See *Braun, Philipp.*

CJ, Singapore. See *Zyfas, Singapore.*

CJ, Thai. See *Berli Jucker, Thai* and *RX, Thai.*

CKD, Philipp. See *Endure, Philipp* and *Largen, Philipp.*

Clairol, Canad. See *Procter & Gamble, Canad.*

Clarben, Port. See *Clarben, Spain.*

Clarben, Spain. Clarben, Vallermoso 28, 28015 Madrid, Spain.
url: www.clarben.com

Clarendon, Irl. See *Clarendon, UK.*

Clarendon, UK. Clarendon Pharma Ltd, 19 King St, Seagrave, Leicestershire, LE12 7LY, UK.

Clarins, Canad. Clarins, 4757 Poirier Blvd, St-Laurent, Quebec, H4R 2A4, Canada.

Clarion, Canad. Clarion Medical Technologies Inc., 125 Fleming Drive, Cambridge, Ontario, N1T 2B8, Canada.

Claris, India. Claris Lifesciences, Nr Parimal Crossing, Ellisbridge, Ahmedabad 380006, India.
url: www.clarislifesciences.com

Claris, Ital. See *Lombarda, Ital.*

Claris, Philipp. See *Macropharma, Philipp.*

Claris, Port. See *Claris, UK.*

Claris, Rus. See *Claris, India.*

Claris, Thai. See *Neopharm, Thai.*

Claris, UK. Claris Lifesciences UK Ltd, Crewe Hall, Golden Gate Lodge, Crewe, Cheshire, CW1 6UL, UK.

Clarmed, Ital. See *Medacta, Ital.*

Classical Remedia, Canad. Classical Remedia Ltd, 412 Dundas St West, Toronto, Ontario, M5T 1G7, Canada.

Clay Park, Hong Kong. See *Hind Wing, Hong Kong.*

Clay Park, USA. Clay-Park Labs Inc., 1700 Bathgate Ave, Bronx, NY 10457, USA.
url: www.claypark.com

Claytone, Fr. See *Terrafor, Fr.*

Clement, Fr. See *Clement-Thekan, Fr.*

Clement Clarke, UK. Clement Clarke International Ltd, Airmed House, Edinburgh Way, Harlow, Middlesex, CM20 2TT, UK.
url: www.clement-clarke.com

Clement Thionville, Fr. Laboratoires Clément-Thionville, 6 rue Joffre, B.P. 60028, 57101 Thionville cdx, France.

Clement-Thekan, Fr. Laboratoires Clément-Thékan, 2-4 rue Chaintron, B.P. 850, 92542 Montrouge cdx, France.

Clin Midy, Fr. See *Sanofi-Aventis, Fr.*

Clinbaxy, Philipp. Clinbaxy Intl, Inc., 1139-1141 Rizal Ave, Cor Mayhaligue St, Sta Cruz, Manila, Philippines.

Clinifood, Singapore. See *Advanced, Singapore.*

Clinigen, Austral. See *Clinigen, UK.*

Clinigen, Austria. See *Clinigen, UK.*

Clinigen, Belg. See *Clinigen, UK.*

Clinigen, Braz. See *Clinigen, UK.*

Clinigen, Cz. See *Clinigen, UK.*

Clinigen, Fin. See *Clinigen, UK.*

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Clinigen, Israel. See *Clinigen, UK.*

Clinigen, Ital. See *Clinigen, UK.*

Clinigen, Neth. See *Clinigen, UK.*

Clinigen, Norw. See *Clinigen, UK.*

Clinigen, NZ. See *Clinigen, UK.*

Clinigen, Port. See *Clinigen, UK.*

Clinigen, Singapore. See *Clinigen, UK.*

Clinigen, Spain. See *Clinigen, UK.*

Clinigen, Swed. See *Clinigen, UK.*

Clinigen, Switz. See *Clinigen, UK.*

Clinigen, Thai. See *Clinigen, UK.*

Clinigen, UK. Clinigen Healthcare Ltd, Pitcairn House, Crown Square, First Ave, Burton-on-Trent, Staffordshire, DE14 2WW, UK.
url: www.clinigen.co.uk

Clinigen, USA. See *Clinigen, UK.*

CliniMed, UK. CliniMed Ltd, Cavell House, Knaves Beech Way, Loudwater, High Wycombe, Buckinghamshire, HP10 9QY, UK.
url: www.clinimed.co.uk

Clinique, Canad. Clinique Laboratories, 121 Bloor St E, Toronto, Ontario, M4W 3N5, Canada.

Clinique Lafontaine, Canad. Clinique Lafontaine Inc., Division Les Importations Ortho, 1645 rue Sigouin, Drummondsville, Quebec, J2C 5R7, Canada.

Clinova, UK. Clinova, Solent Business Centre, Millbrook Rd West, Southampton, Hampshire, SO15 0HW, UK.
url: clinova.co.uk

Clintec, Austria. See *Baxter, Fr.*

Clintec, Belg. See *Baxter, Belg.*

Clintec, Canad. See *Baxter, Canad.*

Clintec, China. See *Baxter, China.*

Clintec, Cz. See *Nestle, Fr.*

Clintec, Denm. See *Baxter, Denm.*

Clintec, Fin. See *Nestle, Fr.*

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Clintec, Gr. See *Baxter, Gr.*

Clintec, Irl. See *Baxter, Irl.*

Clintec, Israel. See *Teva, Israel.*

Clintec, Ital. See *Baxter, Ital.*

Clintec, Neth. See *Nestle, Fr.*

Clintec, Spain. Clintec Nutrición, Parque Empresarial San Fernando, Edif. Londres, San Fernando de Henares, 28830 Madrid, Spain.

Clintec, Thai. See *Osotspa, Thai.*

Clintec, UK. See *Baxter, UK* and *Nestle, UK.*

Clintec, USA. See *Baxter, USA.*

Clintex, Port. See *Labesfal, Port.*

Clissmann, Irl. HE Clissmann, 72 Heather Rd, Dublin 18, Ireland.
url: www.clissmann.com

Clonmel, Irl. Clonmel Healthcare Ltd, Waterford Rd, Clonmel, Co. Tipperary, Ireland.
url: www.clonmel-health.ie

Clonmel, UK. See *Clonmel, Irl.*

CLS, China. CLS Pharma, China.

CLS, Thai. See *Pacific, Thai.*

Cmed, Thai. Cmed Products 1994 Co. Ltd, 9/24-25 Soi Phaholyothin 15, Phaholythin R., Samsennai Phayathai, Bangkok, 10400, Thailand.
url: www.cmedproducts1994.com

CMG, India. CMG Biotech Pvt Ltd, 410 Plot No. 4, DDA Building, Laxmi Nagar, Delhi 110 092, India.
url: www.cmgbiotech.com

CMI, Canad. CMI Cosmetic Manufacturers Inc., 90 Moyal Court, Concord, Ontario, L4K 4R8, Canada.

CMM Medicor, Rus. CMM Medicor, The Centre of Modern Medicine Ltd, Ul. Alexeya Aviridova 15/3, 121374 Moscow, Russia.
url: www.galavit.ru

CMS, China. China Medical System (CMS) Co. Ltd, Building A, 11 Langshan Rd North, Nanshan District, Shenzhen 518057, China.

CMS-Dental, Denm. CMS-Dental ApS, Njalsgade 21, 2300 Copenhagen S, Denmark.
url: www.cmsdentol.dk

CNN, Philipp. CNN Generics Distribution Inc., Rm 210, Lawyers Coop Bldg, 459 Quezon Ave, Cor Banawe, Quezon City, Philippines.

CNP, Ger. CNP Pharma GmbH, Marienplatz 10-12, 94081 Fürstenzell, Germany.

CNS, Austral. CNS Pharma Pty Ltd, Level 4, Deutsche Bank Place, Corner Hunter and Phillip Streets, Sydney, NSW 2000, Australia.

CNS, USA. CNS Inc., 20 Troy Rd, Whippany, Nj 07981, USA.
url: www.cns.com

CNW, Hong Kong. CNW (Hong Kong) Ltd, Rm 605, 6/F, Fo Tan Industrial Ctr, 26-28 Au Pui Wan St, Fo Tan, Shatin, N.T., Hong Kong.
url: www.cnwpharma.com

Co Ord-Med, Hung. Co Ord-Med Információs Iroda, Csaba u 7/a II/1, 1122 Budapest, Hungary.

Cocensys, USA. See *Purdue Frederick, USA.*

Cochon, Fr. See *Tradiphar, Fr.*

codaDOSE, USA. codaDOSE Inc., 5659 Southfield Drive, Atlanta, GA 30542, USA.
url: www.codadose.com

Codal Synto, Hong Kong. See *CNW, Hong Kong* and *Hong Tai Hong, Hong Kong* and *Star, Hong Kong.*

Codal Synto, Malaysia. See *Propharm, Malaysia.*

Codal Synto, Thai. See *Star, Thai.*

Codali, Belg. Codali SA, Ave Henri Dunant 31, 1140 Brussels, Belgium.Marketing Manager
url: www.codali.be

Code, Fr. Laboratoires Code, 177 rue de Paris, 95680 Montlignon, France.

Codepharma, Fr. Lab Codepharma, 80-82 rue Gallieni, 92100 Boulogne-Billancourt, France.

Codexial, Fr. Codexial Dermatologie, 10 rue du Bois-de-la-Champelle, 54500 Vandoeuvre-lès-Nancy, France.
url: www.codexial-dermatologie.com

Codifra, Fr. Laboratoires Codifra, 18 av. Dutarte, 78150 Le Chesney, France.

Codilab, Port. Codilab, Indústria e Comércio de Produtos Farmacêuticos SA, Av. Marechal Gomes da Costa 19, 1800-255 Lisbon, Portugal.

Coel, Pol. Wytwórnia Euceryny Laboratorium Farmaceutyczne Coel SJ, ul. Wł Żeleńskiego 45, 31-353 Kraków, Poland.
url: www.coel.krakow.pl

Cofasa, Venez. Laboratorios Cofasa S.A., Urbanización Industrial Lebrún, Edificio Cofasa, 4to. Piso, Caracas, Venezuela.
url: www.laboratoriocofasa.com

Coffey, Irl. Coffey Healthcare Ltd, 4 Finglas Business Centre, Jamestawn Rd, Dublin 11, Ireland.
url: www.coffeyhealthcare.com

Coghlans, Canad. Coghlan's Ltd, 121 Irene St, Winnipeg, Manitoba, R3T 4C7, Canada.

Cognon-Morin, Fr. Cognon-Morin, ZIN, B.P. 228, 86102 Chatellerault cdx, France.

Coherent, Canad. Coherent-AMT Inc., 555 Trillium Drive, Unit 15, Kitchener, Ontario, N2R 1K3, Canada.

Colfarm, Pol. Zakłady Farmazeutyczne Colfarm SA, ul. Wojska Polskiego 3, 39-300 Mielec, Poland.
url: www.colfarm.pl

Colgate, Arg. See *Colgate-Palmolive, Arg.*

Colgate, Ger. See *Colgate-Palmolive, Ger.*

Colgate Oral, USA. Colgate Oral Pharmaceuticals, 1 Colgate Way, Canton, MA 02021, USA.
url: www.colgateprofessional.com

Colgate Oral Care, Austral. Colgate Oral Care, P.O. Box 3964, Sydney, NSW 2001, Australia.
url: www.colgate.com

Colgate-Hoyt, USA. See *Colgate-Palmolive, USA.*

Colgate-Palmolive, Arg. Colgate-Palmolive Argentina S.A., Av. Antartida Argentina 2269, 1836 Llavallol, Buenos Aires, Argentina.
url: www.colgate.com

Colgate-Palmolive, Austral. See *Colgate Oral Care, Austral.*

Colgate-Palmolive, Austria. See *Colgate-Palmolive, Ger.*

Colgate-Palmolive, Canad. Colgate-Palmolive Canada Inc, Two Morneau Sobeco Centre, 6th Floor, 895 Don Mills Rd, Toronto, Ontario, M3C 1W3, Canada.
url: www.colgate.ca

Colgate-Palmolive, Denm. Colgate Palmolive A/S, Smedeland 9, 2600 Glostrup, Denmark.
url: www.colgate.dk

Colgate-Palmolive, Fin. See *Colgate-Palmolive, Denm.*

Colgate-Palmolive, Ger. Colgate-Palmolive GmbH, Lübecker Str. 128, 22087 Hamburg, Germany.
url: www.colgate.de

Colgate-Palmolive, Gr. Colgate-Palmolive Hellas, Piraeus, Greece.
url: www.colgate.com

Colgate-Palmolive, Irl. See *Colgate-Palmolive, UK.*

Colgate-Palmolive, Ital. Colgate Palmolive Commerciale S.r.l., Via Giorgione 59/63, 00147 Rome (RM), Italy.
url: www.colgate.com

Colgate-Palmolive, Neth. Colgate-Palmolive Nederland BV, 1382 LV Weesp, Netherlands.

Colgate-Palmolive, Norw. See *Colgate-Palmolive, Denm.*

Colgate-Palmolive, Port. Colgate Palmolive Unipessoal Lda, Rua Mário Castelhano no 1, Queluz de Baixo, 2730-120 Barcarena, Portugal.

Colgate-Palmolive, Swed. See *Colgate-Palmolive, Denm.*

Colgate-Palmolive, Switz. Colgate-Palmolive AG, Zurcherstrasse 68, 8800 Thalwil, Switzerland.
url: www.colgate.ch

Colgate-Palmolive, UK. Colgate-Palmolive Ltd, Guilford Business Park, Middleton Rd, Guildford, Surrey, GU2 5JZ, UK.
url: www.colgate-palmolive.co.uk

Colgate-Palmolive, USA. Colgate-Palmolive Co., 300 Park Ave, New York, NY 10022, USA.
url: www.colgate.com

Colin, Belg. Colin Laboratoires NV, Rue Trou-du-Loup 50, 4670 Blegny, Belgium.

Coll, Spain. Coll Farma, Napoles 166, 08013 Barcelona, Spain.

Collagen, Austral. Collagen Biomedical P/L, Unit 1, Chullora Central, Chullora, NSW 2190, Australia.

Collagen, Hong Kong. See *Onstrong, Hong Kong.*

Collagen, Singapore. See *Pharmacon, Singapore.*

Collagen, USA. See *Inamed, USA.*

Collagen Aesthetics, NZ. Collagen Aesthetics Ltd, P.O. Box 25-556, St. Heliers, Auckland, New Zealand.

CollaGenex, Israel. See *CollaGenex, USA.*

CollaGenex, Neth. See *CollaGenex, UK.*

CollaGenex, UK. CollaGenex International Ltd, The Old Stable Block, 7 Buttermarket, Thame, Oxfordshire, OX9 3EW, UK.
url: www.collagenex.com

CollaGenex, USA. CollaGenex Pharmaceuticals Inc., 41 University Drive, Newtown, PA 18940, USA.
url: www.collagenex.com

Collect, Braz. Collect Importação e Comércio Ltda, Brazil.

Collegium, USA. Collegium Pharmaceuticals Inc., 400 Highland Corporate Drive, Cumberland, RI 02864, USA.
url: www.collegiumpharma.com

Collins, Mex. Productos Farmaceuticos Collins S.A. de C.V., Cipres No. 1677, Col. del Fresno, 44900 Guadalajara, Jalisca, Mexico.
url: www.collins.com.mx

Collins Elixir, UK. Collins Elixir Co., P.O. Box 33, Kingsbridge, Devon, TQ7 1YQ, UK.

Colomer, Canad. See *Colomer, USA.*

Colomer, USA. Colomer USA, 5344 Overmyer Dr, Jacksonville, FL 32254, USA.

Coloplast, Arg. Coloplast de Argentina S.A., Hipylito Bouchart 547, Piso 13, 1106 Buenos Aires, Argentina.
url: www.coloplast.com

Coloplast, Belg. Coloplast Belgium NV, Humaniteitslaan 65, 1601 Ruisbroek, Belgium
url: www.coloplast.be

Coloplast, Canad. See *Coloplast, USA.*

Coloplast, Fr. Laboratoires Coloplast, 58 rue Roger-Salengro, Peripole 126, 94126 Fontenay-sous-Bois cdx, France.
url: www.coloplast.fr

Coloplast, Ger. Coloplast GmbH, Kuehnstr. 75, 22045 Hamburg, Germany.

Coloplast, S.Afr. Coloplast A/S, Van Reenens Rd, Woodmead Office Park, 20 Stirrup Lane, Woodmead Ext. 14, Sandton, South Africa.
url: www.coloplast.com

Coloplast, UK. Coloplast Ltd, Peterborough Business Park, Peterboraugh, Cambridgeshire, PE2 0FX, UK.
url: www.coloplast.co.uk

Coloplast, USA. Coloplast Corp., 1955 West Oak Circle, Marietta, GA 30062-2249, USA.
url: www.us.coloplast.com

Columbia, Arg. Laboratorios Columbia de Argentina SA, Cervantes 2950, Buenos Aires, Argentina.

Columbia, Canad. Columbia Laboratories Canada Inc., 600 Peter Morand Cres., Suite 140, Ottawa, Ontario, K1G 5Z3, Canada.

Columbia, Fr. See *Columbia, UK.*

Columbia, Mex. Laboratorios Columbia, S.A. de C.V., Calz. del Hueso No. 160, Col. Ejido de Santa Ursula Coapa, Deleg. Coyoacan, 04850 Mexico D.F., Mexico.

Columbia, S.Afr. Columbia Pharmaceuticals (Pty) Ltd, P.O. Box 7026, Bonaero Park 1622, South Africa.

Columbia, UK. Columbia Laboratories Ltd, 9-10 Tilmore Court, Tilmore Green, Hitchin, Hertfordshire, SG4 7XJ, UK.

Columbia, USA. Columbia Laboratories Inc., 354 Eisenhower Parkway, Second Floor, Plaza 1, Livingston, NY 07039, USA.
url: www.columbialabs.com

Combe, Arg. Lab. Combe Argentina SRL, Pola 2249/51, 1440 Buenos Aires, Argentina.

Combe, Canad. See *Combe, USA.*

Combe, Ger. Combe Pharma Ltd, Sophienstr. 22, 76530 Baden-Baden, Germany.
url: www.combe-pharma.de

Combe, Irl. See *Combe, UK.*

Combe, Israel. See *Medibrands, Israel.*

Combe, Ital. Combe Italia S.r.l., Via G.C. Procaccini 41, 20154 Milan (MI), Italy.
url: www.combeitolia.com

Combe, Spain. Combe Europa, Orense 58, 28020 Madrid, Spain

Combe, UK. Combe International Ltd, 4th Floor, AMP House, Dingwell Rd, Croydon, Surrey, CR9 2AU, UK.
url: www.combe.com

Combe, USA. Combe Inc., 1101 Westchester Ave, White Plains, NY 10604, USA.
url: www.combe.com

Combino, Spain. Combino Pharm, Fructuos Gelabert 6-8, Sant Joan Despi, 08024 Barcelona, Spain.
url: www.combino-pharm.es

Combiphar, Indon. Combiphar PT, Graha Atrium Lt 14, Jl Senen Raya No 135, Jakarta Pusat 10160, Indonesia.
url: www.combiphar.com

Combustin, Ger. Combustin Pharm. Präparate GmbH, Offinger Str. 7, 88525 Hailtingen/Bussen, Germany.
url: www.presselin.de

Comed, India. Comed Chemicals Ltd, 3rd Floor Orient Business Centre, Sayajigunj, Baroda 390 005, India.
url: www.comedchemicals.com

Commerce, USA. See *Del, USA.*

Commerz, Philipp. Commerz Trading International Inc., Unit 54, 5/F ZETA Bldg, Salcedo St, Legaspi Vill., Makati City, Philippines.

Commonwealth Serum, Hong Kong. See *LCH, Hong Kong.*

Commonwealth Serum Laboratories, Austral. See *CSL, Austral.*

Commsept, Canad. Commsept International, a Division of 6091385 Canada Inc., Box 407, Elie, Manitoba, R0H 0H0, Canada.

Community Pharmacy, Thai. Community Pharmacy Public Co. Ltd, 1 Soi Kubon 11, Kannayao, Bangkok 10230, Thailand.
url: www.chumchon.co.th

Comomed, Gr. Comomed Pharmaceuticals, Ypsilanti 61, 17455 Alimos, Greece.
url: www.comomed.gr

Complutense, Spain. Centro PET Complutense SA, C./ Manuel Bartolome Cossio 10, 28040 Madrid, Spain.
url: www.petmadrid.com

Compu, S.Afr. CompuPharm (Pty) Ltd, P.O. Box 30599, Sunnyside 0132, South Africa.

Comvita, Austral. Comvita Australia, 10 Edmondstone St, South Brisbane, Queensland 4101, Australia.
url: www.comvita.com.au

Canba, China. Conba Pharmaceutical Co Ltd, 568 Bin Kang Rd, Riverside Technology Economic Park, High-tech Development Zone, Hangzhou 310052, China.
url: www.jhconba.com

Concept, Hong Kong. See *Primal, Hong Kong.*

Concept, India. Concept Pharmaceuticals Ltd, 167 C.S.T. Rd, Kalina, Santacruz East, Mumboi 400 098, India.
url: www.conceptpharma.net

Concept, Israel. Concept for Pharmacy Ltd, P.O. Box 2105, Kfar Sava 44643, Israel.
url: www.concept-rx.co.il

Concept, Philipp. See *Pharmawealth, Philipp.*

Concept Pharmaceuticals, UK. See *Pierre Fabre, UK.*

Concern, Ukr. OOO Concern APF, Chigorina Street, 18, Kiev, 01042, Ukraine.

Concertina, India. Concertina Pharma Pvt Ltd, 10/A Hudo Complex, Hyderabad 500 035, India.

Concord, UK. See *Archimedes, UK.*

Concordia, Mex. Laboratorios Concordia S.A. de C.V., Ejército Nacional 579, 8 Piso, Miguel Hidalgo Ampliación Granada, 11520 México D.F., Mexico.

Condition, China. Condition Pharmaceutical Co. Ltd, Beijing, China.

Condrugs, Thai. Condrugs International Co. Ltd, 51/507-508 Drive-in Square, Soi 1, Ladprao Rd, Klongjan, Bangkapi, Bangkok 10240, Thailand.

Confab, Canad. Laboratoires Confab Inc., 4355 Blvd Sir Wilfrid Laurier, St-Hubert, Quebec, J3Y 3X3, Canada.

Confab, Hong Kong. See *Pan-Well, Hong Kong.*

Confar, Port. Confar, Lda, Rua Sebastião e Silva 25, Zona Industrial de Massama, 2745-838 Queluz, Portugal.

Conforma, Belg. Conforma, Belgium.

Conifarma, Arg. Consorcio de Integración Farmaceutica SA, Pringles 10, Pisos 2 y 4, 1183 Buenos Aires, Argentina.

Connaught, Canad. See *Aventis Pasteur, Canad.*

Connaught, Israel. See *Dover, Israel.*

Connaught, Norw. See *Sanofi Pasteur, Denm.*

Connaught, NZ. See *CSL, NZ.*

Connaught, USA. See *Sanofi Pasteur, USA.*

Connell, Hong Kong. Connell Bros Co. (HK) Ltd, Rm 601, 6/F Stanhope House, 738 King's Rd, North Point, Hong Kong.

Consilient, UK. Consilient Health (UK) Ltd, 500 Chiswick High Rd, London, W4 5RG, UK.
url: www.consilienthealth.com

Consolidated Chemicals, Irl. See *Whelehan, Irl.*

Constant, India. Constant, Plot No 92 Industrial Area, Phase-1, Panchkula, Haryana, India.

Consupharmo, Mex. Consupharma SA de CV, Pico de Verapaz 435 Piso 2, Tlalpan Jardines de Montana, 14210 Mexico D.F., Mexico.
url: www.consupharma.com

Contact Lens Centre, Austral. Contact Lens Centre Australia, 1/5 Seismic Court, Rowville, Victoria 3178, Australia.
url: www.theratears.com.au

Continental, Cz. See *Continental Pharma, Belg.*

Continental, USA. Continental Consumer Products, 770 Forest, Suite B, Birmingham, MI 48009, USA.

Continental Ethicals, S.Afr. Continental Ethicals (Division of S.A. Druggists Ltd), 1 Corlett Drive, Illovo, Johanesburg 2196, South Africa.

Continental Pharma, Belg. Continental Pharma Inc., Tervurenlaan 270-272 bte 24, 1150 Brussels, Belgium.

Continental Pharma, Switz. See *Vifor, Switz.*

Continental Pharma, Thai. See *Union Medical, Thai.*

Continentales, Mex. Farmacos Continentales S.A. de C.V., Mexico.

Continental-Pharm, Thai. Continental-Pharm Co Ltd, 85/5 Soi Prachoomporn, Chaengwattana Rd, Laksi, Bangkok, Thailand.

Continuum, Canad. Continuum, Station: M. Calgara, Alberta, T2P 2L6, Canada.

Contipro, Malaysia. See *Imeks, Malaysia.*

Contract Pharmacal, USA. Contract Pharmacal Corporation, 135 Adams Avenue, Hauppauge, NY 11788, USA.
url: www.contractpharmacal.com

Controlled Medications, Hong Kong. Controlled Medications Ltd, Unit 204 2/F New Bright Bldg, 11 Sheung Yuet Rd, Kowloon Bay, Kowloon, Hong Kong.
url: www.swedishtrading.com/conmed

Controlled Therapeutics, Pol. See *Medagro, Pol.*

Convatec, Arg. See *BMS, Arg.*

Convatec, Austral. Convatec Australia, Division of Bristol-Myers Squibb, Level 1, 352 Welling Road, Mulgrave, VIC 3170, Australia.
url: www.convatec.com

Convatec, Belg. ConvaTec Belgium BVBA, Parc de l'Alliance, Avenue de Finlande 8, 1420 Braine-l'Alleud, Belgium.
url: www.convatec.be

Convatec, Canad. Convatec Canada, 555 Dr Frederick Philips St, Suite 110, St-Laurent, Quebec, H4M 2X4, Canada.
url: www.convatec.com

Convatec, Fr. See *BMS, Fr.*

Convatec, Irl. See *BMS, Irl.*

Convatec, Israel. See *Philtel, Israel.*

Convatec, Ital. See *BMS, Ital.*

Convatec, Port. See *BMS, Port.*

Convatec, Switz. See *BMS, Switz.*

Convatec, UK. Convatec Ltd, Harrington House, Milton Rd, Ickenham, Uxbridge, Middlesex, UB10 1DE, UK.
url: www.convatec.com

Convatec, USA. ConvaTec, P.O. Box 5254, Princeton, NJ 08543-5245, USA.
url: www.convatec.com

Cooberpharm, Spain. Cooberpharm SL, C Brusi 7, 08006 Barcelona, Spain.
url: www.cooberpharm.com

Cooke, USA. See *United Therapeutics, USA.*

Cook-Waite, USA. See *Kodak, USA.*

Coop. Farm., Ital. Società Cooperativa Farmaceutica (CoFa Farmaceutici), Via Passione 8, 20122 Milan (MI), Italy.
url: www.cofa.it

Cooper, Fr. Coopérotion Pharmaceutique Francaise, 77020 Melun cdx, France.

Cooper, USA. Cooper Surgical, 95 Corporate Drive, Trumbull, CT 06611, USA.

Cooper (Kotep), Gr. KOPER AE, Aristovoulou 64, 118 53 Attikis, Greece.

Cooperation Pharmaceutique, Fr. See *Cooper, Fr.*

Coopervision, Irl. See *Novartis, UK.*

Copernico, Ital. Copernico Farmaceutici S.r.l., Viale Etiopia 8, 00199 Rome (RM), Italy.

Cophana, Belg. Cophano, Garocentre Sud, Chemin de la Reconversion 17, 7110 Houdeng-Goegnies, Belgium.
url: www.cophana.be

Co-Pharma, Irl. See *Co-Pharma, UK.*

Co-Pharma, UK. Co-Pharma Ltd, Unit 4, Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD1 8SS, UK.
url: www.co-pharma.co.uk

Copley, USA. See *Teva, USA.*

Copyfarm, Denm. Copyfarm A/S, Energivej 15, 5260 Odense S, Denmark.
url: www.copyfarm.dk

Copyfarm, Fin. See *Copyfarm, Denm.*

Cor Therapeutics, USA. See *Millenium, USA.*

Coral, Philipp. See *SMHP, Philipp.*

Coral, Rus. Coral-Med, 9 26 Bakinskikh Komissarov ul., 119571 Moscow, Russia.

Coralite, Canad. See *Coralite, USA.*

Coralite, USA. Coralite Dental Products, 7227 North Hamlin Ave, Skokie, IL 60076-3999, USA.

corax, Ger. corax pharma GmbH, Josef-Dietzgen-Str. 3, 53733 Hennef, Germany.
url: www.coraxpharmo.de

Corax, Neth. See *corax, Ger.*

Corbridge, Philipp. Corbridge Group Phils, Inc., 5/F Jater Bldg, 118 West Ave, Quezon City, Philippines.

Corcept, USA. Corcept Therapeutics, 149 Commonwealth Drive, Menlo Park, CA 94025, USA.
url: www.corcept.com

Cord, Hong Kong. See *Pan-Well, Hong Kong.*

Cord, USA. See *Novartis, USA.*

Core Gestra, India. Core Gestra Pvt Ltd, Plot No 55, Patparganj Indl Area, Delhi 110 092, India.

CorePharma, USA. CorePharma LLC, 215 Wood Ave, Middlesex, NJ 08846, USA.
url: www.corepharma.com

Coretex, Canad. See *Coretex, USA.*

Coretex, USA. Coretex Products Inc., 1850 Sunnyside Court, Bakersfield, CA 93308, USA.

Coria, USA. Coria Laboratories Ltd, 3909 Hulen St, Fort Worth, TX 76107, USA.
url: www.coridabs.com

Corifel, Switz. Corifel SA, Via Clemente Maraini 9, 6907 Lugano 7, Switzerland.

Corixa, USA. Corixa Corp., 1900 9th Ave., Suite 1100, Seattle, WA 98104, USA.
url: www.corixa.com

Cork, Singapore. Cork International Pte Ltd, 20 Toh Guan Rd, 08-02 Accord Distri Centre, S 608839, Singapore.

Corman, Ital. Corman S.p.A., Via Sciesa 10, 20084 Lacchiarella (MI), Italy.
url: www.corman.it

CORNE, Mex. Corporacion Operadora de Representaciónes y Negocios S.A. de C.V. (CORNE), Dr Vertis 894, Col. Narvarte, 3020 México D.F., Mexico.

Cornelli, Ital. Cornelli Consulting S.a.s., Corso Indipendenzo 1, 20129 Milan, Italy.
url: www.cornelliconsulting.it

Cornerstone, USA. Cornerstone Therapeutics Inc., 1255 Crescent Green Drive, Suite 250, Cary, NC 27518, USA.
url: www.crtx.com

Corona, India. Corona Remedies Pvt Ltd, 413/414 Saman, Opp. Nalanda Complex, Vastrapur, Ahmedabad 380 015, India.

Coronet, Indon. Coronet Crown PT, Jl Kupang Indah VIII No 9, Surabaya 60225, Jawa Timur, Indonesia.

Corsa, Indon. Corso Industries Ltd PT, Jl KS Tubun IIC/30, Jakarta, DKI Jaya, Indonesia.

Corsalud, Venez. Carporacion de Salud C.A., Av. J. M. Vargas, Edif. Artico Piso 1 Oficina 15B, Sto. Fe Norte Caracas, Caracas, Venezuela.

Cortecs, Irl. See *Provalis, UK.*

Cortecs, UK. See *Provalis, UK.*

Cortex, Ital. Cortex Italia S.r.l., Via Urbano III 2, 20132 Milan (MI), Italy.

Coryne de Bruynes, Mon. Laboratoires Coryne de Bruynes, 1 rue du Gabian, Immeuble Le Thales, MC 98000, Monaco.

Corypharma, Ital. Corypharma S.r.l., Via Bellagamba s.n., 60035 Jesi (AN), Italy.
url: www.corypharma.it

Cos Farma, Ital. Cos-Farma S.r.l., Via di Portonaccio 23/B, 00159 Rome (RM), Italy.

Cosan, Switz. Cosan GmbH, Chriesbaumstrasse 2, 8604 Volketswil ZH, Switzerland.

Cosar, Philipp. See *NextChem, Philipp.*

Cosma, Thai. Cosma Medical Co Ltd, 48 Soi Samarnchant-Barbos, Sukhumvit 42 Rd, Phrakanong, Klongtoey, Bangkok 10110, Thailand.

Cosmair, Canad. See *L'Oreal, Canad.*

Cosmas, India. Cosmas Pharmacls Ltd, B-1/1446/10-B, Y-Block Crossing, Hambran Rd, Ludhiana 141 001, India.
url: www.cosmaspharmacls.com

Cosme, India. Cosme Forma Laboratories Ltd, 501/502 Sigma Technology Street, Hiranandani Gardens, Powai, Mumbai 400 076, India.
url: www.cosmeforma.com

Cosmed, Gr. Cosmed Ltd, N Karaoli 30, 172 35 Daphne, Greece.

Cosmetic Solutions, USA. Cosmetic Solutions, 50 Ramland Rd, Orangeburg, NY 10962, USA.
url: www.cosmeticsolutions.com

Cosmetique Active, Switz. Cosmétique Active (Suisse) SA, Industriestrasse 9, 5432 Neuenhof, Switzerland.

Cosmo, Ital. Cosmo Pharmaceuticals SpA, Via C Colombo 1, 20020 Lainate (MI), Italy.
url: www.comsopharmaceuticals.com

Cosmochema, Ger. See *Heel, Ger.*

Cosmoforma, Port. Cosmoforma, Lda (Laboratórios Casmos), Rua Arco do Carvalhão 14, 1070 Lisbon, Portugal.

Cosmopharm, Gr. Cosmopharm E.P.E., Kazarma Korinthou, P.O. Box 42, 201 00 Korinthos, Greece.

Costec, Arg. Costec S.R.L. Esp. Dermatocosméticas, Av. Corrientes 1296 Piso 7 Dto.76, 1043 Buenos Aires, Argentina.

Cotek, Singapore. See *Zuellig, Singapore.*

Cotekc, Rus. See *Sotex, Rus.*

Cotton Craft, Philipp. See *Alico Impex, Philipp.*

Coty, Canad. Coty Canada Inc., 200 1255 Trans Canada Hwy, Dorval, Quebec, H9P 2V4, Canada.

Country Connections, Canad. Country Connections Inc., Unit 5, 325 Parkdale Rd, St Andrews, Maitoba, R1A 3N9, Canada.

Coup, Gr. Coup O.E., Ag. Varvaras 53, 172 35 Dafni, Greece.

Couvreur, Belg. See *Alcon, Belg.*

Covan, S.Afr. See *Adcock Ingram, S.Afr.*

Cover FX, Canad. Cover FX Skincare Inc., 1681 Flint Rd, Toronto, Ontario, M3J 2W8, Canada.

Covermark, Canad. See *Covermark, USA.*

Covermark, USA. Covermork Cosmetics, D 157 Veterans Drive, Northvale, NJ 07647-9974, USA.

Covex, Hung. See *PannonPharma, Hung.*

Covidien, Austral. Covidien Australia, Level 1, 166 Epping Rd, Lane Cove, NSW 2066, Australia.
url: imaging.covidien.com

Covidien, Austria. Covidien Austria GmbH, Im Campus 21, Europaring F09402, 2345 Brunn/Geb., Austria.

Covidien, Belg. Covidien Belgium, Generaal de Wittelaan 9/5, 2800 Mecheln, Belgium.
url: imaging.covidien.com

Covidien, Canad. Covidien Canada, 7300 Trans Canada, Pointe-Claire, Quebec, H9R 1C7, Canada.
url: imaging.covidien.com

Covidien, Cz. See *Covidien, Irl.*

Covidien, Denm. Covidien Danmark A/S, Langebrogade 6E, 1411 Copenhagen K, Denmark.
url: www.covidien.com

Covidien, Fin. See *Covidien, Ital.*

Covidien, Fr. See *Mallinckrodt, Fr.*

Covidien, Gr. See *Covidien, Irl.*

Covidien, Hung. See *Covidien, Ital.*

Covidien, Irl. Covidien plc, Cherrywood Business Park, Loughlinstown, Co. Dublin, Ireland.
url: www.covidien.com

Covidien, Ital. Covidien EMEA Regional Office, Corso Matteotti 3, 20121 Milan, Italy.
url: www.imaging.covidien.com

Covidien, Neth. Covidien Nederland BV, Hogeweg 105, 5301 LL Zaltbommel, Netherlands.
url: imaging.covidien.com

Covidien, Norw. Covidien Norge AS, Bankv. 1, 1372 Asker, Norway.

Covidien, Pol. See *Covidien, Irl.*

Covidien, Rus. See *Covidien, USA.*

Covidien, Spain. Covidien Spain SL, Avda San Pablo 28, 28820 Coslada, Madrid, Spain.
url: imaging.covidien.com

Covidien, Swed. Covidien Sverige AB, Box 54, 171 74 Solna, Sweden.
url: www.covidien.com

Covidien, USA. Covidien, 675 McDonnell Blvd, Hazelwood, MO 63042, USA.
url: pharmaceuticals.covidien.com

Covis, USA. Covis Pharmaceuticals Inc., 1513 Walnut St, Suite 270, Cary, NC 27511, USA.
url: www.covispharma.com

Cow & Gate, Irl. See *Nutricia, Irl.*

Cow & Gate, Israel. See *Guri, Israel.*

Cow & Gate, UK. See *Nutricia Clinical, UK.*

Cowik, Pol. Hurtownia Farmaceutyczna Cowik Sp. zo.o., ul. Powązkowska 59/151, 01-728 Warsaw, Poland.

Cox, Hong Kong. See *Unipharm, Hong Kong.*

Cox, Irl. See *Actavis, UK.*

Cox, Singapore. See *Pharmed, Singapore* and *Sime Darby, Singapore.*

Cox, UK. See *Actavis, UK.*

CP, Cz. See *Wockhardt, UK.*

CP, Israel. See *Propharm, Israel.*

CP Guojian, China. CP Guojian Pharmaceutical Co. Ltd, 399 Libing Road, Zhangjiang Hi-Tech Park, Shnaghai, 201203, China.
url: www.cpgj-pharm.com

CP Pharma, Hung. C.P. Pharma Gyogszerkereskedelmi Kft, Vasut u 11, 2040 Budaors, Hungary.

CP Pharma, Switz. CP Pharma (Schweiz) AG, Emil Frey-Strasse 85, Postfach 922, 4142 Münchenstein 1, Switzerland.
url: www.cppharma.ch

CP Pharmaceuticals, Hong Kong. See *Vantone, Hong Kong.*

CP Pharmaceuticals, Irl. See *Wockhardt, UK.*

CP Pharmaceuticals, Singapore. See *Medipharm, Singapore.*

CP Pharmaceuticals, UK. See *Wockhardt, UK.*

CP Protea, Austral. See *Sanofi-Aventis, Austral.*

CPB, Belg. See *Sanofi-Aventis, Belg.*

CPC, Hong Kong. See *Sheraton, Hong Kong.*

CPH, Port. Companhia Portuguesa Higiene, SA, Rua dos Bem Lembrados 141, Manique, 2645-471 Alcabideche, Portugal.

CPS Cito, Switz. CPS Cito Pharma Services GmbH, Forchstrasse 4 B, 8610 Uster, Switzerland.
url: www.citopharma.ch

CPU, China. China Pharmaceutical University (CPU) Pharmaceutical Co. Ltd, China.

Craig, NZ. See *Multichem, NZ.*

Cratus, India. Cratus Life Care, 5 Niraj Industrial Estate, Of Mahakali Caves Rd, Andheri East, Mumbai, India.

Craveri, Arg. Craveri S.A.I.C., Arengreen 830, 1405 Buenos Aires, Argentina.
url: www.craveri.com.ar

Crawford, Cz. See *Crawford, UK.*

Crawford, Irl. See *Crawford, UK.*

Crawford, Pol. See *Perffarma, Pol.*

Crawford, UK. Crawford Healthcare Ltd, Unit 1, Adams Court, Adams Hill, Knutsford, Cheshire, WA16 6BA, UK.
url: www.crawfordpharma.com

CreAgri, Malaysia. CreAgri International Sdn Bhd, Wisma Bu 8, Luh Bandar Utama, 47800 Petaling Jaya, Selangor, Malaysia.

Creative Brands, Austral. Creative Brands P/L, 30 Bando Road, Springvale, VIC 3171, Australia.

Creative Nutrition, Canad. Creative Nutrition Canada Corp., Parry Sound, Ontario, P2A 2X2, Canada.

Creekwood, USA. Creekwood Pharmaceutical Inc., 31 Inverness Center Parkway, Birmingham, Alabama, 35242, USA.
url: www.creekwoodpharma.com

Crefar, Port. Crefar, Lda, Rua da Madalena 171, 1149-032 Lisbon, Portugal.

Crelord, China. Crelord Pharmaceuticla Co. Ltd., 16 Longcheng Street, Economic and Technoloical Development ZOne, Taiyuan, Shanxi, 030032, China.
url: www.crelord.com

Creme d'Orient, Fr. Laboratoires Crème d'Orient, 81 rue de l'Amiral-Roussin, 75015 Paris, France.

Cremum, Hung. Cremum Pharma Kft, Nagy Lajos király útja 16-18, 1148 Budapest, Hungary.
url: www.cremum.hu

Creomulsion, USA. Cremulsion, P.O. Box 7329, Marietta, Georgia 30065, USA.
url: www.creomulsion.com

Crescent, India. Crescent Therapeutics Ltd, 4-7-11/4/B Crescent Towers, Raghavendra Nagar, Nacharam, Hyderabad 500 076, India.

Cresco, Neth. Cresco Pharma BV, Weerterveld 49, 6231 NC Meerssen, Netherlands.

CRI, Canad. CRI, 4 Innovation Drive, Dundas, Ontario, L9H 7P3, Canada.

CRI, Rus. 48 Central Research Institute Russia Defence Ministry, Kirov, Russia.

Crinex, Fr. Laboratoires Crinex, B.P. 337, 92541 Montrouge cdx, France.

Crinos, Hong Kong. See *Fandasy, Hong Kong.*

Crinos, Ital. Crinos S.p.A., Via Pavia 6, 20136 Milan (MI), Italy.
url: www.crinos.it

Crinos, Pol. See *Medagro, Pol.*

Cris Flower, Ital. Cris Flower International S.n.c., Via Livorno 61, 00162 Rome, Italy.
url: www.crisflower.com

Crisdy-Na, Philipp. Crisdy-Na Drug Corp., G-Seven Sons & Co Bldg, 5/F 646 Muelle de Binondo, Estraude St, Binondo, Manila, Philippines.

Cristalfarma, Ital. Cristalfarma S.r.l., Via San Giuseppe Cottolengo 15, 20143 Milan (MI), Italy.
url: www.cristalfarma.it

Cristalia, Braz. Cristalia Produtos Químicos Farmacêuticos Ltda, Av. Paoletti 363, 13970000 Itapira, SP, Brazil.
url: www.cristalia.com.br

Cristers, Fr. Les Laboratoires Cristers, 22 quai Gallién, 92150 Suresnes, France.
url: www.cristers.com

Criticare, India. Criticare Laborotories Pvt Ltd, 163/2 Reservoir St, Basovanagudi, Bangalore, 560 004, India.

CrocBloc, Canad. Croc Bloc Products Inc., Unit 1, 200 Zenway Blvd, Vaughan, Ontario, L4H 0L6, Canada.

Crocus, Gr. CROCUS, Aristotelous 79-91, 104 34 Athens, Greece.

Croda, UK. Croda Chemicals Europe, Cowick Hall, Snaith, Goole, North Humberside, DN14 9AA, UK.
url: www.croda.com

Croesus, Philipp. See *Medisys, Philipp.*

Croma, Austria. Croma-Pharma GmbH, Industriezeile 6, A-2100 Leobendorf, Austria.

Croma, Fr. Croma, Atrium Rive Gauche, 19 bd Paul-Vaillant-Couturier, 94854 Ivry-sur-Seine cdx, France.

Croma, Hong Kong. See *Treasure Mountain, Hong Kong.*

Croma, Norw. See *Bausch & Lomb, Swed.*

Croma, Philipp. Cromo Medic Inc., Alegrio Bldg, 2229 Don Chino Roces Ave, Makati City, Philippines.

Crombie, NZ. Crombie and Price, P.O. Box 121, Oamaru, New Zealand.
url: www.crombie-price.co.nz

Crookes, Irl. See *Boots Healthcare, Irl.*

Crookes, Neth. See *Boots Healthcare, Neth.*

Crookes Healthcare, UK. Crookes Healthcare Ltd, D6 Building, Nottingham, Nottinghamshire, NG90 6BH, UK.
url: www.crookes.co.uk

Crookes Laboratories, UK. See *Crookes Healthcare, UK.*

Croslands, India. See *Ranbaxy, India.*

Crosslands, India. See *Ranbaxy, India.*

Crown, Canad. Crown Chemical Products Inc., 6125 Netherhart Rd, Mississauga, Ontario, L5T 1G5, Canada.

Crown, S.Afr. Crown Laboratories Ltd, P.O. Box 100187, Moreleta Plazo 0167, South Africa.

Crown, USA. Crown Laboratories Inc., P.O. Box 1425, Johnson City, TN 37605, USA.
url: www.crownlaboratories.com

Crucell, Belg. See *Crucell, Neth.*

Crucell, Canad. Crucell Vaccines Canada, 19 Green Belt Drive, Toronto, Ontario, M3C 1L9, Canada.
url: www.crucellvaccinescanada.com

Crucell, China. Crucell, Office 1611 Wangjiao Plaza, 175 Yan'an Road East, Shanghai, 200002, China.
url: www.crucell.cn

Crucell, Denm. See *Crucell, Swed.*

Crucell, Fin. See *Crucell, Neth.*

Crucell, Hong Kong. See *Amedis, Hong Kong.*

Crucell, Hung. See *Crucell, Neth.*

Crucell, Irl. See *Crucell, Neth.*

Crucell, Neth. Crucell NV, P.O.Box 2048, 2301 CA Leiden, Netherlands.
url: www.crucell.com

Crucell, Norw. See *Crucell, Swed.*

Crucell, Pol. See *Sanofi Pasteur, Pol.*

Crucell, Spain. Crucell España SA, Paseo de la Castellana 163, 28046 Madrid, Spain.
url: www.crucell.es

Crucell, Swed. Crucell Sweden AB, Gunnar Asplunds Allé 16, 171 63 Solna, Sweden.
url: www.crucell.se

Crucell, Switz. Crucell Switzerland AG, Rehhagstrasse 79, 3018 Bern, Switzerland.
url: www.crucell.ch

Crucell, Thai. See *DKSH, Thai.*

Crucell, UK. Crucell UK Ltd, First Floor Unit E, Home Farm, The Avenue, Apperley Bridge, Bradford, West Yorkshire, BD17 7QX, UK.
url: www.crucell.co.uk

Crucell, USA. Crucell, 4216 Ponce de Leon Blvd, Coral Gables, FL 33146, USA.
url: www.crucell.com

Cruciani, Ital. Cruciani - Prodotti Crual Srl, Via Edoardo Scarfoglio 5, 00159 Rome (RM), Italy.
url: www.crual.it

Cruise, India. Cruise Pharmacia Pvt Ltd, SCF-47 Rishi Nagar Market, Ludhiana 141 001, India.

Cruz, Spain. Fernandez de la Cruz, Crta Sevilla Malaga Km 5.6, Alcalá de Guadaira, 41500 Seville, Spain.

Cryopharma, Mex. Cryopharma, Pizzord y Salud, KM 22.5 Carretera Guadalajara Morelia, Jalisco Zuniga, 45640 Guadalajara, Jalisco, Mexico.

Crystaal, Canad. See *Biovail, Canad.*

CS, Fr. Laboratoires CS Dermatologie, 35 rue d'Artois, 75008 Paris, France.

CS, Hong Kong. See *Keller, Hong Kong.*

CS, Port. CS Portugal, Lda, Rua João de Deus 32, Venda Nova, 2700-488 Amadora, Portugal.

CS, Singapore. See *BlissMed, Singapore.*

CSC, Austria. CSC Pharmaceuticals Handels-GmbH, Gewerbestrasse 18-20, A-2102 Bisamberg, Austria.

CSC, Cz. CSC Praha sro, Pernerová 32/10, 180 00 Prague 8, Czech Republic.

CSC, Ger. CSC Pharmaceuticals Germany GmbH, Sachsentor 6, 21029 Hamburg, Germany.
url: www.csc-pharma.de

CSC, Hung. CSC Pharmaceuticals Llc Magyarországi Kereskedelmi Képviselete, Kakukk u 43, 1121 Budapest, Hungary.

CSC, Pol. See *Medagro, Pol.*

CSC, Rus. CSC Ltd, Kashirskoe Highway 23, 115478 Moscow, Russia.

CSL, Arg. CSL Behring SA, Fray Justo Sarmiento 2350, Pso 4 Edif 2B, 1636 Olivos, Buenos Aires, Argentina.

CSL, Austral. CSL Ltd, 45 Poplar Road, Parkville, VIC 3052, Australia.
url: www.csl.com.au

CSL, Austria. CSL Behring GmbH, Altmannsdorfer Strasse 104, A-1121 Vienna, Austria.

CSL, Belg. CSL Behring, Technologielaan 13, 3001 Leuven, Belgium.
url: www.cslbehring.be

CSL, Braz. CSL Behring Com. de Prods. Farmacêuticos Ltda, Rua Olimpíadas 194, 5 andar, 04551-000 Vila Olimpia São Paulo, Brazil.

CSL, Canad. CSL Behring Canada Inc., 1460 44 Metcalfe St, Ottawa, Ontario, K1P 6L5, Canada.

CSL, China. CSL Behring, Plaza 66, 1366 Nanjing Rd West, Shanghai 160506, China.
url: www.cslbehring.com

CSL, Cz. See *CSL, Ger.*

CSL, Denm. CSL Behring ApS, Lyngby Hovedgade 70B, 1. tv, 2800 Lyngby, Denmark.
url: www.cslbehring.com

CSL, Fin. See *CSL, Ger.*

CSL, Fr. CSL Behring SA, 44 rue Cambronne, 75015 Paris, France.

CSL, Ger. CSL Behring GmbH, Philipp-Reis-Strasse 2, 65795 Hattersheim am Main, Germany.
url: www.cslbehring.de

CSL, Gr. CSL Behring Ltd, Chatzigianni Mexi 5, 115 28 Athens, Greece.

CSL, Hung. CSL Behring, Hungary.

CSL, Indon. See *Dexa, Indon.*

CSL, Irl. See *CSL, UK.*

CSL, Israel. See *CSL, USA.*

CSL, Ital. CSL Behring S.p.A., P.le S. Türr 5, 20149 Milan (MI), Italy.

CSL, Jpn. CSL, Inui Kachidoki Bldg 1-13-1, Kachidoki Chuo-ku, Tokyo 104-0054, Japan.
url: www.csl.com

CSL, Malaysia. See *United Italian, Malaysia.*

CSL, Mex. CSL Behring SA de CV, Blvd Manuel Avila Camacho 36, P 14 T.Esm, 11010 Miguel Hidalgo Lomas de Chapulte, Mexico Df, Mexico.

CSL, Neth. See *CSL, Ger.*

CSL, Norw. See *CSL, Swed.*

CSL, NZ. CSL Biotherapies (NZ) Ltd, 666 Great South Rd, Central Park, Auckland 6, New Zealand.
url: www.csl.com.au

CSL, Philipp. See *Zuellig, Philipp.*

CSL, Pol. See *Imed, Pol.*

CSL, Port. See *CSL, Spain.*

CSL, Singapore. See *United Italian, Singapore.*

CSL, Spain. CSL Behring, Av. Paisos Catalans 34, Esplugues de Llobregat, Barcelona 08950, Portugol.
url: www.cslbehring.es

CSL, Swed. CSL Behring AB, Berga Backe 2, Danderyd, Sweden.
CSL, Switz. CSL Behring (Schweiz) AG, Herostrasse 7, 8048 Zürich, Switzerland.
url: www.cslbehring.com
CSL, Thai. See *Zuellig, Thai.*
CSL, UK. CSL Behring UK Ltd, Hayworth House, Market Place, Haywards Heath, West Sussex, RH16 1DB, UK.
url: www.cslbehring.co.uk
CSL, USA. CSL Behring, P.O. Box 61501, 1020 First Ave, King of Prussia, PA 19406, USA.
url: www.cslbehring-us.com
CSL Biotherapies, Austral. CSL Biotherapies, 45 Poplar Rd, Parkville, Vic 3052, Australia.
url: www.cslbiotherapies.com.au
CSL Biotherapies, Ger. CSL Biotherapies GmbH, Emil-von-Behringstrasse 76, 35401 Marburg, Germany.
CSL Biotherapies, Hong Kong. CSL Biotherapies Asia Pacific Ltd, Unit 1801-1804, 18/F K Wah Ctr, 191 Java Rd, North Point, Hong Kong.
url: www.csl.com.au
CSL Biotherapies, Irl. See *CSL Biotherapies, Ger.*
CSL Biotherapies, Neth. See *CSL Biotherapies, Ger.*
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CSL-Novo, Austral. See *Novo Nordisk, Austral.*
CSO Pharmitalia, Ital. CSO Pharmitalia Contratc Sales Organization Srl, Via S Rita da Cascia 33, 20143 Milano (MI), Italy.
url: www.csopharmitalia.com
CSP, Belg. CSP Benelux SA, chemin de la Reconversion 19, 7110 Houdeng-Goegnies, Belgium.
url: www.csp-epl.com
CSP, Fr. CSP, 76 av. du Midi, B.P. 77, 63802 Cournon cdx, France.
url: www.csp-epl.com
CSPC, China. CSPC Pharmaceutical Group Ltd, 276 West Zhangshan Rd, Shijiazhuang City 050051, China.
url: www.e-cspc.com
CT, China. See *Jiwa, China.*
CT, Cz. See *CT, Ger.*
CT, Denm. See *CT, Ger.*
CT, Ger. CT-Arzneimittel GmbH, Lengeder Str. 42A, 13407 Berlin, Germany.
url: www.ct-arzneimittel.de
CT, Hung. See *CT, Ital.*
CT, Irl. See *CT, Ger.*
CT, Ital. C.T., Laboratorio Farmoceutico S.r.l., Via Dante. Alighieri 71, 18038 San Remo (IM), Italy.
url: www.labct.it
CT, Neth. See *CT, Ger.*
CT, Philipp. See *PharmAsia, Philipp.*
CT, Pol. See *CT, Ger.*
CT, Port. See *CT, Ger.*
CT, Rus. See *Ratiopharm, Rus.*
CTEX, USA. See *Andrx, USA.*
CTI, Denm. See *CTI, UK.*
CTI, Israel. See *CTS, Israel.*
CTI, Neth. See *Cell Therapeutics, UK.*
CTI, Norw. See *CTI, UK.*
CTI, Spain. See *CTI, UK.*
CTI, UK. CTI Life Sciences, BioPark, Broadwater Rd, Welyn Garden City, Hertfordshire, AL7 3AX, UK.
CTRS, Fr. Laboratoires CTRS, 69 rue d'Aguesseau, 92100 Boulogne Billancourt, France.
CTS, Hong Kong. See *DKSH, Hong Kong.*
CTS, Israel. C.T.S. Chemical Industries Ltd, 4 Haharosh St, P.O.Box 10, Hod-Hasharon 45240, Israel.
url: www.cts.co.il
CTS, Rus. See *Lefnir, Rus.*
Cubist, Israel. See *Medison, Israel.*
Cubist, USA. Cubist Pharmaceuticals, 65 Hayden Ave., Lexington, MA 02421, USA.
url: www.cubist.com
Cubit, India. Cubit Healthcare, 85 Chetan Market, Nr Sarangpur Gate, Ahmedabad 380 001, India.
Cuccess, China. Cuccess Pharmaceutical Co. Ltd, 20 Xingong St, Nanjing Technological Development Zone, Nanjing, Jiangsu, 210038, China.
url: www.cuccess.com
Cui Sheng, China. Cui Sheng Pharmaceutical Co. Ltd, Xi'an, China.
Cullen & Davison, Irl. Cullen & Davison Ltd, Killenaule Rd, Fethard, Co Tipperary, Ireland.
Cullen & Davison, UK. See *Cullen & Davison, Irl.*
Culver, Austral. Alberto Culver (Aust) P/L, P.O. Box 253, Parramatta, NSW 2150, Australia.
Culver, Canad. See *Culver, USA.*
Culver, USA. Alberto-Culver Co., 2525 Armitage Ave., Melrose Park, IL 60160, USA.
url: www.alberto.com
Cumberland, USA. Cumberland Swan Holdings Inc., 1 Swan Drive, Smyrna, TN 37167, USA.
url: www.cumberlandswan.com
Cumino, Switz. Cumino GmbH, Switzerland.
Cupal, Irl. See *SSL, UK.*
Cupal, UK. See *SSL, UK.*
Cuprocept, S.Afr. Cuprocept SA, P.O. Box 400, New Germany 3620, South Africa.
Curaden, Ital. Curaden Healthcare S.r.l., Via B. Lanino 42, 20147 Saronno (VA), Italy.
url: www.cureden.it
Curagita, Cz. See *Curagita, Ger.*
Curagita, Ger. Curagita AG, Ringstr. 19 B, 69115 Heidelberg, Germany.
url: www.curagita.com
Curamed, Austria. See *DeltaSelect, Ger.*
Curamed, Ger. See *DeltaSelect, Ger.*
Curamed, Switz. See *Opopharma, Switz.*
Curamed, Thai. See *SPB, Thai.*
Curaprox, UK. Curaprox UK Ltd, Unit 11, Harvard Industrial Estate, Kimbolton, Cambridgeshire, PE23 0NJ, UK.
Curarina, Ger. See *Harras-Curarina, Ger.*
Curasan, Austria. See *Curasan, Ger.*
Curasan, Ger. curasan AG, Lindigstr. 4, 63801 Kleinostheim, Germany.
url: www.curasan.de
Curasan, Hung. See *Pharma-Marketing, Hung.*
Curatek, USA. See *3M, USA.*
Curatio, India. Curatio Healthcare Pvt Ltd, 5 Kasturi Estates, 1st Street, Poes Garden Alwarpet, Chennai 600 018, India.
url: www.curatiohealthcare.com
Curatis, Ger. Curatis Pharma GmbH, Karl-Wiechert-Allee 76, 30625 Hannover, Germany.
url: www.curatis-pharma.de
Cure, Israel. See *Promedico, Israel.*
Cure & Care, India. Cure & Care Biotec Pvt Ltd, A Wing-207 Seema Niwas, Tulinj Road, Nalasopara (E), Thane 401 209, India.
Cure Quick, India. Cure Quick, 20/3 HSIDC, Kamal 132 001, India.
Curewell, India. Curewell Drugs & Pharmaceuticals Pvt Ltd, 810 Chiranjiv Tower, 43 Nehru Place, New Delhi, 110 019, India.
Curex, India. Curex Pharma Products, D-97 98 Basement, Lajpat Nagar, New Delhi 24, India.
Curex, Philipp. See *Curex, India.*
Curtis, Pol. Curtis Healthcare Sp. z.o.o., ul. Żeromskiego 9, 60-544 Poznań, Poland.
url: www.curtish.com.pl
Cusi, Hong Kong. See *Alcon, Hong Kong.*
Cusi, Singapore. See *Pharmaforte, Singapore.*
Cusi, Spain. See *Alcon Cusi, Spain.*
Cusi, UK. See *Pliva, UK.*
Cusi, Venez. See *Leti, Venez.*
Cutis, USA. Cutis Pharma Inc., 68 Cummings Park, Woburn, MA 01801, USA.
url: www.cutispharma.com
Cutter, Canad. See *Bayer, Canad.*
Cutter, Israel. See *Perrigo, Israel.*
Cutter, UK. See *Bayer, UK.*
Cutter, USA. See *Bayer, USA.*
Cuxson, Gerrard, Canad. See *Cuxson, Gerrard, UK.*
Cuxson, Gerrard, Irl. See *Cuxson, Gerrard, UK.*
Cuxson, Gerrard, UK. Cuxson, Gerrard & Co. Ltd, 125 Broadwell Rd, Oldbury, Warley, West Midlands, B69 3BF, UK.
url: www.cuxsongerrard.com
Cuxson, Israel. See *Cuxson, Gerrard, UK.*
CV Directo, Mex. CV Directo, Escape No 10, Fracc. Industrial Alce Blanco, 53370 Naucalpan de Juarez, Mexico.
Cyanamid, Cz. See *Wyeth, Cz.*
Cyanamid, Ger. See *Pfizer, Ger.*
Cyanamid, Ital. See *Wyeth Lederle, Ital.*
Cyanamid, Spain. See *Wyeth, Spain.*
Cyathus, Austria. Cyathus Exquirere Pharmaforschungs GmbH, Rudolfsplatz 2/8, 1010 Vienna, Austria.
url: www.cyathus.eu
Cyathus, Cz. See *Cyathus, Austria.*
Cyathus, Denm. See *Cyathus, Austria.*
Cyathus, Fin. See *Cyathus, Austria.*
Cyathus, Hung. See *Cyathus, Austria.*
Cybele, Philipp. See *Davenben, Philipp.*
Cyclin, USA. Cyclin Pharmaceuticals Inc., 1289 Deming Way, Madison, WI 53717, USA.
url: www.womenshealth.com
Cyclomedica, Denm. See *Cyclomedica, Irl.*
Cyclomedica, Fin. See *Cyclomedica, Irl.*
Cyclomedica, Irl. Cyclomedica Europe, Ulysses House, Foley St, Dublin, Ireland.
url: www.cylopharm.com
Cyclomedica, Neth. See *Cyclomedica, Irl.*
Cyclomedica, Port. See *Cyclomedica, Irl.*
Cyclomedica, Spain. See *Cyclomedica, Irl.*
Cyclopharma, Fr. Cyclopharma Laboratoires, Biopôle Clermont-Limagne, 63360 Saint Beauzine, France.
url: www.cyclopharma.com
Cyclos, Gr. Cyclos AE TETVA & N, Aristotelous 38, 104 33 Athens, Greece.
Cyclotron, Neth. BV Cyclotron VU, De Boelelaan 1081, 1081 HV Amsterdam, Netherlands.
Cymbiotics, Malaysia. See *United Italian, Malaysia.*
Cynacon, USA. See *Ocusoft, USA.*
Cynergen, Indon. Cynergen Health, Indonesia.
Cyno, India. Cyno Pharmaceuticals Ltd, C-50 Preet Vihar, New Delhi 110 092, India.
url: www.cynoindia.com
Cyno Sure, Philipp. Cyno Sure Healthcare Inc., 3rd Floor The Spa Bldg, 80 E Rodriguez Jr Ave, Libis Quezon City, Philippines.
Cynone, Port. See *Remedica, Cyprus.*
Cyntfarm, Pol. Cyntfarm Sp. z.o.o., ul. Grunwaldzka 27, 05-800 Pruszków, Poland.
url: www.cyntfarm.com.pl
Cypress, USA. Cypress Pharmaceutical, 135 Industrial Blvd, Madison, MS 39110, USA.
url: www.cypressrx.com
Cypros, USA. See *Questcor, USA.*
Cytel, USA. See *Epimmune, USA.*
CytoChemia, Ger. CytoChemia AG, Im Bürgerstock 7, 79241 Ihringen, Germany.
url: www.cytochemia.de
CytoChemia, Switz. CytoChemia GmbH, Riedstrasse 1, 6330 Cham, Switzerland.
Cytogen, Cz. See *EUSA, USA.*
Cytogen, Israel. See *Megapharm, Israel.*
Cytogen, USA. See *EUSA, USA.*
Cytosol, Israel. See *Tzamal, Israel.*
Cytosol, USA. Cytosol Ophthalmics, 1325 William White Pl. NE, Lanoir, NC 28645, USA.
url: www.cytosol.com
Cytyc, Irl. See *Screenlink, Irl.*
CZ, Cz. CZ Pharma sro, Zeleny pruh 95/97, 140 00 Prague 4, Czech Republic.
Czet, Pol. Czet Pharma Inc. Sp. zo.o. Przedstawicielstwo w Polsce, ul. Belwederska 26/30, 00-585 Warsaw, Poland.
url: www.czetpharma.com.pl
Cziher, Hung. Cziher Hungary Kft, Kosztolányi D tér 8, 1114 Budapest, Hungary.
D&A Pharma, Fr. D&A Pharma SAS, 79 rue de Miromesnil, 75008 Paris, France.
D&G, Ital. D&G S.r.l., Via Amati 16, 51100 Pistoia (PT), Italy.
D & C Mobility, Canad. D & C Mobility Solutions Inc., 10945 167a Ave N W, Edmonton, Alberta, T5X 2Z1, Canada.
D & M, Chile. D & M Pharma SA, Los Conquistadores 2178, Providencio, Santiago, Chile.
DA, Neth. DA Retailgroep BV, Benjamin Franklinstraat 2, 8013 NC Zwolle, Netherlands.
Da Heng, China. Da Heng Pharmaceutical Co. Ltd, Xi'an, China.
Da Vinci, Canad. See *Foodscience, USA.*
Da Zhong, China. Da Zhong Pharmaceutical Co Ltd, Harbin, China.
Dabur, Hong Kong. See *Controlled Medications, Hong Kong.*
Dabur, India. Dabur Pharmaceuticals Ltd, Kaushambi, Ghaziabad 201 010, India.
url: www.dabur.com
Dabur, Rus. See *Pfizer, Rus.*
Dabur, Thai. See *Bioscience, Thai.*
Dade, China. Dade Pharmaceutical Group Co. Ltd, Zhejiang, China.
Dadeli, China. Dadeli Biopharmaceutical Co. Ltd, Lanzhou, Gansu, China.
Dadongfang, China. Dadongfang Pharmaceutical Co. Ltd, Anhui, China.
Dae Han New, Thai. See *Masu, Thai.*
Daehan, Singapore. See *Uni, Singapore.*
Daewon, China. See *Daewon, Kor.*
Daewon, Hong Kong. See *Ebewe, Hong Kong.*
Daewon, Kor. Daewon Pharm, 299-3 Yongdap Dong, Seongdong Gu, Seoul, Korea.
url: www.daewonpharm.com
Daewon, Philipp. See *New Marketlink, Philipp.*
Daewon, Singapore. See *MD, Singapore.*
Daewoo, Philipp. See *PharmAsia, Philipp.*
Daewoo, Thai. See *Pharmaland, Thai.*
Daewoong, China. Daewoong Pharmaceutical Co. Ltd, China.
url: www.daewoong.com
Daewoong, Philipp. See *Metro, Philipp* and *Qualimed, Philipp.*
Daewoong, Singapore. See *Pharmaforte, Singapore.*
Daewoong, Thai. Daewoong Pharmaceutical (Thailand) Co. Ltd, 209 K Tower 9 Fl Unit 4/2-1, 21 Sukhumvit Rd, Asoke Klongtoey-Nua, Bangkok 10110, Thailand.
url: www.daewoong..com
Daffohils, India. Daffohils Pharma Pvt Ltd, F/109-110, UPSIDC Industrial Area Selaqui, Dehradoon UP, India.
Dafo, China. Dafo Pharmaceutical Co. Ltd, Aoshida Rd, Futian, Shenzhen, Guangdong, 518049, China.
url: www.szdaphne.com
Dafra, Belg. Dafra Pharma NV, Slachthuisstraat 30/7, 2300 Turnhout, Belgium.
url: www.dafra.be
Daiichi, Denm. See *Nycomed, Denm.*
Daiichi, Hong Kong. See *Hong Kong Medical, Hong Kong.*
Daiichi, Indon. See *Kalbe, Indon* and *Otto, Indon.*
Daiichi, Jpn. Daiichi Pharmaceutical Co. Ltd, 1-8 Koami-cho Nihonbashi, Chuo-ku, Tokyo 103-8541, Japan.
url: www.daiichipharm.co.jp
Daiichi, Malaysia. See *Kyowa, Malaysia.*
Daiichi, Singapore. See *Kyowa, Singapore.*
Daiichi, Thai. See *Daiichi Sankyo, Thai.*
Daiichi, USA. Daiichi Pharmaceutical Corp., 11 Phillips Parkway, Montvale, NJ 07645-1810, USA.
url: www.daiichius.com
Daiichi Sankyo, Austria. Daiichi Sankyo Austria GmbH, Effingergasse 21, A-1160 Vienna, Austria.
Daiichi Sankyo, Belg. Daiichi Sankya Belgium NV SA, Parc Scientifique Fleming, Rue Fonds Jean Paques 5, 1348 Louvain-la-Neuve, Belgium.
url: www.daiichi-sankyo.be
Daiichi Sankyo, China. Daiichi Sankyo Pharmaceutical (Shanghai) Co. Ltd, Curie Rd 500, Pudong New Area, Zhangjiang Hi-Tech Park, Shanghai 201203, China.
url: www.daiichisankyo-sh.com.cn
Daiichi Sankyo, Denm. See *Daiichi Sankya, Ger.*
Daiichi Sankyo, Fin. See *Daiichi Sankyo, Ger.*
Daiichi Sankyo, Fr. Daiichi Sankyo France SAS, 1 rue Eugène-et-Armand-Peugeot, 92500 Rueil-Malmaison, France.
url: www.daiichi-sankyo.fr
Daiichi Sankyo, Ger. Daiichi Sankyo Deutschland GmbH, Zieltstattstrasse 48, 81379 Munich, Germany.
url: www.daiichi-sankyo.de
Daiichi Sankyo, Gr. See *Daiichi Sankyo, Ger.*
Daiichi Sankyo, Hong Kong. See *Hong Kong Medical, Hong Kong* and *Tai Tong, Hong Kong.*
Daiichi Sankyo, Hung. See *Daiichi Sankyo, Ger.*
Daiichi Sankyo, Irl. Daiichi Sankyo Ireland Ltd, 301 3 Lake Drive, Citywesy Business Campus, Dublin 24, Ireland.
Daiichi Sankyo, Ital. Daiichi Sankyo Italia S.p.A., Via Paolo di Dono 73, 00142 Rome (RM), Italy.
Daiichi Sankyo, Jpn. Daiichi Sankyo Co. Ltd, 3-5-1 Hihombashi-Hancho, Chuo-ku, Tokyo 103-8426, Japan.
url: www.daiichisankyo.co.jp
Daiichi Sankyo, Malaysia. See *First Pharmoceutical, Malaysia.*
Daiichi Sankyo, Mex. See *Ranbaxy, Mex.*
Daiichi Sankyo, Neth. Daiichi Sankyo Nederland BV, Wilgenlaan 5, 1161 JK Zwanenburg, Netherlands.
Daiichi Sankyo, Norw. See *Nycomed, Norw* and *Weifa, Norw.*
Daiichi Sankyo, Port. Daiichi Sankyo Portugal Lda, Lagoas Park, Edificio 11, 2740-270 Porto Salvo, Portugal.
Daiichi Sankyo, Singapore. See *Kyowa, Singapore.*
Daiichi Sankyo, Spain. Daiichi Sankyo España, C/Acanto 22, 28045 Madrid, Spain.
url: www.daiichi-sankyo.es
Daiichi Sankya, Switz. Daiichi Sankyo (Schweiz) AG, Gewerbestrasse 16, 8800 Thalwil, Switzerland.
url: www.daiichi-sankyo.ch
Daiichi Sankyo, Thai. Daiichi Sankyo (Thailand) Ltd, 10 Fl, Boonmitr Building, 138 Silom Rd, Bangkok 10500, Thailand.
Daiichi Sankyo, UK. Daiichi-Sankyo UK Ltd, Chiltern Place, Chalfont Park, Gerrards Cross, Buckinghamshire, SL9 0BG, UK.
url: www.daiichi-sankyo.co.uk
Daiichi Sankyo, USA. Daiichi Sankya, Two Hilton Court, Parsippany, NJ 07054, USA.
url: www.sankyopharma.com
Dainippon, Jpn. Dainippon Sumitomo Pharmaceutical Co. Ltd, 2-6-8 Dosho-machi, Chuo-ku, Osaka 541-8524, Japan.
url: www.ds-pharma.co.jp
Dainippon, Philipp. See *Eisai, Philipp* and *Zuellig, Philipp.*
Daito, Thai. See *Berli Jucker, Thai.*
Daker Farmasimes, Spain. See *Almirall, Spain.*
Dakota, Cz. See *Dakota, Fr.*
Dakota, Fr. Laboratoires Dakota Pharm, 22 av. Galilée, 92350 Le Plessis-Robinson, France.
Dakryon, USA. See *Medco, USA.*
Daksh, India. Daksh, S.C.O. No. 96 1st Floor, Sector-5, Near Vatika, Panchkula, Haryana 134 112, India.
url: www.dakshpharma.com
Daleco, Neth. Daleco Pharma BV, Polderdijk 3, 4157 JE Enspijk, Netherlands.
Dales, Hong Kong. See *Swiss Worldwide, Hong Kong.*
Dalim, Thai. See *Masu, Thai.*
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Dalkhimfarm, Rus. See *Masterlek, Rus.*
Dalkhimfarm, Ukr. See *Rosfarmak, Ukr.*
Dallas, Arg. Lab. Dallas S.A., Av. Cabildo 86, Piso 7 Of.702/4, 1426 Buenos Aires, Argentina.
Dallas, India. Dallas Pharmaceuticals, 602 'B' Wing, Manubhai Tower, Sayajigunj, Vadodaro 390 005, India.
Dallas Burston Ashbourne, Irl. See *Dallas Burston Ashbourne, UK.*
Dallas Burston Ashbourne, UK. Dallas Burston Ashbourne Ltd, The Rectory, Braybrooke Rd, Arthingworth, Market Harborough, Leicestershire, LE16 8JT, UK.
url: www.dbashbourne.com
Dalmer, China. Laboratorios Dalmer SA, China.
Dalmia, India. Dalmia Healthcare Ltd, 8A Atma Ram House, 1 Tolstoy Marg, New Delhi 110 001, India.
url: www.dalmiahealth.com
Dal-Vita, Austral. Dal-Vita Products Australia P/L, P.O. Box 477, Manly, NSW 1165, Australia.
Damor, Ital. Farmaceutici Damor S.p.A., Via E Scaglione 27, 80145 Naples (NA), Italy.
Damvergis, Gr. Damvergis IA & Co, P.O. Box 3867, 102 10 Athens, Greece.
Danbury, USA. See *Watson, USA.*
Danco, USA. Danco Laboratories, P.O. Box 4816, New York, NY 10185, USA.
url: www.earlyoptianpill.com
Dandong, China. Dandong Pharmaceutical Co. Ltd, 64 Xingqi Rd, Zhenxing, Dondong, Liaoning, 118000, China.
Danes, Chile. See *Grunenthal, Chile.*
Daniel, Canad. Dr Daniel Products, 12 Wynn Rd, Willowdale, Ontario, M2R 1S6, Canada.
Daniel Pasteur, India. Espana Cura Daniel Pasteur, Sco. 317, Sector 38D, Chandigarh 160 014, India.
Daniels, Irl. See *Allphar, Irl.*
Daniels, USA. See *King, USA.*
Danipharm, China. See *Danipharm, Hong Kong.*
Danipharm, Hong Kong. Danipharm Medic Team (Asia Pacific) Ltd, Unit 705, Sun Cheong Industrial Building, 1 Cheung Shun St, Kowloon, Hong Kong.
url: www.danipharm.com
Dankos, Indon. Dankos Indonesia PT, Enseval Bldg, Jl Letjend Suprapto, Cempaka Putih, 10510 Jakarta, DKI Jaya, Indonesia.
Dankos, Malaysia. See *Zyfas, Malaysia.*
Dankos, Philipp. See *Lakeside, Philipp.*
Dankos, Singapore. See *Zyfas, Singapore.*
Danlex, Philipp. Danlex Research Lab. Inc., 701 Bayview Intl Tower II, Roxas Blvd, Manila, Philippines.
Danone Dumex, Malaysia. Donone Dumex (Malaysia) Sdn Bhd, Level 8 & 9 The Gardens South Tower, Mid Valley City, Lingkaran Syed Putra, 59200 Kuala Lumpur, Malaysia.
url: www.dumex.com.my
Danone Dumex, Singapore. See *KWH, Singapore.*
Danpoc, Indon. Danpac Pharma PT, Komplek Apartemen Permata Executive Lt 2, Jl Pos Pengumben, Raya Kelapa Dua, Jakarta Barat 11550, Indonesia.
url: www.danpacpharma.com
Dansk, Israel. See *Promedico, Israel.*

Dansk Droge, Denm. Dansk Droge A/S, Industrigrenen 10, 2635 Ishøj, Denmark.
Dansk Droge, Pol. See *Axellus, Pol.*
Dansk Droge, Rus. See *Sanofi-Aventis, Rus.*
Danval, Spain. See *Servier, Spain.*
Dao-Pharm, Ukr. Dao-Pharm, ul. Kikvidze 1/2, 01103 Kiev, Ukraine.
url: www.daopharm.ru
Dapha, Philipp. See *New Smart, Philipp.*
Daqing, China. Daqing Pharmaceutical Co. Ltd, 12 Zhongqiao Rd, Sa'ertu, Daqing, heilongjiang, 163001, China.
Daquimed, Port. Daquimed SA, Rua Dr. Afonso Cordeiro 194 - 1, 4450-001 Matosinhos, Portugal.
url: www.daquimed.com
Dar Al Dawa, Hong Kong. See *Primal, Hong Kong.*
Dara, USA. Dara BioSciences Inc., 8601 Six Forks Rd, Suite 160, Raleigh, NC 27615, USA.
url: www.darabio.com
Darci, Belg. See *UCB, Belg.*
Darci, Fr. See *UCB Healthcare, Fr.*
Darci, Gr. Darci Pharma (Hellas) AE, Acharnon 36, 145 61 Kifissia, Greece.
Dari, China. Dari Biopharmaceutical Co. Ltd, Guangdong, China.
Darier, Mex. Laboratorios Dermatologicos Darier S.A. de C.V., Av. Insurgentes sur 3579 Torre 3, Piso 8, M Hidalgo Lo Joyo Olimpica, 14020 Mexico D.F., Mexico.
url: www.darier.com.mx
Dario Correia, Port. Dario Correia, Lda, Rua Duque de Palmela 25, 1250 Lisbon, Portugal.
Darnica, Pol. See *Alfpol, Pol.*
Darnitsa, Ukr. Darnitsa, Borispolsky St 13, 02093 Kiev, Ukraine.
Daro, Neth. See *GSK, Neth.*
Darou Pakhsh, Rus. Darou Pakhsh Moscow, Dmitriya Ulyanova St 16/2, of. 69, 117292 Moscow, Russia.
Darrow, Braz. Darrow Laboratórios S.A., Rua Marques de Olinda 69, 22251-040 Rio de Janeiro, RJ, Brazil.
Dartmouth, USA. Dartmouth Pharmaceuticals Inc., 38 Church Ave, Wareham, MA 02751, USA.
url: www.ilovemynails.com
Darvys, Philipp. Darvys Pharma Inc., 5/F Semicon Ctr Bldg, 50 Marcos Highway, Pasig City, Philippines.
Darya-Varia, Indon. Darya-Varia Laboratoria PT, Talavera Office Park, 8th-10th Floor, Jl Letjend TB Simatupang No 22-26, Jakarta 12430, Indonesia.
url: www.darya-varia.com
DAST, Gr. DAST Biotech Pharm Ltd, Larissa 10, 153 51 Pallini, Greece.
Datla, India. Datla Laboratories, 4-1-1-3/6 Flat No GS-5, Kalyan Kutir Apartment C-Block, Nacharam, Hyderabad 560 076, India.
Daudt, Braz. Laboratório Daudt Oliveira Ltda, Rua Simões da Mota 57, 21540-100 Rio de Janeiro, RJ, Brazil.
url: www.odontis.com.br
Dava, USA. Dava Pharmaceuticals Inc., Fort Lee, NJ 07024, USA.
url: www.davapharma.com
Davenben, Philipp. Davenben Enterprises Corp., Unit 1907, 19/F Jollibee Plaza, F Ortigas Jr Ave (formerly Emerald Ave), Ortigas Ctr, Pasig City, Philippines.
Davi, Port. Dávi Farmacêutica, Lda, Estrada do Barrosa, Elospark, Arm. 8, Algueirão, 2725-193 Mem Martins, Portugal.
David, India. Albert David Ltd, 15 Chittaranjan Ave, Kolkata 700 072, India.
url: www.albertdavidindia.com
Davigo, Belg. See *Vitapantol, Belg.*
Davis, Spain. See *Pfizer, Spain.*
Davis & Geck, UK. See *Wyeth, UK.*
Davis & Geck, USA. See *Kendall, USA.*
Davos, Singapore. Davos Life Science Pte Ltd, 16 Tuas South St 5, S 637795, Singapore.
url: www.davoslife.com
Davur, Irl. See *Davur, Spain.*
Davur, Spain. Davur S.L., Teide 4, Parque Empresarial la Marina, San Sebastian de los Reyes, 28700 Madrid, Spain.
url: www.davur.com
Dawnrays, China. Suzhou Dawnrays Pharmaceutical Co Ltd, 22 Tianling Rd, Wuzhong Economical Development Zone, Suzhou, Jiangsu, China.
url: dawnrays.en.echinachem.com
Dawnrays, Hong Kong. See *CNW, Hong Kong.*
Dawnrays, Rus. See *Dawnrays, China.*
Daxin, China. Daxin Pharmaceutical Co. Ltd, 22 Chuangzao Road, Beibei, Chongqing, 400700, China.
url: www.daxinphorm.com
Daxing, China. Daxing Pharmaceutical Co. Ltd, Changchun, China.
Dayang, China. Yantai Dayang Pharmaceutical Co. Ltd., Yantai, China.
Daying, China. Daying Pharmaceutical Co. Ltd, Kaifeng, Henan, China.
Dayinhaiyang, China. Dayinhaiyang Pharmaceutical Co. Ltd, Room 1701 Floor 17, Zhubang 2000 Business Centre, 98 Balizhuang Xili, Chaoyang, Beijing, China.
url: www.dynemed.com.cn
Dayton, USA. Dayton Laboratories Inc., 7760 NW 56th St, Miami, FL 33166, USA.
Dayuan, China. Dayuan Pharmaceutical Co. Ltd, China.
DB, Fr. Laboratoires DB Pharma, 1 bis, rue du Cdt-Rivière, 94210 La Varenne-St-Hilaire, France.
DB, Switz. See *Uhlmann-Eyraud, Switz.*
DBL, Austral. See *Mayne, Austral.*
DBL, Indon. See *Tempo Scan Pacific, Indon.*
DBL, NZ. See *Baxter, NZ.*
DBL, Thai. See *Indochina Healthcare, Thai.*
DBV, Fr. DBV Technologies, 88 av du Général-Leclerc, 92100 Boulogne-Billancourt, France.
url: www.diallertest.com
url: www.dbv-technologies.com
DDD, Austria. See *delta pronatura, Ger.*
DDD, Hong Kong. See *Trinity, Hong Kong.*
DDD, Irl. See *DDD, UK.*
DDD, Israel. See *Chemipal, Israel.*
DDD, Malaysia. See *People's, Malaysia.*
DDD, Singapore. See *Indrugco, Singapore.*
DDD, UK. DDD Ltd, 94 Rickmansworth Rd, Watford, Hertfordshire, WD18 7JL, UK.
url: www.dddgroup.co.uk
DDSA, Neth. See *DDSA Pharmaceuticals, UK.*
DDSA Pharmaceuticals, UK. DDSA Pharmaceuticals Ltd, 310 Old Brompton Rd, London, SW5 9JQ, UK.
De Bardo, Fr. Les Produits de Bardo, 22 rue du Buisson-aux-Fraises, 91300 Massy, France.
url: www.debardo.com
De la Mer, Fr. Laboratoire de la Mer, Parc Technopolitain Atalante, 35419 Saint-Malo, France.
url: www.goemar.com
De Mayo, Braz. De Mayo Industrias Químicas e Farmacêuticas Ltda, Rua Barão de Petrópolis 109, 20251-061 Rio de Janeiro, RJ, Brazil.
De Salute, Ital. De Salute S.r.l., Via A. Biasini 26, 26015 Soresina (CR), Italy.
De Tian, China. De Tian Pharmaceutical Co Ltd, Xian, China.
De Witt, Austria. See *De Witt, UK.*
De Witt, Denm. See *Ferring, Denm.*
De Witt, Fin. See *De Witt, UK.*
De Witt, Gr. See *Casen Fleet, Spain.*
De Witt, Irl. See *Mayrs, Irl.*
De Witt, Neth. See *De Witt, UK.*
De Witt, Norw. See *Ferring, Norw.*
De Witt, NZ. See *Regional Health, NZ.*
De Witt, Pol. See *Ferring, Pol.*
De Witt, Port. See *De Witt, UK.*
De Witt, UK. E.C. De Witt & Co. Ltd, Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire, WA4 4HS, UK.
url: www.ecdewitt.co.uk
De Zhou, China. De Zhou Pharmaceutical Co. Ltd, China.
Deb, Canad. Deb Canada, 42 Thompson Road West, Waterford, Ontario, N0E 1Y0, Canada.
Debat, Denm. See *Ipex, Swed.*
Debat, Fr. See *Fournier, Fr.*
Debat, Hong Kong. See *Wing Wai, Hong Kong.*
Debat, Neth. See *Sanofi-Aventis, Neth.*
Debat, Norw. See *Ipex, Swed.*
Debat, Pol. See *Fournier, Pol.*
Debat, Switz. See *AstraZeneca, Switz.*
Debat, Thai. See *Pacific, Thai.*
Debio, Switz. Debiopharm Recherche Pharmaceutique SA, Chemin Messidor 5-7, 1002 Lausanne, Switzerland.
url: www.debiopharm.com
Debioclinic, Fr. Debioclinic SA, 2 rue du Nouveau Bercy, 94220 Charenton-le-Pont, France.
url: www.debiopharm.com
Debioclinic, Swed. See *Debioclinic, Fr.*
Deca, Ital. Laboratorio Chimico Deca S.r.l., Via Balzaretti 17, 20133 Milan (MI), Italy.
Decafarma, Port. Decafarma Comércio de Produtos Farmacêuticos Lda, Rua Armindo Rodrigues 9-A, 1600-414 Lisbon, Portugal.
Declimed, Ger. See *Desitin, Ger.*
Deco, Hung. Deco, Hungory.
Decomed, Port. Decamed Farmacêutico, Lda, Rua Sebastião e Silva 56, 2745-838 Massama, Portugal.
Decrox, Spain. Decrox, Crta Sevilla Malaga Km 5.6, 41500 Alcala de Guadaira, Seville, Spain.
Dedousis, Gr. Dedousis A AE, Veranzerou 51-53, 10437 Athens, Greece.
Dee, UK. Dee Pharmaceuticals Ltd, Office 3K6 Redwither Tower, Redwither Business Centre, Wrexham, Clwyd, LL13 9XT, UK.
Defeier, China. Defeier Pharmaceutical Co. Ltd, Hebei, China.
Defiante, Austria. See *Defiante, Port.*
Defiante, Belg. See *Defiante, Port.*
Defiante, Fin. See *Defiante, Port.*
Defiante, Gr. See *Defiante, Port.*
Defiante, Ital. See *Defiante, Port.*
Defiante, Neth. Defiante, Netherlands.
Defiante, Port. Defiante Farmacêutica Lda, Rua dos Ferreiros 260, 9000-082 Funchal, Madeira.
url: www.defiante.com
Defiante, Spain. See *Defiante, Port.*
Defuen, Arg. Defuen S.A., Av. Darrego 331, 1414 Buenos Aires, Argentina.
DeGa, Philipp. DeGa International Pharma Corp., Rm 314 Common Goal Tower, Finance cor. Industry St, Madrigal Business Park, Ayala Alabang, Muntinlupa City, Philippines.
Degab, Ger. See *Riemser, Ger.*
Degorts, Mex. Degort's Chemical S.A. de C.V., Alhambra No. 310, Benito Juarez Portales, 03300 Mexico D.F., Mexico.
Degussa, UK. Degussa Ltd, Winterton House, Winterton Way, Macclesfield, Cheshire, SK11 0LP, UK.
url: www.degussa.com
Dekaz, Gr. Dekaz Ltd, 43 Thermopilon Str, Vrilissia 152 35, Greece.
url: www.dekaz.gr
Deklerht, USA. Deklerht, USA.
Del, Canad. Del Pharmaceutics (Canada) Inc., 316 Bayview Drive, Barrie, Ontario, L4N 3V7, Canada.
Del, USA. Del Pharmaceuticals Inc., 726 EAB Plaza, P.O. Box 9357, Uniondale, NY 11553, USA.
url: www.dellabs.com
Del Bel, Arg. Lab. Del Bel S.R.L., Avellaneda 1523, 5000 Cordoba, Argentina.
Del Sol, Arg. Laboratorio Drogueria Del Sol SRL, Barragán 457, 1408 Buenos Aires, Argentina.
Delagrange, Belg. See *Sanofi-Aventis, Belg.*
Delagrange, Fr. See *Sanofi-Aventis, Fr.*
Delagrange, Indon. See *Soho, Indon.*
Delagrange, Neth. See *Sanofi Synthelabo, Neth.*
Delagrange, Port. See *Infar, Port.*
Delagrange, Spain. See *Sanofi-Aventis, Spain.*
Delagrange, Switz. See *Sanofi-Aventis, Switz.*
Delalande, Fr. See *Sanofi-Aventis, Fr.*
Delalande, Ger. See *Sanofi-Aventis, Ger.*
Delalande, Port. See *Confar, Port.*
Delalande, Switz. See *Sanofi-Aventis, Switz.*
Delamac, Austral. Delamac Pharmaceuticals P/L, Suite 1/14 Hill Street, Spring Hill, Qld 4000, Australia.
Delandale, UK. See *Sanofi, UK.*
Delano, Canad. Delano Health Products, G25-300 St-Sacrement St, Montreal, Quebec, H2Y 1X4, Canada.
Delattre-Hemapurine, Belg. Delattre-Hemapurine, Belgium.
Delbert, Fr. Delbert Lab., 56 quai Alphonse-Le-Gallo, 92100 Boulogne-Billancourt, France.
Delegant, Gr. Delegant, Greece.
Delex, Philipp. See *Globo Asiatico, Philipp.*
Delfi, Malaysia. Delfi Marketing Sdn Bhd, Level 10 West Wing, Wisma Consplant 2, No 7 Jln SS 16/1, 47500 Subang Jaya, Selangor, Malaysia.
Delfi, Singapore. Delfi Singapore Pte Ltd, 7 Gul Circle 02-01/06, Keppel DistriCentre, S-629563, Singapore.
Delicias, Mex. Delicias S.A. de C.V., Productos Alimenticias, Apartado Postal No. 376, Zona Industrial, 33000 Chihuahua, Mexico.
Deliz, USA. Deliz Pharmaceutical Corp., Sabana Abaja Industrial Park, Carolina, PR 009290287, USA.
Delmont, USA. Delmont Laboratories Inc., 715 Harvard Ave, P.O. Box 269, Swarthmore, PA 19081, USA.
url: www.delmont.com
Delon, Canad. Laboratoires Delon (1990) Inc., 75 Hymus Blvd, Pointe-Claire, Quebec, H9R 1E2, Canada.
Delpech, Fr. Laboratoire Delpech, 6 rue Danton, 75006 Paris, France.
url: www.labo-delpech.com
Delphi, Neth. Delphi Pharmaceuticals BV, Spoorhaven 39, 2651 AB Berkel en Rodenrijs, Netherlands.
Del-Ray, USA. See *Crown, USA.*
Delta, Arg. Delta Farma S.A., Bacacay 1820/22, 1406 Buenos Aires, Argentina.
Delta, Austral. See *Pharmacia, Austral.*
Delta, Braz. Instituto Terapeutico Delta Ltda, Rua Engenheiro Guilherme Cristiano Frendez 827, 03477-000 São Paulo, SP, Brazil.
Delta, Ger. See *DeltaSelect, Ger.*
Delta, Irl. Delta Laboratories Ltd, 26 Airfield Court, Dublin 4, Ireland.
Delta, Port. Laboratórios Delta, Lda, Rua Direita de Massamá 148, 2745-751 Queluz, Portugal.
url: www.delta.pt
Delta, Singapore. See *Green Cross, Singapore.*
Delta BKB, Ital. Delta BKB S.r.l., V.le Emilio Po 224, 41100 Modena (MO), Italy.
Delta Medical, Rus. Delta Medical, Niknya ul 14 str 1, 125040 Moscow, Russia.
url: www.deltamedical.com.ua
Delta Medical, Ukr. Delta Medical, Ul. Chernovola 43,, Vishneve, Kiev Region, 08132, Ukraine.
url: www.deltamedical.com.ua
delta pronatura, Ger. delta pronatura Dr. Krauss & Dr. Beckmann GmbH & Co. KG, Kurt-Schumacher-Ring 15-17, 63329 Egelsbach, Germany.
url: www.delta-pronatura.de
Delta West, Malaysia. See *Pfizer, Malaysia.*
Deltapharm, Hong Kong. DeltaPharm Ltd, Flat D, 22/F, Boldwin Building, 16-18 Wah Sing St, Kwai Hing, Tsuen Wan, N.T., Hong Kong.
Deltapharma, Gr. See *Deltapharma, UK.*
Deltapharma, UK. Deltapharma Ltd UK, Regent House, 316 Beulah Hill, London, SE19 3HF, UK.
DeltaSelect, Austria. See *DeltaSelect, Ger.*
DeltaSelect, Cz. See *Reg, Cz.*
DeltaSelect, Denm. See *DeltaSelect, Ger.*
DeltaSelect, Ger. Delta Select GmbH, Benzstr. 5, 72793 Pfullingen, Germany.
url: www.deltaselect.de
DeltaSelect, Hung. See *DeltaSelect, Ger.*
DeltaSelect, Irl. See *DeltaSelect, Ger.*
DeltaSelect, Neth. See *DeltaSelect, Ger.*
DeltaSelect, Norw. See *DeltaSelect, Ger.*
DeltaSelect, Rus. See *DeltaSelect, Ger.*
DeltaSelect, Singapore. DeltaSelect, Singapore.
DeltaSelect, Ukr. See *DeltaSelect, Ger.*
Delta-West, Venez. See *Pfizer, Venez.*
Dem, Turk. Dem İlaç Ltd. Şti., İkbaliye Mah. Acibadem Cad. No: 56, Kadiköy, İstanbul, Turkey.
url: www.demilac.com
Demo, China. See *Demo, Gr.*
Demo, Gr. Demo Abee, 21 KM Athens - Lamia, 145 65 Kroneri, Greece.
url: www.demo.gr
Demo, Israel. See *Demo, Gr.*
Demo, Philipp. See *PharmAsia, Philipp.*
Demo, Thai. See *Pharmaland, Thai.*
Democal, Switz. Democal AG, Postfach 1045, 1701 Fribourg-Moncor, Switzerland.
url: www.democal.ch
Demopharm, Switz. See *Democal, Switz.*
Dempsey, Canad. Dempsey Corp., 47 Davies Ave, Toronto, Ontario, M4M 2A9, Canada.
Denamed, Norw. Denamed AS, Strømsv. 48, 2010 Strømmen, Norway.
url: www.denamed.no
Dendreon, USA. Dendreon Corporation, 3005 First Avenue, Seattle, Washington, WA 98121, USA.
url: www.dendreon.com
Dendron, UK. See *DDD, UK.*
Dendy, Austral. Dendy Pharmaceuticals P/L, 44 Cromer St, East Brighton, VIC 3187, Australia.
Denis, India. Denis Chem Lab Ltd, 401 Abhishree Complex, Satellite Road, Ahmedabad 380 015, India.
url: www.denischemlab.com
Denk, Cz. See *Denk, Ger.*
Denk, Ger. E Denk OHG, Munich, Germany.
Denk, Hong Kong. See *Star, Hong Kong* and *Universal, Hong Kong.*
Denk, Singapore. See *Luen Wah, Singapore.*
Denk, Thai. See *Sriprasit, Thai.*
Denolin, Belg. Denolin SA, Rue des Goujons 152, 1070 Brussels, Belgium.
Denolin, Neth. See *Hermes, Neth.*
Denorex, Canad. See *Denorex, USA.*
Denorex, USA. The Denorex Co., 3510 North Lake Creek Drive, Jackson, Wyoming 83001, USA.
Densmore, Fr. Laboratoires Densmore, 7 rue d emillo, BP 486, MC 98012, Monaco.
Dent, USA. See *Grandpa Brands, USA.*
Dentaid, Chile. Laboratorios Dentaid SA, Camino de la Colina 1432, Huechuraba, Santiago, Chile.
Dental Health Products, UK. See *Intrapharm, UK.*
Dental Warehouse, S.Afr. Dental Warehouse (Pty) Ltd, Private Bag X8, Wendywood 2144, South Africa.
url: www.dentalwarehouse.co.za
Dentapharm, Gr. HR Katsoupas - AH Antonopoulos SA - Dentapharm SA, Socratous 48, 104 31 Athens, Greece.
Dentinox, Austria. See *Dentinox, Ger.*
Dentinox, Cz. See *Dentinox, Ger.*
Dentinox, Ger. Dentinox Gesellschaft für Pharmazeutische Präparate Lenk & Schuppan KG, Nunsdorfer Ring 19, 12277 Berlin, Germany.
url: www.dentinox.de
Dentinox, Hung. See *Penta, Hung.*
Dentinox, Pol. See *Miralex, Pol.*
Dentinox, Rus. See *Dentinox, Ger.*
Dentinox, Switz. See *Renapharm, Switz.*
Dentinox, Ukr. See *Artur, Ukr.*
Dentirol, Swed. Dentirol AB, Box 24046, 400 22 Göteborg, Sweden.
url: www.dentirol.se
Dento Medical, Israel. R N Dento Medical Division, Meshek 21, Hdanim 45100, Israel.
Dentomarket, Gr. Dentomarket AE, Greece.
Dentoral, Turk. Dentoral Diş ve Ağız Sağliği İlaç ve Gerecleri San ve Tic Ltd Sti, Koşuyolu Mh Çitlek Sk Sinan Bey, Apt N:2, Kadiköy, Istanbul, Turkey.
Dentoria, Fr. See *Sanofi Synthelabo OTC, Fr.*
Dentorient, Israel. Dentorient Fuss Ltd, 28 Hagdud Haivri St, Tel Aviv, 61021, Israel.
Dentox, UK. Dentox Ltd, P.O. Box 1195, Warwickshire, CV35 0ZY, UK.
url: www.brushtox.co.uk
Dentsply, Austral. Dentsply (Australia) P/L, 11-21 Gilby Road, Mt. Waverley, VIC 3149, Australia.
url: www.dentsply.com.au
Dentsply, Austria. Dentsply DeTrey GmbH, Weinholdstrasse 33, A-8010 Graz, Austria.
Dentsply, Canad. Dentsply Canada Ltd, 161 Vinyl Court, Woodbridge, Ontario, L4L 4A3, Canada.
Dentsply, Denm. See *Dentsply, Swed.*
Dentsply, Fin. See *Tamro, Fin.*
Dentsply, Fr. Dentsply France, 17 rue Michael-Faraday, 78180 Montigny-le-Bretonneux, France.
url: www.dentsply.fr
Dentsply, Ger. Dentsply DeTrey GmbH, De-Trey-Strasse 1, 78467 Constance, Germany.
url: www.dentsply.de
Dentsply, Irl. See *Dentsply, UK.*
Dentsply, Ital. Dentsply Italia S.r.l., Via A Cavaglieri 26, 00173 Rome (RM), Italy.
url: www.dentsply.it
Dentsply, Neth. See *Dentsply, UK.*
Dentsply, Norw. See *Dentsply, UK.*
Dentsply, NZ. Dentsply NZ, 58 Richard Pearse Drive, Auckland, New Zealand.
url: www.dentsply.com
Dentsply, Port. See *Dentsply, Ger.*
Dentsply, Rus. Dentsply Russia Ltd, 129090 Moscow, Russia.
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Dentsply, Spain. Dentsply España, Avda de Burgos 39, 28036 Madrid, Spain.
url: www.dentsply.es
Dentsply, Swed. Dentsply Ltd, Box 2024, 128 21 Skarpnäck, Sweden.
url: www.dentsply.com
Dentsply, UK. Dentsply Ltd, Hamm Moor Lane, Addlestone, Weybridge, Surrey, KT15 2SE, UK.
url: www.dentsply.co.uk
Dentsply, USA. Dentsply International, Susquehanna Commerce Center, 221 W Philadelphia St, P.O. Box 872, York, PA 17405-0872, USA.
url: www.dentsply.com
Denver, Arg. Denver Farma S.A., Natalio Querido 2285, 1605 Munro, Buenos Aires, Argentina.
Dep, Canad. Dep Corporation, 5045 Orbitor Dr., Bldg 7, Suite 300, Mississauga, Ontario, L4W 4Y4, Canada.

Depomed, USA. Depomed, 1360 O'Brien Dr, Menlo Park, CA 94025-1436, USA.
url: www.depomedinc.com

Depotech, USA. See *Skye, USA.*

Deproco, USA. Deproco Inc., 245-C Quigley Blvd, New Castle, DE 19720, USA.

DePuy, Ger. DePuy Orthopädie GmbH, a Johnson & Johnson Company, Konrad-Zuse-Str.19, 66459 Kirkel-Limbach, Germany.
url: www.jnjgateway.com

DePuy, UK. DePuy International Ltd, St Anthonys Rd, Leeds, West Yorkshire, LS11 8DT, UK.

Derek, Singapore. Derek Marketing Pte Ltd, Block 221 Henderson Rd, 05-11 Henderson Building, S 159557, Singapore.

Dergam, Fr. Laboratoires Dergam, 50 rue de Charonne, 75011 Paris, France.
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Derma, UK. Derma UK Ltd, ARC Progress, Mill Lane, Stotford, Bedfordshire, SG5 4NY, UK.
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Dermacyte, Canad. Dermacyte Pharmaceuticals Ltd, 39 Eastbourne Ave, Beaconsfield, Quebec, H9W 5G8, Canada.

Dermadolin, Turk. Dermadolin Üretim ve Pazarlama, Gürsel Mah. 28, Nisan Cad. No: 33/B, Kağıthane, İstanbul, 33400, Turkey.

Dermal, Israel. See *Trupharm, Israel.*

Dermal Enterprises, Canad. Dermal Enterprises Inc., 300 720 King Street West, Toronto, Ontario, M5V 2T3, Canada.

Dermal Laboratories, Irl. See *Fulcrum, Irl.*

Dermal Laboratories, UK. Dermal Laboratories Ltd, Tatmore Place, Gosmore, Hitchin, Hertfordshire, SG4 7QR, UK.
url: www.dermal.co.uk

Dermalogica, Canad. Dermalogica (Canada) Ltd, 300 720 King St West, Toronto, Ontario, M5V 2T3, Canada.

Dermalogix, Canad. See *Dermalogix, USA.*

Dermalogix, USA. Dermalogix Partners Inc., Scarborough, Maine, 04070, USA.

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Dermapharm, Cz. See *Dermapharm, Ger.*

Dermapharm, Denm. See *Dermapharm, Ger.*

Dermapharm, Ger. Dermapharm AG, Luise-Ullrich-Strasse 6, 82031 Grunwald, Germany.
url: www.dermapharm.de

Dermapharm, Neth. See *Dermapharm, Ger.*

Dermapharm, Switz. Dermapharm AG, Bösch 104, 6331 Hunenberg, Switzerland.
url: www.dermapharm.ch

Dermapharm, UK. See *Alliance, UK.*

DermaRite, USA. DermaRite Industries LLC, 3 East 26th St, Paterson, NJ 07514, USA.
url: www.dermarite.com

Derma-Rx, Hong Kong. See *Dermatech, Hong Kong.*

Dermatech, Austral. Dermatech Laboratories, Unit 19, 167 Prospect Highway, Seven Hills, NSW 2147, Australia.
url: www.dermatech.com.au

Dermatech, Hong Kong. Dermatech Co, 13/F SB Commercial Building, 478 Nathan Rd, Kowloon, Hong Kong.
url: www.dermatech.com.hk

Dermatech, NZ. See *Dermatech, Austral.*

Dermatech, Philipp. See *Zenaust, Philipp.*

Dermatech, Singapore. See *Sime Darby, Singapore.*

Dermato Logical, UK. Dermato Logical Ltd, Dermato logical House, P.O. Box 3469, Barnet, Hertfordshire, EN5 9HB, UK.
url: www.aqua-max.co.uk

Dermatological Solutions, Canad. Dermatological Solutions Inc., 108 Avenue Rd, Toronto, Ontario, M5R 2H3, Canada.

Dermatone, Canad. See *Dermatone, USA.*

Dermatone, USA. Dermatone Laboratories Inc., 334 Ella Grasso Turnpike 121, Windsor Locks, Connecticut, 06096-1073, USA.

Dermatonics, UK. Dermatonics Ltd, Unit 3 Bramley Rd, St Ives, Cambridgeshire, PE27 3WS, UK.
url: www.dermatonics.co.uk

Dermik, China. Dermik Pharmaceutical Co. Ltd, 1029 East First St, Green Island Road South, Green City 262500, Shandong, China.

Dermik, Hong Kong. See *Ebewe, Hong Kong.*

Dermik, Israel. See *Medibrands, Israel.*

Dermik, Singapore. See *JDH, Singapore.*

Dermik, USA. See *Sanofi-Aventis, USA.*

DermoDuemila, Ital. DermoDuemila Srl, P.le F.lli Macedone 140, 00124 Casalpalocco (RM), Italy.

Dermofarm, Spain. Dermofarm, Can Sant Joan, Rubi, 08191 Barcelona, Spain.
url: www.dermofarm.com

Dermofarma, Ital. Dermofarma Italia S.r.l., Via Beata Francesca 10, 83100 Avellino (AV), Italy.

Dermogen, Spain. Dermogen, C/San Rafael 3, Alcobendas, 2808 Madrid, Spain.

Dermol, USA. Dermol Pharmaceuticals Inc., 3807 Roswell Rd, Marietta, GA 30062, USA.

Dermophil Indien, Fr. Laboratoires du Dermophil Indien, B.P. 9, 61600 La Ferte-Mace, France.

Dermophil Indien, Switz. See *Uhlmann-Eyraud, Switz.*

Dermoprog, Ital. Dermoprog S.r.l., Via Gorizia 25, 00100 Rome (RM), Italy.

Dermoteca, Port. Dermoteca, SA, Estrada Nacional 117, 2720 Alfragide, Portugal.

Dermpharma, Philipp. Dermpharma Inc., 2266 Aurora Blvd, Pasay City, Philippines.

Dermtek, Canad. Dermtek Pharmaceuticals Ltd, 1600 Trans-Canada Highway, Suite 200, Dorval, Quebec, H9P 1H7, Canada.
url: www.reversa.ca

Desant, Gr. Desant Technology Drug & Cosmetic Mon EPE, Koim Theotokou 15, 145 64 Agios Stefanos, Greece.

Desarrollo, Spain. Desarrollo Farma y Cosmeticos, Pa de la Castellana 143, 28046 Madrid, Spain.

Desbergers, Canad. See *Ratiopharm, Canad.*

Deserving Thyme, Canad. Deserving Thyme Inc., 726 Powell St, Vacouver, British Columbia, V6A 1H6, Canada.

Desilets, Canad. Léo Désilets, Maître Herboriste Inc., 16 rue du Parc, Scotstown, Quebec, J0B 3B0, Canado.

Desitin, Cz. Desitin Arzneimittel SRN, Opletalová 25, P.O. Box 112, 111 21 Prague 1, Czech Republic.

Desitin, Denm. Desitin Pharma A/S, Havnegade 55, tv., 1058 Copenhagen K, Denmark.
url: www.desitin.dk

Desitin, Fin. See *Algol, Fin.*

Desitin, Ger. Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany.
url: www.desitin.de

Desitin, Hong Kong. See *Jacobson, Hong Kong.*

Desitin, Hung. Desitin Pharma Kft, Maros u 12/B IV em., 1122 Budapest, Hungary.

Desitin, Israel. See *Megapharm, Israel.*

Desitin, Malaysia. See *Ranbaxy, Malaysia.*

Desitin, Neth. See *Byk, Neth.*

Desitin, Norw. Desitin Pharma A/S, Niels Leuchsv. 99, 1359 Eiksmarka, Norway.
url: www.desitin.no

Desitin, Pol. See *Ewopharma, Pol.*

Desitin, Singapore. See *Zyfas, Singapore.*

Desitin, Swed. Desitin Pharma AB, Box 2064, 431 02 Mölndal, Sweden.
url: www.desitinpharma.se

Desitin, Switz. Desitin-Pharma GmbH, Gestadeckplatz 2, 4410 Liestal, Switzerland.
url: www.desitin.ch

Desitin, UK. Desitin Pharma Ltd, 3000 Cathedral Hill, Guildford, Surrey, GU2 7YB, UK.
url: www.desitin.co.uk

Desma, Austria. See *Desma, Ger.*

Desma, Ger. Desma GmbH, Peter-Sander-Str. 41b, 55252 Mainz-Kastel, Germany.
url: www.desma-pharma.com

Desma, Gr. See *DMS, Ital.*

Desma, Pol. See *Desma, Ger.*

Desma, Port. See *Desma, Spain.*

Desma, Rus. See *Switch, Rus.*

Desma, Spain. Desma Laboratorio Farmaceutico, Cuatro Amigos 7, 28029 Madrid, Spain.
url: www.desmapharma.com

Desma, Switz. Desma Healthcare BV, Corso San Gottardo 32, 6830 Chiasso, Switzerland.
url: www.desmapharma.com

Desopharmex, Switz. Desopharmex AG, Muttenzerstrasse 107, 4133 Pratteln 1, Switzerland.

Desra, Turk. Desra, Turkey.

Dessau, Cz. See *Riemser, Ger.*

Dessau, Ger. See *Riemser, Ger.*

Deston, USA. See *Trx Pharma, USA.*

Deutsch Chinesische, Hong Kong. Deutsch Chinesische Apotheke (Maple Inc.), 809, Wellborne Commercial Ctr, 8 Java Rd, North Point, Hong Kong.

Deutsche, Chile. See *Sanofi-Aventis, Chile.*

Deutsche, Philipp. See *Pasteur, Philipp.*

Deva, Fr. Devo (Lab), B.P. 3, 38880 Autrans, France.
url: www.lab-devo.com

Deva, Turk. Deva Holding İlaç Grubu, Büyükdere Cad. No:199/A, Levent, İstanbul, 80640 4., Turkey.
url: www.devaholding.com.tr

Deverge, Ital. Dévergè Medicina e Medicalizzazione S.r.l., C.so Chieri 11, 10132 Turin (TO), Italy.
url: www.deverge.it

Devries, Israel. Devries & Co. Ltd, 51 Ahad Ha'am St, Tel Aviv 65206, Israel.

DeVriMed, Neth. DeVriMed, Sterappel 10, 9076 LD St Annaparochie, Netherlands.

Dewcare, India. Dewcare Concept, 102 Shailly, Opposite SAL Hospital, Thaltej, Ahmedabad, India.

Dewitt, Hong Kong. See *IDS, Hong Kong.*

Dewitt, Malaysia. See *JDH, Malaysia.*

Dexa, Hong Kong. See *Health Alliance, Hong Kong.*

Dexa, Indon. Dexa Medica Pharm & Chem PT, Titan Ctr, 3rd Floor, Jl Blvd Bintaro Blok B7/B1 No 05, Bintaro Jaya Sektor 7, Tangerang 15224, Indonesia.

Dexa, Philipp. Dexa Medica Representative Office, Medical Plaza Bldg, Unit 1911, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.

Dexa, Pol. See *Cowik, Pol.*

Dexa, Singapore. See *Apotheca, Singapore* and *JDH, Singapore.*

Dexcel, Denm. See *Vitaflo, Denm.*

Dexcel, Fin. See *Dexcel, UK.*

Dexcel, Ger. Dexcel Pharma GmbH, Rontgenstr. 1, 63755 Alzenau, Germany.
url: www.dexcel-pharma.de

Dexcel, Hung. See *Pro-Pharma, Hung.*

Dexcel, Irl. See *Dexcel, UK.*

Dexcel, Israel. See *Dexxon, Israel.*

Dexcel, Neth. See *Dexcel, UK.*

Dexcel, Norw. See *Dexcel, UK.*

Dexcel, Port. See *Dexcel, UK.*

Dexcel, Singapore. See *Pharmaforte, Singapore.*

Dexcel, Swed. See *Dexcel, UK.*

Dexcel, UK. Dexcel Pharma Ltd, 1 Cottesbrooke Park, Heartlands Business Park, Daventry, Northamptonshire, NN11 5YI, UK.
url: www.dexcel.com

DexGen, USA. DexGen Pharmaceuticals Inc., P.O. Box 675, Manasquan, NJ 08736, USA.
url: www.dexgen.com

Dexin Runsheng, China. Dexin Runsheng Pharmaceutical Co. Ltd, Hebei, China.

Dexo, Fr. Laboratoires Dexo, 179 bureaux de la Colline, 92213 Saint-Cloud cdx, France.

Dexo, Port. See *Dexo, Fr.*

Dexo, Switz. See *Actipharm, Switz* and *Uhlmann-Eyraud, Switz.*

Dexo, Thai. See *Pacific, Thai.*

Dexo, USA. Dexo Pharma, 4424 W 24th Pl., Lawrence, KS 66047, USA.

Dexsil, Fr. DexSil, 34 av des champs Elysées, 75008 Paris, France.
url: dexsil-pharma.com

Dexter, India. Dexter Laboratories Pvt Ltd, 001/C Shree Laxmi Enclave, Kanungo Estate, Mira Road (E), Thane 401 107, India.

Dexter, Spain. Dexter Farmaceutica, Avda Virgen de Montserrat 215, 08026 Barcelona, Spain.

Dexxon, Israel. Dexxon, P.O. Box 50, Hadera 38100, Israel.
url: www.dexxon.co.il

Dexxon, Philipp. See *PharmAsia, Philipp.*

Dey, Canad. See *Dey, USA.*

Dey, Singapore. See *Zuellig, Singapore.*

Dey, USA. Dey LP, 2751 Napa Valley Corporote Drive, Napa, CA 94558, USA.
url: www.deyinc.com

Deyao, China. Deyao Pharmaceutical Co. Ltd., 538 Sanba Middle Road, Decheng, Dezhou, Shangdong, China.
url: www.deyao.cn

Deyer, China. Deyer Pharm, 128 Jinqu Rd, Jinhua, Zhejiang, 321016, China.
url: www.deyer.com

Dey's, India. Dey's Medical Stores (Manufacturing) Ltd, 62 Bondel Rd, Kolkata 700 019, India.
url: www.deysmedicallimited.com

Deyuan, China. Deyuan Pharmaceutical Co. Ltd, 29 Changjiang Rd, Lianyungang, Jiangsu, 222047, China.

Deyuantang, China. Deyuantang Pharmaceutical Co. Ltd, Shanxi, China.

Dezhong, China. Dezhong Pharamceutical Co. Ltd, China.

DHA, Austral. Drug Houses of Australia P/L, Australia.

DHA, Hong Kong. See *US Summit, Hong Kong.*

DHA, Malaysia. See *JDH, Malaysia.*

DHA, Singapore. Drug Houses of Australia (Asia) Pte Ltd, 2 Chia Ping Rd, 09-00 Haw Par Tiger Balm Building, S 619968, Singapore.
url: www.dha.asia

DHP, UK. DHP Healthcare Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QS, UK.

DHU, Austria. See *DHU, Ger.*

DHU, Cz. See *DHU, Ger.*

DHU, Ger. Deutsche Homöopathie-Union, Ottostr. 24, 76227 Karlsruhe, Germany.
url: www.dhu.de

DHU, Malaysia. See *Antah, Malaysia.*

DHU, Rus. See *German Homoeopathic, Rus.*

DHU, Spain. Laboratorios DHU Ibérica, S.A., Pol Ind Francolm Parcela 3, Nave 1-2, Aportodo de Correos 1082, 43006 Tarragona, Spain.
url: www.dhu.es

DHU, Ukr. See *Naturfarm, Ukr.*
url: www.dhu.com

DHY, China. Dahongying (DHY) Pharmaceutical Co. Ltd, Ningbo, China.

Di Ao, China. Di Ao Group Pharmaceutical Co. Ltd, Chengdu, China.

Di Ao Jiu Hong, China. Di Ao Jiu Hong Pharmaceutical Factory, Chengdu, China.

Diabact, Swed. See *Orexo, Swed.*

Diaco, Ital. Laboratori Diaco Biomedicali S.p.A., Via Flavia 124, 34147 Trieste (TS), Italy.

Diafarm, Rus. See *Akti-M, Rus.*

Diafarm, Spain. Diafarm, Avda Arraona 119-123, Barbera del Valles, 08210 Barcelona, Spain.
url: www.diafarm.es

Dial, Canad. The Dial Corporation, 3515 Quilter Court, Burlington, Ontario, L7M 3C3, Canada.

Dialysis Solutions, Canad. Dialysis Solutions Inc., 14 Emmett Place, Whitby, Ontario, L1R 2B4, Canada.

Diamant, Fr. See *Sanofi-Aventis, Fr.*

Diamant, Port. See *Sanofi-Aventis, Port.*

Diamant, Singapore. See *Zuellig, Singapore.*

Diametiss, Canad. See *Diametiss, Fr.*

Diametiss, Fr. Laboratoire Diametiss, Kerguezec, 56680 Plouhinec, France.

Diamo, Switz. DiaMo Narcotics GmbH, Postfach 30, 3613 Steffisburg, Switzerlond.

Diamond, Philipp. Diamond Laboratories Inc., No 8 Feria Rd, Commonwealth Ave, Diliman, Quezon City, Philippines.

Diapharm, Ger. Diapharm Regulatory Services GmbH, Hafenweg 18-20, 48155 Münster, Germany.
url: www.diapharm.com

Diapharm, Gr. Dipharm AE, Argous 43, 145 64 Kifissia, Greece.

Diapharm, UK. See *Diapharm, Ger.*

Diapit, Gr. DIAPIT, Ag Konstantinou 6, 104 31 Athens, Greece.

Diasa, Spain. Diasa Europa, La Cuadriella S/N, Turon-Mieres, 33610 Asturias, Spain.
url: www.diasoeuropa.com

Diater, Spain. Diater, Soledad 37, 28330 San Martin de la Vega, Madrid, Spain.

Diatide, USA. See *Bayer, USA.*

Diatos, Denm. See *Diatos, Fr.*

Diatos, Fin. See *Diatos, Fr.*

Diatos, Fr. Diatos SA, 11 rue Watt second floor, 75013 Paris, France.

Diatos, Gr. See *Diatos, Fr.*

Diatos, Irl. See *Diatos, Fr.*

Diatos, Ital. See *Diatos, Fr.*

Diatos, Neth. See *Diatos, Fr.*

Diatos, Port. See *Diatos, Fr.*

Diatos, Swed. See *Diatos, Fr.*

Diatos, UK. See *Diatos, Fr.*

Diaverum, Hung. Diaverum Hungary, Versec Sor 9 1 Em., 1021 Budapest, Hungary.
url: www.diaverum.com

Diba, Mex. Laboratorios Diba, S.A. de CV, Escorza No. 728, Col. Moderna, 44190 Guadalajara, Jalisco, Mexico.
url: www.diba.com.mx

Dibropharm, Ger. Dibropharm GmbH Distribution & Co. KG, Kleine-Dollen-Str. 5, 76532 Baden-Baden, Germany.

Dicamed, Swed. Dicamed AB, Djupdalsvägen 24, 192 51 Sollentuna, Sweden.
url: www.dicamed.se

Dickinson, USA. Dickinson Brands Inc., 31 East High St, East Hampton, CT 06424, USA.
url: www.witchhazel.com

Dicofar, Arg. Laboratorio Dicofar SRL, Fray Cayetano Rodriguez 3520, 1702 Ciudadela, Buenos Aires, Argentina.

Dicofarm, Ital. Dicofarm S.p.A., Via del Casale della Marcigliana 29, 00138 Rome (RM), Italy.
url: www.dicofarm.it

Dieckmann, Ger. See *MSD, Ger.*

Diedenhofen, Thai. See *Ouiheng, Thai.*

Dielen, Fr. Dielen Laboratoires, Zone Produimer, 50110 Tourlaville, France.
url: www.dielen.fr

Diepha, Fr. See *Diepharmex, Fr.*

Diepharmex, Fr. Laboratoires Diepharmex, 26 rue de l'Industrie, 92400 Corbevoie, France.

Diet Erba, NZ. See *NZ Distributors, NZ.*

Dietaroma, Fr. Diétaroma SA, B.P. 4, 69240 Bourg de Thizy, France.

Dietary Foods, UK. Dietary Foods Ltd, Cumberland House, Brook Street, Soham, Cambridgeshire, CB7 5BA, UK.
url: www.dietaryfoods.co.uk

Dietetique, Rus. See *Pierre Fabre, Rus.*

Dietetique et Sante, Fr. See *Novartis Nutrition, Fr.*

Diethelm, Philipp. Diethelm Phils Inc., Brgy Mamplasan, Binan, Laguna, Philippines.

Diethelm, Switz. Kurt Diethelm, Teufenerstrasse 17, 9042 Speicher, Switzerland.

Diethelm, Thai. Diethelm Keller Logistics Ltd (DKLL), 2533 Sukhumvit Rd, Bangchak, Phrakhanong, Bangkok, 10260, Thailand.
url: www.dksh.co.th

Dietina, Fr. See *Nestle, Fr.*

Difa, Ital. Difa-Cooper S.p.A., Via Milano 160, 21042 Caronno Pertusella (VA), Italy.

Diffucap, Braz. Diffucap-Chemobras Quim Farm Ltda, Rua Goias 1232, 21380-010 Rio de Janeiro, RJ, Brazil.

Digestive Care, USA. Digestive Care Inc., 1120 Win Drive, Bethlehem, PA 18017-7059, USA.
url: www.digestivecare.com

Dihon, China. Kunming Dihon Pharmaceutical Co. Ltd, 45 Keyi Road, Kunming New and High-Tech Industrial Development Zone, Kunming, Yunnan, China.
url: www.dihon.com

Dikang, China. Dikang Pharmaceuticals Co Ltd, Liaoyuan City, China.

Dikang Changjiang, China. Dikang Changjiang Pharmaceutical Co. Ltd, Chongqing, China.

DIL, India. DIL (Duphar-Interfran Ltd), Ghodbunder Rd, Thane (West), 400 610, India.
url: www.dil.net

Dileo, Ukr. Dileo Pharma Ltd, 83D Melnikova St, Kiev, Ukraine.

Dilong, China. Dilong Pharmaceutical Co. Ltd, Bei Sidai Jie, Anda, Suihua, Heilongjiang, 151400, China.
url: www.dilong.net

DiME, UK. DiME, 4 Wintonlea, Monument Way West, Woking, Surrey, GU21 5EN, UK.
url: www.dime-med.com

Dimec, Arg. Droguerma Dimec S.R.L., Santa Fe 4126, 2002 Rosario, Santa Fe, Argentina.

Dimethaid, Fin. See *Dimethaid, UK.*

Dimethaid, Ger. Dimethaid GmbH, Vor dem Schlosstor 9, 39164 Wanzleben, Germany.
url: www.dimethaid.de

Dimethaid, Port. See *Dimethaid, UK.*

Dimethaid, UK. Dimethaid UK Ltd, Spectrum House, 20-26 Cursitor St, London, EC4A 1HY, UK.
url: www.dimethaid.com

Dina, China. Dina Pharmaceutical Co. Ltd, Industrial Development Zone, Xinsheng, Qing'an, Sihua, Heilongjiang, 152400, China.

Dincsa, Turk. Dinçsa İlaç Sanayi ve Ticaret AS, I Organize Sanayi Bolgesi, Avar Cad. No 2, Sincan/Ankara, Turkey.
url: www.dincsa.com

Dinctas, Turk. Dinçtaş İlaç San. A.S., Mithatpasa Cad.No: 49/15, Kızılay, Ankara, 06420, Turkey.

Dinghengsheng, China. Dinghengsheng Pharmaceutical Co Ltd, Qiqihar, China.

Dinno, Fr. Dinno Santé, 1 rue Raoul-Follereau, 77608 Marne-la-Vallée cdx 3, France.
url: www.dinnosante.fr

Dinuo, China. Dinuo Pharmaceutical Co. Ltd, Hunan, China.

Diomed, Irl. See *Dermal Laboratories, UK.*

Diomed, UK. See *Dermal Laboratories, UK.*

Dioptic, Canad. Dioptic Laboratories, Division of Akorn Pharmaceuticals Canada Ltd, 1405 Denison St, Markham, Ontario, L3R 5V2, Canada.
url: www.dioptic.com

Dioptra, Rus. Dioptra ZAO, Miklukho-Maklaya 16/10, 117871 Moscow, Russia.

Dior, Canad. See *Dior, Fr.*

Dior, Fr. Parfums Christian Dior, 33 Avenue Hoche, 75008 Paris, France.

Dioter, Fr. Laboratoires Dioter, 6 chemin des Gorges, 69574 Dardilly cdx, France.
url: www.satori-international.fr

Dipa, Indon. PT Dipa Pharmalab Intersains, Jl Kebon Jeruk Raya No 66, Jakarta 11530, DKI Jaya, Indonesia.
url: www.dpi.dipa.co.id

Direction, China. Direction Pharmaceutical Co. Ltd, Sichuan, China.

Dirinco, Neth. Dirinco BV, Saffierborch 14, 5241 LN Rosmalen, Netherlands.
url: www.dirinco.com

Dirui, UK. See *Econo-Med, UK.*

Disai, China. Xian Disai Biological Pharmaceutical Co., Ltd, 69 Hongmiaopo, Lianhu, Xian, Shaanxi, 710016, China.
url: www.xadisai.com

Discotrade, Israel. See *Dexxon, Israel.*

Discovery, UK. Discovery Pharmaceuticals, The Old Vicarage, Market Place, Castle Donnington, Derbyshire, DE74 2JB, UK.
url: www.discoverypharma.co.uk

Discovery, USA. Discovery Laboratories Inc., 2600 Kelly Rd, Suite 100, Warrington, PA 18976-3646, USA.
url: www.discoverylabs.com

Discus, USA. Discus dental Inc., 8550 Higuera St, Culver City, CA 90232, USA.
url: www.discusdental.com

Discus Dental, Canad. See *Discus, USA.*

Disha, China. Disha Pharmaceutical Group Co., Ltd., 196 High Technology Development Zone, Weihai Road, Weihai, Shandong, 264209, China.
url: www.disha.com.cn

Dishman, Fin. See *Dishman, Neth.*

Dishman, Neth. Dishman Netherlands, Nieuweweg 2a, 3901 BE Veenendaal, Netherlands.
url: www.dishman-netherlands.com

Dishman, Swed. See *Dishman, Neth.*

Dismed, S.Afr. Dismed Pharmaceutical Pty Ltd, Unit A3, Tilbury Business Park, Midbrand, 1685, South Africa.

Dismedica, Braz. Dismedica Distrib. de Prods. Hosp. e Farms. Ltda, Av. das Americas 3500, 22640102 Rio de Janeiro, Rio de Janeiro, Brazil.

Disop, Arg. See *Visiontec, Arg.*

Dispensapharm, Canad. See *Pfizer, Canad.*

Dispersa, Canad. See *Novartis, Canad.*

Dispersa, Ger. See *Novartis, Ger.*

Dispersa, Switz. Dispersa SA, Case postale, 8442 Hettlingen, Switzerland.

Disphar, Fin. See *Disphar, Neth.*

Disphar, Neth. Disphar International BV, Winkelskamp 6, 7255 PZ Hengelo, Netherlands.

Dispolab, Arg. Dispolab Farmaceutica Argentina SA, Libertad 976, Piso 2 B, Buenos Aires, Argentina.

Dispolab, Chile. Dispolab Farmaceutica SA, Santa Victoria 213, Providencia, Santiago, Chile.

Disprofarma, Arg. Disprofarma S.A., Virrey Cevallos 1643, 1135 Buenos Aires, Argentina.
url: www.disprofarma.com.ar

Dissa, Arg. Dissa S.R.L., Pola 2249/51, 1440 Buenos Aires, Argentina.

Dissan, Canad. Groupe Dissan Inc., 9280 Blvd du Golf, Anjou, Quebec, H1J 3A1, Canada.

Dissolvurol, Mon. Laboratoires Dissolvurol, Le Concorde, 11 rue du Gabian, MC 98000, Monaco.

Dista, Austral. See *Lilly, Austral.*

Dista, Belg. See *Lilly, Belg.*

Dista, Fr. See *Lilly, Fr.*

Dista, Irl. See *Lilly, Irl.*

Dista, Neth. See *Lilly, Neth.*

Dista, NZ. See *Lilly, NZ.*

Dista, S.Afr. See *Lilly, S.Afr.*

Dista, Spain. See *Lilly, Spain.*

Dista, Switz. See *Lilly, Switz.*

Dista, UK. See *Lilly, UK.*

Dista, USA. See *Lilly, USA.*

Distri B3, Fr. Laboratoires Distri B3, rue Max Planck, Technopole de Chateau-Gombert, 13013 Marseille, France.
url: www.distrib3.com

Distrifarma, Port. Distrifarma, SA, Condomínio Industrial Queluz Park, Estrada Consiglieri Pedroso 80 Lote 3, Queluz de Baixo, 2745-553 Barcarena, Portugal.

Distriphar, UK. See *Sanofi, UK.*

Distriquimica, Spain. See *Esteve, Spain.*

Divapharma, Cz. See *Divapharma, Ger.*

Divapharma, Fin. See *Divapharma, Ger.*

Divapharma, Ger. Divapharma GmbH, Motzener Strasse 41, 12277 Berlin, Germany.
url: www.divapharma.de

Divapharma, Hung. See *Bayer, Hung.*

Divapharma, Pol. See *Nepentes, Pol.*

Divapharma, Rus. See *Divapharma, Ger.*

Divapharma, Ukr. See *Mavi, Ukr.*

Diversey Lever, Canad. Diversey Lever Canada, a Division of UL Canada Inc., 2401 Bristol Circle, Oakville, Ontario, L6H 6P1, Canada.

Diviser Aquilea, Spain. See *Aquilea, Spain.*

Dixon-Shane, USA. See *RS, USA.*

DJ, USA. See *Biovail, USA.*

Djaya Bima Agung, Indon. See *Dexa, Indon.*

DJO, Ger. See *Ormed, Ger.*

DKSH, Hong Kong. DKSH Hong Kong Ltd, 23/F Tower A, Southmark, 11 Yip Hing St, Wong Chuk Hang, Hong Kong.
url: www.dksh.com

DKSH, Indon. DKSH Healthcare, PT DKSH Indonesia, Menara Jamsostek 22nd floor, Jl. Jend. Gatot, Subroto No 38, 12710 Jakarta, Indonesia.
url: www.dksh.com

DKSH, Malaysia. DKSH Malaysia Sdn Bhd, 74 Jln Universiti, 46700 Petaling Jaya, Selangor, Malaysia.

DKSH, Singapore. DKSH Singapore Pte Ltd, 34 Boon Leat Terrace, S 119866, Singapore.
url: www.dksh.com

DKSH, Thai. DKSH (Thailand) Ltd Healthcare, 280- New Rd, Bangkok 10100, Thailand.
url: www.dksh.com

DKT, India. DKT India, 23 Shah Industrial Estate, Off Veera Desai Rd, Andheri (W), Mumbai, 400 053, India.

DKT, Philipp. DKT Philippines Inc., Suite 801 The Linden Suites, No 37 San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.

DKT, Thai. See *Masa, Thai.*

DLF, Denm. Dansk Lægemiddelforsyning DLF ApS, Lodshusvej 11, 4230 Skælskør, Denmark.

DM, Braz. DM Indústria Farmacêutica Ltda, Av. Piracema 155, 06460-030 Barueri, SP, Brazil.

DMG, Ger. DMG Chemisch-Pharmazeutische Fabrik GmbH, Postfach: 530104, 22531 Hamburg, Germany.

DMG, Ital. DMG Italia S.r.l., Via Laurentina km 26,700, 00040 Pomezia (RM), Italy.
url: www.dmgit.com

DMS, Austria. See *DMS, Ital.*

DMS, Ital. DMS Farmaceutici S.p.A., Via Provinciale per Lecco 78, 22038 Travernerio (CO), Italy.

DNA, Mex. DNA Pharmaceuticals SA de CV, Blvd Avila Camacho 92-A Piso 12 PH, 53500 Naucalpan el Conde, Estado de Mexico, Mexico.

DNBG, Philipp. DNBG Pharmaceuticals Philippines, 181 Molave St Hillside Subd, Bajada, Davao City, Philippines.

DND, China. DND Pharmaceutical Co. Ltd, 2-18A Lane 85, Rongcheng Rd, Pudong, Shanghai, 200120, China.
url: www.dndpharm.com

DnE, Norw. A/S Den norske Eterfabrikk, Eterveien 12, 0690 Oslo, Norway.
url: www.eter.no

DNR, Arg. Laboratorio DNR Farma SRL, Hipolito Vieytes 147, 1603 Villa Martelli, Buenos Aires, Argentina.

Doak, Hong Kong. See *International Medical, Hong Kong.*

Doak, USA. See *Bradley, USA.*

Doc Pharma, Belg. See *Docpharma, Belg.*

Docan, China. Docan Pharmaceutical Co. Ltd, Jinyin Ecological Park An Lute 1, East & West Lakes Taiwan Business Development Zone, Wuhan 430040, China.
url: www.dazy.cn

Docmed, S.Afr. Docmed, South Africa.

Docpharm, Ger. Docpharm Arzneimittelvertrieb GmbH & Co. KGaA, Gewerbestr. 26, 76327 Pfinztal, Germany.
url: www.docpharm.de

Docpharm, Ukr. Docpharm Ltd, ul. Kuibyshev 60/24, 95034 Simpheropal, Ukraine.
url: www.docpharm.com.ua

Docpharma, Austria. See *Docpharma, Belg.*

Docpharma, Belg. Docpharma, 3001 Heverlee, Belgium.
url: www.docpharma.be

Docpharma, Fin. See *Docpharma, Belg.*

Docta, Spain. Docta, Gran Via de les Corts, Catalanes 774, 08013 Barcelona, Spain.

Doctor 10, Arg. Doctor 10 SRL, Alejandro M Cervantes 1594, (1416) C.A.B.A., Buenos Aires, Argentina.

Doctor H, Rus. Doctor H, Russia.

Doctors, Philipp. Doctors Pharmaceuticals, 8 Veterans Rd, West Bicutan, Taguig, Metro Manila, Philippines.

Doctum, Gr. Doctum Pharmaceutical S.A., K. T. Giokaris & Co., Marko Lulu 1 oxil km, 190 02 Peania Attiki, Greece.

Doetsch, Grether, Switz. Doetsch Grether AG, 4002 Basle, Switzerland.
url: www.doetschgrether.ch

Dolhay, Hung. Dolhay Klinika, Domoszló utja 18, 1037 Budapest, Hungary.

Doliage, Fr. Laboratoires Doliage, 81 rue de Verdun, 92150 Suresnes, France.

Dolisos, Canad. Dolisos, 1400 Hocquart St, St-Bruno, Quebec, J3V 6E1, Canada.
url: www.dolisos.ca

Dolisos, Cz. See *Boiron, Cz.*

Dolisos, Fr. See *Boiron, Fr.*

Dolisos, Hung. See *Boiron, Hung.*

Dolisos, Ital. Laboratoires Dolisos Italia S.r.l., Via Pontina Vecchia km 34,200, 00040 Ardea (Rome), Italy.
url: www.dolisos.it

Dolisos, Neth. See *Dolisos, Ital.*

Dollder, Venez. Especialidades Dollder, Av. José María Vargas, Torre El Colegio, Piso 13, Sonto Fé Norte, Caracas, Venezuela.
url: www.dollder.com

Dolorgiet, Cz. See *ProMed, Cz.*

Dolorgiet, Denm. See *Actavis, Denm.*

Dolorgiet, Fin. See *Dolorgiet, Ger.*

Dolorgiet, Ger. Dolorgiet GmbH & Co. KG, Otto-von-Guericke-Str. 1, 53757 St. Augustin/Bonn, Germany.

Dolorgiet, Hung. See *Budapharma, Hung.*

Dolorgiet, Neth. See *Dolorgiet, Ger.*

Dolorgiet, Pol. See *ProMed, Pol.*

Dolorgiet, Rus. See *ProMed, Rus.*

Dolorgiet, Switz. See *Mundipharma, Switz.*

Dolorgiet, Ukr. See *ProMed, Ukr.*

Dom, Spain. See *Salvat, Spain.*

Domac, Spain. Domac SL, Avda de Barcelona 69, 08970 San Joan Despi, Barcelona, Spain.

Dome, Switz. See *Medinova, Switz.*

Dome-Hollister-Stier, Ger. See *Meda Manufacturing, Ger.*

Dome-Hollister-Stier, UK. See *Bayer, UK.*

Domesco, Philipp. See *Endure, Philipp.*

Domestic, Rus. Domestic Medicines ZAO, Generala Dorokhova ul., d. 18, 119530 Moscow, Russia.

Dominguez, Arg. Lab. Dominguez S.A., Av. La Plata 2552, 1437 Buenos Aires, Argentina.

Dominion, Canad. See *Pharmascience, Canad.*

Dominion, UK. See *Pliva, UK.*

Dompe, Cz. See *Dompe, Ital.*

Dompe, Hung. Dompe, Hungary.

Dompe, Ital. Dompè Farmaceutici S.p.A., Via San Martino 12-12/A, 20122 Milan (MI), Italy.
url: www.dompe.it

Dompe, Neth. See *Dompe, Ital.*

Dompe, Philipp. See *Metro, Philipp.*

Dompe, Pol. See *Perffarma, Pol.*

Dompe, Port. See *Dompe, Ital.*

Dompe, Rus. See *Riace, Rus.*

Dompe Biogen, Switz. See *Biogen Dompe, Switz.*

Dompe Biotec, Ital. See *Dompe, Ital.*

Dompe Biotec, Neth. See *Dompe, Ital.*

Doms, Fr. See *Bouchara-Recordati, Fr.*

Doms, Switz. See *Actipharm, Switz.*

Doms-Adrian, Cz. See *Bouchara-Recordati, Fr.*

Doms-Adrian, Fr. See *Bouchara-Recordati, Fr.*

Doms-Adrian, Hong Kong. See *Rich Plan, Hong Kong.*

Doms-Recordati, Fr. See *Bouchara-Recordati, Fr.*

Doms-Recordati, Hong Kong. See *Rich Plan, Hong Kong.*

Don, Israel. See *Manon, Israel.*

Donell, USA. Donell Inc., 501 Fifth Ave, Suite 1214, New York, NY 10017, USA.
url: www.cxproducts.com

Donell DerMedex, USA. See *Donell, USA.*

Dong, Singapore. See *Pharmaforte, Singapore.*

Dong Fang, China. Dong Fang Pharmaceutical Co. Ltd, Chongqing, China.

Dong Kook, Hong Kong. See *CNW, Hong Kong.*

Dong Kook, Philipp. See *Endure, Philipp.*

Dong Kook, Singapore. See *Polymedic, Singapore.*

Dong Kook, Thai. See *Charoen, Thai.*

Dong Wha, Philipp. See *Pharmazel, Philipp.*

Dong-A, Malaysia. See *Pahang, Malaysia.*

Dong-A, Philipp. See *Metro, Philipp.*

Dong-A, Thai. See *Lion, Thai.*

Dongbao, China. Dongbao Pharmaceutical Co. Ltd, Room 1906-9, Shanghai Times Square, 93 Huaihai Rd, Shanghai, 200021, China.
url: www.dongbao.com

Dongeejiao, China. Dongeejiao Pharmaceutical Co. Ltd, 78 Jiao Street, Dong'e, Shandong, 252201, China.
url: www.dongeejiao.com

Dongfang Xiehe, China. Dongfang Xiehe Pharmaceutical Co. Ltd, Beijing, China.

Dongfeng, China. Dongfeng Pharmaceutical Co. Ltd, Jiangxi, China.

Donghai, China. Donghai Pharmaceutical Co. Ltd, Shanghai, China.

Dong-il, Hong Kong. See *Health Care, Hong Kong.*

Dongkang, China. Dongkang Pharmaceutical Co. Ltd, Baiyun, Dongping, Guangzhou, 510440, China.

Dongkwang, Malaysia. See *Propharm, Malaysia.*

Dongle, China. Dongle Pharmaceutical Co. Ltd, Zhuozhou, China.

Dongnam, Philipp. See *Endure, Philipp.*

Dongting, China. Dongting Pharmaceutical Co. Ltd, Hunan, China.

Dongya, China. Dongya Pharmaceuticals Co. Ltd, Taohua Street, Fengcheng, Changshou, Chongqing, 401259, China.
url: www.cqdyyy.com

Dongyu, China. Dongyu Pharmaceutical Co. Ltd, 100-18 Changjiang North Street, Yuhong, Shenyang, Liaoning, 110036, China.

Dongzhitang, China. Dongzhitang Pharmaceutical Co. Ltd, Anhui, China.

Donini, Ital. Donini S.r.l., Via Ecce Homo 18, 37054 Nogara (VR), Italy.

Donjoy, Fr. See *Axmed, Fr.*

Donmed, S.Afr. See *Organon, S.Afr.*

Doppel, China. See *Doppel, Ital.*

Doppel, Ital. Doppel Farmaceutici S.r.l., Via Martiri delle Foibe 1, 29016 Cortemaggiore (PC), Italy.
url: www.doppel.it

DORC, Neth. Dutch Ophthalmic Research Center International, Scheijdelveweg 2, 3214 VN Zuidland, Netherlands.
url: www.dorc.nl

Dormer, Canad. Dormer Laboratories Inc., 91 Kelfield St, Unit 5, Rexdale, Ontario, M9W 5A3, Canada.
url: www.dormer.com

Dorom, Ital. See *Teva, Ital.*

Dorwest, UK. Dorwest Herbs Ltd, Shipton Gorge, Bridport, Dorset, DT6 4LP, UK.
url: www.dorwest.co.uk

Dosa, Arg. Lab. Dosa S.A., Girardot 1369, 1427 Buenos Aires, Argentina.

Doskar, Austria. Doskar Mag. Martin Pharm. Produkte, Schottenring 14, A-1010 Vienna, Austria.

Dossier, Neth. Dossier BV, Waardsedijk Oost 8, 3417 XJ Montfoort, Netherlands.

DOT, India. DOT Pharma, 56/1 Sree Gandha Kawal, Kottigepalaya, Magadi Road, Bangalore 560 091, India.

Double-Crane, China. Double-Crane Pharmaceutical Co. Ltd, 1 Wangjing Lize East Rd, Chaoyang District, Beijing 100102, China.
url: www.dcpc.com

Douglas, Austral. Douglas Pharmaceuticals Australia Ltd, P.O. Box 7004, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153, Australia.
url: www.douglas.com.au

Douglas, Canad. See *Douglas, USA.*

Douglas, Hong Kong. See *Hind Wing, Hong Kong.*

Douglas, Israel. See *Taro, Israel.*

Douglas, Malaysia. See *Schmidt, Malaysia.*

Douglas, NZ. Douglas Pharmaceuticals Ltd, P.O. Box 45-027, Auckland, New Zealand.
url: www.douglas.co.nz

Douglas, Singapore. See *Grafton, Singapore.*

Douglas, Thai. See *JDH Borneo, Thai.*

Douglas, USA. Douglas Laboratories, 600 Boyce Rd, Pittsburgh, Pennsylvania, 15205, USA.

Dovalle, Braz. Farmoterapica Dovalle Indústria Química Farmacêutica Ltda, Rodovia SC 438 Km 3, 88701970 Tubarao, SC, Brazil.

Dover, Israel. Dover Medical & Scientific Equipment Ltd, 11 Hamaalot St, Herzliya 46583, Israel.
url: www.dovermed.co.il

Dow, Canad. See *Sanofi, Canad.*

Dow, UK. Dow Chemical Company Ltd, 2 Heathrow Boulevard, 284 Bath Rd, West Drayton, Middlesex, UB7 0DQ, UK.
url: www.dow.com

Dow, USA. See *Bertek, USA.*

Dow Corning, UK. See *Dow, UK.*

Dow Hickam, USA. See *Bertek, USA.*

DPS, Pol. DPS Pharma, Przedstawicielstwo w Polsce, ul. Bolaton 9 A, 01-971 Warsaw, Poland.

Dr Alson, India. Dr Alson Laboratories Pvt Ltd, 5C/9 New Rohtak Road,, New Delhi 110 005, India.
url: www.alsonlabs.com

DR Jahns, India. D.R. John's Lab Pvt Ltd, 212 Shahpurjat, New Delhi 110 049, India.
url: www.drjahnslab.com

Dr Klein, Ukr. See *Naturfarm, Ukr.*

Dr Kumars, India. Dr Kumars Pharmaceuticals, SCO 421 1st Floor, Motor Market, Manimajra, Chandigarh, India.

Dr P, Ger. Dr. P. Medizinische Dienste by Dr. Panzer GmbH, Kieler Str. 2, 12163 Berlin, Germany.

Dr Zens, Philipp. See *InnoGen, Philipp* and *Westfield, Philipp.*

Drac, Switz. Drac AG, Hauptgasse 29, 3280 Murten, Switzerland.

Draco, Ger. Dr Ausbüttel & Co GmbH, Herdecker Str. 9-15, 58453 Witten, Germany.

Draco, Swed. See *AstraZeneca, Swed.*

Drag, Chile. Drag Pharma Invetec SA, Las Dalias 3193, Macul, Santiago, Chile.

Dragenopharm, Hong Kong. See *International Medical, Hong Kong.*

Dragenopharm, Israel. See *Taro, Israel.*

Drawer, Arg. Lab. Drawer S.A., Dorrego 127, 1878 Quilmes, Buenos Aires, Argentina.

Draximage, Canad. Draximage, 16751 Trans-Canada Highway, Kirkland, Quebec, H9H 4J4, Canada.
url: www.draximage.com

Draximage, Irl. See *Draximage, UK.*

Draximage, Neth. See *Draximage, UK.*

Draximage, UK. Draximage (UK) Ltd, 5 Old Bailey, London, EC4M 7BA, UK.

Draximage, USA. See *Draximage, Canad.*

Draxis, Canad. Draxis Health Inc., 6870 Goreway Dr, Mississauga, Ontario, L4V 1P1, Canada.

DRD, Gr. D.R.D. EPE, Ag. Lavras 111, 111 41 Athens, Greece.

Dreiman, Spain. See *Alcala, Spain.*

Dreluso, Ger. Dreluso Pharmazeutika, Dr Elten & Sohn GmbH, Marktplatz 5, 31840 Hessisch Oldendorf, Germany.
url: www.dreluso.de

Dresden, Cz. See *Asta Medica, Cz.*

Dresden, Pol. See *Pliva Krakow, Pol.*

Dresden, Rus. See *Pliva, Rus.*

Driburg, Arg. Laboratorio Driburg Company SA, Warnes 3112, 1636 Vicente Lopez Olivos, Buenos Aires, Argentina.

Drogsan, Hong Kong. See *Ebewe, Hong Kong.*

Drogsan, Turk. Drogsan Doğa Kaynaklı İlaç Hammaddeleri San. ve Tic. A.Ş., Oğuzlar Mah. 56. Sok 7/3, Balgat, Ankara, 06520, Turkey
url: www.drogsan.com

Dronania, Hung. See *Volmix, Hung.*

Drapa, Switz. Drapa Management AG, Schwerzistrasse 6, 8807 Freienbach, Switzerland.
url: www.drapa.ch

Droreth, Israel. Matzkel Droreth Ltd, 17 Lilienblum St, Tel Aviv 65132, Israel.
url: www.droreth.com

Droser, Arg. Droser SA, Frogato Presidente Sarmiento 2337/39, (1416) Buenos Aires, Argentina.

Drossapharm, Cz. See *Drossapharm, Switz.*

Drossapharm, Ger. Drossapharm GmbH, Wallbrunnstr. 24, 79539 Lörrach, Germany.
url: www.drossapharm.ch

Drossapharm, Israel. See *Gilco, Israel.*

Drossapharm, Philipp. See *Commerz, Philipp.*

Drossapharm, Switz. Drossapharm SA, Postfach 2660, 4002 Basle, Switzerland.
url: www.drossapharm.ch

Droxter, Braz. Droxter Indústria Comércio e Participações Ltda, Rua Vigário Taques Bittencourt 258, 4755060 São Paulo, Brazil.

Drug Research, Gr. Drug Research Hellas SA, Leof. Parnithos 189, 136 71 Acharnai Attici, Greece.
Drug Research, Ital. D.R. Drug Research S.r.l., Via F Turati 3, 22036 Erba (CO), Italy.
Drug Research, Singapore. See *Zyfas, Singapore.*
Drugmaker's Laboratory, Philipp. See *Terramedic, Philipp and Tylid, Philipp.*
Drugtech, Chile. See *Recalcine, Chile.*
Drula, Canad. See *Drula, Ger.*
Drula, Ger. Drula-Fabrik, Dr O Druckery GmbH, Elfser Weg 16, Soest 59485, Germany.
DSE, USA. DSE Healthcare Solutions LLC, 164 Northfield Ave, Edison, NJ 08837, USA.
url: www.dsehealthcare.com
Du Pont, Belg. See *BMS, Belg.*
Du Pont, Canad. See *BMS, Canad.*
Du Pont, Cz. See *Torrex, Cz.*
Du Pont, Denm. See *Meda, Denm.*
Du Pont, Fr. See *BMS, Fr.*
Du Pont, Hong Kong. See *Keller, Hong Kong.*
Du Pont, Irl. See *United Drug, Irl.*
Du Pont, Israel. See *Teva, Israel.*
Du Pont, Norw. See *Meda, Norw.*
Du Pont, Singapore. See *Boots, Singapore.*
Du Pont, Spain. See *BMS, Spain.*
Du Pont, Switz. See *Opopharma, Switz.*
Du Pont, Thai. See *Olic, Thai.*
Du Pont, UK. See *BMS, UK.*
Du Pont, USA. See *BMS, USA.*
Duchesnay, Canad. Duchesnay Inc., 950 Blvd Michèle-Bohec, Blainville, Quebec, J7C 5E2, Canada.
url: www.duchesnay.com
Duchesnay, USA. Duchesnay USA Inc., 919 Conestoga Rd, Building One, Suite 203, Rosemont, PA 19010, USA.
url: www.duchesnayusa.com
Duckbill, India. Duckbill Drugs Pvt Ltd, 162/B/240 Prince Anwar Shah Rd, Kolkata, 700 045, India.
Ducray, Fr. See *Pierre Fabre, Fr.*
Ducto, Braz. Lab. Ducto Ind. Farm. Ltda, Rua VPR 3 Quadra 2-A, Modulos 20/21 DAIA, 75133-600 Anapolis, GO, Brazil.
url: www.ducto.com.br
Dulcis, Mon. See *Allergan, Fr.*
Dumex, Ger. See *Actavis, Ger.*
Dumex, Irl. See *Actavis, UK.*
Dumex, Malaysia. Dumex (Malaysia) Sdn Bhd, 1 Jln 205, 46050 Petaling Jaya, Selangor, Malaysia.
url: www.youngnutrition.net
Dumex, Norw. See *Alpharma, Norw.*
Dumex, NZ. See *CSL, NZ.*
Dumex, Philipp. Dumex Philippines Inc., 3/F IDC Bldg, E Rodriguez Jr Ave, Bo Ugong Norte Libis, Quezon City, Philippines.
Dumex, Port. See *Alpharma, Port.*
Dumex, Switz. See *Medinova, Switz.*
Dumex, Thai. Dumex Ltd, 359 Moo 17 Theparak Rd, Bangsaothong, Samutprakan 10542, Thailand.
Dumex, UK. See *Actavis, UK.*
Dumex-Alpharma, Denm. See *Actavis, Denm.*
Dumex-Alpharma, Fin. See *Alpharma, Fin.*
Dumex-Alpharma, Hong Kong. See *Primal, Hong Kong.*
Dumex-Alpharma, Singapore. See *Sime Darby, Singapore.*
Dumex-Alpharma, Swed. See *Alpharma, Swed.*
Dumex-Alpharma, Switz. See *Medinova, Switz.*
Dumex-Alpharma, Thai. See *Stada, Thai.*
Dunar, Spain. Dunar, Arequipa 1, 28043 Madrid, Spain.
Duncan, Arg. Laboratorios Duncan S.A., Av. San Martmn 6340/42, 1419 Buenos Aires, Argentina.
url: www.duncanbioquim.com.ar
Duncan, Flockhart, Austral. See *GSK, Austral.*
Duncan, Flockhart, Irl. See *GSK, Irl.*
Duncan, Flockhart, UK. See *GSK, UK.*
Duncan, Hong Kong. See *PanWell, Hong Kong.*
Duncan, Ital. See *GSK, Ital.*
Duncan, Philipp. Duncan Pharmaceuticals Inc., 2266 Don Chino Roces Ave, Makati City, Philippines.
Duncan, Spain. See *GSK, Spain.*
Duncan, Thai. See *Pharmadica, Thai.*
Dunhall, USA. Dunhall Pharmaceuticals Inc., Highway 59N, P.O. Box 100, Gravette, AR 72736, USA.
Dunner, China. See *XingYin, China.*
Dunner, Switz. Dr Dünner SA, Artherstrassec 60, 6405 Immensee, Switzerland.
Duobao, China. Duobao Pharmaceutical Co. Ltd, Jiangsu, China.
Duoburuifei, China. Duoburuifei Pharmaceutical Co Ltd, China.
DuoCort, Denm. See *ViroPharma, Belg.*
DuoCort, Irl. See *DuoCort, Swed.*
DuoCort, Swed. DuoCort Pharma AB, Kullagatan 8, S-252 20 Helsingborg, Sweden.
Duomed, Switz. Duomed AG, 9533 Kirchberg, Switzerland.
Duopharm, Ger. Duopharm GmbH, Otto-von-Steinbeis-Str. 16, 83052 Bruckmühl, Germany.
url: www.duopharm.de
Duopharma, Hong Kong. See *Weston, Hong Kong.*
Duopharma, Malaysia. Duopharma Malaysia Sdn Bhd, Lot 2599 Jalan Seruling 59, Kaw 3, Taman Klang Jaya, 41200 Klang, Selangor, Malaysia.
url: www.duopharma.com.my
Duopharma, Philipp. Duopharma Trade (Phils) Inc., Skrene Properties Bldg, 3759 Cuenca cor Emilia St, Palanan, Makati City, Philippines.
Duopharma, Singapore. See *CCM, Singapore.*
Duphar, Fr. See *Solvay, Fr.*
Duphar, Ger. See *Solvay, Ger.*
Duphar, Irl. See *Solvay, Irl.*
Duphar, Neth. See *Solvay, Neth.*
Duphar, NZ. See *Solvay, NZ.*
Duphar, Spain. See *Solvay, Spain.*
Duphar, UK. See *Solvay, UK.*
Duphar Nezel, Spain. See *Solvay, Spain.*
Duphar-Interfran, Thai. See *Union Medical, Thai.*
Dupharma, Denm. Dupharma, Kristinehøj 22 B, 2770 Kastrup, Denmark.
url: www.dupharma.dk
Dupomar, Arg. Dupomar S.A.C.I.F., Venezuela 174, 1095 Buenos Aires, Argentina.
Dupricz, Hung. Dupricz Kft, Orbánhegyi ut 15-17, 1126 Budapest, Hungary.
Dura, USA. See *Elan, USA.*
Durachemie, Ger. See *Mylan dura, Ger.*
Duramed, USA. See *Barr, USA.*
Durascan, Denm. DuraScan Medical Products AS, C F Tietgens Boulevard 40, 5220 Odense S, Denmark.
url: www.durascan.com
Durascan, Fin. See *Durascan, Denm.*
Durban, Spain. Durban, Santos Zarate 20, 04004 Almeria, Spain.
Durbin, UK. Durbin Plc, 180 Northolt Rd, South Harrow, Middlesex, HA2 0LT, UK.
url: www.durbin.co.uk
Durex, Canad. Durex Canada, Division of SSL Canada Inc., 100 Courtland Ave, Concord, Ontario, L4K 3T6, Canada.
url: www.durex.com
Durex, USA. Durex Consumer Products, 3585 Engineering Drive, Suite 200, Norcross, GA 30092-2820, USA.
url: www.durex.com
Durga, India. Durga Pharma, K-185 Surya Plaza, 1st Floor Sarai Julena, New Friends Colony, New Delhi, 110 025, India.
Dusa, Thai. See *Daewoong, Thai.*
DUSA, USA. DUSA Pharmaceuticals Inc., 25 Upton Drive, Wilmington, MA 01887, USA.
url: www.dusapharma.com
Dustbane, Canad. Dustbane Products Ltd, 25 Pickering Place, Ottawa, Ontario, K1G 5P4, Canada.
Dutch Lady, Malaysia. Dutch Lady Milk Industries Bhd, 13 Jln Semangat, 46200 Petaling Jaya, Selangor, Malaysia.
Dutch Ophthalmic, USA. Dutch Ophthalmic USA, One Little River Rd, P.O. Box 968, Kingston, NH 03848, USA.
url: www.dorc.nl
Dutec, Austral. Dutec Diagnostics P/L, P.O. Box 79, Croydon, NSW 2132, Australia.
DWD, India. DWD Pharmaceuticals Ltd, 4th Floor Dalamal House, Nariman Point, Mumbai 400 021, India.
url: www.dwdindia.com
Dyax, USA. Dyax Corp., 300 Technology Square, Cambridge, MA 02139, USA.
url: www.kalbitor.com
Dyckerhoff, Ger. Dyckerhoff Pharma GmbH & Co. KG, Robert-Perthel-Str. 49, 50739 Cologne, Germany.
DYN, Israel. DYN Diagnostics, Ha'eshel 7, 3063 Caesarea Industrial Park, Israel.
url: www.dyn.co.il
Dyna, Philipp. Dyna Drug Corp., 8/F New Divisoria Condo, 608 Sta. Elena St, Binondo, Manila, Philippines.
Dynacren, Ital. Dynacren Laboratorio Farmaceutico del Dott. A. Franciani e di M. Gerosa S.r.l., Via P Nenni 12, Loc Malpensa, 28053 Castelletto Ticino (NO), Italy.
url: www.dynacren.it
Dynagen, USA. See *Able, USA.*
Dynamic, Philipp. Pharma Dynamic Inc., 2/F PDI Bldg, 71 Maysilo St, Mandaluyong City, Philippines.
Dynamit, Austria. Dynamit Nobel Wien GmbH, A-8813 St Lamprecht, Austria.
Dynasty, Philipp. Dynasty Pharmaceuticals, 2432 Legarda St, Sampaloc, Manila, Philippines.
Dynathera, Fr. See *Bouchara-Recordati, Fr.*
Dyntec, Cz. Dyntec sro, Terezín, Czech Republic.
Dyota, India. Dyota Numandis Pharmaceuticals Pvt Ltd, Safal Pegasus Tower A, 7th Floor, 705-708, 100 ft. Road, Prahladnagar, Ahmedabad 380 015, India.
url: www.dyotanumandis.com
Dzwon, India. Dzwon Remedies, 75/C Government Industrial Estate, Kandivli West, Mumbai 400 067, India.
E. Merck, Denm. See *Kemifarma, Denm.*
E. Merck, Irl. See *MSD, Irl.*
E. Merck, UK. See *Merck, UK.*
e+b, Austria. See *e+b, Ger.*
e+b, Ger. e+b GmbH & Co. Pharma KG, Emil-Kemmer-Str. 33, 96103 Hallstadt, Germany.
e+b, Hung. e+b, Hungary.
E Pharma, Fr. Laboratoires E Pharma, ZI Le Malcourlet, 03800 Gannat, France.
e5, USA. e5 Pharma LLC, 3550 NW 126th Ave, Coral Springs, FL 33065, USA.
url: www.e5pharma.com
Eadriex, Philipp. Eadriex Pharmaceuticals Phils Inc., 147 Scout Railos, Kamuning, Quezon City, Philippines.
Eagle, Austral. Eagle Pharmaceuticals P/L, P.O. Box 927, Castle Hill, NSW 1765, Australia.
url: www.eaglepharmaceuticals.com.au
Eakan, China. Guizhou Eakan Pharmaceutical Co., Ltd., 964 Huaxi Avenue South, Guiyang, Guizhou, 550025, China.
url: www.eakan.com
East African, India. East African (India) Overseas, J-57 Rajouri Garden, New Delhi 110 027, India.
East India Pharma, India. East India Pharmaceutical Works Ltd, 6 Little Russell St, Kolkata 700 071, India.
East Lane, Philipp. East Lane Corp., Unit 203 ECPIB Building 1, Ortigas Ave cor Roosevelt St, Greenhills, San Juan City, Philippines.
url: www.eastlane.net
East West, India. East West Pharma, Khasra No. 54, Beldi Salahapur, Haridwar Road, Uttrakhand 247 667, India.
url: www.eastwestpharma.in
Eastern Pharmaceuticals, Irl. See *United Drug, Irl.*
Eastsea, China. Qingdao Eastsea Pharmaceitocal Co Ltd, Zhong Rd, Qingdao Jiaonan, Shanghai, China.
url: www.qdeastsea.net
Eberth, Austria. See *Eberth, Ger.*
Eberth, Denm. See *Alternova, Denm.*
Eberth, Ger. Dr. Friedrich Eberth Arzneimittel, Werksweg 2, 92551 Stulln, Germany.
url: www.eberth.de
Eberth, Switz. See *Uhlmann-Eyraud, Switz.*
Ebewe, Austria. Ebewe Pharma GmbH Nfg KG, Mondseestrasse 11, A-4866 Unterach am Attersee, Austria.
url: www.ebewe.com
Ebewe, China. See *Sandoz, China.*
Ebewe, Cz. See *Avalanche, Cz.*
Ebewe, Denm. See *Nordic Drugs, Denm.*
Ebewe, Fin. See *Novartis, Fin.*
Ebewe, Ger. See *Ebewe, Austria.*
Ebewe, Gr. See *Ebewe, Austria.*
Ebewe, Hong Kong. Ebewe Pharma (ASIA) Ltd, 8/F Eastwood Ctr, 5 A Kung Ngam Village Rd, Shaukeiwan, Hong Kong.
Ebewe, Hung. See *Medico Uno, Hung.*
Ebewe, Irl. See *Ebewe, Austria.*
Ebewe, Israel. Ebewe, Israel.
Ebewe, Ital. Ebewe Italia Srl, V.le SS Pietro e Paolo 56, 00144 Rome (RM), Italy.
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Ebewe, Neth. See *Ebewe, Austria.*
Ebewe, Pol. Ebewe Pharma GmbH Nfg. KG Sp.k., Przedstawicielstwa w Polsce, ul. Hauke-Bosaka 16a, 01-540 Warsaw, Poland.
url: www.ebewe.com
Ebewe, Rus. Ebewe Pharma GmbH Nfg.KG, 3-II Samotchnyi, per D3, st 2, 127473 Moscow, Russia.
url: www.ebewe.ru
Ebewe, Singapore. See *Pharmaforte, Singapore.*
Ebewe, Spain. See *Ebewe, Austria.*
Ebewe, Switz. See *Nycomed, Switz.*
Ebewe, Thai. See *Schumit, Thai.*
Ebewe, Ukr. Ebewe Pharma Ukraine, Khmelnitskoga Street, 29/2B, Office 12, Kiev, 01030, Ukraine.
url: www.ebewe.com
Ebi, Switz. Ebi-Pharm AG, Lindachstrasse 8c, 3038 Kirchlindach, Switzerland.
url: www.ebipharm.ch
Ebos, NZ. Ebos Group Ltd, 324 Cashel St, Christchurch, New Zealand.
url: www.ebos.co.nz
ECE, Philipp. ECE Pharmaceuticals Inc., 111 Scout Fernandez St, Cor Scout Tonillo St, BGY Sacred Heart, Quezon City, Philippines.
Echo, Ital. Echo S.r.l., Via O Rinuccini 40, 50144 Florence (FI), Italy.
Echo, Rus. NPK Echo, Naushiyi Proezd 14a str 3, 117246 Moscow, Russia.
url: www.npk.echo.ru
Eckert, Pol. See *Eckert & Ziegler, Ger.*
Eckert & Ziegler, Cz. See *Eckert & Ziegler, Ger.*
Eckert & Ziegler, Ger. Eckert & Ziegler Isotope Products GmbH, Robert-Rössle-Str. 10, 13125 Berlin, Germany.
url: www.isotopes.com
Eckert & Ziegler, Irl. See *Eckert & Ziegler, Ger.*
Eckert & Ziegler, Neth. See *Eckert & Ziegler, Ger.*
Eckson, USA. Eckson Labs, 1000 N West St, Suite 1200 No.927, Wilmington, DE 19801, USA.
url: www.ecksonlabs.com
Eclat, USA. Éclat Pharmaceuticals, 699 Trade Center Blvd, Suite A, Chesterfield, MO 63005, USA.
url: www.eclatpharma.com
Eclectic Institute, Canad. See *Eclectic Institute, USA.*
Edectic Institute, USA. Eclectic Institute Inc., 36350 SE Industrial Way, Sandy, Oregon, 97055-7377, USA.
Eco, S.Afr. Eco Pharmaceuticals (Pty) Ltd, South Africa.
Eco Lips, Canad. See *Eco Lips, USA.*
Eco Lips, USA. Eco Lips Inc., 2003 Bever Ave SE, Cedar Rapids, Iowa, 52403, USA.
Ecobi, Hong Kong. See *Rich Plan, Hong Kong.*
Ecobi, Ital. Farmaceutici Ecobi s.a.s., Via E. Bazzano 26, 16019 Ronco Scrivia (GE), Italy.
Ecobrands, UK. Ecobrands Ltd, 3 Adam & Eve Mews, London, W8 6UG, UK.
url: www.ecobrands.com
Ecoform, Ital. Ecoform Group Srl, Via F Vezzani 99/r, 16159 Genoa Rivarolo (GE), Italy.
url: www.ecoform.it
Ecofarm, Rus. NPK Ecofarm, Dzerzhinskogo ul 11 of. 408, 300041 Tula, Russia.
Ecofarm, Ukr. Ecofarm, Moscow Ave 9-B, 04073 Kiev, Ukraine.
url: www.proteflazid.com.ua
Ecolab, Austria. Ecolab GmbH, Erdbergstrasse 29, A-1030 Vienna, Austria.
Ecolab, Canad. Ecolab Co., 5105 Tomken Rd, Mississauga, Ontario, L4W 2X5, Canada.
Ecolab, Ger. Ecolab Deutschland GmbH, Reisholzer Werftstr. 38-42, 40589 Düsseldorf, Germany.
Ecolab, Irl. See *Ecolab, UK.*
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Ecolab, Neth. Ecolab BV, Edisonbaan 9-11, 3439 MN Nieuwegein, Netherlands.
Ecolab, Switz. Ecolab GmbH, Kriegackerstrasse 91, 4132 Muttenz, Switzerland.
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Ecolab, Thai. See *Pharmaland, Thai.*
Ecolab, UK. Ecolab UK Healthcare Division, Lotherton Way, Garforth, Leeds, West Yorkshire, LS25 2YJ, UK.
Eco-Med-Poll, Cz. Eco-Med-Poll Prague, Na vlastni pudě, 102 00 Prague 2, Czech Republic.
Econo Med, USA. Econo Med Pharmaceuticals Inc., 4305 Sartin Rd, Burlington, NC 27217-7522, USA.
Econolab, USA. See *Breckenridge, USA.*
Econo-Med, UK. Econo-Med, Trafalgar House, Station Rd, Long Sutton, Lincolnshire, PE12 9BP, UK.
url: www.econo-med.com
Econophar, Belg. Econophar s.a.r.l., Rue Anatole France 119, 1030 Brussels, Belgium.
Ecopharma, Arg. Ecopharma SA, Moreno 1833/35, (1094) Buenos Aires, Argentina.
Ecopharma, Chile. Ecopharma SA, Av. Quilin 3550, Macul, Santiago, Chile.
Ecosol, Norw. See *Andersen, Norw.*
Ecosol, Switz. Ecosol AG, Hinterbergstrasse 24, 6330 Cham, Switzerland.
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ECR, USA. ECR Pharmaceuticals, P.O. Box 71600, Richmond, VA 23255, USA.
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Eczacibasi, Cz. See *Pharmacia, Cz.*
Eczacibasi, Philipp. See *Panject, Philipp.*
Eczacibasi, Rus. Eczacibasi Ilac Sanayi, Mal. Lubyanka ul. 16/4/11, 1, pod. 3, 101000 Moscow, Russia.
Eczacibasi, Turk. Eczacibaşı İlaç A.Ş., Büyükdere Cad., Ali Kaya Sok. No:7, Levent, İstanbul, 80640 1., Turkey.
url: www.eis.com.tr
Eczacibasi, Ukr. Eczacibasi, Chigorina Street, 18, Office 230, 231, Kiev, 01042, Ukraine.
url: www.eczacibasipharmaceuticalsgroup.com
Eczacibasi Baxter, Rus. See *Eczacibasi, Rus.*
Eczacibasi-Baxter, Turk. Eczacibaşı-Baxter Hastane Ürünleri San. ve Tic. A.Ş., Ayazağa Cendere Yolu No: 19, Şişli, İstanbul, Turkey.
url: www.eczacibasi-baxter.com.tr
Eczane, Arg. Lab. Eczone Pharma S.A., Laprida 43, 1870 Avellaneda, Buenos Aires, Argentina.
Edas, Rus. Edas Holding, Serpuhovskaya B 10, 115093 Russia, Russia.
url: www.edas.ru
Eden, India. Eden Health Care Pvt Ltd, 301 Abhishree Complex, Satellite Road, Ahmedabad 380 015, India.
url: www.edenhealthcare.in
Eden, S.Afr. See *Boots Healthcare, S.Afr.*
Ederka, Mex. Farmaceuticos Ederka S.A. de C.V., Calle 3 Num. 1, Fracc. Ind. Benito Juarez, 76130 Queretaro Qro, Mexico.
Edgemont, USA. Edgemont Pharmaceuticals LLC, 7000 North MoPac Expressway, Suite 200, Austin, TX 87831, USA.
url: www.edgemontpharma.com
Edigen, Spain. Edigen, Chile 8-2a planta, oficina 203, Las Matas, 28290 Madrid, Spain.
url: www.edigen.es
Edmond, Denm. See *Pharmacuro, Denm.*
Edmond, Port. See *Edmond Pharma, Ital.*
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Edol, Port. Edol, SA, Av 25 de Abril 6-6A, Linda-a-Velha, 2795-195 Linda-a-Velha, Portugal.
Edwards, Austria. See *Edwards, Switz.*
Edwards, Ger. See *Edwards, Switz.*
Edwards, Switz. Edwards Lifesciences, S.A., Route de l'Etraz 70, 1260 Nyon, Switzerland.
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Edwards, USA. Edwards Pharmaceuticals Inc., 111 Mulberry St, Ripley, MS 38663, USA.
Edwards Lifesciences, USA. Edwards Lifesciences, One Edwards Way, Irvine, CA 92614, USA.
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Efamol, NZ. See *Nutricia, NZ.*
Efamol, UK. See *Nutricia Clinical, UK.*
Efarmes, Spain. See *Lacer, Spain.*
Efeka, Ger. See *Pfizer, Ger.*
EF-EM-ES, Austria. EF-EM-ES - Dr Smetana & Co., Scheidlstrasse 28, A-1180 Vienna, Austria.
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Effik, Ital. Effik Italia S.p.A., Via A Lincoln 7/a, 20092 Cinisello Balsamo (MI), Italy.
url: www.effikitalia.it
Effik, Port. Laboratórios Effik Sociedade Unipessoal Lda, Rua Consiglieri Pedroso No 123, Queluz de Baixo, 2730-065 Barcarena, Portugal.
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url: www.effik.com
Effik, Switz. Effik SA, chemin du Midi 8, 1260 Nyon, Switzerland.
Efupi, Jpn. Efupi Ltd, Songyuan Ootsuka Nishi 1-chome, Osaka 40, Japan.
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Egis, Denm. See *Egis, Hung.*
Egis, Hong Kong. See *Mekim, Hong Kong.*

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Egis, Irl. See *Medimpex, UK.*
Egis, Malaysia. See *Pahang, Malaysia.*
Egis, Neth. See *Medimpex, UK.*
Egis, Philipp. See *PharmAsia, Philipp.*
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Egis, Rus. Egis Pharmaceuticals Ltd, Krasnaya Presnya ul. 1-7, Of. 560, 123242 Moscow, Russia.
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Egis, Singapore. See *Sime Darby, Singapore.*
Egis, Thai. See *Medline, Thai.*
Egis, UK. See *Medimpex, UK.*
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Egis-Servier, Rus. See *Servier, Rus.*
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Ego, Hong Kong. See *Lision Hong, Hong Kong.*
Ego, Irl. See *Ego, UK.*
Ego, Malaysia. See *Somedico, Malaysia.*
Ego, NZ. See *Douglas, NZ.*
Ego, Singapore. See *Grafton, Singapore.*
Ego, UK. Ego Pharmaceuticals (UK) Ltd, 15 Windsor Park, 50 Windosr Ave, Merton, London, SW19 2TJ, UK.
EGS, Ger. See *Pharmonta, Austria.*
EHN, Canad. EHN Inc., 501 317 Adelaide Street West, Toronto, Ontario, M5V 1P9, Canada.
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Eicopen, Venez. Eicopen C.A., Eduardo Calcaco Qta. Eicopen, Urb. Santa Minica Caracas, Caracas, Venezuela.
Eifelfango, Ger. Eifelfango GmbH & Co. KG, Ringener Str. 45, 53474 Bad Neuenahr-Ahrweiler, Germany.
Eifelfango, Switz. See *Agpharm, Switz.*
EIG, Malaysia. EIG Pharma Asia Pacific Sdn Bhd, Lot 11 Jln Astaka U8/88, Seksyen U8, Bukit Jelutong, 40150 Shah Alam, Selangor, Malaysia.
url: www.estheticsgroup.com
Eiken, Jpn. Eiken Chemical Co. Ltd, 5-26-20 Oji, Kita-ku, Tokyo 114-0002, Japan.
url: www.eiken.co.jp
Eipico, Malaysia. See *Averroes, Malaysia.*
Eireceutica, Irl. Eireceutica Ltd, Unit 2 Block E, Nutgrove Business Park, Dublin 14, Ireland.
EirGen, Cz. See *EirGen, Irl.*
EirGen, Denm. See *EirGen, Irl.*
EirGen, Irl. EirGen Pharma Ltd, 64/65 Westside Business Park, Old Kilmeaden Rd, Waterford, Ireland.
Eisai, Austria. See *Eisai, UK.*
Eisai, Belg. See *Eisai, UK.*
Eisai, Canad. Eisai Ltd, 2630 Skymark Ave, Suite 701, Mississauga, Ontario, L4W 5A4, Canada.
url: ca.eisai.com
Eisai, China. Eisai Pharmaceutical Co. Ltd (China), 1601 Nanjing Rd West Park Place 39-40, Jing'an District, Shanghai 200040, China.
Eisai, Cz. See *Eisai, UK.*
Eisai, Denm. See *Cephalon, Denm* and *Eisai, Swed.*
Eisai, Fin. See *Eisai, Swed.*
Eisai, Fr. Laboratoires Eisai, tour Manhattan, La Défense 2, 5-6 place de l'Iris, 92095 Paris-La-Défense, France.
url: www.eisai.com
Eisai, Ger. Eisai GmbH, Lyoner Str. 36, 60528 Frankfurt, Germany.
url: www.eisai.de
Eisai, Gr. See *Eisai, UK.*
Eisai, Hong Kong. Eisai (Hong Kong) Co. Ltd, Rm 2008, Fortress Tower, 250 King's Rd, North Point, Hong Kong.
url: www.eisai.com
Eisai, Hung. See *Eisai, UK.*
Eisai, India. Eisai Pharmaceuticals India Pvt Ltd, 1st Floor B Wing, Marwah Centre, Krishanlal Marwah Marg, Andheri (East), Mumbai 400 072, India.
url: www.eisai.co.in
Eisai, Indon. Eisai Indonesia PT, Central Senayan II/12th Fl, Jl Asia Afrika No 8 Senayan, Jakarta Pusat 10270, DKI Jaya, Indonesia.
Eisai, Irl. See *Eisai, UK.*
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Eisai, Jpn. Eisai Co. Ltd, 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan.
url: www.eisai.co.jp
Eisai, Malaysia. Eisai (M) Sdn Bhd, 74 Jln Universiti, 46200 Petaling Jaya, Selangor, Malaysia.
Eisai, Neth. See *Eisai, UK.*
Eisai, Norw. See *Eisai, Swed.*
Eisai, Philipp. HI-Eisai Pharmaceutical Inc., 20/F Multinational Bancorporation Ctr, 6805 Ayala Ave, Makati City, Philippines.
Eisai, Pol. See *Cephalon, Pol.*
Eisai, Port. See *Eisai, UK.*
Eisai, Rus. See *Janssen-Cilag, Rus.*
Eisai, Singapore. Eisai Asia Regional Services Pte Ltd, 152 Beach Road, 11-04 Gateway East, S 189721, Singapore.
url: www.eisai.com
Eisai, Spain. Eisai Farmaceutica, Avda del Partenon 4, 28042 Madrid, Spain.
url: www.eisai.com
Eisai, Swed. Eisai AB, Box 23060, 104 35 Stockholm, Sweden.
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Eisai, Switz. Eisai Pharma AG, Schaffhauserstrasse 611, 8052 Zürich, Switzerland.
Eisai, Thai. Eisai (Thailand) Marketing Co. Ltd, 6 Fl, Diethelm Tower A, 93/1 Wireless Rd, Bangkok 10330, Thailand.
Eisai, UK. Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, UK.
url: www.eisai.co.uk
Eisai, USA. Eisai Inc., 100 Tice Blvd, Woodcliff Lake, NJ 07677, USA.
url: www.eisai.com
EkoFarmInvest, Ukr. See *Mitek, Ukr.*
Ekohimteh, Rus. Ekohimteh, Leninsky pr-t 117, 394000 G Voronezh, Russia.
url: www.ekohimteh.ru
Ekostatus, Ukr. FPMEP Ekostatus, Borodyanskii per., 3, Kiev, 03608, Ukraine.
url: www.bicyklol.com.ua
EKR, USA. See *Cornerstone, USA.*
EL, Philipp. See *Cathay, Philipp* and *Celsus, Philipp.*
El Monje, Arg. Lab. El Monje Negro, Juan de Garay 269, 1672 San Martin Villa Lynch, Buenos Aires, Argentina.
Eladon, UK. Eladon Ltd, P.O. Box 111, Bangor, Gwynedd, LL57 1ZB, UK.
url: www.elagen.com
Elaiapharm, Switz. See *Interdelta, Switz.*
Elan, Austria. See *Elan, Irl.*
Elan, Canad. See *Draxis, Canad.*
Elan, Cz. See *Elan, Irl.*
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Elan, Fin. See *Elan, UK.*
Elan, Ger. See *Elan, Irl.*
Elan, Gr. See *Elan, Irl.*
Elan, Hung. Elan, Hungary.
Elan, Irl. Elan Pharma (Ireland) Ltd, Treasury Building, Lower Grand Canal Street, Dublin 2, Ireland.
url: www.elan-pharma.ie
Elan, Neth. See *Elan, UK.*
Elan, Norw. See *Meda, Norw.*
Elan, Pol. See *Richter, Pol.*
Elan, Singapore. See *Summit, Singapore.*
Elan, Spain. See *Zeneus, Spain.*
Elan, Switz. See *Voigt, Switz.*
Elan, UK. Elan Pharma Ltd, Abel Smith House, Gunnels Wood Rd, Stevenage, Hertfordshire, SG1 2FG, UK.
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Elan, USA. Elan Phamaceuticals, 7475 Lusk Blvd, San Diego, CA 92121, USA.
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Elanco, Spain. See *Lilly, Spain.*
Elancyl, Fr. See *Galenic, Fr.*
Elanda, Pol. Elanda Zakład Produkcji Środków Farmaceutycznych, ul. Sportowa 9, 97-340 Rozprza, Poland.
url: www.elanda.pl
Elder, India. Elder Pharmaceuticals Pvt. Ltd, Elder House, C-9 Dalia Industrial Estate off Veera Desai Rd, Andheri West, Mumbai 400 053, India.
Elder, Neth. See *ICN, Neth.*
Elder, Philipp. See *QB, Philipp.*
Elder, Singapore. See *Medicell, Singapore.*
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url: www.laboratorioelea.com.ar
Elea, Mex. Laboratorios Elea México SA de CV, Marcelo 9, 3100 Benito Juárez del Valle, Mexico.
Electi, Swed. Electi Medicals Ab, Vastergatan 36, 21121 Malmo, Sweden.
Electra-Box, Swed. Electra-Box Pharma AB, Box 2035, 135 02 Tyreso, Sweden.
url: www.electrabox.com
Electramed, Irl. Electramed Ltd, U2 Kinsealy Business Park, Kinsealy, Co. Dublin, Ireland.
url: www.electramed.ie
Elerte, Fr. Laboratoires des Réalisations Thérapeutiques Elerté, 181-3 rue Andre-Karman, B.P. 101, 93303 Aubervilliers cdx, France.
Elfin, India. Elfin Pharma Pvt Ltd, E-206 Phase 8-B Industrial Area, S.A.S. Nagar 160 055, India.
url: www.elfinpharma.com
Elge, USA. Elge Inc., 1000 Cole, Rosenberg, TX 77471, USA.
url: www.elgeinc.com
Elin, Philipp. Elin Pharmaceuticals Inc., 23, 11th Jamboree St, cor Sct Rallos St, Quezon City, Philippines.
Elisa, India. Elisa Biotech Pvt Ltd, CSC-2/47 Sector 11, Rohini, New Delhi, 110 085, India.
url: www.elisabiotech.com
Elisium, Arg. Elisium S.A., Bacacay 1739, 1406 Buenos Aires, Argentina.
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Elite, India. Elite Pharma Pvt Ltd, 1210-1212 G.I.D.C, Phase-III, Vatva, Ahmedabad 382 445, India.
Elixan Aromatica, Switz. Elixan Aromatica GmbH, Sonnenstrasse 2, 9534 Gähwil, Switzerland.
Elkins-Sinn, USA. See *Wyeth, USA.*
Ellara, Rus. Ellara, F Shtolverka St 20, Petushinskij district, Vladimir, Russia.
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Ellara, Ukr. See *Ellara, Rus.*
Ellem, Ital. See *Pierre Fabre, Ital.*
Elmor, Venez. Laboratorios Elmor S.A., Av. Eugenio Mendoza, Centro Letonia, Piso 16, La Castellana, Apartado Postal 80444, Caracas 1062, Venezuela.
url: www.elmor.com.ve
Elmu, Spain. See *Altana, Spain.*
Elnova, India. Elnova Pharma, Nahan Rd, Village Moginand, Kala-Amb, Sirmour, India.
url: www.elnovapharma.com
Elofar, Braz. Laboratório Farmacêutico Elofar Ltda, Rua Tereza Cristina 85, 88075-970 Florianopolis, SC, Brazil.
Elogis, Gr. Elogis Pharma SA, Kalavrita 2, 145 64 N Kifissia, Greece.
Elorac, USA. Elorac Inc., 100 N Fairway Drive, Suite 134, Vernon Hills, IL 60061, USA.
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Elpen, Malaysia. See *Somedico, Malaysia.*
Elpen, Singapore. See *Green Cross, Singapore.*
Elpen (Ελπεν), Gr. Elpen A.E., 95 Marathonos Ave, 190 09 Pikermi, Greece.
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Elter, Venez. See *Galeno, Venez.*
Elvipe, Gr. Elvipe SA, Piraeus 62, 18547 N Faliro, Greece.
EM, USA. See *EMD, USA.*
Emar, India. Emar Health Care, India.
Embil, Malaysia. See *Pharmaniaga, Malaysia.*
Embil, Philipp. See *Zuellig, Philipp.*
Embil, Rus. See *Schering, Rus.*
Embil, Singapore. See *Pharmaforte, Singapore.*
Embil, Turk. Embil İlaç Ltd. Şti., P. K. 226, Şişli, İstanbul, Turkey.
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Emcure, Philipp. See *Macropharma, Philipp* and *Metro, Philipp.*
Emcure, Rus. See *Actavis, Rus.*
Emcure, Thai. See *Pharmadica, Thai.*
EMD, Canad. EMD Serono, a division of EMD Canada Inc., 200 2695 North Sheridan Way, Mississauga, Ontario, L5K 2N6, Canada.
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EMD Serono, USA. EMD Serono Inc., One Technology Place, Rockland, MA 02370, USA.
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Emerging Pharma, Singapore. See *Sime Darby, Singapore.*
Emgen, India. Emgen Healthcare Pvt Ltd, Tower-B Mansi Complex, Premchand Nagar Rd, Vastrapur, Ahemdabad 380 015, India.
Emil, Hong Kong. See *Hind Wing, Hong Kong.*
Eminence, Canad. Eminence Organic Skin Care, Suite 300, 530 West Broadway, Vancouver, British Columbia, V5Z 1E9, Canada.
Emmaus, USA. Emmaus Medical Inc., 20725 S Western Ave, Suite 136, Torrence, CA 90501-1884, USA.
url: www.emmausmedical.com
Emo-Farm, Cz. See *Emo-Farm, Pol.*
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Emonta, Austria. Emonta Pharma GmbH, Weidelstrasse 21, A-1100 Vienna, Austria.
Emonta, Switz. Emonta GmbH, Unt Rebbergweg 123, 4153 Reinach, Switzerland.
Empifarma, Port. Empifarma Produtos Farmacêuticos SA, Zona Industrial da Pedrulha Fracção B, Estrada Nacional 1, Loreto, 3025-257 Coimbra, Portugal.
Empresa de Nutricion, Arg. Empresa de Nutrición Argentina SRL, Florida 1595, 8003 Bahía Blanca, Buenos Aires, Argentina.
EMS, Braz. EMS Ind. Farmacêutica Ltda, Rodovia SP 101, Km 08, 13186-481 Hortolandia, SP, Brazil.
url: www.ems.com.br
En Ze Jia Shi, China. En Ze Jia Shi Pharmaceutical Co. Ltd, Beijing, China.
Enaleni, S.Afr. Enaleni Pharmaceuticals, P.O.Box 32003, Mobeni 4060, South Africa.
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Enchantress, Canad. Enchantress Hosiery Corp. of Canada Ltd, Unit 1, 70 Weybright Court, Scarborough, Ontario, M1S 4E4, Canada.
Encysive, Cz. See *Encysive, UK.*
Encysive, Denm. See *Encysive, UK.*
Encysive, Fr. See *Encysive, UK.*
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Encysive, Gr. See *Encysive, UK.*
Encysive, Ital. See *Encysive, UK.*
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Encysive, Port. See *Encysive, UK.*
Encysive, UK. Encysive (UK) Ltd, Alder Castle House, 10 Noble St, London, EC2V 7QJ, UK.
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Endo, Canad. See *BMS, Canad.*
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url: www.endofarma.ru
Endo, USA. Endo Pharmaceuticals Inc., 110 Endo Blvd, Chadds Ford, PA 19317, USA.
url: www.endo.com
Endurance, Rus. See *Endurance, USA.*
Endurance, USA. Endurance Products Co., P.O. Box 230489, Tigard, OR 97223, USA.
url: www.endur.com
Endure, Philipp. Endure Medical Inc., 17A Belvedere Tower, San Miguel Ave, Ortigas Complex, Pasig City, Philippines.
Energizer, Canad. Energizer Canada Inc., 165 Kincardine Highway, Walkerton, Ontario, N0G 2V0, Canada.
Energon, Gr. Energon Farmakevtiki, Dilou 13, 121 34 Peristeri, Greece.
Enervit, Ital. Enervit SpA, Viale Monte Rosa 96, 20100 Milan, Italy.
url: www.enervit.com
Eng An, Hong Kong. Eng An Trading Co., Bupa Ctr, 141 Connaught Rd West, Hong Kong.
url: www.eng-an.com.hk
Engelhard, Cz. See *Engelhard, Ger.*
Engelhard, Ger. Engelhard Arzneimittel GmbH & Co. KG, Herzbergstr. 3, 61138 Niederdorfelden, Germany.
url: www.engelhard-am.de
Engelhard, Gr. See *Engelhard, Ger.*
Engelhard, Hong Kong. See *Unico, Hong Kong.*
Engelhard, Hung. See *Engelhard, Ger.*
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Engelhard, Singapore. See *Sime Darby, Singapore.*
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Engelhard, Ukr. See *Naturfarm, Ukr.*
Engelhardt, Hung. See *Kade, Hung.*
English Grains, UK. See *Peter Black, UK.*
English Herbal Medicines, UK. English Herbal Medicines Ltd, Town Park Farm, Brooke, Rutland, LE15 8DG, UK.
url: www.english-herbal.com
Enhua Saide, China. Enhua Saide Pharmaceutical Co. Ltd, Xuzhou, China.
Enorasis, Gr. Enorasis SA, Tropezountos 17 & A Papandreou, 151 27 Attica Melissia, Greece.
Enovachem, USA. Enovachem, 381 Van Ness Ave, Torrance, CA 90501, USA.
url: www.enovachem.us.com
Enshi, China. Shenyang Enshi Pharmaceutical Co. Ltd, 15 Zhenlianger Road, Daoyi Economic Development Zone, Shenyang, Liaoning, 110036, China.
url: www.nsyy.com
ENT Technologies, Austral. ENT Technologies Pty Ltd, Suite 214, 17-33 Milton Parade, Malvern, Victoria 3144, Australia.
ENT Technologies, Hong Kong. See *Four Star, Hong Kong* and *Sino-Asia, Hong Kong.*
Enterprises Importfab, Hong Kong. See *Mita, Hong Kong* and *HPP, Hong Kong.*
Entod, India. Entod Pharmaceuticals Ltd, Ashirwad, S.V. Rd, Bandra (W), Mumbai 400050, India.
url: www.entodpharma.com
Entreprises, China. Entreprises Importfab Inc., China.
Enviroderm, USA. EnviroDerm Pharmaceuticals Inc., 46 Christa McAuliffe Bvld, Plymouth, MA 02360, USA.
url: www.enviroderm.com
Enzifarm, Ukr. OOO NBTS Enzifarm, Stroitelei Street, 35, Ladyzhyn, 24321, Ukraine.
url: www.enzipharm.com
Enzim, Ukr. DP Enzim/ ZAO Enzim, 1st May Street, 60, Vinnytsia, 21050, Ukraine.
url: www.liasten.com
Enzo, India. Enzo Biopharma Ltd, E-54, Sector 6, Noida, India.
Enzon, Canad. See *Enzon, USA.*
Enzon, USA. Enzon, Inc., 685 Route 202/206, Bridgewater, NJ 08807, USA.
url: www.enzon.com
Enzpharma, NZ. eNZpharma Ltd, 27a Cambrai Ave, Mt Roskill, Auckland, New Zealand.
Enzymatic Therapy, Canad. Enzymatic Therapy (Canada) Inc., 2696 Nootka St, Vancouver, British Columbia, V5M 3M5, Canada.
Enzymatic Therapy, USA. Enzymatic Therapy Inc., 825 Challenger Drive, Green Bay, WI 54311, USA.
url: www.enzymatictherapy.com
Enzypharm, Hung. See *Medico Uno, Hung.*
Eon, Hong Kong. See *Pan-Well, Hong Kong.*
EON, Philipp. EON Pharmatek Inc., Unit 703 AIC Burgundy, Empire Tower, ADB Ave Ortigas Centre, Pasig City, Philippines.
Eon, USA. Eon Labs Inc., 1999 Marcus Ave., Lake Success, NY 11042, USA.
url: www.eonlabs.com
E-Pharma, Denm. See *E-Pharma, Ital.*
E-Pharma, Ital. E-Pharma Trento, Via Provina 2, 38040 Ravina di Trento (TN), Italy.
url: www.epharma.it
E-Pharma, Rus. See *Boots, Rus.*
Epicaris, Arg. Lab. Epicaris S.A., Av. Piedrabuena 4190, 1439 Buenos Aires, Argentina.
EpiCept, Cz. See *EpiCept, Ger.*
EpiCept, Ger. EpiCept GmbH, Goethestrasse, 80336 Munich, Germany.
EpiCept, Irl. See *EpiCept, Ger.*
EpiCept, Neth. See *EpiCept, Ger.*
EpiCept, Norw. See *Meda, Norw.*
EpiCept, Port. See *EpiCept, Ger.*
Epiderm, UK. Epiderm Ltd, Wass Lane, Sotby, Market Rasen, LN8 5LH, UK.
url: www.covermark.com
Epien, USA. Epien Medical Inc., 4225 White Bear Pkwy, Suite 600, St Paul, MN 55110, USA.
url: www.epien.com
Epifarma, Ital. Epifarma S.r.l., Via San Rocco 6, 85033 Episcopia (PZ), Italy.
Epimmune, USA. Epimmune Inc., 5820 Nancy Ridge Drive, San Diego, CA 92121, USA.
url: www.cytelcorp.com
EpiPharm, Austral. EpiPharm Pty Ltd, Level 13, 1 Collins St, Melbourne, Vic 3000, Australia.

Epitome, India. Epitome Life Sciences, 85 Chetan Cloth Market, Sarangpur, Ahmedabad 380 002, India.
Epitope, USA. See *Orasure, USA.*
Epsilon, Spain. See *AstraZeneca, Spain.*
Epsilon Health, Gr. Bestoras Vlahos Co - Epsilon Health, K Palama 4, 543 52 Pilaia Thessaloniki, Greece.
EQL, Fin. See *EQL, Swed.*
EQL, Swed. EQL Pharma AB, Magistratsvagen 10, 226 43 Lund, Sweden.
Equazen, Hong Kong. See *Silroc, Hong Kong.*
Equilibre Attitude, Fr. Laboratoires Equilibre Attitude, B.P. 289, 06227 Vallauris cdx, France.
url: www.equitude.com
Equilibre Sinovital, Fr. Equilibre Sinovital, B.P. 41, 59435 Roncq Cedex, France.
url: www.sino-equilibre.com
Equity, S.Afr. Equity Pharmaceuticals (Pty) Ltd, 1 Petunia St, Bryanston 1600, South Africa.
ERA, Denm. ERA Medical ApS, Weidekampsgade 15, st. tv., 2300 Copenhagen S, Denmark.
Eras, Turk. Eras İlaç ve Tibbi Ürünler San.ve Tic Ltd Sti, Altay Çeşme Mh Gülşen Sk Özkanca, Apt N: 1/5, Maltepe, Istanbul, Turkey.
Erbiode, Austria. Erbiode Pharma Service GmbH, Steindorf 65, A-5570 Mauterndorf, Austria.
Erbis, Rus. See *Pulse, Rus.*
Erbis, Ukr. NPTS OOO ERBIS, Raisy Okipnoi, 10B, Kiev, 02002, Ukraine.
Erco, Swed. See *Orion, Swed.*
Ercopharm, Fin. See *Organon, Fin.*
Ercopharm, Neth. See *Multipharma, Neth.*
Ercopharm, Switz. See *Orion, Switz.*
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Er-Em, Turk. Er-Em Farma Diş Tic. Ltd, Turkey.
Erempharma, Fr. Laboratoires Erempharma, 75 rue Bayen, 75017 Paris, France.
Erfa, Belg. Erfa SA, Rue des Cultivateurs 25, 1040 Brussels, Belgium.
url: www.erfa-sa.com
Erfa, Canad. Erfa Canada Inc., 4545 Sherbrooke St W, Westmont, Quebec, H3Z 1E8, Canada.
url: www.erfa.net
Erfar, Gr. Erfar Pharmaceutical Laboratories, Altani, 153 44 Pallini, Greece.
Ergha, Irl. See *Helsinn Birex, Irl.*
Ergoform, Rus. Ergoform, Beskudnikovsky blvd D.59a, 127486 Moscow, Russia.
Erie, Canad. See *Erie, USA.*
Erie, USA. Erie Scientific Co, 20 Post Rd, Portsmouth, New Hampshire 03801, USA.
Eriochem, Arg. Eriochem SA, Ruta 12 Km 452 (16.5), 3100 Parana Avellaneda, Entre Rios, Argentina.
Eris, Austral. Eris Pharmaceuticals (Australia) Pty Ltd, 8-12 Ordish Rd, Dandenong South, Vic 3175, Australia.
Eris, India. See *Enzo, India.*
Erjean, Fr. Laboratoires Erjean, 9 rue de Sébastopol, B.P. 867, 31015 Toulouse cdx 6, France.
Er-Kim, Turk. Er-Kim İlaç San. ve Tic. Ltd. Şti., Gaziumurpaşa Sok. Bimar Plaza, No: 38 D: 11-12, Balmumcu-Beşitaş, İstanbul, Turkey.
url: www.erkim-ilac.com.tr
Erlimpex, Indon. Erlimpex PT, Jl Sultan Agung 83, Semarang 50232, Jawa Tengah, Indonesia.
Ern, Spain. Laboratorios Ern S.A., C/ Pedro IV 499, 08020 Barcelona, Spain.
url: www.ern.es
Ernest Jackson, Irl. See *Ernest Jackson, UK.*
Ernest Jackson, UK. Ernest Jackson & Co. Ltd, 29 High St, Crediton, Devon, EX17 3AP, UK.
url: www.ejackson.co.uk
Erol, Swed. Erol AB, Box 95, 274 22 Skurup, Sweden.
Errekappa, Ital. Errekappa Euroterapici S.p.A., Via C. Menotti 1/A, 20129 Milan (MI), Italy.
url: www.errekappa.it
Errelife, Ital. Errelife Srl, Via XX Settembre 130, 44100 Ferrara (FE), Italy.
url: www.errelife.it
Ertong, China. Ertong Pharmaceutical Co. Ltd., 19 Beijing Road, Harbin Limin Economic and Technological Development Zone, Harbin, Heilongjiang, 150025, China.
url: www.hetzy.com
ErYe, China. ErYe Pharmaceutical Co. Ltd, 859 Panxu Rd, Canglang, Suzhou, Jiangsu, 215002, China.
Esan, Chile. Farmaceutica Esan Ltda, Av. Apoquindo 5555, Of. 1201 Pso 12, Las Condes, Santiago, Chile.
ESBA, USA. ESBA Laboratories Inc., 1001 Jupiter Park Dr, Ste 112, Jupiter, FL 33458, USA.
url: www.esbalabs.com
Escaned, Spain. Escaned, Tomas Breton 46, 28045 Madrid, Spain.
Eschol, Singapore. See *Summit, Singapore.*
Esco, Gr. Esco SA Kostopoulos J & Co, G Septembriou 13, 10432 Athens, Greece.
Esfar, Port. Laboratórios Esfar, SA, Rua da Escala de Medicina Veterinária 15-17, 1049-029 Lisbon, Portugal.
ESI, USA. See *Wyeth, USA.*
Eskom, Rus. Eskom NPK, Russia.
Esma, India. Esma Formulations, SCO-96 Level II, Near Vatika, Sector 5, Panchkula 134 109, India.
Esme, Arg. Lab. Esme S.A.I.C., Uriarte 1686, 1414 Buenos Aires, Argentina.
Esoform, Ital. Esoform S.p.A., Viale del Lavoro 10, 45100 Rovigo (RO), Italy.
url: www.esoform.it
ESP, Canad. See *ESP, USA.*
ESP, USA. ESP Pharma Inc., 2035 Lincoln Highway, Suite 2150, Edison, NJ 08817, USA.
url: www.esppharma.com
Esparma, Austria. See *Esparma, Ger.*
Esparma, Cz. See *Techmed, Cz.*
Esparma, Ger. esparma GmbH, Seepark 7, 39116 Magdeburg, Germany.
url: www.esparma.de
Esparma, Hung. See *Esparma, Ger.*
Esparma, Rus. Esparma, Leninskii prt 148, Of 123-124, 119571 Moscow, Russia.
url: www.esparma-gmbh.ru
Esparma, Ukr. esparma, Akhmatovoi Street, 13, Office 1, Kiev, 02068, Ukraine.
Espe, Austria. Espe HandelsGmbH, Marokkanergasse 9/8, A-1030 Vienna, Austria.
Espe, Cz. See *3M Espe, Ger.*
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Espefa, Pol. Espefa Chemiczno-Farmaceutyczna Spółdzielnia Pracy Espefa, ul. Juliusza Lea 208, 30-133 Kraków, Poland.
url: www.espefa.com.pl
Esro, Switz. Esro SA, Bohnirainstrasse 13, 8800 Thalwil, Switzerland.
url: www.esro.ch
Essedi, Ital. See *Medifood, Ital.*
Essenpharma, Philipp. Essenpharma Inc., 3/F Dr Floro Noza Brosas, Medical Foundation Clinic, 7418 Santillan St, Pasay Rd, Makati City, Philippines.
Essential, NZ. Simply Essential 2000 Ltd, 2 Kamura St., Karitane, Otago, New Zealand.
url: www.essential-nz.com
Essential Health, Singapore. See *Supra Healthcare, Singapore.*
Esseti, China. See *Esseti, Ital.*
Esseti, Ital. Esseti Farmaceutici S.p.A., Via Bellini 7, 89029 Taurianova RC, Italy.
url: www.essetifarma.it
Essex, Austral. See *Schering-Plough, Austral.*
Essex, Chile. See *Schering-Plough, Chile.*
Essex, China. Essex Bio-Technology Ltd, 88 Keji 6th Rd, Hi-Tech Zone, Zhuhai, Guangdong, China.
url: www.essexbio.com
Essex, Ger. Essex Pharma GmbH, Thomas-Dehler-Str. 27, 81737 Munich, Germany.
url: www.essex.de
Essex, Ital. Essex Italia S.p.A., Palazzo Borromini, 20090 Segrate (MI), Italy.
Essex, Neth. See *Schering-Plough, Neth.*
Essex, Philipp. Essex Pharmaceuticals Inc., 12/F San Miguel Properties Ctr, St Francis St, Ortigas Ctr, Mandaluyong City, Philippines.
Essex, Switz. Essex Chemie AG, Weystrasse 20, 6000 Lucerne 6, Switzerland.
url: www.essex.ch
Essilor, Fr. Essilor International, 147 rue de Paris, 94227 Charenton-le-Pont, France.
url: www.essilor.com
Essweil, India. Essweil Pharma, A-2-96/1, Plot No.54 Shri Krishna Nagar Colony, L.B.Nagar, Hyderabad 500 074, India.
Estedi, Spain. Laboratorio Estedi SL, Montseny 41, 08012 Barcelona, Spain.
url: www.estedi.es
Estee Lauder, Canad. Estee Lauder Cosmetics Ltd, 161 Commander Blvd, Agincourt, Ontario, M1S 3K9, Canada.
Ester, India. Ester Formulations, 416/A Lalita Tower, Near Rajpath Hotel, Alkapuri, Baroda, India.
Esteripharma, Mex. Esteripharma Mexico SA de CV, Patricio Sanz 1582, 3100 Del Valle, Mexico DF, Mexico.
Esteve, Cz. See *Esteve, Spain.*
Esteve, Port. Esteve Farma Lda, Av do Forte 3, Edifício Suécia II, Piso 4A, 2790-073 Carnaxide, Portugal.
url: www.esteve.com
Esteve, Spain. Esteve, Avda Virgen Montserrat 221, 08041 Barcelona, Spain.
url: www.esteve.com
Esteves Alves, Port. See *Basi, Port.*
Esthederm, Canad. See *Esthederm, Fr.*
Esthederm, Fr. Institut Esthederm, 3 rue Palatine, 75006 Paris, France.
url: www.esthederm.com
Estroven, UK. Estroven Ltd, P.O.Box 555, Durham, DH1 9EY, UK.
url: www.estroven.co.uk
ET Browne, Canad. See *ET Browne, USA.*
ET Browne, USA. E.T. Browne Drug Co Inc., 440 Sylvan Ave, Englewood Cliffs, NJ 07632, USA.
Etapharm, Austria. Etapharm GmbH, Vormosergasse 3, 1190 Vienna, Austria.
Etex, Chile. Etex Farmaceutica Ltda, Av. Andres Bello 2687, Las Condes, Santiago, Chile.
Ethex, Hong Kong. See *Pan-Well, Hong Kong.*
Ethex, USA. Ethex Corp., 10888 Metro Court, St Louis, MO 63043-2413, USA.
url: www.ethex.com
Ethica, Indon. Ethica Industri Farmasi PT, Jl Pulo Gadung 6, Kawasan Industri Pulo Gadung, Jakarta 13290, Indonesia.
url: www.ethica.co.id
Ethical, Philipp. See *Scheeling, Philipp.*
Ethical, Singapore. See *Kyowa, Singapore.*
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Ethical Research, UK. Ethical Research Marketing, 3A Landgate, Rye, East Sussex, TN31 7LH, UK.
Ethicals, Denm. See *Kemiforma, Denm.*
Ethicon, Fr. Ethicon SAS division of Johnson & Johnson, 1 rue Camille-Desmoulins, TSA 10004, 92787 Issy-les-Moulineaux cdx 9, France.
Ethicon, Ger. Ethicon GmbH, Robert-Koch-Str. 1, 22851 Norderstedt, Germany.
url: www.jnjgateway.com
Ethicon, UK. Ethicon Products Ltd, A division of Johnson & Johnson Medical, P.O. Box 1988, Simpson Parkway, Kirkton Campus, Livingston, EH54 0AB, UK.
url: www.jnjgateway.com
Ethicon, USA. Ethicon Inc., P.O.Box 151, Somerville, NJ 08876-0151, USA.
url: www.ethiconinc.com
Ethicus, Arg. Lab. Ethicus, Argerich 687, 5501 Godoy Cruz, Mendoza, Argentina.
Ethimed, Belg. Ethimed NV, Leuvensestraat 28 B 2, 1800 Vilvoorde, Belgium.
Ethimed, S.Afr. See *Sanofi-Aventis, S.Afr.*
Ethipharm, Pol. See *US Pharmacia, Pol.*
Ethix, India. Ethix Healthcare, 82/33 Kalka-Shimla Highway, Deonghot, Saproon, Solan, 173 211, India.
url: www.ethix.in
Ethnic, Gr. Ethnic Pharmaceutical AE, 18 Chlm. Leof. Marathonos Pallini, 15300 Attici, Greece.
Ethnodex, Fr. See *Biopha, Fr.*
Ethnor, India. Ethnor Ltd, 30 Forjett St, Mumbai 400 036, India.
Ethnor, Venez. See *Janssen-Cilag, Venez.*
Ethypharm, Austria. See *Ethypharm, Fr.*
Ethypharm, Canad. Ethypharm Inc., 200 Blvd Armand Frappier, Laval, Quebec, H7V 4A6, Canada.
Ethypharm, China. Ethypharm Pharmaceutical Co. Ltd, 388 Nanjing West Rd, Ciro's Plaza, Shanghai 200003, China.
url: www.ethypharm.com.cn
Ethypharm, Cz. See *ProMed, Cz.*
Ethypharm, Denm. See *Durascan, Denm.*
Ethypharm, Fin. See *Ethypharm, Fr.*
Ethypharm, Fr. Laboratoires Ethypharm SA, 194 bureaux de la Colline, 92213 St-Cloud, France.
url: www.ethypharm.com
Ethypharm, Hong Kong. See *Primal, Hong Kong.*
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Ethypharm, Neth. See *Ethypharm, Fr.*
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Etifar, Venez. Etifar Laboratorios Eticos-Farmaceuticos, Carretera Barquisimeto - Cebuadare Km.3, Cebadure, Venezuela.
Etnovia, Fin. Etnovia Oy, Teollisuustie 16, 60100 Seinäjoki, Finland.
EU, Neth. EU-Pharma BV, Wilhelminakanaal Noord 7, 4902 VR Oosterhout, Netherlands.
Eubos, Malaysia. See *Propharm, Malaysia.*
Eucerin, Fr. Laboratoires Dermatologiques Eucerin, 111 av. Victor-Hugo, 75116 Paris, France.
url: www.eucerin.com
Eulactol, S.Afr. Eulactol (Pty) Ltd, P.O. Box 3265, Randburg 2125, South Africa.
Eulactol, USA. Eulactol USA Inc., Boca Raton, FL 33433, USA.
Eumedica, Austria. See *Eumedica, Belg.*
Eumedica, Belg. Eumedica SA, Av. Winston Churchill 67, 1180 Brussels, Belgium.
url: www.eumedica.com
Eumedica, Fr. See *Bournonville, Belg.*
Eumedica, Neth. See *Bournonville, Belg.*
Eumedica, UK. See *Bournonville, Belg.*
Eumedis, Belg. See *Therabel, Belg.*
Eupharmed, Ital. EuPharmed Srl, Via Artemisia Gentileschi 26, 80126 Naples (NA), Italy.
Euphoric, India. Euphoric Pharmaceuticals Pvt Ltd, 5th Floor Gedore House, 51-52 Nehru Place, 110019 New Delhi, India.
url: www.euphoricpharma.com
Eureco, Neth. Eureco-Pharma BV, Van Polanenweg 2, 2921 LT Krimpen A/D Ijssel, Netherlands.
Eurim, Austria. Eurim-Pharm Vertriebs GmbH & Co. KG, Walser Bundesstrasse 273, A-5071 Wals bei Salzburg, Austria.
Euro Generics, Philipp. See *Interlink, Philipp* and *Marzan, Philipp.*
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Euro Nippon Kayaku, Pol. See *JKC, Pol.*
Euro Registratie, Neth. Euro Registratie Collectief BV, Van der Giessenweg 5, 2921 LP Krimpen A/D Ijssel, Netherlands.
Euroart, Braz. Euroart Import, Rua Antonia Martins Luis 740, Distrito Industrial Joao Narezzi, CEP 13347404, Brazil.
url: euroartimport.com.br
EuroAsia, Philipp. EuroAsia Pharmaceuticals Inc., 3/F Eurochem Bldg, Cor. Rd 1, Mindanao Ave, Quezon City, Philippines.
EuroCept, Belg. See *EuroCept, Neth.*
EuroCept, China. See *EuroCept, Neth.*
EuroCept, Cz. See *EuroCept, Neth.*
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EuroCept, Ital. See *EuroCept, Neth.*
EuroCept, Neth. EuroCept BV, Trapgans 5, 1244 RL Ankeveen, Netherlands.
url: www.eurocept.nl
EuroCept, Norw. See *EuroCept, Neth.*
EuroCept, Swed. See *EuroCept, Neth.*
Euroderm, Arg. Euroderm Laboratorios S.R.L., Emilio Mitre 1790/94, 1424 Buenos Aires, Argentina.
Euroderm-RDC, Ital. Euroderm-RDC S.p.A., P.le Aquileia 8, 20144 Milan (MI), Italy.
Eurodrug, Hong Kong. Eurodrug Laboratories Ltd, Rm 903, 625 Kings Rd, North Point, Hong Kong.
Eurodrug, Hung. See *Keri, Hung.*
Eurodrug, Malaysia. See *Apex, Malaysia.*
Eurodrug, Mex. Eurodrug Laboratories de México SA de CV, Yucatán 88, 6700 Roma, Mexico.
Eurodrug, Neth. Eurodrug Laboratories, P.O. Box 85769, The Hague, CL 2508, Netherlands.
Eurodrug, Pak. Eurodrug Laboratories, Spencer Distribution Ltd, 17/H Block-6 P.E.C.H.S., P.O. Box 10584, Karachi, Pakistan.
Eurodrug, Philipp. See *Croma, Philipp.*
Eurodrug, Rus. See *Eurodrug, Neth.*
Eurodrug, Singapore. See *JDH, Singapore.*
Eurodrug, Thai. Eurodrug, 8B Fl, Ocean Tower 1, 170 New Ratchapisek Rd, Sukumvit 16 Klongtoey, Bangkok 10110, Thailand.
Euroespes, Spain. Euroespes Biotecnologia Pharma SL, Polgono PG Industrial de Bergondo Cl Parroquia, 15165 A Coruña, Spain.
Euroexim, Spain. Euroexim, C/Emilio Munoz 15, 28037 Madrid, Spain.
Eurofarma, Braz. Eurofarma Laboratórios Ltda, Av. Vereador Jose Diniz 3465, 4603003 São Paulo, SP, Brazil.
url: www.eurofarmalaboratorio.com.br
Eurofarmaco, Ital. Eurofarmaco S.r.l., Via Aurelia 58, 00100 Rome (RM), Italy.
Eurogen, Neth. See *Eurogen, UK.*
Eurogen, UK. EuroGen Pharmaceuticals Ltd, 1st Floor Eagle House, Montpelier Drive, Cheltenham, Gloucestershire, GL50 1TA, UK.
Eurogenerics, Belg. Eurogenerics SA, Esplanade Heysel bte 22, 1020 Brussels, Belgium.
url: www.eurogenerics.be
EuroHealth, Philipp. EuroHealth Care Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.
EuroHealthcare, Philipp. EuroHealthcare Exponents Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.
Eurolab, Arg. Lab. Eurolab Div. Nutricional (Grupo Eurofar SRL), Av. Juan de Garay 3881, 1256 Buenos Aires, Argentina.
Eurolab, S.Afr. See *Eurolab, Arg.*
Euro-Labor, Port. See *Grunenthal, Port.*
Euro-Med, Indon. See *Euro-Med, Philipp.*
Euromed, Ital. Euromed S.r.l., Via A Gentileschi 26, 80126 Naples (NA), Italy.
url: www.euromed.it
Euro-Med, Philipp. Euro-Med Laboratories Phil. Inc., 1000 United Nations Ave, Cor San Marcelino St, Manila, Philippines.
Euromed, Rus. See *Farmamed, Rus.*
Euromex, Mex. Laboratorios Euromex S.A. de C.V., Unicornio No. 142, Col. Prado Churubusco, 04230 Mexico D.F., Mexico.
Euronational, Ital. Euronational Srl, Via Antonelli 17, 28100 Novara (NO), Italy.
url: www.euronational.it
Euroned, Gr. Euroned OE, Pericleous 23, 190 05 Mati Nea Makri Attica, Greece.
Europe Biofarm, Rus. NPO Europe-Biofarm ZAO, Poddubnogo ul. 33a, 400040 Volgograd, Russia.
Europe Cosmetiques, Canad. Europe Cosmetiques Inc., 4930 Chemin Bois Franc, Saint-Laurent, Quebec, H4S 1A7, Canada.
European Community, Rus. C European Community C Ltd, Kashirskoe ul. 24, 115478 Moscow, Russia.
Euro-Pharm, Canad. Euro-Pharm International Canada Inc., 9400 Langelier, Montreal, Quebec, H1P 3H8, Canada.
Europharm, China. See *Europharm, Hong Kong.*
Europharm, Hong Kong. Europharm Laboratories Co. Ltd, 12-14 Dai Wang St, Tai Po Industrial Estate, Tai Po, N.T., Hong Kong.
url: www.europharm.com.hk
Europharm, Rus. See *Europharm, UK.*
Europharm, S.Afr. See *Pfizer, S.Afr.*
Europharm, UK. Europharm Ltd, C4 The Seedbed Centre, Davidson Way, Romford, Essex, RM7 0AZ, UK.
url: europharm.co.uk
Europharm, Ukr. See *Alba, Ukr.*
Europharma, Denm. Europharma DK ApS, Tarp Byvej 81-83 (postboks 4061), 6715 Esjerg N, Denmark.
url: www.europharma.dk
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url: www.europharma.it
Europharma, Philipp. Europharma Inc., 1006 Parktrade Ctr, Madrigal Business Park, Alabang, Muntinlupa City, Philippines.
Europharma, Spain. See *Boehringer Ingelheim, Spain.*
Europhta, Mon. Laboratoires Europhta, Le Concarde, 11 rue du Gabian, MC 98000, Monaco.
Europlant Phytofarm, Pol. Europlant Phytofarm Sp. zo.o., ul. Św. Michała 43, 61-119 Poznań, Poland.
url: www.europlant.com.pl
Eurospital, Ital. Eurospital S.p.A., Via Flavia 122, 34147 Trieste (TS), Italy.
url: www.eurospital.com
Eurosup, Ital. Eurosup, Via Novara 4, 27030 Castello d'Agogna (PV), Italy.
url: www.eurosup.com
Eurovax, Ger. See *Stada, Ger.*
Eurovita, Malaysia. See *JDH, Malaysia.*
Eurovita, Thai. See *Diethelm, Thai.*
Eurowest, Philipp. See *Basic, Philipp.*
EUSA, Austria. See *EUSA, UK.*
EUSA, Belg. See *EUSA, UK.*
EUSA, Canad. EUSA, 3516 rue Griffith, St-Laurent, Quebec, H4T 1A7, Canada.
url: www.eusapharma.com
EUSA, Cz. See *EUSA, UK.*
EUSA, Denm. See *EUSA, UK.*
EUSA, Fin. See *EUSA, UK.*

EUSA, Fr. EUSA Pharma, les Jardins d'Eole, 3 allée des Séquoias, 69760 Limonest, France.
url: www.eusapharma.com

EUSA, Ger. EUSA Pharma GmbH, Grillparzerstr. 18, 81675 München, Germany.
url: www.eusapharma.com

EUSA, Gr. See *EUSA, UK.*

EUSA, Irl. See *EUSA, UK.*

EUSA, Israel. See *CTS, Israel.*

EUSA, Neth. See *EUSA, UK.*

EUSA, Pol. See *EUSA, UK.*

EUSA, Port. EUSA Portugal, Praca Nuni Rodrigues dos Santos n7, 1600-171 Lisbon, Portugal.
url: www.eusapharma.com

EUSA, Swed. See *EUSA, UK.*

EUSA, UK. EUSA Pharma, The Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA, UK.
url: www.eusapharma.com

EUSA, USA. EUSA Pharma (USA) Inc., One Summit Square, 1717 Langhorne-Newtown Rd, Suite 201, Langhorne, PA 19047, USA.
url: www.eusapharma.com

Eutherapie, Belg. See *Servier, Belg.*

Eva, India. Eva Biotech Pvt Ltd, 105 Anand Mangal Complex-1, CG Road, Navrangpura, Ahmedabad, India.
url: www.evobiotech.com

Evacare, India. Evacare Pharma Complex, B/h Marketing Yard, G.I.D.C. Estate, Wadhwan City, Surendranagar 363 035, India.
url: www.evacarelab.com

Evalar, Rus. Evalar JSC, 23/6 Sotsialisticheskaya Str, Biysk, Altai Territory 659332, Russia.
url: www.evalar.ru

Evans, Fin. See *Oriola, Fin.*

Evans, Fr. See *Celltech, Fr.*

Evans, Irl. See *Novartis, UK.*

Evans, Israel. See *Novartis, Israel.*

Evans, Neth. See *GSK, Neth.*

Evans, Norw. See *Mericon, Norw.*

Evans, Singapore. See *Ziwell, Singapore.*

Evans, Spain. See *Celltech, Spain.*

Evans, UK. See *Novartis, UK.*

Evans Medical, Irl. See *GSK, Irl.*

Evans Medical, Israel. See *Novartis, Israel.*

Evans Vaccines, Switz. See *Lifebiotech, Switz.*

Evans Vaccines, UK. See *Novartis, UK.*

Evapharm, Philipp. Evopharma Co, Unit 703 West Twr, Tektite Bldg, PSEC Exchange Rd, Ortigas Ctr, Pasig City, Philippines.
url: www.evapharm.com.ph

Evaux, Fr. Évaux Laboratoires, 67 av de la République, 23110 Évaux-les-Bains, France.
url: www.evaux-laboratoires.fr

Eveline Charles, Conad. Eveline Charles SPAS, 302 City Center East 10205, 101 St, Edmonton, Alberta, T5J 4H5, Canada.

Ever Neuro, Austria. Ever Neuro Pharma GmbH, Oberburgau 3, 4866 Unterach, Austria.

Ever Neuro, China. Ever Neuro Pharma, 22 Guanghua Rd, Chaoyang District, Beijing, 100022, China.
url: www.everpharma.com

Ever Neuro, Cz. See *Ever Neuro, Austria.*

Ever Neuro, Neth. See *Ever Neuro, Austria.*

Ever Neuro, Philipp. See *Globo Asiatico, Philipp.*

Ever Neuro, Thai. See *Schumit, Thai.*

Everett, USA. Everett Laboratories Inc., 29 Spring St, West Orange, NJ 07052, USA.
url: www.everettlabs.com

Everidis, USA. Everidis Health Sciences, 2900 Brannon Ave, St Louis, MO 63139, USA.
url: www.everidisprobiotics.com

Everlife, China. Everlife Pharmaceutical Co. Ltd, Hefei, China.

Evers, Ger. Pharmazeutische Fabrik Evers GmbH & Co. KG, Siemensstr. 4, 25421 Pinneberg, Germany.
url: www.pharmaevers.de

Evers, Hong Kong. See *Pinneberg, Hong Kong.*

Evers, Indon. See *Pharos, Indon.*

Evers, Thai. See *Sriprasit, Thai.*

Evershine, India. Evershine Healthcare, SCF 271 G Floor, Motor Market, Manimajra, Chandigarh, 160 101, India.

Everton, USA. See *Trx Pharma, USA.*

Evisco, Ger. Evisco-Pharma, Klosterplatz 6, 87509 Immenstadt, Germany.
url: www.evisco-pharma.de

Evolabis, Braz. Evolabis Produtos Farmaceuticos Ltda, Rua Urussui 92 Conj 101/104, 4542050 Sao Paulo Itaim Bibi, Sao Paulo, Brazil.

Evolan, Denm. See *Evalan, Swed.*

Evolan, Swed. Evalan Pharma AB, Box 120, 182 12 Danderyd, Sweden.
url: www.evolan.se

Evromedeks, Ukr. Evromedeks, Turgenevskaya Street, 48/13, Office 10, Kiev, 01054, Ukraine.

Evroplant, Ukr. Evroplant Phytopharm Sp.z.o.o, ul Marshal Rokossovskogo 8B, Office 3, 04201 Kiev, Ukraine.

Ewopharma, Cz. Ewopharma sro, Korunni 127, 130 00 Prague 3, Czech Republic.

Ewopharmo, Hung. Ewopharma AG Képviselet, Gyorskocsi u 12 II./3, 1011 Budapest, Hungary.

Ewopharma, Pol. Ewopharma AG Spółka zo.o., ul. Świętokrzyska 36 m 16, 00-116 Warsaw, Poland.

Ewopharma, Ukr. Ewopharma AG, ul. Nikola Pimonenko 13, 6D Office 35, 04050 Kiev, Ukraine.

Exakta, Mex. Pharmacos Exakta S.A. de C.V., Av. del Nino Obrero No. 651, Col. Chapalita Sur, 45040 Guadalajara, Jal., Mexico.

Exalenz, Israel. Exalenz Bioscience Ltd, 4 Ha'maayan St, Modiin, 71700, Israel.
url: www.exalenz.com

Excalibur, Austria. See *Excalibur, UK.*

Excalibur, Canad. Excalibur Chemicals, 1120 McDonald St, Regina, Saskatchewan, S4N 4X3, Canada.

Excalibur, Neth. See *Excalibur, UK.*

Excalibur, Pol. See *Excalibur, UK.*

Excalibur, UK. Excalibur Pharma, 26-28 Bedford Row, London, WC1R 4HE, UK.

Excare, India. Excare Laboratories, 11 Godown Complex, Kothariya Road, Wadhwan City, Surendranagar 363 035, India.
url: www.excarelab.com

Excelentia, Arg. Laboratorios Excelentia S.A., Santo Domingo 4088, 1437 Buenos Aires, Argentino.

Excella, Cz. See *Excella, Ger.*

Excella, Ger. Excella GmbH, Nürnberger Strasse 12, 90537 Feucht, Germany.
url: www.excella-pharma-source.de

Excella, India. Excella Life Sciences Pvt Ltd, R-9 Lower Ground Floor, Green Park Extn, New Delhi 110 016, India.
url: excellalifesciences.com

Excellium, USA. Excellium Pharmaceuticals Inc., 3G Oak Rd, Fairfield, NJ 07004-9600, USA.

Excelvision, Israel. See *Resdevco, Israel.*

Excelvision, Malaysia. See *DKSH, Malaysia.*

Excelvision, Switz. Excelvision AG, Riethofstrasse 1, 8442 Hettlingen, Switzerland.
url: wwwexcelvision.ch

Excelvision, Thai. See *Maxim, Thai.*

Excelvision, Ukr. See *Excelvision, Switz.*

Exel, Belg. See *Nycomed, Belg.*

Exelgyn, Austria. See *Exelgyn, Fr.*

Exelgyn, Denm. See *Nordic Drugs, Denm.*

Exelgyn, Fin. See *Exelgyn, Swed.*

Exelgyn, Fr. Exelgyn, 6 rue Christophe-Colomb, 75008 Paris, France.

Exelgyn, Gr. See *Exelgyn, Fr.*

Exelgyn, Israel. See *Lapidot, Israel.*

Exelgyn, Neth. See *Exelgyn, Fr.*

Exelgyn, Norw. See *Exelgyn, Swed.*

Exelgyn, Port. See *Medirex, Port.*

Exelgyn, Spain. See *Exelgyn, Fr.*

Exelgyn, Swed. Exelgyn, Box 1343, 181 25 Lidingo, Sweden.

Exelgyn, UK. Exelgyn Laboratories, P.O. Box 4511, Henley-on-Thames, Oxfordshire, RG9 5ZQ, UK.

Exelixis, Gr. Exelixis SA, Mesogion 501, 153 43 Aghia Paraskevi, Greece.

Exelixis, USA. Exelixis Inc., 210 East Grand Ave, So. San Francisco, CA 94080, USA.
url: www.exelixis.com

Exflora, Switz. See *Uhlmann-Eyraud, Switz.*

Exir, Rus. See *Darou Pakhsh, Rus.*

Expanpharm, Fr. Laboratoires Expanpharm International, 60 rue Fessart, 92100 Boulogne, France.

Expanpharm, Rus. See *Expanpharm, Fr.*

Expanpharm, Switz. See *Uhlmann-Eyraud, Switz.*

Expanscience, Denm. See *Expanscience, Fr.*

Expanscience, Fr. Laboratoires Expanscience, 10 av. de l'Arche, 92400 Courbevoie, France.
url: www.expanscience.com

Expanscience, Irl. See *Expanscience, Fr.*

Expanscience, Neth. See *Expanscience, Fr.*

Expanscience, Pol. See *Medagro, Pol.*

Expanscience, Port. Laboratorios Expanscience, Rua Pinheiro Chagas, 17 5 Andar, 1050-174 Lisbon, Portugal.

Expanscience, Rus. See *CSC, Rus.*

Expanscience, Spain. Expanscience, Pol. Ind. Los Olivos, Adaptación 33, Getafe, 28906 Madrid, Spain.
url: www.mustela.com

Experimental Production, Rus. See *Veropharm, Rus.*

Expomedica, Port. Expomédica Sociedade Exportadora Importadora de Material Médico Lda, Av. 5 de Outubro 89 -1, 1050-050 Lisbon, Portugal.
url: www.expomedica.pt

Express Care, NZ. Express Care Direct, New Zealand.

Exsymol, Man. Exsymol S.A.M., 4 Avenue du Prince Héréditaire Albert, MC 98000, Monaco.
url: www.exsymol.com

Extractum, Cz. See *Extractum, Hung.*

Extractum, Hung. Extractum Pharma Rt, Megyeri ut 64, 1044 Budapest, Hungary.
url: www.expharma.hu

Extrawell, China. Extrawell-South Asia Pharmaceutical Ltd, East Tower 3303, 753 Dongfeng East Rd, Yuexiu District, Guangzhou 510080, Guangdong, China.
url: www.ew-sap.com

Exxe, Ital. Exxe S.r.l., Via Breda 120, 20126 Milan (MI), Italy.
url: www.exxe.it

Eyekare, India. Eyekare Kilitch Ltd, 41 Ujagar Industrial Estate, WT Patil Marg, Deonar, Mumbai 400 088, India.

Eyelab, Ital. Eyelab srl, Via Aldebaran 21, 95127 Catania (CT), Italy.
url: www.eyelab.it

Eyetech, USA. Eyetech, 3 Times Square, 12th Floor, New York, NY 10036, USA.
url: www.eyetech.com

E-Z-EM, Belg. See *Bracco, Neth.*

E-Z-EM, Canad. E-Z-EM Canada Inc., 11065 L-H Lafontaine, Anjou, Quebec, H1J 2Z4, Canada.
url: www.ezemcanada.com

E-Z-EM, Cz. See *E-Z-EM, UK.*

E-Z-EM, Denm. See *Initios, Denm.*

E-Z-EM, Hung. See *Amersham, Hung.*

E-Z-EM, Irl. See *Bracco, UK.*

E-Z-EM, Israel. See *Promedico, Israel.*

E-Z-EM, Neth. See *Rooster, Neth.*

E-Z-EM, Port. See *Martins & Fernandes, Port.*

E-Z-EM, Swed. See *E-Z-EM, UK.*

E-Z-EM, UK. E-Z-EM Ltd, Avonbury Business Park, Howes Lane, Bicester, Oxfordshire, OX26 2UA, UK.
url: www.ezem.com

E-Z-EM, USA. E-Z-EM, 1111 Marcus Ave, Suite LL26, Lake Success, NY 11042, USA.
url: www.ezem.com

F5 Profas, Spain. F5 Profas, Ed Indubuilding Goico, Via Las Poblados 17, 28033 Madrid, Spain.
url: www.f5profas.com

Fabop, Arg. Lab. Fabop S.A. Ruta Nacional Nro. 19 Km 204, 2432 El Tio, Cordoba, Argentina.

Fabra, Arg. Lab. Fabra S.R.L., Carlos Villate 5271, 1605 Munro, Buenos Aires, Argentina.

Face, Ital. Face Laboratori Farmaceutici S.p.A., Via Sordorella 43, 16162 Genova (GE), Italy

Faces, Canad. Faces Cosmetics Inc., Unit 6, 30 Macintosh Blvd, Vaughan, Ontario, L4K 4P1, Canada.

Fada, Arg. Fada Pharma S.A., Tronador 4890, Piso 11, 1437 Buenos Aires, Argentina.
url: www.fada.com.ar

Faes, Spain. Faes Farma, Alpedrete 24, 28045 Madrid, Spain.
url: www.faes.es

Faes, Ukr. See *Farmasoft, Ukr.*

Fagron, Belg. Fagron nv, Textielstraat 20, 8790 Waregem, Belgium.
url: www.fagron.com

Fagron, Neth. Fagron Pharmaceuticals bv, Hoogeveenenweg 210, 2913 LV Nieuwerkerk A/D Ijssel, Netherlands.

Fahrenheit, Indon. See *Pratapa Nirmala, Indon.*

Fahrenheit, Philipp. See *PNF, Philipp.*

Fahrvitex, Hung. Fahrvitex-B Kft, Dózsa György út 144, 1134 Budapest, Hungary.
url: www.fahrvitex.hu

Fair-Med, Ger. Fair-Med Healthcare, Planckstrasse 13, 22765 Hamburg, Germany.
url: fair-med.eu

Fair-Med, Neth. See *Fair-Med, Ger.*

Foisal, Philipp. See *Alico Impex, Philipp.*

Fako, Turk. Fako İlaçari A.Ş., Büyükdere Cad. No: 205, Levent, İstanbul, 80650 4., Turkey.
url: www.fako.com.tr

Falcon, USA. See *Alcon, USA.*

Falk, Austria. See *Falk, Ger.*

Falk, Belg. See *Falk, Neth.*

Falk, China. See *CMS, China.*

Falk, Cz. See *Ewopharma, Cz.*

Falk, Denm. See *Meda, Denm.*

Falk, Fin. See *Falk, Ger.*

Falk, Ger. Dr. Falk Pharma GmbH, Leinenweberstr. 5, 79108 Freiburg, Germany.
url: www.drfalkpharma.de

Falk, Gr. See *Galenica, Gr.*

Falk, Hong Kong. See *Jacobson, Hong Kong.*

Falk, Hung. See *Medical Consulting, Hung.*

Falk, Indon. See *Darya-Varia, Indon.*

Falk, Irl. See *Falk, UK.*

Falk, Israel. See *Rafa, Israel.*

Falk, Malaysia. See *JDH, Malaysia.*

Falk, Neth. Dr Falk Pharma Benelux BV, Claudius Prinsenlaan 136A, 4818 CP Breda, Netherlands.

Falk, Norw. See *Meda, Norw.*

Falk, Philipp. See *Zuellig, Philipp.*

Falk, Pol. See *Ewopharma, Pol.*

Falk, Port. Dr. Falk Pharma Portugal Lda, Av. José Gomes Ferreiro 11, Edificio Atlas II - 3 Piso, Sala 33, Miraflores, 1495-139 Algés, Portugal.

Falk, Rus. Dr Falk Pharma, Butyrskii Val ul 68/70 str 4,5, 127055 Moscow, Russia.

Falk, Singapore. See *JDH, Singapore.*

Falk, Spain. See *Falk, Ger.*

Falk, Thai. See *Zuellig, Thai.*

Falk, UK. Dr Falk Pharma UK Ltd, Bourne End Business, Cores End Rd, Bourne End, Buckinghamshire, SL8 5AS, UK.

Falk, Ukr. Dr. Falk Pharma GmbH, Krakovskaya Street, 22, Office 317, Kiev, 02094, Ukraine.
url: www.drfalkpharma.com.ua

Fallene, USA. Fallene Ltd, 2555 Industry Lane, West Norriton, PA 19403, USA.
url: www.fallene.com

Falqui, Ital. Falqui Prodotti Farmaceutici S.p.A., Via Fabio Filzi 8, 20124 Milan (MI), Italy.
url: www.falqui.it

FAMA, Ital. F.A.M.A. Istituto Chimico Biologico S.r.l., Via A. Sauli 21, 20127 Milan (MI), Italy.

Famac, Ital. Lab. Famac, Cosmetologia Scientifica, Via G Ripamonti 9, 20136 Milan (MI), Italy.

Famar, Gr. Famar S.A., 63 Ag. Demetriou Str., 174 56 Alimos, Greece.
url: www.famar.gr

Family Health, Rus. Family Health ZAO, Bolshaya Serpukhovskaya st. 60, 113093 Moscow, Russia.
url: www.familyhealth.ru

Family Planning Sales, UK. Family Planning Sales Ltd, 28 Kelburne Rd, Cowley, Oxford, Oxfordshire, OX4 3SZ, UK.

Famy, Denm. See *Famy, UK.*

Famy, Malaysia. See *Antah, Malaysia.*

Famy, Neth. See *Famy, UK.*

Famy, Norw. See *Famy, UK.*

Famy, Philipp. See *DKT, Philipp.*

Famy, Thai. See *Neopharm, Thai.*

Famy, UK. Famy Care Europe Ltd, 1 Wood St, London, EC2V 7WS, UK.

Fandasy, Hong Kong. Fandasy Co. Ltd, Unit A, 18/F Federal Ctr, 77 Sheung On St, Chaiwan, Hong Kong.

Fang Ming, China. Fang Ming Pharmaceutical Co. Ltd, Shandong, China.

Fang Sheng, China. Fang Sheng Pharmaceutical Co. Ltd, Hunan, China.

FangDa, China. FangDa Pharmaceutical Co Ltd, 363 Shen Brick Rd, Qingpu District, Shanghai 201714, China.
url: www.fdyy.com

FangYuan, China. FangYuan Pharmaceutical Co. Ltd, Hahai 108, Xinbei, Changzhou, Jiangsu, China.
url: www.fangyuan-pharma.com

Fannin, Irl. Fannin Ltd, South County Business Park, Leopardstown, Dublin 18, Ireland.
url: www.fannin.ie

Far East, Singapore. Far East Drug Co (Pte) Ltd, 1 Sophia Rd, 08-01 Peace Centre, S 228149, Singapore.

Far East, Thai. Far East Pharmaceutical Ltd Part, 58, 60 Soi Charan 68, Charansanitwong Rd, Bangkok 10700, Thailand.

Faran, Gr. Faron Laboratories S.A., Achias & Trizinias, 145 64 N. Kifissia, Greece.
url: www.faran.gr

Faran, Rus. See *Faran, Gr.*

Faratzi, Gr. Faratzi M SA, Fidippidou 43, 115 27 Goudi, Athens, Greece.

Farbio, Port. Farbio Produtos Farmacêuticos Unipessoal Lda, Rua Correia Teles 70, 1350-103 Lisbon, Portugal.

Farbo, Ital. Farbo s.n.c. del dott. Donato Mele & C., Via Stelvio 12/18, Frazione di Ospiate, 20021 Bollate (MI), Italy.

Farchim, Cz. See *Farchim, Switz.*

Farchim, Switz. Farchim SA, Zl de Planchy, Bulle, Switzerland.

Farco, Austria. See *Farco, Ger.*

Farco, Cz. See *Farco, Ger.*

Farco, Denm. See *Tjellesen, Denm.*

Farco, Ger. Farco-Pharma GmbH Pharmazeutische Präparate, Gereonsmühlengasse 1-11, 50670 Cologne, Germany.
url: www.farco-pharma.de

Farco, Hong Kong. See *Sincerity, Hong Kong.*

Farco, Hung. See *Co Ord-Med, Hung.*

Farco, Irl. See *Allphar, Irl.*

Farco, Israel. See *CTS, Israel.*

Farco, Neth. See *Farco, Ger.*

Farco, Port. See *Farco, Ger.*

Farco, Rus. See *Invar, Rus.*

Farcaral, Mex. Profesional Medica Farcoral S.A. de C.V., Circuito Norte No. 28, Unidad Guadalupe, 72560 Puebla, Mexico.

Fardi, Port. See *Fardi, Spain.*

Fardi, Spain. Fardi, Grassot 16, 08025 Barcelona, Spain.
url: www.fardi.es

Fargim, Ital. FAR.G.IM S.r.l., Via Cervignano 29, 95129 Catania (CT), Italy.

Fargin, Port. See *Tecnifar, Port.*

Faria, Braz. Laboratório Farmacêutico Faria Ltdo, Rua Coronel Delfino Nonato de Faria 151, Sta Terezo, 36020-170 Juiz de Fora, MG, Brazil.

Fariberica, Port. Faribérica, SA, Estrada da Luz 90 - 9 D/E, 1600-160 Lisbon, Portugal.

Farillon, UK. Farillon Ltd, Ashton Rd, Harold Hill, Romford, Essex, RM3 8UE, UK.
url: www.farillon.co.uk

Farko, Pol. Zakład Produkcyjno Usługowy Farko SC, ul. 22 Lipca 4, 89-115 Mrocza, Poland.

FarKoS, Ukr. See *Artur, Ukr.*

Farlab, Port. Farlab Comercio e Representações Lda, Zona Industria da Portelinha APTDO 2050, Av. Associação Comercial e Ind de Gondomar 390/410, 4510-688 Famzeres, Portugal.

Farline, Spain. Farline, C/Sonta Engracia31, 28010 Madrid, Spain.

Farma, Venez. Grupo Farma S.A., Av. Principol, Los Ruices, Edif. Farma, Urb. Los Ruices, Caracas 1071, Venezuela.
url: www.grupafarma.com

Farma 1, Ital. Farma 1 S.r.l., Via privata Maria Teresa 11, 20100 Milan (MI), Italy.

Farma 1000, Ital. Farma 1000 S.r.l., Via G. D'Arezzo 4, 20145 Milan (MI), Italy.

Farma Derma, **Ital.** Farma-Derma S.r.l., Via dei Bersaglieri 10, 40010 Sala Bolognese (BO), Italy.
url: www.farmaderma.it

Farma Iberica, Philipp. See *Metro, Philipp.*

Farma Lepori, Spain. Farma Lepori, Osi 7-9, 08034 Barcelona, Spain.
url: www.farmalepori.com

Farma Plus, Denm. See *Farma Plus, Norw.*

Farma Plus, Norw. Farma Plus AS, Serkedalsveien 108, 0369 Oslo, Norway.
url: www.farmaplus.no

Farma Ratio, Spain. See *Ratiopharm, Spain.*

Farmabion, Spain. See *Alter, Spain.*

Farmaceutica H, Mex. Farmacéutica Hispanoamericana SA de CV, Lago Iseo 184, 11320 Anahuac, Mexico.

Farmachimici, Ital. Farmachimici S.r.l., Via Mercanti 36, 84121 Salerno (SA), Italy.
url: www.farmachimici.it

Farmachrom, Gr. Farmachrom AE, 6th Km Paianias-Markopoulou, 190 03 Attica, Greece.

Farmaco, Pol. Farmaco, ul. Polarna 14, 93-465 Łódź, Poland.

Farmacologica Milanese, Ital. Laboratorio Farmacologico Milanese S.r.l., Via Monterosso 273, 21042 Caronno Pertusella (VA), Italy.
url: www.lfm.it

Farmacom, Pol. See *Grunenthal, Pol* and *Pliva Krakow, Pol.*

Farmaconsult, Belg. Farmaconsult, Platanendreef 45, 9090 Melle, Belgium.
url: www.farmaconsult.be

Farmagal, Arg. Farmagal S.R.L., Bahia Blanca 1660, 1407 Buenos Aires, Argentina.
url: www.farmagal.com.ar

Farmagan, Ital. Farmagan S.A., Via Fosso del Canneto 34, 47891 Galazzana (Rep. San Marino), Italy.

Farmagen, Ital. Farmagen Srl, Viale Leopoldo Muzii 67, 65123 Pescara, Italy.

Farmagen, Rus. Farmagen, Piskarevsky Ave 25, 195248 St Petersburg, Russia.

Farmagon, Norw. Farma Holding AS, Karihaugv. 22, 0186 Oslo, Norway.
url: www.farmagon.no

Farmak, Pol. Farmak Sp. zo.o., ul. Nałęczowska 5a, 02-922 Warsaw, Poland.

Farmak, Rus. See *Farmak, Ukr.*

Farmak, Ukr. OAO Farmak, Frunze Street, 63, Kiev, 04080, Ukraine.
url: www.farmak.ua

Farmaka, Ital. Farmaka S.r.l., Via Vetreria 1, 22070 Grandate (CO), Italy.
url: www.farmaka.it

Farmakochimiki, Gr. Botonia Farmakochimiki A.E., Pigasou 18, 151 25 Marousi, Greece.

Farmakon, Rus. Farmakon, ul. Tsvetochnaya 18, 196084 St Petersburg, Russia.

Farmakon, Ukr. See *Mitek, Ukr.*

Farmakopea, Ital. See *Unifarm, Ital.*

Farmakor, Rus. Farmakor ZAO, Kamennoostrovskijj prosp., d. 67, a/ja 76, 197022 Saint Petersburg, Russia.
url: www.pharmacor.ru

Farmal, Pol. Wytwórnia Farmaceutyczna Farmal, ul. Rycerska 2/33, 42-500 Będzin, Poland.

Farmalab, Braz. Farmalab Industrias Químicas e Farmacêuticas Ltda, Av. BrigADEIRO Faria Lima 1811, 12 degrees andar, 01451-001 São Paulo, SP, Brazil.
url: www.farmalabchiesi.com.br

Farmalex, Gr. Farmalex S.A., 15-17 Anast Tsocha, 115 10 Athens, Greece.

Farmalider, Neth. See *Farmalider, Spain.*

Farmalider, Port. See *Farmalider, Spain.*

Farmalider, Spain. Farmalider, C/ Aragoneses 9, Alcobendas, 28100 Madrid, Spain.

Farmaline, Thai. Farmaline Co. Ltd, 48 Soi Urupong 1, Rama 6 Rd, Rajthevee, Bangkok 10400, Thailand.

Farmalter, Port. Farmalter Produtos Farmaceuticos e Dieteticos Lda, Estrada Marco do Grilo, Zemouto, 2830 Coina, Portugal.

Farmalux, Port. See *Tecnifar, Port.*

Farmamed, Rus. Farmamed, 5 Verchnii per 19 lit A, 194292 St Petersburg, Russia.
url: www.farmamedspb.ru

Farmamos, Rus. Farmamos, St Petersburg, Russia.

Farmamprant, Gr. Farmamprant SA, 15th Km National Rd Athens-Lamia, 145 10 Kifissia, Greece.

Farmamust, Gr. Farmamust Epe, Plateia Pantazopoulou 7, GR-10443 Kolonos Attikis, Greece.

Farmanic, Gr. Farmanic, Fylis 137, 134 51 Kamatero, Greece.

Farmanova, Ital. Farmanova AFM S.r.l., Via Flaminia 287 Sc. A. int.10, 00196 Rome (RM), Italy.
url: www.farmanova.it

Farmapark, Rus. See *Farmstandart, Rus.*

Farmapek, Rus. Farmapek

Farmapek, Turk. Farmapek Tibbi Ürünler Sanayi Ticaret Ltd Sti, Tütuf Paşa Sk N:19/A, Findikzade, Istanbul, Turkey.

Farmapol, Pol. Zakład Chemiczno-Farmaceutyczny Farmapol Sp. zo.o., ul. Św. Wojciech 29, 61-749 Poznań, Poland.
url: www.farmapol.pl

Farmaprojects, Cz. See *Farmaprojects, Spain.*

Farmaprojects, Denm. See *Farmaprojects, Spain.*

Farmaprojects, Neth. See *Farmaprojects, Spain.*

Farmaprojects, Spain. Farmaprojects SA, Santa Eulalia 240-242, L'Hospitalet de Llobregat, 08902 Barcelona, Spain.
url: www.farmaprojects.es

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Farma-Projekt, Pol. Farma-Projekt Sp. zo.o., ul. Salwatorska 14, 30-109 Kraków, Poland.
url: www.farmaprojekt.pl

Farmasa, Braz. Laboratório Americano de Farmocoterapia S/A, Rua Nova York 245, 04560-908 São Paulo, SP, Brazil.
url: www.farmasa.com.br

Farmasa, Mex. Laboratorios Farmasa, S.A. de C.V., Bufalo No. 27, Col. del Valle, 03100 Mexico D.F., Mexico.

Farmasan, Ger. Farmasan Arzneimittel GmbH & Co. KG, Pforzheimer Str. 5, 76227 Karlsruhe, Germany.

Farmasan, Thai. See *JDH Borneo, Thai.*

Farmasierra, Spain. Farmasierra S.A., Ctra de Irun Km 26.2, San Sebastian de Los Reyes, 28100 Madrid, Spain.
url: www.farmasierra.com

Farmasintez, Rus. Farmasintez, ul Tuhachevskogo 3, 664040 Irkutsk, Russia.

Farmasix, Port. Farmasix Produtos Farmacêuticos Sociedade Unipessoal Lda, Quinta da Fonte, Edificio Vasco da Gama 19, 2770-192 Paço de Arcos, Portugal.

Farmasoft, Rus. See *Pharmasoft, Rus.*

Farmasoft, Ukr. Farmasoft LLC, Polovetskaya Street, 14, 04107 Kiev, 04107, Ukraine.

Farmasur, Spain. Farmasur, Pol Store C/H 28-A, 41008 Seville, Spain.

Farmasyn, Gr. Farmasyn A.E., Monis Damastas 6B, 121 33 Peristeri, Greece.

Farmatec, Spain. Laboratorios Farmatec Investigacion SL, C/Paris 120, 08036 Barcelona, Spain.

Farma-Tek, Turk. Farma-Tek Ilaç Ltd. Sti., Kisikli Cad., Oymaci Sok. No: 16/A, Altunizade, Istanbul, 34662, Turkey.
url: www.farma-tek.com

Farmaten, Gr. See *Pharmathen, Gr.*

Farmatrading, Ital. See *Ci & Di, Ital.*

Farmazak, Gr. Pharmazak AU, Naoussa 31, 104 47 Botanical, Athens, Greece.

Farmec, Ital. Farmec S.n.c., Via W Flemming 7, 37026 Pescantina (VR), Italy.

Farmed, Turk. Farmed Ilaç Ltd. Şti., Şenlik Mah, Yeşil Ada Sok. No:5 K: 1, Florya, Istanbul, Turkey.
url: www.farmed.com.tr

Farmedia, Gr. Farmedia S.A., 22 Athinas & Apollonos str, 153 44 Gerakas, Greece.
url: www.farmedia.gr

Farmellas, Gr. Farmellas, Greece.

Farmex, Gr. See *Pharmex (Φαρμεξ), Gr.*

Farmia, Cz. Farmia sro, Czech Republic.
url: www.farmia.sk

Farmia, Hung. Farmia sro, Hungary.
url: www.farmia.sk

Farmigea, Ital. Farmigea S.p.A., Via G. Oliva 8, 56121 Ospedaletto-Pisa, Italy.
url: www.farmigea.it

Farmila, Cz. See *Rephochem, Cz.*

Farmila, Ital. Farmila-Thea Farmaceutici S.p.A., Via E. Fermi 50, 20019 Settimo Milanese (MI), Italy.
url: www.farmila.it

Farmilia, Gr. Farmilia Inc., Favierou 48, 104 38 Athens, Greece.

Farmina, Pol. Farmina Sp. zo.o., ul. Lipska 44, 30-721 Kraków, Poland.
url: www.farmina.pl

Farminova, Port. See *Pfizer, Port.*

Farmitalia, Cz. See *Pfizer, Ital.*

Farmitalia, Israel. See *Perrigo, Israel.*

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Farmitalia Carlo Erba, Austral. See *Pharmacia, Austral.*

Farmitalia Carlo Erba, Fr. See *Pharmacia, Fr.*

Farmitalia Carlo Erba, Ger. See *Pfizer, Ger.*

Farmitalia Carlo Erba, Ital. See *Pfizer, Ital.*

Farmitalia Carlo Erba, UK. See *Pfizer, UK.*

Farmlux, Rus. Farmlux, Trofimova ul 6, 115432 Moscow, Russia.

Farmo Quimica, Chile. Farmo Química del Pacifico SA, Av. Grecia 2208, Nunoa, Santiago, Chile.

Farmochimica, Ital. La Farmochimica Italiana S.r.l., Via Luigi Vanvitelli 3, 20100 Milan (MI), Italy.

Farmogene, Port. See *Pfizer, Port.*

Farmoniks, Ukr. Farmoniks Ltd, Turgenevskaya Street, 15, Kiev, 01054, Ukraine.

Farmoquimica, Braz. Farmaquimica S.A., Av. Luis Carlos Prestes 410, 22775-055 Rio de Janeiro, RJ, Brazil.
url: www.fqm.com.br

Farmoral, Turk. Farmoral, Turkey.

Farmoterapia, Arg. Farmoterapia Internacional S.R.L., Alvear 231 Piso 1 of.1, 1640 Martinez, Buenos Aires, Argentina.

Farmoz, Port. Farmoz Sociedade Técnico Medicinal S.A., Rua Professor Henrique de Barros, Edificio Sagres 3 A, 2685-338 Prior Velho, Portugal.

Farmpreparat, Rus. Farmpreparat, G Azov ul. Kalinina 2, 346780 Rostovskaya Oblast, Russia.
url: www.stellanin.ru

Farmproekt, Rus. See *Antiviral, Rus.*

Farmsintez, Rus. Farmsintez, Bolshoi prt P.S. 77, A, 197022 St Petersburg, Russia.

Farmstandart, Rus. Farmstandart, Dolgoprudnyjj g., Likhachevskijj pr. d. 5, 141700 Moscow, Russia.
url: www.pharmstd.ru

Farmstandart, Ukr. See *Zdravo, Ukr.*

Farm-Synthesis, Ukr. See *Concern, Ukr.*

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Farmygel, Spain. See *Alcala, Spain.*

Farmzaschita, Rus. Farmzaschita, Moscow, Russia.

Faromed, Austria. Faromed GmbH, Johann Straussgasse 7/5, A-1040 Vienna, Austria.

Faros, Rus. Faros-21, ul. Zipovskaya D.9, 350072 Krasnodar, Russia.

Farve, Ital. Farve S.r.l., Via Brenta 26, 36077 Altavilla Vicentina (VI), Italy.

Foshion Fair, Canad. See *Fashian Foir, USA.*

Fashion Fair, USA. Fashion Foir Cosmetics, 820 South Michigan Ave, Chicago, IL 60605, USA.

Fate, UK. Fate Special Foods, Unit E2, Brook Street Business Centre, Brook Street, Tipton, West Midlands, DY4 9DD, UK.

Fatal, Austria. See *Fatol, Ger.*

Fatal, Cz. See *Fotol, Ger.*

Fatol, Ger. Fatol Arzneimittel GmbH, Robert-Koch-Str., 66578 Schiffweiler, Germany.
url: www.fatol.de

Fatol, Hong Kong. See *Mekim, Hong Kong.*

Fatol, Rus. See *Switch, Rus.*

Faulding, Austral. See *Mayne, Austral.*

Faulding, Belg. See *Moyne, Belg.*

Faulding, Canad. See *Mayne, Canad.*

Faulding, Denm. See *Baxter, Denm.*

Faulding, Fr. Faulding Pharmaceuticals SA, 93 Rue Magenta, 92600 Asnières, France.
url: www.maynepharma.com

Faulding, Hong Kong. See *Mayne, Hong Kong.*

Faulding, Irl. See *Mayne, Irl.*

Faulding, Israel. See *Tzamal, Israel.*

Faulding, NZ. See *Mayne, NZ.*

Faulding, Singapore. See *Mayne, Singapore.*

Faulding, Spain. See *Mayne, Spain.*

Faulding, Swed. See *Mayne, Swed.*

Faulding, Thai. See *Indochina Healthcare, Thai.*

Faulding, UK. See *Mayne, UK.*

Faulding, USA. See *Mayne, USA.*

Faulding Consumer, Austral. See *Mayne, Austral.*

Faulding Healthcare, Austral. See *Mayne, Austral.*

Faure, Fr. See *Novartis, Fr.*

Fawns & McAllan, Austral. See *Sigma, Austral.*

Fawns & McAllan, Hong Kong. See *ICH, Hong Kong.*

Fawns & McAllan, NZ. See *Pharmaco, NZ.*

FDC, India. FDC Ltd, 142-48 S.V. Rd, Jogeshwari (West), Mumbai 400 102, India.
url: www.fdcindia.com

FDC, Philipp. See *EON, Philipp.*

FDC, Thai. See *Kaspa, Thai.*

FDC, UK. FDC International Ltd, Unit 6 Fulcrum 1, Solent Way, Whiteley, Fareham, Hampshire, PO15 7FE, UK.

FDS, Rus. See *FDS, UK.*

FDS, UK. FDS Pharma, Hillbrow House, Hillbrow Rd, Esher, Surrey, KT10 9NW, UK.

FDZJ, China. Fudan-Zhangjiang Bio-Pharmaceutical Co Ltd, 308 Cailun Rd, ZJ Hi-tech Park, Shanghai 201210, China.
url: www.fd-zj.com

Febena, Ger. Febena Pharma GmbH, Oskar-Jäger-Str. 115, 50825 Cologne, Germany.
url: www.febena.de

Fecofar, Arg. Fed. Arg. de Coop. Farm., Av. Pte. Peron 2742, 1754 San Justo, Buenos Aires, Argentina.

Federfarma, Ital. FederFARMA.CO SpA, Via Cavriana 14, 20134 Milan (MI), Italy.

Feihong, China. Feihong Pharmaceutical Co. Ltd., 388 Gaoxin Fifthe Road, High and New Technology Development Zone, Nanchang, Jiangxi, 330096, China.
url: www.hang-fei.cn

Feima, China. Feima Pharmaceutical Co. Ltd, Jiangsu, China.

Feiying, China. Feying Pharmaeutical Co. Ltd, Tianjin, China.

Feldhoff, Ger. W. Feldhoff & Comp. Arzneimittel GmbH, Hans-C.-Wirz-Str. 2, 99867 Gotha, Germany.

Felgentrager, Cz. See *Felgentrager, Ger.*

Felgentrager, Ger. Dr. Felgenträger & Co. Ökochem. und Pharma GmbH, Zerbster Str. 7a, 06861 Dassau-Rosslau, Germany.
url: www.dr-felgentraeger.de

Felgentrager, Pol. See *Felgentrager, Ger.*

Felo, Denm. Felo ApS, Jeshøjvej 12, 4700 Næstved, Denmark.

Felton, Austral. Felton, Grimwade & Bickford P/L, P.O. Box 74, Oakleigh South, VIC 3167, Australia.
url: www.fgb.com.au

Fem Care, India. Fem Care Pharma Ltd, 2nd Floor Umiya Complex, Sahyadri Nagar, Cidco, Nashik 422 009, India.
url: www.femcareworld.com

Femi Agran, Israel. Femi Agran, Israel.

Fengan, China. Fengan Biopharmaceutical Co. Ltd, Xiayangdi, Chengguan, Xianju, Taizhou, Zhejiang, 317300, China.
url: www.fengan.com

Fenghuang, China. Fenghuang Pharmaceutical Co. Ltd, 198 Tianjin Rd, Dongying 257400, Lijin, Shandong, China.
url: www.lihuayi.com

Fengyuan, China. See *BBCA, China.*

Fengyuan Tushan, China. Fengyuan Tushan Pharmaceutical Co. Ltd, Bengbu, China.

Fenton, UK. Fenton Pharmaceuticals Ltd, 4J Portman Mansions, Chiltern St, London, W1M 1LF, UK.

Fera, USA. Fera Pharmaceuticals LLC, 15 Birch Hill Rd Ste A, Locust Valley, New York, NY 11560, USA.
url: www.ferapharma.com

Ferakon, Gr. Ferakon EPE (Φερακον ΕΠΕ), Menandrou 85, 104 38 Athens, Greece.

Ferel, Port. Ferel Comércio e Representação Lda, Portugal.

Ferlito, Ital. Ferlito Formaceutici S.p.A., Via E Romarini 31-33, 00016 Monterotondo Scalo (RM), Italy.
url: www.ferlitofarmaceutici.it

Fermenta, Swed. See *Ferring, Swed.*

Fermenta Biotech, Rus. See *Transatlantic, Rus.*

Fermon, Spain. Fermon, Alfonso Alcocer 7, Badalona, 08918 Barcelona, Spain.

FERN, Philipp. Filipina Entrepreneur & Resources Network Inc., G/F Goldloop Twr.I, Escriva Dr., Ortigas Ctr, Pasig City, Philippines.

Fernandez y Canivel, Spain. Fernandez y Canivel SA, C/ Severo Ochoa 13, Parque Tecnológico de Andalucia, 29590 Campanillas, Málaga, Spain.

Ferndale, Hong Kong. See *US Summit, Hong Kong.*

Ferndale, Irl. See *Ferndale, UK.*

Ferndale, UK. Ferndale Pharmaceuticals Ltd, Unit 124, Thorp Arch Estate, Wetherby, West Yorkshire, LS23 7BJ, UK.
url: www.ferndalepharma.co.uk

Ferndale, USA. Ferndale Laboratories Inc., 780 West Eight Mile Rd, Ferndale, MI 48220, USA.
url: www.ferndalelabs.com

Ferol, Hung. Ferol Kft, Czobor u 53, 1147 Budapest, Hungary.

Feron, India. Feron Life Sciences Pvt Ltd, 203 Akashdeep Building, 26 Barakhamba Rd, New Delhi 110 001, India.
url: www.feranlifesciences.com

Feran, Rus. Feron LLC, Volokolamskoe sh. 73, 125242 Moscow, Russia.
url: www.viferon.su

Feron, Ukr. See *Feron, Rus.*

Ferroz, Lynce, Port. Ferraz, Lynce, SA, Rua Consiglieri Pedroso 123, Queluz de Baixo, 2730-056 Barcarena, Portugal.

Ferrer, Austria. See *Ferrer, Spain.*

Ferrer, China. See *Leo, China.*

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Ferrer, Gr. Ferrer-Galenica SA, Greece, Eleitherias 4, 145 64 Kifissia, Greece.

Ferrer, Hong Kong. See *Keller, Hong Kong.*

Ferrer, Indon. See *Darya-Varia, Indon.*

Ferrer, Ital. See *Ferrer, Spain.*

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Ferrer, Philipp. See *Metro, Philipp and Patriot, Philipp.*

Ferrer, Port. Ferrer Azevedos SA, Edificio Azevedos, Estrada Nacional 117-2, 2724-503 Amadora, Portugal.

Ferrer, Rus. See *Egis, Rus.*

Ferrer, Singapore. See *Pharmacon, Singapore.*

Ferrer, Spain. Ferrer Farma, Edifici L'illa, Diagonal 549. 5a planta, 08029 Barcelono, Spain.
url: www.ferrergrupo.com

Ferrer, Switz. See *Lucchini, Switz.*

Ferrer, Thai. See *Pacific, Thai.*

Ferrer, Ukr. See *Farmasoft, Ukr.*

Ferrer-Novag, Mex. See *Novag, Mex.*

Ferrier, Fr. See *Arkopharma, Fr.*

Ferring, Arg. Ferring S.A., Venezuela 174, 1095 Buenos Aires, Argentina.
url: www.ferring.com

Ferring, Austral. Ferring Pharmaceuticals P/L, Suite 2B, Level 2, 802 Pacific Highway, Gordon, NSW 2072, Australia.
url: www.ferring.com

Ferring, Austria. Ferring Arzneimittel GmbH, Wienerbergstrasse 11, A-1100 Vienna, Austria.
url: www.ferring.com

Ferring, Belg. Ferring SA, Hopmarkt 9 bus 3, 9300 Aalst, Belgium.
url: www.ferring.com

Ferring, Braz. Laboratórios Ferring Ltda, Praca São Marcos 624 1-andar, Vila Ida, 05455-050 São Paulo, SP, Brazil.
url: www.ferring.com

Ferring, Canad. Ferring Inc., 200 Yorkland Blvd, Suite 800, Toronto, Ontario, M2J 5C1, Canada.Regulatory & Technical Affairs Manager
url: www.ferring.com

Ferring, Chile. See *Recalcine, Chile.*

Ferring, China. Ferring Pharmaceuticals (Asia) Co. Ltd, GC Tower 10F Unit 01-03, 1088 YuanShen Rd, Pudong New Area, Shanghai 200122, China.
url: www.ferring.com

Ferring, Cz. Ferring-Léčiva as, K Rybníku 475, 252 42 Jesenice u Prahy, Czech Republic.
url: www.ferring.cz

Ferring, Denm. Ferring Lægemidler A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark.
url: www.ferring.dk

Ferring, Fin. Ferringlääkkeet Oy, Tähdenlennonkuja 1, PL 23, 02241 Espoo, Finland.
url: www.ferring.com

Ferring, Fr. Laboratoires Ferring SAS, 7 rue Jean-Baptiste-Clement, 94250 Gentilly, France.Director General
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Ferring, Ger. Ferring Arzneimittel GmbH, Fabrikstr. 7, 24103 Kiel, Germany.
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Ferring, Gr. Ferring EPE, 42 Kapodistriou St, 10432 Athens, Greece.
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Ferring, Hong Kong. Ferring Pharmaceuticals Ltd, Unit A, 9/F Garment Ctr, 576-586 Castle Peak Rd, Kowloon, Hong Kong

Ferring, Hung. Ferring GmbH Gyógyszerkereskedelmi Képviselet, Szekszárdi út 10/b, 1138 Budapest, Hungary.

Ferring, India. Ferring Pharmaceuticals Pvt Ltd, 403/404 Sigma, 4th Floor, Technology St, Central Ave, Hiranandani Gardens, Powai, Mumbai 400 076, India.
url: www.ferring.com

Ferring, Irl. See *United Drug, Irl.*

Ferring, Israel. See *Lapidot, Israel.*

Ferring, Ital. Ferring S.p.A., Via Senigallia 18/2, 20161 Milan (MI), Italy.
url: www.ferring.com

Ferring, Jpn. Ferring Pharmaceuticals Co. Ltd, Toranomon 2-chome Tower 10F, 2-3-17 Toranoman, Minato-ku, Tokyo 105-0001, Japan.
url: www.ferring.com

Ferring, Malaysia. See *United Italian, Malaysia.*

Ferring, Mex. Ferring S.A. de C.V., Av. Nemesio Diez Riega Mza. 2 Lote 15, Col. Parque Industrial Cerrillo II, 52000 Lerma, Mexico.
url: www.ferring.com

Ferring, Neth. Ferring BV, Postbus 184, 2130 AD Hoofddorp, Netherlands.
url: www.ferring.nl

Ferring, Narw. Ferring Legemidler AS, Postboks 4445 Nydalen, 0403 Oslo, Norway.
url: www.ferring.com

Ferring, NZ. See *Pharmaco, NZ.*

Ferring, Philipp. See *Diethelm, Philipp.*

Ferring, Pol. Ferring Pharmaceuticals BV Sp. zo.o., przedstawicielstwo w Polsce, ul. Królowej Marysieńki 11/4, 02-954 Warsaw, Polond.
url: www.ferringpl.com.pl

Ferring, Port. Ferring Portuguesa, Lda, Rua Professor Henrique de Barros, Edificio Sagres, 8 - Sala A, 2685-338 Prior Velho, Portugal.
url: www.ferring.com

Ferring, Rus. Ferring Pharmaceuticals B.V., Karmanitskii per. 9, 119002 Moscow, Russia.
url: www.ferring.ru

Ferring, S.Afr. Ferring (Pty) Ltd, P.O. Box 14358, Clubview 0014, South Africa.
url: www.ferring.com

Ferring, Singapore. See *United Italian, Singapore.*

Ferring, Spain. Ferring, Saturno 1, Edificio Saturno, Pozuelo de Alarcon, 28224 Madrid, Spain.
url: www.ferring.com

Ferring, Swed. Ferring AB, Box 4041, 203 11 Malmö, Sweden.
url: www.ferring.se

Ferring, Switz. Ferring SA, Industriestrasse 50a, 8304 Wallisellen, Switzerland.
url: www.ferring.com

Ferring, Thai. See *Pacific, Thai.*

Ferring, Turk. Ferring Ilaç San ve Tic Ltd Sti, Buyukdere Cad No 71 Nurol Plaza, A Blok Kat. 13m, 34398 Maslak-Sisli, Istanbul, Turkey.
url: www.ferring.com

Ferring, UK. Ferring Pharmaceuticals UK, The Courtyard, Waterside Drive, Langley, Berkshire, SL3 6EZ, UK.
url: www.ferring.com

Ferring, Ukr. Ferring Pharmaceuticals BV, Radishcheva, 10/14, office 206, Kiev, 03680, Ukraine.
url: www.ferring.com

Ferring, USA. Ferring Pharmaceuticals Inc., 400 Rella Bvld, Suffern, NY 10901, USA.
url: www.ferringusa.com

Ferron, Indon. Ferron Par Pharmaceuticals PT, Titan Center 7th Floor, Jalan Boulevard Bintaro Blok B7/B1 No. 05, Bintaro Jaya Sektor 7, Tangerang 15224, Indonesia.
url: www.ferron-pharma.com

Ferron, Philipp. See *Getz, Philipp.*

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url: www.ferrosan.com

Ferrosan, Fin. Oy Ferrosan AB, Kutojantie 11, 02630 Espoo, Finland.
url: www.ferrosan.fi

Ferrosan, Fr. Laboratoires Ferrosan, 64 rue Pierre-Charron, 75008 Paris, France.
url: www.imedeen.fr

Ferrosan, Hung. See *Pharma Natura, Hung.*

Ferrosan, Pol. Ferrosan Poland Sp. zo.o., ul. Włodarzewska 45 D, 02-384 Warsaw, Poland.
url: www.ferrosan.com.pl

Ferrosan, Rus. Ferrosan A/S, Novy Arbat ul. 7, 119019 Moscow, Russia.
url: www.ferrosan.ru

Ferrosan, Swed. Ferrosan AB, Kungsgatan 23, 561 31 Huskvarna, Sweden.
url: www.ferrosan.com

Ferrosan, Ukr. Ferrosan International A/S, Bogomoltsa Street, 4, office 221, 224, Kiev, 01601, Ukraine.
url: www.ferrosan.com

Fertin, Denm. Fertin Pharma A/S, Industrivej 8, 7120 Vejle Øst, Denmark.

Fertin, Norw. See *Meda, Norw.*

FertiPro, Irl. See *Electramed, Irl.*

FGK, Cz. See *FGK, Ger.*

FGK, Ger. FGK Representative Service GmbH, Heimeranstrasse 35, 80339 Munich, Germany.
url: www.fgk-rs.com

FGK, Hung. See *FGK, Ger.*

FHC, Port. FHC Farmacêutica Lda, Parque Industrial de Mortágua, Lote 2, 3450-232 Mortágua, Portugal.

Fher, Ital. Fher, Divisione della Boehringer Ingelheim, Località Prulli 103/C, 50066 Reggello, Italy.

Fher, Spain. See *Boehringer Ingelheim, Spain.*

Fibertone, USA. See *Marlyn, USA.*

FIC, Rus. FIC Medical, Krasnopresnenskaya nab. 12, Gostinitsa International-2, Of. 742, 123610 Moscow, Russia.
url: www.aha.ru

FIC Medical, Ukr. FIC Medical, Proreznaya Street, 22, [kv]. 3, Kiev, 01034, Ukraine.
url: www.ficmedical.com

Fida-Sinax, Singapore. Fida-Sinax Singapore, Singapore.

Fides, Ger. See *Heel, Ger.*

Fides, Spain. See *Rottapharm, Spain.*

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Fides Rottapharm, Spain. See *Rottapharm, Spain.*

FidesLine, Ger. See *Heel, Ger.*

Fidex, Arg. Prod. Farm. Fidex S.A., Grol. Savio Ruta 88 Km 9.5, 7601 Batan Mar del Plata, Buenos Aires, Argentina.
url: www.fidexsa.com.ar

Fidia, Canad. See *Healey Medical, Canad.*

Fidia, Cz. See *Glynn, Cz.*

Fidia, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Fidia, Hung. See *CSC, Hung.*

Fidia, Indon. See *Combiphar, Indon.*

Fidia, Irl. See *Fidia, Ital.*

Fidia, Israel. See *Fidia, Ital.*

Fidia, Ital. Fidia Farmaceutici S.p.A., Via Ponte della Fabbrica 3/A, 35031 Abano Terme (PD), Italy.

Fidia, Malaysia. See *Somedico, Malaysia.*

Fidia, Neth. See *Fidia, Ital.*

Fidia, Pol. See *Pharm Supply, Pol.*

Fidia, Singapore. See *Fidia, Ital.*

Fidia, Thai. See *Diethelm, Thai.*

Fidia, USA. Fidia Pharmaceutical Co., 2000 K St NW, Washington, DC 20006, USA.
url: www.fidiapharma.com

Fidia Oftal, Ital. See *Bausch & Lomb, Ital.*

Fielding, USA. See *Novavax, USA.*

Filadams, Philipp. Filadams Pharma Inc., 37 Mapagkumbaba, Cor Matipid St, Sikatuna Vill, Quezon City, Philippines.

Filaxis, Arg. Laboratorios Filaxis S.A., Carlos Pellegrini 1023, Piso 7, 1009 Buenos Aires, Argentina.
url: www.filaxis.com

Filiz, Turk. Filiz Ecza Deposu Tic. Ltd. Sti., 2 Cad. 81, Sok. No: 12/1, Övecler, Istanbul, Turkey.

Filofarm, Pol. Farmaceutyczna Spółdzielnia Pracy Filofarm, ul. Pułaskiego 39, 85-619 Bydgoszcz, Poland.
url: www.filofarm.com.pl

Filorga, Fr. Laboratoires Filorga, 18 rue de Miromesnil, 75008 Paris, France.
url: www.filorga.com

Fima, Indon. See *Kalbe, Indon.*

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Fimo, Ital. F.I.M.O. S.r.l. Fabbrica Italiana Materiale Odontotecnico e Odontoiatrico, Via Edolo 40, 20125 Milan, Italy.
url: www.fimosrl.it

Finadiet, Arg. Finadiet S.A.C.I.F.I. Esp. Med., Hipolito Yrigoyen 3771, 1208 Buenos Aires, Argentina.
url: www.finadiet.com.ar

Finderm, Ital. Finderm Farmaceutici S.r.l. di Scaccia Fabbio e C., V.le Alcide de Gasperi 165/B, 95100 Catania (CT), Italy.

Finecure, India. Finecure Pharmaceuticals Ltd, 612-615 Anand Mangal Complex III, Nr. Parimal Garden, Ahmedabad 380 006, India.
url: www.finecurepharma.com

Finepharm, Pol. Finepharm Sp z o.o., ul. Wincentego Pola 19 A, 58-500 Jelenia Góra, Poland.
url: www.finepharma.pl

Finest Health Products, Canad. See *Finest Health Products, USA.*

Finest Health Products, USA. Finest Health Products, Murreysville, Pennsylvania, 15668, USA.

Fink, Ger. See *GSK Consumer, Ger.*

Finlay, Philipp. See *Endure, Philipp.*

Finmedical, Ital. Finmedical S.r.l., Vicolo de Bacchettoni 1A, 51100 Pistoia (PT), Italy.

Finusolprima, Indon. See *Kalbe, Indon.*

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FIRMA, Ital. FIRMA-Fabbr. Ital. Ritrav. Medic. Aff. S.p.A., Via di Scandicci 37, 50143 Florence, Italy.

FIRMA, Ukr. See *Berlin-Chemie, Ukr.*

Firma Ferment, Rus. Firma Ferment, Ul. Nizhnie Mnevniki D 37A, 101000 Moscow, Russia.

Firn M, Rus. Firn M, pl. Borby D 15/1 entrance B, 127055 Moscow, Russia.
url: www.firnm.ru

First Aid Research, USA. First Aid Research Corp., 3375 Park Ave, Suite 2003, Wantagh, NY 11793, USA.
url: www.firstaidresearch.com

First Horizon, USA. First Horizon Pharmacuetical Corp., 6195 Shiloh Rd, Alpharetta, GA 30005, USA.
url: www.firsthorizonpharm.com

First Pharm, S.Afr. First Pharm, Durban 4022, South Africa.
url: www.firstpharm.co.za

First Pharmaceutical, Malaysia. First Pharmaceutical Sdn Bhd, 20 Jalan SS 19/5, 47500 Subang Jaya, Selango Darul Ehsan, Malaysia.

Firstpharm, S.Afr. FirstPharm Pharmaceuticals (Pty) Ltd, P.O. Box 22544, KwaZulu-Natal, Glenashley 4022, South Africa.
url: www.firstpharm.co.za

Fisch, Fr. See *Smith & Nephew, Fr.*

Fischer, Ger. See *GSK, Ger.*

Fischer, Israel. Fischer Pharmaceuticals Ltd, P.O. Box 39071, Tel Aviv 61390, Israel.
url: www.dr-fischer.com

Fischer, USA. Fischer Pharmaceuticals Inc., 7040 W Palmetto Park Rd 4, Suite 606, Boca Raton, FL 33433-3407, USA.
url: www.dr-fischer.com

Fisher, Neth. Dr Fisher Farma BV, Vijzelweg 32, 8243 PM Lelystad, Netherlands.

Fisiopharma, Cz. See *Fisiopharma, Ital.*

Fisiopharma, Ital. Fisiopharma S.r.l., Via Carnevali 116, 20158 Milan (MI), Italy.

Fiske, USA. See *Cosmetic Solutions, USA.*

Fisons, Austral. See *Sanofi-Aventis, Austral.*

Fisons, Belg. See *Sanofi-Aventis, Belg.*

Fisons, Braz. See *Aventis, Braz.*

Fisons, Canad. See *Sanofi, Canad.*

Fisons, Denm. See *Sanofi-Aventis, Denm.*

Fisons, Fr. See *Sanofi-Aventis, Fr.*

Fisons, Ger. See *Sanofi-Aventis, Ger.*

Fisons, Hong Kong. See *Primal, Hong Kong.*

Fisons, Irl. See *Sanofi-Aventis, Irl.*

Fisons, Israel. See *Sanofi-Aventis, Israel.*

Fisons, Ital. See *Roche, Ital.*

Fisons, Neth. See *Sanofi-Aventis, Neth.*

Fisons, Norw. See *Sanofi-Aventis, Norw.*

Fisons, Rus. See *Sanofi-Aventis, Rus.*

Fisons, Singapore. See *Sanofi-Aventis, Singapore.*

Fisons, Switz. See *Sanofi-Aventis, Switz.*

Fisons, UK. See *Sanofi, UK.*

Fisons, USA. See *Celltech, USA.*

Fisons Consumer, Austral. See *Sanofi-Aventis, Austral.*

Fitapharm, Ukr. Fitapharm, 19B Rostov St, Simferopol, 95000, Ukraine.
url: www.vitokon.info

Fitoben, Ital. Fitoben srl, Via Tadino 52, 20124 Milan, Italy.
url: www.fitoben.com

Fitobucaneve, Ital. Fitobuconeve S.r.l., Via San Cristoforo 30/32, 20010 Casorezzo (MI), Italy.

Fitolife, Ital. Laboratorio Fitolife S.r.l., Via Domiziana km 55, 80072 Arco Felice Pozzuoli (NA), Italy.
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Fitolon, Rus. Fitolon Research LLC, V.O. 6 Liniya 57 of 28, 199178 Saint-Petersburg, Russia.

Five Coop, Hung. Five Coop Cooperative of Fine Chemicals, Fehérvari ut 160, 1116 Budapest, Hungary.
url: www.fivecoop.hu

FL, Israel. See *Neopharm, Israel.*

Flamel, Fin. See *Flamel, Fr.*

Flamel, Fr. Flamel Technologies, 33 ave du Georges Levy, 69693 Venissieux Cedex, France.
url: www.flamel.com

Flamel, Irl. See *Flamel, Fr.*

Flamel, Neth. See *Flamel, Fr.*

Flamel, Port. See *Flamel, Fr.*

Flamingo, India. Flamingo Pharmaceuticals Ltd, 7/1 Corporate Park, Sion Trombay Road, Chembur, Mumbai 400 071, India.
url: www.flamingopharma.com

Flamingo, Philipp. See *Pasteur, Philipp.*

Flanders, USA. Flanders Inc., P.O. Box 80428, Charleston, SC 29416, USA.
url: www.flandersbuttocksointment.com

Flavir, Rus. Flavir Ltd, Irkutsk, Russia.

Fleet, Austral. C.B. Fleet Co. (Australia) P/L, P.O. Box 716, Braeside, VIC 3195, Australia.
url: www.ozpages.com/cbfleet

Fleet, Braz. See *Euroart, Braz.*

Fleet, China. See *Pioneer, China.*

Fleet, Hong Kong. See *IDS, Hong Kong.*

Fleet, Malaysia. See *United Italian, Malaysia.*

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Fleet, NZ. See *Baxter, NZ.*

Fleet, Philipp. See *Blooming Fields, Philipp.*

Fleet, Rus. See *Ferring, Rus.*

Fleet, Singapore. See *JDH, Singapore.*

Fleet, UK. See *DDD, UK.*

Fleet, USA. C.B. Fleet Co. Inc., 4615 Murray Pl., P.O. Box 11349, Lynchburg, VA 24506, USA.
url: www.cbfleet.com

Fleet-Dewitt, Hong Kong. See *IDS, Hong Kong.*

Fleming, USA. Fleming & Co., 1733 Gilsinn Lane, Fenton, MO 63026, USA.
url: www.flemingcompany.com

Fleming, Venez. See *Rowe-Fleming, Venez.*

Flen, Belg. Flen Pharma, Blauwesteenstraat 87, 2550 Kontich, Belgium.
url: www.flenpharma.com

Flexopharm, Ger. Flexopharm GmbH, Industriestr. 40, 44628 Herne/Ruhrstadt, Germany.
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Flexopharm, Irl. See *Flexopharm, Ger.*

Flexpharma, Fr. Flexpharma, 48 B rue des Belles Feuilles, 75116 Paris, France.

Flex-Power, USA. Flex-Power, 1563 Solano Ave, P.O. Box 171, Berkeley, CA 94706, USA.
url: www.flexpower.com

Flor de Loto, Spain. Flor de Loto SA, C/Platon 6, 08021 Barcelona, Spain.

Flora, Canad. Flora Mfg & Dist. Ltd, 7400 Fraser Park Drive, Burnaby, BC, V5J 5B9, Canada.
url: www.florahealth.com

Flora, Hung. Flora-Trade Kft, Kóbányai ut 10, 2049 Diósd, Hungary.
url: www.flora-trade.hu

Floradix, Ger. See *Salushaus, Ger.*

Flordis, Austral. Flordis Pty Ltd, Level 2, 3 Carlingford Rd, Epping, NSW 2121, Australia.
url: www.flordis.com.au

Floreat, India. Floreat Medica Pvt Ltd, No. 33/2805B Malikayil, Vakkattu Road, Chakkaraparambu, Thammanam P.O., Cochin 682 032, India.
url: www.floreatmedica.com

Florian, Canad. See *Florion, USA.*

Florian, USA. Kerstin Florian International, 100 20492 Crescent Bay Drive, Lake Forest, CA 92630, USA.

Florida, Arg. Droguería Florida S.R.L., Franklin D. Roosevelt 3430/2, 1430 Buenos Aires, Argentina.

Florin, Hung. Florin Rt, Kenyergyaru ut 5, 6725 Szeged, Hungary.
url: www.florin.hu

Floris, Israel. Floris, Misgav 20179, Israel.

Florizel, UK. Florizel Ltd, P.O. Box 138, Stevenage, Hertfordshire, SG2 8YN, UK.

Floxia, Singapore. See *Medicell, Singapore.*

Fluoritab, USA. Fluoritab Corp., P.O. Box 507, Temperance, MI 48182-0507, USA.

Fluoron, Ger. Fluoron Gmbh Gesellschaft fur hochreine Biomaterialien, Magirus-Deutz-Strasse 10, 89077 Ulm, Germany.
url: www.fluoron.de

Flupal, Venez. Laboratorios Flupal C.A., Parcelamiento Industrial La Fe Parcel a Nro. B23, Macarao, Caracas 1000 A, Venezuela.

Flynn, Irl. See *Flynn, UK.*

Flynn, UK. Flynn Pharma Ltd, 2nd Floor, The Maltings, Bridge St, Hitchin, Hertfordshire, SG5 2DE, UK.

FMC Pharma, Irl. FMC Pharma Ltd, Unit 622, Northern Extension, Co. Waterford, Ireland.

FNC, USA. FNC Medical Corp., 6000 Leland St, Ventura, CA 93003, USA.
url: www.fncmedical.com

Focus, Hung. Focus, Hungary.

Focus, India. Focus Healthcare Pvt Ltd, 166 Industrial Focal Point, Phase-9, Moholi 160 062, India.
url: www.arofocus.com

Focus, Pol. See *Mylan, Pol.*

Focus, UK. Focus Pharmaceuticals Ltd, 5 Faraday Court, First Avenue, Centrum 100, Burton-upon-Trent, Staffordshire, DE14 2WX, UK.
url: www.focuspharmaceuticals.co.uk

Focus, USA. Focus Laboratories Inc., North Little Rock, AR 72113, USA.
url: www.focuslaboratories.com

Focus Care, Neth. Focus Care Pharmaceuticals BV, Lagedijk 1-3, 1541 KA Koog A/D Zaan, Netherlands.

Focus Farma, Neth. Focus Farma BV, Papelaan 85G, 2252 EG Voorschoten, Netherlands.

Folares, Philipp. Folares Pharmaceuticals Inc., 2/F SEDCCO Bldg, 120 Rada St, Legaspi Vill., Makati City, Philippines.

Foncoo, China. Dalian Foncoo Pharmaceutical Co., Ltd., 18 Shunkang Street, Yusheun Development Zone, Dalian, Liaoning, 116052, China.
url: www.foncoo.com

Fontane, Ger. Fontane Pharma GmbH, Stölpchenweg 37, 14109 Berlin, Germany.

Fonte, Switz. Fonte SA, Via Guiseppe Cattori 1, 6601 Locarno, Switzerland.
url: www.fontelocarno.ch

Fontelabor, Port. Fontelabor Produtos Farmacêuticos Lda, Quinta da Fonte, Edifício Vasco da Gama 19, Porta Salvo, 2780-730 Paco de Arcos, Portugal.

Fonterra, Indon. Fonterra Brands Indonesia PT, Wisma Staco, 5th Fl, Jl Casablanca Kav 18, Jakarta 12870, Indonesia.

Fonterra, Malaysia. Fonterra Brands (Malaysia) Sdn Bhd, Lot 12 Subang Hi-Tech Industrial Park, Batu Tiga, 40300 Shah Alam, Selangor, Malaysia.

Fonterra, Philipp. Fonterra Brands (Phils) Inc., 19/F Cyber One Tower, 11 Eastwood Ave, Eastwood City Cyber Park, Libis, Quezon City, Philippines.

Fontovit, Braz. Fontovit Laboratórios Ltda, Rua Antônio das Chagas 862, 04714-001 São Paulo, Brazil.
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Food Supplement, UK. See *Health & Diet Food Co., UK.*

Foodscience, Canad. See *Foodscience, USA.*

Foodscience, USA. Foodscience Laboratories, Division of Foodscience Corp., 10 20 New England Drive, Essex Junction, VT 05452, USA.

Foramen, Philipp. See *Biolink, Philipp* and *Interhealthcare, Philipp* and *Salvang, Philipp.*

Ford Medical, UK. Ford Medical Associates Ltd, 8 Wyndham Way, Orchard Heights, Ashford, Kent, TN25 4PZ, UK.
url: www.fordmedical.co.uk

Forder, Arg. Forder Lab. Esp. Dermatologicas, Rivadavia 5747 Piso 5 Dto.A, 1406 Cdad., Buenos Aires, Argentina.

Forest, Canad. See *Seaway Midwest, Canad.*

Forest, Hung. See *Repharma, Hung.*

Forest, Irl. See *Forest Laboratories, UK.*

Forest, Israel. See *Pharmateam, Israel.*

Forest, Singapore. See *Pharmacon, Singapore.*

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Forest Laboratories, Neth. See *Forest Laboratories, UK.*

Forest Laboratories, Pol. See *Nepentes, Pol.*

Forest Laboratories, Port. See *Forest Laboratories, UK.*

Forest Laboratories, UK. Forest Laboratories Europe, Bourne Rd, Bexley, Kent, DA5 1NX, UK.
url: www.forestlabs.com

Forest Laboratories, USA. Forest Laboratories Inc., 909 Third Ave, New York, NY 10022, USA.
url: www.frx.com

Forest Pharmaceuticals, USA. Forest Pharmaceuticals Inc., 13600 Shoreline Drive, St. Louis, MO 63045, USA.
url: www.forestpharm.com

Forgo, India. Forgo Pharmaceuticals Pvt Ltd, 92 Industrial Area, Phase-1, Panchkula, Haryana, India.
url: www.forgopharma.com

Forley, UK. See *Goldshield, UK.*

Formenti, Cz. See *Formenti, Ital.*

Formenti, Hung. See *CSC, Hung.*

Formenti, Ital. Prodotti Formenti S.r.l., Via R. Koch 1/2 - Torre A, 20152 Milan (MI), Italy.

Formenti, Pol. See *Medagro, Pol.*

Formenti, Rus. See *Formenti, Ital.*

Formevet, Ital. Formevet srl, Via Savona 97, 20144 Milan, Italy.
url: www.formevet.it

ForMor, Singapore. ForMor International Asia Pacific Pte Ltd, 9 Temasek Blvd, Tower 2 17-03, S 038989, Singapore.

Formosinho, Port. See *Gestafarma, Port.*

Formula, NZ. Formula Products, P.O. Box 36-443, Northcote, Auckland, New Zealand.

Formulex, Israel. See *Genmedix, Israel.*

Fornet, Fr. Laboratoires Fornet, 7/13 bd Paul-Emile-Victor, 92200 Neuilly-sur-Seine, France.

Fort, Rus. See *Microgen, Rus.*

Fortbenton, Arg. Lab. Fortbenton Co. S.A., Escalada 133, 1407 Buenos Aires, Argentina.
url: www.fortbenton.com.ar

Forte, USA. See *Eon, USA.*

Forte Pharma, Fr. Laboratoires Forté Pharma, Le Patio Palace, 41 avenue Hector Otto, 98000 Monaco, Monaco.
url: www.fortepharma.com

Fortune, Canad. See *Fortune, Hong Kong.*

Fortune, China. See *Fortune, Hong Kong.*

Fortune, Hong Kong. Fortune Pharmacal Co. Ltd, 14A/F Zung Fu Industrial Bldg, 1067 King's Rd, Hong Kong.
url: www.fortunepharm.com

Fortune Star, Indon. Fortune Star Indonesia PT, Wisma Pondok Indah, Suite 407, Jl Sulton Iskandar Muda, Blok V TA, Jakarta 12310, DKI Jaya, Indonesio.

Forum, Austria. See *Britannia Pharmaceuticals, UK.*

Forum, Ger. See *Britannia Pharmaceuticals, UK.*

Forum, Hung. See *Ferol, Hung.*

Forum, Neth. See *Britannia Pharmaceuticals, UK.*

Forum, UK. Forum Health Products Ltd, Betchworth House, 57-65 Station Rd, Redhill, Surrey, RH1 1DL, UK.
url: www.forum-health.co.uk

Foshan Shuanghe, China. Foshan Shuanghe Pharmaceutical Co. Ltd, China.

Fougera, Israel. See *Medison, Israel.*

Fougera, USA. E. Fougera Co., 60 Baylis Rd, Melville, NY 11747, USA.
url: www.fougera.com

Four Star, Hong Kong. Four Star Co. Ltd, Macau Medical Supplier, Edif Airway Block A, 14/F, 209 Av Venceslau Morais, Macau.

Four Ventures, Rus. Four Ventures Enterprises Inc., Ruzheiny Per. 4/4, 119121 Moscow, Russia.
url: www.fourventures.net

Fournier, Austria. See *Fournier, Ger.*

Fournier, Belg. Fournier Pharma SA, Rue des Trois Arbres 16b, 1180 Brussels, Belgium.
url: www.groupe-fournier.com

Fournier, Canad. Fournier Pharma Inc., 1010 Sherbrooke St W, 19th Floor, Montreal, Quebec, H3A 2R7, Canada.
url: www.fournierpharma.com

Fournier, Cz. Fournier Laboratoires, Norbertov 130/3, 162 00 Prague 6, Czech Republic.
url: www.groupe-fournier.fr

Fournier, Denm. See *Solvay, Denm.*

Fournier, Fin. See *Fournier, Fr.*

Fournier, Fr. Laboratoires Fournier SA, 153 rue de Buzenval, 92380 Garches, France.
url: www.groupe-fournier.com

Fournier, Ger. Fournier Pharma GmbH, Justus-von-Liebig Str. 16, 66280 Sulzbach, Germany.

Fournier, Gr. Fournier Hellas, 7 Granikou Str., 151 25 Marousi, Greece.
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Fournier, Hong Kong. See *Wing Wai, Hong Kong* and *Zuellig, Hong Kong.*

Fournier, Hung. Fournier Hungary Kft, Kapás u 38, 1123 Budapest, Hungary.

Fournier, Malaysia. See *Zuellig, Malaysia.*

Fournier, Norw. See *Solvay, Norw.*

Fournier, Pol. Fournier Polska Sp. z.o.o, ul. Grzybowska 80/82, 00-844 Warsaw, Poland.
url: www.fournier.pl

Fournier, Rus. See *Beaufour-Ipsen, Rus.*

Fournier, Singapore. See *Pharmaforte, Singapore.*

Fournier, Swed. See *Selena Fournier, Swed.*

Fournier, Switz. See *Globopharm, Switz.*

Fournier, Thai. See *Pacific, Thai.*

Fournier, Turk. Fournier Laboratuari Tic. Ltd. Şti., A. Adnan Saygun Cad. 58, A Block Daire : 1 Ulus, Beşiktas, İstanbul, 80600, Turkey.
url: www.groupe-fournier.com

Fournier, UK. See *Solvay, UK.*

Fournier, Ukr. See *Solvay, Ukr.*

Fournier-Gerolymatos, Gr. See *Gerolymatos, Gr.*

Fourrts, India. Fourrts Laboratories Pvt Ltd, 1 Fourrts Avenue, Annai Indira Nagar, Okkiyam Thoraipakkam, Chennai 600 096, India.
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Fourrts, Malaysia. See *Zyfas, Malaysia.*

Fourtts, Singapore. See *Zyfas, Singapore.*

Fox, UK. Charles H Fox Ltd, 22 Tavistock St, Covent Garden, London, WC2E 7PY, UK.
url: www.charlesfox.co.uk

FP, Singapore. F.P. Marketing (S'Pore) Pte Ltd, 5 Pereira Rd, 04-03 Asiawide Industrial Building, S 368025, Singapore.

Framingham, Arg. Framingham Pharma SRL, Agoero 363, 1171 Buenos Aires, Argentina.

Framon, Rus. Framon Inc., ul 3 Cherelkovskaya D 15a, 121552 Moscow, Russia.
url: www.framon.ru

Francelab, Arg. Francelab Argentina SA, Lamadrid 665, 1617 Tigre Troncos del Talar, Buenos Aires, Argentina.

Francia, Ital. Francia Farmaceutici Industria Farmaco Biologica S.r.l., Via dei Pestagalli 7, 20138 Milan (MI), Italy.

Franco, Port. See *Gestafarma, Port.*

Franco-Indian, India. Franco-Indian Pharmaceuticals Ltd, 20 Dr E Moses Rd, Mumbai 400 011, India.
url: www.francoindian.com

Franconpharm, Ger. franconpharm Arzneimittel GmbH, Alexandrinenstr. 1, 96450 Coburg, Germany.

Frandiet, Fr. Frandiet SA, ZA des Savines, 101 rue Marc-Seguin, B.P. 315, 07503 Guilherand-Granges cdx, France.

Frankin, China. Frankin Pharmaceutical Lab Co. Ltd, China.

Frankin, Hong Kong. Frankin Pharmaceutical Lab., 15/F China Trade Ctr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.

Frasca, Arg. Laboratorios Frasca S.R.L., B. Blanca 1660, 1407 Buenos Aires, Argentina.

Freeda, USA. Freeda Vitamins Inc., 36 East 41 st St, New York, NY 10017, USA.
url: www.freedavitamins.com

Frega, Canad. See *Pharmalab, Canad.*

Frere, Belg. See *Arkopharma, Belg.*

Fresenius, Belg. See *Fresenius Kabi, Belg.*

Fresenius, Braz. See *Fresenius Kabi, Braz.*

Fresenius, Fr. See *Fresenius Kabi, Fr.*

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Fresenius, Hong Kong. See *Fresenius Kabi, Hong Kong.*

Fresenius, Neth. See *Rooster, Neth.*

Fresenius, Rus. See *Pfizer, Rus.*

Fresenius, Switz. See *Fresenius Kabi, Switz.*

Fresenius, Thai. See *Fresenius Kabi, Thai.*

Fresenius Biotech, Austria. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Cz. See *Fresenius Kabi, Ger.*

Fresenius Biotech, Denm. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Fr. Fresenius Biotech, 41/41 bis avenue de l'Europe, 78147 Velizy Cedex, France.
url: www.fresenius-biotech.de

FreseniusBiotech, Ger. Fresenius Biotech GmbH, Frankfurter Ring 193a, 80807 Munich, Germany.
url: www.fresenius-biotech.com

Fresenius Biotech, Gr. See *Fresenius Biotech, Ger.*

FreseniusBiotech, Irl. See *Fresenius Kabi, Irl.*

Fresenius Biotech, Neth. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Norw. See *Swedish Orphan, Norw.*

Fresenius Biotech, Pol. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Port. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Rus. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Spain. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Swed. See *Fresenius Biotech, Ger.*

Fresenius Biotech, Thai. See *Natural Media, Thai.*

Fresenius Biotech, UK. See *Fresenius Biotech, Ger.*

Fresenius Hemocare, Hong Kong. See *Round World, Hong Kong.*

Fresenius Hemocare, Singapore. See *DKSH, Singapore.*

Fresenius Hemocare, Thai. See *Natural Media, Thai.*

Fresenius Kabi, Arg. Fresenius Kabi Argentina S.A., Lavalleja 1214, 1414 Buenos Aires, Argentina.
url: www.fresenius-kabi.com

Fresenius Kabi, Austral. Fresenius Kabi Australia Pty Ltd, 964 Pacific Highway, Pymble, NSW 2073, Australia.
url: www.fresenius-kabi.com

Fresenius Kabi, Austria. Fresenius Kabi Austria GmbH, Hafnerstrasse 36, A-8055 Graz, Austria.
url: www.fresenius-kabi.at

Fresenius Kabi, Belg. Fresenius Kabi SA, Molenberglei 7, 2627 Schelle, Belgium.
url: www.fresenius-kabi.com

Fresenius Kabi, Braz. Fresenius Kabi Brazil Ltda, Rua Francisco Pereira Coutinho 347, Parque Taquaral, 13085 Campinas, SP, Brazil.
url: www.fresenius-kabi.com

Fresenius Kabi, Canad. See *Calea, Canad.*

Fresenius Kabi, Chile. Lab. Fresenius Kabi Chile Ltda, Calle Nueva 1661 F, Huechuraba, Chile.

Fresenius Kabi, China. Fresenius Kabi (China) Co. Ltd, 15th Floor Raffles City, 1 Dongzhimen South Ave, Beijing, Dongcheng District, China.
url: www.fresenius-kabi.com.cn

Fresenius Kabi, Cz. Fresenius Kabi sro, Křenová 1, 162 00 Prague 6, Czech Republic.

Fresenius Kabi, Denm. Fresenius Kabi, Islands Brygge 57, 2300 Copenhagen S, Denmark.
url: www.fresenius-kabi.dk

Fresenius Kabi, Fin. Fresenius Kabi AB, Rajatorpantie 41 C, 01640 Vantaa, Finland.
url: www.fresenius-kabi.com

Fresenius Kabi, Fr. Fresenius Kabi France, 5 place du Marivel, 92316 Sèvres cdx, France.
url: www.fresenius-kabi.com

Fresenius Kabi, Ger. Fresenius Kabi Deutschland GmbH, Else-Kröner-Str. 1, 61352 Bad Homburg v. d. H., Germany.
url: www.fresenius.de

Fresenius Kabi, Gr. Fresenius Kabi Hellas A.E., 354 Messoghion Ave, 153 41 Agia Paraskevi, Greece.
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Fresenius Kabi, Hong Kong. Fresenius Kabi Hong Kong Ltd, Rm 5101-23, 51/F Sun Hung Kai Ctr, 30 Harbour Rd, Wanchai, Hong Kong.
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Fresenius Kabi, Hung. Fresenius Kabi Hungary Kft, Lajos u 48-66 E ep. I. em, 1036 Budapest, Hungary.

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Fresenius Kabi, Indon. Fresenius Kabi PT, Ariobimo Sentral Building 11th Floor, Jl HR Rasuna Said X2 Kav 5, Jakarta 12950, Indonesia.
url: www.fresenius-kabi.com

Fresenius Kabi, Irl. Fresenius Kabi Ireland, Unit 3B, Fingal Bay Business Park, Balbriggan, Co. Dublin, Ireland.
url: www.fresenius-kabi.com

Fresenius Kabi, Israel. See *Promedico, Israel.*

Fresenius Kabi, Ital. Fresenius Kabi Italia S.p.A., Via Camagre 41, 37063 Isola della Scala (VR), Italy.
url: www.fresenius-kabi.com

Fresenius Kabi, Jpn. Fresenius Kabi Japan Co., 2-1-2 Sannou, Ota-ku, Tokyo 143-0023, Japan.
url: www.fresenius-kabi.co.jp

Fresenius Kabi, Malaysia. See *Antah, Malaysia.*

Fresenius Kabi, Mex. Laboratorios Frenesius Kabi Mexico S.A. de C.V., Paseo del Norte 5300, Km 12.5 Zapopan, San Juan de Oco, 45010 Guadalajara, Jalisco, Mexico.
url: www.freseniuskabi.com.mx

Fresenius Kabi, Neth. Fresenius Kabi, Netherlands.

Fresenius Kabi, Norw. Fresenius Kabi Norge AS, Markedsavd., Gjerdrumsv. 12, 0486 Oslo, Norway.
url: www.fresenius-kabi.com

Fresenius Kabi, NZ. See *Pharmaco, NZ.*

Fresenius Kabi, Philipp. Fresenius Kabi Phils Inc., 16/F Equitable Bank Tower, 8751 Paseo de Roxas, Makati City, Philippines.

Fresenius Kabi, Pol. Fresenius Kabi Polska Sp. zo.o., ul. Hrubieszowska 2, Crown Tower, 01-209 Warsaw, Poland.
url: www.freseniuskabi.com

Fresenius Kabi, Port. Fresenius Kabi Pharma Portugal, Lda, Avenida do Forte 3, Edificio Suécia III, 2795-504 Carnaxide, Portugal.
url: www.fresenius-kabi.com

Fresenius Kabi, Rus. See *Pfizer, Rus.*

Fresenius Kabi, S.Afr. Fresenius Kabi, P.O. Box 4156, Halfway House, South Africa.
url: www.fresenius-kabi.co.za

Fresenius Kabi, Singapore. See *DKSH, Singapore.*

Fresenius Kabi, Spain. Fresenius Kabi España, Marina 16-18, Pl 17, Torre Mapfre-Villa Olimpica, 08005 Barcelona, Spain.
url: www.fresenius-kabi.com

Fresenius Kabi, Swed. Fresenius Kabi, Rapsgatan 7, 751 74 Uppsala, Sweden.
url: www.fresenius-kabi.se

Fresenius Kabi, Switz. Fresenius Kabi (Schweiz) AG, Spichermatt 30, 6371 Stans, Switzerland.
url: www.fresenius-kabi.com

Fresenius Kabi, Thai. Fresenius Kabi Thailand Ltd, The Millennia Building, 2403-4, 24th Floor, 62 Lungsuan Road, Lumpini, Patumwan, Bangkok 10330, Thailand.
url: www.fresenius-kabi.com

Fresenius Kabi, Turk. Fresenius Kabi Turkey, Eski Buyukdere Cad, Ayazaga Yolu No 7, Kat 4 Maslak, 34398 İstanbul, Turkey.
url: www.fresenius-kabi.com

Fresenius Kabi, UK. Fresenius Kabi Ltd, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, UK.
url: www.fresenius-kabi.co.uk

Fresenius Kabi, Ukr. Fresenius Kabi Deutschland GmbH, Sofievskaya Street, 17, office 1, Kiev, 01001, Ukraine.
url: www.fresenius-kabi.com

Fresenius Kabi, USA. Fresenius Kabi, Three Corporate Drive, Lake Zurich, IL 60047, USA.
url: www.fresenius-kabi.com

Fresenius Medical, Austria. See *Fresenius Kabi, Ger.*
url: www.fmc-ag.com

Fresenius Medical, Belg. See *Fresenius Kabi, Belg.*

Fresenius Medical, Canad. Fresenius Medical Care Canada Inc., 11045 Staples Ave, Richmond Hill, Ontario, L4B 4W6, Canada.

Fresenius Medical, Cz. Fresenius Medical Care sro, Lužna 591, 160 00 Prague 6, Czech Republic.

Fresenius Medical, Denm. Fresenius Medical Care Danmark A/S, Herstedvang 14, 2620 Albertslund, Denmark.
url: www.fmc-ag.dk

Fresenius Medical, Fin. Fresenius Medical Care Suomi Oy, Vattuniemenranta 2, 00210 Helsinki, Finland.
url: www.freseniussuomi.fi

Fresenius Medical, Fr. Fresenius Medical Care France, Parc Médicis, 47 av. des Pépinières, 94832 Fresnes cdx, France.

Fresenius Medical, Ger. See *Fresenius Kabi, Ger.*

Fresenius Medical, Gr. See *Fresenius Kabi, Gr.*

Fresenius Medical, Hung. Fresenius Medical Care Magyarország Egeszegugyi Kft, Csévi köz 7/b, 1025 Budapest, Hungary.

Fresenius Medical, Irl. See *Fresenius Kabi, Irl.*

Fresenius Medical, Israel. See *Promedico, Israel.*

Fresenius Medical, Ital. Fresenius Medical Care Italia SpA, Via Crema 8, 26020 Palazzo Pignano (CR), Italy.

Fresenius Medical, Neth. Fresenius Medical Care Nederland BV, Vimmerik 22, 5253 CB Nieuwkuijk, Netherlands.

Fresenius Medical, Norw. See *Vingmed, Norw.*

Fresenius Medical, Pol. Fresenius Medical Care, ul. Krzywa 13, 60-118 Poznań, Poland.

Fresenius Medical, Port. Fresenius Medical Care, Lda, Rua da Boaviagem 35, Lugar de Crestins, Moreira, 4470 MAIA, Portugal.
url: www.fmc-ag.com

Fresenius Medical, Spain. Fresenius Medical Care, Ctra Vallderiolf Km 0.4, La Roca Del Valles, 08430 Barcelona, Spain.
url: www.fmc-ag.com

Fresenius Medical, Swed. Fresenius Medical Care Sverige AB, Djupdalsvägen 24, 192 51 Sollentuna, Sweden.

Fresenius Medical, Switz. See *Fresenius Kabi, Switz.*

Fresenius Medical, UK. Fresenius Medical Care (UK) Ltd, Nunn Brook Rd, Huthwaite, Sutton-in-Ashfield, Nottinghamshire, NG17 2HU, UK.

Fresenius Medical, USA. Fresenius Medical Care North America, 95 Hayden Ave, Lexington, MA 02420, USA.
url: www.fmcna.com

Fresenius-Klinik, Ger. See *Fresenius Kabi, Ger.*

Fresenius-Praxis, Ger. See *Fresenius Kabi, Ger.*

Frezyderm, Gr. Frezyderm, Menandrou 75, 104 37 Athens, Greece.

Frezyderm, Malaysia. See *Apex, Malaysia.*

Friesland, Hong Kong. See *Keller, Hong Kong.*

Friesland, Malaysia. See *Dutch Lady, Malaysia.*

Friesland, Singapore. See *DKSH, Singapore.*

Frik, Turk. Dr. F. Frik İlaç San. ve Tic. Ltd. Sti., Aydınevler Mah. Sanayi cad. No: 22, Küçükyalı, İstanbul, 34854, Turkey.
url: www.frik.com.tr

Frisian Flag, Indon. Frisian Flag, Jl Raya Bogor Km 5, Pasar Rebo, Jakarta 13760, Indonesia.

Friso, Hong Kong. Friso, 17/F Shun Tak Ctr, West Twr, 200 Connaught Rd Central, Hong Kong.
url: www.friso.com.hk

Frisocare, Hong Kong. See *Keller, Hong Kong.*

Frosst, Austral. See *MSD, Austral.*

Frosst, Canad. See *Merck Frosst, Canad.*

Frosst, Ger. See *MSD, Ger.*

Frosst, Neth. See *MSD, Neth.*

Frosst, Port. See *MSD, Port.*

Frosst, Spain. See *MSD, Spain.*

Fruit of the Earth, Canad. Fruit of the Earth, 6090 White Hart Lane, Mississauga, Ontario, L5R 3Y4, Canada.

Frumtost, Spain. See *Allergan, Spain.*

FSC, Hong Kong. See *Four Star, Hong Kong* and *Sino-Asia, Hong Kong.*

FSC, USA. FSC Laboratories Inc., 600 Fairview Rd, Suite 600, Charlotte, NC 28210, USA.
url: www.fsclabs.com

Fu He Hua Xing, China. Fu He Hua Xing Pharmaceutical Group Co. Ltd, China.

Fubang, China. Fubang Biological Co. Ltd, Tonglu Economic Development Zone, Oceania Road, Hangzhou, Zhejiang, 310009, China.

Fuchun, China. Fuchun Pharmceutical Co. Ltd, Changchun, China.

Fucus, Arg. Laboratorio Farmaciutico Argentino S.A., Santiago del Estero 3117, 1640 Martinez, Buenos Aires, Argentina.

Fudan Fuhua, China. Fudan Fuhua Pharmaceutical Co. Ltd, 21/F Building 1, Lane 446, Zhaijiabang Rd, Xuhui, Shanghai, 200031, China.

FuDong, China. FuDong Pharmaceutical Co. Ltd, Shen Yang, China.

Fuer, China. Forwell Biopharm Co. Ltd, 38-2 Yingbin Road, Yanjiao Economic Technological Development Zone, East Beijing, China.
url: www.bioforwell.com

Fuisz, Ger. See *Shire, Ger.*

Fuji, Jpn. Fuji Pharmaceutical Industry Co Ltd, 19-3, Chiyoda-ku, Tokyo, 102-0094, Japan.
url: www.fujipharma.jp

Fujimoto, Jpn. Fujimoto Pharmaceutical Corp., 1-3-40 Nishi-Otsuka, Matsubara, Osaka 580-8514, Japan.
url: www.fujimoto-pharm.co.jp

Fujisawa, Austria. Fujisawa GmbH, Linzerstrasse 221/ E0.2, A-1140 Vienna, Austria.
url: www.fujisawa.at

Fujisawa, Canad. Fujisawa Canada Inc., 625 Cochrane Drive, Suite 800, Markham, Ontario, L3R 9R9, Canada.
url: www.fujisawa.com

Fujisawa, Chile. See *Pharma Invesli, Chile.*

Fujisawa, Cz. See *Astellas, Irl.*

Fujisawa, Denm. See *Astellas, Denm.*

Fujisawa, Ger. See *Astellas, Ger.*

Fujisawa, Hung. See *Pro-Pharma, Hung.*

Fujisawa, Irl. See *Astellas, Irl.*

Fujisawa, Israel. See *Teva, Israel.*

Fujisawa, Ital. See *Astellas, Ital.*

Fujisawa, Neth. See *Astellas, Ger.*

Fujisawa, Philipp. See *Zuellig, Philipp.*

Fujisawa, Spain. See *Astellas, Spain.*

Fujisawa, Swed. See *Astellas, Swed.*

Fujisawa, Switz. See *Astellas, Switz.*

Fujisawa, Thai. See *Berli Jucker, Thai.*

Fujisawa, UK. See *Astellas, UK.*

Fujisawa, USA. See *Astellas, USA.*

Fukang, China. Fukang Pharmaceutical Co. Ltd, 138 Taijiang Cheung Osaka, Fuzhou 350002, China.
url: www.fz-antibiotic.com

Fulcrum, Irl. Fulcrum Medical Marketing, Cahill May Roberts, Pharmapark, Chapelizod, Dublin 20, Ireland.
url: www.fulcrummarketing.ie

Fulford, India. Fulford (India) Ltd, Eureka Towers, Mindspace, Malad Link Rd, Malad (West), Mumbai 400 064, India.
url: www.fulfordindia.com

Fulton, Ital. Fulton Medicinali S.p.A., Via Marconi 28/9, 20020 Arese (MI), Italy.
url: www.fulton.it

Fumouze, Fr. Laboratoires Fumouze, Le Malesherbes, 110-114 rue Victor-Hugo, 92303 Levallois-Perret cdx, France.

Fumouze, Hong Kong. See *Trinity, Hong Kong.*

Fumouze, Israel. See *Naveh, Israel.*

Fumouze, Malaysia. See *Apex, Malaysia.*

Fumouze, Singapore. See *Pan-Malayan, Singapore.*

Fund Trip, Hong Kong. Fund Trip Pharmaceutical Ltd, B1220 Focal Industrial Ctr, 21 Man Lok St, Hunghom, Kowloon, Hong Kong.

Funing, China. Funing Pharmaceutical Co. Ltd, Shenyang, China.

Funk, Spain. See *Almirall, Spain.*

Funke, Cz. See *Funke, Ger.*

Funke, Ger. Pharma Funke GmbH, Oberhausen, Germany.

Furen Futong, China. Furen Futong Pharamceutical Co. Ltd., 9 New Bridge Street, Lishui, Hubei, 437400, China.
url: www.furenfutong.com

Fusen, China. Fusen Pharmaceutical Co. Ltd, Henan, China.

Fusion, India. Fusion Health Care Pvt Ltd, 1-1-118-119 Flat No A-1, Chenoy's Nooks, SD Road, Secunderabad 500 003, India.

Fuso, Hong Kong. See *Hing Ah, Hong Kong* and *Primal, Hong Kong.*

Fustery, Mex. See *Ivax, Mex.*

Futerman, Arg. Futerman International Products, San Martin 2113, 2000 Rosario, Santa Fe, Argentina.
url: www.futerman-welker.com.ar

Future, Canad. Future Formulations, Unit 11, 1080 Tapscott Rd, Scarborough, Ontario, M1X 1E7, Canada.

Future Health, Switz. Future Health Pharma GmbH, Guyer-Zeller-Strasse 10, 8620 Wetzikon, Switzerland.
url: www.futurehealth.ch

Futuremed, Canad. Futuremed Health Care Products LP, 277 Basaltic Rd, Concord, Ontario, L4K 5V3, Canada.

FuXing, China. 186 Xinhua Rd, Jianghan District, Wuhan, Hubei, 431600, China.
url: www.whfxswyy.cn

Fuzheng, China. Fuzheng Yao Ye Pharmaceutical Technology, 305 Jiaotong Rd, Anding, Dingxi, Gansu, 743000, China.
url: www.fuzhengyaoye.cn

G.P. Laboratories, Austral. See *Pfizer, Austral.*

G & W, Canad. See *G & W, USA.*

G & W, USA. G & W Laboratories Inc., 111 Coolidge St, South Plainfield, NJ 07080-3895, USA.
url: www.gwlabs.com

GA, Gr. GA Pharmaceuticals S.A., Agisilaou 46, 173 41 Athens, Greece.
url: www.gap.gr

GA Pharmaceuticals, Hong Kong. See *Health Alliance, Hong Kong.*

GABA, Belg. See *GABA, Neth.*

GABA, Cz. See *GABA, Switz.*

GABA, Fin. See *GABA, Switz.*

GABA, Ger. GABA GmbH, Berner Weg 7, 79539 Lörrach, Germany.
url: www.gaba-dent.de

GABA, Gr. See *GABA, Ger.*

GABA, Israel. See *Teva, Israel.*

GABA, Neth. GABA BV, Bolderweg 1, 1332 AX Almere, Netherlands.
url: www.gaba-bv.nl

GABA, Pol. See *Rada, Pol.*

GABA, Port. See *GABA, Ger.*

GABA, Switz. GABA AG, Pharmazeutische und kosmetische Praparate, Grabetsmattweg, 4106 Therwil, Switzerland.
url: www.gaba.ch

Gabriel, Gr. Gabriel Health Ltd, 14 Gr.Kousidi, 15772 Athens, Greece.

Gache, Venez. Productos Gache S.A., Calle La Industria, Ed. Lemar P.B., Urb. Palo Verde, Caracas, Venezuela.

Gador, Arg. Gador S.A., Darwin 429, 1414 Buenos Aires, Argentina.
url: www.gador.com.ar

Gador, Chile. See *Pasteur, Chile.*

Gahler, Canad. Gahler Enterprises Ltd, 3655 Bonneville Pl, Burnaby, British Colombia, V3N 4S9, Canada.

Gai Pu, China. Gai Pu Pharmaceutical Co Ltd, China.

Gaily, Hong Kong. Gaily Pharmaceutical Co Ltd, Rm 1307, 13/F Leader Ind Ctr, 57-59 Au Pui Wan St, Fo Tan, NT, Hong Kong.

Gaitianli, China. Gaitianli Pharmaceuticla Co. Ltd., 88 Heping South Road, Economic and Development Zone, Qidong, Jiangsu, 226200, China.
url: www.gaitianli.com.cn

Gal, Pol. Sepcjalistyczne Przedsiębiorstwo Rolno-Przetwórcze Gal, ul. Krótka 4, 61-012 Poznań, Poland.
url: www.gal.com.pl

Galagen, USA. See *Hormel, USA.*

Galantica, India. Galantica Pharma India Pvt Ltd, 4th Floor Samrudhi Venture Park, MIDC Central Rd, Andheri (E), Mumbai, 400 093, India.

Galderma, Arg. Galderma Argentina S.A., Av Juramento 1775, Piso 3, 1428 Ed. Juramento Plaza, Buenos Aires, Argentina.
url: www.galderma.com.ar

Galderma, Austral. Galderma Australia P/L, P.O. Box 502, Frenchs Forest, NSW 2086, Australia.
url: www.galderma.com

Galderma, Austria. See *Galderma, Fr.*

Galderma, Belg. Galderma Belgilux SA, Fountain Business Centre Bornem, Gebouw 5, bus 205, Van Kerckhavenstraat 110, 2880 Bornem, Belgium.
url: www.galderma.com

Galderma, Braz. Galderma Brasil Ltda, Av. Nações Unidas, 18001, 6th Floor, Vila Almeida, 04795-100 São Paulo, SP, Brazil.
url: www.galderma.com

Galderma, Canad. Galderma Canada Inc., 7300 Warden Ave, Suite 210, Markham, Ontario, L3R 9Z6, Canada.
url: www.galderma.com

Galderma, Chile. Galdermo Chile Laboratorios Ltda, Europa 2066, Providencia, Santiago, Chile.

Galderma, China. Galderma, 24 Jianguomenwai Ave, Beijing 100004, China.
url: www.galderma.com

Galderma, Cz. See *Galderma, Fr.*

Galderma, Denm. Galderma Svenska, c/o Regus House, Lars Bjørnsstraede 3, 1454 Copenhagen K, Denmark.
url: www.galderma.dk

Galderma, Fin. Galderma Nordic AB, Mannerheimintie 12 B, 00100 Helsinki, Finland.
url: www.galderma.com

Galderma, Fr. Laboratoires Galderma, Tour Europlaza, La Défense 4, 20 av. Andre-Prothin, 92927 La Défense cdx, France.
url: www.galderma.com

Galderma, Ger. Galderma Laboratorium GmbH, Georg-Glock-Str. 8, 40474 Düsseldorf, Germany.
url: www.galderma.de

Galderma, Gr. Galderma Hellas, Pendelis Ave 37A, 15235 Vrilissia Attica, Greece.
url: www.galderma.com

Galderma, Hong Kong. Galderma Hong Kong Ltd, Unit 1303, 13/F CRE Building, 303 Hennessy Rd, Wanchai, Hong Kong.
url: www.galderma.com

Galderma, Hung. See *Ewopharma, Hung.*

Galderma, India. Galderma (India) Pvt Ltd, 23 Steelmade Industrial Estate, 2nd Floor, Marol Village, Andheri (E), Mumbai 400 059, India.
url: www.galderma.com

Galderma, Irl. See *Allphar, Irl.*

Galderma, Israel. See *Luxembourg, Israel.*

Galderma, Ital. Galderma Italia S.p.A., C. Dir. Colleoni Pal. Sirio 3, 20041 Agrate Brianza (MI), Italy.
url: www.galderma.com

Galderma, Malaysia. See *Summit, Malaysia.*

Galderma, Mex. Galderma Mexico S.A. de C.V., Jose Maria Ibarraran No. 20, Col. San Jose Insurgentes, 03900 Mexico D.F., Mexico.
url: www.galderma.com.mx

Galderma, Neth. Galderma S.A., Avelingen-West 5, 4202 MS Gorinchem, Netherlands.
url: www.galderma.com

Galderma, Norw. Galderma Nordic AB, c/o Regus, Ibsenkvartalet, CJ Hambros plass 2 C, 0164 Oslo, Norway.
url: www.galderma.com

Galderma, NZ. See *Pacific, NZ.*

Galderma, Philipp. Galderma Philippines, Unit 2802, 28/F Atlanta Ctr, 31 Annapolis St, Greenhills, San Juan, Metro Manila, Philippines.

Galderma, Pol. Galderma Polska Sp. zo.o., ul. Łączyny 4, 02-820 Warsaw, Poland.

Galderma, Port. Laboratórios Galderma, SA, Av Duque d'Avila 185, 1050-082 Lisbon, Portugal.
url: www.galderma.com

Galderma, Rus. Galderma SA, Strominskiy pereulok, 6, 107076 Moscow, Russia.
url: www.galderma.com

Galderma, S.Afr. Galderma Laboratories SA (Pty) Ltd, P.O. Box 71150, Bryanston 2021, South Africa.
url: www.galderma.com

Galderma, Singapore. See *Summit, Singapore.*

Galderma, Spain. Galderma, C/ Agustin de Foxa 29 - 6 pl, 28036 Madrid, Spain.
url: www.galderma.com

Galderma, Swed. Galderma Nordic AB, Box 15028, 167 15 Bromma, Sweden.
url: www.galderma.com

Galderma, Switz. Galderma SA, Zugerstrasse 8, 6330 Cham, Switzerland.
url: www.galderma.com

Galderma, Thai. See *US Summit, Thai.*

Galderma, UK. Galderma (UK) Ltd, Meridien House, 69-71 Clarendon Rd, Watford, Hertfordshire, WD17 1DS, UK.
url: www.galderma.com

Galderma, USA. Galderma Laboratories Inc., 14501 North Freeway, Fort Worth, TX 76177, USA.
url: www.galdermausa.com

Galderma, Venez. Laboratorios Galderma Venezuela S.A., Av. Lima con Pasea Colón, Edificio Polar (Nestle), Piso 14, Oficina 14A, Plaza Venezuela Los Caobos, Caracas, Venezuela.
url: www.galderma.com.ve

Galen, Canad. See *Pfizer, Canad.*

Galen, Fin. See *Galen, UK.*

Galen, Ger. Galenpharma, GmbH, Wittland 13, 24109 Kiel, Germany.

Galen, Irl. See *Allphar, Irl.*

Galen, Mex. See *Probiomed, Mex.*

Galen, Neth. See *Galen, UK.*

Galen, Norw. See *Galen, UK.*

Galen, Port. See *Galen, UK.*

Galen, Turk. Galen İlaç San A.Ş., Barbaros Mah, Evren Cad. Çim Sok. No: 54 Balmumcu, Kadiköy, İstanbul, 81100, Turkey.

Galen, UK. Galen Ltd, Seagoe Industrial Estate, Craigavon, Northern Ireland, BT63 5UA, UK.
url: www.galen.co.uk

Galen, USA. See *Galen, UK.*

Galena, Cz. See *Ivax, Cz.*

Galena, Pol. Farmaceutyczna Spółdzielnia Pracy Galena, ul. Krucza 62, 50-984 Wrocław, Poland.
url: www.galena.pl

Galena, Rus. See *Ivax, Rus.*

Galena, Thai. See *SPB, Thai.*

Galena, Ukr. See *Ivax, Rus.*

Galena, USA. Galena Biopharma Inc., Suite 208, 310 N State St, Lake Oswego, OR 97034, USA.

Galenic, Fr. Laboratoires Galénic-Elancyl, 45 place Abel-Gance, 92100 Boulogne, France.

Galenica, Gr. Galenica A.E., 2 Achilleos St., 104 37 Athens, Greece.
url: www.galenica.gr

Galenica, Hung. Galenica, Hold u. 16/D, 8200 Veszprém, Hungary.
url: www.galenica.hu

Galenica, Switz. Galenica Vertretungen AG, Untermattweg 8, 3001 Berne, Switzerland.

Galenika, Ger. See *Hetterich, Ger.*

Galenika, Hung. See *Inex, Hung.*

Galenika, Rus. Galenika ad, Moscow, Russia.
url: www.galenika.rs

Galenika, Ukr. Galenika a.d., Batajnički drum b.b., Belgrade, 11080, Serbia.
url: www.galenika.co.yu

Galenium, Indon. Galenium Pharmosia Laboratories PT, Jl Adityawarman No 67, Kebayoran Baru, Jakarta 12160, Indonesia.
url: www.galenium.com

Galenium, Malaysia. See *Germax, Malaysia.*

Galeno, Venez. Galeno Química C.A., 4ta.Transv., Edif.Centro Ind. de Boleita-Piso 1, Urb. Boleita Sur Caracas, Caracas, Venezuela.

Galenogal, Braz. See *Hertz, Braz.*

Galenowe Olsztyn, Pol. Laboratorium Galenowe Olsztyn Sp. zo.o., ul. Spółdzielcza 25 A, 11-001 Dywity, Poland.
url: www.labgal.com.pl

Galenskaya, Ukr. Galenskaya Laboratory d.d., Chigorina Street, 18, Office 314, Kiev, 01042, Ukraine.

Galenus, Gr. Galenus Pharmaceuticals SA, Jean Moreas 33, Halandri, Greece.
url: www.galenus.gr

Galenus, Pol. Farmaceutyczno-Chemiczna Spółdzielnia Pracy Galenus, ul. Senatorska 36, 00-095 Warsaw, Poland.
url: www.fp.com.pl/galenus

Galephar, Neth. See *Zambon, Neth.*

Galephar, Turk. Galephar İlaç, Turkey.

Galephar, USA. See *Cipher, Canad.*

Galex, Cz. Galex, Czech Republic.

Galex, Gr. Galex, Greece.

Galex, Hung. Galex, Hungary.

Galex, Ital. Galex, Italy.
url: www.galex.si

Galex, Neth. Galex, Netherlands.

Galex, Pol. See *PharmaSwiss, Pol.*

Galien, Arg. Lab. Galien S.A., Roque Perez 2543, 1430 Buenos Aires, Argentina.

Galien, Fr. Galien Pharma, ZA Les Hauts Delafourcade, BP 16, 32201 Gimont, France.
url: galien-fr

Gallipot, USA. Gallipot Inc., 2400 Pilot Knob Rd, St Paul, Minnesota, 55120, Hungary.
url: www.gallipot.com

Gallivit, Fr. Gallivit France (Lab), 12 rue du Quatre-Septembre, 75002 Paris, France.

Gall-Reidlinger, Austria. Gall-Reidlinger OHG, Hauptstrasse 1, A-8813 St Lambrecht, Austria.

Galmed, Cz. Galmed as, Ostrava, Czech Republic.

Galpha, India. Galpha Laboratories Ltd, 610 Shah Nahar Ind. Estate, Dr.E Moses Road, Worli (W), Mumbai 400 018, India.
url: www.galpha.com

Galpha, Thai. See *Pharmaland, Thai.*

Galpharm, UK. GalPharm International Ltd, Hugh House, Galpharm Way, Upper Cliffe Rd, Dodworth Business Park, Dodworth, Barnsley, South Yorkshire, S75 3SP, UK.
url: www.galpharm.co.uk

Galpharma, Israel. See *Luxembourg, Israel.*

Gambar, Ital. Laboratori Gambar S.r.l., Via Bolognola 45, 00138 Rome (RM), Italy.
url: www.evapharm.com

Gambro, Austria. See *Gambro, Swed.*

Gambro, Canad. See *Gambro, Swed.*

Gambro, Cz. See *Gambro, Swed.*

Gambro, Denm. Gambro Danmark, Jydekrogen 8, 2625 Vallensbaek, Denmark.
url: www.gambro.dk

Gambro, Fin. Oy Gambro AB, Sahaajankatu 24, Pl 30, 00811 Helsinki, Finland.
url: www.gambro.com

Gambro, Fr. Gambro SAS, 1-3 bvd Charles de Gaulle, 92707 Colombes Cdx, France.
url: www.gambro.com

Gambro, Ger. Gambro Dailaystoren GmbH, Holger-Crafoord-Strasse 26, 72379 Hechingen, Germany.
url: www.hambro.com

Gambro, Irl. See *Gambro, Swed.*

Gambro, Israel. See *Teva, Israel.*

Gambro, Neth. See *Gambro, Swed.*

Gambro, Norw. Gambro Norge NUF, Bjellandv. 24, 3172 Vear, Norway.
url: www.gambro.com

Gambro, Port. See *Gambro, Swed.*

Gambro, Rus. See *Gambro, Fr.*

Gambro, Spain. Gambro, Avda de la Industria 16, Coslada, 28820 Madrid, Spain.
url: www.gambro.com

Gambro, Swed. Gambro, Box 10101, 220 10 Lund, Sweden.
url: www.gambro.se

Gambro, Switz. Gambro Haspal (Schweiz) AG, Sägereistrasse 24, 6152 Glattbrugg, Switzerland.

Gambro, UK. Gambro Lundia AB (UK & Ireland), Lundia House, Unit 3 The Forum, Minerva Business Park, Peterborough, PE2 6FT, UK.
url: www.gambro.com

Gambro, USA. Gambro Healthcare International, 10810 W Collins Ave, Lakewood, CO 80215-4498, USA.
url: www.gambrohealthcare.com

Gamida, Israel. Gamida-MedEquip Ltd, P.O.Box 7804, Petach Tikvah, Israel.

Gamot, Philipp. See *Biolink, Philipp.*

Gan & Lee, Thai. See *DKSH, Thai.*

Ganassini, Ital. Istituto Ganassini S.p.A. di Ricerche Biochimiche, Via Gaggia 16, 20139 Milan (MI), Italy.
url: www.ganassini.it

Ganli, China. Ganli Pharmaceutical Co. Ltd, Beijing, China.

Gaohua, China. Gaohua Pharmaceutical Co. Ltd, Jinan, China.

Gooxiang, China. Gaoxiong Medicine Co. Ltd, 7/F Block D Long Zhu Building, Long Kun North Rd, Haikou, Hainan, China.

Gaoxin, China. Gaoxin Pharmaceutical Factory, Jinhua Enterprise Group Co. Ltd, Fu 40 Dabaiyang South Rd, Weiyang, Xi'an 710016, Shaanxi, China.

Gaozhuo, China. Gaozhuo Pharmaceutical Co. Ltd, Shenzhen, China.

Gap, Gr. See *GA, Gr.*

GAR, Singapore. See *Innomed, Singapore.*

Garden House, Arg. Lab. Garden House S.A., Estomba 1058/60, 1427 Buenos Aires, Argentina.

Garden House, Chile. Laboratorios Garden House Chile SA, Av. Presidente Alessandri 12310, San Bernardo, Santiago, Chile.

Garden State, Hong Kong. See *International Medical, Hong Kong.*

Garec, S.Afr. Garec Pharmaceuticals, P.O. Box 1123, Halfway House 1685, South Africa.

Garnier, Canad. Garnier Canada, 4895 Hickmore, Montreal, Quebec, H4T 1K5, Canada.

Garnier, UK. Laboratoires Garnier, Golden Ltd, 255 Hammersmith Rd, London, W6 8AZ, UK.
url: www.garnier.com

Garraud, Canad. See *Garraud, Fr.*

Garraud, Fr. Garraud-Paris, 9 rue Marc Mahon, 75017 Paris, France.
url: www.garraudparis.com

Garuda, Hung. Garuda Trade Ltd, Baloton u. 22-24, 1055 Budapest, Hungary.
url: www.garuda.hu

Gate, USA. See *Teva, USA.*

Gattefosse, Hong Kong. See *Great Liaison, Hong Kong.*

Gavis, USA. Gavis Pharmaceuticals LLC, 400 Campus Drive, Somerset, NJ 08873, USA.
url: www.gavispharma.com

Gayoso, Spain. Gayoso, Ctar M-300 Km 29.92, 28802 Alcala de Henares, Madrid, Spain.
url: www.laboratorios-gayoso.com

GB, Ital. GB Pharma Srl, Via Ferreri 11, 27100 Pavia (PV), Italy.
url: www.gbpharma.it

GBF, Philipp. GBF Pharma & Medical Supplies, GBF Bldg, D' Garden, Bago Aplaya, Talomo District, Davao City, Philippines.

GC, Singapore. G C Pharmaceutical (S) Pte Ltd, 1 Maritime Square, 10-33A World Trade Centre, S 099253, Singapore.

GC, Venez. Laboratorio Generica de Calidad GC, Av. 20 Puente Restaurador a Río, Edif. Pulmobronk, Parroquia Sta. Teresa, Caracas, Venezuela.

GC-Rise, China. GC-Rise Pharmaceutical Co. Ltd, Guanghua Rd, Oriental Media Center Room 1202 Block A, Chaoyang, Beijing, 100026, China.
url: www.gc-rise.com

GD, Ital. GD Tecnologie Interdisciplinari Farmaceutiche S.r.l., Via Augusto Gaudenzi 29, 00163 Rome (RM), Italy.
url: www.gditalia.biz

Ge Dian Ren Fu, China. Ge Dian Ren Fu Pharmaceutical Co Ltd, Hubei, China.

GE Healthcare, Austral. GE Healthcare Pty Ltd, Building 4B, 21 South St, Rydalmere, NSW 2116, Australia.

GE Healthcare, Austria. GE Healthcare Handels GmbH, Europlaza, Gebäude E, Technologiestrasse 10, A-1120 Vienna, Austria.

GE Healthcare, Belg. GE Healthcare SA, Koningin Astridlaan 49, 1780 Wemmel, Belgium.
url: www.gehealthcare.com

GE Healthcare, Canad. GE Healthcare Canada Inc., C19 2300 Meadowvale Blvd, Mississauga, Ontario, L5N 5P9, Canada.

GE Healthcare, China. GE Healthcare, Hua Rd, Pudong Zhangjiang Hi-Tech Park, Shanghai, 201203, China.

GE Healthcare, Cz. GE Healthcare (South Central Europe) Handels GmbH, Vyskocilova 1422/1a, 140 28 Praha 4, Czech Republic.

GE Healthcare, Denm. GE Healthcare A/S, Huginsvej 8, 3400 Hillerød, Denmark.
url: www.gehealthcare.com

GE Healthcare, Fin. See *GE Healthcare, UK.*

GE Healthcare, Fr. GE Healthcare SA, 11 rue Morane-Saulnier, 78140 Vélizy Villacoublay, France.

GE Healthcare, Ger. GE Healthcare Buchler GmbH & Co KG, Gieselweg 1, 38110 Braunschweig, Germany.
url: www.gehealthcare.de

GE Healthcare, Gr. GE Health Care, Kyprou 156 & Kon/poleos 91, 164 51 Argyroupoli, Greece.

GE Healthcare, Hung. GE Healthcare, Akron ut 2, 2040 Budaörs, Hungary.
url: www.gehealthcare.com

GE Healthcare, Irl. See *GE Healthcare, UK.*

GE Healthcare, Israel. GE Healthcare, Keren Hoyesod 16, Building 15 Tirat Hacarmel, 39120 Haifa, Israel.
url: www.gehealthcare.com

GE Healthcare, Ital. GE Healthcare S.r.l., Via Galeno 36, 20126 Milan (MI), Italy.

GE Healthcare, Neth. GE Healthcare BV, Cygne Centre, 5612 AP Eindhoven, Netherlands.

GE Healthcare, Norw. GE Healthcare AS, Nycov. 2, Postboks 4220 Nydalen, 0401 Oslo, Norway.
url: www.gehealthcare.com

GE Healthcare, NZ. See *Amersham, NZ.*

GE Healthcare, Pol. GE Healthcare (South Central Europe), 2 Stawki, 00-193 Warsaw, Poland.

GE Healthcare, Port. Satis - GE Healthcare, Edificio Ramazzotti, Av. do Forte 6-6A, 2790-072 Carnaxide, Portugal.

GE Healthcare, Rus. See *GE Healthcare, UK.*

GE Healthcare, Spain. GE Healthcare Bio-Sciences SA, Avd de Europa 22, 28108 Alcobendas, Madrid, Spain.

GE Healthcare, Swed. GE Healthcare AB, Solna Strandväg 98, Solna, Stockholm, Sweden.
url: www.gehealthcare.com

GE Healthcare, Switz. GE Healthcare AG, Europastrasse 31, 8152 Glattbrugg, Switzerland.
url: www.gehealthcare.com

GE Healthcare, UK. GE Healthcare, Pollards Wood, Nightingales Lane, Chalfont St Giles, Buckinghamshire, HP8 4SP, UK.
url: www.gehealthcare.com

GE Healthcare, USA. See *Amersham Biosciences, USA.*

Ge Top, Hong Kong. Ge Top International Trading Ltd, 183 Electric Rd, North Point, Hong Kong.
url: www.venergy.hk

Gea, Cz. See *Gea, Denm.*

Gea, Denm. A/S GEA, Kanalholmen 8-12, 2650 Hvidovre, Denmark.
url: www.hexal.dk

Gea, Neth. See *Multipharma, Neth.*

Gea, Pol. See *Hexal, Pol.*

Gea, Switz. See *Ecosal, Switz.*

Gebauer, Canad. See *Gebauer, USA.*

Gebauer, Hong Kong. See *Vantone, Hong Kong.*

Gebauer, USA. Gebauer Co., 4444 East 153rd St., Cleveland, OH 44128, USA.
url: www.gebauerco.com

Gebro, Austria. Gebro Pharma GmbH, A-6391 Fieberbrunn, Austria.
url: www.gebro.com

Gebro, Cz. See *Gebro, Austria.*

Gebro, Denm. See *Medac, Swed.*

Gebro, Hung. See *Sager, Hung.*

Gebro, Spain. Gebro Pharma, C/ Monestir 23, 08034 Barcelona, Spain.
url: www.gebro.com

Gebro, Switz. Gebro Pharma SA, Postfach 397, 4410 Liestal, Switzerland.
url: www.gebro.com

Gedeon Richter, China. Gedeon Richter Plc, 140 Tianlin Rd, Xuhui District, Shanghai 200233, China.

Gedeon Richter, Cz. Gedeon Richter AT, Italská 13, 120 00 Prague 2, Czech Republic.
url: www.richtergedeon.cz

Gedeon Richter, Denm. See *Gedeon Richter, Hung.*

Gedeon Richter, Fr. Gedeon Richter France SARL, 1/3 rue Caumartin, 75009 Paris, France.
url: www.richterfrance.com

Gedeon Richter, Ger. Gedeon Richter Pharma GmbH, Eilerstr. 3 W, 51107 Cologne, Germany.
url: www.gedeonrichter.de

Gedeon Richter, Hong Kong. See *Mekim, Hong Kong.*

Gedeon Richter, Hung. Gedeon Richter Rt, Gyömrői út 19-21, 1103 Budapest, Hungary.

Gedeon Richter, Irl. See *Gedeon Richter, Hung.*

Gedeon Richter, Israel. See *Trima, Israel.*

Gedeon Richter, Ital. Gedeon Richter Italia Srl, Viale cassala 16, 20143 Milan, Italy.
url: www.gedeonrichter.it

Gedeon Richter, Malaysia. See *Pahang, Malaysia.*

Gedeon Richter, Neth. See *Gedeon Richter, Hung.*

Gedeon Richter, Norw. See *Gedeon Richter, Swed.*

Gedeon Richter, Philipp. See *PharmAsia, Philipp.*

Gedeon Richter, Rus. Gedeon Richter, 4 Dobryninsky per 8, 119049 Moscow, Russia.
url: www.g-richter.ru

Gedeon Richter, Singapore. See *Sime Darby, Singapore.*

Gedeon Richter, Spain. Gedeon Richter Ibérica SL, Sabino Arana 28, 08028 Barcelona, Spain.

Gedeon Richter, Swed. Gedeon Richter Nordics AB, Norra Stationsgatan 61, 113 43 Stockholm, Sweden.

Gedeon Richter, Switz. Gedeon Richter (Schweiz) AG, Gewerbestr. 5, 6330 Cham ZG, Switzerland.
url: www.gedeonrichter.ch

Gedeon Richter, Thai. See *Medline, Thai.*

Gedeon Richter, Ukr. Gedeon Richter, Turgenevskaya Street, 17B, 01054 Kiev, Ukraine.
url: www.richter.com.ua

Gedis, Ital. Gedis S.r.l., Via Vezzolano 15, 10153 Turin (TO), Italy.
url: www.gedis.it

Geigy, Austral. See *Novartis, Austral.*

Geigy, Canad. See *Novartis, Canad.*

Geigy, Fr. See *Novartis, Fr.*

Geigy, Ger. See *Novartis, Ger.*

Geigy, Norw. See *Novartis, Norw.*

Geigy, Port. See *Novartis, Port.*

Geigy, Switz. See *Novartis, Switz* and *Novartis Consumer, Switz.*

Geigy, UK. See *Novartis, UK.*

Geigy, USA. See *Novartis, USA.*

Geistlich, Hung. See *SATCO, Hung.*

Geistlich, Irl. Geistlich Pharma, 36 Lower Stephen Street, Dublin 2, Ireland.
url: www.geistlich.com

Geistlich, Neth. See *Multipharma, Neth.*

Geistlich, Singapore. See *DKSH, Singapore.*

Geistlich, Switz. Geistlich-Pharma AG, 6110 Wolhusen, Switzerland.
url: www.geistlich.ch

Geistlich, UK. Geistlich Pharma, Newton Bank, Long Lane, Chester, Cheshire, CH2 3PF, UK.
url: www.geistlich.co.uk

Gejiu, China. Gejiu Biopharmaceutical Co. Ltd, Yunnan, China.

Gelalei, China. Gelalei Pharmaceutical Co. Ltd., 2 Gelalei Street, Xiangfang, Harbin, Heilongjiang, 150049, China.

Gelcaps, Mex. Gelcaps Exp. de Mexico SA de CV, Circuito Centro Civico 27, 53100 Naucalpan de Juarez Ciudad Satel, Estado de Mexico, Mexico.

Gelda, Canad. Gelda Scientific & Industrial Development Corp., 6320 Northwest Drive, Mississauga, Ontario, L4V 1J7, Canada.

Gelfipharma, Ital. Gelfipharma International Srl, Via Milano 88, 26900 Lodi (LO), Italy.

Gelnova, Philipp. See *Endure, Philipp.*

Gelos, Cz. See *Gelos, Spain.*

Gelos, Port. See *Gelos, Spain.*

Gelos, Spain. Gelos, Joan XXIII 10, Esplugues de Llobregat, 08950 Barcelona, Spain.
url: www.gelos.es

Gelpharma, Mex. Gelpharma SA de CV, Priv. Agustin Gutierrez 125, 3340 General Anaya, Mexico DF, Mexico.

Gemardi, Thai. See *Diethelm, Thai.*

Gemepe, Arg. Lab. GeMePe S.A., Jovellanos 886, 1267 Buenos Aires, Argentina.
url: www.gemepe.com.ar

Gemi, Pol. Przedsiębiorstwo Produkcji Farmaceutycznej Gemi, ul. Mickiewicza 36, 05-480 Karczew k/Otwocka, Poland.
url: www.gemi.pl

Gemini, Canad. Gemini Packaging Ltd, 150 12071 Jacobson, Richmond, British Columbia, V6W 1L5, Canada.

Geminis, Arg. Géminis S.A., Flora 582, 1706 Haedo, Buenos Aires, Argentina.

Geminis, Spain. See *Novartis, Spain.*

Gen, Turk. Gen İlaç ve Sağlık Ürünleri San. ve Tic. Ltd. Şti., Hal Yolu Caddesi Bay Plaza, No: 5 K: 5, İçerenköy, İstanbul, Turkey.
url: www.gen-ilac.com

GenAsia, Philipp. GenAsia Biotech L L Corp., UG 41, Cityland Pioneer, 128 Pioneer St, Mandaluyong City, Philippines.

Gencom, China. Gencom Pharmaceutical Co. Ltd, Tianjin, China.

Gencon, USA. See *Barr, USA.*

GenDerm, Canad. See *Medicis, Canad.*

GenDerm, USA. See *Medicis, USA.*

Genedec, Port. Genedec Medicamentos Geréricos Lda, Rua Sebastião e Silva 56, 2745-838 Massamá, Portugal.

Genelabs, Hong Kong. See *Hind Wing, Hong Kong.*

Geneleuk, China. Geneleuk Pharmaceutical Co. Ltd., Mid Jiangshuiquan Road, Lixia, Jinan, Shandong, China.

Genentech, Cz. See *Genentech, USA.*

Genentech, Irl. See *Roche, Irl.*

Genentech, Rus. See *Roche, Rus.*

Genentech, USA. Genentech Inc., 1 DNA Way, South San Francisco, CA 94080-4990, USA.
url: www.gene.com

Genepharm, Austral. See *Ascent, Austral.*

Genepharm, Cz. See *Genepharm, Gr.*

Genepharm, Gr. Genepharma Group A.E., 18 km Marathon Ave, 153 51 Pallini, Greece.
url: www.genepharm.gr

Genepharm, Ital. See *Genepharm, Gr.*

Genepharm, Neth. See *Genepharm, Gr.*

General Chemicals, Gr. General Chemicals Products SA, Aygis 60, 145 64 Kifissia, Greece.

General Dietary, UK. General Dietary Ltd, P.O. Box 38, Kingston-upon-Thames, Surrey, KT2 7YP, UK.

General Drug, Philipp. See *United Home, Philipp.*

General Drugs, Singapore. See *Medicell, Singapore.*

General Drugs, Thai. General Drugs House Co. Ltd, 2-4 Soi Lard Prao 82, Bangkok 10310, Thailand.
url: www.gdh.co.th

General Drugs House, Philipp. See *GBF, Philipp.*

General Electric, Chile. General Electric Inc., Alcántara 200 Piso 11, Las Condes, Santiago, Chile.

General Nutrition, Canad. General Nutrition Canada, 6299 Airport Td, Ste 201, Mississauga, Ontario, L4V 1N3, Canada.

General Pharmaceutical, China. Shanghai General Pharmaceutical Co. Ltd, 889 Shennanlu, Shanghai, 200040, China.

General Sanyang, China. General Sanyang Pharmaceutical Co. Ltd, Industrial Development Zone, Haikou, Hainan, China.

General Topics, Ital. General Topics S.r.l., Località Santigaro 32, 25010 San Felice Del Benaco (BS), Italy.

Generfarma, Spain. Generfarma, Los Centelles 7, 46006 Valencia, Spain.

Generic Health, Austral. Generic Health, Suite 1, 1175 Toorak Rd, Camberwell, VIC 3124, Australia.
url: www.genericehealth.com.au

Generica, Fin. See *Generica, Ger.*

Generica, Ger. Generica KG GmbH & Co, Südwestpark 50, 90449 Nürnberg, Germany.

Genericon, Austria. Genericon Pharma GmbH, Hafnerstrasse 211, A-8054 Graz, Austria.

Genericon, Cz. Genericon sro, Anny Letenské 1108/15, 120 00 Praha 2, Czech Republic.

Genericon, Denm. See *Genericon, Austria.*

Genericon, Fin. See *Genericon, Cz.*

Genericon, Neth. See *Genericon, Austria.*

Generics, Cz. See *Merck, Cz.*

Generics, Denm. See *NM, Denm.*

Generics, Fin. See *Generics, UK.*

Generics, Hung. See *Merck, Hung.*

Generics, Irl. See *Generics, UK.*

Generics, Israel. See *Genmedix, Israel.*

Generics, Neth. See *Generics, UK.*

Generics, Pol. See *Merck, Pol.*

Generics, Spain. See *Generics, UK.*

Generics, UK. Generics (UK) Ltd, Albany Gate, Drakes Lane, Potters Bar, Hertfordshire, EN6 1AG, UK.
url: www.generics.uk.com

Generics Pharmacal, Philipp. See *Filadams, Philipp.*

GeneriNobel, Austria. See *GeneriNobel, Ger.*

GeneriNobel, Ger. GeneriNobel GmbH, Sulzburger Weg 4, 79427 Eschbach, Germany.
url: www.generinobel.com

Generis, Denm. See *Generis, Port.*

Generis, Neth. See *Generis, Port.*

Generis, Port. Generis Farmacêutica SA, Office Park de Beloura, Edificio 4, 2710-444 Sintra, Portugal.
url: www.generis.pt

GeneScience, Hong Kong. See *Primal, Hong Kong.*

Genesis, Gr. Genesis Pharma S.A., 24 Fillelinon St., 152 32 Chalandri, Greece.
url: www.genesispharma.com

Genesis, India. Genesis Biotech Inc, S.C.F.1010 (G.F.), Motor Market, Manimajra, Chandigarh 160 101, India.
url: www.genesisbiotec.in

Genesis, Philipp. Genesis Pharma Inc., 77 Branches Ext, Mendoza Vill, Proj 8, Quezon City, Philippines.

Genesis, Turk. Genesis İlaç ve Sağlık Ürünleri A.Ş., Sadıkoğlu İş MerkeziH, D:44, Hasanpaşa, İstanbul, 34722, Turkey.
url: www.Genesis.gen.tr

Genesis, USA. Genesis Pharmaceuticals, 1721 Maplelane Ave, Hazel Park, MI 48030, USA.
url: www.genesispharm.com

Geness, Rus. Geness Ltd, rp. Krasnoobsk d.25A, Novosibirskaya obl., Russia.

Genetic, Ital. Genetic S.p.A., Contrada Canfora, 84084 Fisciano (SA), Italy.

Genetics, Gr. See *Wyeth, Gr.*

Genetics Institute, Austria. See *Baxter, Ger.*

Genetics Institute, Denm. See *Baxter, Denm* and *Pharmacia, Denm* and *Wyeth Lederle, Denm.*

Genetics Institute, Ger. See *Baxter, Ger.*

Genetics Institute, Switz. See *AHP, Switz.*

Genetics Institute, USA. Genetics Institute, 35 Cambridge Park Drive, Cambridge, MA 02140, USA.
url: www.genetics.com

Geneva, USA. See *Novartis, USA.*

Genevrier, Fr. Laboratoires Génévrier, B.P. 47, 06901 Sophia Antipolis cdx, France.General Manager

Genevrier, Singapore. See *Pan-Malayan, Singapore.*

Genexo, Pol. Genexo Sp. zo.o., ul. Śmiała 51, 01-526 Warsaw, Poland.
url: www.genexo.pl

Genfa, Rus. Genfa Medica, Russia.
url: www.genfamedica.com

Gen-King, USA. See *Kinray, USA.*

Genmedix, Israel. Genmedix Ltd, P.O. Box 8500, New Industrial Zone, Netanya, Israel.
url: www.merck.de

Geno, India. Geno Pharmaceuticals Ltd, Pharmaceutical Complex Tivim Industrial Estate, Karaswada, Mapusa, Goa 403 526, India.
url: www.genopharma.com

Genom, Braz. Genom Farmacêutica Ltda, Av. Ceci 820, 06460-120 Barueri, SP, Brazil.

Genom, India. Genom Biotech Pvt Ltd, A 601/602 Delphi Orchard Ave, Hirnandani Business Park, Powai, Mumbai 400076, India.
url: genomworld.com

Genom, Rus. See *Genom, India.*

Genomma, Arg. Genomma Laboratories Argentina SA, Av. las Heras 1947 Piso 6, (1127) Buenos Aires, Argentina.

Genomma, Mex. Genomma Laboratorios SA de CV, Ed. Samara Antonio Dovali Jaime 70 Piso 2, 1210 Alvaro Obregón Santa Fé, Mexico.

Genop, S.Afr. Genop Healthcare (Pty) Ltd, P.O. Box 3911, Halfway House 1685, South Africa.
url: www.genophealthcare.co.za

Genopharm, Belg. See *Genopharm, Fr.*

Genopharm, Denm. See *Genopharm, Fr.*

Genopharm, Fr. Laboratoires Genopharm, ZI de l'Esplanade, 2 rue Niels Bohr, 77400 Saint-Thibault-des-Vignes, France.
url: www.genopharm.fr

Genopharm, Swed. See *Genopharm, Fr.*

Genopharm, UK. Genopharm Laboratories, UK.
url: www.genopharm.eu

Genosis, UK. Genosis plc, Suite 1, 2nd Floor, 1 Crown Square, Woking, Surrey, GU21 6HR, UK.
url: www.genosis.co.uk

Genovate, Thai. See *Charoen, Thai.*

Genpharm, Canad. Genpharm Inc., 37 Advance Rd, Etobicoke, Ontario, M8Z 2S6, Canada.
url: www.genpharm.ca

Genpharm, Israel. See *Genmedix, Israel.*

Genpharm, USA. See *Medarex, USA.*

Genpharma, Arg. Laboratorios Genpharma SA, Bdo de Irigoyen 546, Piso 1 A, 1072 Buenos Aires, Argentina.

GenRx, Austral. See *Mayne, Austral.*

Gensavis, USA. Gensavis Pharmaceuticals LLC, USA.
url: www.gensavis.com

Gensci, China. GeneScience Pharmaceutical Co. Ltd, 72 Tianhe St, Changchun High-Tech Development Zone, Changchun, Jilin, 130012, China.
url: www.gensci-china.com

Genser, Arg. Alimentos Genser S.A., Cucha Cucha 2548, 1416 Buenos Aires, Argentina.
url: www.genser.com.ar

Gensia, Ger. See *Baxter, Ger.*

Gensia, Swed. See *Gensia, UK.*

Gensia, UK. Gensia Automedics Ltd, Unit 31, Wellington Business Park, Dukes Ride, Crowthorne, Berkshire, RG45 6LS, UK.

Gensia, USA. See *Teva, USA.*

Genta, USA. Genta Inc., 2 Connell Drive, Berkeley Heights, NJ 07922, USA.
url: www.genta.com

Gentech, Arg. Gentech Argentina SA, Presidente Perón 2207, (1646) San Fernando, Buenos Aires, Argentina.

Gentech, India. Gentech Healthcare Pvt Ltd, A-18, 2nd Floor Gentech House, Young Chamber, Commercial Complex, New Delhi 110 009, India.
url: www.gentechhealthcare.com

Gentek, Venez. See *Leti, Venez.*

Gentex, USA. Gentex Pharma LLC, USA.
url: www.gengtexpharma.com

Genthon, Cz. See *Genthon, Neth.*

Genthon, Hong Kong. See *International Medical, Hong Kong.*

Genthon, Irl. See *Genthon, Neth.*

Genthon, Neth. Genthon BV, Microweg 22, 6545 CM Nijmegen, Netherlands.

Genthon, Port. See *Genthon, Neth.*

Gentian, Denm. See *Gentian, UK.*

Gentian, UK. Gentian Generics Ltd, 5th Floor Castle Chambers, 43 Castle St, Liverpool, L2 9TL, UK.

Gentili, Ital. Istituto Gentili S.p.A., Via Benedetto Croce 37, 56125 Pisa (PI), Italy.

GenTop, Cz. GenTop sro, Americka 579/17, Prague, Czech Republic.

Genus, Irl. See *Genus, UK.*

Genus, UK. Genus Pharmaceuticals Ltd, 65 London Rd, Newbury, Berkshire, RG14 1JN, UK.
url: www.genuspharma.com

Genven, Venez. See *Leti, Venez.*

Genzyme, Arg. Genzyme de Argentina SA, Fondo de la Legua 161, 1667 Boulogne sur Mer, Buenos Aires, Argentina.

Genzyme, Austral. Genzyme Australasia P/L, P.O. Box 6207, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153, Australia.
url: www.genzyme.com.au

Genzyme, Austria. See *Genzyme, Neth.*

Genzyme, Belg. Genzyme Belgium, Ikaroslaan 53, 1930 Zaventem, Belgium.
url: www.genzyme.com

Genzyme, Braz. Genzyme do Brasil Ltda, Rua Padre Chico 224, 05008-010 Perdizes São Paulo, SP, Brazil.
url: www.genzyme.com.br

Genzyme, Canad. Genzyme Canada Inc., 800-2700 Matheson Bvld E, East Tower, Mississauga, Ontario, L4W 4V9, Canada.
url: www.genzyme.com

Genzyme, Chile. Genzyme Chile Ltda, Isadora Goyenechea 3120, Of. 2-B, Las Condes, Santiago, Chile.

Genzyme, China. Genzyme Biomedicine (Shanghai) Consulting Co. Ltd, Room 4106, 268 Xizang Rd, Raffles City, Shanghai, 200001, China.

Genzyme, Cz. See *Genzyme, UK.*

Genzyme, Denm. Genzyme A/S, Islands Brygge 57, 2300 Copenhagen S, Denmark.
url: www.genzyme.com

Genzyme, Fin. See *Genzyme, Denm.*

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Genzyme, Ger. Genzyme GmbH, Siemensstr. 5 b, 63263 Neu-Isenberg, Germany.
url: www.genzyme.de

Genzyme, Gr. Genzyme Hellas LLC, 599 Vouliagmenis Ave, 164 52 Argyroupoli, Greece.
url: www.genzyme.com

Genzyme, Hong Kong. See *IDS, Hong Kong* and *Naturest, Hong Kong* and *Vantone, Hong Kong* and *Zuellig, Hong Kong.*

Genzyme, Hung. Genzyme Europe BV Képviselet, Apor Vilmos ter 25-26, 1124 Budapest, Hungary.
url: www.genzyme.com

Genzyme, Irl. See *Genzyme, UK.*

Genzyme, Israel. Genzyme Israel Ltd, P.O. Box 1188, Kfar Saba, Israel.
url: www.genzyme.co.il

Genzyme, Ital. Genzyme S.r.l., Via Scaglia Est 144, 41100 Modena (MO), Italy.
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Genzyme, Jpn. Genzyme Tokyo, 9F, Ichigaya-Tokyu Bldg., 4-2-1 Kudan-Kita, Chiyoda-ku, Tokyo 102-0073, Japan.
url: www.genzyme.co.jp

Genzyme, Malaysia. Genzyme Malaysia Sdn Bhd, Unit E305 East Wing Metropolitan Square, Jln PJU 8/1, Bandar Damansara Perdana, 47820 Petaling Jaya, Selangor, Malaysia.

Genzyme, Neth. Genzyme BV, Gooimeer 10, 1411 DD Naarden, Netherlands.
url: www.genzyme.com

Genzyme, Norw. See *Genzyme, Denm.*

Genzyme, Pol. Genzyme Polska, al. Stanów Zjednoczonych 61a, 04-028 Warsaw, Poland.
url: www.genzyme.com

Genzyme, Port. Genzyme Portugal SA, Taguspark, Edifício Ciencia II, 2, Sala 2D, 2740-120 Porto Salvo, Portugal.

Genzyme, Rus. Genzyme Russia, Sadovaya Plaza, Dolgorukovskaya str. 7, 127006 Moscow, Russia.
url: www.genzyme.com

Genzyme, S.Afr. Genzyme South Africa, Bryanston Corner, 18 Ealing Crescent, Bryanston, Johannesburg, Gauteng 2191, South Africa.
url: www.genzyme.com

Genzyme, Singapore. See *Pharmacon, Singapore.*

Genzyme, Spain. Genzyme, Damian Sanchez Lopez 3, San Sebastian de los Reyes, 28700 Madird, Spain.
url: www.genzyme.com

Genzyme, Swed. See *Genzyme, Denm.*

Genzyme, Switz. Genzyme GmbH, Zugerstrasse 72, 6340 Baar, Switzerland.
url: www.genzyme.com

Genzyme, Thai. See *Berli Jucker, Thai.*

Genzyme, Turk. Genzyme Turkey Ltd, Suleyman Seba Caddesi, BJK Plaza A98 Besiktas, İstanbul 34357, Turkey.
url: www.genzyme.com

Genzyme, UK. Genzyme Therapeutics Ltd, 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford, Oxfordshire, OX4 2SU, UK.
url: www.genzyme.co.uk

Genzyme, Ukr. Genzyme, Degtyarev St 62, 04112 Kiev, Ukraine.
url: www.genzyme.com

Genzyme, USA. Genzyme Corp., 500 Kendall St, Cambridge, MA 02142, USA.
url: www.genzyme.com

Genzyme Biosurgery, Thai. See *Berli Jucker, Thai.*

Geo, India. Geo Pharma Pvt Ltd, Plot No. 7/W Jaibharat Society, 3rd Road, Khar (W), Mumbai, India.

Geofman, Philipp. See *Clinbaxy, Philipp.*

Geolab, Braz. Geolab Indústria Farmacêutica Ltda, VP 1B Quadra 8 Mod. 01 a 08, 75133600 Anapolis, Goias, Brazil.

Geolik, Ukr. Geolik Farma Marketing Group, 1 Magnitogorsk, Kiev, 02094, Ukraine.
url: www.gfmg.com.ua

Geoprodukt, Hung. Geoprodukt Kft, Bartók B u. 7-9, 3909 Mád, Hungary.

Georen, S.Afr. Georen Pharmaceuticals Pty Ltd, Unit 3 Fontainebleau Commercial Park, 69 Martha Rd North, Fontainebleau 2032, South Africa.
url: www.georen.co.za

Gepach, Rus. Gepach International, Novoschukinskaya St 5, 123098 Moscow, Russia.
url: www.gepach.com

Gepepharm, Ger. gepepharm GmbH, Josef-Dietzgen-Str. 3, 53773 Hennef, Germany.

Gerard, Denm. See *NM, Denm.*

Gerard, Irl. Gerard Laboratories, U36 Baldoyle Industrial Estate, Grange Rd, Baldoyle, Dublin 13, Ireland.

Gerard, Israel. See *Genmedix, Israel.*

Gerard, Norw. See *Norgesfarma, Norw.*

Gerard House, UK. See *Chefaro, UK.*

Gerbex, Canad. Gerbex Inc. Produits, 331 Principale St, St-Thomas d'Aquin, Quebec, J0H 2A0, Canada.

Gerda, Fr. Laboratoires Gerda, 6 rue Childebert, 69002 Lyon, France.

Geriatric Pharm. Corp., USA. See *Shire, USA.*

Geri-Care, USA. Geri-Care Pharmaceuticals, 1650 63rd St, Brooklyn, NY 11204, USA.
url: www.gericarepharm.com

Geritrex, USA. Geritrex Corp., 144 Kingsbridge Rd East, Mt Vernon, NY 10550, USA.
url: www.geritrex.com

Gerlach, Ger. Eduard Gerlach GmbH, Bäckerstr. 4-8, 32312 Lübbecke, Germany.

German Homoeopathic, Rus. German Homoeopathic, Vernadskogo pr-t 105, corp. 2, 119526 Moscow, Russia.

German Red Cross, Philipp. See *Endure, Philipp.*

German Remedies, India. German Remedies Ltd, Shivsagar Estate 'A', Dr Annie Besant Rd, Worli, Mumbai 400 018, India.

Germandre, Fr. Germandre (Lab), 9 faubourg d'Antraigues, 07600 Vals-les-Bains, France.

Germania, Austria. Germania Pharmazeutika GmbH, Schuselkagasse 8, A-1150 Vienna, Austria.

Germax, Malaysia. Germax Sdn Bhd, 10 Jln PJU 3/48, Sunway Damansara, Technology Park, 47810 Petaling Jaya, Selangor, Malaysia.
url: www.germax.com.my

Germed, Braz. Germed Farmaceutica Ltda, Rua Dr Emilio Ribas 188 Conj. 71, 13025140 Campinas Cambui, Sao Paulo, Brazil.

Germed, Ital. Germed Pharma SpA, Via Cesare Cantu 11, 20092 Cinisello Balsamo (MI), Italy.
url: www.germedpiva.it

Germiphene, Canad. Germiphene Corporation, 1379 Colborne St E, P.O. Box 1748, Brantford, Ontario, N3T 5V7, Canada.The President

Germiphene, Israel. Germiphene, Israel.

Germo, Ital. Germo S.p.A., Via Giotto 19/21, 20032 Cormano (MI), Italy.
url: www.germo.it

Geroform, Ukr. Geroform, Bereznyakovskaya Street, 29, Kiev, 02098, Ukraine.
url: www.geropharm.ru

Gerolimatos (Γερολιματος), Gr. See *Gerolymatos, Gr.*

Gerolymatos, Gr. Gerolymatos PN AEVE, 13 Asklipiou Str., 145 68 Kryoneri Athens, Greece.
url: www.gerolymatos.gr

Gerolymatos, Hong Kong. See *Primal, Hong Kong.*

Gerolymatos, Singapore. See *Indrugco, Singapore.*

Gerolymatos, Thai. See *US Summit, Thai.*

Geropharm, Rus. Geropharm OOO, Ordinarnaya, d.12, 197136 Saint-Petersburg, Russia.
url: www.geropharm.ru

Gerot, Austria. Gerot-Pharmazeutika GmbH, Arnethgasse 3, A-1160 Vienna, Austria.

Gerot, Cz. See *Horna, Cz.*

Gerot, Hung. Gerot Phormazeutika Magyarországi Közvetlen Kereskedelmi Képviselet, Bajcsy-Zsilinszky út 12, 1051 Budapest, Hungary.

Gerot, Malaysia. See *Germax, Malaysia.*

Gerot, Neth. See *Gerot, Austria.*

Gerot, Pol. Gerot Pharmazeutika GmbH Sp. zo.o., Przedstawicielstwo w Polsce, al. Jana Pawła II 61, 01-031 Warsaw, Poland.
url: www.gerot.pl

Gerot, Rus. See *Lannacher, Rus.*

Gerot, Singapore. See *Green Cross, Singapore.*

Gerot, Switz. See *Orion, Switz.*

Gerube, Jpn. Gerube Japan Co., Cho, Chiyoda-ku, Tokyo 4-chome 10, Japan.

Gerui, China. Gerui Pharmaceutical Co. Ltd, Qingdao, China.

Gervasi, Spain. Gervasi Farmacia, C/Juan XXIII 15-19, 08950 Brcelona, Spain.

GES, Spain. GES Genrécos Españoles, Calquide 6, Portal 2 Oficina F, Las Rozas, 28230 Madrid, Spain.

Gestafarma, Port. Sociedade Farmacêutica Gestafarma, Lda, Rua Dr. Álvaro de Castro 65-7, 1600-058 Lisbon, Portugal.

Getwell, India. Getwell Life Sciences India Pvt Ltd, 305 Bakshi House, 40-41 Nehru Place, New Delhi 110 019, India.
url: www.getwellindia.com

Getz, Philipp. Getz Pharma Pakistan (Pvt) Ltd, 5/F Ortigas Bldg, Ortigas Ave, Pasig City, Philippines.

Geymonat, Hong Kong. See *CNW, Hong Kong.*

Geymonat, Ital. Geymonat S.p.A., Via S. Anna 2, 03012 Anagni (FR), Italy.

Geymonat, Switz. See *Lucchini, Switz.*

Gezzi, Arg. Lab E J Gezzi SRL, 14 de Julio 855 OB Dto. 2, 1427 Buenos Aires, Argentina.

GFR, Canad. GFR Pharma Ltd, 11450 201 A St, Maple Ridge, British Colombia, V2X 0Y4, Canada.

Ghimas, Ital. Ghimas S.p.A., Via Cimarosa 85, 40033 Casalecchio di Reno (BO), Italy.
url: www.ghimas.com

Giempi, Venez. Laboratorios Giempi C.A., Calle Bolívar, Ed. Giempi, Urb. La Trinidad, Caracas 1081, Venezuela.
url: www.giempi.com

GiEnne, Ital. GiEnne Pharma S.p.A., Graupe Therabel, Via Lorenteggio 270/A, 20152 Milan, Italy.

Gifrer Barbezat, Fr. Laboratoires Gifrer Barbezat, 4-10 rue Paul Bert, BP 165, 69153 Decines cdx, France.
url: www.gifrer.fr

Gil, USA. Gil Pharmaceutical, USA.
url: www.gilpharmaceutical.com

Gilbert, Cz. See *Gilbert, Fr.*

Gilbert, Fr. Laboratoires Gilbert, av. du Général-de-Gaulle, B.P.115, 14204 Hérouville-Saint-Clair cdx, France.
url: www.groupebatteur.fr

Gilbert, Hong Kong. See *Unam, Hong Kong.*

Gilbert, Rus. See *Nycomed, Rus.*

Gilbert, Thai. See *Ouiheng, Thai.*

Gilbert, Ukr. See *Nycomed, Ukr.*

Gilco, Israel. Gilco Pharm Ltd, 12 Hayekev St., Rishon LeZiyon 75497, Israel.

Gilead, Austral. Gilead Sciences Pty Ltd, Unit 2, 41 Stamford Rd, Oakleigh, VIC 3166, Australia.
url: www.gilead.com

Gilead, Austria. See *Gilead, UK.*

Gilead, Belg. Gilead Sciences Belgium BVBA/SPRL, Park Lane, Culliganlaan 2G, 1831 Diegem, Belgium.
url: www.gilead.com

Gilead, Braz. See *Gilead, USA.*

Gilead, Canad. Gilead Sciences Canada Inc., Vancouver, Canada.
url: www.gilead.com

Gilead, Chile. See *Pharma Invesi, Chile.*

Gilead, Cz. See *Gilead, UK.*

Gilead, Denm. See *Orphan, Denm.*

Gilead, Fin. See *Gilead, UK.*

Gilead, Fr. Gilead Sciences, 100 Avenue de Suffren, 75015 Paris, France.
url: www.gilead.com

Gilead, Ger. Gilead Sciences GmbH, Fraunhoferstr. 17, 82152 Martinsried/Planegg, Germany.
url: www.gilead-sciences.de

Gilead, Gr. Gilead Sciences, Inc., 2 Rizountos & Thrakis Str., Helliniko, 167 77 Athens, Greece.
url: www.gilead.com

Gilead, Hong Kong. See *IDS, Hong Kong.*

Gilead, Hung. See *Gilead, UK.*

Gilead, Irl. See *Gilead, UK.*

Gilead, Israel. See *Gilead, UK.*

Gilead, Ital. Gilead Sciences S.r.l., Via Marostica 1, 20146 Milan (MI), Italy.
url: www.gilead.com

Gilead, Neth. Gilead Sciences BV, Postbus 1054, 1300 BB Almere, Netherlands.
url: www.gilead.nl

Gilead, Norw. See *Swedish Orphan, Norw.*

Gilead, NZ. Gilead Sciences (NZ), Level 35, 23-29 Albert St, Auckland, New Zealand.

Gilead, Pol. See *Medagro, Pol.*

Gilead, Port. Gilead Sciences Lda, Campo Grande 28 7A, 1700-093 Lisbon, Portugal.

Gilead, Rus. Gilead Sciences, Dmitriya Ulyanova ul. 16, korp. 2, of. 184-185, 117292 Moscow, Russia.
url: www.gilead.com

Gilead, S.Afr. See *Aspen, S.Afr.*

Gilead, Singapore. See *IDS, Singapore.*

Gilead, Spain. Gilead Sciences S.L., Agustin de Foxa 27, Planta 11, 28036 Madrid, Spain.
url: www.gilead.com

Gilead, Swed. Gilead Sciences Sweden AB, Hemvärnsgatan 9, 171 54 Solna, Sweden.
url: www.gilead.com

Gilead, Switz. Gilead Sciences Switzerland Sarl, Turmstrasse 28, 6300 Zug, Switzerland.
url: www.gilead.com

Gilead, Thai. See *Siam Pharm, Thai.*

Gilead, UK. Gilead Sciences Ltd, The Flowers Building, Granta Park, Great Abington, Cambridge, Cambridgeshire, CB21 6GT, UK.
url: www.gilead.com

Gilead, USA. Gilead Sciences Inc., 333 Lakeside Drive, Foster City, CA 94404, USA.
url: www.gilead.com

Gillette, Arg. Gillette Argentina, Gdor. Ugarte 3561, 1605 Munro, Buenos Aires, Argentina.

Gillette, Belg. See *Procter & Gamble, Belg.*

Gillette, Neth. Gillette Nederland BV, Visseringlaan 20, Rijswijk, Netherlands.

Gineladius, Austria. See *Gineladius, Spain.*

Gineladius, Spain. Gineladius SL, Rufino González 50, 28037 Madrid, Spain.

Gingi-Pak, Switz. See *Beldenta, Switz.*

Ginsana, Switz. Ginsana SA, Via Mulini, 6934 Bioggio, Switzerland.

Gintec, Austria. See *Gintec, Ger.*

Gintec, Ger. Gintec International GmbH, Limburger Str. 50, 61462 Königstein, Germany.
url: www.gintec.de

Giovanardi, Ital. Giovanardi Farmaceutici S.n.c. del Dr Benito Giovanardi e Figli, Via Sapeto 28, 16131 Genoa (GE), Italy.
url: www.giovanardi.net

Girard, Switz. See *Uhlmann-Eyraud, Switz.*

Girud, Rus. Girud IN, ul Saratovskoe shosse 8 A, Saratovskaya, 413800 Balakovo, Russia.
url: www.girudin.com

GIS, Thai. GIS Pharma Ltd Part, 1350/714 1 Fl Thairong Tower, Pattanakarn Rd, Suanluang, Bangkok 10250, Thailand.

Gisand, Switz. Gisand AG, Schlaftistrasse 14, 3013 Berne, Switzerland.

Giscard, Arg. Lab. Gastón Giscard S.R.L., Rivadavia 4178 Piso 1 Dto.A, 1205 Buenos Aires, Argentina.

Giuliani, Ital. Giuliani S.p.A., Via Palagi 2, 20129 Milan (MI), Italy.

Giuliani, Neth. See *Giuliani, Ital.*

Giulini, Ger. See *Solvay, Ger.*

Giulini, Israel. See *Gramse, Israel.*

GK Chemical, Canad. GK Chemical Specialties Co. Ltd, 90 Barbados Blvd, Scarborough, Ontario, M1J 1K9, Canada.

GL Pharma, Austria. GL Pharma GmbH, Schlossplatz 1, 8502 Lannach, Austria.

GL Pharma, Cz. See *GL Pharma, Austria.*

GL Pharma, Denm. See *Nordic Drugs, Denm.*

GL Pharma, Hung. G.L. Pharma MKKK, Zsilinszky ut 12, 1051 Budapest, Hungary.

GL Pharma, Neth. See *GL Pharma, Austria.*

GL Pharma, Pol. GL Pharma GmbH Sp z o o, al. Jana Pawła II 61/311, 01-031 Warsaw, Poland.
url: www.gerot.pl

Glades, Canad. See *Glades, USA.*

Glades, USA. Glades Pharmaceuticals, 6340 Sugarloaf Parkway, Duluth, GA 30097, USA.
url: www.glades.com

Gland, India. Gland Pharma Ltd, 6-3-865/1/2, Flat No 201 Green Land Apartments, Ameerpet, Hyderabad 500 016, India.
url: www.glandpharma.com

Gland, Philipp. See *Interlink, Philipp* and *International Apex, Philipp.*

Glaxo, Austria. See *GSK, Austria.*

Glaxo, Belg. See *GSK, Belg.*

Glaxo, Fr. See *GSK, Fr.*

Glaxo, Irl. See *GSK, Irl.*

Glaxo, Jpn. See *GSK, Jpn.*

Glaxo, Rus. See *GSK, Rus.*

Glaxo, Spain. See *GSK, Spain.*

Glaxo, UK. See *GSK, UK.*

Glaxo, USA. See *GSK, USA.*

Glaxo Allen, Ital. See *GSK, Ital.*

Glaxo Wellcome, Austral. See *GSK, Austral.*

Glaxo Wellcome, Austria. See *GSK, Austria.*

Glaxo Wellcome, Belg. See *GSK, Belg.*

Glaxo Wellcome, Braz. See *GSK, Braz.*

Glaxo Wellcome, Canad. See *GSK, Canad.*

Glaxo Wellcome, Denm. See *GSK, Denm.*

Glaxo Wellcome, Fin. See *GSK, Fin.*

Glaxo Wellcome, Fr. See *GSK, Fr.*

Glaxo Wellcome, Ger. See *GSK, Ger.*

Glaxo Wellcome, Gr. See *GSK, Gr.*

Glaxo Wellcome, Hong Kong. See *GSK, Hong Kong.*

Glaxo Wellcome, Irl. See *GSK, Irl.*

Glaxo Wellcome, Israel. See *GSK, Israel.*

Glaxo Wellcome, Ital. See *GSK, Ital.*

Glaxo Wellcome, Mex. See *GSK, Mex.*

Glaxo Wellcome, Neth. See *GSK, Neth.*

Glaxo Wellcome, Norw. See *GSK, Norw.*

Glaxo Wellcome, NZ. See *GSK, NZ.*

Glaxo Wellcome, Port. See *GSK, Port.*

Glaxo Wellcome, Rus. See *GSK, Rus.*

Glaxo Wellcome, S.Afr. See *GSK, S.Afr.*

Glaxo Wellcome, Singapore. See *GSK, Singapore.*

Glaxo Wellcome, Spain. See *GSK, Spain.*

Glaxo Wellcome, Swed. See *GSK, Swed.*

Glaxo Wellcome, Switz. See *GSK, Switz.*

Glaxo Wellcome, Thai. See *GSK, Thai.*

Glaxo Wellcome, UK. See *GSK, UK.*

Glaxo Wellcome, USA. See *GSK, USA.*

GlaxoSmithKline, S.Afr. See *GSK, S.Afr.*

Glenbrook, USA. See *Sanofi-Aventis, USA.*

Glenmark, Braz. Glenmark Farmaceutica Ltda, Rua Alexandre Dumas 1711 3 andar, 04717911 São Paolo Ed Birman 11, Brazil.

Glenmark, Cz. Glenmark Pharmaceuticals sro, Hvězdova 1716/2b, 140 78 Prague 4, Czech Republic.

Glenmark, India. Glenmark Pharmaceuticals Ltd, Glenmark House, B D S Marg, Chakala, Andheri (E), Mumbai 400 099, India.
url: www.glenmarkpharma.com

Glenmark, Irl. See *Glenmark, UK.*

Glenmark, Malaysia. Glenmark Pharmaceuticals Ltd, 21-6-1, Jln 3/50, Diamond Square Business Ctr, Off Jln Gombak, 53000 Kuala Lumpur, Malaysia.

Glenmark, Neth. See *Glenmark, Cz.*

Glenmark, Philipp. Glenmark Philippines Inc., Unit 1105, 11/F Prestige Tower, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

Glenmark, Pol. Glenmark Pharmaceuticals Sp z o o, ul Postepu 6, Mokotow Plaza 1, 02-676 Warsaw, Poland.

Glenmark, Port. See *Glenmark, Cz.*

Glenmark, Rus. Glenmark Impex, Bolshaya Tulskaya Street 10, Building 9, Office 9509, Moscow, 115191, Russia.
url: www.glenmarkcis.com

Glenmork, S.Afr. Glenmark Pharmaceuticals South Africa Pty Ltd, Unit 7 & 8 York House, Tyball Place, 185 Howick Close, Bekker Rd, Vorner Valley, South Africa.
url: www.glenmarkpharma.com

Glenmark, Singapore. See *Uni, Singapore.*

Glenmark, Thai. See *Union Medicol, Thai.*

Glenmark, UK. Glenmark Generics (Europe) Ltd, The Old Sawmill, Hatfield Park, Hatfield, Hertfordshire, AL9 5PG, UK.
url: eu.glenmark-generics.com

Glenmark, Ukr. See *Glenmark, Rus.*

Glenmark, USA. Glenmark Generics Inc. USA, 750 Corporate Drive, Mahwah, NJ 07430, USA.
url: us.glenmark-generics.com

Glenwood, Austria. See *Glenwood, Ger.*

Glenwood, Belg. See *Informed, Belg.*

Glenwood, Canad. Glenwood Laboratories Canada Ltd, 2406 Speers Rd, Oakville, Ontario, L6L 5M2, Canada. Director of Marketing

Glenwood, Ger. Glenwood GmbH, Riedener Weg 23, 82319 Starnberg, Germany.
url: www.glenwood.de

Glenwood, Hong Kong. See *Mita, Hong Kong.*

Glenwood, Switz. See *Galenica, Switz.*

Glenwood, UK. See *Glenwood, Ger.*

Glenwood, USA. Glenwood Inc., 111 Cedar Lane, Englewood, NJ 07631, USA.
url: www.glenwood-llc.com

Gles, Rus. Firma Gles, Kashirskae sh 24, 115478 Moscow, Russia.

GLF, Fr. See *SORAS, Fr.*

Glifarma, Port. See *GSK, Port.*

Global, China. Global Pharmaceutical Co. Ltd, Anhui, China.

Global, Gr. Global development Pharmaceuticals Ltd, Deligianni 3, 144 52 Metamorfosi, Greece.

Global, India. Global Mediciences Ltd, 612-615 Anand Mangal Complex III, Nr. Parimal Garden, Ahmedabad 380 006, India.
url: www.globalmedisciences.com

Global, NZ. Global Medical Solutions (NZ) Ltd, 90 Mountain Rd, Epsom, New Zealand.

Global, Philipp. Global Business Xpress Service Inc., Unit 8D, Lansbergh Place, 170 Tomas Morato, Quezon City, Philippines.

Global, USA. Global Pharmaceuticals Inc., 3735 Castor Ave, Philadelphia, PA 19124, USA.
url: www.globalphar.com

Global Eramas, Indon. See *Tempo Scan Pacific, Indon.*

Global Health, USA. Global Health Products Inc., 1099 Jay St, Suite 100E, Rochester, NY 14611, USA.
url: www.globalhp.com

Global Pharmatrade, Philipp. Global Pharmatrade, Suite 3001 East Twr, PSE Ctr, Exchange Rd, Ortigas Ctr, Pasig City, Philippines.

Globo, Braz. Laboratório Globo Ltda, Av. Montese 840, 31565-150 Belo Horizonte, MG, Brazil.

Globo Asiatico, Philipp. Globo Asiatico Enterprises Inc., JDK Bldg, 127 Maginhawa St, Teachers Village East, Quezon City 1101, Philippines.
url: www.globoasiatico.com.ph

Globopharm, Switz. Globopharm AG, Seestrasse 200, 8700 Kusnacht, Switzerland.
url: www.globopharm.ch

Globus, India. Globus Remedies, B-46, Vivek Vihar-I, New Delhi 110 095, India.

Gloria, Ital. Gloria Maglieria Elastica Srl, Via Diaz 7, 22017 Menaggio (CO), Italy.
url: www.gloriamed.com

Glories, India. Glories Pharmaceuticals Pvt Ltd, S-1 2nd Floor, St Soldier Tower, PVR Complex G-Block, Vikas Puri, New Delhi, India.

Glorious, India. Glorious Healthcare Pvt Ltd, 10-11 Sector A, Vaibhav Nagar, Kanadiya Rd, Indore 452 016, India.
url: www.gloriushealthcare.com

GLS, India. GLS Pharmaceuticals Pvt Ltd, A.O. 80 3rd Floor, Nandeep Ind. Estate, Andheri (E), Mumbai 400 059, India.

Glynn, Cz. Glynn Brothers Chemicals Prague sro, K Betani 1092/19, 148 00 Prague 4, Czech Republic.
url: www.gbc-prague.cz

GM, USA. GM Pharmaceuticals, 912 W Randol Mill Rd, Arlington, TX 76012, USA.

GMP, Indon. Global Multi Pharmalab (GMP) PT, Kawasan Industri Terboyo, Kav A 20-23, Jl Raya Kaligawe KM 6, Semarang 50118, Indonesia.

GN, Ger. See *Biosyn, Ger.*

GNCLS, Ukr. OZ GNCLS Ltd, ul. Vorobiev 8, 61057 Kharkov, Ukraine.
url: www.gncls.com

GNLD, Austral. GNLD International P/L, P.O. Box 419, Beenleigh, Qld 4207, Australia.
url: www.gnld.com.au

GNLD, Canad. GNLD, 202340 Winston Park Drive, Oakville, Ontario, L6H 7T7, Canada.
url: www.gnld.com

GNR, Port. See *Agostinho, Port*

Gobbi, Arg. Lab. Gobbi Novag S.A., F. Onsari 498, 1875 Wilde, Buenos Aires, Argentina.

Godecke, Cz. See *Pfizer, Cz.*

Godecke, Ger. See *Pfizer, Ger.*

Godecke, Israel. See *Pfizer, Israel.*

Godecke, Pol. See *Pfizer, Pol.*

Goedecke, Rus. See *Pfizer, Rus.*

Goemar, Fr. Goëmar, Parc Technopolitain Atalante St-Malo, 41908 St-Jouan des Guerets, 35419 Saint Malo, France.
url: www.goemar.com

Goemar, Philipp. See *Powermist, Philipp.*

Goemar, Rus. See *Goemar, Fr.*

Gojo, Canad. See *Gojo, USA.*

Gojo, USA. Gojo Industries Inc., P.O. Box 991, Akron, OH 44309-0991, USA.
url: www.gojo.com

Golaz, Switz. Laboratoire Golaz SA, Case postale 1067, 1701 Fribourg-Moncor, Switzerland.

Gold & Silver Bell, Thai. Gold & Silver Bell, Thailand.

Gold Coast, Philipp. See *Pacific, Philipp.*

Gold Cross, Austral. See *Biotech, Austral.*

Gold Cross, UK. See *Pfizer, UK.*

Golden Glow, Austral. Golden Glow Natural Health Products, Reply Paid 45, Virginia BC, Qld 4014, Australia.
url: www.goldenglow.com.au

Golden Neo-Life, Conad. Golden Neo-Life Diamite International Ltd, 3 400 Britannia Rd East, Mississauga, Ontario, L4Z 1X9, Canada.

Golden Pride, Canad. Golden Pride, 60 Colannade Rd, Nepean, Ontario, K2E 7J6, Canada.

Goldex, S.Afr. Goldex Healthcare Pty Ltd, South Africa.

Goldfarma, Port. Goldfarma Lda, Rua Professor Francisco Gentil 22-F, 2620-097 Povoa de Santo Adriao, Portugal.

Goldham, Ger. See *Sanochemia, Ger.*

Goldline, USA. See *Ivax, USA.*

Goldmed, Pol. Goldmed Sp. zo.o., ul. Jakuba Kubickiego 19/15, 02-954 Warsaw, Poland.
url: www.sebamed.pl

Goldplus, Singapore. Goldplus Universal Pte Ltd, Blk 1026, Tai Seng Ave 06-3534, Tai Seng Industrial Estate, S 534413, Singapore.
url: www.goldplusuniversal.com.sg

Goldschmidt, Switz. See *Desopharmex, Switz.*

Goldschmidt, UK. See *Degussa, UK.*

Goldshield, Austria. See *Goldshield, UK.*

Goldshield, Denm. See *Goldshield, UK.*

Goldshield, Fin. See *Goldshield, UK.*

Goldshield, Ger. See *Nordend, Ger.*

Goldshield, Hong Kong. See *Universal, Hong Kong.*

Goldshield, Irl. See *Allphar, Irl.*

Goldshield, Israel. See *Pharmateam, Israel.*

Goldshield, Neth. See *Goldshield, UK.*

Goldshield, Norw. See *Goldshield, UK.*

Goldshield, Port. See *Goldshield, UK.*

Goldshield, Singapore. See *Orient, Singapore.*

Goldshield, Spain. Goldshield Pharmaceuticals Ltd, C/ Virgen Del Rosario 34A, 28220 Madrid, Spain.

Goldshield, Swed. See *Goldshield, UK.*

Goldshield, Thai. See *SPB, Thai.*

Goldshield, UK. Goldshield Pharmaceuticals Ltd, NLA Tower, 12-16 Addiscombe Rd, Croydon, Surrey, CR0 0XT, UK.
url: www.goldshieldplc.com

Golf America, Canad. See *Golf America, USA.*

Golf America, USA. Golf America of Southwest Florida Inc., 2049 Crown Drive, St Augustine, FL 32092, USA.

Gomenol, Fr. Laboratoires du Gomenol, 48 rue des Petites-Écuries, 75010 Paris, France.

Gondane-Vitality, Hung. Gondáné Vitality, Veres P u. 74, 4033 Debrecen, Hungary.

Goodfellow, Philipp. Goodfellow Marketing & Sales, Unit 3009 Jollibee Plaza Bldg, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

GoodWay, Indon. GoodWay Farma PT, Jl Pecenongan No 72, Jakarta, DKI Jaya, Indonesia.

Goodwill, Hung. Goodwill Pharma Kft, Széher út 21/b, 1021 Budapest, Hungary.

Goodys, USA. See *GSK Consumer, USA.*

Gordon, Arg. Lab. Gordon S.A.C.I.F.I.A., Malvinas Argentinas 3311, 1644 Victoria, Buenos Aires, Argentina.

Gordon, USA. Gordon Laboratories, 6801 Ludlow St, Upper Darby, PA 19082-2408, USA.
url: www.gordonlabs.com

Gosnii, Rus. See *SSRI, Rus.*

Gosun, China. Gosun Pharmaceutical Co. Ltd, Shenzhen, China.

Gothaplast, Ger. Gothaplast Verbandpflasterfabrik GmbH, Hans-C.-Wirz-Str. 2, 99867 Gotha/Thüringen, Germany.
url: www.gothaplast.de

Gothia, Norw. Gothia Medical AS, Gjerdrumsv. 12, 0484 Oslo, Norway.

Gothia, Swed. Gothia Läkemedel AB, Bolshedens Industriväg 20, 427 50 Billdal, Sweden.

Gouka, Neth. Apotheek Gouka, Groenelaan 111, 3114 CE Schiedam, Netherlands.

Goupil, Fr. See *Sanofi Synthelabo OTC, Fr.*

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GP, UK. See *Derma, UK.*

GPC, Philipp. Gergreg Pharma Corp. (GPC), Suite 1708, 17/F Antel Global Corp, Dona Julia Vargas Ave, Ortigas Ctr, Pasig City, Philippines.

GPH, Singapore. See *Medicell, Singapore.*

GPO, Thai. GPO (The Government Pharmaceutical Organization), 75/1 Rama VI Rd, Ratchathewi, Bangkok 10400, Thailand.

GPP, Rus. GPP, Gosudarstennoe Proizvodstvennoe Predpriyatie Pharmaceutical Factory, ul. Leonida Khrapova D 15-A, 660067 Krasnoyarsky, Russia.

Grace, India. Grace Drugs & Pharmaceuticals, Plot No B-11/7 & 11/8, IDA Uppal, Hyderabad, 500 039, India.

Gracewoy, Canad. Graceway Pharmaceuticals, 302 252 Pall Mall St, London, Ontario, N6A 5P6, Canada.

Graceway, Mex. Graceway de Mexico S de RL de CV, Jaime Bolmes 8, 11510 Miguel Hidalgo los Morales Polan, Mexico DF, Mexico.

Graceway, USA. Graceway Pharmaceuticals LLC, 340 Edgemont Ave, Suite 500, Bristol, TN 37620, USA.
url: www.gracewaypharma.com

Gracia, Indon. Gracia Pharmindo PT, Kawasan Industri Dwipapuri, Blok M-30, Jl Raya Rancaekek Km 24.5, Bandung 45364, Indonesia.
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Gradiens, Hung. Gradiens Kft, Levendula utca 1, 2074 Perbal, Hungary.
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Graf Fruttasan, Switz. Graf Fruttasan AG, Untere Etzmatten 16, 4467 Rothenfluh/BL, Switzerland.
url: www.fruttasan.ch

Grafton, Singapore. Grafton Pharmasia Pte Ltd, 66 Tannery Lane, 01-05A Sindo Building, S 347805, Singapore.
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Graha, Indon. Graha Farma Co. Ltd, Jl Dr. Radjiman 296, Solo, Indonesia.
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Graminex, Rus. Graminex Pharma Ltd, Dm Ulyanova ul 16, 117292 Moscow, Russia.

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Gramon-Bago, Urug. Gramón-Bagó de Uruguay S.A., Av. Joaquín Suárez 3359, Montevideo, 11.700, Uruguay.
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Gramse, Israel. Gramse Pharmaceuticals Ltd, P.O Box 528, New Industrial Park, Yokneam 20692, Israel.
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Granado, Braz. Casa Granado Lab. Farmacias e Drogarias S.A., Travessa do Camércia 17, 20010-080 Rio de Janeiro, RJ, Brazil.
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Grand, China. Grand Pharmaceutical Group Co. Ltd, 5 Gutian Rd, Wuhan 430035, China.
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Grandel, Ger. Dr Grandel GmbH, Pfladergasse 7-13, 86150 Augsburg, Germany.
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Grandel-Synpharma, Ger. See *Grandel, Ger.*

Grandix, India. Grandix Pharmaceuticals Ltd, Jamals Sonu Terrace, 42 Loganathan Nagar, 100 ft. Road, Chennai 600 094, India.
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Grandpa Brands, USA. Grandpa Brands Co., 1820 Airport Exchange Bvld, Erlanger, KY 41018, USA.
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Grands Espaces, Fr. Les Grands Espaces Thérapeutiques, B.P. 6054, 34030 Montpellier cdx 01, France.

Granions, Mon. Laboratoires des Granions, 7 rue de l'Industrie, MC 98000, Monaco.Director General

Grans Remedy, NZ. See *Essential, NZ.*

Grape King, China. See *Putaowang, China.*

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Gray, Arg. Prod. Farmaciuticos Dr. Gray S.A.C.I., Thames 372 Piso 1, 1414 Buenos Aires, Argentina.

Gray, USA. See *Purdue Frederick, USA.*

Great Eastern, Hong Kong. Great Eastern Healthcare Ltd, 9/F, Blk A Kerry TC Warehouse One, 3 Kin Chuen St, Kwai Chung, N.T., Hong Kong.
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Great Wall, China. Great Wall Pharmaceutical Co. Ltd, Beijing, China.

Great Year, Hong Kong. Great Year Trading Co. Ltd, 18/F, 80 Gloucester Rd, Wanchai, Hong Kong.

Greater Pharma, Thai. Greater Pharma Ltd Part, 46, 46/1-2 Soi Charansanitwongs 40, Bangyikhan, Bangkok 10700, Thailand.

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Green Cross, Hong Kong. See *Sunny Plaza, Hong Kong.*

Green Cross, Malaysia. See *Propharm, Malaysia.*

Green Cross, Philipp. See *Vizcarra, Philipp.*

Green Cross, Singapore. Green Cross Pte Ltd, 63 Hillview Ave, 07-06 Lam Soon Industrial Building, S 669569, Singapore.

Green Cross, Thai. See *Diethelm, Thai.*

Green Cross Guangzhou, Malaysia. See *Summit, Malaysia.*

Green Cross Guangzhou, Singapore. See *Grifols, Singapore.*

Green Leaf, Philipp. Green Leaf Herbals Inc., 57, 11th St, New Manila, Quezon City, Philippines.

Green Medicine, Swed. Green Medicine AB, Tegelgårdsgatan 11, 211 33 Malmö, Sweden.
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Green Turtle Bay Vitamin Co., USA. The Green Turtle Bay Vitamin Co., P.O. Box 642, Summit, NJ 07902, USA.
url: www.energywave.com

Green Valley, China. Green Valley Pharmaceutical Co. Ltd., 421 Newton Road, Zhangjiang, Shanghai, 201203, China.
url: www.shgvp.com

Greenco, India. Greenco Biologicals Pvt Ltd, GN-1, Sector V, Salt lake City, Kolkata 700091, India.
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Greenpharma, Braz. Greenpharma Químico e Farmacêutica Ltda, Quadra 2-A Modulos 32/35 DAIA, 75133-600 Anapolis, GO, Brazil.
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Grifols, Canad. See *Grifols, USA.*

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Grifols, Denm. See *Grifols, Ger.*

Grifols, Fin. See *Grifols, Ger.*

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Grifols, Hong Kong. See *Great Year, Hong Kong* and *Keller, Hong Kong.*

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Grifols, Neth. See *Grifols, Spain.*

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Grifols, Philipp. See *Diethelm, Philipp.*

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Grifols, Rus. See *Grifols, Spain.*

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Grimberg, Canad. See *Grimberg, Fr.*

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Grindeks, Ukr. Grindeks, 2 Tverskaja St, Kiev, 03150, Ukraine.
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Gritvak, Rus. Gritvak Inc., Kashirskoe sh 24 korp 2, 115478 Moscow, Russia.

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Grossmann, Hong Kong. See *Koi Cheong, Hong Kong.*

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Grunenthal, Cz. See *Chemotrade, Cz.*

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Grunenthal, Gr. See *Grunenthal, Ger.*

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Grunenthal, Hung. See *Biogal-Teva, Hung.*

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Grunenthal, Israel. See *Grunenthal, Ger.*

Grunenthal, Mex. Grünenthol de Mexica S.A. de C.V., Periferico Sur No. 6677, Col. Ejidos de Tepepan, Deleg. Xochimilco, 16018 Mexica D.F., Mexica.
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Grunenthal, Norw. See *Pfizer, Norw.*

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Grunenthal, Singapore. See *Zuellig, Singapore.*

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Grunenthal, Thai. See *Zuellig, Thai.*

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Grunenthal, Ukr. See *WS, Ukr.*
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Grunenthal, Venez. Grünenthal Venezolano C.A., Av. 1, Torre Centro Profesional Los Samanes Piso 6, Urb. Los Samanes, Caracas, Venezuela.
url: www.grunenthal.com.ve

Grunwalder, Austria. See *Grunwalder, Ger.*

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Gruppo Medica, Philipp. See *Metropolitan, Philipp* and *Zuellig, Philipp.*

Gry, Austria. See *Gry, Ger.*

Gry, Ger. Gry-Pharma GmbH, Kandelstr. 10, 79199 Kirchzarten, Germany.
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GSK Consumer, Austria. See *GSK, Austria.*

GSK Consumer, Belg. See *GSK, Belg.*

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GSK Consumer, Cz. See *GSK, Cz.*

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GSK Consumer, Fin. See *GSK, Fin.*

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GSK Consumer, Hung. See *GSK, Hung.*

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Guerbet, Spain. Laboratorios Farmaceuticos Guerbet SA, Monte Esquinza 28-4, 28010 Madrid, Spain.
url: www.guerbet.com

Guerbet, Switz. Guerbet AG, Winterthurerstrasse 92, 8006 Zurich, Switzerland.
url: www.guerbet-group.com

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Guerbet, Turk. Guerbet Tibbi ve Kimyevi Mad. Tic. A.Ş., Emirhan Cad. Barbaros Plaza, No: 145C Blok K:4, Dikilitaş, İstanbul, 80700, Turkey.
url: www.guerbet.com

Guerbet, UK. Guerbet Laboratories Ltd, Avon House, 435 Stratford Rd, Shirley, B90 4AA, UK.
url: www.guerbet-group.com

Guerbet, USA. Guerbet LLC, 1185 West 2nd St, Bloomington, IN 47403-2160, USA.
url: www.guerbet-us.com

Gufic, India. Gufic Ltd, Subhash Road, A Block, Vile Porle (E), Mumbai 400 057, India.

Gui Long, China. Gui Long Medicine, China.

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Guidotti, Ital. Laboratori Guidotti S.p.A., Via Livornese 897 La Vettola, 56010 Pisa (PI), Italy.
url: www.labguidotti.it

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Guigoz, Fr. Guigoz, B.P. 900, 77446 Marne-la-Vallee cdx 2, France.

Guigoz, Ital. Guigoz, Divisione Dietetici, Viale Richard 5, 20143 Milan (MI), Italy.

Guildford Pharmaceuticals, Neth. See *Guildford Pharmaceuticals, UK.*

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Guilin, China. Guilin Pharmaceutical Co. Ltd, 17 Shanghai Rd, Guilin, Guangxi, China.

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Guinot, Fr. Guinot, 1 rue de la Paix, Paris, France.

Gujarat Terce, India. Gujarat Terce Laboratories Ltd, 209 Samir Opp. Municipal Market, C G Road, Navrangpura, Ahmedabad 380 009, India.

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Gulf Drug, S.Afr. Gulf Drug Company, 22 Burnside Drive, Old Mill Industrial Park, Mount Edgecombe 4300, Durban, South Africa.
url: www.gulfdrug.co.za

Gunal, Turk. T Günal, Turkey.

Gunsa, Turk. Gunsa Guney İlaç San. ve Tic. A.Ş., Mersin Yolu, Yeşil Oba, İstanbul, 01321, Turkey.

Gunther, Braz. Produtos Farmacêuticos Gunther do Brasil Ltda, Rua João Moura 1151, 05412-002 São Paulo, SP, Brazil.

Guo Ao, China. Guo Ao Pharmaceutical Co. Ltd, Changchun, China.

Guo Feng, China. Guo Feng High Tech Pharmaceutical Co. Ltd, Qingdao, China.

Guo Jing, China. Guo Jing Pharmaceutical Co. Ltd, Zhejiang, China.

Guo Yao, China. Guo Yao Group Co Ltd, China.

Guoda, China. Guoda Biopharmaceutical Co. Ltd., 216 Cove Harbour Road, Quingdao Economic and Technological Development Zone, Quingdao, Shandong, 266510, China.
url: www.guodabio.com

Guodi, China. Guodi Pharmaceutical Co. Ltd, Huludao, China.

Guofeng Weiao, China. Guofeng Weiao Pharmaceutical Co. Ltd, Qingdao, China.

GuoGuang, China. GuoGuang Pharmaceutical Co. Ltd, 258 12th Street, Economic and Technological Development Zone, Hangzhou, Zhejiang, 310018, China.
url: www.hzguoguang.com

Guojia, China. Guojia Union Pharmaceutical Co. Ltd, Chengdu, China.

GuoRui, China. GuoRui Pharmaceuticals Co Ltd, Yongding Gate, 12 Outer Ternary Lane A, Chongwen District, Beijing, China.
url: www.guarui.cn

Gupeng, China. Gupeng Pharmaceutical Co. Ltd, Dahuangshan Zhen, Tongshan, Xuzhou, Jiangsu, 221131, China.

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Guri, Israel. Pharma Guri, P.O. Box 15164, Rishon Le Zion 75105, Israel.
url: www.pharmaguri.co.il

Gute, China. Gute Pharmaceutical Co. Ltd, Guizhou, China.

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Guthy Renker, USA. Guthy Renker Corp., 3340 Ocean Park Blvd, Santa Monica, CA 90405, USA.

Gutian, China. Gutian Pharmaceutical Co. Ltd, 1 Chengdong North Rd, Huangtian, Gutian, Ningde, Fujian, 352251, China.

GW, Canad. mge32e

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GW, UK. GW Pharmaceuticals Ltd, Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK.
url: www.gwpharma.co.uk

GX, Philipp. GX International Inc., 8/F ALPAP II Bldg, Trade St, Madrigal Business Park, Ayala Alabang, Muntinlupa City, Philippines.
url: www.gxionline.com

Gynea, Spain. Gynea Laboratorios, Avda Cataluna 127 B, 08184 Palau-Solita i Plegamans, Barcelona, Spain.
url: www.gynea.com

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Gynial, Austria. Gynial GmbH, Schachnerstrasse 20, 1220 Vienna, Austria.

Gynlameda, Ger. Gynlameda GmbH, Hohe Str. 74, 70794 Filderstadt, Germany.
url: www.verhueten-gynefix.de

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H&A, Israel. Health & Aesthetics (H&A) Systems, 32 Tuval St, Ramat Gan, 5252243, Israel.
url: www.hasystems.co.il

H & Care, India. H & Care Pharmaceutical Enterprises, SCF-446 1st Floor M Market, Manimajra, Chandigarh, India.

H & H, Hung. H & H 92 Kft, Kövér Lajos ut 52, 1149 Budapest, Hungary.

H & H, India. H & H Pharmaceutical Pvt Ltd, A/101 Om Chambers, Kranti Marg, Kemps Corner, Mumbai, 400 036, India.

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H2O Plus, Canad. See *H2O Plus, USA.*

H2O Plus, USA. H2O Plus LP, 845 West Madison St, Chicago, IL 60607, USA.

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HAC, Fr. Laboratoires HAC Pharma, Péricentre IV, 8 av. de la Côte de Nacre, 14000 Caen, France.
url: www.hacpharma.com

Hackmey, Israel. Hackmey Ltd, 103 Allenby St, Tel Aviv 65134, Israel.

Hacon, China. Hacon Pharmaceutical Co. Ltd, China.

Haemato, Ger. Haemato-pharm Holding AG, Im Biotechnologiepark, TGZ III, 14943 Luckenwalde, Germany.
url: www.haemato.de

Haemotec, Canad. Haemotec Inc., 383 Joseph Carrier, Vaudreuil, Quebec, J7V 5V5, Conada.

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Haida, China. Haida Pharmaceutical Co. Ltd., Room 802 Xin Hui West Tower, Xian High-tech Industrial Development Zone, Xi'an, Shaanxi, China.

Haier No 3, China. Haier No. 3 Pharmaceutical Co. Ltd, Qingdao, China.

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Haili, China. Haili Pharmaceutical Co. Ltd, 3 Yonggui Industrial Development Zone, Xiuying, Haikou, Hainan, 570000, China.

Hailing, China. Hailing Pharmaceutical Co. Ltd, 281 Nanhai Ave, Haikou, Hainan, 570311, China.
url: www.hailingpharm.com

Hailisheng, China. Hailisheng Pharmaceutical Co. Ltd, 88 Hailisheng Rd, Zhoushan, Zhejiang, China.
url: www.hailisheng.com

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Haini, China. Haini Medicine Co Ltd, Shanghai South Rd 3999, Shanghai 201318, China.

Hairong, China. Hairong Pharmaceutical Co. Ltd, Suchuan, China.

Haisen, China. Haisen Medicine Co. Ltd, 12 Chengshan Rd, Rongcheng, Shandong, China.
url: www.sdhaisen.cn

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Haisike, China. Haisike Pharmaceutical Co. Ltd, Liaoning, China.

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HaiWang Fuyao, China. HaiWang Fuyao Pharmaceutical Co. Ltd., 279 Lower Jinan, Fuzhou, Fujian, 350014, China.
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Haixin, China. Xian Haixin Pharmaceutical Co. Ltd, 20 South Rd, High-Tech Development Zone, Xi'on, China.
url: www.gnhxyy.com

Haiyan, China. Haiyan Pharmaceutical Co. Ltd, 16 Life Park Rd, Changping District, Beijing, China.

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Hal, Ger. Hal Allergie GmbH, Kölner Landstr. 34 a, 40591 Düsseldorf, Germany.
url: www.hal-allergie.de

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Hal, Neth. Haarlems Allergenen Laboratorium BV, Parklaan 125, 2011 KT Haarlem, Netherlands.
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Halal, UK. Halal Pharmaceuticals Ltd, 7 Oxford St, Manchester, M1 4WX, UK.

Haldane, Singapore. Haldane Pharmaceuticals Pte, 286 Jalan Besar, 04-01 TS Bldg, S-208949, Singapore.
url: www.haldanepharma.com

Haledew, India. Haledew Remedies, D/Ground 4-8 Vishwa Residency, Near Vishramnagar, Gurukul Rd, Memnagar, Ahmedabad, 380 052, India.
url: www.rppgroup.in

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Hall, Canad. Hall Laboratories Ltd, 13060-89th Ave, Suite 207, Surrey, British Columbia, V3W 3B2, Canada.

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Halsey, USA. Halsey Drug Co. (Watson), 695 N Perryville Rd, Rockford, IL 61107, USA.
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url: www.hameln-plus.com
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Hameln, Thai. See *JDH Borneo, Thai.*
Hameln, UK. Hameln Pharmaceuticals, Gloucester, Gloucestershire, GL1 4LA, UK.
url: www.hameln.co.uk
Hamilton, Austral. Hamilton Pharmaceuticals P/L, P.O. Box 7, Adelaide, SA 5001, Australia.
url: www.hamiltonlabs.com.au
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Hand-Prod, Pol. Hand-Prod Sp. zo.o., ul. S Leszczyńskiego 40 a, 02-496 Warsaw, Poland.
url: www.hand-prod.com.pl
Hands, India. Hands Pharmaceuticals, P-108, Jadu Colony, Behala, Kolkata 700 034, India.
Handu, China. Handu Pharmaceutical Co. Ltd, South Side Xinmi Railway, Xincun, Xinzheng, Henan, 451150, China.
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url: www.hanosan.de
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Hanseler, Switz. Hänseler AG, Industriestrasse 35, 9100 Herisau, Switzerland.
url: www.haenseler.ch
Hansen, China. Hansen Pharmaceutical Co. Ltd, Hunan, China.
Hanson, China. Hanson Pharmaceutical Co. Ltd, Cangwu Rd Garonne, Building B 9/F, Lianyungang, China.
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Haobang, China. Haobang Pharmaceutical Co. Ltd., 48-1 Nongannan Street, Kuancheng, Changchun, Jilin, 130052, China.
Haochuang, China. Haochuang Pharmaceutical Co. Ltd, 666 City People's Road, Qionghai, Hainan, 571400, China.
Haohai, China. Haohai Biological Technology Co. Ltd, Shanghai, China.
Haohua, China. Haohua International Trading Co. Ltd, F9 Building A, 19 Xiaoying Rd, Chaoyang District, Beijing, 100101, China.
url: www.zhmy.chemchina.com
Haosen, China. Haosen Pharmaceutical Co. Ltd., Ganzhou, Jiangxi, 342400, China.
url: www.jxhaosen.com
Hapra, Cz. Hapra sro, Myslbeková 25, 169 00 Prague 6, Czech Republic.
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url: www.hayaozong.com.cn
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Harbin, Thai. See *Top, Thai.*
Hardis, Ital. Hardis S.p.A., S.S. 7 bis km 19,5, 80029 Sant'Antimo (NA), Italy.
Hargell, Canad. Hargell Ltd, 5050 Dufferin St, Suite 108, North York, Ontario, M3H 5T5, Canada.
Harimex, Neth. Harimex BV, Kieveen 20, 7371 GD Loenen, Netherlands.
url: www.harimex.nl
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Harn, Thai. Harn Thai Pharma Ltd, 2121 New Petchburi Rd, Bangkok 10320, Thailand.
url: www.harnthai.com
Harpers, Malaysia. Harpers Trading (Malaysia) Sdn Bhd, Lot 14 Jalan Bersatu 13/4, 46200 Petaling Jaya, Malaysia.
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url: www.harraspharma.de
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Hartmann, Belg. NV Paul Hartmann SA, 1 Avenue Paul Hartmann, 1480 Saintes, Belgium.
url: be.hartmann.info
Hartmann, Fr. Laboratoires Paul Hartmann, 18 rue des Goumiers, 67730 Châtenois, France.
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Hartmann, Switz. IVF Hartmann AG, Victor-von-Bruns-Strasse 28, 8212 Neuhausen am Rheinfall, Switzerland.
url: www.ivf-hartmann.info
Harvard, USA. The Harvard Drug Group LLC, 31778 Enterprise Dr, Livonia, MI 48150, USA.
url: www.theharvarddruggroup.com
Harvest, China. Harvest Pharmaceutical Co. Ltd, 805 Shanghai Rd, Jinqiao Development Zone, Pudong, Shanghai, 201206, China.
url: www.shharvest.com
Harvest, USA. Harvest Pharmaceuticals Inc., P.O. Box 3586, Radford, VA 24143, USA.
url: www.harvestpharmaceuticals.com
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Harvey-Scruton, UK. Harvey-Scruton Ltd, 4 Barker Lane, York, North Yorkshire, YO1 6JR, UK.
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Hasco-Lek, Pol. Przedsiębiorstwo Produkcji Farmaceutycznej Haco-Lek, ul. Żmigrodzka 242 E, 51-131 Wrocław, Poland.
url: www.hasco-lek.pl
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Haupt, Ger. Haupt Pharma AG, Pfaffenrieder Str. 5-7, 82515 Wolfratshausen, Germany.
url: haupt-pharma.de
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Hautel, Arg. Hautel S.A., Warnes 829 Dto. A, 1414 Buenos Aires, Argentina.
Hauz, India. Hauz Pharma Pvt Ltd, SCF 311 1st Floor, Motor Market, Manimajra, Chandigarh, India.
url: www.hauzpharma.com
Haver, Turk. Haver İlaç Sanayi AŞ, Harbiye M Hürriyet C N: 2/6, Dikmen, Ankara, Turkey.
Haw Par, Austral. See *Haw Par, Singapore.*
Haw Par, Canad. Haw Par Corp. Ltd, P.O. Box 4129, Vancouver, British Columbia, V6B 3Z6, Canada.
Haw Par, Israel. Haw Par, Israel.
Haw Par, Singapore. Haw Par Healthcare Ltd, 401 Commonwealth Drive, 03-03 Haw Par Technocentre, Singapore 149598, Singapore.
url: www.tigerbalm.com
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HB, Braz. H.B. Farma Laboratórios Ltda, Av. Eugenio Borges 1060, 24751-000 São Gonçalo, RJ, Brazil.
HBS, Canad. HBS Distribution Inc., 509 4576 Yonge St, Toronto, Ontario, M2N 6N4, Canada.
HCP, Gr. HCP AE (S. Stavropoulou), Sarantaporou 57, 121 31 Peristeri, Greece.
HCS, Belg. HCS bvba, H Kennisstraat 53, 2650 Edegem, Belgium.
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Healey Medical, Canad. Healey Medical Inc., 181-8 Saint Andrews St E Fergus, Ontario, Canada.
url: www.healeymedical.com
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Health 4 All, Canad. Health 4 All Products Ltd, 545 Welham Rd, Barrie, Ontario, L4N 8Z6, Canada.
Health Alliance, Hong Kong. Health Alliance International Co. Ltd, Rm 601-2 6/F AT Twr, 180 Electric Rd, North Point, Hong Kong.
Health Assure, USA. Health Assure Inc., 26635 West Agoura Rd, Suite 205, Calabasas, CA 91302, USA.
url: www.healthasure.com
Health Biotech, India. Health Biotech Ltd, S.C.O. 162-164 Indian Airlines Building, Top Floor, Sector 34-A, Chandigarh 160 022, India.
url: www.healthbiotech.in
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url: www.biogaia.com
Health for Life, USA. Health for Life Brands Inc., 1643 E Genesee St, Syracuse, NY 13210, USA.
url: www.healthforlife.com
Health Guard, India. Health Guard (I) Pvt Ltd, Plot No 48 First Floor, Industrial Phase-1, Chandigarh, 160 002, India.
Health Imports, UK. Health Imports Ltd, Binbrook Mill, Young Street, Bradford, West Yorkshire, BD8 9RE, UK.
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url: www.health-perception.co.uk
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url: www.hvision.com
Health Vision, Hong Kong. Health Vision Enterprise Ltd, Rm 2504, K Wah Ctr, 191 Java Rd, North Point, Hong Kong.
Health Vision, Philipp. Health Vision Pharmaceutical, Bldg 3022 Zambales Highway, Upper QB, Subic Bay Freeport Zone, Olongapo City, Philippines.
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HealthCare, Ital. HealthCare Pharmaceuticals Srl, Via Domenico Balestrieri 6, 20154 Milan (MI), Italy.
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Healthcare Brands, UK. Healthcare Brands International Ltd, 2nd Floor, The Clock Tower, Talbot St, Nottingham, NG1 5GG, UK.
url: www.healthcarebrandsinternational.com
Healthcare Innovations, UK. Healthcare Innovations, 930 High Rd, London, N12 9RT, UK.
Healthcare Logistics, NZ. Healthcare Logistics, 58 Richard Pearse Drive, Airport Oaks, Auckland, New Zealand.
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url: www.hhcpl.com
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Healtheries, NZ. Healtheries of New Zealand Ltd, P.O. Box 22 045, Otahuhu, Auckland, New Zealand.
url: www.healtheries.co.nz
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url: www.healthfirst.com
Healthline, USA. Healthline Laboratories Inc., 2805 Danbar Dr., Green Bay, WI 54313, USA.
Healthpoint, Canad. Healthpoint Canada ULC, 286 Third Line Rd, Rr 1, Warsaw, Ontario, K0L 3A0, Canada.
Healthpoint, USA. Healthpoint Medical, 3909 Hulen St., Fort Worth, TX 76107, USA.
url: www.healthpoint.com
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Healthypharm, Neth. Healthypharm BV, Nieuwe Donk 9, 4879 AC Etten-Leur, Netherlands.
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url: www.healthyway.com.ua
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Hecht, Ger. Hecht-Pharma GmbH, Fünfhausendorf 1, 21772 Stinstedt, Germany.
url: www.hecht-pharma.de
Heck, Switz. Heck Pharma SA, Studenmatt 9, 1791 Courtaman, Switzerland.
Hedat, Pol. Przedsiębiorstwo Handlowe Hedat SJ, ul. Wrocławska 13, 05-071 Sulejówek, Poland.
url: www.hedat.pl
Heel, Austria. See *Heel, Ger.*
Heel, Belg. Heel Belgium NV, Booiebos 25, B-9031 Drongen, Belgium.
Heel, Canad. See *Heel, Ger.*
Heel, Cz. See *Peithner, Cz.*
Heel, Ger. Biologische Heilmittel Heel GmbH, Dr.-Reckeweg-Str. 2-4, 76532 Baden-Baden, Germany.
url: www.heel.de
Heel, Neth. See *Heel, Belg.*
Heel, Rus. See *Heel, Ger.*
Heel, S.Afr. Heel South Africe (Pty) Ltd, Linbro Business Park, 5 Galaxy Ave, Sandton 2199, South Africa.
url: www.heel.com
Heel, Spain. Laboratorios Heel España SAU, Polígono Industrial la Mina Calle Madroño s/n, 28770 Colmenar Viejo, Madrid, Spain.
Heel, Ukr. See *Kaskad, Ukr.*
Heel, USA. Heel Inc., P.O. Box 11280, Alberquerque, NM 87192-0280, USA.
url: www.heelusa.com
Heer, China. Heer Pharmaceutical Co. Ltd, 1 Guangtai Road, Hi-tech Industrial Development Zone, Xi'an, Shaanxi, 10075, China.
Hefa, Ger. See *Sanavita, Ger.*
Heinz, NZ. See *Heinz-Wattie, NZ.*
Heinz, UK. H.J. Heinz Co. Ltd, South Building, Hayes Park, Hayes, Middlesex, UB4 8AL, UK.
url: www.heinz.co.uk
Heinz-Wattie, NZ. Heinz-Wattie's Australasia Ltd, P.O. Box 439, Hastings, New Zealand.
url: www.watties.co.nz
Hejigong, China. Hejigong Pharmaceutical Co. Ltd, 52 Xiaogang New Street, Baiyun, Guangzhou, 510410, China.
url: www.byshjg.com
Hela, Swed. Hela Pharma AB, Box 164, 521 02 Falköping, Sweden.
url: www.helapharma.se
Helapet, UK. Helapet Ltd, Circle Business Centre, Blackburn Rd, Houghton Regis, Bedfordshire, LU5 5DD, UK.
url: www.helapet.co.uk
Helax, India. Helax Healthcare, 145 - A/5 Harsh Plaza, Old Mandi, Gohana 131 301, India.
url: www.helaxhealthcare.com
Helena, Canad. See *Helena, USA.*
Helena, USA. Helena Laboratories, 1530 Lindbergh Dr, P.O. Box 752, Beaumont, TX 77707, USA.
url: www.helena.com
Helida, China. Helida Pharmaceutical Co. Ltd., 12 Nongzhuan Road, Xinyang, Henan, 464000, China.
Helin, China. Helin Pharmaceutical Co. Ltd., 38 Qingnian Street, Baita, Liaoyang, Liaoning, 111000, China.
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Helios, India. Helios Pharmaceuticals, Helios House 659/1 2nd Lane, Gulabai Tekra, Panchwati, Ahmedabad 380 006, India.
Helios, UK. Helios Healthcare Ltd, P.O. Box 203, Hitchin, Hertfordshire, SG5 2ZQ, UK.
Helix, Canad. Helix Biopharma Corp., 3-305 Industrial Parkway South, Aurora, Ontario, L4G 6X7, Canada.
Helixor, Ger. Helixor Heilmittel GmbH & Co KG, Fischermühle 1, 72348 Rosenfeld, Germany.
url: www.helixor.de
Helm, Cz. See *Helm, Ger.*
Helm, Denm. Helm Skandinavien AS, Winghouse, Ørestads Blvd 73, 2300 Copenhagen S, Denmark.
url: www.helmas.dk
Helm, Ger. Helm Pharmaceuticals GmbH, Nordkanalstrasse 28, 20097 Hamburg, Germany.
url: www.helmag.com
Helm, Irl. See *Helm, Ger.*
Helm, Ital. Helm Italia SRL, Via Vittor Pisani 22, 20124 Milan, Italy.
url: www.helmitalia.com
Helm, Neth. See *Helm, Ger.*
Helm, Port. Helm Produtos Químicos Lda, Estrada Nacional No 10, Km 140,260, 2695-066 Bobadela LRS, Portugal.
Helm, Singapore. See *Iuen Wah, Singapore.*
Helm, Thai. See *Pharmaland, Thai.*
Help, Gr. Help E.P.E., Evag.Zekkas-Balaoritou 4, Athyens, 144 52 Metamorfosi, Greece.
Help, Pol. See *Blubit, Pol.*
Helsinn, Hong Kong. See *Zuellig, Hong Kong.*
Helsinn, Israel. See *Rafa, Israel.*
Helsinn, Port. Helsinn, Lda, Estrada Nacional 249/4 (Km 1.6), Abrunheira, Apartado 155, 2710-901 Sintra, Portugal.
Helsinn, Spain. See *Helsinn Birex, Irl.*
Helsinn, Thai. See *Indochina Healthcare, Thai.*
Helsinn Birex, Austria. See *Helsinn Birex, Irl.*
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Helsinn Birex, Hong Kong. See *Treasure Mountain, Hong Kong.*
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Helsinn Birex, Indon. See *Schering-Plough, Indon.*
Helsinn Birex, Irl. Helsinn Birex Pharmaceuticals Ltd, Damastown, Mulhuddart, Dublin 15, Ireland.
url: www.helsinn.com
Helsinn Birex, Neth. See *Helsinn Birex, Irl.*
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Helsinn Birex, Pol. See *Medagro, Pol.*
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Helvepharm, Switz. Helvepharm AG, Walzmuhlestrasse 60, 8500 Frauenfeld, Switzerland.
url: www.helvepharm.ch

Helvetia, Cz. Helvetia Pharma as, Slezská 949/32, 120 00 Praha 2, Czech Republic.

Helviina, Philipp. See *EON, Philipp.*

Hemasure, Denm. HemaSure AS, Sauntesvej 13, 2820 Gentofte, Denmark.

Hemasure, Swed. See *Hemasure, Denm.*

Hemat, Turk. Hemat İlaç San. İthalat ve İhracat Ltd. Şti., Kosuyolu Cad. Cenap, Şehabettin Sok. No: 73, Kadiköy, İstanbul, Turkey.
url: www.hamatilac.com.tr

HemispheRx, USA. HemispheRx Biopharma Inc., 1 Penn Center, 1617 John F Kennedy Blvd, Philadelphia, PA 19103, USA.
url: www.hemispherx.net

Hemocyl, UK. Hemocyl, Newstel House, 10 Payne St, Port Dundas, Glasgow, G4 0LF, UK.
url: www.hemocyl.com

Hemoderivados, Arg. U.N.C. Hemoderivados, Av. Valparahso SN, 5000 Cordoba, Argentina.
url: www.unc-hemoderivados.com

Hemofarm, Rus. Hemofarm Koncern A.D., Trifonovskaya ul. 45 b, 129272 Moscow, Russia.
url: www.hemofarm.ru

Hemofarm, Ukr, Staronavadnitskaya Street, 4A, Office.19, Kiev, 01015, Ukraine.
url: www.hemofarm.com

Hemopharm, Ger. Hemopharm GmbH, Königsteiner Str. 2, 61350 Bad Homburg v. d. H., Germany.
url: www.hemopharm.de

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Hencer, China. Hencer Pharmacy, 18 Jichang Road, Lishui Economic Development Zone, Lishui, Nanjing, Jiangsu, 211200, China.
url: www.hencer.com

Hengda, China. Hengda Pharmaceutical Co. Ltd., 21 Chuangye Street, Xiaodian, Taiyuan, Shanxi, 030006, China.

Henghe, China. Henghe Pharmaceutical Co. Ltd, 99 Changchun Road, Jilin, Jilin, 132012, China.

Hengji, China. Hengji Pharmaceutical Co. Ltd, 199 Donan Rd, Mianzhu, Deyang, Sichuan, 618200, China.

Hengkang, China. Hengkang Pharmaceutical Co. Ltd, Jiangxi, China.

Hengli, China. Hengli Pharmaceutical co. Ltd, Hebei, China.

Hengrui, China. Hengrui Medicine Co Ltd, 145 New East Renmin Rd, Jiangsu Province, Lianyungang City, China.

Hengshan, China. Shanghai Hengshan Pharmaceutical Co. Ltd, 3777 Jiangchuan Road, Minhang, Shanghai, 201111, China.

Hengsheng, China. Hengsheng Pharmceutical Co. Ltd, 26 Yangchong Rd, Xidu, Hengyang, Hunan, 421200, China.

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Henkel, Austria. Henkel Austria GmbH, Erdbergstrasse 29, A-1030 Vienna, Austria.

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Henkel Hygiene, Gr. Henkel Hygiene SA Greece, Alamanos 10 & Delphon, 151 25 Maroussi, Greece.

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Hennig, Denm. See *Hennig, Ger.*

Hennig, Fin. See *Hennig, Ger.*

Hennig, Ger. Hennig Arzneimittel GmbH & Co. KG, Liebigstr. 1-2, 65439 Flörsheim am Main, Germany.
url: www.hennig-arm.de

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Henning, Hung. Dr Henning, Hungary.

Henning, Israel. Henning, Israel.

Henning Walldorf, Ger. Dr. Georg Friedrich Henning, Chemische Fabrik Walldorf GmbH, Robert-Bosch-Str. 62, 69190 Walldorf, Germany.
url: www.henning-walldorf.com

Henry Schein, Irl. Henry Schein Ireland, Unit 61a, Longmile Centre, Longmile Rd, Dublin 12, Ireland.
url: www.henryschein.ie

Henselwerk, Ger. See *Schoenenberger, Ger.*

Hepart, Switz. Hepart AG, Esslenstrasse 3, 8280 Kreuzlingen, Switzerland.
url: www.hepart.com

Hepatoum, Fr. Laboratoires Hépatoum, B.P. 5, 03270 Saint-Yorre, France.

Heptafarma, Port. Heptafarma Companhia Farmacêutica Sociedade Unipessoal Lda, Quinta da Fonte, Edificio Vasco da Gama 19, Porto Salvo, 2770-192 Paç de Arcos, Portugal.

HePu, China. See *Hope, China.*

Heraeus, Austria. See *Heraeus, Ger.*

Heraeus, Ger. Heraeus Medical GmbH, Philipp-Reis-Str. 8/13, 61273 Wehrheim, Germany.
url: www.heraeus-medical.com

Heraeus Kulzer, China. See *Heraeus, Ger.*

Herb Hands Healing, UK. Herb Hands Healing, Station Rd, Pulham Market, Norfolk, IP21 4XF, UK.

Herba Studio, Pol. Herba Studio, ul. Długa 109, 62-069 Zakrzewo, Poland.
url: www.herbastudio.pl

Herbacos, Cz. Herbacos-Bofarma sro, Štrossová 239, 520 02 Pardubice, Czech Republic.

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Herbal Concepts, UK. Herbal Concepts Ltd, 2 Park St., Woburn, Bedfordshire, MK17 9PG, UK.
url: www.herbal-concepts.co.uk

Herbal Laboratories, Canad. See *Pharmascience, Canad.*

Herbal Laboratories, UK. Herbal Laboratories Ltd, Malew House, 21 Malew St., Castletown, Isle Of Man, IM9 1AD, UK.
url: www.herballaboratories.com

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Herbalife, Canad. Herbalife of Canada Ltd, 120, 4550 25th Street SE, Calgary, Alberta, T2B 3P1, Canada.
url: www.herbalifeww.com

Herbalist, Austria. See *Herbalist, Ger.*

Herbalist, Ger. Herbalist & Doc, Waldseeweg 6, 13467 Berlin, Germany.
url: www.herbalist-doc.com

Herbamed, Switz. Herbamed AG, Untere Au, 9055 Buhler, Switzerland.
url: www.herbamed.ch

Herbapex, Ukr. See *Shanghai Pharma, China.*

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Herbapol Krakow, Pol. Krakowskie Zakłady Zielarskie Herbapol SA, ul. K Chałupnika 14, 310462 Kraków, Poland.
url: www.herbapol.krakow.pl

Herbapol Lodz, Pol. See *Herbapol Lublin, Pol.*

Herbapol Lublin, Pol. Herbapol-Lublin SA, ul. Diamentowa 25, 20-954 Lublin, Poland.
url: www.herbapol.com.pl

Herbapol Poznan, Pol. Poznańskie Zakłady Zielarskie Herbapol SA, ul. Towarowa 47/51, 61-896 Poznań, Poland.
url: www.herbapol.poznan.pl

Herbapol Pruszkow, Pol. Worszowskie Zakłady Zielarskie Herbapol, ul. Ołowkowa 54, 05-800 Pruszków, Poland.
url: www.herbapol.waw.pl

Herbapol Wroclaw, Pol. Wrocławskie Zakłady Zielarskie Herbapol SA, ul. Św Mikołaja 65/68, 50-951 Wrocław, Poland.
url: www.herbapol.pl

Herbaria, Hung. Herbaria Zrt, Dózsa György ut 144, 1134 Budapest, Hungary.
url: www.herbaria.hu

Herborium, Braz. Herbarium Laboratório Botanico Ltda, Rua Maua 838, 80030-200 Curitiba, PR, Brazil.
url: www.herbarium.com.br

Herbasanté, Canad. Les Importations Herbasanté Inc., 6691 Blvd Thimens, Ville St-Laurent, Quebec, H4S 1W2, Canada.

Herbaxt, Fr. Laboratoires Herbaxt, Z.I. Nord, bat 5, 77200 Torcy, France.

Herbcare, Philipp. Herbcare Corp., PDC Compound, Pilar Vill, Las Piñas City, Philippines.

Herbert, Ger. See *Meda, Ger.*

Herbert, USA. See *Allergan, USA.*

Herbes Universelles, Canad. Herbes Universelles, 7, 70e Ave O, Blainville, Quebec, J7C 1R7, Canada.

Herbion, Rus. Herbion Pakistan PVT Ltd, Miklukho-Maklaya ul. 8, str. 3, 117198 Moscow, Russia.
url: www.herbion.com

Herbion, Ukr. Herbion Private Ltd (Pakistan), Mechnikova Street, 16, office 306, Kiev, 01000, Ukraine.

Herbs & Nature, Philipp. Herbs & Nature Corp., Unit G10-B, Regalia Park Tower, P Tuazon Ave, Cubao, Quezon City, Philippines.

Herbs Trading, Rus. Herbs Trading GmbH, Novinskii boulevard, d.3, str. 1, 121099 Moscow, Russia.
url: www.bittner.ru

Heremco, Gr. Heremco, Deligiorgi 49, 104 37 Athens, Greece.

Heritage, Canad. Heritage Brands, 120 Harry Walker Parkway N, Newmarket, Ontario, L3Y 7B2, Canada.

Heritage, USA. Heritage Pharmaceuticals Inc., Eatontown, NJ 07724, USA.

Heritage Consumer, USA. Heritage Consumer Products, 141 South Ave, Suite 2, Fanwood, NJ 07023, USA.

Hermal, Austria. See *Hermal, Ger.*

Hermal, Cz. See *Boots Healthcare, Cz.*

Hermal, Denm. See *Biomet, Denm.*

Hermal, Ger. Hermal Kurt Herrmann GmbH & Co., Scholtzstr. 3, 21465 Reinbek, Germany.

Hermal, Hong Kong. See *Keller, Hong Kong.*

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Hermes, Ger. Hermes Arzneimittel GmbH, Georg-Kalb-Str. 5-8, 82049 Grosshesselohe/Munich, Germany.
url: www.hermes-arzneimittel.de

Hermes, Hung. See *Hermes, Ger.*

Hermes, Neth. Hermes & Co. BV, Van Gijnstraat 20, 2288 GB Rijswijk, Netherlands.

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Hero, Switz. Hero, Postfach, 5600 Lenzburg, Switzerland.

Heromycin, Thai. Heromycin Pharma Co Ltd, 537/2 Sothupradit Rd, Chongnonsee, Yannawa, Bangkok 10120, Thailand.
url: heromycin.com

Herrmann, Pol. See *Boots, Pol.*

Herron, Austral. Herron Pharmaceuticals P/L, P.O. Box 95, Brisbane Market, QLD 4106, Australia.
url: www.herron.com.au

Hertz, Braz. Kley Hertz SA, Rua Comendador Azevedo 224, 90220-150 Porto Alegre, Rio Grande do Sul, Brazil.
url: www.grupohertz.com

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Hetero, India. Hetero Drugs Ltd, 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad 500 082, India.
url: www.heterodrugs.com

Hetero, Rus. See *Makiz-Pharma, Rus* and *Stada, Rus.*

Hetterich, Ger. Chemische Fabrik Dr. Hetterich GmbH & Co. KG, Gebhardtstr. 5, 90762 Furth/Bayern, Germany.

Heumann, Denm. See *Heumann, Ger.*

Heumann, Ger. Heumann Pharma GmbH, Südwestpark 50, 90449 Nürnberg, Germany.
url: www.heumann.de

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Hevert, Ger. Hevert-Arzneimittel GmbH & Co. KG, In der Weiherwiese 1, 55569 Nussbaum, Germany.
url: www.hevert.de

Hexa, Arg. Lab. Hexa-Medinova S.A., Helguera 254/58, 1406 Buenos Aires, Argentina.

Hexal, Austral. Hexal Australia P/L, Level 4, Suite 1-6, 100 Harris St, Pyrmont, NSW 2009, Australia.
url: www.hexal.com.au

Hexal, Austria. Hexal Pharma GmbH, Wilhelminenstrasse 91/II F, A-1160 Vienna, Austria.
url: www.hexal.at

Hexal, Braz. Hexal do Brasil Ltda, Av. Itaborai 1425, 04135-001 São Paulo, SP, Brazil.
url: www.hexal.com.br

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Hexal, Ger. Hexal AG, Industriestr. 25, 83607 Holzkirchen, Germany.
url: www.hexal.de

Hexal, Gr. Hexal Hellas, L. Parnithos 189, 136 71 Acharnes, Greece.

Hexal, Hung. Hexal Hungória Kft, Timár u 20, 1034 Budapest, Hungary.
url: www.hexal.hu

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Hexal, Ital. Hexal SpA, Via Paracelso 16, 20041 Agrate Brianza (MI), Italy.

Hexal, Mex. Laboratories Hexal S.A. de C.V., Calle Candelaria 186, Col. Atlantida, Deleg. Coyoacan, 04370 Mexico D.F., Mexico.
url: www.hexal.com.mx

Hexal, Neth. Hexal BV, Pastoorslaan 28, 2182 BX Hillegom, Netherlands.

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Hexal, Pol. Hexal Polska Sp. zo.o., ul. Domaniewska 50 C, 02-672 Warsaw, Poland.
url: www.hexal.com.pl

Hexal, Rus. Hexal AG, 3, ul. Kulneva, 121170 Moscow, Russia.
url: www.hexal.ru

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Hexal, UK. See *Tillomed, UK.*

Hexanel, Cz. Hexanel sro, Palackého 11, 110 00 Prague 1, Czech Republic.
url: www.hexanel.cz

Hexin, China. Hexin Pharmaceutical Co. Ltd, Chengdu, Sichuan, China.

Hexpharm, Indon. Hexpharm Jaya PT, Gedung Sapta Mulia Lt 3, Jl Rawa Gelam V Kav OR No 3B, Kawasan Industri Pulo Gadung, Jakarta Timur 13820, DKI Jaya, Indonesia.

Heyden, Ger. See *BMS, Ger.*

Heyl, Cz. See *Heyl, Ger.*

Heyl, Ger. Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Goerzallee 253, 14167 Berlin, Germany.
url: www.heyl-berlin.de

Heyl, USA. Heyltx Corp., 925 S Mason Rd, Katy, TX 77450, USA.
url: www.heyltex.com

Hezhi, China. Hezhi Pharmaceutical Co. Ltd, Tianjin, China.

HFA Healthcare, UK. HFA Healthcare Ltd, 30 Blossomfield Rd, Solihull, West Midlans, B91 1NF, UK.
url: www.hfaconsulting.com

Hicin, China. Hicin Pharmaceutical Co. Ltd, 1 Hengfa Road, Economic and Technological Development Zone, Nanjing, Jiangsu, 210046, China.
url: www.hicin.cn

Higote, Arg. Higaté Medical Argentina, Av. Eva Peron 3052, 1650 San Morten Villa Libertad, Buenos Aires, Argentina.

High Chemical, Canad. See *High Chemical, USA.*

High Chemical, USA. High Chemical Co., 3901-A Nebraska St, Levittown, PA 19056, USA.
url: www.sarapin.com

HiGlance, India. HiGlance Laboratories Pvt Ltd, E-12 & 13 UPSIDC, Site-B Surajpur Industrial Area, Greater Noida, Goutam Budh Nagar, Uttar Pradesh, India.
url: www.higlance.com

Hikma, Austria. See *Hikma, Port.*

Hikma, Cz. Hikma Pharmaceuticals, Czech Republic.

Hikma, Fin. See *Hikma, Port.*

Hikma, Ger. Hikma Pharma GmbH, Postfach: 1231, 82154 Gräfelfing, Germany.
url: www.ribosepharm.de

Hikma, Neth. See *Hikma, Port.*

Hikma, Pol. See *TAD, Pol.*

Hikma, Port. Hikma Farmacêutica (Portugal), Lda, Estrada do Rio da Mo 8, 8A e 8B Fervença, 2705-906 Terrugem SNT, Portugal.
url: www.hikma.com

Hikma, Rus. See *Gedeon Richter, Rus.*

Hikma, Ukr. See *Megakom, Ukr.*

Hikma, USA. See *Westward, USA.*

Hill, Canad. Hill Dermaceuticals Inc., Mississauga, Ontario, L4X 2X6, Canada.

Hill, USA. Hill Dermaceuticals Inc., 2650 S. Mellonville Ave, Sanford, FL 32773-9311, USA.
url: www.hillderm.com

Hillcross, UK. See *AAH, UK.*

Hillestad, Canad. See *Hillestad, USA.*

Hillestad, USA. Hillestad Pharmaceuticals, 178 US Highway 51 N, P.O. Box 1700, Woodruff, WI 54569-1700, USA.
url: www.hillestadlabs.com

Himalaya, Rus. See *Transatlantic, Rus.*

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Himalaya Herbal, India. Himalaya Herbal, Makali, Bangalore 562 123, India.
url: www.himalayahealthcare.com

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url: www.himfarm.com.ua

Himmel, USA. Himmel Pharmaceuticals Inc., P.O. Box 5479, Lake Worth, FL 33466, USA.

Himreactive, Rus. Himreactive Zoo, Kuzbasskaya St 19-A, 603950 Nizhny Novgorod, Russia.
url: www.himr.r52.ru

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Hind Wing, Hong Kong. Hind Wing Co. Ltd, Unit No 1103B, 11/F, Block B, Seaview Estate, 2-8 Watson Rd, North Point, Hong Kong.

Hindustan Antibiotic, India. Hindustan Antibiotic Ltd, Pimpri, Pune 411 018, India.

Hing Ah, Hong Kong. Hing Ah Pharma Co. Ltd, Room 503, 5/F, Tower 1, Harbour Ctr, 1 Hok Cheung St, Hung Hom, Kowloon, Hong Kong.

Hing Yip, Hong Kong. Hing Yip Medicine Co., 2/F, Lo Ko House, 133 Gloucester Rd, Hong Kong.

Hiperonline, Turk. Hiperonline İlaç Ltd Sti, Meşrutiyet Cad. N:31/8, Kizilay, Ankara, Turkey.

Hipolabor, Braz. Hipolabor Farmacêutica Ltda, Rodovia BR-262 4600, 31950-640 Sabara, MG, Brazil.
url: www.hipolabor.com.br

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url: www.hippokrat.biz

Hiral, India. Hiral Labs Ltd, 265 Sisona, Bhagwanpur, Roorkee, Uttra Khand, India.
url: www.hirallabs.com

Hisamitsu, Braz. Hisamitsu Farmacêutica do Brasil Ltda, Avenida Fagundes Filho 191, 04304-010 São Judas, Brazil.
url: www.salonpas.com.br

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Hisamitsu, Hung. See *Hisamitsu, Jpn.*

Hisamitsu, Jpn. Hisamitsu Seiyaku, 408 Daikan-machi, Tashiro, Tosu, Saga 841-8686, Japan.
url: www.hisamitsu.co.jp

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Hisamitsu, NZ. See *Pharmaco, NZ.*

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Hisamitsu, UK. Hisamitsu UK Ltd, 500 Chiswick High Rd, London, W4 5RG, UK.
url: www.hisamitsu.co.jp

Hisamitsu, USA. Hisamitsu America Inc., 3528 Torrance Blvd, Suite 112, Torrance, CA 90503, USA.
url: www.salonpas.us

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Hisun, China. Hisun Pharmaceutical Co Ltd, 46 Waisha Rd, Jiaojiang District, Taizhou City, Zhejiang Province, China.
url: www.hisunpharm.com

Hi-Tec, India. Hi-Tec Laboratories Pvt Ltd, 454 Patparganj Indl Area, New Delhi, India.

Hi-Tech, USA. Hi-Tech Pharmacal, 369 Bayview Ave, Amityville, NY 11701, USA.
url: www.hitechpharm.com

Hiteck Bio, China. Hiteck Bio Pharmaceutical Co. Ltd, Economic & Technological Development Zone, Hiteck Science & Technology Park, Wuhan 430056, China.
url: www.hiteck.com.cn

Hizon, Philipp. See *Metro, Philipp.*

HK Pharm, Thai. HK Pharm, Thailand.

HK Pharma, UK. HK Pharma Ltd, P.O. Box 105, Hitchin, Hertfordshire, SG5 2GG, UK.

HLB, Arg. HLB Pharma Group SA, Av. Int. Tomkinson 2054, 1642 San Isidro, Buenos Aires, Argentina.

HLB, Chile. HLB Pharma Group Chile Ltda, Simón Bolivar 1929, Nuñoa, Santiago, Chile.

HMA, Arg. H Medical Argentina SA, Int. Tomkinson 1750, 1642 San Isidro, Buenos Aires, Argentina.

Hobein, Hong Kong. See *Universal, Hong Kong.*

Hobein, Malaysia. See *Propharm, Malaysia.*

Hoch Wertig, Arg. Laboratorio Hoch Wertig, San Luis 2517, (5000) Cordoba B Alto Alberdi, Argentina.

Hochland, Israel. Hochland, Israel.

Hoe, Hong Kong. Hoe Pharma (HK) Ltd, Rm A 7/F Harvest Moon House, 337-339 Nathan Rd, Kowloon, Hong Kong.
url: www.hoepharma.com.my

Hoe, Malaysia. Hoe Pharmaceuticals Sdn Bhd, Suite 8.01, 8th Fl, Menara IGB, Mid Valley City, Lingkaran Syed Putra, 59200 Kuala Lumpur, Wilayah Persekutuan, Malaysia.
url: www.hoepharma.com.my

Hoe, Philipp. See *Markettink, Philipp* and *Metro, Philipp* and *Zuellig, Philipp.*

Hoe, Singapore. See *Summit, Singapore.*

Hoe, Thai. See *US Summit, Thai.*

Hoechst, Austral. See *Sanofi-Aventis, Austral.*

Hoechst, Belg. See *Sanofi-Aventis, Belg.*

Hoechst, Canad. See *Sanofi, Canad.*

Hoechst, Fr. See *Sanofi-Aventis, Fr.*

Hoechst, Ger. See *Sanofi-Aventis, Ger.*

Hoechst, Ital. See *Sanofi-Aventis, Ital.*

Hoechst, Neth. See *Sanofi-Aventis, Neth.*

Hoechst, Rus. See *Sanofi-Aventis, Rus.*

Hoechst, Spain. See *Sanofi-Aventis, Spain.*

Hoechst, Swed. See *Sanofi-Aventis, Swed.*

Hoechst, USA. See *Sanofi-Aventis, USA.*

Hoechst Biotika, Cz. See *Sanofi-Aventis, Cz.*

Hoechst Marion Roussel, Austral. See *Sanofi-Aventis, Austral.*

Hoechst Marion Roussel, Austria. See *Sanofi-Aventis, Austria.*

Hoechst Marion Roussel, Belg. See *Sanofi-Aventis, Belg.*

Hoechst Marion Roussel, Braz. See *Aventis, Braz.*

Hoechst Marion Roussel, Canad. See *Sanofi, Canad.*

Hoechst Marion Roussel, Denm. See *Sanofi-Aventis, Denm.*

Hoechst Marion Roussel, Fin. See *Sanofi-Aventis, Fin.*

Hoechst Marion Roussel, Ger. See *Sanofi-Aventis, Ger.*

Hoechst Marion Roussel, Gr. See *Sanofi-Aventis, Gr.*

Hoechst Marion Roussel, Hong Kong. See *Aventis, Hong Kong.*

Hoechst Marion Roussel, Irl. See *Sanofi-Aventis, Irl.*

Hoechst Marion Roussel, Israel. See *Sanofi-Aventis, Israel.*

Hoechst Marion Roussel, Ital. See *Sanofi-Aventis, Ital.*

Hoechst Marion Roussel, Jpn. See *Aventis, Jpn.*

Hoechst Marion Roussel, Mex. See *Sanofi-Aventis, Mex.*

Hoechst Marion Roussel, Neth. See *Sanofi-Aventis, Neth.*

Hoechst Marion Roussel, Norw. See *Sanofi-Aventis, Norw.*

Hoechst Marion Roussel, NZ. See *Sanofi-Aventis, NZ.*

Hoechst Marion Roussel, Port. See *Sanofi-Aventis, Port.*

Hoechst Marion Roussel, Rus. See *Sanofi-Aventis, Rus.*

Hoechst Marion Roussel, S.Afr. See *Sanofi-Aventis, S.Afr.*

Hoechst Marion Roussel, Singapore. See *Sanofi-Aventis, Singapore.*

Hoechst Marion Roussel, Spain. See *Sanofi-Aventis, Spain.*

Hoechst Marion Roussel, Swed. See *Sanofi-Aventis, Swed.*

Hoechst Marion Roussel, Switz. See *Sanofi-Aventis, Switz.*

Hoechst Marion Roussel, Thai. See *Sanofi-Aventis, Thai.*

Hoechst Marion Roussel, UK. See *Sanofi, UK.*

Hoechst Marion Roussel, USA. See *Sanofi-Aventis, USA.*

Hoeport, Port. See *Sanofi-Aventis, Port.*

Hoernecke, Ger. Carl Hoernecke GmbH, Halberstädter Chaussee 22, 39116 Magdeburg, Germany.
url: www.hoernecke.com

Hoeveler, Austria. Hoeveler Mag. & Co. GmbH, Mosham 40, A-4943 Geinberg, Austria.

Hofmann, Austria. Hofmann Pharma GmbH & Co. KG, St Oswaldweg 20, A-5081 Anif, Austria.

Hofmann, Chile. Droguería Hofmann SAC, Los Gobelinos 2507, Renca, Santoago, Chile.

Hofmann & Sommer, Austria. See *Hofmann & Sommer, Ger.*

Hofmann & Sommer, Ger. Hofmann & Sommer GmbH & Co. KG, Lindenstr. 11, 07426 Königsee, Germany.
url: www.hofmannundsommer.de

Hogil, USA. Hogil Pharmaceutical Corporation, 235 Mamaroneck Ave, Suite 202, White Plains, NY 10605, USA.
url: www.hogil.com

Holden, Philipp. See *Pasteur, Philipp.*

Holding Domestic Medicines, Ukr. See *OI-Ukraine, Ukr.*

Holista, Canad. Holista Health Corp, PO Box 57525, Coquitlam, British Columbia, V3K 5Y9, Canada.
url: www.holistahealth.com

Holistica, Fr. Laboratoires Holistica International, 465 chemin des Jalassières, 13510 Eguilles, France.
url: www.holistica.fr

Holistica, Singapore. See *Polymedic, Singapore.*

Holland & Barrett, UK. Holland & Barrett, Samuel Ryder House, Barling Way, Eliot Park, Nuneaton, Warwickshire, CV10 7RH, UK.
url: www.hollandandbarrett.com

Holland Pharma, Neth. Holland Pharma, Bosberg 41, 7271 Le Borculo, Netherlands.
url: www.hollandpharma.nl

Hollborn, Ger. Dr K Hollborn & Söhne GmbH & Co. KG, Brahestr. 13, 04347 Leipzig, Germany.
url: www.hollborn.de

Holley-Cotec, China. Beijing Holley-Cotec Pharmaceuticals Co Ltd, Room 1601, Full Tower, No 9 Dong san Huan Zhong Road, Chaoyang District, Beijing, 100020, China.
url: www.cotecxin.com

Hollister, Canad. Hollister Ltd, 95 Mary St, Aurora, Ontario, L4G 1G3, Canada.
url: www.hollister.com

Hollister-Stier, Canad. See *Hollister-Stier, USA.*

Hollister-Stier, USA. Hollister-Stier Laboratories LLC, 3525 N. Regal, Spokane, WA 99207, USA.
url: www.hollister-stier.com

Holsten, Ger. Holsten Pharma GmbH, Im Bürgerstock 7, 79241 Ihringen, Germany.
url: www.holstenpharma.de

Home, Port. See *Wyeth Consumer, Port.*

Home Diagnostics, USA. Home Diagnostics Inc., 2300 NW 55th Court, Fort Lauderdale, FL 33309, USA.
url: www.homediagnosticsinc.com

Homeocan, Canad. Homéocan, 3025, boul. de l'Assomption, Montreal, Quebec, H1N 2H2, Canada.
url: www.homeocan.ca

Homeodel, Canad. Homeodel, 20330 Blvd Henri-Bourassa, Quebec, G2M 1L1, Canada.
url: www.homeodel.com

Homeofarm, Pol. Laboratorium Farmaceutyczne Homeofarm Sp. zo.o., ul Jagiellońska 44, 80-366 Gdańsk, Poland.
url: www.homeofarm.pl

Homeopathic Pharmacy, Rus. Homeopathic Pharmacy, Russia.

Homeopathie Boribel, Fr. See *Boiron, Fr.*

Homeopathie Boripharm, Fr. See *Boiron, Fr.*

Homeopathie Complexe, Fr. See *Arkopharma, Fr.*

Homeopathiques de France, Fr. See *Boiron, Fr.*

Homeopathiques du Sud-Ouest, Fr. See *Plantes et Medecines, Fr.*

Homeosyn, Ital. Homeosyn Italia S.r.l., Via Tor Sapienza 30/A, 00155 Rome (RM), Italy.

Homme de Fer, Fr. Laboratoires de l'Homme de Fer, 2 pl. de l'Homme de Fer, 67000 Strasbourg, France.

Hommel, Ger. Hommel Pharma GmbH & Co. KG, Lindenst. 28, 59348 Lueding hausen, Germany.
url: www.hommel-pharma.com

Homviora, Austria. See *Homviora, Ger.*

Homviora, Ger. Homviora Arzneimittel Dr. Hagedorn GmbH & Co., Arabellastr. 5, 81925 München, Germany.
url: www.homviora.de

Homviora, Ukr. Homviora, ul Antonovich 94-96, Apt 3, 03150 Kiev, Ukraine.
url: www.homviora.kiev.ua

Honbase, Hong Kong. Honbase Trading Ltd, Unit 10, 27/F Metropole Square, 2 On Yui St, Sui Lek Yuen, Shatin, NT, Hong Kong.

Honest Ability, Hong Kong. Honest Ability Pharma Ltd, Suite 1318, Delta House, 3 On Yui St, Sui Lek Yuen, Shatin, NT, Hong Kong.
url: www.hap-pharma.com

Hong Feng, China. See *Foncoo, China.*

Hong Kong Medical, Hong Kong. Hong Kong Medical Supplies Ltd, 7/F China Aerospace Centre, 143 Hoi Bun Rd, Kwun Tong, Kowloon, Hong Kong.

Hong Tai Hong, Hong Kong. Hong Tai Hong, Rua de Almirante, Costa Cabral No 68, 1/F, Flat B, Edificio Sun Flat, Macau.

Hong Yi, China. Hong Yi Pharmaceutical Co. Ltd, 789 Jiangxi St, High-Tech Industrial Development Zone, Nanchang, China.

Hong Yuan, China. Hong Yuan Group Pharmaceutical Co. Ltd, Guangdong, China.

Honghui, China. Jiangsu Honghui Medical Co. Ltd, 6 Beijing West Rd, Nanjing 210008, China.
url: www.jshonghui.com.cn

Honglin, China. Honglin Pharmaceutical Co. Ltd, Yanqi Industrial Development Area, Huairou, Beijing, 101407, China.

HongQi, China. HongQi Pharmaceutical Co. Ltd, 6 Xinluo St, Hunnan Hi-Tech Industrial Dev. Zone, Shenyang, China.
url: www.hqyy.com

Hongsheng, China. Hongsheng Pharmaceutical Co. Ltd, Zhejiang, China.

Hongxing, China. Hongxing Pharmaceutical Co. Ltd, Lin Xixi Road, Guye, Tangshan, Hebei, 463000, China.
url: www.tshxyy.com

Honz, China. Honz Pharmaceutical Co. Ltd, 2601 26/F Dongshan Plaza, 69 Xianlie Zhonglu, Guangzhou, Guangdong, 510095, China.
url: www.honz.com.cn

Hope, China. Hope Pharmaceutical Co. Ltd., 2 Jinyinhu South 4th Street, Dongxihu, Wuhan, Hubei, 430047, China.
url: www.hopepharm.cn

Hope, USA. Hope Pharmaceuticals, 8260 E Gelding Drive, Suite 104, Scottsdale, AZ 85260, USA.
url: www.hopepharm.com

HorFerVit, Ger. HorFerVit Pharma GmbH, H.-Brockmann Str. 81, 26131 Oldenburg, Germany.
url: www.horfervit.de

Horii, Jpn. Horii Pharmaceutical Company, 1-2-6, Uchiawajimachi, Chuo-ku, Osaka, Japan.

Horizon, Ger. Horizon Pharma GmbH, Joseph-Meyer-Str. 13-15, 68167 Mannheim, Germany.
url: www.horizonpharma.com

Horizon, USA. See *First Horizon, USA.*

Hormel, Hong Kong. See *IDS, Hong Kong.*

Hormel, Israel. See *Megapharm, Israel.*

Hormel, Singapore. See *JDH, Singapore.*

Hormel, USA. Hormel HealthLabs Inc., 3000 Tremont Rd, Savannah, GA 31405, USA.
url: www.hormelhealthlabs.com

Hormona, Mex. Laboratorios Hormona S.A. de C.V., Blvd. M. Avila Camacho No.470, Col. San Andres Atoto, 53500 Naucalpan de Juarez, Mexico.

Hormonas, Mex. See *Hormona, Mex.*

Hormosan, Ger. Hormosan Pharma GmbH, Wilhelmshöher Str. 106, 60389 Frankfurt/Main, Germany.
url: www.hormosan.de

Horna, Cz. Horna Business Service, Narcisová 2/850, 106 00 Prague 10, Czech Republic.

Horner, Canad. See *Carter Horner, Canad.*

Horus, Fr. Laboratoires Horus Pharma, 148 av. Georges-Guynemer, Cap Var, Bât C1, 06700 Saint-Laurent-du-Var, France.
url: www.horus-pharma.fr

Hos & Ins, India. Hos & Ins, SCF 423-424 Basement, Motor Market, Manimajra, Chandigarh, India.
url: www.hosandins.com

Hospal, Denm. See *Gambro, Denm.*

Hospal, Fr. Hospal SA, 61 ave Tony Garnier, 69357 Lyon cdx 07, France.

Hospira, Austral. Hospira Pty Ltd, Level 3, 390 St Kilda Rd, Melbourne, Victoria 3004, Australia.
url: www.hospira.com.au

Hospira, Austria. See *Astro, Austria.*

Hospira, Belg. Hospira, Brussels, Belgium.
url: www.hospira.be

Hospira, Canad. Hospira Healthcare Corp., 600 1111 Dr Frederik-Philips Blvd, Saint-Laurent, Quebec, H4M 2X6, Canada.

Hospira, China. See *Gaoxiang, China.*

Hospira, Cz. See *Hospira, Neth.*

Hospira, Denm. See *Hospira, Swed.*

Hospira, Fin. See *Hospira, Neth.*

Hospira, Fr. Hospira France, Imm Volta-17 a 19, 17 rue Jeanne Braconnier, France.
url: www.hospira.fr

Hospira, Ger. Hospira Deutschland GmbH, Rablstr. 24, 81669 München, Germany.
url: www.hospira.de

Hospira, Gr. See *Aenorasis, Gr.*

Hospira, Hong Kong. Hospira Ltd, Unit 3A, 16/F Eastwood Ctr, Shaukeiwan, Hong Kong.

Hospira, Hung. See *Pharmacenter, Hung.*

Hospira, Indon. See *Transfarma, Indon* and *Tempo Scan Pacific, Indon.*

Hospira, Irl. See *Hospira, UK.*

Hospira, Israel. See *Hospiro, UK.*

Hospira, Ital. Hospira S.p.A., Via Fosse Ardeatine 2, 20060 Liscate (MI), Italy.

Hospira, Jpn. Hospira Japan Co. Ltd, Shiromi 1-2-27, Chuo-ku, Osaka 540-6026, Japan.
url: www.hospira.co.jp

Hospira, Malaysia. Hospira Malaysia Sdn Bhd, Suite 201 1st Fl Wisma Glomac 3, Kompleks Kelana Centre Point, Jln SS 7/19, 47301 Petaling Jaya, Selangor, Malaysia.
url: www.hospira.com

Hospira, Mex. Hospira S de RL de CV, Prolong. Paseo de la Reforma 1015 TAP, 1376 Alvaro Obregon Desarollo Sta Fé, Mexico DF, Mexico.

Hospira, Neth. Hospira Enterprises BV, Taurusavenue 19-21, 2132 LS Hoofddorp, Netherlands.

Hospira, Norw. See *Hospira, Swed.*

Hospira, NZ. Hospira NZ Ltd, 23 Haining St, Te Aro, Wellington, New Zealand.
url: www.hospira.co.nz

Hospira, Philipp. Hospira Phils.Inc., 39/F Robinsons Equitable Twr, ADB Ave cor POveda Rd, Ortigas Ctr, Pasig City, Philippines.
url: www.hospira.com.ph

Hospira, Pol. See *AstraZeneca, Pol.*

Hospira, Port. See *Hospira, Neth.*

Hospira, Rus. See *Abbott, Rus.*

Hospira, Singapore. Hospira Singapore Pte Ltd, 1 Kallang Way 2A, 06-01, S 347495, Singapore.
url: www.hospira.com

Hospira, Spain. Hospira, Consuegra 7, 28036 Madrid, Spain.
url: www.hospira.es

Hospira, Swed. Hospiro Nordic AB, Postboks 34 116, 100 26 Stockholm, Sweden.
url: www.hospira.com

Hospira, Switz. See *Ospedalia, Switz.*

Hospira, Thai. See *Indochina Healthcare, Thai.*

Hospira, UK. Hospira Ltd, Asmec Centre, Merlin Rd, Brunel, Theale, Berkshire, RG7 4AB, UK.
url: www.hospira.co.uk

Hospira, USA. Hospira Inc., Lake Forest, Illinois, USA.
url: www.hospira.com

Hospital Line, Gr. Hospital Line, K Palama 36, 143 43 Halkidona, Greece.

Hospithera, Belg. SA Hospithera NV, Rue de la Petite Ile, 1070 Brussels, Belgium.
url: www.hospithera.com

Hotz, Ger. See *Riemser, Ger.*

Houde, Fr. See *Sanofi-Aventis, Fr.*

Houghs Healthcare, UK. See *SSL, UK.*

Hovid, Hong Kong. See *Wellgo, Hong Kong.*

Hovid, Malaysia. Hovid Sdn Bhd, 121 Jalan Kuala Kangsar, 30010 Ipoh, Perak, Malaysia.
url: www.hovid.com

Hovid, Philipp. Hovid, Unit 306 AIC Gold Tower Cond., Emerald Ave, Ortigas Ctr, Pasig City, Philippines.
url: www.hovid.com

Hovid, Singapore. See *Galdplus, Singapore.*

Howmedica, Cz. See *Howmedica, Irl.*

Howmedica, Denm. See *Stryker, Swed.*

Howmedica, Fr. See *Stryker, Fr.*

Howmedica, Irl. Howmedica International Inc., Raheen Industrial Estate, Limerick, Ireland.

Howmedica, Ital. Howmedica Divisione Della, Vl. Lucanio 15, 20139 Milan, Italy.

Howmedica, Neth. See *Howmedica, Irl.*

Howmedica, NZ. See *Howmedica, UK.*

Howmedica, Pol. See *Howmedica, Irl.*

Howmedica, Port. See *Howmedica, Irl.*

Howmedica, Spain. See *Stryker, Spain.*

Howmedica, Swed. See *Stryker, Swed.*

Howmedica, UK. Howmedica International Ltd, 622 Western Ave, Park Royal, London, W3 0TF, UK.

Hoyer, Ger. See *Madaus, Ger* and *Schwarz, Ger.*

HPP, Hong Kong. Hong Kong Puis Pharmaceuticals Co Ltd, Flat 31, 8/F Kowloon Bay Industrial Ctr, 15 Wang Hoi Rd, Kowloon, Hong Kong.

HRA, Austria. See *HRA, Fr.*

HRA, Belg. See *HRA, Fr.*

HRA, Canad. See *HRA, Fr.*

HRA, Cz. See *HRA, Fr.*

HRA, Denm. See *Nycomed, Denm.*

HRA, Fin. See *Tamro, Fin.*

HRA, Fr. Laboratoire HRA Pharma, 15 rue Béranger, 75003 Paris, France.
url: www.hra-pharma.com

HRA, Ger. See *HRA, Fr.*

HRA, Gr. See *HRA, Fr.*

HRA, Hung. See *HRA, Fr.*

HRA, Irl. See *HRA, UK.*

HRA, Ital. HRA Pharma Italia srl, Via Benedetto Croce 97, 00142 Rome, Italy.
url: www.hra-pharma.com

HRA, Neth. See *HRA, Fr.*

HRA, Norw. See *Nycomed, Norw.*

HRA, Pol. mip18r

HRA, Port. See *HRA, Fr.*

HRA, Spain. See *HRA, Fr.*

HRA, UK. HRA Pharma UK Ltd, Unit 7 RB Building, 557 Harrow Rd, Kensal Green, London, W10 4RH, UK.
url: www.hra-pharma.com

HRA, USA. HRA Pharma LLC, 88 Leonard St 1224, New York, NY 10013, USA.
url: www.hra-pharma.com

HSL, NZ. Health Support Ltd, P.O. Box 44 027, Point Chevalier, Auckland, New Zealand.
url: www.healthsupport.co.nz

HSPMM, Rus. See *Teva, Rus.*

HTP, Neth. HTP Huisapotheek BV, Nieuwe Donk 3, 4879 AC Etten-Leur, Netherlands.

Hua, Thai. B L Hua & Co. Ltd, 2 Somdej Chaopraya Rd, Klongsan, Bangkok 10600, Thailand.

Hua Lu, China. Hua Lu Pharmaceutical Co Ltd, China.

Hua Shen, China. Hua Shen Group, Chengdu, China.

Hua Shin, Philipp. See *New Smart, Philipp.*

Hua Yuan Zhong Sheng, China. Hua Yuan Zhong Sheng Pharmaceutical Co. Ltd, China.

Huabang, China. Huabang Pharmaceutical Co. Ltd, Chongqing, China.

Huachuang, China. Huachuang Pharmaceutical Co. Ltd, Chongqing, China.

Huada, China. Huada Pharmaceutical Co. Ltd, Yantai, China.

Huading Xiandai, China. Huading Xiandai Pharmaceutical Co. Ltd, Chongqing, China.

Huadong, China. Huadong Medicine, 866 Moganshan Road, Hangzhou, Zhejiang, 310011, China.
url: www.eastchinapharm.com

Huahai, China. Huahai Pharmaceutical Co Ltd, Flaod Bridge Development Zone, Linhai City, Zhejiang, China.

Huajin, China. Huajin Pharmaceutical Co. Ltd, Jin Changan Building Block C 2210-2215, 82 East Fourth Ring Rd, Chaoyang District, Beijing 100020, China.
url: www.hjyy.com

Huakang, China. Huakang Pharmaceutical Co. Ltd, Deyang, China.

Hualan, China. Hualan Biological Engineering Co. Ltd, China.

Huali, China. Huali Pharmaceutical Co. Ltd., 21 South Ring Road, Pingdingshan, Henan, 467001, China.
url: hnhlyy.b2b.hxyjw.com

Huali Deze, China. Huali Deze Pharmaceutical Co. Ltd, Dalian, China.

Huali Nanhu, China. Huali Nanhu Pharmaceutical Co. Ltd, Zhejiang, China.

HuaLiDa, China. HuaLiDa Biotech, Yellow Sea Rd 203, Economic & Technological Development Zone, Tianjin 300457, China.
url: www.hualida.com

Hualong, China. Hualong Bio-Pharmaceutical Co. Ltd, Hulong Biotechnology Park, Zoumaling St, Dongxihu District, Wuhan, Hubei, 430040, China.
url: en.whualong.com

Huan Lian, Rus. Shanghai Huan Lian Pharmaceutical Co Ltd, Russia.

Huana, China. See *Warrant, China.*

Huanan, China. Guangdong Huanan Pharmaceutical Group Co., Ltd., West Lake Industrial Zone, Shilong, Dongguan, Guangdong, 523325, China.
url: www.hn-pharm.com

Huaneng, China. Huaneng Pharmaceutical Co. Ltd, Qingyuan, China.

Huang Long, China. See *Hengrui, China.*

Huanghai, China. Huanghai Pharmaceutical Co. Ltd, Qingdao GuoFeng Group, 28 Chi Quan Rd, Qingdao City 266022, China.

Huangshi FeiYun, China. Huangshi FeiYun Pharmaceutical Co. Ltd, China.

Huangshi Weisheng, China. Huangshi Weisheng Pharmaceutical Co. Ltd, China.

Huanqiu, China. Huanqiu Pharmaceutical Co. Ltd, Anhui, China.

Huanuowei, China. Huanuowei Gene Pharmaceutical Co. Ltd, Guilin, China.

Huaren, China. Huaren Pharmaceutical Co. Ltd., 187 Zhuzhou Road, Qingdao, Shandong, 266101, China.
url: www.qdhuaren.com

Huasen, China. Huasen Pharmaceutical Co. Ltd, Chongqing, China.

Huashan, China. Nantong Huashan Pharmaceutical Co. Ltd, Nantong, China.

Huashidan, China. Huashidan Pharmaceutical Co. Ltd., 45 Henan East Road, Urumqi, Xinjiang, 830011, China.
url: www.huashidan.com

Huashin, China. Huashin Chemical Pharmaceutical Works Co. Ltd, China.

Huataitang, China. Huataitang Pharmaceutical Co. Ltd, Bazhou, Hebei, China.
url: www.huataitang.com

Huatuo Tianya, China. Huatuo Tianya Pharmaceutical Co. Ltd., 100 Longkun South Road, Haikou, Hainan, 571159, China.
url: www.hainantianya.com

Huawei, China. Huawei Pharmaceutical Co. Ltd, Guangdong, China.

HuaXia, China. HuaXia Pharm Group, Huaxia Industrial Park, Taishan Rd 692, Weihai 264205, Shandong, China.
url: www.hua-xia.com

Huaxin, China. Huaxin Pharmaceutical Co. Ltd., 20 Sichuan Rd, Leshan, Bo Yang, Shizhong, Sichuan, 614006, China.
url: www.huaxin-pharma.com

Huayang, China. Huayang Pharmaceutical Co. Ltd, Jiangsu, China.

Huayi, China. Huayi Pharmaceutical Co. Ltd, 11 Shanghai Rd, Baohe Industrial Park, Hefei, Anhui, 230051, China.
url: www.huayi-pharma.com

Huayu, China. Huayu Pharmaceutical Co. Ltd, Wuxi, China.

Huayuan, China. Huayuan Pharmaceutical Co. Ltd, Shanghai, Ningxia, China.

Huayuan Century, China. Huayuan Century Pharmaceutical Co. Ltd., 240B Block A Asia Trade Plaza, 628 Wu Luo Road, Wuchang, Wuhan, Hubei, 430060, China.
url: www.hbhysjyy.com

Huazhong, China. Huazhong Pharmaceutical Co. Ltd, Information Tower Unit 201, 1403 Minsheng Rd, Pudong, Shanghai, 200135, China.
url: www.hpchuazhong.com

Hub, India. See *Sanofi-Aventis, India.*

Hub, USA. HUB Pharmaceuticals LLC, 9339 Charles Smith Ave, Bldg 150, Rancho Cucamonga, CA 91730, USA.
url: www.hubpharmaceuticals.com

Hubei Pharmaceutical, China. Hubei Pharmaceutical Co. Ltd, Hubei, China.

Hubert, UK. Hubert A.C. Thomas & Co., Burry Port, Carmarthenshire, SA16 0TB, UK.

Hubner, Fin. See *Oriola, Fin.*

Huckaby, USA. Huckaby Pharmacal Inc., 11802 Brinley Ave, Suite 201, Louisville, KY 40243, USA.

Hudson, USA. Hudson Corp., 90 Orville Drive, Bohemia, NY 11716, USA.

Hufort, India. Hufort Healthcare Pvt Ltd, Runwal Park, S T Road, Chembur, Mumbai 400 071, India.

Huge, Philipp. Huge Pharma International Corp., 8374 Mayapis St, San Antonio Vill., Makati City, Philippines.

Hugel, Thai. See *Cosma, Thai* and *T Man, Thai.*

Hugh Source, Hong Kong. Hugh Source (International) Ltd, Rm 1312 New East Ocean Centre, 9 Science Museum Rd, Tsim Sha Tsui East, Kowloon, Hong Kong.
url: www.btxa.com

Hui Feng, China. Hui Feng Pharmaceutical Co. Ltd, Ganmaoqing, China.

Hui Pu Sen, China. Hui Pu Sen Pharmaceutical Co. Ltd, Hainan, China.

Hui Ren, China. Hui Ren Pharmaceutical Co. Ltd, Jiangxi, China.

Hui Yin Bi, China. Hui Yin Bi Group, China.

Huida, China. Huida Pharmaceutical Co. Ltd, Datong, China.

Huili, China. Huili Pharmaceutical Co. Ltd, Harbin, China.

Huinan Huifa, China. Huinan Huifa Pharmaceutical Co. Ltd, 8 Yongkang Rd, Chaoyang, Huinan, Tonghua, Jilin, 135100, China.

Huinan Tiantai, China. Huinan Tiantai Pharmaceutical Co. Ltd, China.

Huitian, China. Huitian Biopharmaceutical Co. Ltd, Fujian, China.

Hujiang, China. Hujiang Pharmaceutical Co. Ltd, Guangxi, China.

Huls, Ger. See *Athenstaedt, Ger.*

Human, Cz. See *Humanpharma, Hung.*

Human, Hung. See *Humanpharma, Hung.*

Human, Philipp. See *PharmAsia, Philipp.*

Human, Thai. See *Neopharm, Thai.*

Human BioPlazma, Hung. Human BioPlazma Kft, Tancsics M ut 80, 2100 Godollo, Hungary.

Human Genome, USA. Human Genome Sciences, 14200 Shady Grove Rd, Rockville, MD 20850, USA.
url: www.humangenomesciences.com

Humana, Ital. Humana Italia S.p.A., Viale Liguria 22/A, 20143 Milan (MI), Italy.
url: www.humana.it

Humana, Philipp. See *Chiral, Philipp.*

Humana, Pol. See *DPS, Pol.*

Humanpharma, Hung. Humanpharma Gyógyszergyártó Kft, Táncsics Mihály út 82, 2100 Gödöllő, Hungary.
url: www.human.hu

Humco, Israel. See *Humco, USA.*

Humco, USA. Humco Holdings Group Inc., 7400 Alumax Drive, Texarkana, TX 75501, USA.
url: www.humco.com

Humet, Hung. Humet, Ilka utca 31, 1143 Budapest, Hungary.
url: www.humet.hu

Hungaro-Gen, Hung. Hungaro-Gen Kft, Budai Nagy Antal u. 3 1/3, 1137 Budapest, Hungary.
url: www.hungaro-genkft-c.cegbongeszo.hu

Hunter, Canad. Hunter Amenities International Ltd, 1205 Corporate Dr, Burlington, Ontario, L7L 5V5, Canada.

Huntley, UK. Huntley Pharmaceuticals Ltd, P.O. Box 2752, Marlborough, Wiltshire, SN8 1ZH, UK.
url: www.huntley-pharma.co.uk

Huons, Philipp. See *International Apex, Philipp* and *Largen, Philipp.*

Huons, Thai. See *Schumit, Thai.*

Husnu, Turk. See *Bilim, Turk.*

Husnu Arsan, Turk. Hüsnü Arsan İlaçlari AS, Ayazaga Köyü Yolu, Maslak, Istanbul, Turkey.

Huxley, UK. Huxley Europe Ltd, 26 Whittaker Lane, Prestwich, Manchester, Lancashire, M25 1FX, UK.

Hwang, China. Hwang's Pharmaceutical Co. Ltd, China.

HWS OTC, Austria. HWS-OTC-Service GmbH, Steindorf 65, A-5570 Mauterndorf, Austria.

Hyaltec, Arg. Hyaltec Argentina SA, Maipú 942 Piso 3, C.A.B.A., Argentina.

Hybio, China. Hybio Pharmaceutical Co. Ltd., Hybio Biomedical Park, 2 Gaoxin Central 2nd Road, Shenzhen, Guangdong, 518057, China.
url: www.hybio.com.cn

Hybritech, USA. See *Beckman, USA.*

Hyde, S.Afr. Hyde Pharmaceuticals (Pty) Ltd, 80 Bonza Bay Rd, Beacon Bay 5241, South Africa.

Hydrachem, Singapore. See *Joyson, Singapore.*

Hydration, Canad. Hydration Pharmaceuticals Canada Inc., 2400 Canoe Ave, Coquitlam, British Columbia, V3K 6C2, Canada.
url: www.hydralytecanada.com

Hydration, Singapore. See *MBD, Singapore.*

Hydro, Swed. See *Bioglan, Swed.*

Hydron, Singapore. See *Pharmatech, Singapore.*

Hygene, China. Hygene Biopharmaceutical Co. Ltd., National Health Technology Park, Zhongshan, Guangdong, 528437, China.
url: www.biohygene.com

Hy-Gro, India. Hy-Gro Chemicals Pharmtek Pvt Ltd, 15 Sri Krishna Nagar Colony, Picket, Secunderabad 500 009, India.
url: www.hygrochemicals.com

Hyland, Hong Kong. See *Baxter, Hong Kong.*

Hyland, USA. See *Baxter, USA.*

Hyland Immuno, UK. See *Baxter BioScience, UK.*

Hylands, Canad. Hylands Homeopathic Canada, 381-A, route 139, Sutton, Quebec, J0E 2K0, Canada.

Hyland's Laboratories, USA. See *Standard Homeopathic, USA.*

Hynson, Westcott & Dunning, USA. See *Becton Dickinson, USA.*

Hyperion, Rus. See *Rompharm, Rus.*

Hyperion, USA. Hyperion Therapeutics Inc., 601 Gateway Blvd, Suite 200, South San Francisco, CA 94080, USA.
url: www.hyperiontx.com

Hypermarcas, Braz. Hypermarcas SA, Av. Fernando Cerqueira Coimbra 1000, 6465090 Sao Paulo, Sao Paulo, Brazil.

Hyphens, Malaysia. See *Apex, Malaysia.*

Hyphens, Singapore. See *Pharmaforte, Singapore.*

Hypoguard, Irl. See *Hypoguard, UK.*

Hypoguard, UK. Hypoguard (UK) Ltd, Dock Lane, Melton, Woodbridge, Suffolk, IP12 1PE, UK.
url: www.hypoguard.com

Hyrex, USA. Hyrex Pharmaceuticals, 3494 Democrat Rd, P.O. Box 18385, Memphis, TN 38118-0385, USA.

I & C, Hong Kong. I & C (Hong Kong) Ltd, Rm 1201, 12/F Lemmi Ctr, 50 Hoi Yuen Rd, Kwun Tong Kowloon, Hong Kong.

I Farmacologia, Spain. See *Schwarz, Spain.*

IAE, Philipp. IAE Pharmaceuticals Corp., 25 Kabignayan St, Car Banawe, Quezon City, Philippines.

Iamatica, Gr. Iamatica, Chalandriou 6A, 153 43 Ag. Paraskevi, Greece.

Iapharm, Gr. IAPHARM, 54 Menandrou Str., 104 31 Athens, Greece.
url: www.iapharm.gr

Iasimo, Gr. See *Iasimo, UK.*

Iasimo, UK. Iasimo Ltd, 178 Seven Sisters Rd, London, N7 7PX, UK.

Iasis, Gr. See *Chemipharma, Gr.*

Iason, Austria. Iason Labormedizin GmbH & Co KG, Feldkirchnerstrasse 4, A-8054 Graz, Austria.

Iason, Cz. See *Iason, Austria.*

Iason, Fin. See *Iason, Austria.*

Iason, Ital. See *Iason, Austria.*

Iason, Neth. See *Iason, Austria.*

Iason, Port. See *Iason, Austria.*

Iator, Gr. Iator, Sorou 4, 151 25 Marousi, Greece.

IBA, Ital. IBA, Italy.

IBA, Pol. See *Bioton, Pol.*

IBCH, Rus. Institute of Bioorganic Chemistry of the Russian Academy of Sciences, ul Miklukho-Maklaya 16/10, 117997 Moscow, Russia.
url: www.ibch.ru

Iberoinvesa, Spain. Iberoinvesa Pharma SL, C/Zurbaran 18, 28010 Madrid, Spain.

IBI, Cz. IBI sro, Mysibeková 25, 169 00 Prague 6, Czech Republic.

IBI, Ital. Istituto Biochimico Italiano Giovanni Lorenzini S.p.A., Via Fossignano 2, 04011 Aprillia (LT), Italy.
url: www.ibi-lorenzini.com

IBI, Thai. See *Siam Pharm, Thai.*

IBI International, Cz. IBI International sro, Sokolovská 24, 186 00 Prague 8, Czech Republic.

Ibigen, Ital. Ibigen Srl, Via Fossignano 2, 04011 Aprilia (LT), Italy.

Ibios, Fr. Laboratoire Ibios, 37 av Gabriel Peri, B.P. 232, 92503 Rueil Malmaison cdx, France.

Ibirn, Ital. Istituto Bioterapico Nazionale S.r.l., Via V. Grassi 9/11/13/15, 00155 Rome (RM), Italy.

IBIS, UK. IBIS Products, Stevenage, Hertfordshire, SG1 4QG, UK.

Ibmed, Hung. Ibmed Kft, Gardonyi utca 11, 1222 Budapest, Hungary.

IBN, Ital. IBN Istituto Biologico Nazionale S.r.l., Viale Città d'Europa 681, 00144 Rome (RM), Italy.

IBSA, Austria. See *IBSA, Ital.*

IBSA, Cz. See *IBI, Cz.*

IBSA, Denm. See *Meda, Denm.*

IBSA, Fin. See *IBSA, Ital.*

IBSA, Ger. See *IBSA, Ital.*

IBSA, Hong Kong. See *Mekim, Hong Kong.*

IBSA, Hung. IBSA Pharma Kft, Fodor u 54/b, 1124 Budapest, Hungary.

IBSA, Irl. See *IBSA, Ital.*

IBSA, Israel. See *Genmedix, Israel.*

IBSA, Ital. Ibsa Farmaceutici Italia S.r.l., Via Emilia 99 Frazione San Grato, 26900 Lodi, Italy.
url: www.ibsa.it

IBSA, Malaysia. See *Sun, Malaysia.*

IBSA, Neth. See *IBSA, Switz.*

IBSA, Norw. See *NordicInfu Care, Norw.*

IBSA, Philipp. See *Sonix, Philipp.*

IBSA, Pol. See *Teva, Pol.*

IBSA, Port. See *IBSA, Ital.*

IBSA, Switz. Institut Biochimique SA, Via del Piano, 6915 Pambio-Noranco, Switzerland.
url: www.ibsa.ch

IBSA, Ukr. See *Intermedfarma, Ukr.*

Icaro, Spain. See *AstraZeneca, Spain.*

Icarus, India. Icarus Health Care Pvt Ltd, No.5, 52nd Street, 7th Avenue, Ashok Nagar, Chennai 600 083, India.
url: www.icarushealth.com

ICC, Israel. See *Rekah, Israel.*

ICE, Turk. Intel Chemicals Enterprises Ltd, Turkey.

ICF, Ukr. ICF Medikal, Prorezna St 22, Apt. 3, 01034 Kiev, Ukraine.

Ichthyol, Austria. See *Ichthyol, Ger.*

Ichthyol, Ger. Ichthyol-Gesellschaft Cordes, Hermanni & Co. (GmbH & Co.) KG, Sportallee 85, 22335 Hamburg, Germany.
url: www.ichthyol.de

Ichthyol, Switz. See *Medinova, Switz.*

ICI, Austral. See *AstraZeneca, Austral.*

ICI, Ger. See *AstraZeneca, Ger.*

ICI, India. ICI India Ltd, Khaleeli Centre, 149 Montieth Road, Chennai 600 008, India.

ICI, Ital. See *AstraZeneca, Ital.*

ICI, Neth. See *AstraZeneca, Neth.*

ICI, UK. See *AstraZeneca, UK.*

ICIM, Ital. ICIM International S.r.l., Via Peloritana 28, 20024 Garbagnate Milanese (MI), Italy.

ICIM, Singapore. See *Pharmatech, Singapore.*

ICM, Singapore. ICM, Integrated Contract Manufacturing Pte Ltd, 26 Kallang Place, 05-17, S 339157, Singapore.
url: www.icmpharma.com.sg

ICN, Austral. See *Valeant, Austral.*

ICN, Austria. ICN Pharmaceuticals Austria GmbH, Michael-Pracher-Strasse 25A/7, A-5020 Salzburg, Austria.
url: www.icnpharm.com

ICN, Braz. ICN Farmacêutica Ltda, Rua Geraldo Flausino Gomez 61, andar 10, 04575-060 São Paulo, SP, Brazil.
url: www.icnpharm.com

ICN, Cz. ICN Czech Republic as, Truhlářská 13-15, 110 00 Prague 1, Czech Republic.
url: www.icnpharm.cz

ICN, Denm. See *Medilink, Denm.*

ICN, Fin. See *ICN, Neth.*

ICN, Ger. See *Valeant, Ger.*

ICN, Gr. See *Valeant, Spain.*

ICN, Hong Kong. See *IDS, Hong Kong.*

ICN, Hung. ICN Magyarország Rt, Csatárka u 82-84, 1025 Budapest, Hungary.

ICN, Irl. See *Allphar, Irl.*

ICN, Israel. See *Devries, Israel.*

ICN, Ital. See *Valeant, Ital.*

ICN, Malaysia. See *JDH, Malaysia* and *Pharmaforte, Malaysia.*

ICN, Neth. ICN Pharmaceuticals Holland BV, Stephensonstraat 45, 2723 RM Zoetermeer, Netherlands.
url: www.icnpharm.com

ICN, Norw. See *Medilink, Denm.*

ICN, NZ. See *Pacific, NZ.*

ICN, Pol. ICN Polfa Rzeszów SA, Biuro Marketingu i Sprzedaży, ul. Marynarska 15, 02-674 Warsaw, Poland.
url: www.polfa.com.pl

ICN, Rus. See *Valeant, Rus.*

ICN, Singapore. See *JDH, Singapore.*

ICN, Spain. See *Valeant, Spain.*

ICN, Swed. See *ICN, Neth.*

ICN, Thai. See *Diethelm, Thai.*

ICN, UK. See *Valeant, UK.*

ICN, Ukr. See *Valeant, Ukr.*

ICN, USA. See *Valeant, USA.*

Icon, Philipp. Icon Pharma Corp., 1211 Medical Plaza, Ortigas Bldg, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.

ICPA, India. ICPA Health Products Ltd, 233A Adarsh Indl. Estate, Sahar Road, Andheri (East), Mumbai 400 099, India.
url: www.icpahealth.com

ICT, Ital. Istituto Chemioterapico S.p.A., Strada Bobbiese 108, 29100 Piacenza, Italy.

ICT-Lodi, Ital. See *ICT, Ital.*

ID, Belg. ID Phar bvba, Iddergemsesteenweg 77 B, 9450 Haaltert, Belgium.

ID, Neth. See *ID, Belg.*

ID Biomedical, Canad. ID Biomedical Corp. of Quebec, 525 Cartier Blvd West, Laval, Quebec, H7V 3S8, Canada.

ID Biomedical, China. See *ID Biomedical, Canad.*

ID Pharma, Fr. ID Pharma, 327 B route de Valparc, 74330 Poisy, France.
url: www.idpharma.fr

Idaman, Malaysia. Idaman Pharma Sdn Bhd, 66 Jalan 1/27F, Pusat Bandar Wangsa Maju, 53300 Kuala Lumpur, Malaysia.
url: www.idamanpharma.com

Idaman, Singapore. See *Apotheca, Singapore.*

Ideal Health, UK. Ideal Health Group Ltd, The Common, Potten End, Berkhamstead, Hertfordshire, HP4 2QF, UK.

IDEC, USA. See *Biogen, USA.*

Ideco, Ital. Ideco Srl, Via L Braille 18, 39100 Bolzano (BZ), Italy.
url: www.idecogroup.it

Idelle, Canad. See *Idelle, USA.*

Idelle, USA. Idelle Labs Ltd, 1 Helen of Troy Plaza, El Paso, Texas, 79912, Canada.

Ideosmos, Gr. Ideosmos H & E Alevizopoulos EE, Faron 155, 24100 Kalamata, Greece.

Iderne, Fr. Laboratoires Michel Iderne, Parc d'activités Rosenmeer, 67560 Rosheim, France.

IDI, Ital. IDI Farmaceutici S.p.A., Via dei Castelli Romani 83/85, 00040 Pomezia (RM), Italy.

IDIS, Fin. See *IDIS, UK.*

IDIS, Fr. See *IDIS, UK.*

IDIS, Neth. See *IDIS, UK.*

IDIS, UK. IDIS World Medicines, Idis House, Churchfield Rd, Weybridge, Surrey, KT13 8DB, UK.
url: www.idis.co.uk

IDM, Austria. See *IDM, Fr.*

IDM, Cz. See *IDM, Fr.*

IDM, Denm. See *IDM, Fr.*

IDM, Fr. DM Pharm SAS, 11-15 quai de Dion Bouton, 92816 Puteaux Cedex, France.
url: www.millennium.com

IDM, Gr. See *IDM, Fr.*

IDM, Ital. See *IDM, Fr.*

IDM, Neth. See *IDM, Fr.*

IDM, Norw. See *IDM, Fr.*

IDM, Pol. See *IDM, Fr.*

IDM, Port. See *IDM, Fr.*

IDM, Spain. See *IDM, Fr.*

Idol, Thai. See *JDH Borneo, Thai.*

IDS, Hong Kong. IDS (Hong Kong) Ltd Healthcare Division, 14/F LiFung Ctr, 2 On Ping St, Siu Lek Yuen, Shatin, NT, Hong Kong.
url: www.idsgroup.com

IDS, Malaysia. IDS Marketing, LiFung Centre, Lot 6 Persiaran Perusahaan Seksyen 23, 40300 Shah Alam, Selangor, Malaysia.
url: www.idsmarketing.com

IDS, Singapore. IDS Marketing, Pharmaceutical Division, 279 Jalan Ahmad Ibrahim, 03-01, S-639938, Singapore.

IDS, Thai. IDS Marketing (Thailand) Ltd, 505 Moo 2, Bangpa-in Industrial Estate, Udom Sorayudh Rd, Tambol Klongjig, Amphur Bangpa-in, Ayudhaya 13160, Thailand.
url: www.idsmarketing.com

IDT Impfstoffwerk, Israel. See *Curasan, Ger.*

IE, Turk. See *Ulagay, Turk.*

IE Medica, Philipp. I.E. Medica Trading, 506 RFM Corporate Ctr, Pioneer St, Mandaluyong City, Philippines.

IEPSA, S.Afr. IEPSA (Pty) Ltd, P.O. Box 36482, Menlo Park 0102, South Africa.
url: www.iepsa.co.za

IFA, Mex. See *Investigacion, Mex.*

Ifarm, Pol. Instytut Farmaceutyczny, ul. Rydygiera 8, 01-793 Warsaw, Poland.
url: www.ifarm.waw.pl

Ifars, Indon. Ifars Pharmaceutical Laboratories PT, Jl Raya Solo-SRagen Km 14.9, Kebakkramat Solo, 57762 Jawa, Indonesia.
url: www.ifars.co.id

IFC, Port. IFC Skincare Portugal, Rua Poeta Bocage 14 D, Escritorio A, 1600-581 Lisbon, Portugal.

Ifesa, Spain. See *AstraZeneca, Spain.*

IFET, Gr. I.F.E.T. (Institute of Pharmaceutical Research and Technology S.A.), 18th Km of Marathonos Ave, 153 44 Pallini, Greece.
url: www.ifet.gr

IFET (ΙΦΕΤ), Gr. See *IFET, Gr.*

Ifidesa Aristegui, Spain. Ifidesa Aristegui, Alameda de Urquijo 27 1, Bilbao, 48008 Vizcaya, Spain.

IFS, USA. Innovative Fulfillment Solutions (IFS), 4346 Belgium Blvd, Kansas City, MO 64150, USA.

Ifusa, Mex. Laboratorios Ifusa S.A., Francisco Lorenzana 20, Col. San Rafael, Deleg. Cuauhtemoc, 06470 Mexico D.F., Mexico.

IG, Malaysia. See *Medidata, Malaysia* and *Pharmaniaga, Malaysia.*

Igefarma, Braz. See *Theraskin, Braz.*

i-Health, USA. i-Health Inc., a division of DSM Nutritional Products, Suite 102, 55 Sebethe Drive, Cromwell, CT 06416, USA.
url: www.i-healthinc.com

IIP, Ger. Institut für Industrielle Pharmazie F & E GmbH, Benzstrasse 2a, 63741 Aschaffenburg, Germany.
url: www.iip-gmbh.de

IIP, Port. See *IIP, Ger.*

Ikapharm, Israel. See *Teva, Israel.*

Ikapharmindo, Indon. Ikapharmindo Putramas PT, Jl Pulo Gadung Raya No 29, Kawasan Industri Pulo Gadung, Jakarta 13930, DKI Jaya, Indonesia.
url: www.ikapharmindo.com

Ikaria, Austral. Ikaria Australia Pty Ltd, 695 Burke Rd, Hawthorn East, Vic 3123, Australia.
url: ikariaaust.com

Ikon, India. Ikon Remedies Pvt Ltd, Near Indira Gandhi School, Amravati Road, Dattawadi, Nagpur 440 023, India.

Ikx, Arg. Ikx Cosmetica, Av. Cordoba 2348, (C1120AAG) Capital Federal, Argentina.
url: www.cosmeticaikx.com.ar

Ilacsan, Turk. Ilacsan İlaç San.ve Tic. Ltd, Merkez Efendi Çiftlik Yolu Zeytin, Belde Sit N:33 K:19 D:78, Topkapi, Istanbul, Turkey.
Ildong, Malaysia. See *Somedico, Malaysia.*
Ildong, Philipp. See *Metro, Philipp.*
Ilex, Austria. See *Ilex, UK.*
Ilex, Denm. See *Bayer, Denm.*
Ilex, Hung. See *Schering, Hung.*
Ilex, Norw. See *Schering, Norw.*
Ilex, Pol. See *Schering, Pol.*
Ilex, UK. Ilex Pharmaceuticals Ltd, 1-3 Frederick Sanger Rd, Surrey Research Park, Guildford, Surrey, GU2 7YD, UK.
url: www.ilexonc.com
Ilex, USA. See *Genzyme, USA.*
Iliafarm, Gr. Iliafarm (Ιλιαφαρμ), Levadeias 5, 144 52 Metamorfosi, Greece.
Il-Ko, Turk. Il-ko İlaç ve Kozmetik San. AS, Ornek Kasap Mh Bezmi Alem Cd No 12/3, Findikzade, Istanbul, Turkey.
Ilon Laboratories, UK. See *Farillon, UK.*
Ilsan, Turk. Ilsan Hexal İlaç Ltd. Şti., Gebze Plastikçiler Org. San. Böl., Atatürk Blv. 9. Cad. No: 1, Gebze, Kocaeli, Turkey.
url: www.ilsan.com.tr
Il-Yang, China. Yangzhou Il-Yang Pharm, Gaoyou Mayor Hing Rd 8, Yangzhou 225600, Jiangsu Province, China.
url: www.yangzhouilyang.com
Il-Yang, Singapore. See *Zyfas, Singapore.*
IMA, Braz. Instituto de Medicamentos e Alergia IMA Ltda, Rua Araujo Leitao 193, 20715-310 Rio de Janeiro, RJ, Brazil.
Imaxio, Fr. Imaxio, 181 av Jean-Jaurès, 69007 Lyon, France.
Imbio, Rus. See *Microgen, Rus.*
Imed, Pol. Imed Poland Sp. zo.o., ul. Duchnicka 3, 01-796 Warsaw, Poland.
url: www.imed.com.pl
Imeks, Malaysia. Imeks Pharma Sdn Bhd, 2 Jln 6/33B, MWE Commercial Park Kepong, 52000 Kuala Lumpur, Wilaya Persekutuan, Malaysia.
Imex, Gr. See *Pharmacare, Gr.*
Imgroma, Neth. Imgroma BV, Aldebert van Scharn laan 170 A-2, 6224 JX Maastricht, Netherlands.
Imi, Denm. Imi Pharma A/S, Literbuen 9 Postboks 48, 2740 Skovlunde, Denmark.
Immanence Integral, Canad. Immanence Integral Dermo Correction Inc., Suite 925, Tour de la Cite, 2600 Blvd Laurier, Quebec, G1V 4W2, Canada.
Immapharma, Rus. Immapharma OOO, Gamalei ul. 18, 123098 Moscow, Russia.
url: www.immapharma.ru
Immodal, Austria. Immodal Pharmaka GmbH, Bundesstrasse 44, A-6111 Volders, Austria.
Immunex, USA. See *Amgen, USA.*
Immuno, Arg. See *Baxter Immuno, Arg.*
Immuno, Austria. See *Baxter, Austria.*
Immuno, Belg. See *Baxter, Belg.*
Immuno, Canad. See *Baxter, Canad.*
Immuno, Fr. See *Baxter, Fr.*
Immuno, Ger. See *Baxter, Ger.*
Immuno, Hong Kong. See *Mekim, Hong Kong.*
Immuno, Irl. See *Baxter, Irl.*
Immuno, Israel. See *Teva, Israel.*
Immuno, Ital. See *Baxter, Ital.*
Immuno, Spain. See *Baxter, Spain.*
Immuno, Swed. See *Baxter, Swed.*
Immuno, Switz. See *Baxter, Switz.*
Immuno, UK. See *Baxter BioScience, UK.*
Immuno, USA. See *Baxter, USA.*
Immunomedics, Austria. See *Immunomedics, Ger.*
Immunomedics, Cz. See *Immunomedics, Ger.*
Immunomedics, Ger. Immunomedics Europe, Otto-Roehm-Str. 69, 64293 Darmstadt, Germany.
url: www.immunomedics.com
Immunomedics, Irl. See *Immunomedics, Ger.*
Immunomedics, Ital. See *Immunomedics, Ger.*
Immunomedics, Neth. See *Immunomedics, Ger.*
Immunomedics, Pol. See *Immunomedics, Ger.*
Immunomedics, Port. See *Immunomedics, Ger.*
Immunomedics, Spain. See *Immunomedics, Ger.*
Immunomedics, UK. See *Immunomedics, Ger.*
Immunomedics, USA. Immunomedics, 300 American Rd, Morris Plains, NJ 07950, USA.
url: www.immunomedics.com
Immunopreparat, Rus. See *Microgen, Rus.*
Immunotec, Canad. Immunotec Research, 292 Adrien-Patenaude, Vaudreuil-Dorion, Quebec, J7V 5V5, Canada.
Immunotec, USA. See *Immunotec, Canad.*
Immuron, Austral. Immuron, 39 Leveson St, North Melbourne, Vic 3051, Australia.
url: www.immuron.com
IMO, Ital. Istituto di Medicina Omeopatica S.p.A., Via Vincenzo Monti 6, 20123 Milan (MI), Italy.
url: www.omeoimo.it
Impax, USA. Impax Laboratories Inc., 30831 Huntwood Ave, Hayward, CA 94544, USA.
url: www.impaxlabs.com
Imperial, Hong Kong. See *Unam, Hong Kong.*
Imperial, Malaysia. See *Unam, Malaysia.*
Imperial, Philipp. LR Imperial Inc., 2/F Bonaventure Plaza, Ortigas Ave, Greenhills, San Juan, Philippines.
Imperial, Singapore. See *Far East, Singapore.*
Impharm, UK. See *Intercare, UK.*
Improvit, Arg. Impovit S.R.L., Edison 1177, 1640 Martinez, Buenos Aires, Argentina.
Imrex, Canad. Imrex Inc., 2 Pioneer Drive Rr 5, Komoka, Ontario, N0L 1R0, Canada.
IMS, Hong Kong. See *ICH, Hong Kong.*
IMS, Ital. International Medical Service S.r.l., Via Lauretina 169, 00040 Pomezia (RM), Italy.
url: www.imsonline.it
IMS, USA. See *Celltech, USA.*
Imtix, Austria. See *Imtix, Fr.*
url: www.sangstat.com
Imtix, Belg. See *Imtix, Fr.*
Imtix, Cz. See *Imtix, Fr.*
Imtix, Denm. See *Sangstat, Neth.*
Imtix, Fr. Imtix-SangStat, 58 av Debourg, B.P. 7055, 69348 Lyon cdx 07, France.
url: www.sangstat.fr
Imtix, Neth. See *Sangstat, Neth.*
Imtix, Switz. See *Pro Vaccine, Switz.*
Imtix Sangstat, Israel. See *Medison, Israel.*
Imuna, Cz. Imuna sp, Jarkovska 17, Šarišske Michal'any, Slovenia.
Imunomedica, Cz. Imunomedica as, Chuderov 118, 400 11 Ústí nad Labem, Czech Republic.
url: www.imunomedica.cz
Imvi, Arg. Lab. Imvi S.A. (Div. Humana), Olazabal 1665/71, 1428 Buenos Aires, Argentina.
url: www.imvi.com.ar
In Vitro, Hung. In Vitro Kft, Repülőtéri ut 1, 2120 Dunakeszi, Hungary.
url: www.invitro.hu
In Vitro, NZ. In Vitro Technologies, P.O. Box 14-323, Panmure, New Zealand.
url: www.invitro.co.nz
Inaf, Braz. See *Eurofarma, Braz.*
Inamed, Singapore. See *Pharmacon, Singapore.*
Inamed, USA. Inamed Health, 5540 Ekwill St, Santa Barbara, CA 93111, USA.
url: www.inamed.com
Inava, Fr. See *Pierre Fabre, Fr.*
Inca, Ger. Inca-Pharm GmbH, Rochusstrasse 175-177, 53123 Bonn, Germany.
url: www.inca-pharm.com
Inca, Irl. See *Inca, Ger.*
Inca, Ital. Inca-Pharm Srl, Via Dante Alighieri 3, 03100 Frosinone (FR), Italy.
url: www.inca-pharm.com
Inca, Neth. See *Inca, Ger.*
Incaico, Arg. Lab. Incaico SA, Montiel 156, 1408 Buenos Aires, Argentina.
Incepta, Hong Kong. See *Health Alliance, Hong Kong.*
Inchcape, Hong Kong. See *IDS, Hong Kong.*
Inco, Gr. Inco Hellas AE, 132 Ave Lavriou, Glyka Nera Attikis, Greece.
Inco Veritas, Pol. Inco Veritas SA o/Góra Kalwaria GCHG, ul. Towarowa 8, 05-530 Góra Kalwaria, Poland.
url: www.inco-veritas.com.pl
Incognito, UK. Incognito, 28 Kensington Park Gardens, London, W11 2QS, UK.
url: www.lessmosquito.com
Incomed, India. SP Incomed Pvt Ltd, India.
Incomed, Rus. See *Incomed, India.*
Incyte, USA. Incyte Corp., Route 141 & Henry Clay Rd, Building E336, Wilmington, DE 19880, USA.
url: www.incyte.com
IND, China. IND Pharmaceutical Co. Ltd, Beijing, China.
Ind Biosciences, India. Ind Biosciences, Chandigarh, India.
Indar, Rus. See *Indar, Ukr.*
Indar, Ukr. Indar, 5 Orositeina St, 02099 Kiev, Ukraine.
url: www.indar.kiev.ua
Ind-Chemie, India. Ind-Chemie Health Specialities (P) Ltd, 510 Shah & Nahar Ind. Estate, Dr. E Moses Road, Worli Naka, Mumbai 400 018, India.
Indchemie, Philipp. See *Suhitas, Philipp.*
Indchemie, Thai. See *GIS, Thai.*
Indeco, Arg. Laboratorio Indeco S.A., Jose Marmol 1924, 1602 Florida, Buenos Aires, Argentina.
Indevus, Canad. See *Indevus, USA.*
Indevus, Malaysia. See *DKSH, Malaysia.*
Indevus, Singapore. See *Transmedic, Singapore.*
Indevus, USA. Indevus Pharmaceuticals Inc., 99 Hayden Ave, Suite 200, Lexington, MA 02421, USA.
url: www.indevus.com
Indi, India. Indi Pharma Pvt Ltd, 405/406 Regent Chambers, 208 Nariman Point, Mumbai 400 021, India.
Indian Drugs, India. Indian Drugs & Pharmaceuticals Ltd, IDPL Complex, Delhi-Gurgaon Rd, Dundahera, Gurgaon 122 001, India.
url: idpl.gov.in
Indian Immunologicals, Philipp. See *Maximus, Philipp.*
Indkus, India. Indkus Drugs & Pharma Pvt Ltd, G-3 Pratap Nagar, Near Metro Station, New Delhi 110 007, India.
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Indo Pacific, India. Indo Pacific Life Sciences, 25 Fire Surlong Rd, Guindy, Chennai, 600 032, India.
Indo Sehat, Indon. Indo Sehat Lestari PT, Oyama Bldg 2nd Flr, Jl Laksda Yos Sudarso 76, Jakarta Utara 14350, DKI Jaya, Indonesia.
url: www.indosehat.com
Indochina Healthcare, Thai. Indochina Healthcare Ltd, 23 Fl Olympia Thai Tower, 444 Ratchadapisek Rd, Samsennok Huay Kwang, Bangkok 10320, Thailand.
url: www.ihl-thailand.com
Indoco, India. Indoco Remedies Ltd, Indoco House, 166 CST Rd, Santacruz (East), Mumbai 400 098, India.
url: www.indoco.com
Indoco, Ital. See *Indoco, India.*
Indoco, Philipp. See *Indoco, India.*
Indoco, Thai. See *Union Medical, Thai.*
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Indrugco, Singapore. Indrugco Pte Ltd, 221 Henderson Rd, 07-20 Henderson Building, S 159557, Singapore.
url: www.indrugco.com
Ind-Swift, India. Ind-Swift Ltd, 781 Industrial Area, Phase II, Chandigarh 160 002, India.
url: www.indswiftltd.com
Ind-Swift, Philipp. See *Ambica, Philipp.*
Indu, India. Indu Drugs, 5-35, 278/279 Prasanth Nagar IDA, Kukatpally, Hyderabad 500 072, India.
url: www.indudrugs.com
Ineldea, Fr. Laboratoires Ineldea, Parc Sophia Antipolis, 45 allée des Ormes, Bât C, 06250 Mougins, France.
url: www.ineldea.com
Inex, Hung. Inex-Intherexport, Dozsa Gyorgy út 92/a, 1068 Budapest, Hungary.
INFAI, Austria. See *INFAI, Ger.*
INFAI, Ger. INFAI Institut für biomedizinische Analytik und NMR-Imaging GmbH, Gottfried-Hagen-Str. 60-62, 51105 Köln, Germany.
url: www.infai.de
INFAI, Gr. See *Faran, Gr.*
INFAI, Switz. INFAI CH GmbH, Bahnhofstrasse 29, 9470 Buchs, Switzerland.
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Infamed, Rus. Infamed, P.O. Box 46, 123056 Moscow, Russia.
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Infamed, Ukr. Infamed Ltd, ul Sofia 4, 01001 Kiev, Ukraine.
Infar, India. Infar (India) Ltd, Saturday Club Building, 7 Wood Street, Kolkata 700 016, India.
Infar, Port. Infar, Lda, Estrada de circunvalação, Rameiras, Algés, 1495 Lisbon, Portugal.
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Infectopharm, Austria. See *Infectopharm, Ger.*
Infectopharm, Cz. See *Infectopharm, Ger.*
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url: www.infectopharm.com
Infectopharm, Hung. See *Infectopharm, Ger.*
Infectopharm, Pol. See *Solpharm, Pol.*
Infinity, Venez. Infinity Pharma XXI, C.A., Esq. Puente Restaurador, Edif. Puente Restaurador, Santa Teresa, 1010-A Caracas, Venezuela.
Infirmarius, Ger. Infirmarius GmbH, Daimlerstr. 19-21, 73037 Göppingen, Germany.
url: www.infirmarius.de
Inflabloc, USA. Inflabloc Pharmaceuticals Inc., 2401 Foothill Drive, Salt Lake City, UT 84109, USA.
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Inga, Malaysia. See *Pahang, Malaysia.*
Inga, Philipp. See *Ambica, Philipp.*
Ingens, Arg. Laboratorios Ingens S.A., Fraga 1401, 1427 Buenos Aires, Argentina.
Ingers, Cz. Ingers Industrial Solutions sro, Brno, Czech Republic.
INGfertility, Singapore. See *Pan-Malayan, Singapore.*
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Inibsa, Port. Laboratórios Inibsa, SA, Sintra Business Park, Zona Industrial da Abrunheira, Edifício 1 - 2, 2710-089 Sintra, Portugal.
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Initios, Denm. Initios Medical AB, Symbion Science Park, Fruebjergvej 3, 2100 Copenhagen Ø, Denmark.
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Inkine, USA. InKine Pharmaceutical Company Inc., 1787 Sentry Pkwy, West Bldg 18, Suite 440, Blue Bell, PA 19422, USA.
url: www.inkine.com
Inland, Canad. See *Alcare, Canad.*
Inmunolab, Arg. Lab. Inmunolab S.A., Paysand 1928, 1416 Buenos Aires, Argentina.
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Innocoll, Hung. See *Innocoll, Irl.*
Innocoll, Irl. Innocoll Pharmaceuticals, Dublin Rd, Athlone, County Westmeath, Ireland.
url: www.innocoll-pharma.com
Innocore, Canad. Innocore Sales & Marketing, Unit 2, 85 Chambers Drive, Ajax, Ontario, L1Z 1E2, Canada.
Innocutis, USA. Innocutis Holdings LLC, Charleston, SC 29401, USA.
url: www.innocutis.com
Innoderm, Philipp. Innoderm Inc., Metro Pharma Bldg, 600 Shaw Blvd, Pasig City, Philippines.
InnoGen, Philipp. InnoGen Pharma Group Inc., 29 Scout Bayoran, South Triangle, Tomas Morato Ext, Quezon City, Philippines.
url: www.innogengroup.com
Innogene, Indon. Innogene Kalbiotech Pte Ltd, PLaza Property 3rd Floor, Kompleks Pertokoan Pulomas Blok VII No 1, Jl Perintis Kemerdekaan, Jakarta Timur 13210, Indonesia.
url: www.innogene-kalbiotech.com
Innogene, Malaysia. See *Pahang, Malaysia* and *Zuellig, Malaysia.*
Innogene, Philipp. See *Globo Asiatico, Philipp.*
Innogene, Thai. See *Alliance, Thai.*
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Innomed, Singapore. Innomed, Singapore.
Innopharm, Malaysia. See *Zyfas, Malaysia.*
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Innotech, Cz. See *Innotech, Fr.*
Innotech, Denm. See *Meda, Denm.*
Innotech, Fin. See *Innotech, Fr.*
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Innotech, Ger. See *Fontane, Ger.*
Innotech, Hong Kong. See *Wing Wai, Hong Kong.*
Innotech, Hung. See *Ubepharm, Hung.*
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Innotech, Rus. Innotech International, Group Innothera, Pokhodnyi pr-d 4, str. 7a, Business Centre Tushino et. 3, Of. 7, 125373 Moscow, Russia.
Innotech, Singapore. See *Indrugco, Singapore.*
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Innothera, Cz. See *Innothera, Fr.*
Innothera, Denm. See *Meda, Denm.*
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Innothera, Irl. Innothera Ireland Ltd, Donaghcumper, Dublin Rd, Celbridge, Co. Kildare, Ireland.
url: www.innothera.us
Innothera, Neth. See *Innothera, Fr.*
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Innothera, Rus. See *Innotech, Rus.*
Innothera, Switz. See *Interlabo, Switz.*
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Innovatec, Singapore. See *MBD, Singapore.*
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Innovative Brands, Canad. See *Innovative Brands, USA.*
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Innovex, UK. See *Novex Pharma, UK.*
InnoVisions, USA. Innovisions Inc., USA.
Inno-Vite, Canad. Inno-Vite Inc., 97 Saramia Crescent, Concord, Ontario, L4K 4P7, Canada.
Innovite, USA. See *Endurance, USA.*
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Innovitelle, Philipp. Innovitelle, 2/F Bonaventure Plaza, Ortigas Ave, Greenhills, San Juan, Philippines.
Innovo, Canad. See *Akorn, Canad.*
InnoZen, USA. InnoZen Inc., 6429 Independence Ave, Woodland Hills, CA 91367, USA.
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INO Therapeutics, Canad. See *INO Therapeutics, USA.*
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INO Therapeutics, Port. See *INO Therapeutics, Swed.*
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INO Therapeutics, Swed. INO Therapeutics AB, S-181 81 Lidingo, Sweden.
INO Therapeutics, USA. INO Therapeutics Inc., 6th State Route 173, Clinton, NJ 08809, USA.
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Inopak, Canad. See *Inopak, USA.*
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iNova, Hong Kong. iNova Pharmaceuticals (Hong Kong) Ltd, Unit 01 20/F, Millennium City 3, 370 Kwun Tong Rd, Kowloon, Hong Kong.
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iNova, Singapore. iNova Pharmaceuticals (Singapore) Pte Ltd, 10 Ubi Crescent, 02-51 Ubi Techpark Lobby C, S 408564, Singapore.
url: www.inovapharma.com

iNova, Thai. iNova Pharmaceuticals (Thailand) Ltd, 50 GMM Grammy Place Bldg, 12 Fl Unit B5 Sukhumvit 21 Rd (Asoke), Klongtoeynua Wattana, Bangkok 10110, Thailand.
url: www.inovapharma.com

Inovail, Austral. Inovail Pty Ltd, Level 8, 67 Albert Ave, Chatswood, NSW 2067, Australia.
url: www.genflex.com.au

Inovail, Hong Kong. See *Pharmalink, Hong Kong.*

Inovail, Malaysia. See *Zuellig, Malaysia.*

Inovail, Philipp. See *Invida, Philipp.*

Inovail, Singapore. See *Zuellig, Singapore.*

Inovail, Thai. See *Zuellig, Thai.*

Inpa, Gr. INPA S.A., 154 Kifisias Str., 151 26 Athens, Greece.
url: www.inpa-gr.com

Inpac, Thai. Inpac Pharma Co Ltd, 79/4 M4 Soi Anamai Nagamcharoen Rama 2, Thakham, Bangbon, Bangkok, Thailand.

Inpharma, Denm. See *Inpharma, Norw.*

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Inpharma, Norw. Inpharma AS, Storg. 75, Postboks 300, 3301 Hokksund, Norway.

Inpharzam, Hong Kong. See *Universal, Hong Kong.*

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Inquifave, Venez. Inquifave S.A., Qta. La Trinidad, AvRoosevelt Los Castacos, Urb. El Cementerio, Caracas, Venezuela.

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Inresa, Ger. Inresa Arzneimittel GmbH, Obere Hardtstr. 18, 79114 Freiburg, Germany.
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Insight, Cz. See *Insight, Ger.*

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Insight, Ger. Insight Agents GmbH, Ringstrasse 19 B, 69115 Heidelberg, Germany.
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Insight, Irl. See *Insight, Ger.*

Insight, Neth. See *Insight, Ger.*

Insight, Port. See *Insight, Ger.*

Insight, USA. Insight Pharmaceuticals Corp., 1170 Wheeler Way, Suite 150, Langhorne, PA 19047-1749, USA.

Inspire, USA. Inspire Pharmaceuticals Inc., 4222 Emperor Bvld, Suite 200, Durham, NC 27703, USA.
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Instantron, Canad. See *Instantron, USA.*

Instantron, USA. INstantron Co., 3712 Pawtucket Ave, Riverside, Rhode Island, 02915, USA.

Institute for Molecular Genetics, Rus. See *Pik, Rus.*

Institute of Immunology, Philipp. See *Global, Philipp.*

Institute of Medicine, Rus. Institute of Medicine Pharmaceutical Works Ltd, Efremov, Russia.

Institute of New Medical Technology, Rus. Institute of New Medical Technology Co, Pushkina ul. 21, G Krasnokamsk, 617067 Permskaya Obl., Russia.

Instituto Tecnologico PET, Port. See *Complutense, Spain.*

Instrumed, Canad. Instrumed Surgical, Unit 1, 2255 Dunwin Drive, Mississauga, Ontario, L5L 1A3, Canada.

Insys, USA. Insys Therapeutics Inc., 10220 South 51st St, Suite 2, Phoenix, AZ 85044, USA.
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Intact, Malaysia. Intact Pharma, B 3A 07 Dataran 32, No 2 Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.hoepharma.com.my

Intag, India. Intag Remedies (P) Ltd, Jumbeshwar, Mukum, 334 802, India.

Intas, India. Intas Pharmaceuticals Ltd, Chinubhai Center, Off Nehru Bridge, Ashram Rd, Ahmedabad 380 009, India.
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Intas, Philipp. See *Pharmawealth, Philipp.*

Intas, Singapore. See *Apotheca, Singapore.*

Intas, Thai. See *Union Medical, Thai.*

Intas, Ukr. See *Maxpharma, Ukr.*

Intasol, Rus. Intasol, Russia.

Integra, Philipp. Integra Pharma Inc., Unit 3001-88 Corporate Ctr, cor Sedeño & Valero Sts, Salcedo Vill, Makati City, Philippines.

Integral Health, Mex. Integral Health Services SA de CV, Matanzas 639, 7300 Lindavista, Mexico DF, Mexico.

Integrated Pharmaceutical, Philipp. Integrated Pharmaceutical Inc., 416 Dasmariñas St, Binondo, Manila, Philippines.

Integrative, USA. Integrative Therapeutics Inc., 825 Challenger Drive, Green Bay, WI 54311, USA.
url: www.integrativeinc.com

Integria, Austral. Integria Healthcare, Level 1, Clunies Ross Court, Eight Mile Plains, QLD 4113, Australia.
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Integris, Gr. Integris Pharma Ltd, Nikitara 2, 152 32 Halandri, Greece.

Integrity, USA. See *Xanodyne, USA.*

Intekar, Rus. Intekar Npf, ul. Gamalei 18, 123098 Moscow, Russia.
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Intel, India. Intel Pharmaceuticals, Nohan Rd, Vill. Moginand, Kala-Amb, Sirmour, India.

Inteli, Ukr. Inteli Generics Nord, Ukraine.

Intelligent Therapeutics, UK. Intelligent Therapeutics Ltd, Albany Rd, Gateshead, NE8 3AT, UK.
url: www.intelligenttherapeutics.co.uk

Intelpharm, Rus. Intelpharm Corp., Kostina St 4, 603000 Lower Novgorod, Russia.
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Intendis, Cz. See *Intendis, Ger.*

Intendis, Denm. See *Bayer, Denm.*

Intendis, Fin. See *Intendis, Ger.*

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Intendis, Ger. Intendis Dermatologie GmbH, Max-Dohrn-Str. 10, 10589 Berlin, Germany.
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Intendis, Gr. See *Bayer, Gr.*

Intendis, Hong Kong. See *Pharmalink, Hong Kong* and *Zuellig, Hong Kong.*

Intendis, Hung. See *Bayer Schering, Hung.*

Intendis, Irl. See *Bayer, Irl.*

Intendis, Israel. See *Bayer, Israel.*

Intendis, Ital. Intendis S.p.A., Via E Schering 21, 20090 Segrate (MI), Italy.
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Intendis, Malaysia. See *Zuellig, Malaysia.*

Intendis, Mex. Intendis Mexicana SA de CV, Calzada Mexico Xochimilco 5019, 14370 Huipulco del Tlalpan San Lorenzo, Mexico DF, Mexico.

Intendis, Neth. See *Intendis, Ger.*

Intendis, Norw. See *Schering, Norw.*

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Intendis, Rus. See *Intendis, Ger.*

Intendis, Singapore. See *Zuellig, Singapore.*

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Intendis, Thai. See *Zuellig, Thai.*

Intendis, Turk. İntendis İlaç, Turkey.

Intendis, Ukr. See *Schering, Ukr.*

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Interbat, Hong Kong. See *HealthCare PharmaScience, Hong Kong.*

Interbat, Indon. Interbat PT, Jl Mampang, Prapatan Raya No 81, Jakarta 12790, Indonesia.

Interbat, Philipp. See *Interlink, Philipp.*

Interbelle, Arg. Interbelle Cosmetic S.A., Sanabria 2353 Piso 1, 1417 Buenos Aires, Argentina.

Interbial, Port. See *Bial, Port.*

Intercare, Irl. See *Intercare, UK.*

Intercare, NZ. InterCare Corp. Ltd, P.O. Box 18446, Glen Innes, Auckland, New Zealand.

Intercare, UK. The Intercare Group, Windsor House, Cornwall Road, Harrogate, North Yorkshire, HG1 2PW, UK.
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Intercell, Austria. Intercell AG, Campus Vienna Biocenter 3, 1030 Vienna, Austria.

Intercell, Norw. See *Crucell, Swed.*

Interchem, Ukr. Interchem, Lustdorfskaya St 86, 65080 Odessa, Ukraine.
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Interchemex, Philipp. Interchemex Laboratories Inc., 900 Palace St, BF Int'l, Las Piñas City, Philippines.
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Interchemia, Cz. Interchemia Praha sro, Šafáříková 3/456, 120 00 Prague 2, Czech Republic.

Interdelta, Switz. Interdelta SA, Case postale 791, 1701 Fribourg, Switzerland.

Interfarma, Ukr. Interfarma, Industry St 3G, Kiev, Ukraine.

Interferon Sciences, USA. See *HemispheRx, USA.*

Interhealth, Hung. Interhealth Kft, Homokbánya köz 13, 2049 Diósd, Hungary.
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Interhealthcare, Philipp. INTERHEALTHcare Pharmaceuticals Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.

Interhim, Rus. See *Interchem, Ukr.*

Interko, Turk. Interko, Turkey.

Interlabo, Switz. Interlabo SA, Case postale 8, 42/44 rue Prevost-Martin, 1211 Geneva 9, Switzerland.

Interlink, Philipp. Interlink Pharma Mktg Corp., Unit G-52 South Star Plaza, South Superhighway, Bangkal, Makati City, Philippines.

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Intermed, Gr. See *Unipharma, Gr.*

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Intermedica, Switz. Intermedica SA, Pharmazeutische Produkte, Boulevard de Peralles 17, Case postale 238, 1701 Fribourg, Switzerland.

Intermune, Denm. See *Intermune, Swed.*

Intermune, Ger. InterMune Deutschland GmbH, Rosenstr. 2, 10178 Berlin, Germany.
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Intermune, Norw. See *Intermune, Swed.*

Intermune, Singapore. Intermune, Singapore.

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International Ethical, USA. International Ethical Labs, 1021 Americo Miranda Ave., Reparto Metropolitano, Rio Piedras, PR 00921, Puerto Rico.
url: www.intetlab.com

International Lab Tech, USA. International Laboratory Technology Corp, 3389 Sheridan St, Suite 149, Hollywood, FL 33021, USA.

International Laboratories, UK. See *SSL, UK.*

International Medical, Hong Kong. The International Medical Co. Ltd, Unit 715, 7/F, Block B, Seaview Estate, 2-8 Watson Rd, North Point, Hong Kong.
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International Pharmaceutical, USA. See *Sanofi-Aventis, USA.*

International Pharmaceuticals, Thai. International Pharmaceuticals Ltd, 38/2 Sukhumvit 63 (Soi Ekamai), Kwaeng Prakanong Nua, Khet Wattana, Bangkok 10110, Thailand.

Interneuron, USA. See *Indevus, USA.*

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Interpharm, Austria. Interpharm GmbH, Effingergasse 21, A-1160 Vienna, Austria.
url: www.interpharm.at

Interpharma, Chile. Interpharma SA, Camino a Melipilla 6873, Cerrillos, Santiago, Chile.

Interpharma, Hung. Interpharma Kft, Huba u.10, 1134 Budapest, Hungary.
url: www.interpharma.hu

Interpharma, Spain. Interpharma, Santa Rosa 6, Santa Coloma de Gramanet, 08921 Barcelona, Spain.
url: www.interpharma.es

Interpharmbiotek, Ukr. Interpharmbiotek Ltd, ul. Zabolotny 150, 03680 Kiev, Ukraine.
url: www.interpharmbiotek.com

Interphil, Hong Kong. See *US Summit, Hong Kong.*

Intersan, Ger. Intersan, Institut für pharmazeutische und klinische Forschung GmbH, Einsteinstr. 30, 76275 Ettlingen, Germany.

Intersan, Irl. See *Intersan, Ger.*

Intersan, Switz. See *Uhlmann-Eyraud, Switz.*

Intersect ENT, USA. Intersect ENT, 1555 Adams Drive, Menlo Park, CA 94025, USA.
url: www.intersectent.com

Intersound, Hung. Intersound Kft, Kuruclesi ut 41, 1021 Budapest, Hungary.
url: www.husk.hu

Intersyn, Switz. See *Medinova, Switz.*

InterVax, Hong Kong. See *DKSH, Hong Kong.*

INTES, Ital. See *Alfa Intes, Ital.*

Inthera, Hung. Inthera Kft, Háros u 103, 1222 Budapest, Hungary.

Intra, Venez. Laboratorios Intra S.A., Av. Principal 50-75, Barrio Los Estanques Maracaibo, Zulia, Venezuela.

Intra Pharma, Irl. See *United Drug, Irl.*

Intra-Labs, India. Intra-Labs Pvt Ltd, 43/44 P.S. Lane, B.R.D. Building, Chickpet Cross, Bangalore 560 053, India.
url: www.intralabsindia.com

Intramed, Gr. Intramed, Sardeon 2, 172 37 Ymittos, Greece.

Intramed, S.Afr. Intramed (Pty) Ltd, 6 Gibaud Rd, Port Elizabeth 6001, South Africa.

Intrapharm, Irl. See *United Drug, Irl.*

Intrapharm, UK. Intrapharm Laboratories Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QS, UK.
url: www.intrapharmlabs.com

Intraveno, Irl. See *United Drug, Irl.*

Intsel, Fr. Laboratoires Intsel Chimos, Technopolis, 145 rue J.-J. Rousseau, 92138 Issy-les-Moulineaux cdx, France.
url: www.intselchimos.com

Invado, USA. Invado Pharmaceuticals, Pomona, NY, USA.
url: www.neutrasal.com

Invamed, USA. See *Novartis, USA.*

Invar, Rus. Invar OOO, 53a Strelkovoi Divizii ul. 6/9, 410710 Saratov, Russia.
url: www.invar.ru

Invent, Port. See *Invent, Spain.*

Invent, Singapore. See *MD, Singapore.*

Invent, Spain. Invent Farma SL, Av. Barcelona 69, 08970 Sant Joan Despi, Barcelona, Spain.

Inventia, Philipp. See *IE Medica, Philipp.*

Inventia, Ukr. See *Themis Medicare, India.*

Inverdia, Swed. Inverdia AB, Vretenvägen 8, 171 54 Solna, Sweden.
url: www.inverdia.com

Inverness, USA. Inverness Medical Innovations Inc., 51 Sawyer Rd, Suite 200, Waltham, MA 02453-3448, USA.
url: www.invernessmedical.com

Inverni della Beffa, Ital. See *Sanofi-Aventis, Ital.*

Invest Impex, Israel. Invest Impex Ltd, P.O. Box 86, Azur 58001, Israel.

Investi, Arg. Investi Farma S.A., Lisandro de la Torre 2160, 1440 Buenos Aires, Argentina.

Investigacion, Mex. Investigación Farmacéutica (IFA) S.A. de C.V, Calle 13-E No. 5 CIVAC, 62500 Jiutepec Morelos, Mexico.
url: www.ifa.com.mx

Investigaciones Filosoficas y Cientificas, Mex. Investigaciones Filosoficas y Cientificas S.A. de C.V., Tlacote No. 128, 76230 Juriquilla, Queretaro, Mexico.

Invicta, Irl. See *Pfizer, Irl.*

Invicta, Spain. See *Pfizer, Spain.*

Invicta, UK. See *Pfizer, UK.*

Invida, Austral. Invida, Level 8, 67 Albert Ave, Chatswood, NSW 2067, Australia.
url: www.invida.com.au

Invida, Hong Kong. Invida (Hong Kong) Ltd, Rm 1101, 11/F, 625 Kings Rd, North Point, Hong Kong.
url: www.invida.com

Invida, Philipp. Invida Philippines Inc., 25/F Phil AXA Life Centre, 1286 Sen G Puyat Ave, cor Tindalo St, Makati City, Philippines.
url: www.invida.com

Invida, Singapore. Invida (Singapore) Pte Ltd, 79 Science Park Drive, 05-01 Cintech IV, Singapore Science Park 1, 118264, Singapore.
url: www.invida.com

Invida, Thai. Invida (Thailand) Ltd, 6 Fl Ploenchit Center, 2 Sukhumvit Rd, Kwaeng Klongtoey, Khet Klongtoey, Bangkok 10110, Thailand.
url: www.invida.com

Invision, India. Invision Medi Sciences, 251 1st Floor Bhagyalakshmi Complex, IInd Cross, III rd Main Road, Chamarajpet, Bangalore 560 018, India.
url: www.invisionmedi.com

Inwood, USA. See *Forest Laboratories, USA.*

Inyendis, Hong Kong. See *Pharmalink, Hong Kong.*

Iocom, UK. Iocom (UK) Ltd, Hope Mill, Skipton Rd, Barnoldswick, Lancashire, BB18 6EN, UK.

Iodine Technologies, Rus. Iodine Technologies, Russia.

Iodosan, Ital. See *GSK Consumer, Ital.*

Iolab, Israel. See *Concept, Israel.*

Iolab, Norw. See *Janssen-Cilag, Norw.*

Iolab, USA. See *Novartis Ophthalmics, USA.*

Ioltech, Fr. Laboratoires Ioltech, av. Paul-Langevin, B.P. 5, 17053 La Rochelle cdx 9, France.
url: www.ioltech.com

Ioltech, Ger. See *Zeiss Meditec, Ger.*

Ioltech, Ital. Ioltech Italia Srl, Via Disciplini 3, 20123 Arese (MI), Italy.

Ioltech, Port. See *Ioltech, Fr.*

Iomed, Hong Kong. See *Pan-Well, Hong Kong.*

Iomed, USA. See *Iopharm, USA.*

Ion, USA. Ion Laboratories Inc., 7431 Pebble Drive, Fort Worth, TX 76118, USA.

Ionfarma, Spain. Ionfarma SLU, Perú 228, 08020 Barcelona, Spain.

Ionion, Gr. IONIAN Pharma Ltd, 15-17 Sarantapichou, 114 71 Athens, Greece.
url: www.biotest.com

Ionios (Ιονιος), Gr. See *Ionion, Gr.*

Iopharm, USA. Iopharm, 7509 Flagstone St., Ft Worth, TX 76118, USA.

Ioquin, Austral. See *Alcon, Austral.*

IP, Ital. IP Farma Sas, Via Vigna 6, 80078 Pozzuoli (NA), Italy.

IPA, Ger. Inter Pharm Arzneimittel (IPA) GmbH, Kurt-Schumacher-Str.6, 44534 Lünen, Germany.
url: www.interpharm-arzneimittel.de

Ipca, India. IPCA Laboratories Ltd, 63-E Ipca House, Kandivali Industrial Estate, Charcop, Kandivali (West), Mumbai 400 067, India.

Ipca, Malaysia. See *Zyfas, Malaysia.*

Ipca, NZ. Ipca Pharma (NZ) Pty Ltd, 3-A St Oswalds Rd, Greenlane, Auckland 1061, New Zealand.

Ipca, Port. IPCA Produtos Farmacêuticos Unipessoal Lda, Rua Chanceler Mor 11 R/C Frt, Sala C, Cacém, Sintra, Portugal.

Ipca, Rus. Ipca Laboratories Ltd, Oboucheva ul. 4, korp. 3, of. 159-160, 119421 Moscow, Russia.
url: www.ipcalabs.com

Ipca, Singapore. See *Zyfas, Singapore.*

Ipca, Thai. See *Pacific, Thai.*

Ipca, Ukr. Ipca Laboratories Limited, Patrisa Lumumby Street, 4/6B, Office 1106, 01042 Kiev, Ukraine.
url: www.ipcalabs.com

Ipex, Austria. See *Ipex, Swed.*

Ipex, Denm. See *Ipex, Swed.*

Ipex, Fin. See *Tamro, Fin.*

Ipex, Ger. See *Ipex, Swed.*

Ipex, Norw. See *Ipex, Swed.*

Ipex, Swed. Ipex Medical AB, Box 120, 182 12 Danderyd, Sweden.
url: www.ipex.se

Iphym, Fr. Laboratoires Iphym, chemin de la Sereine, 01700 Beynost, France.
url: www.iphym.com

IPI, Indon. See *Tempo Scan Pacific, Indon.*

IPR, Rus. See *AstraZeneca, Rus.*

IPRAD, Fr. Laboratoires IPRAD, 42-52 rue de l'Aqueduc, 75010 Paris, France.

IPRAD, Philipp. See *Chiral, Philipp.*

IPRAD-Sante, Fr. IPRAD-Santé, 221 rue Lafayette, 75010 Paris, France.

IPS, Neth. IPS, Beeldschermweg 6b, 3821 AH Amersfoort, Netherlands.

IPS, Spain. iPS Farmo, Sagasta 21, 28004 Madrid, Spain.
url: www.ipsfarma.es

Ipsen, Austral. Ipsen Pty Ltd, Suite 42, Waverley Business Centre, 21 Aristoc Rd, Glen Waverley, VIC 3150, Australia.
url: www.beaufour-ipsen.com

Ipsen, Austria. See *Ipsen, Ger.*

Ipsen, Belg. Ipsen NV, Guldensporenpark 87, 9820 Merelbeke, Belgium.
url: www.ipsen.com

Ipsen, Cz. See *Beaufour, Fr.*

Ipsen, Denm. See *Ipsen, Swed.*

Ipsen, Fin. See *Ipsen, Swed.*

Ipsen, Fr. See *Beaufour, Fr.*

Ipsen, Ger. Ipsen Pharma GmbH, Einsteinstr. 30, 76275 Ettlingen, Germany.
url: www.ipsen-pharmo.de

Ipsen, Gr. Ipsen EpE, 63 AG. Dimitriou St., 174 56 Alimos, Greece.
url: www.ipsen.com

Ipsen, Hong Kong. See *IDS, Hong Kong.*

Ipsen, Hung. Ispen Pharma SAS, Árbóc u 6, 1133 Budapest, Hungary.
url: www.ipsen.com

Ipsen, Irl. Ipsen Pharmaceuticals Ltd, 7 Upper Leeson St, Dublin 4, Ireland.
url: www.ipsen.ie

Ipsen, Israel. See *Medison, Israel.*

Ipsen, Ital. Ipsen S.p.A., Via A Figino 16, 20156 Milan (MI), Italy.
url: www.beaufour-ipsen.com

Ipsen, Neth. Ipsen Farmaceutica BV, Taurusavenue 33b, 2132 LS Hoofddorp, Netherlands.

Ipsen, Norw. See *Ipsen, Swed.*

Ipsen, NZ. See *NZ Medical & Scientific, NZ.*

Ipsen, Philipp. Ipsen Biopharma, Rm 2404, 24/F One San Miguel Bldg, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.

Ipsen, Pol. Ipsen Poland Sp. zo.o., al. Jana Pawła II 29, 00-867 Warsaw, Poland.
url: www.ipsen.com

Ipsen, Port. Ipsen Portugal, SA, Alameda Fernão Lopes 16-11, Miraflores, 1495-190 Algés, Portugal.
url: www.beaufour-ipsen.com

Ipsen, Rus. Ipsen, Taganskaya St 19, 109147 Moscow, Russia.

Ipsen, Spain. Ipsen Pharma, Ctra Laurea Miro 395, Sant Feliu de Llobregat, 08980 Barcelona, Spain.
url: www.ipsen.com

Ipsen, Swed. Ipsen Produits Synthèse (IPSEN) AB, Kista Science Tower, Färögatan 33, 164 51 Kista, Sweden.
url: www.ipsen.com

Ipsen, Switz. See *Globopharm, Switz.*

Ipsen, Thai. See *Pacific, Thai.*

Ipsen, UK. Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK.
url: www.ipsen.co.uk

Ipsen, Ukr. See *Mitek, Ukr.*

Ipsen, USA. Ipsen Inc., 27 Maple St., Milford, MA 01757-3650, USA.
url: www.ipsen.com

Ipsen Biotech, Fr. See *Beaufour, Fr.*

Ipso, Ital. Ipso-Pharma S.r.l., Via San Rocco 6, 85033 Episcopia (PZ), Italy.

IQB, Braz. Instituto de Química e Biologia S.A., Rua A 20, 24140-210 Niteroi, RJ, Brazil.
url: www.iqb.com.br

IQFA, Mex. Industrias Químico Farmaceuticas Americanas S.A. de C.V., Lago Peypus No. 215, Col. Anohuac, Deleg. Miguel Hidalga, 11320 Mexico D.F., Mexico.

Iqfasa, Mex. See *IQFA, Mex.*

Iquinosa, Spain. See *Faes, Spain.*

IRBI, Ital. See *Wyeth Lederle, Ital.*

Irisfarma, Spain. See *Lilly, Spain.*

Irmed, Ital. Istituto Ricerche Mediche S.r.l., Via della Consortia 17, 37127 Avesa (VR), Italy.
url: www.irmed.it

Iroko, Austria. See *Iroko, UK.*

Iroko, Belg. See *Iroko, UK.*

Iroko, Canad. See *Iroko, USA.*

Iroko, Ger. See *Iroko, UK.*

Iroko, Hung. See *Iroko, UK.*

Iroko, Irl. See *Iroko, UK.*

Iroko, Neth. See *Iroko, UK.*

Iroko, Norw. See *Orion, Norw.*

Iroko, Port. See *Iroko, UK.*

Iroko, Spain. See *Iroko, UK.*

Iroko, UK. Iroko Products Ltd, 1 Silk St, London, EC2 8HQ, UK.

Iroko, USA. Iroko International LP, Suite 400, One Crescent Drive, Philadelphia, Pennsylvania, 19112, USA.

Irom, Jpn. Irom Pharmaceutical Co. Ltd, 1-2-2 Osaki, Shinagawa-ku, Tokyo 141-0032, Japan.

Iromedica, Rus. See *Santa, Rus.*

Iromedica, Switz. Iromedica AG, Haggenstrasse 45, 9014 St Gallen, Switzerland.
url: www.iromedica.ch

IS Pharma, Fin. See *Sinclair, UK.*

IS Pharma, Irl. See *Sinclair, UK.*

IS Pharma, Neth. See *Sinclair, UK.*

IS Pharma, Norw. See *Sinclair, UK.*

IS Pharma, UK. See *Sinclair, UK.*

IS Pharmaceutical, Denm. See *Hospira, Swed.*

ISA, Arg. Instituto Seroterapico Argentino S.A.I.C., Av. Larrazabal 1848, 1440 Buenos Aires, Argentina.
url: www.isalaboratorios.com.ar

Iscotec, Neth. See *Iscotec, Swed.*

Iscotec, Swed. Iscotec AB, Uppsala Science Park, Dag Hammarskjolds vag 32A, S-751 83 Uppsala, Sweden.

Isdin, Arg. Isdin Argentina SA, Cucha Cucha 2647, Buenos Aires, Argentina.

Isdin, Braz. Isdin Produtos Farmaceuticos Ltda, Rua do Rocio 84, 4552000 Sao Paulo Vila Olimpia, Sao Paulo, Brazil.

Isdin, Chile. Isdin Chile Ltda, Carmencita 25 Of. 82, Las Condes, Santiago, Chile.

Isdin, Port. Isdin Lda, Rua da Ilha dos Amores, Lote 4.08.01.X, Parque das Nações - Zona Norte, Santa Maria dos Olivais, 1990-118 Lisbon, Portugal.

Isdin, Spain. Isdin, Av. Diagonal 520, 08006 Barcelona, Spain.
url: www.isdin.es

Isei, Jpn. Isei Inc., 45-13 Wakabamachi, Yamagata, 990-2495, Japan.

ISI, Arg. See *Scott-Cassaro, Arg.*

ISI, Cz. See *Kedrion, Ital.*

ISI, Ital. See *Kedrion, Ital.*

Isis, Cz. See *Actavis, Ger.*

Isis, Ger. See *Actavis, Ger.*

Isis, Rus. See *Schwarz, Rus.*

Isis Puren, Ger. See *Actavis, Ger.*

Island, Pol. Island Przedsiębiorstwo Handlowe Eksport-Import, ul. Chwarznieńska 192 C, 81-602 Gdynia, Poland.

Iso, Ger. Iso-Arzneimittel GmbH & Co. KG, Bunsenstr. 6-10, 76258 Ettlingen, Germany.
url: www.iso-arznei.de

Isocell, Fr. Laboratoires Isocell, 53 bd Général-Martial-Valin, 75015 Paris, France.
url: www.glisodine.fr

Isodisnatura, Fr. Isodisnatura, 8 rue Christophe-Colomb, 75008 Paris, France.
url: www.isodisnatura.fr

Isomed, Port. See *Isomed, Spain.*

Isomed, Spain. Isomed, Alberto Alcocer 46 Bajo B, 28016 Madrid, Spain.
url: www.isomed.com

Isopharm, Hong Kong. See *CNW, Hong Kong.*

Isotope Institute, Hung. Isotope Institute Kft, Konkoly Thege M u 29-33, 1121 Budapest, Hungary.

Israмedcom, Israel. Israмedcom Ltd, 1 Ha'omanut St, Poleg Industrial Park, Netanya 42504, Israel.

Isse, Turk. İsse International Ltd, Hafta Sokak No 20, 06700 G.O.P., Ankara, Turkey.

Ist. Chim. Inter., Ital. Istituto Chimico Internazionale Dr. Giuseppe Rende S.r.l., Via Salaria 1240, 00138 Rome (RM), Italy.

Ista, USA. Ista Pharmaceuticals, 15295 Alton Parkway, Irvine, CA 92618, USA.
url: www.istavision.com

Istanbul, Turk. İstanbul İlaç San. ve Tic. A.Ş., Okmeydoni Mahmut Şevket Paşa Mah., Mithat Paşa Cad. Keser Sok. No: 1/3, Şişli, İstanbul, Turkey.
url: www.ii.com.tr

Istar, NZ. Istar Ltd, 8 Braithwaite St, Karori, Wellington, New Zealand.

Isu Abxis, Thai. See *Hua, Thai.*

ITA, Ital. Istituto Terapeutico Ambrosiano S.r.l., Italy.

Itaca, Braz. Itaca Laboratórios Ltda, Rua das Oficinas 182, Engenho de Dentro, 20770-010 Rio de Janeiro, RJ, Brazil.
url: www.itacalab.com.br

Italchimici, Cz. See *Italchimici, Ital.*

Italchimici, Hung. See *Italchimici, Ital.*

Italchimici, Ital. Italchimici S.p.A., Via Pontina Km 29000, No 5, 00040 Pomezia (RM), Italy.

Italchimici, Neth. See *Italchimici, Ital.*

Italchimici, Rus. See *Italchimici, Ital.*

Italfarmacia, Ital. Italfarmacia S.r.l., Via Di Tor Sapienza 30/A, 00155 Rome (RM), Italy.
url: www.italfarmacia.com

Italfarmaco, China. See *Italfarmaco, Ital.*

Italfarmaco, Cz. See *Italfarmaco, Ital.*

Italfarmaco, Gr. Italfarmaco Hellas A.E., 183 Syngrou & Saldeon, 171 21 N. Smyrni, Greece.
url: www.italfarmaco.gr

Italfarmaco, Ital. Italfarmaco S.p.A., Viale Fulvio Testi 330, 20126 Milan (MI), Italy.
url: www.italfarmaco.it

Italfarmaco, Pol. mmp351

Italfarmaco, Port. Italfarmaco Farma Produtos Farmacêuticis Lda, Rua Consiglieri Pedroso 123, Queluz de Baixo, 2745-557 Barcarena, Portugal.

Italfarmaco, Rus. Italfarmaco, ul. Gubkina 14 kv 16, 117312 Moscow, Russia.
url: www.italfarmaco.it

Italfarmaco, Spain. Italfarmaco, San Rafael 3, Alcobendas, 28100 Madrid, Spain.
url: www.itfsp.com

Italfarmaco, Ukr. See *Dileo, Ukr.*

Italmex, Mex. Italmex S.A., Calz. de Tlalpan Num. 3218, Col. Ejido Santa Ursula Coapa, Deleg. Coyoacan, 04910 Mexico D.F., Mexico.
url: www.italmex.com.mx

Italzama, Ital. Italzama Srl, Via della Mendola 156, 00135 Rome (RM), Italy.

ITBS, Hong Kong. See *Universal, Hong Kong.*

Item, Denm. See *Kemifarma, Denm.*

ITF, Chile. Lab. ITF Farma Chile SA, Encomenderos 161, Of. 3 B, Las Condes, Santiago, Chile.

ITF, Gr. See *Italfarmaco, Gr.*

ITF, Hung. ITF Pharma Kereskedelmi és Szolgáltató Kft, Duna u 1, 1056 Budapest, Hungary.

ITF, Neth. See *ITF, Hung.*

ITF, Pol. See *ITF, Hung.*

ITF, Port. ITF Farma Lda, Rua Consiglieri Pedroso no 123, Queluz de Baixo, 2745-557 Barcarena, Portugal.
url: www.italfarmaco.it

ITP, Spain. Instituto Tecnologico PET SA, Manuel Bartolomé Cossio 10, 28040 Madrid, Spain.
url: www.petmadrid.com

Ivamed, Ger. See *AstraZeneca, Ger.*

Ivanovo Blood Transfusion, Rus. Ivanovo Regional Blood Transfusion Station, Russia.

Ivax, Arg. Ivax Argentina SA, JJ Castelli 6701, 1605 Munro, Buenos Aires, Argentina.

Ivax, Canad. See *Ivax, USA.*

Ivax, Cz. Ivax-CR as, Pod Habrovou 3, 152 00 Prague 5, Czech Republic.
url: www.ivax.cz

Ivax, Denm. See *Sanofi-Aventis, Denm.*

Ivax, Fr. Ivax SAS, 15 rue del'Hôtel, 92522 Neuilly-sur-Seine, France.
url: www.ivax.com

Ivax, Ger. Ivax Pharma GmbH, Waldecker Str. 11, 64546 Mörfelden-Walldorf, Germany.
url: www.teva-deutschland.de

Ivax, Hong Kong. See *Hong Kong Medical, Hong Kong* and *International Medical, Hong Kong.*

Ivax, Hung. Ivax-CR a s Közvetlen Kereskedelmi Képviselet, Berlini út 47-49, 1045 Budapest, Hungary.

Ivax, Irl. IVAX Ireland, Unit 301, Waterford Industrial Estate, Waterford, Ireland.
url: www.ivax.co.uk

Ivax, Malaysia. See *Averroes, Malaysia.*

Ivax, Mex. Ivax Pharmaceuticals Mexico S.A. de C.V., Calz de Hueso 859, Ex-Hacienda Coapa, 14100 Mexico D.F., Mexico.
url: www.ivax.com

Ivax, Neth. Ivax Farma bv, Tolnasingel 3, 2411 PV Bodegraven, Netherlands.

Ivax, Norw. Ivax, Postboks 688 Skøyen, 0214 Oslo, Norway.
url: www.ivax.com

Ivax, Pol. See *Teva, Pol.*

Ivax, Rus. Ivax AC, Dmitrovskii per. 9, Business-Centre Stoleshniki, et. 5, 103031 Moscow, Russia.
url: www.ivax.com

Ivax, S.Afr. Ivax, South Africa.

Ivax, Singapore. See *FP, Singapore* and *Green Cross, Singapore.*

Ivax, Swed. IVAX Scandinavia AB, Box 386, 111 73 Stockholm, Sweden.
url: www.ivax.se

Ivax, Thai. See *Berli Jucker, Thai.*

Ivax, UK. See *Teva, UK.*

Ivax, USA. Ivax Pharmaceuticals Inc., 4400 Biscayne Blvd, Miami, Fl 33137, USA.
url: www.ivaxpharmaceuticals.com

Ives, India. Ives Drugs, 504 Chetak Centre, 12/2 RNT Marg, Indore 452 001, India.

IVF, Switz. IVF Hartmann AG, 8212 Neuhausen am Rheinfall, Switzerland.

Ivoclar, NZ. Ivoclar Vivadent Ltd, 12 Omega St, Albany, Auckland, New Zealand.

Ivy Corp, USA. Ivy Corporation, P.O. Box 596, W. Caldwell, NJ 07006, USA.

IWA, Cz. See *IWA, Denm.*

IWA, Denm. IWA Consulting Aps, Ølby Center 7, 1, 4600 Køge, Denmark.

IWA, Irl. See *IWA, Denm.*

IWA, Pol. See *IWA, Denm.*

Izotop, Hung. Institute of Isotopes Co Ltd, P.O. Box 851, 1535 Budapest, Hungary.
url: www.izotop.hu

Izvarino, Rus. Izvarino Pharma, VNTSMDL str 1, Leninskii r-n D Izvarino, 142781 Moscow, Russia.
url: www.izvarino-pharma.ru

J&J, S.Afr. See *Janssen-Cilag, S.Afr.*

J&J-Merck, USA. See *Johnson & Johnson, USA* and *Merck, USA.*

J&K, China. Tianjin J&K Pharmaceutical Co., Ltd., Room 1111, Guohua Building 857, Dagunan Raoad, Tianjin, 300200, China.
url: www.jkpharma.com.cn

J. B. Chemicals & Pharmaceuticals, India. J. B. Chemicals & Pharmaceuticals Ltd, Neelam Centre, B Wing 4th floor, Hind Cycle Road Worli, Mumbai 400 030, India.
url: www.jbcpl.com

J & J DeChane, India. J & J DeChane Laboratories Pvt Ltd, 4-1-324 Troop Bazar, Residency Road, Hyderabad 500 001, India.
url: www.dechane.com

Jaapharm, Canad. Jaapharm Canada Inc., 200 Trowers Rd, Unit 1, Woodbridge, Ontario, L4L 5Z7, Canada.

Jaba, Port. Jaba Farmacêutica, SA, Rua da Tapada Grande, Abrunheira, 2711-901 Sintra, Portugal.
url: www.jaba.pt

Jaba Recordati, Port. See *Jaba, Port.*

Jacobsen, Denm. Jacobsen Pharma AS, Vemmingbund Strandvej 111, 6310 Broager, Denmark.

Jacobsen, Fin. See *Jacobsen, Denm.*

Jacobsen, Neth. See *Jacobsen, Denm.*

Jacobson, Hong Kong. Jacobson Medical (Hong Kong) Ltd, 15/F China Trade Ctr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.

Jacobus, Rus. See *Jacobus, USA.*

Jacobus, USA. Jacobus Pharmaceutical Co. Inc., 37 Cleveland Lane, P.O. Box 5290, Princeton, NJ 08540, USA.

Jacoby, Austria. Jacoby Pharmazeutika AG, Teichweg 2, A-5400 Hallein-Kaltenhausen, Austria.

Jacsim, Canad. Les Importations Jacsim Ltd, 1420 Beaulac, St-Laurent, Quebec, H4R 1R7, Canada.

Jadran, Rus. Jadran Galenski Laboratorij d.d., Lomonosovskii prospekt 38, pod. 1, of. 3, 119330 Moscow, Russia.
url: www.jadran.ru

Jadran, Ukr. See *Galenskaya, Ukr.*

Jagsonpal, India. Jagsonpal Pharmaceuticals Ltd, T-210 J, Shahpur Jat, New Dehli 110 049, India.
url: www.jagsonpal.com

Jaillon, Hong Kong. See *Great Liaison, Hong Kong.*

Jaka, Rus. See *Jaka-80, Rus.*

Jaka-80, Rus. Jaka-80, Skornyazhnyi per. 7, korp. 2, kv. 8, 107078 Moscow, Russia.
url: www.jaka80.com.mk

Jaldes, Fr. Laboratoires Jaldes, 10 ac de Poussan, B.P. 30, 34770 Gigean cdx, France.

Jamieson, Canad. Jamieson Laboratories, 4025 Rhodes Drive, Windsor, Ontario, N8W 5B5, Canada.

Jamieson, Hong Kong. See *Universal, Hong Kong.*

Jamieson, Philipp. See *One Pharma, Philipp.*

Jamp, Canad. Jamp Pharma Corp., Suite 203, 1380 Newton, Boucherville, Quebec, J4B 5H2, Canada.

Jane & Co, Canad. See *Jane & Co, USA.*

Jane & Co, USA. Jane & Co LLC, 311 9611 Pulsaki Park Drive, Baltimore, Maryland, 21220, USA.

Janpharm, S.Afr. Janpharm (Pty) Ltd, 15th Rd, Halfway House 1685, South Africa.

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Janssen, Hong Kong. Janssen Pharmaceutica, Unit 1302-1307, Tower 1, Grand Century Place, 193 Prince Edward Rd West, Mongkok, Kowloon, Hong Kong.
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Janssen, Jpn. Janssen Pharmaceutical K.K, 3-5-2 Nishi-kanda, Chiyoda-ku, Tokyo 101-0065, Japan.
url: www.janssen.co.jp

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url: www.janssen-cilag.es

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Janssen, UK. Janssen Ltd, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK.
url: www.janssen.co.uk

Janssen, USA. Janssen Pharmaceutical Inc., 1125 Trenton-Harbourton Road, Titusville, NJ 08560-0200, USA.
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Janssen-Cilag, Arg. Janssen-Cilag Farmaceutica S.A., Mendoza 1259, 1428 Buenos Aires, Argentina.
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Janssen-Cilag, Austral. Janssen-Cilag P/L, Locked Bag 2070, North Ryde, NSW 1670, Australia.
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Janssen-Cilag, Austria. Janssen-Cilag Pharma Vertrieb GmbH, Pfarrgasse 75, A-1232 Vienna, Austria.
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Janssen-Cilag, Belg. Janssen-Cilag SA, Roderveldlaan 1, 2600 Berchem, Belgium.
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Janssen-Cilag, Ger. Janssen-Cilag GmbH, Raiffeisenstr. 8, 41470 Neuss, Germany.
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Janssen-Cilag, Gr. Janssen-Cilag SA, 56 Peace Ave, Larch, 151 21 Athens, Greece.
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Janssen-Cilag, Hung. Janssen-Cilag, West Gate Business Park, 2045 Torokbalint, Hungary.
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Janssen-Cilag, India. See *Johnson & Johnson, India.*

Janssen-Cilag, Indon. Janssen-Cilag, Division of Johnson & Johnson, Indonesia Mampang Park Office, 3/F Jl Mampang Prapatan Raya No 1, Jakarta Selatan 12790, DKI Jaya, Indonesia.

Janssen-Cilag, Irl. Janssen-Cilag Ltd, Block B, Ground Floor, Liffey Valley Office Park, Quarryvale, Co. Dublin, Ireland.
url: www.janssen-cilag.com

Janssen-Cilag, Israel. Janssen Cilag, Division of J-C Health Care Ltd, Kibbutz Shefoyim 60990, Israel.
url: www.janssen-cilag.com

Janssen-Cilag, Ital. Janssen-Cilag S.p.A., Via Michelangelo Buonarroti 23, 20093 Cologno Monzese (MI), Italy.
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Janssen-Cilag, Malaysia. See *Zuellig, Malaysia.*

Janssen-Cilag, Mex. Janssen Cilag S.A. de C.V., Canoa No. 79, Col. Tizapan, Alvaro Obregon, 01090 Mexico D.F., Mexico.
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Janssen-Cilag, Norw. Janssen-Cilag AS, Drammensv. 288, 0283 Oslo, Norway.
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Janssen-Cilag, Rus. Janssen-Cilag, 17 Krylatskaya St, 121614 Moscow, Russia.
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Janssen-Cilag, Singapore. Janssen-Cilag, A Division of Johnson & Johnson Pte Ltd, 2 International Business Park, 07-01 Tower One, The Strategy, S 609930, Singapore.
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Janssen-Cilag, Thai. Janssen-Cilag Ltd, 106 Moo 4, Lad Krabang Industrial Estate, Chalongkrung Rd, Kwaeng Lamplatew, Khet Lad Krabang, Bangkok 10520, Thailand.
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Janssen-Kyowa, Jpn. See *Janssen, Jpn.*

Janssen-Ortho, Canad. Janssen-Ortho Inc., 19 Green Belt Drive, Toronto, Ontario, M3C 1L9, Canada.Medical Director
url: www.janssen-ortho.com

Japan BCG, Malaysia. See *Eisai, Malaysia.*

Japan Tobacco, Jpn. Japan Tobacco Inc., 2-2-1 Toranomon, Minato-ku, Tokyo 105-8422, Japan.
url: www.jti.co.jp

Jason, Canad. See *Jason, USA.*

Jason, USA. Jason Natural Products Inc., 8468 Warner Drive, Culver City, CA 90232-2484, USA.

Jasonpharm, Gr. See *Genzyme, Gr.*

JAV, Thai. J.A.V. Pharmar Co. Ltd, 1848 soi Jaransabitwong, 65 Jaransanitwong Rd, Bangbamru, Bangplad, Bangkok 10700, Thailand.

Javelin, UK. Javelin Pharmaceuticals, Compass House, Vision Park, Histon, Cambridge, CB4 9AD, UK.
url: www.javelinpharmaceuticals.com

Jawa, India. Jawa Pharmaceuticals (India) Pvt Ltd, 129 Udyog Vihar, Phase IV, Gurgaon 122 015, India.
url: www.jawapharma.com

Jaymac, USA. Jaymac Pharmaceuticals, 49 South Service Rd, Sunset, LA 70584, USA.

Jayson, Ukr. Jayson Pharmaceuticals Ltd, ul Lomonosova 8 B, Office 307, 03040 Kiev, Ukraine.

Jazz, USA. Jazz Pharmaceuticals Inc., 3180 Porter Drive, Palo Alto, CA 94304, USA.
url: www.jazzpharma.com

JB Chemicals, India. See *J. B. Chemicals & Pharmaceuticals, India.*

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JB Williams, USA. J. B. Williams Co. Inc., 65 Harriston Road, Glen Rock, NJ 07452-3317, USA.

JC Healthcare, Israel. See *Johnson & Johnson, Israel.*

JC Healthcare, Ital. See *Janssen-Cilag, Ital.*

JCD, Fr. Laboratoires JCD Pharmoccitan, 85 rue des Charmes, 7759 Chartrettes, France.

JDH, Hong Kong. See *IDS, Hang Kong.*

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JDH, Singapore. JDH Pharmaceutical Division, 279 Jalan Ahmad Ibrahim, 03-01, S 639938, Singapore.

JDH Borneo, Thai. JDH Borneo (Thailand) Ltd, 2160/1 Ramkhamhaeng Rd, Hua Mark, Bangkapi, Bangkok 10240, Thailand.

JE IL, Singapore. See *Pharmaforte, Singapore.*

Jean d'Estrees, Canad. See *Jean d'Estrees, Fr.*

Jean d'Estrees, Fr. Jean d'Estrees SAS, 9 rue Ampere, 75017 Paris, France.

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Jean-Marie, Hong Kong. Jean-Marie Pharmacal Co. Ltd, 1/F, GMP Ctr, 12 Dai Fu St, Tai Po Industrial Estate, Tai Po, N.T., Hong Kong.
url: www.jmp.com.hk

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Jebsen, Hong Kong. Jebsen & Co. Ltd, 12/F, Scomber Bldg, 1 Yip Fat St, Wong Chuk Hang, Hong Kong.

Jedmon, Canad. Jedmon Products Ltd, 333 Rimrock Rd, Toronto, Ontario, M3J 3J9, Canada.

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Jelfa, Pol. Przedsiębiorstwo Farmaceutyczne Jelfa SA, ul. Wincentego Pola 21, 58-500 Jelenia Góra, Poland.
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Jelfa, Rus. Pharmaceuticals Works Jelfa SA, Prospekt Mira, Dom 74, str. 1, kv. 92, 129041 Moscow, Russia.
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Jelfa, Ukr. Jelfa, Vasilkovskaya Street, 1, Black 2, Office 207, Kiev, 03040, Ukraine.
url: www.jelfa.com.ua

Jemo, Denm. Jemo-Pharm A/S, Hasselvej 1, 4780 Stege, Denmark.

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Jenapharm, Ger. Jenapharm GmbH & Co. KG, Otto-Schott-Str. 15, 07745 Jena, Germany.
url: www.jenapharm.de

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Jenburkt, India. Jenburkt Pharmaceuticals Ltd, Nirmala Apartments, 93 Jayprakash Road, Andheri (West), Mumbai 400 058, India.
url: www.jenburkt.com

Jengimiel, Venez. Jengimiel C.A., Calle Capitolio, Edificio Indelca, piso 3, local E, Baleita Sur, Caracas, Venezuela.
url: www.jengimiel.com

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Jenson, Norw. See *ACO Hud, Swed.*

Jenson, Pol. See *Mylan, Pol.*

Jenson, UK. Jenson Pharmaceuticals Services Ltd, Carradine House, 237 Regents St, London, N3 3LF, UK.

Jergens, USA. Andrew Jergens Co., 2535 Spring Grove Ave, Cincinnati, OH 45214-1773, USA.
url: www.jergens.com

Jerini, Austria. See *Shire, Ger.*

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Jerini, Ger. Jerini AG, Invalidenstrasse 130, 10115 Berlin, Germany.
url: www.jerini.com

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Jessup, UK. Jessup Marketing, 27 Old Gloucester St, London, WC1N 3XX, UK.
url: www.jessup.co.uk

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JHC Healthcare, UK. JHC Healthcare Ltd, The Maltings, Bridge St, Hitchin, Hertfordshire, SG5 2DE, UK.

JHP, USA. JHP Pharmaceuticals LLC, Morris Corporate Centre 2, One Upper Pond Rd, Building 2, 3rd Floor, Parsippany, NJ 07054, USA.
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Ji Sheng, China. Ji Sheng Pharmaceutical Factory, Nanchang, Jiangxi, China.

Jiabin, China. Jiabin Pharmaceutical Co. Ltd., 24 Jihong Street, Daoli, Harbin, Heilongjiang, 150010, China.

Jiabo, China. Jiabo Pharmaceutical Co., Ltd, 4 High-tech Industrial Development Zone, Quingyuan, Guandong, 511517, China.
url: www.jiabopharm.com

Jiachen, China. Jiachen Biological Engineering Co. Ltd, 15 Jinqiao Rd, Baqiao, Dadukou, Chongqing, 400084, China.

Jiade, China. Jiade Pharmaceutical Co. Ltd, Beijing, China.

Jiahui, China. Jiahui Pharmaceutical Co. Ltd, Xi'an, China.

Jialin, China. Jialin Pharmaceutical Co Ltd, Merrill Lynch Building 12th floor, Workers Stadium East Rd, Chaoyang District, Beijing 100027, China.
url: www.jarlin.com.cn

Jialing, China. Jialing Pharmaceutical Co. Ltd, 257 Xicheng Road, Wuxi, Jiangsu, 214041, China.

Jian Fa, China. Jian Fa Pharmaceutical Co. Ltd, Harbin, China.

Jianfeng, China. Jianfeng Dekang Pharmaceutical Co. Ltd, Hangfu Gongfu, Xihu, Hangzhou, Zhejiang, 311422, China.
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Jianglibao, China. Jianglibao Pharmaceutical Co. Ltd, Area 12 Industrial Ave, Foreign Economic Development Zone, Foshan, Guangdong, 528100, China.

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Jiangxi, China. Jiangxi Pharmaceutical Co Ltd, China.

Jiangzhong, China. Jiangzhong Pharmaceutical Co. Ltd, 788 Huoju Ave, High-Tech Zone, Nanchang, Jiangxi, 330096, China.
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Jiankun, China. Jiankun Pharmaceutical Co. Ltd, Shanghai, China.

Jianlang, China. Jianlang Pharmaceutical Co. Ltd, Yangjia Alley, Yueyanglou, Yueyang, Hunan, 414000, China.
url: www.hnjianlang.com

Jianmin, China. Jianmin Pharmaceutical Co. Ltd, Wuhan, China.

Jiante, China. Jiante Pharmaceutical Co. Ltd, Nadi Rd, Binhu, Wuxi, Jiangsu, 214091, China.

Jiashidaheng, China. Jiashidaheng Pharmaceutical Co. Ltd, Beijing, China.

Jiasite, China. Jiasite Pharmceutical Co. Ltd, Xinjiang, China.

JiCheng, China. JiCheng Pharmaceutical Co. Ltd, 494 Zhong Xing Rd, Shanghai 200071, China.

JiChuan, China. Jichuanjian Pharmaceutical Group, Pagoda Bay, Daqing Road, Taixing, Toizhou, Jiangsu, 225441, China.
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Jida, China. Jida Pharmaceutical Co. Ltd, 389 Kexin Rd, National Hi-Tech Industrial Development Zone, Kunming 650106, Yunnan, China.
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Jiekang, China. Jiekang Pharmaceutical Co. Ltd, Hangzhou, China.

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Jiheng, China. Jiheng Pharmaceutical Co. Ltd, 368 Jianshe St, Hengshui, Hebei, 053000, China.
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Jimin, China. See *Chimin, China.*

Jimin Kexin Shanhe, China. Jimin Kexin Shanhe Pharmaceutical Co. Ltd, 12 Changjiang South Rd, 214000 Wuxi, China.

Jin Lan, China. Jin Lan Pharmaceutical Co. Ltd, China.

Jin Sang Zi, China. Guangxi Golden Throat LLC, 28 Yuejin Road, Liuzhou, Guangxi, China.
url: www.goldenthroat.com

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Jin Yang, HongKong. See *Ebewe, Hong Kong.*

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Jin Yuan, China. Jin Yuan Pharmaceutical Co Ltd, China.

Jinchan, China. Jinchan Biochemical Co. Ltd, Anhui, China.

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Jindian, China. Jindian Pharmaceutical Co. Ltd, Kunming, Yunan, China.

Jinfeng, China. Jinfeng Pharmaceutical Co. Ltd, Qingdao, China.

Jing Wei, China. Jing Wei Pharmaceutical Co Ltd, Guangdong, China.

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Jinjian, China. Jinjian Pharmaceutical Co. Ltd, Deshan Avenue, Changde, Hunan, China.
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Jinma, China. Jinma Pharmaceutical Co. Ltd, 100-1 Jiangnan Road, Tonghua, Jilin, 134001, China.
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Jinshan, China. Fujian Jinshan Bio-Pharmaceutical Co., Ltd., 19th Floor Zhongfu Plaza, 92 East Street, Fuzhou, Fujian, 350001, China.

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url: www.jinshipharm.com

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JinYao, China. JinYao Amino Acid Co Ltd, China.

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Jiu An, China. Jiu An Pharmaceutical Co Ltd, China.

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Jiuyang, China. Jiuyang Pharmaceutical Co. Ltd, Jinzhou, China.

Jiuyuan, China. Jiyuan Gene Engineering Co. Ltd, 23 8th Street, Hangzhou Economic and Technological Development Zone, Hangzhou, Zhejiang, 310018, China.
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Jiuzhitang Siqi, China. Jiuzhitang Siqi Biopharmaceutical Co. Ltd, Hunan, China.

Jiwa, China. Jiwa Pharm Logistics Co. Ltd, Jun Yoo International Plaza 15F E1-2, Zhaojiabang 789, Shanghai, China.
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JL Morison, India. JL Morison (India) Ltd, 79 Crystal, Dr. Annie Besant Road, Warli, Mumbai 400 018, India.
url: www.jlmorisonindia.com

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Jodas, Rus. Jodas Expoim Pvt Ltd, Pererva St 11 Bld 25, Moscow 109651, Russia.
url: www.jodas.ru

Jodquellen, Ger. Jodquellen AG, Ludwigstr. 14, 83646 Bad Tölz, Germany.
url: www.alpamare.de

Jofrain, Mex. Establecimientos Jofrain S.A. de C.V., Calzada de Tlalpan 2621, Coyoacan Xotepingo, 04610 Mexico D.F., Mexico.
url: www.jofrain.com.mx

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Johnson & Johnson, Arg. Johnson & Johnson de Argentina S.A.C. e I., Mendoza 1259 Piso 1, 1428 Buenos Aires, Argentina.
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Johnson & Johnson, Austral. Johnson & Johnson Medical P/L, P.O. Box 134, North Ryde, NSW 2113, Australia.
url: www.jnjgateway.com

Johnson & Johnson, Braz. Johnson e Johnson Indústria e Comércio Ltda, Rua Gerivativa 207, 05501-900 São Paulo, SP, Brazil.
url: www.jnjgateway.com

Johnson & Johnson, Canad. Johnson & Johnson/Merck Consumer Pharmaceuticals of Canada, 890 Woodlawn Rd W, Guelph, Ontario, N1K 1A5, Canada.
url: www.jnjgateway.com

Johnson & Johnson, Chile. Johnson & Johnson Personal Care Chile SA, Av. Kennedy 5454 Piso 5, Vitacura, Santiago, Chile.

Johnson & Johnson, China. Johnson & Johnson Products, China.

Johnson & Johnson, Cz. Johnson & Johnson Medical, Karla Engliše 3201/6, 150 00 Praha 5, Smichov, Czech Republic.
url: www.jnjcz.cz

Johnson & Johnson, Fr. See *Ethicon, Fr.*

Johnson & Johnson, Ger. Johnson & Johnson GmbH, Johnson & Johnson Platz 2, 41470 Neuss, Germany.
url: www.jnjgermany.de

Johnson & Johnson, Gr. See *Janssen-Cilag, Gr.*

Johnson & Johnson, Hong Kong. See *Jacobson, Hong Kong.*

Johnson & Johnson, Hung. Johnson & Johnson Kft, Tó Park, West Gate Business Park, 2045 Törökbálint, Hungary.

Johnson & Johnson, India. Johnson & Johnson Ltd, 30 Forjett Street, Mumbai 400 036, India.
url: www.jnjindia.com

Johnson & Johnson, Irl. Johnson & Johnson (Ireland) Ltd, Airton Rd, Tallaght, Dublin 24, Ireland.
url: www.jnjgateway.com

Johnson & Johnson, Israel. Johnson & Johnson, Kibbutz Shefayim, Israel.
url: www.jnjgateway.com

Johnson & Johnson, Ital. Johnson & Johnson Medical S.p.A., Via del Mare 56, 00040 Pomezia (RM), Italy.
url: www.jnjgateway.com

Johnson & Johnson, Malaysia. Johnson & Johnson Sdn Bhd, Lot 3 & 5 Jln Tandang, 46050 Petaling Jaya, Selangor, Malaysia.

Johnson & Johnson, Neth. Johnson & Johnson Medical BV, Computerweg 14, Amersfoort, Netherlands.

Johnson & Johnson, Norw. See *Janssen-Cilag, Norw.*

Johnson & Johnson, NZ. Johnson & Johnson (NZ) Ltd, Ground Floor Tonkin & Taylor House, 105 Carlton Rd, Newmarket, Auckland, New Zealand.
url: www.jnjgateway.com

Johnson & Johnson, Philipp. Johnson & Johnson, Edison Rd. Barrio Ibayo 1700, Parañaque City, Philippines.

Johnson & Johnson, Port. Johnson & Johnson, Lda, Estrada Consiglieri Pedroso 69 A, Queluz de Baixo, 2745-555 Barcarena, Portugal.

Johnson & Johnson, Rus. Johnson & Johnson, Krylatskaya St 17, Building 2, 121614 Moscow, Russia.
url: www.jnjru.ru

Johnson & Johnson, S.Afr. Johnson & Johnson (Pty) Ltd, P.O. Box 273, Halfway House, Gauteng 1685, South Africa.
url: www.jnjgateway.com

Johnson & Johnson, Singapore. See *DKSH, Singapore.*

Johnson & Johnson, Spain. Johnson Johnson, Paseo de las Doce Estrellas, 5-7, 28042 Madrid, Spain.
url: www.jnjgateway.com

Johnson & Johnson, Switz. See *Uhlmann-Eyraud, Switz.*

Johnson & Johnson, Thai. Johnson & Johnson (Thailand) Co. Ltd, 106 Moo 4 Lat Krabang, Industrial Estate, Chalongkrung Rd, Lumplatew, Lat Krabang, Bangkok 10520, Thailand.
url: www.jnjgateway.com

Johnson & Johnson, Turk. Johnson & Johnson Sihhi Malzeme San. ve Tic. Ltd, Ebulula Cd N:53 1 Levent, Istanbul, Turkey.

Johnson & Johnson, UK. Johnson & Johnson Ltd, Foundation Park, Rocksborough Way, Maidenhead, Berkshire, SL6 3UG, UK.
url: www.jnjgateway.com

Johnson & Johnson, Ukr. See *Johnson & Johnson, Rus.*

Johnson & Johnson, USA. Johnson & Johnson Consumer Products Co., 199 Grandview Rd, Skillman, NJ 08558-9418, USA.
url: www.jnj.com

Johnson & Johnson, Venez. Johnson & Johnson de Venezuela S.A., Av. Rómulo Gallegos, Edif. Johnson & Johnson Piso 8, los Dos Caminos, Caracas 1070, Venezuela.
url: www.jnjgateway.com

Johnson & Johnson ASP, Ger. See *Ethicon, Ger.*

Johnson & Johnson Consumer, Belg. Johnson & Johnson Consumer, Rodeveldlaan 1, 2600 Berchem, Belgium.
url: www.jnj.com

Johnson & Johnson Consumer, Fr. See *Ethicon, Fr.*

Johnson & Johnson Consumer, Mex. Johnson & Johnson Consumo SA de CV, Paseo de los Tamarindos 100, Piso 2, 5120 Cuajimalpa Bosques de las Lomas, Mexico DF, Mexico.

Johnson & Johnson Medical, Arg. Johnson & Johnson Medical S.A., Monsecor Magliano 3061, 1642 San Isidro, Buenos Aires, Argentina.
url: www.jnj.com

Johnson & Johnson Medical, Fr. See *Ethicon, Fr.*

Johnson & Johnson Medical, UK. Johnson & Johnson Medical, Coronation Rd, Ascot, Berkshire, SL5 9EY, UK.
url: www.jnjgateway.com

Johnson & Johnson Medical, USA. Johnson & Johnson Medical Inc., 1 Johnson & Johnson Plaza, New Brunswick, NJ 08933, USA.
url: www.jnj.com

Johnson & Johnson MSD Consumer, UK. Johnson & Johnson MSD Consumer Pharmaceuticals, Enterprise House, Station Rd, Loudwater, High Wycombe, Buckinghamshire, HP10 9UF, UK. Regulatory Affairs Consultant
url: www.jnjmsd.co.uk

Johnson & Johnson WM, Ger. See *Ethicon, Ger.*

Johnson Diversey, Canad. See *Johnson Diversey, USA.*

Johnson Diversey, USA. Johnson Diversey Inc, 8310 16th Street, Sturtevant, Wisconsin, 53177-0902, USA.

Johnson Wax, Canad. See *Johnson Wax, USA.*

Johnson Wax, USA. S.C. Johnson Wax, 1525 Howe St, Racine, WI 53403-5011, USA.
url: www.scjohnsonwax.com

Joint Solutions, Canad. Joint Solutions Alliance Corp., 975 Fraser Drive, Unit 18, Burlington, Ontario, L7L 4X8, Canada.

Jolly-Jatel, Fr. Laboratoires Jolly-Jatel, 28 av. Carnot, 78100 Saint-Germain-en-Laye, France.

Jones, USA. See *King, USA.*

Jose Lea, Singapore. See *Pharmatech, Singapore.*

Jossa-Arznei, Ger. See *Hexal, Ger.*

Joyson, Singapore. Joyson Pte Ltd, 1 Upper Aljunied Link, Block A 05-06, Joo Seng Warehouse, S-367901, Singapore.
url: www.joysonpl.com

JRalph, Philipp. See *One Pharma, Philipp.*

JSJ, USA. JSJ Pharmaceuticals, 3655 Route 202, Suite 116, Doylestown, PA 18901, USA.

Jso-Werk, Ger. See *Iso, Ger.*

Ju Le, China. Ju Le Pharmaceutical Co. Ltd, Chengdu, China.

Jubilant, Belg. Jubilant Pharmaceuticals NV, Axxes Business Park, Guldensporenpark Block C nr. 22, Gelijkvloers Links, 9820 Merelbeke, Belgium.
url: www.jubl.com

Jubilant, Ital. See *Jubilant, Belg.*

Juggat, India. Juggat Pharma, 782, 15th Cross, 1st Phase, JP Nagar, Bangalore 560 078, India.
url: www.jagdale.com

Jugoremedia, Rus. See *Jaka-80, Rus.*

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Jukunda, Ger. Jukunda Naturarzneimittel Dr Ludwig Schmitt GmbH & Co. KG, Postfach: 1330, 82142 Planegg, Germany.
url: www.jukunda.de

Julphar, Malaysia. See *Averroes, Malaysia.*

Julphar, Philipp. See *DeGa, Philipp.*

Julphar, UAE. Gulf Pharmaceutical Industries, Julphar, P.O. Box 997, Ras Al Khaimah, United Arab Emirates.
url: www.julphar.com

Jumont, Philipp. Le Jumont Pharmaceuticals, Suite 502 West Trade Ctr, 132 West Ave, Quezon City, Philippines.

Junan, China. Junan Biopharmaceutical Co. Ltd, Nine Park Industrial Zone, Baodi, Tianjin, China.

Juneng, China. Juneng Pharmaceutical Co. Ltd, Block A Cyber Tower 27/F, 2 South Zhongguancun St, Haidian District, Beijing 100086, China.

Jurong, China. Jurong Pharmaceutical Co. Ltd, Jiangsu, China.

Juste, Spain. Juste, Juan Ignacio Luca de Tena, 8, 28027 Madrid, Spain.
url: www.juste.es

Justesa Imagen, Arg. Justesa Imagen Argentina S.A., Viamonte 1328 Piso 9, 1053 Buenos Aires, Argentina.

Justright, Philipp. Justright Pharmaceuticals, 2163 Menadro St, Pandacan, Manila, Philippines.

Juta, Ger. Juta Pharma GmbH, Gutenbergstr. 13, 24941 Flensburg, Germany.
url: www.jutapharma.de

Jutai, China. Jutai Pharmaceutical Co. Ltd, Zhejiang, China.

Juventis, Philipp. Juventis Pharmaceuticals Phils, Unit 6 Nasson's Bldg, 8467 West Service Rd, South Super Highway, Sun Valley, Paranaque City, Philippines.

Juventus, Spain. Juventus, Julian Camarillo 37, 28037 Madrid, Spain.

Juvise, Fr. Laboratoires Juvise, 149 Blvd Stalingrad, 69100 Villeurbanne, France.
url: www.juvisepharmaceuticals.com

Juvise, Spain. See *Juvise, Fr.*

K2 Health & Wellness, Chile. See *Recalcine, Chile.*

K2 Pharmacare, Chile. See *Recalcine, Chile.*

Kabi, Irl. See *Pfizer, Irl.*

Kabi, S.Afr. See *Adcock Ingram, S.Afr.*

Kabi, Swed. See *Pfizer, Swed.*

Kabi, Switz. See *Pfizer, Switz.*

Kabi Pharmacia, Austral. See *Pharmacia, Austral.*

Kabi Pharmacia, Austria. See *Pharmacia, Austria.*

Kabi Pharmacia, Belg. See *Pfizer, Belg.*

Kabi Pharmacia, Canad. See *Pfizer, Canad.*

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Kabi Pharmacia, Ger. See *Pfizer, Ger.*

Kabi Pharmacia, Israel. See *Promedico, Israel.*

Kabi Pharmacia, Neth. See *Pharmacia, Neth.*

Kabi Pharmacia, NZ. See *Pfizer, NZ.*

Kabi Pharmacia, USA. See *Pfizer, USA.*

Kabivitrum, Fr. See *Pharmacia, Fr.*

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KabiVitrum, UK. See *Pfizer, UK.*

Kabivitrum, USA. See *Pfizer, USA.*

Kade, Denm. See *Kade, Ger.*

Kade, Fin. See *Kade, Ger.*

Kade, Ger. Dr Kade Pharmazeutische Fabrik GmbH, Rigistr. 2, 12277 Berlin, Germany.
url: www.kade.de

Kade, Hong Kong. Kade, Hong Kong.

Kade, Hung. Dr Kade Pharma, Szirtes út 2/a, 1016 Budapest, Hungary.

Kade, Philipp. See *Metro, Philipp.*

Kade, Pol. Dr Kade, Kadefarm Sp. zo.o., ul. Bułgarska 65 a, 60-320 Poznań, Poland.
url: www.kadefarm.pl

Kade, Rus. See *Esparma, Rus.*

Kade, S.Afr. See *Sanofi-Aventis, S.Afr.*

Kade, Switz. See *Doetsch, Grether, Switz.*

Kade, Thai. See *Hua, Thai.*

Kadmon, USA. Kadmon Corp. LLC, 450 East 29th St, New York, NY 10016, USA.
url: www.kadmon.com

Kafetzis, Gr. Kafetzis, Greece.

Kai Bao, China. Kai Bao Pharmaceutical Co. Ltd, 88 Chengpu Rd, Industrial Comprehensive Development Zone, Shanghai, 201401, China.
url: www.xykb.com

Kai Cheong, Hong Kong. Kai Cheong Medical Co Ltd, Unit 1001, Tower 1, Harbour Ctr, 1 Hok Cheung St, Hunghom, Kowloon, Hong Kong.

Kai Yuen, Hong Kong. Kai Yuen Pharmaceuticals Co., 8/F Ngai Wong Commercial Bldg, 11-13 Mongkok Rd, Kowloon, Hong Kong.

Kaicheng, China. Kaicheng Pharmaceutical Co. Ltd, Harbin, China.

Kaifu, China. Kaifu Pharmaceutical Co. Ltd, Wuxi, China.

Kaikai Yuansheng, China. Kaikai Yuansheng Pharmaceutical Co. Ltd, China.

Kairuite, China. Kairuite Pharmaceutical Co. Ltd, China.

Kaixi, China. Kaixi Pharmaceutical Co. Ltd, Wuxi, China.

Kaiyuan, China. Kaiyuon Pharmaceutical Co. Ltd., 68 West Changan Avenue, Xian Science and Technology Industrial Park, Shaanxi, 710075, China.
url: www.kyzhy.com

Kaizen, India. Kaizen Pharmaceuticals, Vill. Katha, P.O. Baddi, Tehsil Nalagarh, Solan, India.

Kaken, Hong Kong. See *Hing Ah, Hong Kong.*

Kaken, Jpn. Kaken Pharmaceutical Co. Ltd, 2-28-8 Honkomagome, Bunkyo-ku, Tokyo 113-8650, Japan.
url: www.kaken.co.jp

Kaketsuken, Thai. See *Berli Jucker, Thai.*

Kalbe, Indon. Kalbe Farma PT, Kawasan Industri Delta Silicon, Jl M H Tharmin Blok A3-1, Lippo Cikarang, Bekasi 12550, Jawa Barat, Indonesia.
url: www.kalbe.co.id

Kalbe, Philipp. See *Lakeside, Philipp.*

Kalbe, Singapore. See *Apotheca, Singapore* and *Sime Darby, Singapore.*

Kali-Chemie, Ger. See *Solvay, Ger.*

Kali-Chemie, Swed. See *Meda, Swed.*

Kalifarma, Spain. See *Solvay, Spain.*

Kalisterra, Fr. Kalisterra, Batiment B, B.P. 54, 217 chemin du Grand-Revoyet, 69230 Saint-Genis Laval, France.

Kalivis, Gr. Kalivis N, Leikosias 48, 156 69 Papagou, Greece.

Kalofolias, Gr. N Kalofolias & Co, Menandrou 54, 104 31 Athens, Greece.

Kalpataru, India. Kalpataru Formulations Pvt. Ltd, 212 Ratnamani Complex, B/h. nagarsheth n o Vando, Gheekanta Road, Ahmedabad 380 001, India.

Kamada, Hong Kong. See *Gaily, Hong Kong.*

Kamada, Israel. Kamada Ltd, Kiryat Weizmann, 7 Sapir St, Ness Ziona 74140, Israel.
url: www.kamada.com

Kamada, Rus. See *Kamada, Israel.*

Kamada, Thai. See *RX, Thai.*

Kamakshi, India. Kamakshi Drugs & Pharmaceuticals, T-331-A 7th Lane, Shivaji Nagar, Narela, New Delhi 110 040, India.

Kamapharm, Israel. See *Kamada, Israel.*

Kamelia, Rus. Kamelia, Gostinichny proezd D 6 K 2, 127106 Moscow, Russia.
url: www.komleia.ru

Kameliya, Rus. Kameliya NPP OOO, Gostinichnyi prospekt d. 6, korp. 2, 127106 Moscow, Russia.
url: www.kamelia.ru

Kamins, Canad. Kamins Dermatologicals Inc/, 325 Stillview Ave, Pointe Claire, Quebec, H9R 2Y6, Canada.

Kampar, Chile. Laboratorios Kampar SA, Andres de Fuenzalida 22, Of. 1103, Providencia, Santiago, Chile.

Kampel Martian, Arg. Lab. Kampel Martian S.A., Av. del Libertador 6550, 5 piso, 1428 Buenos Aires, Argentina.
url: www.kampelmartian.com

Kampel Martian, Chile. See *Baxter, Chile.*

Kamron, India. Kamron Laboratories Ltd, 737 Rakanpur Village, Sola-Santej Road, Tal. Kalol (N.G.), Gandhinagar, India.
url: www.kamronlabs.com

Kang Dini, China. Kang Dini Pharmaceutical Co. Ltd, 202A 2nd Floor Boya International, 1 Lize Road, Chaoyang, Beijing, China.
url: www.bjcontinent.com

Kang Ji Er, China. Kang Ji Er Pharmaceutical Co Ltd, Zhejiang, China.

Kang Le, China. Kang Le Pharmaceutical Co. Ltd, Shaanxi, China.

Kang Ning, China. Kang Ning Pharmaceutical Co. Ltd, Xuzhuang Village, Linqing, Liaocheng 252600, Shandong, China.

Kang Yuan, China. Kang Yuan Pharmaceutical Co Ltd, Hunan, China.

Kangbao, China. Shanxi Kangbao Biological Products Co. Ltd, 69 Shanxi Taihang Rd, Changzhi, China.
url: www.kbzy.cn

Kangchen, China. Kangchen Pharmaceutical Co. Ltd, Beijing, China.

Kangde, China. Kangde Pharmaceutical Co. Ltd, Zhejiang, China.

Kangdini, China. Kangdini Pharmaceutical Co. Ltd, Beijing, China.

Kangerwei, China. Chongqing Kangerwei Pharmaceutical Co., Ltd., 101 Jinyu Road, Yubei, Chongqing, China.

Kanghai, China. See *Luye Sike, China.*

Kanghong, China. Kanghong Pharmaceutical Co. Ltd, 36 Jinniu Shu West, Chengdu, 610036, China.
url: www.cn-kanghong.com

Kangkeer, China. Kangkeer Pharmaceutical Co. Ltd, Chongqing, China.

Kanglaite, China. Zhejiang Konglaite Pharmaceutical Co. Ltd., 11th Street, Xiasha Economic & Technological Development Zone, Hangzhou, Zhejiang, 310018, China.
url: www.kanglaite.com

Kanglaite, Rus. Kanglaite (Elos) Ltd, Balaklovskii pr-T 2 K.2 of 4B-1, 113639 Moscow, Russia.

Kangli, China. Kangli Pharmaceutical Co. Ltd, Jiaozuo, China.

Kangliyuan, China. Kangliyuan Pharmaceutical Co. Ltd, China.

Kanglong, China. Kanglong Pharmaceutical Co. Ltd, Hainan, China.

Kangmei, China. Kangmei Pharmaceutical Co. Ltd, Guangdong, China.

Kangnaier, China. Kangnaier Pharmaceutical Co. Ltd, Jilin, China.

Kangnaike, China. Kangnaike Pharmaceutical Co. Ltd, Beijing, China.

Kangnuo, China. Kangnuo Pharmaceutical Co. Ltd, 66 South Jinming Ave, Jinming Industriol Park, Jinming, Kaifeng, Henan, 475004, China.

Kangpu, China. Kangpu Pharmaceutical Co. Ltd., Hunan, China.

Kangrui, China. Kangrui Pharmaceutical Co. Ltd, Tianjin, China.

Kangshen, China. Kangshen Pharmaceutical Co. Ltd, China.

Kangtai, China. Kangtai Pharmaceutical Co. Ltd, 338 Kangtai Road, Xingyang, Zhengzhou, Henan, 450141, China.

Kangxin, China. North China Pharmaceutical Kangxin Co. Ltd, 27th Floor NCPC Building (Grand Milea Hotel), 56 North Tiyu Street, Shijiazhuang, Hebei, 050015, China.
url: www.ncpc.com/en

Kangya, China. Kangya Pharamceutical Co. Ltd., Fu'an Alley, Jinfeng, Yinchuon, Ningxia, 750002, China.
url: www.nxkangya.com

Kangye, China. Kangye Pharmaceutical Co. Ltd, Handan, China.

Kanion, Israel. See *Chemipal, Israel.*

Kanoldt, Ger. See *Abbott, Ger.*

Kanonfarma, Rus. Kanonfarma Pradaksha ZAO, Barrikadnaya ul., 8/5 A, 123242 Moscow, Russia.
url: www.canonpharma.ru

Kansuk, Turk. Kansuk Laboratuvari San. ve. Tic. A.Ş., Beşyol Mah., Eski Londra Asfalti No:4, Sefaköy, Istanbul, 34620, Turkey.
url: www.kansuk.com

Kao, Canad. Kao Brands Canada Inc., Unit 5, 60 Courtneypark Drive West, Mississauga, Ontario, L5W 0B3, Canada.

Kapharma, Ukr. See *Alba, Ukr.*

Kapl, Malaysia. See *Averroes, Malaysia.*

Kapl, Thai. See *Kaspa, Thai.*

Kappin, UK. Kappin Ltd, Cunard Rd, Park Royal, London, NW10 6PN, UK.

Karamitsos, Gr. Dimitriou Karamitsos, Pilea 101, Thessaloniki, Greece.

Karen, China. Karen Laboratories, China.

Karicare, NZ. See *Nutricia, NZ.*

Karmed, Austria. Karmed Handelsgesmbh, Arsenal Objekt 3, Top 15, 1030 Wenen, Austria.

Karmed, Neth. See *Karmed, Austria.*

Karnataka, India. Karnataka Antibiotics & Pharmaceuticals Ltd (KAPL), Dr. Rajkumar Road, 1st Block, Rajajinagar, Bangalore 560 010, India.

Karnataka, Philipp. See *Pharmawealth, Philipp.*

Karnataka, Rus. See *Karnataka, India.*

Karousatos, Gr. Daphne A & S Co Karousatos, Pallados 2, Glifada, Greece.

Karr, Switz. Karr Dental AG, Zugerstrasse 56, 8810 Horgen, Switzerland.
url: www.karrdental.ch

Karrer, Ger. See *Spirig, Ger.*

Kart, Switz. Laboratoires Kart SA, En Budron A 16, 1052 Le Mont-sur-Lausanne, Switzerland.

Kaskad, Ukr. OOO Kaskad-Medikal, Vasilenko Street, 7, Kiev, 03680, Ukraine.
url: www.heel.com.ua

Kaspa, Thai. Kaspa Pharmaceutical (Thailand) Co Ltd, 261/452 Jaransanitwong Rd, Sai 29/1, Bangkoknoi, Bangkok 10700, Thailand.
url: www.kaspapharma.com

Katadyn, Fr. Katadyn France (Lab), 5 rue Gallice, 38100 Grenable, France.
url: www.katadyn.fr

Kato, Pol. kato Sp. zo.o., ul Marszałkowska 138/82, 00-004 Warsaw, Poland.
url: www.kato.pl

Kato, Singapore. See *JDH, Singapore.*
Katsoupas, Gr. Ch. Katsoupas (Ant. Kouskos O.E.), 48 Socratous Str., 104 31 Athens, Greece.
Kattwiga, Ger. Pharm. Fabrik Kattwiga GmbH, Zur Grenze 30, 48529 Nordhorn, Germany.
url: www.kattwiga.de
Katwijk, Neth. Katwijk Pharma BV, Archimedeseweg 2, 2333 CN Leiden, Netherlands.
Katwijk, Philipp. See *Ascende Medz, Philipp.*
Kawin, China. Kawin Technology Group Co. Ltd, Beijing, China.
Kay, Canad. Mary Kay Cosmetics Ltd, 2020 Meadowvale Blvd, Mississauga, Ontario, L5N 6Y2, Canada.
Kayaku, China. See *Wanle, China.*
Kayaku, Cz. See *Kayaku, Jpn.*
Kayaku, Hong Kong. See *Main Life, Hong Kong.*
Kayaku, Hung. See *Cziher, Hung.*
Kayaku, Indon. See *Kalbe, Indon.*
Kayaku, Jpn. Nippon Kayaku Co. Ltd, 1-11-2 Fujimi, Chiyoda-ku, Tokyo 102-8172, Japan.
url: www.nipponkayaku.co.jp
Kayaku, Malaysia. See *JDH, Malaysia.*
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Kayaku, Singapore. See *JDH, Singapore.*
Kayaku, Thai. See *Masu, Thai.*
Kaz, Canad. See *Kaz, USA.*
Kaz, USA. Kaz Inc., 4411 Route 9, Hudson, NY 12534, USA.
KB, Thai. KB Pharma, Thailand.
Ke Lun, China. Ke Lun Pharm, Heilongjiang, China.
Ke Yi, China. Ke Yi Pharmaceutical Co. Ltd, Hubei, China.
Keatings, S.Afr. See *Adcock Ingram, S.Afr.*
Kechuang, China. Kechuang Pharmaceutical Co. Ltd, 5 Wukexier Rd, Wuhou Science & Technology Garden, Chengdu, Sichuan, 610045, China.
Kedi, China. Kedi Pharmaceutical Co. Ltd, Harbin, China.
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Kedrion, Austria. Kedrion International GmbH, Kärntner Ring 5-7, Top 501, 1010 Vienna, Austria.
url: www.kedrioninternational.com
Kedrion, Denm. See *Kedrion, Ital.*
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Kedrion, Gr. See *Kedrion, Ital.*
Kedrion, Ital. Kedrion S.p.A., Località ai Conti Barga, 55020 Castelvecchio Pascoli (LU), Italy.
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Kedrion, Switz. Kedrion Swiss Sarl, Hauptgasse 29, 3280 Murten, Switzerland.
Kedrion, Thai. See *Biogenetech, Thai.*
Kedrion, USA. Kedrion Biopharma Inc., 485 Massachusetts Ave Suite 300, Cambridge, MA 02139, USA.
url: www.kedrionusa.com
Kee, India. Kee Pharma Ltd, A-1 Community Centre, Naraina Industrial Area, Phase II, New Delhi 110 028, India.
url: www.keepharma.com
Keene, USA. Keene Pharmaceuticals Inc., Keene, TX 76059-0007, USA.
Kehkashan, Ukr. See *Herbion, Ukr.*
Keimdiat, Ger. See *Grandel, Ger.*
Kela, Belg. Kela Veterinaria, Industriepark West 68, B-9100 Sint-Niklass, Belgium.
Kelemata, Ital. Kelémata S.r.l., Via S Quintino 28, 10121 Turin (TO), Italy.
Keller, Austral. Edward Keller Australia Pty Ltd, P.O. Box 888, Hallam, VIC 3803, Australia.
url: www.edwardkeller.com.au
Keller, China. Edward Keller (Shanghai) Co. Ltd, Tomson International Finance Building, 710 Dongfang Rd, Pudong, Shanghai, 200122, China.
Keller, Hong Kong. Edward Keller Ltd, 21/F Southmark, 11 Yip Hing St, Wong Chuk Hang, Hong Kong.
url: www.dksh.com
Keller, Philipp. Edward Keller (Phils) Inc., Camelray Industrial Park 1, Canlubang, Calamba, Laguna, Philippines.
Kellpharm, Irl. Kellpharm Ltd, 20A Beckett Way, Parkwest, Dublin 12, Ireland.
Kemifarma, Denm. Kemifarma Holding ApS, Jægersborg Allé 51, 2920 Charlottenlund, Denmark.
url: www.kemifarma.dk
Kemopharm, Thai. Kemopharm Thailand Co. Ltd, 138 Soi Indamara 18, Vibhavadi Rangsit Rd, Bangkok 10400, Thailand.
Kendall, Canad. See *Kendall McGaw, Canad.*
Kendall, USA. Kendall Health Care Products, 15 Hampshire St, Mansfield, MA 02048, USA.
url: www.kendallhq.com
Kendall McGaw, Canad. Kendall McGaw Canada, P.O. Box 570, 1100 Curity Ave, Peterborough, Ontario, K9J 6Z6, Canada.
Kendall McGaw, USA. See *Braun, USA.*
Kendrick, Mex. Laboratorios Kendrick, S.A. de C.V., Paseo de los Laureles No. 458-205, Col. Bosques de las Lomas, Deleg. Cuajimalpa, 05120 Mexico D.F., Mexico.
url: www.kendrick.com.mx
Kendy, Ukr. See *Rotapharm, Ukr.*
Kener, Mex. Laboratorios Kener S.A. de C.V., Sófocles 118, 11540 Miguel Hidalgo los Morales Polan, Mexico DF, Mexico.
url: www.kener.com.mx
Kenral, Austral. See *Pharmacia, Austral.*
Kenral, Canad. See *Ratiopharm, Canad.*
Kent, UK. Kent Pharmaceuticals Ltd, Wotton Rd, Ashford, Kent, TN23 6LL, UK.
url: www.kentpharm.co.uk
Kent Union, Philipp. See *Pacific Healthcare, Philipp.*
Kenwood, Hong Kong. See *International Medical, Hong Kong.*
Kenwood, USA. See *Bradley, USA.*
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Keri, Cz. See *Keri, Hung.*
Keri, Hung. Keri Pharma Kft, Bartha Boldizsár, 4032 Debrecen, Hungary.
Keri, Neth. See *Keri, Hung.*
Kern, Spain. Kern Pharma, Venus 72, Pol Ind Colon II, Terrassa, 08228 Barcelona, Spain.
url: www.kernpharma.es
Kern, Switz. E Kern AG, Pharmazeutische Krauterspezialitäten, Hauptstrasse 23, 8867 Niederumen, Switzerland.
Kernpharm, Neth. Kernpharm BV, Rooseveltlaan 6, 5466 AB Veghel, Netherlands.
Kerodex, Ital. See *Miba, Ital.*
KerrHawe, Switz. KerrHawe SA, P.O. Box 268, 6934 Bioggio, Switzerland.
url: www.kerrhawe.com
KeRui, China. KeRui Phaemaceutical Co Ltd, Chonqing, China.
Keruide, China. Keruide Pharmaceutical Co. Ltd, Sichuan, China.
Keryos, Ital. Keryos, Via della Filanda 5, 20060 Gessate (MI), Italy.
Keshav, India. Shree Krishna Keshav Labs Ltd, Devashish 3rd Floor, Ahmedabad 380 006, India.
url: www.krishnakeshav.com
Kestrel, UK. Kestrel Healthcare Ltd, Ashfield House, Resolution Rd, Ashby de la Zouch, Leiccestershire, LE65 1HW, UK.
Keton, Mex. Laboratorios Keton de Mexico S.A. de C.V., Lago Xochimilco No. 65, Col. Anahuac, Deleg. Miguel Hidalgo, 11320 Mexico D.F., Mexico.
Kettelhack Riker, Ger. See *Meda, Ger.*
Keun Wha, Philipp. See *Endure, Philipp.*
Kevelt, Rus. AS Kevelt, Russia.
url: www.kevelt.ee
Kevin, India. Kevin Pharma Pvt Ltd, Rohini, Sector-5, B-5, Plot No. 431, New Delhi, India.
Kexing, China. KeXing Biotech Co. Ltd, Shenzhen Science & Technology Industrial Park, Nanshan District, China.
Key, Austral. Key Pharmaceuticals P/L, P.O. Box 1033, North Ryde BC, NSW 1670, Australia.
url: www.keypharm.com.au
Key, Canad. See *Schering, Canad.*
Key, Chile. Key Company SA, Panamericana Norte 5369, Santiago, Chile.
Key, Hong Kong. See *Hind Wing, Hong Kong.*
Key, Israel. See *Luxembourg, Israel.*
Key, NZ. See *Key, Austral.*
Key, USA. See *Schering-Plough, USA.*
Key Oncologics, S.Afr. Key Oncologics, 171 Katherine Rd, Building 1, Sandton, South Africa.
url: www.keyoncologics.co.za
Key Sun, Austral. Key Sun Laboratories, 16 Jubilee Ave, Warriewood, NSW 2102, Australia.
url: www.keysun.com.au
Keyano, Canad. See *Keyano, USA.*
Keyano, USA. Keyano International Inc., 2392 Route 9, Mechanicville, NY 12118, USA.
Keymen, Turk. Keymen, Turkey.
Keyuan, China. Keyuan Pharmaceutical Co. Ltd, 30766 Jingshidong Rd, Jinan, Shanndong, 250103, China.
url: www.keyuanpharm.com
KG, Ital. KG Italia S.r.l., Via Volturno 10/12, 50019 Sesto Fiorentino (FI), Italy.
Khandelwal, India. Khandelwal Laboratories Ltd, 79/87 D. Lad Path, Mumbai 400 033, India.
url: www.khandelwallab.com
Khandelwal, Philipp. See *Pharmasan, Philipp.*
Khandelwal, Thai. See *Community Pharmacy, Thai.*
Kharkov, Ukr. Kharkov Pharmaceutical Ltd, ul. Shevchenko 22, 61013 Kharkov, Ukraine.
url: www.zn.kharkov.ua
KHB, China. Kehua Biopharm (KHB) Co. Ltd, Shanghai, China.
KI, Canad. KI Canada Ltd, 707 Alness St, Toronto, Ontario, M3J 2H8, Canada.
url: www.kicanada.com
Kibion, Cz. See *Kibion, Swed.*
Kibion, Denm. See *Kibion, Swed.*
Kibion, Fin. See *Kibion, Swed.*
Kibion, Ger. See *Kibion, Swed.*
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Kibion, Neth. See *Kibion, Swed.*
Kibion, Norw. See *Kibion, Swed.*
Kibion, Port. See *Kibion, Swed.*
Kibion, Swed. Kibion AB, Kungsgatan 109, 751 05 Uppsala, Sweden.
url: www.kibion.se
Kiehls, Canad. Kiehl's Canada, 4895 Hickmore, Montreal, Quebec, H4T 1K5, Canada.
Kiehls, USA. Kiehl's, New York, NY 10014, USA.
url: www.kiehls.com
Kievmedpreparat, Ukr. See *Arterium, Ukr.*
Kilab, Arg. Laboratorio Kilab SRL, Carlos M Ramirez 1544/46, 1437 Buenos Aires, Argentina.
Kimberley-Clark, USA. Kimberley-Clark Health Care, 1400 Holcomb Bridge Rd, Roswell, Georgia 30076, USA.
url: www.kchealthcare.com
Kimberly-Clark, Canad. See *Kimberly-Clark, USA.*
Kimberly-Clark, USA. Kimberly-Clark Health Care, 1400 Holcomb Bridge Rd, Roswell, GO 30076, USA.
url: www.kchealthcare.com
Kimia, Indon. Kimia Farma PT, Jl 15 Oktober No 58, Dili, Timor Timur, Indonesia.
Kimia, Philipp. See *Croma, Philipp.*
Kin, Spain. Laboratorios Kin S.A., Ciudad de Granada 123, 08018 Barcelona, Spain.
url: www.labkinonline.es
Kinder, Braz. Laboratório Kinder Ltda, Rua VPR 1 Quadra 2-A, Modulo 5 DAIA, 75133-600 Anapolis, GO, Brazil.
url: www.kinder.ind.br
Kinds, India. Kind's Pharma, Haveli At & Post Wadia, Via Samalya, Vadodara 391 520, India.
Kinesys, Canad. Kinesys Pharmaceutical Inc., 415 3771 Jacombs Rd, Richmond, British Columbia, V6V 2L9, Canada.
King, Canad. King Pharmaceuticals Canada, Unit 7, 2915 Argentia Rd, Mississauga, Ontario, L5N 8G6, Canada.
King, Irl. King Pharmaceuticals Ltd, Donegal St, Ballybofey, County Donegal, Ireland.
King, UK. See *King, Irl.*
King, USA. King Pharmaceuticals Inc., 501 Fifth St, Bristol, TN 37620, USA.
url: www.kingpharm.com
Kingswood, USA. Kingswood Laboratories Inc., 10375 Hague Rd, Indianapolis, IN 46256, USA.
Kinray, USA. Kinray, 152-35 10th Ave, Whitestone, NY 11357, USA.
url: www.kinray.com
Kirby, Arg. See *Schering-Plough, Arg.*
Kireen, Malaysia. Kireen Pharmaceutical Sdn Bhd, 9 Jalan Kempas 4, Taman Perindustrian, Tampoi Indah, 81200 Johor Bahru, Johor, Malaysia.
Kirin, China. Kirin Kunpeng (China) Bio-Pharmaceutical Co Ltd, Long Dong Ave 970, Shanghai 201 203, China.
Kirin, Hong Kong. Kirin Pharmaceutical (Asia) Co Ltd, Unit 1002C-D, 10/F Admiralty Centre Tower 1, 18 Harcourt Rd, Admiralty, Hong Kong.
url: www.kirinholdings.co.jp
Kirin, Jpn. Kirin Brewery Co. Ltd, Pharmaceutical Division, 6-26-1 Jingu-mae, Shibuya-ku, Tokyo 150-8011, Japan.
url: www.kirin.co.jp
Kirin, Thai. See *Zuellig, Thai.*
Kirkman, USA. Kirkman Labs Inc., 6400 SW Rosewood, Lake Oswego, OR 97035, USA.
url: www.kirkmanlabs.com
Kiron, Fin. See *Kiron, Neth.*
Kiron, Irl. See *Kiron, Neth.*
Kiron, Neth. Kiron Pharmaceutica BV, Sterreschansweg 79, 6522 GM Nijmegen, Netherlands.
Kiron, Port. See *Kiron, Neth.*
Kironfarma, Port. Kironfarma Produtos Farmacêuticos sociedade Unipessoal Lda, Av. de Sabóia 189, 2765-278 Monte Estoril, Portugal.
Kissei, China. See *Kissei, Jpn.*
Kissei, Hong Kong. See *Hing Ah, Hong Kong* and *Main Life, Hong Kong.*
Kissei, Jpn. Kissei Pharmaceutical Co. Ltd, 19-48 Yoshino, Matsumoto, Nagano 399-8710, Japan.
url: www.kissei.co.jp
Kite, Gr. Kite Hellas E.P.E, 166 Ionias Ave, Greece.
url: www.kite.gr
Kite (Kite), Gr. See *Kite, Gr.*
Kivema, Israel. Kivema Ltd, 33 Hachoresh St, Kfar Shmaryahu 46910, Israel.
Kiwi, Malaysia. See *Antah, Malaysia.*
Kiwi, Neth. Kiwi Farm BV, Haven 215F, 22252 EZ Katwijk, Netherlands.
KK, UK. KK Toiletries Ltd, 2 Westgate, Skelmersdale, Lancashire, WN8 8AZ, UK.
url: www.kktoiletries.co.uk
Klab, Thai. See *GIS, Thai* and *Masu, Thai.*
Klar Sehen, India. Klar Sehen Pvt Ltd, 60A Ashok Aw, 700 040, India.
Klein, Ger. Dr Gustav Klein GmbH & Co. KG, Steinenfeld 3, 77736 Zell am Harmersbach, Germany.
url: www.klein-phytopharma.de
Kleva, Gr. Kleva Ltd, 189 Parnithos Ave, Athens, 136 71 Acharnes, Greece.
url: www.kleva.gr
Kleva, Neth. See *Kleva, Gr.*
Kleva, Singapore. See *Green Cross, Singapore.*
KLJ, USA. KLJ Corp., 1119 Third Ave SW, Carmel, IN 46032, USA.
url: www.entertainers-secret.com
Klinge, Ger. See *Astellas, Ger.*
Klinge, Irl. See *Astellas, Irl.*
Klinge Munich, Switz. See *Ridupharm, Switz.*
Klinge-Nattermann, Ger. See *Actavis, Ger.*
Klinos, Venez. Laboratorios Klinos C.A., 2da. Avenida de Campo Alegre, Torre Credival, Mezzanina, Chacao, Caracas 1060, Venezuela.
Klonal, Arg. Lab. Klonal, Lamadrid esq. T. de Alvear, 1878 Quilmes, Buenos Aires, Argentina.
Klorane, Canad. See *Pierre Fabre, Canad.*
Kloster, S.Afr. Kloster Pharmaceuticals (Pty) Ltd, P.O. Box 2734, Paarl 7620, South Africa.
Klosterfrau, Austria. Maria Clementine Martin Klosterfrau GmbH, Doerenkampgasse 11, A-1105 Vienna, Austria.
Klosterfrau, Canad. See *Klosterfrau, Ger.*
Klosterfrau, Cz. See *Klosterfrau, Ger.*
Klosterfrau, Ger. Maria Clementine Martin Klosterfrau Vertriebsgesellschaft mbH, Gereonsmühlengasse 1-11, 50670 Cologne, Germany.
url: www.klosterfrau.de
Klosterfrau, Hung. See *Klosterfrau, Ger.*
Klosterfrau, Pol. See *Nepentes, Pol.*
Kneipp, Austria. See *Kneipp, Ger.*
Kneipp, Cz. See *Kneipp, Ger.*
Kneipp, Ger. Kneipp-Werke, 97064 Würzburg, Germany.
url: www.kneipp.de
Knoll, Belg. See *Abbott, Belg.*
Knoll, Braz. Knoll SA Produtos Químicos e Farmacêuticos, Estrada dos Bandeirantes 2400, 27710-104 Rio de Janeiro, RJ, Brazil.
Knoll, Canad. See *Abbott, Canad.*
Knoll, Denm. See *Abbott, Swed.*
Knoll, Fin. See *Abbott, Fin.*
Knoll, Fr. See *Abbott, Fr.*
Knoll, Ger. See *Abbott, Ger.*
Knoll, India. See *Abbott, India.*
Knoll, Irl. See *Abbott, UK.*
Knoll, Ital. See *Abbott, Ital.*
Knoll, Mex. Química Knoll de Mexico S.A. de C.V., La Candelaria No.186, Col. Atlantida, Deleg. Coyoacan, 04370 Mexico D.F., Mexico.
Knoll, Neth. Knoll BV, Hettenheuvelweg 41-43, 1101 BM Amsterdam, Netherlands.
Knoll, Norw. See *Abbott, Swed.*
Knoll, NZ. See *Abbott, NZ.*
Knoll, Rus. See *Abbott, Rus.*
Knoll, S.Afr. See *Abbott, S.Afr.*
Knoll, Singapore. See *Boots, Singapore* and *DKSH, Singapore.*
Knoll, Spain. See *Abbott, Spain.*
Knoll, Swed. See *Abbott, Swed.*
Knoll, Switz. See *Abbott, Switz.*
Knoll, Thai. See *Pacific, Thai.*
Knoll, UK. See *Abbott, UK.*
Knoll, USA. See *Abbott, USA.*
Knop, Canad. See *Knop, Chile.*
Knop, Chile. Laboratorio Esp. Med. Knop Ltda, Av. Lib. Bdo. O'higgins 1671, Santiago, Chile.
Kobayashi, Jpn. Kobayashi Pharmaceutical Co. Ltd, 40306 Doshomachi, Chuo-ku, Osaka 541-0045, Japan.
url: www.kobayashi.co.jp
Kobayashi, Thai. See *Charoen, Thai.*
Kocak, Turk. Koçak Farma İlaç A.Ş., Bağlarbaşi Gazi Cad. No:64/66, Üski.idar, İstanbul, Turkey.
url: www.kocakilac.com
Kocsel, Turk. See *Onko, Turk.*
Kodak, USA. Kodak Dental, 343 State St, Rochester, NY 14650, USA.
url: www.kodak.com
koGen, UK. See *Galen, UK.*
Kohler, Austria. Dr Köhler Pharma GmbH, Steckhovengasse 17, A-1130 Vienna, Austria.
Kohler, Cz. See *Reg, Cz.*
Kohler, Ger. Dr Franz Köhler Chemie GmbH, Neue Bergstr. 3-7, 64665 Alsbach-Hähnlein, Germany.
url: www.koehler-chemie.de
Kohler, Hung. See *Kohler, Ger.*
Kohler, Neth. See *Tramedico, Neth.*
Kohler, Rus. See *Kohler, Ger.*
Kohler-Pharma, Ger. Köhler Pharma GmbH, Neue Bergstr. 3-7, 64665 Alsbach, Germany.
url: www.koehler-pharma.de
Kolassa, Austria. Dr. Kolassa & Merz GmbH, Gastgebgasse 5-13, A-1230 Vienna, Austria.
Kolassa, Cz. See *Kolassa, Austria.*
Kolex, Hung. Kolex-Cyberlink Hungary Kft, Apáczai Csere János u 3 fsz., 1052 Budapest, Hungary.
Kolson's, India. Kolson's, 106 Sonal Shopping Center, Station Rd, Nallasopara (W), Thane, Mumbai, 401 203, India.
url: www.kolsonindia.com
Koltzov Institute, Rus. See *Akti-M, Rus.*
Komedic, Malaysia. Komedic Sdn Bhd, 4 Jln PJS 11/14, Bandar Sunway, 46150 Petaling Jaya, Selangor, Malaysia.
Konark, Ukr. Konark LLC, Ave Akademika Glushkov 42 B, 2nd Floor, 03680 Kiev, Ukraine.
url: www.konark.com.ua
Kondon, USA. Kondon Manufacturing, Croswell, MI 48422, USA.
Konet, Hong Kong. Konet Ltd, Flat 02 9/F, Lucky Commercial Centre, 103 Des Voeux Road West, Hong Kong.
Koni-Cofarm, Chile. Laboratorio Koni-Cofarm SA, Crescente Errazuriz 2077, Nunoa, Santiago, Chile.
Konimex, Indon. Konimex PT, Jl K H Wahid Haysim No 162, Jakarta, DKI Jaya, Indonesia.
url: www.konimex.com
Konpharma, Ital. Konpharma Srl, Via Pietro della Valle 1, 00193 Rome (RM), Italy.
Konstantinos, Gr. Konstantinos Leon, Lamprou Katsoni 33, 151 22 Maroussi, Greece.
Konsuma, Venez. See *Farma, Venez.*
Konsyl, China. Konsyl Pharmaceuticals Co. Ltd, China.
Konsyl, Israel. See *Pharmateam, Israel.*
Konsyl, USA. Konsyl Pharmaceuticals, 8050 Industrial Park Rd, Easton, MD 21601, USA.
url: www.konsyl.com
KonTest, India. KonTest Chemicals Ltd, 80/1A Sarat Bose Road, Kolkata 700 025, India.
url: www.kontestchemicals.com
Koolatron, Canad. Koolatron Corp., 27 Catharine Ave, Brantford, Ontario, N3T 1X5, Canada.
Kopran, India. Kopran Ltd, Parijat House, 1076 Dr. E. Moses Road, Worli, Mumbai 400 018, India.
url: www.kopran.com
Kopran, Philipp. See *Pharmasan, Philipp.*
Kopran, Thai. See *Pharmaland, Thai.*
Kora, Ger. See *Kora, Irl.*
Kora, Irl. KoRa Healthcare, Frans Maas House, Swords Business Park, Swords, County Dublin, Ireland.
url: www.kora-health.ie

Kora, UK. See *Kora, Irl.*

Korangi, Port. Korangi S.A., Parque Empresarial Primóvel Edifício A1, r/c Albarraque, 2635-595 Rio de Mouro, Portugal.

KoreaGreen Cross, Malaysia. See *Propharm, Malaysia.*

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Korea Green Pharm, Singapore. See *GC, Singapore.*

Korea Pharma, Singapore. See *Pharma 2000, Singapore* and *Pharmaforte, Singapore.*

Korea United, Hong Kong. See *HealthCare PharmaScience, Hong Kong.*

Korea United, Philipp. See *Qualimed, Philipp.*

Korea United, Singapore. See *Kyowa, Singapore* and *Ziwell, Singapore.*

Korean Drug, Singapore. See *Ziwell, Singapore.*

Korean Ginseng, Philipp. See *Psalmstre, Philipp.*

Korean United, Malaysia. See *Kyowa, Malaysia.*

Korhispana, Spain. Korhispana, PSJ Can Politic 17 3, Hospitalet de Llobregat, 08907 Barcelona, Spain.
url: www.korhispana.com

Kosmidis, Gr. Kosmidis, Greece.

Kotobuki, Jpn. Kotobuki Pharmaceutical Co Ltd, 198 Higashikawahara, Sakaki-machi, Hanishina-gun, Nagono-ken 389-0697, Japan.
url: www.kotobuki-pharm.co.jp

Kotor, Fr. Kotor Pharma (Lab), ZI Toulon-Est, 809 av de Draguignan, B.P. 49, 83087 Toulon cdx 9, France.
url: www.kotorpharma.com

Kotra, Hong Kong. See *Deltapharm, Hong Kong* and *Hind Wing, Hong Kong.*

Kotra, Malaysia. Kotra Pharma (M) Sdn Bhd, No. 1 Jln TTC 12, Cheng Industrial Estate, 75250 Melaka, Melaka, Malaysia.
url: www.kotrapharma.com

Kotra, Singapore. See *Pharmaforte, Singapore.*

Kotsopoulos, Gr. D & K& A Kotsopoulos S.A., 11-15 Aristotelous Str., 104 32 Athens, Greece.
url: www.kotsopoulos.gr

Kotsopoulos (Κωτσοπουλος), Gr. See *Kotsopoulos, Gr.*

Kottas-Heldenberg, Austria. Kottas-Heldenberg Mag. R.u. Sohn, Bauernmarkt 24, A-1014 Vienna, Austria.

Koutsoumani, Gr. Koutsoumani C & E Ltd, Piraeus 16-18, Greece.

Kowa, China. Kowa Pharmaceutical Co. Ltd., 268 Xizang Zhong Rd, Raffles City, Shanghai, 200001, China.
url: www.kowashanghai.cn

Kowo, Ger. Kowa Europe GmbH, Immermannstrasse 43B, 40210 Düsseldorf, Germany.
url: www.kowa-europe.com

Kowa, Irl. See *Kowa, UK.*

Kowa, Jpn. Kowa Co. Ltd, 3-4-14 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8433, Japan.
url: www.kowa.co.jp

Kowa, Malaysia. See *Pharmaforte, Malaysia.*

Kowa, Neth. See *Kowa, Ger.*

Kowa, Philipp. See *DeGa, Philipp.*

Kowa, Thai. See *Biopharm, Thai* and *Masu, Thai.*

Kowa, UK. Kowa Pharmaceutical Europe Co Ltd, Winnersh Triangle, Wokingham, UK.

Kowa, USA. Kowa Pharmaceuticals America Inc., 530 Industrial Park Blvd, Montgomery, AL 36117, USA.
url: www.kowopharma.com

Kowloon, China. Kowloon Pharmaceutical Co. Ltd, Beijing, China.

Koz, Turk. Koz İlaç San. Ve Tic. AS, Eski Edirne Asfalti N:564, GO Paşa, Sultançiftligi, Istanbul, Turkey.

Kozmed, Turk. Kozmed, Tesvikiye Cad. Alhambra, Apt No. 178 K4 D.5, Nisantasi Sisli, 34365 Istanbul, Turkey.
url: www.kozmed.com

K-PAX, USA. K-PAX Inc., 655 Redwood Highway, Suite 346, Mill Valley, CA 94941, USA.
url: www.kpaxpharm.com

KPSS, Canad. See *KPSS, USA.*

KPSS, USA. KPSS Inc., 981 Corporate Blvd, Linthicum Heights, Maryland, 21090, USA.

Kracie, Jpn. Kracie Pharmaceutical Ltd, 20-20 Kaigon 3-chome, Minato-ku, Tokyo 108-8080, Japan.

Kramer, India. Kramer Pharmaceuticals Pvt Ltd, Panjat House, 1076 Dr E Moses Rd, Worli, Mumbai 400 018, India.

Kramer, Philipp. Kramer Pharmaceutical Corp., 60 Cambridge St, Cubao, Quezon City, Philippines.

Kramer, USA. Kramer Laboratories Inc., 8778 SW 8th St, Miami, FL 33174-9990, USA.
url: www.kramerlabs.com

Kramer Novis, USA. Kramer Novis, USA.
url: www.kramernovis.com

Krasfarma, Rus. See *Valenta, Rus.*

Krasnay Zvezda, Rus. Krasnay Zvezda, Russia.

Krasnogorskleksredstva, Rus. Krasnogorskleksredstva, ul Ienina 25, Opaliha, 143444 Moscow, Russia.

Kremers-Urban, USA. Kremers Urban, P.O. Box 427, Mequon, WI 53092, USA.

Kreoma-Farm, Ukr. ZAO KREOMA-FARM, Radishcheva Street, 3, Kiev, 03680, Ukraine.
url: www.kreoma.com.ua

Kreussler, Austria. See *Kreussler, Ger.*

Kreussler, Cz. See *IBI International, Cz.*

Kreussler, Denm. See *Felo, Denm.*

Kreussler, Fin. See *Tamro, Fin.*

Kreussler, Fr. Laboratoire Kreussler Pharma, 2 rue de la Haye, Le Dome, B.P. 10901, 95731 Roissy-Charles-de-Gaulle cdx, France.
url: www.kreussler.fr

Kreussler, Ger. Chemische Fabrik Kreussler & Co. GmbH, Rheingaustr. 87-93, 65203 Wiesbaden, Germany.
url: www.kreussler.com

Kreussler, Hung. See *Repharma, Hung.*

Kreussler, Pol. See *Biotal, Pol.*

Kreussler, Rus. See *Kreussler, Ger.*

Kreussler, Switz. See *Globopharm, Switz.*

Kreussler, Thai. See *Berlin Pharm, Thai.*

Krewel, Denm. See *Krewel, Ger.*

Krewel, Ger. Krewel Meuselbach GmbH, Krewelstr. 2, 53783 Eitorf, Germany.
url: www.krewel-meuselbach.de

Krewel, Rus. See *Krewel, Ger.*

Krewel, Switz. See *Lubapharm, Switz.*

Krewel, Ukr. Krewel Meuselbach GmbH, ul. Vasilkovoska 1, Office 101/5, 03040 Kiev, Ukraine.

Krewel Meuselbach, Cz. Krewel Meuselbach GmbH, Nam. gen. Kutlvašra 6, 140 00 Prague 4, Czech Republic.

Krewel Meuselbach, Pol. Krewel Meuselbach GmbH, Przedstawicielstwo w Polsce, ul. Odyńca 63/24, 02-644 Worsaw, Poland.

Kripps, Canad. Kripps Pharmacy Ltd, 6909 Cambie St, Vancouver, British Columbia, V6P 3H1, Canada.

KRKA, Austria. See *KRKA, Irl.*

KRKA, Cz. KRKA Slovinsko, Mezibranská 7, 110 00 Prague 1, Czech Republic.

KRKA, Denm. See *KRKA, Swed.*

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KRKA, Ger. See *TAD, Ger.*

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KRKA, Hung. KRKA, Királyhágó u 5/a, 1126 Budapest, Hungary.

KRKA, Irl. KRKA Pharma Dublin, 1 Stokes Place, Dublin 2, Ireland.

KRKA, Ital. KRKA Farmaceutici Milano Srl, Viale Achille Papa 30, 20149 Milan, Italy.
url: www.krka.biz

KRKA, Neth. See *KRKA, Irl.*

KRKA, Pol. Krka Polska Sp. za.o., ul. Równoległa 5, 02-235 Warsaw, Poland.
url: www.krkapolska.pl

KRKA, Port. KRKA Farmacêutica Unipessoal Lda, Avenida de Portugal 154, 2765 272 Estoril, Portugal.
url: www.krka.biz

KRKA, Rus. KRKA d.d., ul. 2-ya Zvenigorodskaya, d. 13, Str. 41, et. 5, 125009 Moscow, Russia.
url: www.krka.ru

KRKA, Singapore. See *Uni, Singapore.*

KRKA, Spain. KRKA Farmacéutica SL, C/Lanzarote 9, 28103 San Sebastián de los Reyes, Madrid, Spain.

KRKA, Swed. KRKA Sverige AB, Göta Ark 175, Medborgarplatsen 25, 118 72 Stockholm, Sweden.
url: www.krka.se

KRKA, Ukr. KRKA d. d., Novo mesto, Staronavodnitskaya Street, 13, section B-G, 3rd floor, Kiev, 01015, Ukraine.
url: www.krka.si

Krolton, Arg. Krolton, Labopharma Pharmaceutical Group SA, Balboa 351, 1427 Buenos Aires, Argentina.

Kromme Rijn Apotheek, Pol. See *Mylan, Pol.*

Krotex, Pol. Krotex Poland Sp. zo.o., ul. Rydygiera 8 bl. 18, 01-793 Warsaw, Poland.
url: www.krotex.com.pl

Kruger, Canad. Kruger Products Ltd, 1000 Blvd de la Carriere, Gatineau, Quebec, J8Y 6T5, Canada.

Krugher, Ital. See *KG, Ital.*

Krugmonn, Ger. See *Mundipharma, Ger.*

KSK, Denm. See *KSK, Ger.*

KSK, Ger. KSK-Pharma AG, Finkenstr. 1, 76327 Berghausen, Germany.
url: www.ksk-pharma.de

KSK, Irl. See *KSK, Ger.*

Kuhnil, Singapore. See *Pharmaforte, Singapore.*

Kuhnil, Thai. See *Medline, Thai.*

Kukje, China. Kukje Pharma Ind. Co. Ltd, China.

KunMing, China. KunMing Pharmaceutical Group Co. Ltd, 166 Keyi Rd, State New & High Technology Development Zone, Kunming, Yunan, China.
url: www.kpc.com.cn

Kunzle, Switz. Krauterpfarrer Kunzle AG, 6573 Magadino, Switzerland.

Kur und Stadtapotheke, Austria. Kur- und Stadtapotheke, Oberer Stadtplatz 5, A-6060 Hall in Tirol, Austria.

Kuraray, Jpn. Kuraray Co. Ltd, Shin-Hankyu Bldg, 1-12-39 Umeda, Kita-ku, Osaka 530-8611, Japan.
url: www.kuraray.co.jp

Kurtsan, Israel. See *Kurtsan, Turk.*

Kurtsan, Turk. Kurtsan İlaçları A.S., Keresteciler Sitesi, Kasim Sok. No: 63, Merter, Istanbul, 34010, Turkey.
url: www.kurtsan.com.tr

Kutateladze Institute, Ukr. See *Pharmplanet, Ukr.*

Kutal, Canad. See *Kutol, USA.*

Kutol, USA. Kutol Products Co. Inc., 7650 Camargo Rd, Cincinnati, OH 45243-3009, USA.

KV, China. See *KV, USA.*

KV, Hong Kong. See *Hind Wing, Hong Kong.*

KV, Malaysio. See *Apex, Malaysia.*

KV, Singapore. See *Pan-Malayan, Singapore.*

KV, USA. K.V. Pharmaceutical Co., 2503 S Hanley Rd, St Lois, MO 63144, USA.
url: www.kvpharmaceutical.com

KVZ, Ukr. ZAO Kievskii Vitaminnyi Zavod, Kopylovskaya Street, 38, Kiev, 04073, Ukraine.
url: vitamin.com.ua

KWH, Singapare. KWH Marketing Pte Ltd, 9 Third Lok Yang Rd, S-628004, Singapore.

Kwizda, Austria. Kwizda Pharma GmbH, Effingergasse 21, A-1160 Vienna, Austria.
url: www.kwizda.at

Kwizda, Cz. See *Horna, Cz.*

Kwizda, Fin. See *Kwizda, Austria.*

Kwizda, Ger. Kwizda Pharma GmbH & Co KG, Rüdesheimer Str. 15, 80686 Munich, Germany.
url: www.kwizda.at

Kwizda, Hung. See *Medico Uno, Hung.*

Kwizda, Pol. See *Hand-Prod, Pol.*

Kwizda, Switz. See *AstraZeneca, Switz.*

Kwizda, Ukr. See *Delta Medical, Ukr.*

Kyberg, Ger. Kyberg Pharma Vertiebs GmbH, Keltenring 8, 82041 Oberhaching, Germany.
url: www.kyberg.de

Kylemore, USA. Kylemore Pharmaceuticals, Suwanee, GA 30024, USA.

Kyarin, Hong Kong. See *Main Life, Hong Kong.*

Kyarin, Jpn. Kyorin Pharmaceutical Co. Ltd, 2-5 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8311, Japan.
url: www.kyorin-pharm.co.jp

Kyowa, Hong Kong. See *Tai Tong, Hong Kong.*

Kyowa, Hung. See *Cziher, Hung.*

Kyowa, Indon. See *Kyowa, Jpn.*

Kyowa, Jpn. Kyowa Pharmaceutical Industry Co. Ltd, 5-13-9, Nishinakajima, Yodogawa-ku, Osaka, 532-0011, Japan.
url: www.kyowayakuhin.co.jp

Kyowa, Malaysia. Kyowa Hakko (Malaysia) Sdn Bhd, 20 Jln SS 19/5, 47500 Subang Jaya, Selangor, Malaysia.
url: www.kyawa.co.jp

Kyawo, Singapore. Kyowa Hakko Bio (S) Pte Ltd, 47 Scotts Rd 12-05, Goldbell Towers, S 228233, Singapore.
url: www.kyowa-asean.com

Kyawo, Thai. Kyowa Hakko (Thailand) Ltd, 101/11 Srinakarin Rd, Suanluang, Bangkok 10250, Thailand.
url: www.kyowa-asean.com

Kyowa, UK. Kyowa Hakko (UK) Ltd, 258 Bath Rd, Slough, Berkshire, SL1 4DX, UK.
url: www.kyowa-asean.com

Kyowa Hokko, Philipp. See *Eisai, Philipp.*

Kyowa Hakko, Pol. See *JKC, Pol.*

Kyowa Hakko Kirin, Jpn. Kyowa Hakko Kirin Co Ltd, 1-6-1 Otemachi, Chiyoda-ku, Tokyo, Japan.

Kyowa Hakko Kirin, Thai. Kyowa Hakko Kirin (Thailand) Co. Ltd, 20 Fl Rm 2003B, 323 United Center Bldg, Silom Rd, Silom Bangrak, Bangkok, 10500, Thailand.

Kytta, Ger. See *Pfizer, Ger.*

LA, Arg. Lab. Austral S.A., Av. Olascoaga 951, 8300 Neuquen, Argentina.

La Care, India. La Care Farma Ltd, 3 Road No 1, South City Enclave, Gurgaon, India.

La Care, Rus. See *La Care, India.*

La Haye, USA. See *US Nutraceuticals, USA.*

La Pharmaceuticals, India. La Pharmaceuticals, 465 G I D C - Estate, Phase II, Vatva, Ahmedabad 382 445, India.

La Prairie, Canad. See *La Prairie, USA.*

La Prairie, USA. La Prairie Inc., 14th Floor, 680 Fifth Ave, New York, NY 10019, USA.

Laakefarmos, Swed. See *Orion, Swed.*

Lab Francais du Fractionnement, Fr. Lab Français du Fractionnement et des Biotechnologies, 3 av des Tropiques, B.P. 305, Les Ulis, 91958 Courtaboeuf cdx, France.

Lab Francais du Fractionnement, Neth. See *Lab Francais du Fractionnement, Fr.*

Lab Pharm Milanese, Hung. See *Medimpex, Hung.*

Lab Pharmaceutique, Ukr. See *Formasoft, Ukr.*

Labatec, Switz. Labatec-Pharma SA, Case postale 62, 31 rue du Cardinal-Journet, 1217 Meyrin 2, Switzerland.

Labaz, Fr. See *Sanofi-Aventis, Fr.*

Labaz, Ger. See *Sanofi-Aventis, Ger.*

Labaz, Spain. See *Sanofi-Aventis, Spain.*

Labcatal, Fr. Laboratoires Labcatal, 7 rue Roger-Salengro, B.P. 305, 92541 Montrouge cdx, France.
url: www.labactal.fr

Labcatal, Switz. See *Oligosol, Switz.*

Labcorp, USA. Laboratory Corporation of America, 840 Research Parkway, Suite 102, Oklahoma City, OK 73104, USA.
url: www.labcorp.com

Labesfal, Port. Labesfal, SA, Campo de Besteiros, 3465-051 Campo de Besteiros, Portugal.

Labethica, S.Afr. See *Aspen, S.Afr.*

Labialfarma, Port. Labialfarma, Laboratório de Biologia Alimentar e Farmacêutica Lda, Felgueira, 3450-336 Sobral, Mortágua, Portugal.

Labima, Belg. Labima SA, Ave Van Volxem 328, 1190 Brussels, Belgium.

Labochem, Cz. See *Labochem, Gr.*

Labochem, Gr. Labachem Ltd, 1 Aristonikou str., 116 36 Athens, Greece.

Labochem, Port. See *Labochem, Gr.*

Laboform, Canad. See *Laboform, Pol.*

Laboform, Pol. Innowacyjno-Wdrożeniowe Laboratorium Farmaceutyczne Laboform, ul. Lublichowska 176 b, 83-200 Straogard Gdański, Poland.
url: www.laboform.com.pl

Labomed, Chile. Instituto Farmaceutico Labomed SA, Lira 278, Santiago, Chile.

Labopharm, USA. Labopharm USA Inc., 202 Carnegie Center, Suite 204, Princeton, NJ 08540, USA.
url: www.labopharm.com

Labar, Pol. Farmaceutyczno-Chemiczna Spółzielna Pracy Labor, ul. Długosza 49, 56-162 Wrocław, Paland.
url: www.labar.com.pl

Laborate, India. Laborate Pharmaceutical India Ltd, E-11 Industrial Area, Panipat 132 103, India.
url: www.laborate.com

Laboratoires d'Anjou, Fr. Laboratoires d'Anjou, 16 rue de l'Exposition, 75007 Paris, France.

Laboratoires de Biarritz, Fr. Laboratoires de Biarritz, 20 av Reine-Victoria, 64200 Biarritz, France.
url: www.laboratoires-biarritz.fr

Laboratoires Dermo-Cosmetik, Canad. Laboratoires Dermo-Cosmetik Inc., 68 Stinson, Montreal, Quebec, H4N 2E7, Canada.

Laboratoires Swisse, Canad. Les Laboratoires Swisse Inc., 3560 rue Isabelle, Brossard, Quebec, J4Y 2R3, Canada.

Laboratories for Applied Biology, Canad. See *Laboratories for Applied Biology, UK.*

Laboratories for Applied Biology, Hong Kong. See *Swiss Worldwide, Hong Kong.*

Laboratories for Applied Biology, Irl. See *Allphar, Irl.*

Laboratories for Applied Biology, Malaysia. See *Sime Darby, Malaysia.*

Laboratories for Applied Biology, Singapore. See *Sime Darby, Singapore.*

Laboratories for Applied Biology, UK. Laboratories for Applied Biology Ltd, 91 Amhurst Park, London, N16 5DR, UK.
url: www.cerumol.com

Laboratorio Farm., Israel. See *Premopharm, Israel.*

Laboratorios Chile, Chile. Laboratorios Chile SA, Av. Marathon 1315, Nunoa, Santiago, Chile.

Laborest, Ital. See *Pharma-Natura, Ital.*

Laboris, Braz. Laboris Farmaceutica Ltda, Rua das Oficinas 188, 20770010 Rio de Janeiro, Brazil.

Labormed, Cz. See *Advent, Cz.*

Labormed, Denm. See *Labormed, Pol.*

Labormed, Hung. See *Advent, Cz.*

Labormed, Neth. See *Labormed, Pol.*

Labormed, Pol. Labormed Pharma, Lisi Jar 11, Marki 05-270 ul., Poland.
url: www.labormed.eu

Labormed, Rus. See *Rompharm, Rus.*

Laborterapia, Port. Laborterapia Produtos Farmaceuticos SA, Taguspark, Edificio Inovacao II, Sala 421, 2700 Oeiras, Portugal.

Labrha, Fr. Labrha, 19 place Tolazan, 69001 Lyon, France.
url: www.labrha.com

Labsa, Arg. Laboratorio Sudamericano SRL, General Tomas Guido 2563/81, Burzaco, B1852OFQ Buenos Aires, Argentina.

Lacer, Hong Kong. See *CNW, Hong Kong.*

Lacer, Port. See *Lacer, Spain.*

Lacer, Spain. Lacer, Sardenya 350, 08025 Barcelona, Spain.
url: www.lacer.es

Lachartre, Fr. See *Procter & Gamble, Fr.*

Lachema, Cz. See *Pliva, Cz.*

Lachema, Rus. See *Pliva, Rus.*

Lachifarma, Ital. Lachifarma S.r.l., Laboratorio Chimico Farmaceutico Salentino, S.S. 16, Zona Industriale, 73010 Zollino (LE), Italy.
url: www.lachifarma.com

Laclede, Singapore. See *MBD, Singapore.*

Laclede, USA. Laclede Inc., 2030 East University Drive, Rancho Dominguez, CA 90220, USA.
url: www.laclede.com

Laclin, India. Laclin Pharmaceuticals & Herbals, 130 1st Floor, Meghreji Complex, S.G.Highway, Sarkhej, Ahmedabad 382 210, India.

Lacoer, Ger. See *Loves, Ger.*

LaCorium, UK. LaCorium Health UK, 4th Floor Exchange House, 494 Midsummer Blvd, Milton Keynes, MK9 2EA, UK.
url: lacoriumhealth.com

LaCorium, USA. LaCorium Health USA, 6111 Broken Sound Parkway, NW Suite 365, Boca Raton, FL 33487, USA.
url: lacoriumhealth.com

Lactaid, USA. See *McNeil Consumer, USA.*

Lactalis, Fr. Lactalis Nutrition Sante, Parc d'activites de Torcé, Secteur Est, 35370 Torcé, France.
url: www.lns-nutrition.fr

Lacteol, Fr. See *Axcan, Fr.*

Lacteol, Hong Kong. See *Silroc, Hong Kong.*

Lacteol, Singapore. See *Age D'or, Singapore.*

Lacteol, Switz. See *Uhlmonn-Eyraud, Switz.*

Lacteol, Thai. See *Diethelm, Thai.*

LadeePharma, Cz. See *LadeePharma, Hung.*

LadeePharma, Hung. LadeePharma Kft, Biatorbágy, Hungary.

Laderma, Canad. See *Eulactol, USA.*

Laetitia, Ger. Laetitia Naturprodukte Vertriebs GmbH, Elsässer Str. 4, 81667 Munich, Germany.
url: www.bitterstern.de

Lafare, Ital. LA.FA.RE. S.r.l., Laboratorio Farmaceutico Reggiano, Via S.B. Cozzolino 77, 80056 Ercolano Resina (NA), Italy.

Lafarmen, Arg. Laformen S.A., Rioja 2163/69, 5500 Mendoza, Argentina.

Lafayette, Philipp. Lafayette Pharmaceutical Lab. Inc., 132, 13th Ave, Cubao, Quezan city, Philippines.

Lafayette, USA. See *Mallinckrodt-Baker, USA.*

Lafedar, Arg. Lafedar, Lab. Federales Argentinas S.A., Valentmn Torra 4880, 3100 Entre Rios, Argentina.
url: www.lafedar.com

Lafi, Chile. See *Recalcine, Chile.*

Lafan, Belg. See *Lafon, Fr.*

Lafon, China. See *Lafon, Fr.*

Lafon, Cz. See *Lafon, Fr.*

Lafan, Denm. See *Organon, Denm.*

Lafon, Fr. Laboratoires Lafon, 19 av. du Professeur Cadiot, B.P. 22, 94701 Maisons-Alfort cdx, France.

Lafon, Hong Kong. See *Worldwide, Hong Kong.*

Lafon, Israel. See *Medison, Israel.*

Lafran, Fr. Laboratoires Lafran, 1 rte des Stains, 94387 Bonneuil-sur-Marne cdx, France.

Lagad, UK. Lagad Vision Laboratory Ltd, 1 Haresefair Mews, Romsey, Hampshire, SO51 8JG, UK.

Lagamed, S.Afr. See *Aspen, S.Afr.*

Lagap, Hong Kong. See *Hind Wing, Hong Kong.*

Lagap, Switz. Lagap SA, Via San Gottardo 9, 6943 Vezia, Switzerland.

Lagap, UK. See *Novartis, UK.*

Lagepha, Belg. Lagepha, Belgium.

Lagos, Arg. Lagos Laboratorios Argentina S.R.L., Jorge Newbery 1829, 1426 Buenos Aires, Argentina.
url: www.lagoslab.com.ar

Lai En, China. Lai En Pharmaceutical Co. Ltd, Xuzhou, China.

Lai Mei, China. Lai Mei Pharmaceutical Co. Ltd, Chongqing, China.

Lailan, Spain. See *AstraZeneca, Spain.*

Lainco, Rus. See *Lainco, Spain.*

Lainco, Spain. Lainco, Avda Bizet 8-12, Pol. Ind. Can Jardi, Rubi, 08191 Barcelona, Spain.
url: www.lainco.es

Laitai, China. Laitai Pharmaceutical Co. Ltd, Guangzhou, China.

Lake, USA. See *Wisconsin Pharmacal, USA.*

Lakeside, Mex. Lakeside de Mexico S.A. de C.V., Carr. Mexico Toluca 2822, Lomas de Bezares, 11000 Mexico D.F., Mexico.

Lakeside, Philipp. Lakeside Pharmaceuticals Phils Inc., Unit 304, APC Bldg, 1186 Quezon Ave, Quezon City, Philippines.

Lakeside, USA. See *Sanofi-Aventis, USA.*

Laksun, India. Laksun Lifesciences, G-03 No 53/1-2 Arvind's Kabini, Padmanabha Nagar, Bangalore-560 070, Karnataka, India.

Lalco, Canad. See *Nobel, Canad.*

Lalema, Canad. Lalema Inc., 11450 rue Sherbrooke Est, Montreal, Quebec, H1B 1C1, Canada.

Laleuf, Fr. See *Medix, Fr.*

Lallemand, Pol. See *Merck, Pol.*

Lallemand, Ukr. See *GSK, Ukr.*

Lam Thong, Thai. See *March, Thai.*

L'amar Natural Products, Singapore. See *Goldplus, Singapore.*

Lamas, Canad. See *Lamas, USA.*

Lamas, USA. Lamas Beauty International, 301 6222 Wiltsgire Blvd, Los Angeles, CA 90048, USA.

Lambda, Port. See *Lambda, UK.*

Lambda, UK. Lambda Therapeutic Ltd, Sage House, 319 Pinner Rd, North Harrow, Middlesex, HA1 4HF, UK.

Lambda, USA. See *Bart, USA.*

Lamberts Healthcare, UK. Lamberts Healthcare Ltd, 1 Lamberts Rd, Tunbridge Wells, Kent, TN2 3EH, UK.
url: www.lambertshealthcare.co.uk

Lamda (Λαμδα), Gr. Lamda Pharmaceutical A.E., 6 Thermopylon Str., 152 33 Chalandri, Greece.

Lamepro, Belg. See *Lamepro, Neth.*

Lamepro, Neth. Lamepro BV, Brasem 51, 4941 SE Raamsdonkveer, Netherlands.
url: www.lamepro.nl

Lamoiyan, Philipp. Lamoiyan Corp., Km 15 Service Rd, South Superhighway, Parañaque City, Philippines.

Lampugnani, Ital. Lampugnani Farmaceutici S.p.A., Via Gramsci 4, 20014 Nerviano (MI), Italy.
url: www.lampugnanifarmaceutici.it

Lamsa, Arg. Laboratorio Argentino de Medicamentos SA, El Calden S/N, 6360 Gral. Pico, La Pampa, Argentina.

Lananqi, China. Lananqi Biological Engineering Co. Ltd, Shenzhen, China.

Lancer, India. Lancer Pharmaceuticals Pvt Ltd, SCO 912, 2nd Floor, NAC Manimajara, Chondigarh, India.

Lancome, Canad. See *L'Oreal, Canad.*

Lander, Canad. Lander Co. Canada Ltd, 275 Finchdene Square, Scarborough, Ontario, M1X 1C7, Canada.

Landi, Arg. See *Dimec, Arg.*

Landson, Indon. Landson, PT Pertiwi Agung Pharmaceutical Industries Ltd, Gedung Mensa II, Jl H R Rasuna Said Kav B-35, Kuningan, Jakarta 12910, Indonesia.
url: www.landson.co.id

Landson, Malaysia. See *Zyfas, Malaysia.*

Landson, Singapore. See *Zyfas, Singapore.*

Landsteiner, Mex. Landsteiner Scientific SA de CV, Periferico sur 4124 T.II Zafiro P.8, 1900 Ex-Rancho de Anzaldo, Mexico DF, Mexico.

Lane, Hung. See *Lane, UK.*

Lane, Irl. See *Lane, UK.*

Lane, Pol. See *Axellus, Pol.*

Lane, UK. G.R. Lane Health Products Ltd, Sisson Rd, Gloucester, GL1 3QB, UK.
url: www.laneshealth.com

Langtai, China. Langtai Pharmaceutical Co. Ltd., 96 Taoyuan East Road, Nanhai, Foshan, Guangdong, China.
url: www.langtai.com.cn

Langyi, China. Langyi Pharmaceutical Co. Ltd, Beijing, China.

Lanling, China. Lanling Pharmaceutical Co. Ltd, 58 East Cailing Road, Changzhou, Jiangsu, 213018, China.
url: www.lanlingpharm.com

Lannacher, Austria. Lannacher Heilmittel GmbH, Schlossplatz 1, A-8502 Lannach, Austria.

Lannacher, Cz. See *Horna, Cz.*

Lannacher, Denm. See *Nordic Drugs, Denm.*

Lannacher, Fin. See *Lannacher, Austria.*

Lannacher, Israel. See *Taro, Israel.*

Lannacher, Neth. See *Lannacher, Austria.*

Lannacher, Norw. See *Nordic, Swed.*

Lannacher, Pol. Lannacher Heilmittel GmbH Sp. zo.o., Przedstawicielstwo w Polsce, al. Jana Pawła II 61, 00-031 Warsaw, Poland.

Lannacher, Rus. Lonnacher Heilmittel GmbH, B. Sukharevskaya pl. 16/18, pod. 3, et. 9, 103045 Moscow, Russia.

Lannett, USA. Lannett Co., Inc., 9000 State Rd, Philadelphia, PA 19136, USA.
url: www.lannett.com

Lanpharm, Arg. Lab. Lanpharm SA, J E Uriburu 61, 1027 Buenos Aires, Argentina.

Lansinoh, USA. Lansinoh Laboratories Inc., 333 North Fairfax St, Suite 400, Alexandria, VA 22314, USA.
url: www.lansinoh.com

Lantai, China. Lantai Pharmaceutical Co. Ltd, Xi'an, China.

Lantaka, Philipp. Lantaka Distributors Corp., Unit 228 Cityland 9, Dela Rosa St Condominium, 7648 Dela Rosa St, Makati City, Philippines.

Lantheus, Austral. Lantheus Medical Imaging, Unit 8, Carrick Drive, Tullamarine, Victoria 3042, Australia.
url: www.bmsmedicalimaging.com

Lantheus, Canad. See *Lantheus, USA.*

Lantheus, Chile. See *Lantheus, USA.*

Lantheus, Cz. See *Lantheus, UK.*

Lantheus, Denm. See *Lantheus, UK.*

Lantheus, Fin. See *Lantheus, UK.*

Lantheus, Israel. See *Lantheus, USA.*

Lantheus, Neth. See *Lantheus, UK.*

Lantheus, Port. See *Lantheus, UK.*

Lantheus, Spain. See *Lantheus, UK.*

Lantheus, Swed. See *Lantheus, UK.*

Lantheus, UK. Lantheus Medical Imaging Ltd, Festival House, 39 Oxford St, Newbury, Berkshire, RG14 1JG, UK.

Lantheus, USA. Lantheus Medical Imaging Inc., Bldg 200-2, 331 Treble Cove Rd, N Billerica, MA 01862, USA.
url: www.lantheus.com

Lanzas, Spain. See *Ipsen, Spain.*

Lanzhou Bio, China. Lanzhou Institute of Biological Products, Lanzhou, China.

Laolaifu, China. Laolaifu Pharmaceutical Co. Ltd, Huaxi Ave South, Guiyang, Guizhou, 550025, China.

Laphal, China. See *Laphal, Fr.*

Laphal, Cz. See *Laphal, Fr.*

Laphal, Fr. Laphal Industrie, Avenue de Provence, 13190 Allauch cdx, France.
url: www.laphal.com

Laphal, Hong Kong. See *C & L, Hong Kong* and *Wing Wai, Hong Kong.*

Laphal, Ukr. See *Laphal, Fr.*

Laphi, Fr. See *PPDH, Fr.*

Lapi, Indon. Lapi Laboratories PT, Jl Gedong Panjang Street 32, Jakarta 11240, Indonesia.
url: www.lapilaboratories.com

Lapidot, Israel. A. Lapidot Pharmaceuticals Ltd, 8 Ha'shita St, Industry Park, Caesaria 38900, Israel.
url: www.lapidot.com

Lapreven, Venez. Laboratorio Lapreven S.A., Centro Comercial Bello Monte, Piso 8 Of. 8B y 8C, Caracas, Venezuela.

Laquifa, Port. Laquifa Laboratórios S.A., Rua Alfredo da Silva 3C, 1300-040 Lisbon, Portugal.

Larco, Arg. Laboratorio Larco SA, Campana 3432, (1417) Buenos Aires, Argentina.

Largen, Philipp. Largen Med Inc., 1604 Antel Global Bldg, J Vargas St, Ortigas Center, Pasig City, Philippines.

L'Arguenon, Fr. See *SERB, Fr.*

Larjan, Arg. See *Veinfar, Arg.*

Lark, India. Lark Laboratories (India) Ltd, A-105/2, Okhla Industrial Area Phase 2, New Delhi 110 020, India.

Lark, Philipp. See *Medbridge, Philipp.*

Larken, USA. Larken Laboratories Inc., 276 Nissan Parkway, Suite B, Canton, MS 39046, USA.
url: www.larkenlabs.com

Larkhall Laboratories, UK. Larkhall Laboratories, Forest Road, Charlbury, Chipping Norton, Oxon, OX7 3HH, UK.

Laroche Navarron, Belg. See *Roche, Belg.*

Laroche Navarron, Neth. See *Bournonville, Neth.*

Larose, Canad. Larose & Fils Ltd, 2255 Blvd Industriel, Laval, Quebec, H7S 1P8, Canada.

Lasa, Spain. See *Ipsen, Spain.*

Laser, UK. See *Ceuta, UK.*

Laser, USA. Laser Pharmaceuticals LLC, 6003 Ponders Court, Greenville, SC 29615, USA.
url: www.laserpharmaceuticals.com

Latema, Fr. See *Solvay, Fr.*

Latinofarma, Braz. Latinofarma Indistrias Farmacêuticas Ltda, Rua Dr Tomas Sepe 489, 6711270 Jardim da Gloria Cotia, São Paulo, Brazil.

Lauria, Arg. Lauria, Merlino & Cía. S.C., Av. La Plata 340/44, 1235 Buenos Aires, Argentina.

Laus, Spain. See *Novartis, Spain.*

Lavena, Rus. See *Sopharma, Rus.*

Laves, Ger. Laves-Arzneimittel GmbH, Barbarastr. 14, 30952 Ronnenberg, Germany.
url: www.laves-pharma.de

Laves, Switz. Laves-Arzneimittel GmbH, Lavesstrasse, 6247 Schötz, Switzerland.
url: www.laves-pharma.ch

Lavigor, Spain. Lavigor 7000 SL, Barrio San Mames s/n, Derio, Spain.

Lavipharm, Fr. Laboratoires Lavipharm, 27 rue de Marignan, 75008 Paris, France.

Lavipharm, Gr. Lavipharm Group, Agias Marinas St, 190 02 Peania Attica, Greece.
url: www.lavipharm.gr

Lavipharm, Irl. See *Lavipharm, Gr.*

Lavipharm, Israel. See *Megapharm, Israel.*

Lavipharm, Neth. See *Lavipharm, Gr.*

LAW, Ger. See *Riemser, Ger.*

Lawley, Austral. Lawley Pharmaceuticals, 61 Walcott St, Mt Lawley, Perth, WA 6050, Australia.
url: www.lawleypharm.com.au

Lawson, Canad. See *Lawson, USA.*

Lawson, USA. Lawson Products Inc., 1666 East Touhy Ave, Des Plaines, IL 60018-3683, USA.

Layton, USA. Layton Bioscience Inc., 709 E Evelyn Ave, Sunnyvale, CA 94086, USA.
url: www.laytonbio.com

Lazar, Arg. Laboratorio Dr. Lazar & Cia. S.A., Av. Velez Sarsfield 5855, 1605 Carapachay, Buenos Aires, Argentina.
url: www.lazar.com.ar

Lazuli, Malaysia. Lazuli Sdn Bhd, 18 Jln SS 5 A/9, 47301 Petaling Jaya, Selangor, Malaysia.

LBS, Malaysia. See *Antah, Malaysia.*

LBS, Philipp. See *International Apex, Philipp* and *Pharmawealth, Philipp.*

LBS, Thai. LBS Laboratory Ltd Part, 602 Soi Phanichanant, Sukhumvit 71 Rd, Bangkok 10110, Thailand.
url: www.lbslab.com

LCA, Belg. LCA, Belgium.

LCA, Fr. Laboratoire LCA, 9 allée Promethée, 28000 Chartres, France.

LCH, Hong Kong. Luen Cheong Hong Ltd, 25/F, 200 Gloucester Rd, Wanchai, Hong Kong.

LDA, Arg. Lab. LDA SA, Alcaraz 5294, 1407 Buenos Aires, Argentina.

LDP, Rus. Laboratoire de Development Pharmaceutique, Nikolskaya ul. 19, ot. 9, 109012 Moscow, Russia.

LDP, Spain. See *Torlan, Spain.*

LDP Torlan, Spain. See *Torlan, Spain.*

Le Naturiste, Canad. Le Naturiste JMB Inc., 5900 Henri-Bourassa Ouest, Saint-Laurent, Quebec, H4R 1V9, Canada.

Leader, Hong Kong. Leader Pharmaceutical & Cosmetic Co. Ltd, 2/F, 42 Hankow Rd, Kowloon, Hong Kong.

LeBasi, S.Afr. LeBasi Pharmaceuticals, Jankra Building, 2nd Floor, 3 Greyling St, Northwest 2520, South Africa.

Lebeh, USA. Lebeh, USA.

Leben, India. Leben Laboratories Pvt Ltd, 11 Mahavir Mansion, 70 Trinity Street, Mumbai 400 002, India.
url: www.lebenlab.com

Leciva, Cz. Léčiva as, U Kabelorny 130, 10237 Prague 10, Czech Republic.
url: www.leciva.cz

Leciva, Hung. See *Leciva, Cz.*

Leciva, Rus. Leciva ZAO, Prechistenka 40/2, Bld.1, Gate 2, 5th floor, 113054 Moscow, Russia.

Lectec, USA. LecTec Corp., 5616 Lincoln Dr., Edina, MN 952933-2291, USA.
url: www.lectec.com

Leda, Canad. Leda Health Innovations Inc., 1054 Centre St, Thornhill, Ontario, L4J 8E5, Canada.

Lederle, Austral. See *Wyeth, Austral.*

Lederle, Cz. See *Wyeth, Cz.*

Lederle, Fr. See *Wyeth Lederle, Fr.*

Lederle, Ger. See *Pfizer, Ger.*

Lederle, Hong Kong. See *Wyeth, Hong Kong.*

Lederle, Indon. See *Wyeth, Indon.*

Lederle, Irl. See *Wyeth, Irl.*

Lederle, Israel. See *Neopharm, Israel.*

Lederle, Jpn. See *Wyeth Lederle, Jpn.*

Lederle, Neth. See *Wyeth, Neth.*

Lederle, Norw. See *Wyeth Lederle, Norw.*

Lederle, NZ. See *Wyeth, NZ.*

Lederle, S.Afr. See *Wyeth, S.Afr.*

Lederle, Singapore. See *Wyeth, Singapore.*

Lederle, Switz. See *AHP, Switz.*

Lederle, Thai. See *Wyeth-Ayerst, Thai.*

Lederle, UK. See *Wyeth, UK.*

Lederle, USA. See *Wyeth, USA.*

Lederle Consumer, Canad. See *Whitehall-Robins, Canad.*

Lee, USA. Lee Pharmaceuticals, 1434 Santa Anita Ave., South El Monte, CA 91733, USA.
url: www.leepharmaceuticals.com

Lee-Adams, Canad. Lee-Adams Laboratories, 611 Royalmount Ave, Montreal, Quebec, H4P 2T4, Canada.

Leemed, India. Leemed, F-199 Transport Nagar, Kanpur Road, Lucknow 226 012, India.

Leeming, USA. See *Pfizer, USA.*

Lefnin, Rus. Lefnin OOO, Stasovoi ul. 2-B, 117071 Moscow, Russia.
url: www.lefnin.ru

Legacy, Fr. Laboratoire Legacy Healthcare (France) SAS, 27 av de l'Opéra, 75001 Paris, France.

Legrand, Braz. See *EMS, Braz.*

Legras, Fr. Laboratoires Legras, 114 Bis, rue Michel-Ange, 75016 Paris, France.

Lehn & Fink, USA. See *Reckitt Benckiser, USA.*

Lehning, Canad. See *Lehning, Fr.*

Lehning, Cz. See *Lehning, Fr.*

Lehning, Fr. Laboratoires Lehning, 1-3 rue du Petit-Marais, 57640 Sainte-Barbe, France.
url: www.lehning.com

Leib, Canad. See *Leib, USA.*

Leib, USA. Leib Research, 55 345 State Route 17, Upper Saddle River, NJ 07458, USA.

Leidapharm, Neth. Leidapharm BV, Archimedesweg 2, 2333 CN Leiden, Netherlands.

Leiras, Austria. See *Leiras, Fin.*

Leiras, Cz. See *Leiras, Fin.*

Leiras, Denm. See *Nycomed, Denm.*

Leiras, Fin. Oy Leiras Finland AB, PL 1406, 00101 Helsinki, Finland.
url: www.leiras.fi

Leiras, Indon. See *Dexa, Indon.*

Leiras, Israel. See *Perrigo, Israel.*

Leiras, Norw. See *Schering, Norw.*

Leiras, Rus. See *Schering, Rus.*

Leiras, Singapore. See *MBD, Singapore.*

Leiras, Swed. See *Schering, Swed.*

Leiras, Thai. See *Berli Jucker, Thai.*

Leiras Synthelabo, Fin. See *Leiras, Fin.*

Leitner, USA. Leitner Pharmaceuticals, 340 Edgemont Ave, Ste 300, Bristol, Tennessee 37620, USA.
url: www.leitnerpharmaceuticals.com

Lejal, Philipp. Lejal Laboratories Inc., Km 18 MacArthur Highway, Meycauayan, Bulacan, Philippines.

Lek, China. See *Sandoz, China.*

Lek, Cz. Lek Pharma sro, Jeseniová 30, 130 00 Prague 3, Czech Republic.

Lek, Hong Kong. See *Hind Wing, Hong Kong.*

Lek, Hung. Lek, Verovskova 57, 1526 Ljubljana, Slovenia.

Lek, Neth. See *Lek, Pol.*

Lek, Pol. Lek Polska Sp. za.o., ul. Domaniewska 50 C, 02-672 Warsaw, Poland.
url: www.lek.com.pl

Lek, Rus. Lek, Starokonyushennyi per. 10/10 str. 1, 119002 Mascow, Russia.

Lek, Singapore. See *FP, Singapore.*

Lek, Thai. See *RX, Thai.*

Lek, Ukr. See *Sandoz, Ukr.*

Lek-Am, Pol. Przedsiębiorstwo Farmaceutyczne Lek-Am Sp. zo.o., ul. Padwale 23, 00-261 Warsaw, Poland.
url: www.lekam.pl

Lekfarm, Rus. Lekform, ul. Krasnaya 115, 236000 Kaliningrad, Russia.
url: www.lekfarm.com

Lekhim, Ukr. JSC Lekhim, 23 Shota Rustaveli St, 01033 Kiev, Ukraine.
url: www.lekhim.ua

Leki Natury, Pol. Przedsiębiorstwo Farmaceutyczne Leki Natury, ul. Zielona 30, 08-500 Ryki, Poland.

Lekkhim-Kharkov, Rus. See *Citomed, Rus.*

Lekko, Rus. See *Masterlek, Rus.*

Leksir, Rus. Leksir, Krylatskie kholmy St 30, corp. 9, 121614 Moscow, Russia.
url: www.filtrum.ru

Leksredstva, Rus. Farmstandart-Leksredstva JSC, 1a/18 2-ya Agregatnaya u, 305909 Kursk, Russia.

Lektravy, Ukr. ZAO Lektravy, Kiev Highway 21, 10001 Zhitomir, Ukraine.
url: www.liktravy.com.ua

Lema, Philipp. Lema Pharmaceuticals Inc., Suite 201 Menchavez Bldg, Escario St, Cebu City, Philippines.

Lemon, Fr. See *Proteika, Fr.*

Lemax, Arg. Lemax Laboratorios SRL, Neuquin 923, 1752 Lomas del Mirador, Buenos Aires, Argentina.

Lemery, Cz. See *Medicom, Cz.*

Lemery, India. Lemery, 11 Mahavir Mansion, 70 Trinity St, Mumbai, 400 002, India.

Lemery, Mex. Lemery S.A. de C.V., Calle 1 No. 5-A Interior 101, Mabuel Avila Camacho, 11610 Mexico D.F., Mexico.

Lemery, Rus. See *Sicor, Rus.*

Lemery, Thai. See *Pharmaland, Thai.*

Lemmon, USA. See *Teva, USA.*

Lennod, USA. Lennod, USA.

Lennon, Austral. Lennon Healthcare Research PL, 1 Camelot Place, St Ives, NSW 2075, Australia.

Lennon, S.Afr. See *Aspen, S.Afr.*

Lens, Rus. See *Veropharm, Rus.*

Lensa, Spain. Lensa, Potosi 2-4, 08030 Barcelona, Spain.

Leo, Austral. Leo Pharma Pty Ltd, Level 3, Tower One, 25 Montpelier Rd, Bowen Hills, Qld 4006, Australia.
url: www.leo-pharma.com

Leo, Austria. Leo Pharma Gesellschafttmbh, Mariahilfer Strasse 123/4.OG, A-1060 Vienna, Austria.
url: www.leopharma.com

Leo, Belg. Leo Pharma SA, Sneeuwbeslaan 20, 2610 Wilrijk, Belgium.
url: www.leo-pharma.be

Leo, Canad. Leo Pharma Inc., 123 Commerce Valley Dr. E, Suite 400, Thornhill, Ontario, L3T 7W8, Canada.Director Regulatory Affairs
url: www.leopharma.ca

Leo, China. Leo Pharma Consultancy (Shanghai) Co. Ltd, Unit 9-11A, F39 The Center, 989 Chang Le Rd, Xu Hui, Shanghai, 200031, China.
url: www.leo-pharma.cn

Leo, Cz. See *Leo, Denm.*

Leo, Denm. Leo Pharma A/S

Leo, Fin. Leo Pharma Oy, Äyritie 12 B, 01510 Vantaa, Finland.
url: www.leo-pharma.fi

Leo, Fr. Laboratoires Leo, B.P. 311, 78054 St-Quentin-Yvelines cdx, France.Health Regulatory Affairs Manager
url: www.leo-pharma.com/fr

Leo, Ger. Leo Pharma GmbH, Frankfurter Str. 233, A3, 63263 Neu-Isenburg, Germany.
url: www.leo-pharma.de

Leo, Gr. Leo Pharmaceutical Products Hellos Ltd., 30 Vas. Georgiou & Mikras Asias, 152 33 Calandri, Greece.
url: www.leo-pharma.gr

Leo, Hong Kong. See *Keller, Hong Kong.*

Leo, Hung. See *Medicine & Business, Hung.*

Leo, India. Leo Formulations Pvt Ltd, 1 Vaibhav Shree, 54 Bhaikaka Nagar, Thaltej, Ahmedabad 380 059, India.
url: www.adamasleo.com

Leo, Indon. See *Darya-Varia, Indon.*

Leo, Irl. Leo Laboratories Ltd, 285 Cashel Rd, Dublin 12, Ireland.
url: www.leo.ie

Leo, Israel. See *Dexxon, Israel.*

Leo, Malaysia. See *DKSH, Malaysia* and *Summit, Malaysia.*

Leo, Neth. Leo Pharma BV, Hoge Mossen 16-20, 4822 NH Breda, Netherlands.
url: www.leopharma.com

Leo, Norw. Leo Pharma AS, Postboks 193 Lilleaker, 0216 Oslo, Norway.
url: www.leo.no

Leo, NZ. See *CSL, NZ.*

Leo, Philipp. See *Zuellig, Philipp.*

Leo, Pol. See *Perffarma, Pol.*

Leo, Port. Leo-Farmoceuticos, Lda, Av das Nações Unidas 27, 1600-531 Lisbon, Portugal.
url: www.leopharmo.com

Leo, Rus. See *Onyx, Rus.*

Leo, S.Afr. See *Adcock Ingram, S.Afr.*

Leo, Singapore. Leo Pharma Singapore, 6A Maju Ave, S 556684, Singapore.
url: www.leopharma.com

Leo, Spain. Leo Pharma, Marina 16-18, 08005 Barcelona, Spain.
url: www.farmacusi.es

Leo, Swed. Leo Pharma AB, Box 404, 201 24 Malmö, Sweden.
url: www.leo.se

Leo, Switz. Leo Pharmaceutical Products Sarath Ltd, Eichwatt 5, Postfach 1154, 8105 Regensdorf-Watt, Switzerland.
url: www.leopharma.com

Leo, Thai. See *Olic, Thai.*

Leo, UK. Leo Pharma, Longwick Rd, Princes Risborough, Buckinghamshire, HP27 9RR, UK.
url: www.leo-pharma.co.uk

Leo, USA. Leo Pharma Inc., 1 Sylvan Way, Parsippany, NJ 07054, USA.
url: www.leo-pharma.us

Leo (Λεο), Gr. See *Leo, Gr.*

Leon, Cz. See *Leon, Spain.*

Leon, Gr. See *Aledicine, Gr.*

Leon, Irl. See *Leon, Spain.*

Leon, Neth. See *Leon, Spain.*

Leon, Spain. Laboratorios León Farma, Polígono Industrial Navatejera, C/ La Vallina s/n, 24008 Navatejera, Spain.
url: www.chemogroup.com

Leon, Thai. See *DKSH, Thai.*

Leontik, Gr. Leontik AE, Kon. Palaiologou 6, 10438 Athens, Greece.

Leopold, Austria. Leopold Pharma GmbH, Hafnerstrasse 36, A-8055 Graz, Austria.

Leopold, Cz. See *Leopold, Austria.*

Leovan, Gr. Leovan M. Aedn & Cia EE, 22 Argonayton Str., 167 77 Elliniko, Greece.

Lepetit, Arg. Lepetit Pharma SA, Saladillo 2452/2468, (1440) Buenos Aires, Argentina.

Lepetit, Cz. See *Sanofi-Aventis, Ital.*

Lepetit, Fr. See *Sanofi-Aventis, Fr.*

Lepetit, Ital. See *Sanofi-Aventis, Ital.*

Lepicol, Hong Kong. See *Mekim, Hong Kong.*

Lepine, Canad. Les Produits Sanitaires Lépine Inc., 1105 Bersimis, Chicoutimi, Quebec, G7K 1A4, Canada.

Lepori, Port. See *Angelini, Port.*

Leppin, S.Afr. See *Adcock Ingram, S.Afr.*

Lernapharm, Canad. Lernapharm (Loris) Inc., 2323 Halpern, St Laurent, Quebec, H4S 1S3, Canada.

Lero, Fr. Léro, 20 rue Arago, 92700 Colombes, France.

Leros, Cz. Leros sro, U Narodni galerie 460, 156 15 Prague 5, Czech Republic.
url: www.leros.cz

Lersan, Arg. See *Pharmos, Arg.*

Les 3 Chenes, Ital. Les 3 Chenes Italia S.r.l., Viale Gozzadini 19, 40124 Bologna (BO), Italy.

Lesourd, Fr. Laboratoires Gabriel Lesourd, 6 rue Ste-Isaure, 75018 Paris, France.

Lessel, Braz. See *Mepha, Braz.*

Lestral, Spain. Laboratorios Lestral SA, Avenida de los Madroños 33, 28043 Madrid, Spain.

Lesvi, Spain. See *Vita, Spain.*

Leti, Ger. Leti Pharma GmbH, Stockumer Str. 28, 58453 Witten, Germany.
url: www.leti.de

Leti, Spain. Laboratorios Leti, Gran Via de las Corts Catalanes 184, 08038 Barcelona, Spain.
url: www.leti.com

Leti, Venez. Laboratorio Leti S.A.V., 2a Av., Parcela 3, Manzana J Edif. Leti, Guarenas, Caracas, Venezuela.
url: www.leti.com.ve

Leti Gentek, Venez. See *Leti, Venez.*

Leurquin, Canad. See *Leurquin, Fr.*

Leurquin, China. See *Innoledge, China.*

Leurquin, Fr. Laboratoires Leurquin Mediolanum, 68/88 rue Ampere, 93330 Neuilly-sur-Marne, France.
url: www.mediolanum-farma.com

Leurquin, Hong Kong. See *Innoledge, Hong Kong.*

Leurquin, Switz. See *Uhlmann-Eyraud, Switz.*

Leurquin Mediolanum, Hung. See *Ubepharm, Hung.*

Lev, USA. Lev Pharmaceuticals, 675 Third Ave, Suite 2200, New York, NY 10017, USA.
url: www.levpharma.com

Lever, UK. Lever Faberge, 3 St James Rd, Kingston-upon-Thames, Surrey, KT1 2BA, UK.
url: www.leverfaberge.co.uk

Lever Pond's, Canad. See *Unilever, Canad.*

Levlad, Canad. See *Levlad, USA.*

Levlad, USA. Levlad LLC, 9200 Mason Ave, Chatsworth, CA 91311-6005, USA.

Levofarma, Ital. See *Uno, Ital.*

Levy, Israel. Levy Dental Co Ltd, 27 Kalisher St, 65165 Tel Aviv, Israel.
url: www.dentaldepot.co.il

Lewison, Philipp. Lewison Pharmaceuticals Corp., 88 Teresa Bldg, 15th Ave, Murphy, Cubao, Quezon City, Philippines.

Lexica, India. Lexica Drugs & Formulations Pvt Ltd, F2/2 Krishna Complex Refinary Road, Gorwa, Baroda 380 016, India.

Lexis, USA. Lexis Laboratories, P.O. Box 202887, Austin, TX 78720, USA.

Lexon, UK. Lexon (UK) Ltd, 18 Oxleasow Rd, East Moons Moat, Redditch, Worcestershire, B98 ORE, UK.
url: www.lexonuk.com

Lexus, India. Lexus (India) Organics, 85 Chetan Market, Nr. Sarangpur Gate, Ahmedabad 380 001, India.

Leyh, Ger. Leyh Pharma GmbH, Gewerbegebeit Baierstal, 98596 Trusetal, Germany.

Leyton, Arg. See *Dissa, Arg.*

LF, China. LF Asia Healthcare Co. Ltd, 2000 Main Building 8th Floor, Yishan Li & Fung Plaza, Shanghai, 201103, China.

LF, Singapore. LF Asia Pharmaceutical Division, a Li & Fung Company, 279 Jalan Ahmad Ibrahim, 03-01 S-639938, Singapore.

LF, Thai. LF Asia (Thailand) Ltd, 51 8/5 Maneeya Center 10Fl, Ploenchit, Lumoini, Pathumwan, Bangkok 10330, Thailand.

LFB, Cz. See *LFB, Fr.*

LFB, Denm. See *LFB, Fr.*

LFB, Fin. See *LFB, Fr.*

LFB, Fr. LFB Biomedicaments, 3 av des Tropiques, B.P. 305, Les Ulis, 91958 Courtaboeuf cdx, France.
url: www.lfb.fr

LFB, Ger. Laboratoire Francais du fractionnement st des Biotechnologies, Lebacher Str. 4, 66113 Saarbrücken, Germany.
url: www.lfb.fr

LFB, Neth. See *LFB, Fr.*

LFB, Norw. See *Swedish Orphan, Norw.*

LFB, Port. See *LFB, Fr.*

LG, China. LG Life Sciences, 11th Floor 12B West Tower, Jianguomen Wai Avenue, Chaoyang, Beijing, 100022, China.
url: www.china.lgls.com

LG, Philipp. See *Zuellig, Philipp.*

LG, Pol. See *Sanofi-Aventis, Pol.*

LG Chem, Thai. See *Sanofi Pasteur, Thai.*

LG Life Sciences, India. LG Life Sciences India Pvt Ltd, LG House, AB-3 Safdarjung Enclave, New Delhi 110 029, India.

LG Life Sciences, Malaysia. See *Duopharma, Malaysia.*

LG Life Sciences, Philipp. See *Zuellig, Philipp.*

LG Life Sciences, Rus. See *LG Life Sciences, India.*

LG Life Sciences, Thai. See *Novatec, Thai.*

LG Pharm, Hong Kong. See *Hind Wing, Hong Kong.*

LHT-TEN, Israel. LHT-TEN, Israel.

Li Chung Yun, Canad. Li Chung Yun Co., 5 13550 77th Ave, Surrey, British Colombia, V3W 6Y3, Canada.

Li Jie Xun, China. Li Jie Xun Pharmaceutical Co Ltd, China.

Li Neng Kang Tai, China. Li Neng Kang Tai Pharnaceutical Co. Ltd, Hainan, China.

Liade, Spain. See *Abbott, Spain.*

Lian He, China. Lian He Pharmaceutical Co Ltd, Hebei, China.

Liang Fu, China. Liang Fu Pharmaceutical Co Ltd, Shandong, China.

Lianhuan, China. Lianhuan Pharmaceutical Co. Ltd, 21 Wenfeng Rd, Yangzhou 225009, Jiangsu, China.
url: www.lhpharma.com

Liansheng, China. Liansheng Pharmaceutical Co. Ltd, 3 Jinquan Rd, Langtou, Dandong, Liaoning, 118009, China.

Lianshui, China. Lianshui Pharmaceutical Co. Ltd, 75 Qubei Rd, Huai'An, Jiangsu, Lianshui, 223400, China.

Liaoning Chengda, Philipp. See *Pharma-Surrey, Philipp.*

Liaoyuan Yadong, China. Liaoyuan Yadong Pharmaceutical Co. Ltd, China.

Liba, Turk. Liba Laboratuvarları A.Ş., Otağtepe Cad. No: 5, Kavacık, İstanbul, 81610, Turkey.

Libang, China. Libang Pharmaceutical Co. Ltd, China.

Libbs, Braz. Libbs Farmacêutica Ltda, Rua Josef Kryss 250, 01140-050 São Paulo, SP, Brazil.
url: www.libbs.com.br

LIBP, Hong Kong. See *Hugh Source, Hong Kong.*

Librapharm, Spain. See *Grunenthal, Spain.*

Libytec, Gr. Libytec Pharmaceuticals SA, 24 Vouliagmenis, 167 77, Greece.

Licher, Ger. Licher Medizintechnologie, Langer Acker 18, 30900 Wedemark, Germany.
url: www.lichermt.de

Lichtenstein, Austria. See *Lichtenstein, Ger.*

Lichtenstein, Cz. See *Lichtenstein, Ger.*

Lichtenstein, Ger. Lichtenstein Pharmazeutica GmbH & Co., Industriestrasse 26, 56218 Mulheim-Karlich, Germany.

Lichtwer, Austria. See *Lichtwer, Ger.*

Lichtwer, Canad. Lichtwer Pharma, 145 Idema Road, Markham, Ontario, L3R 1A9, Canada.
url: www.lichtwer.de

Lichtwer, Cz. See *Lichtwer, Ger.*

Lichtwer, Ger. Lichtwer Healthcare GmbH & Co. KG, Wallenroder Str. 8-10, 13435 Berlin, Germany.
url: www.lichtwer.de

Lichtwer, Neth. See *Lichtwer, Ger.*

Lichtwer, Switz. See *Adroka, Switz.*

Lichtwer, UK. Lichtwer Pharma UK, Regency House, Mere Park, Dedmere Rd, Marlow, Buckinghamshire, SL7 1FJ, UK. The Managing Director
url: www.lichtwer.co.uk

Liconsa, Cz. See *Liconsa, Spain.*

Liconsa, Denm. See *Liconsa, Spain.*

Liconsa, Fin. See *Liconsa, Spain.*

Liconsa, Hung. See *Liconsa, Spain.*

Liconsa, Irl. See *Liconsa, Spain.*

Liconsa, Israel. See *Liconsa, Spain.*

Liconsa, Ital. See *Liconsa, Spain.*

Liconsa, Neth. See *Liconsa, Spain.*

Liconsa, Pol. See *ProMed, Pol.*

Liconsa, Port. See *Liconsa, Spain.*

Liconsa, Rus. See *Gedeon Richter, Rus.*

Liconsa, Spain. Liconsa S.A., Gran Via de Carlos III, 98 - 7, 08028 Barcelona, Spain.
url: www.liconsa.com

Liconsa, Swed. See *Liconsa, Spain.*

Liebermann, Austria. See *Liebermann, Ger.*

Liebermann, Ger. Pharma Liebermann GmbH, Hauptstr. 27, 89423 Gundelfingen/Do., Germany.
url: www.pharma-liebermann.de

Lierac, Fr. Laboratoires Liérac, 35 av Franklin-Roosevelt, 75008 Paris, France.

Lierfan, China. Lierfan Pharmaceutical Co. Ltd, Changchun, China.

Life, Israel. See *Rekah, Israel.*

Life Concern, Thai. Life Concern, Thailand.

Life Essence, UK. Life Essence Ltd, 24 St Clairs Rd, Croydon, Surrey, CR0 5NE, UK.

Life Line, India. Life Line Biotech Ltd, B 86 Okhla Industrial Area Phase 2, New Delhi 110 020, India.
url: www.lifelinebiotech.com

Life Medicare, India. Life Medicare & Biotech, A-2 Mohan Co-operative Industrial Estate, Mathura Rood, New Delhi 110 044, India.
url: www.lifemedicarebiotech.com

Life Plus, Canad. See *Life Plus, USA.*

Life Plus, UK. Life Plus Europe Ltd, Little End Rd, Eaton Socan, Cambridgeshire, PE19 8JH, UK.
url: www.lifeplus.com

Life Plus, USA. Life Plus International, 50 Industrial Drive, Batesville, Arkansas, 72501, USA.

Lifebiotech, Switz. LifeBiotech AG, Gattikerstrasse 5, Postfach, 8029 Zurich, Switzerland.

Lifecare, India. Lifecare Innovations Pvt Ltd, B-589 Sushant Lok1, Gurgaon 122 002, India.

Lifeforce, Canad. Lifeforce Nutri-Blends Canada Inc., 106-2293 Leckie Rd, Kelowna, British Columbia, V1X 6Y5, Canada.

Lifeike, China. Lifeike Pharmaceutical Co. Ltd, Fujian, China.

Lifeon, India. Lifeon Paediatrics Ltd, B.S.D. Marg, Govandi, Mumbai 400 088, India.

Lifepharma, China. See *Lifepharma, Ital.*

Lifepharma, Ital. Lifepharma S.p.A., Via dei Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy.

Lifepharma, Rus. See *Italfarmaco, Rus.*

Lifeplan, UK. Lifeplan Products, Elizabethan Way, Lutterworth, Leicestershire, LE17 4ND, UK.
url: www.lifeplan.co.uk

Liferpal, Mex. Liferpal MD, S.A. de C.V., Refineria No. 1266, Col. Alamo Industrial, 44490 Guadalajara, Jalisco, Mexico.

Lifescan, Canad. Lifescan Canada, 4170 Still Creek Drive, Suite 234, Burnaby, British Columbia, V5C 6C6, Canada.
url: www.lifescancanada.com

Lifescan, Fr. Laboratoires Lifescan, Division d'Ortho-Clinical Diagnostics, 1 rue Camille-Desmoulins, TSA 40007, 92787 Issy-les-Moulineaux cdx 9, France.
url: www.lifescanfrance.com

Lifescan, Irl. See *Fulcrum, Irl.*

Lifescan, Ital. See *Johnson & Johnson, Ital.*

Lifescan, Port. See *Johnson & Johnson, Port.*

Lifescan, USA. Lifescan, 1000 Gibraltar, Milpitas, CA 95035-6312, USA.
url: www.lifescan.com

Lifeshine, China. Lifeshine Pharmaceutical Co. Ltd, Beijing, China.

Lifesign, USA. LifeSign LLC, Somerset, NJ 08875-0218, USA.
url: www.lifesignmed.com

Lifesource, India. Lifesource Healthcare, A/39 Nandjyot Indl Estate, Kurla-andheri Rd, Mumbai 400072, India.

Lifesource, Rus. See *Lifesource, India.*

Lifestyle, India. Lifestyle Biosciences, 52 Industrial Area, Phase 1, Chandigarh 160 002, India.

Lifestyle, UK. See *Ultrapharm, UK.*

Lifestyles, Canad. Lifestyles Canada Corp., 8100 Keele St, Vaughan, Ontario, L4K 2A3, Canada.

Lifetech, Hong Kong. Lifetech Enterprises Inc., Suite 3808, New World Tower, 18 Queen's Rd Central, Hong Kong.
url: www.lifetechgroup.com

Ligand, Austria. See *Ligand, UK.*

Ligand, Canad. See *Ligand, USA.*

Ligand, Denm. See *Cephalon, Denm.*

Ligand, Neth. See *Ligand, UK.*

Ligand, Norw. See *Cephalon, Denm.*

Ligand, UK. Ligand Pharmaceuticals UK Ltd, 108 High St, Crawley, West Sussex, RH10 1BB, UK.

Ligand, USA. Ligand Pharmaceuticals Inc., 10275 Science Center Dr, San Diego, CA 92121, USA.
url: www.ligand.com

Ligi, Canad. Ligi Inc., 6 30 Macintosh Blvd, Vaughan, Ontario, L4K 4P1, Canada.

Lihua, China. Ningbo Lihua Pharmaceutical Co. Ltd, 16 Wangjin Rd, Gaoqiao Industrial Park, Yinzhou, Ningbo, Zhejiang, 315010, China.

Li-il, Ger. Li-il GmbH Arzneibäder-Arzneimittel, Leipziger Str. 300, 01139 Dresden, Germany.
url: www.li-il.de

Lijian, China. Lijian Pharmaceutical Co. Ltd, China.

Lijun, China. Lijun Pharmaceutical Co. Ltd, China.

Likang, China. Likang Pharmaceutical Co. Ltd, Gongbei Guihua North Rd, Zhuhai, 519020, China.

Lil' Drug Store, Singapore. See *Capsule, Singapore.*

Lil Drug Store, USA. Lil' Drug Store Products, 1201 Continental Place NE, Cedar Rapids, IA 52402, USA.
url: www.lildrugstore.com

Lilly, Arg. Eli Lilly Interamerica Inc., Av. Scalabrini Ortiz 3333 5 Piso, 1425 Buenos Aires, Argentina.
url: www.lilly-argentina.com

Lilly, Austral. Eli Lilly Australia P/L, 112 Wharf Rd, West Ryde, NSW 2114, Australia.
url: www.lilly.com

Lilly, Austria. Eli Lilly GmbH (Austria), Barichgasse 40-2, A-1030 Vienna, Austria.
url: www.lilly.at

Lilly, Belg. Eli Lilly Benelux SA, Rue de l'Etuve 52 boite 1, 1000 Brussels, Belgium. Medical Information Manager
url: www.lilly.be

Lilly, Braz. Eli Lilly do Brasil Ltda, Avenida Morumbi 8264, 04703-002 São Paulo, SP, Brazil.
url: www.lilly.com.br

Lilly, Canad. Eli Lilly Canada Inc., 3650 Danforth Ave, Toronto, Ontario, M1N 2E8, Canada.
url: www.lilly.ca

Lilly, Chile. Eli Lilly de Chile Ltda, Carmencita 25, Of. 91, Las Condes, Santiago, Chile.

Lilly, China. Eli Lilly Suzhou Pharmaceutical Co Ltd, Corporate Ave Building 1, 21st Floor, 222 Hubin Rd, Luwan District, Shanghai 200021, China.
url: www.lillychina.com

Lilly, Cz. Eli Lilly ČR sro, Pařížská 11, 110 00 Prague 1, Czech Republic.

Lilly, Denm. Eli Lilly Denmark A/S, Nybrovej 110, 2800 Lyngby, Denmark.
url: www.eli-lilly.dk

Lilly, Fin. Oy Eli Lilly Finland AB, Rajatorpantie 41 C 3. krs, PL 16, 01641 Vantaa, Finland.
url: www.lilly.fi

Lilly, Fr. Lilly France, 13 rue Pages, 92158 Suresnes Cdx, France.
url: www.lilly.fr

Lilly, Ger. Lilly Deutschland GmbH, Werner-Reimers-Str. 2-4, 61352 Bad Homburg, Germany.
url: www.lilly-pharma.de

Lilly, Gr. Pharmaserve Lilly, 15th klm National Rd, 145 64 Lamia, Greece.
url: www.lilly.com

Lilly, Hong Kong. Eli Lilly Asia Inc., 27/F CITIC Tower, 1 Tim Mei Ave Central, Hong Kong.
url: www.lilly.com

Lilly, Hung. Lilly Hungária Kft, Madách Imre u 13-14 VII em, 1075 Budapest, Hungary.

Lilly, India. E Lilly and Company (India), Plot No. 92, Sector 32, Gurgaon 122 001, India.
url: www.lilly.com

Lilly, Indon. Eli Lilly Indonesia, Summitmas II Bldg 5th Fl, Jl Jend Sudirman Kav 61-62, Jakarta 12190, DKI Jaya, Indonesia.

Lilly, Irl. Eli Lilly & Co. (Ireland) Ltd, Hyde House, 65 Adelaide Rd, Dublin 2, Ireland. The Managing Director
url: www.lilly.ie

Lilly, Israel. Eli Lilly Israel Ltd, P.O. Box 2160, Herzliya Pituah, Israel.
url: www.lilly.com

Lilly, Ital. Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019 Sesto Fiorentino (FI), Italy.
url: www.lilly.it

Lilly, Jpn. Eli Lilly Japan K.K., 7-1-5 Isogami-dori, Chuo-ku Kobe, Hyago 651-0086, Japan.
url: www.lilly.com

Lilly, Malaysia. Eli Lilly (M) Sdn Bhd, 18.1, 18th Floor, CP Tower, No. 11, Section 16/11, Pusat Dagang Seksyen 16, 46350 Petaling Jaya, Selangor, Malaysia.
url: www.lilly.com

Lilly, Mex. Eli Lilly y Compania de Mexico S.A. de C.V., Calz de Tlalpan No. 2024, Col Compestre Churubusco, Deleg. Coyoacan, 04200 Mexico D.F., Mexico.
url: www.lilly.com.mx

Lilly, Neth. Eli Lilly Nederland, Grootschlag 1-5, 3991 RA Houten, Netherlands.
url: www.lilly.com

Lilly, Norw. Eli Lilly Norge A.S, Grensev. 99, Postboks 6090 Etterstad, 0601 Oslo, Norway.
url: www.lilly.no

Lilly, NZ. Eli Lilly & Co. (NZ) Ltd, P.O. Box 97-046, South Auckland Mail Centre, Wiri, Auckland, New Zealand.
url: www.lilly.co.nz

Lilly, Philipp. Eli Lilly (Phils) Inc., 32/F Wynsum Corporate Plaza, 22 Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

Lilly, Pol. Eli Lilly Polska Sp. zo.o., al. Armii Ludowej 14, 00-638 Worsaw, Poland.
url: www.lilly.home.pl

Lilly, Port. Lilly Farma, Lda, Rua Dr António Loureiro Borges 4, Piso 3, Arquiparque, Miraflores, 1495-131 Algés, Portugal.
url: www.lilly.com

Lilly, Rus. Eli Lilly Vostok SA, Sadovaya-Samotechnaya ul. 24/27, 127051 Moscow, Russia.
url: www.lilly.com

Lilly, S.Afr. Eli Lilly (SA) (Pty) Ltd, 1 Petunia St., Corner Main Road, Brynston 2021, South Africa.
url: www.lilly.co.za

Lilly, Singapore. Eli Lilly (S) Pte Ltd, 7 Temasek Boulevard, 15-01 Suntec City Tower 1, S 038987, Singapore.
url: www.lilly.com.sg

Lilly, Spain. Lilly, Avda de la Industria 30, Alcobendas, 28108 Madrid, Spain.
url: www.lilly.es

Lilly, Swed. Eli Lilly Sweden AB, Box 721, 169 27 Solna, Sweden.
url: www.lilly.se

Lilly, Switz. Eli Lilly (Suisse) SA, 16 Ch. des Coquelicots, Case postale 580, 1214 Vernier/GE, Switzerland.
url: www.lilly.com

Lilly, Thai. See *Diethelm, Thai.*

Lilly, Turk. Lilly İlaç Tic. ltd. Şti., Kısıklı Cad., Kuşbakışı Sok. No: 6 Rainbow Plaza K: 3, Altunizade, İstanbul, 81180, Turkey.
url: www.lilly.com.tr

Lilly, UK. Eli Lilly & Co. Ltd, Lilly House, Priestley Rd, Basingstoke, Hampshire, RG24 9NL, UK.
url: www.lilly.co.uk

Lilly, Ukr. Eli Lilly, Krasnoarmeiskaya Street, 9/2, Office 15, Kiev, 01004, Ukraine.
url: www.lilly.com

Lilly, USA. Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285, USA.
url: www.lilly.com

Lilly, Venez. Eli Lilly y Cia de Venezuela S.A., Av. Orinoco, Torre Uno Pisa 3 Nivel 5, Urb. Las Mercedes Caracas, Caracas, Venezuela.
url: www.lilly.com

Limacom, Belg. Limacom, Belgium.

Limin, China. Limin Pharmaceutical Co. Ltd, Jinan, China.

Lincoln, Canad. See *Lincoln, UK.*

Lincoln, Cz. See *Lincoln, UK.*

Lincoln, Hung. See *Lincoln, UK.*

Lincoln, India. Lincoln Pharmaceuticals Ltd, Nirav Complex, Opp. Navarang High School, Naranpura, Ahmedabad 380 014, India.
url: www.lincolnpharma.com

Lincoln, Singapore. See *Lincoln, UK.*

Lincoln, UK. Lincoln Medical Ltd, 8 Wilton Business Centre, Wilton, Salisbury, Wiltshire, SP2 0AH, UK.

Lincoln Medical, Austria. See *Lincoln, UK.*

Lincoln Medical, Irl. See *Lincoln, UK.*

Lincoln Medical, Neth. See *Lincoln, UK.*

Lincoln Medical, Pol. See *Biomed Krakow, Pol.*

Lincoln Medical, Port. See *Lincoln, UK.*

Linde, Canad. Linde Canada Ltd, 5860 Chedworth Way, Mississauga, Ontario, L5R 1A2, Canada.

Linde, Fr. Linde Healthcare, 40 ave Paul Doumer, 92508 Rueil-Malmaison Cedex, France.
url: www.linde-healthcare.fr

Linde, Ital. Linde Medicale, Via Guido Rossa 3, 20010 Arluno (MI), Italy.

Linde, UK. Linde Gas UK Ltd, Johnson's Bridge Rd, Church Lane, West Bromwich, West Midlands, B71 1LG, UK.
url: www.lindegas.co.uk

Linde Gas, Belg. See *Linde Gas, Neth.*

Linde Gas, Cz. Linde Gas as, U Technoplynu 1324, 198 00 Prague 9 Kyje, Czech Republic.

Linde Gas, Ger. Linde Gas Therapeutics GmbH, Landshuter Str. 19, 85716 Unterschliessheim, Germany.
url: www.linde-gastherapeutics.de

Linde Gas, Neth. Linde Gas Therapeutics Benelux BV, De Keten 7, 5651 GJ Eindhoven, Netherlands.

Linde Gas, Norw. Linde Gas Therapeutics, Postboks 13 Grefsen, 0409 Oslo, Norway.
url: www.linde-gastherapeutics.no

Linde Gaz, Pol. Linde Gaz Polska Sp. zo.o., al. Jana Pawła II 41a, 31-864 Kraków, Poland.
url: www.linde-gaztherapeutics.pl

Linderma, UK. Linderma Ltd, Canon Bridge House, Canon Bridge, Madley, Herefordshire, HR2 9JF, UK.
url: www.linderma.co.uk

Lindopharm, Ger. Lindopharm GmbH, Neustr. 82, 40721 Hilden, Germany.
url: www.lindopharm.de

Lindopharm, Israel. Lindapharm, Israel.

Lindopharm, Port. See *Lindopharm, Ger.*

Lindopharm, Rus. See *Lindopharm, Ger.*

Linepharma, Fr. Linepharma France, 140 bis rue de Rennes, 75006 Paris, France.
url: www.linepharma-lab.com

Linfar, Arg. Laboratories Linfar S.R.L., Emilio Casas Ocampo 2838, 5009 Altos de San Martin, Cordoba, Argentina.
url: www.linfar.com

Ling Tai, China. Ling TaiPharmaceutical Co. Ltd, Peony Jiang, China.

Lingkang, China. Lingkang Pharmaceutical Co. Ltd, Hainan, China.

Lingnan, China. Lingnan Pharmaceutical Co. Ltd., Longyandong, Shahe, Guangzhou, Guangdong, 510520, China.
url: www.lingnanpharma.com

Lingrui, China. Lingrui Pharmaceutical Co. Ltd, Zhengzhou, China.

Linhai, China. Linhai Pharmaceutical Co. Ltd, Tonghua, China.

Link, Austral. Link Medical Products P/L, Level 1 Bridgeport, 3 Brady Street, Mosman, NSW 2088, Australia.

Link, Fr. Link, France.

Link, Irl. See *United Drug, Irl.*

Link, NZ. LinkPharmaceuticals, Level 20, ASB Bank Centre, 135 Albert St, Auckland, New Zealand.

Link, UK. See *Archimedes, UK.*

Links, USA. Links Medical Products, 9247 Research Dr., Irvine, CA 92618, USA.
url: www.linksmed.com

Linuo, China. Linuo Pharmaceutical Group, 30766 East Jingshi Road, Jinan, Shandong, 250100, China.
url: www.lnphar.com

Linuo Kefeng, China. See *Linuo, China.*

Liomont, Mex. Laboratorios Liomont S.A. de C.V., Adolfo Lopez Mateos No.68, Deleg. Cuajimalpa, 05000 Mexico D.F., Mexico.
url: www.liomont.com

Lion, Thai. Lion Corp. (Thailand) Ltd, 666 Rama 3 Rd, Bangpongpang, Yannawa, Bangkok 10120, Thailand.
url: www.lion.co.th

Lipha, Cz. See *Merck, Cz.*

Lipha, Denm. See *Nycomed, Denm.*

Lipha, Fr. See *Merck-Lipha, Fr.*

Lipha, Ger. See *Merck, Ger.*

Lipha, Hong Kong. See *Merck, Hong Kong.*

Lipha, Indon. See *Ikapharmindo, Indon.*

Lipha, Irl. See *MSD, Irl.*

Lipha, Ital. See *Merck, Ital.*

Lipha, Norw. See *Biomet Merck, Norw.*

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Lipha, USA. See *Merck, USA.*

Lipha Sante, Fr. See *Merck-Lipha, Fr.*

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Liphaderm, Fr. See *Merck-Lipha, Fr.*

Lipomed, Austria. See *Lipomed, Ger.*

Lipomed, Cz. See *Lipomed, Ger.*

Lipomed, Denm. See *Lipomed, Ger.*

Lipomed, Fin. See *Lipomed, Ger.*

Lipomed, Fr. See *Lipomed, Ger.*

Lipomed, Ger. Lipomed GmbH, Hegenheimer Strasse 2, 79576 Weil am Rhein, Germany.
url: www.lipomed.com

Lipomed, Gr. See *Lipomed, Ger.*

Lipomed, Irl. See *Lipomed, Ger.*

Lipomed, Israel. See *Margalit, Israel.*

Lipomed, Neth. See *Lipomed, Ger.*

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Lipomed, Pol. See *Lipomed, Ger.*

Lipomed, Port. See *Lipomed, Ger.*

Lipomed, Spain. See *Lipomed, Ger.*

Lipomed, Swed. See *Lipomed, Ger.*

Lipomed, Switz. Lipomed AG, Fabrikmattenweg 4, 4144 Arlesheim, Switzerland.
url: www.lipomed.com

Lipomed, UK. See *Lipomed, Ger.*

Liposome, Gr. See *Wyeth, Gr.*

Liposome Company, Austria. See *Wyeth Lederle, Austria.*

Liposome Company, Canad. See *Draxis, Canad.*

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Liposome Company, Norw. See *Wyeth Lederle, Norw.*

Liposome Company, Singapore. See *Summit, Singapore.*

Liposome Company, USA. See *Elan, USA.*

Liptis, USA. Liptis Pharmaceuticals Inc., 8941 Atlanta Ave., Huntington Beach, CA 92648, USA.
url: www.liptis.com

Lirca, Ital. See *Sanofi-Aventis, Ital.*

Lisapharm, Fr. Laboratoires Lisapharm, 9 Bis, bd Jean-Juares, 92100 Boulogne, France.
url: www.lisapharm.com

Lisapharm, Israel. See *Premopharm, Israel.*

Lisapharma, China. See *Extrawell, China* and *Jiwa, China.*

Lisapharma, Hong Kong. See *Mekim, Hong Kong.*

Lisapharma, Hung. See *Medico Uno, Hung.*

Lisapharma, Israel. See *Premopharm, Israel.*

Lisapharma, Ital. Lisapharma S.p.A., Via Licinio 11, 22036 Erba (CO), Italy.
url: www.lisapharma.it

Lisapharma, Malaysia. See *Zyfas, Malaysia.*

Lisapharma, Pol. See *Imed, Pol.*

Lisapharma, Rus. See *Lisapharma, Ital.*

Lisapharma, Singapore. See *Zyfas, Singapore.*

Lisapharma, Thai. See *Charoen, Thai* and *SPB, Thai.*

Lise Watier, Canad. Lise Watier Cosmétiques Inc., 5600 Côte de Liesse, Montreal, Quebec, H4T 4E1, Canada.

Lisfarma, Braz. See *Genzyme, Braz.*

Lisheng, China. Tianjin LiSheng Pharmaceutical Co., Yellow River Rd 491, Nankai District, Tianjin 300111, China.
url: www.lishengpharma.com

Lishizhen, China. Lishizhen Pharmaceutical Co. Ltd, Donghu New technology Development Zone, Wuhan, Hubei, 430079, China.

Lision Hong, Hong Kong. Lision Hong Ltd, Flat G, 7/F, Valiant Industrial Ctr, 2-12 Au Pui Wan St, Fo Tan, N.T., Hong Kong.
url: www.lision.com.hk

Lisite, China. Lisite Pharmaceutical Co. Ltd, Jinjiang Industrial Park, Chengdu, Sichuan, 610063, China.

Litai, China. Litai Pharmaceutical Co. Ltd, Guangdong, China.

Litha, S.Afr. Litha Healthcare Group Ltd, P.O. Box 8356, Midrand 1685, South Africa.
url: www.lithahealthcare.co.za

Little, Singapore. Little Pharmaceutical Suppliers Pte Ltd, Blk 998 Toa Payah North, 05-10/12 JTC Industrial Estate, S 318993, Singapore.

Little Greave, India. Little Greave Pharmaceuticals, GF-61 Sindhu Nagar, Behind Anand Hospital, Bhawar kuan Main Rd, Indore 452 014, India.
url: www.littlegreave.com

Littman, Philipp. Littman Drug Corp., Unit 810 West Tower, PSE Ctr, Exchange Rd, Ortigas Ctr, Pasig City, Philippines.

Liuan Huayuan, China. Liuan Huayuan Pharmaceutical Co. Ltd, China.

LiveLife, Singapore. Livelife (2002) Pte Ltd, 45A Temple St, S 058590, Singapore
url: www.livelife.com.sg

Liverite, Canad. See *Liverite, USA.*

Liverite, USA. Liverite Products Inc., C 15405 Redhill Ave, Tustin, CA 92780, USA.

Livron, Rus. See *Sanofi-Aventis, Rus.*

Livzon, China. Livzon Pharmaceutical Factory, Beaconsfield Osmanthus North Road, Zhuhai City 519020, China.
url: www.livzon.com.cn

Liwinner, Thai. Liwinner Pharmaceutical Ltd, 37 Soi Phibulupattam Latphrao Rd, Sansennok, Huaikhwang, Bangkok, 10310, Thailand.

Lixin, China. Nanyang Lixin Pharmaceutical Co. Ltd, Zhenping Industrial Park, Nanyang, Henan, 474250, China.

Liye, China. Liye Pharmaceutical Co. Ltd, China.

Lizofarm, Ital. Lizofarm S.r.l., Via Gabriele Colombo 28, 20050 Camparada (MI), Italy.
url: www.lizofarm.it

LKM, Arg. Laboratorio LKM S.A., Monroe 1378, 1428 Buenos Aires, Argentina.

Llogo, Hung. Llogo C&C Kft, Ferenciek tere 2, 1053 Budapest, Hungary.

Llorens, Spain. Llorens, Ciudad de Balaguer 7-11, 08022 Barcelona, Spain.

Llorens, USA. Llorens Pharmaceutical, P.O.Box 720008, Miami, FL 33172, USA.
url: www.llorenspharm.com

Llorente, Spain. Llorente, Ctra el Pardo Km 1, 28035 Madrid, Spain.

Lloyd, Aimee, UK. Lloyd, Aimee & Co. Ltd, Kingsend House, 44 Kingsend, Ruislip, Middlesex, HA4 7DA, UK.

Lloyd, Philipp. See *Randril, Philipp* and *Vitalink, Philipp.*

Loacker Remedia, Ital. Loacker Remedia, Via Brennero 16, 39053 Prato Isarco, Italy.
url: www.loackerremedia.it

Lobana, USA. See *Ulmer, USA.*

Loch, USA. See *Bedford, USA.*

Lockerroom, Canad. Lockerroom Marketing Ltd, 694 Derwent Way, Delta, British Columbia, V3M 5P8, Canada.

Loeffler, Mex. Loeffler SA de CV, Prolongación Ing. Militares 76, 11210 Tlaltenango San Lorenzo, Mexico DF, Mexico.

Loevar, Gr. Loevar Ltd, Koumoundourou 37, 104 37 Athens, Greece.

Lofarma, Hung. See *Lofarma, Ital.*

Lofarma, Ital. Lofarma S.p.A., Viale Cassala 40, 20143 Milan, Italy.
url: www.lofarma.it

Lofco, Canad. Lofco Canada Inc., 19-7321 Victoria Park Ave, Markham, Ontario, L3R 2Z8, Canada.

Lofthouse of Fleetwood, Arg. See *C&V, Arg.*

Logeais, Fr. See *Chiesi, Fr.*

Logeais, Hong Kong. See *CNW, Hong Kong.*

Logeais, Rus. See *Prespharm, Rus.*

Loges, Ger. Dr. Loges & Co. GmbH, Schützenstr. 5, 21423 Winsen, Germany.
url: www.loges.de

Loges, Hong Kong. See *Lision Hong, Hong Kong.*

Logogen, Spain. See *Italfarmaco, Spain.*

Logos, S.Afr. See *MSD, S.Afr.*

Lohmann, Belg. Laboratoires Lohmann & Rauscher SA, Rue des Pontons 25, 4032 Liège (Chênée), Belgium.
url: www.lohmann-rauscher.be

Lohmann, Cz. See *Lohmann, Ger.*

Lohmann, Fr. Laboratoires Lohmann & Rauscher, B.P. 1, 42530 St-Genest-Lerpt, France.
url: www.pharnea.com

Lohmann, Ger. Lohmann & Rauscher GmbH & Co. KG, Irlicher Str. 55, 56567 Neuwied, Germany.
url: www.lohmann-rauscher.de

Lohmann, Ital. Lohmann & Rauscher S.r.l., Via E. Fermi 4, 35030 Sarmeola di Rubano (PD), Italy.

Lokman, Turk. Lokman Laboratuvari İlaç ve Gida San. Koll. Sti., Çalislar Cad. No: 68, Bahçelievler, Istanbul, 34590, Turkey.

Lomapharm, Cz. See *Lomapharm, Ger.*

Lomapharm, Ger. Lomapharm, Rudolf Lohmann GmbH KG Pharmazeutische Fabrik, Langes Feld 5, 31860 Emmerthal, Germany.
url: www.lomapharm.de

Lomapharm, Rus. See *Lomapharm, Ger.*

Lomapharm, Singapore. See *Polymedic, Singapore.*

Lombarda, Ital. Lombarda H, Via Volterra 9, 20146 Milan (MI), Italy.

Longda Xinke, China. Longda Xinke Pharamceutical Co. Ltd, Hangzhou, China.

Longgui, China. Longgui Pharmaceutical Co. Ltd., 3 Xingsui Rd, Economic Development Zone, Suihua, Heilongjiang, 152061, China.

Longhe, China. Longhe Pharmaceutical Co. Ltd., High-tech Industrial and development Zone, Nangang District, Harbin, Heilongjiang, 150090, China.

Longhua, China. Longhua Pharmaceutical Co. Ltd, Fujian, China.

Longjin, China. Longjin Pharmaceutical Co. Ltd, Kunming, China.

Longkema, China. Longkema Biopharmaceutical Co. Ltd, Anhui, China.

Longli, China. Longli Pharmaceutical Co. Ltd, Shandong, China.

LongRun, China. LongRun Pharmaceutical Co. Ltd, 1299 North Haiyuan Road, National High-tech Industrial Development Zone, Kunming, Yunnan, 650101, China.
url: www.longrun.cc

Longshen Rongfa, China. Longshen Rongfa Pharmaceutical Co. Ltd, Gansu, China.

Longshunrong, Philipp. See *Goodfellow, Philipp.*

Loock, S.Afr. Loock Pharmaceuticals, South Africa.
url: www.loockpharmaceuticals.co.za

Lopes, Braz. Lopes Produtos Farmaceuticos S.A., Rodovia BR 491, Km 5, Caixa Postal:62, 37002-970 Varginha, Brazil

Loprofar, Braz. See *Lopes, Braz.*

L'Oreal, Canad. L'Oréal Canada, 2115 rue Crescent, Montreal, Quebec, H3G 2C1, Canada.

L'Oreal, Chile. L'Oreal Chile SA, Americo Vespucio 2288, Conchali, Santiago, Chile.

L'Oreal, Singapore. L'Oreal Singapore Pte Ltd, 3 Killiney Rd, 09-01/06 Winsland House 1, S-239519, Singapore.
url: www.loreal.com.sg

L'Oreal, UK. L'Oreal (UK) Ltd, 255 Hammersmith Rd, London, W6 8AZ, UK.
url: www.loreal.co.uk

Lorex, Denm. See *Pfizer, Denm.*

Lorex, Irl. See *Allphar, Irl.*

Lorex Synthelabo, Irl. See *Allphar, Irl.*

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Lorex Synthelabo, UK. See *Sanofi, UK.*

Lornamead, Canad. See *Lornamead, USA.*

Lornamead, UK. Lornamead UK Ltd, 377-399 Sabre House, London Rd, Camberley, Surrey, GU15 3HL, UK.

Lornamead, USA. Lornamead Inc., 175 Cooper Ave, Tonawanda, NY 14150-6656, USA.

Lorvic, Canad. See *Prof. Pharm. Corp., Canad.*

Lorvic, USA. See *Young, USA.*

Losan, Denm. See *Losan, Ger.*

Losan, Ger. Losan Pharma GmbH, Otto-Hahn-Strasse 13, 79395 Neuenburg, Germany.

Losan, Neth. See *Losan, Ger.*

Lotus, China. Lotus Pharmaceutical Co. Ltd., East Flyover, South Qingdao Road, Weihai, Shangdang.
url: www.weihailotus.com

Lotus, China. See *Pioneer, China.*

Lotus, Malaysia. See *Zuellig, Malaysia.*

Lotus, USA. See *Harvest, USA.*

Lovens, Fin. See *Leo, Fin.*

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Loyal Advance, Hong Kong. Loyal Advance Ltd, 8/F, B2-B4 Tsing Yi Industrial Ctr, Phase 1, Tsing Yi Island, N.T., Hong Kong.

LPB, Ital. LPB Istituto Farmaceutico S.r.l., Largo Umberto Boccioni 1, 21040 Origgio (VA), Italy.

LPC, UK. LPC Medical (UK) Ltd, 30 Chaul End Lane, Luton, Bedfordshire, LU4 8EZ, UK.
url: www.lpcpharma.com

LRC, Israel. See *Promedico, Israel.*

LRC Products, UK. See *Chefaro, UK.*

LRN, Fr. Le Laboratoire de Recherche Nutraceutique, 271 rue du Faubourg Saint-Antoine, 75011 Paris, France.
url: www.LRN.fr

LSI, USA. LSI America Corp., 4732 Twin Valley Drive, Austin, TX 78731-3537, USA.
url: www.ondrox.com

LSP, Thai. Lerd Singh Pharmaceutical Fact Ltd Part, 922 Sukhumvit 50, Prakanong, Klongtoey, Bangkok 10250, Thailand.

LTM, Neth. See *Solvay, Neth.*

LTS, Israel. See *Teva, Israel.*

Lu Yin, China. Lu Yin Pharmaceutical Co. Ltd, Yantai, China.

Lu Zhu, China. Lu Zhu Biological Pharmaceutical Co. Ltd, 22 Tongji North Rd, Economic & Technological development Zone, Beijing 100176, China.
url: www.vaccine.com.cn

Luan, China. Luan Pharmaceutical Co. Ltd, Anqiu, China.

Luar, Arg. Química Luar S.R.L., Angel Carranza 1946, 1414 Buenos Aires, Argentina.

Lubapharm, Switz. Lubapharm SA, Ringstrasse 29, Postfach 434, 4106 Therwil, Switzerland.

Lubapharm Arlesheim, Switz. Lubapharm AG, Postfach 348, 4144 Arlesheim, Switzerland.
url: www.drossapharm.ch

Lubapharm Phlebologie, Switz. See *Lubapharm, Switz.*

Lucchini, Switz. Laboratoire Lucchini SA, Case postale 1214, 1211 Geneva 26, Switzerland.

Luchon, Fr. Laboratoires de Luchon, 22 bd Dardenne, 31110 Luchon, France.
url: www.luchon.com

Lucien, Fr. See *Therabel, Fr.*

Lucienne, Fr. See *Merle, Fr.*

Ludwig, Singapore. See *Apotheca, Singapore.*

Luen Wah, Malaysia. Luen Wah Medical Co Sdn Bhd, No 43-G & 43-1F The Highway Centre, Jln 51/205, 46050 Petaling Jaya, Selangor, Malaysia.

Luen Wah, Singapore. Luen Wah Medical Co (S) Pte Ltd, 40 North Canal Rd, S 059296, Singapore.
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Luganskii, Ukr. OAO Luganskii KHFZ, Kirova Street, 17, Lugansk, 91019, Ukraine.
url: www.lugal.com.ua

Luitpold, Austral. See *Pharmacia, Austral.*

Luitpold, Belg. See *Sankyo, Belg.*

Luitpold, Braz. See *Sankyo, Braz.*

Luitpold, Canad. See *Luitpold, USA.*

Luitpold, Ger. See *Daiichi Sankyo, Ger.*

Luitpold, Ital. See *Daiichi Sankyo, Ital.*

Luitpold, Neth. See *Will-Pharma, Neth.*

Luitpold, S.Afr. See *Pfizer, S.Afr.*

Luitpold, Singapore. See *Kyowa, Singapore.*

Luitpold, Switz. See *Sankyo, Switz.*

Luitpold, USA. Luitpold Pharmaceuticals Inc., One Luitpold Drive, Shirley, NY 11967, USA.
url: www.luitpold.com

Lukang Chenxin, China. Lukang Chenxin Pharmaceutical Co Ltd, Shandong, China.

Lukang Medicine, China. Lukang Medicine Pharmaceutical Co. Ltd., Shandong, China.

Luling, China. Luling Pharmaceutical Co. Ltd, Jiamusi, China.

Lumar, Philipp. See *MG, Philipp.*

Lumen, Philipp. See *Davenben, Philipp.*

Lumiere, Chile. See *Andromaco, Chile.*

Lunan, China. Lunan Pharmaceutical Co. Ltd, 209 Hongqi Rd, Linyi City 276005, Shandang, China.
url: www.lunan.com.cn

Lunan Better, Thai. See *Neopharm, Thai.*

Lundbeck, Arg. Lundbeck Argentina, Dardo Rocha 2358, Piso 2, Martinez, Buenos Aires, Argentina.

Lundbeck, Austral. Lundbeck Australia P/L, Unit 1/10 Inglewood Place, Baulkham Hills, NSW 2153, Australia.
url: www.lundbeck.com

Lundbeck, Austria. Lundbeck-Arzneimittel GmbH, Brigittagasse 22-6, Postfach 201, A-1201 Vienna, Austria
url: www.lundbeck.at

Lundbeck, Belg. Lundbeck SA, Ave Molière 225, 1050 Brussels, Belgium.
url: www.lundbeck.be

Lundbeck, Braz. Lundbeck Brasil Ltda, Rua Lauro Muller 116 sl 2202 a 2205, 22290160 Botafogo, Rio de Janeiro, Brazil.

Lundbeck, Canad. Lundbeck Canada Inc., 413 St-Jacques St W, Suite FB-230, Montreal, Quebec, H2Y 1N9, Canada.
url: www.lundbeck.com

Lundbeck, Chile. Lundbeck Chile Ltda, Av. Vitacura 5250 Of. 401, Vitacura, Santiago, Chile.

Lundbeck, China. See *CMS, China.*

Lundbeck, Cz. Lundbeck Česká Republika sro, Bozděchovo 7, 150 00 Prague 5, Czech Republic.
url: www.lundbeck.com

Lundbeck, Denm. Lundbeck Pharma A/S, Dalbergstrøger 5, 2630 Taastrup, Denmark.
url: www.lundbeck-pharma.dk

Lundbeck, Fin. Oy H. Lundbeck AB, Itäinen Pitkökatu 4, 20520 Turku, Finland.
url: www.lundbeck.fi

Lundbeck, Fr. Laboratoires Lundbeck, 37 av Pierre-1er-de-Serbie, 75008 Paris, France.
url: www.lundbeck.com

Lundbeck, Ger. Lundbeck GmbH, Karnapp 25, 21079 Hamburg, Germany.
url: www.lundbeck.de

Lundbeck, Gr. Lundbeck Hellas S.A., 64 Kifisias Ave, 151 25 Marousi, Greece.
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Lundbeck, Hong Kong. Lundbeck Hong Kong, Rm 5708 Central Plaza, 18 Harbour rd, Wanchai, Hong Kong.
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Lundbeck, India. Lundbeck India Pvt Ltd, 6/A, II Floor, Esteem Regency, Richmond Rd, Bangalore 560 025, India.
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Lundbeck, Indon. Lundbeck Indonesia PT, Menara Jamsotek 22nd Floor, Suite 2204, Jl Jend Gatot Subrota No.38, Jakarta 12710, DKI Jaya, Indonesia.
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Lundbeck, Irl. Lundbeck (Ireland) Ltd, 14 Deansgrange Industrial Estate, Blackrock, Dublin 11, Ireland.
url: www.lundbeck.ie

Lundbeck, Israel. Lundbeck Israel Ltd, 94 Derech Em Hamoshavot, Park Azorim, Brosh Building, Kiryat Arie, Petach Tikva 49130, Israel.
url: www.lundbeck.com

Lundbeck, Ital. Lundbeck Italia S.p.A., Via G Fara 35, 20124 Milan (MI), Italy.
url: www.lundbeck.it

Lundbeck, Malaysia. See *JDH, Malaysia.*

Lundbeck, Mex. Lundbeck de Mexico S.A. de C.V., Av. Insurgentes 1605 Pso 28 T. Murol, Benito Juarez San Jose Insurgente, 3900 Mexico D.F., Mexico.
url: www.lundbeck.com.mx

Lundbeck, Neth. Lundbeck BV, Hettenheuvelweg 37, 1101 BM Amsterdam Z.O., Netherlands.
url: www.lundbeck.com

Lundbeck, Norw. H. Lundbeck A/S, Lysaker torg nr. 10, Postboks 361, 1326 Lysaker, Norway.
url: www.lundbeck.no

Lundbeck, NZ. See *Zuellig, NZ.*

Lundbeck, Philipp. Lundbeck Phils, 3/F Ace Bldg, 101-103 Rada St, Legaspi Vill, Makati City, Philippines.

Lundbeck, Pol. Lundbeck Poland Sp. zo.o., ul. Kryzwickiego 34, 02-078 Worsaw, Poland.
url: www.lundbeck.pl

Lundbeck, Port. Lundbeck Portugal Lda, Quinta da Fonte, Edificio Dom José, Piso 1, 2780-730 Paço de Arcos, Portugal.
url: www.lundbeck.com

Lundbeck, Rus. Lundbeck Export A/S, Horoshovskoe shosse, Building 32A, 123007 Moscow, Russia.
url: www.lundbeck.ru

Lundbeck, S.Afr. Lundbeck South Africa, P.O. Box 2171, North Riding 2162, South Africa.
url: www.lundbeck.co.za

Lundbeck, Singapore. Lundbeck Export A/S, Representative Office, 101 Thomson Road, No. 13-05 United Square, S 307591, Singapore.
url: www.lundbeck.com

Lundbeck, Spain. Lundbeck España, Avda Diagonal 605, 9-1a, 08028 Barcelona, Spain.
url: www.lundbeck.com

Lundbeck, Swed. H. Lundbeck AB, Box 23, 250 53 Helsingborg, Sweden.
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Lundbeck, Switz. Lundbeck (Schweiz) AG, Cherstrasse 4, Postfach, 8152 Opfikon-Glattbrugg, Switzerland.
url: www.lundbeck.ch

Lundbeck, Thai. See *Hua, Thai.*

Lundbeck, Turk. Lundbeck İlaç Tic. Ltd. Sti., Mihribat Cad. No: 238, Marti İş Merkezi, K: 1-2, Kavacik, İstanbul, 81630, Turkey.
url: www.lundbeck.com

Lundbeck, UK. Lundbeck Ltd, Sunningdale House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LF, UK.
url: www.lundbeck.co.uk

Lundbeck, Ukr. Lundbeck, ul Khreschatyk 19A, 01001 Kiev, Ukraine.
url: www.lundbeck.com

Lundbeck, USA. Lundbeck Inc., Four Parkway North, Suite 200, Deerfield, IL 60015, USA.
url: www.lundbeckinc.com

Lunsco, USA. Lunsco Inc., 4657 Wurno Rd, Pulaski, VA 24301, USA.

Luofu Taikang, China. Luofu Taikang Pharmaceutical Co. Ltd, Shamghai, China.

LuoXin, China. LuoXin Pharmaceutical Co. Ltd, High-Tech Industrial Development Zone, Luo Rd, Linyi 276017, Shandong, China.
url: www.luoxin.cn

Luper, Braz. Luper Indústria Farmacêutica Ltda, Rua Doutor Clementino 608, 03059-030 São Paulo, SP, Brazil.
url: www.luper.com.br

Lupin, Austral. See *Generic Health, Austral.*

Lupin, Cz. See *Lupin, India.*

Lupin, India. Lupin Ltd, 159 CST Rd, Kalina, Santacruz (E), Mumbai 400 098, India.
url: www.lupinworld.com

Lupin, Malaysia. See *Pharmaniaga, Malaysia.*

Lupin, Philipp. See *Pascual, Philipp* and *Xeno, Philipp* and *Zynova, Philipp.*

Lupin, Rus. See *Lupin, India.*

Lupin, Ukr. Lupin, 13 Anna Akhmatova, Kiev, 02068, Ukraine.
url: www.lupin.com.ua

Lupin, USA. Lupin Pharmaceuticals Inc., Harborplace Tower, 111 South Calvert St., 21st floor, Baltimore, MD 21202, USA.
url: www.lupinworld.com

Lusal, Port. Lusal Produção Quimico-Farmacêutico Luso-Alemã Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.

Lusalfarma, Port. See *Lusal, Port.*

Lusofarmaco, Cz. See *Lusofarmaco, Ital.*

Lusofarmaco, Hong Kong. See *Mekim, Hong Kong.*

Lusofarmaco, Ital. Istituto Luso Farmaco d'Italia S.p.A., Via Walter Tabagi 8, 20068 Peschiera Borromeo (MI), Italy.
url: www.lusofarmaco.it

Lusofarmaco, Port. See *GSK, Port.*

Lusofarmaco, Rus. See *Berlin Pharm, Rus.*

Lusomedicamenta, Port. Lusomedicamenta Sociedade Técnica Farmacêutica SA, Estrada Cansiglieri Pedroso 69 B, Queluz de Baixa, 2730-055 Barcorena, Portugal.
url: www.lusomedicamenta.com

Lusoterapia, Port. Lusoterapio Sociedade de Comércio de Produtos Quimico Farmacêuticos Lda, Av. Antónia Augusto de Aguiar 128, 1069-133 Lisbon, Portugal.

Lutan, China. See *Lotus, China.*

Lutsia, Fr. See *Boots Healthcare, Fr.*

Lutsia, Ital. See *Boots Healthcare, Ital.*

Luxembourg, Israel. Luxembourg Pharmaceuticals Ltd, 6 Haba'al Shem-tov St, North Industrial Zone, Lod 71289, Israel.

Luya, China. Luya Pharmaceutical Co. Ltd, Shandong, China.

Luye, China. Luye Pharmaceutical Co. Ltd, Zhubong 2000 Business Centre Room 1107, Bali Zhuang Xili 100, Chaoyang District, Beijing 100025, China.
url: www.luye-pharm.com

Luye Sike, China. Luye Sike Pharmaceutical Co. Ltd, 13/F Fongyuan Jinling Hotel, 181 Huju Road, Nanjing, 210003, China.
url: www.luyesike.com

Lv Yin, China. Lv Yin Phormaceutical Co Ltd, China.

Lv Zhou, China. Lv Zhou Pharmaceutical Co Ltd, China.

Lvgu, China. See *Green Valley, China.*

Lvovdialik, Ukr. Lvovdialik DP, st Zelenaya 12, Lvov 79005, Ukraine.
url: www.lvdialik.lviv.ua

Lyempf, Indon. See *Tempo Scan Pacific, Indon.*

Lyka, Rus. See *Reddy, Rus.*

Lyocentre, Fin. Oy Lyocentre-Nordic AB, Harmaaparrankuja 1, 02200 Espoo, Finland.

Lyocentre, Fr. Laboratoires Lyocentre, 24 av Georges Pompidou, B.P. 429, 15004 Aurillac cdx, France.
url: www.lyocentre.fr

Lyofin, Gr. Lyofin, Greece.

Lyomark, China. See *Lyomark, Ger.*

Lyomark, Ger. Lyomark Pharma GmbH, Keltenring 17, 82041 Oberhaching, Germany.

Lyron, Switz. Lyron AG, Postfach 3538, 4002 Basle, Switzerland.

Lysi, Pol. See *Island, Pol.*

Lysoform, Ger. Lysoform Dr. Hons Rosemann GmbH, Kaiser-Wilhelm-Str. 133, 12247 Berlin, Germany.
url: www.lysoform.de

Lyssia, Ger. See *Solvay, Ger.*

M & H, Malaysia. See *Germax, Malaysia.*

M & H, Thai. M & H Manufacturing Co. Ltd, 41 Sukhumvit Rd, Samutprakarn 10270, Thailand.

M2i, Irl. M2i Ltd, 9 Clare St, Dublin 2, Ireland.

M4, Spain. M4 Pharma, C/Marroc 200, 08019 Barcelona, Spain.

M4 Pharma, Spain. M4 Pharma SL, C/Marroc 200, 08019 Barcelona, Spain.

Maabarot, Israel. See *Trima, Israel.*

Maan, India. Maan Pharmaceuticals ltd, 202/A Harikrupa Chambers, Near City Gold Cinema, Ashram Road, Ahmedabad 380 009, India.
url: www.maanpharma.com

Mabo, Spain. Mabo Farma, Ctra M-300 Km, 30.5, Alcalá de Henares, 28820 Madrid, Spain.
url: www.maboformo.com

Mabra, Braz. Mabra Formaceutica ltda, BR-153, Km 5.5 Bloco A, 74675090 Goiania Jardim Guanabora, Goias, Brazil.

MAC, Canad. Make-Up Art Cosmetics (MAC), 201 Bentley St, Markham, Ontario, L3R 3L1, Canada.

Mac, Gr. Mac ASFE Eisag & Emp. Nos. Erg. Exopl.Diagnosis & Diotr. Mich. D, Kartsivani 6, 175 64 Foliro, Greece.

Mac, India. Mac Laboratories Pvt Ltd, Kirol, Vidyavihar, Mumbai 400 086, India.

Mac, Ital. Mac Pharma S.r.l., Via Luigi Scattolin 26/1, 31055 Quinto di Treviso (TV), Italy.
url: www.macpharma.com

Macanthy, Mon. Macanthy (Lab), Les Terrasses du Port 2, av des Ligures, MC 98000, Monaco.

Macarthur, Austral. See *Roche, Austral.*

Maccabi Care, Israel. Maccabi Care, 27 Ha'Merad St, P.O. Box 50493, Tel Aviv 68125, Israel.
url: www.maccabicare.co.il

Machado Malcher, Port. Machado Malcher Lda, Rua Sociedade Farmacêutica 20-1, 1150-340 Lisbon, Portugal.
url: www.machado-malcher.pt

Macheal, Philipp. See *Littman, Philipp* and *Suhitas, Philipp.*

Macherey Nagel Duren, S.Afr. See *Pharmaceutical Enterprises, S.Afr.*

Mack, Belg. See *Vitalpharma, Belg.*

Mack, China. See *Pfizer, Ger.*

Mack, Cz. Heinrich Mack Nachf, Pekařská 16, 150 00 Prague 5, Czech Republic.

Mack, Denm. See *Kemifarma, Denm.*

Mack, Hong Kong. See *Keller, Hong Kong.*

Mack, Hung. See *Keri, Hung.*

Mack, Illert., Ger. See *Pfizer, Ger.*

Mack, Israel. See *Pfizer, Israel.*

Mack, Malaysia. See *Summit, Malaysia.*

Mack, Neth. See *AstraZeneca, Neth.*

Mack, Pol. See *Pfizer, Ger.*

Mack, Rus. See *Ebewe, Rus* and *Pfizer, Rus.*

Mack, Singapore. See *Summit, Singapore.*

Mack, Switz. See *Pfizer, Switz.*

Mack, Thai. See *Zuellig, Thai.*

Mack, Ukr. See *Alex Pharm, Ukr.*

Macleods, India. Macleods Pharmaceuticals Ltd, Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai 400059, India.
url: www.macleodspharma.com

Macleods, Rus. See *Reddy, Rus.*

Maco-Pharma, Fr. MacoPharma, rue Lorthiois, 59420 Mauvaux, France.
url: www.macopharma.fr

Macoven, USA. Macoven Pharmaceuticals Llc, 33219 Forest West St, Magnalia, TX 77354-6815, USA.

Macronova, Swed. Macronova AB, Storgatan 2, 2tr, 852 30 Sundsvall, Sweden.
url: www.macronova.se

MacroPhar, Malaysia. See *Antah, Malaysia.*

Macrophar, Thai. Macrophar Co Ltd, 89 Soi Patanakarn 20, Yaek 4, Patanakarn Rd, Bangkok 10250, Thailand.

Macropharma, Philipp. Macropharma Corp., Suite 1204 Tektite West Tower, PSE Bldg, Ortigas Ctr, Pasig City, Philippines.

Macsil, USA. Macsil Inc., P.O. Box 29276, Philadelphia, PA 19125-0976, USA.

Madariaga, Spain. Madariaga, Electronica, 7, Poligono Urtinsa II, Alcorcon, 28923 Madrid, Spain.

Madaus, Arg. Lab. Dr. Madaus & Co. SA, Av. Luis Maria Campos 585, 1426 Buenos Aires, Argentina.

Madaus, Austria. Madaus GmbH, Lienfeldergasse 91-93, A-1171 Vienna, Austria.

Madaus, Belg. Madaus Pharma SA, Rue des Trois Arbres 16, 1180 Brussels, Belgium.
url: www.madaus.com

Madaus, China. Madaus, Room 3216-3218, 3rd Floor Everbright Guoxin Building, South Zhongguancun St, Haidian District, Beijing 100081, China.

Madaus, Cz. See *Madaus, Ger.*

Madaus, Denm. See *Meda, Denm.*

Madaus, Fin. See *Schering-Plough, Fin.*

Madaus, Fr. Laboratoires Madaus, 55 bis, quai de Grenelle, Immeuble Mercure III, 75015 Paris, France.

Madaus, Ger. Madaus AG, Colonia-Allee 15, 51067 Cologne, Germany.
url: www.madaus.de

Madaus, Hong Kong. See *Trinity, Hong Kong.*

Madaus, Hung. See *Naturprodukt, Hung.*

Madaus, Irl. See *Madaus, Ger.*

Madaus, Israel. See *SLE, Israel.*

Madaus, Ital. Madaus S.r.l., Rivera Francia 3/A, 35127 Padua (PD), Italy.

Madaus, Malaysia. See *Antah, Malaysia.*

Madaus, Neth. See *Byk, Neth.*

Madaus, Norw. See *Meda, Norw.*

Madaus, Philipp. See *Zuellig, Philipp.*

Madaus, Pol. Madaus AG, Przedstawicielstwo w Polsce, ul. Rumiana 65, 02-956 Warsaw, Poland.
url: www.madaus.pl

Madaus, Port. Madaus Farma Portugal Unipessoal Lda, Av. D.João II, Lote 1.02.1 D 2, 1990-090 Lisbon, Portugal.

Madaus, Rus. See *Madaus, Ger.*

Madaus, S.Afr. See *Altana, S.Afr.*

Madaus, Singapore. See *Delfi, Singapore.*

Madaus, Spain. Madaus, FOC 68-82, 08038 Barcelona, Spain.
url: www.madaus.es

Madaus, Switz. See *Zeller, Switz.*

Madaus, Thai. See *Ouiheng, Thai.*

Madaus, Ukr. Madaus GmbH, Bereznyakovskaya Street, 29, Kiev, 02098, Ukraine.

Made, Port. See *Esfar, Port.*

Madhav, India. Madhav BioTec Pvt Ltd, Plot No. 195, Vayupuri, Secunderabad, India.
url: www.madhavbiotech.com

MAE, Neth. MAE Holding BV, Heereweg 217, 2161 BE Lisse, Netherlands.

Maeil, China. See *Maeil, Hong Kong.*

Maeil, Hong Kong. Maeil HK, 17A China Trade Ctr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.
url: www.maeil.com.hk

Maelor, UK. Maelor Pharmaceuticals Ltd, Office Village, Chester Business Park, Chester, CH4 9QZ, UK.
url: www.maelor.plc.uk

Maersk, UK. See *Unomedical, UK.*

Maffioli, Ital. Prodotti Dott. Maffioli S.a.s. di A. Labruzzo & C., Via Firenze 38, 20060 Trezzano Rosa (MI), Italy.

Maggioni, Ital. See *GSK Consumer, Ital.*

Magis, Ital. Magis Farmaceutici S.p.A., Via Cacciamali 34-36-38, Zona Ind. (Loc. Noce), 25125 Brescia (BS), Italy.

Magistra, Switz. Laboratoires Magistra SA, 28 Chemin du Grand-Puits, Case postale 122, 1217 Meyrin 2/Geneva, Switzerland.

Magma, Canad. Magma Enr, 101 4071 rue Blain, Neufchâtel, Quebec, G2B 5C6, Canodo.

Magna, USA. MAGNA Pharmaceuticals Inc., 11802 Brinley Ave, Suite 201, Louisville, KY 40243, USA.
url: www.magnaweb.com

Magnapharma, Pol. Magnapharma Sp. zo.o., ul. Turystyczna 3, 91-615 Łódź, Poland.
url: www.magnapharma.com.pl

Magno-Humphries, USA. Magno-Humphries Laboratories Inc., 8800 S.W. Commercial St, Tigard, OR 97223, USA.
url: www.magno-humphries.com

Magnus, India. Magnus Biotech Pvt Ltd, SCO 15-16, Jamaily Colony Market, Near Mittal Skin Clinic, Karnol 132 001, India.
url: www.magnusbiotech.in.p.in.hostingprod.com

Mahakam Beta, Indon. Mahakam Beta Farma PT, Jl Pulo Kambing II No 21, Pulogadung Industrial Estate, Jakarta 13930, Indonesia.
url: www.betadine-ina.com

Mahakam Beta, Malaysia. See *Somedico, Malaysia.*

Mahdeen, Canad. Mahdeen Mediceuticals, Division of Canmax Laboratories, 6600 Kennedy Rd, 4, Mississauga, Ontario, L5T 2M9, Canada.

Maidi, China. Maidi Pharmaceutical Co. Ltd, Shanxi, China.

Maidihai, China. Maidihai Pharmaceutical Co. Ltd, Beijing, China.

Maigal, Arg. Lab. Maigal Corp., 12 de Octubre 1725, 1416 Buenos Aires, Argentina.

Main Life, Hong Kong. Main Life Corp. Ltd, 9/F Winning Ctr, 46-48 Wyndham St Central, Hong Kong.

Maite Xinghua, China. Maite Xinghua Pharmaceutical Co. Ltd, 1 Maofeng Rd, Liangtian, Baiyun, Guangzhau, Guangdong, 510545, China.

Majestic, Canad. See *Majestic, USA.*

Majestic, USA. Majestic Drug Company Inc., 4996 Main St, P.O.Box 490, South Fallsberg, NY 12779, USA.
url: www.majesticdrug.com

Majistra, Rus. See *Rompharm, Rus.*

Major, USA. See *Harvard, USA.*

Makers, Philipp. See *PNF, Philipp.*

Makiz, Rus. See *Stada, Rus.*

Makiz-Pharma, Rus. Makiz-Pharma ZAO, Avtomobilnyi pr., d. 6, 109029 Moscow, Russia.

Malam, UK. Malam Laboratories Ltd, 37 Oakwood Rise, Heaton, Bolton, BL1 5EE, UK.

Malar, India. Malar Healthcare, 312 Alaknanada Complex, opp. Petrol Pump, Mujmhuda, Baroda, 390 020, India.
url: www.malarhealthcare.com

Malayan, Hong Kong. See *Hind Wing, Hong Kong.*

Malayan, Singapore. See *Luen Wah, Singapore.*

Malaysia Chemist, Singapore. Malaysia Chemist Pte Ltd, 104 Boon Keng Rd, 04-01, S 339775, Singapore.
url: www.malchem.com

Malesci, Ital. Malesci Istituto Farmacobiologico S.p.A., Via Lungo l'Ema 7, 50012 Bagno a Ripoli (FI), Italy.
url: www.malesci.it

Mallard, USA. See *Shire, USA.*

Mallinckrodt, Arg. Mallinckrodt Medical Argentina Ltda, Av. Cyrdoba 1345 Piso 7, 1055 Buenos Aires, Argentina.
url: www.mallinckrodt.com

Mallinckrodt, Austral. Mallinckrodt Australia, Trading as Tyco Healthcare P/L, Unit 4, 310 Ferntree Gully Road, Notting Hill, VIC 3168, Australia.
url: www.mallinckrodt.com

Mallinckrodt, Canad. See *Tyco, Canad.*

Mallinckrodt, China. See *Mallinckrodt, Hong Kong.*

Mallinckrodt, Cz. Mallinckrodt Medical, Czech Republic.

Mallinckrodt, Denm. See *Tyco, Denm.*

Mallinckrodt, Fin. See *Tyco, Fin.*

Mallinckrodt, Fr. Mallinckrodt France, Batiment Sigma 3, Ave du Canada, 91975 Courtaboeuf 2-les-Ulis, France.
url: imaging.mallinckrodt.com

Mallinckrodt, Ger. See *Covidien, Irl.*

Mallinckrodt, Hong Kong. Mallinckrodt Pharmaceuticals, Unit 01-02 12-20 Level 20 Tower, 1 Grand Century Place, 193 Prince Edward Rd West, Kowloon, Hong Kong.
url: www.mallinckrodt.com

Mallinckrodt, Hung. See *Tyco, Hung.*

Mallinckrodt, Irl. Mallinckrodt Medical Imaging, Damastown, Mulhuddart, Dublin 15, Ireland.

Mallinckrodt, Neth. Mallinckrodt Medical BV, Westerduinweg 3, 1755 Le Petten, Netherlands.

Mallinckrodt, Port. See *Tyco, Port.*

Mallinckrodt, Spain. See *Tyco, Spain.*

Mallinckrodt, Swed. See *Tyco, Swed.*

Mallinckrodt, Switz. Mallinckrodt Schweiz AG, Roosstrasse 53, CH-8832 Wollerau, Switzerland.
url: www.mallinckrodt.ch

Mallinckrodt, UK. Mallinckrodt Medical UK Ltd, 10 Talisman Business Centre, London Rd, Bicester, Oxfordshire, OX6 0JX, UK.
url: www.mallinckrodt.com

Mallinckrodt, USA. Mallinckrodt Pharmaceuticals, 675 McDonnell Blvd, Hazelwood, MO 63042, USA.
url: www.mallinckrodt.com

Mallinckrodt-Baker, USA. Mallinckrodt-Baker Inc., 222 Red School Lane, Phillipsburg, NJ 08865, USA.
url: www.mallbaker.com

Mallix, Philipp. See *Am-Europharma, Philipp.*

Malody, India. Malody Healthcare Ltd, B-44 Circle-B, B/h Pakwan-II, SG Road Bodakdev, Ahmedabad, India.

Malpharm, Hong Kong. See *International Medical, Hong Kong.*

Man Xiu Lei Dun, China. Man Xiu Lei Dun Pharmaceutical Co. Ltd, China.

Manchester Pharma, USA. Manchester Pharma, 8236 Benson Court, Fort Collins, CO 80525, USA.
url: www.manchesterpharma.com

Mandar, India. Mandar Pharmaceutical, 103 Shyam Kamal, D Agrawal Market, Vile Parle East, Mumbai, 400 057, India.

Mandri, Spain. Mandri, Pau Claris 182, 08037 Barcelona, Spain.

Maneesh, India. Maneesh Pharmaceuticals Pvt Ltd, 23 Kalpataru Court, Dr C.G. Road, Chembur, Mumbai 400 074, India.
url: www.svizerhealth.com

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Manfred Sauer, Ital. Manfred Sauer Italia Srl, Viale della Repubblica 28, 20037 Paderno Dugnano (MI), Italy.
url: www.manfredsauer.it

Manix, Philipp. DB Manix International Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.

Mankind, India. Mankind Pharma Ltd, 236 Okhla Phase III, New Delhi 110 020, India.
url: mankindpharma.com

Mann, Austria. See *Mann, Ger.*

Mann, Belg. See *Mann, Ger.*

Mann, China. See *Mann, Ger.*

Mann, Cz. See *Mann, Ger.*

Mann, Ger. Dr Gerhard Mann, Chem.-pharm. Fabrik GmbH, Brunsbütteler Damm 165-73, 13581 Berlin, Germany.
url: www.mannpharma.de

Mann, Gr. See *Mann, Ger.*

Mann, Hung. See *Chauvin Ankerpharm, Hung.*

Mann, Irl. See *United Drug, Irl.*

Mann, Malaysia. See *People's, Malaysia.*

Mann, Neth. See *Tramedico, Neth.*

Mann, Pol. See *Bausch & Lomb, Pol.*

Mann, Rus. See *Bausch & Lomb, Rus.*

Mann, S.Afr. See *Novartis, S.Afr.*

Mann, Singapore. See *Indrugco, Singapore.*

Mann, Thai. See *Zuellig, Thai.*

Manne, USA. Manne, P.O. Box 825, Johns Island, SC 29457, USA.

Manon, Israel. Manon Ltd, P.O. Box 3905, Tel Aviv, Israel.

Manor, UK. Manor Drug Co. (Nottingham) Ltd., Manor House, Merlin Way, Quarry Hill Rd, Ilkeston, Derbyshire, DE7 4RA, UK.
url: www.manorpharmacy.co.uk

Mantecorp, Braz. Mantecorp Indústria Química e Farmacêutica Ltda, Rua Antonia das Chagas 1623, 2 andar, 04714-002 São Paulo, Brazil.

Manuell, Mex. Laboratorios Manuell, S.A., Jarcieria 237 Eq.con Plomeros, Col Morelos, Deleg. Venustiano Carranza, 15270 Mexico D.F., Mexico.
url: www.manuell.com

Manx, Neth. See *Manx, UK.*

Manx, UK. Manx Healthcare Ltd, Wedgnock Lane, Warwick, Warwickshire, CV34 5YA, UK.
url: www.manxhealthcare.com

Mao Xiang, China. Mao Xiang Pharmaceutical Co. Ltd, Tonghua, China.

MAP, Fin. MAP Medical Technologies Oy, Elementitie 27, 41160 Tikkakoski, Finland.

Maple, Philipp. See *Ambica, Philipp.*

Mapra, India. Mapra Laboratories Pvt Ltd, 201 Adhyanu Indl Estate, Sun Mill Compound, Lower Parel, Mumbai 400 013, India.

Mar, Arg. Laboratorios Mar S.A., Av. Gaona 3875, 1407 Buenos Aires, Argentina.

Marano, Ital. Marano Benito, Via E Vittorini, Villa Scalea, 90147 Palermo (PA), Italy.

Marathon, USA. Marathon Pharmaceuticals, 1751 Lake Cook Rd, Suite 400, Deerfield, IL 60015, USA.
url: www.marathonpharma.com

Marbiopharm, Rus. Marbiopharm, ul K Marksa 121, Yoshkar-Ola, 424000 respublika Marii El, Russia.
url: www.marbiopharm.ru

Marcel, Mex. Laboratorios Marcel S.A. de C.V., Calzada Gonzalez Gallo 1707, Jalisco, 44870 Guadalajara, Mexico.

Marcelle, Canad. Groupe Marcelle Inc., 9200 Côte de Liesse, Lachine, Quebec, H8T 1A1, Canada.

March, Thai. March Pharmaceuticals Co. Ltd, 655 Praditmanutham Rd, Wangthonglang, Bangkok 10310, Thailand.

Marching, Hong Kong. MPL, Marching Pharmaceutical Ltd, Units 2,4,8-12, 9/F Block B Vigor Ind Bldg, 14-20 Cheung Tat Rd, Tsing Yi, Hong Kong.
url: www.marching.com.hk

Marching, Philipp. See *Pharmawealth, Philipp.*

Marck Biosciences, Philipp. See *International Apex, Philipp.*

Marcmed, Pol. Przedsiębiarstwo Produkcyjno-Handlowe Marcmed, ul. Zamenhofa 29-31, 20-453 Lublin, Poland.
url: www.marcmed.pl

Marco Viti, Ital. Marco Viti Farmaceutici S.p.A., Via Mentana 38, 36100 Vicenza (VI), Italy.

Marcofina, Hong Kong. See *C & L, Hong Kong.*

Mareechi, India. Mareechi Exports Pvt Ltd, B5 Green Park, Delhi 110016, India.

Mareechi, Rus. See *Mareechi, India.*

Marel, Neth. Marel BV, Leiden, Netherlands.

Marfarma, Ital. Marfarma Holding S.p.A., Via Balestrieri 6, 20154 Milan (MI), Italy.
url: www.marfarmaholding.it

Margalit, Israel. Margalit, P.O. Box 16666, Tel Aviv 61166, Israel.

Marien, Austria. See *Marien, Ger.*

Marien, Ger. Marien-Apotheke Prien am Chiemsee, Marktplatz 10, 83209 Prien, Germany.
url: www.marien-prien.de

Marin, USA. AG Marin Pharmaceuticals, 1730 N W 79th Avenue, Miami, FL 33126, USA.

MarinEx, Hong Kong. See *Mekim, Hong Kong.*

Marinex, Pol. Marinex International, ul. Placowa 4, 93-446 Łódź, Poland.
url: www.marinex.com.pl

Marion Merrell, Fr. See *Sanofi-Aventis, Fr.*

Marion Merrell, Pol. See *Sanofi-Aventis, Pol.*

Marion Merrell, Port. See *Sanofi-Aventis, Port.*

Marion Merrell, Spain. See *Sanofi-Aventis, Spain.*

Marion Merrell Dow, Belg. See *Sanofi-Aventis, Belg.*

Marion Merrell Dow, Canad. See *Sanofi, Canad.*

Marion Merrell Dow, Ger. See *Sanofi-Aventis, Ger.*

Marion Merrell Dow, Port. See *Sanofi-Aventis, Port.*

Marion Merrell Dow, Singapore. See *Sanofi-Aventis, Singapore.*

Marion Merrell Dow, Switz. See *Sanofi-Aventis, Switz.*

Marion Merrell Dow, USA. See *Sanofi-Aventis, USA.*

Marjan, Braz. Marjan Indústria e Comércio Ltda, Rua Gibraltar 165, 04755-070 São Paulo, SP, Brazil.
url: www.marjan.com.br

Markdistri, Cz. Markdistri sro, Na flóře 2/1302, 14300 Prague 4, Czech Republic.

Marketlink, Philipp. Marketlink International Corp., 4/F The Taipan Place, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

Marko, Ukr. OOO Marko Farm Ltd, Nagornaya Street, 24/1, Kiev, 04107, Ukraine.

Marlborough Pharmaceuticals, UK. Marlborough Pharmaceuticals, P.O. Box 2957, Marlborough, Wiltshire, SN8 1WS, UK.

Marlin, USA. Marlin Industries, P.O. Box 560, Grover Beach, CA 93483-0560, USA.

Marlop, USA. Marlop Pharmaceuticals Inc., 230 Marshall St., Elizabeth, NY 07206, USA.

Marlyn, Hong Kong. See *Great Liaison, Hong Kong.*

Marlyn, USA. Marlyn Nutraceuticals Inc., 4404 E. Ellwood, Phoenix, AZ 85040, USA.
url: www.naturally.com

Marmir, Pol. Marmir Sp. zo.o., ul. Witomińska 10, 81-311 Gdynia, Poland.

Marnel, USA. Marnel Pharmaceuticals Inc., 206 Luke Drive, Lafayette, LA 70506, USA.

Marpha, Ger. Marpha GmbH, Im Schwarzenborn 4, 35041 Marburg, Germany.

Mars, India. Mars Therapeutics & Chemicals Ltd, 8-290, 1 Goutham Nagar, Ferozguda, Secunderabad 500 011, India.
url: www.mars-therapeutics.com

Mars, Philipp. See *Pasteur, Philipp.*

Mars, UK. Mars Ltd, Dundee Rd, Slough, Berkshire, SL1 4JX, UK.

Marsam, USA. See *Watson, USA.*

Martek, Philipp. See *Pedia Aids, Philipp.*

Martel Hammer, India. Martel Hammer Pharmaceuticals Pvt Ltd, Apeejay Chambers, 5 Wallace St, Mumbai, 400 001, India.

Martin, Arg. Drogueria Martin S.A., Roque Perez 2543, 1430 Buenos Aires, Argentina.

Martin, Cz. See *Martin-Johnson & Johnson, Fr.*

Martin, Fr. See *Martin-Johnson & Johnson, Fr.*

Martin, Pol. See *Janssen-Cilag, Pol.*

Martin, Switz. See *Uhlmann-Eyraud, Switz.*

Martindale, Hong Kong. See *ICH, Hong Kong.*NOTE. There is no connection between Martindale, The Complete Drug Reference, and Martindale Hong Kong

Martindale, Irl. See *Martindale Pharmaceuticals, UK.*

Martindale Pharmaceuticals, UK. Martindale Pharmaceuticals Ltd, Hubert Rd, Brentwood, Essex, CM14 4LZ, UK.
url: www.martindalepharma.co.ukNOTE. There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals

Martinet, Fr. See *Novartis, Fr.*

Martinez Llenas, Spain. Martinez Llenas, Afueras del Barrio de Santa Ines S/N, La Roca del Valles, 08430 Barcelona, Spain.

Martin-Johnson & Johnson, Fr. Laboratoires Martin-Johnson & Johnson-MSD, 1 rue Camille-Desmoulins, TSA 20005, 92797 Issy-les-Moulineaux cdx 9, France.
url: www.proktos.com

Martin-Johnson & Johnson, Switz. See *Uhlmann-Eyraud, Switz.*

Martins & Fernandes, Port. A. Martins & Fernandes, SA, Rua Raul Mesnier du Ponsard 4-B, 1750-243 Lisbon, Portugal.

Martyn, S.Afr. A Martyn Sentinel Drug Store, 128 Smith St, Durban, South Africa.

Maruho, Jpn. Maruho Co. Ltd, 1-5-22 Nakatsu, Kita-ku, Osaka 531-0071, Japan.

Maruishi, Jpn. Maruishi Pharmaceutical Co. Ltd, 2-4-2 Imazunaka, Tsurumi-ku, Osaka 538-0042, Japan.

Maruishi, Neth. See *Rooster, Neth.*

Maruko, China. See *Maruko, Jpn.*

Maruko, Jpn. Maruko Pharmaceutical Co. Ltd, 5-17 Kodama 1-Chome, Nishi-ku, Nagoya 451-0066, Japan.
url: www.maruko-pharm.co.jp

Marvecs, Ital. MarvecsPharma Services S.r.l., Via F. Casati 16, 20124 Milan (MI), Italy.
url: www.marvecspharma.it

Marvecs, Neth. See *Marvecs, Ital.*

Marvel, Rus. Marvel Farm, 3-i Krasnoselskii per. 19, str. 4, et. 5, 107140 Moscow, Russia.

Marx, Fr. Marx, France.

Marzan, Philipp. Marzan Pharma Corp., Sta. Cruz, Manila City, Metro Manila, Philippines.

Masa, Thai. Masa Lab Co. Ltd, 50/25 Soi Thongpan 2, Takham Rd, Bangkunthien, Bangkok 10150, Thailand.

Mascia Brunelli, Ital. Mascia Brunelli S.p.A., Viale Monza 272, 20128 Milan (MI), Italy.
url: www.masciabrunelli.it

Mason, USA. Mason Pharmaceuticals Inc., 4425 Jamboree, Suite 250, Newport Beach, CA 92660, USA.

Mason Natural, USA. Mason Vitamins, 15750 NW 59 Avenue, Miami Lakes, FL 33014, USA.
url: www.masonvitamins.com

Masquad, Singapore. Masquad Pte Ltd, 18 Loon Lay Way, 03-121 TradeHUb 21, S 609966, Singapore.

Masta, UK. Masta Ltd, Moorfield Rd, Yeadon, Leeds, West Yorkshire, LS19 7BN, UK.
url: www.masta.org

Mastelli, Ital. Mastelli S.r.l., Via Bussana Vecchia 32, 18038 Sanremo (IM), Italy.
url: www.mastelli.it

Mastelli, Rus. See *Mastelli, Ital.*

Master, Chile. Laboratorio Farmaceutico Master SA, Av. Irarrazaval 2821, Torre A, Of. 1001, Santiago, Chile.

Master, Port. See *Master Pharma, Ital.*

Master, Ukr. Master Beauty & Healthcare, Ukraine.

Master Pharma, Ital. Master Pharma S.r.l., Via G Chiesi 1, 43100 Parma (PR), Italy.

Master Pharma, Neth. See *Master Pharma, Ital.*

Mastercare, Chile. Mastercore SA, Cruz del Sur 133, Of. 702, Las Condes, Chile.

Masterfarm, Fin. See *Masterfarm, Spain.*

Masterfarm, Rus. Masterfarm, Lenivka ul 3 str 11, 119019 Moscow, Russia.

Masterfarm, Spain. Masterfarm SL, C/Blanquers 85, 17820 Banyoles Girona, Spain.

Masterlek, Rus. Masterlek ZAO, 1-a Volkonskii per. d.11, Str. 2 , 103473 Moscow, Russia.
url: www.masterlek.ru

Masters, Arg. See *Masters, UK.*

Masters, Braz. Masters, Av. Nações Unidas 11.633, Conjunto 154, Brooklin Paulista, Sao Paulo, Brazil.
url: www.mastersglobal.com

Masters, Chile. See *Masters, Braz.*

Masters, Ecuad. See *Masters, UK.*

Masters, Pol. See *Miralex, Pol.*

Masters, UK. Masters Pharmaceutical Ltd, 380 Centennial Ave, Centennial Park, Elstree, Hertfordshire, WD6 3TJ, UK.
url: www.mastersglabol.com

Masters, Venez. See *Masters, Braz.*

Masu, Thai. Masu Co Ltd, 90/2 Soi Suparuam, Ratchada Rd, Bangsue, Bangkok 10800, Thailand.

Materfarma, Port. Materfarma Produtos Farmacêuticos SA, Edifício Botânico, Rua do Campo Alegre 1306 - 3, Sala 310, 4150-174 Porto, Portugal.

Materia Medica, Rus. NPF Materia Medica Holding, 9 bld, 3rd Samotyochnyi per, Moscow 127 473, Russia.
url: www.materiamedica.ru

Matrix, Canad. Matrix Canada, 4895 Hickmore, Montreal, Quebec, H4T 1K5, Canada.

Matrix, USA. See *Chiron, USA.*

Matxin, Singapore. See *Radiance, Singapore.*

Mauermann, Cz. See *Mauermann, Ger.*

Mauermann, Ger. Mauermann-Arzneimittel, Franz Mauermann oHG, Heinrich-Knote-Str. 2, 82343 Pocking, Germany.

Maurer, Ger. See *Sebamed, Ger.*

Maurer & Wirtz, Canad. See *Clarins, Canad.*

Maurino, Arg. Laboratorio Mauriño Hnos., 9 de Julio 245, 1708 Moron, Buenos Aires, Argentina.

Mavena, Ger. Mavena Health Care Deutschland GmbH, Uhlandstrasse 86, 10717 Berlin, Germany.
url: www.mavena.com

Mavena, Switz. Mavena Health Care AG, Haselstrasse 1, 5401 Baden, Switzerland.
url: www.mavena.com

Maver, Chile. Laboratorios Maver SA, Emilio Vaisse 574, Providencia, Santiago, Chile.

Maver, Mex. Productos Maver S.A. de C.V., Av. Oleoducto No. 2804, Fracc. Industrial El Alamo, 44490 Tlaquepaque, Jalisco, Mexico.

Mavi, Ital. Mavi Sud S.r.l., V.le dell'Industria 1, 04011 Aprilia (LT), Italy.
url: www.mavicosmetics.it

Mavi, Mex. Productos Mavi S.A. de C.V., Osa Menor 197, Col. Prado Churubusco, Deleg. Coyoacan, 04230 Mexico D.F., Mexico.

Mavi, Ukr. Mavi GmbH, Shelkovichnaya Street, 42-44, Kiev, 01601, Ukraine.

Max, India. Max India Ltd, 307 Mohan Place, LSC C-Block, Saraswati Vihar, New Delhi 110 034, India.

Max Biocare, Austral. Max Biocare Pty Ltd, Suite 19-20, Level 3 Como Centre, 299 Toorak Rd, South Yarra, Vic 3141, Australia.
url: www.maxbiocare.com

Max Farma, Ital. See *Uno, Ital.*

Max Pharma, Austria. Max Pharma eU, Traubengasse 4/5, 2440 Gramatneusiedl, Austria.

Max Ritter, Switz. Max Ritter Pharma SA, Switzerland.

Maxfarma, Spain. Maxfarma, Salamanca 13, 28020 Madrid, Spain.

Maxi Herbs, Hong Kong. See *Ge Top, Hong Kong.*

Maxim, China. Hainan Maxim Pharmaceutical Co. Ltd., 28 Lingshan Road, Hainan Wen, Meilan, Haikou, Hainan, 570203, China.

Maxim, Thai. Maxim Intercontinental Ltd Part, 640/56-57 Petchburi 22 Rd, Rajthevi, Bangkok 10400, Thailand.

Maxima Medical, Israel. Maxima Medical Ltd, Abba Hillel 7, Ramat Gan, Israel.

Maximus, Philipp. Maximus Healthcare Corp., 18th Floor Citibank Center, 8741 Paseo de Roxas, Makati City, Philippines.

Maxmedic, Ger. MaxMedic Pharma GmbH, Pasinger Str. 16, 82166 Gräfelfing, Germany.
url: www.maxmedic.de

MaxMedica, Swed. MaxMedica AB, Dockplatsen 16, Malmö, Sweden.
url: www.maxmedica.se

Maxo, India. Maxo Chem Limited, B-110, Crystal Plaza, Link Road, Andheri (West), Mumbai 400 053, India.
url: www.maxochem.com

Maxpharma, Ukr. Maxpharma Baltic, Vossoedinenija Ave 7A, Suite 525, 02160 Kiev, Ukraine.
url: www.maxpharma.lt

May & Baker, Austral. See *Sanofi-Aventis, Austral.*

May & Baker, Canad. See *Sanofi, Canad.*

May & Baker, Hong Kong. See *Primal, Hong Kong.*

May & Baker, S.Afr. See *Sanofi-Aventis, S.Afr.*

May & Baker, UK. See *Sanofi, UK.*

Maybelline, Canad. See *L'Oreal, Canad.*

Mayer, USA. Mayer Laboratories Inc., 1950 Addison St, Berkeley, CA 94704, USA.
url: www.mayerlabs.com

Mayinglong, China. Mayinglong Pharmaceutical Group Co. Ltd, 100 Zhoujiawan, Nanhu, Wuchang, Wuhan, Hubei, 430064, China.
url: www.moyinglong.cn

Mayne, Austral. Mayne Pharma P/L, Level 6, 390 St Kilda Road, Melbourne, VIC 3004, Australia.
url: www.maynegroup.com

Mayne, Belg. Mayne Pharmaceuticals SA, Rue de Trois Arbres 16, 1180 Brussels, Belgium.
url: www.maynepharma.com

Mayne, Canad. Mayne Pharma (Canada) Inc., 18100 aut. Transcanadienne, Montreal, Quebec, H9J 4A1, Canada.

Mayne, Cz. See *Mayne, UK.*

Mayne, Denm. See *Hospira, Swed.*

Mayne, Fin. See *Berren, Fin.*

Mayne, Fr. See *Hospira, Fr.*

Mayne, Hong Kong. Mayne Pharma (HK) Ltd, Unit 3A, 16/F Eastwood Ctr, 5A Kung Ngam Village Rd, Shaukeiwan, Hong Kong.
url: www.maynepharma.com

Mayne, Irl. Mayne Pharma (Ireland) Ltd, Unit 31A, Ravensrock Rd, Sandyford Industrial Estate, Foxrock, Dublin 18, Ireland.
url: www.maynepharma.com

Mayne, Malaysia. Mayne Pharma (Malaysia) Sdn Bhd, Suite 201, 1st Fl, Wisma Glomac 3, Kompleks Kelana Centre Point, Jln SS 7/19, 47301 Petaling Jaya, Selangor, Malaysia.
url: www.maynepharma.com

Mayne, Mex. Mayne Pharma Mexico SA de CV, Av. Insurgentes sur 800 Piso 8, 3100 Del Valle, Mexico DF, Mexico.

Mayne, NZ. Mayne Pharma Pty Ltd, P.O. Box 17055, Karori, Wellington, New Zealand.

Mayne, Philipp. See *Asia Pacific, Philipp* and *Zuellig, Philipp.*

Mayne, Pol. See *AstraZeneca, Pol.*

Mayne, Port. Mayne Pharma (Portugal) Lda, Rua Amália Rodrigues 240, 2750-228 Cascais, Portugal.

Mayne, Singapore. Mayne Pharma (Sea) Pte Ltd, 70 Bendemeer Rd, 04-02 Hiap Huat House, S 339940, Singapore.
url: www.maynegroup.com

Mayne, Spain. Mayne Pharma, Alberto Alcocer 7, 28036 Madrid, Spain.
url: www.maynepharma.com

Mayne, Swed. Mayne Pharma (Nordic)AB, Box 34 116, 100 26 Stockholm, Sweden.
url: www.maynegroup.com

Mayne, Thai. See *Indochina Healthcare, Thai.*

Mayne, UK. Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK.
url: www.maynepharma.com

Mayne, USA. Mayne Pharma (USA) Inc., 650 From Rd, Mack-Cali Centre II, Second Floor, Paramus, NJ 07652, USA.
url: www.us.maynepharma.com

Mayo, Mex. Laboratorios Mayo S.A. de C.V., Av. Hidalgo 1337, 44160 Guadalajara, Jalisco, Mexico.

Mayoly-Spindler, China. See *Mayoly-Spindler, Fr.*

Mayoly-Spindler, Cz. See *Mayoly-Spindler, Fr.*

Mayoly-Spindler, Fr. Laboratoires Mayoly-Spindler, 6 av de l'Europe, 78400 Chatou, France.
url: www.mayoly-spindler.com

Mayoly-Spindler, Hong Kong. See *Wing Wai, Hong Kong.*

Mayoly-Spindler, Ital. See *Mayoly-Spindler, Fr.*

Mayoly-Spindler, Malaysia. See *Antah, Malaysia.*

Mayoly-Spindler, Mex. Mayoly Spindler de Mexico SA de CV, Búfalo 27 Piso 1, 3100 Benito Juárez del Valle, Mexico.

Mayoly-Spindler, Pol. See *Perffarma, Pol.*

Mayoly-Spindler, Rus. See *Pro.Med, Rus.*

Mayoly-Spindler, Singapore. See *Polymedic, Singapore.*

Mayoly-Spindler, Switz. See *Uhlmann-Eyraud, Switz.*

Mayoly-Spindler, Thai. See *Charoen, Thai.*

Mayoly-Spindler, Ukr. See *FIC Medical, Ukr.*

Maypo, Mex. Farmacéuticos Maypo SA de CV, Mexico.

Mayrand, USA. See *Merz, USA.*

Mayrhofer, Austria. Mayrhofer Pharmazeutika, Melissenweg 15, A-4021 Linz, Austria.
Mayrs, Irl. David Mayrs Ltd, Broombridge Industrial Estate, Dublin 11, Ireland.
Mazuelos, Spain. See *Farmosur, Spain.*
MBD, Singapore. MBD Marketing (S) Pte Ltd, 3791 Jalan Bukit Merah, 10-05 E-Centre, S 159471, Singapore.
MBP, Ger. Medical Biomaterial Products GmbH, Lederstr. 7, 19304 Neustadt-Glewe, Germany.
url: www.mbp-gmbh.de
McCullough, USA. McCullough Mueller Enterprises, 48 Moosup Valley Rd, Foster, RI 02825, USA.
McGaw, NZ. See *Biomed, NZ.*
McGaw, Singapore. See *Sunward, Singapore.*
McGaw, USA. See *Braun, USA.*
McGhan, Hong Kong. See *Onstrong, Hong Kong.*
McGhan, Singapore. See *Pharmacon, Singapore.*
McGloin, Austral. J. McGloin P/L, P.O. Box 294, Kings Grove, NSW 2208, Australia.
McGloins, Austral. McGloins Pty Ltd, 7/7 Meridian Place, Bella Vista, NSW 2153, Australia.
url: www.mcgloins.com
McGuff, USA. McGuff Pharmaceuticals Inc., 2921 W. MacArthur Blvd, Santa Ana, CA 92704, USA.
url: www.mcguffpharmaceuticals.com
McHenry, USA. McHenry Labs Inc., 1402 Caldwell Lane, Smithville, TX 78957, USA.
url: www.ora5.com
MCM, S.Afr. See *Johnson & Johnson, S.Afr.*
McNeil, Belg. McNeil, Roderveldlaan 1, 2600 Berchem, Belgium.
McNeil, Canad. See *Janssen-Ortho, Canad.*
McNeil, Cz. See *McNeil, UK.*
McNeil, Denm. McNeil Denmark ApS, Bregnerødvej 133, 3460 Birkerød, Denmark.
url: www.mcneil.dk
McNeil, Fin. See *Janssen-Cilag, Fin.*
McNeil, Fr. McNeil Santé Grand Public, 1 rue Camille-Desmoulins, TSA 20005, 92130 Issy-les-Moulineaux, France.
McNeil, Ger. McNeil GmbH & Co. oHG, Raiffeisenstr. 9, 41470 Neuss, Germany.
url: www.jnjgermany.de
McNeil, Hong Kong. See *Jacobson, Hong Kong* and *Janssen, Hong Kong.*
McNeil, Hung. See *Johnson & Johnson, Hung.*
McNeil, Israel. See *Invest Impex, Israel.*
McNeil, Neth. McNeil BV, Dr Paul Janssenweg 150, 5026 RH Tilburg, Netherlands.
McNeil, Norw. See *Janssen-Cilag, Norw.*
McNeil, Pol. See *Pfizer, Pol.*
McNeil, Spain. McNeil Iberica, Antigua Ctra Barcelona Km 32.800, Alcalá de Henares, 28805 Madrid, Spain.
McNeil, Swed. Mcneil Sweden AB, 169 90 Solna, Sweden.
McNeil, UK. McNeil Products Ltd, Foundation Park, Roxborough Way, Maidenhead, Berkshire, SL6 3UG, UK.
McNeil, Ukr. See *Johnson & Johnson, Rus.*
McNeil, USA. RA McNeil Co, 1210 E Dallas Rd, Chattanooga, TN 37405, USA.
McNeil & Argus, India. McNeil & Argus Pharmaceuticals Ltd, 100 Rampur Sarsehri Rd, Ambala Cantt 133 001, India.
url: www.mcneilargusindia.com
McNeil Consumer, Canad. McNeil Consumer Healthcare, 890 Woodlawn Rd W., Guelph, Ontario, N1K 1A5, Canada.Director, Medical, Regulatory, & Professional Services
url: www.mcneilcanada.com
McNeil Consumer, Ger. See *McNeil, Ger.*
McNeil Consumer, USA. McNeil Consumer & Specialty Pharmaceuticals, Camp Hill Rd, Fort Washington, PA 19034, USA.
url: www.tylenol.com
McNeil Healthcare, Irl. See *Johnson & Johnson, Irl.*
McNeil Nutritionals, USA. See *McNeil Consumer, USA.*
McNeil Pharmaceutical, USA. See *Ortho McNeil, USA.*
MCP Pharmaceuticals, UK. See *Roche Diagnostics, UK.*
MCR, USA. MCR American Pharmaceuticals, 16206 Flight Path Drive, Brooksville, FL 34604, USA.
url: www.mcramerican.com
McW, India. McW Healthcare Pvt Ltd, 501 Rafael Tower, Old Palasia, Indore 452 001, India.
url: www.mcwhealthcare.com
MD, Singapore. MD Pharmaceuticals Pte Ltd, 896 Dunearn Rd, 02-01A Sime Darby Centre, S 589472, Singapore.
MD Vision, Fr. MD Vision, ZA Les-Hauts-de-Lafourcade, 32201 Gimont, France.
MD Vision, Neth. See *MD Vision, Fr.*
MDC, India. MDC Pharmaceuticals (P) Ltd, 52 Industrial Area, Phase-1, Chandigarh 160 002, India.
MDE, UK. MDE Diagnostic Ltd, The Surrey Technology Centre, Surrey, GU2 7YG, UK.
url: www.mdediagnostic.co.uk
MDI, S.Afr. MDI, South Africa.
MDM, Ital. MDM S.p.A., Via Volturno 29/B, 20052 Monza (MB), Italy.
url: www.mdmspa.com
MD-Pharm, Cz. MD-Pharm sro, L Hořké 15/66, 747 21 Kravaře, Czech Republic.
MDR, USA. MDR Fitness Corp., 14101 NW 4th St, Sunrise, FL 33325, USA.
url: www.mdr.com
MDS, Belg. MDS Nordion SA, Zoning Industriel, Ave de l'Espérance, 6220 Fleurus, Belgium.
url: www.mds.nordion.com
MDS, Cz. See *MDS, Belg.*
MDS, Neth. See *MDS, Belg.*
MDS, Port. See *MDS, Belg.*
MDS Diagnostics, NZ. MDS Diagnostics, P.O. Box 24-162, Royal Oak, Auckland, New Zealand.
url: www.mdsdiagnostics.com
ME Pharmaceuticals, USA. ME Pharmaceuticals Inc., 2800 Southeast Parkway, Richmond, IN 47374, USA.
Mead Johnson, Arg. See *BMS, Arg.*
Mead Johnson, Austral. See *BMS, Austral.*
Mead Johnson, Braz. See *BMS, Braz.*
Mead Johnson, Chile. See *BMS, Chile.*
Mead Johnson, Denm. See *BMS, Denm.*
Mead Johnson, Fr. See *BMS, Fr.*
Mead Johnson, Ger. See *BMS, Ger.*
Mead Johnson, Gr. See *BMS, Gr.*
Mead Johnson, Hong Kong. See *BMS, Hong Kong.*
Mead Johnson, Indon. Mead Johnson Nutritional Division, Tamara Ctr 11/F, Jl Jend Sudiman Kav 24, Jakarta 12920, DKIJaya, Indonesia.
MeadJohnson, Irl. See *BMS, Irl.*
Mead Johnson, Israel. See *BMS, Israel.*
Mead Johnson, Ital. See *BMS, Ital.*
Mead Johnson, Malaysia. See *DKSH, Malaysia.*
Mead Johnson, Mex. See *BMS, Mex.*
Mead Johnson, NZ. See *BMS, NZ.*
Mead Johnson, Philipp. Mead Johnson (Phil) Inc., 2309 Pasong Tamo Ext, Makati City, Philippines.
Mead Johnson, Pol. See *BMS, Pol.*
Mead Johnson, Port. See *BMS, Port.*
Mead Johnson, Singapore. See *DKSH, Singapore.*
Mead Johnson, Venez. See *BMS, Venez.*
Mead Johnson Laboratories, USA. See *BMS, USA.*
Mead Johnson Nutritionals, Canad. Mead Johnson Nutritionals, Division of Bristol-Myers Squibb Canada Inc., 333 Preston Ave, Suite 700, Ottawa, Ontario, K1S 5N4, Canada.
url: www.meadjohnson.ca
MeadJohnson Nutritionals, Ital. See *BMS, Ital.*
Mead Johnson Nutritionals, Thai. Mead Johnson Nutritionals (Thailand) Ltd, 388 Exchange Tower, 14 Fl Sukhumvit Rd, Klongtoey, Bangkok 10110, Thailand.
Mead Johnson Nutritionals, UK. See *BMS, UK.*
Mead Johnson Nutritionals, USA. Mead Johnson Nutritionals, 2400 W Lloyd Expressway, Evansville, IN 47721-0001, USA.
url: www.meadjohnson.com
Meadow, UK. Meadow Laboratories, 18 Avenue Rd, Chadwell Heath, Romford, Essex, RM6 4JF, UK.
Mebo, Thai. See *Diethelm, Thai.*
Meckel, Austria. See *Meckel, Ger.*
Meckel, Ger. Meckel-Spenglersan GmbH, Steinfeldweg 13, 77815 Bühl, Germany.
url: www.spenglersan.de
Mecom, Rus. See *Abdi, Rus.*
Mecom, Turk. See *Abdi, Turk.*
Mecosin, Indon. Mecosin Indonesia PT, Jl Palmerah Utr 14-A, 11480 Jakarta, Indonesia.
Med, Turk. Med-İlaç San. ve Tic. A.Ş., Bankalar Cad. Bozkurt Han 19/4, Karaköy, İstanbul, 34420, Turkey.
url: www.medilac.com.tr
Med. Prod. Panam., USA. Medical Products Panamericana Inc., 647 W Flagler St, Miami, FL 33130, USA.
Med Immune, Hong Kong. See *Abbott, Hong Kong.*
Meda, Austria. Meda Pharma GmbH, Guglgasse 15, A-1110 Vienna, Austria.
Meda, Belg. Meda Pharma, Chaussée de la Hulpe 166, B-1170 Brussells, Belgium.
url: www.medapharma.be
Meda, Canad. See *Meda, USA.*
Meda, Cz. Meda Pharma sro, Kodaòská 1441/46, 100 10 Praha 10, Czech Republic.
url: www.meda.se
Meda, Denm. Meda AS, Solvang 8, 3450 Allerod, Denmark.
url: www.meda.dk
Meda, Fin. Meda Oy, Lemminkäisenkatu 32, 20520 Turku, Finland.
url: www.meda.fi
Meda, Fr. Meda Pharma, 25 bd Amiral-Bruix, 75116 Paris, France.
url: www.meda.se
Meda, Ger. Meda Pharma GmbH & Co. KG, Benzstr. 1, 61352 Bad Homburg, Germany.
url: www.medapharma.de
Meda, Gr. See *Meda, Swed.*
Meda, Hong Kong. See *Hong Kong Medical, Hong Kong.*
Meda, Hung. Meda Pharma Hungary Kft, Váci ú 91, 1139 Budapest, Hungary.
url: www.medapharma.com
Meda, Irl. Meda Health Sales Ireland Ltd, Office 10, Dunboyne Business Park, Dunboyne, Co Meath, Ireland.
url: www.meda.ie
Meda, Israel. See *Megapharm, Israel.*
Meda, Ital. Meda Pharma S.p.A., Viale Brenta 18, 20139 Milan (MI), Italy.
Meda, Neth. See *Meda, Swed.*
Meda, Norw. Meda A/S, Askerv. 61, 1371 Asker, Norway.
url: www.meda.no
Meda, Pol. Meda Pharmaceuticals Sp. zo.o., al. Jana Pawła II 15, 00-828 Warsaw, Poland.
Meda, Port. Meda Pharma - Produtos Farmacêuticos S.A., Rua do Centro Cultural 13, 1749-066 Lisbon, Portugal.
Meda, Rus. Meda Pharmaceuticals, Naryshkinskaya alleya 5 str 2, 125167 Moscow, Russia.
url: www.medapharma.ru
Meda, Spain. See *Meda, Swed.*
Meda, Swed. Meda AB, Box 906, 170 09 Solna, Sweden.
url: www.meda.se
Meda, Switz. Meda Pharma GmbH, Hegnaustrasse 60, 8602 Wangen, Switzerland.
url: www.meda.se
Meda, Thai. See *Zuellig, Thai.*
Meda, UK. Meda Pharmaceuticals Ltd, Skyway House, Parsonage Rd, Takeley, Bishop's Stortford, Cambridgeshire, CM22 6PU, UK.
url: www.medapharma.co.uk
Meda, Ukr. Meda Pharmaceuticals, 57-B O Honchara St, 6th Floar, Kiev 01054, Ukraine.
url: www.meda.se
Meda, USA. Meda Pharmaceuticals Inc., 265 Davidson Ave, Suite 300, Somerset, NJ 08873-4120, USA.
url: www.medapharma.us
Meda Manufacturing, Ger. Meda Manfacturing GmbH, Neurather Ring 1, 51063 Köln, Germany.
url: www.meda-manufacturing.de
Meda Valeant, Austral. See *Valeant, Austral.*
Medac, Austria. See *Medac, Ger.*
Medac, Belg. medac Belgien, 8 rue des Baillieries, 5081 Meux, Belgium.
url: www.medac.de
Medac, China. See *Medac, Ger.*
Medac, Cz. See *Medac, Ger.*
Medac, Denm. See *Medac, Swed.*
Medac, Fin. Medac, Jorvas High Tech Center, Hirsalantie 11, 02420 Kirkkonummi, Finland.
url: www.medac.se
Medac, Fr. See *Medac, Ger.*
Medac, Ger. medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany.
url: www.medac.de
Medac, Gr. See *Biochem, Gr.*
Medac, Hung. See *Medac, Ger.*
Medac, Irl. See *Medac, Ger.*
Medac, Neth. See *Medac, Ger.*
Medac, Norw. See *Medac, Swed.*
Medac, Pol. medac GmbH Sp. zo.o., Przedstawicielstwo w Polsce, ul. Ładysława 14, 02-066 Warsaw, Poland.
url: www.medac.de
Medac, Port. See *Medac, Ger.*
Medac, Rus. See *Schering, Rus.*
Medac, Spain. See *Medac, Ger.*
Medac, Swed. Medac, Kungsgatan 32, 432 23 Varberg, Sweden.
url: www.medac.se
Medac, Switz. See *Pharma Consulting, Switz.*
Medac, UK. Medac UK, 13 Lynedoch Crescent, Glasgow, G3 6EQ, UK.
Medacta, Ital. Medacta Italia Srl, Via G Stephenson 94, 20157 Milan (MI), Italy.
Medagro, Pol. Medagro International Sp. zo.o., ul. Podleśna 83, Łazy 05-552 Wólka Kosowska, Poland.
url: www.medagro.com.pl
Medana, Cz. See *Medana, Pol.*
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Medana, Pol. Medana Pharma Terpol Group SA, ul. Warcka 3, 98-200 Sieradz, Poland.
url: www.terpol.pl
Medana, Rus. See *Polpharma, Rus.*
Medano, Switz. Medano AG, 6331 Hünenberg, Switzerland.
url: www.medanoag.ch
Medarex, USA. Medarex Inc., 707 State Rd, Princeton, NJ 08540, USA.
url: www.medarex.com
Medarte, Gr. Medarte Pharmaceuticals SA, Spyrou Vrettou 1-0, 144 52 Metamorfosi, Greece.
Medartuum, Swed. Medartuum AB, Sodra Gubberogatan 8, 416 63 Göteborg, Sweden.
url: www.medartuum.se
Medasta, Swed. Medasta Medical/Vet AB, Västergatan 36, 211 21 Malmö, Sweden.
url: www.medasta.se
Medatek, Turk. Medatek Ltd Sti, Ethemefendi Cd, Abdülhalik Renda Sk No 1/11, Erenköy, Istanbul, Turkey.
Medbase, Philipp. Medbase Pharmaceuticals Inc., 603-C Emerald Mansion, F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.
Medbridge, Philipp. Medbridge Inc., 2695 A Rose St, Goodwill Vill., Tambo, Parañaque City, Philippines.
Med-Care, Turk. Med-Care Kimya San. ve Tic. Ltd. Şti., Gümüssuyu Dümen Sok., Gümüspalas Apt. No: 1/6, Taksim, İstanbul, 80090, Turkey.
Medcell, Neth. Medcell Pharma BV, Flevoweg 9 E, 2318 BZ Leiden, Netherlands.
Medchem, Hong Kong. See *Tsun Tsun, Hong Kong.*
Medchem, Philipp. See *GBF, Philipp.*
Medchem, S.Afr. Medchem Pharmaceuticals (Pty) Ltd, P.O. Box 36014, Menlo Park 0102, South Africa.
MedChem, USA. MedChem Manufacturing, 381 Van Ness Ave, Suite 1507, Torrance, CA 90501, USA.
url: www.medchemmanufacturing.com
MedChoice, Philipp. MedChoice Pharma Inc., Unit 1001, 88 Corporate Ctr, Sedeño cor Valero St, Salcedo Vill., Makati City, Philippines.
Medco, USA. Medco Laboratories Inc., P.O. Box 864, Sioux City, IA 51102-0864, USA.
url: www.medcolab.com
Medcor, Neth. Medcor Pharmaceuticals BV, Ketelmeerstraat 142-144, 8226 JX Lelystad, Netherlands.
Med-Derm, USA. See *Crown, USA.*
Medea, Spain. See *Reig Jofre, Spain.*
Medecor, USA. Medecor Pharma, USA.
url: www.tricarevitamin.com
Medefield, Austral. Medefield P/L, 6 Gundah Rd, Mt Kuring-Gai, NSW 2080, Australia.
Medela, Canad. Medela Canada Inc., 4090B Sladeview Cres., Unit 2, Mississauga, Ontario, L5L 5Y5, Canada.
url: www.medela.com
Medentech, Israel. See *Concept, Israel.*
Mederis, Malaysia. Mederis Sdn Bhd, c7-8 Megan Ave 1, 189 Jalan Tun Razak, 50400 Kuala Lumpur, Malaysia.
url: www.mederis.com.my
Medestea, Ital. Medestea Reasearch & Production S.r.l., Via Ribes 5, 10010 Colleretto Giacosa (TO), Italy.
url: www.medestearesearch.it
Medeus, Malaysia. See *Summit, Malaysia.*
Medeus, Spain. See *Zeneus, Spain.*
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Medeva, Austria. See *UCB, UK.*
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Medevale, Cz. Medevale Pharmaservices Ltd, Czech Republic.
Medex, Cz. Medex Praha, Radlická 61, 150 00 Prague 5, Czech Republic.
Medex, India. Medex India Pvt Ltd, DD-36 Kalkajee, New Delhi 110 019, India.
Medexis, Gr. Medexis Ltd, Asklepiou 4, 145 68 Kryoneri, Greece.
Medexport, Hung. See *Medi-Zone, Hung.*
Medexus, Canad. Medexus Inc., 7895 Tranmere Dr, Unit 4, Mississauga, Ontario, L5S 1V9, Canada.
url: www.medexus.ca
Medflorina, Rus. Medflorina, 1st Tverskaya St 13/5, Moscow, Russia.
url: medflorina.ru
Medgamal, Rus. Medgamal, ul Gamalei 18, 123098 Moscow, Russia.
url: www.medgamal.ru
MedGen, Philipp. See *MG, Philipp.*
Medgenix, Belg. Medgenix Benelux SA, Vliegveld 21, 8560 Wevelgem, Belgium.
Medgenn, China. Simcere Medgenn Co. Ltd, Rongchang Rd, Economic and Technological Development Zone,, Yantai, 264006, China.
url: www.medgenn.com
Medhaus, Philipp. Medhaus Pharma Inc., 139 K 1st St, Kamuning, Quezon City, Philippines.
Medhel, Gr. Medhel Hellas AE, 30st klm Athens Laurio, 190 03 Marko Payao, Greece.
Medhouse, Swed. Medhouse AB, Upplandsgatan 2B, 111 23 Stockholm, Sweden.
url: www.medhouse.se
Medi Challenge, S.Afr. Medi Challenge (Pty) Ltd, 1st Floor, Barvic House North, 4 Burke St., Kensington B, Randburg 2125, South Africa.
Medi Globe, India. Medi Globe, G-3 Ashoka Chambers, B-5 Rajendra Park, Pusa Road, New Delhi 110 060, India.
Medi Service, Ital. Medi Service Srl, Via Matteotti 43/b, 20041 Agrate Brianza (MI), Italy.
url: www.mediservice.it
Media Power, Canad. See *Media Power, USA.*
Media Power, USA. Media Power Inc., 60 Yak St, Portland, Maine, 04101, USA.
Medial, Cz. Medial sro, Na dolinach 36/128, 147 00 Prague 4, Czech Republic.
Medial, India. Medial Pharma Ltd, 1122 Rithala (Near Bagga link Service Station), New Delhi 85, India.
Medialyse, Cz. See *Medialyse, Gr.*
Medialyse, Gr. Medialyse SA, 38 Sorou Str, 15125 Marousi, Greece.
Mediam, Fr. Mediam, 85 rue Nelson Mandela, 59120 Loos, France.
Mediam, Irl. See *Mediam, Fr.*
Mediam, Neth. See *Mediam, Fr.*
Mediapharm, Gr. Mediapharm, Velestinou 1, 163 45 Ilioupoli, Greece.
Medibase, Ital. Medibase S.r.l., Via Baldinucci 14/a, 59100 Prato (PO), Italy.
url: www.medibase.it
Medibial, Port. See *Bial, Port.*
Medibrands, Canad. See *Medibrands, Israel.*
Medibrands, Israel. Medibrands, P.O. Box 531, Yokneam 20692, Israel.
url: www.medibrands.com
Medibudget, Switz. Medibudget AG, Gutschstrasse 6, 6312 Steinhausen, Switzerland.
Medic, Denm. Medic Team a/s, Solvang 8, 3450 Allerød, Denmark.
url: www.medicteam.dk
Medic, Ital. Medic Italia Srl, Via della Rimessola 48, 00135 Rome (RM), Italy.
url: www.medicitaliasrl.it
Medic, NZ. Medic Corp. Ltd, Private Bag, Lower Hutt, Wellington, New Zealand.
Medic+Aid, Philipp. Medi+Aid Distributors Inc., 202 Elco Bldg, E Rodriguez Ave, Quezon City, Philippines.

Medica, Arg. Cosmética Médica, Carabobo 13, 1406 Buenos Aires, Argentina.
Medica Korea, Hong Kong. See *Ebewe, Hong Kong.*
Medica Korea, Malaysia. See *Zyfas, Malaysia.*
Medica Korea, Philipp. See *Metro, Philipp.*
Medica Korea, Singapore. See *Zyfas, Singapore.*
Medica Nord, Swed. Medica Clinical Nord Sverige AB, Barnarpsgatan 23, 553 16 Jönköping, Sweden.
url: www.medicanord.se
MedicaPedia, Philipp. See *Zuellig, Philipp.*
Medical, Arg. Química Medical Arg. S.A.C.I., Int. Amaro Avalos 4208, 1605 Munro, Buenos Aires, Argentina.
Medical, Port. See *Gestafarma, Port.*
Medical, Spain. Medical, Manuel Concha Ruiz 1, 14012 Cordoba, Spain.
url: www.laboratoriosmedical.com
Medical Consulting, Hung. Medical Consulting Ltd, Hunfalvy u 8, 1015 Budapest, Hungary.
Medical Developments, Austral. Medical Developments Australia P/L, 7/56 Smith Rd, Springvale, VIC 3171, Australia.
Medical Developments, Ukr. See *Revmoform, Ukr.*
Medical Diagnostics, UK. See *MDE, UK.*
Medical Futures, Canad. Medical Futures, 16 Sims Cres, Suite 29, Richmond Hill, Ontario, L4B 2P1, Canada.
url: www.medfutures.com
Medical International Systems, Singapore. See *Mediquest, Singapore.*
Medical Nutrition, USA. Medical NUtrition, 10 West Forest Ave, Englewood, NJ 07531, USA.
url: www.pbsnutrition.com
Medical Ophthalmics, USA. Medical Ophthalmics Inc., 40146 U.S. Hwy 19 N, Tarpon Springs, FL 34689, USA.
url: www.medicalophthalmics.com
Medical Pharmaquality, Gr. Medical Pharmaquality Farm, Agia Kyriaki 20, 145 61 Kifissia, Greece.
Medical Products, Canad. See *Medical Products, USA.*
Medical Products, USA. Medical Products Labs, 9990 Global Rd, Philadelphia, Pennsylvania, 19115, USA.
Medical Research, Austral. Medical Research Trust, Level 6, 88 Foveaux St, Surrey Hills, NSW 2010, Australia.
Medical Research, Hong Kong. See *Jebsen, Hong Kong.*
Medical Skin Therapy, Canad. See *Medical Skin Therapy, USA.*
Medical Skin Therapy, USA. Medical Skin Therapy Research Inc., 200 701 Del Norte Blvd, Oxnard, CA 93030, USA.
Medical Specialties, Austral. Medical Specialties Australia P/L, 2 McCabe Place, Willoughby, NSW 2068, Australia.
Medical Supply, Thai. Medical Supply Co. Ltd, 101 Sribumpen Rd, Yannawa, Bangkok 10120, Thailand.
Medicalfarm, Ital. Medicalfarm S.r.l., Via Dronero 2, 10144 Turin (TO), Italy.
Medicalia, Spain. Medicalia, Recoletos 19, 280001 Madrid, Spain.
Medicamenta, Cz. Medicamenta as, Fibichová 143/II, 566 17 Vysoké Mýto, Czech Republic.
Medicamenta, Philipp. Medicamenta Inc., 6/F Victoria Bldg, 11th Ave, Kalookan City, Philippines.
Medicamerc, Gr. Medicamerc AE, Elaion 36, N Kifissia, Greece.
Medican, Canad. Medican Pharma Inc., 1120 Victoria St N, Suite 203, Kitchener, Ontario, N2B 3T2, Canada.
Medicap, Hong Kong. See *IDS, Hong Kong.*
Medicap, Rus. See *Mega, Rus.*
Medicap, Thai. See *Neopharm, Thai.*
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Medice, Cz. See *Medice, Ger.*
Medice, Denm. See *Pharmacuro, Denm.*
Medice, Fin. See *Medice, Ger.*
Medice, Ger. Medice, Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany.
url: www.medice.de
Medice, Gr. See *Medice, Ger.*
Medice, Hung. See *Medice, Ger.*
Medice, Irl. See *Medice, Ger.*
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Medice, Norw. See *Algol, Norw.*
Medice, Pol. Medice Arzneimittel Pütter, ul. Choragwi Pancernej 27, 02-951 Warsaw, Poland.
Medice, Port. See *Medice, Ger.*
Medice, Singapore. See *PanMalayan, Singapore.*
Medice, Spain. See *Medice, Ger.*
Medice, Switz. See *Ridupharm, Switz.*
Medicell, Singapore. Medicell Pharmaceuticals Pte Ltd, 12 Tannery Lane, 03-02/03 HB Centre 1, S 347722, Singapore.
url: www.medicellpharma.com
Medichem, Hong Kong. See *Unam, Hong Kong.*
Medichem, Indon. See *Medifarma, Indon.*
Medichem, Malaysia. See *Unam, Malaysia.*
Medichem, Philipp. Medichem Pharmaceuticals Inc., 6/F Dynavision Bldg, Rada St, Legaspi Vill, Makati City, Philippines.
Medichem, Singapore. See *Far East, Singapore.*
Medichemie, Switz. Medichemie AG, Bruhlstrasse 50, 4107 Ettingen, Switzerland.
Medichemie Bioline, Switz. See *Medichemie, Switz.*
MedicHerb, UK. See *Schwabe, UK.*
Medichrom, Gr. Medichrom Avee, 6o xil Paiana, 190 03 Markopoulo, Greece.
Medicina, Gr. Medicina Pharmaceuticals AE, Leof. Siggrou 156, 176 71 Kallithea, Greece.
Medicine & Business, Hung. Medicine & Busines Kft, Zrinyi u 21, 1039 Budapest, Hungary.
Medicine Products, Thai. See *Medicine Supply, Thai.*
Medicine Supply, Thai. Medicine Supply Co. Ltd, 77/11 Moo 4, Petchkasem Rd, Thatamnak, Nakhonchaisri, Nakhonpathom 73120, Thailand.
Medicines Company, Austria. The Medicines Company, Kaerntner Ring 5-7, 1010 Vienna, Austria.
url: www.themedicinescompany.com
Medicines Company, Belg. The Medicines Company, Square de Meeus, 37 4th Floor, 1000 Brussels, Belgium.
url: www.themedicinescompany.com
Medicines Company, Cz. See *Medicines Company, UK.*
Medicines Company, Denm. The Medicines Company, Larsbjornsstraede 3, 1454 Copenhagen, Denmark.
url: www.themedicinescompany.com
Medicines Company, Fin. The Medicines Company, Mannerheimintie 12 B, 00100 Helsinki, Finland.
url: www.themedicinescompany.com
Medicines Company, Fr. The Medicines Company France SAS, 112 ave Kleber, 75116 Paris, France.
url: www.themedicinescompany.com
Medicines Company, Ger. The Medicines Company (Deutschland) GmbH, Nymphenburger Strasse 5, 80335 Munich, Germany.
url: www.themedicinescompany.com
Medicines Company, Gr. The Medicines Company, Greece.
Medicines Company, Hung. See *Medicines Company, UK.*
Medicines Company, Irl. See *Medicines Company, UK.*
Medicines Company, Neth. The Medicines Company, Herengracht 282, 1016 BX Amsterdam, Netherlands.
url: www.themedicinescompany.com
Medicines Company, Norw. The Medicines Company, Torgbygget, Nydalsveien 33, 0484 Oslo, Norway.
url: www.themedicinescompany.com
Medicines Company, Pol. See *Medicines Company, UK.*
Medicines Company, Port. See *Medicines Company, UK.*
Medicines Company, Swed. The Medicines Company, Stureplan 4c 4th Floor, 114 35 Stockholm, Sweden.
url: www.themedicinescompany.com
Medicines Company, Switz. The Medicines Company (Schweiz) GmbH, Balsberg, 8058 Zurich-Flughafen, Switzerland.
url: www.themedicinescompany.com
Medicines Company, UK. The Medicines Company, Suite B, Park House, 11 Milton Park, Abingdon, Oxfordshire, OX14 4RS, UK.
url: www.themedicinescompany.com
Medicines Company, USA. The Medicines Company, NJ 07054, USA.
url: www.themedicinescompany.com
Medicis, Canad. Medicis Canada Ltd, 355 McCaffrey St, St-Laurent, Quebec, H4T 1Z7, Canada.
Medicis, USA. Medicis Pharmaceutical Corp., 8125 N Hayden Dr., Scottsdale, AZ 85258-2463, USA.
url: www.medicis.com
Medico, India. Medico Health Care, 302 Aditraj Arcade, Near Hetvi Tower, 100 Feet Ring Rd, Ahmedabad 380 015, India.
Medico Uno, Cz. See *Medico Uno, Hung.*
Medico Uno, Fin. See *Medico Uno, Hung.*
Medico Uno, Hung. Medico Uno Rt, Viadukt u 12, 2051 Biatorbágy, Hungary.
url: www.medicouno.com
Medico Uno, Neth. See *Medico Uno, Hung.*
Medico-Biological Laboratories, UK. Medico-Biological Laboratories Ltd, Kingsend House, 44 Kingsend, Ruislip, Middlesex, HA4 7DA, UK.
Medicofarma, Pol. Medicofarma Sp. zo.o., ul. Kozienicka 97, 26-600 Radom, Poland.
Medicom, Austria. See *Medicom, Cz.*
Medicom, Canad. AR Medicom Inc., 1200 55e Avenue, Lachine, Montreal, Quebec, H8T 3J8, Canada.
Medicom, Cz. Medicom International sro, Pateřni 7, 635 00 Brno - Bystrc, Czech Republic.
Medicom, Neth. See *Medicom, UK.*
Medicom, Pol. See *Medagro, Pol.*
Medicom, UK. Medicom Consultancy Ltd, 235 Hunts Pond Rd, Fareham, Hampshire, PO14 4PJ, UK.
Medicon, India. Medicon Pharma Lab Pvt Ltd, 15 Pudupet Garden Street, Royapettah, Chennai 600 014, India.
url: www.mediconpharma.com
Medicons, Hung. Medicons Kft, Karoly kiraly ut 39, 2040 Budaors, Hungary.
url: www.medicons.hu
Medicopharm, Austria. Medicopharm Dr H Sorgo GmbH, Thimiggasse 25, A-1180 Vienna, Austria.
Medicor, Rus. See *CMM Medicor, Rus.*
Medicpharma, Thai. See *United Medical, Thai.*
Medicure, USA. Medicure Pharma Inc., Somerset, NJ 08873, USA.
url: www.medicure.com
Medicus, Gr. Medicus S.A., 10 Valaoritou St., 144 52 Metamorfosi, Greece.
Medidata, Malaysia. Medidata Sdn Bhd, 36 Jln PJS 8/6, Sunway Mentari, 46150 Petaling Jaya, Selangor, Malaysia.
Mediderm, Chile. See *Recalcine, Chile.*
Medidis, Neth. Medidis BV, Archimedeslaan 11, 8218 ME Lelystad, Netherlands.
Mediez, India. Mediez Pharma Pvt Ltd, SPO - 1/82 R.B.B., Hanumangarh 335 512, India.
url: www.mediezpharma.com
Medifarm, Rus. Ct. Medifarm, Russia.
Medifarm, Turk. Medifarm, Turkey.
Medifarm, Venez. Medifarm, C.A. Inversiones y Representaciones, C.C. Caroni-Modulo B11 Av. Caurimare, Colinas de Bello Monte, Caracas, Venezuela.
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Medifarm Avene, Venez. See *Medifarm, Venez.*
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Medifarma, Indon. Medifarma Lab Inc. PT, Jl Rawagelam V Blok L Kav 11-13, Kawasan Industri Pulogadung, Jakarta Timur 13930, DKI Jaya, Indonesia.
Medifarma, Ital. Medifarma Srl, Via Guindazzi 44/54, 80040 Pollena Trocchia (NA), Italy.
Medifarma, Mex. Grupo Medifarma S.A. de C.V., Cuancontle No. 7, Col. San Gregorio, Atlapulco Xochimilico, 16600 Mexico D.F., Mexico.
Medifarma, Turk. Medifarma İlaç Sanayi ve Tic. AS, Turkey.
Medifive, Thai. Medifive Pharma Co. Ltd, 51/465-466 Drive-in Square, Soi 3 Ladprao Rd, Klongjan, Bangkok 10240, Thailand.
Mediflor, Fr. See *Merck Medication Familiale, Fr.*
Medifood, Ital. Medifood Italia S.r.l., Via Balbi 31/1, 16126 Genoa (GE), Italy.
url: www.piamfarmaceutici.com
Medigal, Israel. Medigal Ltd, Yokneam Illit 20692, Israel.
url: www.medigal.com
Medigivor, Venez. Corporación Medigivor C.A., Av Ppal Bello Campo, Quinta Alcira N. 83, Chacao 1060, Caracas, Venezuela.
Medigroup, Austral. Medigroup, Level 1, 530 Little Collins St, Melbourne, VIC 3000, Australia.
url: www.medigroup.com.au
Medihealth, India. Medihealth Lifesciences (India) Pvt Ltd, B-4/155 Yamuna Vihar, New Delhi 110 053, India.
url: www.medihealthlifesciences.com
Medihealth, Mex. See *Rhein, Mex.*
Medihelm, Gr. Medihelm, Alexandroupoleos 6, 144 51 Metamorfosi, Greece.
Mediherb, Austral. Mediherb P/L, P.O. Box 713, Warwick, QLD 4370, Australia.
url: www.mediherb.com.au
Medihoney, Austral. Medihoney Pty Ltd, 399 Archerfield Rd, Richlands, 4077 QLD, Australia.
url: www.medihoney.com
Medikon, Indon. Medikon Prima Laboratories PT, Jl Talib I No 26, 11140 Jakarta Barat, DKI Jaya, Indonesia.
url: www.medikon.co.id
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Medilab, Spain. See *Italfarmaco, Spain.*
Medilat, Gr. Medilat, L. Alexandras 117, 114 75 Athens, Greece.
Medi-Lek, Pol. Medi-Lek Sp z o o, ul. Lucerny 108 lok 305, 04-687 Warsaw, Poland.
Medilife, Philipp. Medilife Pharma Inc., Rm 501 West City Plaza Bldg, 66 West Ave, Quezon City, Philippines.
Mediline, Hung. Mediline Kft, Csizma u. 4, 1139 Budapest, Hungary.
url: www.mediline.hu
Mediline, Israel. See *Medibrands, Israel.*
Medilink, Denm. Medilink A/S, Agern Allé 3, 2970 Hørsholm, Denmark.
url: www.medilink.dk
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Medilink, Norw. See *Medilink, Denm.*
Medilink, Swed. See *Medilink, Denm.*
Medilusa, Port. Medilusa Comércio e Indústria de Especialidades Farmacêuticas Lda, Rua Duarte Galvão 13 R/C Esq., 1500-252 Lisbon, Portugal.
Medimar, Gr. Medimar SA, 13 Kifisia, 54 655 Thessaloniki, Greece.
url: www.medimar.gr
MediMar, UK. See *TK, UK.*
Medimetriks, USA. Medimetriks Pharmaceuticals Inc., 363 Route 46 West, Fairfield, NJ 07004-2402, USA.
url: www.medimetriks.com
Medimfoods, Venez. Medimfoods Representaciones C.A., Zona Industrial - 2da, Avenida Diag. a Lab. Leti, Edificio Farvenca Guarenas, Caracas, Venezuela.
Medimmune, Denm. See *Schering-Plough, Denm.*
MedImmune, Fin. See *MedImmune, Neth.*
Medimmune, Gr. See *Schering-Plough, Gr.*
Medimmune, Israel. See *Teva, Israel.*
MedImmune, Neth. MedImmune Oncology Inc., Lagelandseweg 78, 6545 CG Nijmegen, Netherlands.
url: www.medimmune.com
Medimmune, Norw. See *Swedish Orphan, Norw.*
MedImmune, Rus. See *MedImmune, Neth.*
Medimmune, USA. Medimmune Inc., 1 MedImmune Way, Gaithersburg, MD 20878, USA.
url: www.medimmune.com
Medimpex, Austria. See *Medimpex, UK.*
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Medimpex, Fr. Medimpex SA, 1-3 rue Caumartin, 75009 Paris, France.
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Medimpex, Hung. Medimpex Gyógyszernagykereskedelmi Rt, Váci út 168/a, 1138 Budapest, Hungary.
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Medimpex, UK. Medimpex UK Ltd, 127 Shirland Rd, London, W9 2EP, UK.
url: www.medimpexuk.com
Medimport, Cz. Medimport sro, Sázavská 11, 120 00 Prague 2, Czech Republic.
url: www.medimport.cz
Medimport, Mex. Laboratorios Medimport S.A. de C.V., Via Lactea No. 29, Coyoacan Prado Churubusco, 04230 Mexico D.F., Mexico.
Medimprove, Hung. Medimprove Bt, Dalmady Győző u 12, 1182 Budapest, Hungary.
Medinat, Austral. See *DHA, Austral.*
Mediner, Hung. Mediner Kft, Nagy Lajos király tér 5 I/11, 4032 Debrecen, Hungary.
Medinfar, Port. Laboratório Medinfar, SA, Rua Manuel Ribeiro da Pavia 1 - 1, Venda Nova, 2700-547 Amadora, Portugal.
url: www.medinfar.pt
Medinova, Arg. See *Hexa, Arg.*
Medinova, China. Medinova Industrial Co. Ltd, D2-B 4F Shenjian Building, High Technologhy industrial Park, Nanshan, Shenzhen, 518052, China.
url: www.medinova.cn
Medinova, Cz. See *Medinova, Switz.*
Medinova, Hong Kong. See *Great Liaison, Hong Kong.*
Medinova, India. Medinova Labs (Gionova), 57A 2nd Extension, Gandhi Nagar, Jammu, 180 004, India.
Medinova, Indon. See *DKSH, Indon.*
Medinova, Malaysia. See *DKSH, Malaysia.*
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Medinova, Spain. Medinova, C/Collado Mediano S/N, Las Rozas, 28230 Madrid, Spain.
Medinova, Switz. Medinova AG, Eggbuhlstrasse 14, 8052 Zurich, Switzerland.
url: www.medinova.ch
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Medinova (Μεντινοβα), Gr. MENTINOVA AE, Menandrou 58, 104 32 Athens, Greece.
Medinovum, Fin. See *Ratiopharm, Fin.*
Medinsa, Spain. See *Grunenthal, Spain.*
Medinteg, Venez. Medinteg C.A., Calle Perez Pisante c/J Juan Diaz Ed. Sani, Piso 2, U.I. Los Tres Puentes Los Teques, Miranda, Venezuela.
Medintorg, Rus. Medintorg, Prospect Marshala Zhukova 74/2, 123103 Moscow, Russia.
url: medintorg.ru
Mediolanum, Ital. Mediolanum Farmaceutici S.p.A., Via S.G. Cottolengo 15, 20143 Milan (MI), Italy.
url: www.mediolanum.com
Mediorals, Thai. See *Pharmaland, Thai.*
Medipha, Fr. Médipha Santé SAS, 19 av. de Norvège, Les Fjords, Immeuble le Nobel, 91953 Courtaboeuf cdx, France.
Mediphar, Venez. Mediphar C.A., Calle 3B. Edificio Escachia, Piso 3. Local 3C, La Urbina, Caracas, Venezuela.
url: www.mediphar.com
Medipharm, Austria. See *Meditrade, Austria.*
Medipharm, Chile. Medipharm SA, Carrion 1398, Independencia, Santiago, Chile.
Medipharm, Malaysia. Medipharm Industries Sdn Bhd, Intan Business Centre 2, 3rd Floor B-3-9, Lebuh Medan Ipoh, Bandar Baru Medan Ipoh, 31400 Ipoh, Perak, Malaysia.
url: www.medipharm.com.my
Medipharm, Singapore. Medipharm Pte Ltd, 05-43 Shun Li Industrial Park, 61 Kaki Bukit Ave 1, S 417943, Singapore.
Medipharm, Switz. Medipharm SA, Emil Frey-Strasse 99, 4142 Münchenstein, Switzerland.
Medipharma, Arg. Laboratorios Medipharma S.A., Calle 143 1435 e/61 y 62, 1900 La Plata, Buenos Aires, Argentina.
url: www.medipharma.com.ar
Medipharma, Hung. Medipharma Kft, Andrássy út 49, 1087 Budapest, Hungary.
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Mediplants, Gr. Mediplants, 2o chlm. Serron-Thessalonikis, Serres, 621 00 Serres, Greece.
Medi-Plex, USA. See *ECR, USA.*
Mediplus, UK. Mediplus Ltd, Unit 7, Cressex Business Park, The Gateway Centre, Coronation Rd, High Wycombe, Buckinghamshire, HP12 3SU, UK.
url: www.mediplus.co.uk
Medique, Canad. See *Medique, USA.*
Medique, USA. Medique Products, 4159 Shoreline Drive, St. Louis, MO 63045, USA.
url: www.mediqueproducts.com
Mediquest, Singapore. Mediquest Pte Ltd, 1557 Keppel Rd, 03-02, Inchcape Marketing Building, S-089066, Singapore.
Medi-Radiopharma, Cz. See *Medi-Radiopharma, Hung.*
Medi-Radiopharma, Hung. Medi-Radiopharma Ltd, Vadászforduló u 6c, 1221 Budapest, Hungary.
Medirex, Port. Medirex Pharma Lda, Rua Carlos Calisto 4-C, 1400-043 Lisbon, Portugal.
url: www.medirexpharma.com
Medi-Rx, Philipp. Medi-Rx Inc., 11 Mindanao Ave, Pagasa, Quezon City, Philippines.
Medis, Cz. See *Avalanche, Cz.*
Medis, Denm. Medis-Danmark A/S, H C Andersens Boulevard 2, 1780 Copenhagen V, Denmark.
url: www.delta.is
Medis, Hung. See *Actavis, Hung.*
Medis, Israel. Pharma Medis Co. Ltd, P.O. Box 2820, Holon, Israel.
Medis, Ital. See *Actavis, Ital.*
Medis, Neth. Medis, Netherlands.
Medis, Pol. See *Teva, Pol.*
Medis, Port. Medis
Medisa, Switz. Medisa AG, Riedstrasse 1, 6330 Cham, Switzerland.
Medisan, Canad. See *Pfizer, Canad.*
Medisan, Hung. Medisan Hungary Kft, Pasaréti út 61/a, 1026 Budapest, Hungary.
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Medison, Israel. Medison Pharma Ltd, P.O. Box 7090, Petach Tikva 49170, Israel.
url: www.medisan.co.il

Medisorb, Rus. See *Pik, Rus.*

Medisource, Irl. Medisource Ltd, Unit 11, Southern Cross Business Park, Bray, Co. Wicklow, Ireland.
url: www.medisource.ie

Medisource, UK. See *Medisource, Irl.*

Medispan, India. Medispan Ltd, Vijay Plaza, C-32 Second Ave, Anna Nagar, Chennai, 600 040, India.

Medispec, Maloysia. Medispec (M) Sdn Bhd, No 55 & 57 Lorong Sempodan 2, Off Boundary Rd, 11400 Ayer Itam, Penang, Malaysia.
url: www.medispec.com.my

Medispray, Thai. See *IDS, Thoi.*

Medisys, India. Medisys Biotech Pvt Ltd, 2nf Floor SCO 142, Mansa Devi Complex Sector 5, Chandigarh, Kalka Highway, Panchkula, India.
url: medisysbiotech.com

Medisys, Philipp. Medisys Pharma Inc., 2003 Pres. Quirino Ave, Pandacan, Manila, Philippines.
url: medisysbiotech.com

Meditab, Thai. See *Tri Medical, Thoi.*

Meditec, Israel. See *Sam-On, Israel.*

Meditech, Austral. Meditech Int. Pty Ltd, Unit 5, 36 Campbell Ave, Cramer, NSW 2099, Australia.

Medites, Cz. Medites Pharma sro, 1 Maje 1000, 756 61 Rožnov pod Radhoštěm, Czech Republic.

Medithek, Ger. medithek GmbH, Willinghusener Weg 5 a, 22113 Oststeinbek, Germany.
url: www.medithok.com

Meditop, Hung. Meditop Gyógyszeripari Kft, Ady Endre u 1, 2097 Pilisborosjenő, Hungary.
url: www.meditop.hu

Meditrade, Austria. Meditrade Medipharm Pharmahandel GmbH, Mariannengasse 14, A-1090 Vienna, Austria.

Meditrend, Israel. Meditrend, 13 Kehilat Saloniki, Tel Aviv, Israel.

Meditrina, Gr. Meditrina Pharmaceuticals, Messinias 37, 152 34 Chalandri, Greece.

Meditron, Gr. Meditron Pharmaceuticals Ltd, Epidaurus 2, 104 44 Athens, Greece.

Medius, Switz. Medius AG, Neue Bahnhofstrasse 160, 4132 Muttenz, Switzerland.

Medivir, Cz. See *Medivir, Swed.*

Medivir, Denm. See *Medivir, Swed.*

Medivir, Fr. See *Medivir, Swed.*

Medivir, Swed. Medivir AB, Box 1086, 141 22 Huddinge, Sweden.
url: www.medivir.se

Medivis, Ital. Medivis S.r.l., Via Mario Sangiorgi 11, 95127 Catania (CT), Italy.
url: www.medivis.it

Mediwhite, Ital. Mediwhite S.r.l., Via del Forte Bravetta 98, 00164 Rome (RM), Italy.

Mediwin, Fr. See *Mediwin, UK.*

Mediwin, Philipp. See *Ambica, Philipp* and *SMHP, Philipp.*

Mediwin, UK. Mediwin Ltd, Martello Enterprise Centre, Courtwick Lane, Wick, Littlehampton, West Sussex, NB17 7PA, UK.

Medix, Fr. Laboratoires Médix, 18 rue Saint-Mathieu, 78550 Houdan, France.

Medix, Hong Kong. See *Innoledge, Hong Kong.*

Medix, Israel. See *Genmedix, Israel.*

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Medix, Mex. Productos Medix S.A. de C.V., Calz. del Hueso No. 39, Col. Ejido Santa Ursula Coapa, Deleg. Coyoacan, 04910 Mexico D.F., Mexico.

Medix, Pol. See *Perffarma, Pol.*

Medix, Singapore. See *Ziwell, Singapore.*

Medix, Spain. Medix, Alcalá 431, 28027 Madrid, Spain.
url: www.medix.es

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Medizin, Spain. Lab. Medizin Farma SL, C/Del Transporte 32, Poli Ind. Benieto, 46702 Gandia (Valencia), Spain.
url: www.medizinfarma.com

Medi-Zone, Hung. Medi-Zone Pharma Kft, Lovas u 13, 1012 Budapest, Hungary.

Medizone, India. Medizone, CK 59/6 Bulanala, Varanasi, India.

Medley, Braz. Medley S.A. Indústria Farmacêutica, Rua Macedo Costa 55, Jardim Santa Genebra, 13080-010 Campinas, SP, Brazil.
url: www.medley.com.br

Medley, India. Medley Pharmaceuticals Ltd, Medley House, D2, M.I.D.C. Area, Andheri (East), Mumbai 400 093, India.
url: www.medleylab.com

Medley, Philipp. See *Ambica, Philipp.*

Medley, Rus. See *Medley, India.*

Medline, Canad. See *Medline, USA.*

Medline, Thai. Medline Co. Ltd, 736-742 Pracha-U-Thit Rd, Huay Kwang, Bangkok 10320, Thailand.

Medline, USA. Medline Industries Inc., One Medline Place, Mundelein, IL 60060-4486, USA.

Medlink, Philipp. Medlink Pharma Phils Inc., Unit 2002, 20/F Strata 100 Bldg, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

Medlite, Norw. Medlite AS, Postboks 288, 3081 Holmestrand, Norway.
url: www.medlite.no

Medlock, Neth. See *Medlock Medical, UK.*

Medlock Medical, Irl. See *Medlock Medical, UK.*

Medlock Medical, UK. Medlock Medical Ltd, Tubiton House, Medlock St, Oldham, OL1 3HS, UK.

Medlogic, UK. MedLogic Global Ltd, Western Wood Way, Langage Science Park, Plympton, Plymouth, Devon, PL7 5BG, UK.
url: www.mlgl.co.uk

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Medochemie, Gr. Medochemie Hellas AE Paras. & Empor. Farm & P/kon Pr.D.T. Medoc, Pasteur 6, 115 21 Athens, Greece.
url: www.medochemie.com

Medochemie, Hong Kong. See *Star, Hong Kong.*

Medochemie, Malaysia. See *Komedic, Malaysia.*

Medochemie, Neth. Medachemie, Duiven BV, Netherlands.
url: www.fal.duiven.nl

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Medochemie, Rus. Medochemie Ltd, B. Dmitrovka ul. 30/1, kv. 2, 103031 Moscow, Russia.
url: www.medochemie.ru

Medochemie, Singapore. See *Derek, Singapore.*

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Medogar, Israel. Medogar, P.O. Box 49170, Petach Tikva 7003, Israel.
url: www.medogar.co.il

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Medopharm, Austria. See *Medopharm, Ger.*

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Medopharm, Ger. Medopharm Arzneimittel GmbH & Co. KG, Schlossstr. 11-17, 79238 Ehrenkirchen, Germany.
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Medopharm, India. Medopharm, Mohan Mansions, 48 Kasturba Rd, Bangalore, 560 001, India.

Medopharm, Philipp. See *NextChem, Philipp.*

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Medosan, Ital. Medosan S.r.l., Industrie Biochimiche Riunite, Via di Cancelliera 12, 00041 Albano Laziale (RM), Italy.

Medphano, Ger. medphano Arzneimittel GmbH, Maienbergstr. 10-12, 15562 Rüdersdorf, Germany.
url: www.medphano.de

Medpointe, USA. MedPointe Healthcare Inc., 265 Davidson Ave, Suite 300, Somerset, NJ 08873-4120, USA.
url: www.medpointeinc.com

Medpolimer, Rus. Medpolimer, Revolyutsii Sh 69, 195279 St Petersburg, Russia.
url: www.medp.spb.ru

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Medprominvest, Ukr. Medprominvest, Mashinostroitelnaya Street, 44, Kiev, 03680, Ukraine.

Medquimica, Braz. Medquímica Indústria Farmacêutica Ltda, Rua Otacilio Esteves da Silva 40, Granjo Betania, 36045-000 Juiz de Fora, MG, Brazil.

Medra, Austria. Medra Handels-GmbH, Gastgebgasse 5-13, A-1230 Vienna, Austria.

Medreg, Cz. Medreg sro, Krčmářovská 223/33, 196 00 Prague 9, Czech Republic.

Medreg, Pol. See *Glenmark, Pol.*

Medreich, Hong Kong. Medreich Far East Ltd, 27/F, 211 Johnston Rd, Wanchai, Hong Kong.
url: www.medreich.com

Medreich, India. Medreich Saimirra Ltd, 23 Lattice Bridge Rd, 4th Floor, Adyar, Chennai 600 020, India.

Medsan, Turk. Medsan İthalat-İhracat İlaç San. ve Tic. A.Ş., Adnan Saygun Cad. No: 8/6, Yenişehir, Ankara, Turkey.
url: www.medsan.com.tr

Medserve, Switz. medServe GmbH, Wollerauerstrasse 60, 8834 Schindellegi, Switzerland.

Medsintez, Rus. Medsintez, Novouralysk ul Torgobaya 15, 624130 Sverdlovskaya obl, Russia.
url: www.medsintez.com

Medstyle, Chile. Lab Medstyle SA, Mansenor Felix Cabrea 42 Of. 1, Providencia, Santiago, Chile.

Medtech, Canad. Medtech Lab, 120 Harry Walker Parkway N, New Market, Ontario, L3Y 7B2, Canada.

Medtech, USA. Medtech Laboratories Inc., 3510 N Lake Creek, P.O. Box 1108, Jackson, WY 83011-1108, USA.
url: www.medtechinc.com

Meditest, Philipp. Medical test Systems Inc., 5/F Suite B DAO I Bldg, 189 Salcedo St, Legaspi Vill, Makati City, Philippines.

Medtronic, Belg. NV Medtronic Belgium SA, Burgemeester E. Demunterlaan 5, 1090 Brussels, Belgium.
url: www.medtronic.be

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Medtronic, Fr. Medtronic France SAS, 27 quai Alphonse le Gallo, CS 31000, 92513 Boulogne-Billancourt Cedex, France.
url: www.medtronic.fr

Medtronic, Neth. Medtronic BioPharma BV, Earl Bakkenstraat 10, 6422 PJ Heerlen, Netherlands.
url: www.medtronic.com

Medtronic, Norw. Medtronic Norge AS, Postboks 458, 1327 Lysaker, Norway.
url: www.medtronic.no

Medtronic, Spain. Medtronic Iberica SA, C/ Mario de Poortugal 11, 28050 Madrid, Spain.
url: www.medtronic.es

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Medtronic, USA. Medtronic Inc., 710 Medtronic Pkway, Minneapolis, MN 55432-5604, USA.
url: www.medtronic.com

Meduna, Ger. Meduno Arzneimittel GmbH, Ernst-Grote-Str. 23, 30916 Isernhagen, Germany.

Mega, Rus. Mega Products Ltd, 26 Bakinskikh Komissarov St 9, et 17, Of 110, Moscow, Russia.

Mega, Turk. Mega, Turkey.

Mega Lifesciences, Hong Kong. See *IDS, Hong Kong.*

Mega Lifesciences, Malaysia. See *IDS, Malaysia.*

Mega Lifesciences, Philipp. Mega Lifesciences Pty Ltd, Unit 4B, 4/F Eurovilla II Bldg, 118 VA Rufino St, Legaspi Vill, Makati City, Philippines.

Mega Lifesciences, Singapore. See *Goldplus, Singapore.*

Mega Lifesciences, Thai. Mega Lifesciences Pty Ltd, 120 Moo 11 Asia Center Bldg, 9th Fl, Bangna-Trad Rd, Bangna, Bangkok 10260, Thailand.
url: www.megawecare.com

Mega Lifesciences, Ukr. Mega Lifesciences, Solomenskaya Place, 2, office 706, Kiev, 03035, Ukraine.
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Megahealth, Chile. See *Recalcine, Chile.*

Megakom, Ukr. OOO Megakom, 195b, Klochkovskaya str., Kharkov, 61058, Ukraine.
url: www.megacom.com.ua

Megapha, Singapore. Megapha Pte Ltd, 12 Arumugam Rd, 04-08A Cheng Chwee Huat Industrial Building, S 409958, Singapore.

Megapharm, Israel. Megapharm Ltd., Hapnina St 8, Building B First Floor, Raanana 43215, Israel.
url: www.megapharm.co.il

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Mei Da Kang Jia Le, China. Mei Da Kang Jia Le Pharmaceutical Co. Ltd, Sichuan, China.

Mei Ka, China. Mei Ka Pharmaceutical Co. Ltd, Sichuan, China.

Mei Lun, China. Mei Lun Pharmaceutical Group Co. Ltd, Tianjin, China.

Mei Luo, China. Mei Luo Pharmaceutical products, China.

Meichuang, China. Meichuang Pharmaceutical Co. Ltd, Dalian, China.

Meida Kanghua, China. Meida Kanghua Pharmaceutical Co. Ltd, Sichuan, China.

Meien, China. Meien Biological Technology Co. Ltd, Shanghai, China.

Meiji, China. Meiji Pharmaceutical Co. Ltd, Winterless Center Room 302 Block B, 1 West Point Rd, Chaoyang District, Beijing 100026, China.
url: www.meijipharma.com

Meiji, Hong Kong. See *Main Life, Hong Kong.*

Meiji, Indon. Meiji Indonesia PT, Jl Tanah Abang II No 4, Jakarta Pusat 10160, DKI Jaya, Indonesia.
url: www.meiji-indonesia.com

Meiji, Jpn. Meiji Seika Kaisha Ltd, 2-4-16 Kyobashi, Chuo-ku, Tokyo 104-8002, Japan.
url: www.meiji.co.jp

Meiji, Malaysia. See *Somedico, Malaysia.*

Meiji, Singapore. See *Pharma 2000, Singapore.*

Meiji, Thai. Thai Meiji Pharmaceutical Co. Ltd, 8 Fl, Regent House, 183 Rajdamri Rd, Bangkok 10330, Thailand.

Meijisi, China. Meijisi Phamraceutical Co. Ltd, Xiamen, China.

Mein, Spain. See *Fresenius Kabi, Spain.*

Meirui, China. Meirui Pharmaceutical Co. Ltd, 24, 27 Citic Tower, 348 Zhongshan Rd, Nanjing 210009, China.
url: www.meirui-pharma.com

Meitong, China. Meitong Pharmaceutical Co. Ltd., 52 Taijiu Road, Taizhou, Jiangsu, China.

Meiyou, China. Meiyou Pharmaceutical Co. Ltd, Shanghai, China.

Meizler, Braz. Meizler SA, Alameda Jura 149, Alphaville, 06455-010 Barueri, SP, Brazil.
url: www.meizler.com.br

Mekim, Hong Kong. Mekim Ltd, Room 905, Harbour Centre Tower 2, 8 Hok Cheung St, Hunghom, Kowloon, Hong Kong.
url: www.mekim.com

Mekophar, Rus. Mekophar Chemical-Pharmaceutical JSC, Russia.

Mekophar, Ukr. See *Artur, Ukr.*

Mekos, Canad. See *Spexell, Canad.*

Mekos, Denm. Mekos Laboratories ApS, Herredsvejen 2, 3400 Hillerød, Denmark.
url: www.mekos.dk

Mekos, Israel. See *Vitaflo, Denm.*

Mekos, Neth. See *Vitaflo, Denm.*

Mekos, Port. See *Mekos, Denm.*

Melaleuca, Canad. See *Melaleuca, USA.*

Melaleuca, USA. Melaleuca of Canada Inc., 3910 South Yellowstone Highway, Idaho Falls, Idaho, 83402, USA.

Meligen, Rus. See *Adaptogen, Rus.*

Melisana, Belg. Melisana SA, Ave du Faur à Briques 1, 1140 Brussels, Belgium.
url: www.melisana.be

Melisana, Neth. See *Melisana, Belg.*

Melisana, Switz. Melisana AG, Ankerstrasse 53, Postfach, 8026 Zurich, Switzerland.

Mellin, Ital. Mellin, Div. Dietetica Star, Via Matteotti 142, 20041 Agrate Brianza (MI), Italy.

Melora, Port. Melora Portuguesa Produtos Farmacêuticos e Cosméticos Lda, Av. Estados Unidos da América 97, 12 Esq, 1700-167 Lisbon, Portugal.

Melville Biologics, USA. See *Precision, USA.*

Menarini, Arg. Laboratorios Menarini Argentina S.A., Girardot 1689, 1427 Buenos Aires, Argentino.
url: www.menarini.com

Menarini, Austria. See *Menarini, Ital.*

Menarini, Belg. Menarini Benelux SA, Belgicastraat 4, 1930 Zaventem, Belgium. Regulatory Affairs Manager
url: www.menarini.com

Menarini, Cz. See *Berlin-Chemie, Cz.*

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Menarini, Fin. Berlin-Chemie Menarini Finland Oy, Rajatorpantie 41 C, 01640 Vantaa, Finland.

Menarini, Fr. Menarini France, 1 rue du Jura, Silic 528, 94633 Rungis cdx, France.
url: www.menarini.com

Menarini, Gr. Menarini Hellas S.A., Constantinoupouleous & Dambergis 7, 104 45 Athens, Greece.
url: www.menarini.com

Menarini, Hong Kong. See *Mekim, Hong Kong.*

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Menarini, India. Menarini Ravnaq Pharma Ltd, Allahabad Bank Building, 17 Sansad Marg, New Delhi 110 001, India.

Menarini, Indon. See *Dexa, Indon* and *Sanbe, Indon.*

Menarini, Irl. A. Menarini Pharmaceuticals Ireland Ltd, 2nd Floor Castlecourt, Monkstown, Dublin, Ireland.
url: www.menarini.com

Menarini, Ital. A. Menarini Industrie Farmaceutiche Riunite S.r.l., Via Sette Santi 3, 50131 Florence (FI), Italy.
url: www.menarini.com

Menarini, Malaysia. See *Pharmaforte, Malaysia.*

Menarini, Mex. A Menarini Pharma México SRL, Periferico sur No 4118 Torre Zafiro P.1, 1900 Alvaro Obregán Jardines de Pedreg, Mexico.

Menarini, Neth. Menarini Farma Nederland, De Bleek 17, 3447 GV Woerden, Netherlands.
url: www.menarini.com

Menarini, Pol. See *Berlin-Chemie, Pol.*

Menarini, Port. A. Menarini Portugal, Farmacêutica SA, Quinta da Fonte, Edificio D Manuel I Piso 2A, Rua dos Malhões 1, 2770-071 Paç de Arcas, Portugal.
url: www.menarini.com

Menarini, Rus. BC Menarini Pharma GmbH, ul. Shabolovka 31, Str. B, 3rd Floor, 115998 Moscow, Russia.
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Menarini, Singapore. See *Pharmaforte, Singapore.*

Menarini, Spain. Menarini, Alfonso XII 587, Badalana, 08918 Barcelona, Spain.
url: www.menarini.es

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url: www.menarini.com

Menarini, Switz. A Menarini AG, Eggbuhlstrasse 14, 8026 Zurich, Switzerland.
url: www.menarini.ch

Menarini, Thai. See *Biopharm, Thai.*

Menarini, UK. A Menarini Pharma UK srl, Menarini House, Mercury Park, Wycombe Lane, Wooburn Green, Buckinghamshire, HP10 0HH, UK.
url: www.menarini.com

Menarini, Ukr. See *Berlin-Chemie, Ukr.*

Menarini Diagnostics, Fr. A. Menarini Diagnostics, 16 rue Georges-Besse, Silic 46, 92182 Antony cdx, France.
url: www.menarini.fr

Menarini Diagnostics, Irl. See *Menarini Diagnostics, UK.*

Menarini Diagnostics, Port. A. Menarini Diagnósticos Lda, Estrada Nacional 249, Lote 4 - 1, Aboboda, 2785-000 S. Domingos de Rana, Portugal.

Menarini Diagnostics, UK. A. Menarini Diagnostics Ltd, Wharfedale Rd, Winnersh, Workingham, Berkshire, RG41 5RA, UK.
url: www.menarini.com

Mendelejeff, Ital. Stabilimento Chimico Farmaceutico Mendelejeff S.r.l., Via Aurelia 58, 00100 Rome (RM), Italy.

Meng Sheng, China. Meng Sheng Pharmaceutical Co Ltd, Yunnan, China.

Meng Xin, China. Meng Xin Pharmaceutical Co. Ltd, Chifeng, China.

Merley & James, USA. Menley & James Laboratories Inc., 100 Tournament Drive, Suite 210, Horsham, PA 19044-3697, USA.

Mennen, USA. See *Colgate-Palmolive, USA.*

Mensana, Hung. Mensana Pharma Ltd, Hungary.

Mentholatum, Austral. Mentholatum Australasia P/L, P.O. Box 398, Mulgrave North, VIC 3170, Australia.
url: www.mentholatum.com.au

Mentholatum, Canad. Mentholatum Co. of Canada Ltd, 20 Lewis St, Fort Erie, Ontario, L2A 5M6, Canada.
url: www.mentholatum.ca

Mentholatum, Cz. See *Mentholatum, UK.*

Mentholatum, Hong Kong. Mentholatum Asia Pacific Ltd, 1616-21 Tower 2, Grand Central Plaza, 138 Shatin Rural Committee Rd, Shatin, Hong Kong.
url: www.mentholatum.com.hk

Mentholatum, Hung. Mentholatum, Hungary.

Mentholatum, Irl. See *Mentholatum, UK.*

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Mentholatum, Neth. See *Mentholatum, UK.*

Mentholatum, Pol. See *Nepentes, Pol.*

Mentholatum, Rus. See *Delta Medical, Rus.*

Mentholatum, S.Afr. Mentholatum South Africa (Pty) Ltd, Unit G1 Westlake Square, 1 Westlake Drive, Tokai, Cape Town 7945, South Africa.
url: www.mentholatum.com

Mentholatum, Singapore. See *DKSH, Singapore.*

Mentholatum, UK. The Mentholatum Co. Ltd, 1 Redwood Ave, Peel Park Campus, East Kilbride, Glasgow, G74 5PE, UK.
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Mentholatum, Ukr. See *Delta Medical, Ukr.*

Mentholatum, USA. Mentholatum Inc., 707 Sterling Dr., Orchard Park, NY 14127, USA.
url: www.mentholatum.com

Mentiterm, Gr. Mentiterm Farmakefiki EPE, Greece.

Mento, Turk. Mento, Turkey.

Mepha, Braz. Mepha Inv. Des. e Fab. Farm. Ltda, Est. dos Bandeirantes 4015, 22775-112 Rio de Janeiro, RJ, Brazil.

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Mepha, Pol. Mepha Polska Sp. zo.o., ul. Zbożowa 22 H, 20-827 Lublin, Poland.

Mepha, Port. Mepha, Lda, R. Elias Garcia 28 C, Venda Nova, Apartado 6617, 2701-355 Amadora, Portugal. url: www.mepha.pt

Mepha, Singapore. See *Megapha, Singapore.*

Mepha, Switz. Mepha Pharma AG, Postfach 445, 4147 Aesch/BL, Switzerland. url: www.mepha.ch

Mepha, Thai. See *Amcron, Thai.*

Mepha, Ukr. See *Sona-Farm, Ukr.*

Mepharm, Malaysia. Mepharm (Malaysia) Sdn Bhd, 15 Jln USJ 1/19, Taman Subang Permal, 47600 Subang Jaya, Selangor, Malaysia.

Mepra-Pharm, UK. See *Co-Pharma, UK.*

Mepro, Chile. See *Merck, Chile.*

Meprofarm, Indon. Meprofarm PT, Jl Soekamo Hatta 789, Km 11, Gedebage, Bandung 40294, Jawa Barat, Indonesia.

Mercar, Belg. Mercar bvba, Duinendreef 2, 2950 Kapellen, Belgium.

Mercar, Neth. See *Mercar, Belg.*

Mercian, Cz. See *Mercian, Jpn.*

Mercian, Jpn. Mercian Corporation, Tokyo, Japan.

Merck, Arg. Merck Química Argentina S.A.I.C., Panamericana Plaza, Tronador 4890, Piso 5, 1430 Buenos Aires, Argentina. url: www.merck.com.ar

Merck, Austria. Merck GmbH, Zimbagasse 5, A-1140 Vienna, Austria. url: www.merck.at

Merck, Belg. Merck SA, Brusselsesteenweg 288, 3090 Overijse, Belgium. url: www.merck.be

Merck, Braz. Merck S.A. Industrias Químicas, Estrada dos Bandeirantes 1099, 22710-571 Rio de Janeiro, RJ, Brazil. url: www.merck.com.br

Merck, Canad. Merck Canada Inc., 16750 Route Transcanadienne, Kirkland, Quebec, H9H 4M7, Canada.

Merck, Chile. Merck Química Chilena Ltda, Francisco de Paula Taforo 1981, Nunoa, Santiago, Chile.

Merck, Cz. Merck sro, Zděbradská 72, 251 01 Říčany - Jažlovice, Czech Republic.

Merck, Denm. See *Biomet Merck, Denm* and *Merck, Swed.*

Merck, Fin. Merck Oy, Pihatorma 1 C, 02240 Espoo, Finland. url: www.merck.fi

Merck, Ger. Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany. url: www.merck.de

Merck, Gr. Merck E.P.E., 26 Vouliagmenis Ave, 167 77 Elliniko, Greece. url: www.merck.gr

Merck, Hong Kong. Merck Pharmaceutical Ltd, Unit 10-12, 22/F, Paul Y. Ctr, 51 Hung To Rd, Kwan Tung, Hong Kong.

Merck, Hung. Merck Kft, Bocskai út 134-146, 1113 Budapest, Hungary. url: www.merck.de

Merck, India. Merck (India) Ltd, Shiv Sagar Estate 'A', Dr Annie Besant Rd, Worli, Mumboi 400 018, India. url: www.merck.co.in

Merck, Indon. Merck Indonesia PT, Jl TB Simatupang No.8, Pasar Rebo, Jakarta 13760, DKI Jaya, Indonesia. url: www.merck.co.id

Merck, Irl. See *MSD, Irl.*

Merck, Israel. See *Neopharm, Israel.*

Merck, Ital. Merck S.p.A., Via G. Stephenson 94, 20157 Milan (MI), Italy.

Merck, Malaysia. Merck (Malaysia) Sdn Bhd, 4 Jln U1/26, Section U1, Hicom Glenmarie Industrial Park, 40150 Shah Alam, Selangor, Malaysia. url: www.merck.com.my

Merck, Mex. Merck S.A. de C.V., Calle 5 Num 7, 53370 Naucalpan de Juarez, Mexico. url: www.merck.com.mx

Merck, Neth. Merck Nederland BV, Basisweg 34, 1043 AP Amsterdam, Netherlands. url: www.merck.nl

Merck, Norw. Merck AB, Drammensveien 123, 0277 Oslo, Norway. url: www.merck.no

Merck, Philipp. Merck Inc., 24/F GT Tower Intl, 6613 Ayala Ave, cor HV dela Costa St, Salcedo Vill, Makati City, Philippines.

Merck, Pol. Merck Sp. zo.o., ul. Aleje Jerozolimskie 178, 02-486 Warsaw, Poland. url: www.merck.com.pl

Merck, Port. Merck Genéricos Lda, Rua Alfredo da Silva 3-C, Apartado 3185, 1300-040 Lisbon, Portugal. url: www.merck.pt

Merck, Rus. See *Nycomed, Rus.*

Merck, S.Afr. Merck Pharmaceuticals (Pty) Ltd, P.O. Box 1998, Halfway House 1685, South Africa. url: www.merck.com

Merck, Singapore. Merck Pte Ltd, Merck Serono Division, 3 International Business Park, 02-01 Nordic European Centre, S 609927, Singapore. url: www.merck.com.sg

Merck, Spain. Merck Farma Química, Polígono Merck, Mollet del Valles, 08100 Barcelona, Spain. url: www.merck.es

Merck, Swed. E Merck AB, Pharma Division, Frösundaviks allé 1, 195 87 Stockholm, Sweden. url: www.merck.se

Merck, Switz. Merck (Schweiz) AG, Ruchligstrasse 20, 8953 Dietikon, Switzerland. url: www.merck.ch

Merck, Thai. Merck Ltd, 19 Fl, Emporium Tower, 622 Sukhumvit Rd, Klongton Klongtoey, Bangkok 10110, Thailand. url: www.merck.co.th

Merck, Turk. Merck İlaç Ecza ve Kimya Tic. Ltd. Şti., Balabandare Cad. No: 2-4, İstinye, İstanbul, 34460, Turkey. url: www.merck.com.tr

Merck, UK. E. Merck Pharmaceuticals Ltd, Harrier House, High St, West Drayton, Middlesex, UB7 7QG, UK. url: www.merckpharma.co.uk

Merck, Ukr. See *Farmoniks, Ukr.*

Merck, USA. Merck & Co., 1 Merck Dr, White House Station, NJ 08889-1000, USA. url: www.merck.com

Merck, Venez. Merck S.A., Hans Neumann Ed.Corimon p3, Los Cortijos de Lou., Caracas, Venezuela. url: www.merck.com

Merck Bago, Braz. See *Merck, Braz.*

Merck Consumer, Indon. Merck Consumer Healthcare, Perkantoran Hijau Arkadia, F Tower 15th Fl, JL TB Simatupang Kav 88, Pasar Minggu, Jakarta Selatan 12520, Indonesia.

Merck Consumer, Singapore. See *Zuellig, Singapore.*

Merck Consumer, UK. See *Seven Seas, UK.*

Merck dura, Ger. See *Mylan dura, Ger.*

Merck Frosst, Canad. Merck Frosst Canada Ltd, 16711 Trans Canada Highway, Kirkland, Quebec, H9H 3L1, Canada. url: www.merckfrosst.com

Merck Lipha Sante, Pol. See *Merck, Pol.*

Merck Medication Familiale, Fr. Merck Médication Familiale, 18 C boulevard Winston-Churchill, 21070 Dijon, France.

Merck Pharma, Ital. See *Merck, Ital.*

Merck Sante, Denm. See *Nycomed, Denm.*

Merck Sante, Fr. See *Merck-Lipha, Fr.*

Merck Sante, Hong Kong. See *Merck, Hong Kong.*

Merck Sante, Malaysia. See *Merck, Malaysia.*

Merck Sante, Pol. See *Merck, Pol.*

Merck Sante, Singapore. See *Zuellig, Singapore.*

Merck Sante, Spain. See *Merck, Spain.*

Merck Selbstmedikation, Ger. Merck Selbstmedikation GmbH, Rösslerstrasse 96, 64293 Darmstadt, Germany. url: www.merckselbstmedikation.de

Merck Serono, Arg. See *Merck, Arg.*

Merck Serono, Austral. Merck Serono Australia Pty Ltd, 3-4/25 Frenchs Forest Rd, Frenchs Forest, NSW 2086, Australia.

Merck Serono, Austria. See *Merck, Austria.*

Merck Serono, Belg. See *Merck, Belg.*

Merck Serono, China. Merck Serono Co. Ltd, 18F Tower B Gemdale Plaza, 91 Jianguo Rd, Chaoyang District, 100022 Beijing, China. url: www.merckserono.com.cn

Merck Serono, Denm. Merck Serono, Strandvejen 102 B, 4 th, 2900 Hellerup, Denmark. url: www.merckserono.com

Merck Serono, Fr. Merck Serono, 37 rue Saint Romain, 69379 Lyon Cedex 08, France. url: www.merckserono.fr

Merck Serono, Ger. Merck Serono GmbH, Alsfelder Str. 17, 64289 Darmstadt, Germany. url: www.medizinpartner.de

Merck Serono, Gr. See *Merck, Gr.*

Merck Serono, Hong Kong. See *DKSH, Hong Kong* and *Four Star, Hong Kong.*

Merck Serono, Hung. See *Merck, Hung.*

Merck Serono, Irl. Merck Serono, 3013 Lake Drive, Citywest Business Campus, Dublin 24, Ireland.

Merck Serono, Israel. Merck Serono Ltd, 50 Basel St, Herzliya Pituah 46646, Israel.

Merck Serono, Ital. Merck Serono Spa, Via Casilina 125, 00176 Rome, Italy. url: www.merckserono.it

Merck Serono, Malaysia. See *Zuellig, Malaysia.*

Merck Serono, Norw. See *Merck, Norw.*

Merck Serono, Rus. Merck Serono, Smolnaya ul 24 D, 125445 Moscow, Russia.

Merck Serono, UK. Merck Serono, Bedfont Cross, Stanwell Rd, Feltham, Middlesex, TW14 8NX, UK.

Merck Sharp & Dohme, S.Afr. See *MSD, S.Afr.*

Merck Spittal, Singapore. See *Zuellig, Singapore.*

Merck Theramex, Singapore. See *Zuellig, Singapore.*

Merck-Belgolabo, Belg. See *Merck, Belg.*

Merck-Clevenot, Switz. See *Actipharm, Switz.*

Merckle, China. See *Ratiopharm, China.*

Merckle, Cz. See *Ratiopharm, Cz.*

Merckle, Fin. See *Merckle, Ger.*

Merckle, Ger. Merckle GmbH, Graf-Arco-Str. 3, 89079 Ulm, Germany. url: www.merckle.de

Merckle, Rus. See *Ratiopharm, Rus.*

Merckle, Swed. See *Ferring, Swed.*

Merckle, Ukr. See *Ratiopharm, Ukr.*

Merckle Recordati, Ger. Merckle Recordati GmbH, Eberhard-Finckh-Str. 55, 89075 Ulm, Germany.

Merckle-Diadin, Ger. See *Merckle, Ger.*

Merck-Lipha, Fr. Merck Lipha Santé, 37 rue St-Romain, 69008 Lyon, France. url: www.mercksante.fr

Merck-Lipha, Hong Kong. See *Merck, Hong Kong.*

Merck-Lipha, Singapore. See *Zuellig, Singapore.*

Merck-Lipha, Switz. See *Actipharm, Switz.*

Merck-Theramex, Hong Kong. See *Hind Wing, Hong Kong* and *Zuellig, Hong Kong.*

Mercury, Austral. Mercury Pharma Australia Pty Ltd, P.O. Box 333, North Sydney, NSW 2059, Australia.

Mercury, Fin. See *Mercury, UK.*

Mercury, Ger. See *Mercury, UK.*

Mercury, Neth. See *Mercury, UK.*

Mercury, Philipp. Mercury Drug Corp., 7 Mercury Ave, cor E Rodriguez Jr Ave, Bagumbayan 1110, Quezon City, Philippines.

Mercury, UK. Mercury Pharm, NLA Tower, 12-16 Addiscombe Rd, Croydon, Surrey, CR0 0XT, UK.

Meretek, USA. Meretek Diagnostics Inc., 2655 Crescent Drive, Suite C, Lafayette, CO 80026, USA. url: www.meretek.com

Mergers Drugfil, Philipp. Mergers Drugfil Corp/ Han Seo Pharm, 6/F Golden Rock Bldg, 168 Salcedo St, Legaspi Vill, Makati City, Philippines.

Mericon, Norw. Mericon AS, Postboks 1865 Gulset, 3705 Skien, Norway.

Mericon, USA. Mericon Industries Inc., 8819 N Pioneer Rd, Peoria, IL 61615, USA. url: www.mericon-industries.com

Meridian, India. Meridian Medicare Ltd, Shamti, Solan 173 212, India.

Meridian, Israel. See *Teva, Israel.*

Meridian, S.Afr. Meridian Pharma, division of Elttab Pharmaceuticals, South Africa.

Meridian, USA. See *King, USA.*

Merieux, Belg. See *Sanofi Pasteur, Belg.*

Merieux, Fr. See *Sanofi Pasteur, Fr.*

Merieux, Ger. See *Sanofi Pasteur, Ger.*

Merieux, Ital. See *Sanofi Pasteur, Ital.*

Merieux, Switz. See *Sanofi-Aventis, Switz.*

Merieux, UK. See *Sanofi Pasteur, UK.*

Merieux, USA. See *Sanofi Pasteur, USA.*

Merind, India. See *Wockhardt, India.*

Merion, India. Merion Care, SCO 67, First Floor Sec 11, Panchkula, Chandigarh, India.

Merisant, Arg. Merisont Argentino S.R.L., Dardo Rocha 2754 Piso 2 of.2, 1640 Martinez, Buenos Aires, Argentina. url: www.merisant.com

Merisant, Canad. Merisant Co., 2655 North Sheridan Way, Suite 105, Mississauga, Ontario, L5K 2P8, Canada.

Merisant, Thai. See *Diethelm, Thai.*

Merit, USA. Merit Pharmaceuticals, 2611 San Fernando Rd, Los Angeles, CA 90065, USA. url: www.meritpharm.com

Merkez, Turk. Merkez Laboratuvarı İlaç San. ve Tic. A.Ş., Çamlık Mah. Ayça Sok. No: 4, Taşdelen, Ümraniye, İstanbul, Turkey. url: www.merkezlab.com

Merle, Fr. Laboratoires Merle, 4 rue Meissonier, 75017 Paris, France.

Mer-National, S.Afr. See *Adcock Ingram, S.Afr.*

Merqurio, Ital. Merqurio Pharma Srl, Insubrias BioPark, Via Roberto Lepetit 34, 21040 Gerenzano (VA), Italy. url: www.merquriopharma.it

Merrell Dow, Austral. See *Sanofi-Aventis, Austral.*

Merrell Dow, Canad. See *Sanofi, Canad.*

Merrell Dow, Fr. See *Sanofi-Aventis, Fr.*

Merrell Dow, Spain. See *Sanofi-Aventis, Spain.*

Merrell Dow, UK. See *Sanofi, UK.*

Merrell Dow, USA. See *Sanofi-Aventis, USA.*

Merren, Philipp. See *Pasteur, Philipp.*

Mersifarma, Indon. Mersifarma Tirmaku Mercusana PT, Wisma Tiara 4th Floor, Jl Raya Pasar Minggu Km 18/17, Jakarta Selatan 12510, DKI Jaya, Indonesia. url: www.mersifarma.com

Mert, Turk. Mert İlaç San. ve Tic. A.Ş, Hastane Mahallesi Yassı Ören Cadessi, Nakkaş Yolu Hadımköy, İstanbul, Turkey. url: mertpharma.com

Mertens, Arg. Mertens S.A. Esp. Medicinales, Av. Montes de Oca 1731, 1271 Buenos Aires, Argentina.

Mertsel, Turk. Mertsel Ecza Depolan San. Tic. Ltd Sti, 5758 Sk N:4/C KZ 1, Karabağlar, Izmir, Turkey.

Merz, Austria. See *Merz, Ger.*

Merz, Canad. Merz Pharma Canada Ltd, 7 Innovation Drive, Unit 115, Flamborough, Ontario, L9H 7H9, Canada.

Merz, China. See *Merz, Ger.*

Merz, Cz. See *Merck, Cz* and *Naturprodukt, Cz.*

Merz, Denm. See *Meda, Denm.*

Merz, Fin. See *Tamro, Fin.*

Merz, Fr. Merz Pharma France SAS, 40-44 rue Jean Mermoz, B.P. 20042, 78602 Maisons Laffitte cdx, France. url: www.merz.com

Merz, Ger. Merz Pharmaceuticals GmbH, Eckenheimer Landstr. 100, 60318 Frankfurt (Main), Germany. url: www.merz.de

Merz, Hong Kong. See *Weston, Hong Kong.*

Merz, Hung. See *Merz, Ger.*

Merz, Indon. See *Combiphar, Indon.*

Merz, Irl. See *Merz, UK.*

Merz, Israel. See *Megapharm, Israel.*

Merz, Ital. Merz Pharma Italia Srl, Via Felice Casati 16, 20124 Milan (MI), Italy. url: www.merz.com

Merz, Malaysia. See *Germax, Malaysia* and *Summit, Malaysia.*

Merz, Mex. Merz Pharma de Mexico SA de CV, Av. Insurgentes sur 3579 Torre 3 Piso 2, 14020 M Hidalgo la Joya Olimpica, Mexico DF, Mexico.

Merz, Neth. See *Sanofi-Aventis, Neth.*

Merz, Philipp. See *Croma, Philipp* and *Zuellig, Philipp.*

Merz, Pol. See *Natur Produkt, Pol.*

Merz, Port. See *Merz, Ger.*

Merz, Rus. Merz Pharma GmbH & Co KGaA, Jamskogo Polja 1-ja ul. d. 9/13, Of. 503, 125124 Moscow, Russia. url: www.merz.ru

Merz, Singapore. See *Green Cross, Singapore* and *Pharma 2000, Singapore.*

Merz, Spain. Merz Pharma España SL, Avenida de Bruselas 5 3 planta, 28108 Alcobendas, Madrid, Spain.

Merz, Swed. See *Merz, Ger.*

Merz, Switz. Merz Pharma (Schweiz) AG, Postfach, 4123 Allschwil, Switzerland. url: www.merz.ch

Merz, Thai. See *Neopharm, Thai.*

Merz, UK. Merz Pharma UK Ltd, 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire, WD6 3SR, UK. url: www.merzpharma.co.uk

Merz, Ukr. See *Naturprodukt, Ukr.*

Merz, USA. Merz Pharmaceuticals, Greensboro, NC 27419, USA. url: www.merzusa.com

Merz Consumer, Ger. See *Merz, Ger.*

Messer Griesheim, Austria. Messer Griesheim Austria, Gumpoldskirchen, Austria.

Messer Griesheim, Cz. See *Messer Griesheim, Austria.*

Meta, Canad. Meta Pharmaceuticals, 155 Orenda Rd, Brantford, Ontario, L6W 1W3, Canada.

Meta Fackler, Austria. See *Meta Fackler, Ger.*

Meta Fackler, Ger. meta Fackler Arzneimittel GmbH, Philipp-Reis-Str. 3, 31832 Springe, Germany. url: www.metafackler.de

Metab, Canad. Metab Ltd, 9 1922 9th Avenue South East, Calgary, Alberta, T2G 0V2, Canada.

Metabolic Solutions, USA. Metabolic Solutions Inc., 460 Amherst St, Nashua, NH 03063, USA. url: www.metsol.com

Metagenics, Canad. See *Metagenics, USA.*

Metagenics, USA. Metagenics Inc., 100 Avenida la Pata, San Clemente, CA 92673, Canada.

Metanoia, Fr. Métanoïa, 2 allee Albert-Caquot, 51686 Reims cdx 2, France.

Metapharma, Canad. See *Meta, Canad.*

Metapharma, Ital. Metapharma S.p.A., Viale delle Dalie 26, 00042 Anzio (RM), Italy.

Metapharmaka, Switz. Metapharmaka GmbH, Hellgasse 40, 6460 Altdorf UR, Switzerland.

Methapharm, Canad. Methapharm Inc., 81 Sinclair Blvd, Brantford, Ontario, N3S 7X6, Canada. url: www.methapharm.com

Methapharm, USA. Methapharm Inc., 117722 West Sample Rd, Suite 101, Coral Springs, FL 33065, USA. url: www.methapharm.com

Metiska, Indon. Metiska Farma PT, Jl Raya Kebayoran Lama No 557, Jakarta 12220, DKI Jaya, Indonesia.

Metochem, Austria. Metochem-Pharma GmbH, Jochen-Rindt-Strasse 23, A-1230 Vienna, Austria.

Metochem, Cz. See *Metochem, Austria.*

Metrika, USA. Metrika Inc., 510 Oakmead Parkway, Sunnyvale, CA 94085-4022, USA. url: www.metrika.com

Metro, Philipp. Metro Drug Distribution, Mañalac Ave, Sta Maria Indl Estate, Bagumbayan, Bicutan, Taguig, Metro Manila, Philippines.

Metrolink, Philipp. Metrolink Pharma Phils Inc., Unit 2002 Strata 100 Bldg, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

Metropolitan, Philipp. Metropolitan Pharmaceutical Products, 15/F The Paragon Corporate Centre, Industry St, Madrigal Business Park, Ayala Alabang, 1780 Muntinlupa City, Philippines.

Met-Rx, USA. MET-Rx Engineered Nutrition, 90 Orville Drive, Bohemia, NY 11716, USA. url: www.metrx.com

Metz, Philipp. Metz Pharmaceuticals Inc., 27 Sct Bayoran, South Triangle, Quezon City, Philippines.

Meuse, Belg. See *Therabel, Belg.*

Meuselbach, Ger. See *Krewel, Ger.*

Meuselbach, Hung. See *Alcon, Hung.*

Mex-America, Mex. See *Remexa, Mex.*

Mexidant, Rus. Mexidant, Russia. url: www.mexidant.ri

Meyer, India. Meyer Organics Pvt Ltd, A-303, Road No. 32, Wagle Estate, Thane 400 604, India. url: www.meyer.co.in

Meyer, Venez. Meyer Productos Terapéuticos S.A., Urb. Ind. Boleíta Norte Calle E, Edif. Meyer, Aptdo. 70008, Caracas 1071-A, Venezuela. url: www.meyer.com.ve

Meyer Alian, Venez. See *Meyer, Venez.*

Meyer Nature, Venez. See *Meyer, Venez.*

Meyer Zall, S.Afr. Meyer Zall Laboratories (Pty) Ltd, Innovation & Research Building, Nelson Mandela Metropolitan University, Saasveld Road, George 6529, South Africa. url: www.mzl.co.za

Meyer-Haake, Ger. Meyer-Haake GmbH Medical Innovations, Am Joseph 9, 61273 Wehrheim, Germany. url: www.meyer-haake.de

Meyers, Philipp. Meyers Pharm (Phil) Inc., 176 Roosevelt Ave, San Francisco del Monte, Quezon City, Philippines.

Mezina, Denm. Mezina A/S, Energivej 4, 6700 Esbjerg, Denmark.

Mezina, Norw. Mezina AS, Engenes, 4865 Arnli, Norway. url: www.mezina.no

MG, Philipp. MG Prime Pharmaceuticals Inc., G/F Richmack Bldg, 72 Mindanao Ave, Proj. 6, Quezon City, Philippines. url: www.mgprimepharma.com

MG, Spain. Laboratorio Miguel y Garriga, C/Joaquim Costa 18, 08390 Montgat (Barcelona), Spain. url: www.mglab.net

MGI, Canad. See *MGI, USA.*

MGI, Gr. See *MGI, UK.*

MGI, Hong Kong. See *Jacobson, Hong Kong.*

MGI, Irl. See *MGI, UK.*

MGI, Israel. See *Megapharm, Israel.*

MGI, Ital. See *MGI, UK.*

MGI, Malaysia. See *DKSH, Malaysia.*

MGI, Neth. See *MGI, UK.*

MGI, Port. See *MGI, UK.*

MGi, Singapore. See *Pharmaforte, Singapore* and *Transmedic, Singapore.*

MGI, Spain. See *Eisai, Spain.*

MGI, UK. MGI Pharma Ltd, 265 The Strand, London, WC2R 1BH, UK.

MGI, USA. MGI Pharma Inc., 5775 West Old Shakopee Rd, Suite 100, Bloomington, MN 55437-3174, USA.
url: www.mgipharma.com

Mi Flora, Arg. Laboratorios Mi Flora SRL, Gabona 4338, 1429 Buenos Aires, Argentina.

Mianyang, China. Mianyang Pharmaceutical Co. Ltd, 278 Jiannon Rd, Youxian, Mianyang, Sichuan, 621000, China.
url: www.taijimy.com

Miba, Ital. Miba Prodotti Chimici e Farmaceutici S.p.A., Via Falzarego 8, 20021 Baranzate (MI), Italy.

Mibe, Austria. See *Mibe, Ger.*

Mibe, Cz. See *Mibe, Ger.*

Mibe, Denm. See *Mibe, Ger.*

Mibe, Ger. Mibe GmbH Arzneimittel, Münchener Str. 15, 06796 Brehno, Germany.
url: www.mibe.de

Mibe, Neth. See *Mibe, Ger.*

Mibe, Ukr. See *Mibe, Ger.*

Mibe Jena, Ger. mibe Vertriebsgesellschaft mbH, Otto-Schott-Str. 15, 07745 Jena, Germany.
url: www.mibe.de

Michallik, Ger. Fritz Osk. Michallik GmbH & Co. KG, Kisslingweg 60, 75417 Mühlacker, Germany.
url: www.michallik.com

Mickan, Ger. Mickan Arzneimittel GmbH, Industriestr. 5, 76189 Karlsruhe, Germany.
url: www.mickan.de

Micro, India. Micro Labs Ltd, No.27 Race Course Road, Bangalore 560 001, India.
url: www.microlabsltd.com

Micro, Mex. Micro Pharmaceuticals México S de Rl de CV, Guillermo González Camarena 900 Ed Pza S, 1210 Torre B pso 6 Sta De Ctro Ccial, Mexico.

Micro, Philipp. See *Brown & Burk, Philipp* and *Suhitas, Philipp.*

Micro, Rus. See *Micro, India.*

Micro, S.Afr. Micro, South Africa.

Micro, Singapore. See *Naina, Singapore.*

Micro, Thai. See *Cosma, Thai.*

Micro Labs, Ukr. See *Micro, India.*

Microbex, Canad. Microbex, Division of Alliance H Inc., Unit 22A, 4630 Dufferin St, Toronto, Ontario, M3H 5S4, Canada.

Microfar, Arg. Microfar SA, Santos Dumont 4733, Buenos Aires, Argentina.

Microfarm, Pol. Przedsiębiarstwo Produkcyjno-Handlowe Microfarm SC, ul. Krakusa 7, 30-535 Kraków, Poland.

Microgen, Rus. NPO Microgen FGUP, Zubovskii bul'var, d. 4, 119021 Moscow, Russia.
url: www.microgen.ru

Microkhim, Ukr. Microkhim, 33 Lenin St, Rubezhnoe, Luhonsk, Ukraine.
url: www.microkhim.com.ua

Micron, USA. Micron Technology Inc., 800 S Federal Way, Boise, ID 83707, USA.
url: www.micron.com

Microsules, Arg. Microsules Argentina SA, Hipolito Yrigoyen 3771, 1208 Buenos Aires, Argentina.
url: www.microsules.com.ar

Micrylium, Canad. Micrylium Laboratories Inc., 5000-M Dufferin St, Toronto, Ontario, M3H 5T5, Canada.

Midas Care, Malaysia. See *Pahang, Malaysia.*

Midlothian, USA. Midlothian Laboratories, 5323 Perimeter Parkway Ct., Montgomery, AL 36116-5125, USA.
url: www.midlothianlabs.com

Midro, Ger. Midro Lörrach GmbH, Bärenfelser Str. 7, 79539 Lörrach, Germany.
url: www.midro.de

Midro, Israel. See *Promedico, Israel.*

Midro, Switz. Midro Vertrieb AG, Uferstrasse 90, 4019 Basle, Switzerland.
url: www.midro.com

Midsona, Denm. See *Midsona, Swed.*

Midsona, Swed. Midsona Sverige AB, Box 50577, 20215 Malmö, Sweden.
url: www.midsona.se

Midy, Ger. See *Sanofi-Aventis, Ger.*

Midy, Ital. See *Sanofi-Aventis, Ital.*

Midy, Spain. See *Sanofi-Aventis, Spain.*

Midy-Lafarge, Fr. See *GSK, Fr.*

Mikart, USA. Mikart Inc., 1750 Chatthoochee Ave, Atlanta, GA 30318, USA.
url: www.mikart.com

Miklich, Cz. See *Miklich, Spain.*

Miklich, Denm. See *Miklich, Spain.*

Miklich, Ital. See *Miklich, Spain.*

Miklich, Pol. See *Miklich, Spain.*

Miklich, Port. See *Miklich, Spain.*

Miklich, Spain. Miklich Laboratorios SL, C/ Cuevas Bajas s/n, Of. 23, Edificio Picasso, 29004 Malaga, Spain.

Miklos, Hung. Dr Lőrincz Miklós, Bem József u 3, 2120 Dunakeszi, Hungary.

Mikrofarm, Rus. See *Mikrofarm, Ukr.*

Mikrofarm, Ukr. Mikrofarm TOV, vul. Shevchenka 20, 61013 m Harkiv, Ukraine.

Milana, Ital. Milana S.r.l., Via Liborio Giuffrè 50, 90127 Palermo (PA), Italy.

Milance, USA. Milance, USA.

Milano, Thai. Milano Lab Ltd Part, 62 Soi Latphrao 94, Bangkok 10310, Thailand.

Miles, Canad. See *Bayer, Canad.*

Miles, Ital. See *Bayer, Ital.*

Miles, UK. The Miles Group, Fitzwilliam House, 84 Fitzwilliam St, Huddersfield, West Yorkshire, HD1 5BB, UK.

Miles, USA. See *Bayer, USA.*

Miles Consumer Healthcare, USA. See *Bayer, USA.*

Miles Laboratories, USA. See *Bayer, USA.*

Milex, Canad. See *Milex, USA.*

Milex, USA. Milex Products Inc., 350 Randy Rd, Suite 2, Carol Dtraen, IL 60188-1813, USA.
url: www.milexproducts.com

Mili, Ukr. Mili Healthcare, Akademika Bagomoltsa Street, 5, office 1, Kiev, 01024, Ukraine.
url: www.mili.com.ua

Milk Industries, Israel. See *Hackmey, Israel.*

Millenium, USA. Millenium Pharmaceuticals Inc., 40 Landsdowne St., Cambridge, MA 02139, USA.
url: www.mlnm.com

Miller, USA. Miller Pharmacol Group Inc., 350 Randy Rd, Suite 2, Carol Stream, IL 601881831, USA.
url: www.millerpharmacal.com

Millet Roux, Braz. Produtos Farmacêuticos Millet Roux Ltda, Praia de Botafogo 440, 25 andor, 22250-040 Ria de Janeiro, RJ, Brazil.
url: www.milletroux.com.br

Millet-Franklin, Arg. Laboratorios Millet-Fronklin S.A., Thames 121 Piso 1 of. 2, 1609 Boulogne, Buenos Aires, Argentina.
url: www.milletfranklin.com

Millimed, Philipp. See *MG, Philipp.*

Millimed, Thai. Millimed Co Ltd, 193 Moo 1 Suksawad Rd, Pakklongbangprakort, Phra Samutchedi, Samutprakarn 10290, Thailand.
url: www.millimedthailand.com

Millot-Solac, Fr. See *Sanofi-Aventis, Fr.*

Milmet, India. See *Sun, India.*

Milo, Spain. Milo, Pol Ind Centrovia, C/ Los Angeles 60, La Muela, 50196 Zaragoza, Spain.
url: www.laboratoriosmilo.com

Milpharm, Irl. See *Milpharm, UK.*

Milpharm, UK. Milpharm Ltd, Ares, Odyssey Business Park, West End Rd, South Ruislip, HA4 6QD, UK.

Milpharma, Singapore. See *Pharmatech, Singapore.*

Milte, Ital. Milte Italia S.p.A., Via Boscovich 55, 20124 Milan (MI), Italy.
url: www.milte.it

Milumel, Fr. Milumel, Parc d'activités de Torcé, Secteur Est, 35370 Torcé, France.
url: www.milumel.fr

Milupa, Austria. Milupa GmbH, Postfach 2, A-5412 Puch, Austria.

Milupa, Cz. See *Milupa, Austria.*

Milupa, Hong Kong. See *Connell, Hong Kong.*

Milupa, Irl. See *Nutricia, Irl.*

Milupa, Ital. Milupa S.p.A., Via Lepetit 8, 20020 Lainate (MI), Italy.
url: www.milupa.it

Milupa, Pol. See *Nutricia, Pol.*

Milupa, Port. Milupa Portuguesa, Lda, Zona Industrial, 2790-076 Carnaxide, Portugal.

Milupa, Switz. Milupa SA, 1564 Domdidier, Switzerland.
url: www.milupa.ch

Milupa, UK. Milupa Ltd, Division of Nutricia, Newmarket Ave, White Horse Business Park, Trowbridge, Wiltshire, BA14 0XQ, UK.
url: www.milupa4hcps.co.uk

Miluvita, Ital. See *Milupa, Ital.*

Milve, Rus. See *Sopharma, Rus.*

Mimer, Denm. See *Mimer, Swed.*

Mimer, Swed. Mimer Medical, Svärdvägen 3B, 182 33 Danderyd, Sweden.

Minancora, Braz. Minancora & Cia Ltda, Rua do Principe 461, 89201-001 Joinville, SC, Brazil.
url: www.minancora.com.br

Minden, Ger. See *Abbott, Ger.*

Minerva, Gr. Minerva Pharmaceutical S.A., 132 Kiffisou Ave, 121 33 Peristeri, Greece.
url: www.minervapharm.gr

Minerva, Singapore. See *MD, Singapore.*

Minerva (Μινερβα), Gr. See *Minerva, Gr.*

Minghua, China. Shenyang Minghua Pharmaceutical Co., Ltd., 80 North St, Huanggu, Shenyang, Liaoning, 110034, China.
url: www.mhjt.com.cn

Mingshen, China. Mingshen Pharmaceutical Co. Ltd, Xingtai, China.

Mingxin, China. Mingxin Pharmaceutical Co. Ltd, Sichuan, China.

Mingxing, China. Mingxing Pharmaceutical Co. Ltd, Sichuan, China.

Minhai, China. Fuzhou Minhai Parmaceutical Co.ltd, Jingyang Industrial Zone, Fuquing City, Fujian, 350303, China.
url: www.fzmh.com

Ministry of Defence, UK. Ministry of Defence, Whitehall, London, SW1 2HB, UK.

Minntech, Canad. See *Minntech, USA.*

Minntech, USA. Minntech Corporation, 14605 28th Avenue North, Minneapolis, MN 55447, USA.
url: www.minntech.com

Minophagen, China. Minophagen Phaemaceutical Co. Ltd, Room 802(B) Huixin Building, 8 Beichen Dongfu, Chaoyang District, Beijing 100101, China.
url: www.minophagen.co.jp

Minophagen, Jpn. Minophagen Pharmaceutical Co., 3-2-7 Yotsuya, Shinjuka-ku, Tokyo 160-0004, Japan.

Minorock Mandiri, Indon. Minorock Mandiri PT, Jl Kelapa Dua 69, 16951 Jakarta, Indonesia.

Minova, India. Minova Life Sciences Pvt Ltd, 157 1st Main Road, Mysore Road, A.R. Compound, Chamarajpet, Bangalore 560 018, India.
url: www.minovalife.com

Minrad, China. See *Minrad, USA.*

Minrad, USA. Minrad Inc., 50 Cobham Drive, Orchard Park, New York, NY 14127, USA.
url: www.minrad.com

Minsheng, China. Hangzhou Minsheng Pharmaceutical Group Co Ltd, Yuhang Toro 108, Hangzhou City, China.
url: www.mspharm.com.index.asp

Minskinterkaps, Belarus. Minskinterkaps UP, Inzhenernaya St. 26, 220075 Minsk, Belarus.
url: www.mic.by

Minskinterkaps, Rus. See *Minskinterkaps, Belarus.*

Minskinterkaps, Ukr. See *Pharmplanet, Ukr.*

Mint, India. Mint Life Sciences, SCO-6 FF Sector 5, Near KC Theatre, Panchkula, 134 109, India.
url: www.mintlifesciences.com

Mintlab, Chile. Mintlab Co SA, Nueva Andres Bello 1940, Independencia, Santiago, Chile.

MIP, Austria. MIP Pharma Austria GmbH, Maria-Theresien-Strasse 7/11, A-6020 Innsbruck, Austria.

MIP, Denm. See *MIP, Ger.*

MIP, Fin. See *MIP, Ger.*

MIP, Ger. MIP Pharma GmbH, Kirkeler Str. 41, 66440 Blieskastel, Germany.
url: www.mip-pharma.de

MIP, Norw. See *MIP, Ger.*

MIP, Pol. MIP Pharma Polska Sp. zo.o., ul. Orzechowa 5, 80-175 Gdańsk, Poland.

MIP, Swed. See *MIP, Ger.*

Mipharm, Ital. Mipharm S.p.A., Via B Quaronto 12, 20141 Milan (MI), Italy.
url: www.mipharm.it

Mipharm, Neth. See *Mipharm, Ital.*

Mipharm, USA. See *Mipharm, Ital.*

Miquel Otsuka, Spain. See *Otsuka, Spain.*

Mir, Rus. Mir-Pharm, Business Center Rumyantsevo, str 1, blok A, of 735A, Rumyantsevo, Moscow, Russia.
url: www.mirpharm.ru

Mir, Ukr. Mir-Pharm, Otakar Yarosh 18, 61045 Kharkov, Ukraine.
url: www.mirpharm.com.ua

Miracalus, India. Miracalus Pharma Pvt Ltd, 213 Shivai Dongre Industrial Premises, Andheri-Kurla Road, Andheri (E), Mumbai 400 072, India.
url: www.miracalus.com

Miralex, Pol. Miralex Sp. zo.o., ul. Św. Szczepana 25, 61-465 Poznań, Poland.
url: www.miralex.pl

Miralfarma, Spain. Laboratorios Miralfarma SL, Rondo General Mitre 151, Barcelona, Spain.

Mirren, S.Afr. Mirren (Pty) Ltd, P.O. Box 87607, Houghton 2041, South Africa.
url: www.mirren.co.za

Misemer, USA. See *Edwards, USA.*

Misha, India. Misha Biotech Pvt Ltd, SCO-41 D, Chandigarh, India.

Mission, Austral. Mission Pharmacal Australia Pty Ltd., Level 2, 294 New South Head Road, Double Bay, NSW 2028, Australia.
url: www.missionpharmacal.com.au

Mission Happiness, India. Mission Happiness, C-79/2 Rajendra Nagar, Bareilly, Uttar Pradesh, India.

Mission Pharmacal, Canad. See *Mission Pharmacal, USA.*

Mission Pharmacal, Hong Kong. See *International Medical, Hong Kong.*

Mission Pharmacal, Malaysia. See *Somedico, Malaysia.*

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Mission Pharmacal, USA. Mission Pharmacal Co., 10999 IH 10 West, Suite 1000, San Antonio, TX 78230-1355, USA.
url: www.missionpharmacal.com

MIT, Ger. MIT Gesundheit GmbH, Flutstr. 74, 47533 Kleve, Germony.
url: www.mit-gesundheit.com

Mita, Hong Kong. Mita Pharmaceutical Co. Ltd, Rm 1208, 12/F, Phase 1, Metro Ctr, 32 Lam Hing St, Kowloon Bay, Kowloon, Hong Kong.

Mitek, Ukr. OOO Mitek, pereulok Ochakovskii, 3, Kiev, 03151, Ukraine.
url: www.mitek.kiev.ua

Mithra, Belg. Mithra Pharmaceuticals NV, Rue Saint-Georges 5, 4000 Liège, Belgium.
url: www.mithra.be

Mithra, Hong Kong. See *CNW, Hong Kong* and *Hong Kong Medical, Hong Kong.*

Mithra, Neth. See *Mithra, Belg.*

Mitim, Ital. Mitim S.r.l., Via Rodi 27, 25126 Brescia (BS), Italy.

Mitra, India. Mitra Industries (P) Ltd, 14/4 Delhi-Mathura Road, Faridobad, Haryana 121 003, India.
url: www.mitraindustries.com

Mits, India. Mits Healthcare Pvt India, SPO B-62/A, Naraina Phase-2, 110 027, India.
url: www.mitshealthcare.com

Mitsubishi, Austria. See *Mitsubishi, UK.*

Mitsubishi, China. Mitsubishi Pharma Co. Ltd, Banana Park Rd 2, Economic & Technological Development Zone, Guangzhou 510730, China.

Mitsubishi, Denm. See *Biovitrum, Denm.*

Mitsubishi, Fin. See *Mitsubishi, UK.*

Mitsubishi, Ger. Mitsubishi Pharma Deutschland GmbH, Prinzenallee 13, 40549 Düsseldorf, Germany.
url: www.mitsubishi-pharma.de

Mitsubishi, Indon. See *Tanabe, Indon.*

Mitsubishi, Ital. See *Italchimici, Ital.*

Mitsubishi, Jpn. See *Mitsubishi-Tokyo, Jpn.*

Mitsubishi, Malaysia. See *Summit, Malaysia.*

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Mitsubishi, Philipp. See *Pacific Healthcare, Philipp.*

Mitsubishi, Pol. Mitsubishi Corp., al. Jerozolimski 65/79, 00-697 Warsaw, Poland.

Mitsubishi, Thai. See *Diethelm, Thai.*

Mitsubishi, UK. Mitsubishi Pharma Europe Ltd, Dashwood House, 69 Old Broad St, London, EC2M 1QS, UK.
url: www.mitsubishi-pharma.eu

Mitsubishi Guangzhou, Hong Kong. Mitsubishi Pharma Guangzhou, Hong Kong.

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Mitsubishi Tanabe, Hong Kong. See *Hing Ah, Hong Kong* and *Primal, Hong Kong.*

Mitsubishi Tanabe, Jpn. Mitsubishi Tanabe Pharma, 3-2-10-cho, Chuo-ku, Osaka Doshomachi, Japan.
url: www.mt-pharma.co.jp

Mitsubishi Tanabe, Malaysia. See *Pharmaforte, Malaysia.*

Mitsubishi Tanabe, Singapore. See *Pharmaforte, Singapore.*

Mitsubishi Tanabe, Thai. See *Wellchem, Thai.*

Mitsubishi-Tokyo, Hong Kong. See *Hing Ah, Hong Kong.*

Mitsubishi-Tokyo, Jpn. Mitsubishi-Tokyo Pharmaceuticals Inc., 2-6 Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8405, Japan.
url: www.m-pharma.co.jp

Miyarisan, China. Miyarisan Pharmaceuticol Co. Ltd, China.
url: www.miyarisan.com

Miyarisan, Jpn. Miyarisan Pharmaceutical Co., Ltd, 1-10-3 Kaminakazato, Kita-ku, Tokyo 114-0016, Japan.
url: www.miyarisan.com

Mizar, Spain. See *Novartis, Spain.*

MJ Biopharm, Philipp. See *PNF, Philipp.*

MJ Biopharm, Thai. See *Pharmaland, Thai.*

MKR, Canad. MKR International Inc., Unit 6, 8 Thompson Crest, Erin, Ontario, N0B 1T0, Canada.

ML, Neth. See *ML Laboratories, UK.*

ML Laboratories, UK. ML Laboratories Plc, Blaby Hall, Church St, Blaby, Leicestershire, LE8 4FA, UK.
url: www.mllabs.co.uk

MLP, Canad. MLP Cosmetique Inc., 1477 rue Nobel, St-Julie, Quebec, J3E 1Z5, Canada.
url: www.mlpcosmetiques.qc.ca

MM, Canad. MM Therapeutics Inc., Unit 100, 6111 Royalmount Ave, Montreal, Quebec, H4P 2T4, Canada.

MM, India. M.M. Labs., Mahalaxmi Chambers, 22 Bhulabhai Desai Rd, Mumbai 400 026, India.

MMC, India. MMC Healthcare Ltd, 61 Kurinji Street, Fathima Nagar, Valasaravakkam, Chennai 600 087, India.
url: www.mmchealthcareindia.com

Mobius, USA. Mobius Therapeutics LLC, St Louis, MO, USA.
url: www.mobiustherapeutics.com

Mochida, Jpn. Mochida Pharmaceutical Co. Ltd, 1-7 Yotsuya, Shinjuku-ku, Tokyo 160-8515, Japan.
url: www.machide.co.jp

Modern Health Products, UK. See *Lane, UK.*

Modern Manu, Thai. Modern Manu, Pairat Sithinamsuwann, 54/1 Moo 5, Sukarbhiband 1, Bangkapi, Bangkok 10240, Thailand.

Modern Products, Canad. See *Modern Products, USA.*

Modern Products, USA. Mosern Products Inc., 6425 W Executive Drive, Mequon, Wisconsin, 53092, USA.

ModHike, India. ModHike Pvt Ltd, 24 & 25A Selaqui Indl Area, Pharma City, Dehradun 248 197, India.
url: www.modhike.com

Modi-Mundipharma, India. Modi-Mundipharma Ltd, 1400 Hemkunt Tower, 98 Nehru Place, New Delhi 110 019, India.

Moleac, Fr. Moleac Europe, 92 rue de la Victoire, 75009 Paris, France.
url: www.nuraid.com

Moleac, Malaysia. See *Zuellig, Malaysia.*

Moleac, Singapore. Moleac Pte Ltd, Helios 09-07, 11 Biopolis Way, S 138667, Singapore.
url: www.moleac.net

Molekule, India. Molekule (India) Pvt Ltd, AML Centre-2, 3rd Floor, Mahal Industrial Estate, Mahakali Caves Road, Andheri (E), MUMBAI 400 093, India.

Molex Ayus, Indon. Molex Ayus Pharmaceutical, Gedung Sinar Astri Lt IV, Jl Ir H Juanda No 5c, Jakarta 10120, DKI Jaya, Indonesia.

Molitor, Ger. See *Orthim-Molitor, Ger.*

Molnlycke, Austral. Molnlycke Health Care Pty Ltd, Building 1 Ground Floor, 14 Aquatic Drive, Frenchs Forest, NSW 2086, Australia.

Molnlycke, Belg. Mölnlycke Health Care NV, Posthoflei 5, bus 7, B-2600 Berchem, Belgium.
url: www.molnlycke.com

Molnlycke, Canad. Molnlycke Health Care, 2010 Winston Park Dr., Suite 100, Oakville, Ontario, L6H 5R7, Canada.
url: www.tendra.com

Molnlycke, Fr. Laboratoires Mölnlycke Health Care, ZAC du Moulin, av Clement-Ader, B.P. 42, 59118 Wambrechies cdx, France.
url: www.molnlycke.net

Molnlycke, Ger. Mölnlycke Health Care GmbH, Max-Planck Str. 15, 40699 Erkrath, Germany.
url: www.molnlycke.com

Molnlycke, Ital. Molnlycke Health Care S.r.l., Via Marsala 40/c, 21013 Gallarate (VA), Italy.
url: www.molnlycke.net

Molnlycke, Spain. Mölnly Health Care SL, Avda de Bruselas 38 B, 1a Planta, Poligono Industrial Arroyo de la Vega, 28108 Alcobendas (Madrid), Spain.
url: www.molnlycke.com

Molnlycke, Thai. See *Diethelm, Thai.*

Molnlycke, UK. Mölnlycke Healthcare Ltd, The Arenson Centre, Arenson Way, Dunstable, Bedfordshire, LU5 5UL, UK.
url: www.molnlycke.net

Molteni, Austria. See *Molteni, Ital.*

Molteni, Cz. See *Molteni, Ital.*

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Molteni, Ital. L. Molteni & C. dei F.lli Alitti S.p.A., S.S. 67, Fraz. Granatieri, 50018 Scandicci (FI), Italy.

Molteni, Neth. See *Molteni, Ital.*

Molteni, Norw. See *DnE, Norw.*

Molteni, Pol. Molteni Farmaceutici Polska Sp. zo.o., ul. Obrońców Modlina 3, 30-733 Kraków, Poland.
url: www.molteni.com.pl

Molteni, Port. See *Molteni, Ital.*

Molteni, Rus. See *Reddy, Rus.*

Molteni, Spain. See *Molteni, Ital.*

Molteni, Ukr. See *Delta Medical, Ukr.*

Molypharma, Spain. Molypharma, Avda. Dr. Severo Ochoa 37, 4i, Alcobendas, 28100 Madrid, Spain.
url: www.molypharma.es

Mona Lisa, Israel. See *Hackmey, Israel.*

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Monal, Neth. See *Bournonville, Neth.*

Monarch, Canad. See *King, USA.*

Monarch, Cz. See *Monarch, Irl.*

Monarch, Gr. See *Monarch, Irl.*

Monarch, Hung. Monarch, Hungary.

Monarch, Irl. Monarch Pharmaceuticals Ireland Ltd, Alexandra House, The Sweepstakes, Ballsbridge, Dublin 4, Ireland.

Monarch, Ital. See *Monarch, Irl.*

Monarch, Neth. See *Monarch, Irl.*

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Mondeal, NZ. Mondeal Contura Pty Ltd, P.O. Box 480, Pukekohe, New Zealand.

Monelli, Ital. Monelli Ezio & C Srl, Via Viazza 62, 41030 San Prospero (MO), Italy.

Monico, Ital. Monico S.p.A., Via Ponte di Pietra 7, 30173 Mestre (VE), Italy.
url: www.monico.it

Monik, Spain. Monik, Avda de la Playa 1, Conil de la Frontera, 11140 Cadiz, Spain.

Monin, Fr. Laboratoires Monin-Chanteaud, Parc Euromedecine II, rue de la Valsière, 34099 Montpellier cdx 5, France.

Monmouth, Irl. See *Allphar, Irl.*

Monmouth, UK. See *Shire, UK.*

Monodonal Antibodies, USA. See *Quidel, USA.*

Monokem, India. Monokem Laboratories, 46 Shree Krishna Centre, 5th Floor, Nr. Mithkhali, Six Road Navarangpura, Ahmedabad 380 009, India.

Monot, Fr. See *Merck-Lipha, Fr.*

Monsanto, Austral. See *Pharmacia, Austral.*

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Monsanto, Chile. See *Searle, Chile.*

Monsanto, Cz. See *Medicom, Cz.*

Monsanto, Fr. See *Pharmacia, Fr.*

Monsanto, Ital. Monsanto Italiana S.p.A., Via Walter Tobagi 8, 20089 Peschiera Borromeo (MI), Italy.

Monsanto, Port. See *Pfizer, Port.*

Monsanto, Spain. See *Pfizer, Spain.*

Monserrat, Arg. Monserrat y Eclair S.A., Virrey Cevallos 1625/7, 1135 Buenos Aires, Argentina.

Mont Roucous, Fr. Sté des eaux de Mont Roucous, 81230 Lacaune les Bains, France.
url: www.sources-mont-roucous.fr

Montavit, Austria. Montavit GmbH, Salzbergstrasse 96, A-6060 Absam, Austria. The General Manager
url: www.montavit.com

Montavit, Israel. See *Lapidot, Israel.*

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Montavit, Philipp. See *Marketlink, Philipp.*

Montavit, Port. See *Montavit, Austria.*

Montavit, Rus. See *Montavit, Austria.*

Montavit, Thai. Montavit, Thailand.

Montavit, Ukr. Pharmazeutische fabrik MONTAVIT GmbH, ul Mariny Raskovoy 23, Office 1103, 02660 Kiev, Ukraine.
url: www.montavit.kiev.ua

Monte Verde, Arg. Monte Verde SA, Cabildo 86, Piso 4, Buenos Aires, Argentina.

Montebello, Fr. Montebello France SA, av.des Noelles, B.P. 216, 44505 La Baule cdx, France.

Montefarmaco, Cz. See *Montefarmaco, Ital.*

Montefarmaco, Ital. Montefarmaco S.p.A., Via G Galilei 7, 20016 Pero (MI), Italy.
url: www.montefarmaco.com

Monticello, USA. Monticello Drug Co., 1604 Stockton St, Jacksonville, FL 32204-4524, USA.
url: www.monticellocompanies.com

Montpellier, Arg. See *Disprofarma, Arg.*

Montpellier, Rus. See *Bago, Rus.*

Montrose, Cz. See *Montrose, UK.*

Montrose, Hung. Montrose Kft, Hosszüret u 1, 2045 Törökbálint, Hungary.
url: www.montrose.hu

Montrose, UK. Montrose Fine Chemical Co Ltd, Irvine, UK.

Moore, USA. Moore Medical Corp., P.O. Box 1500, New Britain, CT 06050-1500, USA.
url: www.mooremedical.com

Moorfields, Irl. See *Moorfields, UK.*

Moorfields, UK. Moorfields Pharmaceuticals, 25 Provost St, London, N1 7NH, UK.
url: moorfieldspharmaceuticals.co.uk

Moraceae, India. Moraceae Pharmaceuticals Pvt Ltd, 40 Laxmanpuri, Faizabad Road, Indira Nagar, Lucknow 226 016, India.
url: www.moraceae.net

Moraz, UK. See *Intercare, UK.*

More, Mex. More Pharma Corp. S de RL de CV, Av. Ejército Nacional 926, Interior 203, Col Los Morales Seccion Palmas, 11540 DF Mexico, Mexico.
url: www.morepharmacorp.com

More, Philipp. SV More Pharmo Corp., 2/F SV More Group Corp Center, 16 Sct Tuazon cor Roces Ave, Quezon City, Philippines.

Moreno, Port. Farmácia Moreno, Sociedade Unipessoal Ldo, Lg. São Domingos 44, 4050-545 Porto, Portugal.

Morepen, India. Morepen Laboratories ltd, 409 Antriksh Bhawan, 22 Kasturba Gandhi Marg, New Delhi 110 001, India.
url: www.morepen.com

Morgan, Ital. Morgan S.r.l., Via Divisione Folgore 46, 36100 Vicenza (VI), Italy.
url: www.morganpharma.it

Morin, Fr. See *Cognon-Morin, Fr.*

Morinaga, Indon. See *Sanghiang, Indon.*

Morishita, Philipp. Morishita-Seggs Pharmaceuticals Inc., 782 San Rafael St, Mandaluyong City, Philippines.

Morningside, Irl. See *Morningside, UK.*

Morningside, UK. Morningside Healthcare Ltd, 115 Narborough Rd, Leicester, Lesicestershire, LE3 0PA, UK.

Morrith, Spain. See *GSK, Spain.*

Morson, Irl. See *Fulcrum, Irl.*

Morson, UK. See *MSD, UK.*

Morton Grove, USA. Morton Grove Pharmaceuticals Inc., 6451 West Main St, Morton Grove, IL 60053, USA.
url: www.wockhardtusa.com

Morton Salt, USA. Morton Salt, 123 N Wacker Dr., Chicago, IL 60606-1597, USA.
url: www.mortonsalt.com

Moschimfarm, Rus. Moschimfarmpreparaty Im. N.A. Semashko, Bolbsie Kamenskii ul 9, 115172 Moscow, Russia.
url: www.mhfp.ru

Moschimfarm, Ukr. See *Moschimfarm, Rus.*

Moscow Endocrine, Rus. See *Makiz-Pharma, Rus* and *Peptos, Rus.*

Mosfarma, Rus. Moscow Pharmaceutical Factory JSC, Farmatsevticheskii pr 1, 125239 Moscow, Russia.
url: www.mosfarma.ru

Mosi-Guard, UK. Mosi-Guard International Ltd, Moorfield Rd, Yeadon, Leeds, West Yorkshire, LS19 7BN, UK.
url: www.mosiguard.com

Mothersoy, USA. MotherSOY Inc., 424 S Kentucky Ave, Evansville, IN 47714, USA.
url: www.mothersoy.com

Motima, Fr. Laboratoires Motima, 19 rue de Passy, 75016 Paris, France.

Mount Mettur, India. Mount Mettur Pharmaceuticals, 32 9th Street, Dr Radhakrishna Salai, Mylapore, Chennai 600 004, India.

Mount Mettur, Philipp. See *GBF, Philipp.*

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Movetis, Belg. Movetis NV, Veedijk 58, Turnhout, B-2300, Belgium.
url: www.movetis.com

Movetis, Cz. See *Movetis, Belg.*

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Movi Health, Ukr. Movi Health, ul Rybalskaya 13, 01011 Kiev, Ukraine.

Movianto, Irl. Movianto - Cahill May Roberts, Pharmapark, Chapelizod, Dublin 20, Ireland.

Movianto, UK. Movianto UK Ltd, 1 Progress Park, Bedford, MK42 9XE, UK.
url: www.movianto.com

MPCA, Belg. MPCA, Medical & Pharmaceutical Consultancy & Applications bvba, Vrijestraat 28, 9960 Assenede, Belgium.
url: www.mpca.be

MPF, Singapore. See *Luen Wah, Singapore.*

MPI, Belg. MPI, Belgium.

MPM, UK. MPM, UK.

MPM, USA. MPM Medical Inc., 2301 Crown Ct, Irving, TX 75038, USA.
url: www.mpmmedicalinc.com

MPSI, Philipp. Medical & Pharmaceutical Specialties Inc. (MPSI), G/F Aurora Cond., 127 Aglipay St, Mandaluyong City, Philippines.

MR Pharma, Fin. See *MR Pharma, Ger.*

MR Pharma, Ger. MR Pharma GmbH, Waldstrasse 30, D-22889 Tangstedt, Germany.

MR Pharma, Neth. See *MR Pharma, Ger.*

MSD, Arg. Merck Sharp & Dohme (Arg.) Inc., Av. del Libertador 1410, 1638 Vicente Lopez, Buenos Aires, Argentina.
url: www.msd.com.ar

MSD, Austral. Merck Sharp & Dohme (Australia) P/L, P.O. Box 79, Granville, NSW 2142, Australia.
url: www.msd-australia.com.au

MSD, Austria. Merck Sharp & Dohme GmbH, Donau-City Strasse 6, A-1220 Vienna, Austria.
url: www.msd-austria.com

MSD, Belg. Merck Sharp & Dohme B.V., Chaussée de Waterloo 1135, 1180 Brussels, Belgium.
url: www.msd-belgium.be

MSD, Braz. Merck Sharp & Dohme Farma Ltda, Rua Alexandre Dumas 2510, 04717-004 São Paulo, SP, Brazil.
url: www.msd-brazil.com

MSD, Canad. See *Merck Frosst, Canad.*

MSD, Chile. Merck Sharp & Dohme, Av. Americo Vespucio Sur 100, Of. 401, Las Condes, Santiago, Chile.

MSD, China. Merck Sharp & Dohme (China) Ltd, 20/F Park Place, 1601 Nanjing Road (West), Jing'an District, Shanghai 20040, China.
url: www.msdchina.com.cn

MSD, Cz. Merck Sharp & Dohme, Křenová 5, 160 00 Prague 6, Czech Republic.

MSD, Denm. Merck Sharp & Dohme, Smedeland 8, 2600 Glostrup, Denmark.
url: www.msk.dk

MSD, Fin. Suomen MSD Oy, PL 46, 02151 Espoo, Finland.
url: www.msd-finland.com

MSD, Ger. MSD Sharp & Dohme GmbH, Lindenplatz 1, 85540 Haar, Germany.
url: www.msd.de

MSD, Gr. See *MSD, UK.*

MSD, Hong Kong. Merck Sharp & Dohme (Asia) Ltd, 26/F Caroline Ctr, Lee Gardens Two, 28 Yun Ping Rd, Causeway Bay, Hong Kong.
url: www.msd.com.hk

MSD, Hung. Merck Sharp & Dohme Kft, Tartsay Vilmos u 14, 1126 Budapest, Hungary.

MSD, India. MSD Pharmaceuticals Private Ltd, 7th Floor, Tower B, Vatika Towers, Sector-54, Gurgaon 122 002, India.
url: www.msdindia.in

MSD, Indon. Merck Sharp & Dohme, Wisma BNI 46, 27th Fl, Jalan Jendral Sudirman Kav 1, Jakarta 10220, DKI Jaya, Indonesia.
url: www.msd-indonesia.com

MSD, Irl. Merck Sharp & Dohme Ireland (Human Health) Ltd, Pelham House, South County Business Park, Leopardstown, Dublin 18, Ireland.
url: www.msd.ie

MSD, Israel. MSD Israel, P.O. Box 7121, Petach Tikva, Israel.
url: www.merckshardohme.com

MSD, Ital. Merck Sharp & Dohme (Italia) S.p.A., Via G. Fabbroni 6, 00100 Rome (RM), Italy.
url: www.msd-italia.it

MSD, Jpn. See *Banyu, Jpn* and *Schering-Plough, Jpn.*

MSD, Malaysia. Merck Sharp & Dohme Malaysia, 15th Floor Menara Merias, 1 Jln 19/3, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.merckshardohme.com

MSD, Mex. Merck Sharp & Dohme de Mexico S.A. de C.V., Av. Division del Norte No. 3377, Col. Xotepingo, Deleg. Coyoacan, 04610 Mexico D.F., Mexico.
url: www.msd.com.mx

MSD, Neth. Merck Sharp & Dohme BV, Postbus 581, 2003 PC Haarlem, Netherlands.
url: www.msd.nl

MSD, Norw. MSD (Norge) A/S, Solbakken 1, Postboks 458 Brakeroya, 3002 Drammen, Norway.
url: www.msd.no

MSD, NZ. Merck Sharp & Dohme (NZ) Ltd, 109 Carlton Gore Road, Newmarket, Auckland, New Zealand.
url: www.msd.co.nz

MSD, Philipp. Merck Sharp & Dohme, 26/F Philamlife Tower, 8767 Paseo de Roxas, Makati City, Philippines.

MSD, Pol. MSD Polska Sp. zo.o., ul. Chłodna 51, 00-867 Warsaw, Poland.

MSD, Port. Merck Sharp & Dohme, Lda, Edifício Vasco da Gama 19, Quinta da Fonte, Porto Salvo, 2770-192 Paç de Arcos, Portugal.
url: www.msd.pt

MSD, Rus. Merck Sharp & Dohme Idea, Berezhkovskaya nab. 2, Gostinista Slavonic/Radisson, 121095 Moscow, Russia.
url: www.msd.ru

MSD, S.Afr. Merck Sharp & Dohme (Pty) Ltd, Private Bag 3, Halfway House 1685, South Africa.
url: www.merckshardohme.com

MSD, Singapore. Merck Sharp & Dohme (IA) Corp, Singapore Branch, 300 Beach Road, 13-02 The Concourse, S 199555, Singapore.
url: www.msd-singapore.com

MSD, Spain. Merck Sharp & Dohme S.A., Josefa Valcarcel 38, 28027 Madrid, Spain.
url: www.msd.es

MSD, Swed. Merck Sharp & Dohme (Sweden) AB, Box 7125, 192 07 Sollentuna, Sweden.
url: www.msd.se

MSD, Switz. Merck Sharp & Dohme-Chibret SA, Niederlassung von Merck & Co., Inc., USA, Schaffhauserstrasse 136, Postfach, 8152 Glattbrugg, Switzerland.
url: www.msd.ch

MSD, Thai. See *BLH, Thai.*

MSD, Turk. See *Merck, Turk.*

MSD, UK. Merck Sharp & Dohme Ltd, Hertford Rd, Hoddesdon, Hertfordshire, EN11 9BU, UK.
url: www.msd-uk.com

MSD, Ukr. MSD, ul Pirogov 4/26, 5th Floor, 01033 Kiev, Ukraine.

MSD, USA. See *Merck, USA.*

MSD, Venez. Merck Sharp & Dohme de Venezuela, Av. Principal de los Cortijos de Lourdes, Centro Empresarial Senderos P.1 - Los C.Lourde, Caracas, Venezuela.
url: www.msd.com.ve

MSD Chibropharm, Ger. See *MSD, Ger.*

MSD-Chibret, Fr. Laboratoires Merck Sharp & Dohme-Chibret, 3 ave Hache, 75114 Paris cdx 08, France.
url: www.msd-france.com

MSN, India. MSN Laboratories Ltd, MSN House, Plot No: C-24, Industrial Estate Sanathnagar, Hyderabad 18 AP, India.
url: www.msnlabs.com

Mucos, Austria. Mucos Emulsions GmbH, Leberstrasse 96, A-1110 Vienna, Austria.

Mucos, Canad. See *Mucos, Ger.*

Mucos, Cz. Mucos Pharma CZ sro, Uhříněveská 448, 252 43 Průhonice, Czech Republic.
url: www.mucos.cz

Mucos, Ger. Mucos Pharma GmbH & Co. KG, Miraustr. 17, 13509 Berlin, Germany.
url: www.mucos.de

Mucos, Hung. See *PannonPharma, Hung.*

Mucos, Rus. Mucos Pharma GMbH & Co, Kashirskoe sh. 34A, 115522 Moscow, Russia.

Mucos, Ukr. Mucos Pharma, prosp Komarova, 3, Medgorodok, Block 3, Kiev, 03680, Ukraine.
url: www.mucos.com.ua

Mucos, Venez. Caso de Representación Mucos de Venezuela S.A., Calle San Ernesto, Quinta Mucos, Sect. Sorocaimo, La Trinidad, Baruta, Caracas, Venezuela.
url: www.mucos.de

Mueller, Canad. See *Mueller, USA.*

Mueller, USA. Mueller Sports Medicine Inc., One Quench Drive, Prairie du Sac, Wisconsin, 53579, USA.

Mugi, Indon. Mugi Laboratories PT, Jl PLN No 99, Duren Tiga, Jakarta 12760, Indonesia.

Muir Hutchinson, NZ. See *UCB, Austral.*

Mulda, Turk. Mulda Koll Şti., Bomonti, Güvenç Sok. No: 11/4, Şişli, İstanbul, Turkey.

Muller Goppingen, Ger. Chemisch-Pharmazeutische Fabrik Göppingen Carl Müller, Apotheker, GmbH & Co. KG, Bahnhofstr. 33-35 & 40, 73033 Göppingen, Germany.
url: www.mueller-goeppingen.de

Muller Goppingen, Indon. See *Darya-Varia, Indon.*

Multi Mitra, Indon. PT Multi Mitra Biotech, Perkantoran Permata Senayan, Blok C 15-16, Jakarta, Indonesia.

Multicare, Philipp. Multicare Pharmaceuticals Phils Inc., 26/F Rufino Tower, 6784 Ayala Ave, Makati City, Philippines.
url: www.multicare.com.ph

Multichem, NZ. Multichem NZ Ltd, 8 Apollo Drive, Mairangi Bay, Auckland, New Zealand.
url: www.multichem.co.nz

Multilab, Braz. Multilab Ind. e Com. Prods. Farmacêuticos Ltda, RS 401 Km 30 No. 1009, 96700-000 São Jeronimo, RS, Brazil.
url: www.multilab.com.br

Multilan, Chile. See *Organon, Chile.*

Multilan, Israel. See *Neopharm, Israel.*

Multipharma, Neth. Multipharma BV, Postbus 216, 1380 AE Weesp, Netherlands.
url: www.multipharma.nl

Multivitamin Corp, Philipp. The Multivitamin Corp., Unit 2A City Center Bldg, 338 Ortigas Ave, Greenhills, San Juan City, Philippines.

Mundipharma, Austral. Mundipharma, P.O. Box 5214, Sydney, NSW 2001, Australia.
url: www.mundipharma.com

Mundipharma, Austria. Mundipharma GmbH, Apollogasse 16-18, A-1072 Vienna, Austria.
url: www.mundipharma.co.uk

Mundipharma, Belg. Mundipharma, Campus Mechelen, Schaliënhoevedreef, 2800 Mechelen, Belgium.

Mundipharma, China. Mundipharma (China) Pharmaceutical Co. Ltd (MCPC), Room 1808 Block D Central International Trade Center, 6 Jian Guo Men Wai Ave, Chaoyang District, Beijing, 100022, China.
url: www.mundipharma.com

Mundipharma, Cz. Mundipharma GmbH, Turisticka 36, 621 00 Brno, Czech Republic.

Mundipharma, Fin. Mundipharma Oy, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.mundipharma.co.uk

Mundipharma, Fr. Mundipharma, 42 rue d'Aguesseau, 92100 Boulogne-Billancourt, France.
url: www.mundipharma.com

Mundipharma, Ger. Mundipharma GmbH, Mundipharma Str. 2, 65549 Limburg (Lahn), Germany.
url: www.mundipharma.de

Mundipharma, Gr. See *Mundipharma, Ger.*

Mundipharma, Hong Kong. See *Jacobson, Hong Kong.*

Mundipharma, Hung. See *Extractum, Hung.*

Mundipharma, Indon. See *Mahakam Beta, Indon.*

Mundipharma, Irl. Mundipharma Pharmaceutical Co., 54 Fitzwilliam Square, Dublin 2, Ireland.

Mundipharma, Ital. Mundipharma Pharmaceuticals S.r.l., Corso Sempione 4, 20154 Milan (MI), Italy.
url: www.mundipharma.it

Mundipharma, Jpn. Mundipharma KK, Shinagawa Grand Central Tower, 2-15-4 Konan, Minato-ku, Tokyo 108-0075, Japan.
url: www.mundipharma.co.jp

Mundipharma, Malaysia. See *DKSH, Malaysia.*

Mundipharma, Neth. Mundipharma Pharmaceuticals BV, Astronaut 36, 3824 MJ Amersfoort, Netherlands.

Mundipharma, Norw. mundipharma AS, Postboks 218, 1326 Lysaker, Norway.
url: www.mundipharma.com

Mundipharma, Philipp. Mundipharma Distribution GmbH (Philippine Branch), Unit 201 The Taipan Place, F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Mundipharma, Pol. Mundipharma Polska Sp. zo.o., ul. Kochanowskiego 49 A, 01-864 Warsaw, Poland.
url: www.mundipharma.com.pl

Mundipharma, Port. Mundipharma Farmacêutica Lda, Edifício Atrium Saldanha, Praca Duque de Saldanha 106, Lisbon 1050-094, Portugal.

Mundipharma, Rus. See *Mundipharma, Ger.*

Mundipharma, Singapore. See *Cork, Singapore.*

Mundipharma, Spain. Mundipharma Pharmaceuticals, Via de Los Poblados, 1 Ed. Alvento Planta, Baja, 28033 Madrid, Spain.
url: www.mundipharma.co.uk

Mundipharma, Swed. Mundipharma AB, Mölndalsvägen 26, 412 63 Göteborg, Sweden.
url: www.mundipharma.se

Mundipharma, Switz. Mundipharma Medical Co, St Alban-Rheinweg 74, 4020 Basle, Switzerland.
url: www.mundipharma.ch

Mundipharma, Thai. See *JDH Borneo, Thai.*

Mundogen, Spain. See *GSK, Spain.*

Munir, Turk. Münir Şahin İlaç San. ve Tic. A.S., Çavuşoğlu Mah. Sanayii Cad. No: 22, Kortal, İstanbul, 81430, Turkey.
url: www.munirsahin.com

Munro, UK. Munro Wholesale Medical Supplies Ltd, 10 Stroud Rd, Kelvin Industrial Estate, East Kilbride, G75 0YA, UK.

Murdock, USA. See *Natures Way, USA.*

Muro, Israel. See *Megapharm, Israel.*

Muro, USA. Muro Pharmaceutical Inc., 890 East St, Tewksbury, MA 01876-1496, USA.
url: www.muropharm.com

Muromsky, Rus. Muromsky, Russia.

Muscle Marketing, Canad. Muscle Marketing USA Inc., 1290 1500 W Georgia St, Vacouver, British Columbia, V6G 2Z6, Canada.

Muskus, Venez. C Muskus S.A., Calle San Mateo, Quinta Manedor Piso 2, Sorocaima La Trinidad 1010, Caracas, Venezuela.

Mustafa, Philipp. See *International Apex, Philipp.*

MW, Ger. See *Juta, Ger.*

Myadec, Austral. Myadec, Australia.

Mylan, Belg. See *Mylan, USA.*

Mylan, Canad. Mylan Pharmaceuticals ULC, 85 Advance Rd, Etobicoke, Ontario, M8Z 2S6, Canada.

Mylan, Cz. See *Mylan, Fr.*

Mylan, Denm. Mylan ApS, Sluseholmen 2-4, 2450 Copenhagen SV, Denmark.

Mylan, Fin. See *Mylan, Swed.*

Mylan, Fr. Mylan EMEA, 117 allée des Parcs, 69792 Saint Priest cdx, France.
url: www.mylan.fr

Mylan, Ital. Mylan SpA, Viale dell'Innovazione 3, 20126 Milan, Italy.
url: www.mylan.it

Mylan, Jpn. Mylan Pharmaceuticals, 6-8 Chuo-ku, Honmachi 2-chome, Osaka, Japan.

Mylan, Neth. Mylan BV, Dieselweg 25, 3752 LB Bunschoten, Netherlands.

Mylan, NZ. Mylan New Zealand Ltd, P.O. Box 11-183, Ellerslie, Auckland, New Zealand.

Mylan, Pol. Mylan Sp. zo.o., ul. Itzecka 26, 02-135 Warsaw, Poland.
url: www.mylanpolska.pl

Mylan, Port. Mylan Lda, Rua Dr Antonio Loureiro Borges, Edificio Arquiparque 1 R/C Esq., 1499-016 Alges, Portugal.
url: www.mylan.pt

Mylan, S.Afr. See *Mylan, USA.*

Mylan, Spain. Mylan Pharmaceuticals SL, Plom 2-4 5 Planta, 08038 Barcelona, Spain.

Mylan, Swed. Mylan AB, PL 23033, 10435 Stockholm, Sweden.
url: www.mylan.se

Mylan, Thai. See *Atlanta, Thai.*

Mylan, UK. Mylan, Albany Gate, Darkes Lane, Potters Bar, Hertfordshire, EN6 1AG, UK.
url: www.mylan.co.uk

Mylan, USA. Mylan Laboratories Inc., 1500 Corporate Drive, Suite 400, Canonsburg, PA 15317, USA.
url: www.mylan.com

Mylan dura, Ger. Mylan dura GmbH, Wittichstrasse 6, 64295 Darmstadt, Germany.
url: www.mylan-dura.de

Myogen, Ger. See *Inca, Ger.*

Myogen, Irl. See *Allphar, Irl.*

Myogen, Neth. See *Inca, Ger.*

Myra, Hong Kong. See *Unam, Hong Kong.*

Myra, Singapore. See *Far East, Singapore.*

Myra, Thai. See *Olic, Thai.*

Myralis, Braz. Myralis Pharma Ltda EPP, Av. Rogélia Gallardo Alonso 605, 13860000 Aguaí, São Paulo, Brazil.

Myrex Ethica, Philipp. See *MG, Philipp.*

Mystico, India. Mystico Rose Pharma, 281/1 Nagal Sukati Rd Kala, Ambala Dist., Sirmour, India.

Myung, Thai. See *Masu, Thai.*

Myung In, Philipp. See *Biolink, Philipp.*

Myung In, Singapore. See *Ziwell, Singapore.*

Myung Moon, China. Myung Moon Pharmaceutical Co. Ltd, China.

MZ, S.Afr. See *Meyer Zall, S.Afr.*

MZL, S.Afr. MZL Investments, Private Bag X4, Hout Bay 7872, South Africa.

Nabi, USA. Nabi Biopharmaceuticals, 5800 Park of Commerce Blvd NW, Boca Raton, FL 33487, USA.
url: www.nabi.com

Nabiqasim, Philipp. See *EuroAsia, Philipp* and *Patriot, Philipp.*

Nabros, Philipp. See *Ambica, Philipp.*

Nabros, Rus. See *Nizhpharm, Rus.*

Nabros, Thai. See *Pharmaland, Thai.*

Nabros, Ukr. Nabros Pharma Pvt Ltd, Druzhkivka 10, Room 306, 03113 Kiev, Ukraine.

Nadeau, Canad. See *Ratiopharm, Canad.*

Nadinola, Canad. See *Hargell, Canad.*

Naf, Arg. Lab. Naf S.A., Fco. Acuca de Figueroa 886 Piso 1, 1180 Buenos Aires, Argentina.

Nafar, Mex. Nafar Laboratorios SA de CV, Justo Sierra 933, 45235 Zapopan Agua Blanca Indust., Jalisco, Mexico.

Nagase, Jpn. Nagase Medicals Co Ltd, 4-323, Senzo, Itami, Hyogo, 664-0898, Japan.
url: www.nagase-medicals.co.jp

Nagor, UK. Nagor Ltd, P.O. Box 21, Douglas, Isle of Man, IM99 1AX, UK.
url: www.nagor.com

Naina, Singapore. Naina Mohamed & Sons Pte Ltd, 1 Ubi Crescent, 05-04 Number One Building, S 408563, Singapore.
url: www.nainamohamed.com

Naka, Canad. Naka Sales Ltd, Unit 3, 53 Queens Plate Drive, Etobiocoke, Ontario, M9W 6P1, Canada.

Nakorn, Thai. See *TNP, Thai* and *V & V, Thai.*

Nakornpatana, Thai. Nakornpatana Pharm Co. Ltd, 495, 601/5-8 Soi Suthiporn, Prachasongkroh Rd, Dindaeng, Bangkok 10400, Thailand.

NAM, Ital. Natura Alma Mater Srl, Via Tre Settembre 178/c, 47891 Dogana San Marino, Italy.

Nan Guo, China. Nan Guo Pharmaceutical Co., Ltd., 16 Airport Road, Zhanjiang, Guangdong, 524017, China.
url: www.slp.net.cn

Nanbei, China. Nanbei Pharmaceutical Co. Ltd, Shantou, Guangdong, 515071, China.

Nanchang, China. Nanchang Pharmaceutical Co. Ltd, Jiangxi, China.

Nanda, China. Nanda Pharmaceutical Co. Ltd, Nanjing, China.

Nanfang Yingxin, China. Nanfang Yingxin Pharmaceutical Co. Ltd, Shenzhen, China.

Nang Kuang, Thai. See *Novatec, Thai.*

Nangkuang, China. Nangkuang Pharmaceutical Co. Ltd, China.

Nanhai, China. Nanhai Pharmaceutical Co. Ltd, 16-9 70 Yanghe Na 1 Rd, JiangBei, Chongqing, 400010, China.
url: en.keruinh.com

Nanjing, China. Nanjing Pharmaceutical Co. Ltd, 26 Xingang Rd, Economic & Technological Development Zone, Nanjing, China.

Nanjing Baijingyu, Philipp. See *Global Pharmatrade, Philipp* and *Goodfellow, Philipp.*

Nanjing Hencer, Philipp. See *Goodfellow, Philipp.*

Nanjing Hencer, Thai. See *Neopharm, Thai.*

Nanmei, China. Nanmei Pharmaceutical Co. Ltd, Dalian, China.

Nanshaolin, China. Nanshaolin Pharmaceutical Co. Ltd, Fujian, China.

Nanxin, China. Nanxin Pharmaceutical Co. Ltd, Guangzhou International Trade Center West Tower, Sports East Rd, Guangzhou 510620, China.
url: www.gznanxin.com

Nanyang Tianheng, China. Nanyang Tianheng Pharmaceutical Co. Ltd, Beijing, China.

Nanyue, China. Nanyue Pharmaceutical Co. Ltd, 16 Guanlan Hedong Industrial Park, Bao'an, Shenzhen, Guangdong, 518100, China.
url: www.scpharm.com.cn

Napiers, UK. Napiers The Herbalists (Wholesale), 24 Tennant St, Edinburgh, EH6 5ND, UK.

Napp, Cz. See *Mundipharma, Cz.*

Napp, Gr. See *Napp, UK.*

Napp, Hong Kong. See *Jacobson, Hong Kong.*

Napp, Irl. See *Mundipharma, Irl.*

Napp, Port. See *Napp, UK.*

Napp, UK. Napp Pharmaceuticals Ltd, Cambridge Science Park, Milton Rd, Cambridge, Cambridge hire, CB4 0GW, UK.
url: www.napp.co.uk

Naprod, Philipp. See *Ambica, Philipp.*

Naprod, Thai. See *Atlanta, Thai.*

Narco-Med, Denm. See *Organon, Denm.*

Nastech, Israel. See *Tzamal, Israel.*

Nat Druggists, S.Afr. National Druggists (Pty) Ltd, P.O. Box 3253, Durban 4000, South Africa.

Natal Bioproducts, S.Afr. Natal Bioproducts Institute, Private Bag X9043, Pinetown 3600, South Africa.
url: www.nbi-kzn.org.za

Natali, Canad. Natali Products Import Co Inc., Unit 11, 1181 Finch Ave W, Toronto, Ontario, M3J 2V8, Canada.

Natco, India. Natco Pharma Ltd, Natco House, Road No 2, Banjara Hills, Hyderabad 500 033, India.

Natco, Thai. See *United Medical, Thai.*

Nathura, Ital. Nathura S.r.l., Via Meucci 14, 42027 Montecchio Emilia (RE), Italy.
url: www.nathura.com

National Diagnostic, Austral. National Diagnostic Products (Australia) P/L, 7-9 Merriwa St, Gordon, NSW 2072, Australia.
url: www.biodiagnostics.com

National Enzyme, Ukr. See *Pharm Union, Ukr.*

National Vitamin, USA. National Vitamin Co. Inc., 2075 West Scranton Ave, Parterville, CA 93257, USA.
url: www.nationalvitamin.com

Natiris, Venez. Laboratorios Natiri's C.A., Calle 25 entre carrera 21 y 22, Piso 5 Ctra Comercial, Cosmo Barquisimeta, Lara, Venezuela.

Nativelle, Fr. See *Procter & Gomble, Fr.*

Nativelle, Ital. See *Procter & Gomble, Ital.*

Nativelle, Switz. See *Interdelta, Switz.*

Natrahealth, UK. Natrahealth Ltd, Omicron House, Fircroft Way, Edenbridge, Kent, TN8 6EL, UK.
url: www.natrahealth.com

Natrapharm, Philipp. Natrapharm Inc., The Patriot Bldg, Km 18 West Service Rd, South Luzon Expressway, Parañaque City, Philippines.

Natren, USA. Natren Inc., 3105 Willow Lane, Westlake Village, CA 91361, USA.
url: www.natren.com

Nattermann, Ger. See *Cassella-med, Ger.*

Nattermann, Neth. See *Sanofi-Aventis, Neth.*

Nattermann, Pol. See *Sanofi-Aventis, Pol.*

Nattermann, Rus. See *Sanofi-Aventis, Rus.*

Nattermann, S.Afr. See *Sanofi-Aventis, S.Afr.*

Nattermann, Spain. Nattermann, Avda de Leganes 62, Alcorcon, 28925 Madrid, Spain.

Nattermann Tee-Arznei, Ger. See *Cassella-med, Ger.*

Natufarma, Arg. Lab. Natufarma, Av. Cordoba 1745, 3080 Esperanza, Santa Fe, Argentina.
url: www.natufarma.com.or

Natumin, Hung. See *Natumin, Swed.*

Natumin, Malaysia. See *Setia, Malaysia.*

Natumin, Pol. See *Krotex, Pol.*

Natumin, Singapore. See *Alcare, Singapore.*

Natumin, Swed. Natumin Pharma AB, Huskvarna, Sweden.
url: www.natumin.com

Natur Produkt, Pol. Natur Produkt Zdrovit Sp. zo.o., ul. Nocznickiego 31, 01-918 Warsaw, Poland.
url: www.naturprodukt.pl

Natur Produkt, Rus. Natur Produkt, Koryakova 18, 194037 Saint-Petersburg, Russia.

Natura, India. Natura Softcaps Pvt Ltd, India.

Naturactive, Fr. Naturactive Laboratoires, Pierre Fabre, 29 av. du Sidobre, 81106 Castres cdx, France.
url: www.pierre-fabre.com

Natural Balance, Canad. Natural Balance, 4672 Adelaide St, Port Alberni, British Columbia, V9Y 6N4, Canada.

Natural Factors, Canad. Natural Factors Nutritional Products Ltd, 3655 Bonneville Place, Burnaby, British Colombia, V3N 4S9, Canada.

Natural Life, Arg. Natural Life S.A., Tucuman 3516, 1189 Buenos Aires, Argentina.

Natural Media, Thai. Natural Media Co. Ltd, 68/1 Yenakas 2, Chongnonsee, Yannawa, Bangkok 10120, Thailand.

Natural San, Arg. Natural San SRL, Loyola 465, 1414 Buenos Aires, Argentina.

Natural Touch, UK. Natural Touch Ltd, 7 Dragoon House, Hussar Court, Brambles Farm, Waterlooville, Hampshire, PO7 7SE, UK.

Natural Wealth, Hong Kong. See *Winsor, Hong Kong.*

Naturale, Philipp. Naturale Laboratories Inc., 73 Sct Fernandez St, Brgy Laging Handa, Quezon City, Philippines.

Naturally Vitamins, USA. See *Marlyn, USA.*

Naturarzneimittel, Ger. Naturarzneimittel Regneri GmbH & Co. KG, Carl-Zeiss-Str. 4, 76275 Ettlingen, Germany.

Naturatec, Canad. Naturatec (1979) Ltd, 15 230 Principale, St-Sauveur-des-Monts, Quebec, J0R 1R0, Canada.

Naturbec, Canad. Herbages Naturbec Ltee, 1060 Place Verner, Laval, Quebec, H7E 4P2, Canada.

Natur-Drogeriet, Denm. Natur-Drogeriet A/S, Nydamsvej 13-15, 8362 Hørning, Denmark.

Nature Made, Canad. See *Pharmavite, Canad.*

Natures Aid, UK. Natures Aid Health Products, St Georges Park, Kirkham, Preston, Lancashire, PR4 2DQ, UK.

Natures Blend, USA. Nature's Blend
url: www.naturesblend.com

Nature's Bounty, USA. Nature's Bounty Inc., P.O. Box 801612, Boca Raton, FL 33481, USA.
url: www.nbty.com

Natures Care, Singapore. See *Pharmatech, Singapore.*

Natures Cure, Canad. See *Natures Cure, USA.*

Natures Cure, USA. Nature's Cure Inc., 5560 Golden Gate Ave, Oakland, CA 94618-2111, USA.

Natures Gate, Canad. See *Natures Gate, USA.*

Natures Gate, USA. Nature's Gate Herbal Cosmetics, 9200 Mason Ave, Chatsworth, CA 91311, USA.

Natures Own, Austral. See *Sanofi-Aventis, Austral.*

Natures Peak, Canad. Nature's Peak 2007 Ltd, 17724-94 Ave, Edmonton, Alberta, T5T 3G8, Canada.

Natures Remedies, UK. Natures Remedies Ltd, P.O. Box 233, Amersham, Buckinghamshire, HP6 5JA, UK.

Natures Sunshine, Canad. See *Natures Sunshine, USA.*

Natures Sunshine, USA. Nature's Sunshine Products Inc., 1655 N Main St, Spanish Fork, Utah, 84660-1007, USA.

Natures Way, Austral. Nature's Way, 18 Jubilee Ave, Warriewood, NSW 2102, Australia.
url: www.naturesway.com.au

Natures Way, Canad. See *Natures Way, USA.*

Nature's Way, Philipp. See *Sonix, Philipp.*

Natures Way, USA. Nature's Way, 10 Mountain Springs Parkway, Springville, UT 84663, USA.
url: www.naturesway.com

Naturest, Hong Kong. Naturest Co. Ltd, Suite 2508, Bank of America Tower, 12 Harcourt Rd Central, Hong Kong.

Naturex, Mex. See *Maver, Mex.*

Naturfarm, Ukr. ZAO Naturfarm, Pushcha-Voditsa Street, 30A, Kiev, 04075, Ukraine.
url: www.naturfarm.kiev.ua

Naturissima, Venez. Productos Naturissima de Venezuela, Calle del Arenal Edif. Biotech, Urb. La Trinidad, Caracas, Venezuela.

Naturkost, Norw. Naturkost S Rui AS, Postboks 3063, 1506 Moss, Norway.
url: www.naturkost.no

Naturland, Hung. Naturland, Csillagvirág u 8, 1106 Budapest, Hungary.

Naturmed, Ital. Naturmed 2000 S.r.l., Via Prov.le 33 (Resid. Oasi), 19030 Castelnuovo Magra (SP), Italy.

Naturo Aid, Canad. Naturo Aid Pharmaceuticals Inc., 302-20285 Stewart Crescent, Maple Ridge, British Columbia, V2X 8G1, Canada.
url: www.naturoaid.com

Naturopathica, Austral. Naturopathica, P.O. Box 7096, Sydney, NSW 2001, Australia.
url: www.naturopathica.com.au

Naturopathica, UK. Naturopathica Ltd, Lloyds Court, Suite 307, 1 Goodmans Yard, London, E1 8AT, UK.
url: www.skindoctors.co.uk

Naturpharm, Canad. Naturpharm Inc., 63 Hooper Rd, Barrie, Ontario, L4M 9S3, Canada.

Naturpharma, Switz. Naturpharma SA, 5d route des Jeunes, Case postale 8, 1211 Geneva 26, Switzerland.

Naturprodukt, Cz. Naturprodukt CZ sro, Mládežnická 9, 736 01 Havířov, Czech Republic.
url: www.naturpro.cz

Naturprodukt, Hung. Naturprodukt Kft, DEPO Pf: 8, 2046 Törökbálint, Hungary.

Naturprodukt, Ukr. Naturprodukt-Vega Ltd, Gaevaya Street, 48A, Ternopol, 46000, Ukraine.
url: www.naturprodukt.ua

Naturwaren, Cz. Naturwaren OHG, Czech Republic.

Naturwaren, Ital. Naturwaren Italia S.r.l., Centro il Girasole Unità 2.07a, 20084 Lacchiarella (MI), Italy.

Naturwaren, Ukr. See *Naturprodukt, Ukr.*

Natysal, Spain. Naytsal, C/ Molino 2, Meco, 28880 Madrid, Spain.
url: www.natysal.com

Navamedic, Cz. See *Navamedic, Norw.*

Navamedic, Denm. See *Navamedic, Norw.*

Navamedic, Fin. See *Navamedic, Norw.*

Navamedic, Neth. See *Navamedic, Norw.*

Navamedic, Norw. Navamedic ASA, Fornebuveien 42-44, P.O. Box 107, N-1325 Lysaker, Norway.
url: www.navamedic.com

Navamedic, Pol. See *Grunenthal, Pol.*

Navamedic, Port. See *Navamedic, Norw.*

Navarro, Spain. See *Ciclum, Spain.*

Naveh, Israel. Naveh Pharmacy, Yad Harutzim 19, Netanya, Israel.

Naveh, Philipp. See *Wellness, Philipp.*

Navi, Fr. Navi Pharma, Les Horizons bleu, 10 rue des Dauphins, 06600 Antibes, France.

Navidea, USA. Navidea Biopharmaceuticals, 425 Metro Place North, Suite 300, Dublin, OH 43017-1367, USA.
url: www.navidea.com

NB, India. NB Healthcare, SCO 29 3rd Floor, Phase 9 Industrial Aea, Mohali, Punjab, India.

NBF, Ital. N.B.F. Italia S.r.l., Corso di Porta Vittoria 14, 20122 Milan (MI), Italy.

NBI, S.Afr. See *Natal Bioproducts, S.Afr.*

NBTY, Ukr. See *Nature's Bounty, USA.*

NCI, USA. See *Nellson, USA.*

NCPC, China. North China Pharmaceutical Group, East Street East 6, Hoping East Rd, Shijiazhuang 050011, China.
url: www.ncpc.com.cn

NCPC, Philipp. See *DNBG, Philipp.*

NCSN, Ital. NCSN Farmaceutici S.r.l., Via Svetonio 6, 00136 Rome (RM), Italy.

Neaclear, Singapore. See *BlissMed, Singapore.*

Neat Feat, NZ. Neat Feat Products Ltd, P.O. Box 65-256, Mairangi Bay, Auckland, New Zealand.
url: www.neatfeat.co.nz

Nebo, Denm. See *Salfarm, Denm.*

Nebo, Hong Kong. See *Zuellig, Hong Kong.*

Nebo, Norw. See *Andersen, Norw.*

Nebo, Philipp. See *A-Z, Philipp.*

Nebo, Thai. See *Natural Media, Thai.*

Nebo, Venez. See *PG, Venez.*

Neckerman, Braz. Neckerman Indústria Farmacêutica Ltda, Rua das Perobeiras 157, 05879-470 São Paulo, SP, Brazil.

Nectar, India. Nectar Lifesciences Ltd (Neccare), SCO 38-39, Sector 9D, Chandigarh 160 009, India.
url: www.neclife.com

Nectar, Thai. See *Community Pharmacy, Thai.*

Neda, Ger. See *Novartis, Ger.*

Nederlands Vaccin Instituut, Neth. Het Nederlands Vaccin Instituut, Antonie van Leeuwenhoeklaan 9-11, Postbus 457, 3720 AL Bilthoven, Netherlands.
url: www.nvi-vaccin.nl

Nefa, Turk. Nefa İlaç Gida Sağlick ve Kozmetik Ürünleri San. Tic. A.Ş., Darülaceze Cad., Perpa Ticaret Merkezi B Blok. K:11 No: 1746, Okmeydani, İstanbul, Turkey.
url: www.nefa.com.tr

Nefax, Spain. See *Pfizer, Spain.*

Negma, Belg. See *Vitalpharma, Belg.*

Negma, Fr. Laboratoires Negma-Lerads, Imm Strasbourg, av de l'Europe, Toussus-le-Noble, 78771 Mogny-les-Hameaux cdx, France.

Negma, Hung. See *Ubepharm, Hung.*

Negma, Israel. See *Pharmateam, Israel.*

Negma, Spain. See *Negma, Fr.*

NEGPF, China. Northeast General Pharmaceutical Factory, 37 North St, West District Heavy Industries, Shenyang City 110026, China.

Negrin, Gr. Negrin Anna H, Fokidos 59, 11527 Athens, Greece.

Neiadas (Νειάδας), Gr. See *Niadas, Gr.*

Neiss, India. Neiss Labs Ltd, 523-524 Laxmi Plaza, Laxmi Industrial Estate, Link Rood, Andheri (West), Mumbai 400 053, India.
url: www.neisslabs.com

Neitum, Fr. Neitum (Lab), 43 rue des Hérideaux, 69008 Lyon, France.

Neleta, Gr. Neleta Ltd, Omonoia Sq. 12, 10431 Athens, Greece.

Nella, UK. Nella Pharmaceutical Products Ltd, Kincraig Court, Kincraig Rd, Blackpool, Lancashire, FY2 0FY, UK.

Nellson, USA. Nellson Nutraceutical, 5801 Ayala Ave, Irwindale, CA 91706, USA.

Nelson, UK. A Nelson & Co. Ltd, Broadheath House, 83 Parkside, London, SW19 5LP, UK.
url: www.nelsonshomoeopathy.co.uk

Neo Abello, Ital. See *ALK, Ital.*

Neo Dermos, Arg. Neo Dermos S.R.L., Francisco Bilbao 1927, 1406 Buenos Aires, Argentina.

Neo Laboratories, UK. See *Alinter, UK.*

Neo Química, Braz. Laboratório Neo Química Comércio e Indústria Ltda, Rua VPR 1 Quadra 2-A, Modulo 4 DAIA, 75133-600 Anapolis, GO, Brazil.
url: www.neoquimica.com.br

Neocare, Belg. NeoCare, Esplanade Heysel 22b, 1020 Brussels, Belgium.
url: www.neocare.be

Neocare, Neth. Neocare BV, Nieuwe Donk 3, 4879 AC Etten-Leur, Netherlands.

Neoceuticals, UK. Neoceuticals, 3 The Grange, Flaxby, Knaresborough, North Yorkshire, HG5 0RJ, UK.
url: www.neo-ceuticals.com

Neocorp, Ger. Neocorp AG, Am Weidenbach 6, 82362 Weilheim, Germany.
url: www.neocorp.de

Neo-Derm, Philipp. See *Britton, Philipp.*

Neo-Farmaceutica, Port. Neo-Farmacêutica, Lda, Avenida D João II, 1990-090 Lisbon, Portugal.
url: www.neo-farmaceutica.pt

Neolab, Canad. Neolab, 5476 Upper Lachine Rd, Montreal, Quebec, H4A 2A4, Canada.

Neolab, UK. Neolab Ltd., 57 High St, Odiham, Hampshire, RG29 1LF, UK.

Neo-Life, Austral. See *GNLD, Austral.*

Neomed, Cz. Neomed sro, Sodomkova 1474/6, 102 00 Prague 10, Czech Republic.

Neon, India. Neon Laboratories Ltd, 140 Damji Samji Industrial Complex, Mahakali Caves Rd, Andheri (East), Mumbai 400 093, India.
url: www.neongroup.com

Neon, Philipp. See *Elin, Philipp.*

Neon, Ukr. Neon Laboratories Ltd., bulv. Lesi Ukrainki, d. 24, kv. 210, Kiev, 01133, Kiev,, Ukraine.
url: www.neongroup.com

Neopharm, Israel. Neopharm Ltd, 8 Hashiloach St, P.O. Box 7063, Petach Tikva 49170, Israel.
url: www.neopharmisrael.com

NeoPharm, Singapore. See *Zyfas, Singapore.*

Neopharm, Thai. Neopharm Co. Ltd, 13/10 Moo 15, Talingchan-Suphanburi, Bangmaenang, Bangyai, Nonthaburi 11140, Thailand.
url: www.neopharms.com

Neopharma, Denm. See *Neopharma, Swed.*

Neopharma, Fin. See *Neopharma, UK.*

Neopharma, Ger. See *Solvay, Ger.*

Neopharma, Hung. Neopharma, Hungary.

Neo-Pharma, India. Neo-Pharma Pvt Ltd, Kasturi Building, 5th Floor, J. Tata Rd, Mumbai 400 020, India.

Neopharma, Swed. NeoPharma AB, Fyrisborgsgatan 3, Box 22, 751 03 Uppsala, Sweden.
url: www.neopharma.se

Neopharma, UK. NeoPharma Ltd, 57 High St, Odiham, Hampshire, RG29 1LF, UK.

Neopharma, Venez. Comercializadora Neopharma de Venezuela C.A., Av Fco Miranda e Av Elice y C La Joya, Ctro P Miranda, Piso 4 Of. 4-B Chacao, 1010-A Caracas, Venezuela.

Neopharmed, Ital. Neopharmed S.p.A., Via Vitorchiano 151, 00100 Rome (RM), Italy.
url: www.neopharmed.it

Neos-Donner, Ger. See *Optimed, Ger.*

NeoStrata, USA. NeoStrata Co. Inc., 307 College Road East, Princeton, NJ 08540, USA.
url: www.neostrata.com

Neoteric, Canad. See *Neoteric, USA.*

Neoteric, USA. Neoteric Cosmetics Inc., 4880 Havana St, Denver, Colorado, 80239-2416, USA.

Neovita, Ital. Neovita S.a.s. di G. Pirotta & C., Via Solferino 4, 21040 Uboldo (VA), Italy.

Nepalm, Fr. Laboratoires Nepalm Sarl, 136 bis, av des Frères-Luminière, 69008 Lyon, France.

Nepentes, Cz. See *Nepentes, Pol.*

Nepentes, Pol. Nepentes Sp. zo.o., ul. Gwiaździsta 69 F, 01-651 Warsaw, Poland.
url: www.nepentes.com.pl

Nepenthes, Fr. Laboratoires Nepenthes, 163/183 rue Leon Jouhaux, 78500 Sartrouville, France.
url: www.nepenthes.net

Nephron, USA. Nephron Pharmaceuticals Corp., 4121 SW 34th St, Orlando, FL 32811, USA.
url: www.nephronpharm.com

Nephrotech, Gr. Nephrotech SA, Parnithos 44, 144 52 Metamorfosi, Greece.

Nephro-Tech, USA. Nephro-Tech, Inc., P.O. Box 16106, Shawnee, KS 66203, USA.
url: www.nephrotech.com

Neptunus, China. Neptunus Pharmaceutical Co Ltd, Science & Technology Park, Nanshen District, Shenzhen 518057, China.
url: www.neptunus.com

Nes, Israel. Nes, Israel.

Nestle, Arg. Nestlé Argentina S.A., Av. del Libertador 1855, 1836 Vicente Lypez, Buenos Aires, Argentina.
url: www.nestle.com.ar

Nestle, Austral. Nestle Australia Ltd, 1 Homebush Bay Drive, Rhodes, NSW 2138, Australia.
url: www.nestle.com.au

Nestle, Braz. Nestle Indl. e. Coml. Ltda, Av. das Nações Unidas 12495, 04578-902 São Paulo, SP, Brazil.
url: www.nestle.com.br

Nestle, Canad. Nestle Canada Inc., 25 Sheppard Ave W, North York, Ontario, M2N 6S8, Canada.
url: www.nestle.ca

Nestle, China. Nestle China Ltd, Level 9 Tower B LSH PLaza, 8 Wangjing Ave, Chaoyang, Beijing, 100102, China.
url: www.nestle.com

Nestle, Cz. Nestlé Food sro, Prague, Czech Republic.

Nestle, Denm. Nestlé Nutrition a/s, Dampfaergevej 28, Amerikakaj, 2100 Copenhagen Ø, Denmark.
url: www.nestlenutrition.com

Nestle, Fin. Suomen Nestlé Oy, Huopalahdentie 24, 00350 Helsinki, Finland.
url: www.nestle.fi

Nestle, Fr. Nestlé, 7 bd Pierre-Carle, B.P. 900, Noisiel, 77446 Marne-la-Vallée cdx 2, France.
url: www.nestle.fr

Nestle, Hong Kong. Nestle Hong Kong Ltd, 28/F, PCCW Tower, Taikoo Place, 979 King's Rd, Quarry Bay, Hong Kong.
url: www.nestle.com

Nestle, Indon. Nestlé Indonesia PT, Arkadia Office Park, Jl Let Jend TB, Simatupang Kav 88, Jakarta 12520, DKI Jaya, Indonesia.

Nestle, Irl. See *Baxter, Irl.*

Nestle, Israel. See *Megapharm, Israel.*

Nestle, Ital. Nestlé Italiana S.p.A., Viale G. Richard 5, 20143 Milan (MI), Italy.
url: www.nestle.it

Nestle, Malaysia. Nestlé (Malaysia) Bhd, Nestle House, 4, Lorong Pesiaran, 46918 Petaling Jaya, Selangor, Malaysia.
url: www.nestle.com.my

Nestle, Mex. Nestle Mexico S.A. de C.V., Av Ejercito Nacional No. 453, Col. Granada, Deleg. Miguel Hidalgo, 11520 Mexico D.F., Mexico.
url: www.nestle.com.mx

Nestle, Philipp. Nestlé Philippines Inc., 31 Plaza Drive, Rockwell Ctr, Makati City, Philippines.

Nestle, Port. Nestlé Portugal, SA, Rua Alexandre Herculano 8-8A, 2799-554 Linda-a-Velha, Portugal.
url: www.nestle.pt

Nestle, Rus. Nestle Food OOO, Paveletskaya pl. 2, Sr.1, 115054 Moscow, Russia.
url: www.nestle.ru

Nestle, Singapore. Nestle Singapore (Pte) Ltd, 200 Cantonment Rd, 03-01 Southpoint, S 089763, Singapore.

Nestle, Switz. Nestlé Suisse AG, Case postale 352, 1800 Vevey, Switzerland.
url: www.nestle.ch

Nestle, Thai. See *Zuellig, Thai.*
url: www.nestle.com

Nestle, Turk. Nestlé Gida Sanayi AS, Nurol Plaza A Blok Kat 6, Buyukdere Caddesi 255, Maslak/Sisli, 34398 Istanbul, Turkey.
url: www.nestle.com

Nestle, UK. Nestlé Healthcare Nutrition, St George's House, Park Lane, Croydon, Surrey, CR9 1NR, UK.
url: www.nestlenutrition.co.uk

Nestle, USA. Nestle Clinical Nutrition, 800 North Brand Blvd, Glendale, CA 91203, USA.
url: www.nestle.com

Nestle, Venez. Nestle Venezuela S.A., Edificio Polar, Plaza Venezuela, Apartado 3367, Caracas 1010-A, Venezuela.
url: www.nestle.com.ve

Nestle Clinical, Irl. See *Baxter, Irl.*

Nestle Proteika, Fr. See *Proteika, Fr.*

Nestor, India. Nestor, B-24/3, Okhla Industrial Area Phase II, New Delhi 110 020, India.
url: www.nestorpharma.com

Nestor, Philipp. See *International Apex, Philipp* and *Pharmawealth, Philipp.*

Netpharma, Swed. See *Ivax, Swed.*

Nettopharma, Denm. See *Nycomed, Denm.*

Network Health & Beauty, UK. Network Health & Beauty, Network House, Lynchford Lane, Farnborough, Hampshire, GU14 6JF, UK.
url: www.networkhb.com

NeuPharma, Thai. NeuPharma (Thailand) Co. Ltd, 165 Soi Rajvithi, 6 Rajvithi Rd, Samsennai, Payathai Bangkok, 10400, Thailand.

Neuraxpharm, Denm. See *Neuraxpharm, Ger.*

Neuraxpharm, Ger. neuraxpharm Arzneimittel GmbH & Co. KG, Elisabeth-Selbert-Str. 23, 40764 Langenfeld, Germany.
url: www.neuraxpharm.de

Neurim, Austria. See *Nycomed, Austria.*

Neurim, Cz. See *Neurim, UK.*

Neurim, Denm. See *Nycomed, Denm.*

Neurim, Hung. See *Nycomed, Hung.*

Neurim, Irl. See *Neurim, UK.*

Neurim, Israel. Neurim Pharmaceuticals Ltd, 27 Habarzel St, Tel-Aviv, 69710, Israel.
url: www.neurim.com

Neurim, Norw. See *Nycomed, Norw.*

Neurim, Pol. See *Lundbeck, Pol.*

Neurim, Port. See *Nycomed, Denm.*

Neurim, Switz. Neurim Pharmaceuticals AG, Baarerstrasse 135 Zug, CH-6301, Switzerland.
url: www.neurim.com

Neurim, Thai. See *DKSH, Thai.*

Neurim, UK. RAD Neurim Pharmaceuticals EEC Ltd, 1 Forbury Square, The Forbury, Reading, Berkshire, RG1 3EB, UK.
url: www.neurim.com

Neuro Hexal, Ger. See *Hexal, Ger.*

Neurogard, Spain. See *MSD, Spain.*

NeuroGenesis, USA. NeuroGenesis/Matrix Tech. Inc., 120 Park Ave, League City, TX 77573, USA.
url: www.neurogenesis.com

NeurogesX, Port. See *NeurogesX, UK.*

NeurogesX, UK. NeurogesX UK Ltd, 265 Strand, London, WC2R 1BH, UK.

NeurogesX, USA. NeurogesX Inc., 2215 Bridgepointe Parkway, Suite 200, San Mateo, CA 94404, USA.
url: www.neurogesx.com

Neuropharma, Arg. Neuropharma, Pringles 10 Piso 3, 1183 Buenos Aires, Argentina.

Neusc, Spain. Neusc, Ctra S. Hipolit KM 1, C/Sau 1, Gurb-Vic, 08503 Barcelona, Spain.

Neutrogena, Fr. See *Ethicon, Fr.*

Neutrogena, Israel. See *Randi, Israel.*

Neutrogena, Philipp. See *Johnson & Johnson, Philipp.*

Neutrogena, UK. See *Johnson & Johnson, UK.*

Neutrogena, USA. Neutrogena Corp., 5760 W 96th St, Los Angeles, CA 90045-5595, USA.
url: www.neutrogena.com

Neutrogena Dermatologicals, USA. See *Neutrogena, USA.*

Neutron Technology, USA. See *Micron, USA.*

Nevada, Swed. Nevada Pharma AB, Wallingatan 18, 111 24 Stockholm, Sweden.
url: www.nevadapharma.se

Neves, Port. Laboratório J. Neves, Lda, Parque Industrial do Seixal, 2840-069 Paio Pires, Portugal.

Nevzat, Rus. See *Nevzat, Turk.*

Nevzat, Turk. Mustafa Nevzat İlaç San. A.Ş., Pak İş Merkezi, Prof. Dr. Bülent Tarcan Sok. No: 5/1, Gayrettepe, İstanbul, 34349, Turkey.
url: www.mn.com.tr

Nevzat, Ukr. See *Asfarma, Ukr.*

New Asiatic, China. New Asiatic Pharmaceutical Co. Ltd, 978 Chuansha Road, Pudong, Shanghai, 201209, China.
url: www.xinyapharm.com

New Century, Thai. See *Schumit, Thai.*

New Era, Canad. See *Delano, Canad.*

New Farma, Ital. New Farma Soc. Coop. a.r.l., Via Guglielmino 62/D, 95030 Tremestieri (CT), Italy.

New Hualian, China. New Hualian Pharmaceutical Factory Co. Ltd, 217 Folk Rd, Spark Development Zone, Pudong, Shanghai 201419, China.

New Life, Arg. Lab. New Life S.R.L., Ituzaingo 2156, 5500 Mendoza, Argentina.

New Life, India. New Life Styles, Hill Cart Rd, Near SBI Mangaldeep, 734 401, India.

New Life, Thai. See *Far East, Thai.*

New Marketlink, Philipp. New Marketlink Pharmaceutical Corp., TAO Corporate Ctr, 2291 Don Chino Roces Ave, Makati City, Philippines.

New Pharma, Venez. New Pharma C.A., Av. Bolivar Quinta Francelis, Piso 1 Oficina 6, El Paraíso 1020, Caracas, Venezuela.

New Research, Ital. New Research S.r.l., Via della Tenuta di Torrenova 142, 00133 Rome (RM), Italy.

New River, USA. See *Shire, USA.*

New Smart, Philipp. New Smart Formulae Trading Corp., Room 505, Cedar Executive Bldg II, 26 Timog Ave cor Sct Tobias St, Quezon City, Philippines.

New York Blood Center, USA. New York Blood Center Inc., 45-01 Vernon Blvd, Long Island City, NY 11101, USA.
url: nybloodcenter.org

New York Chemical, Thai. New York Chemical, 4 Soi Sailom 1 Phaholyothin, Samsaen Nai Phaya, Bangkok 10400, Thailand.

Newcharoen, Thai. Newcharoen Pharmaceuticals Ltd, 1/5 Moo 13 Klongsam Rd, Klongluang, 12120 Pathumthani, Thailand.
url: www.newcharoen.com

Newco, Canad. Newco Enterprises Inc., 402 5723 10th Street, Calgary, Alberta, T2E 8W7, Canada.

NewFaDem, Ital. New.Fa.Dem. Srl Farmaceutici e Chimici, Zona Industriale ASI, Via Ferrovie dello Stato 1, 80014 Giugliano (NA), Italy.

Newmed, Gr. Lab. Newmed Pharmaceuticals Ltd, Avenue Kifisia 32, 151 25 Marousi, Greece.

Newport, Canad. See *Newport, Irl.*

Newport, Ger. See *Newport, Irl.*

Newport, Hong Kong. See *Great Eastern, Hong Kong.*

Newport, Irl. Newport Pharmaceuticals Ltd, Frank Maas House, Swords Business Park, Swords, Co. Dublin, Ireland.
url: www.newport-pharma.com

Newport, Philipp. See *Marketlink, Philipp.*

Newport Synthesis, Irl. See *Newport, Irl.*

Newton, UK. See *Newton-Corbett, UK.*

Newton-Corbett, UK. Newton-Corbett Ltd, 2 Mansfield Rd, South Croydon, Surrey, CR2 6HN, UK.
url: www.newton-corbett.co.uk

Newtramax, India. Newtramax, Chaman Vatika, Nahan Rd, Puruwala, Sirmour 173 025, India.

Nexis, Spain. Nexis Farmaceutica, Principe de Vergara 112, 28001 Madrid, Spain.
url: www.nexisfarmaceutica.com

Nexmed, Hong Kong. Nexmed (Asia) Ltd, Rm 2208, 22/F Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.

Nexo, Arg. Laboratorio Nexo Pharmaceutical Group SA, Ponferrada 285, 1708 Moron, Buenos Aires, Argentina.

Nexstar, Austral. See *Gilead, Austral.*

Nexstar, Belg. See *Pfizer, Belg.*

Nexstar, Denm. See *Orphan, Denm.*

Nexstar, Ger. See *Gilead, Ger.*

Nexstar, Hong Kong. See *IDS, Hong Kong.*

Nexstar, Irl. See *Gilead, UK.*

Nexstar, Israel. See *Neopharm, Israel.*

Nexstar, Ital. See *Gilead, Ital.*

Nexstar, Neth. See *Gilead, Neth.*

Nexstar, Rus. See *Gilead, Rus.*

Nexstar, Thai. See *Siam Pharm, Thai.*

Nexstar, UK. See *Gilead, UK.*

Nexstar, USA. See *Gilead, USA.*

Next Wave, USA. Next Wave Pharmaceuticals Inc., 20450 Stevens Creek Blvd, Suite 150, Cupertino, CA 95014, USA.

NextChem, Philipp. NextChemical Enterprises, Rm 409 Integrated Professionals Office Bldg, 14 Quezon Ave, Quezon City, Philippines.

NextWave, USA. NextWave Pharmaceuticals Inc., 20450 Stevens Creek Blvd, Suite 150, Cupertino, CA 95014, USA.
url: www.nextwavepharma.com

Nexus, Gr. Nexus Medicals AE, Markopoulou-Sounion Ave, 190 03 Athens Markopoulo, Greece.

Nexus, India. Nexus Pharma, 201 Royale Manor, B/s Rangwala Towers, Nr Law Garden, Ellisbridge, Ahmedabad, 380 006, India.
url: www.nexuspharma.com

Nezel, Spain. See *Solvay, Spain.*

NFI, USA. Nutrition & Fitness Inc., USA.
url: www.nfiproducts.com

NHS, Fr. NHS, 1-7 rue du Jura, Silic 528, 94633 Rungis cdx, France.

Nhwa, China. Nhwa Pharmaceutical Co Ltd, Democratic South Rd, Xuzhou, Jiangsu, China.
url: www.nhwa-group.com

Niadas, Gr. Niadas & Sons S.A., P.O.Box 59, 190 02 Paiania, Greece.

Niagara, Canad. Niagara Pharmaceuticals Inc., 60 Innovation Dr, Flamborough, Ontario, L9H 7P3, Canada.

Niarmedik Plyus, Ukr. See *Alex Pharm, Ukr.*

Nice Pak, Austral. Nice Pak Products, 2-4 Sullivan St, Moorabbin, Vic 3189, Australia.
url: www.nicepak.com.au

Niche, Denm. Niche Pharma, Tvedangen 225, 2730 Herlev, Denmark.
url: www.nichepharma.dk

Niche, Irl. Niche Generics Ltd, Unit 5, Baldoyle Industrial Estate, Dublin 13, Ireland.
url: www.nichegenerics.com

Niche, Singapore. See *Pharma 2000, Singapore.*

Niche, USA. Niche Pharmaceuticals Inc, 200 N Oak St, P.O. Box 449, Roanoake, TX 76262, USA.
url: www.niche-inc.com

Nichi-Iko, Jpn. Nichi-Iko Pharmaceutical Co. Ltd, 1-6-21, Sogawa, Toyama-shi, Toyama-ken, 930-8583, Japan.
url: www.nichiiko.co.jp

Nicholas, Austral. See *Roche, Austral.*

Nicholas, Fr. See *Roche Nicholas, Fr.*

Nicholas, Ger. See *Guerbet, Ger.*

Nicholas, Indon. Nicholas Laboratories PT, Jl Pulobuaran Raya, Block FF 12A, Kawasan Industri Pulo Gadung, Jakarta 13930, Indonesia.

Nicholas, Irl. See *Roche, Irl.*

Nicholas, Neth. See *Roche Consumer, Neth.*

Nicholas, Port. See *Martins & Fernandes, Port.*

Nicholas, Singapore. Nicholas Laboratories Pte Ltd, Singapore.

Nicholas, Swed. See *Meda, Swed.*

Nicholas, Switz. See *Pfizer, Switz.*

Nicholas, UK. See *Roche, UK.*

Nicholas Piramal, India. See *Piramal, India.*

Nicobrand, Austria. See *Nicobrand, UK.*

Nicobrand, Cz. See *Nicobrand, UK.*

Nicobrand, Denm. See *Orion, Denm.*

Nicobrand, Fin. See *UCB, Fin.*

Nicobrand, Gr. See *Nicobrand, UK.*

Nicobrand, Irl. See *Nicobrand, UK.*

Nicobrand, Neth. See *Nicobrand, UK.*

Nicobrand, Norw. See *UCB, Norw.*

Nicobrand, Pol. See *Nicobrand, UK.*

Nicobrand, UK. Nicobrand Ltd, 189 Castleroe Rd, Coleraine, BT51 3RP, UK.

Nicodent, Austral. See *Advil, Austral.*

Nicolich, Chile. See *Saval, Chile.*

Niconovum, Denm. See *Niconovum, Swed.*

Niconovum, Swed. Niconovum AB, Järnvägsgatan 13, 252 24 Helsingborg, Sweden.
url: www.niconovum.se

Nida, Singapore. See *Advanced, Singapore.*

Niddapharm, Ger. See *Stada, Ger.*

Niedermaier, Ger. Dr Niedermaier Pharma GmbH, Taufkirchner Str. 59, 85662 Hohenbrunn bei Munich, Germany.
url: www.niedermaier-pharma.de

Nigaard, Norw. Nigaard Pharma, Jernbaneg. 8, 2004 Lillestrøm, Norway.
url: www.nigaard.com

Nigaard, Swed. Nigaard Pharma AS, Polygonvägen 73, 187 66 Täby, Sweden.
url: www.nigaard.com

Nigy, Fr. Laboratoires Nigy, 6 av de l'Europe, B.P. 51, 78401 Chatou cdx, France.

Nigy, Singapore. See *Polymedic, Singapore.*

Nihon, Hong Kong. See *Eng An, Hong Kong.*

Nihon, Jpn. Nihon Pharmaceutical Co. Ltd, 9-8 Higashikanda 1-chome, Chiyoda-ku, Tokyo 101-0031, Japan.
url: www.nihon-pharm.co.jp

Nike-Med, Rus. Nike-Med, Prospekt Vernadskogo 8a, Russia.

Nikemei, China. Nikemei Pharmaceutical Co. Ltd, Zhongshan, China.

Nikken, Malaysia. See *Pharmaforte, Malaysia.*

Nikken, Thai. See *Masu, Thai.*

Nikkho, Braz. Química E Farmacêutica Nikkho do Brasil Ltda, Rua Jaime Perdigao 431-435, 21920-240 Ilha do Governador, RJ, Brazil.

Nikofarm, Gr. Nikofarm OEED Nikolakopoulos & Co, Koumoundourou 31, 10437 Athens, Greece.

Nikolakopoulos, Gr. A. Nikolakopoulos & Co. O.E, 115 Galatsiou Ave, 111 46 Athens, Greece.

Nikolakopoulos (Νικολακοπουλος), Gr. See *Nikolakopoulos, Gr.*

Ningguo Bangning, China. Ningguo Bangning Pharmaceutical Co. Ltd, Shanghai, China.
url: www.bangningpharma.com

Nion, USA. Nion Corp., 15501 First St, Irwindale, CA 91706, USA.

Nipro, China. Nipro Pharmaceutical Co. Ltd., China.

Nipro, Jpn. Nipro Pharma Corp., 2-2-7 Dosho-machi, Chuo-ku, Osaka 541-0045, Japan.
url: www.np.nipro-pharma.co.jp

Nipro Genepha, Jpn. Nipro Genepha Corp, 5-7, Minamisakaemachi, Kasukabe, Saitama, 344-0057, Japan.
url: www.nipro-genepha.co.jp

NIR, Ukr. OOO NIR, Kharkovskoe highway, 50, Kiev, 02160, Ukraine.
url: www.nir.com.ua

Nitec, Ger. Nitec Pharma GmbH, Joseph-Meyer-Str. 13-15, 68167 Mannheim, Germany.
url: www.nitecpharma.com

Nitec, Port. See *Nitec, Ger.*

Nitecs, Austral. Nitecs P/L, 4 Donald Street, Carlingford, NSW 2118, Australia.

Ni-The, Gr. Ni-The N. A. The Ophilis & Sons Ltd, 52 Psychari, 111 41 Athens, Greece.

Nitin, India. Nitin Pharmaceuticals Pvt Ltd, 92-93 Sector 3, HSIDC Industrial Area, G.T. Road, Karnal, HARYANA 132 001, India.
url: www.nitinpharma.com

Nitro Cadineur, India. Nitro Cadineur, 162 2nd Floor, Jeevan Nagar, Kilokari Ashram, New Delhi, 122 014, India.
url: www.nitrolifecare.com

Nitro Organics, India. Nitro Organics, 2 Mahabir Dal Market, Kanjpura Rd, Karnal, 132 001, India.

Nitten, Jpn. Nitten Eye Co., 76 Banchi, Nishisakurachou, Minami-ku, Nagoya, Japan.

Nitto, Jpn. Nitto Medic Co. Ltd, 1-17-24 Shinkawa, Chuo-ku, Tokyo 104-0033, Japan.

Nitto Denko, China. See *Nitto Denko, Jpn.*

Nitto Denko, Jpn. Nitto Denko Corp., 2-5-25 Umeda, Kita-ku, Osaka 530-0001, Japan.
url: www.nitto.com

Nixoderm, Malaysia. See *Summit, Malaysia.*

Nizhfarm, Ukr. Nizhfarm, Bolshaya Vasilkovskaya Street, 9/2, office 52, Kiev, 01004, Ukraine.
url: www.nizhpharm.ru

Nizhpharm, Rus. Nizhpharm OAO, 7 Salganskaya ul., GSP-459, 603950 Nizhny Novgorod, Russia.
url: www.nizhpharm.com

Nizpharm, Rus. See *Nizhpharm, Rus.*

NK, India. NK Pharma Industries, Plot No.2203, Phase IV G.I.D.C Industrial Area, Vatva, Ahmedabad 382 445, India.
url: www.nkpharmaindustries.com

NM, Denm. NM Pharma A/S, Overgaden neden Vandet 7, 1414 Copenhagen K, Denmark.

NM, Swed. See *Pfizer, Swed.*

Nnodum, USA. Nnodum Corp., P.O. Box 19725, Cincinnati, OH 45219, USA.
url: www.zikspain.com

Nobel, Canad. Nobel Pharm Enrg, 2615 pl. Chasse, Montreal, Quebec, H1Y 2C3, Canada.

Nobel, Jpn. Nobel Pharma Co. Ltd, 12-10 Nohonbashi-kobunacho, Chuo-ku, Tokyo 103-0024, Japan.
url: www.nobelpharma.co.jp

Nobel, Rus. Nobel Ilac San. ve Tic. A.S Rusya, Vavilova cad. 83/7, 117335 Moscow, Russia.
url: www.nobel.com.tr

Nobel, Turk. Nobel İlaç San. ve Tic. A.Ş., Barbaros Bulvarı No: 76-78, Beşiktaş, İstanbul, 34353, Turkey.
url: www.nobel.com.tr

Nobel, Ukr. Nobel Ilac Sanayii Ve Ticaret.A.S, Avtozavodskaya Street, 2, 8th floor, Kiev, 04074 , Ukraine.
url: www.nobel.com.ua

Nobipharm, Pol. Nobipharm Sp. zo.o., ul. Rydygiera 8, 01-793 Warsaw, Poland.
url: www.nobipharm.pol.pl

Nodysis, India. Nodysis Pharma Pvt Ltd, B-8 SKH Co Society, Jaydeep Nagar, Bhandup (E), Mumbai 400 042, India.

Noel, India. Noel, India.

Nogues, Fr. Laboratoires Noguès, 43 rue de Neuilly, 92000 Nanterre, France.

Nogues, Switz. See *Uhlmann-Eyraud, Switz.*

Noir, India. Noir Pharmaceuticals Pvt Ltd, 380/82 J. Sankersett Rd, Sankersett Smriti, Chira Bazar, Mumbai 00 020, India.

Nolt, Arg. Nolt SA, Cervipo 4671 Piso 4'1 C, 1425 Buenos Aires, Argentina.

Nolver, Venez. Nolver C.A., Mult.Empres.Este-To.Libertador Nucleo A, Pso.3-Of.32-A, Chacao, Caracas, Venezuela.

Nomax, USA. Nomax Inc., 40 North Rock Hill Rd, St Louis, MO 63119, USA.
url: www.nomax.com

Noos, Ital. Noos S.r.l., Via Campello Sul Clitunno 34/1, 00181 Rome (RM), Italy.

Nordcliff Thayer, USA. See *GSK Consumer, USA.*

Nordend, Ger. Nordend-Apotheke Dr. Wolfgang Hotz, Friedrich-Ebert-Platz 17, 64289 Darmstadt, Germany.

Nordia, Singapore. See *Zyfas, Singapore.*

Nordiatech, Denm. NorDiaTech A/S, Baldersbuen 29 F, 2640 Hedehusene, Denmark.
url: www.nordiatech.dk

Nordic, Canad. See *Sanofi, Canad.*

Nordic, Cz. Nordic Pharma sro, Nad Svahem 1766/6, 140 00 Prague 4, Czech Republic.
url: www.nordicpharma.com

Nordic, Fr. Nordic Pharma, 76 ave du Midi, Zl de Cournon, 63802 Cournon d'Auvergne, France.
url: www.nordicpharma.com

Nordic, Ger. Nordic Pharma GmbH, Fraunhoferstr. 4, 85737 Ismaning, Germany.
url: www.nordicpharma.de

Nordic, India. Nordic Formulations Pvt Ltd, D-59/105-B 57, Chandrika Nagar Colony, Sigra, Varanasi, India.

Nordic, Irl. See *Nordic, Neth.*

Nordic, Neth. Nordic Pharma BV, Tolweg 15, 3741 LM Baarn, Netherlands.
url: www.nordicpharma.nl

Nordic, Swed. Nordic Drugs AB, Box 300 35, 200 61 Limhamn, Sweden.
url: www.nordicdrugs.se

Nordic, UK. Nordic Pharma UK Ltd, Abbey House, Arlington Business Park, Theale, Reading, Berkshire, RG7 4SA, UK.
url: www.nordicpharmagroup.com

Nordic Drugs, Denm. Nordic Drugs, Gammel Kongevej 135 B, mezz., tv., 1850 Frederiksberg C, Denmark.
url: www.nordicdrugs.com/dk

Nordic Drugs, Fin. Nordic Drugs AB, PL 16, 02241 Espoo, Finland.
url: www.nordicdrugs.se

Nordic Drugs, Norw. See *Nordic, Swed.*

NordicInfu Care, Denm. NordicInfu Care AB, C4 Videnscenter, Krakasvej 17, 3400 Hillerød, Denmark.
url: www.nordicinfucare.dk

NordicInfu Care, Norw. NordicInfu Care, Ingeniør Rybergsg. 48, 3024 Drammen, Norway.

NordicInfu Care, Swed. NordicInfu Care AB, Box 1225, 131 28 Nacka Strand, Sweden.

Nordin, Mex. Química Franco Mexicana Nordin S.A. de C.V., Paseo Lomas Atlas No. 292, Col. Lomas del Valle, 45120 Zapopan, Jal., Mexico.
url: www.nordin.com.mx

Nordion, Neth. See *MDS, Belg.*

Nordion, Spain. See *MDS, Belg.*

Nordisk, Fr. See *Novo Nordisk, Fr.*

Nordisk, Spain. See *Novo Nordisk, Spain.*

Nordisk, USA. See *Novo Nordisk, USA.*

Nordiska, Swed. Nordiska Dental AB, Box 1082, 262 21 Angelholm, Sweden.
url: www.nordiskadental.se

Nordix, Ger. Nordix Pharma Vertrieb GmbH, Pinnauallee 4, 25436 Uetersen, Germany.
url: www.nordix-pharma.com

Nordmark, Austria. See *Nordmark, Ger.*

Nordmark, Cz. See *Nordmark, Ger.*

Nordmark, Ger. Nordmark Arzneimittel GmbH & Co. KG, Pinnauallee 4, 25436 Uetersen, Germany.
url: www.nordmark-pharma.de

Nordmark, Indon. See *Tunggal Idaman, Indon.*

Nordmark, Ital. See *Abbott, Ital.*

Nordmark, Neth. See *Knoll, Neth.*

Nordmark, Rus. See *Grunenthal, Rus* and *Ipsen, Rus.*

Nordmark, Singapore. See *Indrugco, Singapore.*

Nordmark, Thai. See *Pacific, Thai.*

NordMedica, Austria. See *NordMedica, Denm.*

NordMedica, Denm. NordMedica A/S, Jaegersborg Allé 164, 2820 Gentofte, Denmark.
url: www.nordmedica.com

NordMedica, Fin. See *NordMedica, Denm.*

NordMedica, Ger. See *NordMedica, Denm.*

NordMedica, Neth. See *NordMedica, Denm.*

NordMedica, Norw. See *NordMedica, Denm.*

NordMedica, Swed. See *NordMedica, Denm.*

Nore, UK. See *Alinter, UK.*

Noreva, Fr. Laboratoires Noreva-LED, 7 allée Pierre-de-Fermat, BP 80212, 63173 Aubière cdx, France.
url: www.noreva-paris.com

Norgan, Neth. See *Norgine, Neth.*

Norgesfarma, Norw. Norgesfarma AS, Skarerletta 45, Postboks 198, 1471 Lorenskog, Norway.

Norgine, Austral. Norgine P/L, 3/14 Rodborough Road, Frenchs Forest, NSW 2086, Australia.
url: www.norgine.com

Norgine, Austria. Norgine Pharma GmbH, Haidestrasse 4, A-1110 Vienna, Austria.
url: www.norgine.com

Norgine, Belg. Norgine SA, Haasrode Research Park, Romeinsestraat 10, 3001 Heverlee, Belgium.
url: www.norgine.com

Norgine, China. See *Norgine, UK.*

Norgine, Cz. See *Norgine, Fr.*

Norgine, Denm. Norgine Danmark A/S, Stamholmen 151, 6, 2650 Hvidovre, Denmark.

Norgine, Fin. See *Norgine, Neth.*

Norgine, Fr. Laboratoires Norgine Pharma, 23 av. de Neuilly, 75116 Paris, France.
url: www.norgine.com

Norgine, Ger. Norgine GmbH, Im Schwarzenborn 4, 35041 Marburg, Germany.
url: www.norgine.de

Norgine, Gr. See *Norgine, UK.*

Norgine, Hong Kong. See *Treasure Mountain, Hong Kong.*

Norgine, Irl. See *United Drug, Irl.*

Norgine, Ital. Norgine Italia S.r.l., Via Fara 35, 20124 Milan (MI), Italy.
url: www.norgine.com

Norgine, Malaysia. See *Apex, Malaysia.*

Norgine, Neth. Norgine BV, Hogehilweg 7, 1101 CA Amsterdam Zuid-Oost, Netherlands.
url: www.norgine.com

Norgine, Norw. See *Andersen, Norw.*

Norgine, NZ. See *CSL, NZ.*

Norgine, Philipp. See *Zuellig, Philipp.*

Norgine, Port. See *Norgine, Fr.*

Norgine, S.Afr. Norgine (Pty) Ltd, P.O. Box 781247, Gauteng, Sandton 2146, South Africa.
url: www.norgine.com

Norgine, Singapore. See *Grafton, Singapore.*

Norgine, Spain. Norgine de España, Maudes, 51 8 Pl., 28003 Madrid, Spain.
url: www.norgine.com

Norgine, Swed. Norgine Sverige AB, Frösundaviks Allé 15, 4 tr, 169 70 Solna, Sweden.
url: www.norgine.com

Norgine, Switz. Norgine AG, Neue Bahnhofstrasse 160, 4132 Muttenz, Switzerland.
url: www.norgine.com

Norgine, Thai. See *Zuellig, Thai.*

Norgine, UK. Norgine Pharmaceuticals Ltd, Norgine House, Moorhall Rd, Harefield, Uxbridge, Middlesex, UB9 6NS, UK.
url: www.norgine.com

Norgine, Ukr. See *Marko, Ukr.*

Noripharma, Malaysia. See *Pahang, Malaysia.*

Noristan, S.Afr. See *Sanofi-Aventis, S.Afr.*

Noristan Generica, S.Afr. See *Sanofi-Aventis, S.Afr.*

Norit, Austria. See *Solvay, Neth.*

Norit, Cz. See *Solvay, Neth.*

Norit, Denm. See *Medic, Denm.*

Norit, Gr. See *Norit, Neth.*

Norit, Israel. See *Droreth, Israel.*

Norit, Neth. Norit Nederland B.V., P.O. Box 105, Nijverheidsweg Noord 72, 3800 AC Amersfoort, Netherlands.
url: www.norit.com

Norit, Norw. See *Solvay, Norw.*

Norit, Port. See *Norit, Neth.*

Norma, UK. See *Alinter, UK.*

Norma (Νορμα), Gr. Norma Greece A.E., Menandrou 54, 103 31 Athens, Greece.
url: www.normahellas.gr

Normal, Port. Laboratório Normal, Lda, Rua do Centro Empresarial, Edifício 8, Quinta da Beloura, 2710-444 Sintra, Portugal.

Norman, Canad. See *Norman, USA.*

Norman, USA. Merle Norman Cosmetics, 9130 Bellanca Ave, Los Angeles, CA 90045, USA.

Normex, Canad. Les Herbages Normex, 1060 Place Verner, Laval, Quebec, H7E 4P2, Canada.

Normon, Port. Laboratórios Normon SA, Rua Mouzinho da Silveira 10, 1250-167 Lisbon, Portugal.

Normon, Spain. Normon S.A., Ronda de Valdecarrizo 6, Tres Cantos, 28760 Madrid, Spain.
url: www.normon.com

Norpharm, Cz. See *Norpharm, Irl.*

Norpharm, Fin. See *Norpharm, Irl.*

Norpharm, Irl. Norpharm Ltd, 26 Laurence St, Drogheda, County Louth, Ireland.

Norpharm, Neth. See *Norpharm, Irl.*

Norpharm, Pol. See *Norpharm, Irl.*

Norpharm, Port. See *Norpharm, Irl.*

Norpharma, Denm. Norpharma A/S, Slotsmarken 15, 2970 Hørsholm, Denmark.
url: www.norpharma.dk

Norpharma, Norw. See *Andersen, Norw.*

Norpharma, Pol. See *Mundipharma, Pol.*

Norstar, USA. Norstar Consumer Products, 5517 Ninety-fifth Ave, Kenosha, WI 53144, USA.
url: www.norstarcpc.com

Nortech, India. Nortech Remedies, 20 Goyal Intercity Row House, Opp. TV Tower, Drive In Rd, Ahmedabad, India.

North American Biologicals, USA. See *Nabi, USA.*

North Star, Rus. North Star, Russia.

Northern Naturals, Canad. Northern Naturals Health Products Ltd, 8 Jourdenais Rd, Hagensborg, British Columbia, V0T 1H0, Canada.

Northern Research, USA. See *Epien, USA.*

Northfield, Philipp. See *Biolink, Philipp.*

Northia, Arg. Esp. Medicinales Northia S.A.C.I.F.I.A., Madero 135, 1408 Buenos Aires, Argentina.

NorthStar, USA. NorthStar Rx LLC, 4971 Southridge Blvd, Suite 101, Memphis, TN 38141, USA.
url: www.northstarrxllc.com

Norton, Cz. See *Ivax, Irl.*

Norton, Denm. See *Pharmacodane, Denm.*

Norton, Gr. See *Teva, UK.*

Norton, Hung. See *Teva, UK.*

Norton, Israel. See *Promedico, Israel.*

Norton, Neth. See *Teva, UK.*

Norton, NZ. See *Airflow, NZ.*

Norton, Pol. See *Teva, Pol.*

Norton, Rus. See *Ivax, Rus.*

Norton, S.Afr. See *Ivax, S.Afr.*

Norton, Ukr. American Norton Corp., ul Polevaya 61-A, 03058 Kiev, Ukraine.
url: www.nortoncorp.com.ua

Norton Healthcare, Austria. See *Teva, UK.*

Norton Healthcare, Denm. See *Nycomed, Denm.*

Norton Healthcare, Fr. See *Teva, UK.*

Norton Healthcare, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Norton Healthcare, Singapore. See *FP, Singapore* and *Green Cross, Singapore.*

Norton Healthcare, UK. See *Teva, UK.*

Norton Waterford, Irl. See *Ivax, Irl.*

Norwich Eaton, UK. See *Procter & Gamble, UK.*

Norwich-Eaton, Israel. See *Neopharm, Israel.*

Norwood, Canad. Norwood Packaging Ltd, 8519-132nd St, R.R. 4, Surrey, British Columbia, V3W 4N8, Canada.

Noster, Neth. See *Noster, Swed.*

Noster, Port. See *Noster, Swed.*

Noster, Swed. Noster System AB, Baggansgatan 25, S-111 3 1 Stockholm, Sweden.

Nostrum, Port. Sociedade Nostrum, Lda, Rua da Escola de Medicina Veterinária, 15/17, 1049-029 Lisbon, Portugal.

Nostrum, Spain. See *Pfizer, Spain.*

Nourypharma, Ger. See *Essex, Ger.*

Nourypharma, Switz. See *Orion, Switz.*

Nouveau, India. Nouveau Médicament (P) Ltd, 720 Anna Salai, Nandanam, Chennai 600 035, India.
url: www.nouvmed.com

Nova, Braz. Nova Quimica Farmaceutica Ltda, Rua Dr Emilio Ribas 188 conj. 12, 13025140 Campinas Cambui, Sao Paulo, Brazil.

Nova, Denm. See *NordMedica, Denm.*

Nova, Gr. Nova Pharma Gl Karmis OE & Co, Notara 2 & Galatsiou 121, 111 46, Greece.

Nova, Neth. See *Nova, UK.*

Nova, Norw. See *NordMedica, Denm.*

Nova, UK. Nova Laboratories Ltd, Martin House, Gloucester Crescent, Wigston, Leicester, LE18 4YL, UK.
url: www.novalabs.co.uk

Nova Argentia, Arg. Nova Argentia SA, Alvaro Barros 1113, 1838 Luis Guillon, Buenos Aires, Argentina.

Nova Argentia, Ital. Nova Argentia Industria Farmaceutica S.p.A., Via Pascoli 1, 20064 Gorgonzola (MI), Italy.
url: www.novaargentia.it

Novadental, Gr. Novadental Ltd, Veranzerou 23, 104 33 Athens, Greece.

Novaduo, India. Novaduo Pharma, 57-A IInd Extension, Gandhi Nagar, Jammu, 180 004, India.

Novag, Mex. Novag Infancia S.A. de C.V., Claz. de Tlalpan No. 3417, Col. Sta. Ursula Coapa-Coyoacan, 04650 Mexico D.F., Mexico.

Novag, Spain. See *Ferrer, Spain.*

Novagen, Gr. Novagen Pharmaceuticals, Souri 6 & Korinthou, 144 51 Athens, Greece.

Novagen, India. Novagen Pharmaceuticals, 49/3A Hirabhai Market, Diwan Ballubhai Rd, Ahmedabad, India.

Novagen, Philipp. See *Medisys, Philipp* and *Novo Pharm, Philipp.*

Novagen, S.Afr. Novagen Pharma Pty Ltd, P.O.Box 60842, Pierre van Ryneveld, Pretoria 0045, South Africa.
url: www.novagenpharma.co.za

Novalac, Malaysia. See *Harpers, Malaysia.*

Novalac, Singapore. See *Delfi, Singapore.*

Novalis, Fr. See *Wyeth Lederle, Fr.*

Novamed, Braz. See *EMS, Braz.*

NovaMed, China. NovaMed Pharmaceuticals Co Ltd, Central Plaza Room 2601, 227 North Huangpi Road, Shanghai 200003, China.

Novamed, India. Novamed Pharmaceuticals, 49/3A Hirabhai Market, Diwan Ballubhai Rd, Ahmedabad, India.

Novamen, Arg. Novamen SA, Cerrito 1070, Piso 4, Of. 81, 1010 Buenos Aires, Argentina.

Novapharm, Austria. Novapharm GmnH, Feldgasse 19, 4600 Wels, Austria.

Novapharm, Cz. See *Novapharm, Austria.*

Novapharm, Venez. See *Farma, Venez.*

Novapharma, Venez. Novapharma S.A., Av. Principal de los Ruices Edif. Pharma, Urb. Los Ruices, Caracas, Venezuela.

Novaquimica, Braz. Novaquimica Sigma Pharma-Nature's Plus Ltda, Rodovia SP1 01 (Campinas a Monte Mor) Km 08, 13186-481 Hortolandia, SP, Brazil.

Novara, Arg. Laboratorios Novara SRL, Pje Blanque 1130, 2000 Rosario, Santa Fe, Argentina.

Novartis, Arg. Novartis Argentina S.A., Ramallo 1851, 1429 Buenos Aires, Argentina.
url: www.ar.novartis.com

Novartis, Austral. Novartis Pharmaceuticals P/L, P.O. Box 101, North Ryde, NSW 1670, Australia.
url: www.novartis.com

Novartis, Austria. Novartis Pharma GmbH, Brunner Strasse 59, A-1230 Vienna, Austria.
url: www.at.novartis.com

Novartis, Belg. Novartis Pharma SA, Telecom Gardens, Medialaan 40 bus 1, 1800 Vilvoorde, Belgium.
url: www.novartis.com

Novartis, Braz. Novartis Biociencias S.A., Avenida Professor Vicente Rao 90/120, Predio 156 3 degrees ander, 04706-900 São Paulo, SP, Brazil.
url: www.novartis.com.br

Novartis, Canad. Novartis Pharmaceuticals Canada Inc., 385 Bouchard Blvd, Dorval, Quebec, H9S 1A9, Canada.
url: www.novartis.ca

Novartis, Chile. Laboratorio Novartis Chile SA, Francisco meneses 1980, Nunoa, Santiago, Chile.

Novartis, China. Beijing Novartis Pharma Ltd, 2 International Trade Building, Jian Guo Men Wai Ave, Chaoyang District, Beijing 100004, China.
url: www.novartis.com.cn

Novartis, Cz. Novartis Czech Republic sro, V Olšinach 75, 100 00 Prague 10, Czech Republic.
url: www.novartis.com

Novartis, Denm. Novartis Healthcare A/S, Lyngbyvej 172, 2100 Copenhagen Ø, Denmark.
url: www.novartis.dk

Novartis, Fin. Novartis Finland Oy, Metsänneidonkuja 10, 02130 Espoo, Finland.
url: www.novartis.fi

Novartis, Fr. Novartis Pharma SAS, 2-4 rue Lionel-Terray, 92500 Rueil-Malmaison, France.
url: www.fr.novartis.com

Novartis, Ger. Novartis Pharma GmbH, Roonstr. 25, 90429 Nürnberg, Germany.
url: www.novartis.de

Novartis, Gr. Novartis (Hellas) A.E.B.E., 12o chlm. Ethnikis Odou Athinon-Lamias, 144 51 Metamorfosi, Greece.
url: www.novartis.gr

Novartis, Hong Kong. Novartis Pharmaceuticals (HK) Ltd, 37/F Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.
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Novartis, Hung. Novartis Hungária Kft, Bartók Béla út 43-47, 1114 Budapest, Hungary.

Novartis, India. Novartis India Ltd, Pharmaceutical Division, Sandoz House 7th Floor, Shivsagar Estate, Dr. Annie Besant Road, Worli, Mumbai 400 018, India.
url: www.novartis.com

Novartis, Indon. Novartis Indonesia PT, Wisma 46-Kota BNI 35th Floor, Jl Jend Sudirman Kav 1, Jakarta Selatan 10220, DKI Jaya, Indonesia.

Novartis, Irl. Novartis Ireland Ltd, Beech House, Beech Hill Office Campus, Clonskeagh, Dublin 4, Ireland.
url: www.ie.novartis.com

Novartis, Israel. Novartis Ltd, Hasivim 23, Petach Tikva, Israel.
url: www.novartis.com

Novartis, Ital. Novartis Farma S.p.A., Largo Umberto Boccioni 1, 21040 Origgio (VA), Italy.
url: www.novartis.it

Novartis, Jpn. Novartis Pharma K.K., 4-17-30 Nishi-Azabu, Minato-ku, Tokyo 106-8618, Japan.
url: www.novartis.co.jp

Novartis, Malaysia. Novartis Corporation (Malaysia) Sdn Bhd, Lot 9, Jln 26/1, Seksyen 26, Kawansan Perindustrian Hicam, 40400 Shah Alam, Selangor, Malaysia.
url: www.my.novartis.com

Novartis, Mex. Novartis Farmaceutica S.A. de C.V., Calz. de Tlalpan No. 1779, Col. San Diego Churubusco, Deleg. Coyoacan, 04120 Mexico D.F., Mexico.
url: www.mx.novartis.com

Novartis, Neth. Novartis Pharma BV, Postbus 241, 6800 LZ Arnhem, Netherlands.
url: www.novartis.nl

Novartis, Norw. Novartis Norge AS, Brynsalleen 4, Postboks 237 Okern, 0510 Oslo, Norway.
url: www.novartis.no

Novartis, NZ. Novartis New Zealand Ltd, Private Bag 19-999, Avondale, Auckland, New Zealand.
url: www.novartis.com

Novartis, Philipp. Novartis Healthcare Phils Inc., 5/F Asian Reinsurance Bldg, Cor Salcedo & Gamboa St, Legaspi Vill, Makati City, Philippines.

Novartis, Pol. Novartis Poland Sp. zo.o., ul. Marynarska 15, 02-674 Warsaw, Poland.
url: www.novartis.pl

Novartis, Port. Novartis Farma, SA, Rua do Centro Empresarial, Edifício 8, Quinta da Beloura, 2710-444 Sintra, Portugal.
url: www.novartis.com

Novartis, Rus. Zao Novetis Parma AG, B. Palashevski Pereulok 15/A, 103104 Moscow, Russia.
url: www.novartis.ru

Novartis, S.Afr. Novartis South Africa (Pty) Ltd, P.O. Box 92, ZA-Kempton Park, Isando 1600, South Africa.
url: www.novartis.com

Novartis, Singapore. Novartis (Singapore) Pte Ltd, Pharmaceutical Division, 10 Hoe Chiang Road, 09-05/06 Keppel Towers, S 089315, Singapore.
url: www.novartis.com

Novartis, Spain. Novartis Farmaceutica, Gran Via Corts Catolanes 764, 08013 Barcelona, Spain.
url: www.es.novartis.com

Novartis, Swed. Novartis Sverige AB, Box 1150, 183 11 Täby, Sweden.
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Novartis, Switz. Novartis Pharma Schweiz AG, Monbijoustrosse 118, Postfach, 3001 Berne, Switzerland.
url: www.novartis.ch

Novartis, Thai. Novartis (Thailand) Ltd, 159/30 Vibhavadi Rangsit Rd, Laksi, Bangkok 10210, Thailand.
url: www.th.novartis.com

Novartis, Turk. Novartis Ilaç Ltd. Sti., Barbaros Bulvarı No: 83, Besiktas, İstanbul, Turkey.
url: www.novartis.com.tr

Novartis, UK. Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 5SG, UK.
url: www.novartis.co.uk

Novartis, Ukr. Novartis Pharma Services AG, Bereznyakovskaya Street, 29, Kiev, 02098, Ukraine.

Novartis, USA. Novartis Pharmaceuticals Corp., One Health Plaza, East Hanover, NJ 07936-1080, USA.
url: www.pharma.us.novartis.com

Novartis, Venez. Novartis de Venezuela S.A., 3ra. Transversal de Los Ruices Edif. Novartis, (68097) Los Ruices, Caracas, Venezuela.
url: www.novartis.com

Novartis Behring, Ger. Novartis Behring, Novartis Vaccines & Diagnostics GMBH & Co KG, Emil-von-Behring-Str. 76, 35041 Marburg, Germany.
url: www.impfen.de

Novartis Consumer, Arg. See *Novartis, Arg.*

Novartis Consumer, Austral. Novartis Consumer Health Australasia P/L, P.O. Box 4499, Mulgrave, VIC 3170, Australia.
url: www.novartisnutrition.com

Novartis Consumer, Austria. See *Gebro, Austria.*

Novartis Consumer, Belg. See *Novartis, Belg.*

Novartis Consumer, Braz. See *Novartis, Braz.*

Novartis Consumer, Canad. Novartis Consumer Health Canada Inc., 2233 Argentia Rd, Suite 205, Mississauga, Ontario, L5N 2X7, Canada.
url: www.novartis.ca

Novartis Consumer, Cz. See *Novartis, Cz.*

Novartis Consumer, Ger. Novartis Consumer Health GmbH, Zielstattstr. 40, 81379 Munich, Germany.
url: www.novartis-consumerhealth.de

Novartis Consumer, Hong Kong. See *Novartis, Hong Kong.*

Novartis Consumer, Hung. See *Novartis, Hung.*

Novartis Consumer, India. Novartis Consumer Health (India) Ltd, 6th Floor Tiffany building, Hiranandani Business Park, Patlipada, Thane 400 607, India.
url: www.novartis.co.in

Novartis Consumer, Irl. See *Novartis, Irl.*

Novartis Consumer, Israel. See *Novartis, Israel.*

Novartis Consumer, Ital. See *Novartis, Ital.*

Novartis Consumer, Malaysia. See *Novartis, Malaysia.*

Novartis Consumer, Neth. Novartis Consumer Health Benelux, Postbus 2014, 4800 CA Breda, Netherlands.
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Novartis Consumer, NZ. See *Novartis, NZ.*

Novartis Consumer, Pol. Novartis Poland Sp. zo.o., Consumer Health OTC, ul. Bokserska 66, 02-690 Warsaw, Poland.
url: www.novartis.pl

Novartis Consumer, Port. Novartis Consumer Health, Lda, Av Poeto Mistral 2-2, 1069-172 Lisbon, Portugal.
url: www.consumer-health.novartis.com

Novartis Consumer, Rus. Navartis Consumer Health S.A., B. Palashevskii per. d.15, 123104 Moscow, Russia.
url: www.novartis.ru

Novartis Consumer, S.Afr. See *Novartis, S.Afr.*

Novartis Consumer, Spain. Novartis Consumer Health S.A., Marina 206, 08013 Barcelona, Spain.
url: www.novartisconsumerhealth.es

Novartis Consumer, Switz. See *Novartis, Switz.*

Novartis Consumer, UK. Novartis Consumer Health, Wimblehurst Rd, Horsham, West Sussex, RH12 4AB, UK.
url: www.novartis.co.uk

Novartis Consumer, Ukr. See *Novartis, Ukr.*

Novartis Consumer, USA. Novartis Consumer Health Inc., 200 Kimball Drive, Parsippany, NJ 07054-0622, USA.
url: www.novartis.com

Novartis Nutrition, Canad. Novartis Nutrition Corporation, 2233 Argentia Road, Suite 205, West Tower, Mississauga, Ontario, L5N 2X7, Canada.
url: www.ca.novartis.com

Novartis Nutrition, Cz. See *Novartis, Cz.*

Novartis Nutrition, Fr. Laboratoires Novartis Nutrition, B.P. 29, 31250 Revel, France.
url: www.novartisnutrition.com

Novartis Nutrition, Hong Kong. See *Novartis, Hong Kong.*

Novartis Nutrition, Port. See *Novartis Consumer, Port.*

Novartis Nutrition, Singapore. See *Zuellig, Singapore.*

Novartis Nutrition, UK. See *Novartis Consumer, UK.*

Novartis Nutrition, USA. Novartis Nutrition Corp., 1600 Utica Ave. South, Suite 600, St. Louis Park, MN 55416, USA.
url: www.novartisnutrition.com

Novartis Nutrition, Venez. See *Novartis, Venez.*

Novartis Ophthalmics, Arg. See *Novartis, Arg.*

Novartis Ophthalmics, Austral. See *Novartis, Austral.*

Novartis Ophthalmics, Austria. See *Novartis, Austria.*

Novartis Ophthalmics, Braz. See *Novartis, Braz.*

Novartis Ophthalmics, Canad. See *Novartis, Canad.*

Novartis Ophthalmics, Cz. See *Novartis, Cz.*

Novartis Ophthalmics, Fr. See *Novartis, Fr.*

Novartis Ophthalmics, Ger. See *Novartis, Ger.*

Novartis Ophthalmics, Hong Kong. See *Novartis, Hong Kong.*

Novartis Ophthalmics, Hung. See *Novartis, Hung.*

Novartis Ophthalmics, Irl. See *Novartis, UK.*

Novartis Ophthalmics, Malaysia. See *Novartis, Malaysia.*

Novartis Ophthalmics, Port. See *Novartis, Port.*

Novartis Ophthalmics, Rus. Novartis Ophthalmics, Krasnoproletarskaya, d.2/4, str.16, 103006 Moscow, Russia.
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Novartis Ophthalmics, S.Afr. See *Novartis, S.Afr.*

Novartis Ophthalmics, Singapore. See *Novartis, Singapore.*

Novartis Ophthalmics, Swed. See *Novartis, Swed.*

Novartis Ophthalmics, Switz. See *Novartis, Switz.*

Novartis Ophthalmics, Turk. See *Novartis, Turk.*

Novartis Ophthalmics, UK. See *Novartis, UK.*

Novartis Ophthalmics, USA. Novartis Ophthalmics Inc., 11695 Johns Creek Parkway, Duluth, GA 30097, USA.
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Novartis OTC, Singapore. Novartis (Singapore) Pte Ltd OTC Division, 491B River Valley Rd, 14-04 Valley Point, S-248373, Singapore.

Novartis Pharma, Ukr. See *Brupharmexport, Ukr.*

Novartis Sante, Fr. Novartis Santé Familiale SA, 14 bd Richelieu, B.P. 440, 92845 Rueil-Malmaison cdx, France.

Novartis Vaccines, Austral. See *Novartis, Austral.*

Novartis Vaccines, Austria. See *Novartis, Austria.*

Novartis Vaccines, Cz. See *Novartis, Cz.*

Novartis Vaccines, Fin. See *Novartis, Fin.*

Novartis Vaccines, Fr. Novartis Vaccines & Diagnostics SAS, 10 rue Chevreul, 92150 Suresnes, France.

Novartis Vaccines, Ger. Novartis Vaccines Vertriebs GmbH, Rudolf-Diesel-Ring 27, 83607 Holzkirchen, Germany.
url: www.impfen.de

Novartis Vaccines, Gr. See *Novartis, Gr.*

Novartis Vaccines, Hong Kong. See *Zuellig, Hong Kong.*

Novartis Vaccines, Hung. See *Novartis, Hung.*

Novartis Vaccines, Indon. See *Novartis, Indon.*

Novartis Vaccines, Irl. See *Novartis, Irl.*

Novartis Vaccines, Ital. Novartis Vaccines & Diagnostics S.r.l., Via Fiorentina 1, 53100 Siena (SI), Italy.
url: www.novartisvaccines.it

Novartis Vaccines, Neth. See *Novartis, Neth.*

Novartis Vaccines, Philipp. See *Novartis, Philipp.*

Novartis Vaccines, Pol. See *Novartis, Pol.*

Novartis Vaccines, Port. See *Novartis, Port.*

Novartis Vaccines, Rus. See *Novartis, Rus.*

Novartis Vaccines, Singapore. See *Novartis, Singapore.*

Novartis Vaccines, Spain. See *Novartis, Spain.*

Novartis Vaccines, Thai. See *Biogenetech, Thai.*

Novartis Vaccines, UK. Novartis Vaccines, Symphony House, Robert Robinson Ave, The Oxford Science Park, Oxford, Oxfordshire, OX4 4GA, UK.
url: www.chironvaccines.com

Novartis Vaccines, USA. See *Novartis, USA.*

Novartos Consumer, Rus. See *Novartis, Rus.*

NovaSelect, Ital. NovaSelect SpA, Zona Industriale, 85050 Tito Scalo (PZ), Italy.

Novasorel, Ital. Novasorel S.p.a., Via del Corno 12, 40069 Zola Predosa (BO), Italy.
url: www.novasorel.com

Novastra, Port. Novastra Promoção e Comercio Farmaceutico Lda, Rua Humberto Madeira 7 & 7A, Queluz de Baixo, 2730-097 Barcarena, Portugal.

Novatec, Thai. Novatec Healthcare Co Ltd, 599/15 Moo 5 Srinakarin Rd, Samrong-Nua, Muang, Samutprakarn 10270, Thailand.

Novavax, USA. Novavax Inc., 508 Lapp Rd, Malvern, PA 19355, USA.
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Novaxo, Fr. Laboratoires Novaxo, 100 rte de Versailles, 78163 Marly-le-Roi cdx, France.

Noveal, Switz. See *Uhlmann-Eyraud, Switz.*

Novell, Hong Kong. See *CNW, Hong Kong* and *Hong Tai Hong, Hong Kong.*

Novell, Indon. Novell Pharmaceutical PT, Jl Limo No 42 AB, Permata Hijau Senayan, Jakarta 12220, Indonesia.

Novell, Philipp. See *DNBG, Philipp.*

Novell, Singapore. See *Goldplus, Singapore.*

Novell, Thai. Novell Pharmaceutical Laboratories, 12th Fl Unit 6 Srijulsub Tower, 44 Rama 1 Rd, Rongmuang, Bangkok, 10330, Thailand.
url: www.novellpharm.com

Novem, Singapore. Novem Healthcare Pte Ltd, 12 New Industrial Rd 02-01, Morningstar Centre, S 536202, Singapore.
url: novemhealthcare.com

Noven, USA. Noven Pharmaceuticals, 11960 SW 144th St, Miami, Fl. 33186, USA.
url: www.noven.com

Novendia, Gr. Novendia Pharmaceuticals Ltd, 425 Irakliou Ave, 14122 Athens, Greece.
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Noventis, Cz. Noventis sro, Filmová 174, 761 79 Zlín, Czech Republic.

Noventure, Thai. See *Pacific, Thai.*

Novex, Fr. Laboratoire Novex Pharma, 3 rue Maurice Ravel, 92300 levallois Perret, France.

Novex Pharma, UK. Novex Pharma Ltd, Ringside, 79 High St., Bracknell, Berkshire, RG12 1DZ, UK.
url: www.quintiles.com

Novipharm, Austria. Novipharm GmbH, Klagenfurter Strasse 164, A-9210 Portschach, Austria.

Novis, Gr. Novis, Karistou 30, 144 51 Metamorfosi, Greece.

Novo Nordisk, Arg. Novo Nordisk Pharma Argentina S.A., Av. Del Libertador 14099, 1640 Martinez, Buenos Aires, Argentino.
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Novo Nordisk, Austral. Novo Nordisk Pharmaceuticals P/L, Level 3/21 Solent Circuit, Baulkham Hills, NSW 2153, Australia.
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Novo Nordisk, Austria. Novo-Nordisk Pharma GmbH, Erdbrgstrasse 52-60/3/16, A-1030 Vienna, Austria.
url: www.novonordisk.at

Novo Nordisk, Belg. Novo Nordisk Pharma SA, 1070 Brussels, Belgium.Regulatory Affairs Manager
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Novo Nordisk, Braz. Novo Nordisk Farmacêutica do Brasil Ltda, Av. Francisco Matarazzo 1.500, 12/14 andar, 05001-400 São Paulo, SP, Brazil.
url: www.novonordisk.com.br

Novo Nordisk, Canad. Novo Nordisk Canada Inc., 2700 Matheson Blvd E, 3rd Floor, West Tower, Mississauga, Ontario, L4W 4V9, Canada.Manager Regulatory Affairs
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Novo Nordisk, Chile. Lab. Novo Nordisk AS, Av. del Parque 4980 Of. 337, Huechuroba Cuidad Epresarial, Santiago, Chile.

Novo Nordisk, China. Novo Nordisk China, 18F East Tower World Financial Center, 1 East 3rd Middle Ring Road, Chao Yang District, Beijing 100020, China.
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Novo Nordisk, Cz. Novo Nordisk sro, Hadovka Office Park, Evropská 33c/330, 160 00 Prague 6, Czech Republic.
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Novo Nordisk, Denm. Novo Nordisk Scandinavia AB, Region Danmark, Arne Jacobsens Allé 15, 2300 Copenhagen S, Denmark.
url: www.novonordisk.dk

Novo Nordisk, Fin. Novo Nordisk Farma Oy, Itäuulentie 1, 02100 Espoo, Finland.
url: www.novonordisk.fi

Novo Nordisk, Fr. Novo Nordisk Pharmaceutique SA, 32 rue de Bellevue, 92773 Boulogne-Billancourt cdx, France.
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Novo Nordisk, Ger. Novo Nordisk Pharmo GmbH, Brucknerstr. 1, 55127 Mainz, Germany.
url: www.novonordisk.de

Novo Nordisk, Gr. Navo Nordisk Hellas Ltd, 518 Messoghion Ave, 153 42 Agia Paraskevi, Greece.
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Novo Nordisk, Hong Kong. Novo Nordisk Hong Kong Ltd, Unit 507, 5/F, Trade Square, 681 Cheung Sha Wan Rd, Kowloon, Hong Kong.
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Novo Nordisk, Hung. Novo Nordisk Hungária Kft, Felsőzöldmáli út 35, 1025 Budapest, Hungary.
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Novo Nordisk, India. Novo Nordisk India Ltd, Plot No.32, 47-50, EPIP Area, Whitefield, Bangalore 560 066, India.
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Novo Nordisk, Indon. Novo Nordisk Indonesia PT, Perkantoran Hijau Arkadia, Tower B, Penthouse Floor, Jl TB Simatupang Kav 88, Jakarta 12520, Indonesia.
url: www.novonordisk.com

Novo Nordisk, Irl. Novo-Nordisk Pharmaceuticals Ltd, 3/4 Upper Pembroke St, Dublin 2, Ireland.
url: www.novonordisk.ie

Novo Nordisk, Israel. Novo Nordisk Ltd, 20 Hataas St, Kfar Saba 44425, Israel.
url: www.novonordisk.com

Novo Nordisk, Ital. Novo Nordisk Farmaceutici S.p.A., Via Elio Vittorini 129, 00144 Rome (RM), Italy.
url: www.novonordisk.it

Novo Nordisk, Jpn. Novo Nordisk Pharma Ltd, 5-7 Nihonbashi Ohdenma-cho, Chuo-ku, Tokyo 103-8575, Japan.
url: www.novonordisk.co.jp

Novo Nordisk, Malaysia. Novo Nordisk Pharma (Malaysia) Sdn Bhd, Suite 5.07, Level 5, Wisma KT, 14 Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.novonordisk.com

Novo Nordisk, Mex. Novo Nordisk México SA de CV, Montes Urales 715 PB, 11000 Lomas de Chapultepec, Mexico.

Novo Nordisk, Neth. Novo Nordisk Farma, Postbus 443, 2400 AK Alphen aan den Rijn, Netherlands.
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Novo Nordisk, Norw. Novo Nordisk Scandinavia AS, Hauger skolev. 16, Postboks 24, 1351 Rud, Norway.
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Novo Nordisk, NZ. Novo Nordisk Pharmaceuticals Ltd, 58 Richard Pearse Drive, Airport Oaks, Mangere, New Zealand.
url: www.novonordisk.co.nz

Novo Nordisk, Philipp. Novo Nordisk, Suite 21-B, 21/F Wynsum Corporate Plaza, F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Novo Nordisk, Pol. Novo Nordisk Pharma Sp. zo.o., ul. Mineralna 15, 02-274 Warsaw, Poland.
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Novo Nordisk, Port. Novo Nordisk, Lda, Quinta da Fonte, Edifico D José Q54, Piso 1, 2780-730 Paço de Arcos, Portugal.
url: www.novonordisk.pt

Novo Nordisk, Rus. Novo Nordisk A/s, Lomonosovskii prospekt 38, kv. 11, Moscow, Russia.
url: www.novonordisk.ru

Novo Nordisk, S.Afr. Novo-Nordisk (Pty) Ltd, 10A Achter Rd, Paulshof, Sandton 2054, South Africa.
url: www.novonordisk.co.za

Novo Nordisk, Singapore. See *JDH, Singapore.*

Novo Nordisk, Spain. Novo Nordisk Pharma, Calereuga 102, 28033 Madrid, Spain.
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Novo Nordisk, Swed. Novo Nordisk Scandinavia AB, Box 50587, 202 15 Malmö, Sweden.
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Novo Nordisk, Switz. Novo Nordisk Pharma AG, Untere Heslibachstrasse 46, Postfach, 8700 Kusnacht/ZH, Switzerland.
url: www.novonordisk.ch

Novo Nordisk, Thai. Novo Nordisk Pharma (Thailand) Ltd, 4 Fl, Sethiwan Tower, 139 Pan Rd, Silom, Bangkok 10500, Thailand.
url: www.novothai.com

Novo Nordisk, Turk. Novo Nordisk Soğlick Ürünleri Tic. Ltd. Şti., Nispetiye Cad., Akmerkez E-3 Blok Kat:7, Etiler, İstanbul, Turkey.
url: www.novoturk.com

Novo Nordisk, UK. Novo Nordisk Pharmaceuticals Ltd, Novo Nordisk House, Broadfield Park, Brighton Rd, Pease Pottage, Crawley, West Sussex, RH11 9RT, UK.
url: www.novonordisk.co.uk

Novo Nordisk, Ukr. Novo Nordisk A/S, B. Khmelnitskogo Street, 56, Kiev, 01030, Ukraine.
url: www.novonordisk.com.ua

Novo Nordisk, USA. Novo Nordisk Pharmaceuticals Inc., 100 College Rd West, Princeton, NJ 08540, USA.
url: www.novonordisk-us.com

Novo Pharm, Philipp. Novo Pharm Drug, 4628-D Valenzuela St, Sta Mesa, 1017 Manila, Philippines.

Novocol, Canad. Novocol Pharmaceutical of Canada Inc., 25 Wolseley Court, Cambridge, Ontario, N1R 6X3, Canada.

Novocol, Israel. See *Dentorient, Israel.*

Novocol, USA. See *Septodont, USA.*

Novofarm (Νοβοφαρμ), Gr. Novofarm, Elaion 36, 145 64 N. Kifisia, Greece.

Novofarma, Arg. Novofarma S.R.L., Juano Garcia 5008, 1407 Floresta, Buenos Aires, Argentina.

Novogaleno, Ital. Novogaleno S.r.l., Largo Sermoneta 24, 80123 Naples, Italy.

Novogen, Austral. Novogen Laboratories P/L, 140 Wicks Rd, North Ryde, NSW 2113, Australia.
url: www.novogen.com

Novogen, India. See *Novo Nordisk, India.*

Novogen, UK. Novogen Ltd, Castle Hill House, Castle Hill, Windsor, Berkshire, SL4 1PD, UK.
url: www.novogen.com

Novopharm, Canad. Novopharm Ltd, 30 Novopharm Court, Toronto, Ontario, M1B 2K9, Canada.
url: www.novopharm.com

Novopharm, Gr. See *Novofarm (Νοβοφαρμ), Gr.*

Novopharm, Hong Kong. See *Primal, Hong Kong.*

Novopharm, Philipp. See *Diethelm, Philipp.*

Novapharm, Pol. Novopharm, Hurtownia Farmaceutyczna Sampel-B, ul. Jugosłowiańska 122 A, 51-112 Wrocław, Poland.

Novopharm, Singapore. See *Green Cross, Singapore.*

Novopharma, Rus. Novopharma, Russia.
url: www.novopharma.uz

Novopharma, Switz. See *Bausch & Lomb, Switz.*

Novosibkhimfarm, Rus. See *Domestic, Rus.*

Novum, Belg. Novum Pharma s.p.r.l., Xavier de Cocklaan 66 bus 3, 9830 Sint-Martins-Latem, Belgium.

Novum, Mex. Novum Pharma SA de CV, Blvd Juan A de Torres 220-2, 37353 León, Gto Vibar, Mexico.

Novum, Neth. Novum Pharma BV, Van Panhuysstraat 47, 2203 JP Noordwijk, Netherlands.

Novyphar, Belg. Novyphar, Belgium.

NPBI, Neth. NPBI, Burgemeester Haspelslaan 15, 1181 NB Amstelveen, Netherlands.

NPS, USA. NPS Pharmaceuticals, 550 Hills Drive, Bedminster, NJ 07921, USA.

NRIM, Neth. See *NRIM, UK.*

NRIM, UK. NRIM Ltd, Unit 15 Moorcraft, Harlington Rd, Hillingdon, Middlesex, UB8 3HD, UK.
url: www.nrim.co.uk

NSE, Canad. See *NSE, USA.*

NSE, USA. NSE Products Inc., 75 West Center St, Provo, Utah, 84601, USA.

NSID, Israel. See *Pharmateam, Israel.*

NTC, Cz. NTC Pharma, Czech Republic.

NTC, Ital. NTC Srl, Via Luigi Razza 3, 20124 Milan, Italy.

NTC, Neth. See *NTC, Ital.*

Nu Skin, Canad. Nu Skin Canada Inc., Unit 1, Ridgeway Drive, Mississauga, Ontario, L5L 5Z9, Canada.

Nucare, UK. Nucare Plc, 494-496 Honeypot Lane, Stanmore, Middlesex, HA7 1JH, UK.
url: www.nucare.co.uk

Nucitec, Mex. Nucitec SA de CV, Hacienda de Jaltengo 13, 14350 Prado Coapa, Mexico DF, Mexico.

Nuclear, Spain. See *Nucliber, Spain.*

Nucleopharm, Arg. Nucleopharm SRL, Av. Remedios 5341/49, 1440 Buenos Aires, Argentina.

Nucleus, Cz. See *Nucleus, Iceland.*

Nucleus, Denm. See *Nucleus, Iceland.*

Nucleus, Fin. See *Nucleus, Iceland.*

Nucleus, Iceland. Nucleus ehf, Box 55, Nasustanes, 116 Reykjavik, Iceland.

Nucleus, Neth. See *Nucleus, Iceland.*

Nucleus, Pol. See *Nucleus, Iceland.*

Nucliber, Spain. Nucliber S.A., Hierro 9, 28045 Madrid, Spain.
url: www.nucliber.com

Nucron, India. Nucron Pharmaceuticals (P) Ltd, C-7-8 (2), Bhosari, Pune 411 026, India.

Nufarindo, Indon. Nufarindo Pharma Lab, Mangkang Kulon Km 16.5 Kec Tugu, Semarang 50155, Jawa Tengah, Indonesia.

NuLife, India. NuLife Pharmaceuticals, 203 Pleasant Apartments, 15th Lane, Prabhat Road, Pune 411 004, India.
url: www.nulifepharma

Numark, Canad. See *Numark, USA.*

Numark, UK. Numark Management Ltd, 5/6 Fairway Court, Amber Close, Tamworth Business Park, Tamworth, Staffordshire, B77 4RP, UK.
url: www.numarkpharmacists.com

Numark, USA. Numark Laboratories Inc., 164 North Field Ave, Edison, NJ 08818, USA.
url: www.numarklabs.com

Numil, Turk. Numil Gıda Ürünleri San. ve Tic. A.Ş., Yapi Kredi Plaza B Blok, K:9 No: 24, Levent, İstanbul, 80620, Turkey.
url: www.nutricia.com.tr

Nuo De, China. Nuo De Pharm, Jiangsu, China.

Nuo Jin, China. Nuo Jin Pharmaceutical Co. Ltd, Guangzhou, China.

Nuokang, China. Nuokang Biopharmaceutical Inc., Block A Room 701 Tiancheng Tecnology Building, 2 Xinfeng St, Xicheng, Beijing, 100020, China.

Nuova Farmec, Ital. See *Farmec, Ital.*

NuPathe, USA. NuPathe Inc., 227 Washington St, Suite 200, Conshohocken, PA 19428, USA.
url: www.nupathe.com

Nupel, Spain. Laboratorios Asociados Nupel S.L, Rua Carpinteiros 25, 27003 Lugo, Spain.

Nu-Pharm, Canad. Nu-Pharm Inc., 50 Mural St, Units 1 & 2, Richmond Hill, Ontario, L4B 1E4, Canada.The President

Nupharma, Thai. Nupharma & Healthcare Co Ltd, 18 Soi Plubpla, Thungmongkorn Rd, Talingchan, Thailand.

Nuro, USA. Nuro Pharma Inc., Las Vegas, NV 89118, USA.

Nutergia, Fr. Laboratoires Nutergia, B.P. 52, 12700 Capdenac, France.
url: www.nutergia.fr

NutraCea, USA. NutraCea, 1261 Hawks Flight Court, El Dorado Hills, CA 95762, USA.
url: www.nutracea.com

Nutraceutical, Chile. See *Andromaco, Chile.*

Nutraceuticals, UK. Nutraceuticals Ltd, Wortley House, 16 Eastbourne Rd, Hornsea, East Yorkshire, HU18 1QS, UK.
url: www.calciumclear.com

Nutralife, UK. Nutralife UK Ltd, Omicron House, Fircroft Way, Edenbridge, Kent, TN8 6EL, UK.

Nutraloric, USA. Nutraloric, 350 N Lantana, Unit G1, Camarillo, CA 93010, USA.

Nutramax, USA. NutraMax Laboratories Inc., 208 Lakeside Bvld, Edgewood, MD 21040, USA.
url: www.nutramaxlabs.com

Nutramedica, India. Nutramedica Inc, 212 Sapphire heights, A.B. Road, Indore 452 010, India.
url: www.nutramedica.co.in

Nutramedica, Philipp. Nutramedica, 35 Scout Lozano St, Barangay Laging Handa, 1103 Quezon City, Philippines.
url: www.nutramedica.biz

Nutrascience, Philipp. See *Nutramedica, Philipp.*

Nutrasweet, NZ. Nutrasweet Consumer Products, P.O. Box 3872, Auckland, New Zealand.
url: www.nutrasweet.com

Nutravite, Canad. Nutravite, 1470 Leathead Rd, Unit 2, Kelowna, British Columbia, V1X 7J6, Canada.
url: www.nutravite.com

Nutri Gizindo, Indon. Nutri Gizindo Nusantara PT, Jl Jelambar Slt II 4, Jakarta 11460, Indonesia.

Nutri Start, Canad. Nutri Start Vitamin Co Inc., 4612 Sunnymead Way, Victoria, British Columbia, V8Y 3B7, Canada.

Nutri-Advance, Singapore. See *LF, Singapore.*

Nutridys, Fr. Nutrialys Medical Nutrition, Parc Edonia, Bât C, rue de la Terre Victoria, 35760 Saint-Grégoire, France.
url: www.nutrialys.fr

Nutriben, Fr. Laboratoires Nutribén, 1 rue de Terre-Neuve, Bât G, 91967 Les Ulis cdx, France.

Nutri-Chem, Canad. Nutri-Chem Pharmacy Ltd, 1303 Richmond Rd, Ottawa, Ontario, K2B 7Y4, Canada.

Nutrichem Diat, China. See *Nutrichem Diat, Ger.*

Nutrichem Diat, Ger. Nutrichen Diät + Pharma GmbH, 1-3 Am Espan, Roth, 91154, Germany.
url: www.nutrichem.de

Nutricia, Austral. Nutricia Australia P/L, 14-16 Brookhallow Avenue, Baulkham Hills, NSW 2153, Australia.
url: www.nutricia.com

Nutricia, China. Nutricia Pharmaceuticals, Hong Kong New World Tower Room 2401, Huaihoi Zhong Rd 300, Shanghai 200021, China.
url: www.nutriciachina.com

Nutricia, Cz. Nutricia as, Pod Višňovkou 25, 142 01 Prague 4, Czech Republic.

Nutricia, Denm. Nutricia a/s, Rørmosevej 2A, 3450 Allerød, Denmark.
url: www.nutricia.dk

Nutricia, Fin. Nutricia Oy, Linnankatu 26 A, 20100 Turku, Finland.
url: www.nutricia.fi

Nutricia, Fr. Nutricia, 4 rue Joseph-Monier, 92859 Rueil-Malmaison cdx, France.Scientific & Regulatory Affairs Manager
url: www.nutricia.fr

Nutricia, Hong Kong. Nutricia (Asia-Pacific) Ltd, Suite 1505, 15/F Harcourt House, 39 Gloucester Rd, Wonchai, Hong Kong.
url: www.nutricia.com

Nutricia, Indon. Nutricia Indonesia PT, Cyber 2 Building, 16th floor, Jl HR Rasuna Said, Blok X-5 No 13, Jakarta 12950, Indonesia.
url: www.nutricia.co.id

Nutricia, Irl. Nutricia Clinical Ireland Ltd, Deansgrange Business Park, Deonsgrange, Co. Dublin, Ireland.
url: www.nutricia.com

Nutricia, Ital. Nutricia S.p.A., Via Lepetit 8, 20020 Lainate (MI), Italy.
url: www.nutricia.it

Nutricia, Malaysia. See *Zuellig, Malaysia.*

Nutricia, Mex. Nutricianales American S.A. de C.V., Iglesia 2, Torre E Desp. 601, Col. Tizapan de San Angel, 01090 Mexico D.F., Mexico.
url: www.nutricia.com

Nutricia, NZ. Nutricia New Zealand, 37 Banks Rd, Mt Wellington, Auckland, New Zealand.
url: www.nutricia.com

Nutricia, Pol. Nutricia Polska Sp. zo.o., ul. Bobrowiecko 6, 00-728 Warsaw, Poland.
url: www.nutricia.com.pl

Nutricia, Port. Nutricia Portugal. Lda, Rua da Fraternidade Operária, 2794-024 Carnaxide, Portugal.
url: www.nutricia.pt

Nutricia, Singapore. See *Sime Darby, Singapore.*

Nutricia, Thai. See *Berli Jucker, Thai.*

Nutricia, Turk. See *Numil, Turk.*

Nutricia, Venez. See *Klinos, Venez.*

Nutricia Clinical, UK. Nutricia Clinical Care, Nutricia Ltd, Newmarket Ave, White Horse Business Park, Trowbridge, Wiltshire, BA14 0XQ, UK.
url: www.nutricia-clinical-care.co.uk

Nutricia Dietary, UK. See *Nutricia Clinical, UK.*

Nutricia-Bago, Arg. Nutricia-Bagó S.A., Marcelo T de Alvear 590 Piso 1, 1058 Buenos Aires, Argentina.
url: www.nutricia-bago.com.ar

Nutricia-Loma Lindar, USA. See *Nutricia, Mex.*

Nutricion Medica, Spain. Nutrición Medica SL, c/Sangenjo 10, 28034 Madrid, Spain.

Nutricional, Arg. Nutricional Argentina SRL, Av. Pueyrredon 924, Piso 3 F, 1032 Buenos Aires, Argentina.

Nutri-Cology, Canad. See *Nutri-Cology, USA.*

Nutri-Cology, USA. Nutri-Cology, 2300 North Loop Rd, Alameda, CA 94502, USA.

Nutricorp, Canad. Nutricorp International, 4025 Rhodes Drive, Windsor, Ontario, N8W 5B5, Canada.

Nutridiver, Spain. Nutridiver SL, C/del Pont Reixat 5, 08960 Sant Just Desvern, Barcelona, Spain.

Nutridriver, Spain. Nutridriver SL, Avda Mare de Deu de Montserrat 221, 08041 Barcelona, Spain.

Nutri-Dyn, Canad. Nutri-Dyn Products Ltd, 4307 49th Street, Innisfail, Alberta, T4G 1P3, Canada.

Nutrifarma, Turk. Nutrifarma Sağlick Ürün ve Hizm. A.Ş., Büyükdere Cad., Nurol Plazo No:71 K:19, Maslak, İstanbul, 80870, Turkey.
url: www.nutrifarma.com.tr

Nutrifood, Philipp. See *Tridharma, Philipp.*

Nutriforce, Singapore. See *Pharmatech, Singapore.*

Nutrigen, UK. Nutrigen, UK.

Nutrilab, Arg. Laboratorio Nutrilab de E Susana Acosta, San Juan 3130, (2000) Rosario, Santa Fe, Argentina.

Nutrilab, Braz. See *Farmoquimica, Braz.*

Nutrilite, Arg. See *Amway, Arg.*

Nutrimed, Switz. Nutrimed AG, Pharmazeutische und diatetische Produkte, Spalenvorstadt 34, 4051 Basle, Switzerland.
url: www.nutrimed.ch

Nutrimedical, Austral. See *Max Biocare, Austral.*

Nutrimedis, Switz. Nutrimedis SA, Rue de Vevey 218, 1630 Bulle, Switzerland.

Nutrimmune, Canad. Nutrimmune Technologies Inc., Cobourg, Ontario, K9A 4W4, Canada.

Nutripharm, USA. Nutripharm Laboratories Inc., Salem Industrial Park, Building 5, Lebanon, NJ 08833, USA.

Nutripur, Canad. Nutripur Inc., 101 86,des Entreprises, Boisbriand, Quebec, J7G 2T3, Canada.

Nutrisante, Fr. Nutrisanté (Lab), Parc d'activité Sud Loire, BP 1211, 85612 Montaigu cdx, France.
url: www.nutrisante.fr

Nutrisante, Singapore. See *Age D'or, Singapore.*

Nutri-Source, Canad. Les Aliments Nutri-Source Inc., 3560 rue Isabelle, Brossard, Quebec, J4Y 2R3, Canada.

Nutrisoy, USA. See *Mothersoy, USA.*

Nutrition & Sante, Ital. Nutrition & Santé S.p.A., L.go Umberto Boccioni 1, 21040 Origgio (VA), Italy.

Nutrition 21, USA. Nutrition 21, 4 Manhattonville Rd, Purchase, NY 10577, USA.
url: www.nutrition21.com

Nutrition Medical, Israel. See *Megapharm, Israel.*

Nutrivercell, Fr. Nutrivercell, 4 rue Pierre-Fontaine, 91058 Évry cdx, France.
url: www.nutrivercell.com

Nutri-Well, Hong Kong. See *Winsor, Hong Kong.*

Nutri-West, Canad. See *Nutri-West, USA.*

Nutri-West, USA. Nutri-West Pacific Inc., 2132 E Richards St, Douglas, WY 82633, USA.
url: www.nutriwest.com

Nuvia, Fr. Nuvia (Lab), 92 bvd Flandrin, 75116 Paris, France.
url: www.lovamine.fr

Nuvo, Canad. Nuvo Research Inc., 7560 Airport Rd, Unit 10, Mississauga, Ontario, L4T 4H4, Canada.
url: www.nuvoresearch.com

Nuvo, USA. See *Nuvo, Canad.*

Nuvora, USA. Nuvora Inc., 3350 Scott Blvd 502, Santa Clara, CA 95054, USA.
url: www.nuvorainc.com

Nyal, Austral. See *GSK, Austral.*

Nycomed, Arg. Nycomed Argentina, Adolfo Alsina 2954, 1205 Buenos Aires, Argentina.
url: www.nycomed.com

Nycomed, Austral. See *Amersham, Austral.*

Nycomed, Austria. Nycomed Austria GmbH, St Peter-Strasse 25, A-4020 Linz, Austria.

Nycomed, Belg. Nycomed Christiaens, Chris Juliam, Gentsesteenweg 615, 1080 Brussels, Belgium.
url: www.nycomed.be

Nycomed, Braz. Nycomed Pharma Ltda, Rua do Estilo Barrocco 721, 04709-011 São Paulo, Brazil.

Nycomed, Canad. Nycomed Canada Inc., 1st Floor, 435 North Service Rd West, Oakville, Ontario, L6M 4X8, Canada.

Nycomed, China. Nycomed Pharmaceutical Consultancy Co Ltd, 48/F the Exchange SOHO, 299 Tong Ren Rd, Shanghai 20040, China.
url: www.nycomed.com/cn

Nycomed, Cz. Nycomed sro, Novodvorská 994/138, 142 21 Praha 4, Czech Republic.

Nycomed, Denm. Nycomed Danmark, Langebjerg 1, 4000 Roskilde, Denmark.
url: www.nycomed.dk

Nycomed, Fin. See *Oriola, Fin.*

Nycomed, Fr. Nycomed France SAS, 140 av. Jean Lolive, 93695 Pantin cdx, France.

Nycomed, Ger. Nycomed Deutschland GmbH, Moltkestr. 4, 78467 Konstanz, Germany.
url: www.nycomed.de

Nycomed, Gr. Nycomed Hellas, Kifissias 196, 152 31 Halandri, Greece.
url: www.nycomed.com

Nycomed, Hong Kong. See *IDS, Hong Kong.*

Nycomed, Hung. Nycomed Kft, Kankoly Thege Miklós út 29-33, 1121 Budapest, Hungary.

Nycomed, Irl. See *Newport, Irl.*

Nycomed, Israel. See *Medison, Israel.*

Nycomed, Ital. Nycomed S.p.A., Via Libero Temolo 4, 20126 Milan (MI), Italy.
url: www.nycomed.it

Nycomed, Malaysia. Nycomed Division Diethelm Malaysia Sdn Bhd, Lot 3A-01 Level 3A, Block B, HP Towers, 12 Jln Gelenggang, Damansara Heights, 50490 Kuala Lumpur, Malaysia.
url: www.nycomed.com

Nycomed, Mex. Nycomed SA de CV, Av. Primero de Mayo 130, 53519 Naulcalpán de Juárez Industrial, Estado de Mexico, Mexico.

Nycomed, Neth. Nycomed Nederland BV, Jupiterstraat 250, 2132 HK Hoofddorp, Netherlands.
url: www.nycomed.nl

Nycomed, Norw. Nycomed Pharma AS, Drammensv. 852, Postboks 205, 1372 Asker, Norway.
url: www.nycomed.no

Nycomed, Philipp. Nycomed Pharma Philippinen, 5th Floor Kings Court Building, 12129 Chino Roces Ave, 1231 Makati City, Philippines.
url: www.nycomed.com

Nycomed, Pol. Nycomed Polska Sp. zo.o., ul. Dworkowa 3, 00-784 Warsaw, Poland.

Nycomed, Port. See *Nycomed, Denm.*

Nycomed, Rus. Nycomed Pharma AS, Central Office, Timura Frunze ul. 24, 119021 Moscow, Russia.
url: www.nycomed.ru

Nycomed, S.Afr. Nycomed Pty Ltd, 1 Libertas Rd, Cnr Main Rd & Sloane St, Bryanston, Johanessburg 2191, South Africa.
url: www.nycomed.co.za

Nycomed, Singapore. See *FP, Singapore.*

Nycomed, Spain. See *Amersham, Spain.*

Nycomed, Swed. Nycomed AB, Box 1215, 181 24 Lidingo, Sweden.
url: www.nycomed.se

Nycomed, Switz. Nycomed AG, Moosacherstrasse 14, Au, 8820 Wodenswil, Switzerland.
url: www.nycomed.ch

Nycomed, Thai. See *Shiwa, Thai.*

Nycomed, UK. Nycomed UK Ltd, 3 Globside Business Park, Fieldhouse Lane, Marlow, Buckinghamshire, SL7 1HZ, UK.

Nycomed, Ukr. Nycomed, Krasnoarmeiskaya Street, 55, Kiev, 03150, Ukraine.

Nycomed, USA. See *Amersham Biosciences, USA.*

Nycomed Amersham, Canad. See *Amersham, Canad.*

Nycomed Amersham, Denm. See *GE Healthcare, Denm.*

Nycomed Amersham, Swed. See *Amersham, Swed.*

Nycomed Amersham, Switz. See *Nycomed, Switz.*

Nycomed Amersham, UK. See *Amersham, UK.*

Nycomed Amersham, USA. See *Amersham Biosciences, USA.*

Nycomed Amersham Buchler, Ger. See *GE Healthcare, Ger.*

Nycomed Imaging, Canad. See *Amersham, Canad.*

Nycomed Imaging, Denm. See *GE Healthcare, Denm.*

Nycomed Imaging, Norw. See *Amersham, Norw.*

NZ Distributors, NZ. New Zealand Distributors Ltd, P.O. BOX 41014, St Lukes, Auckland, New Zealand.

NZ Medical & Scientific, NZ. New Zealand Medical & Scientific Ltd, P.O. Box 24-138, Royal Oak, Auckland, New Zealand.
url: www.nzms.co.nz

O2, China. O2 Pharmaceuticals, Suite 2401, Zhijun Hitech Business Plaza, 1223 Xie Tu Rd, Shanghai 200032, China.
url: www.o2pharm.com

Oakhurst, USA. Oakhurst Co., 3000 Hempstead Turnpike, Levittown, NY 11756, USA.
url: www.omedicine.com

OBA, Denm. OBA Pharma ApS, Kronprinsessegade 26A (postboks 117), 1004 Copenhagen K, Denmark.

Obagi, Canad. See *Obagi, USA.*

Obagi, Indon. Obagi Indonesia PT, Jl Gunaworman 45, Jakarta 12180, Indonesia.
url: www.obagi.sg

Obagi, Singapore. See *Zoe Nissi, Singapore.*

Obagi, USA. Obagi Medical Products Inc., 3760 Kilroy Airport Way, Suite 500, Long Beach, CA 90806, USA.
url: www.obagi.com

Oberlin, Fr. See *BMS, Fr.*

Obex, NZ. Obex Medical Ltd, 303 Manukau Rd, P.O. Box 26511, Epsom, Auckland, New Zealand.
url: www.obex.co.nz

Obai, Philipp. See *Pharmawealth, Philipp.*

Obalenskoe, Rus. See *Domestic, Rus.*

Obsurge, India. Obsurge Biotech Ltd, 101-102 Adityo Tower, District Center, Laxmi Nagar, Delhi 110 092, India.
url: www.obsurge.com

Occy, Canad. Occy Laboratoire Inc., 925 Montee Gravel, Laval, Quebec, H7X 2B7, Canada.

Ocean Nutrition, Canad. Ocean Nutrition Canada Ltd, 101 Research Drive, Dartmouth, Nova Scotic, B2Y 4T6, Canada.

Oceana, USA. Oceana Therapeutics Inc., 2035 Lincoln Highway, Edison, NJ 08817, USA.
url: www.oceanatherapeutics.com

OCFZP, Pol. OCFZP Biostymulator International Trading Co. Sp. zo.o., ul. Ks. Łysika 6 B, 46-300 Olesno, Poland.

Ochoa, India. Ochoa Laboratories Ltd, C-171, Phase II Hoziery Complex, Noida 201 301, India.

Oclassen, USA. See *Watson, USA.*

O'Connor, USA. See *Columbia, USA.*

Octapharma, Austral. Octapharma Australia Pty Ltd, Jones Bay Wharf, 42/26-32 Pirrama Rd, Pyrmont, NSW 2009, Australia.

Octapharma, Austria. Octapharma Pharmazeutika, Oberlaaer Strasse 235, A-1100 Vienna, Austria.
url: www.octapharma.com

Octapharma, Belg. Octapharma SA, Rue de Stalle 63, 1180 Brussels, Belgium.
url: www.octapharma.com

Octapharma, Braz. Octapharma Brasil Ltda, Av. Ayrton Senna 1850, Loja 118, 22775003 Rio de janeiro Barra da tijuc, Rio de Janeiro, Brazil.

Octapharma, Canad. Octapharma Canada Inc., 2000 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.

Octapharma, China. Octapharma China, Suite 815 Zhongkun Plaza, 59 GaoliangQiaoXiejie, HaiDianQu, Beijing, 100044, China.
url: www.octapharma.com

Octapharma, Cz. See *Octapharma, Austria.*

Octapharma, Denm. See *Octapharma, Swed.*

Octapharma, Fin. Octapharma AB, Myyrmaentie 2 B, 01600 Vantaa, Finland.
url: www.octapharma.com

Octapharma, Fr. Laboratoires Octapharma SA, 70-72 rue du Maréchal-Foch, B.P. 33, 67381 Lingolsheim, France.
url: www.octapharma.com

Octapharma, Ger. Octapharma GmbH, Elisabeth-Selbert-Str. 11, 40764 Langenfeld, Germany.
url: www.octapharma.de

Octapharma, Gr. Octapharma Hellas S.A., 60 Poseidonos Ave, 166 75 Glyfada, Greece.
url: www.octapharma.gr

Octapharma, Hong Kong. See *Weston, Hong Kong.*

Octapharma, Hung. Octapharma Képviselet, Harcsa u 2, 1023 Budapest, Hungary.

Octapharma, Irl. See *Octapharma, UK.*

Octapharma, Israel. See *Medigal, Israel.*

Octapharma, Ital. Octapharma Italy Spa, Via Cisanello 145, 56124 Pisa, Italy.
url: www.octapharma.com

Octapharma, Mex. Octapharma SA de CV, Calzada de México Tacuba 1419, 11230 M Hidalgo Nueva Argentina, Mexico.

Octapharma, Neth. Octapharma, Netherlands.

Octapharma, Norw. Octapharma AS, Furubakken, 2090 Hurdal, Norway.
url: www.octapharma.com

Octapharma, NZ. Octapharma New Zealand Ltd, Lumley Centre, 88 Shortland St, Auckland, New Zealand.

Octapharma, Pol. Octapharma AG Przedstwicielstwo w Polsce, ul. lt 26, 02-135 Warsaw, Poland.
url: octapharma.com

Octapharma, Port. Octapharma Produtos Farmacêuticos Lda, Rua da Graca 14, 1170-169 Lisbon, Portugal.

Octapharma, Rus. Octapharma, Smolensk pl. 3, 121099 Moscow, Russia.

Octapharma, Singapore. See *Steward Cross, Singapore.*

Octapharma, Spain. Octapharma S.A., Diego Garcia, Parque Empresarial de San Fernando, Av. Castilla 2, 28830 Madrid, Spain.
url: www.octapharma.es

Octapharma, Swed. Octapharma Nordic AB, Elersvägen 40, SE-112 75 Stockholm, Sweden.
url: www.octapharma.com

Octapharma, Switz. Octapharma AG, Seidenstrasse 2, Postfach 239, 8853 Lachen, Switzerland.
url: www.octapharma.com

Octapharma, Thai. See *Hua, Thai.*

Octapharma, UK. Octapharma Ltd, The Zenith Building, 26 Spring Gardens, Manchester, M2 1AB, UK.
url: www.octapharma.co.uk

Octapharma, USA. Octapharma USA, Inc., 5885 Trinity Parkway, Suite 350, Centreville, VA 20170, USA.
url: www.octapharmausa.com

October, Rus. Farmstandart October, 5 Aptekarsky pr, 197376 St Petersburg, Russia.

October Pharma, Ukr. See *Alex Pharm, Ukr.*

Ocular Sciences, Fr. See *Essilor, Fr.*

Ocumed, USA. OcuMed Inc., 1307 W. Fillmore, Chicago, IL 60607, USA.
url: www.ocumed.com

Ocusoft, USA. Cynacon/OCuSOFT, 5311 Ave N, P.O. Box 429, Richmond, TX 77406-0429, USA.
url: www.ocusoft.com

Odan, Canad. Odan Laboratories Ltd, 255 Hymus Bvld, Pointe-Claire, Quebec, H9R 1G6, Canada.
url: www.odanlab.com

Odin, Spain. See *AstraZeneca, Spain.*

Oditas, Turk. Oditas A.Ş., Taşkent Cad. 11 Sok. No: 40/10, Bahçelievler, Ankara, Turkey.

Odontofarma, Arg. Odontofarma SA, Av. Rafael Nuñez 4775 PB, Local 22, 5009 Cerro de las Rosas, Cordoba, Argentina.

Odontopharm, Switz. Odontopharm AG, Engestrasse 23, 3012 Bern, Switzerland.

Odyssey, USA. Odyssey Pharmaceuticals Inc, 200 Park Ave., Florham Park, NJ 07932, USA.
url: www.odysseypharm.com

Oenobiol, Fr. Laboratoires Oenobiol, 59 bd Exelmans, 75781 Paris cdx 16, France.
url: www.oenobiol.com

OEP, Philipp. OEP Philippines Inc., Rm 606 Sedcco 1 Bldg, Cor Rada & Legaspi Sts, Legaspi Vill, Makati City, Philippines.

OFF, Ital. Officina Farmaceutica Fiorentina S.r.l. Istituto Biochimico, Quart. Varignano 12-14, 55049 Viareggio (Lucca), Italy.
url: www.off-biolabs.it

Offenbach, Mex. Offenbach Mexicana S.A. de C.V., Cda. del Rosedal 3, Col. Reforma Social, 11650 Mexico D.F., Mexico.

Ofimex, Mex. See *Sanofi-Aventis, Mex.*

Oftagen, Ital. Oftagen Srl, Via GB Olivia 6, 56121 Pisa, Italy.
url: www.oftagen.com

Oftalder, Port. See *Edol, Port.*

Oftalmi, Venez. Laboratorios L.O. Oftalmi C.A., Edificio Santo Domingo, Calle 6, Zona Industrial La Urbina, Apto 66285, Caracas 1061-A, Venezuela.
url: www.oftalmi.com

Ogna, Ital. Giovanni Ogna & Figli S.p.A., Via Figini 41, 20053 Muggiò (MI), Italy.
url: www.ogna.it

Ohara, Jpn. Ohara Pharmaceutical Co. Ltd, 121-15 Toriino, Koka-cho, Koka-shi, Shiga, 520-3403, Japan.
url: www.ohara-ch.co.jp

Ohara, Philipp. See *Crisdy-Na, Philipp.*

Ohm, USA. Ohm Laboratories Inc., 600 College Road East, Princeton, NJ 08540, USA.
url: www.ohmlabs.com

Ohmeda, USA. See *Baxter, USA.*

Ohropax, Switz. See *Uhlmann-Eyraud, Switz.*

Ohta, Hong Kong. See *Primal, Hong Kong.*

OJG, Belg. See *Novum, Belg.*

Okasa, Philipp. See *Sydenham, Philipp.*

Okasa, Rus. See *Veropharm, Rus.*

Okasa, Thai. See *IDS, Thai.*

Oksigon, Rus. Oksigon Inc., Russia.

Oktenifarm, Ukr. Oktenifarm, Engineering St 44, 03680 Kiev, Ukraine.

Olainfarm, Rus. Balitfarm, ul 7 Kozhuchovskaya dom 20, 115193 Moscow, Russia.
url: www.olainfarm.ru

Olainfarm, Ukr. See *Olfa, Ukr.*

Olan-Kemed, Thai. Olan-Kemed Co. Ltd, 176 Ladprao Rd, Bangkok 10900, Thailand.

Olbas, Ger. Deutsche Olbas GmbH, Hutwiesenstr. 14, 71106 Magstadt, Germany.

Olea, Turk. Olea Sağlik Ürünleri İlaç, Alemdağ Cd Bayir SK N:7, Kisikli, Üsküdar, Istanbul, Turkey.

Oleosea, Fr. See *Oleosea, Switz.*

Oleosea, Switz. Oleosea, rue Hans Fries 1, 1700 Fribourg, Switzerland.
url: www.oleosea.com

Olfa, Ukr. OOO Olfa, Dankevicha Street, 4, Kiev, 02232, Ukraine.

Olgunsoy, Turk. Olgunsoy İlaç ve Kozmetik Sanayi A.Ş., 4152 Sok. No: 31, Karabağlar, İzmir, Turkey.
url: www.olgunsoy.com

Olic, Thai. Olic (Thailand) Ltd, 280 New Rd, Bangkok 10100, Thailand.
url: www.dksh.com

Olifen, Rus. See *Masterlek, Rus.*

Oligosol, Switz. Oligosol AG, Untermattweg 8, 3001 Berne, Switzerland.

Olinka, Neth. See *Olinka, UK.*

Olinka, UK. Olinka UK Ltd, 38/40 Chamberlayne Rd, London, NW10 3JE, UK.

Olive, India. Olive Lifesciences, 135 2nd Floor Rear Wing, Brigade Towers, Brigade Rd, Bangalore 560 003, India.
url: olivelifesciences.com

Olive Healthcare, Philipp. See *Singapore Genebio, Philipp.*

OL-Ukraine, Ukr. OOO OL-Ukraine, Predslavinskaya Street, 43/2, Kiev, 03150, Ukraine.

Olvos, Gr. Olvos Science A.E., Achilleos 2, 104 37 Athens, Greece.

Olympus, Denm. See *Olympus, Irl.*

Olympus, Ger. See *Olympus, Irl.*

Olympus, Gr. See *Olympus, Irl.*

Olympus, Irl. Olympus Biotech International Ltd, Raheen Business Park, Limerick, Ireland.

Olympus, Neth. See *Olympus, Irl.*

Olympus, Spain. Olympus Biotech Iberica SLs, Gral. Carlos Castaños, 1.28071 Madrid, Spain.
url: www.olympusbiotech.eu

Olympus, Swed. See *Olympus, Irl.*

OM, Austria. See *OM, Port.*

OM, Cz. See *Pharmedial, Cz.*

OM, Hong Kong. See *Primal, Hong Kong.*

OM, Hung. OM Hungária Kft, Mandula köz 6, 2089 Telki, Hungary.

OM, Indon. See *Corsa, Indon.*

OM, Irl. See *OM, Port.*

OM, Malaysia. See *Pharmaforte, Malaysia.*

OM, Neth. See *OM, Port.*

OM, Philipp. See *Zuellig, Philipp.*

OM, Pol. See *Pharmbos, Pol.*

OM, Port. OM Portuguesa, SA, Rua da Indústria no 2, Quinta Grande, 2720-302 Alfragide, Portugal.
url: www.ompharma.com

OM, Rus. See *Grunenthal, Rus.*

OM, Singapore. See *Pharmaforte, Singapore.*

OM, Switz. OM Pharma, 22 rue du Bois-du-Lan, 1217 Meyrin 2/Geneva, Switzerland.
url: www.ompharma.com

Om Biotec, India. Om Biotec, 4814/24 Mathur Lane, Ansari Road, Darya Ganj, New Delhi 110 002, India.
url: www.ombiotec.com

Ombrelle, Canad. Ombrelle Canada, 4895 Hickmore, Montreal, Quebec, H4T 1K5, Canada.

Omedir, Arg. Laboratorios Omedir S.A., Corvalan 1983/85, 1440 Buenos Aires, Argentina.

Omega, Arg. Esp. Medicinales Omega, Serrano 985, 1414 Buenos Aires, Argentina.

Omega, Austral. Omega Pharma, Suite 51, Level 2, Narabang Way, Belrose, NSW 2085, Australia.
url: www.omegapharma.com.au

Omega, Belg. Omega Pharma, Industriepark De Prijkels, Venecoweg 26, 9810 Nazareth, Belgium.
url: www.omega-pharma.be

Omega, Canad. Omega Laboratories Ltd, 11177 Hamon St, Montreal, Quebec, H3M 3A2, Canada.
url: www.omegalaboratory.com

Omega, Fr. Omega Pharma SA, Rue Chaintron 2/4, B.P. 850, 92120 Montrouge, France.

Omega, Ger. See *Omega, Belg.*

Omega, Gr. Omega Pharma Hellas, 19o chlm. Ethn. Odou Athinon-Lamias, 146 71 N Erithraia, Greece.

Omega, Hong Kong. See *Sino-Asia, Hong Kong.*

Omega, Irl. Omega Diagnostics Ireland Ltd, Unit A6, Southern Cross Business Park, Boghall Rd, Bray, Co. Wicklow, Ireland.
url: www.omegairl.com

Omega, Neth. Omega Pharma Nederland BV, Kralinseweg 201, 3062 Rotterdam, Netherlands.

Omega, Rus. Omega Pharma, Mezhdunarodnaya-2 of. 747, Krasnopresnenskaya Nab 12, 123610 Moscow, Russia.

Omega, Singapore. See *Apex, Singapore.*

Omega, Spain. See *Almirall, Spain.*

Omega, UK. Omega Pharma, Fourth Floor, Hamilton House, Mabledon Place, London, WC1H 9BB, UK.
url: www.omegapharma.co.uk

Omega, Ukr. See *ICF, Ukr.*

Omega Rex, Pol. Omega Rex, ul. Instalatorów 9, 02-237 Warsaw, Poland.

Omegin, Ger. Omegin Dr Schmidgall GmbH, Industriepark 210, 78244 Gottmadingen, Germany.
url: www.omegin.de

Omeofarma, Ital. Omeofarma S.r.l., Via di Morena 12/a, 00043 Ciampino (RM), Italy.

Omicron, Arg. Laboratorio Omicron SA, Calle 23 Esquina Calle 66, 1651 San Martin Villa Zagela, Buenos Aires, Argentina.

Omida, Switz. Omida AG, Homoopathische Heilmittel, Erlistrasse 2, 6403 Kussnacht a.R., Switzerland.

Omikron, Ital. Omikron Italia S.r.l., Viale Bruno Buozzi 5, 00197 Rome (RM), Italy.
url: www.omikronitalia.it

OMJ, Hong Kong. See *Keller, Hong Kong.*

Omni, UK. Omni Nutraceuticals Ltd, 8 St. Thomas Place, Cambridgeshire Business Park, Ely, Cambridgeshire, CB7 4EX, UK.
url: www.omninutra.co.uk

Omnia, Swed. Omnia Läkemedel AB, Järnvägsgatan 11, 252 24 Helsingborg, Sweden.
url: www.omnialakemedel.se

Omnii, USA. Omnii Oral Pharmaceuticals, 1500 N Florida Mango Rd, Suite 1, West Palm Beach, FL 33409, USA.
url: www.omniipharma.com

Omnimed, S.Afr. See *Braun, S.Afr.*

Omninvest, Hung. Omninvest, P.O. Box 112, 1506 Budapest, Hungary.
url: www.omninvest.hu

OmniVision, Denm. See *OmniVision, Swed.*

OmniVision, Ger. OmniVision GmbH, Lindbergstr. 7, 82178 Puchheim, Germany.
url: www.omnivision-pharma.com

OmniVision, Norw. See *OmniVision, Swed.*

OmniVision, Swed. OmniVision AB, Svärdvägen 11C, SE-182 33 Danderyd, Sweden.

OmniVision, Switz. OmniVision AG, Zentralstrasse 100, 8212 Neuhausen am Rheinfall, Switzerland.

Omrix, Austria. See *Omrix, Belg.*

Omrix, Belg. Omrix Biopharmaceuticals SA, Waterloo Rd Center, Chaussee de Waterloo 200, 1640 Rhode-St-Genese, Belgium.
url: www.omrix.com

Omrix, Cz. See *Omrix, Belg.*

Omrix, Denm. See *Omrix, Belg.*

Omrix, Fin. See *Omrix, Belg.*

Omrix, Fr. See *Ethicon, Fr.*

Omrix, Ger. See *Omrix, Belg.*

Omrix, Gr. See *Omrix, Belg.*

Omrix, Irl. See *Omrix, Belg.*

Omrix, Israel. Omrix Biopharmaceuticals Ltd, MDA Blood Center, Tel Hashomer Hospital, Tel Aviv 52621, Israel.
url: www.omrix.com

Omrix, Neth. See *Omrix, Belg.*

Omrix, Norw. See *Omrix, Belg.*

Omrix, Pol. See *Omrix, Belg.*

Omrix, Port. See *Omrix, Belg.*

Omrix, Spain. See *Omrix, Belg.*

Omrix, Swed. See *Omrix, Belg.*

Omsk, Rus. Omsk Farmfabrika, ul. 22 Partsezda D.98 korp.3, 644105 Omsk, Russia.

OMT, Ger. OMT GmbH (Optimal Medical Therapies), Rügenweg 16, 32427 Minden, Germany.
url: www.omtmed.com

Oncogenerika, Cz. See *Oncogenerika, Pol.*

Oncogenerika, Hung. See *Oncogenerika, Pol.*

Oncogenerika, Pol. Oncogenerika Sp zo.o, 5/7 Krzywickiego Street, 02-078 Warsaw, Poland.

Oncogenerix, USA. See *Dara, USA.*

Oncohexal, Ger. See *Hexal, Ger.*

Oncomed, India. See *Om Biotec, India.*

Ondee, Canad. See *Omega, Canad.*

One Pharma, Philipp. One Pharma Co Inc., A Liwanag cor G Diaz St, BFRV Classic 1, Las Piñas City, Philippines.
url: www.onepharma.com.ph

Onedose, Spain. Onedose Pharma SL, C/Ca L'Alegre de Dalt 28, Barcelona 08024, Spain.

Onipharm, Gr. Onipharm Pharmaceuticals Ltd, Leof. Vouliagmenis 85, 166 74 Glifada, Greece.

Onko, Turk. Onko & Koçsel İlaçlari, Koşuyolu Cad. No: 102, Kadiköy, Istanbul, 34718, Turkey.
url: www.onkokocsel.com

Onkoworks, Ger. See *Hospira, Ger.*

Ono, Hong Kong. See *Hing Yip, Hong Kong.*

Ono, Jpn. Ono Pharmaceutical Co. Ltd, 2-1-5 Doshomachi, Chuo-ku, Osaka 541-8526, Japan.
url: www.ono.co.jp

Onset, USA. Onset Therapeutics, 400 Highland Corporate Drive, Cumberland, RI 02864, USA.
url: www.onsettx.com

Onstrong, Hong Kong. Onstrong Ltd, Rm B, 11/F, Bright Growth Medical Ctr, 335 Nathan Rd, Kowloon, Hong Kong.

Ontos, USA. Ontos Inc., 342 NW Pacific Ave, Chehalis, WA 98532, USA.
url: 4myskin.com

Ony, Israel. See *Rafa, Israel.*

Ony, Ukr. See *Artur, Ukr.*

ONY, USA. ONY Inc., 1576 Sweet Home Rd, Amherst, NY 14228, USA.

Onyx, Rus. Onyx Farma, Grokholskii per. 13, str. 2, 129010 Moscow, Russia.

Onyx, USA. Onyx Pharmaceuticals Inc., 249 E Grand Ave, South San Francisco, CA 94080, USA.
url: www.onyx.com

OP, Ital. O.P. Pharma S.r.l., Via Torino 51, 20123 Milan (MI), Italy.

Opakim, Turk. Opakim, Turkey.

OPC, Philipp. See *Endure, Philipp.*

Open, China. Open Medicine Co. Ltd, 16 Baicao Rd West, Hi-tech Zone, Chengdu 611731, Sichuan Province, China.
url: www.zycopen.com

Openfar, Spain. Openfar, C/Collado Mediano SN, 28230 Las Rozas, Madrid, Spain.

Opfermann, Cz. See *Opfermann, Ger.*

Opfermann, Ger. Opfermann Arzneimittel GmbH, Robert-Koch-Str. 2, 51674 Wiehl, Germany.
url: www.opfermann.de

Ophir Shalpharm, Israel. See *Rekah, Israel.*

Ophtalkener, Mex. See *Kener, Mex.*

Ophtapharm, Switz. Ophtapharm SA, Gewerbestrasse 7, 6330 Cham, Switzerland.

Ophtha, Denm. See *Actavis, Denm.*

Ophtha, Norw. See *Actavis, Denm.*

Ophthalmos, Braz. Ophthalmos Ind. e Com. de Prods. Farm. Ltda, Rua das Nhandirobas 471, 04349-030 São Paulo, SP, Brazil.
url: www.ophthalmos.com.br

OPi, Canad. See *OPi, Fr.*

OPi, Cz. See *OPi, Fr.*

OPi, Fr. OPi SA, 3 allee des Sequioas, 69760 Limonest, France.

OPi, Israel. See *OPi, Fr.*

OPi, Neth. See *OPi, Fr.*

OPi, UK. OPi Ltd, Aston House, York Rd, Maidenhead, Berkshire, SL6 1SF, UK.

Opofarm, Braz. See *ICN, Braz.*

Opopharma, Switz. Opopharma SA, Kirchgasse 42, 8001 Zurich, Switzerland.

Opsonin, Hong Kong. See *Sincerity, Hong Kong.*

Optaderm, Philipp. Optaderm Pharma Inc., 821 2/F Cortez Bldg, EDSA South Triangle, Quezon City, Philippines.

Optident, UK. Optident Dental Products, International Development Centre, Valley Drive, Ilkley, West Yorkshire, LS29 8PB, UK.
url: www.optident.co.uk

Optikem, Canad. See *Optikem, USA.*

Optikem, USA. Optikem International Inc., 2172 S Jason St, Denver, CO 80223, USA.

Optima, Ger. Optima Pharmazeutische GmbH, Wittibsmühle 5, 85368 Wang, Germany.
url: www.optimapharma.de

Optima, UK. Optima Health Ltd, 47/48 St Mary St, Cardiff, South Glamorgan, CF10 1AD, UK.
url: www.optimah.com

Optimal, Hong Kong. See *Health Tech, Hong Kong.*

Optimapharma, Canad. See *Taro, Canad.*

Optimed, Ger. Optimed Pharma GmbH, Alfred-Nobel-Str. 5, 50226 Frechen, Germany.

Optimer, Canad. Optimer Pharmaceuticals Canada Inc., 4950 Yonge St, Suite 900, Toronto, Ontario, M2N 6K1, Canada.
url: www.optimerpharma.ca

Optimer, USA. Optimer Pharmaceuticals Inc., 10110 Sorrento Valley Rd, Suite C , San Diego, CA 92121, USA.
url: www.optimerpharma.com

Optimox, USA. Optimox Corp., P.O. Box 3378, Suite 406, Torrance, CA 90510-3378, USA.
url: www.optimox.com

Optimum, USA. See *Magno-Humphries, USA.*

Optipharm, Gr. DT Optipharm Ltd, Ionias 61, 184 50 Nicaia, Greece.

Optopics, USA. Optopics, USA.

Optrex, India. Optrex, India.

Optrex, Malaysia. See *Boots Healthcare, Malaysia.*

Optrex, Singapore. See *Boots, Singapore.*

Opus, UK. See *Trinity, UK.*

Opus Materia, Gr. Opus Materia, Palaiologou 33, 175 64 P. Faliro, Greece.

OPW, Ger. See *Nycomed, Ger.*

OraHealth, USA. OraHealth Corp., 13434 SE 27th Place, Bellevue, WA 98005-4211, USA.
url: www.orahealth.com

Oral 7, Singapore. See *DKSH, Singapore.*

Oral-B, Arg. See *Gillette, Arg.*

Oral-B, Austral. Oral-B Laboratories P/L, 5 Caribbean Drive, Scoresby, VIC 3179, Australia.
url: www.oralb.com

Oral-B, Canad. Oral-B Laboratories Ltd, 4 Robert Speck Parkway, Suite 1000, Mississauga, Ontario, L4Z 4C5, Canada.
url: www.oralb.com

Oral-B, Irl. Oral-B Laboratories Ireland, Green Rd, Newbridge, Country Kildare, Ireland.
url: www.oralb.com

Oral-B, Spain. See *Procter & Gamble, Spain.*

Oral-B, USA. Braun Oral-B Consumer Services, 1 Gillette Park, South Boston, MA 02127-1096, USA.
url: www.oralb.com

Oraldent, UK. Oraldent Ltd, Unit 11, Harvard Industrial Estate, Kimbolton, Cambridgeshire, PE28 0NJ, UK.
url: www.oraldent.co.uk

Oraltek, Switz. Oraltek AG, Schachenstrasse 57, 6010 Kriens, Switzerland.

Oramon, Ger. Oramon Arzneimittel GmbH, Mittelstr. 18, 88471 Laupheim, Germany.

Oramon, Neth. See *Oramon, Ger.*

Oramon, Pol. See *Solpharm, Pol.*

OraPharma, Fin. See *OraPharma, Neth.*

OraPharma, Neth. OraPharma Europe Inc., Professor JH Bavincklaan 7, 1183 AT Amstelveen, Netherlands.

OraPharma, Port. See *OraPharma, Neth.*

OraPharma, Swed. See *OraPharma, Neth.*

OraPharma, USA. OraPharma Inc., 732 Louis Dr., Warminster, PA 18974, USA.
url: www.orapharma.com

Orasure, USA. OraSure Technologies Inc., 220 East First St., Bethlehem, PA 18015, USA.
url: www.orasure.com

Orbis Consumer, UK. See *Kappin, UK.*

Orbit, India. Orbit Life Sciences Pvt Ltd, 13 Kailash Darshan, 4th Floor Nana Chowk, Mumbai 400 007, India.

Orchard, Canad. Orchard International Inc., Unit 1, 275 Superior Blvd, Mississauga, Ontario, L5T 2L6, Canada.

Orchid, Hong Kong. See *Mekim, Hong Kong.*

Orchid, India. Orchid Chemicals & Pharmaceuticals Limited, Orchid Towers, 313 Valluvar Kottam High Road, Nungambakkam, Chennai 600 034, India.
url: www.orchidpharma.com

Orchid, Philipp. See *PharmAsia, Philipp.*

Orchid, Rus. Orchid Healthcare, Obrucheva St 4, Building 3, office 140, 119421 Moscow, Russia.
url: www.orchidpharma.com

Orchid, S.Afr. Orchid Pharmaceuticals SA (Pty) Ltd, Jonkra Building, 3 Greyling St, Potchefstroom 2531, South Africa.
url: www.orchidpharma.com

Orchid, Thai. See *Union Medical, Thai.*

Orchid, Ukr. Orchid Chemicals & Pharmaceuticals, Sribnokilskaya 2-A, Office 45, 02095 Kiev, Ukraine.
url: www.orchidpharma.com

Ordain, India. Ordain Health Care Pvt Ltd, Sri Devi Temple Tower, No.6 2nd Main Road, Sembakkam, Chennai 600 073, India.
url: www.ordainhealth.com

Ordesa, Ital. Ordesa Logistica S.r.l., Via Andrea Doria 48/B, 20124 Milan (MI), Italy.
url: www.ordesa.it

Ordesa, Spain. Ordesa, Ctra del Prat 9-11, Sant Boi de Llobregat, 08830 Barcelona, Spain.
url: www.ordesa.es

Or-Dov, Austral. Or-Dov Pharmaceuticals P/L, P.O. Box 172, Doncaster, VIC 3108, Australia.

Orec, Fr. See *Axmed, Fr.*

Orexo, Denm. See *Orexo, Swed.*

Orexo, Swed. Orexo AB, Box 303, 751 05 Upsala, Sweden.
url: www.orexo.com

Orexo, USA. See *Orexo, Swed.*

Orfi, Spain. See *Wyeth, Spain.*

Organica, Philipp. Organica Nutraceuticals Inc., 191 Mayon St, Sta. Mesa Heights, Quezon City, Philippines.
url: www.sleepasil.com

Organika, Canad. Organika Health Products Inc., 13480 Verdun Place, Richmond, British Columbia, V6V 1V2, Canada.
url: www.organika.ca

Organika, Rus. Organika, Novokuznetsk, Russia.

Organon, Arg. Organon Argentina SA, Sucre 865, 1428 Buenos Aires, Argentina.
url: www.organon.com.ar

Organon, Austral. Organon (Australia) P/L, Private Bag 25, Lane Cove, NSW 2066, Australia.
url: www.organon.com

Organon, Austria. Organon GmbH, Siebenbrunnengasse 21/D/IV, A-1050 Vienna, Austria.
url: www.organon.at

Organon, Belg. Organon SA, Crown Building, Chaussee de la Hulpe 166, 1170 Brussels, Belgium.
url: www.organon.be

Organon, Braz. See *Akzo, Braz.*

Organon, Canad. Organon Canada Ltd, 200 Consillium Place, Suite 700, Scarborough, Ontario, M1H 3E4, Canada.Director Regulatory Affairs
url: www.organon.ca

Organon, Chile. Organon Chile Ltda, Loreley 1582, La Reina, Santiago, Chile.

Organon, China. See *MSD, China.*

Organon, Cz. Organon sro, Pobřežní 3, 186 00 Prague 8, Czech Republic.
url: www.organon.cz

Organon, Denm. Organon AS, Literbuen 9, 2740 Skovlunde, Denmark.
url: www.organon.dk

Organon, Fin. Oy Organon AB, Maistraatinportti 2, PL 101, 00241 Helsinki, Finland.
url: www.organon.fi

Organon, Fr. Organon, 10 rue Godefroy, 92821 Puteaux cdx, France.
url: www.organon.fr

Organon, Ger. See *Essex, Ger.*

Organon, Gr. Organon Hellas S.A., P.O. Box 73892, 167 77 Elliniko, Greece.
url: www.organon.gr

Organon, Hong Kong. Organon (HK) Ltd, 27/F, 88 Hing Fat St, Causeway Bay, Hong Kong.
url: www.organon.com

Organon, Hung. Organon Hungary kereskedelmi Kft, Róbert Károly krt 64-66 III em, 1134 Budapest, Hungary.
url: www.organon.hu

Organon, India. See *Merck, India.*

Organon, Irl. See *United Drug, Irl.*

Organon, Israel. See *Neopharm, Israel.*

Organon, Ital. Organon Italia S.p.A., Via Ostilia 15, 00184 Rome (RM), Italy.
url: www.organon.it

Organon, Jpn. Nippon Organon K.K., 5-90 Tomobuchi-cho 1-chome, Miyakojima-ku, Osaka City 534-0016, Japan.
url: www.organon.jp

Organon, Malaysia. Organon (M) Sdn Bhd, Level 4, Building A, Paremba Square, Saujana Resort, Seksyen U2, 40150 Shah Alam, Selangor, Malaysia.
url: www.organon.com

Organon, Mex. Organon Mexicana S.A. de C.V., Calz. de Camarones No. 134, Col. San Salvador Xochimanca, Deleg. Azcapotzalco, 02870 Mexico D.F., Mexico.
url: www.organon.com.mx

Organon, Neth. Organon Nederland BV, Griekenweg 25, 5342 PX Oss, Netherlands.
url: www.organon.nl

Organon, Norw. Organon AS, Johan Drengsrudsv. 52, Postboks 324, 1372 Asker, Norway.
url: www.organon.no

Organon, NZ. See *Pharmaco, NZ.*

Organon, Philipp. Organon Philippines Inc., 5/F Feliza Bldg, 108 VA Rufino St, Legaspi Vill, MCPO Box 2003, Makati City, Philippines.

Organon, Pol. Organon Polska Sp. zo.o., ul. Poleckzi 21, 02-822 Warsaw, Poland.
url: www.organon.com.pl

Organon, Port. Organon Portuguesa, Lda, Av. Conde Valbom 30, 1069-037 Lisbon, Portugal.
url: www.organon.pt

Organon, Rus. Organon, Smolnaya ul. 24d, 125445 Moscow, Russia.
url: www.organon.ru

Organon, S.Afr. Organon Pharmaceuticals, P.O. Box 75907, Gardenview 2047, South Africa.
url: www.organon.co.za

Organon, Singapore. See *Zuellig, Singapore.*

Organon, Spain. Organon Española, Ctra de Hospitalet 147-149, Ed Amsterdam, Citypark, R Del Dalt, Cornella de Llobregat, 08940 Barcelona, Spain.
url: www.organon.es

Organon, Swed. Organon AB, Fiskhamnsgatan 6A, 414 58 Göteborg, Sweden.
url: www.organon.se

Organon, Switz. Organon SA, Churerstrasse 158, 8808 Pfaffikon/SZ, Switzerland.
url: www.organon.ch

Organon, Thai. Organon (Thailand) Ltd, 14 Fl, Ploenchit Center Building, 2 Sukhumvit Rd, Klongtoey, Bangkok 10110, Thailand.

Organon, Turk. Organon İlaçları A.Ş., Mahir İz Cad. No. 21, Altunizade, İstanbul, 81270, Turkey.
url: www.organon.com.tr

Organon, UK. Organon Laboratories Ltd, Cambridge Science Park, Milton Rd, Cambridge, CB4 0FL, UK.
url: www.organon.com

Organon, Ukr. Organon Agencies B.V., B. Khmelnitskogo Street, 52, Kiev, 01030, Ukraine.

Organon, USA. Organon Inc., 56 Livingston Ave, Roseland, NJ 07068, USA.
url: www.organon-usa.com

Organon, Venez. Organon Venezolana, S.A., Appartado Postal 549, Caracas 1010-A, Venezuela.
url: www.organon.com.ve

Organon (Οργανον), Gr. See *Organon, Gr.*

Organon Teknika, Austral. See *Organon, Austral.*

Organon Teknika, Austria. See *Essex, Ger.*

Organon Teknika, Belg. See *Bio-Merieux, Belg.*

Organon Teknika, Braz. See *Akzo, Braz.*

Organon Teknika, Canad. See *Organon, Canad.*

Organon Teknika, Chile. See *Organon, Chile.*

Organon Teknika, Denm. See *Organon, Denm.*

Organon Teknika, Fin. See *Organon, Fin.*

Organon Teknika, Fr. See *Organon, Fr.*

Organon Teknika, Ger. See *Essex, Ger.*

Organon Teknika, Gr. See *Organon, Gr.*

Organon Teknika, Hong Kong. See *Organon, Hong Kong.*

Organon Teknika, Irl. See *United Drug, Irl.*

Organon Teknika, Israel. See *Tec-O-Pharm, Israel.*

Organon Teknika, Mex. See *Organon, Mex.*

Organon Teknika, Norw. See *Organon, Norw.*

Organon Teknika, Spain. See *Bio-Merieux, Spain.*

Organon Teknika, Switz. See *Organon, Switz.*

Organon Teknika, UK. See *Organan, UK.*

Organon Teknika, USA. See *Bio-Merieux, USA.*

Orient, Hong Kong. Orient Europharma, Rm 605-6 6/F Prosperity Ctr, 25 Chong Yip St, Kwun Tong, Kowloon, Hong Kong.
url: www.oep.com.tw

Orient, Malaysia. Orient Europharma (M) Sdn Bhd, 33 Jln U1/30, Section U1, 40150 Shah Alam, Selangor, Malaysia.

Orient, Singapore. Orient Europharm Pte Ltd, 1 Sophia Rd, 04-12 Peace Centre, S 228149, Singapore.

Oriental, Arg. Oriental Farmaceutica I.C.I.F.A., G. Cossio 6160, 1408 Buenos Aires, Argentina.

Oriental, Philipp. See *Endure, Philipp* and *Phoenix, Philipp.*

Orifarm, Denm. Orifarm Generics A/S, Energivej 15, 5260 Odense S, Denmark.
url: www.orifarm.dk

Orifarm, Fin. See *Orifarm, Denm.*

Orifarm, Norw. Orifarm Generics, Nydalsv. 33, 0484 Oslo, Norway.
url: www.orifarm.no

Orifarm, Swed. Orifarm AB, Box 50231, 202 12 Malmö, Sweden.
url: www.orifarm.com

Oriola, Fin. Oriola Oy, PL 8, 02101 Espoo, Finland.
url: www.oriola.com

Orion, Austral. Orion Laboratories P/L, 85 Briggs St, Welshpool, WA 6106, Australia.
url: www.orion.net.au

Orion, Austria. See *Orion, Fin.*

Orion, Belg. Orion Pharma, Pegasuslaab 5, 1831 Diegem, Belgium.
url: www.orion.fi

Orion, China. See *NovaMed, China.*

Orion, Cz. Orion Pharma sro, Zeleny pruh 95/97, 140 00 Prague 4, Czech Republic.
url: www.orionpharma.cz

Orion, Denm. Orion Pharma A/S, Møllevej 9A, 2990 Nivå, Denmark.
url: www.orionpharma.dk

Orion, Fin. Orion-yhtymä Oyj, Kalkkipellontie 2, 02601 Espoo, Finland.
url: www.orionpharma.com

Orion, Ger. Orion Pharma GmbH, Notkestr. 9, 22607 Hamburg, Germany.
url: www.orionpharma.com

Orion, Gr. See *Organon, Gr.*

Orion, Hong Kong. See *Treasure Mountain, Hong Kong.*

Orion, Hung. Orion Pharma Kft, Xenter 13 Irodaház, 1139 Budapest, Hungary.
url: www.orion.fi

Orion, India. Orion Biotech Pvt Ltd, 215 Platinum Plaza, Bodakdev, Ahmedabad 380 054, India.

Orion, Irl. See *Allphar, Irl.*

Orion, Israel. See *Genmedix, Israel* and *Rafa, Israel.*

Orion, Ital. Orion Pharma Srl, Piazza 4 Novembre 7, 20124 Milan, Italy.
url: www.orion.fi

Orion, Malaysia. See *Apex, Malaysia.*

Orion, Neth. See *Orion, Fin.*

Orion, Norw. Orion Pharma AS, Gjerdrumsv. 8, Postboks 4366 Nydalen, 0402 Oslo, Norway.
url: www.orionpharma.no

Orion, NZ. See *Zuellig, NZ* and *St Ives, NZ.*

Orion, Pol. Orion Oyj SA, Przedstawicielstwo w Polsce, ul. Parandowskiego 19, 01-699 Warsaw, Poland.

Orion, Port. See *Orion, Fin.*

Orion, Rus. Orion Corporation, Orion Pharma, Lyusinovskaya ul. 36, et. 7, 113093 Moscow, Russia.
url: www.orionpharma.ru

Orion, Singapore. See *Pharmacon, Singapore.*

Orion, Spain. Orion Pharma SL, Velazquez 157, 28002 Madrid, Spain.

Orion, Swed. Orion Pharma AB, Box 334, 192 30 Sollentuna, Sweden.
url: www.orionpharma.se

Orion, Switz. Orion Pharma AG, Untermuli 11, 6300 Zug, Switzerland.
url: www.orionpharma.ch

Orion, Thai. See *Harn, Thai.*

Orion, UK. Orion Pharma UK Ltd, 1st Floor Leat House, Overbridge Square, Hambridge Lane, Newbury, Berkshire, RG14 5UX, UK.
url: www.orionpharmo.com

Orion, Ukr. Orian Corporation, Sholudenko Street, 3, office 309, Kiev, 04116, Ukraine.
url: www.orionpharma.com.ua

Orion, USA. See *Lifesign, USA.*

Orion Corp., Denm. See *Orion, Denm.*

Ormed, Ger. ORMED GmbH & Co KG, Merzhauser Str. 112, 79100 Freiburg, Germany.
url: www.djoglobal.de

Orna, Turk. Orna İlaç San. ve Tic Ltd., Çavuşbaşi Cad. Yayabeyi Sok., Arin İş Mer. No. 11, Kovacik, İstanbul, Turkey.

Oro, Turk. Oro İlaçlari Ltd. Şti., Girne Mahallesi, Narlidere Cad. No: 19 K: 3, Maltepe, İstanbul, 81550, Turkey.

Orochemie, Ger. orochemie GmbH & Co. KG, Max-Planck-Str. 27, 70806 Kornwestheim, Germany.
url: www.orochemie.de

OrPha, Switz. OrPha Swiss GmbH, Untere Heslibachstrasse 41a, 8700 Küsnacht ZH, Switzerland.
url: www.orpha.ch

Orpha-Devel, Austria. Orpha-Devel Handels- und Vertriebs GmbH, Wintergasse 85/1b, A-3002 Purkersdorf, Austria.

Orpha-Devel, Cz. See *Orpha-Devel, Austria.*

Orpha-Devel, Denm. See *Orpha-Devel, Austria.*

Orpha-Devel, Fin. See *Orpha-Devel, Austria.*

Orpha-Devel, Gr. See *Orpha-Devel, Austria.*

Orpha-Devel, Hung. See *Orpha-Devel, Austria.*

Orpha-Devel, Irl. See *Orpha-Devel, Austria.*

Orpha-Devel, Neth. See *Orpha-Devel, Austria.*

Orpha-Devel, Norw. See *Vitaflo, Norw.*

Orpha-Devel, Port. See *Orpha-Devel, Austria.*

Orphan, Austral. Orphan Australia pty ltd, 300 Frankston-Dandenong Rd, Dandenong, Victoria 3175, Australia.
url: www.orphan.com.au

Orphan, Austria. See *Orphan, Fr.*

Orphan, Belg. Orphan Europe Benelux BVBA, Koning Albert I Laan 48, 1780 Wemmel, Belgium.

Orphan, Cz. See *Orphan, Fr.*

Orphan, Denm. Swedish Orphan AS, Wilders Plads 5, 1403 Copenhagen K, Denmark.
url: www.swedishorphan.com

Orphan, Fin. See *Orphan Europe, Swed.*

Orphan, Fr. Orphan Europe SARL, Imm Le Guillaumet, 92046 Paris-La Défense, France.
url: www.orphan-europe.com

Orphan, Ger. Orphan Europe (Germany) GmbH, Max-Planck-Str. 6, 63128 Dietzenbach, Germany.
url: www.orphan-europe.com

Orphan, Hung. See *Orphan, Ger.*

Orphan, Irl. See *Orphan, UK.*

Orphan, Ital. Orphan Europe Italy S.r.l., Via Cellini 11, 20090 Segrate (MI), Italy.
url: www.orphan-europe.com

Orphan, Neth. See *Swedish Orphan, Swed.*

Orphan, Pol. Orphan Europe (Germany) GmbH, Przedstawicielstwo w Polsce, ul. Czereśniowa 98, 02-456 Warsaw, Poland.
url: www.orphan-europe.com

Orphan, Spain. Orphan Europe, Gran Via de les Corts Catalanes 649, Despacho No 1, 08010 Barcelona, Spain.
url: www.orphan-europe.com

Orphan, UK. Orphan Europe (UK) Ltd, Isis House, 43 Station Rd, Henley-on-Thames, Oxfordshire, RG9 1AT, UK.
url: www.orphan-europe.com

Orphan Europe, Denm. See *Orphan Europe, Swed.*

Orphan Europe, Norw. See *Orphan Europe, Swed.*

Orphan Europe, Port. See *Orphan, Spain.*

Orphan Europe, Swed. Orphan Europe Nordic AB, Banérgatan 37, 115 22 Stockholm, Sweden.
url: www.orphan-europe.com

Orphan Medical, Canad. See *Orphan Medical, USA.*

Orphan Medical, Israel. See *Tzamal, Israel.*

Orphan Medical, USA. Orphan Medical Inc., 13911 Ridgedale Drive, Suite 250, Minnetonka, MN 55305, USA.
url: www.orphan.com

Orphan Pacific, Jpn. Orphan Pacific Inc., 7-10-4 Nishi-Gotanda, Shinagawa-ku, Tokyo, Japan.
url: www.orphanpacific.com

Orravan, Spain. See *ReigJofre, Spain.*

Orsade, Spain. Orsade, Avda Virgen de Montserrat 221, 08026 Barcelona, Spain.

Ortec, USA. Ortec International Inc., 9920 Kenmore Blvd, Akron, OH 44314, USA.
url: www.cortecinternational.com

Ortega, USA. Ortega, USA.

Orthim-Molitor, Ger. Orthim-Molitor Pharma GmbH, Lindenstr. 55, 33378 Rheda-Wiedenbrück, Germany.

Ortho, Canad. See *Janssen-Ortho, Canad.*

Ortho, Hong Kong. See *Janssen, Hong Kong* and *Jacobson, Hong Kong.*

Ortho, Hung. See *Johnson & Johnson, Hung.*

Ortho, Israel. See *CTS, Israel.*

Ortho, UK. See *Janssen, UK.*

Ortho, Venez. See *Johnson & Johnson, Venez.*

Ortho Biotech, Cz. See *Ortho Biotech, USA.*

Ortho Biotech, UK. See *Janssen, UK.*

Ortho Biotech, USA. Ortho Biotech L.P., 430 Route 22 East, P.O. Box 6914, Bridgewater, NJ 08807-0914, USA.
url: www.orthobiotech.com

Ortho Dermatological, Canad. See *Johnson & Johnson, Canad.*

Ortho Dermatological, USA. See *Ortho Neutrogena, USA.*

Ortho Diagnostic, Belg. Ortho-Clinical Diagnostic SA, Antwerpsesteenweg 19-21, 2340 Beerse, Belgium.

Ortho Diagnostic, UK. See *Johnson & Johnson MSD Consumer, UK.*

Ortho Diagnostic, USA. Ortho-Clinical Diagnostic Inc., 100 Indigo Creek Dr., Rochester, NJ 14626, USA.
url: www.orthoclinical.com

Ortho McNeil, USA. Ortho McNeil Pharmaceutical Inc., 1000 Route 202, P.O. Box 300, Raritan, NJ 08869-0602, USA.
url: www.ortho-mcneil.com

Ortho McNeil Janssen, USA. Ortho-McNeil Janssen Pharmaceuticals Inc., 1125 Trenton-Harbourton Rd, Titusville, NJ 08560-200, USA.

Ortho Neutrogena, USA. OrthoNeutrogena, a Division of Ortho-McNeil Pharmaceutocals Inc., 199 Grandview Rd, Skillman, NJ 08558, USA.
url: www.orthoneutrogena.com

Ortho Pharmaceutical, USA. See *Ortho McNeil, USA.*

Orthodontiki (Ορθοδοντικη), Gr. Orthodontiki, Proxenou Koromila 36, 546 22 Thessaloniki, Greece.

Ortis, Ital. Ortis Laboratoires, Viale dell'Appennino 441, 47100 Forli, Italy.

Orva, Turk. Orva İlaç San. ve Tic A.Ş., Atatürk Organize Sanayi, Bölgesi 100010 Sok. No: 10, Çiğli, İzmir, 35620, Turkey.

Oryx, Canad. See *Arrow, Canad.*

Osaka University, Cz. See *Osaka University, Jpn.*

Osaka University, Jpn. The Research Foundation for Microbial Diseases of Osaka University, 1199 Suita, Osaka, Japan.

Osaka University, Rus. See *Osaka University, Jpn.*

Oscient, Canad. See *Oscient, USA.*

Oscient, USA. Oscient Pharmaceuticals, 1000 Winter Street, Suite 2200, Waltham, MA 02154, USA.
url: www.oscient.com

Osel, Turk. Osel İlaç San ve Tic AS, Akbaba Köyü Fener Caddesi No 11/5, 34820 Beykoz, Istanbul, Turkey.
url: www.osel.com.tr

OSI, USA. OSI Pharmaceuticals, 58 South Service Rd, Melville, NY 11747, USA.
url: www.osip.com

Osmed, India. Osmed Formulations Pvt Ltd, 56-57 Industrial Area, Maxi Rd, Neemanwasa, Ujjain, India.

Osmopharm, Thai. See *JDH Borneo, Thai.*

Osorio de Moraes, Braz. Laboratórios Osorio de Moraes Ltda, Avenida Cardeal Eugenio Pacelli 2281, 32210-001 Contagem, MG, Brazil.

Osoth, Thai. Osoth Inter Laboratories, 757/10 Soi Pradoo 1, Sathupradit 8 Rd, Bangpongpang, Yannawa, Bangkok 10120, Thailand.

Osotspa, Thai. Osotspa Co. Ltd, 2100 Ram Khamhaeng Rd, Hua Mark, Bangkapi, Bangkok 10240, Thailand.

Ospedalia, Switz. Ospedalio AG, Bösch 37, 6331 Hünenberg, Switzerland.
url: www.ospedalio.ch

Osper, India. Osper Pharmaceuticals Pvt Ltd, 506 Vishvadeep Tower, 4 Dist. Centre, Janakapuri, New Delhi 110 058, India.

Osteofit, Hung. Osteofit Kft, Reitter ferenc u 132, 1131 Budapest, Hungary.

Osteohealth, Canad. See *Luitpold, USA.*

Osteohealth, USA. See *Luitpold, USA.*

Osteolab, Chile. See *Recalcine, Chile.*

Ostrem, Canad. Ostrem Chemical Co Ltd, 2310 80th Avenue, Edmonton, Alberta, T6P 1N2, Canada.

OTC Concepts, UK. OTC Concepts Ltd, 2 Park St, Woburn, Milton Keynes, Buckinghamshire, MK17 9PG, UK.

OTL, Belg. See *OTL, Fr.*

OTL, Denm. See *OTL, Fr.*

OTL, Fin. See *OTL, Fr.*

OTL, Fr. OTL Pharma SA, 15 rue de Turbigo, 75002 Paris, France.
url: www.otl-pharma.com

OTL, Neth. See *OTL, Fr.*

OTL, Port. See *OTL, Fr.*

OTL, Spain. See *OTL, Fr.*

OTL, Swed. See *OTL, Fr.*

Otsira, India. See *Aristo, India.*

Otsuka, Austria. See *Otsuka, Ger.*

Otsuka, Canad. See *Otsuka, USA.*

Otsuka, China. Otsuka Pharmaceutical Co Ltd, Headquarters Building Room 1008, 168 Xizang Road, Shanghai 200001, China.
url: www.zjotsuka.com

Otsuka, Cz. See *Otsuka, UK.*

Otsuka, Denm. See *BMS, Denm.*

Otsuka, Fin. See *Otsuka, Swed.*

Otsuka, Fr. Otsuka Pharmaceutical France SAS, Le Coroso, 1 rue Eugene et Armobd Peugeot, 92508 Rueil-Malmaison Cedex, France.
url: www.otsuka-global.com

Otsuka, Ger. Otsuka Pharma GmbH, Grüneburgweg 102, 60323 Frankfurt, Germany.
url: www.otsuka.de

Otsuka, Gr. See *Otsuka, UK.*

Otsuka, Hong Kong. Otsuka Pharmaceutical (HK) Ltd, Rm 1401, Phase 1, Ming An Plaza, 8 Sunning Rd, Causeway Bay, Hong Kong.
url: www.otsuka.com

Otsuka, Hung. See *Otsuka, UK.*

Otsuka, Indon. Otsuka Indonesia PT, Perkantoran Hijau Arkadia, Tower A 3rd Floor, Jl TB Simatupang Kav 88, Jakarta 12520, Indonesia.

Otsuka, Irl. See *Otsuka, UK.*

Otsuka, Jpn. Otsuka Pharmaceutical Co. Ltd, 2-9 Kanda-Tsukasa-cho, Chiyoda-ku, Tokyo 101-8535, Japan.
url: www.otsuka.co.jp

Otsuka, Malaysia. See *Luen Wah, Malaysia.*

Otsuka, Neth. See *Otsuka, UK.*

Otsuka, Norw. See *BMS, Norw.*

Otsuka, Philipp. Otsuka, 3/F King's Court II Bldg, Don Chino Roces Ave, Makati City, Philippines.

Otsuka, Pol. See *BMS, Pol.*

Otsuka, Port. See *Otsuka, UK.*

Otsuka, Singapore. See *Luen Wah, Singapore.*

Otsuka, Spain. Otsuka Pharmaceutical, Provenza 388, 08025 Barcelona, Spain.
url: www.otsuka-europe.com

Otsuka, Swed. Otsuka Pharma Scandinavia AB, Birger Jarlsgatan 39, Stackholm 111 45, Sweden.
url: www.otsukapharma.info

Otsuka, Thai. See *Zuellig, Thai.*

Otsuka, UK. Otsuka Pharmaceuticals (UK) Ltd, 2nd Floor, 3 Furzeground Way, Stockley Park East, Uxbridge, Middlesex, UB11 1EZ, UK.
url: www.otsuka-europe.com

Otsuka, USA. Otsuka America Pharmaceutical Inc, 2440 Research Blvd, Rockville, MD 20850, USA.
url: www.otsuka.com

Otto, Indon. Otto Pharmaceutical Industries Ltd, MENSA I Building, 1st Floor, Jl H R Rasuna Said Kav B-34, Kuningan, Jakarta 12940, Indonesia.
url: www.ottopharm.com

Otto, Malaysia. See *Otto, Indon.*

Otto, Singapore. See *Zyfas, Singapore.*

OTW, Ger. OTW-Naturarzneimittel Regneri GmbH & Co KG, Carl-Zeiss-Str. 4, 76275 Ettlingen, Germony.

Ou Yi, China. Ou Yi Pharmaceutical Co Ltd, Shijiazhuang, China.

Ouhua, China. See *Europharm, Hang Kong.*

Ouiheng, Thai. Ouiheng International Healthcare Co Ltd, 46, 46/2 Soi, Charansanitwongs 40, Choransanitwongs Rd, Bangplad, Bangkok 10700, Thailand.
url: www.ohihealthcare.com

Outdoor Recreations, USA. Outdoor Recreations, USA.

Outremer, Fr. Laboratoires Outremer, 4 lotissement Vinaigri, 97190 Le Gosier, France.

Ovation, Austria. See *Ovation, Irl.*

Ovation, Belg. See *Ovation, Irl.*

Ovation, Canad. See *Lundbeck, USA.*

Ovation, Cz. See *Ovation, Irl.*

Ovation, Denm. See *Orphan, Denm.*

Ovation, Fin. See *Ovation, Irl.*

Ovation, Hong Kong. See *Four Star, Hong Kong* and *Pharmalink, Hong Kong* and *Zuellig, Hong Kong.*

Ovation, Irl. Ovation Healthcare International Ltd, 1 Setanta Place, Dublin 2, Ireland.
url: www.ovationpharma.com

Ovation, Neth. See *Ovation, Irl.*

Ovation, Norw. See *Ovation, Irl.*

Ovation, Port. See *Ovation, Irl.*

Ovation, Swed. See *Ovation, Irl.*

Ovation, USA. See *Lundbeck, USA.*

Ovelle, Irl. Ovelle Ltd, Industrial Estate, Coes Rd, Dundalk, Co. Louth, Ireland.
url: www.ovelle.com

Overseal, UK. Overseal Natural Ingredients Ltd, Park Rd, Overseal, Swadlincote, Derbyshire, DE12 6JX, UK.
url: www.overseal.com

Overseas, India. Overseas Health Care Pvt Ltd, 335 Kms Milestone, National Highway No.1, P.O. Box 25, Phillaur 144 410, India.

Owoc, Pol. See *Chema-Elektromet, Pol.*

Oxbridge, UK. Oxbridge Pharma Ltd, 15 Fitzroy House, Lynwood Drive, Worcester Park, Sutton, Surrey, KT4 7AT, UK.
url: www.oxbridgepharma.com

Oxford Glycosciences, Israel. See *Oxford Glycosciences, UK.*

Oxford Glycosciences, UK. Oxford Glycosciences plc, 86 The Quadrant, Abingdon Science Park, Abingdon, Oxfordshire, OX14 4RY, UK.

Oxford Laboratories, Rus. Oxford Laboratories, 26-1 Bakinskikh Komissarov ul. 9, on. 117, 119571 Moscow, Russia.

Oxford Nutrition, UK. Oxford Nutrition Ltd, Unit 5 Western Units, Pottery Rd, Bovey Tracey, TQ13 9JJ, UK.
url: www.nutrinox.com

Oxford Pharmaceuticals, Irl. See *Masters, UK.*

Oxford Pharmaceuticals, UK. See *Masters, UK.*

Oxo, Port. See *Dimethaid, Ger.*

Oxo, Switz. See *Doetsch, Grether, Switz.*

Oxo, Thai. Oxo Chemie (Thailand) Co. Ltd, 6 Fl, Asoke Towers Com Building, 213/14-15 Sukhumvit 21 Rd, Klongtoey Nua, Watana, Bangkok 10110, Thailand.
url: www.oxochemie.com

Oxochemie, Indon. See *Phoras, Indon.*

Oxytech, India. See *Rishab, India.*

Ozon, Rus. Ozon, g Zhigulevsk, Pesochnaya St 11, 445350 Samarskaya, Russia.

Ozone, Cz. Ozone Laboratories Czech sro, Biskupský Dvůr 2095/8, 110 00 Praha, Czech Repubiic.
url: www.ozonelaboratories.cz

Ozone, Hung. Ozone Laboratories, Szent László tér 6/2/5, 1105 Budapest, Hungary.
url: www.ozonelaboratories.hu

Ozone, India. Ozone Pharmaceuticals Ltd, 1 Ozone House, L.S.C. Block A-3, Janak Puri, New Delhi 110 058, India.
url: www.ozonepharma.com

Ozone, Rus. Ozone Ltd, G Zhigulevsk Pesotsnaya ul. 11, 445 350 Samarskaya, Russia.

P&S, USA. See *Standard Homeopathic, USA.*

P & B, India. P & B Laboratories (P) Ltd, 11 Chokravarti Ashok Road, Kandivili (East), Mumbai 400 101, India.

Pabianice, Hung. See *Polcommerce, Hung.*

Pabianice, Rus. See *Ciech, Rus.*

Pabianice, Ukr. See *Tsiekh Polfa, Ukr.*

Pacific, Austral. See *Allergan, Austral.*

Pacific, China. Pacific Pharmaceutical Co. Ltd., Jinjiang, Fujion, 362211, China.
url: www.pacific-pharmacy.com

Pacific, Hong Kong. See *ICH, Hong Kong.*

Pacific, Israel. See *Genmedix, Israel.*

Pacific, Malaysia. See *Ziwell, Malaysia.*

Pacific, NZ. Pacific Pharmaceuticals Co. Ltd, P.O. Box 11-183, Ellerslie, Auckland, New Zealand.

Pacific, Philipp. Pacific Pharmaceutical Generics Inc., R-303 Lawyers Coop Bldg, 459 Quezon Ave cor Banawe, Quezon City, Philippines.

Pacific, Singapore. See *Ziwell, Singapore* and *Zuellig, Singapore.*

Pacific, Thai. Pacific Healthcare (Thailand) Co. Ltd, 1011 Supalai Grand Tower, Rm 01, 29 Fl Rama III Rd, Chongnonsee, Yannawa, Bangkok 10120, Thailand.
url: www.phc.co.th

Pacific Biosciences, Singapore. Pacific Biosciences Pte Ltd, 101 Thomson Rd, 16-05 United Square, S 307591, Singapore.
url: www.pacbios.com

Pacific Healthcare, Philipp. Pacific Healthcare (Phils) Inc., Penthouse B Prince Bldg, 117 Rada St, Legaspi Vill, Makati City, Philippines.

Pacira, Fin. See *Pacira, UK.*

Pacira, Hung. See *Extractum, Hung.*

Pacira, Pol. See *Mundipharma, Pol.*

Pacira, Port. See *Pacira, UK.*

Pacira, UK. Pacira Ltd, 3 Glory Park Ave, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0DF, UK.

Pacira, USA. Pacira Pharmaceuticals, 5 Sylvan Way, Parsippany, NJ 07054, USA.
url: www.pacira.com

Paddock, USA. Paddock Laboratories Inc., 3940 Quebec Ave North, Minneapolis, MN 55427, USA.
url: www.paddocklabs.com

Padia, Ger. Pädia Arzneimittel GmbH, Gruhlstr. 3, 50374 Erftstadt, Germany.
url: www.paedia.de

Padil, Ital. See *Blue Cross, Ital.*

Padma, Switz. Padma AG, Wiesenstrasse 5, 8603 Schwerzenbach, Switzerland.
url: www.padma.com

Padma, UK. See *Cedar Health, UK.*

Padro, Spain. See *Novartis, Spain.*

PaediHealth, Hong Kong. PaediHealth (HK) Ltd, Level 39, One Exchange Square, 8 Connaught Rd, Central, Hong Kong.
url: www.lactogg.com

Paedpharm, Austral. Paedpharm P/L, P.O. Box 6533, East Perth, WA 6892, Australia.
url: www.paedpharm.com.au

Paesel, Ger. Paesel & Lorei Pharma Vertriebs-und Marketing GmbH, Im Freihafen 8, 47138 Duisburg, Germany.
url: www.paesel-lorei.de

Pagni, Ital. See *Parke, Davis, Ital.*

Pahang, Malaysia. Pahang Pharmacy Sdn Bhd, Lot 5979, Jln Teratai, Off Jln Meru, 41050 Klang, Selangor, Malaysia.

Paines & Byrne, Irl. See *Paines & Byrne, UK.*

Paines & Byrne, NZ. See *NZ Medical & Scientific, NZ.*

Paines & Byrne, Thai. See *Union Medical, Thai.*

Paines & Byrne, UK. Paines & Byrne Ltd, Lovett House, Lovett Rd, Staines, Middlesex, TW18 3AZ, UK.

Pal Midwest, USA. Pal Midwest Ltd, P.O. Box 624, Rockford, IL 61101, USA.

Paladin, Canad. Paladin Laboratories Inc., 100 Blvd Alexis Nihon, Suite 102, St-Laurent, Quebec, H4M 2P2, Canada.
url: www.paladin-labs.com

Paladin, Ger. See *Paladin, Irl.*

Paladin, Irl. Paladin Labs (Europe) Ltd, 5 The Seapoint Building, 44 Clontarf Rd, Dublin 3, Ireland.
url: www.paladinlabs.com

Paladin, Singapore. See *Medicell, Singapore.*

Paladin, UK. See *Paladin, Irl.*

Paladin, USA. mpc1y

Palisades, Canad. See *Palisades, USA.*

Palisades, USA. Palisades Pharmaceuticals Inc., 64 N Summit St, Tenafly, NJ 07670-0579, USA.

Palmares, Ital. See *Ferlito, Ital.*

Palmer, Malaysia. See *Propharm, Malaysia.*

Palmetto, USA. See *Laser, USA.*

Palmical, Ger. See *Riemser, Ger.*

Palmolive Skincare, Austral. See *Colgate Oral Care, Austral.*

Pal-Pak, USA. Pal-Pak Inc., 1201 Liberty St, P.O. Box 299, Allentown, PA 18105, USA.

Pamex, Irl. Pamex Ltd, First Floor, 14 Moneen Business Park, Castlebar, Co. Mayo, Ireland.
url: www.pamex.ie

Pamlab, USA. Pamlab LLC, 4099 Highway 190 East Service, Covington, LA 70433, USA.
url: www.pamlab.com

Pampa, Pol. Pampa Laboratorium Farmaceutyczno-Kosmetyczne, ul. Kościuszki 24, 05-500 Piaseczno, Poland.
url: www.pampa.com.pl

Pan, Hong Kong. See *Sino-Asia, Hong Kong.*

Pan American, USA. Pan American Laboratories, P.O. Box 8950, Mandeville, LA 70470-8950, USA.
url: www.pamlab.com

Panacea, Ger. Panacea Biotec Germany GmbH, Landshuter Allee 8-10, 80637 Munich, Germany.
url: www.panaceabiotec.de

Panacea, India. Panacea Biotec Ltd, B-1 Extn. A-27, Mohan Co-op. Industrial Estate, Mathura Rd, New Delhi 110 044, India.
url: www.panacea-biotec.com

Panacea, Philipp. See *DeGa, Philipp.*

Panacea, Rus. See *Panacea, India.*

Panacea, Thai. See *Biogenetech, Thai.*

Panagakis, Gr. Schepa OE Panagakis G & Co, Veranzerou 33, 104 32 Athens, Greece.

Panagiotis, Gr. Panagiotis Leon & Co LP, Argonauts 22, Argyroupoli, Greece.

Panalab, Arg. Lab. Panalab S.A. Argentina, Av. Del Libertador 6250 Piso 2, 1428 Buenos Aires, Argentina.

Panbiotic, China. Panbiotic Laboratories Co. Ltd, 5-1 Ta-Tong Rd, Niao Sung, Kaohsiung, Taiwan, China.

Panderma, Austria. Panderma Arzneimittel GmbH, Braunlichgasse 40-42, A-2700 Wiener Neustadt, Austria.

Pandrugs, Thai. Pandrugs, Thailand.

Pangaoshou, Philipp. See *Spring Vine, Philipp.*

PanGas, Switz. PanGas AG, Industriepark 10, 6252 Dagmersellen, Switzerlond.
url: www.pangas.ch

Pangea, Israel. See *Medibrands, Israel.*

Panion, Philipp. See *Pharmawealth, Philipp.*

Pan-Ject, Philipp. Pan-Ject Pharmaceuticals Corp., Unit 2G Torre Venezia, Timog Ave cor Sct Santiago St, Quezon City, Philippines.

Panjon, India. Panjon Pharma Ltd, 902 Corporate Avenue, Sonawala Road, Goregaon (E), Mumbai 63, India.
url: www.panjanpharma.com

Pan-Malayan, Singapore. Pan-Malayan Pharmaceuticals Pte Ltd, 138 Joo Seng Rd, 3rd Floor, S 368361, Singapore.
url: www.panmalayan.com.sg

Pannoc, Belg. Pannoc NV, P.B. Box 70, Lammerdries 23, 2250 Olen, Belgium.
url: www.pannoc.be

PannonPharma, Hung. PannonPharma Gyógyszergyártó Kft, Pannonpharma str. 1, 7720 Pecsvarad, Hungary.
url: pannonpharma.hu

Panpharma, Denm. See *NordMedica, Denm.*

Panpharma, Fin. See *Algol, Fin.*

Panpharma, Fr. Laboratoires Panpharma, Zl du Clairay-Luitre, 35133 Fougères, France.
url: www.panpharma.fr

Panpharma, Hong Kong. See *Universal, Hong Kong.*

Panpharma, Norw. See *Farma Plus, Norw.*

Panpharma, Philipp. Panpharma-Meinz Pharmaceuticals Corp., 10/F Feliza Bldg, VA Rufino St, Legaspi Vill, Makati City, Philippines.

Pantafarm, Ital. Pantafarm S.r.l., Via Pomintella 12, Parco Verde, 80049 Somma Vesuviana (NA), Italy.

Pantene, Austral. See *Procter & Gamble, Austral.*

Panto, Spain. See *Almirall, Spain.*

Pantoforma, Spain. See *Almirall, Spain.*

Panvifarm, Gr. Panvifarm, Chalkokondyli 19, 104 32 Athens, Greece.

Pan-Well, Hong Kong. Pan-Well Trading Co., 4/F, Flat D, Goldfield Bldg, 42-44 Connaught Rd West, Hong Kong.

Panzera, Ital. Farmoceutici G.B. Panzera S.r.l., Via de Sanctis 71, 20141 Milan (MI), Italy.

Papaellinas (Παπαελλήνας), Gr. PAPAELLINAS K. AEVE, 26ο chlm. L. Markopaulou, 194 00 Markopoulo, Greece.

Par, Hong Kong. See *US Summit, Hong Kong.*

Par, USA. Par Pharmaceutical Inc., One Ram Ridge Rd, Spring Valley, NY 10977, USA.
url: www.parpharm.com

Paracelsia, Ger. Parocelsia Pharma GmbH, Im Wirrigen 25, 45731 Waltrop, Germany.
url: www.paracelsia.de

Paracelsia, Port. Paracélsia Indústria Farmacêutica SA, Rua Antera de Quentel 639, 4200-068 Porto, Portugal.

Paradise, Canad. Paradise Promotions Ltd, 13 George St, Novar, Ontario, P0A 1R0, Canada.

Parafarm, Pol. Parafarm SC, ul. Stolarska 1/3 m 42, 97-200 Tomaszów Mazowiecki, Poland.
url: www.parafarm.cfp.pl

Paragerm, Indon. Paragerm, Indonesia.

Paranova, Denm. Paranova Danmark A/S, Industriparken 23-25, 2750 Ballerup, Denmark.
url: www.paranova.dk

Paranova, Fin. Paranova Oy, Rajatorpantie 41 C, 01640 Vantaa, Finland.

Paraphar, Singapore. See *Polymedic, Singapore.*

Parapharm, Gr. Parapharm International AE, Ag. Panagouli 91, 142 34 Nea Ionia, Greece.

ParaPRO, USA. ParaPRO LLC, Carmel, IL 46032, USA.

Paras, India. Paras Pharmaceuticals Ltd, 3rd Floor Heritage Complex, SG Road, Thaltej, Ahmedabad 380054, India.
url: paraspharma.com

Paras, Rus. See *Paras, India.*

Parcopharm, Switz. Parcopharm SA, Lättichstrasse 1a, 6340 Baar, Switzerland.

Pardys, India. Pardys Healthcare, 92A Pocek-U&V, Block-B MIG Flats, Shalimar Bagh, New Delhi 110 088, India.

Parema, UK. See *Urgo, UK.*

Paren, Philipp. Paren Pharma Inc., 8 Milan St, Merville, Parañaque City, Philippines.
url: www.paren.org

Parenteral Drugs, India. Parenteral Drugs (India) Ltd, 23-3/1 Shree Ganesh Chambers, AB Rd, Navabuha Indore, 452 001, India.

Parggon, Mex. Laboratorios Parggon S.A. de C.V., Av. Vallarta 7000, Zapopan San Juan de Ocotan, 45019 Jalisco, Mexico.

Pari, Ger. PARI GmbH, Moosstr. 3, 82319 Starnberg, Germany.
url: www.pari.de

Pari, UK. Pari Medical Ltd, The Old Sorting Office, Rosemont Ave, West Byfleet, Surrey, KT14 6LB, UK.
url: www.pari.de

Parke, Davis, Arg. See *Pfizer, Arg.*

Parke, Davis, Austral. See *Pfizer, Austral.*

Parke, Davis, Belg. See *Pfizer, Belg.*

Parke, Davis, Braz. See *Pfizer, Braz.*

Parke, Davis, Canad. See *Pfizer, Canad.*

Parke, Davis, China. See *Pfizer, Ger.*

Parke, Davis, Cz. See *Pfizer, Cz.*

Parke, Davis, Denm. See *Pfizer, Denm.*

Parke, Davis, Fin. See *Pfizer, Fin.*

Parke, Davis, Fr. See *Pfizer, Fr.*

Parke, Davis, Ger. See *Pfizer, Ger.*

Parke, Davis, Hong Kong. See *Warner-Lambert, Hong Kong* and *Zuellig, Hong Kong.*

Parke, Davis, India. See *Pfizer, India.*

Parke, Davis, Irl. See *Pfizer, Irl.*

Parke, Davis, Israel. See *Neopharm, Israel.*

Parke, Davis, Ital. Parke Davis S.p.A., Via C. Colombo 1, 20020 Lainate (Milan), Italy.

Parke, Davis, Malaysia. See *Pfizer, Malaysia.*

Parke, Davis, Mex. See *Pfizer, Mex.*

Parke, Davis, Neth. See *Pfizer, Neth.*

Parke, Davis, NZ. See *Pfizer, NZ.*

Parke, Davis, Pol. See *Pfizer, Pol.*

Parke, Davis, Port. See *Pfizer, Port.*

Parke, Davis, Rus. See *Pfizer, Rus.*

Parke, Davis, S.Afr. See *Pfizer, S.Afr.*

Parke, Davis, Singapore. See *Age D'or, Singapore.*

Parke, Davis, Spain. See *Pfizer, Spain.*

Parke, Davis, Swed. See *Pfizer, Swed.*

Parke, Davis, Switz. See *Pfizer, Switz.*

Parke, Davis, UK. See *Pfizer, UK.*

Parke, Davis, USA. See *Pfizer, USA.*

Parke Davis-Wellcome, Austral. See *GSK, Austral.*

Parkedale, Hong Kong. See *Keller, Hong Kong.*

Parkedale, USA. See *King, USA.*

Parke-Med, S.Afr. See *Pfizer, S.Afr.*

Parkfields, UK. Parkfields Sterile Supply Unit, Pond Lane, Parkfields, Wolverhompton, West Midlands, WV2 1HL, UK.

Parkinpharm, Rus. Parkinpharm, ul Chayanova D 14, 125047 Moscow, Russia.
url: www.parkinpharm.ru

Parma, Hung. Parma Produkt Gyógyszergyártó Kft, Uzsaki u 36/a, 1145 Budopest, Hungary.

Parmed, USA. Parmed Pharmaceuticals Inc., 4220 Hyde Park Blvd, Niagara Falls, NY 14305, USA.
url: www.parmed.com

Parnell, Canad. See *Parnell, USA.*

Parnell, Irl. See *Blackhall, Irl.*

Parnell, USA. Parnell Pharmaceuticals, Inc., 1525 Francisco Blvd, San Rafael, CA 94901, USA.
url: www.parnellpharm.com

Parsenn, Switz. Parsenn-Produkte AG, Abt. Pharmazeutik, Klus, 7240 Kublis, Switzerland.

Parthenon, Canad. See *Parthenon, USA.*

Parthenon, USA. Parthenon Inc., 3311 West 2400 South, Salt Lake City, UT 84119, USA.
url: www.parthenoninc.com

Partner, Rus. Partner, Bolbsaya Yakimanka ul 31, 119180 Moscow, Russia.

Pasadena, USA. See *Akorn, USA.*

Pascal, Canad. See *Pascal, USA.*

Pascal, USA. Pascal Co. Inc., P.O. Box 1478, Bellevue, WA 98009-1478, USA.
url: www.pascaldental.com

Pascoe, Austria. See *Pascoe, Ger.*

Pascoe, Ger. Pascoe Pharmazeutische Präparate GmbH, Schiffenberger Weg 55, 35394 Giessen, Germany.
url: www.pascoe.de

Pascoe, Neth. See *Pascoe, Ger.*

Pascoe, Spain. See *Pascoe, Ger.*

Pascoe, UK. See *Pascoe, Ger.*

Pascual, Hong Kong. See *Yik Kwan, Hong Kong.*

Pascual, Philipp. Pascual Laboratories Inc., L & I Building, 817 EDSA, South Triangle, Quezon City, Philippines.

Pasifik, Turk. Pasifik İlaçları San. ve Tic. Ltd. Şti., Eski Üsküdar Yolu, Sansoz Sitesi C Blok No: 7 D. 2, İçerenköy-Kadiköy, İstanbul, Turkey.

Pasquali, Ital. Pasquali S.r.l., Via L. Longo 39/41, 50019 Sesto Fiorentino (FI), Italy.
url: www.pasqualimed.com

Passauer, Cz. See *Passauer, Ger.*

Passauer, Denm. See *Vitaflo, Denm.*

Passauer, Ger. Herbert J Passauer GmbH & Co. KG, Kirchhainer Damm 62, 12309 Berlin, Germany.

Passauer, Irl. See *Passauer, Ger.*

Passauer, Pol. See *Passauer, Ger.*

Passauer, Port. See *Passauer, Ger.*

Passion for Life, Singapore. See *Pan-Malayan, Singapore.*

Passion for Life, UK. Passion for Life Healthcare Ltd, 1 Bell Court, Leapale Lane, Guildford, Surrey, Gu1 4LY, UK.
url: www.passionforlife.com

Pastaba, Fr. See *Novartis, Fr.*

Pasteur, Chile. Laboratorios Pasteur Ltda, Ignacio Serrano 568, Concepción, Santiago, Chile.

Pasteur, Fr. See *Sanofi Pasteur, Fr.*

Pasteur, Philipp. Pasteur Pharmaceutical Sales, G/F SGS Foundation Bldg, 1335 G Araneta Ave, Sta Mesa Heights, Quezon City, Philippines.

Pasteur Merieux, Austral. See *Aventis Pasteur, Austral.*

Pasteur Merieux, Austria. See *Sanofi Pasteur, Austria.*

Pasteur Merieux, Belg. See *Sanofi Pasteur, Belg.*

Pasteur Merieux, Braz. See *Aventis Pasteur, Braz.*

Pasteur Merieux, Canad. See *Aventis Pasteur, Canad.*

Pasteur Merieux, Cz. See *Sanofi-Aventis, Cz.*

Pasteur Merieux, Denm. See *Sanofi Pasteur, Denm.*

Pasteur Merieux, Fr. See *Sanofi Pasteur, Fr.*

Pasteur Merieux, Ger. See *Sanofi Pasteur, Ger.*

Pasteur Merieux, Hong Kong. See *Aventis, Hong Kong.*

Pasteur Merieux, Irl. See *Sanofi-Aventis, Irl.*

Pasteur Merieux, Israel. See *Promedico, Israel.*

Pasteur Merieux, Ital. See *Sanofi Pasteur, Ital.*

Pasteur Merieux, Neth. See *Sanofi Pasteur, Neth.*

Pasteur Merieux, Norw. See *Sanofi Pasteur, Denm.*

Pasteur Merieux, Singapore. See *Sanofi-Aventis, Singapore.*

Pasteur Merieux, Spain. See *Sanofi Pasteur, Spain.*

Pasteur Merieux, Swed. See *Sanofi Pasteur, Denm.*

Pasteur Merieux, Thai. See *Sanofi Pasteur, Thai.*

Pasteur Merieux, UK. See *Sanofi Pasteur, UK.*

Pasteur Merieux, USA. See *Sanofi Pasteur, USA.*

Pasteur Merieux Connaught, USA. See *Sanofi Pasteur, USA.*

Pasteur Vaccins, Fr. See *Sanofi Pasteur, Fr.*

Pasteur-Merieux, Venez. See *Zuaz, Venez.*

Pasture, Singapore. See *Pacific Biosciences, Singapore.*

Patar, Thai. Patar Lab Ltd, 23 Soi Misuwan 3, Sukhumvit 71 Rd, Phra Khanong nua, Bangkok, Thailand.

Patentex, Fin. See *Patentex, Ger.*

Patentex, Ger. Patentex GmbH, Marschnerstr. 8-10, 60318 Frankfurt/Main, Germany.
url: www.patentex.com

Patentex, Switz. See *Adroka, Switz.*

Patheon, China. See *Patheon, UK.*

Patheon, Rus. See *Novartis Consumer, Rus.*

Patheon, UK. Patheon UK Ltd, Kingfisher Drive, Covingham, Swindon, Wiltshire, SN3 5BZ, UK.
url: www.patheon.com

Pathogenesis, Canad. See *Chiron, Canad.*

Pathogenesis, Denm. See *Orphan, Denm.*

Pathogenesis, Gr. See *Genesis, Gr.*

Pathogenesis, Irl. See *Novartis, UK.*

Pathogenesis, Norw. See *Swedish Orphan, Norw.*

Pathogenesis, UK. See *Novartis, UK.*

Pathogenesis, USA. See *Chiron, USA.*

Patrin, USA. Patrin Pharma, PO Box 1481, Skokie, IL 60076-1481, USA.
url: www.patrinpharma.com

Patriot, Philipp. Patriot Pharmaceuticals Corp., The Patriot Bldg, Km 18 West Service Rd, South Luzon Expressway, Parañaque City, Philippines.

Pautrat, Fr. See *PPDH, Fr.*

Paviour, India. Paviour Pharmaceuticals Pvt Ltd, 311 - 312 Suneja Tower 1, District Centre, Janak Puri, New Delhi 110 058, India.
url: www.paviour.org

Paylos, Arg. Laboratorios Paylos SRL, Dardo Rocha 202, 1873 Avellaneda, Buenos Aires, Argentina.

PB, Ger. PB Pharma GmbH, Lise-Meitner-Str. 10, 40670 Meersbusch, Germany.
url: www.pbpharma.de

PBM, USA. PBM Pharmaceuticals, Linney House, 204 North Main St, Gordonsville, VA 22942, USA.

PC India, India. PC India Pharma Pvt Ltd, 100 Birya Hause, 265 Bazargate St, Fort, Mumbai 400 001, India.
url: www.pcindiagoup.com

Pcgen, Arg. Pcgen SA, Ruiz Huidobra 2764, (1429) Buenos Aires, Argentina.

PCH, Neth. See *Pharmachemie, Neth.*

PCO, Neth. PCO Manufacturing Nederland, Bergweg 210, 3035 BN Rotterdam, Netherlands.

PD, Thai. Thai PD Chemicals Ltd, 2 Soi Chokchairuammitr, Viphavadee Rungsit Rd, Bangkok 10310, Thailand.

PDC, India. PDC Healthcare, SCO No 19, Industrial Area, Phase 2, Chandigarh, India.

PDI, USA. PDI Inc., 2 Nice-Pak Park, Orangeburg, NY 10954, USA.
url: www.pdipdi.com

PDL, Singapore. See *Steward Cross, Singapore.*

PDMS, UK. Pharmaceutical Development & Manufacturing Services Ltd (PDMS), 22 Seagoe Industrial Estate, Craigavan, BT63 5QD, UK.
url: www.pdms-almac.com

PDN, Hong Kong. See *Universal, Hong Kong.*

PDP, Hung. PDP Pharma Kft, Bem rkp 26, 1011 Budapest, Hungary.

PE, Ger. See *RAN, Ger.*

Peach, UK. Peach Ethical Ltd, Unit 24 Chalwyn Industrial Estate, Parkstone, Poole, Dorset, BH12 4PF, UK.

Pearson, Ital. Guglielmo Pearson S.r.l., Via delle Fabbriche 40-40a R, 16158 Voltri (GE), Italy.
url: www.guglielmopearson.it

Peckforton, Irl. See *Alphar, Irl.*

Peckforton, UK. Peckforton Pharmaceuticals Ltd, Crewe Hall, Crewe, Cheshire, CW1 6UL, UK.
url: www.peckforton.com

Pedia Aids, Philipp. Pedia Aids Inc., Casa San Raphael, 70 Scout Tuazon St, South Triangle, Quezon City, Philippines.

PediaCare, Philipp. See *RBC-MDC, Philipp.*

Pediamed, USA. PediaMed Pharmaceuticals, 7310 Turfway Rd, Suite 490, Florence, KY 41042, USA.
url: www.pediamedpharma.com

Pediapharm, Canad. Pediapharm Inc., 1 Place du Commerce, Suite 225, Ils des Soeurs, Quebec, H3E 1A2, Canada.
url: www.pedia-pharm.com

Pediapharm, Chile. See *Recalcine, Chile.*

Pediapharma, Philipp. Pediapharma Inc., Penthouse 4, Landsdale Tower, 86 Mather Ignacia Ave, Quezon City, Philippines.
url: www.pediapharmainc.com

Pediatech, Singapore. See *Zuellig, Singapore.*

Pediatrica, Indon. See *Medifarma, Indon.*

Pediatrica, Malaysia. See *Unam, Malaysia.*

Pediatrica, Philipp. Pediatrica Inc., 3/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Metro Manila, Philippines.

Pediatrica, Singapore. See *Far East, Singapore.*

Pediatrica, Thai. See *Olic, Thai.*

PediatRx, USA. PediatRx, 90 Fairmont Rd West, Califon, NJ 07830, USA.

Pedinol, USA. Pedinol Pharmacal Inc., 30 Banfi Plaza North, Farmingdale, NY 11735, USA.
url: www.pedinol.com

Peerage, India. Peerage Pharma Pvt Ltd, SCO-13 Industrial Area, Phase II, Chandigarh, India.

Pefanic, Gr. Pefanic AE, Achamon 27, 10439 Athens, Greece.

PEI, Irl. PEI Surgical, M50 Business Park, Ballymount Rd Upper, Ballymount, Dublin 12, Ireland.
url: www.pei.ie

Peili, China. Peili Pharmaceutical Co. Ltd, China.

Peiling, China. Taiji Group, Peiling Pharmaceutical Factory, 8 Fu South Rd, Fuling District, Chongqing, China.

Peithner, Austria. Dr Peithner KG nunmehr GmbH & Co., Richard-Strauss-Strasse 13, A-1232 Vienna, Austria.

Peithner, Cz. Dr Peithner Prag sro, Čestmírova 1, 140 00 Prague 4, Czech Republic.
url: www.heel-info.com

Peithner, Hung. Dr Peithner Budapest Kft, Bolg'r 4 fsz. 2-3, 1105 Budapest, Hungary.
url: www.heel-info.com

Pekana, Austria. See *Pekana, Ger.*

Pekana, Canad. See *Pekana, Ger.*

Pekana, Ger. Pekana Naturheilmittel GmbH, Raiffeisenstr. 15, 88353 Kisslegg, Germany.
url: www.pekana.de

Pekana, Hung. See *Pekana, Ger.*

Pekana, Neth. See *Pekana, Ger.*

Pelayo, Spain. Pelayo, Tallers 16, 08001 Barcelona, Spain.

Pelpharma, Austria. Pelpharma Handels GmbH, Jupiterweg 53, A-1140 Vienna, Austria.

Pemberton, Irl. See *United Drug, Irl.*

Pendopharm, Canad. Pendopharm, Division of DE Pharmaceuticals Inc., 8580 Esplanade, Montreol, Quebec, H2P 2R8, Canada.

Pendopharm, Singapore. See *LF, Singapore.*

Penederm, Canad. See *Pharmascience, Canad.*

Penederm, USA. See *Bertek, USA.*

Pengyao, China. Pengyao Pharmaceutical Co. Ltd, Jiangsu, China.

Penmix, Philipp. See *Metro, Philipp.*

Penmix, Singapore. See *Pharmaforte, Singapore.*

Penmix, Thai. See *Cosma, Thai.*

Penn, Arg. Penn Pharmaceuticals SA, Mejico 4805, Villa Martelli, Buenos Aires, Argentina.

Penn, Irl. See *Mayne, Irl.*

Penn, USA. Penn Laboratories, 130 Vintage Dr, Huntsville, AL 35811, USA.
url: www.pennlaboratories.com

Pennex, Israel. See *Gramse, Israel.*

Pennwalt, USA. See *Celltech, USA.*

Pensa, Denm. See *Pensa, Swed.*

Pensa, Ital. Pensa Pharma SpA, Via Ippolito Rosellini 12, 20124 Milan (MI), Italy.

Pensa, Spain. Penso, Av. Virgen de Montserrat 215, 08026 Barcelona, Spain.

Pensa, Swed. Pensa Pharma AB, Birger Jarlsgatan 22, 114 34 Stockholm, Sweden.
url: www.pensapharma.se

Penta, Arg. See *Hexa, Arg.*

Penta, Ger. Penta Arzneimittel GmbH, Werksstr. 3, 92551 Stulln, Germany.
url: www.penta-arzneimittel.de

Penta, Hung. Penta Pharma Kft, Zsak u 3, 9200 Mosonmagyarovar, Hungary.
url: www.pentaparma.hu

Pentaderm, Ital. Pentaderm Industria Chimica e Farmaceutica S.r.l., Via Nazionale Pentimele 157, 89121 Reggio Calabria (RC), Italy.

Pentafarm, Spain. Pentafarm, Galileo 250, 08028 Barcelona, Spain.

Pentaforma, Chile. Pentaforma SA, Av. Pocuro 1915, Providencia, Santiago, Chile.

Pentafarma, Port. Pentafarma, SA, Rua Professor Henrique de Barros, Edificio Sagres 5 A, 2685-338 Prior Velha, Portugal.

Pentamedical, Ital. Pentamedical S.r.l., Via G. Mazzini 1, 20021 Bollate (MI), Italy.

Pentatop, Ger. Pentatop Pharma GmbH, Brunnleitenstr. 3, 82284 Grafrath, Germany.

People's, Malaysia. People's Pharmacy (M) Sdn Bhd, 59-61 Jln Bendahara, 75100 Malacca, Malaysia.

Pepin, Canad. Pepin Boutique de Harnais, 5785 Metropolitan Blvd E, St-Leonard, Quebec, H1P 1X3, Canada.

Peptek, Rus. Peptek ZAO, Miklukho-Maklaya ul. 16/10, 117997 Moscow, Russia.
url: www.peptek.ru

Peptek, Ukr. See *Zdravo, Ukr.*

Peptogen, Rus. Peptogen, pl. Ak. Kurchatova D.2, 117292 Moscow, Russia.
url: www.peptagen.ru

Peptos, Rus. Peptos Pharma, Miklukho-Maklaja ul., d. 16/10, 117997 Moscow, Russia.
url: www.thymodepressin.ru

Percos, India. Percos India Pvt Ltd, Plot No 5, 2nd Floor, Neelkanth Chambers 1, LSC Saini Enclave, New Delhi, 110092, India.

Perez Gimenez, Spain. See *Calmante Vitaminado, Spain.*

Perfarma, Ital. Perfarma D.P. S.a.s., Via Provenzale 47, 00100 Rome (RM), Italy.
url: lapelle.it/perfarma

Perfect Solutions, Canad. See *Perfect Solutions, USA.*

Perfect Solutions, USA. Perfect Solutions Dental Products Inc., 1803 Stonequarter Rd, Richmond, Virginia, 23233, USA.

Perfecta, USA. Perfecta Products Inc., 131 W South Range Rd, North Lima, OH 44452, USA.
url: www.perfectaproducts.com

Perfetti, Ital. Perfetti Health Division Spa, Via XXV Aprile 7, 20020 Lainate (MI), Italy.

Perffarma, Pol. Perffarma Sp. zo.o., ul. Królowej Marysieńki 13 lok. 11, 02-954 Warsaw, Poland.
url: www.perffarma.pl

Performance Health, Canad. See *Performance Health, USA.*

Performance Health, USA. Performance Health Inc., 1017 Boyd Rd, Export, Pennsylvania, 15632, USA.

Perftoran, Rus. Perftoran SPF, 142290 Pushchino, Moscow, Russia.
url: perftoran.ru

Periproducts, UK. Periproducts Ltd, P.O. Box 176, Audit House, 260 Field End Rd, Ruislip, Middlesex, HA4 9YR, UK.
url: www.periproducts.co.uk

Perivita, Neth. See *Perivita, Norw.*

Perivita, Norw. Perivita A/S, Handverksveien 2, N-1405 Langhus, Norway.

Perlier, Canad. See *Perlier, USA.*

Perlier, USA. Perlier Inc., 300 Kennedy Drive, Sayreville, NJ 08872, USA.

Permamed, Pol. See *Magnapharma, Pol.*

Permamed, Switz. Permamed AG, Ringstrasse 29, Postfach 360, 4106 Therwil, Switzerland.
url: www.permamed.ch

Permark, S.Afr. See *Boots Healthcare, S.Afr.*

Permatec, Arg. Permatec Laboratorio Medicinal SA, Combate de los Pozos 336, 1080 Buenos Aires, Argentina.

Pern, UK. Pern Consumer Products Ltd, Quantum House, Hobson Industrial Estate, Burnopfield, County Durham, NE16 6EA, UK.
url: www.pern-consumer.co.uk

Pernix, USA. Pernix Therapeutics Holdings Inc, 33219 Forest West Dr, Magnolia, TX 77354, USA.
url: pernixtx.com

Perrigo, Canad. See *Perrigo, USA.*

Perrigo, Irl. See *Perrigo, UK.*

Perrigo, Israel. Perrigo Ltd, 29 Lehi Street, Bnei Brak 51200, Israel.
url: www.perrigo.com

Perrigo, Pol. See *Omega Rex, Pol.*

Perrigo, UK. Perrigo, Wrafton Laboratories Ltd., Wrafton, Braunton, Devon, EX33 2DL, UK.
url: www.wrafton.com

Perrigo, USA. Perrigo International, Plant 6-RA, 515 Eastern Ave, Allegan, Michigan 49010, USA.

Perryment, Neth. See *Perryment, UK.*

Perryment, UK. Perryment Ltd, 42-46 High St, Esher, Surrey, KT10 9QY, UK.

Persano, Denm. Persana Group A/S, Skaaremosevej 11-14, Blistrup, 3230 Graested, Denmark.
url: www.propharma.dk

Person & Covey, Canad. See *Seaford, Canad.*

Person & Covey, USA. Person & Covey Inc., 616 Allen Ave, Glendale, CA 91201, USA.
url: www.personandcovey.com

Personol Care, USA. Personal Care Group Inc., 225 Summit Ave, Montvale, NJ 07645-1574, USA.

Persos, Gr. Persos Ltd, Aristotelous 38, 10433 Athens, Greece.

Perstorp, Austria. See *Pharmacia, Austria.*

Perstorp, Switz. See *Smith & Nephew, Switz.*

Pertiwi Agung, Malaysia. See *Zyfas, Malaysia.*

Pertiwi Agung, Philipp. See *Lakeside, Philipp.*

Pertiwi Agung, Singapore. See *Zyfas, Singapore.*

Pertussin, USA. Pertussin Laboratories, USA.

Peseri, Cz. Peseri, Czech Republic.

Peseri, Fin. Peseri Trading Ltd, Finland.

PET, Denm. PET-Centret, Århus sygehus, Nørrebogade 44, 8000 Arhus C, Denmark.

Peter, Ital. Peter Italia S.a.s., Via Tommaso Silvestri 22, 00135 Rome (RM), Italy.
url: www.peteritalia.it

Peter Black, UK. Peter Black Healthcare Ltd, William Nadin Way, Swadlincote, Derbyshire, DE11 0BB, UK.
url: www.peterblack.co.uk

Peterer, Switz. Draguerie Peterer SA, Bahnhofstr 5, 9230 Flowil, Switzerland.

Petit, Fr. See *SFPH, Fr.*

Petnet, Spain. See *Petnet, UK.*

Petnet, UK. Petnet Solutions, a division of Siemens Plc, Faraday House, Sir William Siemens Square, Frimley, Camberley, Surrey, Gu16 8QD, UK.

Petrasch, Austria. Petrasch-Pharma GmbH, Schlachthausstrasse 3, A-6850 Dornbirn, Austria.

Petrovax, Rus. Petrovax, Zagorevskaya ul 10 korp. 4, 115598 Moscow, Russia.

Petrus, Austral. Petrus Pharmaceuticals, P.O. Box 1808, West Perth, WA 6872, Australia.

Petsiavas, Gr. Petsiavas, Ag. Anargyron 21, 145 64 K. Kifisia, Greece.
url: www.petsiavas.gr

Petsiavas (Πετσιαβας), Gr. See *Petsiavas, Gr.*

Pezomed, Hung. Pezomed Kft, Dózsa György u 60, H-4440 Nyíregyháza, Hungary.

PFC, Switz. PFC Pharma Focus Consultants AG, Chriesboumstrasse 2, 8604 Volketswil, Switzerland.

Pfeiffer, USA. Pfeiffer Company, 65-71 University Ave, P.O. Box 4447, Atlanta, GA 30302, USA.
url: www.pfeifferpharmaceuticals.com

Pfizer, Arg. Pfizer S.R.L., Virrey Loreto 2477, 1426 Buenos Aires, Argentina.
url: www.pfizer.com

Pfizer, Austral. Pfizer P/L, 38-42 Wharf Rd, West Ryde, NSW 2114, Australia.
url: www.pfizer.com.au

Pfizer, Austria. Pfizer Corporation Austria GmbH, Floridsdorfer Hauptstrasse 1, Postfach 439, 1210 Vienna, Austria.
url: www.pfizer.at

Pfizer, Belg. Pfizer SA, Boulevard de la Plaine 17, 1050 Brussels, Belgium.
url: www.pfizer.com

Pfizer, Braz. Laboratórios Pfizer Ltda, Rua Alexandre Dumas 1860, Chácara Santo Antônio, 04717-904 São Paulo, SP, Brazil.
url: www.pfizer.com.br

Pfizer, Canad. Pfizer Canada Inc., P.O. Box 800, Pointe-Claire, Dorval, Quebec, H9R 4V2, Canada.
url: www.pfizer.ca

Pfizer, Chile. Laboratorio Pfizer de Chile SA, Av. Las Americas 173, Cerrillos, Santiago, Chile.

Pfizer, China. Pfizer, 8-12 Block B Fifth Square, Chaoyangmen North Street, Dongcheng District, Beijing 100010, China.
url: www.pfizer.com.cn

Pfizer, Cz. Pfizer sro, Straupežnického 17, 150 00 Prague 5, Czech Republic.
url: www.pfizer.cz

Pfizer, Denm. Pfizer ApS Danmark, Lautrupvang 8, 2750 Ballerup, Denmark.
url: www.pfizer.dk

Pfizer, Fin. Pfizer Oy, PL 36, 00331 Helsinki, Finland.
url: www.pfizer.fi

Pfizer, Fr. Laboratoires Pfizer, 23-25 av. du Dr-Lannelongue, 75668 Paris cdx 14, France.
url: www.pfizer.com

Pfizer, Ger. Pfizer GmbH, Linkstr. 10, 10785 Berlin, Germany.
url: www.pfizer.de

Pfizer, Gr. Pfizer, 5 Alketou, 116 33 Pagrati, Greece.
url: www.pfizer.com

Pfizer, Hong Kong. Pfizer Corporation Hong Kong Ltd, 16/F Stanhope House, 738 King's Rd, North Point, Hong Kong.
url: www.pfizer.com.hk

Pfizer, Hung. Pfizer Kft, Alkotás út 53, MOM Park F Épület, 1123 Budapest, Hungary.

Pfizer, India. Pfizer Ltd, Patel Estate, S.V. Rd, Jogeshwari West, Mumbai 400 102, India.
url: www.pfizerindia.com

Pfizer, Indon. Pfizer Indonesia PT, Wisma GKBI 10/F Suite 1005, Jl Jend Sudirman Kav 28, Jakarta 10410, DKI Jaya, Indonesia.

Pfizer, Irl. Pfizer Pharmaceuticals, The Pfizer Building, 9 Riverwalk, National Digital Park, Citywest Business Campus, Dublin 24, Ireland.
url: www.pfizer.ie

Pfizer, Israel. Pfizer Pharmaceuticals Ltd, 9 Shenkar St, Herzliya Pituah 46725, Israel.
url: www.pfizer.com

Pfizer, Ital. Pfizer Italiana S.r.l., Via Valbondione 113, 00188 Rome (RM), Italy.
url: www.pfizer.it

Pfizer, Jpn. Pfizer Pharmaceutical Inc., 2-1-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 163-0461, Japan.
url: www.pfizer.co.jp

Pfizer, Malaysia. Pfizer (Malaysia) Sdn Bhd, Level 3 & 4, Bangunan Palm Grove, No 14, Jln Glenmarie, Section U1, 40150 Shah Alam, Selangor, Malaysia.
url: www.pfizer-malaysia.com

Pfizer, Mex. Pfizer S.A. de C.V., Pasea de los Tamarindos No. 40, Basque de las Lomas, 05120 Cuajimalpa, Mexico D.F., Mexico.
url: www.pfizer.com.mx

Pfizer, Neth. Pfizer BV, Roer 266, 2908 AA Capelle a/d Ijssel, Netherlands.
url: www.pfizer.com

Pfizer, Norw. Pfizer AS, Postboks 3, 1324 Lysaker, Norway.
url: www.pfizer.no

Pfizer, NZ. Pfizer Laboratories Ltd, Level 3, Pfizer House, 14 Normanby Rd, Mt Eden, Auckland, New Zealand.
url: www.pfizer.com

Pfizer, Philipp. Pfizer Inc., 23/F Ayala Life-FGU Ctr, 6811 Ayala Ave, Makati City, Philippines.

Pfizer, Pol. Pfizer Polska Sp. zo.o., ul. Postepu 17 B, 02-676 Warsaw, Poland.
url: www.pfizer.com.pl

Pfizer, Port. Laboratórios Pfizer, Lda, Lagoas Park, Edifício 10, 2740-244 Porto Salvo, Portugal.
url: www.pfizer.com

Pfizer, Rus. Pfizer International, Taganskaya ul. 21, 109004 Moscow,, Russia.
url: www.pfizer.com

Pfizer, S.Afr. Pfizer Laboratories (Pty) Ltd, P.O. Box 2271, Cape Town 8000, South Africa.
url: www.pfizer.co.za

Pfizer, Singapore. Pfizer Pte Ltd, 152 Beach Rd, 29-00 Gateway East, S 189721, Singapore.
url: www.pfizer-singapore.com

Pfizer, Spain. Pfizer, Avda Europa 20B, Epmresarial La Moraleja, Alcobendas, 28108 Madrid, Spain.
url: www.pfizer.es

Pfizer, Swed. Pfizer AB, Box 501, 183 25 Täby, Sweden.
url: www.pfizer.se

Pfizer, Switz. Pfizer SA, Scharenmoosstrasse 99, 8052 Zurich, Switzerland.
url: www.pfizer.ch

Pfizer, Thai. Pfizer (Thailand) Ltd, 36-38 Fl, 42 Fl, United Center Building, 323 Silom Rd, Kwang Silom, Khet Bangrak, Bangkok 10500, Thailand.
url: www.pfizer.co.th

Pfizer, Turk. Pfizer İlaçlari Ltd. Sti., Muallim Naci Cad., Bostan Çikmazı No: 3, Ortaköy, İstanbul, 34347, Turkey.
url: www.pfizer.com.tr

Pfizer, UK. Pfizer Ltd, Walton Oaks, Dorking Rd, Tadworth, Surrey, KT20 7NS, UK.
url: www.pfizer.co.uk

Pfizer, Ukr. Pfizer Inc, Bereznyakovskaya Street, 29, Kiev, 02098, Ukraine.
url: www.pfizer.com

Pfizer, USA. Pfizer Inc., 235 East 42nd St, New York, NY 10017-5755, USA.
url: www.pfizer.com

Pfizer, Venez. Pfizer Division Consumo, Av. Principal de los Ruices Edif. Pfizer, Caracas 1010-A, Venezuela.
url: www.pfizer.com

Pfizer Consumer, Austral. See *Pfizer, Austral.*

Pfizer Consumer, Belg. See *Pfizer, Belg.*

Pfizer Consumer, Canad. Pfizer Consumer Healthcare, Division of Pfizer Canada Inc., 2200 Eglinton Ave E, Toronto, Ontario, M1L 2N3, Canada.
url: www.pfizer.ca

Pfizer Consumer, Chile. Pfizer Division Consumer, Alonso de Cordova 5151 Of. 701, Las Condes, Santiago, Chile.

Pfizer Consumer, Ger. See *Pfizer, Ger.*

Pfizer Consumer, Hong Kong. See *Pfizer, Hong Kong.*

Pfizer Consumer, Irl. See *Pfizer, Irl.*

Pfizer Consumer, Ital. Pfizer Consumer Health Care S.r.l., Via Ardeatina Km. 23,500, 00040 Santa Palomba (RM), Italy
url: www.pfizerconsumer.it

Pfizer Consumer, Malaysia. See *Pfizer, Malaysia.*

Pfizer Consumer, Mex. See *Pfizer, Mex.*

Pfizer Consumer, Neth. See *Pfizer, Neth.*

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Pfizer Consumer, Singapore. See *Pfizer, Singapore.*

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Pfizer Sante, Fr. See *Pfizer, Fr.*

Pfleger, Austria. See *Pfleger, Ger.*

Pfleger, Cz. See *ProMed, Cz.*

Pfleger, Ger. Dr R. Pfleger Chemische Fabrik GmbH, 96045 Bamberg, Germany.
url: www.dr-pfleger.de

Pfleger, Israel. See *Gramse, Israel.*

Pfleger, Rus. See *ProMed, Rus.*

Pfleger, Thai. See *Union Medical, Thai.*

Pfleger, Ukr. See *ProMed, Ukr.*

Pfluger, Ger. Homöopathisches Laboratorium A. Pflüger GmbH & Co. KG, Röntgenstr. 4, 33378 Rheda-Wiedenbrück, Germany.
url: www.pflueger.de

Pfrimmer, Ger. See *Pfizer, Ger.*

Pfrimmer, Spain. See *Fresenius Kabi, Spain.*

Pfrimmer Nutricia, Switz. See *Uhlmann-Eyraud, Switz.*

PG, Venez. Pharmaceutical Group PG, C.A., Av Venezuela con Humboldt, CC El Recreo, Trre Sur, Caracas, Venezuela.

PGM, Ger. PGM Pharmazeutische Gesellschaft mbH & Co. München, Fürstenstr 6, 80333 Munich, Germany.
url: www.pgm-muenchen.de

PGN, Arg. Laboratorios PGN SA, O'Brien 1246, 3104 Paraná, Entre Rios, Argentina.

PH&T, Gr. PH&T, Greece.

PH&T, Irl. See *PH&T, Ital.*

PH&T, Ital. PH&T SpA, Via Marostica 1, 20146 Milan, Italy.

Phace, Hung. Phace Kft, Hercegprimas utca 18 1 em, 1051 Budapest, Hungary.

Phafag, Austria. Phafag Pharma Research & Trading GmbH, Schulgasse 5, A-8010 Graz, Austria.

Phagecon, Cz. See *Phagecon, Port.*

Phagecon, Port. Pagecon Servicos e Consultoria Farmaceutica Lda, Rua João Machado 100, Sala 202, 3000-226 Coimbra, Portugal.

Phamar (Φαμαρ), Gr. See *Famar, Gr.*

Phapros, Indon. Phapros Tbk, Gedung RNI, Semarang 50148, Jl Denpasar Raya Kav D III, Kuningan, Jakarta 12950, DKI Jaya, Indonesia.

Pharbenia, Ital. See *Bayer, Ital.*

Pharbest, USA. Pharbest, USA.
url: www.pharbestusa.com

Pharbio, Fin. See *Pharbio, Swed.*

Pharbio, Norw. See *Cederroth, Norw.*

Pharbio, Pol. See *Soraya, Pol.*

Pharbio, Swed. Pharbio Medical International AB, Box 715, 194 27 Upplands Väsby, Sweden.

Pharbita, Ger. See *PB, Ger.*

Pharbita, Israel. See *Genmedix, Israel.*

Pharbita, Singapore. See *FP, Singapore.*

Pharco, Ukr. See *Ukrimpeks, Ukr.*

Pharex, Philipp. Pharex Health Corp, 3/F Cortez Bldg, 821 EDSA South Triangle, Quezon City, Philippines.

Pharlab, Braz. Pharlab Indústria Farmacêutica Ltda, Rua São Francisco 1300, 35590-000 Lagoa da Prata, MG, Brazil.

Pharm Supply, Pol. Pharm Supply AG, ul. Marconich 2 m 9, 02-954 Warsaw, Poland.
url: www.pharmsupply.com.pl

Pharm Union, Ukr. Pharm Union, Narodnogo Opolchenia St. 7, 1st Floor Office 160, 03151 Kiev, Ukraine.
url: www.pharmunion.com.ua

Pharma 2000, Fr. Laboratoires Pharma 2000, Imm Strasbourg, av de l'Europe, Toussus-le-Noble, 78771 Magny-les-Hameaux cdx, France.

Pharma 2000, Singapore. Pharma 2000 Pte Ltd, 59 Ubi Ave 1, 07-11 Bizlink Centre, S 408938, Singapore.
url: www.pharma2000.com.sg

Pharma 3, Philipp. See *One Pharma, Philipp.*

Pharma Biotech, Israel. See *Medison, Israel.*

Pharma Consulting, Switz. Pharma Consulting Marion Senn GmbH, Weissensteinstrasse 24, Postfach, 3400 Burgdorf, Switzerland.
url: www.pharmaconsulting.ch

Pharma Dynamics, S.Afr. Pharma Dynamics (Pty) Ltd, P.O.Box 30958, Tokai 7966, South Africa.
url: www.pharmadynamics.co.za

Pharma Hus, Swed. Pharma Hus AB, Box 8134, 163 08 Spånga, Sweden.
url: pharmanord.se

Pharma Int, Ukr. See *Megakom, Ukr.*

Pharma International, Ukr. See *Megakom, Ukr.*

Pharma Investi, Chile. Pharma Investi de Chile SA, Av. Andres Bello 1495, Providencia, Santiago, Chile.

Pharma Investi, Spain. See *Sanofi-Aventis, Spain.*

Pharma Italia, Ital. Pharma Italia Laboratori Farmaceutici S.r.l., Via Vittor Pisani 93, 70033 Corato (BA), Italy.
url: www.pharmaitalia.com

Pharma Line, Gr. Pharma Line, Th. Petala 41, 143 43 N Chalkidona, Greece.

Pharma Line, Ital. Pharma Line S.r.l., Via Cavriani 8, 46100 Mantova (MN), Italy.
url: www.pharma-line.it

Pharma Logistics, Belg. Pharma Logistics SA, Demeurslaan 71, 1654 Huizingen, Belgium.
url: www.pharma-logistics.com

Pharma Logistik, Austria. Pharma Logistik Austria GmbH, Feldgasse 19, 4600 Wels, Austria.

Pharma Mar, Austria. See *Pharma Mar, Spain.*

Pharma Mar, Belg. See *Pharma Mar, Spain.*

Pharma Mar, Cz. See *Pharma Mar, Spain.*

Pharma Mar, Denm. See *Swedish Orphan, Denm.*

Pharma Mar, Fr. See *Pharma Mar, Spain.*

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Pharma Mar, Gr. See *Pharma Mar, Spain.*

Pharma Mar, Hung. See *Pharma Mar, Spain.*

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Pharma Mar, Ital. See *Pharma Mar, Spain.*

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Pharma Mar, Norw. See *Swedish Orphan, Norw.*

Pharma Mar, Pol. See *Imed, Pol.*

Pharma Mar, Port. See *Pharma Mar, Spain.*

Pharma Mar, Spain. Pharma Mar SA, Polígono Industrial La Mina, Avda de los Reyes 1, 28770 Colmenar Viejo (Madrid), Spain.
url: www.pharmamar.com

Pharma Mar, Switz. PharmaMar AG, Aeschenvorstadt 71, 4051 Basel, Switzerland.

Pharma Mar, UK. See *Pharma Mar, Spain.*

Pharma Medica, Canad. Pharma Medica, 966 Pantera Drive, Unit 31, Mississauga, ON, Canada.
url: www.pharmamedica.com

Pharma Medica, Switz. Pharma Medica AG, Frohheimstrasse 2, 9325 Roggwil TG, Switzerland.
url: www.pharmamedica.ch

Pharma Medica, USA. See *Pharma Medica, Canad.*

Pharma Natura, Hung. Pharma Natura Group Ltd, Apahida u 3, 1077 Budapest, Hungary.

Pharma Nord, Denm. Pharma Nord ApS, Sadelmagervej 30-32, 7100 Vejle, Denmark.
url: www.pharmanord.com

Pharma Nord, Fin. Oy Pharma Nord AB, Rajatorpantie 41 C, 01640 Vantaa, Finland.
url: www.pharmanord.com

Pharma Nord, Fr. Pharma Nord/Pharma Trade Healthcare, Bâtiment D/6, 4 rue de la Grande-Ourse, B.P. 8383, 95805 Cergy-Pontoise cdx, France.

Pharma Nord, Hung. Pharma Nord Kft, Váci út 95, 1139 Budapest, Hungary.
url: www.pharmanord.hu

Pharma Nord, Irl. See *Movianto, Irl.*

Pharma Nord, Malaysia. See *Sun, Malaysia.*

Pharma Nord, Norw. Pharma Nord Norge AS, Syretarnet 25, 3048 Drammen, Norway.
url: www.pharmanord.dk

Pharma Nord, Port. See *Pharma Nord, Denm.*

Pharma Nord, Singapore. See *Zuellig, Singapore.*

Pharma Nord, Thai. See *Biogenetech, Thai.*

Pharma Nord, UK. Pharma Nord UK Ltd, Telford Court, Morpeth, Northumberland, NE61 2DB, UK.
url: www.pharmanord.com

Pharma Nutria, Philipp. See *More, Philipp.*

Pharma Patent, Hung. Pharma Patent Kft, Szentlászlói út 44, 2000 Szentendre, Hungary.

Pharma Start, Rus. See *Pharma Start, Ukr.*

Pharma Start, Ukr. Pharma Start Ltd, Blvd Ivan Lepse 8, 03124 Kiev, Ukraine.
url: www.phs.ua

Pharma Synth, India. Pharma Synth Formulations Ltd, A-10/15, Jhilmil Industrial Area, New Delhi 110 095, India.

Pharma Tek, USA. See *X-Gen, USA.*

Pharma Vam, Rus. Pharma Vam ZAO, Kuskovskaya ul. 20A, Of. 609, Moscow, Russia.
url: www.glutoxim.ru

Pharma Vision, Hung. Pharma Vision Kft, Trombitas utca 11, 1026 Budapest, Hungary.
url: www.imedeen.com

Pharma Wernigerode, Rus. See *Queisser, Rus.*

Pharmabiotics, Chile. See *Recalcine, Chile.*

Pharmabroker, NZ. Pharmabroker Sales Ltd, P.O. Box 302 234, North Harbour Postal Centre, Auckland, New Zealand.

Pharmacal, Switz. See *Democal, Switz.*

Pharmacare, Austral. PharmaCare Laboratories Pty Ltd, 18 Jubilee Ave, Warriewood, NSW 2102, Australia.
url: www.pharmacare.com.au

Pharmacare, Canad. Pharmacare Ltd, 120 Harry Walker Parkway N, New Market, Ontario, L3Y 2B2, Canada.

Pharmacare, China. See *LF, China.*

Pharmacare, Gr. PHARMA-CARE AE, L. Spaton 68, 153 44 Gerakas, Greece.

Pharmacare, Hong Kong. See *Suburfarm, Hong Kong.*

Pharmacare, Ital. Pharmacare Srl, Via Marghera 29, 20149 Milan, Italy.

Pharmacare, Malaysia. See *Medidata, Malaysia.*

Pharmacare, Philipp. Pharmacare Products, 25 Kabignayan St, Banawe, Quezon City, Philippines.

Pharmacare, S.Afr. Pharmacare Ltd, 7 Fairclough Rd, Korsten, Port Elizabeth 6020, South Africa.

Pharmacare, Singapore. See *IDS, Singapore.*

Pharmacare Consumer, S.Afr. See *Aspen, S.Afr.*

Pharmacenter, Hung. Pharmacenter Hungary Kft, Bartok Bela ut 15/A 1/18, 1114 Budapest, Hungary.
url: www.pharmacenter.hu

Pharmacenter, Neth. See *Pharmacenter, Hung.*

Pharmaceutica North America, USA. Pharmaceutica North America Inc., USA.
url: pnarx.com

Pharmaceutical Associates, USA. See *Beach, USA.*

Pharmaceutical Basics, USA. See *Rosemont, USA.*

Pharmaceutical Enterprises, S.Afr. Pharmaceutical Enterprises (Pty) Ltd, Howards Drive, Pinelands, Howard Place 7405, South Africa.

Pharmaceutical Factory of St Petersburg, Rus. Pharmaceutical Factory of St Petersburg, ul Moiseenko 24a, 193144 St Petersburg, Russia.

Pharmaceutical Partners, Canad. Pharmaceutical Partners of Canada, 9050 Yonge St, Suite 306, Richmond Hill, Ontarion, L4C 9S6, Canada.

Pharmaceutical Specialties, USA. Pharmaceutical Specialties Inc., P.O. Box 6298, Rochester, MN 55903-6298, USA.
url: www.psico.com

Pharmachem, Ger. Pharmachem GmbH & Co KG, Nassäckerstr. 37-39, 07381 Pössneck, Germany.
url: www.pharma-poessneck.de

Pharmachem, S.Afr. Pharmachem Pharmaceuticals, Private Bag X12, 335 Frederick St, Pretoria West 0117, South Africa.
url: pharmachemsa.co.za

Pharmachem, UK. M & A Pharmachem Ltd, Allenby Laboratories, Wigan Rd, Westhoughton, Bolton, BL6 2LA, UK.
url: www.mapharmachem.co.uk

Pharmachemie, Austria. See *Pharmachemie, Neth.*

Pharmachemie, China. See *Xian-Janssen, China.*

Pharmachemie, Cz. See *Pharmachemie, Neth.*

Pharmachemie, Denm. See *Pharmachemie, Neth.*

Pharmachemie, Fin. See *Pharmachemie, Neth.*

Pharmachemie, Gr. Spiros Terzimbassis & Co., Pharma-Chemie, Simmachiki Str., Ionia, 570 08 Thessaloniki, Greece.
url: www.pharmachemie.gr

Pharmachemie, Hong Kong. See *US Summit, Hong Kong.*

Pharmachemie, Indon. Pharmachemie, Indonesia.

Pharmachemie, Israel. See *Teva, Israel.*

Pharmachemie, Malaysia. See *United Italian, Malaysia.*

Pharmachemie, Neth. Pharmachemie BV, Swensweg 5, 2031 GA Haarlem, Netherlands.
url: www.tevapharmachemie.com

Pharmachemie, Philipp. See *Marketlink, Philipp* and *Metro, Philipp.*

Pharmachemie, Port. See *Pharmachemie, Neth.*

Pharmachemie, Rus. See *Teva, Rus.*

Pharmachemie, S.Afr. Pharmachemie (Pty) Ltd, P.O. Box 7115, Johannesburg 2000, South Africa.

Pharmachemie, Singapore. See *FP, Singapore.*

Pharmachemie, Thai. See *Pacific, Thai.*

Pharmachim, Bulg. Pharmachim, 16 Iliensko Chaussee, Sofia, Bulgaria.

Pharmachim, Cz. See *Pharmachim, Bulg.*

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Pharmachim, Rus. See *Sopharma, Rus.*

Pharmacia, Arg. See *Pfizer, Arg.*

Pharmacia, Austral. Pharmacia Australia P/L, P.O. Box 46, Rydalmere, NSW 2116, Australia.
url: www.pharmacia.com.au

Pharmacia, Austria. Pharmacia Austria GmbH, Oberlaaer Strasse 251, A-1100 Vienna, Austria.
url: www.pharmacia.at

Pharmacia, Belg. See *Pfizer, Belg.*

Pharmacia, Braz. Pharmacia Brasil Ltda, Avenida Chucri Zaidan 940, 7 degrees andar, Condominio Market Place, Tower II, 04589-906 São Paulo, SP, Brazil.
url: www.pharmacia.com.br

Pharmacia, Canad. See *Pfizer, Canad.*

Pharmacia, Cz. Pharmacia & Upjohn sro, Křenová 7/439, 162 00 Prague 6, Czech Republic.
url: www.pharmacia.com

Pharmacia, Denm. See *Pfizer, Denm.*

Pharmacia, Fin. See *Pfizer, Fin.*

Pharmacia, Fr. Pharmacia SAS, B.P. 210, 78051 St-Quentin-Yvelines cdx, France.
url: www.pharmacia.fr

Pharmacia, Ger. See *Pfizer, Ger.*

Pharmacia, Hong Kong. See *Pfizer, Hong Kong.*

Pharmacia, Hung. See *Pfizer, Hung.*

Pharmacia, India. See *Pfizer, India.*

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Pharmacia, Israel. See *Perrigo, Israel.*

Pharmacia, Ital. See *Pfizer, Ital.*

Pharmacia, Mex. See *Pfizer, Mex.*

Pharmacia, Neth. Pharmacia BV, Postbus 17, 34407 AA Woerden, Netherlands.
url: www.pharmacia.com

Pharmacia, Norw. See *Pfizer, Norw.*

Pharmacia, NZ. See *Pfizer, NZ.*

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Pharmacia, S.Afr. See *Pfizer, S.Afr.*

Pharmacia, Singapore. Pharmacia Singapore Pte Ltd, 101 Thomson Rd, 31-04/05 United Square, S 307591, Singapore.
url: www.pharmacia.com

Pharmacia, Spain. See *Pfizer, Spain.*

Pharmacia, Swed. See *Pfizer, Swed.*

Pharmacia, Switz. See *Pfizer, Switz.*
url: www.pharmacia.ch

Pharmacia, Thai. Pharmacia (Thailand) Ltd, 6 Fl, White Group Building, 75 Soi Sangchan-Rubia, Sukhumvit 42, Sukhumvit Rd Prakanong, Klongtoey, Bangkok 10110, Thailand.
url: www.pharmacia.com

Pharmacia, UK. Pharmacia Ltd, Ramsgate Rd, Sandwich, Kent, CT13 9NJ, UK.

Pharmacia, USA. See *Pfizer, USA.*

Pharmacia, Venez. See *Pfizer, Venez.*

Pharmacia Consumer, Canad. See *Pfizer Consumer, Canad.*

Pharmacia Upjohn, Austral. See *Pharmacia, Austral.*

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Pharmacia Upjohn, Singapore. See *Pharmacia, Singapore.*

Pharmacia Upjohn, Spain. See *Pfizer, Spain.*

Pharmacia Upjohn, Swed. See *Pfizer, Swed.*

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Pharmacia Upjohn, Thai. See *Pharmacia, Thai.*

Pharmacia Upjohn, UK. See *Pfizer, UK.*

Pharmacia Upjohn, USA. See *Pfizer, USA.*

Pharmacie Centrale des Armees, Fr. Pharmacie Centrale des Armées, B.P. 04, 45998 Orleans Armees, France.

Pharmacie Centrale des Hopitaux, Fr. See *AGEPS, Fr.*

Pharmacie de France, Switz. See *Doetsch, Grether, Switz.*

Pharmaclon, Rus. Pharmaclon, Presnenskiy val 17d, 123557 Moscow, Russia.
url: www.pharmaclon.ru

Pharmaclon, Rus. Pharmaclon NPP Ltd, ul Bolbshaya Molchanovka 34 str 2, 121069 Moscow, Russia.
url: www.pharmaclon.ru

Pharmaco, Hung. Pharmaco, Hungary.

Pharmaco, NZ. Pharmaco (NZ) Ltd, 49 George St, Newmarket, Auckland, New Zealand.

Pharmaco, S.Afr. Pharmaco Distribution (Pty) Ltd, P.O. Box 786522, Sandton 2146, South Africa.
url: www.pharmaco.co.za

Pharmacobel, Belg. Laboratoires Belges Pharmacobel SA, Ave de Scheut 46-50, 1070 Brussels, Belgium.

Pharmacodane, Denm. PharmaCoDane ApS, Marielundvej 46A, 2730 Herlev, Denmark.
url: www.pharmacodane.dk

Pharmacodane, Fin. See *Pharmacodane, Denm.*

Pharmacodane, Norw. See *Pharmacodane, Denm.*

Pharmacodane, Swed. See *Pharmacodane, Denm.*

Pharmacon, Braz. See *Cristalia, Braz.*

Pharmacon, Gr. Pharmacon AFE, Naipliou 17, 144 52 Metamorfosi, Greece.

Pharmacon, India. Pharmacon Healthcare, SCF-446 Motor Market, Manimajra, Chandigarh 160 101, India.

Pharmacon, S.Afr. Pharmacon Pty Ltd, Constantia Kloof, Gauteng, South Africa.

Pharmacon, Singapore. Pharmacon, 8 Kaki Bukit Rd 2, 04-27/28 Ruby Warehouse Complex, S-417841, Singapore.
url: www.pharmacon.com.sg

Pharmacon, Singapore. Pharmacon (Pte) Ltd, 8 Kaki Bukit Rd, 04-27/28 Ruby Warehouse Complex, S 417841, Singapore.
url: www.pharmacon.com.sg

Pharmacor, Austral. Pharmacor, Suite 401, Level 4, 7 Oaks Ave, Dee Why, NSW 2099, Australia.
url: www.pharmacor.com.au

Pharmacore, Indon. Pharmacore Labs, Jl Arjuna Utara, No 52, Jakarta 11510, Indonesia.
url: www.pharmacore-labs.com

Pharmacos Abug, Mex. Pharmacos Abug S.A. de C.V., Lago Ginebra 359, Col. Cinco de Mayo, Deleg. Miguel Hidalgo, 11470 Mexico D.F., Mexico.

Pharmacosmos, Denm. Pharmacosmos AS, Rørvangsvej 30, 4300 Holbaek, Denmark.
url: www.pharmacosmos.com

Pharmacosmos, Fin. See *Pharmacosmos, Denm.*

Pharmacosmos, Irl. See *Pharmacosmos, Denm.*

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Pharmacosmos, Swed. See *Pharmacosmos, Denm.*

Pharmacosmos, Thai. See *Natural Media, Thai.*

Pharmacross, Chile. Pharmacross Biocross SA, Av. 11 de Septiembre 1881, Of. 2107, Providencia, Santiago, Chile.

Pharmaction, Hong Kong. See *International Medical, Hong Kong.*

Pharmacuro, Denm. Pharmacuro ApS, Saxogade 20, 4180 Sorø, Denmark.

Pharmacyclics, USA. Pharmacyclics Inc., 999 East Arques Avenue, Sunnyvale, CA 94085, USA.
url: www.pharmacyclics.com

Pharmacypria, Gr. PHARMACYPRIA, Paster 6, 115 21 Ampelokipoi, Greece.

Pharmadass, UK. Pharmadass Ltd, HealthAid House, Marlborough Hill, Harrow, Middlesex, HA1 1UD, UK.
url: www.healthaid.co.uk

PharmaDerm, USA. PharmaDerm, 4126 Steve Reynolds Blvd, Norcross, GA 30093, USA.
url: www.pharmaderm.com

Pharmadeveloppement, Fr. Pharma Développement, 40 rue des Bergers, 75015 Paris, France.

Pharmadica, Thai. Pharmadica Co. Ltd, 4 Fl, Pharmaland Building, 15/56 Moo 1 Soi Supapong, Srinakarin Rd, Nongborn Pravej, Bangkok 10260, Thailand.

Pharmadiet, Spain. Pharmadiet SLU, Blanquers 85, 17820 Banyoles, Girona, Spain.
url: www.pharmadiet.es

Pharmadigm, USA. See *Inflabloc, USA.*

Pharmador, S.Afr. See *Protea, S.Afr.*

Pharmadorf, Arg. PharmaDorf SA, Virrey Loreto 3878, 1427 Buenos Aires, Argentina.

Pharma-Export, UK. Pharma-Export Ltd, Suite 206, Canada House, 272 Field End Rd, Eastcote, Middlesex, HA4 9NA, UK.

Pharmafabre, Gr. Pharma Fabre Hellas S.A., 85 Lavriou Ave, 190 02 Paiania, Greece.

Pharmafabre (Φαρμαφαμπρ), Gr. See *Pharmafabre, Gr.*

Pharmafactory, Switz. pharmafactory ag, De Castellaweg 41, 3280 Greng bei Murten, Switzerland.

Pharmafair, USA. See *Bausch & Lomb, USA.*

Pharmafar, Ital. Pharmafar S.r.l., Corso V Emanuele II 82, 10121 Turin (TO), Italy.

Pharmaffiliates, India. Pharmaffiliates Healthcare, SCO 193, Sector 16, Panchkula, Haryana 134 109, India.

Pharmafina, Chile. See *Recalcine, Chile.*

Pharmafontana, Hung. Pharmafontana Rt, Csillagvirag utca 8, 1106 Budapest, Hungary.

Pharmaforte, Malaysia. Pharmaforte (M) Sdn Bhd, 2 Jln PJU 3/49, Sunway Damansara, 47810 Petaling Jaya, Selangor, Malaysia.
url: www.pharmaforte.com.my

Pharmaforte, Singapore. Pharmaforte Singapore Pte Ltd, 6 Tagore Drive, 03-11 Tagore Industrial Building, S 787623, Singapore.
url: www.pharmaforte.com.sg

Pharmafrica, S.Afr. Pharmafrica (Pty) Ltd, P.O. Box 18397, Hillbrow 2038, South Africa.

Pharmagalen, Ger. See *Galen, Ger.*

Pharmagen, S.Afr. Pharmagen, 28 Electron Ave, Isando 1600, South Africa.

Pharmagen, Turk. See *Sanofi-Aventis, Turk.*

Pharmagenics, UK. Pharmagenics Healthcare Ltd, 251 Walworth Rd, London, SE17 1RL, UK.

Pharmagenus, Spain. See *Uriach, Spain.*

Pharmagic, Ital. PharmaGIC S.r.l., Via Gerano 5, 00156 Rome (RM), Italy.

Pharma-Global, Irl. See *UnitedDrug, Irl.*

Pharma-Global, UK. See *Nucare, UK.*

Pharmaherb, Hung. Pharmaherb Kft, Bank utca 6, 1054 Budapest, Hungary.

Pharmahex, Philipp. See *Blooming Fields, Philipp.*

Pharmahof, Thai. Pharmahof Co Ltd, 99 Moo 2 Tumbon Bangtoey, Aumpeur Sampharn, Nakornpathom 73210, Thailand.

Pharmaidea, Ital. Pharmaidea Srl a socio unico, Via del Commercio 5, 25039 Travagliato (BS), Italy.
url: www.pharmaidea.com

Pharmakern, Port. PharmaKern Portugal Produtos Farmacêuticos Sociedade Unipessoal Lda, Edificio Atlas II, av. José Gomes Ferreira 11, SL 31 Miraflores, 1495-139 Algés, Portugal.

Pharmakin, Venez. Pharmakin C.A., Av Libertador, Multicentro Emp Este T Libertador, Nucleo A, Piso 15, Of A-154, Chacao, Caracas, Venezuela.

Pharmakin Korea, Venez. See *Pharmakin, Venez.*

Pharmakochimiki (Φαρμακοχημική), Gr. See *Farmakochimiki, Gr.*

Pharmakon, Ger. See *Asconex, Ger.*

Pharmakon, Switz. Pharmakon SA, Burglistrasse 39, 8304 Wallisellen, Switzerland.
url: www.pharmakon.ch

Pharmakon, USA. Pharmakon Laboratories Inc., 6050 Jet Port Industrial Blvd, Tampa, FL 33634, USA.
url: www.pharmakonlabs.com

Pharmakos, Switz. Pharmakos AG, Lowenstrasse 59, 8001 Zurich, Switzerland.

Pharmalab, Arg. Pharmalab, Division de Stonglass SA, Av. Santa Fe 3312, Piso 7 C, 1425 Buenos Aires, Argentina.

Pharmalab, Canad. Pharmalab (1982) Inc., 8750 boul. de-la-Rive-Sud, Levis, QC, G6V 6N6, Canada.

Pharmalab, Fr. Pharma-Lab, 3 rue d'Edimbourg, 75008 Paris, France.
url: www.pharmacerp.com

Pharmalab, Irl. See *Pharmalab, UK.*

Pharmalab, S.Afr. See *Sanofi-Aventis, S.Afr.*

Pharmalab, UK. Pharmalab Ltd, Tubiton House, Oldham, OL1 3HS, UK.

Pharmaland, Thai. Pharmaland (1982) Co. Ltd, Pharmaland Building, 56 Soi Supapong 1, Srinakarin Rd, Nongborn Pravej, Bangkok 10250, Thailand.

Pharmalex (Φαρμαλεξ), Gr. See *Farmalex, Gr.*

Pharmalink, Denm. See *Pharmalink, Swed.*

Pharmalink, Ger. See *Pharmalink, Swed.*

Pharmalink, Hong Kong. PharmaLink Hong Kong Ltd, Rm 1101, 11/F 625 Kings Rd, North Point, Hong Kong.
url: www.pharmalink.com

Pharmalink, India. Pharmalink (India) Pharmaceuticals Pvt Ltd, 1 Ashoknagar Bungalows, Behind Sundarvan, Satellite Raad, Ahmedabad 380 015, India.
url: www.pharmalink.com

Pharmalink, Neth. See *Pharmalink, Swed.*

Pharmalink, Norw. See *Pharmalink, Swed.*

Pharmalink, Philipp. See *Zuellig, Philipp.*

Pharmalink, Swed. Pharmalink AB, Box 625, 194 26 Upplands Väsby, Sweden.
url: www.pharmalink.se

Pharmalink, Thai. PL Asia Pacific (Thailand) Ltd, 6 Fl, Ploenchit Ctr, 2 Sukhumvit Rd, Kwaeng, Klongtoey, Bangkok 10110, Thailand.
url: www.pharmalink.com

Pharmall, Gr. Pharmall EEBE, Koropi Attici AG Asomatoi, 19400 Attici, Greece.

Pharmalogic, Israel. Pharmalogic Ltd, 11 Shoham St, Tel Aviv 69359, Israel.

Pharmamag, Canad. Pharmamag Inc., 736 Ave du Chateau, Quebec City, Quebec, G1X 3P3, Canada.

Pharmamagist, Hung. Pharmamagist Kft, Patakhegyi út 83-85, 1028 Budapest, Hungary.

Pharma-Marketing, Hung. Pharma-Marketing Kft, Boris u 4, 1031 Budapest, Hungary.

Pharmamed, Rus. See *Actavis, Rus.*

PharmaMetics, Austral. See *Max Biocare, Austral.*

Pharma-Natura, Ital. Pharma Natura S.r.l., Via Vicinale di Parabiago, 20014 Nerviano (MI), Italy.

Pharma-Natura, S.Afr. Pharma-Natura (Pty) Ltd, P.O. Box 494, Bergvlei 2012, South Africa.
url: www.pharma.co.za

Pharmanel, Gr. Pharmanel A.E., 106 Marathonos Ave, 153 44 Gerakas, Greece.
url: www.pharmanel.gr

Pharmanex, USA. Pharmanex Inc., 74 West Center, Provo, UT 84601, USA.
url: www.pharmanex.com

Pharmaniaga, Hong Kong. See *Ebewe, Hong Kong.*

Pharmaniaga, Malaysia. Pharmaniaga Marketing Sdn Bhd, P.O. Box 2030, Pusat Business Bukit Raja, 40800 Shah Alam, Selangor, Malaysia.
url: www.pharmaniaga.com.my

Pharmanik (Φαρμανικ), Gr. See *Farmanic, Gr.*

Pharmanovia, Denm. Pharmanovia A/S, Jaegerborg Allé 164, 2820 Gentofte, Denmark.

Pharmanovia, Fin. See *Pharmanovia, Denm.*

Pharmaplan, S.Afr. Pharmaplan (Pty) Ltd, P.O. Box 7115, Johannesburg 2000, South Africa.
url: www.pharmaplan.co.za

PharmaPure, USA. See *PureTek, USA.*

Pharma-Q, S.Afr. Pharma-Q Holdings Pty Ltd, 50 Commando Rd, Industria West, 2093 Johannesburg, South Africa.
url: www.pharmaq.co.za

Pharmaregie, Rus. Pharmaregie Distribution, Lesnaya ul. 43, Of. 701, 101509 Moscow, Russia.

Pharma-Regist, Cz. See *Pharma-Regist, Hung.*

Pharma-Regist, Hung. Pharma-Regist Kft, Október 6 u 7, 1051 Budapest, Hungary.

Pharmarex, Hung. Pharmarex Fejleszto es Kereskedelmi Kft, Arboc u 6 IV em, 1133 Budapest, Hungary.

Pharmarte, Ital. Pharmarte Srl, Viale Liegi 49, 00198 Rome (RM), Italy.

Pharmasac, Port. Pharmasac Produtos Farmacêuticos Lda, Portugal.

Pharmasan, Philipp. Pharmasan Inc., 6 Agatha St, Sta Teresita Vill, Lamuan, Marikina City, Philippines.

Pharmasant, Thai. See *Central, Thai.*

Pharmascience, Canad. Pharmascience Inc., 6111 Royalmount Ave, Suite 100, Montreal, Quebec, H4T 2T4, Canada.
url: www.pharmascience.com

Pharmascience, Fr. See *Expanscience, Fr.*

Pharmascience, Hong Kong. See *Hind Wing, Hong Kong* and *Jacobson, Hong Kong.*

Pharmascience, Israel. See *Pharmascience, Canad.*

Pharmascience, Malaysia. See *Ranbaxy, Malaysia.*

Pharmascience, Singapore. See *JDH, Singapore.*

Pharmascience, USA. See *Pharmascience, Canad.*

Pharmascope, Fin. See *Pharmascope, Irl.*

Pharmascope, Irl. Pharmascope Ltd, Unit 107, Ashbourne Industrial Estate, County Meath, Ireland.

Pharmascript, S.Afr. Pharmascript Pharmaceuticals, 1 Stirrup Lane, Woodmead Office Park, Johannesburg, Gauteng 2128, South Africa.

Pharmasearch, Irl. Pharmasearch Ltd, IDA Industrial Estate, Dublin Rd, County Loghreo, Ireland.

Pharmasearch, Neth. See *Pharmasearch, Irl.*

Pharmasearch, Port. See *Pharmasearch, Irl.*

Pharmaselect, Austria. Pharmaselect Handels GmbH, Ernst-Melchior-Gasse 20, 1020 Vienna, Austria.
url: www.pharmaselect.at

Pharmaselect, Cz. See *Pharmaselect, Austria.*

Pharmaselect, Gr. See *Pharmaselect, Austria.*

Pharmaselect, Hung. See *Pharmaselect, Austria.*

Pharmaserve, Gr. Pharmaserve SA, Mesogeion 335, 15310 Aghia Paraskevi, Greece.

Pharmaserve, Singapore. See *Polymedic, Singapore.*

Pharmashalom, Israel. Pharmashalom Ltd, 21 Hamelaha St, Park Afek, Rosh Ha'ayin, Israel.

PharmAsia, Philipp. PharmAsia-Cuvest Inc., 3/F Montepino Bldg, Gamboa cor Amorsolo St, Legaspi Vill, Makati City, Philippines.

Pharmaskin, Rus. Pharmaskin, Leninskaya Sloboda D 19, Russia.
url: pharmaskin.ru

Pharmasoft, Rus. NPK Pharmasoft, Avtozavodskaya ul.22, 115280 Moscow, Russia.

Pharmasol, Rus. See *Janssen-Cilag, Rus.*

Pharmasol, Singapore. See *Joyson, Singapore.*

Pharmasol, Thai. See *Hua, Thai.*

Pharmasol, UK. Pharmasol Ltd, North Way, Walworth Industrial Estate, Andover, Hampshire, SP10 5AZ, UK.
url: www.pharmasol.co.uk

Pharmason, Denm. Pharmason ApS, Bredgade 79, 5942 Vissenbjerg, Denmark.

Pharmaspec, Philipp. Pharmaspec NA Inc., 3/F Hizon Bldg, 29 Quezon Ave, Quezon City, Philippines.

Pharmastra, Fr. Pharmastra, Usines Chimiques et Pharmaceutiques de Strasbourg, 40 rue du Canal, 67460 Souffelweyersheim, France.
url: www.pharmastra.com

Pharmasud, Mex. Pharmasud SA de CV, Insurgentes Sir 664, Piso 9, 3100 Del Valle, Mexico DF, Mexico.

Pharmasure, UK. Pharmasure Ltd, 29 Watford Metro Centre, Dwight Rd, Watford, WD18 9SB, UK.

Pharma-Surrey, Philipp. Pharma-Surrey Intl, 46 Bulusan St, Sta. Mesa Heights, Quezon City, Philippines.

PharmaSwiss, Cz. PharmaSwiss Česka republika sro, Jankovcova 1569/2c, 170 00 Prafue 7, Czech Republic.
url: www.pharmaswiss.com

PharmaSwiss, Gr. PharmaSwiss Hellas AE, Pentelis Ave 53, PC 15235 Vrilissia, Athens, Greece.
url: www.pharmaswiss.com

PharmaSwiss, Hung. PharmaSwiss Magyarország Kft, Zichy G u. 5 fszt/1, 1146 Budapest, Hungary.
url: www.pharmaswiss.com

PharmaSwiss, Israel. PharmaSwiss Israel, 85 Medinat Hayehudim, Herzliya, Israel.

PharmaSwiss, Neth. See *PharmaSwiss, Switz.*

PharmaSwiss, Pol. PharmaSwiss Sp. z o.o., ul. Walbrzyska 11, 02-739 Warsaw, Poland.
url: www.pharmaswiss.com

PharmaSwiss, Switz. PharmaSwiss SA, Bundesplatz 1, 6300 Zug, Switzerland.
url: www.pharmaswiss.com

Pharmasynthez, Ukr. See *Geofik, Ukr.*

Pharmateam, Israel. Pharmateam Marketing, 5 Hamarpe St, P.O. Box 405, 91003 Jerusalem, Israel.
url: www.pharmateam.co.il

Pharmatec, Neth. See *Multipharma, Neth.*

Pharmatec, S.Afr. See *Adcock Ingram, S.Afr.*

Pharmatech, India. Pharmatech Healthcare, 49 Hirabhai Market, Diwan Ballubhai Road, Ahmedabad, India.

Pharma-Tech, India. Pharma-Tech India, 1711 Gurukrupa Estate, Aslali, Tal. Daskroi, Ahmedabad 382 427, India.

Pharmatech, Singapore. Pharmatech Resources (FE) Pte Ltd, 150 Kampong Ampat, 06-02A KA Ctr, S 368324, Singapore.
url: www.pharmatechresources.com

Pharmatechnica, Philipp. Pharmatechnica Lab. Inc., 5 Marquecilla St, San Francisco del Monte, Quezon City, Philippines.

Pharmatel, Austral. Pharmatel Fresenius Kabi Pty Ltd, Unit 6, 6-18 Bridge Road, Hornsby, NSW 2077, Australia.

Pharmatel, Malaysia. See *Imeks, Malaysia.*

Pharmatel, NZ. See *Pharmaco, NZ.*

Pharmaten (Φαρματεν), Gr. See *Pharmathen, Gr.*

Pharmatex, Ital. Pharmatex Italia S.r.l., Via Appiani 22, 20121 Milan (MI), Italy.
url: www.pharmatex.it

Pharmatex, Malaysia. See *Averroes, Malaysia.*

Pharmatex, Pol. See *Bioton, Pol.*

Pharmathen, Austria. See *Pharmathen, Gr.*

Pharmathen, Cz. See *Pharmathen, Gr.*

Pharmathen, Denm. See *Orifarm, Denm.*

Pharmathen, Gr. Pharmathen Pharmaceutical S.A., 6, Dervenakion Str., 153 51 Pallini Attiki, Greece.
url: www.pharmathen.com

Pharmathen, Hong Kong. See *Health Alliance, Hong Kong.*

Pharmathen, Irl. See *Pharmathen, Gr.*

Pharmathen, Neth. See *Pharmathen, Gr.*

Pharmathen, Philipp. See *Ascende Medz, Philipp.*

Pharmathen, Pol. See *Celon, Pol.*

Pharmathen, Port. See *Pharmathen, Gr.*

Pharmathen, Thai. See *Berli Jucker, Thai.*

Pharmatika, Hung. Pharmatika, Hungary.

Pharmaton, Cz. See *Boehringer Ingelheim, Cz.*

Pharmaton, Ger. See *Boehringer Ingelheim, Ger.*

Pharmaton, Indon. See *Boehringer Ingelheim, Indon.*

Pharmaton, Israel. See *Pharmashalom, Israel.*

Pharmaton, Malaysia. See *Boehringer Ingelheim, Malaysia.*

Pharmaton, Rus. See *Boehringer Ingelheim, Rus.*

Pharmaton, S.Afr. See *Altana, S.Afr.*

Pharmaton, Singapore. See *DKSH, Singapore.*

Pharmaton, Switz. Pharmaton SA, 6934 Bioggio, Switzerland.

Pharmaton, Thai. See *Boehringer Ingelheim, Thai.*

Pharmatre, Ital. Pharmatre SpA, Via Liborio Coccetti 8, 06034 Foligno (PG), Italy.
url: www.pharmatre.it

Pharmatrix, Arg. Pharmatrix, Div. de Therabel Pharma S.A., Arenales 259, 1704 Ramos Mejia, Buenos Aires, Argentina.
url: www.pharmatrix.com.ar

Pharmatrix, Philipp. Pharmatrix Corp., 27/F Unit 2702 Jollibee Plaza, Emerald Ave, Ortigas Center, Pasig City, Philippines.

Pharmaval, Ital. Pharmaval srl, Via Acque 6/1, 36050 Bolzano Vicentino (VI), Italy.
url: www.pharmaval.it

Pharma-Vinci, Denm. Pharma-Vinci A/S, Undalsvej 6, 3300 Ferderiksvaerk, Denmark.

Pharma-Vinci, Rus. See *Pharma-Vinci, Denm.*

Pharmavit, Cz. See *BMS, Cz.*

Pharmavita, Chile. Laboratorios Pharmavita SA, Nueva Leones 7 Of. 607, Providencia, Santiago, Chile.

Pharmavite, Canad. Pharmavite Corp., 55 Thorney Brae Drive, Thornhill, Ontario, L3T 3G5, Canada.

Pharmawealth, Philipp. Phil Pharmawealth Inc., Suite 3001 East Tower, PSE Ctr Exchange Rd, Ortigas Ctr, Pasig City, Philippines.
url: www.philpharmawealth.com

Pharmax, Hong Kong. See *Hind Wing, Hong Kong.*

Pharmax, Hung. Pharmax Ltd, Flora utca 7, 1037 Budapest, Hungary.
url: www.pharmax.hu

Pharmax, Irl. See *Allphar, Irl.*

Pharmax, Singapore. See *Naina, Singapore.*

Pharmax, UK. See *Forest Laboratories, UK.*

Pharmaxim, Denm. Pharmaxim, Praestevej 11, 9520 Skørping, Denmark.
url: www.pharmaxim.com

Pharmaxis, Austral. Pharmaxis Ltd, 2/10 Rodborough Rd, Frenchs Forest, NSW 2086, Australia.
url: www.pharmaxis.com.au

Pharmaxis, Denm. See *Nigaard, Swed.*

Pharmaxis, Fin. See *Pharmaxis, UK.*

Pharmaxis, Ger. See *Pharmaxis, UK.*

Pharmaxis, Irl. See *Pharmaxis, UK.*

Pharmaxis, Ital. See *Italchimici, Ital.*

Pharmaxis, Neth. See *Pharmaxis, UK.*

Pharmaxis, Norw. See *Pharmaxis, UK.*

Pharmaxis, Port. See *Pharmaxis, UK.*

Pharmaxis, UK. Pharmaxis Pharmaceuticals Ltd, The Priory, Stomp Rd, Burnham, Buckinghamshire, SL1 7LW, UK.
url: www.pharmaxis.com

Pharmaxis, USA. Pharmaxis Inc., 1 East Uwchlan Ave, Suite 405, Exton, PA 19341, USA.
url: www.pharmaxis.com

Pharmazam, Spain. See *Zambon, Spain.*

Pharmazan, Denm. Pharmazan Pharmaceuticals ApS, Kilde Alle 22 1 sal, 3600 Frederikssund, Denmark.

Pharmazel, Philipp. Pharmazel Inc., Philippines.

Pharmbos, Pol. Pharmbos Sp. zo.o., ul. Liceny 108 lok. 301, 04-687 Warsaw, Poland.

Pharmco, S.Afr. Pharmco Holdings Ltd., 16a Drake Ave, Eastleigh Ridge, Edenvale 1609, South Africa.

Pharmcom, Denm. See *Pharmcom, Fin.*

Pharmcom, Fin. Pharmcom Oy, Keijumäki 6B 30, 02130 Espoo, Finland.

Pharm-D, Malaysia. See *Summit, Malaysia.*

Pharmed, Austria. Pharmed, Sackstrasse 4, A-8011 Graz, Austria.

Pharmed, India. Pharmed Medicare, Pharmed Gardens, Whitefield Rd, Bangalore 560 048, India.
url: www.pharmedmedicare.com

Pharmed, Singapore. Pharmed Import & Export Pte Ltd, 149 Rochor Rd, B1-16/17/18 Fu Lu Shou Complex, S 188425, Singapore.

Pharmedex, Cz. Pharmedex sra, Prague, Czech Republic.

Pharmedia (Φαρμεντια), Gr. See *Farmedia, Gr.*

Pharmedial, Cz. Pharmedial sro, Na zajezdu 10, 101 00 Prague 10, Czech Republic.

Pharmedic, Philipp. See *Huge, Philipp.*

Pharmedica, S.Afr. Pharmedica Laboratories (Pty) Ltd, Rattray Rd, Dawn, East London, South Africa.
Pharmeg, Ital. Pharmeg srl, Via dei Giardini 34, 85033 Episcopia (PZ), Italy.
Pharmel, Canad. Pharmel Inc., 8699 8e Ave, Montreal, Quebec, H1Z 2X4, Canada.
Pharmelac, Fr. See *Innothera, Fr.*
Pharmelle, USA. Pharmelle LLC, S. William Dillard Drive, Building 3, number 109, Gilbert, AZ 85233, USA.
url: www.pharmelle.com
Pharmethic, Belg. Pharmethic SA, Rue de Vivier 89-93, 1050 Brussels, Belgium.
Pharmethica, Neth. Pharmethica BV, Ronde Tocht 11, 1507 CC Zaandam, Netherlands.
Pharmetics, Canad. Pharmetics Inc., 3695 Autoroute des Laurentides, Laval, Quebec, H7L 3H7, Canada.
Pharmeurop, Fr. See *Pfizer, Fr.*
Pharmex (Φαρμεξ), Gr. Farmex AE, Avlonos 156, 104 43 Athens, Greece.
Pharmexco, UK. Pharmexco Ltd, 5-6 Zennor Rd, London, SW12 0PS, UK.
Pharmia, Fin. Pharmia Oy, Kalliotie 2, 04360 Tuusula, Finland.
url: www.pharmia.fi
Pharmics, USA. Pharmics Inc., 2702 South 3600 West, Suite H, Salt Lake City, UT 84119, USA.
url: www.pharmics.com
Pharminar, Thai. Pharminar Co. Ltd, 398/11 Sathupradit Khwang Bang Phongphang Khet Yan Nawa, Bangkok, 10120, Thailand.
Pharming, Cz. See *Pharming, Neth.*
Pharming, Irl. See *Pharming, Neth.*
Pharming, Neth. Pharming Group NV, Darwinweg 24, 2333 CR Leiden, Netherlands.
Pharming, Pol. See *Pharming, Neth.*
Pharming, Port. See *Pharming, Neth.*
Pharming, Swed. See *Pharming, Neth.*
Pharminicio, Spain. Pharminicio SLU, Pso de la Habana 9-11, 28036 Madrid, Spain.
Pharmion, Austria. See *Pharmion, UK.*
Pharmion, Denm. See *Celgene, Denm.*
Pharmion, Ger. See *Celgene, Ger.*
Pharmion, Hong Kong. See *IDS, Hong Kong* and *Jacobson, Hong Kong.*
Pharmion, Hung. See *Pharmion, USA.*
Pharmion, Irl. See *Allphar, Irl.*
Pharmion, Neth. Pharmion, Netherlands.
Pharmion, Norw. See *Celgene, Denm.*
Pharmion, Philipp. See *GenAsia, Philipp.*
Pharmion, Thai. See *Siam Pharm, Thai.*
Pharmion, UK. Pharmion Ltd, McClintock Building, Granta Park, Gt Abington, Cambridgeshire, CB1 6GX, UK.
url: www.pharmion.com
Pharmion, USA. Pharmion Corp., 2525 28th St., Suite 200, Boulder, CO 80301, USA.
url: www.pharmion.com
Pharmis, Port. Pharmis Biofarmacêutica Lda, Praceta do Farol, Lote 101, 2750-341 Cascais, Portugal.
Pharmix, Pol. Pharmix SA, ul. Stoneczna 96, 05-500 Stara Iwiczna, Poland.
Pharmmalaysia, Singapore. See *Apotheca, Singapore.*
Pharmoccitan, Fr. See *JCD, Fr.*
Pharmodontal, Belg. Pharmodontal SA, Grondwetlaan 87, 1083 Brussels, Belgium.
Pharmodontal, Neth. See *Pharmodontal, Belg.*
Pharmonta, Austria. Pharmonta Mag. pharm. Dr Fischer, Montanastrasse 7, A-8112 Gratwein, Austria.
url: www.pharmonta.com
Pharmonta, Ger. See *Pharmonta, Austria.*
Pharmore, Ger. Pharmore GmbH, Gildestr. 75, 49479 Ibbenbüren, Germany.
url: www.pharmore.de
Pharmos, Arg. Pharmos S.A., Saladillo 2450, 1440 Buenos Aires, Argentina.
Pharmout, Port. Pharmout Farmacêutica Internacional Lda, Rua da Quinta das Romeiras 104 - 7, 1495-236 Algés, Portugal.
Pharmpartners, Philipp. See *Biolink, Philipp.*
Pharmplanet, Ukr. Pharmplanet Ltd, V. Chayky Str. 4, Chayky, Kyivo-Svyatoshyn, Kiev, 08130, Ukraine.
url: www.pharmplanet.com.ua
Pharmsintez, Rus. Farmsintez ZAO, Kronverkskij prosp., d. 71/46, 197198 Saint Petersburg, Russia.
url: www.pharmsynthez.com
Pharmsynthez, Ukr. See *Geolik, Ukr.*
Pharmuka, Fr. See *Sanofi-Aventis, Fr.*
Pharmy, Fr. Laboratoires Pharmy II, Strategy Center, 26 rue des Gaudines, 78100 Saint-Germain-en-Laye, France.
Pharmygiene, Fr. Laboratoires Pharmygiène-SCAT, 2-4 rue Chaintron, B.P. 850, 92542 Montrouge cdx, France.
Pharmygiene, Neth. See *Pharmygiene, Fr.*
Pharmygiene, Rus. See *FIC, Rus.*
Pharmygiene, Ukr. See *FIC Medical, Ukr.*
Pharno-Wedropharm, Ger. Pharno-Wedropharm GmbH, Heinrichstrasse 3, 21244 Buchholz, Germany.
PharOS, Cz. See *PharOS, Gr.*
PharOS, Gr. PharOS - Pharmaceutical Oriented Services Ltd, 87 Marathonos Ave, Pallini Attikis 15351, Greece.
Pharos, Indon. Pharos Indonesia PT, Jl Limo No 40, Permata Hijau, Senayan, Jakarta 12220, DKIJaya, Indonesia.
Pharos, Ital. See *PharOS, Gr.*
PharOS, Neth. See *PharOS, Gr.*
Pharos, Singapore. See *Polymedic, Singapore.*
Phas, Arg. See *Roche-Posay, Arg.*
PHC, Indon. Pharma Health Care (PHC) PT, Graha Atrium 15th Fl, Jl Sene Raya 135, Jakarta, DKIJaya, Indonesia.
Phebra, Austral. Phebra Pty Ltd, 332 Burns Bay Rd, Lane Cove, NSW 2066, Australia.
Phergal, Spain. Laboratorios Phergal SA, Hierro 79 Torrejon de Ardoz, 28850 Madrid, Spain.
Philip Harris, UK. See *Hameln, UK.*
Phillips Yeast, UK. See *Seven Seas, UK.*
Philopharm, Ger. See *Mibe, Ger* and *Mibe Jena, Ger.*
Philopharm, Rus. See *Queisser, Rus.*
Philtel, Israel. Philtel Pharmaceuticals Ltd, P.O. Box 3918, Kiryat Arie, Petach Tikva 49130, Israel.
Philusa, Philipp. Philusa Corp., 28 Shaw Blvd cor. Pioneer St, 1600 Pasig City, Philippines.
url: www.philusa.com.ph
Phoenix, Arg. Laboratorios Phoenix S.A.I.C.F., Humahuaca 4065, 1192 Buenos Aires, Argentina.
url: www.phoenix.com.ar
Phoenix, Austria. Phoenix Arzneiwarengrosshandlung GmbH, Albert Schweitzer Gasse 3, A-1140 Vienna, Austria.
Phoenix, Hung. Phoenix Pharma Rt, Keleti Márton u 19, Pf 46, 2151 Fót, Hungary.
Phoenix, Irl. See *Fulcrum, Irl.*
Phoenix, Philipp. Phoenix Pharmaceuticals Inc., Asian Mansion II, G/F No 3, 108 Dela Rosa St, Legaspi Village, Makati City, Philippines.
Phoenix, UK. See *Hameln, UK.*
Phoenix-Elea, Arg. See *Phoenix, Arg.*
Phoinix Pharm (Φοινιξ Φαρμ), Gr. FOINIX FARM EPE, Anavrytis 5, 111 43 Athens, Greece.
Phonix, Ger. Phönix Laboratorium GmbH, Benzstr. 10, 71149 Bondorf, Germany.
url: www.phoenix-lab.de
Phonix, Neth. See *Phonix, Ger.*
Photocure, Denm. See *Photocure, Norw.*
Photocure, Fin. See *Photocure, Norw.*
Photocure, Norw. PhotoCure ASA, Hoffsvein 48, 0377 Oslo, Norway.
url: www.photocure.com
Photocure, Swed. See *Photocure, Norw.*
Photocure, USA. PhotoCure ASA, 161 Washington St, Conshohocken, PA 19428, USA.
PHT, Ital. PHT Pharma S.r.l., Via L. Ariosto 34, 20145 Milan (MI), Italy.
url: www.phtpharma.it
Physan, Spain. Physan, Camino de las Huertas 2, Edificio 2 C, 7, 28223 Pozuelo de Alarcón, Madrid, Spain.
url: www.laphysan.es
Physician Recommended Nutriceuticals, USA. Physician Recommended Nutriceuticals (PRN), 502 West Germantown Pike, Suite 610, Plymouth Meeting, PA 19462, USA.
url: www.prnomegahealth.com
Physicians Formula, Canad. See *Physicians Formula, USA.*
Physicians Formula, USA. Physicians Formula Inc., 1055 W 8th St, Azusa, CA 91702, USA.
Physicians Science & Nature, USA. Physicians Science & Nature, USA.
Phytaroma, Fr. See *Plantes et Medecines, Fr.*
Phythea, Fr. Phythea, 13 rue Elsa-Triolet, 77176 Savigny-le-Temple, France.
url: www.phytalgic.com
Phyto Health, India. See *Phyto Health, Neth.*
Phyto Health, Neth. Phyto Health Pharma, P.O. Box 14, 2280 AA Rijswijk, Netherlands.
Phyto Kemo, Indon. Phyto Kemo Agung Farma PT, Jl Mesjid No 90, Susukan-Pasar Rebo, Jakarta Timur 13750, Indonesia.
url: www.phytokemo.com
Phytobiolab, Fr. Lab Phytobiolab, 9 allée de Corrèze, 31770 Colomiers, France.
PhytoCon, Ger. PhytoCon GmbH & Co KG, Koblenzer Str. 48-56, 56626 Andernach, Germany.
PhytoCon, UK. See *PhytoCon, Ger.*
Phytodiet, Fr. Laboratoires Phytodiet, B.P. 68012, 57028 Metz cdx 01, France.
Phytofarm Kleka, Pol. See *Europlant Phytofarm, Pol.*
Phytofrance, Fr. LAPHT Phytofrance, Complex La Gastade, 34130 Candillargues, France.
url: www.phytofrance.com
Phytologic, Austral. Phytologic Pty Ltd, 1-7 Doody St, Alexandria, NSW 2015, Australia.
Phytomedica, Fr. Laboratoires Phytomedica, ZI Les Milles, B.P. 5000, Parc d'activités de Pichaury, 13791 Aix-en-Provence cdx 3, France.
url: www.phytomedica-labo.com
Phytomedicine, Austral. Phytomedicine P/L, P.O. Box 1995, Dee Why, NSW 2099, Australia.
url: www.phytomedicine.com.au
Phytopharm, Rus. See *Farmstandart, Rus.*
Phytopharm, Ukr. Phytopharm JSC, ul. Sibirtseva, 2 Artemovsk, Donetsk 84500, Ukraine.
url: www.fitofarm.dn.ua
Phytopharma, Switz. Phytopharma SA, Chemin des Golettes 4a, 1666 Grandvillard, Switzerland.
url: www.phytopharma.ch
Phyto-Sante, Canad. Phyto-Sante Ltee, 2496 Montbray rue, Ste Foy, Quebec, G1V 1E8, Canada.
Phytosolba, Fr. Laboratoires Phytosolba, 89 rue Salvador-Allende, 95870 Bezons, France.
Phytotec, Hung. Phytotec Hungária Kft, Lotz Károly u 3, 1026 Budapest, Hungary.
Piam, Ital. Vecchi & C. Piam di G. Assereto, E. Maragliano e C. S.a.p.a., Via Padre G. Semeria 5, 16131 Genoa (GE), Italy.
url: www.piamfarmaceutici.com
Piam, Singapore. See *Zyfas, Singapore.*
Picco, Thai. Picco Pharma Co Ltd, 1/104 Soi Chokechai 4, Latraphrao Rd, Latphrao, Bangkok 10230, Thailand.
Picharn, Thai. Picharn c/o The Picharn Co. Ltd, 53/43 Soi Amornphan 5, Viphavadi-Rangsit Rd, Jatujak, Bangkok 10900, Thailand.
Pickles, UK. J. Pickles & Sons, Beech House, 62 High St, Knaresborough, North Yorkshire, HG5 0EA, UK.
url: www.jpicklesheathcare.com
Picot, Switz. See *Ridupharm, Switz.*
Pidek, India. Pidek Pharmaceuticals, AO-4 Goyal Market, GT Rd, Moga, 142 001, India.
Pidi, China. Pidi Pharmaceutical Co. Ltd, Guangdong, China.
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Pierre Fabre, Fin. See *Algol, Fin.*
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Pierre Fabre, Hong Kong. See *Orient, Hong Kong.*
Pierre Fabre, Hung. See *Ewopharma, Hung.*
Pierre Fabre, Indon. See *Darya-Varia, Indon.*
Pierre Fabre, Irl. See *Pierre Fabre, UK.*
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Pierre Fabre, Malaysia. See *Orient, Malaysia.*
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Pierre Fabre, Philipp. See *Zuellig, Philipp.*
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Pierre Fabre, Turk. See *Sanofi-Aventis, Turk.*
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Pierre Fabre, USA. See *Genesis, USA.*
Pierre Fabre Dermatologie, Cz. See *Pierre Fabre, Cz.*
Pierre Fabre Dermatologie, Fin. See *Pierre Fabre, Fr.*
Pierre Fabre Dermatologie, Fr. See *Pierre Fabre, Fr.*
Pierre Fabre Dermatologie, Pol. See *Pierre Fabre, Pol.*
Pierre Fabre Dermo Kosmetik, Austria. See *Pierre Fabre, Ger.*
Pierre Fabre Dermo Kosmetik, Ger. See *Pierre Fabre, Ger.*
Pierre Fabre Dermo-Cosmetique, Arg. See *Pierre Fabre, Arg.*
Pierre Fabre Dermo-Cosmetique, Canad. See *Pierre Fabre, Canad.*
Pierre Fabre Dermo-Cosmetique, Irl. See *Pierre Fabre, UK.*
Pierre Fabre Dermo-Cosmetique, Port. See *Pierre Fabre, Port.*
Pierre Fabre Dermo-Cosmetique, Rus. See *Pierre Fabre, Rus.*
Pierre Fabre Oral Care, Arg. See *Pierre Fabre, Arg.*
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Pierre Fabre Sante, Singapore. See *Summit, Singapore.*
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Pierre Rolland, Fr. See *Acteon, Fr.*
Pierre Rolland, Rus. See *Acteon, Rus.*
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url: www.pierrel-group.com
Pierson, USA. Pierson Laboratories Inc., 506 Lake Hosea Dr., Saluda, NC 28773-7721, USA.
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Piette, Thai. See *International Pharmaceuticals, Thai.*
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Pik, Ukr. See *Pik, Rus.*
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url: www.pileje-micronutrition.fr
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Pilkington Barnes-Hind, USA. See *Wesley, USA.*
Pinewood, Austria. See *Pinewood, Irl.*
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Pint, Hung. See *WI Pharma, Hung.*
Pint, Israel. See *Gilco, Israel.*
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Piramal, Gr. See *Piramal, India.*
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Plan B, USA. See *Barr, USA.*
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Plantamed, Ger. See *Bionorica, Ger.*
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Plantier, Fr. See *Viatris, Fr.*
Plantorgan, Ger. See *Sanofi-Aventis, Ger.*
Plantorgan, Neth. See *Bipharma, Neth.*
Plants, Ital. Plants, Laboratorio della Dott.ssa Luisa Coletta, Viaria C, Zona Industriale, 98040 Giammoro (ME), Italy.
url: www.laboratorioplants.com
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Plastchim, Rus. See *Sopharma, Rus.*
Plata, Arg. Lab. Pharma del Plata S.R.L., Valentin Torra 5450, 3100 Pque.Ind.G. Belgrano, Entre Rios, Argentina.

Platinum, Philipp. See *Medisys, Philipp.*
Platinum, Thai. See *Pharmaland, Thai.*
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Plethico, Malaysia. See *Pharmaniaga, Malaysia.*
Plethico, Rus. See *Rezlov, Rus.*
Plethico, Ukr. See *Rezlov, Ukr.*
Pliva, China. See *Baker Norton, China.*
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Pliva, Denm. See *Pliva, UK.*
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Pliva, Neth. See *Pliva Krakow, Pol.*
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Pliva, Spain. See *Edigen, Spain.*
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Pliva Krakow, Rus. See *Pliva, Rus.*
Pliva Lachema, Pol. See *Pliva Krakow, Pol.*
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Pliva-Lachema, Rus. See *Pliva, Rus.*
Plos, Arg. See *Alcon, Arg.*
Plough, Port. See *Schering-Plough, Port.*
Plough, UK. See *Schering-Plough, UK.*
Plough, USA. See *Schering-Plough, USA.*
PLT, USA. PL Thomas & Co, Inc., 1 Speedwell Avenue, Morristown, NJ 07960, USA.
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Plumbland, Arg. Plumbland Holdings Ltd, Paraguay 914 Piso 8 A, 1057 Buenos Aires, Argentina.
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Plurilab, Port. Plurilab Produtos Farmacêuticos e Dietéticos Lda, Portugal.
Plurisystem, Ital. Plurisystem S.a.s. di Arippa Lionello & C., Via F.Vezzani 99r, 16159 Rivarolo (GE), Italy.
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Plus Pharma, Denm. See *Plus Pharma, Austria.*
Plus Pharma, Hung. See *Plus Pharma, Austria.*
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PMC, Austral. See *AstraZeneca, Austral.*
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Poehlmann, Switz. See *Renapharm, Switz.*
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Poen Vision, Mex. Poen Vision SA de CV, Montecito 38, Piso 7 Of. 30, 3810 Nápoles Benito Juárez, Mexico DF, Mexico.
Pohl, Austria. See *Pohl, Ger.*
Pohl, Cz. See *Merck, Cz.*
Pohl, Denm. See *Pohl, Ger.*
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Pohl, Israel. See *Megapharm, Israel.*
Pohl, Neth. See *Tramedico, Neth.*
Pohl, Norw. See *Meda, Norw.*
Pohl, Swed. See *Meda, Swed.*
Pohl, Switz. See *Lubapharm, Switz.*
Pohl, Thai. See *Stada, Thai.*
Pohl, UK. See *Merck Serono, UK.*
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Pohl-Boskamp, Hung. See *Merck, Hung.*
Pohl-Boskamp, Norw. See *Pohl-Boskamp, Swed.*
Pohl-Boskamp, Philipp. See *Croma, Philipp.*
Pohl-Boskamp, Rus. See *Pohl, Ger.*
Pohl-Boskamp, Singapore. See *DKSH, Singapore.*
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Pohl-Boskamp, Ukr. See *Artur, Ukr.*
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Polcoma, Austral. See *Polcopharma, Austral.*
Polcommerce, Hung. Polcommerce Kft a Ciech, Polfa Ltd képviselője, Ötvös János u 1-3, 1021 Budapest, Hungary.
Polcopharma, Austral. Polcopharma, F. Polley & Co. Pty Ltd, P.O. Box 100, Epping, NSW 2121, Australia.
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Polfa, Cz. See *Polfa Ciech, Cz.*
Polfa, Hung. See *Polcommerce, Hung.*
Polfa, Rus. See *Warsaw-Polfa, Rus.*
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Polfa Pabianice, Fin. See *Polfa Pabianice, Pol.*
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Polfarmex, Pol. Polfarmex SA, ul. Józefów 9, 99-300 Kutno, Poland.
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Poli, Cz. See *Medicom, Cz.*
Poli, Hong Kong. See *International Medical, Hong Kong.*
Poli, Pol. See *Medagro, Pol.*
Poli, Rus. See *European Community, Rus.*
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Polichem, Austria. See *Polichem, Switz.*
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Polichem, Hong Kong. See *US Summit, Hong Kong.*
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Polichem, Pol. See *Medagro, Pol.*
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Polichem, Ukr. See *Dileo, Ukr.*
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Polipharm, Singapore. See *MD, Singapore.*
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Polpharma, Cz. See *Polfa Ciech, Cz.*
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PolyMedica, USA. PolyMedica Pharmaceuticals (USA) Inc., 11 State St, Woburn, MA 01801, USA.
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Polymer Technology, Canad. See *Bausch & Lomb, Canad.*
Polymer Technology, USA. See *Bausch & Lomb, USA.*
Ponce, Venez. Ponce & Benzo Sucesores C.A., Edificio Ponce & Benzo, 2da. Avenida, Urb. Santa Eduvigis, Caracas, Venezuela.
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Pond's, Philipp. See *Cyno Sure, Philipp* and *DKT, Philipp.*
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Ponroy, Fr. See *Yves Ponroy, Fr.*
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Porton, Israel. See *Medogar, Israel.*
Porton, USA. See *Ipsen, USA.*
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Potter's, UK. Potters (Herbal Supplies) Ltd, 1 Botanic Court, Martland Park, Wigan, WN5 0JZ, UK.
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Powderject, USA. See *Chiron, USA.*
Power Bar, Canad. See *Nestle, Canad.*
Powermist, Philipp. Powermist Pharma Corp., Suite 2601 Medical Plaza Ortigas, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.
Poythress, USA. See *ECR, USA.*
Pozitron, Hung. Pozitron Diagnosztika Kft, Hunyadi János út 9, 1117 Budapest, Hungary.
PP Lab, Thai. See *Picharn, Thai.*
PP Nature Balance, Austria. See *PP Nature Balance, Ger.*
PP Nature Balance, Ger. PP Nature Balance GmbH, Habichthorst 34-36, 22459 Hamburg, Germany.
url: www.pp-nature-balance.de
PPDH, Fr. PPDH SA, 247 bis rue des Pyrenees, 75020 Paris, France.
Praelia, USA. See *Vestiq, USA.*
Prafa, Indon. Prafa PT, Talavera Office Park, 8th-10th Floor, Jl Letjen TB, Simatupang No 22-26, Jakarta 12430, Indonesia.
Prairie Naturals, Canad. Prairie Naturals, 56 Fawcett Rd, Coquitlam, British Columbia, V3K 6V5, Canada.
Praise, Ital. Praise Corporation Srl, Via Degli Zavattari 1, 20052 Monza, Italy.
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Pras, Spain. See *Almirall, Spain.*
Prasco, USA. Prasco Laboratories, 6125 Commerce Court, Mason, OH 45040, USA.
url: www.prasco.com
Prasfarma, Spain. See *Almirall, Spain.*
Pratapa Nirmala, Indon. Pratapa Nirmala PT, Jl Raden Saleh Raya 4, 10430 Jakarta, DKI Jaya, Indonesia.
Prater, Chile. Laboratorio Prater SA, Av. P Aguirre Cerda 5291, Cerrillos, Santiago, Chile.
Prati-Donaduzzi, Braz. Prati-Donaduzzi & Cia Ltda, Rua Mitsugoro Tanaka 145 C.Indl.Nilton A, 85903630 Toledo, Parana, Brazil.
Prats, Spain. Prats, Travesera del Dalt 44, 08024 Barcelona, Spain.
Praxair, Canad. Praxair Canada Inc., Suite 1200, 1 City Centre Drive, Mississauga, Ontario, L5B 1M2, Canada.
Praxico, Hung. See *Lilly, Hung.*
Praxipharm, Hung. Praxipharm Kft, Tompa Mihály u. 15, 1029 Budapest, Hungary.
Prebio, Singapore. See *MD, Singapore.*
Precimex, Mex. Precimex S.A. de C.V., Calderón de la Barca 27, Miguel Hidalgo Palmos Polanca, 11560 Mexico DF, Mexico.
url: www.precimex.com.mx
Precision, USA. Precision Pharma Services Inc., 155 Duryea Rd, Melville, NY 11747, USA.
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Preferred Nutrition, Canad. Preferred Nutrition Inc., 153 Perth St, Acton, Ontario, L7J 1C9, Canada.
PregLem, UK. PregLem, a Division of Richter UK Ltd, 127 Shirland Rd, Maida Vale, London, W9 2EP, UK.
url: www.preglem.com
Prem, India. Prem Pharmaceuticals Ltd, 501 Alankar Point, Geeta Bhawan Square, P.O. Box No 117 GPO, Indore, 452 001, India.
Premia, UK. Premia Cosmetics Ltd, UK.
url: www.premiacos.com
Premier, Irl. Premier Medicof Ltd, Dromin, Kilmallock, Co. Limerick, Ireland.
Premier, S.Afr. See *Sandoz, S.Afr.*
Premier, Thai. Premier Pharma Supply Co Ltd, 62/340 Moo, 5 Terdphrakiat Rd, Watchalaw, Bangkruay, Nonthaburi 11130, Thailand.
Premier, USA. See *AP, USA.*
Premier Dental, USA. Premier Dental, 1710 Romano Drive, Plymouth Meeting, PA 18462, USA.
url: www.premusa.com
Premier Research, Ger. Premier Research GmbH, Birkenweg 14, 64295 Darmstadt, Germany.
Premier Research, Neth. See *Premier Research, Ger.*
Premium, Port. Premium Pharma Sociedade Técnico Medicinal Lda, Rua da Tapa Grande 2, Abrunheira, 2710-089 Sintra, Portugal.
Premopharm, Israel. Premopharm (Israel) Ltd, P.O. Box 319, Ra'anana, Israel.
Prempharm, Canad. Prempharm Inc., 85 Advance Rd, Etobicoke, Ontario, M8Z 2S6, Canada.
Prescriptives, Canad. Prescriptives Co Dist., 161 Commander Blvd, Agincourt, Ontario, M1S 3K9, Canada.
President Pharmagenesis, China. Presdident Pharmagenesis Pharmaceutical Co. Ltd, 16 Orange Bridge Creek, Qi Avenue, Suzhou, Jiangsu, 215001, China.
url: 6400434.czvv.com/
Prespharm, Rus. Prespharm, Krasnoproletarskaya ul. 2/4, str. 16, 103006 Moscow, Russia.
Presselin, Ger. See *Combustin, Ger.*
Prestige, Canad. Prestige Brands International, 120 Harry Walker Parkway N, Newmarket, Ontario, L3Y 2B2, Canada.
Prestige, Irl. See *Prestige, UK.*
Prestige, UK. Prestige Brands (UK) Ltd, 3 Scotlands Drive, Farnham Common, Slough, Berkshire, SL2 3ES, UK.
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Prestige, USA. Prestige Brands International, 3510 N Lake Creek Dr., Wilson, WY 83014, USA.
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Prestium, USA. Prestium Pharma Inc., 411 S State St, Suite E-100, Newtown, PA 18940, USA.
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Preval, Canad. See *Preval, USA.*
Preval, USA. Preval Group LLC, 1 51 Nonesuch River Plaza, Scarborough, Maine, 04074, USA.
Preventys, Fr. Laboratoires Preventys, 9 Chemin du Roc-Fleuri, 13100 Aix-en-Provence, France.
Prevor, Fr. Laboratoires Prevor, B.P. 1, Moulin de Verville, 95760 Valmondios, France.
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PriCara, USA. See *Ortho McNeil Janssen, USA.*
Prieto, Arg. Laboratorios Prieto S.A., Maza 1869/73, 1240 Buenos Aires, Argentina.
Primal, Hong Kong. Primal Chemical Co. Ltd, Flat A, 7/F, Hoi Bun Industrial Bldg, 6 Wing Yip St, Kwun Tong, Kowloon, Hong Kong.
Prime, Singapore. See *Uni, Singapore.*
Prime Enterprises, Canad. See *Prime Enterprises, USA.*
Prime Enterprises, USA. Prime Enterprises Inc., 16363 NW 49th Ave, Miami Lakes, CA 33014-6316, USA.
PrimeDrug, Philipp. PrimeDrug Marketing Corp., 5/F RBC Corporate Ctr, Don Jesus Blvd, Alabang Hills, Muntinlupa City, Philippines.
Primera, Philipp. Primera Pharmo Corp., 3/F JGS Bldg, 30 Scout Tuason St, Diliman, Quezon City, Philippines.
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Primex, Fin. Primex Pharmaceuticals Oy, Hernesaarenranta 3, 00150 Helsinki, Finland.
Primex, Irl. See *Primex, Fin.*
Primex, Neth. See *Primex, Fin.*
Primex, Singapore. See *MBD, Singapore.*
Primex, Spain. See *Primex, Fin.*
Primus, USA. PrimusPharmaceuticals, 4725 N Scottsdale Rd, Suite 200, Scottsdale, AZ 85251, USA.
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Princeps, Ital. Princeps S.r.l., Via Donatori di Sangue snc, 12026 Piasco (CN), Italy.
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Princeton, USA. See *BMS, USA.*

Principle Healthcare, UK. Principle Healthare Ltd., Airedale Business Centre, Millennium Road, Skipton, North Yorkshire, BD23 2TZ, UK.
url: www.principleonline.co.uk

Prisfar, Port. Prisfar, SA, Rua Antero de Quentel 629, 4200-068 Porto, Portugal.
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Prism, USA. Prism Pharmaceuticals Inc., 1016 West Ninth Ave, Suite 130, King of Prussia, PA 19406, USA.
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Pro Bio, UK. Pro Bio Healthcare Ltd, Daresbury Innovation Cebtre, Keswick Lane, Daresbury, WA4 4FS, UK.
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Pro Concepta, Switz. Pro Concepta Zug AG, Lindenstrasse 12, 6341 Baar/Zug, Switzerland.
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Pro Doc, Canad. Pro Doc limitée, 2925 Industrial Blvd, Laval, Quebec, H7L 3W9, Canada.

Pro Farma, Switz. Pro Farma AG, Lindenstrasse 12, 6341 Baar, Switzerland.
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Pro Medica, Swed. See *Schering-Plough, Swed.*

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Pro Vaccine, Switz. Pro Vaccine AG, Lindenstrasse 12, Linden-Park, 41 Baar/Zug, Switzerland.
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Pro Vita, Hung. Pro Vita Pharma KBt, Szabadsag ter 23, 4761 Porcsalma, Hungary.

Probiomed, Mex. Probiomed, S.A. de C.V., San Esteban 88, Azcapotzalco Santo Tomas, 2020 Mexico D.F., Mexico.
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Probiomics, Austral. Probiomics Ltd, Suite 1A, Level 2, 802 Pacific Highway, Gordon, NSW 2072, Australia.
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Probios, Port. Probios, Ldo, Rua João Chagas 53-A, Escritório 201, 1495-072 Algés, Portugal.
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Probiotics, Hong Kong. See *Treasure Mountain, Hong Kong.*

Probiotics, Singapore. See *Goldplus, Singapore.*

Probiotics International, Hong Kong. See *Primal, Hong Kong* and *Treasure Mountain, Hong Kong.*

Pro-Biotiks, USA. Pro Biotiks Inc., 2331 Rulon White Blvd, Suite C, Ogden, UT 92251, USA.

Probus, Indon. See *Mediframa, Indon.*

Procare, Austral. See *Biovital, Austral.*

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Procter & Gamble, Austria. Procter & Gamble Austria GmbH, Guglgasse 7-9, A-1030 Vienna, Austria.
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Procter & Gamble, Belg. Procter & Gamble Pharmaceuticals SA, Temselaan 100, 1853 Strombeek-Bever, Belgium.
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Procter & Gamble, Braz. Procter & Gamble do Brasil S.A., Av. Maria Coelho Aguiar 251, Bloco E- Andares 4./5, Jd São Luiz, 05805-000 Paulo, SP, Brazil.
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Procter & Gamble, Canad. Procter & Gamble Inc., P.O. Box 355, Station A, Toronto, Ontario, M5W 1C5, Canada.
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Procter & Gamble, China. Procter & Gamble China Co. Ltd, Lin He Xi Tai International Plaza 161, Tianhe, Guangzhou, 510620, China.
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Procter & Gamble, Cz. See *Procter & Gamble, Ger.*

Procter & Gamble, Denm. See *Procter & Gamble, UK.*

Procter & Gamble, Fin. See *Oriola, Fin.*

Procter & Gamble, Fr. Procter & Gamble Pharmaceuticals France, 96 av Charles-de-Gaulle, 92201 Neuilly-sur-Seine cdx, France.
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Procter & Gamble, Ger. Procter & Gamble Pharmaceuticals Germany GmbH, Dr-Otto-Rohm Str 2-4, 64331 Weiterstadt, Germany.
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Procter & Gamble, Gr. Procter & Gamble Hellas Ltd, Kronos Business Centre, 49 Agiou Konstantinou St, 15124 Maroussi, Greece.
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Procter & Gamble, Hong Kong. See *Keller, Hong Kong.*

Procter & Gamble, Irl. See *Procter & Gamble (H&B Care), UK.*

Procter & Gamble, Israel. See *Neopharm, Israel.*

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Procter & Gamble, Mex. Procter & Gamble de Mexico S.A. de C.V., Loma Florida 32, Lomas de Vistahermosa, Del. Cuajimalpa, 05100 Mexico D.F., Mexico.
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Procter & Gamble, Neth. Procter & Gamble Pharmaceuticals, Watermanweg 100, 3067 GG Rotterdam, Netherlands.
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Procter & Gamble, Norw. See *Roche, Norw.*

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Procter & Gamble, Swed. Procter & Gamble Nordic Inc., filial Sverige, Box 273 03, 102 54 Stockholm, Sweden.
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Procter & Gamble, UK. Procter & Gamble Pharmaceuticals UK Ltd, Rusham Park Technical Centre, Whitehall Lane, Egham, Surrey, TW20 9NW, UK.
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Procter & Gamble, USA. Procter & Gamble, 1 or 2, Procter & Gamble Plaza, Cincinnati, OH 45201, USA.
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Procter & Gamble (H&B Care), UK. Procter & Gamble (Health & Beauty Care) Ltd, The Heights, Brooklands, Weybridge, Surrey, KT13 0XP, UK.
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Prodeal, Canad. Le Groupe Prodeal Ltee, 3560 rue Isabelle, Brossard, Quebec, J4Y2R3, Canada.

Prodemdis, Canad. Prodemdis Enr., 4355 Sir Wilfrid Laurier Blvd, St-Hubert, Quebec, J3Y 3X3, Canada.
url: www.confab.ca

Pro-Derma, Canad. Pro-Derma Inc., 104 de la Couronne, Le Gardeur, Quebec, J5Z 5E9, Canada.

Prodes, Hung. See *PDP, Hung.*

Prodes, Spain. See *Almirall, Spain.*

Prodesfarma, Austria. See *Almirall, Spain.*

Prodesfarma, Chile. See *Grunenthal, Chile.*

Prodotti, Braz. Prodotti Laboratório Farmacêutico Ltda, Avenida João Dias 1084, Santo Amaro, 04724-001 São Paulo, SP, Brazil.

Prodotti, Hung. See *CSC, Hung.*

Product Excellence, Canad. Product Excellence Inc., 156 Romina Drive, Concord, Ontario, L4K 4Z7, Canada.

Products & Technology, Spain. Products & Technology SL, Industria 29, Pol. Industrial Conde de Sert, 08755 Castellbisbal, Barcelona, Spain.

Produits Dentaires, Switz. Produits Dentaires SA, 18 rue des Bosquets, 1800 Vevey, Switzerland.
url: www.pdsa.ch

Proel, Gr. Proel S.A., Dilou 9, 121 34 Peristeri, Greece.
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Proethic, USA. ProEthic Pharmaceuticals Inc., 5331 Perimeter Parkway Court, Montgomery, AL 36116, USA.
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Prof. Pharm. Corp., Canad. Professional Pharmaceutical Corporation, 9200 Cote-de-Liesse Blvd, Lachine, Quebec, H8T 1A1, Canada.

Profarm, Pol. Przedsiębiorstwo Produkcji Farmaceutyczno-Kosmetyczne Profarm, ul. Słupska 18, 84-300 Lębork, Poland.

Profarma, Cz. Profarma sro, Liberecká 20, 466 01 Jablonec nad Nisou, Czech Republic.
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Profarma, Ital. Profarma srl, Via Androne 60, 95124 Catania, Italy.

Profarma, Thai. See *International Pharmaceuticals, Thai.*

Professional Dietetics, Ital. Professional Dietetics Srl, Via Ciro Menotti 1/A, 20129 Milan (MI), Italy.
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Professional Disposables, Canad. See *Professional Disposables, USA.*

Professional Disposables, USA. Professional Disposables International Inc., Two Nice-Pak Park, Orangeburg, NY 10962-1376, USA.

Professional Health, Canad. Professional Health Products, 4307-49 St, Innisfail, AB, T4G 1P3, Canada.

Professional Supplies, USA. See *SoftRinse, USA.*

Profic Organic, India. Profic Organic Ltd, B-222 Layak Ram Complex, Badarpur, New Delhi 110 044, India.
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Profile, Denm. See *Swedish Orphan, Denm.*

Profile, Irl. See *Profile, UK.*

Profile, Narw. See *Nigaard, Norw.*

Profile, Spain. See *Profile, UK.*

Profile, UK. Profile Therapeutics plc, Heath Place, Bognor Regis, West Sussex, PO22 9SL, UK.
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Profoot, Canad. See *Profoot, USA.*

Profoot, USA. Profoot Inc., 74 20th Street, Brooklyn, NY 11232, USA.

Proge, Ital. Proge Farm S.r.l., Largo Donegani 4/A, 28100 Novara (NO), Italy.
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Progen, Ital. Progen S.r.l., Via Farfisa 18, 60021 Camerano (AN), Italy.
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Progress, Thai. See *Medicine Supply, Thai.*

Prohealth, India. Prohealth Vitamins Pvt Ltd, S.C.O. 162-164, India Airlines Building, Sec-34 A, Chandigarh, India.

Pro-Health, NZ. Pro-Health Products Ltd, P.O. Box 28-545, Remuera, Auckland, New Zealand.
url: www.nicobrevin.com

Prohealth, Philipp. Prohealth Pharma Phils Inc., Suite 2603C, 26/F East Wing Tektite Tower, Exchange Rd, Ortigas Ctr, Posig City, Philippines.

Prolab, Pol. Farmaceutyczne Przeds. Produkcyjno-Analityczno-Handlowe Prolab Halkiewicz i Ratajczyk Sp.J, ul. Przemysłowa 3, Proterek, 89-100 Nakło n/Noteciq, Poland.
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Pro-LDK, Fr. See *Montebello, Fr.*

Prolisok, Ukr. Prolisok OD, sV Vilshanka, Vasilkovsky, 08671 Kiev, Ukraine.
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Promeco, Mex. See *Boehringer Ingelheim, Mex.*

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Promed, Ger. See *AstraZeneca, Ger.*

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ProMed, Turk. ProMed İlaç Kozmetik San. ve Tic Ltd Sti, Turkey.

ProMed, Ukr. ProMed CS Praga AS, Heroes of Stalingrad 4, Building 8, Suite 22, Kiev 04210, Ukraine.
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Promedica, Fr. See *Chiesi, Fr.*

Promedica, Hong Kong. See *William, Hong Kong.*

Promedica, Ital. See *Chiesi, Ital.*

Promedica, Malaysia. See *Antah, Malaysia.*

Promedica, Neth. See *Multipharma, Neth.*

Promedica, Port. See *Chiesi, Ital.*

Promedica, Rus. See *Prespharm, Rus.*

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Promedica, Thai. See *Pacific, Thai.*

Promedico, Israel. ProMedico Ltd, 4 Baltimor St, Petach Tikva 49510, Israel.
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Promefarm, Ital. Promefarm S.r.l., Corso Indipendenza 6, 20129 Milan, Italy.

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Prometic, USA. ProMetic BioSciences Inc., 155 Willowbrooke Blvd, Suite 460, Wayne, NJ 07470, USA.
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Promius, USA. Promius Pharma LLC, Bridgewater, NJ 08807, USA.
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Promonta, Ger. See *Lundbeck, Ger.*

Promonta, Hung. See *Lundbeck, Ger.*

Prompt Cure, India. Prompt Cure Pharm Pvt Ltd, 21-25 G. T. Karnal Road, Libaspur, New Delhi 110 042, India.

Pronova, Austria. See *Pronova, Norw.*

Pronova, Cz. See *Pronova, Norw.*

Pronova, Fin. See *Pronova, Norw.*

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Pronova, Irl. See *Pronova, Norw.*

Pronova, Neth. See *Pronova, Norw.*

Pronova, Norw. Pronova Biocare AS, Lysaker Torg 8, N-1324 Lysaker, Norway.

Pronova, Philipp. See *Patriot, Philipp.*

Pronova, Port. See *Pronova, Norw.*

Pronova, Spain. See *Pronova, Norw.*

Pronova, USA. Pronova Corp., P.O. Box 144281, Coral Gables, FL 33114, USA.
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Pronova Biocare, Pol. See *Solvay, Pol.*

Pronovo, Turk. Pronovo, Turkey.

Pronutri, Fr. Laboratoires Pronutri, 5ème ave, 17ème rue, B.P. 556, 06516 Carros cdx, France.
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Propan, S.Afr. See *Adcock Ingram, S.Afr.*

Propan-Vernleigh, S.Afr. See *Adcock Ingram, S.Afr.*

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Propharm, Malaysia. Propharm (M) Sdn Bhd, 640-A, 4th Mile, Ipoh Rd, 51200 Kuala Lumpur, Wilayah Persekutuan, Malaysia.

Propharma, Denm. See *Persano, Denm.*

Pro-Pharma, Hung. Pro-Pharma, Berlini út 47-49, 1045 Budapest, Hungary.

Pro-Pharma, Ukr. Pro-Pharma, Mikhail Kotelnikov St 1, Office 95-97, Kiev, Ukraine.

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Pro-Pharma, USA. Pro-Pharma, USA.

Prorea, Switz. Prorea Pharma AG, Rebgasse 2, 4410 Liestal, Switzerland.
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Prosam, USA. Prosam Labs LLC, 1209 Orange St, Wilmington, New Castle, DE 19801, USA.

Prosan, Hong Kong. See *CNW, Hong Kong.*

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Pro-Shop, Canad. Pro-Shop Inc., Unit 7, 401 45th St West Pakwa Park, Saskatoon, Saskatchewan, S7L 5Z9

Prospa, Belg. See *Grunenthal, Belg.*

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ProStrakan, Cz. See *ProStrakan, UK.*

ProStrakan, Denm. See *ProStrakan, UK.*

ProStrakan, Fin. See *ProStrakan, UK.*

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ProStrakan, Ger. Prostrakan Pharma GmbH, Monschauer Str. 1, 40549 Düsseldorf, Germany.
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ProStrakan, Gr. ProStrakan, Th. Kiteas, 50 Panagouli Str., Athens 14231, Greece.
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ProStrakan, Hong Kong. See *Orient, Hong Kong.*

ProStrakan, Hung. See *ProStrakan, UK.*

ProStrakan, Irl. See *ProStrakan, UK.*

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ProStrakan, Neth. ProStrakan BV, P/a Burgemeester van Hasselstraat 50 b, 4611 BH Bergen Op Zoom, Netherlands.
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ProStrakan, Norw. See *ProStrakan, UK.*

ProStrakan, Philipp. See *Zuellig, Philipp.*

ProStrakan, Port. See *ProStrakan, UK.*

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ProStrakan, Swed. ProStrakan AB, Gaijersgatan 2, 216 18 Malmö, Sweden.
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ProStrakan, UK. ProStrakan Group Ltd, Buckholm Mill, Buckholm Mill Brae, Galashiels, Scotland, TD1 2HB, UK.
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ProStrakan, USA. ProStrakan, 1430 US State Highway 206, Bedminster, NJ 07921-2652, USA.
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Protalix, Israel. Protalix Biotherapeutics, P.O. Box 455, Karmiel, Israel.

Protan, Arg. Protan SRL, Av. Roca 546 (Sur), Santiago del Estero, Argentina.

Protasis, Gr. Protasis Pharmaceuticals Ltd, Greece.

Protea, S.Afr. Protea Pharm (Pty) Ltd, P.O. Box 553, Isando 1600, South Africa.

Protech, India. Protech Biosystems Pvt Ltd, 145-146 Pace City-I, Sector 37, Gurgaon, Haryana 122001, India.
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Protech, Rus. See *Protech, India.*

Protector, Canad. Protector Canada Inc., Unit 23, 1111 Flint Rd, Downsview, Ontario, M3J 3C7, Canada.

Proteika, Fr. Proteika SA, Lab de Dietetique Medicale, 2 av des Noelles, B.P. 216, 44505 La Baule cdx, France.
url: www.proteika.com

Protein, Mex. Protein S.A. de C.V., Damas 120, Benito Juarez San Jose Insurgente, 3900 Mexico DF, Mexico.

Protein Sciences, USA. Protein Sciences Corp., 1000 Research Parkway, Meriden, CT 06450, USA.
url: www.proteinsciences.com

Protek-Pharma, Ukr. OOO Protek-Pharma, Vulitsya Semena Sklyarenka, Kiev, Ukraine.
url: www.protek-pharma.kiev.ua

Protherapix, Malaysia. Protherapix Sdn Bhd, 9-2-3 Jln 3/109F, Danau Business Center, Tmn Danau Desa, 58100 Kuala Lumpur, Malaysia.

Protherics, UK. Protherics UK Ltd, Blaenwaun, Ffostrasol, Llandysul, Ceredigion, SA44 5JT, UK.
url: www.btgplc.com

Protherics, USA. Protherics Inc., 5214 Maryland Way, Suite 405, Brentwood, TN 37027, USA.
url: www.protherics.com

Protifast, Fr. Protifast SAS, ZA les Pins Verts, 33650 Saucats, France.

Protina, Austria. See *Protina, Ger.*

Protina, Cz. See *Protina, Ger.*

Protina, Ger. Protina Pharmazeutische Gesellschaft mbH, Adalperostr. 37, 85737 Ismaning, Germany.
url: www.protina.de

Protina, Hung. See *Beaco, Hung.*

Protina, Switz. See *Doetsch, Grether, Switz.*

Proton, Gr. Proton Pharma SA, Achaia 4 & Trizinia, 145 64 N Kifissia, Greece.

Proton, Venez. See *Rowe-Fleming, Venez.*

Proula, Venez. Proula Medicamentos, Av. 3 No. 29 Edif. Eva, 2do. Piso, Merida, Venezuela.
url: www.proulamed.com

Provalis, Irl. See *Provalis, UK.*

Provalis, UK. Provalis Healthcare, Newtech Square, Deeside Industrial Park, Deeside, Flintshire, CH5 2NT, UK.
url: www.provalis.co.uk

Provefarma, Arg. Laboratorio Provefarma SA, Calle 4 e/5 y 7, 3017 Sauce Viejo, Santa Fe, Argentina.

Provit, Mex. Provit S.A. de C.V., Nino Artillero No. 500, C.U. Independencia, 50070 Toluca, Mexico.

Provita, Ital. Provita Industria Farmaceutica S.r.l., Via Dora 7, 00198 Rome, Italy.

PruGen, USA. PruGen Inc. Pharmaceuticals, 8711 East Pinnacle Peak Rd, Suite C-201, PMB 225, Scottsdale, AZ 85255, USA.
url: www.prugen.com

PRX, USA. See *Par, USA.*

PS, Ital. P.S. Pharma S.r.l., Via Tenuta di Terranova 142, 00133 Rome (RM), Italy.

PSA, Philipp. See *Ambica, Philipp* and *Suhitas, Philipp.*

Psalmstre, Philipp. Psalmstre Enterprises, 5/F JMJ Bldg, P Sanchez, cor P Antonio Sts, Sta Mesa, Manila, Philippines.

PSI, Belg. PSI supply nv, Axxes Business Pork, Guldensporenpark 22 Block C, 9820 Merelbeke, Belgium.

PSI, Ital. Programmi Sanitari Integrati S.r.l., Via G Lanza 3, 20121 Milan (MI), Italy.
url: www.programmisanitariintegrati.it

PSI, Neth. See *PSI, Belg.*

Psicofarm, Arg. Psicofarm SA, Cóndor 1851, 1437 Buenas Aires, Argentina.

Psicofarma, Mex. Laboratorio Psicofarma S.A. de C.V., Calz. de Tlalpan No. 4369, Col. Toriello Guerra, 14050 Mexico D.F., Mexico.
url: www.psicofarma.com.mx

PSK, Ger. See *ProStrakan, Ger.*

Pskovskaya, Rus. Pskovskaya Pharmaceutical Factory, Pskovskaya, Russia.

PSM, Malaysia. See *Zuellig, Malaysia.*

PSM, NZ. PSM Healthcare Ltd, P.O. Box 76-401, Manukau City, Auckland, New Zealand.
url: www.psm.co.n

Psychatropics, India. Psychotropics India Ltd, A-32, Sector 11, Faridabad, Haryana 121 007, India.
url: www.psychoindia.com

Psyco Remedies, India. Psyco Remedies, 227 Civil St, Ludhiana 141 001, India.

PT Triyasa Nagamas, China. See *PT Triyasa Nagamas, Indonesia.*

PT Triyasa Nagamas, Indonesia. PT Triyaso Nagomas Farma, No. 75 Jl.Rawa Udang, Pulogadung Industrial Estate, Jakarta, 13920, Indonesia.
url: www.triyasa.com

Pu Kang, China. Pu Kang Pharm, 200 Queensland Rd, Minhang District, Shanghai 201111, China.
url: www.shpukang.com

Pu Luo Kang Yu, China. Pu Luo Kang Yu Pharmaceutical Co. Ltd, Zhejiang, China.

Pu Sheng, China. Pu Sheng Pharmaceutical Co. Ltd, Wuhan, China.

Pude, China. Pude Pharmaceutical Co Ltd, Economic & Development Zone, Datong 037300, China.

Pudu, China. Pudu Pharmaceutical Co. Ltd, Sichuan, China.

Puebla, Arg. Lab. Puebla S.R.L., Andres Lamas 2427, 5009 Barrio Escobar, Cordoba, Argentina.

Puerto Galiano, Spain. Puerto Galiano, Calle 'S', 4, Parque Europolis, Las Rozas, 28230 Madrid, Spain.
url: www.puertogaliano.com

Puhua, China. Puhua Pharmaceutical Co. Ltd, 1105 Huoju Road, Changchun High-Tech Development Zone, Changchun, Jilin, 130012, China.
url: www.pan-chinopharm.com

Pulitzer, Ital. Pulitzer Italiana S.r.l., Via Tiburtina 1004, 00100 Rome (RM), Italy.

Pulmomed, Rus. Pulmomed ZAO, Leninskii prospekt 33, korp. 3, et 3, 117071 Moscow, Russia.
url: www.pulmomed.ru

Pulmopharm, Ger. See *Novartis Behring, Ger.*

Pulse, India. Pulse Pharma, 4F10 Bollard Estate, Tarnaka, Secundarabad 500 017, India.

Pulse, Rus. FC Pulse Ltd, Leningradskaya ul 29, Khimki, 141400 Moscow, Russia.

Pulsion, Ger. Pulsion Medical Systems AG, Joseph-Wild-Str. 20, 81829 Munich, Germany.
url: www.pulsion.com

Pulsion, Intl. See *Pulsion, UK.*

Pulsion, Israel. See *Concept, Israel.*

Pulsion, Neth. See *Pulsion, Ger.*

Pulsion, Singapore. See *Unimed, Singapore.*

Pulsion, UK. Pulsion Medical UK Ltd, Unit C4, Heathrow Corporate Park, Green Lane, Hounslow, TW4 6JG, UK.
url: www.pulsion.com

PuraCap, USA. PuraCap Pharmaceutical LLC, 1001 Durham Ave, South Plainfield, NJ 07080, USA.
url: www.puracap.com

Purdue, Canad. Purdue Pharma, 575 Granite Court, Pickering, Ontario, L1W 3W8, Canada.

Purdue, USA. See *Purdue Frederick, USA.*

Purdue Frederick, Canad. See *Purdue, Canad.*

Purdue Frederick, USA. The Purdue Frederick Co., One Stamford Forum, 201 Tresser Blvd, Stamford, CT 06901-3431, USA.
url: www.pharma.com

Pure Health, India. Pure Health Pvt Ltd, 128/2 Swarup Nagari, Karve Rd, Kothrud, Pune 411 029, India.

Pure-Li, Canad. Pure-Li Natural Products Ltd, 545 Welham Rd, Barrie, Ontario, L4N 8Z6, Canada.

PureTek, USA. PureTek Corp., 1245 Aviation Place, San Fernando, CA 91340, USA.
url: www.puretekcorp.com

Purewin, India. Purewin Labs Pvt Ltd, KH No 21-25, GT Karnal Rd, Libaspur, Delhi 110 042, India.

Purissimus, Arg. Purissimus S.A., Juan F.Segum 4635, 1425 Buenos Aires, Argentina.
url: www.purissimus.com

Purity Health, Canad. Purity Health Products, a division of Sunopta Inc., 6 Commerce Crescent, Acton, Ontario, L7J 2X3, Canada.

Purity Life, Canad. Purity Life Health Products, 6 Commerce Cres., Acton, Ontario, L7J 2X3, Canada.
url: www.puritylife.com

Purna, Belg. Purna Pharmaceuticals NV, Rijksweg 17, 2870 Puurs, Belgium.
url: www.purna.be

Purzer, China. Purzer Pharmaceutical Co. Ltd, 105 Guangfu South Road, Songshan, Taipei, Taiwan, China.
url: www.purzer.com.tw

Puspa, Indon. Puspa Pharma, Jl Kemandoran VIII No 1, Kebayoran Lama, Jakarta Selatan 12210, DKI Jaya, Indonesia.
url: www.puspapharma.com

Putaowang, China. Putaowang BioTech Co. Ltd, 60 Sec. 3 Longgang Rd, Zhongli City, TaoYuan 320, Taiwan, China.
url: www.grapeking.com.tw

Putchubun, Thai. Putchubun Dispensary Co Ltd, 413/1 Soi Issaparp, 25 Issaparp Rd, Wat Arun, Bangkok 10600, Thailand.

Puzhang, China. Puzhong Pharmaceutical Co. Ltd, Jiangsu, China.

Pynogin, UK. Pynogin GmbH, Gee Lawsan Distribution Centre, Unit 15 South Nottingham & Wilford Industrial Estate, Wilford, Nottingham, Nottinghamshire, NG11 7EP, UK.

Pyridam, Indon. Pyridam Farma Tbk. PT, Jl Kemandoran 8 No 16, Jakarta 12210, DKI Jaya, Indonesia.
url: www.pyridam.com

Q Check, India. Q Check Speciality Care, 81/1 Old Mambalam Road, Saidapet, Chennai 600 015, India.

Q Pharma, Spain. Laboratorios Q Pharma S.L., Portugal 23, 03003 Alicante, Spain.
url: www.q-pharma.net

QB, Philipp. QB International Trade, Unit 17-A Belvedere Tower, San Miguel Ave, Ortigas Complex, Pasig City, Philippines.

Qdem, UK. Qdem Pharmaceuticals Ltd, Unit 198, Cambridge Science Park, Milton Rd, Cambridge, CB4 0AB, UK.
url: www.qdem.co.uk

Qestmed, S.Afr. Qestmed Ltd, Unit 2, Gazelle Place, Corporate Park, Old Pretoria Main Rd, Midrand 1685, South Africa.

QHP, USA. Quality Health Products Inc., P.O. Box 433, Indiana, PA 15701, USA.
url: www.qhpinc.com

Qi Du, China. Qi Du Pharmaceutical Co. Ltd, Shandong, China.

Qi Li, China. Qi Li Pharmaceutical Co. Ltd, Haikou, China.

Qian Jin Xiang Jiang, China. Qian Jin Xiang Jiang Medicine Co. Ltd, Hunan, China.

Qian Long, China. Qianlong Pharmaceutical Co. Ltd, 51 Qianyang East Rd, Qianjiang, Hubei, 433100, China.

Qiangji, China. Qiangji Pharmaceutical, Xinshi, Longhu, Chaoan, Chaozhou, Guangdong, 515636, China.

Qianhong, China. Qianhong Biopharmaceutical Co. Ltd, Changzhou, China.

Qianjiang, China. Qianjiang Pharmaceutical Co. Ltd, Zhang Hua Nan Lute 1, Qianjiang 433133, China.
url: www.qjzy.com

Qiaoguang, China. Qiaoguang Pharmaceutical Co. Ltd, Guangzhou, China.

QIF, Braz. See *Hexal, Braz.*

Qilu, China. Qilu Pharmaceutical Co Ltd, Industrial Rd 243, Jinan City, Shandong Province, China.

Qinba, China. Qinba Pharmaceutical Co. Ltd, 24 Fl Building A, Zengxin Mansion, 5 1st Gaoxin Rd, Xi'an, Shaanxi, 710075, China.
url: www.qbcp.com.cn

Qing Hua Zi Guang, China. Qing Hua Zi Guang Pharmaceutical Co. Ltd, Beijing, China.

Qing Hua Zi Guang Gu Han, China. Qing Hua Zi Guang Gu Han Bio-Pharmaceutical Co. Ltd, China.

Qing Yu Tang, China. Qing Yu Tang Pharmaceutical Co. Ltd, Chongqing, China.

Qingan, China. Qingan Pharmaceutical Co. Ltd, Shanghai, China.

Qingfeng, China. Qingfeng Pharmaceutical Co. Ltd, Jiangxi, China.

Qinghai, China. Qinghai Pharmaceutical Co. Ltd, China.

Qingjiang, China. Qingjiang Pharmaceutical Co. Ltd, Jiangsu, China.

Qinwutian, China. Qinwutian Pharmaceutical Co. Ltd, Beijing, China.

Qixing, Ukr. Qixing, Ukraine.

Qiyun, China. Qiyun Pharmaceutical Co. Ltd, Sichuan, China.

Qiyunsheng, China. Qiyunsheng Pharmaceutical Co. Ltd, Dalian, China.

Q-Med, Ital. Q-Med ICT S.r.l., Via Mario Borsa 11-13, 26845 Codogno (LO), Italy.

Q-Med, S.Afr. See *Galderma, S.Afr.*

Q-Med, UK. Q-Med (UK) Ltd, Castle Court, 41 London Rd, Reigate, Surrey, RH2 9RJ, UK.

Q-Med, USA. Q-Med Scandinavia Inc., 103 Carnegie Center, Suite 301, Princeton, NJ 08540, USA.
url: www.deflux.com

Q-Pharm, Ger. Q-Pharm AG, Bahnhofstr. 1-3, 23795 Bad Segeberg, Germany.
url: www.qpharm.de

Q-Pharma, Arg. Laboratorios Q-Pharma Argentina SA, Av. Chorroarin 710, Buenos Aires, Argentina.

QR, China. Qi Rui (QR) Pharmaceutical Co. Ltd, 12/F Block A New Yangtze River Plaza, 2 Youyi Road, Wuchang, Wuhan, 430061, China.
url: www.qrpharma.net

QSA, Cz. See *QSA, Ger.*

QSA, Ger. QSA Global GmbH, Gieselweg 1, 38110 Braunschweig, Germany.

QSA, Port. See *QSA, Ger.*

Qualicare, Switz. Qualicare AG, Florenz-Strasse 7, 4142 Münchenstein, Switzerland.
url: www.qualicare.ch

Qualifarma, Ital. Qualifarma S.r.l., Via Roma 22, 29010 Vernasca (PC), Italy.
url: www.qualifarma.it

Qualigen, Spain. Qualigen SL, Av Barcelona 69, 08970 Sant Joan Despi, Barcelona, Spain.
url: www.qualigen.es

Qualimed, Austral. See *Sanofi-Aventis, Austral.*

Qualimed, Philipp. Qualimed Pharma Inc., 801 One Corporate Ctr, Julia Vargas cor Meralco Ave, Ortigas Ctr, Pasig City, Philippines.

Qualiphar, Belg. Qualiphar SA, Rijksweg 9, 2880 Bornem, Belgium.
url: www.qualiphar.be

Qualiphar, Neth. See *Qualiphar, Belg.*

Qualitest, USA. Qualitest Products Inc., 130 Vintage Drive, Huntsville, AL 35811, USA.

Quality, Hong Kong. Quality Pharmaceutical Laboratory Ltd, 21/F, 23/F Mai On Industrial Bldg, 19-21 Kung Yip St, Kwai Chung NT, Hong Kong.

Quality Formulations, USA. Quality Formulations Laboratories Inc., 110 Pennsylvania Ave., Paterson, NJ 07503, USA.
url: www.qualityformulations.com

Qualix, Spain. See *Lacer, Spain.*

Quamed, Indon. Quamed PT, Jl Johar No 5, Jakarta 10350, DKI Jaya, Indonesia.

Quangang, China. Quangang Pharmaceutical Co. Ltd, Shandong, China.

Quantum, Canad. See *Quantum, USA.*

Quantum, USA. Quantum Inc., 754 Washington St, Eugene, Oregon, 97401, USA.

Quanxin, China. Quanxin Biopharmaceutical Co. Ltd, Kunming, China.

Quatromed, S.Afr. Quatromed, 10 Lindley St., Bethlehem 9700, South Africa.

Queisser, Austria. See *Queisser, Ger.*

Queisser, Cz. See *Queisser, Ger.*

Queisser, Ger. Queisser Pharma GmbH & Co., Schleswiger Str. 74, 24941 Flensburg, Germany.
url: www.queisser.de

Queisser, Pol. Queisser Pharma Polconsult, Przedstawicielstwo w Polsce, ul. Kubickiego 17 m 9, 02-954 Warsaw, Poland.
url: www.queisser.pl

Queisser, Rus. Queisser Pharma GmbH.& Co., Lyusinovskaya ul. 36, Of. 73, 113093 Moscow, Russia.
url: www.queisser.ru

Queisser, Ukr. Queisser, Office 117 Bozhan 16, Kiev, Ukraine.
url: www.queisser.com

Quemifarm, Venez. See *Sankyo, Venez.*

Quesada, Arg. Quesada Farmaceutica SA, Jose Ingenieros 3080, 1643 Beccar, Buenos Aires, Argentina.

Quest, Canad. See *Boehringer Ingelheim, Canad.*

Quest, India. Quest Pharmaceuticals, SCF-14, A Block Market, Ranjit Ave, Amritsar 143 001, India.

Quest, Malaysia. See *JDH, Malaysia.*

Quest, UK. Quest Vitamins Ltd, 8 Venture Way, Aston Science Park, Birmingham, B7 4AP, UK.
url: www.questvitamins.co.uk

Questcor, USA. Questcor Pharmaceuticals Inc., 3260 Whipple Rd, Union City, CA 94578, USA.
url: www.questcor.com

Quidel, USA. Quidel Corp., 10165 McKellar Court, San Diego, CA 92121, USA.
url: www.quidel.com

Quidnovi, Ital. Quidnovi Pharma S.p.A., Via Muzio Attendolo 13, 20141 Milan (MI), Italy.
url: www.quidnovi.it

Quies, Fr. Laboratoires Quies, 4 rue Ambroise-Croizat, 91120 Palaiseau, France.

Quifoven, Venez. Quifoven C.A., Calle La Guarita, Edif. Los Frailes, Piso 4 Of. 404 Chuao, Caracas, Venezuela.

Quilaban, Port. Quilaban Química Laboratorial Analítica Lda, Beloura Office Park, Rua do Centro Empresarial, Ed. 11, 2710-693 Sintra, Portugal.

Quim-Far, Venez. Laboratorios Quim-Far C.A., Chacaito-Quinta Nueva Segovia, Urb. Bello Monte Caracas, Caracas, Venezuela.

Química y Farmacia, Mex. Química y Farmacia, S.A. de C.V., Av. Insurgentes sur 619 Desp 602, Benito Juarez Napoles, 3810 Mexico D.F., Mexico.

Quimifar, Spain. Quimifar, Comadran 37, Pol Ind Can Salvatella, Barbera del Valles, 08210 Barcelona, Spain.
url: www.quimifar.es

Quimpe, Spain. Quimpe, Cruz 47-49, Alhaurin el Grande, 29120 Malaga, Spain.

Quimpharma, Mex. Laboratorios Quimpharma SA de CV, Calle de Pino 343 Int. 46, 6400 Sta. Ma. la Ribera, Mexico.

Quinnova, USA. Quinnova Pharmaceuticals, 301 S State St, Suite N001, Newton, PA 18940, USA.
url: www.quinnova.com

Quinoderm, Hong Kong. See *Mekim, Hong Kong.*

Quinoderm, Irl. See *Allphar, Irl.*

Quinoderm, Switz. See *Golaz, Switz.*

Quinoderm, UK. See *Adams, UK.*

Quintesence, Cz. Quintesence sro, Tenisová 845/6, 102 00 Praha 10, Czech Republic.

Quintiles, Port. Quintiles SL, Lagoas Park, Edificio 7 Piso 0, 2740-299 Porto Salvo, Portugal.

Quiris, Ger. Quiris Healthcare GmbH & Co KG, Am Kreuzkamp 5-7, 33334 Gütersloh, Germany.
url: www.quiris.de

Qwatro, Canad. Qwatro Corp., Unit 6, 110 Claireport Crescent, Toronto, Ontario, M9W 6P3, Canada.

QX, Philipp. QX Pharmaceuticals Inc., Tao Corporate Ctr, 2291 Don Chino Roces Ave Ext, 1226 Makati City, Philippines.
url: www.qxpharmaceuticals.com

R&D, Canad. See *Watson, USA.*

R&D, USA. See *Watson, USA.*

R+N, Gr. R+N FARMAKEVTIKA AEVE, Katechaki 58, 115 25 N. Psychiko, Greece.

R & D, Mon. R & D Pharma, 7 bd des Moulins, 98000 Monaco, Monaco.

Ra, Turk. Ro Tibbi Cihazlar San. ve Tic. A.Ş., Nenehatun Cad., No. 103/7-8, Gaziosmanpaşa, Ankara, 06700, Turkey.

Raam, Mex. Laboratorio Raam de Sahuayo SA de CV, Blvd Lázoro Cardenas 794 Sur, 59000 Noria de Montes, Michoacan, Mexico.

RAAS, China. RAAS Blod Products Co. Ltd, Beidou Rd 55, Minhang District, Shanghai 200245, China.
url: www.raas-corp.com

Rabi & Solabo, Fr. Laboratoires Rabi & Solabo, 67 rue Voltaire, 92150 Suresnes, France.

Rada, Pol. Rada Sp.J., ul. Starościńska 1, 02-516 Warsaw, Poland.
url: www.elmex.pl

Rada, Rus. Rada Pharma, P.O. Box 90, 111024 Moscow, Russia.
url: www.radapharma.ru

Radelkis, Hung. Radelkis Kft, Hungary.

Radiance, Singapore. Radiance Healthcare Pte Ltd, 50 Kallang Pudding Rd, 05-08 Golden Wheel, S 349326, Singapore.
url: www.matxin.co.in

Radicura, India. Radicura Pharmaceuticals Pvt Ltd, B-117 Okhla Industrial Area, Phase 1, New Delhi 110 020, India.

Radiol, Israel. See *Devries, Israel.*

Radyum, Turk. Radyum Laboratuvarı İlaç San. ve Tic. A.Ş., Fevzipaşa Bulvarı, Yeni Han No: 49/ K: 3, Çankaya, İzmir, Turkey.

Rafa, Israel. Rafa Laboratories Ltd, Hamarpeh St 5, P.O. Box 405, Jerusalem 91003, Israel.
url: www.rafa.co.il

Rafarm, Gr. Rafarm A.E., 12 Korinthou Str., 154 51 N. Psichiko, Greece.
url: www.rafarm.gr

Rafarm, Hong Kong. See *Sino-Asia, Hong Kong.*

Raffles, Singapore. See *Sanofi-Aventis, Singapore.*

Raffo, Arg. Lab. Raffo S.A., Av. Cabildo 86, 1426 Buenos Aires, Argentina.

Raffo, Chile. Laboratorios Raffo SA, Simon Bolivar2183, Nunoa, Santiago, Chile.

Raga, Spain. Raga, C./Paseo de la Castellana 153, 28046 Madrid, Spain.
url: www.laboratoriosraga.com

Rainbow, Ukr. Rainbow Ltd, 49 Shcherbakov St, Kiev, 04111, Ukraine.

Rak, Turk. See *Ra, Turk.*

Raldex, Gr. Raldex, Greece.

Rallis, India. Rallis India Ltd, Rallis House, 21 D Sukhadvala Marg, Fort, Mumbai 400 001, India.

Ram, USA. See *Bradley, USA.*

Ramini, Ital. Ramini S.p.A., Via di Vallerano 96, 00128 Rome (RM), Italy.
url: www.raminispa.it

Ramon Sala, Spain. See *Reig Jofre, Spain.*

RAN, Ger. R.AN. Novesia AG Arzneimittel, Hürtgener Str. 6, 41464 Neuss/Rhein, Germany.
url: www.ran-novesia-arznei.de

Rana, Rus. Rana Clinic llc, Zoologicheskaya ul 22, 123242 Moscow, Russia.

Ranbaxy, Austral. Ranbaxy Australia Pty Ltd, Suite 4.02, Building D, Level 4, 12-24 Talavera Rd, North Ryde, 2113 NSW, Australia.
url: www.ranbaxy.com

Ranbaxy, Austria. See *Ranbaxy, UK.*

Ranbaxy, Belg. See *Ethimed, Belg.*

Ranbaxy, Braz. Ranbaxy S.P. Medicamentos Ltda, Avenida das Americas 1155, Sala 1201 a 1204, Barra da Tijuca, 22631-000 Rio de Janeiro, RJ, Brazil.
url: www.ranbaxy.com

Ranbaxy, Canad. Ranbaxy Pharmaceuticals Canada Inc., 200 2680 Matheson Blvd E, Mississauga, Ontario, L4W 0A5, Canada.

Ranbaxy, China. Ranbaxy Laboratories Ltd, Beijing Lanmark Tower-1, 8 North Dongsanhuan Road, Chaoyang, Beijing, 100004, China.
url: www.ranbaxy.com

Ranbaxy, Cz. See *Interchemia, Cz.*

Ranbaxy, Denm. See *Ranbaxy, Swed.*

Ranbaxy, Fin. See *Ranbaxy, UK.*

Ranbaxy, Fr. Ranbaxy-Pharmacie Génériques (RAB) (Lab), 4 place Louis-Armand, 75601 Paris, France.

Ranbaxy, Hong Kong. See *Hind Wing, Hong Kong.*

Ranbaxy, Hung. See *Medico Uno, Hung.*

Ranbaxy, India. Ranbaxy Laboratories Ltd, Plot 90, Sector 32, Gurgaon 122001, India.
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Ranbaxy, Irl. See *Ranbaxy, UK.*

Ranbaxy, Ital. Ranbaxy Italia SpA, Piazza Filippo Meda 3, 20121 Milan (MI), Italy.
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Ranbaxy, Malaysia. Ranbaxy (Malaysia) Sdn Bhd, Box #8, Wisma Selangor Dredging, 5th Floor, South Block, 142-A Jalan Ampang, 50450 Kuala Lumpur, Kuala Lumpur, Malaysia.
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Ranbaxy, Mex. Ranbaxy Mexico SA de CV, Av. Gral. Manuel Avila Camacho 767 Piso, 11000 Miguel Hidalgo Lomas de Chapulte, Mexico.

Ranbaxy, Neth. See *Ranbaxy, UK.*

Ranbaxy, Norw. See *Meda, Norw.*

Ranbaxy, Philipp. See *Aldril, Philipp* and *Medhaus, Philipp* and *Randril, Philipp.*

Ranbaxy, Pol. Ranbaxy (Poland) Sp. zo.o., ul. Kubickiego 11, 02-954 Warsaw, Poland.
url: www.ranbaxy.com.pl

Ranbaxy, Port. Ranbaxy Portugal, Rua do Campo Alegre 1306, Sala 301/302, Edificio Botânico, 4150-174 Porto, Portugal.

Ranbaxy, Rus. Ranbaxy Laboratories Ltd, Techno Park, Office Centre, 45-48 Russian Exhibition Centre, Prospekt Mira, 129223 Moscow, Russia.
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Ranbaxy, S.Afr. Ranbaxy (SA) (Pty) Ltd, Third Floor, Outspan House, 1006 Lenchen Avenue North, Centurion, Pretoria, South Africa.
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Ranbaxy, Singapore. See *Zyfas, Singapore.*

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Ranbaxy, UK. Ranbaxy (UK) Ltd, Consolidated Pneumatic House, 6th Floor, 97-107 Uxbridge Rd, Ealing, London, W5 5TL, UK.
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Ranbaxy, Ukr. Ranbaxy Laboratories Limited, Grishko Street, 3A, 4th floor, Kiev, 02140, Ukraine.
url: www.ranbaxy.com.ua

Ranbaxy, USA. Ranbaxy Pharmaceuticals Inc., 600 College Rd E, Suite 2100, Princeton, NJ 08540, USA.
url: www.ranbaxy.com

Randall, Mex. Randall Laboratories, S.A de C.V., Lago Rodolfo No. 58, M Hidalgo Granada, 11520 Mexico D.F., Mexico.

Randi, Israel. Randi, 5 Plotiski St, Rishon Lezion, Israel.

Randob, USA. Randob Laboratories Ltd, 6 Walnut St., P.O. Box 440, Cornwall, NY 12518, USA.

Randril, Philipp. Randril Internationol Co. Inc., Unit 2205-A, 22/F West Tower, PSEC Exchange Rd, Ortigas Ctr, Pasig City, Philippines.

Ransom, Irl. See *Ransom, UK.*

Ransom, UK. William Ransom & Sons plc, Alexander House, 40A Wilbury Way, Hitchin, Hertfordshire, SG4 0AP, UK.
url: www.williamransom.com

Rapide, Spain. See *Baxter, Spain* and *Bieffe, Spain.*

Rapidscan, Denm. See *Dupharma, Denm.*

Rapidscan, Irl. See *Rapidscan, UK.*

Rapidscan, Neth. See *Rapidscan, UK.*

Rapidscan, UK. Rapidscan Pharma Solutions EU Ltd, Regents Place, 338 Euston Rd, London, NW1 3BT, UK.
url: www.rapiscan-mpi.com

Rapimed, S.Afr. See *Sekunjalo, S.Afr.*

Rappai, Switz. Dr F. Rappai Pharmazeutika, Postfach, 8952 Schlieren-Zürich, Switzerland.
url: www.rappai.ch

Rapross, India. Rapross Pharmaceuticals, 2nd Floor Garg Plaza, 5 Community Centre, Sector-8, Rohini, New Delhi 110 085, India.
url: www.rapross.com

Raptakos, India. Raptakos Brett & Co. Ltd, 253 Dr Annie Besant Rd, Worli, Mumbai 400 030, India.
url: www.raptakos.com

Raptakos, Malaysia. See *Zyfas, Malaysia.*

Raptakos, Singapore. See *Zyfas, Singapore.*

Raptakos, Thai. See *Union Medicol, Thai.*

Raptor, USA. Raptor Pharmaceutical Corp., 9 Commercial Blvd, Suite 200, Novato, CA 94949, USA.
url: www.raptorpharma.com

Rare Disease Therapeutics, Canad. Rare Disease Therapeutics Inc., Scarborough, Ontario, M1H 2W4, Canada.

Rare Disease Therapeutics, USA. Rare Disease Therapeutics, 1101 Kermit Drive, Suite 608, Nashville, TN 37217, USA.
url: www.raretx.com

Rass, India. Rass Health Care, Plot 195, 2nd Floor, Road No 6, 3rd Cross Rd, Vayupuri, Secunderabad 94, India.
url: www.madhavbiotech.com

Ratio, Spain. See *Ratiopharm, Spain.*

Ratiopharm, Austria. Ratiopharm Arzneimittel Vertriebs-GmbH, Albert-Schweitzer-Gasse 3, A-1140 Vienna, Austria.
url: www.ratiopharm.at

Ratiopharm, Belg. ratiopharm Belgium nv, Sint Lambertusstraat 141, B-1200 Brussels, Belgium.
url: www.ratiopharm.be

Ratiopharm, Braz. See *Mepha, Braz.*

Ratiopharm, Canad. Ratiopharm, 6975 Creditview Rd, Unit 5, Mississauga, Ontario, L5N 8E9, Canada.
url: www.ratiopharm.ca

Ratiopharm, China. ratiopharm International, Room 2508 Ocean Terminal, Yan'an East Rd 550, Shonghai 200 001, China.

Ratiopharm, Cz. Ratiopharm CZ sro, Bělehradská 54, 120 00 Prague 2, Czech Republic.

Ratiopharm, Denm. Ratiopharm A/S, Slotsmarken 12, st.tv, 2970 Hørsholm, Denmark.
url: www.ratiopharm.dk

Ratiopharm, Fin. ratiopharm Oy, PL 67, 02631 Espoo, Finland.
url: www.ratiopharm.fi

Ratiopharm, Fr. Laboratoire ratiopharm, 19 bd Paul Vaillant-Couturier, BP 250, 94203 Ivry-sur-seine cdx, France.
url: www.ratiopharm.com

Ratiopharm, Ger. ratiopharm GmbH, Graf-Arco-Str. 3, 89079 Ulm/Donautal, Germany.
url: www.ratiopharm.de

Ratiopharm, Hong Kong. See *CNW, Hong Kong* and *Hong Tai Hong, Hong Kong.*

Ratiopharm, Hung. ratiopharm Hungária Kft, Uzsoki u 36/a, 1145 Budapest, Hungary.
url: www.ratiopharm.hu

Ratiopharm, Irl. See *Ratiopharm, UK.*

Ratiopharm, Ital. Ratiopharm Italia S.r.l., Strada 1, Palazzo F10, 20090 Milan (MI), Italy.
url: www.ratiopharm.it

Ratiopharm, Neth. See *Ratiopharm, Ger.*

Ratiopharm, Norw. ratiopharm AS, Billingstadsletta 19 A, Postboks 12, 1375 Billingstad, Norway.
url: www.ratiopharm.no

Ratiopharm, Pol. ratiopharm Polska Sp. zo.o., ul. Powisińska 4, 02-920 Warsaw, Poland.
url: www.ratiopharm.pl

Ratiopharm, Port. Ratiopharm, Lda, Edifício Tejo, 6 piso, Rua Quinta do Pinheiro, 2790-143 Carnaxide, Portugal.
url: www.ratiopharm.pt

Ratiopharm, Rus. Ratiopharm Group, Vspolny per. 19/20, str. 2, 123001 Moscow, Russia.
url: www.ranbaxy.com

Ratiopharm, Spain. Ratiopharm, Avenida de Burgos 16, 28036 Madrid, Spain.
url: www.ratiopharm.es

Ratiopharm, Swed. Ratiopharm AB, Box 1265, 25221 Helsingborg, Sweden.
url: www.ratiopharm.se

Ratiopharm, Thai. See *Berli Jucker, Thai.*

Ratiopharm, UK. Ratiopharm UK Ltd, 5 Jackson Close, Grove Rd, Cosham, Portsmouth, Hampshire, PO6 1UP, UK.
url: www.ratiopharm.co.uk

Ratiopharm, Ukr. ratiopharm, Shelkovichnaya Street, 42-44, 11th floor, Kiev, 01601, Ukraine.
url: www.ratiopharm.ua

Ravensberg, Ger. Ravensberg GmbH, Schneckenburgstr. 46, 78467 Constance, Germany.

Ravizza, Ital. See *Abbott, Ital.*

Ravizza, Neth. See *Will-Pharma, Neth.*

Rawleigh, Canad. Rawleigh, 60 Colonnade Rd, Nepean, ON, K2E 7J6, Canada.

Rayere, Mex. Farmaceuticos Rayere S.A., Alambra 621, Benito Juarez Portales, 03300 Mexico D.F., Mexico.

Raymos, Arg. Lab. Raymos S.A.I.C., Vuelta de Obligado 2775, 1428 Buenos Aires, Argentina.
url: www.raymos.com

Raza, Hong Kong. See *Ebewe, Hong Kong.*

Razak, Rus. See *Pfizer, Rus.*

RB, Irl. See *RB, UK.*

RB, UK. RB-Medical Engineer Ltd, Unit 2, Alton Road Industrial Estate, Ross-on-Wye, UK.

RBC-MDC, Philipp. RBC-MDC Corp., 2nd Floor RBC Corporate Center, Don Jesus Boulevard, Alabang Hills, Cupang, Muntinlupa City, Philippines.
url: rbc-mdc.com

RCA, Ital. Ricerca Cosmetica Avanzata S.r.l., Via Consortile, Zona Industriale Loc. Penitro, 04023 Formia (LT), Italy.
url: www.rcacosmesi.it

RDC, Ital. See *Euroderm-RDC, Ital.*

React, Arg. React SRL, Av. Alvarez Jonte 5526, (1407) Buenos Aires, Argentina.

Realdyme, Fr. Sté Réaldyme, 28700 Garancières-en-Beauce, France.

Reall, Switz. Medical Concepts Reall-YS S.à.r.l, Ave Villardin 22, 1009 Pully, Switzerland.

Reanal, Hung. Reanal Finomvegyszergyar Rt, Telepes u 53, 1147 Budapest, Hungary.
url: www.reanal.com

Reanal, Rus. See *Reanal, Hung.*

Reasearch Foundation, Philipp. See *Zuellig, Philipp.*

Recalcine, Chile. Corporacion Farmaceutica Recalcine, Pedro de Valdivia 295, Providencia, Santiogo, Chile.
url: www.recalcine.cl

Recalcine, Thai. See *DKSH, Thai.*

Reccius, Chile. Laboratrios Reccius Ltda, Pucara 5326, Nunoa, Santiago, Chile.

Recetario, Chile. See *Recalcine, Chile.*

Recip, China. See *Recip, Swed.*

Recip, Denm. See *Meda, Denm.*

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Recip, Gr. See *Recip, Swed.*

Recip, Neth. See *Recip, Swed.*

Recip, Norw. See *Nycomed, Norw.*

Recip, Port. See *Recip, Swed.*

Recip, Swed. Recip AB, Bränningevägen 12, 120 54 Årsta, Sweden.
url: www.recip.se

Recip, USA. See *Meda, USA.*

Recipharm, Denm. See *Vitaflo, Denm.*

Reckeweg, Cz. See *Reckeweg, Ger.*

Reckeweg, Ger. Pharmazeutische Fabrik Dr. Reckeweg & Co. GmbH, Berliner Ring 32, 64625 Bensheim, Germany.
url: www.reckeweg.de

Reckeweg, Neth. See *Reckeweg, Ger.*

Reckitt & Colman, Austral. See *Reckitt Benckiser, Austral.*

Reckitt & Colman, Belg. See *Reckitt Benckiser, Belg.*

Reckitt & Colman, Cz. See *Reckitt Benckiser, UK.*

Reckitt & Colman, Hong Kong. See *Reckitt Benckiser, Hong Kong.*

Reckitt & Colman, Irl. See *Reckitt Benckiser, Spain.*

Reckitt & Colman, Israel. See *Meditrend, Israel.*

Reckitt & Colman, Ital. See *Reckitt Benckiser, Ital.*

Reckitt & Colman, Norw. See *Nycomed, Norw.*

Reckitt & Colman, S.Afr. See *Reckitt Benckiser, S.Afr.*

Reckitt & Colman, Singapore. See *Zuellig, Singapore.*

Reckitt & Colman, Thai. See *Reckitt Benckiser, Thai.*

Reckitt & Colman, UK. See *Reckitt Benckiser, UK.*

Reckitt & Colman, USA. See *Reckitt Benckiser, USA.*

Reckitt Benckiser, Arg. Reckitt Benckiser Argentina SA, Ruta Provincial No 36 y Diag. Pto. Moreno, (1890) Florencio Varela Ingeniero Allan, Buenos Aires, Argentina.

Reckitt Benckiser, Austral. Reckitt Benckiser Pharmaceuticals, P.O. Box 138, West Ryde, NSW 2114, Australia.
url: www.reckittbenckiser.com

Reckitt Benckiser, Austria. See *Reckitt Benckiser, Ger.*

Reckitt Benckiser, Belg. Reckitt Benckiser SA/NV, Allée de la Recherche 20, 1070 Brussels, Belgium.
url: www.reckittbenckiser.com

Reckitt Benckiser, Braz. Reckitt Benckiser (Brasil) Ltda, Rodovia Raposo Tavares 8015 Km 18, 5577900 Sao Paulo, Brazil.

Reckitt Benckiser, Canad. Reckitt Benckiser (Canada) Inc., unit 2, 1680 Tech Ave, Mississauga, Ontario, L4W 5S9, Canada.

Reckitt Benckiser, Chile. Reckitt Benckiser Chile SA, Av. Kennedy 5454, Of. 1101, Vitacura Santiago, Chile.

Reckitt Benckiser, Cz. See *Reckitt Benckiser, UK.*

Reckitt Benckiser, Denm. Reckitt Benckiser Healthcare (Scandinavia A/S), Vandtarnsvej 83 A, 2860 Söborg, Denmark.
url: www.rb.com

Reckitt Benckiser, Fin. See *Novartis, Fin.*

Reckitt Benckiser, Fr. Laboratoires Reckitt Benckiser Healthcare France, 15 rue Ampère, 91748 Massy cdx, France.

Reckitt Benckiser, Ger. Reckitt Benckiser Deutschland GmbH, Theodor-Heuss-Anlage 12, 68165 Mannheim, Germany.
url: www.reckittbenckiser.de

Reckitt Benckiser, Gr. Reckitt Benckiser (Hellas) SA, 59-61 Agiou Konstantinou Str. & Kifissias Ave, Building B 4th Floor, 151 24 Maroussi, Greece.
url: www.rb.com

Reckitt Benckiser, Hong Kong. Reckitt Benckiser Hong Kong Ltd, 1203-5 Allied Kajima Bldg, 138 Gloucester Rd, Hong Kong.
url: www.reckitt.com

Reckitt Benckiser, Hung. Reckitt Benckiser, Lajos utca 48-66 B, 1036 Budapest, Hungary.
url: www.reckittbenckiser.com

Reckitt Benckiser, India. Reckitt Benckiser (India) Ltd, Enkay Centre 2nd Floor, Vanijya Nikunj Udyog Vihar, Phase V, Gurgaon 122 016, India.
url: www.reckittbenckiser.com

Reckitt Benckiser, Irl. Reckitt Benckiser, Pharmapark, Chapelizod, Dublin 20, Ireland.
url: www.reckittbenckiser.com

Reckitt Benckiser, Israel. Reckitt Benckiser, 10 Hasadnaot St, P.O.B. 12367, Herzliya IZ 46733, Israel.
url: www.reckittbenckiser.com

Reckitt Benckiser, Ital. Reckitt Benckiser Healthcare Italia, Via Lampedusa 11/A, 20141 Milan (MI), Italy.

Reckitt Benckiser, Malaysia. Reckitt Benckiser (Overseas) Ltd, Unit No 1101, Level 11, Uptown 2, 2 Jln SS 21-37, Damansara Uptown, 47400 Petaling Jaya, Selangor, Malaysia.
url: www.reckittbenckiser.com

Reckitt Benckiser, Neth. Reckitt Benckiser Healthcare BV, Gebouw Aquarius, 2132 WY Hoofddorp, Netherlands.

Reckitt Benckiser, Norw. See *Nycomed, Norw.*

Reckitt Benckiser, NZ. Reckitt Benckiser Pharmaceuticals, Private Bag 93121, Henderson, Auckland, New Zealand.
url: www.reckittbenckiser.com

Reckitt Benckiser, Philipp. Reckitt Benckiser, 22/F Equitabel Bank Twr, 8751 Paseo de Roxas, Makati City, Philippines.

Reckitt Benckiser, Pol. See *Boots, Pol.*

Reckitt Benckiser, Port. Reckitt Benckiser Healthcare Lda, Rua D Cristovão da Gama No 1 - 1 C/D, 1400-113 Lisbon, Portugal.

Reckitt Benckiser, Rus. Reckitt Benckiser Ltd, Kozhevincheskaya ul 14, 115114 Moscow, Russia.

Reckitt Benckiser, S.Afr. Reckitt Benckiser Pharmaceuticals (Pty) Ltd, P.O. Box 164, Isando 1600, South Africa.
url: www.reckittbenckiser.com

Reckitt Benckiser, Singapore. See *Zuellig, Singapore.*

Reckitt Benckiser, Spain. Reckitt Benckiser Espana, Paseo de Gracia 9, 08007 Barcelona, Spain.
url: www.reckittbenckiser.com

Reckitt Benckiser, Swed. Reckitt Benckiser Sweden, Waterfront Building, Klarabergsviadukten 63, 111 64 Stockholm, Sweden.
url: www.rb.com

Reckitt Benckiser, Switz. Reckitt Benckiser Healthcare (Switzerland) AG, Untermüli 11, 6300 Zug, Switzerland.

Reckitt Benckiser, Thai. Reckitt Benckiser (Thailand) Ltd, 9 Fl, Vanissa Building, 29 Soi Chidlom, Ploenchit Rd, Patumwan, Bangkok 10330, Thailand.
url: www.reckittbenckiser.com

Reckitt Benckiser, Turk. Reckitt Benckiser (Turkey) AS, Hakki Yeten Caddesi, Suleyman Seba Kompleksi, Selenium Plaza 10C, Istanbul, Turkey.
url: www.rb.com

Reckitt Benckiser, UK. Reckitt Benckiser plc, Dansom House, Hull, Humberside, HU8 7DS, UK.
url: www.reckittbenckiser.com

Reckitt Benckiser, Ukr. Reckitt Benckiser Household & Healthcare, Moscow Prospect, 9, Block 4, office 4-201, Kiev, 04073, Ukraine.
url: www.reckittbenckiser.com

Reckitt Benckiser, USA. Reckitt Benckiser, Morris Corporate Center IV, 399 Interpace Parkway, P.O. Box 225, Parsippany, NJ 07054-0225, USA.
url: www.reckittbenckiser.com

Reckitt Piramal, India. See *Piramal, India.*

Reckitts, Irl. See *Sanofi-Aventis, Irl.*

Recofarma, Ital. See *Recordati, Ital.*

Recoly, Belg. Recoly NV, 63 Ave Blücher, 1180 Brussels, Belgium.
url: www.recoly.com

Recoly, Rus. See *Recoly, Belg.*

Recon, Singapore. See *Zyfos, Singapore.*

Recordati, Austria. See *Recordati, Irl.*

Recordati, China. See *Abbott, China* and *Unico, China.*

Recordati, Cz. See *Recordati, Ital.*

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Recordati, Fin. See *Recordati, Irl.*

Recordati, Ger. See *Recordati, Ital.*

Recordati, Gr. Recordati Hellas Pharmaceuticals SA, Zoodochou Pigis 7, 152 31 K. Chalandri, Athens, Greece.
url: www.recordati.com

Recordati, Hong Kong. See *Unico, Hong Kong.*

Recordati, Hung. See *Recordati, Ital.*

Recordati, Irl. Recordati Ireland Ltd, Raheens East, Ringaskiddy, County Cork, Ireland.
url: www.recordati.com

Recordati, Ital. Recordati Industria Chimica e Farmaceutica S.p.A., Via M. Civitali 1, 20148 Milan (MI), Italy.

Recordati, Malaysia. See *Summit, Malaysia.*

Recordati, Neth. See *Recordati, Ital.*

Recordati, Pol. See *Fournier, Pol.*

Recordati, Port. Recordati Portuguesa, Lda, Rua Domingos Sequeira 27-B, Loja A, 1350-119 Lisbon, Portugal.
url: www.recordati.it

Recordati, Singapore. See *MD, Singapore* and *Orient, Singapore.*

Recordati, Spain. Recordati España SL, Isla de la Palma 37, San Sebastian de las Reyes, 30588 Madrid, Spain.
url: www.recardati.it

Recordati, Thai. See *DKSH, Thai.*

Recordati, UK. Recordati Pharmaceuticals Ltd, Isis House, 43 Station Rd, Henley-on-Thames, Oxfordshire, RG9 1AT, UK.
url: www.recordati.com

Recordati, Ukr. Recordati Ukraine Ltd, Glubochickaya 40, Kiev, 04050, Ukraine.

Recordati, USA. Recordati Rare Diseases Inc., Lebanon, NJ 08833, USA.
url: www.recordatiraretdiseases.com

Recsei, USA. Recsei Laboratories, 330 S Kellogg, Building M, Goleta, CA 93117-3875, USA.

Red Leaf, Canad. Red Leaf Medical Inc., Suite 504, 703 Evans Ave, Toronto, Ontario, M9C 5E9, Canada.

Reddy, Braz. Dr Reddy's Farmaceutica do Brasil Ltda, Av. Guido Caloi 1985 Cj 11, 5802140 Sao Paulo, Brazil.

Reddy, Hung. Reddy, Hungary.

Reddy, India. Dr. Reddy's Laboratories Ltd, Greenlands, Ameerpet, Hyderabad 500 016, India.
url: www.drreddys.com

Reddy, Ital. Dr Reddy's Srl a socio unico, Via Fermanda Wittgens 3, 20123 Milan (MI), Italy.

Reddy, Malaysia. See *Pahang, Malaysia* and *Zyfas, Malaysia.*

Reddy, Philipp. See *Britton, Philipp.*

Reddy, Rus. Dr Reddy's Laboratories Ltd, 18 Dolgorukovskaya, Str. 3, 127006 Moscow, Russia.
url: www.drreddys.com

Reddy, S.Afr. Dr Reddy's Laboratories (Pty) Ltd, 3rd Floor, TA Bank Building, 160 Jan Smuts Ave, Rosebank, 2196, South Africa.

Reddy, Singapore. See *Zyfas, Singapore.*

Reddy, Spain. Reddy Pharma Iberica SA, 10 Las Matas, 28290 Madrid, Spain.
url: www.drreddys.com

Reddy, Thai. See *Neopharm, Thai.*

Reddy, Ukr. Dr. Reddy's, Patrisa Lumumby Street, 7, Kiev, 01042, Ukraine.
url: www.drreddys.com

Reddy, USA. Dr Reddy's Laboratories Inc., 200 Somerset Corporate Bvld, Building II, Bridgewater, NJ 08807, USA.
url: www.drreddys.com

Redel, Ger. See *Cesra, Ger.*

Reder, Mex. Comercializadora Reder D de RL de CV, Arequipa 693, 7300 Gustavo A Madero Lindavista, Mexico DF, Mexico.

Redex, USA. Redex Industries, 1176 Salem Parkway, Salem, OH 44460, USA.
url: www.uddercream.com

Redino, Ger. See *Stada, Ger.*

Redi-Products, USA. See *Aplicare, USA.*

Redken, Canad. See *L'Oreal, Canad.*

Reed & Carnrick, Canad. See *GSK Consumer, Canad.*

Reed & Carnrick, Neth. See *Byk, Neth.*

Reed & Carnrick, USA. See *Schwarz, USA.*

Reedco, USA. See *GSK Consumer, USA.*

Reese, USA. Reese Pharmaceutical Co. Inc., 10617 Frank Ave, Cleveland, OH 44106, USA.
url: www.reesechemical.com

Reevax, India. Reevax Pharma Pvt Ltd, 502 Rohni Apartments, Srinagar Colony Road, Hyderabad 500 073, India.
url: www.reevax.com

Refnot, Rus. See *Pharmaclon, Rus.*

Reg, Cz. Reg-Pharm sro, Fialková 45, 106 00 Prague 10, Czech Republic.

Rega, Port. Rega Farmo Promoção de Produtos Farmacêuticos SA, Rua João Chagas 53, Piso 3, 1495-764 Cruz Quebrada, Portugal.

Regen, Switz. Regen Lab SA, en Budron B 2, 1052 Le Mont sur Lausanne, Switzerland.

Regena, Switz. Regena AG, Riedholzstrasse 1, 6030 Ebikon, Switzerland.

Regenaplex, Ger. Regenaplex Homöopathische Komplexmittel, Robert-Basch-Str. 3, 78467 Constance, Germany.
url: www.regenaplex.de

Regeneron, Fr. See *Regeneron, UK.*

Regeneron, Neth. See *Regeneron, UK.*

Regeneron, UK. Regeneron UK Ltd, 40 Bank St, London, E14 5DS, UK.
url: www.regeneron.com

Regeneron, USA. Regeneron Pharmaceuticals, 777 Old Saw Mill River Rd, Tarrytown, NY 10591, USA.
url: www.regeneron.com

Regent, Canad. See *Regent, USA.*

Regent, Ital. See *Molnlycke, Ital.*

Regent, Switz. See *Globopharm, Switz.*

Regent, USA. Regent Medical Americsa LLC, 250 3585 Engineering Drive, Norcross, Georgia, 30092, USA.

Regent Medical, Irl. See *Molnlycke, UK.*

Regent Medical, Neth. See *Molnlycke, UK.*

Regent Medical, Norw. See *Molnlycke, UK.*
Regent Medical, Swed. See *Molnlycke, UK.*
Regent Medical, UK. See *Molnlycke, UK.*
Regent-GM, Hong Kong. See *Universal, Hong Kong.*
Regime, Canad. Regime Industries Ltd, 205 20050 Stewart Crescent, Maple Ridge, British Colombia, V2X 0T4, Canada.
Regina, UK. Regina Health Ltd, NLA Tower, 12-16 Addiscombe Rd, Croydon, Surrey, CR0 0XT, UK.
url: www.reginahealthcare.com
Regiomedica, Cz. See *Regiomedica, Ger.*
Regiomedica, Denm. See *Regiomedica, Ger.*
Regiomedica, Ger. Regiomedica GmbH, Teichstrasse 66, D-79539 Lorrach, Germany.
Regiomedica, Neth. See *Regiomedica, Ger.*
Regional Health, Austral. Regional Health Care Products Group, Medi-Consumables P/L, 3-11 Primrose Ave, Rosebery, NSW 2018, Australia.
url: www.rhcg.com.au
Regional Health, NZ. Regional Health Ltd, 23a William Pickering Drive, Albany, Auckland 1330, New Zealand.
url: www.rhcg.com.au
Reig Jofre, Israel. See *Reig Jofre, Spain.*
Reig Jofre, Spain. Reig Jofre, Gran Capitan 10, Sant Joan Despi, 08970 Barcelona, Spain.
url: www.reigjofre.com
Rekah, Israel. Rekah Ltd, P.O. Bos 25, Azor 58190, Israel.
url: www.rekah.co.il
Rekawan, Ger. See *Riemser, Ger.*
Relax, UK. Relax UK Ltd, Temple House, 2 Barbour Gardens, Colchester, Essex, CO2 9SA, UK.
url: www.dontbugmepatch.co.uk
Reliable, Canad. Reliable Maintenance Products Ltd, 345 Regent St South, Sudbury, Ontario, P3C 4E1, Canada.
Reliance, India. Reliance Life Sciences Pvt Ltd, B-1 Navratna Ave, Nr Sola Rly Crossings, Ghatlodia, Ahmedabad 380 061, India.
Reliance, Philipp. See *Ambica, Philipp.*
Reliant, USA. Reliant, 110 Allen Rd, Liberty Corner, NJ 07938, USA.
url: www.reliantrx.com
Relonchem, Irl. See *Relonchem, UK.*
Relonchem, UK. Relonchem Ltd, 27 Old Gloucester St, London, WC1 3XX, UK.
url: www.relonchem.com
Relyo, Gr. Relyo Hellas A.E., Faviorou 48, 104 38 Athens, Greece.
Remark, Neth. Remark BV, Industrieweg 24, 7949 AK Meppel, Netherlands.
Remed, Philipp. Remed Pharmaceuticals Inc., Unit 1113 11/F A/C Burgundy Empire Twr, ADB Ave cor Sapphire & Garnet St, Ortigas Center, Pasig City, Philippines.
Remedi, Malaysia. See *Pharmaniaga, Malaysia.*
Remedia, Austria. Remedia Homöopathie, Mag.pharm. Robert Muntz GmbH, Hauptstrasse 4, 7000 Eisenstadt, Austria.
Remedica, Cyprus. Remedica Ltd, Limassol Industrial Estate, P.O. Box 51706, 3508 Limassol, Cyprus.
url: www.remedica.eu
Remedica, Hong Kong. See *Ebewe, Hong Kong* and *Primal, Hong Kong.*
Remedica, Hung. See *Remedica, Cyprus.*
Remedica, Malaysia. See *JDH, Malaysia.*
Remedica, Philipp. See *Corbridge, Philipp.*
Remedica, Port. See *Remedica, Cyprus.*
Remedica, Singapore. See *JDH, Singapore.*
Remedica, Thai. See *Pharmadica, Thai.*
Remedina, Gr. Remedina, Gounari 23 and Areos, 134 51 Kamatero Attiki, Greece.
Remek, Gr. Remek S.A., 3 Koleti Str., 144 52 Metamorfosi, Greece.
Remexa, Mex. Representaciones Mex-America S.A. de C.V.,, Diagonal 20 de Noviembre No. 264, Col. Obrera, Deleg. Cuauhtemoc, 06800 Mexico D.F., Mexico.
url: www.remexa.com
Remington, Canad. Remington Medical Equipment Ltd, 9 401 Bentley St, Markham, Ontario, L3R 9T2, Canada.
Renapharm, Switz. Renapharm S.A., Rue du Château 3, 1636 Broc, Switzerland.
Renapharma, Denm. See *Renapharma, Swed.*
Renapharma, Fin. See *Renapharma, Swed.*
Renapharma, Norw. Renapharma, Postboks 8664, 7452 Trondheim, Norway.
url: www.renapharma.no
Renapharma, Swed. Renapharma AB, Box 938, 751 09 Uppsala, Sweden.
url: www.renapharma.se
Renata, Philipp. See *Interlink, Philipp.*
Renata, Thai. See *GIS, Thai.*
Renaud, Canad. Laboratoire Dr Renaud Inc., 2805 Place Louis R Renaud, Laval, Quebec, H7V 0A3, Canada.
Renaudin, Fr. Laboratoires Renaudin, ZA Errobi, 64250 Itxassou, France.
Rendell, China. See *Rendell, UK.*
Rendell, NZ. See *NZ Medical & Scientific, NZ.*
Rendell, UK. W.J. Rendell Ltd, Ickleford Manor, Hitchin, Hertfordshire, SG5 3XE, UK.
Renfeng, China. Renfeng Pharmaceutical Co. Ltd., 5 Yuming Avenue, Industrial Park, Fuzhou, Jiangxi, 344000, China.
url: www.jxrf.cn
RenFu, China. RenFu Pharmaceutical Co. Ltd, Wuhan, China.
Renhe, China. Renhe Pharmaceutical Co. Ltd, Jiangxi, China.
Renhetang, China. Renhetang Pharmaceutical Co. Ltd, Shandong, China.
Renhu, China. Renhu Pharmaceutical Co. Ltd, Shanghai, China.
Renovati, Philipp. Renovati Pharma Inc., 3270 Gasanco Bldg, Merville Annex Rd, Pasay City, Philippines.
Renrenkang, China. Renrenkang Pharmaceutical Co. Ltd, Guangdong, China.
Rentschler, Austria. See *Medice, Ger.*
Rentschler, Cz. See *Medice, Ger.*
Rentschler, Ger. See *Medice, Ger.*
Rentschler, Israel. See *Medice, Ger.*
Rentschler, Singapore. See *PMR, Singapore.*
Repha, Ger. Repha GmbH Biologische Arzneimittel, Alt-Godshorn 87, 30855 Langenhagen, Germany.
url: www.repha.de
Rephachem, Cz. Rephachem as, Pod Brentovou 6/555, 150 05 Prague 5, Czech Republic.
url: www.rephachem.cz
Repharma, Hung. Repharma Kft, Victor Hugo u 35 V/36, 1132 Budapest, Hungary.
Replekpharm, Rus. See *Sotex, Rus.*
Reprefar, Port. See *Pierre Fabre, Port.*
Requa, USA. Requa Inc., 540 Barnum Ave., P.O. Box 2348, Bridgeport, CT 06608, USA.
url: www.requa.com
Resdevco, Israel. Resdevco Ltd, P.O. Box 3338, Jerusalem, Israel.
Research Foundation, Philipp. See *Zuellig, Philipp.*
Research Industries Corp., USA. See *Edwards Lifesciences, USA.*
Resfar, Ital. See *Calao Resfar, Ital.*
Resinag, Israel. See *Promedico, Israel.*
Resinag, Switz. Resinag AG, Grienbachstrasse 17, 6300 Zug, Switzerland.
Resinag, Ukr. See *Revmofarm, Ukr.*
Resource Medical, UK. ReSource Medical UK Ltd, 187 Manchester Rd, Thornton Lodge, Huddersfield, HD1 3JG, UK.
url: www.resource-medical.co.uk
Respa, USA. Respa Pharmaceuticals Inc., P.O. Box 88222, Carol Stream, IL 60188, USA.
Restan, S.Afr. See *Novartis, S.Afr.*
Restiva, Ital. See *Pfizer, Ital.*
Retinoids, Rus. Retoinoids, ul Plekhanova D 2/46, Stroenie 5, 111123 Moscow, Russia.
url: www.retinoids.ru
Retrain, Spain. Retrain, Alfonso XII 587, Badalona, 08912 Barcelona, Spain.
Retsyfarm, Ukr. See *Solvay, Ukr.*
Retterspitz, Ger. Retterspitz GmbH, Laufer Str. 17-19, 90571 Schwaig, Germany.
url: www.retterspitz.de
Reuabuen, USA. See *Novartis, USA.*
Reuffer, Mex. Reuffer Laboratorios S.A. de C.V., Juan de Dios Arias 78, Cuauhtemoc Vista Alegre, 06860 Mexico D.F., Mexico.
Revifar, Gr. Revifar AE, Mayer 6, 10438 Athens, Greece.
Revival & Development, Rus. Revival & Development Ltd, K Marx ul. 51A, 394000 G Voronezh, Russia.
Revlon, Canad. Revlon Canada Inc., 2501 Stanfield Rd, Mississauga, Ontario, L4Y 1R9, Canada.
Revmofarm, Ukr. Revmofarm Ltd, ul. Basil Verhovintsa 12, Office 108, 03148 Kiev, Ukraine.
Rex, NZ. Rex Medical, P.O. Box 23-025, Papatoetoe, Auckland, New Zealand.
Rexcel, India. See *Ranbaxy, India.*
Rextar, India. See *Ranbaxy, India.*
Reyon, Philipp. See *Endure, Philipp.*
Rez, Cz. Ústav jaderneho vyzkumu Řež as, Řež u Prahy, Czech Republic.
Rezlov, Rus. Rezlov, Leninskii pr-t 148 of. 223, 119571 Moscow, Russia.
Rezlov, Ukr. Rezlov LLC, ul Trutenko 2, 03022 Kiev, Ukraine.
url: www.plethico.com
RFMDOU, Thai. See *Aventis Pasteur, Thai* and *Wellchem, Thai.*
RGR, Canad. RGR Pharma Ltd, 6220 Westar Drive, La Salle, Ontario, N9J 0B5, Canada.
RH, USA. See *Cangene, Canad.*
Rhein, Mex. Siegfried Rhein S.A. de C.V., Bosque de Alisos 47-B Piso 3, Cuajimalpa Bosques de las Lomas, 5120 Mexico D.F., Mexico.
Rheingold, Ger. See *RAN, Ger.*
Rhein-Pharma, Ger. See *AstraZeneca, Ger.*
Rhema, Singapore. See *Delfi, Singapore.*
Rhine, India. Rhine Biogenics Pvt Ltd, 24/470(6) Nurani Junction, Palakkad 678 004, India.
Rhiza, Philipp. See *InnoGen, Philipp.*
Rhodia, Israel. Rhodia Israel Ltd, P.O. Box 8443, Netanya, Israel.
Rhodia, Norw. See *Organon, Norw.*
Rhodia, Thai. See *Pacific, Thai.*
Rhodiola, China. Rhodiola Pharamceutical Co. Ltd, Jinjiang Industrial Park, Chengdu, 610063, China.
url: www.xzyy.cn
Rhone, Spain. See *Sanofi-Aventis, Spain.*
Rhone-Poulenc, Canad. See *Sanofi, Canad.*
Rhone-Poulenc, Ger. See *Sanofi-Aventis, Ger.*
Rhone-Poulenc, Ital. See *Sanofi-Aventis, Ital.*
Rhone-Poulenc, Neth. See *Sanofi-Aventis, Neth.*
Rhone-Poulenc Aventis, Ital. See *Sanofi-Aventis, Ital.*
Rhone-Poulenc Rorer, Arg. See *Sanofi-Aventis, Arg.*
Rhone-Poulenc Rorer, Austral. See *Sanofi-Aventis, Austral.*
Rhone-Poulenc Rorer, Austria. See *Sanofi-Aventis, Austria.*
Rhone-Poulenc Rorer, Belg. See *Sanofi-Aventis, Belg.*
Rhone-Poulenc Rorer, Canad. See *Sanofi, Canad.*
Rhone-Poulenc Rorer, Denm. See *Sanofi-Aventis, Denm.*
Rhone-Poulenc Rorer, Fin. See *Sanofi-Aventis, Fin.*
Rhone-Poulenc Rorer, Fr. See *Sanofi-Aventis, Fr.*
Rhone-Poulenc Rorer, Ger. See *Sanofi-Aventis, Ger.*
Rhone-Poulenc Rorer, Gr. See *Sanofi-Aventis, Gr.*
Rhone-Poulenc Rorer, Hong Kong. See *Aventis, Hong Kong.*
Rhone-Poulenc Rorer, Irl. See *Sanofi-Aventis, Irl.*
Rhone-Poulenc Rorer, Israel. See *Sanofi-Aventis, Israel.*
Rhone-Poulenc Rorer, Ital. See *Sanofi-Aventis, Ital.*
Rhone-Poulenc Rorer, Jpn. See *Aventis, Jpn.*
Rhone-Poulenc Rorer, Mex. See *Sanofi-Aventis, Mex.*
Rhone-Poulenc Rorer, Neth. See *Sanofi-Aventis, Neth.*
Rhone-Poulenc Rorer, Norw. See *Sanofi-Aventis, Norw.*
Rhone-Poulenc Rorer, Pol. See *Sanofi-Aventis, Pol.*
Rhone-Poulenc Rorer, Port. See *Sanofi-Aventis, Port.*
Rhone-Poulenc Rorer, Rus. See *Sanofi-Aventis, Rus.*
Rhone-Poulenc Rorer, S.Afr. See *Sanofi-Aventis, S.Afr.*
Rhone-Poulenc Rorer, Singapore. See *Sanofi-Aventis, Singapore.*
Rhone-Poulenc Rorer, Spain. See *Sanofi-Aventis, Spain.*
Rhone-Poulenc Rorer, Swed. See *Sanofi-Aventis, Swed.*
Rhone-Poulenc Rorer, Switz. See *Sanofi-Aventis, Switz.*
Rhone-Poulenc Rorer, Thai. See *Sanofi-Aventis, Thai.*
Rhone-Poulenc Rorer, UK. See *Sanofi, UK.*
Rhone-Poulenc Rorer, USA. See *Sanofi-Aventis, USA.*
Rhone-Poulenc Rorer Consumer, Canad. See *Sanofi, Canad.*
Rhone-Poulenc Sante, Thai. See *Sanofi-Aventis, Thai.*
Rho-Pharm, Canad. See *Sanofi, Canad.*
Rhoxalpharma, Canad. Rhoxalpharma Inc., 145 Jules-Leger St, Boucherville, Quebec, J4B 7K8, Canada.
url: www.rhoxalpharma.com
Ri Zhongtian, China. Ri Zhongtian Pharmaceutical Co. Ltd, Hainan, China.
Riace, Rus. Farma Riace, Vysheslavcev 2-jj per., d. 17, 127018 Moscow, Russia.
url: www.pharmariace.ru
Ribex, Ital. See *Pfizer, Ital.*
Ribi, USA. See *Corixa, USA.*
Ribosepharm, Ger. See *Hikma, Ger.*
Ribosepharm, Neth. See *Hikma, Ger.*
RiC, Pol. Przedsiębiorstwo Farmaceutyczne RiC, ul. Cybernetyki 11, 02-677 Warsaw, Poland.
Rica, Hung. Rica Hungaria Zrt, Budafoki ut 187-189, 1117 Budapest, Hungary.
url: www.rica.hu
Rice Steele, Irl. Rice Steele & Co. Ltd, Cookstown Industrial Estate, Tallaght, Dublin 24, Ireland.
Ricerfarma, Malaysia. See *Pharmaniaga, Malaysia.*
Rich Plan, Hong Kong. Rich Plan International Ltd, Flat 9, 16/F, Block C, Wah Lok Industrial Ctr, 31-41 Shan Mei St, Fotan, Shatin, N.T., Hong Kong.
Richard, Fr. Laboratoires Richard, rue du Progrès, Zl des Reys de Saulce, 26270 Saulce-sur-Rhone, France.
Richardson-Vicks, Austral. See *Procter & Gamble, Austral.*
Richardson-Vicks, Israel. See *Neopharm, Israel.*
Richardson-Vicks, USA. See *Procter & Gamble, USA.*
Richardson-Vicks Personal Care, USA. See *Procter & Gamble, USA.*
Richborough, UK. See *Pfizer, UK.*
Richet, Arg. Lab. Richet S.A., Tres Arroyos 1829, 1416 Buenos Aires, Argentina.
Richlife, Hong Kong. See *Jebsen, Hong Kong.*
Richmond, Arg. Lab. Richmond, Av. Elcano 4938, 1427 Buenos Aires, Argentina.
Richmond, Canad. See *Rivex, Canad.*
Richmond Ophthalmics, Canad. See *Rivex, Canad.*
Richter, Austria. Richter Pharma, Feldgasse 19, A-4600 Wels, Austria.
Richter, Pol. Richter Gedeon Ltd SA, Przedstawicielstwo w Polsce, ul. Królowej Marysieńki 70, 02-954 Warsaw, Poland.
url: www.gedeonrichter.pl
Richwood, USA. See *Shire, USA.*
Rickard Lanes, UK. Rickard Lane's & WH Box Ltd, 24 Tennant St, Edinburgh, EH6 5ND, UK.
url: www.rickardlanes.com
Rico, USA. See *Bart, USA.*
Ricola, Canad. Ricola, Canada.
Ricola, USA. Ricola Inc., 6 Campus Drive, 2nd Floor South, Parsippany, NJ 07054, USA.
url: www.ricola.com
RID, USA. R.I.D. Inc., 609 N Mednik Ave, Los Angeles, CA 90022-1320, USA.
Rider, Chile. Laboratorios Rider SA, Placer 1348, Santiago, Chile.
Ridupharm, Switz. Ridupharm, Emil Frey-Strasse 99, 4142 Münchenstein, Switzerland.
Riel, Austria. Riel GmbH & Co. KG, Gasselberg 53-54, A-8564 Krottendorf-Gaisfeld, Austria.
Riemser, Austria. See *Riemser, Ger.*
Riemser, Cz. See *Riemser, Ger.*
Riemser, Denm. See *Riemser, Ger.*
Riemser, Fin. See *Riemser, Ger.*
Riemser, Ger. Riemser Arzneimittel AG, An der Wiek 7, 17493 Greifswald/Insel Riems, Germany.
url: www.riemser.de
Riemser, Gr. See *Riemser, Ger.*
Riemser, Hong Kong. See *Hind Wing, Hong Kong.*
Riemser, Israel. See *Riemser, Ger.*
Riemser, Neth. See *Riemser, Ger.*
Riemser, Norw. See *Riemser, Ger.*
Riemser, Pol. See *Riemser, Ger.*
Riemser, Swed. See *Riemser, Ger.*
Riemser, Thai. See *Diethelm, Thai.*
Riemser, Ukr. See *Artur, Ukr.*
Riker, Austral. See *3M, Austral.*
Riker, Canad. See *3M, Canad.*
Riker, Mex. See *3M, Mex.*
Riker, Neth. See *3M, Neth.*
Riker, S.Afr. See *3M, S.Afr.*
Riker, UK. See *3M, UK.*
Riker, USA. See *3M, USA.*
Rimafar, Spain. See *Belmac, Spain.*
Rimsa, Mex. Rimsa, Representaciones e Investigaciones Medicas S.A. de C.V., Av. Acoxpa No. 464, Prado Coapa, Deleg. Tlapan Fracc., 14350 Mexico D.F., Mexico.
url: www.gruporimsa.com.mx
Rinter Corona, Spain. Laboratorios Rinter Corona SL, Parque Industrial el Bierzo, C/Burdeos parcela 8, 24400 Ponferrada, León, Spain.
Riom, Fr. See *Organon, Fr.*
Rishab, India. Rishab Healthcare Pvt Ltd, 417 Industrial Area Phase I, Panchkula, Haryana, India.
Rising Pharmaceuticals, USA. Rising Pharmaceuticals Inc., 3 Pearl Court, Suite A/B, Allendale, NJ 07401, USA.
url: www.risingpharma.com
Ritsert, Austria. See *Ritsert, Ger.*
Ritsert, Ger. Dr. E. Ritsert GmbH & Co. KG, Klausenweg 12, 69412 Eberbach, Germany.
url: www.ritsert.de
Ritter, Hong Kong. See *IDS, Hong Kong* and *Mekim, Hong Kong* and *Suburfarm, Hong Kong.*
Ritter, Malaysia. See *JDH, Malaysia.*
Ritter, Singapore. See *JDH, Singapore.*
Ritter, Thai. See *Osotspa, Thai.*
Ritz, India. Ritz Pharma, 301 Aditraj Arcade, 100 feet Ring Road, Satellite, Ahmedabad, India.
Rius, Spain. Rius Garriga, Pujadas 95, 08005 Barcelona, Spain.
Riva, Canad. Laboratoire Riva Inc., 660 Industrial Blvd, Blainville, Quebec, J7C 3V4, Canada.
Rivadis, Fr. Laboratoires Rivadis, B.P. 111, Zl de Louzy, 79103 Thouars cdx, France.
url: www.labo-rivadis.fr
Rivan, Hung. Rivan Kft, Törökbálinti ut 3/B, 1121 Budapest, Hungary.
River, Ital. River Pharma Srl, Via Roma 32, 20077 Melegnano (MI), Italy.
River, Singapore. See *MBD, Singapore.*
River Foods, Austral. River Foods, 1/3 Macquarie Drive, Thomastown, VIC 3074, Australia.
Rivero, Arg. P.L. Rivero & Co SAIC, Avenida Boyaca 419, 1406 Buenos Aires, Argentina.
url: www.rivero.com.ar
Rivers Edge, USA. River's Edge Pharmaceutical, Suwanee, GA 30024, USA.
Rivex, Canad. Rivex Pharma Inc., 3-305 Industrial Parkway S, Aurora, Ontario, L4G 6X7, Canada. Director Scientific Affairs
Rivex Ophthalmics, Canad. See *Rivex, Canad.*
Riviera, Austria. Riviera Handelsgesellschaft.m.b.h., Penzingerstrasse 54, A-1140 Vienna, Austria.
Riviera, Cz. See *Riviera, Austria.*
Rivopharm, Switz. Rivopharm SA, Centro Insema, 6928 Manno, Switzerland.
RK Medicare, India. R.K. Medicare Pvt Ltd, 14/58 Chopasni Housing Board, Jodhpur 342 008, India.
url: www.rkmedicare.com
RKG, Ital. RKG S.r.l., Via Ciro Menotti 1/A, 20129 Milan, Italy.
RLC, USA. RLC Labs, 2404 West 12th Street, Suite 4, Tempe, AZ 85281, USA.
url: www.rlclabs.com
R-mark, Cz. R-mark sro, Zbraslavské n.455, 156 00 Prague 5, Czech Republic.
RND, India. RND Laboratories Pvt Ltd, 434 Sector-3, Niladree Vihar, Chandrashekharapur, Bhubaneshwar, 751 021, India.
Ro+Ten, Ital. Ro+Ten srl, Via Monte Cervino 50, 20862 Arcore (MB), Italy.
url: www.roplusten.com
Robapharm, Cz. See *Pierre Fabre, Cz.*
Robapharm, Fr. See *Pierre Fabre, Fr.*
Robapharm, Ger. See *Pierre Fabre, Ger.*
Robapharm, Hung. See *Ewopharma, Hung.*
Robapharm, Spain. Robapharm España, Ramon Trias Fargas 7-11, Edificio Marina Village, 08005 Barcelona, Spain.
Robapharm, Switz. Robapharm SA, Gewerbestrasse 18, 4123 Allschwil, Switzerland.
url: www.robapharm.ch
Robapharm, Thai. See *Berli Jucker, Thai.*
Robert, Canad. Robert et Fils Inc., 1212 Louvain Ouest, Montreal, Quebec, H4N 1G5, Canada.
Robert, Singapore. See *Pharmacon, Singapore.*
Robert, Spain. Robert, Gran via de Carlos III 98, 08028 Barcelona, Spain.
Robert & Carriere, Canad. See *Anglo-French Laboratories, Canad.*
Roberts, Canad. See *Shire Biochem, Canad.*
Roberts, Israel. See *Medison, Israel* and *Pharmateam, Israel.*
Roberts, USA. See *Shire, USA.*
Roberts & Sheppey, UK. Roberts & Sheppey (Melrose) Ltd, Manor Farm House, Ickford, Aylesbury, Buckinghamshire, HP18 9JB, UK.
url: www.melrose-skincare.co.uk
Robins, Austral. See *Whitehall, Austral.*
Robins, Hong Kong. See *US Summit, Hong Kong.*
Robins, Irl. See *Wyeth, Irl.*
Robins, Israel. See *Neopharm, Israel.*
Robins, Swed. See *Wyeth Lederle, Swed.*
Robins, Switz. See *Whitehall-Robins, Switz.*
Robins, UK. See *Wyeth, UK.*
Robins, USA. See *Wyeth Consumer, USA.*

Robinson, UK. Robinson Healthcare, Lawn Rd, Carlton-in-Lindrick Industrial Estate, Worksop, Nottinghamshire, S81 9LB, UK.
url: www.robinsoncare.com

Robugen, Austria. See *Robugen, Ger.*

Robugen, Ger. Robugen GmbH Pharmazeutische Fabrik, Alleenstr. 22-6, 73730 Esslingen, Germany.
url: www.robugen.de

Robugen, Hong Kong. See *Mekim, Hong Kong.*

RoC, Belg. See *Johnson & Johnson Consumer, Belg.*

RoC, Fr. See *Ethicon, Fr.*

RoC, UK. See *Johnson & Johnson, UK.*

Roche, Arg. Productos Roche S.A.Q. e I., Ruta 9 Km 34, 1610 Ricardo Rojas Tigre, Buenos Aires, Argentina.
url: www.roche.com

Roche, Austral. Roche Products P/L, P.O. Box 255, Dee Why, NSW 2099, Australia.
url: www.roche.com

Roche, Austria. Roche Austria GmbH, Engelhorngasse 3, A-1211 Vienna, Austria.
url: www.roche.at

Roche, Belg. Roche SA/NV, Rue Dante 75, 1070 Brussels, Belgium.
url: www.roche.be

Roche, Braz. Produtos Roche Químicos e Farmacêuticos S.A., Avenida Engenheiro Billings 1729, 05321-900 São Paulo, SP, Brazil.
url: www.roche.com

Roche, Canad. Hoffmann-La Roche Ltd, 2455 Meadowpine Blvd, Mississauga, Ontario, L5N 6L7, Canada.Medical Information Manager
url: www.rochecanada.com

Roche, Chile. Productos Roche Ltda, Av. Quilin 3750, Macul, Santiago, Chile.

Roche, China. Roche Pharmaceutical Ltd, 720 Cai Lun Rd, Building 5, Shanghai 201203, Pudong, China.
url: www.roche.com.cn

Roche, Cz. Roche sro, Dukelských hrdinů 52, 170 00 Prague 7, Czech Republic.

Roche, Denm. Roche A/S, Industriholmen 59, 2650 Hvidovre, Denmark.
url: www.roche.com

Roche, Fin. Roche Oy, Sinimäentie 10 B, PL 12, 02631 Espoo, Finland.
url: www.roche.fi

Roche, Fr. Produits Roche, 52 bd du Parc, 92521 Neuilly-sur-Seine cdx, France.
url: www.roche.com

Roche, Ger. Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen, Germany.
url: www.roche.de

Roche, Gr. Roche (Hellas) S.A., 4 Alamanas & Delfon St., 151 25 Marousi, Greece.
url: www.roche.gr

Roche, Hong Kong. Roche Hong Kong Ltd, 802 The Lee Gardens, 33 Hysan Ave, Causeway Bay, Hong Kong.
url: www.roche.com

Roche, Hung. Roche (Magyarország) Kft, Edison u 1, 2040 Budaörs, Hungary.

Roche, India. Roche Pharmaceuticals, 434 Sector-3 Niladree Vihar, Chandrashekharapur, Bhubaneswar, 751 021, India.

Roche, Indon. Roche Indonesia PT, Artha Graha Building 21-22 Fl, Sudirman Central Business District Lot 25, Jl Jend Sudirman Kav 51-52, Jakarta 12190, DKI Jaya, Indonesia.
url: www.roche.co.id

Roche, Irl. Roche Pharmaceuticals (Ireland) Ltd, 3004 Lake Drive, City West, Naas Rd, Dublin 24, Ireland.
url: www.roche.ie

Roche, Israel. Roche Pharmaceuticals (Israel) Ltd, P.O. Box 7543, Petach Tikva, Israel.
url: www.roche.com

Roche, Ital. Roche S.p.A., Viale G.B. Stucchi 110, 20052 Monza (MB), Italy.
url: www.roche.com

Roche, Jpn. Nippon Roche K.K., Nippon Roche Building, 6-1 Shiba 2-chome, Minato-ku, Tokyo 105-8532, Japan.
url: www.roche.com

Roche, Malaysia. See *DKSH, Malaysia.*

Roche, Mex. Grupo Roche Syntex de Mixico, S.A. de C.V., Carr. Mexico-Toluca 2822, Miguel Hidalgo Lomas de Bezares, 11000 Mexico D.F., Mexico.
url: www.roche.com

Roche, Neth. Roche Nederland BV, P.O. Box 42, 3640 AA Mijdrecht, Netherlands.
url: www.roche.com

Roche, Norw. Roche Norge AS, Kristoffer Robinsv. 13, Postboks 41 Haugenstua, 0915 Oslo, Norway.
url: www.roche.no

Roche, NZ. Roche Products (New Zealand) Ltd, P.O. Box 12-492, Penrose, Auckland, New Zealand.
url: www.roche.co.nz

Roche, Philipp. Roche (Phils) Inc., 2252 Don Chino Roces Ave, Makati City, Philippines.

Roche, Pol. Roche Polska Sp. zo.o., ul. Domaniewska 39 B, 02-672 Warsaw, Poland.
url: www.roche.pl

Roche, Port. Roche Farmacêutica Química, Lda, Estrada Nocional 249, 2720-413 Amadora, Portugal.
url: www.roche.pt

Roche, Rus. Hoffmann La Roche Ltd, Smolnaya St 24D, 125445 Moscow, Russia.

Roche, S.Afr. Roche Products (Pty) Ltd, P.O. Box 129, Gauteng, Isando 1600, South Africa.
url: www.roche.co.za

Roche, Singapore. Roche Singapore Pte Ltd, 1 Kim Seng Promenade, 15-07/12 Great World City, S 237994, Singapore.
url: www.roche.com

Roche, Spain. Roche Farma, Josefa Valcarcel 42, 28027 Madrid, Spain.
url: www.roche.es

Roche, Swed. Roche AB, Box 47327, 100 74 Stockholm, Sweden.
url: www.roche.se

Roche, Switz. Roche Pharma (Schweiz) AG, Schonmattstrasse 2, 4153 Reinach, Switzerland.
url: www.roche.com

Roche, Thai. Roche Thailand Ltd, 19 Fl, Rasa Tower, 555 Phaholyathin Rd, Chatuchak, Bangkok 10900, Thailand.
url: www.rochethai.com

Roche, Turk. Roche Müstahzarlori San. A.Ş., Mecidiyeköy Yolu No: 102, Mecidiyeköy Şişli, İstanbul, 34387, Turkey.
url: www.roche.com.tr

Roche, UK. Roche Products Ltd, Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW, UK.
url: www.rocheuk.com

Roche, Ukr. Hoffman-La Roche Ltd, 2-B Muzeyniy per, 2nd Floar, 01001 Kiev, Ukraine.
url: www.roche.com

Roche, USA. Roche Pharmaceuticals, 340 Kingsland St, Nutley, NJ 07110-1199, USA.
url: www.roche.us

Roche, Venez. Productos Roche S.A., Edificio Roche, Av. Diego Cisneros/Los Ruices, Corocas 1062, Venezuela.
url: www.roche.com.ve

Roche Consumer, Austral. See *Roche, Austral.*

Roche Consumer, Belg. See *Bayer, Belg.*

Roche Consumer, Ger. See *Bayer, Ger.*

Roche Consumer, Hung. See *Roche, Hung.*

Roche Consumer, Irl. See *Roche, Irl.*

Roche Consumer, Neth. Roche Consumer Health, Meerenakkerplein 5-6, 5652 BJ Eindhoven, Netherlands.
url: www.roche.com

Roche Consumer, S.Afr. See *Roche, S.Afr.*

Roche Consumer, Singapore. See *DKSH, Singapore.*

Roche Consumer, UK. See *Bayer, UK.*

Roche Diagnostics, Austral. Roche Diagnostics, P.O. Box 955, Castle Hill, NSW 1765, Australia.
url: www.rochediagnostics.com.au

Roche Diagnostics, Braz. See *Roche, Braz.*

Roche Diagnostics, Canad. Roche Diagnostics, Division of Hoffman-La Roche Ltd, 201 Armand-Frappier Bvld, Laval, Quebec, H7V 4A2, Canada.
url: www.rochediagnostics.ca

Roche Diagnostics, Cz. See *Roche, Cz.*

Roche Diagnostics, Fr. Roche Diagnostics, 2 av. du Vercors, B.P. 59, 38242 Meylan cdx, France.
url: www.rochediagnostics.fr

Roche Diagnostics, Irl. See *Roche Diagnostics, UK.*

Roche Diagnostics, Israel. See *Teva, Israel.*

Roche Diagnostics, Ital. See *Roche, Ital.*

Roche Diagnostics, Mex. Roche Division Diagnosticos, Av. Paseo de la Reforma 2620 Piso 8, 11950 Miguel Hidalgo Lomas Altas, Mexico DF, Mexico.

Roche Diagnostics, NZ. Roche Diagnostics NZ Ltd, P.O. Box 62-089, Auckland, New Zealand.
url: www.roche-diagnostics.com

Roche Diagnostics, Spain. See *Roche, Spain.*

Roche Diagnostics, UK. Roche Diagnostics Ltd, Charles Ave, Burgess Hill, West Sussex, RH15 9RY, UK.
url: www.roche-diagnostics.com

Roche Nicholas, Cz. See *Roche, Cz.*

Roche Nicholas, Fr. Laboratoires Roche Nicholas, 33 Rue de l'Industrie, 74240 Gaillard, France.
url: www.roche.com

Roche Nicholas, Ger. See *Bayer, Ger.*

Roche Nicholas, Hong Kong. See *CNW, Hong Kong.*

Roche Nicholas, Indon. See *Corsa, Indon.*

Roche Nicholas, Israel. See *Devries, Israel.*

Roche Nicholas, Neth. See *Roche Consumer, Neth.*

Roche Nicholas, Spain. See *Roche, Spain.*

Roche-Posay, Arg. Lab. Pharmaceutique La Roche-Posay, Avenida Raque Saenz Pena 1155, 7 Piso, 1041 Buenos Aires, Argentina.
url: www.laroche-posay.com

Roche-Posay, Braz. La Roche Posay, L'Oreal-Belocap. Divisao Cosmetica Ativa, Rua São Bento 8, 14 andar, 20090-010 Rio de Janeiro, RJ, Brazil.
url: www.laroche-posay.com

Roche-Posay, Conad. Laboratoires la Roche-Posay Canada, 4895 Hickmore, Montreal, Quebec, H4T 1K5, Canada.

Roche-Posay, Chile. See *L'Oreal, Chile.*

Roche-Posay, Fr. Laboratoires Pharmaceutiques La Roche-Posay, B.P. 23, 86270 La Roche-Posay, France.

Roche-Posay, Irl. La Roche-Posay Cosmetique Active, Styne House, Upper Hatch St., Dublin 8, Ireland.

Roche-Posay, Mex. La Roche-Posay Mexico, Oklahoma 14, Col. Napoles, 03810 Mexico D.F., Mexico.
url: www.laroche-posay.com

Roche-Posay, Singapore. See *L'Oreal, Singapore.*

Roche-Posay, Switz. See *Cosmetique Active, Switz.*

Roche-Posay, UK. See *L'Oreal, UK.*

Roche-Posay, USA. La Roche-Posay Laboratoire Pharmaceutique, 112 Madison Ave, 12th Floor, New York, NY 10016, USA.
url: www.laroche-posay.com

Rochester, Canad. Rochester Midland Ltd. 851 Progress Court, Oakville, Ontario, L6J 5A8, Canada.

Rochester, USA. Rochester Pharmaceuticals, Rochester, NY 14625, USA.

Roddensers, Philipp. Roddensers Pharmaceuticals, R 2030 W Soliven Shopping Complex, EDSA, Greenhills, San Juan, Metro Manila, Philippines.

Rodisma, Ger. Rodisma-Med Pharma GmbH, Kölner Str. 48, 51149 Cologne, Germany.
url: www.rodisma.de

Rodleben, Cz. See *UCB, Cz.*

Rodlen, USA. Rodlen Laboratories, Subsidiary of Winston Laboratories Inc., 100 Fairway Drive, Ste 134, Vernon Hills, IL 60061, USA.
url: www.winstonlabs.com

Rodler, Ger. See *McNeil, Ger.*

Roehr, Philipp. See *Biolink, Philipp.*

Roemmers, Arg. Roemmers S.A.I.C.F., Fray Justo Sarmiento 2350, 1636 Olivos, Buenos Aires, Argentina.
url: www.roemmers.com.ar

Roemmers, Chile. See *Pharma Investi, Chile.*

Roemmers, Venez. Laboratorios Roemmers, 2a Av Campo Alegre, Torre Credival, 1060 Caracas, Venezuela.

Roemmers Medihe, Venez. See *Roemmers, Venez.*

Roemmers Osmoph, Venez. See *Roemmers, Venez.*

Roemmers Poen, Venez. See *Roemmers, Venez.*

Roemmers Rowe, Venez. See *Roemmers, Venez.*

Roemmers-Klinos, Venez. Roemmers-Klinos, 2a Av.Campo Alegre To.Credival Mzz., Chacao, Urb. La Trinidad Caracas, Caracas, Venezuela.

Roer, Hung. Roer Pharma Kft, Tóth István ut 55, 1155 Budapest, Hungary.

Roerig, Austral. See *Pfizer, Austral.*

Roerig, Belg. See *Pfizer, Belg.*

Roerig, Chile. See *Pfizer, Chile.*

Roerig, Ital. See *Pfizer, Ital.*

Roerig, Port. See *Pfizer, Port.*

Roerig, Swed. See *Pfizer, Swed.*

Roerig, USA. See *Pfizer, USA.*

Rofina, Arg. See *Roemmers, Arg.*

Roge-Cavailles, Fr. Rogé-Cavaillès SAS, 11 av. Dubonnet, 92400 Courbevoie, France.

Roger, Spain. See *UCB, Spain.*

Rogers, Canad. Rogers Pharmaceuticals Ltd, 330 Marwood Drive, Unit 4, Oshawa, Ontario, L1H 8B4, Canada.

Roha, Canad. See *Roha, Ger.*

Roha, Ger. roha Arzneimittel GmbH, Rockwinkeler Heerstr. 100, 28355 Bremen, Germany.
url: www.roha-bremen.de

Roha, Hong Kong. See *Hind Wing, Hong Kong.*

Roha, Hung. See *Roha, Ger.*

Roha, Irl. See *United Drug, Irl.*

Roha, Israel. See *Dexxon, Israel.*

Roha, Neth. See *Roha, Ger.*

Roha, Pol. See *Zymella, Pol.*

Roha, Port. See *Vivalife, Port.*

Roha, Rus. See *Roha, Ger.*

Roha, Singapore. See *Pharmaforte, Singapore.*

Roha, Spain. See *Roha, Ger.*

Roha, Switz. See *Merz, Switz.*

Rohm, S.Afr. See *Sanofi-Aventis, S.Afr.*

Rohto Mentholatum, Singapore. See *DKSH, Singapore.*

Rohto-Mentholatum, Thai. Rohto-Mentholatum (Thailand) Ltd, 5 Fl, Q House Bldg, 38 Convent Rd, Silom Bangrak, Bangkok 10500, Thailand.

Roi Surya, Indon. Roi Surya Prima PT, Jl Kapas Krampung 57, Surabaya, Jawa Timur, Indanesia.

Rokitan, Austria. Rokitan GmbH, Grosse Mohrengasse 10, 1020 Vienna, Austria.
url: www.rokitan.com

Rokitan, Neth. See *Rokitan, Austria.*

Rolab, S.Afr. See *Sandoz, S.Afr.*

Roland, Austria. See *Nycomed, Ger.*

Roland, Cz. See *Berlin-Chemie, Cz.*

Roland, Ger. See *Nycomed, Ger.*

Rolfe, S.Afr. See *Boots Healthcare, S.Afr.*

Rolland, Switz. See *Merck, Switz.*

RoLo, Ital. RoLo Srl, Via Cadore 20, 20092 Cinisello Balsamo (MI), Italy.

Roma, Canad. Roma Marketing Inc., 127 700 Lawrence Ave W, Toronto, Ontario, M6A 3B4, Canada.

Romark, USA. Romark Laboratories, 3000 Bayport Drive, Suite 200, Tampa, FL 33607, USA.
url: www.romark.com

Romilo, Canad. See *St Laurent, Canad.*

Rominafort, Arg. Rominafort SH, Av. Monroe 5471, (1431) Buenos Aires, Argentina.

Romofarm, Spain. See *Almirall, Spain.*

Rompharm, Rus. Rompharm, Leninskii prospekt 32, et. 3, 119991 Moscow, Russia.
url: www.rompharm.ru

Romsa, Mex. Lab. Quim. Farmaceutico Romsa de Mexico S.A., Metalurgia No. 2820, P. Industrial el Alamo, 45560 Tlaquepoque, Jalisco, Mexica.

Ronava, Venez. Productos Ronava C.A., Final calle Mara, Edif.Ronava Zona Ind. El Marqué, Caracas, Venezuela.
url: www.ronava.com.ve

Rongchang, China. Rongchang Pharmaceutical Co. Ltd, 1 Rongchang Road, Economic & Technological Development Zone, Yantai, Shandong, China.
url: www.rongchang.com

Rongtai, China. Rongtai Pharmaceutical Co. Ltd, Guangdong, China.

Ronnet, Arg. Ronnet Labaratoires S.A., Jose Enrique Rodo 5940, Buenos Aires, Argentina.

Ronsen, China. Ronsen Pharmaceutical Co. Ltd, 7 Park Rd, High-Tech Zone, Chengdu 610063, China.
url: www.ronsen.com

Rontag, Arg. Lab. Rontag S.A., Arcos 2626, 1428 Buenos Aires, Argentina.

Roomi, Philipp. See *Huge, Philipp.*

Rooster, Neth. J.H. Rooster & Zn. BV, Netherlands.

Roques, Fr. See *Chiesi, Fr.*

Rorer, Austral. See *Sanofi-Aventis, Austral.*

Rorer, Canad. See *Sanofi, Canad.*

Rorer, Fr. See *Sanofi-Aventis, Fr.*

Rorer, Ger. See *Sanofi-Aventis, Ger.*

Rorer, Irl. See *Sanofi-Aventis, Irl.*

Rorer, Ital. See *Sanofi-Aventis, Ital.*

Rorer, Neth. See *Sanofi-Aventis, Neth.*

Rorer, Spain. See *Sanofi-Aventis, Spain.*

Rorer, UK. See *Sanofi, UK.*

Rorer, USA. See *Sanofi-Aventis, USA.*

Rosa-Phytopharma, Fr. Laboratoires Rosa-Phytopharma, 68 rue Jean-Jaques-Rousseau, 75001 Paris, France.

Rosa-Phytopharma, Rus. See *FIC, Rus.*

Rosa-Phytopharma, Switz. See *Golaz, Switz.*

Rosa-Phytopharma, Ukr. See *FIC Medical, Ukr.*

Rosch & Handel, Austria. Rösch & Handel, Gudrunstrasse 150, A-1100 Vienna, Austria.

Rosco, Norw. See *Andersen, Norw.*

Rose, India. Rose Pharmaco Pvt Ltd, C2 & 3 Sara Industrial Estate Ltd, Selaqui, Rampur, Chakrata Road, Dehradun 248 197, India.
url: www.rosepharmaco.com

Rosee de la Reine, Fr. See *Mont Roucous, Fr.*

Rosell, Canad. Institut Rosell Inc., 8380 Blvd Saint-Laurent, Montreal, Quebec, H2P 2M6, Canado.

Rosell, Cz. Institut Rosell, Czech Republic.

Rosell, Ukr. See *Pharm Union, Ukr.*

Rosell Lallemand, Singapore. See *MD, Singapore.*

Rosemont, Irl. See *Rosemont, UK.*

Rosemont, Neth. See *Rosemont, UK.*

Rosemont, Thai. See *Star, Thai.*

Rosemont, UK. Rosemont Pharmaceuticals Ltd, Rosemont House, Yorkdale Industrial Park, Braithwaite St, Leeds, West Yorkshire, LS11 9XE, UK.
url: www.rosemontpharma.com

Rosemont, USA. Rosemont Pharmaceutical Corp., 301 South Cherokee St, Denver, CO 80223, USA.

Rosen, Ger. Rosen Pharma GmbH, Kirkeler Str. 41, 66440 Blieskastel, Germany.
url: www.rosen-pharma.de

Rosfarmak, Ukr. Rosfarmak, Most Vasilkovskaya St 72, Office 17, 03150 Kiev, Ukroine.

Rosken, Hong Kong. See *Suburfarm, Hong Kong.*

Rosken, Singapore. See *JDH, Singapore.*

Rospaw, Arg. Laboratorio Rospaw SRL, Santos Dumont 4744, Buenos Aires, Argentina.

Ross, Canad. See *Abbott, Canad.*

Ross, Hong Kong. See *Abbott, Hong Kong.*

Ross, Israel. See *Promedico, Israel.*

Ross, USA. Ross Products, Division of Abbott Laboratories Inc., 625 Cleveland Ave, Columbus, OH 43215, USA.
url: www.rosslabs.com

Rossendorf, Cz. Verein für Kenverfahrenstechnik und Analytik Rossendorf EV, Czech Republic.

Rosso, China. Rossa Pharmaceutical Ltd, Room A06 International Trade Building, Luohu, Shenzhen, China.
url: www.szshikang.cn

Rostro, Arg. See *Genser, Arg.*

Rosunifarm, Rus. Rosunifarm, Russia.

Roszdrava, Rus. FGU PKNPK Roszdrava - EPMBP, 3 Cherepkovskaya ul 15-a, 121552 Moscow, Russia.

Rotam Reddy, China. Rotam Reddy Pharmaceutical Co. Ltd, Venture Building Room 1601, 600 Tianshan Rd, Changning District No 1, Shanghai 200051, China.

Rotapharm, Ukr. Rotapharm Ltd, Igorevskaya 12B, Kiev, 04070, Ukraine.

Roter, NZ. See *NZ Medical & Scientific, NZ.*

Roter, Switz. See *Galenica, Switz.*

Roterpharma, Irl. See *Allphar, Irl.*

Rotexmedica, Ger. Rotexmedica GmbH Arzneimittelwerk, Bunsenstr. 4, 22946 Trittau, Germany.
url: www.rotexmedica.com

Rotexmedica, Malaysia. See *Duopharma, Malaysia.*

Rotexmedica, Philipp. See *Duopharma, Philipp.*

Rotexmedica, Singapore. See *CCM, Singapore.*

Roth, Austria. G Roth & Söhne Pharmazeutische Präparate GmbH, Wagnerstrasse 29, A-2371 Hinterbruhl, Austrio.

Rothpharma, Austria. See *Roth, Austria.*

Rotop, Cz. See *Rotop, Ger.*

Rotop, Fin. See *Rotop, Ger.*

Rotop, Ger. Rotop Pharmaka AG, Bautzner Landstr. 45, 01454 Radeberg, Germany.
url: www.rotop-pharmaka.de

Rotop, Neth. See *Rotop, Ger.*

Rotop, Port. See *Rotop, Ger.*

Rotop, Spain. See *Rotop, Ger.*

Rotta, Hong Kong. See *IDS, Hong Kong.*

Rotta, Israel. See *Teva, Israel.*

Rotta, Ital. See *Rottapharm, Ital.*

Rotta, Malaysia. See *Antah, Malaysia.*

Rotta, Philipp. See *Zuellig, Philipp.*

Rotta, Port. See *Delta, Port.*

Rotta, Singapore. See *Sime Darby, Singapore.*

Rotta, Thai. See *Diethelm, Thai.*

Rottapharm, Chile. See *Silesia, Chile.*

Rottapharm, China. Rottapharm Pharmaceuticals, Henghua International Office 710B, 26 Yuetanbeijie, Xicheng District, Beijing, 100045, China.

Rottapharm, Cz. See *Medicom, Cz.*

Rottapharm, Fin. See *Algol, Fin.*

Rottapharm, Fr. Rottapharm Sarl, 83-85 bd Vincent-Auriol, 75013 Paris, France.
url: www.rottapharm.fr

Rottapharm, Ger. See *Opfermann, Ger.*

Rottapharm, Gr. Rottapharm, Greece.

Rottapharm, Hong Kong. See *IDS, Hong Kong.*

Rottapharm, Hung. See *CSC, Hung.*

Rottapharm, Irl. Rottapharm Ireland, Damastawn Industrial Park, Mulhuddart, Dublin 15, Ireland.
url: www.rotta.com

Rottapharm, Ital. Rottapharm S.p.A., Via Valosa di Sopra 9, 20052 Monza (MB), Italy.
url: www.rottapharm.com

Rottapharm, Malaysia. See *Antah, Malaysia.*

Rottapharm, Neth. See *Rottapharm, Irl.*

Rottapharm, Pol. Rottapharm, Poland.

Rottapharm, Rus. Rottapharm srl, Ostrovityanova ul 14 of 108, 117321 Moscow, Russia.

Rottapharm, Singapore. Rottapharm Singapore, 151 Chin Swee Rd 15-05, Manhattan House, S 169876, Singapore.

Rottapharm, Spain. Rottapharm, Ctra Barcelona 2, Almacera, 46132 Valencia, Spain.
url: www.rottapharm.com

Rottapharm, Thai. See *Diethelm, Thai.*

Rottapharm, Ukr. See *Protek-Pharma, Ukr.*

Rottendorf, Rus. See *Bayer, Rus.*

Rougier, Canad. See *Ratiopharm, Canad.*

Rougier, Hong Kong. See *Pan-Well, Hong Kong.*

Round World, Hong Kong. Round World International Ltd, Rm 5-7, 21/F Remington Ctr, 23 Hung To Rd, Kwun Tong, Kowloon, Hong Kong.

Roussel, Austral. See *Sanofi-Aventis, Austral.*

Roussel, Fr. See *Sanofi-Aventis, Fr.*

Roussel, Irl. See *Sanofi-Aventis, Irl.*

Roussel, Ital. See *Sanofi-Aventis, Ital.*

Roussel, Neth. See *Sanofi-Aventis, Neth.*

Roussel, Pol. See *Sanofi-Aventis, Pol.*

Roussel, Port. See *Sanofi-Aventis, Port.*

Roussel, S.Afr. See *Sanofi-Aventis, S.Afr.*

Roussel, Spain. See *Sanofi-Aventis, Spain.*

Roussel, Swed. See *Sanofi-Aventis, Swed.*

Roussel, Switz. See *Sanofi-Aventis, Switz.*

Roussel, UK. See *Sanofi, UK.*

Roussel, USA. See *Sanofi-Aventis, USA.*

Roussel Diamant, Fr. See *Sanofi-Aventis, Fr.*

Roussel Nutrition, Fr. See *Sanofi-Aventis, Fr.*

Roussel-Diamant, Rus. See *Sanofi-Aventis, Rus.*

Roux-Ocefa, Arg. Lab. Roux-Ocefa S.A., Montevideo 79/81, 1019 Buenos Aires, Argentina.

Rovafarm, Arg. See *Pierre Fabre, Arg.*

Rovi, Austria. See *Rovi, Spain.*

Rovi, Port. Laboratórios Farmacêuticos Rovi SA, Av. Defensores de Chaves 15 - 5 B, 1000-109 Lisbon, Portugal.

Rovi, Spain. Rovi, Julian Camarillo 35, 28037 Madrid, Spain.
url: www.rovi.es

Rovifarma, Spain. See *Pfizer, Spain.*

Rowa, Cz. See *Swisspharma, Cz.*

Rowa, Ger. Rowa Wagner GmbH & Co. KG Arzneimittelfabrik, Frankenforster Str. 77, 51427 Bergisch Gladbach, Germany.
url: www.rowa.ie

Rowa, Hong Kong. See *Jacobson, Hong Kong.*

Rowa, Hung. See *SATCO, Hung.*

Rowa, Irl. Rowa Pharmaceuticals Ltd, Bantry, Co. Cork, Ireland.
url: www.rowa.ie

Rowa, Israel. See *Megapharm, Israel.*

Rowa, Malaysia. See *JDH, Malaysia.*

Rowa, Philipp. See *Marketlink, Philipp.*

Rowa, Rus. See *Switch, Rus.*

Rowa, Singapore. See *JDH, Singapore.*

Rowa, Thai. See *JDH Borneo, Thai.*

Rowa, UK. See *Rowa, Irl.*

Rowa Wagner, Hong Kong. See *Deutsch Chinesische, Hong Kong.*

Rowa-Wagner, Pol. See *Vitamed, Pol.*

Rowe-Fleming, Venez. Laboratorios Rowe-Fleming C.A., Av.La Habana con calle Quito Edif. Vizcaya, Los Caobos Entrada B Pent House, Caracas, Venezuela.

Rowex, Irl. See *Rowa, Irl.*

Rowex, Neth. See *Rowa, Irl.*

Rowfarma, Mex. Rowfarma de Mexico S de RL de CV, Insurgentes Sur 664 Piso 11, 3200 Del Valle, Mexico DF, Mexico.

Roxall, Ger. Roxall Medizin GmbH, Carl-Petersen-Str. 4, 20535 Hamburg, Germany.
url: www.roxall.de

Roxane, USA. Roxane Laboratories Inc., a Subsidiary of Boehringer Ingelheim, P.O. Box 16532, Columbus, OH 43216, USA.
url: www.roxane.com

Royal, Chile. See *Alpes Chemie, Chile.*

Royale, Philipp. See *Britton, Philipp.*

Royce, Singapore. See *Summit, Singapore.*

Royton, Braz. Royton Química Farmacêutica Ltda, Avenida Doutor Cardoso de Melo 1318, 04548-004 São Paulo, SP, Brazil.
url: www.royton.com.br

RPF, Ital. Ricerca Prodotti Farmaceutici srl, Via Grottole 80/B, 81020 Castel Morrone (CE), Italy.
url: www.rpf-srl.it

RPG, India. RPG Life Sciences Ltd, Ceat Mahal 463, Dr Annie Besant Rd, Worli, Mumbai 400 030, India.
url: www.rpglifesciences.com

RPH, Fin. See *RPH, Swed.*

RPH, Norw. See *Vitaflo, Norw.*

RPH, Swed. RPH Pharmaceuticals AB, Lagervägen 7, 13650 Jordbro, Sweden.

RS, USA. R & S Pharma, 8407 Austin Tracy Rd, Fountain Run, KY 42133, USA.
url: www.rspharma.com

Rubimed, Neth. Rubimed BV, Ganskamer 4, 8162 JG Epe, Netherlands.

Rubio, Malaysia. See *Zyfas, Malaysia.*

Rubio, Neth. See *Rubio, Spain.*

Rubio, Port. See *Rubio, Spain.*

Rubio, Singapore. See *Zyfas, Singapore.*

Rubio, Spain. Rubio, Industria 29, Pol Ind Comte de Sert, Castellbisol, 08755 Barcelona, Spain.
url: www.laboratoriosrubio.com

Rubio, Thai. See *JDH Borneo, Thai.*

Rudefsa, Mex. See *Sanofi Synthelabo, Mex.*

Rueckert, Malaysia. See *People's, Malaysia.*

Rueckert, Philipp. See *Zuellig, Philipp.*

Rueckert, Singapore. See *Indrugco, Singapore.*

Rueckert, Thai. See *Sriprasit, Thai.*

Rugby, USA. See *Watson, USA.*

Ruhrpharm, Ger. Ruhrpharm AG, Heidsieker Heide 114, 33739 Bielefeld, Germany.
url: www.ruhrpharm.de

Rui Er, China. Rui'Er Pharmaceutical Co. Ltd, 32 Haidian East Rd, Longhua, Haikou, Hainan, 570100, China.

Rui Feng, China. Rui Feng Pharmaceutical Group Co Ltd, China.

Rui Nian Qian Jin, China. Rui Nian Qian Jin Pharmaceutical Co. Ltd, Jiangsu, China.

Rui Yang, China. Rui Yang Pharmaceutical Co. Ltd, 6 Erlang Mountain Rd, Yiyuan, Shandong, China.

Ruibang, China. Ruibang Pharmaceutical Co. Ltd, Zhejiang, China.

Ruide Hetong, China. Ruide Hetong Pharmaceutical Co Ltd, Beijing, China.

Ruige, China. Ruige Pharmaceutical Co. Ltd, Heilongjiang, China.

Ruinian Baisite, China. Ruinian Baisite Pharmaceutical Co. Ltd, Nanjing, China.

Ruixin, China. Ruixin Pharmaceutical Co. Ltd, Zhejiang, China.

Ruiying, China. Ruiying Pharmaceutical Group Ltd, New Asia Building Room 815, 89 Jiangsu Road, Shanghai, China.

Ruizhu, China. Ruizhu Pharmaceutical Co. Ltd, 28 High-Tech Industrial Park, Wuhan Economic and Technological Development Zone, Wuhan, Hubei, 420100, China.

Run Bang, China. Run Bang Pharmaceutical Co. Ltd, Jiangsu, China.

Rundu Mintong, China. Rundu Mintong Pharmaceutical Co. Ltd, Zhuhai, China.

Runkang, China. Runkang Pharmaceutical Co. Ltd, Chongqing, China.

Rusan, India. Rusan Pharma Ltd, 58-D Government Industrial Estate, Charkop, Kandivli (West), Mumbai 400 067, India.
url: www.rusanpharma.com

Rusan, Rus. See *Promo-Med, Rus.*

Russ, USA. See *UCB, USA.*

Russian Institute of Gerontology, Rus. Russian Institute of Gerontology, Russia.

Rutland Biodynamics, UK. Rutland Biodynamics Ltd, Town Park Farm, Brooke, Rutland, LE15 8DG, UK.

Rutti, Philipp. WM Rutti Inc., 75 Retiro cor Ipo St, La Loma, Quezon City, Philippines.

RW, Canad. RW Packaging Ltd, 200 Omand's Creek Blvd, Winnipeg, Manitoba, R2R 1V7, Canada.

RX, Hong Kong. RX Co, Hong Kong.

RX, Thai. RX Company Ltd, 93/90 Soi Prachanukul 2, Ratchadapisek Rd, Bangsue, Bangkok 10800, Thailand.
url: www.rx.co.th

Rx Pharma, Singapore. Rx Pharma Pte Ltd, 1 Bukit Batok Crescent, 08-19 WCEGA Plaza, 658064, Singapore.
url: rxpharmasingapore.com

Rybar, Irl. See *Fulcrum, Irl.*

Rybar, UK. See *Shire, UK.*

Rydelle, Fr. See *Farnet, Fr.*

Rydelle, USA. See *Johnson Wax, USA.*

Rye, Singapore. See *Pan-Malayan, Singapore.*

Rystan, USA. Rystan Inc., 47 Center Ave., P.O. Box 214, Little Falls, NJ 07424-0214, USA.

Ryukakusan, Jpn. Ryukakusan Co Ltd, 2-5-12, Higashi-Kanda, Chiyoda-ku, Tokyo, 101-0031, Japan.
url: www.ryukakusan.co.jp

S & B, Neth. See *Multipharma, Neth.*

S & K, Cz. See *S & K, Ger.*

S & K, Ger. S & K Pharma, Schumann & Kohl GmbH, Maienbergstr. 10-12, 15562 Rüdersdorf, Germany.

S Co Pharma, Thai. S Co Pharma, 212/99 Soi Phetkasem 16, 2 Phetkasem Rd, Bangkok, 10600, Thailand.

S Med, Austria. S Med Handels GmbH, Zachgasse 1, A-1220 Vienna, Austria.
url: www.smed.at

S Med, Neth. See *S Med, Austria.*

SA Druggists, S.Afr. See *Aspen, S.Afr.*

SA Druggists Self Med, S.Afr. See *Aspen, S.Afr.*

Saarstickstoff-Fatol, Ger. See *Fatol, Ger.*

Saba, Turk. Saba İlaç San. ve Tic. A.Ş., Yildiz Cad. No: 55/1, Beşiktaş, İstanbul, 34353, Turkey.
url: www.sabapharm.com

Sabater, Spain. See *Generfarma, Spain.*

Sabax, S.Afr. See *Adcock Ingram, S.Afr.*

Sabex, Canad. Sabex Inc., 145 Jules-Leger St, Boucherville, Quebec, J4B 7K8, Canada.Manager Regulatory Affairs

Sabora, Fin. Sabora Pharma Oy, Hiisimetsänkatu 40, 03600 Karkkila, Finland.
url: www.saborapharm.fi

SAD, Denm. See *Amternes, Denm.*

Safeline, S.Afr. See *Sandoz, S.Afr.*

Safetec, Canad. See *Safetec, USA.*

Safetec, USA. Safetec of America Inc., 887 Kensington Ave, Buffalo, NY 14215-2720, USA.

Safire, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Saga, India. Saga Laboratories, Plot No.1409, Phase III GIDC Estate, Vatva, Ahmedabad 382 445, India.

Sage, Canad. See *Sage, USA.*

Sage, USA. Sage Products Inc., 3909 Three Oaks Rd, Cary, IL 60013, USA.

Sager, Hung. Sager Pharma Kft, Pálya u 9, 1012 Budapest, Hungary.

Sagitta, Cz. See *Sagitta, Ger.*

Sagitta, Ger. Sagitta Arzneimittel GmbH, Frühlingstr. 7, Postfach: 1262, 83618 Feldkirchen-Westerham, Germany.

Sagmel, Rus. Sagmel Inc., Kashenkin Lug ul. 4, et. 5, 127427 Moscow, Russia.
url: www.sagmel.ru

Sahabat, Indon. Sahabat Lingkungan Hidup, Jl Embong Malang 80, Subaraya, Indonesio.

Sahar, Philipp. Sahar Int'l Trading Inc., 354 Aguirre Ave, Phase 3, BF Homes, Parañaque City, Philippines.
url: www.saharint.com

Sahin, Turk. See *Munir, Turk.*

Saibaoer, China. Saibaoer Pharmaceutical Co. Ltd, Shenzhen, China.

Saida, China. Saida Biological Pharmaceutical Co. Ltd, Shanghai, China.

Sailike, China. Sailike Pharmaceutical Co. Ltd, Hainan, China.

Sailuojin, China. Sailuojin Pharmaceutical Co. Ltd, China.

Saimirra, Malaysia. See *Medidata, Malaysia* and *Zyfas, Malaysia.*

Saimirra, Singapore. See *Zyfas, Singapore.*

Sain, India. Sain Medicaments Pvt Ltd, 10 HVES Building, Sultan Bazar, Hyderabad 500 095, Andhra Pradesh, India.

Sainuo, China. Sainuo Biopharmaceutical Co. Ltd, China.

Sairaalapalvelu, Fin. Suomen Sairaalapalvelu Oy, Vattuniemenranta 2, 00210 Helsinki, Finland.

Saisheng, China. Saisheng Pharamceutical Co. Ltd, Beijing, China.

Saite, China. Saite Phormaceutical Co. Ltd., 205 South State Road, Shandong Economic Development Zone, Xintai, Shandong, 271200, China.
url: www.sdlkst.com

Saiwei, China. Saiwei Pharmaceutical Co. Ltd, Chongqing, China.

Sal-Bert, Hung. Sal-Bert Kft, József A u. 82, 3304 Eger, Hungary.
url: www.gyogy-salbert.hu

Salcura, UK. Salcura Ltd, Europarc Innovation Centre, Innovation Way, Grimsby, DN37 9TT, UK.
url: www.salcura.naturalhealthbureau.co.uk

Salf, Ital. Salf Laboratorio Farmacologico S.p.A., Via G. Marconi 2, 24069 Cenate Sotto (BG), Italy.
url: www.salfaspa.it

Salfarm, Denm. Salfarm Danmark A/S, Fabriksvej 21, 6000 Kolding, Denmark.
url: www.salfarm.dk

Salix, USA. Salix Pharmaceuticals Inc., 1700 Perimeter Park Drive, Morrisville, NC 27560-8404, USA.
url: www.solix.com

Salmon, Switz. Salmon Pharma, St Jakobs-Strasse 110, Postfach, 4002 Basle, Switzerland.

Salonpas, UK. Salonpas (UK) Ltd, Unit B, 32a Eveline Rd, Mitchum, Surrey, CR4 3LE, UK.

Salters, S.Afr. See *Adcock Ingram, S.Afr.*

Salubris, China. Salubris Pharmaceutical Co. Ltd, Shenzhen, China.

Salud, India. Salud Care Pvt Ltd, 172B Manicktala Main Rd, Kolkata 700 054, India.
url: www.saludcare.co.in

Salus, Canad. See *Flora, Canad.*

Salus, Denm. See *Tjellesen, Denm.*

Salus, Fin. See *Salus, Ger.*

Salus, Ger. Salus Pharma GmbH, Otto-von-Steinbeis-Str. 16, 83052 Bruckmühl, Germany.
url: www.saluspharma.de

Salus, Ital. Salus Researches S.p.A., Via Aurelia 58, 00100 Rome (RM), Italy.

Salus, Mex. Laboratorios Salus S.A. de C.V., KM 22.5 Carretera Guadalajara Morelia, Jalisco Zuniga, 45640 Guadalajara, Jalisco, Mexico.

Salus, Pol. Salus International Sp. zo.o., ul. Mtyńska 3, 40-098 Katowice, Poland.
url: www.salusint.com.pl

Salus, UK. Salus (UK) Ltd, 17 Grosvenor Grange, Woolston, Warrington, WA1 4SF, UK.
url: www.salusuk.com

Salushaus, Ger. Salus-Haus Dr. med. Otto Greither Nachf. GmbH & Co KG, Bahnhofstr. 24, 83052 Bruckmühl, Germany.
url: www.salus.de

Salusif, Port. Salusif, Lda, Rua do Centro Cultural 10 r/c, 1700 Lisbon, Portugal.

Salutas, Cz. See *Salutas, Ger.*

Salutas, Ger. Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany.
url: www.salutas.de

Salutas, Philipp. See *Diethelm, Philipp.*

Salutas, Singapore. See *Novem, Singapore.*

Salvat, Fin. See *Salvat, Spain.*

Salvat, Neth. See *Salvat, Spain.*

Salvat, Spain. Laboratorios Salvat SA, Gall 30-36, Esplugas de Llobregat, 08950 Barcelona, Spain.
url: www.salvatlab.es

Sam Chun Dang, Hong Kong. See *Ebewe, Hong Kong.*

Sam Chun Dang, Malaysia. See *Zyfas, Malaysia.*

Sam Chun Dang, Philipp. See *Medbridge, Philipp.*

Sam Chun Dang, Singapore. See *Zyfas, Singapore.*

SAM Nordic, Fin. S Ahlen Medical Nordic (SAM Nordic), Eteläesplanadi 24, 00130 Helsinki, Finland.
url: www.samnordic.se

Samaritan, Irl. Samaritan Pharmaceuticals Ireland Inc. Ltd, Athlone, Ireland.

Samarth, India. Samarth Pharma Pvt Ltd, Ram Mandir Rd, Goregaon (W), Mumbai 400 104, India.

Samarth, Philipp. See *Pharmawealth, Philipp.*

Sambrook, Gr. Sambrook Pharmaceuticals AE, Kazantzakis & Ag., 135 61 St Anargyroi, Greece.

Samchully, Malaysia. See *Zyfas, Malaysia.*

Samchully, Singapore. See *Zyfas, Singapore.*

Sameko, Neth. Sameko Farma BV, Archimedesweg 2, 2333 CN Leiden, Netherlands.

Samik, Singapore. See *Advanced, Singapore.*

Samjin, Philipp. See *Metro, Philipp.*

Samjin, Singapore. See *Zyfas, Singapore.*

Samnam, Singapore. See *Pharmaforte, Singapore.*

Sam-On, Israel. Meditec/Sam-On Ltd, P.O. Box 1224, Bat-Yam 59602, Israel.
url: www.meditec.co.il

Samson-Med, Rus. Samson-Med, Moscow Highway Dom 13, 196158 Saint-Petersburg, Russia.
url: www.samson-med.com.ru

Samuel, Cz. Archie Samuel sro, Slunná 16, 617 00 Brno, Czech Republic.

Samuel, Neth. See *Samuel, Cz.*

Samuelow, Israel. D Samuelow Importing & Marketing Ltd, 5 Hayetzira St, Ra'Anana, 43663, Israel.

Samyang, Singapore. See *Sime Darby, Singapore.*

SAN, Neth. Samenwerkende Apothekers Nederland BV, Europalaan 2, 3526 KS Utrecht, Netherlands.

San Ai, China. San Ai Pharmaceutical Co Ltd, Fujian, China.

San Carlo, Ital. San Carlo Farmaceutici S.r.l., Via Procoio 28, 00065 Fiano Romano (RM), Italy.

San Ceferino, Arg. San Ceferino SA, Corrientes 453/67, (5900) Villa Maria, Cordoba, Argentina.

San Jin, China. San Jin Pharmaceutical Co. Ltd, Guilin, Hunan, China.

San Lian, China. San Lian Pharmaceutical Co. Ltd, Harbin, China.

San Marino, Philipp. San Marino Lab Corp., 25 Kabignayan cor Banawe St, Quezon City, Philippines.

Sanabo, Port. See *Novartis, Port.*

Sanamed, Austria. Sanamed GmbH, Rudolf Waisenhorngasse 32, A-1230 Vienna, Austria.

Sanat, India. Sanat Products Ltd, 3rd Floor Sagar Plaza, Laxmi Nagar Distt. Centre, Vikas Marg, New Delhi 110 092, India.
url: www.sanat.co.in

Sanavita, Ger. Sanavita Pharmaceuticals GmbH, Lohstrasse 2, 59368 Werne, Germany.
url: www.sanavita.net/en

Sanbe, Indon. Sanbe Farma PT, Jl Taman Sari 10, Bandung 40116, Jawa Barat, Indonesia.

Sanbe, Philipp. See *Endure, Philipp.*

Sanbe, Singapore. See *Joyson, Singapore.*

Sancai, China. Sancai Medicine Group, Guangdong, China.

Sanchao, China. Sanchao Pharmaceutical Co. Ltd, 288 Guandian Economic Development Zone, Mingguang, Anhui, China.
url: www.ahsch.com

Sancilio, USA. Sancilio & Co Inc., 3874 Fiscal Court, Suite 200, Riviera Beach, Florida, FL 33404, USA.
url: www.sancilio.com

Sancor, Arg. Sancor Coop. Unidas Ltdas, Tacuari 202 Pisa 3, 1071 Buenos Aires, Argentina.

Sanderson, Chile. Laboratorio Sanderson SA, Carlos Fernandez 244, Santiago, Chile.

Sandersons, UK. Sandersons (Chemists) Ltd, 37 Oakwood Rise, Heaton, Bolton, BL1 5EE, UK.

Sandipro, Belg. See *Nycomed, Belg.*

Sandoz, Arg. Sandoz SA, Cramer 4130, 1429 Buenos Aires, Argentina.

Sandoz, Austral. Sandoz P/L, P.O. Box 688, North Ryde, NSW 1670, Australia.

Sandoz, Austria. See *Novartis, Austria.*

Sandoz, Belg. See *Novartis, Belg.*

Sandoz, Braz. Sandoz do Brasil Industria Farmaceutica Ltda, Rod Celso Garcia Cid PR 445 KM 87, 86185520 Cambé Gleba-Jacutinga, Brazil.

Sandoz, Canad. Sandoz Canada Inc., Pharmaceutical Division, 385 boul. Bouchard, Dorval, Quebec, H9R 4P5, Canada.

Sandoz, China. Sandoz China Shanghai Novartis Trading Ltd, Huaihai Plaza Room 801, 1045 Huoi Hai Rd, Shanghai 200031, China.
url: www.sandoz.com.cn

Sandoz, Cz. Sandoz, Jeseniova 30, 130 00 Prague 3, Czech Republic.
url: www.sandoz.cz

Sandoz, Denm. Sandoz A/S, Edvard Thomsens Vej 14, DK-2300 Copenhagen S, Denmark.
url: www.sandoz.dk

Sandoz, Fin. See *Novartis, Fin*

Sandoz, Fr. Sandoz, 49 avenue Georges-Pompidou, 92593 Levallois-Perret cdx, France.
url: www.sandoz.fr

Sandoz, Ger. Sandoz Pharmaceuticals GmbH, Raiffeisenstr. 11, 83607 Holzkirchen, Germany.
url: www.sandoz.de

Sandoz, Gr. See *Novartis, Gr.*

Sandoz, Hong Kong. See *Hind Wing, Hong Kong.*

Sandoz, Hung. See *Novartis, Hung.*

Sandoz, India. Sandoz Pvt Ltd, Peninsula Corporate Park, 7th Floor Tower 1, G Kadam Marg, Lower Parel, Mumbai, 400 013, India.

Sandoz, Indon. Sandoz Indonesia PT, Jl. TB. Simatupang, Kp. Gedong, Pasar Reba, Jakarta Timur 13760, DKI Jaya, Indonesia.
url: www.sandoz.com

Sandoz, Irl. See *Novartis, Irl.*

Sandoz, Israel. See *Novartis, Israel.*

Sandoz, Ital. See *Novartis, Ital.*

Sandoz, Malaysia. Sandoz Marketing Office, Lifung Ctr, Lot 6 Persiaran Perusahaan, Seksyen 23, Kawasan Persahaan, 40300 Shah Alam, Selangor, Malaysia.

Sandoz, Mex. Sandoz, Div. Novartis Farmaceutica SA de CV, Augusto Rodin 128, 3730 San Juan Mixcoac, Mexico DF, Mexico.

Sandoz, Neth. See *Novartis, Neth.*

Sandoz, Norw. Sandoz AS, Jernbanev. 4, 1400 Ski, Norway.
url: www.sandoz.no

Sandoz, Philipp. See *Novartis, Philipp.*

Sandoz, Pol. See *Iek, Pol.*

Sandoz, Port. See *Novartis, Port.*

Sandoz, Rus. See *Sanofi-Aventis, Rus.*

Sandoz, S.Afr. Sandoz (Division of Novartis SA (Pty) Ltd), 72 Steel Rd, Spartan Kempton Park, South Africa.
url: www.sandoz.co.za

Sandoz, Singapore. See *FP, Singapore.*

Sandoz, Spain. See *Novartis, Spain.*

Sandoz, Swed. See *Novartis, Swed.*

Sandoz, Switz. Sandoz Pharmaceuticals AG, Schachenstrasse 24, Postfach, 5012 Schanenwerd, Switzerland.

Sandoz, Thai. See *Novartis, Thai.*

Sandoz, Turk. Sandoz İlaç San. ve Tic. AS, Küçükbakkalköy Mah. Şehit Şakir Elkovan Cad. No. 2, Kadiköy, Istanbul, Turkey.

Sandoz, UK. Sandoz Pharmaceuticals, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.

Sandoz, Ukr. Sandoz Pharmaceuticals d.d., Borshchagovskaya Street, 145, Kiev, 03056, Ukraine.
url: www.sandoz.com

Sandoz, USA. See *Novartis, USA.*

Sandoz, Venez. See *Novartis, Venez.*

Sandoz Consumer, USA. See *Novartis Consumer, USA.*

Sandoz Nutrition, Port. See *Novartis Consumer, Port.*

Sandoz Nutrition, USA. See *Novartis Nutrition, USA.*

Sandoz OTC, Switz. See *Novartis, Switz.*

Sanfer, Mex. Laboratorios Sanfer S.A. de C.V., Calz. de Tlalpan No. 550, Col. Moderna, Deleg. Benito Juarez, 03510 Mexico D.F., Mexico.
url: www.sanfer.com.mx

Sang, Thai. Sang Thai, 148/19-21 Nanglinjee Rd, Tungmahamek, Bangkok 10120, Thailand.

Sang Udom, Thai. Sang Udom Pharmacy Lp, 24-26 Songsawad Rd, Samyek, Sampantawong, Bangkok 10100, Thailand.

Sang-A, Malaysia. See *Sun, Malaysia.*

Sang-A, Singapore. See *Sime Darby, Singapore.*

Sang-A Pharm, Singapore. See *Sime Darby, Singapore.*

Sanghai, China. Sanghai Pharmaceutical Co. Ltd, Nanchang, Jiangxi, China.

Sanghiang, Indon. Sanghiang Perkasa/Morinaga, Gedung Graha Kirana, Lt 5, Suite 501, Jl Yos Sudarso Kav 88, Jakarta Utara 13260, DKI Jaya, Indonesia.

Sangstat, Hong Kong. See *Aventis, Hong Kong.*

Sangstat, Malaysia. See *Summit, Malaysia.*

Sangstat, Neth. SANGSTAT BV, Bovenkerkerweg 6-8, 1185 XE Amstelveen, Netherlands.
url: www.sangstat.com

Sangstat, Singapore. See *Summit, Singapore.*

Sangstat, UK. See *Genzyme, UK.*

Sangstat, USA. See *Genzyme, USA.*

Sangtian, China. Sangtian Pharmaceutical Co. Ltd, Chongqing, China.

Sanhome, China. Sanhome Pharmaceutical Co. Ltd, 16th Floor Science & Technology Building, 222 Zhujiang Rd, Nanjing 210018, China.
url: www.sanhome.com

Sanico, Belg. Sanico S.A., Industriezone 4, Veedijk 59, 2300 Turnhout, Belgium.

Sanico, Switz. See *Uhlmann-Eyraud, Switz.*

Sanify, India. Sanify Healthcare Pvt Ltd, Opp.Hotel Marc Royale, Zirakpur Kalka Highway, Zirakpur, Punjab 140 603, India.
url: www.sanifyhealthcare.com

Sani-Marc, Canad. Sani-Marc Inc., 42 rue de l'Artisan, Victoriaville, Quebec, G6P 7E3, Canada.

Saninter, Port. Saninter, SA, Av Duque d'Ávila no 193, 1050-082 Lisbon, Portugal.

Sanis, Canad. Sanis Health inc., Suite 102, 333 Champlain St, Dieppe, New Brunswick, E1A 1P2, Canada.

Sanitalia, Ital. Sanitalia S.n.c. di Battaglia & C., Strada dei Tadini 5, 10131 Turin (TO), Italy.

Sanitari, Ital. Sanitari Cesero Snc, Via Everado 3/A, Fontane di Villorba, 31020 Treviso (TV), Italy.

Sanitas, Arg. Instituto Sanitas Arg. SACIPQ y M., Saladillo 2452, 1440 Buenos Aires, Argentina.

Sanitas, Chile. Instituto Sanitas SA, Avda Americo Vespucio 1260, Quilicura, Santiago, Chile.

Sanitas, Ital. Sanitas Lab. Chimico Farmaceutico S.r.l., Via Guala 4, 15057 Tortona (AL), Italy.
url: www.sanitas-farma.it

Sanitas, Port. See *Menarini, Port.*

Sanjing, China. Sanjing Pharmaceutical Co Ltd, China.

Sanjing Aifuxi, China. Sanjing Aifuxi, China.

Sanjing Hailing, China. Sanjing Hailing Pharmaceutical Co. Ltd, Harbin, China.

Sanjing Qianhe Wangkui, China. Sanjing Qianhe Wangkui Pharmaceutical Co. Ltd, Harbin, China.

SanJiu, China. China Resources Sanjiu Medical & Pharmaceutical Co Ltd, 1028 North Central Ave, Silver Lake intersection, Luohu District, Shenzhen City 518029, China.
url: www.999.com.cn

Sanjiu Aidefu, China. Sanjiu Aidefu Pharmaceutical Co. Ltd, Hebei, China.

SanJiu JiShi, China. Sanjiu Jishi Bio-Pharmaceutical Co., Ltd, P.O. Box 1, Gucheng, Dingxing, Baoding, Hebei, 072656, China.
url: www.999jishi.com

Sanjiu Yimin, China. Sanjiu Yimin Pharmaceutical Co. Ltd, 20 Fuxin St (W), Chongqing, Shandong, 250300, China.
url: www.999drug.com.cn

Sanjivani, India. Sanjivani Parenteral Ltd, 205 PN Kothari Industrial Estate, LBS Marg, Bhandup (West), Mumbai 400078, India.
url: www.sanjivani.co.in

Sanjivani, Rus. See *Sanjivani, India.*

Sankyo, Austral. See *Pharmacia, Austral.*

Sankyo, Austria. Sankyo Pharmazeutika Austria GmbH, Effingergasse 21, A-1160 Vienna, Austria.
url: www.sankyo-pharma.com

Sankyo, Belg. Sankyo Pharma Belgium SA, Parc Scientifique Fleming LLN, Rue Fond Jean Paques 5, 1348 Louvain-la-Neuve, Belgium.
url: www.sankyo-pharma.com

Sankyo, Braz. Sankyo Pharma Brasil Ltda, Alameda Xingu 706, 06455-960 Alphaville-Barueri, SP, Brazil.
url: www.sankyo.com.br

Sankyo, Cz. See *IBI International, Cz.*

Sankyo, Denm. See *Gea, Denm.*

Sankyo, Fr. See *Fornet, Fr.*

Sankyo, Ger. See *Daiichi Sankyo, Ger.*

Sankyo, Hong Kong. See *Hing Ah, Hong Kong* and *Keller, Hong Kong.*

Sankyo, Hung. See *Budapharma, Hung.*

Sankyo, Irl. See *Allphar, Irl.*

Sankyo, Israel. See *Daiichi Sankyo, Jpn.*

Sankyo, Ital. See *Daiichi Sankyo, Ital.*

Sankyo, Neth. See *Will-Pharma, Neth.*

Sankyo, Norw. See *Weifa, Norw.*

Sankyo, NZ. See *Wilson, NZ.*

Sankyo, Philipp. See *Diethelm, Philipp.*

Sankyo, Pol. Sankyo Pharma, ul. Cybernetyki 11, 02-677 Warsaw, Poland.

Sankyo, Port. Sankyo Pharma Portugal, Lda, Lagoas Park, Edificio 11, 2740-270 Porto Salvo, Portugal.
url: www.sankyo-pharma.com

Sankyo, Singapore. See *DKSH, Singapore.*

Sankyo, Spain. See *Daiichi Sankyo, Spain.*

Sankyo, Switz. Sankyo Pharma (Schweiz) AG, Gewerbestrasse 16, 8800 Thalwil, Switzerland.
url: www.sankyopharma.ch

Sankyo, Thai. Thai Sankyo Co. Ltd, 18 Fl, Tipco Tower, 118/1 Rama 6 Rd, Phayathai, Bangkok 10400, Thailand.
url: www.sankyo-pharma.com

Sankyo, UK. Sankyo Pharma UK Ltd, Sankyo House, Reptan Place, White Lion Rd, Amersham, Buckinghamshire, HP7 9LP, UK.
url: www.sankyo-pharma.com

Sankyo, USA. Sankyo Pharma, Two Hilton Court, Parsippany, NJ 07054, USA.
url: www.sankyopharma.com

Sankyo, Venez. Sankyo Pharma Venezuela S.A., 1ra. Transversal de Boleita Sur, Edificio Voge B, 4to. piso, local 4-A, Caracas 1070-A, Venezuela.
url: www.sankyo.com.ve

Sankyo Luitpold, Braz. See *Sankyo, Braz.*

Sanli, Turk. Sanli İlaç San. A.Ş., Atatürk Cad. No: 142, Pasaport, İzmir, Turkey.
url: www.sanliilac.com.tr

Sanmenxia Sinoway, China. Sanmenxia Sinoway Pharmaceutical Co. Ltd, Soong Rd East, Sanmenxia, China.

Sano, Turk. Sano, Turkey.

Sanobia, Port. Saniôbia, Lda, Rua Joaquim Paço d'Darcos 11, 1500-365 Lisbon, Portugal.

Sanochemia, Austria. Sanochemia Pharmazeutika AG, Boltzmanngasse 9a-11, A-1091 Vienna, Austria.
url: www.sanochemia.at

Sanochemia, Cz. See *Sanochemia, Austria.*

Sanochemia, Ger. Sanochemia Diagnostics Deutschland GmbH, Stresemannallee 4c, 41460 Neuss, Germany.
url: www.sandiag.de

Sanochemia, Hung. See *Sanochemia, Ger.*

Sanochemia, Irl. See *Sanochemia, Austria.*

Sanochemia, Ital. See *Molteni, Ital.*

Sanochemia, Port. See *Sanochemia, Austria.*

Sanochemia, Spain. See *Sanochemia, Austria.*

Sanochemia, Switz. Sanochemia Diagnostics International Ltd, Baarerstrasse 96/PF 2252, 6302 Zug, Switzerland.
url: www.sanochemia.com

Sanochemia, UK. Sanochemia UK Ltd, Argentum, 510 Bristol Business Park, Coldharbour Lane, Bristol, Avon, BS16 1EJ, UK.
url: www.sanochemia.de

Sanochemica, Austria. Sanochemica Pharmazeutica AG, Boltzmanngasse 11, 1090 Wenen, Austria.

Sanochemica, Neth. See *Sanochemica, Austria.*

Sanofi, Canad. Sanofi Canada, 2150 St Elzear Blvd West, Laval, Quebec, H7L 4A8, Canada.
url: www.sanofi.ca

Sanofi, China. Sanofi China, Room 3108, Plaza 66, 1266 Nanjing West Road, Shanghai 200040, China.
url: www.sanofi.cn

Sanofi, Denm. See *Sanofi-Aventis, Denm.*

Sanofi, Irl. See *Sanofi-Aventis, Irl.*

Sanofi, Israel. See *BMS, Israel.*

Sanofi, Neth. See *Sanofi Synthelabo, Neth.*

Sanofi, Switz. See *Sanofi-Aventis, Switz.*

Sanofi, Thai. See *Sanofi Synthelabo, Thai.*

Sanofi, UK. Sanofi UK, 1 Onslow St, Guildford, Surrey, GU1 4YS, UK.
url: www.sanofi.co.uk

Sanofi, USA. See *Sanofi-Aventis, USA.*

Sanofi BMS, Norw. See *Sanofi-Aventis, Norw.*

Sanofi Consumer, Canad. See *Sanofi, Canad.*

Sanofi Labaz, Neth. See *Sanofi Synthelabo, Neth.*

Sanofi Midy, Neth. See *Sanofi Synthelabo, Neth.*

Sanofi Omnimed, S.Afr. See *Braun, S.Afr.*

Sanofi Pasteur, Arg. See *Sanofi-Aventis, Arg.*

Sanofi Pasteur, Austral. Sanofi Pasteur Pty Ltd, Talavera Corporate Centre, Building D, 12-24 Talavera Rd, Macquarie Park, NSW 2113, Australia.

Sanofi Pasteur, Austria. Sanofi Pasteur MSD GmbH, Campus 21, Europaring F11/402, A-2345 Brunn am Gebirge, Austria.
url: www.spmsd.com

Sanofi Pasteur, Belg. Sanofi Pasteur MSD NV, Ave Jules Bordet 13, 1140 Brussels, Belgium.
url: www.apmsd.com

Sanofi Pasteur, Braz. Sanofi Pasteur Ltda, Rua do Rócio 351, 10 andar, 04552-905 São Paulo, Brazil.

Sanofi Pasteur, Canad. Sanofi Pasteur Ltd, 1755 Steeles Ave West, Toronto, Ontario, M2R 3T4, Canada.

Sanofi Pasteur, Chile. See *Sanofi-Aventis, Chile.*

Sanofi Pasteur, China. Sanofi Pasteur, 7th Floor, 112 Jian Guo Lu, Chaoyang District, Beijing 100022, China.
url: www.sanofipasteur.cn

Sanofi Pasteur, Cz. See *Sanofi-Aventis, Cz.*

Sanofi Pasteur, Denm. Sanofi Pasteur MSD, Parallelvej 12, 2.sal, 2800 Lyngby, Denmark.
url: www.spmsd.com

Sanofi Pasteur, Fin. See *Sanofi-Aventis, Fin.*

Sanofi Pasteur, Fr. Sanofi Pasteur MSD SNC, 8 rue Jonas-Salk, 69367 Lyon cdx 07, France.
url: www.spmsd.fr

Sanofi Pasteur, Ger. Sanofi Pasteur MSD GmbH, Paul-Ehrlich-Str. 1, 69181 Leimen, Germany.
url: www.spmsd.com

Sanofi Pasteur, Gr. See *Sanofi Pasteur, Fr.*

Sanofi Pasteur, Hong Kong. See *Sanofi-Aventis, Hong Kong.*

Sanofi Pasteur, Hung. See *Sanofi-Aventis, Hung.*

Sanofi Pasteur, Indon. Sanofi Pasteur, Aventis Building - FL.IV, Jalan Jendral A. Yani, Pulo Mas, Jakarta 13210, Indonesia.
url: www.sanofipasteur.com

Sanofi Pasteur, Irl. Sanofi Pasteur MSD Ltd, c/o Allphar Services Ltd, Belgard Rd, Tallaght, Dublin 24, Ireland.
url: www.spmsd.com

Sanofi Pasteur, Israel. See *Sanofi-Aventis, Israel.*

Sanofi Pasteur, Ital. Sanofi Pasteur MSD SpA, Via degli Aldobrandeschi 15, 00163 Rome (RM), Italy.
url: www.spmsd.it

Sanofi Pasteur, Jpn. Sanofi Pasteur, Tokyo Opera City Tower, 3-20-2 Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1488, Japan.
url: www.sanofipasteur.jp

Sanofi Pasteur, Malaysia. See *Sanofi-Aventis, Malaysia.*

Sanofi Pasteur, Mex. Sanofi Pasteur SA de CV, AV. Universidad 1738, 4000 Coyoacán, Mexico.

Sanofi Posteur, Neth. Sanofi Pasteur MSD NV, Taurusavenue 31a, 2132 LS Hoofddorp, Netherlands.
url: www.spmsd.com

Sanofi Pasteur, Norw. Sanofi Pasteur MSD, Hamangskogen 60, 1338 Sondvika, Norway.
url: www.spmsd.com

Sanofi Pasteur, Philipp. Sanofi Pasteur, 4/F Feliza Bldg, 108 V A Rufino St, Legaspi Village, 1229 Makati City, Philippines.
url: www.sanofipasteur.com.ph

Sanofi Pasteur, Pol. Sanofi Pasteur Sp z o o, ul. Bonifraterska 17, 00-203 Warsaw, Poland.
url: www.sanofipasteur.pl

Sanofi Pasteur, Port. Sanofi Pasteur MSD S.A., Estrada de Alfragide 67, Lote F Sul, Piso 2 - Alfrapark, 2610-008 Amadora, Portugal.

Sanofi Pasteur, Rus. Sanofi Pasteur, 22 Tverskaya St, Business Centre Summit, 125009 Moscow, Russia.
url: www.sanofipasteur.ru

Sanofi Pasteur, S.Afr. Sanofi Pasteur, Private Bag X207, Midrand 1683, Johannesburg, South Africa.
url: www.sanofipasteur.co.za

Sanofi Pasteur, Singapore. See *Sanofi-Aventis, Singapore.*

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url: www.spmsd.com

Sanofi Pasteur, Swed. Sanofi Pasteur MSD, Vretenvägen 10, 171 54 Salna, Sweden.
url: www.spmsd.se

Sanofi Pasteur, Switz. Sanofi Pasteur MSD AG, Lattichstrasse 6, 6340 Baar, Switzerland.
url: www.sanofipasteur.com

Sanofi Posteur, Thai. Sanofi Pasteur Ltd, 4 Fl, VTT I Bldg, 3195/9 Rama IV Rd, Klongtoey, Bangkok 10110, Thailand.
url: www.sanofipasteurthailand.com

Sanofi Pasteur, Turk. Sanofi Pasteur Aşi Ticaret AS, Cemil Aslan Güder Cad. Çigdem Sok. No 3, Gayrettepe, Istanbul, Turkey.

Sanofi Pasteur, UK. Sanofi Pasteur MSD Ltd, Mallards Reach, Bridge Ave, Maidenhead, Berkshire, SL6 1QP, UK.
url: www.spmsd.co.uk

Sanofi Pasteur, USA. Sanofi Pasteur Inc, Discovery Drive, P.O. Box 187, Swiftwater, PA 18370-0187, USA.
url: www.sanofipasteur.us

Sanofi Pasteur, Venez. See *Sanofi-Aventis, Venez.*

Sanofi Synthelabo, Arg. See *Sanofi-Aventis, Arg.*

Sanofi Synthelabo, Austral. See *Sanofi-Aventis, Austral.*

Sanofi Synthelabo, Austria. Sanofi-Synthelabo GmbH, Koppstrosse 116, A-1160 Vienna, Austria.
url: www.sanofi-synthelabo.at

Sanofi Synthelabo, Belg. See *Sanofi-Aventis, Belg.*

Sanofi Synthelabo, Braz. Sanofi Synthelabo Farmacêutica Ltda, Av. Brasil 22.155, 21670-000 Rio de Janeiro, RJ, Brazil.
url: www.sanofi-synthelabo.com.br

Sanofi Synthelabo, Canad. See *Sanofi, Canad.*

Sanofi Synthelabo, Chile. See *Sanofi-Aventis, Chile.*

Sanofi Synthelabo, Cz. See *Sanofi-Aventis, Cz.*

Sanofi Synthelabo, Denm. See *Sanofi-Aventis, Denm.*

Sanofi Synthelabo, Fin. Sanofi-Synthelabo Oy, Vatuniemenranta 2, 00210 Helsinki, Finland.
url: www.sanofi-synthelabo.com

Sanofi Synthelabo, Fr. See *Sanofi-Aventis, Fr.*

Sanofi Synthelabo, Ger. See *Sanofi-Aventis, Ger.*

Sanofi Synthelabo, Gr. See *Sanofi-Aventis, Gr.*

Sanofi Synthelabo, Hong Kong. See *Sanofi-Aventis, Hong Kong.*

Sanofi Synthelabo, Hung. See *Sanofi-Aventis, Hung.*

Sanofi Synthelabo, India. Sanofi Synthelabo, Gandhi Mansion, 20 Altamount Road, Mumbai 400 026, India.

Sanofi Synthelabo, Indon. See *Sanofi-Aventis, Indon.*

Sanofi Synthelabo, Irl. See *Sanofi-Aventis, Irl.*

Sanofi Synthelabo, Israel. See *CTS, Israel.*

Sanofi Synthelabo, Ital. See *Sanofi-Aventis, Ital.*

Sanofi Synthelabo, Mex. Sanofi-Synthelabo de Mexico S.A. de C.V., Km 37.5 Autopista Mexico-Qro, 54730 Cuautitlan Izcali, Mexico.
url: www.sanofi-synthelabo.com.mx

Sanofi Synthelabo, Neth. Sanofi Synthelabo, Govert Van Wijnkade 48, 3144 EG Maassluis, Netherlands.
url: www.sanofi-synthelabo.nl

Sanofi Synthelabo, Norw. Sanofi-Synthelabo AS, Leif Tronstads plass 4, Postboks 413, 1302 Sandvika, Norway.
url: www.sanofi-synthelabo.com

Sanofi Synthelabo, NZ. See *Sanofi-Aventis, NZ.*

Sanofi Synthelabo, Philipp. See *Sanofi-Aventis, Philipp.*

Sanofi Synthelabo, Port. See *Sanofi-Aventis, Port.*

Sanofi Synthelabo, Rus. See *Sanofi-Aventis, Rus.*

Sanofi Synthelabo, S.Afr. See *Sanofi-Aventis, S.Afr.*

Sanofi Synthelabo, Spain. See *Sanofi-Aventis, Spain.*

Sanofi Synthelabo, Swed. Sanofi-Synthelabo AB, Box 14142, 167 14 Bromma, Sweden.
url: www.sanofi-synthelabo.com

Sanofi Synthelabo, Switz. See *Sanofi-Aventis, Switz.*

Sanofi Synthelabo, Thai. Sanofi-Synthelabo (Thailand) Ltd, 9-11 Fl, Gypsum Metropolitan Tower, 539/2 Sri-Ayudhya Rd, Phyathai, Rajthevee, Bangkok 10400, Thailand.
url: www.sanofi-synthelaboamo.com

Sanofi Synthelabo, Turk. See *Sanofi-Aventis, Turk.*

Sanofi Synthelabo, UK. See *Sanofi, UK.*

Sanofi Synthelabo, USA. See *Sanofi-Aventis, USA.*

Sanofi Synthelabo, Venez. See *Sanofi-Aventis, Venez.*

Sanofi Synthelabo OTC, Fr. Sanofi Synthelabo OTC, 9 rue du President-Allende, 94258 Gentilly cdx, France.
url: www.sanofi-synthelabo.com

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Sanofi Torrent, India. See *Torrent, India.*

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Sanofi Winthrop, UK. See *Sanofi, UK.*

Sanofi Winthrop, USA. See *Sanofi-Aventis, USA.*

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url: www.aventispharma.com

Sanofi-Aventis, Austral. Sanofi-Aventis, Talavera Corporate Centre, Building D, 12-24 Talavera Rd, Macquarie Park, NSW 2113, Australia.
url: www.sanofi-aventis.com.au

Sanofi-Aventis, Austria. Sanofi-Aventis GmbH, Saturn Tower, Leonard Bernstein Strasse 10, A-1220 Vienna, Austria.
url: www.sanofi-aventis.at

Sanofi-Aventis, Belg. Sanofi-Aventis Belgium SA, Twin Squares, Building Navona, Culliganlaan 1C, 1831 Diegem, Belgium.
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Sanofi-Aventis, Braz. Sanofi-Aventis Farmacêutica Ltda, Av Major Sylvio de M Padilha 5200, 05677-000 Ed Atlanta São Paulo, Brazil.

Sanofi-Aventis, Canad. See *Sanofi, Canad.*

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Sanofi-Aventis, Denm. Sanofi-Aventis Denmark A/S, Slotsmarken 13, 2970 Hørsholm, Denmark.
url: www.sanofi-aventis.dk

Sanofi-Aventis, Fin. Sanofi-Aventis Group, Huopalahdentie 24, PL 22, 00351 Helsinki, Finland.
url: www.sanofi-aventis.fi

Sanofi-Aventis, Fr. Sanofi-Aventis, 174 av de France, 75635 Paris cdx 13, France.
url: www.sanofi-aventis.fr

Sanofi-Aventis, Ger. Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt, Germany.
url: www.sanofi-aventis.de

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url: www.sanofi-aventis.hk

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Sanofi-Aventis, Indon. Sanofi-Aventis, Jl Jend Ahmad Yani, Pulo Mas, Jakarta 13210, Indonesia.
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Sanofi-Aventis, Irl. Sanofi-Aventis (Ireland) Ltd, 18 Riverwalk, National Digital Park, Citywest Business Compus, Dublin 24, Ireland.
url: www.sanofi-aventis.com

Sanofi-Aventis, Israel. Sanofi-Aventis Israel, 9 Haomanut St, Netanya 42170, Israel.
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Sanofi-Aventis, Ital. Sanofi-Aventis S.p.A., Viale Bodio 37/B, 20158 Milan (MI), Italy.
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Sanofi-Aventis, Jpn. Sanofi-Aventis, Tokyo Opera City Tower, 20-2 Nishishinjuku 3-chome, Shinjuku-ku, Tokyo 163-1488, Japan.
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url: www.sanofi-aventis.com.my

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url: www.sanofi-aventis.com.mx

Sanofi-Aventis, Neth. Sanofi Aventis Netherlands BV, Kampenringweg 45 DE, 2803 PE Gouda, Netherlands.
url: www.sanofi-aventis.nl

Sanofi-Aventis, Norw. Sanofi-Aventis, Strandv. 15, Postboks 133, 1325 Lysoker, Norway.
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Sanofi-Aventis, NZ. Sanofi-Aventis NZ Ltd, Level 8, James & Wells Tower, Ellerslie, Auckland, New Zealand.
url: www.sanofi-aventis.com

Sanofi-Aventis, Philipp. Sanofi-Aventis Phils Inc., 3/F Feliza Bldg, 108 VA Rufino St, Legaspi Village, 1229 Makati City, Philippines.
url: www.sanofi-aventis.ph

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Sanofi-Aventis, S.Afr. Sanofi-Aventis Pharma (Pty) Ltd, Sanofi-Aventis House, 2 Bond St, Grand Central Ext 1, Midrand 1685, South Africa.
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Sanofi-Aventis, Singapore. Sanofi-Aventis Singapore Pte Ltd, 6 Raffles Quay, 18-00, S-048580, Singapore.
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url: www.sanofi-aventis.se

Sanofi-Aventis, Switz. Sanofi-Aventis (Schweiz) AG, 11 rue de Veyrot, 1217 Meyrin 1/GE, Switzerland.
url: www.sanofi-aventis.ch

Sanofi-Aventis, Thai. Sanofi-Aventis (Thailand) Ltd, 87/2 CRC Tower, 24 Fl All Seasons Place, Wireless Rd, Lampini, Pathumwan, Bangkok 10330, Thailand.
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Sanofi-Aventis, UK. See *Sanofi, UK.*

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Sanofi-Aventis, USA. Sanofi-Aventis Pharmaceuticals, 300 Somerset Corporate Bvld, Bridgewater, NJ 08807-2854, USA.
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Sanofi-Aventis, Venez. Sanofi-Aventis, Edificio Torre la Castellana, Pisos 7 y 8, Avenida Eugenio Mendoza con calle José A. Lamas, Urb. La Costellana, Caracas 1060, Venezuela.
url: www.sanofi-aventis.com

Sanofi-Aventis OTC, Fr. See *Sanofi-Aventis, Fr.*

Sanofi-Aventis OTC, Ital. See *Sanofi-Aventis, Ital.*

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Sanopharma, Hung. Sanopharma Gyogyszerkereskedelmi Rt, Szent Istvan Ter. 6, 5601 Bekescsaba, Hungary.

Sanorania, Ger. See *Lichtenstein, Ger.*

Sanorania, Switz. See *Medipharm, Switz.*

Sanorell, Ger. Sanorell Pharma GmbH & Co., Rechtmurgstr. 27, 72270 Baiersbronn, Germany.
url: www.sanorell.de

Sanova, Austria. Sanova Pharma GmbH, Postfach 3, A-1110 Vienna, Austria.

Sanova, Denm. See *Tjellesen, Denm.*

Sanovel, Rus. See *Sanovel, Turk.*

Sanovel, Turk. Sonovel İlaç San. ve Tic. A.Ş., Büyükdere Cad. Dereboyu Sok., Zağra İş Merkezi C Blok K: 2, Maslak, İstanbul, 80670, Turkey.
url: www.sanovel.com

Sanquin, Austria. See *Sanquin, Neth.*

Sanquin, Cz. See *Sanquin, Neth.*

Sanquin, Fin. Sanquin Oy, Mannerheimintie 5 C, 00100 Helsinki, Finland.
url: www.sanquin.fi

Sanquin, Irl. See *Sanquin, Neth.*

Sanquin, Neth. Sanquin, Plesmanlaan 125, 1066 CX Amsterdam, Netherlands.
url: www.sanquin.com

Sanquin, Pol. See *Sanquin, Neth.*

Sanquin, Port. See *Sanquin, Neth.*

Sanrui, China. Sanrui Pharmaceutical Co. Ltd, Nanjing, China.

Sanshun, China. Sanshun Pharmaceutical Co. Ltd, Shenzhen, China.

SantGall, Arg. Sant Gall Friburg Q.C.I., Av. Brasil 3131/3, 1260 Buenos Aires, Argentina.

Santa, Gr. SANTA N. MPALANOS ABEE, Leof. Dimokratias 145, 136 71 Acharnes, Greece.

Santa, Rus. Santa OOO, a/ya 100, 119311 Moscow, Russia.

Santa, Turk. Santa Farma İlaç San. A.Ş., Okmeydanı Boruçiçeği Sok. No: 20, Şişli, Istanbul, 34382, Turkey.
url: www.santafarma.com

Santarus, USA. Santarus, Inc., 10590 West Ocean Air Drive, Suite 200, San Diego, CA 92130, USA.
url: www.santarus.com

Sante Naturelle, Canad. Santé Naturelle (AG) Ltée, 369 Charles Péguy, La Prairie, Quebec, J5R 3E8, Canada.
url: www.santenaturelle.ca

Santen, Austria. See *Santen, Fin.*

Santen, China. Santen Pharmaceutical (China) Co Ltd, Suzhou Industrial Park, Bay Bridge Lane 169, Suzhou 215026, China.

Santen, Cz. Santen Oy, Business Centre Chronos, Vaclavske nam 66, 110 00 Prague 1, Czech Republic.

Santen, Denm. Santen, Kongeledet 1, 2920 Charlottenlund, Denmark.
url: www.santen.dk

Santen, Fin. Santen Oy, Niittyhaankatu 20, PL 33, 33721 Tampere, Finland.
url: www.santen.fi

Santen, Ger. Santen GmbH, Industriestrasse 1, 82110 Germering, Germany.
url: www.santen.de

Santen, Gr. See *Santen, Fin* and *Santen, Ger.*

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Santen, Indon. See *Ferron, Indon.*

Santen, Jpn. Santen Pharmaceutical Co Ltd, 3-9-19 Shimoshinjo, Higashi-Yodogawa-ku, Osaka 533-8651, Japan.
url: www.santen.co.jp

Santen, Neth. See *Santen, Fin.*

Santen, Norw. Santen Norge, Sjøsenteret Vallø, 3150 Tolvsrod, Norway.
url: www.santen.no

Santen, Philipp. See *Croma, Philipp.*

Santen, Pol. Santen Oy SA, Przedstawicielstwo w Polsce, ul. Bitwy Warszawskiej 1920r 18/107, 02-366 Warsaw, Poland.
url: www.santen.com.pl

Santen, Port. See *Santen, Swed.*

Santen, Rus. Santen AO, Mytnaya ul. 1, pod. 1, et. 6, 117049 Moscow, Russia.
url: www.santen.ru

Santen, Singapore. See *JDH, Singapore.*

Santen, Swed. Santen Pharma AB, Solna torg 3, 171 45 Solna, Sweden.
url: www.santen.se

Santen, Thai. See *Diethelm, Thai.*

Santen, USA. Santen Inc., 555 Gateway Drive, Napa, CA 94558, USA.
url: www.santeninc.com

Santhera, Canad. See *Santhera, USA.*

Santhera, USA. Santhera Pharmaceuticals (USA) Inc., 40 Warren St, Charlestown, MA 02129, USA.
url: www.santhera.com

Santipharma, Port. Santipharma Lda, Portugal.

Santisa, Broz. Santisa Laboratório Farmaceutico S/A, Rua Monsenhor Claro 690, 17015130 Bauru Centro, Sao Paulo, Brazil.

Santiveri, Spain. Santiveri, Encuny 8, 08038 Barcelona, Spain.
url: www.santiveri.es

Sanum-Kehlbeck, Cz. See *Sanum-Kehlbeck, Ger.*

Sanum-Kehlbeck, Ger. Sanum-Kehlbeck GmbH & Co. KG, Hasseler Steinweg 9-12, 27318 Hoya, Germany.
url: www.sanum.com

Sanus, Braz. See *Biolab Sanus, Braz.*

Sanus, Gr. San us, Greece.

Sanval, Braz. Sanval Comércio e Indústria Ltda, Rua Lagrange 401, 04761-050 São Paulo, SP, Brazil.
url: www.sanval.com.br

Sanwa, Jpn. Sanwa Kagaku Kenkyusho Co Ltd, 35 Higashi-Sotobori-cho, Higashi-ku, Nagoya 461-8631, Japan.
url: www.skk-net.com

Sanwei, China. Sanwei Biotech Co Ltd, Shanghai, China.

Sanxia, China. Sanxia Pharmaceutical Co. Ltd, Yichang, China.

Sanye, China. Sanye Pharmaceutical Group Co. Ltd, 46 Jinken Rd, Longhua, Haikou, Hainan, 570226, China.
url: www.sanye.com.cn

Sanyu, China. Sanyu Pharmaceutical Co. Ltd, Shanxi, China.

Sapco, India. Sapco Laboratories, No. 35 Padmavathi Nagar, 2nd Street, Virugambakkam, Chennai 600 092, India.
url: www.sapcolaboratories.com

Saphar, S.Afr. See *Adcock Ingram, S.Afr.*

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Sarabhai Piramal, India. Sarabhai Piramal Pharma Ltd, Dr Vikram Sarabhai Marg, Wadi Wadi, Vadodara 390 007, India.

Sarantis, Gr. GR Sarantis Ltd, Amarousiou-Holandriou 26, 151 25 Maroussi, Greece.

Sarbach, Fr. See *Solvay, Fr.*

Sarget, Fr. See *Viatris, Fr.*

Sarget, Spain. See *Viatris, Spain.*

Sari Husada, Indon. Sari Husada Tbk PT, Cyber 2 Bldg, 15th Fl, Jl HR Rasuna Said, Blok X-5 No 13, Jakarta 12950, Indonesia.

Sark, Ital. See *GSK Consumer, Ital.*

SarPharm, Ital. Sarda Pharmaceuticals S.r.l., Via Castiglione 92/B, 09132 Cagliari (CA), Italy.

Sarthak, India. Sarthak Biotech Pvt Ltd, Plot No 198-A, Sector 3 (HSIIDC), Karr, Karnal 132 001, India.
url: www.sarthakbiotech.net

SATCO, Hung. SATCO Kereskedelmi Kft, Fehérvári út 89-95, 1119 Budapest, Hungary.

Satis, Port. Satis Radioisótopos e Protecções contra Sobretensões Eléctricas Lda, Av. do Forte 4, 2795-502 Carnaxide, Portugal.

Sato, Jpn. Sato Pharmaceutical Co. Ltd, 27 1-chome, Minato-ku, Tokyo 107-0051, Japan.

Sato, Singapore. See *IDS, Singapore.*

Sato, Thai. See *Diethelm, Thai.*

Sauba, Fr. See *GSK, Fr.*

Sauter, Austral. See *Roche, Austral.*

Savage, USA. See *Altana, USA.*

Saval, Chile. Laboratorios Saval SA, Avenida Presidente Eduardo Frei Montalva 4600, Santiago, Chile.
url: www.saval.cl

Savant, Arg. Savant Pharm SA, Ruta Nacional Nro 19 Km. 204, Cordoba, Argentina.

Savi, Mex. Savi Distribuciones SA de CV, Mayas 10, 53150 Naucalpan Sta. Cruz Acatlan, Mexico DF, Mexico.

Savient, USA. Savient Pharmaceuticals Inc., One Tower Center, 14th Floor, East Brunswick, NJ 08816, USA.
url: www.savientpharma.com

Savio, Ital. Istituto Biochimico Nazionale Savio S.r.l., Via E. Bazzano 14, 16019 Ronco Scrivia (GE), Italy.

Saviour, India. Saviour Mediscinces, No 1 Ground Floor Jayshree Building, Jay Raj Nagar, Borivali (W), Mumbai, India.

Savoma, Ital. Savoma Medicinali S.p.A., Via Baganza 2/A, 43100 Parma (PR), Italy.
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Savoy, India. Savoy Biotech, SCF-355 1st Floor, Manimajra, Chandigarh 160 101, India.

Savoy, Singapore. See *Polymedic, Singapore.*

Savoy, UK. See *Alinter, UK.*

Sawai, Jpn. Sawai Pharmaceutical Co. Ltd, 2-30 Miyahara 5-Chome, Yodogawa-ku, Osaka, 532-0003, Japan.
url: www.sawai.co.jp

Say, Turk. Say İlaç San. ve Tic. Ltd. A.Ş., Bağdat Cad., Göker Apt. No: 314, D: 2, Caddebostan, İstanbul, Turkey.

Sayntek, Rus. Sayntek Ltd, ul Kalinina 13, St Petersburg, Russia.

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SBL, Austria. See *SBL, Swed.*

SBL, Canad. See *Crucell, USA.*

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SBL, Neth. See *SBL, Swed.*

SBL, Norw. SBL Vaccin Norge, C. J. Hansensv. 3 A, 2007 Kjeller, Norway.
url: www.sblvaccin.se

SBL, Port. See *SBL, Swed.*

SBL, Swed. SBL Vaccin AB, Lundagatan 2, 105 21 Stockholm, Sweden.
url: www.sblvaccin.se

SC Johnson, UK. SC Johnson Ltd, Frimley Green, Camberley, Surrey, GU16 7AJ, UK.
url: www.scjohnsan.co.uk

Scaglietti, Ital. Scaglietti Srl, Via Tagliamento n 6, 41050 Montale Rangone (MO), Italy.
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Scan, Irl. See *Harn, Thai.*

Scan Biotech, Ukr. See *Alter, Ukr.*

Scan Lab, Thai. See *Harn, Thai.*

Scan-Anida, Pol. Scan-Anida Sp. zo.o., ul. Motyla 26, 30-733 Kraków, Poland.
url: www.scananida.com.pl

Scand Pharm, Denm. See *Scand Pharm, Swed.*

Scand Pharm, Norw. See *Norgesfarma, Norw.*

Scand Pharm, Swed. Scandinavian Pharmaceuticals-Generics AB, Box 23033, 104 35 Stockholm, Sweden.
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Scandinavian Biopharma, Swed. Scandinavian Biopharma Distribution AB, Svärdsvägen 3 B, 182 33 Danderyd, Sweden.

Scandinavian Formulas, USA. Scandinavian Formulas Inc., 140 East Church St, Sellersville, PA 18960, USA.
url: www.scandinavianformulas.com

Scandinavian Health Care, Norw. Scandinavian Health Care AS, Grini Naeringspark 1, 1361 Østerås, Norway.
url: www.shc.no

Scandinavian Laboratories, Pol. See *Marinex, Pol.*

Scandinavian Natural Health & Beauty, USA. Scandinavian Natural Health & Beauty Products Inc., 13 North Seventh St, Perkasie, PA 18944, USA.
url: www.scandinaviannaturals.com

Scandipharm, Arg. Difa-Axcan Scandipharm, Achaval Rodriguez 82, 5000 Nueva Cordoba, Cordoba, Argentina.

Scandipharm, Israel. See *Megapharm, Israel.*

Scandipharm, USA. See *Axcan, USA.*

Scania, Swed. See *Nordiska, Swed.*

Scanpharm, Cz. See *Scanpharm, Denm.*

Scanpharm, Denm. Scanpharm A/S, Topstykket 12, 3460 Birkerød, Denmark.
url: www.scanpharm.dk

Scanpharm, Hong Kong. See *Winsor, Hong Kong.*

Scanpharm, Philipp. See *Phoenix, Philipp.*

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Schafer, Arg. Laboratorios Schafer de Frederico Hogner, 25 de Mayo 259, (2840) Gualeguay, Entre Rios, Argentina.

Schaffer, USA. Schaffer Laboratories, 3128 Pacific Coast Highway, Number 98, Torrance, CA 90505, USA.
url: www.schafferlabs.com

Schaper & Brummer, Austria. See *Schaper & Brummer, Ger.*

Schaper & Brummer, China. See *GC-Rise, China.*

Schaper & Brummer, Cz. See *Schaper & Brummer, Ger.*

Schaper & Brummer, Ger. Schaper & Brümmer GmbH & Co. KG, Bahnhofstr. 35, 38259 Salzgitter, Germany.
url: www.schaper-bruemmer.de

Schaper & Brummer, Malaysia. See *JDH, Malaysia.*

Schaper & Brummer, Norw. See *Schaper & Brummer, Ger.*

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Schaper & Brummer, Singapore. See *Bionax, Singapore.*

Schaper & Brummer, Spain. See *Schaper & Brummer, Ger.*

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Schaper & Brummer, Thai. See *Diethelm, Thai.*

Schaper & Brummer, Ukr. See *Alpen, Ukr.*

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url: www.scharperhealthcare.com

Scheele, Philipp. See *Metro, Philipp.*

Scheeling, Philipp. Scheeling Pharma Care Link Inc., Rm 302 OMM-CITRA Tower, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.

Scheffler, Cz. See *Scheffler, Ger.*

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Schein, UK. Henry Schein Ltd, Centurion Close, Gillingham, Kent, ME8 0SB, UK.
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Schein, USA. See *Watson, USA.*

Scherax, Ger. See *ALK Abello, Ger.*

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Scherer, Thai. See *Kemopharm, Thai* and *Osotspa, Thai* and *Sriprasit, Thai* and *Star, Thai.*

Scherer, USA. Scherer Laboratories Inc., 28161 N. Keith Drive, Lake Forest, IL 60045, USA.
url: www.schererlabs.com

Scherimed, Spain. See *Schering, Spain.*

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url: www.schering.com.ar

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Schering, Austria. Schering Wien GmbH, Scheringgasse 2, A-1147 Vienna, Austria.
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Schering, Denm. See *Bayer, Denm.*

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Schering, Ger. See *Bayer, Ger.*

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Schering, Indon. See *Bayer, Indon.*

Schering, Irl. See *Clissmann, Irl.*

Schering, Israel. See *Perrigo, Israel.*

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Schering, Malaysia. See *Zuellig, Malaysia.*

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Schering, Singapore. See *Zuellig, Singapore.*

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Schering, Turk. Schering Alman İlaç ve Ecza Tic. Ltd. Şti., Nuh Kuyusu Cad. No: 10, Vizyan İş Merkezi, Zeynepkamil-Üsküdar, Istanbul, Turkey.
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Schering, UK. See *Bayer, UK.*

Schering, Ukr. Schering AG, Kudryavskii spusk, 7, Kiev, 04053, Ukraine.
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Schering, USA. See *Schering-Plough, USA.*

Schering, Venez. Schering de Venezuela S.A., Segunda Avenida de Campo Alegre, Edif. Torre Cari Pisas 1, 2 y 3, Apartado 66802, Caracas 1061-A, Venezuela.
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Schering-Plough, Austria. See *Aesca, Austria.*

Schering-Plough, Belg. Schering-Plough SA, Rue de Stalle 67, 1180 Brussels, Belgium.
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Schering-Plough, Braz. Schering Plough, Rua Antônio das Chagas 1623 2 degrees ander, 04714-0024 São Paulo, SP, Brazil.
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Schering-Plough, Canad. Schering-Plough Healthcare Products Canada Inc., 6400 Northam Drive, Mississauga, Ontario, L4V 1J1, Canada.
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Schering-Plough, Irl. See *Pfizer, Irl.*

Schering-Plough, Israel. See *Trading, Israel.*

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Schering-Plough Healthcare, USA. Schering-Plough HealthCare Products, Three Connell Drive, P.O. Box 603, Berkeley Heights, NJ 07922-0603, USA.
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Schiapparelli, Cz. See *Schiapparelli, Ital.*

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Schiapparelli Searle, Ital. See *Monsanto, Ital.*

Schiapparelli Searle, USA. See *Sanofi-Aventis, USA.*

Schieffer, Ger. See *Bayer, Ger.*

Schieffer, Neth. See *Roche Consumer, Neth.*

Schiff, USA. Schiff Nutrition International/Weider Nutrition International, 2002 S 5070 West, Salt Lake City, UT 84104, USA.
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Schittenhelm, Ger. Dr Schittenhelm Pharma GmbH & Co KG, Bamberger Str. 32, 96132 Schlüsselfeld, Germany.
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Schiwa, Swed. See *Dicamed, Swed.*

Schluttig, Denm. See *Schluttig, Ger.*

Schluttig, Ger. Pharma Resources Dr Schluttig GmbH, Otto-Hahn-Str. 46, 63303 Dreieich, Germany.

Schmid, Israel. Schmid, Israel.

Schmid, USA. See *Durex, USA.*

Schmidgall, Austria. Dr A & L Schmidgall, Wolfganggasse 45-7, A-1121 Vienna, Austria.
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Schmidgall, Cz. See *Schmidgall, Austria.*

Schmidgall, Hung. See *Penta, Hung.*

Schmidgall, Pol. See *Goldmed, Pol.*

Schmidgall, Rus. See *Santa, Rus.*

Schmidt, Malaysia. Schmidt Biomedtech Sdn Bhd, 5/F Wisma Damain, No 18A, lot 318, Jln 51A/223, 46100 Petaling Jaya, Selangor, Malaysia.
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Scholl, Arg. See *Schering-Plough, Arg.*

Scholl, Canad. See *Schering-Plough, Canad.*

Scholl, Fr. See *SSL, Fr.*

Scholl, Hung. See *SSL, Hung.*

Scholl, Israel. See *Dexxon, Israel.*

Scholl, Switz. See *SSL, Switz.*

Scholl, UK. See *SSL, UK.*

Scholl, USA. See *Schering-Plough Healthcare, USA.*

Schoning-Berlin, Ger. Schöning Pharmazeutische Präparate GmbH & Co. KG, Porschestr. 22-24, 12107 Berlin, Germany.
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Schuck, Ger. Schuck GmbH, Industriestr. 11, 90571 Schwaig b. Nürnberg, Germany.
url: www.schuck-arzneimittel.de

Schuco, UK. Schuco Internationol Ltd, Challenge House, 1 Tyndhurst Ave, London, N12 0NE, UK.
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Schulke, Pol. Schulke Polska Sp z o o, ul. Rydygiera 8, 01-793 Warsaw, Poland.
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Schulke, Rus. Schülke, Prospekt Vernadskogo 84, Korpus 2, 119606 Moscow, Russia.
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Schulke & Mayr, Austria. Schülke & Mayr GmbH, Zieglergasse 8/3, A-1070 Vienna, Austria.
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Schulke & Mayr, Cz. See *Schulke & Mayr, Austria.*

Schulke & Mayr, Ger. Schülke & Mayr GmbH, Robert-Koch-Str. 2, 22851 Norderstedt, Germany.
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Schulke & Mayr, Singapore. See *Radiance, Singapore.*

Schulke & Mayr, Switz. Schülke & Mayr AG, Obere Zaune 12, 8001 Zurich, Switzerland.
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Schulke & Mayr, Thai. See *Diethelm, Thai.*

Schulke & Mayr, Ukr. See *Oktenifarm, Ukr.*

Schumacher, Ger. Dr. Schumacher GmbH, Am Roggenfeld 3, 34323 Malsfeld, Germany.
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Schur, Ger. Schur Pharmazeutika GmbH & Co. KG, Schorlemerstr. 68, 40547 Dusseldorf, Germany.

Schurholz, Ger. See *Sanofi-Aventis, Ger.*

Schwabe, Austria. See *Austroplant, Austria.*

Schwabe, Belg. See *VSM, Belg.*

Schwabe, Cz. Arzneimittel Schwabe International GmbH, Čestmírová 1, 140 00 Prague 4, Czech Republic.

Schwabe, Fin. See *Schwabe, Ger.*

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Schwabe, Hung. See *Schwabe, Ger.*

Schwabe, Indon. See *Phapros, Indon.*

Schwabe, Ital. See *Loacker Remedia, Ital.*

Schwabe, Malaysia. See *Antah, Malaysia.*

Schwabe, Neth. See *VSM, Neth.*

Schwabe, Norw. See *Schwabe, Ger.*

Schwabe, Philipp. See *Zuellig, Philipp.*

Schwabe, Pol. See *Medagro, Pol.*

Schwabe, Port. See *Schwabe, Ger.*

Schwabe, Rus. Dr Willmar Schwabe GmbH & Co, Vernadskogo pr-t 105, corp. 2, 119256 Moscow, Russia.

Schwabe, Singapore. See *MD, Singapore.*

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Schwabe, Switz. Schwabe Pharma AG, Erlistrasse 2, Postfach, 6403 Kussnacht a.R., Switzerland.
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Schwabe, Thai. See *Zuellig, Thai.*

Schwabe, UK. Schwobe Pharma (UK) Ltd, Alexander House, Mere Park, Dedmere Road, Marlow, Buckinghamshire, SL7 1PD, UK.
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Schwabe, Ukr. See *Naturprodukt, Ukr.*

Schwabe Extracta, Ger. See *Schwabe, Ger.*

Schwabe-Curamed, Ger. See *DeltaSelect, Ger.*

Schwartz, Philipp. See *Zuellig, Philipp.*

Schwarz, Austria. See *Schwarz, Ger.*

Schwarz, Canad. See *Schwarz, USA.*

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Schwarz, Denm. See *UCB, Denm* and *Biolac, Swed.*

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Schwarz, Ger. Schwarz Pharma Deutschland GmbH, Alfred-Nobel-Str. 10, 40789 Monheim, Germany.
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Schwarz, Hong Kong. Schwarz Pharma (HK) Ltd, Units 4912-4913, 49/F The Center, 99 Queens Rd Central, Hong Kong.
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Schwarz, Hung. See *Schwarz, Ger.*

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Schwarz, Israel. See *Medis, Israel.*

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Schwarz, Malaysia. See *Ranbaxy, Malaysia.*

Schwarz, Neth. See *Schwarz, Ger.*

Schwarz, Norw. See *Andersen, Norw* and *Meda, Norw.*

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Schwarz, Pol. See *UCB, Pol.*

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Schwarz, Singapore. See *Zyfas, Singapore.*

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Schwarz, Switz. See *Globopharm, Switz.*

Schwarz, Thai. See *Berli Jucker, Thai.*

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Schwarz, USA. Schwarz Pharma Inc., 6140 W Executive Drive, Mequon, WI 53092, USA.
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Schwarzhaupt, Austria. See *Schwarzhaupt, Ger.*

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Schwarzhaupt, Hong Kong. See *US Summit, Hong Kong.*

Schwarzhaupt, Thai. See *Pacific, Thai.*

Schwarzkopf, Canad. See *Dep, Canad.*

Schwarzwalder, Ger. Schwarzwälder Natur-Heilmittel, Marktplatz 4, 93183 Kollmunz, Germany.

Schworer, Ger. Pharma Schwörer GmbH, Goethestr. 29, 69257 Wiesenbach, Germany.
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Schwulst, S.Afr. See *Alliance, S.Afr.*

SciClone, China. See *SciClone, Hong Kong.*

SciClone, Hong Kong. SciClone Pharmaceuticals International Ltd, Rm 3401A Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.
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SciClone, Indon. See *Tempo Scan Pacific, Indon.*

SciClone, Ital. Sciclone Pharmaceuticals Italy S.r.l., Via Lisbona 11, 00198 Rome (RM), Italy.

SciClone, Malaysia. See *DKSH, Malaysia.*

SciClone, Philipp. See *Zuellig, Philipp.*

SciClone, Rus. SciClone, Russia.

SciClone, Singapore. See *Zuellig, Singapore.*

SciClone, Thai. See *Diethelm, Thai.*

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Scientific, S.Afr. See *Scipharm, S.Afr.*

Scientific Hospital Supplies, Austral. Scientific Hospital Supplies, 14-16 Brookhollow Avenue, Norwest Business Park, Baulkham Hills, NSW 2153, Australia.

Scientific Hospital Supplies, Irl. See *Nutricia, Irl.*

Scientific Hospital Supplies, Israel. See *Megaphorm, Israel.*

Scientific Hospital Supplies, NZ. See *Nutricia, NZ.*

Scientific Hospital Supplies, UK. See *SHS, UK.*

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SciGen, Hong Kong. See *Zuellig, Hong Kong.*

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SciGen, Thai. See *Cosma, Thai.*

Scios, Israel. See *Scios, USA.*

Scios, Singapore. See *Scios, USA.*

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Scipharm, S.Afr. Scipharm Ltd, P.O. Box 13119, Verna Valley 1686, South Africa.
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Sclavo, Israel. See *Promedico, Israel.*

Scope, UK. Scope Ophthalmics, 3000 Manchester Business Park, Aviator Way, Manchester, M22 5TG, UK.
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Scot, Israel. See *Trupharm, Israel.*

Scotia, Cz. See *Scotia, UK.*

Scotia, Denm. See *Norpharma, Denm.*

Scotia, Hong Kong. See *Health Care, Hong Kong.*

Scotia, Irl. See *Scotia, UK.*

Scotia, S.Afr. See *Pfizer, S.Afr.*

Scotia, UK. Scotia Pharmaceuticals Ltd, Scotia House, Castle Business Park, Stirling, Stirlingshire, FK9 4TZ, UK.

Scott, Canad. See *Lander, Canad.*

Scott-Cassara, Arg. Scott-Cassara, Gaona 4302, 1407 Buenos Aires, Argentina.

Scot-Tussin, USA. Scot-Tussin Pharmacal Co. Inc., 32 West Hamden Rd, P.O. Box 8217, Cranston, RI 02920-0217, USA.
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SCS, USA. See *Sanofi-Aventis, USA.*

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Sea-Band, UK. Sea-Band Ltd, Lancaster Rd, Hinckley, Leicestershire, LE10 0AW, UK.
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Seagull, India. Seagull Pharma, 401-404 Imperial Tower, C Block Community Centre, Naraina Vihar, Delhi 110 028, India.
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Searle, Arg. See *Pfizer, Arg.*

Searle, Austral. See *Pharmacia, Austral.*

Searle, Belg. See *Continental Pharma, Belg.*

Searle, Braz. See *Pharmacia, Braz.*

Searle, Canad. See *Pfizer, Canad.*

Searle, Chile. Monsanto Chile C e I Ltda, Del Inca 4446, Piso 4, Las Condes, Santiago, Chile.

Searle, Cz. See *Pharmacia, Cz.*

Searle, Denm. See *Pfizer, Denm* and *Pharmacia, Denm.*

Searle, Fin. See *Pfizer, Fin.*

Searle, Fr. See *Pharmacia, Fr.*

Searle, Ger. See *Pfizer, Ger.*

Searle, Gr. Searle Ltd, Thiseos 67, 17671 Kallithea, Greece.

Searle, Irl. See *Pfizer, Irl.*

Searle, Israel. See *Perrigo, Israel.*

Searle, Ital. See *Monsanto, Ital.*

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Searle, Pol. See *Pfizer, Pol.*

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Searle, S.Afr. See *Pfizer, S.Afr.*

Searle, Singapore. See *Pharmacia, Singapore.*

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Searle, UK. See *Pfizer, UK.*

Searle, USA. See *Pfizer, USA.*

Seatrace, USA. Seatrace Pharmaceuticals, P.O. Box 7200, Gadsden, AL 35906, USA.

Seattle Genetics, USA. Seattle Genetics Inc., 21823 30th Drive SE, Bothell, WA 98021, USA.
url: www.seagen.com

Seaway Midwest, Canad. Seaway Midwest Ltd, 1255 Fewster Dr., Mississauga, Ontario, L4W 1A3, Canada.

Sebamed, Ger. Sebapharma GmbH & Co. KG, Binger Str. 80, 56154 Boppard, Germany.
url: www.sebamed.com

Sebapharma, Hong Kong. See *Mekim, Hong Kong.*

Sebapharma, Thai. See *Ouiheng, Thai.*

Sebela, USA. Sebela Pharmaceuticals Inc., USA.
url: www.sebelapharma.com

Seber, Port. Seber Portuguesa Farmacêutica, SA, Rua Norberto de Oliveira 1-5, 2620-111 Póvoa de St Adrião, Portugal.

SecFarm, Pol. SecFarm Sp. zo.o., ul. Korkowa 120, 04-502 Warsaw, Poland.

Se-cure, Singapore. See *Age D'or, Singapore.*

Sedapharm, Hong Kong. See *Primal, Hong Kong.*

Sedate, India. Sedate Health Care Pvt Ltd, 115-A Vardhman Tower, Plot 16-18, Community Centre, Preet Vihar, New Delhi, 110092, India.
url: sedatehealthcarepvtltd_ww.indiabizclub.com

Sedate, Rus. See *Sedate, India.*

Sedico, Rus. Sedico, Stariaalexciveskoya 5 office 262, 129626 Moscow, Russia.
url: www.sedico.net

Sedifa, Ital. See *Sedifa, Mon.*

Sedifa, Mon. Laboratoires Sédifa, 4 av. Prince-Héréditaire-Albert, Fontvieille, MC 98000, Monaco.
url: www.sedifa-laboratoire.mc

SEDR, Israel. See *Rafa, Israel.*

Sefarma, Ital. Sefarma S.r.l., Via Robert Koch 1.2, 20152 Milan, Italy.

Segix, Ital. Segix Italia S.r.l., Via del Mare 36, 00040 Pomezia (RM), Italy.
url: www.segixitalia.it

Seid, Spain. Seid, Ctra Sabadell Granollers Km 15, Llissa de Vall, 08185 Barcelona, Spain.
url: www.lab-seid.com

Seikagaku, China. See *Baker Norton, China.*

Seiko Eiyo, China. Seiko Eiyo Yakuhin Pharmaceutical Co. Ltd, China.

Seiko Eiyo, Hong Kong. See *Primal, Hong Kong.*

Sekpharma, S.Afr. See *Sekunjalo, S.Afr.*

Sekunjalo, S.Afr. Sekunjalo Healthcare, Sekunjalo House, Block F The Terraces, Steenberg Office Park, Tokal, Cape Town, 7945, South Africa.
url: www.sekunjalo.com

Selamine, Irl. Selamine Ltd, Unit 4/5 Willsborough Cluster, Clonshaugh, Dublin 17, Ireland.

Selen, Turk. Selen, Turkey.

Selena, Swed. See *Selena Fournier, Swed.*

Selena Fournier, Denm. See *Ipex, Swed.*

Selena Fournier, Norw. See *Ipex, Swed.*

Selena Fournier, Swed. Selena Fournier AB, Box 1266, 172 25 Sundbyberg, Sweden.
url: www.selena.se

Selenium Pharma, Hung. Selenium Pharma Kft, Berényi u 8, 1016 Budapest, Hungary.

Self-Care Products, UK. Self-Care Products Ltd, 30 Sycamore Rd, Amersham, Buckinghamshire, HP6 5DR, UK.

Sel-J, Philipp. Sel-J Pharmaceuticals, L-8 B2 Villanueva Compd, CAA Rd, J Aguilar Ave, Pamplona, Las Piña City, Philippines.

Sella, Ital. Sella A. Lab. Chim. Farm. S.r.l., Via Vicenza 67, 36015 Schio (VI), Italy.
url: www.sellafarmaceutici.it

Selmag, Switz. Selmag-Weibel, 3054 Schupfen/BE, Switzerland.

Semar, Spain. See *Sanofi-Aventis, Spain.*

Semomed, Switz. See *Doetsch, Grether, Switz.*

Semper, Denm. Semper AB, Gammel Kongevej 1, 2. sal, 1610 Copenhagen V, Denmark.
url: www.semper.dk

Semper, Fin. See *Arla, Fin.*

Semper, Norw. See *Nycomed, Norw.*

Seneca, USA. See *Beach, USA.*

Senese, Ital. Industria Farmaceutica Galenica Senese S.r.l., Via Cassia Nord 351, 53014 Monteroni d'Arbia (SI), Italy.
url: www.galenicasenese.it

Senetek, USA. Senetek plc, 620 Airpark Rd, Napa, CA 94558, USA.
url: www.senetek.net

Seng, Hong Kong. See *Health Alliance, Hong Kong.*

Seng, Thai. See *Sang, Thai.*

Senju, China. See *Eisai, China.*

Senju, Jpn. Senju Pharmaceutical Co. Ltd, 2-5-8 Hiranomachi, Chuo-ku, Osaka 541-0046, Japan.

Senju, Pol. See *Mitsubishi, Pol.*

Senosiain, Mex. Laboratorios Senosiain S.A. de C.V., Andres Bello 45 Piso 10,20,21, Col. Chapultepec, Miguel Hidalgo, 11560 Mexico D.F., Mexico.

Sensible Life, Canad. Sensible Life Products, 34 7 Innovation Drive, Flamborough, Ontario, L9H 7H9, Canada.

Sensomed, Philipp. Sensomed Phils Inc., Unit 1508 Orient Square Bldg, 26 F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Seoul Pharma, Singapore. See *Pharmaforte, Singapore.*

Sepharma, Ital. See *Sefarma, Ital.*

Sepracor, Canad. Sepracor Pharmaceuticals Inc., 100 6790 Century Ave, Mississauga, Ontario, L5N 2V8, Canada.

Sepracor, USA. Sepracor, 84 Waterford Drive, Marlborough, MA 01752, USA.
url: www.sepracor.com

Septa, Spain. Septa Chemifarma, Sierra Guadarrama 11, Pol. Ind. 2, San Fernando de Henares, 28850 Madrid, Spain.

Septodont, Austral. Specialites Septodont Pty Ltd., P.O. Box 288, Emu Plains, NSW 2750, Australia.

Septodont, Austria. See *Septodont, Ger.*

Septodont, Belg. Septodont NV-SA, Grondwetlaan 87, 1083 Brussels, Belgium.

Septodont, Canad. See *Septodont, Fr.*

Septodont, China. Septodont Shanghai, Room G/H floor 32, Jia Li Mansion, 1228 Yan An Rd (West), Shanghai, 20052, China.
url: www.septodont.cn

Septodont, Cz. See *Septodont, Fr.*

Septodont, Denm. See *CMS-Dental, Denm.*

Septodont, Fin. See *Sirowa, Fin.*

Septodont, Fr. Specialites Septodont, 58 rue du Pont de Creteil, Saint-Maur des Fosses 94100, France.
url: www.septodont.fr

Septodont, Ger. Septodont GmbH, Felix-Wankel-Strasse 9, 53839 Niederkassel, Germany.
url: www.septodont.de

Septodont, Irl. See *Septodont, UK.*

Septodont, Israel. See *Septodont, Fr.*

Septodont, Neth. See *Septodont, Belg.*

Septodont, Norw. See *Denamed, Norw.*

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Septodont, Rus. See *STI Dent, Rus.*

Septodont, Spain. See *Septodont, UK.*

Septodont, Switz. See *Odontopharm, Switz.*

Septodont, UK. Septodont Ltd, Units R & S, Orchard Business Centre, St. Barnabas Close, Allington, Maidstone, Kent, ME16 0JZ, UK.
url: www.septodont.co.uk

Septodont, USA. Septodont Inc., 245-C Quigley Blvd, New Castle, DE 19720, USA.
url: www.septodontinc.com

Sequus, Austria. See *Three Rivers, USA.*

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Serag-Weissner, Cz. See *Serag-Wiessner, Ger.*

Serag-Wiessner, Ger. Serag-Wiessner KG, Zum Kugelfang 8-12, 95119 Naila, Germany.
url: www.serag-wiessner.de

SERB, Fr. Laboratoires SERB, 40 Avenue George V, 75008 Paris, France.
url: www.serb-labo.com

SERB, Irl. See *SERB, Fr.*

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Serdex, Indon. See *Corsa, Indon.*

Serdex, Port. See *Confar, Port.*

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Serdia, India. Serdia Pharmaceuticals (India) Ltd, Serdia House, Off Dr S.S. Rao Rd, Parel, Mumbai 400 012, India.
url: www.serdiapharma.com

Serelyspharma, Mon. Laboratoire Sérélyspharma, 5 rue du Gabian, 98000 Monaco, Monaco.
url: www.serelyspharma.com

Sermedica, Port. Sermédica Especialidades Farmacêuticas Lda, Av. Antonio Augusto de Aguiar 128, 1069-133 Lisbon, Portugal.

Sermmitr, Thai. Sermmitr c/o The Sermmitr Co. Ltd, 82, 84 Arkarn 2, Ratchamnoen Ave, Bangkok 10200, Thailand.

Serolab, Switz. Serolab SA, CP 43, 1618 Châtel-St-Denis, Switzerland.
url: www.serolab.ch

Serolam, Fr. See *Grimberg, Fr.*

Serolam, Israel. See *Trima, Israel.*

Serono, Arg. Serono Argentina S.A., Thames 158, 1642 San Isidro, Buenos Aires, Argentina.
url: www.serono.com

Serono, Austral. Serono Australia P/L, Allambie Grove Business Park, 4/25 Frenchs Forest Rd (East), Frenchs Forest, NSW 2086, Australia.
url: www.serono.com

Serono, Austria. Serono Austria GmbH, Widerhofergasse 3/24, A-1090 Vienna, Austria.
url: www.serono.com

Serono, Belg. Serono Benelux SA, Heysel Esplanade b11, 1020 Brussels, Belgium.
url: www.serono.com

Serono, Braz. Serono Produtos Farmacêuticos Ltda, Rua Dr Eduardo de Souza Aranha 387, 11 degrees andar, 04543-121 São Paulo, SP, Brazil.
url: www.serono.com.br

Serono, Canad. Serono Canada Inc., 1075 North Service Rd, Suite 100, Oakville, Ontario, L6M 2G2, Canada.
url: www.serono-canada.com

Serono, Cz. Serono Pharma Services sro, Betlemská 1, 110 00 Prague 1, Czech Republic.
url: www.ares-serono.com

Serono, Denm. Serono Nordic, Strandvejen 102 B, 4.th, 2900 Hellerup, Denmark.
url: www.serono.com

Serono, Fin. Serono Nordic, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.serono.com

Serono, Fr. Laboratoires Serono, L'Arche du Parc, 738 rue Yves-Kermen, 92658 Boulogne cdx, France.
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Serono, Ger. Serono GmbH, Alsfelder Str. 17, 64289 Darmstadt, Germany.

Serono, Gr. Serono Hellas A.E., 3-5 Konitsis St., 151 25 Marousi, Greece.
url: www.serono.gr

Serono, Hong Kong. Serono Hong Kong Ltd, Rm 2004-6, 20/F, Alliance Building, 130-136 Connaught Rd Central, Hong Kong.
url: www.serono.com

Serono, Hung. See *Pharma-Marketing, Hung.*

Serono, Indon. See *DKSH, Indon.*

Serono, Irl. See *Allphar, Irl.*

Serono, Israel. See *ASI, Israel.*

Serono, Ital. Industria Farmaceutica Serono S.p.A., Via Casilina 125, 00176 Rome (RM), Italy.
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Serono, Malaysia. See *Antah, Malaysia.*

Serono, Mex. Serono de Mexico S.A. de C.V., Av. Insurgentes Sur No. 1898 Piso 16, Colonia Florida, 01030 Mexico D.F., Mexico.
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Serono, Neth. Serono Benelux, Alexanderstraat 3-5, 2514 TJ The Hague, Netherlands.
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Serono, Norw. Serono Nordic AB, Luhrtoppen 2, 1470 Lorenskog, Norway.
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Serono, NZ. See *Douglas, NZ.*

Serono, Philipp. See *Diethelm, Philipp.*

Serono, Pol. See *Ares, Pol.*

Serono, Port. Serono, Lda, Rua Tierno Galvan 16B, 16 piso-Esc.1, 1070-274 Lisbon, Portugal.
url: www.serono.com

Serono, Rus. Serono Pharma International, Usievicha ul. 20, Building 1, Business Centre Sokol Plaza, 125190 Moscow, Russia.
url: www.serono.com

Serono, S.Afr. Serono South Africa (Pty) Ltd, P.O. Box 1877, Fourways 2055, South Africa.
url: www.serono.com

Serono, Singapore. See *Grafton, Singapore.*

Serono, Swed. Serono Nordic AB, Box 1803, 171 21 Solna, Sweden.
url: www.serono.com

Serono, Turk. Serono İlaç Paz. ve Tic. A.Ş., Kayişdagği Cad., Karaman Çiftliği Yolu Kar Plaza Blok No: 45, K: 7, İçerenköy, İstanbul, 81120, Turkey.
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Serono, UK. Serono UK Ltd, Bedfont Cross, Stanwell Rd, Feltham, Middlesex, TW14 8NX, UK.
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Serono, USA. See *EMD Serono, USA.*

Serono, Venez. Serono de Venezuela S.A., Avenida Venezuela con Calle Mohedano, Edificio Torre Centuria, Piso 3, Oficinas 3-A y 3-B, Urbanización El Rosal, Caracas 1060, Venezuela.
url: www.serono.com

Serono OTC, Ital. See *Serono, Ital.*

Seroyal, Canad. Seroyal International Inc., 44 E Beaver Creek Rd, Unit 17, Richmond Hill, Ontario, L4B 1G8, Canada.

Serozym, Fr. See *Grimberg, Fr.*

SERP, Mon. SERP, le Triton, 5 rue du Gabian, MC 98000, Monaco.

Serra Pamies, Hong Kong. See *Hind Wing, Hong Kong.*

Serra Pamies, Spain. Serra Pamies, Ctra de Castellvell 24, Reus, 43206 Tarragona, Spain.
url: www.lsp.es

Serral, Mex. Serral S.A. de C.V., Adolfo Prieto No. 1009, Col. del Valle, Deleg. Benito Juarez, 03100 Mexico D.F., Mexico.
url: www.serral.com.mx

Serranita, Arg. La Serranita, Lab. de Esp. Medic. y Cosmet., Calle 49 3752, 1653 Villa Ballester, Buenos Aires, Argentina.

Sertex, Arg. Laboratorio Sertex S.R.L., Brown 2862, 2000 Rosario, Santa Fe, Argentina.
url: www.rosario.com.ar/sertex/

Serum Institute, India. Serum Institute of India Ltd, 501 Dalamal Tower, 211 Nariman Point, Mumbai 400 021, India.
url: www.seruminstitute.com

Serum Institute, Philipp. See *Interlink, Philipp.*

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Serum-Werk Bernburg, Ger. Serumwerk Bernburg AG, Hallesche Landstr. 105 b, 06406 Bernburg, Germany.
url: www.serum-werk.de

Serum-Werk Bernburg, Rus. Serumwerk Bernburg AG, Kary Tsetkin ut 4, 127299 Moscow, Russia.
url: www.serumwerk.com

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Serve, Ukr. OOO Serve Ukraine, Vorovskogo Street, 24, Kiev, 01054, Ukraine.

Servier, Arg. Servier Argentina S.A., Av. Belgrano 1480, 1093 Buenos Aires, Argentina.
url: www.servier.com

Servier, Austral. Servier Laboratories (Australia) P/L, P.O. Box 196, Hawthorn, VIC 3122, Australia.
url: www.servier.com.au

Servier, Austria. Servier Pharma GmbH, Mariahilfe Strasse 20/5, A-1070 Vienna, Austria.
url: www.servier.com

Servier, Belg. Servier Benelux SA, Riverside Business Park, Blvd International 57, 1070 Brussels, Belgium.
url: www.servier.com

Servier, Braz. Servier Do Brasil Ltda, Rua Mario Piragibe 23, Lins de Vasconcelos, 20720-320 Rio de Janeiro, RJ, Brazil.
url: www.servier.com.br

Servier, Canad. Servier Canada Inc., 235 blvd Armand-Frappier, Laval, Quebec, H7V 4A7, Canada.
url: www.servier.com

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Servier, China. Servier International, World Financial Center West Building, East 3rd Ring Road, Chaoyang District, Beijing 100020, China.
url: www.servier.com.cn

Servier, Cz. Servier sro, Sladkovského nám 1, 130 00 Prague 3, Czech Republic.

Servier, Denm. Servier Danmark A/S, Roskildevej 39, 2000 Frederiksberg, Denmark.
url: www.servier.com

Servier, Fin. Servier Finland Oy, Vanhankyläntie 44 C, PL 157, 04401 Järvenpää, Finland.
url: www.servier.com

Servier, Fr. Laboratoires Servier, 22 rue Garnier, 92200 Neuilly-sur-Seine, France.
url: www.servier.com

Servier, Ger. Servier Deutschland GmbH, Elsenheimer Str. 53, 80687 Munich, Germany.
url: www.servier.de

Servier, Gr. Servier Greece E.P.E, L. Synggrou 181, 171 21 N. Smyrni, Greece.
url: www.servier.com

Servier, Hong Kong. Servier Hong Kong Ltd, Rm 1901, 19/F The Lee Gardens, 33 Hysan Ave, Causeway Bay, Hong Kong.

Servier, Hung. Servier Hungária Kft, Váci út 1-3, 1062 Budapest, Hungary.

Servier, Indon. Les Laboratoires Servier (PT Parvico Bersaudara), Menara Kadin Indonesia 18/Fl, Jl HR Rasuna Said X-5 Kav 2-3, 12950 Jakarta, Indonesia.

Servier, Irl. Servier Laboratories (Ireland) Ltd, Block 2, West Pier Business Campus, Old Dunleary Road, Dun Laoghaire, Co. Dublin, Ireland.
url: www.servier.ie

Servier, Israel. See *Teva, Israel.*

Servier, Ital. Servier Italia S.p.A., Via Luca Passi 85, 00166 Rome (RM), Italy.
url: www.servier.com

Servier, Malaysia. See *Zuellig, Malaysia.*

Servier, Mex. Laboratorios Servier Mexico SA de CV, Paseo de las Palmas 830 PH, 11000 Lomas de Chapultepec, Mexico DF, Mexico.

Servier, Neth. Servier Nederland BV, Einsteinweg 82, 2333 CD Leiden, Netherlands.
url: www.servier.com

Servier, NZ. Servier Laboratories (NZ) Ltd, 2nd Floor, 29 Union St., Auckland, New Zealand.
url: www.servier.com

Servier, Philipp. Servier Phils Inc., Orion Bldg, No 2 Orion cor Mercedes St, Bel-Air, Makati City, Philippines.

Servier, Pol. Servier Polska Sp. za.o., ul. Jana Kazimierza 10, 01-248 Warsaw, Poland.
url: www.servier.pl

Servier, Port. Servier Portugal, Lda, Av António Agusto de Aguiar 128, 1069-133 Lisbon, Portugal.
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Servier, Rus. Laboratory Servier, Paveletskaya pl. 2, str. 3, 113054 Moscow, Russia.
url: www.servier.com

Servier, S.Afr. Servier Laboratories (SA) (Pty) Ltd, P.O. Box 930, Rivonia 2128, South Africa.
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Servier, Singapore. Servier (S) Pte Ltd, 510 Thomson Rd, 09-02 SLF Building, S 298135, Singapore.
url: www.servier.com

Servier, Spain. Servier, Avda de Madronos 33, 28043 Madrid, Spain.
url: www.servier.com

Servier, Swed. See *Servier, Denm.*

Servier, Switz. Servier (Suisse) SA, 10 rue de la Bergère, 1242 Satigny, Switzerland.
url: www.servier.com

Servier, Thai. Servier (Thailand) Ltd, 15 Fl, Ploenchit Center Building, 2 Sukhumvit Rd, Klongtoey, Bangkok 10110, Thailand.
url: www.servier.com

Servier, Turk. Servier İlaç ve Araştırma A.Ş., Maslak Giz Kule Meydan Sok. No: 28 K: 22-23, Mediditköy, Istanbul, 80650, Turkey.
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Servier, UK. Servier Laboratories Ltd, Wexham Springs, Framewood Rd, Wexham, Slough, Buckinghamshire, SL3 6RJ, UK.
url: www.servier.co.uk

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Servier, Venez. Laboratorios Servier S.A., Final Calle Vargas, Edif.Ctro. Berimer Nivel Mezanina, Caracas, Venezuela.
url: www.servier.com

Servinox, Spain. Servinox Farma SL, C/Cuco 3, 28760 Tres Cantos, Spain.

Servipharm, Hong Kong. See *Unipharm, Hong Kong.*

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Servocare, India. Servocare Lifesciences, S.C.F. 246, New Motor Market, Manjjara, Chandigarh 160 101, India.

Sesderma, Spain. Sesderma, Poligana Industrial de Rafelbunol, C/ Massamagrell 3, Rafelbunol, 46138 Valencia, Spain.
url: www.sesderma.com

Setia, Malaysia. Setia Kombinasi Sdn Bhd, Suite 2-2 Taman OUG Square, Jln Awan Makmur 1, 58200 Kuala Lumpur, Malaysia.
url: www.setiakombinasi.com

Seton, Cz. See *SSL, UK.*

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Seton, Neth. See *SSL, UK.*

Seton, NZ. See *Pharmaco, NZ.*

Seton, Pol. See *SSL, Pol.*

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Seton, USA. Seton Pharmaceuticals Llc, Atlantic Corporate Center, 2317 Highway 34, Manasquan, NJ 08736-1443, USA.
url: www.setonpharmaceuticals.com

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Sevapharma, Cz. Sevopharma as, Korunní 108, 101 03 Prague 10, Czech Republic.
url: www.sevapharma.cz

Seven Seas, Fin. See *Seven Seas, UK.*

Seven Seas, Hong Kong. See *Zuellig, Hong Kong.*

Seven Seas, Irl. Seven Seas (Ireland) Ltd, 7 The Anchorage, Charlotte Quay, Dublin 4, Ireland.
url: www.sevenseas.ie

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Seven Seas, UK. Seven Seas Ltd, Hedon Rd, Marfleet, Hull, HU9 5NJ, UK.
url: www.sseas.com

Seven Stars, Thai. See *Charoen, Thai.*

Sevene, Fr. Sevene Pharma, Mazet Pailhès, 30170 Monoblet, France.

Sevens, Gr. SEVENS LTD, Alkmanous 53, 115 28 Ilissia, Greece.

Seventy BG, Ital. Seventy BG Srl, Corsa di Porta Vittoria 14, 20122 Milan (MI), Italy.
url: www.seventybg.it

Seyer, USA. Seyer Pharmotec Inc., P.O. Box 9270, Caguas, PR 00725, Puerto Rico.
url: www.spharmatec.com

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SFD, Port. Sociedade Farmacêutica de Desenvolvimento, Lda, Rua Duque d'Ávila no 193, 1050-082 Lisbon, Portugal

SFPH, Fr. SFPH, 13 rue de l'Epinette, 77165 St-Soupplets, France.

SG, India. SGPharma Pvt Ltd, 542, 3/10 Bhuta Niwas, Dr.Ambedkar Road, Matunga(E), Mumbai 400 019, India.
url: www.sgpharma.com

Sha Pu Ai Si, China. Sha Pu Ai Si Pharmaceutical Co. Ltd, Zhejiang, China.

Shaji, China. Shaji Pharmaceutical Co Ltd, China.

Shaklee, Canad. Shaklee Canada Inc., 952 Century Dr, Burlington, Ontario, L7L 5P2, Canada.
url: www.shaklee.ca

Shalaks, India. Shalaks Pharmaceuticals, C-3 Puja House, Karampura Community Centre, Milan Complex, New Delhi 110 015, India.
url: www.shalaks.com

Shalpharm, Israel. See *Rekah, Israel.*

Shandon Kexing, Thai. See *Alliance, Thai.*

Shandong Kexing, Philipp. See *Goodfellow, Philipp.*

Shanghai Bio, China. Shanghai Institute of Biological Products, Shanghai, China.

Shanghai Clonbiotech, Thai. See *Neopharm, Thai.*

Shanghai IBP, Philipp. See *Global Pharmatrade, Philipp.*

Shanghai No 1, China. Shanghai No 1 Biochemical & Pharmaceutical Co. Ltd, 1317 Jianchuan Rd, Minhang, Shanghai 200080, China.

Shanghai Pharma, China. Shanghai Pharma Group, 200 Taicang Rd, Shanghai 200020, China.
url: www.pharm-sh.com.cn

Shanghai RAAS, Thai. See *Charoen, Thai.*

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Shanghai Yanan, Thai. See *Premier, Thai.*

Shangwei, China. Shangwei Pharmaceutical Co. Ltd, Jiangsu, China.

Shanqing, China. Shanqing Pharmaceutical Co. Ltd, Beizhen, China.

Shantha, India. Shantha Biotechnics Pvt Ltd, Serene Chambers, Riad No 7 Banjara Hills, Hyderabad 500 034, India.
url: www.shanthabiotech.com

Shantha, Philipp. See *Medtest, Philipp.*

Shantha, Thai. See *Biogenetech, Thai.*

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Shanxi, Philipp. See *Endure, Philipp.*

Sharp Dohme, Spain. See *MSD, Spain.*

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Sheng Bao Kang, China. Shenzhen Kang Sheng Bao Bio-Technology Co. Ltd, Block 2 Fu An Industrial Park, Da Yang Development Zone, Fu Yang, Shenzhen, Bao An District, China.
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Shengbao, China. Shengbao Pharmaceutical Co. Ltd, Zhenjiang, China.

Shengbaoluo, China. Shengbaoluo Pharmaceutical Co. Ltd, 29 Xinming Road, National High-Tech Development Zone, Wuxi, Jiangsu, 214111, China.
url: www.sempoll.com

Shengbaotang, China. Shengbaotang Pharamceutical Co. Ltd, Guangxi, China.

Shengda, China. Shengda Pharmaceutical Co. Ltd., 24 Jiangua Road, Zhangjiokau, Hebei, 075000, China.
url: www.shengdayaoye.com

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Shenghe, China. Shenghe Pharmaceutical Co. Ltd, Tonghua, China.

Shenghuaxi, China. Shenghuaxi Pharmaceutical Co. Ltd, Chongqing, China.

Shengjitang, China. Shengjitang Pharmaceutical Co. Ltd, Guizhou, China.

Shenglang, China. Shenglang Pharmaceutical Co. Ltd, Jiangsu, China.

Shengma, China. Shangma Pharmaceutical Co. Ltd., Huangli, Wujin, Changzhou, Jiangsu, 213151, China.
url: www.smpharm.cn

Shengquan, China. Shengquan Pharmaceutical Co. Ltd, Guizhou, China.

Shengtai, China. Shengtai Pharmaceutical Co. Ltd., 99 Beijing Road, Harbin Limin Economic and Technological Development Zone, Harbin, Heilongjiang, 150025, China.
url: www.shengtaizhiyao.com

Shengying, China. Shengying Pharmaceutical Co. Ltd, Anhui, China.

Shengyong, China. Shengyong Pharmaceutical Co. Ltd, Beijing, China.

Shengyuan, China. Shengyuan Pharmaceutical Co. Ltd, 62 West Road, Yancheng, Jiangsu, 224500

Shenhua, China. Shenhua Pharmaceutical Co. Ltd, Jiangsu, China.

Shenlong, China. See *Honghui, China.*

Shennong, China. See *Huayuan Century, China.*

Shenwei, China. Shenwei Pharmaceutical Co. Ltd, Guangdong, China.

Shenyang First, China. Shenyang First Pharmaceutical Factory, Hing Wah Street South, West District 54, Shenyang City 110023, China.

Shenyang Medical, China. Shenyang Medical University Pharmaceutical Co. Ltd, Shenyang, China.

Shenyang Sunshine, Philipp. See *Goodfellow, Philipp.*

Shenzhen, Philipp. See *Dynasty, Philipp.*

Shenzhen Zhijun, Hong Kong. Shenzhen Zhijun Pharmaceutical Co Ltd, Guanlan Hi-Tech Ind. Zone, Baoan District, Shenzhen, Hong Kong.
url: www.szzhijun.com

Shenzhen Zhijun, Thai. See *Charoen, Thai.*

Sheraton, Hong Kong. Sheraton Worldwide Drugs Co. Ltd, 3/F Flat A & 6/F Flat B, Heep Cheung Commercial Bldg, 251 Temple St, Tsimshatsui, Kowloon, Hong Kong.

Sherman, USA. Sherman Pharmaceuticals Inc., P.O. Box 1377, Mandeville, LA 70470-1377, USA.

Sherrington, Philipp. See *Suhitas, Philipp.*

Sherwood, USA. See *Kendall, USA.*

Shi Dai, China. Shi Dai Pharm, Chengdu, China.

Shi Xin, China. Shi Xin Pharmaceutical Co Ltd, China.

Shide, China. Shide Pharmaceutical Co. Ltd, Shenyang, China.
url: en.shide.cn

Shield, India. Shield Healthcare Pvt Ltd, No 66 Second Cross St, Pallavan Nagar Extn, Maduravoyal, Chennai 600 095, India.
url: www.shieldhealthcare.co.in

Shield, Irl. Shield Health Ltd, Unit 1, Thompson Business Park, Clane, Co. Kildare, Ireland.
url: www.healthyandessential.ie

Shield, USA. Shield Manufacturing Inc., 425 Fillmore Ave, Tonawanda, NY 14150, USA.
url: www.shieldsports.com

Shigaken, China. Shigaken Pharmaceutical Ind. Co. Ltd., China.

Shigaken, Singapore. See *Luen Wah, Singapore.*

Shihuida, China. Shihuida Pharmaceutical Co. Ltd, 105 Yixian Rd, Shanghai, 200439, China.
url: www.shihuidapharma.com

Shiji Huayang, China. Shiji Huayang Pharmaceutical Co. Ltd, Hangtian South Rd, Longquanyi, Chengdu, Sichuan, 610100, China.

Shijiazhuang, Philipp. See *Health Saver, Philipp* and *Steinbach, Philipp.*

ShiJiaZhuang No 4, China. ShiJiaZhuang No 4 Pharmaceutical Co. Ltd, China.

ShiKangTe, China. ShiKongTe Pharmaceutical Co. Ltd, 699 Shanghai Bao Feng Rd, Jiading District, Shanghai, China.

Shin Poong, China. Shin Poong Pharmaceutical Co. Ltd, 8 Mu Ning Rd, Tianjin, 300457, China.

Shin Poong, Kor. Shin Poong Pharm. Co. Ltd, 748-31 Yoksam-Dong, Kangnam-Ku, Seoul 135-925, Korea.
url: www.shinpoong.co.kr

Shin Poong, Malaysia. See *Zyfas, Malaysia.*

Shin Poong, Philipp. Phil Shin Poong Pharma Inc., Unit 1110 Cityland Shaw Tower, Shaw Blvd cor St Francis St, Mandaluyong City, Philippines.

Shin Poong, Rus. See *Shin Poong, Kor.*

Shin Poong, Singapore. See *Zyfos, Singapore.*

Shince, India. Shince Pharmaceuticals Pvt Ltd, 3/805 A, Mugalivakkam Main Road, Madanandhapuram, Porur, Chennai 600 116, India.
url: www.shincepharma.com

Shine, Philipp. See *Global Pharmatrade, Philipp* and *International Apex, Philipp.*

Shinfuso, Hong Kong. See *Primal, Hong Kong.*

Shinfuso, Thai. See *Asian TJD, Thai.*

Shinto, India. Shinto Biotech Ltd, 110 Industrial Area, Phase-II, Panchkula 134 113, India.

Shinyaku, China. See *Harvest, China.*

Shinyaku, Hong Kong. See *Hing Ah, Hong Kong.*

Shinyaku, Jpn. Nippon Shinyaku Co. Ltd, 14 Nishinosho-Monguchi-cho, Kisshoin, Minami-ku, Kyoto 601-8550, Japan.

Shinyaku, Malaysia. See *Wellchem, Malaysia.*

Shinyaku, Philipp. See *Marketlink, Philipp.*

Shinyaku, Singapore. See *Wellchem, Singapore.*

Shinyaku, Thai. See *Asian TJD, Thai.*

Shiono, Jpn. Shiono Chemical Co Ltd, 2-10-8, Yaesu, Chuo-ku, Tokyo, 104-0028, Japan.
url: www.shiono.co.jp

Shionogi, China, 3rd Floor 318A Far East International Plaza, 319 Xian Xia Road, Shanghai, 200051, China.
url: www.shionogi.co.jp

Shionogi, Cz. See *Shionogi, Irl.*

Shionogi, Irl. Shionogi Ireland, Airside Business Park, County Dublin, Ireland.

Shionogi, Jpn. Shionogi & Co. Ltd, 3-1-8 Dosho-machi, Chuo-ku, Osaka 541-0045, Japan.
url: www.shionogi.co.jp

Shionogi, Port. See *Shionogi, Irl.*

Shionogi, USA. Shionogi USA Inc., 100 Campus Drive, Florham Park, NJ 07932, USA.
url: www.shionogiusa.com

Shiqiao, China. Shiqiao Biological Pharmaceutical Co. Ltd, North Industrial Zone, Beishicao, Shunyi, Beijing, 101301, China.
url: www.sciecure.com

Shire, Austral. Shire Australia Pty Ltd, Level 9, Avaya House, 123 Epping Rd, North Ryde, NSW 2113, Australia.

Shire, Austria. See *Shire, Ger.*

Shire, Belg. Shire Belgium bvba, Lambroekstraat 5a, 1831 Diegem, Belgium.
url: www.shire.com

Shire, Braz. Shire Farmaceutica Brasil Ltda, Av. das Nações Unidas, 14171 Torre Ebony, 4794000 São Paulo, Brazil.

Shire, Canad. Shire Canada Inc., 500 2250 Alfred-Nobel Blvd, Saint-Laurent, Quebec, H4S 2C9, Canada.

Shire, Cz. See *Shire, UK.*

Shire, Denm. See *Meda, Denm.*

Shire, Fin. See *Shire, UK.*

Shire, Fr. Shire France, 160 rue de Paris, 92771 Boulogne-Billancourt, France.
url: www.shire.com

Shire, Ger. Shire Deutschland GmbH, Friedrichstrasse 149, Berlin 10117, Germany.
url: www.shire.com

Shire, Gr. Shire Hellas SA (HGT), 29 Michalakopoulou Street, 115 28 Athens, Greece.
url: www.shire.com

Shire, Hong Kong. See *IDS, Hong Kong.*

Shire, Hung. See *Shire, UK.*

Shire, Irl. Shire Pharmaceuticals Ireland Ltd, 5 Riverwalk, Citywest Business Campus, Dublin 24, Ireland.
url: www.shireireland.com

Shire, Israel. See *Medison, Israel.*

Shire, Ital. Shire Italia S.p.A., Corso Italia 29, 50123 Florence (FI), Italy.
url: www.shireitalia.it

Shire, Malaysia. See *JDH, Malaysia.*

Shire, Neth. See *Shire, UK.*

Shire, Norw. Shire Human Genetic Therapies, Smuget 1 B, 1371 Asker, Norway.

Shire, Philipp. See *GenAsia, Philipp.*

Shire, Pol. Shire Polska Sp z o o, Warsaw Financial Center, ul. Emilii Plater 53, 00-113 Warsaw, Poland.
url: www.shire.com

Shire, Port. See *Shire, Spain.*

Shire, Rus. Shire Pharmaceutical Contracts Ltd, Regus Smolensky Passage, Smolensky Square 3, 121099 Moscow, Russia.
url: www.shire.com

Shire, Singapore. See *JDH, Singapore.*

Shire, Spain. Shire Pharmaceuticals Iberica, Paseo Pintor Rosales 40, Bajo Izda, 28008 Madrid, Spain.
url: www.shire.com

Shire, Swed. Shire Human Genetic Therapies AB, Svärdvägen 11 D, 182 33 Danderyd, Sweden.

Shire, Thai. See *DKSH, Thai.*

Shire, UK. Shire Plc, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP, UK.
url: www.shire.com

Shire, USA. Shire Pharmaceuticals, 725 Chesterbrook Blvd, Wayne, PA 19087-5637, USA.
url: www.shire.com

Shire Biochem, Canad. Shire Biochem Inc., 275 Armand-Frappier Bvld, Laval, Quebec, H7V 4A7, Canada.
url: www.shire.com

Shire Biologics, Canad. Shire Biologics, Division of Shire Biochem Inc., 2323 Parc Technologique Bvld, Sainte-Foy, Quebec, G1P 4R8, Canada.

Shire Richwood, USA. See *Shire, USA.*

Shiseido, Canad. Shiseido Canada Inc., 60 Leek Crescent, Richmond Hill, Ontario, L4B 1H1, Canada.

Shiwa, Thai. Shiwa Chemicals Co. Ltd, 34/1 Sukhumvit 39, (Soi Prompong), Bangkok 10110, Thailand.

Shoals, USA. See *Shire, USA.*

Shou Chan, Philipp. See *New Smart, Philipp.*

Shouhe Jinhai, China. Shouhe Jinhai Pharmaceutical Co Ltd, 27 Dasha Rd, Qingdao City 266042, China.

Shree Ganesh, India. Shree Ganesh Pharmaceuticals, 542 1/10 Bhuta Niwas, Dr Ambedkar Rd, Matunga (E), Mumbai 400 019, India.

Shreshtha, India. Shreshtha Formulations, 33 Narmada Nagar, Annpurna Rd, Indore 452 009, India.

Shreya, India. Shreya Life Sciences Pvt Ltd, Shreya House 301/A, Pereira Hill Rd, Andheri (E), Mumbai 400 099, India.

Shreya, Rus. See *Marvel, Rus.*

Shrrishti, India. Shrishti Health Care, 86 Third Cross, P&T Colony, R.T.Nagar, Bangalore 560 032, India.
url: www.shrrishti.in

SHS, Cz. See *SHS, UK.*

SHS, Denm. SHS International, Rørmosevej 2A, 3450 Allerød, Denmark.
url: www.shs-nutrition.com

SHS, Irl. SHS Ireland, Block 1, Deansgrange Business Park, Deansgrange, Dublin, Ireland.
url: www.shs-nutrition.com

SHS, Israel. See *Megapharm, Israel.*

SHS, Malaysia. See *Somedico, Malaysia.*

SHS, Pol. See *Nutricia, Pol.*

SHS, Singapore. See *Pharma 2000, Singapore.*

SHS, UK. SHS International Ltd, 100 Wavertree Boulevard, Liverpool, Merseyside, L7 9PT, UK.
url: www.shsweb.co.uk

SHS, USA. SHS North America/Scientific Hospital Supplies, P.O. Box 117, Gaithersburg, MD 20884, USA.
url: www.shsna.com

SHS Nutricia, UK. See *SHS, UK.*

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Shu Tai Bao, China. Shu Tai Bao Pharmaceutical Co. Ltd, Jiangsu, China.

Shuai Ke, China. Shuai Ke Pharmaceutical Co Ltd, Henan, China.

Shuang Cheng, China. Shuang Cheng Pharmaceutical Co. Ltd, 1901 Nanyang Mansion, Binhai Ave, Longhua, Haikou, Hainan, 570105, China.

Shuang Jing, China. Shuang Jing Pharmaceutical Co. Ltd, Qingdao, China.

Shuangding, China. Shuangding Pharmaceutical Co. Ltd, Shenyang, China.

Shuangke, China. Shuangke Pharmaceutical Co. Ltd, Anhui, China.

Shuanglu Lisheng, China. Shuanglu Lisheng Medicine Co. Ltd, Beijing, China.

Shuangqi, China. Shuangqi Pharmaceutical Co. Ltd, Erwei Rd, Ruyi Development Zone, Huhhot, Inner Mongolia, 010010, China.

Shuguang, China. Shuguang Pharmaceutical Co. Ltd, Beijing, China.

Shule, China. Shule Pharmaceutical Co. Ltd, Sichuan, China.

Shulke & Mier, Ukr. See *Medprominvest, Ukr.*

Shunfeng, China. Guangdong ShunFeng Pharmaceutical Co., Ltd., Jinju Tsui Street, Shunde District, Foshan, Guangdong, 528300, China.
url: www.shunfeng.com.cn

Shuntian, China. Shuntian Pharmaceutical Co. Ltd, Shanxi, China.

Shunxin Xiangyun, China. Shunxin Xiangyun Pharmaceutical Co. Ltd, Linhe Industrial Development Zone, Shunyi, Beijing, 101300, China.
url: www.xyyaoye.com.cn

Shutaishen, China. Shutaishen Pharmaceutical Co. Ltd, Beijing, China.

Shyndec, China. Shyndec Pharmaceutical Co Ltd, 858 Yuyuan Road, Shanghai 200050, China.
url: www.shyndec.cn

Si Bao, China. Si Bao Pharmaceutical Co. Ltd, Hubei, China.

Si Huan, China. Si Huan Biological Co Ltd, Jiangsu, China.

Si Huan Ke Bao, China. Si Huan Ke Bao Pharmaceutical Co. Ltd, Beijing, China.

Siam Bheasach, Malaysia. See *Luen Wah, Malaysia.*

Siam Bheasach, Thai. See *Siam Pharm, Thai.*

Siam Medicare, Thai. Siam Medicare Co. Ltd, 77/37 Sai Senanikom 1, Phaholyothin Rd, Bangkok 10900, Thailand.

Siam Pharm, Thai. Siam Pharmaceutical Co. Ltd, 171/1 Soi Choke Chai Ruammitr, Vibhavadi-Rangsit Rd, Bangkok 10900, Thailand.
url: www.siam-pharm.com

Siar, Ital. Siar Pharma S.r.l., Via G. Verdi 33, 20060 Bussero (MI), Italy.

Sibangde, China. Sibangde Pharmaceutical Co. Ltd, Shandong, China.

Sichuan Pharmaceutical, China. Sichuan Pharmaceutical Co. Ltd, Sichuan, China.

Sichuang, China. Sichuang Pharmaceutical Co. Ltd, 176 Keyi Rd, Kunming, Yunnan, 650106, China.

Sicomed, Hong Kong. See *Hong Kong Medical, Hong Kong.*

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Sicomed, Rus. See *Rompharm, Rus.*

Sicor, Rus. Sicor Europe SA, Leningradskii prospekt 37a, k. 14, Business-centre Zapadny Most, 125167 Moscow, Russia.
url: www.sicor.com

Sicor, USA. See *Teva, USA.*

Sideck, Ital. Sideck Farmaceutici S.r.l., Via Tremestieri 2 trav. n. 16, 95030 Mascalucia (CT), Italy.

Sidefarma, Port. Sidefarma SA, Rua da Guine 26, 2689-514 Prior Velho, Portugal.

Sidefarma, Thai. See *Zuellig, Thai.*

Sidhbali, India. Sidhbali Formulations, NH-58 Narsan Khurd, Roorkee, Dist. Haridwar, Uttrakhand, 247 667, India.

Sidmak, India. Sidmak Laboratories (India) Ltd, National Highway No.8, Abrama, Valsad 396 001, India.
url: www.sidmak.com

Sidmak, USA. See *Pliva, USA.*

Sidroga, Switz. Sidroga AG, Postfach, 4800 Zofingen, Switzerland.
url: www.sidroga.com

Sidus, Arg. Laboratorios Sidus S.A., Av. del Libertador 742, 1638 Vicente Lopez, Buenos Aires, Argentina.
url: www.sidus.com.ar

Sidus, China. See *Sidus, Arg.*

Sieger, Gr. Sieger Pharma AE, Kifisia 48-50, 115 26 Athens, Greece.

Siegfried, Cz. See *Siegfried, Switz.*

Siegfried, Ger. Siegfried Pharma GmbH, Hofer Strasse 25, 81737 Munich, Germany.

Siegfried, Neth. See *Siegfried, Ger.*

Siegfried, Switz. Siegfried CMS AG, 4800 Zofingen, Switzerland.

Siegfried, Thai. See *Diethelm, Thai.*

Siemens, Canad. See *Siemens, USA.*

Siemens, Fr. Siemens Medical Solutions Diagnostics, 49-51 quai de Dion-Bouton, 92815 Puteaux cdx, France.

Siemens, Ger. Siemens & Co., Heilwasser und Quellenprodukte des Staatsbades Bad Ems GmbH & Co. KG, Arzbacher Str. 78, 56130 Bad Ems, Germany.
url: www.emser.de

Siemens, Ital. Siemens Healthcare Diagnostics Srl, Viale Piero e Alberto Pirelli 10, 20126 Milan (MI), Italy.
url: www.siemens.com

Siemens, S.Afr. Siemens Southern Africa, 300 Janadel Ave, Halfway House, Midrand 1685, South Africa.
url: www.siemens.co.za

Siemens, Switz. See *Ecosol, Switz.*

Siemens, USA. Siemens Medical Solutions, 511 Benedict Ave, Tarrytown, NY 10591, USA.

Sienna, India. Sienna Formulations Pvt Ltd, 3 Matruchhaya Apartment, Arunoday Society Lane 4, Alkapuri, Vadodara 390007, Gujarat, India.
url: www.sienna.co.in

Siesta, India. Siesta Pharmaceuticals, A-802 Windsor Plaza, Alkapuri, Barodo 390 005, India.

Sifa, Turk. Şifa Kimya İlaç Kozmetik San. ve Tic. A.Ş., 2. Organize Sanayi Bölgesi, Krim Cad. No:15 Selçuklu, Selçuklu, Konya, Turkey.
url: www.sifakimya.com

Sifar, Turk. Sifar İlaçları Tic. ve San. A.Ş., Dr. Faruk Ayanoglu Cad. No: 26 D: 1, Fenerbahçe, İstanbul, 34726, Turkey.
url: www.sifar.com.tr

Sifarma, Ital. Sifarma S.p.A., Via Brunelleschi 12, 20146 Milan (MI), Italy.
url: www.sifarma.it

Sifauman, Port. Sifauman Especialidades Farmacêuticas Lda, Portugal.

SIFFRA, Ital. S.I.F.FR.A Farmaceutici S.r.l., Via Pontida 1/a, 20025 Legnano (MI), Italy.
url: www.siffra.it

SIFI, Cz. See *SIFI, Ital.*

SIFI, Ital. Società Industria Farmaceutica Italiana S.p.A., Via Ercole Patti 36 Lavinaio, 95020 Aci Sant' Antonio (CT), Italy.
url: www.sifi.it

SIFI, Mex. Laboratorios Sifi de Mexico SA de CV, Homero 418 Piso 10, 11560 Miguel Hidalgo Polanco, Mexico DF, Mexico.

SIFI, Rus. See *Schering-Plough, Rus* and *Zambon, Rus.*

SIFI, Singapore. See *Green Cross, Singapore.*

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Sigillata, Ital. See *Sigillata, UK.*

Sigillato, Neth. See *Sigillato, UK.*

Sigillata, UK. Sigillata Ltd, Suite 23, Park Royal House, 23 Park Royal Rd, London, NW10 7JH, UK.

Sigma, Arg. Laboratorios Sigma, Chaco 667, 5000 Cordoba Capital, Argentina.

Sigmo, Austral. Sigma Pharmaceuticals P/L, 96 Merrindale Drive, Croydon, VIC 3136, Australia.
url: www.sigmaco.com.au

Sigma, Braz. See *Novaquimica, Braz.*

Sigma, Hong Kong. See *GSK, Hong Kong.*

Sigma, India. See *Maneesh, India.*

Sigma, NZ. See *Zuellig, NZ.*

Sigma, Philipp. See *Zenaust, Philipp.*

Sigma, Rus. TNK Sigma, G Dankov Zaitseva ul 8, 399851 Lipetskaya, Russia.
url: www.enterosgel.ru

Sigmo, Singapore. See *Goldplus, Singapore.*

Sigman, India. Sigman Wellness, 102 Shailly, Opp. SAL Haspita, Nr St Kabir School Thaltej, Ahmedabad, India.

Sigmapharm, Austria. Sigmapharm Arzneimittel GmbH & Co KG, Leystrasse 129, A-1204 Vienna, Austria.
url: www.sigmopharm.at

Sigmopharm, Hung. Sigmapharm, Dunadülö u 33, 1212 Budapest, Hungary.

Sigmapharm, Switz. See *Ridupharm, Switz.*

Sigmor, Ital. Sigmor Italia S.p.A., Via Sombreno 11, 24011 Almè (BG), Italy.

Sigma-Tau, Canad. Sigma-Tau Pharmaceuticals Inc., 200 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.
url: www.sigma-tau.com

Sigma-Tau, China. See *Sigma-Tau, Ital.*

Sigma-Tau, Cz. See *Sigma-Tau, Ital.*

Sigma-Tau, Fr. Sigma-Tau France, 5 av. de Verdun, 94202 Ivry sur Seine, France.
url: www.sigma-tau.it

Sigma-Tau, Ger. Sigma-Tau Arzneimittel GmbH, Shadowstr. 44, 40212 Dusseldorf, Germany.
url: www.sigma-tau.de

Sigma-Tau, Hong Kong. See *Keller, Hong Kong* and *Sino-Asia, Hong Kong.*

Sigma-Tau, Irl. See *Sigma-Tau, Ital.*

Sigma-Tau, Ital. Sigma Tau S.p.A., Via Pontina Km. 30,400, 00040 Pomezia (Rome), Italy.
url: www.sigma-tau.it

Sigma-Tau, Neth. Sigma-Tau Ethiforma B.V., Postbus 100/72, 9400 CB Assen, Netherlands.
url: www.sigma-tau.it

Sigma-Tau, Philipp. See *Diethelm, Philipp.*

Sigma-Tau, Rus. See *Riace, Rus.*

Sigma-Tau, Spain. Sigma Tau Espana, Poligono Azque, Apt. do 1144, Alcalá de Henares, 28815 Madrid, Spain.
url: www.sigma-tau.com

Sigma-Tau, Switz. Sigma-Tau Pharma AG, Luzernerstrasse 2, 4800 Zofingen, Switzerland.
url: www.sigma-tau.ch

Sigma-Tau, UK. Sigma-Tau Pharma Ltd, Abbey House, 1650 Arlington Business Park, Reading, Berkshire, RG7 4SA, UK.
url: www.sigma-tau.co.uk

Sigmo-Tau, USA. Sigma-Tau Pharmaceuticals Inc., 800 S Frederick Ave, Suite 300, Gaithersburg, MD 20877, USA.
url: www.sigmatau.com

Signova, India. Signova Pharma Pvt Ltd, 24 Baninagar 1st Bye Lane, Piyoli Phukan Rd, Rehabari, Guwahati 781 008, India.

Silanes, Mex. Laboratorios Silanes S.A. de C.V., Amores No. 1304, Col. del Valle, Deleg. Benito Juarez, 03100 Mexico D.F., Mexico.
url: www.silanes.com.mx

Silarx, USA. Silarx Pharmaceuticals Inc., 19 West St, Spring Valley, NY 10977, USA.
url: www.silarx.com

Silco, Venez. See *Silva, Venez.*

Silesia, Chile. Laboratorios Silesia SA, Av. Chile Espana 325, Santiago, Chile.

Silom, Singapore. See *Alcare, Singapore.*

Silom, Thai. Silom Medical Co. Ltd, 35/3 Suparaj Soi 1, Phaholyothin Rd, Samsennai, Bangkok 10400, Thailand.

Silroc, Hong Kong. Silroc International (HK) Ltd, Unit C, 5/F, Skyline Tower, 18 Tong Mi Rd, Mongkok, Kowloon, Hong Kong.

Silva, Venez. Laboratorios Silca, Silva & Cia., Sucs. S.A., Paraderos a Venus 221, Caracas, Venezuela.

Silvergate, USA. Silvergate Pharmaceuticals Inc., 6251 Greenwood Plaza Blvd, Suite 101, Greenwood Village, CO 80111, USA.
url: www.silvergatepharma.com

Silvestre, Braz. Silvestre Labs. Química & Farmacêutica Ltda., Av. Vinte e Quatro S/N, 21941-590 Rio de Janeiro, RJ, Brazil.
url: www.silvestrelabs.com.br

Simaport, Port. Simaport Comércio de Produtos Médico-Dentários Lda, Rua Prof. Henrique de Barros, Edifício Sagres 1 A, 2685-338 Prior Velho, Portugal.

Simayla, S.Afr. See *Zydus, S.Afr.*

Simcere, China. Simcere Pharmaceutical Co. Ltd, Basaltic Ave 699-18, Nanjing 210042, China.
url: www.simcere.com

Simco, Switz. See *Unipharma, Switz.*

Sime Darby, Malaysia. Sime Darby Marketing Sdn Bhd, F-F10, Mezzanine F1, Lot PT 11101, Kompleks Sime Darby, Jln Kewajipan, 47600 Subang Jaya, Selangor, Malaysia.

Sime Darby, Singapore. Sime Darby Marketing, A Division of Sime Darby Singapore Ltd, 896 Dunearn Rd, 04-03 Sime Darby Centre, S 589472, Singapore.

Simesa, Ital. Simesa S.p.A., Via F. Sforza Palazza Galileo, 20080 Basiglio (MI), Italy.

Simex, Indon. Simex Pharmaceutical Indonesia PT, Komplek Ruko Mitra Bahari 2, Jl. Pakin No 1, Blok E No. 15-16, Jakarta 14450, Indonesia.
url: www.simexpharmaceutical.com

Simons, Ger. Georg Simons GmbH, Eckenheimer Landstr. 100, 60318 Frankfurt, Germany.
url: www.simons.de

Simpex, Rus. See *Panacea, India.*

Sin Sin, Philipp. See *Philusa, Philipp.*

Sinbia, Fr. See *Pierre Fabre, Fr.*

Sincerity, Hong Kong. Sincerity (Asia) Co. Ltd, 1/F, Blk E, Nam Pak Hong Bldg, 24 Bonham Strand W, Hong Kong.

Sinclair, Austral. See *Sinclair, UK.*

Sinclair, Austria. See *Sinclair, Ger.*

Sinclair, Fr. See *CS, Fr.*

Sinclair, Ger. Sinclair Pharma GmbH, Westhafen Tower, Westhafenplatz 1, 60327 Frankfurt am Main, Germany.
url: www.sinclairpharma.com

Sinclair, Hong Kong. See *DKSH, Hong Kong.*

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Sinclair, Israel. See *Rafa, Israel.*

Sinclair, Ital. Sinclair S.r.l., Viale F. Restelli 29, 20124 Milan (MI), Italy.
url: www.sinclairpharma.com

Sinclair, Malaysia. See *Apex, Malaysia.*

Sinclair, Port. See *Sinclair, Spain.*

Sinclair, Singapore. See *Masquad, Singapore.*

Sinclair, Spain. Sinclair Pharmaceutical España SL, Av. de Castilla 2, Edificio Dublin planta 2, Parque Empresarial de San Fernando, 28830 San Fernando de Henares, Spain.

Sinclair, Switz. Sinclair Pharma GmbH, Tösstalstrasse 46a, 8488 Turbenthal, Switzerland.

Sinclair, UK. Sinclair IS Pharma plc, Whitfield Court, 30-32 Whitfield St, London, W1T 2RQ, UK.
url: www.sinclairispharma.com

Sindan, Pol. Sindan, ul. Puławska 314, 02-818 Warsaw, Poland.
url: www.sindan.pl

Sindon, Thai. See *RX, Thai.*

Sine, China. Sine Pharmaceutical Co Ltd, 905 Jinqiao Rd, Pudong, Shanghai, China.
url: www.sinepharm.com

Sinensix, Thai. See *Diethelm, Thai.*

SinGad, Denm. SinGad Pharma, Vibe Allé 5 blok 2B, 2980 Kokkedal, Denmark.

Singapore Genebio, Philipp. Singapore Genebia, Unit 1702, 17th Floor Jollibee Centre, San Miguel Ave, Pasig City, Metro Manila, Philippines.

Singapore Pharmaceutical, Singapore. Singapore Pharmaceutical Pte Ltd, 61 Kaki Bukit Ave 1, Shunli Industrial Park 05-31, S 417943, Singapore.

Singer, Hong Kong. See *Zuellig, Hong Kong.*

Singer Natura, Neth. Singer Natura BV, Kattegat 4d, 3446 CL Woerden, Netherlands.

Sinkhai, India. Sinkhai Healthcare Ltd, 4A-1 A Wing 4th Floor, Gundecha Onclave Kherani Rd, Saki Naka, Andheri (East), Mumbai, 400 072, India.

Sinnex, Hung. Sinnex ltd, Montevideo St 3/A, 1037 Budapest, Hungary.
url: www.sinnex.hu

Sino-Asia, Hong Kong. Sino-Asia Pharmaceutical Supplies Ltd, Rm 12 15/F, Honour Industrial Ctr, 6 Sun Yip St, Chai Wan, Hong Kong.

Sinobiopharma, China. Sinobiopharma Inc., 69 Olympic Street, Xinchang Tech Park, Nanjing, Jiangsu, 210019, China.
url: www.sinobp.com

Sinochem, Philipp. See *2 World Traders, Philipp.*

Sinopharm, Thai. See *Pharmahof, Thai.*

Sinovac, China. Sinovac Biotech Co Ltd, 39 Shangdi Xi Rd, Haidion District, Beijing 100085, China.
url: www.sinovac.com.cn

Sinphar Tian-Li, China. Sinphar Tian-Li Pharmaceutical Co. Ltd, Hongzhou, China.

Sinsin, Israel. Sinsin, Israel.

Sinteropico, Braz. Laboratório Sinterapico Industrial e Farmacêutica Ltda, Rua Olegario Cunha Lobo 177, 12940-000 Atibaia, SP, Brazil.

Sintesina, Arg. Sintesina S.A., Av. Pte. Arturo Illia 4194, 1613 Los Polvorines, Buenos Aires, Argentina.

Sintetica, Switz. Sintetica SA, Via Penate 5, casella postale 1764, 6850 Mendrisio, Switzerland.

Sintetica-Bioren, Switz. Sintetica-Biaren SA, 4 rue des Îles, 2108 Couvet, Switzerland.
url: www.sintetica-bioren.com

Sintexline, Spain. Sintexline SA, Poligono Industrial La Red, Calle 11 no 2, 41500 Alcala de Guadaira (Seville), Spain.

Sintez, Rus. Sintez OAO, Tverskaya ul. 20, Of. 530, 125009 Moscow, Russia.
url: www.sintezmos.narod.ru

Siomond, India. Siomand Pharmaceutical Pvt Ltd, 664 - B / III, Military Road, Anand Parbat, New Delhi 110 005, India.
url: www.siomondpharma.com

Sipaco, Denm. See *Niche, Denm.*

Sipaco, Fr. See *Sipaco, Port.*

Sipaco, Port. Sipaco Internacianal, Avda 5 de Outubro 267,6, 01600 Lisbon, Portugal.

Sipaco, Spain. See *Sipaco, Port.*

Siphar, Switz. Siphar SA, Casella postale 32, 6814 Cadempino, Switzerland.

Siping Aimo, China. Siping Aimo Pharmaceutical Co. Ltd, 2988 Dalu Development Zone, Tiedong, Siping, Jilin, 136001, China.
url: www.aimpharm.com.cn

Sipra, India. Sipra Remedies, Yashmuna 14, Ram Mandir Rd, Near Tilak Hall, Vile Porle (E), Mumbai, India.

SiRC, Singapore. See *Zyfas, Singapore.*

Sircle, USA. Sircle Labs Inc., PO Box 238, Ridgeland, MS 39158, USA.
url: www.sirclelabs.com

Sirius, USA. Sirius Laboratories Inc., 100 Fairway Drive, Suite 130, Vernon Hills, IL 60061, USA.
url: www.siriuslabs.com

Sirowa, Fin. Sirowa Helsinki, Rajatorpantie 41 C, 01640 Vantaa, Finland.

Sirton, China. See *Sirton, Ital.*

Sirton, Ital. Sirton Pharmaceuticals S.p.A., Piazza XX Settembre 2, 22079 Villa Guardia (CO), Italy.
url: www.sirton.it

Sirval, Ital. Sirval S.r.l., Via Maloia 8, 20158 Milan (MI), Italy.

Sistas, Turk. Sistaş İlaç San. A.Ş., Nafiz Gürman Mah., Turunçlu Sok. No: 17 A Blok, Merter, İstanbul, Turkey.
url: www.sistasilac.com

Sisu, Canad. Sisu Enterprises Co Inc., 104A-3430 Brighton Ave, Burnaby, British Columbia, V5A 3H4, Canada.
url: www.sisuhealth.com

SIT, Austria. See *SIT, Ital.*

SIT, Belg. See *SIT, Ital.*

SIT, Cz. See *SIT, Ital.*

SIT, Denm. See *SIT, Ital.*

SIT, Fin. See *SIT, Ital.*

SIT, Hung. See *SIT, Ital.*

SIT, Irl. See *SIT, Ital.*

SIT, Ital. Specialità Igienico Terapeutiche S.r.l., C.so Cavour 70, 27035 Mede (PV), Italy.

SIT, Neth. See *SIT, Ital.*

SIT, Norw. See *SIT, Ital.*

SIT, Philipp. See *SIT, Ital.*

SIT, Spain. See *SIT, Ital.*

SIT, Swed. See *SIT, Ital.*

SIT, Thai. See *Olic, Thai.*

Siu Guan, Malaysia. See *Averraes, Malaysia.*

Siu Guan, Philipp. See *Caan, Philipp* and *RBC-MDC, Philipp.*

Sivaderm, Arg. Lab. Sivaderm S.A., Sarmiento 2171 Pso. 8 Dto.A, 1044 Buenos Aires, Argentina.
url: www.sivaderm.com

Siwei, China. Siwei Pharamceutical Co. Ltd, Shandong, China.

Sixtem, Ital. Sixtem Life Srl, Via Adige 34, 50019 Sesto Fiorentino (FI), Italy.

SJ Pharm, USA. SJ Pharmaceuticals, 4587 Damascus Rd, Memphis, TN 38118, USA.
url: www.sjpharmacol.com

SJA, Gr. S.J.A PHARM, Arkoleon 11, 10445 Athens, Greece.

SK, China. SK Chemical Co. Ltd, China.

SK, Kor. SK Chemicals, 948-1 Daechi 3-dong, Gangnam-gu, Seoul (135-283), Korea.
url: www.skchemicals.com

SK, Philipp. See *Metro, Philipp.*

SK, Singapore. See *Wellchem, Singapore.*

SK, Thai. See *Casma, Thai.*

SKF, China. See *GSK, China.*

Skills, Ital. Skills in Farmacia S.r.l., Piazza Buonarroti 32, 20145 Milan (MI), Italy.
url: www.skillsfarmacia.it

Skin Care, Canad. See *Skin Care, USA.*

Skin Care, USA. Laboratory Skin Care Inc., Tahoe City, CA 96145-7469, USA.

Skin Shield, Austral. See *Skin Shield, NZ.*

Skin Shield, NZ. Skin Shield Products Ltd, 57 Woodside Ave, Northcote, Auckland, New Zealand.
url: skinshield.co.nz

Skinceuticals, Canad

SkinMedica, USA. SkinMedica Inc., 5909 Sea Lion Place, Ste H, Carlsbad, CA 92008, USA.
url: www.skinmedica.com

Skinvisible, Canad. See *Skinvisible, USA.*

Skinvisible, USA. Skinvisible Inc., 6320 S Sandhill Rd, Suite 10, Las Vegas, NV 89120, USA.
url: www.skinvisible.com

SKL, Braz. SKL Pharma Ltda, Av. Gabriela Mistral 464, 3701000 Sao Paula, Brazil.

Skopinski, Rus. Skopinski Farm Workd ZAO, 7-ya Kozhukhovskaya ul. 20, 115193 Moscow, Russia.

SK-RIT, Belg. See *GSK, Belg.*

Skye, USA. SkyePharma Inc., 10450 Science Center Drive, San Diego, CA 92121, USA.
url: www.skyepharma.com

Skyepharma, Austria. See *Skyepharma, UK.*

SkyePharma, Canad. See *Skye, USA.*
Skyepharma, Denm. See *Norpharma, Denm.*
Skyepharma, Neth. See *Skyepharma, UK.*
Skyepharma, Norw. See *Mundipharma, Norw.*
SkyePharma, Pol. See *Mundipharma, Pol.*
Skyepharma, UK. SkyePharma plc, 105 Piccadilly, London, W1V 9FN, UK.
Skymax, India. Skymax Laboratories Pvt Ltd, B-206 Shapath-IV, Opp. Karnavati Club, SG Highway, Ahmedabad 380 051, Gujarat, India.
url: skymaxindia.net
SL Pharm, China. SL Pharmaceutical Co. Ltd, Jinyu Building, 100 West Third Ring Rd, Haidian, Beijing, 100037, China.
url: www.slpharm.com.cn
Slate, USA. Slate Pharmaceuticals Inc., 318 Blackwell St, Suite 240, Durham, NC 27701, USA.
url: www.testopel.com
Slavic, Rus. Slavic Pharmacy LLC, Moscow, Russia.
SLE, Israel. Salomon, Levin, & Elstein Ltd, P.O. Box 8077, Kiryat Nordau, Netanya, Israel.
Slovakofarma, Hung. Slovakofarma Hungary Kft, Berlini út 47-49, 1045 Budapest, Hungary.
Slovakofarma, Singapore. See *Sime Darby, Singapore.*
Slovakofarma, Thai. See *Medline, Thai.*
SM, Gr. SM Pharmaceuticals ltd, Ag Oroys 43-45, 185 45 Piraeus, Greece.
url: www.smpharmaceuticals.com
SM, Philipp. See *PNF, Philipp.*
SM, Thai. SM Pharmaceutcal Co. Ltd, 82, 84 Arkarn 2, Ratchdamnoen Ave, Bangkok 10200, Thailand.
SM, Venez. Laboratorio Farmaceutico S.M. C.A., Av. 59-A N99 L20 Circun.2 Apdo. 552, Cab El Sajarito Maracaibo, Zulia, Venezuela.
SMA Nutrition, Irl. See *Wyeth, UK.*
SMA Nutrition, UK. See *Wyeth, UK.*
Smaller, Spain. See *ASAC, Spain.*
Smart, S.Afr. Smart Pharmaceuticals Pty Ltd, Post Net Suite 67, Private Bag X3, Glosderry 7702, South Africa.
url: www.smartpharmaceuticals.co.za
Smart Intermed, Gr. Smart Intermed S Mitsiou - A Kondylis & Co EE, Vas Sophias 112, 115 27 Athens, Greece.
SmartScience, Singapore. See *MD, Singapore.*
Smartshield, Canad. See *Smartshield, USA.*
Smartshield, USA. Smartshield Sunscreens, 2282 Vantage St, Dallas, TX 75207, USA.
Smashbox, Canad. See *Smashbox, USA.*
Smashbox, USA. Smashbox Beauty Cosmetics Inc., 8538 Warner Drive, Culver City, CA 90232, USA.
SMB, Belg. Laboratoires S.M.B. SA, Rue de la Pastorale 26-28, 1080 Brussels, Belgium.
url: www.smb.be
SMB, Chile. Laboratorios SMB Farma SA, Av. Bulnes 377, Dpto 305, Santiago, Chile.
SMB, Cz. See *SMB, Belg.*
SMB, Fin. See *SMB, Belg.*
SMB, Fr. See *SMB, Belg.*
SMB, Irl. See *SMB, Belg.*
SMB, Malaysia. See *Apex, Malaysia.*
SMB, Neth. See *Bournonville, Neth.*
SMB, Philipp. See *Britton, Philipp.*
SMB, Port. See *SMB, Belg.*
SMB, Singapore. See *Pan-Malayan, Singapore.*
SMB, Thai. See *Berlin Pharm, Thai.*
Smetana, Austria. See *EF-EM-ES, Austria.*
SMHP, Philipp. Sherryville Medical & Healthcare Products, Manor Building, 2629 Taft Ave, Malate 1004, Manila, Philippines.
Smith, Hung. See *Abbott, Hung.*
Smith & Nephew, Austral. Smith & Nephew P/L, 315 Ferntree Gully Road, Mt Waverley, VIC 3149, Australia.
url: www.smith-nephew.com
Smith & Nephew, Austria. See *Smith & Nephew Healthcare, UK.*
Smith & Nephew, Belg. See *GSK, Belg.*
Smith & Nephew, Canad. Smith & Nephew Inc., 4707 Levy St, St-Laurent, Quebec, H4R 2P9, Canada.
url: www.smith-nephew.com
Smith & Nephew, Cz. See *Smith & Nephew Healthcare, UK.*
Smith & Nephew, Denm. Smith & Nephew A/S, Slotsmarken 14, 2970 Hørsholm, Denmark.
url: www.smith-nephew.com
Smith & Nephew, Fin. Smith & Nephew Oy, Ayritie 12 C, 01510 Vantaa, Finland.
url: www.smith-nephew.com
Smith & Nephew, Fr. Smith & Nephew SA, 25 bd Alexandre-Oyon, 72019 Le Mans cdx 2, France.
url: www.smith-nephew.com
Smith & Nephew, Ger. Smith & Nephew GmbH, Osterbrooksweg 71, 22869 Schenefeld, Germany.
url: www.smith-nephew.de
Smith & Nephew, Gr. See *Smith & Nephew Healthcare, UK.*
Smith & Nephew, Hong Kong. Smith & Nephew Ltd, Units 813-816, 8/F Delta House, 3 On Yiu St, Shatin, N.T., Hong Kong.
url: www.smith-nephew.com
Smith & Nephew, Hung. See *Beiersdorf, Hung.*
Smith & Nephew, Irl. Smith & Nephew Medical, Carraig Court, George's Ave, Blackrock, Co. Dublin, Ireland.
url: www.smith-nephew.com
Smith & Nephew, Ital. Smith & Nephew S.r.l., Via De Capitani 2A, 20041 Agrate Brianza (MI), Italy.
url: www.smith-nephew.com
Smith & Nephew, Malaysia. See *Zuellig, Malaysia.*
Smith & Nephew, Neth. See *GSK, Neth.*
Smith & Nephew, Norw. Smith & Nephew AS, Postboks 224, 1379 Nesbru, Norway.
url: www.smith-nephew.com
Smith & Nephew, NZ. Smith & Nephew Ltd, P.O. Box 442, Auckland, New Zealand.
url: www.smith-nephew.com
Smith & Nephew, Philipp. See *East Lane, Philipp.*
Smith & Nephew, Port. See *Smith & Nephew Healthcare, UK.*
Smith & Nephew, S.Afr. Smith & Nephew Pharmaceuticals (Pty) Ltd, P.O. Box 92, Pinetown 3600, South Africa.
url: www.smith-nephew.com
Smith & Nephew, Singapore. See *Zuellig, Singapore.*
Smith & Nephew, Spain. Smith Nephew, Fructous Gelabert 2-4, Sant Joan Despi, 08970 Barcelona, Spain.
url: www.smith-nephew.com
Smith & Nephew, Swed. Smith & Nephew AB, Box 143, 431 22 Mölndal, Sweden.
url: www.smith-nephew.se
Smith & Nephew, Switz. Smith & Nephew AG, Glutz Blotzheim-Strasse 1, 4502 Solothurn, Switzerland.
url: www.smith-nephew.ch
Smith & Nephew, Thai. Smith & Nephew Ltd, 344/3 Soi Rongrien Yepun, Rama IX Rd, Bangapi, Huay Kwang, Bangkok 10320, Thailand.
url: www.smith-nephew.com
Smith & Nephew, UK. See *Smith & Nephew Healthcare, UK.*
Smith & Nephew, USA. Smith & Nephew United, 11775 Starkey Rd, Largo, FL 33773-1970, USA.
url: www.smith-nephew.com
Smith & Nephew Healthcare, UK. Smith & Nephew Healthcare Ltd, Healthcare House, Goulton St, Hull, HU3 4DJ, UK.
url: www.smith-nephew.com
Smith & Nephew Pharmaceuticals, UK. See *Smith & Nephew Healthcare, UK.*
Smith & Nephew SoloPak, USA. See *SoloPak, USA.*
Smith Kline & French, Canad. See *GSK, Canad.*
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Smith Kline & French, Spain. See *GSK, Spain.*
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Smith Kline Dauelsberg, Ger. See *GSK, Ger.*
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SmithKline Beecham, Ital. See *GSK, Ital.*
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SmithKline Beecham, Mex. See *GSK Consumer, Mex.*
SmithKline Beecham, Neth. See *GSK, Neth.*
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SmithKline Beecham, Singapore. See *GSK, Singapore.*
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SmithKline Beecham OTC, Ger. See *GSK Consumer, Ger.*
SmithKline Beecham Sante, Fr. See *GSK, Fr.*
SmithKline Consumer, Canad. See *GSK Consumer, Canad.*
SmithKline Diagnostics, USA. See *Beckman, USA.*
SMTL, UK. Surgical Materials Testing Laboratory, Princess of Wales Hospital, Coity Rd, Bridgend, Mid Glamorgan, CF31 1RQ, UK.
url: www.smtl.co.uk
Snow Brand, Hong Kong. Snow Brand Hong Kong Co Ltd, Hong Kong.
Snow Leopard, China. See *Xuebao, China.*
Soapopular, Canad. Soapopular Inc., Suite 102, 370 Queens Quay West, Toronto, Ontario, M5V 3J3, Canada.
Sobet, Ukr. Sobet and K Private Company, Kulparkovskaya Street, 95, Lviv, 79021, Ukraine.
Sobio, Fr. See *GSK, Fr.*
Socobom, Belg. Socobom, Louisalaan 149 bus 24, 1050 Brussels, Belgium.
url: www.socobom.com
Socofar, Port. Socofar - Sociedade Comercial de Especialidades Farmacêutics S.A., Rua Padre Luis Aparicio 3, 1150 Lisbon, Portugal.
Socopharm, Fr. Laboratoires Socopharm, Chemin de Marcy, 58800 Corbigny, France.
Sodhan, Turk. Sodhan Aşi ve Kan. Ürünleri, Libya Cad. Becerikli Sok. No: 13/1-2, Kocatepe, Ankara, Turkey.
url: www.sodhan.com
Sodia, Fr. Laboratoires Sodia, av. Robert Schuman, 51100 Reims, France.
Sodietal, Fr. See *Novartis Nutrition, Fr.*
SoDiFarm, Ital. So.Di.Farm Srl, Via Adige 5, 66020 Sambuceto di S Giovanni Teatino (CH), Italy.
url: www.sodifarm.it
Sodilac, Fr. Sodilac, 176 av. Charles-de-Gaulle, 92522 Neuilly-sur-Seine cdx, France.
Soekami, Fr. See *Roche Nicholas, Fr.*
Sofar, Ital. Sofar S.p.A., Via Firenze 40, 20060 Trezzano Rosa (MI), Italy.
url: www.sofarfarm.it
Sofex, Port. Sofex Farmacêutica, Lda, Rua Sebastião e Silva 25, Zona Industrial de Massamá, 2745-838 Queluz, Portugal.
Sofibel, Fr. See *Fumouze, Fr.*
SofLens, S.Afr. See *Bausch & Lomb, S.Afr.*
SoftRinse, USA. SoftRinse Corp., 2411 Third St South, Wisconsin Rapids, WI 54494, USA.
Sofus, Denm. See *Sofus, Swed.*
Sofus, Norw. See *Sofus, Swed.*
Sofus, Swed. Sofus Stockholm Consulting AB, Torsgatan 4, 111 23 Stockholm, Sweden.
url: www.sofus.se
Soho, Indon. Soho Industri Pharmasi PT, Jl Pulo Gadung No 5, Kawasan Industri Pulo Gadung, Jakarta Timur 13920, DKI Jaya, Indonesia.
Sojar, Arg. Sojar S.A., Velez Sarsfield 870, 2013 Rosario, Santa Fe, Argentina.
Sol, Fr. Sol France, rue de Compas 8, Z.I. des Béthunes, 95060 Saint-Ouen-l'Aumône, France.
url: www.sol.it
Sol, Neth. See *Sol, Fr.*
Solace, USA. Solace Nutrition, One Research Court, Suite 450, Rockville, MD 20850, USA.
url: www.solacenutrition.com
Solagran, Rus. Solagran Ltd, Nakhimova per. 11/1, 634012 G Tomsk, Russia.
Solamed, Hung. Solamed Trading Co Ltd, Kléh István u 9, 1126 Budapest, Hungary.
url: www.solamed.hu
Solara, Mex. Solara Farmaceutica SA de CV, Av Paseo de las Palmas 330 PB, 11000 Lomas de Chapultepec, Mexico DF, Mexico.
Solas, Indon. Solas PT, Jl Industri No 18, Cimareme-Padalarang, Bandung 40553, Jawa Barat, Indonesia.
Solba, Fr. See *Phytosolba, Fr.*
Solco, China. See *Solco, Switz.*
Solco, Cz. See *ICN, Cz.*
Solco, Fin. See *Oriola, Fin.*
Solco, Ger. See *Valeant, Ger.*
Solco, Hong Kong. See *Kai Cheong, Hong Kong.*
Solco, Indon. See *Pharos, Indon.*
Solco, Malaysia. See *Pharmaforte, Malaysia.*
Solco, Rus. See *Valeant, Rus.*
Solco, Singapore. See *Pharmaforte, Singapore.*
Solco, Swed. See *Valeant, Ger.*
Solco, Switz. Solco Basel SA, Ruhrbergstrasse 21, 4127 Birsfelden, Switzerland.
url: www.solco.ch
Solco, Thai. See *Diethelm, Thai.*
Solco, UK. See *Valeant, UK.*
Soldan, Canad. See *Soldan, Ger.*
Soldan, Ger. Dr. C. Soldan GmbH, Herderstr. 5-9, 90427 Nürnberg, Germany.
url: www.soldan.com
Solea, Ital. Solea S.a.s., Via Cassoli 22, 42100 Reggio Emilia (RE), Italy.
Solfran, Mex. Laboratorios Solfran S.A., Altos Hornos No. 2721, Fracc. Ind. el Alamo, 45590 Tlaquepaque, Jalisco, Mexico.
Solgar, Canad. See *Solgar, USA.*
Solgar, UK. See *Boots, UK.*
url: www.solgar.co.uk
Solgar, USA. Solgar Vitamin Co. Inc., 500 Willow Tree Rd, Leonia, NJ 07605, USA.
url: www.solgar.com
Solitaire, India. Solitaire Pharmacia Pvt Ltd, Plot No 73, Industrial Area, Phase II, Chandigarh 160002, India.
url: solitairepharmacia.tradeindia.com
Soll, Gr. Soll Hellas AE, 17 Chilm Leof., Spaton Attikis, TK 19004, Greece.
Solmer, Switz. Solmer SA, Postfach 100, 6976 Castagnola-Suisse, Switzerland.
SoloPak, USA. SoloPak Pharmaceuticals Inc., 1845 Tonne Rd, Elk Grove Village, IL 60007-5125, USA.
Solpharm, Pol. Solpharm Sp z o o, ul. Zwycięzców 42/93, 03-938 Warsaw, Poland.
url: www.solpharm.pl
Solpro, Mex. Solpro S.A. de C.V., Ciruelos No. 137, Local 26, Centro Comercial El Pinar, Jurica, 76100 Queretaro, Mexico.
url: www.solpro.com.mx
Solstice, USA. Solstice Neurosciences, 701 Gateway Blvd, Suite 250, South San Francisco, CA 94080, USA.
url: www.solsticeneuro.com
Soludia, Fr. Laboratoires Soludia, Rte de Revel, 31450 Fourquevaux, France.
url: www.soludia.com
Solumed, Canad. Les Enterprises Solumed Inc., 2109 Le Chatelier, Laval, Quebec, H7L 5B3, Canada.
Solus, India. See *Ranbaxy, India.*
Solvang, Philipp. Solvang Pharma Inc., 238 Tomas Morato Ave, South Triangle, Quezon City, Philippines.
Solvay, Austral. Solvay Pharmaceuticals, Division of Solvay Biosciences P/L, Locked Bag 1070, Pymble, NSW 2073, Australia.
url: www.solvaypharmaceuticals.com
Solvay, Austria. Solvay Pharma GmbH, Donaustrasse 106, A-3400 Klosterneuburg, Austria.
url: www.solvaypharma.at
Solvay, Belg. Solvay Pharma & Cie S.N.C., Blue Planet Building, Ave Bourgemestre E. Demunter 3, 1090 Brussels, Belgium.
url: www.solvaypharmaceuticals.com
Solvay, Braz. Solvay Farma Ltda, Rua Sergipe 120, 1243000 São Paulo, São Paulo, Brazil.
Solvay, China. See *Abbott, China.*
Solvay, Cz. Solvay Pharma sro, Bieblová 19, 150 00 Prague 5, Czech Republic.
Solvay, Denm. Solvay Pharma ApS, Hørkær 28, 2730 Herlev, Denmark.
url: www.solvay-pharma.dk
Solvay, Fin. See *Algol, Fin.*
Solvay, Fr. Solvay Pharma, 42 rue Rouget-de-Lisle, B.P. 22, 92151 Suresnes cdx, France.
url: www.solvaypharmaceuticals.com
Solvay, Ger. Solvay Arzneimittel GmbH, Hans-Böckler-Allee 20, 30173 Hannover, Germany.
url: www.solvay-arzneimittel.de
Solvay, Gr. Solvay Pharma M.E.P.E., Agiou Dimitriou 63, 174 56 Alimos, Greece.
url: www.solvay.com
Solvay, Hong Kong. See *Keller, Hong Kong.*
Solvay, Hung. Solvay Pharma Kft, Hegyalja út 100/a, 1112 Budapest, Hungary.
url: www.solvaypharma.hu
Solvay, India. See *Abbott, India.*
Solvay, Indon. Solvay Pharma Indonesia PT, Wisma 46 Kota BNI Lt 12.01, Jl Jend Sudirman Kav 1, Jakarta 10220, DKI Jaya, Indonesia.
Solvay, Irl. Solvay Healthcare Ltd, Belgard Rd, Tallaght, Dublin 24, Ireland.
url: www.solvaypharmaceuticals.com
Solvay, Israel. See *Perrigo, Israel.*
Solvay, Ital. Solvay Pharma S.p.A., Via della Libertà 30, 10095 Grugliasco (TO), Italy.
url: www.solvaypharmaceuticals.com
Solvay, Malaysia. See *Zuellig, Malaysia.*
Solvay, Neth. Solvay Pharma BV, C J Van Houtenlaan 36, 1381 CP Weesp, Netherlands.
url: www.solvaypharmaceuticals.com
Solvay, Norw. Solvay Pharma AS, Hamang Terrasse 55, Postboks 248, 1301 Sandvika, Norway.
url: www.solvay.no
Solvay, NZ. Solvay Interox (N-Z) Ltd, P.O. Box 62-005, Mt Wellington, Auckland, New Zealand.
url: www.solvay.com
Solvay, Philipp. Solvay Pharma Inc. Philippines, 6/F Port Royal Place, 118 Rada St, Legaspi Vill, Makati City, Philippines.
Solvay, Pol. Solvay Pharmaceuticals GmbH (Sp. zo.o.), Przedstawicielstwo w Polsce, ul. Orzycka 6, 02-695 Warsaw, Poland.
url: www.solvaypharma.pl
Solvay, Port. Solvayfarma, Lda, Av. Marechal Gomes da Costa 33, 1800-255 Lisbon, Portugal.
url: www.solvaypharmaceuticals.com
Solvay, Rus. Solvay Pharma GmbH, Vavilova ul. 24, et. 5, 119991 Moscow, Russia.
url: www.solvay-pharma.ru
Solvay, S.Afr. Solvay Pharma (Pty) Ltd, P.O. Box 5278, halfway House 1685, South Africa.
url: www.solvaypharmaceuticals.com
Solvay, Singapore. See *Sime Dorby, Singapore.*
Solvay, Spain. Solvay Pharma, Avda Diagonal 507-509, 08029 Barcelona, Spain.
url: www.solvaypharma.es
Solvay, Swed. Solvay Pharma AB, Sisjö Kullegata 8, 421 32 Västra Frölunda, Sweden.
url: www.solvaypharmaceuticals.com
Solvay, Switz. Solvay Pharma AG, Untermattweg 8, 3027 Bern, Switzerland.
url: www.solvaypharmaceuticals.com
Solvay, Thai. See *Berli Jucker, Thai.*
Solvay, Turk. Solvay İlaç Sanayi ve Ecza Tic. Ltd. A.Ş., Aydınevler Moh., Sanayi Cad. No. 22, Kat: 2, Küçükyalı, İstanbul, 34854, Turkey.
url: www.solvayilac.com
Solvay, UK. Solvay Healthcare, Mansbridge Rd, West End, Southampton, Hampshire, SO18 3JD, UK.
url: www.solvayhealthcare.co.uk
Solvay, Ukr. Solvay Pharma, Zhovtneva Ploscha 12, Dnipropetrovsk, 49027, Ukraine.
url: www.solvay.com
Solvay, USA. Solvay Pharmaceuticals Inc., 901 Sawyer Road, Marietta, GA 30062, USA.
url: www.solvaypharmaceuticals-us.com
Solvay Duphar, Swed. See *Meda, Swed.*
Solymes, Fr. See *Sanofi-Aventis, Fr.*

Soma, Braz. See *Theraskin, Braz.*

Somak, Canad. Somak International Inc., 1985 rue Monterey, Laval, Quebec, H7L 3T6, Canada.

Somapharm, Canad. Somapharm (Division of Bariatrix Nutrition Inc.), 4905 Fairway, Lachine, Quebec, H8T 1B7, Canada.

Somaxon, USA. Somaxon Pharmaceuticals, 3570 Carmel Mountain Rd, San Diego, CA 92130, USA.
url: www.somaxon.com

Somedico, Malaysia. Somedico Sdn Bhd, 28 Jln PJU 3.45, Sunway Damansara, 47810 Petaling Jaya, Selangor, Malaysia.

Somex, Irl. See *Somex, UK.*

Somex, UK. Strandhaven ltd trading as Somex Pharma, 600 High RD, Seven Kings, Ilford, Essex, IG3 8BS, UK.

Sommerville, UK. Marie Sommerville Health Ltd, 69 Alexander Ave, Eaglesham, Glasgow, G76 0DS, UK.

Somyurek, Turk. HV Somyürek Veresesi, Tevfikpaşa No 20/3, Kiziltoprak, Istanbul, Turkey.

Sona-Farm, Ukr. OOO Sona-Farm, Nikolaya Grinchenko Street, 4, Kiev, 03038, Ukraine.
url: sonapharm.com.ua

Song He, China. Song He Pharmaceutical Co. Ltd, Harbin, China.

Sonix, Philipp. Sonix Pharmaceuticals Inc., Unit 2207, 88 Corporate Ctr, Sedeno cor Valero Sts, Salcedo Vill, Makati City, Philippines.

Sonphar, Spain. Laboratorios Sonphar SL, Castillejos 177, 08013 Barcelona, Spain.

Sons, Mex. Laboratorios Química Son's S.A. de C.V., Av. 23 Poniente No. 2302-A, 72410 Puebla, Pue., Mexico.

Sooft, Ital. Sooft Italia S.r.l., Contrada Molino 17, 63025 Montegiorgio (AP), Italy.
url: www.sooft.it

Sopar, Gr. Sopar Pharma Ltd Greece, Av. Kamaterou 2-4, 134 51 Kamatero, Greece.

Sopar, Neth. See *Will-Pharma, Neth.*

Sopharm, Fr. Sopharm, 40 rue des Bergers, 75015 Paris, France.

Sopharma, Bulg. Sopharma Pharmaceuticals, 16 Iliensko Shosse Str., 1220 Sofia, Bulgaria.
url: www.sopharma.bg

Sopharma, Pol. Sopharma Poland Sp. zo.o., ul. Szyszkowa 58, 02-285 Warsaw, Poland.

Sopharma, Rus. Sopharma AO, Taganskaya ul. 19, et. 10, 109147 Moscow, Russia.
url: www.sopharma.bg

Sopharma, Singapore. See *LF, Singapore.*

Sopharma, Ukr. Sopharma, Prospect Mira, 13, Kiev, 02105,, Ukraine.
url: www.sopharma.bg

Sopherion, Canad. See *Sopherion, USA.*

Sopherion, USA. Sopherion Therapeutics Inc., 200 104 Carnegie Centre, Princeton, NJ 08540, USA.

Sophia, Mex. Laboratorios Sophia S.A. de C.V., Poniente 44 2702, Azcapotzalco, Xochimanca, 2870 Mexico D.F., Mexico.
url: www.sophia.com.mx

Sophien, Ger. Sophien-Arzneimittel GmbH, Handwerkerstr. 2a, 56070 Koblenz, Germany.
url: www.sophien-arzneimittel.de

Soprolin, Fr. Laboratoires Soprolin Sarl, 27 rue du Bedat, B.P. 116, 47203 Marmande cdx, France.
url: www.supro.tm.fr

SORAS, Fr. SORAS-GLF SA, 94 rue de l'Abbe-Groult, 75015 Paris, France.
url: www.embryolisse.com

Soraya, Pol. Soraya SA - Cederrath International, ul. Polna 21, 05-250 Radzymin, Poland.
url: www.pharbio.pl

Soreq, Israel. Soreq Nuclear Research Center, Yavne, 81800, Israel.
url: www.soreq.gov.il

Soria, Spain. Soria Natural SA, Polígono La Sacea, Garray-Soria 42162, Spain.

Soria Natural, Spain. Soria Natural, Pol Ind La Sacea 1, Garray, 42162 Soria, Spain.
url: www.sorianatural.es

Sorin, Ital. See *Nycomed, Ital.*

Sorin-Maxim, Fr. Laboratoires Sorin-Maxim, rue Claude-Bernard, 12700 Capdenac, France.

Sorres, Canad. Sorres Pharma Inc., Suite 100, 6111 Royalmount Ave, Montreal, Quebec, H4P 2T4, Canada.

SoSe, Gr. SoSe, Greece.

SoSe, Ital. So.Se. Pharm S.r.l., Via Castelli Romani 22, 00040 Pomezia (Rome), Italy.
url: www.sasepharm.it

Soteks, Rus. See *Sotex, Rus.*

Sotex, Rus. Sotex ZAO, Kashirskoe sh. 22, korp. 4, 115201 Moscow, Russia.
url: www.sotex.ru

Source, Canad. Source Medical Corp., 60 International Bvld, Toronto, Ontario, M9W 6J2, Canada.

South Ocean, China. South Ocean Pharmaceutical Co. Ltd, Zhejiang, China.

Southern Cross, Austral. Southern Cross Pharma Pty Ltd, 56 Illabunda Drive, Malua Bay, NSW 2536, Australia.

Southwest, China. Southwest Pharmaceutical Co. Ltd, 21 Tianxingqiao, Shapingba District, Chngqing 400038, China.

Southwest Synthetic, China. Southwest Synthetic, Fortune Building 18th Floor Block B, 9 Honghu East Rd, Yubei District, Chongqing 401121, China.
url: www.fsspc.com

Sovedis, Fr. Laboratoires Sovedis, 9 av. d'Arromanches, 94100 Saint-Maur des Fosses, France.

Sovereign, UK. See *Waymade, UK.*

Soylu, Turk. Soylu İlaç Sanayi ve Ticaret Ltd, Esentepe Mh Milangaz Cd No 69 Kartal, Istanbul, Turkey.

Sozin-Flora, India. Sozin-Flora Pharma Ltd, Nr. Govt. School, Nahan Road, Kala Amb, Sirmour 173 030, Himachal Pradesh, India.
url: www.sozinpharma.com

SP, Denm. See *Schering-Plough, Denm.*

SP, Spain. See *Schering-Plough, Spain.*

SPA, Cz. See *Medicom, Cz.*

SPA, Ital. Società Prodotti Antibiotici S.p.A., Via Biella 8, 20143 Milan (MI), Italy.

SPA, Philipp. See *Zuellig, Philipp.*

SPA, Pol. See *Medagro, Pol.*

SPA, Rus. See *SPA, Ital.*

Spagyros, Switz. Spagyros AG, Tannackerstrasse 7, 3073 Gumlingen, Switzerland.

Spaly, Spain. See *Lilly, Spain.*

Sparks, NZ. David Sparks Ltd, P.O. Box 83-122, Edmonton, Auckland, New Zealand.

SparMed, Switz. SparMed AG, Innere Guterstrasse 2, 6300 Zug, Switzerland.
url: www.sparmed.com

SPB, Thai. S.P.B. Pharma Co. Ltd, Apt 14B, Sathorn Park Place, 27/44 Sauth Sathorn, Sathorn, Bangkok 10120, Thailand.

Specia, Fr. See *Sanofi-Aventis, Fr.*

Special Product's Line, Ital. Special Product's Line S.p.A., Via Campobello 15, 00040 Pomezia (RM), Italy.
url: www.specialspa.it

Specialised Therapeutics, Austral. Specialised Therapeutics Australia Pty Ltd, 6 Westbrook St, Suite 4/3, East Kew, Victoria 3102, Australia.
url: www.abraxisbio.com

Speciality European Pharma, Belg. See *Speciality European Pharma, UK.*

Speciality European Pharma, Denm. See *Speciality European Pharma, UK.*

Speciality European Pharma, Fr. Speciality European Pharma France SAR, 28 rue de Londres, 75009 Paris, France.
url: www.specialityeuropeanpharma.com

Speciality European Pharma, Ger. See *SpePharm, Ger.*

Speciality European Pharma, Ital. Speciality European Pharma Italy Srl, Viale Medaglie d'Oro 399, 00136 Rome, Italy.
url: www.specialityeuropeanpharma.com

Speciality European Pharma, Neth. See *Speciality European Pharma, UK.*

Speciality European Pharma, UK. Speciality European Pharma Ltd, 16 John St, London, WC1N 2DL, UK.
url: www.specialityeuropeanpharma.com

Speciality Meditech, India. Speciality Meditech Pvt Ltd, 7-61 Bapuji Nagar main Road, Nachoram, Hyderabad 500 076, India.

Specifar, Cz. See *Specifar, Gr.*

Specifar, Denm. See *Specifar, Gr.*

Specifar, Fin. See *Specifar, Gr.*

Specifar, Gr. Specifar Pharmaceuticals S.A., 1, 28 Octovriou str., 123 51 Ag. Varvara, Greece.
url: www.specifar.gr

Specifar, Ital. See *Specifar, Gr.*

Specifar, Neth. See *Specifar, Gr.*

Specifar, Pol. See *Specifar, Gr.*

Specifar, Singapore. See *Goldplus, Singapore.*

Specifar (Σπεσιφαρ), Gr. See *Specifar, Gr.*

Specpharm, S.Afr. See *Enaleni, S.Afr.*

Spectrum, Fin. See *Spectrum, Neth.*

Spectrum, Neth. Spectrum Pharmaceuticals BV, Prins Bernhardplein 200, 1097 JB Amsterdam, Netherlands.

Spectrum, Spain. See *Spectrum, Neth.*

Spectrum, UK. Spectrum Thea, Fernbank House, Springwood Way, Macclesfield, Cheshire, SK10 2XA, UK.
url: www.spectrum-thea.co.uk

Spectrum, USA. Spectrum Pharmaceuticals Inc., 157 Technology Drive, Irvine, CA 92618, USA.
url: www.spectrumpharm.com

Spectrum Brands, USA. Spectrum Brands Inc., Six Concourse Parkway, Suite 3300, Atlanta, GA 30328, USA.
url: www.spectrumbrands.com

Spedrog, Arg. Spedrog Caillon S.A.I.y C., Alte. Fco. J. Segui 2106, 1416 Buenos Aires, Argentina.

Spefar, Venez. Laboratorios Spefar Venezolanos S.A., Calle Las Piedritas, Zona Industrial de la Trinidad, Edif. Spefar, Caracas, Venezuela.
url: www.spefar.com.ve

Spenco, Hong Kong. See *CNW, Hong Kong.*

SpePharm, Cz. See *SpePharm, Neth.*

SpePharm, Denm. See *SpePharm, Neth.*

SpePharm, Ger. SpePharm GmbH, Stefan-George-Ring 29, 81929 Munich, Germany.
url: www.spepharm.com

SpePharm, Irl. See *SpePharm, UK.*

SpePharm, Neth. SpePharm Holding BV, Kingsfordweg 151, 1043 GR Amsterdam, Netherlands.
url: www.spepharm.com

SpePharm, Norw. See *SpePharm, Neth.*

SpePharm, Pol. See *SpePharm, Neth.*

SpePharm, UK. SpePharm UK Ltd, 2B Bonkside, Hanborough Business Park, Long Hanborough, Witney, Oxfordshire, OX29 8LJ, UK.
url: www.spepharm.com

Sperko, Rus. See *Sperko, Ukr.*

Sperko, Ukr. Sperko Ukrayina SP TOV, 600-Letiya Street, 25, Vinnytsia, 21027, Ukraine.

Spexell, Canad. Spexell Pharma, 15 Jarvis Ave, Aurora, Ontario, L4G 6W8, Canada.
url: www.spexell.com

Speywood, Cz. See *Speywood, UK.*

Speywood, Switz. See *Opopharma, Switz.*

Speywood, UK. Speywood Laboratories Ltd, Unit 9, Ash Rd, Wrexham Industrial Estate, Wrexham, Clwyd, LL13 9QS, UK.

Speywood, USA. See *Ipsen, USA.*

Spineda, Arg. Spineda, Pérez y Hnos. Y Cia SRL, Zado 3735, 1431 Villa Urquiza, Buenos Aires, Argentina.

Spirig, Austria. See *Spirig, Ger.*

Spirig, Cz. See *Spirig, Switz.*

Spirig, Fr. Laboratoires Spirig SA, 109 bd d'Haussonville, 54000 Nancy, France.
url: www.laboratoires-spirig.com

Spirig, Ger. Spirig Pharma GmbH, Schertlinstr. 27, 86159 Augsburg, Germany.
url: www.spirig-pharma.de

Spirig, Neth. See *Spirig, Ger.*

Spirig, Pol. See *ICN, Pol.*

Spirig, Singapore. See *Summit, Singapore.*

Spirig, Switz. Spirig Pharma AG, Postfach 111, 4622 Egerkingen, Switzerland.

Spirig, Ukr. See *Delta Medical, Ukr.*

Spirit, Austral. Spirit Pharmaceuticals Pty Ltd, 117 Harrington St, The Rocks, Sydney, NSW 2000, Australia.

Spirit, UK. Spirit Healthcare Ltd, Spirit House, Selbury Drive, Oadby, Leicester, LE2 5NG, UK.
url: www.spirit-healthcare.co.uk

Spiromed, Hung. Spiromed Co. Ltd, Kaptárkö u 2, 1118 Budapest, Hungary.

Spitzner, Ger. W. Spitzner, Arzneimittelfabrik GmbH, Bunsenstr. 6-10, 76275 Ettlingen, Germany.
url: www.spitzner.de

SPM, Philipp. See *Endure, Philipp.*

Spofa, Cz. Spofa as, Podébradská 5, 180 47 Prague 9, Czech Republic.

Spofa, Pol. See *Salus, Pol.*

Spring Vine, Philipp. Spring Vine Herbal Trading, 1154 CM Recto Ave, Sta Cruz, Manila, Philippines.

Spyfarma, Spain. Laboratorios Spyfarma S.A., Ctra Sevilla Malaga Km 5.5 Km, Alcalá de Guadaira, 41500 Seville, Spain.
url: www.spyfarma.com

Square, Malaysia. See *Medispec, Malaysia.*

Square, Philipp. See *Lema, Philipp.*

Square, Thai. Pharma Square Co. Ltd, 5 Fortune Town, 4 Fl, Rm 22-26, Ratchadapisek Rd, Bangkok 103320, Thailand.

Squibb, Austral. See *BMS, Austral.*

Squibb, Canad. See *BMS, Canad.*

Squibb, Fr. See *BMS, Fr.*

Squibb, Ger. See *BMS, Ger.*

Squibb, Ital. See *BMS, Ital.*

Squibb, Neth. See *BMS, Neth.*

Squibb, Spain. See *BMS, Spain.*

Squibb, Switz. See *BMS, Switz.*

Squibb, UK. See *BMS, UK.*

Squibb, USA. See *BMS, USA.*

Squibb, Venez. See *BMS, Venez.*

Squibb Diagnostics, Canad. See *BMS, Canad.*

Squibb Diagnostics, USA. See *BMS, USA.*

Squibb-Heyden, Ger. See *BMS, Ger.*

Squibb-Novo, USA. See *BMS, USA.*

Sresan, India. Sresan Pharmaceuticals, Sresan House, 14 Nagarjuna Nagar 2nd Street, Rangarajapuram, Chennai 600 024, India.
url: www.sresan.com

Sri Jay, Rus. See *Astellas, Rus.*

Srichand, Thai. Srichand United Dispensary Co. Ltd, 1193 Rama 9 Rd, Suanluang, Bangkok, 10250, Thailand.
url: www.srichand.co.th

Sriprasit, Malaysia. See *Imeks, Malaysia.*

Sriprasit, Singapore. See *Joyson, Singapore.*

Sriprasit, Thai. Sriprasit Dispensary R O P, 617 Charoen Rath Rd, Klongsarn, Bangkok 10600, Thailand.
url: www.sriprasit.com

Sriprasit Pharma, Thai. See *Sriprasit, Thai.*

SRK, Switz. See *ZLB, Switz.*

SRS, Philipp. SRS Pharmaceuticals Pvts Ltd, Unit 1118 Vitykand Herrera Twr, VA Rufino cor Valero Sts, Makati City, Philippines.

SSI, Pol. Statens Serum Instuitut Polska, ul. Grójecka 22/24 m 53, 02-021 Warsaw, Poland.

SSI, Swed. SSI Sverige, Carlsgatan 12A, Slagthuset, 211 20 Malmö, Sweden.

SSK, Turk. SSK Iloç ve Tibbi Malzeme Sanayi Müessesesi, Topkapi, Istanbul, Turkey.

SSL, Austral. SSL International, 225 Beach Rd, Mordilloc, VIC 3195, Australia.
url: www.sslaustralia.com.au

SSL, Cz. See *SSL, UK.*

SSL, Fr. SSL Healthcare France SA, 49 av Georges-Pompidou, 92593 Levallois-Perret cdx, France.
url: www.ssl-international.com

SSL, Gr. SSL Hellas SA, 10 Km Nat. Rd Athens-Lamia, 144 51 Metamorfosi, Greece.
url: www.ssl-international.com

SSL, Hong Kong. See *IDS, Hong Kong.*

SSL, Hung. SSL Magyarország Kft, Váci út 95, 1139 Budapest, Hungary.
url: www.ssl-international.com

SSL, Irl. SSL Healthcare Ireland Ltd, A10, Calmont Park, Ballymount, Dublin 12, Ireland.
url: www.ssl-international.com

SSL, Israel. See *SSL, UK.*

SSL, Ital. SSL Healthcare Italia S.p.A., Via M. E. Lepido 178/5, 40132 Bologna (BO), Italy.
url: www.ssl-international.com

SSL, Malaysia. See *Zuellig, Malaysia.*

SSL, Norw. See *SSL, Swed.*

SSL, NZ. SSL New Zealand Ltd, c/-54 Carbine Rd, Mount Wellington, Auckland, New Zealand.
url: www.ssl-international.com

SSL, Pol. SSL Healthcare Polska Sp. zo.o., ul. Szturmowa 2 a, 02-678 Warsaw, Poland.
url: www.ssl-international.com

SSL, Singapore. See *DKSH, Singapore.*

SSL, Swed. SSL Sverige AB, Box 1326, 171 26 Solna, Sweden.
url: www.ssl-international.com

SSL, Switz. SSL Healthcare Schweiz AG, Rheinstrasse 81, 4133 Pratteln, Switzerland.
url: www.ssl-international.com

SSL, Thai. See *Diethelm, Thai.*

SSL, UK. SSL International plc, 35 New Bridge St., London, EC4V 6BW, UK.
url: www.ssl-international.com

SSM, Turk. SSM Steril Sağlick Malzemeleri San. ve Tic. A. Ş., Katip Salih Sok. No:6, Kosuyolu, İstanbul, 34718, Turkey.
url: www.steril.com

SSP, Thai. SSP Laboratories Ltd, 101 Soi Chaengwatana 13, Chaengwatana Rd, Thungsonghong Laksi, Bangkok 10210, Thailand.

SSPC, China. Sino-Swed Pharmaceutical Corp. Ltd, Room 1801-1805 China Resources Building, 8 Jianguomen Bei Ave, Beijing 100005, China.
url: www.sspc.com.cn

SSRI, Rus. State Scientific-Research Institute for Specially Pure Biological Products, Pudozhskaya ul. 7, 197110 Saint Petersburg, Russia.

SSW, Ger. See *GSK, Ger.*

ST, Thai. ST Pharma, 1937/16 Soi Ramkamhaeng 21, Bankkapi, Bangkok 10240, Thailand.

St Carlos, Philipp. St Carlos Pharma, 5.84 Moo 2 Tiwanon Rd, Banklang, Amphur Muang, Phathumthani 12000, Philippines.
url: www.stcarlos.com

St Ives, NZ. St Ives Medical, P.O. Box 65-069, Auckland, New Zealand.

St Laurent, Canad. St Laurent Laboratoire, 1010 Berlier St, Laval, Quebec, H7L 3R9, Canada.

St Petersburg Institute of Vaccines & Sera, Rus. St Petersburg Institute of Vaccines & Sera, St Peterburg, Russia.

Stada, Austria. Stada Arzneimittel GmbH, Heiligenstadter Strasse 52/2/8, A-1190 Vienna, Austria.
url: www.stada.at

Stada, China. Stada Pharmaceuticals (Beijing) Ltd, Industrial Development Zone, 15 Yunteng Rd, Miyun, Beijing 101500, China.
url: www.stadabeijing.com

Stada, Cz. Stada Pharma International as, Hnevkovská 58, 148 00 Prague 4, Czech Republic.

Stada, Denm. See *Pharmacodane, Denm.*

Stada, Fin. See *Stada, Ger.*

Stada, Ger. Stada GmbH, Stadastr. 2-18, 61118 Bad Vilbel, Germany.
url: www.stada.de

Stada, Hong Kong. Stada Pharmaceuticals (Asia) Ltd, 2513-2516 Paul Y Ctr, 51 Hung To Rd, Kwun Tong, Hong Kong.
url: www.stada.de

Stada, Hung. See *Biogal-Teva, Hung.*

Stada, Irl. See *Stada, Ger.*

Stada, Malaysia. See *Antah, Malaysia.*

Stada, Neth. See *Stada, Ger.*

Stada, Norw. See *Pharmacodane, Denm.*

Stada, Philipp. See *Croma, Philipp.*

Stada, Pol. Stada Pharma International GmbH Sp. zo.o. Oddział w Polsce, ul. Kubickiego 17 m 28, 02-954 Warsaw, Poland.
url: www.stada.de

Stada, Port. Stada Lda, Quinta da Fonte, Edifício D Amelia, Piso 1 Ala B, 2770-229 Paço de Arcos, Portugal.

Stada, Rus. Stada Pharma, Calganskaya ul 7, 603950 Nizhny Novgorod, Russia.
url: www.stada.ru

Stada, Singapore. See *JDH, Singapore.*

Stada, Spain. Laboratorio Stada S.L., Frederic Mompou 5, Sant Just Desvern, 08960 Barcelona, Spain.
url: www.stada.es

Stada, Swed. Stadapharm AB, Adelgatan 11, 211 22 Malmö, Sweden.

Stada, Thai. Stada Asiatic Co. Ltd, 41/18 Rama III Rd, Chongnonsee, Yannawa, Bangkok 10120, Thailand.

Stada, Ukr. Stada, Bolshaya Vasilkovskaya, 9/2, office 52, Kiev, 01004, Ukraine.
url: www.stada.de

Stada, USA. STADA Pharmaceuticals Inc., 5 Cedar Brook Drive, Cranbury, NJ 08512, USA.
url: www.stadausa.com

Stadapharm, Ger. See *Stada, Ger.*

Stadmed, India. Stadmed Pvt Ltd, AA-21 Sector-1, Salt Lake City, Kolkata 700 064, India.
url: www.stadmed.co.in

Stafford, Mex. See *GSK Consumer, Mex.*

Stafford-Miller, Austral. Stafford Miller Ltd, P.O. Box 406, North Ryde, NSW 1670, Australia.

Stafford-Miller, Braz. See *GSK, Braz.*

Stafford-Miller, Denm. See *Meda, Denm.*

Stafford-Miller, Fin. See *Tamro, Fin.*

Stafford-Miller, Fr. See *GSK, Fr.*

Stafford-Miller, Hong Kong. See *Trinity, Hong Kong.*

Stafford-Miller, Irl. See *United Drug, Irl.*

Stafford-Miller, Israel. See *CTS, Israel.*

Stafford-Miller, Ital. See *GSK Consumer, Ital.*

Stafford-Miller, Mex. See *GSK Consumer, Mex.*

Stafford-Miller, Norw. See *Meda, Norw.*

Stafford-Miller, NZ. See *GSK, NZ.*

Stafford-Miller, Port. See *GSK, Port.*

Stafford-Miller, Spain. See *GSK, Spain.*
Stafford-Miller, Switz. See *Doetsch, Grether, Switz.*
Stafford-Miller, UK. See *GSK, UK.*
Stafford-Miller Continental, Belg. See *GSK, Belg.*
Stalder, Philipp. See *BCP, Philipp.*
Stallergenes, Austria. Stallergenes Österreich GmbH, Wipplingerstrasse 21, Top 9, 1010 Vienna, Austria. url: www.stallergenes.at
Stallergenes, Belg. Stallergenes Belgium SA, Chaussée de Louvain 277, 1410 Waterloo, Belgium. url: www.stallergenes.com
Stallergenes, Cz. See *Stallergenes, Fr.*
Stallergenes, Fr. Stallergènes SA, 6 rue Alexis-de-Tocqueville, 92183 Antony cdx, France. url: www.stallergenes.fr
Stallergenes, Ger. Stallergenes GmbH & Co KG, Carl-Friedrich-Gauss-Str. 50, 47475 Kamp-Lintfort, Germany. url: www.stallergenes.de
Stallergenes, Hung. See *Stallergenes, Fr.*
Stallergenes, Irl. See *Stallergenes, Fr.*
Stallergenes, Ital. Stallergenes Italia S.r.l., Viale Certosa 191 Ang. Via Tribulo 2, 20151 Milan (MI), Italy.
Stallergenes, Neth. Stallergenes BV, Postbus 1067, 1300 BB Almere, Netherlands.
Stallergenes, Pol. See *Ewopharma, Pol.*
Stallergenes, Spain. Stallergenes Ibérica SA, Ramón Turró 91, 08005 Barcelona, Spain.
Stallergenes, Switz. See *Trimedal, Switz.*
Stallion, India. Stallion Laboratories Pvt Ltd, 817, 8th Floor Devpath, C.G. Road, Ahmedabad 380 006, India. url: www.stallionlabs.com
Stallion, Philipp. See *Ambica, Philipp.*
Stalwart, India. Stalwart Remedies Pvt Ltd, 304 Signature 1, Urmi Cross Roads, Productivity Road, Alakapuri, Baroda, India.
Stanback, USA. See *GSK, USA.*
Stancare, India. See *Ranbaxy, India.*
Standard, Hong Kong. See *Kai Yuen, Hong Kong.*
Standard, Philipp. See *Pharmawealth, Philipp.*
Standard, Singapore. See *Hospira, Singapore* and *MD, Singapore.*
Standard Chem, Malaysia. See *Summit, Malaysia.*
Standard Chem & Pharm, China. Standard Chemical & Pharmaceutical Co. Ltd, 6020 Tuku, Tuku Village, Sinying District, Tainan 73055, China. url: www.standard.com.tw
Standard Chem & Pharm, Thai. See *Union Medical, Thai.*
Standard Drug, USA. Standard Drug Company, 1279 N 7th St, Riverton, IL 62561, USA.
Standard Homeopathic, Canad. Standard Homeopathic Canada Inc., 381-A Route 139, Sutton, Quebec, J0E 2K0, Canada.
Standard Homeopathic, USA. Standard Homeopathic Co. & Hylands, P.O. Box 61067, 210 W 131st St, Los Angeles, CA 90061, USA. url: www.hylands.com
Stanley, Canad. Stanley Pharmaceuticals Ltd, Division of Vita Health Products Ltd, 150 Beghin Ave, Winnipeg, Manitoba, R2J 3W2, Canada.
Stanley, Israel. See *Manon, Israel.*
Stanningley, UK. Stanningley Pharma Ltd, BioCity, Pennyfoot St, Nottingham, NG1 1GF, UK. url: www.stanningleypharma.co.uk
Star, China. Star Pharmaceutical Ltd, 21/F Haitian Building, Midhill Garden, 1 Jinmaozhong Rd, Haiku, Hainan, 570125, China. url: starpharm.listedcompany.com
Star, Hong Kong. Star Medical Supplies Ltd, Unit E, 1/F Hop Hing Industrial Bldg, 704 Castle Peak Rd, Lai Chi Kok, Kowloon, Hong Kong.
Star, Thai. Star Lab Co. Ltd, 542 Vipavadi Rangsit Rd, Din Dang, Bangkok 10400, Thailand.
Star, USA. Star Pharmaceuticals Inc., 1881 W. State Road 84, Suite 101, Fort Lauderdale, FL 33315, USA. url: www.starpharm.com
Stargen, Gr. Stargen Ltd, Favierou 48 (5th floor), 104 38 Athens, Greece.
Starmel, Gr. Starmel Pharmaceuticals, Ioanni Polemi 44, Thessaloniki 54248, Greece. url: www.starmel.com
Stasisport, Belg. Stasisport Pharma NV, Square Marie Curie 50, 1070 Anderlecht, Belgium.
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State Industrial, Canad. See *State Industrial, USA.*
State Industrial, USA. State Industrial Products, 3100 Hamilton Ave, Cleveland, OH 44114, USA.
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Stauffacher, Switz. Stauffacher Apotheke, Dr Langer AG, Birmensdorferstrasse 1, 8004 Zurich, Switzerland.
STD, Cz. See *STD, UK.*
STD, Hung. See *Vicis, Hung.*
STD, Irl. See *STD, UK.*
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STD, UK. STD Pharmaceutical Products Ltd, Plough Lane, Hereford, Herefordshire, HR4 0EL, UK. url: www.stdpharm.co.uk
Stedman, India. Stedman Pharmaceuticals Pvt Ltd, 3-A Adyar Bridge Road, Adyar, Chennai 600 020, India. url: www.stedmanpharma.com
Stegropharm, Ger. StegroPharm Arzneimittel GmbH, St.-Johann-Str. 8, 80999 Munich, Germany.
Steierl, Austria. See *Steierl, Ger.*
Steierl, Ger. Steierl Pharma GmbH, Mühlfelder Str. 48, 82211 Herrsching, Germany. url: www.steierl.de
Steierl, Hung. See *Steierl, Ger.*
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Steigerwald, Ger. Steigerwald Arzneimittelwerk GmbH, Havelstr. 5, 64295 Darmstadt, Germany. url: www.steigerwald.de
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Steigerwald, Switz. See *Hanseler, Switz.*
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Steiner, Ger. Steiner & Co. Deutsche Arzneimittel Gesellschaft mbH & Co. KG, Ostpreussendamm 72/74, 12207 Berlin, Germany. url: www.steinerarznei-berlin.de
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Stella, Canad. Stella Pharmaceutical Canada Inc., 407-220 Duncan Mill Rd, Don Mills, Ontario, M3B 3J5, Canada. url: www.nutribar.com
Stellar, Canad. Stellar International Inc., Stellar Healthcare, 82 Wellington St S, Suite 201, London, Ontario, N6B 2K3, Canada. url: www.stellarint.com
Stellar, India. Stellar Bio-Labs, SCF-509 2nd Floor, Motor Market, Manimajra, Chandigarh 160 101, India.
Stellar, USA. See *Star, USA.*
Stendhal, Mex. Especificos Stendhal SA de CV, Carretera Picacho Ajusco 130-303, 14390 Tlalpan Jardines en Montana, Mexico DF, Mexico.
Step, Arg. Step Argentina S.A., Saenz 314, 1832 Lomas de Zamora, Buenos Aires, Argentina.
Stephar, Neth. Stephar BV, van Giesenweg 5, 2921 LN Krimpen aan den Ijssel, Netherlands.
Sterfil, India. Sterfil Laboratories Pvt. Ltd, S-3, Khira I.E, S.V.Road, Santacruz (W), Mumbai 400 054, India.
Sterigen, Canad. Laboratoires Sterigen Inc., 42 St-Cyrille, Upton, Quebec, J0H 2E0, Canada.
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SteriMax, Canad. SteriMax Inc., Suite 3, 2740 Matheson Blvd East, Mississauga, Ontario, L4W 4X3, Canada.
SteriPharm, Fr. SteriPharm France Sarl, 4 rue des Bonnes-Gens, 67000 Strasbourg, France. url: www.steripharm.biz
SteriPharm, Ukr. See *Pharmplanet, Ukr.*
Steris, Canad. See *Steris, USA.*
Steris, USA. Steris Corp., 5960 Heisley Rd, Mentor, OH 44060, USA.
Sterkem, India. Sterkem Pharma Pvt Ltd, S-3 Khira Ind. Estate, SV Rd, Santacruz (W), Mumbai, 400 054, India.
Sterling, Canad. See *GSK, Canad.*
Sterling, India. Sterling Lab., 203 Swiss Complex, 33 Race Course Road, Bangalore 580 001, India.
Sterling, Indon. Sterling Products Indonesia PT, Graha Paramitha 5/F, Jl Denpasar Raya Blok D II, HR Rasuna Said, Kuningan, Jakarta 12950, DKI Jaya, Indonesia.
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Stern, Ger. See *AstraZeneca, Ger.*
Sterop, Belg. Sterop, Avenue de Scheut 46-50, 1070 Brussels, Belgium. url: www.sterop.be
Sterwin, UK. See *Sanofi, UK.*
Stetifarm, Venez. See *Leti, Venez.*
Stevens, USA. Jerome Stevens Pharmaceuticals Inc., 60 Da Vinci Drive, Bohemia, NY 11716, USA.
Steward Cross, Singapore. Steward Cross Pte Ltd, 801 Lor 7 Toa Payoh, Wearnes Technology Annexe Building, 06-06, S 319319, Singapore. url: www.stewardcross.com
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Stichting, Austria. See *Stichting, Neth.*
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Stichting, Neth. Stichting Registratiebeheer, Bosstraat 69, 3766 AC Soest, Netherlands.
Stiefel, Arg. Stiefel Argentina S.A., Av. Federico Lacroze 3194, 1426 Buenos Aires, Argentina. url: www.stiefel.com
Stiefel, Austral. Stiefel Laboratories P/L, Unit 2, 10 Salisbury Road, Castle Hill, NSW 2154, Australia. url: www.stiefel.com
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Stiefel, Canad. Stiefel Canada Inc., 6635 Henri-Bourassa Blvd W, Montreal, Quebec, H4R 1E1, Canada. Manager Marketing & Corporate Services url: www.stiefel.ca
Stiefel, Chile. Laboratorios Stiefel de Chile y Cia Ltda, Av. Americo Vespucio 1220, Penalolen, Santiago, 693 25 60, Chile. url: www.stiefel.com
Stiefel, China. See *GSK, China.*
Stiefel, Denm. Stiefel Laboratories (Nordic) ApS, Havnegade 39, 1058 Copenhagen K, Denmark. url: www.stiefel.com
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Stiefel, Fr. Laboratoires Stiefel (France), 6 Av. de l'Imperatrice Josephine, 92500 Reuil-Malmaison, France. url: www.stiefel.com
Stiefel, Ger. Stiefel Laboratorium GmbH, Mühlheimer Str. 231, 63075 Offenbach am Main, Germany. url: www.stiefel-gmbh.de
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Stiefel, Hong Kong. Stiefel Laboratories (Hong Kong) Ltd, 601B, 6F, Tower 2, Cheung Sha Wan Plaza, 833 Cheung Sha Wan Rd, Kowloon, Hong Kong. url: www.stiefel.com
Stiefel, Hung. See *Mediner, Hung.*
Stiefel, India. Stiefel India Pvt Ltd, 552 Bldg. No. 5, Solitaire Corporate Park, Andheri-Ghatkopar Link Road, Chakala, Andheri (E), Mumbai 400 093, India. url: www.stiefel.com
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Stiefel, Malaysia. See *DKSH, Malaysia.*
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Stiefel, Philipp. Stiefel Philippines Inc., Suite 1604 West Tower, Philippine Stock Exchange Ctr, Exchange Rd, Ortigas Ctr, Pasig City, Philippines.
Stiefel, Pol. Stiefel Polska Sp. zo.o., ul. Kamionkowska 51, 03-812 Warsaw, Poland. url: www.stiefel.com
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Stiefel, S.Afr. Stiefel Laboratories SA (Pty) Ltd, P. O. Box 12657, Clubview, Pretoria 0014, South Africa. url: www.stiefel.com
Stiefel, Singapore. Stiefel Laboratories (Pte) Ltd, 103 Gul Circle, S 629589, Singapore.
Stiefel, Spain. Stiefel, Coto de Donana 11-13 Area, Andalucia Sector 1, Pinto, 28320 Madrid, Spain. url: www.stiefel.com
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Stiefel, Thai. Stiefel Laboratories (Thailand) Ltd, 33 Fl, Phaholyothin Place Building, 408/143 Phaholylothin Rd, Samsenni Phayathai, Bangkok 10400, Thailand. url: www.stiefel.com
Stiefel, UK. Stiefel Laboratories (UK) Ltd, Holtspur Lane, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0AU, UK. url: www.stiefel.co.uk
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Stiefel, USA. Stiefel Laboratories Inc., 255 Alhambra Circle, Coral Gables, FL 33134, USA. url: www.stiefel.com
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Stila, USA. Stila Corp., 314 4470 West Sunset Blvd, Los Angeles, CA 90027, USA.
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Stirol, Ukr. Stirolbioform, Gorlovskoi divizii Street, 97, Gorlovka, Donetskaya region, 84610, Ukraine.
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Stockhausen, USA. Stockhausen Inc., 2401 Doyle St, Greensboro, NC 27406, USA. url: www.stockhausen-inc.com
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Stomygen, Ital. Gruppo Stomygen S.r.l., Via F. Jorini 69, 00149 Rome (RM), Italy. url: www.stomygen.com
Stonebridge, USA. Stonebridge Pharmaceuticals, 6340 Sugarloaf Pkwy, Suite 400, Duluth, GA 30097, USA. url: www.stonebridgepharma.com
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Stragen, Denm. Stragen Nordic A/S, Hesselvej 41, 3660 Stenløse, Denmark. url: www.stragennordic.com
Stragen, Fin. See *Stragen, Denm.*
Stragen, Ger. Stragen Pharma GmbH, Eupener Str. 135-137, 50933 Köln, Germany. url: www.stragen.de
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Stragen, Switz. Stragen Pharma SA, 3 rue de Senger, 1211 Geneva 4, Switzerland. url: www.stragen.ch
Stragen, UK. Stragen UK Ltd, Castle Court, 41 London Rd, Reigate, Surrey, UK.
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Strallhofer, Austria. Mag. Dr. Till Strallhofer, St-Veit-Gasse 56, A-1130 Vienna, Austria.
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Strand, Malaysia. See *Pharmaniaga, Malaysia.*
Strassenburg, India. Strassenburg Pharmaceuticals Ltd, P-6 CIT Rd, 4th Floor, Kolkata, 700 014, India.
Strathmann, Ger. Strathmann GmbH & Co. KG, Sellhopsweg 1, 22459 Hamburg, Germany. url: www.strathmann.de
Strathmann, Hung. Strathmann Ag & Co Képviselete, Ipoly u 5/f, 1133 Budapest, Hungary.
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Stratus, USA. Stratus Pharmaceuticals Inc., 14377 SW 142nd St, P.O. Box 4632, Miami, FL 33186, USA. url: www.stratuspharmaceuticals.com
Streger, Mex. Streger S.A., Km. 8 Antigua Carretera Xalapa-Coatepec, 91500 Consolapa-Coatepec, Veracruz, Mexico.
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Streuli, Switz. G. Streuli & Co. AG, 8730 Uznach, Switzerland.
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Strides, Philipp. See *Medhaus, Philipp.*
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Stroder, Ital. Ist. Farmaco Biologico Stroder S.r.l., Via di Ripoli 207/V, 50126 Florence (FI), Italy.
Stroms, Canad. Stroms Enterprises Ltd, DBA L'Occitane en Provence, Toronto, Ontario, M6B 4K3, Canada.
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Stryker, Fr. Stryker France, ZAC ave de Satolas Green, 69330 Pusignan, France. url: www.stryker.fr
Stryker, Spain. Stryker Howmedica Iberica, Manuel Tovar 35, 28034 Madrid, Spain. url: www.stryker.es
Stryker, Swed. Stryker AB, Krusegatan 19 (Box 50425), SE-202 14 Malmö, Sweden. url: www.nordic.stryker.com
Stryker, Switz. Stryker SA, Grand Rue 92, 1820 Montreux, Switzerland. url: www.stryker.ch
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Stulln, Ger. Pharma Stulln GmbH, Werksstr. 3, 92551 Stulln, Germany. url: www.pharmastulln.de
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SU, Neth. SU BioMedicine, Utrechtseweg 48, 3704 HE Zeist, Netherlands.
Su Lan, China. Su Lan Biomedical Science & Tecnology Co. Ltd, Suzhou, China.
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Substipharm, Fr. Laboratoires Substipharm, 264 rue du Fbg-St-Honore, 75008 Paris, France. url: www.substipharm.com
Suburfarm, Hong Kong. Suburfarm Investment & Trading Co. Ltd, Medical Health Care Division, Unit 7A-B, 39/F Cable TV Tower, 9 Hoi Shing Rd, Tsuen Wan, N.T., Hong Kong.
Sucampo, Jpn. Sucampo Pharma Ltd, Sukurabashi-Toyo Building 4th Floor, Osaka 5300002, Japan. url: www.sucampo.com
Sucampo, Switz. Sucampo AG, Baarerstrasse 22, 6300 Zug, Switzerland. url: www.sucampo.com
Sucampo, UK. Sucampo Pharma Europe Ltd, 99 Park Drive, Milton Park, Abingdon, Oxfordshire, OX14 4RY, UK. url: www.sucampo.com
Sucampo, USA. Sucampo Pharma LLC, 4520 East West Highway, Bethesda, MD 20814, USA. url: www.sucampo.com

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Su-Heung, Philipp. See *Biolink, Philipp.*
Suhitas, Philipp. Suhitas Pharmaceuticals Inc., 3rd Flr Centrepoint Building, Pasong Tamo cor, Export Bank Drive, Makati City, Philippines.
Suilun, China. Suilun Pharmaceutical Co. Ltd, Industrial Zone, Pinghu, Jiaxing, Zhejiang, 314204, China.
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Sulphur Zdroj, Pol. Przedsiębiorstwo Faraceutyczne Sulphur Zdrój Exim, ul. J Rokosza 18, 28-100 Busko Zdrój, Poland.
url: www.busko-zdroj.sulphur.com.pl
Sumitomo, China. Sumitomo Pharmaceuticals (Suzhou) Co. Ltd, Su Chun Industrial Square Building 22, Industrial Park, 428 Xing Long St, Suzhou 215126, China.
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Sumitomo, Jpn. See *Dainippon, Jpn.*
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Summerberry, Canad. Summerberry Products, 1882 Big Chief Rd, Orillia, Ontario, L3V 6H3, Canada.
Summers, USA. Summers Laboratories Inc., 103 G.P. Clement Dr., Collegeville, PA 19426-2044, USA.
url: www.sumlab.com
Summit, Malaysia. Summit Co (M) Sdn Bhd, Lot 6, Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.ussummit.com.my
Summit, Port. See *Dario Correia, Port.*
Summit, Singapore. Summit Company (S) Ltd, 10 Pandan Crescent, 02-05 UE Tech Park, S 128466, Singapore.
url: www.ussummit.com.sg
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Sun, Braz. Sun Farmaceutica Ltda, Luis Goes 519, 4043250 Sao Paulo, Brazil.
Sun, Canad. Sun Pharmaceutical Industries Inc., 1111 Flint Rd, Unit 23, Downsview, Ontario, M3J 3C7, Canada.
Sun, China. Sun Pharmaceutical Industries Ltd, Zhao Feng Universe Building, 1800 West Zhongshan Rd 22D, Shanghai 200235, China.
url: www.sunpharma.com.cn
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Sun, India. Sun Pharmaceutical Industries Ltd, Acme Plaza, Andheri Kurla Rd, Andheri (E), Mumbai 400 059, India.
url: www.sunpharma.com
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Sun, Malaysia. Sun Pharmaceutical, 512, Block E, Phileo Damansara 1, Jln 16/11, 46350 Petaling Jaya, Selangor, Malaysia.
Sun, Mex. Sun Pharma de México SA de CV, Margaritas 17-A, 1030 Florida, Mexico.
Sun, Neth. Sun Pharmaceutical Industries Europe BV, Polaris ave 87, 2132 JH Hoofddorp, Netherlands.
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Sun, Rus. Sun Pharmaceutical Industries Ltd, Profsoyuznaya ul. 57, Of. 722, 117420 Moscow, Russia.
url: www.sunpharma.ru
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Sun, UK. SunPharmaceuticals UK Ltd, 4100 Park Approach, Thorpe Park, Leeds, LS 15 8GB, UK.
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Sun, USA. Sun Pharmaceutical Industries Inc., 705 E Muberry St, Bryan, OH 435076, USA.
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Sun Hing, Hong Kong. Sun Hing Pharmaceutical Co. Ltd, Rm 1012, Blk 3, Nan Fung Ind City, 18 Tin Hau Rd, Tuen Mun, N.T., Hong Kong.
Sun Labs, Canad. Sun Labs Ltd, 15 6400 Millcreek Dr, Mississauga, Ontario, L5N 3E7, Canada.
Sun Ventures, Rus. Sun Ventures OOO, Rustaveli ul. 14, Str. 6, 127254 Moscow, Russia.
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url: www.sunevamedical.com
Sun-Farm, Pol. Sun-Farm Sp. zo.o., Człekówka 75, 05-340 Kołbiel, Poland.
url: www.sunfarm.pl
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Sunij, India. Sunij Pharma Pvt Ltd, T-1/B National Park, Gulbai Tekra, Ahmedabad 380 015, India.
url: www.sunijpharma.com
Sunny Plaza, Hong Kong. Sunny Plaza Ltd, 704, 7/F Kwai Hung Holdings Ctr, 89 Kings Rd, North Point, Hong Kong.
Sunnyhope, China. Sunnyhope Pharmaceutical Co. Ltd, 3 Gao Peng Ave 9F Block A, High-Tech Zone, Chengdu 610041, Sichuan, China.
url: www.sunnyhope.com
SunOpta, Canad. SunOpta Inc., 2838 Bovaird Drive West, Brampton, Ontario, L7A 0H2, Canada.
url: www.sunopta.com
Sunovion, Canad. Sunovion Pharmaceuticals Canada Inc., 6790 Century Ave, Suite 100, Mississauga, Ontario, L5N 2V8, Canada.
url: www.sunovion.com
Sunovion, USA. Sunovion Pharmaceuticals Inc., 84 Waterford Drive, Marlborough, MA 01752, USA.
url: www.sunovion.com
Sunpab, Philipp. Sunpab Health Care Products Phils Inc., 202 Elco Bldg, E Rodriguez Sr Ave, Quezon City, Philippines.
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Sunrex, Fr. Sunrex, 12 rue de Presbourg, 75016 Paris, France.
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Sunrise, India. Sunrise Remedies Pvt Ltd, 104 Sahjanand Complex, SG Highway, Thaltej Char Rasta, Ahmedabad 380 059, India.
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Sunshine, China. Shenyang Sunshine Pharmaceutical Co. Ltd, 3 A1 Road 10, Shenyang Economy & Technology Development Zone, Shenyang, 110027, China.
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Sunshine, India. Sunshine Pharma, SCF 355, 2nd Floor, Motor Market, Manimajra, Chandigarh, India.
Sunspot, Austral. Sunspot Products P/L, Level 3, Suite 303, 20 Bungan St, Mona Vale, NSW 2103, Australia.
url: www.sunspot.com.au
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Sunstar, Fr. Sunstar France SAS, 55/63 rue Anatole France, 92300 Levallois-Perrêt, France.
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Sunstar, UK. Sunstar, The Old Hatchery, Blind Lane, Bedale, North Yorkshire, DL8 1BW, UK.
url: www.jp.sunstar.com
Sunstone, China. Sunstone Pharmaceutical Co. Ltd, Hi-tech Development Zone, Tangshan, 063020, China.
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Sunward, Malaysia. Sunward Pharmaceutical Sdn Bhd, 9 Jln Kempas 4, Taman Perindustrian, Tampoi Indah, 81200 Tampoi, Johor, Malaysia.
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Sunward, Thai. See *Charoen, Thai.*
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url: www.smn.com.mx
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url: superasite.com.br
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SuperGen, USA. SuperGen Inc., 4140 Dublin Blvd, Suite 200, Dublin, CA 94568, USA.
url: www.supergen.com
Superlife, Mex. Superlife SA de CV, Gabriel Mancera 242, 3100 Bénito Juárez del Valle, Mexico.
Supernus, USA. Supernus Pharmaceuticals Inc., 1550 East Gude Drive, Rockville, MD 20850, USA.
url: wwww.supernus.com
SupHerb, Israel. Supherb, Israel.
url: supherb.co.il
Suphong, Thai. Suphong Bhaesaj, Thailand.
Supplements Aromatik, Canad. Supplements Aromatik Inc., 2334 Blvd Marie-Victorin, Varennes, Quebec, J3X 1R4, Canada.
Supply Chain Solutions, NZ. Supply Chain Solutions, 74 Westney Rd, Aiport Oaks, Auckland, New Zealand.
Support, Braz. Support Produtos Nutricionais Ltda, Vincente Pinzon 173, 2 andar, 04547-130 São Paula, Brazil.
Supra Ferbindo, Indon. See *Tempo Scan Pacific, Indon.*
Supra Healthcare, Singapore. Supra Healthcare Pte Ltd, 16A Koo Koon Circle, S-629048, Singapore.
url: www.suprahealthcare.sg
Surar, Arg. Surar Pharma SA, Luis Viale 965, Buenos Aires, Argentina.
Surge, Philipp. See *EuroAsia, Philipp.*
Surgicraft, UK. Surgicraft Ltd, 8 Padgets Lane, Clews Sauth Moons Moat, Redditch, Worcestershire, B98 7ST, UK.
url: www.surgicraft.co.uk
Surgimed, Venez. Laboratorio Surgimed, Av. F.Solano con Los Manguitos Piso 5 Of.13, Resid. Libertador, Caracas, Venezuela.
Surtech, Irl. Surtech International Ltd, Ireland.
Survival, Arg. Lab. Survival SRL, Castillo 1531, 1414 Buenos Aires, Argentina.
Survival Technology, USA. See *King, USA.*
Surya, Hong Kong. See *HealthCare PharmaScience, Hong Kong.*
Surya, Singapore. See *Polymedic, Singapore.*
Surya Dermato, Indon. Surya Dermato Medica (SDM) Lab PT, Jl Paseban Raya 21, 60293 Jakarta Pusat, DKI Jaya, Indonesia.
Sussex, UK. Sussex Pharmaceutical Ltd, Charlwoods Rd, East Grinstead, Sussex, RH19 2HL, UK.
Sustime, Philipp. See *Primera, Philipp.*
Sutton, Canad. HJ Sutton Industries Ltd, 8701 Jane St, Unit C, Vaughan, Ontario, L4K 2M6, Canada.
Suzhong, China. Suzhong Pharmaceutical Group, 1 Suzhong Road, Jiangyan, Jiangsu, 225500, China.
url: www.suzhongyy.com
Suzhong Haixin, China. Suzhong Haixin Pharmaceutical Co. Ltd, Yitai Li Building 20th Floor, Zhao Jia Bang Rd 446, Shanghai 200031, China.
url: www.szhxpharma.com
Suzhou No 1, China. Suzhiu No 1 Pharmaceutical Co. Ltd, 171 Xiyuan Road, Suzhou, Jiangsu, 215007, China.
url: www.suzhouyiyao.com
Suzhou No 3, China. Suzhou No 3 Pharmaceutical Co. Ltd, China.
Suzhou No 4, China. Suzhou No 4 Pharmaceutical Co. Ltd, Suzhou, China.
Suzhou No 6, China. Suzhou No. 6 Pharmaceutical Factory, 64 Mudu St, Suzhou, Jiangsu, 215101, China.
Svizera, India. See *Maneesh, India.*
SVR, Fr. Laboratoires SVR Cosmétologie Médicale, ZAC de la Tremblaie, rue de la Mare-a-Blot, 91220 Le Plessis-Pâté, France.
SVR, Ital. Laboratoires SVR Italia, Viale Regina Giovanna 17, 20129 Milan (MI), Italy.
url: www.labo-svr.com
SVUS, Cz. SVUS Pharma as, Smetanovo nábřeží 1238/20a, 500 02 Hradec Králové, Czech Republic.
url: www.svus.cz
Swabplus, Canad. Swabplus Canada Inc., 2 125 Norfinch Drive, North York, Ontario, M3N 1W8, Canada.
Swedish Orphan, Austria. See *Swedish Orphan, Swed.*
Swedish Orphan, Belg. See *Swedish Orphan, UK.*
Swedish Orphan, Canad. See *Swedish Orphan, USA.*
Swedish Orphan, Cz. See *Swedish Orphan, Swed.*
Swedish Orphan, Denm. Swedish Orphan A/S, Wilders Plads 5, 1403 Copenhagen K, Denmark.
url: www.swedishorphan.com
Swedish Orphan, Fin. Oy Swedish Orphan Biovitrum AB, Keilaranta 19, 7th Floor, 02150 Espoo, Finland.
url: www.sobi.com
Swedish Orphan, Fr. Swdish Orphan International SARL, 1 rue Devés, Neuilly sur Seine cdx, France.
url: www.swedishorphan.com
Swedish Orphan, Ger. Swedish Orphan Biovitrum (SOBI) GmbH, Robert-Bosch-Str. 11b, 63255 Langen, Germany.
url: www.sobi.com
Swedish Orphan, Gr. See *Swedish Orphan, Swed.*
Swedish Orphan, Irl. See *Fulcrum, Irl.*
Swedish Orphan, Ital. Swedish Orphan Biovitrum Srl, Strada Quarta 6/1d, 43100 Parma, Italy.
url: www.biovitrum.com
Swedish Orphan, Neth. See *Swedish Orphan, UK.*
Swedish Orphan, Norw. Swedish Orphan Biovitrum AS, Trollasv. 6, 1414 Trollasen, Norway.
url: www.sobi.com
Swedish Orphan, Pol. See *Orphan, Pol.*
Swedish Orphan, Port. Swedish Orphan International AB, Centro Empresarial Torres de Lisboa, Rua Tomas da Fonseca, Torre G, 1 Piso, 1600-209 Lisbon, Portugal.
Swedish Orphan, Rus. Swedish Orphan Biovitrum, Preschistenka St 40/2 Bld 1, 119034 Moscow, Russia.
url: www.swedishorphan.com
Swedish Orphan, Spain. Swedish Orphan Biovitrum SL, C/ Principe de Vergara 12, 1 Planta, 28001 Madrid, Spain.
url: www.sobi.com
Swedish Orphan, Swed. Swedish Orphan AB, Drottninggatan 98, 111 60 Stockholm, Sweden.
url: www.swedishorphan.com
Swedish Orphan, UK. Swedish Orphan Biovitrum Ltd, 1 Fordham House Court, Fordham House Estate, Newmarket Rd, Cambridge, CB7 5LL, UK.
url: www.sobi.com
Swedish Orphan, USA. Swedish Orphan Biovitrum Inc., SOBI, Times Building, Suite 401, 32 Parking Plaza, Ardmore, PA 19003, USA.
url: www.sobi.com
Swedpharm, Chile. Lab. Swedpharm, Monseñor Felix Cabrera 41 Of. 1, Providencia, Santiago, Chile.
Sween, USA. See *Coloplast, USA.*
Swiss Biotech, India. Swiss Biotech, 45, Sector 3, HSIIDC, Karnal 132 001, Haryana, India.
url: www.swissbiotechkarnal.com
Swiss Caps, Israel. Swiss Caps, Israel.
Swiss Caps, UK. Swiss Caps UK Ltd, Suite 1, Old Coach House, Robin Hoods Well, Skelbrooke, Doncaster, DN6 8LS, UK.
Swiss Health, Philipp. See *GPC, Philipp.*
Swiss Herbal, Canad. Swiss Herbal Remedies Ltd, 35 Leek Cres, Richmond Hill, Ontario, L4B 4C2, Canada.
url: www.swissherbal.com
Swiss Herbal, UK. Swiss Herbal Remedies Ltd, St Mary Street, Cardiff, CF10 1AT, UK.
Swiss Parenterals, Philipp. See *International Apex, Philipp.*
Swiss Pharm, Thai. See *Pharmadica, Thai.*
Swiss Pharma, Philipp. See *Metro, Philipp* and *PharmAsia, Philipp.*
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Swiss Precision, Switz. Swiss Precision Diagnostics GmbH, 47 route de Saint-Georges, 1213 Petit-Lancy, Geneva, Switzerland.
url: www.swissprecisiondiagnostics.com
Swiss Serum, Malaysia. See *DKSH, Malaysia.*
Swiss Serum Institute, Israel. See *Droreth, Israel.*
Swiss Worldwide, Hong Kong. Swiss Worldwide Ltd, 9C Ho King Bldg, 128 On Ling Rd, Yuen Long, Hong Kong.
Swiss-American, USA. Swiss-American Products Inc., 2055 Luna Rd, 126 Carrollton, TX 75006, USA.
url: www.elta.net
Swisshealth, UK. SwissHealth, P.O. Box 34104, London, NW10 7FD, UK.
url: www.swisshealth.com
Swissphar, Neth. See *Will-Pharma, Neth.*
Swissphar, Switz. Swissphar AG, Marktgasse 10, 4310 Rheinfelden, Switzerland.
url: www.swissphar.ch
Swisspharm, S.Afr. See *Altana, S.Afr.*
Swisspharma, Cz. Swissspharma sro, Koněvová 141, 130 00 Prague 3, Czech Republic.
Swiss-Pharma, Ger. See *Falk, Ger.*
Switch, Rus. Switch Import/Export, Pushkinskaya ul 12/2-21, 191040 Saint Petersburg, Russio.
url: www.switch-spb.ru
Sydenham, Philipp. Sydenham Sales & Distribution, 3/F AP Warehouse front of SM Southmall, Almanza, Las Piñas City, Philippines.
Sydney Ross, Braz. See *GSK, Braz.*
Sykocure, India. Sykocure Lifesciences, Plot No 92, Industrial Area Phase-1, Panchkula, 134 113, India.
Sylk, UK. Sylk Ltd, P.O. Box 340, Rickmansworth, Hertfordshire, WD3 5WD, UK.
Symbiopharm, Austria. See *Symbiopharm, Ger.*
Symbiopharm, Ger. SymbioPharm GmbH, Auf den Lüppen, 35745 Herborn-Hörbach, Germany.
url: www.symbiopharm.de
SymbioPharm, Hung. See *Symbiopharm, Ger.*
Symbiosis, India. Symbiosis Pharmaceuticals Pvt Ltd, Suketi Road, Kala Amb, Sirmour 173 030, India.
Symbiotic, India. Symbiotic Drugs & Diabetic Care Pvt Ltd, 305 Mahajan Tower, L.S.C. Shrestha Vihar, Delhi 110 092, India.
url: www.symbioticdrugs.com
SymPhar, Denm. See *SymPhar, Pol.*
SymPhar, Fin. See *SymPhar, Pol.*
SymPhar, Neth. See *SymPhar, Pol.*
SymPhar, Pol. SymPhar Sp. za.o., ul. Grójecka 186/516, 02-390 Warsaw, Poland.
Synapse, Irl. Synapse Medical, Unit 12, Keypoint Business Park, Rosemount Business Park Drive, Ballycoolin Rd, Dublin 11, Ireland.
url: www.synapsemedical.ie
Synapsya, Fr. Laboratoire Synapsya, 19 place Tolozan, 69001 Lyon, France.
Synco, Denm. See *Chiron, Neth.*
Synco, Hong Kong. Synco (HK) Ltd, Blk D, 3/F, Sun View Industrial Bldg, 3 On Yip St, Chaiwan, Hong Kong.
url: www.synco-pharma.com
Synco, Singapore. See *Singapore Pharmaceutical, Singapore.*
Syncom, Philipp. See *Pharmasan, Philipp.*
Syncro, Arg. See *Armstrong, Arg.*
Syndicate, India. Syndicate Overseas, M-4 Himland House, Commercial Complex, Karmpura, New Delhi 110 015, India.
url: www.syndicateoverseas.com
Synergen, Philipp. Synergen Pharma Inc., 1908 Cityland 10 Twr 1, HV Dela Costa St cor Ayala Ave, Makati City, Philippines.
Synergia, Fr. Laboratoires Synergia, B.P. 345, 42015 Saint Etienne Cedex 2, France.
url: www.synergia-ltd.com
Syner-Med, UK. Syner-Med (Pharmaceutical Products) Ltd, Beech House, 840 Brighton Rd, Purley, Surrey, CR8 2BH, UK.
url: www.syner-med.com
Synmedic, India. Synmedic Laboratories, 202-207 Sai Plaza, 187-188 Sant Nagar, East of Kailash, New Delhi 110 065, India.
Synmedic, Philipp. See *Ambica, Philipp* and *Pharmasan, Philipp.*
Synmedic, Switz. Synmedic AG, Gerhardstrasse 1, Postfach, 8036 Zurich, Switzerland.
url: www.synmedic.ch
Synmedic, Ukr. Synmedic, 19 Moscow Ave, Kiev, 04655, Ukraine.
url: www.synmedic.com.ua
Synmosa, Malaysia. See *Apex, Malaysia* and *Zyfas, Malaysia.*
Synmosa, Singapore. See *Zyfas, Singapore.*
Synmosa, Thai. See *Harn, Thai.*
Synokem, India. Synokem Pharmaceuticals Ltd, F-301-302, Friends Tower, Paschim Vihar Commercial Complex, New Delhi 110 063, India.
SynPenn, Philipp. See *B-Phar, Philipp.*
Syntex, Belg. See *GSK, Belg.*
Syntex, Canad. See *Roche, Canad.*
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Syntex, Ger. See *Roche, Ger.*
Syntex, Indon. See *Darya-Varia, Indon.*
Syntex, Mex. Syntex S.A. de C.V., Cerrada de Bezares 9, Miguel Hidalgo Lomas de Bezares, 11910 Mexico D.F., Mexico.
Syntex, Neth. See *Roche, Neth.*
Syntex, NZ. See *Roche, NZ.*
Syntex, S.Afr. See *Roche, S.Afr.*
Syntex, Spain. See *Roche, Spain.*
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Syntex, Switz. See *Uhlmann-Eyraud, Switz.*
Syntex, UK. See *Roche, UK.*
Syntex, USA. See *Roche, USA.*
Synteza, Pol. Przedsiębiorstwa Farmaceutyczno-Chemiczne Synteza Sp zo.o., ul. Św. Michał 67/71, 60-594 Poznań, Poland.
url: www.synteza.com
Synthelabo, Belg. See *Sanofi-Aventis, Belg.*
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Synthesis, Rus. Synthesis ZAO, Constitution prospekt 7, 640008 Kurgan, Russia.
Synthiko, India. See *Synokem, India.*
Syntho, India. Syntho Pharmaceuticals, 31/16 Old Rajinder, Nagar, New Delhi 110060, India.
url: www.eyepharma.in
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Synthon, Neth. Synthon BV, Microweg 22, 6503 GN Nijmegen, Netherlands.
url: www.synthon.com
Synthon, Pol. See *Polpharma, Pol.*
Synthon, Port. See *Synthon, Spain.*
Synthon, Spain. Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llabregat, Spain.
url: www.synthon.es
Syntro, India. See *Synokem, India.*
Syosset, USA. Syosset Laboratories Inc., 150 Eileen Way, Syosset, NY 11791, USA.
Syria, Ital. Syrio Pharma S.p.A., Via C. Hajech 10, 20129 Milan (MI), Italy.
Sysco, Canad. Sysco Corp., 400 21 Four Seasons Place, Toronto, Ontario, M8B 6J8, Canada.
Sysmed, India. Sysmed Laboratories Pvt Ltd, 81/20 G.I.D.C, Makarpura, Baroda 390 010, India.
Systacare, India. Systacare Remedies, 50 Ind. Estate Post Office, Rayon & Silk Mills, GT Rd, Amritsar, 143 104, India.
Systagenix, Irl. See *Systagenix, UK.*
Systagenix, Ital. Systagenix Wound Management, Via Riccardo Gigante 4/5, 00143 Rome, Italy.
url: www.systagenix.it
Systagenix, UK. Systagenix Wound Management, 1st Floor, 2 City Place, Gatwick Airport, West Sussex, RH6 0PA, UK.
url: www.sytagenix.com
Systopic, India. Systopic Laboratories Pvt Ltd, 101 Pragati Chambers, Commercial Complex, Ranjit Nagar, New Dehli 110 008, India.
url: www.systopic.com
Syxyl, Ger. Syxyl GmbH & Co. KG, Gereonsmühlengasse 5, 50670 Cologne, Germany.
url: www.syxyl.de
Szabo, Arg. Laboratorio Szabó SA, Tacuari 1560, 1139 Buenos Aires, Argentina.
Szama, Arg. Lab. Szama S.A., Lafuente 161, 1406 Buenos Aires, Argentina.
url: www.szama.com
T/I, USA. See *Fischer, USA.*
T Man, Thai. T Man Pharma Ltd, Part, 101/2 Soi Moungsakul, Bangkuntian, Bangkok 10150, Thailand.
url: www.tmanpharma.com
T3A Pharma, Hung. See *Beaco, Hung.*
Tablets, India. Tablets (India) Ltd, R.A. Building, IV Floor, 72 Marshalls Road, Chennai 600 008, India.
url: www.tabletsindia.com
Tabs n Caps, Denm. Tabs n Caps Pack ApS, Tejrvej 27, 3500 Vaerløse, Denmark.
Tabuk, Cz. See *Tabuk, Pol.*
Tabuk, Hung. See *Tabuk, Pol.*
Tabuk, Malaysia. See *Averroes, Malaysia.*
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Tabuk, Pol. Tabuk Poland Sp. zo.o., ul. Capri 2/77, 02-762 Warsaw, Poland.
url: www.tpmc.com.sa
Tack Fung, Hong Kong. Tack Fung Medical Supplies Co., Rm 504, Tien Cheung Hong Bldg, 77-81 Jervois St Central, Hong Kong.
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TAD, Fin. See *TAD, Ger.*
TAD, Ger. TAD Pharma GmbH, Heinz-Lohmann-Str. 5, 27472 Cuxhaven, Germany.
url: www.tad.de
TAD, Gr. See *TAD, Ger.*
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TAD, Irl. See *TAD, Ger.*
TAD, Ital. TAD Pharma Italia S.r.l., Via Felice Casati 16, 20124 Milan (MI), Italy.
url: www.tadph.com
TAD, Neth. See *TAD, Ger.*
TAD, Pol. TAD Pharma GmbH Sp. z o.o. Przedstawicielstwo w Polsce, ul. Chorągwi Pancernej 27, 02-951 Warsaw, Poland.
url: www.tad.de
TAD, Port. See *TAD, Ger.*
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Taejoon, Singapore. See *Pharmaforte, Singapore.*
Taejoon, Thai. See *Masu, Thai.*
Tafarm, Gr. Tafarm, Christianoupoleos 108, 111 46 Galatsi, Greece.
Tai An, China. Tai An Pharmaceutical Factory, Shandong, China.
Tai Fu, China. Tai Fu Pharmaceutical Co. Ltd, China.
Tai Guk, Hong Kong. See *CNW, Hong Kong.*
Tai Guk, Singapore. See *Polymedic, Singapore.*
Tai Le, China. Tai Le Pharmaceutical Co. Ltd, Sichuan, China.
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Tai Sheng, China. ShanXi Tai Sheng Pharmaceutical Co. Ltd, Economic & Technological Development Zone, Shanxi 037300, China.
Tai Tong, Hong Kong. Tai Tong Co. Ltd, Rm 901-902, Alliance Bldg, 130-136 Connaught Rd Central, Hong Kong.
Tai Yu, Philipp. See *Cathay, Philipp and Endure, Philipp and Medicamenta, Philipp.*
Taibao, China. Taibao Pharmaceutical Co. Ltd, Changsha, China.
Taige, China. Taige Pharmaceutical Co. Ltd, 19km Office, Aipart Road, Harbin, Heilongjiang, China.
Taihe, China. Taihe Pharmaceutical Co. Ltd, 234 Jinyuan Road, Binhai, Tianjin, China.
url: www.taihezhiyao.com
Taiha, China. See *Jing Wei, China.*
Taiho, Cz. See *Taiho, UK.*
Taiho, Jpn. Taiho Pharmaceutical Co. Ltd, 1-27 Kanda-Nishiki-cho, Chiyoda-ku, Tokyo 101-8444, Japan.
url: www.taiho.co.jp
Taiho, Malaysia. See *Luen Wah, Malaysia.*
Taiho, Rus. See *Grindex, Rus.*
Taiho, Singapore. See *Luen Wah, Singapore.*
Taiho, Thai. See *Diethelm, Thai.*
Taiho, UK. Taiho Pharma Europe Ltd, 55 Colmore Row, Birmingham, West Midlands, B3 2AS, UK.
Taihuatang, China. Taihuatang Pharmaceutical Co. Ltd, Sichuan, China.
Taiji, China. Taiji Pharmaceutical Co. Ltd, Sichuan, China.
Taikang, China. Taikang Pharmaceutical Co. Ltd, Zhejiang, China.
Tailison, China. Tailison Pharmoceutical Co. Ltd, Haiyan Economic Development Zone, 200 North Bridge Rd, Zhejiang 314300, China.
url: www.tailison.com
Tailong, China. Tailong Pharmaceutical Co. Ltd, Henan, China.
Tairong, China. Tairong Pharmoceutical Co. Ltd, 2 Longzhou Ave, Changyang, Hubei, China.
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Taisho, China. See *Taisha, Jpn.*
Taisho, Indon. Taisho Pharmaceutical Indonesia Tbk PT, Wisma Tamara 10th Fl, Jl J Sudirman Kav 24, Jakarta 12920, Indonesia.
Taisho, Jpn. Taisho Pharmaceutical Co. Ltd, 3 Ohara Ichiba, Kouka-chou, Kouka-shi, Shiga-ken, 520-3433, Japan.
url: www.taishoyakuhin.co.jp
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Taisho, Philipp. See *Zuellig, Philipp.*
Taisho, Thai. See *DKSH, Thai.*
Taisho Toyama, Jpn. Taisho Toyama Pharmaceutical Co. Ltd, 3-25-1, Takada, Toshima-ku, Tokyo, Japan.
Taitai, China. Taitai Pharmaceutical Co. Ltd, Shenzhen, China.
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Taiyang, China. Taiyang Pharmaceutical Industry Co Ltd, Double Bridge East Road, Chaoyang District 1, Beijing 100024, China.
url: www.taiyongpharm.com
Taiyo, Jpn. Taiyo Pharmaceutical Industry Co. Ltd, 24-11 Taikou 1-chome, Nakamura-ku, Nagoya-shi, Aichi-ken, 453-0801, Japan.
url: www.taiyo-yakuhin.com
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TaiYuan, China. TaiYuan Pharmaceutical Co Ltd, Changchun, China.
Taj, Indio. Taj Pharmaceuticals Ltd, 434 Laxmi Plaza, Laxmi Industrial Estate, New Link Road, Andheri (W), Mumbai 400 053, India.
url: www.tajpharmaceuticals.com
Takata, Jpn. Takata Seiyaku Co Ltd, 13-10 2-chome, Torigoe, Taito-ku, Tokyo, Japan.
url: www.takata-seiyaku.co.jp
Takeda, Austria. Takeda Pharma GmbH, Seidengasse 33-35/4, A-1070 Vienna, Austria.
url: www.takeda.com
Takeda, Belg. Takeda Belgium SCA/CVA, Gentsesteenweg 615, 1080 Brusseks, Belgium.
url: www.takeda.be
Takeda, Canad. Takeda Canada Inc., Suite 400, 6750 Century Ave, Mississauga, Ontario, L5N 2V8, Canada.
Takeda, China. Takeda Pharmaceutical (China) Co Ltd, Floor 23 Building B Ping An International Financial Center, 3 Xin Yuan South Rd, Chaoyang District, Beijing 10027, China.
url: www.takeda.com
Takeda, Cz. See *Medicom, Cz.*
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Takeda, Fr. Laboratoires Takeda, 15 quai de Dion-Bouton, 92816 Puteaux cdx, France.
url: www.takeda.com
Takeda, Ger. Takeda Pharma GmbH, Viktoriaallee 3-5, 52066 Aachen, Germany.
url: www.takeda.de
Takeda, Gr. Takeda, Greece.
Takeda, Hang Kong. Takeda Chemical Industries Ltd, Unit 1801-2, 18/F Fook Lee Commercial Ctr, Town Place, 33 Lockhart Rd, Wanchai, Hong Kong.
url: www.takeda.com
Takeda, Hung. See *Takeda, UK.*
Takeda, Indon. Takeda Indonesia PT, Mashil Tower 15/F Jl Jend Sudirman Kav 25, Jakarta 12920, DKI Jaya, Indonesia.
Takeda, Irl. Takeda Ireland Ltd, Bray Business Park, Kilruddery, Co Wicklow, Ireland.
url: www.takeda.ie
Takeda, Israel. See *Promedico, Israel.*
Takeda, Ital. Takeda Italia Farmaceutici S.p.A., Via Elio Vittorini 129, 00144 Rome (RM), Italy.
url: www.takeda.it
Takeda, Jpn. Takeda Chemical Industries Ltd, 4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645, Japan.
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Takeda, Malaysia. See *Luen Wah, Malaysia* and *Zuellig, Malaysia.*
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Takeda, Spain. See *Takeda, UK.*
Takeda, Swed. Takeda Pharmaceuticals Nordics AB, c/o Regus, Solna Strandväg 78, 171 54 Solna, Sweden.
Takeda, Switz. Takeda Pharma AG, Alpenblickstrasse 26, 8853 Lachen, Switzerland.
url: www.takeda.ch
Takeda, Thai. Takeda (Thailand) Ltd, 12A Fl, Si Ayutthaya Building, Si Ayutthaya Rd, 487/1 Ratchathewi, Bangkok 10400, Thailand.
url: www.takeda.com
Takedo, UK. Takeda UK Ltd, Takeda House, The Mercury Centre, Wycombe Lane, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0HH, UK.
url: www.takeda.co.uk
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Takeda, USA. Takeda Pharmaceuticals America, 475 Half Day Rd, Suite 500, Lincolnshire, IL 60069, USA.
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Talcris, Arg. Talcris S.A., Congreso 2160 PB. A, 1428 Buenos Aires, Argentina.
Talecris, Austria. See *Talecris, Ger.*
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Talecris, Ger. Talecris Biotherapeutics GmbH, Lyoner Strasse 15, 60528 Frankfurt, Germany.
url: www.talecris.de
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Talecris, USA. Talecris Biotherapeutics, P.O.Box 110526, 4101 Research Commons, 79 TW Alexander Drive, Research Triangle Park, North Carolina 27709, USA.
url: www.talecris.com
Talent, India. Talent Healthcare, A/10/4 Parth Indraprasth Tower, Nr. Vastrapur Sarkari Vasahat, P. O. Vastrapur, Ahmedabad 380 052, India.
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url: www.talion-a.ru
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Tallin, Cz. See *ProMed, Cz.*
Tallin, Pol. Tallin Pharmaceutical Plant, Poland.
Tallinn, Rus. See *BMS, Rus.*
Talon, USA. Talon Therapeutics Inc., 400 Oyster Point Blvd, Suite 200, South San Francisco, CA 94080, USA.
url: www.talonrx.com
Tolya, Turk. Talya Farma Iloç, Yali Side Beldesi, Turgut Şen Işhani, 1001 Sokak No 1 Side, Antalya, Turkey.
url: www.talyafarma.com
Tamag, Hung. Tamag Bt, Kukolloi u 10, 2220 Vecses, Hungary.
url: www.tafedim.hu
Tamar, Israel. Tamar Marketing, Rishon-Lezion 75652, Israel.
Tamilnadu Dadha, India. See *Sun, India.*
Tamro, Fin. Tamro Distribution/Pharmakon, Rajatorpantie 41 B, Pl 11, 01640 Vantaa, Finland.
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Tanabe, Hong Kong. See *Primal, Hong Kong.*
Tanabe, Indon. Tanabe Indonesia PT, Jl Tanah Abang III No 8, Jakarta Pusat 10160, DKI Jaya, Indonesia.
Tanabe, Jpn. See *Mitsubishi-Tokyo, Jpn.*
Tanabe, Malaysia. See *Pharmaforte, Malaysia.*
Tanabe, Singapore. See *Pharmaforte, Singapore.*
Tanabe, Thai. See *Wellchem, Thai.*
Tanabe Seiyaku, China. Tianjin Tanobe Seiyaku Co. Ltd, Hong Kong Rd, Xiqing District, Tianjin 300385, China.
url: www.tanabe.com.cn
Tanabe Seiyaku, India. See *Talent, India.*
Tanais, Rus. Tanais, Russia.
Tanalize, Turk. Tanalize Cosmetics, Ömerli Beldesi, Fabrikalar Yolu No: 43, Ömerli, İstanbul, 34797, Turkey.
url: www.tanalize.com
Tanapat Bhaesaj, Thai. Tanapat Bhaesaj, Thailand.
Tangshi, China. Tangshi Pharmaceutical Co. Ltd, Suzhou, China.
Tanic, Gr. Tanic Pharmaceuticals Ltd, Athenas 67, 131 22 Ilion Attici, Greece.
Tanki, Arg. Tanki S.A., Erezcano 3161, 1437 Buenos Aires, Argentina.
Tanner, Switz. Tanner SA, Riedstrasse 7-9, 6330 Cham, Switzerland.
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Tanning Research, Canad. Tanning Research Labs, 108 Newbold Court, London, Ontario, N6E 1Z7, Canada.
Tanning Research, USA. Tanning Research Labs Inc., P.O. Box 265111, Daytone Beach, FL 32126-5111, USA.
url: www.htropic.com
Tanta, Canad. Tanta Pharmaceuticals Inc., 1009 Burns St East, Whitby, Ontario, L1N 6A6, Canada.
TAP, Canad. See *Abbott, Canad.*
TAP, USA. TAP Pharmaceutical Products Inc., 675 North Field Drive, Lake Forest, IL 60045, USA.
url: www.tap.com
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Tarbis, Spain. See *Ferrer, Spain.*
Tarchomin, China. See *Polfa Tarchomin, Pol.*
Tarchomin, Hung. See *Polcommerce, Hung.*
Tarchomin, Rus. Tarchomin Pharmaceutical Works Polfa S.A., Sr. Pereyaslavskaya ul. 13, str. 2, 129110 Moscow, Russia.
Target, Gr. Target Pharma, Menandrou 54, 104 31 Athens, Greece.
Targof, India. Targof Pure Drugs Ltd, No 1-3-183/40/70/1, Opposite II Park Gandhi, Nagar Hyderabad 500380, India.
Tarmac, USA. Tarmac Products Inc., 13295 NW 107th Ave, Hialeah Gardens, FL 33018, USA.
url: www.tarmacproducts.com
Taro, Canad. Taro Pharmaceuticals Inc., 130 East Drive, Bramalea, Ontario, L6T 1C3, Canada.Director Research & Development
url: www.taro.ca
Taro, Israel. Taro Pharmaceutical International, 14 Hakitor St, P.O. Box 10347, Haifa Bay 26110, Israel.
url: www.taro.co.il
Taro, Philipp. See *Zuellig, Philipp.*
Taro, Singapore. See *Apotheca, Singapore.*
Taro, Thai. See *Union Medical, Thai.*
Taro, UK. Taro Pharmaceuticals (UK) Ltd, 1st Floor, Prince of Wales House, 3 Bluecoats Ave, Hertfordshire, SG14 1PB, UK.
url: www.taropharma.co.uk
Taro, USA. Taro Pharmaceuticals USA Inc., 5 Skyline Drive, Hawthorne, NY 10532-9998, USA.
url: www.tarousa.com
Taro Consumer, USA. See *Taro, USA.*
Tarus, UK. See *Chemidex, UK.*
Tasly, China. Tasly Pharmaceutical Co Ltd, Tasly TCM Garden, 2 Pujihe East Road, Beichen District, Tianjin 300410, China.
url: www.tasly.com
Tatkhimfarm, Rus. Tatkhimfarmpreparaty, Kazan, Belomorskaya St 260, 420091 Tatarstan, Russia.
Tatsumi, Jpn. Tatsumi Chemical Co. Ltd, Yasuhi Hisashi 3-chome, Kanazawa 406, Japan.
Tau, Spain. See *AstraZeneca, Spain.*
Taurus, Ger. Taurus Pharma GmbH, Benzstr. 11, 61352 Bad Homburg, Germany.
url: www.tauruspharma.de
Taurus, India. Taurus Laboratories Pvt Ltd, 8 2nd Floor Ruchi Apartments, CG Road, Navrangpura, Ahmedabad, Gujarat, 380 009, India.
Taylor, USA. See *Akorn, USA.*
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url: www.taymed.com.tr
Tayuyna, Braz. Laboratorio Tayuyna Ltda, Av. Amplélio Gazzetta 889, 13460000 Nova Odessa Pq. Indl. Fritz B, São Paolo, Brazil.
T-Boma, Hong Kong. Trenton-Boma Ltd, Rm 1901, Clifford Centre, 782 Cheung Sha Wan Rd, Kowloon, Hong Kong.
TC Pharma-Chem, Thai. TC Pharma-Chem Co Ltd, 488 Soi Chalermsaok, Phaholyotin Rd, Chankasem, Jatujak, Bangkok 10900, Thailand.
url: www.tcpharmachem.com
TC Technocare, Israel. See *TP, Israel.*
Team, China. Team Pharmaceutical Co. Ltd, China.
Teamm, USA. See *Accentia, USA.*
Tebao, China. Tebao Bio Co. Ltd, Xiamen, China.
Tec, USA. Tec Laboratories Inc., 7100 Tec Labs Way SW, Albany, OR 97321, USA.
url: www.teclabsinc.com
Tecefarma, Spain. See *Menarini, Spain.*
Techmed, Cz. Techmed sro, 664 55 Moutnice 37, Czech Republic.
Technica, India. Technica Labs & Pharma Pvt Ltd, 75 Rajpur Road, Dehradun 248 001, Uttaranchal, India.
url: www.technicalab.com
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url: www.techlab.co.za
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Techni-Pharma, Mon. Techni-Pharma, 7 rue de l'Industrie, B.P. 717, MC 98014, Monaco.
Technipro, Austral. Technipro Marketing P/L, 13 Bourke St, North Parramatta, NSW 2150, Australia.
url: www.geocities.com/technipro_australia
Technipro, NZ. See *Pharmaco, NZ.*

Technobio, Mex. Technobio SA de CV, Sur 101 B 216, 9090 Iztapalapa Héroes de Churubusco, Mexico.

Technogen, Rus. Technogen, Russia.

Technolabor, Spain. Technolabor AC SA, Calle de la Granja 82, 28108 Alcobendas (Madrid), Spain.

Technomedservis, Rus. Technomedservis, Vorontcovskaja ul. 23, 109147 Moscow, Russia.

Technopark, Rus. Technopark Center, Russia.

Technopharm, Irl. Technopharm Compounding Ltd, Unit 2, 88/89 Furze Rd, Sandyford Industrial Estate, Dublin 18, Ireland.
url: www.technopharm.com

Techpool, China. Techpool Biopharmaceutical Co. Ltd., 89 Goopu Road, Gaotang Sci-Tech Industrial Park, Tianhe, Guangzhou, Guangdong, 510520, China.
url: www.techpool.com.cn

Techsphere, Arg. Techsphere de Argentina, Av. Bernardino Rivadavia 843, (1870) Avellaneda, Buenos Aires, Argentina.

Tecnifar, Port. Tecnifar, SA, Rua Tierno Galvan, Torre 3, 12 Piso, 1099-036 Lisbon, Portugal.

Tecnimede, Port. Tecnimede, SA, Rua Prof. Henrique de Barros, Edificio Sagres, 5B, 2685-338 Prior Velho, Portugal.
url: www.grupo-tm.com

Tecnimede, Spain. Tecnimede Espana, Avda. Pio XII, 92, Edificio URAL A, Planta 16, Puerta 4, 28036 Madrid, Spain.
url: www.grupotecnimede.com

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Tecnofarma, Chile. Tecnofarma SA, Las Violetas 2169, Santiago, Chile.

Tecnafarma, Mex. Tecnofarma S.A. de C.V., Azafran No. 123, Col. Granjas Mexica, 08400 Mexico D.F., Mexico.
url: www.tecnofarma.com.mx

Tecnonat, Arg. Tecnonat S.A., 24 de Noviembre 368, 1170 Buenos Aires, Argentina.
url: www.tecnonat.com

Tecnopharma, Ital. Tecnopharma Srl, Via Sestri 29A/3, 16154 Genoa, Italy.
url: www.tecnopharma.net

Tec-O-Pharm, Israel. Tec-O-Pharm, P.O. Box 45054, Jerusalem 91450, Israel.
url: www.toplibra.co.il

Tecsolpar, Spain. Tecsolpar, Parque Tecnológica de Asturias 19, 33428 Llanera, Asturias, Spain.
url: www.tecsolpar.es

Tedec Meiji, Israel. See *Trima, Israel.*

Tedec Meiji, Port. Tedec Meiji Farma SA Sucursal, Av. António Augusto de Aguiar 163, 5 Dto, 1050-14 Lisbon, Portugal.

Tedec Meiji, Spain. Tedec Meiji Farma, Ctra M-300, Km 30.5, Alcalá de Henares, 28820 Madrid, Spain.
url: www.tedecmeiji.com

Tedec-Meiji, Thai. See *Meiji, Thai.*

Tedequim, Arg. Laboratorios Tedequim SRL, Bv. de los Palacos 6136, (5147) Cordoba, Argentina.

Tefeng, China. Tefeng Pharmaceutical Co. Ltd, Room 215 Science Building, 458 Northwest Road, Urumqi, Xinjiang, China.
url: www.tefeng.com

Teguhsindo, Indon. Teguhsindo Lestaritama, Jl Kebayoran Lama No 557, Jakarta 12220, DKI Jaya, Indonesia.
url: www.teguhsindo.com

Teijin, China. Teijin Pharma Co. Ltd, Chang Fu Gong Office 609, Jian Guo Men Wai Ave, Chaoyang, Beijing, 100022, China.

Teijin, Hong Kong. See *Hind Wing, Hong Kong.*

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Teijin, Jpn. Teijin Ltd, 2-1-1 Uchisaiwai-cho, Chiyoda-ku, Tokyo 100-8585, Japan.
url: www.teijin.co.jp

Teijin, Malaysia. See *Somedico, Malaysia.*

Teijin, Philipp. See *Croma, Philipp.*

Teijin, Rus. Teijin, Krosnapresnenskaya 6 D.12, World Trade Center Entrance 3, Office 802A, 123610 Moscow, Russia.
url: teijin-russia.ru

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Teikoku, Ital. See *Teikoku, UK.*

Teikoku, Jpn. Teikoku Hormone Mfg Co. Ltd, 2-5-1 Shibaura, Minato-ku, Tokyo 108-8532, Japan.
url: www.teikoku-hormone.co.jp

Teikoku, UK. Teikoku Pharma UK Ltd, 7th Floor Central House, 1 Ballards Lane, Finchley, London, N3 1LQ, UK.

Teikoku Seiyaku, China. See *Teikoku Seiyaku, Jpn.*

Teikoku Seiyaku, Jpn. Teikoku Seiyaku Co. Ltd, 567 Sanbonmatsu, Ochi-cho, Okawa-gun, Kagawa 769-2695, Japan.
url: ww.teikoku.co.jp

Teingro, Arg. Teingro SA, Suipacha 60/62 Bis, (2000) Rosario, Santa Fe, Argentina.

Tek, Thai. See *Neopharm, Thai.*

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Teka, Turk. Teka Teknik Cihazlar San. ve Tic. A.S., Altan Erbulak Sok. No: 3, Mecidiyeköy, Istanbul, 80300, Turkey.
url: www.tekateknik.com.tr

Tekhnolog, Ukr. Tekhnolog, Zaliznyaka Street, 3, Uman, 20300, Ukraine.

Teknafarma, Ital. Teknofarma S.p.A., Strada Comunale da Bertolla alla Abbadia di Stura 14, 10156 Turin, Italy.

Teleflex, Ital. Teleflex Medical S.r.l., Via Torino 5, 20039 Varedo (MI), Italy.
url: www.teleflexmedical.com

Telluride, USA. Telluride Pharm. Corp, 300 Valley Rd, Hillsborough, NJ 08844-4656, USA.
url: www.tellpharm.com

Tema, S.Afr. Tema Medical (Pty) Ltd, P.O. Box 3467, Cramerview 2060, South Africa.

Temapharm, Cz. See *Temapharm, Pol.*

Temapharm, Pol. Temapharm Sp zoo, ul. Zwirki i Wigury 81, 02-091 Warsaw, Poland.
url: www.temapharm.com

Temis, Arg. Lab. Temis Lostaló S.A., Zepita 3178, 1285 Buenos Aires, Argentina.
url: www.temislostalo.com.or

Temis, Spain. Temis Farma SL, Randa General Mitre 151, 08022 Barcelona, Spain.

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Temmler, Ger. Temmler Pharma GmbH & Co. KG, Temmlerstr. 2, 35039 Marburg/Lahn, Germany.
url: www.temmler.de

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Tempo Scan Pacific, Indon. Tempo Scan Pacific PT, Gedung Bina Mulia II, Jl HR Rasuna Said Kav 11, Jakarta 12950, DKI Jaya, Indonesia.

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Tems, Turk. Tems, Turkey.

Tendem, Neth. Tendem BV, Punterweg 30, 8042 PB Zwolle, Netherlands.
url: www.tendem.nl

Tendem-Haco, Neth. See *Tendem, Neth.*

Tender, Canad. Tender Corp. Canada, P.O. Box 31018, Barrie, Ontario, L4M 5A5, Canada.
url: www.tendercorp.com

Tender, Israel. See *Meditrend, Israel.*

Tenlec, Denm. See *Tenlec, UK.*

Tenlec, UK. Tenlec Pharma Ltd, Broadlands, Amberstone, Hailsham, East Sussex, BN27 1PQ, UK.

Tentan, Ger. Tentan Deutschland GmbH, Hauptstr. 49, 35614 Asslar-Werdorf, Germany.
url: www.tentan.de

Tentan, Switz. Tentan AG, Brunnliweg 16, 4433 Ramlinsburg, Switzerland.
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Teofarma, Gr. Teofarma, Ag Dimitriou 63, 174 56 Alimos, Greece.

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Teofarma, Ital. Teofarma, Via F.lli Cervi 8, 27010 Valle Salimbene (PV), Italy.
url: www.teofarma.com

Teofarma, Neth. Teofarma, Netherlands.

Teofarma, Port. Teofarma srl, c/o Indiconta, Rua Domingos Sequeira 27, 1350-119 Lisbon, Portugal.

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Teofarma, Switz. Farmaceutica Teofarma Suisse SA, Via Somaini 10, 6901 Lugano, Switzerland.

Teofarma, UK. See *Teofarma, Ital.*

Teamed, Switz. Teomed AG, Turnigerstrasse 71, Postfach 20, 8606 Greifensee, Switzerland.
url: www.teomed.ch

Teral, USA. Teral Inc., Ave Santiago De, Ponce, PR 00732, Puerto Rica.

Terali, Fr. Terali, ZA La Haute-Limougère, 23 rue Christaphe-Plantin, BP 24, 37230 Fondettes, France.

Terapeutico, Ital. Laboratorio Terapeutico M.R. S.r.l., Via Domenico Veneziana 13, 50143 Florence (FI), Italy.
url: www.mr1930.it

Terapia, Cz. See *Terapia, Roum.*

Terapia, Hung. See *Medico Uno, Hung.*

Terapia, Roum. The Terapia Medicinal Drugs Enterprise, Cluj-Napoca, Roumania.

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Tercica, Gr. See *Ipsen, Gr.*

Tercica, Irl. Tercica Europe Ltd, 2 Harbourmaster Place, International Financial Services Centre, Dublin 1, Ireland.

Tercica, Israel. See *Medison, Israel.*

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Tercica, Pol. See *Ipsen, Pol.*

Tercica, USA. Tercica, 2000 Sierra Point Parkway, Brisbane, CA 94005, USA.
url: www.tercica.com

Terme di Tabiano, Ital. Termi di Tabiano SpA, Viale Alle Terme 32, 43030 Tabiano (PR), Italy.
url: www.termeditabiano.it

Terra, Turk. Terra Ilaç ve Kimyo Sanayi Tic. A.S., Bulgurlu Mah., Alemdağ Cad. Masaldan İş Merkezi No: 46 B Blok K: 3, Üsküdar, Istanbul, Turkey.
url: www.terrailac.com.tr

Terra-Bio, Ger. Terra-Bio-Chemie GmbH, Lindenbergstr. 5, 79199 Kirchzarten, Germany.
url: www.terra-bio.de

Terraclouds, Singapore. Terraclouds Pte Ltd, Singapore.

Terrafor, Fr. Laboratoires Terrafor, B.P. 62, 76302 Sotteville-les-Rouen cdx, France.
url: www.terrafor.com

Terrain, USA. Terrain Pharmaceuticals LLC, 701 Tyner Way Incline Village, NV 89451, USA.
url: www.terrainrx.com

Terramedic, Philipp. Terromedic Inc., ENE Industrial Complex, Brgy San Antonia, San Pedro, Laguna, Philippines.

Terrier, Mex. See *Columbia, Mex.*

Terumo, Ital. Terumo Italia Srl, V.le Simone Martini 143/145, 00142 Rome (RM), Italy.

Terumo, Jpn. Teruma Corp., 2-44-1 Hatagaya, Shibuya-ku, Tokyo 151-0072, Japan.
url: www.terumo.co.jp

Tetesept, Ger. tetesept Pharma GmbH, Marschnerstr. 10, 60318 Frankfurt, Germany.
url: www.merz.de

Tetra, Israel. Tetra Pharm, 1 Azrieli Center, Raund Bldg, 24 floor, Tel Aviv 67021, Israel.
url: www.sebocalm.co.il

Tetrafarm, Arg. Laboratorios Tetrafarm SA, Calle 15 1547, 1884 Berazategui, Buenos Aires, Argentina.

Tetrafarma, Port. Tetrafarma Produtos Farmaceuticos Lda, Rua Helena Aragão 20 R/C Frente, Massama, 2745-879 Queluz, Portugal.

Teuto, Braz. Laboratório Teuto-Brasileiro Ltda, VP 7-D Modulo 11 Quadra 13, 75133-600 Anapolis, GO, Brazil.
url: www.teuto.com.br

Teva, Austria. See *Teva, Ger.*

Teva, Belg. Teva Belgium, Laarstraat 16, 2610 Wilrijk, Belgium.
url: www.tevabelgium.be

Teva, Braz. Teva Farmaceutica Ltda, Rua James Joule 92-15 CJ 151 e 152, 4576080 São Paulo, Brazil.

Teva, Canad. Teva Neuroscience G.P.-S.E.N.C., 999 de Maisonneuve W, Suite 550, Montreal, Quebec, H3A 3L4, Canada.
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Teva, China. See *Baker Norton, China.*

Teva, Cz. Teva Pharmaceuticals CR sro, Andrysková 21, 636 00 Brno, Czech Republic.
url: www.teva.cz

Teva, Denm. Teva, Parallelvej 10, 2800 Lyngby, Denmark.
url: www.tevapharm.dk

Teva, Fin. See *Teva, Swed.*

Teva, Fr. Teva Pharma SA, 53-55 ter, rue du Capitaine Guynemer, 92400 Courbevoie, France.
url: www.tevapharm.com

Teva, Ger. TEVA Generics GmbH, Kondelstrasse 10, 79199 Kirchzarten, Germany.
url: www.teva-deutschland.de

Teva, Gr. Teva Pharmaceuticals Hellas SA, 166 A Kifissias Ave & 2 Sofokleous St, 151 26 Maroussi, Greece.
url: www.tevapharm.com

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Teva, Israel. Teva Pharmaceuticals Ind. Ltd, 5 Basel St, Petach Tikva 49131, Israel.
url: www.tevapharm.com

Teva, Ital. Teva Pharma Italia S.r.l., V.le G. Richard 7, 20143 Milan (MI), Italy.
url: www.tevapharm.com

Teva, Jpn. Teva Pharmaceuticals Inc., 45MT 5th Floor Building 7, Toranomon 5-chome, Toranomon, Minato-ku, Tokyo, 1050001, Japan.
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Teva, Mex. Teva Pharmaceuticals Mexico SA de CV, Pasaje Interlomas 16, Piso 15, 52784 San Fernando la Herradura, Estado de Mexico, Mexico.

Teva, Neth. Teva Pharma BV, Industrieweg 23, Mijdrecht, Netherlands.

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Teva, Pol. Teva Pharmaceuticals Polska Sp. zo.o, ul. Domaniewska 50 A, 02-672 Warsaw, Poland.
url: www.teva.pl

Teva, Port. Teva Pharma Produtos Farmacêuticos Lda, Lagoas Park, Edificio 1, Piso 3, 2740-264 Porto Salvo, Portugal.

Teva, Rus. Teva Pharmaceutical Industries Ltd., Nauchny proezd 8, of. 226, 117246 Moscow, Russia.
url: www.teva.ru

Teva, S.Afr. Teva Pharmaceuticals (Pty) Ltd, P.O.Box 1590, Ruimsig, Roodepoort, Gauteng 1732, South Africa.
url: www.tevapharm.com

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Teva, Spain. Teva Genericos Espanola S.L., Guzman El Bueno 133, Edificio Britannia 4 A, 28003 Madrid, Spain.
url: www.tevaeurope.com

Teva, Swed. Teva Sweden AB, Sundstorget 2, 251 10 Helsingborg, Sweden.
url: www.teva.se

Teva, Switz. Teva Pharma AG, Industriestrasse 111, 4147 Aesch, Switzerland.
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Teva, Thai. See *RX, Thai* and *Union Medical, Thai.*

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Teva, Ukr. Teva, Moskovskaya Street, 43/11, 2nd floor, Kiev, 01015, Ukraine.

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Teva Kowa, Jpn. See *Kowa, Jpn.*

Teva Pharma, Ger. See *Teva, Ger.*

Teva Tuteur, Arg. Teva Tuteur S.A., Encarnación Ezcurra 365, Piso 3, Puerto Madero, Buenos Aires, Argentina.
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Texel, Canad. Texel, une Division de Ads Inc., 485 rue des Erables, St Elzear, Quebec, G0S 2J0, Canada.

Texinfine, Fr. Texinfine, 60 rue Dugueslin, 69466 Lyon cdx 06, France.

Textilease, USA. Textilease Medique Products, 900 Lively Blvd, Wood Dale, IL 60191, USA.

TG United, USA. TG United Pharmaceuticals Inc., 16255 Aviation Loop Dr, Brooksville, FL 34604, USA.

Thackray, UK. See *DePuy, UK.*

Thai FD, Thai. Thai FD Co. Ltd, 78/9 Moo 1, Mahasawat, Bongkrui, Nonthaburi, 11130, Thailand.

Thai Otsuka, Thai. Thai Otsuka Pharmaceutical Co. Ltd, 11 Fl, Regent House Building, 183 Rajdamri Rd, Khwang Lumpini, Khet Pathumwan, Bangkok 10330, Thailand.
url: www.thai-otsuka.co.th

Thai Red Cross, Thai. See *Biogenetech, Thai.*

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Thalgo, Fr. Lab Thalgo Nutrition, Domaine des Châtaigniers, 83520 Roquebrune-sur-Argens, France.
url: www.thalgo.com

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The Results Company, Canad. The Results Company Inc., Parry Sound, Ontario, P2A 2X4, Canada.

Thea, Austria. See *Thea, Fr.*

Thea, Belg. Thea Pharma NV SA, Jan Broeckaertlaan 18/11, B-9230 Wetteren, Belgium.
url: www.thea.be

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Thea, Fr. Laboratoires Théa, 12 rue Louis-Blériot, 63000 Clermont-Ferrand cdx 2, France.
url: www.laboratoires-thea.fr

Thea, Ger. Théa Pharma GmbH, Revierstr. 10, 44379 Dortmund, Germany.
url: www.theapharma.de

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Thea, Ital. Thea Farmaceutici S.r.l., Via Gioberti 1, 20123 Milan, Italy.

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Thea, Norw. Thea Nordic AB, Ekornrudveien 31 A, 1410 Kolbotn, Norway.

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url: www.thebepharmaceuticals.co.za

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url: www.therabel.com

Therabel, Fr. Laboratoires Thérabel Lucien Pharma, 123 rue Jules-Guesde, 92309 Levallois-Perret cdx, France.
url: www.therabel.com

Therabel, Ger. Therabel Pharma Deutschland GmbH, Neustr. 82, 40721 Hilden, Germany.

Therabel, Ital. Therabel Gienne Pharmo S.p.A., Via Lorenteggio 270/A, 20152 Milan (MI), Italy.
url: www.therabel.com

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url: www.therakos.com

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url: www.theramex.it

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url: www.torrent.com.br
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Torrex, Cz. Torrex Pharma sro, Na Květnici 33, 140 00 Prague 4, Czech Republic.
Torrex, Hung. Torrex Pharma Kft, Petőfi Sandor u 12, 1052 Budapest, Hungary.
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Torrex Chiesi, Hung. Torrex Chiesi Kft, Kristóf tér 4, III/1-3, H-1052 Budapest, Hungary.
Torrex Chiesi, Pol. Torrex Chiesi Polska Sp. zo.o., ul. Biała 3, 00-895 Warsaw, Poland.
url: www.torrex-chiesi.pl
Tosara, Irl. Tosara Products Ltd, Baldoyle Industrial Estate, Grange Rd, Dublin 13, Ireland.
Tosara, Spain. See *Tosara, Irl.*
Tosara, UK. See *Forest Laboratories, UK.*
Tosi, Hong Kong. See *Sincerity, Hong Kong.*
Total Health Antiaging Research, Canad. Total Health Antiaging Research Inc., 1110 Bloor St E, Mississauga, Ontario, L4Y 2N7, Canada.
Toulade, Fr. Laboratoires Toulade, av. du Docteur-Aubry, 76280 Criquetot-L'Esneval, France.
Towa, Jpn. Towa Pharmaceutica Co. Ltd Inc., 11/2 Shinbashicha, Kadoma, Osaka, 571-8580, Japan.
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Towa, Philipp. See *Crisdy-Na, Philipp.*
Tower, Canad. See *Tower, USA.*
Tower, USA. Tower Laboratories, 8 Essex Industrial Park Rd, Centerbrook, Connecticut, 06409, USA.
Toyama, China. See *Nanxin, China.*
Toyama, Jpn. Toyama Chemical Co., Ltd, 3-2-5 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.
url: www.toyama-chemical.co.jp
Toyo, Hong Kong. See *Hing Yip, Hong Kong.*
Toyo Kasei, Jpn. Toyo Kasei Pharmaceutical Co. Ltd, 19-20 5-chome, Yodogawa-ku, Osaka 533-0031, Japan.
TP, Israel. TP Technology Pharmaceuticals Ltd, P.O. Box 3531, Caesarea 38900, Israel.
TP, Thai. TP Drug Lab Co. Ltd, 67 Sukhumvit 62, Prakanong, Bangkok 10250, Thailand.
TPW, Malaysia. See *United Italian, Malaysia.*
Tracymed, Gr. Tracymed Th. Nikolas & Co LP, Rizountos 67, 167 77, Greece.
Trade Technocrats, Canad. Trade Technocrats Ltd, Unit 18, 130 Dynamic Drive, Scarborough, Ontario, M1V 5C9, Canada.
Tradenet, Hung. Tradenet Kft, Őszirózsa u. 15, 2040 Budaörs, Hungary.
Trading, Israel. Trading Pharma A.G., P.O.Box 7012, Petach Tikva 49170, Israel.
Tradiphar, Fr. Laboratoires Tradiphar, 176 rue de l'Arbrisseau, 59000 Lille, France.
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Tradiphar, Rus. See *Torlan, Rus.*
Tradis-Gat, Israel. Tradis-Gat, P.O. Box 7775, Petach Tikva, Israel.
Trahan, Thai. *See Diethelm, Thai.*
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Tramedico, Neth. Tramedico BV, Pampuslaan 186, 1382 JS Weesp, Netherlands.
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Trans, India. Trans Pharmaceuticals, A-9 Co-Op. Industrial Estate, Ajanta Rd, Mehrun Village, Jalgaon 425 001, Maharashtra, India.
Trans Canaderm, Canad. See *Stiefel, Canad.*
Transatlantic, Rus. Transatlantic International, Ulof Palme ul. 1, Section 5, 119590 Moscow, Russia.
url: www.transatlantic.ru
Transatlantic, Ukr. Transatlantic Ukraine Ltd, ul Metallistov 20, 03057 Kiev, Ukraine.
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Transfarma, Philipp. See *Metro, Philipp.*
Transmedic, Singapore. Transmedic Pte Ltd, 5 Jalan Kilang Barat, 9th Fl Petro Ctr, S 159349, Singapore.
url: www.transmedic.com.sg
Transpen, UK. Transpen Marketing Ltd, Office 3, Roe Lee Industrial Estate, Whalley New Rd, Blackburn, Lancashire, BB1 9SU, UK.
url: www.acustat.co.uk
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Travenol, UK. See *Baxter BioScience, UK.*
Travenol, USA. See *Baxter, USA.*
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TRB, Braz. TRB Pharma Indústria Química e Farmacêutica Ltda, Av. Giuseppina V. Di Napali 1100, 13086-550 Campinas, SP, Brazil.
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TRB, China. See *Extrawell, China.*
TRB, Cz. See *TRB, Arg.*
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TRB, Hong Kong. See *Chemedica, Hong Kong.*
TRB, Singapore. See *Pharmaforte, Singapore.*
Treasure Mountain, Hong Kong. Treasure Mountain Development Co. Ltd, 19/F Chit Lee Commercial Bldg, 30-36 Shaukeiwan Rd, Hong Kong.
url: www.tmdcl.com.hk
Tree of Life, Israel. Tree of Life, P.O. Box 7735, Petah Tikva 49130, Israel.
Treeful, China. Treeful Pharmaceutical Co. Ltd, 168 Hua Ji Rd, Minhang District, Shanghai 201108, China.
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Trendful, Hong Kong. Trendful Development Ltd, Room 1217 China Merchants Tower, Shun Tak Ctr, 168-200 Connaught Rd Central, Hong Kong.
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Trenker, Hong Kong. See *Europharm, Hong Kong.*
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Treupha, Switz. Treupha SA, Zurcherstrasse 59, 5401 Baden, Switzerland.
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Trevenodd, Philipp. Trevenodd Corp., Philippines.
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Tria, Gr. Tria AE, Ethn. Antistasis 26, 17237 Daphne, Greece.
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Triaktivin, Ger. Triaktivin GmbH, Gahlener Str. 113, 46569 Hünxe, Germany.
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Trianon, Canad. Trianon Laboratories Inc., 660 Industriel Blvd, Blainville, Quebec, J7C 3V4, Canada.
Trianon, Philipp. Trianon International Inc., 503 Narra Bldg, 2276 Pasong Tamo Ext, Makati City, Philippines.
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Tribest, S.Afr. Tribest Products, P.O. Box 7286, Roggebaai, Cape Town 8012, South Africa.
Trident, Singapore. Trident Pharm Pte Ltd, 10 Upper Aljunied Linl, 03-02 Johnson Control Bldg, S-367904, Singapore.
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Tridharma, Philipp. Tridharma Marketing Corp., 48 Warehouse 5A, Ignacio Complex, A Rodriguez Ave, Manggahan, Pasig City, Philippines.
Tridoss, India. See *Wockhardt, India.*
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Trigenesis, India. Trigenesis Life Sciences Pvt Ltd, No.72, 1st Floor, 5th Main Road, Chamarajpet, Bangalore 560 018, India.
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Trima, Israel. Trima, Kibbutz Ma'abarot 40230, Israel.
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Trima, Singapore. See *Green Cross, Singapore.*
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Trimed, Austral. Trimed, 105 Hay St, Subiaco, Western Australia 6008, Australia.
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Trimedal, Switz. Trimedal AG, Postfach 114, 8306 Bruttisellen, Switzerland.
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Trimen, USA. Trimen Inc., P.O. Box 309, New Oxford, PA 17350, USA.
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Trinity, Hong Kong. Trinity Trading Co. Ltd, Unit 7A-B, 39/F Cable TV Tower, 9 Hoi Shing Rd, Tsuen Wan, N.T., Hong Kong.
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Trinity, S.Afr. Trinity Pharma Pty Ltd, 381 Rossouw St, Die Wilgers, Pretoria 0184, South Africa.
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Tri-Prime, China. Tri-Prime Genetic Engineering Co. Ltd, 1 Jin Yuan Road, Daxing Industrial Development Zone, Beijing, 102600, China.
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Troikaa, India. Troikaa Pharmaceuticals Ltd, Commerce House 1, Satya Marg, Bodakdev, Ahmedabad 380 054, India.
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Trommsdorff, Ger. Trommsdorff GmbH & Co. KG Arzneimittel, Trommsdorffstr. 2-6, 52477 Alsdorf, Germany.
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Trovis, USA. Trovis Pharmaceuticals LLC, 5 Science Park, New Haven, Connecticut, CT 06511, USA.
Troy, USA. Troy Healthcare LLC, 130 Lions Drive, Hazleton, PA 18202, USA.
Trumac, India. Trumac Healthcare, S.C.F-450, 1st Floor M.Market, Manimajra, Chandigarh, India.
Trupharm, Israel. Trupharm, P.O. Box 8105, Netanya, Israel.
Truw, Ger. Truw Arzneimittel GmbH, Königstr. 12, 33330 Gütersloh, Germany.
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Truxton, USA. C.O. Truxton Inc., 136 Harding Ave, Bellmawr, NJ 08099, USA.
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Tryon, USA. Tryon Laboratories, 27368 Via Industria, Temecula, CA 92590, USA.
TS, Ital. Farmaceutici T.S. S.r.l., Via M.G. dell'Unità 13, 00046 Grottaferrata (Rome), Italy.
TS Pharma, Thai. TS Pharma, Thailand.
TS Reform, Neth. TS Reform BV, Gelreweg 9, 3843 AN Harderwijk, Netherlands.
url: www.tsproducts.nl
Tsaprazis, Gr. Tsaprazis Ioannis & Co, Michalakopoulou 157, 115 27 Athens, Greece.
url: www.tsaprazis.gr
Tsiekh Polfa, Ukr. OOO Tsiekh Polfa in Ukraine, Vasilkovskaya Street, 1, office 312, Kiev, 03040, Ukraine.
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Tsitomed, Rus. Tsitomed Ltd, Muchnoy per. 2, 191023 St Petersburg, Russia.
TsSKB-Progress, Rus. TsSKB-Progress Federal State Unitary Enterprise, Russia.
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Tsumura, Jpn. Tsumura & Co., 12-7 Nibancho, Chiyoda-ku, Tokyo 102-8422, Japan.
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Tsun Tsun, Hong Kong. Tsun Tsun Trading Co. Ltd, Rm 502, Sea View Estate 5/F, Blk B, Watson Rd, Hong Kong.
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url: www.tsuruhara-seiyaku.co.jp
TTK, India. TTK Healthcare Ltd, 6 Cathedral Road, Chennai 600 086, India.
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TTK, Philipp. See *Davenben, Philipp.*
TTN, Thai. TTN Thitiratsanon Co. Ltd, 157/9 Prannok Rd, Siriraj Bangkoknoi, Bangkok 10700, Thailand.
Tubilux, Ital. Tubilux Pharma S.p.A., Via Costarica 20/22, 00040 Pomezia (RM), Italy.
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Tubilux, Malaysia. See *Somedico, Malaysia.*
Tubilux, Port. See *Davi, Port.*
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Tum, Turk. Tum Ekip İlaç A.Ş., Bayraktar Bulvarı, Beyit Sok. No:26 Y. Dudullu, Ümraniye, İstanbul, 34775, Turkey.
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Tunggal Idaman, Indon. Tunggal Idaman Abdi PT, Jl Jend A Yani No 7, Jakarta 13230, DKI Jaya, Indonesia.
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Tuo Bin, China. Tuo Bin Pharmaceutical Factory, Shantou Special Economic Zone, China.
Tuopeng, China. Tuopeng Pharmaceutical Co. Ltd, Hubei, China.
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Turimed, Switz. Turimed SA, Hertistrasse 8, 8304 Wallisellen, Switzerland.
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url: tvpharm.com.vn
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Twardy, Ger. Astrid Twardy GmbH, Feringastr. 4, 85774 Unterföhring, Germany.
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Twin Laboratories, Canad. See *Twin Laboratories, USA.*
Twin Laboratories, USA. Twin Laboratories Inc., 3133 Orchard Vista Drive Se, Grand Rapids, Michigan, 49546, USA.
Twinlab, USA. Twinlab Corp., 600 East Quality Drive, American Fork, UT 84003-3302, USA.
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Twinluck, China. Twinluck Pharmaceutical Co. Ltd, Fengcun West Baolin Temple, Yongding, Mentougou, Beijing 102308, China.
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Two Hip, USA. Two Hip, 547 Cityscape Place, San Jose, CA, USA.
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Tyco, Canad. Tyco Healthcare, 7500 Trans-Canada Hwy, Pointe-Claire, Quebec, H9R 5H8, Canada.
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Tyco, Denm. Tyco Healthcare Denmark A/S, Langebrogade 6E,4.th, 1411 Copenhagen K, Denmark.
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Tyco, Norw. Tyco Healthcare Norge AS, Lensmannslia 1, 1386 Asker, Norway.
Tyco, Port. Tyco Healthcare Portugal Lda, Estrada do Outeiro de Polima, Lote 10, 1 Piso, Abóboda, 2785-521 S. Domingos de Rana, Portugal.
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url: www.tycohealthcare.com
Tyco, UK. Tyco Healthcare, 154 Fareham Rd, Gosport, Hampshire, PO13 0AS, UK.
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Tyler, Canad. AN Tyler Distributing, Canada.
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Tylid, Philipp. Tylid Philippines Inc., 2514 Cityland 10 Twr 1, 156 H V Dela Costa St, Ayala North 1226, Makati City, Philippines.
Tylstin, Canad. Tylstin Medical, 130 4600 Highway 7, Woodbridge, Ontario, L4L 4Y7, Canada.
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Typharm, UK. Typharm Ltd, 14D Wendover Rd, Rackheath Industrial Estate, Norwich, Norfolk, NR13 6LH, UK.
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Tyson, USA. Tyson Nutraceuticals Inc., 3535 Lomita Blvd, Unit A, Torrance, CA 90505, USA.
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Tzamal, Israel. Tzamal Pharma Ltd, 20 Hamgshimim St, P.O. Box 7004, Kiryat Matalon, Petach Tikva, Israel.
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UDL, USA. UDL Laboratories Inc., 1718 Northrock Court, Rockford, IL 61103, USA.
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Udomphon, Thai. Udomphon (Phihalab) Co Ltd, 2282 Sukhumvit Rd, Bang Chak, Phra Kanong, Bangkok 10110, Thailand.
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Ufsa, Turk. Ufsa İlaç Sanayi ve Ticaret AS, Turkey.
Uhlmann-Eyraud, Switz. F. Uhlmann-Eyraud SA, 28 chemin du Grand-Puits, 1217 Meyrin 2/Geneva, Switzerland.
Ukrimpeks, Ukr. Ukrimpeks Farm, prosp Heroes of Stalingrad 6, Building 3, Suite 1, 04211 Kiev, Ukraine.
Ukrmedprom, Rus. See *Ukrmedprom, Ukr.*
Ukrmedprom, Ukr. Ukrmedprom, 8 Vorobyova St, 61057 Kharkov, Ukraine.
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Ulmer, USA. Ulmer Pharmacal Co., 1614 Industry Ave, P.O. Box 408, Park Rapids, MN 56470, USA.
url: www.lobanaproducts.com
Ultimark, Canad. See *Ultimark, USA.*
Ultimark, USA. Ultimark Products LLC, 2250 Hickory Rd, Plymouth Meeting, Pennsylvania, 19462, USA.
Ultimate, Turk. Ultimate, Turkey.
Ultra, Hung. Ultra Marketing Kft, Mexikói ut 33, 1145 Budapest, Hungary.
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Ultra, India. Ultra Chiron Pharmaceuticals Pvt Ltd, 575 Phase-IX Industrial Area, Mohali, 160 055 Chandigarh, India.
Ultra, Mex. Ultra Laboratorios SA de CV, Av. Doctor R Michel 2920, 44490 Guadalajara Pque. Ind. El Alamo, Jalisco, Mexico.
Ultrabalance, Canad. See *Ultrabalance, USA.*
Ultrabalance, USA. Ultrabalance Inc., 9770 44th Ave N W, Gig Harbor, Washington, 98332, USA.
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Ultradent, Israel. See *Dento Medical, Israel.*
Ultradent, USA. Ultradent Products Inc., 505 W 10200 South, South Jordan, Utah, 84095, USA.
url: www.ultradent.com
Ultramark, India. Ultramark Healthcare Pvt Ltd, Ultramark House, Geeta Vihar, Threekay Lane, Ferozepur Road, Ludhiana 142 021, India.
Ultramed, Philipp. See *Cathay, Philipp* and *Natrapharm, Philipp.*
Ultrapac, Canad. Le Groupe Ultrapac, 1899 Lionel Bertrand, Boisbriand, Quebec, J7H 1N8, Canada.
Ultrapharm, UK. Ultrapharm Ltd, Centenary Business Park, Henley-on-Thames, Oxfordshire, RG9 1DS, UK.
url: www.gfdiet.com
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Umeda, Thai. Umeda Co Ltd, 26/18-21 Ram-Indra Rd, Bangkok 10230, Thailand.
url: www.umeda.co.th
Umedica, Philipp. See *Ambica, Philipp.*
Umut, Turk. Umut İlaç Ticaret ve San Ltd Sti, Akpinar Mahallesi Fatih Caddesi No 17, 34885 Sancaktepe-Kartal, Istanbul, Turkey.
url: www.umutilac.com.tr
Unam, Hong Kong. Unam Corp Ltd, 3/F Chiu Lung Bldg, 25 Chiu Lung St Central, Hong Kong.
Unam, Malaysia. Unam Pharmaceutical (M) Sdn Bhd, Letter Box 116, 10th Fl UBN Tower, 10 Jln P Ramlee, 50250 Kuala Lumpur, Kuala Lumpur, Malaysia.
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Underberg, Switz. Underberg AG, Industriestrasse 31, 8305 Dietlikon, Switzerland.
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Uni, Singapore. Uni Drug House Pte Ltd, 61 Kaki Bukit Ave 1, 05-31 Shunli Industrial Park, S 417943, Singapore.
Unia, Neth. See *Unia, Pol.*
Unia, Pol. Zakłady Farmaceutyczne Unia Spółdzielnia Pracy, ul. Chłodna 56/60, 00-872 Warsaw, Poland.
url: www.uniapharm.pl
Uniao Quimica, Braz. União Química Farmacêutica Nacional S.A., Avenida dos Bandeirantes 5386, 04071-900 São Paulo, SP, Brazil.
url: www.uniaoquimica.com.br
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Unichem, India. Unichem Laboratories Ltd, Prabhat Estate, Off S.V. Rd, Jogeshwari (W), Mumbai 400 102, India.
url: www.unichemlabs.com
Unichem, Malaysia. See *Antah, Malaysia.*
Unichem, Philipp. See *Ambica, Philipp.*
Unichem, Rus. See *Transatlantic, Rus.*
Unichem, S.Afr. Unichem SA, 1st Floor Romm 32-34, Andrina Building, Klinkenberg Rd, Van Der Hoffpark 2531, South Africa.
Unichem, Singapore. See *Uni, Singapore.*
Unichem, UK. Unichem Ltd, Unichem House, Cox Lane, Chessington, Surrey, KT9 1SN, UK.
url: www.unichem.co.uk
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url: www.unicity.com
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url: www.unicitynetwork.com.sg
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url: www.unicohk.com
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Unicorn, Canad. TC Unicorn Ltd, 500 Finchdene Square, SCarborough, Ontario, M1X 1C2, Canada.
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Unicorn, Hong Kong. See *Chun Cheong, Hong Kong.*
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url: www.unicorp.hu
Unicure, India. Unicure Remedies Pvt Ltd, F/25 BIDC Estate, Gorwa, Baroda 390 016, India.
url: www.unicurepharma.com
Unicure, Philipp. See *ECE, Philipp.*
Uniderm, Israel. See *Promedico, Israel.*
Uniderm, Ital. Uniderm Farmaceutici S.r.l., Ple F. il Macedone 140, 00124 Casalpalocco (RM), Italy.
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Unifa, Port. See *CPH, Port.*
Unifarm, Ital. Unifarm S.p.A., Via Provina 3, 38040 Ravina (TN), Italy.
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Unifarma, Spain. See *Unipharma, Spain.*
Unifirst, Canad. See *Medique, USA.*
Unigen, Thai. Unigen Life Sciences Ltd, 1 Silom Rd, Zuellig House Level 8 & 9, Bangkok 10500, Thailand.
url: www.unigen-lifesciences.com
Unigene, Neth. See *Unigene, UK.*
Unigene, Port. See *Unigene, UK.*
Unigene, UK. Unigene UK Ltd, 191 Sparrows Herne, Bushey Heath, Hertfordshire, WD23 1AJ, UK.
Unigreg, Irl. See *Unigreg, UK.*
Unigreg, UK. Unigreg Ltd, Enterprise House, 181-9 Garth Rd, Morden, Surrey, SM4 4LL, UK.
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Unilab, Hung. Unilab, Hungary.
Unilab, Malaysia. See *DKSH, Malaysia.*
Unilab, Philipp. Unilab Nutritionals Inc., 4/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Metro Manila, Philippines.
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Unilever, USA. Unilever HPC, 33 Benedict Place, Greenwich, CT 06830, USA.
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Unilfarma, Port. See *Boehringer Ingelheim, Port.*
Unimarck, India. Unimarck Pharma (India) Ltd, S.C. O 2641, Sector 32-D, Chandigarh 160 030, India.
Unimed, Cz. Unimed Bohemia sro, U Dvora 25, 779 00 Olomouc, Czech Republic.
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Unimed, Israel. See *Megapharm, Israel.*
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Unimed, Singapore. Unimed Healthcare Pte Ltd, 52 Ubi Ave 3, The Frontier 04-34, S-408867, Singapore.
Unimed, UK. See *Solvay, UK.*
Unimed, USA. See *Solvay, USA.*
Unimex, Philipp. Unimex Inc., 1104 Shaw Towers, Shaw Blvd cor St Francis St, Mandaluyong City, Philippines.
Union, Singapore. Union Chem & Pharm Pte Ltd, 113 Eunos Ave 3, Gordon Industrial Building, 409838, Singapore.
url: www.union.com.sg
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Union Drug, Thai. Union Drug Laboratories Co Ltd, 2601 Sukhumvit Rd, Bangjak, Prakanong, Bangkok 10260, Thailand.
Union Health, Ital. Union Health Srl, Via Roccamandolfi 1, 00100 Rome (RM), Italy.
Union Korea, Philipp. See *International Apex, Philipp.*
Union Medical, Thai. Union Medical (Thailand) Co. Ltd, 513/199-200 Jaransanitwong Rd, Soi 37 Bangkoknoi, Bangkok 10700, Thailand.
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Union-Swiss, Malaysia. See *Zuellig, Malaysia.*
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Unipack, Austria. Unipack GmbH, Braunlichgasse 40-42, A-2700 Wiener Neustadt, Austria.
Unipath, Canad. See *Unipath, UK.*
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Unipath, Ital. Unipath Div. Unilever Italia S.p.A., Via Nino Bonnet 10, 20154 Milan (MI), Italy.
Unipath, UK. Unipath Ltd, Priory Business Park, Bedford, Bedfordshire, MK44 3UP, UK.
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url: www.unipath.com
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Uniphar, Irl. See *Allphar, Irl.*
Unipharm, Hong Kong. Unipharm Trading Co., Unit 1-6A, 11/F Mita Centre, 552-566 Castle Peak Rd, Kwai Chung, N.T., Hong Kong.
Unipharm, Israel. Unipharm Ltd, P.O. Box 21429, Tel Aviv, Israel.
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Unipharm, Mex. Unipharm de Mexico SA de CV, Tamarindos XV-A Lote 10 y 11, 91697 Veracruz C Ind. Bruno Pagliai, Veracruz, Mexico.
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Unipharm, Turk. Unipharm İlaç San. ve Tic. A.S., Gursel Mah. İlkem Sok. No: 5/1-2, Kağıthane, İstanbul, 80270, Turkey.
Unipharm, Ukr. Unipharm Inc, Mechnikova Street, 3, 2nd Floor Right Wing, Kiev, 01133, Ukraine.
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Unipharma, Fr. See *Ideme, Fr.*
Unipharma, Gr. Uni-Pharma Kleon Tsetis, Pharmaceutical Laboratories S.A., 14th km National Rd 1, 145 64 Kifissia, Greece.
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Unipharma, Spain. Unipharma, Mino 8, 08022 Barcelona, Spain.
url: www.unipharma.com
Unipharma, Switz. Unipharma SA, Via Pian Scairolo 6, 6917 Barbengo, Switzerland.
url: www.unipharma.ch
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Unique, Rus. Unique Pharmaceutical Laboratories, Sadovaya-Kudrinskaya ul. 3, 123242 Moscow, Russia.
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url: www.jbcpl.com
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UniQure, Neth. uniQure biopharma BV, Meibergdreef 61, 1105 BA Amsterdam, Netherlands.
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url: www.uniroyalbiotech.com
Uni-Sankyo, India. Uni-Sankyo Ltd, Plot No.13 Sagar Society, Road No.2, Banjara Hills, Hyderabad 500 034, India.
url: www.pubergen.com
Unison, Hong Kong. See *Health Alliance, Hong Kong.*
Unison, Malaysia. See *Pahang, Malaysia.*
Unison, Philipp. See *Justright, Philipp.*
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Unison, Thai. Unison Laboratories Co. Ltd, 160 Soi Onnuch, Sukhumvit Rd, Ladkrabang, Bangkok 10520, Thailand.
url: www.unisonlab.com
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United American, Singapore. See *Far East, Singapore.*
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United Bakers, Canad. United Bakers Corp., 12 Dickson St, Fredericton, New Brunswick, E3A 5A7, Canada.
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url: www.unitedbiotechindia.com
United Cell Biotech, China. United Cell Biotechnology Co. Ltd, 1150 Guiqiao Road, Jinqiao, Pudong, Shanghai, 202106, China.
url: www.unitedbiotech.com.cn
United Douglas, Philipp. United Douglas Pharm Philippines Inc., 2601B East Twr PSEC, Exchange Rd, Ortigas Ctr, Pasig City, Philippines.
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United Drug, Thai. See *Diethelm, Thai.*
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United Drugs, Hong Kong. See *Hind Wing, Hong Kong.*
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United Italian, Malaysia. United Italian Trading (M) Sdn Bhd, No 1, 2nd Floor, The Highway Centre, Jln 51/205, 46050 Petaling Jaya, Selangor, Malaysia.
url: www.uitm.net
United Italian, Singapore. United Italian Trading Corp Pte Ltd, 65 Upper Paya Lebar Rd, 06-03 Guang Ming Industrial Building, S 534817, Singapore.

United Lab, China. The United Laboratories International Holdings Ltd, Sanzao Science & Technology Industrial Park, Zhuhai, China.
url: www.tul.com.cn

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United Laboratories, Philipp. United Laboratories, 66 United St, Mandaluyong City, Philippines.

United Laboratories, Singapore. See *Zuellig, Singapore.*

United Lifecare, India. United Lifecare Pvt Ltd, A/2 G.P.Park, Udhna Magdalla Road, Bhatar, Surat 395 001, India.

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United Medical, Thai. United Medical Co Ltd, 124 Moo 7 Rd, Bangkhuntien, Bangkok 10150, Thailand.
url: www.medicpharma.co.th

United Nordic, Denm. See *Nycomed, Denm.*

United Pharma, Pol. See *Farma-Projekt, Pol.*

United Research, USA. United Research Laboratories, 1100 Orthodox St, Philadelphia, PA 19124, USA.
url: www.urlmutual.com

United Therapeutics, Austria. See *United Therapeutics, UK.*

United Therapeutics, Cz. See *United Therapeutics, UK.*

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United Therapeutics, Neth. See *United Therapeutics, UK.*

United Therapeutics, Port. See *United Therapeutics, UK.*

United Therapeutics, UK. United Therapeutics Europe Ltd, Unither House, Curfew Bell Road, Chertsey, Surrey, KT16 9FG, UK.
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United Therapeutics, USA. United Therapeutics Corp., 1110 Spring St, Silver Spring, MD 20910, USA.
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Unither, USA. See *United Therapeutics, USA.*

UniVaccin, Ger. UniVaccin GmbH, Lise-Meitner-Str. 21, 25524 Itzehoe, Germany.
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Universal, Fin. See *Universal, Spain.*

Universal, Hong Kong. Universal Pharmaceutical Lab Ltd, Eastern Ctr, G/F & 1/F, Unit 1-5, 1065 King's Rd, Quarry Bay, Hong Kong.

Universal, Port. See *Universal, Spain.*

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Universal Medicare, India. Universal Medicare Ltd, Sion-Trombay Road, Deonar, Mumbai 400 088, India.

Universal Medikit, India. Universal Medikit Pvt Ltd, 1505/1 Universal Square, Shantinagar, Nagpur 440 002, India.
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University Medical, Canad. See *University Medical, USA.*

University Medical, USA. University Medical Products USA Inc., 88 Maxwell, Irvine, CA 92618, USA.

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Unomedical, UK. Unomedical Ltd, 27 Thornhill Rd, North Moons Moat, Redditch, Worcestershire, B98 9NL, UK.
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Upjohn, Switz. See *Pfizer, Switz.*

Upjohn, UK. See *Pfizer, UK.*

Upjohn, USA. See *Pfizer, USA.*

UPM, USA. UPM Pharmaceuticals Inc., 6200 Seaforth St, Baltimore, MD 21224, USA.
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UPSA, China. See *UPSA, Fr.*

UPSA, Cz. See *UPSA, Fr.*

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UPSA, Hong Kong. See *Wing Wai, Hong Kong.*

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UPSA, Neth. See *UPSA, Fr.*

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Upsamedica, Spain. See *BMS, Spain.*

Upsamedica, Switz. Upsamedica SA, Neuhofstrasse 6, 6341 Baar, Switzerland.
url: www.bms.ch

Upshars-Smith, NZ. See *Baxter, NZ.*

Upsher Smith, Israel. See *Meditrend, Israel.*

Upsher-Smith, USA. Upsher-Smith Laboratories Inc., 14905 23rd Ave North, Minneapolis, MN 55447, USA.
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Upsifarma, Port. Upsifarma, Lda, S. Domingos à Lapa 8, Letra H, 1200-835 Lisbon, Portugal.

Upson, Thai. Upson, Thailand.

Uquifa, Port. See *Uquifa, Spain.*

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Urbion, Spain. Urbion Farma, Avda Portugal, Parcela 85 Pol Allendeduero, Aranada de Duero, 09400 Burgos, Spain.

Urgo, Belg. See *Fournier, Belg.*

Urgo, Cz. See *Urgo, Fr.*

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Urgo, Israel. See *Perrigo, Israel.*

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Urgo, Rus. See *Urgo, Fr.*

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Urgo, UK. Urgo Ltd, Sullington Rd, Shepshed, Loughborough, Leicestershire, LE12 9JJ, UK.

Urgo, Ukr. See *Delta Medical, Ukr.*

Uriach, Cz. See *Uriach, Spain.*

Uriach, Hung. J Uriach & Cia, Hungary.

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Uriage, Fr. Laboratoires Dermatologiques Uriage, 98 av de la Republique, 92400 Courbevoie, France.
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Urit, UK. See *Econo-Med, UK.*

URL, USA. United Research Laboratories, 1100 Orthodox St, Philadelphia, PA 19124, USA.
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Urocor, USA. See *Labcorp, USA.*

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Ursapharm, Belg. See *Ursapharm, Neth.*

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Ursapharm, Ger. Ursapharm Arzneimittel GmbH & Co. KG, Industriestr. 35, 66129 Saarbrücken, Germany.
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Ursapharm, Israel. See *Kivema, Israel.*

Ursapharm, Malaysia. See *Pharmaforte, Malaysia.*

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Ursapharm, Rus. See *Santen, Rus.*

Ursapharm, Singapore. See *Pharmaforte, Singapore.*

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Urtekram, Denm. Urtekram International A/S, Klostermarken 20, 9550 Mariager, Denmark.

US Bioscience, Denm. See *Orphan, Denm* and *Schering-Plough, Denm.*

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US Bioscience, USA. US Bioscience Inc., 26111 Miles Rd, Cleveland, OH 44128, USA.
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US Food & Pharmaceuticals, USA. US Food & Pharmaceuticals, 313 West Beltline Highway, Suite 184, Madison, WI 53713, USA.

US Nutra, USA. See *US Nutraceuticals, USA.*

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US Pharmaceutical, USA. US Pharmaceutical Corp., 2401-C Mellon Court, Decatur, GA 30035, USA.
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US Pharmacia, Neth. See *US Pharmacia, Pol.*

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US Pharmacia, Ukr. US Pharmacia International Inc., Marshal Rokossovskogo St 8B, Suite 9, 04201 Kiev, Ukraine.

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US Surgical, USA. Unites States Surgical Corp., 150 Glover Ave, Norwalk, CT06856, USA.
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Usana, Canad. See *USANA, USA.*

Usana, Hong Kong. Usana Hong Kong Ltd, Unit 2504-06, 25/F, World Trade Centre, 280 Gloucester Rd, Causeway Bay, Hong Kong.

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Usana, Mex. Usana México SA de CV, Blvd Manuel Avila Camacho 138 Piso 3 Lo, 11000 Lomas de Chapultepec, Mexico.

Usana, Singapore. Usana, Singapore.

USANA, USA. USANA, Inc., 3838 West Parkway Blvd, Salt Lake City, UT 84120, USA.
url: www.usana.com

USB, Pol. See *Schering-Plough, Pol.*

USB, USA. See *US Bioscience, USA.*

USL, NZ. USL Medical Consumer Products, P.O. Box 15645, Waitakere 0640, Auckland, New Zealand.

USP, India. USP Life Sciences, SCO 6, FF Sector 5, Near KC Theatre, Panchkula 134 109, India.

USV, India. US Vitamins Ltd, B.S. Devshi Marg, Govandi, Mumbai 400 088, India.
url: www.usvindia.com

USV, Israel. See *Medibrands, Israel.*

USV, Rus. See *USV, India.*

USV, Singapore. See *Zyfas, Singapore.*

USV, Ukr. USV Limited, pl. Solomenskaya, 2, Office 102, Kiev, 03035, Ukraine.
url: www.usvindia.com

UT, Fr. See *Merck-Lipha, Fr.*

Utandningstester, Denm. See *Utandningstester, Swed.*

Utandningstester, Norw. See *Utandningstester, Swed.*

Utandningstester, Swed. Utandningstester i Sverige AB, Södra vägen 53, 412 54 Göteborg, Sweden.
url: www.utandningstester.se

Utopian, Philipp. See *Justright, Philipp.*

Utopian, Thai. Utopian Co. Ltd, 602 Moo 3, Teparak Rd, Muang, Samuthprakarn 10270, Thailand.

Uzara, Ger. See *Stada, Ger.*

Uzdrowisko Ciechocinek, Pol. Przedsiębiorstwo Uzdrowisko Ciechocinek SA, ul. Kościuszki 10, 87-720 Ciechocinek, Poland.

V & V, Thai. V & V Bangkok, 94/7 Soi Yimprakrob, Ngamwongwan, Nonthaburi, Thailand.

Vaccina, S.Afr. Vaccina CC, P.O. Box 75804, Gardenview 2047, South Africa.

Vachon, Canad. Les Laboratoires Vachon Inc., 8700 de-la-Rive-Sud Blvd, Levis, Quebec, G6V 6N6, Canada.

Vaia, Gr. Vaia SA, 1, 28 Octovriou St, Ag. Varvara, 12351 Athens, Greece.

Vaia, Ital. See *Vaia, Gr.*

Vaia, Neth. See *Vaia, Gr.*

Vakcina, Hung. Vakcina Kft, Rákóczi u 64, 3636 Sajógalgóc, Hungary.

Valda, Canad. See *Bayer, Canad.*

Valda, Ital. See *GSK, Ital.*

Valdecasas, Mex. Laboratorios Valdecasas S.A., Av. Insurgentes Sur No. 4058, Deleg. Tlalpan, 14430 Mexico D.F., Mexica.

Vale, Cz. See *Vale, Irl.*

Vale, Irl. Vale Pharmaceuticals Ltd, Unit 1 b Gurtnafleur Business Park, Gurtnafleur, Clonmel, Co. Tipperary, Ireland.

Vale, Pol. See *Vale, Irl.*

Valeant, Arg. Valeant Argentina SA, Av. Int. Tomkinson 2054, 1642 San Isidro, Argentina.

Valeant, Austral. Valeant Pharmaceuticals Australasia Pty Ltd, Level 7, Suite 7.02, 3 Rider Boulevard, P.O.Box, 3188 Rhodes, NSW 2138, Australia.
url: www.valeant.com

Valeant, Austria. Valeant Pharmaceuticals Austria GmbH, Pharmaziegasse 5, A-9020 Klagenfurt, Austria.

Valeant, Braz. Valeant Farmacêutica do Brasil Ltda, Rua Geraldo Flausino Gomes 61, 10 andar, 04575-060 São Paulo, Brazil.

Valeant, Canad. Valeant Canada Ltd, 4787 rue Lévy, Montreal, Quebec, H4R 2P9, Canada.

Valeant, Cz. Valeant Czech Pharma sro, Truhlářská 1104/13 1103/15, 110 00 Praha 1, Czech Republic.
url: www.valeant.cz

Valeant, Denm. See *Medilink, Denm.*

Valeant, Fin. See *Medilink, Denm.*

Valeant, Ger. Valeant Pharmaceuticals Germany GmbH, Düsseldorfer Str. 40 A, 65760 Eschborn, Germany.
url: www.valeant.com

Valeant, Hong Kong. See *IDS, Hong Kong.*

Valeant, Hung. Valeant Pharma Magyarország Kft, Csatárka út 82-84, 1025 Budapest, Hungary.
url: www.valeant.com

Valeant, Indon. See *Combiphar, Indon.*

Valeant, Irl. See *Allphar, Irl.*

Valeant, Ital. Valeant Pharmaceuticals S.r.l., Via Vittor Pisani 19, 20124 Milan (MI), Italy.
url: www.valeant.com

Valeant, Malaysia. See *IDS, Malaysia.*

Valeant, Mex. Valeant Pharmaceuticals Inter., SA de VC, Blvd Avila Camacho 40 P.20 T Esmeralda, 11000 Lomas de Chapultepec, Mexico.

Valeant, Neth. See *Valeant, UK.*

Valeant, Norw. See *Medilink, Denm.*

Valeant, NZ. See *Supply Chain Solutions, NZ.*

Valeant, Pol. See *ICN, Pol.*

Valeant, Port. See *Valeant, Spain.*

Valeant, Rus. Valeant Pharmaceuticals International, 1st Tverskaya-Yamskaya, 23, Building 1, Parus Business Center, Moscow, Russia.
url: www.valeant.com

Valeant, Singapore. See *JDH, Singapore.*

Valeant, Spain. Valeant Pharmaceuticals Iberica S.A., Muntoner 239-253, Atico, Barcelona, Spain.
url: www.valeant.com

Valeant, Thai. See *Zuellig, Thai.*

Valeant, UK. Valeant Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire, RG24 8WG, UK.
url: www.valeant.com

Valeant, Ukr. Vlaenat Pharmaceuticals International, Semi Khokhlovykh Street, 15, 6th floor, Kiev, 04119, Ukraine.
url: www.valeant.com

Valeant, USA. Valeant Pharmaceuticals Inc., 3300 Hyland Drive, Costa Mesa, CA 92626, USA.
url: www.valeant.com

Valeas, Cz. See *Valeas, Ital.*

Valeas, Ital. Valeas S.p.A., Via Vallisneri 10, 20133 Milan (MI), Italy.

Valensa, USA. See *US Nutraceuticals, USA.*

Valenta, Rus. Valenta Pharmaceuticals, Generala Dorokhova St 18-2, 119530 Moscow, Russia.
url: valentapharm.com

Valenta, Ukr. Valenta Pharm, ul. Basseyna 21A, Office 5, 01004 Kiev, Ukraine.
url: valentapharm.com

Valeo, Canad. Valeo Pharma Inc., 16 667 Hymus Blvd, Kirkland, Quebec, H9H 4R9, Canada.

Valetudo, Ital. Valetudo Divisione Biogena Srl, Via Ghiaie 6, 24030 Presezzo (BG), Italy.

Validus, USA. Validus Pharmaceuticals Inc., 119 Cherry Hill Rd, Suite 310, Parsippany, NJ 07054, USA.
url: www.validuspharma.com

Valioravinto, Fin. Oy Valioravinto Ab, Intanummenkatu 44, 68600 Pietarsaari, Finland.

Valles de Aloe, Arg. Valles de Aloe, Manuel Artigas 5316 Dpto.5, 1440 Buenos Aires, Argentina.

Valma, Chile. Laboratorio Valma Ltda, Miguel de Atero 2883, Santiago, Chile.

ValMed, USA. ValMed Inc., 15280 NW 79th Court, Suite 109, First Floor, Miami Lakes, FL 33016, USA.
url: www.valmed.com

Valmor, Venez. Laboratorios Valmor C.A., Av. Fco. de Miranda, Edif. Easo Torre Norte P.1 Of. E, El Rosal, Caracas, Venezuela.
url: www.valmorca.com.ve

Valomed, Spain. See *Italfarmaco, Spain.*

Valtec, Canad. See *Omega, Canad.*

Valuge, Arg. Valuge S.A., Cuyo 2870, 1640 Martinez, Buenos Aires, Argentina.

Valwater, Neth. Valwater BV, HL Wichersstraat 1/2, 9723 AD Groningen, Netherlands.

Vam, Rus. See *Pharma Vam, Rus.*

Vamsler, Philipp. Vamsler Phils Inc., 141 Scout de Guia St, Quezon City, Philippines.

Vana, Thai. Vana Corp Ltd, 2038 Sukhumvit Rd, Bangkok 10260, Thailand.
url: www.atlantic-lab.com

Vanden Bogaerde, Belg. Vanden Bogaerde SA, Avenue de l'Araucaria 34/2-3, 1020 Brussels, Belgium.

Vanfar, Arg. Droguería Vanfar, Camarones 3898, 1407 Buenos Aires, Argentina.

Vangard, USA. Vangard Labs Inc., P.O. Box 1268, Glasgow, KY 42142-1268, USA.

Vanguard, India. Vanguard Therapeutics Pvt Ltd, 17/3, S.R. Nagar, Hyderabad 500 038, India.
url: www.vanguardtherapeutics.com

Vannier, Arg. Lab. Vannier S.A., H. Irigoyen 2321 5to Piso, 1089 Buenos Aires, Argentina.

Vantone, Hong Kong. Vantone Medical Supplies Co. Ltd, Flat J, 10/F International Industrial Ctr, 2-8 Kwei Tei St, Fotan, N.T., Hong Kong.

Vargas, Venez. Laboratorios Vargas S.A., Las Piedras a Puente Restaurador, Edif. Vargas, Caracas, Venezuela.

Varifarma, Arg. Lab. Varifarma S.A., Ernesto de las Carreras 2469, 1643 Beccar, Buenos Aires, Argentina.

Varipharm, Ger. See *MSD, Ger.*

Varun, India. Varun Life Sciences Pvt Ltd, 9 Shankeshwar Darshan, AG Pawar Cross Lane, Byculla, Mumbai, 400027, India.

Vatring, USA. Vatring Pharmaceuticals, 225 North 11th St, Wytheville, VA 24382, USA.
url: www.vatring.net

Vaxines, Philipp. Vaxines Trading Inc., Blk 13, Lot 3B M Consing St, BF Resort Vill, Talon 2, Las Piñas City, Philippines.

Vebas, Ital. Vebas S.r.l., Via Benaco 1/3, 20098 San Giuliano Milanese (MI), Italy.

Vecchi, Malaysia. See *Zyfas, Malaysia.*

Vecchi, Singapore. See *Zyfas, Singapore.*

Vector, Rus. Vector-Medica Ltd, ul M Gorbkogo 17a, 630099 Novosibirsk, Russia.

Veda, Fr. See *Zambon, Fr.*

Vedim, Ger. See *UCB, Ger.*

Vedim, Ital. Vedim Pharma S.r.l., Via Praglia 15, 10044 Pianezza (TO), Italy.

Vedim, Pol. See *UCB, Pol.*

Vedim, Port. Vedim Pharma, Lda, Rua Carlos Calisto 4-B, 1400-043 Lisbon, Portugal.

Vedim, Spain. See *UCB, Spain.*

VEG, Ital. VEG Srl, Via Guindazzi 44/54, 80040 Pollena Trocchia (NA), Italy.

Vegal, Spain. Vegal Farmaceutica, Tramontana 44, Pozuelo de Alarcon, 28223 Madrid, Spain.

Vegemedica, Fr. Vegemedica (Lab), 15 av de la République, Le Port, 83000 Toulon, France.

Vegetal, Ital. Vegetal-Progress S.r.l., Località Novero 8, 10070 Cirie (TO), Italy.
url: www.vegetal-progress.it

Veil, UK. See *Blake, UK.*

Veinfar, Arg. Veinfar, Esp. Medicinales Larjan, Av. Piedrabuena 4190, 1439 Buenos Aires, Argentina.
url: www.veinfar.com.ar

Velates, Ital. Velates Srl, Via L Valla 16, 20141 Milan (MI), Italy.

Velin, Denm. Velin-Pharma A/S, 66 Kongevejen, 3480 Fredensborg, Denmark.

Velin, Neth. See *Velin, Denm.*

Velka, Gr. Velka Hellas A.E., 12 Korinthou Str., 154 51 N. Psychiko, Greece.

Veltipharm, Gr. Veltipharm, Deligiorgi 55-59, 104 37 Athens, Greece.

Velvian, Ger. Velvian GmbH, Carl-Zeiss-Ring 9, 85737 Ismaning, Germany.

Velvian, Neth. See *Velvian, Ger.*

Vemedia, Belg. ABC Chemicals Vemedia, Parc Industriel 19, 1440 Wauthier-Braine, Belgium.
url: www.abc-chemicals.com

Vemedia, Neth. See *Solvay, Neth.*

Vemedia, Spain. Vemedia Pharma Hispania SA, Tuset 10, 08006 Barcelona, Spain.

Vencare, India. Vencare Formulations Pvt Ltd, 38/10 1st Floor, New Timber Yard Layout, Mysare Rd, Bangalore 560 026, India.

Vendiz, Philipp. vendiz Pharmaceuticals Inc., 116 Esteban Abada St, Loyola Heights, Quezon City, Philippines.

Vendrell, Spain. Laboratorios Vendrell SA, C/Suomi 8, Pl el Clot de Moja, 08734 Olerdola (Barcelona), Spain.

Venifer, Gr. Venifer Hellas Pharmaceuticals SA, Kosma Aitolou 3, 151 25 Maroussi, Greece.

Venipharm, Fr. Venipharm, 422 Bureaux de la Colline, 92213 Saint-Cloud, France.
url: www.venipharm.com

Vensat, India. Vensat Bio, 516 Ring Road Mall, Sector-3, Rohini, New Delhi 110 085, India.
url: www.madhavbiotech.com

Vent-3, Arg. Lab. Vent-3 SRL, Juan D. Jufre 4820, 5014 Secc. 4a Bo. Jose I Diaz, Cordoba, Argentina.

Ventaglio, Chile. Laboratorios Ventaglio LTDA, Tobalaba 155 Of. 1001, Providencia, Santiago, Chile.

Venter, Spain. Venter Pharma SL, Almagro 1, 28010 Madrid, Spain.

Ventiv, Hung. Ventiv Health Magyarország Kft, Hovat u 14-24, 1027 Budapest, Hungary.

Venus, Hung. Venus Kft, Park u 5, 2370 Dabas, Hungary.
url: www.venuskft.hu

Venus, India. Venus Remedies, 51-52 Industrial Area, Phase 1, Panchkula 134 109, India.

Venus, Thai. See *Cosma, Thai.*

Venus, Ukr. See *Venus, India.*

Vepex, Hung. Vepex Biotechnika Iyd, P.O. Box 521, 6701 Szeged, Hungary.

Vera, Hung. Vera Pharma Kft, Rákos köz 22, 1028 Budapest, Hungary.

Veracity, USA. Veracity Pharmaceuticals Inc., 6601 Lyons Rd, Coconut Creek, FL 33073, USA.
url: www.veracitypharma.com

Veresne, Arg. Veresne SA, Santiago del Estero 286 Piso 3 Of. 2, 1075 Buenos Aires, Argentina.

Verheilen, Philipp. See *PrimeDrug, Philipp.*

Veridien, Canad. See *Veridien, USA.*

Veridien, USA. Veridien Corp., F 7600 Bryan Dairy Rd, Largo, FL 33777-1433, USA.

Veripalvelu, Fin. Suomen Punainen Risti Veripalvelu, Kivihaantie 7, 00310 Helsinki, Finland.
url: www.veripalvelu.redcross.fi

Verisfield, Gr. Verisfield (UK) Ltd, 14 Kerassountas Str, GR-115 28 Athens, Greece.
url: www.verisfield.gr

Verla, Ger. Verla-Pharm, Arzneimittelfabrik, Apotheker H.J.v. Ehrlich GmbH & Co. KG, Hauptstr. 98, 82327 Tutzing, Germany.
url: www.verla.de

Verla, Hung. See *Verla, Ger.*

Verla, Switz. See *Biomed, Switz.*

Verma, Gr. Verma Drugs SA, Andrianou 75, Ag Asomatoi, 194 00 Koropi, Greece.

Verman, Fin. Oy Verman AB, Vanhankyläntie 44 B, PL 152, 04401 Järvenpää, Finland.
url: www.verman.fi

Vernin, Fr. Laboratoires Vernin, France.

Vernleigh, S.Afr. See *Adcock Ingram, S.Afr.*

Veron, Ger. Veron Pharma Vertriebs-GmbH, Kohlenhofstr. 10, 67663 Kaiserslautern, Germany.
url: www.veronpharma.de

Veropharm, Rus. Veropharm ZAO, Bolshaya Pochtovaya ul. 36, 105082 Moscow, Russia.
url: www.veropharm.ru

Versalya, Spain. Versalya Pharma SL, San Rafael 3, 28108 Alcobendas, Madrid, Spain.

Versapharm, USA. VersaPharm Inc., 1775 West Oak Parkway, Suite 800, Marietta, GA 30062-2260, USA.
url: www.versapharm.com

Vertex, Canad. Vertex Pharmaceuticals (Canada) Inc., 275 Armand-Frappier Blvd, Laval, Quebec, H7v 4A7, Canada.

Vertex, Denm. See *Vertex, UK.*

Vertex, Neth. See *Vertex, UK.*

Vertex, Norw. See *Vertex, UK.*

Vertex, Rus. Vertex Pharmaceutical Co., 24 Liniya, V.O. 27a, 199026 Saint-Petersburg, Russia.

Vertex, UK. Vertex Pharmaceuticals (Europe) Ltd, 86-88 Jubilee Ave, Milton Park, Abingdon, Oxfordshire, OX14 4RW, UK.
url: www.vrtx.com

Vertex, USA. Vertex Pharmaceuticals Inc., 130 Waverly St, Cambridge, MA 02139, USA.
url: www.vrtx.com

Vertical, USA. Vertical Pharmaceuticals Inc., 3 Kellogg Court, Suite 19, Edison, NJ 08817, USA.
url: www.verticalpharma.com

Vertos, Singapore. See *Pharma 2000, Singapore.*

Verum, Port. Verum Pharma Produtos Farmaceuticos Unipessoal Ldo, Avenida Sidonio Pais 24, res-do-chao esquerdo, 1000 Lisbon, Portugal.

Verum, USA. See *Victory, USA.*

Vesale, Belg. Vesale, Belgium.

Vesco, Thai. See *TC Pharma-Chem, Thai.*

Vestiq, USA. Vestiq Pharmaceuticals, 3000 Aerial Center Drive, Suite 160, Morrisville, NC 27560, USA.
url: vestiqpharmaceuticals.com

Vetco, USA. Vetco Pharmaceuticals, 105 Baylis Rd, Second Floor, Melville, NY 11747-1155, USA.

Vetoquinol, Canad. Vetoquinol NA Inc., 2000 Chemin Georges, Lavaltrie, Quebec, J5T 3S5, Canada.
url: www.vetoquinal.ca

Vetprom, Rus. Vetprom Radomir, Russia.

Vetter, Rus. See *Pfizer, Rus.*

Vetter, Ukr. See *Pfizer, Ukr.*

Veximp, Hung. Veximp Altalanos Kft, Foti ut 56, 1047 Budapest, Hungary.

VHB, India. VHB Pharmaceuticals Pvt Ltd, 40-B/2 Shankar Smruti, Sir Bhalchandra Rd, Dadar (E), Mumbai 400 014, India.
url: www.vhbgroup.com

Viamedica, Spain. Viamedica, Po de Recoletos 19, 28001 Madrid, Spain.

Vianex, Fin. See *Vianex (Βιανεξ), Gr.*

Vianex, Israel. See *Vianex (Βιανεξ), Gr.*

Vianex, Neth. See *Vianex (Βιανεξ), Gr.*

Vianex, Spain. See *Vianex (Βιανεξ), Gr.*

Vianex (Βιανεξ), Gr. Vianex S.A., Tatoiou Str., 18th Km Lamia National Rd, 146 10 Nea Erythrea, Greece.
url: www.vianex.gr

Viatria, Swed. Viatria AB, Kemistvägen 17, 183 79 Täby, Sweden.

Viatris, Arg. See *Pharmadorf, Arg.*

Viatris, Austria. Viatris Pharma GmbH, Liesinger Flur-Gasse 2C, A-1230 Vienna, Austria.
url: www.viatris.at

Viatris, Belg. Viatris SA/NV, Chaussee de la Hulpe 166, Terhulpsesteenweg, 1000 Brussels, Belgium.
url: www.viatris.be

Viatris, Cz. See *Medo, Cz.*

Viatris, Denm. See *AstraZeneca, Denm.*

Viatris, Fr. Viatris, Av J.F. Kennedy, 33701 Mérignac cdx, France.
url: www.viatris.fr

Viatris, Ger. See *Medo, Ger.*

Viatris, Gr. See *Meda, Swed.*

Viatris, Hong Kong. See *Health Vision, Hong Kong.*

Viatris, Hung. See *Meda, Hung.*

Viatris, Israel. See *Megapharm, Israel.*

Viatris, Ital. See *Medo, Ital.*

Viatris, Neth. Viatris BV, Verrijn Stuartweg 60, 1112 AX Diemen, Netherlands.
url: www.viatris.nl

Viatris, Norw. See *Sonten, Norw.*

Viatris, Pol. See *Pliva Krakow, Pol.*

Viatris, Port. Viatris Farmacêutica SA, Rua do Centra Cultural 13, 1749-066 Lisbon, Portugal.
url: www.viatris.pt

Viatris, Rus. See *Pliva, Rus.*

Viatris, Spain. Viatris Pharmaceuticals S.A.U., Avenida de Castilla 2, Edificio Berlmn - 2a Planta, San Fernando de Henares, 28830 Madrid, Spain.
url: www.viatris.com

Viatris, Switz. VIATRIS GmbH, Hegnaustrasse 60, 8602 Wangen, Switzerland.
url: www.viatris.ch

Viatris, Thai. See *Zuellig, Thai.*

Viatris, UK. See *Meda, UK.*

Viatris, USA. See *Mylan, USA.*

Vican, Gr. Vican, Ermou 1, 144 52 Metamorfosi, Greece.

Vichy, Canad. See *L'Oreal, Canad.*

Vichy, Chile. See *L'Oreal, Chile.*

Vichy, Fr. Laboratoires Vichy, Cosmétique Active France, Le Doublon, bat A, 11 av. Dubonnet, 92407 Courbevoie cdx, France.
url: www.vichy.fr

Vichy, USA. Vichy LLC, 575 Fifth Ave, New York, NY 10017, USA.
url: www.vichy.com

Vicis, Hung. Vicis Pharma Kft, Kapás u 11-15, Buda Business Center, 1027 Budapest, Hungary.

Vickmans, Hong Kong. Vickmans Laboratories Ltd, 2/F China Trade Cyr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.

Vicks, Spain. Laboratorios Vicks SL, Avenida de Bruselas 24, Madrid, Spain.

Vicks, USA. See *Procter & Gamble, USA.*

Vicks Health Care, USA. See *Procter & Gamble, USA.*

Victory, USA. Victory Pharmaceuticals, 12707 High Bluff Drive, Suite 200, San Diego, CA 92130, USA.

Victus, Venez. Victus de Venezuela C.A., Av Fco de Miranda, Ctra de Seguros La Paz, Piso 3, Ala Oeste Boleita Sur, Caracas, Venezuela.

Vida, Hong Kong. Vida Laboratories Ltd, Unit 919 Vanta Industrial Ctr, 21 Tai Lin Pai Rd, Kwai Chung, N.T., Hong Kong.
url: www.vidalab.com

Vida, Port. See *Atral, Port.*

Vidant, UK. Vidant Pharma Ltd, 10 Wellington St, Cambridge, CB1 1HW, UK.
url: www.eradicil.info

Vidara, USA. Vidara Therapeutics Inc., 1000 Holcomb Woods Parkway, Suite 270, Roswell, GA 30076, USA.
url: www.vidararx.com

Vidhyasam, Thai. Vidhyasam Co Ltd, 43 Bldg 8 Rathdamnern Rd, Phra Nakorn, Bangkok 10200, Thailand.

Vie et Sante, Fr. See *Isodisnatura, Fr.*

Vieira, Port. Raul Vieira, Lda, Rua dos Correeiros 41, 1100 Lisbon, Portugal.

Vifel, Gr. Vifel Ltd, Ag. Ponton 123, 17677 Kallithea, Greece.

Vifiteh, Rus. Vifiteh JSC, ul Skobelevskaya 22, 117624 Moscow, Russia.
url: www.vifiteh.ru

Vifor, Austral. Vifor Pharma Pty Ltd, Level 8, 80 Dorcas St, Southbank, VIC 3006, Australia.

Vifor, Austria. See *Vifor, Fr.*

Vifar, Belg. See *Vifor, Fr.*

Vifar, China. See *UCB, China.*

Vifor, Cz. See *Vifor, Switz.*

Vifor, Denm. See *Renapharma, Swed.*

Vifor, Fin. See *Sairaalapalvelu, Fin.*

Vifor, Fr. Vifor France SA, 7-13 Blvd Paul-Emile Victor, 92200 Neuilly-sur-Seine, France.

Vifar, Ger. Vifor Deutschland GmbH, Landsberger Str. 302, 80687 München, Germany.

Vifor, Gr. See *Genesis, Gr* and *Nycomed, Gr.*

Vifar, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Vifar, Hung. See *Galenica, Hung.*

Vifor, Indon. See *Combiphar, Indon.*

Vifor, Irl. See *Vifor, Fr.*

Vifor, Israel. See *CTS, Israel.*

Vifor, Ital. Vifor Pharma Italia Srl, Regus Business Centre, Via Luca Gaurico 9/11, 00143 Rome, Italy.
url: www.viforpharma.com

Vifor, Malaysia. See *DKSH, Malaysia.*

Vifor, Neth. See *NPBI, Neth.*

Vifor, Norw. See *Vifor, Swed.*

Vifor, Philipp. See *Zuellig, Philipp.*

Vifor, Pol. See *Iek, Pol.*

Vifor, Port. See *Ferraz, Lynce, Port* and *Confar, Port.*

Vifor, Rus. Vifor International Inc., 3 Tverskaya-Yamskaya, Dom 44, 125047 Moscow, Russia.
url: www.viforpharma.ru

Vifor, Singapore. See *United Italian, Singapore.*

Vifor, Spain. See *Vifor, Fr.*

Vifor, Swed. Vifor Pharma Nordiska AB, Tarshamnsg. 30 A, 164 40 Kista, Sweden.

Vifor, Switz. Vifor SA, Route de Moncor 10, 1752 Villars-sur-Glâne, Switzerland.
url: www.vifor.ch

Vifor, Thai. See *Diethelm, Thai.*

Vifor, UK. Vifor Pharma UK Ltd, The Old Stables, Bagshot Park, Surrey, GU19 5PJ, UK.
url: www.viforpharma.co.uk

Vifor, Ukr. See *Vifor, Rus.*

Vifor, USA. See *Vifor International, Switz.*

Vifor International, Switz. Vifor (International) AG, Pharmazeutische Spezialitäten, Rechenstrasse 37, Postfach, 9001 St Gallen, Switzerland.
url: www.vifor.com

Vigan, Fr. See *Bailleul, Fr.*

ViiV, Austral. ViiV Healthcare, Level 4, 436 Johnston St, Abbotsford, Vic 3067, Australia.
url: www.viivhealthcare.com

ViiV, Austria. See *ViiV, UK.*

ViiV, Belg. ViiV Healthcare, rue du Tilleul 13, 1332 Genval, Belgium.
url: www.viivhealthcare.com

ViiV, Canad. ViiV Healthcare Shire Canada, 7333 Mississauga Rd, Mississauga, Ontario, L5N 6L4, Canada.

ViiV, Cz. See *ViiV, UK.*

ViiV, Denm. See *GSK, Denm.*

ViiV, Fin. See *ViiV, UK.*

ViiV, Fr. ViiV Healthcare, 100 route de Versailles, 78163 Marly-Le-Roi Cedex, France.
url: www.viivhealthcare.com

ViiV, Ger. ViiV Healthcare GmbH, Prinzregentenplatz 9, 81675 Munich, Germany.
url: www.viivhealthcare.com

ViiV, Gr. See *ViiV, UK.*

ViiV, Hung. See *ViiV, UK.*

ViiV, Neth. ViiV Healthcare, Huis ter Heideweg 62, 3705 LZ Zeist, Netherlands.
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ViiV, Norw. See *GSK, Norw.*

ViiV, Port. ViiV Healthcare, Rua Dr Antonia Loureiro Borges 3, Arquiparque, Miraflores, 1495-131 Alges, Portugal.

ViiV, Spain. ViiV Healthcare, PTM Severo Ochoa 2, 28760 Tres Cantos, Madrid, Spain.
url: www.viivhealthcare.com

ViiV, Switz. ViiV Healthcare, Talstrasse 3-5, 3053 Münchenbuchsee, Switzerland.
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ViiV, Thai. See *GSK, Thai.*

ViiV, UK. ViiV Healthcare, 980 Great West Rd, Brentford, Middlesex, TW8 9GS, UK.
url: www.viivhealthcare.com

ViiV, USA. ViiV Healthcare, Five Moore Drive, Research Triangle Park, North Carolina, USA.
url: www.viivhealthcare.com

Vi-Jon, Canad. See *Vi-Jon, USA.*

Vi-Jon, USA. Vi-Jon Inc., 8515 Page Ave, St Louis, Missouri, 63114, USA.

Vilan, Rus. See *Yugrafarm, Rus.*

Vilar, Rus. Farm Vilar ZAO, Grina ul. 7, 117216 Moscow, Russia.
url: www.farmvilar.ru

Vilar, Ukr. See *Mitek, Ukr.*

Vilberry, India. Vilberry Healthcare, Vilberry House Plot P64, Milap Nagar, MIDC Residential Zone, Dombivali (E) 421 201, India.
url: www.vilberry.com

Vilco, Gr. Vilco S.A., 11-15 Aristotelous Str., 104 32 Athens, Greece.
url: www.vilco.gr

Vilco, India. Vilco Laboratories Pvt Ltd, Waksons 7B, 3rd Floor Firdaus Building, Chimbai Road, Bandra (W), Mumbai 400 050, India.
url: www.vilcolabs.com

Vinameks, Ukr. Vinameks Ukroine, Saksaganskoga St 48, Office 2, 01033 Kiev, Ukraine.

Vinos, Spain. Laboratorios Viñas SA LV, Provenza 386, 08025 Barcelona, Spain.

Vinas, Switz. See *Galaz, Switz.*

Vincenti, Venez. Laboratorios Vincenti C.A., Urb. Industrial Santa Cruz, Calle Roma, Edif., Centro Proa, Piso 2 Guarenas, Caracas, Venezuela.
url: www.vincentilab.com

Vinci, Spain. See *Pfizer, Spain.*

Vindex, USA. Vindex Pharmaceuticals, Cordova, TN 38088, USA.
url: www.vindexpharm.com

Vingmed, Norw. Vingmed AS, Fjordv. 1, Postboks 374, 1363 Høvik, Norway.
url: www.vitaline.com

Vinova, Malaysia. Vinova Pharma Sdn Bhd, 31 Jln USJ 1/1B, Regalia Business Centre, Taman Subang Mewah, 47500 Subang Jaya, Selangor, Malaysia.
url: www.vpharmahealth.com

Viofar, Gr. Viofar E.P.E, Ethn. Antistaseos and triphillas 76A, 136 71 Acharnai, Greece.

Vioser, Gr. Vioser A.E., Kanari 5, 141 22 N. Heraklion, Greece.
url: www.bioser.gr

Vipharm, Cz. See *Vipharm, Pol.*

Vipharm, Fin. See *Vipharm, Pol.*

Vipharm, Hung. See *Vipharm, Pol.*

Vipharm, Neth. See *Vipharm, Pol.*

Vipharm, Pol. Vipharm SA, ul. Przewoźników 11, 03-691 Warsaw, Poland.
url: www.vipharm.pl

Vips-Med, Rus. Vips-Med Ltd, Zavadskay proezd 4, Fryazino, 141190 Moscow, Russia.
url: www.vipsmed.ru

Vir, Port. Laboratórios Vir Portugal Lda, Av. Conselheiro Fernando de Sousa 19, 18 andar, 1070-072 Lisbon, Portugal.

Vir, Spain. Industria Química Farmaceutica Vir, Laguna 42-44, Pol In Urtinsa II, Alcorcon, 28923 Madrid, Spain.

Viratek, USA. See *Valeant, USA.*

Virchow, India. Virchow Graup, Plot No 4, SV Co-op Industrial Estate, IDA Jeedimetla, Hyderabad 500 055, India.

Virgo, Philipp. Virgo Pharmaceutical Lab, Virgo Bldg, 270 N S Amoranto Ave, Sta Mesa Hts, Quezon City, Philippines.

ViroPharma, Belg. ViraPharma SPRL, Rue Mantoyer 47, B-1000 Brussels, Belgium.
url: www.viropharma.com

ViroPharma, Denm. See *ViroPharma, Belg.*

ViroPharma, Ger. ViroPharma GmbH, Terminalstrasse Mitte 18, 85356 Munich, Germany.
url: www.viropharma.eu

ViroPharma, Irl. See *ViroPharma, UK.*

ViroPharma, Neth. See *ViroPharma, Belg.*

ViroPharma, Norw. See *ViroPharma, Belg.*

ViroPharma, Spain. ViroPharma Spain SLU, Calle Ribera del Loira 46, 28042 Madrid, Spain.
url: www.viropharma.eu

ViroPharma, UK. ViroPharma Ltd, Chatsworth House, 29 Broadway, Maidenhead, Berkshire, SL6 1LY, UK.
url: www.viropharma.com

ViroPharma, USA. ViroPharma Inc., 397 Eagleview Blvd, Exton, PA 19341, USA.
url: www.viropharma.com

Virox, Canad. Virox Technologies Inc., 2770 Coventry Rd, Oakville, Ontario, L6H 6R1, Canada.

Virtus, USA. Virtus Pharmaceuticals LLC, 2640 Causeway Center Drive, Tampa, FL 33619, USA.
url: www.virtusrx.com

Vis, Pol. Zakłady Chemiczno-Farmaceutyczne Visz Sp. zo.o., ul. Krawiecka 3, 41-902 Bytom, Poland.
url: www.vis-farm.pl

Visfarm, Spain. See *Novartis, Spain.*

Vishpha, Ukr. Vishpha Pharmaceutical Co. Ltd, 5 Lermontov St, Zhytomyr, 10014, Ukraine.
url: www.vishpha.ua

Vision, Canad. See *Vision, USA.*

Visian, USA. Vision Pharmaceuticals Inc., Mitchell, SD 57301, USA.
url: www.visionpharm.com

Visiontec, Arg. Visiontec, Division Oftalmologica de Latinmarket SA, Moreno 1401/05, 1093 Buenos Aires, Argentina.

Vista, India. Vista Health Care, Building No. 25, Galla No.13 Arihant Complex, Village Purna, Thane, Bhiwandi, India.

Vista, Philipp. Vista Pharma, 2/F The Gateway Ctr, South Superhighwat cor, San Gregorio St, Paseo de Magallanes, 1232 Makati City, Philippines.

Vistakan, USA. Vistakon Pharmaceuticals LLC
url: www.vistakonpharmaceutical.com

Vistapharm, USA. VistaPharm, 2224 Cahaba Valley Drive, Suite B3, Birmingham, AL 35242, USA.
url: www.vistapharm.com

Visufarma, Ital. Visufarma S.p.A., Via Canino 21, 00191 Rome (RM), Italy.
url: www.visufarma.it

Vita, Austria. *See Vita, Spain.*

Vita, Ital. *See Sanofi-Aventis, Ital.*

Vita, Port. *See Vita, Spain.*

Vita, Spain. Grupo Vita/Vita Cientifica S.L., Avda de Barcelona 69, Sant Juan Despi, 08970 Barcelona, Spain.
url: www.grupovita.es

Vita, Venez. Laboratorios Vita, Av.Principal Mari Perez, Edif. Vita, Mari Perez Caracas, Caracas, Venezuela

Vita Api, Fr. Laboratoire Vita Api, Espace Coralia, 6 ZA des Playes-Jean Monnet Sud, 424 rue de Lisbonne, 83500 La Seyne-sur-Mer, France.
url: www.vita-api.fr

Vita Elan, Spain. *See Zeneus, Spain.*

Vita Green, Hong Kong. Vita Green Health Products Co Ltd, Rm 1005 Manning House, 48 Queens Rd Central, Hong Kong.
url: www.vitagreen.com

Vita Health, Canad. Vita Health Products Inc., 150 Beghin Ave, Winnipeg, Manitoba, R2J 3W2, Canada.
url: www.vitahealth.ca

Vita Health, Malaysia. *See Medispec, Malaysia and Zuellig, Malaysia.*

Vita Health, Singapore. Vita Health Laboratories Pte Ltd, 371 Beach Rd, Keypoint 20-01/07, S 199597, Singapore.

Vita Health, Switz. Vita Health Care AG, 3177 Laupen, Switzerland.

Vita Healthcare, UK. Vita Healthcare Ltd, Palladium House, 1-4 Argyll St, London, W1V 2LD, UK.

Vita Kimya, Turk. Vita Kimya Laboratuvari, Katip Sinan Cami Sk No 3/1, Dizdariye, Çemberlitaş, Istanbul, Turkey.

Vita Research, Ital. Vita Research, Via Variante di Cancelliera 4, 00040 Ariccia (RM), Italy.
url: www.vitaresearch.com

Vitabalans, Cz. *See Vitabalans, Fin.*

Vitabalans, Denm. *See Vitabalans, Fin.*

Vitabalans, Fin. Vitabalans Oy, Varastokatu 8, 13500 Hämeenlinna, Finland.
url: www.vitabalans.fi

Vitabalans, Hung. *See Vitabalans, Fin.*

Vitabalans, Pol. *See Vitabalans, Fin.*

Vitabalans, Swed. *See Vitabalans, Fin.*

Vitabiotics, Cz. *See Vitabiotics, UK.*

Vitabiotics, Hong Kong. *See Mekim, Hong Kong.*

Vitabiotics, Hung. Vitabiotics, Hungary.

Vitabiotics, Indon. Vitabiotics Utama Indonesia PT, Jl Pemuda No 44, Jakarta Timur 13220, DKI Jaya, Indonesia.

Vitabiotics, Irl. *See Allphar, Irl.*

Vitabiotics, Philipp. *See Endure, Philipp.*

Vitabiotics, Rus. *See Vitabiotics, UK.*

Vitabiotics, UK. Vitabiotics Ltd, 1 Apsley Way, London, NW2 7HF, UK.
url: www.vitabiotics.com

Vitabiotics, Ukr. *See Vitabiotics, UK.*

Vitaco, Austral. Vitaco Health Australia Pty Ltd, Level 1, 82 Waterloo Rd, North Ryde, NSW 2113, Australia.
url: www.vitaco.com.au

Vitae, Mex. Vitae Laboratorios S.A. de C.V., Euclides No. 3214, Fracc. Vallarta San Jarge, 44690 Guadalajara, Jalisco, Mexico.

Vitafarma, Rus. Vitafarma Firma, 1st St Yamskogo D 17, 125124 Moscow, Russia.
url: www.vitafarma.ru

Vitafarma, Spain. Vitaforma, C/Florida 29, Hernani, 20120 Guipuzcoa, Spain.
url: www.vitafarma.es

Vitaflo, Denm. Vitaflo Scandinovia AB, Nygade 1, 2. 19, 3600 Frederikssund, Denmark.
url: www.vitaflo.net

Vitaflo, Fin. *See Tamro, Fin.*

Vitaflo, Irl. *See Allphar, Irl.*

Vitaflo, Norw. Vitaflo Scandinavio AB, Postboks 107, 1325 Lysaker, Norway.
url: www.vitaflo.net

Vitaflo, Swed. Vitaflo Scandinavia AB, Box 53063, 400 14 Göteborg, Sweden.
url: www.vitaflo.net

Vitaflo, UK. Vitaflo Ltd, 11 Century Building, Brunswick Business Park, Liverpool, Merseyside, L3 4BL, UK.
url: www.vitaflo.co.uk

Vitaglow, Austral. *See Blackmores, Austral.*

Vita-Health, Hong Kong. *See Great Liaison, Hong Kong and Hind Wing, Hong Kong.*

Vital Healthcare, Philipp. *See Pharmasan, Philipp.*

Vital Life, UK. Vital Life International Ltd, 8 Cloisters Business Centre, Battersea Park Rd, Nine Elms, London, SW8 4BG, UK.
url: www.vital-life.org.uk

Vital Science, Canad. Vital Science Corp., Unit 6, 93 Woodstream Blvd, Woodbridge, Ontario, L4L 7Y7, Canada.

Vitalab, Canad. Vitalab, Suite 8, 3145 rue Harvey, St Hubert, Quebec, J3Y 3T7, Canada.

Vitalan, Thai. *See International Pharmaceuticals, Thai.*

Vitalco, Fr. Vitalco, 7 rue Paul-Lelong, 75002 Paris, France.
url: www.vitalco.com

Vitalia, UK. Vitalia Health Ltd, P.O. Box 2492, Marlow, Buckinghamshire, SL7 2WW, UK.
url: www.vitalia-health.co.uk

Vitaline, Fin. *See Sairaalapalvelu, Fin.*

Vitaline, Irl. *See Vitaline, UK.*

Vitaline, Norw. *See Vingmed, Norw.*

Vitaline, Swed. Vitaline Scandinavia AB, Box 938, 751 09 Uppsala, Sweden.

Vitaline, UK. Vitaline Pharmaceuticals UK Ltd, Chiltern House, Unit P, Howland Rd, Thame, Oxfordshire, OX9 3GQ, UK.
url: www.vitalinepharmaceuticals.co.uk

Vitaline, USA. Vitaline Corp., 9 Monroe Parkway, Suite 250, Lake Oswego, OR 97035, USA.
url: www.vitaline.com

Vitalink, Philipp. Vitalink Health Products Inc., 103 Scout de Guia, cor Tomas Morato Ave, Quezon City, Philippines.

Vitalion, Port. Vitalian Lda, Rua Elias Garcia 28, Venda Nova, 2700-327 Amadora, Portugal.

Vitalis, Philipp. Vitalis Pharma Pils, Unit 2-G Torre Venezia, Timog Ave cor, Sct Santiago St, Quezon City, Philippines.

Vitality, Canad. Vitality Products Inc., 8585 123rd St, Surrey, British Colombia, V3W 6E2, Canada.

Vitality, USA. *See Pan American, USA.*

Vitalpharma, Belg. Vitalpharma SA, Drie bomenstraat 16, 1180 Brussels, Belgium.

Vitamed, Israel. Vitamed Ltd, P.O. Box 114, Binyamina 30550, Israel.

Vitamed, Pol. Hurtownia Farmaceutyczna Vitamed, ul. Ostrowskiego 24, 97-213 Smardzewice, Poland.

Vitamed, Turk. Vitamed, Turkey.

VitoMed, USA. VitaMed, USA.
url: www.vitamed.com

Vitamedica, Fin. *See Vitamedica, Irl.*

Vitamedica, Irl. Vitamedica Europe Ltd, Unit 34, 11 Dublin, Ireland.

Vitamedica, Neth. *See Vitamedica, Irl.*

Vitamex, Pol. *See Ferrosan, Pol.*

Vitaminerals, Canad. *See Vitaminerals, USA.*

Vitominerals, USA. Vitaminerals Inc., 1815 Flower St, Glendale, CA 91201, USA.

Vitaminkosar, Hung. VitaminKosár Kft, Nádortiget ut 7/c, 1117 Budapest, Hungary.
url: vitaminkosar.hu

Vitapan, Braz. Vitapon Indústria Farmacêutica Ltda, Rua VPR 01 Qd. 2-A-Mod.1 DAIA, 75133600 Anapolis, Goias, Brazil.

Vitapantal, Belg. Laboratoire Vitapantol, Rue de l'Ourchet 17, 1367 Gerompont (Bomal), Belgium.
url: www.vitapantal.be

Vitaplex, Austral. Vitaplex Products, P.O. Box 270, Gymea, NSW 2227, Australia.

Vitaresearch, Ger. *See Vita Research, Ital.*

Vitarum, Arg. Vitarum, Ayacucho 153, Piso 1 B, 5000 Cordoba, Argentina.

Vitazan, Canad. Vitazan Herbs & Vitamins Inc., 3405 F X Tessier, Vaudreuil-Dorion, Quebec, J7V 5V5, Canada.

Vitelle, Austral. *See Mayne, Austral.*

Vitorgan, Ger. vitOrgan Arzneimittel GmbH, Brunnwiesenstr. 21, 73760 Ostfildern, Germany.
url: www.vitorgan.de

Vitoria, Port. Laboratórios Vitória, SA, Rua Elias Garcia 28, Venda Nova, 2700-327 Amadora, Portugal.

Vitroforma, Thai. *See Medline, Thai.*

Vitrolife, Swed. Vitrolife AB, Mölndalsvägen 30, 412 63 Göteborg, Sweden.
url: www.vitrolife.com

Viva, Canad. Viva Pharmaceuticals Inc., 13880 Viking Place, Richmond, British Columbia, V6V 1K8, Canada.

Vivalife, Port. Vivolife Laboratórios Lda, Rotunda Nuno R. Santos, 2685 Portela de Sacavim, Portugal.

Vivax, Cz. Vivox, Czech Republic.

Vivax, Gr. Vivox Pharmaceuticals Ltd Greece, Dervenakion 38, 153 44 Athens Gerakas, Greece.

Vivox, Venez. Vivax Pharmaceuticals, Final calle Vargas Torre Este, Piso 2 Ed.Ctro.Berimer, Urb. Boleito Norte, Caracas, Venezuela.

Vivax Colmed, Venez. *See Vivax, Venez.*

Vivax Gynopharm, Venez. *See Vivax, Venez.*

Vivax Optipharm, Venez. *See Vivax, Venez.*

Viviar, Spain. Viviar, Pol Ind Pista de Ademuz, Autov Valencia-Liria Km 9.4, Paterna, 46980 Valencia, Spain.

Vivid, Indio. Vivid Biotek Pvt Ltd, 30 Roni Jhonsi Rd, Jhandewalan, Delhi 110055, India.

Vivier, Canad. Vivier Canada Inc., 288 Adrien-Patenaude, Vaudreuil-Dorion, Quebec, J7V 5V5, Canada.

Vivipharma, Ital. Vivipharma S.A., Via Guardia del Consiglio 15, 47891 Galazzano (RSM), Italy.
url: www.vivipharma.com

Vivo Health, Singapare. *See Alcare, Singapore.*

Vivus, Austria. *See Vivus, USA.*

Vivus, Denm. *See Abbott, Denm.*

Vivus, Norw. *See Abbott, Norw.*

Vivus, USA. Vivus Inc, 1172 Castro St, Mountain View, CA 94040, USA.
url: www.vivus.com

Vizcarra, Philipp. Vizcarra Pharmaceutical Inc., Segundina Bldg, 464 United Nations Ave, Ermita, Manila, Philippines.

VK Reagent, Ukr. VK Reagent, 5 Murmansk St., Kiev, 02660, Ukraine.
url: www.metonat.ua

Vocate, Gr. Vacate A.E., Gounari 150, 166 74 Glyfada, Greece.
url: www.vocate.gr

Voco, Cz. *See Voco, Ger.*

Voco, Denm. *See Voco, Ger.*

Voco, Fr. *See Voco, Ger.*

Voco, Ger. Voco GmbH, Anton-Flettner-Strasse 1-3, 27472 Cuxhaven, Germany.
url: www.voco.de

Voco, Pol. *See Voco, Ger.*

Vogel, Fin. A Vogel Oy, Kumitehtaankatu 5, 04260 Kerava, Finland.

Vogel, UK. *See Bioforce, UK.*

Voigt, Switz. Voigt Industrie Services AG, Hofstrasse 50, 8590 Romanshorn 1, Switzerland.

Volchem, Ital. Volchem S.r.l., Via E Dandolo 14 Frazione di Grossa, 35010 Gazzo (PD), Italy.
url: www.volchem.it

Volkspharma, Ger. Volkspharma GmbH, Gutermannstrasse 25, 86154 Augsburg, Germany.
url: www.volkspharma.com

Volkspharma, Irl. *See Volkspharma, Ger.*

Volmix, Hung. Volmix Ltd, Thökölu ut 76, 1146 Budapest, Hungary.
url: www.volmix.hu

Volta, Chile. Laboratorio Volta Ltda, Jose Miguel Carrera 14-A Complejo Ind., Los Libertadores Colina, Santiaga, Chile.

Vonnace, Philipp. Vonnace Pharmaceuticals Corp, 2/F Teresa Bldg 15th Ave, Murphy, Cubao, Quezon City, Philippines.

Vortech, USA. Vortech Pharmaceuticals, 6851 Chase Rd, Dearborn, MI 48126, USA.

Votania, Gr. Votania SA, Pegasus 18, 151 25 Marousi, Greece.

VP, Spain. VP Pharma Baru, Valle de Tabolina Nave 3, 16 Madrid, Spain.

Vramed, Rus. *See Sopharma, Rus.*

VS, Thai. VS Pharma Co Ltd, 222 Onnuch 46, Sukhumvit 77, Suanluang, Bangkok 10500, Thailand.

VSM, Belg. VSM Belgium, Prins Boudewijnlaan 17 unit 7, 2550 Kontich, Belgium.
url: www.vsm.be

VSM, Neth. VSM Geneesmiddelen BV, Postbus 9321, 1800 GH Alkmaar, Netherlands.
url: www.vsm.nl

VUAB, Cz. VUAB Pharma as, Vltavská 53, 252 63 Roztoky, Czech Republic.

Vulm, Cz. Vulm Cz as, Olivova 1888, 251 01 Říčany, Czech Republic.

VVS, Ukr. VVS Ltd, Promishlennaya Street, 3, v. Hotov, Kiev-Svyatoshinskyy region, 08171, Ukraine.
url: www.vvs-ltd.com.ua

Vysali, Philipp. *See Paren, Philipp.*

Waas Anita, Spain. Waas Anita SA, Calle Generale Prim 13, Madrid, Spain.

Wabosan, Austria. Wabosan Arzneimittelvertriebs GmbH, Anton Anderer Platz 6, A-1210 Vienna, Austria.

Waca, Arg. *See Vanfar, Arg.*

Wagner, Hung. Wagner Pharmafax Kft, Gyógyszer Business Center, Kassai u 56-58/b, 1041 Budapest, Hungary.

Wainhouse, NZ. Wainhouse Distribution Ltd, 2-6 Argyle St, Morningside, Auckland, New Zealand.
url: www.wainhousedist.co.nz

Wakamoto, Hong Kong. *See Tai Tang, Hong Kong.*

Wakamoto, Jpn. Wakamoto Pharmaceutical Co. Ltd, 1-5-3 Nihonbashi-Muromachi, Chuo-ku, Tokyo 103-8330, Japan.
url: www.wakamoto-pharm.co.jp

Wakefield, USA. *See Ivax, USA.*

Wala, Ger. Wala Heilmittel GmbH, Dorfstr. 1, 73087 Bad Boll/Eckwälden, Germany.
url: www.walaarzneimittel.de

Wala, Neth. Wala Nederland BV, Vernijn Stuartlaan 48, 2288 EN Rijswijk, Netherlands.

Wala, Switz. Wala Schweiz GmbH, Waaghausgasse 3, 3011 Berne, Switzerland.

Waldheim, Austria. *See Sanochemia, Austria.*

Walker, Arg. Laboratorio Walker S.R.L., E. Zeballos 249, 2000 Rosario, Santa Fe, Argentina.
url: www.laboratoriowalker.com.ar

Walker Pharmacal, USA. Walker Pharmacal, 4200 Laclede Ave, St Louis, MO 63108, USA.

Wallace, India. Wallace Pharmaceuticals Ltd, 101/2 Floral Deck Plaza, Off Central MIDC Rd, Andheri (East), Mumboi 400 093, India.
url: www.wallacepharma.net

Wallace, Singapore. *See Polymedic, Singapore.*

Wallace, USA. *See Medpointe, USA.*

Wallace Mfg Chem., UK. *See Alinter, UK.*

Wallace Pharma, UK. *See Alinter, UK.*

Walmark, Cz. Wolmark a.s., Oldrichovice 44, Trinec, Czech Republic.

Walmark, Hung. Walmark Kft, Kiss Ernö u. 1-3, 1046 Budapest, Hungary.
url: www.walmark.eu

Walmark, Pol. Walmark Sp. z o.o., ul. Teatralna 9, 41-200 Sosnowiec, Poland.
url: www.walmark.pl

Walmark, Singapore. *See Indrugco, Singapore.*

Walnut, Philipp. *See Medicamenta, Philipp.*

Walsh, USA. Walsh Dohmen, USA.

Wampole, Canad. Wampole Brands Inc., 5950 Cote-de-Liesse, Montreal, Quebec, H4T 1E2, Canada.

Wampole, USA. Wampole Laboratories, 2 Research Way, Princeton, NJ 08540, USA.
url: www.wampolelabs.com

Wan Bang, Chino. Wan Bang Biochemical Pharmaceutical Co. Ltd, China.

Wan Ji, China. Wanji Pharmaceutical Co., Ltd, 6F Wanji Building, 4 Shuibei Yi Rd, Shenzhen, Guangdong, 518020, China.
url: www.wanjigroup.com

Wan Lian, China. Wan Lian Pharmaceutical Co. Ltd, Zhejiang, China.

Wan Long, China. Wan Long Pharmaceutical Co. Ltd, Xi'an, China.

Wan Te, China. Wan Te Pharmaceutical Co. Ltd, 279 Nanhai Rd, Haikou, Hainan, China.

Wan Xing, China. Wan Xing Bio-Pharmaceutical Co Ltd, Shanghai, China.

Wanbei, China. Wanbei Pharmaceutical Co. Ltd, 24 Huaihai Road, Suzhou, Anhui, 234000, China.
url: www.wbpharm.com

Wanbury, India. Wanbury Ltd, BSEL Techpark, B Wing 10th Floor Sector 30-A, Opp. Vashi Railway Station, Vashi, Navi Mumbai, 400705, India.
url: www.wanbury.com

Wandashan, China. Wandashan Pharmaceutical Co. Ltd., 309 Provincial Rd, Peidezhen, Mishan, Jixi, Heilongjiang, 158306, China.
url: www.wdsyy.com

Wandel, Mex. Formacéutico Wandel SA de CV, Conkal MZ 391 Lt 1, 14200 Tlalpan Ejidos de Padierna, Mexico.

Wander, Austria. *See Novartis, Austria.*

Wander, Belg. *See Novartis, Belg.*

Wander, Ger. *See Novartis, Ger.*

Wander, Neth. *See Novartis, Neth.*

Wander, Philipp. *See Zuellig, Philipp.*

Wander, S.Afr. *See Sandoz, S.Afr.*

Wander, Switz. *See Wander Health Care, Switz.*

Wander Health Care, Switz. Wander AG, Fabrikstrasse 10, 3176 Neuenegg, Switzerland.
url: www.wander.ch

Wander OTC, Switz. *See Wander Health Care, Switz.*

Wanglintang, China. Wanglintang Pharmaceutical Co. Ltd, Juanba, Donghu, Zigong, Sichuan, 643219, China.
url: www.wanglintang.com.cn

Wanhe, China. Wanhe Pharmaceutical Co/ Ltd., 8 Gaoxin Middle 1st Road, Nanshan, Shenzhen, Guangdong, 518057, China.
url: www.wanhe-phar.com

Wanhui Shuanghe, China. Wanhui Shuanghe Pharmaceutical Co. Ltd, 1 Shangyuan Rd, Shilong Industry Development Zone, Mentougou, Beijing, 102308, China.

Wanjie High Tech, China. Wanjie High Tech Co. Ltd, Shandong, China.

Wanle, China. Wanle Pharmaceutical Co. Ltd, Wanle Building, 4 Bagua Rd, Futian, Shenzhen, 518029, China.
url: www.wanle.com.cn

Wanma, China. Wanma Pharmaceutical Co. Ltd., 989 Moganshan Rd, Gongshu, Hangzhou, Zhejiang, 310011, China.
url: www.wmpha.com.cn

Wanqing, China. Wanqing Pharmaceutical Co. Ltd, Suzhou, China.

Wansheng, China. Jilin Wansheng Pharmaceutical Co Ltd, 40 Minkang Rd, Changhe, Liuhe County, China.

Wansui, China. Wansui Pharmaceutical Co. Ltd., 10 Beihai Road, Cangzhou Economic and Technological Development Zone, Cangzhou, Hebei, 061000, China.
url: www.longlife-group.com

Wantong, China. Tonghua Wantong Pharmaceutical Co. Ltd, 66 Wantong Rd, Tonghua City, 134001, China.
url: www.wtyy.com

Wantong, Rus. *See Wantong, China.*

Wanze, China. Wanze Pharmaceutical Co. Ltd, Chifeng, China.

Warner, India. Warner Hindustan Ltd, 254-B Nirlon House, Dr. Annie Besant Road, Worli, Mumbai 400 025, India.

Warner Chilcott, Belg. Warner Chilcott Pharmaceuticals BVBA, Pegasuslaan 5, 1831 Diegem, Belgium.

Warner Chilcott, Canad. *See Warner Chilcott, USA.*

Warner Chilcott, Cz. *See Warner Chilcott, Irl.*

Warner Chilcott, Fin. *See Warner Chilcott, Irl.*

Warner Chilcott, Fr. Warner Chilcott France, Immeuble Le Jean-Monnet, 11 place des Vosges, 92061 Paris-La Défense cdx, France.

Warner Chilcott, Ger. Warner Chilcott Deutschland GmbH, Dr-Otto-Röhm-Str. 2-4, 64331 Weiterstadt, Germany.
url: www.wcrx.de

Warner Chilcott, Irl. Warner Chilcott plc, 1 Grand Canal Square, Docklands, Dublin 2, Ireland.
url: www.wcrx.com

Warner Chilcott, Neth. Warner Chilcott Nederland BV, Lichtenauerlaan 102-120, 3062 ME Rotterdam, Netherlands

Warner Chilcott, Spain. Warner Chilcott Iberia SL, WTC Almeda Park, Edificio 1, 2 pl., Placa de la Pau s/n, 08940 Cornella de Llobregat (Barcelona), Spain.

Warner Chilcott, Swed. *See Warner Chilcott, UK.*

Warner Chilcott, UK. Warner Chilcott UK Ltd, 1 The Heights, Brooklands, Weybridge, Surrey, KT13 0NY, UK.
url: www.wcrx.com

Warner Chilcott, USA. Warner Chilcott Laboratories, 100 Enterprise Drive, Rockaway, NJ 07866, USA.
url: www.warnerchilcott.com

Warner-Lambert, Austral. *See Pfizer, Austral.*

Warner-Lambert, Belg. *See Pfizer, Belg.*

Warner-Lambert, Braz. *See Pfizer, Braz.*

Warner-Lambert, Canad. *See Pfizer Consumer, Canad.*

Warner-Lambert, Denm. *See Pfizer, Denm.*

Warner-Lambert, Fin. *See Pfizer, Fin.*

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Warner-Wellcome, Ger. See *Pfizer, Ger.*
Warner-Wellcome, Spain. See *Pfizer, Spain.*
Warner-Wellcome, USA. See *Pfizer, USA.*
Warrant, China. Warrant Pharmaceutical Co. Ltd., 4th Floor block 3 Huasheng Gardens, 338 Shaoshan North Road, Changsha, Hunan, China.
url: www.warrant.com.cn
Warrick, USA. See *Schering-Plough, USA.*
Warsaw-Polfa, Rus. Warsaw Pharmaceutical Work Polfa, Kutuzovskii prospekt 13, kv. 84/85, 121248 Moscow, Russia.
Wasip, Canad. Wasip Ltd, Unit 1, 605 Middlefield Rd, Toronto, Ontario, M1V 5B9, Canada.
Wassen, Ital. Wassen Italia S.r.l., Via Canova 25, 20145 Milan, Italy.
url: www.wassen.it
Wassen, UK. Wassen International Ltd, 14 The Mole Business Park, Leatherhead, Surrey, KT22 7BA, UK.
url: www.wassen.com
Wasserman, Spain. See *Chiesi, Spain.*
Wassermann, Denm. See *Wassermann, Ital.*
Wassermann, Ital. Alfa Wassermann S.p.A., Via Enrico Fermi 1, 65020 Alanno (PE), Italy.
url: www.alfawassermannproduzione.it
Wassermann, Malaysia. See *Antah, Malaysia* and *Emerging Pharma, Malaysia* and *Zyfas, Malaysia.*
Wassermann, Neth. See *Wassermann, Ital.*
Wassermann, Philipp. See *Corbridge, Philipp.*
Wassermann, Spain. See *Wassermann, Ital.*
Watanabe, Hong Kong. See *Eng An, Hong Kong.*
Water Concepts, Canad. See *Water Concepts, USA.*
Water Concepts, USA. Water Concepts Inc., 39 South Barrington Rd, South Barrington, IL 60010, USA.
WaterJourney, Canad. See *Water Journey, USA.*
Water Journey, USA. Water Journey Ltd, 75 Shrewsbury Drive, Livingston, NJ 07-39, USA.
Watkins, Canad. See *Watkins, USA.*
Watkins, USA. Watkins Inc., 150 Liberty St, Winona, Minnesota, 55987-0570, USA.
Watsin Genetech, China. Watsin Genetech Co. Ltd, 7 Keji Central 1st Road, Nanshan, Shenzhen, Guangdong, 518057, China.
url: www.watsin-gene.com
Watson, Canad. See *Watson, USA.*
Watson, China. Watson Pharmaceutical Co. Ltd, Eton Place 31/F, 555 Pudong Ave, Shanghai 200120, China.
url: www.watsonpharma.com.cn
Watson, S.Afr. Watson Pharma, 1st Floor Block C, Sandton Close 1, Sandown, Gauteng 2196, South Africa.
Watson, USA. Watson Pharmaceuticals Inc., 311 Bonnie Circle, Corona, CA 91720, USA.
url: www.watsonpharm.com
Watsons, Canad. Watsons Pharmaceuticals, 3 Ontario St, Port Hope, Ontario, L1A 3T5, Canada.
Wattie, NZ. See *Heinz-Wattie, NZ.*
Wave, India. Wave Pharmaceuticals Ltd, 410 Ansal Chambers, New Delhi 110066, India.
Wave, Rus. See *Wave, India.*
Waves, India. Waves Bio-Tech Pvt Ltd, 487 / 30, KH-569 Ground Floor, Peeragarhi, New Delhi 110 087, India.
url: www.wavesbiotech.com
Waymade, UK. Waymade Healthcare plc, Sovereign House, Miles Gray Rd, Basildon, Essex, SS14 3FR, UK.
url: www.waymadehealthcare.plc.uk
Waymar, Canad. Waymar Pharmaceuticals Inc., 330 Marwood Drive, Unit 4, Oshawa, Ontario, L1H 8B4, Canada.
WC Bio-Pharm, Canad. W.C. Bio-Pharm Inc., 13480 Verdun Pl, Richmond, British Columbia, V6V 1V2, Canada.
url: wcbiopharm.com
WE, USA. WE Pharmaceuticals Inc, P.O. Box 1142, Ramona, CA 92065, USA.
url: www.wepharma.com
Wealth, Ital. Wealth Pharma S.r.l., Via Carlo Porta 10, 00153 Rome (RM), Italy.
url: www.wealthpharma.com
Wearnes, Malaysia. See *Apex, Malaysia.*
Weber & Weber, Austria. See *Weber & Weber, Ger.*
Weber & Weber, Ger. Weber & Weber GmbH & Co. KG, Herrschinger Str. 33, 82266 Inning/Ammersee, Germany.
url: www.weber-weber.de
Wecome, China. Wecome Pharmaceutical Co. Ltd, 8 Xixi Villa, 658 Wensan West Road, Hangzhou, Zhejiang, 310012, China.
Wedgewood, USA. Wedgewood Pharmacy, 405 Heron Drive, Suite 200, Swedesboro, NJ 08085, USA.
url: www.wedgewoodpharmacy.com
Weeks & Leo, USA. Weeks & Leo Inc., 4000 NW 100th Street, Des Moines, Iowa, USA.
url: www.weeksandleo.com
Wei Kang, China. Wei Kong Pharmaceutical Co. Ltd, 15 Xinggong North Rd, Economic Development Zone, Jiangshan 324100, Zhejiang, China.
url: www.zjwkzy.com
Wei Lun, China. Wei Lun Biological Pharmaceutical Co Ltd, Guangdong, China.
Wei Men, China. Wei Men Pharmaceutical Co Ltd, Guizhou, China.
Weiao, China. Weiao Pharmaceutical Co. Ltd, 63 Gold Buildings Room 502, Xi'an Rd, Chengdu 610030, China.
Weida, China. Weida Pharmaceutical Co. Ltd, China.
Weider, USA. See *Schiff, USA.*
Weierkang, China. Weierkang Biochemical Pharmaceutical Co. Ltd, Jinan, China.
Weifa, Norw. Weifa AS, Hausmannsg. 6, Postboks 9113 Grönland, 0133 Oslo, Norway.
url: www.weifa.no
Weifa, Thai. See *Harn, Thai.*
Weifang, China. Shandong Weifang Pharmaceutical Factory Co., Ltd., 1 West Beigong Street, Weicheng District, Weifang, Shandong, 261021, China.
url: www.weifangpharm.com
Weigao, China. Weigao Pharmaceutical Group Co. Ltd., Shandong, China.
Weike, China. Weike Biopharmaceutical Co. Ltd, Shanghai, China.
Weimer, Ger. See *Biokanol, Ger.*
Weimer, Hong Kong. See *Hong Kong Medical, Hong Kong.*
Weimer, Singapore. See *JDH, Singapore.*
Weimer, Thai. See *Schumit, Thai.*
Weimin, China. Weimin Pharmaceutical Co. Ltd, Datong, China.
Weiqida, China. Weiqida Pharmaceutical Co. Ltd, Shanxi, China.
Weishi, China. Weishi (Rugao) Pharmaceutical Co. Ltd, 139 Po Hing Road, Rugao, Jiangsu, China.
url: www.vanworld.com.cn
Weite, China. Weite Pharmaceutical Co. Ltd, Hunan, China.
Weiwu Guangming, China. Shenzhen Weiwu Guangming Biological Products Co., Ltd., Guangming Street, Bao'an District, Shenzhen, Guangdong, 518107, China.
url: www.szwg.com
Weixin, China. Weixin Pharmaceutical Co. Ltd, 181 Taibai South Road, Yanta, Xi'an, Shaanxi, China.
Weixing Bio Product, China. Weixing Institute of Biological Products Co. Ltd, 51a-3 Dongzhan Street, Dadong, Shenyang, Liaoning, 110044, China.
Welcker-Lyster, Canad. See *Ratiopharm, Canad.*
Welding, Ger. Welding GmbH & Co KG, Hamburg, Germany.
Welding, Neth. See *Welding, Ger.*
Weleda, Austria. Weleda GmbH & Co. KG, Hosenedelgasse 27, A-1220 Vienna, Austria.
url: www.weleda.at
Weleda, Canad. See *Weleda, Ger.*
Weleda, Fr. Laboratoires Weleda, 9 rue Eugene-Jung, 68330 Huningue, France.
url: www.weleda.com
Weleda, Ger. Weleda AG, Möhlerstr. 3-5, 73525 Schwäbisch Gmünd, Germany.
url: www.weleda.de
Weleda, Irl. See *Weleda, UK.*
Weleda, Neth. Weleda Nederland BV, Platinastraat 161, 2718 SR Zoetermeer, Netherlands.
Weleda, S.Afr. See *Pharma-Natura, S.Afr.*
Weleda, Swed. Weleda AB, Skillebyholm 4, 153 91 Järna, Sweden.
url: www.weleda.se
Weleda, Switz. Weleda AG, Stollenrain 11, 4144 Arlesheim, Switzerland.
url: www.weleda.ch
Weleda, UK. Weleda (UK) Ltd, Heanor Rd, Ilkeston, Derbyshire, DE7 8DR, UK.
url: www.weleda.co.uk
Welfide, Malaysia. See *Antah, Malaysia.*
Welfide, Singapore. See *Alpha Therapeutic, Singapore.*
Welfide, Thai. See *Diethelm, Thai.*
Well, Port. Well Pharma SA, Rua Dr Eduardo Santos Silva 449, 4200-284 Porto, Portugal.
Well Favoured, Hong Kong. Well Favoured Ltd, 9/F Henley Centre, 9-15 Bute St, Mongkok, Kowloon, Hong Kong.
Wellchem, Malaysia. Syarikat Wellchem Sdn Bdh, 928-929 Jln 17/38, 46400 Petaling Jaya, Selangor, Malaysia.
url: www.wellchem.com
Wellchem, Singapore. Wellchem Pharmaceuticals Pte Ltd, 221 Henderson Rd, 04-15 Henderson Building, S 159557, Singapore.
url: www.wellchem.com.sg
Wellchem, Thai. Wellchem Pharmaceutical Co. Ltd, 99/287-288 Nonsee Rd, Yannawa, Bangkok 10120, Thailand.
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Wellgo, Hong Kong. Wellgo Pharmaceutical Co. Ltd, Unit 03-08, 22/F Millenium City, 378 Kwun Tong Rd, Kwun Tong, Kowloon, Hong Kong.
Wellhealth, Philipp. See *Ad-Drugstel, Philipp.*
Wellmex, Malaysia. Wellmex Sdn Bhd, 23-26 Jln Bidara 1, Taman Bidara, 68100 Batu Caves, Selangor, Malaysia.
Wellness, Philipp. WellnessPRO Inc., 902 Richmond Plaza, Lourdes St cor, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.
Wellpharma, Ital. Wellpharma S.r.l., Via Ninfea 110, 25049 Iseo (BS), Italy.
url: www.wellpharma.it
Wellso, China. Wellso Pharmaceutical Co. Ltd., 8th Floor Shenzhou Tower, 31 Zhongguancun South Street, Haidan, Beijing, 100081, China.
url: www.sihuan.com.cn
Wellspring, Canad. Wellspring Pharmaceuticals Canada Corp., 400 Iroquois Shore Rd, Oakville, Ontario, L6H 1M5, Canada.
url: www.wellspringpharm.com
Wellspring, USA. Wellspring Pharmaceutical Corp., 9040 Town Center Parkway, Suite 205, Bradenton, FL 34202, USA.
url: www.wellspringpharm.com
Welman, China. Welman Pharmaceutical Co. Ltd, China Guangdong Building 33 A-C, 11 Tianhe Rd, 510075 Guangzhou, China.
url: www.welman.com.cn
Welt, Arg. Lab. Welt S.A.I.C., Tronador 3030/2, 1430 Buenos Aires, Argentina.
Welti, Switz. Dr Heinz Welti AG, Althofstrasse 12, 5432 Neuenhof, Switzerland.
Weltrap, Arg. Lab. Weltrap S.A., Balcarce 1072, 2000 Rosario, Santa Fe, Argentina.
Weluga, Hong Kong. mfh12x; mth1k
Wenchun, China. Wenchun Pharmaceutical Co. Ltd, Mudanjiang, China.
Werfen, Arg. Werfen Medical Argentina SA, Corlos Pellegrini 1141, Buenos Aires, Argentina.
url: www.werfen.com.ar
Wermar, Mex. Wermar Pharmaceuticals SA de CV, Enrique Gonzalez Martinez 200, 6400 Cuauhtemoc Sta. Maria la Ribera, Mexico DF, Mexico.
Wernigerode, Austria. See *Wernigerode, Ger.*
Wernigerode, Cz. See *Wernigerode, Ger.*
Wernigerode, Ger. Pharma Wernigerode GmbH, Dornbergsweg 35, 38855 Wernigerode, Germany.
url: www.pharmawernigerode.de
Wernigerode, Rus. See *Queisser, Rus.*
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Wescrib, Philipp. Wescrib Co, 2 San Diego St, Canumay, Valenzuela City, Philippines.
Wesley, USA. Wesley Pharmacal Inc., 114 Railroad Drive, Ivyland, PA 18974, USA.
West Penetone, Canad. West Penetone Inc., 10900 Secant St, Anjou, Quebec, H1J 1S5, Canada.
West Point, USA. See *Endo, USA.*
Westbrook, UK. See *Croda, UK.*
WestCan, Canad. See *Vita Health, Canad.*
West-Coast, Thai. See *Union Medical, Thai.*
Western Allergy, Canad. Western Allergy Services Ltd, 151 Brunel Rd, Unit 35, Mississauga, Ontario, L4H 2H6, Canada.
Western Medical, USA. Western Medical Supply Inc., USA.
url: www.westernmedicalsupply.com
Westfalen, Ger. Westfalen AG, Industrieweg 43, 48155 Münster, Germany.
Westfalen, Neth. See *Westfalen, Ger.*
Westfield, Philipp. Westfield Pharmaceuticals Inc., Rm 212 Jocfer Bldg, Commonwealth Ave, Diliman, Quezon City, Philippines.
Westlake, USA. Westlake Laboratories Inc., 24700 Center Ridge Rd, Cleveland, OH 44145, USA.
url: www.westlake-labs.com
Westmont, Hong Kong. See *Unam, Hong Kong.*
Westmont, Indon. See *Westmont, Philipp.*
Westmont, Malaysia. See *Unam, Malaysia.*
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Westmont, Singapore. See *Far East, Singapore.*
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Weston, Hong Kong. Weston Pharmaceutical Ltd, Unit 26, 8/F Tower A, Southmark, 11 Yip Hing St, Wong Chuk Hang, Hong Kong.
Westport, USA. Westport Pharmaceuticals, 10 South Broadway, Suite 2000, St Louis, MO 63102, USA.
url: zephrex-d.com
Westward, Philipp. See *B-Phar, Philipp.*
Westward, USA. West-Ward Pharmaceutical Corp., 465 Industrial Way West, Eatontown, NJ 07724, USA.
Westwood, Canad. See *BMS, Canad.*
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Westwood, USA. See *BMS, USA.*
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WH Nutritionals, USA. WH Nutritionals LLC, 1000 N West St, Wilmington, DE 19801, USA.
Whan In, Singapore. See *MD, Singapore.*
Wharton, Philipp. See *Britton, Philipp.*
Whelehan, Irl. Whelehan Group, T.P. Whelehan, 3 Northern Cross Business Park, Finglas, Dublin 11, Ireland.
url: www.tpwhelehan.ie
Whitby, USA. See *UCB, USA.*
White, Canad. White Ophthalmic Services & Supply Co Ltd, 339 50th Ave SE, Calgary, Alberta, T2G 2B3, Canada.
White Swan, China. White Swan Pharmaceutical Co. Ltd, Harbin High-Tech Group, Harbin Development Zone, 2 Tianping Road, Harbin, 150078, China.
url: www.hgk-group.com
Whitehall, Austral. Whitehall Laboratories Australia P/L, Private Mailbag 1, Punchbowl, NSW 2196, Australia.
Whitehall, Belg. See *Wyeth, Belg.*
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Whitehall, Israel. See *Neopharm, Israel.*
Whitehall, Norw. See *Wyeth Lederle, Norw.*
Whitehall, NZ. Whitehall, P.O. Box 12736, Penrose, Auckland, New Zealand.
Whitehall, Pol. See *Wyeth, Pol.*
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Whitehall Consumer, Austral. Whitehall Consumer Healthcare Pty Ltd, 17-19 Solent Circuit, Norwest Business Park, Baulkham Hills, NSW 2153, Australia.
Whitehall Consumer, NZ. See *Whitehall, NZ.*
Whitehall-Robins, Canad. Whitehall-Robins Inc., 5975 Whittle Rd, Mississauga, Ontario, L4Z 3M6, Canada. Director Medical Services
Whitehall-Robins, Mex. See *Wyeth, Mex.*
Whitehall-Robins, Switz. Whitehall-Robins AG, Grafenauweg 10, 6301 Zug 7, Switzerland.
Whitehall-Robins, USA. See *Wyeth Consumer, USA.*
WH-Pharma, Cz. WH-Pharma sro, Kutna Hora, Czech Republic.
WI Pharma, Hung. WI Pharma Kft, Miskolci u 50, 1147 Budapest, Hungary.
Wick, Ger. Wick Pharma Zweigniederlassung der Procter & Gamble GmbH, Sulzbacher Str. 40, 65824 Schwalbach, Germany.
Widatra Bhakti, Indon. Widatra Bhakti PT, Wisma Tugu Raden Saleh 6th Floor, Jln Raden Saleh No 44, 10330 Jakarta, Indonesia.
url: www.widatra.com
Widmer, Austria. Louis Widmer GmbH, Itzlinger Hauptstrasse 34, A-5020 Salzburg, Austria.
Widmer, Belg. Louis Widmer NV, Haverheidelaan 9, 9140 Temse, Belgium.
Widmer, Cz. See *Widmer, Switz.*
Widmer, Fin. Louis Widmer Oy, Sömäisten rantatie 29, 00580 Helsinki, Finland.
Widmer, Ger. Louis Widmer GmbH, Grossmattstr. 11, 79618 Rheinfelden/Baden, Germany.
url: www.louis-widmer.com
Widmer, Neth. See *Widmer, Belg.*
Widmer, Philipp. See *Zuellig, Philipp.*
Widmer, Switz. Dermatologica Widmer, Laboratoires Louis Widmer AG, 8952 Schlieren, Switzerland.
Wiedemann, Ger. Wiedemann Pharma GmbH, Pilotyweg 14, 82541 Münsing, Germany.
url: www.wiedemann-pharma.de
Wierhom, Arg. Wierhom Pharma S.A., Arismendi 2441, 1427 Buenos Aires, Argentina.
Wild, Switz. Dr Wild & Co. AG, Lange Gasse 4, 4002 Basle, Switzerland.
url: www.wild-pharma.com
William, Hong Kong. William Pharm, 801-D Causeway Bay, Commercial Building, 1-5 Sugar St, Causeway Bay, Hong Kong.
Williams, USA. Williams Laboratories Inc., 5 Anngina Drive, Unit B, Enfield, CT 06082, USA.
url: www.williamlabs.com
Willmar, Thai. See *JDH Borneo, Thai.*
Willore, Philipp. Willore Pharma Corp., Unit 1514 Medical Plaza, 25 San Miguel Ave, Ortigas Business Ctr, 1605 Pasig City, Philippines.
Willow, India. Willow Pharmaceuticals Pvt Ltd, SCO 299, 2nd Floor, Panchkula, India.
Will-Pharma, Austria. See *Will-Pharma, Belg.*
Will-Pharma, Belg. Will-Pharma SA, Rue du Manil 80, 1301 Wavre, Belgium.
url: www.willpharma.com
Will-Pharma, Neth. Will-Pharma BV, Wilgenlaan 5, 1161 JK Zwanenburg, Netherlands.
Willpharma, Thai. See *Berli Jucker, Thai.*
Willvonseder, Austria. Willvonseder & Marchesani, Heinrich-v-Buol-Gasse 45, A-1211 Vienna, Austria.
Wilson, NZ. Wilson Consumer Products Ltd, P.O. Box 105-125, Auckland, New Zealand.
url: www.wilson.co.nz
Win Medica, Gr. Win Medica Pharmaceuticals Ltd, Papadiamantopoulou 41, 115 28 Ilissia Athens, Greece.
Windlas, India. Windlas Biotech Ltd, 40/1 Mohabewala Industrial Area, SBI Road, Saharanpur Highway, Dehradun 248 002, India.
url: www.windlasbiotech.com
Windsor, Irl. See *Allphar, Irl.*
Wing Wai, Hong Kong. Wing Wai Trading Co., Unit E, 2/F Freder Ctr, 3 Mok Cheong St, Kowloon, Hong Kong.
Wings, India. Wings Pharmaceuticals Pvt Ltd, J-13, Udyog Nagar Industrial Area, Delhi 110 041, India.
url: www.wingspharma.com
Winguide Huangpu, China. Winguide Huangpu Pharmaceutical Co. Ltd, Shanghai, China.
Win-Medicare, India. Win Medicare Ltd, 1400 Hemkunt Tower, 98 Nehru Place, New Delhi, 110 019
Win-Medicare, Thai. See *Union Medical, Thai.*
Winsome, India. Winsome Laboratories Pvt Ltd, B 257, Naraina Industrial Area, New Delhi 110028, India.
url: www.winsomelabs.com
Winsor, Hong Kong. Winsor & Co., Rm 1707-1707A, Wu Sang House, 655 Nathan Rd, Kowloon, Hong Kong.
Winsunny, China. Winsunny Pharmaceutical Co. Ltd, 8 Kwong Yuen Street East, Tongzhou Industrial Development Zone, Tongzhou District, Beijing 101113, China.
url: www.bjwsyy.com
Wintac, Malaysia. See *Zyfas, Malaysia.*
Wintac, Singapore. See *Zyfas, Singapore.*

Winteam, China. Winteam Pharmaceutical Co. Ltd., 2 Qiaoxi Road, Shunde, Foshan, Guangdong, China.
url: www.winteamgroup.com

Wintech, India. Wintech Pharmaceuticals, 17 Broadway Shopping Centre, Dr. Ambedkar Road, Dadar T.T., Mumbai 400 014, India.
url: www.wintechpharma.com

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Winthrop, Fr. See *Sanofi-Aventis, Fr.*

Winthrop, Ger. Winthrop Arzneimittel GmbH, Industriestr. 10, 82256 Fürstenfeldbruck, Germany.
url: www.winthrop.de

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Winthrop, Turk. Winthrop İlaç AS, Turkey.

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Winzer, Ger. Dr Winzer Pharma GmbH, Brunsbütteler Damm 165-173, 13581 Berlin, Germany.
url: www.drwinzer.de

Wisconsin Pharmacal, UK. See *Wisconsin Pharmacal, USA.*

Wisconsin Pharmacal, USA. Wisconsin Pharmacal Co., 1 Pharmacal Way, Jackson, WI 53037, USA.
url: www.pharmacalway.com

Wise, UK. Wise Pharmaceuticals Ltd, Unit 7, Hani Wells Business Park, Hardicker St, Manchester, M19 2RB, UK.
url: www.wisepharmaceuticals.com

WL, Fin. WL-Medical Oy, Karvaamakuja 4, 00380 Helsinki, Finland.
url: www.wl-medical.fi

WLN, Irl. WLN Trading Ltd, P.O. Box 111, Cavan, County Cavan, Ireland.
url: www.maybebabyovulation.com

WLN, UK. See *WLN, Irl.*

WN, Canad. WN Pharmaceuticals Ltd, 2000 Brigantine Drive, Coquitlam, British Colombia, V3K 7B5, Canada.

Wo Wu, China. Wo Wu Biotechnology Co. Ltd, Zhejiang, China.

Wockhardt, Canad. Wockhardt UK Ltd, 2000 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.

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Wockhardt, India. Wockhardt Ltd, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.
url: www.wockhardtin.com

Wockhardt, Irl. See *Wockhardt, UK.*

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Wockhardt, Pol. See *Wockhardt, UK.*

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Wockhardt, UK. Wockhardt UK Ltd, Ash Rd North, Wrexham Industrial Estate, Wrexham, Clwyd, LL13 9UF, UK.
url: www.wockhardt.co.uk

Wockhardt, Ukr. Wockhardt, Akhmatovai Street, 13, Office 1, Kiev, 02068, Kiev, street., Ukraine.
url: www.wockhardtin.com

Wockhardt, USA. Wockhardt USA LLC, 20 Waterview Blvd, 3rd Floor, Parsippany, NJ 07054
url: www.wockhardtusa.com

Woelm, Ger. See *McNeil, Ger.*

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Woikoski, Fin. Oy Woikoski Ab, Virransalmentie 2023, 52920 Voikoski, Finland.

Wolff, Austria. See *Wolff, Ger.*

Wolff, Cz. See *Hapra, Cz.*

Wolff, Denm. See *Leo, Swed.*

Wolff, Ger. Dr. August Wolff Arzneimittel GmbH & Co. KG, Sudbrackstr. 56, 33611 Bielefeld, Germany.
url: www.wolff-arzneimittel.de

Wolff, Gr. See *Wolff, Ger.*

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Women First, USA. Women First Healthcare Inc., 5355 Mira Sorrento Pl., Suite 700, San Diego, CA 92121, USA.
url: www.womenfirst.com

Womens Capital, USA. See *Barr, USA.*

Womens Choice, USA. Women's Choice Pharmaceuticals, 219 South William Dillard Dr., Building 3-123, Gilbert, AZ 85233, USA.
url: wcpharma.com

Women's Health Institute, USA. See *Wisconsin Pharmacal, USA.*

Woods, Austral. H.W. Woods P/L, P.O. Box 1005, Huntingdale, VIC 3166, Australia.

Woodward, Canad. See *Woodward, USA.*

Woodward, USA. Woodward Laboratories, Inc., 125-B Columbia, Aliso Viejo, CA 92656-1458, USA.
url: www.woodwardlabs.com

Wooridul, Singapore. See *Pharmaforte, Singapore.*

World Foods, UK. World Foods Brand Management Ltd, Unit 7 Decade Close, High Carr Business Park, Newcastle under Lyme, Staffordshire, ST5 7UH, UK.

World Markets, Pol. World Markets Sp. zo.o., ul. Olecka 23, 04-980 Warsaw, Poland.

World Medicine, UK. World Medicine Ltd, 23 The Kilns, Thaxted Rd, Saffron Walden, Essex, CB10 2UQ, UK.
url: www.worldmedicine.co.uk

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World Medico, Canad. World Medico Ltd, 411 Central St, Warman, Saskatchewan, S0K 4S0, Canada.

World Pioneer, Hong Kong. World Pioneer Ltd, Rm 3509 AIA Tower, 183 Electric Rd, North Point, Hong Kong.

Worldwide, Hong Kong. Worldwide Resources Pharmaceutical Ltd, Unit 20-21, 15/F Goldfield Industrial Ctr, 1 Sui Wo Rd, Fotan, Shatin, Hong Kong.

Worth, India. Worth Medicines Pvt Ltd, 921-A Industrial Area, Phase-II, Chandigarh, Indio.

Worwag, Cz. Wörwag Pharma GmbH & Co, Slezská 509, 500 03 Hradec Králové, Czech Republic.
url: www.woerwagpharma.cz

Worwag, Denm. See *Worwag, Ger.*

Worwag, Fin. See *Worwag, Ger.*

Worwag, Ger. Wörwag Pharma GmbH & Co. KG, Calwer Str. 7, 71034 Böblingen, Germany.
url: www.woerwagpharma.de

Worwag, Hong Kong. See *Jacobson, Hong Kong.*

Worwag, Hung. Wörwag Pharma Képviselet, Zöldkő út 9/b, 1025 Budapest, Hungary.

Worwag, Pol. Wörwag Pharma Spółka Komandytowa, Przedstawicielstwo w Polsce, ul. Fasolowa 45 m 43, 02-482 Warsaw, Poland.
url: www.woerwagpharma.pl

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Worwag, Rus. Wörwag Pharma GmbH, Varshavskoe Shosse, 125 ZH, 11 floor, 117545 Moscow a/ya 43, Russia.
url: www.woerwagpharma.ru

Worwag, Ukr. Wörwag Pharma, Degtyarevskaya Street, 62, Kiev, 04112, Ukraine.
url: www.woerwag.de

WP, Ital. WP i-Health Care Products Srl, Viale dei Caduti per la Resistenza 711, 00128 Rome (RM), Italy.
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WPR, Irl. WPR Healthcare Ltd, Unit 10 Ashbourne Business Park, Rath, Ashbourne, Co. Meath, Ireland.

WPU, China. Beijing Peking University WPU Biotech Co. Ltd, Beijing, China.

WR Enterprises, Canad. WR Enterprises Inc., 260 Okangan Ave East, Pentincton, British Columbia, V2A 3J7, Canada.

Wrapsa, S.Afr. Wrapsa Packaging & Manufacturing (Pty) Ltd, P.O. Box 7779, Centurion 0046, South Africa.
url: www.wrapsa.co.za

WraSer, USA. WraSer Pharmaceuticals, 148 Weisenberger Rd, Suite D, Madison, MS 39130, USA.
url: www.wraser.com

Wrigley, USA. Wm. Wrigley Jr. Co., P.O. Box 3900, Peoria, IL 61614, USA.
url: www.wrigley.com

Wu Ji, China. Wu Ji Pharmaceutical Co. Ltd, Zhangzhou, China.

Wu Zhou Tong, China. Wu Zhou Tong Pharmaceutical Co Ltd, China.

Wufeng, China. Wufeng Pharmaceutical Factory, Hangzhou, China.

Wuhan, China. Wuhan Biochemistry Laboratories, Wuhan Donghu New Technology Development Zone, Miaoshan, Wuhan, 430223, China.

Wuhan, Philipp. See *2 World Traders, Philipp.*

Wuhan Institute, China. Wuhan Institute of Biological Products, Wuhan, China.

Wuhan Wujing, China. Wuhan Wujing Medicine Co Ltd, 1 King Road, Xin Bridge Tech Industrial Park, East & West Lakes Jinyinhu, Wuhan City 430040, China.

Wunderpharm, Arg. Laboratorio Wunderpharm S.R.L., Remedios 5322, 1440 Buenos Aires, Argentina.

Wushi, China. Wushi Pharmaceutical Co. Ltd, Hubei, China.

Wusuli Jiang, China. Wusuli Jiang Pharmaceutical Co. Ltd, Heilongjiang, China.

Wuxi No 7, China. Wuxi No 7 Pharmaceutical Co. Ltd, Fangqiao, Xuelang, Taihu, Wuxi, Jiangsu, 214125, China.

Wuzhong, China. Wuzhong Biopharmaceutical Co. Ltd, Room 7-8 9/F Bank of China, 110 Dongwu North Road, Suzhou, Jiangsu, 215128, China.
url: www.wzyy.cn

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Wyeth, Arg. See *Wyeth-Whitehall, Arg.*

Wyeth, Austral. Wyeth Pharmaceuticals, Division of Wyeth Australia P/L, Locked Bag 5002, Baulkham Hills BC, NSW 2153, Australia.
url: www.wyeth.com.au

Wyeth, Austria. See *Pfizer, Austria.*

Wyeth, Belg. Wyeth, Division of AHP Pharma, Parc Scientifique Einstein, Rue du Bosquet 15, 1348 Louvain-la-Neuve, Belgium.
url: www.wyeth.be

Wyeth, Braz. Laboratórios Wyeth-Whitehall Ltda, Rua Alexandre Dumas 2200, 5th Floor, 04717-004 São Paulo, SP, Brazil.
url: www.wyeth.com.br

Wyeth, Canad. Wyeth Canada, 1025 Marcel Lourin Blvd, St-Laurent, Quebec, H4R 1J6, Canada.
url: www.wyeth.com

Wyeth, Chile. Laboratorios Wyeth Inc., Los Tres Antonios 2526, Santiago, Chile.

Wyeth, Cz. Wyeth Whitehall Czech sro, Novadvorská 994, 142 21 Prague 4, Czech Republic.

Wyeth, Denm. Wyeth Denmark, Produktionsvej 12, 2600 Glostrup, Denmark.
url: www.wyeth.dk

Wyeth, Fin. Wyeth, Rajatorpantie 41 C, 01640 Vantaa, Finland.
url: www.wyeth.fi

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Wyeth, Gr. Wyeth Hellas, 126 Kyprou Ave, 164 52 Argyroupolis, Greece.
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Wyeth, Hong Kong. Wyeth (Hong Kong) Ltd, 22/F Oxford House, 979 King's Rd, Taikoo Place, Island East, Hong Kong.

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Wyeth, India. RBC, Mahindra Towers, 4th Floor, Dr. G. M. Bhosale Road, Mumbai 400 018, India.
url: www.wyethindia.com

Wyeth, Indon. Wyeth Indonesia PT, Graha Paramita 12/F, Jl Denpasar Blok D No 2, 12920 Jakarta, DKI Jaya, Indonesia.

Wyeth, Irl. Wyeth Laboratories Ltd, M50 Business Park, Ballymount Road Upper, Walkinstown, Dublin 12, Ireland.
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Wyeth, Israel. See *Dexxon, Israel* and *Neopharm, Israel.*

Wyeth, Malaysia. Wyeth (Malaysia) Sdn Bhd, 701-901 Block C (Menara Glomac), Kelana Business Centre, 97 Jln SS 7/2, Kelana Jaya, 47301 Petaling Jaya, Selangor, Malaysia.
url: www.wyeth.com

Wyeth, Mex. Wyeth S.A. de C.V., Avenida 1 de mayo No. 127, Col. San Andres Atoto, 53500 Naucalpan, Mexico.
url: www.wyeth.com

Wyeth, Neth. Wyeth Pharmaceuticals BV, Planetenweg 99, 2132 HL Hoofddorp, Netherlands.
url: www.wyeth.nl

Wyeth, Norw. Wyeth, Drammensv. 145 B, 0213 Oslo, Norway.
url: www.wyeth.no

Wyeth, NZ. Wyeth (NZ) Ltd, Level 1, 15 Vestey Drive, Mount Wellington, Auckland, New Zealand.
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Wyeth, Philipp. Wyeth Philippines Inc., 2236 Don Chino Roces Ave, Makati City, Philippines.

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Wyeth, Rus. Wyeth, Voroncovskaja ul. d. 17, 109147 Moscow, Russia.

Wyeth, S.Afr. Wyeth South Africa (Pty) Ltd, Thornhill Office Park, 94 Bekker Rd, Vorna Valley Ext. 60, Midrand 1685, South Africa.
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Wyeth, Singapore. Wyeth (S) Pte Ltd, 111 Somerset Rd, 11-01 Singapore Power Building, S 238164, Singapore.
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Wyeth, Spain. Wyeth Orfi, Ctra Burgos, Km-23, Desvio Algete Km, 1, San Sebastian de los Reyes, 28070 Madrid, Spain.
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Wyeth, Thai. Wyeth (Thailand) Ltd, 23 Fl Silom Complex Bldg, 191 Silom Rd, Silom, Bangrak, Bangkok 10500, Thailand.

Wyeth, Turk. Wyeth İlaçları A.Ş., Büyükdere Cad., Maya Akar Center No: 100/102 K: 9, Esentepe, İstanbul, 80280, Turkey.
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Wyeth, UK. Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 0PH, UK.
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Wyeth, USA. Wyeth Laboratories, 500 Arcola Rd, Collegeville, PA 19426, USA.
url: www.wyeth.com

Wyeth, Venez. Laboratorios Wyeth S.A., Av. Río Caura, Centro Empresarial Torre Humboldt, Piso 21, Prados del Este, Caracas 1080, Venezuela.
url: www.wyeth.com

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Wyeth Consumer, Canad. Wyeth Consumer Healthcare Inc., 5975 Whittle Rd, Mississauga, Ontario, L4Z 3M6, Canada.

Wyeth Consumer, Chile. Wyeth Consumer Healthcare, Del Inca 4446, Of. 201, Las Condes, Santiago, Chile.

Wyeth Consumer, Hong Kong. Wyeth (Hong Kong) Ltd Consumer Healthcare, Rm 1401-1404, 14/F CC Wu Bldg, 302-308 Hennessy Rd, Wanchai, Hong Kong.

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Wyeth Consumer, Ital. Wyeth Consumer Healthcare S.p.A., Via G. Puccini 3, 20121 Milan (MI), Italy.
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url: www.wyeth.com

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Wyeth Lederle, Austria. Wyeth-Lederle Pharma GmbH, Storchengasse 1, A-1150 Vienna, Austria.
url: www.wyeth.at

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Wyeth Lederle, Fr. Wyeth-Lederle, Le Wilson 2, 80 av du Général-de-Gaulle, Puteaux, 92031 Paris-La Défense cdx, France.
url: www.wyeth.com

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Wyeth Lederle, Ital. Wyeth Lederle S.p.A., Via Nettunense 90, 04011 Aprilia (LT), Italy.
url: www.wyethlederle.it

Wyeth Lederle, Jpn. Wyeth Lederle Japan Ltd, Hattori Bldg, 5th Floor, 1-10-3 Kyobashi, Chuo-ku, Tokyo 104-0031, Japan.
url: www.wlj.co.jp

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Wyeth Lederle, Norw. Wyeth Lederle Norge, P.O. Box 313, Skøyen, 0213 Oslo, Norway.
url: www.wyeth.no

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Wyeth Lederle, Port. Wyeth Lederle Portugal (Farma), Lda, Rua Dr António Loureiro Borges 2, Arquiparque-Miraflores, 1495-131 Algés, Portugal.
url: www.wyeth.pt

Wyeth Lederle, Swed. Wyeth Lederle Nordiska AB, Box 1822, 171 24 Solna, Sweden.
url: www.wyeth.se

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Wyeth-Ayerst, Israel. See *Dexxon, Israel* and *Neopharm, Israel.*

Wyeth-Ayerst, Thai. Wyeth-Ayerst (Thailand) Ltd, 23 Fl, Silom Complex Building, 191 Silom Rd, Bangkok 10500, Thailand.
url: www.wyeth.com

Wyeth-Ayerst, USA. See *Wyeth, USA.*

Wyeth-Whitehall, Arg. Wyeth-Whitehall S.A., Ing. Enrique Butty 275, 1001 Buenos Aires, Argentina.
url: www.wyeth.com

Wynlit, Irl. See *Wynlit, UK.*

Wynlit, UK. Wynlit Laboratories Ltd, 153 Furzehill Rd, Boreham Wood, Hertfordshire, WD6 2DR, UK.

Wynn, Port. Wynn Industrial Pharma SA, Office Park de Belloura, Edificio 4, 2710-444 Sintra, Portugal.

Wyvern, UK. Wyvern Medical Ltd, P.O. Box 17, Ledbury, Herefordshire, HR8 2ES, UK.
url: www.wyvernmedical.co.uk

X Pharma, Hung. X Pharma Kft, Csoka u 20, 2006 Szentendre, Hungary.

Xactdose, USA. See *Alpharma, USA.*

Xanodyne, USA. Xanodyne Pharmaceuticals Inc., 400 Valley Rd, Suite 303, Mount Arlington, NJ 07856, USA.
url: www.xanodyne.com

Xcel, USA. See *Valeant, USA.*

Xediton, Canad. Xediton Pharmaceuticals Inc., 1215b North Service Rd West, Oakville, Ontario, L6M 2W2, Canada.

Xeno, Philipp. Xeno Pharmaceuticals Phils Inc., 14/F Pryce Ctr, 1179 Chino Roces Ave, Makati City, Philippines.
url: www.xenopharms.com

Xeolas, Denm. See *Arrow, Denm.*

Xeolas, Fin. See *Xeolas, Irl.*

Xeolas, Irl. Xeolas Pharmaceuticals Ltd, 97 Furry Park Rd, Killester, Dublin 5, Ireland.

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Xepa-Soul Pattinson, Hong Kong. See *Tack Fung, Hong Kong.*

Xepa-Soul Pattinson, Malaysia. Xepa-Soul Pattinson (M) Sdn Bhd, 1-5 Cheng Industrial Estate, 75250 Melaka, Malaysia.
url: www.xepasoul.com

Xepa-Soul Pattinson, Singapore. See *Grafton, Singapore.*

Xepol, Swed. Xepol AB, Engelbrekts kyrkogata 7 B, 114 26 Stockholm, Sweden.
url: www.xepol.se

Xeragen, S.Afr. See *Firstpharm, S.Afr.*

X-Gen, USA. X-Gen Pharmaceuticals Inc., P.O. Box 445, Big Flats, NY 14814, USA.
url: www.x-gen.us

Xi Cheng, China. Xi Cheng Pharmaceutical Co Ltd, China.

Xia Du, China. Xia Du Pharmaceutical Co. Ltd, China.

Xian Feng, China. Xian Feng Pharmaceutical Co. Ltd, Hainan, China.

Xian Jiaoda, China. Xi'an Jiaoda Pharmaceutical Group, 21 Xinxi Avenue, Xinxing Industrial Park, Gaoxin, Xian, Shaanxi, 710119, China.

Xiang Rui, China. Xiang Rui Biological Products Co. Ltd, Beijing, China.

Xiang Yang, China. Xiang Yang Pharmaceutical Co. Ltd, 52400 Zhanjiang, Guangdong Province, China.

Xiangju, China. Shaanxi Xiangju Pharmaceutical Co. Ltd, Xiangju Road, Shangluo, Shaanxi, 726000, China.
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Xiangyu, China. Xiangyu Pharmaceutical Co. Ltd, Shandong, China.

Xian-Janssen, China. Xian-Janssen Pharmaceutical Co. Ltd, China Central Place 14th Floor, Tower 3, 77 Jian Guo Rd, Chaoyang District, Beijing 100025, China.
url: www.xian-janssen.com.cn

Xianju, China. Xianju Pharmaceutical Co. Ltd, Wenyi 40, Hangzhou, Zhejiang, China.
url: www.xjpharma.com

Xianqiang, China. Xianqiang Pharmaceutical Co. Ltd, 6 Gongye Ave, Economic Tecnology Development Zone, Taipi, Conghua, Guangdong, 510900, China.

Xianzhen, China. Xianzhen Pharmaceutical Co. Ltd, 42 Xingsheng South Rd, Anshan, Liaoning, 114014, China.
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Xibaishou, China. Xibaishou Pharmaceutical Co. Ltd, China.

Xidian, China. Xidian Pharmaceutical Technology Development Co. Ltd, Jilin, China.

Xiehe, China. Xiehe Pharmaceutical Group, 1 Yinhe Road, Huiji, Zhengzhou, Henan, China.
url: www.zzxh.cn

Xieli, China. Xieli Pharmaceutical Co. Ltd, Room 608 Building D, Hi-tech International Plaza, 186 Tianyun Road, Chengdu, Sichuan, 610041, China.
url: www.xielipharm.com

Xieon, India. Xieon Life Sciences Pvt Ltd, 171, Sector 3 HSIDC, Karnal 132 001, India.
url: www.xieonlife.com

Xili, China. Xili Pharmaceutical Co. Ltd, Shandong, China.

Ximena Polanco, Chile. Laboratorio Ximena Polanco, Dresden 4640, Santiago, Chile.

Xin Bang, China. Xin Bang Pharmaceutical Co. Ltd, Guizhou, China.

Xin Donggang, China. Zhejiang Donggang Pharmaceutical Co., Ltd., 259 Binghai Rd, Yantou Industrial Park, Jiangjiang, Taizhou, Zhejiang, 318000, China.

Xin Gang Union, China. Xin Gang Union Pharmaceutical Co. Ltd, Shenzhen, China.

Xin Ma, China. Xin Ma Pharmaceutical Co. Ltd, Shenyang, China.

Xin Si Dun, China. Xin Si Dun Pharmaceutical Co. Ltd, Sichuan, China.

Xinan, China. Xinan Pharmaceutical Co. Ltd, Hainan, China.

Xinbai, China. Xinbai Pharmaceutical Co. Ltd., Nanjing Economic and Technological Development Zone, 68 Xingang Road, Nanjing, Jiangsu, 210038, China.
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Xinbao, China. Xinbao Pharmaceutical Co. Ltd, Suzhou, Jiangsu, China.

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Xincat, China. Xincat Pharmaceutical Co Ltd, High-Tech Zone, 1st Lutai Ave, Shandong Zibo 255087, China.
url: www.xincat.com.cn

Xinchang, China. Xinchang Pharmaceutical Co. Ltd, 98 Xinchang Road, Chengguan, Xinchang, Zhejiang, 312500, China.
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Xindazhou, China. Xindazhou Pharmaceutical Co. Ltd, Xindazhou Industrial Village, Meilan District, Haikou, Hainan, 571127, China.

Xing Qi, China. Xing Qi Pharmaceutical Co., Ltd, A4 Street 12, No. 3 Shenyang Economic and Technological Development Zone, Shenyang City, Liaoning, China.

Xing Qun, China. Xing Qun Pharmaceutical Co. Ltd, Guangzhou, China.

Xing Tai, Hong Kong. See *Four Star, Hong Kong* and *Sino-Asia, Hong Kong.*

Xing'an, China. Xing'an Pharmaceutical Co. Ltd, Nanshaolin Development Zone, Xitanwei, Licheng, Putian, Fujian, 351131, China.

Xinganjiang, China. Xinganjiang Pharmaceutical Co. Ltd, Shanghang North Gate, Ji'an, Jiangxi, 343000, China.
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Xingao, China. Xingao Pharmaceutical Co. Ltd, Chengdu, China.

Xinghu, China. Xinghu Bioscience Co. Ltd, Zhaoqing, Guangdong, China.

Xinghua, China. Xinghua Pharmaceutical Co. Ltd, Shaanxi, China.

Xinghui, China. Xinghui Pharmaceutical Co. Ltd, China.

Xinglin Baima, China. Xinglin Baima Pharmaceutical Co. Ltd, Jiangxi, China.

Xingsha, China. Xingsha Pharmacueticals Co. Ltd, 36 Mei Road, Haichang, Xiamen
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url: www.xhzy.com

Xinhuada, China. Xinhuada Pharmaceutical Co. Ltd, Yueyang, China.

Xinjiang, China. Xinjiang Pharmaceutical Co. Ltd, China.

Xinlibang, China. Xinlibang Pharmaceutical Co. Ltd, Chengdu, China.

Xinpeng, China. Xinpeng Pharmaceutical Co. Ltd, Shenzhen, China.

XinShiDai, China. XinShiDai Pharmaceutical Co. Ltd, 1 North Outer Ring Rd, Fei County, Shandong 273400, China.

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Xinzhongzheng, China. Xinzhongzheng Pharmaceutical Co. Ltd, Hainan, China.

Xiuzheng, China. Xiuzheng Pharmaceutical Co. Ltd, 66 Xiuzheng Rd, Liuhe, Jilin, 135300, China.
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Xoma, USA. Xoma (USA) LLC, 2910 Seventh St, Berkeley, CA 94710, USA.
url: www.xoma.com

Xspire, USA. Xspire Pharma, 121 Marketridge Drive, Ridgeland, MS 39157-6027, USA.
url: xspirerx.com

Xttrium, USA. Xttrium Laboratories Inc., 415 West Pershing Rd, Chicago, IL 60609, USA.
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Xudang Haipu, China. Xudang Haipu Pharmaceutical Co Ltd, 879 Shanghai Rd, Pudong, Jinqiao, Shanghai 201206, China.

Xuebao, China. Xuebao Pharmaceutical Co., Ltd., 8 Dongmen Flyover, Jiangyin, Jiangsu province, China.
url: www.xuebao.com.cn

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Ya Bao, China. Ya Bao Pharmaceutical Group Co Ltd, Sichuan, China.

Yabang, China. Yabang Pharma Group, 1 Yabang Zhong Rd, Changzhou, Jiangsu, 213163, China.
url: www.yabang.biz

Yabang Qiangsheng, China. See *Yabang, China.*

Yabo, China. Yabo Pharmaceutical Co. Ltd, China.

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Yacca, India. Yacca Pharmaceuticals Pvt Ltd, 11th Km. Stone, Dehradun Road, Roorkee, Uttrakhand 247 667, India.

Yada, China. Yada Pharmaceutical Co. Ltd, Hunan, China.

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Yafeng, China. Yafeng Pharmaceutical Co. Ltd, 68 Jinqu Rd, Wucheng, Jinhua, Zhejiang, 321017, China.

Yake, China. Yake Pharmaceutical Co. Ltd, Zhejiang, China.

Yakult, Jpn. Yakult Honsha Co., Ltd, 1-19 Higashi Shimbashi 1-chome, Minato-ku, Tokyo, Japan.
url: www.yakult.co.jp

Yalacta, Fr. Laboratoires Yalacta, 97 rue du Général Moulin, 14050 Caen cdx, France.

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url: www.yamanouchi.com

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Yamanouchi, Port. Yamanouchi Farma, Lda, Edificio Cinema, RuaJosé Fontana, no 1, 2770-101 Paço de Arcos, Portugal.
url: www.yamanouchi-eu.com

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Yandi, China. Yandi Biological Engineering Co. Ltd, Hunan, China.

Yang Jiang, China. Yang Jiang Pharmaceutical Co. Ltd, Guangdong, China.

Yang Zhou, China. Yang Zhou Pharmaceutical Co. Ltd, 7 South Wenfeng Rd, 225009 Yangzhou, Jiangsu, China.

Yangling Huasheng, China. Yangling Huasheng Biopharmaceutical Co. Ltd, China.

Yangshengtang, China. Yangshengtang Pharmaceutical Co. Ltd, Hainan, China.

Yangtian, China. Yangtian Pharmaceutical Co. Ltd., 8 Xin Da Road, Gaoxin West, Chengdu, Sichuan, 611731, China.
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Yanjing, China. Yanjing Pharmaceutical Co. Ltd, Beijing, China.

Yanshen, China. Yanshen Biotechnology Co. Ltd, China Innovation Tech. Building, Hi-Tech Park, Changzhou, Jiangsu, China.

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Yaoda, China. Shenyang Yaoda Pharmaceutical Co. Ltd, 103 Wenhua River Rd, Shenyang, Liaoning, 110016, China.
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Yash, India. Yash Pharma Laboratories Pvt Ltd, 14 Ruby House, L.J. Road, Mahim (W), Mumbai 400 016, India.
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Yasoo, USA. Yasoo Health, P.O. Box 3608, Johnson City, TN 37602, USA.
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Yatai, China. Yatai Pjarmaceutical Co. Ltd, 1152 Yunji Road, Shaoxing, Zhejiang, 312030, China.
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Yawei, China. Dalian Yawei Pharmaceutical Co., Ltd., 1 Shenming Rd, Jinzhou, Dalian, Liaoning, China.

Yazhou, China. Yazhou Pharmaceutical Co. Ltd, Dongguan, China.

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Yerba, USA. Yerba Prima, 740 jefferson Ave, Ashland, Oregon, 97520-3743, USA.

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Yi Chuang, China. Yi Chuang Pharmaceutical Co. Ltd, Dandong, China.

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Yier, China. Yier Pharamceutical Co. Ltd, Hainan, China.

Yige, China. Yige Pharmaceutical Co. Ltd., 1689 North Second Ring Road, Xiangtan, Hunan, China.
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Yik Kwan, Hong Kong. Yik Kwan Pharmaceuticals Co. Ltd, Flat A10, 6/F Merit Industrial Ctr, 94 To Kwa Wan Rd, Kowloon, Hong Kong.

Yimin, China. Beijing Yimin Pharmaceutical Co. Ltd., 14 Guangming Street, Shunyi, Beijing, 101300, China.
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Yiqiao, China. Yiqiao Pharmaceutical Co Ltd, 7 Riverside Road West, Hunan 415500, China.

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Yongguang, China. Yongguang Pharmaceutical Co., Ltd, 16 Yanchang Rd, Sanhe, Hebei, China.

Yongli, China. Yongli Pharmaceutical Co. Ltd, 42-2 Weiguo Lu, Badaojiang Qu, Baishan, Jilin, 134300, China.

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Yu Heng, China. Yu Heng Pharmaceutical Co. Ltd, Harbin, China.

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YuanCe, China. YuanCe Pharmaceutical Co. Ltd, Beijing, China.

Yuanlijian, China. Yuanlijian Pharmaceutical Co. Ltd., Floor 22 Union Bank East Building, 887 Jiangcheng Road, Hangzhou, Zhejiang, 310009, China.

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Zambon, Fr. Laboratoires Zambon France, 13 rue René-Jaques, 92138 Issy-les-Moulineaux, France.
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Zaozhuang, China. Zaozhuang Pharmaceutical Co. Ltd, 18 Songshan Rd, New & High Technological Development Zone, Zaozhuang, Shandong, 277000, China.
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url: www.yzzbzy.com
Zhong Hao, China. See *Haohua, China.*
Zhong Hua, China. Zhong Hua, Shanghai, China.
Zhong Sheng, China. Zhong Sheng Pharmaceutical Co. Ltd, Guangdong, China.
Zhong Xiang Kang Shen, China. Zhong Xiang Kang Shen Pharmaceutical Group Co Ltd, China.
Zhong Yi, China. Zhong Yi Pharmaceutical Co. Ltd, Zhejiang, China.
Zhongdan, China. Zhongdan Pharmaceutical Co. Ltd, Jiangsu, China.
Zhongguan, China. Zhongguan Pharmaceutical Co. Ltd, 6 XiYuan ZiEr St, Chongwen, Beijing, China.
Zhonggui, China. Zhonggui Pharmaceutical Co. Ltd, Heilongjiang, China.
Zhonghai, China. Zhonghai Pharmaceutical Co. Ltd, Shanghai, China.
Zhonghe, China. Zhonghe Pharmaceutical Co. Ltd., 168 Nanhai Avenue, Haikou, Hainan, China.
url: www.zhonghe.cn
Zhonghui, China. Zhonghui Pharmaceutical Co. Ltd, Shuanggou, Jiangdou, Yangzhou, Jiangsu, 225200, China.
Zhongjia, China. Zhongjia Pharmaceutical Co. Ltd, Hubei, China.
Zhongkai, China. See *Wuzhong, China.*
Zhongke Yuan, China. Zhongke Yuan Instituite of Medical Biology, China.
Zhonglian, China. Zhonglian Pharmaceutical Co. Ltd, 704 Pengji Industrial Zone, Luohu, Shenzhen, Guangdong, 518004, China.
ZhongNuo, China. ZhongNuo Pharmaceutical Co. Ltd, 47 Harvest Rd, Shijiazhuang City 050041, China.
Zhongqi, China. Zhongqi Biopharmaceutical Co. Ltd, Zhejiang, China.
Zhongrui Kangzhi, China. See *Honz, China.*
Zhongsheng Haitian, China. Zhongsheng Haitian Pharmaceutical Co. Ltd., 42/F Jinhuang Building, 20 Nanjing Road, Hexi, Tianjin, 300042, China.
Zhongshi, China. Zhongshi Pharmaceutical Co. Ltd, Weifang, China.
Zhongtai, China. Zhongtai Pharmaceutical Co. Ltd, Henan, China.
ZhongTian, China. ZhongTian Pharmaceutical Co. Ltd, Taizhou, China.
ZhongXi, China. ZhongXi Pharmaceutical Co. Ltd, 446 Waiqingsong Rd, Jiading District, Shanghai 201806, China.
url: www.zhongxi.com.cn
Zhongxin, China. Zhongxin Pharmaceutical Co. Ltd, Beijing, China.
Zhongxing Hanfang, China. Zhongxing Hanfang Pharmaceutical Co. Ltd., 8th Floor Garden technology Building, 281 Fuzhou Road, Donghu, Nanchang, Jiangxi, 330002, China.
Zhongyuanwei, China. Zhongyuanwei Pharmaceutical Co. Ltd, Shanxi, China.
Zhuhai, Philipp. See *Global Pharmatrade, Philipp.*
Zhuoyikangna, China. Zhuoyikangna Pharmaceutical Co. Ltd, 7-1 Xiamen St, Fengmanqu, Jilin, 132013, China.
url: www.jlzykn.com
Zhytomyr, Ukr. Zhytomyr Ltd, ul. Lermontov 5, 10014 Zhytomyr, Ukraine.
url: vishpha.ua
Zi Fu, China. Zi Fu Pharmaceutical Co. Ltd, Shenzhen, China.
Ziaja, Pol. Ziaja Ltd Zakład Produkcji Leków Sp. zo.o., ul. Jesienna 9, 80-298 Gdańsk, Poland.
url: www.ziaja.com
Zicam, Canad. See *Zicam, USA.*
Zicam, USA. Zicam LLC, 8515 E Anderson Drive, Scottsdale, AZ 85255, USA.
Zichuan, China. Zichuan Pharamceutical Co. Ltd, Shandong, China.
Ziguanggu Hannanyue, China. Ziguanggu Hannanyue Pharmaceutical Co. Ltd, Hunan, China.
Zihua, China. Zihua Pharmaceutical Co. Ltd, Quanzhou, Fujian, China.
Zila, Gr. See *Zila, UK.*
Zila, Neth. See *Zila, UK.*
Zila, Philipp. Zila, Philippines.
Zila, Port. See *Zila, UK.*
Zila, UK. Zila Ltd, Thames House, Wellington St, London, SE18 6NZ, UK.
Zila, USA. Zila Inc., 5227 N. 7th St., Phoenix, AZ 85014-2817, USA.
url: www.zila.com
Zilly, Ger. Fritz Zilly GmbH, Eckbergstr. 18, 76534 Baden-Baden, Germany.
Zim, Philipp. See *Ambica, Philipp.*
Zimaia, Port. Laboratório Zimaia, SA, Rua de Andaluz 38, 1050-006 Lisbon, Portugal.
Zimalaya, India. Zimalaya Drugs Pvt Ltd, 14C Chander Nagar AB Rd, Gandhi Nagar, Near Church, Par Nawada, Nawada, 805 110, India.
Zinnia, India. Zinnia Life Sciences, 122 Vinayaga Layout, Maranhalli, Vijayanagar, Bangalore 560 040, India.
Zio, Rus. See *Actavis, Rus* and *Anvi, Rus.*
Ziololek, Pol. Przedsiębiorstwo Farmaceutyczne Ziołołek Sp. zo.o., ul. Pamiątkowa 5, 61-512 Poznań, Poland.
url: www.ziololek.com.pl
Zitonggong, China. Zitonggong Pharmaceutical Co. Ltd, Sichuan, China.
Ziwell, Malaysia. Ziwell Mediacl Sdn Bhd, Lot A2-14, PJ Industrial Park, Seksyen 13, Jln Kemajuan, 46200 Petaling Jaya, Selangor, Malaysia.
Ziwell, Singapore. Ziwell Medical (S) Pte Ltd, 1 Ubi Crescent, 05-03 Number One Building, S 408563, Singapore.
Zizhu, China. Zizhu Pharmaceutical Co. Ltd, 27 Chaoyang North Rd, Beijing, 100024, China.
url: www.zizhu-pharm.com.cn
Zizine, Fr. Laboratoire Zizine, 69 rue de Wattignies, B.P. 500 18, 75560 Paris cdx 12, France.
url: www.atozizine.com
ZLB, Austria. ZLB Behring GmbH, Altmannsdorfer Strasse 104, A-1121 Vienna, Austria.
ZLB, Belg. ZLB Behring NV, Technologielaan 13, 3001 Leuven, Belgium.
url: www.zlbbehring.com
ZLB, Braz. ZLB Behring Com. de Prods Farmaceuticos Ltda, Rua Prof. Haidée Silva Martins 510, 04693030 São Paolo, Brazil.
ZLB, Denm. See *CSL, Denm.*
ZLB, Fin. See *Veripalvelu, Fin.*
ZLB, Ger. See *CSL, Ger.*
ZLB, Gr. ZLB Behring, Michalakopoulou 35, 115 28 Athens, Greece.
url: www.zlbbehring.com
ZLB, Indon. See *Dexa, Indon.*
ZLB, Ital. See *CSL, Ital.*
ZLB, Neth. See *CSL, Ger.*
ZLB, Norw. See *ZLB, Swed.*
ZLB, Spain. ZLB Behring, Via Augusta 252-260, 08017 Barcelona, Spain.
url: www.zlbbehring.es
ZLB, Swed. ZLB Behring AB, Berga Backe 2, 182 17 Danderyd, Sweden.
url: www.zlbbehring.se

ZLB, Switz. ZLB Behring AG, Wankdorfstrasse 10, 3000 Berne 22, Switzerland.
url: www.zlbbehring.com

ZLB, UK. ZLB Behring UK Ltd, Breckland House, St Nicholas St, Thetford, Norfolk, IP24 1BT, UK.
url: www.zlb.com

ZLB, USA. See *CSL, USA.*

ZLB Behring, Hong Kong. ZLB Behring, Unit 1206-1208, 12/F K Wah Ctr, 191 Java Rd, North Point, Hong Kong.

ZLB Behring, Philipp. See *Zuellig, Philipp.*

Zodak, India. Zodak, S.C.O. No 96 1st Floor, Sector-5, Near Vatika, Panchkula 134 112, India.

Zodiac, Braz. Zodiac Prods. Farms. S.A., Rua Venancio Aires 417, 05024-030 São Paulo, SP, Brazil.

Zodley, India. See *Daksh, India.*

Zoe Nissi, Singapore. Zoe Nissi Pte Ltd, Cisco Center II, 20 Jalan Affi 06-01, S-409179, Singapore.
url: www.obagi.sg

Zogenix, USA. Zogenix Inc., 12671 High Bluff Drive, Suite 200, San Diego, CA 92130, USA.
url: www.zogenix.com

Zoja, Hong Kong. See *Deutsch Chinesische, Hong Kong.*

Zoki, Thai. See *Asian TJD, Thai.*

Zorka, Rus. See *Hemofarm, Rus.*

Zota, India. Zota Healthcare Pvt Ltd, Zota House, 2/896 Hira-Modi St, Sagrampura, Surat, 395 002, India.
url: www.zotahealthcare.com

Zubit, India. Zubit Lifecare, Cubit House 13/369/1, Panchratna Estate, Changodar, Ahmedabad, India.
url: zubitlifecare.com

Zuellig, Hong Kong. Zuellig Pharma Ltd, Suite 608, 6/F, Devon House, Taikoo Place, Quarry Bay, Hong Kong.
url: www.zuelligpharma.com

Zuellig, Malaysia. Zuellig Pharma Sdn Bhd, Level 3A, No 10, Jln Bersatu 13/4, 46200 Petaling Jaya, Selangor, Malaysia.
url: www.zuelligpharma.com

Zuellig, NZ. Zuellig Pharma, 316-318 Richmond Road, Grey Lynn, Auckland, New Zealand.
url: www.zuelligpharma.com

Zuellig, Philipp. Zuellig Pharma Corp., Km 14 West Service Rd, South Superhighway cor, Edison Ave, Parañaque City, Philippines.

Zuellig, Singapore. Zuellig Pharma Pte Ltd, 15 Changi North Way, 01-01, S 498770, Singapore.
url: www.zuelligpharma.com

Zuellig, Thai. Zuellig Pharma Ltd, 8-9 Ploenchit Center, 2 Sukhumvit Rd, Kwang Klongtoey, Khet Klongtoey, Bangkok 10110, Thailand.
url: www.zuelligpharma.com

Zuiko, Philipp. See *Kramer, Philipp.*

Zuo Li, China. Zuo Li Pharmaceutical Co. Ltd, Zhejiang, China.

Zuoz, Venez. Zuoz Pharma S.A., Esquina Puente Restaurador a Río, Av. Oeste 20, Santa Teresa, Caracas, Venezuela.
url: www.zuozpharma.com.ve

Zuoz Innothera, Venez. See *Zuoz, Venez.*

Zuoz Solvay, Venez. See *Zuoz, Venez.*

Zurego, UK. Zurego Ltd, P.O. Box 275, Stockport, SK7 0DG, UK.
url: www.spotner.co.uk

Zurita, Braz. Zurita Laboratório Farmacêutico Ltda, Rua Domingos Graziano 104, 13600-000 Araras, SP, Brazil.
url: www.zurita.com.br

Zuventus, India. Zuventus Healthcare Ltd, 3101-3108, Building 3C Oberoi Garden Estate, Chandivili, Andheri (E), Mumbai 400 072, India.

Zwintscher, Ger. See *Naturarzneimittel, Ger.*

Zwitter, Gr. Zwitter, L Pentelis 34-36, 152 34 Chalandri, Greece.

Zyber, USA. Zyber Pharmaceuticals, P.O. Box 40, Gonzales, LA 70707-0040, USA.
url: www.zyberphar.com

Zydus, Braz. Zydus Healthcare Brasil Ltda, Alameda Jaú 1905 Conj. 41 e 47, 1420002 São Paulo, Brazil.

Zydus, Fr. Zydus France, 25 rue des Peupliers, 92000 Nanterre, France.

Zydus, India. Zydus Cadila Healthcare Ltd, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, India.
url: www.zyduscadila.com

Zydus, Philipp. Zydus Philippines Inc., Unit 603 Don Tim Bldg, 5438 Pres Osmena Highway, Makati City, Philippines.

Zydus, S.Afr. Zydus Healthcare SA (Pty) Ltd, Adrina Building 1st Floor, 32-34 Klinkenberg St, Potchefstroom, 2351, South Africa.

Zydus Cadila, Philipp. See *Zydus, Philipp.*

Zydus Cadila, Singapore. See *Zyfas, Singapore.*

Zydus Cadila, Thai. See *Pharmaland, Thai.*

Zyfas, Malaysia. The Zyfas Medical Co., 7 Jln Molek 3/10, Taman Molek, 81100 Johor Bahru, Johor, Malaysia.

Zyfas, Singapore. Zyfas Medical Co, 102E Pasir Panjang Rd, 02-10/11 Citilink Warehouse Complex, S 118529, Singapore.

Zyg, Philipp. See *Global Pharmatrade, Philipp.*

Zyg, Thai. See *Pharmaland, Thai.*

Zylera, USA. Zylera Pharmaceuticals, 2530 Meridian Parkway, Suite 300, Research Triangle Park, NC 27713, USA.
url: www.zylera.com

Zyma, Belg. See *Novartis, Belg.*

Zyma, Fr. See *Novartis Sante, Fr.*

Zyma, Ger. See *Novartis Consumer, Ger.*

Zyma, Irl. See *Novartis, Irl.*

Zyma, Port. See *Novartis Consumer, Port.*

Zyma, Spain. See *Novartis, Spain.*

Zyma, Swed. See *Novartis, Swed.*

Zyma, Switz. See *Novartis, Switz* and *Novartis Consumer, Switz.*

Zyma, UK. See *Novartis, UK.*

Zymella, Pol. Zymella Pharma Sp. zo.o., ul. Kruczkowskiego 39 a, 41-813 Zabrze, Poland.
url: www.zymellapharma.com

Zymo, USA. ZymoGenetics Inc., 1201 Eastlake Ave East, Seattle, Washington 98102-3702, USA.
url: www.zymogenetics.com

Zynova, Philipp. Zynova Pharmaceuticals Inc., Unit 18B, 9 Strata 2000 Bldg, F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Zytras, India. Zytras Life Sciences, S.C.O. 377 (1st Floor), Mugal Canal, Karnal, Haryana 132 001, India.
url: www.zytras.com

Pharmaceutical Terms in Various Languages

The following index lists some of the commoner pharmaceutical forms and routes in English and a number of major European languages. It is provided as an aid to the non-native speaker in interpreting packaging, product information, or prescriptions written in another language, but the reader is cautioned that care is required: some terms translate poorly or not at all between languages, and the equivalences may not be exact. In addition, in many languages changes in number (singular or plural) and grammatical case can result in substantial changes to the form of words. Words in this list are given in the most neutral form, that is, singular (except for those forms such as drops or granules which are naturally plural) and in the nominative case.

Terms have been included in English and the following languages, which are indicated by the abbreviation in brackets following the term: Czech (cs), Dutch (nl), French (fr), German (de), Greek (el), Hungarian (hu), Italian (it), Lithuanian (lt), Polish (pl), Portuguese (pt), Spanish (es), and Swedish (sv). We hope to add terms in other languages once we are able to validate them.

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A

aceite—oil (es)
adagalópohár—cup (measuring) (hu)
additif de bain—bath additive (fr)
additivo per il bagno—bath additive (it)
aditivo para banho—bath additive (pt)
aditivo para el baño—bath additive (es)
administrering i munhålan—buccal or oromucosal use/route (sv)
administrering i örat—auricular use/route (sv)
administrering i urinröret—urethral use/route (sv)
administrering via munslemhinnan—buccal or oromucosal use/route (sv)
aerosol—spray (es)
aerosol belégzésre—aerosol inhaler (hu)
aérosol doseur—aerosol inhaler (fr)
aerosol inhaler—*see under* inhaler
aerosolinhalator—aerosol inhaler (nl)
aerossol inalador dosificador—aerosol inhaler (pt)
aerozol—spray (pl)
aerozol do gardła—throat spray (pl)
aerozol do nosa—nasal spray (pl)
aerozol do stosowania miejscowego—topical spray (pl)
aerozol do stosowania w jamie ustnej—mouth spray (pl)
aerozol doustny—mouth spray (pl)
aerozol na skórę—cutaneous spray (pl)
aerozol podjęzykowy—sublingual spray (pl)
aerozolinis inhaliatorius—aerosol inhaler (lt)
afleveringsysteem voor intra-uterien gebruik—intra-uterine system (nl)
akių gelis—eye gel (lt)
akių įdėklas—ocular insert (lt)
akių lašai—eye drops (lt)
akių losjonas—eye lotion (lt)
akių ploviklis—eye wash (lt)
akių tepalas—eye ointment (lt)
aliejus—oil (lt)
ampola—ampoule (pt)
ampolla—ampoule (es,it)
ampoule
—ampola (pt)
—ampolla (es,it)
—ampoule (fr)
—ampul (nl)
—ampulė (lt)
—ampulka (cs)
—ampułka (pl)
—ampull (sv)
—ampulla (hu)
—Ampulle (de)
—fiala (it)
—vial (es)
—φύσιγγα (el)
ampoule—ampoule (fr)
ampoule-seringue—prefilled syringe (fr)
ampul—ampoule (nl)
ampulė—ampoule (lt)
ampulka—ampoule (cs)
ampułka—ampoule (pl)
ampułkostrzykawka—prefilled syringe (pl)
ampull—ampoule (sv)
ampulla—ampoule (hu)
Ampulle—ampoule (de)
användning för inhalation—inhalation (route) (sv)
användning i munhålan—buccal or oromucosal use/route (sv)
användning i örat—auricular use/route (sv)
Anwendung am Auge—ocular use/route (de)
Anwendung am Ohr—auricular use/route (de)
Anwendung auf der Haut—cutaneous use/route (de)
Anwendung in der Harnröhre—urethral use/route (de)
Anwendung in der Mundhöhle—buccal or oromucosal use/route (de)
Anwendung in der Nase—nasal use/route (de)
aplicación tópica—topical application (es)
apósito—dressing (es)
apósito adhesivo—plaster (dressing or adhesive plaster) (es)
apósito adhesivo medicamentoso—medicated plaster (es)
apósito biológico—medicated bandage (es)
apósito con impregnación—medicated dressing (es)
apósito impregnado—medicated dressing (es)
apósito medicamentoso—medicated dressing (es)
application locale—topical application (fr)
applicazione topica—topical application (it)
Applikationsspritze für Zubereitungen zum Einnehmen—oral syringe (de)
arbatinis šaukštelis—teaspoon (5mL) (lt)
ask—box (sv)
Augenbad—eye lotion (de)
Augenbad—eye wash (de)
Augendusche—eye wash (de)
Augengel—eye gel (de)
Augeninsert—ocular insert (de)
Augensalbe—eye ointment (de)
Augenspüllösung—eye lotion (de)
Augenspülung—eye wash (de)
Augentropfen—eye drops (de)
auricular gebruik—auricular use/route (nl)
auricular use/route
—administrering i örat (sv)
—användning i örat (sv)
—Anwendung am Ohr (de)
—auricular gebruik (nl)
—fülészeti alkalmazás (hu)
—podanie do ucha (pl)
—ušní podání (cs)
—uso auricolare (it)
—uso auricular (pt)
—vartoti į ausį (lt)
—vía ótica (es)
—voie auriculaire (fr)
—ωτική χρήση (el)
ausų lašai—ear drops (lt)

B

Bad—bath (de)
bad—bath (nl,sv)
badadditief—bath additive (nl)
Badezusatz—bath additive (de)
badtillsats—bath additive (sv)
bagno—bath (it)
bagno oculare—eye wash (it)
bain—bath (fr)
bain de bouche—mouthwash (fr)
balm
—Balsam (de)
—balsam (pl,sv)
—bálsamo (es,pt)
—balsamo (it)
—balsem (nl)
—balzamas (lt)
—balzám (cs)
—balzsam (hu)
—baume (fr)
—Ölbalsam (de)
—βάλσαμο (el)
Balsam—balm (de)
balsam—balm (pl,sv)
bálsamo—balm (es,pt)
balsamo—balm (it)
balsem—balm (nl)
balzám—balm (cs)
balzamas—balm (lt)
balzsam—balm (hu)
bandage (*see also* dressing)
—Bandage (de)
—bandage (fr,sv)
—bandaż (pl)
—benda (it)
—binda (sv)
—Binde (de)
—bindel (sv)
—bintas (lt)
—fascia (it)
—förband (sv)
—Kompressionsbandage (de)
—kötszer (hu)
—ligadura (pt)
—obinadlo (cs)
—obvaz (cs)
—opaska (pl)
—Stützverband (de)
—tvarstis (lt)
—venda (es)
—vendaje (es)
—Verband (de)
—verband (nl)
—Wundverband (de)
—zwachtel (nl)
—επίδεσμος (el)
medicated bandage
—apósito biológico (es)
—bandage médicamenteux (fr)
—bandaż leczniczy (pl)
—benda medicata (it)
—geïmpregneerd verband (nl)
—Heilverband (de)
—impregnált kötszer (hu)
—léčivý obvaz (cs)
—medicininis bintas (lt)
—medicininis tvarstis (lt)
—medicinskt förband (sv)
—medikamenthaltiger Verband (de)
—medikamentöser Wundverband (de)
—obvaz s léčivou látkou (cs)
—vendaje medicalizado (es)
—wirkstoffhaltiger Verband (de)
—επίδεσμος εμποτισμένος (el)
Bandage—bandage (de)
bandage—bandage (fr,sv)
bandage médicamenteux—medicated bandage (fr)
bandaż—bandage (pl)
bandaż leczniczy—medicated bandage (pl)
banho—bath (pt)
baño—bath (es)
baño ocular—eye wash (es)
barniz de uñas medicamentoso—medicated nail lacquer (es)
barnsäker förslutning—child-resistant closure (sv)
barra cutánea (for skin)—medicated stick (es)
barrita medicamentosa—medicated stick (es)
barstomieji milteliai—dusting (cutaneous) powder (lt)
bath
—Bad (de)
—bad (nl,sv)
—bagno (it)
—bain (fr)
—banho (pt)
—baño (es)
—kąpiel (pl)
—koupel (cs)
—vonelė (lt)
—λουτρό (el)
bath additive
—additif de bain (fr)
—additivo per il bagno (it)
—aditivo para banho (pt)
—aditivo para el baño (es)
—badadditief (nl)
—Badezusatz (de)
—badtillsats (sv)
—dodatek do kąpieli leczniczej (pl)
—fürdőadalék (hu)
—přísada do koupele (cs)
—vonios priedas (lt)
—προσθετικό λουτρού (el)
bâton médicamenteux—medicated stick (fr)
baume—balm (fr)
be cukraus—sugar-free (lt)
bedörzsölő—embrocation (hu)
belégzés—inhalation (hu)

cs=Czech; de=German; el=Greek; es=Spanish; fr=French; hu=Hungarian; it=Italian; lt=Lithuanian; nl=Dutch; pl=Polish; pt=Portuguese; sv=Swedish

belégző készülék—inhaler (hu)
belégzőpor—powder for inhalation (hu)
belsőleges gél—oral gel (hu)
belsőleges oldat—oral solution (hu)
belsőleges oldatos cseppek—oral drops (hu)
belsőleges paszta—oral paste (hu)
belsőleges por—oral powder (hu)
belsőleges szuszpenzió—oral suspension (hu)
benda—bandage (it)
benda medicata—medicated bandage (it)
Beutel—sachet (de)
bevont tabletta—coated tablet (hu)
bez cukru—sugar-free (cs,pl)
bicchiere dosatore—cup (measuring) (it)
binda—bandage (sv)
Binde—bandage (de)
bindel—bandage (sv)
bintas—bandage (lt)
blaasspoeling—bladder irrigation (nl)
bladder irrigation—*see under* irrigation
Blaseninstillation—bladder irrigation (de)
Blasenspülung—bladder irrigation (de)
blíster—coated tablet (es)
boião—jar (pt)
boîte—box (fr)
bolsa—sachet (es)
bolsita—sachet (es)
borogató kenőcs—poultice (hu)
botella—bottle (es)
bottiglia—bottle (it)
bottle
—botella (es)
—bottiglia (it)
—bouteille (fr)
—butelis (lt)
—buteliukas (small bottle) (lt)
—butelj (sv)
—butelka (pl)
—flacone (it)
—Flasche (de)
—flaska (sv)
—fles (nl)
—frasco (es,pt)
—láhev (cs)
—üveg (hu)
—vial (es)
—φιάλη (el)
bouchon—cap (fr)
bouchon à vis—screw cap (fr)
bouchon à visser—screw cap (fr)
bouteille—bottle (fr)
box
—ask (sv)
—boîte (fr)
—caixa (pt)
—caja (es)
—dėžė (lt)
—dėžutė (small box) (lt)
—doboz (hu)
—doos (nl)
—Faltschachtel (de)
—kartong (sv)
—krabička (cs)
—låda (sv)
—pudełko (pl)
—scatola (it)
—Schachtel (de)
—κουτί (el)
Brausegranulat—effervescent granules (de)
Brausepulver—effervescent powder (de)
Brausetablette—effervescent tablet (de)
breakable or dividable tablet—*see under* tablet
bruisgranulaat—effervescent granules (nl)
bruispoeder—effervescent powder (nl)
bruistablet—effervescent tablet (nl)
brusgranulat—effervescent granules (sv)
bruspulver—effervescent powder (sv)
brustablett—effervescent tablet (sv)
buccal or oromucosal use/route
—administrering i munhålan (sv)
—administrering via munslemhinnan (sv)
—användning i munhålan (sv)
—Anwendung in der Mundhöhle (de)
—buckal administrering (sv)
—bukální podání (cs)
—orální podání (cs)
—oromucosaal gebruik (nl)
—podanie na śluzówkę jamy ustnej (pl)
—szájnyálkahártyán történő alkalmazás (hu)
—vartoti ant burnos gleivinės (lt)
—via bucal (pt)
—vía bucal (es)
—via oromucosale (it)
—voie buccale (fr)
—χρήση στο στοματικό βλεννογόνο (el)
buccal tablet—*see under* tablet
buccale tablet—buccal tablet (nl)
Buccaltablette—buccal tablet (de)
buckal administrering—buccal or oromucosal use/route (sv)
buckaltablett—buccal tablet (sv)
bukální podání—buccal or oromucosal use/route (cs)
bukální tableta—buccal tablet (cs)
bukkális tabletta—buccal tablet (hu)
burk—jar (sv)
burnoje disperguojamoji tabletė—orodispersible tablet (lt)
burnos ploviklis—mouthwash (lt)
burnos purškalas—mouth spray (lt)
butelis—bottle (lt)
buteliukas—vial (lt)
buteliukas (small bottle)—bottle (lt)
butelj—bottle (sv)
butelka—bottle (pl)

C

caixa—box (pt)
čaj—tea (cs)
caja—box (es)
čajová lžička—teaspoon (cs)
candeletta—pessary (it)
cap
—bouchon (fr)
—cápsula de cierre (es)
—cápsula de fecho (pt)
—capsula di chiusura (it)
—capuchon (fr)
—dangtelis (lt)
—Deckel (de)
—dop (nl)
—Kappe (de)
—kapsyl (sv)
—kupak (hu)
—lock (sv)
—opercule (fr)
—Schnappdeckel (de)
—tampa (pt)
—tappo (it)
—Verschluss (de)
—vičko (cs)
—wieczko (pl)
—πώμα (el)
screw cap
—bouchon à visser (fr)
—bouchon à vis (fr)
—cierre de rosca (es)
—csavaros kupak (hu)
—fecho com rosca (pt)
—Schraubdeckel (de)
—Schraubverschluss (de)
—schroefdop (nl)
—skruvkork (sv)
—skruvlock (sv)
—šroubovací uzávěr (cs)
—tampa roscada (pt)
—tappo a vite (it)
—užsukamas dangtelis (lt)
—zakrętka (pl)
—závitový uzávěr (cs)
—βιδωτό πώμα (el)
cápsula—capsule (es,pt)
capsula—capsule (it)
capsula a rilascio prolungato—extended-release capsule (it)
cápsula blanda—soft capsule (es)
cápsula de cierre—cap (es)
cápsula de fecho—cap (pt)
cápsula de liberación prolongada—extended-release capsule (es)
cápsula de liberación retardada—extended-release capsule (es)
cápsula de libertação prolongada—extended-release capsule (pt)
cápsula de libertação retardada—extended-release capsule (pt)
capsula di chiusura—cap (it)
cápsula dura—hard capsule (es,pt)
cápsula gastro-resistente—enteric-coated (gastro-resistant) capsule (pt)
capsula gastroresistente—enteric-coated (gastro-resistant) capsule (it)
cápsula gastrorresistente—enteric-coated (gastro-resistant) capsule (es)
cápsula mole—soft capsule (pt)
capsula molle—soft capsule (it)
capsula rigida—hard capsule (it)
cápsula vaginal—vaginal capsule (es,pt)
capsula vaginale—vaginal capsule (it)
capsule
—capsula (it)
—cápsula (es,pt)
—capsule (fr,nl)
—gélule (fr)
—Kapsel (de)
—kapsel (sv)
—kapsle (cs)
—kapsulė (lt)
—kapsułka (pl)
—kapszula (hu)
—tobolka (cs)
—καψάκιο (el)
—κάψουλα (el)
enteric-coated (gastro-resistant) capsule
—cápsula gastro-resistente (pt)
—capsula gastroresistente (it)
—cápsula gastrorresistente (es)
—enterokapsel (sv)
—gélule à enrobage entérique (fr)
—gélule gastro-résistante (fr)
—gyomornedv-ellenálló kapszula (hu)
—kapsle enterosolventní (cs)
—kapsułka dojelitowa (pl)
—maagsapresistente capsule (nl)
—magensaftresistente Kapsel (de)
—skrandyje neiri kapsulė (lt)
—γαστροανθεκτική κάψουλα (el)
—γαστροανθεκτικό καψάκιο (el)
extended-release capsule
—capsula a rilascio prolungato (it)
—cápsula de liberación prolongada (es)
—cápsula de liberación retardada (es)
—cápsula de libertação prolongada (pt)
—cápsula de libertação retardada (pt)
—capsule met verlengde afgifte (nl)
—depotkapsel (sv)
—gélule à libération prolongée (fr)
—gélule à libération retardée (fr)
—kapsułka o przedłużonym uwalnianiu (pl)
—pailginto atpalaidavimo kapsulė (lt)
—retard kapszula (hu)
—Retardkapsel (de)
—retardovaná tobolka (cs)
—tobolka s prodlouženým uvolňováním (cs)
—κάψουλα παρατεταμένης αποδέσμευσης (el)
—καψάκιο παρατεταμένης αποδέσμευσης (el)
hard capsule
—cápsula dura (es,pt)
—capsula rigida (it)
—gélule (fr)
—hård kapsel (sv)
—harde capsule (nl)
—Hartkapsel (de)
—kemény kapszula (hu)
—kieta kapsulė (lt)
—tvrdá tobolka (cs)
—twarda kapsułka (pl)
—σκληρή κάψουλα (el)
—σκληρό καψάκιο (el)
soft capsule
—cápsula blanda (es)
—cápsula mole (pt)
—capsula molle (it)
—capsule molle (fr)
—lágy kapszula (hu)
—měkká tobolka (cs)
—miękka kapsułka (pl)
—minkšta kapsulė (lt)
—mjuk kapsel (sv)
—Weichkapsel (de)
—zachte capsule (nl)
—μαλακή κάψουλα (el)
—μαλακό καψάκιο (el)
vaginal capsule
—capsula vaginale (it)
—cápsula vaginal (es,pt)
—capsule vaginale (fr)
—capsule voor vaginaal gebruik (nl)
—hüvelykapszula (hu)
—kapsułka dopochwowa (pl)
—makšties kapsulė (lt)
—poševni tobolka (cs)
—Vaginalkapsel (de)
—vaginalkapsel (sv)
—vaginální tobolka (cs)
—κολπική κάψουλα (el)
—κολπικό καψάκιο (el)
capsule—capsule (fr,nl)
capsule met verlengde afgifte—extended-release capsule (nl)
capsule molle—soft capsule (fr)
capsule vaginale—vaginal capsule (fr)
capsule voor vaginaal gebruik—vaginal capsule (nl)
capuchon—cap (fr)
cartina—sachet (it)
cartouche—cartridge (fr)
cartridge
—cartouche (fr)
—cartuccia (it)
—cartucho (es,pt)
—cylinderampull (sv)
—Kartusche (de)
—patron (hu)
—Patrone (de)
—patroon (nl)
—užtaisas (lt)
—wkład (pl)
—zásobní vložka (cs)
—φυσίγγιο (el)
cartuccia—cartridge (it)
cartucho—cartridge (es,pt)
cataplasma—poultice (es,it,pt)
cataplasme—poultice (fr)
cerotto—plaster (dressing or adhesive plaster) (it)
cerotto medicato—medicated plaster (it)
cerotto transdermico—transdermal patch (it)
chá—tea (pt)
chá medicinal—tea (herbal or medicinal) (pt)
champô—shampoo (pt)
champú—shampoo (es)
chewable tablet—*see under* tablet
chewing gum
—goma de mascar (es)
—gomma da masticare (it)
—gomme à mâcher (fr)
—guma do żucia (pl)
—Kaugummi (de)
—kauwgom (nl)
—kramtomoji guma (lt)
—pastilha elástica (pt)
—rágógumi (hu)
—tuggummi (sv)
—žvýkací guma (cs)
—žvýkačka (cs)

—μασώμενο κόμμι (el)
child-resistant closure
—barnsäker förslutning (sv)
—chiusura a prova di bambino (it)
—cierre de seguridad a prueba de niños (es)
—dětský bezpečnostní uzávěr (cs)
—fecho resistente à abertura por crianças (pt)
—fermeture de sécurité enfant (fr)
—gyermekbiztos zárás (hu)
—kindergesicherter Verschluss (de)
—kinderveilige sluiting (nl)
—tampa de segurança (pt)
—vaikų neatidaromas uždoris (lt)
—zamknięcie zabezpieczające przed dostępem dzieci (pl)
—πώμα ασφαλείας για παιδιά (el)
chiusura a prova di bambino—child-resistant closure (it)
cierre de rosca—screw cap (es)
cierre de seguridad a prueba de niños—child-resistant closure (es)
čípek—suppository (cs)
clister—enema (pt)
clistere—enema (it)
clistere da ritenzione—retention enema (it)
coated tablet—*see under* tablet
colher de chá—teaspoon (pt)
colher de sobremesa—dessertspoon (pt)
colher de sopa—tablespoon (pt)
colírio—eye drops (pt)
colirio—eye drops (es)
collirio—eye drops (it)
collutoire—throat spray (fr)
colluttorio—mouthwash (it)
collyre—eye drops (fr)
colutorio—mouthwash (es)
combinatieverpakking—combination pack (nl)
combination pack
—combinatieverpakking (nl)
—confezione combinata (it)
—kombinált csomagolás (hu)
—kombinationsförpackning (sv)
—kombinované balení (cs)
—kombinuotas pakelis (lt)
—Kombipackung (de)
—pack combinado (pt)
—pacote combinado (pt)
—paquete combinado (es)
—preparat złożony (pl)
—συσκευασία συνδυασμού (el)
compressa a rilascio modificato—modified release tablet (it)
compressa a rilascio prolungato—extended-release tablet (it)
compressa—tablet (it)
compressa buccale—buccal tablet (it)
compressa dispersibile—dispersible tablet (it)
compressa divisibile—breakable or dividable tablet (it)
compressa effervescente—effervescent tablet (it)
compressa gastroresistente—enteric-coated (gastro-resistant) tablet (it)
compressa masticabile—chewable tablet (it)
compressa orodispersibile—orodispersible tablet (it)
compressa rivestita—coated tablet (it)
compressa rivestita con film—film-coated tablet (it)
compressa solubile—soluble tablet (it)
compressa sublinguale—sublingual tablet (it)
compressa vaginale—vaginal tablet (it)
compresse imprégnée—medicated dressing (fr)
comprimé—tablet (fr)
comprimé à croquer—chewable tablet (fr)
comprimé à enrobage entérique—enteric-coated (gastro-resistant) tablet (fr)
comprimé à libération modifiée—modified release tablet (fr)
comprimé à libération prolongée—extended-release tablet (fr)
comprimé buccal—buccal tablet (fr)
comprimé dispersible—dispersible tablet (fr)
comprimé effervescent—effervescent tablet (fr)
comprimé enrobé—coated tablet (fr)
comprimé fondant—orodispersible tablet (fr)
comprimé gastrorésistant—enteric-coated (gastro-resistant) tablet (fr)
comprimé orodispersible—orodispersible tablet (fr)
comprimé pelliculé—film-coated tablet (fr)
comprimé sécable—breakable or dividable tablet (fr)
comprimé soluble—soluble tablet (fr)
comprimé sublingual—sublingual tablet (fr)
comprimé vaginal—vaginal tablet (fr)
comprimido—tablet, pastille (es)
comprimido—tablet (pt)
comprimido bucal—buccal tablet (es,pt)
comprimido bucodispersable—orodispersible tablet (es)
comprimido con cubierta pelicular—film-coated tablet (es)
comprimido con recubrimiento—coated tablet (es)
comprimido con recubrimiento entérico—enteric-coated (gastro-resistant) tablet (es)
comprimido de liberación modificada—modified release tablet (es)
comprimido de liberación prolongada—extended-release tablet (es)
comprimido de liberación retardada—extended-release tablet (es)
comprimido de libertação modificada—modified release tablet (pt)
comprimido de libertação prolongada—extended-release tablet (pt)
comprimido dispersable—dispersible tablet (es)
comprimido dispersível—dispersible tablet (pt)
comprimido divisível—breakable or dividable tablet (pt)
comprimido efervescente—effervescent tablet (es,pt)
comprimido fraccionable—breakable or dividable tablet (es)
comprimido gastroresistente—enteric-coated (gastro-resistant) tablet (pt)
comprimido gastrorresistente—enteric-coated (gastro-resistant) tablet (es)
comprimido masticable—chewable tablet (es)
comprimido mastigável—chewable tablet (pt)
comprimido orodispersível—orodispersible tablet (pt)
comprimido para mastigar—chewable tablet (pt)
comprimido recubierto—coated tablet (es)
comprimido recubierto con película—film-coated tablet (es)
comprimido revestido—coated tablet (pt)
comprimido revestido por película—film-coated tablet (pt)
comprimido soluble—soluble tablet (es)
comprimido solúvel—soluble tablet (pt)
comprimido sublingual—sublingual tablet (es,pt)
comprimido vaginal—vaginal tablet (es, pt)
concentraat voor (oplossing voor) infusie—concentrate for infusion (solution) (nl)
concentrado para perfusão—concentrate for infusion (solution) (pt)
concentrate for infusion (solution)
—concentraat voor infusie, concentraat voor oplossing voor infusie (nl)
—concentrado para perfusão (pt)
—concentrato per soluzione per infusione (it)
—concentré pour perfusion (fr)
—Infusionslösungskonzentrat (de)
—koncentrat do sporządzania roztworu do infuzji (pl)
—koncentrát pro přípravu infuzního roztoku (cs)
—koncentrat till infusionslösning (sv)
—koncentrat till infusionsvätska (sv)
—koncentratas infuziniam tirpalui (lt)
—koncentrátum oldatos infúzióhoz (hu)
—Konzentrat zur Herstellung einer Infusionslösung (de)
—solución concentrada para infusión (es)
—solution à diluer pour perfusion (fr)
—πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση (el)
—συμπύκνωμα προς έγχυση (el)
concentrato per soluzione per infusione—concentrate for infusion (solution) (it)
concentré pour perfusion—concentrate for infusion (solution) (fr)
confezione combinata—combination pack (it)
contenitore monodose—single-dose container (it)
copo dosificador—cup (measuring) (pt)
copo-medida—cup (measuring) (pt)
cough mixture (*see also* cough syrup)
—hoestdrank (nl)
—hostmedicin (sv)
—Hustensaft (de)
—Hustensirup (de)
—jarabe para la tos (es)
—köptető (hu)
—mikstūra nuo kosulio (lt)
—sciroppo per la tosse (it)
—sirop antitussif (fr)
—sirop contre la toux (fr)
—sirop pectoral (fr)
—sirup proti kašli (cs)
—syrop na kaszel (pl)
—xarope para a tosse (pt)
—μείγμα για το βήχα (el)
cough syrup—*see above, and also under* syrup
crayon médicamenteux—medicated stick (fr)
cream
—crema (es,it)
—Creme (de)
—créme (pt)
—crème (fr,nl)
—kräm (sv)
—krem (pl)
—krém (cs,hu)
—kremas (lt)
—κρέμα (el)
vaginal cream
—crema vaginale (it)
—crema vaginal (es)
—crème vaginale (fr)
—créme vaginal (pt)
—crème voor vaginaal gebruik (nl)
—hüvelykrém (hu)
—krem dopochwowy (pl)
—makšties kremas (lt)
—poševni krém (cs)
—Vaginalcreme (de)
—vaginalkräm (sv)
—vaginální krém (cs)
—κολπική κρέμα (el)
crema—cream (es,it)
crema vaginal—vaginal cream (es)
crema vaginale—vaginal cream (it)
Creme—cream (de)
créme—cream (pt)
crème—cream (fr,nl)
créme vaginal—vaginal cream (pt)
crème vaginale—vaginal cream (fr)
crème voor vaginaal gebruik—vaginal cream (nl)
csavaros kupak—screw cap (hu)
cseppek—drops (hu)
cucchiaino—teaspoon (it)
cucchiaio da tavola—tablespoon (it)
cucchiaio da tè—teaspoon (it)
cucharada sopera—tablespoon (es)
cucharadita de postre—dessertspoon (es)
cucharadita de té—teaspoon (es)
cuillère à café—teaspoon (fr)
cuillère à dessert—dessertspoon (fr)
cuillère à soupe—tablespoon (fr)
cukor mentes—sugar-free (hu)
cup (measuring)
—adagalópohár (hu)
—bicchiere dosatore (it)
—copo dosificador (pt)
—copo-medida (pt)
—dozavimo taurelė (lt)
—godet (fr)
—kopp (sv)
—maatbekertje (nl)
—matavimo taurelė (lt)
—Messbecher (de)
—miarka (pl)
—odměrka (cs)
—vaso dosificator (es)
—κύπελλο (el)
curativo—dressing (pt)
cutaan gebruik—cutaneous use/route (nl)
cutaneous emulsion—*see under* emulsion
cutaneous paste—*see under* paste
cutaneous solution—*see under* solution
cutaneous sponge—*see under* sponge
cutaneous spray—*see under* spray
cutaneous use/route
—Anwendung auf der Haut (de)
—cutaan gebruik (nl)
—kožní podání (cs)
—külsőleges alkalmazás (hu)
—kutan administrering (sv)
—kutan användning (sv)
—kutant bruk (sv)
—podanie na skórę (pl)
—uso cutáneo (es)
—uso cutâneo (pt)
—uso cutaneo (it)
—vartoti ant odos (lt)
—via cutanea (it)
—voie cutanée (fr)
—δερματική χρήση (el)
cylinderampull—cartridge (sv)
czopek—suppository (pl)
czopek dopochwowy—vaginal suppository (pl)

D

dalinama tabletė—breakable or dividable tablet (lt)
Dampf zur Inhalation—vapour inhalation (de)
dangtelis—cap (lt)
dantenos—gum (lt)
dantų gelis—dental gel (lt)
dantų pasta—toothpaste (lt)
dávkovací aerosol—aerosol inhaler (cs)
Deckel—cap (de)
deelbare tablet—breakable or dividable tablet (nl)
delbar tablett—breakable or dividable tablet (sv)
dělitelná tableta—breakable or dividable tablet (cs)
dengta tabletė—coated tablet (lt)
dental gel—*see under* gel
Dentalgel—dental gel (de)
dentalgel—dental gel (sv)
dentífricio—toothpaste (it)
dentífrico—toothpaste (es)
depotkapsel—extended-release capsule (sv)
depotplåster—transdermal patch (sv)

depottablett—extended-release tablet (sv)
desertinis šaukštas—dessertspoon (10mL) (lt)
dessertlepel—dessertspoon (n.b. 8 mL) (nl)
dessertsked—dessertspoon (sv)
dessertspoon (10mL)
—colher de sobremesa (pt)
—cucharadita de postre (es)
—cuillère à dessert (fr)
—desertinis šaukštas (lt)
—dessertlepel (n.b. 8 mL) (nl)
—dessertsked (sv)
—dezertní lžička (cs)
—gyeremek kanál (hu)
—łyżka deserowa (pl)
—κουταλάκι του γλυκού (el)
dětský bezpečnostní uzávěr—child-resistant closure (cs)
dėžė—box (lt)
dezertní lžička—dessertspoon (cs)
dėžutė—small box (lt)
dispergeerbare tablet—dispersible tablet (nl)
dispergerbar tablett—dispersible tablet (sv)
disperguojamoji tabletė—dispersible tablet (lt)
dispersible tablet—*see under* tablet
disposable syringe—*see under* syringe
dispositif intra-utérin—intra-uterine device (fr)
dispositif transdermique—transdermal patch (fr)
dispositivo de libertação intra-uterino—intra-uterine system (pt)
dispositivo intrauterino—intra-uterine system (es,it)
diszpergálódó tabletta—dispersible tablet (hu)
DIU—intra-uterine device (es,fr)
doboz—box (hu)
dodatek do kąpieli leczniczej—bath additive (pl)
doos—box (nl)
dop—cap (nl)
doseerspuit voor orale toediening—oral syringe (nl)
Dosier-Aerosol—aerosol inhaler (de)
dospåse—sachet (sv)
douche (vaginal)
—douche vaginale (fr)
—ducha vaginal (es)
—duche vaginal (pt)
—hüvelyöblítés (hu)
—irrigálás (hu)
—lavanda vaginale (it)
—płyn do irygacji pochwy (pl)
—slidsköljning (sv)
—Vaginaldusche (de)
—vaginaldusch (sv)
—vaginale douche (nl)
—vaginalinis apsiplovimas (lt)
—vaginální výplach (cs)
—κολπική κλύσις (el)
douche vaginale—douche (vaginal) (fr)
dozavimo taurelė—cup (measuring) (lt)
Dragée—coated tablet (de)
dragée—coated tablet (fr)
dragerad tablett—coated tablet (sv)
drank—oral solution (nl)
dražė—coated tablet (cs)
dressing (*see also* bandage)
—förband (sv)
—apósito (es)
—curativo (pt)
—fasciatura (it)
—gasa (es)
—Gaze (de)
—kompres (cs,nl)
—kompress (sv)
—kötszer (hu)
—krytí (cs)
—obvaz (cs)
—omslag (sv)
—opatrunek (pl)
—pansement (fr)
—penso (pt)
—Sterilkompresse (de)
—tvarstis (lt)
—verbandgaas (nl)
—Wundgaze (de)
—Wundkompresse (de)
—επίθεμα (el)
medicated dressing
—apósito con impregnación (es)
—apósito impregnado (es)
—apósito medicamentoso (es)
—compresse imprégnée (fr)
—garza impregnata (it)
—garza medicata (it)
—geïmpregneerd verbandgaas (nl)
—imprägnierte Verband (de)
—impregnált kötszer (hu)
—impregnuotasis tvarstis (lt)
—krytí s léčivou látkou (cs)
—léčivý obvaz (cs)
—medicinskt kompress (sv)
—medicinskt omslag (sv)
—opatrunek leczniczy (pl)
—pansement médicamenteux (fr)
—penso impregnado (pt)
—Salbengaze (de)
—salvkompress (sv)
—εμποτισμένο επίθεμα (el)
—επίδεσμος εμποτισμένος (el)
Drogenextrakt—extract (de)
droppar—drops (sv)
drops
—cseppek (hu)
—droppar (sv)
—druppels (nl)
—gocce (it)
—gotas (es,pt)
—gouttes (fr)
—kapky (cs)
—krople (pl)
—lašai (lt)
—Tropfen (de)
—σταγόνες (el)
ear drops
—ausų lašai (lt)
—gocce auricolari (it)
—gotas auriculares (pt)
—gotas óticas (es)
—gouttes otiques (fr)
—krople do uszu (pl)
—Ohrentropfen (de)
—oldatos fülcsepp (hu)
—oordruppels (nl)
—örondroppar (sv)
—solution pour instillation auriculaire (fr)
—ušní kapky (cs)
—ωτικές σταγόνες (el)
eye drops
—akių lašai (lt)
—Augentropfen (de)
—colírio (pt)
—colirio (es)
—collirio (it)
—collyre (fr)
—gotas oftálmicas (es,pt)
—krople do oczu (pl)
—oční kapky (cs)
—ögondroppar (sv)
—oldatos szemcsepp (hu)
—oogdruppels (nl)
—οφθαλμικές σταγόνες (el)
nasal drops
—gocce nasali (it)
—gotas nasais (pt)
—gotas nasales (es)
—gouttes nasales (fr)
—instillation nasale (fr)
—krople do nosa (pl)
—näsdroppar (sv)
—Nasentropfen (de)
—neusdruppels (nl)
—nosies lašai (lt)
—nosní kapky (cs)
—oldatos orrcsepp (hu)
—ρινικές σταγόνες (el)
oral drops
—belsőleges oldatos cseppek (hu)
—druppels voor oraal gebruik (nl)
—geriamieji lašai (lt)
—gocce per uso orale (it)
—gotas orais (pt)
—gotas orales (es)
—gouttes orales (fr)
—kapky k vnitřnímu užití (cs)
—krople doustne (pl)
—orala droppar (sv)
—perorální kapky (cs)
—Tropfen zum Einnehmen (de)
—πόσιμες σταγόνες (el)
Druckgasinhalation—aerosol inhaler (de)
druppels—drops (nl)
druppels voor oraal gebruik—oral drops (nl)
ducha vaginal—douche (vaginal) (es)
duche vaginal—douche (vaginal) (pt)
Durchstechflasche—vial (de)
dusting (cutaneous) powder—*see under* powder

E

ear drops—*see under* drops
EDO—single-dose container (de)
édulcoré—artificially sweetened (fr)
eetlepel—tablespoon (nl)
effervescent granules—*see under* granules
effervescent powder—*see under* powder
effervescent tablet—*see under* tablet
egyadagos tartály—single-dose container (hu)
egyszer használatos eldobható fecskendő—disposable syringe (hu)
Einlauf—enema (de)
Einmalspritze—disposable syringe (de)
Einreibung—embrocation (de)
Einzeldosisbehältnis—single-dose container (de)
ekstraktas—extract (lt)
EL—tablespoon (de)
eliksir—elixir (pl)
eliksyras—elixir (lt)
elisir—elixir (it)
Elixier—elixir (de)
elixir
—eliksir (pl)
—eliksyras (lt)
—elisir (it)
—Elixier (de)
—elixir (es,nl,pt,sv)
—élixir (fr)
—elixír (cs,hu)
—ελιξήριο (el)
elixir—elixir (es,nl,pt,sv)
élixir—elixir (fr)
elixír—elixir (cs,hu)
előretöltött fecskendő—prefilled syringe (hu)
embrocation (*see also* liniment)
—bedörzsölő (hu)
—Einreibung (de)
—embrocation (fr)
—linimento (es,it,pt)
—Liniment (de)
—liniment (sv)
—mazání (cs)
—mazidło (pl)
—płyn do wcierania (pl)
—skystas tepalas (lt)
—smeersel (nl)
—εντριβή (el)
embrocation—embrocation (fr)
emplastro—plaster (dressing or adhesive plaster) (pt)
emplastro medicamentoso—plaster (pt)
emplâtre—plaster (dressing or adhesive plaster) (fr)
emplâtre médicamenteux—medicated plaster (fr)
emulsão—emulsion (pt)
emulsão cutânea—cutaneous emulsion (pt)
emulsão tópica—topical emulsion (pt)
emulsie—emulsion (nl)
emulsie voor cutaan gebruik—cutaneous emulsion (nl)
emulsie voor topisch gebruik—topical emulsion (nl)
emulsija—emulsion (lt)
emulsion
—emulsão (pt)
—emulsie (nl)
—emulsija (lt)
—Emulsion (de)
—emulsion (sv)
—emulsión (es)
—émulsion (fr)
—emulsione (it)
—emulsja (pl)
—emulze (cs)
—emulzió (hu)
—γαλάκτωμα (el)
cutaneous emulsion
—emulsão cutânea (pt)
—emulsie voor cutaan gebruik (nl)
—emulsión cutánea (es)
—émulsion pour application cutanée (fr)
—Emulsion zur Anwendung auf der Haut (de)
—emulsione cutanea (it)
—emulsja na skórę (pl)
—kožní emulze (cs)
—külsőleges emulzió (hu)
—kutan emulsion (sv)
—odos emulsija (lt)
—δερματικό γαλάκτωμα (el)
topical emulsion
—emulsão tópica (pt)
—emulsie voor topisch gebruik (nl)
—emulsión de aplicación tópica (es)
—émulsion pour application locale (fr)
—emulsión tópica (es)
—Emulsion zur topischen Anwendung (de)
—emulsione per uso topico (it)
—emulsja do stosowania miejscowego (pl)
—emulze k zevnímu použití (cs)
—külsőleges emulzió (hu)
—topická emulze (cs)
—topikal emulsion (sv)
—vietinė emulsija (lt)
—τοπικό γαλάκτωμα (el)
Emulsion—emulsion (de)
emulsion—emulsion (sv)
émulsion—emulsion (fr)
emulsión—emulsion (es)
emulsión cutánea—cutaneous emulsion (es)
emulsión de aplicación tópica—topical emulsion (es)
émulsion pour application cutanée—cutaneous emulsion (fr)
émulsion pour application locale—topical emulsion (fr)
emulsión tópica—topical emulsion (es)
Emulsion zur Anwendung auf der Haut—cutaneous emulsion (de)
Emulsion zur topischen Anwendung—topical emulsion (de)
emulsione—emulsion (it)
emulsione cutanea—cutaneous emulsion (it)
emulsione per uso topico—topical emulsion (it)
emulsja—emulsion (pl)
emulsja do stosowania miejscowego—topical emulsion (pl)
emulsja na skórę—cutaneous emulsion (pl)
emulze—emulsion (cs)
emulze k zevnímu použití—topical emulsion (cs)
emulzió—emulsion (hu)
endosbehållare—single-dose container (sv)
endosförpackning—single-dose container (sv)
enema
—clister (pt)
—clistere (it)
—Einlauf (de)
—enema (es,pt)

—enteroclisma (it)
—Klistier (de)
—klizma (hu,lt)
—Klysma (de)
—klysma (nl,sv)
—klystýr (cs)
—klyzma (cs)
—lavemang (sv)
—lavemangsvätska (sv)
—lavement (fr)
—lewatywa (pl)
—rektalvätska (sv)
—vloeistof voor rectaal gebruik (nl)
—wlewka doodbytnicza (pl)
—υποκλυσμός (el)
retention enema
—clistere da ritenzione (it)
—enema de retenção (pt)
—enema de retención (es)
—klizmos užlaikymas (lt)
—klystýr (cs)
—lavement de rétention (fr)
—lewatywa retencyjna (pl)
—retenciós klizma (hu)
—retentieklysma (nl)
—Retentionseinlauf (de)
—retentionslavemang (sv)
—υποκλυσμός κατακράτησης (el)
enema—enema (es,pt)
enema de retenção—retention enema (pt)
enema de retención—retention enema (es)
engångsspruta—disposable syringe (sv)
enjuague bucal—mouthwash (es)
enteric-coated (gastro-resistant) capsule—*see under* capsule
enteric-coated (gastro-resistant) tablet—*see under* tablet
enteroclisma—enema (it)
enterokapsel—enteric-coated (gastro-resistant) capsule (sv)
enterosolventní tableta—enteric-coated (gastro-resistant) tablet (cs)
enterotablett—enteric-coated (gastro-resistant) tablet (sv)
envase unidosis—single-dose container (es)
epiduraal gebruik—epidural use/route (nl)
epidural administrering—epidural use/route (sv)
epidural användning—epidural use/route (sv)
epidural use/route
—epiduraal gebruik (nl)
—epidural administrering (sv)
—epidural användning (sv)
—epidurale Anwendung (de)
—epiduralis alkalmazás (hu)
—epidurální podání (cs)
—epiduralt bruk (sv)
—podanie nadtwardówkowe (pl)
—uso epidurale (it)
—vartoti epiduraliai (lt)
—via epidurale (it)
—via epidural (pt)
—vía epidural (es)
—voie péridurale (fr)
—επισκληρίδια χρήση (el)
epidurale Anwendung—epidural use/route (de)
epiduralis alkalmazás—epidural use/route (hu)
epidurální podání—epidural use/route (cs)
epiduralt bruk—epidural use/route (sv)
éponge—sponge (fr)
éponge pour application cutanée—cutaneous sponge (fr)
éponge vaginale—vaginal sponge (fr)
esparadrapo—plaster (dressing or adhesive plaster) (es)
esponja—sponge (es,pt)
esponja cutánea—cutaneous sponge (es)
esponja cutânea—cutaneous sponge (pt)
esponja vaginal—vaginal sponge (es,pt)
espuma—foam (es,pt)
espuma de aplicación rectal—rectal foam (es)
espuma de aplicación vaginal—vaginal foam (es)
espuma rectal—rectal foam (es,pt)
espuma vaginal—vaginal foam (es,pt)
Esslöffel—tablespoon (de)
estratto—extract (it)
evőkanál—tablespoon (hu)
extended-release capsule—*see under* capsule
extended-release tablet—*see under* tablet
extract
—Drogenextrakt (de)
—ekstraktas (lt)
—estratto (it)
—extract (nl)
—extracto (es,pt)
—extrait (fr)
—extrakt (sv)
—ištrauka (lt)
—kivaonat (hu)
—výtažek (cs)
—wyciąg (pl)
—εκχύλισμα (el)
extract—extract (nl)
extracto—extract (es,pt)
extrait—extract (fr)
extrakt—extract (sv)
eye drops—*see under* drops
eye gel—*see under* gel
eye lotion—*see under* lotion
eye ointment—*see under* ointment
eye wash
—akių ploviklis (lt)
—Augenbad (de)
—Augendusche (de)
—Augenspülung (de)
—bagno oculare (it)
—baño ocular (es)
—oční voda (cs)
—ögonbad (sv)
—ögonsköljvätska (sv)
—oogwassing (nl)
—płyn do przemywania oczu (pl)
—solução para lavagem oftálmica (pt)
—solution pour lavage oculaire (fr)
—solution pour lavage ophtalmique (fr)
—szem öblítő folyadék (hu)
—διάλυμα οφθαλμικής πλύσης (el)

F

Faltschachtel—box (de)
fascia—bandage (it)
fasciatura—dressing (it)
fecho com rosca—screw cap (pt)
fecho resistente à abertura por crianças—child-resistant closure (pt)
fecskendő—syringe (hu)
fermeture de sécurité enfant—child-resistant closure (fr)
Fertigspritze—prefilled syringe (de)
fiala—ampoule, vial (it)
film-coated tablet—*see under* tablet
filmdragerad tablett—film-coated tablet (sv)
filmomhulde tablet—film-coated tablet (nl)
filmtabletta—film-coated tablet (hu)
Filmtablette—film-coated tablet (de)
fiolka—vial (pl)
flacon—vial (fr)
flacon monodose—single-dose container (fr)
flaconcino—vial (it)
flacone—bottle (it)
Flasche—bottle (de)
flaska—bottle (sv)
fles—bottle (nl)
Flüssigkeit zur Einnahme—oral solution (de)
foam
—espuma (es,pt)
—hab (hu)
—mousse (fr)
—pěna (cs)
—pianka (pl)
—putos (lt)
—Schaum (de)
—schiuma (it)
—schuim (nl)
—skum (sv)
—αφρός (el)
rectal foam
—espuma de aplicación rectal (es)
—espuma rectal (es,pt)
—mousse rectale (fr)
—pěna do konečníku (cs)
—pianka doodbytnicza (pl)
—rektální pěna (cs)
—Rektalschaum (de)
—rektalskum (sv)
—Schaum zur rektalen Anwendung (de)
—schiuma rettale (it)
—schuim voor rectaal gebruik (nl)
—tiesiosios žarnos putos (lt)
—végbélhab (hu)
—ορθικός αφρός (el)
vaginal foam
—espuma de aplicación vaginal (es)
—espuma vaginal (es,pt)
—hüvelyhab (hu)
—makšties putos (lt)
—mousse vaginale (fr)
—pianka dopochwowa (pl)
—poševni pěna (cs)
—Schaum zur vaginalen Anwendung (de)
—schiuma vaginale (it)
—schuim voor vaginaal gebruik (nl)
—vaginální pěna (cs)
—Vaginalschaum (de)
—vaginalskum (sv)
—κολπικός αφρός (el)
fogászati gél—dental gel (hu)
fogpaszta—toothpaste (hu)
förband—bandage, dressing (sv)
förfylld spruta—prefilled syringe (sv)
frasco—bottle (es,pt)
frasco para injectáveis—vial (pt)
frystorkat pulver—lyophilised powder (sv)
fülészeti alkalmazás—auricular use/route (hu)
fumenti—vapour inhalation (it)
fürdőadalék—bath additive (hu)

G

gąbka—sponge (pl)
gąbka dopochwowa—vaginal sponge (pl)
gąbka na skórę—cutaneous sponge (pl)
galvos losjonas—scalp lotion (lt)
gargalas—gargle (lt)
gargarisme—gargle (fr)
gargarismo—gargle (es,it)
gargle
—gargalas (lt)
—gargarisme (fr)
—gargarismo (es,it)
—gorgeldrank (nl)
—Gurgellösung (de)
—gurgelvatten (sv)
—kloktadlo (cs)
—roztwór do płukania gardła (pl)
—solução para gargarejar (pt)
—solución para gargarismos (es)
—toroköblítö (hu)
—γαργαρίσμα (el)
garza impregnata—medicated dressing (it)
garza medicata—medicated dressing (it)
gas (for inhalation)
—gás para inalação (pt)
—gas para inhalación (es)
—gas per inalazione (it)
—Gas zur Inhalation (de)
—gaz do inhalacji (pl)
—gaz pour inhalation (fr)
—inhalációs gáz (hu)
—inhalatiegas (nl)
—inhalationsånga (sv)
—Inhalationsgas (de)
—inhalationsgas (sv)
—inhaliacinės dujos (lt)
—plyn k inhalaci (cs)
—αέριο για εισπνοή (el)
gás para inalação—gas for inhalation (pt)
gas para inhalación—gas for inhalation (es)
gas per inalazione—gas for inhalation (it)
Gas zur Inhalation—gas for inhalation (de)
gasa—dressing (es)
gastro-enteraal gebruik—gastroenteral use/route (nl)
gastroenteral administrering—gastroenteral use/route (sv)
gastroenteral användning—gastroenteral use/route (sv)
gastroenteral use/route
—gastro-enteraal gebruik (nl)
—gastroenteral administrering (sv)
—gastroenteral användning (sv)
—gastroenteralis alkalmazás (hu)
—gastroenterální podání (cs)
—gastroenteralt bruk (sv)
—gastrointestinale Anwendung (de)
—podanie do przewodu pokarmowego (pl)
—uso gastrointestinale (it)
—vartoti į skrandį ir žarnyną (lt)
—via gastroentérica (pt)
—vía gastroentérica (es)
—voie gastro-entérale (fr)
—γαστρεντερική χρήση (el)
gastroenteralis alkalmazás—gastroenteral use/route (hu)
gastroenterální podání—gastroenteral use/route (cs)
gastroenteralt bruk—gastroenteral use/route (sv)
gastrointestinale Anwendung—gastroenteral use/route (de)
gaz do inhalacji—gas (for inhalation) (pl)
gaz pour inhalation—gas (for inhalation) (fr)
Gaze—dressing (de)
geïmpregneerd verband—medicated bandage (nl)
geïmpregneerd verbandgaas—medicated dressing (nl)
gel
—Gel (de)
—gel (cs,es,fr,it,nl,pt,sv)
—gél (hu)
—gelis (lt)
—żel (pl)
—γέλη (el)
dental gel
—dantų gelis (lt)
—Dentalgel (de)
—dentalgel (sv)
—fogászati gél (hu)
—gel dentaire (fr)
—gel dental (es,pt)
—gel dentale (it)
—gel voor dentaal gebruik (nl)
—żel dozębowy (pl)
—zubní gel (cs)
—οδοντική γέλη (el)
eye gel
—akių gelis (lt)
—Augengel (de)
—gel oftálmico (es,pt)
—gel oftalmico (it)
—gel ophtalmique (fr)
—oční gel (cs)
—ögongel (sv)
—ooggel (nl)
—szemgél (hu)
—żel do oczu (pl)
—οφθαλμική γέλη (el)
oral gel
—belsőleges gél (hu)
—gel oral (es,fr,pt)
—gel orale (it)

cs=Czech; de=German; el=Greek; es=Spanish; fr=French; hu=Hungarian; it=Italian; lt=Lithuanian; nl=Dutch; pl=Polish; pt=Portuguese; sv=Swedish

—gel voor oraal gebruik (nl)
—Gel zur Anwendung in der Mundhöhle (de)
—Mundgel (de)
—munhålegel (sv)
—oral gel (sv)
—perorální gel (cs)
—ústní gel (cs)
—valgomasis gelis (lt)
—żel doustny (pl)
—πόσιμη γέλη (el)
topical (cutaneous) gel
—gél, bőrön való alkalmazásra (hu)
—gel cutâneo (pt)
—gel cutaneo (it)
—gel de aplicación tópica (es)
—gel k zevnímu použití (cs)
—gel per uso topico (it)
—gel pour application cutanée (fr)
—gel pour application locale (fr)
—gel tópico (es)
—gel voor lokaal gebruik (nl)
—Gel zur Anwendung auf der Haut (de)
—Gel zur topischen Anwendung (de)
—topický gel (cs)
—topikal gel (sv)
—vietinis gelis (lt)
—żel na skórę (pl)
—τοπική γέλη (el)
urethral gel
—gel do močové trubice (cs)
—gel uretrale (it)
—gel urétral (fr)
—gel uretral (es,pt)
—gel voor urethraal gebruik (nl)
—Gel zur Anwendung in der Harnröhre (de)
—húgycsőgél (hu)
—šlaplės gelis (lt)
—uretralgel (sv)
—uretrální gel (cs)
—żel do cewki moczowej (pl)
—ουρηθρική γέλη (el)
vaginal gel
—gel de aplicación vaginal (es)
—gel vaginale (it)
—gel vaginal (es,fr,pt)
—gel voor vaginaal gebruik (nl)
—hüvelygél (hu)
—makšties gelis (lt)
—poševni gel (cs)
—Vaginalgel (de)
—vaginalgel (sv)
—vaginální gel (cs)
—żel dopochwowy (pl)
—κολπική γέλη (el)
Gel—gel (de)
gel—gel (cs,es,fr,it,nl,pt,sv)
gél—gel (hu)
gél, bőrön való alkalmazásra—topical gel (hu)
gel cutâneo—topical gel (pt)
gel cutaneo—topical gel (it)
gel de aplicación tópica—topical gel (es)
gel de aplicación vaginal—vaginal gel (es)
gel dentaire—dental gel (fr)
gel dental—dental gel (es,pt)
gel dentale—dental gel (it)
gel do močové trubice—urethral gel (cs)
gel k zevnímu použití—topical gel (cs)
gel oftálmico—eye gel (es,pt)
gel oftalmico—eye gel (it)
gel ophtalmique—eye gel (fr)
gel oral—oral gel (es,fr,pt)
gel orale—oral gel (it)
gel per uso topico—topical gel (it)
gel pour application locale/cutanée—topical gel (fr)
gel tópico—topical gel (es)
gel urétral—urethral gel (fr)
gel uretral—urethral gel (es,pt)
gel uretrale—urethral gel (it)
gel vaginal—vaginal gel (es,fr,pt)
gel vaginale—vaginal gel (it)
gel voor dentaal gebruik—dental gel (nl)
gel voor lokaal gebruik—topical gel (nl)
gel voor oraal gebruik—oral gel (nl)
gel voor urethraal gebruik—urethral gel (nl)
gel voor vaginaal gebruik—vaginal gel (nl)
Gel zur Anwendung auf der Haut—topical gel (de)
Gel zur Anwendung in der Harnröhre—urethral gel (de)
Gel zur Anwendung in der Mundhöhle—oral gel (de)
Gel zur topischen Anwendung—topical gel (de)
gelis—gel (lt)
gélule—capsule, hard capsule (fr)
gélule à enrobage entérique—enteric-coated (gastro-resistant) capsule (fr)
gélule à libération prolongée—extended-release capsule (fr)
gélule à libération retardée—extended-release capsule (fr)
gélule gastro-résistante—enteric-coated (gastro-resistant) capsule (fr)
geriamasis švirkštas—oral syringe (lt)
geriamasis tirpalas—oral solution (lt)
geriamieji lašai—oral drops (lt)
geriamieji milteliai—oral powder (lt)
geriamoji suspensija—oral suspension (lt)
geriamosios granulės—oral granules (lt)
gerklės purškalas—throat spray (lt)
gerti—oral use/route (lt)
globules (homoeopathic)
—globulės (homeopatinės) (lt)
—globules (fr)
—Globuli (de)
—globuli (it,nl,sv)
—glóbulos (homeopáticos) (es)
—golyócskák (hu)
—granules (fr)
—granuli (it)
—grânulos (pt)
—peletki (pl)
—pigułki (pl)
—piliulės (lt)
—Streukügelchen (de)
—σταγονίδια (ομοιπαθητικής) (el)
—καταπότια (el)
globules—globules (homoeopathic) (fr)
globulės (homeopatinės)—globules (homoeopathic) (lt)
Globuli—globules (homoeopathic) (de)
globuli—globules (homoeopathic) (it, nl,sv)
globulka—pessary, vaginal suppository (pl)
glóbulos (homeopáticos)—globules (homoeopathic) (es)
gocce—drops (it)
gocce auricolari—ear drops (it)
gocce nasali—nasal drops (it)
gocce per uso orale—oral drops (it)
godet—cup (measuring) (fr)
golyócskák—globules (homoeopathic) (hu)
gom—gum (nl)
goma—gum (es,pt)
goma de mascar—chewing gum (es)
gomma—gum (it)
gomma da masticare—chewing gum (it)
gomme—gum (fr)
gomme à mâcher—chewing gum (fr)
gorgeldrank—gargle (nl)
gotas—drops (es,pt)
gotas auriculares—ear drops (pt)
gotas nasais—nasal drops (pt)
gotas nasales—nasal drops (es)
gotas oftálmicas—eye drops (es,pt)
gotas orais—oral drops (pt)
gotas orales—oral drops (es)
gotas óticas—ear drops (es)
gouttes—drops (fr)
gouttes nasales—nasal drops (fr)
gouttes orales—oral drops (fr)
gouttes otiques—ear drops (fr)
gőz belégzésre—vapour inhalation (hu)
granulaat—granules (nl)
granulaat voor drank—granules for oral solution (nl)
granulaat voor oraal gebruik—oral granules (nl)
granulaat voor orale suspensie—granules for oral suspension (nl)
granulado—oral granules (pt)
granulado—granules (es,pt)
granulado efervescente—effervescent granules (es,pt)
granulado oral—oral granules (es)
granulado para solução oral—granules for oral solution (pt)
granulado para solución oral—granules for oral solution (es)
granulado para suspensão oral—granules for oral suspension (pt)
granulado para suspensión oral—granules for oral suspension (es)
Granulat—granules, oral granules (de)
granulat—granules, oral granules (pl)
granulat—granules (sv)
granulát—granules (cs)
granulat do sporządzania roztworu doustnego—granules for oral solution (pl)
granulat do sporządzania zawiesiny doustnej—granules for oral suspension (pl)
granulat för oral användning—oral granules (sv)
granulat musujący—effervescent granules (pl)
granulat till oral lösning—granules for oral solution (sv)
granulat till oral suspension—granules for oral suspension (sv)
Granulat zum Einnehmen—oral granules (de)
Granulat zur Herstellung einer Lösung zum Einnehmen—granules for oral solution (de)
Granulat zur Herstellung einer Suspension zum Einnehmen—granules for oral suspension (de)
granulato—granules (it)
granulato effervescente—effervescent granules (it)
granulato per soluzione orale—granules for oral solution (it)
granulato per sospensione orale—granules for oral suspension (it)
granulato per uso orale—oral granules (it)
granulátum—oral granules (hu)
granulátum—granules (hu)
granulátum belsőleges oldathoz—granules for oral solution (hu)
granulátum belsőleges szuszpenzióhoz—granules for oral suspension (hu)
granules
—granulaat (nl)
—granulado (es,pt)
—Granulat (de)
—granulat (pl,sv)
—granulát (cs)
—granulato (it)
—granulátum (hu)
—granulés (fr)
—granulės (lt)
—gránulos (es)
—zrněný prášek (cs)
—κοκκία (el)
effervescent granules
—Brausegranulat (de)
—bruisgranulaat (nl)
—brusgranulat (sv)
—granulado efervescente (es,pt)
—granulat musujący (pl)
—granulato effervescente (it)
—granulés effervescents (fr)
—peszgőgranulátum (hu)
—putojančios granulės (lt)
—šnypščiosios granulės (lt)
—šumivý granulát (cs)
—šumivý zrněný prášek (cs)
—αναβράζοντα κοκκία (el)
oral granules
—geriamosios granulės (lt)
—granulaat voor oraal gebruik (nl)
—granulado oral (es)
—granulado (pt)
—Granulat (de)
—granulat (pl)
—granulat för oral användning (sv)
—Granulat zum Einnehmen (de)
—granulato per uso orale (it)
—granulátum (hu)
—granulés oraux (fr)
—gránulos orales (es)
—perorální zrněný prášek (cs)
—πόσιμα κοκκία (el)
granules—globules (homoeopathic) (fr)
granulés—granules (fr)
granulės—granules (lt)
granulés effervescents—effervescent granules (fr)
granules for oral solution
—granulaat voor drank (nl)
—granulado para solução oral (pt)
—granulado para solución oral (es)
—granulat do sporządzania roztworu doustnego (pl)
—granulat till oral lösning (sv)
—Granulat zur Herstellung einer Lösung zum Einnehmen (de)
—granulato per soluzione orale (it)
—granulátum belsőleges oldathoz (hu)
—granulės geriamajam tirpalui (lt)
—granulés pour solution buvable (fr)
—zrněný prášek pro přípravu perorálního roztoku (cs)
—κοκκία για πόσιμο διάλυμα (el)
granules for oral suspension
—granulaat voor orale suspensie (nl)
—granulado para suspensão oral (pt)
—granulado para suspensión oral (es)
—granulat do sporządzania zawiesiny doustnej (pl)
—granulat till oral suspension (sv)
—Granulat zur Herstellung einer Suspension zum Einnehmen (de)
—granulato per sospensione orale (it)
—granulátum belsőleges szuszpenzióhoz (hu)
—granulės geriamajai suspensijai (lt)
—granulés pour suspension buvable (fr)
—zrněný prášek pro přípravu perorální suspenze (cs)
—κοκκία για πόσιμο εναιώρημα (el)
granulės geriamajai suspensijai—granules for oral suspension (lt)
granulės geriamajam tirpalui—granules for oral solution (lt)
granulés oraux—oral granules (fr)
granulés pour solution buvable—granules for oral solution (fr)
granulés pour suspension buvable—granules for oral suspension (fr)
granuli—globules (homoeopathic) (it)
gránulos—granules (es)
grânulos—globules (homoeopathic) (pt)
gránulos orales—oral granules (es)
gum
—dantenos (lt)
—gom (nl)
—goma (es,pt)
—gomma (it)
—gomme (fr)
—guma (cs,pl)
—gumi (hu)
—Gummi (de)
—gummi (sv)
—κόμμι (el)
guma—gum (cs,pl)
guma do żucia—chewing gum (pl)
gumi—gum (hu)
Gummi—gum (de)
gummi—gum (sv)
Gurgellösung—gargle (de)

gurgelvatten—gargle (sv)
gyeremek kanál—dessertspoon (10mL) (hu)
gyermekbiztos zárás—child-resistant closure (hu)
gyógyszeres hüvelyszivacs—vaginal sponge (hu)
gyógyszeres körömlakk—medicated nail lacquer (hu)
gyógyszeres lemezke—insert (hu)
gyógyszeres rúd—medicated stick (hu)
gyógytea—tea (herbal or medicinal) (hu)
gyógyszeres tapasz—plaster (hu)
gyomornedv-ellenálló kapszula—enteric-coated (gastro-resistant) capsule (hu)
gyomornedv-ellenálló tabletta—enteric-coated (gastro-resistant) tablet (hu)

H

Haarwaschmittel—shampoo (de)
hab—foam (hu)
hajasfejbőr kezelésre szánt oldat—scalp lotion (hu)
halsspray—throat spray (sv)
hard capsule—*see under* capsule
hård kapsel—hard capsule (sv)
harde capsule—hard capsule (nl)
Hartkapsel—hard capsule (de)
Hautspray—cutaneous spray (de)
Heftpflaster—plaster (dressing or adhesive plaster) (de)
Heilverband—medicated bandage (de)
helyi alakalmazású oldat—topical solution (hu)
herbata—tea (pl)
hintőpor—topical powder (hu)
hoestdrank—cough mixture (nl)
hoestsiroop—cough syrup (nl)
hoeststroop—cough syrup (nl)
hólyagöblítő oldat—bladder irrigation (hu)
hoofdlotion—scalp lotion (nl)
hostmedicin—cough mixture, cough syrup, linctus (sv)
hubka—sponge (cs)
hudsvamp—cutaneous sponge (sv)
húgycsőgél—urethral gel (hu)
huidspray—cutaneous spray (nl)
huile—oil (fr)
Hustensaft—cough mixture, cough syrup (de)
Hustensirup—cough syrup, cough mixture (de)
hüvelygél—vaginal gel (hu)
hüvelyhab—vaginal foam (hu)
hüvelykapszula—vaginal capsule (hu)
hüvelykenőcs—vaginal ointment (hu)
hüvelykrém—vaginal cream (hu)
hüvelykúp—pessary (hu)
hüvelykúp—vaginal suppository (hu)
hüvelyöblítés—douche (vaginal) (hu)
hüvelyoldat—vaginal solution (hu)
hüvelytabletta—vaginal tablet (hu)

I

įdėklas—insert (lt)
impianto—implant (it)
impiastro—poultice (it)
impiastro medicato—medicated plaster (it)
implant
—impianto (it)
—implant (fr,pl)
—implantaat (nl)
—implantas (lt)
—Implantat (de)
—implantat (sv)
—implantát (cs)
—implantátum (hu)
—implante (es,pt)
—εμφύτευμα (el)
implant—implant (fr,pl)
implantaat—implant (nl)
implantas—implant (lt)
Implantat—implant (de)
implantat—implant (sv)
implantát—implant (cs)
implantátum—implant (hu)
implante—implant (es,pt)
imprägnierte Verband—medicated dressing (de)
impregnált kötszer—medicated bandage (hu)
impregnált kötszer—medicated dressing (hu)
impregnuotasis tvarstis—medicated dressing (lt)
inalação por vaporização—vapour inhalation (pt)
inalador—inhaler (pt)
inalatore—inhaler (it)
inalatore con dosatore—aerosol inhaler (it)
inalatore pressurizzato a dose predeterminata—aerosol inhaler (it)
inalazione—inhalation (it)
Infus—tea (herbal or medicinal) (de)
infusão—infusion (pt)
infusie—infusion (nl)
infusion
—infusão (pt)
—infusie (nl)
—infusione (it)
—infusion (sv)
—infuze (cs)
—infuzija (lt)
—infúzió (hu)
—perfusão (pt)
—perfusion (fr)
—έγχυση (el)
solution for infusion
—infusionslösning (sv)
—Infusionslösung (de)
—infusionsvätska (sv)
—infuzinis tirpalas (lt)
—infuzní roztok (cs)
—Lösung zur Infusion (de)
—oldatos infúzió (hu)
—oplossing voor infusie (nl)
—roztwór do infuzji (pl)
—solução para perfusão (pt)
—solución para infusión (es)
—solution pour perfusion (fr)
—soluzione per infusione (it)
—διάλυμα για έγχυση (el)
infusion—infusion (sv)
infusion—tea (fr)
infusión—tea (es)
infusione—infusion (it)
infusionslösning—solution for infusion (sv)
Infusionslösung—solution for infusion (de)
Infusionslösungskonzentrat—concentrate for infusion (solution) (de)
infusionsvätska—solution for infusion (sv)
infuze—infusion (cs)
infuzija—infusion (lt)
infuzinis tirpalas—solution for infusion (lt)
infúzió—infusion (hu)
infuzní roztok—solution for infusion (cs)
inhalace—inhalation (cs)
inhalációs alkalmazás—inhalation (route) (hu)
inhalációs gáz—gas (for inhalation) (hu)
inhalacja parowa—vapour inhalation (pl)
inhalační podání—inhalation (route) (cs)
inhalador—inhaler (es)
inhalador aerosol—aerosol inhaler (es)
inhalateur—inhaler (fr)
inhalatie—inhalation (nl)
inhalatie—inhalation (route) (nl)
inhalatiedamp—vapour inhalation (nl)
inhalatiegas—gas (for inhalation) (nl)
inhalatieoplossing—solution for inhalation (nl)
inhalatiepoeder—powder for inhalation (nl)
inhalatiesuspensie—suspension for inhalation (nl)
inhalation (*as preparation/process*)
—belégzés (hu)
—inalazione (it)
—inhalace (cs)
—inhalatie (nl)
—inhalation (sv)
—inhaliacija (lt)
—εισπνοή (el)
powder for inhalation
—belégzőpor (hu)
—inhalatiepoeder (nl)
—inhalationspulver (sv)
—inhaliaciniai milteliai (lt)
—pó para inalação (pt)
—polvere per inalazione (it)
—polvo para inhalación (es)
—poudre pour inhalation (fr)
—prášek k inhalaci (cs)
—proszek do inhalacji (pl)
—Pulver zur Inhalation (de)
—κόνις για εισπνοή (el)
solution for inhalation
—inhalatieoplossing (nl)
—Inhalationslösung (de)
—inhalationsvätska (sv)
—inhaliacinis tirpalas (lt)
—oldat belégzésre (hu)
—roztok k inhalaci (cs)
—roztwór do inhalacji (pl)
—solução para inalação (pt)
—solución para inhalación (es)
—solution pour inhalation (fr)
—soluzione per inalazione (it)
—διάλυμα για εισπνοή (el)
suspension for inhalation
—inhalatiesuspensie (nl)
—inhaliacinė suspencija (lt)
—sospensione per inalazione (it)
—suspensão para inalação (pt)
—suspension för inhalation (sv)
—suspensión para inhalación (es)
—suspension pour inhalation (fr)
—Suspension zur Inhalation (de)
—suspenze k inhalaci (cs)
—szuszpenzió belégzésre (hu)
—zawiesina do inhalacji (pl)
—εναιώρημα για εισπνοή (el)
vapour inhalation
—Dampf zur Inhalation (de)
—fumenti (it)
—gőz belégzésre (hu)
—inalação por vaporização (pt)
—inhalacja parowa (pl)
—inhalatiedamp (nl)
—inhalationsånga (sv)
—inhaliaciniai garai (lt)
—přípravek k inhalaci parou (cs)
—suffumigi (it)
—vapeur pour inhalation (fr)
—vapor para inhalación (es)
—εισπνεόμενος ατμός (el)
inhalation (*route*)
—användning för inhalation (sv)
—inhalációs alkalmazás (hu)
—inhalační podání (cs)
—inhalatie (nl)
—inhalation (sv)
—inhaliuoti (lt)
—podanie wziewne (pl)
—uso inalatorio (it)
—via inalatória (pt)
—via inalatoria (it)
—vía inhalatoria (es)
—voie inhalée (fr)
—zur Inhalation (de)
—χρήση δία εισπνοής (el)
inhalation—inhalation (sv)
inhalationsaerosol—aerosol inhaler (sv)
inhalationsånga—vapour inhalation (sv)
inhalationsånga—gas (for inhalation) (sv)
Inhalationsgas—gas (for inhalation) (de)
inhalationsgas—gas (for inhalation) (sv)
Inhalationslösung—solution for inhalation (de)
inhalationspulver—powder for inhalation (sv)
inhalationsspray—aerosol inhaler (sv)
inhalationsvätska—solution for inhalation (sv)
inhalátor—inhaler (cs)
Inhalator—inhaler (de)
inhalator—inhaler (nl,pl,sv)
inhalator aerozolu—aerosol inhaler (pl)
inhaler
—belégző készülék (hu)
—inhalador (pt)
—inhalatore (it)
—inhalador (es)
—inhalateur (fr)
—inhalátor (cs)
—Inhalator (de)
—inhalator (nl,pl,sv)
—inhaliatorius (lt)
—συσκευή εισπνοής (el)
aerosol inhaler
—inhalatore pressurizzato a dose predeterminata (it)
—aerosol belégzésre (hu)
—aérosol doseur (fr)
—aerosolinhalator (nl)
—aerossol inalador dosificador (pt)
—aerozolinis inhaliatorius (lt)
—dávkovací aerosol (cs)
—Dosier-Aerosol (de)
—Druckgasinhalation (de)
—inhalatore con dosatore (it)
—inhalador aerosol (es)
—inhalationsaerosol (sv)
—inhalationsspray (sv)
—inhalator aerozolu (pl)
—αερόλυμα εισπνοής (el)
inhaliacija—inhalation (lt)
inhaliacinė suspencija—suspension for inhalation (lt)
inhaliacinės dujos—gas (for inhalation) (lt)
inhaliaciniai garai—vapour inhalation (lt)
inhaliaciniai milteliai—powder for inhalation (lt)
inhaliacinis tirpalas—solution for inhalation (lt)
inhaliatorius—inhaler (lt)
inhaliuoti—inhalation (route) (lt)
iniezione—injection (it)
injecção—injection (pt)
injectie—injection (nl)
injekce—injection (cs)
injekcija—injection (lt)
injekció—injection (hu)
injektion—injection (sv)
—ένεση (el)
powder for injection
—injekciniai milteliai (lt)
—pó para uso injectável (pt)
—poeder voor injectie (nl)
—polvere per soluzione iniettabile (it)
—polvo para solución inestable (es)
—por injekcióhoz (hu)
—poudre pour solution injectable (fr)
—prášek pro přípravu injekčního roztoku (cs)
—proszek do sporządzania roztworu do wstrzykiwań (pl)
—pulver till injektionsvätska (sv)
—Pulver zur Herstellung einer Injektionslösung (de)
—κόνις για ένεση (el)
solution for injection
—injektionslösning (sv)
—injectievloeistof (nl)

cs=Czech; de=German; el=Greek; es=Spanish; fr=French; hu=Hungarian; it=Italian; lt=Lithuanian; nl=Dutch; pl=Polish; pt=Portuguese; sv=Swedish

—injekcinis tirpalas (lt)
—injekční roztok (cs)
—Injektionslösung (de)
—injektionsvätska (sv)
—lösning till injektionsvätska (sv)
—Lösung zur Injektion (de)
—oldatos injekció (hu)
—oplossing voor injectie (nl)
—roztwór do wstrzykiwań (pl)
—solução injectável (pt)
—solución inestable (es)
—solution injectable (fr)
—soluzione iniettabile (it)
—ενέσιμο διάλυμα (el)
suspension for injection
—injekcinė suspensija (lt)
—injekční suspenze (cs)
—Injektionssuspension (de)
—sospensione iniettabile (it)
—suspensão injectável (pt)
—suspensie voor injectie (nl)
—suspensión inestable (es)
—suspension injectable (fr)
—suspension till injektionsvätska (sv)
—Suspension zur Injektion (de)
—szuszpenziós injekció (hu)
—zawiesina do wstrzykiwań (pl)
—ενέσιμο εωαιώρημα (el)
injekce—injection (cs)
injekcija—injection (lt)
injekcinė suspensija—suspension for injection (lt)
injekciniai milteliai—powder for injection (lt)
injekcinis tirpalas—solution for injection (lt)
injekció—injection (hu)
injekciós üveg—vial (hu)
injekční lahvička—vial (cs)
injekční roztok—solution for injection (cs)
injekční stříkačka—syringe (cs)
injekční suspenze—suspension for injection (cs)
injektion—injection (sv)
injektionsflaska—vial (sv)
injektionslösning—solution for injection (sv)
Injektionslösung—solution for injection (de)
Injektionssuspension—suspension for injection (de)
injektionsvätska—solution for injection (sv)
inlägg—insert (sv)
inserción—insert (es)
insert
—gyógyszeres lemezke (hu)
—įdėklas (lt)
—inlägg (sv)
—inserción (es)
—Insert (de)
—insert (fr,nl)
—inserto (es,it,pt)
—inzert (cs)
—wkładka (pl)
—ένθεμα (el)
ocular insert
—akių įdėklas (lt)
—Augeninsert (de)
—insert ophtalmique (fr)
—inserto oculare (it)
—inserto oftálmico (es,pt)
—očni inzert (cs)
—ögonlamell (sv)
—ooginsert (nl)
—system terapeutyczny do oczu (pl)
—szemészeti gyógyszeres lemezke (hu)
—οφθαλμικό ένθεμα (el)
—σκεύασμα ενδοφθαλμικής εισαγωγής (el)
Insert—insert (de)
insert—insert (fr,nl)
insert ophtalmique—ocular insert (fr)
inserto—insert (es,it,pt)
inserto oculare—ocular insert (it)
inserto oftálmico—ocular insert (es,pt)
instillation nasale—nasal drops (fr)
intra-arterial use/route
—intraarterialis alkalmazás (hu)
—intraarteriální podání (cs)
—intra-arterieel gebruik (nl)
—intra-arteriell administrering (sv)
—intra-arteriell användning (sv)
—intraarterielle Anwendung (de)
—intra-arteriellt bruk (sv)
—podanie dotętnicze (pl)
—uso endoarterioso (it)
—vartoti į arteriją (lt)
—via endoarteriosa (it)
—via intra-arterial (pt)
—vía intraarterial (es)
—voie intra-artérielle (fr)
—ενδοαρτηριακή χρήση (el)
intraarterialis alkalmazás—intra-arterial use/route (hu)
intraarteriální podání—intra-arterial use/route (cs)
intra-arterieel gebruik—intra-arterial use/route (nl)
intra-arteriell administrering—intra-arterial use/route (sv)
intra-arteriell användning—intra-arterial use/route (sv)
intraarterielle Anwendung—intra-arterial use/route (de)
intra-arteriellt bruk—intra-arterial use/route (sv)
intra-articulair gebruik—intra-articular use/route (nl)
intra-articular use/route
—intra-articulair gebruik (nl)
—intraarticularis alkalmazás (hu)
—intra-artikulär administrering (sv)
—intra-artikulär användning (sv)
—intraartikuläre Anwendung (de)
—intraartikulární podání (cs)
—intra-artikulärt bruk (sv)
—podanie dostawowe (pl)
—uso intra-articolare (it)
—vartoti į sąnarį (lt)
—via intra-articular (pt)
—vía intraarticular (es)
—voie intra-articulaire (fr)
—ενδοαρθρική χρήση (el)
intraarticularis alkalmazás—intra-articular use/route (hu)
intra-artikulär administrering—intra-articular use/route (sv)
intra-artikulär användning—intra-articular use/route (sv)
intraartikuläre Anwendung—intra-articular use/route (de)
intraartikulární podání—intra-articular use/route (cs)
intra-artikulärt bruk—intra-articular use/route (sv)
intracavernalis alkalmazás—intracavernosal use/route (hu)
intracaverneus gebruik—intracavernosal use/route (nl)
intracavernosal use/route
—intracavernalis alkalmazás (hu)
—intracaverneus gebruik (nl)
—intrakavernös administrering (sv)
—intrakavernös användning (sv)
—intrakavernöse Anwendung (de)
—intrakavernöst bruk (sv)
—intrakavernózní podání (cs)
—podanie do ciała jamistego (pl)
—uso intracavernoso (it)
—vartoti į akytkūnį (lt)
—via intracavernosa (it,pt)
—vía intracavernosa (es)
—voie intracaverneuse (fr)
—ενδοσηραγγική χρήση (el)
intradermaal gebruik—intradermal use/route (nl)
intradermal användning—intradermal use/route (sv)
intradermal use/route
—intradermaal gebruik (nl)
—intradermal användning (sv)
—intradermale Anwendung (de)
—intradermalis alkalmazás (hu)
—intradermální podání (cs)
—intrakutan administrering (sv)
—intrakutant bruk (sv)
—podanie śródskórne (pl)
—uso intradermico (it)
—vartoti į odą (lt)
—via intradérmica (pt)
—via intradermica (it)
—vía intradérmica (es)
—voie intradermique (fr)
—ενδοδερμική χρήση (el)
intradermale Anwendung—intradermal use/route (de)
intradermalis alkalmazás—intradermal use/route (hu)
intradermální podání—intradermal use/route (cs)
intrakavernös administrering—intracavernosal use/route (sv)
intrakavernös användning—intracavernosal use/route (sv)
intrakavernöse Anwendung—intracavernosal use/route (de)
intrakavernöst bruk—intracavernosal use/route (sv)
intrakavernózní podání—intracavernosal use/route (cs)
intrakutan administrering—intradermal use/route (sv)
intrakutant bruk—intradermal use/route (sv)
intralaesionaal gebruik—intra-lesional use/route (nl)
intralaesionalis alkalmazás—intra-lesional use/route (hu)
intraläsionale Anwendung—intra-lesional use/route (de)
intra-lesional use/route
—intralaesionaal gebruik (nl)
—intralaesionalis alkalmazás (hu)
—intraläsionale Anwendung (de)
—intralesionell administrering (sv)
—intralesionell användning (sv)
—intralesionellt bruk (sv)
—intralezionální podání (cs)
—podanie doogniskowe (pl)
—uso intralesionale (it)
—uso intralesional (pt)
—vartoti į pažeistą vietą (lt)
—vía intralesional (es)
—voie intralésionelle (fr)
—ενδοβλαβική χρήση (el)
intralesionell administrering—intra-lesional use/route (sv)
intralesionell användning—intra-lesional use/route (sv)
intralesionellt bruk—intra-lesional use/route (sv)
intralezionální podání—intra-lesional use/route (cs)
intramusculair gebruik—intramuscular use/route (nl)
intramuscular use/route
—intramusculair gebruik (nl)
—intramuscularis alkalmazás (hu)
—intramuskulär administrering (sv)
—intramuskulär användning (sv)
—intramuskuläre Anwendung (de)
—intramuskulární podání (cs)
—intramuskulärt bruk (sv)
—podanie domięśniowe (pl)
—uso intramuscolare (it)
—vartoti į raumenis (lt)
—via intramuscular (pt)
—vía intramuscular (es)
—voie intramusculaire (fr)
—ενδομυική χρήση (el)
intramuscularis alkalmazás—intramuscular use/route (hu)
intramuskulär administrering—intramuscular use/route (sv)
intramuskulär användning—intramuscular use/route (sv)
intramuskuläre Anwendung—intramuscular use/route (de)
intramuskulární podání—intramuscular use/route (cs)
intramuskulärt bruk—intramuscular use/route (sv)
intraperitoneaal gebruik—intraperitoneal use/route (nl)
intraperitoneal administrering—intraperitoneal use/route (sv)
intraperitoneal användning—intraperitoneal use/route (sv)
intraperitoneal use/route
—intraperitoneaal gebruik (nl)
—intraperitoneal administrering (sv)
—intraperitoneal användning (sv)
—intraperitoneale Anwendung (de)
—intraperitonealis alkalmazás (hu)
—intraperitoneální podání (cs)
—intraperitonealt bruk (sv)
—podanie dootrzewnowe (pl)
—uso intraperitoneale (it)
—vartoti į pilvaplėvės ertmę (lt)
—via intraperitoneal (pt)
—vía intraperitoneal (es)
—voie intrapéritonéale (fr)
—ενδοπεριτοναϊκή χρήση (el)
intraperitoneale Anwendung—intraperitoneal use/route (de)
intraperitonealis alkalmazás—intraperitoneal use/route (hu)
intraperitoneální podání—intraperitoneal use/route (cs)
intraperitonealt bruk—intraperitoneal use/route (sv)
intratekal administrering—intrathecal use/route (sv)
intratekal användning—intrathecal use/route (sv)
intratekální podání—intrathecal use/route (cs)
intratekalt bruk—intrathecal use/route (sv)
intrathecaal gebruik—intrathecal use/route (nl)
intrathecal use/route
—intratekal administrering (sv)
—intratekal användning (sv)
—intratekální podání (cs)
—intratekalt bruk (sv)
—intrathecaal gebruik (nl)
—intrathecalis alkalmazás (hu)
—intrathekale Anwendung (de)
—podanie dooponowe (pl)
—uso intratecale (it)
—vartoti intratekaliai (lt)
—via intratecal (pt)
—vía intratecal (es)
—voie intrarachidienne (fr)
—ενδορραχιαία χρήση (el)
intrathecalis alkalmazás—intrathecal use/route (hu)
intrathekale Anwendung—intrathecal use/route (de)
intra-uterien gebruik—intrauterine use/route (nl)
intrauterin administrering—intrauterine use/route (sv)
intrauterin alkalmazás—intrauterine use/route (hu)
intrauterin användning—intrauterine use/route (sv)
intrauterine Anwendung—intrauterine use/route (de)
intra-uterine device (IUD)/intra-uterine system
—afleveringsysteem voor intra-uterien gebruik (nl)
—dispositif intra-utérin (fr)
—dispositivo de libertação intra-uterino (pt)
—dispositivo intrauterino (es)
—dispositivo intrauterino (it)
—DIU (es,fr)
—intrauterinní inzert (cs)
—Intrauterinpessar (de)
—intrauterint inlägg (sv)
—IUP (de)
—livmoderinlägg (sv)
—méhen belüli gyógyszerleadó rendszer (hu)
—nitroděložní tělísko (cs)
—sistema intra-uterino (pt)
—spiraaltje (nl)
—spiral (sv)

—stérilet (fr)
—system terapeutyczny domaciczny (pl)
—Vaginalpessar (de)
—vartojimo į gimdą sistema (lt)
—wkładka domaciczna (pl)
—σύστημα ενδομήτριας χορήγηση (el)

intrauterine use/route
—intra-uterien gebruik (nl)
—intrauterin administrering (sv)
—intrauterin alkalmazás (hu)
—intrauterin användning (sv)
—intrauterine Anwendung (de)
—intrauterinní podání (cs)
—intrauterint bruk (sv)
—podanie wewnątrzmaciczne (pl)
—uso intrauterino (it)
—vartoti į gimdą (lt)
—via intrauterina (it)
—via intra-uterina (pt)
—vía intrauterina (es)
—voie intra-utérine (fr)
—ενδομήτρια χρήση (el)

intrauterinní inzert—intra-uterine system (cs)
intrauterinní podání—intrauterine use/route (cs)
Intrauterinpessar—intra-uterine system (de)
intrauterint bruk—intrauterine use/route (sv)
intrauterint inlägg—intra-uterine system (sv)
intravénás alkalmazás—intravenous use/route (hu)
intraveneus gebruik—intravenous use/route (nl)
intravenös administrering—intravenous use/route (sv)
intravenös användning—intravenous use/route (sv)
intravenöse Anwendung—intravenous use/route (de)
intravenöst bruk—intravenous use/route (sv)

intravenous use/route
—intravénás alkalmazás (hu)
—intraveneus gebruik (nl)
—intravenös administrering (sv)
—intravenös användning (sv)
—intravenöse Anwendung (de)
—intravenöst bruk (sv)
—intravenózní podání (cs)
—nitrožilní podání (cs)
—podanie dożylne (pl)
—uso endovenoso (it)
—vartoti į veną (lt)
—via endovenosa (it)
—via intravenosa (pt)
—vía intravenosa (es)
—voie intraveineuse (fr)
—ενδοφλέβια χρήση (el)

intravenózní podání—intravenous use/route (cs)
intravesicaal gebruik—intravesical use/route (nl)

intravesical use/route
—intravesicaal gebruik (nl)
—intravesicalis alkalmazás (hu)
—intravesikal administrering (sv)
—intravesikal användning (sv)
—intravesikale Anwendung (de)
—intravesikalt bruk (sv)
—intravezikální podání (cs)
—podanie do pęcherza moczowego (pl)
—uso endovescicale (it)
—vartoti į šlapimo pūslę (lt)
—via intravesical (pt)
—vía intravesical (es)
—voie intravésicale (fr)
—ενδοκυστική χρήση (el)

intravesicalis alkalmazás—intravesical use/route (hu)
intravesikal administrering—intravesical use/route (sv)
intravesikal användning—intravesical use/route (sv)
intravesikale Anwendung—intravesical use/route (de)
intravesikalt bruk—intravesical use/route (sv)
intravezikální podání—intravesical use/route (cs)
inzert—insert (cs)
irrigálás—douche (vaginal) (hu)

irrigation
bladder irrigation
—Blaseninstillation (de)
—blaasspoeling (nl)
—Blasenspülung (de)
—hólyagöblítő oldat (hu)
—irrigazione vescicale (it)
—líquido para irrigação vesical (pt)
—líquido para irrigación vesical (es)
—roztok do močového měchýře (cs)
—roztok k výplachu močového měchýře (cs)
—roztwór do irygacji pęcherza moczowego (pl)
—šlapimo pūslės ploviklis (lt)
—solución para instilación de la vejiga urinaria (es)
—solution pour irrigation vésiculaire (fr)
—spolvätska för urinblåsan (sv)
—διάλυμα για έκπλυση ουροδόχου κύστεως (el)

irrigazione vescicale—bladder irrigation (it)
ištrauka—extract (lt)
IUD—*see* intra-uterine device/intra-uterine system
IUP—intra-uterine system (de)

J

jar
—boião (pt)
—burk (sv)
—kelímek (cs)
—plačiakaklis indas (lt)
—pot (fr,nl)
—słoik (pl)
—tarro (es)
—tégely (hu)
—vasetto (it)
—Weithalsgefäss (de)
—βάζο (el)

jarabe—syrup, linctus (es)
jarabe para la tos—cough syrup (es)
jarabe para la tos—cough mixture (es)
jednodávkový obal—single-dose container (cs)
jednorázová injekční stříkačka—disposable syringe (cs)
jeringa—syringe (es)
jeringa desechable—disposable syringe (es)
jeringa para uso oral—oral syringe (es)
jeringa precargada—prefilled syringe (es)

K

kąpiel—bath (pl)
kapky—drops (cs)
kapky k vnitřnímu užití—oral drops (cs)
Kappe—cap (de)
Kapsel—capsule (de)
kapsel—capsule (sv)
kapsle—capsule (cs)
kapsle enterosolventní—enteric-coated (gastro-resistant) capsule (cs)
kapsulė—capsule (lt)
kapsułka—capsule (pl)
kapsułka dojelitowa—enteric-coated (gastro-resistant) capsule (pl)
kapsułka dopochwowa—vaginal capsule (pl)
kapsułka o przedłużonym uwalnianiu—extended-release capsule (pl)
kapsyl—cap (sv)
kapszula—capsule (hu)
karštas kompresas—poultice (lt)
kartong—box (sv)
Kartusche—cartridge (de)
kataplazm—poultice (pl)
kataplazma—poultice (cs)
Kaugummi—chewing gum (de)
Kautablette—chewable tablet (de)
kauwgom—chewing gum (nl)
kauwtablet—chewable tablet (nl)
kávéskanál—teaspoon (5mL) (hu)
kávová lžička—teaspoon (5mL) (cs)
keelspray—throat spray (nl)
kelímek—jar (cs)
kemény kapszula—hard capsule (hu)
kempinė—sponge (lt)
kenőcs—ointment (hu)
kieta kapsulė—hard capsule (lt)
kietoji pastilė—lozenge (lt)
kietoji tabletė—lozenge (lt)
kindergesicherter Verschluss—child-resistant closure (de)
kinderveilige sluiting—child-resistant closure (nl)
kivaonat—extract (hu)
Klistier—enema (de)
klizma—enema (hu,lt)
klizmos užlaikymas—retention enema (lt)
kloktadlo—gargle (cs)
Klysma—enema (de)
klysma—enema (nl,sv)
klystýr—enema (cs)
klyzma—enema (cs)
kombinált csomagolás—combination pack (hu)
kombinationsförpackning—combination pack (sv)
kombinované balení—combination pack (cs)
kombinuotas pakelis—combination pack (lt)
Kombipackung—combination pack (de)
kompres—dressing (cs,nl)
kompress—dressing (sv)
Kompressionsbandage—bandage (de)
koncentrat do sporządzania roztworu do infuzji—concentrate for infusion (solution) (pl)
koncentrát pro přípravu infuzního roztoku—concentrate for infusion (solution) (cs)
koncentrat till infusionslösning—concentrate for infusion (solution) (sv)
koncentrat till infusionsvätska—concentrate for infusion (solution) (sv)
koncentratas infuziniam tirpalui—concentrate for infusion (solution) (lt)
koncentrátum oldatos infúzióhoz—concentrate for infusion (solution) (hu)
Konzentrat zur Herstellung einer Infusionslösung—concentrate for infusion (solution) (de)
Kopfhaut-Lotion—scalp lotion (de)
kopp—cup (sv)
köptető—cough mixture (hu)
köptető szirup—cough syrup (hu)
kötszer—bandage, dressing (hu)
koupel—bath (cs)
kožní emulze—cutaneous emulsion (cs)
kožní hubka—cutaneous sponge (cs)
kožní pasta—cutaneous paste (cs)
kožní podání—cutaneous use/route (cs)
kožní roztok—cutaneous solution (cs)
kožni sprej—cutaneous spray (cs)
krabička—box (cs)
kräm—cream (sv)
kramtomoji guma—chewing gum (lt)
kramtomoji tabletė—chewable tablet (lt)
krem—cream (pl)
krém—cream (cs,hu)
krem dopochwowy—vaginal cream (pl)
kremas—cream (lt)
krople—drops (pl)
krople do nosa—nasal drops (pl)
krople do oczu—eye drops (pl)
krople do uszu—ear drops (pl)
krople doustne—oral drops (pl)
kruidenthee—tea (herbal or medicinal) (nl)
krytí—dressing (cs)
krytí s léčivou látkou—medicated dressing (cs)
külsőleges alkalmazás—cutaneous use/route (hu)
külsőleges emulzió—cutaneous emulsion (hu)
külsőleges emulzió—topical emulsion (hu)
külsőleges gyógyszeres szivacs—cutaneous sponge (hu)
külsőleges oldat—cutaneous solution (hu)
külsőleges paszta—cutaneous paste (hu)
külsőleges permet—cutaneous spray (hu)
külsőleges por—dusting (cutaneous) powder (hu)
kupak—cap (hu)
kutan administrering—cutaneous use/route (sv)
kutan användning—cutaneous use/route (sv)
kutan emulsion—cutaneous emulsion (sv)
kutan lösning—cutaneous solution (sv)
kutan pasta—cutaneous paste (sv)
kutan spray—cutaneous spray (sv)
kutan svamp—cutaneous sponge (sv)
kutant bruk—cutaneous use/route (sv)

L

låda—box (sv)
lágy kapszula—soft capsule (hu)
láhev—bottle (cs)
läkemedelsblandning i flytande form—mixture (sv)
lápis cutâneo (skin)—medicated stick (pt)
lašai—drops (lt)
laužiama tabletė—breakable or dividable tablet (lt)
lavanda vaginale—douche (vaginal) (it)
lavemang—enema (sv)
lavemangsvätska—enema (sv)
lavement—enema (fr)
lavement de rétention—retention enema (fr)
léčivá kožní tyčinka (for skin)—medicated stick (cs)
léčivá náplast—medicated plaster (cs)
léčivý čaj—tea (herbal or medicinal) (cs)
léčivý lak na nehty—medicated nail lacquer (cs)
léčivý obvaz—medicated bandage (cs)
léčivý obvaz—medicated dressing (cs)
leczniczy lakier do paznokci—medicated nail lacquer (pl)
leukoplast—plaster (dressing or adhesive plaster) (cs)
leukoplaszt—plaster (dressing or adhesive plaster) (hu)
lewatywa—enema (pl)
lewatywa retencyjna—retention enema (pl)
ligadura—bandage (pt)

linctus (*see also* syrup)
—hostmedicin (sv)
—jarabe (es)
—mikstūra nuo kosulio (lt)
—mixtur (sv)
—sciroppo (it)
—sirop (fr)
—sirup (cs)
—Sirup (de)
—stroop (nl)
—syrop (pl)
—szirup (hu)
—xarope (pt)
—μαλακτικό σιρόπι (el)

liniment (*see also* embrocation)
—Liniment (de)
—liniment (fr,sv)
—linimentas (lt)

—linimento (es,it,pt)
—linimentum (hu)
—mazání (cs)
—mazidło (pl)
—płyn do wcierania (pl)
—skystas tepalas (lt)
—smeersel (nl)
—αλοιφή εντριβής (el)
Liniment—liniment, embrocation (de)
liniment—liniment, embrocation (sv)
liniment—liniment (fr)
linimentas—liniment (lt)
linimento—embrocation (es,it,pt)
linimento—liniment (es,it,pt)
linimentum—liniment (hu)
liofilizado—lyophilised powder (pt)
liofilizált por—lyophilised powder (hu)
liofilizat—lyophilised powder (pl)
liofilizuoti milteliai—lyophilised powder (lt)
líquido para irrigação vesical—bladder irrigation (pt)
líquido para irrigación vesical—bladder irrigation (es)
livmoderinlägg—intra-uterine system (sv)
loção—lotion (pt)
loção capilar—scalp lotion (pt)
loción—lotion (es)
loción ocular—eye lotion (es)
loción oftálmica—eye lotion (es)
lock—cap (sv)
lokaal gebruik—topical application (nl)
lokal administrering—topical application (sv)
lokaliai milteliai—topical powder (lt)
lokaliai tirpalas—topical solution (lt)
lokális oldat—topical solution (hu)
lokalt bruk—topical application (sv)
lokalus purškalas—topical spray (lt)
lösbar Tablette—soluble tablet (de)
losjonas—lotion (lt)
löslig tablett—soluble tablet (sv)
lösning—solution (sv)
lösning för hårbotten—scalp lotion (sv)
lösning för nebulisator—nebuliser solution (sv)
lösning till injektionsvätska—solution for injection (sv)
Lösung—solution (de)
Lösung für einen Inhalationsgerät—nebuliser solution (de)
Lösung für einen Vernebler—nebuliser solution (de)
Lösung zur Anwendung auf der Haut—cutaneous solution (de)
Lösung zur Anwendung auf der Kopfhaut—scalp lotion (de)
Lösung zur Anwendung in der Nase—nasal (nasal wash) solution (de)
Lösung zur Infusion—solution for infusion (de)
Lösung zur Injektion—solution for injection (de)
Lösung zur topischen Anwendung—topical solution (de)
Lösung zur vaginalen Anwendung—vaginal solution (de)
lotio—lotion (cs)
Lotio—lotion (de)
lotion
—loção (pt)
—loción (es)
—losjonas (lt)
—lotio (cs)
—Lotio (de)
—Lotion (de)
—lotion (fr,nl,pl,sv)
—lozione (it)
—oldat belégzésre (hu)
—omývadlo (cs)
—płyn do stosowania na skórę (pl)
—λοσιόν (el)
eye lotion
—akių losjonas (lt)
—Augenbad (de)
—Augenspüllösung (de)
—loción ocular (es)
—loción oftálmica (es)
—lozione oculare (it)
—oční voda (cs)
—ögonsköljvätska (sv)
—ögonvatten (sv)
—oogwassing (nl)
—płyn do przemywania oczu (pl)
—solução para lavagem oftálmica (pt)
—solution ophtalmique (fr)
—szemöblítő (hu)
—οφθαλμικό πλύμα (el)
scalp lotion
—galvos losjonas (lt)
—hajasfejbőr kezelésre szánt oldat (hu)
—hoofdlotion (nl)
—Kopfhaut-Lotion (de)
—loção capilar (pt)
—lösning för hårbotten (sv)
—Lösung zur Anwendung auf der Kopfhaut (de)
—lotion capillaire (fr)
—lozione per cuoio capelluto (it)
—omývadlo vlasové pokožky (cs)
—płyn do stosowania na skórę głowy (pl)
—roztok do kštice (cs)
—κρανιακό πλύμα (el)
Lotion—lotion (de)
lotion—lotion (fr,nl,pl,sv)
lotion capillaire—scalp lotion (fr)
lozenge (*see also* pastille, tablet)
—kietoji pastilė (lt)
—kietoji tabletė (lt)
—Lutschtablette (de)
—pastiglia (it)
—pastilha (pt)
—pastilka (cs)
—pastill (sv)
—pastilla desleíble (es)
—pastilla disgregable orale (es)
—pastille à sucer (fr)
—pastille (fr)
—pastylka do ssania (pl)
—sugtablett (sv)
—szopogató tabletta (hu)
—zuigtablet (nl)
—ρόμβος (el)
—τροχίσκος (el)
lozione—lotion (it)
lozione oculare—eye lotion (it)
lozione per cuoio capelluto—scalp lotion (it)
Lutschpastille—pastille (de)
Lutschtablette—lozenge (de)
lyofilisaat—lyophilised powder (nl)
lyofilizát—lyophilised powder (cs)
Lyophilisat—lyophilised powder (de)
lyophilisat—lyophilised powder (fr)
lyophilised powder
—frystorkat pulver (sv)
—liofilizado (pt)
—liofilizált por (hu)
—liofilizat (pl)
—liofilizuoti milteliai (lt)
—lyofilisaat (nl)
—lyofilizát (cs)
—Lyophilisat (de)
—lyophilisat (fr)
—polvere liofilizzata (it)
—polvo liofilizado (es)
—poudre lyophilisée (fr)
—λυοφιλομένη κόμις (el)
łyżeczka do herbaty—teaspoon (pl)
łyżka deserowa (10mL)—dessertspoon (pl)
łyżka stołowa—tablespoon (pl)

M

maagsapresistente capsule—enteric-coated (gastro-resistant) capsule (nl)
maagsapresistente tablet—enteric-coated (gastro-resistant) tablet (nl)
maatbekertje—cup (measuring) (nl)
magensaftresistent Tablette—enteric-coated (gastro-resistant) tablet (de)
magensaftresistente Kapsel—enteric-coated (gastro-resistant) capsule (de)
makšties gelis—vaginal gel (lt)
makšties kapsulė—vaginal capsule (lt)
makšties kempinė—vaginal sponge (lt)
makšties kremas—vaginal cream (lt)
makšties putos—vaginal foam (lt)
makšties tabletė—vaginal tablet (lt)
makšties tepalas—vaginal ointment (lt)
makšties tirpalas—vaginal solution (lt)
makšties žvakutė—vaginal suppository (lt)
maść—ointment (pl)
maść do nosa—nasal ointment (pl)
maść do oczu—eye ointment (pl)
maść doodbytnicza—rectal ointment (pl)
maść dopochwowa—vaginal ointment (pl)
mast—ointment (cs)
mast do konečníku—rectal ointment (cs)
matavimo taurelė—cup (measuring) (lt)
matsked—tablespoon (sv)
mazání—liniment, embrocation (cs)
mazidło—liniment, embrocation (pl)
medicated bandage—*see under* bandage
medicated dressing—*see under* dressing
medicated nail lacquer—*see* nail lacquer, medicated
medicated plaster—*see under* plaster
medicated stick
—barra cutánea (for skin) (es)
—barrita medicamentosa (es)
—bâton médicamenteux (fr)
—crayon médicamenteux (fr)
—gyógyszeres rúd (hu)
—lápis cutâneo (for skin) (pt)
—léčivá kožní tyčinka (for skin) (cs)
—medicinale stift (nl)
—medicininė lazdelė (gydomoji) (lt)
—medicinskt stift (sv)
—medizinischer Fettstift (de)
—medizinischer Lippenstift (for lips) (de)
—stick medicamentoso (es)
—stick medicato (it)
—Stift zur Anwendung auf der Haut (for skin) (de)
—sztyft na skórę (for skin) (pl)
—δερματικό ραβδίο (for skin) (el)
—εμποτισμένη ράβδος (el)
medicinale stift—medicated stick (nl)
medicinflaska—vial (sv)
medicininė lazdelė (gydomoji)—medicated stick (lt)
medicininins bintas—medicated bandage (lt)
medicininins tvarstis—medicated bandage (lt)
medicinskt förband—medicated bandage (sv)
medicinskt kompress—medicated dressing (sv)
medicinskt nagellack—medicated nail lacquer (sv)
medicinskt omslag—medicated dressing (sv)
medicinskt omslag—poultice (sv)
medicinskt plåster—medicated plaster (sv)
medicinskt stift—medicated stick (sv)
medikamenthaltiger Verband—medicated bandage (de)
medikamentöser Wundverband—medicated bandage (de)
medizinischer Fettstift—medicated stick (de)
medizinischer Lippenstift—medicated stick (for lips) (de)
méhen beüli gyógyszerleadó rendszer—intra-uterine system (hu)
měkká pastilka—pastille (cs)
měkká tobolka—soft capsule (cs)
mélange—mixture (fr)
mengsel—mixture (nl)
Messbecher—cup (measuring) (de)
mezcla—mixture (es)
miarka—cup (pl)
miękka kapsułka—soft capsule (pl)
mieszanka—mixture (pl)
mikstura—mixture (pl)
mikstūra—mixture (lt)
mikstūra nuo kosulio—cough mixture (lt)
mikstūra nuo kosulio—linctus (lt)
milteliai—powder (lt)
milteliai geriamajam tirpalui—powder for oral solution (lt)
minkšta kapsulė—soft capsule (lt)
minkštoji pastilė—pastille (lt)
miscela—mixture (it)
Mischung—mixture (de)
mistura—mixture (it,pt)
mixtur—linctus (sv)
mixtur—mixture (sv)
mixtura—mixture (hu)
mixture
—läkemedelsblandning i flytande form (sv)
—mélange (fr)
—mengsel (nl)
—mezcla (es)
—mieszanka (pl)
—mikstura (pl)
—mikstūra (lt)
—miscela (it)
—Mischung (de)
—mistura (it,pt)
—mixtura (hu)
—mixtur (sv)
—směs (cs)
—μείγμα (el)
mjuk kapsel—soft capsule (sv)
modified release tablet—*see under* tablet
modifikuoto atpalaidavimo tabletė—modified release tablet (lt)
módosított hatóanyagleadású tabletta—modified release tablet (hu)
mondspoeling—mouthwash (nl)
mondspray—mouth spray (nl)
mousse—foam (fr)
mousse rectale—rectal foam (fr)
mousse vaginale—vaginal foam (fr)
mouth spray—*see under* spray
mouthwash
—bain de bouche (fr)
—burnos ploviklis (lt)
—colluttorio (it)
—colutorio (es)
—enjuague bucal (es)
—mondspoeling (nl)
—Mundspülung (de)
—munsköljvätska (sv)
—munvatten (sv)
—roztok pro ústní výplachy (cs)
—roztwór do płukania jamy ustnej (pl)
—solução para lavagem da boca (pt)
—szájöblítő (hu)
—ústní voda (cs)
—στοματικό διάλυμα (el)
—διάλυμα για στοματικές πλύσεις (el)
Mundgel—oral gel (de)
Mundspray—mouth spray (de)
Mundspülung—mouthwash (de)
munhålegel—oral gel (sv)
munhålepasta—oral paste (sv)
munhålespray—mouth spray (sv)
munhålespray—throat spray (sv)
munsköljvätska—mouthwash (sv)
munsönderfallende tablett—orodispersible tablet (sv)
munspray—mouth spray (sv)
munvatten—mouthwash (sv)

N

nagellak—medicated nail lacquer (nl)
nail lacquer, medicated
—barniz de uñas medicamentoso (es)
—gyógyszeres körömlakk (hu)
—léčivý lak na nehty (cs)
—leczniczy lakier do paznokci (pl)
—medicinskt nagellack (sv)
—nagellak (nl)
—smalto medicato per unghie (it)
—vaistinis nagų lakas (lt)
—vernis à ongles médicamenteux (fr)

—verniz para as unhas medicamentoso (pt)
—wirkstoffhaltiger Nagellack (de)
—φαρμακευτικό βερνίκι νυχιών (el)
nalewka—tincture (pl)
náplast—plaster (dressing or adhesive plaster) (cs)
nasaal gebruik—nasal use/route (nl)
näsaerosol—nasal spray (sv)
nasal administrering—nasal use/route (sv)
nasal användning—nasal use/route (sv)
nasal drops—*see under* drops
nasal lösning—nasal solution (sv)
nasal solution (nasal wash)—*see under* solution
nasal ointment—*see under* ointment
nasal spray—*see under* spray
nasal use/route
—Anwendung in der Nase (de)
—nasaal gebruik (nl)
—nasal administrering (sv)
—nasal användning (sv)
—nasale Anwendung (de)
—nasalis alkalmazás (hu)
—nasalt bruk (sv)
—nosní podání (cs)
—podanie donosowe (pl)
—uso nasale (it)
—vartoti į nosį (lt)
—via nasal (pt)
—vía nasal (es)
—voie nasale (fr)
—ρινική χρήση (el)
nasal wash—*see* nasal solution, *under* solution
nasale Anwendung—nasal use/route (de)
nasalis alkalmazás—nasal use/route (hu)
Nasalsalbe—nasal ointment (de)
nasalt bruk—nasal use/route (sv)
nasalvätska—nasal solution (sv)
näsdroppar—nasal drops (sv)
Nasenspray—nasal spray (de)
Nasenspüllösung—nasal solution (de)
Nasenspülung—nasal solution (de)
Nasentropfen—nasal drops (de)
nässalva—nasal ointment (sv)
nässpray—nasal spray (sv)
nebuliser solution
—lösning för nebulisator (sv)
—Lösung für einen Inhalationsgerät (de)
—Lösung für einen Vernebler (de)
—oldat porlasztásra (hu)
—purškiamasis tirpalas (lt)
—roztok k rozprašování (cs)
—roztwór do nebulizacji (pl)
—solução para inalação por nebulização (pt)
—solución para nebulización (es)
—solución para nebulizador (es)
—solution pour inhalation par nébuliseur (fr)
—soluzione da nebulizzare (it)
—verneveloplossing (nl)
—διάλυμα εκνεφωτή (el)
—διάλυμα για εισπνοή με εκνεφωτή (el)
nebulizador—spray (es)
nebulizador de aplicación tópica—topical spray (es)
nebulizador faríngeo—throat spray (es)
nebulizador nasal—nasal spray (es)
nebulizador oral—mouth spray (es)
neusdruppels—nasal drops (nl)
neusspoeling—nasal (nasal wash) solution (nl)
neusspray—nasal spray (nl)
neuszalf—nasal ointment (nl)
nitroděložní tělísko—intra-uterine system (cs)
nitrožilní podání—intravenous use/route (cs)
nosies lašai—nasal drops (lt)
nosies ploviklis—nasal (nasal wash) solution (lt)
nosies purškalas—nasal spray (lt)
nosies tepalas—nasal ointment (lt)
nosies tirpalas—nasal (nasal wash) solution (lt)
nosní kapky—nasal drops (cs)
nosní mast—nasal ointment (cs)
nosní podání—nasal use/route (cs)
nosní roztok—nasal (nasal wash) solution (cs)
nosní sprej—nasal spray (cs)
nyelvalatti spray—sublingual spray (hu)
nyelvalatti tabletta—sublingual tablet (hu)

O

obalená tableta—coated tablet (cs)
obinadlo—bandage (cs)
obklad—poultice (cs)
obvaz—bandage, dressing (cs)
obvaz s léčivou látkou—medicated bandage (cs)
oční gel—eye gel (cs)
očni inzert—ocular insert (cs)
oční kapky—eye drops (cs)
oční mast—eye ointment (cs)
oční podání—ocular use/route (cs)
oční voda—eye lotion (cs)
oční voda—eye wash (cs)
oculair gebruik—ocular use/route (nl)
ocular insert—*see under* insert
ocular use/route
—Anwendung am Auge (de)
—oční podání (cs)
—oculair gebruik (nl)
—okulär administrering (sv)
—okulär användning (sv)
—podanie do oka (pl)
—szemészeti alkalmazás (hu)
—uso ocular (pt)
—uso oftalmico (it)
—vartoti akims (lt)
—via oftalmica (it)
—vía oftálmica (es)
—voie ophtalmique (fr)
—οφθαλμική χρήση (el)
odměrka—cup (measuring) (cs)
odos emulsija—cutaneous emulsion (lt)
odos kempinė—cutaneous sponge (lt)
odos milteliai—dusting (cutaneous) powder (lt)
odos pasta—cutaneous paste (lt)
odos purškalas—cutaneous spray (lt)
odos tirpalas—cutaneous solution (lt)
ögonbad—eye wash (sv)
ögondroppar—eye drops (sv)
ögongel—eye gel (sv)
ögonlamell—ocular insert (sv)
ögonsalva—eye ointment (sv)
ögonsköljvätska—eye lotion (sv)
ögonsköljvätska—eye wash (sv)
ögonvatten—eye lotion (sv)
Ohrentropfen—ear drops (de)
oil
—aceite (es)
—aliejus (lt)
—huile (fr)
—olaj (hu)
—olej (cs,pl)
—olejek (pl)
—óleo (pt)
—olie (nl)
—olio (it)
—olja (sv)
—Öl (de)
—έλαιο (el)
ointment
—kenőcs (hu)
—maść (pl)
—mast (cs)
—onguent (fr)
—pomada (es,pt)
—pommade (fr)
—Salbe (de)
—salva (sv)
—tepalas (lt)
—ungüento (es)
—unguento (it)
—zalf (nl)
—αλοιφή (el)
eye ointment
—akių tepalas (lt)
—Augensalbe (de)
—maść do oczu (pl)
—oční mast (cs)
—ögonsalva (sv)
—onguent ophtalmique (fr)
—oogzalf (nl)
—pomada oftálmica (es,pt)
—pommade ophtalmique (fr)
—szemkenőcs (hu)
—unguento oftalmico (it)
—οφθαλμική αλοιφή (el)
nasal ointment
—maść do nosa (pl)
—Nasalsalbe (de)
—nässalva (sv)
—neuszalf (nl)
—nosies tepalas (lt)
—nosní mast (cs)
—orrkenőcs (hu)
—pomada de aplicación nasal (es)
—pomada nasal (es,pt)
—pomata nasale (it)
—pommade nasale (fr)
—unguento nasale (it)
—ρινική αλοιφή (el)
rectal ointment
—mast do konečníku (cs)
—maść doodbytnicza (pl)
—pomada de aplicación rectal (es)
—pomada rectal (es,pt)
—pommade rectale (fr)
—rektální mast (cs)
—Rektalsalbe (de)
—rektalsalva (sv)
—tiesiosios žarnos tepalas (lt)
—unguento rettale (it)
—végbélkenőcs (hu)
—zalf voor rectaal gebruik (nl)
—ορθική αλοιφή (el)
vaginal ointment
—húvelykenőcs (hu)
—makšties tepalas (lt)
—maść dopochwowa (pl)
—pomada de aplicación vaginal (es)
—pomada vaginal (es,pt)
—pommade vaginale (fr)
—poševni mast (cs)
—unguento vaginale (it)
—vaginální mast (cs)
—Vaginalsalbe (de)
—vaginalsalva (sv)
—zalf voor vaginaal gebruik (nl)
—κολπική αλοιφή (el)
okulär administrering—ocular use/route (sv)
okulär användning—ocular use/route (sv)
Öl—oil (de)
olaj—oil (hu)
Ölbalsam—balm (de)
oldat—solution (hu)
oldat belégzésre—solution for inhalation (hu)
oldat belégzésre—lotion (hu)
oldat porlasztásra—nebuliser solution (hu)
oldatos fülcsepp—ear drops (hu)
oldatos infúzió—solution for infusion (hu)
oldatos injekció—solution for injection (hu)
oldatos orrcsepp—nasal drops (hu)
oldatos szemcsepp—eye drops (hu)
oldódó tabletta—soluble tablet (hu)
olej—oil (cs,pl)
olejek—oil (pl)
óleo—oil (pt)
olie—oil (nl)
olio—oil (it)
olja—oil (sv)
omhulde tablet—coated tablet (nl)
omslag—dressing (sv)
omývadlo—lotion (cs)
omývadlo vlasové pokožky—scalp lotion (cs)
onguent—ointment (fr)
onguent ophtalmique—eye ointment (fr)
oogdruppels—eye drops (nl)
ooggel—eye gel (nl)
ooginsert—ocular insert (nl)
oogwassing—eye lotion (nl)
oogwassing—eye wash (nl)
oogzalf—eye ointment (nl)
oordruppels—ear drops (nl)
opaska—bandage (pl)
opatrunek—dressing (pl)
opatrunek leczniczy—medicated dressing (pl)
opercule—cap (fr)
oplosbare tablet—soluble tablet (nl)
oplossing—solution (nl)
oplossing voor cutaan gebruik—cutaneous solution (nl)
oplossing voor infusie—solution for infusion (nl)
oplossing voor injectie—solution for injection (nl)
oplossing voor lokaal gebruik—topical solution (nl)
oplossing voor nasaal gebruik—nasal solution (nl)
oplossing voor rectaal gebruik—rectal solution (nl)
oplossing voor vaginaal gebruik—vaginal solution (nl)
oraal gebruik—oral use/route (nl)
oral administrering—oral use/route (sv)
oral användning—oral use/route (sv)
oral drops—*see under* drops
oral gel—*see under* gel
oral gel—oral gel (sv)
oral granules—*see under* granules
oral lösning—oral solution (sv)
oral pasta—oral paste (sv)
oral paste—*see under* paste
oral powder—*see under* powder
oral solution—*see under* solution
oral suspension—*see under* suspension
oral suspension—oral suspension (sv)
oral syringe—*see under* syringe
oral use/route
—gerti (lt)
—oraal gebruik (nl)
—oral administrering (sv)
—oral användning (sv)
—oralis alkalmazás (hu)
—oralt bruk (sv)
—perorální podání (cs)
—podanie doustne (pl)
—uso orale (it)
—via oral (pt)
—vía oral (es)
—voie orale (fr)
—zum Einnehmen (de)
—από στόματος χρήση (el)
oral vätska—oral solution (sv)
orala droppar—oral drops (sv)
oralis alkalmazás—oral use/route (hu)
orální pasta—oral paste (cs)
orální podáni—buccal or oromucosal use/route (cs)
orální sprej—mouth spray (cs)
oralt bruk—oral use/route (sv)
oralt pulver—oral powder (sv)
orodispergeerbare tablet—orodispersible tablet (nl)
orodispersible tablet—*see under* tablet
oromucosaal gebruik—buccal or oromucosal use/route (nl)
örondroppar—ear drops (sv)
orrkenőcs—nasal ointment (hu)
orröblítő—nasal solution (hu)
orrpermet—nasal spray (hu)
örtte—tea (herbal or medicinal) (sv)
osztható tabletta—breakable or dividable tablet (hu)
ovule—pessary (fr,nl)
ovulė—pessary (lt)
óvulo—pessary (pt)
ovulo—pessary (it)
óvulo vaginal—pessary (es,pt)

P

pack combinado—combination pack (pt)
Packung—poultice (de)
pacote combinado—combination pack (pt)
pailginto atpalaidavimo kapsulė—extended-release capsule (lt)
pailginto atpalaidavimo tabletė—extended-release tablet (lt)
paketėlis—sachet (lt)
pansement—dressing (fr)
pansement médicamenteux—medicated dressing (fr)
papas—poultice (pt)
papje—poultice (nl)
paquete combinado—combination pack (es)
parche transdérmico—transdermal patch (es)
pasta—paste (cs,es,it,lt,nl,pl,pt,sv)
pasta cutánea—cutaneous paste (es)
pasta cutânea—cutaneous paste (pt)
pasta cutanea—cutaneous paste (it)
pasta de aplicación tópica—topical paste (es)
pasta dental—toothpaste (es)
pasta dentífrica—toothpaste (es,pt)
pasta dentifricia—toothpaste (it)
pasta do stosowania miejscowego—topical paste (pl)
pasta do zębów—toothpaste (pl)
pasta doustna—oral paste (pl)
pasta k zevnímu použití—topical paste (cs)
pasta na skórę—cutaneous paste (pl)
pasta oral—oral paste (es,pt)
pasta para aplicação tópica—topical paste (pt)
pasta per uso orale—oral paste (it)
pasta per uso topico—topical paste (it)
pasta tópica—topical paste (pt)
pasta voor cutaan gebruik—cutaneous paste (nl)
pasta voor lokaal gebruik—topical paste (nl)
pasta voor oraal gebruik—oral paste (nl)
paste
—pasta (cs,es,it,lt,nl,pl,pt,sv)
—Paste (de)
—paszta (hu)
—pâte (fr)
—φύραμα (el)
cutaneous paste
—kožní pasta (cs)
—külsőleges paszta (hu)
—kutan pasta (sv)
—odos pasta (lt)
—pasta cutánea (es)
—pasta cutânea (pt)
—pasta cutanea (it)
—pasta na skórę (pl)
—pasta voor cutaan gebruik (nl)
—Paste zur Anwendung auf der Haut (de)
—pâte pour application cutanée (fr)
—δερματικό φύραμα (el)
oral paste
—belsőleges paszta (hu)
—munhålepasta (sv)
—oral pasta (sv)
—orální pasta (cs)
—pasta doustna (pl)
—pasta oral (es,pt)
—pasta per uso orale (it)
—pasta voor oraal gebruik (nl)
—Paste zum Einnehmen (de)
—pâte orale (fr)
—valgomoji pasta (lt)
—στοματική πάστα (el)
—στοματικό φύραμα (el)
topical paste
—pasta de aplicación tópica (es)
—pasta do stosowania miejscowego (pl)
—pasta k zevnímu použití (cs)
—pasta para aplicação tópica (pt)
—pasta per uso topico (it)
—pasta tópica (pt)
—pasta voor lokaal gebruik (nl)
—Paste zur topischen Anwendung (de)
—pâte pour application locale (fr)
—topická pasta (cs)
—topikal pasta (sv)
—vietinė pasta (lt)
—τοπικό φύραμα (el)
Paste—paste (de)
Paste zum Einnehmen—oral paste (de)
Paste zur Anwendung auf der Haut—cutaneous paste (de)
Paste zur topischen Anwendung—topical paste (de)
pastiglia—lozenge, pastille (it)
pastilha—lozenge (pt)
pastilha elástica—chewing gum (pt)
pastilha mole—pastille (pt)
pastilka—lozenge, pastille (cs)
pastill—lozenge, pastille (sv)
pastilla—pastille, tablet (es)
pastilla desleíble—lozenge (es)
pastilla disgregable orale—lozenge (es)
pastille à sucer—lozenge (fr)
pastille (*see also* lozenge)
—comprimido (es)
—Lutschpastille (de)
—měkká pastilka (cs)
—minkštoji pastilė (lt)
—pastiglia (it)
—pastilha mole (pt)
—pastilka (cs)
—pastill (sv)
—pastilla (es)
—Pastille (de)
—pastille (nl)
—pastylka miękka (pl)
—pasztilla (hu)
—pâte à sucer (fr)
—παστίλλια (el)
pastille—lozenge (fr)
Pastille—pastille (de)
pastille—pastille (nl)
pastylka do ssania—lozenge (pl)
pastylka miękka—pastille (pl)
paszta—paste (hu)
pasztilla—pastille (hu)
pâte—paste (fr)
pâte à sucer—pastille (fr)
pâte dentifrice—toothpaste (fr)
pâte orale—oral paste (fr)
pâte pour application cutanée—cutaneous paste (fr)
pâte pour application locale—topical paste (fr)
patron—cartridge (hu)
Patrone—cartridge (de)
patroon—cartridge (nl)
peletki—globules (homoeopathic) (pl)
pěna—foam (cs)
pěna do konečníku—rectal foam (cs)
penso—dressing, plaster (pt)
penso impregnado—medicated dressing (pt)
perfusão—infusion (pt)
perfusion—infusion (fr)
permet—spray (hu)
permet bőrre—topical spray (hu)
perorální gel—oral gel (cs)
perorální kapky—oral drops (cs)
perorální podání—oral use/route (cs)
perorální prášek—oral powder (cs)
perorální roztok—oral solution (cs)
perorální zrněný prášek—oral granules (cs)
pesar—pessary (cs)
pessaire—pessary (fr)
Pessar—pessary (de)
pessar—pessary (sv)
pessary
—candeletta (it)
—globulka (pl)
—húvelykúp (hu)
—ovule (fr,nl)
—ovulė (lt)
—óvulo vaginal (es,pt)
—óvulo (pt)
—ovulo (it)
—pesar (cs)
—pessaire (fr)
—Pessar (de)
—pessar (sv)
—Scheidenpessar (de)
—vaginální kulička (cs)
—Vaginalovulum (de)
—vagitorium (sv)
—κολπικό υπόθετο (el)
peszgőgranulátum—effervescent granules (hu)
pezsgőpor—effervescent powder (hu)
pezsgőtabletta—effervescent tablet (hu)
Pflaster—medicated plaster (de)
Pflaster—plaster (dressing or adhesive plaster) (de)
pianka—foam (pl)
pianka doodbytnicza—rectal foam (pl)
pianka dopochwowa—vaginal foam (pl)
pigułka—pill (pl)
pigułki—globules (homoeopathic) (pl)
pil—pill (nl)
píldora—pill (es)
piliulė—pill (lt)
piliulės—globules (homoeopathic) (lt)
pill (*see also* tablet)
—pigułka (pl)
—pil (nl)
—píldora (es)
—piliulė (lt)
—Pille (de)
—piller (sv)
—pillola (it)
—pílula (pt)
—pilula (hu)
—pilule (fr)
—pilulka (cs)
—χάπι (el)
Pille—pill (de)
piller—pill (sv)
piller—tablet (sv)
pillola—pill (it)
pillules—*see* globules
pílula—pill (pt)
pilula—pill (hu)
pilule—pill (fr)
pilulka—pill (cs)
plačiakaklis indas—jar (lt)
plåster—plaster (dressing or adhesive plaster) (sv)
plaster—plaster (dressing or adhesive plaster) (pl)
plaster (dressing or adhesive plaster)
—apósito adhesivo (es)
—cerotto (it)
—emplastro (pt)
—emplâtre (fr)
—esparadrapo (es)
—Heftpflaster (de)
—leukoplast (cs)
—leukoplaszt (hu)
—náplast (cs)
—penso (pt)
—Pflaster (de)
—plåster (sv)
—plaster (pl)
—pleister (nl)
—pleistras (lt)
—przylepiec (pl)
—ragtapasz (hu)
—sparadrap (fr)
—tapasz (hu)
—tirita (es)
—wondpleister (nl)
—Wundpflaster (de)
—Wundschnellverband (de)
—αυτοκόλλητο έμπλαστρο (el)
medicated plaster
—apósito adhesivo medicamentoso (es)
—cerotto medicato (it)
—emplastro medicamentoso (pt)
—emplâtre médicamenteux (fr)
—gyógyzseres tapasz (hu)
—impiastro medicato (it)
—léčivá náplast (cs)
—medicinskt plåster (sv)
—plaster leczniczy (pl)
—vaistinis pleistras (lt)
—wirkstoffhaltiges Pflaster (de)
—εμποτισμένο έμπλαστρο (el)
—φαρμακούχο έμπλαστρο (el)
plaster leczniczy—medicated plaster (pl)
pleister—plaster (dressing or adhesive plaster) (nl)
pleister voor transdermaal gebruik—transdermal patch (nl)
pleistras—plaster (dressing or adhesive plaster) (lt)
plėvele dengta tabletė—film-coated tablet (lt)
płyn do irygacji pochwy—douche (vaginal) (pl)
płyn do przemywania oczu—eye lotion (pl)
płyn do przemywania oczu—eye wash (pl)
płyn do stosowania na skórę—lotion (pl)
płyn do stosowania na skórę głowy—scalp lotion (pl)
płyn do wcierania—embrocation (pl)
płyn do wcierania—liniment (pl)
plyn k inhalaci—gas (for inhalation) (cs)
pó—powder (pt)
pó cutâneo—dusting (cutaneous) powder (pt)
pó efervescente—effervescent powder (pt)
pó oral—oral powder (pt)
pó para aplicação tópica—topical powder (pt)
pó para inalação—powder for inhalation (pt)
pó para solução oral—powder for oral solution (pt)
pó para uso injectável—powder for injection (pt)
pó tópico—topical powder (pt)
podání pod jazyk—sublingual use/route (cs)
podanie do cewki moczowej—urethral use/route (pl)
podanie do ciała jamistego—intracavernosal use/route (pl)
podanie do oka—ocular use/route (pl)
podanie do pęcherza moczowego—intravesical use/route (pl)
podanie do przewodu pokarmowego—gastroenteral use/route (pl)
podanie do ucha—auricular use/route (pl)
podanie domięśniowe—intramuscular use/route (pl)
podanie donosowe—nasal use/route (pl)
podanie doodbytnicze—rectal use/route (pl)
podanie doogniskowe—intra-lesional use/route (pl)
podanie dooponowe—intrathecal use/route (pl)
podanie dootrzewnowe—intraperitoneal use/route (pl)
podanie dopochwowe—vaginal use/route (pl)
podanie dostawowe—intra-articular use/route (pl)
podanie dotętnicze—intra-arterial use/route (pl)
podanie doustne—oral use/route (pl)
podanie dożylne—intravenous use/route (pl)
podanie na skórę—cutaneous use/route (pl)
podanie na śluzówkę jamy ustnej—buccal or oromucosal use/route (pl)
podanie nadtwardówkowe—epidural use/route (pl)
podanie podjęzykowe—sublingual use/route (pl)
podanie podskórne—subcutaneous use/route (pl)

podanie przezskórne—transdermal use/route (pl)
podanie śródskórne—intradermal use/route (pl)
podanie wewnątrzmaciczne—intrauterine use/route (pl)
podanie wziewne—inhalation (route) (pl)
poeder—powder (nl)
poeder voor drank—powder for oral solution (nl)
poeder voor injectie—powder for injection (nl)
poeder voor lokaal gebruik—topical powder (nl)
poeder voor oraal gebruik—oral powder (nl)
pojemnik jednodawkowy—single-dose container (pl)
polévková lžíce—tablespoon (cs)
poliežuvinė tabletė—sublingual tablet (lt)
poliežuvinis purškalas—sublingual spray (lt)
polvere—powder (it)
polvere effervescente—effervescent powder (it)
polvere liofilizzata—lyophilised powder (it)
polvere per costituire una soluzione orale—powder for oral solution (it)
polvere per inalazione—powder for inhalation (it)
polvere per soluzione iniettabile—powder for injection (it)
polvere per uso cutaneo—dusting (cutaneous) powder (it)
polvere per uso orale—oral powder (it)
polvere per uso topico—topical powder (it)
polvo—powder (es)
polvo cutáneo—dusting (cutaneous) powder (es)
polvo de aplicación cutánea—dusting (cutaneous) powder (es)
polvo de aplicación local—topical powder (es)
polvo de aplicación oral—oral powder (es)
polvo de aplicación tópica—topical powder (es)
polvo efervescente—effervescent powder (es)
polvo liofilizado—lyophilised powder (es)
polvo oral—oral powder (es)
polvo para inhalación—powder for inhalation (es)
polvo para reconstituir una solución oral—powder for oral solution (es)
polvo para solución inestable—powder for injection (es)
polvo para solución oral—powder for oral solution (es)
pomada—ointment (es,pt)
pomada de aplicación nasal—nasal ointment (es)
pomada de aplicación rectal—rectal ointment (es)
pomada de aplicación vaginal—vaginal ointment (es)
pomada nasal—nasal ointment (es,pt)
pomada oftálmica—eye ointment (es, pt)
pomada rectal—rectal ointment (es,pt)
pomada vaginal—vaginal ointment (es, pt)
pomata nasale—nasal ointment (it)
pommade—ointment (fr)
pommade nasale—nasal ointment (fr)
pommade ophtalmique—eye ointment (fr)
pommade rectale—rectal ointment (fr)
pommade vaginale—vaginal ointment (fr)
por—powder (hu)
por belsőleges oldathoz—powder for oral solution (hu)
por injekcióhoz—powder for injection (hu)
poševni gel—vaginal gel (cs)
poševni krém—vaginal cream (cs)
poševni mast—vaginal ointment (cs)
poševni pěna—vaginal foam (cs)
poševni roztok—vaginal solution (cs)
poševní tableta—vaginal tablet (cs)
poševni tobolka—vaginal capsule (cs)
pot—jar (fr,nl)
potahovaná tableta—film-coated tablet (cs)
poudre—powder (fr)
poudre effervescente—effervescent powder (fr)
poudre lyophilisée—lyophilised powder (fr)
poudre orale—oral powder (fr)
poudre pour application cutanée—dusting (cutaneous) powder (fr)
poudre pour application locale—topical powder (fr)
poudre pour inhalation—powder for inhalation (fr)
poudre pour solution buvable—powder for oral solution (fr)
poudre pour solution injectable—powder for injection (fr)

poultice
—borogató kenőcs (hu)
—cataplasma (es,it,pt)
—cataplasme (fr)
—impiastro (it)
—karštas kompresas (lt)
—kataplazma (cs)
—kataplazm (pl)
—medicinskt omslag (sv)
—obklad (cs)
—Packung (de)
—papas (pt)
—papje (nl)
—šuteklis (lt)
—Umschlag (de)
—Wärmepackung (de)
—κατάπλασμα (el)

powder
—milteliai (lt)
—pó (pt)
—poeder (nl)
—polvere (it)
—polvo (es)
—por (hu)
—poudre (fr)
—prášek (cs)
—proszek (pl)
—Puder (de)
—puder (sv)
—pudra (lt)
—Pulver (de)
—pulver (sv)
—κόνις (el)
dusting (cutaneous) powder
—barstomieji milteliai (lt)
—külsőleges por (hu)
—odos milteliai (lt)
—pó cutâneo (pt)
—polvere per uso cutaneo (it)
—polvo cutáneo (es)
—polvo de aplicación cutánea (es)
—poudre pour application cutanée (fr)
—puder (sv)
—puder leczniczy (pl)
—Pulver zur Anwendung auf der Haut (de)
—strooipoeder (nl)
—zásyp (cs)
—δερματική κόνις (el)
effervescent powder
—Brausepulver (de)
—bruispoeder (nl)
—bruspulver (sv)
—pezsgőpor (hu)
—pó efervescente (pt)
—polvere effervescente (it)
—polvo efervescente (es)
—poudre effervescente (fr)
—proszek musujący (pl)
—šnypščiantys, putojantys milteliai (lt)
—šumivý prašek (cs)
—αναβράζουσα κόνις (el)
oral powder
—belsőleges por (hu)
—geriamieji milteliai (lt)
—oralt pulver (sv)
—perorální prášek (cs)
—pó oral (pt)
—poeder voor oraal gebruik (nl)
—polvere per uso orale (it)
—polvo de aplicación oral (es)
—polvo oral (es)
—poudre orale (fr)
—proszek doustny (pl)
—Pulver zum Einnehmen (de)
—πόσιμη κόνις (el)
topical powder
—hintőpor (hu)
—lokaliai milteliai (lt)
—pó para aplicação tópica (pt)
—pó tópico (pt)
—poeder voor lokaal gebruik (nl)
—polvere per uso topico (it)
—polvo de aplicación local (es)
—polvo de aplicación tópica (es)
—poudre pour application locale (fr)
—puder (sv)
—puder leczniczy (pl)
—Pulver zur topischen Anwendung (de)
—zásyp k zevnímu použití (cs)
—τοπική κόνις (el)

powder for inhalation—*see under* inhalation
powder for injection—*see under* injection

powder for oral solution
—milteliai geriamajam tirpalui (lt)
—pó para solução oral (pt)
—poeder voor drank (nl)
—polvere per costituire una soluzione orale (it)
—polvo para reconstituir una solución oral (es)
—polvo para solución oral (es)
—por belsőleges oldathoz (hu)
—poudre pour solution buvable (fr)
—prášek pro přípravu perorálního roztoku (cs)
—proszek do sporządzania roztworu doustnego (pl)
—pulver till oral lösning (sv)
—Pulver zur Herstellung einer Lösung zum Einnehmen (de)
—κόνις για πόσιμο διάλυμα (el)

prášek—powder (cs)
prášek k inhalaci—powder for inhalation (cs)
prášek pro přípravu injekčního roztoku—powder for injection (cs)
prášek pro přípravu perorálního roztoku—powder for oral solution (cs)
předplněná injekční stříkačka—prefilled syringe (cs)
prefilled syringe—*see under* syringe
preparação para pulverização sublingual—sublingual spray (pt)
preparat złożony—combination pack (pl)
přípravek k inhalaci parou—vapour inhalation (cs)
přísada do koupele—bath additive (cs)
proszek—powder (pl)
proszek do inhalacji—powder for inhalation (pl)
proszek do sporządzania roztworu do wstrzykiwań—powder for injection (pl)
proszek do sporządzania roztworu doustnego—powder for oral solution (pl)
proszek doustny—oral powder (pl)
proszek musujący—effervescent powder (pl)
przylepiec—plaster (dressing or adhesive plaster) (pl)
pudełko—box (pl)
puder—powder, dusting powder, topical powder (sv)
Puder—powder (de)
puder leczniczy—dusting (cutaneous) powder, topical powder (pl)
pudra—powder (lt)
Pulver—powder (de)
pulver—powder (sv)
pulver till injektionsvätska—powder for injection (sv)
pulver till oral lösning—powder for oral solution (sv)
Pulver zum Einnehmen—oral powder (de)
Pulver zur Anwendung auf der Haut—dusting (cutaneous) powder (de)
Pulver zur Herstellung einer Injektionslösung—powder for injection (de)
Pulver zur Herstellung einer Lösung zum Einnehmen—powder for oral solution (de)
Pulver zur Inhalation—powder for inhalation (de)
Pulver zur topischen Anwendung—topical powder (de)
pulvérisation cutanée—cutaneous spray (fr)
pulverização cutânea—cutaneous spray (pt)
pulverização nasal—nasal spray (pt)
pulverización sublingual—sublingual spray (es)
pulverizador—spray (pt)
pulverizador cutâneo—cutaneous spray (pt)
pulverizador nasal—nasal spray (pt)
purškalas—spray (lt)
purškiamasis tirpalas—nebuliser solution (lt)
putojančios granulės—effervescent granules (lt)
putos—foam (lt)

R

Rachenspray—throat spray (de)
rágógumi—chewing gum (hu)
rágótabletta—chewable tablet (hu)
ragtapasz—plaster (dressing or adhesive plaster) (hu)
récipient unidose—single-dose container (fr)
recipiente unidose—single-dose container (pt)
rectaal gebruik—rectal use/route (nl)
rectal foam—*see under* foam
rectal ointment—*see under* ointment
rectal solution—*see under* solution

rectal use/route
—podanie doodbytnicze (pl)
—rectaal gebruik (nl)
—rectalis alkalmazás (hu)
—rektal administrering (sv)
—rektal användning (sv)
—rektale Anwendung (de)
—rektální podání (cs)
—rektalt bruk (sv)
—uso rettale (it)
—vartoti į tiesiąją žarną (lt)
—via rectal (pt)
—vía rectal (es)
—voie rectale (fr)
—ορθική χρήση (el)

rectalis alkalmazás—rectal use/route (hu)
rektal administrering—rectal use/route (sv)
rektal användning—rectal use/route (sv)
rektale Anwendung—rectal use/route (de)
rektallösning—rectal solution (sv)
Rektallösung—rectal solution (de)
rektální mast—rectal ointment (cs)
rektální pěna—rectal foam (cs)
rektální podání—rectal use/route (cs)

rektální roztok—rectal solution (cs)
Rektalsalbe—rectal ointment (de)
rektalsalva—rectal ointment (sv)
Rektalschaum—rectal foam (de)
rektalskum—rectal foam (sv)
rektalt bruk—rectal use/route (sv)
rektalvätska—rectal solution, enema (sv)
resoriblett—sublingual tablet (sv)
retard kapszula—extended-release capsule (hu)
retard tabletta—extended-release tablet (hu)
Retardkapsel—extended-release capsule (de)
retardovaná tableta—extended-release tablet (cs)
retardovaná tobolka—extended-release capsule (cs)
Retardtablette—extended-release tablet (de)
retenciós klizma—retention enema (hu)
retentieklysma—retention enema (nl)
retention enema—*see under* enema
Retentionseinlauf—retention enema (de)
retentionslavemang—retention enema (sv)
roztok—solution (cs)
roztok do konečníku—rectal solution (cs)
roztok do kštice—scalp lotion (cs)
roztok do močového měchýře—bladder irrigation (cs)
roztok k inhalaci—solution for inhalation (cs)
roztok k rozprašování—nebuliser solution (cs)
roztok k výplachu močového měchýře—bladder irrigation (cs)
roztok k výplachu nosu—nasal (nasal wash) solution (cs)
roztok k zevnímu použití—topical solution (cs)
roztok pro ústní výplachy—mouthwash (cs)
roztwór—solution (pl)
roztwór do infuzji—solution for infusion (pl)
roztwór do inhalacji—solution for inhalation (pl)
roztwór do irygacji pęcherza moczowego—bladder irrigation (pl)
roztwór do nebulizacji—nebuliser solution (pl)
roztwór do nosa—nasal (nasal wash) solution (pl)
roztwór do płukania gardła—gargle (pl)
roztwór do płukania jamy ustnej—mouthwash (pl)
roztwór do stosowania miejscowego—topical solution (pl)
roztwór do wstrzykiwań—solution for injection (pl)
roztwór doodbytniczy—rectal solution (pl)
roztwór dopochwowy—vaginal solution (pl)
roztwór doustny—oral solution (pl)
roztwór na skórę—cutaneous solution (pl)

S

sáček—sachet (cs)
sachet
—Beutel (de)
—bolsa (es)
—bolsita (es)
—cartina (it)
—dospåse (sv)
—paketėlis (lt)
—sáček (cs)
—Sachet (de)
—sachet (fr,it,nl)
—saqueta (pt)
—saquito (es)
—saszetka (pl)
—sobre (es)
—tasak (hu)
—φακελλίσκος (el)
Sachet—sachet (de)
sachet—sachet (fr,it,nl)
Saft—oral solution (de)
Salbe—ointment (de)
Salbengaze—medicated dressing (de)
salva—ointment (sv)
salvkompress—medicated dressing (sv)
sampon—shampoo (hu)
šampón—shampoo (cs)
šampūnas—shampoo (lt)
sans sucre—sugar-free (fr)
saqueta—sachet (pt)
saquito—sachet (es)
saszetka—sachet (pl)
scalp lotion—*see under* lotion
scatola—box (it)
Schachtel—box (de)
schampo—shampoo (sv)
Schaum—foam (de)
Schaum zur rektalen Anwendung—rectal foam (de)
Schaum zur vaginalen Anwendung—vaginal foam (de)
Scheidenpessar—pessary (de)
schiuma—foam (it)
schiuma rettale—rectal foam (it)
schiuma vaginale—vaginal foam (it)
Schmelztablette—orodispersible tablet (de)
Schnappdeckel—cap (de)
Schraubdeckel—screw cap (de)
Schraubverschluss—screw cap (de)
schroefdop—screw cap (nl)
schudmixtuur—suspension (nl)
schuim—foam (nl)
schuim voor rectaal gebruik—rectal foam (nl)
schuim voor vaginaal gebruik—vaginal foam (nl)
Schwamm—sponge (de)
Schwämmchen zur Anwendung auf der Haut—cutaneous sponge (de)
sciroppo—syrup, linctus (it)
sciroppo per la tosse—cough syrup (it)
sciroppo per la tosse—cough mixture (it)
screw cap—*see under* cap
sem açúcar—sugar-free (pt)
senza zucchero—sugar-free (it)
seringa—syringe (pt)
seringa descartável—disposable syringe (pt)
seringa para uso oral—oral syringe (pt)
seringa pré-cheia—prefilled syringe (pt)
seringue à usage unique—disposable syringe (fr)
seringue—syringe (fr)
seringue pour administration orale—oral syringe (fr)
seringue préremplie—prefilled syringe (fr)
shampoo
—champô (pt)
—champú (es)
—Haarwaschmittel (de)
—sampon (hu)
—šampón (cs)
—šampūnas (lt)
—schampo (sv)
—Shampoo (de)
—shampoo (it,nl)
—shampooing (fr)
—szampon (pl)
—υγρό λουσίματος (el)
—σαμπουάν (el)
Shampoo—shampoo (de)
shampoo—shampoo (it,nl)
shampooing—shampoo (fr)
sin azúcar—sugar-free (es)
single-dose container
—contenitore monodose (it)
—EDO (de)
—egyadagos tartály (hu)
—Einzeldosisbehältnis (de)
—endosbehållare (sv)
—endosförpackning (sv)
—envase unidosis (es)
—flacon monodose (fr)
—jednodávkový obal (cs)
—pojemnik jednodawkowy (pl)
—récipient unidose (fr)
—recipiente unidose (pt)
—verpakking voor eenmalig gebruik (nl)
—vienadozė talpyklė (lt)
—περιέκτης μίας δόσης (el)
sirap—syrup (sv)
siringa—syringe (it)
siringa per somministrazione orale—oral syringe (it)
siringa preriempita—prefilled syringe (it)
siringa usa e getta—disposable syringe (it)
siroop—syrup (nl)
sirop—syrup, linctus (fr)
sirop antitussif—cough syrup, cough mixture (fr)
sirop contre la toux—cough syrup, cough mixture (fr)
sirop pectoral—cough syrup, cough mixture (fr)
Sirup—syrup, linctus (de)
sirup—syrup, linctus (cs)
sirup proti kašli—cough syrup, cough mixture (cs)
sirupas—syrup (lt)
sirupas nuo kosulio—cough syrup (lt)
sistema intra-uterino—intra-uterine system (pt)
sistema transdérmico—transdermal patch (pt)
skrandyje neiri kapsulė—enteric-coated (gastro-resistant) capsule (lt)
skrandyje neiri tabletė—enteric-coated (gastro-resistant) tablet (lt)
skruvkork—screw cap (sv)
skruvlock—screw cap (sv)
skum—foam (sv)
skystas tepalas—liniment, embrocation (lt)
šlapimo pūslės ploviklis—bladder irrigation (lt)
šlaplės gelis—urethral gel (lt)
slidsköljning—douche (vaginal) (sv)
słoik—jar (pl)
smalto medicato per unghie—medicated nail lacquer (it)
smeersel—liniment, embrocation (nl)
smelttablet—orodispersible tablet (nl)
směs—mixture (care may not be phceutical) (cs)
šnypščianti, putojanti tabletė—effervescent tablet (lt)
šnypščiantys, putojantys milteliai—effervescent powder (lt)
šnypščiosios granulės—effervescent granules (lt)
sobre—sachet (es)
sockerfri—sugar-free (sv)
soft capsule—*see under* capsule
soluble tablet—*see under* tablet
solução—solution (pt)
solução cutânea—cutaneous solution (pt)
solução injectável—solution for injection (pt)
solução nasal—nasal (nasal wash) solution (pt)
solução oral—oral solution (pt)
solução para gargarejar—gargle (pt)
solução para inalação—solution for inhalation (pt)
solução para inalação por nebulização—nebuliser solution (pt)
solução para lavagem da boca—mouthwash (pt)
solução para lavagem oftálmica—eye lotion (pt)
solução para lavagem oftálmica—eye wash (pt)
solução para perfusão—solution for infusion (pt)
solução para pulverização bucal—mouth spray (pt)
solução rectal—rectal solution (pt)
solução tópica—topical solution (pt)
solução vaginal—vaginal solution (pt)
solución—solution (es)
solución concentrada para infusión—concentrate for infusion (solution) (es)
solución cutánea—cutaneous solution (es)
solución dérmica—cutaneous solution (es)
solución inestable—solution for injection (es)
solución nasal—nasal (nasal wash) solution (es)
solución oral—oral solution (es)
solución para gargarismos—gargle (es)
solución para infusión—solution for infusion (es)
solución para inhalación—solution for inhalation (es)
solución para instilación de la vejiga urinaria—bladder irrigation (es)
solución para nebulización—nebuliser solution (es)
solución para nebulizador—nebuliser solution (es)
solución rectal—rectal solution (es)
solución tópica—topical solution (es)
solución vaginal—vaginal solution (es)
solution à diluer pour perfusion—concentrate for infusion (solution) (fr)
solution
—lösning (sv)
—Lösung (de)
—oldat (hu)
—oplossing (nl)
—roztok (cs)
—roztwór (pl)
—solução (pt)
—solución (es)
—solution (fr)
—soluzione (it)
—tirpalas (lt)
—διάλυμα (el)
cutaneous solution
—kožní roztok (cs)
—külsőleges oldat (hu)
—kutan lösning (sv)
—Lösung zur Anwendung auf der Haut (de)
—odos tirpalas (lt)
—oplossing voor cutaan gebruik (nl)
—roztwór na skórę (pl)
—solução cutânea (pt)
—solución cutánea (es)
—solución dérmica (es)
—solution pour application cutanée (fr)
—soluzione cutanea (it)
—δερματικό διάλυμα (el)
nasal solution (nasal wash)
—Lösung zur Anwendung in der Nase (de)
—nasal lösning (sv)
—nasalvätska (sv)
—Nasenspüllösung (de)
—Nasenspülung (de)
—neusspoeling (nl)
—nosies ploviklis (lt)
—nosies tirpalas (lt)
—nosní roztok (cs)
—oplossing voor nasaal gebruik (nl)
—orröblítő (hu)
—roztok k výplachu nosu (cs)
—roztwór do nosa (pl)
—solução nasal (pt)
—solución nasal (es)
—solution nasale (fr)
—soluzione nasale (it)
—ρινικό διάλυμα για πλύση (el)
—ρινικό πλύμα (el)
oral solution
—belsőleges oldat (hu)
—drank (nl)
—Flüssigkeit zur Einnahme (de)
—geriamasis tirpalas (lt)

—oral lösning (sv)
—oral vätska (sv)
—perorální roztok (cs)
—roztwór doustny (pl)
—Saft (de)
—solução oral (pt)
—solución oral (es)
—solution buvable (fr)
—soluzione orale (it)
—πόσιμο διάλυμα (el)
rectal solution
—oplossing voor rectaal gebruik (nl)
—rektallösning (sv)
—Rektallösung (de)
—rektální roztok (cs)
—rektalvätska (sv)
—roztok do konečníku (cs)
—roztwór doodbytniczy (pl)
—solução rectal (pt)
—solución rectal (es)
—solution rectale (fr)
—soluzione rettale (it)
—tiesiosios žarnos tirpalas (lt)
—végbéloldat (hu)
—ορθικό διάλυμα (el)
topical solution
—helyi alakalmazású oldat (hu)
—lokaliai tirpalas (lt)
—lokális oldat (hu)
—Lösung zur topischen Anwendung (de)
—oplossing voor lokaal gebruik (nl)
—roztok k zevnímu použití (cs)
—roztwór do stosowania miejscowego (pl)
—solução tópica (pt)
—solución tópica (es)
—solution pour application locale (fr)
—soluzione per uso topico (it)
—topický roztok (cs)
—topikal lösning (sv)
—τοπικό διάλυμα (el)
vaginal solution
—hüvelyoldat (hu)
—Lösung zur vaginalen Anwendung (de)
—makšties tirpalas (lt)
—oplossing voor vaginaal gebruik (nl)
—poševni roztok (cs)
—roztwór dopochwowy (pl)
—solução vaginal (pt)
—solución vaginal (es)
—solution vaginale (fr)
—soluzione vaginale (it)
—vaginallösning (sv)
—Vaginallösung (de)
—vaginální roztok (cs)
—vaginalvätska (sv)
—κολπικό διάλυμα (el)
solution—solution (fr)
solution buvable—oral solution (fr)
solution for infusion—*see under* infusion
solution for inhalation—*see under* inhalation
solution for injection—*see under* injection
solution injectable—solution for injection (fr)
solution nasale—nasal solution (fr)
solution ophtalmique—eye lotion (fr)
solution pour application cutanée—cutaneous solution (fr)
solution pour application locale—topical solution (fr)
solution pour inhalation—solution for inhalation (fr)
solution pour inhalation par nébuliseur—nebuliser solution (fr)
solution pour instillation auriculaire—ear drops (fr)
solution pour irrigation vésiculaire—bladder irrigation (fr)
solution pour lavage oculaire—eye wash (fr)
solution pour lavage ophtalmique—eye wash (fr)
solution pour perfusion—solution for infusion (fr)
solution pour pulvérisation buccale—mouth spray (fr)
solution pour pulvérisation nasale—nasal spray (fr)
solution pour pulvérisation sublinguale—sublingual spray (fr)
solution rectale—rectal solution (fr)
solution vaginale—vaginal solution (fr)
soluzione—solution (it)
soluzione cutanea—cutaneous solution (it)
soluzione da nebulizzare—nebuliser solution (it)
soluzione iniettabile—solution for injection (it)
soluzione nasale—nasal solution (it)
soluzione orale—oral solution (it)
soluzione per inalazione—solution for inhalation (it)
soluzione per infusione—solution for infusion (it)
soluzione per uso topico—topical solution (it)
soluzione rettale—rectal solution (it)
soluzione vaginale—vaginal solution (it)
sospensione—suspension (it)
sospensione iniettabile—suspension for injection (it)
sospensione per inalazione—suspension for inhalation (it)
sospensione per uso orale—oral suspension (it)
sparadrap—plaster (dressing or adhesive plaster) (fr)
spiraaltje—intra-uterine device (nl)
spiral—intra-uterine device (sv)
spolvätska för urinblåsan—bladder irrigation (sv)
sponge
—éponge (fr)
—esponja (es,pt)
—gąbka (pl)
—hubka (cs)
—kempinė (lt)
—Schwamm (de)
—spons (nl)
—spugna (it)
—svamp (sv)
—szivacs (hu)
—σπόγγος (el)
cutaneous sponge
—éponge pour application cutanée (fr)
—esponja cutánea (es)
—esponja cutânea (pt)
—gąbka na skórę (pl)
—hudsvamp (sv)
—kožní hubka (cs)
—külsőleges gyógyszeres szivacs (hu)
—kutan svamp (sv)
—odos kempinė (lt)
—Schwämmchen zur Anwendung auf der Haut (de)
—spons voor cutaan gebruik (nl)
—spugna per applicazione cutanea (it)
—δερματικός σπόγγος (el)
vaginal sponge
—éponge vaginale (fr)
—esponja vaginal (es,pt)
—gąbka dopochwowa (pl)
—gyógyszeres hüvelyszivacs (hu)
—makšties kempinė (lt)
—spons voor vaginaal gebruik (nl)
—spugna vaginale (it)
—svamp i underlivet (sv)
—vaginální hubka (cs)
—Vaginalschwamm (de)
—vaginalsvamp (sv)
—κολπικός σπόγγος (el)
spons—sponge (nl)
spons voor cutaan gebruik—cutaneous sponge (nl)
spons voor vaginaal gebruik—vaginal sponge (nl)
spray
—aerosol (es)
—aerozol (pl)
—nebulizador (es)
—permet (hu)
—pulverizador (pt)
—purškalas (lt)
—Spray (de)
—spray (es,fr,it,nl,pt,sv)
—sprej (cs)
—vaporizador (es)
—εκνέφωμα (el)
cutaneous spray
—aerozol na skórę (pl)
—Hautspray (de)
—huidspray (nl)
—kožni sprej (cs)
—külsőleges permet (hu)
—kutan spray (sv)
—odos purškalas (lt)
—pulvérisation cutanée (fr)
—pulverização cutânea (pt)
—pulverizador cutâneo (pt)
—spray cutané (fr)
—spray cutáneo (es)
—spray cutaneo (it)
—Spray zur Anwendung auf der Haut (de)
—δερματικό εκνέφωμα (el)
mouth spray
—aerozol do stosowania w jamie ustnej (pl)
—aerozol doustny (pl)
—burnos purškalas (lt)
—mondspray (nl)
—Mundspray (de)
—munhålespray (sv)
—munspray (sv)
—nebulizador oral (es)
—orální sprej (cs)
—solução para pulverização bucal (pt)
—solution pour pulvérisation buccale (fr)
—spray buccal (fr)
—spray oral (es,fr,pt)
—spray per uso orale (it)
—spray voor oromucosaal gebruik (nl)
—száj permet (hu)
—ústní sprej (cs)
—στοματικό εκνέφωμα (el)
nasal spray
—aerozol do nosa (pl)
—näsaerosol (sv)
—Nasenspray (de)
—nässpray (sv)
—nebulizador nasal (es)
—neusspray (nl)
—nosies purškalas (lt)
—nosní sprej (cs)
—orrpermet (hu)
—pulverização nasal (pt)
—pulverizador nasal (pt)
—solution pour pulvérisation nasale (fr)
—spray nasale (it)
—spray nasal (es,pt)
—ρινικό εκνέφωμα (el)
sublingual spray
—aerozol podjęzykowy (pl)
—nyelvalatti spray (hu)
—poliežuvinis purškalas (lt)
—preparação para pulverização sublingual (pt)
—pulverización sublingual (es)
—solution pour pulvérisation sublinguale (fr)
—spray souslingual (fr)
—spray sublingual (pt)
—spray sublinguale (it)
—spray voor sublinguaal gebruik (nl)
—sprej pod jazyk (cs)
—Sublingualspray (de)
—sublingualspray (sv)
—sublingvální sprej (cs)
—υπογλώσσιο εκνέφωμα (el)
throat spray
—aerozol do gardła (pl)
—collutoire (fr)
—gerklės purškalas (lt)
—halsspray (sv)
—keelspray (nl)
—munhålespray (sv)
—nebulizador faríngeo (es)
—Rachenspray (de)
—spray para a garganta (pt)
—spray para la garganta (es)
—spray per la gola (it)
—spray pour la gorge (fr)
—Spray zur Anwendung auf der Hals (de)
—sprej do krku (cs)
—torok permet (hu)
—λαρυγγικό εκνέφωμα (el)
topical spray
—aerozol do stosowania miejscowego (pl)
—lokalus purškalas (lt)
—nebulizador de aplicación tópica (es)
—permet bőrre (hu)
—spray de aplicación tópica (es)
—spray per uso topico (it)
—spray pour application locale (fr)
—spray tópico (pt)
—spray voor lokaal gebruik (nl)
—Spray zur topischen Anwendung (de)
—sprej k zevnímu použití (cs)
—topikal spray (sv)
—topische Spray (de)
—τοπικό εκνέφωμα (el)
Spray—spray (de)
spray—spray (es,fr,it,nl,pt,sv)
spray buccal—mouth spray (fr)
spray cutané—cutaneous spray (fr)
spray cutáneo—cutaneous spray (es)
spray cutaneo—cutaneous spray (it)
spray de aplicación tópica—topical spray (es)
spray nasal—nasal spray (es,pt)
spray nasale—nasal spray (it)
spray oral—mouth spray (es,fr,pt)
spray para a garganta—throat spray (pt)
spray para la garganta—throat spray (es)
spray per la gola—throat spray (it)
spray per uso orale—mouth spray (it)
spray per uso topico—topical spray (it)
spray pour application locale—topical spray (fr)
spray pour la gorge—throat spray (fr)
spray souslingual—sublingual spray (fr)
spray sublingual—sublingual spray (pt)
spray sublinguale—sublingual spray (it)
spray tópico—topical spray (pt)
spray voor lokaal gebruik—topical spray (nl)
spray voor oromucosaal gebruik—mouth spray (nl)
spray voor sublinguaal gebruik—sublingual spray (nl)
Spray zur Anwendung auf der Hals—throat spray (de)
Spray zur Anwendung auf der Haut—cutaneous spray (de)
Spray zur topischen Anwendung—topical spray (de)
sprej—spray (cs)
sprej do krku—throat spray (cs)
sprej k zevnímu použití—topical spray (cs)
sprej pod jazyk—sublingual spray (cs)
Spritze—syringe (de)
spruta—syringe (sv)
spruta för oral användning—oral syringe (sv)
spugna—sponge (it)
spugna per applicazione cutanea—cutaneous sponge (it)
spugna vaginale—vaginal sponge (it)
spuit—syringe (nl)
šroubovací uzávěr—screw cap (cs)

cs=Czech; de=German; el=Greek; es=Spanish; fr=French; hu=Hungarian; it=Italian; lt=Lithuanian; nl=Dutch; pl=Polish; pt=Portuguese; sv=Swedish

stérilet—intra-uterine system (fr)
Sterilkompresse—dressing (de)
stick medicamentoso—medicated stick (es)
stick medicato—medicated stick (it)
Stift zur Anwendung auf der Haut (skin)—medicated stick (de)
stolpiller—suppository (sv)
stosowanie miejscowe—topical application (pl)
Streukügelchen—globules (homoeopathic) (de)
střikačka pro perorální podání—oral syringe (cs)
strooipoeder—dusting (cutaneous) powder (nl)
stroop—syrup, linctus (nl)
strzykawka—syringe (pl)
strzykawka do podawania leku doustnie—oral syringe (pl)
strzykawka jednorazowa—disposable syringe (pl)
Stützverband—bandage (de)
subcutaan gebruik—subcutaneous use/route (nl)
subcutan alkalmazás—subcutaneous use/route (hu)
subcutaneous use/route
—podanie podskórne (pl)
—subcutaan gebruik (nl)
—subcutan alkalmazás (hu)
—subkutan administrering (sv)
—subkutan användning (sv)
—subkutane Anwendung (de)
—subkutánní podání (cs)
—subkutant bruk (sv)
—uso sottocutaneo (it)
—vartoti po oda (lt)
—via sottocutanea (it)
—via subcutânea (pt)
—vía subcutanea (es)
—voie sous-cutanée (fr)
—υποδόρια χρήση (el)
subkutan administrering—subcutaneous use/route (sv)
subkutan användning—subcutaneous use/route (sv)
subkutane Anwendung—subcutaneous use/route (de)
subkutánní podání—subcutaneous use/route (cs)
subkutant bruk—subcutaneous use/route (sv)
sublinguaal gebruik—sublingual use/route (nl)
sublingual administrering—sublingual use/route (sv)
sublingual användning—sublingual use/route (sv)
sublingual Anwendung—sublingual use/route (de)
sublingual spray—*see under* spray
sublingual tablet—*see under* tablet
sublingual tablett—sublingual tablet (sv)
sublingual use/route
—podání pod jazyk (cs)
—podanie podjęzykowe (pl)
—sublinguaal gebruik (nl)
—sublingual administrering (sv)
—sublingual användning (sv)
—sublingual Anwendung (de)
—sublingualis alkalmazás (hu)
—sublinguální podání (cs)
—sublingualt bruk (sv)
—uso sublinguale (it)
—vartoti po liežuviu (lt)
—via sublingual (pt)
—vía sublingual (es)
—voie sublinguale (fr)
—υπογλώσσια χρήση (el)
sublingualis alkalmazás—sublingual use/route (hu)
sublinguální podání—sublingual use/route (cs)
Sublingualspray—sublingual spray (de)
sublingualspray—sublingual spray (sv)
sublingualt bruk—sublingual use/route (sv)
Sublingualtablette—sublingual tablet (de)
sublingvální sprej—sublingual spray (cs)
sublingvální tableta—sublingual tablet (cs)
suffumigi—vapour inhalation (it)
sugar-free
—be cukraus (lt)
—bez cukru (cs,pl)
—cukor mentes (hu)
—sans sucre (note also édulcoré, artificially sweetened) (fr)
—sem açúcar (pt)
—senza zucchero (it)
—sin azúcar (es)
—sockerfri (sv)
—suikervrij (nl)
—utan socker (sv)
—zuckerfrei (de)
—χωρίς ζάχαρη (el)
sugtablett—lozenge (sv)
suikervrij—sugar-free (nl)
šumivá tableta—effervescent tablet (cs)
šumivý granulát—effervescent granules (cs)
šumivý prašek—effervescent powder (cs)
šumivý zrněný prášek—effervescent granules (cs)
supositório—suppository (pt)
supositorio—suppository (es)
supositorio de aplicación vaginal—vaginal suppository (es)
supositório vaginal—vaginal suppository (pt)
supp—suppository (sv)
suppositoire—suppository (fr)
suppositoire vaginal—vaginal suppository (fr)
Suppositorium—suppository (de)
suppositorium—suppository (sv)
suppository
—čípek (cs)
—czopek (pl)
—stolpiller (sv)
—supositório (pt)
—supositorio (es)
—suppositoire (fr)
—Suppositorium (de)
—suppositorium (sv)
—supposta (it)
—supp (sv)
—végbélkúp (hu)
—Zäpfchen (de)
—zetpil (nl)
—žvakutė (lt)
—υπόθετο (el)
vaginal suppository
—czopek dopochwowy (pl)
—globulka (pl)
—hüvelykúp (hu)
—makšties žvakutė (lt)
—supositorio de aplicación vaginal (es)
—supositório vaginal (pt)
—suppositoire vaginal (fr)
—supposta vaginale (it)
—vaginální čípek (cs)
—vaginaltablett (sv)
—Vaginalzäpfchen (de)
—vagitorium (sv)
—κολπικό υπόθετο (el)
supposta—suppository (it)
supposta vaginale—vaginal suppository (it)
suspensão—suspension (pt)
suspensão injectável—suspension for injection (pt)
suspensão oral—oral suspension (pt)
suspensão para inalação—suspension for inhalation (pt)
suspensie—suspension (nl)
suspensie voor injectie—suspension for injection (nl)
suspensie voor oraal gebruik—oral suspension (nl)
suspensija—suspension (lt)
suspension
—schudmixtuur (nl)
—sospensione (it)
—suspensão (pt)
—suspensie (nl)
—suspensija (lt)
—Suspension (de)
—suspension (fr,sv)
—suspensión (es)
—suspenze (cs)
—szuszpenzió (hu)
—zawiesina (pl)
—εναιώρημα (el)
oral suspension
—belsőleges szuszpenzió (hu)
—geriamoji suspensija (lt)
—oral suspension (sv)
—sospensione per uso orale (it)
—suspensão oral (pt)
—suspensie voor oraal gebruik (nl)
—suspension buvable (fr)
—suspensión oral (es)
—Suspension zum Einnehmen (de)
—suspenze perorální (cs)
—zawiesina doustna (pl)
—πόσιμο εναιώρημα (el)
suspensión—suspension (es)
Suspension—suspension (de)
suspension—suspension (fr,sv)
suspension buvable—oral suspension (fr)
suspension for inhalation—*see under* inhalation
suspension för inhalation—suspension for inhalation (sv)
suspension for injection—*see under* injection
suspensión inestable—suspension for injection (es)
suspension injectable—suspension for injection (fr)
suspensión oral—oral suspension (es)
suspensión para inhalación—suspension for inhalation (es)
suspension pour inhalation—suspension for inhalation (fr)
suspension till injektionsvätska—suspension for injection (sv)
Suspension zum Einnehmen—oral suspension (de)
Suspension zur Inhalation—suspension for inhalation (de)
Suspension zur Injektion—suspension for injection (de)
suspenze—suspension (cs)
suspenze k inhalaci—suspension for inhalation (cs)
suspenze perorální—oral suspension (cs)
šuteklis—poultice (lt)
svamp—sponge (sv)
svamp i underlivet—vaginal sponge (sv)
švirkštas—syringe (lt)
syringe
—fecskendő (hu)
—injekční stříkačka (cs)
—jeringa (es)
—seringa (pt)
—seringue (fr)
—siringa (it)
—Spritze (de)
—spruta (sv)
—spuit (nl)
—strzykawka (pl)
—švirkštas (lt)
—σύριγγα (el)
disposable syringe
—egyszer használatos eldobható fecskendő (hu)
—Einmalspritze (de)
—engångsspruta (sv)
—jednorázová injekční stříkačka (cs)
—jeringa desechable (es)
—seringa descartável (pt)
—seringue à usage unique (fr)
—siringa usa e getta (it)
—strzykawka jednorazowa (pl)
—vienkartinis švirkštas (lt)
—wegwerpspuit (nl)
—σύριγγα μιας χρήσης (el)
oral syringe
—Applikationsspritze für Zubereitungen zum Einnehmen (de)
—doseerspuit voor orale toediening (nl)
—geriamasis švirkštas (lt)
—jeringa para uso oral (es)
—seringa para uso oral (pt)
—seringue pour administration orale (fr)
—siringa per somministrazione orale (it)
—spruta för oral användning (sv)
—střikačka pro perorální podání (cs)
—strzykawka do podawania leku doustnie (pl)
—szájfecskendő (hu)
—σύριγγα για χορήγηση από στόματος (el)
prefilled syringe
—ampoule-seringue (fr)
—ampułkostrzykawka (pl)
—előretöltött fecskendő (hu)
—Fertigspritze (de)
—förfylld spruta (sv)
—jeringa precargada (es)
—předplněná injekční střikačka (cs)
—seringa pré-cheia (pt)
—seringue préremplie (fr)
—siringa preriempita (it)
—užpildytas švirkštas (lt)
—voorgevulde spuit (nl)
—προγεμισμένη σύριγγα (el)
syrop—syrup, linctus (pl)
syrop na kaszel—cough syrup, cough mixture (pl)
syrup
—jarabe (es)
—sciroppo (it)
—sirap (sv)
—siroop (nl)
—sirop (fr)
—sirup (cs)
—Sirup (de)
—sirupas (lt)
—stroop (nl)
—syrop (pl)
—szirup (hu)
—xarope (pt)
—σιρόπι (el)
cough syrup
—hoestsiroop (nl)
—hoeststroop (nl)
—hostmedicin (sv)
—Hustensaft (de)
—Hustensirup (de)
—jarabe para la tos (es)
—köptető szirup (hu)
—sciroppo per la tosse (it)
—sirop antitussif (fr)
—sirop contre la toux (fr)
—sirop pectoral (fr)
—sirup proti kašli (cs)
—sirupas nuo kosulio (lt)
—syrop na kaszel (pl)
—xarope para a tosse (pt)
—σιρόπι για το βήχα (el)
system terapeutyczny do oczu—ocular insert (pl)
system terapeutyczny domaciczny—intra-uterine system (pl)
system transdermalny—transdermal patch (pl)
système transdermique—transdermal patch (fr)
száj permet—mouth spray (hu)
szájban diszpergálódó tabletta—orodispersible tablet (hu)
szájfecskendő—oral syringe (hu)
szájnyálkhártyán történő alkalmazás—buccal or oromucosal use/route (hu)
szájöblítő—mouthwash (hu)

szampon—shampoo (pl)
szem öblítő folyadék—eye wash (hu)
szemészeti alkalmazás—ocular use/route (hu)
szemészeti gyógyszeres lemezke—ocular insert (hu)
szemgél—eye gel (hu)
szemkenőcs—eye ointment (hu)
szemöblítő—eye lotion (hu)
szirup—syrup, linctus (hu)
szivacs—sponge (hu)
szopogató tabletta—lozenge (hu)
sztyft na skórę (for skin)—medicated stick (pl)
szuszpenzió—suspension (hu)
szuszpenzió belégzésre—suspension for inhalation (hu)
szuszpenziós injekció—suspension for injection (hu)

T

tablespoon (15mL)
—colher de sopa (pt)
—cucchiaio da tavola (it)
—cucharada sopera (es)
—cuillère à soupe (fr)
—eetlepel (nl)
—EL (de)
—Esslöffel (de)
—evőkanál (hu)
—łyżka stołowa (pl)
—matsked (sv)
—polévková lžíce (cs)
—valgomasis šaukštas (lt)
—valgomasis šaukštas su kaupu (heaped tablespoon) (lt)
—κουτάλι (el)

tablet
—compressa (it)
—comprimé (fr)
—comprimido (es,pt)
—pastilla (es)
—piller (sv)
—tableta (cs)
—tabletė (lt)
—tabletka (cs,pl)
—tablet (nl)
—tabletta (hu)
—Tablette (de)
—tablett (sv)
—δισκίο (el)

breakable or dividable tablet
—compressa divisibile (it)
—comprimé sécable (fr)
—comprimido divisível (pt)
—comprimido fraccionable (es)
—dalinama tabletė (lt)
—deelbare tablet (nl)
—delbar tablett (sv)
—dělitelná tableta (cs)
—laužiama tabletė (lt)
—osztható tabletta (hu)
—tablet met breukgleuf (nl)
—tabletka podzielna (pl)
—Tablette mit Bruchrille (de)
—teilbare Tablette (de)
—διαιρούμενο δισκίο (el)
—θραυστό δισκίο (el)

buccal tablet
—buccale tablet (nl)
—Buccaltablette (de)
—buckaltablett (sv)
—bukální tableta (cs)
—bukkális tabletta (hu)
—compressa buccale (it)
—comprimé buccal (fr)
—comprimido bucal (es,pt)
—tabletka podpoliczkowa (pl)
—žandinė tabletė (lt)
—στοματικό δισκίο (el)
—δισκίο παρειάς (el)

chewable tablet
—compressa masticabile (it)
—comprimé à croquer (fr)
—comprimido masticable (es)
—comprimido mastigável (pt)
—comprimido para mastigar (pt)
—Kautablette (de)
—kauwtablet (nl)
—kramtomoji tabletė (lt)
—rágótabletta (hu)
—tabletka do rozgryzania i żucia (pl)
—tuggtablett (sv)
—žvýkací tableta (cs)
—μασώμενο δισκίο (el)

coated tablet
—bevont tabletta (hu)
—blíster (es)
—compressa rivestita (it)
—comprimé enrobé (fr)
—comprimido con recubrimiento (es)
—comprimido recubierto (es)
—comprimido revestido (pt)
—dengta tabletė (lt)
—Dragée (de)
—dragée (fr)
—dragerad tablett (sv)
—dražé (cs)
—obalená tableta (cs)
—omhulde tablet (nl)
—tabletka drażowana (pl)
—überzogene Tablette (de)
—επικαλυμμένο δισκίο (el)

dispersible tablet
—compressa dispersibile (it)
—comprimé dispersible (fr)
—comprimido dispersable (es)
—comprimido dispersível (pt)
—dispergeerbare tablet (nl)
—dispergerbar tablett (sv)
—disperguojamoji tabletė (lt)
—diszpergálódó tabletta (hu)
—tableta pro přípravu perorální suspenze (cs)
—tabletka do sporządzania zawiesiny doustnej (pl)
—Tablette zur Herstellung einer Suspension zum Einnehmen (de)
—διασπειρόμενο δισκίο (el)

effervescent tablet
—Brausetablette (de)
—bruistablet (nl)
—brustablett (sv)
—compressa effervescente (it)
—comprimé effervescent (fr)
—comprimido efervescente (es,pt)
—pezsgőtabletta (hu)
—šnypščianti, putojanti tabletė (lt)
—šumivá tableta (cs)
—tabletka musująca (pl)
—αναβράζον δισκίο (el)

enteric-coated (gastro-resistant) tablet
—compressa gastroresistente (it)
—comprimé à enrobage entérique (fr)
—comprimé gastrorésistant (fr)
—comprimido con recubrimiento entérico (es)
—comprimido gastroresistente (pt)
—comprimido gastrorresistente (es)
—enterosolventní tableta (cs)
—enterotablett (sv)
—gyomornedv-ellenálló tabletta (hu)
—maagsapresistente tablet (nl)
—magensaftresistent Tablette (de)
—skrandyje neiri tabletė (lt)
—tabletka dojelitowa (pl)
—γαστροανθεκτικό δισκίο (el)

extended-release tablet
—compressa a rilascio prolungato (it)
—comprimé à libération prolongée (fr)
—comprimido de liberación prolongada (es)
—comprimido de liberación retardada (es)
—comprimido de libertação prolongada (pt)
—depottablett (sv)
—pailginto atpalaidavimo tabletė (lt)
—retard tabletta (hu)
—retardovaná tableta (cs)
—Retardtablette (de)
—tablet met verlengde afgifte (nl)
—tableta s prodlouženým uvolňováním (cs)
—tabletka o przedłużonym uwalnianiu (pl)
—δισκίο παρατεταμένης αποδέσμευσης (el)

film-coated tablet
—compressa rivestita con film (it)
—comprimé pelliculé (fr)
—comprimido con cubierta pelicular (es)
—comprimido recubierto con película (es)
—comprimido revestido por pelicula (pt)
—filmdragerad tablett (sv)
—filmomhulde tablet (nl)
—filmtabletta (hu)
—Filmtablette (de)
—plėvele dengta tabletė (lt)
—potahovaná tableta (cs)
—tabletka powlekana (pl)
—επικαλυμμένο με λεπτό υμένιο δισκίο (el)

modified release tablet
—compressa a rilascio modificato (it)
—comprimé à libération modifiée (fr)
—comprimido de liberación modificada (es)
—comprimido de libertação modificada (pt)
—modifikuoto atpalaidavimo tabletė (lt)
—módosított hatóanyagleadású tabletta (hu)
—tablet met gereguleerde afgifte (nl)
—tableta s řízeným uvolňováním (cs)
—tabletka o zmodyfikowanym uwalnianiu (pl)
—tablett med modifierad frisättning (sv)
—Tablette mit modifizierte Wirkstofffreisetzung (de)
—δισκίο ελεγχόμενης αποδέσμευσης (el)

orodispersible tablet
—burnoje disperguojamoji tabletė (lt)
—compressa orodispersibile (it)
—comprimé fondant (fr)
—comprimé orodispersible (fr)
—comprimido bucodispersable (es)
—comprimido orodispersível (pt)
—munsönderfallende tablett (sv)
—orodispergeerbare tablet (nl)
—Schmelztablette (de)
—smelttablet (nl)
—szájban diszpergálódó tabletta (hu)
—tableta dispergovatelná v ústech (cs)
—tabletka ulegająca rozpadowi w jamie ustnej (pl)
—δισκίο διασπειρόμενο στο στόμα (el)

soluble tablet
—compressa solubile (it)
—comprimé soluble (fr)
—comprimido soluble (es)
—comprimido solúvel (pt)
—lösbar Tablette (de)
—löslig tablett (sv)
—oldódó tabletta (hu)
—oplosbare tablet (nl)
—tableta pro přípravu perorálního roztoku (cs)
—tabletka do sporządzania roztworu doustnego (pl)
—tirpinamoji tabletė (lt)
—Trinktablette (de)
—διαλυτό δισκίο (el)

sublingual tablet
—compressa sublinguale (it)
—comprimé sublingual (fr)
—comprimido sublingual (es,pt)
—nyelvalatti tabletta (hu)
—poliežuvinė tabletė (lt)
—resoriblett (sv)
—sublingual tablett (sv)
—Sublingualtablette (de)
—sublingvální tableta (cs)
—tablet voor sublinguaal gebruik (nl)
—tabletka podjęzykowa (pl)
—υπογλώσσιο δισκίο (el)

vaginal tablet
—compressa vaginale (it)
—comprimé vaginal (fr)
—comprimido vaginal (es,pt)
—hüvelytabletta (hu)
—makšties tabletė (lt)
—poševní tableta (cs)
—tablet voor vaginaal gebruik (nl)
—tabletka dopochwowa (pl)
—vaginální tableta (cs)
—Vaginaltablette (de)
—vaginaltablett (sv)
—κολπικό δισκίο (el)

tablet—tablet (nl)
tablet met breukgleuf—breakable or dividable tablet (nl)
tablet met gereguleerde afgifte—modified release tablet (nl)
tablet met verlengde afgifte—extended-release tablet (nl)
tablet voor sublinguaal gebruik—sublingual tablet (nl)
tablet voor vaginaal gebruik—vaginal tablet (nl)
tableta—tablet (cs)
tableta dispergovatelná v ústech—orodispersible tablet (cs)
tableta pro přípravu perorální suspenze—dispersible tablet (cs)
tableta pro přípravu perorálního roztoku—soluble tablet (cs)
tableta s prodlouženým uvolňováním—extended-release tablet (cs)
tableta s řízeným uvolňováním—modified release tablet (cs)
tabletė—tablet (lt)
tabletka—tablet (cs,pl)
tabletka do rozgryzania i żucia—chewable tablet (pl)
tabletka do sporządzania roztworu doustnego—soluble tablet (pl)
tabletka do sporządzania zawiesiny doustnej—dispersible tablet (pl)
tabletka dojelitowa—enteric-coated (gastro-resistant) tablet (pl)
tabletka dopochwowa—vaginal tablet (pl)
tabletka drażowana—coated tablet (pl)
tabletka musująca—effervescent tablet (pl)
tabletka o przedłużonym uwalnianiu—extended-release tablet (pl)
tabletka o zmodyfikowanym uwalnianiu—modified release tablet (pl)
tabletka podjęzykowa—sublingual tablet (pl)
tabletka podpoliczkowa—buccal tablet (pl)
tabletka podzielna—breakable or dividable tablet (pl)
tabletka powlekana—film-coated tablet (pl)
tabletka ulegająca rozpadowi w jamie ustnej—orodispersible tablet (pl)
tablett—tablet (sv)
tablett med modifierad frisättning—modified release tablet (sv)
tabletta—tablet (hu)
Tablette—tablet (de)
Tablette mit Bruchrille—breakable or dividable tablet (de)
Tablette mit modifizierte Wirkstofffreisetzung—modified release tablet (de)

Tablette zur Herstellung einer Suspension zum Einnehmen—dispersible tablet (de)
tampa—cap (pt)
tampa de segurança—child-resistant closure (pt)
tampa roscada—screw cap (pt)
tampão—tampon (pt)
tampon
—tampão (pt)
—Tampon (de)
—tampon (cs,fr,hu,nl,pl)
—tampón (es)
—tamponas (lt)
—tampone (it)
—tampong (sv)
—επίπωμα (el)
Tampon—tampon (de)
tampon—tampon (cs,fr,hu,nl,pl)
tampón—tampon (es)
tamponas—tampon (lt)
tampone—tampon (it)
tampong—tampon (sv)
tandkräm—toothpaste (sv)
tandpasta—toothpaste (nl)
tapasz—plaster (dressing or adhesive plaster) (hu)
tappo a vite—screw cap (it)
tappo—cap (it)
tarro—jar (es)
tasak—sachet (hu)
te—tea (herbal or medicinal) (sv)
tea (herbal or medicinal)
—čaj (cs)
—chá (pt)
—chá medicinal (pt)
—gyógytea (hu)
—herbata (pl)
—Infus (de)
—infusión (es)
—infusion (fr)
—kruidenthee (nl)
—léčivý čaj (cs)
—örtte (sv)
—Tee (de)
—te (sv)
—thee (nl)
—thé (fr)
—tisana (es,it)
—tisane (fr)
—vaistažolių arbata (lt)
—zioła do zaparzania (pl)
—τσάι (el)
—φαρμακευτικό τσάι (el)
—φυτικό τσάι (el)
teáskanál—teaspoon (hu)
teaspoon (5mL)
—arbatinis šaukštelis (lt)
—čajová lžička (cs)
—colher de chá (pt)
—cucchiaino (it)
—cucchiaio da tè (it)
—cucharadita de té (es)
—cuillère à café (fr)
—kávéskanál (hu)
—kávová lžička (cs)
—łyżeczka do herbaty (pl)
—teáskanál (hu)
—Teelöffel (de)
—tesked (sv)
—theelepel (n.b. 3 mL) (nl)
—TL (de)
—κουταλάκι (el)
Tee—tea (de)
Teelöffel—teaspoon (de)
tégely—jar (hu)
teilbare Tablette—breakable or dividable tablet (de)
teinture—tincture (fr)
tepalas—ointment (lt)
tesked—teaspoon (5mL) (sv)
thé—tea (fr)
thee—tea (nl)
theelepel—teaspoon (nl)
throat spray—*see under* spray
tiesiosios žarnos putos—rectal foam (lt)
tiesiosios žarnos tepalas—rectal ointment (lt)
tiesiosios žarnos tirpalas—rectal solution (lt)
timbre transdermique—transdermal patch (fr)
tincture
—nalewka (pl)
—teinture (fr)
—tinctuur (nl)
—Tinktur (de)
—tinktur (sv)
—tinktúra (hu)
—tinktūra (lt)
—tinktura (cs)
—tintura (es,it,pt)
—βάμμα (el)
tinctuur—tincture (nl)
Tinktur—tincture (de)
tinktur—tincture (sv)
tinktura—tincture (cs)
tinktúra—tincture (hu)
tinktūra—tincture (lt)
tintura—tincture (es,it,pt)
tirita—plaster (dressing or adhesive plaster) (es)
tirpalas—solution (lt)
tirpinamoji tabletė—soluble tablet (lt)
tisana—tea (herbal or medicinal) (es,it)
tisane—tea (herbal or medicinal) (fr)
TL—teaspoon (de)
tobolka—capsule (cs)
tobolka s prodlouženým uvolňováním—extended-release capsule (cs)
toothpaste
—dantų pasta (lt)
—dentifricio (it)
—dentífrico (es)
—fogpaszta (hu)
—pasta dental (es)
—pasta dentífrica (es,pt)
—pasta dentifricia (it)
—pasta do zębów (pl)
—pâte dentifrice (fr)
—tandkräm (sv)
—tandpasta (nl)
—Zahnpaste (de)
—zubní pasta (cs)
—οδοντόκρεμα (el)
—οδοντόπαστα (el)
topical application
—aplicación tópica (es)
—application locale (fr)
—applicazione topica (it)
—lokaal gebruik (nl)
—lokal administrering (sv)
—lokalt bruk (sv)
—stosowanie miejscowe (pl)
—topické podání (cs)
—topikal administrering (sv)
—topikalt bruk (sv)
—topische Anwendung (de)
—uso topico (it,pt)
—vartoti lokaliai (lt)
—zevní podání (cs)
—τοπική χρήση (el)
topical emulsion—*see under* emulsion
topical gel—*see under* gel
topical paste—*see under* paste
topical powder—*see under* powder
topical solution—*see under* solution
topical spray—*see under* spray
topická emulze—topical emulsion (cs)
topická pasta—topical paste (cs)
topické podání—topical application (cs)
topický gel—topical gel (cs)
topický roztok—topical solution (cs)
topikal administrering—topical application (sv)
topikal emulsion—topical emulsion (sv)
topikal gel—topical gel (sv)
topikal lösning—topical solution (sv)
topikal pasta—topical paste (sv)
topikal spray—topical spray (sv)
topikalt bruk—topical application (sv)
topische Anwendung—topical application (de)
topische Spray—topical spray (de)
torok permet—throat spray (hu)
toroköblítö—gargle (hu)
transdermaal gebruik—transdermal use/route (nl)
transdermal administrering—transdermal use/route (sv)
transdermal användning—transdermal use/route (sv)
transdermal patch
—cerotto transdermico (it)
—depotplåster (sv)
—dispositif transdermique (fr)
—parche transdérmico (es)
—pleister voor transdermaal gebruik (nl)
—sistema transdérmico (pt)
—system transdermalny (pl)
—système transdermique (fr)
—timbre transdermique (fr)
—transdermales Pflaster (de)
—transdermales therapeutisches System (de)
—transdermální náplast (cs)
—transdermální terapeutický systém (cs)
—transdermalt plåster (sv)
—transderminis pleistras (lt)
—transzdermális tapasz (hu)
—διαδερμικό έμπλαστρο (el)
transdermal use/route
—podanie przezskórne (pl)
—transdermaal gebruik (nl)
—transdermal administrering (sv)
—transdermal användning (sv)
—transdermale Anwendung (de)
—transdermalis alkalmazás (hu)
—transdermální podání (cs)
—transdermalt bruk (sv)
—uso transdermico (it)
—vartoti transdermaliai (lt)
—via transdérmica (pt)
—via transdermica (it)
—vía transdérmica (es)
—voie transdermique (fr)
—διαδερμική χρήση (el)
transdermale Anwendung—transdermal use/route (de)
transdermales Pflaster—transdermal patch (de)
transdermales therapeutisches System—transdermal patch (de)
transdermalis alkalmazás—transdermal use/route (hu)
transdermální náplast—transdermal patch (cs)
transdermální podání—transdermal use/route (cs)
transdermální terapeutický systém—transdermal patch (cs)
transdermalt bruk—transdermal use/route (sv)
transdermalt plåster—transdermal patch (sv)
transderminis pleistras—transdermal patch (lt)
transzdermális tapasz—transdermal patch (hu)
Trinktablette—soluble tablet (de)
Tropfen—drops (de)
Tropfen zum Einnehmen—oral drops (de)
tuggtablett—chewable tablet (sv)
tuggummi—chewing gum (sv)
tvarstis—bandage, dressing (lt)
tvrdá tobolka—hard capsule (cs)
twarda kapsułka—hard capsule (pl)

U

überzogene Tablette—coated tablet (de)
Umschlag—poultice (de)
ungüento—ointment (es)
unguento—ointment (it)
unguento nasale—nasal ointment (it)
unguento oftalmico—eye ointment (it)
unguento rettale—rectal ointment (it)
unguento vaginale—vaginal ointment (it)
urethraal gebruik—urethral use/route (nl)
urethral gel—*see under* gel
urethral use/route
—administrering i urinröret (sv)
—Anwendung in der Harnröhre (de)
—podanie do cewki moczowej (pl)
—urethraal gebruik (nl)
—urethralis alkalmazás (hu)
—uretral administrering (sv)
—uretral användning (sv)
—uretrální podání (cs)
—uretralt bruk (sv)
—uso uretrale (it)
—vartoti į šlaplę (lt)
—via uretral (pt)
—vía uretral (es)
—voie urétrale (fr)
—ουρηθρική χρήση (el)
urethralis alkalmazás—urethral use/route (hu)
uretral administrering—urethral use/route (sv)
uretral användning—urethral use/route (sv)
uretralgel—urethral gel (sv)
uretrální gel—urethral gel (cs)
uretrální podání—urethral use/route (cs)
uretralt bruk—urethral use/route (sv)
ušní kapky—ear drops (cs)
ušní podání—auricular use/route (cs)
uso auricolare—auricular use/route (it)
uso auricular—auricular use/route (pt)
uso cutáneo—cutaneous use/route (es)
uso cutâneo—cutaneous use/route (pt)
uso cutaneo—cutaneous use/route (it)
uso endoarterioso—intra-arterial use/route (it)
uso endovenoso—intravenous use/route (it)
uso endovescicale—intravesical use/route (it)
uso epidurale—epidural use/route (it)
uso gastrointestinale—gastroenteral use/route (it)
uso inalatorio—inhalation (route) (it)
uso intra-articolare—intra-articular use/route (it)
uso intracavernoso—intracavernosal use/route (it)
uso intradermico—intradermal use/route (it)
uso intralesional—intra-lesional use/route (pt)
uso intralesionale—intra-lesional use/route (it)
uso intramuscolare—intramuscular use/route (it)
uso intraperitoneale—intraperitoneal use/route (it)
uso intratecale—intrathecal use/route (it)
uso intrauterino—intrauterine use/route (it)
uso nasale—nasal use/route (it)
uso ocular—ocular use/route (pt)
uso oftalmico—ocular use/route (it)
uso orale—oral use/route (it)
uso rettale—rectal use/route (it)
uso sottocutaneo—subcutaneous use/route (it)
uso sublinguale—sublingual use/route (it)
uso topico—topical application (it,pt)
uso transdermico—transdermal use/route (it)
uso uretrale—urethral use/route (it)
uso vaginal—vaginal use/route (pt)
uso vaginale—vaginal use/route (it)
ústní gel—oral gel (cs)
ústní sprej—mouth spray (cs)
ústní voda—mouthwash (cs)
utan socker—sugar-free (sv)
üveg—bottle (hu)
užpildytas švirkštas—prefilled syringe (lt)
užsukamas dangtelis—screw cap (lt)
užtaisas—cartridge (lt)

V

vaginaal gebruik—vaginal use/route (nl)
vaginal administrering—vaginal use/route (sv)
vaginal användning—vaginal use/route (sv)
vaginal capsule—*see under* capsule
vaginal cream—*see under* cream
vaginal foam—*see under* foam
vaginal gel—*see under* gel
vaginal ointment—*see under* ointment
vaginal solution—*see under* solution
vaginal sponge—*see under* sponge
vaginal suppository—*see under* suppository
vaginal tablet—*see under* tablet
vaginal use/route
—podanie dopochwowe (pl)
—uso vaginale (it)
—uso vaginal (pt)
—vaginaal gebruik (nl)
—vaginal administrering (sv)
—vaginal användning (sv)
—vaginale Anwendung (de)
—vaginalis alkalmazás (hu)
—vaginální podání (cs)
—vaginalt bruk (sv)
—vartoti į makštį (lt)
—vía vaginal (es)
—voie vaginale (fr)
—κολπική χρήση (el)
Vaginalcreme—vaginal cream (de)
vaginaldusch—douche (vaginal) (sv)
Vaginaldusche—douche (vaginal) (de)
vaginale Anwendung—vaginal use/route (de)
vaginale douche—douche (vaginal) (nl)
Vaginalgel—vaginal gel (de)
vaginalgel—vaginal gel (sv)
vaginalinis apsiplovimas—douche (vaginal) (lt)
vaginalis alkalmazás—vaginal use/route (hu)
Vaginalkapsel—vaginal capsule (de)
vaginalkapsel—vaginal capsule (sv)
vaginalkräm—vaginal cream (sv)
vaginallösning—vaginal solution (sv)
Vaginallösung—vaginal solution (de)
vaginální čípek—vaginal suppository (cs)
vaginální gel—vaginal gel (cs)
vaginální hubka—vaginal sponge (cs)
vaginální krém—vaginal cream (cs)
vaginální kulička—pessary (cs)
vaginální mast—vaginal ointment (cs)
vaginální pěna—vaginal foam (cs)
vaginální podání—vaginal use/route (cs)
vaginální roztok—vaginal solution (cs)
vaginální tableta—vaginal tablet (cs)
vaginální tobolka—vaginal capsule (cs)
vaginální výplach—douche (vaginal) (cs)
Vaginalovulum—pessary (de)
Vaginalpessar—intra-uterine system (de)
Vaginalsalbe—vaginal ointment (de)
vaginalsalva—vaginal ointment (sv)
Vaginalschaum—vaginal foam (de)
Vaginalschwamm—vaginal sponge (de)
vaginalskum—vaginal foam (sv)
vaginalsvamp—vaginal sponge (sv)
vaginalt bruk—vaginal use/route (sv)
vaginaltablett—vaginal suppository (sv)
vaginaltablett—vaginal tablet (sv)
Vaginaltablette—vaginal tablet (de)
vaginalvätska—vaginal solution (sv)
Vaginalzäpfchen—vaginal suppository (de)
vagitorium—pessary, vaginal suppository (sv)
vaikų neatidaromas uždoris—child-resistant closure (lt)
vaistažolių arbata—tea (herbal or medicinal) (lt)
vaistinis nagų lakas—medicated nail lacquer (lt)
vaistinis pleistras—plaster (lt)
valgomasis gelis—oral gel (lt)
valgomasis šaukštas—tablespoon (lt)
valgomasis šaukštas su kaupu—heaped tablespoon (lt)
valgomoji pasta—oral paste (lt)
vapeur pour inhalation—vapour inhalation (fr)
vapor para inhalación—vapour inhalation (es)
vaporizador—spray (es)
vapour inhalation—*see under* inhalation
vartojimo į gimdą sistema—intra-uterine system (lt)
vartoti akims—ocular use/route (lt)
vartoti ant burnos gleivinės—buccal or oromucosal use/route (lt)
vartoti ant odos—cutaneous use/route (lt)
vartoti epiduraliai—epidural use/route (lt)
vartoti į akytkūnį—intracavernosal use/route (lt)
vartoti į arteriją—intra-arterial use/route (lt)
vartoti į ausį—auricular use/route (lt)
vartoti į gimdą—intrauterine use/route (lt)
vartoti į makštį—vaginal use/route (lt)
vartoti į nosį—nasal use/route (lt)
vartoti į odą—intradermal use/route (lt)
vartoti į pažeistą vietą—intra-lesional use/route (lt)
vartoti į pilvaplėvės ertmę—intraperitoneal use/route (lt)
vartoti į raumenis—intramuscular use/route (lt)
vartoti į sąnarį—intra-articular use/route (lt)
vartoti į skrandį ir žarnyną—gastroenteral use/route (lt)
vartoti į šlapimo pūslę—intravesical use/route (lt)
vartoti į šlaplę—urethral use/route (lt)
vartoti į tiesiąją žarną—rectal use/route (lt)
vartoti į veną—intravenous use/route (lt)
vartoti intratekaliai—intrathecal use/route (lt)
vartoti lokaliai—topical application (lt)
vartoti po liežuviu—sublingual use/route (lt)
vartoti po oda—subcutaneous use/route (lt)
vartoti transdermaliai—transdermal use/route (lt)
vasetto—jar (it)
vaso dosificator—cup (measuring) (es)
végbélhab—rectal foam (hu)
végbélkenőcs—rectal ointment (hu)
végbélkúp—suppository (hu)
végbéloldat—rectal solution (hu)
venda—bandage (es)
vendaje—bandage (es)
vendaje medicalizado—medicated bandage (es)
Verband—bandage (de)
verband—bandage (nl)
verbandgaas—dressing (nl)
verneveloplossing—nebuliser solution (nl)
vernis à ongles médicamenteux—medicated nail lacquer (fr)
verniz para as unhas medicamentoso—medicated nail lacquer (pt)
verpakking voor eenmalig gebruik—single-dose container (nl)
Verschluss—cap (de)
via bucal—buccal or oromucosal use/route (pt)
vía bucal—buccal or oromucosal use/route (es)
via cutanea—cutaneous use/route (it)
via endoarteriosa—intra-arterial use/route (it)
via endovenosa—intravenous use/route (it)
via epidural—epidural use/route (pt)
vía epidural—epidural use/route (es)
via epidurale—epidural use/route (it)
via gastroentérica—gastroenteral use/route (pt)
vía gastroentérica—gastroenteral use/route (es)
via inalatória—inhalation (route) (pt)
via inalatoria—inhalation (route) (it)
vía inhalatoria—inhalation (route) (es)
via intra-arterial—intra-arterial use/route (pt)
vía intraarterial—intra-arterial use/route (es)
via intra-articular—intra-articular use/route (pt)
vía intraarticular—intra-articular use/route (es)
via intracavernosa—intracavernosal use/route (it,pt)
vía intracavernosa—intracavernosal use/route (es)
via intradérmica—intradermal use/route (pt)
via intradermica—intradermal use/route (it)
vía intradérmica—intradermal use/route (es)
vía intralesional—intra-lesional use/route (es)
via intramuscular—intramuscular use/route (pt)
vía intramuscular—intramuscular use/route (es)
via intraperitoneal—intraperitoneal use/route (pt)
vía intraperitoneal—intraperitoneal use/route (es)
via intratecal—intrathecal use/route (pt)
vía intratecal—intrathecal use/route (es)
via intrauterina—intrauterine use/route (it)
via intra-uterina—intrauterine use/route (pt)
vía intrauterina—intrauterine use/route (es)
via intravenosa—intravenous use/route (pt)
vía intravenosa—intravenous use/route (es)
via intravesical—intravesical use/route (pt)
vía intravesical—intravesical use/route (es)
via nasal—nasal use/route (pt)
vía nasal—nasal use/route (es)
via oftalmica—ocular use/route (it)
vía oftalmica—ocular use/route (es)
via oral—oral use/route (pt)
vía oral—oral use/route (es)
via oromucosale—buccal or oromucosal use/route (it)
vía ótica—auricular use/route (es)
via rectal—rectal use/route (pt)
vía rectal—rectal use/route (es)
via sottocutanea—subcutaneous use/route (it)
via subcutânea—subcutaneous use/route (pt)
vía subcutanea—subcutaneous use/route (es)
via sublingual—sublingual use/route (pt)
vía sublingual—sublingual use/route (es)
via transdérmica—transdermal use/route (pt)
via transdermica—transdermal use/route (it)
vía transdérmica—transdermal use/route (es)
via uretral—urethral use/route (pt)
vía uretral—urethral use/route (es)
vía vaginal—vaginal use/route (es)
vial
—buteliukas (lt)
—Durchstechflasche (de)
—fiala (it)
—fiolka (pl)
—flaconcino (it)
—flacon (fr)
—frasco para injectáveis (pt)
—injectieflacon (nl)
—injekciós üveg (hu)
—injekční lahvička (cs)
—injektionsflaska (sv)
—medicinflaska (sv)
—vial (es)
—φιαλίδιο (el)
vial—ampoule, bottle, vial (es)
vičko—cap (cs)
vienadozė talpyklė—single-dose container (lt)
vienkartinis švirkštas—disposable syringe (lt)
vietinė emulsija—topical emulsion (lt)
vietinė pasta—topical paste (lt)
vietinis gelis—topical gel (lt)
vloeistof voor rectaal gebruik—enema (nl)
voie auriculaire—auricular use/route (fr)
voie buccale—buccal or oromucosal use/route (fr)
voie cutanée—cutaneous use/route (fr)
voie gastro-entérale—gastroenteral use/route (fr)
voie inhalée—inhalation (route) (fr)
voie intra-artérielle—intra-arterial use/route (fr)
voie intra-articulaire—intra-articular use/route (fr)
voie intracaverneuse—intracavernosal use/route (fr)
voie intradermique—intradermal use/route (fr)
voie intralésionelle—intra-lesional use/route (fr)
voie intramusculaire—intramuscular use/route (fr)
voie intrapéritonéale—intraperitoneal use/route (fr)
voie intrarachidienne—intrathecal use/route (fr)
voie intra-utérine—intrauterine use/route (fr)
voie intraveineuse—intravenous use/route (fr)
voie intravésicale—intravesical use/route (fr)
voie nasale—nasal use/route (fr)
voie ophtalmique—ocular use/route (fr)
voie orale—oral use/route (fr)
voie péridurale—epidural use/route (fr)
voie rectale—rectal use/route (fr)
voie sous-cutanée—subcutaneous use/route (fr)
voie sublinguale—sublingual use/route (fr)
voie transdermique—transdermal use/route (fr)
voie urétrale—urethral use/route (fr)
voie vaginale—vaginal use/route (fr)
vonelė—bath (lt)
vonios priedas—bath additive (lt)
voorgevulde spuit—prefilled syringe (nl)
výtažek—extract (cs)

W

Wärmepackung—poultice (de)
wegwerpspuit—disposable syringe (nl)
Weichkapsel—soft capsule (de)
Weithalsgefäss—jar (de)
wieczko—cap (pl)
wirkstoffhaltiger Nagellack—medicated nail lacquer (de)
wirkstoffhaltiger Verband—medicated bandage (de)
wirkstoffhaltiges Pflaster—medicated plaster (de)
wkład—cartridge (pl)
wkładka—insert (pl)
wkładka domaciczna—intra-uterine system (pl)
wlewka doodbytnicza—enema (pl)

wondpleister—plaster (dressing or adhesive plaster) (nl)
Wundgaze—dressing (de)
Wundkompresse—dressing (de)
Wundpflaster—plaster (dressing or adhesive plaster) (de)
Wundschnellverband—plaster (dressing or adhesive plaster) (de)
Wundverband—bandage (de)
wyciąg—extract (pl)

X

xarope—syrup, linctus (pt)
xarope para a tosse—cough syrup (pt)
xarope para a tosse—cough mixture (pt)

Z

zachte capsule—soft capsule (nl)
Zahnpaste—toothpaste (de)
zakrętka—screw cap (pl)
zalf—ointment (nl)
zalf voor rectaal gebruik—rectal ointment (nl)
zalf voor vaginaal gebruik—vaginal ointment (nl)
zamknięcie zabezpieczające przed dostępem dzieci—child-resistant closure (pl)
žandinė tabletė—buccal tablet (lt)
Zäpfchen—suppository (de)
zásobní vložka—cartridge (cs)
zásyp—dusting (cutaneous) powder (cs)
zásyp k zevnímu použití—topical powder (cs)
závitový uzávěr—screw cap (cs)
zawiesina—suspension (pl)
zawiesina do inhalacji—suspension for inhalation (pl)
zawiesina do wstrzykiwań—suspension for injection (pl)
zawiesina doustna—oral suspension (pl)
żel—gel (pl)
żel do cewki moczowej—urethral gel (pl)
żel do oczu—eye gel (pl)
żel dopochwowy—vaginal gel (pl)
żel doustny—oral gel (pl)
żel dozębowy—dental gel (pl)
żel na skórę—topical gel (pl)
zetpil—suppository (nl)
zevní podání—topical application (cs)
zioła do zaparzania—tea (herbal or medicinal) (pl)
zrněný prášek—granules (cs)
zrněný prášek pro přípravu perorální suspenze—granules for oral suspension (cs)
zrněný prášek pro přípravu perorálního roztoku—granules for oral solution (cs)
zubní gel—dental gel (cs)
zubní pasta—toothpaste (cs)
zuckerfrei—sugar-free (de)
zuigtablet—lozenge (nl)
zum Einnehmen—oral use/route (de)
zur Inhalation—inhalation (route) (de)
žvakutė—suppository (lt)
žvýkací guma—chewing gum (cs)
žvýkací tableta—chewable tablet (cs)
žvýkačka—chewing gum (cs)
zwachtel—bandage (nl)

Greek Terms

α

αέριο για εισπνοή—gas (for inhalation) (el)
αερόλυμα εισπνοής—aerosol inhaler (el)
αλοιφή—ointment (el)
αλοιφή εντριβής—liniment (el)
αναβράζον δισκίο—effervescent tablet (el)
αναβράζοντα κοκκία—effervescent granules (el)
αναβράζουσα κόνις—effervescent powder (el)
από στόματος χρήση—oral use/route (el)
αυτοκόλλητο έμπλαστρο—plaster (dressing or adhesive plaster) (el)
αφρός—foam (el)

β

βάζο—jar (el)
βάλσαμο—balm (el)
βάμμα—tincture (el)
βιδωτό πώμα—screw cap (el)

γ

γαλάκτωμα—emulsion (el)
γαργαρίσμα—gargle (el)
γαστρεντερική χρήση—gastroenteral use/route (el)
γαστροανθεκτική κάψουλα—enteric-coated (gastro-resistant) capsule (el)
γαστροανθεκτικό δισκίο—enteric-coated (gastro-resistant) tablet (el)
γαστροανθεκτικό καψάκιο—enteric-coated (gastro-resistant) capsule (el)
γέλη—gel (el)

δ

δερματική κόνις—dusting (cutaneous) powder (el)
δερματική χρήση—cutaneous use/route (el)
δερματικό γαλάκτωμα—cutaneous emulsion (el)
δερματικό διάλυμα—cutaneous solution (el)
δερματικό εκνέφωμα—cutaneous spray (el)
δερματικό ραβδίο (skin)—medicated stick (el)
δερματικός σπόγγος—cutaneous sponge (el)
διαδερμική χρήση—transdermal use/route (el)
διαδερμικό έμπλαστρο—transdermal patch (el)
διαιρούμενο δισκίο—breakable or dividable tablet (el)
διάλυμα—solution (el)
διάλυμα για έγχυση—solution for infusion (el)
διάλυμα για εισπνοή—solution for inhalation (el)
διάλυμα για εισπνοή με εκνεφωτή—nebuliser solution (el)
διάλυμα για έκπλυση ουροδόχου κύστεως—bladder irrigation (el)
διάλυμα για στοματικές πλύσεις—mouthwash (el)
διάλυμα εκνεφωτή—nebuliser solution (el)
διάλυμα οφθαλμικής πλύσης—eye wash (el)
διαλυτό δισκίο—soluble tablet (el)
διασπειρόμενο δισκίο—dispersible tablet (el)
δισκίο—tablet (el)
δισκίο διασπειρόμενο στο στόμα—orodispersible tablet (el)
δισκίο ελεγχόμενης αποδέσμευσης—modified release tablet (el)
δισκίο παρατεταμένης αποδέσμευσης—extended-release tablet (el)
δισκίο παρειάς—buccal tablet (el)

ε

έγχυση—infusion (el)
εισπνεόμενος ατμός—vapour inhalation (el)
εισπνοή—inhalation (el)
εκνέφωμα—spray (el)
εκχύλισμα—extract (el)
έλαιο—oil (el)
ελιξήριο—elixir (el)
εμποτισμένη ράβδος—medicated stick (el)
εμποτισμένο έμπλαστρο—medicated plaster (el)
εμποτισμένο επίθεμα—medicated dressing (el)
εμφύτευμα—implant (el)
εναιώρημα—suspension (el)
εναιώρημα για εισπνοή—suspension for inhalation (el)
ενδοαρθρική χρήση—intra-articular use/route (el)
ενδοαρτηριακή χρήση—intra-arterial use/route (el)
ενδοβλαβική χρήση—intra-lesional use/route (el)
ενδοδερμική χρήση—intradermal use/route (el)
ενδοκυστική χρήση—intravesical use/route (el)
ενδομήτρια χρήση—intrauterine use/route (el)
ενδομυική χρήση—intramuscular use/route (el)
ενδοπεριτοναϊκή χρήση—intraperitoneal use/route (el)
ενδορραχιαία χρήση—intrathecal use/route (el)
ενδοσηραγγική χρήση—intracavernosal use/route (el)
ενδοφλέβια χρήση—intravenous use/route (el)
ένεση—injection (el)
ενέσιμο διάλυμα—solution for injection (el)
ενέσιμο εωαιώρημα—suspension for injection (el)
ένθεμα—insert (el)
εντριβή—embrocation (el)
επίδεσμος—bandage (el)
επίδεσμος εμποτισμένος—medicated bandage (el)
επίδεσμος εμποτισμένος—medicated dressing (el)
επίθεμα—dressing (el)
επικαλυμμένο δισκίο—coated tablet (el)
επικαλυμμένο με λεπτό υμένιο δισκίο—film-coated tablet (el)
επίπωμα—tampon (el)
επισκληρίδια χρήση—epidural use/route (el)

θ

θραυστό δισκίο—breakable or dividable tablet (el)

κ

κατάπλασμα—poultice (el)
καταπότια—globules (homoeopathic) (el)
καψάκιο—capsule (el)
καψάκιο παρατεταμένης αποδέσμευσης—extended-release capsule (el)
κάψουλα—capsule (el)
κάψουλα παρατεταμένης αποδέσμευσης—extended-release capsule (el)
κοκκία για πόσιμο διάλυμα—granules for oral solution (el)
κοκκία για πόσιμο εναιώρημα—granules for oral suspension (el)
κολπική αλοιφή—vaginal ointment (el)
κολπική γέλη—vaginal gel (el)
κολπική κάψουλα—vaginal capsule (el)
κολπική κλύσις—douche (vaginal) (el)
κολπική κρέμα—vaginal cream (el)
κολπική χρήση—vaginal use/route (el)
κολπικό διάλυμα—vaginal solution (el)
κολπικό δισκίο—vaginal tablet (el)
κολπικό καψάκιο—vaginal capsule (el)
κολπικό υπόθετο—vaginal suppository (el)
κολπικό υπόθετο—pessary (el)
κολπικός αφρός—vaginal foam (el)
κολπικός σπόγγος—vaginal sponge (el)
κόμμι—gum (el)
κόνις—powder (el)
κόνις για εισπνοή—powder for inhalation (el)
κόνις για ένεση—powder for injection (el)
κόνις για πόσιμο διάλυμα—powder for oral solution (el)
κουταλάκι—teaspoon (el)
κουταλάκι του γλυκού—dessertspoon (el)
κουτάλι—tablespoon (el)
κουτί—box (el)
κρανιακό πλύμα—scalp lotion (el)
κρέμα—cream (el)
κύπελλο—cup (measuring) (el)

λ

λαρυγγικό εκνέφωμα—throat spray (el)
λοσιόν—lotion (el)
λουτρό—bath (el)
λυοφιλομένη κόμις—lyophilised powder (el)

μ

μαλακή κάψουλα—soft capsule (el)
μαλακό καψάκιο—soft capsule (el)
μαλακτικό σιρόπι—linctus (el)
μασώμενο δισκίο—chewable tablet (el)
μασώμενο κόμμι—chewing gum (el)
μείγμα—mixture (el)
μείγμα για το βήχα—cough mixture (el)

ο

οδοντική γέλη—dental gel (el)
οδοντόκρεμα—toothpaste (el)
οδοντόπαστα—toothpaste (el)
ορθική αλοιφή—rectal ointment (el)
ορθική χρήση—rectal use/route (el)
ορθικό διάλυμα—rectal solution (el)
ορθικός αφρός—rectal foam (el)
ουρηθρική γέλη—urethral gel (el)
ουρηθρική χρήση—urethral use/route (el)
οφθαλμικές σταγόνες—eye drops (el)
οφθαλμική αλοιφή—eye ointment (el)
οφθαλμική γέλη—eye gel (el)
οφθαλμική χρήση—ocular use/route (el)
οφθαλμικό ένθεμα—ocular insert (el)
οφθαλμικό πλύμα—eye lotion (el)

π

παστίλλια—pastille (el)
περιέκτης μίας δόσης—single-dose container (el)
πόσιμα κοκκία—oral granules (el)
πόσιμες σταγόνες—oral drops (el)
πόσιμη γέλη—oral gel (el)
πόσιμη κόνις—oral powder (el)
πόσιμο διάλυμα—oral solution (el)
πόσιμο εναιώρημα—oral suspension (el)
προγεμισμένη σύριγγα—prefilled syringe (el)
προσθετικό λουτρού—bath additive (el)
πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση—concentrate for infusion (solution) (el)
πώμα—cap (el)
πώμα ασφαλείας για παιδιά—child-resistant closure (el)

ρ

ρινικές σταγόνες—nasal drops (el)
ρινική αλοιφή—nasal ointment (el)
ρινική χρήση—nasal use/route (el)
ρινικό διάλυμα για πλύση—nasal solution (el)
ρινικό εκνέφωμα—nasal spray (el)
ρινικό πλύμα—nasal solution (el)
ρόμβος—lozenge (el)

σ

σαμπουάν—shampoo (el)
σιρόπι—syrup (el)
σιρόπι για το βήχα—cough syrup (el)
σκεύασμα ενδοφθαλμικής εισαγωγής—ocular insert (el)
σκληρή κάψουλα—hard capsule (el)
σπόγγος—sponge (el)
σταγόνες—drops (el)
σταγονίδια (ομοιοπαθητικής)—globules (homoeopathic) (el)
στοματική πάστα—oral paste (el)

στοματικό διάλυμα—mouthwash (el)
στοματικό δισκίο—buccal tablet (el)
στοματικό εκνέφωμα—mouth spray (el)
στοματικό φύραμα—oral paste (el)
συμπύκνωμα προς έγχυση—concentrate for infusion (solution) (el)
σύριγγα—syringe (el)
σύριγγα για χορήγηση από στόματος—oral syringe (el)
σύριγγα μιας χρήσης—disposable syringe (el)
συσκευασία συνδυασμού—combination pack (el)
συσκευή εισπνοής—inhaler (el)
σύστημα ενδομήτριας χορήγηση—intra-uterine system (el)

τ

τοπική γέλη—topical gel (el)
τοπική κόνις—topical powder (el)
τοπική χρήση—topical application (el)
τοπικό γαλάκτωμα—topical emulsion (el)
τοπικό διάλυμα—topical solution (el)
τοπικό εκνέφωμα—topical spray (el)
τοπικό φύραμα—topical paste (el)
τροχίσκος—lozenge (el)
τσάι—tea (el)

υ

υγρό λουσίματος—shampoo (el)
υπογλώσσια χρήση—sublingual use/route (el)
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Methyl Carboprost, A:2133·1
Methyl Catechol, A:1666·1
Methyl Chloride, A:2197·2
Methyl Cyanide, A:2167·1
Methyl 2-cyanoacrylate, A:2490·1
Methyl Cysteine Hydrochloride, A:1669·1
Methyl Dacisteine, A:1669·2
Methyl Diacetylcysteinate, A:1669·2
Methyl *N*,*S*-diacetyl-L-cysteinate, A:1669·2
Methyl Diethylacetylsalicylate, A:91·3
β-Methyl Digoxin, A:1433·1
Methyl Ethyl Ketone, A:2197·2
Methyl *O*-(2-ethylbutyryl)salicylate, A:91·3
Methyl Flavone Carboxylic Acid, A:2360·2
Methyl Fluorosulfate, A:2558·1
Methyl Fluorosulphate, A:2558·1
Methyl Fluorosulphonate, A:2558·1
Methyl Gentisate, A:91·3
Methyl Hydroxybenzoate, A:1757·1
Methyl 2-hydroxybenzoate, A:92·1
Methyl 4-hydroxybenzoate, A:1757·1
Methyl Hydroxypropyl Cellulose, A:2189·2
Methyl Isobutyl Ketone, A:2197·1
Methyl Methacrylate, A:2558·2
Methyl 2-methylacrylate, A:2558·2
Methyl 2-methylpropenoate, A:2558·2
Methyl Mitomycin, A:849·2
Methyl Nicotinate, A:91·3
Methyl Parahydroxybenzoate, A:1757·1
Methyl Phenidate Hydrochloride, A:2326·1
Methyl α-phenyl-2-piperidylacetate, A:2326·1
Methyl Phthalate, A:2153·3
Methyl Polysiloxane, A:2209·3
Methyl pyridine-3-carboxylate, A:91·3
Methyl Sal., A:92·1
Methyl Salicylate, A:92·1
Methyl Salicylate Cream, Compound, B:3441·1
Methyl Sulphone, A:2493·3
Methyl Sulphoxide, A:2182·2
Methyl Terbutyl Ether, A:2196·3
Méthyl Tert-butyl Éther, A:2196·3
Methyl *tert*-Butyl Ether, A:2196·3
Methyl Tertiary Butyl Ether, A:2196·3
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Methyl Undecenoate, A:597·1
Methyl Violet, A:1761·1
Methylacetopyronone, A:1749·2
Methylacetoxyprogesterone, A:2288·1
Methylal, A:2493·2
4-[(2-Methylallyl)amino]hydratropic acid, A:20·2
4-Methyl-Amino-Antipyrine, A:54·1
1-Methylamino-1-deoxy-D-glucitol, A:2550·3
2-(Methylamino)-1-phenyl-1-propan-1-one, A:2325·2
4-(2-Methylaminopropyl)phenol sulfate, A:1469·3
4-Methylaminorex, A:158·2
l-Methylamphetamine, A:1668·3
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6′-Methyl-6′-apo-β-caroten-6′-one, A:2179·2
N^{ω}-Methyl-L-arginine, A:2631·2
Methylarsinic Acid, A:2619·2
N-Methyl-D-Aspartate, A:2497·1
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Methylatropine Nitrate, A:1310·2
Méthylatropine, Nitrate de, A:1310·2
Methylatropini Bromidum, A:1310·2
Methylatropini Nitras, A:1310·2
Methylatropinii Bromidum, A:1310·2
Methylatropinii Nitras, A:1310·2
Methylatropinium Bromatum, A:1310·2
Methylatropinium Nitrát, A:1310·2
Methylatropiniumbromid, A:1310·2
Methylatropinium-bromid, A:1310·2
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Methylbenactyzii Bromidum, A:1861·3
Methylbenactyzium Bromide, A:1861·3
Méthylbénactyzium, Bromure de, A:1861·3
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Methylbenzethonii Chloridum, A:1760·3
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Méthylbenzéthonium, Chlorure de, A:1760·3
3-(4-Methylbenzylidene)bornan-2-one, A:1703·2
3-(4-Methylbenzylidene)camphor, A:1703·2
3-Methylbutaanzuur, A:2641·2
3-Methylbutanoic acid, A:2641·2
2-Methylbutan-2-ol, A:2169·1
3-Methylbuttersäure, A:2641·2
3-Methylbutyl 2-hydroxybenzoate, A:21·2
Methylcathinone, A:2325·1
Methylcellulose, A:2197·3
Méthylcellulose, A:2197·3
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Methylcellulosum, A:2197·3
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Methylcephaëline Hydrochloride, A:932·3
Methylchlorid, A:2197·2
Methylchloroform, A:2217·3
Methylchloroisothiazolinone, A:1759·2
Methylcloxazolam, A:1085·1
Methylcobalamin, A:2108·1
6α-Methylcompactin, A:1425·2
Methylcysteine Hydrochloride, A:1669·1
β-Methyldigoxin, A:1433·1
o-Methyldihydroartemisinin, A:648·1
2α-Methyldihydrotestosterone Propionate, A:2270·1
4-Methyl-2,5-Dimethoxyamfetamine, A:2330·3
Methyldinitrobenzamide, A:932·1
Methyldinoprost, A:2133·1
4-Methyl-1,3-dioxolan-2-one, A:2205·2
N-Methyldiphenethylamine Hydrochloride, A:2492·2
2-Methyl-1,2-di(3-pyridyl)propan-1-one, A:2559·1
3-*O*-Methyldobutamine, A:1366·3
Methyldopa, A:1431·1
Méthyldopa, A:1431·1
α-Methyldopa, A:1434·1
3-*O*-Methyldopa, A:908·1
α-Methyldopa Hydrazine, A:900·3

α-Methyldopamine, A:1434·1
Methyldopate Hydrochloride, A:1431·1
Methyldopum, A:1431·1
Methyldopum Hydratum, A:1431·1
Methyldronat, B:3441·1
Méthyle, Nicotinate de, A:91·3
Méthyle, Parahydroxybenzoate de, A:1757·1
Méthyle (Parahydroxybenzoate De) Sodique, A:1757·2
Méthyle, Salicylate de, A:92·1
Methyleenblauw, A:1559·1
Methylenblåt, A:1559·1
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Methylene Bis-Benzotriazolyl Tetramethylbutylphenol, A:1697·1
Methylene Blue, A:1559·1
Methylene Chloride, A:2181·2
Méthylène, Chlorure de, A:2181·2
Methylene Glycerin, A:2186·2
16-Methylene-17-alpha-acetoxy-19 Norprogesterone, A:2270·2
6-Methyleneandrosta-1,4-diene-3,17-dione, A:792·2
2,2′-Methylenebis(4-chlorophenol), A:152·3
2,2′-Methylenebis(6-chlorothymole), A:1740·1
3,3′-Methylenebis(4-hydroxycoumarin), A:1352·2
Methylenebis(Hydroxytoluenesulphonic Acid) Polymer, A:1160·2
Methylenebis(phosphonic acid), A:1186·1
2,2′-Methylenebis(3,4,6-trichlorophenol), A:1754·1
Méthylènecycline Chlorhydrate, A:322·3
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3,4-Methylenedioxyamphetamine, A:2330·3
1-(3,4-Methylenedioxybenzyl)piperazine, A:2318·2
Methylenedioxycinnamic Acid, A:2558·1
3,4-Methylenedioxycinnamic acid, A:2558·1
3,4-Methylenedioxyethamfetamine, A:2330·3
3,4-Methylenedioxyethylamfetamine, A:2330·3
3,4-Methylenedioxy-*N*-Hydroxyamfetamine, A:2330·3
Methylenedioxymethamfetamine, A:2325·2
Methylenedioxymethamphetamine, A:2325·2
3,4-Methylenedioxymethamphetamine, A:2325·2
3,4-Methylenedioxymethcathinone, A:2318·3
3,4-Methylenedioxypyrovalerone, A:2318·3
6-Methyleneoxytetracycline Hydrochloride, A:322·3
Methylenesulfathiazole, A:300·2
Methylenetanshinquinone, A:2492·1
5,10-Methylenetetrahydrofolate, A:2068·1
5,10-Methylenetetrahydrofolic Acid, A:2068·1
Methyleni Chloridum, A:2181·2
Methylenii Caeruleum, A:1559·1
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Methylergobrevin, B:3441·1
Methylergol Carbamide Maleate, A:908·2
Méthylergométrine, Hydrogénomaléate de, A:2137·3
Methylergometrine Maleate, A:2137·3
Méthylergométrine, Maléate de, A:2137·3
Methylergometrini Hydrogenomaleas, A:2137·3
Methylergometrini Maleas, A:2137·3
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Methylergonovine Maleate, A:2137·3
6-*O*-Methylerythromycin, A:266·2
Methyl-4-esculetol Monoethanoate Sodium, A:2557·3
Methylestrenolone, A:2297·3
Methylestrenolonum, A:2297·3
Methylfenobarbital, A:533·1
α-Methylfentanyl, A:62·3
3-Methylfentanyl, A:62·3
Methylfluorethe, A:1899·3
Methyl-Gag, B:3441·1
Methyl-GAG, A:830·2
6′*N*-Methylgentamicin C_{1A} Sulphate, A:324·2
N-Methylglucamine, A:2550·3
Methylglucamine Diatrizoate, A:1581·3
N-Methylglycine, A:2164·2
Methylglyoxal Bisguanylhydrazone (Mitoguazone), A:830·2
Methylglyoxyl, A:2072·2
Methylhippuric Acid, A:2220·2
Methylhomatropinium Bromatum, A:2007·3
Methylhomatropinium Bromide, A:2007·3
Methylhydrazine, A:866·1, A:2565·2
Methylhydrocupreine Hydrobromide, A:2529·2
Methyl-4-hydroxybenzoat, A:1757·1
Methylhydroxyethylcellulose, A:2189·1
Méthylhydroxyéthylcellulose, A:2189·1
Methylhydroxyethylcellulosum, A:2189·1
α-Methyl-ω-hydroxypoly(oxyethylene), A:2194·2
Methylhydroxypropylcellulose, A:2189·2
Methylhydroxypropylcellulose Phthalate, A:2189·3
Methylhydroxypropylcellulosi Phthalas, A:2189·3
Methylhydroxypropylcellulosum, A:2189·2
Methylhydroxyquinoline Methylsulphate, A:2558·2
Methylhydroxyquinoline Metilsulfate, A:2558·2
Methylhyoscini Nitras, A:1846·1
Methyli Nicotinas, A:91·3
Methyli Salicylas, A:92·1
(Methylidynetrithio)triacetic acid, A:1768·2
1-Methylimidazole-2-thiol, A:2345·2
Methylin, B:3441·1
Methylis Methacrylas, A:2558·2
Methylis Nicotinas, A:91·3
Methylis Oxybenzoas, A:1757·1
Methylis Parahydroxybenzoas, A:1757·1
Methylis Parahydroxybenzoas Natricum, A:1757·2
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Methylis Paraoxibenzoas, A:1757·1
Methylis Salicylas, A:92·1
Méthylisobutylcétone, A:2197·1
Methylisobutylketon, A:2197·1
Methylisothiazolinone, A:1759·2
2-Methyl-4-isothiazolin-3-one, A:1759·2
2-Methyl-3(2*H*)-isothiazolone, A:1759·2
1-Methyl-D-lysergic Acid Butanolamide, A:677·1
Methylmelubrin, A:53·3
Methylmercadone, A:941·2
Methylmercaptoimidazole, A:2345·2
Methylmercury, A:2556·1
Methylmethacrylate, A:2558·2
4-Methylmethcathinone, A:2325·2
Methylmethionine Sulfonium Chloride, A:2558·1
17-Methyl-9α,13α,14α-morphinan-3-ol, A:2492·3
Methylmorphine, A:40·2
Methylmorphine Phosphate, A:40·2
Methylnaltrexone Bromide, A:1861·3
Methylnaltrexone Sulfate, A:1862·1
Methylnaltrexonii Bromidum, A:1861·3
Methylnaphthochinonum, A:2122·1
Methylnaphthochinonumnatrium Bisulfurosum, A:2122·2
2-Methyl-1,4-naphthoquinone, A:2122·1
2-Methyl-1,4-naphthylene diacetate, A:2122·1
N-Methylnicotinamide, A:2084·3
Methylnicotinat, A:91·3
3-*O*-Methyl-6-*O*-nicotinoylmorphine, A:1670·3
Methyl-nikotinát, A:91·3
2-Methyl-5-Nitroimidazole-1-Acetic Acid, A:940·1
2-Methyl-5-nitroimidazole-1-propanol, A:949·1
2-(2-Methyl-5-nitroimidazol-1-yl)ethanol, A:936·1
1-Methyl-4-Nitro-5-Thioimidazole, A:1943·2
α-Methylnoradrenaline, A:1434·1
7α-Methylnorethynodrel, A:2309·2
Methylnortestosterone, A:2297·3
7-α-Methyl-19-Nortestosterone, A:2233·2
17α-Methyl-19-nortestosterone, A:2297·3
Methylon, B:3441·1
Methylone, A:2318·3
3-Methyl-1-(5-oxohexyl)-7-propylxanthine, A:1479·1
Methylparaben, A:1757·1
Methylparaben Sodium, A:1757·2
Methylparaben Sodná Sůl, A:1757·2
Methylparabenum, A:1757·1
Methylparabenum Natricum, A:1757·2
Methylpartricin, A:588·1
2-Methyl-2,4-pentanediol, A:2188·3
4-Methylpentan-2-one, A:2197·1
5-Methyl-2-pentylphenol, A:1736·3
Methylperidol Hydrochloride, A:1088·3
Methylperone Hydrochloride, A:1083·2
(*R,S*)-α-Methylphenethylamine, A:2316·1
(+)-α-Methylphenethylamine sulphate, A:2319·1
(*R,S*)-α-Methylphenethylamine sulphate, A:2316·2
(*S*)-α-Methylphenethylammonium sulphate, A:2319·1
Methylpheni, B:3441·1
Methylphenidate, A:2326·1
d-threo-Methylphenidate, A:2320·3
Méthylphénidate, A:2326·1
Méthylphénidate, Chlorhydrate de, A:2326·1
Methylphenidate Hydrochloride, A:2326·1
d-Methylphenidate Hydrochloride, A:2320·3
Methylphenidathydrochlorid, A:2326·1
Methylphenidati Hydrochloridum, A:2326·1
Methylphenidatum, A:2326·1
Methylphenobarbital, A:533·1
Méthylphénobarbital, A:533·1
Methylphenobarbitalum, A:533·1
Methylphenobarbitone, A:533·1
Methylphenol, A:1749·1
5-Methyl-1-phenyl-2(1*H*)-pyridone, A:2592·1
2-Methyl-1,4-phenylenediamine, A:2583·3
(5-Methyl-3-phenyl-4-isoxazolyl)penicillin Sodium, A:336·2
1-Methyl-4-Phenyl-4-Propionoxypiperidine, A:123·1
3-Methyl-1-phenyl-2-pyrazolin-5-one, A:1370·2
N-Methyl-2-phenylsuccinimide, A:538·2
1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine, A:123·1
Methylphytylnaphthochinonum, A:2122·2
Methylpred, B:3441·1
Methyl-Pred, B:3441·1
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Methylprednisolonacetat, A:1642·3
Methylprednisolon-acetát, A:1642·3
Methylprednisolone, A:1642·2
Méthylprednisolone, A:1642·2
6α-Methylprednisolone, A:1642·2
Methylprednisolone Acetate, A:1642·3
Methylprednisolone 21-acetate, A:1642·3
Méthylprednisolone, Acétate de, A:1642·3
Methylprednisolone Hemisuccinate, A:1642·3
Méthylprednisolone, Hémisuccinate de, A:1642·3
Methylprednisolone Hydrogen Succinate, A:1642·3
Méthylprednisolone, Hydrogénosuccinate de, A:1642·3
Methylprednisolone Sodium Hemisuccinate, A:1642·3
Methylprednisolone Sodium Succinate, A:1642·3
Methylprednisolone 21-(sodium succinate), A:1642·3
Méthylprednisolone, Succinate Sodique de, A:1642·3
Methylprednisolonhydrogensuccinat, A:1642·3
Methylprednisolon-hydrogen-sukcinát, A:1642·3
Methylprednisoloni Acetas, A:1642·3
Methylprednisoloni Hemisuccinas, A:1642·3
Methylprednisoloni Hydrogenosuccinas, A:1642·3
Methylprednisoloni Natrii Succinas, A:1642·3
Methylprednisolonum, A:1642·2
16β-Methylprednisone, A:1642·2
2-Methylpropane, A:1799·2
2-Methyl-1-propanol, A:2190·3
2-Methyl-1-propene homopolymer, A:2202·3
2-Methylpropyl Alcohol, A:2190·3
(15*S*)-15-Methylprostaglandin $F_{2\alpha}$, A:2133·1
4-Methyl-1*H*-pyrazole, A:1553·1
4-Methylpyrazole, A:1553·1
4′-*O*-Methylpyridoxine, A:2513·1
N-Methyl-2-(2-pyridyl)ethylamine, A:2455·3
1-Methylpyrrolidin-2-one, A:2207·1
Methylpyrrolidon, A:2206·3
Methylpyrrolidone, A:2207·1
N-Methylpyrrolidone, A:2206·3
N-Méthylpyrrolidone, A:2206·3
N-Methyl-2-pyrrolidone, A:2206·3
Methylpyrrolidonum, A:2206·3
N-Methylpyrrolidonum, A:2206·3
5-Methylquinolin-8-ol, A:949·2
Methylrosaniline Chloride, A:1761·1
Methylrosanilinii Chloridum, A:1761·1
Methylrosanilinium Chloride, A:1761·1
Méthylrosanilinium, Chlorure de, A:1761·1
Methylrosaniliniumchlorid, A:1761·1
Methylrosanilinium-chlorid, A:1761·1
Methylsalicylat, A:92·1
Methyl-salicylát, A:92·1
Methylscopolamine Nitrate, A:1846·1
Methylscopolamini Nitras, A:1846·1
Methylselenocysteine, A:2087·2
β-Methylserine, A:2098·2
6β-[(Methyl[^{75}Se]seleno)methyl]-19-Norcholest-5(10)-En-3β-Ol, A:2228·1
Methylsilanol Hydroxyproline Aspartate, A:2088·3
Methylsilanol Mannuronate, A:2088·3
Methylstanazole, A:2304·2
Methylsulfathiazole, A:367·3
Methylsulfonylmethane, A:2493·3
Methylsulphonylmethane, A:2493·3
Methylsynephrine Hydrochloride, A:1463·2
Methyltestosteron, A:2291·3
Methyltestosterone, A:2291·3
Méthyltestostérone, A:2291·3
Methyl-1-testosterone, A:2291·3
Methyltestosteronum, A:2291·3
4-Methyl-1-tetradecylpyridinium chloride, A:1761·2
5-Methyltetrahydrofolate, A:2066·2
5-Methyl-Tetrahydrofolic Acid, A:2068·1
Methyltheobromine, A:1203·3
7-Methyltheophylline, A:1203·3
α-Methylthiofentanyl, A:62·3
3-Methylthiofentanyl, A:62·3
3-Methyl-2-Thiohydantoin, A:2336·2
Methylthioninii Chloridum, A:1559·1
Methylthioninii Chloridum Hydricum, A:1559·1
Methylthioninium Chloride, A:1559·1
Méthylthioninium, Chlorure de, A:1559·1
Methylthioniniumchlorid, A:1559·1
Methylthioninium-chlorid Hydrát, A:1559·1
3-*O*-Methyltolcapone, A:917·2
5-(3-Methyl-Triazeno-1-Yl)-Imidazole-4-Carboxamide, A:776·3
5-(3-Methyl-Triazen-1-Yl)-Imidazole-4-Carboxamide, A:866·1
Methyltrimethylene Glycol, A:2172·2
Methyltrypsin, A:1837·1
α-Methyltyramine, A:1434·1
α-Methyltyrosine, A:1433·3
(±)-α-Methyl-DL-Tyrosine, A:1433·3
(-)-α-Methyl-L-tyrosine, A:1433·3
α-Methyl-*p*-Tyrosine, A:1433·3
Methyluric Acid, A:1206·3
1-Methyluric Acid, A:1237·1
(*E*)-8-Methyl-*N*-vanillylnon-6-enamide, A:35·1
Methylxanthine, A:1206·3
1-Methylxanthine, A:1237·1
3-Methylxanthine, A:1237·1
Methyneuron, B:3441·1
Methypranolol, A:2009·2
Methysergid, A:677·1
Methysergide, A:677·1
Méthysergide, A:677·1
Methysergide Maleate, A:677·1
Méthysergide, Maléate de, A:677·1
Methysergidi Maleas, A:677·1
Methysergidum, A:677·1
Methysticin, A:2537·3
Metibasol, B:3441·1
Metica, B:3441·1
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Meticil, B:3441·1
Meticilina Sódica, A:323·3
Meticillin Sodium, A:323·3
Méticilline Sodique, A:323·3
Meticillinum Natricum, A:323·3
Meticlorpindol, A:930·2
Meticlotiazida, A:1430·3
Meticone, B:3441·1
Meticortelone, B:3441·1
Meticorten, B:3441·2
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Meticrano, A:1433·1
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Metifor, B:3441·2
Metikseenihydrokloridi, A:909·2
Metikseno Hidrochloridas, A:909·2
Metil, B:3441·2
Metil *N*-butilcetona, A:2197·1
Metil Carboprost, A:2133·1
Metil Cianuro, A:2167·1
Metilal, A:2493·2
Metilaminolevulinato, Hidrocloruro de, A:740·1
Metilarsinato de Sodio, A:2619·2
Metilat, B:3441·2
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Metilbenacticio, Bromuro de, A:1861·3
Metilbenceno, A:2216·2
Metilbencetonio, Cloruro de, A:1760·3
Metilbenzocuato, A:936·1
Metilbetasone Solubile, B:3441·2
Metilbromuro de Hioscina, A:1846·1
Metilbromuro de Homatropina, A:2007·3
Metilbromuro de Octatropina, A:1866·2
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